Moving Curative Therapies Forward in Hematologic Malignancies

WITH ELIAS JABBOUR, MD

PEER EXCHANGE
Panel Unpacks Sequencing Strategies in Metastatic CRC

OncPathways
MET Inhibitors Find Their Niche in NSCLC

AACR CONFERENCE HIGHLIGHTS
Updates on Genomic Markers in SOLID TUMORS, Novel Approaches to iNHL

THORACIC NIGHT LIVE
Experts Break Down Exciting Personalized Breakthroughs for NSCLC

CLINICAL TRIAL IN FOCUS
Rachel R. Grisham, MD, Discusses Developments in KRAS-Mutant OVARIAN CANCER

CLINICAL PERSPECTIVES
Gene Signatures Guide De-escalation Approaches in HER2+ BREAST CANCER

UNIVERSITY OF CHICAGO MEDICINE COMPREHENSIVE CANCER CENTER
TERAVOLT Registry Data Guide Future of Lung Cancer Care
With Marina Chiara Garassino, MD
In ER+/HER2- metastatic breast cancer (mBC)

Can improving ER antagonism and degradation unlock a brighter future?

Complex mechanisms of estrogen receptor (ER) signaling have been associated with tumor growth.¹⁻³
In ER+/HER2– mBC, the ER pathways are involved in tumor progression and treatment escape mechanisms that enable endocrine resistance.\textsuperscript{1,2,4,5}

\textbf{To strengthen the fight against resistance, could advancements in ER antagonism and degradation help decrease the ER pathway’s downstream effects?}

\textsuperscript{HER2=human epidermal growth factor receptor 2.}


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Strategic Alliance Partnership

Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 54.
Elias Jabbour, MD, has been at the forefront of investigative efforts aimed at transforming care for patients with hematologic malignancies. As cochair of the 5th Annual Live Medical Crossfire®: Hematologic Malignancies, a live, interactive, virtual webcast sponsored by Physicians’ Education Resource®, LLC (PER®), Jabbour aims to help distill the latest research into best clinical practices to further advance the treatment paradigm for patients with these cancers.

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Clinical Perspectives
Immune-Related Gene Signatures May Guide De-escalation Approaches in HER2+ Breast Cancer

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OncClub brings the global oncology community together to spotlight innovative research efforts that seek to move the needle forward in cancer care.

Spotlight research efforts that have recently published or are anticipated to be published in an academic journal

Share efforts with your colleagues to promote awareness on important areas of active investigation

Generate conversation around pivotal data in the field and how to best apply lessons learned to clinical practice

Did you participate on a trial that is trending on Twitter?

Boost awareness and facilitate pivotal discussions with your colleagues around the world by joining OncClub.

Scan the code to learn more!

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- Highly visible exposure of the published data
- Supplementary Q&A on interview with fellow study authors/colleagues
- Featured spots on OncLive® TV
- Potential podcast episode highlighting your work
- Potential Twitter takeover to host a live Q&A on research

For more information on OncClub, please contact:

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Chairman’s Letter

The Future of Care Relies on Translation

INNOVATION AND COLLABORATION ARE 2 of the driving forces behind the rapid improvements in oncology care, especially over the past year. Although connections were limited to video conference calls rather than in-person meetings, the dissemination of information, including the latest data reported out from clinical studies, has not slowed down.

Over 2 weeks, the American Association for Cancer Research Virtual Annual Meeting 2021, showcased abstracts involving pivotal data from ongoing studies across malignancies. Our conference highlights section shines a light in particular on hematologic advances for patients with indolent non-Hodgkin lymphoma. Data from the phase 3 CHRONOS-3 study (NCT02367040) showed that patients treated with copanlisib (Aliqopa) and rituximab (Rituxan) had a median progression-free survival of 21.5 months (95% CI, 17.8-33.0) compared with 13.8 months (95% CI, 10.2-17.5) with rituximab/placebo (HR, 0.520; 95% CI, 0.393-0.688; \( P < .0001 \)).

These data, although impressive, are just the tip of the iceberg for hematologists and oncologists as their significance depends on their successful translation into clinical practice. Ancillary meetings and programs held around major conferences are critical to ensure that investigators and their peers are not only armed with the latest findings, but also have explored and debated alternative options through roundtable case discussions.

Elias Jabbour, MD, highlights the importance of these meetings, such as the 5th Annual Live Medical Crossfire®: Hematologic Malignancies, sponsored by Physicians’ Education Resource®, LLC (PER®), of which he is the cochair. The 1-day meeting, which will air as a live, interactive webcast on July 17, will distill the most controversial clinical issues and new findings in the field of hematologic malignancies, such as those from CHRONOS-3, through panel discussions with renowned experts.

“It’s not a meeting where people will come and listen all day long. It’s more practical: What did I learn today, and how I can treat my patient better tomorrow if I see him in the clinic?” Jabbour said in an interview.

In addition to live meetings, OncLive®’s robust video programs, including Peer Exchange, The Talk, Rapid Readouts, and Insights, provide a platform for experts to debate and clarify the latest information and provide their perspectives on how to translate these data from bench to bedside. The latest addition to the OncLive® offerings is Thoracic Night Live, a video program that spotlights the most noteworthy topics and pivotal studies in lung cancer that have been discussed at medical meetings throughout the year.

In this issue, Nicholas C. Rohs, MD; Isabel Preeshagul, DO, MBS; and Joshua K. Sabari, MD, break down the topline precision medicine data from the 2020 World Conference on Lung Cancer for patients with non-small cell lung cancer harboring \( HER2 \), \( EGFR \), \( KRAS \), or \( MET \) mutations.

For coverage of the latest clinical data from key opinion leaders in the field, visit onclive.com and follow OncLive® on Twitter at @OncLive. To find more information, register, and explore PER®’s extensive selection of hybrid collaborative offerings, visit gotoper.com.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCE

ONE KEY **MAY NOT FIT EVERY LOCK**

TECENTRIQ aims to unlock options for your patients

Learn about our approvals at

[TECENTRIQ-HCP.com/Unlock]
THE PRECISION MEDICINE REVOLUTION has become a major component of cancer treatment. Multiple FDA approvals and an increasing number of clinical trials examining molecular target-based therapeutics, including second- or even third-generation drugs against a well-defined target, present an ever-widening array of drugs for routine cancer care based on the discovery of specific molecular targets within the tumor (somatic abnormalities) or within the germline.

Further, recent regulatory approvals have been granted for precision medicine-based drug delivery agnostic to the cancer’s site of origin. Reasonable use of the particular antineoplastic requires the documented presence of the specific molecular target. Examples include a level of mutations within tumors cells to suggest the potential benefits of checkpoint inhibitors and the presence of a microsatellite unstable molecular signature to similarly suggest the potential benefits of this class of immunotherapeutic drugs. Whereas the current effect of the precision medicine revolution has been argued by some to be excessively hyped, others have provided strong arguments against this conclusion.

However, the promise of precision medicine at the individual patient and physician level cannot be assumed to follow regulatory decisions. Rather, it falls to the drug manufacturers to market the use of targeted therapeutics in specific clinical settings and to molecular diagnostic companies to advertise approvals of their platforms by the FDA as options for tumor agnostic approaches to disease management.

A potential magnitude of disassociation may exist between clinical trial data, regulatory approval, and medical society or insurance company pathway recommendations for obtaining molecular information essential to deliver a targeted therapeutic and the “real world” of community oncology care in the United States. This was highlighted in a recent report that examined medical records of women with ovarian cancer and the percentage of whom had undergone germline testing for the presence of a BRCA mutation. Results of clinical germline testing for patients in Georgia and California were linked with Surveillance, Epidemiology, and End Results data for individuals who received a diagnosis of breast or ovarian cancer from 2013 to 2017. Only 34.3% of 14,689 patients with ovarian cancer had undergone germline testing.

This rather distressing result occurred despite the fact that multiple national medical organizations and widely accepted medical pathways have, for a number of years, strongly recommended that this information be obtained to evaluate the potential risk of breast and ovarian cancer in family members of patients with a diagnosis of cancer. A low rate of germline testing is also increasingly being seen in patients with prostate and pancreatic cancer. Further, where appropriate, prophylactic surgical procedures (eg, bilateral oophorectomy, mastectomy) have been shown to reduce the risk of subsequent malignancies in BRCA mutation carriers.

Finally, recently reported phase 3 trial results have demonstrated the major benefits associated with the delivery of PARP inhibitors as a maintenance therapy approach in women with ovarian cancer who are BRCA mutation positive. Despite the extensive evidence of the clinical utility associated with obtaining this specific germline (and somatic) mutation data, there is an evident strong disassociation between what is clearly optimal care and the reality of real-world clinical oncology.

A number of possible reasons can be cited for these disquieting results, beginning with the observation that the speed of changes in our understanding of the biology of individual cancers and the corresponding modification in our therapeutic armamentarium continues to rapidly accelerate. This state of affairs makes it increasingly difficult for non-tumor-specific oncology...
From the Editor

specialists to stay up-to-date with the spectrum of multiple modifications in disease management. The academic oncologist who specializes in understanding the biology and treatment of a single cancer (eg, breast cancer) or group of malignancies (eg, gynecologic cancers) or a member of a large community oncology practice who may have a similar opportunity to focus on a limited set of diseases will almost certainly be in a superior position to deal with these rapidly expanding changes.

However, for the generalist who may routinely be responsible for the care of multiple cancer types in any given day, the ability to keep up with the changes in treatment, particularly new molecularly-based therapeutic options, may be daunting.

Although oncologists will certainly never intentionally deny their patients the best possible care they can provide, the outcome may be the same if they are not aware of new developments, they do not have the time to be regularly updated, or they do not have accessible, robust decision-support tools that may help them apply best practice in a given clinical situation.

When considering the decision to employ a precision medicine approach, it is necessary to highlight the fact this increasingly requires next-generation sequencing rather than a single test of a specific molecular abnormality. There are additional issues to consider with the implementation of this expanded molecular testing strategy.

There are many questions that should be asked. Which testing platform among the many available will be optimal in a given practice? Will insurance pay for such testing? How easy is it to interpret the results reported? What decision-support tools are provided by the company to assist the clinician? How realistically available (eg, geographical location, eligibility criteria) to an individual clinician and patient are clinical trials that may be suggested by the molecular results?

Further complicating the issue of testing is a situation where the results indicate that the off-label use of an existing commercially available antineoplastic could be useful. How does the physician obtain insurance company approval or possible compassionate use of the drug by obtaining it from the manufacturer? If an oncology practice has no or limited experience in this area, the learning curve, as well as time and effort required for an individual agent, can potentially be a significant impediment. Again, it is not the lack of desire by the physician to help the patient but instead objectively pragmatic concerns for how to deal with an often complex and ill-defined bureaucracy.

And if the physician is unsuccessful in securing a potentially promising drug, it is not difficult to imagine the effect of that disappointment on the patient and the patient’s health care team.

REFERENCES
Infirgratinib Gets Go Ahead in Cholangiocarcinoma

The FDA has granted accelerated approval to infirgratinib (Truseltiq) for patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring an FGFR2 fusion or rearrangement.

The agency based its decision on data from a phase 2, single arm trial (NCT02150967) of patients with advanced cholangiocarcinoma who had received at least 1 prior treatment. Results from the trial showed that infirgratinib, an ATP-competitive, FGFR1-3 tyrosine kinase inhibitor, elicited a confirmed objective response rate of 23% (95% CI, 16%-32%) in 108 patients. Responses comprised 1 complete response and 24 partial responses. The median duration of response with the agent was 5.0 months (95% CI, 3.7-9.3). Eight patients maintained a response for at least 6 months; 1 patient had a response of at least 12 months.

Additional data presented during the 2021 Gastrointestinal Cancers Symposium showed that 66 patients achieved disease stability. The median progression-free survival was 7.3 months (95% CI, 5.6-7.6), with a 4-month progression-free survival rate of 35%. The median overall survival in these patients was 12.2 months (95% CI, 10.7-14.9).

Sotorasib Enters Treatment Landscape for NSCLC With KRAS G12C Mutations

Sotorasib (Lumakras), a novel treatment for adult patients with non–small cell lung cancer (NSCLC) whose tumors harbor KRAS G12C mutations, has received accelerated approval.

Specifically, the FDA approved the indication for the RAS inhibitor for patients who have received at least 1 prior systemic therapy.

The regulatory agency also approved 2 companion diagnostics: the QIAGEN therascreen KRAS QRG PCR kit for tissue analysis and the Guardant360 CDx assay for plasma samples. Of note, the FDA specifies that if no mutation is detected in a plasma specimen, the tumor tissue should be tested.

The approval was based on data from 124 patients enrolled in the phase 1/2 CodeBreak 100 trial (NCT03600883). The objective response rate was 36% (95% CI, 28%-45%) with a complete response rate of 2% and a partial response rate of 35%. The median duration of response was 10 months (range, 1.3-11.1) and 58% of patients had a response lasting at least 6 months. The disease control rate achieved with sotorasib was 81% (95% CI, 73%-87%).

Subcutaneous Depot Formulation of Leuprolide Mesylate Adds Option for Advanced Prostate Cancer

The FDA has approved a 6-month subcutaneous depot formulation of leuprolide mesylate (Camcevi) as a ready-to-use treatment for patients with advanced prostate cancer.

The agency based its decision on data from a phase 3 study (NCT02234115) of 137 patients with advanced prostate cancer who received the agent via a 42-mg injection every 6 months. Data showed that 97% of study participants achieved the primary end point of suppression of serum testosterone (≤ 50 ng/dL) by day 28. The mean testosterone concentration was suppressed below castrate levels to 17.6 ng/dL on day 28. Further, by the end of the study, 95.9% of the study participants had a serum testosterone level of 20 ng/dL or lower.

Leuprolide mesylate, a gonadotropin-releasing hormone, resulted in a significant reduction in prostate-specific antigen levels following the first injection; the decline lasted until the end of the study.

Amivantamab Expands Treatment Options for EGFR+ NSCLC

The FDA granted accelerated approval to amivantamab-vmjw (Rybrevant) for adult patients with non–small cell lung cancer (NSCLC) who harbor EGFR exon 20 insertion mutations and whose disease has progressed on or following platinum-based chemotherapy. The Guardant360 CDx liquid biopsy assay also received approval as a companion diagnostic for the agent.

The approval of the bispecific antibody was based on data from 81 patients enrolled in the phase 1 CHRYSLALIS trial (NCT02609776). Results showed that amivantamab elicited an overall response rate of 40% (95% CI, 29%-51%) comprising a complete response rate of 3.7% and a partial response rate of 36%. The median duration of response was 11.1 months (95% CI, 6.9-not estimable) and 63% of patients had a response lasting at least 6 months.

Of particular interest, investigators reported interstitial lung disease (ILD) in 13.7% of patients treated with amivantamab, with 0.7% experiencing grade 3 ILD. Three patients discontinued treatment because of ILD. If ILD is suspected, the FDA recommends the immediate withholding of amivantamab and permanent discontinuation if confirmed.

Adjuvant Nivolumab Advances Care for Resected Esophageal or GEJ Cancer

The FDA has approved nivolumab (Opdivo) for the adjuvant treatment of patients with completely resected esophageal or gastroesophageal junction (GEJ) cancer with residual pathologic disease who have received neoadjuvant chemoradiation therapy. Resection parameters were defined as those patients with negative margins.

Results from the phase 3 CheckMate 577 trial (NCT02743494), which led to the FDA approval, showed that the PD-1–blocking antibody doubled the median disease-free survival compared with placebo, at 22.4 months (95% CI, 16.6-34.0) vs 11.0 months (95% CI, 8.3-14.3), respectively. Nivolumab also achieved a 31% reduction in the risk of disease recurrence or death vs placebo (HR, 0.69; 95% CI, 0.56-0.85; P = .0003). Of note, investigators observed a disease-free survival benefit regardless of tumor PD-L1 expression and histology.

The median duration of treatment in the investigative arm was 10.1 months (range, < 0.1-14) compared with 9.0 months (< 0.1-15) in the placebo arm. For the 532 patients treated with nivolumab, 61% were exposed for more than 6 months and 54% were exposed for more than 9 months.

The median disease-free survival for patients treated with nivolumab was 22.4 months (95% CI, 16.6-34.0) vs 11 months (95% CI, 8.3-14.3) with placebo (HR, 0.69; 95% CI, 0.56-0.85; P = .0003).
Nominate a dedicated and deserving nurse to be an Oncology Nurse Champion!

Do you know a nurse who goes above and beyond to make a measurable difference to improve patient outcomes through exceptional supportive care?

We are now accepting nominations from health care professionals, colleagues, patients, friends, and family of outstanding nurses who demonstrate these admirable qualities:

• Ability to help educate both patients and families about the cancer they face and their treatment path
• Knack for showing kindness, patience, and compassion in the face of difficulties faced by their patients
• Understanding of the science and how treatments are designed to overcome their patient’s cancer
• Aptitude to go above and beyond in Supportive Care for Patients and Patient Families

Scan the code to nominate a nurse to become an Oncology Nurse Champion!
**Drug Spotlight | AXICABTAGENE CILOLEUCEL (YESCARTA)**

**Axi-cel Elicits Durable Response in Relapsed/Refractory FL**

*by KYLE DOHERTY*

AXICABTAGENE CILOLEUCEL (YESCARTA; AXI-CEL), a CD19-directed CAR T-cell therapy, showed promising efficacy data and a favorable safety profile in adult patients with relapsed or refractory follicular lymphoma (FL), according to data from the phase 2 ZUMA-5 trial (NCT03105336).

On March 5, 2021, the FDA granted accelerated approval to axi-cel for adult patients with relapsed/refractory FL after 2 or more lines of systemic therapy. Results from ZUMA-5 showed that axi-cel elicited an objective response rate (ORR) of 91% (95% CI, 83%-96%) among 81 patients in the primary efficacy analysis, 60% (95% CI, 49%-71%) of whom had complete remission (CR). The median duration of response (DOR) was not reached and the median time to response was 1 month.1,2

In an interview with OncologyLive®, Henry Chi Hang Fung, MD, chair of the Department of Bone Marrow Transplant and Cellular Therapies at Fox Chase Cancer Center in Philadelphia, Pennsylvania, discussed how the durable response of axi-cel fills an unmet need for this patient population and the potentially exciting future of the therapy.

**Q Please provide an overview of the patient population in the ZUMA-5 trial.**

[Patients in ZUMA-5 had] relapsed/refractory indolent lymphoma, including FL and marginal zone lymphoma [MZL]. Approximately three-quarters of these patients had FL and [the remaining] patients had MZL. The median age was 61 years old, so a bit of a younger population. Most had advanced disease. Approximately 50% to 70% of patients had 3 to 4 prior regimens (median of 3; range, 1-10) and a third of them had [previous] lenalidomide [Revlimid].

**Q What was noteworthy about the efficacy data in the trial?**

The response was approximately 92%, which is an amazing response, similar to if not better than [what we see in] newly diagnosed patients and not [something you usually see in] relapsed/refractory patient population. The question is now, how many of them had CR? Response is great, but to have any meaningful, durable response, you need a CR. You can’t just have a response. [The CR rate] was approximately 60% in FL, which is pretty good for a patient population that has failed multiple regimens. Very few of them can achieve complete remission with other treatments.

[Even] more important is the DOR. For a patient with first relapse, the best you can achieve is approximately 2 years. For second relapse, it’s probably 1 year at best. Median survival has not been reached yet, we need longer follow-up, but it’s at least 18 months.

**Q Please describe the mechanism of action of axi-cel.**

Axi-cel is a CAR T-cell therapy. T cells are not effective by themselves in the patient’s body due to a number of reasons. We collect the patient’s T cells and genetically modify them in a manufacturing facility; in this case, Kite Gilead. These genetically modified cells are targeting a protein on the surface of the lymphoma cells, CD19. We modify these cells and then give it back to the patient [where] they will further expand in the patient’s body. Not only will they attack the lymphoma cells but, unlike chemotherapy, they can persist in the body for quite a while. They can stay in the body for up to 18 months or even 2 years, and they may continue working in the patient’s body. This is not the traditional cytotoxic chemotherapy that tries to kill everything. This is a targeted therapy.

**Q What should clinicians know about axi-cel in terms of safety?**

There are 2 main adverse effects. One is cytokine release syndrome and the other is central nervous system toxicity. Both can be potentially life-threatening. Now that we have experience [using this agent], events are very manageable and the chance of that the patient will die from this treatment is very small.

You need to have an experienced group, an experienced team to utilize this treatment, which has limited the patient access. Most of the treatment centers that are certified by the company and by the FDA are major hospitals and academic centers. It will potentially be difficult to get this treated to the [wider] community.

**Q How does this approval affect the treatment standards for relapsed/refractory FL?**

This is a great addition for these patients, especially if they have failed 2 prior regimens. As I said, most of them only have a response to other treatments for a year. This is much longer, and you just need a little more follow-up that will probably conserve it.

At the same time, as 1 treatment, it’s an intense treatment and a complicated treatment; [the administration] lasts for approximately 2 months. I think it’s very important that we consider quality of life for patients with cancer and a treatment-free period. We don’t want [the patient] to have treatment continuously. We don’t know [how long this therapy will last]. Some are very optimistic; oncologists will tell you this could last for many years, but we don’t know. We don’t have that follow-up [data]. It could be long, potentially, or even curative.

**Q What does the future hold for axi-cel?**

[Future] studies need to examine patients with earlier disease. We need to identify a patient population that has a high risk of failed first-line treatment and for those with first relapse. We need more prospective studies to determine if this [treatment] is beneficial.

At the same time, targeted therapy is evolving. This is one of the first-generation CAR T-cell therapies and we have many others coming, which may be more effective and more convenient with less toxicity. This is a moving target and overall good for our patients.

I think this is a breakthrough of CAR T-cell therapy. The first T-cell infusions I did in clinical trial was around 1996. Now we’re in 2021, a quarter of a century [later]. There’s been a lot of work and a lot of failures. But finally, it has come to fruition and there are 4 indications now. It is exciting for our patients, [and although it is] limited to relapsed/refractory disease, we can, hopefully soon, prove its use earlier with better outcomes that could potentially be curative. This is just a step; we have to [keep moving forward].

**REFERENCES**


PIVOTAL CLINICAL TRIAL

ZUMA-5 (NCT03105336) was phase 2, single-arm, open label, multicenter trial that evaluated the efficacy and safety of axi-cel in adult patients with relapsed or refractory FL after 2 or more lines of systemic therapy, including the combination of an anti-CD20 monoclonal antibody and an alkylating agent. Following lymphodepleting chemotherapy, axi-cel was administered as a single intravenous infusion.

BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Median age (years, range)</th>
<th>61 (34-79)</th>
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<tbody>
<tr>
<td>n = 146</td>
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<table>
<thead>
<tr>
<th>Histology (%)</th>
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<tbody>
<tr>
<td>Follicular lymphoma</td>
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<tr>
<td>Marginal zone lymphoma</td>
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<table>
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<tr>
<th>Prior therapies (%)</th>
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<tbody>
<tr>
<td>3 (range, 2-9)</td>
</tr>
<tr>
<td>22%</td>
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<tr>
<td>32%</td>
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<tr>
<td>46%</td>
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<table>
<thead>
<tr>
<th>Treatment characteristics (n = 81)</th>
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</thead>
<tbody>
<tr>
<td>Median number of prior systemic therapies</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>≥ 4</td>
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</table>

EFFICACY RESULTS IN THE ZUMA-5 TRIAL

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Primary efficacy analysis (n = 81)*</th>
<th>All leukapheresed patients (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>91% (83%-96%)</td>
<td>89% (83%-94%)</td>
</tr>
<tr>
<td>CR (95% CI)</td>
<td>60% (49%-71%)</td>
<td>62% (53%-70%)</td>
</tr>
<tr>
<td>PR (95% CI)</td>
<td>31% (21%-42%)</td>
<td>28% (20%-36%)</td>
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Responders (n = 74)

<table>
<thead>
<tr>
<th>Median DOR, months (95% CI)</th>
<th>NE (20.8-NE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month rate of continued remission (95% CI)</td>
<td>76.2% (63.9%-84.7%)</td>
</tr>
<tr>
<td>18-month rate of continued remission (95% CI)</td>
<td>74.2% (61.5%-83.2%)</td>
</tr>
<tr>
<td>Median follow-up for DOR, months</td>
<td>14.5</td>
</tr>
</tbody>
</table>

CR, complete remission; DOR, duration of response; ORR, objective response rate; PR, partial remission.

*Patients included in the primary efficacy analysis have at least 9 months of potential follow-up from the date of first response.

BOXED WARNING

- Cytokine release syndrome
- Neurologic toxicities

Because of the risk of central nervous system and neurologic toxicities axi-cel is available only through the Yescarta and Tecartus REMS (risk evaluation and mitigation strategy Program).

