



# Maximum Fair Price (MFP) Explanation for Imbruvica

## Introduction

In August 2022, President Biden signed the Inflation Reduction Act of 2022 (IRA) (P.L. 117-169) into law. For the first time, the law provides Medicare with the ability to directly negotiate the prices of certain high expenditure, single source drugs without generic or biosimilar competition. On March 15, 2023, the Centers for Medicare & Medicaid Services (CMS) issued [initial guidance](#) for the Medicare Drug Price Negotiation Program (the “Negotiation Program”), including requests for public comment on key elements. On June 30, 2023, CMS issued [revised guidance](#) detailing the requirements and parameters of the Negotiation Program for the first cycle of negotiations.<sup>1</sup> CMS engaged in negotiations with participating manufacturers between October 1, 2023 and August 1, 2024. These negotiations resulted in agreements establishing prices (which the IRA refers to as “maximum fair prices” or “MFPs”) that will be effective beginning in 2026 (the first cycle of negotiations is referred to as negotiations for “initial price applicability year 2026” because any agreed-upon prices will be effective in 2026). CMS published the agreed-upon MFPs on August 15, 2024.

The MFP explanation for Imbruvica for the agreed-upon MFP that resulted from the negotiations for initial price applicability year 2026 with Pharmacyclics LLC, the manufacturer of Imbruvica (the “Primary Manufacturer”), provides information about the negotiations for Imbruvica. This information includes CMS’ perspective on the data considered that had the greatest impact in CMS’ determination of offers and consideration of counteroffers during the negotiation process through which the parties reached agreement on an MFP.<sup>2</sup> In some respects, the Primary Manufacturer had a different perspective on the relevant data. The parties to the negotiation had productive exchanges during the negotiation meetings described below in which they discussed their respective views, and these exchanges resulted in the exchange of offer(s) and counteroffer(s) among the parties and, ultimately, an agreed-upon MFP for Imbruvica.

On the basis of the factors described below and the related considerations and evidence, CMS negotiated with the Primary Manufacturer in good faith and consistent with the requirements of the law on behalf of people with Medicare and the Medicare program. Throughout the negotiation process and in accordance with the IRA, CMS’ goal was to achieve agreement with the Primary Manufacturer on the lowest possible MFP for Imbruvica that would be consistent with the process defined in the IRA for these price negotiations. CMS believes that the agreed-upon MFP achieves this aim. The negotiation

---

<sup>1</sup> The [Medicare Drug Price Negotiation Program: Revised Guidance, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026](#), is referred to throughout this document as the revised guidance.

<sup>2</sup> Section 1195(a)(2) of the Social Security Act (the “Act”) requires CMS to publish an explanation for the MFP with respect to the factors as applied under section 1194(e) for each selected drug. The MFP explanation is discussed in section 60.6.1 of the [revised guidance](#).

process ended in both parties agreeing to an MFP of \$9,319.00 for Imbruvica by the conclusion of the negotiation period on August 1, 2024.<sup>3</sup> The agreed-upon MFP is set to take effect on January 1, 2026.

The MFP explanation contains the following components:

- MFP Explanation Narrative for Imbruvica
  - Summary of the Negotiation Process
  - Indications for Imbruvica
  - Factors Applied
  - Manufacturer-Specific Data
  - Evidence about Imbruvica and Therapeutic Alternatives to Imbruvica
    - Therapeutic Alternatives
    - Outcomes and Additional Considerations
  - Citations to Data Reviewed during the Negotiation Process for Imbruvica
- Redacted Negotiation Meeting Summaries for Imbruvica
- Redacted Data Submitted by the Primary Manufacturer and Other Interested Parties for Imbruvica

## MFP Explanation Narrative for Imbruvica

### Summary of the Negotiation Process

CMS followed the negotiation process laid out in the IRA and in the revised guidance. On August 29, 2023, CMS announced the 10 selected drugs for the first cycle of negotiations, which included Imbruvica. The Primary Manufacturers of the selected drugs signed agreements to participate in the Negotiation Program by the deadline in the IRA of October 1, 2023 and submitted information on the selected drugs by the deadline in the IRA of October 2, 2023.

CMS collected relevant data from numerous sources, such as written submissions from the Primary Manufacturers and other interested parties in response to an information collection request issued for the Negotiation Program (referred to as the “Negotiation Program information collection request” throughout this document), feedback from patient-focused listening sessions, meetings between CMS and the Primary Manufacturers to discuss the information submitted, and CMS’ literature review.<sup>4</sup>

Using the information collected, CMS then developed initial offers for the selected drugs, which were based on the factors outlined in the IRA for CMS’ determination of offers and which CMS developed in accordance with the process described in the revised guidance.<sup>5</sup> As required by the IRA, CMS’ initial offers each included a concise justification on the range of evidence and other information within the negotiation factors that CMS found compelling during the development of the initial offer. The Primary

---

<sup>3</sup> The MFP is expressed as the price per 30-days equivalent supply. See section 60.1 of the [revised guidance](#) and the [Negotiated Prices for Initial Price Applicability Year 2026 Fact Sheet](#) for additional information.

<sup>4</sup> The Negotiation Program information collection request is available on the Office of Management and Budget’s (OMB’s) website at the following link: [https://www.reginfo.gov/public/do/PRAViewICR?ref\\_nbr=202306-0938-013](https://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=202306-0938-013).

<sup>5</sup> Section 1194(e) of the Act requires CMS to consider certain data as the basis for all offers and counteroffers in the negotiation. These data, which are referred to in this document as the “negotiation factors,” are discussed in more detail later in this document. More information on the negotiation factors is also available in sections 50, 60.3 and 60.4 of the [revised guidance](#). CMS’ process for developing the initial offers is described in section 60.3 of the revised guidance.

Manufacturers each responded by declining CMS' initial offer and providing a written counteroffer and justification for such offer, including considerations based on the negotiation factors.

CMS considered each counteroffer proposed by the Primary Manufacturers and declined each counteroffer. CMS and each Primary Manufacturer then held three negotiation meetings. These meetings included extensive discussion of the negotiation factors, including any new information consistent with the factors that may have become available about the selected drugs or therapeutic alternatives, CMS' initial offer and the Primary Manufacturer's written counteroffer, and, in some cases, additional proposals for an MFP.

Across the first cycle of negotiations for all ten selected drugs, more than 50 revised offers or counteroffers were proposed by CMS or a Primary Manufacturer, not including the ten initial offers CMS made and the ten written counteroffers provided by Primary Manufacturers. During the negotiation meetings, CMS revised its initial offer for each selected drug upwards at least once in response to the discussions with the Primary Manufacturer. While many of the details of the negotiations are confidential between CMS and each Primary Manufacturer, the frequency of revised offers and counteroffers in the first cycle of negotiations indicates the robustness of the negotiations that occurred for each of the ten drugs. CMS' approach to its negotiations with each Primary Manufacturer turned on the particular details relevant to each selected drug and was sensitive to the issues raised during the course of CMS' conversations with the Primary Manufacturer. CMS anticipates this drug-specific approach will continue to inform CMS' negotiations with participating manufacturers in future cycles of negotiation.

Overall, in six of ten negotiations CMS moved more than the Primary Manufacturer during the meetings and for the final offer (if applicable) prior to reaching agreement, and in four of ten negotiations the Primary Manufacturer moved more than CMS prior to reaching agreement. For five of the selected drugs, this process of exchanging revised offers and counteroffers resulted in CMS and the Primary Manufacturer reaching an agreement on a negotiated price for the selected drug in association with a negotiation meeting. In four of these cases, CMS accepted a revised counteroffer proposed by the Primary Manufacturer. For the remaining five selected drugs, CMS sent a written final offer to the Primary Manufacturer, consistent with the process described in the revised guidance, and in each instance, the Primary Manufacturer accepted CMS' offer on or before the statutory deadline. Throughout the negotiation process, CMS and the Primary Manufacturers exchanged perspectives about a range of topics related to the negotiation factors, and while the parties did not always agree, CMS appreciated the Primary Manufacturers' engagement.

A detailed timeline of the negotiation process for Imbruvica is below.

- August 29, 2023: CMS announced the 10 selected drugs for initial price applicability year 2026
- October 1, 2023: Deadline for the Primary Manufacturer to sign an agreement to participate in the Negotiation Program
- October 2, 2023: Deadline for the Primary Manufacturer and the public to submit information related to Imbruvica in response to the Negotiation Program information collection request
- October 27, 2023: CMS met with the Primary Manufacturer regarding its response to the Negotiation Program information collection request
- November 6, 2023: CMS held a patient-focused listening session for Imbruvica
- February 1, 2024: CMS provided the Primary Manufacturer with CMS' initial offer
- March 1, 2024: The Primary Manufacturer rejected CMS' initial offer and provided CMS with a counteroffer

- March 29, 2024: CMS rejected the Primary Manufacturer’s counteroffer and invited the Primary Manufacturer to a negotiation meeting
- April 26, 2024: CMS and the Primary Manufacturer met for the first negotiation meeting
- May 31, 2024: CMS and the Primary Manufacturer met for the second negotiation meeting
- June 27, 2024: CMS and the Primary Manufacturer met for the third negotiation meeting
- August 1, 2024: The negotiation period ended
- August 15, 2024: MFP of \$9,319.00 was published

## Indications for Imbruvica

Imbruvica belongs to a class of medications called kinase inhibitors which help stop the spread of cancer cells. It is used alone or with other drugs to treat adults with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or Waldenström’s macroglobulinemia (WM), which are types of blood cancer. It is also used to treat adults and children aged 1 year and older with chronic graft versus host disease after being treated unsuccessfully with one or more therapies.<sup>6</sup>

For Imbruvica, CMS included the following indications in its assessment<sup>7</sup>:

Description of indication	Terminology used in this document
<ul style="list-style-type: none"> <li>• Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)</li> <li>• Adult patients with CLL/SLL with 17p deletion</li> </ul>	CLL/SLL
<ul style="list-style-type: none"> <li>• Adult patients with Waldenström’s macroglobulinemia</li> </ul>	WM
<ul style="list-style-type: none"> <li>• Adult and pediatric patients aged 1 year and older with chronic graft versus host disease after failure of one or more lines of systemic therapy</li> </ul>	cGVHD

*Table 1.* cGVHD = chronic graft versus host disease; WM = Waldenström’s macroglobulinemia. 17p deletion is a genetic mutation that may be observed in some patients with CLL/SLL. For purposes of CMS’ consideration of indications for Imbruvica, CMS grouped certain indications using the terminology as shown in this table. CMS’ use of the terms listed here does not alter the FDA-approved indications for Imbruvica.

<sup>6</sup> To compose this brief description, CMS used various sources, including MedlinePlus, a free online health information resource for patients and the general public. MedlinePlus is a service of the National Library of Medicine (NLM), a part of the U.S. National Institutes of Health (NIH). For more information about any drugs or conditions mentioned in this document, MedlinePlus can be accessed at: <https://medlineplus.gov/>.

<sup>7</sup> CMS’ process for identifying indications for a selected drug was to identify the FDA-approved indication(s) not otherwise excluded from coverage or otherwise restricted under section 1860D-2(e)(2) of the Act, using prescribing information approved by the FDA for the selected drug, in accordance with section 1194(e)(2)(B) of the Act. CMS considered off-label use when identifying indications if such use was included in nationally recognized, evidence-based guidelines and recognized in CMS-approved Part D compendia. CMS included indications that met these criteria during the negotiation period. Indications newly approved by FDA or included in nationally recognized, evidence-based guidelines and recognized in CMS-approved Part D compendia after the end of the negotiation period were not included.

