Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness, Value and Value-Based Price Benchmarks

Final Evidence Report and Meeting Summary

November 1, 2016

Institute for Clinical and Economic Review

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We would also like to thank Margaret Webb of ICER for her contributions to this report.

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The Midwest CEPAC is an independent committee of medical evidence experts from across the Midwest, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about Midwest CEPAC is available at https://icer-review.org/programs/midwest-cepac/.

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External Input

The following organizations, companies, and individuals provided input and/or feedback that helped guide the ICER team as we shaped our scope and report. None of these groups is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

External Input Received from:

Aetna

AstraZeneca

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Genentech

Lungevity

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List of Acronyms Used in this Report

AE	Adverse event
AJCC	American Joint Committee on Cancer Staging
ASCO	American Society of Clinical Oncology
BI	Budget impact
BSA	Body surface area
CI	Confidence interval
CIS-PEM	Cisplatin+pemetrexed
COPD	Chronic obstructive pulmonary disease
ECOG PS	Eastern Cooperative Oncology Group Performance Status score
EGFR	Epidermal growth factor receptor
FDA	US Food and Drug Administration
HR	Hazard ratio
HrQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
irAE	Immune-related adverse events
ITT	Intention to treat
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed death 1 receptor
PD-L1	Programmed death ligand 1
PF	Progression-free
PFS	Progression-free survival
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Progression
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
QoL	Quality of life
RCT	Randomized controlled trial
RECIST	Response evaluation criteria in solid tumors
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TNM	Tumor, lymph nodes, metastasis
Tx	Treatment
USPSTF	US Preventive Services Task Force
WAC	Wholesale acquisition cost

Executive Summary

Background

Lung cancer is the number one cause of cancer death in the United States, expected to cause 158,000 deaths in 2016, and accounting for 26.5% of all cancer deaths.[1] Lung cancer includes different pathological types, broadly divided into small-cell lung cancer and non-small cell lung cancer (NSCLC).[2] Patients with NSCLC commonly present with advanced disease (i.e., distant spread, malignant effusion, or bilateral lung disease). The prognosis is generally poor at diagnosis; five-year survival from 2006-2012 was 31.4% in patients with regional spread and 4.9% in patients with distant spread.[3] Previously, advanced NSCLC was treated with chemotherapy. In recent years, the treatment of some advanced NSCLCs has changed based on the determination of driver mutations in tumors. Patients with mutations that involve the kinase region of the epidermal growth factor receptor (EGFR) are now typically treated with tyrosine kinase inhibitors (TKIs) as first-line therapy. More recently, immunotherapy aimed at altering checkpoint inhibition through the programmed death 1 (PD-1) receptor or its ligand (PD-L1) have demonstrated benefit in at least some patients with NSCLC.

Topic in Context

In patients with advanced NSCLC, although chemotherapy can extend survival, it is not curative in patients with advanced disease, and many patients may be unable to tolerate the side effects of the most potent regimens. These potent chemotherapy regimens are typically platinum-based chemotherapy doublets (e.g., cisplatin + paclitaxel, carboplatin + gemcitabine, etc.), and they continue to be recommended as first-line therapy for patients with advanced NSCLC without a driver mutation.[4]

For NSCLC patients with EGFR mutations (referred to as EGFR+ NSCLC), major guidelines, such as those from the National Comprehensive Cancer Network (NCCN), list tyrosine kinase inhibitors (TKIs) as first-line therapy.[4] The main TKIs used as first-line therapy for advanced NSCLC include afatinib (Gilotrif®, Boehringer Ingelheim), erlotinib (Tarceva®, Genentech), and gefitinib (Iressa®, AstraZeneca). TKIs are administered orally once daily, generally until disease progression. The most common adverse reactions are rash, which can be severe, and diarrhea.[5,6] In general, however, rates of serious adverse events are much lower with TKI therapy than with a platinum doublet. Treatment with first-line TKI therapy typically costs approximately $90,000 per year.[7] Despite treatment with a TKI, nearly all patients with advanced NSCLC will eventually progress.[2]

Tumor cells can produce substances that alter the immune response to the tumor, such as by affecting a regulatory "checkpoint" or brake on the T cell response to the tumor, thus allowing the tumor to evade the immune system. Immunotherapy aimed at inhibiting such a checkpoint through the PD-1 receptor or its ligand, PD-L1, have demonstrated benefit in at least some patients with NSCLC.[8] Agents focused on this pathway include nivolumab (Opdivo®, Bristol-Myers Squibb) and pembrolizumab (Keytruda®, Merck), which are antibodies to PD-1, as well as atezolizumab (Tecentriq®, Genentech), an antibody to PD-L1. We use the term "PD-1 immunotherapy" to refer to both groups of antibodies.

A minority of patients respond to PD-1 immunotherapy, but a substantial proportion of those who do respond appear to have prolonged responses and improved survival.[8,9] Tumor expression of PD-L1 appears to be helpful in selecting appropriate patients for PD-1 based therapies; however, there are concerns about the comparability of various methods used to assess levels of expression.[8] The FDA-labeled indication for pembrolizumab is for patients whose tumors express PD-L1. While nivolumab does not carry such a restriction, response rates are higher in tumors with PD-L1 expression with nivolumab as well.[8] However, some tumors that do not express PD-L1 respond to PD-1 immunotherapy. As such, a potential question is whether only treating patients based on PD-L1 expression would result in missing an opportunity for therapy in a percentage of patients.

PD-1 immunotherapy is administered intravenously every two to three weeks and is continued until disease progression. Fatigue is common with these agents, and more serious immune-mediated events, including pneumonitis and encephalitis, have been seen. These immune events are uncommon, and serious adverse events overall are much less common with PD-1 immunotherapy than with docetaxel. Treatment with PD-1 immunotherapy has been estimated to cost approximately $150,000 per year.[7]

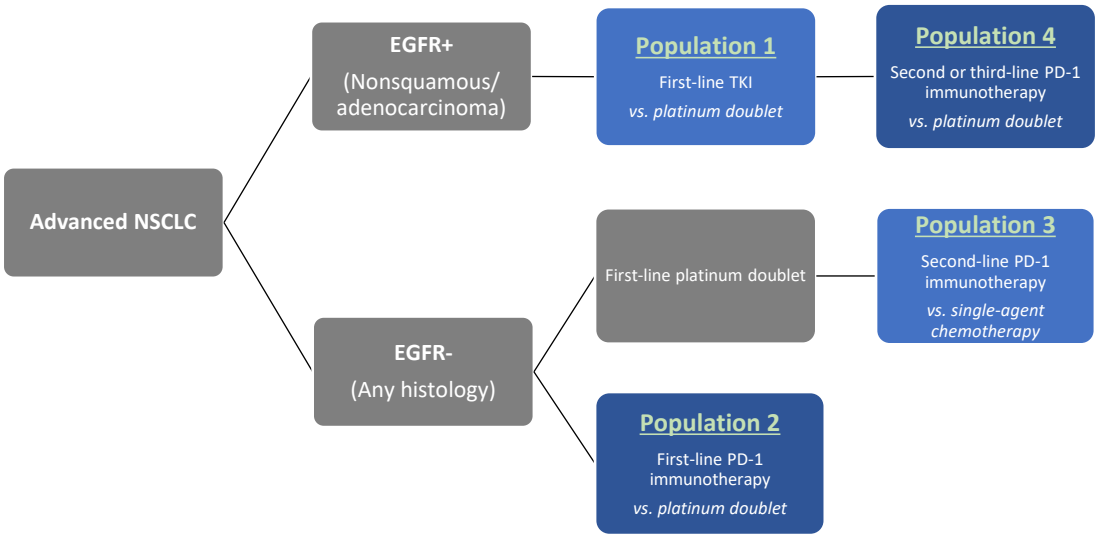
Among the insights provided by discussions with patients and patient groups were:

- Lung cancer patients experience unusual stigma, being blamed for their disease given the association with smoking behavior.
- Because of prior smoking, lung cancer patients have high rates of vascular and pulmonary comorbidities.
- In rural and low-income community settings, patients may not receive the same care they would receive for advanced NSCLC in major medical centers; this includes not all patients receiving appropriate molecular testing.
- "Financial toxicity" can be a major issue, placing patients and their families at high risk for suffering economic hardship or even bankruptcy; as smoking has become less common in patients of higher socioeconomic status, lung cancer is now disproportionately affecting patients who have fewer resources available to deal with the illness.

- Given the emergence of new therapies, many patients have a goal of staying stable until the next trial/therapy becomes available.

In this review, we sought to assess the comparative clinical effectiveness and comparative value of first-line TKI therapy for EGFR+ advanced NSCLC (population P1), and of PD-1 immunotherapy as second-line therapy (after a platinum doublet) for advanced NSCLC without a driver mutation (population P3); we also assessed PD-1 immunotherapy as first-line therapy for advanced NSCLC without a driver mutation (population P2), and as second- or third-line therapy after TKI therapy in EGFR+ advanced NSCLC (population P4). Figure ES1 presents these populations and therapies of interest (the light blue boxes, populations 1 and 3, represent FDA-approved indications for TKI and PD-1 immunotherapy, respectively).

Figure ES1. Populations and therapies of focus



Comparative Clinical Effectiveness

Although we had originally planned the scope of the evaluation of PD-1 immunotherapy to look at patients without any driver mutation (populations 3 and 2), both because of limitations in the evidence and because the clinical concern was around the EGFR mutation, we focused on EGFR- patients rather than patients without any driver mutation. We found very limited evidence on PD-1 immunotherapy when used as first-line treatment, although preliminary results of two trials have been announced in press releases, and we also found very limited evidence on its use as second- or third-line therapy in EGFR+ patients who have been treated with TKIs.

Our literature search identified 3,072 potentially relevant references, of which 44 references met our inclusion criteria; these citations related to 17 individual studies and seven systematic reviews.

We identified 11 key randomized trials of afatinib, erlotinib, or gefitinib in chemotherapy-naïve patients with an EGFR mutation. Ten of the 11 trials were rated fair quality and compared a TKI to a platinum doublet: two published Phase III RCTs of afatinib and four published Phase III trials each of erlotinib and gefitinib. One good-quality RCT directly compared afatinib and gefitinib.

We identified four key RCTs comparing PD-1 immunotherapy to single-agent docetaxel. All four trials provided evidence that informed our analysis of the use of PD-1 immunotherapy in EGFR- patients in the second-line setting (population P3); we found no studies that focused on first-line use in EGFR- patients (population P2) or on treatment of EGFR+ patients who had progressed after TKI therapy (population P4).

Results

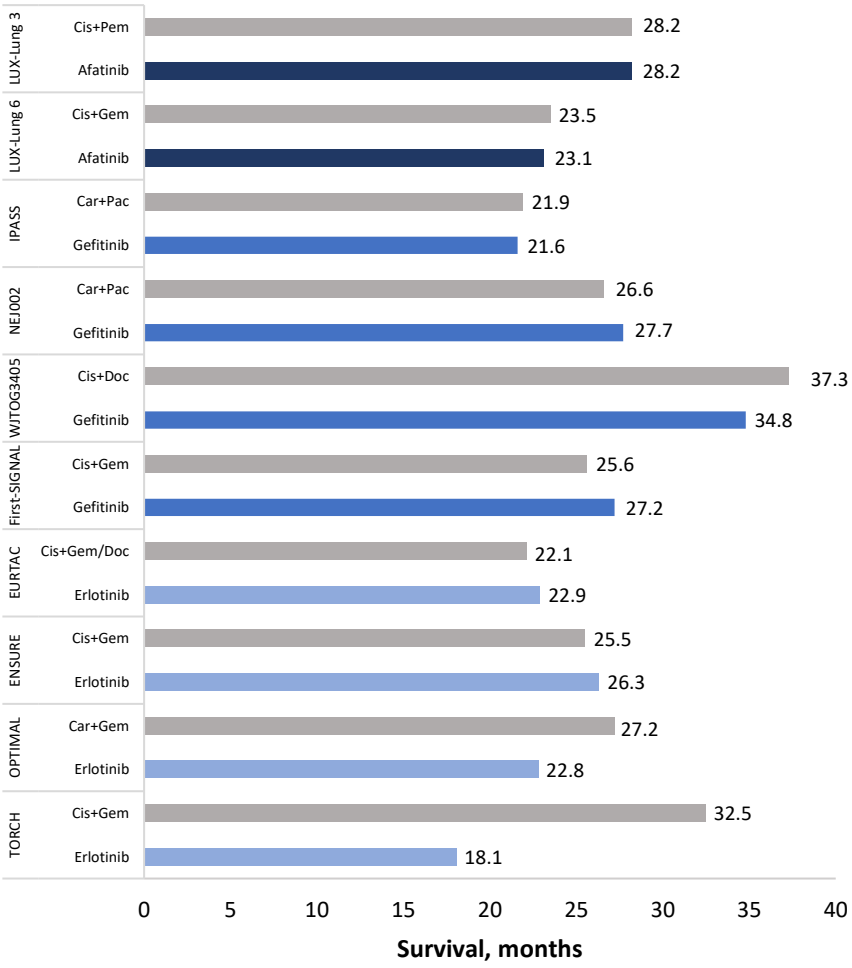
Tyrosine Kinase Inhibitors

- *Our review of the evidence on first-line TKI therapy for EGFR+ advanced NSCLC found inadequate evidence to distinguish between the three TKIs on patient-important outcomes such as overall survival overall survival (OS) and quality of life (QoL).*
- *Evidence from randomized controlled trials (RCTs) indicates that all three agents provide statistically-significant improvements in progression free survival (PFS) relative to platinum doublet chemotherapy.*
- *RCTs comparing TKIs with platinum doublet chemotherapy had high rates of crossover and showed no benefit in OS.*
    - *The most likely explanation for the lack of OS benefit seen in RCTs of TKIs with high rates of crossover is that treatment with a TKI improves survival whenever it is given in the sequence of therapy, such that patients randomized to chemotherapy who receive TKI therapy at the time of progression have similar survival in comparison to patients treated initially with a TKI.*
    - *Observational data suggest that first-line TKI therapy as a class increases OS by approximately 8.9 months, although there is substantial uncertainty in this figure.*
- *Rash, diarrhea, and liver function abnormalities are the most common side effects with TKIs. All TKIs appear to be better tolerated than chemotherapy with platinum doublets, which have much higher rates of hematologic toxicity.*
- *QoL improvements were greater with TKI therapy than with chemotherapy.*

Overall Survival

Improving overall survival (OS) and quality of life (QoL) are generally the patient-important goals of cancer therapy. Assessing the true survival benefit of an emerging therapy can be difficult when study participants are permitted to cross over to receive the alternative study treatment after tumor progression, and the key studies included in the sample set for this review had high levels of crossovers (approximately 45 to 90% of patients in the chemotherapy arms crossed over to treatment with a TKI). The ten randomized trials comparing a TKI with a platinum-based chemotherapy doublet all included data on OS, but no study showed statistical differences between the arms.

Figure ES2. Overall survival: TKIs vs. platinum-based chemotherapy doublets



	HR	95% CI	p-value
LUX-Lung 3	0.88	0.66-1.17	0.39
LUX-Lung 6	0.93	0.72-1.22	0.61
IPASS	1.00	0.76-1.33	0.99
NEJ002	0.887	0.63-1.24	0.483
WJTOG3405	1.252	0.88-1.78	NR
First-SIGNAL	1.043	0.50-2.18	NR
EURTAC	1.04	0.65-1.68	0.87
ENSURE	0.91	0.63-1.31	0.607
OPTIMAL	1.19	0.83-1.71	0.2663
TORCH	1.58	0.70-3.57	NR

Cis=cisplatin; Car=carboplatin; pem=pemetrexed; gem=gemcitabine; pac=paclitaxel; doc=docetaxel

One phase IIb randomized trial compared afatinib and gefitinib and found no statistically significant difference in OS (27.9 months vs. 25.0 months; hazard ratio [HR] 0.87, 95% CI 0.66-1.15; p=0.33).[10] The authors noted that survival data were not yet mature, with a median duration of follow-up of 27.3 months. Given the paucity of head-to-head data comparing TKIs, we performed indirect comparisons of the TKIs using Bayesian network meta-analyses (NMAs). Our results did not show statistical differences between agents, and we did not identify any subgroups for whom the TKIs had differential effects on overall survival. We also conducted meta-analyses stratified by the two common EGFR mutations (i.e., exon Del19 and L858R, respectively), and we did not find a differential effect of TKIs in these two subgroups.

It appears most likely that the explanation for the lack of OS benefit seen in randomized trials of TKIs with high rates of crossover is that treatment with a TKI improves survival *whenever* it is given in the sequence of therapy, such that patients randomized to chemotherapy who receive TKI therapy at the time of progression have similar survival in comparison to patients treated initially with a TKI. We attempted to estimate the likely OS benefit with TKI therapy by examining OS rates in 261 EGFR+ patients and 176 EGFR- patients in a trial of gefitinib vs. carboplatin+paclitaxel; gefitinib would only be expected to be of benefit in the EGFR+ patients. OS in EGFR+ patients randomized to gefitinib was 21.6 months and OS in EGFR- patients randomized to chemotherapy was 12.7 months. This difference of 8.9 months provides an estimated OS advantage with TKI therapy.

Although this estimate comes from data from a randomized trial, this is an observational post-hoc analysis of the results in subgroups of the original trial population and there are important reasons to be concerned that it could be affected by confounding: EGFR+ status could be a marker for less aggressive NSCLC, and could also identify a group of patients with fewer comorbidities as it is seen more often in non-smokers. We are, however, unlikely to get direct trial evidence that provides the survival benefit of administering a TKI to patients with EGFR+ advanced NSCLC, as it would be felt to be unethical to withhold TKI therapy at the time of progression in a randomized trial.

Progression-Free Survival

Compared with a platinum doublet, improvements in median PFS were similar across the trials of the TKIs (4-month benefit with afatinib, 3-5 months with gefitinib, and 3-9 months with erlotinib). Results from our network meta-analysis yielded hazard ratios of 0.38, 0.45, and 0.30 for afatinib, gefitinib, and erlotinib, respectively.

Only one randomized trial directly compared two TKIs, afatinib and gefitinib. In this trial of 319 patients, those randomized to afatinib had a slightly longer median PFS but the treatment effect was statistically significant (11.0 months vs. 10.9 months; HR 0.73, 95% CI 0.57 to 0.95; p=0.017); although the difference in median PFS was only 0.1 months, the survival curves generally showed

greater separation after 12 months.[10] Our network meta-analysis combined both direct and indirect evidence on PFS for the TKIs and showed no statistically significant differences among these agents.

Quality of Life and Symptom Control

We identified six RCTs, representing two trials for each individual TKI, that investigated the impact of TKIs on quality of life (QoL) in patients with NSCLC. The one head-to-head trial did not assess QoL. Overall, all six trials indicated that TKIs provided statistically significant improvements relative to comparator treatment on at least one QoL outcome. All six studies showed that TKIs had a greater benefit on at least one symptom-related outcome.

Harms

Relative to a platinum doublet, there were lower rates of discontinuation due to adverse events (AEs) and fewer AEs of grade 3 or greater with the TKIs. Platinum-based chemotherapy doublets were associated with a higher incidence of hematological AEs such as anemia and neutropenia, whereas the most common adverse events among the TKIs included dermatologic toxicity (skin rash), hepatotoxicity (elevated levels of aspartate aminotransferase and/or alanine aminotransferase), and diarrhea. Among TKIs, afatinib appears to have a higher incidence of diarrhea and rash (approximately 10 and 15 percent, respectively), while a greater proportion of patients developed increased aminotransferase concentrations with gefitinib (approximately 18 percent).

Controversies and Uncertainties

There are relatively few head-to-head studies of TKIs, and our network meta-analyses (NMAs) show wide credible intervals for the HR for PFS when comparing the three TKIs we evaluated for first-line therapy. As such, the evidence is inadequate to determine whether there are important clinical differences in the effectiveness of these therapies. The results of a single head-to-head trial do suggest a small PFS benefit of afatinib over gefitinib; however, the current data are not sufficiently mature to assess whether afatinib provides an OS benefit.

Creating relative estimates of OS among the TKIs is problematic given the very wide credible intervals seen in the NMAs, as well as the additional uncertainties generated by the effects of crossovers within the trials. As discussed previously, our largest uncertainties fall around the effect of TKIs, as a class, on OS, given that the randomized results within each of the trials were likely biased by crossovers.

Although we are estimating the survival benefit conferred by adding TKI therapy to the prior standard of care of a platinum doublet, it is important to note that TKI treatment has already

become standard of care for patients with advanced EGFR+ NSCLC, and that those patients with the T790M mutation (about half of EGFR+ patients who progress) will also be treated at the time of progression with the TKI osimertinib.[4,11] Second-line TKI therapy in such patients likely provides additional survival benefits; analysis of this type of treatment pathway was beyond the scope of our review.

Comparative Clinical Effectiveness: Summary

For patients with EFGR+ advanced NSCLC, we have high certainty that TKI therapy provides at least a small net health benefit ("B+") relative to platinum chemotherapy. This reflects high certainty that first-line treatment with TKI therapy is better tolerated than platinum chemotherapy and achieves at least equivalent OS, and moderate certainty that TKI therapy provides a clinically meaningful OS benefit.

Our review found inadequate evidence to distinguish between the three TKIs on patient-important outcomes such as OS and QoL. A head-to-head randomized trial, as well as our network meta-analysis, provide evidence that treatment with afatinib likely provides a small benefit in PFS compared with gefitinib; this is a surrogate endpoint and no statistically significant differences were seen in OS.

PD-1 Immunotherapies

Although our initial scope described three distinct populations of patients who might be treated with PD-1 immunotherapy, all relevant evidence came from four randomized trials applicable to population P3 (patients without a driver mutation treated second-line with PD-1 immunotherapy after progression on a platinum doublet). We discuss this population first in sequence, followed by discussions of populations P2 (first-line treatment for patients without a driver mutation) and P4 (second- or third-line treatment for EGFR+ patients), as well as our limited ability to extrapolate from population P3 to these other populations. *[Please see the Supplement, starting on page 102, for a discussion of evidence relevant to population P2 that became available after the report was published, as well as a limited discussion of an additional trial relevant to population P3.]*

Higher levels of PD-L1 are associated with a higher likelihood of response to PD-1 immunotherapy. However, PD-L1 expression levels were not comparable among trials because the investigators used different testing methods and cut-offs. For this same reason, subgroup analyses stratified by PD-L1 expression level were not comparable across drugs even at the same cut point. Because of this, we could not perform quantitative analyses comparing the efficacy of the PD-1 immunotherapies with each other.

PD-1 Immunotherapies for Patients without a Driver Mutation who have Progressed after Treatment with a Platinum Doublet (Second-Line)

- *Trials of PD-1 immunotherapies used different assays to measure PD-L1 levels and had different PD-L1 cut-points both as entry criteria and for subgroup analyses. Given the barriers to comparing results across trials and patient populations, we found inadequate evidence to distinguish among the PD-1 immunotherapies on any outcome.*
- *Evidence from RCTs indicates that in patients with advanced NSCLC without a driver mutation who have progressed after treatment with a platinum doublet, PD-1 immunotherapies improve survival compared with docetaxel.*
- *Patients with tumors that express high levels of PD-L1 are more likely to respond to PD-1 immunotherapies. However, only a minority of patients overall respond to these agents, even among those with high PD-L1 levels on assays. Conversely, even with negative PD-L1 level results, some patients do respond to PD-1 immunotherapy.*
- *Among the minority of patients who do respond to PD-L1 immunotherapy, improvements in survival can be substantial. However, because of the limited follow-up in the existing studies, we are uncertain of exactly how large this benefit is.*
- *The most common adverse events seen with PD-1 immunotherapies are fatigue, nausea, and decreased appetite. Serious immune-related adverse events, including pneumonitis and encephalitis, can occur with these agents; these adverse events are not typically seen with chemotherapy. Overall, however, PD-1 immunotherapy is better tolerated than docetaxel.*

<u>Overall Survival</u>

All four key studies of PD-1 immunotherapies evaluated overall survival, although only two studies stratified results by mutation status. Median OS was not reported in the EGFR- subgroup; however, statistically significant risk reductions indicate that the PD-1 immunotherapies provided a survival benefit over docetaxel in patients without an EGFR+ tumor. In the KEYNOTE-010 trial, pembrolizumab (2mg/kg and 10mg/kg groups combined) showed improved survival relative to single-agent docetaxel (HR 0.66, 95% CI 0.55-0.80). EGFR- patients treated with nivolumab in the CheckMate 057 trial saw a similar benefit (HR 0.66, 95% CI 0.51-0.86). Although the key trials of atezolizumab and nivolumab in squamous-cell carcinoma only reported OS in the overall populations, risk reductions were similar to those seen in EGFR- patients in the KEYNOTE-010 and CheckMate 057 trials: overall survival favored both atezolizumab (HR 0.73, 95% CI 0.53-0.99; p=0.040) and nivolumab in squamous-cell carcinoma (HR 0.59, 95% CI 0.44-0.78) relative to single-agent docetaxel. Absolute improvements in median OS were 2-3 months during the time of primary analysis.

Despite statistical risk reductions and clinically-significant absolute survival gains, we have substantial uncertainty about the true survival benefits of PD-1 immunotherapy over time. It is probable that the survival curves for PD-1 immunotherapy and docetaxel have different shapes, such that typical statistics for survival analyses (hazard ratios and median survival) do not present an adequate description of the results. Notwithstanding this, it appears that there is a subpopulation of patients with NSCLC (who cannot be definitely identified prior to treatment) who have clinically important, durable responses to PD-1 immunotherapy (median durations of response that are generally a year or more longer than with docetaxel). However, trial duration has not been long enough to ascertain the length of these responses or the percentage of patients who will experience prolonged responses.

We examined whether PD-1 immunotherapies have differential efficacy according to histological diagnosis. We found no consistent effect, since among the trials, two suggested greater efficacy in patients with non-squamous NSCLC, and two suggested greater efficacy in patients with squamous NSCLC.

We compared EGFR+ and EGFR- groups in a meta-analysis, expecting it to inform our evaluation of second- or third-line use of immunotherapies in EGFR+ NSCLC. The results showed an OS benefit in the EGFR- subgroup (HR 0.66, 95% CI 0.58-0.74) but no benefit in the EGFR+ subgroup (HR 1.12, 95% CI 0.69-1.81); the test for interaction with EGFR status was statistically-significant (p=0.036).

Progression-Free Survival

All four key studies also evaluated PFS and found small and inconsistent results related to benefits, as well as the predictive value of PD-L1 expression level on the magnitude of benefit. As with OS, we conducted a network meta-analysis using parametric survival curves. Our meta-analysis of nivolumab and atezolizumab showed no PFS benefit at one month but hazard ratios that improved over time; a similar trend was seen with pembrolizumab. Due to the small number of trials, almost all credible intervals crossed one and heavily overlapped.

We also used HRs to explore subgroup effects when survival curves were not available. Subgroup meta-analysis using HRs suggested that histology (squamous vs. non-squamous NSCLC) was not an effect modifier for PFS (p=0.104). Our meta-analysis of EGFR- and EGFR+ subgroups suggested that EGFR status *is* an effect modifier for PFS (p=0.002) with a PFS benefit in EGFR- patients (HR 0.80, 95% CI 0.72-0.90) and an *increased* risk of progression or death in EGFR+ patients (HR 1.57, 95% CI 1.07-2.31).

Quality of Life and Symptom Control

Two trials evaluated QoL, and the evidence was inadequate to assess the effects of PD-1 immunotherapy compared with docetaxel. Limited evidence from two trials showed no benefits of PD-1 immunotherapy compared with docetaxel for control of symptoms.

Harms

The PD-1 immunotherapies were well tolerated in the key trials, with safety profiles that were generally superior to docetaxel. Patients treated with atezolizumab, nivolumab, or pembrolizumab had lower rates of discontinuation due to treatment emergent adverse events (TEAEs), fewer grade 3-4 TEAEs, and fewer treatment-related deaths compared to patients treated with docetaxel. The higher rates of grade 3-4 TEAEs observed with docetaxel were attributable mainly to hematologic toxicity.

PD-1 immunotherapies have been associated with immune-related adverse events, which may include dermatologic toxicity (e.g., rash, pruritus), diarrhea or colitis, hepatotoxicity (elevations in serum levels of aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), pulmonary inflammatory complications (e.g., pneumonitis, pneumonia), and endocrinopathies (e.g., hypothyroidism).[12] The most common adverse events seen with PD-1 immunotherapies are fatigue, nausea, and decreased appetite.

Controversies and Uncertainties

Although the comparator in all four trials of PD-1 immunotherapies was docetaxel, we found no head-to-head trials comparing these agents. As such, there are limitations in the evidence for assessing whether there are any important differences in outcomes with the three agents we evaluated. Two of the agents, nivolumab and pembrolizumab are directed at PD-1; atezolizumab is directed at PD-L1. Although this different target might argue for considering atezolizumab separately, our meta-analysis suggests little heterogeneity of effect across these three agents.

It seems likely that the the difference in the shapes of the survival curves for docetaxel compared with PD-1 immunotherapy is created by two populations in the PD-1 immunotherapy arms of the trials: a majority of patients who do not have sustained responses to therapy and have a high hazard for progression/mortality, and a minority of patients who do have sustained responses and have a much lower hazard. This is also reflected in the median duration of response results seen in the trials. There are relatively few data to allow assessment of whether there is a very long tail of responders beyond two years, but this is clearly an important issue in understanding the potential benefit of PD-1 immunotherapy.

Patients with higher levels of PD-L1 expression had better responses to all three agents, but different cutpoints and assays were used for each agent in the randomized trials. As such, it is difficult to be certain whether the effect of PD-L1 expression is the same for the three therapies.

Although the scope of this assessment was for PD-1 immunotherapy in patients without a driver mutation, the data available to us do not provide that exact subgroup and so patients with anaplastic lymphoma kinase (ALK) and KRAS mutations are not separately broken out. We were primarily concerned about assessing therapy in patients who are EGFR-; two of the four trials provide these subgroup data, and a third trial was in patients with squamous cell carcinoma which has a low rate of EGFR mutations.[4]

Comparative Clinical Effectiveness: Summary

Even with uncertainties about the duration of benefit with PD-1 immunotherapies, the current evidence base gives us high certainty that a substantial minority of patients with EGFR- advanced NSCLC do respond and achieve important gains in overall survival ("A").

Trials of PD-1 immunotherapies used different assays to measure PD-L1 levels and had different PD-L1 cut-points both as entry criteria and for subgroup analyses. Given the barriers in comparing results across trials and patient populations, we found inadequate evidence to distinguish among the PD-1 immunotherapies on any outcome.

PD-1 Immunotherapies for First-Line Treatment of Patients without a Driver Mutation

[Please see the Supplement, starting on page 102, for a discussion of evidence relevant to this population that became available after the report was published.]

We currently have no direct evidence from randomized trials comparing PD-1 immunotherapies with a platinum doublet for first line treatment of advanced NSCLC. We have chosen to look at this question because patients are already being treated with first-line PD-1 immunotherapy in the absence of published evidence from randomized trials. If similar response rates to what was seen with second-line therapy are achieved with first-line PD-1 immunotherapy, it could delay or even obviate the need for chemotherapy for a proportion of patients.

Two trial results of note have been announced, but details are only currently available via press release. The Keynote 024 trial reportedly showed benefits in both OS and PFS with first-line pembrolizumab.[13] The CheckMate 026 trial reportedly showed no benefit in its primary outcome of PFS with first-line nivolumab.[14] Both of these trials were performed in patients with tumors that express PD-L1, but the cutpoints for the analyses were different and used different assays, which

might explain the conflicting results. We expect these results to become available in the near future, and they will provide direct evidence on this issue.

Comparative Clinical Effectiveness: Summary

[Please see the Supplement, starting on page 102, for a discussion of evidence relevant to this population that became available after the report was published.]

There are substantial uncertainties about the efficacy of first-line PD-1 immunotherapies in NSCLC. While it seems possible that a proportion of patients would achieve durable responses that would delay the need for treatment with chemotherapy, the evidence base is insufficient ("I").

PD-1 Immunotherapies for Second- or Third-Line Treatment of EGFR+ NSCLC

We currently have no direct evidence comparing PD-1 immunotherapies with a platinum doublet as subsequent-line treatment (after TKIs) of EGFR+ advanced NSCLC. We are looking at this issue, however, as we were informed by clinical experts that some clinicians are using PD-1 immunotherapy in preference to chemotherapy in this setting.

Few EGFR+ patients were in the trials discussed above comparing PD-1 immunotherapies with docetaxel; however, two such trials did report on this subgroup. As discussed above, our meta-analysis suggests that the effects on OS of PD-1 immunotherapy compared with docetaxel was different in EGFR- and EGFR+ patients. This analysis suggests that there is little if any benefit with PD-1 immunotherapy compared with docetaxel in EGFR+ patients treated after progression on TKI therapy and prior to treatment with a platinum doublet. As such, there are reasons to be concerned that PD-1 immunotherapy could be inferior to a platinum doublet (which is more efficacious than docetaxel monotherapy).

Comparative Clinical Effectiveness: Summary

Although the evidence base is insufficient ("I"), indirect evidence raises concerns that in patients with EGFR+ advanced NSCLC who have progressed after TKI therapy, treatment with PD-1 immunotherapy may be inferior to a platinum-based chemotherapy doublet. There is, therefore, currently no evidence to support the use of PD-1 immunotherapy in this setting.

Other Benefits and Disadvantages

Because of the distribution of smoking behavior within the United States, lung cancer has become more common among patients in lower socioeconomic groups. Thus treatments for the disease will

disproportionately affect these groups, and any economic burdens/financial toxicities of treatments will be felt more greatly. Additionally, we were told that lung cancer is a stigmatized disease, so patients with advanced NSCLC suffer from this additional burden as well.

Patients with NSCLC have high rates of comorbid vascular and pulmonary disease, and many such patients may not have qualified for the clinical trials that assessed these newer therapies. TKI therapy is well tolerated and can be administered even to those with a poor performance status. The safety and efficacy of PD-1 immunotherapy in such patients is less clear.

Comparative Value

- *[After the publication of the Evidence Report, the FDA approved atezolizumab with a broader indication than was assumed in these analyses. The evidence for this approval is discussed briefly in the Supplement starting on page 102. This report's modeling and conclusions related to the long-term value for money of atezolizumab should only be applied to the narrower subpopulation that was analyzed. Additionally, after the meeting of the Midwest CEPAC, the FDA expanded the indication of pembrolizumab to a broader second-line population.]*
- *Cost-effectiveness estimates were quite similar across the TKIs, ranging from $110,840 to $147,244 per QALY gained.*
- *Because we did not find adequate evidence to distinguish among the TKIs, we did not calculate a separate value-based price benchmark for each of these drugs, but instead calculated average percentage discounts (or premiums) across all three agents.*
    - *The average discount to achieve a cost-effectiveness threshold of $100,000/QALY would be approximately 21%.*
    - *A premium could be added to each drug's list price to achieve $150,000/QALY; the average of these would represent an approximately 15% increase in price.*
- *Cost-effectiveness estimates for PD-1 immunotherapies were $219,179 per QALY gained for atezolizumab, $236,492 for pembrolizumab, and $415,950 for nivolumab; there is substantial uncertainty in these estimates, and the results are not directly comparable because of differences in labeled or expected indications for each drug as well as the type of assay used for PD-1/PD-L1 expression.*
- *The ICER value-based price benchmark to achieve $100,000 to $150,000/QALY for atezolizumab represents a 31%-53% discount from the WAC list price. For pembrolizumab, the other agent with a testing requirement, the discount is 39%-61% to achieve these thresholds. The ICER value-based price benchmark for nivolumab among all patients (i.e., no testing requirement) requires a 57%-68% discount from the WAC list price to achieve these thresholds.*

The primary aim of our analysis was to estimate the long-term costs, outcomes, and cost-effectiveness of treatment for advanced NSCLC for two distinct populations, namely, first-line therapy with TKIs versus chemotherapy doublet (cisplatin+pemetrexed) for EGFR+ patients, and second-line therapy with PD-1 immunotherapy versus docetaxel in EGFR- patients who progressed

on a first-line chemotherapy doublet. Due to a lack of publicly available comparative evidence, we did not model second- or third-line PD-1 immunotherapy for EGFR+ patients or first-line PD-1 immunotherapy in patients without a driver mutation.

Outcomes were modeled using a partition survival model with three health states: progression-free, progression, and death. Using one-week cycle lengths and a lifetime horizon, the model was analyzed from a health system perspective. A 3% discount rate for future costs and outcomes was applied. Parametric survival curves for PFS were fit in both first and second-line therapy, using available data from the literature. Assessing the benefit of TKIs on OS is difficult because of high crossover rates in randomized trials; we therefore assumed an OS benefit of approximately nine months for TKI therapy, based on comparisons of patients who only receive TKIs with patients who only receive chemotherapy. For second-line PD-1 immunotherapy, we used derived time-dependent hazard ratios (HRs) for modeling survival data. Health state utilities, adverse events and costs were obtained from the literature. Model outcomes included estimates of total costs, quality adjusted life years (QALYs), life-years gained, time in progression free and post-progression health states, and incremental cost-effectiveness ratios. Details on model inputs and estimation are available in the full report and appendices.

The short-term (one and five year) potential budget impact of PD-1 immunotherapies was also calculated using model outputs. (Potential budget impact of TKI treatment was not analyzed, given the established, longer-term presence of TKIs for first-line treatment of EGFR+ NSCLC.) The budget impact model assumed varying levels of uptake over the different time periods to derive drug costs and associated cost-savings from the treatment strategies included.

Incremental Costs per Outcomes Achieved

Modeled costs and outcomes for the four first-line treatment regimens in an EGFR+ population are shown in table ES1, with incremental results for each TKI compared to cisplatin+pemetrexed shown in table ES2. Use of each of the first-line TKI regimens (with the assumption of a 9-month gain in median survival for each regimen) resulted in a 0.84 life-year gain in survival relative to cisplatin+pemetrexed. QALYs gained versus cisplatin+pemetrexed were also very similar across all three regimens, ranging from 0.59 for gefitinib to 0.62 and 0.63 for afatinib and erlotinib, respectively. Cost-effectiveness estimates were quite similar across the TKIs, ranging from $110,840 to $147,244 per QALY gained, which is not surprising given the assumption of equal gain in median OS across the TKIs. Any differences observed were due to trial-based point estimates for the duration of progression-free survival; as noted previously, we do not feel there is sufficient information to distinguish the clinical benefit of the three TKIs, so any differences in cost-effectiveness ratios should be interpreted with great caution.

Table ES1. Results by regimen for first-line EGFR+ patients

	CIS-PEM	AFAT	ERLO	GEFI
Total Costs	$111,443	$195,398	$204,789	$177,281
Drug Costs	$32,042	$89,872	$102,726	$71,548
PFS Supp. Care Costs	$10,217	$20,364	$22,520	$15,571
Administration Costs	$1,145	$0	$0	$0
Progression Costs	$14,845	$34,466	$30,735	$42,834
Death Costs	$48,192	$46,953	$46,953	$46,953
Adverse Event Costs	$5,002	$3,744	$1,855	$375
Total QALYs	0.88	1.50	1.51	1.47
PFS QALYs	0.42	0.83	0.91	0.64
Progression QALYs	0.46	0.67	0.60	0.84
Total Life Years (OS)	1.22	2.06	2.06	2.06
PFS LYs	0.54	1.06	1.16	0.81
Progression LYs	0.68	1.00	0.90	1.25
Median PFS (months)	5.1	10.4	11.5	7.9
Median OS (months)	12.5	21.4	21.4	21.4

Table ES2. Incremental results for first-line EGFR+ patients

	CIS-PEM	AFAT	ERLO	GEFI
ICER (QALYs)	--	$135,095	$147,244	$110,840
ICER (LYs)		$100,120	$111,318	$78,514
Incremental Costs	--	$83,956	$93,346	$65,838
Drug Costs	--	$57,830	$70,684	$39,506
PFS Supp. Care Costs	--	$10,147	$12,303	$5,354
Administration Costs	--	-$1,145	-$1,145	-$1,145
Progression Costs	--	$19,621	$15,890	$27,989
Death Costs	--	-$1,239	-$1,239	-$1,239
Adverse Event Costs	--	-$1,259	-$3,147	-$4,628
Incremental QALYs	--	0.62	0.63	0.59
PFS QALYs	--	0.41	0.49	0.22
Progression QALYs	--	0.21	0.14	0.38
Incremental Life Years (OS)	--	0.84	0.84	0.84
PFS LYs	--	0.52	0.63	0.28
Progression LYs	--	0.32	0.21	0.56

Deterministic results of second-line PD-1 immunotherapy are shown in table ES3**,** with incremental results for the same population and therapeutic group shown in table ES4. Use of each of the second-line immunotherapy regimens resulted in a gain in survival and QALYs relative to docetaxel (from 0.26 incremental QALYs for nivolumab to 0.87 for pembrolizumab). Incremental costs versus docetaxel ranged from a low of $107,472 for nivolumab to $205,714 for pembrolizumab. Pembrolizumab had the longest median PFS, resulting in higher treatment costs. Incremental cost-effectiveness estimates ranged from $219,179 per QALY gained relative to docetaxel for atezolizumab to $415,950 per QALY for nivolumab.

Table ES3. Results by regimen for second-line PD-1 immunotherapy patients

	DOCX	ATEZ: TC2/3 or IC2/3	NIVO: All Comers	PEMB: PD-L1 >50%
Total Costs	**$94,405**	**$206,190**	**$201,877**	**$300,119**
Drug Costs	$11,816	$114,334	$120,657	$195,670
PFS Supp. Care Costs	$9,044	$14,448	$15,020	$24,766
Administration Costs	$1,170	$1,802	$2,771	$3,036
Progression Costs	$4,648	$27,725	$15,242	$28,695
Death Costs	$48,457	$47,011	$47,819	$46,166
Adverse Event Costs	$19,270	$870	$367	$1,785
Total QALYs	**0.57**	**1.08**	**0.83**	**1.44**
PFS QALYs	0.31	0.48	0.50	0.82
Progression QALYs	0.27	0.60	0.33	0.62
Total Life Years (OS)	**1.04**	**2.02**	**1.47**	**2.59**
PFS LYs	0.47	0.74	0.77	1.26
Progression LYs	0.57	1.28	0.70	1.32
Median PFS (months)	4.2	3.9	4.2	9.5
Median OS (months)	8.5	14.8	11.1	25.8

Table ES4. Incremental results for second-line PD-1 immunotherapy patients

	DOCX	ATEZ: TC2/3 or IC2/3	NIVO: All Comers	PEMB: PD-L1 >50%
ICER (QALYs)	--	**$219,179**	**$415,950**	**$236,492**
ICER (LYs)		$114,303	$249,169	$133,212
Incremental Costs	--	**$111,785**	**$107,472**	**$205,714**
Drug Costs	--	$102,519	$108,841	$183,855
PFS Supp. Care Costs	--	$5,404	$5,976	$15,721
Administration Costs	--	$631	$1,601	$1,866
Progression Costs	--	$23,077	$10,594	$24,047
Death Costs	--	-$1,446	-$637	-$2,290
Adverse Event Costs	--	-$18,400	-$18,902	-$17,485
Incremental QALYs	--	**0.51**	**0.26**	**0.87**
PFS QALYs	--	0.18	0.19	0.51
Progression QALYs	--	0.33	0.06	0.36
Incremental Life Years (OS)	--	**0.98**	**0.43**	**1.54**
PFS LYs	--	0.27	0.30	0.79
Progression LYs	--	0.71	0.14	0.76

Sensitivity Analyses

Detailed results of the sensitivity analyses can be found in the full report. In one-way sensitivity analyses, results were most sensitive to the PFS and OS hazard ratios, drug costs, and (for TKIs) the assumption of a 9-month OS benefit. Results of the probabilistic sensitivity analyses (PSA) showed substantial variability in model outcomes, particularly in second-line immunotherapies. For first-line TKI regimens, the credible range of possible incremental cost-effectiveness ratios included the commonly-cited thresholds of $100,000 - $150,000 per QALY gained. In contrast, the credible range of PSA results for second-line immunotherapies are substantially wider, due to uncertainty around PFS and OS hazard ratios; thus, the mean incremental cost-effectiveness ratios for PD-L1 immunotherapies should be interpreted with caution.

Potential Budget Impact Model

Output from the cost-effectiveness model was used to calculate the potential budget impact of PD-1 immunotherapy versus docetaxel for the treated population. (We decided against calculating the budget impact of TKIs as first-line therapy since all interventions in this class have an established

presence in the market.) Applying prevalence data from the literature resulted in a candidate population size for atezolizumab and pembrolizumab of approximately 59,400 individuals in the US. Use of nivolumab is not restricted to patients whose tumors express PD-L1, resulting in a total of 99,000 individuals eligible for nivolumab. For this analysis of potential budget impact, we assumed a 50% uptake pattern for nivolumab, and 25% uptake each for atezolizumab and pembrolizumab in the eligible PD-L1 positive population. For the eligible population of second-line NSCLC patients whose tumors do *not* express PD-L1, we assumed a 75% uptake pattern for nivolumab because of the lack of other effective treatment alternatives. Total numbers of patients treated by five years would be approximately 14,850 each for atezolizumab and pembrolizumab, and 59,400 for nivolumab (i.e., 29,700 of 59,400 for PD-L1 positive, and 29,700 of 39,600 for PD-L1 negative).

After one year of treatment, budget impact is estimated to be $118.4 million for atezolizumab, $214.3 million for pembrolizumab, and $528.9 million for nivolumab (Table ES5). Total budget impact for nivolumab is much higher due to the larger number of patients assumed to receive nivolumab. Across the full five-year time horizon, average budget impact per year is estimated as approximately $230.8 million for atezolizumab, $429.8 million for pembrolizumab, and $987.8 million for nivolumab. This annualized potential budget impact is 26% of the budget impact threshold of $904 million for atezolizumab, 48% of the threshold for pembrolizumab, and 109% of the threshold for nivolumab.

Table ES5. Estimated total potential budget impact (BI) of PD-1 immunotherapy

		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
	Eligible Population	Number Treated	Annual BI per Patient*	Total BI (millions)	Number Treated	Weighted BI per Patient*	Average BI per year (millions)
Atezolizumab	59,400	2,970	$39,900	$118.4	14,850	$77,800	$230.8
Pembrolizumab	59,400	2,970	$72,200,	$214.3	14,850	$144,800	$429.8
Nivolumab†	99,000	11,880	$44,500	$528.9	59,400	$83,200	$987.8

*Weighted budget impact calculated by subtracting cost offsets from drug costs for one-year horizon. For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

†Includes PD-L1 positive and negative patients.

Value-based Price Benchmarks

The ICER value-based price benchmark for a drug is comprised of two components: 1) the price range that would align with reasonable long-term cost-effectiveness levels between $100,000–$150,000 per additional QALY; and, 2) if relevant, another price beyond which the potential short-term budget impact would exceed a target for health care affordability ($904 million per year over 5 years), a threshold at which policymakers may need to consider special measures to manage short-term affordability, even for drugs that are priced in alignment with their long-term added value for patients. Because we made the assumption of an 8.9-month gain in median survival across all of

the first-line TKI regimens, and because we did not find adequate evidence to distinguish among these agents, we did not calculate a separate value-based price benchmark for each of these drugs. Instead, we calculated the average of the percentage discounts (or premiums) that would need to be applied to each drug to bring its estimated cost-effectiveness to $100,000 or $150,000 per QALY gained. The average discount to achieve $100,000/QALY would be approximately 21%. Because the base case cost-effectiveness estimates were less than $150,000/QALY for each TKI treatment, a premium could be added to each drug's price to achieve $150,000/QALY; the average of these would represent an approximately 15% increase in price. Applying these percentages to the average price per tablet across the three TKI treatments, $239, results in a value-based price benchmark range from $189 to $274.

Our value-based benchmark prices for each PD-1 immunotherapy treatment are provided in Table ES6. In this case, one of the evaluated drugs, nivolumab, is projected to exceed the budget impact threshold ($904 million) under base case assumptions; however, the discounts required to achieve $100,000 and $150,000 per QALY gained would bring the potential budget impact well below the threshold. As noted previously, the potential budget impacts of atezolizumab and pembrolizumab do not exceed our stated threshold when annualized over a five-year time horizon.

Therefore, the ICER value-based price benchmark for atezolizumab is $4,026 to $5,954 per 1200 mg vial. This price represents a 31%-53% discount from the WAC list price of atezolizumab. The ICER value-based price benchmark for pembrolizumab is $1,719 to $2,694 per 100 mg vial, representing a 39%-61% discount from the WAC list price. The ICER value-based price benchmark for nivolumab (all comers) is $799 to $1,064 per 100 mg vial, representing a 57%-68% discount from the WAC list price.

Table ES6. Value-based price benchmarks for PD-1 immunotherapy treatments for NSCLC patients under assumed product uptake patterns

	WAC Price per Vial	Cost to Achieve $100K/QALY	Cost to Achieve $150K/QALY	Value-Based Price Benchmark
Atezolizumab	$8,620	$4,026	$5,954	$4,026 to $5,954
Pembrolizumab	$4,381	$1,719	$2,694	$1,719 to $2,694
Nivolumab*	$2,470†	$799	$1,064	$799 to $1,064

*Includes PD-L1 positive and negative patients
†100 mg vial

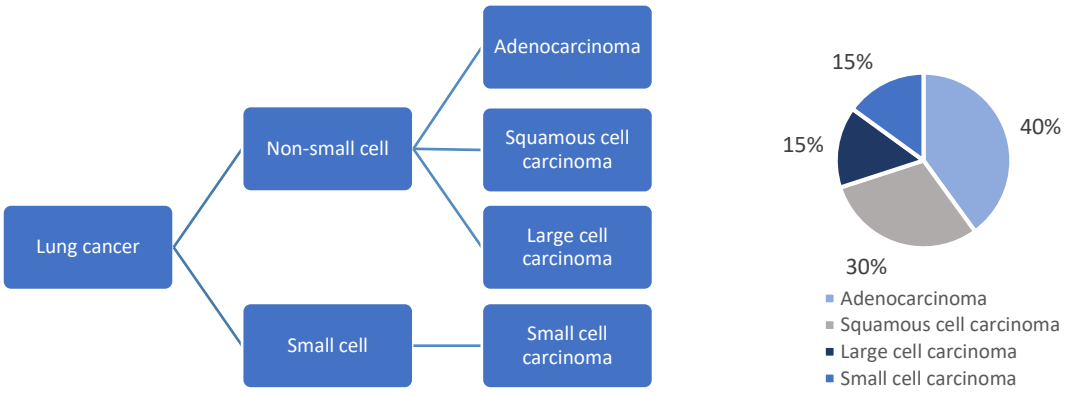
1. Background

Introduction

Lung cancer is the number one cause of cancer death in the United States, expected to cause 158,000 deaths in 2016, and accounting for 26.5% of all cancer deaths.[1] It is the second most common cancer in both men (after prostate cancer) and women (after breast cancer), with 118,000 and 106,000 new cases expected in 2016, respectively.[15] The median age at death is 72.[1] Lung cancer rates reflect smoking behavior, and the incidence of lung cancer peaked in men in 1992 with 69.5 cases per 100,000 and in women in 2005 with 53.8 cases per 100,000; those rates declined by 2013 to 52.2 and 47.7 cases per 100,000, respectively, reflecting earlier declines in the prevalence of smoking.[3,16]

Lung cancer includes different pathological types (see Figure 1), broadly divided into small-cell lung cancer and non-small cell lung cancer (NSCLC).[2] NSCLC makes up about 85% of lung cancers and comprises mainly squamous cell carcinoma, adenocarcinoma, and large-cell lung cancer.[17] Stage at diagnosis is a primary factor in patient survival, and patients with NSCLC commonly present with advanced disease (i.e., distant spread, malignant effusion, or bilateral lung disease); 24% have regional spread at presentation, and 55% have distant spread.[3] Prognosis is generally poor at diagnosis; five-year survival from 2006-2012 was 31.4% in patients with regional spread and 4.9% in patients with distant spread.

Figure 1. Histological diagnoses in lung cancer



Source: American Cancer Society. Lung Cancer (Non-Small Cell). 2016; http://www.cancer.org/acs/groups/cid/documents/webcontent/003115-pdf.pdf. Accessed August 15, 2016.

Previously, advanced NSCLC was treated with chemotherapy with a platinum-based chemotherapy doublet (e.g., cisplatin+paclitaxel, carboplatin+gemcitabine, etc.). In recent years, the treatment of

some advanced NSCLCs has changed based on the determination of driver mutations in tumors. Among the most common of these driver mutations that affect therapeutic decisions are those involving the kinase region of the epidermal growth factor receptor (EGFR). More recently, immunotherapy aimed at altering checkpoint inhibition through the programmed death 1 (PD-1) receptor or its ligand (PD-L1) have demonstrated benefit in at least some patients with NSCLC. Questions remain, however, regarding the appropriate sequence of treatment with these newer agents, the role of certain tests to inform treatment decisions, and management of the costs of these therapies.

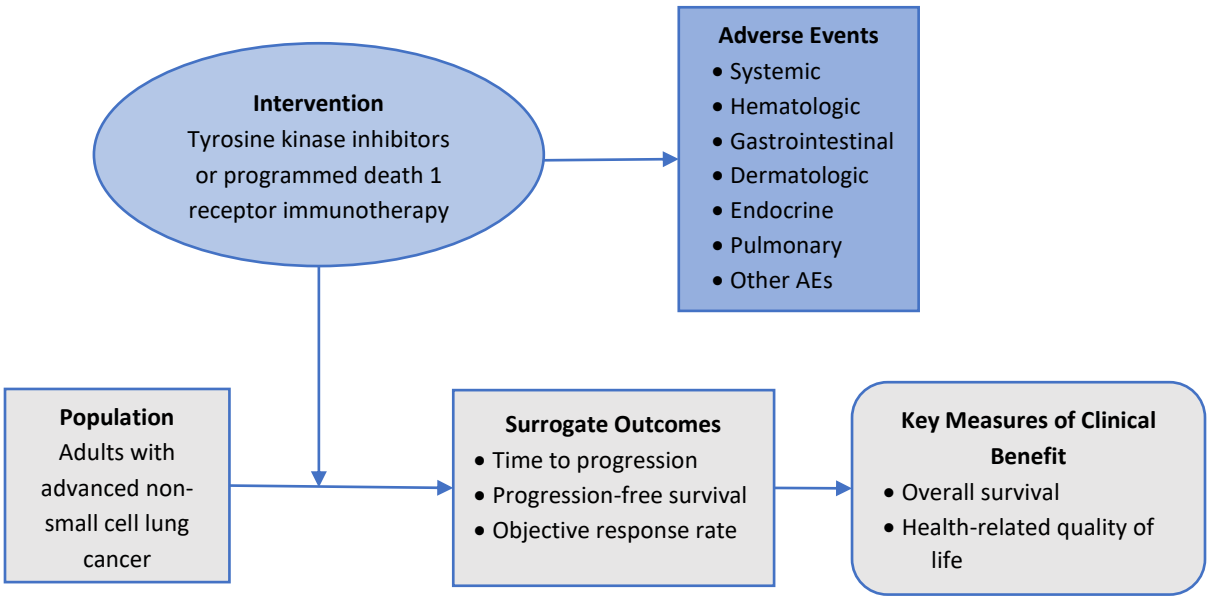
Scope of the Assessment

This assessment evaluates the health and economic outcomes of certain tyrosine kinase inhibitors (TKIs) and programmed death 1 (PD-1) agents in the treatment of advanced non-small cell lung cancer (NSCLC). The effects of both classes of agents are evaluated in EGFR-positive (EGFR+) NSCLC, and PD-1 agents are evaluated in NSCLC without a driver mutation (EGFR-). The scope is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework.

Analytic Framework

The analytic framework for this assessment is depicted in Figure 2.

Figure 2. Analytic Framework: Management of Advanced Non-Small Cell Lung Cancer



Populations

The four populations of focus for the review were adults with advanced NSCLC who:

P1) Have an EGFR+ tumor and have not previously been treated for advanced disease
P2) Have a tumor without a driver mutation and have not previously been treated for advanced disease
P3) Have a tumor without a driver mutation that has progressed after first-line treatment with a platinum-based chemotherapy doublet (e.g., cisplatin+paclitaxel, carboplatin+gemcitabine, etc.)
P4) Have an EGFR+ tumor that has progressed after first-line or first- and second-line TKI therapy (patients who do not develop a T790M mutation will only receive first-line TKI therapy)

Interventions

P1) The TKIs erlotinib, gefitinib, and afatinib
P2) A treatment sequence of PD-1 immunotherapy (i.e., nivolumab, pembrolizumab, or atezolizumab), followed by a platinum-based chemotherapy doublet at the time of progression
P3) PD-1 immunotherapy (after progression on a platinum-based chemotherapy doublet)
P4) PD-1 immunotherapy (after progression on first-line or first- and second-line TKI therapy)

Comparators

P1) A platinum-based chemotherapy doublet
P2) A treatment sequence of a platinum-based chemotherapy doublet, followed by PD-1 immunotherapy at the time of progression
P3) Single-agent chemotherapy (e.g., docetaxel)
P4) A platinum-based chemotherapy doublet

Outcomes

This review examined key clinical outcomes that occur in all four populations of patients being treated for advanced NSCLC, including surrogate outcomes common to cancer trials. Outcomes of interest included:

- Overall survival
- Disease progression-related measures (progression-free survival, time to progression)
- Objective response rate
- Symptom control
- Health-related quality of life
- Treatment-related adverse events

- Rates of key adverse events by type (e.g., systemic, gastrointestinal, dermatologic, etc.)
- Rates of Grade 3 or 4 adverse events
- Discontinuation due to adverse events
- Treatment-related deaths

Timing

Evidence on intervention effectiveness and harms was derived from studies of any duration.

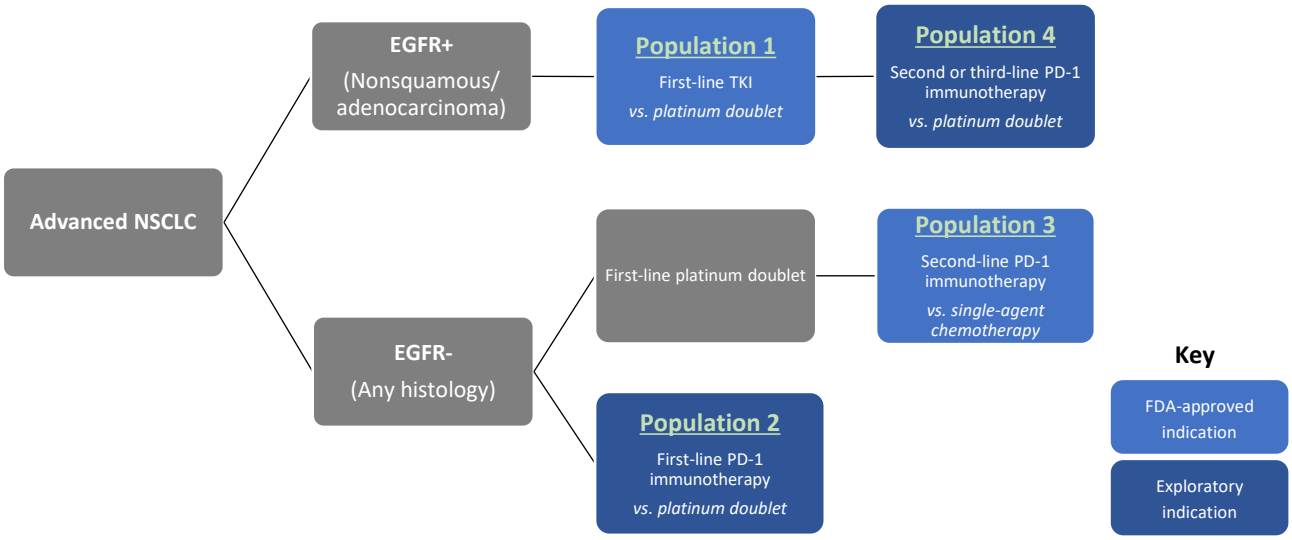
Settings

All relevant settings were considered, including inpatient, clinic, and office settings.

2. The Topic in Context

As discussed above, the prognosis in patients with advanced NSCLC has been poor, and new therapies are needed for this common malignancy. Although chemotherapy can extend survival, it is not curative in patients with advanced disease, and many patients may be unable to tolerate the side effects of the most potent regimens. These potent chemotherapy regimens are typically platinum-based chemotherapy doublets (e.g., cisplatin + paclitaxel, carboplatin + gemcitabine, etc.), in combination with bevacizumab in some patients, and they continue to be recommended as first-line therapy for patients with advanced NSCLC without a driver mutation.[4] Figure 3 presents the populations and therapies of interest for this review (the light blue boxes, populations 1 and 3, represent FDA-approved indications [*at the time of the Evidence Report*] for TKI and PD-1 immunotherapy, respectively).

