Unsupported Price Increase Report

Unsupported Price Increases Occurring in 2023

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About ICER

The Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs. For more information about ICER, please visit www.icer.org.

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The findings contained within this report are current as of the date of publication. Readers should be aware that new information may emerge following the publication of this report that could potentially influence the assessment.

Table of Contents

List of Acronyms and Abbreviations Used in this Report

BTC	Biliary tract cancer
CI	Confidence interval
CPI	Consumer price index
DMFS	Distant metastasis-free survival
DTC	Differentiated thyroid cancer
EGFR	Epidermal growth factor receptor
FDA	Food and Drug Administration
GCCS	CogState global cognition composite score
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HFmrEF	Heart failure and mildly reduced ejection fraction
HFpEF	Heart failure and preserved ejection fraction
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICER	Institute for Clinical and Economic Review
JAK	Janus kinase
NSCLC	Non-small cell lung cancer
OS	Overall survival
PD-L1	Programmed death ligand-1
PET	Positron emission tomography amyloid
PFS	Progression-free survival
RCC	Renal cell carcinoma
RCT	Randomized controlled trial
RFS	Recurrence-free survival
RR	Relative risk
TKI	Tyrosine kinase inhibitor
TNBC	Triple-negative breast cancer
TPS	Tumor proportion score
UPI	Unsupported price increase
US	United States
WAC	Wholesale acquisition cost

Executive Summary

The price of many existing drugs, both brand and generic, can increase substantially over time, and questions are frequently raised regarding whether these price increases are justified. State policymakers have been particularly active in seeking measures to address this issue.[1-3]

Despite these initiatives, there had been no systematic approach at a state or national level to determine whether certain price increases are justified by new clinical evidence or other factors. Starting in 2019, the Institute for Clinical and Economic Review (ICER) has published reports assessing whether new clinical evidence or other information has appeared that could support the price increases of drugs whose recent, substantial price increases have had the largest impact on national drug spending. This is the sixth of these reports.

Following methods similar to our prior report, we first obtained a list of the 250 drugs with the largest sales revenue in the previous calendar year (2023) in the United States (US); this information came from SSR Health LLC, an independent investment research firm. We then excluded from this list 62 drugs whose increase in wholesale acquisition cost (WAC) was not more than 2% greater than the increase in the medical consumer price index (CPI). A detailed description of the entire UPI Protocol is available separately. For each of the remaining 188 drugs, we estimated, where possible, the increase in spending in the US during 2022-2023 that was due to increases in net price as opposed to increases in volume. For the 15 drugs whose net price increases were responsible for the greatest impact on national drug spending, we asked manufacturers for early input as to whether our figures on change in net price, sales volume, and overall net revenue were correct. After applying manufacturer corrections, we generated a list of the top 10 drugs based on the increase in spending in the US due to increases in net price.

Assessments were then performed on these 10 drugs to determine whether there was new clinical evidence in the prior two years that demonstrated "moderate/high-quality new evidence or analyses of a substantial improvement in net health benefit compared with what was previously believed." Drugs judged to have evidence that meets this standard are reported as having price increases "with new clinical evidence." To arrive at this judgment, ICER accepted and reviewed submissions from manufacturers and/or performed an independent systematic review of publicly available results from randomized controlled trials (RCTs). For drugs with multiple indications, evidence was sought for indications responsible for at least 10% of a drug's utilization. ICER reviewed the quality of the new evidence using the widely-accepted evidence grading system called GRADE.[4] For evidence that was felt to be high or moderate quality, ICER then assessed the magnitude of the additional net clinical benefit compared with what was previously believed.

Table ES1 on the following page shows the results of the evidence assessments for the 10 drugs included in the report. Five were judged to have price increases unsupported by new clinical

evidence and five were found to have price increases with new clinical evidence. The unsupported net price increases of these five drugs produced a total of $815 million incremental added costs to US payers in 2023.

This year's report includes three checkpoint inhibitor oncology drugs, each with multiple moderate- to high-quality trials and multiple newly approved indications. Two of the checkpoint inhibitor drugs, pembrolizumab and nivolumab, have multiple newly approved smaller indications, each of which accounts for less than 10% of the drug's use. Our UPI protocol did not anticipate the current situation with checkpoint inhibitors. However, it states that if a manufacturer notes that a combination of indications of a drug exceeds 10% of overall utilization and each of the indications individually has moderate- or high-quality evidence of a substantial new benefit compared with what was previously believed, ICER will consider this to be a price increase with new evidence. For pembrolizumab, we identified multiple new high or moderate-quality evidence across six new sub-indications that account for at least 10% of its use and, as such, concluded that pembrolizumab had a price increase with new clinical evidence. For nivolumab, we are uncertain whether a combination of the three sub-indications where we identified new high or moderate-quality evidence accounts for greater than 10% of its use as required by the UPI Protocol. However, we feel that it would be unfair to disadvantage a therapy that has evidence in support of three new indications in a single cycle. As such, we also concluded that nivolumab had a price increase with new clinical evidence.

An area of uncertainty in the UPI Reports is the net price estimates. These estimates are obtained from SSR Health, LLC, the best available source for net price estimates. We examine the pricing data to identify anomalies that suggest net price estimates may be incorrect and, if found, exclude drugs where this is the case. To further help limit this uncertainty, we allow manufacturers of the top 15 drugs on the UPI list to correct the estimates for net price.

It is also important to note that ICER does not currently have the capacity to perform full economic analyses in conjunction with the evaluation of clinical evidence for the drugs in its UPI Reports. Therefore, even though five drugs did have new clinical evidence, this UPI Report does not attempt to determine whether the price increases were fully justified by meeting a health-benefit price benchmark that might be determined by a formal cost-effectiveness analysis. Instead, our assessment focused on whether new evidence existed that *could* justify a price increase. By identifying whether there is, or is not, new evidence of improved safety or effectiveness for drugs with substantial price increases, we hope we have taken an important first step in providing the public and policymakers with information they can use to advance the public debate on drug price increases.

Table ES1. Drugs Selected for Assessment

Drug (Generic)	2022 to 2023 Percentage Change*		Increase in Drug Spending Due to Net Price Change (in Millions)
	WAC	Net Price	
Drugs with Price Increases Unsupported by New Clinical Evidence			
Biktarvy (Bictegravir, Emtricitabine, and Tenofovir Alafenimide)	5.9%	3.8%	$359
Darzalex (Daratumumab)	7.6%	3.7%	$190
Entresto (Sacubitril/Valsartan)	6.2%	3.6%	$108
Cabometyx (Cabozantinib)	7.5%	5.9%	$86
Xeljanz (Tofacitinib)	6.0%	6.7%	$72
Drugs with Price Increases with New Clinical Evidence†			
Keytruda (Pembrolizumab)	4.1%	2.8%	$364
Imfinizi (Durvalumab)	3.0%	9.9%	$203
Opdivo (Nivolumab)	4.0%	3.8%	$194
Tagrisso (Osimertinib)	3.7%	6.6%	$137
Prolia (Denosumab)	9.9%	4.5%	$113

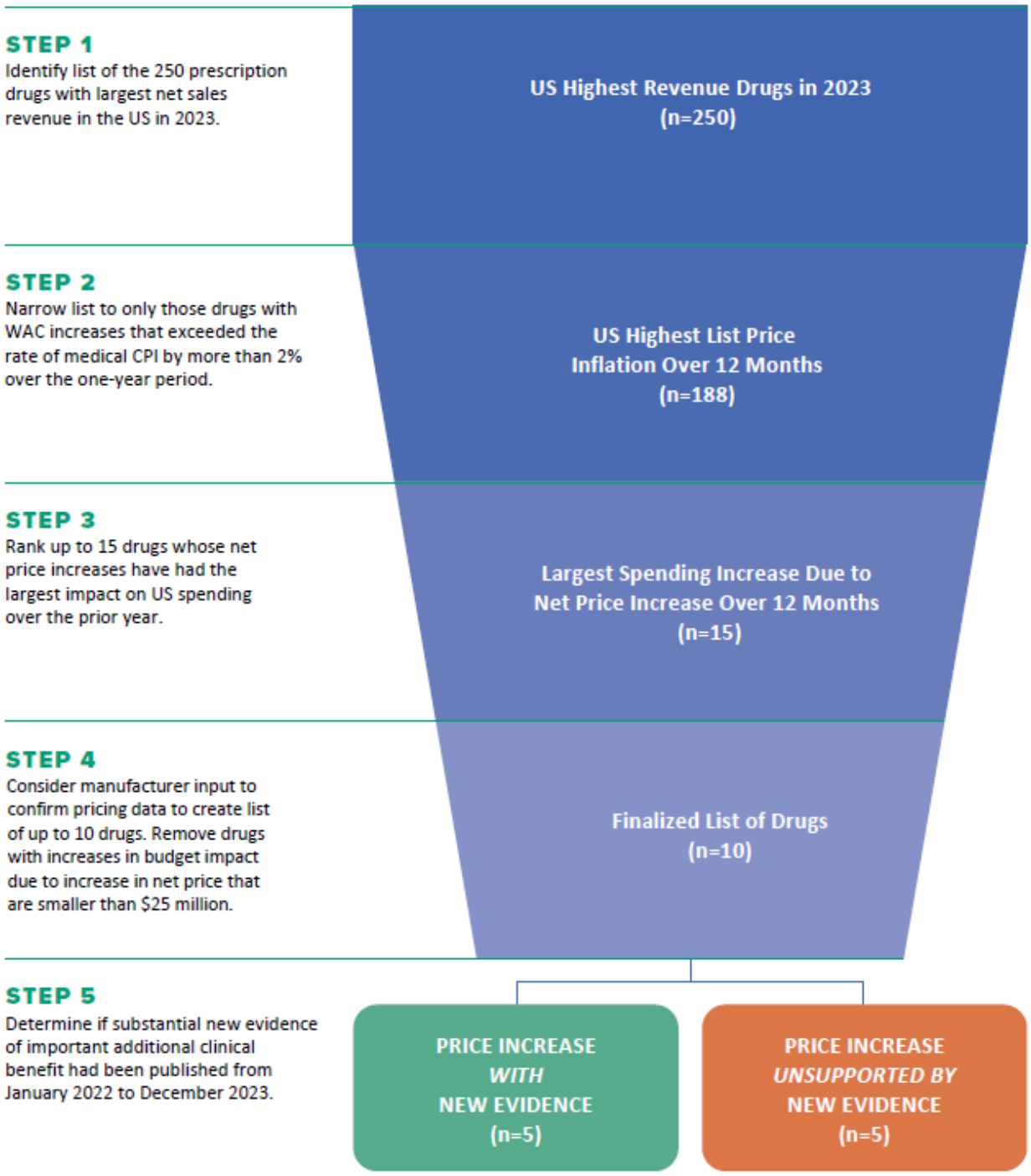
WAC: wholesale acquisition cost

*Year-over-year percentage changes were estimated by averaging over the four quarterly changes in price (i.e., Q1 2022 to Q1 2023; Q2 2022 to Q2 2023; Q3 2022 to Q3 2023 and; Q4 2022 to Q4 2023).

†This is not a determination that the new evidence necessarily justified these price increases.

Figure ES1 on the following page shows the flow and process by which we selected the drugs for review.

Figure ES1. Drug Selection Process



1. Introduction

The price of many existing drugs, both brand and generic, can increase substantially over time, and questions are frequently raised regarding whether these price increases are justified. State policymakers have been particularly active in seeking measures to address this issue.[1-3]

In 2019, the Institute for Clinical and Economic Review (ICER) published its first Unsupported Price Increase (UPI) Report after we organized a multi-stakeholder advisory group to provide input into the design of an approach for such reports. The advisory group was comprised of representatives from patient groups, drugmakers, and insurers representing Medicaid and the private market. The first report looked back at two years of price increases and three years of new evidence.

ICER again worked with this group to develop a revised UPI Protocol for the reports. For this year's report, the protocol was changed for therapies that are being evaluated in sequential report years. The change clarifies that if ICER had determined a finding of a price increase *with new evidence* for a therapy based on more than one item of evidence in the prior review and the items addressed completely distinct aspects of the therapy (such as demonstrating new evidence for different indications for that therapy), ICER may re-consider evidence that was available during the prior review period if it falls within the two-year timeframe of the current review.

The annual UPI Report may evaluate up to 13 drugs that have experienced substantial price increases. As described in later sections, this year's UPI Report evaluated changes in the evidence base for 10 drugs and assessed whether there was potential evidentiary support for price increases.

An area of uncertainty in the UPI Reports is the net price estimates. These estimates are obtained from SSR Health, LLC, the best available source for net price estimates. We examine the pricing data to identify anomalies that suggest net price estimates may be incorrect and, if found, exclude drugs where this is the case. To further help limit this uncertainty, we allow manufacturers of the top 15 drugs on the UPI list to correct the estimate for net price. It is also important to note that ICER does not currently have the capacity to perform full economic analyses on the therapies evaluated in this report, nor would the time needed to develop full ICER Reports (at least eight months) provide information in a useful timeframe for the public and policymakers. Therefore, this UPI Report is not intended to determine whether a price increase for a drug is fully justified by new clinical evidence or meets an ICER health-benefit price benchmark. Instead, the analyses focused on whether substantial new evidence existed that *could* justify a price increase. By identifying whether there is, or is not, new evidence of improved safety or effectiveness for drugs with substantial price increases, we hope to take an important first step in providing the public and policymakers with information they can use to advance the public debate on drug price increases.

2. Selection of Drugs to Review

The goal of the drug selection process was to identify the top 10 drugs whose estimated net price increases over a one-year period would have caused the greatest increase in drug spending in the US. Up to three additional drugs could be selected based on nominations received from the public. A detailed description of the entire UPI Protocol is available separately.

ICER obtained a list of the 250 drugs with the largest net sales revenue in the US in 2023. This information came from SSR Health, LLC, an independent investment research firm. For each drug, we then determined the average WAC price changes over a one-year period. For this UPI Report, we looked at the average price in 2023 compared with the average price in 2022.

Table 2.1. List of Top 250 Drugs with the Highest Net Sales Revenue (in Millions) in the US in 2023

Drug Name	Revenue†	Δ WAC‡
Ranking†: 1-50		
Keytruda	**$15,115**	**4.1%**
Humira	**$12,160**	**8.2%**
Biktarvy	**$9,692**	**5.9%**
Ozempic	**$9,139**	**4.9%**
Dupixent	**$8,808**	**6.4%**
Eliquis	**$8,592**	**6.0%**
Stelara	**$6,966**	**4.0%**
Skyrizi	**$6,753**	**8.2%**
Eylea	$5,886	-2.9%
Trikafta	$5,477	0.0%
Trulicity	**$5,433**	**5.0%**
Opdivo	**$5,283**	**4.0%**
Darzalex	**$5,277**	**7.6%**
Revlimid	$5,266	0.0%
Ocrevus	**$5,214**	**5.5%**
Mounjaro	**$4,834**	**5.6%**
Jardiance	**$4,676**	**4.1%**
Wegovy	$4,274	0.0%
Prevnar family	$4,204	1.2%
Entyvio	**$3,793**	**6.0%**§
Enbrel	**$3,650**	**9.1%**
Ibrance	**$3,150**	**7.9%**
Entresto	**$3,067**	**6.2%**
Invega Sustenna / Trinza	**$2,897**	**7.1%**
Rinvoq	**$2,824**	**8.3%**
Hemlibra	**$2,775**	**3.0%**
Vraylar	**$2,755**	**5.1%**
Orencia	**$2,754**	**6.0%**
Prolia	**$2,733**	**9.9%**
Imbruvica	**$2,665**	**6.3%**
Cosentyx	**$2,636**	**8.2%**
Jakafi	**$2,594**	**5.6%**
Xtandi	**$2,540**	**4.9%**
Verzenio	**$2,509**	**5.7%**
Botox	$2,476	1.0%
Xolair	**$2,425**	**6.5%**
Comirnaty	**$2,404**	**1405786 314.7%**
Vyvanse	**$2,377**	**5.1%**
Xarelto	**$2,365**	**4.9%**
Pomalyst	**$2,357**	**7.3%**
Shingrix	**$2,336**	**6.9%**
Imfinzi	**$2,317**	**3.0%**
Tagrisso	**$2,276**	**3.7%**
Tecentriq	**$2,160**	**3.8%**
Tremfya	**$2,147**	**4.9%**
Vabysmo	$2,137	0.0%
Gardasil / 9	**$2,083**	**6.6%**
Paxlovid	$1,960	-55.8%
Vyndaqel/Vyndamax	**$1,863**	**5.5%**
Trelegy Ellipta	**$1,849**	**2.9%**
Ranking†: 51-100		
ProQuad / M-M-R II / Varivax	**$1,837**	**4.9%**
Ingrezza	**$1,836**	**7.7%**
Taltz	**$1,832**	**5.1%**
Calquence	**$1,815**	**3.3%**
Xifaxan	**$1,808**	**6.2%**
Tepezza	$1,781	1.8%
Otezla	**$1,777**	**7.5%**
Descovy	**$1,772**	**5.9%**
Genvoya	**$1,752**	**5.9%**
Ultomiris	$1,750	0.0%
Soliris	$1,734	0.0%
Spikevax	$1,720	i
Cabometyx	**$1,615**	**7.5%**
Rybelsus	**$1,604**	**4.9%**
Kesimpta	**$1,528**	**8.3%**
Xgeva	**$1,527**	**9.9%**
Fluzone	**$1,527**	**5.8%**
Arexvy	$1,499	i
Perjeta	**$1,484**	**8.0%**
Cimzia	**$1,476**	**5.9%**
Enhertu	**$1,471**	**5.8%**
Farxiga / Xigduo	**$1,452**	**2.9%**
Sprycel	**$1,446**	**7.3%**
Benlysta	**$1,396**	**5.9%**
Yervoy	**$1,388**	**4.0%**
Rexulti	**$1,379**	**6.5%**
Actemra	**$1,362**	**7.4%**
Lenvima	**$1,343**	**7.6%**
Triumeq	**$1,336**	**5.9%**
Uptravi	**$1,326**	**7.9%**
Opsumit	**$1,292**	**7.8%**
Dovato	**$1,285**	**5.9%**
Xywav	**$1,273**	**5.1%**
Creon	**$1,268**	**5.3%**
Lynparza	**$1,253**	**6.6%**
Activase / TNKase	**$1,237**	**3.2%**
Jynarque	$1,231	i
Austedo	**$1,225**	**6.7%**
Nucala	**$1,218**	**5.6%**
Tyvaso	**$1,208**	**4.3%**
Promacta	**$1,205**	**10.2%**
Bridion	**$1,155**	**6.9%**
Xeljanz	**$1,154**	**6.0%**
Januvia	$1,151	**4.9%**
Remicade	$1,143	0.0%
Simponi / Aria	$1,124	1.4%
Rituxan	$1,097	0.0%
Venclexta	$1,087	**8.3%**
Linzess	$1,073	**5.2%**
Erleada	**$1,065**	**5.0%**
Ranking†: 101-150		
Vyvgart	$1,046	1.8%
Kisqali	**$1,032**	**8.0%**
Odefsey	**$1,012**	**5.9%**
Tysabri	**$998**	**4.5%**
Tivicay	**$996**	**5.9%**
Fasenra	**$992**	**3.0%**
Adcetris	**$978**	**7.9%**
Krystexxa	**$974**	**5.1%**
Veklury	**$971**	**9.9%**
Strensiq	$937	0.0%
Kyprolis	**$921**	**7.7%**
Pluvicto	$921	i
Symtuza	**$913**	**6.9%**
Nurtec ODT	**$909**	**3.6%**
Abrysvo	$888	i
Tasigna	**$884**	**10.2%**
Abilify Maintena	**$867**	**6.5%**
Takhzyro	**$852**	**3.1%**
Kadcyla	**$842**	**7.5%**
Sandostatin / LAR	**$829**	**3.0%**
Yescarta	$811	i
Reblozyl	**$811**	**3.8%**
Evenity	**$809**	**9.7%**
Ubrelvy	**$803**	**5.2%**
Repatha	**$793**	**7.7%**
Tafinlar / Mekinist	**$791**	**9.1%**
Trodelvy	**$778**	**4.8%**
Brilinta	**$744**	**2.9%**
Cabenuva	**$731**	**3.5%**
Epidiolex	$719	-1.9%
Padcev	**$717**	**6.9%**
Neulasta	$710	0.0%
Nplate	**$710**	**7.8%**
Abraxane	$709	0.0%
Novolog / Mix	$705	-1.8%
Myrbetriq	**$688**	**3.9%**
Ilaris	**$686**	**3.5%**
Mavyret	$659	0.0%
Inlyta	**$642**	**10.1%**
Trintellix	**$641**	**5.1%**
Juluca	**$636**	**5.9%**
Sublocade	**$630**	**5.0%**
Humalog / Mix	$623	-2.1%
Opdualag	**$617**	**3.0%**
Spinraza	$611	i
Humulin / Mix	$610	-0.9%
Spravato	**$589**	**7.4%**
Wakix	**$582**	**7.0%**
Symbicort	**$575**	**3.0%**
Implanon / Nexplanon	**$573**	**3.7%**
Ranking†: 151 - 200		
Xyrem	**$570**	**5.2%**
Tezspire	**$567**	**5.8%**
Blincyto	**$566**	**7.7%**
Evrysdi	**$562**	**6.5%**
Vaxneuvance	$561	1.2%
Nuplazid	**$549**	**8.9%**
Fabrazyme	**$544**	**5.0%**
Breo Ellipta	**$542**	**9.4%**
Exondys 51	$541	-4.4%
Libtayo	$539	2.1%
Avastin	$538	0.0%
Exparel	**$538**	**5.6%**
Gattex	$537	i

Drug Name	Revenue†	Δ WAC‡
Avonex	**$537**	**6.0%**
Prezista / Prezcobix	**$533**	**6.5%**
Erbitux	**$529**	**5.1%**
Victoza	**$524**	**4.3%**
Alecensa	**$520**	**5.3%**
Vumerity	**$512**	**5.3%**
Mvasi	$511	0.0%
Lucentis	$509	-0.3%
Aubagio	**$496**	**7.8%**
RotaTeq	**$493**	**3.0%**
Boostrix	$491	-0.1%
Emgality	**$482**	**4.1%**
Briviact	**$481**	**6.0%**
Saxenda	$480	0.0%
Alprolix	**$476**	**4.3%**
Xiaflex	**$475**	**8.0%**
Phesgo	$471	0.0%
Fluarix / FluLaval	$469	1.4%
Carvykti	$469	i
Caplyta	**$462**	**5.6%**
Vectibix	**$461**	**7.7%**
Aranesp	$452	0.0%
Bosulif	**$445**	**10.0%**
Basaglar	$443	0.0%
Gazyva	**$440**	**7.2%**
Beyfortus	$439	i
Lutathera	$427	i
Advate	**$424**	**2.8%**
Advair	$422	-2.9%
Venofer	**$415**	**5.6%**

Drug Name	Revenue†	Δ WAC‡
Remodulin	$415	0.0%
Novoseven / RT	**$414**	**3.3%**
Amvuttra	**$411**	**3.8%**
Vemlidy	**$410**	**5.9%**
Lonsurf	**$405**	**6.0%**
Qulipta	**$405**	**5.0%**
Cyramza	**$402**	**5.1%**
Ranking†: 201-250		
Vivitrol	**$401**	**7.6%**
Rylaze	**$394**	**6.4%**
Bexsero	**$388**	**4.5%**
Tukysa	**$386**	**12.0%**
Breztri	**$383**	**3.0%**
Restasis	$382	0.2%
Polivy	**$381**	**4.6%**
Menveo	**$374**	**3.0%**
Zolgensma	**$372**	**4.4%**
Eloctate	**$369**	**4.2%**
Herceptin	$368	0.0%
Tradjenta	**$367**	**4.0%**
Ninlaro	**$365**	**7.0%**
Premarin family	**$361**	**5.0%**
Infanrix / Pediarix	**$361**	**2.6%**
Orenitram ER	**$359**	**6.9%**
Gilenya	**$359**	**8.2%**
Abecma	$358	i
Injectafer	**$357**	**6.5%**
Flovent	$351	0.0%
Opzelura	**$338**	**2.9%**

Drug Name	Revenue†	Δ WAC‡
Pulmozyme	**$337**	**6.0%**
Forteo	**$336**	**5.0%**
Multaq	**$335**	**5.0%**
Anoro Ellipta	**$335**	**3.0%**
Synjardy / XR	**$334**	**4.1%**
Epclusa	$331	0.0%
Aristada	**$328**	**3.8%**
Rezurock	**$328**	**7.6%**
Oxbryta	$324	i
Zeposia	**$324**	**7.3%**
Copaxone	$321	0.0%
Iclusig	**$321**	**7.0%**
Zejula	**$320**	**4.3%**
Thymoglobulin	**$316**	**5.0%**
Ruxience	$309	0.0%
Acthar	**$305**	**3.1%**
Zirabev	$304	0.0%
Lantus	$303	0.9%
Aimovig	**$303**	**7.8%**
Breyanzi	**$303**	**8.7%**
Orladeyo	**$300**	**5.4%**
Adderall XR	$299	0.0%
Nexviazyme	**$294**	**4.8%**
Kalydeco	$291	0.0%
Zepzelca	**$290**	**8.6%**
Syfovre	$275	i
Myozyme / Lumizyme	**$275**	**5.0%**
Vascepa	$274	0.0%
Dificid	**$274**	**4.9%**

Bolding indicates the 188 drugs subset from the greater 250 that had a WAC price increase greater than medical CPI + 2%
WAC: wholesale acquisition cost
Insufficient WAC change information was denoted by i
*No WAC change percentage is given when WAC data required to calculate WAC percentage change were not available in one or more quarters. Had the WAC percentage increases been larger than medical CPI + 2%, the drugs where WAC was unavailable still would not have been included in the list of drugs to be assessed.
†Net sales revenue in 2023, in millions.
‡Four quarter WAC change.
§Provided by manufacturer.

We then determined which of those drugs had a WAC price increase over the one-year period that exceeded the rate of medical CPI + 2%. This was calculated as the difference between the average medical CPI using unadjusted rates, which was 0.48% for 2023 relative to 2022. The medical CPI is one of eight major components of the CPI recorded and reported by the US Bureau of Labor Statistics.[5] Medical CPI comprises medical care services (professional services, hospital and related services, and health insurance) and medical care commodities (medical drugs, equipment, and supplies).[6] Drugs whose WAC price percentage increases had not exceeded the rate of medical CPI + 2% (2.48%) were removed from further evaluation. Our intent in choosing the overall medical CPI and not its subcomponents was to reflect inflation in drug prices relative to inflation in the overall price of medical care.

Among those 188 drugs with a WAC price increase greater than the medical CPI + 2%, we determined *net* price changes over the one-year period. WAC and net price change per unit over the one-year period were adjusted for percentage change in price across different dosing strengths for any drug, if applicable, considering the relative sales volume of the various dosing strengths. Net price information was obtained from SSR Health. Drugs for which pricing information was deemed unreliable (e.g., because the net price was higher than WAC price in at least one of the eight quarters in which data were captured) were excluded from this review.

We then ranked those drugs whose net price increases had the largest impact on US spending over the prior year. Table 2.2 shows the top 15 drugs listed by the effect of net price increases on US spending. Manufacturers were given the opportunity to correct these figures early in the process; however, the data presented in Table 2.2 represent spending-determined rankings prior to manufacturer feedback. After the receipt of manufacturer feedback, we arrived at the top 10 drugs derived from SSR Health based on their corrected increase in drug spending due to net price change.

Table 2.2. Top 15 Drugs with WAC Percentage Change Greater Than Medical Care CPI* + 2% Ranked by Increase in Spending Due to Net Price Change, Prior to Manufacturer Feedback

Drug Name	Rank
Biktarvy	1
Keytruda	2
Imfinzi	3
Opdivo	4
Darzalex	5
Jakafi	6
Tagrisso	7
Entyvio	8
Xeljanz	9
Prolia	10
Genvoya	11
Cabometyx	12
Entresto	13
Kisqali	14
Ocrevus	15

*Medical care CPI was 0.48% in 2023.

Table 2.3 shows the 10 drugs that were chosen for assessment. These drugs were selected from Table 2.2 after manufacturer review and proposed revisions had occurred. Thus, rankings and estimates of increases in drug spending were subject to change between Table 2.2 and Table 2.3.

Table 2.3. Drugs Selected for Assessment

Drug (Generic)	2022 to 2023 Percentage Change*		Increase in Drug Spending Due to Net Price Change (in Millions)
	WAC	Net Price	
Keytruda (Pembrolizumab)	4.1%	2.8%	$364
Biktarvy (Bictegravir, Emtricitabine, and Tenofovir Alafenimide)	5.9%	3.8%	$359
Imfinizi (Durvalumab)	3.0%	9.9%	$203
Opdivo (Nivolumab)	4.0%	3.8%	$194
Darzalex (Daratumumab)	7.6%	3.7%	$190
Tagrisso (Osimertinib)	3.7%	6.6%	$137
Prolia (Denosumab)	9.9%	4.5%	$113
Entresto (Sacubitril/Valsartan)	6.2%	3.6%	$108
Cabometyx (Cabozantinib)	7.5%	5.9%	$86
Xeljanz (Tofacitinib)	6.0%	6.7%	$72

WAC: wholesale acquisition cost

*Year-over-year percentage changes were estimated by averaging over the four quarterly changes in price (i.e., Q1 2022 to Q1 2023; Q2 2022 to Q2 2023; Q3 2022 to Q3 2023 and; Q4 2022 to Q4 2023).

3. Assessments (Main List)

Table 3.1. Assessment Results

Drug (Generic)	2022 to 2023 Percentage Change*		Increase in Drug Spending Due to Net Price Change (in Millions)
	WAC	Net Price	
Drugs with Price Increases Unsupported by New Clinical Evidence			
Biktarvy (Bictegravir, Emtricitabine, and Tenofovir Alafenimide)	5.9%	3.8%	$359
Darzalex (Daratumumab)	7.6%	3.7%	$190
Entresto (Sacubitril/Valsartan)	6.2%	3.6%	$108
Cabometyx (Cabozantinib)	7.5%	5.9%	$86
Xeljanz (Tofacitinib)	6.0%	6.7%	$72
Drugs with Price Increases with New Clinical Evidence†			
Keytruda (Pembrolizumab)	4.1%	2.8%	$364
Imfinizi (Durvalumab)	3.0%	9.9%	$203
Opdivo (Nivolumab)	4.0%	3.8%	$194
Tagrisso (Osimertinib)	3.7%	6.6%	$137
Prolia (Denosumab)	9.9%	4.5%	$113

WAC: wholesale acquisition cost

*Year-over-year percentage changes were estimated by averaging over the four quarterly changes in price (i.e., Q1 2022 to Q1 2023; Q2 2022 to Q2 2023; Q3 2022 to Q3 2023 and; Q4 2022 to Q4 2023).

†This is not a determination that the new evidence necessarily justified these price increases.

3.1 Keytruda® (pembrolizumab, Merck)

Introduction

Keytruda® (pembrolizumab, Merck) is a programmed death ligand-1 (PD-L1) blocking antibody that was originally approved by the FDA in 2014.[7] It is indicated for the treatment of 19 different cancers (covering a range of sub-indications), including melanoma, non-small cell lung cancer, triple-negative breast cancer, renal cell carcinoma, urothelial cancer, head and neck squamous cell cancer, endometrial cancer, cervical cancer, colorectal cancer, gastric cancer, esophageal cancer, hepatocellular carcinoma, biliary tract cancer, cutaneous squamous cell carcinoma, classical Hodgkin Lymphoma, primary mediastinal large B-cell lymphoma, microsatellite instability-high or mismatch repair deficient cancer, microsatellite instability-high or mismatch repair deficient colorectal cancer, Merkel cell carcinoma, and tumor mutational burden-high cancer.

Based on input from manufacturers, the indications or broad combination of indications that account for greater than 10% of pembrolizumab use include:

- Non-small cell lung cancer (NSCLC)
- Triple-negative breast cancer (TNBC)

- Genito-urinary cancers: Renal Cell Carcinoma & Urothelial cancer
- Head and Neck Squamous Cell Cancer & Melanoma

We provide more information on the combination of sub-indications that meet the 10% utilization threshold that impacts our evidence review below.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for pembrolizumab increased by approximately 4.1%, while its estimated net price increased by 2.8%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $364 million. All pricing information was obtained from SSR Health, LLC.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on pembrolizumab as of January 2022. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24-months review timeframe (January 2022 – December 2023) (see Appendix Table K1). In addition, we reviewed the RCT and non-RCT information Merck submitted to us to consider as new clinical information (109 references [41 conference presentations and 68 published manuscripts]).

We identified six references (5-manufacturer submitted; 1 from ICER's systematic literature review) related to six trials (KEYNOTE-671, KEYNOTE-091, KEYNOTE-355, KEYNOTE-A39, KEYNOTE-859, AND KEYNOTE-966[8-13]) that met our criteria of new moderate- to high-quality evidence on the benefits and/or harms of pembrolizumab. In addition, we identified 10 abstracts that support the six trials listed above.[14-23] The identified trials inform the use of pembrolizumab for six sub-indications across five cancers (NSCLC, TNBC, urothelial carcinoma, gastric cancer, and biliary tract cancer). Although the use of pembrolizumab in each of these sub-indications does not account for at least 10% of its use, our UPI protocol allows us to consider a combination of indications that exceeds 10% of overall utilization if each indication has new evidence that could support a price increase. Based on manufacturer input, the use of pembrolizumab across these six sub-indications accounts for at least 10% of its use. Additional details on each trial are provided below (Table 3.4). Of the remaining 93 references submitted by the manufacturer, 15 articles were excluded because they did not meet our UPI review criteria, while 78 articles did not meet our criteria for new moderate-to-high-quality evidence. The reasons for exclusion are described in Tables 3.2 and 3.3 below. (Appendix Table A1 provides additional information on each study).