## Factors Applied

Consistent with the IRA, CMS considered certain negotiation factors as the basis for determining all offers and counteroffers during the negotiation process.

The following negotiation factors are referred to in this document as “manufacturer-specific data”<sup>8</sup>:

- Research and development (R&D) costs of the Primary Manufacturer for Imbruvica and the extent to which the Primary Manufacturer has recouped R&D costs;
- Current unit costs of production and distribution of Imbruvica;
- Prior Federal financial support for novel therapeutic discovery and development with respect to Imbruvica;
- Data on pending and approved patent applications, exclusivities recognized by the FDA, and applications and approvals for New Drug Applications and Biologics License Applications for Imbruvica;<sup>9</sup> and
- Market data and revenue and sales volume data for Imbruvica in the United States (U.S.).

The following negotiation factors are referred to in this document as “evidence about Imbruvica and therapeutic alternatives to Imbruvica”<sup>10</sup>:

- The extent to which Imbruvica represents a therapeutic advance as compared to existing therapeutic alternatives and the costs of such existing therapeutic alternatives;
- Prescribing information approved by the FDA for Imbruvica and therapeutic alternatives to Imbruvica;
- Comparative effectiveness of Imbruvica and therapeutic alternatives to Imbruvica, taking into consideration the effects of Imbruvica and therapeutic alternatives to Imbruvica on specific populations, such as individuals with disabilities, the elderly, the terminally ill, children, and other patient populations; and
- The extent to which Imbruvica and therapeutic alternatives to Imbruvica address unmet medical needs for a condition for which treatment or diagnosis is not addressed adequately by available therapy.

The below sections describe how CMS considered and applied these factors during the negotiation process. CMS considered these factors, taking into account all data in totality during the negotiation process.

CMS and the Primary Manufacturer did not always agree on the information presented below, and the Primary Manufacturer was not restricted to consideration of these factors during the negotiation process but was free to discuss any topics with CMS it deemed relevant to its consideration of offer(s) and counteroffer(s) for Imbruvica.

---

<sup>8</sup> These factors are listed at section 1194(e)(1) of the Act.

<sup>9</sup> New Drug Applications are approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act and Biologics License Applications are approved under section 351(a) of the Public Health Service Act.

<sup>10</sup> These factors are listed at section 1194(e)(2) of the Act. In accordance with section 1194(e)(2) and section 1182(e) of Title XI of the Act, CMS did not use evidence from comparative clinical effectiveness research in a manner that treats extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, non-disabled, or not terminally ill, and, consistent with section 1182(e) of Title XI of the Act, did not use quality adjusted life years (QALYs).

## Manufacturer-Specific Data

CMS considered the information submitted by the Primary Manufacturer related to the manufacturer-specific data factors. These factors include R&D costs and the extent to which the Primary Manufacturer has recouped R&D costs, current unit costs of production and distribution, prior Federal financial support, data on pending and approved patents and exclusivities recognized by the FDA, and market data, including revenue and sales volume data for the drug in the United States. CMS considered these factors in totality, as part of its application of the negotiation factors during the negotiation process.

The Primary Manufacturer provided CMS with information for each of these factors in response to the Negotiation Program information collection request.<sup>11</sup> For R&D costs, CMS requested information separated into various categories of costs related to R&D, including acquisition costs, pre-clinical research costs, post-Investigational New Drug costs, costs of failed or abandoned products related to Imbruvica, and other allowable direct costs. CMS also requested the global and U.S. total lifetime net revenue for Imbruvica to provide insight into the extent to which the Primary Manufacturer has recouped R&D costs. CMS requested current average unit costs of production for Imbruvica and current average unit costs of distribution for Imbruvica separately, as well as a description of the methodology the Primary Manufacturer used to estimate such costs. For information related to prior Federal financial support, CMS requested the total amount of Federal financial support received, as well as a breakdown by various types of financial support, like tax credits and National Institutes of Health funding. CMS requested information on patents, both expired and unexpired, issued by the U.S. Patent and Trademark Office, patent applications, regulatory exclusivity periods, and active and pending FDA applications and approvals. For market data, CMS requested information about the prices for Imbruvica and volume dispensed for other payers in the U.S. market, including commercial payers (e.g., the U.S. commercial average net price), Medicaid (Medicaid Best Price), and other Federal payers (the Federal supply schedule price and the Big Four price).

Throughout the negotiation process, CMS holistically considered the information submitted by the Primary Manufacturer related to the manufacturer-specific data negotiation factors for the purpose of negotiating an MFP for Imbruvica. For example, CMS applied information on prices for Imbruvica available to other payers in the U.S. market and how they compared to any offers or counteroffers when considering whether a potential price was consistent with CMS' aim to arrive at an agreement on the lowest possible MFP. The totality of CMS' application of these factors, in conjunction with application of the factors described below, informed CMS' negotiation of the MFP with the Primary Manufacturer.

## Evidence about Imbruvica and Therapeutic Alternatives to Imbruvica

CMS considered information related to the negotiation factors regarding evidence about Imbruvica and therapeutic alternatives to Imbruvica. CMS' holistic consideration of clinical benefit included evidence from sources such as: pivotal clinical trials, pre-specified subgroup analyses, clinical practice guidelines, expert consensus statements, comparative clinical evidence, published literature reviews, real-world evidence, and FDA prescription drug labeling, among others. CMS evaluated the evidence based on a variety of considerations, including relevance and credibility, giving priority to well-designed and well-

---

<sup>11</sup> In accordance with the revised guidance, CMS treats R&D costs and the extent to which they are recouped, unit costs of production and distribution, pending patent applications, and market, revenue, and sales volume data as proprietary, unless the information that is provided to CMS is already publicly available. For more information, see section 40.2.1 of the [revised guidance](#).

conducted studies, as stated in the revised guidance.<sup>12</sup> In general, CMS prioritized direct comparative evidence (e.g., head-to-head randomized controlled trials) when available. CMS also reviewed mixed and/or indirect treatment comparisons (e.g., network meta-analyses) when available and real-world evidence (e.g., observational studies) when available as part of its holistic assessment of comparative evidence.

In addition to information from the Primary Manufacturer, CMS received information from the public, including from patients during the patient-focused listening session held by CMS on November 6, 2023.<sup>13</sup> Patient input was important to CMS' consideration of the evidence about Imbruvica and therapeutic alternatives to Imbruvica, including to help identify outcomes of interest for patients and to understand additional considerations such as patients' preferences regarding treatment. For example, speakers at the patient-focused listening session shared their appreciation of having access to a diverse array of treatment options, including options with oral routes of administration. This was one consideration among the many that informed CMS' understanding of the factors regarding evidence about Imbruvica and its therapeutic alternatives. Throughout all of the patient-focused listening sessions for the first cycle of negotiations, speakers provided insight on the importance of affordability and access, which provided CMS helpful context for the speakers' described experiences.

## Therapeutic Alternatives

The IRA directs CMS to compare Imbruvica to therapeutic alternatives in its determination of offers and consideration of counteroffers for Imbruvica.<sup>14</sup> In the revised guidance, CMS defines a therapeutic alternative for the first cycle of negotiations as a pharmaceutical product that is clinically comparable to the selected drug.<sup>15</sup>

Importantly, use of the term “therapeutic alternative” in this MFP explanation is limited to the purposes and definition outlined in the IRA and the revised guidance. Use of this term does not suggest that CMS believes such drugs are interchangeable or otherwise universally appropriate to prescribe for an individual in place of Imbruvica or that these are the only pharmaceutical treatments that might be used by a person with one of the indications treated by Imbruvica. CMS trusts that patients and health care providers will continue to choose the therapy that best suits a given patient's needs based on the patient's health, history, experience, and preferences, the provider's expertise, FDA-approved prescribing information, and relevant clinical guidelines, as applicable.

During the negotiation process, CMS identified therapeutic alternatives to Imbruvica based on a holistic consideration of the available evidence from a range of sources. In addition to the sources listed above,

---

<sup>12</sup> In section 50.2 of the [revised guidance](#), CMS stated, “When reviewing the literature from the public and manufacturer submissions as well as literature from CMS' review, CMS will consider the source, rigor of the study methodology, current relevance to the selected drug and its therapeutic alternative(s), whether the study has been through peer review, study limitations, degree of certainty of conclusions, risk of bias, study time horizons, generalizability, study population, and relevance to the negotiation factors listed in section 1194(e)(2) of the Act to ensure the integrity of the contributing data within the negotiation process. CMS will prioritize research, including both observational research and research based on randomized samples, that is methodologically rigorous, appropriately powered (i.e., has sufficient sample size) to answer the primary question of the research, and structured to avoid potential false positive findings due to multiple subgroup analyses.”

<sup>13</sup> The redacted transcript for this patient-focused listening session is available at the following link: <https://www.cms.gov/files/document/imbruvica-transcript-110623.pdf>.

<sup>14</sup> See section 1194(e)(2) of the Act and sections 50, 60.3 and 60.4 of the [revised guidance](#) for additional information.

<sup>15</sup> This definition appears in Appendix C of the [revised guidance](#).

such as data submitted by the Primary Manufacturer and the public and widely accepted clinical guidelines, other examples of data sources used include the following: drug classification systems commonly used in the public and commercial sector for formulary development, indications included in CMS-approved Part D compendia, and drug or drug class reviews.

The following table lists the therapeutic alternatives, among all clinically comparable alternatives that CMS reviewed, which were particularly relevant to CMS’ consideration, due to guideline recommendations, utilization in the Medicare population, and other considerations.

Indication	Therapeutic Alternatives
CLL/SLL	<ul style="list-style-type: none"> <li>• Acalabrutinib</li> <li>• Zanubrutinib</li> <li>• Combination regimen of venetoclax with obinutuzumab</li> <li>• Combination regimen of venetoclax with rituximab</li> </ul>
WM	<ul style="list-style-type: none"> <li>• Zanubrutinib</li> <li>• Combination regimen of bendamustine with rituximab (BR)</li> <li>• Combination regimen of dexamethasone, rituximab, and cyclophosphamide (DRC)</li> </ul>
cGVHD	<ul style="list-style-type: none"> <li>• Belumosudil</li> <li>• Ruxolitinib</li> </ul>

*Table 2.* cGVHD = chronic graft versus host disease; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; WM = Waldenström’s macroglobulinemia. Use of the term “therapeutic alternative” in this MFP explanation is limited to the purposes and definition outlined in the IRA and the revised guidance. Use of this term does not suggest that CMS believes such drugs are interchangeable or otherwise universally appropriate to prescribe for an individual in place of Imbruvica or that these are the only pharmaceutical treatments that might be used by a person with one of the indications treated by Imbruvica. CMS trusts that patients and health care providers will continue to choose the therapy that best suits a given patient’s needs based on the patient’s health, history, experience, and preferences, the provider’s expertise, FDA-approved prescribing information, and relevant clinical guidelines, as applicable.

CMS considered utilization for Imbruvica and its therapeutic alternatives by indication as one part of its application of the negotiation factors.