Figure 3. Populations and therapies of focus



Tyrosine Kinase Inhibitors (TKIs)

Mutations affecting the tyrosine kinase region of the epidermal growth factor receptor (EGFR) are found in approximately 10 to 15% of patients with adenocarcinoma in the United States, but in up to 50% of patients from Asia.[2,18] EGFR mutations are more common in non-smokers with NSCLC and less common in squamous cell NSCLC (approximately 2.7% with EGFR mutations).[4]

For NSCLC patients with EGFR mutations (referred to as EGFR+ NSCLC), major guidelines, such as those from the National Comprehensive Cancer Network (NCCN), list tyrosine kinase inhibitors (TKIs) as first-line therapy.[4] The main TKIs used as first-line therapy for advanced NSCLC include afatinib (Gilotrif®, Boehringer Ingelheim), erlotinib (Tarceva®, Genentech), and gefitinib (Iressa®, AstraZeneca). The US Food and Drug Administration (FDA) approved both erlotinib and afatinib for use in the first-line setting in 2013, and granted approval to gefitinib in 2015; these medications are approved for treatment of advanced NSCLC with the two most common EGFR mutations: frame deletions in exon 19 and the substitution of arginine for leucine at codon 858 in exon 21 (L858R).[18] There is some evidence that the type of EGFR mutation may influence response to TKI therapy, including possible differences in response between exon 19 and L858R mutations.[18-20]

TKIs are administered orally once daily (see Table 1), generally until disease progression. The most common adverse reactions are rash, which can be severe, and diarrhea.[5,6] In general, however, rates of serious adverse events are much lower with TKI therapy than with a platinum doublet. Treatment with first-line TKI therapy typically costs approximately $90,000 per year.[7]

Platinum-based chemotherapy doublets have been the comparators for most trials of TKIs.[20] There are few head-to-head trials comparing TKIs.

As discussed in detail in section 4, trials of TKIs have generally shown improvements in progression-free survival (PFS) compared with chemotherapy, but no improvement in OS, which is likely due to the high rates of crossover between treatment arms that occurred in these trials.

Despite treatment with a TKI, nearly all patients with advanced NSCLC will eventually progress.[2] A common mechanism of TKI resistance is a T790M mutation. Commonly, patients who progress and have a T790M mutation are treated second-line with osimertinib (Tagrisso®, AstraZeneca), a TKI that is effective in EGFR+ tumors with this mutation.[4] For patients who progress on first-line TKI therapy but do not have a T790M mutation, or who progress on osimertinib, guidelines suggest proceeding with chemotherapy doublet treatment as in patients without a driver mutation.[4]

Table 1. TKIs of interest for the evidence review

	Administration	Recommended dose	Treatment Duration	Unit Price (USD)α
Afatinib (Gilotrif®) ***Boehringer Ingelheim***	Oral	40 mg, once daily	Until progression or no longer tolerated by the patient	$233.05/tablet
Erlotinib (Tarceva®) ***Genentech***	Oral	150 mg, once daily	Until progression or unacceptable toxicity	$241.52/tablet
Gefitinib (Iressa®) ***AstraZeneca***	Oral	250 mg, once daily	Until progression or unacceptable toxicity	$241.20/tablet

α Unit price reflects the wholesale acquisition price listed on Red Book Online (Greenwood Village, CO: Truven Health Analytics. http://www.micromedexsolutions.com/. Accessed July 19, 2016).

PD-1 immunotherapy

Tumor cells can produce substances that alter the immune response to the tumor, such as by affecting a regulatory "checkpoint" or brake on the T cell response to the tumor, and thus allowing the tumor to evade the immune system. Immunotherapy aimed at inhibiting such a checkpoint through the PD-1 receptor or its ligand, PD-L1, have demonstrated benefit in at least some patients with NSCLC.[8] Agents focused on this pathway include nivolumab (Opdivo®, Bristol-Myers Squibb) and pembrolizumab (Keytruda®, Merck), which are antibodies to PD-1, as well as atezolizumab (Tecentriq®, Genentech), an antibody to PD-L1. We use the term "PD-1 immunotherapy" to refer to both groups of antibodies. Both nivolumab and pembrolizumab received FDA approval for NSCLC in 2015. Atezolizumab, which was approved for advanced or metastatic urothelial carcinoma in May of 2016, is not yet indicated for NSCLC; the FDA is expected to issue a final decision on the use of atezolizumab in NSCLC by October 19, 2016. PD-1 immunotherapy is recommended as second-line treatment in patients with advanced NSCLC without a driver mutation who progress on a chemotherapy doublet.[4]

A minority of patients respond to PD-1 immunotherapy, but a substantial proportion of those who do respond appear to have prolonged responses and improved survival.[8,9] Tumor expression of PD-L1 appears to be helpful in selecting appropriate patients for PD-1 based therapies; however, there are concerns about the comparability of various methods used to assess levels of expression.[8] The FDA-labeled indication for pembrolizumab is for patients whose tumors express PD-L1. While nivolumab does not carry such a restriction, response rates are higher in tumors with PD-L1 expression with nivolumab as well.[8] However, some tumors that do not express PD-L1 respond to PD-1 immunotherapy. As such, a potential question is whether only treating patients based on PD-L1 expression would result in missing an opportunity for therapy in a percentage of patients. Additionally, a proportion of patients have tissue that is not assessable for PD-L1 using current assays.[21-23]

Pembrolizumab is administered every three weeks, and atezolizumab is likely to be approved using an every 3-week dosing schedule; nivolumab is administered every two weeks (see Table 2). Both are given by intravenous infusion until disease progression. Fatigue is common with these agents, and more serious immune-mediated events, including pneumonitis and encephalitis, have been seen. These immune events are uncommon, and serious adverse events overall are much less common with PD-1 immunotherapy than with docetaxel.

Most patients studied in trials of PD-1 immunotherapy have received prior treatment with a chemotherapy doublet, whether or not they were EGFR+ and/or had received prior TKI therapy.[21,22,24] The alternative treatment in this setting would typically be single-agent chemotherapy with an agent that was not used in the original doublet, such as docetaxel.

Recently, researchers and clinicians have begun exploring the use of PD-1 agents in patients who have not received a chemotherapy doublet.[25] This includes using PD-1 immunotherapy as first-line treatment in patients with NSCLC without a driver mutation or as third-line therapy (after osimertinib) in patients with EGFR+ NSCLC.

Treatment with PD-1 immunotherapy has been estimated to cost approximately $150,000 per year.[7] In addition to questions of the comparative effectiveness of these agents, both among the agents and compared with alternative therapies, the use of PD-L1 levels to select patients for treatment is likely to affect estimates of cost-effectiveness.[26]

Multiple trials are currently underway looking at PD-1 immunotherapy in advanced NSCLC. Issues being studied include the use of these therapies first line, and the use of PD-1 immunotherapies in combination with each other or with other therapies. We summarize relevant ongoing studies in Appendix H.

Table 2. PD-1 immunotherapies of interest for the evidence review

	Administration	Recommended dose	Treatment Duration	Price (USD)β
Atezolizumab (Tecentriq®) ***Genentech***	Intravenous infusion	1200 mg on first day of every 3-week cycleα	Until disease progression or unacceptable toxicity	• $7.18/mg • $8,620.00/20 mL vial
Nivolumab (Opdivo®) ***Bristol-Myers Squibb***	Intravenous infusion	3 mg/kg over 60 minutes every 2 weeks	Until disease progression or unacceptable toxicity	• $24.70/mg • $2,470.00/10 mL vial • $988.19/4 mL vial
Pembrolizumab (Keytruda®) ***Merck***	Intravenous infusion	2 mg/kg over 30 minutes every 3 weeks	Until disease progression or unacceptable toxicity	• $43.81/mg • $4,380.74/4 mL vial

α Atezolizumab has not yet been approved for NSCLC in the US. Dose represents that used in POPLAR trial[24] (as well as approved dose for urothelial cancer); β Price reflects the wholesale acquisition price listed on Red Book Online (Greenwood Village, CO: Truven Health Analytics. http://www.micromedexsolutions.com/. Accessed July 19, 2016).

Definitions

We provide the following definitions to help with interpretation of the study results presented throughout this report.

Response Criteria: Note, trials prior to 2009 typically used response evaluation criteria in solid tumors (RECIST) version 1.0 criteria,[27] while trials after 2009 typically used RECIST version 1.1 criteria.[28] The definitions below reflect version 1.1; for most cases of patients with advanced NSCLC, there is close agreement between the two versions in assessing measures of response.[29]

- *Progressive disease:* At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study); in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm **OR** unequivocal progression of existing non-target lesions **OR** the appearance of one or more new lesions.
- *Complete response:* Disappearance of all target and non-target lesions, and normalization of tumor marker levels. Any pathologic lymph nodes (whether target or non-target) must have a reduction in the short axis to <10 mm.
- *Partial response:* At least a 30% decrease in the sum of the diameters of target lesions and not meeting criteria for progressive disease or complete response.
- *Objective response:* Complete response or partial response.

- *Advanced disease:* Stage IIIB or IV lung cancer according to American Joint Committee on Cancer Staging (AJCC) TNM staging (editions 6 or 7).[a30,31]
    - *Stage IIIb NSCLC:* Cancer is present in the lung and lymph nodes (on the opposite side of the chest from the affected lung or near the collarbone), has spread to different lobes of the same lung, or has grown into the structures surrounding the lung (i.e., the mediastinum, heart, aorta, trachea, esophagus, backbone, or carina).
    - *Stage IV NSCLC*: Cancer has spread to both lungs, to fluid in the area around the lungs or heart, or to another part of the body, such as the brain, bones, liver or adrenal glands.

Eastern Cooperative Oncology Group (ECOG) performance status: a measure of functional status and ability to perform activities of daily living on a 6-point scale: 0 (fully active); 1 (restricted only in strenuous activity); 2 (ambulatory and capable of self-care but unable to work); 3 (capable of only limited self-care, confined to bed or chair >50% of waking hours); 4 (completely disabled); 5 (dead).[32]

Toxicity criteria for adverse events: Grade 3 adverse events are severe or medically significant, but not life threatening. Hospitalization or prolongation of hospitalization is required, and the event limits the patient's ability for self-care. Grade 4 adverse events are life threatening and require urgent intervention.

Insights Gained from Discussions with Patients and Patient Groups

Lung cancer, unlike most other cancers and serious illnesses, is a disease where the patient often feels blamed for the illness because of the strong association with prior smoking behavior. As such, lung cancer has an unusual stigma that affects the interactions that patients with lung cancer have with family, friends, and providers. We were told that patients with lung cancer and breast cancer are at the highest risk for depression among cancer patients, and that lung cancer patients have higher levels of fatigue, distress, and anxiety than other cancer patients. High levels of anxiety may be due, in part, to breathing difficulties and other symptoms of the disease.

Because of prior smoking, lung cancer patients are at particularly high risk for comorbidities that can affect their ability to participate in clinical trials and/or receive specific therapies. Particularly important and common comorbidities include vascular disease (cardiovascular, peripheral arterial, and cerebrovascular) and chronic obstructive pulmonary disease (COPD). As such, the results of

[a] Tumor, Lymph Node, Metastasis (TNM). The TNM system for lung cancer is based on the size of the original tumor (**T**) and whether it has grown into nearby areas, whether the cancer is present in the lymph nodes (**N**), and whether the cancer has spread to other organs (metastasis-**M**).

clinical trials in which these comorbidities are underrepresented may not generalize well to the patient population as a whole.

With TKI therapy in particular, there can be heightened anxiety around adverse events and reporting these events. Patients have heard that development of rash may be associated with better response to TKIs,[33] but also have concerns about therapy being discontinued if adverse events are reported. This may affect the frequency of adverse events reported in the published literature.

In certain settings, such as rural or low-income community clinics, patients may not receive the same care as they would in major medical centers. We heard that some patients do not receive molecular testing (or are not apprised of the results of such tests) and are being put directly on chemotherapy without regard to the individual clinical characteristics of their disease. Access to innovative and emerging therapies is out of reach for those who live far from major centers without the resources to travel for treatment. Such patients may be less likely to receive adequate support, participate in clinical trials where emerging treatment may be available, or receive education on their diagnosis, prognosis, and treatment options.

Multiple patient groups raised the issue of the "financial toxicity" of treatment for lung cancer, with patients and their families at high risk for suffering economic hardship or even bankruptcy. The financial toxicity of cancer reflects the cost of the medications, administration of the medications, travel to receive treatments and other care, missing work, and even requirements for new clothing as a result of weight loss. As patients live longer, treatment costs accumulate over time. Additionally, as smoking has become less common in patients of higher socioeconomic status, lung cancer is now disproportionately affecting patients who have fewer resources available to deal with the illness. We heard that some of these patients just expect to die and so do not seek treatment at all.

Studies have not adequately addressed high rates of distress in NSCLC patients, and patients in clinical trials (who typically have significant resources provided by the trial and do not need to pay for medications) may not show similar levels of distress compared to patients treated outside of such trials.

Several groups commented that there is inadequate evidence from clinical trials on appropriate sequencing of therapies. We heard that as better therapies for NSCLC have been developed, patients have a goal of staying stable until the next trial/therapy becomes available. This is similar to the situation with HIV in the early 1990s.

3. Summary of Coverage Policies and Clinical Guidelines

All of the drugs under review in this report are covered by private insurers for use within their FDA labeled indications. The FDA labeled indication for pembrolizumab includes a companion diagnostic test to provide evidence of the expression of the protein PD-L1, which is required by payers. Some payers, such as Anthem, have developed treatment "pathways," or recommended regimens for providers. Anthem's pathway recommends afatinib or erlotinib for EGFR + first-line treatment, and nivolumab as second-line treatment for both squamous and non-squamous metastatic disease. We have also summarized here the clinical guidelines available for the treatment of advanced non-small cell lung cancer. We reviewed the National Comprehensive Cancer Network's (NCCN) guidelines for non-small cell lung cancer, version 4.2016, for treatments within scope. We also reviewed the most recent American College of Chest Physician (ACCP) guidelines, published in 2013.

National Comprehensive Cancer Network (NCCN)

Population P1: For patients with EGFR mutations, not previously treated, NCCN guidelines recommend the TKIs erlotinib, gefitinib, and afatinib for first line therapy.

Population P2: For patients without a driver mutation, not previously treated, NCCN guidelines recommend treating with a platinum-based chemotherapy doublet as first line therapy (in combination with bevacizumab in some patients with non-squamous NSCLC).

Population P3: For patients without a driver mutation who progress on a chemotherapy doublet, NCCN guidelines recommend second-line treatment with PD-1 immunotherapy, which currently includes nivolumab and pembrolizumab.

Population P4: For patients with EGFR mutations who have progressed after first-line or first- and second-line TKI therapy, NCCN guidelines recommend treating with a platinum-based chemotherapy doublet (in combination with bevacizumab in some patients with non-squamous NSCLC).

American College of Chest Physicians (ACCP)
(http://journal.publications.chestnet.org/article.aspx?articleID=1685102)

The American College of Chest Physicians published guidelines on the treatment of NSCLC in 2013. As a result, these guidelines do not include afatinib or any of the PD-1 immunotherapies, which had not yet been approved by the FDA. We included these guidelines as added context to the clinical environment. ACCP recommends, as a general approach, that patients with good performance

status (PS) and stage IV non-small cell lung cancer should receive a platinum-based chemotherapy regimen. For patients that are EGFR+, ACCP recommends gefitinib or erlotinib as first-line therapy. ACCP also suggests erlotinib as a maintenance therapy for those patients that do not experience disease progression after 4 cycles of platinum-based double agent chemotherapy.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the comparative clinical effectiveness of TKIs and PD-1 immunotherapy in the treatment of advanced NSCLC, we abstracted evidence from available clinical studies of these agents, whether in published, unpublished, or in abstract form.

Therapies of interest included:

1. *TKIs for chemotherapy-naïve patients with an EGFR+ tumor (population 1 as described in Section 1)*
    - Afatinib
    - Gefitinib
    - Erlotinib

2. *PD-1 immunotherapy for patients without an EGFR+ tumor who are either chemotherapy-naïve or have progressed after first-line treatment with a platinum doublet, and patients who have an EGFR+ tumor that has progressed after first- or second-line treatment with a TKI (populations 2-4 as described in Section 1)*
    - Atezolizumab
    - Nivolumab
    - Pembrolizumab

As described previously in the Background section, comparators of interest included 1) platinum-based chemotherapy doublets for the first- and third-line EGFR+ treatment populations (populations 1 and 4), 2) platinum-based chemotherapy doublets for the first -line EGFR- treatment population (population 2) and 3) single-agent chemotherapy for the EGFR- population that has progressed after treatment with a platinum doublet (population 3). Our review focused on clinical benefits (i.e., overall and progression-free survival, biochemical response, and health-related quality of life), and potential harms (drug-related adverse events). We focused attention on both descriptive and quantitative analyses of these outcomes, including direct comparisons available from the individual trials as well as indirect comparisons between the newer regimens.

4.2 Methods

Study Selection

We included evidence from randomized controlled trials (RCTs), comparative observational studies, and high-quality systematic reviews where available. We excluded single-arm studies, studies

without an active control arm, and studies from an early clinical development phase (i.e., phase I). In recognition of the rapidly evolving evidence base for NSCLC, we supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature that met ICER standards for review (for more information, see (http://icerreview.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on NSCLC regimens followed established best methods.[34] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[35] The PRISMA guidelines include a checklist of 27 items, further detail of which is available in Appendix Table A1.

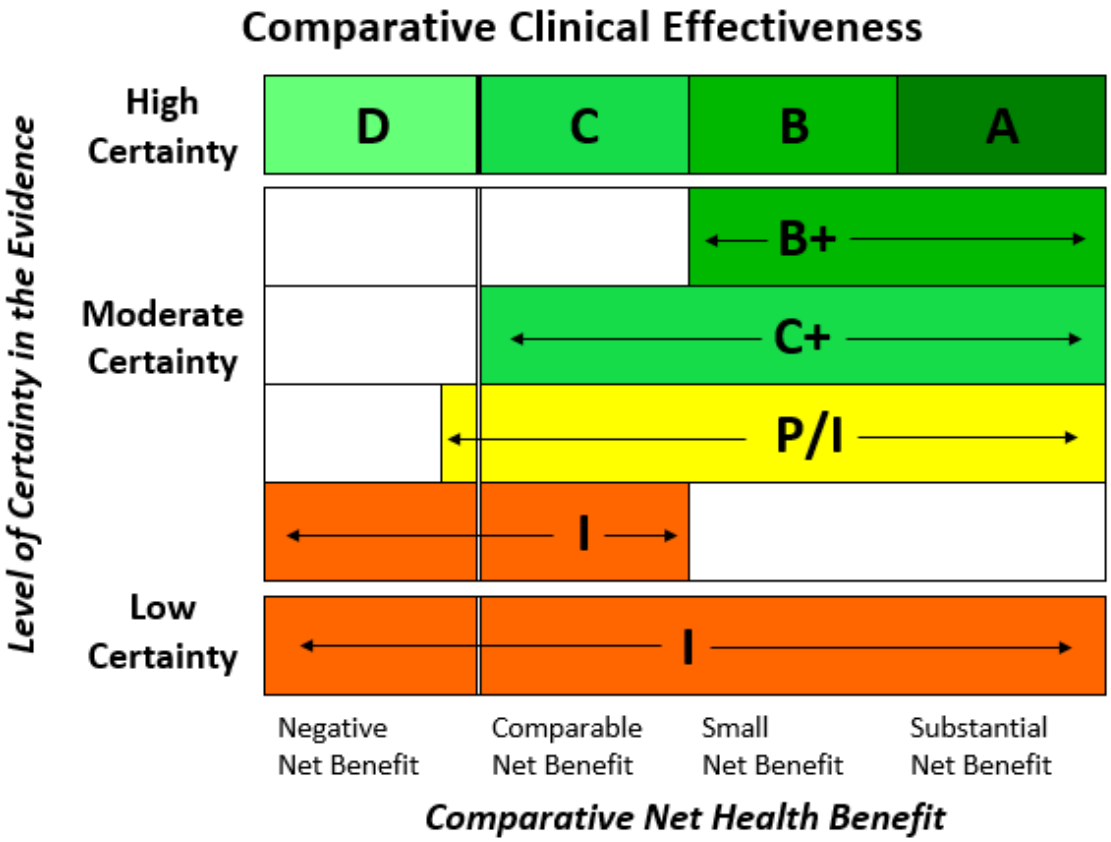
The timeframe for our search spanned the period from January 1996 to June 8, 2016 and focused on MEDLINE, EMBASE, and Cochrane-indexed articles. We limited each search to studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analyses. Further details on the search algorithm are available in Appendix Tables A2, A3, and A4. Additional searches were performed to identify relevant grey literature based on an organization and source checklist developed by the Canadian Agency for Drugs and Technologies in Health (https://www.cadth.ca/resources/finding-evidence/grey-matters). Other grey literature sources included sites deemed relevant specifically for NSCLC, such as clinical societies, research foundations, and advocacy organizations. Further information on methods for study selection, data extraction, quality assessment, assessment for publication bias, and our approach to meta-analyses of the data can be found in the appendices.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 4) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

- The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
- The level of **certainty** in the best point estimate of net health benefit.[36]

Figure 4. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" - Either moderate certainty that the best point estimate of comparative net health benefit is comparable or inferior; or any situation in which the level of certainty in the evidence is low

4.3 Results

Study Selection

Our literature search identified 3,072 potentially relevant references (see Appendix Figure B1), of which 44 references met our inclusion criteria; these citations related to 17 individual studies and seven systematic reviews. Primary reasons for study exclusion included use of a combination regimen not approved by the FDA, comparison to a treatment that does not reflect current best practice (e.g., single-agent docetaxel in treatment-naïve EGFR+ patients), study population out of

our scope, and non-comparative study design. Overall, we identified 36 references relevant to population 1 (first-line EGFR+) and eight references germane to population 3 (second-line EGFR-); we did not identify any relevant references for populations 2 and 4 (first-line EGFR- and second- or third-line EGFR+, respectively). *[Please see the Supplement, starting on page 102, for a discussion of evidence relevant to population P2 that became available after the report was published, as well as a limited discussion of an additional trial relevant to population P3.]* Details of the included studies are described in Appendix Table B1 and in the sections that follow; previous systematic reviews are described in Appendix G.

Tyrosine Kinase Inhibitors for First-Line Treatment of EGFR+ NSCLC

Our review of TKIs in patients with EGFR+ advanced NSCLC focused on first-line use of afatinib, erlotinib, and gefitinib (population 1 as described above). We assessed these therapies in relation to platinum-based chemotherapy doublets, which combined either cisplatin or carboplatin with gemcitabine, pemetrexed, paclitaxel, or docetaxel. The sections that follow discuss the overall survival (OS), progression-free survival (PFS), tumor response, symptom control, quality of life (QoL), and harms associated with the interventions of focus.

Summary

- Our review of the evidence on first-line TKI therapy for EGFR+ advanced NSCLC found inadequate evidence to distinguish between the three TKIs on patient-important outcomes such as OS and QoL.
- Evidence from RCTs indicates that all three agents provide statistically-significant improvements in PFS relative to platinum doublet chemotherapy. A head-to-head randomized trial, as well as our network meta-analysis, provide evidence that treatment with afatinib likely provides a small benefit in PFS compared with gefitinib; this is a surrogate endpoint and no statistically significant differences were seen in OS.
- RCTs comparing TKIs with platinum doublet chemotherapy had high rates of crossover, and showed no benefit in OS.
    - The most likely explanation for the lack of OS benefit seen in RCTs of TKIs with high rates of crossover is that treatment with a TKI improves survival *whenever* it is given in the sequence of therapy, such that patients randomized to chemotherapy who receive TKI therapy at the time of progression have similar survival in comparison to patients treated initially with a TKI.
    - Observational data suggest that first-line TKI therapy as a class *increases OS by approximately 8.9 months*, although there is substantial uncertainty in this figure.

    - Patients and clinicians should be aware that it is possible that the OS benefit with TKIs may be somewhat longer than this estimate in patients with tumors that have the exon 19 deletion, and somewhat shorter than this estimate in patients with tumors with the L858R mutation.
    - Limitations in the evidence base preclude and definite conclusions as to whether the likely PFS benefit seen with afatinib over gefitinib would translate into a clinically important benefit in OS.
- Rash, diarrhea, and liver function abnormalities are the most common side effects with TKIs. All TKIs appear to be better tolerated than chemotherapy with platinum doublets, which have much higher rates of hematologic toxicity.
- QoL improvements were greater with TKI therapy than with chemotherapy.

For patients with EFGR+ advanced NSCLC, we have high certainty that TKI therapy provides at least a small net health benefit ("B+") relative to platinum chemotherapy.

Study Selection

Our literature search identified 36 references of afatinib, erlotinib, or gefitinib in chemotherapy-naïve patients with an EGFR mutation; these citations related to 13 individual studies and five systematic reviews (see Appendix Table B1 and Appendix G). Ten of the 13 studies were rated fair quality and compared a TKI to a platinum doublet: two published Phase III RCTs of afatinib and four published Phase III trials each of erlotinib and gefitinib. An additional study evaluated gefitinib in comparison to standard chemotherapy, however this study was only published in a conference abstract and therefore not rated for quality. Finally, two studies (one good-quality phase IIb RCT and one fair-quality matched-pair case control study) directly compared two TKIs of interest (afatinib vs. gefitinib and gefitinib vs. erlotinib, respectively). Although the studies we deemed fair quality possessed many elements of a good quality study (e.g., comparability between study arms at baseline, use of valid instruments to evaluate outcomes, no differential attrition), we were concerned that the open-label design of these trials and high crossover rates could have potentially introduced biased estimates of treatment effect. We did not assign a quality rating to the remaining twelve documents, which were obtained from conference proceedings and previous systematic reviews. Appendix Table C1 presents the number of good, fair, poor, and unrated studies identified for each population of focus.

Key Studies

We considered 11 RCTs to be key studies of interest for this review, ten of which compared a TKI to a platinum-based chemotherapy doublet and one which compared afatinib to gefitinib (see Table 3). Important outcomes from each trial are also provided in Appendix Table B1, and described in further detail in the sections that follow. The trials specified similar inclusion criteria: each trial

included treatment-naïve adult patients (≥18 years of age) with measurable, advanced (stage IIIb/IV) or recurrent NSCLC. All but three key trials[37-39] were limited to EGFR+ patients; trials that did not restrict study inclusion criteria to EGFR+ patients provided results in this subgroup. The LUX-Lung 7 trial of afatinib vs. gefitinib provided the only direct randomized trial evidence comparing TKIs.

Trial populations were similar with respect to age, ECOG performance status, and disease stage: the median age was around 60 years, most patients had limited restrictions on their ability to perform daily activities (ECOG PS of 0-1), and around 90% of patients had stage IV NSCLC. With the exception of the TORCH trial, which compared erlotinib to cisplatin + gemcitabine, nearly all patients in each trial had a histological diagnosis of adenocarcinoma. The percentage of Asian patients was high in most trials, except for EURTAC and TORCH, which were conducted in European countries and Canada. Frequency of current or former smoking varied, and only one trial (First-SIGNAL trial of gefitinib vs. cisplatin + gemcitabine) was restricted to never-smokers. All of the key studies were open-label, and all but one trial (the phase IIb LUX-Lung 7 trial of afatinib vs. gefitinib) were phase III. There was no universal comparator treatment because standard of care for NSCLC varied by country, but cisplatin or carboplatin plus gemcitabine was the most commonly used comparator.

Table 3. Key studies: TKIs

Key Trials	Patient Characteristics	Treatment	Comparator	Harms (Tx Arm)
LUX-Lung 3[40,41α] Median f/u: 16.4 m	Median age: 61; Asian: 72% ECOG PS=1: 61% Never smoker: 68% Stage IV: 89%	Afatinib (n=230) Median OS: 28.2 m Median PFS: 11.1 m	Cisplatin+Pemetrexed (n=115) Median OS: 28.2 Median PFS: 6.9 m	D/C due to AEs: 10% TEAE ≥ Grade 3: 49% Tx-related deaths: 4
LUX-Lung 6[41,42α] Median f/u: 16.6 m	Median age: 58; Asian: 100% ECOG PS=1: 76% Never smoker: 77% Stage IV: 94%	Afatinib (n=242) Median OS: 23.1 m Median PFS: 11.0 m	Cisplatin+Gemcitabine (n=122) Median OS: 23.5 m Median PFS: 5.6 m	D/C due to AEs: 9% TE-SAEs: 6% Tx-related deaths: 1
LUX-Lung 7[10] Median f/u: 27.3 m	Median age: 63; Asian: 57% ECOG PS=1: 69% Never smoker: 67% Stage IV: 97%	Afatinib (n=160) Median OS: 27.9 m Median PFS: 11.0 m	Gefitinib (n=159) Median OS: 25.0 m Median PFS: 10.9 m	D/C due to AEs: 11% TE-SAEs: 11% Tx-related deaths: 0
IPASS[38,43] Median f/u: 17.0 m	Median age: 57; Asian: 100% ECOG PS=1: 64% Never smoker: 94% Stage IV: 76%	Gefitinib (n=132)β Median OS: 21.6 m Median PFS: 9.5 m	Carboplatin+Paclitaxel (n=129)β Median OS: 21.9 m Median PFS: 6.3 m	D/C due to AEs: 7% SAEs: 16% AE-related deaths: 4%
NEJ002[44,45] Median f/u: 23.1 m	Mean age: 63; Asian: 100% ECOG PS=1: 50% Never smoker: 62% Stage IV: 75%	Gefitinib (n=114) Median OS: 27.7 m Median PFS: 10.8 m	Carboplatin+Paclitaxel (n=114) Median OS: 26.6 m Median PFS: 5.4 m	D/C due to AEs: NR AEs ≥ Grade 3: 41% Tx-related deaths: NR
WJTOG3405[46,47] Median f/u: 59.1 m	Median age: 64; Asian: 100% ECOG PS=1: 37% Never smoker: 69% Stage IV: 48%	Gefitinib (n=86) Median OS: 34.8 m Median PFS: 9.2 m	Cisplatin+Docetaxel (n=86) Median OS: 37.3 m Median PFS: 6.3 m	D/C due to AEs: 16% SAEs: NR Tx-related deaths: 1
First-SIGNAL[37] Median f/u: 34 m	Median age: 57; Asian: 100% ECOG PS=1: 68% Never smoker: 100% Stage IV: 90%	Gefitinib (n=26)β Median OS: 27.2 m Median PFS: 8.0 m	Cisplatin+Gemcitabine (n=16)β Median OS: 25.6 m Median PFS: 6.3 m	D/C due to AEs: NR AEs ≥ Grade 3: 29% Tx-related deaths: 0
EURTAC[48,49] Median f/u: 40.7 m (erlotinib) vs. 22.1 m (chemo)	Median age: 65; Asian: 0 ECOG PS=1: 53% Never smoker: 69% Stage IV: 92%	Erlotinib (n=86) Median OS: 22.9 m Median PFS: 10.4 m	Cisplatin+Gemcitabine/ Docetaxel (n=87) Median OS: 22.1 m Median PFS: 5.1 m	D/C due to AEs: 13% SAEs: 32% Tx-related deaths: 1
ENSURE[50] Median f/u: 28.9 m (erlotinib) vs. 27.1 m (chemo)	Median age: 57; Asian: 100% ECOG PS=1: 79% Never smoker: 71% Stage IV: 92%	Erlotinib (n=110) Median OS: 26.3 m Median PFS: 11.0 m	Cisplatin+Gemcitabine (n=107) Median OS: 25.5 m Median PFS: 5.5 m	D/C due to AEs: 3% SAEs: 14% Tx-related deaths: NR
OPTIMAL[51,52] Median f/u: 15.6 m	Median age: 58; Asian: 100% ECOG PS=0-1: 94% Never smoker: 71% Stage IV: 90%	Erlotinib (n=82) Median OS: 22.8 m Median PFS: 13.1 m	Carboplatin+Gemcitabine (n=72) Median OS: 27.2 m Median PFS: 4.6 m	D/C due to AEs: 1% SAEs: 12% Tx-related deaths: 0
TORCH[39] Median f/u: 24.3 m	Median age: 62; Asian: 3% ECOG PS=1: 50% Never smoker: 21% Stage IV: 89%	Erlotinib (n=20)β Median OS: 18.1 m Median PFS: 9.7 m	Cisplatin+Gemcitabine (n=19)β Median OS: 32.5 m Median PFS: 6.9 m	D/C due to AEs: NR SAEs: NR Tx-related deaths: NR

α Outcomes from independent review; β EGFR+ subgroup, AEs reflect overall population; f/u= follow-up; NR=not reported; ECOG PS=Eastern Cooperative Oncology Group Performance Status; OS=overall survival; PFS=progression-free survival; HR=hazard ratio; ORR=objective response rate; D/C=discontinuation; AEs=adverse events; Tx=treatment; NR=not reported

Clinical Benefits

A detailed review of each clinical outcome of interest is presented in the sections that follow. All key studies were designed primarily to measure improvement in PFS, with the exception of the First-SIGNAL and TORCH trials of gefitinib and erlotinib, respectively, in which the primary endpoint was overall survival.

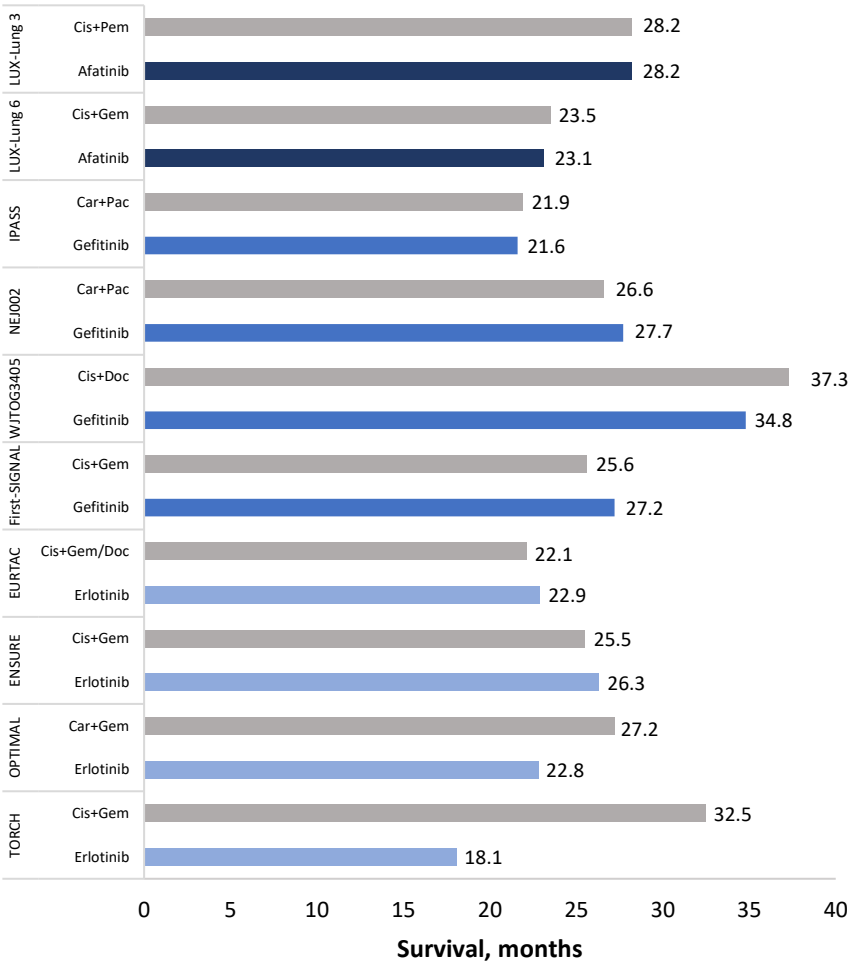
Overall Survival

RCTs had high rates of crossover and showed no OS benefit for TKIs compared with a platinum-based chemotherapy doublet. The most likely explanation for the lack of OS benefit seen in RCTs of TKIs with high rates of crossover is that treatment with a TKI improves survival whenever it is given in the sequence of therapy, such that patients randomized to chemotherapy who receive TKI therapy at the time of progression have similar survival in comparison to patients treated initially with a TKI. Observational data suggest that first-line TKI therapy as a class increases OS by approximately 8.9 months, although there is substantial uncertainty in this figure. Limitations in the evidence base preclude determining whether there are clinically important OS differences between the TKIs.

Improving overall survival (OS) and quality of life (QoL) are generally the patient-important goals of cancer therapy. Assessing the true survival benefit of an emerging therapy can be difficult when study participants are permitted to cross over to receive the alternative study treatment after tumor progression, and the key studies included in the sample set for this review had high levels of crossovers (approximately 45 to 90% of patients in the chemotherapy arms crossed over to treatment with a TKI; see Appendix Table C3 for crossover rates). We present OS data here, noting that these results are likely biased estimates of the true survival benefit of the TKIs.

The ten randomized trials comparing a TKI with a platinum-based chemotherapy doublet all included data on OS, but no study showed statistical differences between the arms. Median OS was similar between TKIs, ranging from 18.1-26.3 months with erlotinib, 21.6-34.8 months with gefitinib, and 23.1-28.2 months with afatinib. Platinum doublet regimens produced comparable median survival results. Hazard ratios were also comparable across trials, ranging from 0.88-1.58 with confidence intervals that all crossed 1. These results are presented in Figure 5.

Figure 5. Overall survival: TKIs vs. platinum-based chemotherapy doublets



	HR	95% CI	p-value
LUX-Lung 3	0.88	0.66-1.17	0.39
LUX-Lung 6	0.93	0.72-1.22	0.61
IPASS	1.00	0.76-1.33	0.99
NEJ002	0.887	0.63-1.24	0.483
WJTOG3405	1.252	0.88-1.78	NR
First-SIGNAL	1.043	0.50-2.18	NR
EURTAC	1.04	0.65-1.68	0.87
ENSURE	0.91	0.63-1.31	0.607
OPTIMAL	1.19	0.83-1.71	0.2663
TORCH	1.58	0.70-3.57	NR

Cis=cisplatin; Car=carboplatin; pem=pemetrexed; gem=gemcitabine; pac=paclitaxel; doc=docetaxel

We identified only two studies evaluating differences between TKIs through direct comparison. One phase IIb randomized trial, LUX-Lung 7, compared afatinib and gefitinib and found no statistically significant difference in OS (27.9 months vs. 25.0 months; hazard ratio [HR] 0.87, 95% CI 0.66-1.15; p=0.33).[10] The authors noted that survival data were not yet mature, with a median duration of follow-up of 27.3 months. A small observational study that compared gefitinib and erlotinib found no statistically significant difference in OS.[53]

Given the paucity of head-to-head data comparing TKIs, we performed indirect comparisons of the TKIs using Bayesian network meta-analyses (NMAs). NMA was felt to be appropriate as the populations of the individual trials were sufficiently similar for comparisons of the relative effects of

TKI therapy compared with a platinum doublet across the trials. Detailed descriptions of methods and results can be found in Appendix D. Our results did not show statistical differences between agents, which aligns with the findings of previously published network meta-analyses (see Haspinger and Zhang in Appendix G for detailed descriptions of these studies).[20,54]

We did not identify any subgroups for whom the TKIs had differential effects on overall survival. We also conducted meta-analyses stratified by the two common EGFR mutations (i.e., exon Del19 and L858R, respectively), and we did not find a differential effect of TKIs in these two subgroups (p=0.115, see Appendix E).

Challenges in Estimating Impact of TKIs on Overall Survival

As discussed above, the assessment of benefit of TKIs on OS is problematic due to high rates of crossover from chemotherapy to TKIs in the randomized trials, which is understandable for ethical reasons but has the potential to dilute estimates of treatment effect over longer periods of follow-up.[40,49,55] PFS and OS appear to be substantially correlated in NSCLC in trials where patients rarely cross over, but are much less correlated in trials where crossing over is more common.[56] It appears most likely that the explanation for the lack of OS benefit seen in randomized trials of TKIs with high rates of crossover is that treatment with a TKI improves survival *whenever* it is given in the sequence of therapy, such that patients randomized to chemotherapy who receive TKI therapy at the time of progression have similar survival in comparison to patients treated initially with a TKI.

However, in estimating a potential incremental benefit of any of the TKI therapies in our analysis relative to treatment with a chemotherapy doublet alone, we need an estimate of the improvement in OS for the class. Several pieces of evidence inform such an estimate. For instance, historical survival rates in trials of platinum doublets are substantially lower than survival rates in both arms of trials of TKIs.[40,55,57,58] Although suggestive, this may only reflect secular trends toward improved survival in patients with advanced NSCLC. In the OPTIMAL trial comparing erlotinib with carboplatin+gemcitabine, an analysis looked at OS in subgroups defined by post-trial therapy.[59] In the erlotinib arm, 30 patients received no post-trial therapy, and 1 patient received another TKI (TKI-only group); in the chemotherapy arm, 16 patients received no post-trial therapy and 4 patients received other chemotherapy (chemotherapy-only group). Median OS in the 31 patients who had only received TKI therapy was 20.7 months, and OS in the 20 patients who had received only chemotherapy was 11.2 months. It is likely, however, that these groups would not have had prognostic balance at baseline.

Within-trial comparisons offer a less biased evaluation of possible survival benefit with TKIs. A single RCT that compared gefitinib with carboplatin+paclitaxel, the IPASS trial, provided the best within-trial evidence that we found:[43]

- There were 261 EGFR+ patients and 176 EGFR- patients
- Gefitinib treatment would not be expected to improve OS in patients who are EGFR-, as can be seen by its lack of benefit on PFS in EGFR- patients. In IPASS, for example, EGFR- patients had a significantly higher risk of progression when treated with gefitinib relative to chemotherapy (HR 2.85, 95% CI 2.05-3.98).[38]
- As in other trials, treatment with gefitinib compared with a platinum doublet did not significantly improve OS among all patients (median OS 18.8 months vs. 17.4 months; HR 0.90, 95% CI 0.79-1.02), in the EGFR+ subgroup (21.6 months vs. 21.9 months; HR 1.00), or in the EGFR- subgroup (11.2 months vs. 12.7 months; HR 1.18).
- Comparing OS in EGFR+ patients in the TKI arm of the trial (21.6 months) with OS in EGFR- patients in the chemotherapy arm of the trial (12.7 months) can give us an estimate of the size of the improvement in OS with TKI therapy for EGFR+ patients, since EGFR- patients initially treated with chemotherapy would not be expected to benefit from crossing over to TKI therapy.
- For EGFR+ patients, this difference between arms (21.6 vs. 12.7 months) gives an *estimated median OS advantage with gefitinib compared with carboplatin/paclitaxel of 8.9 months*.
- Given the actual results seen in IPASS, this is a conservative estimate among the possible pairwise comparisons (as contrasted with, for instance, comparing the OS of all EGFR+ patients with OS of all EGFR- patients).

There are important reasons to be wary of this estimate of an 8.9-month survival advantage. It is controversial whether EGFR+ status is a marker for improved prognosis per se,[60-62] and EGFR+ status may also be associated with improved survival because it is more common in non-smokers. Thus, the better survival seen in IPASS in EGFR+ patients could be due to EGFR status itself rather than the benefits of TKI therapy in EGFR+ patients. However, most estimates of any improved prognosis with EGFR+ tumors are small, and in IPASS, most patients were non-smokers, including 94% of EGFR+ patients and 90% of EGFR- patients.[43]

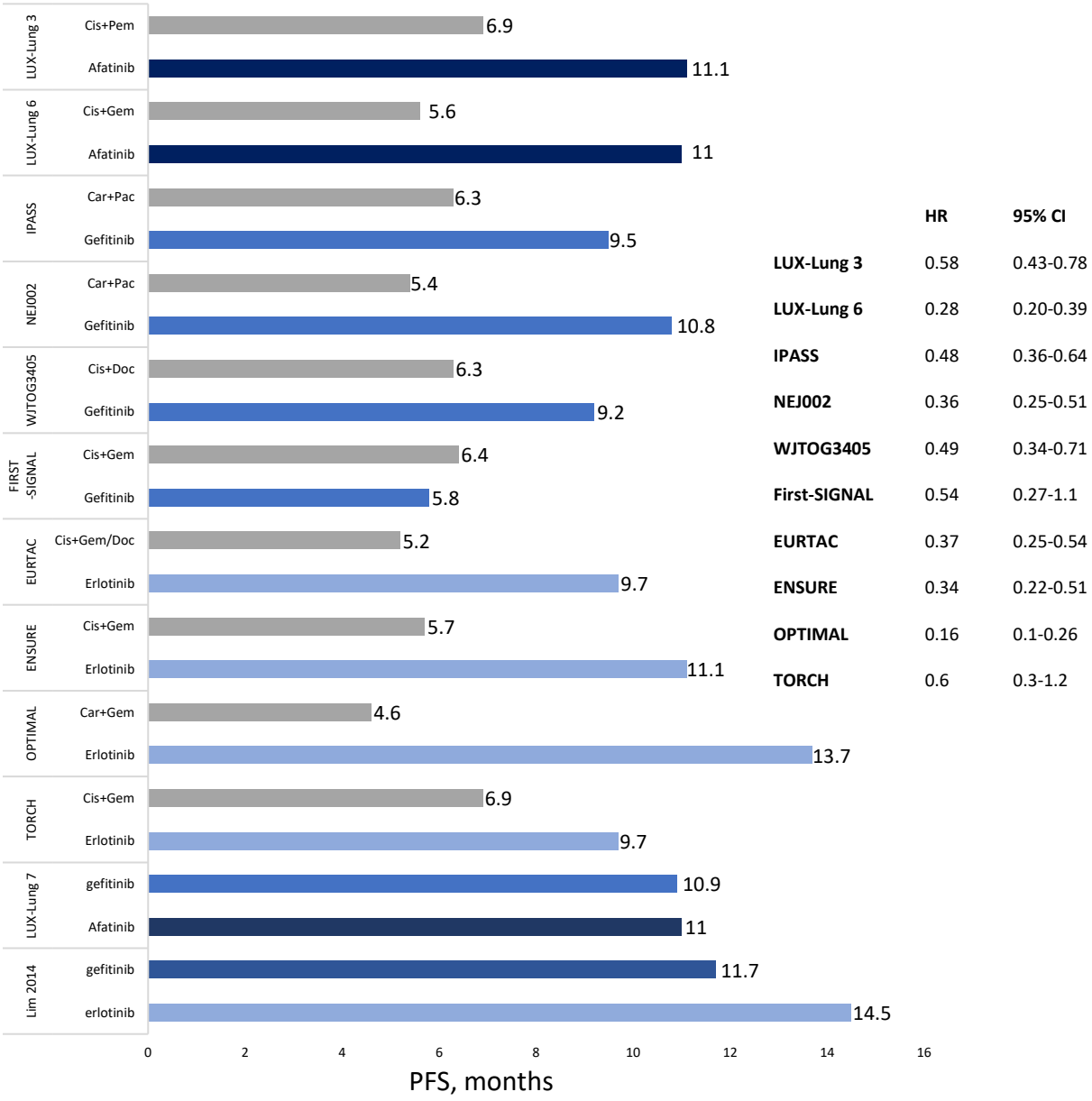
Although this estimate comes from data from a randomized trial, this is an observational post-hoc analysis of the results in subgroups of the original trial population. We are, however, unlikely to get direct trial evidence that provides the survival benefit of administering a TKI to patients with EGFR+ advanced NSCLC, as it would be felt to be unethical to withhold such therapy in a randomized trial.

Progression-free Survival

Evidence from RCTs indicates that all three TKIs provide statistically-significant improvements in PFS relative to platinum doublet chemotherapy, with HRs ranging from 0.30 to 0.45 (absolute improvements typically in the 3- to 6-month range). A head-to-head randomized trial, as well as our network meta-analysis, provide evidence that treatment with afatinib likely provides a small benefit in PFS compared with gefitinib, however, PFS is mostly a surrogate endpoint.

All 11 key studies assessed PFS, ten of which compared a TKI to a platinum-based chemotherapy doublet, and one which compared afatinib to gefitinib. We identified an additional retrospective observational study[53] (described above) of gefitinib versus erlotinib. With the exception of the First-SIGNAL and TORCH trials of gefitinib and erlotinib, respectively, all key studies measured improvement in PFS as a primary endpoint. PFS is calculated from the time of the start of treatment to disease progression or death. Although it is a surrogate endpoint that is commonly considered in regulatory processes, the extent to which it correlates with overall survival varies, particularly when crossover rates are high (see discussion in "Challenges in Estimating Impact of TKIs on Overall Survival"). In general, TKIs improved PFS compared with platinum doublets, but there is insufficient evidence to distinguish the effects between individual TKIs. Figure 6 presents median PFS from these trials.

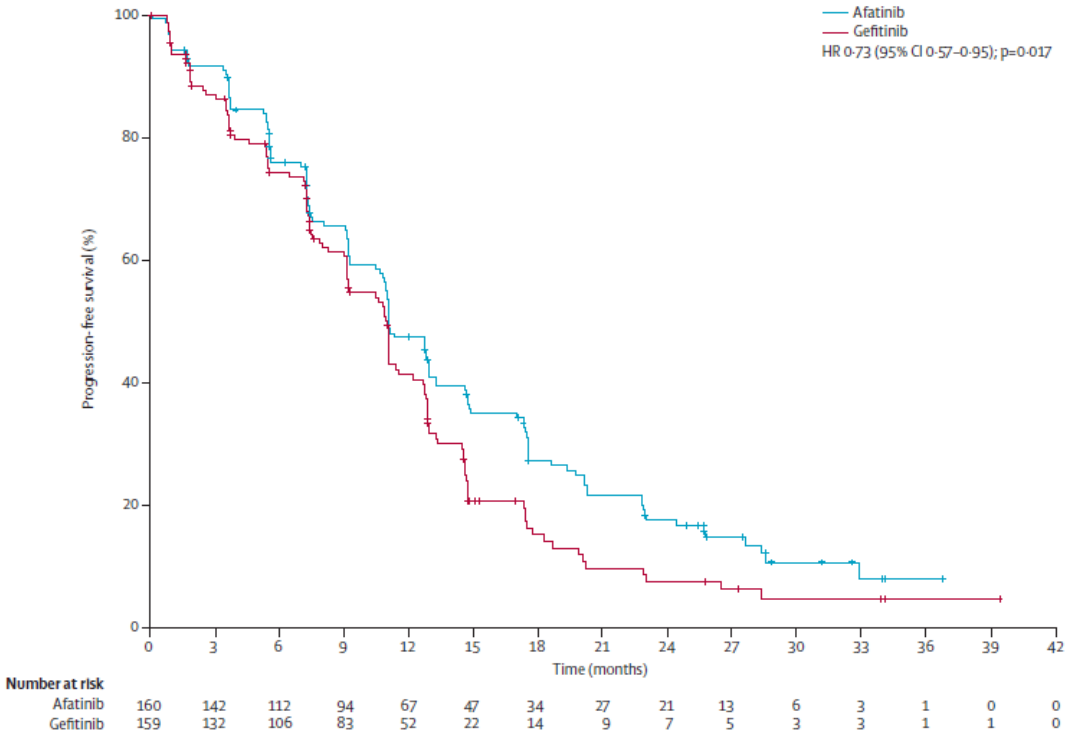
Figure 6. Progression-free survival: TKIs vs. platinum-based chemotherapy doublets



Cis=cisplatin; Car=carboplatin; pem=pemetrexed; gem=gemcitabine; pac=paclitaxel; doc=docetaxel

Only one phase IIb trial, LUX-Lung 7, directly compared two TKIs, afatinib and gefitinib. In this trial of 319 patients, those randomized to afatinib had a slightly longer median PFS but the treatment effect was statistically significant (11.0 months vs. 10.9 months; HR 0.73, 95% CI 0.57 to 0.95; p=0.017); although the difference in median PFS was only 0.1 months, the survival curves generally showed greater separation after 12 months (Figure 7).[10] The previously-described retrospective observational study found no statistically significant difference in PFS with gefitinib or erlotinib.[53]

Figure 7. Progression-free survival curve in LUX-Lung 7



Source: Park K, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): A phase 2B, open-label, randomised controlled trial. The Lancet Oncology. 2016;17(5):577-589.

Compared with a platinum doublet, improvements in median PFS were similar across the trials of the TKIs (4-month benefit with afatinib, 3-5 months with gefitinib, and 3-9 months with erlotinib). A single trial of gefitinib versus cisplatin+gemcitabine (First-SIGNAL trial) did not find statistical differences in median PFS. The PFS curves crossed at seven months, with the gefitinib arm showing less progression during the first seven months but more progression afterwards.[37] A single study (TORCH) of erlotinib versus cisplatin + gemcitabine failed to show statistical improvements in PFS in a subgroup analysis of 39 EGFR+ patients; this was likely due to the small sample size.[39] In the eight trials that found statistical improvements in PFS with TKIs, hazard ratios showed risk reductions for progression that ranged from 0.28-0.58 with afatinib, 0.30-0.49 with gefitinib, and 0.16-0.33 with erlotinib. Results from our network meta-analysis yielded hazard ratios of 0.38, 0.45, and 0.30 for afatinib, gefitinib, and erlotinib, respectively.

Our network meta-analysis combined both direct and indirect evidence on PFS for the TKIs, and showed no statistical differences among these agents. Results were similar when the network included all regimens of platinum-based doublets combined, or cisplatin-based and carboplatin-based regimens analyzed separately (Appendix D).

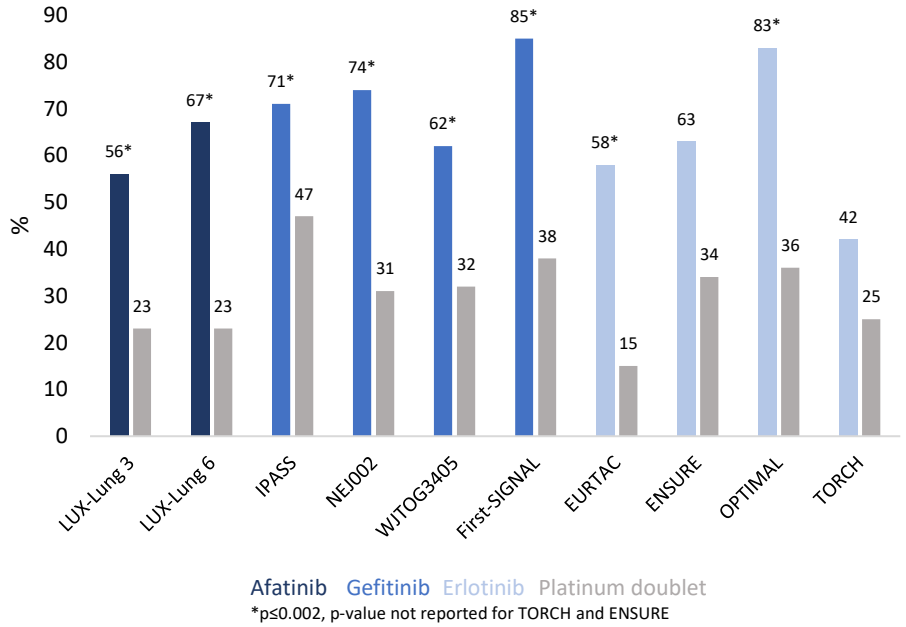
There is some evidence to suggest that the efficacy of TKIs varies slightly by type of EGFR mutation. A meta-analysis of seven trials that reported subgroup results for the two common types of EGFR mutations suggested that the type of mutation modified the effect of TKIs on PFS (p=0.004). Del 19 was associated with a greater PFS benefit than L858R (HR 0.28 [95% CrI 0.20-0.35] vs. 0.48 [0.36-0.43], see Appendix E).

Objective Response Rate

Evidence from randomized trials shows higher objective response rates (ORRs) with TKI therapy than with a platinum doublet. A head-to-head trial found a higher ORR with afatinib compared to gefitinib.

Figure 8 presents response data from each of the key trials. The majority of studies evaluated tumor response using RECIST criteria. Objective response was universally defined as a partial or complete response. Relative to therapy with a platinum doublet, a significantly greater proportion of patients had a partial response or better with the studied TKIs. Among the TKIs, the objective response rate (ORR) varied substantially, with no clear differences between agents: ORRs ranged from 56-67% with afatinib, 62-85% with gefitinib, and 42-83% with erlotinib. However, LUX-Lung 7 that compared afatinib and gefitinib head-to-head, found a significantly higher ORR with afatinib (70% vs. 56%; Odds ratio [OR] 1.87, 95% CI 1.18-2.99; p=0.0083).[10]

Figure 8. Objective response rate: TKIs vs. platinum-based chemotherapy doublets



*p≤0.002, p-value not reported for TORCH and ENSURE

Quality of Life

Quality of life (QoL) improvements were greater with TKI therapy than with a platinum doublet. Evidence is inadequate to distinguish QoL benefits among the TKIs.

We identified six RCTs, representing two trials for each individual TKI, that investigated the impact of TKIs on quality of life (QoL) in patients with NSCLC. The one head-to-head trial did not assess QoL. Comparisons across agents and trials were problematic, as different instruments were used for different drugs and clinically relevant improvement and worsening were defined accordingly. Overall, all six trials indicated that TKIs provided significant improvements relative to comparator treatment on at least one QoL outcome and five of them were clinically meaningful. Results are summarized in Table 4. Additional details are presented in Appendix C.

Table 4. Improvement with TKIs on QoL domains

Trial name	QoL instrument	Domain	Improvement in mean score	Clinically meaningful improvement
LUX-Lung 3	QLQ C30	Global Health Status/QoL	Y	N
		Physical Functioning	Y	N
		Role Functioning	Y	N
		Cognitive Functioning	Y	N
		Emotional Functioning	N	N
		Social Functioning	N	N
LUX-Lung 6	QLQ C30	Global Health Status/QoL	Y	Y
		Physical Functioning	Y	Y
		Role Functioning	Y	Y
		Cognitive Functioning	Y	Y
		Emotional Functioning	Y	Y
		Social Functioning	Y	Y
IPASS	FACT-L	Physical well-being Functional well-being Social well-being Emotional well-being LCS Relationship with doctor	Y	Y
	TOI	Physical well-being Functional well-being LCS	Y	Y
NEJ002	The Care Notebook	Physical well-being	Y	Y
		Mental well-being	N	N
		Life well-being	Y	Y
ENSURE	FACT-L	See IPASS	NR	Y
	TOI	See IPASS	NR	Y
OPTIMAL	FACT-L	See IPASS	Y for subscales: Physical well-being Emotional well-being LCS	Y
	TOI	See IPASS	NR	Y

<u>Symptom Control</u>

Symptom control was greater with TKI therapy than with a platinum doublet. Evidence is inadequate to distinguish symptom control benefits among the TKIs.

The same six trials that evaluated patient QoL also measured symptom control, using subscales from the QoL questionnaires. Again, all six studies showed that TKIs had a greater benefit on at least one symptom-related outcome. Symptoms that showed improvement with TKI therapy in at

least one trial included dyspnea,[63] pain,[21] and a composite symptom score that included shortness of breath, weight loss, clarity of thinking, cough, good appetite, chest tightness, and ease of breathing.[38,64] Symptoms that showed delayed deterioration with TKI therapy in at least one trial included dyspnea,[63,65] cough,[63,65] pain,[65] shortness of breath,[66] and a composite score.[55]

Harms

Rash, diarrhea, and liver function abnormalities are the most common side effects with TKIs. All TKIs appear to be better tolerated than chemotherapy with platinum doublets, which have much higher rates of hematologic toxicity. Afatinib appears to have higher rates of diarrhea and rash, while liver function abnormalities are more common with gefitinib.

Adverse event (AE) frequencies and rates of Grade 3-4 (severe and life-threatening) events are reported by regimen in Table 5. The values in Table 5 represent weighted averages across trials. Relative to a platinum doublet, there were lower rates of discontinuation due to AEs and fewer AEs of grade 3 or greater with the TKIs. Platinum-based chemotherapy doublets were associated with a higher incidence of hematological AEs such as anemia and neutropenia, whereas the most common adverse events among the TKIs included dermatologic toxicity (skin rash), hepatotoxicity (elevated levels of aspartate aminotransferase and/or alanine aminotransferase), and diarrhea. Among TKIs, afatinib appears to have a higher incidence of diarrhea and rash, while a greater proportion of patients developed increased aminotransferase concentrations with gefitinib. These findings are consistent with previous systematic reviews, which are described in detail in Appendix G (Haspinger, Zhang).[20,54]

Table 5. Grade 3-4 adverse events: TKIs

%	Afatinib[α]	Gefitinib	Erlotinib	PBCD
Treatment-related deaths	1	0	1	1
D/C due to AEs	9	8	8	15
≥Grade 3 AES	45	37	35	62
Grade 3-4 AEs, %				
Anemia	0	2	3	9
Appetite loss	3	4	1	4
Diarrhea	10	3	4	1
Fatigue	2	6	7	9
Increased ALT[ǂ]	3	18	2	2
Increased AST	0	17	2	3
Nausea	1	0	0	3
Neutropenia	1	1	0	42
Rash[Ω]	15	8	9	3

Values represent weighted averages across key trials; α 1 study only reported treatment-related AEs; ǂ 3 studies reported elevated aminotransferase and were integrated into both ALT and AST calculations; Ω 3 studies included reported as acne/rash; D/C=discontinuation; AEs=adverse events; ALT=alanine aminotransferase; ASP=aspartate aminotransferase; PBCD=platinum-based chemotherapy doublets

Controversies and Uncertainties

There are relatively few head-to-head studies of TKIs, and our NMAs show wide credible intervals for the HR for PFS when comparing the three TKIs we evaluated for first-line therapy. As such, the evidence is inadequate to determine whether there are important clinical differences in the effectiveness of these therapies. The results of LUX-Lung 7 do suggest a PFS benefit of afatinib over gefitinib. In preliminary input, manufacturers questioned whether the unblinded nature of this trial and evaluation time bias (which can arise if the timing of assessment for progression has different patterns between the arms of the trial) might have influenced results, but progression was assessed in a blinded fashion and our NMAs show similar estimates of effect (trend toward PFS benefit for afatinib) regardless of whether LUX-Lung 7 was included in the network. The current data are not sufficiently mature to assess whether afatinib provides an OS benefit.

