Adjuvant Advances Steal the Spotlight at ASCO 2021

PEER EXCHANGE
Advances in ENDOMETRIAL CANCER
Shine Light on Personalized Medicine

Emerging Immune Checkpoint Research Focuses on CD137

Copanlisib and Rituximab Combo Demonstrates Superiority Across iNHL

CLINICAL TRIAL IN FOCUS
Philip A. Philip, MD, PhD, Discusses AVENGER 500 for PANCREATIC CANCER

CLINICAL PERSPECTIVES
Johann S. de Bono, MBChB, PhD, MSc, FRCP, FMedSci, on Advances in mCRPC With tDDR Alterations

UNIVERSITY OF WISCONSIN CARBOLE CANCER CENTER
Definition of Oligometastatic GEJ Remains Elusive
by Nataliya V. Uboha, MD, PhD
GAVRETO™—the only once-daily targeted RET therapy for patients with RET+ metastatic NSCLC and advanced thyroid cancers.1

INDICATIONS
GAVRETO (pralsetinib) is indicated for the treatment of:

• Adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test
• 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 and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION
Interstitial Lung Disease (ILD)/Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3/4, and 0.5% with fatal reactions. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.

Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. 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 GAVRETO based on the severity.

Hypertension: Serious hepatic adverse reactions occurred in 2.1% of patients treated with GAVRETO. Increased aspartate aminotransferase (AST) occurred in 69% of patients, including Grade 3/4 in 5% and increased alanine aminotransferase (ALT) occurred in 46% of patients, including Grade 3/4 in 6%. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years). Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

Grade ≥ 3 hemorrhagic events occurred in 2.5% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event. Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage.

Tumor Lysis Syndrome (TLS): Cases of TLS have been reported in patients with medullary thyroid carcinoma receiving GAVRETO. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing. Withhold GAVRETO for at least 5 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 GAVRETO after resolution of wound healing complications has not been established.

Based on findings from animal studies and its mechanism of action, GAVRETO 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 non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose.

Common adverse reactions (≥25%) were constipation, hypertension, fatigue, musculoskeletal pain and diarrhea. Common Grade 3/4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased calcium (corrected), decreased sodium, increased AST, increased ALT, decreased platelets and increased alkaline phosphatase.

Avoid coadministration of GAVRETO with strong CYP3A inhibitors or combined P-gp and strong CYP3A inhibitors. If coadministration cannot be avoided, reduce the GAVRETO dose. Avoid coadministration of GAVRETO with strong CYP3A inducers. If coadministration cannot be avoided, increase the GAVRETO dose.

You are encouraged to report side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see Brief Summary of full Prescribing Information for GAVRETO on adjacent pages.

INDICATIONS AND USAGE
Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer
GAVRETO is indicated for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

RET-Mutant Medullary Thyroid Cancer
GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

RET Fusion-Positive Thyroid Cancer
GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with RET fusion-positive advanced or metastatic thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

WARNINGS AND PRECAUTIONS
Interstitial Lung Disease/Pneumonitis
Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with GAVRETO. Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3-4, and 0.5% with fatal reactions. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.

Hypertension
Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate GAVRETO in patients with uncontrolled hypertension.

Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least once weekly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

Hypertension
Optimize blood pressure prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

Hepatotoxicity
Serious hepatic adverse reactions occurred in 2.1% of patients treated for GAVRETO. Increased AST occurred in 69% of patients, including Grade 3 or 4 in 5% and increased ALT occurred in 46% of patients, including Grade 3 or 4 in 6%. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years). Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

Risk of Impaired Wound Healing
GAVRETO can cause impaired wound healing through its inhibition of the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing. Withhold GAVRETO for at least 5 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 GAVRETO after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity
GAVRETO can cause fetal harm when administered to a pregnant woman. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 1 week after the final dose.

Clinical Trials 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 pooled safety population included exposures to GAVRETO as a single agent in 400 mg orally once daily in 438 patients with RET-altered solid tumors, including with RET fusion-positive NSCLC (n=220), and RET-altered thyroid cancer (n=138) in ARROW. Among 438 patients who received GAVRETO, 47% were exposed for 6 months or longer and 23% were exposed for greater than one year. The most common adverse reactions (≥25%) were constipation, hypertension, fatigue, musculoskeletal pain.
and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased calcium (corrected), decreased sodium, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased platelets, and increased alkaline phosphatase.

**RET Fusion-Positive Non-Small Cell Lung Cancer**

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 220 patients with metastatic rearranged during transfection (RET fusion-positive) non-small cell lung cancer (NSCLC) in ARROW. Among the 220 patients who received GAVRETO, 42% were exposed for 6 months or longer and 19% were exposed for greater than one year. The median age was 60 years (range: 26 to 87 years); 52% were female, 50% were White, 41% were Asian, and 4% were Hispanic/Latino.

Serious adverse reactions occurred in 45% of patients who received GAVRETO. The most frequent serious adverse reaction (in ≥ 2% of patients) was pneumonia, pneumonitis, sepsis, urinary tract infection, and pyrexia. Fatal adverse reaction occurred in 5% of patients; fatal adverse reaction which occurred in >1 patient included pneumonia (n=3) and sepsis (n=2).

Permanent discontinuation due to an adverse reaction occurred in 15% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation which occurred in >1 patient included pneumonitis (1.8%), pneumonia (1.8%), and sepsis (1%).

Dosage interruptions due to an adverse reaction occurred in 60% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥ 2% of patients included neutropenia, pneumonitis, anemia, hypertension, pneumonia, pyrexia, increased aspartate aminotransferase (AST), increased blood creatine phosphokinase, fatigue, leukopenia, thrombocytopenia, vomiting, increased alanine aminotransferase (ALT), sepsis, and dyspnea.

Dose reductions due to adverse reactions occurred in 36% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in ≥ 2% of patients included neutropenia, anemia, pneumonitis, neutrophil count decreased, fatigue, hypertension, pneumonia, and leukopenia.

**Adverse Reactions (≥ 15%) in RET Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>GAVRETO N=220</th>
<th>Grades 1-4 (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>74</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>49</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>42</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Decreased calcium (corrected)</td>
<td>39</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>36</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>35</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Decreased creatinine</td>
<td>33</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>29</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Increased potassium</td>
<td>26</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>61</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>58</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>56</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>27</td>
<td>3.2</td>
<td></td>
</tr>
</tbody>
</table>

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 216 to 218 patients.

