Q 26:

Selected Drug - IMBRUVICA

Respondent Name – *****

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Representative of a Patient Advocacy Organization

Q 27. Questions on Prescribing Information

What prescribing information has been approved by the FDA for the selected drug and for therapeutic alternative(s) to the selected drug?

A. Selected Drug

The selected drug, IMBRUVICA (ibrutinib), is a Bruton's tyrosine kinase (BTK) inhibitor that initially received accelerated approval in 2013 for the treatment of mantle cell lymphoma (MCL) in patients who had received at least one prior therapy. In 2016, the U.S. Food and Drug Administration (FDA) approved the drug for treatment of chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma with 17p deletion. [1]

When FDA announced additional approval of IMBRUVICA to treat patients with Waldenström's macroglobulinemia (WM), Richard Pazdur, M.D., director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research stated, "[t]oday's approval highlights the importance of development of drugs for supplemental indications. Continued research has discovered new uses of Imbruvica." WM is a rare form of non-Hodgkin lymphoma. [2]

In 2016, FDA expanded the IMBRUVICA label to include overall survival data in previously treated CLL patients [3], added new indications for small lymphocytic lymphoma [3], and for use in first-line treatment of CLL [4].

In its 2017 announcement that IMBRUVICA received an additional accelerated approval and became the first treatment specifically approved to treat marginal zone lymphoma (MZL), Darrin Beaupre, M.D., Ph.D., Head of Early Development and Immunotherapy at Pharmacyclics LLC, stated, "[t]his milestone marks the fifth patient population for whom Imbruvica is now approved and broadens the number of patients who may be treated with the medication. We continue to research Imbruvica across many disease areas, including but not limited to other B-cell malignancies." [5]

In addition to the lymphoma label expansions, IMBRUVICA was approved in 2017 for treatment of adult patients with chronic graft versus host disease (cGVHD) after failure of one or more treatments. As was the case with the drug's approval in MZL, IMBRUVICA became the first FDA-approved therapy for the treatment of cGVHD. [6] Once again, FDA emphasized the benefit of researching new uses of existing treatments.

> "Patients with cGVHD who do not respond to other forms of therapy—typically corticosteroids to suppress their immune system—now have a treatment option specifically indicated to treat their condition. This approval highlights how a known treatment for cancer is finding a new use in treating a serious and life-threatening condition that may occur in patients with blood cancer who receive a stem cell transplant." Richard Pazdur, M.D., Director of the FDA's Oncology Center of Excellence and Acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. [7]

In 2022, the cGVHD indication was expanded to include pediatric patients over 1 year of age. [8]

In May 2023, the accelerated approval indications in MCL and MZL were voluntarily withdrawn because the Phase 3 confirmatory studies were not sufficient for traditional approval. [9]

The dosing for IMBRUVICA, according to the FDA approved label is:

420 mg taken orally once daily for:

- adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) [10]
- adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion [10]
- adult patients with Waldenström's macroglobulinemia (WM) [10]
- adult patients with chronic graft versus host disease (cGVHD) [10]

240 mg/m2 taken orally once daily (up to a dose of 420 mg) for:

- pediatric patients age 1 year and older with cGVHD [10]

B. Therapeutic Alternatives

1. Indication: Adult patients with chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL).

a. **CALQUENCE® (acalabrutinib)** 100 mg orally approximately every 12 hours [11]

b. **BRUKINSA® (zanubrutinib)** 160 mg taken orally twice daily or 320 mg taken orally once daily until disease progression or unacceptable toxicity [12]

2. Indication: Adult patients with Waldenström's macroglobulinemia (WM).

a. BRUKINSA® (zanubrutinib) 160 mg taken orally twice daily or 320 mg taken orally once daily until disease progression or unacceptable toxicity. [12]

b. CALQUENCE® (acalabrutinib) CALQUENCE® (acalabrutinib) is used off-label to treat WM.

3. Indication: Adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

The selected drug, IMBRUVICA® is the only BTK inhibitor approved for treating cGVHD and the only FDA approved treatment for children under 12 years of age with cGVHD.

Please provide information about how the selected drug and its therapeutic alternative(s) are used in the course of care for the condition or disease treated by each indication.

According to NCCN Guidelines, the most appropriate frontline treatment for CLL and SLL depends on patient-specific factors, including characteristics of the cancer and mutation status, age, and comorbidities. Subsequent lines of therapy of therapy are chosen based on the previous treatment as well as the factors outlined above. [13]

In WM, the BTK inhibitors, including IMBRUVICA, are often used as initial therapy in elderly patients and other individuals unable to tolerate systemic chemotherapy. There is divergence of opinion among experts on whether to reserve BTK inhibitors for relapsed or refractory disease in other patients or to incorporate their use in initial treatment. [15] IMBRUVICA can be used with or without coadministration of rituximab (375 mg/m^2) once a week for weeks 1-4 and 17-20.

If the selected drug is used off-label to treat a certain disease or condition, please indicate this and provide evidence from nationally recognized, evidence-based guidelines and recognized by CMS-approved Part D compendia, as applicable.