We also received preliminary input from manufacturers about the importance of considering the specific EGFR mutation when comparing agents across studies, but we found similar estimates of relative effect on PFS when we constructed networks for the two most common mutations individually. Other such input addressed the implications of the different populations being studied (predominantly Caucasian or Asian) on the results; however, we received input from various experts that once EGFR status is controlled for, ethnicity does not appear to be an effect modifier for TKI treatment.

The concerns mentioned above apply mainly to estimates of PFS, where benefits relative to platinum-based chemotherapy have been observed for each of the TKIs. Potentially more problematic issues for creating relative estimates of OS among the TKIs are the very wide credible intervals seen in the NMAs, and also the additional uncertainties generated by the effects of crossovers within the trials. As discussed previously, our largest uncertainties fall around the effect of TKIs as a class on OS, given that the randomized results within each of the trials were problematic due to the crossover effect. Had we used those results, we would have concluded that TKIs have no effect on OS. We received preliminary input from manufacturers suggesting that we use the OS benefit seen for afatinib in the exon 19 deletion subgroups of LUX-Lung 3 and LUX-Lung 6. If we used the point estimates from these trials, even in this subgroup we would have seen a smaller OS benefit than we chose to apply to the TKIs as a class, and would additionally have concluded that afatinib (and perhaps the other TKIs) substantially *worsens* survival in patients with the L858R mutation. This seems unlikely, given that a PFS benefit was observed in this subgroup. However, we do think the PFS results across all the TKI trials suggest that there may be a larger OS benefit with TKIs in patients with tumors with exon 19 deletions and a smaller OS benefit in tumors with the L858R mutation. We do not feel we have a good way to estimate this differential benefit, however, given the crossover concerns.

Although we are estimating the survival benefit conferred by adding TKI therapy to the prior standard of care of a platinum doublet, it is important to note that TKI treatment has already become standard of care for patients with advanced EGFR+ NSCLC, and that those patients with the T790M mutation (about half of EGFR+ patients who progress) will also be treated at the time of progression with the TKI osimertinib.[4,11] Second-line TKI therapy in such patients likely provides additional survival benefits, although analysis of this type of treatment pathway was beyond the scope of our review. Similarly, although not commonly used as a comparator in the clinical trials, modern chemotherapy for adenocarcinoma would typically include maintenance treatment with pemetrexed, which has been shown to improve overall survival (OS).[67] However, given the evidence base, our analysis does not consider the incremental effectiveness nor the incremental cost of maintenance pemetrexed. (Separate from this use as maintenance therapy, pemetrexed is used as a component of many initial chemotherapy regimens, and we do consider this use in our analysis.)

Cisplatin appears to be slightly more effective than carboplatin, although it has not been a universal comparator in all relevant TKI trials.[68] Analyses that adjusted for this where possible gave similar results, and we received expert input that this difference in effectiveness is not felt to be an important concern in interpreting results of trials that used a chemotherapy doublet as a comparator.

Finally, we heard some concerns from patient groups that rash may have been underreported in the clinical trials of TKIs because of patient concerns that they might be taken off therapy if they accurately reported this adverse event. Although this is an important consideration in thinking about the estimates of adverse event rates, overall rates of all serious adverse events appear to be substantially lower with TKIs than with platinum doublets.

PD-1 Immunotherapies

Although our initial scope described three distinct populations of patients who might be treated with PD-1 immunotherapy (described above and below), all relevant evidence came from four randomized trials applicable to population P3. We discuss this population first in sequence, followed by discussions of populations P2 and P4, as well as our limited ability to extrapolate from population P3 to these other populations. Summaries of the results are provided in the sections discussing each population. [Please see the Supplement, starting on page 102, for a discussion of evidence relevant to population P2 that became available after the report was published, as well as a limited discussion of an additional trial relevant to population P3.]

Our review of PD-1 immunotherapy in patients with advanced NSCLC focused on atezolizumab, nivolumab, and pembrolizumab in three distinct populations: in patients with a tumor that does not have a driver mutation and has progressed after first-line treatment with a platinum-based chemotherapy doublet (population P3); in patients with a tumor that does not have a driver mutation who have not previously been treated for advanced disease (population P2); in patients with an EGFR+ tumor that has progressed after first-line or first- and second-line TKI therapy (population P4). As described previously in Section 4.1, we assessed these therapies in relation to single-agent docetaxel in patients without a driver mutation, and relative to a platinum-based chemotherapy doublet in patients without a driver mutation who were not previously treated for advanced disease or with an EGFR+ tumor receiving second- or third-line treatment. The sections that follow discuss the overall survival, progression-free survival, response, quality of life, symptom control, and harms associated with these agents in each of the populations of interest.

Study Selection

Our literature search identified eight references that met our criteria for atezolizumab, nivolumab, or pembrolizumab; these citations related to one systematic review (see Appendix G) and four individual studies, all four of which were deemed good quality and compared a PD-1

immunotherapy to single-agent docetaxel. We identified one phase IIb RCT of atezolizumab, two phase III RCTs of nivolumab, and one phase II/III trial of pembrolizumab. In addition, three conference abstracts associated with the two nivolumab studies were included in our study set. All four trials provided evidence that informed our analysis of the use of PD-1 immunotherapy in EGFR- patients in the second-line setting (P3); we found no studies that focused on first-line use in EGFR- patients (P2) or on treatment of EGFR+ patients who had progressed after TKI therapy (P4). As discussed below, results from two trials of PD-1 immunotherapy in a first-line setting are expected to become available in the near future. *[Please see the Supplement, starting on page 102, for a discussion of evidence relevant to this population that became available after the report was published.]* Appendix Table C1 presents the number of studies identified for each population of focus.

Key Studies

We considered four RCTs to be key studies of interest for this review, which are summarized in Table 6. Important outcomes from each trial are also provided in Appendix Table B1, and described in further detail in the sections that follow.

Table 6. Key trials of PD-1 immunotherapies

Key Trials	Patient Characteristics	Treatment	Comparator	Harms (Treatment Arm)
CheckMate 017 (nivolumab)	Median age: 63 Asian: 2% ECOG PS=1: 76% Never smoker: 6% 1 prior therapy: 100% Non-squamous: 0 EGFR+: NR EGFR-: NR	Nivolumab (n=135) Min. follow-up: 11 m	Docetaxel (n=137)	D/C due to TEAEs: 3% AE ≥ Grade 3: 7% Tx-related deaths: 0
		Overall Median OS: 9.2 m Median PFS: 3.5 m	 Median OS: 6.0 m Median PFS: 2.8 m	
		OS HR: 0.59 (95% CI 0.44-0.79) PFS HR: 0.62 (95% CI 0.47-0.81)		
		EGFR+ (NR)		
		EGFR- (NR)		
CheckMate 057 (nivolumab)	Median age: 62 Asian: 3% ECOG PS=1: 69% Never smoker: 20% 1 prior therapy: 88% Non-squamous: 100% EGFR+: 14% EGFR-: 58%	Nivolumab (n=292) Follow-up (OS): 13.2 m (Additional follow-up 17.2 m)	Docetaxel (n=290)	D/C due to TEAEs: 5% AE ≥ Grade 3: 46% Tx-related deaths: 1
		Overall Median OS: 12.2 m 18-m OS: 39 m[α] Median PFS: 2.3 m	 Median OS: 9.4 m 18-m OS: 23 m[α] Median PFS: 4.2 m	
		OS HR: 0.72 (95% CI 0.60-0.88) PFS HR: 0.91 (95% CI 0.76-1.09)		
		EGFR+ OS HR: 1.18 (95% CI 0.69-2.00) PFS HR: 1.46 (95% CI 0.90-2.37)		
		EGFR- OS HR: 0.66 (95% CI 0.51-0.86) PFS HR: 0.83 (95% CI 0.65-1.06)		
KEYNOTE-010 (pembrolizumab)	Mean age: 63.0 Asian: 21% ECOG PS=1: 66% Never smoker: 19% 1 prior therapy: 70% Non-squamous: 70% EGFR+: 8% EGFR-: 85%	Pembrolizumab (n=344)[∞] Median follow-up: 13.1 m	Docetaxel (n=343)	D/C due to AEs: 10% AE ≥ Grade 3: 13% Tx-related deaths: 3
		Overall Median OS: 10.4 m Median PFS: 3.9 m	 Median OS: 8.5 m Median PFS: 4.0 m	
		OS HR: 0.71 (95% CI 0.58-0.88) PFS HR: 0.88 (0.74-1.05)		
		EGFR+ OS HR: 0.88 (95% CI 0.45-1.70) PFS HR: 1.79 (95% CI 0.94-3.42)		
		EGFR- OS HR: 0.66 (95% CI 0.55-0.80) PFS HR: 0.83 (95% CI 0.71-0.98)		
POPLAR (atezolizumab)	Median age: 62 Asian: NR ECOG PS=1: 68% Never smoker: 20% 1 prior therapy: 66% Non-squamous: 66% EGFR+: 11%[Ω] EGFR-: 89%[Ω]	Atezolizumab (n=144) Median follow-up: 14.8 m	Docetaxel (n=143) Median follow-up: 15.7 m	D/C due to AEs: 8% AE ≥ Grade 3: 40% Tx-related deaths: NR
		Overall Median OS: 12.6 m Median PFS: 2.7 m	 Median OS: 9.7 m Median PFS: 3.0 m	
		OS HR: 0.73 (95% CI 0.53-0.99) PFS HR: 0.94 (95% CI 0.72-1.23)		
		EGFR+ (NR)		
		EGFR- (NR)		

Ω Of 83 patients with known EGFR status; α Overall survival with extended follow-up at 18 months; ∞ KEYNOTE-010 included two dosing groups, however we only report results from the 2mg/kg group as this dose is consistent with pembrolizumab's FDA prescribing information at the time of publication; NR=not reported; ECOG PS=Eastern Cooperative Oncology Group Performance Status; OS=overall survival; PFS=progression-free survival; HR=hazard ratio; D/C=discontinuation; AEs=adverse events; Tx=treatment

All four studies corresponded to our third population of interest (i.e., patients without a driver mutation who had disease recurrence or progression after treatment with a platinum-based doublet chemotherapy regimen). These studies were not exclusively composed of patients with a tumor without a driver mutation; however, our intended focus was to split out patients with and without an EGFR+ tumor because of concerns of effect modification by EGFR status. Even in this subgroup (patients with an EGFR- tumor), only two of the key studies (KEYNOTE-010 trial of pembrolizumab; CheckMate 057 trial of nivolumab) presented subgroup analyses in these patients.[21,22] We present these results; we also present results from the overall populations of the remaining two studies, as they likely approximate the efficacy of the therapies in patients with an EGFR- tumor. One of the remaining studies (Checkmate 017 trial of nivolumab) was composed entirely of patients with squamous-cell NSCLC, who were not likely to have an EGFR+ tumor,[22] while 89% of patients in the final key study (POPLAR trial of atezolizumab) had an EGFR- tumor.[24] Although the KEYNOTE-010 trial assessed relevant outcomes at two different doses of pembrolizumab (2 mg/kg and 10 mg/kg), we report results only from the 2 mg/kg group, as this dose is consistent with FDA's labeled indication for pembrolizumab at the time of this report's publication; subgroup analyses used combined results.

The trials specified similar inclusion criteria and trial populations were similar with respect to age and ECOG performance status. The proportion of never smokers was around 20% in all trials except for the CheckMate 017 trial of nivolumab (6%), where all patients had squamous NSCLC, and were thus more likely to have a history of smoking. The percentages of EGFR+ patients were generally low in these trials, ranging from 8% to 14% when reported. EGFR mutations are uncommon in squamous NSCLC, and the frequency was not reported in CheckMate 017. According to our scope, we focused on reporting results in EGFR- patients whenever possible and describe results in the population as a whole as an approximation when necessary, given the small proportion of EGFR+ patients in the trials.

All patients had provided tumor specimens for PD-L1 testing. However, PD-L1 expression levels were not comparable among trials because the investigators used different testing methods and cut-offs. For this same reason, subgroup analyses stratified by PD-L1 expression level were not comparable across drugs even at the same cut point. Furthermore, the KEYNOTE-010 trial was restricted to patients with at least 1% PD-L1 expression in tumor cells and provided no data on the effectiveness of pembrolizumab in PD-L1-negative patients.

Clinical Benefits

A detailed review of each clinical outcome of interest is presented in the sections that follow. All key studies were designed to measure improvement in overall survival as the primary outcome.

PD-1 Immunotherapies for Patients without a Driver Mutation who have Progressed after Treatment with a Platinum Doublet

Summary

- Trials of PD-1 immunotherapies used different assays to measure PD-L1 levels and had different PD-L1 cut-points both as entry criteria and for subgroup analyses. Given the barriers in comparing results across trials and patient populations, we found inadequate evidence to distinguish among the PD-1 immunotherapies on any outcome.
- Evidence from RCTs indicates that in patients with advanced NSCLC without a driver mutation who have progressed after treatment with a platinum doublet, PD-1 immunotherapies improve survival compared with docetaxel.
- Patients with tumors that express high levels of PD-L1 are more likely to respond to PD-1 immunotherapies. However, only a minority of patients overall respond to these agents, even among those with high PD-L1 levels on assays. Conversely, even with negative PD-L1 level results, some patients do respond to PD-1 immunotherapy.
- Among the minority of patients who do respond to PD-L1 immunotherapy, improvements in survival can be substantial. However, because of the limited follow-up in the existing studies, we are uncertain of exactly how large this benefit is.
- The most common adverse events seen with PD-1 immunotherapies are fatigue, nausea, and decreased appetite. Serious immune-related adverse events, including pneumonitis and encephalitis, can occur with these agents; these adverse events are not typically seen with chemotherapy. Overall, however, PD-1 immunotherapy is better tolerated than docetaxel.
- Evidence was inadequate to evaluate improvements in QoL with PD-1 immunotherapies.

Even with uncertainties about the duration of benefit with PD-1 immunotherapies, the current evidence base gives us high certainty that a substantial minority of patients with EGFR- advanced NSCLC do respond and achieve important gains in overall survival (“A”).

Overall Survival

PD-1 immunotherapies improve survival overall compared with docetaxel. This improvement reflects prolonged benefits in a minority of patients and no benefit in the majority of patients, making standard descriptive statistics of survival benefit (median survival and hazard ratios) potentially misleading in understanding the overall effects of these therapies. Additionally, trials were not long enough to fully assess the survival benefit in patients who do respond to PD-1 immunotherapy. Higher levels of PD-L1 are associated with higher levels of response to PD-1

immunotherapies. The lack of comparability of the study populations precludes determining whether there are clinically important OS differences between the PD-1 immunotherapies.

All four key studies of PD-1 immunotherapies evaluated overall survival, although only two studies stratified results by mutation status. Median OS was not reported in the EGFR- subgroup, however statistically significant risk reductions indicate that the PD-1 immunotherapies provided a survival benefit over docetaxel in patients without an EGFR+ tumor. In the KEYNOTE-010 trial, pembrolizumab (2mg/kg and 10mg/kg groups combined) showed improved survival relative to single-agent docetaxel (HR 0.66, 95% CI 0.55-0.80). EGFR- patients treated with nivolumab in the CheckMate 057 trial saw a similar benefit (HR 0.66, 95% CI 0.51-0.86). Although the key trials of atezolizumab and nivolumab in squamous-cell carcinoma only reported OS in the overall populations, risk reductions were similar to those seen in EGFR- patients in the KEYNOTE-010 and CheckMate 057 trials: overall survival favored both atezolizumab (HR 0.73, 95% CI 0.53-0.99; p=0.040) and nivolumab in squamous-cell carcinoma (HR 0.59, 95% CI 0.44-0.78) relative to single-agent docetaxel. Absolute improvements in median OS were 2-3 months during the time of primary analysis. Extended follow-up in the CheckMate 057 showed a 16-month gain in overall survival with nivolumab for patients with non-squamous histology. These results are presented in Table 7.

Table 7. Overall survival: PD-1 immunotherapy vs. docetaxel

	CheckMate 017		CheckMate 057		KEYNOTE-010		POPLAR	
	NIVO	DOCX	NIVO	DOCX	PEMB	DOCX	ATEZ	DOCX
Overall population								
Median OS, m (95% CI)	9.2 (7.3-13.3)	6.0 (5.1-7.3)	12.2 (9.7-15.0) Extended f/u: 39 (34-45)	9.4 (8.1-10.7) Extended f/u: 23 (19-28)	10.4 (9.4-11.9)	8.5 (7.5-9.8)	12.6 (9.7-16.4)	9.7 (8.6-12.0)
HR (95% CI)	0.59 (0.44-0.79)		0.72 (0.60-0.88)		0.71 (0.58-0.88)		0.73 (0.53-0.99)	
EGFR- population								
HR (95% CI)	NR		0.66 (0.51-0.86)		0.66 (0.55-0.80)		NR	

NIVO=nivolumab; DOCX=docetaxel; PEMB=pembrolizumab; ATEZ=atezolizumab; OS=overall survival; m=months; HR=hazard ratio; f/u=follow-up; NR=not reported

Despite statistical risk reductions and clinically-significant absolute survival gains, we have substantial uncertainty about the true survival benefits of PD-1 immunotherapy over time. It is probable that the survival curves do not show proportional hazards, the assumption that underlies one of the most common ways of modeling and reporting relative benefits in survival analysis. This is demonstrated by OS curves that cross at 6 months in the CheckMate 057 trial of nivolumab and a general observation that OS curves flattened out after 15-18 months in the PD-1 immunotherapy

arms in all of the key trials. To address this concern, we conducted a network meta-analysis of parametric survival curves using Bayesian methods to capture time-varying HRs for OS. The analysis showed a trend toward decreasing median HRs over time for two of the agents (nivolumab: from 0.81 at 3 months to 0.46 at 18 months; atezolizumab: from 0.85 at 3 months to 0.51 at 18 months). The median HR with pembrolizumab stayed constant at 0.64 to 0.65 over time. Due to the small number of trials in the network, and the small number of events at each time point, all the credible intervals around the time-varying HR point estimates crossed 1.0 and overlapped with each other. Therefore, while evidence indicates that all of the PD-1 immunotherapies provide a significant OS benefit versus docetaxel, we have uncertainty about the true magnitude of this effect (Appendix D).

As discussed in the Controversies and Uncertainties section on page 50, notwithstanding our concerns about the proportional hazards assumption, it appears that there is a subpopulation of patients with NSCLC who have clinically important, durable responses to PD-1 immunotherapy. We explored PD-L1 expression and histology as two possible predictors of efficacy in patients treated with PD-1 immunotherapy. Also as discussed in that section, studies employed different thresholds and assays for measuring PD-L1 expression, making it difficult to draw conclusions across agents. However, subgroup analyses of three studies suggest that higher levels of PD-L1 expression correlate with better overall survival; the fourth study, the CheckMate 017 trial of nivolumab in patients with squamous NSCLC, did not show a consistent association between PD-L1 expression and survival. Subgroup analyses by PD-L1 expression level (not specific to EGFR- patients) are presented in Table 8.

Table 8. Overall survival according to PD-L1 expression level (vs. docetaxel)

	PD-L1 Expression Threshold	HR (95% CI)	PD-L1 Expression Threshold	HR (95% CI)
Nivolumab (CheckMate 017)	<10% <1%	0.70 (0.48-1.01) 0.58 (0.37-0.92)	≥10% ≥1%	0.50 (0.28-0.89) 0.69 (0.45-1.05)
Nivolumab (CheckMate 057)	<10% <1%	1.00 (0.76-1.31) 0.90 (0.66-1.24)	≥10% ≥1%	0.40 (0.26-0.59) 0.59 (0.43-0.82)
Pembrolizumab (KEYNOTE-010)	1-49%	0.76 (0.60-0.96)	≥50%	0.53 (0.40-0.70)
Atezolizumab (POPLAR)*	<median expression TC0 and IC0	1.1 (0.63-1.93) 1.04 (0.62-1.75)	TC3 or IC3TC1/2/3 or IC1/2/3	0.49 (0.22-1.07) 0.59 (0.40-0.85)

We also examined whether PD-1 immunotherapies have differential efficacy according to histological diagnosis. In the POPLAR and KEYNOTE-010 trials of atezolizumab and pembrolizumab, respectively, hazard ratios for OS with PD-1 immunotherapy compared with docetaxel were somewhat *lower* in patients with non-squamous NSCLC (atezolizumab HR 0.69 [95% CI 0.47-1.01]; pembrolizumab HR 0.63 [95% CI 0.50-0.79]) than in patients with squamous NSCLC (atezolizumab HR 0.80 [95% CI 0.49-1.30]; pembrolizumab HR 0.74 [95% CI 0.50-1.09]). In contrast, in the two CheckMate trials, which evaluated nivolumab in squamous- and non-squamous cell histologies, a *higher* hazard ratio was seen in the study of patients with non-squamous NSCLC (HR 0.72 [95% CI HR 0.60-0.88] vs. HR 0.59 [95% CI 0.44-0.79]). These results are reported in Table C4 of Appendix C. Subgroup meta-analyses of these data suggested that histology (squamous vs. non-squamous) was not an effect modifier for OS (p=0.847, see Appendix E).

Even though the use of PD-1 immunotherapy in EGFR+ NSCLC was not in scope for this particular scenario, we compared EGFR+ and EGFR- groups in the meta-analysis, expecting it to inform our evaluation of second- or third-line use of immunotherapies in EGFR+ NSCLC. The results showed an OS benefit in the EGFR- subgroup (HR 0.66, 95% CI 0.58-0.74) but no benefit in the EGFR+ subgroup (HR 1.12, 95% CI 0.69-1.81); the test for interaction with EGFR status was statistically-significant (p=0.036).

Progression-free Survival

PD-1 immunotherapies show small and inconsistent results on PFS compared with docetaxel. As with OS, this may represent effects in a mixed population of responders and non-responders; patients with tumors that express high levels of PD-L1 are more likely to have improvements in PFS with PD-1 immunotherapies.

All four key studies also evaluated PFS and found small and inconsistent results related to benefits, as well as the predictive value of PD-L1 expression level on the magnitude of benefit. The results are presented in Table 9.

The CheckMate 017 and CheckMate 057 trials compared nivolumab to docetaxel in patients with squamous and non-squamous NSCLC, respectively. In CheckMate 017, nivolumab improved median PFS (3.5 months vs. 2.8 months (HR 0.62, 95% CI 0.47 to 0.81; p<0.001).[23] Among the 225 (83%) patients with quantifiable PD-L1 expression at baseline, PD-L1 expression level was not found to be predictive of PFS. In contrast, CheckMate 057 found no difference in PFS overall; however, among 455 (78%) patients with quantifiable PD-L1 expression, higher PD-L1 expression was associated with an improvement in PFS with nivolumab at all three pre-specified levels (HR 0.70 for ≥1% vs. 0.54 for ≥5% vs. 0.52 for ≥10%).[22]

In KEYNOTE-010, EGFR- patients treated with pembrolizumab (2mg/kg and 10mg/kg groups combined) had a small PFS benefit (HR 0.83, 95% CI 0.71 to 0.98). In the total study population (EGFR+ and EGFR- patients), PFS was improved with pembrolizumab 2 mg/kg compared with docetaxel in patients with tumors with PD-L1 expression ≥50% (median PFS 5.0 months vs. 4.1 months; HR 0.59, 95% CI 0.44 to 0.78; p=0.0001). PFS did not differ by treatment in patients with lower PD-L1 expression.

In POPLAR, there was no statistically significant difference in median PFS between arms, either in the total population[24] or subgroups with different PD-L1 expression levels. There was, however, a non-significant trend toward greater PFS benefit with higher PD-L1 expression level (see Table 9).

Table 9. Progression-free survival according to PD-L1 expression level (vs. docetaxel)

	PD-L1 Expression Threshold	HR (95% CI)	Median PFS (months)	
			PD-1 immunotherapy	Docetaxel
Nivolumab (CheckMate 017)	≥10%	0.58 (0.33-1.0)	3.7	3.3
	≥5%	0.54 (0.32-0.90)	4.8	3.1
	≥1%	0.67 (0.44-1.0)	3.3	2.8
	<1%	0.66 (0.43-1.0)	3.1	3.0
Nivolumab (CheckMate 057)	≥10%	0.52 (0.37-0.75)	5.0	3.7
	≥5%	0.54 (0.39-0.76)	5.0	3.8
	≥1%	0.70 (0.53-0.94)	4.2	4.5
	<1%	1.19 (0.88-1.61)	2.1	3.6
Pembrolizumab (KEYNOTE-010)	≥50%	0.59 (0.45-0.78)	5.0	4.1
	≥1%	0.88 (0.74-1.05)	3.9	4.0
Atezolizumab (POPLAR)*	TC3 or IC3	0.60 (0.31-1.16)	7.8	3.9
	TC2/3 or IC2/3	0.72 (0.47-1.10)	3.4	2.8
	TC1/2/3 or IC1/2/3	0.85 (0.63-1.16)	2.8	3.0
	TC0 and IC0	1.12 (0.72-1.77)	1.7	4.1

*TC0-3: percentages of tumor cells expression PD-L1 <1% (TC0), ≥1% and <5% (TC1), ≥5% and <50% (TC2), and ≥50% (TC3); IC0-3: percentages of tumor area occupied by PD-L1-positive tumor infiltrating immune cells <1% (IC0), ≥1% and <5% (IC1), ≥5% and <10% (IC2), and ≥10% (IC3).

As with OS, we conducted a network meta-analysis using parametric survival curves for PFS due to the concern that the proportional hazards assumption was violated. Our meta-analysis of nivolumab and atezolizumab showed no PFS benefit at one month but hazard ratios that improved over time; a similar trend was seen with pembrolizumab. Due to the small number of trials, almost all credible intervals crossed one and heavily overlapped. (Appendix D).

We also used HRs to explore subgroup effects when survival curves were not available. Subgroup meta-analysis using HRs suggested that histology (squamous vs. non-squamous NSCLC) was not an effect modifier for PFS (p=0.104, see Appendix E). Our meta-analysis of EGFR- and EGFR+ subgroups suggested that EGFR status *is* an effect modifier for PFS (p=0.002) with a PFS benefit in

EGFR- patients (HR 0.80, 95% CI 0.72-0.90) and an *increased* risk of progression or death in EGFR+ patients (HR 1.57, 95% CI 1.07-2.31).

Objective Response Rate

Objective response rates (ORRs) and duration of response provide another way to assess the benefits of PD-1 immunotherapies, given the difficulties with interpreting median survival and hazard ratios for OS. Patients with tumors that expressed high levels of PD-L1 had significantly higher ORRs with PD-1 immunotherapies than docetaxel, and duration of response was much greater with PD-1 immunotherapies. In some trials, among patients who had responded to PD-1 immunotherapy, the duration of response at the time of trial completion could not be reported as a median number because the halfway point for that duration had not been reached.

Treatment response was evaluated in each of the key PD-1 immunotherapy studies, although no study stratified response endpoints by EGFR mutation status. Nevertheless, the majority of patients participating in the trials of focus did not have a driver mutation, so results from the ITT population may indicate what the response would look like in patients without an EGFR+ tumor.

Table 10 presents response data from the key studies. Objective response rate (ORR) was universally defined as a partial response or better using RECIST v1.1 criteria. Nivolumab- and pembrolizumab-treated patients had significantly higher rates of response relative to docetaxel (18-20% vs. 9-12%). Moreover, the responses were durable and still ongoing at the time of analysis. While atezolizumab and docetaxel produced almost identical ORRs (15%), the median duration of response was about seven months longer with atezolizumab.

Interestingly, while nivolumab and pembrolizumab were associated with higher rates of objective response relative to docetaxel, patients treated with these agents also had more progressive disease. This phenomenon may indicate that PD-1 immunotherapies are best suited for patients with certain clinical characteristics, such as a higher level of PD-L1 expression (see Table 11). As with overall survival, objective response rates among those treated with PD-1 immunotherapy were higher in the subgroups that had greater levels of PD-L1 expression. The CheckMate 017 trial, which evaluated nivolumab in patients with advanced squamous-cell NSCLC, was the only key trial that did not show an association between PD-L1 expression and response.

Table 10. Treatment response: PD-1 immunotherapy vs. docetaxel

	CheckMate 017[23]		CheckMate 057[22]		KEYNOTE-010[21]		POPLAR[24]	
	NIVO	DOCX	NIVO	DOCX	PEMB	DOCX	ATEZ	DOCX
Objective Response, % (95% CI)	20.0 (14-28)	8.8 (5-15)	19.2 (15-24)	12.4 (9-17)	18.0 (14.1-22.5)	9.3 (6.5-12.9)	14.6 (NR)	14.7 (NR)
Odds ratio (95% CI)	2.6 (1.3-5.5)		1.7 (1.1-2.6)		NR		NR	
p-value	0.008		0.02		0.0005		NR	
Median time to response, months (range)	2.2 (1.6-11.8)	2.1 (1.8-9.5)	2.1 (1.2-8.6)	2.6 (1.4-6.3)	2.1 (2.1-4.1)	2.1 (2.1-4.1)	NR	NR
Median duration of response, months (range)	Not reached (2.9-20.5+)	8.4 (1.4-15.2+)	17.2 (1.8-22.6+)	5.6 (1.2-15.2+)	Not reached (4.2-12.5)	6 (2.7-6.1)	14.3 (11.6-NE)	7.2 (5.6-12.5)
Progressive disease, n (%)	56 (41)	48 (35)	129 (44)	85 (29)	124 (37)α	89 (29)α	NR	NR

+ indicates a censored value due to ongoing response at time of analysis; α discontinued treatment due to progressive disease; ATEZ=atezolizumab; DOCX=docetaxel; NIVO=nivolumab; PEMB=pembrolizumab; NR=not reported; NE=non-estimable

Table 11. Objective response according to PD-L1 expression level (vs. docetaxel)

	PD-L1 Expression Threshold	PD-1 immunotherapy ORR (%)	Docetaxel ORR (%)
Nivolumab (CheckMate 017)	≥10%	19	9
	<1%	17	10
	Total population	20.0	8.8
Nivolumab (CheckMate 057)	≥10%	37	13
	<1%	9	15
	Total population	19.2	12.4
Pembrolizumab (KEYNOTE-010)	≥50%	30.2	7.9
	Total population	18.0	9.3
Atezolizumab (POPLAR)*	TC3 or IC3	37.5	13.0
	TC0 and IC0	7.8	9.8
	Total population	14.6	14.7

Quality of Life

Evidence was inadequate to assess the effects of PD-1 immunotherapies compared with docetaxel on quality of life.

Two trials evaluated QoL, although the results have only appeared in one published abstract and one unpublished abstract submitted to us by the manufacturer of pembrolizumab. CheckMate 017 assessed patient-reported health status using the EQ-5D preference-based health state utility measure (EQ-5D index; scaled from 0-1) and visual analog scale (EQ-VAS; scaled from 0-100). The minimum clinically-important difference (MID) is defined as 0.08 for the EQ-5D index and 7 for the EQ-VAS.[69] While both EQ-5D and EQ-VAS were statistically significantly higher during a 48-week and 54-week follow-up than at baseline in the nivolumab arm ($p \leq 0.05$), they were not different from baseline in the docetaxel arm at week 18, after which the sample size dropped below 10 and no analysis was conducted. EQ-VAS was found to have a statistically and clinically significant deterioration at the first follow-up after treatment discontinuation in the docetaxel arm, while no deterioration was observed in the nivolumab arm. Statistical tests comparing the nivolumab and docetaxel arms were not reported. KEYNOTE 010 measured change in QLQ-C30 global QoL score from baseline to 12 weeks. The improvement in QLQ-C30 was 8.3 points (95% CI 2.42-14.26, p=0.006) greater with pembrolizumab 2 mg/kg compared to docetaxel in patients with PD-L1 expression ≥50%. No statistically significant difference was found in patients with PD-L1 expression ≥1%.

Symptom Control

Limited evidence showed no benefits of PD-1 immunotherapies on symptom control compared with docetaxel.

Two trials assessed symptom improvement with nivolumab. The evidence was insufficient to show any benefit with nivolumab on symptom control. Both CheckMate 017 and CheckMate 057 trials measured symptom burden using the LCSS average symptom burden index (LCSS ASBI), computed by averaging 6 individual symptom scores (anorexia, fatigue, cough, dyspnea, hemoptysis, and pain). The minimally important difference (MID) was defined as a change of ≥10 points on a 0-100 scale. At 27-week follow-up in CheckMate 057, symptom improvement rates were similar in the nivolumab and docetaxel arms (17.8% vs. 19.7%), and no changes in mean LCSS ASBI scores exceeded the MID in either arm.[70] Similarly, CheckMate 017 found little difference in symptom improvement at week 12 (20.0% vs. 21.9%).[71]

Harms

Fatigue, nausea, and loss of appetite are the most common adverse events seen with PD-1 immunotherapies. Immune-related adverse events can occur and can affect various organs, including the lungs, brain, liver, and skin. Some of these events can be severe. Overall, severe adverse events, primarily hematologic adverse events, are more common with docetaxel than with PD-1 immunotherapy.

Treatment emergent adverse event (TEAE) frequencies and rates of Grade 3-4 (severe and life-threatening) events are reported by regimen in Table 12. We did not identify a single study that stratified safety outcomes by EGFR mutation status and therefore report data from the overall study populations.

The PD-1 immunotherapies were well tolerated in the key trials, with safety profiles that were generally superior to docetaxel. Patients treated with atezolizumab, nivolumab, or pembrolizumab had lower rates of discontinuation due to TEAEs, fewer grade 3-4 TEAEs, and fewer treatment-related deaths compared to patients treated with docetaxel. The higher rates of grade 3-4 TEAEs observed with docetaxel were attributable mainly to hematologic toxicity.

Table 12. Grade 3-4 treatment-related harms: PD-1 immunotherapy

	POPLAR[α]		CheckMate 017		CheckMate 057		KEYNOTE-010[β]	
	ATEZ	DOCX	NIVO	DOCX	NIVO	DOCX	PEMB	DOCX
Treatment-related deaths, n (%)	1 (0.7)	3 (2)	0	3 (2)	1 (0.3)	1 (0.3)	3 (0.9)	5 (2)
D/C due to TEAEs %	1	18	3	10	5	15	4	10
≥Grade 3 TEAES, %	11	39	7	55	10	54	13	35
	Grade 3-4 AEs, %							
Alopecia	0	1	0	1	0	0	0	1
Anemia	NR	NR	0	3	<1	3	1	2
Asthenia	1	3	0	4	<1	2	<1	2
Decreased appetite	2	0	1	1	0	1	1	1
Diarrhea	1	4	0	2	1	1	1	2
Dyspnea	7	2	NR	NR	<1	0	0.6	1.3
Fatigue	NR	NR	1	8	1	5	1	4
Hypothyroidism	1	0	0	0	0	0	0	0
Musculoskeletal pain	2	2	0	0	NR	NR	0	0
Myalgia	1	3	0	0	<1	0	0	0
Nausea	1	0	0	2	1	1	<1	<1
Leukopenia	NR	NR	1	4	0	8	0	2.6
Neutropenia	0	12	0	30	<1	27	0	12
Febrile Neutropenia	0	8	0	10	0	10	0	4.9
Peripheral neuropathy	0	1	0	2	0	1	0	0.3
Pneumonia	6	2	0	0	0	2	0.9	1.3
Pneumonitis	NR	NR	0	0	1	<1	1.8	0.3
Rash	NR	NR	0	2	<1	0	<1	0

α POPLAR AEs are all-cause. Values were estimated from chart; β Grade 3-5 TEAEs, PEMB results are reported from treatment arm that received 2 mg/kg; AE=Adverse event; D/C=discontinuation; TEAEs=treatment emergent adverse events; ATEZ=atezolizumab; DOCX=docetaxel; NIVO=nivolumab; PEMB=pembrolizumab; NR=not reported

PD-1 immunotherapies have been associated with immune-related adverse events (irAEs), which may include dermatologic toxicity (e.g., rash, pruritus), diarrhea or colitis, hepatotoxicity (elevations in serum levels of aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), pulmonary inflammatory complications (e.g., pneumonitis, pneumonia), and endocrinopathies (e.g., hypothyroidism).[12] The most common adverse events seen with PD-1 immunotherapies are fatigue, nausea, and decreased appetite. Table 13 presents the most frequently-reported treatment-related AEs of any grade of severity, as well as AEs with possible immune etiology. Immune-

mediated TEAEs occurred with greater frequency with the PD-1 immunotherapies relative to docetaxel.

Table 13. Common treatment-related adverse events with PD-1 immunotherapy (any grade) and TEAEs of immune etiology

	POPLAR[α]		CheckMate 017		CheckMate 057		KEYNOTE-010	
%	ATEZ	DOCX	NIVO	DOCX	NIVO	DOCX	PEMB	DOCX
Fatigue	20	35	16	33	16	29	14	25
Nausea	12	27	9	23	12	26	11	15
Decreased appetite	18	16	11	19	10	16	14	16
Asthenia	6	13	10	14	10	18	6	11
Diarrhea	7	22	8	20	8	23	7	18
	Immune-mediated TEAS							
Pruritus	NR	NR	2	0	8	1	7	2
Rash	NR	NR	4	6	9	3	9	5
Hypothyroidism	6	0	4	0	7	0	7	<1
Pneumonitis	3	NR	5	0	3	1	5	2
AST	4	NR	2	1	3	1	3	1
ALT	4	NR	2	1	3	1	5	1
Colitis	NR	NR	1	0	1	0	1	0

α POPLAR values were estimated from chart; hypothyroidism and immune-mediated TEAEs not specifically treatment-related; TEAE=treatment emergent adverse events; AST=aspartate aminotransferase; ALT=alanine aminotransferase; NR=not reported

Controversies and Uncertainties

Although the comparator in all four trials of PD-1 immunotherapies was docetaxel, we found no head-to-head trials comparing these agents. As such, it is difficult to assess whether there are any important differences in outcomes with the three agents we evaluated. Two of the agents, nivolumab and pembrolizumab are directed at PD-1; atezolizumab is directed at PD-L1. Although this different target might argue for considering atezolizumab separately, our meta-analysis suggests little heterogeneity of effect across these three agents.

There are some concerns about appropriate assessment of progression with immunotherapies. There may be a phenomenon of "pseudoprogression", where the enhanced immune reaction with therapy can lead to lesions appearing to have progressed on imaging even if no actual progression

has occurred. Although this has been felt to be important in assessing response to immunotherapies with other tumor types, clinical experts had differing opinions as to whether this is an important issue in NSCLC.

We received a number of comments regarding how to appropriately summarize the effects of PD-1 immunotherapy, as survival curves suggest that the proportional hazards assumption may not be valid, and that there may be a long survival tail among responders to therapy. Our analysis did suggest violations of proportional hazards, particularly for the trials of atezolizumab and nivolumab. It seems likely that the difficulty in using a proportional hazards model is generated by two populations in the PD-1 immunotherapy arms of the trials: a majority of patients who do not have sustained responses to therapy and have a high hazard for progression/mortality, and a minority of patients who do have sustained responses and have a much lower hazard. This is also reflected in the median duration of response results seen in the trials (Table 9). There are relatively few data to allow assessment of whether there is a very long tail of responders beyond two years, but this is clearly an important issue in understanding the potential benefit of PD-1 immunotherapy.

We received comments that squamous and non-squamous histologies should be analyzed separately, given the apparently different responses to nivolumab in CheckMate 017 (squamous histology) and CheckMate 057 (non-squamous histology). However, as discussed above, we found no consistent direction of differences across the three PD-1 immunotherapies when we looked at the squamous and non-squamous subgroups, and we received expert input suggesting that there is not convincing evidence of a differential effect across subgroups. As such, we have chosen to present combined data for the PD-1 immunotherapies across these histologic subtypes.

Patients with higher levels of PD-L1 expression had better responses to all three agents, but different cutpoints and assays were used for each agent in the randomized trials (see appendix Table C5). As such, it is difficult to be certain whether the effect of PD-L1 expression is the same for the three therapies. The issue of whether histology is an effect modifier is raised by the lack of association between PD-L1 levels and response to nivolumab in patients with squamous histology in CheckMate 017. We do not have data on whether PD-L1 levels predict response to treatment in patients with squamous histology treated in POPLAR and KEYNOTE-010, however given the lack of an overall subgroup effect discussed above, we present combined data for both histologies when looking at responses at different levels of PD-L1 expression.

Although the scope of this assessment was for PD-1 immunotherapy in patients without a driver mutation, the data available to us do not provide that exact subgroup and so patients with anaplastic lymphoma kinase (ALK) and KRAS mutations are not separately broken out. We were primarily concerned about assessing therapy in patients who are EGFR-, and two of the four trials provide these subgroup data, and a third trial was in patients with squamous cell carcinoma who have a low rate of EGFR mutations.[4] In the trial of atezolizumab, approximately 11% of patients

were EGFR+ but results were not stratified. We did not detect important heterogeneity when we included this trial in the meta-analysis of EGFR- patients. However, given our estimation, as discussed below, that PD-1 immunotherapy may have no benefit in patients with EGFR+ tumors, the estimates of benefit for atezolizumab may be slightly diluted by including a percentage of patients we believe may not be receiving benefit from treatment.

PD-1 Immunotherapies for First-Line Treatment of Patients without a Driver Mutation

[Please see the Supplement, starting on page 102, for a discussion of evidence relevant to this population that became available after the report was published.]

We currently have no direct evidence from randomized trials comparing PD-1 immunotherapies with a platinum doublet for first line treatment of advanced NSCLC. In the randomized trials, objective response rates (ORRs) were 9 to 15% with docetaxel monotherapy in patients who had received prior chemotherapy,[21-24] but response rates with platinum-based doublets as first-line treatment are 24 to 30%.[68] Given this, the comparator response rate that would be expected with standard-of-care chemotherapy should be much higher with a first-line platinum doublet than the response rate seen with second-line docetaxel. However, although we can expect that first-line PD-1 immunotherapy will be no worse than when it is used second-line, it is possible that the response rate is substantially better in this setting.

We have chosen to look at this question because patients are already being treated with first-line PD-1 immunotherapy in the absence of published evidence from randomized trials. If similar response rates to what was seen with second-line therapy are achieved with first-line PD-1 immunotherapy, it could delay or even obviate the need for chemotherapy for a proportion of patients.

Two trial results of note have been announced, but details are only currently available via press release. The Keynote 024 trial reportedly showed benefits in both OS and PFS with first-line pembrolizumab.[13] The CheckMate 026 trial reportedly showed no benefit in its primary outcome of PFS with first-line nivolumab.[14] Both of these trials were performed in patients with tumors that express PD-L1, but the cutpoints for the analyses were different and used different assays, which might explain the conflicting results. We expect these results to become available in the near future, and they will provide direct evidence on this issue.

Summary

[Please see the Supplement, starting on page 102, for a discussion of evidence relevant to this population that became available after the report was published.]

There are substantial uncertainties about the efficacy of first-line PD-1 immunotherapies in NSCLC. While it seems possible that a proportion of patients would achieve durable responses that would delay the need for treatment with chemotherapy, the evidence base is insufficient ("I").

PD-1 Immunotherapies for Second- or Third-Line Treatment of EGFR+ NSCLC

We currently have no direct evidence comparing PD-1 immunotherapies with a platinum doublet as subsequent-line treatment (after TKIs) of EGFR+ advanced NSCLC. We are looking at this issue, however, as we were informed by clinical experts that some clinicians are using PD-1 immunotherapy in preference to chemotherapy in this setting.

Few EGFR+ patients were in the trials discussed above comparing PD-1 immunotherapies with docetaxel, however two such trials did report on this subgroup. As discussed above, our meta-analysis (Appendix E) suggests that the effects on OS of PD-1 immunotherapy compared with docetaxel was different in EGFR- and EGFR+ patients. This analysis suggests that there is little if any benefit with PD-1 immunotherapy compared with docetaxel in EGFR+ patients treated after progression on TKI therapy and prior to treatment with a platinum doublet. As such, there are reasons to be concerned that PD-1 immunotherapy could be inferior to a platinum doublet (which is more efficacious than docetaxel monotherapy, as discussed above).

Summary

Although the evidence base is insufficient ("I"), indirect evidence raises concerns that in patients with EGFR+ advanced NSCLC who have progressed after TKI therapy, treatment with PD-1 immunotherapy may be inferior to a platinum-based chemotherapy doublet. There is, therefore, currently no evidence to support the use of PD-1 immunotherapy in this setting.

5. Other Benefits or Disadvantages

Our reviews seek to provide information on other benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples include but are not limited to:

1. Methods of administration that improve or diminish patient acceptability and adherence
2. A public health benefit, e.g., reducing new infections
3. Treatment outcomes that reduce disparities across various patient groups
4. More rapid return to work or other positive effects on productivity (if not considered a benefit as part of comparative clinical effectiveness)
5. New mechanisms of action for treatments of clinical conditions for which the response to currently available treatments varies significantly among patients for unknown reasons (substantial heterogeneity of treatment effect)

As discussed above, because of the distribution of smoking behavior within the United States, lung cancer has become more common among patients in lower socioeconomic groups. Thus treatments for the disease will disproportionately affect these groups, and any economic burdens/financial toxicities of treatments will be felt more greatly. Additionally, we were told that lung cancer is a stigmatized disease, and so patients with advanced NSCLC suffer from this additional burden as well.

Although patient groups discussed with us the importance of outcomes of treatment such as reductions in distress and anxiety, these were not well captured in the clinical trials. The trials did show reductions in symptom burden with newer therapies, and it is possible that these would predict reductions in these other outcomes.

Patients with NSCLC have high rates of comorbid vascular and pulmonary disease and many such patients may not have qualified for the clinical trials that assessed these newer therapies. TKI therapy is well tolerated and can be administered even to those with a poor performance status. The safety and efficacy of PD-1 immunotherapy in such patients is less clear.

6. Comparative Value

6.1 Overview

We conducted analyses of the outcomes, costs, and cost-effectiveness of treatment for advanced NSCLC for two distinct populations:

1. First-line treatment with TKIs versus chemotherapy doublet (cisplatin+pemetrexed) for EGFR+ patients (population 1); and
2. Second-line treatment with PD-1 immunotherapy versus docetaxel among patients without the EGFR mutation who have progressed on a first-line chemotherapy doublet (population 3).

As noted in the evidence review, there was no published or otherwise publicly-available direct comparative evidence for second- or third-line treatment with PD-1 immunotherapy in EGFR+ patients who have progressed on TKI therapy (population 2), or first-line treatment with PD-1 immunotherapy in patients without a driver mutation (population 4). Therefore, these populations were not explicitly modeled.

Analyses were carried out using a simulation model based on partition survival curves. Drug cost estimates were based on average wholesale acquisition costs and estimates of adverse events and other clinical parameters from relevant clinical trial data.

We also used outputs from this model to inform a population-based analysis of the one- and five-year potential budget impact of different treatment regimens. As described further in Section 6.3, we conducted analyses only for PD-1 immunotherapies, given the established and long-term presence of TKIs for first-line treatment of EGFR+ NSCLC. Potential budget impact was assessed using assumed levels of uptake over these timeframes and included assessment of drug costs as well as potential cost savings from treatment. We attempted to estimate whether the potential budget impact for any new drug at list price would surpass a threshold related to growth targets for net health care cost growth at the national level.

6.2 Prior Published Evidence on Costs and Cost-Effectiveness of NSCLC Treatments

A review of the literature for prior economic models yielded several published cost-effectiveness models comparing treatment regimens within the TKI and PD-1 immunotherapy classes.

For TKI therapy, we found one study that closely resembled our analysis in terms of treatments used, perspective and setting.[72] The authors developed a Markov model with a lifetime horizon, simulating the costs and outcomes of three treatments, erlotinib, afatinib and cisplatin-pemetrexed, as first-line therapy in stage IIIb/IV NSCLC. The authors of the study reported an incremental cost-effectiveness ratio of $41,106/QALY gained in the comparison of erlotinib to cisplatin-pemetrexed as first-line therapy. The total costs and QALYs accrued in both treatment strategies are lower than in our model (Table 14). There are three key differences between these two analyses that may account for these differing results. First, the study used PFS and OS data directly from RCTs, using a declining exponential approximation of survival beyond the trial data, whereas our analysis estimated survival using HRs for treatment effect derived from the NMA. Additionally, our analysis assumed a fixed OS benefit of nine months for treatment with TKI. Second, the Ting analysis included fewer adverse events in the model, which could contribute to the lower overall costs. Third, the analysis used a monthly cycle length, whereas our analysis used a weekly cycle length, which could potentially impact transition through the stages of the model and thus the total costs and utilities accrued.

Other cost-effectiveness analyses of TKIs differed from our analysis in the intervention and comparators included, in treatment groups, or in setting. A manufacturer-funded analysis compared targeted therapy based on testing available tumor tissue versus carboplatin plus paclitaxel in EGFR+ patients.[73] This model found an incremental cost-effectiveness ratio of $110,644 per quality-adjusted life year (QALY) in the cohort with tumor tissue available during the first biopsy, and an incremental cost-effectiveness ratio of $122,219 per QALY in the cohort with rebiopsy (i.e., in those patients with no availability of tumor tissue for testing in the first biopsy). Another manufacturer-funded study reported that afatinib was cost-effective versus erlotinib at an incremental cost-effectiveness ratio of $77,504/QALY gained.[74] A third manufacturer-funded study modeled a population in Singapore and found that EGFR testing plus gefitinib was dominant over a strategy of chemotherapy with no EGFR testing.[75]

The literature review for PD-1 immunotherapy CEAs found one recent manufacturer-funded analysis comparing pembrolizumab to docetaxel.[76] This study reported an incremental cost-effectiveness ratio of $168,619/QALY gained, substantially lower than the corresponding incremental cost-effectiveness ratio in our analysis (Table 14). The major reason for the difference appears to be that the utility values used in this study, which were based on data collected in the KEYNOTE-010 trial, were higher than those used in our analysis. This is evidenced by the fact that the two analyses actually produce similar estimates of the cost per life-year gained when quality of life adjustments are not included (approximately $135,500 per life-year gained). Other differences in the study include the use of a treatment stopping rule at two years regardless of whether disease progression or adverse events occurred, lower terminal care costs, and the inclusion of only the 80% of total costs assumed to be paid by a third-party payer. However, as stated above, the major difference appears to be the different utility values used in the two analyses.

Among other PD-1 immunotherapy CEAs, an analysis comparing nivolumab with docetaxel in patients who had progressed after first-line platinum-based chemotherapy yielded an incremental cost-effectiveness ratio of CHF177,478/QALY gained (US$182,839/QALY gained).[26] In patients with PD-L1 ≥ 1% and those with PD-L1 ≥ 10%, the incremental cost-effectiveness ratios were CHF133,267/QALY gained (US$137,292/QALY gained) and CHF124,891/QALY gained (US$128,663/QALY gained) respectively. Results of this analysis are not directly comparable with our analysis since it was conducted in a different health care system with a different cost structure.

Table 14. Published cost-effectiveness analyses of TKI and PD-1 treatments

Comparison with prior economic models				
TKI Therapy	**Institute for Clinical and Economic Review**		**Ting et al, 2015[72]**	
	Erlotinib	**Cisplatin-Pemetrexed**	**Erlotinib**	**Cisplatin-Pemetrexed**
Costs	$204,789	$111,443	$46,592	$40,555
Effectiveness	1.51 QALYs	0.88 QALYs	0.44 QALYs	0.28 QALYs
ICER	$147,244/QALY gained		$40,106/QALY gained	
PD-1 immunotherapy	**Institute for Clinical and Economic Review**		**Huang et al, 2016*[76]**	
	Pembrolizumab	**Docetaxel**	**Pembrolizumab**	**Docetaxel**
Costs	$300,119	$94,405	$297,443	$136,921
Effectiveness	1.44 QALYs	0.57 QALYs	1.71 QALYS	0.76 QALYs
ICER	$236,492/QALY gained		$168,619/QALY gained	

*20-year time horizon; ICER=Incremental cost-effectiveness ratio

6.3 Incremental Costs per Outcome Achieved

Cost-Effectiveness Model: Methods

[After the publication of the Evidence Report, the FDA approved atezolizumab with a broader indication than was assumed in these analyses. The evidence for this approval is discussed briefly in the Supplement starting on page 102. This report's modeling and conclusions related to the long-term value for money of atezolizumab should only be applied to the narrower subpopulation that was analyzed. Additionally, after the meeting of the Midwest CEPAC, the FDA expanded the indication of pembrolizumab to a broader second-line population.]

Study Aims

The primary aim of this analysis was to estimate the cost-effectiveness of various treatments for two populations. First, we compared first-line treatments for treatment-naïve patients with EGFR+ NSCLC. Second, we compared second-line treatments for NSCLC patients without the EGFR mutation who have progressed after first-line chemotherapy. In trials, each PD-1 immunotherapy was compared to docetaxal in slightly different populations. Docetaxal efficacy was assumed not to vary with PD-L1 levels and was therefore pooled across all trials. The specific comparisons are given below:

1. First-line TKI treatment strategies for EGFR+ NSCLC
    - Cisplatin+pemetrexed platinum-based chemotherapy doublet (baseline comparator)
    - Afatinib (Gilotrif®, Boehringer Ingelheim, AFAT)
    - Erlotinib (Tarceva®, Genentech, ERLO)
    - Gefitinib (Iressa®, AstraZeneca, GEFI)

2. Second-line PD-1 immunotherapy treatment strategies for EGFR- NSCLC
    - Docetaxel (baseline comparator, DOCX)
    - Atezolizumab (Tecentriq®, Genentech, ATEZ)
    - Nivolumab (Opdivo®, Bristol-Myers Squibb, NIVO)
    - Pembrolizumab (Keytruda®, Merck, PEMB)

Key Assumptions

We made a number of key assumptions to inform our model, as described in Table 15.

Table 15. Key modeling assumptions

Assumption	Rationale
8.9-month increase in TKI median OS vs. CIS-PEM	Comparing patients who only receive TKIs with patients who only receive chemotherapy during and after the intervention period indicates OS is approximately 9 months longer in patients who received only a TKI versus patients who received only chemotherapy
Proportional hazards assumption holds throughout for TKIs	Proportional hazards modeling used in each TKI clinical trial serving as input to network meta-analysis
Time-dependent HRs for immunotherapies	In recognition of PD-1 immunotherapies' violation of the proportional hazard assumption; differential survival modeled using digitized Kaplan-Meier data
Docetexal survival curve pooled across all PD1 trials	Docetexal efficacy is not expected to vary over PD-L1 levels
No vial sharing occurred	Vial sharing illegal for Medicare beneficiaries receiving drugs on outpatient basis
Mean weight: 74.13 kg	Based on KEYNOTE-001 second-line NSCLC cohort
Mean height: 1.78 m	To derive average patient BSA of 1.92 m^2 (Burmaster 1998)[77]

OS=overall survival; CIS-PEM=cisplatin+pemetrexed; TKIs=tyrosine kinase inhibitors; HRs=hazard ratios; NSCLC=non-small cell lung cancer

Model Structure

The model framework is depicted in Figure 9. Outcomes were modeled using a partition survival approach and three health states: progression-free (PF), progression (PRO), and death (see Figure 10). Advantages of partition survival models are that they are less data intensive than other more complex modeling approaches, and that they can use available data commonly reported in clinical trial publications. For each treatment regimen, a hypothetical patient population will spend time in the PF health state and the PRO health state. The mean time, quality adjusted time, and costs spent in each health state are summed to provide estimates of life expectancy, quality adjusted life expectancy, and total costs. We used a cycle length of one week to reflect the dosing schedules for the included drug regimens. We utilized a health system perspective (i.e., direct medical care costs only) and a lifetime horizon, modeling patients from treatment initiation until death. As recommended by the US Guidelines for the Economic Evaluation of Health Technologies, costs and health outcomes were discounted at a rate of 3% per year.[78] We developed the model in Microsoft Excel (Redmond, WA).

Figure 9. Model framework: Management of advanced NSCLC

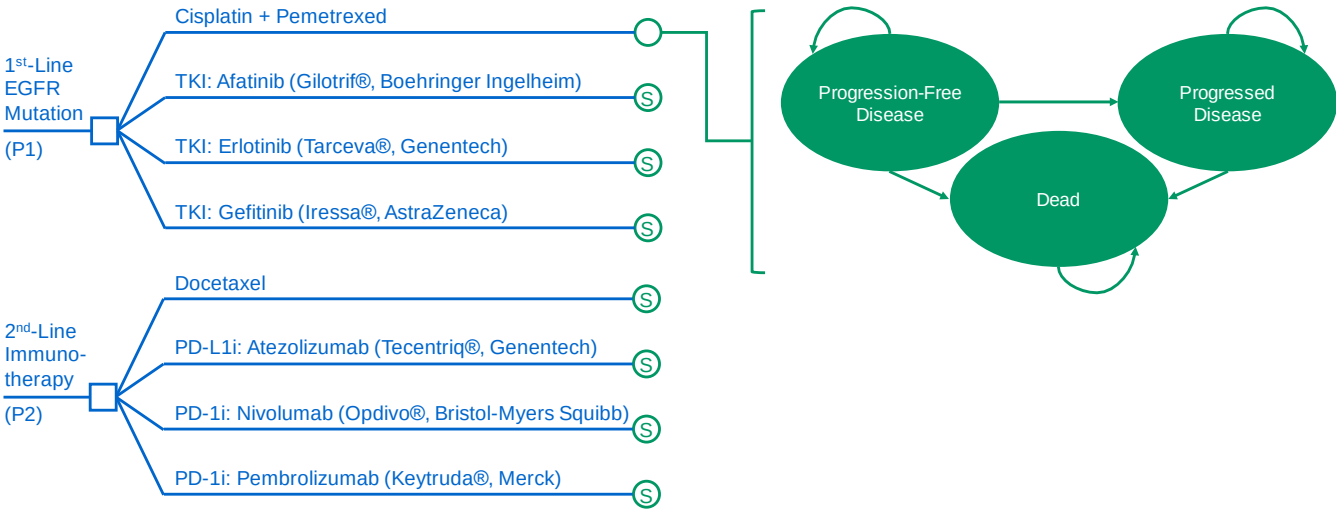
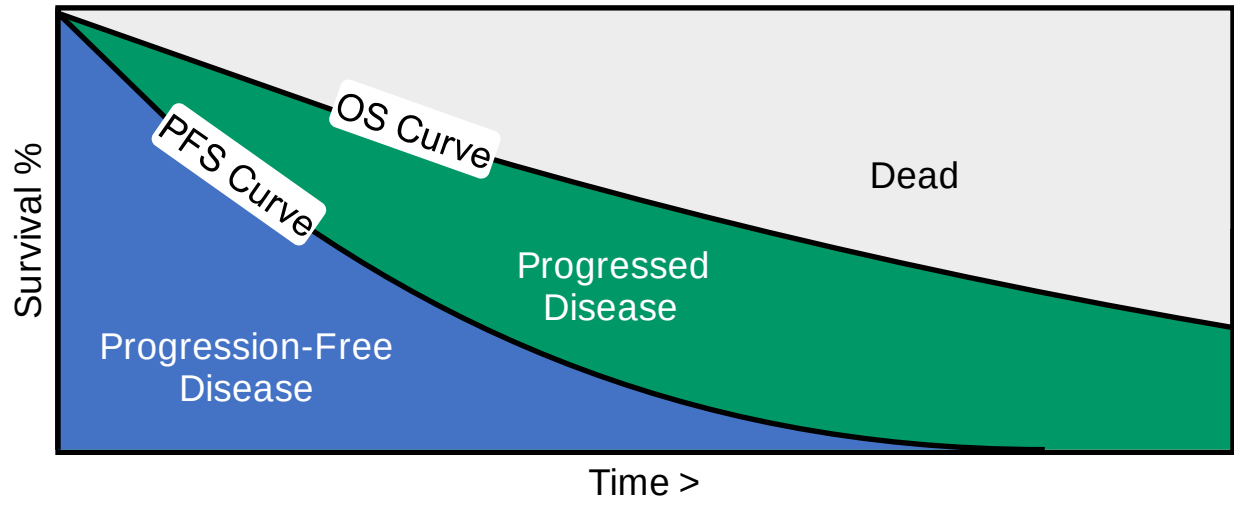


Figure 10. Partition survival model approach



Treatment Strategies

The included treatment regimens were based on FDA-labeled indications for first-line EGFR+ NSCLC treatment with TKIs, and second-line NSCLC treatment with PD-1 immunotherapy among those without EGFR mutations. The primary baseline comparator in the first-line setting was a platinum-based chemotherapy doublet of cisplatin plus pemetrexed, as this is likely the most effective platinum doublet option for most patients with NSCLC. We recognize, however, that several recent

trials have involved comparisons to other chemotherapy regimens and/or placebo. To account for the various trials and trial comparisons, a network meta-analysis was conducted (see Appendix D for further details and results).