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions
- Serious infections
- Prolonged cytopenias
- Hypogammaglobulinemia
- Secondary malignancies
- Effects on ability to drive and use machines

COMMONLY REPORTED ADVERSE EFFECTS IN THE ZUMA-5 TRIAL

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Axicabtagene ciloleucel (N = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
</tr>
<tr>
<td>Fever</td>
<td>85%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>49%</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>49%</td>
</tr>
<tr>
<td>Headache</td>
<td>45%</td>
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</tbody>
</table>

REFERENCE

INDICATIONS
Retevmo is a kinase inhibitor indicated for the treatment of:

- adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
- adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

These indications are approved under accelerated approval based on overall response rate (ORR) and duration of response (DoR). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

Please see Important Safety Information and Brief Summary of Prescribing Information for Retevmo on subsequent pages.
Response in patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC), advanced or metastatic RET fusion-positive thyroid cancer (non-medullary thyroid cancer (non-MTC)), and advanced or metastatic RET-mutant MTC

<table>
<thead>
<tr>
<th>Treatment naive (n=39)</th>
<th>Previously treated with platinum chemotherapy (n=105)</th>
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</thead>
<tbody>
<tr>
<td><strong>85% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>64% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>(95% CI: 70, 94)</td>
<td>(95% CI: 54, 73)</td>
</tr>
<tr>
<td>0% CR + 85% PR</td>
<td>1.9% CR + 62% PR</td>
</tr>
<tr>
<td><strong>Median DoR</strong> not yet reached</td>
<td><strong>Median DoR</strong> was 17.5 months</td>
</tr>
<tr>
<td>(95% CI: 12, NE); median follow-up: 7.4 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>(95% CI: 12, NE); median follow-up: 12.1 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Previously treated (n=19)**

<table>
<thead>
<tr>
<th><strong>100% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</th>
<th><strong>79% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% CI: 63, 100)</td>
<td>(95% CI: 54, 94)</td>
</tr>
<tr>
<td>12.5% CR + 88% PR</td>
<td>5.3% CR + 74% PR</td>
</tr>
<tr>
<td><strong>Median DoR</strong> not yet reached</td>
<td><strong>Median DoR</strong> was 18.4 months</td>
</tr>
<tr>
<td>(95% CI: NE; NE); median follow-up: 8.8 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>(95% CI: 7, NE); median follow-up: 17.5 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Previously treated (n=8)**

<table>
<thead>
<tr>
<th><strong>73% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</th>
<th><strong>69% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% CI: 62, 82)</td>
<td>(95% CI: 55, 81)</td>
</tr>
<tr>
<td>11% CR + 61% PR</td>
<td>9% CR + 60% PR</td>
</tr>
<tr>
<td><strong>Median DoR</strong> not yet reached</td>
<td><strong>Median DoR</strong> was 22.0 months</td>
</tr>
<tr>
<td>(95% CI: NE; NE); median follow-up: 7.8 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>(95% CI: 19, 1, NE); median follow-up: 14,1 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Find RET. Find results on Retevmo.com.**

**Adverse Reactions and Laboratory Abnormalities**

- The most common adverse reactions, including laboratory abnormalities, (>25%) were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.

- Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequent serious adverse reaction (in >2% of patients) was pneumonia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3). Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received Retevmo. Adverse reactions resulting in permanent discontinuation in patients who received Retevmo included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).

- Dose interruptions due to an adverse reaction occurred in 42% of patients who received Retevmo. Adverse reactions requiring dosage interruption in ≥2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation.

- Dose reductions due to an adverse reaction occurred in 31% of patients who received Retevmo. Adverse reactions requiring dosage reductions in ≥2% of patients included ALT increased, AST increased, QT prolongation, and fatigue.
Important Safety Information for Retevmo® (selpercatinib 40 mg, 80 mg capsules) (Cont’d)

Retevmo can cause concentration-dependent QT interval prolongation. An increase in QTcF interval >500 ms was measured in 6% of patients and an increase in the QTcF interval of ≥ 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradycardia, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Serious, including fatal, hemorrhagic events can occur with Retevmo. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminases. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Retevmo has the potential to adversely affect wound healing. Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Retevmo after resolution of wound healing complications has not been established.

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Retevmo and for 1 week after the final dose.

Severe adverse reactions (Grade 3-4) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspnea (2.3%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequently reported serious adverse reaction (in ≥ 2% of patients) was pneumonia.

Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in ≥1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3).

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were dry mouth (39%), diarrhea (37%), hypertension (35%), fatigue (35%), edema (33%), rash (27%), constipation (25%), nausea (23%), abdominal pain (23%), headache (23%), cough (18%), prolonged QT interval (17%), dyspnea (16%), vomiting (15%), and hemorrhage (13%).

Laboratory abnormalities (all grades; Grade 3-4) ≥20% worsening from baseline in patients who received Retevmo in LIBRETTO-001, were AST increased (31%; 8%), ALT increased (45%; 9%), increased glucose (44%; 22%), decreased leukocytes (43%; 1.6%), decreased albumin (42%; 0.7%), decreased calcium (41%; 3.8%), increased creatinine (37%; 1.0%), increased alkaline phosphatase (36%; 2.3%), decreased platelets (33%; 2.7%), increased total cholesterol (31%; 0.1%), decreased sodium (27%; 7%), decreased magnesium (24%; 0.6%), increased potassium (24%; 1.2%), increased bilirubin (23%; 2.0%), and decreased glucose (22%; 0.7%).

Concomitant use of acid-reducing agents decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid concomitant use of proton-pump inhibitors (PPIs), histamine-2 (H2) receptor antagonists, and locally-acting antagonists with Retevmo. If coadministration cannot be avoided, take Retevmo with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antagonist).

Concomitant use of strong and moderate CYP3A inhibitors decreases selpercatinib plasma concentrations which may reduce the risk of Retevmo adverse reactions including QTc interval and antitumor activity. Avoid concomitant use of strong and moderate CYP3A inhibitors with Retevmo. If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the Retevmo dosage as recommended and monitor the QT interval with ECGs more frequently.

Concomitant use of strong and moderate CYP3A inducers decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid coadministration of Retevmo with strong and moderate CYP3A inducers.

Concomitant use of Retevmo with CYP2CB and CYP3A substrates increases their plasma concentrations which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of Retevmo with CYP2CB and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2CB and CYP3A substrates provided in their approved product labeling.

The safety and effectiveness of Retevmo have not been established in pediatric patients less than 12 years of age. The safety and effectiveness of Retevmo have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced RET fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of Retevmo for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older.

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [Clcr] ≥ 30 mL/min, estimated by Cockcroft-Gault). A recommended dosage has not been established for patients with severe renal impairment or end-stage renal disease.

Reduce the dose when administering Retevmo to patients with severe hepatic impairment (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST). No dosage modification is recommended for patients with mild or moderate hepatic impairment. Monitor for Retevmo-related adverse reactions in patients with hepatic impairment.

SE HCP ISI AIIL 25AUG2020

Please see Brief Summary of Prescribing Information for Retevmo on subsequent pages.

BRIEF SUMMARY: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE RETEVMO (selpercatinib) is a kinase inhibitor indicated for the treatment of:

- Adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutated medullary thyroid cancer (MTC) who require systemic therapy
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy are radioactive iodine-refractory if radioactive iodine is inappropriate

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Hepatotoxicity
Serious hepatic adverse reactions occurred in 2.6% of patients treated with RETEVMO. Increased AST occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased ALT occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 1 day to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years).

Monitor ALT and AST prior to initiating RETEVMO, every second day during the first 3 months, then monthly thereafter and as clinically indicated. Without, reduce dose or permanently discontinue RETEVMO based on the severity.

Hypertension
Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.4% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertensive medications.

Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating RETEVMO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Without, reduce dose, or permanently discontinue RETEVMO based on the severity.

QT Interval Prolongation
RETEVMO can cause concentration-dependent QT interval prolongation. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. RETEVMO has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.

Monitor patients who are at significant risk of developing QTC prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating RETEVMO and during treatment.

Monitor the QT interval more frequently when RETEVMO is coadministered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Without, dose reduce or permanently discontinue RETEVMO based on the severity.

Hemorrhagic Events
Serious including fatal hemorrhagic events can occur with RETEVMO. Grade 3 hemorrhagic events occurred in 2.3% of patients treated with RETEVMO including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis.

Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage.

Hypersensitivity
Hypersensitivity occurred in 4.3% of patients receiving RETEVMO, including Grade 3 hypersensitivity in 1.8%. The median time to onset was 1.7 weeks (range: 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminases.

If hypersensitivity occurs, withhold RETEVMO and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume RETEVMO at a reduced dose and increase the dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETEVMO for recurrent hypersensitivity.

Risk of Impaired Wound Healing
Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, RETEVMO has the potential to adversely affect wound healing.

Withhold RETEVMO for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of RETEVMO after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity
Based on data from animal reproduction studies, and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposure that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for at least 1 week after the final dose.

ADVERSE REACTIONS

Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

RETEVMO (selpercatinib) capsules, for oral use

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVMO (n=702)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39</td>
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<tr>
<td>Constipation</td>
<td>25</td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35</td>
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Table 1: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001 (Cont.)

<table>
<thead>
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<th>Adverse Reaction</th>
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<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>General</td>
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<td>Fatigue</td>
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<td>Skin</td>
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<td>Rash</td>
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<td>Investigations</td>
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<tr>
<td>Prolonged QT interval</td>
<td>17</td>
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<tr>
<td>Blood and Lymphatic System</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>15</td>
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</tbody>
</table>

1 Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 675 to 692 patients.

In healthy subjects administered RETEVMO 160 mg orally twice daily, serum creatinine increased 18% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

DRUG INTERACTIONS

Effects of Other Drugs on RETEVMO

Acid-Reducing Agents

Concomitant use of RETEVMO with acid-reducing agents decreases selpercatinib plasma concentrations, which may reduce the RETEVMO anti-tumor activity. Avoid concomitant use of PPIs, H2 receptor antagonists, and locally acting antacids with RETEVMO. If coadministration cannot be avoided, take RETEVMO with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally acting antacid).

Strong and Moderate CYP3A4 Inhibitors

Concomitant use of RETEVMO with a strong or moderate CYP3A inhibitor increases selpercatinib plasma concentrations, which may increase the risk of RETEVMO adverse reactions, including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with RETEVMO. If concomitant use of strong or moderate CYP3A inhibitors cannot be avoided, reduce the RETEVMO dosage and monitor the QT interval with ECGs more frequently.

Strong and Moderate CYP3A4 Inducers

Concomitant use of RETEVMO with a strong or moderate CYP3A inducer decreases selpercatinib plasma concentrations, which may reduce the RETEVMO anti-tumor activity. Avoid coadministration of strong or moderate CYP3A inducers with RETEVMO.

Effects of RETEVMO on Other Drugs

CYP2B6 and CYP3A4 Substrates

RETEVMO is a moderate CYP2B6 inhibitor and a weak CYP3A4 inhibitor. Concomitant use of RETEVMO with CYP2B6 and CYP3A substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of RETEVMO with CYP2B6 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2B6 and CYP3A substrates provided in their approved product labeling.

Drugs that Prolong QT Interval

RETEVMO is associated with QTc interval prolongation. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal studies, and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. There are no available data on RETEVMO use in pregnant women to inform drug-associated risk. Administration of selpercatinib to pregnant rats during the period of organogenesis resulted in embryolethality and malformations at maternal exposures that were approximately equal to the human exposure at the clinical dose of 160 mg twice daily. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Selpercatinib administration to pregnant rats during the period of organogenesis at oral doses ≥ 100 mg/kg (approximately 3.6 times the human exposure based on the area under the curve [AUC] at the clinical dose of 160 mg twice daily) resulted in 100% post-implantation loss. At the dose of 50 mg/kg (approximately equal to the human exposure [AUC] at the clinical dose of 160 mg twice daily), 6 of 8 females had 100% early resorptions; the remaining 2 females had high levels of early resorptions with only 3 viable fetuses across the 2 litters. All viable fetuses had decreased fetal body weight and malformations (2 with short tail and one with small snout and localized edema of the neck and thorax).

Lactation

Risk Summary

There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with RETEVMO and for 1 week after the final dose.
Females and Males of Reproductive Potential

Based on animal data, RETEVMO can cause embryolethality and malformations at doses resulting in exposures less than or equal to the human exposure at the clinical dose of 160 mg twice daily.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating RETEVMO.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the final dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the final dose.

Infertility

RETEVMO may impair fertility in females and males of reproductive potential.

Pediatric Use

The safety and effectiveness of RETEVMO have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced RET fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of RETEVMO for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. The safety and effectiveness of RETEVMO have not been established in these indications in patients less than 12 years of age.

The safety and effectiveness of RETEVMO have not been established in pediatric patients for other indications.

Animal Toxicity Data

In 4-week general toxicology studies in rats, animals showed signs of physisal hypertrophy and tooth dysplasia at doses resulting in exposures ≥ approximately 3 times the human exposure at the 160 mg twice daily clinical dose. Minipigs also showed signs of minimal to marked increases in physisal thickness at the 15 mg/kg high dose level (approximately 0.3 times the human exposure at the 160 mg twice daily clinical dose). Rats in both the 4- and 13-week toxicology studies had malocclusion and tooth discoloration at the high dose levels (≥1.5 times the human exposure at the 160 mg twice daily clinical dose) that persisted during the recovery period.

Geriatric Use

Of 702 patients who received RETEVMO, 34% (239 patients) were ≥ 65 years of age and 10% (67 patients) were > 75 years of age. No overall differences were observed in the safety or effectiveness of RETEVMO between patients who were ≥65 years of age and younger patients.

Renal Impairment

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [CrCl] ≥ 30 mL/min, estimated by Cockcroft-Gault). The recommended dosage has not been established for patients with severe renal impairment (CrCl < 30 mL/min) or end-stage renal disease.

Hepatic Impairment

Reduce the dose when administering RETEVMO to patients with severe (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST) hepatic impairment. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) or moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) hepatic impairment. Monitor for RETEVMO-related adverse reactions in patients with hepatic impairment.

Rx only.

Additional information can be found at www.retevmo.com.

Lilly

Eli Lilly and Company, Indianapolis, IN 46285, USA

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SE HCP BS 08MAY2020

RETEVMO™ (selpercatinib) capsules, for oral use

SE HCP BS 08MAY2020
**Drug Spotlight | ISATUXIMAB-IRFC (SARCLISA)**

**Isatuximab Combination Looks to Improve Outcomes for Early Relapsed Multiple Myeloma**

_by KYLE DOHERTY_

**COMBINATION THERAPIES, IN PARTICULAR** those using 3 and 4 drugs, have improved response rates and survival outcomes for patients with relapsed or refractory multiple myeloma. For patients who experience early relapse, data from the phase 3 IKEMA study (NCT03275285) supported the use of isatuximab-irfc (Sarclisa), a CD38-directed cytolytic antibody, plus carfilzomib (Kyprolis) and dexamethasone (Isa-Kd) in patients who received 1 to 3 prior lines of therapy. The FDA approved the combination for this patient population on March 31, 2021.

Specifically, Isa-Kd reduced the risk of disease progression by 45% (HR, 0.548; 95% CI, 0.366-0.822; _P_ = .0032) compared with carfilzomib and dexamethasone (Kd) alone. The median progression-free survival (PFS) was not reached with isatuximab vs 20.27 months with Kd (95% CI, 15.77-not reached). Response rates were similar between the 2 cohorts (86.6% vs 82.9%, respectively); however, more complete responses were reported with Isa-Kd compared with Kd (39.7% vs 27.6%, respectively).

In an interview with OncologyLive®, Thomas G. Martin, MD, clinical professor of medicine in the Adult Leukemia and Bone Marrow Transplantation Program, associate director of the Myeloma Program, at the University of California, San Francisco, and coleader of the Cancer Immunology & Immunotherapy Program at the Helen Diller Family Comprehensive Cancer Center, spoke on the approval and potential future directions for the agent. [Based on data from] preclinical studies, isatuximab was selected because of its ability to induce apoptosis. We conducted the phase 1 study of isatuximab plus carfilzomib [NCT02332850] because in a xenograft model when we combined the 2 [drugs] we saw regression of the tumor compared with moderate suppression of growth [when studied independently]. In results from the phase 1 trial, isatuximab plus carfilzomib showed an ORR of approximately 50% in carfilzomib-refractory patients. I think that shows there is a synergy between these 2 drugs.

**What should clinicians know about Isa-Kd in terms of safety?**

In general, the CD38 monoclonal antibodies have been very well tolerated. For isatuximab specifically, the most prevalent adverse effect is infusion-associated reaction, which can occur with the first and, much less so, the second infusion. With the first infusion a patient may experience fever, hives, chills, etc. Approximately 20% to 30% of the time, you have to stop the infusion, give more premedications, and then reinstitute the infusion at a slower rate.

In general, almost every patient can continue their first infusion. Once they’re past their first infusion, the adverse effects are really modest. Occasionally patients will [experience] fatigue, but I honestly don’t know if it’s [Isa-Kd-related] or from the steroid premedication.

**How does this approval shift the treatment paradigm?**

[Typically], patients develop relapsed disease on lenalidomide maintenance. For patients on lenalidomide maintenance, as long as it’s feasible for them to come to the center to get intravenous medication, I think the Isa-Kd is a great regimen. It’s our go-to if patients relapse on lenalidomide maintenance. [Additionally,] if they become resistant to IMiD, I think switching to a CD38 antibody plus a proteasome inhibitor makes a lot of sense.

**What does the future hold for isatuximab?**

One of the biggest deficits in the current approval for isatuximab is the dosing strategy. There’s a clinical trial that is ongoing that is evaluating subcutaneous administration [NCT04045795]. Investigators need to lengthen out the dosage interval because in all prior isatuximab studies the agent is administered weekly for 4 weeks and then every other week ongoing. It’s probably all right to switch to every 4 weeks. They need to publish data on the subcutaneous dosing, they need to get it FDA approved, and they need studies looking at Q4 week dosing.

The other mechanism of action that we have to remind ourselves of with CD38 antibodies is that many of the immunosuppressive cells in the microenvironment of the bone marrow actually express CD38. It is possible that isatuximab and daratumumab [Darzalex] could in fact rid the marrow of some of these immunosuppressive effects of regulatory T cells, B cells, etc. Administration of these CD38s together with bispecific antibodies may be a very potent strategy, especially in the relapsed or refractory setting.

**REFERENCE**

PIVOTAL CLINICAL TRIAL

IKEMA (NCT03275285) was a phase 3, 2-arm, open label, multicenter trial that evaluated isatuximab in combination with carfilzomib (Kyprolis) and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy. Treatment was administered in both groups in 28-day cycles until disease progression or unacceptable toxicity.

BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Isatuximab, carfilzomib, and dexamethasone (n = 179)</th>
<th>Carfilzomib and dexamethasone (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years, range)</td>
<td>65 (33-86)</td>
<td>63 (33-90)</td>
</tr>
<tr>
<td>Cytogenetic risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>23.5%</td>
<td>25.2%</td>
</tr>
<tr>
<td>Standard</td>
<td>63.7%</td>
<td>63.4%</td>
</tr>
<tr>
<td>Unknown</td>
<td>12.8%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Prior lines of therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>41.1%</td>
<td>44.7%</td>
</tr>
<tr>
<td>2</td>
<td>35.8%</td>
<td>29.3%</td>
</tr>
<tr>
<td>3</td>
<td>18.4%</td>
<td>24.4%</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>1.7%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

Efficacy results in the IKEMA trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Isatuximab, carfilzomib, and dexamethasone (n = 179)</th>
<th>Carfilzomib and dexamethasone (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>NR (NR-NR)</td>
<td>20.27 (15.77-NR)</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>86.6% (80.7%-91.2%)</td>
<td>82.9% (75.1%-89.1%)</td>
</tr>
<tr>
<td>CR (95% CI)</td>
<td>39.7%</td>
<td>27.6%</td>
</tr>
<tr>
<td>VGPR (95% CI)</td>
<td>33.0%</td>
<td>28.5%</td>
</tr>
<tr>
<td>PR (95% CI)</td>
<td>14.0%</td>
<td>26.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Isatuximab plus carfilzomib and dexamethasone (n = 177)</th>
<th>Carfilzomib and dexamethasone (n = 122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades (Grade 3 or 4)</td>
<td>All grades (Grade 3 or 4)</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>66% (39%)</td>
<td>5% (0.4%)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>64% (31%)</td>
<td>18% (2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>57% (1%)</td>
<td>28% (1%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>51% (3%)</td>
<td>41% (1%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>42% (21%)</td>
<td>8% (1%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>40% (1%)</td>
<td>20% (0.4%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>39% (1%)</td>
<td>38% (0%)</td>
</tr>
</tbody>
</table>

WARNINGS AND PRECAUTIONS

- Infusion-related reactions
- Neutropenia
- Secondary primary malignancies
- Laboratory test interference
- Embryo-fetal toxicity

COMMONLY REPORTED ADVERSE EFFECTS IN THE IKEMA TRIAL

<table>
<thead>
<tr>
<th>References</th>
</tr>
</thead>
</table>
The OS endpoint was measured from the date of randomization until death by any cause in the final analysis, which included 371 patients randomized 2:1 to receive XOSPATA or a

<table>
<thead>
<tr>
<th>FLT3-TKD</th>
<th>FLT3-ITD</th>
<th>FLT3-ITD-TKD</th>
</tr>
</thead>
</table>

AZA: azacitidine 75 mg/m² once daily by SC injection or IV infusion for 7 days.¹

Gilteritinib (XOSPATA) sets a standard in relapsed or refractory FLT3m+ AML.¹,³

Gilteritinib (XOSPATA) is the ONLY Category 1 recommendation in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for patients with relapsed or refractory FLT3m+ AML¹

XOSPATA was evaluated in a Phase 3, open-label, multicenter, randomized clinical trial compared with a prespecified salvage chemotherapy in adult patients with relapsed or refractory FLT3m+ AML.¹,⁴ Prespecified salvage chemotherapy regimens included high-intensity combinations MEC² and FLAG-IDA³ and low-intensity regimens LDAC⁴ and AZA.⁵,⁶

³FLT3 mutation status: FLT3-ITD, FLT3-TKD, and FLT3-ITD-TKD.¹
⁴The OS endpoint was measured from the date of randomization until death by any cause in the final analysis, which included 371 patients randomized 2:1 to receive XOSPATA or a prespecified salvage chemotherapy regimen.¹
²MEC: mitoxantrone 8 mg/m², etoposide 100 mg/m², and cytarabine 1000 mg/m² once daily by IV infusion Days 1 to 5.¹
³FLAG-IDA: granulocyte colony-stimulating factor 300 mcg/m² once daily by SC injection Days 1 to 5, fludarabine 30 mg/m² once daily by IV infusion Days 2 through 6, cytarabine 2000 mg/m² once daily by IV infusion Days 2 through 6, idarubicin 10 mg/m² once daily by IV infusion Days 2 through 4.¹
⁴LDAC: cytarabine 20 mg twice daily by SC injection or IV infusion for 10 days.¹
⁵AZA: azacitidine 75 mg/m² once daily by SC injection or IV infusion for 7 days.¹

AML = acute myeloid leukemia; CI = confidence interval; FDA = Food and Drug Administration; FLT3 = FMS-like tyrosine kinase 3; HR = hazard ratio; ITD = internal tandem duplication; IV = intravenous; LDAC = low-dose cytarabine; m = mutation-positive; NCCN = National Comprehensive Cancer Network; OS = overall survival; SC = subcutaneous; TKD = tyrosine kinase domain.

INDICATION
XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
XOSPATA is contraindicated in patients with hypersensitivity to gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials.

WARNING: DIFFERENTIATION SYNDROME
Patients treated with XOSPATA have experienced symptoms of differentiation syndrome, which can be fatal or life-threatening if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, or renal dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

WARNINGS AND PRECAUTIONS

Differentiation Syndrome (See BOXED WARNING) 3% of 319 patients treated with XOSPATA in the clinical trials experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with XOSPATA included fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as 2 days and up to 75 days after XOSPATA initiation and has been observed with or without concomitant leukocytosis. If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt XOSPATA until signs and symptoms are no longer severe.

Posterior Reversible Encephalopathy Syndrome (PRES) 1% of 319 patients treated with XOSPATA in the clinical trials experienced posterior reversible encephalopathy syndrome (PRES) with symptoms including seizure and altered mental status. Symptoms have resolved after discontinuation of XOSPATA. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XOSPATA in patients who develop PRES.

Prolonged QT Interval XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). 1% of the 317 patients with a post-baseline QTc measurement on treatment with XOSPATA in the clinical trials were found to have a QTc interval greater than 500 msec and 7% of patients had an increase from baseline QTc greater than 60 msec. Perform electrocardiogram (ECG) prior to initiation of treatment with XOSPATA, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and reduce XOSPATA dosage in patients who have a QTcF >500 msec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration.

Pancreatitis 4% of 319 patients treated with XOSPATA in the clinical trials experienced pancreatitis. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of XOSPATA in patients who develop pancreatitis.

Embryo-Fetal Toxicity XOSPATA can cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 6 months after the last dose of XOSPATA. Advise males with female partners of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 4 months after the last dose of XOSPATA. Pregnant women, patients becoming pregnant while receiving XOSPATA or male patients with pregnant female partners should be apprised of the potential risk to the fetus.

ADVERSE REACTIONS
Fatal adverse reactions occurred in 2% of patients receiving XOSPATA. These were cardiac arrest (1%) and one case each of differentiation syndrome and pancreatitis. The most frequent (≥5%) nonhematological serious adverse reactions reported in patients were fever (13%), dyspnea (9%), renal impairment (8%), transaminase increased (6%) and noninfectious diarrhea (5%).

7% discontinued XOSPATA treatment permanently due to an adverse reaction. The most common (>1%) adverse reactions leading to discontinuation were aspartate aminotransferase increased (2%) and alanine aminotransferase increased (2%).