Table 3.2. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Duplicate submission	2
Outcome not relevant to scope	2
Indication accounts for less than 10% of use	3
Study published outside of the timeframe of our review	8

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.3. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence

Reasons	Number of References
Low-quality evidence	25
Previously known information about pembrolizumab related to efficacy	50
Previously known information about pembrolizumab related to safety	2
Previously known information about pembrolizumab related to cost-effectiveness	1

Table 3.4. New Evidence

Baseline Evidence (Before January 2022)	New Evidence
Pembrolizumab was originally approved for use in individuals with non-small cell lung cancer (NSCLC) in 2015 based on the KEYNOTE-001 trial.[24]	**KEYNOTE-671** was a phase III RCT that evaluated the efficacy and safety of perioperative pembrolizumab in patients with early-stage NSCLC.[8,14] Data from this trial led to a new sub-indication for NSCLC: for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
	KEYNOTE-091 was a phase III RCT that evaluated the efficacy and safety of the adjuvant use of pembrolizumab in patients with completely resected stage IB-IIIA NSCLC.[9,19-23] Data from this trial led to a new sub-indication for NSCLC: as a single agent for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥4 cm), II or IIIA NSCLC.
Based on progression-free survival data from KEYNOTE-355, pembrolizumab in combination with chemotherapy was granted accelerated approval in 2020 for use in individuals who have locally recurrent	**KEYNOTE-355** was a phase III RCT evaluating the efficacy and safety of pembrolizumab in combination with chemotherapy compared to chemotherapy alone

unresectable or metastatic triple-negative breast cancer whose tumors express PD-L1.[10]	in patients with advanced triple-negative breast cancer. **Cortes et al. 2022** present the results of the planned final analysis of overall survival (OS), which showed prolonged survival with pembrolizumab with chemotherapy compared to chemotherapy alone.[25]
Prior to April 2023, pembrolizumab was not indicated for the treatment of urothelial cancer.[7]	**KEYNOTE-869** was a multi-cohort study that evaluated the safety of pembrolizumab plus enfortumab vedotin in patients with locally advanced or metastatic urothelial cancer who are not eligible for any platinum-containing therapy.[26] While data from this trial led to accelerated approval for the use of pembrolizumab plus enfortumab vedotin in patients with locally advanced or metastatic urothelial cancer *who are not eligible for any platinum-containing therapy* in April 2023, additional data was needed to confirm clinical benefit in this population. **KEYNOTE-A39** was a confirmatory phase III open-label randomized trial that evaluated the efficacy and safety of pembrolizumab plus enfortumab vedotin compared to chemotherapy in patients with previously untreated locally advanced or metastatic urothelial carcinoma.[11,27] Data from this trial led to the removal of the accelerated approval language in December 2023 and shifted the indication to the use of EV+P for the treatment of locally advanced or metastatic urothelial cancer (*regardless of eligibility for platinum-containing therapy).*
Prior to November 2023, pembrolizumab was not indicated for the treatment of HER2-negative gastric or gastroesophageal junction adenocarcinoma.[7]	**KEYNOTE-859** was a phase III RCT that evaluated the efficacy and safety of pembrolizumab in combination with chemotherapy compared to placebo and chemotherapy in patients with HER2-negative advanced gastric cancer.[13,17,18] Data from this trial led to a new sub-indication in gastric cancer: in combination with fluoropyrimidine- and platinum-containing chemotherapy as first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma.

Prior to October 2023, pembrolizumab was not indicated for the treatment of locally advanced unresectable or metastatic biliary tract cancer.[7]	**KEYNOTE-966** was a phase III RCT that evaluated the efficacy and safety of pembrolizumab in combination with gemcitabine and cisplatin chemotherapy compared to gemcitabine and cisplatin alone in patients with advanced biliary tract cancer.[12,15,16] Data from this trial led to the approval of pembrolizumab for the treatment of locally advanced unresectable or metastatic biliary tract cancer.

New Evidence

KEYNOTE-671 was a Phase III RCT that evaluated the efficacy and safety of perioperative pembrolizumab in patients with early-stage NSCLC.[8,14] Patients received either neoadjuvant pembrolizumab (n=397) or placebo (n=400) followed by surgery and then adjuvant pembrolizumab or placebo once every three weeks for up to 13 cycles. The trial evaluated both event-free survival (including progression, recurrence, or death) and overall survival (OS). Patients who received pembrolizumab had significantly longer event-free survival compared to placebo (hazard ratio [HR] 0.58; 95% confidence interval [CI] 0.46 to 0.72; p<0.001).[8] At a later data cut-off point, there was a significant improvement in OS in patients who received pembrolizumab compared to placebo (HR: 0.72; 95%CI: 0.56-0.93; p=0.005).[14] No new safety signals for pembrolizumab were observed.

KEYNOTE-091 was a Phase III RCT that evaluated the efficacy and safety of the adjuvant use of pembrolizumab in patients with completely resected stage IB-IIIA NSCLC.[9,19-23] Patients received either pembrolizumab (n=590) or placebo (n=587). The primary endpoints were disease-free survival in the overall population and in patients with programmed cell death ligand 1 (PD-L1) tumor proportion score (TPS) of > 50%. Prolonged disease-free survival was observed in patients who received pembrolizumab compared to placebo in the overall population (HR: 0.76; 95%CI: 0.63 – 0.91; p=0.0014); statistical significance was not observed in the PD-L1 TPS >50% subgroup (HR: 0.82; 95%CI: 0.57 – 1.18; p=0.14). No new safety signals for pembrolizumab were observed.

KEYNOTE-355 was a Phase III RCT that evaluated the efficacy and safety of pembrolizumab in combination with chemotherapy in patients with advanced triple-negative breast cancer (TNBC).[10,25] Patients received either pembrolizumab with chemotherapy (n=566) or placebo and chemotherapy (n=281) with co-primary endpoints of progression-free survival (PFS) and OS. The primary endpoints were PFS and OS in patients with tumors that expressed PD-L1 and had a combined positive score (CPS) of greater than 10 (CPS-10), greater than 1 (CPS-1), and in the overall intention-to-treat (ITT) population. Data on PFS was previously reported in 2020.[10] Cortes et al. 2022 present the final results, including overall survival.[25] Patients in the CPS-10 subgroup who received pembrolizumab had significantly prolonged survival compared to chemotherapy alone (median OS: 23 v. 16.1 months; HR: 0.73; 95%CI: 0.55 – 0.95; p=0.0185). Consistent with the previously reported PFS

results, results for OS were not statistically significant in the CPS-1 subgroup (HR: 0.86; 95%CI: 0.72 – 1.04; p=0.1125) and the ITT population (HR: 0.89; 95%CI: 0.76 – 1.05; significant not tested). No new safety signals for pembrolizumab were observed.

KEYNOTE-A39 was a confirmatory Phase III open-label randomized trial that evaluated the efficacy and safety of enfortumab vedotin combined with pembrolizumab (EV+P) compared to chemotherapy in patients with previously untreated locally advanced metastatic urothelial carcinoma.[11,27] Patients received either EV+P (n=442) or placebo and chemotherapy (n=444) and the primary endpoints were PFS and OS. Both PFS (median 12.5 v. 6.3 months; HR: 0.45 [95%CI: 0.38-0.54]) and OS (median 31.5 v. 16.1 months; HR: 0.47; 95% CI: 0.38-0.58; p<0.00001) were prolonged with EV+P versus chemotherapy. No new safety signals for pembrolizumab were observed.

KEYNOTE-859 was a Phase III RCT that evaluated the efficacy and safety of pembrolizumab in combination with chemotherapy in patients with HER2-negative advanced gastric cancer.[13,17,18] Patients received either pembrolizumab with chemotherapy (n=790) or placebo and chemotherapy (n=789). The primary outcome was OS. Patients who received pembrolizumab with chemotherapy had longer OS compared to chemotherapy alone (median of 12.9 v. 11.5 months; HR: 0.78; 95%CI 0.7 – 0.87; p<0.0001). No new safety signals for pembrolizumab were observed.

KEYNOTE-966 was a Phase III RCT that evaluated the efficacy and safety of pembrolizumab in combination with gemcitabine and cisplatin chemotherapy in patients with advanced biliary tract cancer.[12,15,16] Patients received either pembrolizumab with gemcitabine and cisplatin (n=533) or placebo with gemcitabine and cisplatin (n=536). The primary outcome was OS. An improvement in OS was observed in patients who received pembrolizumab with chemotherapy (median OS: 12.7 months) compared to those who received chemotherapy (median: 10.9) [HR: 0.83; 95%CI: 0.72-0.95; p=0.0034). No new safety signals for pembrolizumab were observed.

Rating of New Evidence (Quality and Magnitude):

KEYNOTE-671, 091, 859, and 966: These were all Phase III RCTs that provide high-quality evidence of a substantial net benefit of pembrolizumab, which led to the approval of new indications or sub-indications (see Table 3.4) for pembrolizumab during our timeframe.

KEYNOTE-355: The FDA approved pembrolizumab for the treatment of advanced TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test in 2020 based on progression-free survival data. Cortes et al. 2022 present new evidence from the KEYNOTE-355 trial on the planned final analysis of overall survival, a patient-important outcome for cancer treatments. KEYNOTE-355 provides high-quality evidence of a substantial benefit of pembrolizumab plus chemotherapy for advanced TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test.

KEYNOTE-A39: The FDA granted accelerated approval of pembrolizumab for the treatment of locally advanced or metastatic urothelial carcinoma in 2023 based on data from a safety study (KEYNOTE-869). KEYNOTE-A39 was a confirmatory Phase III open-label RCT for patients with locally advanced or metastatic urothelial carcinoma that led to the removal of the "accelerated approval" language in the FDA label. The trial was open-label, providing moderate-quality evidence of substantial benefit in this population.

Based on manufacturer input, the use of pembrolizumab across these six sub-indications accounts for at least 10% of its use.

Conclusion

After careful review of the evidence, we conclude that pembrolizumab (Keytruda®) had a price increase *with* new clinical evidence.

3.2 Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide, Gilead)

Introduction

Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide, Gilead) is a once-daily, fixed-dose combination therapy that combines bictegravir (BIC), a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor, emtricitabine (FTC) and tenofovir alafenamide (TAF), both of which are HIV-1 nucleoside analog reverse transcriptase inhibitors.[28] It was approved in 2018 for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 14 kg.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) increased by approximately 5.9%, while its estimated net price increased by 3.8%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $359 million. Pricing information for WAC was obtained from SSR Health, LLC, while the manufacturer provided the estimate of change in net price and budget impact due to net price changes.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information outlined in the FDA label and related published literature to assess the baseline evidence on BIC/FTC/TAF as of January 2022. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24-month review timeframe (January 2022 – December 2023) (see Appendix Table K1). In addition, we reviewed the RCT and non-RCT information that Gilead submitted to us to consider as new clinical information (14 references including seven conference presentations and seven published manuscripts).

Of the 14 references submitted by the manufacturer, four articles were excluded because they did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.5 (Appendix Table B1 provides additional information on each study). Eight of the remaining 10 references were excluded as they were previously known information about BIC/FTC/TAF related to efficacy and safety (see Table 3.6). Finally, we excluded two studies because of low-quality evidence. We did not identify any new study in our independent systematic literature review.

Table 3.5. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Outcomes not relevant to scope	1
Indication accounts for less than 10% of use	3

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.6. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence

Reasons	Number of References
Previously known information about BIC/FTC/TAF related to efficacy and safety	8
Low-quality evidence	2

Example of Submitted Study

The **ALLIANCE** trial was a Phase 3, randomized, active-controlled, non-inferiority trial that evaluated BIC/FTC/TAF versus dolutegravir/emtricitabine/tenofovir disoproxil fumarate (TDF) in individuals with HIV-1 and hepatitis B virus (HBV) coinfection.[29] The trial met the criteria for non-inferiority on the co-primary endpoints of the proportion of participants with plasma HIV-1 RNA less than 50 copies per mL and plasma HBV DNA less than 29 IU/mL at week 48 (prespecified non-inferiority margin: -12%). Furthermore, BIC/FTC/TAF demonstrated superiority over the TDF-based regimen in suppressing HBV DNA at 48 weeks (63% vs. 43%; difference 16. 6 [95% confidence interval (CI): 5.9 to 27.3]; p=0.002), although by 96 weeks, the suppression rates were comparable between the two groups (75% vs. 70%; difference: 2.6 [95%CI: -8.3 to 13.4]; p=0.64). The incidence of adverse events was similar across the two treatment groups.

Decision: Study did not meet UPI criteria as the utilization for this indication is less than 10%.

Reason for Decision: ALLIANCE is the first randomized study to compare BIC/FTC/TAF, a TAF-based regimen, to a TDF-based regimen in patients with HIV-1 and HBV coinfection. However, based on manufacturer input, it is unlikely that use in HIV-1 and HBV coinfection accounts for at least 10% of the overall utilization of BIC/FTC/TAF.

Conclusion

After careful review of the evidence, we conclude that bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®) had a price increase *unsupported by* new clinical evidence.

3.3 Imfinzi® (durvalumab, AstraZeneca)

Introduction

Imfinzi® (durvalumab, AstraZeneca) is a programmed death-ligand (PD-L1) blocking antibody approved by the FDA in 2017.[30] It is approved as a single agent or in combination with other agents for several indications, including the treatment of unresectable stage III non-small cell lung cancer (NSCLC), metastatic NSCLC, extensive-stage small cell lung cancer, locally advanced or metastatic biliary tract cancer, unresectable hepatocellular carcinoma, and primary advanced or recurrent endometrial cancer. Based on the information provided by the manufacturer, all indications account for more than 10% of its use.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for durvalumab increased by approximately 3%, while its estimated net price increased by 9.9%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $203 million. All pricing information was obtained from SSR Health, LLC.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on durvalumab as of January 2022. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24-month review timeframe (January 2022 – December 2023) (see Appendix Table K1). In addition, we reviewed the RCT and non-RCT information that AstraZeneca submitted to us to consider as new clinical information (33 references [19 conference presentations and 14 published manuscripts]).

Of the 33 references submitted by the manufacturer, seven articles were excluded because they did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.7 (Appendix Table C1 provides additional information on each study). Following our systematic literature review and the review of the remaining 26 articles submitted by the manufacturer, we identified 12 references related to three trials (POSEIDON, TOPAZ-1, and HIMALAYA) that met our criteria of new and potentially moderate- to high-quality evidence on the benefits and/or harms of durvalumab (Table 3.9). Additional details on these trials are provided below. Of the remaining 14 references submitted by the manufacturer, 13 presented previously known information about durvalumab, and one was considered low-quality evidence (Table 3.8).

Table 3.7. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Population not relevant to scope	1
Intervention or comparison not relevant to scope	2
Outcomes not relevant to scope	4

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.8. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence

Reasons	Number of References
Previously known information related to efficacy or safety or cost-effectiveness	13
Low quality evidence	1

Table 3.9. Summary of New Evidence

Baseline Evidence (Before January 2022)	New Evidence
Prior to November 2022, durvalumab was not indicated for adult patients with metastatic NSCLC (mNSCLC).	The POSEIDON study was a three-arm RCT that evaluated durvalumab plus tremelimumab plus chemotherapy (D/T/CT), durvalumab plus chemotherapy (D/CT), and chemotherapy alone in first-line mNSCLC.[31] Based on the evidence from the POSEIDON trial, the FDA approved durvalumab in combination with tremelimumab and platinum-based chemotherapy for the treatment of adult patients with mNSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.
Prior to September 2022, durvalumab was not indicated for adult patients with locally advanced or metastatic biliary tract cancer (BTC).	The TOPAZ-1 study was a Phase III RCT that evaluated durvalumab plus gemcitabine plus cisplatin versus gemcitabine plus cisplatin in locally advanced or metastatic BTC patients.[32] Based on evidence from the TOPAZ-1 trial, durvalumab, in combination with gemcitabine and cisplatin, was approved by the FDA as a treatment for adult patients with locally advanced or metastatic BTC.

Baseline Evidence (Before January 2022)	New Evidence
Prior to October 2022, Durvalumab was not indicated for unresectable hepatocellular carcinoma (uHCC).	The **HIMALAYA** trial was a three-arm Phase III RCT that evaluated durvalumab + a single high dose of tremelimumab, durvalumab only, and sorafenib only in patients with uHCC.[33] Based on evidence from the **HIMALAYA** trial, durvalumab, in combination with tremelimumab, was approved as a treatment for adult patients with uHCC.

FDA: Food and Drug Administration, RCT: randomized controlled trial

New Evidence

The **POSEIDON** study was an open-label Phase III RCT that enrolled 997 patients with mNSCLC. Patients were randomized to receive either durvalumab plus tremelimumab plus chemotherapy (D/T/CT), durvalumab plus chemotherapy (D/CT), or chemotherapy alone.[31,34,35] Progression-free survival was significantly improved with D/T/CT (hazard ratio [HR] 0.72; 95% CI 0.60 to 0.86; p = 0.0003) and D/CT (HR 0.74; 95% CI 0.62 to 0.89; p = 0.001) versus chemotherapy alone. Overall survival was also significantly improved on D/T/CT (HR 0.77; 95% CI 0.65 to 0.92; p = 0.003) compared to chemotherapy alone. A similar trend in overall survival was observed with D/CT, although statistical significance was not reached. Higher rates of treatment-related adverse events (52% vs. 44%) and discontinuation due to AEs (15% vs. 10%) were observed with D/T/CT versus chemotherapy alone.

The **TOPAZ-1** study was a Phase III trial RCT that evaluated durvalumab versus placebo in combination with chemotherapy in 685 patients with advanced BTC.[32,36,37] Patients treated with durvalumab plus chemotherapy had a longer overall survival compared with placebo plus chemotherapy (12.8 months vs. 11.5 months; HR 0.80; 95% CI 0.66 to 0.97; p = 0.021). Consistent with overall survival, progression-free survival (HR 0.75; 95% CI 0.63 to 0.89; p = 0.001) and objective response rate (26.7% vs. 18.7%; odds ratio 1.60; 95% CI 1.11 to 2.31) benefits were also in favor of the durvalumab plus chemotherapy group. Similar rates of Grade 3 or 4 adverse events were observed in both groups (durvalumab 75.7% vs. placebo 77.8%).

The **HIMALAYA** study was a Phase III RCT that enrolled 1,171 patients with unresectable hepatocellular carcinoma and no previous systemic treatment.[33,38-40] Patients were randomized to either receive a combination of tremelimumab and durvalumab, referred to as the STRIDE regimen (single tremelimumab regular interval durvalumab), or durvalumab alone, or sorafenib alone. The primary endpoint of the superiority of the STRIDE regimen versus sorafenib on overall survival was achieved (Median overall survival: 16.43 months vs. 13.77 months; HR 0.78; 95% CI, 0.65 to 0.93; P=0.0035). In addition, the secondary endpoint of non-inferiority of durvalumab versus sorafenib was also achieved (HR, 0.86; 95% CI, 0.73 to 1.003; non-inferiority margin, 1.08). Other secondary

endpoints were also in favor of the STRIDE regimen, although median progression-free survival was not significantly different among all three groups. Similar rates of Grade 3 or 4 adverse events were observed in the STRIDE versus sorafenib group (50.5% vs. 52.4%).

Rating of New Evidence (Quality and Magnitude)

Based on the evidence from the POSEIDON trial, the FDA approved durvalumab in combination with tremelimumab and platinum-based chemotherapy for the treatment of adult patients with mNSCLC. The trial was open-label, providing moderate-quality evidence of a substantial benefit with durvalumab plus tremelimumab plus chemotherapy in this population.

Based on evidence from the TOPAZ-1 study, the FDA approved durvalumab to be used in combination with gemcitabine and cisplatin for adult patients with locally advanced or metastatic BTC. The estimated median OS benefit appeared to be small (only five weeks). However, the estimated 2-year overall survival was 25% (vs. 10% in the placebo arm), and it appeared that there may be some long-term survivors beyond two years with durvalumab. As such, we consider this a substantial benefit. We believe TOPAZ-1 provides high-quality evidence of a substantial benefit of treatment with durvalumab plus chemotherapy in this population.

Based on evidence from the HIMALAYA trial, durvalumab, in combination with tremelimumab, was approved as a treatment for adult patients with unresectable hepatocellular carcinoma. The trial was open-label, providing moderate-quality evidence of a substantial benefit with durvalumab plus tremelimumab in this population.

Conclusion

After careful review of the evidence, we conclude that durvalumab (Imfinzi®) had a price increase *with* new clinical evidence.

3.4 Opdivo® (nivolumab, Bristol Myers Squibb)

Introduction

Opdivo® (nivolumab, Bristol Myers Squibb) is a PD-L1 blocking antibody approved by the FDA in 2014 as a monotherapy administered by intravenous infusion for adult patients with unresectable or metastatic melanoma.[41] Since then, it has been indicated for use either as a single agent or in combination with other therapies for these specific conditions: non-small cell lung cancer, malignant pleural mesothelioma, renal cell carcinoma, classical Hodgkin Lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma, esophageal cancer, gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma. Many of these indications frequently cover a range of sub-indications.[41]

We did not receive input from the manufacturer on which indications account for greater than 10% of use. However, based on market share research[42], the following indications account for greater than 10% of nivolumab's use:

- Melanoma
- Non-small cell lung cancer (NSCLC)
- Renal cell carcinoma (RCC)

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for durvalumab increased by approximately 4.0%, while its estimated net price increased by 3.8%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $194 million. All pricing information was obtained from SSR Health, LLC.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on nivolumab as of January 2022. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2022 – December 2023) (see Appendix Table K1). Our literature search identified five references related to three indications that met our criteria of new and potentially moderate to high-quality evidence on the benefits and/or harms of nivolumab (see Table 3.10).[43-47] We are uncertain whether the use of nivolumab in each of the indications where we identified new evidence accounts for at least 10% of its use; our review and clinical input suggest it is unlikely. However, since our UPI protocol allows us to consider a combination of indications that exceeds 10% of overall utilization if each indication has new evidence that could support a price

increase, these trials were further evaluated. BMS did not submit any further references to be considered for our review.

Table 3.10. Summary of New Evidence

Baseline Evidence (Before January 2022)	New Evidence
Prior to October 2023, nivolumab was approved as adjuvant treatment for patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection based on evidence in patients with completely resected Stage IIIB/C or Stage IV melanoma.	CheckMate 76K was a Phase III trial that evaluated nivolumab versus placebo in patients with resected stage IIB/C melanoma.[43] Based on the evidence from the CheckMate 76K trial, the FDA approved nivolumab in resected stage IIB/C melanoma.
Prior to March 2022, nivolumab was not approved as a neoadjuvant treatment for resectable non-small cell lung cancer.	CheckMate 816 was a Phase III trial that evaluated the efficacy and safety of neoadjuvant nivolumab plus chemotherapy compared with chemotherapy alone in patients with resectable NSCLC.[44] Based on the evidence from the CheckMate 816 trial, the FDA approved nivolumab in combination with platinum-doublet chemotherapy as neoadjuvant treatment in patients with resectable NSCLC.
Prior to May 2022, nivolumab was not approved as a first-line treatment for patients with unresectable advanced or metastatic esophageal squamous-cell carcinoma.	CheckMate 648 was a Phase III trial that evaluated nivolumab plus chemotherapy, nivolumab plus ipilimumab, and chemotherapy alone in previously unresectable advanced, recurrent, or metastatic esophageal squamous-cell carcinoma patients.[47] Based on the evidence from the CheckMate 648 trial, the FDA approved nivolumab plus ipilimumab AND nivolumab plus chemotherapy for the first-line treatment of patients with unresectable advanced or metastatic esophageal squamous-cell carcinoma.

FDA: Food and Drug Administration, RCT: randomized controlled trial

New Evidence

The **CheckMate 76K** study was a Phase III RCT that enrolled 790 patients with resected stage IIB/C melanoma.[43] Patients were randomized 2:1 to receive nivolumab 480 mg or placebo every four weeks for 12 months. The primary endpoint of the trial, recurrence-free survival (RFS), was significantly improved on nivolumab compared to placebo (hazard ratio [HR] 0.42; 95% CI 0.30 to 0.59; p<0.0001. Distant metastasis-free survival (DMFS) was also significantly improved in patients treated with nivolumab versus placebo (HR 0.47; 95% CI 0.30 to 0.72). Discontinuations due to treatment-related adverse events were higher in the nivolumab group (15%) compared to placebo (3%). One patient died in the nivolumab group because of acute kidney injury and heart failure.

The **CheckMate 816** study was an open-label Phase III RCT that evaluated nivolumab plus chemotherapy (n=179) versus chemotherapy alone (n=179) in patients with stage IB to IIIA resectable NSCLC.[44,45] Event-free survival was significantly improved with nivolumab plus chemotherapy (HR 0.63; 97.38% CI 0.43 to 0.91; p=0.005) compared with chemotherapy alone. More patients treated with nivolumab plus chemotherapy achieved a complete pathological response (24% vs. 2%; odds ratio [OR] 13.94; 99% CI 3.49 to 55.75; p<0.001) than chemotherapy alone. In the first interim analysis, although OS favored patients treated with nivolumab plus chemotherapy (HR 0.57; 99.67% CI, 0.30 to 1.07; P=0.008), it did not reach the prespecified boundary for statistical significance (0.0033). The safety profile was similar across the two arms.

The **CheckMate 648** study was an open-label Phase III RCT that evaluated 970 patients with untreated, unresected, recurrent, or metastatic esophageal squamous-cell carcinoma.[47] Patients were randomized to either receive nivolumab plus chemotherapy (n = 321), nivolumab plus ipilimumab (n =325), or chemotherapy alone (n =324). Median OS was significantly longer with nivolumab plus chemotherapy compared to chemotherapy alone (13.2 months vs. 10.7 months; HR 0.74; 0.74; 99.1% CI, 0.58 to 0.96; P=0.002). Similarly, median OS was longer with nivolumab plus ipilimumab versus chemotherapy alone (12.7 months vs. 10.7 months; HR 0.64; 98.6% CI 0.46 to 0.90; p=0.001). However, treatment with either nivolumab plus chemotherapy or nivolumab plus ipilimumab did not result in a significant progression-free survival (PFS) benefit in the overall population, although a statistically significant benefit was observed with nivolumab plus chemotherapy in patients with tumor-cell programmed death ligand-1 expression of 1% or greater. Discontinuations due to treatment-related adverse events were higher in the nivolumab plus chemotherapy group (34%) compared to nivolumab plus ipilimumab (18%) or chemotherapy alone (19%).

Rating of New Evidence (Quality and Magnitude)

Based on the evidence from the CheckMate 76K trial, the FDA approved nivolumab for the treatment of resected stage IIB/C melanoma. Evidence from the CheckMate 76K trial indicates that nivolumab improves surrogate outcomes (RFS and DMFS); data on OS were not provided. However, analyses have shown a correlation between these surrogate outcomes and OS in patients with

melanoma receiving checkpoint inhibitors.[48,49] As such, the observed benefit was considered substantial, although we downgraded the quality of evidence for indirectness. New data presented at the European Society for Medical Oncology conference in September 2024 (outside our review time frame) on the CheckMate 76K trial show a waning in RFS and DMFS benefits, suggesting a downgrade in the rating of the magnitude of the benefit to minimal. However, since the manufacturer would not have been aware of these additional data at the time of the price increase, we focused our rating of the evidence only on the data available during our review timeframe. Therefore, we conclude that based on the evidence available during our review timeframe, CheckMate 76K provides moderate-quality evidence of a substantial benefit of treatment with nivolumab in this population.

Based on the evidence from the CheckMate 816 trial, nivolumab, in combination with chemotherapy, was approved for the treatment of resected NSCLC based on event-free survival and pathological response. Data on OS was not significant, although there was a trend toward improvement. The trial was open-label, providing moderate-quality evidence of a substantial benefit of treatment with nivolumab in this population.

Based on the evidence from the CheckMate 648 trial, nivolumab, either in combination with ipilimumab or in combination with chemotherapy, was approved as first-line treatment for unresected, advanced, or metastatic esophageal squamous-cell carcinoma based on improvement in PFS and OS. This trial provides high-quality evidence of a substantial benefit of treatment with nivolumab in this population.

Conclusion

We are uncertain whether a combination of the sub-indications for nivolumab where we identified new high or moderate-quality evidence accounts for greater than 10% of nivolumab's use as required by the UPI Protocol. However, the Protocol had not anticipated the current situation with checkpoint inhibitors, where we are seeing multiple moderate- to high-quality trials and multiple newly approved indications within a review cycle for a single drug. As discussed each year in section 8 of the Protocol, ICER has committed to flexibility when such circumstances arise. We feel that it would be unfair to disadvantage a therapy that has evidence in support of three new indications in a single cycle and, as such, conclude that, even if these three new indications account for less than 10% of nivolumab's use, nivolumab (Opdivo®) had a price increase *with* new clinical evidence.

3.5 Darzalex® (daratumumab, Johnson & Johnson)

Introduction

Darzalex® (daratumumab, Johnson & Johnson) is an anti-CD38 monoclonal antibody that was approved in 2015.[50] It is indicated for the treatment of adult patients with multiple myeloma as both a monotherapy and in combination with other agents.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for Darzalex increased by approximately 7.6%, while its estimated net price increased by 3.7%.
This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $190 million. All pricing information was obtained from SSR Health, LLC.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on daratumumab as of January 2022. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24-month review timeframe (January 2022 – December 2023) (see Appendix Table K1). Our literature search identified 20 articles, none of which met our inclusion criteria of new and potentially moderate- to high-quality evidence on the benefits and/or harms of daratumumab. Johnson & Johnson did not submit any additional references to be considered for our review.

Conclusion

After careful review of the evidence, we conclude that daratumumab (Darzalex®) had a price increase *unsupported* by new clinical evidence.

3.6 Tagrisso® (osimertinib, AstraZeneca)

Introduction

Tagrisso® (osimertinib, AstraZeneca) is an oral kinase inhibitor originally approved by the FDA in 2015 for the treatment of metastatic EGFR T790M mutation-positive NSCLC who were previously treated with EGFR tyrosine kinase inhibitor (TKI) therapy.[51] It has since gained indications as first-line treatment for locally advanced or metastatic NSCLC with EGFR exon 19 deletions or 21 L858R mutations in combination with pemetrexed and platinum-based chemotherapy, first-line treatment for metastatic NSCLC with EGFR exon 19 deletions or 21 L859R mutations, and adjuvant therapy after tumor resection for NSCLC with EGFR exon 19 deletions or 21 L858R mutations. The manufacturer has confirmed that adjuvant treatment for EGFR-mutation positive NSCLC after tumor resection has a utilization greater than 10%.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for osimertinib increased by approximately 3.7%, while its estimated net price increased by 6.6%.
This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $137 million. All pricing information was obtained from SSR Health, LLC.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on osimertinib as of January 2022. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24-month review timeframe (January 2022 – December 2023) (see Appendix Table K1). In addition, we reviewed the RCT and non-RCT information AstraZeneca submitted to us to consider as new clinical information (nine references [two conference presentations and seven published manuscripts]).

Of the nine references submitted by the manufacturer, two articles were excluded because they did not meet our UPI review criteria. The primary reason for excluding these studies is provided in Table 3.11. (Appendix Table F1 provides additional information on each study). Following our systematic literature review and the review of the remaining seven articles submitted by the manufacturer, we identified one reference related to one RCT [ADAURA] that met our criteria of new and potential moderate- to high-quality evidence on the benefits and/or harms of osimertinib (Table 3.13). Additional details on this trial are provided below. The remaining six references submitted by the manufacturer presented previously known information about osimertinib (Table 3.12).

Table 3.11. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study population outside approved label indication during our timeframe	2

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.12. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence

Reasons	Number of References
Previously known information about osimertinib related to efficacy	4
Previously known information about osimertinib related to cost-effectiveness	2

Table 3.13. Summary of New Evidence

Baseline Evidence (Before January 2022)	New Evidence
The FDA approved osimertinib as an adjuvant treatment for EGFR-mutated NSCLC in 2020 based on evidence of disease-free survival (surrogate outcome) benefit in the ADAURA randomized controlled trial (RCT).[52] Overall survival (OS) data were not mature at the time of FDA approval.	The ADAURA trial was a phase III RCT that evaluated the efficacy and safety of adjuvant osimertinib compared to placebo in patients with EGFR-mutated NSCLC. Tsuboi et al. 2023 present the result of the planned final analysis of overall survival in the ADAURA trial. The analysis showed that osimertinib significantly improves overall survival compared to placebo.[53]

EGFR: epidermal growth factor receptor, FDA: Food and Drug Administration, NSCLC: non-small cell lung cancer, RCT: randomized controlled trial

New Evidence

The **ADAURA** study was a phase III double-blind RCT that evaluated adjuvant treatment with osimertinib versus placebo in 682 patients with resected EGFR-mutated NSCLC. Data on the primary endpoint, disease-free survival in patients with stage II to IIA disease, was previously reported in 2020.[52] Tsuboi et al. 2023 present the final results, including OS.[53] In the overall population (stage IB to IIIA NSCLC), a significant benefit in 5-year overall survival was observed in participants who received adjuvant osimertinib compared to placebo (88% v. 78%; hazard ratio: 0.49; 95% confidence interval: 0.34 to 0.7; p<0.001). Similar results were observed among subgroups, including a cohort of participants with stage II and IIA disease. Disease-free survival was also maintained. No new safety signals were identified in this analysis.

