Ibrutinib EU Indications Expanded in CLL and Waldenström Macroglobulinemia

The European Commission has expanded the approval of ibrutinib (Imbruvica) to include use in combination with obinutuzumab (Gazyva; EU; Gazyva, US) for adult patients with previously untreated chronic lymphocytic leukemia (CLL), and also in combination with rituximab (Rituxan) for the treatment of adult patients with Waldenström macroglobulinemia (WM).¹

The expanded indications stem from a positive recommendation from the European Medicines Agency's Committee for Medicinal Products for Human Use in June 2018.

“The data supporting both the CLL and WM approvals show significant improvements in progression-free survival with the use of ibrutinib-based therapy versus the standard of care study comparators respectively,” Alessandra Tedeschi, MD, medical director, Department of Hematology, Niguarda Hospital, Milan, Italy, stated in a press release. “These approvals therefore provide healthcare professionals with new chemotherapy-free options for patients with these complex blood cancers.”

The approval for the expanded indication in CLL is based on results of the phase III iLLUMINATE (PCYC1130) study, which showed that the combination led to a 77% reduction in the risk of progression or death versus chlorambucil plus obinutuzumab in patients with CLL or small lymphocytic lymphoma.²

At a median follow-up of 31.3 months, the median progression-free survival (PFS) was not reached (95% CI, 15.1–33.6–not estimable) compared with 19 months (95% CI, 15.1–22.1) for chlorambucil and obinutuzumab (HR, 0.23; 95% CI, 0.15-0.37; P<.0001).

The international, open-label, randomized, phase III iLLUMINATE trial randomized 229 patients 1:1 to receive 420 mg of continuous ibrutinib daily plus 1000 mg of obinutuzumab split on days 1 and 2, and on days 8 and 15 of cycle 1, and day 1 of the subsequent 28-day cycles for 6 cycles; or 0.5 mg/kg of chlorambucil with patients with 17p deletion [del(17p)]/TP53 mutations, 11q deletion [del(11q)], and/or unmutated IGHV disease—rate of undetectable minimal residual disease (uMRD), overall response rate (ORR), overall

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agents that are available?]

My general feeling is that you should use your best drugs upfront, because unfortunately, a large number of patients do not make it to second-line therapy. Especially in ALK-positive disease, CNS metastases tend to be a big deal, and the second- and third-generation agents have a lot more activity in the brain. As such, we would really like to use those agents for those patients upfront.

Q: How do these agents compare with each other in terms of efficacy? [In terms of] the second-generation agents, alectinib has shown efficacy over crizotinib and brigatinib (Alunbrig) has [over crizotinib] as well. Cerititinib (Zykadia) has only been compared with chemotherapy; we don’t have data on that agent versus crizotinib at this point.

Q: Will researchers stop using crizotinib as a comparator arm in future trials now that several agents have been shown to be more effective? That’s a good question. If you have access to these drugs, like in the United States, it’s a different question than if you’re in other countries that don’t have the same access that we do. If you’re developing a new drug for ALK-positive NSCLC, I believe that [the comparator arm] has to at least be one of the second-generation agents. Otherwise, in 3 to 5 years, whenever you get your results, they’ll be dated, and people won’t know how to interpret them. At this point, in order to conduct an effective study, [the investigational agent] will need to be compared with a second-generation agent.

Q: Are there any emerging agents that have shown some promise in this area? [To my knowledge, lorlatinib is the newest third-generation inhibitor. What is [on the horizon] are the drugs that are developed for other [oncogenic rearrangements]. TRK inhibitors, such as entrectinib (Rozlytrek), [might be useful in patients with ALK or ROS1 rearrangements]. What remains to be seen is how those agents fit into the paradigm, because they’re all coming out with data for the different genomic targets.

Q: How do these agents compare with each other in terms of efficacy? [Crizotinib has shown activity, and lorlatinib has certainly shown a lot of exciting activity. Because ALK and ROS1 [alterations] are so similar, a lot of these agents have activity against both. One important point to remember, however, is that alectinib did not have any activity in patients with ROS1-positive disease. Therefore, when you’re thinking about what to give those patients, don’t consider alectinib.

