California Unsupported Price Increase Report

An Evaluation of Drug Price Increases During 2020 in California

October 20, 2022

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About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 24% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/pharmacy benefit managers and life science companies. There are no life science companies relevant to this report who participate in this program. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/.

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.

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List of Acronyms and Abbreviations Used in this Report

ALL	Acute lymphoblastic leukemia
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CPI	Consumer Price Index
CR	Complete response
FDA	Food and Drug Administration
GER	General Evidence Response
HR	Hazard ratio
ICER	Institute for Clinical and Economic Review
N	Total number
n	Number
N/A	Not applicable
OR	Overall response
PFS	Progression-free survival
Ph+	Philadelphia chromosome
RCT	Randomized controlled trial
UPI	Unsupported price increase
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, until recently there has been no systematic initiative to determine whether major 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 at the national level assessing whether new clinical evidence or other information has appeared that could support the price increases of drugs, and this report is the first to conduct a similar analysis at the state level.

ICER has received funding from the California Health Care Foundation to produce a state-specific report for California. In 2017, California passed SB-17, a drug transparency law requiring manufacturers to report increases to prescription drugs' wholesale acquisition cost (WAC).[2] In this report, ICER leveraged the 2020 SB-17 reports on brand and specialty drugs with the most significant year-over-year spending increases to evaluate whether there is new evidence that could justify any underlying price increase contributing to the increase in spending. Because the SB-17 reports are published approximately 11 months after the time period they highlight, this California UPI report is being published *after* the national UPI report that examines the same period of price increases.

ICER's review started with two publicly available lists of drugs with the highest year-over-year increase in total spending in California: 1) the top 25 specialty drugs; and 2) the top 25 branded drugs. These lists do not provide information on the actual increase in total spending due to the individual drugs. From these lists, we eliminated drugs that had net price year-over-year increases that were less than 2% more than the medical Consumer Price Index (CPI) based on data from SSR Health LLC, an independent investment research firm; medical CPI was 4.11% in 2020. We then ranked drugs by their level of year-over-year absolute increase in spending in California and selected up to five drugs from each list for further evaluation. If there were fewer than five drugs with net price increases at this level on one of the two lists, additional drugs could be selected from the other list, up to a maximum of 10 drugs for review. Through this approach, we developed a set of 10 drugs for review comprising six specialty drugs and four branded drugs. A detailed description of the entire California UPI Protocol is available separately.

We then asked the manufacturers of these 10 drugs for early input as to whether our figures on net price, if available, were correct. After applying manufacturer corrections, we had a remaining list of three drugs where the increase in net price was either more than 2% above medical CPI or where the change in net price was uncertain. One of the 10 drugs was removed from the final list due to a

clerical error on our part. At the time the error was discovered, the manufacturer would not have had adequate time to respond with potential corrections to our estimate of net price change.

Assessments were then performed on these three drugs to determine whether, in the two years prior to the price increase (2019-2020), there was new clinical evidence representing "moderate/high-quality new evidence or analyses that demonstrates a substantial improvement in net health benefit compared with what was previously believed." Drugs judged to have evidence that met this standard were reported as having price increases "with new clinical evidence." To arrive at this judgment, ICER accepted and reviewed submissions from manufacturers and 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 shows the results of the evidence assessments for the three drugs included in the report. All three were judged to have price increases unsupported by new clinical evidence. All three drugs had WAC increases above medical CPI but below medical CPI plus 2%. Manufacturers did not provide net price estimates for any of these three drugs, and for two of the drugs SSR Health, LLC did not have reliable net price estimates; for one drug, net price was estimated to have increased more than medical CPI plus 2%. Although we are more uncertain about the net price changes of two of these drugs, we note that the manufacturers could have had these drugs removed from the report if they notified ICER that the net price increases were less than CPI plus 2%.

Table ES1. Drugs Selected for Assessment

Drug (Specialty or Brand)	2019 to 2020 Percentage Change		California Increased Spending Ranking
	WAC	Net Price	
Drugs with Price Increases Unsupported by New Clinical Evidence			
Revlimid® (Specialty)	5.9%	Unknown*	14 (Specialty)
Sprycel® (Specialty)	6.0%	9.6%	22 (Specialty)
Emgality® (Brand)	4.6%	Unknown*	6 (Brand)

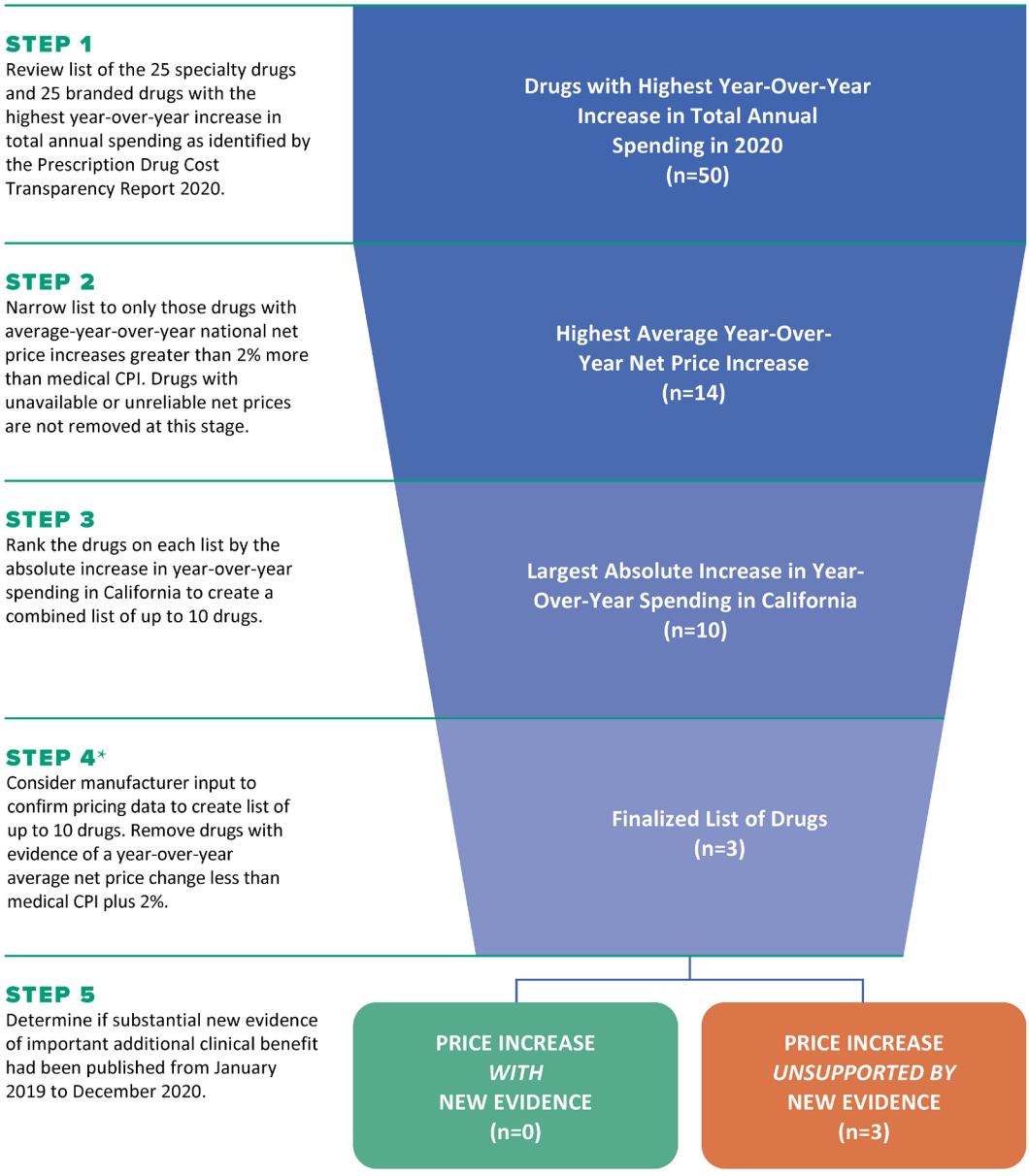
WAC: wholesale acquisition cost

*Either not reported or no reliable pricing data available from SSR Health.

The SB-17 report looks at the most frequently prescribed drugs, the most costly drugs by total annual plan spending, and the drugs with the highest year-over-year increase in total annual plan spending in California. Because information on volume and changes in net price in California is not available, the increase in spending for many drugs may be primarily, or even entirely, due to increased volume rather than increases in net price. Thus, drugs with increased utilization can be listed by the state of California even without significant increases in list or net pricing.

California's drug price transparency laws are an important first step in examining price increases. Under SB-17, however, the year-over-year changes in net drug prices in California are not reported. Laws focusing on increases in total drug spending risk identifying drugs without significant price increases that are being prescribed more often due to many possible factors. States seeking to identify drugs for which increases in spending may be inappropriate should incorporate a requirement for reporting of net price increases at the state level across all payers.

Figure ES1. Drug Selection Process



*One of the 10 drugs was removed from the final list due to a clerical error as discussed in the text.

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.

In 2019, with funding from Arnold Ventures, we launched a new line of annual ICER reports, named Unsupported Price Increase (UPI) reports, to evaluate whether drugs with substantial price increases at the national level have recent high-quality evidence that could potentially justify these increases. To guide our work, we receive input from a multi-stakeholder advisory group comprised of representatives from patient advocacy organizations, drugmakers, and insurers.

As a complement to the national UPI report, ICER has received funding from the California Health Care Foundation to produce a state-specific report for California. In 2017, California passed SB-17, a drug transparency law. In this report, ICER leveraged the annual SB-17 reports on brand and specialty drugs with the most significant year-over-year spending increases to evaluate whether there is new evidence that could justify any increase in price. Because the SB-17 reports are published approximately 11 months after the time period they highlight, the California UPI report is published *after* the national UPI report that examines the same period of price increases. By evaluating whether those major drugs with spending increases that also had substantial net price increases had supporting new clinical evidence, ICER hopes to aid the state of California in determining whether unsupported price increases are an important driving factor behind increases in state drug spending.

ICER does not have the capacity to perform full economic analyses on the large number of therapies that will be subject to analysis as part of this report process, 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, neither the national nor the state UPI reports is intended to determine whether a price increase for a drug is fully justified by new clinical evidence or meets an ICER health-benefit based price benchmark. Instead, we frame our analyses as determining whether substantial new evidence exists that *could* justify price increases.

2. Selection of Drugs to Review

As described in greater detail below, the process for ICER's review started with two publicly available lists of drugs ranking those with the highest year-over-year increase in total spending in California: 1) the top 25 specialty drugs; and 2) the top 25 branded drugs. These lists do not provide information on the actual increase in total spending due to the individual drugs. From these lists, we eliminated drugs that appeared to have had net price year-over-year increases that are less than 2% higher than the rate of inflation for that year in the medical Consumer Price Index (CPI). Starting at the top of the list of drugs with the highest increase in spending, we then selected up to five drugs from each list for review. If there were fewer than five drugs on either list with net price increases >2% above the medical CPI, additional drugs could be selected from the other list, up to a maximum of 10 drugs for review. Further details on the process are provided below.

2.1. Creating the List of Drugs with Price Increases

ICER used lists from the 2020 California SB-17 report showing the 25 specialty drugs and the 25 branded drugs with the highest year-over-year increases in total spending in (Table 2.1).

We then used information from SSR Health LLC, an independent investment research firm, to examine net price increases for all the drugs on these lists and we removed any drugs that had an average year-over-year **national** net price increase that was less than 2% more than the medical CPI. This was calculated as the difference between the average medical CPI using unadjusted rates, which was 4.11% for 2020 relative to 2019. The medical CPI is one of eight major components of the CPI recorded and reported by the United States 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).[5] Our intent in choosing the overall medical CPI and not its subcomponents is to reflect inflation in drug prices relative to inflation in the overall price of medical care.

This step removed 36 drugs from the list, leaving 14 drugs with increases in net price ≥6.11% or whose change in net price could not be reliably determined from the SSR Health data. We ranked the 14 drugs by the absolute increase in year-over-year spending in California with a goal of reviewing the top five drugs from both the specialty drugs list and the branded drugs list. As there were only four drugs on the branded drugs list, we created a final set of drugs for review comprising six specialty drugs and four branded drugs.

ICER contacted the manufacturers of each of the 10 drugs on the combined final list to inform them that their drugs would potentially be reviewed as part of the California UPI review. Manufacturers were invited to comment on whether net prices for their drug(s) had increased less than 6.11%, in which case we would remove their drug(s) from further evaluation. We received assurances that

net prices had increased less than 6.11% from the manufacturers of six of the 10 drugs. For three of the drugs, manufacturers chose not to provide information on net price changes. For one drug, Tagrisso®, a clerical error led to ICER incorrectly concluding that the manufacturer had provided information that the net price increase was less than 6.11%. In fact, the manufacturer never provided information on net price change, but we felt the company was not given adequate opportunity to do so, and so the drug was removed from the review. The final list of selected drugs for this assessment is shown in Table 2.3.

Table 2.1. Rankings from California Top 25 Year-Over-Year Increased Spending Lists (Specialty and Brand)

Rank*	Drug Name*	Δ WAC	Rank	Drug Name	Δ WAC
Specialty			**Brand**		
1	Biktarvy®	5.9%	**1**	Jardiance®	6.0%
2	Humira®	7.3%	**2**	Eliquis®	6.06%
3	Stelara®	4.7%	**3**	Alvesco®	0.0%
4	Descovy®	5.9%	**4**	Victoza®	4.9%
5	Trikafta®	0.0%	**5**	Ozempic®	4.9%
6	Dupixent®	3.0%	**6**	Emgality®	4.6%
7	Baqsimi One Pack®	0.0%	**7**	Baqsimi One Pack®	0.0%
8	Cosentyx®	7.3%	**8**	Farxiga®	4.0%
9	Otezla®	5.4%	**9**	Pradaxa®	N/A
10	Trulicity®	5.1%	**10**	Entresto®	7.3%
11	Risankizumab®	N/A	**11**	Aimovig®	4.7%
12	Ozempic®	4.9%	**12**	Novolog®	0.0%
13	Tremfya®	4.8%	**13**	Vascepa®	9.0%
14	Revlimid®	5.9%	**14**	Xarelto®	4.8%
15	Lenvima®	5.6%	**15**	Lantus®	0.1%
16	Xeljanz®	5.3%	**16**	Insulin®	N/A
17	Takhzyro®	3.0%	**17**	Januvia®	4.9%
18	Symtuza®	4.4%	**18**	Trintellix®	5.1%
19	Posaconazole®	N/A	**19**	Vyvanse®	5.8%
20	Tagrisso®	2.0%	**20**	Linzess®	5.0%
21	Imbruvica®	7.5%	**21**	Repatha®	-45.6%
22	Sprycel®	6.0%	**22**	Proair®	3.0%
23	Latuda®	4.9%	**23**	Advair®	-0.20%
24	Kovaltry®	N/A	**24**	Humalog®	0.0%
25	Taltz®	6.0%	**25**	Trelegy®	5.0%

N/A: not applicable or not identified, WAC: wholesale acquisition cost

*California 2020 SB-17 rankings of highest year-over-year increase in total spending.

Table 2.2. Drugs from California Top 25 Increased Spending Lists with Net Price Percentage Change Greater than Medical Care CPI* Plus 2%

Drug Name	California Increased Spending Ranking	Net Price % Change (SSR Health or Manufacturer Corrections)	WAC % Change (SSR Health or Manufacturer Corrections)
Specialty Drugs Top 25 Increased Year-Over-Year Spending			
Humira®	2	<6.11%†	7.3%
Revlimid®	14	Unknown	5.9%
Takhzyro®	17	<6.11%†	3.0%
Tagrisso®	20	Unconfirmed‡	2.0%
Imbruvica®	21	<6.11%†	7.5%
Sprycel®	22	9.6%	6.0%
Brand Drugs Top 25 Increased Year-Over-Year Spending			
Alvesco®	3	<6.11%†	0.0%
Emgality®	6	Unknown	4.6%
Pradaxa®	9	<6.11%†	Unknown
ProAir®	22	<6.11%†	3.0%

WAC: wholesale acquisition cost, unknown: either not reported or no reliable pricing data available from SSR Health

*Medical care CPI was 4.11% in 2020.

†Manufacturer submitted pricing evidence to suggest that the net price increase was less than medical care CPI plus 2%.

‡The net price change for Tagrisso® was never confirmed by the manufacturer but this was not recognized due to a clerical error. Tagrisso® was removed from the final list of drugs due to this error.

Table 2.3. Drugs Selected for Assessment

Drug (Specialty or Brand)	2019 to 2020 Percentage Change		California Increased Spending Ranking
	WAC	Net Price	
Drugs with Price Increases Unsupported by New Clinical Evidence			
Revlimid® (Specialty)	5.9%	Unknown*	14 (Specialty)
Sprycel® (Specialty)	6.0%	9.6%	22 (Specialty)
Emgality® (Brand)	4.6%	Unknown*	6 (Brand)

WAC: wholesale acquisition cost

*Either not reported or no reliable pricing data available from SSR Health.

3. Assessments

3.1. Revlimid® (Lenalidomide, Bristol Myers Squibb)

Introduction

Revlimid® (lenalidomide, Bristol Myers Squibb) is a thalidomide analogue that was first approved by the Food and Drug Administration (FDA) in 2005.[6] Its mechanism of action is threefold: a direct anti-tumor effect, inhibition of angiogenesis, and immunomodulation. It is indicated for the treatment of five different hematologic diseases: multiple myeloma, myelodysplastic syndromes, mantle cell lymphoma, follicular lymphoma, and marginal zone lymphoma.[7] Follicular and marginal zone lymphomas were added as indications in 2019. In multiple myeloma, lenalidomide is specifically indicated to be used in combination with dexamethasone, or as maintenance therapy following autologous hematopoietic cell transplantation.

Based on information provided by the manufacturer, the only indication that accounts for greater than 10% of lenalidomide's use is multiple myeloma. In particular, the manufacturer provided information that follicular lymphoma and marginal zone lymphoma in aggregate do not account for greater than 10% of lenalidomide's use.

Price Increase

Lenalidomide was ranked 14th on California's specialty drugs with the highest year-over-year increase in total spending. Over the 12 months (four quarters) for which price changes were assessed, the WAC for lenalidomide increased by approximately 5.9%. SSR Health considered its estimates of change in net price over the same 12-month period to be potentially not reliable. The manufacturer did not provide information related to lenalidomide's change in net price. All pricing information was obtained from SSR Health.

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 lenalidomide as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24 months review timeframe (see Table A1 in Appendix A). In addition, we reviewed the RCT and non-RCT information that Bristol Myers Squibb submitted to us to consider as new clinical information (45 references [14 conference abstracts and 31 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 lenalidomide (Table A1, Appendix A). Of the 45 references submitted by the manufacturer, 23 articles were excluded because they did not meet

our UPI review criteria, while the remaining 22 articles were considered low quality (see Tables 3.1 and 3.2). As an example, we highlighted the submitted article (Leonard 2019) that did not meet the UPI criteria.

Table 3.1. Studies Not Meeting UPI Review Criteria

Primary Reason for Exclusion*	Number of References
Study population outside approved label indication	1
Indication accounts for less than 10% of use	8
Outcomes not relevant to scope	4
Intervention/comparison not relevant to scope	10

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

Table 3.2. Studies Not Meeting Criteria for New Moderate- to High-Quality Evidence

Reason for Exclusion	Number of References
Low-quality evidence	1
Previously known information about lenalidomide related to efficacy	21

Study Not Meeting UPI Review Criteria

Leonard 2019 was a Phase III RCT in 358 patients with relapsed and/or refractory follicular lymphoma (N=295) or marginal zone lymphoma (N=63).[8] Patients were randomized to receive lenalidomide plus rituximab (N=178) or placebo plus rituximab (N=180). Patients received oral lenalidomide 20 mg daily (or placebo) on days one to 21 plus intravenous rituximab 375 mg/m^2 on days one, eight, 15, and 22 of Cycle 1 and day one of Cycles 2 to 5 every 28 days. Key outcomes, including progression-free survival (PFS), overall response (OR) rate, and complete response (CR) rate were assessed by blinded independent central review based on tomography/magnetic resonance imaging scans. The median follow-up was 28.3 months. PFS was superior in the lenalidomide plus rituximab group (hazard ratio [HR]: 0.46; 95% confidence interval [CI]: 0.34-0.62; P<0.0001); median PFS was 39.4 months for lenalidomide plus rituximab, compared to 14.1 months for placebo plus rituximab. The rate of OR was 78% (95% CI: 71-83%) in the lenalidomide plus rituximab group and 53% (95% CI: 46-61%) in the placebo plus rituximab group (P<0.0001), and 34% (95% CI: 27-41%) of those in the lenalidomide plus rituximab group achieved CR compared to 18% (95% CI: 13-25%) in the placebo plus rituximab group (P=0.001). When examining those with follicular or marginal zone lymphoma separately, PFS, OR, and CR were improved in the follicular lymphoma group (PFS: P<0.0001, OR: P<0.0001, CR: P=0.004) but not for those with marginal zone lymphoma where there were no significant differences between those who received lenalidomide plus rituximab and those who received placebo plus rituximab (PFS: P=0.998, OR: P=0.131, CR: P=0.129). In terms of safety, those who received lenalidomide plus rituximab were more likely to experience grade 3 or 4 adverse events (69%) compared to the placebo group (32%), which was mostly attributable to neutropenia and leukopenia.

Reason(s) for Not Meeting UPI Review Criteria: Leonard 2019 is a high-quality RCT conducted to examine the efficacy and safety of lenalidomide plus rituximab for the treatment of follicular and marginal zone lymphoma. Although lenalidomide appeared to substantially improve outcomes of patients with both follicular and marginal zone lymphoma, based on input from the manufacturer, these indications do not account for greater than 10% of use (either as single indications or in aggregate) and therefore did not meet the UPI criteria for assessing new evidence as outlined in our protocol. We had not previously considered the possibility that new evidence could be generated during a UPI review cycle for two or more separate indications that in aggregate account for greater than 10% of use, and the UPI Protocol implies that this would not be considered as potentially providing new evidence for a price increase. We decided during this review cycle that we would, under Section 8 of the Protocol, have evaluated the aggregate indications and evidence. However, as noted above, the manufacturer informed ICER that even in aggregate, follicular lymphoma and marginal zone lymphoma do not account for greater than 10% of the use of lenalidomide.

Conclusion

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

3.2. Sprycel® (Dasatinib, Bristol Myers Squibb)

Introduction

Sprycel® (dasatinib, Bristol Myers Squibb) is a protein tyrosine kinase inhibitor whose main targets are BCR-ABL (i.e., Philadelphia chromosome or Ph+), the Src family of kinase, c-Kit, EPHA2, and platelet derived growth factor receptors. Its action inhibits the growth of cancer cells. In particular, strong inhibition of the activated BCR-ABL kinase distinguishes dasatinib from other chronic myeloid leukemia (CML) treatments, such as imatinib and nilotinib.[9] Dasatinib was first approved by the FDA in 2006 for the treatment of CML with resistance or intolerance to prior therapy (specifically adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML) and Ph+ acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy. In 2010, the FDA added an indication for *newly* diagnosed adults with Ph+ CML in chronic phase. Approval for pediatric patients came in 2017 with indications for pediatric Ph+ chronic lymphocytic leukemia (CLL) and pediatric Ph+ ALL.[10]

Based on information provided by the manufacturer, the indications that account for greater than 10% of dasatinib's use include:

- Chronic phase Ph+ CML in adults
- Ph+ ALL in adults
- CML in adults.

Price Increase

Dasatinib was ranked 22nd on California's specialty drugs with the highest year-over-year increase in total spending. Over the 12 months (four quarters) for which price changes were assessed, the WAC for dasatinib increased by approximately 6.0%. The change in net price over the same 12-month period was estimated at 9.6%. The manufacturer did not provide information related to dasatinib's change in net price over the 12-month period. All pricing information was obtained from SSR Health.

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 dasatinib as of January 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24-month review timeframe (see Table B1 in Appendix B). In addition, we reviewed the RCT and non-RCT information Bristol Myers Squibb submitted to us to consider as new clinical information (30 references [12 conference presentations and 18 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 dasatinib (Table B1, Appendix B). Of the 30 references submitted by the manufacturer, 12 articles were excluded because they did not meet our UPI review criteria, while the remaining 18 articles were considered low quality (see Tables 3.3 and 3.4). As an example, we highlighted the submitted article (Chen 2020) that did not meet the UPI criteria.

Table 3.3. Studies Not Meeting UPI Review Criteria

Primary Reason for Exclusion*	Number of References
Indication accounts for less than 10% of use	1
Intervention/comparison not relevant to scope	7
Outcomes not relevant to scope	2
Duplicate evidence	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 3.4. Studies Not Meeting Criteria for New Moderate- to High-Quality Evidence

Reason for Exclusion	Number of References
Low-quality evidence	3
Previously known information about dasatinib related to efficacy	14
Previously known information about dasatinib related to safety	1

Study Not Meeting UPI Review Criteria

Shen 2020 was a Phase III open-label RCT that included 189 pediatric patients aged 0-8 years with Ph+ ALL.[11] Pediatric patients with Ph+ ALL were randomized to receive daily dasatinib 80 mg/m^2 (N=92) or imatinib 300 mg/m^2 (N=97) on day eight of remission induction, which continued until completion of chemotherapy. Key outcomes, including event-free survival, relapse, death, and overall survival were collected. Of note, interim analyses showed improvement in three-year event-free survival in the dasatinib group and thus randomization was stopped and imatinib was replaced with dasatinib in patients still receiving treatment. The four-year event-free survival rate was higher in the dasatinib group (71%, 95% CI: 56.2-89.6%) compared to the imatinib group (48.9%, 95% CI: 32.0-74.5%) (P=0.005). The overall survival rate was also higher in the dasatinib group (88.4%, 95% CI: 81.3-96.1%) compared to the imatinib group (69.2%, 95% CI: 55.6-86.2%) (P=0.005). The four-year cumulative relapse risk was lower in the dasatinib group (19.8%, 95% CI: 4.2-35.4%) compared to the imatinib group (34.4%, 95% CI: 15.6-53.2%) (P=0.005). In terms of safety, serious adverse effects did not differ between the groups.

Reason(s) for Not Meeting UPI Review Criteria: Shen 2020 is a high-quality RCT conducted to examine the efficacy and safety of dasatinib for the treatment of pediatric Ph+ ALL. Based on input from the manufacturer, this indication does not account for greater than 10% of use and therefore did not meet the UPI criteria for assessing new evidence as outlined in our protocol.