The primary baseline comparator in the second-line setting was single-agent chemotherapy with docetaxel. While our initial intent was also to conduct network meta-analysis to support the modeling of PD-1 immunotherapy, study populations for primary analyses were not comparable due to differences in entry criteria and/or assays used to determine PD-L1 positivity. We therefore assessed the clinical impact of each PD-1 immunotherapy agent based on treatment effects observed versus docetaxel in the key clinical trial (or trials, in the case of nivolumab). The base case PD-1 immunotherapy strategies were chosen based on labeled or expected label indications: both PD-L1 negative and positive patients for nivolumab, and PD-L1 positive only for pembrolizumab (>50%) and atezolizumab (TC 2/3 or IC 2/3).

Model Inputs: Clinical

We fit parametric survival curves to progression-free survival (PFS) Kaplan-Meier data for the universal comparator for TKIs (cisplatin+pemetrexed) in the first-line setting, utilizing the approach described by Hoyle and Henley.[79] First, we extracted data points from digitized copies of available survival curves, then used the extracted values, the number of surviving patients at each time interval, and maximum likelihood functions to estimate the underlying individual patient data.

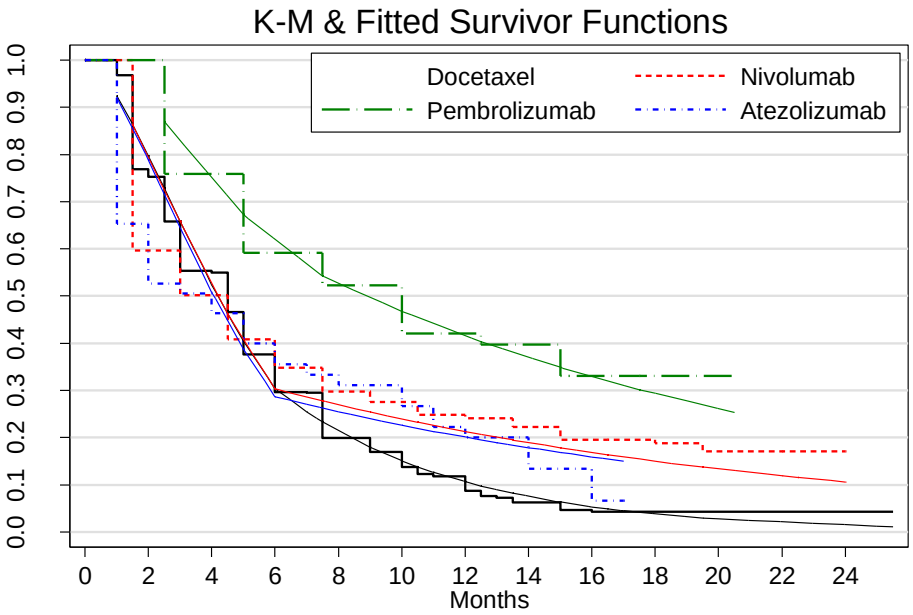
Our network meta-analysis of randomized trials showed that, for patients with EGFR+ advanced NSCLC, treatment with TKIs improves PFS compared with a platinum-based doublet, but has little effect on OS. Assessing the benefit of TKIs on OS is difficult, as there were high crossover rates in the randomized trials.[40,42,49] As noted in Section 4, comparisons of patients who only receive TKIs with patients who only receive chemotherapy indicates OS is approximately 9 months longer in patients who received only a TKI than in those with only chemotherapy. We therefore assumed a base case in which treatment with any TKI at any point during therapy for EGFR+ advanced NSCLC improves median OS by approximately 9 months (modeled range: 6 – 13 months). A universal hazard ratio (HR 0.48; range 0.38-0.58) was derived to approximate median OS benefit, and was applied to the baseline cisplatin+pemetrexed curve. For transparency, the TKI OS hazard ratios versus cisplatin-based doublets estimated by the network meta-analysis are shown in Appendix Table D4. All base case model results reflect the use of this assumed OS benefit parameter.

Because survival data for the PD-1 immunotherapies appear to violate the proportional hazards assumption, we derived time-dependent hazard ratios using digitized survival curve data. Specifically, for PFS and for OS separately, we explored the time point (6, 8, 10 or 12 months) where "flattening" of the survival curves occurred. We fit alternate proportional hazard models to these alternate time points and explored goodness-of-fit to see if the predicted survival curves over- or underestimated the Kaplan-Meier estimates at the corresponding time point. This exploration

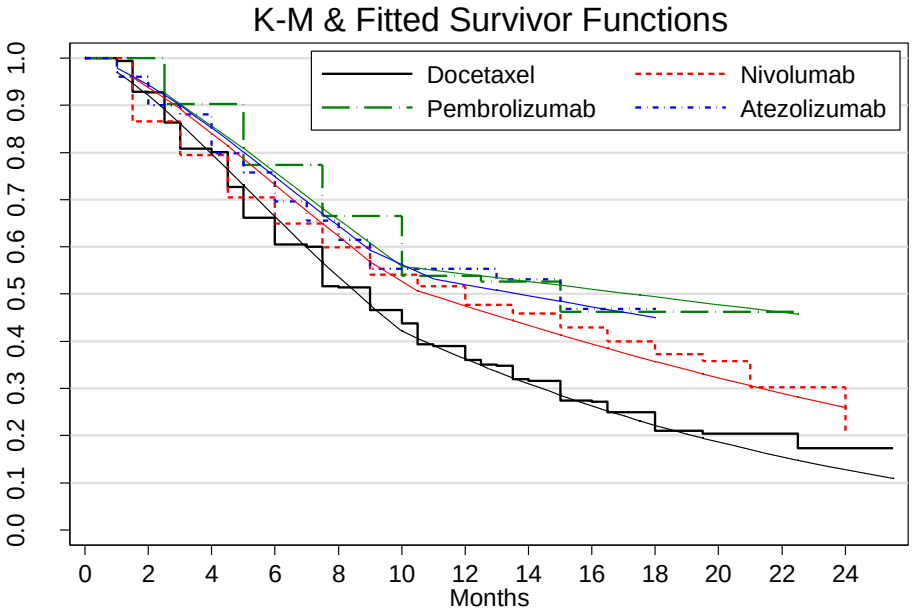
revealed that the best time-point to split the survival curves into phases was 6 months for PFS and 10 months for OS. Therefore 0-6 months and 0–10 months correspond to the first phases of the PFS and OS curves, respectively. We fit several parametric proportional hazard models (Weibull, Gompertz, exponential) to the first phase of the survival curves to select the best fit based on the Akaike information criterion (AIC). A similar process was used to identify the best parametric proportional hazard model for the second phase of the survival curves. For the second phase, we tested the statistical significance of equality of HR among PD-L1s compared to docetaxel. The final second phase models were used to extrapolate the survival curve over the remaining time horizon.

We found that for PFS, a Weibull proportional hazard model with PD-1-immunotherapy-specific HRs best fit the first phase (0-6 months) of the survival curve (Figure 11a). A Gompertz proportional hazards model with a common HR across all PD-1 immunotherapies (test of differential HR p-value = 0.25) was selected for the second phase (Figure 11a). For OS, a Weibull proportional hazard model with PD-1-immunotherapy-specific HRs best fit the first phase (0-10 months) of the survival curve (Figure 11b). A Gompertz proportional hazard model with PD-1-immunotherapy-specific HRs (test of differential HR p-value = 0.008) was selected for the second phase (Figure 11b). Extrapolated curves are shown in Figure 12.

Figure 11: Modeled Fit to (a) Progression-free and (b) Overall Survival curves

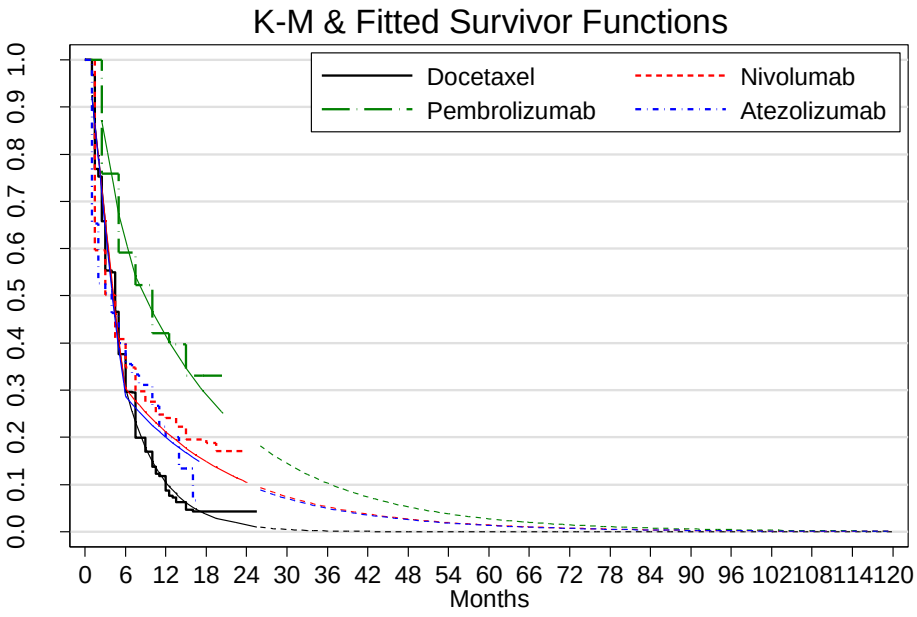


Fitted with Weibull (< 6 mo) & Gompertz (> 6 mo) distributions

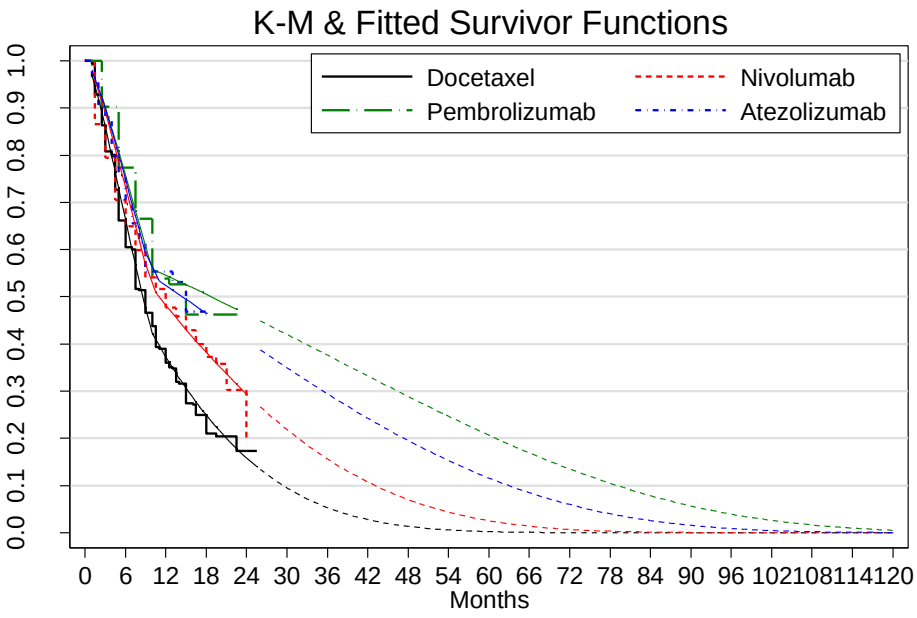


Fitted with Weibull (< 10 mo) & Gompertz (> 10 mo) distributions

Figure 12: Extrapolated model fit to (a) Progression-free and (b) Overall Survival.



Fitted with Weibull (< 6 mo) & Gompertz (> 6 mo) distributions



Fitted with Weibull (< 10 mo) & Gompertz (> 10 mo) distributions

Model Inputs: Adverse Events

The model included Grade 3/4 adverse events that occurred in at least 5% of patients for any of the treatment comparators (Table 16), and were derived from key clinical trials and/or each drug's prescribing information. Because some of the adverse event rates for some regimens were reported only if the event occurred in >10% of patients, we also conducted a scenario analysis with this cutoff.

Table 16. Adverse events per regimen

Grade 3/4 Adverse Events	CIS-PEM[40]	DOCX[80]	AFAT[81]	ERLO[49]	GEFI[82]	ATEZ[24]	NIVO[83]	PEMB[84]
Anemia	6.3%	9.0%	*	1.0%	*	*	*	5.0%
Diarrhea	0.0%	3.0%	15.0%	5.0%	3.0%	1.0%	*	0.0%
Dyspnea	*	*	*	*	*	7.0%	*	2.0%
Fatigue	12.6%	*	*	6.0%	*	*	*	7.0%
Hyponatremia	*	*	*	*	*	*	5.0%	9.0%
Infection	*	10.0%	*	*	*	*	*	*
Leukopenia	8.1%	49.0%	*	*	*	*	*	*
Nausea	3.6%	5.0%	*	*	*	1.0%	*	0.0%
Neuromotor	*	5.0%	*	*	*	*	*	*
Neutropenia	18.0%	65.0%	*	*	*	*	*	*
Paronychia/Nail disorders	0.0%	1.0%	11.0%	*	0.1%	*	*	*
Pneumonitis/Pneumonia	*	*	*	1.0%	*	6.0%	0.4%	0.2%
Pulmonary/respiratory tract infection	*	21.0%	*	*	*	*	*	1.0%
Rash	0.0%	*	*	13.0%	*	*	0.4%	0.0%
Skin reactions	*	1.0%	16.0%	*	2.0%	*	*	*
Stomatitis	0.9%	2.0%	9.0%	*	0.3%	*	*	*

*=Not reported; CIS-PEM=cisplatin+pemetrexed; DOCX=docetaxel; AFAT=afatinib; ERLO=erlotinib; GEFI=gefitinib; ATEZ=atezolizumab; NIVO=nivolumab; PEMB=pembrolizumab

Model Inputs: Drug Utilization and Costs

The estimation of drug utilization (Appendix F) was derived from several factors, including the dosing schedule, where the dose may be fixed by weight or by body surface area (BSA; see Key Assumptions). If a regimen is based on treat-to-progression, the treatment utilization and cost were applied to all patients who remain in the PF health state over time. If a finite number of cycles is used (as with cisplatin+pemetrexed), patients may remain in the PF state without active treatment. No vial sharing was assumed to occur. Drug unit costs were applied to the utilization estimates to calculate total estimated drug treatment costs.

We used the wholesale acquisition cost (WAC) for each drug and noted each available formulation (Table 17). Based on the regimen-specific dosage specified above, the model utilized the lowest-cost combination of tablets and/or vials for each regimen. For atezolizumab and pembrolizumab, we applied a one-time cost of $274 for PD-L1 level testing in the base case analysis.[85]

Table 17. Drug unit costs

Drug Cost Parameters	Default	< Range >		Distribution	Reference
Cisplatin per mg	$0.36	$0.29	$0.43	Normal	Redbook
Cisplatin administration	$91.72	$73.38	$110.06	Normal	CPT 96417 & 96415
Cisplatin dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Pemetrexed 500 mg vial	$3,162.00	$2,529.60	$3,794.40	Normal	Redbook
Pemetrexed 100 mg vial	$632.40	$505.92	$758.88	Normal	Redbook
Pemetrexed administration	$136.15	$108.92	$163.38	Normal	CPT 96413
Pemetrexed dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Docetaxel per mg	$9.55	$7.64	$11.46	Normal	Redbook
Docetaxel administration	$136.15	$108.92	$163.38	Normal	CPT 96413
Docetaxel dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Afatanib 40 mg tablet	$233.05	$186.44	$279.66	Normal	Redbook
Afatanib dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Erlotinib 150 mg tablet	$241.52	$193.22	$289.83	Normal	Redbook
Erlotinib dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Gefitinib 250 mg tablet	$241.20	$192.96	$289.44	Normal	Redbook
Gefitinib dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Atezolizumab 1200 mg vial	$8,620.00	$6,896.00	$10,344.00	Normal	Redbook
Atezolizumab administration	$136.15	$108.92	$163.38	Normal	CPT 96413
Atezolizumab dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Nivolumab 100 mg vial	$2,470.48	$1,976.38	$2,964.58	Normal	Redbook
Nivolumab 40 mg vial	$988.19	$790.55	$1,185.83	Normal	Redbook
Nivolumab administration	$136.15	$108.92	$163.38	Normal	CPT 96413
Nivolumab dose intensity	100.0%	80.0%	100.0%	Beta	Assumption
Pembrolizumab 100 mg vial	$4,380.74	$3,504.59	$5,256.89	Normal	Redbook
Pembrolizumab administration	$136.15	$108.92	$163.38	Normal	CPT 96413
Pembrolizumab dose intensity	100.0%	80.0%	100.0%	Beta	Assumption

Costs per adverse event were based on data from the Centers for Medicare and Medicaid Services (CMS) list of Medicare Severity-Diagnosis Related Groups (MS-DRGs) for the fiscal year 2016,[86] and are shown in Appendix F.

To estimate costs in the progression health state, we assumed the following subsequent therapies for the modeled populations: (1) first-line TKI-treated patients received a chemotherapy doublet of cisplatin+pemetrexed; (2) first-line cisplatin+pemetrexed patients received docetaxel; (3) second-line PD-1 immunotherapy patients received docetaxel; and (4) second-line docetaxel patients received gemcitabine monotherapy. The cost of each subsequent regimen was multiplied by the cumulative proportion of patients within the progressed disease health state during each weekly model cycle. Subsequent regimen costs were derived by calculating the average weekly cost of regimens for cisplatin+pemetrexed, docetaxel and gemcitabine[87] (Table 18); the treatment duration we utilized to calculate the average weekly cost of post-progression therapy was the average months spent in the progressed state per drug class. This equated to 13.5 months of post-TKI cisplatin+pemetrexed therapy, 7.5 months of post-PD-1 immunotherapy (and cisplatin+pemetrexed) docetaxel therapy, and 7.1 months of post-docetaxel gemcitabine therapy, based on the modeled regimens.

Table 18. Post-progression costs

Original Treatment	Subsequent Treatment	Cost/Week
CIS-PEM	DOCX	$307
DOCX	GEM-CIS	$49
AFAT	CIS-PEM	$550
ERLO	CIS-PEM	$550
GEFI	CIS-PEM	$550
ATEZ: TC2/3 or IC2/3	DOCX	$307
NIVO: all comers	DOCX	$307
PEMB: PD-L1 > 50%	DOCX	$307

CIS-PEM=cisplatin+pemetrexed; DOCX=docetaxel; AFAT=afatinib; ERLO=erlotinib; GEFI=gefitinib; ATEZ=atezolizumab; NIVO=nivolumab; PEMB=pembrolizumab; GEM-CIS=gemcitabine+cisplatin

Model Inputs: Health State Utilities

Health state utilities were derived from publicly available literature and applied to the disease states of progression-free and progressed disease (Appendix F). We assumed that health state utility values did not vary across the treatments evaluated in the model. For the progression-free health state, different utilities were applied depending on whether the patient was receiving first- or second-line treatment, to represent decreased quality of life due to progression following first-line treatment. We applied a regimen-weighted disutility for experiencing any grade 3/4 adverse event; the total percentage of patients who experienced any grade 3/4 adverse events for each

regimen was multiplied by the adverse event disutility and then subtracted from the first month of PFS for each regimen. We assumed that the total time with a grade 3/4 adverse event for patients experiencing any grade 3/4 adverse event was one month.

Model Outcomes

The model estimated the amount of time, on average, patients spend progression-free and in progression. Unadjusted and utility-adjusted time spent in each health state was summed to provide estimates of life expectancy and quality-adjusted life expectancy.

Model outcomes of interest for each intervention included:

- Quality adjusted life years (discounted)
- Life years (discounted)
- Mean time in the progression-free and post-progression health states (discounted)
- Pre-progression, post-progression, and total costs (discounted)
- Incremental cost-effectiveness ratios for each intervention versus the standard comparator (cisplatin+pemetrexed or docetaxel), in pairwise comparisons

Sensitivity Analyses

The model programming allows for flexible and comprehensive sensitivity analyses. One-way sensitivity analyses used 95% confidence intervals from clinical evidence as ranges, where available. When 95% confidence intervals were not available, uncertainty ranges were based on plausible values from the published literature. We also conducted a probabilistic sensitivity analysis (PSA) by jointly varying all model parameters over 4,000 simulations, then calculating 95% credible range estimates for each model outcome.

Finally, we ran four scenario analyses: (1) omitting our assumption of an 8.9-month overall survival benefit and utilizing NMA OS hazard ratios from TKI/ cisplatin+pemetrexed crossover populations; (2) using PD-1 immunotherapy PFS and OS HRs directly from the published trials and applying them to non-time-adjusted baseline curves while assuming proportional hazards over the entire time horizon (i.e., we assumed the proportional hazards assumption was not violated by observed trial data); (3) employing a similar curve-fitting approach as the base case to estimate outcomes for the following PD-L1 subpopulations: (a) atezolizumab TC 1/2/3 or IC 1/2/3, (b) nivolumab PD-L1 >10%, and (c) pembrolizumab PD-L1 >1%; and (4) in recognition of different thresholds for adverse event reporting among study drugs, we explored a scenario in which we only included adverse events with at least one drug reporting >10% of patients experiencing the event instead of the base case threshold of >5%.

Cost-Effectiveness Model: Results

Base Case Results

The results of the pairwise comparisons are provided in Tables 19a and 19b for the first-line setting with TKIs, and Tables 20a and 20b for the second-line setting with PD-L1 immunotherapies. These tables report detailed results for each regimen in each line as well as the incremental results versus their respective baseline comparators. Reported survival results will not perfectly match those seen in clinical trials because of our approach in anchoring hazard ratios to the baseline survival curves for cisplatin+pemetrexed and docetaxel (rather than use of observed survival curves in each trial). All results presented below are based on deterministic analyses (i.e., based on point estimates for all model parameters), due to wide confidence intervals for some of the model estimates. Probabilistic results are listed in Appendix F.

Table 19a. Results by regimen for first-line EGFR+ patients

	CIS-PEM	AFAT	ERLO	GEFI
Total Costs	$111,443	$195,398	$204,789	$177,281
Drug Costs	$32,042	$89,872	$102,726	$71,548
PFS Supp. Care Costs	$10,217	$20,364	$22,520	$15,571
Administration Costs	$1,145	$0	$0	$0
Progression Costs	$14,845	$34,466	$30,735	$42,834
Death Costs	$48,192	$46,953	$46,953	$46,953
Adverse Event Costs	$5,002	$3,744	$1,855	$375
Total QALYs	0.88	1.50	1.51	1.47
PFS QALYs	0.42	0.83	0.91	0.64
Progression QALYs	0.46	0.67	0.60	0.84
Total Life Years (OS)	1.22	2.06	2.06	2.06
PFS LYs	0.54	1.06	1.16	0.81
Progression LYs	0.68	1.00	0.90	1.25
Median PFS (months)	5.1	10.4	11.5	7.9
Median OS (months)	12.5	21.4	21.4	21.4

Table 19b. Incremental results for first-line EGFR+ patients

	CIS-PEM	AFAT	ERLO	GEFI
ICER (QALYs)	--	$135,095	$147,244	$110,840
ICER (LYs)		$100,120	$111,318	$78,514
Incremental Costs	--	$83,956	$93,346	$65,838
Drug Costs	--	$57,830	$70,684	$39,506
PFS Supp. Care Costs	--	$10,147	$12,303	$5,354
Administration Costs	--	-$1,145	-$1,145	-$1,145
Progression Costs	--	$19,621	$15,890	$27,989
Death Costs	--	-$1,239	-$1,239	-$1,239
Adverse Event Costs	--	-$1,259	-$3,147	-$4,628
Incremental QALYs	--	0.62	0.63	0.59
PFS QALYs	--	0.41	0.49	0.22
Progression QALYs	--	0.21	0.14	0.38
Incremental Life Years (OS)	--	0.84	0.84	0.84
PFS LYs	--	0.52	0.63	0.28
Progression LYs	--	0.32	0.21	0.56

Use of each of the first-line TKI regimens (with the assumption of an 8.9-month gain in median survival for each regimen) resulted in a 0.84 life-year gain in survival relative to cisplatin+pemetrexed. QALYs gained versus cisplatin+pemetrexed were also very similar across all three regimens, ranging from 0.59 for gefitinib to 0.62 and 0.63 for afatinib and erlotinib, respectively. Incremental costs versus cisplatin+pemetrexed were somewhat lower for gefinitib ($65,838) than for the other TKIs, which was a function of a shorter duration of time spent in the progression-free state (and a consequently shorter duration of treatment). Cost-effectiveness estimates were quite similar across the TKIs, ranging from $110,840 - $147,244 per QALY gained, which is not surprising given the assumption of equal gain in median OS across the TKIs.

Table 20a. Results by regimen for second-line PD-1 immunotherapy patients

	DOCX	ATEZ: TC2/3 or IC2/3	NIVO: All Comers	PEMB: PD-L1 >50%
Total Costs	**$94,405**	**$206,190**	**$201,877**	**$300,119**
Drug Costs	$11,816	$114,334	$120,657	$195,670
PFS Supp. Care Costs	$9,044	$14,448	$15,020	$24,766
Administration Costs	$1,170	$1,802	$2,771	$3,036
Progression Costs	$4,648	$27,725	$15,242	$28,695
Death Costs	$48,457	$47,011	$47,819	$46,166
Adverse Event Costs	$19,270	$870	$367	$1,785
Total QALYs	**0.57**	**1.08**	**0.83**	**1.44**
PFS QALYs	0.31	0.48	0.50	0.82
Progression QALYs	0.27	0.60	0.33	0.62
Total Life Years (OS)	**1.04**	**2.02**	**1.47**	**2.59**
PFS LYs	0.47	0.74	0.77	1.26
Progression LYs	0.57	1.28	0.70	1.32
Median PFS (months)	4.2	3.9	4.2	9.5
Median OS (months)	8.5	14.8	11.1	25.8

Table 20b. Incremental results for second-line PD-1 immunotherapy patients

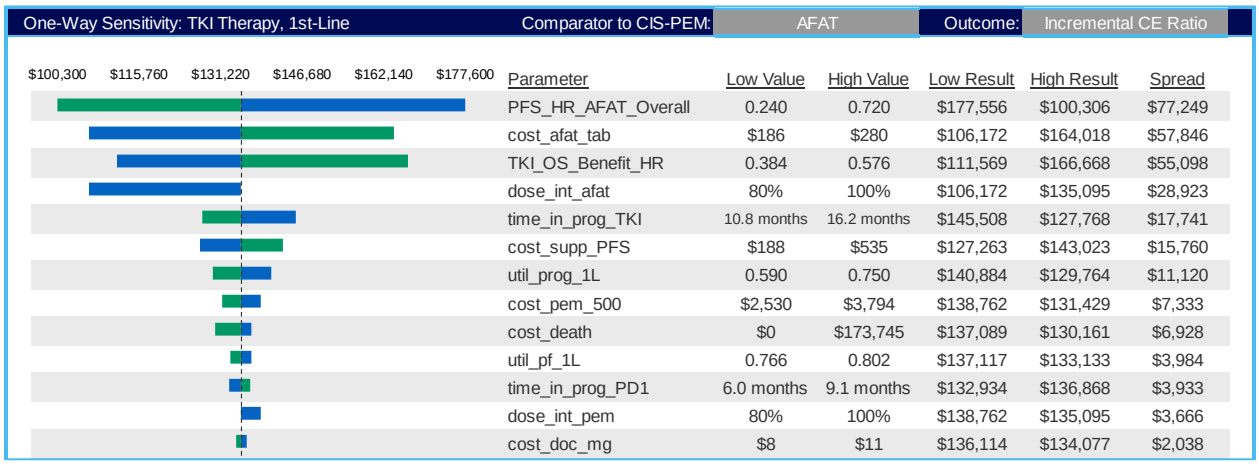
	DOCX	ATEZ: TC2/3 or IC2/3	NIVO: All Comers	PEMB: PD-L1 >50%
ICER (QALYs)	--	**$219,179**	**$415,950**	**$236,492**
ICER (LYs)		$114,303	$249,169	$133,212
Incremental Costs	--	**$111,785**	**$107,472**	**$205,714**
Drug Costs	--	$102,519	$108,841	$183,855
PFS Supp. Care Costs	--	$5,404	$5,976	$15,721
Administration Costs	--	$631	$1,601	$1,866
Progression Costs	--	$23,077	$10,594	$24,047
Death Costs	--	-$1,446	-$637	-$2,290
Adverse Event Costs	--	-$18,400	-$18,902	-$17,485
Incremental QALYs	--	**0.51**	**0.26**	**0.87**
PFS QALYs	--	0.18	0.19	0.51
Progression QALYs	--	0.33	0.06	0.36
Incremental Life Years (OS)	--	**0.98**	**0.43**	**1.54**
PFS LYs	--	0.27	0.30	0.79
Progression LYs	--	0.71	0.14	0.76

Use of each of the second-line immunotherapy regimens resulted in a gain in survival (range: 0.43 incremental life-years for nivolumab to 1.54 life-years for pembrolizumab) relative to docetaxel. On a quality-adjusted basis, QALYs gained versus docetaxel ranged from 0.26 for nivolumab to 0.87 for pembrolizumab. Incremental costs versus docetaxel ranged from a low of $107,472 for nivolumab to $205,714 for pembrolizumab. Cost-effectiveness estimates ranged from $219,179 per QALY gained relative to docetaxel for atezolizumab to $415,950 per QALY for nivolumab. Again, it is important to stress that this analysis was based on the within-trial experience for each agent. The contrast of primary interest is on the incremental outcomes, costs, and cost-effectiveness of each PD-1 immunotherapy in relation to docetaxel, not on comparisons between the PD-1 immunotherapies themselves.

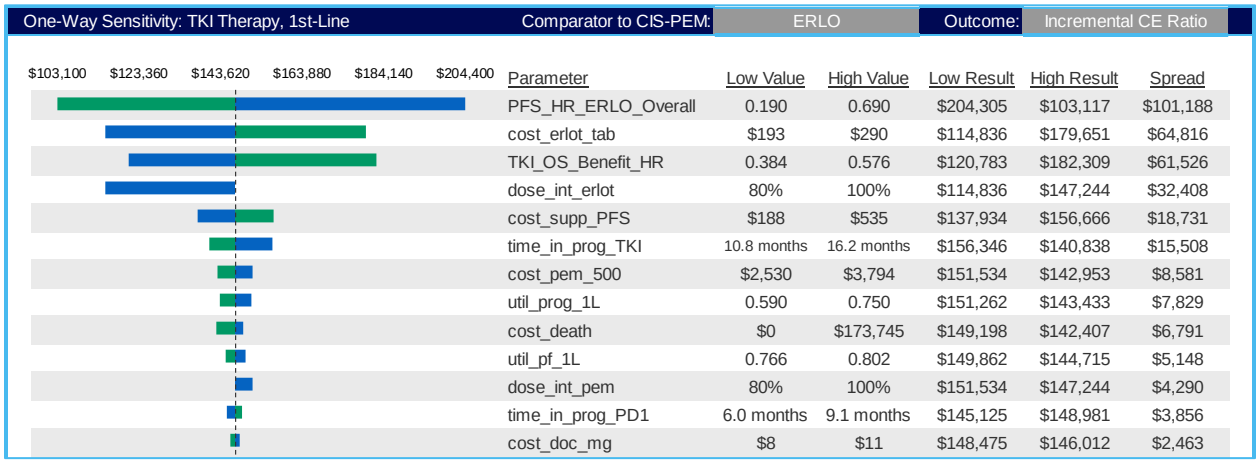
Sensitivity Analyses

Detailed findings from the one-way sensitivity analyses can be found below. In each one-way analysis, results were most sensitive to PFS and OS HRs, drug costs, and (for TKIs) the assumption of an 8.9-month OS benefit.

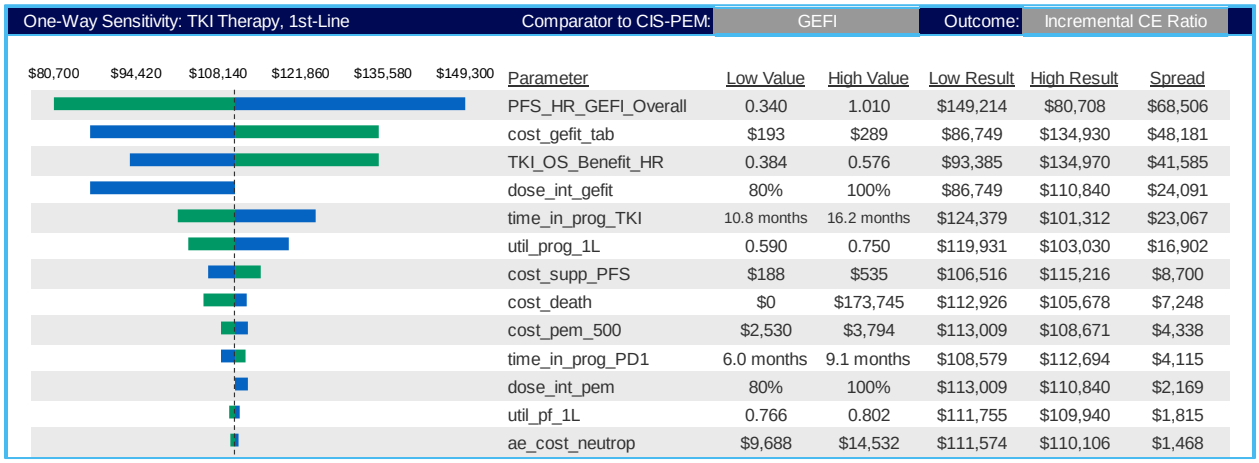
Figure 13a. One-way sensitivity analysis results: Tornado diagrams for TKIs



Parameter	Low Value	High Value	Low Result	High Result	Spread
PFS_HR_AFAT_Overall	0.240	0.720	$177,556	$100,306	$77,249
cost_afat_tab	$186	$280	$106,172	$164,018	$57,846
TKI_OS_Benefit_HR	0.384	0.576	$111,569	$166,668	$55,098
dose_int_afat	80%	100%	$106,172	$135,095	$28,923
time_in_prog_TKI	10.8 months	16.2 months	$145,508	$127,768	$17,741
cost_supp_PFS	$188	$535	$127,263	$143,023	$15,760
util_prog_1L	0.590	0.750	$140,884	$129,764	$11,120
cost_pem_500	$2,530	$3,794	$138,762	$131,429	$7,333
cost_death	$0	$173,745	$137,089	$130,161	$6,928
util_pf_1L	0.766	0.802	$137,117	$133,133	$3,984
time_in_prog_PD1	6.0 months	9.1 months	$132,934	$136,868	$3,933
dose_int_pem	80%	100%	$138,762	$135,095	$3,666
cost_doc_mg	$8	$11	$136,114	$134,077	$2,038

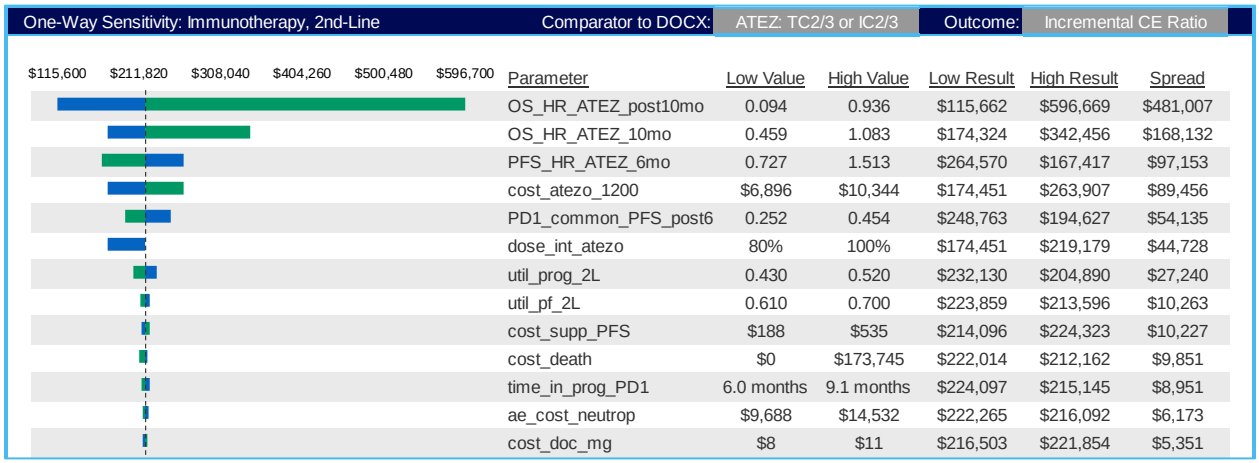


Parameter	Low Value	High Value	Low Result	High Result	Spread
PFS_HR_ERLO_Overall	0.190	0.690	$204,305	$103,117	$101,188
cost_erlot_tab	$193	$290	$114,836	$179,651	$64,816
TKI_OS_Benefit_HR	0.384	0.576	$120,783	$182,309	$61,526
dose_int_erlot	80%	100%	$114,836	$147,244	$32,408
cost_supp_PFS	$188	$535	$137,934	$156,666	$18,731
time_in_prog_TKI	10.8 months	16.2 months	$156,346	$140,838	$15,508
cost_pem_500	$2,530	$3,794	$151,534	$142,953	$8,581
util_prog_1L	0.590	0.750	$151,262	$143,433	$7,829
cost_death	$0	$173,745	$149,198	$142,407	$6,791
util_pf_1L	0.766	0.802	$149,862	$144,715	$5,148
dose_int_pem	80%	100%	$151,534	$147,244	$4,290
time_in_prog_PD1	6.0 months	9.1 months	$145,125	$148,981	$3,856
cost_doc_mg	$8	$11	$148,475	$146,012	$2,463



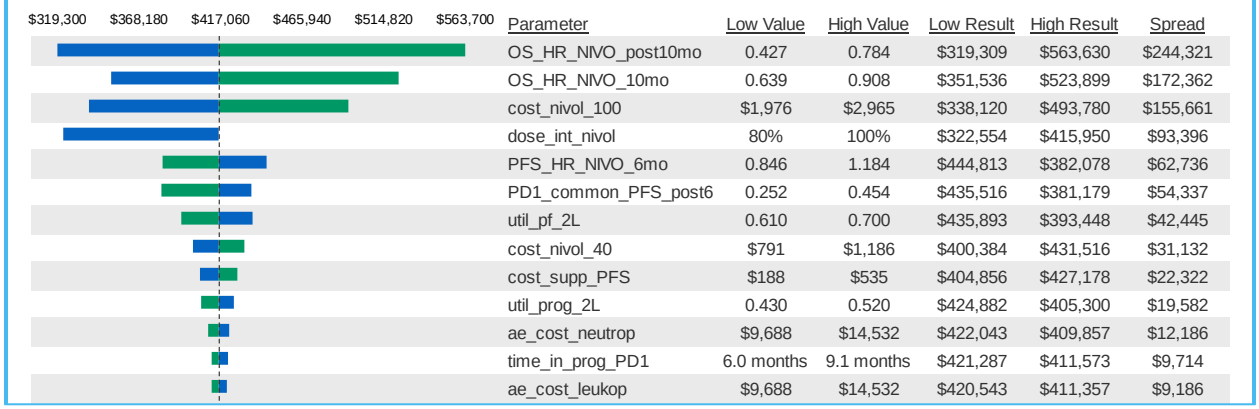
Parameter	Low Value	High Value	Low Result	High Result	Spread
PFS_HR_GEFI_Overall	0.340	1.010	$149,214	$80,708	$68,506
cost_gefit_tab	$193	$289	$86,749	$134,930	$48,181
TKI_OS_Benefit_HR	0.384	0.576	$93,385	$134,970	$41,585
dose_int_gefit	80%	100%	$86,749	$110,840	$24,091
time_in_prog_TKI	10.8 months	16.2 months	$124,379	$101,312	$23,067
util_prog_1L	0.590	0.750	$119,931	$103,030	$16,902
cost_supp_PFS	$188	$535	$106,516	$115,216	$8,700
cost_death	$0	$173,745	$112,926	$105,678	$7,248
cost_pem_500	$2,530	$3,794	$113,009	$108,671	$4,338
time_in_prog_PD1	6.0 months	9.1 months	$108,579	$112,694	$4,115
dose_int_pem	80%	100%	$113,009	$110,840	$2,169
util_pf_1L	0.766	0.802	$111,755	$109,940	$1,815
ae_cost_neutrop	$9,688	$14,532	$111,574	$110,106	$1,468

Figure 13b. One-way sensitivity analysis results: Tornado diagrams for immunotherapies



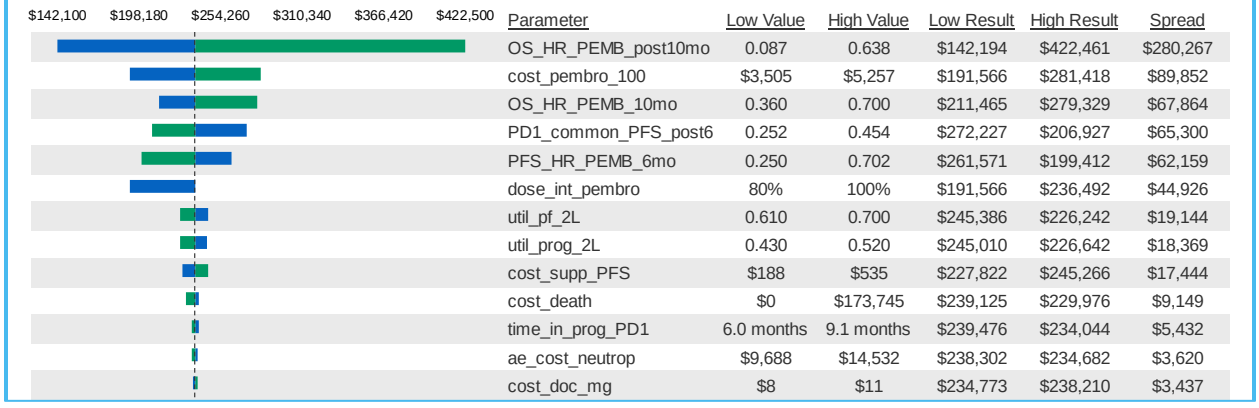
One-Way Sensitivity: Immunotherapy, 2nd-Line | Comparator to DOCX: ATEZ: TC2/3 or IC2/3 | Outcome: Incremental CE Ratio

Parameter	Low Value	High Value	Low Result	High Result	Spread
OS_HR_ATEZ_post10mo	0.094	0.936	$115,662	$596,669	$481,007
OS_HR_ATEZ_10mo	0.459	1.083	$174,324	$342,456	$168,132
PFS_HR_ATEZ_6mo	0.727	1.513	$264,570	$167,417	$97,153
cost_atezo_1200	$6,896	$10,344	$174,451	$263,907	$89,456
PD1_common_PFS_post6	0.252	0.454	$248,763	$194,627	$54,135
dose_int_atezo	80%	100%	$174,451	$219,179	$44,728
util_prog_2L	0.430	0.520	$232,130	$204,890	$27,240
util_pf_2L	0.610	0.700	$223,859	$213,596	$10,263
cost_supp_PFS	$188	$535	$214,096	$224,323	$10,227
cost_death	$0	$173,745	$222,014	$212,162	$9,851
time_in_prog_PD1	6.0 months	9.1 months	$224,097	$215,145	$8,951
ae_cost_neutrop	$9,688	$14,532	$222,265	$216,092	$6,173
cost_doc_mg	$8	$11	$216,503	$221,854	$5,351



One-Way Sensitivity: Immunotherapy, 2nd-Line | Comparator to DOCX: NIVO: All Comers | Outcome: Incremental CE Ratio

Parameter	Low Value	High Value	Low Result	High Result	Spread
OS_HR_NIVO_post10mo	0.427	0.784	$319,309	$563,630	$244,321
OS_HR_NIVO_10mo	0.639	0.908	$351,536	$523,899	$172,362
cost_nivol_100	$1,976	$2,965	$338,120	$493,780	$155,661
dose_int_nivol	80%	100%	$322,554	$415,950	$93,396
PFS_HR_NIVO_6mo	0.846	1.184	$444,813	$382,078	$62,736
PD1_common_PFS_post6	0.252	0.454	$435,516	$381,179	$54,337
util_pf_2L	0.610	0.700	$435,893	$393,448	$42,445
cost_nivol_40	$791	$1,186	$400,384	$431,516	$31,132
cost_supp_PFS	$188	$535	$404,856	$427,178	$22,322
util_prog_2L	0.430	0.520	$424,882	$405,300	$19,582
ae_cost_neutrop	$9,688	$14,532	$422,043	$409,857	$12,186
time_in_prog_PD1	6.0 months	9.1 months	$421,287	$411,573	$9,714
ae_cost_leukop	$9,688	$14,532	$420,543	$411,357	$9,186



One-Way Sensitivity: Immunotherapy, 2nd-Line | Comparator to DOCX: PEMB: PD-L1 >50% | Outcome: Incremental CE Ratio

Parameter	Low Value	High Value	Low Result	High Result	Spread
OS_HR_PEMB_post10mo	0.087	0.638	$142,194	$422,461	$280,267
cost_pembro_100	$3,505	$5,257	$191,566	$281,418	$89,852
OS_HR_PEMB_10mo	0.360	0.700	$211,465	$279,329	$67,864
PD1_common_PFS_post6	0.252	0.454	$272,227	$206,927	$65,300
PFS_HR_PEMB_6mo	0.250	0.702	$261,571	$199,412	$62,159
dose_int_pembro	80%	100%	$191,566	$236,492	$44,926
util_pf_2L	0.610	0.700	$245,386	$226,242	$19,144
util_prog_2L	0.430	0.520	$245,010	$226,642	$18,369
cost_supp_PFS	$188	$535	$227,822	$245,266	$17,444
cost_death	$0	$173,745	$239,125	$229,976	$9,149
time_in_prog_PD1	6.0 months	9.1 months	$239,476	$234,044	$5,432
ae_cost_neutrop	$9,688	$14,532	$238,302	$234,682	$3,620
cost_doc_mg	$8	$11	$234,773	$238,210	$3,437

Results of the probabilistic sensitivity analysis (PSA) can be found in Appendix F. Our findings show substantial variability in model outcomes, particularly in second-line immunotherapies. However,

for first-line TKI regimens, the range of possible incremental cost-effectiveness ratios included commonly-cited thresholds of $100,000 - $150,000 per QALY gained. In contrast, the possible range of results from PSAs on second-line immunotherapies are substantially wider due to parameter uncertainty, particularly in PFS and OS HRs; thus, the mean incremental cost-effectiveness ratios for PD-L1 immunotherapies should be interpreted with great caution.

Scenario analysis results are also presented in Appendix F. In general, the scenario results involve adjustments to PFS and OS based on specific populations and should be interpreted with great caution, as the hazard ratios used to derive survival were: (a) highly uncertain in the case of TKI OS, and (b) based on off-label indications in the case of PD-1 immunotherapies. A full accounting of parameter uncertainty in PSA lead to notably different results in many cases. With this caveat, we present the deterministic and probabilistic estimates to explore the hypothetical impacts of targeted NSCLC therapy.

In scenario 1, we omitted our assumption of an 8.9-month OS benefit, and utilized OS HRs from a NMA of TKI/ cisplatin+pemetrexed crossover populations. As expected, this resulted in a notable decrease in overall survival for TKIs, which lowered both drug costs and progression costs because fewer patients were alive to accrue these costs. However, clinical benefits were also severely diminished, leading to inferior survival and QALY estimates relative to cisplatin+pemetrexed for gefitinib, and relatively high cost-effectiveness ratios in afatinib and erlotinib.

In Scenario 2 we assumed proportional hazards using trial-reported PFS and OS HRs for the entire time horizon, and applied them to a docetaxel baseline Weibull curve; the docetaxel baseline Weibull curve was unadjusted by time as in the base case. The following HRs were used: (1) Atezolizumab TC2/3 or IC2/3, PFS: 0.72 (0.47 to 1.10), OS: 0.54 (0.33 to 0.89); (2) Nivolumab all comers, PFS: 0.77 (0.52 to 1.13), OS: 0.67 (0.55 to 0.83); and (3) Pembrolizumab PD-L1 >50%, PFS: 0.59 (0.44 to 0.78), OS: 0.54 (0.38 to 0.77). Without adjusting for survival curves “flattening” over time, health outcomes were notably worse, and costs were lower due to decreased survival for each drug. In the scenario, pembrolizumab PD-L1 >50% continued to have the highest cost but also the highest gain in QALYs, followed by atezolizumab TC2/3 or IC2/3, and nivolumab all comers. The incremental cost-effectiveness ratios remained high, ranging from $286,568/QALY gained for atezolizumab to $424,195/QALY gained for nivolumab.

In scenario 3 we employed a similar curve fitting approach as the base case to estimate outcomes for the following PD-L1 subpopulations: (a) Atezolizumab 1/2/3, (b) Nivolumab PD-L1 >10%, and (c) Pembrolizumab PD-L1 >1%. Compared to the indicated/base case populations, survival and quality-adjusted survival were slightly worse for Atezolizumab, higher for nivolumab, and similar for pembrolizumab, although a higher proportion of pembrolizumab survival was spent in the progressed disease state. This resulted in slightly lower atezolizumab cost due to less time in PFS, higher nivolumab cost due to increased survival and time in PFS, and decreased cost for

pembrolizumab due to less time spent in PFS. Incremental cost-effectiveness ratios were somewhat lower than in the base case for atezolizumab and pembrolizumab, and substantially lower for nivolumab in this more selected population.

Finally, scenario 4, in which we included AEs with at least one drug reporting >10% of patients experiencing the event instead of the base case threshold of >5%, showed only a modest decrease in cost for all drug regimens, without a notable impact on overall results.

Prices for each drug that would achieve cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained are presented in Table 21 for first-line TKI treatments and Table 22 for second-line PD-1 immunotherapy treatments, along with the wholesale acquisition cost per tablet or vial.

Table 21. Threshold analysis for price per drug for first-line TKI treatments

Willingness-to-pay	AFAT (40mg)	ERLO (150 mg)	GEFI (250 mg)
$50,000	$96	$97	$119
$100,000	$176	$171	$220
$150,000	$257	$246	$320
WAC price per tablet	**$233**	**$242**	**$241**

Table 22. Threshold analysis for price per drug for second-line PD-1 immunotherapy

Willingness-to-pay	ATEZ TC2/3 or IC2/3 (1200 mg)	NIVO all comers (100 mg)	PEMB PD-L1 >50% (100 mg)
$50,000	$2,099	$534	$744
$100,000	$4,026	$799	$1,719
$150,000	$5,954	$1,064	$2,694
WAC price per vial	**$8,620**	**$2,470**	**$4,381**

6.4 Potential Budget Impact

[After the publication of the Evidence Report, the FDA approved atezolizumab with a broader indication than was assumed in these analyses. The evidence for this approval is discussed briefly in the Supplement starting on page 102. This report's modeling and conclusions related to the long-term value for money of atezolizumab should only be applied to the narrower subpopulation that was analyzed. Additionally, after the meeting of the Midwest CEPAC, the FDA expanded the indication of pembrolizumab to a broader second-line population.]

We also used the cost-effectiveness model to estimate the potential total budgetary impact of PD-1 immunotherapy treatments for NSCLC patients, based on assumed patterns of product uptake.

Potential Budget Impact Model: Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total incremental cost of using PD-1 immunotherapy rather than docetaxel for the treated population, calculated as incremental health care costs (including drug costs) minus any offsets in these costs from averted health care events. We did not include the other population modeled above (adults with advanced NSCLC who have an EGFR+ tumor and have not previously been treated for advanced disease) in this budget impact analysis, as all three of the TKIs evaluated in that population are in established use based on clinical guidelines, and with many years of market experience in two of the three cases. We also do not consider the potential budgetary implications of using these drugs for other indications than NSCLC.

Note that this analysis is performed from an *ex ante* perspective; that is, it treats all of the drugs being evaluated as though they will be new to market, whether or not they have already been launched. We therefore estimated the net costs of using each drug rather than docetaxel, assuming no current use of the drug. We did allow for differential uptake of the PD-1 immunotherapies by product, however, based on currently-available market share data. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year time frame was of primary interest, given the potential for cost offsets to accrue over time.

The potential budget impact analysis included the entire candidate population for treatment, which was considered to be adults with advanced NSCLC who have a tumor that has progressed after first-line treatment with a platinum-based chemotherapy doublet.

To estimate the size of the potential candidate population for treatment with atezolizumab, we first determined the estimated prevalence of NSCLC in the US. Lung cancer prevalence in 2013 was estimated to be 415,707 patients.[88] Of those, 85% are estimated to have NSCLC and 70% of those to have advanced disease.[89] This would result in an estimate of 247,346 persons with advanced NSCLC in the US. Pembrolizumab is approved for use in second-line treatment in patients whose tumors demonstrate PD-L1 expression, and we anticipate that atezolizomab will be approved for a similar population. Taube reported that approximately 60% of NSCLC cancer specimens demonstrated PD-L1 expression.[90] Stinchcombe and Socinski state that: "While it is difficult to estimate the proportion of patients who receive second-line treatment, approximately 40%–50% of patients did so in recent first-line trials."[91] We, therefore, assumed that 40% of patients would receive second-line treatment. Applying these percentages resulted in a candidate population size of approximately 59,400 individuals in the US. Use of nivolumab is not restricted to use in patients whose tumors express PD-L1. We therefore applied the 40% assumption for second-line treatment

to the 40% of patients with tumors that do not express PD-L1, resulting in an additional candidate population for nivolumab of approximately 39,600 patients (i.e., a total of 99,000 individuals).

ICER's methods for estimating potential budget impact and calculating value-based benchmark prices are described in detail elsewhere.[92] Briefly, our calculations assume that the utilization of new drugs occurs without any payer, provider group, or pharmacy benefit management controls in place, to provide an estimate of "unmanaged" drug uptake by five years after launch.

In general, we examine six characteristics of the drug or device and the marketplace to estimate "unmanaged" uptake. These characteristics are listed below:

- Magnitude of improvement in clinical safety and/or effectiveness
- Patient-level burden of illness
- Patient preference (ease of administration)
- Proportion of eligible patients currently being treated
- Primary care versus specialty clinician prescribing/use
- Presence or emergence of competing treatments of equal or superior effectiveness

Based on our assessment of these criteria, we assign a new drug or device to one of four categories of unmanaged drug uptake patterns: 1) very high (75% uptake by year 5); 2) high (50% uptake by year 5); 3) intermediate (25% uptake by year 5); and 4) low (10% uptake by year 5). In this analysis, we assumed a 50% uptake pattern for nivolumab, and 25% uptake each for atezolizumab and pembrolizumab in the eligible PD-L1 positive population. We assumed that uptake would be high for nivolumab because it does not require PD-L1 testing, and intermediate for atezolizumab and pembrolizumab because of the need for PD-L1 testing in second-line NSCLC patients. This is in line with recent market share information for nivolumab and pembrolizumab.[93,94] For the eligible population of second-line NSCLC patients whose tumors do not express PD-L1, we assumed a 75% uptake pattern for nivolumab. We assumed that uptake would be very high in this population because of the lack of other effective treatment alternatives.

Using this approach to estimate potential budget impact, we then compared our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation, this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA each year, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 23.

For 2015-16, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability is calculated to total approximately $904 million per year for new drugs.

Table 23. Calculation of potential budget impact threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2015-2016 (est.) +1%	3.75%	World Bank, 2015
2	Total health care spending ($)	$3.08 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	13.3%	CMS National Health Expenditures (NHE), Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$410 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.4 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	34	FDA, 2014
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$452 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$904 million	Calculation

Potential Budget Impact Model: Results

Table 24 below presents the potential budget impact of one year and five years of utilization of each drug in the candidate population, assuming the uptake patterns previously described. Results are presented for both one-year and five-year time horizons.

Results from the potential budget impact model showed that in the first year, with the uptake pattern assumptions mentioned above, atezolizumab and pembrolizumab would each be given to an estimated 2,970 individuals, and nivolumab to approximately 11,880 (5,940 each from the PD-L1 positive and negative populations). Over the entire five-year time horizon, we estimate that "unmanaged" uptake would lead to approximately 14,850 persons receiving atezolizumab, 14,850

receiving pembrolizumab, and 59,400 receiving nivolumab for one or more years (29,700 for PD-L1 positive, and 29,700 for PD-L1 negative).

After one year of treatment, net annual costs ranged from $39,900 per patient for atezolizumab to $72,200 per patient for pembrolizumab. One-year budget impact is estimated to be $118.4 million for atezolizumab, $214.3 million for pembrolizumab, and $528.9 million for nivolumab. Total budget impact for nivolumab is much higher due to the larger number of patients assumed to receive nivolumab.

Across the full five-year time horizon, the weighted potential budgetary impact (i.e., adjusted for differing periods of drug utilization and associated cost-offsets) ranges from approximately $77,800 per patient receiving atezolizumab to $144,800 per patient receiving pembrolizumab. Average budget impact per year is estimated as approximately $230.8 million for atezolizumab, $429.8 million for pembrolizumab, and $987.8 million for nivolumab. This annualized potential budget impact is 26% of the budget impact threshold of $904 million for atezolizumab, 48% of the threshold for pembrolizumab, and 109% of the threshold for nivolumab.

Table 24. Estimated total potential budget impact (BI) of PD-1 immunotherapy

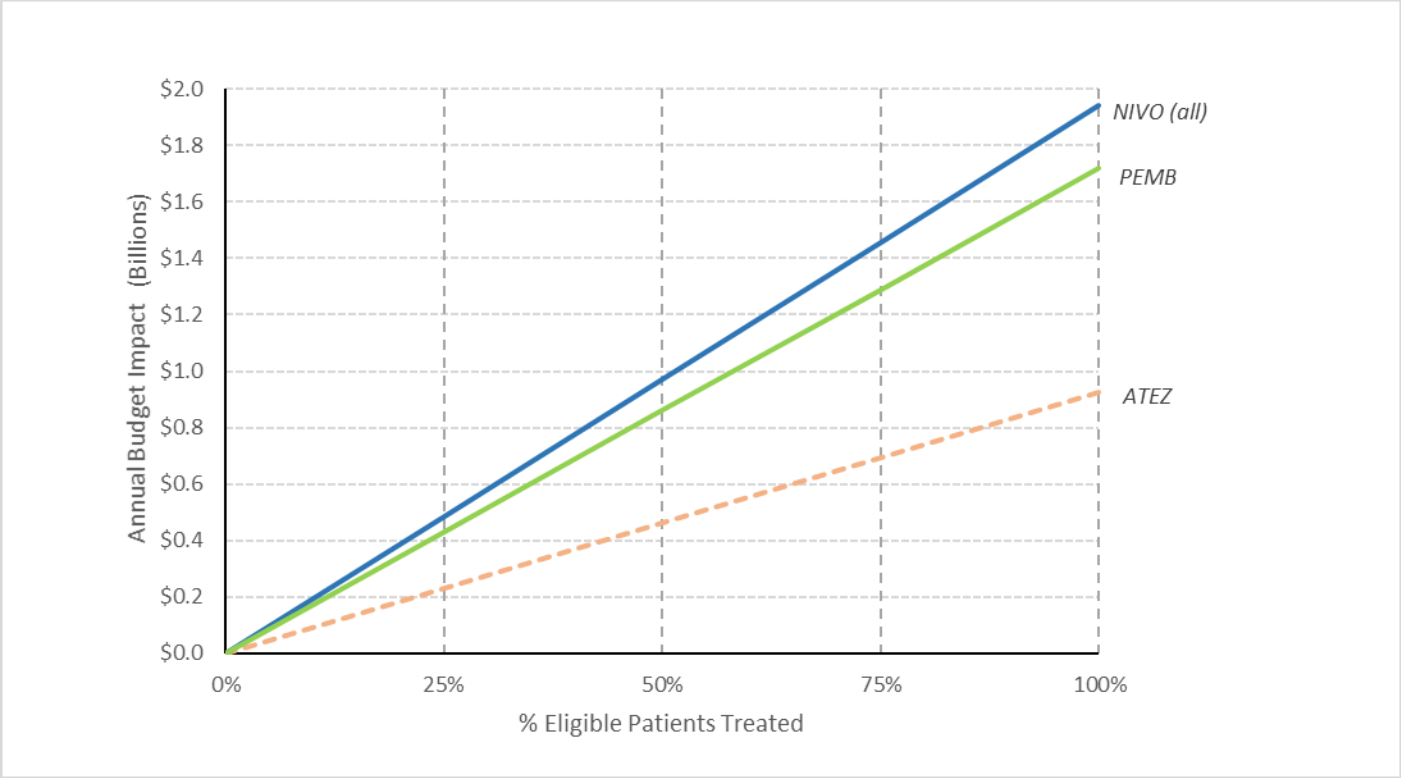
		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
	Eligible Population	Number Treated	Annual BI per Patient*	Total BI (millions)	Number Treated	Weighted BI per Patient*	Average BI per year (millions)
Atezolizumab	59,400	2,970	$39,900	$118.4	14,850	$77,800	$230.8
Pembrolizumab	59,400	2,970	$72,200	$214.3	14,850	$144,800	$429.8
Nivolumab†	99,000	11,880	$44,500	$528.9	59,400	$83,200	$987.8

Figure 14 shows the relationship between varying possible uptake patterns and potential budget impact for each drug. The vertical axis shows the annualized potential budget impact, and the horizontal axis represents the percentage of eligible patients treated over a five-year period. The colored lines demonstrate how quickly the annual potential budget impact increases with increasing percentages of patients treated at the list prices used in this analysis.