Of course, some of the TKIs are exciting. Repotrectinib (TPX-0005) was just presented at the 2019 ASCO Annual Meeting and showed very exciting activity, including in patients who had resistance mutations to other drugs, including the G2032R [resistance] mutation; this is kind of the gatekeeper of mutations. That’s exciting. With ALK and ROS1, it’s almost less exciting to see what the new [next]-generation agent is than it is to see if there are new agents that can overcome the resistance mechanisms and extend PFS. [This area] is starting to mimic the world of EGFR with osimertinib (Tagrisso).

Q: Are there any combination strategies under investigation? There is a lot of excitement on the immunotherapy end. Unfortunately, toxicity is a big concern when combining immunotherapy agents with TKIs. Therefore, at this point, I’m not sure of any combinations that have proven effective. I know in the EGFR-positive space, VEGF inhibitors combined with TKIs are showing promise, but I believe more work needs to be done in this field for the treatment of these patients.

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survival (OS), infusion-related reactions (IRRs), and safety. Patients who progressed on chlorambucil/obinutzumab, determined by IRC, were permitted to cross over to second-line therapy with single-agent ibrutinib.

To be eligible for enrollment, treatment-naïve patients were ≥65 or <65 years of age with a Cumulative Illness Rating Scale (CIRS) score ≥6, creatinine clearance (CrCl) <70 mL/min, and/or del(17p) or TP53 mutation. The median age was 71 years (range, 40-87) and 65% of patients had high-risk genomic features. Fifty-two percent of patients overall had either Rai III or IV disease, while bulky disease was in 27% of ibrutinib-treated patients and 38% of patients who received chlorambucil therapy.

In the ibrutinib cohort, 62% of patients had unmutated IGHV disease, 12% had del(11q), and 16% had del(17p) and/or TP53 mutations. In the chlorambucil/obinutzumab arm, 53% of patients had unmutated IGHV disease, 19% had del(11q), and 20% had del(17p) and/or TP53-mutant disease. Thirty-three percent of patients in the ibrutinib cohort had a CIRS score >6 versus 31% of those treated with chemoimmunotherapy; 23% in the ibrutinib arm had CrCl <60 mL/min compared with 33% of those who received chlorambucil.

Moreover, patients with high-risk disease—which includes those with 17p deletion/TP53 mutation, 11q deletion, or unmutated IGHV—who were treated with the ibrutinib combination experienced an 85% reduction in the risk of progression or death (HR, 0.15; 95% CI, 0.09-0.27). The IRC-evaluated overall response rate (ORR) was 89% in ibrutinib/obinutzumab arm versus 73% in the chlorambucil/obinutzumab arm. OS had not yet been reached in either arm (HR, 0.92; 95% CI, 0.48-1.72; P = .81). Forty-six patients (40%) on the chlorambucil arm have crossed over to treatment with ibrutinib monotherapy, Moreno added.

Ibrutinib/obinutzumab also led to an improvement in ORR and complete response (CR) or CR with incomplete bone marrow recovery (CRI) rate when assessed by IRC and investigator assessment. In the IRC assessment, the ORR and CR/CRI rates were 88% and 19% with ibrutinib/obinutzumab versus 73% and 8% with chlorambucil/obinutzumab, respectively. The ORR and CR/CRI rates via investigator assessment was 91% and 41% versus 81% and 16%, respectively.

The combination of ibrutinib and obinutzumab for the first-line treatment of patients with CLL or small lymphocytic lymphoma, also based on the iLLUMINATE data, was approved by the FDA in January 2019.

For the recommendation in the WM indication, the approval was based on data from the phase III iNNOVATE (PCYC-1127) trial, which showed that the combination had an estimated 30-month PFS rate, which was assessed by an IRC, of 79% compared with 41% for those who received rituximab/placebo in patients with
Sustained increases in hemoglobin level arm remained on treatment at the data cutoff. 72% versus 32%, respectively (P <.0001). The median time to next treatment was not reached for the ibrutinib arm versus 18 months for the control arm (HR, 0.096; P <.0001).