Rating of New Evidence (Quality and Magnitude)

The FDA approved osimertinib as an adjuvant treatment for EGFR-mutated NSCLC in 2020 based on disease-free survival benefit in the ADAURA trial. Tsuboi 2023 reports new evidence from the ADAURA trial on the planned final analysis of overall survival, a patient-important outcome for

cancer treatments. The ADAURA trial provides high-quality evidence of a substantial benefit of adjuvant treatment with osimertinib for EGFR-mutated NSCLC.

Conclusion

After careful review of the evidence, we conclude that osimertinib (Tagrisso®) had a price increase *with* new clinical evidence.

3.7 Prolia® (Denosumab, Amgen)

Introduction

Prolia® (denosumab, Amgen), a monoclonal antibody used to manage osteoporosis in patients at high risk of fractures, was first approved by the FDA in 2010.[54] It is specifically indicated for the treatment of osteoporosis in the following patients: postmenopausal women at high risk for fracture, men at high risk for fracture, men and women with glucocorticoid-induced osteoporosis at high risk for fracture, men undergoing androgen deprivation therapy for nonmetastatic prostate cancer at high risk for fracture, and women receiving adjuvant aromatase inhibitor therapy for breast cancer at high risk for fracture. Based on information provided by the manufacturer, all indications, other than the treatment of osteoporosis in men, account for >10% of use.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for Prolia increased by approximately 9.9%, while its estimated net price increased by 4.5%.
This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $113 million. All pricing information was obtained from SSR Health, LLC.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on denosumab as of January 2022. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24-month review timeframe (January 2022 – December 2023) (see Appendix Table K1). In addition, we reviewed the RCT and non-RCT information Amgen submitted to us to consider as new clinical information (30 references [four conference presentations and 26 published manuscripts]). Of the 30 references submitted by the manufacturer, we identified one reference (Curtis 2023) that met our criteria of new and potential moderate-to-high quality evidence on the benefits and/or harms of denosumab (Table 3.16) Of the remaining 29 references, nine articles were excluded because they did not meet our UPI review criteria, 10 were determined to be low-quality, five were previously known information, four were cost-effectiveness studies from a non-US perspective, and one study showed new evidence of no improved efficacy with denosumab (see Tables 3.14 and 3.15). Additional details on each study are provided in Appendix Table G1.

Table 3.14. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study population outside approved label indication	6
Outcomes not relevant to scope	3

For simplicity, we provide a single reason for excluding each study, although there may be multiple reasons why a study was excluded.

Table 3.15. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence

Reasons	Number of References
Low-quality evidence	10
Cost-effectiveness from a non-US perspective	4
New evidence of no clinical improvement with denosumab	1
Previously known information about denosumab related to efficacy	4
Previously known information about denosumab related to cost-effectiveness	1

Table 3.16. New Evidence

Baseline Evidence (Before January 2022)	New Evidence
Evidence from the FREEDOM randomized controlled trial indicates that denosumab reduces fracture risk in postmenopausal women with osteoporosis.[55] However, there are currently no head-to-head trials that have compared the anti-fracture efficacy of denosumab with other available osteoporosis therapies, such as oral (e.g., alendronate) and intravenous bisphosphonates (e.g. zoledronic acid). One comparative observational study conducted in Denmark reports a similar risk of fracture with denosumab and alendronate over a 3-year period.[56]	**Curtis et al. 2023** was a well-designed retrospective observational study that evaluated the comparative effectiveness of denosumab versus alendronate in 478,651 treatment-naïve postmenopausal women with osteoporosis.[57,58] This study showed a greater reduction in fracture risk with denosumab compared to alendronate in this population.

New Evidence

Curtis et al. 2023 was a retrospective observational study that evaluated the comparative effectiveness of denosumab versus alendronate in treatment-naïve postmenopausal women with osteoporosis in the United States.[57] The study included Medicare fee-for-service beneficiaries who newly initiated denosumab (n=89,115) or alendronate (n=389,536) between 2012 and 2018. Significant reductions in major osteoporotic fractures (relative risk [RR]: 0.61; 95% confidence interval [CI]: 0.48 – 0.74), hip fracture (RR: 0.64; 95% CI, 0.39–0.90), nonvertebral fractures (RR: 0.57; 95%CI: 0.42 – 0.71), non-hospital vertebral fracture (RR: 0.50; 95% CI, 0.35–0.64), and hospitalized vertebral fractures (RR: 0.7; 95%CI: 0.4 – 1.01) were observed in patients who received denosumab compared to alendronate. An increase in the magnitude of fracture risk reduction was observed with increasing duration of exposure to denosumab. For example, the risk of major

osteoporotic fractures reduced by 9% (0.91; 0.85-0.97) at year 1, 12% (0.88; 0.83-0.93) at year 2, 18% (0.82; 0.77-0.87) at year 3, and 31% (0.69; 0.62-0.76) at year 5.

Rating of New Evidence (Quality and Magnitude)

Curtis et al. 2023 was an abstract presented at the American College of Rheumatology Convergence Conference; therefore, detailed methodologies were not provided. However, our assessment incorporated the additional information that was published in the full publication in 2024 (outside our review time frame) since it provides a complete picture of the methodology underlying the evidence reported in **Curtis et al. 2023**.[58] We note that the results of this study could reflect adherence to an oral medication (alendronate) compared with a clinician-administered medication (denosumab), but this would still be relevant for prevention of fractures from osteoporosis; however, it would not extrapolate to a comparison between denosumab and a clinician-administered bisphosphonate such as zoledronic acid. Based on dose (time on treatment) response gradient, this study provides moderate-quality evidence of substantial improvement in fracture outcomes with denosumab versus alendronate that was not previously known in postmenopausal women with osteoporosis.

Conclusion

After careful review of the evidence, we conclude that denosumab (Prolia®) had a price increase *with* new clinical evidence.

3.8 Entresto® (sacubitril-valsartan, Novartis)

Introduction

Entresto® (sacubitril/valsartan, Novartis) is a twice-daily, single-tablet regimen that combines sacubitril (a neprilysin inhibitor) and valsartan (an angiotensin II receptor blocker).[59] It was approved by the FDA in 2015 and is indicated for reducing the risk of cardiovascular death and hospitalization in patients with chronic heart failure. The label notes that "benefits of sacubitril/valsartan *are most clearly evident in chronic heart failure patients with left ventricular ejection fraction below normal*." Sacubitril/valsartan is also approved for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients (ages one year and older). Based on the information provided by the manufacturer, only the first indication accounts for greater than 10% of use.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for sacubitril/valsartan increased by approximately 6.2%, while its estimated net price increased by 3.6%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $108 million. All pricing information was obtained from SSR Health, LLC.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on sacubitril/valsartan as of January 2022. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (January 2022 – December 2023) (see Appendix Table K1). In addition, we reviewed the RCT and non-RCT information Novartis submitted to us to consider as new clinical information (20 references [nine conference presentations and 11 published manuscripts]). However, none of the identified or submitted articles met our criteria of new moderate to high-quality evidence on the benefits and/or harms of sacubitril/valsartan (Appendix Table H1). Of the 20 references submitted by the manufacturer, 13 articles were excluded because they did not meet our UPI review criteria, while the remaining 7 articles were considered to be previously known information related to efficacy (see Tables 3.17 and 3.18). As an example, we highlighted a submitted article (PERSPECTIVE) that was considered previously known information.

Table 3.17. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Study published outside of the timeframe of our review	11
Indication accounts for less than 10% of use	1
Outcomes not relevant to scope	1

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.18. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence

Reasons	Number of References
Previously known information about sacubitril-valsartan related to efficacy	7

Example of Submitted Study

PERSPECTIVE was a non-inferiority randomized controlled trial that assessed the effect of long-term treatment with sacubitril/valsartan, compared with valsartan only, on cognitive function in patients with heart failure and mildly reduced and preserved ejection fraction (HFmrEF and HFpEF).[60]

Decision: Study was excluded under our protocol.

Reason for Decision: PERSPECTIVE was considered to be a qualifying new moderate-to-high-quality evidence to support a price increase for sacubitril/valsartan in the 2023 UPI Report. According to our UPI Protocol, for therapies that are being evaluated in sequential report years, we will not reconsider the same evidence that supported a finding of price increase in the prior year.

Conclusion

After careful review of the evidence, we conclude that sacubitril/valsartan (Entresto®) had a price increase *unsupported by* new clinical evidence.

3.9 Cabometyx® (cabozantinib, Exelixis)

Introduction

Cabometyx® (cabozantinib, Exelixis) is a once-daily, oral, kinase inhibitor that first received FDA approval in 2016.[61] It is indicated for the treatment of advanced renal cell carcinoma (RCC) in combination with nivolumab, in patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib, and in patients ≥12 years old with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible. We did not receive input from the manufacturer on which indications account for greater than 10% of use.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for cabozantinib increased by approximately 7.5%, while its estimated net price increased by 5.9%. This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $86 million. Pricing information for WAC was obtained from SSR Health, LLC, while the manufacturer provided the estimate of the change in net price and budget impact due to net price changes.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information outlined in the FDA label and related published literature to assess the baseline evidence on cabozantinib as of January 2022. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24-month review timeframe (January 2022 – December 2023) (see Appendix Table K1). In addition, we reviewed the RCT and non-RCT information that Exelixis submitted to us to consider as new clinical information (27 references including three conference presentations and 24 published manuscripts).

Of the 27 references submitted by the manufacturer, seven articles were excluded because they did not meet our UPI review criteria. The primary reasons for excluding these studies are provided in Table 3.19 (Appendix Table I1 provides additional information on each study). Of the remaining 20 references, nine were excluded as they were previously known information about cabozantinib related to efficacy and safety. Finally, we excluded 11 studies because of low-quality evidence (see Table 3.20). We did not identify any new studies in our independent systematic literature review.

Table 3.19. Studies Not Meeting UPI Review Criteria

Reason	Number of References
Intervention/comparison not relevant to scope	5
Outcomes not relevant to scope	1
Indication accounts for less than 10% of use	1

For simplicity, we provide a single reason for exclusion of each study, although there may be multiple reasons why a study was excluded.

Table 3.20. Studies Not Meeting Criteria for New Moderate to High-Quality Evidence

Reasons	Number of References
Previously known information about cabozantinib related to efficacy and safety	9
Low-quality evidence	11

Example of Submitted Study

Cella et al. 2022 present the prespecified patient-reported outcomes (PRO) from the CheckMate 9ER trial.[62] CheckMate 9ER was a Phase III, open-label, randomized 1:1, multicenter trial that evaluated the efficacy and safety of nivolumab plus cabozantinib versus sunitinib in 651 patients with previously untreated advanced clear-cell RCC. Evidence demonstrating treatment with nivolumab plus cabozantinib resulted in improved progression-free survival and overall survival compared to sunitinib was presented in a previous publication.[63] Cella et al. 2022 reported a statistically significant treatment difference (2.38, 95% confidence interval [CI] 1.20 to 3.56; p <0.0001) in the mean Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19) total score change from the baseline, favoring nivolumab plus cabozantinib. Patients receiving nivolumab plus cabozantinib experienced a longer median time to deterioration in FKSI-19 total score compared to those receiving sunitinib (6.24 months vs. 3.48 months; hazard ratio 0.70, 95% CI 0.56 to 0.86; p =0.001). Similarly, there was a statistically significant improvement in both EQ-5D-3L visual analog scale (treatment difference 3.48, 95% CI 1.58 to 5.39; p =0.0004) and EQ-5D-3L UK utility index scores (treatment difference 0.04, 95% CI 0.01 to 0.07; p =0.004) in the nivolumab plus cabozantinib compared to the sunitinib monotherapy.

Decision: Study did not meet the criteria for new moderate to high-quality evidence.

Reason for decision: CheckMate 9ER was an open-label trial that provided moderate-quality evidence on the substantial benefit of nivolumab plus cabozantinib on overall survival and progression-free survival compared to sunitinib alone. These results were reported before the current evidence review time frame.[63] While the updated findings presented by Cella et al. 2022 on the PROs are consistent with the previously reported evidence on the benefit of nivolumab plus cabozantinib, the open-label design of the trial is a potential cause of bias, given the subjective nature of the PROs evaluated. Additional limitations include inconsistent schedules for collecting PRO data between the two groups, the small sample size in the comparator group, and the exploratory nature of the analysis, which did not account for multiplicity. Given these limitations,

the new evidence from Cella et al. 2022 is considered to be low quality. Under the UPI protocol, we do not assess the magnitude of benefit in the absence of moderate or high-quality evidence. Additionally, even if we considered this moderate quality, data on PRO benefits had been previously presented, and findings from this study would not have changed what was previously understood.[64]

Conclusion

After careful review of the evidence, we conclude that cabozantinib (Cabometyx®) had a price increase *unsupported by* new clinical evidence.

3.10 Xeljanz® (tofacitinib, Pfizer)

Introduction

Xeljanz® (tofacitinib, Pfizer) is a Janus kinase (JAK) inhibitor that first received FDA approval in 2012.[65] It is indicated for the treatment of adults with rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis, as well as children aged 2 years and older with polyarticular course juvenile idiopathic arthritis. We did not receive input from the manufacturer on which indications account for greater than 10% of use; since it did not affect the conclusions of our review, we did not attempt to obtain additional information from clinical experts or payers on this issue.

Price Increase

Over the 12 months (four quarters) for which price changes were assessed, the WAC for tofacitinib increased by approximately 6.0%, while its estimated net price increased by 6.7%.
This net price change over the assessed four quarters resulted in an estimated increase in drug spending of $72 million. Pricing information for WAC and net pricing was obtained from SSR Health, LLC, while the manufacturer provided the estimate of budget impact due to net price changes.

Review of Clinical Evidence

We reviewed the safety and clinical effectiveness information provided in the FDA label as well as related published literature to assess the baseline evidence on tofacitinib as of January 2022. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24-month review timeframe (January 2022 – December 2023) (see Appendix Table K1). Our literature search identified 28 articles, none of which met our inclusion criteria of new and potentially moderate- to high-quality evidence on the benefits and/or harms of tofacitinib. Pfizer did not submit any additional references to be considered for our review.

Conclusion

After careful review of the evidence, we conclude that tofacitinib (Xeljanz®) had a price increase *unsupported* by new clinical evidence.

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APPENDIX

Appendix A. Keytruda®

Appendix Table A1. References Submitted by Merck

Citation	Decision
O'Malley, D. M., Bariani, G. M., Cassier, P. A., Marabelle, A., Hansen, A. R., Acosta, A. D. J., Miller, W. H., Safra, T., Italiano, A., Mileshkin, L., Xu, L., Jin, F., Norwood, K., & Maio, M. (2022). Pembrolizumab in Patients With Microsatellite Instability-High Advanced Endometrial Cancer: Results From the KEYNOTE-158 Study. *Journal of Clinical Oncology*, *40*(7), 752–761. https://doi.org/10.1200/JCO.21.01874	Low-quality evidence
O'Malley DM, Mendonca Bariani G, Cassier PA, et al. Pembrolizumab in patients with microsatellite instability-high (MSI-H) advanced endometrial cancer: updated results from KEYNOTE-158. *Presented at European Society of Medical Oncology (ESMO) Congress*; September 19, 2021; Virtual. 3.	Low-quality evidence
Maio, M et al. "Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study." *Annals of oncology: official journal of the European Society for Medical Oncology* vol. 33,9 (2022): 929-938. doi:10.1016/j.annonc.2022.05.519	Low-quality evidence
D.M. O'Malley, G.M. Bariani, P.A. Cassier, A. Marabelle, A.R. Hansen, A. De Jesus Acosta, W.H. Miller, T. Safra, A. Italiano, L. Mileshkin, M. Amonkar, L. Yao, F. Jin, K. Norwood, M. Maio, "Health-related quality of life with pembrolizumab monotherapy in patients with previously treated advanced microsatellite instability high/mismatch repair deficient endometrial cancer in the KEYNOTE-158 study." *Gynecologic oncology* vol. 166,2 (2022): 245-253. doi:10.1016/j.ygyno.2022.06.005	Low-quality evidence
Mary O'Brien, Luis Paz-Ares, Sandrine Marreaud, Urania Dafni, Kersti Oselin, Libor Havel, Emilio Esteban, Dolores Isla, Alex Martinez-Marti, Martin Faehling, Masahiro Tsuboi, Jong-Seok Lee, Kazuhiko Nakagawa, Jing Yang, Ayman Samkari, Steven M Keller, Murielle Mauer, Nitish Jha, Rolf Stahel, Benjamin Besse, Solange Peters, "Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial." The Lancet. Oncology vol. 23,10 (2022): 1274-1286. doi:10.1016/S1470-2045(22)00518-6	New moderate to high quality evidence
Paz-Ares L, O'Brien ME, Mauer M, Dafni U, Oselin K, Havel L, Gonzalez EE, Isla D, Martinez-Marti A, Faehling M, Tsuboi M. VP3-2022: Pembrolizumab (pembro) versus placebo for early-stage non-small cell lung cancer (NSCLC) following complete resection and adjuvant chemotherapy (chemo) when indicated: Randomized, triple-blind, phase III EORTC-1416-LCG/ETOP 8-15–PEARLS/KEYNOTE-091 study. Annals of Oncology. 2022 Apr 1;33(4): 451-3.doi: 10.1016/j.annonc.2022.02.224	Supporting evidence for trial above

Citation	Decision
Peters S, Besse B, Marreaud S, Dafni U, Oselin K, Havel L, Gonzalez EE, Isla D, Martinez-Marti A, Faehling M, Tsuboi M. 930MO PD-L1 expression and outcomes of pembrolizumab and placebo in completely resected stage IB-IIIA NSCLC: Subgroup analysis of PEARLS/KEYNOTE-091. Annals of Oncology. 2022 Sep 1;33:S971-2.doi: 10.1016/j.annonc.2022.07.1056	Supporting evidence for trial above
Besse B, Havel L, Peters S, Marreaud SI, Jha N, Oselin K, Gonzalez EE, Casado MI, Martinez-Marti A, Faehling M, Lee JS. 120MO Adjuvant pembrolizumab versus placebo for early-stage NSCLC after resection and optional chemotherapy: Updated results from PEARLS/KEYNOTE-091. Immuno-Oncology and Technology. 2023 Dec 1;20.doi: 10.1016/iotech/iotech100589	Supporting evidence for trial above
Mary E.R. O'Brien et al., EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 study of pembrolizumab versus placebo for completely resected early-stage non-small cell lung cancer (NSCLC): Outcomes in subgroups related to surgery, disease burden, and adjuvant chemotherapy use. JCO 40, 8512-8512(2022). DOI:10.1200/JCO.2022.40.16_suppl.8512	Supporting evidence for trial above
Oselin K, Shim BY, Okada M, Bryl M, Bonanno L, Demirag G, Colantonio I, Kimmich M, Janzic U, Vansteenkiste JF, Bernabe Caro R. Pembrolizumab vs placebo for early-stage non–small-cell lung cancer after resection and adjuvant therapy: Subgroup analysis of patients who received adjuvant chemotherapy in the phase 3 PEARLS/KEYNOTE-091 study. doi: 10.1200/JCO.2023.41.16_suppl.8520	Supporting evidence for trial above
A.V. Balar, D.E. Castellano, P. Grivas, D.J. Vaughn, T. Powles, J. Vuky, Y. Fradet, J.-L. Lee, L. Fong, N.J. Vogelzang, M.A. Climent, A. Necchi, D.P. Petrylak, E.R. Plimack, J.Z. Xu, K. Imai, B.H. Moreno, J. Bellmunt, R. de Wit, P.H. O'Donnell, "Efficacy and safety of pembrolizumab in metastatic urothelial carcinoma: results from KEYNOTE-045 and KEYNOTE-052 after up to 5 years of follow-up." Annals of oncology: official journal of the *European Society for Medical Oncology* vol. 34,3 (2023): 289-299. doi:10.1016/j.annonc.2022.11.012	Previously known information about pembrolizumab related to efficacy
Morales-Barrera R, Castellano DE, O'Donnell PH, Grivas P, Vuky J, Powles T, Potvin KR, Cheng SY, Rosenbaum E, Hahn NM, Keizman D. Health-related quality of life (HRQoL) for patients with advanced/metastatic urothelial carcinoma (UC) enrolled in KEYNOTE-052 who are potentially platinum ineligible. *Journal of Clinical Oncology* doi:10.1200/JCO.2022.40.16_suppl.4561	Low-quality evidence
Wakelee H, Liberman M, Kato T, Tsuboi M, Lee SH, Gao S, Chen KN, Dooms C, Majem M, Eigendorff E, Martinengo GL, Bylicki O, Rodríguez-Abreu D, Chaft JE, Novello S, Yang J, Keller SM, Samkari A, Spicer JD; KEYNOTE-671 Investigators. "Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer." The New England journal of medicine vol. 389,6 (2023): 491-503. doi:10.1056/NEJMoa2302983	New moderate to high quality evidence

Citation	Decision
J.D. Spicer, S. Gao, M. Liberman, T. Kato, M. Tsuboi, S-H. Lee, K-N. Chen, C. Dooms, M. Majem, E. Eigendorff, G. Martinengo, O. Bylicki, M.C. Garassino, D. Rodriguez Abreu, J. Chaft, S. Novello, J. Yang, S.M. Keller, A. Samkari and H. Wakelee. "LBA56 Overall survival in the KEYNOTE-671 study of perioperative pembrolizumab for early-stage non-small-cell lung cancer (NSCLC)." Annals of Oncology. NSCLC, EARLY STAGE| VOLUME 34, SUPPLEMENT 2, S1297-S1298, OCTOBER 2023. DOI:https://doi.org/10.1016/j.annonc.2023.10.052	Supporting evidence for trial above
Kelley, Robin Kate et al. "Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial." Lancet (London, England) vol. 401,10391 (2023): 1853-1865. doi:10.1016/S0140-6736(23)00727-4	Supporting evidence for trial above
Changhoon Yoo et al., Health-related quality of life (HRQoL) in the phase 3 KEYNOTE-966 study of pembrolizumab (pembro) plus gemcitabine and cisplatin (gem/cis) versus placebo plus gem/cis for advanced biliary tract cancer (BTC).. JCO 41, 4003-4003(2023). DOI:10.1200/JCO.2023.41.16_suppl.4003	Supporting evidence for trial above
133MO Pembrolizumab (pembro) plus gemcitabine and cisplatin (gem/cis) compared with gem/cis alone for patients (pts) with advanced biliary tract cancer (BTC): Updated efficacy and safety from KEYNOTE-966, Finn, R.S. et al. Annals of Oncology, Volume 34, S1523	Supporting evidence for trial above
Rha, Sun Young et al. "Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial." The Lancet Oncol. vol. 24,11 (2023): 1181-1195. doi:10.1016/S1470-2045(23)00515-6	New moderate to high quality evidence
Lowery M, Wyrwicz L, Oh DY, Shiu KK, Weber PY, Bai Y, Lee J, Rivera F, Alves G, Garrido M, Fernández MG. 1516P Health-related quality of life (hrqol) analysis from KEYNOTE-859: First-line (1L) pembrolizumab (pembro)+ chemotherapy (chemo) for advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. Annals of Oncology. 2023 Oct 1;34:S854-5. doi: 10.1016/j.annonc.2023.09.1429	Supporting evidence for trial above
Rha SY, Wyrwicz L, Yañez P, et al. Pembrolizumab + Chemotherapy for Advanced HER2-Negative Gastric or Gastroesophageal Junction Cancer: Updated Results From the KEYNOTE-859 Study. *Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting*; May 31-June 4, 2024; Chicago, IL.	Study published outside of the timeframe of our review
de Castro G Jr, Kudaba I, Wu YL, Lopes G, Kowalski DM, Turna HZ, Caglevic C, Zhang L, Karaszewska B, Laktionov KK, Srimuninnimit V, Bondarenko I, Kubota K, Mukherjee R, Lin J, Souza F, Mok TSK, Cho BC. "Five-Year Outcomes With Pembrolizumab Versus Chemotherapy as First-Line Therapy in Patients With Non-Small-Cell Lung Cancer and Programmed Death Ligand-1 Tumor Proportion Score ≥ 1% in the KEYNOTE-042 Study." *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* vol. 41,11 (2023): 1986-1991. Doi:10.1200/JCO.21.02885	Previously known information about pembrolizumab related to efficacy

Citation	Decision
Remei Blanco, Manuel Dómine, José Luis González, Sami Loutfi, Jordi Alfaro, Juana Saldaña, Jaime Rubio, Begoña Campos, Julia Hidalgo, Andrés Barba, Diego Márquez, Maria Martin, Amaya Olaverri, Ernest Nadal,. Pembrolizumab as first-line treatment for advanced NSCLC in older adults: A phase II clinical trial evaluating geriatric and quality-of-life outcomes, *Lung Cancer*, Volume 183, 2023, 107318, ISSN 0169-5002.doi:10.1016/j.lungcan.2023.107318.	Previously known information about pembrolizumab related to efficacy
Garassino MC, Gadgeel S, Speranza G, Felip E, Esteban E, Dómine M, Hochmair MJ, Powell SF, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Kurata T, Gray JE, Schwarzenberger P, Jensen E, Pietanza MC, Rodríguez-Abreu D. "Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study." *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* vol. 41,11 (2023): 1992-1998. doi:10.1200/JCO.22.01989	Previously known information about pembrolizumab related to efficacy
Aggarwal, Himani et al. "Real-world maintenance therapy and survival outcomes for pembrolizumab plus pemetrexed and platinum for non-small-cell lung cancer in USA." *Immunotherapy* vol. 15,4 (2023): 267-281. doi:10.2217/imt-2022-0166	Previously known information about pembrolizumab related to efficacy
Novello S, Kowalski DM, Luft A, Gümüş M, Vicente D, Mazières J, Rodríguez-Cid J, Tafreshi A, Cheng Y, Lee KH, Golf A, Sugawara S, Robinson AG, Halmos B, Jensen E, Schwarzenberger P, Pietanza MC, Paz-Ares L. "Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* vol. 41,11 (2023): 1999-2006. doi:10.1200/JCO.22.01990	Previously known information about pembrolizumab related to efficacy
Kümmel S, Cortés J, Dent R, Pusztai L, McArthur H, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M. Pembrolizumab vs placebo+ chemotherapy as neoadjuvant treatment, followed by pembrolizumab vs placebo as adjuvant treatment for early triple-negative breast cancer (TNBC): Phase 3 KEYNOTE-522 study. *European Journal of Surgical Oncology*. 2022 Feb 1;48(2):	Previously known information about pembrolizumab related to efficacy
Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Untch M, Fasching PA, Cardoso F, Andersen J, Patt D, Danso M, Ferreira M, Mouret-Reynier M-A, Im S-A, Ahn J-H, Gion M, Baron-Hay S, Boileau J-F, Ding Y, Tryfonidis K, Aktan G, Karantza V, O'Shaugnessy J, for the KEYNOTE-522 Investigators. Event-free survival with pembrolizumab in early triple-negative breast cancer. *NEJM*. 2022 386 556-567. 10.1056/NEJMoa2112651.	Previously known information about pembrolizumab related to efficacy
Javier Cortés, Rebecca Dent, Lajos Pusztai, Heather McArthur, Sherko Kuemmel, Carsten Denkert, Yeon Hee Park, Rina Hui, Masato Takahashi, Carlos Barrios, Yalin Zhu, Xiaoli Zhang, Wilbur Pan, Vassiliki Karantza, Joyce O'Shaughnessy, Peter Schmid; Abstract PS14-05: Safety evaluation from the KEYNOTE-522 study of neoadjuvant pembrolizumab (or placebo) plus chemotherapy followed by adjuvant pembrolizumab (or placebo) in patients with early triple-negative breast cancer (TNBC). *Cancer Research, American Association for Cancer Research.*	Study published outside of the timeframe of our review

Citation	Decision
Dent RA, Cortés J, Pusztai L, McArthur HL, Kuemmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M. 135MO HRQoL with neoadjuvant pembrolizumab+ chemotherapy vs placebo+ chemotherapy, followed by adjuvant pembrolizumab vs placebo for early-stage TNBC: Results from KEYNOTE-522. Annals of Oncology. 2022 Sep 1;33:S600-1. doi: 10.1016/j.annonc.2022.07.170	Previously known information about pembrolizumab related to efficacy
Cortés J, Haiderali A, Huang M, Pan W, Fox GE, Park J, Frederickson AM, Fasching PA, O'Shaughnessy J. 169P Neoadjuvant pembrolizumab+ chemotherapy followed by adjuvant pembrolizumab for treatment of high-risk, early-stage triple-negative breast cancer: A network meta-analysis. *Annals of Oncology.* 2022 Sep 1;33:S615-6. Doi: 10.1016/j.annonc.2022.07.204	Low-quality evidence
Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer Cortes, Javier, Hope S. Rugo, David W. Cescon, Seock-Ah Im, Mastura M. Yusof, Carlos Gallardo, Oleg Lipatov et al. "Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer." The New England journal of medicine vol. 387,3 (2022): 217-226. doi:10.1056/NEJMoa2202809	New moderate to high quality evidence
Hope Rugo, Peter Schmid, Zbigniew Nowecki, David Cescon, Seock-Ah Im, Mastura Yusof, Carlos Gallardo, Hiroji Iwata, Carlos Barrios, Sherene Loi, Xuan Zhou, Xiaoli Zhang, Wilbur Pan, Vassiliki Karantza, Javier Cortés; Abstract PS14-08: Safety evaluation from the KEYNOTE-355 study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy in patients with previously untreated, locally recurrent inoperable or metastatic triple-negative breast cancer. *Cancer Res* 1 May 2024; 84 (9_Supplement): PS14–08. https://doi.org/10.1158/1538-7445.SABCS23-PS14-08	Study published outside of the timeframe of our review
Haiderali, A., Huang, M., Pan, W., Fox, G., Maciel, D., & Frederickson, A. (2022). HSR22-145: Pembrolizumab Plus Chemotherapy for First-Line Treatment of Advanced Triple-Negative Breast Cancer – A Network Meta-Analysis. *Journal of the National Comprehensive Cancer Network*, *20*(3.5), HSR22–145. https://doi.org/10.6004/jnccn.2021.7297	Low-quality evidence
Cescon, D. W., Schmid, P., Rugo, H. S., Im, S.-A., Md Yusof, M., Gallardo, C. E., Lipatov, O., Barrios, C. H., Perez Garcia, J. M., Iwata, H., Masuda, N., Torregroza Otero, M. A., Gokmen, E., Loi, S., Haiderali, A., Zhou, X., Guo, Z., Martin Nguyen, A., & Cortés, J. (2022). 164O Health-related quality of life (HRQoL) with pembrolizumab (pembro) + chemotherapy (chemo) vs placebo (pbo) + chemo as 1L treatment for advanced triple-negative breast cancer (TNBC): Results from KEYNOTE-355. *Annals of Oncology*, *33*, S197–S198. https://doi.org/10.1016/j.annonc.2022.03.183	Previously known information about pembrolizumab related to efficacy
Huang, M., Haiderali, A., Hu, P., Mitashri, C., & Pan, W. (2022). HSR22-146: Health Utility in Patients With Previously Untreated Locally Recurrent Inoperable or Metastatic TNBC. *Journal of the National Comprehensive Cancer Network*, *20*(3.5), HSR22–146. https://doi.org/10.6004/jnccn.2021.7148	Previously known information about pembrolizumab related to efficacy

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Huang, M., O'Shaughnessy, J., Haiderali, A., Pan, W., Hu, P., Chaudhuri, M., Le Bailly De Tilleghem, C., Cappoen, N., & Fasching, P. A. (2022). Q-TWiST analysis of pembrolizumab combined with chemotherapy as first-line treatment of metastatic triple-negative breast cancer that expresses PD-L1. *European Journal of Cancer (1990)*, *177*, 45–52. https://doi.org/10.1016/j.ejca.2022.09.029	Previously known information about pembrolizumab related to efficacy
Fasching, P. A., Huang, M., Haiderali, A., Pan, W., Hu, P., Chaudhuri, M., Le Bailly De Tilleghem, C., Cappoen, N., & O'Shaughnessy, J. (2022). 159P Q-TWiST analysis of pembrolizumab combined with chemotherapy as first-line treatment of metastatic TNBC that expresses PD-L1. *Annals of Oncology*, *33*, S192–S193. https://doi.org/10.1016/j.annonc.2022.03.177	Previously known information about pembrolizumab related to efficacy
Huang, Min et al. "Cost-effectiveness of pembrolizumab plus chemotherapy as first-line treatment in PD-L1-positive metastatic triple-negative breast cancer." Immunotherapy vol. 14,13 (2022): 1027-1041. doi:10.2217/imt-2022-0082	Low-quality evidence
Bedke, J., Rini, B., Plimack, E. R., Stus, V., Gafanov, R., Waddell, T., Nosov, D., Pouliot, F., Soulieres, D., Melichar, B., Vynnychenko, I., Azevedo, S. J., Borchiellini, D., McDermott, R. S., Tamada, S., Nguyen, A. M., Wan, S., Perini, R. F., Molife, L. R., … Powles, T. (2022). Health-related Quality of Life Analysis from KEYNOTE-426: Pembrolizumab plus Axitinib Versus Sunitinib for Advanced Renal Cell Carcinoma. *European Urology*, *82*(4), 427–439. https://doi.org/10.1016/j.eururo.2022.06.009	Previously known information about pembrolizumab related to efficacy
Plimack, E. R., Powles, T., Stus, V., Gafanov, R., Nosov, D., Waddell, T., Alekseev, B., Pouliot, F., Melichar, B., Soulieres, D., Borchiellini, D., McDermott, R. S., Vynnychenko, I., Chang, Y.-H., Tamada, S., Atkins, M. B., Molife, L. R., Li, C., Perini, R., … Rini, B. I. (2024). Pembrolizumab Plus Axitinib Versus Sunitinib as First-line Treatment of Advanced Renal Cell Carcinoma: 43-month Follow-up of the Phase 3 KEYNOTE-426 Study"[Eur Urol 84(5) (2023) 449-454]. *European Urology*, *85*(2), e58–e59. https://doi.org/10.1016/j.eururo.2023.11.016	Previously known information about pembrolizumab related to efficacy
Rini, B. I., Plimack, E. R., Stus, V., Gafanov, R., Waddell, T., Nosov, D., Pouliot, F., Alekseev, B., Soulieres, D., Melichar, B., Vynnychenko, I. O., Azevedo, S. J., Borchiellini, D., McDermott, R. S., Bedke, J., Tamada, S., Wu, S., Burgents, J., Molife, L. R., & Powles, T. (2023). Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: 5-year analysis of KEYNOTE-426. *Journal of Clinical Oncology*, *41*(17_SUPPL), LBA4501–LBA4501. https://doi.org/10.1200/JCO.2023.41.17_suppl.LBA4501	Previously known information about pembrolizumab related to efficacy
Powles, T., Plimack, E. R., Stus, V., Waddell, T., Gafanov, R., Pouliot, F., Nosov, D., Melichar, B., Soulieres, D., Borchiellini, D., Vynnychenko, I., McDermott, R. S., Azevedo, S. J., Tamada, S., Kryzhanivska, A., Li, C., Burgents, J. E., Molife, L. R., Rini, B. I., & Bedke, J. (2022). Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): Analysis of progression after first subsequent therapy in KEYNOTE-426. *Journal of Clinical Oncology*, *40*(16_suppl), 4513–4513. https://doi.org/10.1200/JCO.2022.40.16_suppl.4513	Previously known information about pembrolizumab related to efficacy