Conclusion

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

3.3. Emgality® (Galcanezumab, Eli Lilly)

Introduction

Emgality® (galcanezumab, Eli Lilly) is a calcitonin-gene related peptide monoclonal antibody approved by the FDA in 2018 for the preventive treatment of migraine. The FDA added an indication for episodic cluster headache in June 2019.[12] Based on information provided by the manufacturer, the only indication that accounts for greater than 10% of galcanezumab's use is preventive treatment of migraine in adults.

Price Increase

Galcanezumab was ranked 6th on California's brand name drugs with the highest year-over-year increase in total spending. Over the 12 months (four quarters) for which price changes were assessed, the WAC for galcanezumab increased by approximately 4.6%. SSR Health considered its estimates of change in net price over the same 12-month period to be potentially not reliable. The manufacturer did not provide information related to galcanezumab's change in net price over the 12-month period. All pricing information was obtained from SSR Health.

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 galcanezumab as of December 2019. Following that, we conducted an independent systematic literature review, limited to RCTs, over the 24-month review timeframe (see Table C1 in Appendix C). In addition, we reviewed the RCT and non-RCT information Eli Lilly submitted to us to consider as new clinical information (54 references [seven editorial/commentary/correction articles and 47 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 galcanezumab (Table C1, Appendix C). Of the 54 references submitted by the manufacturer, 32 article were excluded because they did not meet our UPI review criteria, while the remaining 22 articles were considered previously known information about galcanezumab related to either efficacy or safety (see Tables 3.5 and 3.6). As an example, we highlighted one of the submitted articles (Goadsby 2019) that did not meet the UPI criteria and was classified as an indication accounting for less than 10% of use.

Table 3.5. Studies Not Meeting UPI Review Criteria

Primary Reason for Exclusion*	Number of References
Study published outside of the timeframe of our review	4
Study population outside approved label indication	2
Indication accounts for less than 10% of use	5
Editorial/commentary article/correction	7
Outcomes not relevant to scope	14

*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

Reason for Exclusion	Number of References
Previously known information about galcanezumab related to efficacy	19
Previously known information about galcanezumab related to safety	3

Study Not Meeting UPI Review Criteria

Goadsby 2019 was a Phase III RCT that evaluated the effectiveness of galcanezumab in adult patients with a history of cluster headache episodes.[13] Patients were randomized to receive either galcanezumab 300 mg (n=49) or placebo (n=57) subcutaneously at baseline and month one. The mean difference in the reduction of cluster headache attacks across weeks one to three was 3.5 attacks per week between patients in the galcanezumab arm (8.7 attacks) and placebo arm (5.2 attacks) (95% CI: 0.2-6.7, p=0.04). The only between-group difference in adverse events was for injection-site pain, which was reported by 8% of reports in the galcanezumab arm and 0% in the placebo arm. The study concluded that patients receiving subcutaneous galcanezumab 300 mg had a 50% reduction in weekly cluster headache attacks as compared to those receiving placebo.

Reason(s) for Not Meeting UPI Review Criteria: Goadsby 2019 was a well-conducted study, which enrolled patients with cluster headaches. Based on input from the manufacturer, this indication does not account for greater than 10% of use and therefore did not meet the UPI criteria for assessing new evidence as outlined in our protocol.

Conclusion

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

References

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APPENDIX

Appendix A. Revlimid®

Table A1. References Submitted by Bristol Myers Squibb

Citation	Decision
AUGMENT (NCT01938001); Leonard, John P., et al. "AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma." Journal of Clinical Oncology 37.14 (2019): 1188-1199.	Indication accounts for less than 10% of use
AUGMENT (NCT01938001); Gribben, John G., et al. "Efficacy and time to next treatment following lenalidomide/rituximab (R2) or rituximab/placebo in patients with R/R indolent NHL (AUGMENT)." (2019): 7514-7514.	Indication accounts for less than 10% of use
AUGMENT (NCT01938001); Izutsu, Koji, et al. "Analysis of Japanese patients from the AUGMENT phase III study of lenalidomide+ rituximab (R2) vs. rituximab+ placebo in relapsed/refractory indolent non-Hodgkin lymphoma." International journal of hematology 111.3 (2020): 409-416.	Indication accounts for less than 10% of use
AUGMENT (NCT01938001); Leonard, J. P., et al. "AUGMENT Phase III Study: Lenalidomide/Rituximab (R2) Improved Efficacy Over Rituximab/Placebo in Relapsed/Refractory Follicular Lymphoma Patients Irrespective of POD24 Status" Poster Presentation. International Conference on Malignant Lymphoma Palazzo dei Congressi, Lugano, Switzerland (2019).	Indication accounts for less than 10% of use
AUGMENT (NCT01938001); Trněný, Marek, et al. "Subgroup Analyses of Elderly Patients Aged≥ 70 Years in AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R2) vs Rituximab Plus Placebo (R-Placebo) in Patients with Relapsed/Refractory (R/R) Indolent Non-Hodgkin Lymphoma (iNHL)." American Society of Hematology (ASH) 2019. Orlando, FL. 134 (2019): 347.	Indication accounts for less than 10% of use
Liu, Zhaoyu, et al. "Efficacy of rituximab combined with lenalidomide in patients with recurrent follicular lymphoma." International Journal of Clinical and Experimental Medicine 12.9 (2019): 11708-11715.	Indication accounts for less than 10% of use
MAGNIFY (NCT01996865); Coleman, Morton, et al. "Patients with Relapsed/Refractory Marginal Zone Lymphoma in the MAGNIFY Phase IIIb Interim Analysis of Induction R2 Followed By Maintenance." AMERICAN SOCIETY OF HEMATOLOGY (ASH) New Orleans, LA (2020).	Indication accounts for less than 10% of use
MAGNIFY (NCT01996865); Lansigan, Frederick, et al. "Subgroup analyses of elderly patients aged≥ 70 years in MAGNIFY: A phase IIIb interim analysis of induction R2 followed by maintenance in relapsed/refractory indolent non-Hodgkin lymphoma." AMERICAN SOCIETY OF HEMATOLOGY (ASH) New Orleans, LA (2020)	Indication accounts for less than 10% of use
ELOQUENT-2 (NCT01239797); Dimopoulos, Meletios A., et al. "Elotuzumab, lenalidomide, and dexamethasone in RRMM: Final overall survival results from the phase 3 randomized ELOQUENT-2 study." Blood cancer journal 10.9 (2020): 1-10.	Intervention/comparison not relevant to scope
ENDURANCE (NCT01863550); Kumar, Shaji K., et al. "Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial." The Lancet Oncology 21.10 (2020): 1317-1330.	Intervention/comparison not relevant to scope
GRIFFIN (NCT02874742); Voorhees, Peter M., et al. "Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial." Blood 136.8 (2020): 936-945.	Intervention/comparison not relevant to scope

Citation	Decision
MAIA (NCTNCT02252172); Facon, Thierry, et al. "Daratumumab plus lenalidomide and dexamethasone for untreated myeloma." New England Journal of Medicine 380.22 (2019): 2104-2115.	Intervention/comparison not relevant to scope
MAIA (NCTNCT02252172); Perrot, Aurore, et al. "Faster and sustained improvement in health-related quality of life (HRQoL) for newly diagnosed multiple myeloma (NDMM) patients ineligible for transplant treated with daratumumab, lenalidomide, and dexamethasone (D-Rd) versus Rd alone: MAIA." (2019): 8016-8016.	Intervention/comparison not relevant to scope
Minarik, Jiri, et al. "Overall survival benefit of ixazomib, lenalidomide and dexamethasone (IRD) over lenalidomide and dexamethasone (RD) in RRMM patients treated in routine clinical practice: results from the Czech registry of monoclonal gammopathies (RMG)." (2019): 3139-3139.	Intervention/comparison not relevant to scope
NA(NCT02471820); Terpos, Evangelos, et al. "Effect of induction therapy with lenalidomide, doxorubicin and dexamethasone on bone remodeling and angiogenesis in newly diagnosed multiple myeloma." International Journal of Cancer 145.2 (2019): 559-568.	Intervention/comparison not relevant to scope
Phase 1b Study of Carfilzomib Administered Once Weekly in Combination With Lenalidomide and Dexamethasone in Subjects With Multiple Myeloma (NCT02335983); Alsina, Melissa, et al. "A phase 1b study of once-weekly carfilzomib combined with lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma." American journal of hematology 96.2 (2021): 226-233.	Intervention/comparison not relevant to scope
StaMINA (NCT01109004); Hari, Parameswaran, et al. "Long-term follow-up of BMT CTN 0702 (STaMINA) of postautologous hematopoietic cell transplantation (autoHCT) strategies in the upfront treatment of multiple myeloma (MM)." (2020): 8506-8506.	Intervention/comparison not relevant to scope
SWOG S0777 (NCT00644228); Durie, Brian GM, et al. "Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT)." Blood cancer journal 10.5 (2020): 1-11.	Intervention/comparison not relevant to scope
Barth, Peter, et al. "Comparative effectiveness of lenalidomide, bortezomib, and their combinations as first-line treatment of older patients with myeloma." Blood 134 (2019): 3155.	Low-quality evidence
Cransac, Amélie, et al. "Adherence to immunomodulatory drugs in patients with multiple myeloma." PLoS One 14.3 (2019): e0214446.	Outcomes not relevant to scope
Jackson, Graham, et al. "Productivity losses in patients with newly diagnosed multiple myeloma following stem cell transplantation and the impact of maintenance therapy." European journal of haematology 103.4 (2019): 393-401.	Outcomes not relevant to scope
Uyl-de Groot, Carin A., et al. "Lenalidomide as maintenance treatment for patients with multiple myeloma after autologous stem cell transplantation: A pharmaco-economic assessment." European journal of haematology 105.5 (2020): 635-645.	Outcomes not relevant to scope
Zamagni, Elena, et al. "Patient Characteristics, Treatment Outcomes and Healthcare Resource Utilization across Europe in Multiple Myeloma Patients Ineligible for Stem Cell Transplantation Who Received Lenalidomide-or Bortezomib-Based Regimens." Blood 134 (2019): 4772.	Outcomes not relevant to scope

Citation	Decision
(UMIN000009042); Ishida, Tadao, et al. "Continuous lenalidomide treatment after bortezomib-melphalan-prednisolone therapy for newly diagnosed multiple myeloma." Annals of hematology 99.5 (2020): 1063-1072.	Previously known information about lenalidomide related to efficacy
Alonso, Rafael, et al. "Prolonged lenalidomide maintenance therapy improves the depth of response in multiple myeloma." Blood Advances 4.10 (2020): 2163-2171.	Previously known information about lenalidomide related to efficacy
Baz, Rachid, et al. "Lenalidomide-based response-adapted therapy for older adults without high risk myeloma." British journal of haematology 184.5 (2019): 735-743.	Previously known information about lenalidomide related to efficacy
BMT CTN 0702 (NCT01109004); Stadtmauer, Edward A., et al. "Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: results of the BMT CTN 0702 trial." Journal of clinical oncology 37.7 (2019): 589.	Previously known information about lenalidomide related to efficacy
Chari, Ajai, et al. "Treatment patterns and clinical and economic outcomes in patients with newly diagnosed multiple myeloma treated with lenalidomide- and/or bortezomib-containing regimens without stem cell transplant in a real-world setting." Clinical Lymphoma Myeloma and Leukemia 19.10 (2019): 645-655.	Previously known information about lenalidomide related to efficacy
Covut, Fahrettin, et al. "Meta-Analyses of Clinical Trials Comparing the Progression Free Survival and Adverse Events in Treated Versus Observed Patients with Smoldering and Indolent Multiple Myeloma." Blood 134 (2019): 2196.	Previously known information about lenalidomide related to efficacy
Dhakal, Binod, et al. "Association of adverse events and associated cost with efficacy for approved relapsed and/or refractory multiple myeloma regimens: A Bayesian network meta-analysis of phase 3 randomized controlled trials." Cancer 126.12 (2020): 2791-2801.	Previously known information about lenalidomide related to efficacy
FIRST (NCT00689936); Belch, Andrew, et al. "Continuous lenalidomide and low-dose dexamethasone in patients with transplant-ineligible newly diagnosed MM: FIRST trial subanalysis of Canadian/US patients." Cancer medicine 9.23 (2020): 8923-8930.	Previously known information about lenalidomide related to efficacy
FORTE (NCT02203643); Gay, Francesca, et al. "Survival analysis of newly diagnosed transplant-eligible multiple myeloma patients in the randomized FORTE trial." Blood 136 (2020): 35-37.	Previously known information about lenalidomide related to efficacy
Hari P, Ung B, Abouzaid S, Agarwal A, Parikh K. Lenalidomide maintenance post-transplantation in newly diagnosed multiple myeloma real-world outcomes and costs. Future Oncol. 2019 Dec;15(35)4045-4056. doi 10.2217fon-2019-0422. Epub 2019 Oct 18. PMID 31625415.	Previously known information about lenalidomide related to efficacy
HOVON-87/NMSG18 (NTR1630); Nielsen, Lene Kongsgaard, et al. "Health-related quality of life in transplant ineligible newly diagnosed multiple myeloma patients treated with either thalidomide or lenalidomide-based regimen until progression: a prospective, open-label, multicenter, randomized, phase 3 study." haematologica 105.6 (2020): 1650.	Previously known information about lenalidomide related to efficacy
IFM 2009 (NCT01191060); Roussel, Murielle, et al. "Health-related quality of life results from the IFM 2009 trial: treatment with lenalidomide, bortezomib, and dexamethasone in transplant-eligible patients with newly diagnosed multiple myeloma." Leukemia & Lymphoma 61.6 (2020): 1323-1333.	Previously known information about lenalidomide related to efficacy
Joseph, Nisha S., et al. "Long-term follow-up results of lenalidomide, bortezomib, and dexamethasone induction therapy and risk-adapted maintenance approach in newly diagnosed multiple myeloma." Journal of Clinical Oncology 38.17 (2020): 1928.	Previously known information about lenalidomide related to efficacy

Citation	Decision
Kumar, Lalit, et al. "VRd versus VCd as induction therapy for newly diagnosed multiple myeloma: A Phase III, randomized study." Clinical Lymphoma, Myeloma and Leukemia 19.10 (2019): e361.	Previously known information about lenalidomide related to efficacy
MYELOMA XI (ISRCTN49407852); Jackson, Graham H., et al. "Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial." The Lancet Oncology 20.1 (2019): 57-73.	Previously known information about lenalidomide related to efficacy
MYELOMA XI (ISRCTN49407852); Pawlyn, Charlotte, et al. "Lenalidomide maintenance prolongs progression-free survival and does not impact the aggressiveness of clinical relapse: data from long-term follow up of the Myeloma XI Trial." Blood 134 (2019): 1889.	Previously known information about lenalidomide related to efficacy
Olszewski, Adam, et al. "Comparative effectiveness of lenalidomide, bortezomib, and their combination as first-line treatment of older patients with myeloma." Clinical Lymphoma, Myeloma and Leukemia 19.10 (2019): e9.	Previously known information about lenalidomide related to efficacy
Patel, Dilan A., et al. "Minimal residual disease negativity and lenalidomide maintenance therapy are associated with superior survival outcomes in multiple myeloma." Bone Marrow Transplantation 55.6 (2020): 1137-1146.	Previously known information about lenalidomide related to efficacy
POLLUX (NCT02076009); Bahlis, Nizar J., et al. "Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study." Leukemia 34.7 (2020): 1875-1884.	Previously known information about lenalidomide related to efficacy
Ramasamy, Karthik, et al. "Relative efficacy of treatment options in transplant-ineligible newly diagnosed multiple myeloma: results from a systematic literature review and network meta-analysis." Leukemia & lymphoma 61.3 (2020): 668-679.	Previously known information about lenalidomide related to efficacy
Modi, Dipenkumar, et al. "Lenalidomide maintenance after second autologous stem cell transplant improves overall survival in multiple myeloma." Leukemia & Lymphoma 61.8 (2020): 1877-1884.	Previously known information about lenalidomide related to efficacy
NCT01169337; Lonial, Sagar, et al. "Randomized trial of lenalidomide versus observation in smoldering multiple myeloma." Journal of Clinical Oncology 38.11 (2020): 1126.	Study population outside approved label indication

Appendix B. Sprycel®

Table B1. References Submitted by Bristol Myers Squibb

Citation	Decision
Chinese Children's Cancer Group study ALL-2015 (CCCGALL-2015), Shen et al., Blood, 2019	Duplicate Information
DADI Trial (UMIN000011099), Murai et al., Hemasphere, 2019	Duplicate Information
Chinese Children's Cancer Group study ALL-2015 (CCCGALL-2015), Shen et al., JAMA Oncology, 2020	Indication accounts for less than 10% of use
Yu et al., Variables associated with patient-reported symptoms in persons with chronic phase chronic myeloid leukemia receiving tyrosine kinase inhibitor therapy, Medicine, 2019	Intervention/comparison not relevant to scope
Caocci et al., Long-term mortality rate for cardiovascular disease in 656 chronic myeloid leukaemia patients treated with second- and third-generation tyrosine kinase inhibitors, International Journal of Cardiology, 2020	Intervention/comparison not relevant to scope
Pediatric Philadelphia Positive Acute Lymphoblastic Leukemia (CA180-372), Hunger et al., Pediatric Blood & Cancer, 2020	Intervention/comparison not relevant to scope
Chang et al., Combination chemotherapy plus dasatinib leads to comparable overall survival and relapse-free survival rates as allogeneic hematopoietic stem cell transplantation in Philadelphia positive acute lymphoblastic leukemia, Cancer Medicine, 2019	Intervention/comparison not relevant to scope
Li et al., An oral, chemotherapy-free regimen (Dasatinib Plus Prednisone) as induction and consolidation for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia, British journal of haematology, 2020	Intervention/comparison not relevant to scope
Li et al., Clinical Analysis of Dasatinib and Chemotherapy Followed by Allogeneic Hematopoietic Stem Cell Transplantation for Treatment of Patients with Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia, 2020	Intervention/comparison not relevant to scope
Dasatinib (DAS) a 2G-TKI and Peg-IFNa2b in pts with newly diagnosed CP-CML (Eudract Number 2012-003389-42), Roy et al., Hemasphere, 2020	Intervention/comparison not relevant to scope
Caocci et al., Recurrent arterial occlusive events in patients with chronic myeloid leukemia treated with second- and third-generation tyrosine kinase inhibitors and role of secondary prevention, International Journal of Cardiology, 2019	Low-quality evidence
SIMPLICITY(NCT01244750) Goldberg et al., Clinical Lymphoma Myeloma And Leukemia, 2020	Low-quality evidence
Zheng et al., Impact of tyrosine kinase inhibitors on the statural growth in children with acute lymphoblastic leukemia, Leukemia Research, 2020	Low-quality evidence
Yue et al., Safety and cost-effectiveness analysis of Ponatinib versus other tyrosine kinase inhibitors in patients with chronic myeloid leukemia in the United States, Value in Health, 2019	Outcomes not relevant to scope
DASISION trial (NCT00481247), Breccia et al., Association of High Body Mass Index with Response Outcomes in Patients with CML-CP Treated with Dasatinib Versus Imatinib in the First Line: Exploratory Post Hoc Analysis of the Phase 3 DASISION Trial, Blood, 2019	Outcomes not relevant to scope
Efficace et al., Health-related quality of life of newly diagnosed chronic myeloid leukemia patients treated with first-line dasatinib versus imatinib therapy, Leukemia, 2020	Previously known information about dasatinib related to efficacy

Citation	Decision
Okamoto et al., Assessment of estimated glomerular filtration rate in patients with chronic myeloid leukemia following discontinuation of tyrosine kinase inhibitors, International Journal of Hematology, 2020	Previously known information about dasatinib related to efficacy
First-line DADI trial (UMIN000011099), Kimura et al., Lancet Hematology, 2020	Previously known information about dasatinib related to efficacy
DASFREE (NCT018500004) Shah et al., Clinical Lymphoma, Myeloma & Leukemia, 2019	Previously known information about dasatinib related to efficacy
DASFREE (NCT01850004) Shah et al., Leukemia & Lymphoma, 2020	Previously known information about dasatinib related to efficacy
Klink et al., Real-World Effectiveness of First-Line (1L) Dasatinib Versus 1L Imatinib in Newly Diagnosed Patients with Chronic Phase Chronic Myeloid Leukemia (CP-CML), Blood, 2020	Previously known information about dasatinib related to efficacy
DASCERN trial (NCT01593254) Cortes et al., Leukemia, 2020	Previously known information about dasatinib related to efficacy
The New TARGET System Study (UMIN00003581), Kizaki et al., International journal of hematology, 2019	Previously known information about dasatinib related to efficacy
DASISION (NCT00254423), Maiti et al., Cancer, 2020	Previously known information about dasatinib related to efficacy
Ph+ALL213 Study (#UMIN000012173), Sugiura et al., Blood, 2019	Previously known information about dasatinib related to efficacy
Treatment Free Remission Accomplished By Dasatinib (NCT02268370), Kim et al., Blood, 2019	Previously known information about dasatinib related to efficacy
JALSG CML212 (#UMIN000007909), Matsumara et al., Blood, 2020	Previously known information about dasatinib related to efficacy
Dasatinib Combined With Chemotherapy in Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia (NCT02523976), Guang ji et al., Blood, 2019	Previously known information about dasatinib related to efficacy
DASISION trial (NCT00481247), Breccia et al., Impact of Comorbidities on Response Outcomes in Patients with Chronic Myeloid Leukemia in Chronic Phase Treated with First-Line Dasatinib Versus Imatinib: Exploratory Post Hoc Analysis of DASISION, Blood, 2020	Previously known information about dasatinib related to efficacy
Kolibaba et al., A Real-World Assessment of Hepatic Dysfunction Among Chronic Phase Chronic Myeloid Leukemia (CP-CML) Patients Receiving First-Line (1L) Tyrosine Kinase Inhibitors (TKIs) in the United States, Blood, 2020	Previously known information about dasatinib related to safety

Appendix C. Emgality®

Appendix Table C1. References Submitted by Eli Lilly

Citation	Decision
Bangs ME, Kudrow D, Wang S, et al. Correction to: Safety and tolerability of monthly galcanezumab injections in patients with migraine: integrated results from migraine clinical studies. BMC Neurol. 2020;20(1):90.	Correction article
Ford JH, Stauffer VL, McAllister P, et al. Correction to: Functional impairment and disability among patients with migraine: evaluation of galcanezumab in a long-term, open-label study. Qual Life Res. 2021;30(2):455-464.	Correction article
Rosen N, Pearlman E, Ruff D, Day K, Jim Nagy A. Correction to 100% Response Rate to Galcanezumab in Patients With Episodic Migraine: Results From the Phase 3, Randomized, Double-Blind, Placebo-Controlled EVOLVE-1 and EVOLVE-2 Studies. Headache: The Journal of Head and Face Pain. 2019;59(8):1428-1428	Correction article
Silberstein SD, Stauffer VL, Day KA, Lipsius S, Wilson MC. Correction to: Galcanezumab in episodic migraine: subgroup analyses of efficacy by high versus low frequency of migraine headaches in phase 3 studies (EVOLVE-1 & EVOLVE-2). J Headache Pain. 2019;20(1):118	Correction article
Goadsby PJ, Terwindt GM, Ruff DD, et al. Response to 'Do different treatment strategies of galcanezumab have similar effect on migraine?' Eur J Neurol. 2020;27(5).	Editorial/commentary article
Nichols R, Skljarevski V, Dell'Agnello G, Hundemer HP, Aurora SK. Letter to the editor regarding European Headache Federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. J Headache Pain. 2019;20(1):22	Editorial/commentary article
Nichols R, Detke HC, Hundemer HP, Aurora SK. Approvals and indications of CGRP antibodies. The Lancet Neurology. 2019;18(8):718	Editorial/commentary article
Dodick DW, Goadsby PJ, Lucas C, et al. Phase 3 randomized, placebo-controlled study of galcanezumab in patients with chronic cluster headache: Results from 3-month double-blind treatment. Cephalalgia. 2020;40(9):935-948	Indication accounts for less than 10% of use
Goadsby PJ, Dodick DW, Leone M, et al. Trial of galcanezumab in prevention of episodic cluster headache. N Engl J Med. 2019;381(2):132-141	Indication accounts for less than 10% of use
Kudrow D, Andrews JS, Rettiganti M, et al. Treatment outcomes in patients treated with galcanezumab vs placebo: post hoc analyses from a phase 3 randomized study in patients with episodic cluster headache. Headache: The Journal of Head and Face Pain. 2020;60(10):2254-2264.	Indication accounts for less than 10% of use
Wenzel R, Bardos J, Aurora S. Anti-CGRP in cluster headache therapy: a response. Neurol Sci. 2020;41(9):2641-2641.	Indication accounts for less than 10% of use
Wenzel R, Smith TR, Clark AS. Cluster headache: opportunities for pharmacists to improve care. Journal of Pharmacy Practice. 2020;35(2):281-288.	Indication accounts for less than 10% of use
Dou Z, Eshraghi J, Guo T, et al. Performance characterization of spring actuated autoinjector devices for Emgality and Aimovig. Current Medical Research and Opinion. 2020;36(8):1343-1354	Outcomes not relevant to scope
Faya P, Borer MW, Griffiths KL, Parekh BS. Potency assignment of biotherapeutic reference standards. Journal of Pharmaceutical and Biomedical Analysis. 2020;191:113577.	Outcomes not relevant to scope