The OS rate at 30 months was 94% versus 92%, in the combination versus control arms, respectively. Dimopoulos noted that 30 patients in the control arm crossed over to receive single-agent ibrutinib.

The FDA approved this combination as a treatment option across all lines of therapy for patients with WM in August 2018.

With five European Commission approvals in 5 years, this latest [European Commission] decision further extends the potential reach and impact ibrutinib can have for patients,” said Craig Tendler, MD, vice president, Clinical Development and Global Medical Affairs, Oncology, Janssen Research & Development, LLC. “We remain committed to a comprehensive clinical development program for ibrutinib, including exploring its use in other combinations, to address the needs of more and more patients with B-cell malignancies.”

REFERENCES


Genomic Assays Answer Adjuvant Questions in Early-Stage Breast Cancer

Mohammad Razaq, MD

Questions on how to best use adjuvant chemotherapy and endocrine therapy, plus the need for extended endocrine therapy in women with early-stage hormone receptor (HR)-positive, HER2-negative breast cancer, have only been partly answered.

Despite trials showing a benefit to more intensive therapy in women of high clinical risk, and the utility of genomic assays, experts in the space continue to grapple with these queries, explained Alan B. Astrow, MD.

“We want to minimize the risk of recurrences, but we also want to minimize the risk of adverse events (AEs) from the medications,” said Astrow, a professor of medicine at Weill Cornell Medicine, and chief of hematology and medical oncology at New York Methodist Hospital.

In an interview during the 2019 OncLive® State of the Science Summit™ on Breast Cancer, Astrow discussed the latest efforts to personalize patient care in early-stage, HR-positive, HER2-negative breast cancer.

Q: OncLive®: Could you discuss the management of patients with early-stage, HR-positive, HER2-negative breast cancer?

Astrow: I focused on two issues in this area. Specifically, [I discussed] how long women need to be on adjuvant hormonal therapy. Is 5 years enough or should it be 7.5 years? Do women need 10 or more years of adjuvant therapy?

I also discussed whether there are new tests available that might help inform that decision. Additionally, [I covered] whether there is any new information that would help us decide if younger women with HR-positive, node-negative breast cancer who have an intermediate-risk Oncotype DX score—specifically, women under the age of 50, with an Oncotype DX score between 11 and 25—need chemotherapy plus (Continued on page 4)
Could you discuss the need for adjuvant therapy and the incremental benefit of adding 2.5 years and 5 years of therapy?

It’s been known for a long time that women who are going to receive adjuvant hormonal therapy require at least 5 years of treatment. The standard for many years was 5 years of tamoxifen, which is the oldest of our antiestrogen treatments. Until recently, 5 years was thought to be the right length of therapy. About 10 years ago, perhaps a little longer, we received additional information from the ATLAS trial, which showed that 10 years of tamoxifen was better for women. Patients who received 10 years of therapy had fewer recurrences compared with those who received 5 years. That’s an important piece of information.

We’ve learned that the difference between 10 years and 5 years is modest. It may be that some women need the longer length of treatment, but not all. There has been an effort to find a marker that might predict who really needs 10 years of therapy compared with 5 years.

The second issue that I discussed was how long women need to be on an aromatase inhibitor (AI) for. We learned that many women experience a better outcome with an AI than they do with tamoxifen. There was an important trial called the MA.17 trial where women who had received tamoxifen for 5 years were randomized to receive letrozole versus placebo. Those who received letrozole for 5 years had fewer recurrences than those who received placebo.

The question was whether patients needed another 5 years of therapy or whether 2.5 years would be enough. The data indicate that 10 years of an AI is the maximum amount of time we want to recommend [this treatment] for any woman. Once patients finish 5 years, the incremental benefit of continuing therapy is modest.

Moreover, there are toxicities. It becomes a discussion between the doctor and the patient about the relative benefits and risks of extending AI therapy. In terms of toxicities, women complain of pains in their muscles and joints, hot flashes, and vaginal dryness; some women also complain of fatigue. AIs can also lead to increased risk for osteoporosis and potential fractures. The longer a patient is on one of these agents, the greater the risk of one of those AEs happening. In fact, these studies point to compliance issues. Many women who were on the longer course of AI treatment stopped therapy before they completed the 5-year course.