Clinically relevant laboratory abnormalities <20% of patients who received GAVRETO included increased phosphate (10%).

**RET-altered Thyroid Cancer**

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 138 patients with RET-altered Thyroid Cancer in ARROW. Among the 138 patients who received GAVRETO, 68% were exposed for 6 months or longer, and 40% were exposed for greater than one year.

The median age was 59 years (range: 18 to 83 years); 36% were female, 74% were White, 17% were Asian, and 6% were Hispanic/Latino.

Serious adverse reactions occurred in 39% of patients who received GAVRETO. The most frequent serious adverse reactions (in ≥ 2% of patients) were pneumonia, pneumonitis, urinary tract infection, pyrexia, fatigue, diarrhea, dizziness, anemia, hyponatremia, and ascites. Fatal adverse reactions occurred in 2.2% of patients; fatal adverse reactions that occurred in >1 patient included pneumonia (n=2).

Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation which occurred in >1 patient included fatigue, pneumonia, and anemia.

Dosage interruptions due to an adverse reaction occurred in 67% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥ 2% of patients included neutropenia, hypertension, diarrhea, fatigue, pneumonitis, anemia, increased blood creatine phosphokinase, pneumonia, urinary tract infection, musculoskeletal pain, vomiting,
pyrexia, increased AST, dyspnea, hypocalcemia, cough, thrombocytopenia, abdominal pain, increased blood creatinine, dizziness, headache, decreased lymphocyte count, stomatitis, and syncope.

Dose reductions due to adverse reactions occurred in 44% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in ≥ 2% of patients included neutropenia, anemia, hypertension, increased blood creatine phosphokinase, decreased lymphocyte count, pneumonitis, fatigue, and thrombocytopenia.

### Adverse Reactions (≥ 15%) in RET-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>GAVRETO N=138</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Musculoskeletal Pain
^1                      | 42            | 0.7*         |
| Gastrointestinal  |               |              |
| Constipation       | 41            | 0.7*         |
| Diarrhea
^2                      | 34            | 5*           |
| Abdominal Pain
^3                      | 17            | 0.7*         |
| Dry Mouth          | 17            | 0            |
| Stomatitis
^4                      | 17            | 0.7*         |
| Nausea             | 17            | 0.7*         |
| Vascular           |               |              |
| Hypertension       | 40            | 21*          |
| General            |               |              |
| Fatigue
^5                      | 38            | 6*           |
| Edema
^6                      | 29            | 0            |
| Pyrexia            | 22            | 2.2*         |
| Nervous System     |               |              |
| Headache
^7                      | 24            | 0            |
| Peripheral Neuropathy
^8                      | 20            | 0            |
| Dizziness
^9                      | 19            | 0.7*         |
| Dyseusiasis
^10                     | 17            | 0            |
| Respiratory        |               |              |
| Cough
^11                    | 27            | 1.4*         |
| Dyspnea
^12                     | 22            | 2.2*         |
| Skin and Subcutaneous |         |              |
| Rash
^13                    | 24            | 0            |
| Metabolism and Nutrition |       |              |
| Decreased Appetite   | 15            | 0            |

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 135 to 138 patients.

Clinically relevant laboratory abnormalities in patients who received GAVRETO included increased phosphate (40%).

### DRUG INTERACTIONS

#### Effects of Other Drugs on GAVRETO

**Strong CYP3A Inhibitors**

Avoid coadministration with strong CYP3A inhibitors. Coadministration of GAVRETO with a strong CYP3A inhibitor increases pralsetinib exposure, which may increase the incidence and severity of adverse reactions of GAVRETO.

Avoid coadministration of GAVRETO with combined P-gp and strong CYP3A inhibitors. If coadministration with a combined P-gp and strong CYP3A inhibitor cannot be avoided, reduce the GAVRETO dose.

**Strong CYP3A Inducers**

Coadministration of GAVRETO with a strong CYP3A inducer decreases pralsetinib exposure, which may decrease efficacy of GAVRETO. Avoid coadministration of GAVRETO with strong CYP3A inducers. If coadministration of GAVRETO with strong CYP3A inducers cannot be avoided, increase the GAVRETO dose.

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

**Risk Summary**

Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. There are no available data on GAVRETO use in pregnant women to inform drug-associated risk. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once 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 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study, once daily oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in 100% post-implantation loss at dose levels ≥20 mg/kg (approximately 1.8 times the human exposure based on area under the curve [AUC] at the clinical dose of 400 mg). Post-implantation loss also occurred at the 10 mg/kg dose level (approximately 0.6 times the human exposure based on AUC at the clinical dose of 400 mg). Once daily oral administration of pralsetinib at dose levels ≥5 mg/kg (approximately 0.2 times the human AUC at the clinical dose of 400 mg) resulted in an increase in visceral malformations and variations (absent or small kidney and ureter, absent uterine horn, malpositioned kidney or testis, retroesophageal aortic arch) and skeletal malformations and variations (vertebral and rib anomalies and reduced ossification).

Lactation

Risk Summary

There are no data on the presence of pralsetinib or its metabolites in human milk or their effects on either 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 GAVRETO and for 1 week after the final dose.

Females and Males of Reproductive Potential

Based on animal data, GAVRETO can cause embryolethality and malformations at doses resulting in exposures below the human exposure at the clinical dose of 400 mg daily.

Pregnancy Testing

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

Contraception

GAVRETO can cause fetal harm when administered to a pregnant woman.

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. GAVRETO may render hormonal contraceptives ineffective.

Males

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

Infertility

Based on histopathological findings in the reproductive tissues of male and female rats and a dedicated fertility study in which animals of both sexes were treated and mated to each other, GAVRETO may impair fertility.

Pediatric Use

The safety and effectiveness of GAVRETO have not been established in pediatric patients with RET fusion-positive NSCLC or in pediatric patients younger than 12 years old with RET-mutant MTC or RET-fusion thyroid cancer.

Animal Toxicity Data

In a 4-week repeat-dose toxicity study in non-human primates, phalangeal dysplasia in the femur occurred at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. In rats there were findings of increased phalangeal thickness in the femur and sternum as well as tooth (incisor) abnormalities (fractures, dentin matrix alteration, ameloblast/odontoblast degeneration, necrosis) in both 4- and 13-week studies at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. Recovery was not assessed in the 13-week toxicity study, but increased phalangeal thickness in the femur and incisor degeneration did not show evidence of complete recovery in the 28-day rat study. Monitor growth plates in adolescent patients with open growth plates. Consider interrupting or discontinuing therapy based on the severity of any growth plate abnormalities and based on an individual risk-benefit assessment.