As can be seen in Figure 14, potential budget impact of atezolizumab is estimated to be below an annual threshold of $904 million until approximately 98% of eligible patients are treated. Approximately 53% of eligible patients could be treated with pembrolizumab before potential budget impact reached $904 million. The annualized potential budget impact for nivolumab at list

price would rise to $904 million if approximately 47% of eligible patients (regardless of PD-L1 status) are treated.

Figure 14. Potential budget impact of PD-1 immunotherapy treatments for NSCLC patients over different assumed product uptake patterns



Note: Colored lines represent the annualized budget impact of different uptake patterns (eligible patients treated) at the list price of each drug.

6.5 Value-based Benchmark Prices

[After the publication of the Evidence Report, the FDA approved atezolizumab with a broader indication than was assumed in these analyses. The evidence for this approval is discussed briefly in the Supplement starting on page 102. This report's modeling and conclusions related to the long-term value for money of atezolizumab should only be applied to the narrower subpopulation that was analyzed. Additionally, after the meeting of the Midwest CEPAC, the FDA expanded the indication of pembrolizumab to a broader second-line population.]

Our value-based benchmark prices for each PD-1 immunotherapy treatment are provided in Table 25. The ICER value-based price benchmark for a drug is comprised of two components: 1) the price

range that would align with reasonable long-term cost-effectiveness levels between $100,000–$150,000 per additional QALY; and, 2) if relevant, another price beyond which the potential short-term budget impact would exceed a target for health care affordability ($904 million per year over 5 years), a threshold at which policymakers may need to consider special measures to manage short-term affordability, even for drugs that are priced in alignment with their long-term added value for patients. In this case, one of the evaluated drugs, nivolumab, is projected to exceed that budget impact threshold under base case assumptions; however, the discounts required to achieve $100,000 and $150,000 per QALY gained would bring the potential budget impact below that threshold. As noted previously, the potential budget impacts of atezolizumab and pembrolizumab do not exceed our stated threshold when annualized over a five-year time horizon. The price of each drug that could be charged and not exceed the $904 million annual benchmark is higher than the price range that would achieve $100,000 to $150,000 per QALY gained.

Therefore, the ICER value-based price benchmark for atezolizumab, with all the assumptions mentioned previously regarding five-year uptake patterns and net costs, is $4,026 to $5,954 per 1200 mg vial. This price represents a 31%-53% discount from the WAC list price of atezolizumab. The ICER value-based price benchmark for pembrolizumab is $1,719 to $2,694 per 100 mg vial, representing a 39%-61% discount from the WAC list price. The ICER value-based price benchmark for nivolumab (all comers) is $799 to $1,064 per 100 mg vial, representing a 57%-68% discount from the WAC list price.

Table 25. Value-based price benchmarks for PD-1 immunotherapy treatments for NSCLC patients under assumed product uptake patterns

	WAC Price per Vial	Cost to Achieve $100K/QALY	Cost to Achieve $150K/QALY	Value-Based Price Benchmark
Atezolizumab	$8,620	$4,026	$5,954	$4,026 to $5,954
Pembrolizumab	$4,381	$1,719	$2,694	$1,719 to $2,694
Nivolumab*	$2,470†	$799	$1,064	$799 to $1,064

*Includes PD-L1 positive and negative patients
†100 mg vial

Because we made the assumption of an 8.9-month gain in median survival across all of the first-line TKI regimens, and because we did not find adequate evidence to distinguish among these agents, we did not calculate a separate value-based price benchmark for each of these drugs. Instead, we calculated the average of the percentage discounts (or premiums) that would need to be applied to each drug to bring its estimated cost-effectiveness to $100,000 or $150,000 per QALY gained. The average discount to achieve $100,000/QALY would be approximately 21%. Because the base case cost-effectiveness estimates were less than $150,000/QALY for each TKI treatment, a premium could be added to each drug's price to achieve $150,000/QALY; the average of these would

represent an approximately 15% increase in price. Applying these percentages to the average price per tablet across the three TKI treatments, $239, results in a value-based price benchmark range from $189 to $274.

6.6 Summary and Comment

[After the publication of the Evidence Report, the FDA approved atezolizumab with a broader indication than was assumed in these analyses. The evidence for this approval is discussed briefly in the Supplement starting on page 102. This report's modeling and conclusions related to the long-term value for money of atezolizumab should only be applied to the narrower subpopulation that was analyzed. Additionally, after the meeting of the Midwest CEPAC, the FDA expanded the indication of pembrolizumab to a broader second-line population.]

The primary aim of this analysis was to estimate the cost-effectiveness of treating NSCLC patients with first-line TKIs versus a chemotherapy doublet (cisplatin+pemetrexed) for EGFR+ patients (population 1), and second-line treatment with PD-1 immunotherapy versus docetaxel among patients who have progressed on a first-line chemotherapy doublet (population 3). For first-line treatment using TKIs targeted at an EGFR mutation, our primary analysis generated similar incremental cost-effectiveness ratios, ranging between approximately $110,000 and $150,000 per QALY gained, relative to comparator treatment with cisplatin+pemetrexed. These ratios are within commonly-cited thresholds for the cost-effectiveness of health interventions (i.e., $50,000-$150,000 per QALY gained), although both deterministic and probabilistic sensitivity analyses suggest some uncertainty in these findings. There is additional uncertainty created by our need to estimate OS benefits from observational data, given the effects of cross-overs in the randomized trials. Our results for second-line PD-1 immunotherapies were more uncertain. In base case analyses, cost-effectiveness ratios ranged from approximately $220,000/QALY for atezolizumab using TC 2/3 or IC 2/3, to approximaltey $240,000/QALY for pembrolizumab using PD-L1 >50%, to approximately $420,000 per QALY gained for nivolumab (all comers). However, findings for all analyses varied widely in both deterministic and probabilistic sensitivity analyses, as a result of wide confidence regions around key parameters such as PFS and OS HRs. These results should therefore be interpreted with great caution.

We also estimated the potential budget impact of each PD-1 immunotherapy treatment, assuming 25% uptake in the eligible PD-L1 positive population for atezolizumab and pembrolizumab; for nivolumab, we assumed 50% uptake in the eligible PD-L1 positive population and 75% uptake in the eligible population of second-line NSCLC patients whose tumors do not express PD-L1. With these assumptions, treatment of the larger population eligible for nivolumab would exceed the budget impact threshold of $904 million for a new drug; however, the discounts required to achieve $100,000 and $150,000 per QALY gained would bring the potential budget impact below that threshold. If we assume greater uptake rates, the potential budget impact for atezolizumab would approach an annual threshold of $904 million only at an assumed uptake of 98%. Uptake of

atezolizumab would need to approach 98% of its eligible population to exceed the $904 million annual threshold, while the potential budget impact of pembrolizumab would exceed the threshold at around 53% uptake.

We note several additional limitations of our analysis. The cost-effectiveness analysis was conducted from a health system perspective, and so does not incorporate costs and effects that might be relevant from a societal perspective, such as productivity, transportation, or caregiver costs. However, among the largest cost drivers in our model were the costs of the drugs themselves, and all patients were assumed to have a similar severity of disease. Any residual differences in transportation time or time in treatment would be unlikely to have materially affected our findings. We also assumed that there would be no vial sharing for any infused drug, in the absence of published and credible data on the frequency of this practice in NSCLC. If vial sharing does occur in actual practice for some patients, our analysis would overestimate drug costs for the affected regimens, although to a currently unknown extent.

In addition, our assumptions regarding treatment received after progression necessitated assumptions that do not reflect current clinical practice. For example, patients with NSCLC treated with chemotherapy typically receive maintenance therapy (e.g., pemetrexed), and many of those who progress on first-line TKI treatment now receive the TKI osimertinib as second-line therapy. However, most of the original trials of the TKIs were performed before these were standard options, and consideration of these regimens would require additional assumptions regarding survival after first-line progression in the absence of adequate data.

While our analysis included reported adverse events that occurred in at least 5% of patients for any regimen of interest, we did exclude adverse events that occurred in <5% of patients across all regimens, which may have ruled out certain rare but expensive events. However, given that drug costs represented the majority of total costs for any given regimen in our analysis, the effects of adding rare adverse events to our analysis would not be expected to materially change our findings.

Finally, the levels of regimen uptake in the marketplace by five years were based on reasoned assumptions regarding current market share and likely uptake, but actual uptake and market share may vary from these estimates. Additionally, costs for drugs already on the market (i.e., pembrolizumab) were not considered as part of the background treatment costs; rather, the potential budget impact analysis was performed from the perspective of replacing the comparator regimen with each of the PD-1 immunotherapies.

In summary, targeted regimens for first- and second-line use in NSCLC appears to confer clinical benefits in terms of lengthening progression-free and overall survival as well as improved quality of life. At current wholesale acquisition costs, the estimated cost-effectiveness of each of the TKIs appears to fall within commonly-accepted thresholds. While the cost-effectiveness of PD-1

immunotherapies exceeds these thresholds, there is greater uncertainty in these findings given variability in estimates of overall and progression-free survival.

7. Summary of the Votes and Considerations for Policy

7.1 About the Midwest CEPAC Process

During Midwest CEPAC public meetings, the Midwest CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of the medical technologies or treatments under examination, and the supplementary information presented. Panel members typically serve for two or more years and are intentionally selected to represent a range of expertise and diverse perspectives. To maintain the objectivity of the Midwest CEPAC Panel and ground the conversation in the interpretation of the published evidence, they are not pre-selected based on the topic being addressed. Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to Midwest CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Midwest CEPAC Panel during their deliberation, and they help form recommendations with the Midwest CEPAC Panel on ways the evidence can be applied to policy and practice.

At each meeting, after the Midwest CEPAC Panel votes, a policy roundtable discussion is held with the Midwest CEPAC Panel, clinical experts, and representatives from provider groups, payers, and patient groups. This is intended to bring stakeholders into the discussion on how best to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the October 20, 2016 meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, providers, and payers address the important questions related to the treatment of advanced non-small cell lung cancer. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, starting at 03:46:00), the Midwest CEPAC Panel voted on key questions concerning the comparative clinical effectiveness and comparative value of treatment options for advanced non-small cell lung cancer. These questions are developed by the ICER research team for each assessment, with input

from the Midwest CEPAC Advisory Board to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with comments reflecting considerations mentioned by Midwest CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the Midwest CEPAC Panel made use of a value assessment framework with four different components of long term value for money, a concept which represents the long-term perspective, at the individual patient level, on patient benefits and the incremental costs to achieve those benefits. The four components of long term value for money are comparative clinical effectiveness, incremental cost per outcomes achieved, other benefits or disadvantages, and contextual considerations regarding the illness or therapy.

Figure 15. Care Value Framework

There are four elements to consider when deliberating on long term value for money:

- ***Comparative clinical effectiveness*** is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.
- ***Incremental cost per outcomes achieved*** is the average per-patient incremental cost of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a ratio: a "cost per outcome achieved." Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of incremental costs per outcomes achieved, ICER follows common academic and World Health Organization (WHO) standards by using cost per quality-adjusted life years (QALYs) and adopting thresholds at $100,000 per QALY and $150,000 per QALY as guides to reasonable ratios of incremental costs per outcomes achieved.

- ***Other benefits or disadvantages*** refers to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of other benefits include mechanisms of treatment delivery that require many fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether other benefits or disadvantages such as these are important enough to factor into the overall judgment of care value. There is no quantitative measure for other benefits or disadvantages.
- ***Contextual considerations*** include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether the condition affects priority populations. There is no quantitative measure for the role of contextual considerations in an overall judgment of care value.

7.2 Voting Results

1. In patients with EGFR+ advanced NSCLC, is the evidence adequate to distinguish the net health benefit among the TKIs erlotinib, gefitinib, and afatinib?

Yes: 1 votes	***No: 9 votes***

2. In patients with EGFR+ advanced NSCLC, is the evidence adequate to demonstrate that the net health benefit of first-line treatment with a TKI is greater than that of treatment with a platinum doublet?

Yes: 10 votes	*No: 0 votes*

Comments: Members of the Midwest CEPAC commented that the lower burdens and harms of TKI therapy made its net health benefits clearly superior to chemotherapy.

3. Given the available evidence on net health benefit with TKI therapy, the additional cost of TKI therapy, and taking into account other benefits, disadvantages, and contextual considerations, what is the long-term value for money of TKI therapy?

Low: 0 votes	***Intermediate: 9 votes***	*High: 1 vote*

4. In patients with EGFR- advanced NSCLC who have progressed after treatment with a platinum doublet, is the evidence adequate to distinguish the net health benefit among the PD-1 immunotherapies nivolumab, pembrolizumab, and atezolizumab?

Yes: 0 votes	***No: 10 votes***

5. In patients with EGFR- advanced NSCLC who have progressed after treatment with a platinum doublet, is the evidence adequate to demonstrate that the net health benefit of treatment with each of the following PD-1 immunotherapies used for their actual or expected labeled indications is greater than that of treatment with docetaxel?

    a) Nivolumab (indicated for treatment irrespective of PD-L1 level)

Yes: 8 votes	*No: 2 votes*

    Comments: A member of the Midwest CEPAC who voted "no" felt that the evidence did not indicate an overwhelming benefit.

    b) Pembrolizumab (indicated for treatment for PD-L1 level ≥50%)*

Yes: 10 votes	*No: 0 votes*

    c) Atezolizumab (anticipated indication for treatment for PD-L1 test of TC 2/3 or IC 2/3)*

Yes: 8 votes	*No: 2 votes*

*****Atezolizumab was approved with a broader indication (no PD-L1 testing required) just prior to the meeting. As such, this question did not apply to the actual indication for atezolizumab and is not directly relevant to policy issues around atezolizumab. Midwest CEPAC members who voted "no"

indicated that their vote was a result of this fact. Additionally, after the meeting, the FDA expanded the indication of pembrolizumab to a broader second-line population.

6. Given the available evidence on net health benefit with PD-1 immunotherapy, the additional cost of PD-1 immunotherapy, and taking into account other benefits, disadvantages, and contextual considerations, in patients with EGFR- advanced NSCLC who have progressed after treatment with a platinum doublet, what is the long-term value for money of each of the following PD-1 immunotherapies used for its actual or anticipated labeled indications?

    a) Nivolumab (indicated for treatment irrespective of PD-L1 level)

Low: 6 votes	*Intermediate: 4 votes*	*High: 0 votes*

    b) Pembrolizumab (indicated for treatment for PD-L1 level ≥50%)*

Low: 3 votes	***Intermediate: 7 votes***	*High: 0 votes*

    c) Atezolizumab (anticipated indication for treatment for PD-L1 test of TC 2/3 or IC 2/3)*

Low: 4 votes	***Intermediate: 6 votes***	*High: 0 votes*

    Comments: Members of the Midwest CEPAC discussed the high costs of nivolumab relative to its benefits as explaining their "low" votes.

    A Midwest CEPAC council member noted that the ICER for pembrolizumab was above the $100-$150K range in explaining their "low" vote.

    *****Atezolizumab was approved with a broader indication (no PD-L1 testing required) just prior to the meeting. As such, this question did not apply to the actual indication for atezolizumab and is not directly relevant to policy issues around atezolizumab. Additionally, after the meeting, the FDA expanded the indication of pembrolizumab to a broader second-line population.

7. In patients with advanced NSCLC without a driver mutation who have not previously been treated for advanced disease, is the evidence adequate to demonstrate that the net health benefit of treatment with pembrolizumab in patients with a positive test for PD-L1 using the pembrolizumab assays is greater than that of treatment with a platinum doublet?

Yes: 10 votes	*No: 0 votes*

8. In patients with EGFR+ advanced NSCLC who have progressed after treatment with a platinum doublet, is the evidence adequate to demonstrate that the net health benefit of treatment with PD-1 immunotherapy is greater than that of treatment with docetaxel?

Yes: 2 votes	***No: 8 votes***

7.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion about the treatment options for relapsed or refractory multiple myeloma with a Policy Roundtable that included two clinical experts, two patient representatives, and a payer representative. The policy roundtable discussion with the Midwest CEPAC Panel reflected multiple perspectives and opinions, and therefore, none of the recommendations below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below.

Roundtable Participant	Association
James Jett, MD	Professor of Medicine, Division of Oncology, Cancer Center, National Jewish Health
Karen Loss	Lung Cancer Survivor
Jay Moore, MD	Senior Clinical Officer, Anthem Blue Cross Blue Shield
Jyoti Patel, MD	Professor of Medicine, Director of Thoracic Oncology, University of Chicago
Don Stranathan	Lung Cancer Survivor

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Patients, Clinicians, and Researchers

Take various steps to increase the number of patients enrolling in clinical trials and to enhance the role that patients play in identifying key outcome measures for future research

Given the rapid evolution of new therapies for NSCLC, patients and clinicians often lack information on comparative clinical effectiveness of different treatment options that is necessary to help them tailor care for the individual patient. It is therefore critically important that barriers to participation in clinical trials be reduced. Patient groups can help by encouraging patients to participate in clinical trials and by taking a leadership role in identifying key outcome measures that matter most to patients. Clinicians should encourage patients to consider participating in research, and should develop the practice infrastructure needed to make that participation as seamless as possible. Researchers should work directly with patient groups and clinicians to ensure that trial design and implementation present the lowest barriers possible to participation. Additionally, researchers

should continue to develop and administer registries to collect real-world evidence, and clinicians should ensure that information from their patients is included in such registries.

Patients and Patient Advocacy Groups

Seek action by manufacturers, insurers, and policymakers to address the affordability of treatments for lung cancer.

New therapies for advanced NSCLC are dramatically changing the prognosis of the disease. These therapies are very expensive and it is anticipated that future management will involve combination treatments with these agents. Patients are experiencing financial toxicity, and patient groups should use their influence with all parties to move pricing and coverage decisions to improve affordability.

Purchasers and Insurers

In conjunction with a movement toward a more value-based pricing system, purchasers and insurers should design insurance plans that protect patients from significant financial toxicity.

Patients are at times forgoing effective therapies for advanced NSCLC, and instead choosing options such as hospice, not based on treatment preferences but out of concern for the financial burdens that such therapies will create for their families. If prices for therapies are brought into alignment with added value for patients, insurers should develop coverage mechanisms that allow access to these therapies without undue financial burdens.

Similar mechanisms of action and the lack of evidence to distinguish whether TKI drugs differ in their risks and benefits suggests that these drugs might be considered for step therapy in insurance coverage, but justification of step therapy for these and other cancer drugs faces a high burden given that even minor differences among treatments may have important clinical consequences for individual patients.

The three TKIs used for first-line treatment of EGFR+ advanced NSCLC have similar mechanisms of action, similar side effect profiles, and produce similar outcomes. This therefore represents an area where step therapy and/or tiering patient out-of-pocket payments could be considered. However, there remain concerns that even minor differences in drug profiles could be important for individual patients, making use of strong formulary management policies challenging. Consideration of step therapy, in particular, should only be done in close consultation with clinical

experts and input from patients. In addition, if any policies of this nature are considered, they must provide safeguards that allow clinicians and patients to exercise reasonable clinical judgment by allowing them to choose non-preferred options without substantial administrative or financial burdens.

Incentives for clinicians that encourage the use of high-value care options are reasonable if applied to clinically equivalent options. Efforts should be taken to share the benefits of more cost-effective care options with patients by reducing their financial burden.

When clinicians are incentivized to follow more cost-effective pathways, the choice of treatments on those pathways should also include benefits to patients, such as reduced co-payments. It is important to make it clear to patients that incentives are not creating barriers to individualized patient-clinician decision making where appropriate.

Genetic testing of lung cancer tumors is standard practice, and CMS should revisit its current payment criteria for tumor testing to avoid delaying the receipt of actionable information.

Biopsy of lung cancer is frequently performed in the hospital setting. As up-front testing expands and has become more expensive, some centers receiving bundled payments are avoiding the costs of such testing by delaying sending material for testing until two weeks after patient discharge from the hospital. This does not decrease total costs of care, but potentially delays the receipt of information central to clinical decision making. Payment mechanisms that do not encourage such delays should be evaluated.

Insurers and Manufacturers

PD-1 immunotherapy may be an appropriate area for considering innovative outcomes-based payment mechanisms, particularly in the treatment of patients who are not tested for PD-L1 levels.

Given the current list prices for PD-1 immunotherapy options, even significant discounts are unlikely to bring the long-term value for money of these treatments into a reasonable range. In addition, only a minority of patients respond to treatment. The proportion of patients responding is even lower when treatment is not based on tumor PD-L1 levels. Thus, PD-1 immunotherapy is an area where manufacturers and insurers could reasonably explore innovative payment mechanisms linked to the outcomes of individual patients. For example, refunds or significant rebates could be given when patients do not benefit from treatment. This kind of payment mechanism could remove disincentives for attempting a trial of therapy in patients with a lower likelihood of response, but who might see important clinical benefits if they were in the minority of patients who do respond.

Insurers and Clinicians

First-line PD-L1 testing may be needed to guide appropriate care for all patients

With recent evidence demonstrating benefits of first-line treatment with PD-1 immunotherapy in patients with PD-L1 positive advanced NSCLC, clinicians should consider evaluating PD-L1 status as part of the initial tests performed on the tumor. Insurers will want to have coverage that mirrors accepted clinical practice. More generally, insurers will want to consider coverage for testing when the results provide patients and clinicians with actionable information for treatment or significantly improved prognostic information.

Manufacturers and Researchers

Develop studies to allow populations and subpopulations to be compared across different PD-1 immunotherapies

Currently manufacturers are using different tests for PD-L1, and this interferes with the ability of clinicians and guideline developers to compare results across agents. Manufacturers and researchers should work to standardize testing, both with existing markers such as PD-L1 and with new markers as they are developed.

Clinicians

Caution should be exercised in using PD-1 immunotherapy in patients with EGFR+ advanced NSCLC

Limited evidence suggests that in patients with EGFR+ tumors who have progressed on TKI therapy, PD-1 immunotherapy is not superior to chemotherapy and may be inferior. For most such patients, consideration should be given to only administering PD-1 immunotherapy within the context of a clinical trial.

This is the first Midwest CEPAC review of treatment options for non-small cell lung cancer.

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Supplement

In this Supplement, we discuss important new evidence regarding population P2 (first-line use of PD-1 immunotherapy), and briefly discuss an additional trial regarding population P3 (second-line use of PD-1 immunotherapy).

First-Line PD-1 Immunotherapy

At the time of the posting of the Evidence Report the only information on two randomized trials of first-line PD-1 immunotherapy in patients with advanced NSCLC was limited to general information in press releases. On October 9, 2016, one of those trials, Keynote 024, was published online.[95] Information regarding the other trial, CheckMate 026, was presented at a meeting of the European Society of Medical Oncology (ESMO) on the same date.[96,97] Below we evaluate the results of Keynote 024 and the available information on CheckMate 026 for first-line PD-1 immunotherapy in patients with advanced NSCLC.

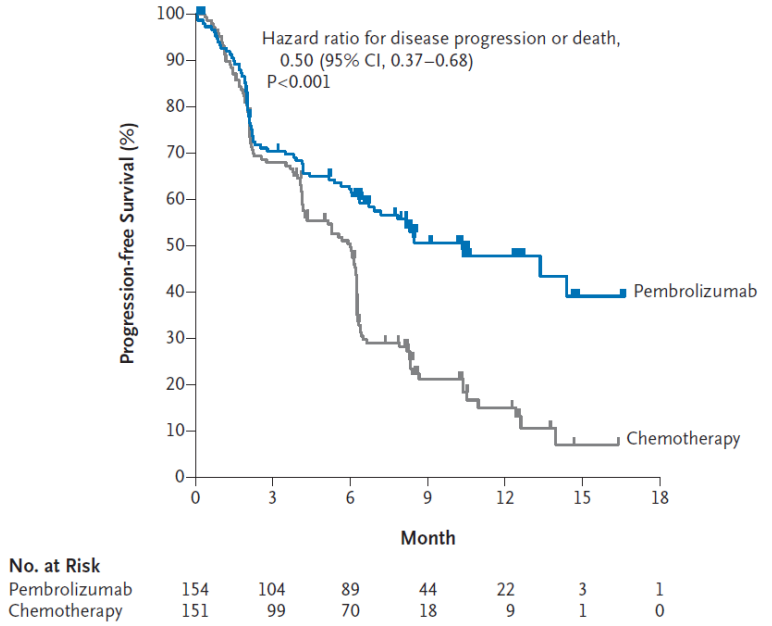
Keynote 024 was an open label trial in patients with previously untreated advanced NSCLC that demonstrated ≥50% PD-L1 expression and no EGFR driver mutation or ALK translocation. Patients were randomly assigned to treatment with pembrolizumab 200 mg every three weeks or a platinum-based chemotherapy doublet. This fixed dose of pembrolizumab is in contrast with the weight-based dosing used in the second-line trial of pembrolizumab, Keynote 010. For patients randomized to chemotherapy, investigators could choose from five chemotherapy regimens for non-squamous NSCLC, and among three of these regimens (not containing pemetrexed) for squamous NSCLC; patients who received pemetrexed as part of the doublet could continue on pemetrexed maintenance therapy, and the most common regimen was carboplatin plus pemetrexed. Patients who progressed on chemotherapy could cross over to treatment with pembrolizumab.

The primary outcome of Keynote 024 was progression-free survival (PFS), and the trial was stopped early for benefit at a median duration of follow-up of 11.2 months (see Table S1). PFS was longer in patients treated with pembrolizumab than chemotherapy (10.3 versus 6 months; HR 0.50, 95% CI 0.37-0.68) (see Figure S1). As was seen with second-line PD-1 immunotherapy (and discussed in the full report), the survival curves for PFS for pembrolizumab and chemotherapy do not appear to have similar shapes to each other, and so the HR and median survival estimates may not fully describe the PFS results. Overall survival (OS) was also longer with pembrolizumab (HR 0.60, 95% CI 0.41-0.89), although median survival was not reached in either group (half of patients were still alive at the time of analysis) (see Figure S2). The objective response rate was higher with pembrolizumab (44.8% versus 27.8%), and the median duration of response was not reached with pembrolizumab (versus a 6.3 month median duration of response with chemotherapy)

Table S1. Summary Evidence Table

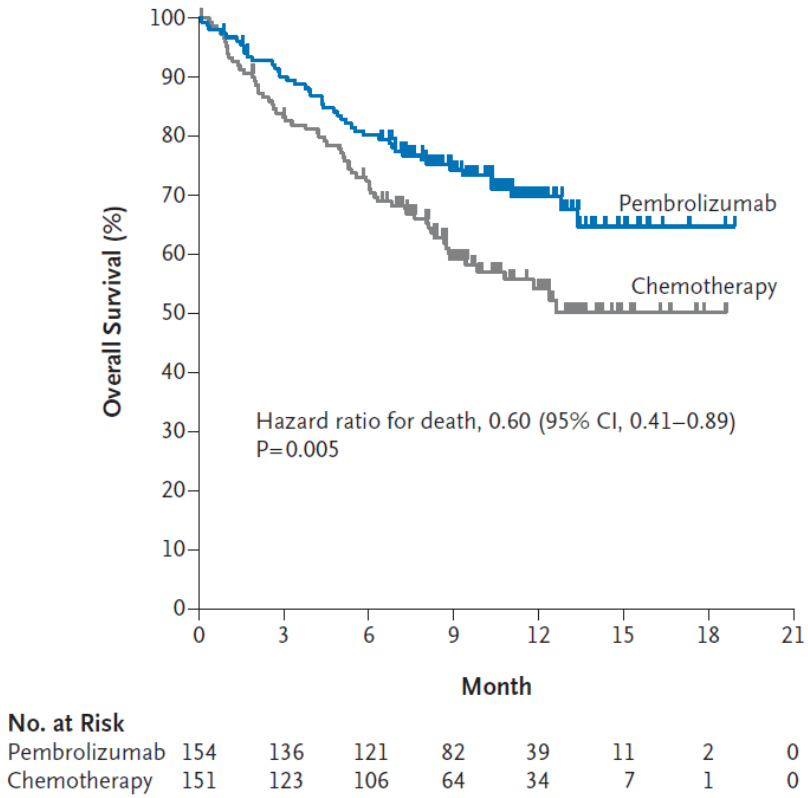
Author & Year of Publication (Trial) Quality rating	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Reck M** **NEJM 2016** **(Keynote 024)** **Good**	RCT Multicenter Open-label Phase III Early data cutoff median follow-up: 11.2 m Location 142 sites in 16 countries	1) pembrolizumab (n=154) 2) investigator's choice of platinum-based chemotherapy doublet (n=151) followed by optional pemetrexed as maintenance therapy in non-squamous patients Dosing schedule 1) Pembrolizumab 200 mg/3 weeks up to 35 cycles 2)Paclitaxel 200 mg/m2 + carboplatin AUC 5 or 6 followed by optional pemetrexed 500 mg/m2 Q3W OR pemetrexed 500 mg/m2 + carboplatin AUC 5 or 6 followed by optional pemetrexed 500 mg/m2 Q3W (non-squamous only) OR pemetrexed 500 mg/m2 + cisplatin 75 mg/m2 followed by optional pemetrexed 500 mg/m2 Q3W (non-squamous only) OR gemcitabine 1250 mg/m2 on day 1 and 8+ carboplatin AUC 5 or 6 OR gemcitabine 1250 mg/m2 on day 1 and 8+ cisplatin 75 mg/m2 once every 21 days for 4 to 6 cycles	Treatment-naive advanced NSCLC; without EGFR or ALK mutation; ≥50% PD-L1 expression; ECOG PS 0-1; adequate end-organ function; measurable disease (RECIST vs. 1.1)	Age, median (range) 1) 64.5 (33-90) 2) 66.0 (38-85) Male, n (%) 1) 92 (59.7) 2) 95 (62.9) East Asian, n (%) 1) 21 (13.6) 2) 19 (12.6) ECOG PS=1, n (%) 1) 99 (64.3) 2) 98 (64.9) Non-squamous, n (%) 1) 125 (81.2) 2) 124 (82.1) Smoker (never), n (%) 1) 5 (3.2) 2) 19 (12.6)	Median PFS, m 1) 10.3 2) 6.0 HR=0.50 95% CI 0.37-0.68 p<0.001 OS at 6 m, % 1) 80.2 1) 72.4 HR=0.60 95% CI 0.41-0.89 p=0.005 (median OS not reached) ORR, n (%) 1) 69 (44.8) 2) 42 (27.8)	Any treatment related SAE, any grade n (%) 1) 33 (21.4) 2) 31 (20.7) Any treatment related AE, grade 3-5, n (%) 1) 41 (26.6) 2) 80 (53.3) Any treatment related SAE, grade 3-5, n (%) 1) 29 (18.8) 2) 29 (19.3) Treatment related anemia, grade 3-5, n (%) 1) 3 (1.9) 2) 29 (19.3) Treatment related neutropenia, grade 3-5, n (%)1) 0 2) 20 (13.3) Treatment related decreased platelet count, grade 3-5, n (%) 1) 0 2) 9 (6.0) Treatment related thrombocytopenia, grade 3-5, n (%) 1) 0 2) 8 (5.3) Any immune-mediated AE, grade 3-5, n (%) 1) 15 (9.7) 2) 1 (0.7) Treatment-related death, n (%) 1) 1 (0.6) 2) 3 (2.0) Discontinuation d/t treatment related AEs, grade 3-5, n (%) 1) 8 (5.2) 2) 9 (6.0)

Figure S1. Progression-free survival in Keynote 024



Source: Reck M, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016

Figure S2. Overall survival in Keynote 024



Source: Reck M, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016

Fewer patients treated with pembrolizumab than chemotherapy had grade 3-5 treatment-related adverse events (AEs) (26.6% versus 53.3%), however the rates of serious AEs were similar (21.4% versus 20.7%); this difference between severe and serious AEs with chemotherapy reflects high rates of severe hematologic toxicity that was not considered serious. Lower-grade AEs that were much more common with chemotherapy included nausea, vomiting, decreased appetite, and fatigue. Immune-related AEs occurred in many more patients treated with pembrolizumab (29.2% versus 4.7%), as did severe immune-related AEs (9.7% versus 0.7%); these latter included severe skin reactions, pneumonitis, and colitis.

The results of Keynote 024 show large benefits on PFS and OS with first-line pembrolizumab versus chemotherapy with a platinum doublet. The trial has several limitations. As with other trials of PD-1 immunotherapy for NSCLC, few patients were followed past one year, leading to substantial uncertainty about the duration of benefit with pembrolizumab. The trial was stopped early for benefit in PFS and OS, which can exaggerate the apparent PFS and OS benefits.[98] The trial allowed patients to cross over from chemotherapy to pembrolizumab which may have reduced the apparent OS benefit (as was noted for TKI therapies in the full report).

In the larger context of clinical trials of first-line PD-1 immunotherapy, CheckMate 026 reported results with first-line nivolumab in patients with advanced NSCLC and PD-L1 ≥1% at ESMO.[96,97] The primary outcome of this trial was PFS in patients with PD-L1 ≥5%. In these patients, compared with a platinum doublet, the reported results show no benefit on PFS (4.2 months versus 5.9 months; HR 1.15, 95% CI 0.91-1.45) or on OS (14.4 months versus 13.2 months; HR 1.02, 95% CI 0.80-1.30). In patients with PD-L1 ≥50%, there was also no benefit on PFS (HR 1.07) or OS (HR 0.90). These results are markedly inferior to those seen in Keynote 024 and may reflect differences in the patient population (such as the different levels and assays of PD-L1 activity) or differences between the agents.

As such, the benefit of first-line PD-1 immunotherapy has not been demonstrated as a class. Given the limited time-frame available for review of the evidence from Keynote 024, we have not attempted to perform an economic analysis of pembrolizumab as first-line PD-1 immunotherapy for this Supplement.

We have high certainty that first-line pembrolizumab provides at least a small health benefit ("B+") relative to platinum chemotherapy. This reflects high certainty that first-line treatment with pembrolizumab is better tolerated than platinum chemotherapy and provides at least some benefit for OS, and moderate certainty that pembrolizumab provides a substantial OS benefit.

Second-Line PD-1 Immunotherapy

The Phase III Oak trial of atezolizumab in the second-line setting was presented at ESMO on October 9, 2016.[99] The results of Oak were broadly similar to those of the Phase II Poplar trial of atezolizumab already discussed in the Evidence Report. However, in contrast to Poplar, Oak found a benefit with atezolizumab in PD-L1 negative patients. As in other trials of PD-1 immunotherapy, patients were more likely to respond with higher levels of PD-L1. Subgroup analyses of OS results from Oak that are relevant to issues addressed in the Evidence Report include identical hazard ratios in squamous and non-squamous histologies, and a trend toward harm in EGFR+ patients. These results are consistent with our findings in the Report.

Supplement References

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APPENDICES

Appendix A. Evidence Review Methods

Table A1. PRISMA 2009 Checklist

TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.

RESULTS (continued)		
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table A2. Search strategy of Ovid Medline on June 8, 2016

1	Erlotinib.ti,ab
2	Gefitinib.ti,ab
3	Afatinib.ti,ab
4	Nivolumab.ti,ab
5	Pembrolizumab.ti,ab
6	Atezolizumab.ti,ab
7	1 or 2 or 3 or 4 or 5 or 6
8	randomized controlled trial.pt.
9	controlled clinical trial.pt.
10	randomized.ab.
11	placebo.ab.
12	drug therapy.fs.
13	randomly.ab.
14	trial.ab.
15	groups.ab.
16	observational study.pt.
17	exp case-control studies/
18	exp cohort studies/
19	exp cross-over studies/
20	exp matched-pair analysis/
21	multicenter study.pt.
22	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
23	16 or 17 or 18 or 19 or 20 or 21
24	comparative study.pt. or compare.ab,ti. or compares.ab,ti. or compared.ab,ti. or comparing.ab,ti. or comparison.ab,ti. or comparison.ab,ti. or comparative.ab,ti. or effective.ab,ti. or effectiveness.ab,ti. or versus.ab,ti. or vs.ab,ti.
25	23 and 24
26	22 or 25
27	exp carcinoma, non-small-cell lung/
28	(lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.
29	nsclc.ti,ab.
30	27 or 28 or 29
31	7 and 26 and 30
32	exp animals/
33	humans.sh.
34	32 not 33
35	31 not 34
36	limit 35 to english language
37	(case reports or comment or congresses or editorial or letter or review).pt
38	36 not 37

Table A3. Search strategy of Cochrane Central Register of Controlled Trials on June 8, 2016

1	Erlotinib.ti,ab
2	Gefitinib.ti,ab
3	Afatinib.ti,ab
4	Nivolumab.ti,ab
5	Pembrolizumab.ti,ab
6	Atezolizumab.ti,ab
7	1 or 2 or 3 or 4 or 5 or 6
8	exp carcinoma, non-small-cell lung/
9	(lung and (cancer$ or carcin$ or neoplasm$ or tumour$ or tumor$) and ((non-small or nonsmall) and cell)).ti,ab.
10	nsclc.ti,ab.
11	8 or 9 or 10
12	exp animals/
13	humans.sh.
14	12 not 13
15	7 and 11
16	15 not 14
17	Limit 16 to English language

Table A4. Search strategy of Embase on June 8, 2016

49	#48 NOT [medline]/lim
48	4 AND 46 AND 47
47	5 OR 6 OR 7 OR 8 OR 9 OR 10
46	23 OR 45
45	35 AND 44
44	36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43
43	'vs.':ab
42	'vs.':ti
41	'versus':ab
40	'versus':ti
39	'effective*':ab
38	'effective*':ti
37	'compar*':ab
36	'compar*':ti
35	24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34
34	'cross-over study'/de OR 'cross-over study'
33	'matched-pair analysis'/de OR 'matched-pair analysis'
32	'case* and control*':ab
31	'case* and control*':ti
30	'cohort*':ab
29	'cohort*':ti
28	'case control study'/de OR 'case control study'
27	'follow-up'/de OR 'follow-up'
26	'prospective study'/de OR 'prospective study'
25	'longitudinal study'/de OR 'longitudinal study'
24	'cohort analysis'/de OR 'cohort analysis'
23	22 AND 13
22	21 NOT (18 OR 20)
21	11 OR 12
20	19 NOT 14
19	16 OR 17
18	15 NOT 14
17	'random sampl*':ti OR 'random digit*':ti OR 'random effect*':ti OR 'random survey':ti OR 'random regression':ab
16	'random sampl*':ti OR 'random digit*':ti OR 'random effect*':ti OR 'random survey':ti OR 'random regression':ti
15	book:pt OR editorial:pt OR letter:pt OR review:pt
14	'randomized controlled trial'/de OR 'randomized controlled trial'
13	[humans]/lim
12	random*:ti OR placebo*:ti OR 'single blind*':ti OR 'double blind*':ti OR 'triple blind*':ab
11	random*:ti OR placebo*:ti OR 'single blind*':ti OR 'double blind*':ti OR 'triple blind*':ti
10	'atezolizumab':ti OR 'atezolizumab':ab
9	'pembrolizumab':ti OR 'pembrolizumab':ab
8	'nivolumab':ti OR 'nivolumab':ab
7	'afatinib':ti OR 'afatinib':ab
6	'gefitinib':ti OR 'gefitinib':ab
5	'erlotinib':ti OR 'erlotinib':ab
4	1 OR 2 OR 3
3	lung:ab AND (cancer*:ab OR carcin*:ab OR neoplasm*:ab OR tumour*:ab OR tumor*:ab) AND ('non small':ab OR nonsmall:ab) AND cell:ab
2	lung:ti AND (cancer*:ti OR carcin*:ti OR neoplasm*:ti OR tumour*:ti OR tumor*:ti) AND ('non small':ti OR nonsmall:ti) AND cell:ti
1	'non small cell lung carcinoma'/de

We performed screening at both the abstract and full-text level. Two investigators screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Two investigators reviewed full papers and provided justification for exclusion of each excluded study.

We used criteria modified slightly from those published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" as described below:[100,101]

Good: Meets all criteria: Comparable groups were assembled initially and maintained throughout the study; reliable and valid measurement instruments were used and applied equally to the groups; interventions were spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, for RCTs, at least modified intention to treat (mITT) analysis was done for RCTs.[102]

Fair: Studies were graded "fair" if any or all of the following problems occurred, without the fatal flaws noted in the "poor" category: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments were acceptable (although not the best) and generally applied equally; some but not all important outcomes were considered; and some but not all potential confounders were addressed.

Poor: Studies were graded "poor" if any of the following fatal flaws existed: Groups assembled initially were not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments were used or not applied equally among groups (including not masking outcome assessment); and key confounders were given little or no attention. For RCTs, intention to treat analysis was lacking.

Appendix B. PRISMA and Evidence Review Table

Figure B1. PRISMA flow Chart Showing Results of Literature Search for NSCLC

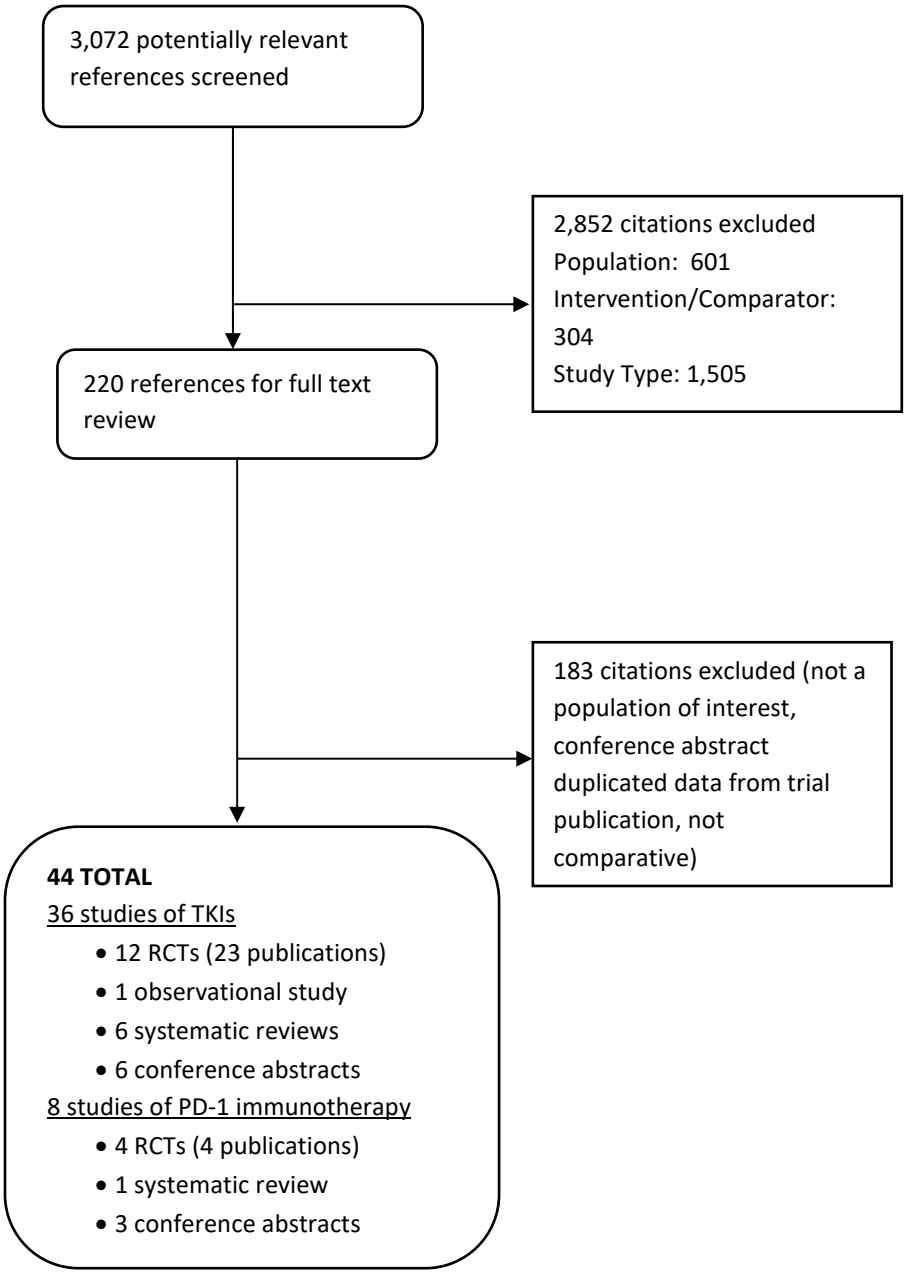


Table B1. Summary evidence table

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Sequist LV** **J Clin Oncol 2013** **(LUX-Lung 3)[40]** ***Fair***	RCT Multicenter Open-label Phase III Primary data cutoff median follow-up: 16.4 m <u>Location</u> 133 centers in 25 countries in Asia, Europe, North America, South America, and Australia	1) Afatinib (n=230) 2) Cisplatin + pemetrexed (n=115) <u>Dosing schedule</u> 1) 40 mg/day 2) 75 mg/m^2 + 500 mg/m^2 once every 21 days up to 6 cycles	Treatment-naive advanced lung adenocarcinoma; harboring EGFR mutation; ECOG PS 0-1; adequate end-organ function; measurable disease (RECIST vs. 1.1)	Age, median (range) 1) 61.5 (28-86) 2) 61.0 (31-83) Male, n (%) 1) 83 (36.1) 2) 38 (33.0) White, n (%) 1) 61 (26.5) 2) 30 (26.1) East Asian, n (%) 1) 165 (71.7) 2) 83 (72.2) ECOG PS=1, n (%) 1) 138 (60.0) 2) 73 (63.5) Stage IV, n (%) 1) 210 (91.3) 2) 98 (85.2) Smoker (never), n (%) 1) 155 (67.4) 2) 81 (70.4)	Median PFS, m 1) 11.14 2) 6.90 HR=0.58 95% CI 0.43-0.78 p<0.001 25th percentile OS, m (immature) 1) 16.6 1) 14.8 HR=1.12 95% CI 0.73-1.73 p=0.60 Time to deterioration for worsening of cough HR=0.60 95% CI 0.41-0.87 p=0.007 Dyspnea HR=0.68 95% CI 0.50-0.93 p=0.01 Pain NS	AEs ≥3, n (%) Diarrhea 1) 33 (14.4) 2) 0 Rash/acne 1) 37 (16.2) 2) 0 Stomatitis/mucositis 1) 20 (8.7) 2) 1 (0.9) Paronychia 1) 26 (11.4) 2) 0 Fatigue 1) 3 (1.3) 2) 14 (12.6) Treatment-related death 1) 4 2) 0 Discontinuation d/t AEs 1) 23 (10.0) 2) 17 (15.3)

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Yang JC-H** **J Clin Oncol 2013** **(LUX-Lung 3)[63]** ***Fair***	See Sequist LV J Clin Oncol 2013	See Sequist LV J Clin Oncol 2013 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 and Lung Cancer-13 questionnaires	See Sequist LV J Clin Oncol 2013	See Sequist LV J Clin Oncol 2013	QLQ-C30, mean treatment difference (95% CI) Global health status/QoL -3.18 (-5.75 to -0.61) p=0.015 Physical -4.80 (-7.47 to -2.13) p<0.001 Role -4.40 (-7.40 to -1.40) p=0.004 Emotional NS Cognitive -3.16 (-5.47 to -0.85) p=0.007 Social NR	

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Wu Y-L** **Lancet Oncol 2014** **(LUX-Lung 6)[42]** ***Fair***	RCT Multicenter Open-label Phase III Median follow-up (PFS): 16.6 m (IQR 4.7-9.4) <u>Location</u> 36 centers in China, Thailand, and South Korea	1) Afatinib (n=242) 2) Cisplatin + gemcitabine (n=122) <u>Dosing schedule</u> 1) 40 mg/day 2) 75 mg/m^2 on day 1 + 1000 mg/m^2 on day 1 and day 8, in a 3-week schedule for maximum of 6 cycles	EGFR mutation-positive, treatment-naïve, stage IIIB or IV lung adenocarcinoma; ECOG PS 0–1; measurable disease (RECIST vs. 1.1); adequate organ function	Age, median(range) 1) 58 (49-65) 2) 58 (49-62) Male, n (%) 1) 87 (36.0) 2) 39 (32.0) Asian, % 1) 100 2) 100 ECOG PS=1, n (%) 1) 194 (80.2) 2) 81 (66.4) Stage IV, n (%) 1) 226 (93.4) 2) 116 (95.1) Smoker (never), n (%) 1) 181 (74.8) 2) 99 (81.1) Uncommon EGFR mutation, n (%) 1) 26 (10.7) 2) 14 (11.5)	Median PFS, m (95% CI) 1) 11.0 (9.7-13.7) 2) 5.6 (5.1-6.7) HR=0.28 95% CI 0.20-0.39 p<0.0001 ORR, n (%) 1) 162 (66.9) 2) 28 (23.0) OR=7.28 95% CI 4.36-12.18 p<0.0001 Median OS, m (95% CI) (immature) 1) 22.1 (20.0-NE) 2) 22.2 (18.0-NE) HR =0.95 95% CI 0.68-1.33 p=0.76 Improvement in overall health status/QOL, n (%) 1) 143 (62.7) 2) 33 (32.7) p<0.0001	AEs ≥3, n (%) Diarrhea 1) 13 (5.4) 2) 0 Rash or acne 1) 35 (14.6) 2) 0 Stomatitis or mucositis 1) 13 (5.4) 2) 0 Vomiting 1) 2 (0.8) 2) 22 (19.5) Anemia 1) 1 (0.4) 2) 10 (9) Treatment-related death 1) 1 2) 1 Discontinuation d/t AEs 1) 21 (8.8) 2) 45 (39.8)

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Geater SL J Thorac Oncol 2015** **(LUX-Lung 6)[65]** ***Fair***	**See Wu Y-L Lancet Oncol 2014**	See Wu Y-L Lancet Oncol 2014 QLQ-C30	See Wu Y-L Lancet Oncol 2014	See Wu Y-L Lancet Oncol 2014	Significantly greater improvements with afatinib in global health status/QoL, physical functioning, role functioning, and social functioning Longer time to deterioration with afatinib vs. cisplatin/gemcitabine for cough, dyspnea, and pain, and all functioning scales and global health status/QoL Improvements in mean scores with afatinib vs. cisplatin/gemcitabine for cough, dyspnea, and pain. Better mean scores over time for all functioning scales, and global health status/QoL	See Wu Y-L Lancet Oncol 2014

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Yang J C-H Lancet Oncol 2015** **(LUX-Lung 3 and LUX-Lung 6)[41]** ***Fair***	See Sequist LV J Clin Oncol 2013 and Wu Y-L Lancet Oncol 2014 *Data cutoff* LUX-Lung 3: Nov 14, 2013 LUX-Lung 6: Dec 27, 2013 *Median follow-up* LUX-Lung 3: 41 m (IQR 35–44) LUX-Lung6: 33 m (IQR 31–37)	See Sequist LV J Clin Oncol 2013 and Wu Y-L Lancet Oncol 2014	See Sequist LV J Clin Oncol 2013 and Wu Y-L Lancet Oncol 2014	See Sequist LV J Clin Oncol 2013 and Wu Y-L Lancet Oncol 2014	Median OS, m LUX-Lung 3 1) 28.2 (24.6-33.6) 2) 28.2 (20.7-33.2) HR=0.88 95% CI 0.66-1.17 p=0.39 LUX-Lung 6 1) 23.1 (20.4-27.3) 2) 23.5 (18.0-25.6) HR=0.93 95% CI 0.72-1.22 p=0.61	See Sequist LV J Clin Oncol 2013 and Wu Y-L Lancet Oncol 2014

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Park K** **Lancet Oncol 2016** **(LUX-Lung 7)[10]** ***Good***	RCT Multicenter Open-label Phase IIb Median follow-up (PFS): 27.3 m <u>Location</u> 64 sites in Australia, Canada, China, France, Germany, Ireland, Norway, Republic of Korea, Singapore, Spain, Sweden, Taiwan, and United Kingdom	1) Afatinib (n=160) 2) Gefitinib (n=159) <u>Dosing schedule</u> 1) 40 mg/day 2) 250 mg/day	Age ≥18; common EGFR mutation; treatment-naïve; stage IIIB or IV lung adenocarcinoma; ECOG PS 0–1; measurable disease (RECIST vs. 1.1); adequate organ function	Age, median (range) 1) 63 (30-86) 2) 63 (32-89) Male, n (%) 1) 69 (43) 2) 53 (33) Asian, n (%) 1) 94 (59) 2) 88 (55) ECOG PS=1, n (%) 1) 109 (68) 2) 112 (70) Stage IV, n (%) 1) 152 (95) 2) 156 (98) Smoker (never), n (%) 1) 106 (66) 2) 106 (67) EGFR mutation, % L858R 42 Del19 58	Median PFS, m (95% CI) 1) 11.0 (10.6-12.9) 2) 10.9 (9.1-11.5) HR=0.73 95% CI 0.57-0.95 p=0.017 Median OS, m (95% CI) (immature) 1) 27.9 (25.1-32.2) 2) 25.0 (20.6-29.3) HR=0.87 95% CI 0.66-1.15 p=0.33 ORR, n (%) 1) 112 (70) 2) 89 (56) OR=1.87 95% CI 1.18-2.99 p=0.0083	AEs ≥3, n (%) Diarrhea 1) 20 (13) 2) 2 (1) Rash/acne 1) 15 (9) 2) 5 (3) Fatigue 1) 9 (6) 2) 0 Increased ALT/AST 1) 0 2) 14 (9) Treatment-related death 1) 0 2) 1 Discontinuation d/t AEs 1) 18 (11) 2) 17 (11)

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Mok TS** **N Engl J Med** **2009** **(IPASS)[38]** ***Fair***	RCT Multicenter Open-label Phase III Median follow-up (PFS): 5.6 m <u>Location</u> 87 centers in Hong Kong, elsewhere in China, Indonesia, Japan, Malaysia, the Philippines, Singapore, Taiwan, and Thailand	Overall study population 1) Gefitinib (n=609) 2) Carboplatin + paclitaxel (n=608) EGFR mutation, n (%) L858R 42 or Del19 58 1) 130 (98) 2) 121 (99) <u>Dosing schedule</u> 1) 250 mg/day 2) carboplatin at a dose calculated to produce an AUC of 5-6 mg/ml per min over 15-60 min + 200 mg/m^2 paclitaxel on day one, every 21 days up to 6 cycles	Age ≥18; stage IIIB or IV lung adenocarcinoma; nonsmokers (<100 cigarettes in lifetime) or former light smokers (stopped smoking ≥15 years previously and had total of ≤10 pack-years of smoking); no previous chemotherapy or biologic or immunologic therapy; ECOG PS 0-2; measurable disease (RECIST vs. 1.1); adequate hepatic function and neutrophil count	Overall study population Age, median (range) 1) 57 (24-84) 2) 57 (25-84) Stage IV, n (%) 1) 459 (75) 2) 463 (76) EGFR+ population Male, n (%) 1) 24 (18.2) 2) 26 (20.2) Asian, % 100 ECOG PS 0/1, n (%) 1) 119 (90.2) 2) 122 (94.6) Smoker (never), n (%) 1) 124 (93.9) 2) 122 (94.6)	PFS HR=0.48 95% CI 0.36-0.64 p<0.001 OS HR=0.78 95% CI 0.50-1.20 p=0.33 ORR, n (%) 1) 94 (71.2) 2) 61 (47.3) OR=2.75 95% CI 1.65-4.60 p<0.001 Sustained clinically relevant improvement, % [1] *Trial Outcome Index (sum of physical and functional wellbeing, and lung-cancer subscale)	Overall study population Discontinuation d/t AEs 1) 6.9% 2) 13.6%

[1]

	FACT-L	TOI*	LCS
1)	77	70	76
2)	45	38	54

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Fukuoka M** **J Clin Oncol 2011** **(IPASS)[43]** ***Fair***	See Mok TS N Engl J Med 2009 Median follow-up (OS): 17.0 m	See Mok TS N Engl J Med 2009	See Mok TS N Engl J Med 2009	See Mok TS N Engl J Med 2009	Median OS, m 1) 21.6 2) 21.9 HR=1.00 95% CI 0.76-1.33 p=0.99 Median PFS, m 1) 9.5 2) 6.3 HR=0.48 95% CI 0.36-0.64 p<0.001	See Mok TS N Engl J Med 2009

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Thongprasert S** **J Thorac Oncol 2011** **(IPASS)[103]** ***Fair***	See Mok TS N Engl J Med 2009	See Mok TS N Engl J Med 2009	See Mok TS N Engl J Med 2009	See Mok TS N Engl J Med 2009	Median Toxicity-free survival, m 1) 12.1 2) 0.5 HR=0.29 95% CI 0.21-0.39 p<0.001 Time to worsening in HrQoL, m (95% CI) FACT-L 1) 15.6 (11.0-NC) 2) 3.0 (1.5-5.3) TOI 1) 16.6 (11.1-NC) 2) 2.9 (1.5-7.0) LSC 1) 11.3 (11.0-NC) 2) 2.9 (2.1-6.9)	See Mok TS N Engl J Med 2009

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Maemondo M** **N Engl J Med 2010** **(NEJ002)[45]** ***Fair***	Multicenter Open-label Phase III Median follow-up: 527 days (>17 m) <u>Location</u> 43 institutions in Japan	1) Gefitinib (n=114) 2) Carboplatin + paclitaxel (n=114) <u>Dosing schedule</u> 1) 250 mg/day (until progression, intolerable toxicity, or withdrawal of consent) 2) carboplatin at a dose calculated to produce an AUC of 6 over 1 hr + 200 mg/m^2 paclitaxel over 3 hrs, on day 1 every 21 days, for at least 3 cycles	Presence of advanced non-small-cell lung cancer harboring sensitive EGFR mutations; absence of T790M; no history of chemotherapy; age ≤75	Age, mean (range) 1) 63.9 (43-75) 2) 62.6 (35-75) Male, n (%) 1) 42 (36.8) 2) 41 (36.0) Asian, % 100 ECOG PS=1, n (%) 1) 59 (51.8) 2) 55 (48.2) Stage IV, n (%) 1) 88 (77.2) 2) 84 (73.7) Smoker (never), n (%) 1) 75 (65.8) 2) 66 (57.9) L858R: 42.5% Del19: 51.3%	Median PFS, m (95% CI) 1) 10.8 2) 5.4 HR=0.30 95% CI 0.22-0.41 p<0.001 ORR, n (%) 1) 84 (73.7) 2) 35 (30.7) p<0.001 Median OS, m 1) 30.5 2) 23.6 p=0.31 2-year survival, % 1) 61.4 2) 46.7	AEs ≥3, n (%) Neuropathy 1) 0 2) 7 (6.2) Arthralgia 1) 1 (0.9) 2) 8 (7.1) AST/ALT elevation 1) 30 (26.3) 2) 1 (0.9) Neutropenia 1) 1 (0.9) 2) 74 (65.5) Anemia 1) 0 2) 6 (5.3)

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Oizumi S** **Oncologist 2012** **(NEJ002)[66]** ***Fair***	See Maemondo M N Engl J Med 2010	See Maemondo M N Engl J Med 2010 Deterioration: score change from baseline by one of 11 points (9.1%) in a direction indicating a worse QoL at any timepoint	See Maemondo M N Engl J Med 2010	See Maemondo M N Engl J Med 2010	Significant differences between treatment arms in deterioration of pain and shortness of breath (HR 0.34; 95% CI, 0.23– 0.50; p<0.0001) and daily functioning (HR 0.43; 95% CI, 0.28 – 0.65; p<0.0001); difference in anxiety between arms NS Gefitinib superior on physical well-being scale (p<0.0001), daily functioning (p=0.007), social functioning (p=0.035), and subjective QoL (p=0.042) .	See Maemondo M N Engl J Med 2010

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Inoue A** **Ann Oncol 2013** **(NEJ002)[44]** ***Fair***	See Maemondo M N Engl J Med 2010 Median follow-up: 704 days	See Maemondo M N Engl J Med 2010	See Maemondo M N Engl J Med 2010	See Maemondo M N Engl J Med 2010	Median OS, m Updated in Dec 2009 1) 27.7 2) 26.6 HR=0.887 95% CI 0.634-1.241 1-yr survival rate 1) 85.0% 2) 86.8% 2-yr survival rate 1) 57.9% 2) 53.7%	See Maemondo M N Engl J Med 2010