For many node-negative patients, 5 years of an AI is adequate. Some may even find that if they’ve received 2.5 to 5 years of tamoxifen, 2.5 years of an AI may be adequate. It’s really the node-positive women who appear to have the most benefit from a longer course of AIs, and that is consistent with recent ASCO guidelines.

Could you discuss the findings from the Trans-aTTom trial?

The Trans-aTTom trial shows that women with a high Breast Cancer Index (BCI) benefit from a long course of tamoxifen. Of course, this conclusion comes from a planned analysis, but it’s retrospective. It’s an intriguing result, but it has to be considered in the context of other trials, which should become available soon. There are other assays that compete with the BCI, such as the EndoPredict assay. We’ll have to see how that plays out. It may turn out to be a test that is used in standard practice. I would note that in the Trans-aTTom trial, investigators only reported on node-positive patients. It would be node-positive patients for whom you might consider ordering the BCI. However, this is not quite ready for standard practice.

I also reviewed the presentation given by Joseph A. Sparano, MD, of Albert Einstein College of Medicine, at the 2019 ASCO Annual Meeting. In his talk, Sparano explained the addition of clinical parameters to the genomic results regarding the Oncotype DX assay. I listened carefully to Dr Sparano’s talk at the meeting, and I’ve read the paper that has been published in the New England Journal of Medicine. I listened to his presentation again online, and I’ve also listened to other peoples’ takes on that presentation. It’s not the easiest study to follow. We know from the TAILORx results that chemotherapy does not add benefit to hormonal therapy for women over age 50 with an Oncotype DX recurrence score of 25 or less. The question was on women younger than the age of 50 and whether they benefit from the addition of chemotherapy if they have an Oncotype DX score between 11 and 25. The paper showed that patients with a score between 15 and 20 had, roughly, a 2% benefit with the addition of chemotherapy. Those whose scores fell between 21 and 25 had a 7% benefit to chemotherapy plus endocrine therapy versus endocrine therapy alone. Therefore, we were not quite sure what to do with those women, primarily those who had a Oncotype DX score between 15 and 25.

In the presentation at the 2019 ASCO Annual Meeting, investigators showed that in women with a score between 15 and 25 who were younger than age 40, there doesn’t appear to be a benefit to chemotherapy and endocrine therapy versus endocrine therapy alone. The women in whom [that combined approach] is beneficial are those between 40 and 50 years of age.

Sparano suggested that chemotherapy does not generally induce permanent menopause in women who are 40 years or younger. However, those between 40 and 50 years—particularly between 45 and 50 years—are more likely to be put into permanent menopause by adding chemotherapy to endocrine therapy. The hypothesis is that most of the benefit we’re seeing in women age 50 or younger with an intermediate-risk Oncotype DX score is coming from ovarian suppression. Perhaps a woman who is 45 years old with an Oncotype DX score of 23 might not necessarily need chemotherapy. The hypothesis is that ovarian suppression provides the same benefit as chemotherapy does for that group of women. The argument was not that easy to follow at the 2019 ASCO Annual Meeting, but that’s the claim. It’s a hypothesis, but it’s a very plausible hypothesis.

Although there were no presentations for the MammaPrint assay at the 2019 ASCO Annual Meeting, it’s a good assay as well. It, too, is indicated in the ASCO guidelines for women who are of high clinical risk and in whom we’re trying to decide whether or not chemotherapy is needed. These would be women with 1 to 3 positive nodes, grade 3 estrogen receptor (ER)-positive cancer, or large ER-positive cancers. It is plausible to use less often in this country than Oncotype DX. MammaPrint has caught on a little bit more in Europe.

Could you discuss the findings from the Trans-aTTom trial?

You have to be familiar with the data. Beyond that, you have to know your patient and discuss the information with them to try to jointly come up with a plan that’s best for each individual patient.