Hepatic Impairment

GAVRETO has not been studied in patients with moderate hepatic impairment (total bilirubin >1.5 to 3.0 × upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe hepatic impairment (total bilirubin >3.0 × ULN and any AST). No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST).
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 52.
Positive data from large phase 3 trials presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting may result in the establishment of an earlier role for adjuvant therapies initially introduced for metastatic disease. However, experts say that uptake in clinical practice will depend upon the perceived benefits of adjuvant treatment compared with the toxicities and the costs of additional therapy.

**From the Editor**

Scientific Communication Requires a Course Correction
By Maurie Markman, MD

**ONCOLOGY & BIOTECH NEWS®**

**EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY BREAST CANCER 2021 VIRTUAL CONGRESS**

**30** Shorter Duration of Adjuvant Trastuzumab Shows Long-Term Survival Benefit in Select HER2+ Early Breast Cancer

**32** Ribociclib/Endocrine Therapy Improves OS Regardless of Age in Advanced HR+/HER2- Breast Cancer

**33** Atezolizumab Plus Carboplatin Induces Early Efficacy Signals in Invasive Lobular Breast Carcinoma

**Clinical Trial in Focus**

**36** Novel Combination May Break Outcomes Stalemate in Pancreatic Cancer

**Clinical Perspectives**

**40** Talazoparib Likely to Induce Response in mCRPC With tDDR Alterations

**DEPARTMENTS**

**Tepotinib (Tepmetko)**

Shine at ASCO 2021

12 From the Editor

Scientific Communication Requires a Course Correction
By Maurie Markman, MD

14 Medical World News®

FDA Digest

15 Pipeline Report

22 Drug Spotlight: Tepotinib (Tepmetko)
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- METASTATIC BREAST CANCER (mBC)
In ER+/HER2- mBC, the ER pathways are involved in tumor progression and treatment escape mechanisms that enable endocrine resistance.1,2,4,5

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


© 2021 sanofi-aventis U.S. LLC. All rights reserved. MAT-US-2104905-v1.0-05/2021
Questions Linger Around COVID-19’s Origin

WAS IT NATURAL ZOONOTIC spillover that catapulted SARS-CoV-2 from an emerging virus into a pandemic pathogen or was it something much more sinister? Is it at all possible that a lab leak in Wuhan, China, was the spark that lit the fuse?

Debate and discussion about the origin of the virus that causes COVID-19 have been at the forefront of the global consciousness since the first cases were reported in December 2019.

Early on, whispers of a potentially engineered virus quickly grew to a roar and fueled speculation that China was behind the pandemic. This narrative was so pervasive that, in February 2020, a group of 27 public health scientists published a letter in The Lancet disputing the lab leak theory and announcing their support of their counterparts in China: the scientists, public health officials, and medical professionals combating the pandemic.1

“The rapid, open, and transparent sharing of data on this outbreak is now being threatened by rumors and misinformation around its origins,” wrote the authors, who all declared no competing interests in their disclosures as recommended by the International Committee of Medical Journal Editors. “We stand together to strongly condemn conspiracy theories suggesting that COVID-19 does not have a natural origin.”

And although it’s true that analyses of the genomic sequence of the virus subsequently pointed to natural origins, the questions regarding China’s role persisted, led by pesky discrepancies and conflicting reports.

Fast forward to June 2021 and new evidence that has breathed new life into those origin questions. In an update to the February 2020 letter, The Lancet has published an addendum with revised disclosure statements from virologist and investigator Peter Daszak, one of the 27 authors.2 In the revised document, Daszak noted that his remuneration is paid solely in the form of a salary from EcoHealth Alliance, a New York-based nonprofit research foundation of which he is president. The company has reportedly worked directly with Wuhan laboratories and funded gain-of-function research at China’s Wuhan Institute of Virology.

Consider, too, other odd associations. Recent reports have uncovered financial ties between Google and EcoHealth Alliance. This comes after accusations that the tech giant funded gain-of-function research at China’s Wuhan Institute of Virology. As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

JOIN US ON SOCIAL MEDIA | WWW.ONCLIVE.COM
FACEBOOK ONCLIVE | TWITTER @ONCLIVE
LINKEDIN ONCLIVE | YOUTUBE ONCLIVETV

For a full list of references, see the article at bit.ly/2SZX01e.
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!
WE ARE ENTERING A most interesting time in our nation’s history. There is legitimate optimism that the COVID-19 pandemic, which has resulted in almost 600,000 deaths in the United States, is finally coming under control, with most normal daily activities already returning to prepandemic states. The economy is rapidly improving, as unemployment levels fall, and in certain industries, there even appears to be a shortage of workers as businesses ready to substantially expand services and operations.

Schools that have offered only virtual learning since early 2020 are planning to return to in-person classes beginning in the fall. Some are even considering offering enhanced in-person activities during the normally quiet summer months to permit students to catch up on relevant experiences that were severely curtailed during the pandemic. Travel-related activities, including family vacations, deferred over the past year are rapidly accelerating, coinciding nicely with the warm summer months.

Finally, we must acknowledge the truly spectacular success associated with the FDA-approved COVID-19 vaccines. This includes the remarkably short timeline from initial laboratory evaluation to clinical trial implementation, rigorous scientific review, widespread real-world deployment of the products, and, most importantly, the highly favorable and now well-documented population-based effect of vaccination in the noninvestigative setting. Adding to these superlatives is the widespread emergence of which appears to be successfully prevented by the available vaccines, even if not quite as effectively as the initial virus against which the vaccine products were created.

Based on this information, the overall picture related to COVID-19 in the Unites States is encouraging, and we might suspect that the American public would be relatively united with favorable views of efforts of public health officials and organizations at the national, state, and local levels to successfully control this terrible event and return us to our prepandemic state.

Unfortunately, such a conclusion would be far from accurate. Results of a recent poll conducted by the Robert Wood Johnson Foundation and the Harvard T.H. Chan School of Public Health from February 11 to March 15, 2021, found that 52% of respondents (N = 1305) had “a great deal” or “quite a lot” of trust in the CDC, the national organization responsible for coordinating efforts to prevent and successfully control such infectious disasters.1 At the state and local levels, public health agencies had an even lower percentage of individuals (41%) who reported having high public trust; the National Institutes of Health and the FDA scored even lower, with 37% of respondents expressing “a great deal” or “quite a lot” of trust in both government organizations.