The most frequent (≥5%) grade ≥3 nonhematological adverse reactions reported in patients were transaminase increased (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/arthritis (7%), and fatigue/malaise (6%).

Other clinically significant adverse reactions occurring in ≤10% of patients included: electrocardiogram QT prolonged (9%), hypersensitivity (8%), pancreatitis (5%), cardiac failure (4%), pericardial effusion (4%), acute febrile neutrophilic dermatosis (3%), differentiation syndrome (3%), pericarditis/myocarditis (2%), large intestine perforation (1%), and posterior reversible encephalopathy syndrome (1%).

Lab Abnormalities Shifts to grades 3-4 nonhematologic laboratory abnormalities in XOSPATA treated patients included phosphate decreased (14%), alanine aminotransferase increased (13%), sodium decreased (12%), aspartate aminotransferase increased (10%), calcium decreased (6%), creatinine increased (6%), triglycerides increased (6%), creatinine increased (3%), and alkaline phosphatase increased (2%).

DRUG INTERACTIONS

Combined P-gp and Strong CYP3A Inducers Concomitant use of XOSPATA with a combined P-gp and strong CYP3A inducer decreases XOSPATA exposure which may decrease XOSPATA efficacy. Avoid concomitant use of XOSPATA with combined P-gp and strong CYP3A inducers.

Strong CYP3A Inhibitors Concomitant use of XOSPATA with a strong CYP3A inhibitor increases XOSPATA exposure. Consider alternative therapies that are not strong CYP3A inhibitors. If the concomitant use of these inhibitors is considered essential for the care of the patient, monitor patient more frequently for XOSPATA adverse reactions. Interrupt and reduce XOSPATA dosage in patients with serious or life-threatening toxicity.

Drugs that Target 5HT2B Receptor or Sigma Nonspecific Receptor Concomitant use of XOSPATA may reduce the effects of drugs that target the 5HT2B receptor or the sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these drugs with XOSPATA unless their use is considered essential for the care of the patient.

SPECIFIC POPULATIONS

Lactation Advise women not to breastfeed during treatment with XOSPATA and for 2 months after the last dose.
XOSPATA® (gilteritinib) tablets for oral use

The following is a brief summary of full Prescribing Information. Please see the package insert for full prescribing information.

**WARNING: DIFFERENTIATION SYNDROME**

Patients treated with XOSPATA have experienced symptoms of differentiation syndrome, which can be fatal or life-threatening if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, or renal dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

**INDICATIONS AND USAGE**

XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.

**DOSE AND ADMINISTRATION**

**Patient Selection**

Select patients for the treatment of AML with XOSPATA based on the presence of FLT3 mutations in the blood or bone marrow. Information on FDA-approved tests for the detection of a FLT3 mutation in AML is available at [http://www.fda.gov/CompanionDiagnostics](http://www.fda.gov/CompanionDiagnostics).

**Recommended Dosage**

The recommended starting dose of XOSPATA is 120 mg orally once daily with or without food. Response may be delayed. In the absence of disease progression or unacceptable toxicity, treatment for a minimum of 6 months is recommended to allow time for a clinical response. Do not break or crush XOSPATA tablets. Administer XOSPATA tablets orally about the same time each day. If a dose of XOSPATA is missed or not taken at the usual time, administer the dose as soon as possible on the same day, and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

**Dose Modification**

Assess blood counts and blood chemistries, including creatine phosphokinase, prior to the initiation of XOSPATA, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of therapy. Perform electrocardiogram (ECG) prior to initiation of treatment with gilteritinib, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt or reduce XOSPATA dosage in patients who have a QTcF >500 msec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration.

**CONTRAINDICATIONS**

XOSPATA is contraindicated in patients with hypersensitivity to gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials.

**WARNINGS AND PRECAUTIONS**

**Differentiation Syndrome**

Of 319 patients treated with XOSPATA in the clinical trials, 3% experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with XOSPATA included fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as 2 days and up to 75 days after XOSPATA initiation and has been observed with or without concomitant leukocytosis. Of the 11 patients who experienced differentiation syndrome, 9 (82%) recovered after treatment or after dose interruption of XOSPATA. If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt XOSPATA until signs and symptoms are no longer severe.

**Posterior Reversible Encephalopathy Syndrome (PRES)**

Of 319 patients treated with XOSPATA in the clinical trials, 1% experienced posterior reversible encephalopathy syndrome (PRES) with symptoms including seizure and altered mental status. Symptoms have resolved after discontinuation of XOSPATA. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XOSPATA in patients who develop PRES.

**Prolonged QT Interval**

XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). Of the 317 patients with a post-baseline QTc measurement on treatment with XOSPATA in the clinical trial, 1% were found to have a QTc interval greater than 500 msec and 7% of patients had an increase from baseline QTc greater than 60 msec. Perform electrocardiogram (ECG) prior to initiation of treatment with gilteritinib, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and reduce XOSPATA dosage in patients who have a QTcF >500 msec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration.

**Pancreatitis**

Of 319 patients treated with XOSPATA in the clinical trials, 4% experienced pancreatitis. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of XOSPATA in patients who develop pancreatitis.

**Embryo-Fetal Toxicity**

Based on findings in animals and its mechanism of action, XOSPATA can cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 6 months after the last dose of XOSPATA. Advise males with female partners of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 4 months after the last dose of XOSPATA. Pregnant women, patients becoming pregnant while receiving XOSPATA or male patients with pregnant female partners should be apprised of the potential risk to the fetus.

**ADVERSE REACTIONS**

**Clinical Trial Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety profile of XOSPATA is based on 319 patients with relapsed or refractory AML treated with gilteritinib 120 mg daily in three clinical trials. The median duration of exposure to XOSPATA was 3.6 months (range 0.1 to 43.4 months).

Fatal adverse reactions occurred in 2% of patients receiving XOSPATA. These included cardiac arrest (1%) and one case each of differentiation syndrome and pancreatitis. The most frequent (>5%) nonhematological serious adverse reactions reported in patients were fever (13%), dyspnea (9%), renal impairment (8%), transaminase increased (6%) and noninfectious diarrhea (5%).

Of the 319 patients, 91 (29%) required a dose interruption due to an adverse reaction; the most common adverse reactions leading to dose interruption were aspartate aminotransferase increased (6%), alanine aminotransferase increased (6%) and fever (4%). Twenty patients (6%) required a dose reduction due to an adverse reaction. Twenty-two (7%) discontinued XOSPATA treatment permanently due to an adverse reaction.

The most common (>1%) adverse reactions leading to discontinuation were aspartate aminotransferase increased (2%) and alanine aminotransferase increased (2%).

Overall, for the 319 patients, the most frequent (≥10%) all-grade nonhematological adverse reactions reported in patients were transaminase increased (51%), myalgia/arthritis (50%), fatigue/malaise (44%), fever (41%), mucositis (41%), edema (40%), rash (36%), noninfectious diarrhea (35%), dyspnea (35%), nausea (30%), cough (28%), constipation (28%), eye disorders (25%), headache (24%), dizziness (22%), hypotension (22%), vomiting (21%), renal impairment (21%), abdominal pain (18%), neuropathy (18%), insomnia (15%) and dysgeusia (11%). The most frequent (≥5%) grade ≥3 nonhematological adverse reactions reported in patients were transaminase increased (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/arthritis (7%), and fatigue/malaise (6%).

Shifts to grades 3-4 nonhematologic laboratory abnormalities included phosphate decreased (14%), alanine aminotransferase increased (13%), sodium decreased...
DRUG INTERACTIONS

**Combined P-gp and Strong CYP3A Inducers**

Concomitant use of XOSPATA with a combined P-gp and strong CYP3A inducer decreases gilteritinib exposure which may decrease XOSPATA efficacy. Avoid concomitant use of XOSPATA with combined P-gp and strong CYP3A inducers.

**Strong CYP3A Inhibitors**

Concomitant use of XOSPATA with a strong CYP3A inhibitor increases gilteritinib exposure. Consider alternative therapies that are not strong CYP3A inhibitors. If the concomitant use of these inhibitors is considered essential for the care of the patient, monitor patient more frequently for XOSPATA adverse reactions. Interrupt and reduce XOSPATA dosage in patients with serious or life-threatening toxicity.

**Drugs that Target 5HT2B Receptor or Sigma Nonspecific Receptor**

Concomitant use of gilteritinib may reduce the effects of drugs that target the 5HT2B receptor or the sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these drugs with XOSPATA unless their use is considered essential for the care of the patient.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on findings from animal studies and its mechanism of action, XOSPATA can cause fetal harm when administered to a pregnant woman. There are no available data on XOSPATA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, administration of gilteritinib to pregnant rats during organogenesis caused adverse developmental outcomes including embryo-fetal lethality, suppressed fetal growth, and teratogenicity at maternal exposures (AUC(0-24h)) approximately 0.4 times the AUC in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

**Data**

**Animal Data**

In an embryo-fetal development study in rats, pregnant animals received oral doses of gilteritinib of 0, 0.3, 3, 10, and 30 mg/kg/day during the period of organogenesis. Maternal findings at 30 mg/kg/day (resulting in exposures approximately 0.4 times the AUC24 in patients receiving the recommended dose) included decreased body weight and food consumption. Administration of gilteritinib at the dose of 30 mg/kg/day also resulted in embryo-fetal death (post implantation loss), decreased fetal body and placental weight, and decreased numbers of ossified sternebrae and sacral and caudal vertebrae, and increased incidence of fetal gross external (anasarca, local edema, exencephaly, cleft lip, cleft palate, short tail, and umbilical hernia), visceral (microphthalmia, atrial and/or ventricular defects, and malformed/absent kidney, and malpositioned adrenal, and ovary), and skeletal (sterneoschisis, absent rib, fused rib, fused cervical arch, malsegmented cervical vertebra, and absent thoracic vertebra) abnormalities.

Single oral administration of [14C] gilteritinib to pregnant rats resulted in transfer of radioactivity to the fetus similar to that observed in maternal plasma on day 14 of gestation. In addition, distribution profiles of radioactivity in most maternal tissues and the fetus on day 18 of gestation were similar to that on day 14 of gestation.

**Lactation**

**Risk Summary**

There are no data on the presence of gilteritinib and/or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Following administration of radiolabeled gilteritinib to lactating rats, milk concentrations of radioactivity were higher than radioactivity in maternal plasma at 4 and 24 hours post-dose. In animal studies, gilteritinib and/or its metabolite(s) were distributed to the tissues in infant rats via the milk. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during treatment with XOSPATA and for 2 months after the last dose.

**Females and Males of Reproductive Potential**

**Pregnancy testing**

Pregnancy testing is recommended for females of reproductive potential within seven days prior to initiating XOSPATA treatment.

**Contraception**

**Females**

Advise females of reproductive potential to use effective contraception during treatment and for at least 6 months after the last dose of XOSPATA.

**Males**

Advise males of reproductive potential to use effective contraception during treatment and for at least 4 months after the last dose of XOSPATA.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

Of the 319 patients in clinical studies of XOSPATA, 43% were age 65 years or older, and 13% were 75 years or older. No overall differences in effectiveness or safety were observed between patients age 65 years or older and younger patients.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenicity studies have not been performed with gilteritinib. Gilteritinib was not mutagenic in a bacterial mutagenesis (Ames) assay and was not clastogenic in a chromosome aberration test assay in Chinese hamster lung cells. Gilteritinib was positive for the induction of micronuclei in bone marrow cells from 65 mg/kg (195 mg/m²) the mid dose tested (approximately 2.6 times the recommended human dose of 120 mg). The effect of XOSPATA on human fertility is unknown. Administration of 10 mg/kg/day gilteritinib in the 4-week study in dogs (12 days of dosing) resulted in degeneration and necrosis of germ cells and spermatid giant cell formation in the testes as well as single cell necrosis of the epididymal duct epithelia of the epididymal head.

**Animal Toxicology and/or Pharmacology**

In the 13-week oral repeated dose toxicity studies in rats and dogs, target organs of toxicity included the eye and kidney.

**Manufactured for and Distributed by:** Astellas Pharma US, Inc., Northbrook, IL 60062

**Marketed by:**

Astellas Pharma US, Inc., Northbrook, IL 60062

**Revised:** 05/2019

**Rx Only**

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[astellas logo]

077-0501-PM
ELIAS JABBOUR, MD, OF The University of Texas MD Anderson Cancer Center in Houston, says he works at a pace of “200 miles per minute” and always has several dozen research projects going simultaneously.

“People may say, ‘Well, pick one project and finish it and go to the second.’ I say the opposite. I say pick 10 or 15, because then you can succeed in half of them. If you have one project and you fail, you fail 100%,” said Jabbour, a professor of medicine in the Department of Leukemia.

His drive is demonstrated by the more than 500 research articles he has authored or coauthored and the many leukemia therapies he has helped develop. Among them are combinations of chemotherapy and novel agents for patients with acute lymphoblastic leukemia (ALL), clofarabine (Clolar) in myeloid malignancies, hypomethylating agents (HMA) in acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), tyrosine kinase inhibitor (TKI) therapy in chronic myeloid leukemia (CML), and triplet therapy in AML.

Jabbour has recently led or contributed to studies of regimens that have markedly improved survival in patients with ALL. These include hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) plus ponatinib (Iclusig) as frontline therapy for adults with Philadelphia chromosome (Ph)-positive ALL and inotuzumab ozogamicin (Besponsa) in combination with the low-intensity chemotherapy regimen of mini-hyper-CVD (mini-hyperfractionated cyclophosphamide, vincristine, and dexamethasone) with or without blinatumomab (Blincyto) for older patients (≥ 60 years) with Ph-negative ALL.1,2

“He has designed a number of clinical trials that incorporate diverse forms of immune therapy and targeted therapies that are really transforming the care of our patients, resulting in very high rates of response and improved survival. They even question the role of allogeneic stem cell transplantation [SCT] for some of these patients who, in the past, were considered to have high-risk [disease] and were universally transplanted,” said Guillermo Garcia-Manero, MD, who leads MD Anderson’s MDS program.

Susan M. O’Brien, MD, formerly of MD Anderson and now associate director for clinical science at Chao Family Comprehensive Cancer Center at the University of California, Irvine (UCI), noted Jabbour’s role in bringing inotuzumab ozogamicin and blinatumomab from the lab to the clinic. “He was very involved in the development of the 2 antibodies that we have for relapsed ALL, which have now become standard of care,” she said. “He’s extremely focused on trying to improve outcomes for patients with leukemia, and that’s very clear when you talk to him. He’s really quite dedicated to advancing the field.”

Jabbour attributes his productivity to an intense desire to help patients who lack effective treatment options, inspiration from early mentors in his native Lebanon, and the examples set by industrious colleagues
such as his friends and frequent collaborators Garcia-Manero, O’Brien, and Hagop M. Kantarjian, MD, a fellow Lebanese American and world leader in leukemia treatment who chairs MD Anderson’s Department of Leukemia. Both O’Brien and Kantarjian are Giants of Cancer Care® award winners in the leukemia category.

“What makes me proud is to be able to help people who come to see me. I have been able to design a trial for them that really improved their survival, and I’m very happy with this,” Jabbour said in a recent interview with OncologyLive®. “When I see people referred to me because I have a treatment that can save a life—that is a huge reward.”

As he contributes to the rapid pace of change in the field, Jabbour is also working to promote the sharing of new findings and best clinical practices with his colleagues across the country and around the world.

To that end, he is cochairing the 5th Annual Live Medical Crossfire®: Hematologic Malignancies, an interactive virtual webcast that Physicians’ Education Resource®, LLC (PER®) is hosting on July 17. Experts will present current standards of practice and clinical trials for a range of hematologic malignancies and engage in exchanges with the audience.

Because hematological cancers are rarer than solid tumors, information on treatment practices is somewhat less available, so hematologists are particularly interested in learning what their peers are doing, Jabbour said.

“It’s not a meeting where people will come and listen all day long. It’s more practical: What did I learn today, and how can I treat my patient better tomorrow if I see him in the clinic?” Jabbour said. “For example, Dr A from Brooklyn had seen this patient, and this is what he did for him. Well, Dr B from upstate had a similar patient but did something different. So they learn from each other, and then we learn from them.”

The conference will review developments involving the full gamut of hematological malignancies. Jabbour will lead sessions on AML, ALL, CML, chronic lymphocytic leukemia, and MDS/myeloproliferative neoplasms. Other sessions will cover multiple myeloma, lymphomas, and therapies across malignancies.

In ALL, for example, the speakers will include experts on chimeric antigen receptor (CAR) T-cell therapies, bispecific T-cell engagers, antibody-drug conjugates, and minimal residual disease (MRD) management using next-generation sequencing (NGS) assays, Jabbour said. In the AML session he expects to hear about novel therapies such as FLT3 inhibitors and antibodies and how to integrate them into practice. Additionally, he expects commentary on the new standard of care of HMA plus BCL2 inhibitors such as venetoclax (Venclexta) for the treatment of older adults, and investigational menin inhibitors.

**DISCOVERIES IN ALL**

Much of Jabbour’s work focuses on ALL. Relapsed/refractory (R/R) ALL has historically been associated with a poor prognosis, with a cure rate of less than 10% in adult ALL and 30% in pediatric ALL. In adult ALL, the complete remission rate with a standard chemotherapy regimen has been 30% to 40% in the first relapse and 20% to 25% in the second relapse. Five-year survival rates across subtypes is 89% for patients younger than 20 years but only 38% for those 20 years and older.

However, new regimens are revolutionizing the ALL treatment landscape, especially among older patients. Jabbour was principal investigator for a phase 2 trial (NCT01424982) that evaluated the combination of hyper-CVAD plus ponatinib as frontline therapy for patients with previously untreated Ph-positive ALL.

Ponatinib is a third-generation BCR-ABL inhibitor active against ABL1 T315I mutations, which are believed to confer resistance to imatinib (Gleevec) and other TKIs.

During the study, patients received 8 cycles of hyper-CVAD alternating with high-dose methotrexate/cytarabine approximately every 21 days. Ponatinib was dosed at 45 mg daily for the first 14 days of cycle 1 and then, as per a protocol amendment, at 30 mg daily for subsequent cycles, with a further reduction to 15 mg daily for those who reached complete molecular response.

**Fast Facts**

**Treatment of Acute Lymphoblastic Leukemia (ALL)⁹,¹²**

**FOCUS ON MARKERS**

- Cytogenetics and molecular profiling are necessary for appropriate risk stratification in patients with ALL.
- Assessment of the Philadelphia-like signature is essential for decisions regarding postremission therapy and treatment at relapse.
- Minimal residual disease (MRD) is an important assessment marker for risk stratification in ALL and is the best predictor of overall survival.
- Monitoring MRD with real-time quantitative polymerase chain reaction, flow cytometry, or high-throughput–based platforms should be considered a standard practice.

**RELAPSED OR REFRACTORY DISEASE**

- Prognosis with standard chemotherapy:
  - First relapse: complete remission rate 30% to 40%
  - Second relapse: 20% to 25%
  - Adult patients who proceed to allogeneic stem cell transplantation: 10% to 30%
- Novel immunotherapy agents are more effective than conventional therapy for patients with relapsed or refractory disease

**CLINICAL RELEVANCE**

**TOP LINE DATA FROM NCT01371630**

- **Therapy:** inotuzumab ozogamicin plus combination chemotherapy
- **Patient population:** 96 patients with a median age of 37 years
- **Efficacy outcomes:**
  - Overall response rate: 80%
  - Complete response rate: 57%
  - MRD-negativity rate: 83%
  - Estimated 3-year overall survival rate: 33% (95% CI, 23%-43%)
Patients with CD20 expression of 20% or greater also received rituximab (Rituxan) for the first 4 cycles. Twelve doses of intrathecal chemotherapy were administered to prevent central nervous system (CNS) involvement. Maintenance therapy comprised of monthly vincristine, oral prednisone, and daily ponatinib also was given.1 Overall, 86 patients were treated on the study, according to long-term data. The median age was 46 years (range, 21-80), and 23% of participants were 60 years or older. After a median follow-up of 43 months, the regimen resulted in estimated 5-year continuous rates for complete remission, event-free survival, and overall survival (OS) of 84%, 68%, and 73%, respectively. The 3-year OS rate was 66% among patients who underwent hematopoietic stem cell transplant (HSCT) in first remission (n = 18) and 90% for patients who did not undergo HSCT (n = 57; P = .07).5 Kantarjian listed the ponatinib trial among several advances that Jabbour has spearheaded since he became ALL section chief at MD Anderson in 2015. “He has made tremendous discoveries that are changing the way we treat and the way we’re going to treat ALL in the future,” Kantarjian said. “With his endeavors we’re going to be able to cure many more patients, probably 70% or more, with less-intensive chemotherapy and with a shorter course of the whole treatment. Right now it’s about 18 months, but soon we’re going to shrink it down to a year or less.”

Jabbour pointed to other developments that are improving outcomes, including the addition of rituximab to chemotherapy for patients with precursor B-cell ALL, CAR T-cell therapies, and the use of MRD measurements to evaluate response and select treatments.

“We have the tools to cure this disease. I’m saying this with confidence for 2 reasons. No. 1, we have a better understanding of the biology of ALL and therefore we’re able to tailor our therapy strategy based on biology. And second, we have new drugs that, after being tested, have shown promising results,” Jabbour said.

The growing recognition of genetically heterogeneous ALL subtypes, the continuing introduction of new therapies, and the proliferation of successful sequencing studies mean there is no standard of care at the moment, he said.

“I don’t have one therapy that fits all, which is good. The future is to better tailor therapy according to biology and to move away from intensive chemotherapy to more of a targeted approach that can improve the outcome without inducing a lot of toxicities,” Jabbour said.

One emerging approach involves moving novel therapies from the salvage setting to the front line to deintensify chemotherapy, avoid relapse due to TKI resistance, and improve survival. In a recent study, Jabbour and colleagues added sequential blinatumomab to hyper-CVAD to treat patients with newly diagnosed Ph-negative pre-B-cell ALL. Early results of the ongoing phase 2 trial (NCT02877303) were reported at the 62nd American Society of Hematology Annual Meeting and Exposition in December 2020 (ASH 2020).6 There were 34 evaluable patients, with a median age of 36 years (range, 17-59). They received hyper-CVAD alternating with high-dose methotrexate and cytarabine for up to 4 cycles, followed by 4 cycles of blinatumomab at standard doses. Patients with CD20-positive disease received 8 doses of ofatumumab (Arzerra) or rituximab. Prophylactic intrathecal chemotherapy was administered 8 times in the first 4 cycles. Maintenance therapy involved alternating blocks of POMP chemotherapy (mercaptopurine, vincristine, methotrexate, and prednisone) plus blinatumomab. Starting with the 10th patient, the protocol was amended so that those with high-risk disease features received the blinatumomab after 2 hyper-CVAD cycles to avoid the risk of early relapse.6

With a median follow-up of 22 months (range, 1-40), the 2-year complete remission and OS rates were 79% and 86%, respectively. Five patients (15%) relapsed, 12 (35%) underwent allogeneic SCT in first remission (including 1 additional patient who relapsed post-SCT), and 17 (50%) were in continuous remission and were on treatment or completed maintenance at the time of reporting.6 All relapses occurred in patients with established poor-risk features, including 2 during hyper-CVAD cycles before the protocol was amended. Four patients developed grade 2/3 cytokine release syndrome, which resolved with corticosteroids and interruption of blinatumomab. In all, 14 patients (41%) had a neurological adverse event (AE) of any grade due to blinatumomab. One patient discontinued blinatumomab due...
to a blinatumomab-related adverse event of grade 2 encephalopathy and dysphasia.\textsuperscript{6}

**A FUTURE BEYOND CHEMOTHERAPY**

Investigators at MD Anderson and other centers also are testing ways to maximize the benefits of newer agents in adults with ALL, particularly older patients with poor prognoses who are not suitable for intensive chemotherapy. Jabbour has played a leading role in studies that have demonstrated the efficacy of the mini-hyper-CVD regimen combined with antibody therapies both in frontline and salvage settings in Ph-negative ALL.\textsuperscript{7,8}

In March, Jabbour and colleagues published long-term follow-up data from a single-arm phase 2 study (NCT01371630) evaluating salvage therapy in patients with relapsed or refractory (R/R) Ph-negative ALL using inotuzumab ozogamicin plus mini-hyper-CVD with or without blinatumomab. Patients received mini-hyper-CVD alternating with methotrexate/cytarabine plus inotuzumab on day 3 of each of the first 4 courses, with a total of 8 courses every 4 weeks. Participants with CD20-positive expression also received rituximab, and intrathecal therapy was administered as CNS prophylaxis. They also were eligible for POMP maintenance therapy for 3 years.\textsuperscript{9}

Starting with the 68th patient on the study, investigators added 4 courses of blinatumomab to the consolidation phase of therapy and lowered the dose of weekly inotuzumab to reduce the risk of veno–occlusive disease.

