

Rapid Advances in ALK+ and ROS1+ NSCLC Bring Forth New Challenges



Conor E. Steuer, MD

The treatment of patients with non-small cell lung cancer (NSCLC) who have oncogenic rearrangements, such as ALK or ROS1, has rapidly advanced in recent years with the rise of second- and third-generation inhibitors, said

Conor E. Steuer, MD. However, with that progress, sequencing questions have emerged as well as the challenge of acquired resistance.

“Both ALK and ROS1 [alterations] represent some of the great advancements in NSCLC treatment over the past decade or so, as they are now two of the FDA-recommended genomic alterations to test for as well as treat,” added Steuer. “The field is rapidly moving, starting with the FDA approval of crizotinib (Xalkori) to third-generation agents that are now approved.”

In an interview during the 2019 *OncLive*® State of the Science Summit™ on Non-Small

Cell Lung Cancer, Steuer, assistant professor in the Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, discussed emerging agents in the treatment of patients with ALK- or ROS1-positive NSCLC and the sequencing challenges that have resulted in the space.

Q: *OncLive*®: What recent advances have been made in ALK- and ROS1-positive NSCLC?

Steuer: ALK is a fusion protein that is formed in combination with EML4 and is found in about 3% to 7% of patients. Some of the questions that are arising are, “How do you choose between these agents?” There are also questions in terms of sequencing. Patients with ALK-positive disease have a tendency to develop brain metastases, which is a very concerning symptom.

What’s the best way to approach this with newer agents that have good central nervous system (CNS) penetration? ROS1 is less common than ALK; it’s found in about 1% of patients. Currently,

there is 1

FDA-approved agent—crizo-

tinib. However, many other agents have shown excellent efficacy and new data [with these agents were] just presented at the 2019 ASCO Annual Meeting. Another question that will arise again has to do with resistance mutations is, “how do we best overcome them and give the best options to our patients?”

Q: In terms of sequencing, what factors do you take into consideration?

If I can get 10 months out of crizotinib, then another 10 to 15 months out of alectinib (Alecensa) in the second-line setting, and then maybe use lorlatinib (Lorbrena), [I’m wondering whether I] should do that? Or, should I just use alectinib and maybe get an increased progression-free survival (PFS) and then [use a] third-generation agent? How do I best use [the

(Continued on page 2)

IN THIS ISSUE

Rapid Advances in ALK+ and ROS1+ NSCLC Bring Forth New Challenges (Page 1)

Ibrutinib EU Indications Expanded in CLL and Waldenstrom Macroglobulinemia (Page 2)

Genomic Assays Answer Adjuvant Questions in Early-Stage Breast Cancer (Page 3)

Ibrutinib EU Indications Expanded in CLL and Waldenstrom Macroglobulinemia

The European Commission has expanded the approval of ibrutinib (Imbruvica) to include use in combination with obinutuzumab (Gazyvaro, 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 patients with CLL or small lymphocytic lymphoma.^{2,3} At a median follow-up of 31.3 months, the median progression-free survival (PFS) was not reached (95% CI, 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 on days 1 and 15 of each 28-day cycle for 6 cycles plus the obinutuzumab regimen.

The primary endpoint was PFS as assessed by an Independent Review Committee (IRC); secondary endpoints were PFS in a high-risk patient population—those 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

(Continued on page 2)

To learn more, please visit:

OncLive.com

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. Ceritinib (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. ■

survival (OS), infusion-related reactions (IRRs), and safety. Patients who progressed on chlorambucil/obinutuzumab, 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/obinutuzumab 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/obinutuzumab arm versus 73% in the chlorambucil/obinutuzumab 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/obinutuzumab 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 investi-

gator assessment. In the IRC assessment, the ORR and CR/CRi rates were 88% and 19% with ibrutinib/obinutuzumab versus 73% and 8% with chlorambucil/obinutuzumab, respectively. The ORR and CR/CRi rates via investigator assessment were 91% and 41% versus 81% and 16%, respectively.

In the high-risk population, the IRC-assessed ORR rates with ibrutinib/obinutuzumab and chlorambucil/obinutuzumab were 90% and 68%, respectively; the CR/CRi rates were 14% and 4%.