Further, and perhaps even more disturbing, when asked their opinion regarding the overall effectiveness of the existing public health system across the country in protecting us from health threats and preventing illness, 34% of those participating in the poll provided a positive response, a decrease from 42% when the same question was posed in 2009.1 Of note, in the same poll, high public trust in nurses (71%), in health care workers whom respondents knew (70%), and doctors (67%) far exceeded that of public health agencies.

We can only speculate the reasons for this rather stunning gap between the confidence expressed in the public health community and the overall objective success in vaccination strategies, improvement in the general economy, and return to relatively normal activities from the devastation of this pandemic. It is likely that communication related to complex, poorly understood, rapidly evolving, and often contradictory information frequently

“If the message gets lost because of the inability to effectively communicate, or trust in the messenger is diminished, our society as a whole suffers the unfortunate consequences.”
From the Editor

leads to more confusion rather than enlightenment. Further, differences in opinions within the scientific and public health communities that are then widely disseminated online and in the traditional media may be another contributing factor.

Consider a few examples of events over the past few months that emphasize this point. The CDC is responsible for providing recommendations to governmental health agencies at the federal, state, regional, and local levels for strategies to control and prevent serious infectious events. However, at times it has appeared to many that the recommendations were potentially at least partly politically motivated or at the very least poorly considered. The recent rather sudden change in recommendations for wearing masks for the fully vaccinated population falls into this category.²,³

Although the CDC has regularly proclaimed that its recommendations are based on the science, this particular statement appears to have been poorly communicated or at least inadequately vetted within the public health community for how it would affect existing policies and how the recommendations might be effectively implemented.³ One prominent academic in this area was quoted as saying, “CDC’s been great in ‘21, but on this one they declared victory too early.”² Clearly, this and similar statements do not provide overwhelming support for the CDC, nor confidence in how the organization communicates with academic peers and the public.

As a second example, at the time of writing this commentary, the question of the origin of the virus that led to the COVID-19 pandemic remains a matter of great controversy. This topic, which involves complex national and international considerations, has led to widespread disagreements within the highest levels of the academic viral, epidemiology, and public health communities.⁴ The concern here are the very public disagreements, which include claims of potentially serious professional conflict-of-interest accusations among scientists and the organizations they represent. These cannot be viewed positively in the eyes of the American public, who are routinely asked to trust the observations and opinions of these individuals and groups.

The intent of this commentary has been to highlight both the complexity and importance of effective communication regarding highly relevant public health issues. Of course, this concern relates to communication regarding cancer topics, such as discussions around the critical issues of smoking cessation and weight control, as well as messages encouraging vaccination strategies known to reduce the risk of cancer. If the message gets lost because of the inability to effectively communicate, or trust in the messenger is diminished, our society as a whole suffers the unfortunate consequences.

References

**FDA DIGEST**

**Technetium Tc 99m Tilmanocept Injection is Approved for Pediatric Patients**

The FDA has approved technetium Tc 99m tilmanocept injection (Lymphoseek) for accurate, precise lymph node identification for pediatric patients with melanoma, rhabdomyosarcoma, and other types of solid tumors.

The radioactive diagnostic was evaluated in a study that demonstrated the agent was safe and effective for those 1 month and older. Investigators reported that less than 1% of patients experienced injection site irritation and/or pain, and no serious adverse events were reported.

In October 2014, the FDA expanded the use of technetium Tc 99m tilmanocept injection as a lymphatic mapping agent for solid tumors, where it is a component of the intraoperative procedure. The efficacy and safety of the therapy was confirmed in 3 open-label, multicenter, single-arm trials of adult patients with melanoma, breast cancer, or squamous cell carcinoma of the oral cavity, skin, and lip. When investigators evaluated lymphatic mapping efficacy in a study of 23 pediatric patients, the overall rate of lymph node detection, defined as at least 1 lymph node detected, was 96%; the median number of lymph nodes detected in this population was 3.

[TO READ MORE, VISIT bit.ly/3j9e22v.]

**Ravulizumab-cwvz Gets Go-ahead in Pediatric Paroxysmal Nocturnal Hemoglobinuria**

The FDA has approved the expanded use of ravulizumab-cwvz (Ultomiris) to include adolescents and children 1 month or older with paroxysmal nocturnal hemoglobinuria (PNH). The decision marks the first treatment approved by the FDA for pediatric patients with PNH, a rare blood disease that arises when mutation of PIGA occurs in bone marrow stem cells, leading to hemolysis.

Ravulizumab is a long-acting C5 inhibitor approved for its demonstrated efficacy inhibiting terminal complement-mediated intravascular hemolysis in patients with PNH as well as complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome.

The expanded indication was supported by data from a phase 3 trial (NCT03406507). Findings from the analysis demonstrated that no patients experienced breakthrough hemolysis during the 26-week initial evaluation period. One patient experienced breakthrough hemolysis at 1.8 years during the extension period but had adequate C5 inhibition (C5 < 0.5 μg/mL) at the time of onset.

[TO READ MORE, VISIT bit.ly/3yGbwq.]

**Plinabulin Plus G-CSF Application Receives Action Date for CIN Prevention**

The FDA has granted a priority review to the new drug application (NDA) seeking approval of plinabulin plus granulocyte colony-stimulating factor for the prevention of chemotherapy-induced neutropenia (CIN).

Plinabulin is a novel, intravenous small molecule that acts as a selective immunomodulating microtubule-binding agent with immune anticancer activities. The agent has shown synergistic activity with pegfilgrastim (Neulasta), reversing the immune suppressive profile of the colony-stimulating factor.

The NDA submission includes findings from the phase 3 PROTECTIVE-2 trial (NCT03294577), which evaluated plinabulin plus pegfilgrastim vs pegfilgrastim alone in patients with breast cancer who were receiving a chemotherapy regimen that included docetaxel, doxorubicin, and cyclophosphamide. In addition, data from 5 supportive trials enrolling over 1200 patients were included in the application.

Specifically, data from PROTECTIVE-2 demonstrated that the combination of plinabulin and pegfilgrastim (n = 110) was 53% more effective in reducing the incidence of CIN compared with pegfilgrastim alone (n = 111; 21.6% and 46.4%, respectively; P = .0001). The study met its primary end point, the rate of prevention of grade 4 neutropenia in cycle 1, with the addition of plinabulin improving the rate of prevention from 13.6% to 31.5% compared with pegfilgrastim alone (P = .0015).

The FDA is expected to decide on the application by November 30, 2021.