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Bensimon, A., Lai, Y., Xu, R., Bhattacharya, R., & Shinde, R. (2022). PCR71 Health State Utilities in Patients with Advanced Renal Cell Carcinoma Receiving First-Line Pembrolizumab Plus Axitinib or Sunitinib. *Value in Health*, *25*(7), S554. https://doi.org/10.1016/j.jval.2022.04.1416	Low-quality evidence
Aran, D., Granot-Hershkovitz, E., Amar-Farkash, S., & Rosenberg-Katz, K. (2023). Head-to-head effectiveness and safety of pembrolizumab plus axitinib vs. nivolumab plus ipilimumab in metastatic renal cell carcinoma in the United States. *Journal of Clinical Oncology*, *41*(16_suppl), 4532–4532. https://doi.org/10.1200/JCO.2023.41.16_suppl.4532	Low-quality evidence
Shah, N. J., Shinde, R., Moore, K., Sainski-Nguyen, A., Le, L., Cao, F., Song, R., Singhal, P., & Motzer, R. J. (2022). Healthcare resource utilization (HCRU) and costs for patients (pts) with metastatic renal cell carcinoma (mRCC) receiving first-line (LOT1) pembrolizumab plus axitinib (P+A) or ipilimumab plus nivolumab (I+N). *Journal of Clinical Oncology*, *40*(16_suppl), 4528–4528. https://doi.org/10.1200/JCO.2022.40.16_suppl.4528	Low-quality evidence
Shah, N. J., Sura, S. D., Shinde, R., Shi, J., Singhal, P., Perini, R. F., & Motzer, R. J. (2023). Real-world clinical outcomes of patients with metastatic renal cell carcinoma receiving pembrolizumab + axitinib vs. ipilimumab + nivolumab. *Urologic Oncology*, *41*(11), 459.e1–459.e8. https://doi.org/10.1016/j.urolonc.2023.08.009	Low-quality evidence
Choueiri, T. K., Eto, M., Motzer, R., De Giorgi, U., Buchler, T., Basappa, N. S., Méndez-Vidal, M. J., Tjulandin, S., Hoon Park, S., Melichar, B., Hutson, T., Alemany, C., McGregor, B., Powles, T., Grünwald, V., Alekseev, B., Rha, S. Y., Kopyltsov, E., Kapoor, A., … Porta, C. G. (2023). Lenvatinib plus pembrolizumab versus sunitinib as first-line treatment of patients with advanced renal cell carcinoma (CLEAR): extended follow-up from the phase 3, randomised, open-label study. *The Lancet Oncology, 24*(3), 228–238. https://doi.org/10.1016/S1470-2045(23)00049-9	Previously known information about pembrolizumab related to efficacy
Grunwald, V., Powles, T., Eto, M., Kopyltsov, E., Rha, S. Y., Porta, C., Motzer, R., Hutson, T. E., Mendez-Vidal, M. J., Hong, S.-H., Winquist, E., Goh, J. C., Maroto, P., Buchler, T., Takagi, T., Burgents, J. E., Perini, R., He, C., Okpara, C. E., … Choueiri, T. K. (2023). Phase 3 CLEAR study in patients with advanced renal cell carcinoma: outcomes in subgroups for the lenvatinib-plus-pembrolizumab and sunitinib arms. *Frontiers in Oncology*, *13*, 1223282–1223282. https://doi.org/10.3389/fonc.2023.1223282	Previously known information about pembrolizumab related to efficacy
Motzer, R. J., Porta, C., Eto, M., Powles, T., Grünwald, V., Hutson, T. E., Alekseev, B., Rha, S. Y., Merchan, J. R., Goh, J. C., Kapoor, A., De Giorgi, U., Melichar, B., Hong, S.-H., Gurney, H., Rodriguez-Lopez, K., He, C. S., Okpara, C., McKenzie, J., & Choueiri, T. K. (2023). Final prespecified overall survival (OS) analysis of CLEAR: 4-year follow-up of lenvatinib plus pembrolizumab (L+P) vs sunitinib (S) in patients (pts) with advanced renal cell carcinoma (aRCC). *Journal of Clinical Oncology*, *41*(16_suppl), 4502–4502. https://doi.org/10.1200/JCO.2023.41.16_suppl.4502	Previously known information about pembrolizumab related to efficacy

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Grünwald V, Powles T, Kopyltsov E, Kozlov V, Alonso-Gordoa T, Eto M, Hutson T, Motzer R, Winquist E, Maroto P, Keam B, Procopio G, Wong S, Melichar B, Rolland F, Oya M, Rodriguez-Lopez K, Saito K, McKenzie J, Porta C. "Survival by Depth of Response and Efficacy by International Metastatic Renal Cell Carcinoma Database Consortium Subgroup with Lenvatinib Plus Pembrolizumab Versus Sunitinib in Advanced Renal Cell Carcinoma: Analysis of the Phase 3 Randomized CLEAR Study." *European urology oncology* vol. 6,4 (2023): 437-446. doi:10.1016/j.euo.2023.01.010	Previously known information about pembrolizumab related to efficacy
Porta, C. G., Eto, M., Motzer, R. J., De Giorgi, U. F. F., Buchler, T., Basappa, N. S., Mendez Vidal, M. J., Tjulandin, S., Park, S. H., Melichar, B., Hutson, T. E., Alemany, C., McGregor, B., He, C. S., Perini, R., Mody, K., McKenzie, J., & Choueiri, T. K. (2022). 1449MO Updated efficacy of lenvatinib (LEN) + pembrolizumab (PEMBRO) vs sunitinib (SUN) in patients (pts) with advanced renal cell carcinoma (aRCC) in the CLEAR study. *Annals of Oncology*, *33*, S1205–S1206. https://doi.org/10.1016/j.annonc.2022.07.1552	Previously known information about pembrolizumab related to efficacy
Motzer, R., George, S., Merchan, J. R., Hutson, T. E., Song, X., Perini, R. F., Xie, R., Bapat, U., & Puente, J. (2023). Characterization and Management of Adverse Reactions From the CLEAR Study in Advanced Renal Cell Carcinoma Treated With Lenvatinib Plus Pembrolizumab. *The Oncologist (Dayton, Ohio)*, *28*(6), 501–509. https://doi.org/10.1093/oncolo/oyac269	Previously known information about pembrolizumab related to safety
Voss, M. H., Powles, T., McGregor, B. A., Porta, C., Grünwald, V., Merchan, J. R., Rolland, F., Maroto-Rey, P., Goh, J. C., Xing, D., Perini, R. F., McKenzie, J., Mody, K., & Motzer, R. J. (2022). Impact of subsequent therapies in patients (pts) with advanced renal cell carcinoma (aRCC) receiving lenvatinib plus pembrolizumab (LEN + PEMBRO) or sunitinib (SUN) in the CLEAR study. *Journal of Clinical Oncology*, *40*(16_suppl), 4514–4514. https://doi.org/10.1200/JCO.2022.40.16_suppl.4514	Previously known information about pembrolizumab related to efficacy
Motzer, R., Porta, C., Alekseev, B., Rha, S. Y., Choueiri, T. K., Mendez-Vidal, M. J., Hong, S.-H., Kapoor, A., Goh, J. C., Eto, M., Bennett, L., Wang, J., Pan, J. J., Saretsky, T. L., Perini, R. F., He, C. S., Mody, K., & Cella, D. (2022). Health-related quality-of-life outcomes in patients with advanced renal cell carcinoma treated with lenvatinib plus pembrolizumab or everolimus versus sunitinib (CLEAR): a randomised, phase 3 study. *Lancet oncology/Lancet. Oncology*, *23*(6), 768–780. https://doi.org/10.1016/S1470-2045(22)00212-1	Low-quality evidence
Powles, Thomas et al. "Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial." *The Lancet*. Oncology vol. 23,9 (2022): 1133-1144. doi:10.1016/S1470-2045(22)00487-9	Previously known information about pembrolizumab related to efficacy

Citation	Decision
Choueiri, T. K., Tomczak, P., Park, S. H., Venugopal, B., Symeonides, S., Hajek, J., Ferguson, T., Chang, Y.-H., Lee, J. L., Haas, N., Sawrycki, P., Sarwar, N., Gross-Goupil, M., Thiery-Vuillemin, A., Mahave, M., Saretsky, T. L., Zhang, P., Willemann-Rogerio, J., Quinn, D. I., & Powles, T. B. (2021). 653O Pembrolizumab (pembro) vs placebo as adjuvant therapy for patients (pts) with renal cell carcinoma (RCC): Patient-reported outcomes (PRO) in KEYNOTE-564. *Annals of Oncology*, *32*, S679–S680. https://doi.org/10.1016/j.annonc.2021.08.049	Study published outside of the timeframe of our review
Choueiri, T. K., Tomczak, P., Park, S. H., Venugopal, B., Symeonides, S., Hajek, J., Ferguson, T., Chang, Y.-H., Lee, J. L., Haas, N., Sawrycki, P., Sarwar, N., Gross-Goupil, M., Thiery-Vuillemin, A., Mahave, M., Kimura, G., Perini, R. F., Saretsky, T. L., Bhattacharya, R., … Powles, T. (2024). Patient-Reported Outcomes in KEYNOTE-564: Adjuvant Pembrolizumab Versus Placebo for Renal Cell Carcinoma. *The Oncologist (Dayton, Ohio)*, *29*(2), 142–150. https://doi.org/10.1093/oncolo/oyad231	Previously known information about pembrolizumab related to efficacy
Lai, Y., Bensimon, A. G., Gao, E., Bhattacharya, R., Xu, R., Chevure, J., Imai, K., & Haas, N. B. (2023). Cost-Effectiveness Analysis of Pembrolizumab as an Adjuvant Treatment of Renal Cell Carcinoma Post-nephrectomy in the United States. *Clinical Genitourinary Cancer*, *21*(5), 612.e1–612.e11. https://doi.org/10.1016/j.clgc.2023.03.016	Low-quality evidence
Harrington, K. J., Burtness, B., Greil, R., Soulieres, D., Tahara, M., de Castro Jr, G., Psyrri, A., Brana, I., Baste, N., Neupane, P., Bratland, A., Fuereder, T., Hughes, B. G. M., Mesia, R., Ngamphaiboon, N., Rordorf, T., Wan Ishak, W. Z., Lin, J., Gumuscu, B., … Rischin, D. (2023). Pembrolizumab With or Without Chemotherapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: Updated Results of the Phase III KEYNOTE-048 Study. *Journal of Clinical Oncology*, *41*(4), 790–802. https://doi.org/10.1200/JCO.21.02508	Previously known information about pembrolizumab related to efficacy
Tahara M, Greil R, Rischin D, Harrington KJ, Burtness B, De Castro G, Psyrri A, Brana I, Neupane P, Bratland Å, Fuereder T. 659MO Pembrolizumab with or without chemotherapy for first-line treatment of recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): 5-year results from KEYNOTE-048. *Annals of Oncology*. 2022 Sep 1;33:S844.doi: 10.1016/annonc/annonc1056	Previously known information about pembrolizumab related to efficacy
Soulieres D, Harrington KJ, Le Tourneau C, Silva JD, Licitra LF, Ahn MJ, Soria A, Machiels JP, Mach N, Mehra R, Burtness B. 658MO Pembrolizumab (pembro) vs standard-of-care (SOC) in previously treated recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): 6-year follow-up of KEYNOTE-040. *Annals of Oncology*. 2022 Sep 1;33:S843.doi: 10.1016/j.annonc.2022.07.782	Previously known information about pembrolizumab related to efficacy

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Danny Rischin, Kevin J. Harrington, Richard Greil, Denis Soulières, Makoto Tahara, Gilberto de Castro Jr, Amanda Psyrri, Irene Braña, Prakash Neupane, Åse Bratland, Thorsten Fuereder, Brett G.M. Hughes, Ricard Mesía, Nuttapong Ngamphaiboon, Tamara Rordorf, Wan Zamaniah Wan Ishak, Ruey-Long Hong, René Gonzalez Mendoza, Liyi Jia, Diana Chirovsky, Josephine Norquist, Fan Jin, Barbara Burtness, "Pembrolizumab alone or with chemotherapy for recurrent or metastatic head and neck squamous cell carcinoma: Health-related quality-of-life results from KEYNOTE-048." *Oral oncology* vol. 128 (2022): 105815. doi:10.1016/j.oraloncology.2022.105815	Previously known information about pembrolizumab related to efficacy
Borse, R. H., Ramakrishnan, K., Gandhi, J., Dhankhar, P., & Chirovsky, D. "Cost-effectiveness of pembrolizumab for the first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma in the United States." *Journal of medical economics* vol. 25,1 (2022): 954-965. doi:10.1080/13696998.2022.2095826	Previously known information about pembrolizumab related to efficacy/cost-effectiveness
K.J. Harrington, E.E.W. Cohen, D. Soulières, J. Dinis, L. Licitra, M.-J. Ahn, A. Soria, J.-P. Machiels, N. Mach, R. Mehra, B. Burtness, R.F. Swaby, J. Lin, J. Ge, N. Lerman, C. Le Tourneau, "Pembrolizumab versus methotrexate, docetaxel, or cetuximab in recurrent or metastatic head and neck squamous cell carcinoma (KEYNOTE-040): Subgroup analysis by pattern of disease recurrence." *Oral oncology* vol. 147 (2023): 106587. doi:10.1016/j.oraloncology.2023.106587	Previously known information about pembrolizumab related to efficacy
Eggermont, Alexander M M et al. "Five-Year Analysis of Adjuvant Pembrolizumab or Placebo in Stage III Melanoma." *NEJM* evidence vol. 1,11 (2022): EVIDoa2200214. doi:10.1056/EVIDoa2200214	Previously known information about pembrolizumab related to efficacy
Aguiar-Ibáñez, R., Scherrer, E., Grebennik, D. et al. Time and productivity loss associated with immunotherapy infusions for the treatment of melanoma in the United States: a survey of health care professionals and patients. *BMC Health Serv Res* 23, 136 (2023). https://doi.org/10.1186/s12913-022-08904-4	Low-quality evidence
Georgina V Long, Jason J Luke, Muhammad A Khattak, Luis de la Cruz Merino, Michele Del Vecchio, Piotr Rutkowski, Francesco Spagnolo, Jacek Mackiewicz, Vanna Chiarion-Sileni, John M Kirkwood, Caroline Robert, Jean-Jacques Grob, Federica de Galitiis, Dirk Schadendorf, Matteo S Carlino, Peter Mohr, Reinhard Dummer, Jeffrey E Gershenwald, Charles H Yoon, Xi Lawrence Wu, Mizuho Fukunaga-Kalabis, Clemens Krepler, Alexander M M Eggermont, Paolo A Ascierto, "Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma (KEYNOTE-716): distant metastasis-free survival results of a multicentre, double-blind, randomised, phase 3 trial." *The Lancet*. Oncology vol. 23,11 (2022): 1378-1388. doi:10.1016/S1470-2045(22)00559-9	Previously known information about pembrolizumab related to efficacy
Luke, Jason J et al. "Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial." *Lancet* (London, England) vol. 399,10336 (2022): 1718-1729. doi:10.1016/S0140-6736(22)00562-1	Low-quality evidence

Citation	Decision
Georgina V. Long et al., Distant metastasis-free survival with pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: The phase 3 KEYNOTE-716 study.. *JCO* 40, LBA9500-LBA9500(2022). DOI:10.1200/JCO.2022.40.17_suppl.LBA9500	Low-quality evidence
Long G, Luke J, Khattak A, de la Cruz Merino L, Del Vecchio M, Rutkowski P, Spagnolo F, Mackiewicz J, Chiarion-Sileni V, Kirkwood J, Robert C, Grob J, De Galitiis F, Schadendorf D, Carlino M, Mohr P, Dummer R, Gershenwald J, Yoon C, Wu L, Kalabis M, Krepler C, Eggermont A, Ascierto P. . Pembrolizumab as adjuvant therapy in resected stage II melanoma: analysis of distant metastasis-free survival from the phase 3 KEYNOTE-716 study. *N Engl J Med*.	Study published outside of the timeframe of our review
Muhammad A. Khattak, Jason J. Luke, Georgina V. Long, Paolo A. Ascierto, Piotr Rutkowski, Dirk Schadendorf, Caroline Robert, Jean-Jacques Grob, Luis de la Cruz Merino, Michele Del Vecchio, Francesco Spagnolo, Jacek Mackiewicz, Vanna Chiarion-Sileni, Matteo S. Carlino, Peter Mohr, Federica De Galitiis, Merrick I. Ross, Zeynep Eroglu, Ke Chen, Ruixuan Jiang, Mizuho Fukunaga-Kalabis, Clemens Krepler, Alexander M.M. Eggermont, John M. Kirkwood, "Adjuvant pembrolizumab versus placebo in resected high-risk stage II melanoma: Health-related quality of life from the randomized phase 3 KEYNOTE-716 study." *European journal of cancer* (Oxford, England: 1990) vol. 176 (2022): 207-217. doi:10.1016/j.ejca.2022.08.004	Previously known information about pembrolizumab related to efficacy
Unger JM, Darke A, Othus M, Truong TG, Khushalani N, Kendra K, Lewis KD, Faller B, Funchain P, Buchbinder EI, Tarhini AA, Kirkwood JM, Sharon E, Sondak V, Guild SR, Grossmann K, Ribas A, Patel SP. "Effectiveness of Adjuvant Pembrolizumab vs High-Dose Interferon or Ipilimumab for Quality-of-Life Outcomes in Patients With Resected Melanoma: A Secondary Analysis of the SWOG S1404 Randomized Clinical Trial." *JAMA oncology* vol. 9,2 (2023): 251-260. doi:10.1001/jamaoncol.2022.5486	Low-quality evidence
Zhang, S., Bensimon, A. G., Xu, R., Jiang, R., Greatsinger, A., Zhang, A., Fukunaga-Kalabis, M., & Krepler, C. (2023). Cost-Effectiveness Analysis of Pembrolizumab as an Adjuvant Treatment of Resected Stage IIB or IIC Melanoma in the United States. *Advances in Therapy*, *40*(7), 3038–3055. https://doi.org/10.1007/s12325-023-02525-x	Low-quality evidence
Makker, V., Colombo, N., Casado Herráez, A., Santin, A. D., Colomba, E., Miller, D. S., Fujiwara, K., Pignata, S., Baron-Hay, S., Ray-Coquard, I., Shapira-Frommer, R., Ushijima, K., Sakata, J., Yonemori, K., Kim, Y. M., Guerra, E. M., Sanli, U. A., McCormack, M. M., Smith, A. D., Keefe, S., … Study 309–KEYNOTE-775 Investigators (2022). Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. *The New England journal of medicine*, *386*(5), 437–448. https://doi.org/10.1056/NEJMoa2108330	Previously known information about pembrolizumab related to efficacy

Citation	Decision
Makker V, Colombo N, Casado Herráez A, Monk BJ, Mackay H, Santin AD, Miller DS, Moore RG, Baron-Hay S, Ray-Coquard I, Ushijima K, Yonemori K, Kim YM, Guerra Alia EM, Sanli UA, Bird S, Orlowski R, McKenzie J, Okpara C, Barresi G, Lorusso D.. "Lenvatinib Plus Pembrolizumab in Previously Treated Advanced Endometrial Cancer: Updated Efficacy and Safety From the Randomized Phase III Study 309/KEYNOTE-775." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* vol. 41,16 (2023): 2904-2910. doi:10.1200/JCO.22.02152	Previously known information about pembrolizumab related to efficacy
Lorusso, D., Colombo, N., Casado Herraez, A., Santin, A. D., Colomba, E., Miller, D. S., Fujiwara, K., Pignata, S., Baron-Hay, S. E., Ray-Coquard, I. L., Shapira-Frommer, R., Kim, Y. M., McCormack, M., Massaad, R., Martin Nguyen, A., Zhao, Q., McKenzie, J., Prabhu, V. S., & Makker, V. (2022). 20MO Time to deterioration in quality of life in patients (pts) with advanced endometrial cancer (aEC) treated with lenvatinib plus pembrolizumab (L+P) or treatment of physician's choice (TPC). *Annals of Oncology*, *33*, S391–S392. https://doi.org/10.1016/j.annonc.2022.04.038	Low-quality evidence
Makker, V., Lorusso, D., Moore, R., Miller, D., Mackay, H., Santin, A., Ushijima, K., Kim, Y. M., Sanli, U., Yonemori, K., Xie, R., Barresi, G., McKenzie, J., & Colombo, N. (2023). Characterization of tumor response with lenvatinib plus pembrolizumab in study 309/KEYNOTE-775 (177). *Gynecologic Oncology*, *176*, S68–S69. https://doi.org/10.1016/j.ygyno.2023.06.563	Previously known information about pembrolizumab related to efficacy
Makker, V., Colombo, N., Santin, A., Miller, D. S., Fujiwara, K., Pignata, S., Ray-Coquard, I. L., Kim, Y. M., Guerra, E. M., Huang, J., Barresi, G., McKenzie, J., & Lorusso, D. (2022). Efficacy of next line of therapy after treatment with lenvatinib (LEN) in combination with pembrolizumab (pembro) versus treatment of physician's choice (TPC) in patients (pts) with advanced endometrial cancer (aEC): Exploratory analysis of Study 309/KEYNOTE-775. *Journal of Clinical Oncology*, *40*(16_suppl), 5587–5587. https://doi.org/10.1200/JCO.2022.40.16_suppl.5587	Outcome not relevant to scope
Colomba, E., Lorusso, D., Mackay, H., Moore, R., Yonemori, K., Kim, Y. M., Sanli, U. A., Xie, R., Barresi, G., McKenzie, J., & Makker, V. (2023). 748P Outcomes for patients (pts) with advanced endometrial cancer (aEC) who completed pembrolizumab (pembro) and continued lenvatinib (LEN) in the phase III Study 309/KEYNOTE-775. *Annals of Oncology*, *34*, S512–S513. https://doi.org/10.1016/j.annonc.2023.09.1927	Previously known information about pembrolizumab related to efficacy
Makker V, Colombo N, Herráez AC, et alO018/#482 Updated safety of lenvatinib + pembrolizumab vs treatment of physician's choice in patients with advanced endometrial cancer: study 309/keynote-775 International Journal of Gynecologic Cancer 2022;32:A11. doi: 10.1136/ijgc-2022-igcs.20	Previously known information about pembrolizumab related to safety

Citation	Decision
Lorusso D, Colombo N, Herraez AC, Santin AD, Colomba E, Miller DS, Fujiwara K, Pignata S, Baron-Hay SE, Ray-Coquard IL, Shapira-Frommer R, Kim YM, McCormack M, Massaad R, Nguyen AM, Zhao Q, McKenzie J, Prabhu VS, Makker V. "Health-Related Quality of Life in Patients With Advanced Endometrial Cancer Treated With Lenvatinib Plus Pembrolizumab or Treatment of Physician's Choice." *European journal of cancer* (Oxford, England: 1990) vol. 186 (2023): 172-184. doi:10.1016/j.ejca.2023.03.015	Low-quality evidence
Zhao, Q., Trueman, D., Burn, O., & Bodnar, C. (2022). PCR283 Health-Related Quality of Life in Patients With Advanced or Recurrent Endometrial Cancer Who Have Disease Progression on or Following Prior Treatment With a Platinum-Containing Therapy: Analysis of EQ-5D Utility Scores. *Value in Health*, *25*(12), S445–S445. https://doi.org/10.1016/j.jval.2022.09.2216	Low-quality evidence
Lorusso, D., Makker, V., Herraez, A. C., Monk, B. J., Mackay, H., Santin, A. D., Miller, D. S., Moore, R., Baron-Hay, S., Ray-Coquard, I., Shapira-Frommer, R., Ushijima, K., Yonemori, K., Kim, Y. M., Guerra Alia, E. M., Sanli, U. A., Huang, J., McKenzie, J., Barresi, G., & Colombo, N. (2022). 2022-RA-653-ESGO The impact of histology, prior therapy, and dMMR status on lenvatinib + pembrolizumab outcomes in patients with advanced endometrial cancer: A subgroup analysis of Study 309/KEYNOTE-775. *Endometrial Cancer*, *32*(Suppl 2), A102–A102. https://doi.org/10.1136/ijgc-2022-ESGO.223	Previously known information about pembrolizumab related to efficacy
Diaz, L. A., Shiu, K.-K., Kim, T.-W., Jensen, B. V., Jensen, L. H., Punt, C., Smith, D., Garcia-Carbonero, R., Benavides, M., Gibbs, P., de la Fourchardiere, C., Rivera, F., Elez, E., Le, D. T., Yoshino, T., Zhong, W. Y., Fogelman, D., Marinello, P., & Andre, T. (2022). Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. *Lancet oncology/Lancet. Oncology*, *23*(5), 659–670. https://doi.org/10.1016/S1470-2045(22)00197-8	Previously known information about pembrolizumab related to efficacy
Shiu KK, André T, Kim TW, Jensen BV, Jensen LH, Punt CJ, Smith D, Garcia-Carbonero R, Alcaide-Garcia J, Gibbs P, De la Fouchardiere C. LBA32 Pembrolizumab versus chemotherapy in microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): 5-year follow-up of the randomized phase III KEYNOTE-177 study. *Annals of Oncology.* 2023 Oct 1;34:S1271-2.doi:10.1016/j.annonc.2023.10.024	Previously known information about pembrolizumab related to efficacy
Jin, H., Amonkar, M., Aguiar-Ibáñez, R., Thosar, M., Chase, M., & Keeping, S. (2022). Systematic literature review and network meta-analysis of pembrolizumab versus other interventions for previously untreated, unresectable or metastatic, MSI-high or MMR-deficient CRC. *Future Oncology (London, England)*, *18*(17), 2155–2171. https://doi.org/10.2217/fon-2021-1633	Low-quality evidence

Citation	Decision
Aguiar-Ibáñez, R., Hardern, C., van Hees, F., Lee, D., Patel, A., Chhabra, N., Baluni, G., Amonkar, M., Lai, Y., Xu, R., Massaad, R., & Fogelman, D. (2022). Cost-effectiveness of pembrolizumab for the first-line treatment of patients with unresectable or metastatic MSI-H/dMMR colorectal cancer in the United States. *Journal of Medical Economics*, *25*(1), 469–480. https://doi.org/10.1080/13696998.2022.2043634	Indication accounts for less than 10% of use
Monk, Bradley J et al. "First-Line Pembrolizumab + Chemotherapy Versus Placebo + Chemotherapy for Persistent, Recurrent, or Metastatic Cervical Cancer: Final Overall Survival Results of KEYNOTE-826." *J Clin Oncology : official journal of the American Society of Clinical Oncology* vol. 41,36 (2023): 5505-5511. Doi:10.1200/JCO.23.00914	Previously known information about pembrolizumab related to efficacy
Monk, B. J., Tewari, K. S., Dubot, C., Caceres, M. V., Hasegawa, K., Shapira-Frommer, R., Salman, P., Yañez, E., Gümüş, M., Hurtado de Mendoza, M. O., Samouëlian, V., Castonguay, V., Arkhipov, A., Tekin, C., Li, K., Martin Nguyen, A., Monberg, M. J., Colombo, N., & Lorusso, D. (2023). Health-related quality of life with pembrolizumab or placebo plus chemotherapy with or without bevacizumab for persistent, recurrent, or metastatic cervical cancer (KEYNOTE-826): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet oncology/Lancet. Oncology*, *24*(4), 392–402. https://doi.org/10.1016/S1470-2045(23)00052-9	Previously known information about pembrolizumab related to efficacy
Monk B, Tewari K, Dubot C, Caceres MV, Hasegawa K, Shapira-Frommer R, Salman P, Yanez E, Gümüş M, De Mendoza MO, Samouëlian V. Patient-Reported outcomes from the phase 3 randomized, double-blind, KEYNOTE-826 trial of pembrolizumab plus chemotherapy versus placebo plus chemotherapy for the first-line treatment of persistent, recurrent, or metastatic cervical cancer (023). *Gynecologic Oncology*. 2022 Aug 1;166:S18.doi: 10.1016/S0090-8258(22)01241-0	Previously known information about pembrolizumab related to efficacy
Adenis, A., Kulkarni, A. S., Girotto, G. C., de la Fouchardiere, C., Senellart, H., van Laarhoven, H. W. M., Mansoor, W., Al-Rajabi, R., Norquist, J., Amonkar, M., Suryawanshi, S., Bhagia, P., & Metges, J.-P. (2022). Impact of Pembrolizumab Versus Chemotherapy as Second-Line Therapy for Advanced Esophageal Cancer on Health-Related Quality of Life in KEYNOTE-181. *Journal of Clinical Oncology*, *40*(4), 382–391. https://doi.org/10.1200/JCO.21.00601	Study published outside of the timeframe of our review
Hu, J., Ye, Z., Xu, Z., Hao, Z., & Wang, Y. (2022). Cost-effectiveness analysis of pembrolizumab vs. chemotherapy as second-line treatment for advanced esophageal carcinoma in the United States. *Frontiers in Public Health*, *10*, 941738–941738. https://doi.org/10.3389/fpubh.2022.941738	Indication accounts for less than 10% of use

Citation	Decision
Metges, J.-P., Kato, K., Sun, J.-M., Shah, M. A., Enzinger, P. C., Adenis, A., Doi, T., Kojima, T., Li, Z., Kim, S.-B., Cho, B. C., Mansoor, W., Li, S.-H., Sunpaweravong, P., Alsina, M., Buchschacher, G. L., Wu, J., Shah, S., Bhagia, P., & Shen, L. (2022). First-line pembrolizumab plus chemotherapy versus chemotherapy in advanced esophageal cancer: Longer-term efficacy, safety, and quality-of-life results from the phase 3 KEYNOTE-590 study. *Journal of Clinical Oncology*, *40*(4_suppl), 241–241. https://doi.org/10.1200/JCO.2022.40.4_suppl.241	Previously known information about pembrolizumab related to efficacy
García MD, Shah S, Joo S, Valderrama A, Zhang S, Zhang Y, Enzinger P. P-285 Q-TWiST analysis for pembrolizumab plus chemotherapy versus chemotherapy as first-line treatment for patients with advanced esophageal cancer in the KEYNOTE-590 study. *Annals of Oncology*. 2022 Jun 1;33:S348. doi: 10.1016/j.annonc.2022.04.374	Previously known information about pembrolizumab related to efficacy
Qu, T., Zhang, S., Zhong, Y., Meng, Y., Guo, H., Joo, S., & Enzinger, P. C. "Cost Effectiveness of Adding Pembrolizumab to Platinum and Fluoropyrimidine-Based Chemotherapy as First-Line Treatment for Advanced Esophageal Cancer: A US Healthcare Payer's Perspective." *Pharmaco Economics* vol. 40,12 (2022): 1247-1259. doi:10.1007/s40273-022-01196-w	Indication accounts for less than 10% of use
Janjigian, Y. Y., Kawazoe, A., Xu, J., Lonardi, S., Metges, J.-P., Wyrwicz, L. S., Shen, L., Ostapenko, Y., Bilici, M., Lowery, M. A., Valderrama, A., Guan, Y., Li, K., Shih, C.-S., & Rha, S. Y. (2024). Health-related quality of life (HRQOL) with pembrolizumab (pembro) plus trastuzumab (tras) and chemotherapy (chemo) in first-line HER2-positive (HER2+) advanced gastric cancer: KEYNOTE-811 trial results. *Journal of Clinical Oncology*, *42*(3_suppl), 286–286. https://doi.org/10.1200/JCO.2024.42.3_suppl.286	Study published outside of the timeframe of our review
Bratland Å, Munoz-Couselo E, Mortier L, Roshdy O, González R, Schachter J, Arance AM, Grange F, Meyer N, Joshi AJ, Billan S, Hughes BGM, Grob JJ, Ramakrishnan K, Ge J, Gumuscu B, Swaby RF, Gutzmer R. "Health-Related Quality of Life with Pembrolizumab in Patients with Locally Advanced or Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma: KEYNOTE-629." *Dermatology and therapy* vol. 13,12 (2023): 3165-3180. doi:10.1007/s13555-023-01059-y	Previously known information about pembrolizumab related to efficacy
Li, X. J., Muston, D., Ramakrishnan, K., Black, C., Hughes, R., Weston, G., & Lucherini, S. (2022). Budget Impact of Keytruda for the Treatment of Patients with Recurrent or Metastatic (R/M) and Locally Advanced (LA) Cutaneous Squamous Cell Carcinoma (cSCC) in the United States. *International Journal of Radiation Oncology, Biology, Physics*, *112*(5), e55–e55. https://doi.org/10.1016/j.ijrobp.2021.12.126	Outcome not relevant to scope
Armand P, Zinzani PL, Lee HJ, et al. Five-year follow-up of KEYNOTE-087: pembrolizumab monotherapy for relapsed/refractory classical Hodgkin lymphoma. Blood. 2023;142(10):878-886. (2024). *Blood*, *144*(3), 341–341. https://doi.org/10.1182/blood.2024025229	Previously known information about pembrolizumab related to efficacy