Citation	Decision
Ford JH, Schroeder K, Nyhuis AW, Foster SA, Aurora SK. Cycling through migraine preventive treatments: implications for all-cause total direct costs and disease-specific costs. JMCP. 2019;25(1):46-59.	Outcomes not relevant to scope
Ford JH, Ye W, Nichols RM, Foster SA, Nelson DR. Treatment patterns and predictors of costs among patients with migraine: evidence from the United States medical expenditure panel survey. Journal of Medical Economics. 2019;22(9):849-858	Outcomes not relevant to scope
Ford JH, Schroeder K, Buse DC, et al. Predicting initiation of preventive migraine medications: exploratory study in a large U.S. medical claims database. Current Medical Research and Opinion. 2020;36(1):51-61	Outcomes not relevant to scope
Ford JH, Foster SA, Nichols RM, et al. A real-world analysis of patient-reported outcomes in patients with migraine by preventive treatment eligibility status in the US and Europe. J Patient Rep Outcomes. 2020;4(1):53	Outcomes not relevant to scope
Foster SA, Chen CC, Ding Y, et al. Economic burden and risk factors of migraine disease progression in the US: a retrospective analysis of a commercial payer database. Journal of Medical Economics. 2020;23(11):1356-1364	Outcomes not relevant to scope
Hindiyeh NA, Zhang N, Farrar M, Banerjee P, Lombard L, Aurora SK. The role of diet and nutrition in migraine triggers and treatment: a systematic literature review. Headache: The Journal of Head and Face Pain. 2020;60(7):1300-1316	Outcomes not relevant to scope
Igarashi H, Ueda K, Jung S, Cai Z, Chen Y, Nakamura T. Social burden of people with the migraine diagnosis in Japan: evidence from a population-based cross-sectional survey. BMJ Open. 2020;10(11):e038987	Outcomes not relevant to scope
Iyengar S, Johnson KW, Ossipov MH, Aurora SK. CGRP and the trigeminal system in migraine. Headache: The Journal of Head and Face Pain. 2019;59(5):659-681.	Outcomes not relevant to scope
Martinez JM, Hindiyeh N, Anglin G, et al. Assessment of immunogenicity from galcanezumab phase 3 trials in patients with episodic or chronic migraine. Cephalalgia. 2020;40(9):978-989.	Outcomes not relevant to scope
Roessler T, Zschocke J, Roehrig A, Friedrichs M, Friedel H, Katsarava Z. Administrative prevalence and incidence, characteristics and prescription patterns of patients with migraine in Germany: a retrospective claims data analysis. J Headache Pain. 2020;21(1):85.	Outcomes not relevant to scope
Speck RM, Shalhoub H, Wyrwich KW, et al. Psychometric validation of the role function restrictive domain of the migraine specific quality-of-life questionnaire version 2. 1 electronic patient-reported outcome in patients with episodic and chronic migraine. Headache: The Journal of Head and Face Pain. 2019;59(5):756-774.	Outcomes not relevant to scope
Speck RM, Shalhoub H, Ayer DW, Ford JH, Wyrwich KW, Bush EN. Content validity of the Migraine-Specific Quality of Life Questionnaire version 2.1 electronic patient-reported outcome. J Patient Rep Outcomes. 2019;3(1):39	Outcomes not relevant to scope
Ailani J, Pearlman E, Zhang Q, Nagy AJ, Schuh K, Aurora SK. Positive response to galcanezumab following treatment failure to onabotulinumtoxinA in patients with migraine: post hoc analyses of three randomized double-blind studies. Eur J Neurol. 2020;27(3):542-549	Previously known information about galcanezumab related to efficacy
Ailani J, Andrews JS, Rettiganti M, Nicholson RA. Impact of galcanezumab on total pain burden: findings from phase 3 randomized, double-blind, placebo-controlled studies in patients with episodic or chronic migraine (EVOLVE-1, EVOLVE-2, and REGAIN trials). J Headache Pain. 2020;21(1):123	Previously known information about galcanezumab related to efficacy
Detke HC, Millen BA, Zhang Q, et al. Rapid onset of effect of galcanezumab for the prevention of episodic migraine: analysis of the evolve studies. Headache: The Journal of Head and Face Pain. 2020;60(2):348-359.	Previously known information about galcanezumab related to efficacy

Citation	Decision
Ford JH, Ayer DW, Zhang Q, et al. Two randomized migraine studies of galcanezumab: Effects on patient functioning and disability. Neurology. 2019;93(5):e508-e517	Previously known information about galcanezumab related to efficacy
Ford JH, Kurth T, Starling AJ, et al. Migraine headache day response rates and the implications to patient functioning: an evaluation of 3 randomized phase 3 clinical trials of galcanezumab in patients with migraine. Headache: The Journal of Head and Face Pain. 2020;60(10):2304-2319.	Previously known information about galcanezumab related to efficacy
Goadsby PJ, Dodick DW, Martinez JM, et al. Onset of efficacy and duration of response of galcanezumab for the prevention of episodic migraine: a post-hoc analysis. J Neurol Neurosurg Psychiatry. 2019;90(8):939-944	Previously known information about galcanezumab related to efficacy
Kielbasa W, Helton DL. A new era for migraine: Pharmacokinetic and pharmacodynamic insights into monoclonal antibodies with a focus on galcanezumab, an anti-CGRP antibody. Cephalalgia. 2019;39(10):1284-1297	Previously known information about galcanezumab related to efficacy
Martin V, Samaan KH, Aurora S, et al. Efficacy and safety of galcanezumab for the preventive treatment of migraine: a narrative review. Adv Ther. 2020;37(5):2034-2049.	Previously known information about galcanezumab related to efficacy
Mulleners WM, Kim BK, Láinez MJA, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. The Lancet Neurology. 2020;19(10):814-825.	Previously known information about galcanezumab related to efficacy
Ossipov MH, Raffa RB, Pergolizzi Jr JV. Galcanezumab: a humanized monoclonal antibody for the prevention of migraine and cluster headache. Drugs Today. 2020;56(1):5	Previously known information about galcanezumab related to efficacy
Ruff DD, Ford JH, Tockhorn-Heidenreich A, et al. Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure. Cephalalgia. 2019;39(8):931-944.	Previously known information about galcanezumab related to efficacy
Ruff DD, Ford JH, Tockhorn-Heidenreich A, et al. Efficacy of galcanezumab in patients with episodic migraine and a history of preventive treatment failure: results from two global randomized clinical trials. Eur J Neurol. 2020;27(4):609-618.	Previously known information about galcanezumab related to efficacy
Sakai F, Ozeki A, Skljarevski V. Efficacy and safety of galcanezumab for prevention of migraine headache in Japanese patients with episodic migraine: A phase 2 randomized controlled clinical trial. Cephalalgia Reports. 2020;3:251581632093257	Previously known information about galcanezumab related to efficacy
Shibata M, Nakamura T, Ozeki A, Ueda K, Nichols RM. Migraine-specific quality-of-life questionnaire (MSQ) version 2. 1 score improvement in Japanese patients with episodic migraine by galcanezumab treatment: Japan phase 2 study. JPR. 2020;Volume 13:3531-3538	Previously known information about galcanezumab related to efficacy
Silberstein SD, Stauffer VL, Day KA, Lipsius S, Wilson MC. Galcanezumab in episodic migraine: subgroup analyses of efficacy by high versus low frequency of migraine headaches in phase 3 studies (EVOLVE-1 & EVOLVE-2). J Headache Pain. 2019;20(1):75.	Previously known information about galcanezumab related to efficacy
Smitherman TA, Tietjen GE, Schuh K, et al. Efficacy of galcanezumab for migraine prevention in patients with a medical history of anxiety and/or depression: a post hoc analysis of the phase 3, randomized, double-blind, placebo-controlled REGAIN, and pooled EVOLVE-1 and EVOLVE-2 studies. Headache: The Journal of Head and Face Pain. 2020;60(10):2202-2219.	Previously known information about galcanezumab related to efficacy
Stauffer VL, Wang S, Voulgaropoulos M, Skljarevski V, Kovacik A, Aurora SK. Effect of galcanezumab following treatment cessation in patients with	Previously known information about galcanezumab related to efficacy

Citation	Decision
migraine: results from 2 randomized phase 3 trials. Headache: The Journal of Head and Face Pain. 2019;59(6):834-847	
Stauffer VL, Turner I, Kemmer P, et al. Effect of age on pharmacokinetics, efficacy, and safety of galcanezumab treatment in adult patients with migraine: results from six phase 2 and phase 3 randomized clinical trials. J Headache Pain. 2020;21(1):79.	Previously known information about galcanezumab related to efficacy
Yang CP, Lee CF, Dell'Agnello G, Hundemer HP, Lipsius S, Wang SJ. Safety and efficacy of galcanezumab in Taiwanese patients: a post-hoc analysis of phase 3 studies in episodic and chronic migraine. Current Medical Research and Opinion. 2020;36(10):1653-1666	Previously known information about galcanezumab related to efficacy
Bangs ME, Kudrow D, Wang S, et al. Safety and tolerability of monthly galcanezumab injections in patients with migraine: integrated results from migraine clinical studies. BMC Neurol. 2020;20(1):25	Previously known information about galcanezumab related to safety
Oakes TM, Kovacs R, Rosen N, et al. Evaluation of cardiovascular outcomes in adult patients with episodic or chronic migraine treated with galcanezumab: data from three phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies. Headache: The Journal of Head and Face Pain. 2020;60(1):110-123.	Previously known information about galcanezumab related to safety
Stauffer VL, Wang S, Bonner J, et al. Evaluation of injection-site-related adverse events with galcanezumab: a post hoc analysis of phase 3 studies in participants with migraine. BMC Neurol. 2020;20(1):194.	Previously known information about galcanezumab related to safety
Johnson KW, Morin SM, Wroblewski VJ, Johnson MP. Peripheral and central nervous system distribution of the CGRP neutralizing antibody [125 I] galcanezumab in male rats. Cephalalgia. 2019;39(10):1241-1248.	Study population outside approved label indication
Kielbasa W, Quinlan T. Population pharmacokinetics of galcanezumab, an anti-CGRP antibody, following subcutaneous dosing to healthy individuals and patients with migraine. The Journal of Clinical Pharmacology. 2020;60(2):229-239	Study population outside approved label indication
Ford JH, Foster SA, Stauffer VL, Ruff DD, Aurora SK, Versijpt J. Patient satisfaction, health care resource utilization, and acute headache medication use with galcanezumab: results from a 12-month open-label study in patients with migraine. PPA. 2018;12:2413-2424	Study published outside of the timeframe of our review
Ford JH, Stauffer VL, McAllister P, et al. Functional impairment and disability among patients with migraine: evaluation of galcanezumab in a long-term, open-label study. Qual Life Res. 2021;30(2):455-464.	Study published outside of the timeframe of our review
Ford J, Tassorelli C, Leroux E, et al. Changes in patient functioning and disability: results from a phase 3, double-blind, randomized, placebo-controlled clinical trial evaluating galcanezumab for chronic migraine prevention (Regain). Qual Life Res. 2021;30(1):105-115.	Study published outside of the timeframe of our review
Foster SA, Balkaran BL, Cambron-Mellott MJ, et al. Demographic and clinical characteristics of prevention-eligible patients with migraine in the US: a linked national survey and administrative claims database study. Current Medical Research and Opinion. 2021;37(3):443-457.	Study published outside of the timeframe of our review

Appendix D. ICER Systematic Literature Review

Table D1. ICER Systematic Literature Review Results

Drug	Search Yield	References Screened in Full-Text	New Evidence Identified
Revlimid®	66	15	1
Sprycel®	11	5	2
Emgality®	32	13	7

Evidence identified for the three drugs overlaps with references submitted by their respective manufacturers.

Table D2. Search Strategy in PubMed

1	((Revlimid OR lenalidomide OR Sprycel OR dasatinib OR Emgality OR galcanezumab-gnlm OR 'Pro Air' OR albuterol) AND (('Randomized controlled trial' OR 'randomised 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 2019/01/01:2020/12/01[dp])

Appendix E. 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 California 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 California 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
    a) ICER applies the same evidentiary standards to real-world evidence that it applies to all other forms of evidence and is happy to consider real-world evidence as part of the California UPI report.

b) High-quality real-world evidence 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 California 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 California 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
	Bristol Myers Squibb	
	Revlimid®	
1.	**Evidence Supporting Revlimid's Value**: Important evidence that was within the specified criteria and that supports lenalidomide's value was excluded; however, new robust evidence was published during 2019-2020 that has altered previous understanding of lenalidomide value, such as: • Clinical and RWE demonstrating long-term effectiveness, longer time to next treatment, and safety of lenalidomide maintenance in MM (Alonso et al., 2020; Hari et al., 2020; Joseph et al., 2020; Leonard et al., 2019; Modi et al., 2020; Patel et al., 2020) • Improved PFS using lenalidomide maintenance among various subgroups, including high-risk and elderly MM populations, regardless of transplant eligibility (Jackson et al., 2019) • RWE of improved survival using lenalidomide regimens in MM patients (Barth et al., 2019; Zamagni et al., 2019) • Survival benefits of combination therapies with lenalidomide in MM (Durie et al., 2020; Ramasamy et al., 2020) • Efficacy and safety of lenalidomide regimens in lymphoma supporting new indications and additional long-term and subgroup analyses (Lansigan et al., 2020; Leonard et al., 2019; Liu et al., 2019) To assist ICER with the systematic review in Phase I, BMS provided 45 scientific publications that support lenalidomide's safety, clinical effectiveness, and economic value. ICER indicated in its response that none of the evidence met the review process criteria, thereby excluding high-quality evidence of the added net health benefit of lenalidomide. BMS reviewed ICER's response to each submitted article and provided a summary below of those to be reconsidered for inclusion.	Please see GERs 1a, 1b, 5a, 5b.
2.	**Revlimid Indications for Review**: ICER only considers reviewing evidence related to an indication if current use is at least 10% of overall utilization. This arbitrary utilization threshold diminishes the value of investigating the benefit of a treatment for subtypes and penalizes companies for targeting areas of high unmet need. Further, it devalues justifiable price increases for multi-indication therapies in areas like hematology. Lenalidomide use in lymphoma and MM indications meets either ICER's prevalent utilization criterion (10% or more of the drug's utilization) or the rapid-increase utilization criteria (use for an indication is rapidly increasing) to support an increase in price in California. ICER, however, excluded high quality new evidence submitted for FL and MZL. Exclusion of evidence in subtypes diminishes the value of innovation and discredits the unmet need of those patients with specific types of lymphoma. FL and MZL are rare and incurable cancers with a high burden of relapse and disease progression despite treatment. FL and MZL represent 22% and 7% of non-Hodgkin lymphomas, respectively (NHL Subtypes, n.d.). Relapse rates range from 21% to 74% in relapsed/refractory FL and 3.1% to 37% among relapsed/refractory MZL patients (Bentur et al., 2018; Nakamura et al., 2012; Raderer et al., 2005; Summerfield et al., 2004). The unmet need in patients with relapsed or refractory FL or MZL is evident based on high relapse rates, increased risk of lingering and cumulative chemotherapy-related	Please see GERs 5a and 5b. In line with clinical practice and FDA labeling, marginal zone lymphoma and follicular lymphoma are considered distinct indications and we have followed this in our report. Although the AUGMENT trial is a high-quality RCT that demonstrates improved outcomes of patients with both follicular and marginal zone lymphoma, based on input from the manufacturer, these indications do not account for greater than 10% of use (either as single indications or in aggregate) and therefore did not meet the UPI criteria for assessing new evidence as outlined in our protocol. During this UPI review cycle, we would have allowed evidence for two or more separate indications that in aggregate account for greater than 10% of use, to potentially provide

#	Comment	Response
	toxicities, and shortened PFS outcomes with each subsequent line of therapy after the first-line therapy (Link et al., 2019; MacDonald et al., 2016). Alternative treatment options such as lenalidomide are needed to delay progression, confer durable responses, and reduce chemotherapy-related toxicities (Chiu et al., 2019; Denlinger et al., 2018). BMS remains committed to bringing forth innovative medicines for patients with unmet medical needs, as is evident in the 2019 FDA approval of lenalidomide in combination with rituximab for the treatment of patients with relapsed or refractory FL and MZL.	new evidence for a price increase. In aggregate, per the manufacturer, the two new indications for lenalidomide account for less than 10% of use.
3.	**Revlimid and Combination Therapy:** ICER excluded important trials that evaluated novel combination therapies with lenalidomide with the reason "intervention/comparison not relevant to scope." Combination therapies are essential to managing many cancers, particularly the use of lenalidomide in MM. The standard of care has been evolving with innovation in front-line combination therapy regimens. These studies are crucial for optimizing treatment options for patients. New therapy combinations with lenalidomide in the selected 2019-2020 publications show improved clinical outcomes relative to existing therapy combinations. The discovery of how lenalidomide can be optimized in different combination therapies requires investment in research across multiple stakeholders, organizations, and patient groups due to disease complexity. The exclusion of these studies does not align with ICER's stated methodology.	Please see GERs 1c and 5a.
4.	**Leonard et al., 2019** **Impact and Implications:** The AUGMENT study is a large, randomized phase 3 clinical trial that compared lenalidomide plus rituximab (R2) to placebo plus rituximab in FL or MZL patients. This study, lead to the approval of R2 for patients with RR FL or MZL in 2019. Additional analyses on longer duration follow-up and subgroups have also been reported. FL and MZL are subtypes of lymphoma, an approved indication that comprises at least 10% of overall lenalidomide utilization. **Outcome**: PFS was significantly superior in the R2 group versus placebo plus rituximab (HR: 0.46; 95% CI, 0.34 to 0.62; P < .001). Median PFS was 39.4 months (95% CI, 22.9 months to not reached) with R2 14.1 months (95% CI, 11.4 to 16.7 months) with placebo plus rituximab. PFS improved in all prespecified subgroups. Grade 3 or 4 neutropenia and leukopenia were higher with R2; no other grade 3 or 4 adverse event differed by 5% or more between groups.	Please see GERs 5a and 5b. Please see the response to Comment 2.
5.	**Gay et al., 2020** **Impact and Implications:** This study reported new evidence that was not previously known on survival analysis in the FORTE trial, a randomized, open-label, phase 2 trial. Transplant-eligible NDMM patients were randomized to receive carfilzomib (K) lenalidomide (R) dexamethasone (d) induction followed by autologous stem-cell transplantation (ASCT) and KRd consolidation), 12 KRd cycles or K-cyclophosphamide(C)-d induction, followed by ASCT and KCd consolidation.	Please see GER 1a, 1b, and 5a.

#	Comment	Response
	Longer duration follow-up allowed for PFS evaluation. Additionally, no data on KR maintenance vs R alone were previously available. **Outcome**: The benefit of KRd-ASCT vs KCd-ASCT was observed overall and in subgroups. 3-year OS was 90% with KRd-ASCT vs 83% with KCd-ASCT. KRd-ASCT vs KCd-ASCT PFS HR (95% CI) was 0.53 (0.37-0.77). After a median follow-up of 31 months from randomization to maintenance, 46% of MRD-positive patients at randomization turned negative in KR versus 32% in R (P=0.04). During maintenance, a similar proportion of patients experienced more than one grade 3-4 adverse events in the two arms.	
6.	**Hari et al., 2019** **Impact and Implications:** This study presented new evidence from an extended RCT and evaluated new evidence related to TTNT that was not previously known. Treatment patterns and costs associated with post-ASCT R maintenance therapy in real-world MM patient populations had not been previously studied. This study evaluated TTNT and demonstrated the importance of real-word evidence with R maintenance, which reduced outpatient costs and extended TTNT. **Outcome**: R maintenance improved TTNT and reduced outpatient costs in the first 12 months post ASCT ($3761 versus $5360; p<0.0001, mainly due to lower intravenous and chemotherapy-related costs and significantly (p<0.0001) lower pharmacy usage).	Please see GER 1a, 1b, and 5a.
7.	**Nielsen et al., 2020** **Impact and Implications:** This study presented new evidence that was not previously known on the impact of long-term treatment with immunomodulatory drugs on HRQoL. Data about HRQoL during up to 1 year maintenance therapy with R and thalidomide were presented. These types of data are rarely reported in the current literature. HRQoL subscales data were shown from the open-label, randomized HOVON-87/NMSG18 study, a phase 3 study in NDMM transplant ineligible patients, comparing melphalan-prednisolone in combination with thalidomide or lenalidomide, followed by maintenance therapy until progression (MPT-T or MPR-R). **Outcome:** A sub-analysis of patients who started maintenance therapy and were treated for at least three months showed that R resulted in a clinically & statistically meaningful improvement in global QoL (p=0.003), physical (p<0.001), and role functioning over time (p<0.001). In contrast, there was no clinical benefit of thalidomide maintenance treatment, with clinically relevant worsening of peripheral neuropathy. The side effect profile of treatment did not negatively affect global QoL, but it was, however, clinically relevant for the patients.	Please see GER 1a, 1b, and 5a.
8.	**Modi et al., 2020** **Impact and Implications:** This was the first study demonstrating survival benefit of maintenance therapy following second ASCT. It reported on a retrospective	We have reevaluated the study by Modi et al. and still conclude that this does not alter prior beliefs about lenalidomide's efficacy in multiple

#	Comment	Response
	analysis of relapsed MM patients undergoing salvage ASCT, which demonstrated a survival benefit with the use of lenalidomide maintenance after second ASCT. **Outcome:** R maintenance was associated with improved PFS (HR 0.46, p = 0.009) and OS (HR 0.25, p = 0.009) compared to no-maintenance. At a median follow-up of 58 months from second ASCT, 3-year PFS and OS for no-maintenance, lenalidomide, and bortezomib maintenance were 11.2%, 29.9%, and 0%, respectively; and 58.5%, 83.3%, and 67.5% respectively.	myeloma. In reviewing treatment algorithms and discussions with clinical providers, lenalidomide following a second autologous stem cell transplantation would be considered standard and thus this finding is confirming an *a priori* belief about the efficacy of lenalidomide. Please see GER 5a.
9.	**Clinical Evidence Supporting Revlimid Use in MM:** FIRST (NCT00689936) (Belch et al., 2020) This study reported outcomes in the Canadian/US subgroup of the phase 3 FIRST trial and advanced the understanding of the continuous treatment in the United States. It demonstrated significant improvement in PFS and OS with lenalidomide in combination with low-dose dexamethasone until disease progression (Rd continuous) vs melphalan, prednisone and thalidomide (MPT) in transplant-ineligible patients with MM. Rd continuous also extended PFS vs fixed-duration Rd for 18 cycles. The findings support the role of Rd continuous as a standard of care for transplant-ineligible patients with MM.	Please see GER 1a, 1b, and 5a.
10.	**Clinical Evidence Supporting Revlimid Use in MM:** GRIFFIN (NCT02874742) (Voorhees et al., 2020) The phase 2 GRIFFIN trial is the first trial to demonstrate quadruplet combination therapy in patients with NDMM. This trial evaluated the addition of daratumumab to lenalidomide, bortezomib, and dexamethasone (D-RVd) induction and consolidation with lenalidomide (R) maintenance, in conjunction with autologous stem cell transplant (ASCT) in patients with newly diagnosed MM in the United States. This readout reported the primary efficacy and updated secondary efficacy and safety results of the randomized phase of the trial. The primary end point, stringent complete response (sCR) rate by the end of post-ASCT consolidation, was 42.4% for D-RVd vs 32.0% for RVd (OR: 1.57; 95% CI: 0.87-2.82; 1-sided P = .068). With longer follow-up, responses deepened with improved sCR rates for D-RVd. Serious AEs were reported in 39.4% of patients in the D-RVd group and 51.0% in the RVd group. Four second primary malignancies were observed in the D-RVd group, and one secondary primary malignancy was observed in the RVd group.	Please see GER 1c. This intervention is not relevant to the scope as the primary aim of this study was to evaluate the addition of daratumumab to the Revlimid® + Velcade® + dexamethasone regimen.
11.	**Clinical Evidence Supporting Revlimid Use in MM:** MYELOMA XI (ISRCTN49407852) (Pawlyn et al., 2019) This long-term follow up of the randomized, phase 3, adaptive design trial presented updated PFS, TTNT, and an exploratory analysis estimating the aggressiveness of relapse for MM patients who received lenalidomide maintenance or observation. The median PFS was 41 months [95% CI 38-45] for patients allocated to lenalidomide and 21 months [19-23] for observation (HR	Please see GER 1a, 1b, and 5a.

#	Comment	Response
	0.50 [0.44-0.56], p <0.01). TTNT was also significantly longer with lenalidomide compared to observation. The median TTNT was 52 months for patients allocated to lenalidomide and 28 months for observation (HR 0.55 [0.49-0.62] p < 0.01). The trial found no difference in the aggressiveness of relapse.	
12.	**Clinical Evidence Supporting Revlimid Use in MM:** StaMINA (NCT01109004) (Hari et al., 2020) This study evaluated long-term lenalidomide maintenance in MM patients. It reported on six-years follow up of data and the results of lenalidomide discontinuation beyond three years. The results from the largest RCT of further interventions following frontline transplantation in MM support lenalidomide as maintenance beyond 3 years based on the higher probability of PFS observed at the 6-year time point. It showed that discontinuation, even after 38 months, was associated with inferior PFS (79.5% vs. 61% at 5 years; HR = 1.91, p = 0.0004).	Please see GER 1a, 1b, and 5a.
13.	**Real-world and Modeled Evidence of Revlimid's Value in Multiple Myeloma:** Alonso et al., 2020; this study was a real-world clinical practice analysis of the impact of prolonged treatment with lenalidomide on the kinetics of minimal residual disease (MRD) and its prognostic potential. MM patients who received lenalidomide maintenance and whose MRD levels were observed during the treatment period by multiparametric flow cytometry or next-generation sequencing were evaluated. With lenalidomide maintenance, the percentage of patients with less than a complete response was reduced from 32.4% to 12.9%, and the final number of patients who achieved MRD negativity increased from 26.6% to 51.8%. The results support the role of lenalidomide maintenance therapy, not only to sustain, but also to increase the depth of disease response with a PFS benefit.	Please see GER 1a, 1b, and 5a.
14.	**Real-world and Modeled Evidence of Revlimid's Value in Multiple Myeloma:** Chari et al., 2019; this study was a real-world commercial and Medicare claims analysis of clinical and economic outcomes among patients with MM who received lenalidomide- and/or bortezomib-containing therapy and did not receive stem cell transplant. Lenalidomide-containing therapy resulted in longer median duration of treatment and median time to next treatment compared to bortezomib-containing therapy. Costs associated with outpatient-physician and chemotherapy-related visits were also significantly lower.	Please see GER 4b and 5a.
15.	**Real-world and Modeled Evidence of Revlimid's Value in Multiple Myeloma:** Dhakal et al., 2020; despite the demonstrated benefit of lenalidomide in MM, a lack of head-to-head comparisons across the MM landscape persists. This study was unique in using a Bayesian statistical approach and conducting a network meta-analysis of all phase 3 RCTs with the aim of ranking different treatments in terms of efficacy, safety, and cost. Of the 14 treatment options, daratumumab, lenalidomide, and dexamethasone prolonged PFS the most.	Please see GER 4a.
16.	**Real-world and Modeled Evidence of Revlimid's Value in Multiple Myeloma:** Jackson et al., 2019; this study was the first to evaluate the impact of lenalidomide maintenance therapy on productivity from a patient and societal	Please see GER 4b.