[TO READ MORE, VISIT bit.ly/3gJnfa2.]

**GUIDELINE UPDATE**

**ASCO Releases Guideline Recommendation for Hereditary Breast Cancer**

The American Society of Clinical Oncology (ASCO) has issued a rapid guideline update for patients with high-risk, early HER2-negative, BRCA-mutant breast cancer that recommends offering 1 year of adjuvant olaparib (Lynparza).

The recommendation is supported by data from the OlympiA trial (NCT02032823), which examined the agent vs placebo in patients with BRCA1/2-mutant, early HER2-negative breast cancer. Results, presented at the 2021 ASCO Annual Meeting, indicated that after a median follow-up of 2.5 years, patients who received olaparib experienced a 42% reduction in invasive disease-free survival, including local and metastatic recurrence of breast cancer, other new cancers, and death due to any cause, (HR, 0.58; 99.5% CI, 0.41-0.82; P < .0001). Additionally, investigators noted a difference in 3-year invasive disease-free survival rate between olaparib and placebo of 8.8% (95% CI, 4.5%-13.0%; stratified HR, 0.58; 99.5% CI, 0.41-0.82; P < .0001).

At the time of presentation the overall survival data were considered immature but were not significantly different between the 2 study cohorts at a median follow-up of 2.5 years (HR, 0.68; 99% CI, 0.44-1.05; P = .024). Moreover, the difference in 3-year overall survival rate between the 2 arms was 3.7% (95% CI, 0.3%-7.1%).

This update builds on the published recommendations from ASCO, the American Society for Radiation Oncology, and the Society of Surgical Oncology issued in 2020. Specifically, the recommendations state that 1 year of adjuvant olaparib should be offered following the completion of neoadjuvant chemotherapy and local treatment, including radiation. For patients who underwent surgery first, adjuvant olaparib is recommended for those with triple-negative breast cancer and tumor size greater than 2 cm or any involved axillary nodes.

Further, adjuvant olaparib is recommended for patients with hormone receptor–positive disease with at least 4 involved axillary lymph nodes. For those who had neoadjuvant chemotherapy, olaparib is recommended for patients with triple-negative breast cancer and any residual cancer.

For patients with residual disease, estrogen receptor–positive status, and estrogen receptor–status/tumor grade score of at least 3, the guidelines suggest adjuvant olaparib.

[TO READ MORE, VISIT bit.ly/3gKoGQe and bit.ly/31NdL5h.]
Companion for Trastuzumab Deruxtecan in NSCLC Hinges on New Partnership

Daiichi Sankyo Inc is collaborating with Guardant Health, Inc, to develop a companion diagnostic for fam-trastuzumab deruxtecan-nxki (Enhertu), which is being studied to treat patients with advanced metastatic HER2-mutated non–small cell lung cancer (NSCLC).

The Guardant360 CDx is a liquid biopsy assay that provides comprehensive genomic profiling results to guide treatment in all solid tumors and is approved for use as a companion diagnostic for several tumor types, including NSCLC.

A blood-based assay would be faster, simpler, and less invasive for the patient, said Gilles Gallant, PhD, FOPQ, senior vice president, global head in oncology development, oncology research and development at Daiichi Sankyo, in an interview with OncologyLive®. “We need to demonstrate that [blood-based] assays are [as] good [as], if not better, than taking a piece of the tumor.”

Trastuzumab deruxtecan is being studied in the phase 2 DESTINY-Lung01 trial (NCT03505710) as a second-line treatment for patients with HER2-mutated metastatic NSCLC who have received at least 1 prior antancer regimen that must have contained a platinum-based chemotherapy drug.

To Read More, Visit bit.ly/3vpSqBI.

Research Partnership Pushes TLR9 Agonist SD-101 Development Forward

The University of Texas MD Anderson Cancer Center and the immuno-oncology company TriSalus Life Sciences have announced a strategic research collaboration to evaluate SD-101, an investigational toll-like receptor 9 (TLR9) agonist, in combination with checkpoint inhibitors for the treatment of patients with pancreatic cancer and hepatocellular carcinoma (HCC).

The initial study of the collaboration will enroll patients with uveal melanoma–related liver metastases with additional studies planned for patients with metastatic pancreatic ductal adenocarcinoma (PDAC) and colorectal cancer. Additional trials in HCC and locally advanced PDAC are being developed.

SD-101 is delivered intravascularly via TriSalus Life Sciences’ FDA-cleared, proprietary pressure-enabled drug delivery (PEDD) technology, a method not previously possible with standard direct injection delivery.

Small prospective and retrospective studies reported that more therapy could be delivered into the vasculature of liver metastases and pancreatic solid tumors with PEDD technology vs standard end-hole microcatheters. The novel approach has the potential to overcome barriers of the tumor microenvironment, such as abnormal vascularity, interstitial fluid pressure, and solid stress.

To Read More, Visit bit.ly/2SAYKsy.

Three-Year Collaboration Looks to Produce Next-Generation DDR Therapies

Artios Pharma, a company devoted to developing precision medicine–based treatments based on DNA damage response (DDR) mechanisms, is entering into a global research collaboration with Novartis to develop next-generation DDR targets that will synergize with Novartis’ radioligand therapies.

As part of the 3-year collaboration, Artios and Novartis will pursue target discovery and validation. Novartis will identify as many as 3 exclusive DDR targets and receive worldwide rights on these targets to be used in combination with its radioligand therapies, which have been shown to improve overall survival and quality of life, particularly in patients with bone metastases.

Novartis’ radioligand therapies deliver targeted radiation to a subset of cancer cells, with minimal effect on surrounding healthy cells. Artios has demonstrated expertise in DDR drug discovery, including the identification and development of the PARP inhibitor olaparib (Lynparza), which has indications in the treatment of ovarian cancer, breast cancer, pancreatic cancer, and prostate cancer.

To Read More, Visit bit.ly/3woXwzc.

Checkmate Pharmaceuticals Looks to Boost Immune Response in PD-1–Refractory Melanoma

Checkmate Pharmaceuticals announced the initiation of dosing in the phase 2 CMP-001-010 trial (NCT04698187), which will evaluate the safety and efficacy of the combination of vidutolimod (CMP-001) and nivolumab (Opdivo) for patients with PD-1–refractory advanced melanoma.

Investigators are also evaluating the safety and efficacy of vidutolimod/nivolumab vs nivolumab alone in patients with metastatic or unresectable melanoma in a phase 2/3 trial (NCT04695977). Findings from both trials are expected to support a biologics license application for the doublet. The primary outcome measure for both trials is objective response rate.