Citation	Decision
Zinzani, P.L., Ramchandren, R., Santoro, A., Paszkiewicz-Kozik, E., Gasiorowski, R., Johnson, N.A., de Oliveira, J.S.R., Buccheri, V., Perini, G.F., Dickinson, M. and McDonald, A., 2020. 886MO Health-related quality of life (HRQoL) from KEYNOTE-204: A phase III, randomized, open-label study of pembrolizumab (pembro) vs brentuximab vedotin (BV) in relapsed or refractory classical Hodgkin lymphoma (R/R cHL). *Annals of Oncology*, 31, p.S649.doi: 10.1016/j.annonc.2020.08.004	Study published outside of the timeframe of our review
Zinzani PL, Ramchandren R, Santoro A, Paszkiewicz-Kozik E, Gasiorowski R, Johnson NA, de Oliveira JS, Buccheri V, Perini GF, Dickinson M, McDonald A. Quality-of-life analysis of pembrolizumab vs brentuximab vedotin for relapsed/refractory classical Hodgkin lymphoma. *Blood Advances*. 2022 Jan 25;6(2):590-9.doi: https://doi.org/10.1182/bloodadvances.2021004970	Low-quality evidence
Laliberté, F., Raut, M., Yang, X., Germain, G., Nahar, A., Desai, K. D., MacKnight, S. D., Sen, S. S., & Duh, M. S. (2021). Real-World Healthcare Resource Utilization in Patients with Classical Hodgkin Lymphoma Treated with Pembrolizumab and Nivolumab in the USA. *Targeted Oncology*, *16*(1), 85–94. https://doi.org/10.1007/s11523-020-00778-y	Low-quality evidence
Masatoshi Kudo, Richard S. Finn, Julien Edeline, Stéphane Cattan, Sadahisa Ogasawara, Daniel H. Palmer, Chris Verslype, Vittorina Zagonel, Laetitia Fartoux, Arndt Vogel, Debashis Sarker, Gontran Verset, Stephen L. Chan, Jennifer Knox, Bruno Daniele, Thomas Yau, Ellen B. Gurary, Abby B. Siegel, Anran Wang, Ann-Lii Cheng, Andrew X. Zhu, "Updated efficacy and safety of KEYNOTE-224: a phase II study of pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib." *European journal of cancer* (Oxford, England : 1990) vol. 167 (2022): 1-12. doi:10.1016/j.ejca.2022.02.009	Previously known information about pembrolizumab related to efficacy
Zinzani PL, Thieblemont C, Melnichenko V, et al. Pembrolizumab in relapsed or refractory primary mediastinal large B-cell lymphoma: final analysis of KEYNOTE-170. Blood. 2023;142(2):141-145. (2024). *Blood*, *143*(13), 1316–1316. https://doi.org/10.1182/blood.2024024192	Previously known information about pembrolizumab related to efficacy
Maio, M., Amonkar, M. M., Norquist, J. M., Ascierto, P. A., Manzyuk, L., Motola-Kuba, D., Penel, N., Cassier, P. A., Bariani, G. M., De Jesus Acosta, A., Doi, T., Longo, F., Miller, W. H., Oh, D.-Y., Gottfried, M., Wang, R., Norwood, K., & Marabelle, A. (2022). Health-related quality of life in patients treated with pembrolizumab for microsatellite instability–high/mismatch repair–deficient advanced solid tumours: Results from the KEYNOTE-158 study. *European Journal of Cancer*, *169*, 188–197. https://doi.org/10.1016/j.ejca.2022.03.040	Previously known information about pembrolizumab related to efficacy

Appendix B. Biktarvy®

Appendix Table B1. References Submitted by Gilead

Citation	Decision
Avihingsanon, A., Lu, H., Leong, C. L., Hung, C.-C., Koenig, E., Kiertiburanakul, S., Lee, M.-P., Supparatpinyo, K., Zhang, F., Rahman, S., D'Antoni, M. L., Wang, H., Hindman, J. T., Martin, H., Baeten, J. M., & Li, T. (2023). Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 and hepatitis B coinfection (ALLIANCE): a double-blind, multicentre, randomised controlled, phase 3 non-inferiority trial. *The Lancet HIV*, *10*(10), e640–e652. https://doi.org/10.1016/S2352-3018(23)00151-0	Indication accounts for less than 10% of use
Switch to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in people living with HIV aged 65 and older: W24 results of the BICOLDER study - IMEA 57. Allavena C. et al. *HIV. Glasgow 2022. Abstract (published in JIAS)* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9585422/	Previously known information about bictegravir/emtricitabine /tenofovir alafenamide, related to efficacy
1466. Antiretroviral (ART) Virologic Suppression (VS) and Patient Reported Outcomes (PROs) at 6 Months in the Clinical Opportunities and Management to Exploit Bictegravir/Emtricitabine/ Tenofovir Alafenamide (B/F/TAF) an Asynchronous Connection Key. (COMEBACK) Study Roden L, et al. *Open Forum Infectious Diseases 2022 Abstract* https://doi.org/10.1093/ofi d/ofac492.1293	Previously known information about bictegravir/emtricitabine /tenofovir alafenamide related to efficacy
Bictegravir/emtricitabine/tenofovir alafenamide in older individuals with HIV: Results of a 96- week, phase 3b, open- label, switch trial in virologically suppressed people ≥65 years of age Maggiolo F et al. *HIV Med 2022* https://doi.org/10.1111/hiv.13319	Previously known information about bictegravir/emtricitabine /tenofovir alafenamide related to efficacy
Powis, KM. Pharmacokinetics and Virologic Outcomes of Bictegravir in Pregnancy and Postpartum IMPAACT 2023 Poster. *Conference of Retroviruses and Opportunistic Infections.* https://www.croiconferen ce.org/wp-content/uploads/sites/2/posters/2023/IMPAACT_P HARMACOKINETICS_AND_VIROLOGIC_15Feb 23-133209845782009090.pdf	Indication accounts for less than 10% of use
Jordan E Lake, Ana N Hyatt, Han Feng, Paula Debroy, Aaren Kettelhut, Hongyu Miao, Liming Peng, Shalender Bhasin, Susan Bell, Nahid Rianon, Todd T Brown, Nicholas T Funderburg, A Randomized Clinical Trial of Transgender Women Switching to B/F/TAF: The (mo)BETTA Trial, *Open Forum Infectious Diseases*, Volume 10, Issue 4, April 2023, ofad178, https://doi.org/10.1093/ofid/ofad178	Previously known information about bictegravir/emtricitabine /tenofovir alafenamide related to efficacy
Rodriguez, CA. One Year Outcome of Bictegravir/Emtricitabine/ Tenofovir Alafenamide (B/F/TAF) in Virologically Suppressed Children ≥ 2 Years Weighing	Previously known information about bictegravir/emtricitabine

Citation	Decision
14 to < 25 kg. *International AIDS Conference 2022 Poster/Abstract* https://www.natap.org/20 22/IAC/IAC_90.htm	/tenofovir alafenamide related to efficacy
Pozniak A. Restarting Bictegravir/Emtricitabine/ Tenofovir Alafenamide (B/F/TAF) After Virologic Rebound: A Pooled Analysis of Studies in People With HIV-1. *European AIDS Clinical Society 2023 Poster* https://presentations.gilead.com/files/5816/9765/36 20/Pozniak_EACS23_Poster_Rapid_Restart_Submission_09Oct2023.pdf	Previously known information about bictegravir/emtricitabine /tenofovir alafenamide related to efficacy
D'Antoni, Michelle L. PhD; Andreatta, Kristen MS; Acosta, Rima BS; Martin, Hal MD; Chang, Silvia MS; Martin, Ross MS; White, Kirsten L. PhD. Brief Report: Bictegravir/Emtricitabine/Tenofovir Alafenamide Efficacy in Participants With Preexisting Primary Integrase Inhibitor Resistance Through 48 Weeks of Phase 3 Clinical Trials. *JAIDS Journal of Acquired Immune Deficiency Syndromes* 89(4):p 433-440, April 1, 2022. DOI: 10.1097/QAI.0000000000002888	Low-quality evidence
Sax PE, Arribas JR, Orkin C, Lazzarin A, Pozniak A, DeJesus E, Maggiolo F, Stellbrink HJ, Yazdanpanah Y, Acosta R, Huang H, Hindman JT, Martin H, Baeten JM, Wohl D; GS-US-380-1489 and GS-US-380-1490 study investigators. Bictegravir/emtricitabine/tenofovir alafenamide as initial treatment for HIV-1: five-year follow-up from two randomized trials. *EClinicalMedicine*. 2023 May 11;59:101991. doi: 10.1016/j.eclinm.2023.101991.	Previously known information about bictegravir/emtricitabine /tenofovir alafenamide related to efficacy
Andreatta K, Sax PE, Wohl DA, D'Antoni ML, Huang H, Hindman J, Callebaut C, Martin H. 1561. Efficacy of Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) Versus Dolutegravir (DTG)-Based 3-Drug Regimens in Adults With HIV Who Have Suboptimal Antiretroviral Adherence. *Open Forum Infect Dis. 2023* Nov 27;10(Suppl 2):ofad500.1396. doi: 10.1093/ofid/ofad500.1396.	Low-quality evidence
Sax, P. E., Andreatta, K., Molina, J. M., Daar, E. S., Hagins, D., Acosta, R., D'Antoni, M. L., Chang, S., Martin, R., Liu, H., Blair, C., McNicholl, I., Gallant, J., Collins, S. E., Martin, H., & White, K. L. (2022). High efficacy of switching to bictegravir/emtricitabine/tenofovir alafenamide in people with suppressed HIV and preexisting M184V/I. *AIDS (London, England)*, *36*(11), 1511–1520. https://doi.org/10.1097/QAD.0000000000003244	Previously known information about bictegravir/emtricitabine /tenofovir alafenamide related to efficacy
Zhang, Haeyoung; Hindman, Jason T.; Lin, Ludwig; Davis, Maggie; Shang, Justin; Xiao, Deqing; Avihingsanon, Anchalee; Arora, Priyanka; Palaparthy, Ramesh; Girish, Sandhya; Marathe, Dhananjay D. A study of the pharmacokinetics, safety, and efficacy of bictegravir/emtricitabine/tenofovir alafenamide in virologically suppressed pregnant women with HIV. *AIDS* 38(1):p F1-F9, January 01, 2024. DOI: 10.1097/QAD.0000000000003783	Indication accounts for less than 10% of use

Citation	Decision
Marcelin, AG. The Virostar study: Analysis of emergent resistance-associated mutations at first- or second-line HIV-1 virologic failure with second generation InSTIs in 2- and 3-drug regimens. *HIV Glasgow 2022 Poster* https://hivglasgow.org/wp-content/uploads/2023/01/ P225_Marcelin.pdf	Outcomes not relevant to scope

Appendix C. Imfinzi®

Appendix Table C1. References Submitted by AstraZeneca

Citation	Decision
Spigel DR, Faivre-Finn C, Gray JE, et al. Five-Year Survival Outcomes from the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2022;40(12):1301-1311.	Previously known information about durvalumab related to efficacy or safety or cost-effectiveness
Naidoo J, Vansteenkiste JF, Faivre-Finn C, et al. Characterizing immune-mediated adverse events with durvalumab in patients with unresectable stage III NSCLC: A post-hoc analysis of the PACIFIC trial. *Lung Cancer*. 2022;166:84-93.	Previously known information about durvalumab related to efficacy or safety or cost-effectiveness
Senan S, Özgüroğlu M, Daniel D, et al. Outcomes with durvalumab after chemoradiotherapy in stage IIIA-N2 non-small-cell lung cancer: an exploratory analysis from the PACIFIC trial. *ESMO Open*. 2022;7(2):100410.	Previously known information about durvalumab related to efficacy or safety or cost-effectiveness
Hui R, Naidoo J, Garassino MC, et al. 118P Impact of grade ≥2 pneumonitis (G2+ pns) on patient reported outcomes (Pros) with durvalumab (D) after chemoradiotherapy (Crt) in unresectable stage III NSCLC. *Annals of Oncology*. 2022;33:S87.	Previously known information about durvalumab related to efficacy or safety or cost-effectiveness
Mooradian M, Taylor S, Ramsden R, et al. POSC110 Cost-effectiveness of durvalumab following chemoradiotherapy in unresectable stage III NSCLC patients in the US: an update based on 5-Year PACIFIC data. *Value in Health*. 2022;25(1):S108.	Previously known information about durvalumab related to efficacy or safety or cost-effectiveness
Hussain S, Klugarova J, Klugar M. Cost-effectiveness analyses of durvalumab consolidation therapy versus no consolidation therapy after chemoradiotherapy in stage-III NSCLC. *Lung Cancer*. 2022;170:11-19.	Previously known information about durvalumab related to efficacy or safety or cost-effectiveness
Girard N, Christoph DCC, Garassino MC, et al. 58O Real-world overall survival (Os) with durvalumab (D) after chemoradiotherapy (Crt) in patients (Pts) with unresectable stage III non-small cell lung cancer (NSCLC): Interim analysis from the PACIFIC-R study. *Immuno-Oncology and Technology*. 2022;16:100163.	Previously known information about durvalumab related to efficacy or safety or cost-effectiveness
Girard N, Bar J, Garrido P, et al. Treatment Characteristics and Real-World Progression-Free Survival in Patients With Unresectable Stage III NSCLC Who Received Durvalumab After Chemoradiotherapy: Findings From the PACIFIC-R Study. *J Thorac Oncol*. 2023;18(2):181-193.	Previously known information about durvalumab related to efficacy or safety or cost-effectiveness

Citation	Decision
Waterhouse D, Yong C, Frankart A, et al. Durvalumab real-world treatment patterns and outcomes in patients with stage III non-small-cell lung cancer treated in a US community setting. Future Oncol. 2023;19(28):1905-1916.	Previously known information about durvalumab related to efficacy or safety or cost-effectiveness
Mooradian MJ, Allen A, Cai L, et al. Real-world outcomes with durvalumab after chemoradiotherapy in patients with unresectable stage III NSCLC (SPOTLIGHT) [poster]. *Presented at European Lung Cancer Congress (ELCC)*; March 30 – April 2, 2022; Virtual. Abs116P.	Previously known information about durvalumab related to efficacy or safety or cost-effectiveness
Whitaker RM, Cai L, Wang A, et al. 12AP SPOTLIGHT Real-world study: outcomes with or without durvalumab after CRT in patients with unresectable stage III NSCLC. *J Thorac Onc*. 2023;18(4):S111.	Previously known information about durvalumab related to efficacy or safety or cost-effectiveness
Alkadimi M, Moore A, Frei CR, et al. Treatment interruptions and discontinuations among patients with stage III unresectable non–small cell lung cancer treated with durvalumab at the Veterans Health Administration. *JCO*. 2022;40(16_suppl).Abs8554.	Previously known information about durvalumab related to efficacy or safety or cost-effectiveness
Moore A, Nooruddin Z, Reveles KR, et al. EP05.02-013 Immune-related adverse effects and durvalumab treatment patterns in VHA patients with unresectable stage III NSCLC. *J Thorac Oncol*. 2022;17(9):S288.	Outcomes not relevant to scope
Moore AM, Nooruddin Z, Reveles KR, et al. Durvalumab Treatment Patterns for Patients with Unresectable Stage III Non-Small Cell Lung Cancer in the Veterans Health Administration (VHA): A Nationwide, Real-World Study. *Curr Oncol*. 2023;30(9):8411-8423. Published 2023 Sep 13.	Outcomes not relevant to scope
Moore AM, Nooruddin Z, Reveles KR, et al. Health Equity in Patients Receiving Durvalumab for Unresectable Stage III Non-Small Cell Lung Cancer in the US Veterans Health Administration. *Oncologist.* 2023;28(9):804-811.	Outcomes not relevant to scope
Haque R, McGary, Yang M, et al. Utilization of extended-interval, fixed-dosing of durvalumab, every 4 weeks, in U.S. patients with unresectable stage III NSCLC following concurrent chemoradiation [poster]. *Presented at North America Conference on Lung Cancer (NACLC)*. December 1-3, 2023. Chicago, Illinois.	Outcomes not relevant to scope
Johnson ML, Cho BC, Luft A, et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. J Clin Oncol. 2023;41(6):1213-1227. doi:10.1200/JCO.22.00975	New moderate to high quality evidence

Citation	Decision
Peters S, Cho BC, Luft A et al. Durvalumab ± Tremelimumab + Chemotherapy in First-Line Metastatic NSCLC: 5-Year Overall Survival Update from the POSEIDON Study [presentation]. Presented at: European Society for Medical Oncology (ESMO) Immuno-Oncology Congress; December 6-8, 2023; Geneva, Switzerland.	Supporting evidence for trial above
Garon EB, Cho BC, Luft A, et al. Patient-reported outcomes with durvalumab, with or without tremelimumab, plus chemotherapy as first-line treatment for metastatic non-small-cell lung cancer (POSEIDON). Lung Cancer. 2023; 186:107422.	Supporting evidence for trial above
Paz-Ares L, Chen Y, Reinmuth N, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN [article and supplementary data]. *ESMO Open*. 2022;7(2):100408.	Previously known information about durvalumab related to efficacy or safety or cost-effectiveness
Oh D-Y, He AR, Qin S, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer [article and supplementary appendix]. NEJM Evid. 2022;1(8). Doi:10.1056/EVIDoa2200015.	New moderate to high quality evidence
Oh D-Y et al. Updated overall survival from the Phase 3 TOPAZ-1 study of durvalumab or placebo plus GemCis in patients with advanced BTC [poster]. Presented at: European Society of Medical Oncology (ESMO); September 9-13, 2022. Paris, France. Poster 56P.	Supporting evidence for trial above
Burris H, Okusaka T, Vogel A, et al. Patient-reported outcomes for the Phase 3 TOPAZ-1 study of durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer [poster]. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, IL. Poster 4070.	Supporting evidence for trial above
Kim JW, Lee JH, Yoon, J, et al. Health-related quality of life in patients with gemcitabine/cisplatin and durvalumab +/- tremelimumab in chemotherapy-naiive advanced biliary tract cancer [poster]. *American Society of Clinical Oncology (ASCO) Annual Meeting; 2022*	Study population outside approved label indication
Rimini M, Fornaro L, Londardi S, et. al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer: An early exploratory analysis of real-world data. Liver International. 2023;42(8). Doi.org/10.1111/liv.15641.	New moderate to high quality evidence
Gerhard F, Muller C, Chater J, et al. TREATMENT WITH GEMCITABINE/CISPLATIN AND DURVALUMAB FOR BILIARY TRACT CANCER – FIRST REAL-WORLD DATA FROM A GERMAN PATIENT COHORT [Poster]; The Liver Meeting: Boston, Massachusetts Nov 10-14, 2023 http://dx.doi.org/10.1097/HEP.0000000000000580; 4148-A	New moderate to high quality evidence

Citation	Decision
Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma [article and supplementary appendix]. NEJM Evid. 2022;1(8).	New moderate to high quality evidence
Sangro B, et al. Four-year overall survival update from the phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Presented at World GI Congress, June 28-July 1, 2023	Supporting evidence for trial above
Sangro B, Galle PR, Kelley RK, et al. Patient-reported outcomes from the Phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma [poster]. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, IL. Poster 4074.	Supporting evidence for trial above
Qin L, et al. The impact of treatment and treatment status on health state utility in patients with unresectable hepatocellular carcinoma: an EQ 5D analysis from HIMALAYA. Presented at European Association for the Study of the Liver Congress 2022.	Supporting evidence for trial above
Healey M, et al. Incidence and Costs Associated with Clinically Significant Events in Real-World Patients with Unresectable Hepatocellular Carcinoma on Systemic Therapy [poster]. *Presented at ASCO GI*, January 19-21, 2023.	Intervention not relevant to scope
Qin L, Chan S, Le Nouveau P et al. Matching adjusted indirect comparison (MAIC) of single tremelimumab regular interval durvalumab (STRIDE) versus atezolizumab with bevacizumab (A+B) for the treatment of unresectable hepatocellular carcinoma (uHCC) [Poster]. *Presented at International Society for Pharmacoeconomics and Outcomes (ISPOR):* May 7-10, 2023, Boston, MA, USA. Poster CO70	Low-quality evidence
Sah J, Genestier V, Qin L. A Total Cost of Care Analysis of Immune-Oncology (IO) Treatments for Unresectable Hepatocellular Carcinoma (uHCC): A Canadian Payer Perspective [poster]. *Presented at ISPOR Europe 2023. November 12-15, 2023.*	Comparison not relevant to scope

Appendix D. Opdivo®

Appendix Table D1. References Submitted by Bristol-Myers Squibb

Citation	Decision
N/A	N/A

Appendix E. Darzalex®

Appendix Table E1. References Submitted by Johnson & Johnson

Citation	Decision
N/A	N/A

Appendix F. Tagrisso®

Appendix Table F1. References Submitted by AstraZeneca

Citation	Decision
Herbst RS, Wu Y-L, John T, et al. Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIA non-small-cell lung cancer: updated results from the phase III randomized ADAURA trial. *J Clin Oncol.* 2023;41:1830-1840.	Previously known information about osimertinib related to efficacy
Tsuboi M, Herbst RS, John T, et al. Overall survival with osimertinib in resected EGFR-mutated NSCLC. N Engl J Med. 2023. DOI: 10.1056/NEJMoa2304594	New moderate to high quality evidence
John T, Grohé C, Goldman JW, et al. Three-year safety, tolerability, and health-related quality of life outcomes of adjuvant osimertinib in patients with resected Stage IB to IIIA EGFR-mutated NSCLC: updated analysis from the Phase 3 ADAURA trial. *J Thorac Oncol*. 2023;18(9):1209-1221.	Previously known information about osimertinib related to efficacy
Verhoek A, Cheema P, Melosky B, et al. Evaluation of cost effectiveness of adjuvant osimertinib in patients with resected EGFR mutation positive non small cell lung cancer. *Pharmacoecon Open*. 2023;7(3):455–467.	Previously known information about osimertinib related to cost-effectiveness
Apple J, Dolph M, Lee R, et. al. Cost-effectiveness Model Assessing Adjuvant Osimertinib in Epidermal Growth Factor Positive Early Stage Non-Small Cell Lung Cancer Following Complete Resection in the United States. *Poster presentation at AMCP Nexus 2022*, October 11–14, National Harbor, MD, USA.	Previously known information about osimertinib related to cost-effectiveness
Planchard D, Jänne PA, Cheng Y, et al. Osimertinib with or without chemotherapy in EGFR-mutated advanced NSCLC. *N Engl J Med*. 2023;389(21):1935-1948.	Study population outside approved label indication during our timeframe
Jänne PA, Planchard D, Kobayashi K, et al. CNS efficacy of osimertinib with or without chemotherapy in epidermal growth factor receptor-mutated advanced non-small-cell lung cancer. *J Clin Oncol*. Published online December 2, 2023. doi:10.1200/JCO.23.02219	Study population outside approved label indication during our timeframe
Nieva J, Karia PS, Okhuoya P, et al. A real-world (rw) observational study of long-term survival (LTS) and treatment patterns after first-line (1L) osimertinib in patients (pts) with epidermal growth factor receptor (EGFR) mutation-positive (m) advanced non-small cell lung cancer (NSCLC) [poster]. *Presented at: European Society for Medical Oncology (ESMO) Congress*; Oct 20-24, 2023; Madrid, Spain. Poster 1344P.	Previously known information about osimertinib related to efficacy
Shenolikar R, Liu S, Shah A, Tse J, Cao Y, Near A. Real-world treatment patterns of metastatic non-small cell lung cancer patients receiving epidermal growth factor receptor tyrosine kinase inhibitors. *Cancer Med*. 2023;12(1):159-169. doi:10.1002/cam4.4918	Previously known information about osimertinib related to efficacy

Appendix G. Prolia®

Appendix Table G1. References Submitted by Amgen

Citation	Decision
Curtis J, Arora T, Liu Y, Lin T, Spangler L, Brunetti V, Stad R, McDermott M, Bradbury B, Kim M.Comparative Effectiveness of Denosumab versus Alendronate Among Postmenopausal Womenwith Osteoporosis in the U.S. Medicare Program [abstract]. *Arthritis Rheumatol*. 2023; 75 (suppl9). https://acrabstracts.org/abstract/comparative-effectiveness-of-denosumab-versus-alendronate-among-postmenopausal-women-with-osteoporosis-in-the-u-s-medicare-program/	New moderate to high quality evidence
Kim, M., Lin, T., Arora, T., Zhao, H., Balasubramanian, A., Stad, R. K., O'Kelly, J., Spangler, L., Bradbury, B. D., & Curtis, J. R. (2023). Comparability of Osteoporosis Treatment Groups Among Female Medicare Beneficiaries in the United States. *Journal of Bone and Mineral Research*, 38(6), 829–840. https://doi.org/10.1002/jbmr.4817	Outcomes not relevant to scope
Curtis J, Arora T, Liu Y, Brunetti V, Lin T, Spangler L, Stad R, McDermott M, Bradbury B, Kim M.Comparative Effectiveness of Denosumab versus Zoledronic Acid Among PostmenopausalWomen with Osteoporosis in the U.S. Medicare Program [abstract]. *Arthritis Rheumatol*. 2023; 75(suppl 9). https://acrabstracts.org/abstract/comparative-effectiveness-of-denosumab-versus-zoledronic-acid-among-postmenopausal-women-with-osteoporosis-in-the-u-s-medicare-program/	Low-quality evidence
Curtis J et al. (2023) Comparative Effectiveness of Denosumab versus Bisphosphonates among Treatment-Experienced Postmenopausal Women with Osteoporosis in the U.S. Medicare Program. *American Society for Bone and Mineral Research 2023*.	Low-quality evidence
Spangler, L., Nielson, C. M., Brookhart, M. A., Hernandez, R. K., Stad, R. K., & Lin, T.-C. (2023). Cardiovascular Safety in Postmenopausal Women and Men With Osteoporosis Treated With Denosumab and Zoledronic Acid: A Post-Authorization Safety Study. *JBMR Plus*, 7(10), e10793–e10793. https://doi.org/10.1002/jbm4.10793	Previously known information about denosumab related to efficacy
Everts-Graber, J., Bonel, H., Lehmann, D., Gahl, B., Häuselmann, H., Studer, U., Ziswiler, H.-R., Reichenbach, S., & Lehmann, T. (2023). Comparison of anti-fracture effectiveness of zoledronate, ibandronate and alendronate versus denosumab in a registry-based cohort study. *Osteoporosis International*, 34(11), 1961–1973. https://doi.org/10.1007/s00198-023-06863-y	Low-quality evidence
Lyu, H., Zhao, S. S., Zhang, L., Wei, J., Li, X., Li, H., Liu, Y., Yin, P., Norvang, V., Yoshida, K., Tedeschi, S. K., Zeng, C., Lei, G., Tang, P., & Solomon, D. H. (2023). Denosumab and incidence of type 2 diabetes among adults with osteoporosis: population based cohort study. *BMJ (Online)*, *381*, e073435–e073435. https://doi.org/10.1136/bmj-2022-073435	Outcomes not relevant to scope
Liu, T.-C., Hsu, C.-N., Lee, W.-C., Wang, S.-W., Huang, C.-C., Lee, Y.-T., Fu, C.-M., Chen, J.-B., & Li, L.-C. (2023). Denosumab Is Superior to Raloxifene in Lowering Risks of Mortality and Ischemic Stroke in Osteoporotic Women. *Pharmaceuticals (Basel, Switzerland)*, *16*(2), 222. https://doi.org/10.3390/ph16020222	Outcomes not relevant to scope
Wu, T., Tsou, Y., Wu, W., Lee, R., Wang, J., & Yeh, K. (2024). Five-Year Outcomes of Continuous Treatment with Zoledronic Acid Versus Denosumab in Older Men with High Fracture Risk: Risk Factor Analysis of Bone Density	Low-quality evidence

Citation	Decision
Improvement and Incidence of New Fracture. *Journal of Clinical Pharmacology*, *64*(4), 469–477. https://doi.org/10.1002/jcph.2378	
Hans, D., McDermott, M., Huang, S., Kim, M., Shevroja, E., & McClung, M. (2023). Long-term effect of denosumab on bone microarchitecture as assessed by tissue thickness–adjusted trabecular bone score in postmenopausal women with osteoporosis: results from FREEDOM and its open-label extension. *Osteoporosis International*, *34*(6), 1075–1084. https://doi.org/10.1007/s00198-023-06708-8	Previously known information about denosumab related to efficacy
Kim M, McGrath L, Pritchard D, Samai P, Lin J, Stad R, Spangler L, McDermott M, Bradbury B,Brookhart M. Comparative Effectiveness of Osteoporosis (OP) Therapies Among a Population ofPostmenopausal (PM) Women in the United States (U.S.) [abstract]. *Arthritis Rheumatol*. 2022; 74(suppl 9). https://acrabstracts.org/abstract/comparative-effectiveness-of-osteoporosis-op-therapies-among-a-population-of-postmenopausal-pm-women-in-the-united-states-u-s/	Low-quality evidence
Kang, T., Park, S. Y., Lee, S. H., Park, J. H., & Suh, S. W. (2022). Comparison of Denosumab and Zoledronic Acid in Postmenopausal Women With Osteoporosis: Bone Mineral Density (BMD) and Trabecular Bone Score (TBS). *Journal of Korean Medical Science*, *37*(13), e68–e68. https://doi.org/10.3346/jkms.2022.37.e68	Low-quality evidence
Boschitsch, E., Naegele, O., Klinger, A., & Brix-Samoylenko, H. (2022). Long-term persistence with denosumab: real-world data from the Austrian Osteoporosis Clinic (AOC). A retrospective data analysis. *Osteoporosis International*, *33*(1), 263–272. https://doi.org/10.1007/s00198-021-06102-2	Low-quality evidence
Rupp, T., von Vopelius, E., Strahl, A., Oheim, R., Barvencik, F., Amling, M., & Rolvien, T. (2022). Beneficial effects of denosumab on muscle performance in patients with low BMD: a retrospective, propensity score-matched study. *Osteoporosis International*, *33*(10), 2177–2184. https://doi.org/10.1007/s00198-022-06470-3	Low-quality evidence
Kim, S.-J., Kim, J. W., & Lee, D.-W. (2022). Denosumab versus zoledronic acid in elderly patients after hip fracture. *Journal of Orthopaedic Surgery (Hong Kong)*, *30*(3), 10225536221147082–10225536221147082. https://doi.org/10.1177/10225536221147082	Low-quality evidence
Händel, M. N., Cardoso, I., von Bülow, C., Rohde, J. F., Ussing, A., Nielsen, S. M., Christensen, R., Body, J. J., Brandi, M. L., Diez-Perez, A., Hadji, P., Javaid, M. K., Lems, W. F., Nogues, X., Roux, C., Minisola, S., Kurth, A., Thomas, T., Prieto-Alhambra, D., Ferrari, S. L., … Abrahamsen, B. (2023). Fracture risk reduction and safety by osteoporosis treatment compared with placebo or active comparator in postmenopausal women: systematic review, network meta-analysis, and meta-regression analysis of randomised clinical trials. *BMJ (Clinical research ed.)*, *381*, e068033. https://doi.org/10.1136/bmj-2021-068033	New evidence of no improved efficacy on clinical fractures
Nakura, N., Hirakawa, K., Takayanagi, S., & Mihara, M. (2023). Denosumab prevented periprosthetic bone resorption better than risedronate after total hip arthroplasty. *Journal of Bone and Mineral Metabolism*, *41*(2), 239–247. https://doi.org/10.1007/s00774-023-01405-2	Study population outside approved label indication
Kobayakawa, T., Miyazaki, A., Takahashi, J., & Nakamura, Y. (2022). Verification of efficacy and safety of ibandronate or denosumab for postmenopausal osteoporosis after 12-month treatment with romosozumab as sequential therapy: The prospective VICTOR study. *Bone (New York, N.Y.)*, *162*, 116480–116480. https://doi.org/10.1016/j.bone.2022.116480	Previously known information about denosumab related to efficacy