#	Comment	Response
	perspective. Modelling the impact of maintenance therapy alone for these patients reduced average productivity losses by just over 10%. Compared with therapies that require intravenous and subcutaneous administration, the use of oral maintenance therapies, such as lenalidomide, could also help decrease administration and indirect costs.	
17.	**Clinical Evidence Supporting Revlimid's Value in Lymphoma:** AUGMENT (NCT01938001) (Gribben et al., 2019; J. Leonard et al., 2019); important NHL subtypes (follicular lymphoma) and subgroups (patients who relapse within two years of initial chemoimmunotherapy i.e. POD24) were examined for the potential impact of receiving (R2) vs R and placebo. R2 demonstrated improvement in efficacy over R with placebo, including in patients with POD24, patients who have historically been associated with worse outcomes, and in elderly and Japanese subgroups. Sensitivity to next treatment and median PFS was superior for R2 over R with placebo.	Please see GER 5a and 5b. Please see the response to Comment 2.
18.	**Clinical Evidence Supporting Revlimid's Value in Lymphoma:** MAGNIFY (NCT01996865) (Coleman et al., 2020; Lansigan et al., 2020); MAGNIFY is a multicenter, phase IIIb trial in patients with FL, MZL, or mantle cell lymphoma (MCL) in which optimal lenalidomide duration is being explored. Efficacy results for these lymphoma subtypes and in advanced-age patients demonstrate that R2 is active with a tolerable safety profile.	Please see GER 5a and 5b. Please see the response to Comment 2.
	Sprycel®	
1.	**Evidence Supporting Sprycel's Value:** Important evidence within the specified criteria and supporting dasatinib's value were excluded. To assist ICER with the systematic review, BMS provided 30 scientific publications that support dasatinib's safety, clinical effectiveness, and economic value. ICER indicated in its response that none of the evidence met the review process criteria, thereby excluding high-quality evidence of the added net health benefit of dasatinib. BMS has reviewed ICER's response to each submitted article and is elucidating why 19 of the 30 studies originally submitted should be further reconsidered for inclusion. For example, the Cortes et al. (2020) study was categorized as "previously known information related to dasatinib efficacy;" however, this was the first prospective randomized trial to provide evidence on the benefit of an early switch to dasatinib relative to staying on imatinib following poor response to first-line imatinib. Findings from this study further support new evidence of usage for dasatinib within the CML indication.	Please see GER 1a, 1b, and 5a.
2.	**Sprycel Indications for Consideration:** Dasatinib use in CML and ALL, meets either ICER's prevalent utilization criterion (10% or more of the drug's utilization) or the rapid-increase utilization criteria (use for an indication is rapidly increasing) to support an increase in price in California. ICER should include high-quality evidence for the added value of the approved pediatric Ph+ ALL subpopulation within the ALL indication. ALL, including pediatric Ph+ ALL, represents greater than 10% of dasatinib utilization as indicated in the data submitted to ICER previously. Dasatinib evidence and newly approved indications specific to pediatric populations are important to those patients with ALL, ensuring effective and safe therapies for populations with high unmet needs. Excluding these studies ignores	Please see GER 5a and 5b. In line with clinical practice and FDA labeling, Ph+ ALL in a pediatric population is considered a distinct indication from Ph+ ALL in adults and we have followed this in our report.

#	Comment	Response
	the continued research, innovation, and value provided to pediatric patients. ICER's indication criteria should consider subpopulations that contribute to indications that comprise at least 10% of the drug's utilization.	
3.	**Outcome**: HRQoL **Prior Evidence**: Provides HRQOL differences between first line dasatinib and imatinib CML treatment arms. EQ-5D was 0.77 and 0.79 at baseline and 0.80 and 0.82 at one year for dasatinib and imatinib, respectively. HRQOL differences between treatment arms were non-significant (Labeiet et al., 2015). **New Evidence**: First-line dasatinib CML patients reported significantly better disease-specific HRQOL outcomes in impact on daily life ($\Delta = 8.7$, $p = 0.002$), satisfaction with social life ($\Delta = 13.45$, $p = 0.001$) and symptom burden ($\Delta = 7.69$, $p = 0.001$), compared to imatinib treatment arm (Efficace et al., 2019). **New Evidence Implications**: First study showing dasatinib's HRQOL improvement vs. standard of care. Findings can support clinical-decision making for first-line treatment decisions.	Please see GER 1a, 1b, and 5a.
4.	**Outcome**: Major molecular response (MMR) **Prior Evidence**: Retrospective study found improved response rates and EFS when dasatinib was administered early after imatinib resistance (Quinta's-Cardama et al., 2009). **New Evidence**: MMR at 12 months was 29% among dasatinib patients and 13% among imatinib patients (p=0.005). Accounting for treatment crossover, a higher proportion of dasatinib patients achieved MMR vs imatinib patients at 24 months (64% vs. 41%) (Cortes et al., 2020; DASCERN trial). **New Evidence Implications**: First prospective randomized trial to demonstrate benefit of early switching to dasatinib vs. remaining on imatinib within the CML indication.	Please see GER 1a, 1b, and 5a.
5.	**Outcome**: Discontinuation after sustained deep molecular response **Prior Evidence**: Limited evidence of sustained deep molecular response in a large CML cohort after discontinuation of first-line dasatinib only. Prior studies included small numbers of patients receiving first-line dasatinib or nilotinib (e.g., Rea et al., 2017 and Saussele et al., 2018). **New Evidence**: 55% of patients had treatment-free remission at 6 months after dasatinib discontinuation; median follow-up was 23.3 months. Estimated treatment-free remission at 6 months was 55.2% (Kimura et al., 2020; DADI trial). **New Evidence Implications**: Study findings indicate patients with CML can safely discontinue dasatinib after first-line treatment and having achieved sustained deep molecular response.	Please see GER 1a, 1b, and 5a.

#	Comment	Response
6.	**Outcome**: Treatment-free remission (TFR) **Prior Evidence**: Demonstrates second-line or subsequent dasatinib discontinuation among CML patients after sustained deep molecular response for at least 1 year is achievable. Overall treatment-free remission at 6 months was 49% (Imagawa et al., 2015). **New Evidence**: Two-year TFR was 51% in first-line patients, and 42% in subsequent-line patients. Two-year progression-free survival was 99% in all patients (Shah et al., 2019; DASFREE trial). **New Evidence Implications**: Study findings show two-year TFR is feasible after dasatinib discontinuation. Results can inform treatment decisions in first-line and subsequent settings for patients considering TFR.	Please see GER 1a, 1b, and 5a.
7.	**Clinical Evidence and Value Supporting Sprycel's Use in ALL:** CA180-372/COG AALL1122 (Hunger et al., 2020) is a phase 2 trial of dasatinib and chemotherapy in pediatric patients with newly diagnosed pediatric Ph+ ALL. Findings from this trial showed a lower percentage of pediatric patients treated with dasatinib and chemotherapy required hematopoietic stem cell transplantation compared to previous trials conducted with imatinib, with comparable survival outcomes. The 5-year EFS 54.6% (95% CI, 44.5-63.6) and OS was 81.7% (95% CI, 82.8-87.9), compared to 60.3%/71.5% in EsPhALL 2004, and 57%/71.8% in EsPhALL 2010 (Biondi et al., 2012; Biondi et al., 2018). The FDA granted dasatinib's approval in this pediatric Ph+ ALL population based on findings from this study.	Please see GER 5a and 5b. In line with clinical practice and FDA labeling, Ph+ ALL in a pediatric population is considered a distinct indication from Ph+ ALL in adults and we have followed this in our report.
8.	**Clinical Evidence and Value Supporting Sprycel's Use in ALL:** CCCGALL-2015 (Shen et al., 2020) is a phase III randomized study to determine whether dasatinib given at 80 mg is more effective than imatinib at 300 mg in improving event-free survival in pediatric Ph+ ALL. Dasatinib exhibited a higher efficacy and tolerable safety profile in comparison to imatinib, with a greater 4-year event-free survival rate and overall survival rate. The 4-year event-free survival rate in the dasatinib group was significantly better than in the imatinib group (71.0% vs. 48.9%, p=0.005, log-rank test). The 4-year overall survival rate was also higher in the dasatinib group vs imatinib group (88.4% vs. 69.2%, p=0.04, log rank test). Study findings also showcase improved outcomes of dasatinib treatment at a dosage of 80 mg/m^2 per day compared to recent pediatric phase 2 trials of dasatinib given at a dosage of 60 mg/m^2 per day.	Please see GER 5a and 5b. In line with clinical practice and FDA labeling, Ph+ ALL in a pediatric population is considered a distinct indication from Ph+ ALL in adults and we have followed this in our report.
9.	**Clinical Evidence Demonstrating New Findings on Efficacy and Long-term Outcomes of Sprycel:** Maiti et al., 2020 provided the longest follow-up data available for dasatinib, with a median follow up of 6.5 years. Findings showed the 10-year overall survival, transformation-free survival, event-free survival, and failure-free survival rates were 89%, 95%, 86%, and 65%, respectively, among patients with chronic-phase chronic myeloid leukemia. This study supports the long-term impact of dasatinib on efficacy and safety in CML patients, as well as improved survival outcomes.	Please see GER 1a, 1b, and 5a.

#	Comment	Response
10.	**Clinical Evidence Demonstrating New Findings on Efficacy and Long-term Outcomes of Sprycel:** Findings from the DASISION trial (Breccia et al., 2019) found that patients with a high BMI treated with dasatinib demonstrated a significantly faster time to response compared with imatinib; specifically, more patients with a high BMI treated with dasatinib achieved MMR compared with those treated with imatinib (79.8% vs. 59.8%; p=0.0004); additionally, 54.1% of patients with a high BMI achieved MR4.5 with dasatinib, compared with 34.6% with imatinib (p=0.0013).	Please see GER 1a, 1b, and 5a.
11.	**Clinical Evidence Demonstrating New Findings on Efficacy and Long-term Outcomes of Sprycel:** Breccia et al., 2020 is a post hoc analysis of DASISION at 5-years' follow-up, which evaluated the effect of comorbidities on response outcomes with dasatinib vs imatinib. Molecular response rates were significantly higher with dasatinib than imatinib in patients with Charlson Comorbidity Index (CCI) 5-6. Time to response was significantly faster with dasatinib than imatinib in both the CCI 5-6 and CCI ≥7 groups. These findings demonstrate the benefit of first-line treatment with dasatinib in CML-CP patients with comorbidities. Results also demonstrate the importance of treatment choice when assessing a patient based on their comorbid conditions.	Please see GER 1a, 1b, and 5a.
12.	**High-Quality Real-World Evidence Demonstrating Value of Sprycel:** Goldberg et al., 2020, a large, real-world observational study of CP-CML patients, highlighted the importance of evaluating CV-risk profile and comorbidities prior to first-line tyrosine kinase inhibitors (TKI) therapy. Findings showed the incidence of CV-related hospitalizations and length of stay were lowest among patients receiving dasatinib. These real-world findings suggest dasatinib has the most preferable CV safety outcomes in comparison to other TKIs (imatinib and nilotinib).	Please see GER 4a and 5a.
13.	**High-Quality Real-World Evidence Demonstrating Value of Sprycel:** Economic and cost-effectiveness data are also critical for understanding an intervention's value, which may lead to improved patient access. Yue et al., 2019 is a high-quality study which used a Markov state transition model to compare the cost-effectiveness of second-line TKI for treatment practice of CML patients over a life-long time horizon. Findings indicate dasatinib is a cost-effective treatment option for CML patients, which provides improved clinical benefits compared to other second-line TKIs. Dasatinib resulted in an ICER of $79,114.19/QALY compared to nilotinib.	Please see GER 4a.

Appendix F. Manufacturer Comments

Full-text manufacturer comments begin on the following page.

Bristol Myers Squibb™

September 15, 2022
Re: Preliminary Report, Unsupported Price Increases Occurring in 2020 in California Notification, REVLIMID®

Bristol Myers Squibb (BMS) disagrees with ICER's response to the evidence BMS submitted on the effectiveness, safety, patient-reported outcomes, and economic impacts of REVLIMID® (lenalidomide) for its FDA-approved indications in lymphoma and multiple myeloma (MM). We outline here the importance and quality of the evidence that has been published between 2019-2020. A narrative summary is provided below, and a tabulation of evidence inclusive of study details and safety (n=39) is provided in Appendix 1. BMS reaffirms that the research presents new evidence that is high quality based on the GRADE method of evaluating research and meets the ICER criteria of being for an indication with at least 10% of lenalidomide's utilization.

Evidence Supporting Revlimid's Value: Important evidence that was within the specified criteria and that supports lenalidomide's value was excluded; however, new robust evidence was published during 2019-2020 that has altered previous understanding of lenalidomide value, such as:

- Clinical and real-world evidence (RWE) demonstrating long-term effectiveness, longer time to next treatment, and safety of lenalidomide maintenance in MM (Alonso et al., 2020; Hari et al., 2020; Joseph et al., 2020; Leonard et al., 2019; Modi et al., 2020; Patel et al., 2020)
- Improved progression-free survival (PFS) using lenalidomide maintenance among various subgroups, including high-risk and elderly MM populations, regardless of transplant eligibility (Jackson et al., 2019)
- RWE of improved survival using lenalidomide regimens in MM patients (Barth et al., 2019; Zamagni et al., 2019)
- Survival benefits of combination therapies with lenalidomide in MM (Durie et al., 2020; Ramasamy et al., 2020)
- Efficacy and safety of lenalidomide regimens in lymphoma supporting new indications and additional long-term and subgroup analyses (Lansigan et al., 2020; Leonard et al., 2019; Liu et al., 2019)

To assist ICER with the systematic review in Phase I, BMS provided 45 scientific publications that support lenalidomide's safety, clinical effectiveness, and economic value. ICER indicated in its response that none of the evidence met the review process criteria, thereby excluding high-quality evidence of the added net health benefit of lenalidomide. BMS reviewed ICER's response to each submitted article and provided a summary below of those to be reconsidered for inclusion. Table 1 highlights some of the high-quality evidence of added net health benefit that BMS submitted to ICER and merit reconsideration in accordance with the CA UPI protocol.

Revlimid Indications for Review: ICER only considers reviewing evidence related to an indication if current use is at least 10% of overall utilization. This arbitrary utilization threshold diminishes the value of investigating the benefit of a treatment for subtypes and penalizes companies for targeting areas of high unmet need. Further, it devalues justifiable price increases for multi-indication therapies in areas like hematology. Lenalidomide use in lymphoma and MM indications meets either ICER's prevalent utilization criterion (10% or more of the drug's utilization) or the rapid-increase utilization criteria (use for an indication is rapidly increasing) to support an increase in price in California. ICER, however, excluded high quality new evidence submitted for follicular lymphoma (FL) and marginal zone lymphoma (MZL). Exclusion of evidence in subtypes diminishes the value of innovation and discredits the unmet need of those patients with specific types of lymphoma. FL and MZL are rare and incurable cancers with a high burden of relapse and disease progression despite treatment. FL and MZL represent 22% and 7% of non-Hodgkin lymphomas, respectively (NHL Subtypes, n.d.). Relapse rates range from 21% to 74% in relapsed/refractory FL and 3.1% to 37% among relapsed/refractory MZL patients (Bentur et al., 2018; Nakamura et al., 2012; Raderer et al., 2005; Summerfield et al., 2004). The unmet need in patients with relapsed or refractory FL or MZL is evident based on high relapse rates, increased risk of lingering and cumulative chemotherapy-related toxicities, and shortened PFS outcomes with each subsequent line of therapy after the first-line therapy (Link et al., 2019; MacDonald et al., 2016). Alternative treatment options such as lenalidomide are needed to delay progression, confer durable responses, and reduce chemotherapy-related toxicities (Chiu et al., 2019; Denlinger et al., 2018). BMS remains committed to bringing forth innovative medicines for patients with unmet medical needs, as is evident in the 2019 FDA approval of lenalidomide in combination with rituximab for the treatment of patients with relapsed or

refractory FL and MZL.

Revlimid and Combination Therapy: ICER excluded important trials that evaluated novel combination therapies with lenalidomide with the reason "intervention/comparison not relevant to scope." Combination therapies are essential to managing many cancers, particularly the use of lenalidomide in MM. The standard of care has been evolving with innovation in front-line combination therapy regimens. These studies are crucial for optimizing treatment options for patients. New therapy combinations with lenalidomide in the selected 2019-2020 publications show improved clinical outcomes relative to existing therapy combinations. The discovery of how lenalidomide can be optimized in different combination therapies requires investment in research across multiple stakeholders, organizations, and patient groups due to disease complexity. The exclusion of these studies does not align with ICER's stated methodology.

The table below reviews key examples of high-quality new evidence that supports indications with at least 10% utilization and respective approvals during 2019-2020 for lenalidomide in patients with MM or lymphoma.

Table 1. Highlights of Evidence of the Value of Lenalidomide in MM & Lymphoma

Reference, Disease & Outcome	Impact and Implications	Outcome
Leonard et al., 2019 Lymphoma PFS	The AUGMENT study is a large, randomized phase 3 clinical trial that compared lenalidomide plus rituximab (R^2) to placebo plus rituximab in FL or MZL patients. This study, lead to the approval of R^2 for patients with RR FL or MZL in 2019. Additional analyses on longer duration follow-up and subgroups have also been reported. FL and MZL are subtypes of lymphoma, an approved indication that comprises at least 10% of overall lenalidomide utilization.	PFS was significantly superior in the R^2 group versus placebo plus rituximab (HR: 0.46; 95% CI, 0.34 to 0.62; P < .001). Median PFS was 39.4 months (95% CI, 22.9 months to not reached) with R^2 14.1 months (95% CI, 11.4 to 16.7 months) with placebo plus rituximab. PFS improved in all prespecified subgroups. Grade 3 or 4 neutropenia and leukopenia were higher with R^2; no other grade 3 or 4 adverse event differed by 5% or more between groups.
Gay et al., 2020 MM OS & PFS	This study reported new evidence that was not previously known on survival analysis in the FORTE trial, a randomized, open-label, phase 2 trial. Transplant-eligible NDMM patients were randomized to receive carfilzomib (K) lenalidomide (R) dexamethasone (d) induction followed by autologous stem-cell transplantation (ASCT) and KRd consolidation), 12 KRd cycles or K-cyclophosphamide(C)-d induction, followed by ASCT and KCd consolidation. Longer duration follow-up allowed for PFS evaluation. Additionally, no data on KR maintenance vs R alone were previously available.	The benefit of KRd-ASCT vs KCd-ASCT was observed overall and in subgroups. 3-year OS was 90% with KRd-ASCT vs 83% with KCd-ASCT. KRd-ASCT vs KCd-ASCT PFS HR (95% CI) was 0.53 (0.37-0.77). After a median follow-up of 31 months from randomization to maintenance, 46% of MRD-positive patients at randomization turned negative in KR versus 32% in R (P=0.04). During maintenance, a similar proportion of patients experienced more than one grade 3-4 adverse events in the two arms.

Reference, Disease & Outcome	Impact and Implications	Outcome
Hari et al., 2019 MM Time to next treatment (TTNT)	This study presented new evidence from an extended RCT and evaluated new evidence related to TTNT that was not previously known. Treatment patterns and costs associated with post-ASCT R maintenance therapy in real-world MM patient populations had not been previously studied. This study evaluated TTNT and demonstrated the importance of real-word evidence with R maintenance, which reduced outpatient costs and extended TTNT.	R maintenance improved TTNT and reduced outpatient costs in the first 12 months post ASCT ($3761 versus $5360; p<0.0001, mainly due to lower intravenous and chemotherapy-related costs and significantly (p<0.0001) lower pharmacy usage).
Nielsen et al., 2020 MM HRQoL	This study presented new evidence that was not previously known on the impact of long-term treatment with immunomodulatory drugs on HRQoL. Data about HRQoL during up to 1 year maintenance therapy with R and thalidomide were presented. These types of data are rarely reported in the current literature. HRQoL subscales data were shown from the open-label, randomized HOVON-87/NMSG18 study, a phase 3 study in NDMM transplant ineligible patients, comparing melphalan-prednisolone in combination with thalidomide or lenalidomide, followed by maintenance therapy until progression (MPT-T or MPR-R).	A sub-analysis of patients who started maintenance therapy and were treated for at least three months showed that R resulted in a clinically & statistically meaningful improvement in global QoL (p=0.003), physical (p<0.001), and role functioning over time (p<0.001). In contrast, there was no clinical benefit of thalidomide maintenance treatment, with clinically relevant worsening of peripheral neuropathy. The side effect profile of treatment did not negatively affect global QoL, but it was, however, clinically relevant for the patients.
Modi et al., 2020 MM OS & PFS	This was the first study demonstrating survival benefit of maintenance therapy following second ASCT. It reported on a retrospective analysis of relapsed MM patients undergoing salvage ASCT, which demonstrated a survival benefit with the use of lenalidomide maintenance after second ASCT.	R maintenance was associated with improved PFS (HR 0.46, p = 0.009) and OS (HR 0.25, p = 0.009) compared to no-maintenance. At a median follow-up of 58 months from second ASCT, 3-year PFS and OS for no-maintenance, lenalidomide, and bortezomib maintenance were 11.2%, 29.9%, and 0%, respectively; and 58.5%, 83.3%, and 67.5% respectively.

ASCT: autologous stem-cell transplantation; CI: confidence interval; HR: hazard ratio; HRQoL: health-related quality of life; MM: multiple myeloma; OS: overall survival; PFS: progression-free survival; R: Revlimid (lenalidomide); TTNT: time to next treatment
Notes: Quality of evidence as rated by BMS using GRADE criteria: Leonard et al., 2019 – high; Gay et al., 2020 – high; Hari et al., 2019 – moderate; Nielsen et al., 2020 – high; Modi et al., 2020 - moderate

Additional evidence submitted to ICER is reviewed below. Based in part on this evidence-based review, the value of lenalidomide increased during the UPI timeframe. The peer-reviewed evidence testifies to the importance of investing in and accelerating the research necessary to optimize lenalidomide use and long-term value for patient care.

Clinical Evidence Supporting Revlimid Use in MM

Lenalidomide is an oral IMiD® (immunomodulatory) agent with proven effectiveness and safety among NDMM and relapsed or refractory MM (RRMM) patients (McCarthy et al., 2012; Richardson et al., 2009). Research on subpopulations, different comparators, and long-term follow up published during 2019-2020 have continued to deepen the knowledge of lenalidomide value in MM. Survival improvements in MM have been derived from the introduction of thalidomide, bortezomib, and lenalidomide, but several new therapies, often combined with lenalidomide, have been approved. The past few years have witnessed continuing advances in the understanding of

myeloma biology and the impact of specific drugs and combinations in patient subpopulations. Achieving the full promise of therapies in MM will require ongoing long-term investment in developing the evidence necessary to inform optimal care. The following sections summarize recent evidence of lenalidomide's value in NDMM, RRMM, and post-autologous stem cell transplant (ASCT) populations.

FIRST (NCT00689936) (Belch et al., 2020)
This study reported outcomes in the Canadian/US subgroup of the phase 3 FIRST trial and advanced the understanding of the continuous treatment in the United States. It demonstrated significant improvement in PFS and OS with lenalidomide in combination with low-dose dexamethasone until disease progression (Rd continuous) vs melphalan, prednisone and thalidomide (MPT) in transplant-ineligible patients with MM. Rd continuous also extended PFS vs fixed-duration Rd for 18 cycles. The findings support the role of Rd continuous as a standard of care for transplant-ineligible patients with MM.

GRIFFIN (NCT02874742) (Voorhees et al., 2020)
The phase 2 GRIFFIN trial is the first trial to demonstrate quadruplet combination therapy in patients with NDMM. This trial evaluated the addition of daratumumab to lenalidomide, bortezomib, and dexamethasone (D-RVd) induction and consolidation with lenalidomide (R) maintenance, in conjunction with autologous stem cell transplant (ASCT) in patients with newly diagnosed MM in the United States. This readout reported the primary efficacy and updated secondary efficacy and safety results of the randomized phase of the trial. The primary end point, stringent complete response (sCR) rate by the end of post-ASCT consolidation, was 42.4% for D-RVd vs 32.0% for RVd (OR: 1.57; 95% CI: 0.87-2.82; 1-sided P = .068). With longer follow-up, responses deepened with improved sCR rates for D-RVd. Serious AEs were reported in 39.4% of patients in the D-RVd group and 51.0% in the RVd group. Four second primary malignancies were observed in the D-RVd group, and one secondary primary malignancy was observed in the RVd group.

MYELOMA XI (ISRCTN49407852) (Pawlyn et al., 2019)
This long-term follow up of the randomized, phase 3, adaptive design trial presented updated PFS, TTNT, and an exploratory analysis estimating the aggressiveness of relapse for MM patients who received lenalidomide maintenance or observation. The median PFS was 41 months [95% CI 38-45] for patients allocated to lenalidomide and 21 months [19-23] for observation (HR 0.50 [0.44-0.56], p <0.01). TTNT was also significantly longer with lenalidomide compared to observation. The median TTNT was 52 months for patients allocated to lenalidomide and 28 months for observation (HR 0.55 [0.49-0.62] p < 0.01). The trial found no difference in the aggressiveness of relapse.

StaMINA (NCT01109004) (Hari et al., 2020)
This study evaluated long-term lenalidomide maintenance in MM patients. It reported on six-years follow up of data and the results of lenalidomide discontinuation beyond three years. The results from the largest RCT of further interventions following frontline transplantation in MM support lenalidomide as maintenance beyond 3 years based on the higher probability of PFS observed at the 6-year time point. It showed that discontinuation, even after 38 months, was associated with inferior PFS (79.5% vs. 61% at 5 years; HR = 1.91, p = 0.0004).

Real-world and Modeled Evidence of Revlimid's Value in Multiple Myeloma: ICER's CA UPI protocol states, "Studies reporting patient-reported outcomes and other real-world data will be highly relevant." However, ICER' initial assessment excluded several high-quality, peer-reviewed, real-world studies based on the GRADE method for evaluation. The following section highlights high-quality real-world evidence that demonstrate new evidence of lenalidomide's value that should be included in the body of evidence.

Alonso et al., 2020
This study was a real-world clinical practice analysis of the impact of prolonged treatment with lenalidomide on the kinetics of minimal residual disease (MRD) and its prognostic potential. MM patients who received lenalidomide maintenance and whose MRD levels were observed during the treatment period by multiparametric flow cytometry or next-generation sequencing were evaluated. With lenalidomide maintenance, the percentage of patients with less than a complete response was reduced from 32.4% to 12.9%, and the final number of patients who achieved MRD

negativity increased from 26.6% to 51.8%. The results support the role of lenalidomide maintenance therapy, not only to sustain, but also to increase the depth of disease response with a PFS benefit.