In all, 96 patients with a median age of 37 years (range, 17-87) were treated. The overall response rate (ORR) was 80%; 77 patients responded, including 55 (57%) who achieved a complete response (CR). The MRD negativity rate among responders was 83% (62 of 75 patients). Forty-four (46%) patients underwent later allogeneic SCT. Among the 29 patients who received blinatumomab along with inotuzumab, the ORR was 90%, including a CR rate of 52%.\textsuperscript{9}

The estimated 3-year OS rate for the entire population was 33% (95% CI, 23%-43%). Those treated according to the original protocol had a higher 3-year OS rate of 36% (95% CI, 17%-54%) and median OS of 13.9 months compared with 33% (95% CI, 22%-45%) and 13.4 months, respectively, for those who received a lower dose of inotuzumab ozogamicin plus blinatumomab.\textsuperscript{9}

Veno-occlusive disease of any grade occurred in 10 (10%) patients; the rates were 13% with the original schedule and 3% with the use of lower-dose inotuzumab ozogamicin and sequential blinatumomab.

Jabbour said treating patients with ALL without any chemotherapy remains a future goal, but recent studies have had promising results. In the phase 2 GIMEMA trial (NCT02744768) conducted in Italy, 63 adults with newly diagnosed Ph-positive ALL were treated with dasatinib (Sprycel) plus blinatumomab. At a median follow-up of 18 months, OS rate was 95% and disease-free survival rate was 88%. Overall, the regimen was well tolerated, with 21 grade 3 or higher AEs observed, investigators said.\textsuperscript{10}

The Italian group, Gruppo Italiano Malattie Ematologiche dell'Adulto, has announced plans for a phase 3 multicenter study (NCT04722848) of ponatinib plus blinatumomab vs chemotherapy plus imatinib for adults with newly diagnosed Ph-positive ALL. Patients in the control arm who do not achieve a complete hematologic response and/or MRD negativity after the sixth consolidation cycle may cross over to receive blinatumomab, and those who develop an \textit{ABL1} mutation will switch to the experimental arm. After 2 cycles of blinatumomab in the experimental arm and after consolidation in the control arm, patients aged 18 to 65 years will be stratified for transplant allocation.\textsuperscript{11}

Other trends Jabbour noted include the reduced need for transplant due to improved survival and cure rates in populations such as adults with Ph-positive ALL and the use of CAR T-cell therapy that may replace transplantation for some patients. Numerous trials are underway to optimize CAR T therapies and minimize toxicities, and CD22-directed and CD19/CD22 bispecific therapies are being developed to circumvent CD19 escape as a cause of relapse. He also highlighted the importance of NGS-based MRD evaluation as an essential tool to gauge response, abandon ineffective regimens, allow shorter courses of treatment, and confirm cure.

“One of the most exciting things in ALL is eventually to be able to shorten therapy, if we’re able to define short-term therapy based on response. If we can assess for MRD with a very deep technique and if I find true responders, then these patients will be spared the need for intensive chemotherapy or prolonged therapy,” he said.

In an article published last year in the \textit{American Society of Clinical Oncology Education Book}, Jabbour and his coauthors describe MRD data as perhaps the most important predictor of OS. Investigators are now using NGS data to explore individualized or subset-specific treatment algorithms.

“It will be crucial to design prospective clinical studies with modular data to evaluate optimal strategies for specific patient subtypes, or ‘personalized’ medicine, testing immunotherapy and combinations of molecularly targeted drugs or drug combinations,” they wrote.\textsuperscript{12}

**NEW REGIMENS IN AML**

Treatment of patients with AML has also changed dramatically in recent years, with 11 new drug therapies approved since 2017.\textsuperscript{13,14} Jabbour’s contributions include leading a phase 2 study (NCT01289457) that tested idarubicin and cytarabine induction chemotherapy in combination with clofarabine (CIA) or fludarabine (FIA) in patients with newly diagnosed AML.\textsuperscript{15}

The therapies had similar efficacy in younger patients (< 50 years), although FIA was associated with a better toxicity profile. In a sensitivity analysis that censored patients at the time of allogeneic SCT, median OS was 18 months and not reached in the CIA and FIA arms, and the 2-year OS rates were 43% and 53%, respectively ($P = .17$).

Jabbour said he is “fascinated” by the role of BCL2 inhibitors, which have led to new standards of care in AML. He pointed to last year’s landmark phase 3 VIALE-A trial (NCT02993523) of venetoclax plus azacitidine, which showed a sharp reduction in the risk of death compared with azacitidine plus placebo in older adults (median age, 76 years; range, 49-91). At a median follow-up of 20.5 months, the median OS was 14.7 months in the azacitidine/venetoclax group and 9.6 months in the control group (HR for death, 0.66; 95% CI, 0.52-0.85; $P < .001$).\textsuperscript{16}

“We have a new standard of care, and the question is, can we cure more younger patients?” Jabbour said. “The cure rate is really improving at a very high speed,
which is quite, quite good. Of course, for the subset of patients with very bad disease, we urgently need new drugs.”

He noted that venetoclax may improve responses in patients with newly diagnosed AML or R/R AML, when added to the FLAG-IDA regimen, which comprises fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin. According to phase 1b/2 results from an MD Anderson study (NCT03214562) presented at ASH 2020, the combination demonstrated robust efficacy across subgroups with an acceptable safety profile in participants with treatment-naïve or R/R AML.17

Among 62 patients who completed at least 1 cycle of therapy prior to analysis, the ORR was 84%. For participants treated with the recommended phase 2 dose, the ORR was 96% in the newly diagnosed cohort (n = 27) and 74% in the R/R setting (n = 19). The composite complete response rates, comprised of the complete plus partial or incomplete hematologic recovery, were 76%, 89%, and 58%, respectively, for the entire population, the treatment-naïve, and the R/R groups.17

Moreover, deep responses were observed as indicated by the MRD-negativity rates among patients with a composite complete response: 83% in the overall population (39 of 47 patients), 96% among those newly diagnosed (23 of 24), and 82% among those with R/R disease (9 of 11).17

Investigators in several trials are adding further targeted therapies to the combination of HMAs and BCL2 inhibitors, Jabbour said. He is also looking forward to more data on menin pathway inhibitors, which are aimed at activity facilitated by MLL/KMT2A rearrangements (MLLr) and NPM1c mutations that occur in 5% to 10% of acute leukemias and are associated with poor outcomes.

In a phase 1/2a KOMET-001 trial (NCT04752163), the menin pathway inhibitor, in patients with acute leukemias, including ALL and AML, with KMT2A or NPM1 alterations. Additionally, the menin inhibitor, in patients with acute leukemias, including ALL and AML, with KMT2A or NPM1 alterations.

In CML, Jabbour said there is a need for new drugs and combinations that will provide more patients with long-term, deep molecular responses and allow them to stop therapy. He noted that studies are underway to extend use of BCL2 inhibitors and HMAs to CML. He is involved in a number of trials of potential new regimens. These include the third-generation BCR-ABL inhibitor, olverembutinib (HQP1351) in a phase 1 study (NCT04260022) in patients with CML or Ph-positive ALL and chemotherapy plus ponatinib in a phase 2 study (NCT01429820) in patients with ALL. In patients with Ph-positive or BCR-ABL-positive R/R ALL, phase 2 studies include evaluations of low-intensity chemotherapy with ponatinib and blinatumomab (NCT03147612) and the combination of blinatumomab, methotrexate, cytarabine, and ponatinib (NCT03263572).

Several other menin inhibitors also are in development. Kura Oncology, Inc reported clinical activity with a tolerable safety profile in 6 of 8 evaluable patients with R/R AML who received its agent KO-539. The phase 1/2a KOMET-001 trial (NCT04067336) is ongoing, with genetically defined expansion cohorts.19 Daichi Sankyo has launched a phase 1/2 trial (NCT04752163) of the menin inhibitor DS-1594b with or without azacitidine, venetoclax, or mini-hyper-CVD in R/R acute leukemias. And in March, Janssen Research & Development initiated a phase 1 study (NCT04811560) of INJ-75276617, a menin pathway inhibitor, in patients with acute leukemias, including ALL and AML, with KMT2A or NPM1 alterations.

In CML, Jabbour said there is a need for new drugs and combinations that will provide more patients with long-term, deep molecular responses and allow them to stop therapy. He noted that studies are underway to extend use of BCL2 inhibitors and HMAs to CML. He is involved in a number of trials of potential new regimens. These include the third-generation BCR-ABL inhibitor, olverembutinib (HQP1351) in a phase 1 study (NCT04260022) in patients with CML or Ph-positive ALL and chemotherapy plus ponatinib in a phase 2 study (NCT01429820) in patients with ALL. In patients with Ph-positive or BCR-ABL-positive R/R ALL, phase 2 studies include evaluations of low-intensity chemotherapy with ponatinib and blinatumomab (NCT03147612) and the combination of blinatumomab, methotrexate, cytarabine, and ponatinib (NCT03263572).

**BRILLIANT AND CARING**

Jabbour’s passion for medicine began during his childhood. He was deeply inspired by his godfather, a surgeon who treated people injured during Lebanon’s long civil war from the mid-1970s until 1990. As a teenager Jabbour shadowed his godfather in the clinic and sought to emulate him.

“I wanted to become a physician to help people and to pay back to the community,” he said. After medical school he had an internship with Georges Chahine, MD, a hematologist and medical oncologist in Beirut who had previously treated a relative of Jabbour’s. “He had an amazing, human way of caring for patients with cancer.

It was like, wow, I want to be like him,” Jabbour recalled.

During a visit to Lebanon, Kantarjian met Jabbour, who vowed to work for him some day. After studying in France, Jabbour had a fellowship at MD Anderson. With Lebanon struggling with war and civil conflict, he canceled plans to return there. “He’s such a brilliant person that I offered him a position as a leukemia researcher,” Kantarjian said.

“Since then he has been one of the fastest-rising stars in leukemia at MD Anderson and in the world.” When O’Brien left MD Anderson for UCI, Kantarjian asked Jabbour to succeed her as ALL section chief.

Jabbour says he became an oncologist not only because of his inspiring mentors but also because it allows him to make a big difference in the lives of people who are suffering. “The relationship you establish with your patient—you become like his adviser, his confidant. He will share with you all kinds of stories about his life. There’s nothing in medicine that can forge or create this bond between a physician and his patient...like oncology,” he said.

“I picked oncology because we need to make progress, and I felt the field was evolving dynamically,” he added. “It’s so much fun, not in a way where you laugh, but the fun of working hard to find a cure to help somebody. This is priceless.”

Garcia-Manero said Jabbour not only treats his patients with great compassion and creates life-extending treatments, but also takes the time to offer free advice to patients around the world. He also is a mentor to young oncologists, including many in Lebanon who have gone on to become the country’s top leukemia experts. Before the pandemic, Jabbour was also a world traveler, sharing his knowledge with other oncologists and relishing opportunities to meet and talk with local people in places he visited.

“He is an extremely caring individual, and he’s totally devoted to the care of his patients,” Garcia-Manero said. “He’s one of the busiest clinicians at MD Anderson—not in the department, but at MD Anderson. He’s an extreme collegial individual who basically cannot say no to anything you ask him. I’m very proud to work with him.”
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Neoadjuvant Nivolumab/Chemotherapy Improves pCR in Resectable NSCLC

by MATTHEW FOWLER

NEoadjuvant Treatment with Nivolumab (Opdivo) combined with chemotherapy led to a significant improvement in pathologic complete response (pCR) rate vs chemotherapy alone in patients with resectable non–small cell lung cancer (NSCLC), according to results of the CheckMate 816 trial (NCT02998528) presented at week 1 of the American Association for Cancer Research Virtual Annual Meeting 2021.

Additional findings showed that the combination did not decrease the ability to perform surgery.

“CheckMate 816 is the first phase 3 trial to show a benefit of neoadjuvant immunotherapy plus chemotherapy, and this has the potential to represent a new treatment option for patients with early-stage, resectable non–small cell lung cancer,” Patrick Forde, MBCh, said during a press conference held ahead of the meeting. Forde is an associate professor of oncology and director of the thoracic clinical research program at The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and is an associate member of the Bloomberg~Kimmel Institute for Cancer Immunotherapy in Baltimore, Maryland.

“We know that neoadjuvant adjuvant chemotherapy is recommended for patients with resectable non–small cell lung cancer. However, the 5-year overall survival gain is only 5%,” explained Forde, adding that previous phase 2 studies demonstrated that neoadjuvant therapy with nivolumab, either as monotherapy or in combination with chemotherapy, demonstrated encouraging pCR rates.

As a result, investigators randomly assigned patients 1:1 to receive treatment with either 360 mg nivolumab every 3 weeks plus platinum-doublet chemotherapy (n = 179) every 3 weeks for 3 cycles or chemotherapy alone (n = 179) every 3 weeks for 3 cycles. Both regimens were followed by surgery within 6 weeks after treatment.

The primary end points were pCR, defined as no residual viable tumor in both the resected lung specimen and the sampled lymph nodes after surgery by blinded independent pathological review (BIPR) and event-free survival by blinded independent central review (BICR). Overall survival, major pathological response per BIPR, and time to death or distant metastases served as secondary end points. Key exploratory end points were objective response rate per BICR and potential predictive biomarkers, including PD-L1 and tumor mutational burden.

To be eligible, patients had to have clinical stage IB (≥ 4 cm) to IIA resectable NSCLC, ECOG performance status 0 to 1, and no known EGFR/ALK alterations.

Forde noted that the study continues to mature for data from the event-free survival coprimary end point.

In the intention-to-treat (ITT) population, the pCR rate with nivolumab plus chemotherapy was improved to 24%, compared with 2.2% with chemotherapy alone (OR, 13.94; 99% CI, 3.49-55.75; P < .0001). Among patients who completed resection, patients treated with the combination regimen demonstrated a pCR rate of 30.5%, compared with 3.2% in patients who received chemotherapy only. Similarly, an analysis of the primary tumor only in the intention-to-treat population showed an improvement in pCR with the combination treatment vs chemotherapy alone (25.7% vs 2.8%, respectively).

In an exploratory analysis, the pCR rate...
with nivolumab plus ipilimumab (Yervoy) in the ITT population was 20.4% (95% CI, 13.4%-29.0%).

Moreover, this improvement in pCR was consistent across subgroups, including disease stage (IB/II, 26.2% vs 4.8%, respectively; ≥ IIIA, 23.0% vs 0.9%), NSCLC subtype, PD-L1 status (< 1%, 16.7% vs 2.6%; ≥ 1%, 32.6% vs 2.2%), and tumor mutational burden status (low, 22.4% vs 1.9%; high, 30.8% vs 2.7%). Patients treated with nivolumab plus chemotherapy also were more likely to have circulating tumor DNA (ctDNA) clearance compared with patients treated with chemotherapy alone (56% vs 34%, respectively), in particular between cycle 1 and cycle 3 of neoadjuvant therapy. “Indeed, those patients who did have ctDNA clearance appear to be more likely to have a pathological complete response at the time of surgery,” Forde said.

In addition, the combination regimen increased the major pathological response rate, defined as 10% or less viable tumor in the lung and lymph nodes, to 36.9%, compared with 8.9% in the chemotherapy-alone arm. Presurgery objective response rate on imaging in the combination arm was 53.6% compared with 37.4% in the chemotherapy arm, and radiographic down-staging rates were 30.7% compared with 23.5%, respectively.

Lastly, 83.2% of patients who received nivolumab in addition to chemotherapy went on to receive definitive surgery, compared with 75.4% of patients in the chemotherapy arm.

Surgery was canceled because of adverse effects (AEs) in 2 patients in each arm (1% each) and due to disease progression in 12 patients (7%) in the combination arm and 17 patients (9%) in the chemotherapy-alone arm. Grades 3 to 4 treatment-related AEs occurred in 33.5% vs 36.9%, respectively, and surgery-related AEs in 11.4% vs 14.8%.

REFERENCE

<p>| TABLE. Efficacy Results in the CheckMate 816 Trial |</p>
<table>
<thead>
<tr>
<th>Outcome</th>
<th>ITT population</th>
<th>Patients with resection</th>
<th>Primary tumor analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab plus chemotherapy (n = 179)</td>
<td>Chemotherapy (n = 179)</td>
<td>Nivolumab plus chemotherapy (n = 141)</td>
</tr>
<tr>
<td>pCR rate</td>
<td>24.0%</td>
<td>2.2%</td>
<td>30.5%</td>
</tr>
<tr>
<td>OR, 13.94; 99% CI, 3.49-55.75; P&lt; .0001</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>MPR rate</td>
<td>36.9%</td>
<td>8.9%</td>
<td>46.8%</td>
</tr>
<tr>
<td>OR, 5.70; 95% CI, 3.16-10.26</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

ITT, intention to treat; MPR, major pathological response; NR, not reported; ORR, objective response rate; pCR, pathological complete response.

Durable Activity With Atezolizumab Points to New Genomic Markers in Advanced Solid Tumors

by AUDREY STERNBERG

ATEZOLIZUMAB (TECENTRIQ) ELICITED DURABLE clinical activity irrespective of microsatellite instability (MSI) status in patients with advanced solid tumors with a tumor mutational burden (TMB) of more than 16 mutations per megabase (mut/Mb). Results from an analysis of the multibasket phase 2 MyPathway (NCT02091141) study were presented during the American Association for Cancer Research Virtual Annual Meeting 2021.

In the efficacy population of 42 patients with high TMB (≥ 16 mut/Mb), the confirmed objective response rate (ORR) was 38.1% (95% CI, 23.6%-54.4%), comprised of both complete (CR) and partial responses (PRs). The disease control rate (DCR) in this group was 61.9% (95% CI, 45.6%-76.4%). “Among patients with a FoundationOne [CDx] TMB of at least 16 mut/Mb, we observed meaningful clinical activity regardless of MSI status, suggesting that there are genomic mechanisms other than MSI that drive response to atezolizumab in this population,” said Claire F. Friedman, MD, one of the lead authors of the study and an oncologist at Memorial Sloan Kettering Cancer Center in New York, New York, during a presentation of the data.

 Previous studies have suggested that immune checkpoint inhibitors targeting PD-1 or PD-L1 may result in better response rates in tumors with high TMB. For example, the PD-1 inhibitor pembrolizumab (Keytruda) recently received FDA approval for use in solid tumors with a TMB of 10 mut/Mb or higher. However, the proper threshold for treatment has been disputed, with retrospective studies suggesting that a threshold of 16 mut/Mb may enrich for response in various tumor types.
In the current analysis, investigators assessed activity and safety of atezolizumab in patients with advanced solid tumors categorized into 2 groups: high TMB and other TMB expression (≥ 10 and < 16 mut/Mb). Patients received atezolizumab 1200 mg every 3 weeks until loss of clinical benefit. Eligible patients on the atezolizumab arm of the MyPathway study (n = 121) were aged at least 18 years, had any advanced solid tumors, a TMB of 10 mut/Mb or more by a clinical laboratory improvement amendments (CLIA) assay, and no satisfactory alternative treatment options. Patients could not have had prior treatment with a checkpoint inhibitor. The primary end point was investigator-assessed ORR by RECIST 1.1 in patients with high TMB with secondary outcomes of duration of response (DOR), DCR, progression-free survival (PFS), and safety. Outcomes in patients with other TMB expression levels were exploratory end points.

In the atezolizumab arm, 56 patients had high TMB expression and 62 had other TMB expression by CLIA. The FoundationOne CDx assay was used for the TMB testing in the primary analysis to limit variability in TMB measurements between different gene panels. The resulting efficacy population included 90 patients; 42 had high TMB and 48 had other TMB expression. The majority of patients in efficacy population were female (45.2% vs 71.4%, respectively), White (88.1% vs 69.4%), and had an ECOG performance status of 1 (73.8% vs 65.3%).

Patients with high TMB expression had a median number of prior lines of therapy of 2 (range, 0-13) vs 3 (range, 0-14) in the lower-expression group. In patients with high TMB, there were 3 CRs and 13 PRs. Median PFS was 5.7 months (95% CI, 2.7-8.5), the median overall survival (OS) was 19.8 months (95% CI, 19.8-not evaluable), and the DCR was 61.9% (95% CI, 45.6%-76.4%). In the group of patients with TMB expression of at least 10, the ORR was 2.1% (95% CI, 0.1%-11.1%), comprised of 1 PR, and the DCR was 22.9% (95% CI, 12.0%-37.3%). Median PFS and OS were 1.8 months (95% CI, 1.4-2.6) and 11.4 (95% CI, 5.3-15.7), respectively. The median DOR was not reached in either group.

In the total cohort with any CLIA testing for TMB (n = 42), patients with high TMB expression had an ORR of 28.6% (95% CI, 17.3%-42.2%) vs 3.1% (95% CI, 0.4%-10.8%) with other TMB expression (n = 48). Of note, overall agreement between FoundationOne CDx and other assays was 74.4%, or in 29 of 39 patients assessed.

Response rates increased in step with incremental TMB cutoffs, with a log odds ratio of response for an increase of 1 mut/Mb resulting in a slope of 0.119 (95% CI, 0.078-0.160).

To investigate the correlation with MSI status, investigators stratified patients into 3 groups: high TMB and high MSI (n = 11), high TMB and not high MSI (n = 30), and TMB between 10 and less than 16 and not high MSI (n = 45). The ORRs in these groups were 54.5%, 30.0%, and 2.2%, respectively, with corresponding DCRs of 72.7%, 56.7%, and 22.2%. Similarly, patients with high TMB who were also stratified by PD-L1 status by tumor proportion scores of less than 1 (n = 15), between 1 and 50 (n = 5), and 50 or greater (n = 6) had ORRs of 33.3%, 40.0%, and 50.0%, respectively.

“This suggests that atezolizumab has meaningful activity in patients with tumors characterized by a TMB of at least 16 mut/Mb, regardless of MSI status,” Friedman said. “In subgroups by PD-L1 status, we observed meaningful activity in subgroups, although [they] are numerically increased with higher tumor proportion or combined positive scores.”

In patients with high TMB by FoundationOne CDx, notable responses were seen in 10 patients with colorectal cancer (ORR, 70%; 95% CI, 34.8%-93.3%) and in 1 patient with biliary tract cancer determined to be MSI not high who had a CR. Other tumor types with response included breast and head and neck cancers that were MSI not high and pancreatic and cervical cancers that were MSI high.

Atezolizumab was generally well tolerated, with a low rate of study drug withdrawal and no dose reductions or deaths related to study drug. Treatment-emergent adverse effects were noted in 90.9% of patients, with 33.1% considered serious events and 47.9% being grade 3 or higher. Treatment-related adverse effects occurred in 56.2%, with serious events accounting for 6.6% of the population and grade 3 or greater events in 12.4%.

REFERENCES
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Copanlisib/Rituximab Improves PFS in Relapsed Indolent Non-Hodgkin Lymphoma

by GINA MAURO

THE COMBINATION OF COPANLISIB (Aliqopa) and rituximab (Rituxan) was associated with a 48% reduction in the risk of disease progression or death compared with rituximab plus placebo in patients with relapsed indolent non-Hodgkin lymphoma (NHL), according to primary results from the phase 3 CHRONOS-3 study (NCT02367040) presented at the American Association for Cancer Research Virtual Annual Meeting 2021.

At a median follow-up of 19.2 months, findings showed that the median progression-free survival (PFS) with copanlisib/rituximab was 21.5 months (95% CI, 17.8-33.0) compared with 13.8 months (95% CI, 10.2-17.5) with rituximab/placebo (HR, 0.520; 95% CI, 0.393-0.688; P < .0001). Moreover, the combination of copanlisib/rituximab demonstrated a manageable safety profile consistent with prior reports of copanlisib and rituximab as single agents.

“Copanlisib represents the first PI3K inhibitor to be safely combined with rituximab and the first to demonstrate broad and superior efficacy in combination with rituximab across indolent histologic subtypes,” Matthew J. Matasar, MD, associate member of Lymphoma Service in the Department of Medicine at Memorial Sloan Kettering Cancer Center in New York, New York, said in a virtual presentation of the data.

“Overall, this combination of copanlisib plus rituximab represents a potential new treatment option for patients with relapsed disease across all subtypes of indolent B-cell lymphoma.”

Single-agent rituximab is a standard treatment for patients with relapsed, indolent NHL who have had a long remission following rituximab-based treatment or who are unwilling or unfit to undergo chemotherapy. However, the benefit of this approach is short lived, Matasar said.

Copanlisib, which is currently indicated for the treatment of patients with relapsed follicular lymphoma (FL) who have previously received 2 or more systemic therapies, is a potent, pan-class I PI3K inhibitor that has selective activity against the α and δ isoforms.

The CHRONOS-3 study enrolled patients with CD20-positive indolent B-cell lymphoma; this included those with grades 1 to 3a FL, marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), and lymphoplasmacytic lymphoma (LPL)/Waldenström macroglobulinemia (WM). These patients had relapsed following rituximab, a rituximab biosimilar, or an anti-CD20 antibody. Patients also needed to be progression and treatment free for at least 12 months since receiving the last rituximab-containing regimen or for at least 6 months and unwilling or unfit to receive chemotherapy.

Patients were treated with either copanlisib/rituximab (n = 307) or placebo/rituximab (n = 151). Copanlisib was administered intravenously (IV) at 60 mg on days 1, 8, and 15 of a 28-day cycle; rituximab was given at 375 mg/m² on days 1, 8, 15, and 22 during cycle 1 and on day 1 of cycles 3, 5, 7, and 9. In the control arm, placebo was given at 60 mg IV on days 1, 8, and 15 of a 28-day cycle.