Citation	Decision
Geusens, P., Bevers, M. S., Rietbergen, B., Messina, O. D., Lespessailles, E., Oliveri, B., Chapurlat, R., Engelke, K., Chines, A., Huang, S., Saag, K. G., & Bergh, J. P. (2022). Effect of Denosumab Compared With Risedronate on Bone Strength in Patients Initiating or Continuing Glucocorticoid Treatment. *Journal of Bone and Mineral Research,* 37(6), 1136–1146. https://doi.org/10.1002/jbmr.4551	Previously known information about denosumab related to efficacy
Wadiura, L. I., Butylina, M., Reinprecht, A., Aretin, M., Mischkulnig, M., Gleiss, A., Pietschmann, P., & Kerschan-Schindl, K. (2022). Denosumab for Prevention of Acute Onset Immobilization-Induced Alterations of Bone Turnover: A Randomized Controlled Trial. *Journal of Bone and Mineral Research*, *37*(11), 2156–2164. https://doi.org/10.1002/jbmr.4694	Study population outside approved label indication
Agarwal, S., Shiau, S., Kamanda-Kosseh, M., Bucovsky, M., Kil, N., Lappe, J. M., Stubby, J., Recker, R. R., Guo, X. E., Shane, E., & Cohen, A. (2023). Teriparatide Followed by Denosumab in Premenopausal Idiopathic Osteoporosis: Bone Microstructure and Strength by HR-pQCT. *Journal of Bone and Mineral Research*, *38*(1), 35–47. https://doi.org/10.1002/jbmr.4739	Study population outside approved label indication
Hu, Y. J., Chines, A., Shi, Y., Seeman, E., & Guo, X. E. (2022). The effect of denosumab and alendronate on trabecular plate and rod microstructure at the distal tibia and radius: A post-hoc HR-pQCT study. *Bone (New York, N.Y.)*, *154*, 116187–116187. https://doi.org/10.1016/j.bone.2021.116187	Study population outside approved label indication
Haines, M. S., Kimball, A., Meenaghan, E., Santoso, K., Colling, C., Singhal, V., Ebrahimi, S., Gleysteen, S., Schneider, M., Ciotti, L., Belfer, P., Eddy, K. T., Misra, M., & Miller, K. K. (2022). Denosumab increases spine bone density in women with anorexia nervosa: a randomized clinical trial. *European Journal of Endocrinology*, *187*(5), 697–708. https://doi.org/10.1530/EJE-22-0248	Study population outside approved label indication
Kiritopoulos, D., Nystrom, A., Ullmark, G., Sorensen, J., Petren-Mallmin, M., Milbrink, J., Hailer, N. P., & Mallmin, H. (2022). Denosumab prevents acetabular bone loss around an uncemented cup: analysis of secondary outcomes in a randomized controlled trial. *Acta Orthopaedica*, *93*, 709–720. https://doi.org/10.2340/17453674.2022.4537	Study population outside approved label indication
Luo, C., Qin, S.-X., Wang, Q.-Y., Li, Y.-F., Qu, X.-L., Yue, C., Hu, L., Sheng, Z.-F., Wang, X.-B., & Wan, X.-M. (2023). Cost-effectiveness analysis of five drugs for treating postmenopausal women in the United States with osteoporosis and a very high fracture risk. *Journal of Endocrinological Investigation*, *46*(2), 367–379. https://doi.org/10.1007/s40618-022-01910-7	Low-quality evidence
Nargesi, S., Barghazan, S. H., Sani'ee, N., & Kemmak, A. R. (2022). Economic Evaluation of Denosumab for Treatment of Postmenopausal Osteoporosis: A Systematic Review. *Iranian Journal of Public Health*, *51*(7), 1502–1512. https://doi.org/10.18502/ijph.v51i7.10084	Previously known information about denosumab related to cost-effectiveness
You, R., Mori, T., Ke, L., Wan, Y., Zhang, Y., Luo, F., Feng, D., Yu, G., & Liu, J. (2022). Which injected antiosteoporotic medication is worth paying for? A cost-effectiveness analysis of teriparatide, zoledronate, ibandronate, and denosumab for postmenopausal osteoporotic women in China. *Menopause (New York, N.Y.)*, *29*(2), 210–218. https://doi.org/10.1097/GME.0000000000001911	Cost effectiveness of a non-US perspective
Choo, Y. W., Mohd Tahir, N. A., Mohamed Said, M. S., Li, S. C., & Makmor Bakry, M. (2022). Cost-effectiveness of Denosumab for the Treatment of Postmenopausal Osteoporosis in Malaysia. *Osteoporosis International*, *33*(9), 1909–1923. https://doi.org/10.1007/s00198-022-06444-5	Cost effectiveness of a non-US perspective

Citation	Decision
Jung-Yoon Kang, Leejung Choi, Ben Johnson, & Hyowon Yang. (2022). Cost-Effectiveness of Denosumab for the Treatment of Postmenopausal Osteoporosis in South Korea. *Journal of bone metabolism*, 83–92.	Cost effectiveness of a non-US perspective
You, R., Liu, J., Ke, L., Wan, M., Zhang, Y., Yu, G., & Mori, T. (2022). Cost-Effectiveness of Sequential Denosumab/Zoledronic Acid Compared With Zoledronic Acid Monotherapy for Postmenopausal Osteoporotic Women in China. *Frontiers in Pharmacology*, *13*, 816248–816248. https://doi.org/10.3389/fphar.2022.816248	Cost effectiveness of a non-US perspective

Appendix H. Entresto®

Appendix Table H1. References Submitted by Novartis

Citation	Decision
Solomon, S. D., McMurray, J. J. ., Anand, I. S., Ge, J., Lam, C. S. ., Maggioni, A. P., Martinez, F., Packer, M., Pfeffer, M. A., Pieske, B., Redfield, M. M., Rouleau, J. L., van Veldhuisen, D. J., Zannad, F., Zile, M. R., Desai, A. S., Claggett, B., Jhund, P. S., Boytsov, S. A., … Lefkowitz, M. P. (2019). Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *The New England Journal of Medicine*, 381(17), 1609–1620. https://doi.org/10.1056/NEJMoa1908655	Study published outside of the timeframe of our review
Morrow, D. A., Velazquez, E. J., Desai, A. S., DeVore, A. D., Lepage, S., Park, J.-G., Sharma, K., Solomon, S. D., Starling, R. C., Ward, J. H., Williamson, K. M., Zieroth, S., Hernandez, A. F., Mentz, R. J., & Braunwald, E. (2024). Sacubitril/Valsartan in Patients Hospitalized With Decompensated Heart Failure. *Journal of the American College of Cardiology*, 83(12), 1123–1132. https://doi.org/10.1016/j.jacc.2024.01.027	Study published outside of the timeframe of our review
Robert J. Mentz, Brian L. Claggett, Ian J. Kulac, Jonathan H. Ward, Adrian F. Hernandez, David A. Morrow, Randall C. Starling, Eric J. Velazquez, Kristin M. Williamson, Akshay S. Desai, Shelley Zieroth, Martin Lefkowitz, John J.V. McMurray, Eugene Braunwald, Scott D. Solomon (2023). Renal Outcomes in PARAGLIDE-HF and PARAGON-HF. *European Society of Cardiology Congress 2023.*	Previously known information about sacubitril-valsartan related to efficacy
Vaduganathan, M., Mentz, R. J., Claggett, B. L., Miao, Z. M., Kulac, I. J., Ward, J. H., Hernandez, A. F., Morrow, D. A., Starling, R. C., Velazquez, E. J., Williamson, K. M., Desai, A. S., Zieroth, S., Lefkowitz, M., McMurray, J. J. ., Braunwald, E., & Solomon, S. D. (2023). Sacubitril/valsartan in heart failure with mildly reduced or preserved ejection fraction: a pre-specified participant-level pooled analysis of PARAGLIDE-HF and PARAGON-HF. *European Heart Journal.*	Previously known information about sacubitril-valsartan related to efficacy
Pieske, B., Wachter, R., Shah, S. J., Baldridge, A., Szeczoedy, P., Ibram, G., Shi, V., Zhao, Z., & Cowie, M. R. (2021). Effect of Sacubitril/Valsartan vs Standard Medical Therapies on Plasma NT-proBNP Concentration and Submaximal Exercise Capacity in Patients With Heart Failure and Preserved Ejection Fraction: The PARALLAX Randomized Clinical Trial. *JAMA : the Journal of the American Medical Association,* 326(19), 1919–1929. https://doi.org/10.1001/jama.2021.18463	Study published outside of the timeframe of our review
McMurray, J. Neprilysin inhibition does not affect cognitive function in patients with heart failure. *Presented as a Hot Line session at European Society of Cardiology*, Barcelona, Spain, August 2022	Previously known information about sacubitril-valsartan related to efficacy
Shaddy, R. (2022) Angiotensin receptor neprilysin inhibition in pediatric patients with heart failure due to systemic left ventricular systolic dysfunction: Primary results of the PANORAMA-HF trial. *Presented at European Society of Cardiology,* Barcelona, Spain, August 27, 2022	Indication accounts for less than 10% of use
Thomas, M., Khariton, Y., Fonarow, G. C., Arnold, S. V., Hill, L., Nassif, M. E., Chan, P. S., Butler, J., Thomas, L., DeVore, A. D., Hernandez, A. F., Albert, N. M., Patterson, J. H., Williams, F. B., & Spertus, J. A. (2021). Association between sacubitril/valsartan initiation and real-world health status trajectories over 18 months in heart failure with reduced ejection fraction. *ESC Heart Failure*, 8(4), 2670–2678. https://doi.org/10.1002/ehf2.13298	Study published outside of the timeframe of our review

Citation	Decision
Shen, X., Sullivan, G., Adelsberg, M., Francis, M., Schwartz, T., Petrilla, A., Abbas, C., & Cristino, J. (2021). THE ASSOCIATION BETWEEN SACUBITRIL/VALSARTAN UTILIZATION AND HEALTHCARE COSTS FOR PATIENTS WITH HEART FAILURE WITH REDUCED EJECTION FRACTION (HFREF) IN MEDICARE SHARED SAVINGS PROGRAM PARTICIPANTS IN 2018. *Journal of the American College of Cardiology*, 77(18), 523–523. https://doi.org/10.1016/S0735-1097(21)01882-9	Study published outside of the timeframe of our review
Shen, X., Sullivan, G., Adelsberg, M., Francis, M., Schwartz, T., Petrilla, A., Abbas, C., & Cristino, J. (2021). 90-DAY EPISODIC COSTS OF HEART FAILURE WITH REDUCED EJECTION FRACTION (HFREF) PATIENTS RECEIVING SACUBITRIL/VALSARTAN COMPARED TO OTHER TREATMENT WITHIN THE MEDICARE BUNDLED PAYMENT FOR CARE INITIATIVE (BPCI) MODEL 2, 2016-2018. *Journal of the American College of Cardiology*, 77(18), 541–541. https://doi.org/10.1016/S0735-1097(21)01900-8	Study published outside of the timeframe of our review
Greene, S. J., Choi, S., Lippmann, S. J., Mentz, R. J., Greiner, M. A., Hardy, N. C., Hammill, B. G., Luo, N., Samsky, M. D., Heidenreich, P. A., Laskey, W. K., Yancy, C. W., Peterson, P. N., Curtis, L. H., Hernandez, A. F., Fonarow, G. C., & O'Brien, E. C. (2021). Clinical Effectiveness of Sacubitril/Valsartan Among Patients Hospitalized for Heart Failure With Reduced Ejection Fraction. *Journal of the American Heart Association*, 10(16), e021459–e021459. https://doi.org/10.1161/JAHA.121.021459	Study published outside of the timeframe of our review
Blumer, V., Choi, S., Greene, S. J., Hardy, N. C., Greiner, M. A., Carnicelli, A., Shen, X., Lippmann, S. J., Peterson, P., Allen, L. A., Fonarow, G. C., Mentz, R. J., & OBrien, E. C. (2021). Abstract 10738: Comparative Outcomes of Sacubitril/Valsartan Use Among Medicare Beneficiaries NaïVe to Renin-angiotensin System Inhibitors and Hospitalized with Heart Failure. *Circulation (New York,N.Y.), 144*(Suppl_1).https://doi.org/10.1161/circ.144.suppl_1.10738	Study published outside of the timeframe of our review
Xian Shen P, Taylor T. Schwartz MPH, Sullivan G, et al. Sacubitril/Valsartan in Medicare Alternative Payment Models. *The American Journal of Accountable Care®.* 2023;11.	Outcomes not relevant to scope
Chapman, B., Hellkamp, A. S., Thomas, L. E., Albert, N. M., Butler, J., Patterson, J. H., Hernandez, A. F., Williams, F. B., Shen, X., Spertus, J. A., Fonarow, G. C., & DeVore, A. D. (2022). Angiotensin Receptor Neprilysin Inhibition and Associated Outcomes by Race and Ethnicity in Patients With Heart Failure With Reduced Ejection Fraction: Data From CHAMP-HF. *Journal of the American Heart Association,* 11(12), e022889–e022889. https://doi.org/10.1161/JAHA.121.022889	Previously known information about sacubitril-valsartan related to efficacy
Bhatt AS, Vaduganathan M, Jena BP, et al. Comparative effectiveness of sacubitril/valsartan versus angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in patients with de novo heart failure with mildly reduced and preserved ejection fraction. *Eur J Heart Fail*. Published online April 7, 2024. doi:10.1002/ejhf.3233	Study published outside of the timeframe of our review
Spahillari A et al. (2024) Late-breaking oral presentation, *Heart Failure Association 2024*	Study published outside of the timeframe of our review
Cohen LP et al. (2024) Late-breaking oral presentation, *Heart Failure Association 2024*	Study published outside of the timeframe of our review
Basile, C., Paolillo, S., Gargiulo, P., Marzano, F., Asile, G., Parlati, A. L. M., Chirico, A., Nardi, E., Buonocore, D., Colella, A., & Perrone-Filardi, P. (2023). Sacubitril/valsartan reduces cardiac decompensation in heart failure with preserved ejection fraction: a meta-analysis. *Journal of Cardiovascular*	Previously known information about sacubitril-valsartan related to efficacy

Citation	Decision
Medicine (Hagerstown, Md.), 24(1), 44–51. https://doi.org/10.2459/JCM.0000000000001411	
Haseeb, M. T., Aslam, M. N., Avanteeka, F., Khalid, U. A. R., Ahmad, D. Z., Senaratne, M., Almaalouli, B., & Hirani, S. (2023). Comparison of Efficacy and Safety of Angiotensin Receptor-Neprilysin Inhibitors in Patients With Heart Failure With Reduced Ejection Fraction: A Meta-Analysis. *Cureus* (Palo Alto, CA), 15(3), e36392–e36392. https://doi.org/10.7759/cureus.36392	Previously known information about sacubitril-valsartan related to efficacy
Rahhal, A., Kasem, M., Orabi, B., Hamou, F., Abuyousef, S., Mahfouz, A., Alyafei, S., Shoukry, A. E., & Ahmed, E. (2023). Effectiveness of Sacubitril/Valsartan in Heart Failure with Reduced Ejection Fraction Using Real-World Data: An Updated Systematic Review and Meta-Analysis. *Current problems in cardiology*, *48*(1), 101412. https://doi.org/10.1016/j.cpcardiol.2022.101412	Previously known information about sacubitril-valsartan related to efficacy

Appendix I. Cabometyx®

Appendix Table I1. References Submitted by Exelixis

Citation	Decision
Brose MS, Robinson BG, Sherman SI, et al. Cabozantinib for previously treated radioiodine-refractory differentiated thyroid cancer: Updated results from the phase 3 COSMIC-311 trial. *Cancer*. 2022; 128(24): 4203-4212. doi:10.1002/cncr.34493	Previously known information related to efficacy
M.S. Brose, B. Keam, B. Robinson, et al. Capdevila Castillon, 604P Cabozantinib versus placebo in patients with radioiodine-refractory differentiated thyroid cancer who progressed after prior VEGFR-targeted therapy: Outcomes from COSMIC-311 by BRAF status, *Annals of Oncology*, Volume 34, Supplement 4, 2023, Pages S1708-S1709, ISSN 0923-7534, https://doi.org/10.1016/j.annonc.2023.10.319.	Previously known information related to efficacy
Capdevila, Jaume, Robinson, Bruce, Sherman, Steven, et al. Cabozantinib versus placebo in patients (pts) with radioiodine-refractory (RAIR) differentiated thyroid cancer (DTC) who progressed after prior VEGFR-targeted therapy: Outcomes in prespecified subgroups based on histology subtypes. *J Clin Oncol.* 2022;40(16_suppl):6081. doi:10.1200/JCO.2022.40.16_suppl.6081.	Previously known information related to efficacy
Wu D, Jia B, Jia M, Zhao H, Zhao H, Zhou J. Comparative efficacy and safety of systemic therapy for advanced hepatocellular carcinoma: a systematic review and network meta-analysis. *Frontiers in Oncology.* 2023;13.	Low-quality evidence
El-Khoueiry AB, Meyer T, Cheng A-L, et al. Safety and efficacy of cabozantinib for patients with advanced hepatocellular carcinoma who advanced to Child–Pugh B liver function at study week 8: a retrospective analysis of the CELESTIAL randomised controlled trial. *BMC Cancer.* 2022;22:1-10.	Previously known information related to efficacy
Storandt MH, Gile JJ, Palmer ME, Zemla TJ, Ahn DH, Bekaii-Saab TS, Jin Z, Tran NH, Mahipal A. Cabozantinib Following Immunotherapy in Patients with Advanced Hepatocellular Carcinoma. *Cancers.* 2022; 14(21):5173. https://doi.org/10.3390/cancers14215173	Low-quality evidence
Freemantle N, Mollon P, Meyer T, et al. Quality of life assessment of cabozantinib in patients with advanced hepatocellular carcinoma in the CELESTIAL trial. *European journal of cancer (1990).* 2022;168:91-98.	Low-quality evidence
Kelley RK, Miksad R, Cicin I, et al. Efficacy and safety of cabozantinib for patients with advanced hepatocellular carcinoma based on albumin-bilirubin grade. *Br J Cancer*. 2022;126(4):569-575. doi:10.1038/s41416-021-01532-5	Low-quality evidence
Solimando, A. G., Susca, N., Argentiero, A., Brunetti, O., Leone, P., De Re, V., Fasano, R., Krebs, M., Petracci, E., Azzali, I., Nanni, O., Silvestris, N., Vacca, A., & Racanelli, V. (2022). Second-line treatments for Advanced Hepatocellular Carcinoma: A Systematic Review and Bayesian Network Meta-analysis. *Clinical and Experimental Medicine,* 22(1), 65–74. https://doi.org/10.1007/s10238-021-00727-7	Low-quality evidence
Ahn, D., Park, N. J., Locker, M. C., Zhou, Z.-Y., Nie, X., Wang, T., & Yu, S. (2023). 1000P Real-world clinical outcomes of cabozantinib (cabo) as a second-line (2L) treatment for advanced hepatocellular carcinoma (aHCC). *Annals of Oncology*, *34*, S613–S613. https://doi.org/10.1016/j.annonc.2023.09.2144	Previously known information related to efficacy
Baudry, E., Naoun, N., Auclin, E., Saldana, C., Barthelemy, P., Geoffrois, L., Thibault, C., de Vries-Brilland, M., Borchiellini, D., Maillet, D., Hirsch, L., Vauchier, C., Carril-Ajuria, L., Colomba, E., Bernard-Tessier, A., Escudier, B., Flippot, R., & Albigès, L. (2023). Efficacy and safety of cabozantinib rechallenge	Intervention/comparison not relevant to scope

Citation	Decision
in metastatic renal cell carcinoma: A retrospective multicentric study. *European Journal of Cancer* (1990), 193, 113292–113292.	
McGregor, B., Geynisman, D. M., Burotto, M., Suárez, C., Bourlon, M. T., Barata, P. C., Gulati, S., Huo, S., Ejzykowicz, F., Blum, S. I., Del Tejo, V., Hamilton, M., May, J. R., Du, E. X., Wu, A., Kral, P., Ivanescu, C., Chin, A., Betts, K. A., … Porta, C. (2023). A Matching-adjusted Indirect Comparison of Nivolumab Plus Cabozantinib Versus Pembrolizumab Plus Axitinib in Patients with Advanced Renal Cell Carcinoma. *European Urology Oncology*, *6*(3), 339–348. https://doi.org/10.1016/j.euo.2023.01.012	Low-quality evidence
Loo Gan, C., Huang, J., Pan, E., Xie, W., Schmidt, A. L., Labaki, C., Meza, L., Bouchard, G., Li, H., Jackson-Spence, F., Sánchez-Ruiz, C., Powles, T., Kumar, S. A., Weise, N., Hall, W. A., Rose, B. S., Beuselinck, B., Suarez, C., Pal, S. K., … McKay, R. R. (2023). Real-world Practice Patterns and Safety of Concurrent Radiotherapy and Cabozantinib in Metastatic Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. *European Urology Oncology*, 6(2), 204–211. https://doi.org/10.1016/j.euo.2022.10.004	Intervention/comparison not relevant to scope
Navani, V., Wells, J. C., Boyne, D. J., Cheung, W. Y., Brenner, D. M., McGregor, B. A., Labaki, C., Schmidt, A. L., McKay, R. R., Meza, L., Pal, S. K., Donskov, F., Beuselinck, B., Otiato, M., Ludwig, L., Powles, T., Szabados, B. E., Choueiri, T. K., & Heng, D. Y. C. (2023). CABOSEQ: The Effectiveness of Cabozantinib in Patients With Treatment Refractory Advanced Renal Cell Carcinoma: Results From the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). *Clinical Genitourinary Cancer*, 21(1), 106.e1–106.e8. https://doi.org/10.1016/j.clgc.2022.07.008	Previously known information related to efficacy
Procopio G, Claps M, Pircher C, et al. A multicenter phase 2 single arm study of cabozantinib in patients with advanced or unresectable renal cell carcinoma pre-treated with one immune-checkpoint inhibitor: The BREAKPOINT trial (Meet-Uro trial 03). *Tumori Journal*. 2023;109(1):129-137. doi:10.1177/03008916221138881	Low-quality evidence
Choueiri, T. K., Wang, F., & Motzer, R. J. (2023). Cabozantinib plus Nivolumab and Ipilimumab in Renal-Cell Carcinoma Reply. *The New England Journal of Medicine*, 389(5), 477–478. https://doi.org/10.1056/NEJMc2306786	Intervention/comparison not relevant to scope
Thouvenin, J., Alhalabi, O., Carlo, M., Carril-Ajuria, L., Hirsch, L., Martinez-Chanza, N., Negrier, S., Campedel, L., Martini, D., Borchiellini, D., Chahoud, J., Lodi, M., Barthelemy, P., Hasanov, E., Hahn, A. W., Gil, T., Viswanathan, S. R., Bakouny, Z., Msaouel, P., … Malouf, G. G. (2022). Efficacy of Cabozantinib in Metastatic MiT Family Translocation Renal Cell Carcinomas. *The Oncologist* (Dayton, Ohio), 27(12), 1041–1047.	Previously known information related to efficacy
Santoni, M., Massari, F., Bracarda, S., Grande, E., Matrana, M. R., Rizzo, M., De Giorgi, U., Basso, U., Aurilio, G., Incorvaia, L., Martignetti, A., Molina-Cerrillo, J., Mollica, V., Rizzo, A., & Battelli, N. (2022). Cabozantinib in Patients with Advanced Renal Cell Carcinoma Primary Refractory to First-line Immunocombinations or Tyrosine Kinase Inhibitors. *European Urology Focus*, *8*(6), 1696–1702. https://doi.org/10.1016/j.euf.2022.02.004	Previously known information related to efficacy
Geynisman, D. M., Burotto, M., Porta, C., Suarez, C., Bourlon, M. T., Huo, S., Del Tejo, V., Du, E. X., Yang, X., Betts, K. A., Choueiri, T. K., & McGregor, B. (2022). Temporal Trends in Grade 3/4 Adverse Events and Associated Costs of Nivolumab Plus Cabozantinib Versus Sunitinib for Previously Untreated Advanced Renal Cell Carcinoma. *Clinical Drug Investigation*, *42*(7), 611–622. https://doi.org/10.1007/s40261-022-01170-6	Outcomes not relevant to scope

Citation	Decision
Motzer, R. J., Powles, T., Burotto, M., Escudier, B., Bourlon, M. T., Shah, A. Y., Suárez, C., Hamzaj, A., Porta, C., Hocking, C. M., Kessler, E. R., Gurney, H., Tomita, Y., Bedke, J., Zhang, J., Simsek, B., Scheffold, C., Apolo, A. B., & Choueiri, T. K. (2022). Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial. *The Lancet Oncology*, *23*(7), 888–898. https://doi.org/10.1016/S1470-2045(22)00290-X	Previously known information related to efficacy
Cella, D., Motzer, R. J., Suarez, C., Blum, S. I., Ejzykowicz, F., Hamilton, M., Wallace, J. F., Simsek, B., Zhang, J., Ivanescu, C., Apolo, A. B., & Choueiri, T. K. (2022). Patient-reported outcomes with first-line nivolumab plus cabozantinib versus sunitinib in patients with advanced renal cell carcinoma treated in CheckMate 9ER: an open-label, randomised, phase 3 trial. *The Lancet Oncology*, *23*(2), 292–303. https://doi.org/10.1016/S1470-2045(21)00693-8	Low-quality evidence
Quhal, F., Mori, K., Laukhtina, E., Rajwa, P., Mostafaei, H., Pradere, B., Shariat, S. F., & Schmidinger, M. (2022). Immunotherapy-based combinations in the first-line treatment of metastatic renal cell carcinoma with sarcomatoid features: A systematic review and network meta-analysis. *European Urology*, 81, S591–S592. https://doi.org/10.1016/S0302-2838(22)00467-5	Low-quality evidence
Nocera, L., Karakiewicz, P., Wenzel, M., Tian, Z., Shariat, S. F., Saad, F., Chun, F. K. H., Briganti, A., Kapoor, A., & Lalani, A.-K. (2022). Clinical Outcomes and Adverse Events after First-Line Treatment in Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-Analysis. *Journal of Urology*, *207*(1), 16–24. https://doi.org/10.1097/ju.0000000000002252	Low-quality evidence
Lee, C.-H., Voss, M. H., Carlo, M. I., Chen, Y.-B., Zucker, M., Knezevic, A., Lefkowitz, R. A., Shapnik, N., Dadoun, C., Reznik, E., Shah, N. J., Owens, C. N., McHugh, D. J., Aggen, D. H., Laccetti, A. L., Kotecha, R., Feldman, D. R., & Motzer, R. J. (2022). Phase II Trial of Cabozantinib Plus Nivolumab in Patients With Non-Clear-Cell Renal Cell Carcinoma and Genomic Correlates. *Journal of Clinical Oncology*, *40*(21), 2333–2341. https://doi.org/10.1200/JCO.21.01944	Indication accounts for less than 10% of use
Niewada, M., Macioch, T., Konarska, M., Mela, A., Goszczynski, A., Przekopinska, B., Rajkiewicz, K., Wysocki, P., & Krzakowski, M. (2023). Immune checkpoint inhibitors combined with tyrosine kinase inhibitors or immunotherapy for treatment-naive metastatic clear-cell renal cell carcinoma-A network meta-analysis . Focus on cabozantinib combined with nivolumab. *Frontiers in Pharmacology*, *13*, 1063178–1063178. https://doi.org/10.3389/fphar.2022.1063178	Low-quality evidence
Pal, S. K., Albiges, L., Tomczak, P., Suárez, C., Voss, M. H., de Velasco, G., Chahoud, J., Mochalova, A., Procopio, G., Mahammedi, H., Zengerling, F., Kim, C., Osawa, T., Angel, M., Gupta, S., Khan, O., Bergthold, G., Liu, B., Kalaitzidou, M., … Choueiri, T. K. (2023). Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial. *The Lancet* (British Edition), 402(10397), 185–195. https://doi.org/10.1016/S0140-6736(23)00922-4	Intervention/comparison not relevant to scope
Choueiri, T. K., McDermott, D. F., Merchan, J., Bauer, T. M., Figlin, R., Heath, E. I., Michaelson, M. D., Arrowsmith, E., D'Souza, A., Zhao, S., Roy, A., Perini, R., Vickery, D., & Tykodi, S. S. (2023). Belzutifan plus cabozantinib for patients with advanced clear cell renal cell carcinoma previously treated with immunotherapy: an open-label, single-arm, phase 2 study. *The Lancet Oncology,* 24(5), 553–562. https://doi.org/10.1016/S1470-2045(23)00097-9	Intervention/comparison not relevant to scope

Appendix J. Xeljanz®

Appendix Table J1. References Submitted by Pfizer

Citation	Decision
N/A	N/A

Appendix K. ICER Systematic Literature Review

Appendix Table K1. ICER Systematic Literature Review Results

Drug	Search Yield (+ gray literature)	References Screened in Full-Text	New Moderate to High Quality Evidence Identified
Keytruda®	98 (+ 3 references)	12	6*
Biktarvy®	56	0	0
Imfinzi®	51 (+ 2 references)	3	3*
Opdivo®	102 (+2 references)	6	5
Darzalex®	20	1	0
Tagrisso®	13	1	1*
Prolia®	41	1	0
Entresto®	46	6	0
Cabometyx®	10	0	0
Xeljanz®	28	1	0

* New evidence identified overlaps with references submitted by manufacturer

Appendix Table K2. Example of a Search Strategy in PubMed

((Keytruda OR pembrolizumab) AND (('Randomized controlled trial' OR 'randomized control trial' OR 'controlled clinical trial' OR RCT) NOT ('case report' OR 'human tissue' OR 'practice guideline' OR questionnaire OR chapter OR 'conference review' OR editorial OR letter OR note OR review OR 'short survey' OR animal OR nonhuman OR 'animal experiment')) AND 2022/01/01:2023/12/31[dp])

Appendix L. ICER Responses to Manufacturer Comments

General Evidence Response

General Evidence Response (GER): Many public comments from manufacturers focused on the evaluation and interpretation of evidence within the ICER UPI Report. The following is a combined response to such questions and comments. This should allow all stakeholders to see, in a single place, how ICER is thinking about evidence with regard to the UPI Report. Additionally, to avoid redundancy, we will respond to some individual public comments by referencing one or more of the sections below.

1. New Clinical Evidence
    a. Over a two-year period, there will virtually always be new published information about widely used medications. However, for ICER to consider such information as potentially providing support for a price increase, there must be some question that was evaluated such that there is an answer that could be counted, *a priori*, as **not** supporting a price increase had the results come out differently. For instance, if the HR for survival with a therapy has been shown to be 0.72 with four years of follow-up and at eight years of follow-up the HR is now calculated to be 0.75, there must have been a prior belief about what that HR might have been at eight years for this to be assessed as to whether it supports a price increase. Without that prior belief, we are unable to know whether this is a favorable or unfavorable result for the drug under consideration.
    b. New evidence must provide information different from what was previously believed to support a price increase. In the example above, if it were assumed that the HR for survival would persist over time, and at eight years of follow-up the HR was again 0.75, this would not be considered support. In contrast, had there been serious reasons for concern that the effect of therapy decreased substantially over time, a HR of 0.75 at eight years could provide support.
    c. High-quality evidence about a therapy does not provide high-quality evidence about the background therapy that was used in the clinical trial. For example, a new RCT of a therapy for osteoporosis that included calcium and vitamin D in both the intervention and placebo arms of the trial does not provide new evidence for calcium and vitamin D even if the new therapy is only approved when used with such background treatment.

2. Real-World Evidence (RWE)
    a. ICER applies the same evidentiary standards to RWE that it applies to all other forms of evidence and is happy to consider RWE as part of the UPI Report.
    b. High-quality RWE can be particularly valuable in assessing effectiveness of therapies and issues around adherence.
3. Quality of Observational Evidence
    a. As noted in the UPI Protocol, ICER only reviewed observational studies as part of the UPI Report process that were submitted by manufacturers.
    b. As noted in the UPI Protocol, ICER is using GRADE to assess quality of evidence. Most high-quality comparative observational studies generate only low-quality evidence using GRADE for the comparison being assessed. That is, the quality of the observational studies is only one factor that goes into assessing the quality of the evidence provided by those studies. Factors that can sometimes increase the quality of evidence from high-quality observational studies include large (or very large) magnitude of effect, dose response, or all plausible residual confounding working opposite to the effect being seen.
4. Modeling and Meta-Analyses
    a. Models and meta-analyses provide ways of interpreting and combining evidence but are not new evidence in and of themselves. Occasionally, models and meta-analyses lead to a new understanding of evidence that is substantially different from what was previously believed. Under these circumstances, models and meta-analyses could contribute as "new evidence" within the UPI Report.
    b. Economic outcomes are explicitly part of the UPI process and can count as new clinical evidence if the results are different from what had been previously believed.
5. Importance of Studies
    a. As discussed in the Introduction, ICER recognizes that studies and trials that confirm prior beliefs, increase quality of evidence, and examine new aspects of a therapy's benefits are vitally important. Nothing in the UPI Report should be taken to suggest that studies that fail to support large price increases of the most expensive drugs used in the US are somehow not worth having been performed. That is not the bar that UPI is using. The UPI Report is assessing the fairness of price increases, not the value of research.
    b. Studies evaluating the benefits of a therapy in a small population are also clearly important. ICER does not believe, however, that demonstrating new benefits in a small population justifies large price increases in the most expensive drugs.