Chari et al., 2019
This study was a real-world commercial and Medicare claims analysis of clinical and economic outcomes among patients with MM who received lenalidomide- and/or bortezomib-containing therapy and did not receive stem cell transplant. Lenalidomide-containing therapy resulted in longer median duration of treatment and median time to next treatment compared to bortezomib-containing therapy. Costs associated with outpatient-physician and chemotherapy-related visits were also significantly lower.

Dhakal et al., 2020
Despite the demonstrated benefit of lenalidomide in MM, a lack of head-to-head comparisons across the MM landscape persists. This study was unique in using a Bayesian statistical approach and conducting a network meta-analysis of all phase 3 RCTs with the aim of ranking different treatments in terms of efficacy, safety, and cost. Of the 14 treatment options, daratumumab, lenalidomide, and dexamethasone prolonged PFS the most.

Jackson et al., 2019
This study was the first to evaluate the impact of lenalidomide maintenance therapy on productivity from a patient and societal perspective. Modelling the impact of maintenance therapy alone for these patients reduced average productivity losses by just over 10%. Compared with therapies that require intravenous and subcutaneous administration, the use of oral maintenance therapies, such as lenalidomide, could also help decrease administration and indirect costs.

Clinical Evidence Supporting Revlimid's Value in Lymphoma: In 2019, lenalidomide was approved by the FDA to be used in combination with rituximab or a rituximab product for the treatment of patients with previously treated FL or MZL (FDA Approves Lenalidomide for Follicular and Marginal Zone Lymphoma, 2019). FL and MZL are two common subtypes of indolent non-Hodgkin lymphoma (Freedman & Jacobsen, 2020; Marginal Zone Lymphoma (MZL), 2018).

ICER excluded important evidence of lenalidomide's value in treating lymphoma on the basis of "indication accounts for less than 10% of use;" however, lenalidomide has demonstrated significant efficacy and safety in lymphoma subtypes. Ongoing clinical trials examining the use of lenalidomide are important to optimally integrate lenalidomide into lymphoma treatment paradigms and provide further treatment options where there is an unmet need. The studies below summarize additional recent (2019-2020) evidence that led to indication approvals and highlight of lenalidomide's value in previously treated FL and MZL.

AUGMENT (NCT01938001) (Gribben et al., 2019; J. Leonard et al., 2019)
Important NHL subtypes (follicular lymphoma) and subgroups (patients who relapse within two years of initial chemoimmunotherapy i.e. POD24) were examined for the potential impact of receiving (R^2) vs R and placebo. R^2 demonstrated improvement in efficacy over R with placebo, including in patients with POD24, patients who have historically been associated with worse outcomes, and in elderly and Japanese subgroups. Sensitivity to next treatment and median PFS was superior for R^2 over R with placebo.

MAGNIFY (NCT01996865) (Coleman et al., 2020; Lansigan et al., 2020)
MAGNIFY is a multicenter, phase IIIb trial in patients with FL, MZL, or mantle cell lymphoma (MCL) in which optimal lenalidomide duration is being explored. Efficacy results for these lymphoma subtypes and in advanced-age patients demonstrate that R^2 is active with a tolerable safety profile.

Summary: The high-quality published evidence presented in this response, focusing on the years 2019–2020, has elevated the relative value of lenalidomide compared with previous years and other therapies in MM and lymphoma. The improved efficacy and effectiveness of lenalidomide relative to standard of care in the maintenance of MM and the FDA-approved lymphoma indications supported by evidence pre- and post-2019 are some notable examples. We appreciate the opportunity to summarize this important evidence and provide further context for ICER's assessment.

Bristol Myers Squibb™

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APPENDIX 1. Evidence Table

Please note that information included in the following table are based on abstractions from the full publications and are provided as such for ease of viewing.

Abbreviations:
AHCT: autologous hematopoietic cell transplantation
ASCT: autologous stem cell therapy
CR: complete response
EFS: event-free survival
FL: follicular lymphoma
HCRU: health care resource utilization
HR: hazard ratio
HRQoL: health-related quality of life
ITT: intention to treat
ND: newly diagnosed
NHL: non-Hodgkin lymphoma
NR: not reported
MM: multiple myeloma
MPT: melphalan, prednisone, and thalidomide
MZL: marginal zone lymphoma
ORR: overall response rate
OS: overall survival
POD24: relapsed within 2 years of initial chemotherapy
PR: partial response
QALY: quality-adjusted life year
R^2: lenalidomide + rituximab
RR: relapsed or refractory
RVD: lenalidomide, bortezomib, and dexamethasone
sCR: stringent complete response
SCT: stem cell transplantation
TNE: transplant ineligible
TTNT: time to next treatment
TTNLT: time to next anti-lymphoma treatment
VCd: bortezomib, cyclophosphamide, and dexamethasone
VMP: bortezomib (Velcade), melphalan, and prednisone
VRd: bortezomib, lenalidomide, and dexamethsone

Trial/Study Name	Design	New Evidence	Impact/ Implications
Multiple Myeloma			
Clinical Evidence of Revlimid's Value in MM (n = 31)			
Baz, Rachid, et al. "Lenalidomide-based response-adapted therapy for older adults without high-risk myeloma." British Journal of Haematology 184.5 (2019): 735-743.	A phase II study evaluating a response-adapted therapy for older adults newly diagnosed with MM without high-risk features who were ineligible for high-dose therapy and stem cell transplant. Patients were started on single-agent lenalidomide, and low-dose dexamethasone was added in the event of progressive disease, in a response-adapted approach. The primary endpoint was progression-free survival (PFS). From February 2010 to June 2013, 27 eligible patients were enrolled at Moffitt Cancer Center	After a median follow-up of 69 months, the median PFS of single-agent lenalidomide was 29 months [95% confidence interval (CI), 25.7–73.5]. Twelve patients (44%) had PD, and dexamethasone was added to lenalidomide for nine of them. Additionally, five patients died of other unrelated causes without disease progression. Patients on single-agent lenalidomide with t(11;14) had a lower median PFS than those without this abnormality (median PFS 16 months vs. 36 months, respectively; P = 0.001). Moreover, patients on single agent lenalidomide with deletion 13q had a lower median PFS than those without this abnormality (median PFS 19 months vs. 36 months, respectively; P = 0.013). Similarly, patients with two or more cytogenetic abnormalities had lower PFS than those with one or no cytogenetic abnormalities (median 20.4 months vs. 30.2 months vs. 73.6 months, respectively; P = 0.05). The most common grades 3 or 4 adverse events potentially related to study treatment included neutropenia, febrile neutropenia, infections, anemia, venous thromboembolic disease, thrombocytopenia and fatigue. Grades 3 or 4 neutropenia were noted in 67% of patients and febrile neutropenia in 15% of patients.	These data suggest that this approach could be considered for the treatment of older adults newly diagnosed with MM, in the absence of high-risk features, and for patients who may be intolerant to dexamethasone and bortezomib.

Trial/Study Name	Design	New Evidence	Impact/ Implications
BMT CTN 0702 (NCT01109004); Stadtmauer, Edward A., et al. "Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: results of the BMT CTN 0702 trial." Journal of Clinical Oncology 37.7 (2019): 589.	A phase III study at 54 US transplantation centers enrolled patients ≤70 years old with symptomatic MM and who received at least two cycles of any regimen as initial systemic therapy without disease progression. 758 patients were enrolled from June 2010 through November 2013. All enrolled patients received high-dose melphalan followed by mobilized autologous peripheral-blood stem-cell infusion. Subsequent therapy was based on random assignment at the time of enrollment. The second phase of therapy started between 60 and 120 days after the first AHCT, once patients had sufficiently recovered. Patients randomly assigned to a second transplantation (AHCT/AHCT + R) received high-dose melphalan followed by autologous peripheral-blood stem-cell infusion. Patients randomly assigned to RVD consolidation (AHCT + RVD + R) received four cycles of R, bortezomib and dexamethasone. After their initial interventions, all patients received R.	The estimates of 38-month PFS were 58.5% (95% CI, 51.7% to 64.6%), 57.8% (95% CI, 51.4% to 63.7%), and 53.9% (95% CI, 47.4% to 60%) for AHCT/AHCT + lenalidomide, AHCT + RVD + lenalidomide, and AHCT + lenalidomide, respectively. For AHCT/AHCT + lenalidomide, AHCT + RVD + lenalidomide, and AHCT + lenalidomide, the OS rates were 81.8% (95% CI, 76.2% to 86.2%), 85.4% (95% CI, 80.4% to 89.3%), and 83.7% (95% CI, 78.4% to 87.8%). Among all reported nonhematologic grade 3 to 5 toxicities during the 38-month period, the majority occurred in the first year after enrollment, and the percentage of patients with at least one grade 3 to 5 toxicity by 1 year was similar across treatment arms (49%, 47%, and 48% in the AHCT/AHCT + R, AHCT + RVD + R, and AHCT + R arms, respectively).	This study highlights contemporary outcomes of patients with MM when treated with a standard approach of a multidrug induction followed by ASCT consolidation and maintenance. Single AHCT + lenalidomide maintenance was reinforced as a standard approach for this population.
ELOQUENT-2 (NCT01239797); Dimopoulos, Meletios A., et al. "Elotuzumab, lenalidomide, and dexamethasone in RRMM: Final overall survival results from the phase 3 randomized ELOQUENT-2 study." Blood Cancer Journal 10.9 (2020): 1-10.	ELOQUENT-2 is a phase 3, open-label, multicenter, randomized study that evaluated elotuzumab plus lenalidomide/dexamethasone (ERd) versus lenalidomide/dexamethasone (Rd) in patients with relapsed or refractory multiple myeloma (RRMM). Eligible patients were ≥18 years of age and had MM, measurable disease, and 1–3 prior lines of therapy with documented progression after their most recent therapy. The co-primary endpoints were PFS (time from randomization	This study presents the final OS analysis of ELOQUENT-2 after the longest follow-up to date for any antibody-based triplet in patients with RRMM and 1–3 prior lines of therapy (minimum of 70.6 months). Patients treated with ERd had an 8.7-month increase in median OS compared with those receiving Rd (48.3 months vs 39.6 months). This represented a statistically significant reduction in the risk of death for ERd over Rd, with an HR of 0.82 (95.4% Cl, 0.676–0.995 when given to	The durable and sustained efficacy of ERd, combined with long-term safety and tolerability profile, supports this regimen as a standard for care for patients with RRMM and 1–3 prior lines of therapy.

Trial/Study Name	Design	New Evidence	Impact/ Implications
	to first documented tumor progression or death) and ORR (partial response or better). OS was a key secondary endpoint, defined as time from randomization to the date of death from any cause.	three decimal places; P = 0.0408). All-cause grade 3–4 AEs occurred in 77% (ERd) and 68% (Rd) of patients.	
FIRST (NCT00689936); Belch, Andrew, et al. "Continuous lenalidomide and low-dose dexamethasone in patients with transplant-ineligible newly diagnosed MM: FIRST trial subanalysis of Canadian/US patients." Cancer Medicine 9.23 (2020): 8923-8930.	The FIRST trial was an open-label, three-group, phase 3 randomized trial conducted at 246 treatment centers in 18 countries in Europe, North America, and the Asia–Pacific region. Enrollment occurred from August 2008 through March 2011. Patients were randomly assigned in a 1:1:1 ratio to receive lenalidomide–dexamethasone in 28-day cycles until disease progression, lenalidomide–dexamethasone in 28-day cycles for 72 weeks (18 cycles), or MPT in 42-day cycles for 72 weeks (12 cycles). The primary end point was PFS with continuous lenalidomide–dexamethasone as compared with MPT. Secondary end points included OS, overall rate of response (partial response or better), time to response, duration of response, time to treatment failure, time to second-line antimyeloma therapy, health-related quality of life, and safety. A total of 1623 patients were randomly assigned.	Outcomes in the Canadian/US subgroup (104 patients per arm) are reported in this analysis. Rd continuous demonstrated a significant improvement in PFS vs MPT (median, 29.3 vs 20.2 months; HR, 0.69 [95% CI, 0.49-0.97]; p = 0.03326) and an improvement vs Rd18 (median, 21.9 months). Median OS was 56.9 vs 46.8 months with Rd continuous vs MPT (p = 0.15346) and 59.5 months with Rd18. The most common grade 3/4 treatment-emergent adverse events were neutropenia (28.4%, 30.1%, and 52.0%), anemia (23.5%, 21.4%, and 23.5%), and infections (37.3%, 30.1%, and 24.5%) with Rd continuous, Rd18, and MPT, respectively.	These results were consistent with those in the intent-to-treat population, confirming the benefit of Rd continuous vs MPT in the Canadian/US subgroup and supporting the role of Rd continuous as a standard of care for transplant-ineligible patients with NDMM. Together, these results further support Rd continuous therapy as the standard of care for transplant-ineligible patients with NDMM.

Trial/Study Name	Design	New Evidence	Impact/ Implications
FORTE (NCT02203643); Gay, Francesca, et al. "Survival analysis of newly diagnosed transplant-eligible multiple myeloma patients in the randomized FORTE trial." Blood 136 (2020): 35-37.	Phase 2 trial in which 474 newly diagnosed multiple myeloma patients aged 65 years and younger who are eligible for autologous stem cell transplantation (ASCT). Patients were randomized 1:1:1 to four 28-day carfilzomib-cyclophosphamide-dexamethasone (KCd) cycles followed by ASCT and four KCd consolidation cycles (KCd_ASCT); or four 28-day carfilzomib-lenalidomide-dexamethasone (KRd) cycles followed by ASCT and four KRd consolidation cycles (KRd_ASCT); or twelve KRd cycles (KRd_12). Patients who completed consolidation were randomized to lenalidomide (R) versus carfilzomib-lenalidomide (KR) maintenance.	PFS was significantly improved for in the KRd+ASCT arm compared to the KCd+ASCT arm. After a median follow-up from R1 of 45 months, median PFS was not reached with KRd_ASCT, 57 months with KRd12 and 53 months with KCd_ASCT (KRd_ASCT vs KCd_ASCT: HR 0.53, P<0.001; KRd_ASCT vs KRd12: HR 0.64, P=0.023; KRd12 vs KCd_ASCT: HR 0.82, P=0.262). During maintenance, a similar proportion of patients experienced ≥1 grade (G)3-4 hematologic adverse events (AEs)/serious AEs (SAEs) in the 2 arms (KR 22% vs R 23%); the most frequent were neutropenia (KR 18% vs R 21%) and thrombocytopenia (KR 3% vs R 3%). Rate of ≥1 G3-4 non-hematologic AEs/SAEs was higher with KR (27%) compared with R (15%), P=0.012.	Treatment with KRd_ASCT significantly improved PFS compared with both KRd12 and KCd_ASCT. Maintenance with KR also improved PF

Trial/Study Name	Design	New Evidence	Impact/ Implications
GRIFFIN (NCT02874742); Voorhees, Peter M., et al. "Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial." Blood 136.8 (2020): 936-945.	Multicenter, randomized, open-label, active-controlled, phase 2 study in which patients (n=207) 18 to 70 years of age at study entry with newly diagnosed multiple myeloma (NDMM) eligible for autologous stem cell transplantation (ASCT) were randomly assigned patients in a 1:1 ratio to daratumumab plus lenalidomide, bortezomib, and dexamethasone (D-RVd) or RVd.	This readout reports the primary efficacy and updated secondary efficacy and safety results of the randomized phase of the trial. The primary end point of sCR by the end of post-ASCT consolidation was achieved in 42 patients (42.4%) in the D-RVd group and 31 patients (32.0%) in the RVd group (OR, 1.57; 95% CI, 0.87-2.82; 1-sided *P* = .068). Secondary end points of ORR (ORR; 99.0% vs 91.8%; P = .0160) and rate of VGPR or better (90.9% vs 73.2%; *P* = .0014) by the end of consolidation were higher in the D-RVd group. With longer follow-up (median, 22.1 months), responses deepened; sCR rates improved for D-RVd vs RVd (62.6% vs 45.4%; P = .0177). Grade 3/4 hematologic adverse events were more common with D-RVd. More infections occurred with D-RVd. Grade 3/4 infection rates were similar.	Results of this study indicate that the combo of D-RVd may be a potential new standard of care among transplant-eligible NDMM patients and provide rationale for ongoing phase 3 PERSEUS registration study.

Trial/Study Name	Design	New Evidence	Impact/ Implications
HOVON-87/NMSG18 (NTR1630); Nielsen, Lene Kongsgaard, et al. "Health-related quality of life in transplant ineligible newly diagnosed multiple myeloma patients treated with either thalidomide or lenalidomide-based regimen until progression: a prospective, open-label, multicenter, randomized, phase 3 study." Haematologica 105.6 (2020): 1650.	A randomized, phase 3 study in newly diagnosed transplant ineligible patients with multiple myeloma, comparing melphalan-prednisolone in combination with thalidomide or lenalidomide, followed by maintenance therapy until progression (MPT-T or MPR-R). Symptomatic patients with NDMM >65 years of age or transplant ineligible patients ≤65 years were included. Patients were randomized between nine 28-day induction cycles of MPT, followed by thalidomide maintenance (MPT-T) or nine 28-day induction cycles of MPR followed by lenalidomide maintenance (MPR-R). Maintenance treatment was given until progression, intolerable side effects or other conditions that required treatment discontinuation.	More patients discontinued MPT-T than MPR-R (first year discontinuation rate; 68% vs. 30%; P<0.001). At the start of maintenance, there was a significant difference in HRQoL in constipation, side effects of treatment and neuropathy (less in MPR treated patients) and diarrhea (less in MPT treated patients). During maintenance treatment, a statistically significant reduction in appetite loss was reported in both arms (thalidomide P=0.003, lenalidomide P<0.001). In addition, during lenalidomide maintenance, a significant improvement was observed in global QoL (P=0.003, clinically relevant at T3), physical- (P<0.001) and role functioning (P<0.001, clinically relevant at T4), fatigue (P<0.001) and dyspnea (P=0.004). In contrast, no significant improvement occurred during thalidomide maintenance. There was statistically significant worsening of peripheral neuropathy symptoms (P<0.001, clinically relevant at both T3 and T4). Between arms, there were clinically meaningful differences in physical and role functioning (better with lenalidomide), in appetite loss (worse with lenalidomide) and in neuropathy (worse with thalidomide).	This study supports the current paradigm of continuous treatment, not only improving survival, but also maintaining, and even improving, specific subscales of HRQoL.

Trial/Study Name	Design	New Evidence	Impact/ Implications
IFM 2009 (NCT01191060); Roussel, Murielle, et al. "Health-related quality of life results from the IFM 2009 trial: treatment with lenalidomide, bortezomib, and dexamethasone in transplant-eligible patients with newly diagnosed multiple myeloma." Leukemia & Lymphoma 61.6 (2020): 1323-1333.	The IFM 2009 trial was a phase 3, multicenter, randomized, open-label study in patients with NDMM aged > 65 years (N = 700). Patients were randomized (1:1) to either RVd for three 3-week cycles as induction therapy followed by 5 cycles as consolidation therapy (RVd-alone); or RVd for three 3-week cycles as induction therapy followed by ASCT and then RVd for consolidation (RVd-ASCT)) for 2 cycles. Patient-reported outcomes, including HRQoL were assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life-Core 30 Questionnaire (QLQ-C30) and the EORTC Quality of Life Questionnaire for Patients with Multiple Myeloma (QLQ-MY20).	In the RVd-alone group, QLQ-C30 global QoL scores increased from baseline to the end of the consolidation phase (6.4 points; p = .0002) and were sustained during maintenance therapy and further follow-up. In the RVd-ASCT group, an overall increase in QLQ-C30 global QoL (13.8, p < .0001) was observed from baseline to the end of the consolidation period, which was sustained during maintenance therapy and further follow-up. In this study, 1 year of lenalidomide maintenance therapy was not associated with clinically significant toxicities and did not adversely affect HRQoL.	This analysis shows that both RVd treatment strategies followed by 1 year of lenalidomide maintenance therapy provided clinically meaningful improvements in the most distressing disease-related symptoms from a patient perspective, namely fatigue and pain, and that these translated into clinically meaningful improvements in physical functioning, role functioning, and global HRQoL. In an era where patient QoL is becoming increasingly important in healthcare decision-making, this analysis of data from the IFM 2009 trial demonstrated that RVd-based strategies followed by 1 year of R maintenance therapy are a valuable option for the management of patients with NDMM.
Kumar, Lalit, et al. "VRd versus VCd as induction therapy for newly diagnosed multiple myeloma: A Phase III, randomized study." Clinical Lymphoma, Myeloma and Leukemia 19.10 (2019): e361.	A randomized trial to compare VRd versus VCd for induction in patients with newly diagnosed MM. Overall 125 patients (median age years (range, to) were randomly assigned to receive 4 cycles of VRd (n=65) or VCd (n=60).	On intention to treat analysis – after 4 cycles – 61.5% of patients in VRd arm achieved ≥VGPR compared to 48.3% in VCd arm, p 0.09 (primary end point). CR rates were superior in the VRD arm; 35.4 % (sCR-9.2%) vs 18.3% (sCR-5%), p< 0.02. Hematologic toxicity and peripheral neuropathy were not significantly different in 2 arms.	Further evaluation of VRd compared to other regimens is warranted.
MAIA (NCTNCT02252172); Facon, Thierry, et al. "Daratumumab plus lenalidomide and dexamethasone for untreated myeloma." New England Journal of Medicine 380.22 (2019): 2104-2115.	MAIA is a randomized, open-label, phase 3 trial. Newly diagnosed MM patients were enrolled from March 2015 through January 2017 at 176 sites in 14 countries across North America, Europe, the Middle East, and the Asia–Pacific region. Patients (n=737) were randomly assigned in a 1:1 ratio, to receive daratumumab plus	The Kaplan–Meier estimate of the percentage of patients who were alive without disease progression at 30 months was 70.6% (95% CI, 65.0 to 75.4) in the daratumumab group and 55.6% (95% CI, 49.5 to 61.3) in the control group. The hazard ratio for disease progression or death in the daratumumab group as compared with the control	The results of this trial led to an FDA approved indication for daratumumab in combination with lenalidomide and dexamethasone for patients with newly diagnosed MM ineligible for autologous stem cell transplant, offering another combination treatment option with lenalidomide.

Trial/Study Name	Design	New Evidence	Impact/ Implications
	lenalidomide and dexamethasone (daratumumab group) or lenalidomide and dexamethasone alone (control group). The primary end point was progression-free survival.	group was 0.56 (95% CI, 0.43 to 0.73; P<0.001). Daratumumab plus lenalidomide and dexamethasone was associated with a higher incidence of neutropenia and infections. The most common adverse events of grade 3 or 4 were neutropenia (50.0% in the daratumumab group vs. 35.3% in the control group), anemia (11.8% vs. 19.7%), lymphopenia (15.1% vs. 10.7%), and pneumonia (13.7% vs. 7.9%).	
MAIA (NCTNCT02252172); Perrot, Aurore, et al. "Faster and sustained improvement in health-related quality of life (HRQoL) for newly diagnosed multiple myeloma (NDMM) patients ineligible for transplant treated with daratumumab, lenalidomide, and dexamethasone (D-Rd) versus Rd alone: MAIA." (2019): 8016-8016.	MAIA is a randomized, open-label, phase 3 trial. Newly diagnosed multiple myeloma patients were enrolled from March 2015 through January 2017 at 176 sites in 14 countries across North America, Europe, the Middle East, and the Asia–Pacific region. Patients (n=737) were randomly assigned in a 1:1 ratio, to receive daratumumab plus lenalidomide and dexamethasone (daratumumab group) or lenalidomide and dexamethasone alone (control group). The EORTC QLQ-C30 and EQ-5D-5L questionnaires were completed by patients using an electronic device at baseline and every 3 months during treatment; interim results are presented for first 12 months.	Compliance rates were high and comparable at baseline (> 90%) and through month 12 (> 80%) for both groups (D-Rd [n = 368]; Rd [n = 369]). Improvement in Global Health Status (GHS) occurred in both groups; however, for D-Rd, significantly greater improvement was observed at cycle 3 (LS mean change; D-Rd: 4.5 [95% CI: 2.4, 6.6], Rd: 1.5 [95% CI: -0.7, 3.7]; [p = 0.0454]) and increasing improvement occurred across all time points. Significant improvement and clinically meaningful benefit in HRQoL for D-Rd was also observed in EQ-5D-5L Visual Analog Scale (VAS) scores (LS mean change; D-Rd: 10.1 [95% CI: 8.1, 12.1], Rd: 4.9 [95% CI: 2.8, 7.0]; [p = 0.0002]).	Assessment of patient-reported outcomes alongside efficacy endpoints provides patient perspective on their quality of survival and overall value of HRQoL while on treatments.

Trial/Study Name	Design	New Evidence	Impact/ Implications
MYELOMA XI (ISRCTN49407852); Jackson, Graham H., et al. "Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial." The Lancet Oncology 20.1 (2019): 57-73.	An open-label, randomized, phase 3, adaptive design trial with three randomization stages done at 110 National Health Service hospitals in England, Wales, and Scotland. Eligible patients for maintenance randomization were aged 18 years or older and had symptomatic or non-secretory multiple myeloma. Patients (n=1917) were randomly assigned (1:1 from Jan 13, 2011, to Jun 27, 2013, and 2:1 from Jun 28, 2013, to Aug 11, 2017) to lenalidomide maintenance (10 mg orally on days 1–21 of a 28-day cycle).	This study adds evidence on the significant efficacy of maintenance R in more aggressive disease states, such as patients with cytogenetic high-risk disease or patients ineligible for transplantation. It showed a significant benefit of R maintenance therapy in terms of progression-free survival, which was consistent across both patients eligible and ineligible for transplantation, as well as patients across all cytogenetic risk groups. A preplanned subgroup analysis indicated an overall survival benefit in transplantation-eligible patients across all cytogenetic risk groups, even those with high-risk disease, when treated with lenalidomide maintenance therapy after transplantation (3-year overall survival in transplant-eligible patients 87.5% [95% CI 84.3–90.7] with lenalidomide and 80.2% [76.0–84.4] with observation; HR 0.69 [95% CI 0.52–0.93]; p=0.014).	The PFS results of the Myeloma XI trial suggests that the use of lenalidomide as maintenance therapy should be considered for patients with newly diagnosed multiple myeloma, irrespective of cytogenetic risk after autologous stem-cell transplantation.
MYELOMA XI (ISRCTN49407852); Pawlyn, Charlotte, et al. "Lenalidomide maintenance prolongs progression-free survival and does not impact the aggressiveness of clinical relapse: data from long-term follow up of the Myeloma XI Trial." Blood 134 (2019): 1889.	An open-label, randomized, phase 3, adaptive design trial with three randomization stages done at 110 National Health Service hospitals in England, Wales, and Scotland. Eligible patients for maintenance randomization were aged 18 years or older and had symptomatic or non-secretory multiple myeloma, had completed their assigned induction therapy as per protocol and had achieved at least a minimal response to protocol treatment, including lenalidomide. Patients (n=1917) were randomly assigned to R maintenance (10 mg orally on days 1–21 of a 28-day cycle) or observation,	R was associated with a significant improvement in PFS compared to observation. The median PFS was 41 months [95% CI 38,45] for those allocated to R and 21 [19,23] for observation (HR 0.50 [0.44,0.56], P <0.01). This was consistent in both the TE (median PFS R 64 [54,76] vs observation 32 [28,36], HR 0.52 [0.45,0.61] P <0.01) and TNE (median PFS R 26 [22,31] vs observation 11 [9,13], HR 0.47 [0.40,0.55] P <0.01) pathways. TTNT was also significantly longer with R compared to observation. There was no difference in TCR between patients receiving R (median 6.3	Lenalidomide maintenance does not impact aggressiveness of relapse.