Vidutolimod, an advanced generation toll-like receptor 9 agonist that is delivered as a biologic-like particle, converts the tumor microenvironment from cold to hot and stimulates antitumor cytotoxic T lymphocytes. When combined with checkpoint inhibitors, vidutolimod has the potential to improve outcomes for patients with anti-PD-1-refractory disease.

The agent is under evaluation in combination with pembrolizumab (Keytruda). Results of the phase 1 CMP-001-001 trial (NCT02680184) showed local and distant responses in patients with advanced melanoma with disease progression on prior PD-1 blockade.

To Read More, Visit bit.ly/3ztPhDP.
INDICATIONS
DARZALEX FASPRO™ is indicated for the treatment of adult patients with multiple myeloma:
• in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
• in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
• in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
• as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation.

WARNINGS AND PRECAUTIONS
Hypersensitivity and Other Administration Reactions
Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO™.

Systemic Reactions
In a pooled safety population of 490 patients who received DARZALEX FASPRO™ as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 2: 3.9%, Grade 3: 1.4%). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 9 minutes to 3.5 days). Of the 84 systemic administration-related reactions that occurred in 52 patients, 73 (87%) occurred on the day of DARZALEX FASPRO™ administration. Delayed systemic administration-related reactions have occurred in less than 1% of the patients.
Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension.
Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO™. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO™ depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 7 minutes (range: 0 minutes to 4.7 days) after starting administration of DARZALEX FASPRO™. Monitor for local reactions and consider symptomatic management.
**Efficacy consistent with intravenous daratumumab**
- DARZA**L**AX FASPRO™ demonstrated a non-inferior overall response rate (ORR) vs intravenous daratumumab in an open-label, randomized study assessing monotherapy in 522 patients1
  - ORR was 41% (95% CI: 35%, 47%) for DARZA**L**AX FASPRO™ (n=263) and 37% (95% CI: 31%, 43%) for intravenous daratumumab (n=259)2
- Eligible patients were required to have relapsed or refractory multiple myeloma who had received ≥3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who were double-refractory to a PI and an immunomodulatory agent3
- In a single arm of a multicohort, open-label trial, DARZA**L**AX FASPRO™ with lenalidomide and dexamethasone (DRd) was evaluated in 65 patients with multiple myeloma who had received ≥1 prior multiple myeloma therapy. The ORR was 91% (95% CI: 81%, 97%)4
- In a single arm of a multicohort, open-label trial, DARZA**L**AX FASPRO™ with bortezomib, melphalan, and prednisone (DVMP) was evaluated in 67 patients with newly diagnosed multiple myeloma who were ineligible for a transplant. The ORR was 88% (95% CI: 78%, 95%)4

**Fewer systemic ARRs vs intravenous daratumumab**
- Nearly 3x reduction in systemic administration-related reactions (ARRs) with DARZA**L**AX FASPRO™ vs intravenous daratumumab observed in the COLUMBA trial (13% of patients on DARZA**L**AX FASPRO™ had a systemic ARR of any grade vs 34% with intravenous daratumumab)1,3
- Both systemic ARRs, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZA**L**AX FASPRO™. See Important Safety Information for more details1

*For intravenous daratumumab, median durations of 16 mg/kg infusions for the first, second, and subsequent infusions were approximately 7, 4, and 3 hours, respectively2

In clinical trials of DARZA**L**AX FASPRO™, DARZA**L**AX® (daratumumab), and the Prescribing Information for DARZA**L**AX®, the term “infusion reactions” was used instead of “systemic administration-related reactions.”

**Neutropenia**
Daratumumab may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZA**L**AX FASPRO™ until recovery of neutrophils. In lower body weight patients receiving DARZA**L**AX FASPRO™, higher rates of Grade 3-4 neutropenia were observed.

**Thrombocytopenia**
Daratumumab may increase thromboctopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZA**L**AX FASPRO™ until recovery of platelets.

**Embryo-Fetal Toxicity**
Based on the mechanism of action, DARZA**L**AX FASPRO™ can cause fetal harm when administered to a pregnant woman. DARZA**L**AX FASPRO™ may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZA**L**AX FASPRO™ and for 3 months after the last dose.

The combination of DARZA**L**AX FASPRO™ with lenalidomide is contraindicated in pregnant women, because lenalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

**Interference with Serological Testing**
Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted.

**Interference with Determination of Complete Response**
Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some DARZA**L**AX FASPRO™-treated patients with IgG kappa myeloma protein.

**ADVERSE REACTIONS**
The most common adverse reaction (≥20%) with DARZA**L**AX FASPRO™ monotherapy is; upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, pyrexia, cough, muscle spasms, back pain, vomiting, upper respiratory tract infection, peripheral sensory neuropathy, constipation, and pneumonia.

The most common hematologic laboratory abnormalities (≥40%) with DARZA**L**AX FASPRO™ are: decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

Please see Brief Summary on adjacent pages.
**INDICATIONS AND USAGE**

DARZALEX FASPRO is indicated for the treatment of adult patients with multiple myeloma:

- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients who relapsed or refractory multiple myeloma who have received at least one prior therapy.
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

**CONTRAINDICATIONS**

DARZALEX FASPRO is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation (see Warnings and Precautions and Adverse Reactions).

**WARNINGS AND PRECAUTIONS**

**Hypersensitivity and Other Administration Reactions**

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO.

**Systemic Reactions**

In a pooled safety population of 490 patients who received DARZALEX FASPRO as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 3: 3.9%, Grade 2: 1.4%). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 9 minutes to 3.5 days). Of the 94 systemic administration-related reactions that occurred in 52 patients, 73 (87%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in less than 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, and hypotension.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids [see Dosage and Administration (2.3) in Full Prescribing Information]. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO depending on dosage regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions [see Dosage and Administration (2.3) in Full Prescribing Information].

**Local Reactions**

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 7 minutes (range: 0 minutes to 4.7 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management.

**Neutropenia**

Daratumumab may increase neutropenia induced by background therapy [see Adverse Reactions]. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO, higher rates of Grade 3-4 neutropenia were observed.

**Thrombocytopenia**

Daratumumab may increase thrombocytopenia induced by background therapy [see Adverse Reactions]. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX FASPRO until recovery of platelets.