## Outcomes and Additional Considerations

Outcomes are measurable effects or impacts of a treatment or intervention. Outcomes can be used to measure differences in the safety or effectiveness of different treatments. Patient-centered outcomes are outcomes identified by patients that are important to how they feel, function, or survive. To consider comparative effectiveness between Imbruvica and therapeutic alternatives to Imbruvica, CMS identified clinically relevant and patient-centered outcomes of interest from the body of available literature to evaluate for each indication of Imbruvica. CMS then identified evidence comparing Imbruvica to therapeutic alternatives based on these outcomes. The following table includes a non-exhaustive list of outcomes that were of interest to CMS in its consideration of Imbruvica:

Indication	Effectiveness Outcomes	Safety Outcomes
CLL/SLL	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Progression-free survival</li> <li>• Overall response rate</li> </ul>	<ul style="list-style-type: none"> <li>• Cardiovascular events (e.g., atrial fibrillation, hypertension)</li> <li>• Hemorrhage</li> <li>• Infection</li> <li>• Neutropenia</li> <li>• All grade 3-4 adverse events</li> </ul>
WM	<ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Progression-free survival</li> <li>• Treatment response rate</li> </ul>	<ul style="list-style-type: none"> <li>• Cardiovascular events (e.g., atrial fibrillation, hypertension)</li> <li>• Hemorrhage</li> <li>• Infection</li> <li>• Neutropenia</li> <li>• All grade 3-4 adverse events</li> </ul>
cGVHD	<ul style="list-style-type: none"> <li>• Overall response rate</li> </ul>	<ul style="list-style-type: none"> <li>• Serious adverse events</li> <li>• Tolerability (e.g., discontinuation due to adverse events)</li> </ul>

*Table 3.* cGVHD = chronic graft versus host disease; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; WM = Waldenström’s macroglobulinemia. Outcomes identified in this table were of interest to CMS in its evaluation of Imbruvica. Evidence to support an assessment may not have been available for every outcome of interest

Outcomes, like those listed above, were identified as being of interest to CMS based on their importance to patients and their ability to measure how effective and safe a drug is when used to treat these indications. For example, overall survival and progression-free survival are key outcomes that are often used to evaluate effectiveness of treatments for patients with CLL/SLL or WM. In addition, the risk of adverse events, including atrial fibrillation and hypertension, reflects an important safety consideration when evaluating drugs for these indications.

Additionally, CMS considered the extent to which Imbruvica represents a therapeutic advance as compared to existing therapeutic alternatives, and the extent to which Imbruvica and its therapeutic alternatives address an unmet medical need. CMS also evaluated access, equity, and health outcomes for specific populations (including individuals with disabilities, the elderly, individuals who are terminally ill, children, and other patient populations).

For the purpose of negotiating the MFP for Imbruvica, CMS holistically considered the negotiation factors regarding evidence about Imbruvica and its therapeutic alternatives, including consideration of the clinical benefit of Imbruvica in the context of its therapeutic alternatives. For example, CMS applied its understanding of the comparative effectiveness of Imbruvica and its therapeutic alternatives for each of the identified indications, including, for example, consideration of each therapy’s use in treatment-naïve and previously treated patients with CLL/SLL or WM, when negotiating with the Primary Manufacturer. CMS’ holistic assessment was informed by additional contextual considerations, such as patient subgroups (e.g., children), treatment complexity (e.g., route of administration), FDA safety labeling, and patient preferences.

Throughout the negotiation process, including the development of the initial offer and in the consideration of any offers and counteroffers, CMS applied these and other factors regarding evidence about Imbruvica and therapeutic alternatives. The totality of CMS' application of these factors, in conjunction with application of the manufacturer-submitted data negotiation factors described above, informed CMS' negotiation of the MFP with the Primary Manufacturer.

## Citations to Data Reviewed during the Negotiation Process for Imbruvica

CMS provides below a list of citations representative of evidence that CMS reviewed during the negotiation process, including citations provided by the Primary Manufacturer and the public in response to the Negotiation Program information collection request, those included in CMS' initial offer concise justification, and other citations which were considered during the evaluation of the Primary Manufacturer's counteroffer and during negotiation meetings.

Consistent with the IRA and section 1182(e) of Title XI of the Act, CMS did not use evidence from comparative clinical effectiveness research in a manner that treats extending the life of an individual who is elderly, disabled, or terminally ill as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill, and, consistent with section 1182(e) of Title XI of the Act, did not use quality adjusted life years (QALYs). Inclusion on this list of a citation that contains such evidence does not mean that CMS used such evidence in the course of the negotiation.

This list is intended to provide insight into the range of evidence that various parties, including CMS and the Primary Manufacturer, identified as being relevant to the negotiation. This list does not represent the totality of evidence that CMS reviewed and considered as part of its holistic consideration of the negotiation factors in the determination of any offers and consideration of any counteroffers.

1. AbbVie Reports Third-Quarter 2023 Financial Results [Internet]. AbbVie Inc.; 2023 Oct 27. [cited 2024 Mar 1] Available from: <https://investors.abbvie.com/newsreleases/news-release-details/abbvie-reports-third-quarter-2023-financial-results>.
2. AbbVie Seeks New Indication for IMBRUVICA® (ibrutinib) in Pediatric Patients with Chronic Graft Versus Host Disease (cGVHD)[Internet]. Illinois: AbbVie. 2022 Feb 28 [cited 2023 Sep 21]. Available from: <https://news.abbvie.com/2022-02-28-AbbVie-Seeks-New-Indication-for-IMBRUVICA-R-ibrutinib-in-Pediatric-Patients-with-Chronic-Graft-Versus-Host-Disease-cGVHD>.
3. Adkins C, Takakura W, Spiegel BMR, Lu M, Vera-Llonch M, Williams J, Almario CV. Prevalence and Characteristics of Dysphagia Based on a Population-Based Survey. *Clinical Gastroenterology and Hepatology*. 2020;18(9):1970-9.e2. doi: 10.1016/j.cgh.2019.10.029.
4. Allan JN, Shanafelt T, Wiestner A, Moreno C, O'Brien SM, Li J, et al. Long-term efficacy of first-line ibrutinib treatment for chronic lymphocytic leukaemia in patients with TP53 aberrations: a pooled analysis from four clinical trials. *British Journal of Haematology*. 2022;196(4):947-53.
5. Alrawashdh N, Persky DO, McBride A, Sweasy J, Erstad B, Abraham I. Comparative Efficacy of First-Line Treatments of Chronic Lymphocytic Leukemia: Network Meta-Analyses of Survival Curves. *Clinical Lymphoma Myeloma and Leukemia*. 2021;21(11):e820-e31. doi: 10.1016/j.clml.2021.06.010.
6. Al-Sawaf O, Zhang C, Robrecht S, Tandon M, Panchal A, Fink AM, et al. Venetoclax-Obinutuzumab For Previously Untreated Chronic Lymphocytic Leukemia: 4-Year Follow-Up Analysis Of The Randomized CLL14 Study. *Hematological Oncology*. 2021;39(S2). doi: 10.1002/hon.49\_2880.
7. Areas of Study [Internet]. Pharmacyclics LLC; 2024 [cited 2023 Sep 20]. Available from: <https://www.pharmacyclics.com/home/areas-of-study.html>.
8. Aslam M, Vaezi MF. Dysphagia in the elderly. *Gastroenterol Hepatol (N Y)*. 2013;9(12):784-95. PubMed PMID: 24772045; PubMed Central PMCID: PMC3999993.

9. AstraZeneca. Calquence (acalabrutinib) [package insert]. U.S. Food and Drug Administration. Revised 2024 Jun. Available from:  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/210259s010lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/210259s010lbl.pdf).
10. AstraZeneca. Calquence (acalabrutinib) [package insert]. U.S. Food and Drug Administration. Revised 2022 Mar. Available from:  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2022/210259s009lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/210259s009lbl.pdf).
11. Baird K, Cooke K, Schultz KR. Chronic graft-versus-host disease (GVHD) in children. *Pediatr Clin North Am.* 2010;57(1):297-322. doi: 10.1016/j.pcl.2009.11.003. PubMed PMID: 20307722; PubMed Central PMCID: PMC2872081.
12. Ball G, Levine MAH, Thabane L, Tarride JE. Health Technology Reassessment: Addressing Uncertainty in Economic Evaluations of Oncology Drugs at Time of Reimbursement Using Long-Term Clinical Trial Data. *Curr Oncol.* 2023;30(7):6596-608. Epub 20230710. doi: 10.3390/curroncol30070484. PubMed PMID: 37504344; PubMed Central PMCID: PMC10378704.
13. Barbier M, Durno N, Bennison C, Örtli M, Knapp C, Schwenkglens M. Cost-effectiveness and budget impact of venetoclax in combination with rituximab in relapsed/refractory chronic lymphocytic leukemia in Switzerland. *The European Journal of Health Economics.* 2022;23(5):837-46. doi: 10.1007/s10198-021-01398-7.
14. Barr PM, Owen C, Robak T, Tedeschi A, Bairey O, Burger JA, et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv.* 2022;6(11):3440-50. doi: 10.1182/bloodadvances.2021006434. PubMed PMID: 35377947; PubMed Central PMCID: PMC9198904.
15. Barrientos JC. Management of Chronic Lymphocytic Leukemia in the Elderly. *Cancer Control.* 2015;22(4 Suppl):17-23. doi: 10.1177/107327481502204s04. PubMed PMID: 26618342; PubMed Central PMCID: PMC4763599.
16. BeiGene. Brukinsa (zanubrutinib) [package insert]. U.S. Food and Drug Administration. Revised 2023 Apr. Available from:  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2023/213217s010lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213217s010lbl.pdf).
17. BeiGene. Brukinsa (zanubrutinib) [package insert]. U.S. Food and Drug Administration. Revised 2024 Mar. Available from:  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/213217s011lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213217s011lbl.pdf).
18. Blazar BR, Murphy WJ, Abedi M. Advances in graft-versus-host disease biology and therapy. *Nat Rev Immunol.* 2012;12(6):443-58. Epub 20120511. doi: 10.1038/nri3212. PubMed PMID: 22576252; PubMed Central PMCID: PMC3552454.
19. Brem EA, O'Brien S. Is a BTKi or BCL2i preferable for first “novel” therapy in CLL? The case for BTKis. *Blood Advances.* 2022;6(4):1361-4. doi: 10.1182/bloodadvances.2019001204.
20. Brennan Z. IRA impact: AstraZeneca and Merck CEOs warn of oncology drug development shifts [Internet]. *Endpoints News*; 2022 Nov 11 [cited 2023 Oct 2]. Available from:  
<https://endpts.com/ira-impact-astrazeneca-and-merck-ceos-warn-of-oncology-drug-development-shifts/>.
21. Brennan Z. Q&A with Genentech CEO Alexander Hardy on Medicare's drug price negotiations [Internet]. *ENDPOINT News*; 2023 Jun 20 [cited 2023 Oct 2]. Available from:  
<https://endpts.com/qa-with-genentech-ceo-alexander-hardy-on-medicares-drug-price-negotiations/>.
22. Brown JR, Eichhorst B, Hillmen P, Jurczak W, Kaźmierczak M, Lamanna N, et al. Zanubrutinib or Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia. *N Engl J Med.* 2023;388(4):319-32. Epub 20221213. doi: 10.1056/NEJMoa2211582. PubMed PMID: 36511784.