- Mantle Cell Lymphoma: In BTK inhibitor-naïve patients with a first relapse of MCL or primary refractory MCL, IMBRUVICA may be used if acalabrutinib and zanubrutinib are unavailable. [16]
- Hairy Cell Leukemia (HCL): HCL is a rare B-cell malignancy with an unmet need in patients failing to benefit from purine nucleoside analogs (PNA). A recent phase 2 study of IMBRUVICA showed promising results. [9]
- Primary CNS lymphoma (PCNSL): PCNSL is a rare form of lymphoma in the central nervous system without evidence of systemic involvement. It comprises approximately 2% of all primary brain tumors. [11] Approximately 80–90% of PCNSL cases are diffuse-large B-cell lymphomas (DLBCL). Several studies have investigated the use of IMBRUVICA alone and in combination with chemotherapy as an option for treating PCNSL. These studies have shown high (and durable) treatment response and tolerability despite a high rate of Aspergillus infections.

It is important to note that the BTK inhibitors, including IMBRUVICA, are increasingly being studied in combination with other treatment options. The attached table sets forth clinical studies listed on clinicaltrials.gov that are currently recruiting patients. The studies examine IMBRUVICA as a treatment for additional oncologic indications and in combination with other treatments. Other BTK inhibitors are currently studied for non-cancer uses, including in treating multiple sclerosis.

We strongly urge CMS to actively monitor the impact that the drug negotiation program has on manufacturer-sponsored studies of existing treatments. The cost/benefit balance for rare cancers is particularly fragile. For patients, competition is both meaningful and beneficial when it results in improved treatments as well as expanding knowledge of how existing treatments can be used – alone and with other therapies. The BTK inhibitor class is an example where we expect that, without pricing intervention, the set of available products and our understanding of their value would evolve over time to the benefit of patients.

References

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2. FDA Expands Approved Use of Imbruvica (ibrutinib) for Waldenström's Macroglobulinemia (drugs.com)
3. 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 (drugs.com)
4. FDA Approves Imbruvica (ibrutinib) for the First-Line Treatment of Chronic Lymphocytic Leukemia (drugs.com)
5. U.S. FDA Approves Imbruvica (ibrutinib) as First Treatment Specifically Indicated for Relapsed/Refractory Marginal Zone Lymphoma (MZL) (drugs.com)
6. FDA Approves Imbruvica (ibrutinib) for Chronic Graft Versus Host Disease (drugs.com)
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10. Dosing & Administration - CLL/SLL | IMBRUVICA® (ibrutinib) HCP (imbruvicahcp.com)
11. Calquence Full Prescribing Information (den8dhaj6zs0e.cloudfront.net)
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Question 28: Therapeutic Impact and Comparative Effectiveness

Because BTK inhibitors are a relatively new class of drugs targeting rare cancers, we are concerned that the drug negotiation program could have an unintended impact on their further research and development. Unless a specific treatment has significant use over a long time period, it is unlikely that generic competition would provide a significant benefit to patients. In fact, the BTK inhibitor class demonstrates the potential for improved, next-generation treatments that create in-class competition based on quality and value to patients; this is of higher value to patients than entry of a generic competitor to the first generation thereapy, IMBRUVICA. Ideally, a competitive landscape pressures innovators to continue studying treatments for new indications as well as their use alone and with other therapies to improve patient outcomes. Cancer patients have experienced improved survival and better quality of life due to expanded uses of treatments as well as expanded treatment offerings within new classes of therapies. We have significant concerns that the drug negotiation program could inject new considerations into both product development and manufacturer interest in label expansions.

We strongly believe that there are insufficient head-to-head studies among the BTK inhibitors to conclusively determine that there is a superior treatment option for all patients. Although clinical guidelines and recommendations have recently recognized that newe. R BTK inhibitors offer fewer side effects and may enable patients to stay on] treatment longer, the drug price negotiation program will, we fear, prioritize negotiated discounted price over therapeutic advantages. The lower the negotiated price, the more likely it will be that patients will have new step therapy protocols driving their treatment and, ultimately, their health outcomes. These utilization management strategies are particularly inappropriate when applied to cancer treatments generally and the BTK inhibitor class specifically. Resistance to subsequent covalent BTK inhibitors can arise through multiple mechanisms, including acquired mutations in BTK at the binding site of covalent BTK inhibitors. This means that a plan-driven decision to treat a

patient with IMBRUVICA, or one of the other BTK inhibitors would, at some point in time, render another covalent BTK inhibitor ineffective. [19] Rare cancer patients generally have few treatment options and any external forces (including drug price) driving choice of therapy could result in patients exhausting all available treatments more quickly than they would if their cancer and overall health status drove treatment decisions.

For patients, the bottom line is that all available treatment options should be listed on Part D plan formularies. In addition, CMS should carefully consider both the high-volume indications and the more rare uses of IMBRUVICA and other drugs selected for this initial year of the drug price negotiation program.

References

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Question 30: Addressing Unmet Medical Needs

- BTK inhibitors have led to improved survival and quality of life for patients. This is, in part, due to the fact that these treatments offer patients the opportunity to avoid receiving their treatment in an infusion center. [20]
- Richter's syndrome (RS) is a very rare and aggressive histologic transformation of CLL that results in a very poor prognosis. Further studies on combinations of BTK inhibitors with other treatments could confirm what small studies have found – that IMBRUVICA plus a PD-1 inhibitor can significantly improve outcomes for these patients.

Attached, please see our table outlining rare cancer studies of IMBRUVICA and other BTK inhibitors and the unmet medical needs the studied treatment addresses.

References

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