**Embryo-Fetal Toxicity**

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose (see Use in Specific Populations). The combination of DARZALEX FASPRO with lenalidomide is contraindicated in pregnant women, because lenalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

**Interference with Serological Testing**

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs may cause inhibition of antibodies to minor antigens in the patient's serum [see References]. The determination of a patient's ABO and Rh blood type are not impacted [see Drug Interactions].

In study by blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO. Type and screen patients prior to starting DARZALEX FASPRO [see Dosage and Administration (2.1) in Full Prescribing Information].

**Interference with Determination of Complete Response**

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein [see Drug Interactions]. This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO-treated patients with IgG kappa myeloma protein.

**ADVERSE REACTIONS**

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

- Hypersensitivity and Other Administration Reactions [see Warning and Precautions].
- Neutropenia [see Warning and Precautions].
- Thrombocytopenia [see Warning and Precautions].

**Clinical Trials 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.

**Newly Diagnosed Multiple Myeloma**

In Combination with Bortezomib, Melphalan and Prednisone

The safety of DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) was evaluated in a single-arm cohort of PLEIADES [see Clinical Studies (14.1) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 6, once every 3 weeks from weeks 7 to 54 and once every 4 weeks starting with week 55 until disease progression or unacceptable toxicity (N=67) in combination with bortezomib, melphalan, and prednisone. Among these patients, 93% were exposed for 8 months or longer and 19% were exposed for greater than one year.

Serious adverse reactions occurred in 38% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia and pyrexia. Fatal adverse reactions occurred in 3.0% of patients. Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 4.5% of patients. The adverse reaction resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient was neutropenic sepsis.

Dose interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 51% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included thrombocytopenia, neutropenia, anemia, and pneumonia.

The most common adverse reactions (≥20%) were upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diarrhea, cough, insomnia, vomiting, and back pain.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) in PLEIADES.

| Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES |
|------------------|------------------|--------------------|
| Adverse Reaction  | All Grades (%)   | Grades 3+ (%)      |
| **Infections**    |                  |                    |
| Upper respiratory tract infection* | 39              | 0                  |
| Bronchitis         | 16               | 0                  |
| Pneumonia*        | 15               | 7                  |

*Indicates a common adverse reaction.
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES (continued)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>37</td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>36</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>34</td>
</tr>
<tr>
<td>Edema peripheral*</td>
<td>13</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>34</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Coughf</td>
<td>24</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>22</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>21</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>12</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>13</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
</tr>
</tbody>
</table>

* Upper respiratory tract infection includes nasopharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, tonsillitis, upper respiratory tract infection, and viral pharyngitis.

** Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, pneumonia, and pneumonia bacterial.

† Fatigue includes asthenia, and fatigue.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone</strong></td>
</tr>
<tr>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
</tr>
<tr>
<td>Decreased platelets</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
</tr>
</tbody>
</table>

# Only grade 3 adverse reactions occurred.

Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES

Table 3: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (D-Rd) in PLEIADES

DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

Released/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) was evaluated in a single-arm cohort of PLEIADES [see Clinical Studies (14.2) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=65) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO. Serious adverse reactions in ≥5% of patients included pneumonia, influenza and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than one patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in ≥5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased.

The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 3 summarizes the adverse reactions in patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) in PLEIADES.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) include:

- General disorders and administration site conditions: infusion reaction, injection site reaction, chills
- Infections: herpes zoster, urinary tract infection, influenza, sepsis
- Musculoskeletal and connective tissue disorders: arthralgia, muscle spasms
- Nervous system disorders: headache, paresthesia
- Metabolism and nutrition disorders: hypocalcemia, hyperglycemia
- Respiratory, thoracic and mediastinal disorders: dyspnea, pulmonary edema
- Cardiac disorders: atrial fibrillation

Table 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) in PLEIADES.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone</strong></td>
</tr>
<tr>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
</tr>
<tr>
<td>Decreased platelets</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
</tr>
</tbody>
</table>

* Denominator is based on the safety population treated with D-VMP (N=67).
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

- Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal chest pain
- Nervous system disorders: dizziness, headache, paresthesia
- Skin and subcutaneous tissue disorders: rash, pruritus
- Gastrointestinal disorders: abdominal pain
- Infections: influenza, sepsis, herpes zoster
- Metabolism and nutrition disorders: decreased appetite
- Cardiac disorders: atrial fibrillation
- General disorders and administration site conditions: chills, infusion reaction, injection site reaction
- Vascular disorders: hypotension, hypertension

Table 4 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) in PLEIADES.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone (D-Rd) (N=260)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>94 (34)</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82 (58)</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>86 (9)</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>89 (52)</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45 (8)</td>
</tr>
</tbody>
</table>

- Denominator is based on the safety population treated with D-Rd (N=65).

Monotherapy

The safety of DARZALEX FASPRO as monotherapy was evaluated in COLUMBA (see Clinical Trials (14.2) in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/m² units administered subcutaneously or daratumumab 16 mg/kg administered intravenously; each administered once weekly from week 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity. Among patients receiving DARZALEX FASPRO, 37% were exposed for 6 months or longer and 1% were exposed for greater than one year.

Serious adverse reactions occurred in 26% of patients who received DARZALEX FASPRO. Fatal adverse reactions occurred in 5% of patients. Fatal adverse reactions occurring in more than one patient were general physical health deterioration, septic shock, and respiratory failure.

Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 2 patients were thrombocytopenia and hypercalcemia.

Dosage interruptions due to an adverse reaction occurred in 26% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruption in >5% of patients included thrombocytopenia.

The most common adverse reaction (≥20%) was upper respiratory tract infection.

Table 5 summarizes the adverse reactions in COLUMBA.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO (N=260)</th>
<th>Intravenous Daratumumab (N=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade ≥3 (%)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>24 (18)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8 (5)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (10)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (4)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (10)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>13 (2)</td>
<td>34 (5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13 (0)</td>
<td>13 (1)</td>
</tr>
<tr>
<td>Chills</td>
<td>6 (0)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10 (2)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>9 (3)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6 (1)</td>
<td>11 (1)</td>
</tr>
</tbody>
</table>

Adverse reactions occurring in ≤5% of patients treated with DARZALEX FASPRO in COLUMBA are described below with the incidence of antibodies in other studies or to other daratumumab products or other hyaluronidase products may be misleading.

Postmarketing Experience

The following adverse reactions have been identified with use of intravenous daratumumab. 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.