23. Brown JR, Moslehi J, O'Brien S, Ghia P, Hillmen P, Cymbalista F, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. *Haematologica*. 2017;102(10):1796-805. Epub 20170727. doi: 10.3324/haematol.2017.171041. PubMed PMID: 28751558; PubMed Central PMCID: PMC5622864.
24. Brullo C, Villa C, Tasso B, Russo E, Spallarossa A. Btk Inhibitors: A Medicinal Chemistry and Drug Delivery Perspective. *Int J Mol Sci*. 2021;22(14). Epub 20210716. doi: 10.3390/ijms22147641. PubMed PMID: 34299259; PubMed Central PMCID: PMC8303217.
25. Bryan J, Borthakur G. Role of rituximab in first-line treatment of chronic lymphocytic leukemia. *Therapeutics and Clinical Risk Management*. 2010;7(null):1-11. doi: 10.2147/TCRM.S5855.
26. Burger JA, Tedeschi A, Barr PM, Robak T, Owen C, Ghia P, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. *New England Journal of Medicine*. 2015;373(25):2425-37. doi: doi:10.1056/NEJMoa1509388.
27. Buske C, Tedeschi A, Trotman J, García-Sanz R, MacDonald D, Leblond V, et al. Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study. *J Clin Oncol*. 2022;40(1):52-62. Epub 20211004. doi: 10.1200/jco.21.00838. PubMed PMID: 34606378; PubMed Central PMCID: PMC8683240.
28. Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, et al. Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia. *New England Journal of Medicine*. 2014;371(3):213-23. doi: doi:10.1056/NEJMoa1400376.
29. Byrd JC, Hillmen P, Ghia P, Kater AP, Chanan-Khan A, Furman RR, et al. Acabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. *J Clin Oncol*. 2021;39(31):3441-52. Epub 20210726. doi: 10.1200/jco.21.01210. PubMed PMID: 34310172; PubMed Central PMCID: PMC8547923.
30. Byrd JC, Hillmen P, O'Brien S, Barrientos JC, Reddy NM, Coutre S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. *Blood*. 2019;133(19):2031-42. doi: 10.1182/blood-2018-08-870238.
31. Byrd JC, Hillmen P, O'Brien S, Barrientos JC, Reddy NM, Coutre S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. *Blood*. 2019;133(19):2031-42. Epub 20190306. doi: 10.1182/blood-2018-08-870238. PubMed PMID: 30842083; PubMed Central PMCID: PMC6509542.
32. Cancer Facts & Figures 2023. American Cancer Society; 2023. Available from: <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf>.
33. Carpenter PA, Kang HJ, Yoo KH, Zecca M, Cho B, Lucchini G, et al. Ibrutinib Treatment of Pediatric Chronic Graft-versus-Host Disease: Primary Results from the Phase 1/2 iMAGINE Study. *Transplantation and Cellular Therapy*. 2022;28(11):771.e1-.e10. doi: 10.1016/j.jtct.2022.08.021.
34. Center for Drug Evaluation and Research. CDER Breakthrough Therapy Designation Approvals. U.S. Food and Drug Administration; 2023 Dec 31. Available from: <https://www.fda.gov/media/95302/download>.
35. Center for Drug Evaluation and Research. New Drug Therapy Approvals 2022. U.S. Food and Drug Administration; 2023 Jan 10. Available from: <https://www.fda.gov/drugs/novel-drug-approvals-fda/new-drug-therapy-approvals-2022>.
36. Center for Drug Evaluation and Research. Novel New Drugs 2013 Summary. U.S. Food and Drug Administration; 2024 Jan. Available from: <http://wayback.archive->

[it.org/7993/20161022200106/http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM381803.pdf](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM381803.pdf).

37. Chan WL, Chong VCL, Wee IJY, Poon LM, Chan EHL, Lee J, et al. Efficacy and safety of front-line treatment regimens for Waldenstrom macroglobulinaemia: a systematic review and meta-analysis. *Blood Cancer J.* 2023;13(1):140. Epub 20230907. doi: 10.1038/s41408-023-00916-5. PubMed PMID: 37679351; PubMed Central PMCID: PMC10485051.
38. Chanan-Khan A, Liu T, Yang K, Cohen A, Fahrbach K, Campbell J, Tang B. Network meta-analysis of progression free survival in the treatment of relapsed or refractory chronic lymphocytic leukemia. *Journal of Clinical Oncology.* 2022;40(16\_suppl):e19514-e. doi: 10.1200/JCO.2022.40.16\_suppl.e19514.
39. Chanan-Khan A, Yang K, Liu T, Cohen A, Fahrbach K, Wang Y, Tang B. Efficacy of first-line treatment for chronic lymphocytic leukemia: A Bayesian network meta-analysis. *Journal of Clinical Oncology.* 2022;40(16\_suppl):e19526-e. doi: 10.1200/JCO.2022.40.16\_suppl.e19526.
40. Chatterjee A, Shapouri S, Manzoor BS, Ravelo A, Sail K, Qendri V, et al. Cost-effectiveness of a 12-month fixed-duration venetoclax treatment in combination with obinutuzumab in first-line, unfit chronic lymphocytic leukemia in the United States. *Journal of Managed Care & Specialty Pharmacy.* 2021;27(11):1532-44. doi: 10.18553/jmcp.2021.27.11.1532. PubMed PMID: 34714110.
41. Chaudhary MA, Lubinga SJ, Smare C, Hertel N, Penrod JR. Cost-effectiveness of nivolumab in patients with NSCLC in the United States. *Am J Manag Care.* 2021;27(8):e254-e60. Epub 20210801. doi: 10.37765/ajmc.2021.88726. PubMed PMID: 34460179.
42. Chen ST, Azali L, Rosen L, Zhao Q, Wiczer T, Palettas M, et al. Hypertension and incident cardiovascular events after next-generation BTKi therapy initiation. *Journal of Hematology & Oncology.* 2022;15(1):92. doi: 10.1186/s13045-022-01302-7.
43. Comparison of Time to Next Treatment Between Patients With Chronic Lymphocytic Leukemia Initiating First-Line Ibrutinib or Acalabrutinib, Overall and in a Subgroup With High-Risk Characteristics [Internet]. Johnson & Johnson; 2022 Dec 12 [cited 2023 Oct 2]. Available from: [https://www.jnj.com/media-center/press-releases/real-world-study-shows-patients-treated-with-imbruvica-ibrutinib-were-less-likely-to-initiate-a-next-line-treatment-than-patients-on-acalabrutinib-in-first-line-chronic-lymphocytic-leukemia#\\_edn1](https://www.jnj.com/media-center/press-releases/real-world-study-shows-patients-treated-with-imbruvica-ibrutinib-were-less-likely-to-initiate-a-next-line-treatment-than-patients-on-acalabrutinib-in-first-line-chronic-lymphocytic-leukemia#_edn1).
44. Coutre SE, Byrd JC, Hillmen P, Barrientos JC, Barr PM, Devereux S, et al. Long-term safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia in 3 pivotal studies. *Blood Advances.* 2019;3(12):1799-807. doi: 10.1182/bloodadvances.2018028761.
45. Crawford S, Li H, Srivastava B, Martin P, Gahn J, Rogers KA. EE91 Clinical Consequences and Associated Costs of Treating Patients With Chronic Lymphocytic Leukemia (CLL) With Bruton Tyrosine Kinase Inhibitors (BTKis) in the First-Line (1L) and Relapsed/Refractory (R/R) Settings. *Value in Health.* 2024;27(6):S74. doi: 10.1016/j.jval.2024.03.391.
46. Davids MS, Telford C, Abhyankar S, Waweru C, Ringshausen I. Matching-adjusted indirect comparisons of safety and efficacy of acalabrutinib versus other targeted therapies in patients with treatment-naïve chronic lymphocytic leukemia. *Leukemia & Lymphoma.* 2021;62(10):2342-51. doi: 10.1080/10428194.2021.1913144.
47. de Claro RA, McGinn KM, Verdun N, Lee S-L, Chiu H-J, Saber H, et al. FDA Approval: Ibrutinib for Patients with Previously Treated Mantle Cell Lymphoma and Previously Treated Chronic Lymphocytic Leukemia. *Clinical Cancer Research.* 2015;21(16):3586-90. doi: 10.1158/1078-0432.CCR-14-2225.
48. Deering KL, Sundaram M, Harshaw Q, Trudeau J, Barrientos JC. Health-related quality of life and treatment satisfaction in Chronic Lymphocytic Leukemia (CLL) patients on ibrutinib compared to other CLL treatments in a real-world US cross sectional study. *Plos one.*

- 2022;17(10):e0270291. doi: 10.1371/journal.pone.0270291. PMID: 36201482; PMCID: PMC9536620.
49. Development and Update of Guidelines [Internet]. Pennsylvania: National Comprehensive Cancer Network. Available from: <https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines>.
  50. Dickerson T, Wiczer T, Waller A, Philippon J, Porter K, Haddad D, et al. Hypertension and incident cardiovascular events following ibrutinib initiation. *Blood*. 2019;134(22):1919-28. doi: 10.1182/blood.2019000840.
  51. Dimopoulos MA, Opat S, D'Sa S, Jurczak W, Lee HP, Cull G, et al. Zanubrutinib Versus Ibrutinib in Symptomatic Waldenström Macroglobulinemia: Final Analysis From the Randomized Phase III ASPEN Study. *J Clin Oncol*. 2023;41(33):5099-106. Epub 20230721. doi: 10.1200/jco.22.02830. PubMed PMID: 37478390; PubMed Central PMCID: PMC10666987.
  52. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Overall Survival With Daratumumab, Lenalidomide, and Dexamethasone in Previously Treated Multiple Myeloma (POLLUX): A Randomized, Open-Label, Phase III Trial. *J Clin Oncol*. 2023;41(8):1590-9. Epub 20230104. doi: 10.1200/jco.22.00940. PubMed PMID: 36599114; PubMed Central PMCID: PMC10022849.
  53. Dimopoulos MA, Tedeschi A, Trotman J, García-Sanz R, Macdonald D, Leblond V, et al. Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia. *N Engl J Med*. 2018;378(25):2399-410. Epub 20180601. doi: 10.1056/NEJMoa1802917. PubMed PMID: 29856685.
  54. Dreyling M, Goy A, Hess G, Kahl BS, Hernández-Rivas J-Á, Schuier N, et al. Long-term Outcomes With Ibrutinib Treatment for Patients With Relapsed/Refractory Mantle Cell Lymphoma: A Pooled Analysis of 3 Clinical Trials With Nearly 10 Years of Follow-up. *HemaSphere*. 2022;6(5):e712. doi: 10.1097/hs9.0000000000000712. PubMed PMID: 35441128; PubMed Central PMCID: PMC9010121.
  55. Drug Patent and Exclusivity Study. United States Patent and Trademark Office. Available from: [https://www.uspto.gov/sites/default/files/documents/USPTO\\_Drug\\_Patent\\_and\\_Exclusivity\\_Study\\_Report.pdf](https://www.uspto.gov/sites/default/files/documents/USPTO_Drug_Patent_and_Exclusivity_Study_Report.pdf).
  56. Exclusivity and Generic Drugs: What Does it Mean?. U.S. Food & Drug Administration. Available from: <https://www.fda.gov/media/111069/download>.
  57. FDA Approves Imbruvica (ibrutinib) for Chronic Graft Versus Host Disease [Internet]. *Drugs.com*; 2017 Aug 17 [cited 2023 Oct 2]. Available from: <https://www.drugs.com/newdrugs/fda-approves-imbruvica-ibrutinib-chronic-graft-versus-host-4567.html>.
  58. FDA Approves Imbruvica (ibrutinib) for the First-Line Treatment of Chronic Lymphocytic Leukemia [Internet]. *Drugs.com*; 2016 Mar 4 [cited 2023 Oct 2]. Available from: <https://www.drugs.com/newdrugs/fda-approves-imbruvica-ibrutinib-first-line-chronic-lymphocytic-leukemia-4353.html>.
  59. FDA Expands Approved Use of Imbruvica (ibrutinib) for Waldenström's Macroglobulinemia [Internet]. *Drugs.com*; 2015 Jan 29 [cited 2023 Oct 2]. Available from: <https://www.drugs.com/newdrugs/fda-expands-approved-imbruvica-ibrutinib-waldenstr-m-s-macroglobulinemia-4154.html>.
  60. Fisher A, Goradia H, Martinez-Calle N, Patten P, Munir T. The evolving use of measurable residual disease in chronic lymphocytic leukemia clinical trials. *Front Oncol*. 2023;13:1130617. Epub 20230222. doi: 10.3389/fonc.2023.1130617. PubMed PMID: 36910619; PubMed Central PMCID: PMC9992794.