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Watanabe S** **J Thorac Oncol 2014** **(NEJ002)[104]** ***Fair***	See Maemondo M N Engl J Med 2010	See Maemondo M N Engl J Med 2010	See Maemondo M N Engl J Med 2010	See Maemondo M N Engl J Med 2010 Common EGFR mutation, n 1) 109 2) 106 Uncommon EGFR mutation, n 1) 5 2) 5	Common mutation Median OS, m 1) 29.3 2) 28.0 p=0.378 Median PFS, m 1) 11.4 2) 5.4 ORR, % 1) 76 2) 32 Uncommon mutation Median OS, m 1) 11.9 2) 22.8 p=0.102 Median PFS, m 1) 2.2 2) 5.9 ORR, % 1) 20 2) 20	See Maemondo M N Engl J Med 2010

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Mitsudomi T** **Lancet Oncol 2010** **(WJTOG3405)[46]** ***Fair***	Multicenter Open-label Phase III Median follow-up: 81 days (74-1253) <u>Location</u> 36 centers in Japan	1) Gefitinib (n=86) 2) Cisplatin + docetaxel (n=86) <u>Dosing schedule</u> 1) 250 mg/day 2) 80 mg/m^2 over 90 min + 60 mg/m^2 docetaxel over 1 hr, once every 21 days for 3-6 cycles	Advanced or recurrent NSCLC; harboring activating EGFR mutations; age ≤75; ECOG PS 0-1 measurable or non-measurable disease (RECIST); adequate organ function.	Age, median (range) 1) 64 (34-74) 2) 64 (41-75) Male, n (%) 1) 27 (31) 2) 26 (30) Asian, % 100 ECOG PS=1, n (%) 1) 30 (35) 2) 34 (40) Stage IV, n (%) 1) 41 (48) 2) 41 (48) Smoker (never), n (%) 1) 61 (71) 2) 57 (66) L858R 49 Del19 51	Median PFS, m (95% CI) 1) 9.2 (8.0-13.0) 2) 6.3 (5.8-7.8) HR=0.489 95% CI 0.336-0.710 p<0.0001 Median OS, m (95% CI) 1) 30.9 (24.1-NE) 2) Not reached (15.0-NE) HR=1.638 95% CI 0.749-3.582 p=0.211 ORR, n (%) 1) 36 (62.1) 2) 19 (32.2) P<0.0001	AEs ≥3, n (%) AST 1) 14 (16) 2) 1 (0.1) ALT 1) 24 (32) 2) 2 (0.2) Leukocytopenia 1) 0 2) 43 (49) Neutropenia 1) 0 2) 74 (19) Anemia 1) 0 2) 15 (17)

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Mitsudomi T** **J Clin Oncol 2012** **(WJTOG3405)[105]**	See Mitsudomi T Lancet Oncol 2010 Median follow-up: 34 m	See Mitsudomi T Lancet Oncol 2010	See Mitsudomi T Lancet Oncol 2010	See Mitsudomi T Lancet Oncol 2010	Median OS, m (95% CI) 1) 36 (26.3 -) 2) 39 (31.2 -) HR=1.185 95% CI 0.767-1.829	See Mitsudomi T Lancet Oncol 2010
Abstract **Yoshioka H** **J Clin Oncol 2014** **(WJTOG3405)[47]**	See Mitsudomi T Lancet Oncol 2010 Median follow-up: 59.1 m	See Mitsudomi T Lancet Oncol 2010	See Mitsudomi T Lancet Oncol 2010	See Mitsudomi T Lancet Oncol 2010	Median OS, m (95% CI) 1) 34.8 (26.0 -39.5) 2) 37.3 (31.2 -45.5) HR=1.252 95% CI 0.883-1.775	See Mitsudomi T Lancet Oncol 2010

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Han J-Y** **J Clin Oncol 2012** **(First-SIGNAL)[37]** ***Fair***	Multicenter Open-label Phase III Median follow-up: 34 m <u>Location</u> 3 major hospitals in Korea	Overall study population 1) Gefitinib (n=159) 2) Cisplatin + gemcitabine (n=150) EGFR+ 1) Gefitinib (n=26) 2) Cisplatin + gemcitabine (n=16) <u>Dosing schedule</u> 1) 250 mg/day 2) 80 mg/m^2 every 21 days + 1250 mg/m^2 paclitaxel on day 1 and 8 every 21 up to 9 cycles	Chemotherapy-naïve; never-smoker; age >18 years; stage IIIB or IV lung adenocarcinoma; measurable or nonmeasurable disease; ECOG PS 0-2; adequate bone marrow, liver, and renal function	Overall study population Age, median (range) 1) 57.0 (32-74) 2) 56.5 (19-74) Male, n (%) 1) 19 (12) 2) 16 (11) Asian, % 100 ECOG PS=1, n (%) 1) 104 (65) 2) 105 (70) Stage IV, n (%) 1) 142 (89) 2) 136 (91)	EGFR+ subgroup Median OS, m 1) 27.2 2) 25.6 HR=1.043 95% CI 0.498-2.182 PFS 1) 8.0 2) 6.3 HR=0.544 95% CI 0.269-1.100 p=0.086 ORR, n (%) 1) 22 (84.6) 2) 6 (37.5) p=0.002 QLQ-C30 NS LC13 NS	*NR for EGFR+* Overall study population AEs ≥3, n (%) Any 1) 46 (28.9) 2) 102 (68) Treatment-related death 1) 0 2) 1

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Poster presentation **Singh C** **J ImmunoTher Cancer 2014**[106]	RCT	1) Gefitinib (n=30) 2) Cisplatin + paclitaxel (n=30) <u>Dosing schedule</u> 1) 250 mg/day 2) NR	Metastatic non-small-cell lung cancer and EGFR mutations who had not previously received chemotherapy	NR	Median PFS, m 1) 10 2) 5 Median OS, m 1) 30 2) 24 ORR, % 1) 70 2) 30	NR

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Rosell R** **Lancet Oncol** **2012** **(EURTAC)[49]** ***Fair***	RCT Multicenter Open-label Phase III Median follow-up: 1) 18.9 m 2) 14.4 m	1) Erlotinib (n=86) 2) Cisplatin* + docetaxel or gemcitabine (n=87) <u>Dosing schedule</u> 1) 150 mg/day 2) 3 week cycles of 75 mg/m^2 + 75 mg/m^2 on day 1 or 75 mg/m^2 on day 1 + 1250 mg/m^2 on days 1 and 8 *Patients ineligible for cisplatin: carboplatin (3 wk cycles of AUC 6 on day 1 with 75 mg/m^2 docetaxel on day 1, or AUC 5 on day 1 with 1000 mg/m^2 gemcitabine on days 1 and 8)	Stage IIIb or IV NSCLC; measurable disease; activating EGFR mutations; age ≥18; no history of chemotherapy for metastatic disease	Age, median (range)1) 65 (24-82) 2) 65 (29-82) Female, n (%) 1) 58 (67) 2) 68 (78) ECOG PS=1, n (%) 1) 47 (55) 2) 45 (52) Stage IV, n (%) 1) 78 (91) 2) 82 (94) Never smoked, n (%) 1) 57 (66) 2) 63 (72) Adenocarcinoma, n (%) 1) 82 (95) 2) 78 (90)	Median OS, m (95% CI) 1) 19.3 (14.7-26.8) 1) 19.5 (16.1-NE) HR =1.04 95% CI 0.65-1.68 p=0.87 Median PFS, m (95% CI) 1) 9.7 (8.4-12.3) 2) 5.2 (4.5-5.8) HR=0.37 95% CI 0.25-0.54 p<0.0001 Rate of PFS at 1 yr, % (95% CI) 1) 40 (28-52) 2) 10 (4-20)	AEs ≥3, n (%) Fatigue 1) 5 (6) 2) 16 (20) p=0.0086 Rash 1) 11 (13) 2) 0 p=0.0007 Neutropenia, thrombocytopenia 1) 0, 0 2) 18 (22), 12 (15 p<0.0001, p=0.0003 Treatment-related death 1) 1 (1) 2) 2 (2) Discontinuation d/t AE 1) 11 (13) 2) 19 (23)

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Costa C** **Clin Cancer Res** **2014** **(EURTAC)[48]** ***Fair***	See Rosell R Lancet Oncol 2012 Updated results Median follow-up as of January 25, 2013 1) 40.7 m 2) 22.1 m Crossover permitted at time of progression; 80% of chemotherapy group received erlotinib	See Rosell R Lancet Oncol 2012 1) n=50 2) n=45	Subanalysis of 95 patients for whom pretreatment tumor specimens were available	Age <65, n (%) 1) 23 (46) 2) 21 (47) Female, n (%) 1) 34 (68) 2) 37 (82) ECOG PS=1, n (%) 1) 27 (54) 2) 24 (53) Stage IV, n (%) 1) 44 (88) 2) 43 (96) Never smoked, n (%) 1) 32 (64) 2) 32 (71) Adenocarcinoma, n (%) 1) 47 (94) 2) 40 (89) T790M mutation, n (%) 1) 34 (68) 2) 28 (62)	Median overall survival (overall pop. EURTAC), m 1) 22.9 2) 22.1 Median PFS Overall pop. EURTAC, m 1) 10.4 2) 5.1 HR=0.33 95% CI 0.23-0.49 p<0.0001 No T790M mutation, m (95% CI) 1) 15.8 (8.8-NR) 2) 5.1 (1.1-6.7) With T790M mutation, m (95% CI) 1) 9.7 (6.9-12.9) 2) 6.0 (4.1-7.7)	See Rosell R Lancet Oncol 2012

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Wu YL** **Ann Oncol** **2015** **(ENSURE)[50]** ***Fair***	RCT Multicenter Open-label Phase III Median duration of follow-up: 1) 28.9 m 2) 27.1 m <u>Location</u> China, Malaysia, Philippines Interim analysis (cutoff July 20, 2012)	1) Erlotinib (n=110) 2) Gemcitabine + cisplatin (n=107) <u>Dosing schedule</u> 1) 150 mg/day until progression/ unacceptable toxicity 2) 1250 mg/m^2 days 1 and 8 + 75 mg/m^2 day 1, every 3 weeks, up to 4 cycles	Age ≥18 years; stage IIIb/IV EGFR+ NSCLC; EGOG PS 0-2; no prior exposure to chemotherapy or agents targeting HER receptors; no brain metastases	Age, median (range)1) 57.5 (33-79) 2) 56.0 (30-78) Male, % 1) 38.2 2) 39.3 ECOG PS=1, % 1) 78.9 2) 79.8 Stage IV, % 1) 90.9 2) 93.5 Never smoker, % 1) 71.8 2) 69.2 Adenocarcinoma, % 1) 94.5 2) 94.4 Squamous-cell, % 1) 1.8 2) 1.9	Median OS, m 1) 26.3 1) 25.5 HR=0.91 95% CI 0.63-1.31 p=0.607 Median PFS, m (95% CI) 1) 11.0 2) 5.5 HR=0.34 95% CI 0.22-0.51 p<0.0001 ORR, % 1) 62.7 2) 33.6 p=NR	AEs ≥3, n (%) Neutropenia 1) 1 (1) 2) 26 (25) Anemia 1) 1 (1) 2) 13 (13) Leukopenia 1) 1 (1) 2) 15 (14) Thrombocytopenia 1) 0 2) 7 (7) Rash 1) 7 (6) 2) 1 (1) Discontinuation d/t AE 1) 3 (3) 2) 13 (13)

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Wu YL J Thorac Oncol 2013** **(ENSURE)[107]**	See Wu YL Ann Oncol 2015 Updated analysis (cutoff November 19, 2012)	See Wu YL Ann Oncol 2015	See Wu YL Ann Oncol 2015	See Wu YL Ann Oncol 2015	Median PFS, m 1) 11.0 2) 5.5 HR=0.33 95% CI 0.23-0.47 p<0.0001 ORR, % 1) 68.2 1) 39.3 p<0.0001 Disease control rate, % 1) 91.8 1) 82.2 p=0.0354	See Wu YL Ann Oncol 2015

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Wu YL J Thorac Oncol 2014** **(ENSURE)[108]**	See Wu YL Ann Oncol 2015 Data cutoff November 19, 2012 QoL analysis based on Functional Assessment of Cancer Therapy-Lung (FACT-L) and Lung Cancer Subscale (LCS) Trial outcome index (TOI; ≥6-point decline in LCS score + physical and functional scores from baseline) QoL (≥6-point decline in TOI + social and emotional scores from baseline)	See Wu YL Ann Oncol 2015	See Wu YL Ann Oncol 2015	See Wu YL Ann Oncol 2015	Time to symptomatic progression (≥3-point decline in LCS from baseline), m 1) 13.8 2) 5.5 HR=0.56 95% CI 0.36-0.87 p=0.0076 Time to deterioration TOI, m 1) 11.4 2) 4.2 HR=0.51 95% CI 0.34-0.76 p=0.0006 QoL, m 1) 8.2 2) 2.8 HR=0.64 95% CI 0.44-0.93 p=0.0168	See Wu YL Ann Oncol 2015

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Zhou C** **Lancet Oncol** **2011** **(OPTIMAL)[109]** ***Fair***	RCT Multicenter Open-label Phase III Median duration of follow-up: 15.6 m Primary analysis data cutoff: August 16, 2010 <u>Location</u> 22 centers in China	1) Erlotinib (n=82) 2) Gemcitabine + carboplatin (n=72) <u>Dosing schedule</u> 1) 150 mg/day until progression/ unacceptable toxicity 2) 1000 mg/m^2 days 1 and 8 + AUC 5 day 1, every 3 weeks, up to 4 cycles	Age ≥18 years; stage IIIb/IV EGFR+ NSCLC; measurable disease (RECIST); EGOG PS 0-2; no prior exposure to systemic anticancer therapy Exclusion: uncontrolled brain metastases	Age, median (range)1) 57 (31-74) 2) 59 (36-78) Male, n (%) 1) 34 (41) 2) 29 (40) ECOG PS=2, n (%) 1) 7 (9) 2) 3 (4) Stage IV, n (%) 1) 71 (87) 2) 67 (93) Non-smoker, n (%) 1) 59 (72) 2) 50 (69) Adenocarcinoma, n (%) 1) 72 (88) 2) 62 (86)	OS data not mature at primary analysis Deaths, n (%) 1) 16 (20) 1) 12 (17) Median PFS, m (95% CI) 1) 13.1 (10.58-16.53) 2) 4.6 (4.21-5.42) HR=0.16 95% CI 0.10-0.26 p<0.0001 ORR, n (%) 1) 68 (83) 2) 26 (36) p<0.0001 Disease control rate, n (%) 1) 79 (96) 2) 59 (82) p=0.0022	AEs ≥3, n (%) Any event 1) 14 (17) 2) 47 (65) Neutropenia 1) 0 2) 30 (42) Thrombocytopenia 1) 0 2) 29 (40) Anemia 1) 0 2) 9 (13) Treatment-related death 1) 0 2) 0 Discontinuation d/t AE 1) 1 (1) 2) 4 (6)

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Zhou C** **J Thorac Oncol** **2011** **(OPTIMAL)**[51]	See Zhou C Lancet Oncol 2011	See Zhou C Lancet Oncol 2011	See Zhou C Lancet Oncol 2011	See Zhou C Lancet Oncol 2011	Clinically-relevant improvement in FACT-L score, % 1) 73 2) 29.6 OR=6.9 95% CI 3.07-15.48 p<0.0001 Clinically-relevant improvement in LCS score, % 1) 75.7 2) 31.5 OR=6.77 95% CI 3.04-15.05 p<0.0001	See Zhou C Lancet Oncol 2011

<table>
<tr><th>Author & Year of Publication (Trial)
Quality rating</th><th>Study Design and Duration of F/u</th><th>Interventions (n)
Dosing schedule</th><th>Major Inclusion and Exclusion Criteria</th><th colspan="2">Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr><td>Publication

Chen G
Ann Oncol
2013

(OPTIMAL)[110]

Fair</td><td>See Zhou C Lancet Oncol 2011

Updated data cutoff January 7, 2011</td><td>See Zhou C Lancet Oncol 2011</td><td>See Zhou C Lancet Oncol 2011</td><td>Mean baseline score
FACT-L
1) 94.43
2) 92.89

TOI
1) 55.76
2) 55.52

LCS
1) 18.46
2) 19.52</td><td>Updated median PFS, m (95% CI)
1) 13.7 (10.58-15.28)
2) 4.6 (4.21-5.42
HR=0.164
95% CI 0.105-0.256
p<0.0001

Clin-rel. improvement, %
FACT-L
1) 74.3
2) 31.5

TOI
1) 73.0
2) 25.9

LCS
1) 77.0
2) 31.5

Median time to improvement, m
<table><tr><td></td><td>FACT-L</td><td>TOI</td><td>LCS</td></tr><tr><td>1)</td><td>1.51</td><td>2.79</td><td>1.48</td></tr><tr><td>2)</td><td>3.19</td><td>3.48</td><td>3.15</td></tr><tr><td>p</td><td>0.007</td><td>0.003</td><td>0.001</td></tr></table></td><td>See Zhou C Lancet Oncol 2011</td></tr>
</table>

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Zhou C** **Ann Oncol** **2015** **(OPTIMAL)[52]** ***Fair***	See Zhou C Lancet Oncol 2011 Median follow-up for OS: 25.9 m Data cutoff: December 21, 2012	See Zhou C Lancet Oncol 2011	See Zhou C Lancet Oncol 2011	See Zhou C Lancet Oncol 2011	Median OS, m 1) 22.8 2) 27.2 HR=1.19 95% CI 0.83-1.71 p=0.2663 Clinical characteristics did not have significant impact on OS	See Zhou C Lancet Oncol 2011

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Gridelli C** **J Clin Oncol** **2012** **(TORCH)[39]** ***Fair***	RCT Multicenter Open-label Phase III Median duration of follow-up: 24.3 m <u>Location</u> Italy and Canada	1) Erlotinib (n=380) 2) Cisplatin + gemcitabine (n=380) <u>Dosing schedule</u> 1) 150 mg/day until progression 2) 80 mg/m^2 day 1 + 1200 mg/m^2 on days 1 and 8, every 3 weeks, up to 6 cycles Note: After progression, patients crossed over to opposite treatment arm	Stage IIIb/IV NSCLC; ≥1 target/nontarget lesion (RECIST); age <70 (no age restrictions for Canadian centers); ECOG PS 0-1; no prior treatment with anti-EGFR agents; adequate bone marrow, hepatic, and renal function; asymptomatic brain metastases eligible	Age, median (range)1) 63 (27-79) 2) 62 (34-81) Male, n (%) 1) 252 (66) 2) 252 (66) ECOG PS=1, n (%) 1) 183 (48) 2) 195 (51) Stage IV, n (%) 1) 334 (88) 2) 343 (90) Never smoker, n (%) 1) 78 (21) 2) 79 21) Adenocarcinoma, n (%) 1) 210 (55) 2) 212 (56) EGFR+, n (%) 1) 19 (14) 2) 20 (15)	*Subset of patients with EGFR Mutations* Median OS, m (95% CI) 1) 18.1 (12.4-NE) 1) 32.5 (17.3-NE) HR=1.58 95% CI 0.70-3.57 Median PFS, m (95% CI) 1) 9.7 (5.7-18.2) 2) 6.9 (6.6-9.6) HR=0.60 95% CI 0.30-1.20 ORR, % 1) 42.1 2) 25.0	*Overall study population* AEs ≥3, n (%) Anemia 1) 17 (5) 2) 30 (8) Neutropenia 1) 1 (0.3) 2) 79 (22) Thrombocytopenia 1) 0 2) 42 (11) Skin rash 1) 40 (11) 2) 1 (0.3)

<table>
<tr><th>Author & Year of Publication (Trial)
Quality rating</th><th>Study Design and Duration of F/u</th><th>Interventions (n)
Dosing schedule</th><th>Major Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr>
<td>Publication

Di Maio M
J Thorac Oncol
2012

(TORCH)[111]

Fair</td>
<td>See Gridelli C J Clin Oncol 2012
See Gridelli C J Clin Oncol 2012

EORTC-C30 and EORTC QLQ-LC13

Best QoL response criteria
Improved: ≥10 pt improvement since baseline

Stable: <10 pt change since baseline

Worse: ≥10 pt worsening since baseline</td>
<td>See Gridelli C J Clin Oncol 2012
See Gridelli C J Clin Oncol 2012</td>
<td>See Gridelli C J Clin Oncol 2012
See Gridelli C J Clin Oncol 2012</td>
<td>See Gridelli C J Clin Oncol 2012
See Gridelli C J Clin Oncol 2012</td>
<td>EGFR+ patients
Best QoL response
Global QoL, n (%)
<table>
<tr><th></th><th>Improved</th><th>Stable</th><th>Worse</th></tr>
<tr><td>1)</td><td>6 (40)</td><td>5 (33)</td><td>4 (27)</td></tr>
<tr><td>2)</td><td>8 (50)</td><td>4 (25)</td><td>4 (25)</td></tr>
</table>
Physical Functioning, n (%)
<table>
<tr><th></th><th>Improved</th><th>Stable</th><th>Worse</th></tr>
<tr><td>1)</td><td>5 (33)</td><td>6 (40)</td><td>4 (27)</td></tr>
<tr><td>2)</td><td>8 (50)</td><td>3 (19)</td><td>5 (31)</td></tr>
</table>
Pain, n (%)
<table>
<tr><th></th><th>Improved</th><th>Stable</th><th>Worse</th></tr>
<tr><td>1)</td><td>7 (47)</td><td>5 (33)</td><td>3 (20)</td></tr>
<tr><td>2)</td><td>9 (56)</td><td>4 (25)</td><td>3 (19)</td></tr>
</table>
Dyspnea, n (%)
<table>
<tr><th></th><th>Improved</th><th>Stable</th><th>Worse</th></tr>
<tr><td>1)</td><td>6 (40)</td><td>6 (40)</td><td>3 (20)</td></tr>
<tr><td>2)</td><td>6 (38)</td><td>7 (44)</td><td>3 (19)</td></tr>
</table>
Cough, n (%)
<table>
<tr><th></th><th>Improved</th><th>Stable</th><th>Worse</th></tr>
<tr><td>1)</td><td>7 (47)</td><td>5 (33)</td><td>3 (20)</td></tr>
<tr><td>2)</td><td>7 (44)</td><td>5 (31)</td><td>4 (25)</td></tr>
</table>
</td>
<td>See Gridelli C J Clin Oncol 2012
See Gridelli C J Clin Oncol 2012</td>
</tr>
</table>

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Lim SH** **J Thorac Oncol 2014**[53] ***Fair***	Matched-pair case-control Consecutive selection of patients <u>Location</u> Samsung Medical Center, Seoul, Korea	1) Gefitinib (n=121) 2) Erlotinib (n=121) <u>Dosing schedule</u> 1) 250 mg/day until progressive disease or unacceptable toxicity 2) 150 mg/day until progressive disease or unacceptable toxicity	Clinically proven recurrent or advanced/metastatic stage IIIb/IV NSCLC with EGFR mutation; brain metastasis included if underwent whole-brain radiotherapy or stereotactic radiosurgery; first-line or second-line or higher after failure of prior cytotoxic chemotherapy	Age, median (range)1) 58 (29-85) 2) 58 (30-84) Male, n (%) 1) 53 (43.8) 2) 53 (43.8) ECOG PS=0-1, n (%) 1) 110 (91) 2) 110 (91) Stage IV, n (%) 1) 90 (74) 2) 88 (73) Never smoker, n (%) 1) 77 (64) 2) 77 (64) 1 prior regimen, n (%) 1) 65 (54) 2) 82 (68) Adenocarcinoma, n (%) 1) 119 (98) 2) 117 (97)	Subset of patients treated with first-line EGFR TKIs Median OS, m (95% CI) 1) 24.5 (8.6-40.4) 2) Not reached Median PFS, m (95% CI) 1) 11.7 (6.7-16.7) 2) 14.5 (8.7-20.4) p=0.507 ORR, % 1) 76.7 2) 90.0 p=0.431	Dose adjustment, n 1) 1 2) 22

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Fehrenbacher L** **Lancet** **2016** **(POPLAR)[24]** ***Good***	RCT Multicenter Open-label Phase II Median duration of follow-up 1) 14.8 2) 15.7 Primary analysis cutoff date: May 8, 2015 <u>Location</u> 13 countries in Europe and N. America	1) Atezolizumab (n=144) 2) Docetaxel (n=143) <u>Dosing schedule</u> 1) 1200 mg until progression or unacceptable toxicity 2) 75 mg/m^2 every 3 weeks on day 1 until progression or unacceptable toxicity No crossover permitted	Age ≥18; ECOG PS 0-1; measurable disease (RECIST); adequate hematological and end-organ function; provided tumor specimens for PD-L1 testing Exclusion: Active/untreated CNS metastases; history of pneumonitis, autoimmune or chronic viral diseases	Age, median (range)1) 62 (42-82) 2) 62 (36-84) Male, n (%) 1) 93 (65) 2) 76 (53) ECOG PS=1, n (%) 1) 96 (68) 2) 97 (68) Squamous, n (%) 1) 49 (34) 2) 48 (34) Never smoker, n (%) 1) 27 (19) 2) 29 (20) 1 prior regimen, n (%) 1) 93 (65) 2) 96 (67) EGFR+, n (%) 1) 10 (12) 2) 8 (10)	Median OS, m (95% CI) 1) 12.6 (9.7-16.4) 2) 9.7 (8.6-12.0) HR=0.73 95% CI 0.53-0.99 p=0.04 Median PFS, m (95% CI) 1) 2.7 (2.0-4.1) 2) 3.0 (2.8-4.1) HR=0.94 95% CI 0.72-1.23 ORR, n (%) 1) 21 (15) 2) 21 (15 Duration of response, m (95% CI) 1) 14.3 (11.6-NE) 2) 7.2 (5.6-12.5)	AEs ≥3, n (%) Any event 1) 57 (40) 2) 71 (53) Discontinuation d/t AE 1) 11 (8) 2) 30 (22)

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Borghaei H** **N Engl J Med** **2015** **(CheckMate 057)[22]** ***Good***	RCT Multicenter Open-label Phase III Interim analysis minimum follow-up: 13.2 m Additional follow-up minimum: 17.2 m	1) Nivolumab (n=292) 2) Docetaxel (n=290) <u>Dosing schedule</u> 1) 3 mg/kg every 2 weeks 2) 75 mg/m^2 every 3 weeks	Documented stage IIIB or IV or recurrent nonsquamous NSCLC after radiation therapy or surgical resection; disease recurrence or progression during/after one prior platinum-based doublet chemotherapy regimen Primary endpoint: OS	Age, median (range)1) 61 (37-84) 2) 64 (21-85) Male, n (%) 1) 151 (52) 2) 168 (58) White, n (%) 1) 267 (91) 2) 266 (92) ECOG PS=1, n (%) 1) 208 (71) 2) 194 (67) Stage IV, n (%) 1) 272 (93) 2) 266 (92) Smoker, n (%) 1) 231 (79) 2) 227 (78) EGFR+, n (%) 1) 44 (15) 2) 38 (13)	Median OS, m (95% CI) 1) 12.2 (9.7-15.0) 1) 9.4 (8.1-10.7) 1-yr OS rate, % (95% CI) 1) 51 (45-56) 2) 39 (33-45) HR=0.73 96% CI 0.59-0.89 p=0.002 Median PFS, m (95% CI) 1) 2.3 (2.2-3.3) 2) 4.2 (3.5-4.9) Rate of PFS at 1 yr, % (95% CI) 1) 19 (14-23) 2) 8 (5-12) HR=0.92 95% CI 0.77-1.1 p=0.39 ORR, % (95% CI) 1) 19 (15-24) 2) 12 (9-17) p=0.02	AEs ≥3, n (%) Any event 1) 30 (10) 2) 144 (54) Neutropenia 1) 0 2) 73 (27) Febrile neutropenia 1) 0 2) 26 (10) Leukopenia 1) 0 2) 22 (8) Treatment-related death 1) 1 2) 1 Discontinuation d/t TEAE 1) 5% 2) 15%

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Abstract **Horn L** **Eur J Cancer** **2015** **(CheckMate 057)[70]**	See Borghaei H N Engl J Med 2015	See Borghaei H N Engl J Med 2015	See Borghaei H N Engl J Med 2015	See Borghaei H N Engl J Med 2015	18 m OS rate, % 1) 39 2) 23 Symptom improvement rate by wk 12, n (%) 1) 52 (18) 2) 57 (20)	See Borghaei H N Engl J Med 2015

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics		Outcomes	Harms
Publication **Brahmer J** **N Engl J Med** **2015** **(CheckMate 017)[23]** ***Good***	RCT Multicenter Open-label Phase III Minimum follow-up: 11 m	1) Nivolumab (n=135) 2) Docetaxel (n=137) <u>Dosing schedule</u> 1) 3 mg/kg every 2 weeks 2) 75 mg/m^2 every 3 weeks	Stage IIIB or IV squamous-cell NSCLC; disease recurrence after 1 prior platinum-containing regimen; age ≥18; ECOG PS <2; submitted pretreatment tumor-tissue specimen for biomarker analyses Excluded: prior T-cell costimulation, checkpoint-targeted agents, or docetaxel; >1 prior systemic therapy for metastatic disease	Age, median (range)1) 62 (39-85) 2) 64 (42-84) Male, n (%) 1) 111 (82) 2) 97 (71) White, n (%) 1) 122 (90) 2) 130 (95) ECOG PS=1, n (%) 1) 106 (79) 2) 100 (73) Stage IV, n (%) 1) 105 (78) 2) 112 (82) Smoker, n (%) 1) 121 (90) 2) 129 (94) Squamous, n (%) 272 (100)	Median OS, m (95% CI) 1) 9.2 (7.3-13.3) 1) 6.0 (5.1-7.3) HR =0.59 95% CI 0.44-0.78 p<0.001 1-yr OS rate, % (95% CI) 1) 42 (34-50) 2) 24 (17-31) Median PFS, m (95% CI) 1) 3.5 (2.1-4.9) 2) 2.8 (2.1-3.5) HR=0.62 95% CI 0.47-0.81 p<0.001 1-yr PFS rate, % (95% CI) 1) 21 (14-28) 2) 6 (3-12) ORR, % (95% CI) 1) 20 (14-28) 2) 9 (5-15) OR=2.6 (1.3-5.5) p=0.008	AEs ≥3, n (%) Any event 1) 9 (7) 2) 71 (55) Fatigue 1) 1 (1) 2) 10 (8) Neutropenia 1) 0 2) 38 (30) Febrile neutropenia 1) 0 2) 13 (10) Treatment-related death, n 1) 0 2) 3 Discontinuation d/t TEAE, % 1) 3 2) 10

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics		Outcomes	Harms
Abstract **Gralla RJ J Thorac Oncol 2015** **(CheckMate 017)[71]**	See Brahmer J N Engl J Med 2015	See Brahmer J N Engl J Med 2015	See Brahmer J N Engl J Med 2015	See Brahmer J N Engl J Med 2015 Baseline LCSS ASBI 1) 29.6 (SD 16.4) 2) 29.6 (SD 14.7)		Week 12 meaningful symptom improvement (≥10 pt decrease), % (95% CI) 1) 20.0 (13.6-27.7) 2) 21.9 (15.3-29.8) Statistically significant improvements in LCSS ASBI at each assessment (vs. baseline) wks. 12-54 with nivolumab No statistically significant improvement in LCSS ASBI from baseline – wk 18 with docetaxel	See Brahmer J N Engl J Med 2015
Abstract **Reck M Ann Oncol 2015** **(CheckMate 017)[69]**	See Brahmer J N Engl J Med 2015	See Brahmer J N Engl J Med 2015 Minimally important difference (MID) EQ-5D: 0.08 EQ-VAS: 7	See Brahmer J N Engl J Med 2015	See Brahmer J N Engl J Med 2015 Baseline mean EQ-VAS (SD) 1) 63.7 (18.2) 2) 66.3 (20.5) Baseline mean EQ-5D (SD) 1) 0.683 (0.208) 2) 0.663 (0.284)	<u>Nivolumab</u> EQ-VAS at wks. 12, 20 to 36, and 48 higher vs. B/L (p≤0.05); wks. 24 -36 and 48 >MID EQ-5D index at wks. 16 to 30 and wks. 42 to 54 improved vs. B/L (p≤0.05); wks. 42-54 >MID <u>Docetaxel</u> EQ-VAS and EQ-5D index scores did not differ significantly from B/L to wk 18, after which <10 patients in sample		See Brahmer J N Engl J Med 2015

Author & Year of Publication (Trial) *Quality rating*	Study Design and Duration of F/u	Interventions (n) Dosing schedule	Major Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Publication **Herbst R** **Lancet** **2015** **(Keynote-010)[21]** ***Good***	RCT Multicenter Open-label Phase III Minimum follow-up: 8 m Median Follow-up: 13.1 m	1) Pembrolizumab 2 mg/kg (n=345) 2) Pembrolizumab 10 mg/kg (n=346) 2) Docetaxel (n=343) <u>Dosing schedule</u> 1) 2 mg/kg every 3 weeks 2) 10 mg/kg every 3 weeks 3) 75 mg/m^2 every 3 weeks TPS=tumor proportion score	Age≥18; progression as per RECIST 1.1 after two or more cycles of platinum-doublet chemotherapy; PD-L1 expression≥1% in tumor cells; ECOG 0 or 1. Exclusion: previous treatment with PD-1 checkpoint inhibitors or docetaxel, known active brain metastases or carcinomatous meningitis, active autoimmune disease requiring systemic steroids, and interstitial lung disease or history of pneumonitis requiring systemic steroids.	Age, median (range) 1) 63 (56-69) 2) 63 (56-69) 3) 62 (56-69) Male, n (%) 1) 212 (62) 2) 213 (62) 3) 209 (61) White, n (%) 1) 246 (72) 2) 250 (72) 3) 251 (73) ECOG PS=1, n (%) 1) 229 (67) 2) 225 (65) 3) 224 (65) Smoker, n (%) Former or current 1) 279 (81) 2) 285 (82) 3) 269 (78) EGFR+, n (%) 1) 28 (8) 2) 32 (9) 3) 26 (8)	Docetaxel as ref. Median OS, m (95% CI) 1) 10.4 (9.4-11.9) HR=0.71, 95% CI 0.58-0.88; p=0.0008 2) 12.7 (10.0-17.3) HR=0.61, 95% CI 0.49-0.75; p<0.0001 3) 8.5 (7.5-9.8) Median PFS, m (95% CI) 1) 3.9 2) 4.0 HR=0.88, 95% CI 0.74-1.05; p=0.07 3) 4.0 <u>PD-L1 TPS≥50%</u> Median OS, m (95% CI) 1) 14.9 HR=0.54, 95% CI 0.38-0.77; p=0.0002 2) 17.3 HR=0.50, 95% CI 0.36-0.70; p<0.0001 3) 8.2 Median PFS, m (95% CI) 1) 5.0 HR=0.59, 95% CI 0.44-0.78; p=0.001 2) 5.2 HR=0.59, 95% CI 0.45-0.78; p<0.001 3) 4.1	Grade 3-5 AE, n (%) Any 1) 43 (13) 2) 55 (16) 3) 109 (35) Neutropenia 1) 0(0) 2) 0(0) 3) 38 (12) Treatment-related death, n 1) 3 2) 3 3) 5 Discontinuation d/t TEAE, n (%) 1) 15 (4) 2) 17 (5) 3) 31 (10)

Appendix C. Additional Results from Evidence Review

Table C1. Results of literature search

	Population 1 (1st-line EGFR+)	Population 2 (1st-line EGFR-)	Population 3 (2nd-line EGFR-)	Population 4 (2nd- or 3rd-line EGFR+)
Good quality studies, n	1	0	4	0
Fair quality studies, n	23	0	0	0
Poor quality studies, n	0	0	0	0
Not rated, n*	12	0	4	0
Total number of relevant references	**36**	**0**	**8**	**0**

*We did not rate systematic reviews or conference abstracts for quality.

Table C2. EGFR mutations in key TKI trials

Key Trials	1) Treatment 2) Comparator	Exon 19 deletion (%)	Exon 21 L858R (%)	Other (%)
LUX-Lung 3	1) Afatinib 2) Cisplatin+Pemetrexed	1) 49 2) 50	1) 40 2) 41	1) 11 2) 10
LUX-Lung 6	1) Afatinib 2) Cisplatin+Gemcitabine	1) 51 2) 51	1) 38 2) 38	1) 11 2) 12
LUX-Lung 7	1) Afatinib 2) Gefitinib	1) 58 2) 58	1) 42 2) 42	NR
IPASSα	1) Gefitinib 2) Carboplatin+Paclitaxel	1) 50 2) 57	1) 48 2) 36	1) 6 2) 10
NEJ002	1) Gefitinib 2) Carboplatin+Paclitaxel	1) 51 2) 52	1) 43 2) 42	1) 6 2) 6
WJTOG3405	1) Gefitinib 2) Cisplatin+Docetaxel	1) 58 2) 43	1) 42 2) 57	NR

FIRST SIGNAL	1) Gefitinib 2) Cisplatin+Gemcitabine	64[β]	36[β]	NR
EURTAC	1) Erlotinib 2) Cisplatin+Gemcitabine/ Docetaxel	1) 66 2) 67	1) 34 2) 33	NR
ENSURE	1) Erlotinib 2) Cisplatin+Gemcitabine	1) 52 2) 57	1) 48 2) 43	NR
OPTIMAL	1) Erlotinib 2) Carboplatin+Gemcitabine	1) 52 2) 54	1) 48 2) 46	NR
TORCH	1) Erlotinib 2) Cisplatin+Gemcitabine	NR	NR	NR

α Eleven patients had multiple mutations and are counted once for each type of mutation they had; β total across treatment arms

Table C3. Crossover rates in TKI trials

Trial	Assigned treatment	Duration of treatment	Median (range)	Crossover after progression (% total)
IPASS	gefitinib	daily until progression	5.6 (0.1 to 22.8)	68.2% Platinum doublets 54.5% carboplatin + paclitaxel
	carboplatin +paclitaxel	every 3 weeks until progression or up to 6 cycles	4.1 (0.7 to 5.8)	64.3% TKI 47.3% gefitinib
First-SIGNAL	gefitinib	daily until progression	163 days (11 to 885)	65% platinum doublets
	carboplatin +paclitaxel	every 3 weeks until progression or up to 9 cycles	6 cycles (1 to 9)	75% TKI
WJTOG3405	gefitinib	daily until progression	165 days (22 to 1100)	19.8% platinum doublets
	carboplatin +paclitaxel	every 3 weeks until progression or 3-6 cycles	64 days (1 to 106) 4 cycles (1 to 6)	59.3% TKI
NEJ002	gefitinib	daily until progression	308 days (14 to 1219)	45.6% carboplatin-paclitaxel
	carboplatin +paclitaxel	every 3 weeks until progression or at least 3 cycles	4 cycles (1 to 7)	93.0% gefitinib
TORCH	erlotinib	daily until progression	NR	NR

	cisplatin +gemcitabine	every 3 weeks until progression or up to 6 cycles	5	NR
OPTIMAL	erlotinib	daily until progression	55.5 weeks (3.1 to 93.0)	35.4% chemotherapy only 59.8% chemotherapy alone or in combination
	cisplatin +gemcitabine	every 3 weeks until progression or up to 4 cycles	10.4 weeks (1.0 to 18.9) 4 cycles (1 to 6)	36.1 TKI only 69.5% TKI alone or in combination
ENSURE	erlotinib	daily until progression	NR	59.1% at least 1 platinum compounds 54.5% at least 1 antimetabolites
	cisplatin +gemcitabine	every 3 weeks until progression or up to 4 cycles	NR	85.6% TKI 51.9% erlotinib
LUX LUNG 3	afatinib	daily until progression	11.0 months	71% subsequent chemotherapy
	cisplatin +pemetrexed	every 3 weeks until progression or up to 6 cycles	6 cycles (1 to 9)	75% TKI
LUX LUNG 6	afatinib	daily until progression	398 days (IQR 173 to 537)	41.7% cisplatin + gemcitabine
	cisplatin +gemcitabine	every 3 weeks until progression or up to 6 cycles	89 days (IQR 60 to 119) 4 cycles	48.4% TKI
EURTAC	erlotinib	daily until progression	8.2 months (0.3 to 32.9)	37.2% chemotherapy
	PD	every 3 weeks until progression or up to 4 cycles	2.8 months (0.7 to 5.1) 4 cycles (1 to 6)	75.86% TKIs 74.71% erlotinib
LUX LUNG 7	afatinib	daily until progression	13.7 months (IQR 7.4 to 24.3)	37.5% TKI
	gefitinib	daily until progression	11.5 months (IQR 6.2 to 18.8)	49.1% TKI

Additional Quality of Life Results: TKIs

For afatinib, both LUX-Lung 3 and LUX-Lung 6 used the Global Health Status/ Quality of Life and functioning scale domains in the European Organization for Research and Treatment of Cancer

(EORTC) Quality of Life Questionnaire C30 (QLQ-C30) questionnaires and measured changes in score, proportion of patients with improvement (≥ 10 points), and time-to-deterioration (time to first instance of worsening ≥ 10 points). Each scale was standardized to a range from 0 to 100 and a 10-point change was used as the threshold for clinical importance.[112] The longitudinal analysis of LUX-Lung 3 showed that compared with patients on cisplatin plus pemetrexed, patients on afatinib had significantly better scores over time on Global Health Status/QoL (p=0.015), physical (p<0.001), role (p=0.004), and cognitive (p=0.007) functioning. However, measurements of the clinical importance of QoL changes, including proportions of patients with clinically meaningful improvement and time-to-deterioration in QoL and functioning were not significantly different between study arms.[63] However, in LUX-Lung 6, patients on afatinib showed clinically meaningful improvements on the Global Health Status/QoL scale. Specifically, the afatinib arm had a higher proportion of patients with improvement (63% vs. 33%; p<0.0001), and a longer time to deterioration (HR 0.56, 95% CI 0.41 to 0.77; p=0.0002) compared to patients on cisplatin plus gemcitabine. In addition, function scales, including physical, role, emotional, cognitive, and social, were all improved in the afatinib arm compared to the chemotherapy arm.[65]

Two trials used different instruments to measure the effects of gefitinib on QoL compared to carboplatin plus paclitaxel. The IPASS trial measured quality of life using percentage of patients with sustained clinically relevant improvement on the Functional Assessment of Cancer Therapy-Lung (FACT-L; 0 to 136 scale) and Trial Outcome Index (TOI; 0 to 84 scale) (increase of 6 points or more, maintained for at least 21 days); the TOI is the sum of physical well-being, functional well-being, and lung-cancer subscales on the FACT-L. In EGFR+ patients, gefitinib showed greater proportions of patients improving on both measurements (FACT-L: 70.2% improved vs. 44.5% improved; OR 3.01, 95% CI 1.79 to 5.07; p<0.0001; TOI: 70.2% improved vs. 38.3% improved; OR 3.96, 95% CI 2.33 to 6.71; p<0.0001).[38] Similarly, time-to-worsening, with worsening defined as a decrease of 6 points maintained for at least 21 days, was also longer with gefitinib than with carboplatin/paclitaxel on both FACT-L (15.6 months vs. 3.0 months) and TOI (16.6 months vs. 2.9 months).[103] The NEJ002 trial assessed benefits of gefitinib compared to carboplatin/paclitaxel on QoL using The Care Notebook questionnaires. The questionnaires contain three major scales, including physical well-being, mental well-being, and life well-being. Patients who received gefitinib were more likely to improve and less likely to get worse (by at least 1 point on a 0-10 scale) compared with patients who received chemotherapy on physical well-being (25% improved and 36% worse with gefitinib vs. 21% improved and 66% worse with chemo; p<0.0001) and life well-being (53% improved and 17% worse with gefitinib vs. 42% improved and 47% worse with chemo; p<0.0001), while no difference was found for mental well-being.[66]

Two trials compared erlotinib to doublets containing gemcitabine using the same instruments and criteria for clinical importance as used in the IPASS trial. In the ENSURE trial, time-to-deterioration was significantly longer with erlotinib compared to cisplatin-gemcitabine (TOI: 11.4 vs. 4.2 months; HR 0.51, 95% CI 0.34 to 0.76; p=0.0006; FACT-L: 8.2 vs. 2.8 months; HR 0.64, 95% CI 0.44 to 0.93;

p=0.0168).[108] In the final analysis of OPTIMAL, a higher proportion of patients on erlotinib achieved improvement in QoL compared to patients on chemotherapy (FACT-L: 74.3% vs. 31.5%; TOI: 73.0% vs. 25.9%).[110]

Table C4. Overall survival by histological diagnosis

Drug	Trial	Overall HR	Squamous HR	Non-Squamous HR
Nivolumab	CheckMate 017		0.59 (0.44-0.79)	
Nivolumab	CheckMate 057			0.73 (0.60-0.88)
Atezolizumab	POPLAR	0.73 (0.53-0.99)	0.80 (0.49-1.30)	0.69 (0.47-1.01)
Pembrolizumab	KEYNOTE-010	0.71	0.74 (0.50-1.09)	0.63 (0.50-0.79)

Table C5. PD-L1 tests and cutpoints in the key trials

Trial name	PD-L1 test	Measurement and cutpoints	Subgroups
CheckMate 017	Immunohistochemical assay (Dako North America) using a rabbit antihuman PD-L1 antibody (clone 28-8, Epitomics)	percentage of PD-L1 -expressing tumor cells: ≥1%, ≥5%, and ≥10%	a) <1% b) ≥1% c) <5% d) ≥5% e) <10% f) ≥10%
CheckMate 057	same as above	same as above	same as above
KEYNOTE-010	Immunohistochemical assay (Dako North America) using a murine 22C3 antihuman PD-L1 antibody (Merck & Co., Inc.)	percentage of PD-L1 -expressing tumor cells: ≥1% and ≥50%	a) ≥1% b) ≥50%
POPLAR	VENTANA SP142 PD-L1 immunohistochemistry assay (Ventana Medical Systems)	a) percentage of PD-L1 -expressing tumor cells: TC3≥50%, TC2 ≥5% and <50%, TC1≥1% and <5%, TC0<1% b) percentage of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells: IC3≥10%, IC2 ≥5% and <10%, IC1≥1% and <5%, IC0<1%	a) TC3 or IC3 b) TC2/3 or IC2/3 c) TC1/2/3 or IC1/2/3 d) TC0 and IC0

Appendix D. Meta-Analysis Methods and Results

Network Meta-Analysis Methods

In addition to summary evidence tables, we performed quantitative indirect comparisons using Bayesian network meta-analysis (NMA) where possible.[113] Results are summarized in the report text. Review of the deviance information criterion (DIC) statistics as well as comparison of the residual deviance (resdev) to the number of unconstrained data points was used to assess the best model fit under multiple alternative assumptions. Given the expectation of at least some degree of heterogeneity in patient populations and/or study design, there is a general preference for a random-effects approach. So we took this approach for TKIs. However, the available network of immunotherapies is constructed of primarily single-study connections, which made the only feasible approach a fixed-effects model (to preserve statistically-significant effects observed in trials) and selected subgroup analyses (to address heterogeneity).[114]

Quantitative analyses focused attention on the effects of the regimens of interest on progression-free and/or overall survival, and were conducted using the NetMetaXL tool (http://www.netmetaxl.com/), a publicly-available and validated Excel-based tool for specifying and analyzing Bayesian indirect comparisons in a WinBUGS environment. For these outcomes, adjusted hazard ratios from the randomized trials were log-transformed and entered into the spreadsheet, and 95% confidence intervals were used to specify variance estimates (i.e., standard errors). A total of 40,000 iterations each were employed for both "burn-in" (for model convergence) and model (for model results) simulations.

We also conducted sensitivity analyses in which digitized information from the progression-free survival and overall survival curves for each immunotherapy trial were used to inform assessment of hazard ratios at multiple timepoints to determine whether the assumption of a proportional hazard holds true, based on established methods.[115]. Both Weibull and Gompertz distribution were modeled and whichever better fitted the data was used as input to the economic model. In this instance, 30,000 iterations were used for both burn-in and model simulations.

Subgroup Meta-Analysis Methods

We recognized that there would be heterogeineity among individual trials and subgroups of patients. Thus, we also explored the sources of heterogeneity in the effects of TKIs and immunotherapies through subgroup meta-analysis. Overall meta-analysis results using both random effects model and fixed effect model are presented to show the extent of heterogeneity among trials. For TKIs, subgroups by mutation type (DEL19 and L858R) were compred using a mixed effects model, which assumes fixed effects between groups and random effects among individual

trials within groups. For immunotherapies, subgroups by histology (squamous and non-squamous) were compared. All these analyses were conducted in the Comprehensive Meta-Analysis v2 and the forest plots were generated using the CADTH forest plot tool.

Figure D1. Overall survival network diagram of TKIs (all platinum doublets combined)

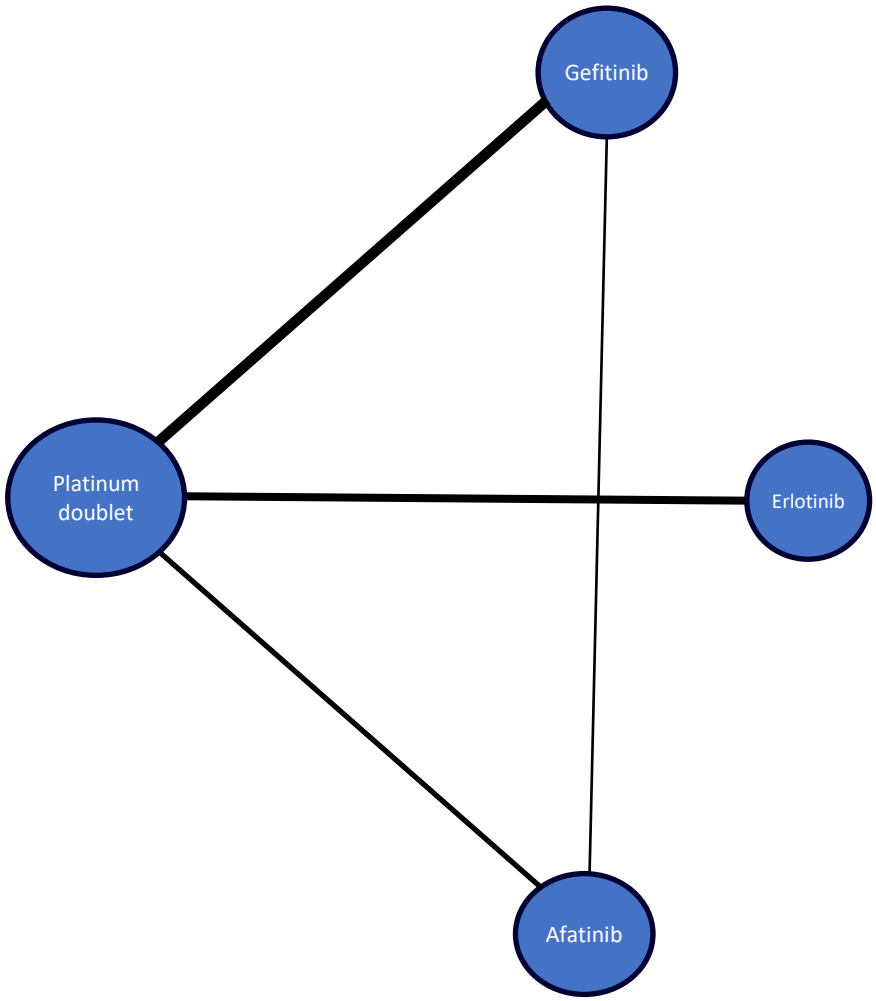


Table D1. Overall survival studies of TKIs (all platinum doublets combined)

Study name	Treatment 1	Treatment 2	n1	n2	LogHR	LogSE
LUX LUNG 3	afatinib	platinum doublet	230	115	-0.1278	0.1461
LUX LUNG 6	afatinib	platinum doublet	242	122	-0.0726	0.1345
LUX LUNG 7	afatinib	gefitinib	160	159	-0.1393	0.1417
IPASS	gefitinib	platinum doublet	132	129	0	0.1428
NEJ002	gefitinib	platinum doublet	114	114	-0.1199	0.1713
WJTOG3405	gefitinib	platinum doublet	86	86	0.2247	0.1781
FIRST-SIGNAL	gefitinib	platinum doublet	26	16	0.0421	0.3769
ENSURE	erlotinib	platinum doublet	110	107	-0.0943	0.1868
OPTIMAL	erlotinib	platinum doublet	82	72	0.1740	0.1844
TORCH	erlotinib	platinum doublet	19	20	0.4574	0.4156

Table D2. Network meta-analysis of TKIs: Overall survival (all platinum doublets combined)

afatinib			
0.90 (0.72 to 1.13)	platinum doublet		
0.88 (0.68 to 1.13)	0.97 (0.79 to 1.19)	gefitinib	
0.83 (0.57 to 1.19)	0.92 (0.68 to 1.23)	0.94 (0.66 to 1.34)	erlotinib

RE Model:
resdev, 7.292 vs. 10;
DIC = -2.755

Figure D2. Overall survival network diagram of TKIs (cisplatin-based and carboplatin-based doublets as separate groups)

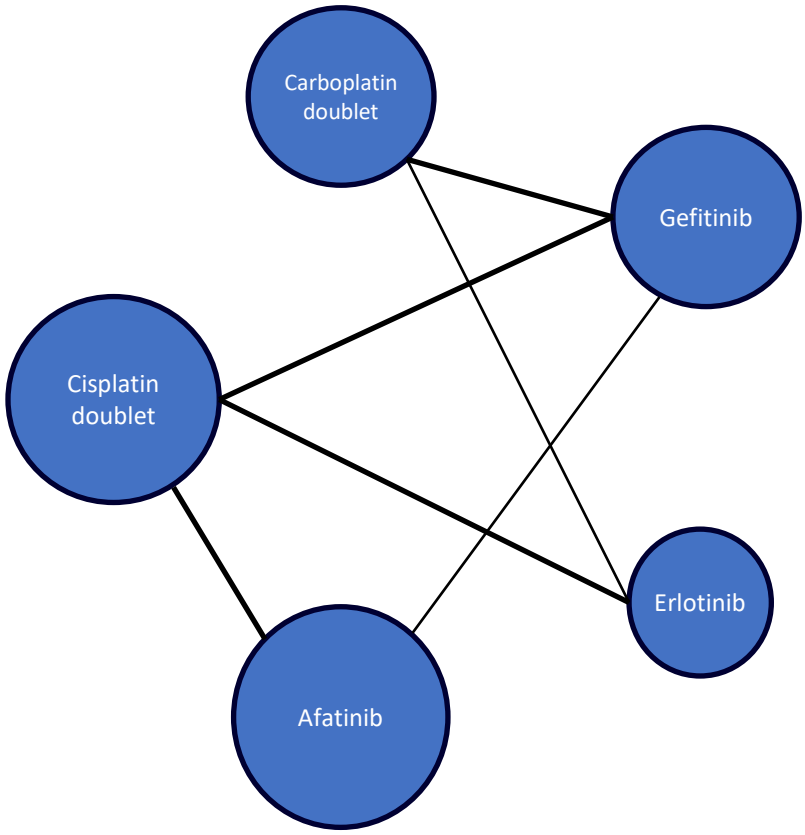


Table D3. Overall survival studies of TKIs (cisplatin-based and carboplatin-based doublets as separate groups)

Study name	Treatment 1	Treatment 2	n1	n2	LogHR	LogSE
LUX LUNG 3	afatinib	cisplatin doublet	230	115	-0.1278	0.1461
LUX LUNG 6	afatinib	cisplatin doublet	242	122	-0.0726	0.1345
LUX LUNG 7	afatinib	gefitinib	160	159	-0.1393	0.1417
IPASS	gefitinib	carboplatin doublet	132	129	0	0.1428
NEJ002	gefitinib	carboplatin doublet	114	114	-0.1199	0.1713
WJTOG3405	gefitinib	cisplatin doublet	86	86	0.2247	0.1781
FIRST-SIGNAL	gefitinib	cisplatin doublet	26	16	0.0421	0.3769
ENSURE	erlotinib	cisplatin doublet	110	107	-0.0943	0.1868
OPTIMAL	erlotinib	carboplatin doublet	82	72	0.1740	0.1844
TORCH	erlotinib	cisplatin doublet	19	20	0.4574	0.4156

Table D4. Network meta-analysis of TKIs: Overall survival (cisplatin-based and carboplatin-based doublets as separate groups)

RE Model:
resdev, 7.902 vs. 10;
DIC = 1.106

afatinib				
0.92 (0.71 to 1.18)	**cisplatin doublet**			
0.85 (0.57 to 1.26)	0.93 (0.64 to 1.33)	**carboplatin doublet**		
0.85 (0.63 to 1.15)	0.93 (0.70 to 1.24)	1.00 (0.76 to 1.33)	**gefitinib**	
0.81 (0.53 to 1.21)	0.89 (0.62 to 1.25)	0.95 (0.65 to 1.37)	0.95 (0.64 to 1.37)	**erlotinib**

Figure D3. Progression-free survival network diagram of TKIs (all platinum doublets combined)

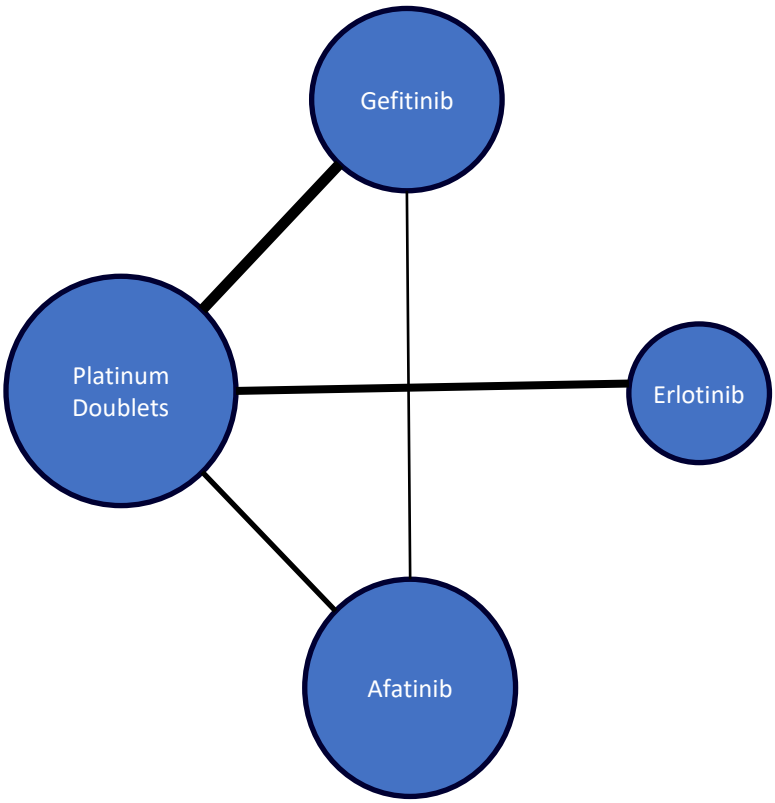


Table D5. Progression-free survival studies of TKIs (all platinum doublets combined)

Study name	Treatment 1	Treatment 2	n1	n2	LogHR	LogSE
LUX LUNG 3	afatinib	platinum doublet	230	115	-0.5447	0.1519
LUX LUNG 6	afatinib	platinum doublet	242	122	-1.2730	0.1704
LUX LUNG 7	afatinib	gefitinib	160	159	-0.3147	0.1303
IPASS	gefitinib	platinum doublet	132	129	-0.7340	0.1468
NEJ002	gefitinib	platinum doublet	114	110	-1.2040	0.1588
WJTOG3405	gefitinib	platinum doublet	86	86	-0.7154	0.1909
FIRST-SIGNAL	gefitinib	platinum doublet	26	16	-0.6088	0.3593
ENSURE	erlotinib	platinum doublet	110	107	-1.0788	0.2145
OPTIMAL	erlotinib	platinum doublet	82	72	-1.8326	0.2438
TORCH	erlotinib	platinum doublet	19	20	-0.5447	0.3755

Table D6. Network meta-analysis of TKIs: Progression-free survival (all platinum doublets combined)

erlotinib			
0.79 (0.33 to 1.96)	**afatinib**		
0.66 (0.30 to 1.50)	0.84 (0.42 to 1.64)	**gefitinib**	
0.30 (0.16 to 0.58)	0.38 (0.20 to 0.70)	0.45 (0.28 to 0.74)	**platinum doublet**

RE Model:
resdev, 10.53 vs. 10;
DIC = 5.55

Figure D4. Progression-free survival network diagram of TKIs (cisplatin-based and carboplatin-based doublets as separate groups)