The combination of ibrutinib and obinutuzumab 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 iNOVATE (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

previously untreated and relapsed/refractory WM, at a median follow-up of 30.4 months.^{4,5}

The double-blind, placebo-controlled, parallel assignment, randomized phase III iNNOVATE trial included 150 relapsed/refractory or treatment-naïve patients with confirmed symptomatic Waldenström macroglobulinemia. Patients were enrolled at 45 sites in 9 countries between July 2014 and January 2016.

The median patient age was 69 and 33% were aged ≥ 75 years. Forty-five percent of patients had not received prior therapy. Thirty-eight percent were considered high risk per the International Prognostic Scoring System for Waldenström Macroglobulinemia, and 79% of patients had extramedullary disease at baseline. Among 136 patients with available baseline mutational data, 85% had MYD88L265P mutations and 36% had CXCR4WHIM mutations.

The median number of prior therapies in patients with relapsed disease was 2 (range, 1-6), and 85% had prior rituximab. Patients who had prior rituximab had to have achieved at least a minimal response to their last rituximab-based treatment.

Patients received IV rituximab at 375 mg/m² once weekly for 4 straight weeks, followed by another 4-week rituximab course after a 3-month interval. Ibrutinib, at 420 mg, or placebo were taken once daily continuously. PFS was the primary endpoint, with secondary endpoints including ORR, hematological improvement measured by hemoglobin, time-to-next treatment, OS, and safety.

The PFS benefit with the combination was observed across key subgroups, including previously untreated patients (HR, 0.34; 95% CI, 0.12-0.95), relapsed patients (HR, 0.17; 95% CI, 0.08-0.36), MYD88L265P/CXCR4-mutation wild-type (WT; HR, 0.17; 95% CI, 0.06-0.49), MYD88L265P/CXCR4WHIM (HR, 0.24; 95% CI, 0.09-0.66), and MYD88WT/CXCR4-mutation WT (HR, 0.21; 95% CI, 0.04-1.08).

The 24-month PFS rate in treatment-naïve patients was 84% in the experimental arm versus 59% in the control arm. In relapsed patients, the 30-month PFS rates were 80% vs 22%, respectively.

In the overall population, the ORR was 92% with the ibrutinib combination versus 47% with rituximab alone ($P < .0001$). The major response rate (at least a partial response) was 72% versus 32%, respectively ($P < .0001$).

Three-fourths of patients in the combination arm remained on treatment at the data cutoff. Sustained increases in hemoglobin level

occurred in 73% of the ibrutinib/rituximab group versus 41% of the rituximab-alone arm ($P < .0001$). 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

1. Janssen Announces European Commission Approval of Imbruvica (ibrutinib) for Expanded Use in Two Indications. Janssen. Published August 13, 2019. <https://yhoo.it/2yUYabx>. Accessed August 13, 2019.
2. Moreno C, Greil R, Demirkan F, et al. Ibrutinib + obinutuzumab versus chlorambucil + obinutuzumab as first-line treatment in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL): results from phase 3 iLLUMINATE. Presented at: 2018 ASH Annual Meeting; December 1 to 4, 2018; San Diego, California. Abstract 691.
3. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicenter, randomized, open-label, phase 3 trial [published online ahead of print, December 3, 2018]. *Lancet Oncol*. doi: 10.1016/S1470-2045(18)30788-5.
4. Dimopoulos MA, Tedeschi A, Trotman J, et al. Randomized phase 3 trial of ibrutinib/rituximab vs placebo/rituximab in Waldenström's macroglobulinemia. *J Clin Oncol*. 2018;36 (suppl; abstr 8003).
5. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in Waldenström's macroglobulinemia [published online June 1, 2018]. *N Engl J Med*. doi: 10.1056/NEJMoa1802917.

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)

hormonal therapy or if hormonal therapy alone is adequate.

Q: 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.17R 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 next 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 com-

pliance 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.

Q: 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. I'd say MammaPrint tends to be used less often in this country than Oncotype DX. MammaPrint has caught on a little bit more in Europe.

Q: 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. ■

To learn more, please visit:

OncLive.com