61. Flowers ME, Martin PJ. How we treat chronic graft-versus-host disease. *Blood*. 2015;125(4):606-15. Epub 20141114. doi: 10.1182/blood-2014-08-551994. PubMed PMID: 25398933; PubMed Central PMCID: PMC4304105.
62. Ghia P, Pluta A, Wach M, Lysak D, Kozak T, Simkovic M, et al. ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *Journal of Clinical Oncology*. 2020;38(25):2849-61. doi: 10.1200/jco.19.03355. PubMed PMID: 32459600.
63. Ghia P, Sharman JP, Burger J, Barrientos J, Patel S, Krigsfeld G, Srikanthan S, Messahel B, Khan W. A phase 2 study evaluating dose modification approaches for ibrutinib (ibr) monotherapy or ibrutinib + venetoclax (I+V) combination in patients (pts) with previously untreated chronic lymphocytic leukemia (CLL): TAILOR. *European Hematology Association*; 2024 May 14. Abstract PB2542. Available from: <https://library.ehaweb.org/eha/2024/eha2024-congress/421307/paolo.ghia.a.phase.2.study.evaluating.dose.modification.approaches.for.html>.
64. Grogan J. The Inflation Reduction Act Is Already Killing Potential Cures [Internet]. *Wall Street Journal*; 2022 Nov 3 [cited 2023 Oct 2]. Available from: <https://www.wsj.com/articles/the-inflation-reduction-act-killing-potential-cures-pharmaceutical-companies-treatment-patients-drugs-prescriptions-ira-manufacturers-11667508291>.
65. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-60. Epub 20180314. doi: 10.1182/blood-2017-09-806398. PubMed PMID: 29540348.
66. Hamerton L, Gomes K, Fougeray R, Hook ES, Gomes MV, Hauch O, Bullement A. A UK cost-effectiveness analysis of trifluridine/tipiracil for heavily pretreated metastatic gastroesophageal cancers. *Future Oncol*. 2023;19(9):643-50. Epub 20230428. doi: 10.2217/fon-2022-0662. PubMed PMID: 37115022.
67. Hess G, Rule S, Jurczak W, Jerkeman M, Santucci Silva R, Rusconi C, et al. Health-related quality of life data from a phase 3, international, randomized, open-label, multicenter study in patients with previously treated mantle cell lymphoma treated with ibrutinib versus temsirolimus. *Leukemia & Lymphoma*. 2017;58(12):2824-32. doi: 10.1080/10428194.2017.1326034.
68. Hillmen P, Brown JR, Eichhorst BF, Lamanna N, O'Brien SM, Qiu L, et al. ALPINE: zanubrutinib versus ibrutinib in relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. *Future Oncology*. 2020;16(10):517-23. doi: 10.2217/fon-2019-0844.
69. Hillmen P, Eichhorst B, Brown JR, Lamanna N, O'Brien SM, Tam CS, et al. Zanubrutinib Versus Ibrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Interim Analysis of a Randomized Phase III Trial. *J Clin Oncol*. 2023;41(5):1035-45. Epub 20221117. doi: 10.1200/jco.22.00510. PubMed PMID: 36395435; PubMed Central PMCID: PMC9928683.
70. Huang Q, Deering KL, Harshaw Q, Leslie LA. Real-world Clinical Outcomes of First-Line Ibrutinib or Chemoimmunotherapy in Patients with Chronic Lymphocytic Leukemia by Risk Status. *Advances in Therapy*. 2022;39(7):3292-307. doi: 10.1007/s12325-021-01991-5.
71. Jacobs R, Lu X, Emond B, Morrison L, Kinkead F, Lefebvre P, et al. Time to Next Treatment in Patients with Chronic Lymphocytic Leukemia Initiating First-Line Ibrutinib or Acalabrutinib. *Future Oncology*. 2024;20(1):39-53. doi: 10.2217/fon-2023-0436.
72. Kadmon Pharmaceuticals, LLC. REZUROCK (belumosudil) [package insert]. U.S. Food and Drug Administration. Revised 2021 Jul. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/214783s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214783s000lbl.pdf).

73. Karr M, Roeker L. A History of Targeted Therapy Development and Progress in Novel–Novel Combinations for Chronic Lymphocytic Leukemia (CLL). *Cancers*. 2023;15(4):1018. PubMed PMID: doi:10.3390/cancers15041018.
74. Kater AP, Owen C, Moreno C, Follows G, Munir T, Levin M-D, et al. Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities. *NEJM Evidence*. 2022;1(7):EVIDo2200006. doi: doi:10.1056/EVIDo2200006.
75. Liang Y, Gale RP. Zanubrutinib in Chronic Lymphocytic Leukemia. *N Engl J Med*. 2023;388(18):1720. doi: 10.1056/NEJMc2302350. PubMed PMID: 37133596.
76. Lipsky A, Lamanna N. Managing toxicities of Bruton tyrosine kinase inhibitors. *Hematology*. 2020;2020(1):336-45. doi: 10.1182/hematology.2020000118.
77. Liu R, Yeh YC, Yang HK, Gao X, Tang B. PCN80 Cost Minimization Analysis Of Zanubrutinib For The Treatment Of Adult Patients With Mantle Cell Lymphoma Who Have Received At Least One Prior Therapy From The Payer Perspective In The United States. *Value in Health*. 2020;23:S37-S8. doi: 10.1016/j.jval.2020.04.1582.
78. Lovell AR, Jammal N, Bose P. Selecting the optimal BTK inhibitor therapy in CLL: rationale and practical considerations. *Therapeutic Advances in Hematology*. 2022;13:20406207221116577. doi: 10.1177/20406207221116577.
79. Lu X, Emond B, Morrison L, Kinkead F, Lefebvre P, Lafeuille M-H, et al. Real-World Comparison of First-Line Treatment Adherence Between Single-Agent Ibrutinib and Acalabrutinib in Patients with Chronic Lymphocytic Leukemia. *Patient Preference and Adherence*. 2023;17(null):2073-84. doi: 10.2147/PPA.S417180.
80. Lucero KT, Obodozie-Ofoegbu OO, Nooruddin Z, Ryan K, Castillo A, Moore AM, et al. Health disparity in use of novel agents for first-line therapy in Black and White patients with chronic lymphocytic leukemia in the Department of Veterans Affairs. *Journal of Managed Care & Specialty Pharmacy*. 2023;29(4):420-30. doi: 10.18553/jmcp.2023.29.4.420. PubMed PMID: 36989449.
81. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). *European Heart Journal - Cardiovascular Imaging*. 2022;23(10):e333-e465. doi: 10.1093/ehjci/jeac106.
82. MacEwan JP, Dennen S, Kee R, Ali F, Shafrin J, Batt K. Changes in mortality associated with cancer drug approvals in the United States from 2000 to 2016. *J Med Econ*. 2020;23(12):1558-69. Epub 20201109. doi: 10.1080/13696998.2020.1834403. PubMed PMID: 33161782.
83. Mato Anthony R, Woyach Jennifer A, Brown Jennifer R, Ghia P, Patel K, Eyre Toby A, et al. Pirtobrutinib after a Covalent BTK Inhibitor in Chronic Lymphocytic Leukemia. *New England Journal of Medicine*. 2023;389(1):33-44. doi: 10.1056/NEJMoa2300696.
84. Mato AR, Barrientos JC, Ghosh N, Pagel JM, Brander DM, Gutierrez M, et al. Prognostic Testing and Treatment Patterns in Chronic Lymphocytic Leukemia in the Era of Novel Targeted Therapies: Results From the informCLL Registry. *Clinical Lymphoma Myeloma and Leukemia*. 2020;20(3):174-83.e3. doi: 10.1016/j.clml.2019.10.009.
85. McGregor B, Geynisman DM, Burotto M, Porta C, Suarez C, Boursillon MT, et al. Grade 3/4 Adverse Event Costs of Immuno-oncology Combination Therapies for Previously Untreated Advanced Renal Cell Carcinoma. *The Oncologist*. 2023;28(1):72-9. doi: 10.1093/oncolo/oyac186.

86. Mela Osorio MJ, Pavlovsky A, Pavlovsky C, Fernandez II, Clavijo M, Miroli A, et al. Impact of Ibrutinib in Quality of Life (QoL) in Patients with Chronic Lymphocytic Leukemia (CLL): Real World Experience in Argentina. *Blood*. 2022;140(Supplement 1):12403-4. doi: 10.1182/blood-2022-165626.
87. Molica S, Giannarelli D, Montserrat E. Comparison Between Venetoclax-based and Bruton Tyrosine Kinase Inhibitor-based Therapy as Upfront Treatment of Chronic Lymphocytic Leukemia (CLL): A Systematic Review and Network Meta-analysis. *Clinical Lymphoma Myeloma and Leukemia*. 2021;21(4):216-23. doi: 10.1016/j.clml.2020.10.012.
88. Moreno C, Greil R, Demirkan F, Tedeschi A, Anz B, Larratt L, et al. First-line treatment of chronic lymphocytic leukemia with ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab: final analysis of the randomized, phase III iLLUMINATE trial. *Haematologica*. 2022;107(9):2108-20. Epub 20220901. doi: 10.3324/haematol.2021.279012. PubMed PMID: 35021599; PubMed Central PMCID: PMC9425310.
89. Munir T, Brown JR, O'Brien S, Barrientos JC, Barr PM, Reddy NM, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol*. 2019;94(12):1353-63. Epub 20191013. doi: 10.1002/ajh.25638. PubMed PMID: 31512258; PubMed Central PMCID: PMC6899718.
90. Munir T, Genovez V, Genestier V, Ryan K, Liljas B, Gaitonde P. Cost-effectiveness of acalabrutinib regimens in treatment-naïve chronic lymphocytic leukemia in the United States. *Expert Review of Pharmacoeconomics & Outcomes Research*. 2023;23(5):579-89. doi: 10.1080/14737167.2023.2196408.
91. Narezkina A, Akhter N, Lu X, Emond B, Panjabi S, Forbes SP, et al. Real-World Persistence and Time to Next Treatment With Ibrutinib in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Including Patients at High Risk for Atrial Fibrillation or Stroke. *Clinical Lymphoma Myeloma and Leukemia*. 2022;22(11):e959-e71. doi: 10.1016/j.clml.2022.07.004.
92. National Cancer Institute. Cancer Disparities [Internet]. National Institutes of Health; 2022 Mar 28 [cited 2023 Oct 2]. Available from: <https://web.archive.org/web/20231128172223/https://www.cancer.gov/about-cancer/understanding/disparities>.
93. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). National Institutes of Health; 2017 Nov 27. Available from: [https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_8.5x11.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).
94. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 1.2024. National Comprehensive Cancer Network, Inc. Available from: <https://www.nccn.org/>.
95. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Version.2.2024. National Comprehensive Cancer Network, Inc. Available from: <https://www.nccn.org/>.
96. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Hematopoietic Cell Transplant. Version 3.2023. National Comprehensive Cancer Network, Inc. Available from: <https://www.nccn.org/>.
97. Noy A, de Vos S, Coleman M, Martin P, Flowers CR, Thieblemont C, et al. Durable ibrutinib responses in relapsed/refractory marginal zone lymphoma: long-term follow-up and biomarker analysis. *Blood Advances*. 2020;4(22):5773-84. doi: 10.1182/bloodadvances.2020003121.