Trial/Study Name	Design	New Evidence	Impact/ Implications
	and stratified by allocated induction and intensification treatment, and center.	months [95% CI 5.0, 8.1]) and observation (8.1 months [7.0, 9.7]), HR 1.06 [0.87, 1.29]. This was consistent for the TE and TNE pathways.	
POLLUX (NCT02076009); Bahlis, Nizar J., et al. "Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study." Leukemia 34.7 (2020): 1875-1884.	POLLUX is an ongoing, randomized, open-label, multicenter, phase 3 study in patients with RRMM eligible patients had progressive disease during or after their last regimen, received and responded to at least one prior line of therapy, and had a creatinine clearance ≥30 mL/min. Prior lenalidomide exposure was allowed, but patients with lenalidomide-refractory disease were excluded from participation. Patients (n=569) were randomly assigned (1:1) to Rd (lenalidomide: 25 mg orally on Days 1–21 of each 28-day cycle; dexamethasone: 40 mg orally weekly) with or without daratumumab.	Updated efficacy and safety after >3.5 years of follow-up are presented. At a median (range) follow-up of 44.3 (0–50.9) months, D-Rd significantly prolonged PFS compared with Rd in the ITT population (median 44.5 [95% CI, 34.1–not estimable] vs 17.5 [95% CI, 13.9–20.8] months; HR, 0.44; 95% CI, 0.35–0.55; P < 0.0001). The most common (≥5%) grade 3/4 TEAEs observed with D-Rd and Rd included neutropenia, febrile neutropenia, anemia, thrombocytopenia, lymphopenia, pneumonia, diarrhea, fatigue, hypokalemia, and cataracts. The percentage of patients with TEAEs leading to treatment discontinuation was similar between groups (D-Rd, 14.8; Rd, 14.6%).	These updated findings continue to support the use of D-Rd in patients with RRMM after first relapse.
StaMINA (NCT01109004); Hari, Parameswaran, et al. "Long-term follow-up of BMT CTN 0702 (STaMINA) of postautologous hematopoietic cell transplantation (autoHCT) strategies in the upfront treatment of multiple myeloma (MM)." (2020): 8506-8506.	This phase III trial of transplant-eligible patients with symptomatic MM <71 years of age within 12 months of initiating therapy and without prior progression was designed to compare long-term outcomes among patients randomized on the BMT CTN 0702 protocol (described below). Patients continued to receive R as maintenance therapy until disease progression or discontinuation due to toxicity, death, or withdrawal from the study. Patients in the trial were randomly assigned 1:1:1 to receive melphalan ASCT and 4 cycles of RVD consolidation versus tandem melphalan	The initial STaMINA trial (BMT CTN 0702, NCT01109004) aimed to demonstrate an association between additional PFS and OS benefit, and further interventions following ASCT in the treatment of MM. After the initial analysis, the study protocol was amended to evaluate long-term results and additional benefits of R maintenance until disease progression in the BMT CTN 07LT follow-up trial (NCT02322320). Long-term follow up of patients managed post-ASCT shows that discontinuation, even after 38 months, was associated with inferior PFS (79.5% vs. 61% at	The study results suggest that lenalidomide maintenance beyond 3 years may be a feasible approach in MM based on the higher probability of PFS observed at the 6-year time point.

Trial/Study Name	Design	New Evidence	Impact/ Implications
	200mg/m2 ASCT or versus a single ASCT. Randomization was stratified by disease risk and center. All arms included R maintenance (at maximum tolerated dose of 5 to 15 mg orally daily until progression) with dose modifications for toxicities.	5yr; HR = 1.91, p = 0.0004) but similar OS.	
SWOG S0777 (NCT00644228); Durie, Brian GM, et al. "Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT)." Blood Cancer Journal 10.5 (2020): 1-11.	The SWOG S0777 randomized (1:1), open-label phase 3 trial that compared bortezomib, lenalidomide and dexamethasone (VRd) with lenalidomide and dexamethasone (Rd) in patients aged 18 years or older with newly diagnosed myeloma. Between April 2008 and February 2012, 525 patients at 139 participating SWOG and NCTN institutions were randomly assigned: 264 to VRd and 261 to Rd.	This report outlined longer-term outcomes with a data cut at May 15, 2018. Both PFS and OS were improved with VRd versus Rd adjusting for age (P-values: 0.013 [PFS]; 0.033 [OS])). Median duration of Rd maintenance was 17.1 months. The addition of bortezomib to lenalidomide dexamethasone for induction therapy results in a statistically significant and clinically meaningful improvement in PFS as well as better OS. The treatment emergent adverse events were well-balanced between the VRd and Rd treatment groups. The grade 3 or worse neurologic toxic effects were significantly more frequent in the VRd group than the Rd group (34.6% versus 11.3%: P < 0.0001). The number of second cancers was 19/235 (8%) with VRd and 16/225 (7%) with Rd.	With longer-term follow up, the benefits of VRd over Rd are maintained as in the prior analyses. VRd continues to represent an appropriate standard of care irrespective of age.
(UMIN000009042); Ishida, Tadao, et al. "Continuous lenalidomide treatment after bortezomib-melphalan-prednisolone therapy for newly diagnosed multiple myeloma." Annals of Hematology 99.5 (2020): 1063-1072.	A multicenter, open-label, single-arm, phase II study was designated to evaluate the efficacy and safety of the bortezomib (Velcade) plus melphalan and prednisone (VMP) induction therapy followed by lenalidomide and dexamethasone (Rd) consolidation and lenalidomide (R) maintenance in transplant-ineligible patients with newly diagnosed symptomatic multiple myeloma. The primary end point of this study was PFS. Eighty-three eligible	The median PFS was 28.0 months (95% CI 19.6–36.7) and the median OS was 55.3 months (95% CI 51.6–NA). In total, 57 patients underwent R maintenance therapy. Among the patients who received R maintenance therapy, median PFS was significantly improved in patients who had achieved a very good partial response (VGPR) or better (41.8 vs 20.7 months, p = 0.0070). The most frequently observed grade 3 or higher adverse events during R	Lenalidomide maintenance therapy was found to be more effective in the patients who achieved deep response before maintenance therapy. Thus, this sequential treatment of reduced VMP and lenalidomide might be a suitable approach for transplant-ineligible patients with NDMM, especially for patients over 75 years of age.

Trial/Study Name	Design	New Evidence	Impact/ Implications
	patients were enrolled between October 2012 and August 2014.	maintenance therapy were anemia (7.4%) and neutropenia (24.1%). Thus, VMP induction therapy followed by Rd consolidation and R maintenance is considered a well-tolerated and effective regimen in transplant ineligible NDMM.	
Alonso, Rafael, et al. "Prolonged lenalidomide maintenance therapy improves the depth of response in multiple myeloma." Blood Advances 4.10 (2020): 2163-2171.	A retrospective analysis on 139 patients with newly diagnosed MM from 3 health centers who had available minimal residual disease (MRD) data. Patients included in the study received lenalidomide maintenance treatment during first-line therapy from 2010 through 2018.	With R maintenance, the percentage of patients with <CR was reduced to 12.9% (n = 18), and the final number of patients who achieved MRD negativity increased from 37 to 72. Globally, achievement of MRD-negative status at any time (before or during maintenance) was associated with improved PFS (median PFS, 83 months for MRD negative vs 48 months for MRD positive, P = .01. A therapy-related AE grade >2 was observed in 34.6% of these patients (n = 46). The most common AEs included neutropenia (13.5%), thrombocytopenia (5.3%), fatigue (5.3%), and diarrhea (5.3%).	The monitoring of MRD kinetics identifies patients with different prognoses and may help in their clinical management.
Barth, Peter, et al. "Comparative effectiveness of lenalidomide, bortezomib, and their combinations as first-line treatment of older patients with myeloma." Blood 134 (2019): 3155.	A retrospective claims analysis that identified Medicare beneficiaries with myeloma receiving first-line RD, VD, RVD, or VCD in 2007-2015, using Medicare claims linked to data from cancer registry (SEER-Medicare). In each comparative analysis, a separate propensity score was fit. After generating adequately balanced cohorts to minimize indication bias, two survival endpoints were analyzed (measured from start of first-line therapy): EFS (defined as start of a 2nd-line agent, hospice enrollment, or death, censored in case of an autologous transplant) and OS. 6,076 eligible MM patients	In the analysis of RD vs. VD, RD demonstrated better EFS (median 1.0 vs 0.6y) and marginally better OS (median 2.7 vs 2.3y). RD resulted in more frequent VTE (RR, 1.44; 95%CI, 1.13-1.83), but less neuropathy (RR, 0.39; 95%CI, 0.29-0.53), without significant difference in hospitalization (RR, 0.96; 95%CI, 0.87-1.06) or anemia (RR, 0.95; 95%CI, 0.89-1.00).	RD may be the preferred doublet. VCD appears to offer no benefit over the VD doublet.

Trial/Study Name	Design	New Evidence	Impact/ Implications
	receiving first-line therapy between 2007 and 2015 were identified.		
Chari, Ajai, et al. "Treatment patterns and clinical and economic outcomes in patients with newly diagnosed multiple myeloma treated with lenalidomide-and/or bortezomib-containing regimens without stem cell transplant in a real-world setting." Clinical Lymphoma Myeloma and Leukemia 19.10 (2019): 645-655.	Patient claims (n=3075 patients) were obtained from Truven Health MarketScan Commercial and Medicare Supplemental Databases from October 2009 to May 2015. Patients with NDMM who received lenalidomide- and/or bortezomib-containing therapy and did not receive SCT were analyzed. Duration of treatment (DOT), TTNT, and health care utilization and costs were evaluated. Comparisons in this analysis were conducted only within the doublet (Rd vs. Vd) or triplet (RVd vs. CyBord) regimens. Patients who met the above criteria with any of these combinations as first-line therapy were assigned to the appropriate doublet or triplet cohort.	Rd versus Vd resulted in longer median DOT (12.0 vs. 5.9 months; P < .0001) and median TTNT (36.7 vs. 24.4 months; HR, 0.78; 95% confidence interval [CI], 0.68-0.90; P = .0005). Year 1 costs were greater with Rd versus Vd (difference = $14,964; P = .0009), primarily owing to higher pharmacy costs; costs associated with outpatient-physician (adjusted difference = −$9434 [P < .0001]) and chemotherapy-related (adjusted difference = −$44,592 [P < .0001]) visits were significantly lower with Rd versus Vd treatment. Median DOT (14.8 vs. 9.0 months; P < .0001) and median TTNT (35.7 vs. 22.3 months; P = .0007) were longer with RVd versus CyBord; year 1 costs were comparable.	Patients who received continuous treatment with any regimen had longer TTNT compared with those who did not, supporting the benefit seen with continuous treatment in clinical trials of transplant-ineligible patients with NDMM. The clinical benefit of a longer DOT along with decreased health care costs over a 3-year period seen with the lenalidomide-based regimens investigated in this real-world analysis may help inform treatment decisions in transplant-ineligible patients with NDMM.
Cransac, Amélie, et al. "Adherence to immunomodulatory drugs in patients with multiple myeloma." PLoS One 14.3 (2019): e0214446.	All consecutive multiple myeloma patients, with at least two consecutive dispensations of thalidomide, lenalidomide or pomalidomide in the hospital were included in this prospective study. IMID adherence was measured using a specific questionnaire and the medication possession ratio. Relationship between the questionnaire scores and variables of interest was evaluated by multiple linear regression with a robust variance estimator.	Medication adherence for each IMID and each patient was estimated with the questionnaire score and the MPR. The mean questionnaire score was 8.2±1.2, with the highest scores for lenalidomide, followed by thalidomide and then pomalidomide.	The high adherence to IMIDs reported here, regardless of the drug, is encouraging considering the efficacy, toxicity and elevated cost of IMIDs. The specific questionnaire should be used with caution to evaluate IMID adherence.

Trial/Study Name	Design	New Evidence	Impact/ Implications
Dhakal, Binod, et al. "Association of adverse events and associated cost with efficacy for approved relapsed and/or refractory multiple myeloma regimens: A Bayesian network meta-analysis of phase 3 randomized controlled trials." Cancer 126.12 (2020): 2791-2801.	A Bayesian network meta-analysis (NMA) of phase 3 randomized controlled trials (RCTs). Scopus, Cochrane, PubMed Publisher, and Web of Science were searched from January 1999 to July 2018 for phase 3 RCTs of regimens (approved by the US Food and Drug Administration) used in RRMM. The relative ranking of agents was assessed with surface under the cumulative ranking (SUCRA) probabilities. The primary efficacy, safety, and cost outcomes were progression-free survival with the regimen, grade 3 to 4 AEs, and the total cost per cycle (regimen cost plus average cost of managing AEs).	Fifteen studies including 7718 patients and evaluating 14 different regimens were identified. Daratumumab, lenalidomide, and dexamethasone were ranked highest for reducing progression (HR, 0.13; 95% credible interval, 0.09-0.19; SUCRA, 1) but carried the highest probability of total cost per cycle ($41,420; 95% Credible Interval [CrCl], $58,665-$78,041; SUCRA, 0.02). Panobinostat, bortezomib, and dexamethasone were the least effective and least safe (SUCRA, 0.24), whereas bortezomib, thalidomide, and dexamethasone emerged as least effective with the highest total cost per cycle (SUCRA, 0.33). The NMA suggested that single-agent dexamethasone was the safest of all regimens (median AEs, 0.8; 95% credible interval [CrI], 0-1.2; SUCRA, 0.98), whereas panobinostat, bortezomib, and dexamethasone were the worst in terms of safety (median AEs, 3.7; 95% CrI, 2.7-5.8; SUCRA, 0.10). Among the doublet combinations, carfilzomib and dexamethasone had the highest probability of being safe (median AEs, 1.6; 95% CrI, 0.9-3; SUCRA, 0.68), whereas ixazomib, lenalidomide, and dexamethasone carried the highest probability of being safe among the triplet combinations (median AEs, 2.7; 95% credible interval [CrCl], 1.5-5.2; SUCRA, 0.35).	The results of this NMA can provide additional guidance for the decision-making process when one is choosing the most appropriate regimen for RRMM.

Trial/Study Name	Design	New Evidence	Impact/ Implications
Hari P, Ung B, Abouzaid S, Agarwal A, Parikh K. Lenalidomide maintenance post-transplantation in newly diagnosed multiple myeloma real-world outcomes and costs. Future Oncol. 2019 Dec;15(35)4045-4056. doi 10.2217fon-2019-0422. Epub 2019 Oct 18. PMID 31625415.	In this retrospective observational study from the perspective of US payers, administrative claims data were obtained from the Truven MarketScan Commercial and Encounters Database from 1 January 2011 to 30 September 2016. Patients, who received a first-line treatment regimen for MM followed by ASCT, were assigned to one of two cohorts based on their maintenance treatment post-ASCT: R maintenance (R-maintenance) or no maintenance therapy. Of the 297 patients who received R only, 47 received lenalidomide before the index date and were excluded from the present study; 250 of the 297 (84.2%) patients who received R maintenance after the index date were included in the study.	Patients in the R maintenance cohort were less likely initiate a next-line treatment compared with those in the no-maintenance cohort (24.0 vs 42.5%) and had significant longer TTNT (HR: 0.43; 95% CI: 0.31–0.60; $p < 0.0001$). Outpatient costs were significantly lower in the R maintenance versus no-maintenance cohort during months 0–12 (USD 3761 vs USD 5360; adjusted difference USD 1708; $p < 0.0001$), mainly due to lower intravenous MM and chemotherapy-related costs and significantly lower pharmacy usage ($p < 0.0001$).	Using a US claims database, this study examined real-world data on R maintenance therapy to understand its effectiveness outside the RCT setting and suggested that lenalidomide clinical benefits translate to the real-world setting. Patients with NDMM who received R maintenance treatment remained on therapy for ≥1 year after ASCT and had significantly prolonged TTNT compared with those who received no maintenance therapy. They were also less likely to experience disease progression within the study period.
Jackson, Graham, et al. "Productivity losses in patients with newly diagnosed multiple myeloma following stem cell transplantation and the impact of maintenance therapy." European Journal of Haematology 103.4 (2019): 393-401.	A cross-sectional online patient survey was conducted across the UK, Germany, France, Spain and Italy. A partitioned survival model was used to estimate productivity loss and the impact of maintenance therapy, using human capital (HC) and friction cost approaches.	Of the 115 eligible survey respondents, 76.5% were economically active at the time of diagnosis and highlighted return to work as an important factor affecting their quality of life; only 39.1% of respondents were economically active post-ASCT. HC analyses estimated average total productivity losses per ASCT patient at EUR 290,601 over a 20-year period. Modelling the impact of maintenance therapy alone for these patients reduced average productivity losses by just over 10%.	Patients with NDMM aspire to engage in productive lives post-ASCT, but most are unable to do so. Access to treatments extending remission and supporting engagement in a productive life can have a positive impact both for patients and wider society. The significant productivity losses experienced by patients with NDMM post-ASCT aged <65 years are reduced by lenalidomide maintenance therapy, according to the model and HC approach.
Joseph, Nisha S., et al. "Long-term follow-up results of lenalidomide, bortezomib, and dexamethasone induction therapy and risk-adapted maintenance	This study identified 1,000 consecutive patients with myeloma who were treated with RVD induction therapy between January 2007 and August 2016. Response assessment as defined by the International Myeloma Working Group (IMWG) was	Overall, 753 patients received maintenance. Six hundred of these patients (60.7%) received lenalidomide maintenance therapy alone based on standard-risk cytogenetics, and 107 patients (10.7%) received IMID and PI maintenance therapy, predominantly with	This analysis, in addition to the currently available literature, provides a strong rationale for adapting multidrug combination strategies in the up-front treatment of patients with myeloma and makes a strong case for risk-adapted maintenance.

Trial/Study Name	Design	New Evidence	Impact/ Implications
approach in newly diagnosed multiple myeloma." Journal of Clinical Oncology 38.17 (2020): 1928.	available for 977 patients.	RVD. Both in the univariable and multivariable analysis, lack of maintenance therapy was a significant predictor for progression or death (PFS: hazard ratio [HR], 1.6; 95% CI, 1.12 to 2.29; P = .01; OS: HR, 2.3; 95% CI, 1.52 to 3.49; P = .0001). Secondary primary malignancies (SPMs) were observed in 33 patients (3.3%). Twenty-six SPMs (4.3%) occurred among patients receiving lenalidomide maintenance. Twenty-one SPMs (4%) occurred among patients receiving lenalidomide after transplantation.	
Modi, Dipenkumar, et al. "Lenalidomide maintenance after second autologous stem cell transplant improves overall survival in multiple myeloma." Leukemia & Lymphoma 61.8 (2020): 1877-1884.	A retrospective study of consecutive adult MM patients who underwent second ASCT after progression following first ASCT at Karmanos Cancer Institute. From January 2000 to December 2018, 111 MM patients underwent second ASCT. Patients undergoing planned tandem ASCT were excluded. Maintenance therapy was defined as monotherapy with either lenalidomide or subcutaneous bortezomib. Outcomes among three groups were compared: no-maintenance therapy, R maintenance, and bortezomib maintenance following second ASCT. Thirty-eight of 111 patients (34%) received maintenance therapy after second ASCT. Of 38 patients with maintenance therapy after second ASCT, 23 (61%) received lenalidomide and 15 (39%) received bortezomib. The primary objective was evaluation of PFS and OS among three groups.	At a median follow-up of 47.8 months from second ASCT, 56 of the 73 patients (77%) in the no-maintenance group progressed, as compared with 13 of 23 patients (57%) in the R maintenance, and 11 of 15 patients (73%) in the bortezomib maintenance. The median time to progression was 13 months in the no-maintenance group, 25 months in the R maintenance, and 19 months in the bortezomib maintenance (global p = 0.02). R maintenance after second ASCT was associated with significantly superior PFS (HR 0.46, p = 0.009), OS (HR 0.25, p = 0.009), and lower progression (HR 0.51, p = 0.01. No difference in the rate of second primary malignancy between the no-maintenance, lenalidomide, and bortezomib maintenance groups was observed (9.5% vs. 6.4% vs. 7.8%, p = 0.84).	R maintenance therapy after second ASCT appears to prolong PFS and OS. In addition, close follow up for second primary malignancy in this patient population is warranted.
Olszewski, Adam, et al. "Comparative effectiveness of	Medicare beneficiaries with myeloma receiving first line RD, VD, or RVD in 2007-	In the analysis of RD vs VD, RD has demonstrated better TTF (median 1.0 vs 0.6 years;	RD may be the preferred doublet, despite the prevalent use of VD in this population.

Trial/Study Name	Design	New Evidence	Impact/ Implications
lenalidomide, bortezomib, and their combination as first-line treatment of older patients with myeloma." Clinical Lymphoma, Myeloma and Leukemia 19.10 (2019): e9.	2015 were identified using Medicare claims linked to cancer registry data (SEER-Medicare). Using propensity score analysis, pseudo-randomized cohorts were generated, balancing multiple baseline factors, including socio-economic and performance status, time from diagnosis, presence of baseline hypercalcemia, renal disease, anemia, neuropathy, DVT, and other comorbidities. After confirming the balance, two survival endpoints were analyzed: OS and time to treatment failure (TTF).	HR, 0.74; 95% CI, 0.68-0.81) and OS (median 2.7 vs 2.3 years; HR 0.91, 95% CI, 0.83-0.99). RD resulted in more frequent thromboembolism (RR, 1.44; 95%CI, 1.13-1.83), but less neuropathy (RR, 0.39; 95% CI, 0.29-0.53), without significant difference in the rates of hospitalization (RR, 0.96; 95% CI, 0.87-1.06) or anemia (RR, 0.95; 95% CI, 0.89-1.00).	
Patel, Dilan A., et al. "Minimal residual disease negativity and lenalidomide maintenance therapy are associated with superior survival outcomes in multiple myeloma." Bone Marrow Transplantation 55.6 (2020): 1137-1146.	A retrospective cohort study on patients with multiple myeloma who received an AHCT at Vanderbilt University Medical Center between January 2000 and July 2014 (n=433). The period in which AHCT was performed was 2000–2014. Post-AHCT maintenance therapy choice was based on guidelines, which recommend lenalidomide for standard-risk disease and bortezomib for high-risk disease based on cytogenetics. Choice of either regimen was based on physician preference. The clinical outcomes studied were OS and PFS. Patients included in the study were started on choice on maintenance therapy at day +100 post-AHCT (n = 433). Patients were evenly distributed between lenalidomide (35.6%, 154/433), bortezomib (36%, 156/433), or no maintenance therapy (28.4%, 123/433).	The results show that R maintenance significantly improved MRD negativity at day +365 compared with no maintenance therapy (92.9% vs 24.4%, $p = 0.012$) or bortezomib (92.9% vs 41.6%, $p = 0.01$). Lenalidomide resulted in significantly improved PFS compared with no maintenance (not reached vs 44 months, $p < 0.05$) or bortezomib maintenance (not reached vs 50 months, $p < 0.05$). In patients with high-risk cytogenetics, R maintenance resulted in significantly improved OS compared with no maintenance (not reached vs 22 months, $p < 0.05$). Contrary to the author's previous publication evaluating PFS and OS outcomes and toxicities of R maintenance therapy compared with bortezomib maintenance in MM patients post-AHCT, maintenance therapy choice and cytogenetics risk did not impact PFS or OS. A low incidence of secondary malignancies, 4%, was seen with prolonged lenalidomide administration.	Maintenance therapy with either lenalidomide or bortezomib has been shown to improve outcomes, though neither have been directly compared. Maintenance therapy following AHCT for multiple myeloma improves the depth of response as assessed by MRD. Use of either agent has been shown to be superior to no maintenance. The choice of either agent for maintenance therapy must be assessed on a case-by-case basis considering factors such as ease of administration, adherence, side effects, and tolerability, including the rare, but potentially meaningful risk of secondary hematologic and solid tumor malignancies with prolonged lenalidomide administration.