### TABLE. Efficacy Results in the CHRONOS-3 Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rituximab plus copanlisib (n = 307)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>21.5 (17.8-33.0)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.520; 95% CI, 0.393-0.688; P &lt; .0001</td>
</tr>
<tr>
<td>Centrally assessed ORR</td>
<td>81%</td>
</tr>
</tbody>
</table>

| Follicular lymphoma                          | Rituximab plus copanlisib (n = 184) | Placebo plus rituximab (n = 91) |
|                                              | Median PFS, months (95% CI)         | 22.2 (17.8-33.1)                   | 18.7 (10.2-21.1)                        |
|                                              | HR, 0.58; 95% CI, 0.40-0.83; P = .001                                           |
| Centrally assessed ORR                       | 85%                               | 54%                                    |

| Marginal zone lymphoma                       | Rituximab plus copanlisib (n = 66) | Placebo plus rituximab (n = 29) |
|                                              | Median PFS, months (95% CI)         | 22.1 (13.8-NE)                    | 11.5 (5.6-16.3)                        |
|                                              | HR, 0.48; 95% CI, 0.25-0.92; P = .012                                           |
| Centrally assessed ORR                       | 76%                               | 41%                                    |

| Small lymphocytic lymphoma                   | Rituximab plus copanlisib (n = 35) | Placebo plus rituximab (n = 15) |
|                                              | Median PFS, months (95% CI)         | 14.2 (10.9-20.5)                   | 5.7 (3.5-11.0)                        |
|                                              | HR, 0.24; 95% CI, 0.11-0.53; P < .0001                                         |
| Centrally assessed ORR                       | 77%                               | 13%                                    |

<table>
<thead>
<tr>
<th>Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia</th>
<th>Rituximab plus copanlisib (n = 22)</th>
<th>Placebo plus rituximab (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>33.4 (15.5-NE)</td>
<td>16.6 (4.4-27.4)</td>
</tr>
<tr>
<td>HR, 0.44; 95% CI, 0.16-1.23; P = .054</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centrally assessed ORR</td>
<td>68%</td>
<td>56%</td>
</tr>
</tbody>
</table>

NE, not estimable; ORR, objective response rate; PFS, progression-free survival.
The primary end point of the trial was PFS by central review; secondary end points were objective response rate (ORR), disease control rate, duration of response, complete response rate, time to progression, overall survival, safety, and patient-reported outcomes (PROs). Tertiary end points included pharmacokinetics, biomarkers, and additional PROs.

Baseline characteristics were similar between the 2 arms. The median age of study participants was 63 years (range, 28-91) and 52.0% were male. Additionally, 14.6% of patients had a medical history of diabetes, and 36.5% had history of hypertension. When broken down by histology, 60.0% of patients had FL; of these patients, 19.0% had grade 1 disease, 27.9% had grade 2 disease, and 13.1% had grade 3 disease. Moreover, 20.7% had MZL, 10.9% had SLL, and 8.3% had LPL/WM.

The median time since the last systemic therapy received was 25.2 months (range, 0.8-192.5), and the median time since initial diagnosis was 63.2 months (range, 10.3-349.2). Additionally, 80.3% of patients were progression and treatment free for at least 12 months since their last rituximab-containing regimen, and 19.7% of patients were unwilling/unfit to receive chemotherapy. Moreover, 48.3% of patients had undergone at least 1 prior line of systemic therapy, 25.1% had received 2 prior lines, and 26.6% had 3 prior lines.

The primary efficacy data also showed that the PFS benefit was observed across all histologies (TABLE).

Additionally, the centrally assessed ORR was significantly higher with copanlisib/rituximab vs placebo/rituximab, at 81.0% vs 48.0%, respectively ($P < .0001$).

Regarding safety, all-grade treatment-emergent adverse effects (TEAEs) occurred in 100% and 91.8% of patients on copanlisib/rituximab and placebo/rituximab, respectively. Grade 3 TEAEs were reported in 53.4% and 43.2% of patients, respectively, and grade 4 TEAEs were experienced by 35.8% and 13.0% of patients, respectively.

All-grade serious TEAEs occurred in 47.2% and 18.5% of patients on copanlisib/rituximab and placebo/rituximab, respectively. Grade 3 serious TEAEs occurred in 26.7% and 13.0% of patients, respectively; grade 4 TEAEs were in 13.0% and 0.7%, respectively.

The most common all-grade TEAEs on the copanlisib/rituximab arm were hyperglycemia (69.4%) and hypertension (49.2%), which Matasar noted were toxicities associated with copanlisib. Grade 3 and 4 hyperglycemia occurred in 48.2% and 8.1% of patients, respectively. Grade 3 and 4 hypertension was observed in 39.7% and 0% of patients, respectively. Grade 4 neutropenia occurred in 8.8% of patients on copanlisib/rituximab.

Pneumonitis was an AE of special interest, and it was observed in 6.8% (grade 3, 2.0%; grade 4, 0.7%) of patients on copanlisib compared with 1.4% (grade 3, 0.7%) of those on placebo/rituximab.

Grade 5 TEAEs were reported in 6 patients (2.0%) treated with copanlisib/rituximab; one of these effects, pneumonitis, was related to study treatment. One patient on rituximab/placebo died.

“...across indolent histologic subtypes.”

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IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients who received IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA® in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA®, respectively. The mechanism for the bleeding events is not well understood. Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jirovecii pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: In 645 patients with B-cell malignancies who received IMBRUVICA® as a single agent, grade 3 or 4 neutropenia occurred in 23% of patients, grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 3%, based on laboratory measurements. Monitor complete blood counts monthly.

Cardiac Arrhythmias and Cardiac Failure: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA®. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% of 1,476 patients who received IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. At baseline and then periodically, monitor patients clinically for cardiac arrhythmias and cardiac failure. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias and cardiac failure appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension: Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months). Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.
Second Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,476 patients who received IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA®. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA® and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during the same time period.

ADVERSE REACTIONS
The most common adverse reactions (≥30%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (54.5%)*, diarrhea (43.8%), fatigue (39.1%), musculoskeletal pain (38.8%), neutropenia (38.6%)*, rash (35.8%), anemia (35.0%)*, and bruising (32.0%).

The most common Grade ≥ 3 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (20.7%)*, thrombocytopenia (13.6%)*, pneumonia (8.2%), and hypertension (8.0%).

Approximately 9% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions.

Approximately 4-10% (CLL/SLL), 9% (MCL), and 7% (WM [5%] and MZL [13%]) of patients discontinued due to adverse reactions.

*Treatment-emergent decreases (all grades) were based on laboratory measurements.

DRUG INTERACTIONS
CYP3A Inhibitors: Co-administration of IMBRUVICA® with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Dose modifications of IMBRUVICA® may be recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA® if strong inhibitors are used short-term (e.g., for ≤ 7 days). See dose modification guidelines in USPI sections 2.3 and 7.1.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS
Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe hepatic impairment. In patients with mild or moderate impairment, reduce recommended IMBRUVICA® dose and monitor more frequently for adverse reactions of IMBRUVICA®.

Please see Brief Summary on the following pages.

IMBRUVICA® (ibrutinib) capsules, for oral use

INDICATIONS AND USAGE

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients who received IMBRUVICA. Major hemorrhage (≥ Grade 3, serious, or any central nervous system event; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA, respectively.

The mechanism for the bleeding events is not well understood. Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA without anticoagulant or antiplatelet therapy experienced major hemorrhage. The addition of anticoagulant therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without anticoagulant therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding. Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding [see Clinical Studies (14) in Full Prescribing Information].

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA in clinical trials [see Adverse Reactions]. Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jirovecii pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: In 645 patients with B-cell malignancies who received IMBRUVICA as a single agent, grade 3 or 4 neutropenia occurred in 22% of patients, grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 3%, based on laboratory measurements.

Monitor complete blood counts monthly.

Cardiac Arrhythmias and Cardiac Failure: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA. Grade 3 or greater ventricular tachycardias occurred in 0.2% of patients, Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% of 1,476 patients who received IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias [see Adverse Reactions].

At baseline and then periodically, monitor patients clinically for cardiac arrhythmias and cardiac failure. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias and cardiac failure appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines [see Dosage and Administration (2.2) in Full Prescribing Information].

Hypertension: Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months). Monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust antihypertensive medication throughout treatment with IMBRUVICA as appropriate.

Second Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,476 patients who received IMBRUVICA in clinical trials. The most frequent secondary primary malignancy was non-melanoma skin cancer (6%).

IMBRUVICA® (ibrutinib)

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2- to 4-times higher than those reported in patients with hematologic malignancies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose. [see Use in Specific Populations].

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

• Hemorrhage [see Warnings and Precautions]
• Infections [see Warnings and Precautions]
• Cytopenias [see Warnings and Precautions]
• Cardiac Arrhythmias and Cardiac Failure [see Warnings and Precautions]
• Hypertension [see Warnings and Precautions]
• Second Primary Malignancies [see Warnings and Precautions]
• Tumor Lysis Syndrome [see Warnings and Precautions]

Clinical Trials Experience: Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

The data in the WARNINGS AND PRECAUTIONS reflect exposure to IMBRUVICA in 6 trials as a single agent at ≥ 420 mg orally once daily in 475 patients and at ≥ 560 mg orally once daily in 174 patients and in 4 trials administered in combination with other drugs at ≥ 420 mg orally once daily in 827 patients. Among these 1,476 patients with B-cell malignancies, 87% were exposed for 0 months or longer and 68% were exposed for greater than one year. In this pooled safety population of 1,476 patients with B-cell malignancies, the most common adverse reactions (≥ 30%) were thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, and bruising.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure to IMBRUVICA in one single-arm, open-label clinical trial (Study 1102) and five randomized controlled clinical trials (RESONATE, RESONATE-2, HELIOS, ILLUMINATE, and E1912) in patients with CLL/SLL (n=2,016 total, including n=1,133 patients exposed to IMBRUVICA). In general, patients with creatinine clearance (CLcr) ≥ 30 ml/min, AST or ALT ≥ 2.5 x ULN, or total bilirubin ≥ 1.5 x ULN (unless of non-hepatic origin) were excluded from these trials. In Study E1912, patients with AST or ALT > 3 x ULN or total bilirubin > 2.5 x ULN were excluded. Study 1102 included 51 patients with previously treated CLL/SLL. RESONATE included 386 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab. RESONATE-2 included 267 randomized patients with treatment naïve CLL or SLL who were 65 years or older and received single agent IMBRUVICA or chlorambucil. HELIOS enrolled study 1102 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with BR or placebo in combination with BR. ILLUMINATE included 228 randomized patients with treatment naïve CLL/SLL who were 65 years or older or with coexisting medical conditions and received IMBRUVICA in combination with obinutuzumab or chlorambucil in combination with obinutuzumab. E1912 included 510 patients with previously untreated CLL/SLL who were 70 years or younger and received IMBRUVICA in combination with rituximab or received fludarabine, cyclophosphamide, and rituximab (FCR). The most common adverse reactions in patients with CLL/SLL receiving IMBRUVICA (≥30%) were thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, bruising, and nausea.

Four to 10 percent of patients with CLL/SLL receiving IMBRUVICA discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, neutropenia, arthralgia, rash, and thrombocytopenia. Adverse reactions leading to dose reduction occurred in approximately 8% of patients. Study 1102: Adverse reactions and laboratory abnormalities from Study 1102 (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 1 and 2.
† One patient death due to histiocytic sarcoma.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>59</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomatits</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising</td>
<td>51</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sinusits</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Skin infection</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal pain</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, unspecified</td>
<td>Second malignancies</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Stomatits*</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

Table 2: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Percent of Patients (N=51)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets decreased</td>
<td>69</td>
<td>12</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>53</td>
<td>26</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>43</td>
<td>0</td>
</tr>
</tbody>
</table>

* Based on laboratory measurements per IWCLL criteria and adverse reactions. Treatment-emergent Grade 4 thrombocytopenia (8%) and neutropenia (12%) occurred in patients.

Table 4: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th></th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>51</td>
<td>23</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>36</td>
<td>0</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

Table 5: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th></th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>51</td>
<td>23</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>36</td>
<td>0</td>
</tr>
</tbody>
</table>
**IMBRUVICA® (ibrutinib)**

Patients with CLL/SLL in RESONATE-2

Adverse reactions described below in Table 5 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=135)</th>
<th>Chlorambucil (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42</td>
<td>17</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Stomatits*</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Bruising*</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin infection*</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension*</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

**IMBRUVICA® (ibrutinib)**

HELIOS: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + BR (N=287)</th>
<th>Placebo + BR (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>34</td>
<td>26</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
<td>23</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Bruising*</td>
<td>20</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA + Obinutuzumab (N=287)</th>
<th>Placebo + Obinutuzumab (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>48</td>
<td>64</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>36</td>
<td>28</td>
</tr>
</tbody>
</table>
| Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo + BR. 

**iLLUMINATE**: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + Obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median of 5.1 months in iLLUMINATE in patients with previously untreated CLL/SLL.

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=113)</th>
<th>Chlorambucil (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>48</td>
<td>64</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>36</td>
<td>28</td>
</tr>
</tbody>
</table>
| Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo + BR. 

**iLLUMINATE**: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + Obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median of 5.1 months in iLLUMINATE in patients with previously untreated CLL/SLL.

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>48</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>36</td>
</tr>
</tbody>
</table>
| Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo + BR. 

**iLLUMINATE**: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + Obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median of 5.1 months in iLLUMINATE in patients with previously untreated CLL/SLL.

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>48</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>36</td>
</tr>
</tbody>
</table>
| Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo + BR. 

**iLLUMINATE**: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + Obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median of 5.1 months in iLLUMINATE in patients with previously untreated CLL/SLL.

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>48</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>36</td>
</tr>
</tbody>
</table>
| Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo + BR. 

**iLLUMINATE**: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + Obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median of 5.1 months in iLLUMINATE in patients with previously untreated CLL/SLL.

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>48</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>36</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

**IMBRUVICA® (ibrutinib)**

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=135)</th>
<th>Chlorambucil (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>55</td>
<td>67</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>47</td>
<td>58</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>36</td>
<td>39</td>
</tr>
</tbody>
</table>

Treatment-emergent Grade 4 thrombocytopenia (1% in the IMBRUVICA arm vs 3% in the chlorambucil arm) and neutropenia (11% in the IMBRUVICA arm vs 12% in the chlorambucil arm) occurred in patients.
Table 8: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA + Obinutuzumab (N=113)</th>
<th>Chlorambucil + Obinutuzumab (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms
† Includes one event with a fatal outcome

E1912: Adverse reactions described below in Table 9 reflect exposure to IMBRUVICA + rituximab with a median duration of 34.3 months and exposure to FCR with a median of 4.7 months in E1912 in patients with previously untreated CLL/SLL who were 70 years or younger.

Table 9: Adverse Reactions Reported in at Least 15% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in E1912 (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA + Obinutuzumab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td>23</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 10: Select Laboratory Abnormalities (≥ 15% Any Grade), New or Worsening from Baseline in Patients Receiving IMBRUVICA (E1912)

<table>
<thead>
<tr>
<th>Hematology abnormalities</th>
<th>IMBRUVICA + Obinutuzumab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils decreased</td>
<td>53</td>
<td>30</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>43</td>
<td>7</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>26</td>
<td>0</td>
</tr>
</tbody>
</table>

Based on laboratory measurements per IWCLL criteria

<table>
<thead>
<tr>
<th>Chemistry abnormalities</th>
<th>IMBRUVICA + Obinutuzumab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine increased</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>AST increased</td>
<td>25</td>
<td>3</td>
</tr>
</tbody>
</table>
Additional Important Adverse Reactions: Cardiovascular Events: Data on cardiovascular events are based on randomized controlled trials with IMBRUVICA (n=2,115; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm). The incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular, and ventricular tachycardia) of any grade was 1.0% versus 0.4% and of Grade 3 or greater was 0.3% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. The incidence of atrial fibrillation and atrial flutter of any grade was 0.4% versus 1.6% and for Grade 3 or greater was 0.4% versus 0.5% in patients treated with IMBRUVICA compared to patients in the control arm. The incidence of ischemic cerebrovascular accidents, ischemic stroke, cerebral ischemia, and transient ischemic attack was 0.4% versus 0.3% and Grade 3 or greater was 0.3% versus 0.2% in patients treated with IMBRUVICA compared to patients in the control arm, respectively.

Diarrhea: In randomized controlled trials (n=2,211; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), diarrhea of any grade occurred at a rate of 43% of patients treated with IMBRUVICA compared to 19% of patients in the control arm. Grade 3 diarrhea in IMBRUVICA-treated patients occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. Less than 1% (0.3%) of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Based on data from 1,050 of these patients, the median time to first onset was 3 days (range, 0 to 708) versus 26 days (range, 0 to 492) for any grade diarrhea and 117 days (range, 3 to 414) versus 194 days (range, 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 7 days (range, 1 to 659) versus 4 days (range, 1 to 367) for any grade diarrhea and 7 days (range, 1 to 78) versus 19 days (range, 1 to 58) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively.

Visual Disturbance: In randomized controlled trials (n=2,211; median treatment duration of 19.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm), blurred vision and decreased visual acuity of any grade occurred in 11% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (5% Grade 1 and <1% Grade 2 and 3).

Based on data from 1,050 of these patients, the median time to first onset was 91 days (range, 0 to 617) versus 100 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 60% versus 71% had complete resolution and 15% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 37 days (range, 1 to 457) versus 26 days (range, 1 to 721) in IMBRUVICA-treated subjects compared to the control arm, respectively.

Long-Term Safety: The safety data from long-term treatment with IMBRUVICA over 5 years of 1,284 patients (treatment-naive CLL/SLL n=162, relapsed/refractory CLL/SLL n=646, relapsed/refractory MCL n=370, and WM n=106) were analyzed. The median treatment duration was 51 months (range, 0 to 96 months) for CLL/SLL, 11 months (range, 0 to 97 months) for MCL, and 47 months (range, 0 to 61 months) for WM. The cumulative rate of hypertension increased over time. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 7% (year 1-2), 9% (year 2-3), 9% (year 3-4), and 9% (year 4-5); the overall cumulative rate was 14%.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hematologic disorders: hematopoietic failure including acute and/or fatal events, hematocrit <30%
- Respiratory disorders: interstitial lung disease
- Metabolic and nutrition disorders: tumor lysis syndrome
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onycholysis, panniculitis, neutrophil dermatoses
- Infections: hepatitis B reactivation
- Nervous system disorders: peripheral neuropathy

Drug Interactions: Effect of CYP3A Inhibitors on Ibrutinib: The coadministration of IMBRUVICA with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors [see Dosage and Administration (2.3) in Full Prescribing Information]. If these inhibitors will be used short-term (such as anti-infectives for seven days or less) [see Dosage and Administration (2.3) in Full Prescribing Information]. Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers [see Clinical Pharmacology (12.3) in Full Prescribing Information].

Use in Specific Populations: Pregnancy: Risk Summary: IMBRUVICA can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities (see Data). Advise pregnant women of the potential risk to a fetus. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the general population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data: Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or marginal zone lymphoma (MZL) and 26 times the exposure in patients with CLL/SLL or Waldenström's Macroglobulinemia (WM) administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily. Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Contraindications: Second primary malignancies: Advise males with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 week after the last dose.

Females and Males of Reproductive Potential: Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating IMBRUVICA.

Lactation: Advise females: IMBRUVICA can cause fetal harm when administered to pregnant women [see Use in Specific Populations]. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month following the last dose.

PEDIATRIC USE: The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

Geriatric Use: Of the 1,124 patients in clinical studies of IMBRUVICA, 64% were ≥ 65 years of age, while 23% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades), pneumonia (Grade 3 or higher), thrombocytopenia, hypertension, and atrial fibrillation occurred more frequently among older patients treated with IMBRUVICA.

Hepatic Impairment: Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.
IMBRUVICA® (ibrutinib)

Reduce the recommended dose when administering IMBRUVICA to patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients more frequently for adverse reactions of IMBRUVICA [see Dosage and Administration (2.4), Clinical Pharmacology (12.3) in Full Prescribing Information].

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- Hemorrhage: Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see Warnings and Precautions].
- Infections: Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection [see Warnings and Precautions].
- Cardiac arrhythmias and cardiac failure: Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, chest discomfort, or edema [see Warnings and Precautions].
- Hypertension: Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy [see Warnings and Precautions].
- Second primary malignancies: Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see Warnings and Precautions].
- Tumor lysis syndrome: Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions].
- Embryo-fetal toxicity: Advise women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions, Use in Specific Populations].
- Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose [see Use in Specific Populations].
- Advise males with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose [see Use in Specific Populations, Nonclinical Toxicology (13.1) in Full Prescribing Information].
- Lactation: Advise women not to breastfeed during treatment with IMBRUVICA and for 1 week after the last dose [see Use in Specific Populations].
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day [see Dosage and Administration (2.1) in Full Prescribing Information].
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose [see Dosage and Administration (2.1) in Full Prescribing Information].
- Advise patients of the common side effects associated with IMBRUVICA [see Adverse Reactions]. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions].
- Advise patients that they may experience loose stools or diarrhea and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration [see Adverse Reactions].

Active ingredient made in China.

Distributed and Marketed by: Pharmacyclics LLC Sunnyvale, CA USA 94085
and
Marketed by: Janssen Biotech, Inc. Horsham, PA USA 19044

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KRAS Pathway Opens Door for Patients With Difficult-to-Treat Ovarian Cancer

by DENISE MYSHKO

DUAL BLOCKADE OF THE RAF/MEK and FEK pathways presents an opportunity for investigators to enhance and expand the number of patients with recurrent low-grade serous ovarian cancer (LGSOC) who can benefit from targeted therapies. LGSOC, which accounts for between 1.02% and 3.64% of all ovarian carcinomas and 4.66% of serous ovarian carcinomas, is molecularly unique from high-grade serous ovarian cancer (HGSOC) with approximately 70% of patients harboring a RAS pathway-associated mutation: approximately 30% have KRAS-mutant disease; 20% have NRAS-, BRAF-, or ARAF-mutant disease; and 20% have other RAS-associated gene mutations.

Investigators are seeking to capitalize on the proficiency of this target in the phase 2 RAMP 201 study (NCT04625270), which will evaluate the dual RAF/MEK inhibitor VS-6766 alone and in combination with the FAK/PYK2 inhibitor defactinib.

LGSOC has a distinct molecular profile, explained Rachel N. Grisham, MD, in an interview. “Patients with low-grade serous ovarian cancer are more likely to have alterations affecting the MAP kinase pathway, and the most frequent alteration that we see in these patients is KRAS mutation. Prior studies looking at single-agent MEK inhibitors have shown promising response rates as high as 25%,” she said, adding that VS-6766 aims to provide a deeper and more sustained response. Grisham serves as section head of ovarian cancer and director of gynecologic medical oncology at Memorial Sloan Kettering Cancer Center, in New York, New York.

A PATH FORWARD

LGSOC is less biologically aggressive compared with HGSOC and has a lower sensitivity to chemotherapy. Treatment options for patients with LGSOC have been limited and recommended first line therapies include platinum chemotherapy combinations or treatment with aromatase inhibitors such as anastrozole or letrozole. Options for patients who experience disease recurrence are limited to rechallenge with chemotherapy, or trametinib (Mekinist) or fulvestrant (Faslodex).

Response rates, however, are limited with less than 10% of patients treated with chemotherapy experiencing a response, 14% with letrozole. Despite 25% of patients achieving a response with trametinib, approximately 31% to 35% of patients discontinue treatment with MEK inhibitors because of adverse effects (AEs). LGSOC is less aggressive biologically compared with HGSOC and typically presents without p53 mutations or homologous recombination deficiency, Grisham explained. “In patients with HGSOC, these alterations allow for platinum-based chemotherapy and PARP inhibitors to work well,” she said.

The dual inhibitory mechanism of action of VS-6766 blocks MEK kinase activity as well as RAF phosphorylation of MEK, which results in the blockade of the RAS pathway, thus limiting compensatory MEK activation. Further, this allows the agent to more completely inhibit ERK signaling and...
Confers enhanced therapeutic activity; however, following this inhibition there is a compensatory increase in FAK signaling. Investigators hypothesized that adding defactinib would result in more effective inhibition of downstream signaling pathway. By combining a FAK inhibitor with the dual MEK and RAF inhibitor, we hope that these tumor cells will not develop resistance to MEK/RAF inhibitors, Grisham said.

In results from a subgroup of patients with refractory LGSOC (n = 21) from the phase 1 FRAME trial (NCT03875820), the combination elicited an overall response rate (ORR) of 52%. The response was improved among patients with KRAS mutations (n = 10) with an ORR of 70% compared with 44% (n = 4/9) in patients with KRAS wild-type disease.

Based on these data, the FDA granted breakthrough therapy designation for the combination of VS-6766 and defactinib to treat patients with recurrent LGSOC regardless of KRAS status after at least 1 prior line of therapy.

**AN UNMET NEED IN OVARIAN CANCER**

Building on early efficacy data for this patient population, RAMP 201 is an adaptive, 2-part, randomized, open-label trial to evaluate the efficacy and safety of VS-6766 alone and in combination with defactinib in patients with recurrent LGSOC with or without a KRAS mutation.

The first part of the study will determine the optimal regimen of either VS-6766 monotherapy or VS-6766 in combination with defactinib. Patients with recurrent LGSOC will be randomized 1:1 in each treatment arm (FIGURE).

Investigators are enrolling between 104 to 134 total patients; 64 patients will be enrolled will be enrolled to the first part of the study. The expansion phase will add between 20 and 30 patients with KRAS mutations and between 20 and 40 patients without KRAS mutations.