98. Noy A, de Vos S, Thieblemont C, Martin P, Flowers CR, Morschhauser F, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. *Blood*. 2017;129(16):2224-32. doi: 10.1182/blood-2016-10-747345.
99. O'Brien SM, Brown JR, Byrd JC, Furman RR, Ghia P, Sharman JP, Wierda WG. Monitoring and Managing BTK Inhibitor Treatment-Related Adverse Events in Clinical Practice. *Frontiers in Oncology*. 2021;11.
100. Ostrom QT, Gittleman H, de Blank PM, Finlay JL, Gurney JG, McKean-Cowdin R, et al. American Brain Tumor Association Adolescent and Young Adult Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. *Neuro-Oncology*. 2015;18(suppl\_1):i1-i50. doi: 10.1093/neuonc/nov297.
101. Pharmacyclics. Imbruvica (ibrutinib) [package insert]. U.S. Food and Drug Administration. Revised 2024 May. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2024/205552s042,210563a018,217003s003lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/205552s042,210563a018,217003s003lbl.pdf).
102. Pharmacyclics. Imbruvica (ibrutinib) [package insert]. U.S. Food and Drug Administration. Revised 2023 May. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2023/205552s040,210563s017lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/205552s040,210563s017lbl.pdf).
103. Quartermaine C, Ghazi Sanam M, Yasin A, Awan Farrukh T, Fradley M, Wiczer T, et al. Cardiovascular Toxicities of BTK Inhibitors in Chronic Lymphocytic Leukemia. *JACC: CardioOncology*. 2023;5(5):570-90. doi: 10.1016/j.jacc.2023.09.002.
104. Radhakrishnan C, Sefidani Forough A, Cichero JAY, Smyth HE, Raidhan A, Nissen LM, Steadman KJ. A Difficult Pill to Swallow: An Investigation of the Factors Associated with Medication Swallowing Difficulties. *Patient Prefer Adherence*. 2021;15:29-40. Epub 20210111. doi: 10.2147/PPA.S277238. PubMed PMID: 33469272; PubMed Central PMCID: PMC7810703.
105. Raedler LA. Imbruvica (Ibrutinib): First Drug Approved for the Treatment of Patients with Waldenström's Macroglobulinemia. *Am Health Drug Benefits*. 2016;9(Spec Feature):89-92. PubMed PMID: 27668052; PubMed Central PMCID: PMC5013861.
106. Rai KR, Stilgenbauer S. Selection of initial therapy for symptomatic or advanced chronic lymphocytic leukemia/small lymphocytic lymphoma. *UpToDate*. Waltham, MA: UpToDate; 2022.
107. Rogers KA, McLaughlin E, Wei L, Anghelina MI, Ali MK, Andritsos LA, et al. Extended Follow up of a Phase 2 Study of Ibrutinib in Hairy Cell Leukemia. *Blood*. 2022;140(Supplement 1):6494-5. doi: 10.1182/blood-2022-165795.
108. Roy N, Stemple J, Merrill RM, Thomas L. Dysphagia in the elderly: preliminary evidence of prevalence, risk factors, and socioemotional effects. *Ann Otol Rhinol Laryngol*. 2007;116(11):858-65. doi: 10.1177/000348940711601112. PubMed PMID: 18074673.
109. Rule S, Jurczak W, Jerkeman M, Rusconi C, Trneny M, Offner F, et al. Ibrutinib versus temsirolimus: 3-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study. *Leukemia*. 2018;32(8):1799-803. doi: 10.1038/s41375-018-0023-2.
110. Salles GA, Callet-Bauchu E, Besson H, Doyle M, Garside J, Spacek M, Doubek M. Single-Agent Ibrutinib vs Real-World (RW) Treatments for Patients with Chronic Lymphocytic Leukemia (CLL) and del11q: Adjusted Comparison of RESONATE-2TM and RESONATEM with RW Databases. *Blood*. 2018;132:4427. doi: 10.1182/blood-2018-99-112172.

111. Sarosiek S, Gustine JN, Flynn CA, Leventoff C, Little M, White T, et al. Dose reductions in patients with Waldenström macroglobulinaemia treated with ibrutinib. *British Journal of Haematology*. 2023;201(5):897-904. doi: 10.1111/bjh.18643.
112. Sarosiek S, Treon S, Palomba ML, Dimopoulos MA, Castillo J, Peltier HM et al. Dose adjustment outcomes in patients with Waldenström macroglobulinemia treated with ibrutinib. *European Hematology Association*; 2024 May 14. Abstract P2070. Available from: <https://library.ehaweb.org/eha/2024/eha2024-congress/420157/shayna.sarosiek.dose.adjustment.outcomes.in.patients.with.waldenstrm.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dp2070>.
113. Schiele JT, Quinzler R, Klimm HD, Pruszydlo MG, Haefeli WE. Difficulties swallowing solid oral dosage forms in a general practice population: prevalence, causes, and relationship to dosage forms. *Eur J Clin Pharmacol*. 2013;69(4):937-48. Epub 20120929. doi: 10.1007/s00228-012-1417-0. PubMed PMID: 23052416.
114. Schouten A. Notes on the Preclinical Development of Imbruvica (Ibrutinib). *Knowledge Ecology International*; 2023 Oct 2. Report No. 2023.6. Available from: <https://www.keionline.org/wp-content/uploads/KEI-BN-2023-4.pdf>.
115. Seabury SA, Goldman DP, Gupta CN, Khan ZM, Chandra A, Philipson TJ, Lakdawalla DN. Quantifying Gains in the War on Cancer Due to Improved Treatment and Earlier Detection. *Forum Health Econ Policy*. 2016;19(1):141-56. doi: 10.1515/fhep-2015-0028. PubMed PMID: 31419891.
116. Senate Finance Committee, Wyden R. Principles for Drug Pricing Reform. *United States Senate*; 2021 Jun 22. Available from: <https://www.finance.senate.gov/imo/media/doc/062221%20SFC%20Drug%20Pricing%20Principles.pdf>.
117. Seymour JF, Byrd JC, Ghia P, Kater AP, Chanan-Khan A, Furman RR, et al. Detailed safety profile of acalabrutinib vs ibrutinib in previously treated chronic lymphocytic leukemia in the ELEVATE-RR trial. *Blood*. 2023;142(8):687-99. doi: 10.1182/blood.2022018818.
118. Shadman M, Manzoor BS, Sail K, Tuncer HH, Allan JN, Ujjani C, et al. Treatment Discontinuation Patterns for Patients With Chronic Lymphocytic Leukemia in Real-World Settings: Results From a Multi-Center International Study. *Clin Lymphoma Myeloma Leuk*. 2023;23(7):515-26. Epub 20230324. doi: 10.1016/j.clml.2023.03.010. PubMed PMID: 37076367.
119. Shanafelt TD, Wang XV, Hanson CA, Paietta EM, O'Brien S, Barrientos J, et al. Long-term outcomes for ibrutinib-rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. *Blood*. 2022;140(2):112-20. doi: 10.1182/blood.2021014960. PubMed PMID: 35427411; PubMed Central PMCID: PMC9283968.
120. Sharman JP, Burger J, Barrientos J, Patel S, Krigsfeld G, Srikanthan S et al. A phase 2 study evaluating dose modification approaches for ibrutinib monotherapy or ibrutinib + venetoclax combination in patients with previously untreated chronic lymphocytic leukemia: TAILOR. *European Hematology Association*; 2024 May 14. Abstract PB2542. Available from: <https://library.ehaweb.org/eha/2024/eha2024-congress/421307/paolo.ghia.a.phase.2.study.evaluating.dose.modification.approaches.for.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dpb2542>.
121. Sharman JP, Burger JA, Barrientos J, Kuruvilla P, Patel S, Krigsfeld G, et al. Tailor: Interventional Study Evaluating Physician's Choice of Ibrutinib Monotherapy or Ibrutinib-Venetoclax Combination Using Dose Modifications and Alternate Dosing Approaches in Patients with Untreated Chronic Lymphocytic Leukemia. *Blood*. 2023;142:6564. doi: 10.1182/blood-2023-174751.

122. Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naïve chronic lymphocytic leukaemia (ELEVATE-TN): a randomised, controlled, phase 3 trial. *The Lancet*. 2020;395(10232):1278-91. doi: 10.1016/S0140-6736(20)30262-2.
123. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(1):17-48. doi: 10.3322/caac.21763. PubMed PMID: 36633525.
124. Sivina M, Kim E, Wierda WG, Ferrajoli A, Jain N, Thompson P, et al. Ibrutinib induces durable remissions in treatment-naïve patients with CLL and 17p deletion and/or TP53 mutations. *Blood*. 2021;138(24):2589-92. doi: 10.1182/blood.2021012315.
125. Smith TW, Owusu HF, Wormser D, Woo J. Real-World Evaluation of the Treatment Landscape for Chronic Lymphocytic Leukemia. *Blood*. 2021;138(Supplement 1):1559-. doi: 10.1182/blood-2021-147885.
126. Smolej L, Vodárek P, ěcsiová D, Šimkovič M. Chemoimmunotherapy in the First-Line Treatment of Chronic Lymphocytic Leukaemia: Dead Yet, or Alive and Kicking? *Cancers (Basel)*. 2021;13(13). Epub 20210623. doi: 10.3390/cancers1313134. PubMed PMID: 34201565; PubMed Central PMCID: PMC8267736.
127. Stegemann S, Gosch M, Breitzkreutz J. Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy. *Int J Pharm*. 2012;430(1-2):197-206. Epub 20120415. doi: 10.1016/j.ijpharm.2012.04.022. PubMed PMID: 22525080.
128. Stephens DM. NCCN Guidelines Update: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. *Journal of the National Comprehensive Cancer Network*. 2023;21(5.5):563-6. doi: 10.6004/jnccn.2023.5007.
129. Sudhapalli P, Piena M, Palaka A, Mato A, van de Wetering G, Manzoor B, Sail K. Systematic Literature Review And Network Meta-Analysis Comparing Therapies For Treatment-Naïve Patients With Chronic Lymphocytic Leukemia. *European Hematology Association (EHA); 2020*. Poster EP725. Available from: <https://library.ehaweb.org/eha/2020/eha25th/294643/kavita.sail.systematic.literature.review.and.network.meta-analysis.comparing.html>.
130. T Low J, B Peters K. Ibrutinib in primary central nervous system diffuse large B-cell lymphoma. *CNS Oncology*. 2020;9(1):CNS51. doi: 10.2217/cns-2019-0022.
131. Take the next step in the treatment of high-risk classical Hodgkin lymphoma in children with ADCETRIS [Internet]. Pfizer Inc; 2024. Available from: <https://www.adcetris.com/pediatric-classical-hodgkin-lymphoma/>.
132. Tam CS, Allan JN, Siddiqi T, Kipps TJ, Jacobs R, Opat S, et al. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. *Blood*. 2022;139(22):3278-89. doi: 10.1182/blood.2021014488.
133. Tam CS, Brown JR, Kahl BS, Ghia P, Giannopoulos K, Jurczak W, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *The Lancet Oncology*. 2022;23(8):1031-43. doi: 10.1016/S1470-2045(22)00293-5.
134. Tam CS, Opat S, D'Sa S, Jurczak W, Lee HP, Cull G, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood*. 2020;136(18):2038-50. doi: 10.1182/blood.2020006844. PubMed PMID: 32731259; PubMed Central PMCID: PMC7596850.
135. Tam CS, Robak T, Ghia P, Kahl BS, Walker P, Janowski W, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukemia and 17p deletion. *Haematologica*. 2021;106(9):2354-63. Epub 20210901. doi: 10.3324/haematol.2020.259432. PubMed PMID: 33054121; PubMed Central PMCID: PMC8409041.