Trial/Study Name	Design	New Evidence	Impact/ Implications
Ramasamy, Karthik, et al. "Relative efficacy of treatment options in transplant-ineligible newly diagnosed multiple myeloma: results from a systematic literature review and network meta-analysis." Leukemia & Lymphoma 61.3 (2020): 668-679.	In this systematic literature review (SLR), articles from January 1, 1988 to July 2, 2019 were reviewed to identify relevant randomized controlled trials (RCT) evaluating efficacy in transplant-ineligible (TNE) patients with NDMM. The original searches were carried out in March 2016. Subsequent updates were carried out in November 2016, August 2017, January 2018, and July 2019. The population was limited to patients with NDMM or untreated MM who were aged ≥65 years or aged <65 years and TNE. Eight trials identified by a systematic literature review were included in the primary analysis; hazard ratios (HRs) OS and PFS were used. The analysis included 44 publications describing 26 RCTs.	Although newer treatment combination regimens are becoming available, their role in the management of NDMM remains undefined. The results of the NMA were reported, including the newer regimens D + Rd, RVd, and daratumumab plus VMP (VMP + D), in addition to established options Rd, MP, MPT, and VMP. Analysis of OS showed evidence of Rd superiority over MP, MPT, and VMP (all HR and CIs >1). RVd was the only therapy with evidence of superiority over Rd (HR 0.72, 95% CrI 0.52, 0.96). The impact on OS for VMP + D versus Rd could not be assessed due the absence of mature OS data for VMP + D.	This analysis supports the findings of the primary studies identified in the SLR, indicating that first-line treatment with Rd provides OS and PFS benefits over the currently approved regimens available to TNE patients with NDMM. Moreover, it establishes RVd as a promising emerging therapeutic option that extends OS and PFS compared with Rd for TNE patients with NDMM.
Uyl-de Groot, Carin A., et al. "Lenalidomide as maintenance treatment for patients with multiple myeloma after autologous stem cell transplantation: A pharmaco-economic assessment." European Journal of Haematology 105.5 (2020): 635-645.	A partitioned survival model was developed to assess the lifetime costs and benefits for patients with NDMM. Efficacy was taken from a pooled (simple pooling) meta-analysis of clinical trial data. Costs and subsequent therapy data were taken from sources appropriate for the Dutch market. Model outcome measures included quality-adjusted life years (QALYs), costs (in 2016 EUR), and life years (LYs). An incremental cost-effectiveness ratio (ICER) was reported in terms of cost per QALY gained to allow evaluation against the willingness to pay (WTP) threshold of EUR 50000 for MM.	This study was the first examination of cost-effectiveness of lenalidomide as maintenance therapy following ASCT in patients with newly diagnosed multiple myeloma from a Dutch healthcare perspective. Compared with no-MT, R maintenance produced an incremental LY gain of 2.79 and an incremental QALY gain of 2.46. This resulted in an ICER of EUR 30143 per QALY gained. Probabilistic results were consistent with those calculated from the deterministic analysis and indicated a 99.9% probability of R maintenance being cost-effective at the WTP threshold for MM of EUR 50000/QALY gained.	Lenalidomide is cost-effective after ASCT vs no maintenance therapy in the Netherlands. By extending PFS, lenalidomide delays the cost burdens associated with relapse and subsequent treatment lines. The present study provides a model for estimations in other EU countries; although the discount rates, HCRU rates, cost inputs, and utility values may vary across countries.

Trial/Study Name	Design	New Evidence	Impact/ Implications
Zamagni, Elena, et al. "Patient Characteristics, Treatment Outcomes and Healthcare Resource Utilization across Europe in Multiple Myeloma Patients Ineligible for Stem Cell Transplantation Who Received Lenalidomide-or Bortezomib-Based Regimens." Blood 134 (2019): 4772.	Physicians from Austria, Belgium, France, Germany, Italy, Spain, and Netherlands abstracted retrospective data from medical records of patients with MM who received 1L LEN- or 1L BORT-based regimens between Jun 1, 2015 and Nov 30 2016. Data collected included patient demographics, clinical characteristics, treatment patterns, health outcomes (e.g. PFS, TTNT), and HCRU. Health outcomes were compared for LEN- and BORT-based regimens using the Kaplan-Meier estimator. HCRU was calculated as means per month, per usage type. Patients with complete resource use data for an HCRU category were included in the analysis for that category. 59 physicians provided data on 453 patients.	Within the follow up period, patients treated with 1L LEN-based regimens received significantly fewer lines of treatment (mean [SD] 1.55 [0.64] vs 1.75 [0.69] lines; $P < 0.01$) vs patients treated with 1L BORT-based regimens. Significant differences in PFS ($P < 0.01$) were observed; the probability of maintaining PFS was higher for patients receiving 1L LEN- vs 1L BORT-based regimens at 12 (94% vs 85%) and 24 months (76% vs 63%) post-1L initiation. A significantly longer TTNT (median 45.7 vs 36.5 months; $P < 0.01$) was observed for patients receiving 1L LEN vs those receiving 1L BORT.	This study provides real-world evidence to support 1L LEN-based regimens as providing clinically meaningful benefits for patients.
Lymphoma			
Clinical Evidence of Revlimid's Value in Lymphoma (n=8)			
AUGMENT (NCT01938001); Leonard, John P., et al. "AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma." Journal of Clinical Oncology 37.14 (2019): 1188-1199.	AUGMENT is a phase III, multicenter, double-blind, randomized trial of R^2 versus placebo plus rituximab was conducted in patients with relapsed and/or refractory follicular or marginal zone lymphoma. Patients received lenalidomide or placebo for 12 cycles plus rituximab once per week for 4 weeks in cycle 1 and day 1 of cycles 2 through 5 (every 28 days). The primary end point was progression-free survival. Eligible patients had MZL or FL (grades 1 to 3a) requiring treatment per investigator assessment; at least one prior chemotherapy, immunotherapy, or chemoimmunotherapy and two or more previous doses of	The primary end point of PFS was significantly superior in the R^2 group (HR, 0.46; 95% CI, 0.34 to 0.62; $P < .001$). Median PFS assessed by IRC was 39.4 months (95% CI, 22.9 months to not reached) with R^2 versus 14.1 months (95% CI, 11.4 to 16.7 months) with placebo plus rituximab. PFS assessed by investigator also showed superiority with R^2 versus placebo plus rituximab (HR, 0.51; 95% CI, 0.38 to 0.69; $P < .0001$; the median PFS was 25.3 months; 95% CI, 21.2 months to not reached versus 14.3 months; 95% CI, 12.4 to 17.7 months). PFS probability at 2 years also favored R^2. OS results are maturing, with an HR of 0.61	The magnitude of efficacy differences between the two treatments is clinically meaningful and suggests that R^2 should be considered as a standard of care for patients with relapsed or refractory indolent NHL. This study led to lenalidomide indication approvals for FL and MZL.

Trial/Study Name	Design	New Evidence	Impact/ Implications
	rituximab; and relapsed, refractory, or progressive disease and not rituximab-refractory disease. A total of 358 patients were randomly assigned to R^2 (n = 178) or placebo plus rituximab (n = 180).	(95% CI, 0.33 to 1.13). Numerically fewer deaths in treated patients have been observed with R^2 versus placebo plus rituximab (15 versus 26), although the trial was not powered to detect OS differences. Grade 3 or 4 neutropenia (50% v 13%) and leukopenia (7% v 2%) were higher with R^2; no other grade 3 or 4 adverse event differed by 5% or more between groups.	
AUGMENT (NCT01938001); Gribben, John G., et al. "Efficacy and time to next treatment following lenalidomide/rituximab (R^2) or rituximab/placebo in patients with R/R indolent NHL (AUGMENT)." Poster presented at: 2019 ASCO Annual Meeting.	AUGMENT is a multicenter, double-blind, randomized phase III study of R^2 versus placebo plus rituximab (R-placebo) in patients with relapsed and/or refractory follicular or marginal zone lymphoma. The primary endpoint was PFS by 2007 IWG.	Median PFS was superior for R^2 over Placebo plus rituximab (39.4 vs 14.1 months; HR = 0.46; P < 0.0001). As of June 22, 2018, median TTNLT, TTNCT, and PFS2 were not reached for R^2, and were significantly longer than placebo plus rituximab (HR = 0.54, 0.50, and 0.52, respectively). For 49/178 (28%) R^2 and 80/180 (44%) Placebo plus rituximab patients receiving next anti-lymphoma therapy, response was generally higher with R^2 (57% ORR; 31% CR) than placebo plus rituximab (36% ORR; 16% CR).	Patients who receive R^2 may be more sensitive to subsequent therapy than those treated with R-placebo.

Trial/Study Name	Design	New Evidence	Impact/ Implications
AUGMENT (NCT01938001); Izutsu, Koji, et al. "Analysis of Japanese patients from the AUGMENT phase III study of lenalidomide+ rituximab (R^2) vs. rituximab+ placebo in relapsed/refractory indolent non-Hodgkin lymphoma." International journal of hematology 111.3 (2020): 409-416.	AUGMENT is a multicenter, double-blind, randomized phase III study ofR^2 versus placebo plus rituximab (R-placebo) in patients with relapsed and/or refractory follicular or marginal zone lymphoma. Considering the different treatment landscapes for iNHL globally, subgroup analysis was performed in Japanese patients enrolled in the AUGMENT study. Data reported in this report focused on Japanese patients from AUGMENT and reflect 36 patients (n = 18, each group).	The primary endpoint of PFS by IRC was superior in the R^2 group vs the R-placebo group (HR 0.32; 95% CI 0.11–0.96). PFS as assessed by investigator also showed HR in favor of R^2 (HR 0.62; 95% CI 0.23–1.67); median PFS by investigator was NR (95% CI 16.7–NE) vs 19.3 months (95% CI 13.9–NE) for the R^2 and R-placebo groups, respectively. More patients in the R^2 group (67%) had at least one grade 3/4 AE compared with the R-placebo group (22%).	The results reported for the Japanese subgroup were consistent with that of the global AUGMENT study. Although this study was a placebo-controlled trial, these results suggest that R^2 may be a new treatment option for Japanese patients with RR iNHL.
AUGMENT (NCT01938001); Leonard, J. P., et al. "AUGMENT Phase III Study: Lenalidomide/Rituximab (R^2) Improved Efficacy Over Rituximab/Placebo in Relapsed/Refractory Follicular Lymphoma Patients Irrespective of POD24 Status" Oral Presentation. International Conference on Malignant Lymphoma Palazzo dei Congressi, Lugano, Switzerland (2019).	AUGMENT is a multicenter, double-blind, randomized phase III study of R^2 versus placebo plus rituximab (R-placebo) in patients with relapsed and/or refractory follicular or marginal zone lymphoma. Data reported in this study were on patients with relapsed/refractory (R/R) FL grade 1–3a after ≥ 1 prior systemic therapy but were not refractory to rituximab. 147 FL grade 1–3a patients were randomized to R^2 and 148 to R-placebo. The objective of this analysis was to evaluate the potential impact of progression of disease within 2 years (POD24) on efficacy in the randomized phase III AUGMENT study of lenalidomide/rituximab (R^2) versus R-placebo.	Median PFS was improved in patients receiving R^2 vs R-placebo, irrespective of POD24 status: median PFS months for R^2: 30.4 (16.8-NR) vs 13.8 (6.7-16.9) for R/placebo; (HR = 0.41 [95% CI, 0.24–0.68, p = 0.0004] with POD24 and HR = 0.43 [95% CI, 0.28–0.65, p < 0.0001] with no POD24).	Based on favorable efficacy, R^2 is an important option in FL patients with POD24.
AUGMENT (NCT01938001); Trněný, Marek, et al. "Subgroup Analyses	AUGMENT is a multicenter, double-blind, randomized phase III study of R^2 versus placebo plus rituximab (R-	R^2 had demonstrated improvement of PFS vs R-placebo in both < 70 and ≥ 70 years subgroups, with HR of	These data show that R^2 maintained efficacy improvements vs R-placebo in patients ≥ 70 y, despite higher

Trial/Study Name	Design	New Evidence	Impact/ Implications
of Elderly Patients Aged≥ 70 Years in AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R^2) vs Rituximab Plus Placebo (R-Placebo) in Patients with Relapsed/Refractory (R/R) Indolent Non-Hodgkin Lymphoma (iNHL)." Oral Presentation at: American Society of Hematology (ASH) 2019. Orlando, FL. 134 (2019).	placebo) in patients with relapsed and/or refractory follicular or marginal zone lymphoma. Post-hoc analyses were performed by dividing patients into age < 70 years and ≥ 70 years subgroups, the latter group considered unfit for chemotherapy. Of 358 patients randomized (R^2, n = 178; R-placebo, n = 180), 267 patients were age < 70 years (R^2, n = 131; R-placebo, n = 136), and 91 patients were age ≥ 70 years (R^2, n = 47; R-placebo, n = 44).	0.41 (95% CI, 0.29-0.59) and HR of 0.66 (95% CI, 0.37-1.18), respectively. In patients ≥ 70 years, median PFS with R^2 vs R-placebo was 24.9 vs 14.3 months; ORR/CR was 81%/26% vs 59%/16%; and TTNLT was not reached in either arm. In patients ≥ 70 years, 75% of R^2 patients vs 36% of R-placebo patients had ≥ 1 grade 3/4 AE, mainly due to neutropenia (50% vs 7%). All other grade 3/4 AEs occurred in < 10% of patients ≥ 70 years in both treatment arms. One grade 5 AE occurred in patients ≥ 70 years (R-placebo arm).	unfit status and lower overall lenalidomide treatment. Thus, R^2 is an effective and available treatment option for patients with iNHL, including those with advanced age.
Liu, Zhaoyu, et al. "Efficacy of rituximab combined with lenalidomide in patients with recurrent follicular lymphoma." International Journal of Clinical and Experimental Medicine 12.9 (2019): 11708-11715.	A total of 60 recurrent FL patients, admitted to The Second Hospital of Shanxi Medical University from February 2010 to December 2015, were randomly assigned into the control group and the observation group at a 1:1 ratio. The control group received rituximab combined with CHOP-chemotherapy regimen, and the observation group received lenalidomide in addition. Eligible patients met the relevant diagnostic criteria of recurrent FL grade 1, 2, or 3a and were aged ≥ 18 years. The overall response rate (ORR) after 6 cycles of chemotherapy was compared in both groups and classified as CR, PR, SD, and PD, according to the response evaluation criteria in lymphoma.	The ORR was higher in the observation group (83.33%) than that in the control group (66.67%) (P<0.05). No significant differences were observed for the control group vs. the observation group in incidences of adverse events. The 2-and 3-year PFS in the observation group were significantly higher than those in the control group (both P<0.05). The 2- and 3-year survival in the observation group were significantly higher than those in the control group (both P<0.05).	Combined therapy of rituximab and lenalidomide for patients with recurrent FL not only improves short-term clinical benefit rate, but also the progression of disease, and prolongs the survival period of patients. This therapy may be a new option of treatment for recurrent FL.
MAGNIFY (NCT01996865); Coleman, Morton, et al. "Patients with Relapsed/Refractory Marginal Zone Lymphoma in the MAGNIFY Phase	MAGNIFY is a multicenter, phase IIIb trial in patients with R/R FL grades 1-3b, transformed FL (tFL), MZL, or mantle cell lymphoma. Data presented in this study focus on induction R^2 in efficacy-evaluable MZL patients	The median PFS for the MZL population was 40.9 months (95% CI, 27.8-NR) and for the overall population was 41.2 months (95% CI, 38.7-NR). Overall response rate for the MZL population was 66% with 39% CR/CRu, and median	The results show that R^2 effects are consistent across iNHL histological subgroups. The MAGNIFY trial is ongoing to compare R^2 vs rituximab extended treatment in patients with RR FL and MZL.

Trial/Study Name	Design	New Evidence	Impact/ Implications
IIIb Interim Analysis of Induction R^2 Followed By Maintenance." Poster Presented at: American Society Of Hematology (ASH) New Orleans, LA (2020).	compared with the overall population of FL grades 1-3a+MZL (not including FL grade 3b, tFL, or MCL) receiving ≥ 1 treatment with baseline/post-baseline assessments. Patients received 12 cycles of R^2 followed by 1:1 randomization in patients with stable disease, partial response, or complete response/complete response unconfirmed (CR/CRu) to R^2 versus rituximab maintenance for 18 months. The primary end point is PFS. As of November 30, 2019, 393 patients with FL grades 1-3a and MZL enrolled; 76 (19%) had MZL.	duration of response was 38.6 months (95% CI, 29.4-not reached [NR]). Most common (≥ 10%) grade 3/4 AEs were neutropenia (41%; 1 patient [1%] had febrile neutropenia), thrombocytopenia (13%), and leukopenia (11%).	
MAGNIFY (NCT01996865); Lansigan, Frederick, et al. "Subgroup analyses of elderly patients aged≥ 70 years in MAGNIFY: A phase IIIb interim analysis of induction R^2 followed by maintenance in relapsed/refractory indolent non-Hodgkin lymphoma." Oral Presentation at: American Society Of Hematology (ASH) New Orleans, LA (2020)	MAGNIFY is a multicenter, phase IIIb trial in patients with R/R FL grades 1-3b, transformed FL (tFL), MZL. Data presented in this study focused on induction R^2 in efficacy-evaluable FL grade 1-3a and MZL patients (not including FL grade 3b, tFL or MCL) receiving ≥ 1 treatment with baseline/post-baseline assessments. Patients received 12 cycles of R^2 followed by 1:1 randomization in patients with stable disease, partial response, or complete response/complete response unconfirmed (CR/CRu) to R^2 versus rituximab maintenance for 18 months. The primary end point was PFS. Post-hoc analyses were performed by analyzing data from patients aged ≥ 70 years at time of study entry. As of November 30, 2019, 393 patients had enrolled and 152 (39%) were aged ≥ 70 years.	Median PFS in patients ≥ 70 years of age is 40.1 months and 41.2 months in all patients. Overall response rate and CR/CRu were 75% and 39%, with a median duration of response that was not reached (95% CI, 27.1-NR) in the ≥ 70 subgroup. In patients ≥ 70 years, neutropenia (35%) was the only grade 3/4 TEAE occurring in > 10% of patients (febrile neutropenia occurred in 3 patients [2%]).	These results suggest that R^2 may be considered as a treatment option for advanced-age patients with R/R FL and MZL.

Bristol Myers Squibb™

Appendix 2: ***Indications & Important Safety Information***

REVLIMID® (lenalidomide) in combination with dexamethasone (dex) is indicated for the treatment of adult patients with multiple myeloma (MM).

REVLIMID is indicated as maintenance therapy in adult patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT).

REVLIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

REVLIMID is only available through a restricted distribution program, Lenalidomide REMS.

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, AND VENOUS AND ARTERIAL THROMBOEMBOLISM

Embryo-Fetal Toxicity

Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVLIMID treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the Lenalidomide REMS program.

Information about the Lenalidomide REMS program is available at www.lenalidomiderems.com or by calling the manufacturer's toll-free number 1-888-423-5436.

Hematologic Toxicity (Neutropenia and Thrombocytopenia)

REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q MDS had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q MDS should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors.

Venous and Arterial Thromboembolism

REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with MM who were treated with REVLIMID and dexamethasone therapy. Monitor for and advise patients about signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks.

CONTRAINDICATIONS

Pregnancy: REVLIMID can cause fetal harm when administered to a pregnant female and is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to the fetus.

Severe Hypersensitivity Reactions: REVLIMID is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.

For a complete list of **Warnings & Precautions** and the **Most Common Adverse Reactions** please refer to the REVLIMID Full Prescribing Information.

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September 15, 2022

Re: Preliminary Report, Unsupported Price Increases Occurring in 2020 in California Notification, SPRYCEL®

BMS submitted substantial quality evidence to support Sprycel's (dasatinib) value to patients, providers, and payers; however, dasatinib may not have warranted being included in this assessment at the onset, as previously communicated. BMS disagrees with ICER's response to the evidence that has been submitted and outlines here the importance and quality of the evidence published between 2019-2020. A narrative summary is provided below, and a tabulation of evidence including study details and safety (n=19) is provided in Appendix 1.

Evidence Supporting Sprycel's Value: Important evidence within the specified criteria and supporting dasatinib's value were excluded. To assist ICER with the systematic review, BMS provided 30 scientific publications that support dasatinib's safety, clinical effectiveness, and economic value. ICER indicated in its response that none of the evidence met the review process criteria, thereby excluding high-quality evidence of the added net health benefit of dasatinib. BMS has reviewed ICER's response to each submitted article and is elucidating why 19 of the 30 studies originally submitted should be further reconsidered for inclusion. For example, the Cortes et al. (2020) study was categorized as "previously known information related to dasatinib efficacy;" however, this was the first prospective randomized trial to provide evidence on the benefit of an early switch to dasatinib relative to staying on imatinib following poor response to first-line imatinib. Findings from this study further support new evidence of usage for dasatinib within the CML indication.

Sprycel Indications for Consideration: Dasatinib use in CML and ALL, meets either ICER's prevalent utilization criterion (10% or more of the drug's utilization) or the rapid-increase utilization criteria (use for an indication is rapidly increasing) to support an increase in price in California. ICER should include high-quality evidence for the added value of the approved pediatric Ph+ ALL subpopulation within the ALL indication. Acute lymphocytic leukemia (ALL), including pediatric Ph+ ALL, represents greater than 10% of dasatinib utilization as indicated in the data submitted to ICER previously. Dasatinib evidence and newly approved indications specific to pediatric populations are important to those patients with ALL, ensuring effective and safe therapies for populations with high unmet needs. Excluding these studies ignores the continued research, innovation, and value provided to pediatric patients. ICER's indication criteria should consider subpopulations that contribute to indications that comprise at least 10% of the drug's utilization.

Table 1 below reviews key submitted studies we believe provide new evidence of dasatinib's impact on various patient outcomes. These were initially excluded by ICER as being previously known evidence. However, the data generated from these clinical studies substantially build upon previously known evidence, and thus warrant reconsideration. These data showcase new findings on efficacy and long-term outcomes of dasatinib for patients with unmet needs, including improvements in quality-of-life measures, sustained treatment-free remission, and response rates.

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Table 1: Highlights of New Evidence of the Value of Sprycel[1]

Outcome	Prior Evidence	New Evidence	New Evidence Implications
Health-related quality of life (HRQOL)	Provides HRQOL differences between first line dasatinib and imatinib CML treatment arms. EQ-5D was 0.77 and 0.79 at baseline and 0.80 and 0.82 at one year for dasatinib and imatinib, respectively. HRQOL differences between treatment arms were non-significant (Labeiet et al., 2015).	First-line dasatinib CML patients reported significantly better disease-specific HRQOL outcomes in impact on daily life ($\Delta = 8.7$, $p = 0.002$), satisfaction with social life ($\Delta = 13.45$, $p = 0.001$) and symptom burden ($\Delta = 7.69$, $p = 0.001$), compared to imatinib treatment arm (Efficace et al., 2019).	First study showing dasatinib's HRQOL improvement vs. standard of care. Findings can support clinical-decision making for first-line treatment decisions.
Major molecular response (MMR)	Retrospective study found improved response rates and EFS when dasatinib was administered early after imatinib resistance (Quinta´s-Cardama et al., 2009).	MMR at 12 months was 29% among dasatinib patients and 13% among imatinib patients (p=0.005). Accounting for treatment crossover, a higher proportion of dasatinib patients achieved MMR vs imatinib patients at 24 months (64% vs 41%) (Cortes et al., 2020; DASCERN trial).	First prospective randomized trial to demonstrate benefit of early switching to dasatinib vs. remaining on imatinib within the CML indication.
Discontinuation after sustained deep molecular response	Limited evidence of sustained deep molecular response in a large CML cohort after discontinuation of first-line dasatinib only. Prior studies included small numbers of patients receiving first-line dasatinib or nilotinib (e.g., Rea et al., 2017 and Saussele et al., 2018).	55% of patients had treatment-free remission at 6 months after dasatinib discontinuation; median follow-up was 23.3 months. Estimated treatment-free remission at 6 months was 55.2% (Kimura et al., 2020; DADI trial).	Study findings indicate patients with CML can safely discontinue dasatinib after first-line treatment and having achieved sustained deep molecular response.
Treatment-free remission (TFR)	Demonstrates second-line or subsequent dasatinib discontinuation among CML patients after sustained deep molecular response for at least 1 year is achievable. Overall treatment-free remission at 6 months was 49% (Imagawa et al., 2015).	Two-year TFR was 51% in first-line patients, and 42% in subsequent-line patients. Two-year progression-free survival was 99% in all patients (Shah et al., 2019; DASFREE trial).	Study findings show two-year TFR is feasible after dasatinib discontinuation. Results can inform treatment decisions in first-line and subsequent settings for patients considering TFR.

[1]Quality of evidence as rated by BMS using GRADE criteria: Efficace et al., 2019: moderate-quality; Cortes et al., 2020: high-quality; Kimura et al., 2020: high-quality; Shah et al., 2019: high-quality.
HRQOL: health-related quality of life; MMR: major molecular response; CML: chronic myelogenous leukemia; TFR: treatment-free remission; EFS: event-free survival; OS: overall survival

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Based in part on this evidence-based review, the value of dasatinib relative to other therapies in CML and ALL, has elevated. The peer-reviewed evidence testifies to BMS's commitment to investing and accelerating research necessary to optimize medication use and continued value for patients.

Achieving the full promise of therapies across these indications will require long-term investment in developing the evidence necessary to inform optimal care. The following sections summarize recent evidence (2019-2020) of dasatinib's clinical value as well as new evidence of efficacy, safety, and patient reported outcomes arising from clinical trials and real-world data.

Clinical Evidence and Value Supporting Sprycel's Use in ALL

ICER's UPI review criteria limits dasatinib's assessment to only indications representing greater than 10% use, excluding high-value clinical evidence for the ALL-pediatric population. In totality, ALL patients treated with dasatinib represent greater than 10% utilization. Results from two clinical trials for pediatric Ph+ ALL should be included as new evidence in ICER's assessment, as they demonstrate dasatinib's clinical value in the pediatric population, as well as long term safety and efficacy (Shen et al., 2020; Hunger et al., 2020).

CA180-372/COG AALL1122 (Hunger et al., 2020) is a phase 2 trial of dasatinib and chemotherapy in pediatric patients with newly diagnosed pediatric Ph+ ALL. Findings from this trial showed a lower percentage of pediatric patients treated with dasatinib and chemotherapy required hematopoietic stem cell transplantation compared to previous trials conducted with imatinib, with comparable survival outcomes. The 5-year EFS 54.6% (95% CI, 44.5-63.6) and OS was 81.7% (95% CI, 82.8-87.9), compared to 60.3%/71.5% in EsPhALL 2004, and 57%/71.8% in EsPhALL 2010 (Biondi et al., 2012; Biondi et al., 2018). The Food and Drug Administration (FDA) granted dasatinib's approval in this pediatric Ph+ ALL population based on findings from this study.

CCCGALL-2015 (Shen et al., 2020) is a phase III randomized study to determine whether dasatinib given at 80 mg is more effective than imatinib at 300 mg in improving event-free survival in pediatric Ph+ ALL. Dasatinib exhibited a higher efficacy and tolerable safety profile in comparison to imatinib, with a greater 4-year event-free survival rate and overall survival rate. The 4-year event-free survival rate in the dasatinib group was significantly better than in the imatinib group (71.0% vs. 48.9%, p=0.005, log-rank test). The 4-year overall survival rate was also higher in the dasatinib group vs imatinib group (88.4% vs 69.2%, p=0.04, log rank test). Study findings also showcase improved outcomes of dasatinib treatment at a dosage of 80 mg/m2 per day compared to recent pediatric phase 2 trials of dasatinib given at a dosage of 60 mg/m2 per day.