Patients will be randomized to receive VS-6766 4.0 mg orally, twice weekly for 3 weeks and then 1 week off or VS6766 2 mg orally, twice weekly along with defactinib 200 mg orally twice a day for 3 weeks and then 1 week off until progression. Secondary end points include ORR, duration of response, disease control rate, progression-free survival, and overall survival.

Investigators will determine the parameters of the expansion phase of the trial based on ORR data and will evaluate efficacy and safety parameters of the regimen selected.

“This is an innovative design to get the results that we need as quickly as possible for this patient population,” Grisham said. “If the combination is more effective, but considerably more toxic, then we may not go forward with the combination. If it doesn’t seem as though the FAK inhibitor is adding to the efficacy, then we would go forward with just the single agent, the dual MEK/RAF inhibitor.”

Grisham noted that recruitment has been faster than expected in the months since the study opened. “We expect that to increase as we open more sites both across the United States and soon in Europe. Hopefully, if we continue at this pace, the study will be complete in less than 2 years,” she said.

Verastem Oncology, the developer of both VS-6766 and defactinib, plan to use data from RAMP 201 to support an accelerated approval of the combination.

**ONGOING RESEARCH**

In addition to patients with LGSOC, the FRAME study has enrolled patients with KRAS-mutant non–small cell lung cancer (NSCLC), KRAS G12V–mutant NSCLC, pancreatic cancer, colorectal cancer, and KRAS-mutant endometrioid cancer.

At the American Association for Cancer Research Virtual Annual Meeting 2021, clinical activity was reported in patients with KRAS-mutant NSCLC (n = 20) who were included in the FRAME trial. Patients had a median of 3 prior lines of treatment (range, 1–5). With a data cutoff of March 5, 2021, the ORR was 15% and the disease control rate was 65%. Of note, investigators reported an ORR of 100% in the 2 patients with KRAS G12V mutations. Further analysis showed a median progression-free survival of 16 weeks and 7 patients remaining on treatment at least 24 weeks.

The phase 1b/2 RAMP 202 trial (NCT04620330) was initiated to evaluate the combination in patients with NSCLC with recurrent G12V or other KRAS mutations. The trial will measure effectiveness, including ORR, and safety of the combination vs VS-6766 alone.

Outside of the FRAME trial, investigators are evaluating the dual inhibitor therapy for the treatment of patients with metastatic uveal melanoma in a phase 2 study (NCT04720417).

“For decades, LGSOC has been a disease that, unfortunately, is less responsive to chemotherapy but that was the option that we had. Now we have these studies looking at exciting new drug combinations that hopefully will be giving us really impressive and sustainable response rates,” Grisham said.
**Immune-Related Gene Signatures May Guide De-escalation Approaches in HER2+ Breast Cancer**

**by KRISTI ROSA**

**DISTINCT GENE SIGNATURES**, with the exception of estrogen receptor (ER) signaling and BRCA1/2, are associated with improvements in pathologic complete response (pCR) and invasive disease-free survival (iDFS) in patients with HER2-positive breast cancer who received trastuzumab (Herceptin) and pertuzumab (Perjeta) alone or in combination with paclitaxel, according to data from a translational analysis of the ADAPT trial (NCT01779206).

Results presented during the European Society for Medical Oncology Breast Cancer Virtual Congress 2021 indicated that the pCR rate with the addition of paclitaxel to trastuzumab and pertuzumab (arm B; n = 42) was 78.6% vs 24.4% with trastuzumab and pertuzumab alone (arm A; n = 92). RNA expression data were available for 117 patients.

For the combined analysis of arms A and B, investigators found that ER signaling and ERBB2 signatures were favorable indicators for achieving a pCR and that PTEN signature was unfavorable. In an analysis of arm A alone, ER signaling and ERBB2 and FOXA1 signatures were favorable for achieving pCR and that BRCA1/2 signature was unfavorable.

Moreover, at a median follow-up of 60 months, a total of 13 iDFS events were observed; 11 were in arm A, and 2 were in arm B. No iDFS events occurred after achieving a pCR. Results from the combined analysis of the 2 arms indicated that immune-related signatures such as tumor inflammation signatures, cytotoxic cells, cytotoxicity, macrophages, MHC2, PD-1, and IDO1, as well as ER signaling signature, were favorable indicators for improved iDFS.

In the arm A-only analysis, additional immune-related signatures—such as HLA class I antigen presenting machinery, CD8-positive T cells, interferon-γ, inflammatory cytokines, PD-L1, PD-L2, and regulatory T cells—were favorable for a better iDFS, but BRCA1/2 signature was not.

Overall, 10 gene expression signatures were associated with pCR and/or iDFS, 3 gene expression signatures were linked with pCR, and 8 gene expression signatures were associated with iDFS in arms A and B combined.

Independently in the neoadjuvant chemotherapy-free arm A, 18 gene expression signatures were associated with pCR and/or iDFS. Independent of ER signaling and ERBB2 and FOXA1 signatures, 4 gene expression signatures were associated with pCR, and 16 gene expression signatures were associated with iDFS.

“Activation of immune-related genes and pathways appears to be associated with improved iDFS in the entire cohort as well as the neoadjuvant chemotherapy-free arm A,” Monika Graeser, MD, of the University Medical Center Hamburg in Germany, said in a presentation of the data. “Patients with upregulated immune-related gene signatures in their tumors could be candidates for de-escalation concepts in HER2-positive early breast cancer.”

HER2 is amplified and overexpressed in approximately 20% of all breast cancers. Over the past 2 decades, the prognosis for patients with early-stage, HER2-positive breast cancer has significantly improved with the advent of HER2-targeted therapies. However, a high proportion of patients are still overtreated with toxic chemotherapy regimens, according to Graeser. Robust prognostic and predictive biomarkers are needed to establish new de-escalation or escalation strategies for this population.

A total of 134 patients were randomized in a 5:2 fashion. Trastuzumab was given every 3 weeks, starting at 8 mg/kg and de-escalated to 6 mg/kg; pertuzumab was also given every 3 weeks, starting at 840 mg an-de-escalated to 420 mg; and paclitaxel was given once weekly at 80 mg/m².

Treatment was given for 12 weeks, and surgery was performed within 3 weeks of completion. Adjuvant therapy was applied according to national guidelines, but chemotherapy could be omitted per investigator discretion.

Translational analysis aiming to identify the association of RNA expression signatures and stromal tumor-infiltrating lymphocytes (sTILs) measured at baseline and at 3 weeks with pCR and iDFS were also presented. Investigators performed Spearman correlations within RNA expression signatures that were significantly associated with pCR and/or iDFS. Immune-related signatures formed a separate cluster, according to Graeser. ERBB2, BRCA1/2, and FOXA1 signatures were not correlated with immune-related signatures. Moreover, ER signaling and PTEN signature were not found to correlate with other signatures; they were independent markers, Graeser noted.

Correlations within RNA expression signatures and sTILs were also examined at baseline (n = 119) and at week 3 (n = 76). No significant correlation was observed between sTILs (at baseline, week 3, or at the delta of the 2) and pCR and iDFS.

“We could see that baseline sTILs correlated with immune-related gene signatures,” Graeser said. “As such, we postulate that immune-related gene signatures can augment morphological data from sTILs regarding immune processes and outcome estimation.”

The investigators projected that multiplex immunohistochemistry could potentially play a key role in examining immune cells in the future.

**REFERENCE**

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IN 2015, WHEN THEN President Barack Obama unveiled the country’s Precision Medicine Initiative in a State of the Union address, some $200 million was directed through the National Institutes of Health (NIH) to facilitate data-sharing and bring returns on this investment, including projects that would allow the collection of genetic samples in minority communities.

“Five years down the road, we’ve realized that there have been several challenges for a full-fledged implementation of the Precision Medicine Initiative, combined with the effective representative samples from multiple ethnic minorities,” said Kashyap Patel, MD, chief executive officer of Carolina Blood and Cancer Care Associates, based in Rock Hill, South Carolina. Patel is the current president of the Community Oncology Alliance (COA) and associate editor of Evidence-Based Oncology.

Patel moderated a discussion, “Disparities in Cancer Care: Sources and Solutions,” which took place March 22, 2021. This was the first webcast of a new initiative by The American Journal of Managed Care®. This initiative, the Oncology Value Coalition, brings together experts in oncology care for online discussions in topics of interest.

Last fall, Patel said, a damning report came from the American Association for Cancer Research, when its assessment on disparities in cancer found the following (FIGURE):

- 34% of all deaths from cancer in those aged 25 to 74 could be prevented by 2035 if disparities in access to care were eliminated; and
- from 2003 to 2006, disparities cost the nation $230 billion in direct medical costs, and indirect costs to society were more than $1 trillion.

“We have failed to address the core issue of bringing equity in access, to get access to research and access to testing,” Patel said.

Disparities in outcomes occur can arise from poverty or lack of transportation, said Karen Winkfield, MD, PhD, a radiation oncologist who last year became executive director of the Meharry-Vanderbilt Alliance in Nashville, Tennessee.

“There are many factors why minority patients may not be able to reach the doctor’s office, and then we blame them for the shortcomings that they have,” Patel said. “That’s beyond their control.”

Winkfield said access issues include testing. As a radiation oncologist, she has seen many patients with breast cancer. “And I cannot tell you how many times there would be a patient who had come, perhaps from an outside institution, who had a biopsy that was done, had their lumpectomy done, and they did not have Oncotype testing as part of that,” she said, referring to the 21-gene test that evaluates recurrence score.

The issue of disparities in cancer is multifactorial, as it can cover not only race, ethnic, and cultural issues, but also gender identification, said Debra Patt, MD, PhD, MBA, an Austin-based breast cancer specialist with Texas Oncology who is secretary of COA.

“Some issues are cultural and some are about trust. Some issues are socioeconomic and some are our exclusion criteria.”

Patt brought up a topic familiar to the whole panel: Medicaid access, or lack of it. Patel and Patt are based in states that have not expanded Medicaid, and Winkfield recently relocated from Wake Forest University in North Carolina, which is among them.

Black patients are more likely to have aggressive breast and prostate cancer and multiple myeloma, while Hispanic populations are likely to have higher rates of cervical and hepatobiliary cancers. But as a physician in 1 of 12 the states that have not expanded Medicaid, Patt said knows geography plays a role, too.

“We have a large portion of adult Texans who don’t have access to health care, period. And so, between ages 19 to 65, that’s about 25% of adults in Texas who don’t have...
access to insurance. We know that patient population, that they’re 6 times more likely to present with advanced cancer, and they die more rapidly of their disease because they present with advanced cancer,” Patt said. “I think the access issue is a real hurdle that has to be overcome. We have to talk about it transparently because it factors into this.”

**IMPLICATIONS OF UNDERSAMPLING MINORITY PATIENTS**

Patel said minority groups also are under-represented in genome-wide association studies that are used in drug development. According to a recent study, the degree to which they are underrepresented is astonishing: By 2017, of 35 million samples, 80% were of Northern European ancestry, even though this population is less than 10% of the population worldwide.5,6

The implications are significant. “What shocks me is that when you look into the personalized medicine, we all are different biologically. So the starting point of the designer drug development process does not have information on who we are,” Patel said.

“Precision medicine has widened the gap to the point that patients of minority [groups] may live [shorter lives] compared to those who are represented in the drug development process,” Patel said. “How do we address that?”

As a breast cancer specialist, Patt sees how this happens up close: If the payer doesn’t cover the test, the test doesn’t happen. In metastatic breast cancer, that’s a lot of missed opportunity. Communicating the need for a test can be more challenging if there are economic and cultural barriers. “Is policy actually a coverage determination policy?” she asked. “I think if we could change those things that it would help.”

**BRINGING CLINICAL TRIALS TO PEOPLE**

Patel spoke of the need to bring clinical trials to underserved areas and involve community oncologists to not only to reduce travel times for rural patients, but also to reduce the level of intimidation some may feel in dealing with an academic center. Winkfield, who earlier in her career was a clinical fellow at Harvard, said there are equally impressive examples of trials close to patients who live far from academic centers.

“There are great examples of community oncologists who are doing the good work of bringing clinical trials right into people’s backyard to make it better for them...to make it more accessible,” Winkfield said. Institutions and national organizations should look for ways to support this work, and she agreed with Patel that “it’s been a long time coming.”

Patt, who manages breast cancer trials for Texas Oncology, said there’s considerable administrative work to bring them to the community level, but it’s worth it. “We have 70 to 80 clinical trials at any given time, and it’s a lot of sweat equity,” she said. “It’s IVs every week and a lot of administrative time and support. But I think it’s really meaningful that community oncologists need to have this as a priority.”

The doctors agreed that more digitization of the administrative work would ease that burden and make trials more cost-effective. Winkfield noted that a “silver lining” of COVID-29 is that oncology practices have learned they can do some administrative steps remotely, such as consents.

**CHANGE IN WASHINGTON**

Is there opportunity for the Biden administration to expand Medicaid access to more patients, or can more be done to help oncology practices reduce disparities? The most obvious recent step is the new round of incentives in the American Rescue Plan of 2021 for the 12 states that have not expanded Medicaid. The panel discussed “carrots and sticks” that can be used in the drug approval process if manufacturers are not doing enough to enroll minority patients, and Winkfield noted the recent spate of withdrawn indications in lung and bladder cancer as a sign that FDA is enforcing requirements.7,8

CMS can take an approach called coverage with evidence development, although attempts to do so in the area of chimeric antigen receptor T-cell therapy have been met with some pushback. Reducing disparities in cancer care has been a major agenda item for every major cancer group in the past year. Patel noted that the second part of the 21st Century Cures Act features an inclusivity mandate—meaning that drugs cannot be approved unless they will treat diverse populations. It will be up to the research community to help hold the pharmaceutical industry’s feet to the fire, he said.

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**FIGURE. Why Disparities Exist?**

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For a full list of references, see the article at Onclive.com.
Patient Experiences Can Affect a Practice’s Financial Health

by MICHAEL BLACKMAN, MD

WHEN CONSIDERING THE ‘HEALTH’ of a medical practice, much of the focus is on financial indicators: missing collections at the time of service, recurring denials, poor claims management, and aging patient balances. However, there is another area needing attention that is often overlooked: patient satisfaction.

The patient experience is a critical factor in the success of any healthcare practice, and its importance is increasing with the rise of health care consumerism. Studies also show a direct correlation between patient experience and profitability. For example, positive patient experience is associated with increased profitability, and a negative patient experience is even more strongly associated with decreased profitability.¹

The link to clinical outcomes is the reason why patient satisfaction has become an important and more frequently used measurement to help access healthcare quality. Since passage of the Affordable Care Act in 2010, the Centers for Medicare & Medicaid Services has also tied Medicare reimbursements to patient satisfaction scores, making these metrics even more of a priority.

THE EFFECT OF COVID-19

The shift to value-based care and the consumerization of health care has been increasing for years, the COVID-19 pandemic put the spotlight on the patient experience. However, as individuals re-evaluated the ways in which they have consumed and received healthcare, and overall, how their preferred providers have reacted to the COVID-19 pandemic.

In Accenture’s “COVID-19 Consumer Health Experience Survey 2020,” 25% of patients who believe their provider is handling COVID-19 poorly say they will not seek further care from the practice – or will wait at least a year until doing so. More concerning, perhaps, is that 64% of patients say they will likely switch providers if their expectations are not met.²

How providers respond to these changing demands and expectations will make or break their financial recovery and future success.

Building Blocks for Creating A Positive Patient Experience

The stakes are high for providers to deliver an exemplary patient experience. If your practice is not already doing so, it’s time to put a stronger emphasis on the patient’s satisfaction.

Here are 5 strategies that can help your practice deliver a positive patient experience and set the foundation for improved financial performance:

► Make a good first impression: A patient’s first interaction often takes place before they even enter the practice. A patient could have seen and read an online review or have received a recommendation from a friend as they were searching for quality health care. Considering you never get a second chance to make a first impression, ensure that your presence, both digitally and physically, is a credible one. Routinely monitor the online review sites where you have a presence and, when possible, set a consistent cadence of responding to both negative and positive reviews, making your patients feel heard. Leverage social media and your website to share important health information to demonstrate your role as a trusted resource in your community.

► Encourage greater patient engagement: Encourage patients to play a more active role in their health and overall care experience. Place emphasis on collaboration by considering the patient’s input and involvement to determine the best course of treatment or care. Instead of simply sending an appointment reminder for a yearly check-up, leverage e-newsletters to educate your patient population on common topics such as allergies, wellness exams, flu season, or even more localized health-related news. Drive greater patient engagement through the use of patient messaging solutions, which offer the ability for providers to check in with patients about their progress or health status.

► Improve access to care: During the pandemic, patients and providers alike relied on virtual care services to not only continue care during periods of quarantines and shutdowns, but also to keep all individuals safe from exposure to the virus. Now that patients are accustomed to telehealth and appreciate its convenience, consider the possibilities for patients who may have previously faced transportation issues, or other social factors that have impeded their access to care. Barring inequities with broadband access in some parts of the country and specific communities, consider educational outreach.

► Add omnichannel conveniences: Virtual visits are not the only conveniences today’s patients expect from their providers. Offering an online portal for scheduling appointments, accessing health records, viewing test results and paying bills gives patients more flexibility to manage their care when and where they want. Medical Group Management Association’s Digital Payment Progress Report found that 77% of providers still send paper bills, even though 52% of patients prefer electronic billing.³

► Improve practice workflow: Leverage innovative technology to transform your practice and make internal processes more efficient. Clinical time should be focused on patients and clinical issues, so the more intuitive the user interface is for providers, the better. Your health IT vendor’s user experience and software design principles should be guided by user-informed persona research and data analysis. Clinicians and office personnel should be able to complete necessary tasks while maintaining patient engagement. In-person communication from the provider can also help set expectations so the patient does not feel ignored during the visit. ▶

Michael Blackman, MD is chief medical officer at Greenway Health, a health information technology services provider in Tampa, Florida.

For a full list of references, see the article at OncLive.com
THE PAST YEAR PRESENTED opportunities for innovative and collaborative change across the spectrum of oncology care, as investigators and institutions worked to adapt practice during the COVID-19 pandemic. Patients with lung cancer were identified as an at-risk group for developing severe complications as a result of SARS-CoV-2 infection, and thoracic oncologists were fast to respond with the establishment of the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT). The global registry collected characteristics and outcomes of patients with thoracic cancers affected by COVID-19, providing oncologists with a database of knowledge for the treatment of similar cases in their clinics.

Data from the registry showed a 34.6% death rate (n=66/191), with 52 (79%) deaths attributed to complications from COVID-19 only and 7 (11%) as cancer progression only. Further, 3 (5%) deaths were due to complications from COVID-19 and cancer progression.1

Marina Chiara Garassino, MD, chief investigator of research for TERAVOLT, spoke with OncologyLive® about stepping up to meet this unprecedented challenge in thoracic oncology.

Garassino, formerly with the Fondazione IRCCS Istituto Nazionale dei Tumori in Milan, Italy, and now a professor in the Department of Medicine, Section of Hematology/Oncology, at the University of Chicago Medicine in Illinois, also discussed the revolution in lung cancer treatment, the COVID-19 pandemic, and what 2021 holds for the field.

Q In the past decade, patients with lung cancer have benefitted from several new treatment avenues, including immunotherapy and targeted treatments. Where does the field stand now?

Throughout my career, I’ve been a part of many studies that have advanced the field, including the identification of patients who are good candidates for targeted-agent therapies for genetic alterations. I was an investigator on 2 trials–CheckMate 017 [NCT01642004] and CheckMate057 [NCT01673867]–the results of which showed for the first time the effectiveness of immunotherapy [in non–small cell lung cancer]. Additionally, results of the KEYNOTE-189 trial [NCT02578680] showed that immunotherapy and chemotherapy together were superior to chemotherapy alone.

Now oncologists have multiple avenues to treat patients with lung cancer, including targeted therapies for many patients who have never smoked and chemotherapy combined with immunotherapy for patients without targetable alterations. Survival rates have increased, and many patients live several years. That said, the next big unmet need is figuring out how to overcome resistance to these therapies. To treat patients with lung cancer, it is important to have multidisciplinary teams like we have at UChicago Medicine, where specialists in different fields share the best treatment strategies for every single patient.

Q COVID-19 has been particularly tough on patients with lung cancer, and you made headlines in 2020 with the TERAVOLT registry. Can you expand on how the registry came to be?

When the pandemic began, I was in Milan. The city was totally unprepared, and we were hit really hard. I sent an email to all my friends in the field around the globe saying that they needed to be prepared, because the virus would spread everywhere. I said we needed to collect data to help cancer patients. In 1 week, we were able to write the protocol, get IRB [institutional review board] approval, and share the protocol with 220 centers around the world. We were able to present our first data within a month, which showed that patients with thoracic cancer with COVID-19 had a 32% mortality rate, higher than other patients with cancer. The community of oncologists came together and ultimately collected data on more than 1500 patients. This information helped us continue to treat our patients during the pandemic. We were also able to demonstrate that
immunotherapy and targeted treatments did not worsen infections.

What does the TERAVOLT research mean for patients with thoracic cancer in 2021?
We issued a call to action to the World Health Organization and other agencies to advocate for early vaccinations for patients with thoracic malignancies. [The information will also allow us] to better treat these patients if they do get COVID-19. It was a wonderful academic effort and incredible opportunity, and now we are working on the final paper of our results.

What does 2021 hold for the future of lung cancer research?
This is a transition year. Of course, we want the survival rate to be 100% and we don’t want patients to become resistant to therapies. Several things are at the forefront now.

The research will focus on putting the treatments in the correct sequence. Another big [area of] development this year will be in neoadjuvant therapy. We are going to continue to find more targeted agents to overcome this resistance. Cancer metabolism will play a big role.

For immunotherapies, we will not just target T cells, but also macrophages and other components of the immune system. Also, vaccines and cellular therapies are now emerging. Patients must be aware of the multiple possibilities to treat lung cancer, and they must be active in selecting the right treatments based on their desires and needs.

You recently moved to University of Chicago Medicine. How will that affect your research?
I’m excited to be a part of the University of Chicago Medicine Comprehensive Cancer Center. I love the diversity and the tradition of research and innovation. I’m looking forward to working with colleagues in different fields. I’m interested in the idea of immune metabolism to shape and create the best condition for immunotherapy. I’m also looking forward to doing more research in artificial intelligence to improve early diagnosis and personalized medicine.

When I first started in this field, my friends told me I was treating a dreadful disease because many of my patients died. But throughout my career, I have seen a revolution in treatments. I see patients living longer. It’s been incredible to dedicate my life to this.

REFERENCE
TREATMENT ADVANCES FOR PATIENTS with non-small cell lung cancer (NSCLC) who harbor HER2, EGFR, KRAS, and MET mutations have generated significant excitement and set the stage for further research aimed at generating better tolerated, more effective, and optimally sequenced treatments.

Nicholas C. Rohs, MD, an assistant professor of medicine, hematology, and medical oncology at the Icahn School of Medicine of Mount Sinai in New York, New York, moderated a discussion on advances with targeted therapies in NSCLC, highlighting the latest and most pivotal data in the thoracic space and how the data apply to clinical practice. This discussion was part of a recent edition of Thoracic Night Live, a video program in lung cancer from OncLive®.

Rohs was joined by Isabel Preeshagul, DO, MBS, an assistant professor and thoracic medical oncologist at Memorial Sloan Kettering Cancer Center, and Joshua K. Sabari, MD, an assistant professor and thoracic medical oncologist in the Department of Medicine at the Grossman School of Medicine at NYU Langone Health’s Perlmutter Cancer Center, both based in New York, New York.

HER2-DIRECTED ADVANCES

HER2 mutations account for 1% to 4% of all lung adenocarcinomas, Rohs said, which has made the data from the phase 2 DESTINY-Lung01 study (NCT03505710) with fam-trastuzumab deruxtecan-nxki (Enhertu) all the more exciting. The trial was divided into 2 cohorts of patients with HER2 overexpression and an activating HER2 mutation.

At the 2020 American Society for Clinical Oncology Virtual Scientific Program, findings from the mutation cohort (n = 42) were presented, demonstrating an objective response rate (ORR) of 61.9% (95% CI, 45.6%-76.4%), a disease control rate (DCR) of 90.5% (95% CI, 77.4%-97.3%), and a median progression-free survival (PFS) of 14 months with the antibody-drug conjugate (ADC).¹

“All you need to do is look at the waterfall plot, which speaks for itself,” Preeshagul said.

The data, which Rohs called “pretty exciting,” led to the incorporation of the agent into the National Comprehensive Cancer Network guidelines for patients with pretreated HER2-mutant advanced NSCLC. Additionally, these data provided the basis for an FDA breakthrough therapy designation for the treatment of patients with metastatic NSCLC whose tumors have a HER2 mutation and who had disease progression on or after platinum-based therapy.²

Findings from the cohort of patients with HER2 overexpression, defined as immunohistochemistry 2+ and 3+, were presented at the 2020 World Conference on Lung Cancer (2020 WCLC) and showed an ORR by independent central review of 24.5% (95% CI, 13.3%-38.9%) and a DCR of 69.4% (95% CI, 3.2-not estimable [NE]) in...
49 evaluable patients. The median duration of response (DOR) was 6.0 months.3

Regarding adverse effects (AEs), Rohs pointed to the increased risk for pneumoni-
tis, including grade 5 events. Pneumonitis is “not common, but it’s something we’ll have to deal with [when using trastuzumab deruxtecan],” Sabari said. He added that none of the patients he has treated with the drug to date have developed pneumonitis.