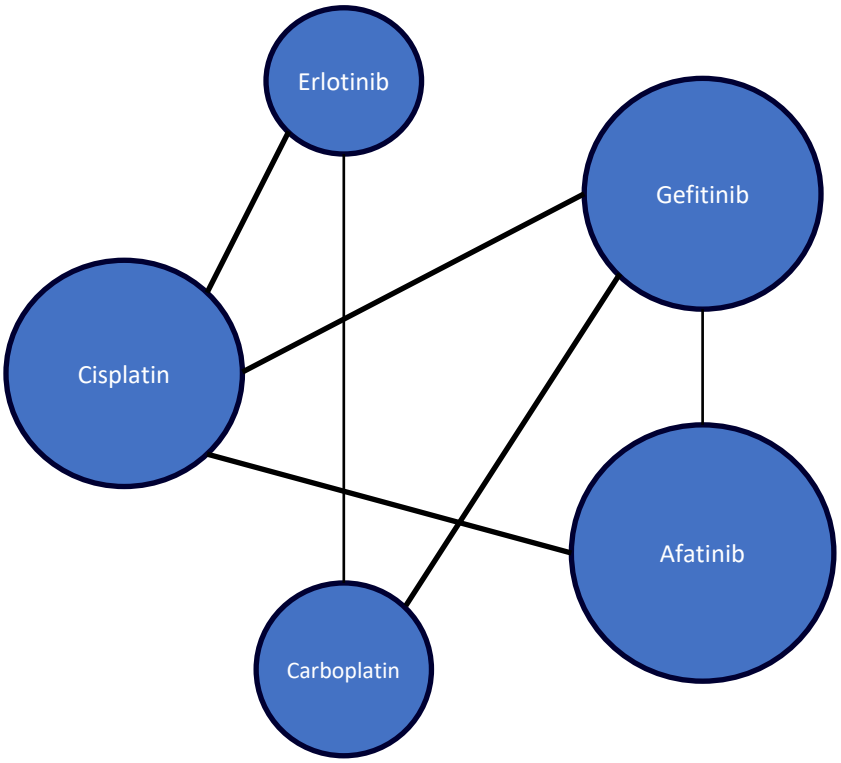


Table D7. Progression-free survival studies of TKIs (cisplatin-based and carboplatin-based doublets as separate groups)

Study name	Treatment 1	Treatment 2	n1	n2	LogHR	LogSE
LUX LUNG 3	afatinib	cisplatin doublet	230	115	-0.5447	0.1519
LUX LUNG 6	afatinib	cisplatin doublet	242	122	-1.2730	0.1704
LUX LUNG 7	afatinib	gefitinib	160	159	-0.3147	0.1303
IPASS	gefitinib	carboplatin doublet	132	129	-0.7340	0.1468
NEJ002	gefitinib	carboplatin doublet	114	110	-1.2040	0.1588
WJTOG3405	gefitinib	cisplatin doublet	86	86	-0.7154	0.1909
FIRST-SIGNAL	gefitinib	cisplatin doublet	26	16	-0.6088	0.3593
ENSURE	erlotinib	cisplatin doublet	110	107	-1.0788	0.2145
OPTIMAL	erlotinib	carboplatin doublet	82	72	-1.8326	0.2438
TORCH	erlotinib	cisplatin doublet	19	20	-0.5447	0.3755

Table D8. Network meta-analysis of TKIs: Progression-free survival (cisplatin-based and carboplatin-based doublets as separate groups)

RE Model:
resdev, 10.19 vs. 10;
DIC = 5.092

erlotinib				
0.86 (0.39 to 2.00)	**afatinib**			
0.62 (0.30 to 1.31)	0.71 (0.37 to 1.34)	**gefitinib**		
0.36 (0.19 to 0.69)	0.41 (0.24 to 0.72)	0.58 (0.34 to 1.01)	**cisplatin**	
0.21 (0.10 to 0.44)	0.24 (0.11 to 0.54)	0.34 (0.19 to 0.60)	0.59 (0.28 to 1.17)	**carboplatin**

Figure D5. Overall survival and progression-free survival network diagram of PD-1 immunotherapies

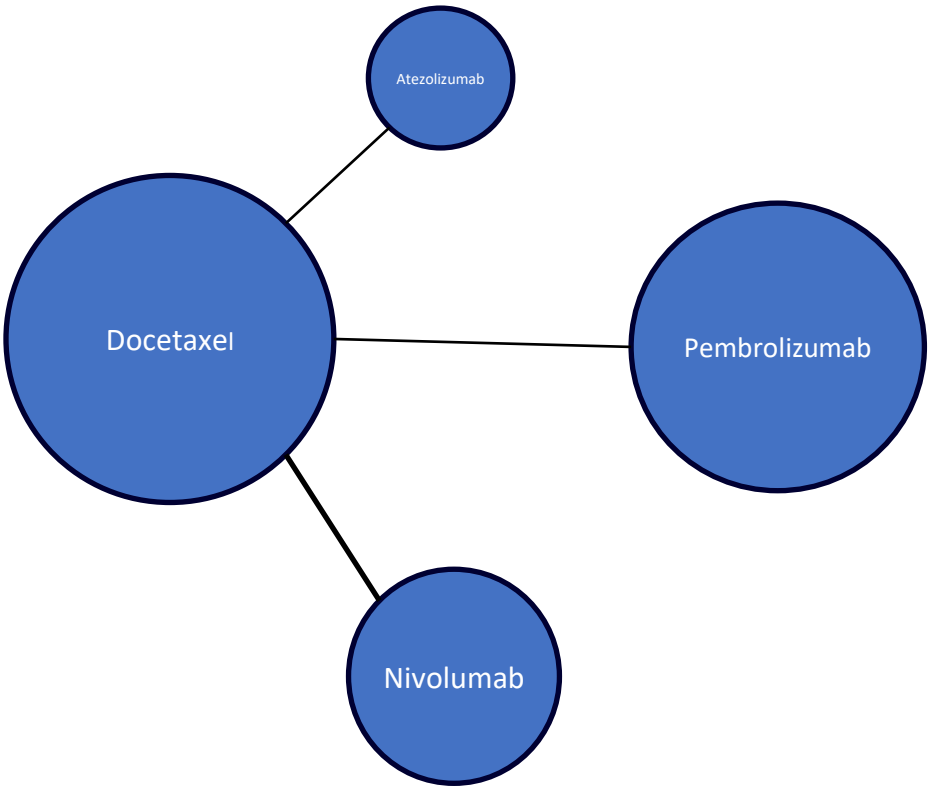


Table D9. Overall survival studies of PD-1 immunotherapies

Study name	Treatment 1	Treatment 2	n1	n2	LogHR	LogSE
CheckMate 017	nivolumab	docetaxel	135	137	-0.5276	0.1493
CheckMate 057	nivolumab	docetaxel	168	172	-0.4155	0.1333
POPLAR	atezolizumab	docetaxel	144	143	-0.3147	0.1594
KEYNOTE-010	pembrolizumab	docetaxel	581*	294	-0.4155	0.0956

*pembrolizumab 2mg/kg and 10mg/kg combined

Table D10. Network meta-analysis of PD-1 immunotherapies: Overall survival

Nivolumab			
0.95 (0.73 to 1.25)	Pembrolizumab		
0.86 (0.60 to 1.24)	0.90 (0.63 to 1.30)	Atezolizumab	
0.63 (0.52 to 0.76)	0.66 (0.55 to 0.80)	0.73 (0.53 to 1.00)	Docetaxel

FE Model:
resdev, 3.3 vs. 4;
DIC = -2.564

Table D11. Progression-free survival studies of PD-1 immunotherapies

Study name	Treatment 1	Treatment 2	n1	n2	LogHR	LogSE
CheckMate 017	nivolumab	docetaxel	135	137	-0.4780	0.1389
CheckMate 057	nivolumab	docetaxel	168	172	-0.1863	0.1248
POPLAR	atezolizumab	docetaxel	144	143	-0.0619	0.1366
KEYNOTE-010	pembrolizumab	docetaxel	581*	294	-0.1863	0.0822

*pembrolizumab 2mg/kg and 10mg/kg combined

Table D12. Network meta-analysis of PD-1 immunotherapies: Progression-free survival

Nivolumab			
0.88 (0.69 to 1.12)	**Pembrolizumab**		
0.77 (0.56 to 1.07)	0.88 (0.65 to 1.21)	**Atezolizumab**	
0.73 (0.61 to 0.87)	0.83 (0.71 to 0.97)	0.94 (0.72 to 1.23)	**Docetaxel**

FE Model:
resdev, 5.428 vs. 4;
DIC = -1.324

Table D13. Network meta-analysis of parametric OS curves: hazard ratios (Weibull distribution)

OS HR	6 months			12 months			24 months			60 months		
ref=docetaxel	median	LL	UL	median	LL	UL	median	LL	UL	median	LL	UL
nivolumab	0.65	0.30	1.39	0.52	0.21	1.29	0.42	0.14	1.20	0.32	0.09	1.08
pembrolizumab	0.64	0.15	2.65	0.64	0.12	3.50	0.65	0.09	4.61	0.65	0.06	6.65
atezolizumab	0.70	0.17	2.87	0.57	0.11	3.07	0.47	0.07	3.29	0.37	0.04	3.60

Figure D6. Network meta-analysis of parametric OS curves: hazard ratios (Weibull distribution)

Blue: nivolumab Red: pembrolizumab Green: atezolizumab Orange: docetaxel

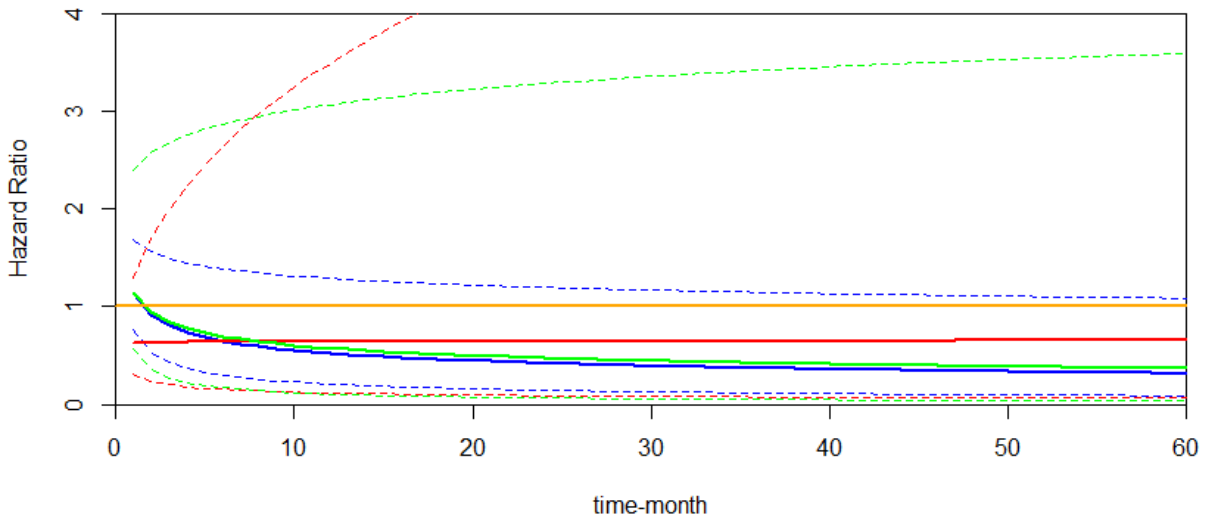


Table D14. Network meta-analysis of parametric OS curves: proportions of OS (Weibull distribution)

Proportion of OS	6 months	12 months	24 months	60 months
	median	median	median	median
ref=docetaxel	61.7%	34.5%	9.5%	0.1%
nivolumab	64.9%	46.4%	25.5%	5.4%
pembrolizumab	73.6%	50.6%	22.1%	1.3%
atezolizumab	64.1%	44.5%	22.9%	3.9%

Figure D7. Network meta-analysis of parametric OS curves: proportions of OS (Weibull distribution)

Blue: nivolumab Red: pembrolizumab Green: atezolizumab Orange: docetaxel

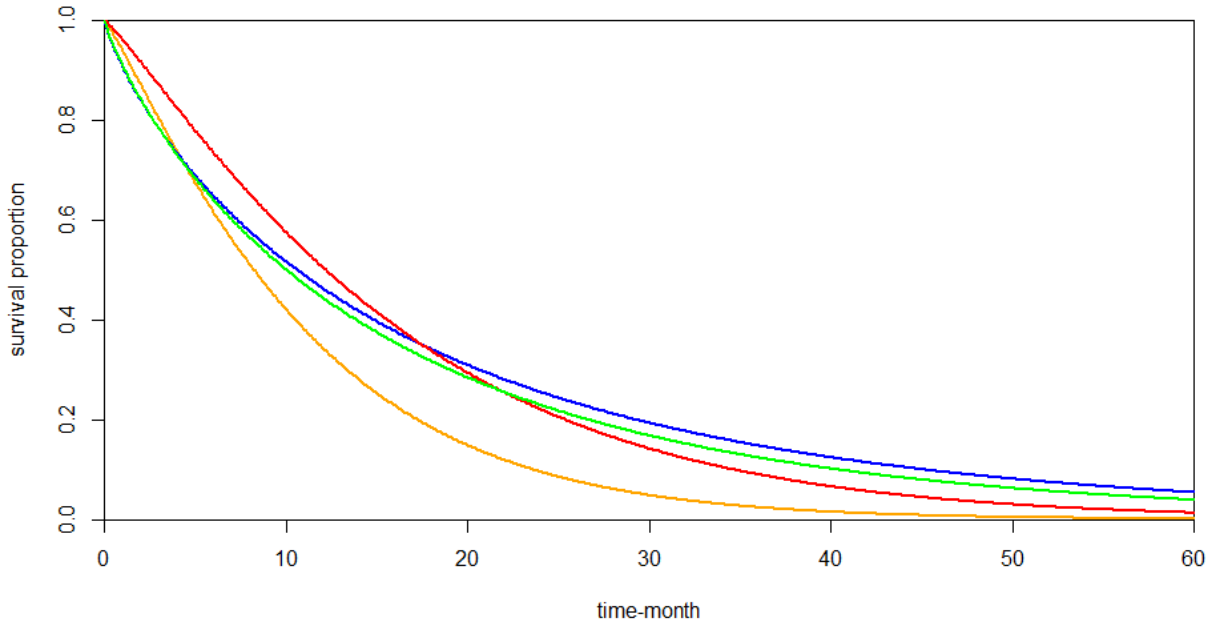


Table D15. Network meta-analysis of parametric PFS curves: hazard ratios (Gompertz distribution)

PFS HR	1 month			3 months			6 months			9 months			12 months		
ref=docetaxel	median	LL	UL	median	LL	UL	median	LL	UL	median	LL	UL	median	LL	UL
nivolumab	1.17	0.85	1.61	0.87	0.57	1.33	0.56	0.31	0.99	0.36	0.17	0.74	0.23	0.09	0.56
pembrolizumab	0.71	0.38	1.30	0.60	0.27	1.32	0.47	0.16	1.34	0.37	0.10	1.36	0.28	0.06	1.39
atezolizumab	1.09	0.65	1.86	0.97	0.49	1.98	0.83	0.31	2.17	0.70	0.20	2.38	0.59	0.13	2.61

Figure D8. Network meta-analysis of parametric PFS curves: hazard ratios (Gompertz distribution)

Blue: nivolumab Red: pembrolizumab Green: atezolizumab Orange: docetaxel

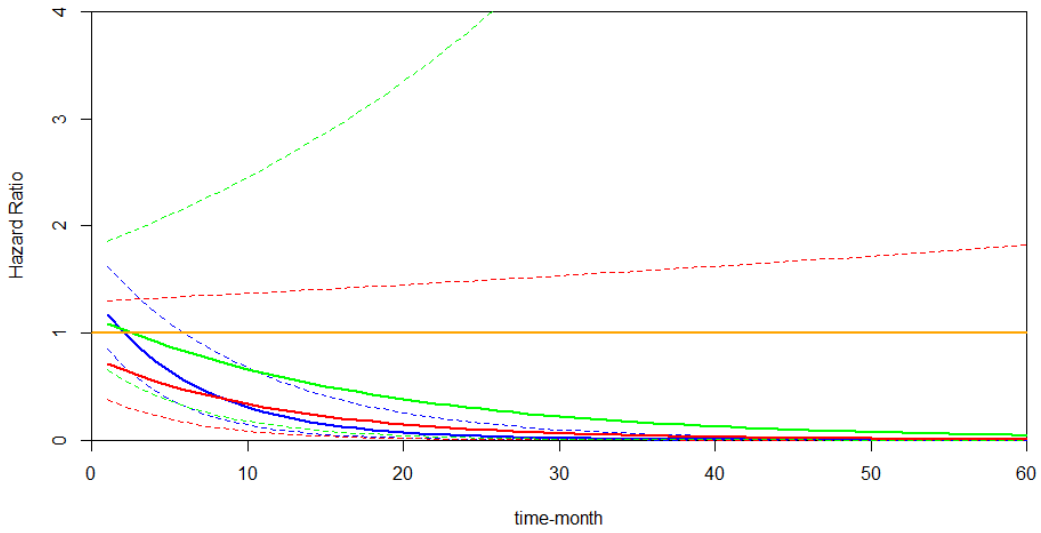
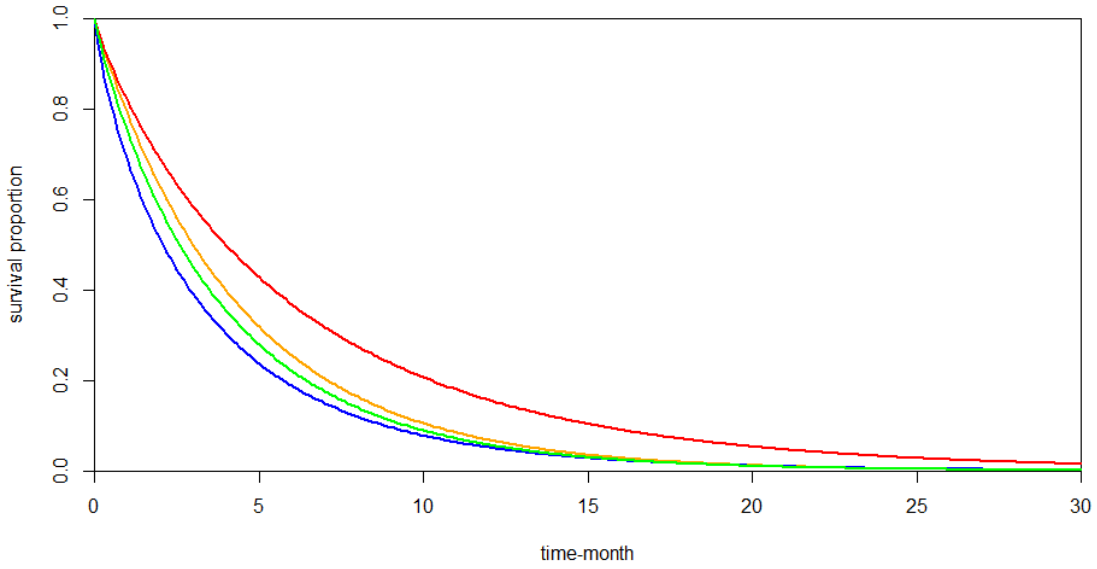


Table D16. Network meta-analysis of parametric PFS curves: proportions of PFS (Gompertz distribution)

Proportion of PFS	1 months	3 months	6 months	9 months	12 months
	median	median	median	median	median
ref=docetaxel	78.9%	50.0%	25.5%	13.1%	6.7%
nivolumab	68.6%	39.0%	18.8%	9.6%	5.1%
pembrolizumab	81.8%	58.5%	36.8%	23.8%	15.6%
atezolizumab	74.9%	45.1%	22.1%	11.1%	5.7%

Figure D9. Network meta-analysis of parametric PFS curves: proportions of PFS (Gompertz distribution)

Blue: nivolumab Red: pembrolizumab Green: atezolizumab Orange: docetaxel



Appendix E. Subgroup Meta-Analysis Methods and Results

Figure E1. Overall meta-analysis of TKIs: Overall survival

I^2=5.036. P=0.391

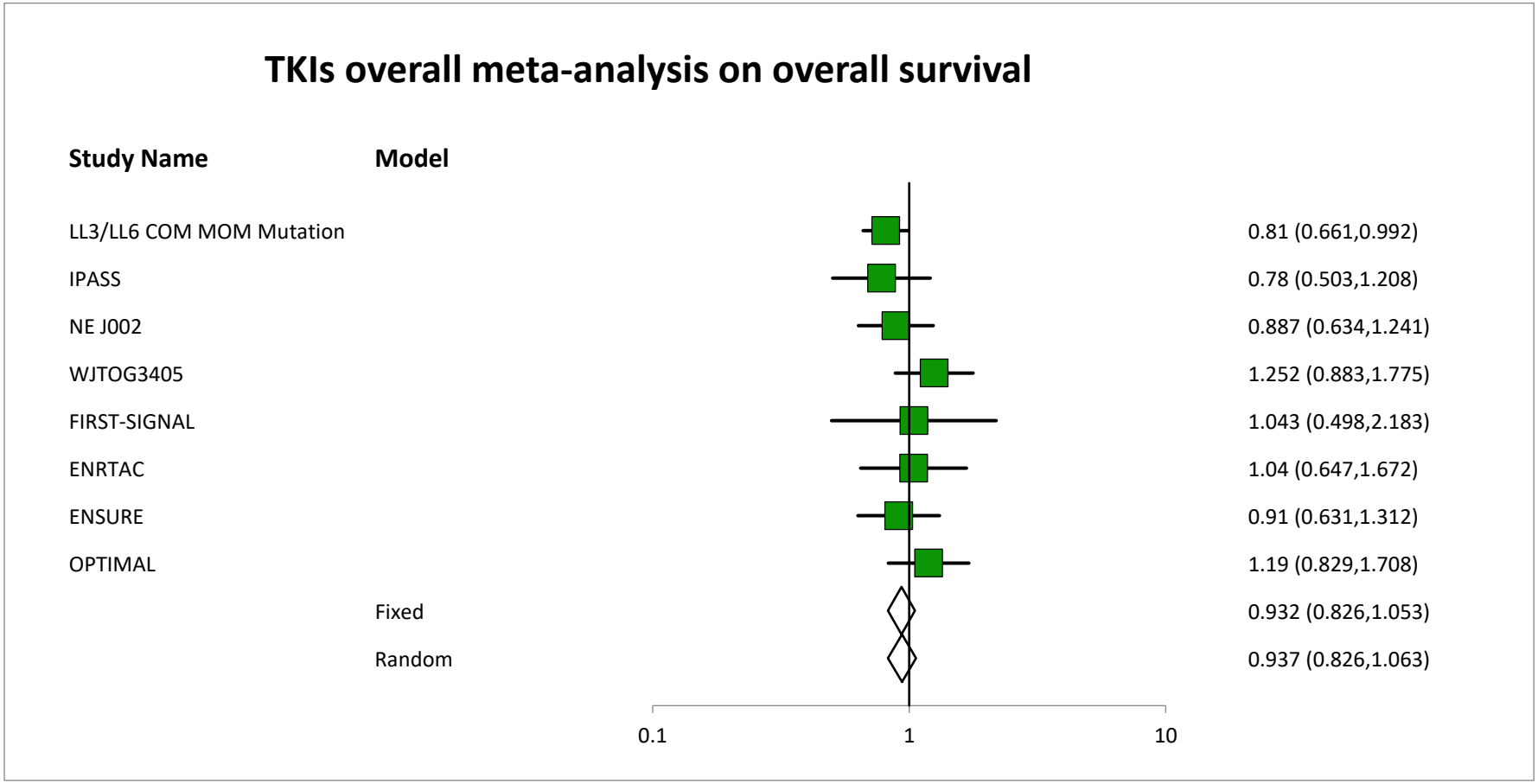


Figure E2. Subgroup meta-analysis of TKIs: Overall survival by mutation type

Mixed Effects Analysis: P=0.115

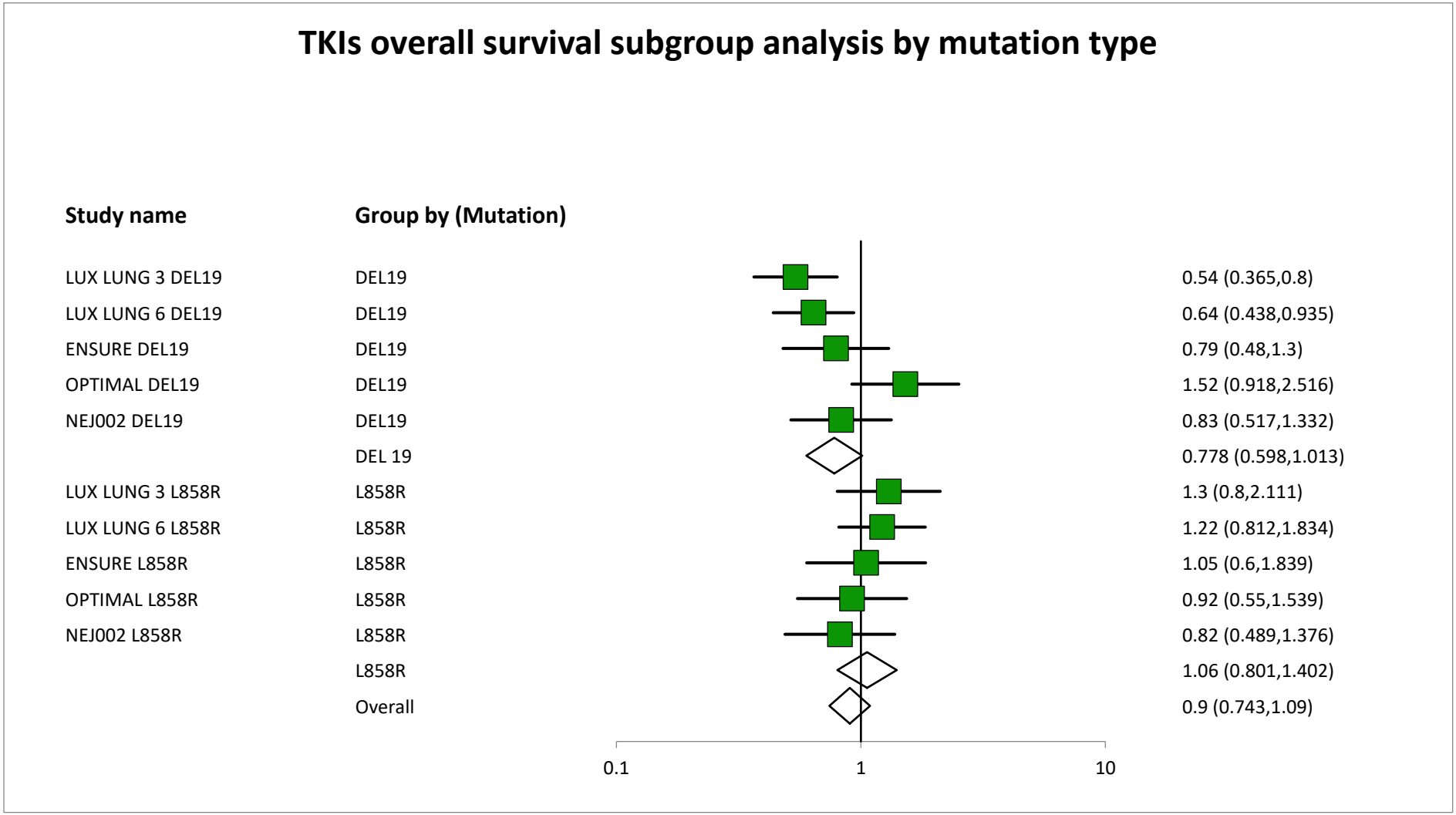


Figure E3. Overall meta-analysis of TKIs: Progression-free survival

I^2=70.285. P<0.0001

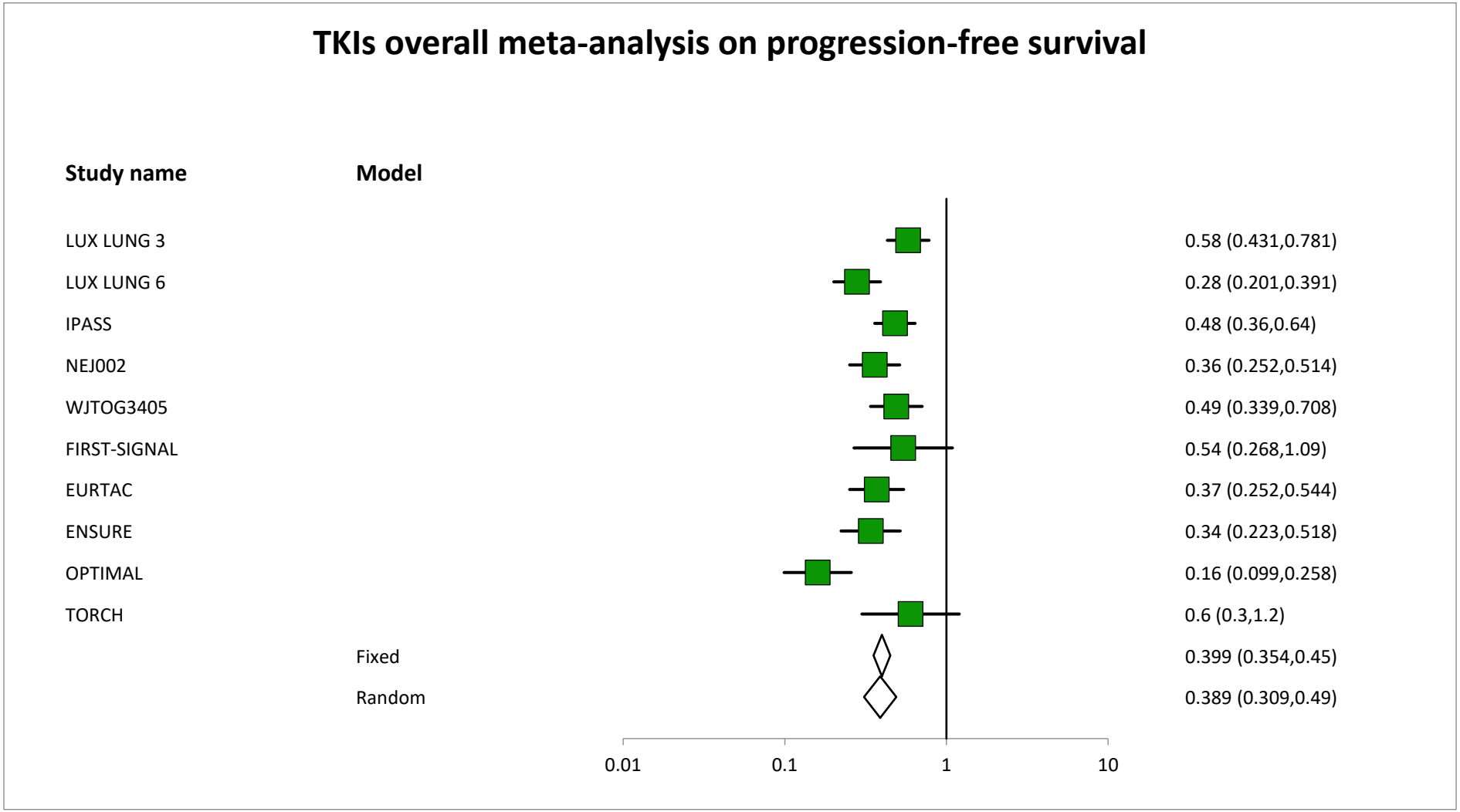


Figure E4. Subgroup meta-analysis of TKIs: Progression-free survival by mutation type

Mixed Effects Analysis: P=0.004

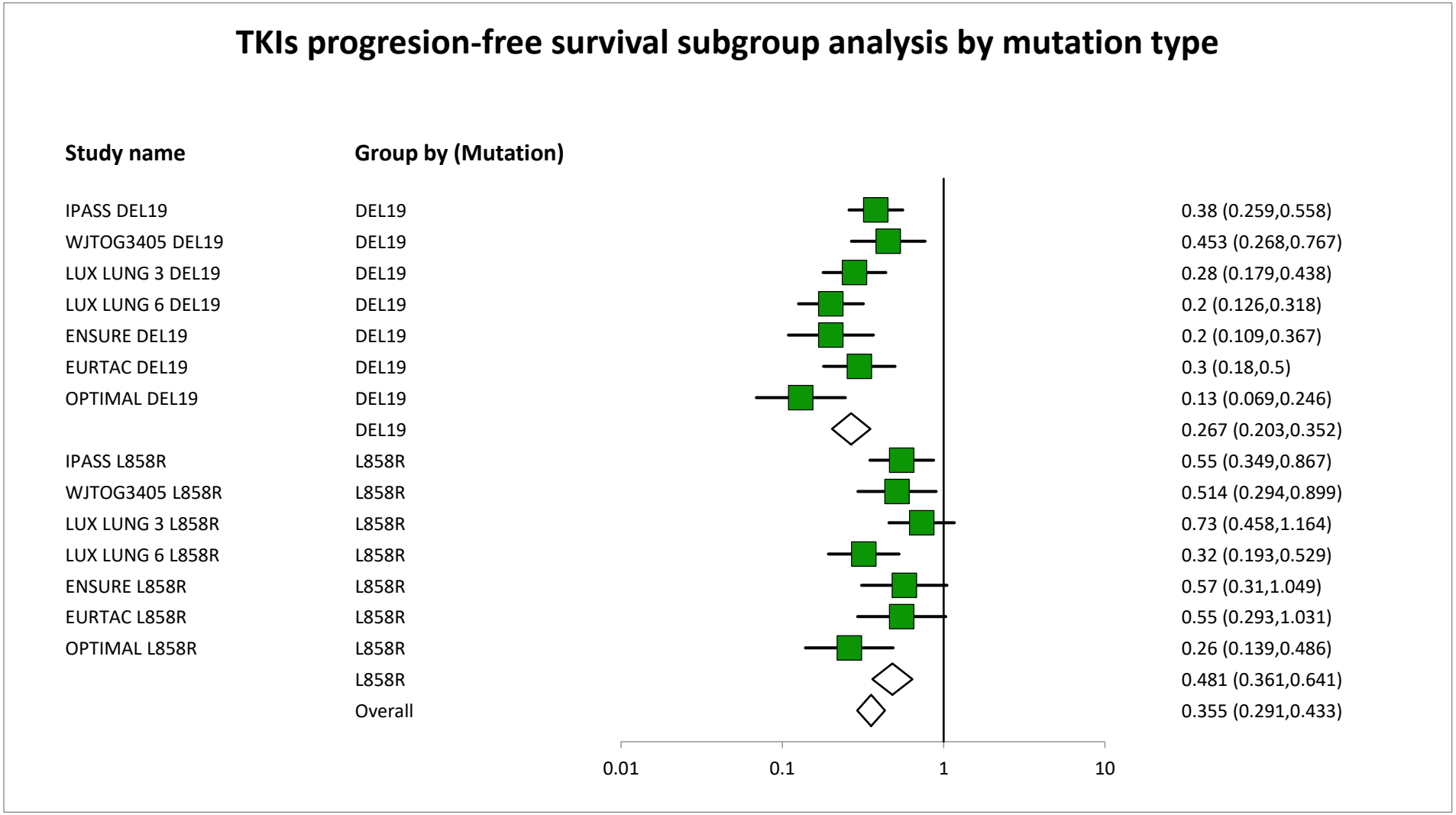


Figure E5. Overall meta-analysis of PD-1 immunotherapies: Overall survival

I^2<0.001. P=0.670

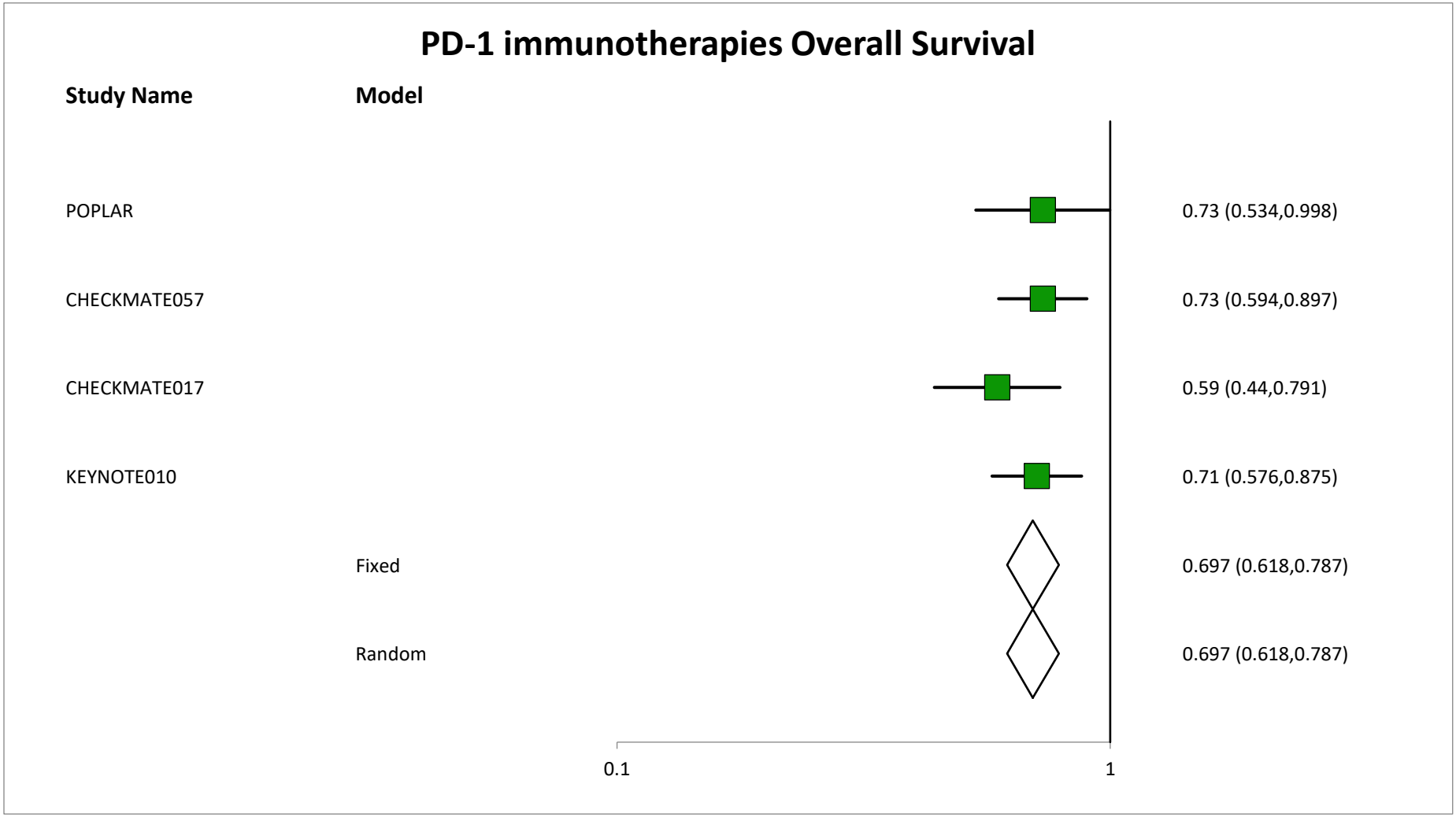


Figure E6. Subgroup meta-analysis of PD-1 immunotherapies: Overall survival by mutation type

Mixed Effects Analysis: P=0.036

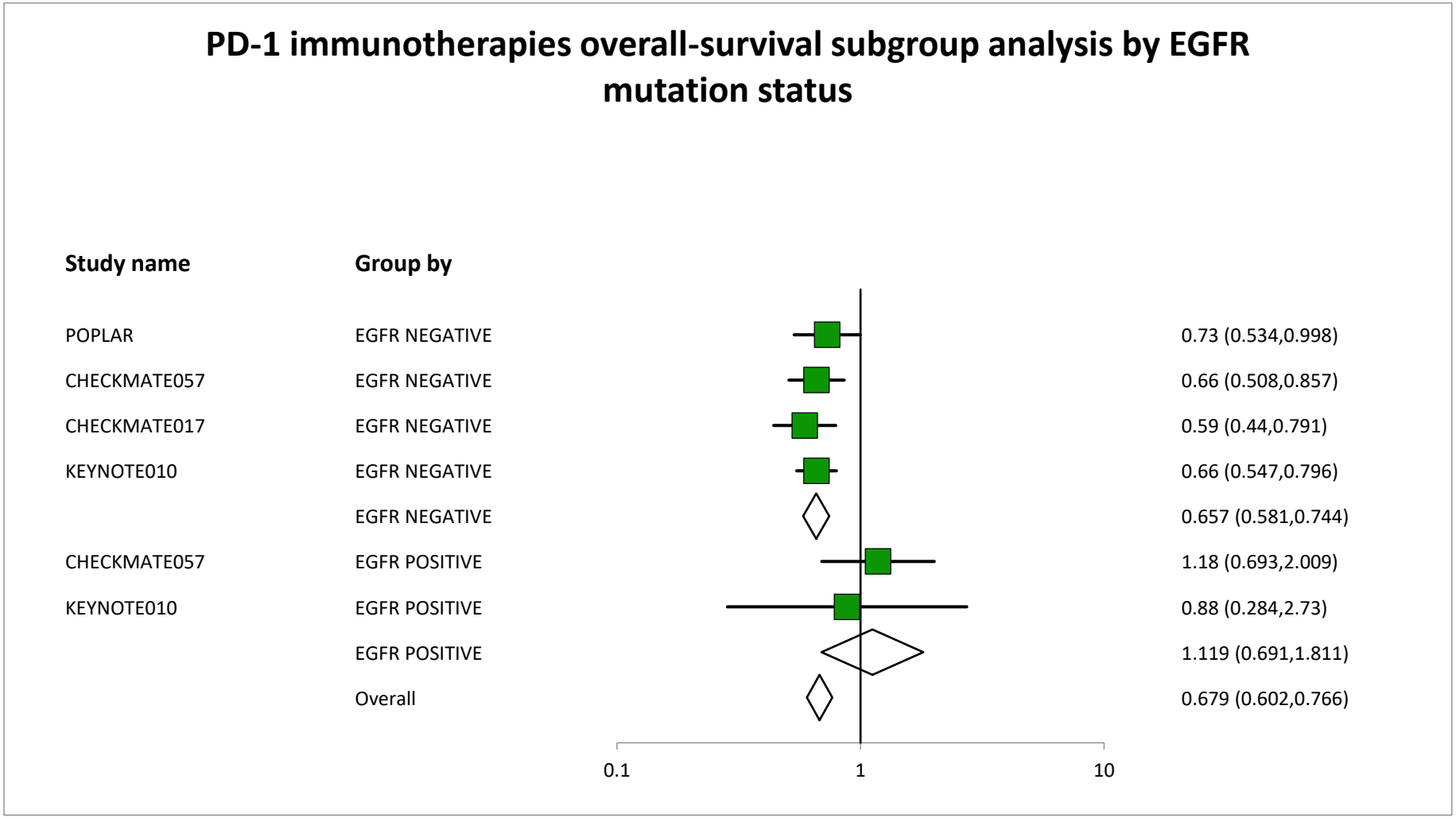


Figure E7. Subgroup meta-analysis of PD-1 immunotherapies: Overall survival by histology

Mixed Effects Analysis: P=0.847

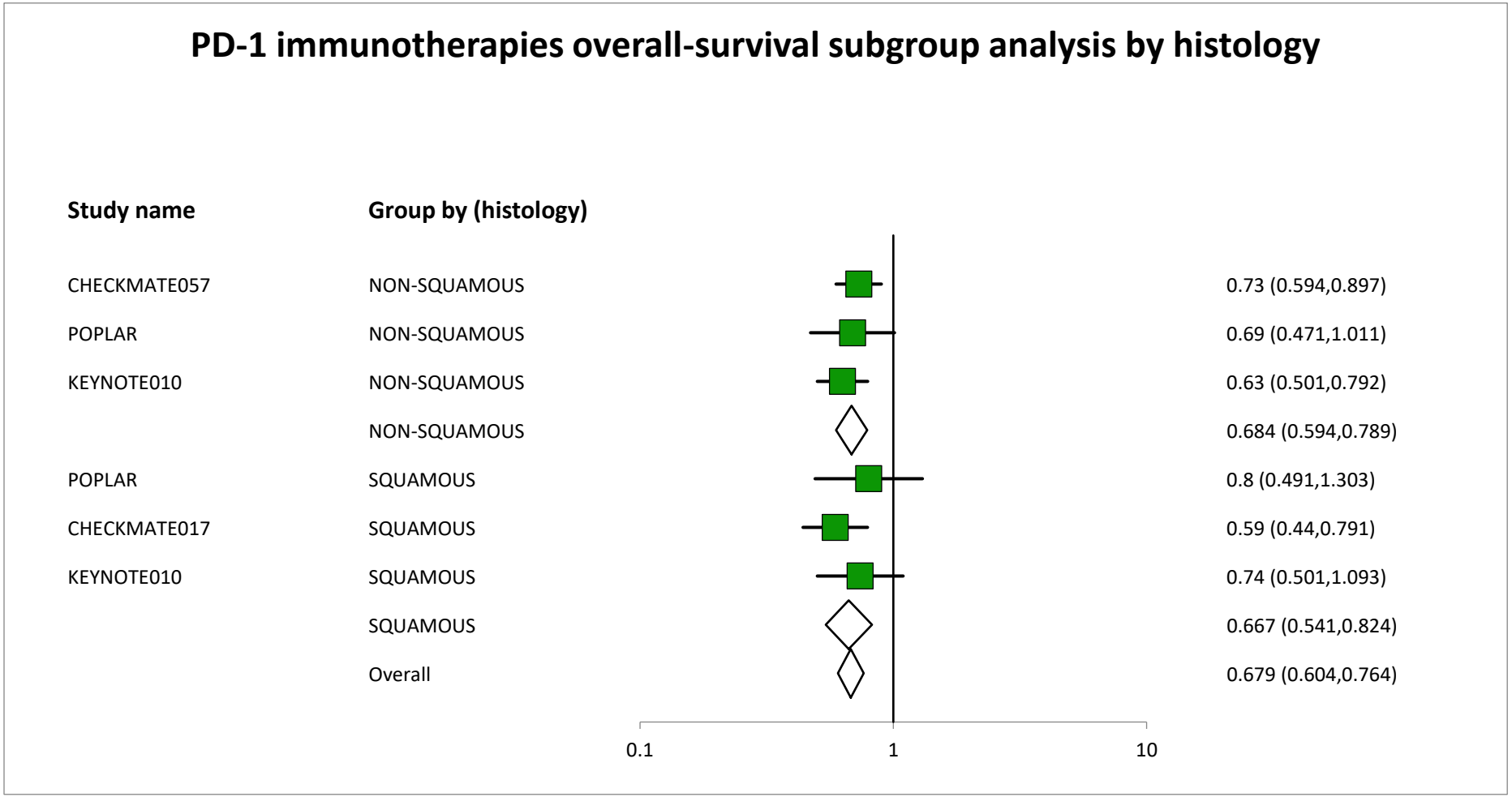


Figure E8. Overall meta-analysis of PD-1 immunotherapies: Progression-free survival

I^2=55.485. P=0.081

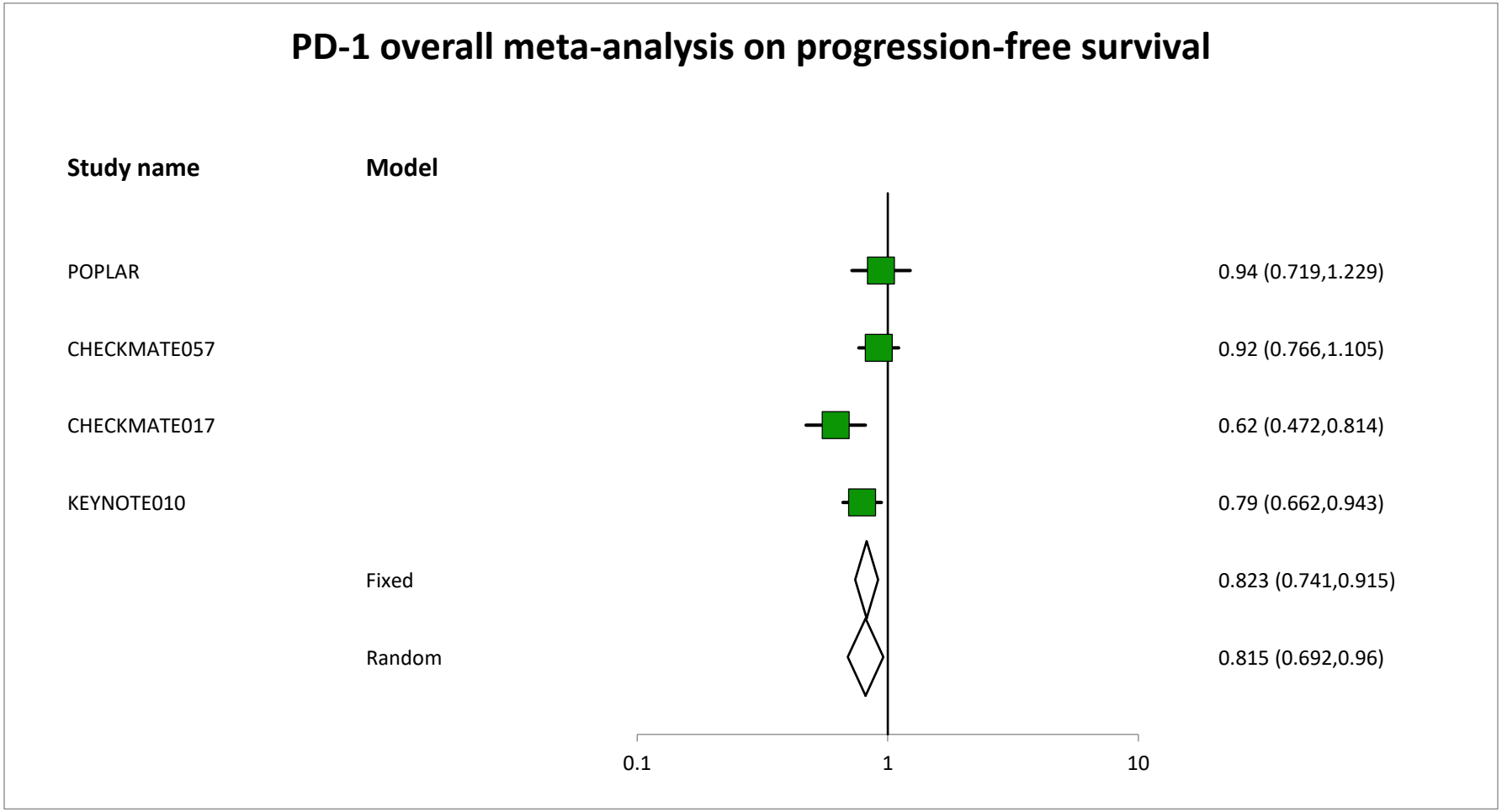


Figure E9. Subgroup meta-analysis of PD-1 immunotherapies: Progression-free survival by mutation type

Mixed Effects Analysis: P=0.002

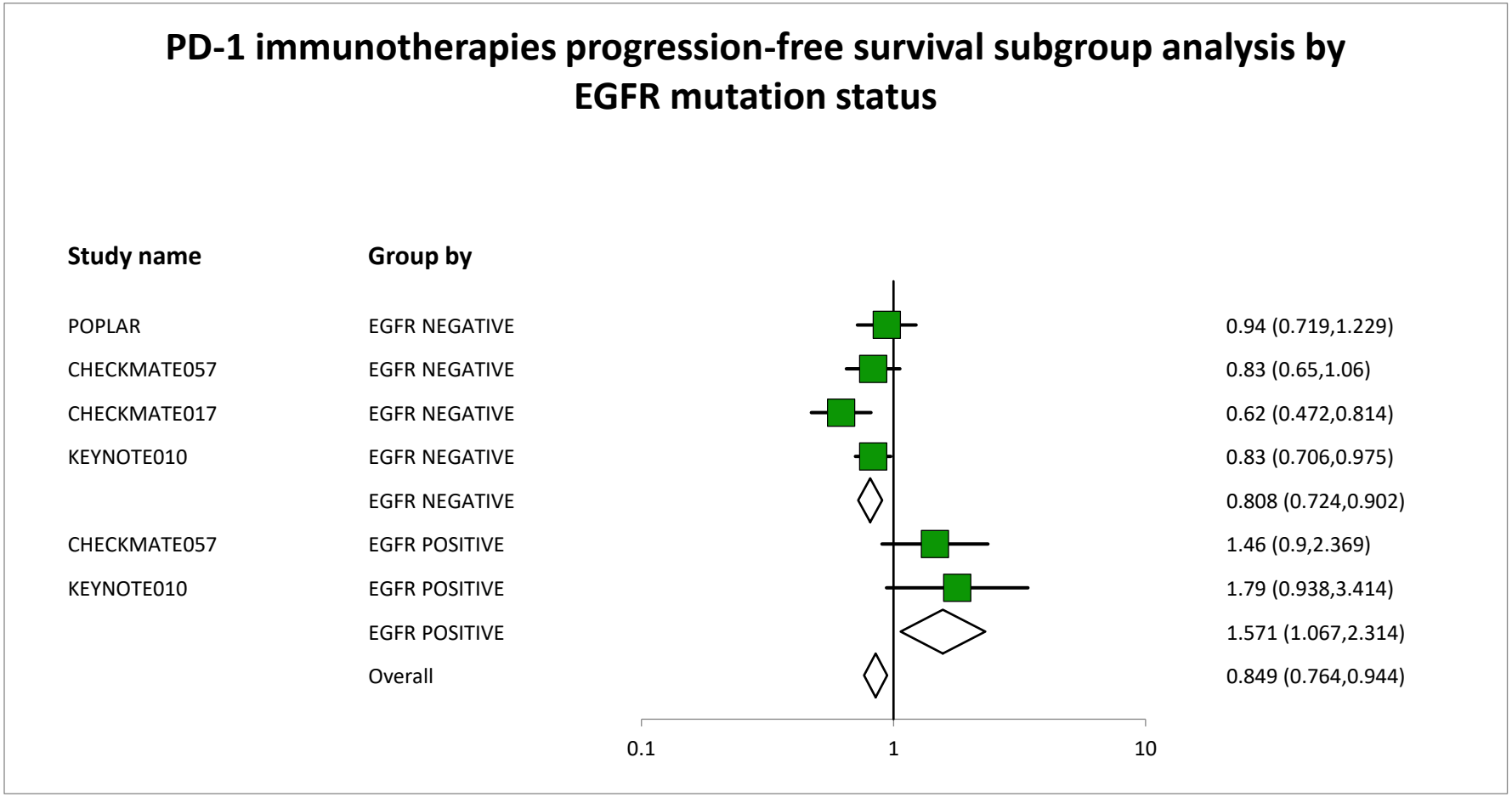
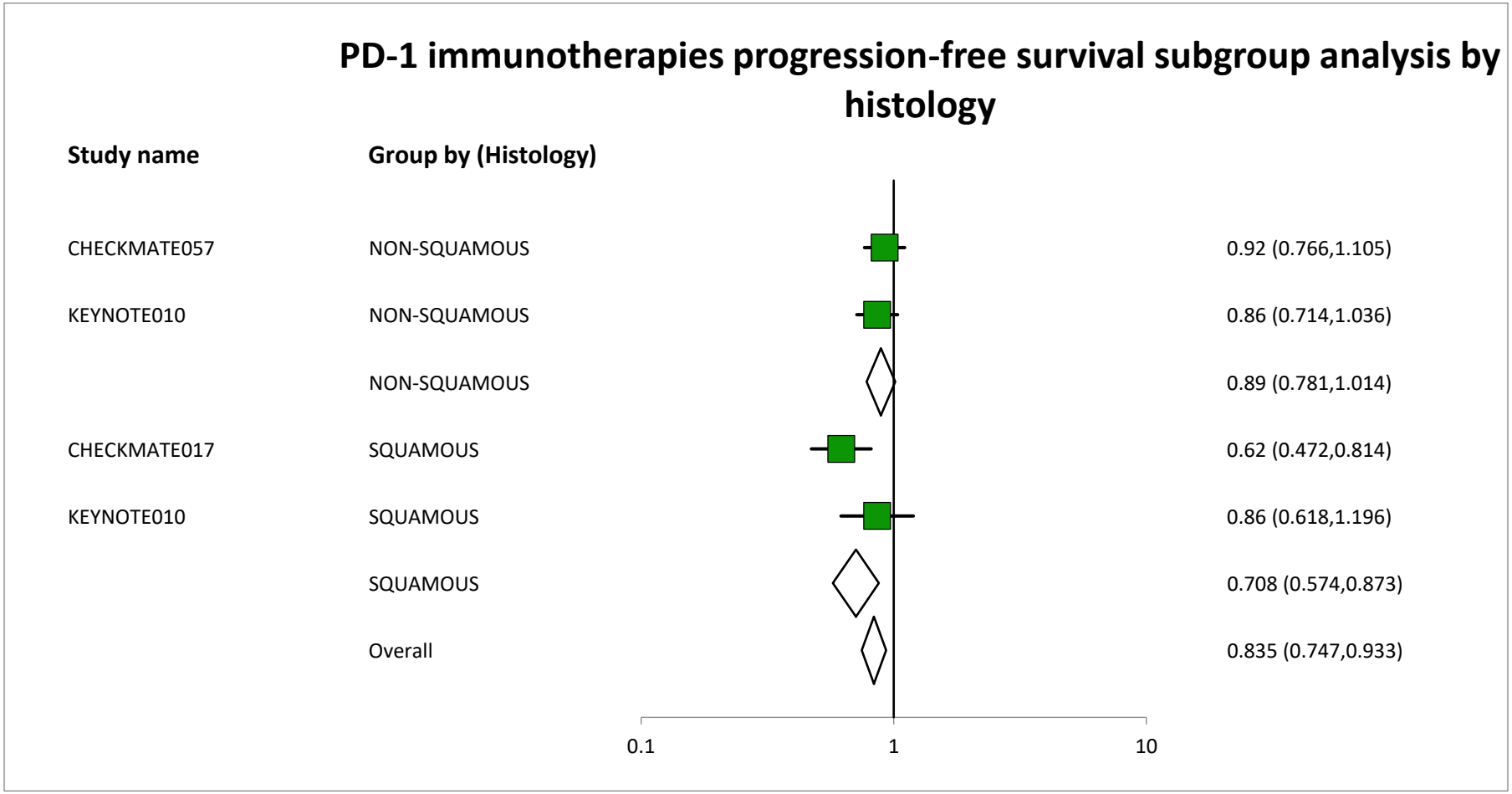


Figure E10. Subgroup meta-analysis of PD-1 immunotherapies: Progression-free survival by histology

Mixed Effects Analysis: P=0.104



Appendix F. Comparative Value Supplemental Information

Model Survival Curve Fitting

The candidate model curves for cisplatin+pemetrexed in the first-line model included the distributional forms Weibull, exponential, log-normal, and log-logistic. We selected the Weibull parametric function in the base case based on face validity, the Akaike Information Criterion (AIC), a graphical assessment of each parametric function, and a knowledge of the expected extrapolation of the progression free survival times (Table F1). Low values for AIC indicate a better mathematical assessment of the fit of the parametric function to the data. It is of note that, while log-logistic and log-normal distributions had generally lower AIC values than the Weibull curves, the tendencies of the former functions to extrapolate long tails was evident on inspection and these distributions were thus ruled out.

Base case PFS and OS curves for cisplatin+pemetrexed were derived from parametric fits to Kaplan-Meier data from a phase III, non-inferiority, randomized study of cisplatin plus gemcitabine compared with cisplatin+pemetrexed in chemotherapy-naïve patients with advanced-stage NSCLC.[2] Curves for docetaxel (Table F1), atezolizumab, nivolumab, and pembrolizumab (Table F2) were fit simultaneously using a 2-stage proportional hazard model, and we then examined goodness-of-fit to see if the predicted survival curves over- or underestimated the Kaplan-Meier estimates at the corresponding time points. This exploration revealed that the best time-point to split the survival curves into phases was 6 months for PFS and 10 months for OS. Within-model hazard ratios (and 95% CIs) were generated using this approach and utilized in the decision model to calculate atezolizumab, nivolumab, and pembrolizumab curves versus the baseline docetaxel curve. Baseline curve parameters for cisplatin-pemetrexed and docetaxel are listed in Table F1.