Clinical Evidence Demonstrating New Findings on Efficacy and Long-term Outcomes of Sprycel

ICER's exclusion of published evidence in dasatinib's assessment excludes new and important clinical evidence. These high-quality clinical trial studies extend current knowledge on the safety and efficacy data of dasatinib to better inform clinical decision making among the overall patient population and high-risk sub-groups.

Maiti et al., 2020 provided the longest follow-up data available for dasatinib, with a median follow up of 6.5 years. Findings showed the 10-year overall survival, transformation-free survival, event-free survival, and failure-free survival rates were 89%, 95%, 86%, and 65%, respectively, among patients with chronic-phase chronic myeloid leukemia. This study supports the long-term impact of dasatinib on efficacy and safety in CML patients, as well as improved survival outcomes.

Findings from the DASISION trial (Breccia et al., 2019) found that patients with a high BMI treated

with dasatinib demonstrated a significantly faster time to response compared with imatinib; specifically, more patients with a high BMI treated with dasatinib achieved major molecular response (MMR) compared with those treated with imatinib (79.8% vs 59.8%; p = 0.0004); additionally, 54.1% of patients with a high BMI achieved $MR^{4.5}$ with dasatinib, compared with 34.6% with imatinib (p= 0.0013).

Breccia et al., 2020 is a post hoc analysis of DASISION at 5-years' follow-up, which evaluated the effect of comorbidities on response outcomes with dasatinib vs imatinib. Molecular response rates were significantly higher with dasatinib than imatinib in patients with Charlson Comorbidity Index (CCI) 5-6. Time to response was significantly faster with dasatinib than imatinib in both the CCI 5-6 and CCI ≥ 7 groups. These findings demonstrate the benefit of first-line treatment with dasatinib in CML-CP patients with comorbidities. Results also demonstrate the importance of treatment choice when assessing a patient based on their comorbid conditions.

High-Quality Real-World Evidence Demonstrating Value of Sprycel

ICER states in the UPI protocol that "studies reporting patient-reported outcomes and other real-world data will be highly relevant." However, ICER' dasatinib assessment discounted several peer-reviewed, real-world studies, based on their assessment using the GRADE criteria, which largely excluded any real-world observational data. Real-world evidence was also excluded based on outcomes deemed "not relevant to scope." ICER's assessment does not define these terms or provide an explanation as to why these studies would be excluded based on this criterion.

Goldberg et al., 2020, a large, real-world observational study of CP-CML patients, highlighted the importance of evaluating cardiovascular (CV)-risk profile and comorbidities prior to first-line tyrosine kinase inhibitors (TKI) therapy. Findings showed the incidence of CV-related hospitalizations and length of stay were lowest among patients receiving dasatinib. These real-world findings suggest dasatinib has the most preferable CV safety outcomes in comparison to other TKIs (imatinib and nilotinib).

Economic and cost-effectiveness data are also critical for understanding an intervention's value, which may lead to improved patient access. Yue et al., 2019 is a high-quality study which used a Markov state transition model to compare the cost-effectiveness of second-line TKI for treatment practice of CML patients over a life-long time horizon. Findings indicate dasatinib is a cost-effective treatment option for CML patients, which provides improved clinical benefits compared to other second-line TKIs. Dasatinib resulted in an ICER of $79,114.19/quality-adjusted life-year (QALY) compared to nilotinib.

These studies provide examples of dasatinib's significant outcomes compared to other TKI therapies. As real-world outcomes may differ substantially from clinical trial outcomes (Webster & Smith, 2019), the availability of new real-world evidence studying the comparative value of a healthcare intervention not previously studied in real-world settings should be considered an added evidence-based value for the intervention. Excluding this evidence precludes data that enables health care decision-making, and which provides valuable information for patients.

Summary

BMS disagrees with ICER's exclusion of clinical trial and real-world studies that demonstrate dasatinib's value and clinical effectiveness, including those highlighted above. The evidence presented in this response to ICER's dasatinib assessment supports the elevated clinical and economic value that dasatinib has brought to patients with CML and ALL. Results arising from clinical trials and real-world evidence exhibited dasatinib's enhanced benefits for CML patients in terms of efficacy, safety, cost-effectiveness, patient reported outcomes, and feasibility to discontinue long-term treatment. For ALL, clinical trial results reported dasatinib's greater efficacy and safety outcomes when compared to 1st generation TKIs. This new evidence exhibits benefits that previously had not been published, which support the pricing of dasatinib during the 2019-2020 timeframe.

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APPENDIX 1. Evidence Table

Please note that information included in the following Table are based on abstractions from the full publications and are provided as such for ease of viewing.

Abbreviations

AE: Adverse event
BMI: Body mass index
CCyR: Complete cytogenetic response
CI: Confidence interval
CR: Complete response
DMR: Deep molecular response
EFS: Event-free survival
HCT: hematopoietic cell transplantation
HRQOL: Health-related quality of life
IND: Induction
IC: Intensive consolidation
MR: Molecular response
MMR: Major molecular response
OR: Odds ratio
OS: Overall survival
PFS: Progression-free survival
QALY: Quality adjusted life year
TFR: Treatment-free remission
TKI: Tyrosine kinase inhibitor
TRAE: Treatment-related adverse event

Trial	Design	New Evidence	Impact/ Implications
Chinese Children's Cancer Group study ALL-2015 (CCCGALL- 2015), Shen et al., JAMA Oncology, 2020	Prospective, multi-institutional randomized clinical trial where children aged 0 to 18 years with ALL, received MRD directed, risk-stratified treatment of either dasatinib (80mg/m2 per day) or imatinib mesylate (300mg/m2 per day)	The 4-year event-free survival rate in the dasatinib group was 71.0% vs. 48.9% in the imatinib group (p=0.005). The 4-year overall survival rate was 88.4% in the dasatinib group vs 69.2% the imatinib group (p=0.04). The 4-year cumulative risk of any relapse was significantly lower in the dasatinib group vs. the imatinib group (19.8% vs 34.4%, p=0.01). Frequencies of common serious toxic effects did not differ significantly between dasatinib and imatinib treatment arms. The number of patients with Infections followed by pancreatitis were the most common adverse effects, occurring equally in both treatment arms.	Study findings showcase significant benefit of dasatinib vs imatinib in pediatric Ph+ALL, as well as improved outcomes of dasatinib treatment at a dosage of 80 mg/m2 per day compared to recent pediatric phase 2 trials of dasatinib given at a dosage of 60 mg/m2 per day.
Pediatric Philadelphia Positive Acute Lymphoblastic Leukemia (CA180-372), Hunger et al., Pediatric Blood & Cancer, 2020	Open label, single-arm, phase II trial of dasatinib and chemotherapy in pediatric patients with newly- diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia	The 5-year EFS was 54.6% (95% CI, 44.5-63.6) and OS was 81.7% (95% CI, 82.8- 87.9) versus 60.3%/71.5% in EsPhALL2004, and 57%/71.8% in EsPhALL2010. The primary toxicities were febrile neutropenia and infection. 48 (45%) patients had events including 38 relapses and 9 treatment-related deaths.	Study findings demonstrate dasatinib plus EsPhALL chemotherapy is an effective treatment in pediatric Ph+ALL.
First-line DADI trial (UMIN0000 11099), Kimura et al., Lancet Hematology, 2020	The first-line DADI trial was a single-arm, multicenter, phase 2 trial done at 23 hospitals in Japan.	32 patients (55%) had treatment-free remission at 6 months after dasatinib discontinuation. Median follow-up was 23.3 months. Estimated treatment- free remission at 6 months was	Study findings indicate patients with CML can safely discontinue dasatinib after first-line treatment after having achieved sustained deep molecular response.

		55.2%. The most common haematological adverse event was anaemia (21%); three (4%) of 68 treated patients had grade 3 neutropenia and one had grade 4 lymphopenia.	
DASFREE (NCT018500 004) Shah et al., Clinical Lymphoma, Myeloma & Leukemia, 2019	An open-label, single-arm phase 2 study measuring treatment-free remission (TFR) after discontinuation of dasatinib in patients with chronic myeloid leukemia in chronic phase (CML-CP) and deep molecular response (DMR)	Two-year TFR was 46% in all patients, 51% in first-line patients, and 42% in subsequent- line patients. Adverse events were consistent with dasatinib's known safety profile.	Study findings show two-year TFR is feasible after dasatinib discontinuation. Results can inform treatment decisions in first-line and subsequent settings for patients considering TFR
DASFREE (NCT018500 04) Shah et al., Leukemia & Lymphoma, 2020	DASFREE is an open-label, single-arm, multicenter phase II trial assessing TFR after dasatinib discontinuation in patients with CML-CP (N=84).	At 1 year, TFR was 48% in all enrolled patients. At 2 years, TFR was 46% in all patients, 51% in first- line patients, and 42% in subsequent- line patients. At 2 years, PFS was 99% in all patients; 100% in first-line patients, and 98% in subsequent-line patients. Common AEs of any grade included musculoskeletal and connective tissue disorders, infections, gastrointestinal disorders and nervous system disorders. Dasatinib-related grade 3/4 AEs were experienced in 4 patients (9%) on treatment after restarting dasatinib.	Study findings demonstrate safety and feasibility of discontinuing dasatinib, and provide important clinical information for TFR among CML-CP patients, which can inform clinical decision-making.
DASCERN trial (NCT015932 54) Cortes et al., Leukemia, 2020	DASCERN is an open-label, randomized, international, multicenter phase 2b trial of dasatinib vs. imatinib in patients with Philadelphia chromosome-positive (Ph+) CML-CP	Rate of major molecular response (MMR) at 12 months was 29% among dasatinib patients and 13% among imatinib patients (p=0.005). After ≥2 years of follow-up, 45 patients (52%) crossed over to dasatinib. Among patients who crossed over, the 2-year	First prospective randomized trial to demonstrate benefit of early switching to dasatinib vs. remaining on imatinib within the CML indication

		cumulative MMR rate was 64% with dasatinib and 41% with imatinib (66% and 67%, respectively by intent-to-treat). Treatment-related AEs of any grade occurred in 141 (82%) dasatinib patients and 67 (78%) imatinib patients. Grade 3/4 treatment-related AEs occurred in 60 (35%) and 36 (42%) patients in the dasatinib and imatinib arms, respectively.	
(NCT00254423), Maiti et al., Cancer, 2020	Between November 2005 and August 2014, patients were randomly assigned to receive 100 mg daily or 50 mg twice daily. After June 2009, all patients started with 100 mg daily.	With a median follow-up of 6.5 years, the cumulative complete cytogenetic response rate at 11 years was 92.6%, the major molecular response (MR) rate was 88.2%, and the MR4.5 rate was 79.5%. The 10-year overall survival, transformation-free survival, event-free survival, and failure-free survival rates were 89%, 95%, 86%, and 65%, respectively. Common grade 3 and 4 AEs included: fatigue (13%), skeletal pain (8%), infections (11%), sexual/reproductive symptoms (4%), and hypertension (3%). Treatment discontinuation because of toxicity and loss of response, occurred in 14% and 5% of patients, respectively.	Study provides the longest follow-up data available for dasatinib, with a median follow up of 6.5 years. Findings demonstrate the long-term impact of dasatinib on efficacy and safety in CML patients, as well as improved survival outcomes.
JALSG CML212 (#UMIN000 007909), Matsumara et al., Blood, 2020	The JALSG CML212 study is a multicentral open-labeled prospective randomized controlled phase 3 study	Achievement rates of $MR^{4.5}$ by 18 months were 33.0% in the nilotinib arm and 30.8% in the dasatinib arm, with no statistically significant difference (p=0.62). No statistically significant difference was found in	Achievement rates of MR4.5, as well as PFS, EFS, and OS between nilotinib and dasatinib were similar. These findings have important implications in treatment decision-making among de novo CML-CP patients.

		PFS, EFS, OS, MRR rates or CCyR rates, between the two treatment arms. Grade 3/4 adverse events observed with ≥10% frequencies were lipase elevation (11.5%) in the nilotinib arm and neutropenia (12.8%) and thrombocytopenia (16.8%) in the dasatinib arm.	
DASISION trial (NCT00481247), Breccia et al., Impact of Comorbidities on Response Outcomes in Patients with Chronic Myeloid Leukemia in Chronic Phase Treated with First-Line Dasatinib Versus Imatinib: Exploratory Post Hoc Analysis of DASISION, Blood, 2020	DASISION was a multinational, open-label, phase 3 trial assessing dasatinib vs imatinib for newly diagnosed CML-CP. Patients were randomized to receive 100 mg dasatinib (n = 259) or 400 mg imatinib (n = 260) once daily.	In the CCI 2-4 group, MMR rate was 85.7% with dasatinib and 57.1% with imatinib (p = 0.25). MMR rate was significantly higher with dasatinib vs imatinib (81.1% vs 64.8%, P =0.0033) in the CCI 5-6 group. Median time to MMR in the CCI 5-6 group was significantly shorter with dasatinib than imatinib (15.0 vs 24.0 months; HR, 1.64; 95% CI, 1.23-2.19; P = 0.0006). Median time to MMR was significantly shorter in the CCI ≥ 7 group with dasatinib vs imatinib (12.0 vs 21.4 months; p = 0.0279). Grade 3-4 treatment-related adverse events were reported in 0% vs 14% (dasatinib vs imatinib) of patients with CCI 2-4, 8% vs 9% of pts with CCI 5-6, and 24% vs 13% of pts with CCI ≥ 7. A similar proportion of patients died in each treatment arm in the CCI 5-6 and CCI ≥ 7 groups.	These findings demonstrate the benefit of first-line treatment with dasatinib in CML-CP patients with comorbidities. Results also highlight the importance of treatment choice when assessing a patient based on their comorbid conditions.
DASISION trial (NCT00481247), Breccia et al., Association of High Body Mass Index with Response Outcomes in Patients with CML-CP	Exploratory post hoc analysis of the phase 3 DASISION trial (NCT00481247) to investigate the association of high BMI with treatment responses with 1L TKIs.	Median time to CCyR was significantly shorter with dasatinib versus imatinib in patients with a high BMI (3.1 vs 6.1 months; P < 0.0001). A significantly higher proportion of	Study results indicate that high BMI patients treated with dasatinib have improved outcomes compared to high BMI patients treated with imatinib. Findings suggest

Treated with Dasatinib Versus Imatinib in the First Line: Exploratory Post Hoc Analysis of the Phase 3 DASISION Trial, Blood, 2019		dasatinib patients with high BMI achieved MMR vs high BMI patients treated with imatinib (79.8% vs 59.8%; p = 0.0004); and a greater number of high BMI dasatinib patients achieved MR $^{4.5}$ vs imatinib patients (54.1% vs 34.6%, p=0.0013). No adverse events by treatment arm were reported.	BMI may impact treatment responses to TKIs.
SIMPLICIT Y(NCT01244750) Goldberg et al., Clinical Lymphoma Myeloma And Leukemia, 2020	Observational study of patients with CP-CML in Europe and the U.S. who are treated with 1L TKIs, which assesses the incidence of CV-related hospitalizations, subsequent length of stay (LOS), and associated costs among patients with CP-CML in a real-world setting.	808 patients received first-line TKI therapy: imatinib (n=243), dastinib (n=301), or nilotinib (n=264). Incidence of CV-related hospitalizations was lowest for dasatinib (4.3%), followed by imatinib 4.5%) and nilotinib (8.0%).Total CV- related LOS was lowest for dasatinib (36 days) compared to 81 and 98 days for imatinib and nilotinib, respectively. Cardiac failure was the most common CV-related event: the rate per 1000 patient-years was 3.0 for imatinib, 3.2 for dasatinib, and 7.2 for nilotinib. No adverse events by treatment arm were reported.	Incidence of CV-related safety outcomes were lower among patients receiving dasatinib in comparison to other TKIs (imatinib and nilotinib). Study findings indicate CV-risk profile are comorbidities are important factors to consider in treatment decision-making for first-line TKI therapies.
Yu et al., Variables associated with patient-reported symptoms in persons with chronic phase chronic myeloid leukemia receiving tyrosine kinase inhibitor therapy, Medicine, 2019	Anonymous Chinese-language questionnaires were distributed to adults with chronic-phase CML receiving TKI therapy >3 months regarding symptoms' incidence, severity, and HRQoL.	Patients who received nilotinib (OR=0.5, p<0.001) or dasatinib (OR=0.5, p<0.001) compared with imatinib, and achieved CCyR but not CMR, experienced significantly fewer symptoms. The top 5 common TKI-related symptoms were fatigue (77%), periorbital and lower limb edema (72%), chest distress and shortness of breath (61%), memory deterioration (54%) and skin color change (44%).	Study findings can inform hematologists of factors associated with higher HRQOL, to support clinical decision-making in CML patients receiving TKI therapy.

Caocci et al., Long-term mortality rate for cardiovascul ar disease in 656 chronic myeloid leukaemia patients treated with second- and third-generation tyrosine kinase inhibitors, International Journal of Cardiology, 2020	Retrospective cohort study with 656 adult CP-CML patients diagnosed and treated consecutively with 2nd/3rd generation (G) TKI, frontline or with subsequent lines of treatment in 19 Italian centers, between 2012 and 2017.	Nilotinib and ponatinib were significantly associated to peripheral arterial disease compared to dasatinib and bosutinib (7.3% and 5.9% versus 1.7% and 1.6%, respectively; p=0.02). Bosutinib and ponatinib showed higher association with stroke compared with nilotinib and dasatinib (5% and 3% versus 0.7% and 0%, respectively; p=0.01. The 15-year OS was 83±3.6%. 37 deaths occurred. 12 deaths were due to CV-related complications.	Study results can inform clinical-decision making for CP-CML patients at risk of CV disease. Findings support the need to develop prevention strategies based on CV risk factors (e.g., hypertension, obesity).
Klink et al., Real-World Effectiveness of First-Line (1L) Dasatinib Versus 1L Imatinib in Newly Diagnosed Patients with Chronic Phase Chronic Myeloid Leukemia (CP-CML), Blood, 2020	A retrospective, observational, US multi-site cohort study was conducted among adults with newly diagnosed Philadelphia chromosome- positive CP-CML treated with 1L dasatinib or 1L imatinib between January 2014 and September 2018.	Higher rates of MMR were observed in dasatinib vs imatinib patients (79% vs 65%, P <0.01). Median time to MMR was significantly shorter among dasatinib vs imatinib patients (11.9 vs 14.7 months, P < 0.01). Dasatinib patients also had higher rates of DMR (44% vs 25%, p<0.01) as well as shorter median time to DMR (30.3 vs 66.1 months, p<0.01) compared to imatinib patients. OS was also significantly longer among dasatinib vs imatinib patients (98% vs 89%, p < 0.01). No differences in safety or adverse events by treatment were reported.	Study findings indicate dasatinib results in better outcomes compared imatinib in the first-line real-world setting, with higher rates of MMR and DMR, and improved OS. Results can inform treatment decisions in first-line setting for CP-CML patients.
Treatment Free Remission Accomplished By Dasatinib (NCT02268370), Kim et al., Blood, 2019	A single arm, phase II interventional study to determine if using dasatinib (DA) can lead to a successful treatment-free remission (TFR) after failing a first attempt of TKI discontinuation following imatinib (IM).	58 (44.3%) of 131 patients experienced molecular relapse after imatinib discontinuation with a mRFS rate of 59.1% and 56.8% at 6 and 12 months, respectively. Median time to MMR, MR4 and MR4.5 was 0.94,	Findings suggest dasatinib rechallenge is feasible with a failed TFR attempt with imatinib

		1.95, and 2.48, respectively, among patients who started dasatinib and achieved MR4.5 (n=49). The TFR2 rate after DA discontinuation was18.5% at 6 months, TFR2 using loss of MMR as a definition of molecular relapse was 20.4%, while TFR2 using two consecutive losses of MR4 was 25.4%. No safety or adverse events were reported.	
Efficace et al., Health-related quality of life of newly diagnosed chronic myeloid leukemia patients treated with first-line dasatinib versus imatinib therapy, Leukemia, 2020	Multicenter propensity-matched case- control study to compare HRQOL of newly diagnosed CML patients treated with front-line dasatinib (cases) or imatinib (controls). Patient-reported HRQOL was assessed with the EORTC QLQ-C30 and the EORTC QLQ-CML24 questionnaires.	Patients treated with dasatinib reported better disease- specific HRQOL outcomes in impact on daily life ($\Delta = 8.72$, $p = 0.002$), satisfaction with social life ($\Delta = 13.45$, $p = 0.001$), and symptom burden ($\Delta = 7.69$, $p = 0.001$). Patients treated with dasatinib, also reported a lower prevalence of many symptoms compared to imatinib patients. Muscle cramps were reported by 66 (70%) and 28 (30%) patients treated with imatinib and dasatinib, respectively. Proportion of patients experiencing fatigue was similar between treatment arms. Other AEs reported included problems of frequent urination, acid indigestion or heartburn, dry mouth, and constipation.	First study showing dasatinib's HRQOL improvement vs. standard of care. Findings can support clinical decision-making for first-line treatment decisions.
Yue et al., Safety and cost-effectiveness analysis of Ponatinib versus other tyrosine kinase inhibitors in patients with chronic myeloid leukemia in the United States, Value in Health, 2019	A Markov state transition model was conducted to compare cost- effectiveness of second-line TKI for treatment of CML patients who failed or were intolerant to first-line TKI	Total lifetime medical costs after allo-SCT per CML patient was $2,226,616, $2,272,596, and $2,362,797 for nilotinib, dasatinib, bosutinib, respectively. Dasatinib resulted in an ICER of	Study indicates dasatinib is a cost-effective option for CML patients, and can provide improved clinical benefits compared to other second-line TKIs.

	using a US commercial payer perspective over a life-long time horizon.	$79,114.19/QALY compared to nilotinib. No safety or adverse events by treatment were reported.	
Ph+ALL213 Study (#UMIN000 012173), Sugiura et al., Blood, 2019	The Ph+ALL213 study was a single-arm, multicenter phase II study for ND Ph+ALL.	Hematological response after induction (IND) were 73 (93.6%) CR, 4 (5.1%) CRi, and 1 (1.3%) PD, and 40 (56%) patients achieved MCR after IC. The 3-year EFS and OS were 67.2% and 82.8% respectively. Of the patients who transplanted at CR1, the 3-year EFS and OS were 74.1% and 86.1% respectively. Grade 4 neutropenia/ thrombocytopenia in IND, IC, and C1-1 was reported in 51.3%/ 48.7%, 93.5%/ 5.2%, and 97.2%/ 70.8%, respectively, whereas grade 4 non-hematological AEs were noted in 2.6%, 9.1%, and 8.5%, respectively.	Study findings demonstrate dasatinib's value in reducing relapse before allo-HCT in ALL patients
Chang et al., Combination chemotherapy plus dasatinib leads to comparable overall survival and relapse-free survival rates as allogeneic hematopoieti c stem cell transplantation in Philadelphia positive acute lymphoblastic leukemia, Cancer Medicine, 2019	A retrospective study that analyzed the outcomes of adult patients with Ph+ ALL (n=70) treated with either combination chemotherapy plus dasatinib or combination chemotherapy plus dasatinib followed by allogeneic HSCT.	30 (42.9%) patients underwent allogeneic HSCT while 40 (57.1%) received only chemotherapy plus dasatinib. Overall survival rates, including 1-year, 2-year and 3-year rates, were similar between transplant and non-transplant groups. 1-year OS was 93.3% in transplants versus 100% in non-transplant group (p = 0.20); 2-year OS was 89.8% vs 86.2%, respectively (p = 0.72), and 3-year OS was 76% vs 71.3% (P = 0.56) in the transplant versus nontransplant groups, respectively. There were no significant differences in RFS rates between groups (70.5% vs	Patients receiving allogeneic HSCT had similar outcomes to those who received chemotherapy plus dasatinib alone. There may be minimal benefit of HSCT in patients receiving TKIs.

		80.1% in transplant vs non-transplant, respectively, p=0.94). No safety or adverse events by treatment were reported.	

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APPENDIX 2: Indications & Important Safety Information

SPRYCEL® (dasatinib) is indicated for the treatment of adult patients with: newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase; chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib; and philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

SPRYCEL® is indicated for the treatment of pediatric patients 1 year of age and older with: philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase and newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) in combination with chemotherapy.

WARNINGS AND PRECAUTIONS

Myelosuppression and Bleeding Events: Severe thrombocytopenia, neutropenia, and anemia may occur. Use caution if used concomitantly with medications that inhibit platelet function or anticoagulants. Monitor complete blood counts regularly. Transfuse and interrupt SPRYCEL when indicated.

Fluid Retention: Fluid retention, sometimes severe, including pleural effusions. Manage with supportive care measures and/or dose modification.

Cardiovascular Toxicity: Monitor patients for signs or symptoms and treat appropriately.

Pulmonary Arterial Hypertension (PAH): SPRYCEL (dasatinib) may increase the risk of developing PAH which may be reversible on discontinuation. Consider baseline risk and evaluate patients for signs and symptoms of PAH during treatment. Stop SPRYCEL if PAH is confirmed.

QT Prolongation: Use SPRYCEL with caution in patients who have or may develop prolongation of the QT interval.

Severe Dermatologic Reactions: Individual cases of severe mucocutaneous dermatologic reactions have been reported.

Tumor Lysis Syndrome: Tumor lysis syndrome has been reported. Maintain adequate hydration and correct uric acid levels prior to initiating therapy with SPRYCEL

Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of reproductive potential of potential risk to fetus and to use effective contraception.

Effects on Growth and Development in Pediatric Patients: epiphyses delayed fusion, osteopenia, growth retardation, and gynecomastia have been reported. Monitor bone growth and development in pediatric patients.

For further details regarding Safety Information including Adverse Reactions please refer to the SPRYCEL Full Prescribing Information

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APPENDIX 3: PICO Table

PICO Component	Criteria
Patients	• Newly diagnosed adults with Ph+ CML in chronic phase • Adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib • Pediatric patients 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy • Adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy
Intervention	SPRYCEL®
Comparison	Iclusig (ponatinib) Tasigna (nilotinib) Bosulif (bosutinib monohydrate) Gleevac (imatinib)

Outcomes	• Clinical:
	  ○ Effectiveness (e.g. response, survival, death, durability)
	  ○ Safety (adverse events)
	• Economic (HCRU)
	• PRO (HRQoL)

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APPENDIX 4: PRISMA Diagram