“The pneumonitis for this drug does not worry me as much as using a combination of a PD-1 inhibitor and a CTLA-4 inhibitor,” Sabari said, adding that the administration of a PD-1/PD-L1 inhibitor should be avoided in the frontline setting, if possible, to reduce the risk of interstitial lung disease.

UPDATES IN EGFR+ NSCLC

Amivantamab-vmjw (Ryrevant), a bispecific antibody of EGFR and c-MET, has opened the door for agents designed to treat an underserved subset of patients with NSCLC whose disease harbors EGFR exon 20 insertion mutations.

Data from the phase 1 CHRYSLIS trial (NCT02609776), presented during the 2020 WCLC, demonstrated an ORR by blinded independent central review of 40% (95% CI, 29%-51%) and a clinical benefit rate of 74% in 81 patients,4 which Sabari called “impressive.” In terms of safety, Sabari said amivantamab is a “relatively well-tolerated medication overall.”

In May, the FDA granted accelerated approval to amivantamab for the treatment of patients with EGFR-positive metastatic NSCLC who harbor exon 20 insertion mutations and whose disease has progressed on or after platinum-based chemotherapy.5 The ongoing phase 3 MARIPOSA trial (NCT04487080), which is evaluating the addition of amivantamab to lazertinib, could enhance the central nervous system (CNS) penetration of the drug.

Another agent in development for patients with EGFR exon 20 insertion is the oral tyrosine kinase inhibitor (TKI) mocertinib (TAK-788). The FDA granted the new drug application priority review in April.6

Findings from the phase 1/2 trial, which served as the basis for the application, showed a confirmed ORR of 43% (95% CI, 24%-63%) in 28 patients treated with mocertinib 160 mg. The median DOR was 14 months (95% CI, 5-not reached), and all 12 patients had a confirmed partial response. The median PFS was 7.3 months (95% CI, 4.4-15.6).7

Preclinical activity of the agent does not show substantial CNS penetration; however, Sabari noted that comparative efficacy and high rate of rash and diarrhea have led to less excitement about the drug.

“Thinking about strategic combinations that have great CNS activity and also potentially have resistance mechanism coverage is going to be really important going forward,” Sabari said.

WHAT’S NEW WITH KRAS G12C?

KRAS G12C mutations account for approximately 13% of all lung adenocarcinomas, Rohs said, and novel KRAS inhibitors are needed to improve outcomes for these patients and fill an unmet need.

On May 28, 2021, the FDA granted accelerated approval to sotorasib (Lumakras) for the treatment of patients with KRAS G12C-mutated locally advanced or metastatic NSCLC after at least 1 previous systemic therapy based on data from the phase 1/2 CodeBreaK 100 trial (NCT03600883).8 Findings from the trial, presented at the 2020 WCLC, showed that sotorasib elicited an ORR of 37.1% (95% CI, 28.6%-46.2%) in 124 heavily pretreated patients, the median PFS was 6.8 months (95% CI, 5.1-8.2), and the disease control rate was 80.6% (95% CI, 72.6%-87.2%).9,10 Further, findings published in The New England Journal of Medicine reported overall survival analysis of 12.5 months (95% CI, 10-NE).10 The agent demonstrated efficacy in predefined subgroups including in patients with STK11, KEAP1, TP53 comutations.

If sotorasib can demonstrate sustained superiority in the ongoing confirmatory phase 3 CodeBreak 200 trial (NCT04303780), it will likely become the new standard of care, Sabari said, calling it a “clear win” for patients.

Another agent under investigation in this population is adagrasib, which elicited an ORR of 45% among 51 evaluable patients and a clinical benefit rate of 96%, according to findings from the phase 1b/2 KRystal-1 trial (NCT03785249) presented at the 2021 European Lung Cancer Conference.11 The median duration of treatment was 8.2 months (range, 1.4-13.1). Results of an exploratory analysis demonstrated a 64% ORR in patients whose tumors harbor KRAS G12C and STK11 comutations (n = 14).

“This a very interesting space because you have 2 drugs that have decent activity but the durability really seems to be an issue, so clearly combinations are the way forward,” Sabari said.

MARKED PROGRESS WITH MET

MET exon 14 skipping mutations represent approximately 3% to 4% of lung adenocarcinomas, but amplifications can be found in up to 6% of cases, Rohs said.

On February 3, 2021, the FDA granted accelerated approval to tepotinib (Tepmetko) for the treatment of adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations based on data from the phase 2 VISION study (NCT02864992).12

In treatment-naive and previously treated patients, tepotinib showed “meaningful responses,” Rohs said. Specifically, the agent elicited an ORR of 43% (95% CI, 32%-56%) and a median DOR of 10.8 months (95% CI, 6.9-NE) among 69 treatment-naive patients. The ORR and median DOR for 83 previously treated patients were 43% (95% CI, 33%-55%) and 11.1 months (95% CI, 9.5-18.5), respectively.13

The indication followed the May 6, 2020, approval of capmatinib (Tabrecta) for the same patient population.14 In terms of deciding between the 2 agents, Rohs advised letting the “slight differences in AE profiles guide us [in terms of treatment decisions].”

Crizotinib (Xalkori)—the first drug to show activity in this setting—is also an option. However, Sabari said that he has “lost interest in it” because of the lack of comparative CNS activity and poor response rate.

In terms of combinations, dual EGFR and MET inhibition is an area of interest and is under study in both the TATTON (NCT02143466) and ORCHARD (NCT03944772) trials, despite the fact that toxicity has been flagged as an issue.

“Is [a] MET inhibitor the answer after progression on a third-generation TKI? [The mutation] only [presents in] 15% to 20% [of patients],” Sabari said. “We need the prospective studies in order to understand [the best path forward].”

For a full list of references, see the article at OncLive.com.
MET Inhibitors Find Their Niche in NSCLC

by JANE DE LARTIGUE, PhD

THREE-QUARTERS OF ALL CASES of lung adenocarcinoma, the most common type of non-small cell lung cancer (NSCLC), are defined by oncogenic driver events involving receptor tyrosine kinase–orchestrated cellular signaling pathways. Armed with this knowledge, investigators have increasingly divided NSCLCs into subsets based on the presence of targetable aberrations, paving the way for an era of personalized medicine.

Since the MET receptor’s carcinogenic role in lung cancer was first described in the 1990s, research efforts to add the receptor to the list of actionable targets in NSCLC have often faltered. Despite the strong rationale behind their development, a host of MET inhibitors with varied mechanisms of action failed to impress in clinical trials.

In the past year, however, the identification of biomarkers permitting optimal patient selection has proved to be the key to success. The FDA has approved 2 MET inhibitors, capmatinib (Tabrecta) and tepotinib (Tepmetko), for the treatment of patients with advanced NSCLC harboring MET exon 14 skipping mutations. These mutations, which vary across major histological subtypes, have been detected in approximately 4% of adenocarcinomas.

Meanwhile, a greater understanding of aberrant MET signaling may help in the development of additional strategies. MET dysregulation not only is a primary oncogenic driver in NSCLC but also is strongly implicated in resistance to targeted therapies in other patient subpopulations, most notably in those treated with EGFR inhibitors.

Ongoing clinical trials are examining MET and EGFR inhibitor doublet therapy in an effort to overcome this mechanism of resistance, and recent data paint a promising picture of this type of combination therapy.

As an alternative to this strategy, several companies are pursuing MET x EGFR bispecific antibodies to target both pathways with a single drug. In May, one such drug, amivantamab-vmjjw (Rybrevant), became the first agent to gain FDA approval for the treatment of patients with EGFR exon 20 insertion mutations, another mechanism of resistance to EGFR inhibition. Investigators are also examining amivantamab for the treatment of patients with NSCLC whose tumors harbor MET exon 14 skipping mutations.

Multikinase inhibitors generally have failed to improve outcomes in patients with NSCLC. Early clinical trials of these and other MET inhibitors were conducted mainly in unselected patient populations, but even in patients selected for MET overexpression, as measured by immunohistochemistry (IHC), the results were disappointing.

Yet MET inhibitors continue to be pursued. Among them are several drugs with novel mechanisms of action, such as telsiotuzumab vedotin, an antibody-drug conjugate composed of a MET-targeted antibody conjugated to the cytotoxic drug monomethyl auristatin E. Results from an ongoing phase 2 trial of telsiotuzumab vedotin in patients with MET-positive advanced NSCLC (NCT03539536) were presented at the American Association for Cancer Research Annual Meeting 2021 in April. In patients with squamous NSCLC, MET positivity was defined as IHC staining of at least 75% of tumor cells at 1+ intensity. In nonsquamous NSCLC, positive MET staining was further divided into high (≥50% at 3+) and intermediate levels (25%-49% at 3+).

Among patients with EGFR wild-type nonsquamous NSCLC, the objective response rate (ORR) was 35.1% (95% CI, 20.2%-52.5%), with ORRs of 53.8% (95% CI, 25.1%-80.8%) and 25.0% (95% CI, 9.8%-46.7%) in those with high and intermediate MET expression, respectively. In patients with EGFR-mutant nonsquamous NSCLC, the ORR was 13.3% (95% CI, 3.8%-30.7%) and responses were observed only in those with high MET expression. In the squamous cohort, the ORR was 14.3% (95% CI, 3.3%-36.3%). All responses were partial. Grade 3 or higher adverse events (AEs) occurred in 44% of patients and, in addition to cancer progression, included pneumonia and hyponatremia.

MET EXON 14 MUTATIONS

Although MET protein overexpression is the most common manifestation of MET dysregulation in NSCLC and is associated with poor
**THE MET NETWORK**

**MET'S ROLE IN CANCER**

by JANE DE LARTIGUE, PhD

**MET IS A PROTO-ONCOGENE THAT** encodes a receptor tyrosine kinase (RTK) also known as the hepatocyte growth factor (HGF) receptor because its only known activating ligand is HGF. Sometimes, HGF is referred to as scatter factor in a nod to the role of MET signaling in motility and invasion.

The MET protein is predominantly found on the surface of epithelial cells, whereas HGF is produced by mesenchymal cells. In normal cells, the MET pathway functions in a variety of important biological processes, including embryogenesis and tissue repair in adults. Dysregulated MET signaling, however, plays a role in oncogenesis by promoting cell proliferation, survival, and angiogenesis, in addition to motility and invasion.

MET functions as a classic RTK (FIGURE); ligand binding triggers dimerization, which enables autophosphorylation at key tyrosine residues that serve as docking sites for adaptor proteins, thereby triggering downstream signaling cascades, such as PI3K/AKT, and MAPK.

Initially synthesized as a precursor protein, the mature MET protein is generated by proteolytic cleavage, yielding 2 subunits linked by a disulfide bridge. MET is composed of several domains: an extracellular domain through which it binds to HGF, and an intracellular portion containing a juxtamembrane domain, the catalytic domain, and a C-terminal domain wherein the docking sites are located.

MET signaling is dysregulated across a number of tumor types via various mechanisms. In lung cancer, the most common manifestation is protein overexpression. With MET protein expression detected by immunohistochemical analysis, the reported prevalence of MET-expressing lung cancers varies widely, from 15% to 20% at the lower end of the spectrum to 70% at the upper end, depending on the antibody used and the cutoff employed to determine positivity.

**MET** gene amplification is observed in 2% to 5% of non–small cell lung cancers (NSCLCs). Primarily identified using fluorescence in situ hybridization (FISH), **MET** amplification is distinguished from polyploidy, which is not an oncogenic driver, by detection of the **MET:**CEP7 ratio. CEP7 is a FISH probe that detects the centromeric region of chromosome 7. In polyploidy, each copy of the **MET** gene is associated with a centromere; thus, the **MET:**CEP7 ratio remains constant. High levels of **MET** amplification (**MET:**CEP7 ≥ 5) occur in fewer than 0.5% of NSCLC cases.

Another important mechanism of MET dysregulation in lung cancer is **MET** mutations, particularly those that result in a phenomenon known as exon 14 skipping. Occurring in an estimated 3% to 4% of patients with lung adenocarcinoma, **MET** exon 14 mutations are particularly enriched in the sarcomatoid subtype; tend to be found more commonly in elderly, nonsmoking patients; and are mutually exclusive with most other lung cancer drivers, barring a few exceptions, notably **MET** amplification.

These mutations occur at sites where intron splicing normally takes place during the processing of precursor messenger RNA (mRNA) into mature mRNA. The mutations result in exon 14 being spliced out, hence, “skipping” the protein region encoded by this exon. Exon 14 encodes part of the MET juxtamembrane domain, which contains a tyrosine residue to which the ubiquitin ligase CBL binds. The resulting ubiquitination tags MET for degradation, helping to tightly control its activity. Thus, exon 14 skipping means the activated MET receptor fails to be properly degraded, resulting in sustained MET signaling.

For a full list of references, see the article at OncLive.com.
prognosis, it has not proved to be an effective biomarker of response to MET inhibitors in most cases.\(^7,8\)

Recently, a heterogeneous group of mutations that lead to loss of MET exon 14, which results in MET activation by impairing MET protein degradation, has emerged as a better biomarker of response to MET inhibitors in NSCLC.

**Crizotinib**

Following multiple case reports of patients with MET exon 14–mutant NSCLC responding to MET inhibitors\(^7\) and positive preliminary results from an expansion cohort of the PROFILE 1001 trial of crizotinib in patients with MET exon 14 mutations (NCT00585195)\(^8\), numerous clinical trials were launched to evaluate MET inhibitors in this patient population.

Updated results from the PROFILE-1001 expansion cohort were recently published. Among 65 treatment-naïve or previously treated patients with MET exon 14–mutant NSCLC, the ORR with crizotinib therapy was 32% (95% CI, 21%-45%), including 3 complete responses (CRs). Median progression-free survival (PFS) was 7.3 months (95% CI, 5.4-9.1)\(^9\).

**Capmatinib**

Most notably, research efforts in MET exon 14–mutant NSCLC have recently culminated in the approvals of 2 novel selective MET inhibitors. Capmatinib became the first FDA-approved MET inhibitor in May 2020, based on results of GEOMETRY Mono-1 trial (NCT02414139), a multicohort trial in patients with MET-dysregulated NSCLC.\(^8\)

The phase 2 studied included 97 patients with MET exon 14 mutations, 69 of whom had received 1 or 2 prior lines of therapy and 28 of whom were treatment naïve. Patients were treated with capmatinib 400 mg twice daily.

The ORR was 41% (95% CI, 29%-53%) in previously treated patients and 68% (95% CI, 48%-84%) when capmatinib was used in the front line, with a median duration of response (DOR) of 9.7 months and 12.6 months, respectively. The most common AEs among all study patients were peripheral edema, nausea, and vomiting, which were predominantly grade 1 or 2.\(^9\) The FDA also approved FoundationOne CDx, a next-generation sequencing-based assay, as a companion diagnostic to identify patients with MET exon 14 skipping mutations who are eligible for treatment with capmatinib.\(^9\)

**Tepotinib**

In February 2021, the FDA approved the selective MET inhibitor tepotinib.\(^10\) Investigators evaluated tepotinib in the pivotal phase 2 VISION trial (NCT02864992), a single-arm, multicohort study. All patients received oral tepotinib 500 mg once daily.

According to a primary analysis of data from cohort A, which enrolled patients with MET exon 14 skipping mutations, 99 patients had been followed for at least 9 months at the cutoff of January 1, 2020. The ORR by independent review was 46% (95% CI, 36%-57%) for these patients. ORRs were comparable between patients whose mutation status was determined by liquid biopsy (ORR, 48%) vs tissue biopsy (ORR, 50%). The most common AEs included peripheral edema, nausea, and diarrhea; peripheral edema was the most common AE of grade 3 or higher.\(^11\)

Updated results were reported at the recent International Association for the Study of...
Lung Cancer World Conference on Lung Cancer (WCLC 2020). The ORR was 44.7% (95% CI, 36.7%-53.0%) among 152 patients, 83 of whom had received prior therapy, with a median DOR of 11.1 months and a median PFS of 8.9 months (95% CI, 8.2-11.2). ORRs were 44.9% (95% CI, 32.9%-57.4%) and 46.6% (95% CI, 33.7%-55.9%) in treatment-naive and previously treated patients, respectively.22

Tepotinib therapy also demonstrated clinical benefit in patients with brain metastases treated during the VISION trial, according to findings presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting. Among 23 patients who were part of cohort A, the ORR was 47.8% (95% CI, 51.6%-89.8%) by RECIST v1.1 criteria.23

**Savolitinib**

Savolitinib is another MET inhibitor in development in patients with MET exon 14 skipping–mutant NSCLC. AstraZeneca, which is developing this drug, entered into a global licensing and joint development and commercialization agreement with Hutchmed (formerly Hutchison China MediTech Limited) in 2011.24

According to phase 2 trial (NCT02897479) data presented at the 2020 ASCO Virtual Scientific Program, savolitinib elicited an ORR of 49.2% by independent review in 61 response-evaluable patients with MET exon 14–mutant NSCLC. Investigators administered savolitinib orally, once daily, on a weight-based schedule (600 mg for patients weighing ≥ 50 kg and 400 mg for those < 50 kg). The most common treatment-related AEs included peripheral edema, nausea, increased alanine and aspartate aminotransferase levels, vomiting, and hypoalbuminemia.25 These data served as the basis for the recent submission of a new drug application to the Chinese regulatory authorities.24

**OVERCOMING RESISTANCE**

**Combination Therapies**

MET dysregulation, particularly MET gene amplification, has been identified as a mechanism of acquired resistance to EGFR inhibitors in patients with EGFR-mutant NSCLC. MET amplification is estimated to occur in 5% to 20% of this patient population in response to treatment with EGFR inhibitors, particularly patients who receive third-generation drugs, such as osimertinib (Tagrisso), in the frontline setting.3 Thus, combination therapy with MET inhibitors and EGFR inhibitors has become a prominent therapeutic strategy in clinical development.

The combination of savolitinib plus osimertinib is being studied in 1 arm of the phase 1 TATTON study (NCT02143466). Final results from parts B and D, the dose-expansion portion of this arm, were presented at WCLC 2020. Patients in part B (n = 138) received oral savolitinib 600 mg once daily, except for the final 21 patients enrolled, who received weight-based dosing: 300 mg for patients weighing 55 kg or less and 600 mg for those weighing more than 55 kg. Patients in part D (n = 42) all received oral savolitinib 300 mg once daily. Part B was divided into 3 cohorts: patients who had previously received a third-generation EGFR inhibitor (cohort 1), those who had not received a third-generation EGFR inhibitor and were negative for the T790M point mutation in the EGFR gene (cohort 2), and patients who had not received a third-generation EGFR inhibitor and were T790M positive (cohort 3). In part D, all patients were third-generation EGFR inhibitor naïve and T790M negative.

ORRs in the part B cohorts were 33% (95% CI, 22%-46%), 65% (95% CI, 50%-78%), and 67% (95% CI, 41%-87%), respectively, and median PFS was 5.5 months (95% CI, 4.1-7.7), 9.1 months (95% CI, 5.5-12.8), and 11.1 months (95% CI, 4.1-22.1). In part D, the ORR was 62% (95% CI, 46%-76%) and median PFS was 9.0 months (95% CI, 5.6-12.7 months). The combination was generally well tolerated, with grade 3 and higher AEs occurring in 62% of patients in part B and 50% of patients in part D.11 Investigators are evaluating the combination further in the ongoing phase 2 SAVANNAH trial (NCT03778229).

The combination of tepotinib and the EGFR inhibitor gefitinib (Iressa) was evaluated in comparison with standard platinum doublet chemotherapy in phase 2 of the INSIGHT trial (NCT01982955). Eligible patients had EGFR-mutant, T790M-negative, MET-altered NSCLC, with MET alteration defined as protein overexpression (IHC 2+ or 3+) or gene amplification.

The trial was terminated early due to low recruitment. However, preplanned analyses demonstrated that although survival outcomes did not differ between the 2 groups overall, subsets of patients with high (IHC 3+) MET overexpression or MET amplification had improved median PFS and overall survival (OS) vs the chemotherapy group. For patients with MET amplification and EGFR inhibitor resistance, the median PFS was 16.6 months with tepotinib vs 4.2 months with chemotherapy (HR, 0.13; 90% CI, 0.04-0.43) and median OS, respectively, was 37.3 vs 13.1 months (HR, 0.08; 90% CI, 0.01-0.51).12

In the INSIGHT 2 trial (NCT03940703), investigators are evaluating the combination of tepotinib and osimertinib in patients with MET-amplified, EGFR-mutant NSCLC who had progressed on first-line osimertinib.

Capmatinib also has been explored in combination with gefitinib. In final findings from a phase 1b/2 study (NCT01610336) presented at 2021 ASCO, the regimen resulted in a median OS of 13.9 months (95% CI, 11.6-15.7) among 100 patients after a median follow-up of 12.2 months (range, 0.9-70.2). The most frequently reported AEs (≥ 25% of patients) were nausea, decreased appetite, peripheral edema, hypoalbuminemia, vomiting, and rash.13

**Bispecific Antibodies**

An alternative strategy in clinical development is the use of bispecific antibodies targeting EGFR and MET simultaneously. Amivantamab has demonstrated significant promise in the treatment of patients with EGFR exon 20 insertion mutations, another mechanism of acquired resistance to EGFR inhibitors.

The FDA approved the drug for patients with locally advanced or metastatic NSCLC with the EGFR exon 20 mutation based on findings from the ongoing phase 1 CHRYSALIS trial (NCT02609776). Participants received amivantamab at 1050 mg (weighing < 80 kg) or 1400 mg (weighing ≥ 80 kg). Among 81 patients who had received prior platinum-based chemotherapy, the ORR was 40% (95% CI, 29%-51%), including 3 CRs, and the median DOR was 11.1 months.14 In a different part of the CHRYSALIS trial, investigators are evaluating amivantamab in patients with MET exon 14 skipping mutations.15
IN THE TREATMENT OF **METASTATIC EGFRm NSCLC**

**FIRST-LINE TAGRISSO: TO FIND EVERY ELIGIBLE PATIENT TEST, KNOW, TREAT**

GIVE ELIGIBLE PATIENTS A CHANCE AT GROUNDBREAKING EFFICACY

**FLAURA study design:** Randomized, double-blind, active-controlled trial in 556 patients with metastatic EGFRm NSCLC who had not received prior systemic treatment for advanced disease. Patients were randomized 1:1 to either TAGRISSO (n=279; 80 mg orally, once daily) or EGFR-TKI comparator (n=277; gefitinib 250 mg or erlotinib 150 mg orally, once daily). All US patients in the comparator arm received erlotinib. Crossover was allowed for patients in the EGFR-TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation. Patients with CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was **PFS** based on investigator assessment (according to RECIST v1.1). Secondary endpoints included **OS**, **ORR**, **CNS PFS**, and **DoR**. To provide strong control for the type I error rate, the primary endpoint of PFS and endpoints of OS and CNS PFS were tested sequentially.¹ ²

**INDICATION**

- TAGRISSO is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test

**IMPORTANT SAFETY INFORMATION**

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.7% of the 1479 TAGRISSO-treated patients; 0.3% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
- Heart rate-corrected QT (QTC) interval prolongation occurred in TAGRISSO-treated patients. Of the 1479 TAGRISSO-treated patients in clinical trials, 0.8% were found to have a QTC >500 msec, and 3.1% of patients had an increase from baseline QTC >60 msec. No QTC-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTC interval. Permanently discontinue TAGRISSO in patients who develop QTC interval prolongation with signs/symptoms of life-threatening arrhythmia
- Cardiomyopathy occurred in 3% of the 1479 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.2% of 1233 patients who had baseline and at least one follow-up LVEF assessment. In the ADAURA study, 1.5% (5/325) of TAGRISSO-treated patients experienced LVEF decreases ≥10% from baseline and a drop to <50%. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For asymptomatic congestive heart failure, permanently discontinue TAGRISSO
- Keratitis was reported in 0.7% of 1479 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist

**GIVE ELIGIBLE PATIENTS A CHANCE AT GROUNDBREAKING EFFICACY**

**Median PFS**

18.9 **vs** 10.2 months for TAGRISSO vs erlotinib/gefitinib¹

HR=0.46 (95% CI: 0.37, 0.57); **P**<0.0001

**Median OS**

38.6 **vs** 31.8 months for TAGRISSO vs erlotinib/gefitinib¹

HR=0.80% (95% CI: 0.64, 1.00); **P**=0.0462

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IN THE TREATMENT OF METASTATIC EGFRm NSCLC

• TAGRISSO is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer

INDICATION

• Heart rate-corrected QT (QTc) interval prolongation

IMPORTANT SAFETY INFORMATION

control for the type I error rate, the primary endpoint of PFS and endpoints of OS and CNS PFS were tested sequentially.1-4

PFS based on investigator assessment (according to RECIST v1.1). Secondary endpoints included OS, ORR, CNS PFS, and DoR. To provide strong

with CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was

comparator (n=277; gefitinib 250 mg or erlotinib 150 mg orally, once daily). All US patients in the comparator arm received erlotinib. Crossover

FLAURA study design:

GIVE ELIGIBLE PATIENTS A CHANCE AT GROUNDBREAKING EFFICACY

FIRST-LINE TAGRISSO:

mutations, as detected by an FDA-approved test

with signs/symptoms of life-threatening arrhythmia

the QTc interval. Permanently discontinue TAGRISSO

those who are taking medications known to prolong

congestive heart failure, electrolyte abnormalities, or

patients with congenital long QTc syndrome,

periodic monitoring with ECGs and electrolytes in

QTc-related arrhythmias were reported. Conduct

had an increase from baseline QTc >60 msec. No

found to have a QTc >500 msec, and 3.1% of patients

TAGRISSO-treated patients in clinical trials, 0.8% were

occurred in TAGRISSO-treated patients. Of the 1479

Permanently discontinue TAGRISSO if ILD is confi rmed

indicative of ILD (eg, dyspnea, cough and fever).

worsening of respiratory symptoms which may be

cases were fatal. Withhold TAGRISSO and promptly

3.7% of the 1479 TAGRISSO-treated patients; 0.3% of

medications may be involved in the development of QTc prolongation.