Table F1. Distribution parameters for parametric survival curve fits

	AIC	lambda	gamma
PFS Curve Parameters, CIS-PEM			
Exponential	4041.97	0.155113682	--
Weibull	3960.928	0.080052304	1.300616392
Log-Logistic	3854.272	0.024972141	2.30206052
Log-Normal	3878.121	1.5824939	0.76770564
OS Curve Parameters, CIS-PEM			
Exponential	4915.896	0.06348231	--
Weibull	4829.679	0.022652501	1.355254013
Log-Logistic	4780.298	0.00846728	1.968570805
Log-Normal	4760.848	2.420395	0.857419484
PFS Curve Parameters, DOCX			
Weibull (1st 6 mo)	--	0.0794942	1.510885647
Gompertz (6+ mo)	--	0.178334	-0.0021675
OS Curve Parameters, DOCX			
Weibull (1st 10 mo)	--	0.0300417	1.458434354
Gompertz (10+ mo)	--	0.0606	0.0200

Table F2. Progression-free survival hazard ratios in second-line immunotherapy patients

2nd Line Immunotherapy	Default	< Range >		SE	Distribution	Reference
PFS Hazard Ratios vs. DOCX						
ATEZ: TC2/3 or IC2/3, <6 months	1.05	0.73	1.51	0.19	LogNormal	Proportional hazards model
NIVO: All Comers, <6 months	1.00	0.85	1.18	0.09	LogNormal	Proportional hazards model
PEMB: PD-L1 >50%, <6 months	0.42	0.25	0.70	0.26	LogNormal	Proportional hazards model
Common PFS HR, Month 6+	0.34	0.25	0.45	0.15	LogNormal	Proportional hazards model
OS Hazard Ratios vs. DOCX						
ATEZ: TC2/3 or IC2/3, <10 months	0.71	0.46	1.08	0.22	LogNormal	Proportional hazards model
ATEZ: TC2/3 or IC2/3, Month 10+	0.30	0.09	0.94	0.59	LogNormal	Proportional hazards model
NIVO: All Comers, <10 months	0.76	0.64	0.91	0.09	LogNormal	Proportional hazards model
NIVO: All Comers, Month 10+	0.58	0.43	0.78	0.15	LogNormal	Proportional hazards model
PEMB: PD-L1 >50%, <10 months	0.50	0.36	0.70	0.17	LogNormal	Proportional hazards model
PEMB: PD-L1 >50%, Month 10+	0.24	0.09	0.64	0.51	LogNormal	Proportional hazards model

Table F3. Survival hazard ratios in treatment-naïve EGFR positive patients

1st Line TKIs: EGFR+	Default	< Range >		SE	Probabilistic	Distribution	Reference
PFS Hazard Ratios vs. CIS-PEM							
AFAT	0.41	0.24	0.72	0.28	0.37	LogNormal	NMA
ERLO	0.36	0.19	0.69	0.33	0.30	LogNormal	NMA
GEFI	0.58	0.34	1.01	0.28	0.39	LogNormal	NMA
OS Hazard Ratios vs. CIS-PEM							
AFAT	0.48	0.38	0.58	0.10	0.51	LogNormal	Assumption
ERLO	0.48	0.38	0.58	0.10	0.41	LogNormal	Assumption
GEFI	0.48	0.38	0.58	0.10	0.51	LogNormal	Assumption

Model Inputs

Table F4. Treatment Regimens and Dosing

	Dosage	Schedule	Route	Duration
Cisplatin	75 mg/m^2	1x/cycle	IV	6 21-day cycles
Pemetrexed	500 mg/m^2	1x/cycle	IV	6 21-day cycles
Docetaxel	75 mg/m^2	every 3 weeks	IV	until progression
Afatinib	40 mg	1x daily	oral	until progression
Erlotinib	150 mg	1x daily	oral	until progression
Gefitinib	250 mg	1x daily	oral	until progression
Atezolizumab	1200 mg	every 3 weeks	IV	until progression
Nivolumab	3 mg/kg	every 2 weeks	IV	until progression
Pembrolizumab	2 mg/kg	every 3 weeks	IV	until progression

Table F5. Other Cost Parameters

Progression/Supportive Care Costs	Default	< Range >		SE	Distribution	Reference
PD-1 Assay Cost	$274	$219	$329	$28	Normal	MarketScan
End of Life Cost	$50,000	$0	$173,745	$44,323	Gamma	Graham et al.
Prog Supportive Care Cost	$108.55	$100.60	$116.53	$4.06	Normal	Graham et al.
PFS Supportive Care Cost	$360.48	$187.57	$535.50			Graham et al.
TKI Time in Progression (months)	13.5	10.8	16.2	1.4	Normal	Assumption, within-model average of AFAT/ERLO/GEFI
PD-1 Time in Progression (months)	7.5	6.0	9.1	0.8	Normal	Assumption, within-model average of ATEZ/NIVO/PEMB
Cost of Gemcitabine, per mg	$0.05	$0.04	$0.06	$0.01	Normal	Redbook

Table F6. Adverse Event Costs

Cost per Adverse Event	Default	< Range >		SE	Distribution	Reference[116]
Anemia	$12,110	$9,688	$14,532	$1,236	Normal	DRG 808
Diarrhea	$6,462	$5,170	$7,755	$659	Normal	DRG 391
Dyspnea	$3,951	$3,161	$4,741	$403	Normal	DRG 204
Fatigue	$6,136	$4,909	$7,363	$626	Normal	DRG 947
Hyponatremia	$6,133	$4,907	$7,360	$626	Normal	DRG 640
Infection	$10,314	$8,251	$12,377	$1,052	Normal	DRG 177
Leukopenia	$12,110	$9,688	$14,532	$1,236	Normal	DRG 808
Nausea	$6,462	$5,170	$7,755	$659	Normal	DRG 391
Neuromotor	$6,926	$5,541	$8,311	$707	Normal	DRG 945
Neutropenia	$12,110	$9,688	$14,532	$1,236	Normal	DRG 808
Paronychia/Nail disorders	$7,788	$6,230	$9,345	$795	Normal	DRG 602
Pneumonitis/Pneumonia	$7,728	$6,183	$9,274	$789	Normal	DRG 193
Pulmonary/Respiratory Infx.	$10,314	$8,251	$12,377	$1,052	Normal	DRG 177
Rash	$7,429	$5,943	$8,914	$758	Normal	DRG 606
Skin reactions	$7,429	$5,943	$8,914	$758	Normal	DRG 606
Stomatitis	$8,101	$6,481	$9,721	$827	Normal	DRG 157

Table F7. Health state utilities

Quality of Life Parameters	Default	< Range >		SE	Distribution	Reference
Health State Utilities						
1L PF disease, on treatment	0.78	0.77	0.80	0.01	Beta	LUX-Lung[117]
1L Progressed disease	0.67	0.59	0.75	0.04	Beta	Chouaid et al.[118]
2L PF disease, on treatment	0.65	0.61	0.70	0.02	Beta	Nafees et al.[119]
2L Progressed disease	0.47	0.43	0.52	0.02	Beta	Nafees et al.[119]
Adverse Event Disutilities						
Anemia	0.090	0.059	0.120	0.015	Beta	Nafees et al.[119]
Diarrhea	0.047	0.016	0.077	0.016	Beta	Nafees et al.[119]
Dyspnea	0.050	0.026	0.074	0.012	Beta	Doyle et al.[120]
Fatigue	0.073	0.037	0.110	0.018	Beta	Nafees et al.[119]
Hyponatremia	0.090	0.059	0.120	0.015	Beta	Nafees et al.[119]
Infection	0.047	0.016	0.077	0.016	Beta	Nafees et al.[119]
Leukopenia	0.090	0.059	0.120	0.015	Beta	Nafees et al.[119]
Nausea	0.048	0.016	0.080	0.016	Beta	Nafees et al.[119]
Neuromotor	0.069	0.045	0.093	0.012	Beta	Doyle et al.[120]
Neutropenia	0.090	0.059	0.120	0.015	Beta	Nafees et al.[119]
Paronychia/Nail disorders	0.032	0.010	0.055	0.012	Beta	Nafees et al.[119]
Pneumonitis/Pneumonia	0.073	0.037	0.110	0.018	Beta	Nafees et al.[119]
Pulmonary/Respiratory Infx.	0.046	0.024	0.068	0.011	Beta	Doyle et al.[120]
Rash	0.032	0.010	0.055	0.012	Beta	Nafees et al.[119]
Skin reactions	0.032	0.010	0.055	0.012	Beta	Nafees et al.[119]
Stomatitis	0.032	0.010	0.055	0.012	Beta	Nafees et al.[119]

Probabilistic and Scenario Analysis Results

Table F8a. Probabilistic base case results: TKI therapy, 1st-line (results by regimen)

	CIS-PEM		AFAT		ERLO		GEFI	
	Mean	**Credible Range**	**Mean**	**Credible Range**	**Mean**	**Credible Range**	**Mean**	**Credible Range**
Total Costs	$136,106	($60,594 - $431,119)	$224,596	($127,692 - $508,724)	$235,536	($133,696 - $533,804)	$205,732	($113,933 - $493,528)
Drug Costs	$32,019	($25,487 - $38,657)	$94,903	($57,557 - $145,024)	$109,372	($62,702 - $179,542)	$75,637	($46,960 - $116,724)
PFS Supp. Care Costs	$10,217	($9,660 - $10,791)	$21,544	($13,341 - $32,505)	$24,059	($14,351 - $38,926)	$16,426	($10,750 - $24,463)
Administration Costs	$1,146	($978 - $1,312)	$0	$0	$0	$0	$0	$0
Progression Costs	$15,033	($11,937 - $18,505)	$33,639	($10,735 - $57,577)	$29,478	($1,555 - $55,667)	$42,524	($22,783 - $65,690)
Death Costs	$72,705	($77 - $366,886)	$70,788	($75 - $354,961)	$70,775	($75 - $356,320)	$70,765	($75 - $358,419)
Adverse Event Costs	$4,986	($3,687 - $6,466)	$3,724	($2,778 - $4,807)	$1,851	($1,193 - $2,640)	$381	($131 - $764)
Total QALYs	0.88	(0.81 - 0.95)	1.53	(1.24 - 1.86)	1.55	(1.26 - 1.89)	1.50	(1.21 - 1.84)
PFS QALYs	0.42	(0.40 - 0.44)	0.87	(0.55 - 1.31)	0.97	(0.59 - 1.54)	0.67	(0.44 - 0.99)
Progression QALYs	0.46	(0.39 - 0.53)	0.65	(0.21 - 1.09)	0.57	(0.03 - 1.07)	0.83	(0.45 - 1.22)
Total Life Years (OS)	1.22	(1.16 - 1.29)	2.09	(1.70 - 2.55)	2.10	(1.70 - 2.58)	2.09	(1.68 - 2.58)
PFS LYs	0.54	(0.51 - 0.56)	1.11	(0.70 - 1.66)	1.24	(0.75 - 1.97)	0.86	(0.56 - 1.26)
Progression LYs	0.69	(0.62 - 0.76)	0.97	(0.32 - 1.58)	0.86	(0.05 - 1.56)	1.23	(0.69 - 1.81)
Median PFS (months)	5.1	(4.86 - 5.55)	11.0	(6.70 - 16.59)	12.3	(7.39 - 20.04)	8.4	(5.32 - 12.45)
Median OS (months)	12.4	(11.76 - 13.14)	21.7	(17.51 - 26.71)	21.8	(17.51 - 27.17)	21.7	(17.28 - 27.17)

Table F8b. Probabilistic base case results: TKI therapy, 1st-line (incremental results)

Incremental Results	CIS-PEM		AFAT		ERLO		GEFI	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
ICER (QALYs)	--	--	$136,613	($85,626 - $222,278)	$149,250	($90,315 - $249,030)	$112,645	($68,633 - $185,897)
Incremental Costs	--	--	$88,490	($51,356 - $135,327)	$99,430	($55,748 - $163,845)	$69,627	($39,244 - $108,181)
Drug Costs	--	--	$62,884	($25,110 - $113,005)	$77,353	($29,810 - $147,698)	$43,619	($14,018 - $85,237)
PFS Supp. Care Costs	--	--	$11,327	($3,288 - $22,101)	$13,842	($4,152 - $28,497)	$6,209	($505 - $14,297)
Administration Costs	--	--	-$1,146	(-$1,312 - -$978)	-$1,146	(-$1,312 - -$978)	-$1,146	(-$1,312 - -$978)
Progression Costs	--	--	$18,605	(-$4,392 - $42,173)	$14,445	(-$12,816 - $40,468)	$27,490	($8,367 - $50,661)
Death Costs	--	--	-$1,917	(-$10,198 - -$2)	-$1,930	(-$10,636 - -$2)	-$1,940	(-$10,261 - -$2)
Adverse Event Costs	--	--	-$1,263	(-$3,084 - $413)	-$3,135	(-$4,818 - -$1,644)	-$4,606	(-$6,130 - -$3,256)
Incremental QALYs	--	--	0.65	(0.38 - 0.96)	0.67	(0.39 - 0.99)	0.62	(0.35 - 0.94)
PFS QALYs	--	--	0.45	(0.13 - 0.88)	0.55	(0.17 - 1.11)	0.25	(0.02 - 0.57)
Progression QALYs	--	--	0.19	(-0.24 - 0.60)	0.11	(-0.41 - 0.59)	0.37	(0.00 - 0.75)
Incremental Life Years (OS)	--	--	0.87	(0.49 - 1.32)	0.87	(0.48 - 1.33)	0.87	(0.46 - 1.35)
PFS LYs	--	--	0.58	(0.17 - 1.11)	0.70	(0.21 - 1.43)	0.32	(0.03 - 0.73)
Progression LYs	--	--	0.29	(-0.36 - 0.89)	0.17	(-0.62 - 0.88)	0.55	(0.00 - 1.11)

Table F9a. Probabilistic base case results: PD-1 immunotherapy, 2nd-line (results by regimen)

	DOCX		ATEZ: TC2/3 or IC2/3		NIVO: All Comers		PEMB: PD-L1 >50%	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total Costs	$123,176	($43,541 - $400,568)	$303,258	($114,790 - $741,307)	$290,883	($109,836 - $753,798)	$431,817	($173,841 - $1,085,836)
Drug Costs	$13,176	($8,063 - $28,354)	$162,664	($58,945 - $534,595)	$170,014	($64,412 - $540,549)	$273,109	($103,639 - $846,396)
PFS Supp. Care Costs	$10,401	($6,551 - $24,496)	$22,643	($7,245 - $83,100)	$23,288	($8,066 - $82,098)	$38,084	($13,370 - $131,050)
Administration Costs	$1,304	($793 - $2,825)	$2,559	($913 - $8,242)	$3,910	($1,444 - $12,416)	$4,276	($1,638 - $13,391)
Progression Costs	$5,746	($1,203 - $21,066)	$49,974	($4,651 - $168,870)	$23,408	($2,892 - $107,479)	$53,394	($1,964 - $173,274)
Death Costs	$73,269	($115 - $348,401)	$64,552	($96 - $310,337)	$69,894	($106 - $334,917)	$61,181	($90 - $297,208)
Adverse Event Costs	$19,280	($16,456 - $22,205)	$867	($476 - $1,400)	$369	($136 - $737)	$1,773	($1,109 - $2,594)
Total QALYs	0.72	(0.39 - 2.02)	1.77	(0.60 - 4.29)	1.22	(0.53 - 3.11)	2.31	(0.84 - 5.07)
PFS QALYs	0.34	(0.22 - 0.74)	0.69	(0.25 - 2.25)	0.71	(0.27 - 2.24)	1.15	(0.45 - 3.57)
Progression QALYs	0.37	(0.06 - 1.68)	1.08	(0.10 - 3.57)	0.51	(0.06 - 2.31)	1.15	(0.04 - 3.85)
Total Life Years (OS)	1.32	(0.66 - 3.99)	3.35	(1.04 - 8.54)	2.18	(0.91 - 6.03)	4.23	(1.40 - 9.68)
PFS LYs	0.53	(0.35 - 1.14)	1.06	(0.38 - 3.49)	1.09	(0.42 - 3.45)	1.78	(0.70 - 5.48)
Progression LYs	0.79	(0.12 - 3.52)	2.29	(0.21 - 7.61)	1.09	(0.13 - 4.85)	2.45	(0.09 - 7.95)
Median PFS (months)	4.1	(3.25 - 5.09)	4.1	(3.02 - 5.55)	4.1	(3.25 - 5.32)	10.3	(5.09 - 19.12)
Median OS (months)	8.9	(6.24 - 14.53)	27.8	(7.16 - 240.13)	13.7	(7.62 - 29.25)	46.2	(10.15 - 240.13)

Table F9b. Probabilistic base case results: PD-1 immunotherapy, 2nd-line (incremental results)

	DOCX		ATEZ: TC2/3 or IC2/3		NIVO: All Comers		PEMB: PD-L1 >50%	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
ICER (QALYs)	--	--	$170,930	($64,586 - $505,317)	$331,784	($138,782 - $623,479)	$193,745	($81,526 - $406,837)
Incremental Costs	--	--	$180,082	($50,440 - $568,827)	$167,707	($50,857 - $562,088)	$308,642	($105,256 - $923,343)
Drug Costs	--	--	$149,488	($49,913 - $507,052)	$156,838	($55,199 - $516,297)	$259,933	($94,525 - $820,031)
PFS Supp. Care Costs	--	--	$12,241	($159 - $57,034)	$12,887	($1,278 - $57,995)	$27,683	($6,434 - $105,266)
Administration Costs	--	--	$1,255	(-$60 - $5,480)	$2,606	($522 - $9,654)	$2,972	($695 - $10,361)
Progression Costs	--	--	$44,228	($2,334 - $152,849)	$17,663	($1,280 - $87,010)	$47,649	(-$563 - $156,456)
Death Costs	--	--	-$8,717	(-$63,937 - -$5)	-$3,375	(-$25,575 - -$3)	-$12,088	(-$84,108 - -$9)
Adverse Event Costs	--	--	-$18,414	(-$21,421 - -$15,530)	-$18,911	(-$21,850 - -$16,052)	-$17,507	(-$20,480 - -$14,586)
Incremental QALYs	--	--	1.05	(0.15 - 2.79)	0.51	(0.11 - 1.52)	1.59	(0.41 - 3.68)
PFS QALYs	--	--	0.35	(0.01 - 1.50)	0.37	(0.04 - 1.50)	0.81	(0.22 - 2.81)
Progression QALYs	--	--	0.71	(-0.04 - 2.35)	0.14	(-0.07 - 0.85)	0.78	(-0.10 - 2.55)
Incremental Life Years (OS)	--	--	2.03	(0.26 - 5.59)	0.86	(0.19 - 2.51)	2.91	(0.62 - 6.67)
PFS LYs	--	--	0.53	(0.01 - 2.30)	0.56	(0.06 - 2.32)	1.24	(0.33 - 4.28)
Progression LYs	--	--	1.50	(-0.08 - 5.01)	0.30	(-0.15 - 1.81)	1.66	(-0.22 - 5.42)

Table F10a. Scenario 1: OS benefit turned off for TKI therapies (results by regimen)

	CIS-PEM	AFAT	ERLO	GEFI
Total Costs	$111,443	$170,653	$176,016	$144,989
Drug Costs	$32,042	$89,872	$102,726	$71,548
PFS Supp. Care Costs	$10,217	$20,364	$22,520	$15,571
Administration Costs	$1,145	$0	$0	$0
Progression Costs	$14,845	$8,608	$668	$9,090
Death Costs	$48,192	$48,066	$48,247	$48,405
Adverse Event Costs	$5,002	$3,744	$1,855	$375
Total QALYs	0.88	1.00	0.93	0.81
PFS QALYs	0.42	0.83	0.91	0.64
Progression QALYs	0.46	0.17	0.01	0.18
Total Life Years (OS)	1.22	1.31	1.18	1.08
PFS LYs	0.54	1.06	1.16	0.81
Progression LYs	0.68	0.25	0.02	0.26
Median PFS (months)	5.1	10.4	11.5	7.9
Median OS (months)	12.5	13.4	12.0	10.8

Table F10b. Scenario 1: OS benefit turned off for TKI therapies (incremental results)

	CIS-PEM	AFAT	ERLO	GEFI
ICER (QALYs)	--	$506,274	$1,364,304	-$521,117
ICER (LYs)		$691,975	-$1,744,709	-$232,828
Incremental Costs	--	$59,211	$64,573	$33,546
Drug Costs	--	$57,830	$70,684	$39,506
PFS Supp. Care Costs	--	$10,147	$12,303	$5,354
Administration Costs	--	-$1,145	-$1,145	-$1,145
Progression Costs	--	-$6,236	-$14,177	-$5,755
Death Costs	--	-$126	$55	$213
Adverse Event Costs	--	-$1,259	-$3,147	-$4,628
Incremental QALYs	--	0.12	0.05	-0.06
PFS QALYs	--	0.41	0.49	0.22
Progression QALYs	--	-0.29	-0.45	-0.28
Incremental Life Years (OS)	--	0.09	-0.04	-0.14
PFS LYs	--	0.52	0.63	0.28
Progression LYs	--	-0.43	-0.67	-0.42

Table F10c. Scenario 1: OS benefit turned off for TKI therapies (probabilistic results by regimen)

	CIS-PEM		AFAT		ERLO		GEFI	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total Costs	$134,997	($60,182 - $436,631)	$202,712	($102,330 - $505,109)	$215,068	($105,173 - $510,572)	$175,665	($82,653 - $481,605)
Drug Costs	$32,126	($25,722 - $38,537)	$94,698	($57,314 - $146,083)	$110,937	($61,204 - $179,761)	$75,447	($45,891 - $116,707)
PFS Supp. Care Costs	$10,226	($9,661 - $10,792)	$21,489	($13,631 - $32,099)	$24,416	($14,072 - $39,511)	$16,478	($10,423 - $24,461)
Administration Costs	$1,143	($985 - $1,307)	$0	$0	$0	$0	$0	$0
Progression Costs	$14,999	($11,879 - $18,469)	$11,794	($0 - $39,473)	$6,865	($0 - $35,058)	$11,803	($0 - $37,690)
Death Costs	$71,491	($66 - $371,246)	$70,977	($66 - $367,019)	$70,997	($65 - $369,309)	$71,562	($66 - $370,870)
Adverse Event Costs	$5,012	($3,609 - $6,595)	$3,753	($2,780 - $4,814)	$1,853	($1,204 - $2,674)	$376	($126 - $762)
Total QALYs	0.88	(0.81 - 0.95)	1.10	(0.75 - 1.57)	1.12	(0.74 - 1.66)	0.90	(0.60 - 1.36)
PFS QALYs	0.42	(0.40 - 0.44)	0.87	(0.56 - 1.29)	0.99	(0.58 - 1.57)	0.67	(0.43 - 0.99)
Progression QALYs	0.46	(0.39 - 0.53)	0.23	(0.00 - 0.77)	0.13	(0.00 - 0.66)	0.23	(0.00 - 0.72)
Total Life Years (OS)	1.22	(1.16 - 1.29)	1.45	(0.98 - 2.14)	1.45	(0.95 - 2.19)	1.20	(0.77 - 1.86)
PFS LYs	0.54	(0.51 - 0.56)	1.11	(0.71 - 1.64)	1.26	(0.74 - 2.00)	0.86	(0.54 - 1.26)
Progression LYs	0.69	(0.62 - 0.76)	0.34	(0.00 - 1.15)	0.20	(0.00 - 0.99)	0.34	(0.00 - 1.07)
Median PFS (months)	5.1	(4.86 - 5.55)	11.0	(6.93 - 16.59)	12.5	(7.16 - 20.27)	8.4	(5.32 - 12.45)
Median OS (months)	12.4	(11.76 - 13.14)	14.8	(9.69 - 22.34)	14.7	(9.46 - 22.80)	12.1	(7.62 - 19.35)

Table F10d. Scenario 1: OS benefit turned off for TKI therapies (incremental probabilistic results)

	CIS-PEM		AFAT		ERLO		GEFI	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
ICER (QALYs)	--	--	$308,583	(-$2,685,680 - $2,793,613)	$336,608	(-$2,962,168 - $2,857,088)	$1,990,074	(-$3,829,139 - $5,168,614)
Incremental Costs	--	--	$67,715	($28,137 - $121,609)	$80,071	($27,810 - $155,414)	$40,668	($8,248 - $82,677)
Drug Costs	--	--	$62,572	($23,411 - $114,360)	$78,810	($28,887 - $146,777)	$43,321	($12,737 - $85,431)
PFS Supp. Care Costs	--	--	$11,263	($3,508 - $21,850)	$14,190	($3,933 - $29,260)	$6,252	($211 - $14,159)
Administration Costs	--	--	-$1,143	(-$1,307 - -$985)	-$1,143	(-$1,307 - -$985)	-$1,143	(-$1,307 - -$985)
Progression Costs	--	--	-$3,205	(-$16,978 - $25,310)	-$8,134	(-$17,712 - $19,405)	-$3,196	(-$16,764 - $22,127)
Death Costs	--	--	-$514	(-$4,160 - $669)	-$494	(-$4,008 - $877)	$71	(-$1,947 - $2,163)
Adverse Event Costs	--	--	-$1,259	(-$3,140 - $465)	-$3,158	(-$4,877 - -$1,571)	-$4,636	(-$6,278 - -$3,222)
Incremental QALYs	--	--	0.22	(-0.13 - 0.70)	0.24	(-0.14 - 0.77)	0.02	(-0.29 - 0.48)
PFS QALYs	--	--	0.45	(0.14 - 0.87)	0.57	(0.16 - 1.14)	0.25	(0.01 - 0.56)
Progression QALYs	--	--	-0.23	(-0.50 - 0.31)	-0.33	(-0.52 - 0.20)	-0.23	(-0.50 - 0.26)
Incremental Life Years (OS)	--	--	0.23	(-0.24 - 0.91)	0.23	(-0.27 - 0.96)	-0.02	(-0.46 - 0.65)
PFS LYs	--	--	0.57	(0.18 - 1.10)	0.72	(0.20 - 1.46)	0.32	(0.01 - 0.72)
Progression LYs	--	--	-0.34	(-0.72 - 0.45)	-0.49	(-0.74 - 0.29)	-0.35	(-0.72 - 0.39)

Table F11a. Scenario 2: Weibull model for DOCX curves with trial-reported HRs applied to derive PD-1 curves (results by regimen)

Results by Regimen	DOCX	ATEZ: TC2/3 or IC2/3	NIVO: All Comers	PEMB: PD-L1 >50%
Total Costs	$92,130	$157,838	$151,688	$171,077
Drug Costs	$10,229	$79,453	$77,075	$91,808
PFS Supp. Care Costs	$7,684	$9,572	$9,191	$10,937
Administration Costs	$1,013	$1,251	$1,770	$1,422
Progression Costs	$3,935	$16,789	$13,305	$15,222
Death Costs	$50,000	$49,904	$49,980	$49,904
Adverse Event Costs	$19,270	$870	$367	$1,785
Total QALYs	0.47	0.70	0.61	0.71
PFS QALYs	0.26	0.33	0.32	0.38
Progression QALYs	0.20	0.37	0.29	0.33
Total Life Years (OS)	0.84	1.29	1.10	1.29
PFS LYs	0.41	0.51	0.49	0.58
Progression LYs	0.43	0.78	0.62	0.70
Median PFS (months)	4.2	5.1	4.9	5.8
Median OS (months)	8.5	13.1	11.3	13.1

Table F11b. Scenario 2: Weibull model for DOCX curves with trial-reported HRs applied to derive PD-1 curves (incremental results)

Incremental Results	DOCX	ATEZ: TC2/3 or IC2/3	NIVO: All Comers	PEMB: PD-L1 >50%
ICER	--	$286,568	$424,195	$326,023
Incremental Costs	--	$65,708	$59,559	$78,947
Drug Costs	--	$69,224	$66,846	$81,579
PFS Supp. Care Costs	--	$1,888	$1,508	$3,253
Administration Costs	--	$238	$757	$409
Progression Costs	--	$12,854	$9,370	$11,287
Death Costs	--	-$95	-$19	-$95
Adverse Event Costs	--	-$18,400	-$18,902	-$17,485
Incremental QALYs	--	0.23	0.14	0.24
PFS QALYs	--	0.07	0.05	0.11
Progression QALYs	--	0.16	0.09	0.13
Incremental Life Years (OS)	--	0.44	0.26	0.44
PFS LYs	--	0.10	0.08	0.17
Progression LYs	--	0.34	0.18	0.27

Table F11c. Scenario 2: Weibull model for DOCX curves with trial-reported HRs applied to derive PD-1 curves (probabilistic results by regimen)

	DOCX		ATEZ: TC2/3 or IC2/3 Trial HR		NIVO: All Comers Trial HR		PEMB: PD-L1 >50% Trial HR	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total Costs	$118,198	($39,967 - $431,729)	$185,737	($90,055 - $487,766)	$179,269	($84,472 - $492,073)	$197,537	($99,706 - $504,334)
Drug Costs	$10,242	($7,554 - $13,626)	$81,253	($54,620 - $119,098)	$78,966	($54,118 - $113,703)	$92,665	($63,646 - $131,544)
PFS Supp. Care Costs	$7,761	($6,184 - $9,735)	$9,928	($6,904 - $14,180)	$9,521	($6,651 - $13,409)	$11,184	($8,177 - $15,235)
Administration Costs	$1,017	($752 - $1,355)	$1,285	($830 - $1,893)	$1,806	($1,208 - $2,620)	$1,441	($991 - $2,034)
Progression Costs	$3,754	($1,830 - $5,706)	$17,381	($5,411 - $34,099)	$13,057	($4,901 - $23,826)	$15,366	($5,173 - $29,897)
Death Costs	$76,149	($74 - $384,980)	$75,021	($72 - $380,279)	$75,546	($73 - $381,106)	$75,086	($72 - $379,676)
Adverse Event Costs	$19,275	($16,419 - $22,229)	$868	($475 - $1,382)	$372	($139 - $735)	$1,795	($1,112 - $2,603)
Total QALYs	0.47	(0.36 - 0.62)	0.72	(0.47 - 1.07)	0.61	(0.45 - 0.84)	0.72	(0.51 - 1.01)
PFS QALYs	0.26	(0.21 - 0.33)	0.34	(0.23 - 0.49)	0.33	(0.23 - 0.46)	0.38	(0.28 - 0.52)
Progression QALYs	0.20	(0.09 - 0.35)	0.38	(0.12 - 0.73)	0.28	(0.10 - 0.51)	0.33	(0.11 - 0.65)
Total Life Years (OS)	0.84	(0.62 - 1.15)	1.32	(0.82 - 2.07)	1.10	(0.78 - 1.56)	1.30	(0.86 - 1.94)
PFS LYs	0.41	(0.33 - 0.51)	0.52	(0.36 - 0.74)	0.50	(0.35 - 0.70)	0.59	(0.43 - 0.80)
Progression LYs	0.43	(0.19 - 0.75)	0.80	(0.25 - 1.54)	0.60	(0.22 - 1.09)	0.71	(0.24 - 1.37)
Median PFS (months)	4.1	(3.25 - 5.09)	5.3	(3.71 - 7.62)	5.1	(3.48 - 7.16)	6.0	(4.40 - 8.08)
Median OS (months)	8.6	(6.47 - 11.53)	13.8	(8.54 - 21.88)	11.4	(8.08 - 16.13)	13.5	(9.00 - 20.04)

Table F11d. Scenario 2: Weibull model for DOCX curves with trial-reported HRs applied to derive PD-1 curves (incremental probabilistic results)

	DOCX		ATEZ: TC2/3 or IC2/3 Trial HR		NIVO: All Comers Trial HR		PEMB: PD-L1 >50% Trial HR	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
ICER (QALYs)	--	--	$271,018	($133,752 - $946,335)	$429,302	($226,256 - $837,072)	$318,983	($175,927 - $665,956)
Incremental Costs	--	--	$67,539	($37,313 - $106,079)	$61,071	($35,082 - $96,613)	$79,339	($48,581 - $119,017)
Drug Costs	--	--	$71,011	($44,947 - $108,087)	$68,723	($44,289 - $102,709)	$82,422	($54,680 - $119,931)
PFS Supp. Care Costs	--	--	$2,168	(-$352 - $5,504)	$1,761	(-$504 - $4,686)	$3,423	($1,362 - $6,166)
Administration Costs	--	--	$268	(-$181 - $790)	$789	($219 - $1,525)	$424	(-$8 - $932)
Progression Costs	--	--	$13,627	($2,837 - $29,501)	$9,304	($2,459 - $18,563)	$11,612	($2,950 - $24,885)
Death Costs	--	--	-$1,128	(-$6,349 - $0)	-$602	(-$3,227 - -$1)	-$1,062	(-$5,891 - -$1)
Adverse Event Costs	--	--	-$18,406	(-$21,403 - -$15,510)	-$18,903	(-$21,878 - -$16,049)	-$17,480	(-$20,578 - -$14,503)
Incremental QALYs	--	--	0.25	(0.06 - 0.52)	0.14	(0.07 - 0.24)	0.25	(0.11 - 0.45)
PFS QALYs	--	--	0.08	(-0.01 - 0.19)	0.06	(-0.01 - 0.16)	0.12	(0.05 - 0.21)
Progression QALYs	--	--	0.17	(-0.03 - 0.46)	0.08	(-0.02 - 0.19)	0.13	(-0.02 - 0.33)
Incremental Life Years (OS)	--	--	0.48	(0.08 - 1.05)	0.26	(0.11 - 0.47)	0.46	(0.18 - 0.87)
PFS LYs	--	--	0.11	(-0.02 - 0.28)	0.09	(-0.03 - 0.24)	0.18	(0.07 - 0.32)
Progression LYs	--	--	0.37	(-0.06 - 0.97)	0.17	(-0.05 - 0.42)	0.28	(-0.04 - 0.69)

Table F12a. Scenario 3: PD-1 immunotherapy subpopulations (results by regimen)

	DOCX	ATEZ 1/2/3	NIVO >10%	PEMB >1%
Total Costs	$94,405	$193,609	$219,305	$259,688
Drug Costs	$11,816	$102,555	$127,255	$156,697
PFS Supp. Care Costs	$9,044	$12,792	$15,725	$19,521
Administration Costs	$1,170	$1,616	$2,922	$2,431
Progression Costs	$4,648	$28,716	$26,012	$33,028
Death Costs	$48,457	$47,060	$47,023	$46,226
Adverse Event Costs	$19,270	$870	$367	$1,785
Total QALYs	0.57	1.05	1.09	1.37
PFS QALYs	0.31	0.43	0.53	0.65
Progression QALYs	0.27	0.62	0.56	0.72
Total Life Years (OS)	1.04	1.99	2.01	2.53
PFS LYs	0.47	0.66	0.81	1.01
Progression LYs	0.57	1.32	1.20	1.52
Median PFS (months)	4.2	4.2	5.1	8.1
Median OS (months)	8.5	18.2	20.0	19.4

Table F12b. Scenario 3: PD-1 immunotherapy subpopulations (incremental results)

	DOCX	ATEZ 1/2/3	NIVO >10%	PEMB >1%
ICER (QALYs)	--	$206,488	$240,409	$207,242
ICER (LYs)		$104,966	$128,682	$111,053
Incremental Costs	--	$99,203	$124,899	$165,282
Drug Costs	--	$90,740	$115,439	$144,881
PFS Supp. Care Costs	--	$3,748	$6,681	$10,476
Administration Costs	--	$445	$1,752	$1,261
Progression Costs	--	$24,068	$21,363	$28,380
Death Costs	--	-$1,396	-$1,434	-$2,231
Adverse Event Costs	--	-$18,400	-$18,902	-$17,485
Incremental QALYs	--	0.48	0.52	0.80
PFS QALYs	--	0.12	0.22	0.35
Progression QALYs	--	0.36	0.30	0.45
Incremental Life Years (OS)	--	0.95	0.97	1.49
PFS LYs	--	0.19	0.34	0.53
Progression LYs	--	0.76	0.63	0.96

Table F12c. Scenario 3: PD-1 immunotherapy subpopulations (probabilistic results by regimen)

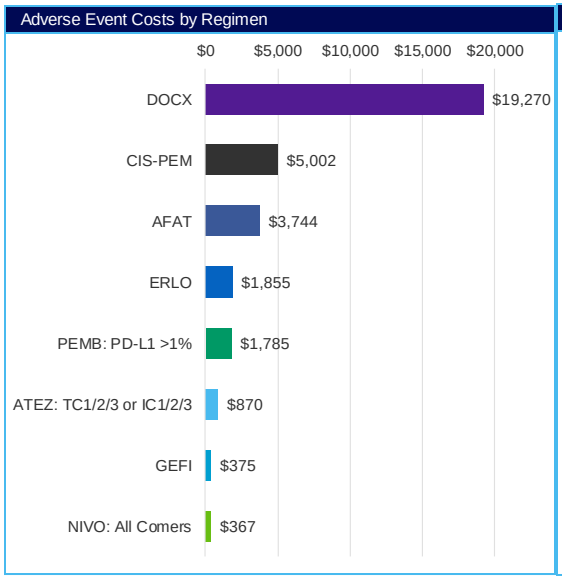
	DOCX		ATEZ 1/2/3		NIVO >10%		PEMB >1%	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total Costs	$122,050	($43,234 - $416,240)	$273,273	($108,115 - $673,328)	$308,264	($128,640 - $772,764)	$363,344	($153,711 - $897,657)
Drug Costs	$13,214	($8,219 - $27,629)	$138,393	($58,754 - $428,763)	$173,741	($75,532 - $539,747)	$211,689	($92,479 - $662,222)
PFS Supp. Care Costs	$10,437	($6,605 - $24,324)	$18,822	($7,358 - $68,130)	$23,215	($9,439 - $80,245)	$28,694	($11,918 - $101,228)
Administration Costs	$1,306	($805 - $2,866)	$2,195	($936 - $6,997)	$3,999	($1,693 - $12,134)	$3,291	($1,471 - $10,059)
Progression Costs	$5,827	($1,211 - $21,574)	$47,739	($7,603 - $163,040)	$40,977	($5,881 - $153,769)	$56,800	($8,356 - $169,799)
Death Costs	$72,024	($92 - $362,367)	$65,258	($83 - $340,065)	$65,964	($82 - $338,128)	$61,078	($76 - $318,098)
Adverse Event Costs	$19,242	($16,395 - $22,279)	$867	($470 - $1,354)	$369	($134 - $725)	$1,793	($1,104 - $2,606)
Total QALYs	0.72	(0.39 - 2.01)	1.61	(0.62 - 4.11)	1.60	(0.68 - 4.06)	2.11	(0.77 - 4.60)
PFS QALYs	0.34	(0.22 - 0.74)	0.59	(0.25 - 1.86)	0.72	(0.32 - 2.24)	0.89	(0.40 - 2.79)
Progression QALYs	0.38	(0.06 - 1.69)	1.02	(0.16 - 3.49)	0.88	(0.12 - 3.34)	1.22	(0.18 - 3.62)
Total Life Years (OS)	1.34	(0.67 - 4.08)	3.08	(1.11 - 8.35)	2.99	(1.19 - 8.15)	3.96	(1.31 - 8.97)
PFS LYs	0.53	(0.35 - 1.13)	0.90	(0.39 - 2.90)	1.11	(0.49 - 3.40)	1.37	(0.63 - 4.28)
Progression LYs	0.80	(0.12 - 3.59)	2.18	(0.35 - 7.43)	1.88	(0.26 - 7.08)	2.59	(0.38 - 7.75)
Median PFS (months)	4.1	(3.25 - 5.09)	4.3	(3.02 - 5.55)	5.6	(3.94 - 9.00)	8.5	(5.32 - 14.06)
Median OS (months)	8.9	(6.47 - 14.98)	27.8	(8.54 - 176.47)	28.0	(10.15 - 106.84)	36.1	(8.54 - 240.13)

Table F12d. Scenario 3: PD-1 immunotherapy subpopulations (incremental probabilistic results)

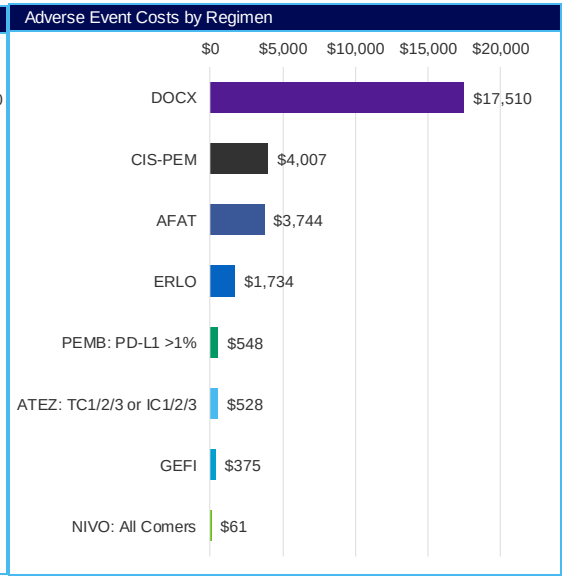
	DOCX		ATEZ 1/2/3		NIVO >10%		PEMB >1%	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
ICER (QALYs)	--	--	$170,097	($74,417 - $441,451)	$211,000	($91,559 - $401,942)	$174,188	($81,723 - $370,790)
Incremental Costs	--	--	$151,224	($50,479 - $470,185)	$186,215	($68,037 - $584,426)	$241,295	($89,921 - $736,502)
Drug Costs	--	--	$125,179	($49,428 - $403,831)	$160,527	($66,104 - $515,824)	$198,475	($82,715 - $634,564)
PFS Supp. Care Costs	--	--	$8,384	($270 - $41,855)	$12,778	($2,311 - $56,891)	$18,256	($4,950 - $75,644)
Administration Costs	--	--	$889	(-$89 - $4,254)	$2,693	($727 - $9,800)	$1,985	($463 - $7,297)
Progression Costs	--	--	$41,912	($5,583 - $146,335)	$35,150	($3,871 - $133,954)	$50,973	($5,291 - $152,523)
Death Costs	--	--	-$6,766	(-$48,352 - -$3)	-$6,060	(-$41,391 - -$4)	-$10,946	(-$75,168 - -$6)
Adverse Event Costs	--	--	-$18,375	(-$21,402 - -$15,498)	-$18,873	(-$21,860 - -$16,031)	-$17,449	(-$20,457 - -$14,500)
Incremental QALYs	--	--	0.89	(0.19 - 2.47)	0.88	(0.27 - 2.36)	1.39	(0.35 - 3.05)
PFS QALYs	--	--	0.24	(0.01 - 1.13)	0.38	(0.08 - 1.48)	0.55	(0.17 - 2.03)
Progression QALYs	--	--	0.65	(0.03 - 2.07)	0.50	(0.01 - 1.80)	0.84	(0.03 - 2.33)
Incremental Life Years (OS)	--	--	1.75	(0.34 - 4.95)	1.65	(0.47 - 4.48)	2.62	(0.59 - 5.80)
PFS LYs	--	--	0.37	(0.01 - 1.70)	0.58	(0.12 - 2.28)	0.84	(0.26 - 3.12)
Progression LYs	--	--	1.38	(0.07 - 4.49)	1.07	(0.02 - 3.79)	1.79	(0.05 - 4.98)

Figure F1. Scenario 4: Including AEs with at least one drug reporting >10% of patients experiencing the event (base case threshold of >5%)

>5%



>10%



Appendix G. Previous Technology Assessments and Systematic Reviews

We identified four completed technology assessments: three from the National Institute for Health and Care Excellence (NICE) in the UK and one from the Pan-Canadian Oncology Drug Review (pCODR). These reviews of afatinib, erlotinib, and gefitinib are summarized below. Of note, NICE expects to publish a final appraisal document of pembrolizumab in January 2017 and is currently suspending the appeal stage of nivolumab to allow the manufacturer to make a further submission that includes a patient access scheme. We also identified six systematic reviews of the TKIs and a single systematic review of the PD-1 immunotherapies for NSCLC.

Technology Assessments

NICE Gefitinib (2010), Erlotinib (2012), Afatinib (2014)

- **Gefitinib: https://www.nice.org.uk/guidance/ta192**
- **Erlotinib: https://www.nice.org.uk/guidance/ta258**
- **Afatinib: https://www.nice.org.uk/guidance/ta310**

NICE recommends gefitinib, erlotinib, and afatinib for first-line treatment of patients with locally advanced or metastatic NSCLC if they test positive for the epidermal growth factor receptor tyrosine kinase mutation and the manufacturer provides the drugs at a discounted price agreed under the patient access scheme.

Pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee Final Recommendation: Afatinib (Giotrif) for first line treatment of EGFR Mutation Positive Advanced NSCLC (May 2, 2014)

(https://www.cadth.ca/sites/default/files/pcodr/pcodr-giotrif-nsclc-fn-rec.pdf)

The pCODR expert review committee issued a final recommendation (based on the MM-003 trial) that afatinib should be funded if cisplatin-pemetrexed is currently the main treatment option for first-line treatment of EGFR mutation positive advanced or metastatic adenocarcinoma with an ECOG performance status of 0-1. The review committee also recommended funding afatinib as an alternative to gefitinib, provided that cost-effectiveness is improved to an "acceptable" level. Despite the lack of head-to-head evidence, the committee believed afatinib to and gefitinib to provide similar clinical benefit and expressed a commitment to providing access to more treatment options. They noted that afatinib was cost-effective compared to cisplatin-pemetrexed but may not be considered cost-effective relative to gefitinib.

Previous systematic reviews

Several recent systematic reviews and meta-analyses have compared the three EGFR TKIs of interest to one another as well as to platinum-based chemotherapy doublets in chemo-naïve patients with EGFR mutations. These studies have consistently reported superior efficacy with the TKIs relative to chemotherapy, albeit no study has shown improvements in overall survival, which is likely due to high rates of crossover between therapies. Comparisons between TKIs have consistently shown no statistical differences in PFS, ORR, or OS, although toxicity profiles have varied across agents.

Haspinger ER, Agustoni F, Torri V, et al. Is there evidence for different effects among EGFR-TKIs? Systematic review and meta-analysis of EGFR tyrosine kinase inhibitors (TKIs) versus chemotherapy as first-line treatment for patients harboring EGFR mutations. Crit Rev Oncol Hematol. 2015;94:213-227.

Haspinger et al. performed a systematic review and meta-analysis of all phase II/III RCTs published up to June 2014 that examined afatinib, erlotinib, or gefitinib in previously-untreated patients with NSCLC and an EGFR-mutation. The literature search identified 9 RCTs, which involved 1,774 EGFR-mutated patients. Direct comparisons of each of the TKIs versus a platinum-based chemotherapy doublet showed statistically significant differences in favor of the TKIs for both PFS and ORR but no difference in overall survival. Indirect comparisons between TKIs did not show statistical differences for PFS, ORR, or OS, although safety profiles varied; afatinib had more events of diarrhea and rash compared to both erlotinib and gefitinib, while gefitinib had a higher rate of hypertransaminasemia. There were no differences in treatment discontinuation and treatment-related deaths across agents.

Des Guetz G, Landre T, Uzzan B, et al. Is there a Survival Benefit of First-Line Epidermal Growth Factor Receptor Tyrosine-Kinase Inhibitor Monotherapy Versus Chemotherapy in Patients with Advanced Non-Small-Cell Lung Cancer?: A Meta-Analysis. Targ Oncol. 2016;11:41-47.

A meta-analysis from Des Guetz and colleagues examined eight phase III RCTs of first-line treatment of advanced NSCLC with afatinib, erlotinib, or gefitinib versus a platinum-based chemotherapy doublet. The analysis included 2,962 patients with EGFR mutations. Compared to chemotherapy, TKIs significantly improved PFS (HR 0.37, 95% CI 0.29-0.49) but not overall survival (HR 0.98, 95% CI 0.87-1.10). The authors suggested that a high level of crossover between both groups might explain why the TKIs showed an improved PFS without parallel improvement in OS. Comparisons between TKIs showed no significant differences between gefitinib and erlotinib or afatinib and erlotinib. Grade 3-4 adverse effects differed between TKIs and chemotherapy, with rashes and diarrhea occurring more frequently with TKIs (RR 4.60, 95% CI 2.37-8.95; and RR 3.88, 95% CI 2.00-7.56) and nausea/vomiting (RR 0.22, 95% CI 0.06-0.54), neutropenia (RR 0.06, 95% CI 0.04-0.08),

thrombocytopenia (RR 0.11, 95% CI 0.04-0.32), and anemia (RR 0.10, 95% CI 0.04-0.27) occurring more frequently with chemotherapy.

Haaland B, Tan PS, de Castro G, and Lopes G. Meta-Analysis of First-Line Therapies in Advanced Non-Small-Cell Lung Cancer Harboring EGFR-Activating Mutations. J Thorac Oncol. 2014;9:805-811.

Another meta-analysis of gefitinib, erlotinib, afatinib, and chemotherapy in previously untreated patients with advanced non-small-cell lung cancer harboring EGFR-activating mutations reported similar results. Compared to chemotherapy, the analysis showed each of the TKIs to improve PFS and ORR but not OS. Outcomes did not statistically differ between individual TKIs. Similar to the findings of other analyses, diarrhea, rash, and pruritus occurred more frequently with the TKIs, whereas anorexia, anemia, fatigue, nausea, vomiting, alopecia, and neutropenia were more common with chemotherapy.

Zhang Y, Sheng J, Yang Y, et al. Optimized selection of three major EGFR-TKIs in advanced EGFR-positive non-small cell lung cancer: a network meta-analysis. Oncotarget. 2016;7(15):20093-20108.

In a series of analyses of TKI therapy in chemo-naïve and previously treated EGFR+ patients, Zhang and colleagues found similar efficacy among the TKIs for ORR, PFS, and disease control rate relative to chemotherapy. Patients with EGFR exon 19 deletion showed superior numerical data with respect to ORR, 1-year PFS, 1-year OS, and 2-year OS compared with 21 L858R patients. Among the TKIs, afatinib had the highest risk of diarrhea, while gefitinib presented the greatest risk of elevated liver transaminase.

Popat S, Mok T, Yang JC-H, et al. Afatinib in the treatment of EGFR mutation-positive NSCLC-A network meta-analysis. Lung Cancer. 2014;85:230-238.

Popat and colleagues assessed the relative efficacy of afatinib, erlotinib, and gefitinib by conducting a systematic literature review and network meta-analysis; eight of the 21 studies reviewed by the authors reported results from patients with an EGFR+ mutation and were included in the network. Similar to the findings of other analyses, Popat et al. did not find statistical differences in overall survival between treatments. However, this study did suggest that afatinib might have a slight PFS benefit compared to gefitinib (HR 0.60, 95% CI 0.34-0.99) in patients with common EGFR mutations.

Greenhalgh J, Dwan K, Boland A, et al. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. Cochrane Database of Systematic Reviews. 2016;5.

A review from the Cochrane Collaboration of first-line treatment with afatinib, erlotinib, and gefitinib in non-squamous, EGFR+ NSCLC did not find a statistically-significant overall survival

benefit with single-agent use of the TKIs (vs. chemotherapy), but did find a significant PFS benefit with each of the agents of interest. The most commonly reported grade 3-4 AEs were rash and diarrhea with the TKIs, while myelosuppression, fatigue, and anorexia were common with chemotherapy. Quality of life and symptoms were improved in one or more indices measured in two trials each for the three TKIs of focus.

Melosky B, Chu Q, Juergens R, et al. Pointed Progress in Second-Line Advanced Non-Small-Cell Lung Cancer: The Rapidly Evolving Field of Checkpoint Inhibition. J Clin Oncol. 2016;34:1676-1688.

We identified a single systematic review of the PD-1 immunotherapies. The review included 20 studies of PD-1 immunotherapies in the second-line setting, three of which were RCTS. Melosky and colleagues reviewed the phase II POPLAR trial of atezolizumab as well as the two phase III CheckMate trials of nivolumab in squamous and non-squamous NSCLC, respectively. Relative to docetaxel, atezolizumab showed a trend toward better overall survival, particularly in patients with increased PD-L1 expression. Nivolumab improved overall survival in patients with both squamous and nonsquamous carcinoma, although PD-L1 expression was only associated with overall survival in those with nonsquamous disease. The authors concluded that PD-1 immunotherapy is safe compared to standard chemotherapy and is best suited for patients with higher levels of PD-L1 expression and no EGFR mutations.

Appendix H. Ongoing Studies

Trial	Study Design	Estimated Completion	Comparators	Patient Population	Primary Outcomes
Afatinib					
A Randomised, Open-label, Phase III Study of BIBW 2992 Versus Chemotherapy as First-line Treatment for Patients with Stage IIIB or IV Adenocarcinoma of the Lung Harbouring an EGFR Activating Mutation **NCT00949650**	RCT	October 2016	• Afatinib • Cisplatin + Pemetrexed	N=345 Age 18 years and older Inclusion Criteria: • Stage IIIB/IV NSCLC • EGFR mutation positive • ECOG score of 0-1 • Life expectancy of at least 3 months Exclusion Criteria: • Prior chemotherapy for relapsed or metastatic NSCLC or EGFR TKIs • Radiotherapy within 4 weeks • Active brain metastases • Any significant illness or organ dysfunction • Hep B, Hep C or HIV carrier	Primary: • PFS [Time Frame: every 12 weeks until death] Secondary: • ORR • OS • DC • QoL • ECOG PS

Trial	Study Design	Estimated Completion	Comparators	Patient Population	Primary Outcomes
Gefitinib vs. Erlotinib					
A Randomized, Open-label Phase II Trial of Erlotinib 100mg Daily Versus Gefitinib 250mg Daily in Patients with Advanced Non-Small Cell Lung Cancer Who Harbor EGFR Mutations. **NCT01955421**	RCT	June 2016	• Erlotinib 100mg • Gefitinib 250mg	N=224 Age 18 years and older Inclusion Criteria: • Stage IIIB or IV NSCLC • EGFR mutation, including exon 19 or exon 21 L858R • Measurable disease according to RECIST 1.1 • ECOG PS 0-2 • Adequate organ function Exclusion Criteria: • Prior treatment with EGFR TKIs • Radiotherapy within 4 weeks • Active brain metastases • Any other current malignancy or malignancy diagnosed within in past 3 years	Primary: • Disease control rate [Time Frame: 2 years] Secondary: • PFS • AEs

Trial	Study Design	Estimated Completion	Comparators	Patient Population	Primary Outcomes
Nivolumab					
An Open-Label, Randomized Phase 3 Trial of Nivolumab, or Nivolumab Plus Ipilimumab, or Nivolumab Plus Platinum Doublet Chemotherapy Versus Platinum Doublet Chemotherapy in Subjects with Chemotherapy-Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) **NCT02477826**	RCT	December 2020	• Nivolumab • Nivolumab + Ipilimumab • Nivolumab + Platinum doublet chemotherapy • Platinum doublet chemotherapy	N=1980 Age 18 years and older Inclusion Criteria: • Stage IV or recurrent NSCLC • No prior systemic anti-cancer therapy • Have PD-L1 immunohistochemical testing • ECOG PS 0-1 • Measurable disease according to RECIST 1.1 Exclusion Criteria: • CNS metastases • Suspected autoimmune diseases • Hep B, Hep C or HIV positive	Primary: • OS, PFS [Time Frame: 48 months] Secondary: • ORR • Symptoms

Trial	Study Design	Estimated Completion	Comparators	Patient Population	Primary Outcomes
An Open-label Randomized Multinational Phase 3 Trial of Nivolumab Versus Docetaxel in Previously Treated Subjects with Advanced or Metastatic Non-Small Cell Lung Cancer (CheckMate 078: Checkpoint Pathway and nivolumab Clinical Trial Evaluation 078) **NCT02613507**	RCT	January 2019	• Nivolumab • Docetaxel	N=500 Age 18 years and older Inclusion Criteria: • Stage IIIB/IV or recurrent NSCLC • Disease progression during or after one prior platinum containing doublet chemotherapy • ECOG PS 0-1 • Measurable disease according to RECIST 1.1 Exclusion Criteria: • CNS metastases • Suspected autoimmune diseases • Prior docetaxel or checkpoint inhibitors	Primary: • OS [Time Frame: 37 months] Secondary: • ORR • PFS • Symptoms

Trial	Study Design	Estimated Completion	Comparators	Patient Population	Primary Outcomes
An Open-Label, Randomized, Phase 3 Trial of Nivolumab Versus Investigator's Choice Chemotherapy as First-Line Therapy for Stage IV or Recurrent PD-L1+ Non-Small Cell Lung Cancer (CheckMate 026) **NCT02041533**	RCT	January 2018	• Nivolumab • Physician's choice chemotherapy	N=535 Age 18 years and older Inclusion Criteria: • Stage IV or recurrent NSCLC • No prior systemic anticancer therapy • ECOG PS 0-1 • Measurable disease according to RECIST 1.1 Exclusion Criteria: • EGFR mutation or ALK translocation • CNS metastases • Suspected autoimmune diseases	Primary: • PFS [Time Frame: 33 months] Secondary: • ORR • PFS • Symptoms

Trial	Study Design	Estimated Completion	Comparators	Patient Population	Primary Outcomes
An Open-Label Randomized Phase III Trial of BMS-936558 (Nivolumab) Versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-Small Cell Lung Cancer (NSCLC) **NCT01642004**	RCT	January 2017	• Nivolumab • Docetaxel	N=352 Age 18 years and older Inclusion Criteria: • Stage III/IV or recurrent NSCLC • progression during/after one prior platinum doublet-based chemotherapy • ECOG PS 0-1 • Measurable disease according to RECIST 1.1 Exclusion Criteria: • CNS metastases • Active or suspected autoimmune disease	Primary: • OS [Time Frame: 25 months] Secondary: • ORR • OS

Trial	Study Design	Estimated Completion	Comparators	Patient Population	Primary Outcomes
A Master Protocol of Phase 1/2 Studies of Nivolumab in Advanced NSCLC Using Nivolumab as Maintenance After Induction Chemotherapy or as First-line Treatment Alone or in Combination with Standard of Care Therapies (CheckMate 370: Checkpoint Pathway and nivolumab Clinical Trial Evaluation 370) **NCT02574078**	RCT	April 2022	• Nivolumab • Investigator's choice chemotherapy	N=1953 Age 18 years and older Inclusion Criteria: • Stage IV NSCLC • ECOG PS 0-2 • Tumor tissue available for biomarker evaluation Exclusion Criteria: • CNS metastases • Suspected autoimmune diseases • Hep B, Hep C, history of testing positive for HIV or AIDS	Primary: • OS [Time Frame: 60 months] • PFS [Time Frame: 48 months] Secondary: • ORR • DOR

Trial	Study Design	Estimated Completion	Comparators	Patient Population	Primary Outcomes
Pembrolizumab					
A Randomized Open-Label Phase III Trial of MK-3475 Versus Platinum Based Chemotherapy in 1L Subjects with PD-L1 Strong Metastatic Non-Small Cell Lung Cancer **NCT02142738**	RCT	May 2018	• Pembrolizumab • Cisplatin or carboplatin + • Gemcitabine or paclitaxel or pemetrexed	N=305 Age 18 years and older Inclusion Criteria: • Stage IV NSCLC • No driver mutations • PD-L1 strong expression determined by IHC • ECOG PS 0-1 • Adequate organ function Exclusion Criteria: • CNS metastases • Autoimmune diseases	Primary: • PFS [Time Frame: 2 years] Secondary: • ORR • OS

Trial	Study Design	Estimated Completion	Comparators	Patient Population	Primary Outcomes
A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) Versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer **(Keynote 042)** **NCT02220894**	RCT	February 2018	• Pembrolizumab • Carboplatin + • Paclitaxel or pemetrexed	N=1240 Age 18 years and older Inclusion Criteria: • advanced or metastatic NSCLC • No driver mutations • PD-L1 positive determined by IHC • ECOG PS 0-1 • Adequate organ function • No prior systemic chemotherapy Exclusion Criteria: • CNS metastases • Autoimmune diseases	Primary: • OS [Time Frame: 2.5 years] Secondary: • PFS

Trial	Study Design	Estimated Completion	Comparators	Patient Population	Primary Outcomes
A Phase II/III Randomized Trial of Two Doses of MK-3475 (SCH900475) Versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer **NCT01905657**	RCT	March 2019	• Pembrolizumab low/high dose • Docetaxel	N=1034 Age 18 years and older <u>Inclusion Criteria</u>: • NSCLC with progression after at least 2 cycles of platinum-containing doublets • PD-L1 positive determined by IHC • ECOG PS 0-1 <u>Exclusion Criteria</u>: • prior docetaxel • CNS metastases • Active autoimmune disease • History of HIV, Hep B or Hep C	<u>Primary</u>: • OS, AEs [Time Frame: 3 years] <u>Secondary</u>: • ORR • DOR

Trial	Study Design	Estimated Completion	Comparators	Patient Population	Primary Outcomes
Atezolizumab					
A Phase III, Open-label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab Compared with Docetaxel in Patients with Non-Small Cell Lung Cancer After Platinum Failure [OAK] **NCT02008227**	RCT	June 2017	• Atezolizumab • Docetaxel	N=1225 Age 18 years and older Inclusion Criteria: • Advanced or metastatic NSCLC • progression during or after platinum-containing regimen • measurable disease according to RECIST 1.1 • ECOG PS 0-1 Exclusion Criteria: • Prior docetaxel • CNS metastases • History of autoimmune disease	Primary: • OS [Time Frame: 4.5 years] Secondary: • ORR • DOR • PFS

Trial	Study Design	Estimated Completion	Comparators	Patient Population	Primary Outcomes
A Phase III Study of Atezolizumab (MPDL3280A) Compared With Cisplatin or Carboplatin + Pemetrexed in Patients With Stage IV Non-Squamous Non-Small Cell Lung Cancer (NSCLC)1 [IMpower110] **NCT02409342**	RCT	March 2019	• Atezolizumab • Pemetrexed + (carboplatin or cisplatin)	n=570 Age 18 years and older Inclusion Criteria: • ECOG PS 0,1 • Treatment-naïve Stage IV non-squamous NSCLC • PD-L1 status • Adequate hematologic and end organ function Exclusion Criteria: • CNS metastases, malignancies (within 5 years) • History of pneumonitis, IPF, organizing pneumonia, autoimmune diseases, HIV+, Hepatitis B or C, CV disease • Prior CD137 agonists or immune checkpoint blockade therapies, anti-PD-1 and anti-PD-L1 antibodies • Severe infection	Primary: • PFS Secondary: • ORR • DOR • OS • TTD • Safety