136. Tang PA, Pond GR, Chen EX. Influence of an independent review committee on assessment of response rate and progression-free survival in phase III clinical trials. *Ann Oncol*. 2010;21(1):19-26. Epub 20091029. doi: 10.1093/annonc/mdp478. PubMed PMID: 19875758.
137. Teusink-Cross A, Davies SM, Grimley MS, Chandra S, Flannery A, Dandoy CE, et al. Ibrutinib for the treatment of chronic graft-vs-host disease in pediatric hematopoietic stem cell transplant patients: A single-center experience. *Pediatric Transplantation*. 2020;24(3):e13692. doi: 10.1111/petr.13692.
138. Thiyagalingam S, Kulinski AE, Thorsteinsdottir B, Shindelar KL, Takahashi PY. Dysphagia in Older Adults. *Mayo Clin Proc*. 2021;96(2):488-97. doi: 10.1016/j.mayocp.2020.08.001. PubMed PMID: 33549267.
139. Tohidi-Esfahani I, Warden A, Malunis E, DeNardis PL, Haurat J, Black M, et al. WhiMSICAL: A global Waldenström's Macroglobulinemia patient-derived data registry capturing treatment and quality of life outcomes. *Am J Hematol*. 2021;96(6):E218-e22. Epub 20210409. doi: 10.1002/ajh.26173. PubMed PMID: 33755232.
140. Treon SP, Tripsas CK, Meid K, Warren D, Varma G, Green R, et al. Ibrutinib in Previously Treated Waldenström's Macroglobulinemia. *New England Journal of Medicine*. 2015;372(15):1430-40. doi: doi:10.1056/NEJMoa1501548.
141. Treon SP, Xu L, Yang G, Zhou Y, Liu X, Cao Y, et al. MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia. *New England Journal of Medicine*. 2012;367(9):826-33. doi: doi:10.1056/NEJMoa1200710.
142. Treon SP. How I treat Waldenström macroglobulinemia. *Blood*. 2015;126(6):721-32. doi: 10.1182/blood-2015-01-553974.
143. U.S. FDA Approves Imbruvica (ibrutinib) as First Treatment Specifically Indicated for Relapsed/Refractory Marginal Zone Lymphoma (MZL) [Internet]. *Drugs.com*; 2017 Jan 19 [cited 2023 Oct 2]. Available from: <https://www.drugs.com/newdrugs/u-s-fda-approves-imbruvica-ibrutinib-first-specifically-indicated-relapsed-refractory-marginal-zone-4476.html>.
144. U.S. FDA Expands Imbruvica (ibrutinib) Label to Include Overall Survival Data in Previously Untreated Chronic Lymphocytic Leukemia (CLL) and New Indication for Small Lymphocytic Lymphoma (SLL) Patients [Internet]. *Drugs.com*; 2016 May 9 [cited 2023 Oct 2]. Available from: <https://www.drugs.com/newdrugs/u-s-fda-expands-imbruvica-ibrutinib-label-include-overall-survival-data-previously-untreated-4477.html>.
145. Update on Imbruvica (ibrutinib) U.S. Accelerated Approvals for Mantle Cell Lymphoma and Marginal Zone Lymphoma Indications [Internet]. *Drugs.com*; 2023 Apr 6 [cited 2023 Oct 2]. Available from: [https://www.drugs.com/clinical\\_trials/update-imbruvica-ibrutinib-u-s-accelerated-approvals-mantle-cell-lymphoma-marginal-zone-lymphoma-20751.html](https://www.drugs.com/clinical_trials/update-imbruvica-ibrutinib-u-s-accelerated-approvals-mantle-cell-lymphoma-marginal-zone-lymphoma-20751.html).
146. Update on Imbruvica (ibrutinib) U.S. Accelerated Approvals for Mantle Cell Lymphoma and Marginal Zone Lymphoma Indications [Internet]. Illinois: AbbVie, Inc.; 2023 Apr 6 [cited 2023 Oct 2]. Available from: <https://news.abbvie.com/2023-04-06-Update-on-IMBRUVICA-R-ibrutinib-U-S-Accelerated-Approvals-for-Mantle-Cell-Lymphoma-and-Marginal-Zone-Lymphoma-Indications>.
147. Various manufacturers. Bendamustine [package insert]. U.S. Food and Drug Administration.
148. Various manufacturers. Cyclophosphamide [package insert]. U.S. Food and Drug Administration.
149. Various manufacturers. Dexamethasone [package insert]. U.S. Food and Drug Administration.
150. Various manufacturers. Fludarabine [package insert]. U.S. Food and Drug Administration.
151. Various manufacturers. Rituximab [package insert]. U.S. Food and Drug Administration.

152. Visentin A, Mauro FR, Cibien F, Vitale C, Reda G, Fresa A, et al. Continuous treatment with Ibrutinib in 100 untreated patients with TP53 disrupted chronic lymphocytic leukemia: A real-life campus CLL study. *Am J Hematol*. 2022;97(3):E95-e9. Epub 20211221. doi: 10.1002/ajh.26437. PubMed PMID: 34904743.
153. Waldron J. Bristol Myers CEO already reassessing portfolio in wake of US pricing law: report [Internet]. Fierce Biotech; 2022 Nov 21 [cited 2023 Oct 2]. Available from: <https://www.fiercebiotech.com/biotech/bristol-myers-already-reassessing-portfolio-wake-ira-ceo-tells-ft>.
154. Waller EK, Miklos D, Cutler C, Arora M, Jagasia MH, Pusic I, et al. Ibrutinib for Chronic Graft-versus-Host Disease After Failure of Prior Therapy: 1-Year Update of a Phase 1b/2 Study. *Biology of Blood and Marrow Transplantation*. 2019;25(10):2002-7. doi: 10.1016/j.bbmt.2019.06.023.
155. Wang E, Mi X, Thompson MC, Montoya S, Notti RQ, Afaghani J, et al. Mechanisms of Resistance to Noncovalent Bruton's Tyrosine Kinase Inhibitors. *N Engl J Med*. 2022;386(8):735-43. doi: 10.1056/NEJMoa2114110. PubMed PMID: 35196427; PubMed Central PMCID: PMC9074143.
156. Wang M, Goy A, Martin P, Ramchandren R, Alexeeva J, Popat R, et al. Efficacy and Safety of Single-Agent Ibrutinib in Patients with Mantle Cell Lymphoma Who Progressed after Bortezomib Therapy. *Blood*. 2014;124(21):4471. doi: 10.1182/blood.V124.21.4471.4471.
157. Wang ML, Blum KA, Martin P, Goy A, Auer R, Kahl BS, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood*. 2015;126(6):739-45. doi: 10.1182/blood-2015-03-635326.
158. Wang ML, Jurczak W, Jerkeman M, Trotman J, Zinzani PL, Belada D, et al. Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma. *New England Journal of Medicine*. 2022;386(26):2482-94. doi: 10.1056/NEJMoa2201817.
159. Wang ML, Jurczak W, Zinzani PL, Eyre TA, Cheah CY, Ujjani CS, et al. Pirtobrutinib in Covalent Bruton Tyrosine Kinase Inhibitor Pretreated Mantle-Cell Lymphoma. *J Clin Oncol*. 2023;41(24):3988-97. Epub 20230516. doi: 10.1200/jco.23.00562. PubMed PMID: 37192437; PubMed Central PMCID: PMC10461952.
160. Wierda WG, Allan JN, Siddiqi T, Kipps TJ, Opat S, Tedeschi A, et al. Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia: Primary Analysis Results From the Minimal Residual Disease Cohort of the Randomized Phase II CAPTIVATE Study. *Journal of Clinical Oncology*. 2021;39(34):3853-65. doi: 10.1200/jco.21.00807. PubMed PMID: 34618601.
161. Wierda WG, Brown J, Abramson JS, Awan F, Bilgrami SF, Bociek G, et al. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 2024;22(3):175-204. doi: 10.6004/jnccn.2024.0018.
162. Wierda WG, Brown J, Abramson JS, Awan F, Bilgrami SF, Bociek G, et al. NCCN Guidelines(R) Insights: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 3.2022. *J Natl Compr Canc Netw*. 2022;20(6):622-34. doi: 10.6004/jnccn.2022.0031. PubMed PMID: 35714675.
163. Wolff D, Fatobene G, Rocha V, Kroger N, Flowers ME. Steroid-refractory chronic graft-versus-host disease: treatment options and patient management. *Bone Marrow Transplant*. 2021;56(9):2079-87. Epub 20210703. doi: 10.1038/s41409-021-01389-5. PubMed PMID: 34218265; PubMed Central PMCID: PMC8410585.
164. Wolowacz SE, Briggs A, Belozeroff V, Clarke P, Doward L, Goeree R et al. Estimating Health-State Utility for Economic Models in Clinical Studies: An ISPOR Good Research Practices Task

- Force Report. *Value Health*. 2016;19(6):704-19. doi: 10.1016/j.jval.2016.06.001. PubMed PMID: 27712695.
165. Woyach JA, Barr PM, Kipps TJ, Barrientos JC, Ahn IE, Ghia P, et al. Characteristics and Clinical Outcomes of Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Receiving Ibrutinib for  $\geq 5$  Years in the RESONATE-2 Study. *Cancers (Basel)*. 2023;15(2). Epub 20230113. doi: 10.3390/cancers15020507. PubMed PMID: 36672456; PubMed Central PMCID: PMC9857192.
166. Woyach JA, Ruppert AS, Heerema NA, Zhao W, Booth AM, Ding W, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. *New England Journal of Medicine*. 2018;379(26):2517-28. doi: doi:10.1056/NEJMoa1812836.
167. Wu L, Ran T, He J, Panjabi S, Lu X. Real-world clinical outcomes in patients receiving either ibrutinib or chemo-immunotherapy (CIT) as first-line (1L) treatment for chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL): A retrospective analysis. *Journal of Clinical Oncology*. 2022;40(16\_suppl):e19057-e. doi: 10.1200/JCO.2022.40.16\_suppl.e19057.
168. Yang G, Zhou Y, Liu X, Xu L, Cao Y, Manning RJ, et al. A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenström macroglobulinemia. *Blood*. 2013;122(7):1222-32. doi: 10.1182/blood-2012-12-475111.
169. Youron P, Singh C, Jindal N, Malhotra P, Khadwal A, Jain A, et al. Quality of life in patients of chronic lymphocytic leukemia using the EORTC QLQ-C30 and QLQ-CLL17 questionnaire. *European Journal of Haematology*. 2020;105(6):755-62. doi: 10.1111/ejh.13503.
170. Yu J, Lal LS, Anderson A, DuCharme M, Parasuraman S, Weisdorf D. Healthcare resource utilization and costs among patients with steroid-resistant chronic graft-versus-host disease in the United States: a retrospective claims database analysis. *Curr Med Res Opin*. 2021;37(5):755-9. Epub 20210310. doi: 10.1080/03007995.2021.1893676. PubMed PMID: 33615925.
171. Zeiser R, Polverelli N, Ram R, Hashmi SK, Chakraverty R, Middeke JM, et al. Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease. *N Engl J Med*. 2021;385(3):228-38. doi: 10.1056/NEJMoa2033122. PubMed PMID: 34260836.