Toxicities that can prolong the QT interval

a QTc >450 msec. Advise patients to consult a

Advise females of reproductive potential to use

pregnant women of the potential risk to a fetus.

potential prior to initiating TAGRISSO. Advise

consider permanent discontinuation of TAGRISSO

consultation. If no other etiology can be identifi ed,

systemic involvement, and consider dermatology

Verify pregnancy status of females of reproductive

potential prior to initiating TAGRISSO. Advise

pregnant women of the potential risk to a fetus. Advise

females of reproductive potential to use effective contraception during treatment with

TAGRISSO and for 6 weeks after the final dose.

Advise males with female partners of reproductive

potential to use effective contraception for 4 months

after the fi nal dose

• Most common (≥20%) adverse reactions, including laboratory abnormalities, were leukopenia, lymphopenia, thrombocytopenia, diarrhea, anemia, rash, musculoskeletal pain, nail toxicity, neutropenia, dry skin, stomatitis, fatigue, and cough

TAGRISSO® (osimertinib) tablets, for oral use

Brief Summary of Prescribing Information.

For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

Adjuvant Treatment of EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)

TAGRISSO is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1) in the full Prescribing Information].

First-line Treatment of EGFR Mutation-Positive Metastatic NSCLC

TAGRISSO is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1) in the full Prescribing Information].

Previously Treated EGFR T790M Mutation-Positive Metastatic NSCLC

TAGRISSO is indicated for the treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy [see Dosage and Administration (2.1) in the full Prescribing Information].

INDICATIONS AND USAGE

For complete prescribing information consult official package insert.

TAGRISSO® (osimertinib) tablets, for oral use

Adverse Reactions

Dosage Modifications

Table 1. Recommended Dosage Modifications for TAGRISSO (cont’d)

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Adverse Reaction*</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac (see Warnings and Precautions (5.1) in the full Prescribing Information)</td>
<td>QTc interval greater than 500 msec on at least 2 separate ECGs</td>
<td>Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if QTc is greater than or equal to 481 msec, then resume at 40 mg dose.</td>
</tr>
<tr>
<td>Cardiac (see Warnings and Precautions (5.1) in the full Prescribing Information)</td>
<td>Symptomatic congestive heart failure</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
<tr>
<td>Other (see Adverse Reactions (6.1) in the full Prescribing Information)</td>
<td>Adverse reaction of Grade 3 or greater severity</td>
<td>Withhold TAGRISSO for up to 5 weeks.</td>
</tr>
<tr>
<td>Other (see Adverse Reactions (6.1) in the full Prescribing Information)</td>
<td>Improvement to Grade 0-2 within 3 weeks</td>
<td>Resume at 80 mg or 40 mg daily.</td>
</tr>
<tr>
<td>Other (see Adverse Reactions (6.1) in the full Prescribing Information)</td>
<td>Permanent discontinuation</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
</tbody>
</table>

*Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v.4.0). QTc = QT Interval corrected for heart rate.

Erythema Multiforme and Stevens-Johnson Syndrome

Postmarketing cases consistent with Stevens-Johnson syndrome (SJS) and erythema multiforme major (EMM) have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if SJS or EMM is suspected and permanently discontinue if confirmed.

Cataract

Postmarketing cases of cataract have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if cataract suspect, evaluate for systemic involvement, and consider dermatology consultation. If no other etiology can be identified, consider permanent discontinuation of TAGRISSO based on severity.

Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, embryotoxic post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended clinical dose. If TAGRISSO is administered to a pregnant woman, advise her of the potential risk to her fetus. Advise males of reproductive potential to use effective contraception during treatment in combination with TAGRISSO and for 6 weeks after the final dose. Advise females with female partners of reproductive potential to use effective contraception for 4 months after the final dose [see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information].

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Intestinal Lung Disease/Preauritis [see Warnings and Precautions (5.1) in the full Prescribing Information]
- QTc Interval Prolongation [see Warnings and Precautions (5.2) in the full Prescribing Information]
- Cardiomyopathy [see Warnings and Precautions (5.3) in the full Prescribing Information]
- Keratitis [see Warnings and Precautions (5.4) in the full Prescribing Information]
- Erythema Multiforme and Stevens-Johnson syndrome [see Warnings and Precautions (5.5) in the full Prescribing Information]
- QTc interval greater than or equal to 500 msec on at least 2 separate ECGs

Cardiac

Across clinical trials, cardiomyopathy (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 3% of the 1479 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥ 10% points from baseline to less than 50% LVEF occurred in ≥ 5233 patients who had baseline and at least one follow-up LVEF assessment. In the AURA study, 15% (225) of patients treated with TAGRISSO experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50%.

Conduct cardiac monitoring, including assessment of LVEF at baseline and at least one follow-up assessment. Patients with a history of interstitial lung disease, drug induced interstitial disease or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from enrollment in these studies.

Clinical Trials Experience

When used in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions section reflect exposure to TAGRISSO in 1479 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in three randomized, controlled trials [ADAlRA (n=237), FlaURA (n=293), and AURA2 (n=278)], two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study [AURA1 (n=173)]. See Warnings and Precautions (5.1) in the full Prescribing Information]. Among 1479 patients who received TAGRISSO, 81% were exposed for 6 months or longer and 60% were exposed for greater than one year. In this postulated safety population, the most common adverse reactions in ≥ 20% of 1479 patients who received TAGRISSO were diarrhea (47%), rash (45%), musculoskeletal pain (38%), nausea (30%), dry skin (30%), stomatitis (26%), fatigue (21%), and cough (20%). The most common laboratory abnormalities in ≥ 20% of 1479 patients who received TAGRISSO were leucopenia (65%), lymphopenia (62%), thrombocytopenia (53%), anemia (47%), and neutropenia (39%).
Clinically relevant adverse reactions in ADAURA in <10% of patients receiving TAGRISSO were alopecia (8%), epistaxis (6%), interstitial lung disease (3%), palmar-plantar erythrodysesthesia syndrome (1.8%), keratitis (0.6%), QTcF prolongation (0.6%), and erythema multiform (0.3%). QTc interval prolongation represents the incidence of patients who had a QTcF prolongation >500msec.

Table 3. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in ADAURA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=337)</th>
<th>PLACBO (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>Grade 3 or higher</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Anemia (N=337)</td>
<td>30 (9)</td>
<td>12 (0.3)</td>
</tr>
<tr>
<td>Leukopenia (N=337)</td>
<td>54 (16)</td>
<td>12 (0.3)</td>
</tr>
<tr>
<td>Neutropenia (N=337)</td>
<td>23 (7)</td>
<td>25 (0.7)</td>
</tr>
<tr>
<td>Neutrophilia (N=337)</td>
<td>26 (8)</td>
<td>18 (0.5)</td>
</tr>
</tbody>
</table>

Table 4. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3 or higher</td>
<td>Any Grade</td>
</tr>
</tbody>
</table>

Table 5. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in FLAURA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>Grade 3 or higher</td>
<td>Any Grade</td>
</tr>
</tbody>
</table>

Table 6. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA (cont'd)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>Grade 3 or higher</td>
</tr>
</tbody>
</table>

Table 7. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA (cont'd)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>Grade 3 or higher</td>
</tr>
</tbody>
</table>

Table 8. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA (cont'd)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>Grade 3 or higher</td>
</tr>
</tbody>
</table>
chemotherapy-treated patients. The trial population characteristics were: median age 67 years, age less than 65 (58%), female (64%), Asian (66%), never smokers (68%), and EGFR PS 0 or 1 (100%).

Serious adverse reactions were reported in 16% of patients treated with TAGRISSO and 26% in the chemotherapy comparator group. No single serious adverse reaction was reported in 2% or more patients treated with TAGRISSO. One patient (0.4%) treated with TAGRISSO experienced a fatal adverse reaction (ILD/pneumonitis). Dose reductions occurred in 29% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (1.8%), neutropenia (1.1%), and diarrhea (1.1%). Adverse reactions resulting in permanent discontinuation of TAGRISSO occurred in 7% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3%).

Tables 6 and 7 summarize common adverse reactions and laboratory abnormalities which occurred in TAGRISSO-treated patients in AURA3.

Table 6. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in AURA3*  

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3/4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>28 1.1</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>34 1.2</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 0.5</td>
<td>6</td>
</tr>
<tr>
<td>Skin Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>23 0.8</td>
<td>14</td>
</tr>
<tr>
<td>Nail toxicity†</td>
<td>22 0.8</td>
<td>15</td>
</tr>
<tr>
<td>Pruritus‡</td>
<td>13 0.5</td>
<td>6</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>22 0.8</td>
<td>40</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15 0.5</td>
<td>36</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>17 0.6</td>
<td>14</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10 0.4</td>
<td>9</td>
</tr>
</tbody>
</table>

A patient with known risk of Torsades de pointes. If not feasible to adjust the QTc interval with TAGRISSO is unknown. When feasible, avoid co-administering TAGRISSO with strong CYP3A inducers. Avoid co-administering TAGRISSO with strong CYP3A inducers. Increase the TAGRISSO dosage when co-administering with a strong CYP3A4 inducer if concurrent use is unavoidable [see Dosage and Administration (2.4) in the full Prescribing Information]. No dose adjustments are required when TAGRISSO is used with moderate or weak CYP3A inducers. Avoid co-administering TAGRISSO with strong CYP3A inducers. Increase the TAGRISSO dosage when co-administering with a strong CYP3A4 inducer if concurrent use is unavoidable [see Clinical Pharmacology (12.3) in the full Prescribing Information]. Increased BCRP or P-gp substrate exposure may increase the risk of exposure-related toxicity. Monitor for adverse reactions of the BCRP or P-gp substrate, otherwise continued in its approved labeling, when co-administered with TAGRISSO.

Table 7. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in AURA3 (cont’d)  

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or Grade 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>43 0.5</td>
<td>79 3.1</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63 8</td>
<td>61 10</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>46 0.7</td>
<td>48 1.2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27 1.2</td>
<td>49 1.2</td>
</tr>
</tbody>
</table>

Laboratory Abnormality*  

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or Grade 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>27 1.8</td>
<td>9 1.5</td>
</tr>
<tr>
<td>HPV associated</td>
<td>26 1.8</td>
<td>8 1.5</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>19 0.5</td>
<td>15 1.5</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>16 0.5</td>
<td>17 1.5</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>19 0.5</td>
<td>18 1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or Grade 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hyponatremia†</td>
<td>26 2.2</td>
<td>36 1.5</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>19 0.5</td>
<td>15 1.5</td>
</tr>
<tr>
<td>Hyponatremia‡</td>
<td>16 0.5</td>
<td>17 1.5</td>
</tr>
<tr>
<td>Hyperkalemia‡</td>
<td>19 0.5</td>
<td>18 1.5</td>
</tr>
</tbody>
</table>

座標: (osimertinib) tablets, for oral use

through the end of organogenesis (gestation days 2-20) at a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical exposure, osimertinib caused post-implanation loss and early embryonic death. When administered during organogenesis from implantation through the closure of the hard palate (gestation days 6 to 16) at doses of 1 mg/kg/day and above (0.1 times the AUC observed at the recommended clinical dose of 80 mg once daily) an equivocal increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at a dose of 30 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.

Lactation

Risk Summary

There are no data on the presence of osimertinib or its active metabolites in human milk, the effects of osimertinib on the breastfed infant or on milk production. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death [see Use in Specific Populations (8.1) in the full Prescribing Information]. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise women not to breastfeed during treatment with TAGRISSO and for at least the final dose.

Females and Males of Reproductive Potential

Based on animal data, TAGRISSO can cause malformations, embryo lethality, and postnatal death at doses resulting in exposures 1.5 times or less than the human exposure at the clinical dose of 80 mg daily [see Use in Specific Populations (8.1) in the full Prescribing Information]. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise women not to breastfeed during treatment with TAGRISSO and for at least the final dose.

Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action [see Clinical Pharmacology (12.3) in the full Prescribing Information], TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryolethality and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended clinical dose (see Data). Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

When administered to pregnant rats prior to embryonic implantation

† NCI CTCAE v4.0

‡ Includes fatigue, asthenia.

§ Includes pruritus, pruritus generalized, eyelid pruritus.

¶ Includes nail disorders, nail bed disorders, nail bed inflammation, nail bed abnormalities which occurred in TAGRISSO-treated patients in AURA3.

TAGRISSO was ILD/pneumonitis (3%).

The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3%).

Forty-three percent (43%) of the 1479 patients in ADAURA (n=337), who had both baseline and at least one on-study laboratory measurement available (TAGRISSO 279, Chemotherapy comparator 131).

† Hyperglycemia is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (TAGRISSO 279, Chemotherapy comparator 131).

‡ Hyperglycemia is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (TAGRISSO 279, Chemotherapy comparator 131).

§ Includes stomatitis and mouth ulceration.

ǁ Includes hyperglycemia, hyperkalemia, and hyperuricemia.
Sequencing Therapy in Metastatic CRC Is a Marathon, Not a Sprint

by CHRISTINA T. LOGUIDICE

ACTIONABLE MUTATIONS IDENTIFIED IN colorectal cancer (CRC) have contributed significantly to the expansion of the therapeutic options available for patients with metastatic disease. For patients with unresectable, metastatic CRC (mCRC), palliative chemotherapy regimens remain the cornerstone of care. An increased focus on molecular profiling, such as the identification of BRAF or RAS mutations, microsatellite instability and DNA mismatch repair status, has increased the number of options available for patients in the first-line setting.1

Despite these advances, which includes marked improvements in overall survival (OS), treatment goals for patients who experience progression following frontline therapy focus on preservation of quality of life (QOL) and delayed disease progression.2 “[When selecting second-line treatment], it’s really weighing the risks and the benefits,” Joleen M. Hubbard, MD, said during a recent OncLive Peer Exchange®. “We’re just trying to balance that quality and that quantity as long as we can.”

Hubbarb and other members of a panel of gastrointestinal cancer experts unpacked the available options and strategic sequencing decisions for patients moving into the second-line setting and beyond. Although they made clear that considerable work still needs to be done in treating mCRC, they shared their insights on the growing number of clinically relevant treatment options and how they these use these agents in their own practices. “Treatment of metastatic colorectal cancer is like a marathon, rather than a sprint. We’re thinking [approximately] 2, 3, 4+ lines of therapy,” moderator Tanios S. Bekaii-Saab, MD, said.

SECOND-LINE TREATMENT

In the second-line setting, the panelists said response to treatment is low. “From the various second-line trials that we have, it ranges anywhere from 5% to 15%. Sometimes it’s upward of 20%, but that’s really optimistic. Usually, we’re seeing a very minimal response,” Hubbard said.

She explained that in this setting, treatment response usually isn’t the goal given currently available treatment options. Instead, the goal is to enhance progression-free survival (PFS) and to help patients maintain as much QOL as possible. The exception to this is a patient who is highly symptomatic. “If they’re RAS/BRAF wild type and they haven’t used an EGFR inhibitor before, that might be a situation where I’d use an EGFR inhibitor to try to augment the response,” Hubbard said. Otherwise, she said she usually continues treatment with a VEGF inhibitor.
Although Hubbard said she usually uses FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) or FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin, irinotecan) in the first-line setting, in the second-line setting she is mostly using an irinotecan-based regimen, usually FOLFIRI (folinic acid, 5-fluorouracil, irinotecan), rather than reintroducing oxaliplatin, because many patients have some residual peripheral neuropathy. She explained that this is a setting where treatment can be adjusted to help improve a patient’s QOL. “If patients have a nice response but are getting fatigued from chemotherapy, you can go back to maintenance fluoropyrimidine, bevacizumab. You can go to a single agent, to irinotecan. There are a lot of things you can do to help ensure the quality of treatment because it’s a marathon,” she said.

The panelists proceeded to discuss rechallenging patients with oxaliplatin versus changing their treatment but noted that is only an option for select patients who do not have problematic neuropathy (grade ≥ 2). “There’s always the [risk of] oxaliplatin hypersensitivity that you may see on some records. You must discuss it with the patient. Some of it’s very serious, and I would never rechallenge such patients,” Cathy Eng, MD, said.

They also noted that there may be a role for rechallenging patients with an anti-EGFR therapy, which is an approach currently under investigation. “The schools of thought are if you have a sufficient amount of time that has passed between your last EGFR, and you did have a good response to it and then acquired resistance to it, [you’re a likely candidate because you developed] that resistance through the KRAS clones, which tend to go away, usually at approximately 6 to 8 months, on average,” Kanwal P.S. Raghav, MD, MBBS, said.

The panelists explained that circulating tumor DNA, or liquid biopsy, is the most effective way to detect these clones. “The only way we are able to detect these alterations easily is through obtaining 1 to 2 tubes of blood and sending that off for molecular testing. What we’ve found is that just rebiopsying a tumor lesion, maybe a liver lesion, you might miss some of those resistance alterations. It’s really where the liquid biopsy performs at its best, particularly in comparison with a more conventional tumor tissue biopsy,” John H. Strickler, MD, said.

Subsequently, before considering rechallenging patients with anti-EGFR therapy, the panelists encouraged health care providers to test patients for these clones via liquid biopsy. However, they said, if liquid biopsy poses a financial hardship to a patient, it could be reasonable to wait 6 to 8 months after the patient’s initial exposure and then reintroduce anti-EGFR therapy since this is the period during which the clones usually disappear. They also emphasized that anti-EGFR rechallenge is only appropriate for patients who previously had a good response to this treatment but then progressed, and it is not for patients who had primary resistance to an anti-EGFR therapy.

### BRAF-MUTATED mCRC

Patients with BRAF V600E-mutated mCRC have aggressive tumors that are often resistant to chemotherapy. Before some of the newer agents were approved, life expectancy was typically up to 1 year, with many patients unable to reach second-line therapy, Strickler explained. In these patients, the BRAF inhibitor encorafenib (Braftovi) in combination with the anti-EGFR antibody cetuximab (Erbitux) has been shown to be superior to traditional standards of care, and the combination was approved by the FDA on April 8, 2020, for previously treated adult patients with mCRC with a BRAF V600E mutation detected by an FDA-approved test. Approval was based on data from the randomized, active-controlled, open-label multicenter BEACON CRC trial (NCT02928224), which showed a median OS of 8.4 months in the encorafenib plus cetuximab arm compared with 5.4 months in the control arm, in which patients received either irinotecan or FOLFIRI with cetuximab.

“It’s intriguing to me that here we’re adding an EGFR inhibitor, the RAF inhibitor, in patients who technically, because of the BRAF V600E mutations, would not respond to EGFR inhibitors,” Bekait-Saab said. He explained that the BEACON CRC trial also included an arm that added a MEK inhibitor but that this agent did not add sufficient benefit to warrant FDA approval.

Raghav shared his insights on why anti-EGFR does not work in patients with BRAF mutations. “It’s the EGFR, RAS, RAF, MEK pathway, and essentially with BRAF mutations, just like with KRAS mutations, the activation is downstream, so adding a single-agent anti-EGFR is probably not going to be effective,” he said. “[But if you use] a BRAF inhibitor, you block the originating signal, and then you add an anti-EGFR to block that upregulation that happens once you block the BRAF signal. The effect is still being brought about by BRAF, but the EGFR is preventing the escape mechanism from that BRAF.” He added that when you add a BRAF inhibitor in mCRC, it results in upregulation of EGFR, which is different from what has been observed with melanoma.

“Adding the MEK was just another layer that we thought would add a significant benefit because now you’re blocking all 3 players in that pathway,” Raghav said. He explained although there was some benefit to adding the MEK inhibitor, it was not significantly better than the doublet and it added toxicity.

When examining the updated results of the BEACON CRC trial, the median OS for both the doublet arm with encorafenib plus cetuximab and the triplet arm that added the MEK inhibitor binimetinib (Mektovi) was 9.3 months vs 5.9 months in the control arm. The confirmed overall response rate (ORR) was 26.8% for the triplet, 19.5% for the doublet, and 1.8% for controls. The rate of adverse events grade 3 or higher was similar between the triplet and control arms, occurring in 65.8% and 64.2% of patients, respectively, and lower in the doublet arm, occurring in 57.4%.

“The other intriguing aspect of BEACON CRC is when you add the EGFR inhibitor to the RAF inhibitor, you end up with fewer toxicities than with either alone. When you
add the MEK inhibitor you end up with a nuclear explosion. But those 2, the cetuximab and encorafenib, seem to abrogate each other’s toxicity,” Bekaii-Saab said. It is still unclear why that is; Hubbard noted that similar results have been observed in melanoma research.

Based on the BEACON CRC findings, Stickler said the encorafenib plus cetuximab combination has become his preferred regimen in the second-line setting and beyond for patients with BRAF V600E-mutated mCRC. Bekaii-Saab pointed out that when comparing patients receiving the regimen in the second line versus third line, those who received it in the second line fared better.

**THIRD-LINE TREATMENT AND BEYOND**

Although the panelists felt clinical trial should be the first choice for patients in the salvage-line setting, they discussed 2 FDA-approved treatments that can be considered for such patients: regorafenib (Stivarga) and TAS-102 (trifluridine/tipiracil; Lonsurf). They reiterated that in later lines, as in the second line, achieving response is not necessarily the goal. “Even if you’re able to control the disease at this stage, you will get some mileage in OS over time,” Raghav said.

In clinical trials of regorafenib, Raghav said OS ranged from 6 months to almost 9 months, with some real-world data also showing a survival of approximately 9 months. “Clearly, these agents do benefit a small subset of patients in whom they can cause disease control,” he said. He explained that regorafenib could be used as a third-line option, but that better biomarkers are needed to identify which patients derive the most benefit from it.

A challenge with regorafenib has been its toxicity profile, but a study led by Bekaii-Saab showed a lower incidence of AEs when a dose escalation strategy was used. Instead of starting patients on the standard 160-mg dose, they were titrated from 80 mg to 120 mg to 160 mg on a weekly basis, depending on tolerability. “This dosing strategy did meet its primary end point of superiority, a better quality of life, better toxicity profile, and even better survival,” Bekaii-Saab said, noting that patients in the dose-escalation cohort reached an OS of 10 months.

**TAS-102** has shown a similar OS as regorafenib, with a median OS between 7 and 8 months, a 2-month benefit over placebo. Real-world use of TAS-102 was assessed in the PRECONNECT study (NCT03306394), which showed safety and efficacy comparable to that observed in clinical trials, with QOL maintained during treatment. The panelists noted that an interesting aspect of this study was that approximately 33% of patients had previously received regorafenib. “[The study] showed that you can use TAS-102 at any point in the patient’s disease. Before or after regorafenib, it still has the same degree of efficacy,” Hubbard said.

Raghav said he usually uses regorafenib before he uses TAS-102 because there are some data for TAS activity in patients previously treated with regorafenib but no data for the reverse. Additionally, because most of his patients have come off chemotherapy, such as FOLFIRI, TAS-102 can be particularly difficult for them to tolerate. “I give them TAS-102 and then they require transfusions…bottom line is that I’m not really using it regularly for most patients,” he said.

The panelists proceeded to briefly discuss data from Japan that showed OS is more favorable when using regorafenib before an EGFR inhibitor (ie, cetuximab) vs doing the reverse in patients who are KRAS wild type. “That study was cut short, and we think it does need some additional validation in the United States, so that led to the REVERCE II trial,” Strickler said. REVERCE II (NCT04117945) is an ongoing phase 2 trial that is estimated to enroll 124 patients with mCRC who will be treated with regorafenib followed by cetuximab or panitumumab or the reverse sequencing. “It could be very constructive if that’s positive here as well,” Strickler said.

The panelists concluded their discussion of second-line and subsequent treatments by examining the novel agent fruquintinib, a selective oral inhibitor of VEGF receptors 1, 2, and 3, which showed benefit in the phase 3 FRESCO trial (NCT02314819) in China and was subsequently approved there in 2018. The agent, which is now being studied in the United States and globally in the phase 3 FRESCO-2 trial (NCT04322539), includes patients with mCRC who have progressed on or were intolerant to chemotherapy, biologics, and TAS-102 or regorafenib.

“[In China, fruquintinib was given to] patients who were failed by all starter lines of therapy. Although only 30% of patients had prior bevacizumab, they noticed an improvement of almost 3 months for OS. This was a similar study design with a 2:1 ratio versus placebo and improved progression-free survival almost double. That’s why it was approved in China,” Eng said. FRESCO-2 will also have a 2:1 randomization and will require prior treatment with TAS-102, regorafenib, or both.
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