#	Comment	Response/Integration
	Amgen	
1.	**Since Prolia's approval, Amgen has consistently invested in and generated evidence from randomized controlled trials and observational research studies to drive greater understanding on how Prolia improves patient outcomes.** Our 2024 UPI submission reflects Prolia's expanded evidence portfolio, including several real-world evidence (RWE) comparative effectiveness studies in over one million patients, collectively, and randomized controlled trials (RCTs) across more than 300 patients. Many patients are unable to participate in RCTs due to limited information about participation opportunities, strict inclusion/exclusion criteria, barriers related to access to trial sites (*e.g.,* transportation), or the extensive time commitment dictated by trial protocols. As iterated by CMS and the FDA, RWE provides unique insights about the efficacy and safety of medicines across broader and more diverse communities than what is typically included in clinical trials. These data capture use in additional patient populations and can achieve larger samples critical for assessing both safety and efficacy in patients traditionally under-represented in RCTs. Similar to the standards adhered to by prospective interventional research, real-world studies that leverage fit-for-purpose datasets can and should be held to high methodological standards to ensure replicability, validity, and generalizability.	Thank you for your comment
2.	**In this report, ICER recognizes the Curtis *et al.* (2023) study as compelling new evidence of Prolia's fracture risk reduction versus alendronate.** Curtis *et al.* exemplifies the insights that rigorous RWE can offer. It is one of the largest and most robust head-to-head studies to compare fracture risk reduction for Prolia vs. another osteoporosis treatment. Using Medicare fee-for-service claims, investigators identified a large sample of 478,651 postmenopausal women, the population most impacted by osteoporosis. Outcomes showed that Prolia reduced the risk of major osteoporotic fractures by 39%, hip fractures by 36%, nonvertebral fractures by 43%, non-hip nonvertebral fractures by 50%, and hospitalized vertebral fractures by 30% compared to alendronate. Patients remaining on Prolia also experienced greater reductions in fracture risk over five years and beyond than those taking alendronate, highlighting Prolia's long-term effectiveness – a very meaningful outcome for people living with osteoporosis.	Thank you for your comment

#	Comment	Response/Integration
	Exelixis	
1.	Exelixis would like to clarify that CABOMETYX, the tablet formulation of cabozantinib, received its first FDA approval on April 25, 2016; this was for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy. On December 19, 2017, the initial indication was expanded to encompass all patients with advanced RCC regardless of prior treatment. CABOMETYX is also approved by the FDA in combination with nivolumab as a first-line treatment for patients with advanced RCC; for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib; and for adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible. Globally, over 100,000 patients have been treated with CABOMETYX.	Thank you for your comment. We have made this correction.
2.	The data that served as the basis for the FDA approvals of CABOMETYX in the forms of kidney, liver and thyroid cancer showed impressive efficacy relative to other active therapies. However, ICER deemed the vast majority of the supportive data and publications we submitted as previously known information related to efficacy, low-quality evidence or not relevant to the scope of the assessment. Exelixis firmly believes the totality of the data and publications we provided are highly relevant to ICER'S assessment as they underscore the significant and lasting impact of CABOMETYX on treatment practices and outcomes for these life-threatening diseases. Furthermore, benefit in patient subgroups is often published concurrently with primary results and is conducted solely to demonstrate the robustness of the findings and the consistency of the benefit across a variety of clinically important subgroups. Additionally, health-related quality of life data are standardly collected in pivotal studies, and these analyses have consistently supported the risk/benefit profile of CABOMETYX. However, these data are not always publicly available at the time of initial publication, which Exelixis believes is a critical flaw in ICER's methodology.	Please see GER 1a, 1b & 5a
3.	High risks of failure are inherent to drug discovery, development and commercialization. These activities therefore require persistent commitment to scientific excellence in conjunction with an enduring sense of urgency to meaningfully translate learnings into significant advancements for patients. Since 2000, Exelixis has invested over 68% of its total revenue – more than $5.3 billion – into R&D efforts, and we continue to spend the largest portion of our revenue in this area. Exelixis' ambitious	Exelixis's investments in research and development provide helpful context, in concert with the price increase data presented in this Report on Cabometyx.

#	Comment	Response/Integration
	plans include potentially expanding the CABOMETYX label in the U.S. to improve current standards of care so that more patients may benefit from this therapy, further growth of our candidate product pipeline, acceleration of progress through robust and thoughtful clinical trials and the advancement of additional preclinical programs into early clinical development. These activities require tremendous financial resources, and at present, CABOMETYX and COMETRIQ® (the capsule formulation of cabozantinib) are the only products Exelixis sells and therefore the only source of meaningful revenue for the company.	
4.	At Exelixis, we are committed to ensuring that all patients in need can access our medicines. When Exelixis contemplates a change to the wholesale acquisition cost (WAC) for CABOMETYX, we not only consider the clinical value proposition of CABOMETYX relative to its competitor prescription drugs, but also the competitive market generally and the existing price points of competitors. The process by which we price CABOMETYX therefore reflects both the clinical and societal value of this flagship product while directly supporting our ability to discover, develop and introduce novel therapies with the potential to improve treatment outcomes and make meaningful differences in the lives of patients with cancer.	Thank you for providing this additional context.
	Gilead	
1.	**ICER's UPI report must accurately encompass the unmet needs plaguing HIV, which are closely tied to racial disparities, income inequality, stigma, and other social drivers of health.** HIV disproportionately impacts historically marginalized communities with the greatest unmet needs but the poorest access to quality care. Reducing HIV-related disparities and health inequities is a primary goal of the White House's National HIV/AIDS Strategy, and the DHHS, which recommends BIKTARVY as a first line regimen, provides special HIV treatment guidance for specific populations like older people, transgender people, and women. To push back on the institutional neglect these groups have faced, ICER must acknowledge the ample, ongoing data on BIKTARVY's efficacy, safety, limited drug-drug interactions, high barrier to the development of treatment resistant HIV, and adherence "forgiveness," all of which cater to the unique life circumstances and diversity of PWH. Appropriately appraising research derived from these communities, among others, will be critical to ending HIV and enabling equitable treatment.	Thank you. Responses to specific comments are below.

#	Comment	Response/Integration
2.	**Phase 3 RCT data in HIV/HBV coinfection:** People living with HIV experience higher rates of HBV due to shared transmission routes and risk factors.[14,15,16] Coinfection heightens the risk of liver-related mortality and morbidity among people with HIV, further increasing disease burden.[17] The ALLIANCE trial was the first of its kind, a double-blind Phase 3 RCT comparing TDF and TAF-based regimens in HIV/HBV coinfection.[18] BIKTARVY simultaneously suppressed HIV and HBV and was superior to DTG+FTC/TDF in lowering HBV DNA levels at 48 weeks. Importantly, these new data differentiate BIKTARVY as the only INSTI-based STR recommended as an initial regimen for HBV coinfection. **ICER rejected this high-quality new evidence with the rationale that HBV coinfection accounts for less than 10% of use.** This fails to recognize that HBV is likely vastly underdiagnosed, and DHHS guidelines suggest as many as 15% of PWH also have HBV.[19] ICER also fails to appreciate the significant risk of patient harm that can result from inappropriate HIV treatment selection for PWH who have HBV, which are highlighted by both FDA and clinical guideline warnings on the importance of testing for HBV in PWH, the risk of serious hepatocellular injury resulting from HBV reactivation, and the risk of developing HBV drug resistance via use of HIV regimens with inadequate HBV coverage.[19] To avoid perpetuating marginalized groups' clinical exclusion and health disparities, ICER should appropriately value new benefits for *all* patient subgroups.	We agree that the ALLIANCE trial provides important new evidence. However, earlier communication with the manufacturer, where they cited HealthVerity data, a closed claims-EMR dataset that includes 159,004 HIV patients treated with Biktarvy from 2018 to 2023 in the U.S., suggested HBV coinfection is responsible for only 6.4% of the drug's utilization. Under the UPI protocol, evidence for indications that are less than 10% of the drug's use cannot be used to support a price increase. Please see GER 5b.
3.	**Viral rebound and restart data addressing critical evidence gaps:** In the real-world care continuum, antiretroviral treatment (ART) interruption is not uncommon and can quickly result in viral rebound, which is higher among Black Americans, unhoused persons, and people on government-funded insurance like Medicaid and Medicare.[20] When PWH return to care, it is critical that treatment be quickly restarted, especially if the virus has returned to detectable levels. Clinical decision-making in this setting has been obscured by a dearth of data, since most studies are in treatment naïve or switching PWH who are *virally suppressed*. The Pozniak *et al.* 2023 study offered new insights about BIKTARVY's efficacy in achieving viral resuppression among treatment- experienced PWH with viremia.[21] The majority of participants achieved viral resuppression within 30 days of treatment with BIKTARVY, and even among those who were not resuppressed, no treatment emergent resistance occurred.[22] A second 48-week study supported BIKTARVY's ability to achieve high viral suppression for restarting participants who were retained in care, again	ICER did not exclude this study because it was a pooled analysis; it was excluded because the findings were consistent with previously known information. Additionally, this is a conference poster with limited information on how the analysis was done and how outcomes were defined. In the absence of a full publication that provides additional details about the methods, we consider this abstract to provide low-quality evidence. Please see GER 1a and 1b.

#	Comment	Response/Integration
	without viral resistance.[23] Contrary to ICER's response, efficacy in PWH restarting ART was not previously known for BIKTARVY and remains unexplored for most comparators. Penalizing pooled analyses like the Pozniak study for incorporating prior clinical trial data is an overly simplistic interpretation of "previously known." Collating expansive data collected over several years strengthens rather than weakens the findings, and the conclusions from the analysis are entirely distinct from any prior publication. Further, a pooled approach is often the only option for exploring use in smaller subgroups, such as those re-engaging in care after treatment interruption, and is one of few options that allow for evaluation of treatment effects across the broad spectrum of PWH. ICER overlooks the acute unmet need being addressed by both studies, as well as the health equity implications, since social drivers of health influence care retention.24	
4.	**Pregnancy data leading to a new FDA label expansion and clinical guidelines update:** HIV is the leading cause of death for women of reproductive age worldwide.[25] In spite of this, pregnant PWH have few verifiably safe, effective treatment options due to the scarcity of data in this difficult-to-study group, and the risk of perinatal transmission heightens the importance of achieving full viral suppression.[26] Study 5310 suggests BIKTARVY maintains a pharmacokinetic profile anticipated to suppress viral loads in pregnant PWH, and in the study, BIKTARVY was well tolerated and achieved virologic suppression in 100% of patients during pregnancy, delivery, and through 18 weeks postpartum.[27,28] No cases of virologic failure or treatment emergent resistance were observed, and 100% of neonates were HIV negative, supporting BIKTARVY's robust efficacy for both mother and child. **ICER claims this information was previously known but this is patently incorrect: prior to 2024, *even DHHS guidelines cited "insufficient data to recommend" BIKTARVY's use in pregnant PWH.*[29]** The DHHS Perinatal guidelines update on January 31, 2024 specifically states that "[b]ased on new data about pharmacokinetics in pregnancy [in Study 5310] …, bictegravir (BIC) is now recommended as an *Alternative* ARV for use in pregnancy and for people who are trying to conceive; it was previously categorized as *Insufficient Data to Recommend* use in pregnancy."[29] Study 5310's novel findings directly resulted in an expansion of BIKTARVY's FDA prescribing information and an update to DHHS guidelines, making BIKTARVY the only	We reviewed the study again and realized that this indication accounts for less than 10% of Biktarvy's use. In addition, the update to the guideline was made in January 2024, which is outside of our timeline. The rationale for excluding this has now been revised.

#	Comment	Response/Integration
	second-generation INSTI-based STR with FDA approval and in-label clinical trial data exclusively in virologically suppressed adults who are pregnant. By enabling use in a high-need population, Study 5310 had powerful implications for health equity and a profound real-world impact. A second phase 4 study reinforced BIKTARVY's pharmacokinetics, safety, and efficacy in a diverse population of pregnant PWH, including 68% Black and 11% Hispanic/Latine mother-infant pairs.[30] **Classifying this study's outcomes as *"out of scope"* overlooks clear similarities with the endpoints detailed in BIKTARVY's new FDA label,** which should serve as a guide for *"baseline safety and clinical effectiveness."* Further, it undermines valuable data in groups typically excluded from randomized clinical trials.	
5.	**Comparative data demonstrating greater adherence *"forgiveness"* versus a relevant therapeutic alternative:** Many ARTs can only maintain viral suppression if taken consistently as prescribed, but the reality is that many patients are not able to achieve perfect adherence due to challenging life circumstances such as stigma, food insecurity, or transportation barriers.[31] Adherence *"forgiveness"* is an important consideration when deciding between DHHS A1 recommended treatments for PWH.[32] Gilead's 2023 Andreatta *et al.* study is the first to examine BIKTARVY's efficacy across varying adherence levels and compare this to DTG-based three drug regimens.[33] Unlike DTG + 2 NRTIs, which had significantly lower virologic suppression among patients with low adherence, BIKTARVY was consistently effective at all levels of adherence through 144 weeks. With 31% of PWH reporting suboptimal adherence in the U.S., these findings have important implications for the patient experience given the link between adherence and social determinants of health.[34] **In contradiction to ICER's suggestion that this *"comparison is not relevant to scope,"* DTG + 2 NRTIs are included in DHHS initial treatment guidelines and should be considered within the scope of ICER's assessment.** Further, because adherence is directly tied to treatment efficacy, adherence *"forgiveness"* constitutes important new evidence of *"improved clinical or economic outcomes compared with what was previously believed."*	We have re-evaluated this study, and we agree that evidence on adherence "forgiveness" is important. However, we have substantial concerns about the analysis because there is no evidence that the adherence categories were pre-specified, as the categories defined in this analysis are different from what was evaluated in the individual studies. Additionally, the comparator arm of the meta-analysis includes different treatment regimens. In the absence of a published protocol and a full publication that provides additional details about the methods, we consider this abstract to provide low-quality evidence on adherence forgiveness. Our rationale for excluding this study has been revised accordingly.
6.	**Analyses of high-quality clinical trials prompting an FDA label expansion to include individuals with M184V/I resistance:** One of the greatest challenges to ending the HIV epidemic is the emergence of viral drug resistance.[35] Once HIV drug resistance occurs, it cannot be reversed or cured, which can jeopardize future treatment options for PWH.[36] Resistance continues to	We have re-evaluated this study. We found that data from studies 1848 and 1844 already demonstrated the efficacy and safety of switching to Biktarvy in virologically suppressed adults, including individuals with M184V/I resistance. These findings were published in 2019. As such, we consider this study to be consistent with previously known information

#	Comment	Response/Integration
	receive clinical and public health attention because it may hinder the ability of ART to suppress and block replication of the virus over the course of an individual's life.[37] Resistance may lead to individual treatment failure and, as the DHHS guidelines note, may limit future treatment options and can potentially lead to the transmission of treatment-resistant HIV within communities. This is of particular concern for older PWH, since longer lifetime use of ART expands opportunities for cumulative resistance; this higher prevalence of pre-existing mutations paired with greater comorbidities/polypharmacy substantially limits treatment options.[38,39] An ideal ART for this group will achieve robust viral suppression even in the presence of pre-existing mutations, while minimizing drug-drug interactions that could interfere with comedications. **Within ICER's UPI review timeframe, Gilead published 2 pooled analyses demonstrating BIKTARVY's efficacy in participants with M184V/I and INSTI resistance, both common among treatment experienced- PWH.**[40,41] The Sax *et al.* study was the first to pool data from clinical trial participants with M184V/I resistance and demonstrate BIKTARVY's efficacy in this specific population (which, in line with ICER's threshold, represented 10% of participants). Its novel findings even prompted major regulatory and guideline updates, which made BIKTARVY the first and only INSTI-based STR that is FDA approved and DHHS recommended for PWH who are virally suppressed with M184V/I resistance in February 2024. **ICER's dismissal of Sax *et al.*'s outcomes as *"out of scope"* seems misaligned and inconsistent given that the study's endpoints came directly from randomized controlled trials (including two of BIKTARVY's pivotal trials), which ICER has highly regarded in prior UPI reports.** Further, M184V/I is a prevalent resistance mutation that continues to proliferate. As physicians assess which treatments will be most effective in ART-experienced patients, these new data in PWH with pre-existing resistance will be meaningful to clinical decision making.	about Biktarvy.[66] Our rationale for excluding this study has been revised accordingly.
7.	**Two additional studies exclusively in PWH aged 65+ provided further resistance, efficacy, and safety data for this specific population.**[42,43] The BICOLDER study demonstrated that BIKTARVY is safe and effective in older PWH, even those with a long history of HIV infection, multiple comorbidities, and comedications. The Maggiolo *et al.* study was a phase 3b trial in	Thank you for your comments. As these results are expectedly consistent with previous findings, we considered it to be previously known information related to Biktarvy. Please see GER 1a and 1b.

#	Comment	Response/Integration
	older, virologically suppressed PWH. BIKTARVY achieved high virologic suppression through week 96, no treatment-emergent resistance, and stable CD4 counts. ICER incorrectly determined both studies to be *"previously known information."* **ICER overlooks the nuance of the BICOLDER study, which included participants with an unusually high prevalence of comorbidities and comedications – two critical factors limiting choice of ART regimen among older PWH. ICER should not have dismissed the Maggiolo *et al.* data simply because it was the final analysis: 96-week data are *more* relevant for older, ART-experienced populations that value long-term efficacy given their limited remaining treatment options.** ICER's rejection of a final analysis contradicts standard research practice in which staged read-outs are common and longer timeframes are valued as a reflection of real-world use.	
	Merck	
1.	While ICER states the UPI Report focuses on assessing price increases, not the value of research, the use of the GRADE system penalizes an important component of the body of evidence used to inform decision making. ICER included 6 references and 10 abstracts related to 6 trials that met ICER's criteria of new moderate- to high-quality evidence on the benefits and/or harms of pembrolizumab, out of 108 references provided by Merck. Among the remaining publications, ICER identified 29 publications as "Low-quality evidence," 46 as providing "previously known information," 9 as outside the timeframe for ICER's review, and 3 as providing new evidence of "no clinical improvement." These publications describe analyses that were rigorously designed for their intended purposes, and we would caution against suggestions that these analyses were insufficiently robust to assess the hypotheses they tested, the endpoints and populations they evaluated, or the timeframes they explored. Additionally, we believe many of these publications meet ICER's criteria for high quality evidence for the reasons below and suggest that ICER consider appropriate updates when finalizing the 2024 UPI Assessment report: *We note that, based on the information provided by ICER and presented in 'Appendix Table X1. References Submitted by Merck', the number of publications identified by ICER as 'Low-quality evidence' is actually 28.	Please see GER 5a and 5b. Responses to specific comments are also provided below.
2.	The publications by Long et al (2022), on the KEYNOTE-716 RCT, reported on new high-quality evidence not previously reported or known before the period of assessment, and should have been considered by ICER as new high-quality evidence. These	Pembrolizumab was approved in 2021 for the treatment of stage IIB/IIC melanoma based on the surrogate outcome of recurrence-free survival (RFS). ICER would consider a confirmation of the surrogate

#	Comment	Response/Integration
	publications report the significant benefit of pembrolizumab compared to placebo regarding distant metastasis free survival (DMFS), defined as the time from randomization to the development of any distant metastasis or death. DMFS assesses the efficacy of a treatment in preventing the development of metastatic disease, which results in substantially shortened overall survival and more negative impacts (e.g. in terms of decreased Health Related Quality of Life (HRQoL) and increased financial impact) for patients. Consequently, DMFS is a relevant outcome in the assessment of adjuvant therapies. DMFS from KEYNOTE-716 was first reported in the aforementioned publications by Long et al (2022).	outcome as new evidence. However, data presented by Long et al. (2022) is for a second surrogate outcome, distant metastasis-free survival, and there is uncertainty about what would have counted as a negative result relative to RFS. As such, we conclude that this evidence is consistent with previously known information. Please see GER 1a
3.	The publication by Dent et al (2022) relates to the patient-reported outcomes analyses of KEYNOTE-522, which is a high-quality clinical trial following GRADE's criteria. In its guidance for the 2024 UPI assessment, ICER mentions that 'Studies reporting patient-reported outcomes […] will be highly relevant.' The findings of this publication demonstrated that patients with TNBC maintain their health-related quality of life (HRQoL) when receiving pembrolizumab in combination to neoadjuvant chemotherapy, followed by pembrolizumab in the adjuvant setting (when compared to neoadjuvant chemotherapy), meaning that there is no deterioration in the HRQoL of patients when adding pembrolizumab in the perioperative setting. These findings are highly relevant and augment information about the clinical benefit seen with this regimen.	Given our prior belief about the benefit of pembrolizumab, we do not consider data showing "no worsening" in QoL reported in Dent et al. (2022) or the HRQoL studies listed below as new clinical evidence that supports a price increase. For clarity, we have revised our reason for exclusion to "consistent with previously known information." Please see GER 1a and 1b.
4.	Two publications have been excluded by ICER based on reportedly 'New evidence of no improved efficacy on quality of life'. Of note, in the KEYNOTE-426 trial, pembrolizumab + axitinib showed significantly improved OS, PFS, and ORR over sunitinib. Demonstration of similar QoL for pembrolizumab + axitinib vs. sunitinib in the publication by Bedke et al (2022) is a positive finding since it shows that improvements in clinical outcomes are achieved with pembrolizumab without deterioration of QoL for patients. Similarly, Rischin et al (2022) demonstrated that, in KEYNOTE-048, the health-related QoL of patients with recurrent or metastatic head and neck squamous cell carcinoma treated with pembrolizumab (alone or with chemotherapy) was maintained, while patients experienced significant improvements in OS, compared to outcomes of patients treated with cetuximab-chemotherapy. Again, this is a positive finding since it demonstrated that improvements in OS were achieved with pembrolizumab (alone or with chemotherapy) without a detriment in the QoL of patients treated.	Please see GER 1a and 1b (and response to comment 3).

#	Comment	Response/Integration
5.	For similar reasons, the Cescon and Khattak publications should not have been excluded by ICER as 'Low quality evidence': Cescon et al (2022) reported that the addition of pembrolizumab to chemotherapy did not result in a decrease in HRQoL in patients with previously untreated, PD-L1 positive (CPS≥10) advanced TNBC, therefore resulting in similar HRQoL and reinforcing the clinical benefit demonstrated in KEYNOTE-355 (another high-quality clinical trial as per GRADE's criteria). Khattak et al (2022) reported stable EORTC QLQ-C30 and EQ-5D HRQoL scores for both adjuvant pembrolizumab and placebo arms among patients with resected high-risk stage II melanoma based on KEYNOTE-716, another high- quality clinical trial.	Please see GER 1a and 1b (and response to comment 3).
6.	The publication by Motzer et al (2023) currently appears as excluded because the 'Study [was] published outside the timeframe of our review'. However, the publication date for this study was May 31, 2023, which is within the scope of this assessment.	We have reviewed the original article submitted, which falls within our timeframe, and have concluded that this presents previously known information about pembrolizumab related to efficacy. Our report has been updated.
7.	A real-world study assessing the health care resource utilization (HCRU) of pembrolizumab + axitinib vs. ipilimumab + nivolumab also warrants ICER's consideration. This study reported significantly higher mean medical and total (i.e. medical plus pharmacy) per patient per month (PPPM) costs, and significantly higher HCRU, with ipilimumab + nivolumab, including higher mean PPPM ambulatory visits, inpatient stays, and ICU stays. The differences were large in magnitude, supporting a higher qualification of the study quality according to the GRADE criteria.	Shah et al.2022 is an abstract that provides few details on methods. Based on the limited evidence available, we conclude that this study provides low-quality evidence on health care resource utilization. Please see GER 3b.
8.	A real-world study assessing clinical outcomes of pembrolizumab + axitinib vs. ipilimumab + nivolumab has been excluded on the basis of reporting 'Previously known information about pembrolizumab related to efficacy'. To the best of our knowledge, this is the first real-world study comparing these two treatment combinations for a US population, as direct head-to-head clinical trial are not available. Based on multivariable analysis, pembrolizumab + axitinib was associated with statistically significantly longer real-world time-on-treatment (adjusted HR -aHR-: 0.53 [95% CI, 0.40, 0.71]), real-world time-to-next-treatment (aHR: 0.60 [95% CI, 0.42, 0.87]), and real-world progression-free survival (aHR, 0.70 [95% CI, 0.49, 0.99]) compared to ipilimumab + nivolumab ($p < 0.01$).	We have re-evaluated Shah et al. 2023 and agree that we should not have excluded it as previously known information. However, Shah et al. 2023 is an observational study that provides data on surrogate outcomes. Using GRADE criteria, evidence from Shah et al. 2023 is considered low quality in the absence of specific criteria that would increase the quality of evidence.

#	Comment	Response/Integration
9.	Additionally, while we appreciate this opportunity to comment on the findings of the report prepared by ICER, we reiterate our disagreement with the inclusion of pembrolizumab as part of this assessment. ICER's methodology of identifying drugs for assessment (as part of the UPI Assessments) focuses on comparing WAC price increases with medical Consumer Price Index (mCPI) over a one-year period, and determining the corresponding budget impact associated to the price change, to identify the list of drugs with 'substantial price increases'. However, the inclusion of pembrolizumab in the 2024 ICER UPI assessment is the result of an artifact caused by the use of mCPI's, which showed extreme variability between December 2021-December 2022 and December 2022-December 2023 (the period of UPI assessment), declining from 4% to 0.5%, respectively. There are important limitations of using a short window of one year for this assessment. A longer time horizon to estimate the change in inflation provides for a more appropriate and stable measure to use as a benchmark to compare against the change in WAC price.	Thank you for this suggestion. We developed the UPI protocol (and revise it yearly) with a multistakeholder group that includes manufacturers. Those manufacturers in our multistakeholder group discussion thought that the year-over-year approach would be beneficial to drugmakers in years with high inflation. In addition, our 2% "bonus" over CPI-M is meant to provide some insulation against volatility.
10.	Additionally, there are several limitations with the use of the mCPI as the inflation point of reference, including: 1) mCPI only accounts for the medical costs to consumers, and does not include the costs to other healthcare stakeholders such as the employers, 2) the Bureau of Labor Statistics has reported difficulties estimating the prices of some of the components, such as health insurance, 3) it is not inclusive of all the medical care components, for example, it does not include Medicaid, and 4) mCPI is not the standard inflation measure used by the Centers for Medicare and Medicaid Services (CMS) when evaluating prescription drug pricing; for example, CMS uses cumulative CPI-U since the launch of a product as a component of the Medicaid statutory rebate amount, and the IRA uses current and historical benchmark CPI-U values in the determination of Medicare Part B and Part D inflation penalty calculations.	The UPI protocol was developed (and revised yearly) with a multistakeholder group that includes manufacturers. We acknowledge that there is not one perfect source for inflation estimates, but other health economists have recommended the use of medical CPI to estimate the net present value of pharmaceutical prices.
11.	Given the above, we would urge ICER to reconsider its methodology around using a single year change in inflation and mCPI as a measure of inflation for this assessment.	See response to comment 9 and 10
12.	Whether examined during the lifespan of pembrolizumab or the assessment period of 2022-2023, pembrolizumab's price increase has tracked very closely to or below inflation as measured by CPI-U or CPI-Core, which are commonly used and less variable inflation measures.	Thank you for providing this context.

#	Comment	Response/Integration
13.	We also urge ICER to carefully consider the methodology applied to the evidence base of treatments with numerous indications. A 10% use threshold per indication is not suited to products like pembrolizumab, that have a large number of indications. At present, pembrolizumab has 41 FDA-approved indications,[1] and this number may continue to grow due to ongoing investments in clinical development. While ICER's indication-specific threshold of 10% of overall product use seems designed for products with a limited number of approved uses, when product use is dispersed across a broad range of disease types and patient populations, it is unlikely that any one indication will reach this threshold. Disregarding relevant evidence in these circumstances because the 10% usage threshold has not been reached would not be appropriate, and may disincentivize innovation.	Thank you. We agree that our protocol did not anticipate drugs like pembrolizumab and other checkpoint inhibitors where there are multiple moderate to high-quality trials across multiple small indications within a review cycle. As discussed in our report, ICER has committed to flexibility when such un-anticipated circumstances arise. This flexibility was applied in evaluating these therapies.

Appendix M. Manufacturer Comments

Amgen Response to ICER's 2024 National UPI: Manufacturer Input II

Amgen appreciates the opportunity to comment on ICER's 2024 National Unsupported Price Increase (UPI): Manufacturer Input II of Prolia®. Amgen is committed to investment in innovation and making critical treatments accessible to patients through the responsible pricing of our medicines, considering both economic and social value as well as the clinical and economic burden of diseases. We are dedicated to developing ground-breaking therapies that treat and prevent diseases with poor prognoses among patient populations with large unmet medical needs, to ultimately improve patients' lives. By transforming the promise of science and biotechnology into therapies that have the power to restore health, we strive to serve patients. Amgen's medicines make a difference for those facing serious illnesses, and together with partners and stakeholders, we are working to overcome access challenges and improve care capabilities.

Since Prolia's approval, Amgen has consistently invested in and generated evidence from randomized controlled trials and observational research studies to drive greater understanding on how Prolia improves patient outcomes. Our 2024 UPI submission reflects Prolia's expanded evidence portfolio, including several real-world evidence (RWE) comparative effectiveness studies in over one million patients, collectively, and randomized controlled trials (RCTs) across more than 300 patients. Many patients are unable to participate in RCTs due to limited information about participation opportunities, strict inclusion/exclusion criteria, barriers related to access to trial sites (*e.g.,* transportation), or the extensive time commitment dictated by trial protocols.[1] As iterated by CMS and the FDA,[2,3] RWE provides unique insights about the efficacy and safety of medicines across broader and more diverse communities than what is typically included in clinical trials. These data capture use in additional patient populations and can achieve larger samples critical for assessing both safety and efficacy in patients traditionally under-represented in RCTs. Similar to the standards adhered to by prospective interventional research, real-world studies that leverage fit-for-purpose datasets can and should be held to high methodological standards to ensure replicability, validity, and generalizability.

In this report, ICER recognizes the Curtis *et al.* (2023) study as compelling new evidence of Prolia's fracture risk reduction versus alendronate. Curtis *et al.* exemplifies the insights that rigorous RWE can offer. It is one of the largest and most robust head-to-head studies to compare fracture risk reduction for Prolia vs. another osteoporosis treatment.[4,5] Using Medicare fee-for-service claims, investigators identified a large sample of 478,651 postmenopausal women, the population most impacted by osteoporosis. Outcomes showed that Prolia reduced the risk of major osteoporotic fractures by 39%, hip fractures by 36%, nonvertebral fractures by 43%, non-hip nonvertebral fractures by 50%, and hospitalized vertebral fractures by 30%[*] compared to alendronate. Patients remaining on Prolia also experienced greater reductions in fracture risk over five years and beyond than those taking alendronate, highlighting Prolia's long-term effectiveness – a very meaningful outcome for people living with osteoporosis.

[*]hospitalized vertebral fracture risk reduction was not statistically significant

The continuous need for improved outcomes is critical in a disease where one in three women worldwide, over the age of 50, will suffer a fragility fracture due to osteoporosis, and two out of three women in the U.S. with postmenopausal osteoporosis at high risk of fracture will break a bone in their lifetime.[6,7] The burden of disease will continue to grow as an aging population increases the prevalence of this devastating condition. Despite this, there is a large gap in the management and treatment of osteoporosis, especially in the post-fracture setting, with a staggering four out of five patients remaining undiagnosed and untreated after a fracture.[8] Without proper care or access to effective therapeutic options, these patients may face painful and disabling fractures in the future and are at double the risk for a subsequent fracture.[9] These areas of high unmet medical need are core areas of focus for Amgen. We continually apply our expertise, striving for solutions that improve health outcomes and dramatically improve people's lives, and Prolia is no exception.

Amgen stands behind the excellence of our products and is deeply committed to our mission of serving people living with serious disease through innovative, effective, and safe therapeutics. It is Amgen's hope that stakeholders recognize the holistic value that treatments like Prolia provide to those affected by osteoporosis and related fracture and the community at large.

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Institute for Clinical and Economic Review
2024 Unsupported Price Increase Report

Exelixis, Inc. Response to CABOMETYX® (cabozantinib) Assessment

October 25, 2024

Exelixis appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) 2024 Unsupported Price Increase (UPI) Report and its preliminary assessment of CABOMETYX® (cabozantinib). Exelixis is aligned with ICER's goal to ensure sustainable access to high-value health care for all Americans. We are also supportive of an evidence-based value assessment that employs rigorous and transparent methodologies that comprehensively evaluate the totality of available clinical data and real-world evidence for an approved treatment regimen. Exelixis respectfully disagrees with ICER's preliminary assessment that for the 12 months for which price changes were assessed, CABOMETYX had a price increase unsupported by new clinical evidence. This response focuses on inaccuracies identified in ICER's initial assessment, why we believe our submitted data and publications are supportive of the clinical value proposition for CABOMETYX, and contributing factors that validate the current pricing of our flagship treatment.

As an organization, Exelixis is driven by a singular focus to bring life-enhancing cancer treatments to patients. Throughout the past three decades, we have invested heavily in drug discovery and research and development (R&D) activities to evolve into the multi-platform cancer company we are today. We are focused on innovating both with small molecules and biotherapeutics to build a diversified portfolio of potential cancer treatments, all with the goal of bringing the next generation of medicines and regimens to patients in need. In keeping with our stated focus to develop innovative, effective, tolerable and durable treatments for patients with cancer, Exelixis has undertaken an expansive clinical development program for CABOMETYX that has led to five approvals by the U.S. Food and Drug Administration (FDA).

Exelixis would like to clarify that CABOMETYX, the tablet formulation of cabozantinib, received its first FDA approval on April 25, 2016; this was for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy. On December 19, 2017, the initial indication was expanded to encompass all patients with advanced RCC regardless of prior treatment. CABOMETYX is also approved by the FDA in combination with nivolumab as a first-line treatment for patients with advanced RCC; for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib; and for adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible. Globally, over 100,000 patients have been treated with CABOMETYX.

The data that served as the basis for the FDA approvals of CABOMETYX in the forms of kidney, liver and thyroid cancer showed impressive efficacy relative to other active therapies. However, ICER deemed the vast majority of the supportive data and publications we submitted as previously known information related to efficacy, low-quality evidence or not relevant to the scope of the assessment. Exelixis firmly believes the totality of the data and publications we provided are highly relevant to ICER'S assessment as they underscore the significant and lasting impact of CABOMETYX on treatment practices and outcomes for these life-threatening diseases. Furthermore, benefit in patient subgroups is often published concurrently with primary results and is conducted solely to demonstrate the robustness of the findings

and the consistency of the benefit across a variety of clinically important subgroups. Additionally, health-related quality of life data are standardly collected in pivotal studies, and these analyses have consistently supported the risk/benefit profile of CABOMETYX. However, these data are not always publicly available at the time of initial publication, which Exelixis believes is a critical flaw in ICER's methodology.