## Redacted Negotiation Meeting Summaries for Imbruvica

Below are summaries of the negotiation meetings between CMS and the Primary Manufacturer, which include redacted information regarding the negotiation meetings and exchange of offers and counteroffers in the meetings.



---

**SUBJECT:** Meeting Summary from Negotiation Meeting between the Centers for Medicare & Medicaid Services (CMS) and Pharmacyclics LLC regarding Imbruvica on April 26, 2024

**Background:** Sections 11001 and 11002 of the Inflation Reduction Act of 2022 (IRA) (P.L. 117-169), signed into law on August 16, 2022, established the Medicare Drug Price Negotiation Program (hereafter the “Negotiation Program”) to enable the Centers for Medicare & Medicaid Services (CMS) to negotiate maximum fair prices (MFPs) with willing manufacturers for certain high expenditure, single source drugs and biological products. Pharmacyclics LLC (hereafter “the Primary Manufacturer”) chose to enter into an agreement to participate in the Negotiation Program for Imbruvica (hereafter “the Selected Drug”).

In accordance with revised guidance and in the course of negotiation for the Selected Drug, CMS invited the Primary Manufacturer to a negotiation meeting when rejecting the Primary Manufacturer’s counteroffer, and the Primary Manufacturer accepted CMS’ invitation. CMS shared a proposed meeting agenda with the Primary Manufacturer approximately two weeks before the meeting. The Primary Manufacturer had the opportunity to request additions or edits to the agenda at least one week ahead of the meeting. This document includes a summary prepared by CMS of the first negotiation meeting, which was held on April 26, 2024 between 10:00 AM ET and 12:30 PM ET.

**CMS Attendees:**

1. Dan Heider, Director, Division of Rebate Agreements and Drug Price Negotiation
2. Min Kwon, Division of Rebate Agreements and Drug Price Negotiation
3. Tina Li, Medicare Drug Rebate and Negotiations Group
4. Corey Rosenberg, Deputy Director, Division of Rebate Agreements and Drug Price Negotiation
5. Emily Shaw, Representative from the Office of the General Counsel
6. Lara Strawbridge, Deputy Director of Policy, Medicare Drug Rebate and Negotiations Group

**Primary Manufacturer Attendees:**

1. [REDACTED]
2. [REDACTED]
3. [REDACTED]
4. [REDACTED]
5. [REDACTED]
6. [REDACTED]

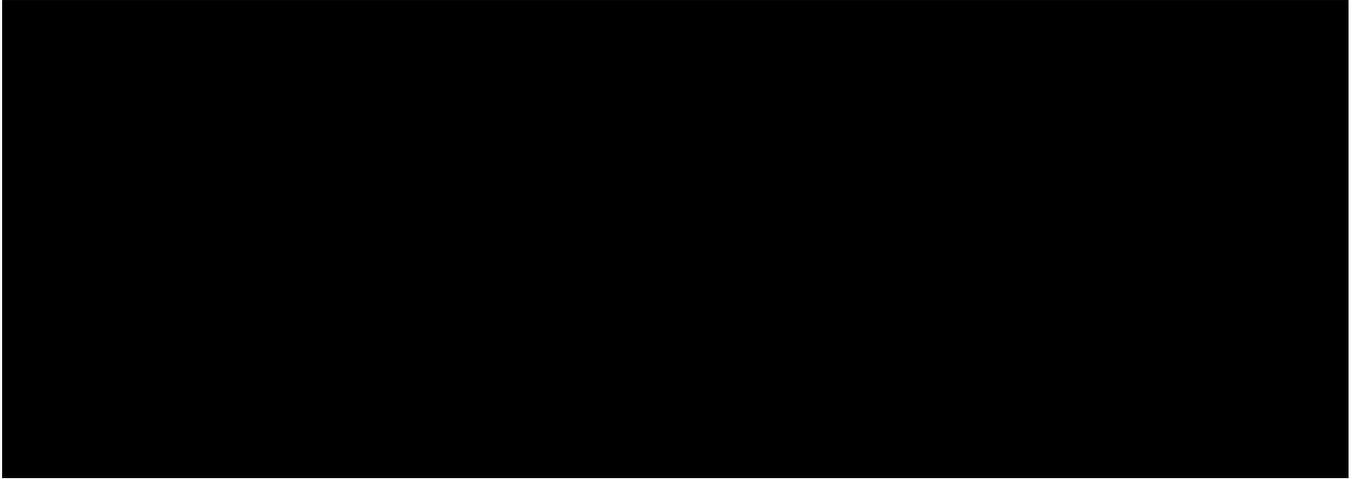
**Topics:** The discussion focused on topics outlined in the final agenda for the meeting, which was as follows:<sup>1</sup>

- Introductions and meeting reminders
- Discussion of initial offer and questions from the Primary Manufacturer
- Discussion of counteroffer and questions from CMS
- Any other considerations that CMS and the Primary Manufacturer would like to discuss
- Next steps

---

<sup>1</sup> Note: This agenda may be inclusive of topics proposed by the Primary Manufacturer.

**Offers/Counteroffers Exchanged:**





---

**SUBJECT:** Meeting Summary from Negotiation Meeting between the Centers for Medicare & Medicaid Services (CMS) and Pharmacylics LLC regarding Imbruvica on May 31, 2024

**Background:** Sections 11001 and 11002 of the Inflation Reduction Act of 2022 (IRA) (P.L. 117-169), signed into law on August 16, 2022, established the Medicare Drug Price Negotiation Program (hereafter the “Negotiation Program”) to enable the Centers for Medicare & Medicaid Services (CMS) to negotiate maximum fair prices (MFPs) with willing manufacturers for certain high expenditure, single source drugs and biological products. Pharmacylics LLC (hereafter “the Primary Manufacturer”) chose to enter into an agreement to participate in the Negotiation Program for Imbruvica (hereafter “the Selected Drug”).

In accordance with revised guidance and in the course of negotiation for the Selected Drug, because CMS and the Primary Manufacturer did not reach agreement on an MFP in the first negotiation meeting held on April 26, 2024, each party had the opportunity to request one additional negotiation meeting, resulting in a maximum of three meetings. The Primary Manufacturer requested a second negotiation meeting and CMS accepted the invitation. CMS shared a proposed meeting agenda with the Primary Manufacturer approximately two weeks before the meeting. The Primary Manufacturer had the opportunity to request additions or edits to the agenda at least one week ahead of the meeting. This document includes a summary prepared by CMS of the second negotiation meeting, which was held on May 31, 2024 between 10:00 AM ET and 12:30 PM ET.

**CMS Attendees:**

1. Dan Heider, Director, Division of Rebate Agreements and Drug Price Negotiation
2. Min Kwon, Division of Rebate Agreements and Drug Price Negotiation
3. Tina Li, Medicare Drug Rebate and Negotiations Group
4. Joel McElvain, Representative from the Office of the General Counsel
5. Corey Rosenberg, Deputy Director, Division of Rebate Agreements and Drug Price Negotiation
6. Lara Strawbridge, Deputy Director of Policy, Medicare Drug Rebate and Negotiations Group

**Primary Manufacturer Attendees:**

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.

**Topics:** The discussion focused on topics outlined in the final agenda for the meeting, which was as follows:<sup>1</sup>

- Introductions and meeting reminders
- Any additional information from the Primary Manufacturer on comparative adverse event evidence across BTKis (including head-to-head studies, economic adverse event burden, and real-world evidence on the management of cardiovascular adverse events)
- Unmet medical need re: cGVHD and oral suspension
- Commercial net price
- Therapeutic alternative selection
- FDA applications and approvals

---

<sup>1</sup> Note: This agenda may be inclusive of topics proposed by the Primary Manufacturer.

- Patient perspective
- Therapeutic advance
- R&D and acquisition costs
- Patents and exclusivities
- Discussion of Primary Manufacturer's request to understand the pathway for voluntary termination
- Any other considerations that CMS and the Primary Manufacturer would like to discuss
- Next steps

**Offers/Counteroffers Exchanged:**





---

**SUBJECT:** Meeting Summary from Negotiation Meeting between the Centers for Medicare & Medicaid Services (CMS) and Pharmacylics LLC regarding Imbruvica on June 27, 2024

**Background:** Sections 11001 and 11002 of the Inflation Reduction Act of 2022 (IRA) (P.L. 117-169), signed into law on August 16, 2022, established the Medicare Drug Price Negotiation Program (hereafter the “Negotiation Program”) to enable the Centers for Medicare & Medicaid Services (CMS) to negotiate maximum fair prices (MFPs) with willing manufacturers for certain high expenditure, single source drugs and biological products. Pharmacylics LLC (hereafter “the Primary Manufacturer”) chose to enter into an agreement to participate in the Negotiation Program for Imbruvica (hereafter “the Selected Drug”).

In accordance with revised guidance and in the course of negotiation for the Selected Drug, because CMS and the Primary Manufacturer did not reach agreement on an MFP in the second negotiation meeting, which was requested by the Primary Manufacturer and held on May 31, 2024, CMS had the opportunity to request one additional negotiation meeting, resulting in a maximum of three meetings. CMS requested a third negotiation meeting and the Primary Manufacturer accepted the invitation. CMS shared a proposed meeting agenda with the Primary Manufacturer approximately two weeks before the meeting. The Primary Manufacturer had the opportunity to request additions or edits to the agenda at least one week ahead of the meeting. This document includes a summary prepared by CMS of the third negotiation meeting, which was held on June 27, 2024 between 10:00 AM ET and 12:30 PM ET.

**CMS Attendees:**

1. Dan Heider, Director, Division of Rebate Agreements and Drug Price Negotiation
2. Min Kwon, Division of Rebate Agreements and Drug Price Negotiation
3. Tina Li, Medicare Drug Rebate and Negotiations Group
4. Joel McElvain, Representative from Office of the General Counsel
5. Corey Rosenberg, Deputy Director, Division of Rebate Agreements and Drug Price Negotiation
6. Lara Strawbridge, Deputy Director of Policy, Medicare Drug Rebate and Negotiations Group

**Primary Manufacturer Attendees:**

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.

**Topics:** The discussion focused on topics outlined in the final agenda for the meeting, which was as follows:<sup>1</sup>

- Introductions and meeting reminders
- Discuss overview of prior discussions and next steps after third meeting
- Revised offer/counteroffer price discussion
  1. Adjustment due to R&D recoupment and acquisition costs
  2. Adjustment due to patents, exclusivities, and FDA approvals
  3. New information informing comparative benefit since the May 31 meeting
- Any other considerations that CMS and the Primary Manufacturer would like to discuss

---

<sup>1</sup> Note: This agenda may be inclusive of topics proposed by the Primary Manufacturer.

- Next steps

**Offers/Counteroffers Exchanged:**