High risks of failure are inherent to drug discovery, development and commercialization. These activities therefore require persistent commitment to scientific excellence in conjunction with an enduring sense of urgency to meaningfully translate learnings into significant advancements for patients. Since 2000, Exelixis has invested over 68% of its total revenue – more than $5.3 billion – into R&D efforts, and we continue to spend the largest portion of our revenue in this area. Exelixis' ambitious plans include potentially expanding the CABOMETYX label in the U.S. to improve current standards of care so that more patients may benefit from this therapy, further growth of our candidate product pipeline, acceleration of progress through robust and thoughtful clinical trials and the advancement of additional preclinical programs into early clinical development. These activities require tremendous financial resources, and at present, CABOMETYX and COMETRIQ® (the capsule formulation of cabozantinib) are the only products Exelixis sells and therefore the only source of meaningful revenue for the company.

At Exelixis, we are committed to ensuring that all patients in need can access our medicines. When Exelixis contemplates a change to the wholesale acquisition cost (WAC) for CABOMETYX, we not only consider the clinical value proposition of CABOMETYX relative to its competitor prescription drugs, but also the competitive market generally and the existing price points of competitors. The process by which we price CABOMETYX therefore reflects both the clinical and societal value of this flagship product while directly supporting our ability to discover, develop and introduce novel therapies with the potential to improve treatment outcomes and make meaningful differences in the lives of patients with cancer.

# # #

October 25, 2024

Sarah K. Emond, MPP
President
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108

DELIVERED ELECTRONICALLY

RE: ICER UPI 2024 Manufacturer Submission #2

Dear Ms. Emond:

On behalf of Gilead Sciences, Inc., we would like to take this opportunity to submit our comments on ICER's preliminary Unsupported Price Increase (UPI) Assessment of BIKTARVY® (bictegravir/ emtricitabine/ tenofovir alafenamide [B/F/TAF]).

Gilead is a research-based biopharmaceutical company that discovers, develops, and commercializes innovative medicines in areas of unmet medical need. Gilead's therapeutic areas of focus include HIV/AIDS, liver diseases, cancer, and respiratory diseases. Gilead is committed to human immunodeficiency virus (HIV) elimination through consistent research and development, responsible pricing, and public health investment. We price our HIV medicines based on three key pillars: value to individuals and society, access to our life-saving medicines for people who can benefit from them, and sustainability to governments, payers and to our continued commitment to R&D. This, in turn, enables Gilead to continue investing in transformative innovations and research that we hope, one day, helps end the HIV epidemic.

As a reflection of our commitment to these goals, we have continually priced BIKTARVY far below its clinical and economic value for its role in suppressing HIV, preventing transmission, and generating savings to society. We are disappointed that ICER included BIKTARVY in its report despite the 2023 WAC price increase being consistent with WAC price increases across branded oral HIV drugs. **In addition, we have identified several areas in which ICER's report fails to consider the significance of the evidence supporting BIKTARVY and the impact it has had – and continues to have – on people with HIV (PWH)**. In this letter, we highlight how ICER's report ignores the totality of evidence illustrating the unique ways BIKTARVY is helping end the HIV epidemic.

ICER dismissed 14 new pieces of evidence in over 8,000 PWH, disregarding breakthrough evidence across historically underrepresented and underserved populations, including data that led to *two new FDA approvals and a clinical guideline update.* We are particularly concerned about ICER's assessment of critical new evidence in:

1. **HBV Co-Infection:** New randomized controlled trial (RCT) data published in *The Lancet HIV* demonstrated superiority in hepatitis B virus (HBV)/HIV coinfection.
2. **Viral Rebound and Treatment Restart:** Two new studies presented at EACS 2023 and abstract published in *Open Forum Infectious Diseases* showed BIKTARVY's success in PWH restarting ART, an understudied but common treatment scenario.
3. **Pregnant Women:** Study 5310 published in *AIDS* was the first study to provide evidence of BIKTARVY's safety and efficacy in pregnant PWH and provided crucial pharmacokinetic data in pregnancy. This led to a

2024 FDA label update making BIKTARY the only second-generation integrase strand transfer inhibitor (INSTI) based single tablet regimen (STR) with FDA approval and in-label clinical trial data exclusively in virologically suppressed adults who are pregnant.

4. **Adherence *"Forgiveness"***: Comparative evidence (abstract published in *Open Forum Infectious Diseases*) demonstrate BIKTARVY's consistent efficacy despite suboptimal adherence, which is especially valuable for communities facing barriers to consistent care.
5. **Populations with Viral Drug Resistance:** New evidence published in *AIDS* and *J Acquir Immune Defic Syndr* support BIKTARVY's efficacy in PWH with pre-existing viral drug resistance. This novel evidence helped BIKTARVY become, at the time of FDA approval, the first and only INSTI-based STR that is FDA approved and is U.S. Department of Health and Human Services (DHHS) guideline recommended for people who are virologically suppressed with M184V/I resistance.
6. **Aging Populations:** Two studies published in *J Int AIDS Soc* and *HIV Med* conducted exclusively in PWH aged 65+ provide further resistance, efficacy, and safety data for this specific population, which experiences a higher prevalence of comorbidities than the HIV population overall.

Below we further detail the role that BIKTARVY plays in helping end the HIV epidemic and explain the significance of the new BIKTARVY evidence that ICER rejected.

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There is no cure for HIV and people living with HIV face lower life expectancies, disproportionate quality of life challenges, and the continued fear that their disease will fail to respond to the drugs that are keeping them alive. HIV affects approximately 1.2 million people in the U.S., with nearly 31,800 new cases in 2022 alone.[1,2,3] It is much more than a medical diagnosis: beyond disabling physical effects and death if left untreated; it is intimately intertwined with discrimination and stigma, creating additional hardships that permeate nearly all aspects of life. As a pioneer in antiviral development, Gilead has helped transform HIV from a fatal illness to a manageable chronic condition. We introduced the first HIV STR and today 75% of people worldwide living with HIV receive a Gilead-innovated treatment regimen, including 16.5 million people in low- and middle-income countries.[4] Our focus extends beyond medicine — we take action to help remedy health inequities and break down barriers to care, forming partnerships with advocates and organizations across the country to bring about positive change.

Gilead's complete, once-a-day STR, BIKTARVY, is the #1 prescribed HIV treatment in the U.S., and has been studied in >4,400 virologically suppressed and treatment-naïve PWH of various ages, race/ethnicities, and genders in clinical trials.[5,6,7] This includes 5 years of clinical efficacy and safety data and zero cases of treatment emergent resistance, making BIKTARVY the only guideline-recommended INSTI-based STR with such data.[8] Moreover, 160 phase 4 studies of BIKTARVY in over 97,000 PWH have provided insights in specific populations such as pregnant PWH, late presenters, people who are over age 65, those with comorbidities, Black, Latine, transgender women, and those with pre-existing viral resistance.[9] Because of these robust data and its synergistic drug combination, BIKTARVY's clinical guideline recommendations encompass the broadest population of PWH with the fewest caveats for use among STRs, offering added value through simplified clinical decision-making.[10] Gilead has invested immense resources and years of world-class research to ensure BIKTARVY is not only available, but clinically proven to be safe and effective across the heterogenous population of PWH.[11] From its early-stages, BIKTARVY was developed with the intention of meeting the diverse needs and preferences of real people, and Gilead is dedicated to exploring how to further address unmet need, reduce disease burden, and improve the patient experience for as many people as possible.

ICER's UPI report must accurately encompass the unmet needs plaguing HIV, which are closely tied to racial disparities, income inequality, stigma, and other social drivers of health. HIV disproportionately

impacts historically marginalized communities with the greatest unmet needs but the poorest access to quality care. Reducing HIV-related disparities and health inequities is a primary goal of the White House's National HIV/AIDS Strategy, and the DHHS, which recommends BIKTARVY as a first line regimen, provides special HIV treatment guidance for specific populations like older people, transgender people, and women.[12,13] To push back on the institutional neglect these groups have faced, ICER must acknowledge the ample, ongoing data on BIKTARVY's efficacy, safety, limited drug-drug interactions, high barrier to the development of treatment-resistant HIV, and adherence "forgiveness," all of which cater to the unique life circumstances and diversity of PWH. Appropriately appraising research derived from these communities, among others, will be critical to ending HIV and enabling equitable treatment.

The significance of the studies submitted by Gilead and our key concerns with ICER's UPI evaluation are as follows.

1) Phase 3 RCT data in HIV/HBV coinfection: People living with HIV experience higher rates of HBV due to shared transmission routes and risk factors.[14,15,16] Coinfection heightens the risk of liver-related mortality and morbidity among people with HIV, further increasing disease burden.[17] The ALLIANCE trial was the first of its kind, a double-blind Phase 3 RCT comparing TDF and TAF-based regimens in HIV/HBV coinfection.[18] BIKTARVY simultaneously suppressed HIV and HBV and was superior to DTG+FTC/TDF in lowering HBV DNA levels at 48 weeks. Importantly, these new data differentiate BIKTARVY as the only INSTI-based STR recommended as an initial regimen for HBV coinfection. **ICER rejected this high-quality new evidence with the rationale that HBV coinfection accounts for less than 10% of use.** This fails to recognize that HBV is likely vastly underdiagnosed, and DHHS guidelines suggest as many as 15% of PWH also have HBV.[19] ICER also fails to appreciate the significant risk of patient harm that can result from inappropriate HIV treatment selection for PWH who have HBV, which are highlighted by both FDA and clinical guideline warnings on the importance of testing for HBV in PWH, the risk of serious hepatocellular injury resulting from HBV reactivation, and the risk of developing HBV drug resistance via use of HIV regimens with inadequate HBV coverage.[19] To avoid perpetuating marginalized groups' clinical exclusion and health disparities, ICER should appropriately value new benefits for *all* patient subgroups.

2) Viral rebound and restart data addressing critical evidence gaps: In the real-world care continuum, antiretroviral treatment (ART) interruption is not uncommon and can quickly result in viral rebound, which is higher among Black Americans, unhoused persons, and people on government-funded insurance like Medicaid and Medicare.[20] When PWH return to care, it is critical that treatment be quickly restarted, especially if the virus has returned to detectable levels. Clinical decision-making in this setting has been obscured by a dearth of data, since most studies are in treatment naïve or switching PWH who are *virally suppressed*. The Pozniak *et al.* 2023 study offered new insights about BIKTARVY's efficacy in achieving viral resuppression among treatment-experienced PWH with viremia.[21] The majority of participants achieved viral resuppression within 30 days of treatment with BIKTARVY, and even among those who were not resuppressed, no treatment emergent resistance occurred.[22] A second 48-week study supported BIKTARVY's ability to achieve high viral suppression for restarting participants who were retained in care, again without viral resistance.[23]

Contrary to ICER's response, efficacy in PWH restarting ART *was not previously known for BIKTARVY and remains unexplored for most comparators*. Penalizing pooled analyses like the Pozniak study for incorporating prior clinical trial data is an overly simplistic interpretation of "previously known." Collating expansive data collected over several years strengthens rather than weakens the findings, and the conclusions from the analysis are entirely distinct from any prior publication. Further, a pooled approach is often the only option for exploring use in smaller subgroups, such as those re-engaging in care after treatment interruption, and is one of few options that allow for evaluation of treatment effects across the broad spectrum of PWH. ICER

overlooks the acute unmet need being addressed by both studies, as well as the health equity implications, since social drivers of health influence care retention.[24]

3) Pregnancy data leading to a new FDA label expansion and clinical guidelines update: HIV is the leading cause of death for women of reproductive age worldwide.[25] In spite of this, pregnant PWH have few verifiably safe, effective treatment options due to the scarcity of data in this difficult-to-study group, and the risk of perinatal transmission heightens the importance of achieving full viral suppression.[26] Study 5310 suggests BIKTARVY maintains a pharmacokinetic profile anticipated to suppress viral loads in pregnant PWH, and in the study, BIKTARVY was well tolerated and achieved virologic suppression in 100% of patients during pregnancy, delivery, and through 18 weeks postpartum.[27,28] No cases of virologic failure or treatment emergent resistance were observed, and 100% of neonates were HIV negative, supporting BIKTARVY's robust efficacy for both mother and child.

ICER claims this information was previously known but this is patently incorrect: prior to 2024, *even DHHS guidelines cited "insufficient data to recommend" BIKTARVY's use in pregnant PWH.*[29] The DHHS Perinatal guidelines update on January 31, 2024 specifically states that "[b]ased on new data about pharmacokinetics in pregnancy [in Study 5310] …, bictegravir (BIC) is now recommended as an *Alternative* ARV for use in pregnancy and for people who are trying to conceive; it was previously categorized as *Insufficient Data to Recommend* use in pregnancy."[29] Study 5310's novel findings directly resulted in an expansion of BIKTARVY's FDA prescribing information and an update to DHHS guidelines, making BIKTARVY the only second-generation INSTI-based STR with FDA approval and in-label clinical trial data exclusively in virologically suppressed adults who are pregnant. By enabling use in a high-need population, Study 5310 had powerful implications for health equity and a profound real-world impact. A second phase 4 study reinforced BIKTARVY's pharmacokinetics, safety, and efficacy in a diverse population of pregnant PWH, including 68% Black and 11% Hispanic/Latine mother-infant pairs.[30] **Classifying this study's outcomes as *"out of scope"* overlooks clear similarities with the endpoints detailed in BIKTARVY's new FDA label,** which should serve as a guide for *"baseline safety and clinical effectiveness."* Further, it undermines valuable data in groups typically excluded from randomized clinical trials.

4) Comparative data demonstrating greater adherence *"forgiveness"* versus a relevant therapeutic alternative: Many ARTs can only maintain viral suppression if taken consistently as prescribed, but the reality is that many patients are not able to achieve perfect adherence due to challenging life circumstances such as stigma, food insecurity, or transportation barriers.[31] Adherence *"forgiveness"* is an important consideration when deciding between DHHS A1 recommended treatments for PWH.[32] Gilead's 2023 Andreatta *et al.* study is the first to examine BIKTARVY's efficacy across varying adherence levels and compare this to DTG-based three drug regimens.[33] Unlike DTG + 2 NRTIs, which had significantly lower virologic suppression among patients with low adherence, BIKTARVY was consistently effective at all levels of adherence through 144 weeks. With 31% of PWH reporting suboptimal adherence in the U.S., these findings have important implications for the patient experience given the link between adherence and social determinants of health.[34] **In contradiction to ICER's suggestion that this *"comparison is not relevant to scope,"* DTG + 2 NRTIs are included in DHHS initial treatment guidelines and should be considered within the scope of ICER's assessment.** Further, because adherence is directly tied to treatment efficacy, adherence *"forgiveness"* constitutes important new evidence of *"improved clinical or economic outcomes compared with what was previously believed."*

5) Analyses of high-quality clinical trials prompting an FDA label expansion to include individuals with M184V/I resistance: One of the greatest challenges to ending the HIV epidemic is the emergence of viral drug resistance.[35] Once HIV drug resistance occurs, it cannot be reversed or cured, which can jeopardize future treatment options for PWH.[36] Resistance continues to receive clinical and public health attention because it may hinder the ability of ART to suppress and block replication of the virus over the course of an individual's life.[37]

Resistance may lead to individual treatment failure and, as the DHHS guidelines note, may limit future treatment options and can potentially lead to the transmission of treatment-resistant HIV within communities. This is of particular concern for older PWH, since longer lifetime use of ART expands opportunities for cumulative resistance; this higher prevalence of pre-existing mutations paired with greater comorbidities/polypharmacy substantially limits treatment options.[38,39] An ideal ART for this group will achieve robust viral suppression even in the presence of pre-existing mutations, while minimizing drug-drug interactions that could interfere with comedications.

Within ICER's UPI review timeframe, Gilead published 2 pooled analyses demonstrating BIKTARVY's efficacy in participants with M184V/I and INSTI resistance, both common among treatment experienced-PWH.[40,41] The Sax *et al.* study was the first to pool data from clinical trial participants with M184V/I resistance and demonstrate BIKTARVY's efficacy in this specific population (which, in line with ICER's threshold, represented 10% of participants). Its novel findings even prompted major regulatory and guideline updates, which made BIKTARVY the first and only INSTI-based STR that is FDA approved and DHHS recommended for PWH who are virally suppressed with M184V/I resistance in February 2024. **ICER's dismissal of Sax *et al.*'s outcomes as *"out of scope"* seems misaligned and inconsistent given that the study's endpoints came directly from randomized controlled trials (including two of BIKTARVY's pivotal trials), which ICER has highly regarded in prior UPI reports.** Further, M184V/I is a prevalent resistance mutation that continues to proliferate. As physicians assess which treatments will be most effective in ART-experienced patients, these new data in PWH with pre-existing resistance will be meaningful to clinical decision making.

6) Two additional studies exclusively in PWH aged 65+ provided further resistance, efficacy, and safety data for this specific population.[42,43] The BICOLDER study demonstrated that BIKTARVY is safe and effective in older PWH, even those with a long history of HIV infection, multiple comorbidities, and comedications. The Maggiolo *et al.* study was a phase 3b trial in older, virologically suppressed PWH. BIKTARVY achieved high virologic suppression through week 96, no treatment-emergent resistance, and stable CD4 counts. ICER incorrectly determined both studies to be *"previously known information."* **ICER overlooks the nuance of the BICOLDER study, which included participants with an unusually high prevalence of comorbidities and comedications – two critical factors limiting choice of ART regimen among older PWH. ICER should not have dismissed the Maggiolo *et al.* data simply because it was the final analysis: 96-week data are *more* relevant for older, ART-experienced populations that value long-term efficacy given their limited remaining treatment options.** ICER's rejection of a final analysis contradicts standard research practice in which staged read-outs are common and longer timeframes are valued as a reflection of real-world use.

In conclusion, ICER's exclusion of the above evidence undermines its own report. Gilead is confident in the value of BIKTARVY's new clinical evidence and continues to invest in research that addresses unmet needs, reduces health disparities, and improves the patient experience for PWH. This research will be critical to reaching the CDC's goals of viral suppression among 95% of PWH and a 75% reduction in new HIV infections by 2025.[44] Ending the HIV epidemic remains at the heart of Gilead's mission, and we encourage ICER to support this effort by revising its evaluation of these studies to capture the realities of complex diseases like HIV.

Sincerely,

Rekha Ramesh
Vice President, US Policy

Betty Chiang
Vice President, US Medical Affairs

APPENDIX – Summary of Gilead's Response to ICER

New Evidence	ICER's Rationale	Gilead's Response
ALLIANCE Trial Avihingsanon A, Lu H, Leon CL et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 and hepatitis B coinfection (ALLIANCE): a double-blind, multicentre, randomised controlled, phase 3 non-inferiority trial. Lancet HIV. 2023 Oct;10(10):e640-e652. Link	Indication accounts for less than 10% of use	• HBV is likely vastly underdiagnosed. • DHHS guidelines suggest as many as 15% of PWH also have HBV.[xlv] • ICER's "10% of use" criterium risks arbitrarily excluding critical subpopulations.
Pozniak *et al.* 2023 Pozniak A, Orkin C, Maggiolo F, *et al.* Restarting Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) after virologic rebound: A pooled analysis of studies in people with HIV-1. Presented at: European AIDS Conference; October 18-21, 2023; Warsaw, Poland. Link	Previously known information about bictegravir/emtricitabine /tenofovir alafenamide related to efficacy	• Pooled analyses should not be considered "previously known" simply because they incorporate prior clinical trial data. Collating expansive data collected over several years strengthens rather than weakens the findings, and the conclusions from the analysis are entirely distinct from any prior publication. • A pooled approach is also often the only option for exploring use in smaller subgroups, such as those re-engaging in care after treatment interruption.
Study 5310 Zhang H, Hindman JT, Lin L, *et al.* Pharmacokinetics, safety, and efficacy of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in virologically suppressed pregnant women with HIV. Presented at International AIDS Society; July 23-26, 2023; Brisbane, Australia. Link	Previously known information about bictegravir/emtricitabine /tenofovir alafenamide related to efficacy	• Prior to Study 5310, DHHS perinatal guidelines cited "insufficient data to recommend" BIKTARVY's use in pregnant PWH; the January 2024 guidelines update specifically cites the "new data on pharmacokinetics" for its move to recommend BIKTARVY in pregnant PWH, making clear this evidence was new and meaningful. • Study 5310's novel findings directly resulted in an expansion of BIKTARVY's FDA prescribing information and an update to DHHS guidelines.
Powis *et al.* 2023 Powis KM, Pinilla M, Bergam L, *et al.* Pharmacokinetics and	Outcomes not relevant to scope	• This study's outcomes have clear similarities with endpoints detailed in BIKTARVY's new FDA label. These should not be considered "out of scope" since ICER regards prescribing

Virologic Outcomes of Bictegravir in Pregnancy and Postpartum. Presented at: IMPAACT; February 21, 2023. Link		information as a source of "baseline safety and clinical effectiveness." • This study's diverse sample makes it especially valuable for assessing outcomes in pregnant PWH who are typically excluded from clinical trials.
Sax *et al.* 2022 **Sax PE, Andreatta K, Molina JM, *et al.* High efficacy of switching to bictegravir/emtricitabine/tenofovir alafenamide in people with suppressed HIV and preexisting M184V/I. *AIDS*. 2022;36(11):1511-1520.** Link	Outcomes not relevant to scope	• Endpoints came directly from clinical trials, which ICER has highly regarded in prior UPI reports. • M184V/I is a prevalent resistance mutation that continues to proliferate. • Outcomes reported in this study are helpful for clinical decision-making.
Andreatta *et al.* 2023 Andreatta K, Sax PE, Wohl DA, D'Antoni ML, Huang H, Hindman J, Callebaut C, Martin H. 1561. Efficacy of Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) Versus Dolutegravir (DTG)-Based 3-Drug Regimens in Adults With HIV Who Have Suboptimal Antiretroviral Adherence. *Open Forum Infect Dis. 2023* Nov 27;10(Suppl 2):ofad500.1396. doi: 10.1093/ofid/ofad500.1396. Link	Comparison is not relevant to scope	• BIKTARVY was compared to DTG + 2 NRTIs; such regimens are included in DHHS initial treatment guidelines and should be considered within the scope of ICER's assessment. • Adherence is directly tied to treatment efficacy, so adherence "forgiveness" constitutes important new evidence of "improved clinical or economic outcomes compared with what was previously believed."
BICOLDER Allavena C, Joly V, Assoumou L, *et al.* Switch to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in people living with HIV aged 65 years or older: W24 results of the BICOLDER study – IMEA 057. *J Int Aids Soc*. 2022 Oct; 25(Suppl 6):e26009. Link	Previously known information about bictegravir/emtricitabine /tenofovir alafenamide, related to efficacy	• BICOLDER was unique from prior studies due to the high prevalence of comorbidities and comedication use among participants. • These are important factors since drug-drug interactions can determine which ART are safe and effective for older PWH.

Maggiolo *et al.* 2023 Maggiolo F, Rizzardini G, Molina JM, *et al.* Bictegravir/emtricitabine/tenofovir alafenamide in older individuals with HIV: Results of a 96-week, phase 3b, open-label, switch trial in virologically suppressed people ≥65 years of age. *HIV Med*. 2023;24(1):27-36. doi:10.1111/hiv.13319. Link	Previously known information about bictegravir/emtricitabine /tenofovir alafenamide related to efficacy	• 96-week data like Maggiolo *et al.* should not be dismissed as "previously known" simply because earlier analyses, *e.g.,* a 24-week readout, are available; this mistakenly assumes that long-term data and short-term data will be the same. • Open-label data are uniquely valuable in HIV since they better reflect time on treatment in the real-world. • Long-term data are also more relevant for older, ART-experienced populations; for this group, a potentially higher prevalence of resistance mutations and comorbidities limits their remaining treatment options, making ART with long-term efficacy especially valuable.

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October 22, 2024

Sarah K. Emond, MPP
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RE: ICER: Draft UPI Assessment for Review/Comment

Dear Mrs. Emond:

We appreciate the opportunity to comment on the draft report for the assessment of pembrolizumab's price increase in 2023 as part of ICER's 2024 UPI Assessment, in which ICER has recognized the comprehensive, high quality evidence published for pembrolizumab during the assessment period, across several tumor types, and has concluded that 'pembrolizumab (Keytruda®) had a price increase with new clinical evidence'.

Since the launch of pembrolizumab a decade ago, Merck has made immense progress in how cancer is diagnosed and treated. In the US, pembrolizumab has been approved by the FDA for 41 indications across 18 cancer types plus two tumor agnostic approvals in MSI-H and TMB-H.[1] In 2022 and 2023 alone, there were six new oncology indications approved by the FDA for pembrolizumab for certain cancers (one for MSI-H/dMMR advanced endometrial cancer, two in earlier stages of non-small cell lung cancer -NSCLC-, one in metastatic bladder cancer, one in HER2 negative gastric cancer, and one in biliary tract cancer) and one indication was fully approved in December 15, 2023 (for pembrolizumab in combination with enfortumab vedotin, for the treatment of adult patients with locally advanced or metastatic urothelial cancer, after accelerated approval of this combination on April 3, 2023 for patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin-containing chemotherapy).

While ICER states the UPI Report focuses on assessing price increases, not the value of research,[2] the use of the GRADE system penalizes an important component of the body of evidence used to inform decision making. ICER included 6 references and 10 abstracts related to 6 trials that met ICER's criteria of new moderate- to high-quality evidence on the benefits and/or harms of pembrolizumab, out of 108 references provided by Merck. Among the remaining publications, ICER identified 29 publications as "Low-quality evidence,"* 46 as providing "previously known information," 9 as outside the timeframe for ICER's review, and 3 as providing new evidence of "no clinical improvement." These publications describe analyses that were rigorously designed for their intended purposes, and we would caution against suggestions that these analyses were insufficiently robust to assess the hypotheses they tested, the endpoints and populations they evaluated, or the timeframes they explored. Additionally, we believe many

* We note that, based on the information provided by ICER and presented in 'Appendix Table X1. References Submitted by Merck', the number of publications identified by ICER as 'Low-quality evidence' is actually 28.

of these publications meet ICER's criteria for high quality evidence for the reasons below and suggest that ICER consider appropriate updates when finalizing the 2024 UPI Assessment report:

- The publications by Long et al (2022),[3,4] on the KEYNOTE-716 RCT, reported on new high-quality evidence not previously reported or known before the period of assessment, and should have been considered by ICER as new high-quality evidence. These publications report the significant benefit of pembrolizumab compared to placebo regarding distant metastasis free survival (DMFS), defined as the time from randomization to the development of any distant metastasis or death. DMFS assesses the efficacy of a treatment in preventing the development of metastatic disease, which results in substantially shortened overall survival and more negative impacts (e.g. in terms of decreased Health Related Quality of Life (HRQoL) and increased financial impact) for patients. Consequently, DMFS is a relevant outcome in the assessment of adjuvant therapies. DMFS from KEYNOTE-716 was first reported in the aforementioned publications by Long et al (2022).[3,4]
- The publication by Dent et al (2022)[5] relates to the patient-reported outcomes analyses of KEYNOTE-522, which is a high-quality clinical trial following GRADE's criteria. In its guidance for the 2024 UPI assessment, ICER mentions that 'Studies reporting patient-reported outcomes […] will be highly relevant.' The findings of this publication demonstrated that patients with TNBC maintain their health-related quality of life (HRQoL) when receiving pembrolizumab in combination to neoadjuvant chemotherapy, followed by pembrolizumab in the adjuvant setting (when compared to neoadjuvant chemotherapy), meaning that there is no deterioration in the HRQoL of patients when adding pembrolizumab in the perioperative setting. These findings are highly relevant and augment information about the clinical benefit seen with this regimen.
- Two publications have been excluded by ICER based on reportedly 'New evidence of no improved efficacy on quality of life'.[6,7] Of note, in the KEYNOTE-426 trial, pembrolizumab + axitinib showed significantly improved OS, PFS, and ORR over sunitinib. Demonstration of similar QoL for pembrolizumab + axitinib vs. sunitinib in the publication by Bedke et al (2022) is a positive finding since it shows that improvements in clinical outcomes are achieved with pembrolizumab without deterioration of QoL for patients.[6] Similarly, Rischin et al (2022)[7] demonstrated that, in KEYNOTE-048, the health-related QoL of patients with recurrent or metastatic head and neck squamous cell carcinoma treated with pembrolizumab (alone or with chemotherapy) was maintained, while patients experienced significant improvements in OS, compared to outcomes of patients treated with cetuximab-chemotherapy. Again, this is a positive finding since it demonstrated that improvements in OS were achieved with pembrolizumab (alone or with chemotherapy) without a detriment in the QoL of patients treated.
- For similar reasons, the Cescon and Khattak publications should not have been excluded by ICER as 'Low quality evidence':
    - Cescon et al (2022)[8] reported that the addition of pembrolizumab to chemotherapy did not result in a decrease in HRQoL in patients with previously

untreated, PD-L1 positive (CPS≥10) advanced TNBC, therefore resulting in similar HRQoL and reinforcing the clinical benefit demonstrated in KEYNOTE-355 (another high-quality clinical trial as per GRADE's criteria).
    - Khattak et al (2022)[9] reported stable EORTC QLQ-C30 and EQ-5D HRQoL scores for both adjuvant pembrolizumab and placebo arms among patients with resected high-risk stage II melanoma based on KEYNOTE-716, another high-quality clinical trial.
- The publication by Motzer et al (2023)[10] currently appears as excluded because the 'Study [was] published outside the timeframe of our review'. However, the publication date for this study was May 31, 2023, which is within the scope of this assessment.
- A real-world study assessing the health care resource utilization (HCRU) of pembrolizumab + axitinib vs. ipilimumab + nivolumab[11] also warrants ICER's consideration. This study reported significantly higher mean medical and total (i.e. medical plus pharmacy) per patient per month (PPPM) costs, and significantly higher HCRU, with ipilimumab + nivolumab, including higher mean PPPM ambulatory visits, inpatient stays, and ICU stays. The differences were large in magnitude, supporting a higher qualification of the study quality according to the GRADE criteria.[12,13]
- A real-world study assessing clinical outcomes of pembrolizumab + axitinib vs. ipilimumab + nivolumab[14] has been excluded on the basis of reporting 'Previously known information about pembrolizumab related to efficacy'. To the best of our knowledge, this is the first real-world study comparing these two treatment combinations for a US population, as direct head-to-head clinical trial are not available. Based on multivariable analysis, pembrolizumab + axitinib was associated with statistically significantly longer real-world time-on-treatment (adjusted HR -aHR-: 0.53 [95% CI, 0.40, 0.71]), real-world time-to-next-treatment (aHR: 0.60 [95% CI, 0.42, 0.87]), and real-world progression-free survival (aHR, 0.70 [95% CI, 0.49, 0.99]) compared to ipilimumab + nivolumab ($p < 0.01$).

Additionally, while we appreciate this opportunity to comment on the findings of the report prepared by ICER, we reiterate our disagreement with the inclusion of pembrolizumab as part of this assessment.

- ICER's methodology of identifying drugs for assessment (as part of the UPI Assessments) focuses on comparing WAC price increases with medical Consumer Price Index (mCPI) over a one-year period, and determining the corresponding budget impact associated to the price change, to identify the list of drugs with 'substantial price increases'.[15] However, the inclusion of pembrolizumab in the 2024 ICER UPI assessment is the result of an artifact caused by the use of mCPI's, which showed extreme variability between December 2021-December 2022 and December 2022-December 2023 (the period of UPI assessment), declining from 4% to 0.5%, respectively.[16] There are important limitations of using a short window of one year for this assessment. A longer time horizon to estimate the change in inflation provides for a more appropriate and stable measure to use as a benchmark to compare against the change in WAC price.

- Additionally, there are several limitations with the use of the mCPI as the inflation point of reference, including: 1) mCPI only accounts for the medical costs to consumers, and does not include the costs to other healthcare stakeholders such as the employers,[17] 2) the Bureau of Labor Statistics has reported difficulties estimating the prices of some of the components, such as health insurance,[17] 3) it is not inclusive of all the medical care components, for example, it does not include Medicaid,[17] and 4) mCPI is not the standard inflation measure used by the Centers for Medicare and Medicaid Services (CMS) when evaluating prescription drug pricing; for example, CMS uses cumulative CPI-U since the launch of a product as a component of the Medicaid statutory rebate amount, and the IRA uses current and historical benchmark CPI-U values in the determination of Medicare Part B and Part D inflation penalty calculations.
- Given the above, we would urge ICER to reconsider its methodology around using a single year change in inflation and mCPI as a measure of inflation for this assessment.
- Whether examined during the lifespan of pembrolizumab or the assessment period of 2022-2023, pembrolizumab's price increase has tracked very closely to or below inflation as measured by CPI-U or CPI-Core, which are commonly used and less variable inflation measures.

We also urge ICER to carefully consider the methodology applied to the evidence base of treatments with numerous indications.

- A 10% use threshold per indication is not suited to products like pembrolizumab, that have a large number of indications. At present, pembrolizumab has 41 FDA-approved indications,[1] and this number may continue to grow due to ongoing investments in clinical development. While ICER's indication-specific threshold of 10% of overall product use seems designed for products with a limited number of approved uses, when product use is dispersed across a broad range of disease types and patient populations, it is unlikely that any one indication will reach this threshold. Disregarding relevant evidence in these circumstances because the 10% usage threshold has not been reached would not be appropriate, and may disincentivize innovation.

Thank you again for this opportunity to provide input. If you have any questions, please feel free to contact me.

Sincerely,

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