Immune System: Anaphylactic reaction
Gastrointestinal: Pancreatitis
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

**DRUG INTERACTIONS**

**Effects of Daratumumab on Laboratory Tests**

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiotreitol (DTT) to disrupt daratumumab binding (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs. If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX FASPRO-treated patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Risk Summary

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products in pregnancy may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX FASPRO-treated patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

**Data**

Animal Data

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs). No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose. There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

**Lactation**

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant populations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide and dexamethasone, advise women not to breastfeed during treatment with DARZALEX FASPRO. Refer to lenalidomide prescribing information for additional information.

**Data**

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

**Females and Males of Reproductive Potential**

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations).

**Contraception**

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose. Additionally, refer to the lenalidomide labeling for additional recommendations for contraception.

**Pediatric Use**

Safety and effectiveness of DARZALEX FASPRO in pediatric patients have not been established.

**REFERENCES**


**PATIENT COUNSELING INFORMATION**

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

**Hypersensitivity and Other Administration Reactions**

Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: tachy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing (see Warnings and Precautions).

**Neutropenia**

Advise patients to contact their healthcare provider if they have a fever (see Warnings and Precautions).

**Thrombocytopenia**

Advise patients to contact their healthcare provider if they have bruising or bleeding (see Warnings and Precautions).

**Embryo-Fetal Toxicity**

Advise pregnant women of the potential hazard 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 avoid becoming pregnant during treatment with DARZALEX FASPRO and for at least 3 months after the last dose (see Use in Specific Populations).

Advise patients that lenalidomide has the potential to cause fetal harm and has specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide is only available through a REMS program (see Use in Specific Populations).

**Interference with Laboratory Tests**

Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion (see Warnings and Precautions).

Advise patients that DARZALEX FASPRO can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response (see Warnings and Precautions).

**Hepatitis B Virus (HBV) Reactivation**

Advise patients to inform healthcare providers if they have ever had or might have had a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again (see Adverse Reactions).

**Product of Switzerland**

Manufactured by: Janssen Biotech, Inc.
Horsham, PA 19044
U.S. License Number 1864

© 2020 Janssen Pharmaceutical Companies cp-144555v1
MET Inhibition Looks to Advance NSCLC Treatment Landscape

by JESSICA HERGERT

THE PRESENCE OF MET ALTERATIONS in patients with non–small cell lung cancer (NSCLC) has been associated with a worse survival outcome, but there are no targeted treatment options available for this subpopulation.

In February, the FDA granted accelerated approval to tepotinib (Tepmetko) for adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations based on data from the phase 2 VISION trial (NCT02864992). Analysis of 2 patients cohorts demonstrated an overall response rate of 43% (95% CI, 32%-56%) with a median duration of response of 10.8 months (95% CI, 6.9-not estimable) among 69 treatment-naïve patients. The response rate among 83 previously treated patients was 43% (95% CI, 33%-55%) with a median duration of response of 11.1 months (95% CI, 9.5-18.5).

In an interview with OncologyLive®, Paul K. Paik, MD, clinical director of the thoracic oncology service at Memorial Sloan Kettering Cancer Center in New York, New York, discussed the clinical implications of tepotinib on the NSCLC armamentarium.

How do you see the approval of tepotinib affecting the treatment landscape for patients with NSCLC?

The importance of the approval of tepotinib can be thought of in a few different ways. First, of course, it has to do with [a particular subset of patients with NSCLC] who have MET exon 14 skipping alterations. This is a subset that tends to be fairly older; the median age [when these patients receive a diagnosis] is 73 to 74 years across all series. And as way of contrast, the median age for most of our trials in lung cancer is the lower 60s. For some other oncogene-addicted cancers, these are patients who are in their lower 50s; so many of these patients are older. A lot of them are in their 80s, and they have special considerations when it comes to trying to figure out which treatments will be effective but also what treatments will be well tolerated.

These are also patients who generally are not represented in the pivotal upfront trials. There’s been a need for better treatments for these patients. The approval of tepotinib is 1 step forward in that regard, having a fairly well-tolerated oral agent that is effective in this patient population. That’s probably the most important aspect of the recent approval.

Another reason why it’s important is that [MET is] yet another driver alteration that we’ve been able to target in lung cancer. For me, the more [targets] we’re able to find for our patients, the greater the chance is that we’ll be able to offer some other options for these [individuals]. As it relates to biomarker testing in this population, word’s getting out that we should be performing next-generation sequencing as a standard of care for all of our patients at the time of diagnosis. This [approval] helps in [supporting] guideline recommendations for doing this in [patients with] lung adenocarcinoma and squamous cell lung cancer.

What is the incidence rate of patients with NSCLC who harbor MET exon 14 skipping mutations?

The incidence of MET exon 14 skipping alterations in NSCLC for all-comers is approximately 3% to 4%, depending on the series that you end up looking at. It tends to be more common in patients who have lung adenocarcinoma than in patients with squamous lung cancer. Importantly, there’s a rare histologic subtype of NSCLC—these patients have sarcomatoid carcinomas, which are pretty treatment refractory. We find MET exon 14 skipping alterations in approximately [one-fourth to one-third] of these patients. It’s a subpopulation who should definitely be tested for these alterations.

What are some highlights from the VISION trial design and efficacy data?

One of the unique aspects [of the VISION trial] was that ctDNA [circulating tumor DNA] testing was built in. We had serial assessment, a molecular assessment for the determination of resistance and sensitivity. Some of these data were presented in our article in the New England Journal of Medicine and will be presented at other meetings. [These data] have been valuable in terms of trying to map out what the next steps are going to be for the developments of the field.

Oral therapies are important for a few different reasons. One tends to be psychological. [Patients are] trying to regain a sense of independence and freedom after [receiving a] diagnosis of cancer. Oral therapies generally lend themselves to that because you’re not tied to the sort of cancer institute [where you have to go] every couple of weeks or every few weeks. And so there’s a lot more flexibility in terms of assessments and obtaining the drug. [Another reason is] that, by and large, the oral therapies that we’ve developed that are targeted tend to be pretty well tolerated. Again, that has been an important boost in the treatment landscape, particularly for our elderly patients.

What do you foresee for tepotinib in terms of broadening its efficacy?

Things that we’re already beginning to think about include exactly how to increase the efficacy and also potentially manage the adverse effects with MET inhibition.

[This includes] trying to figure out why patients develop resistance to this [agent], and still we’re in the early stages of figuring this out. The data presented [thus far] have shown nicely what some of these resistance profiles are, depending on the kind of MET inhibitor that’s used. We’re beginning to understand that the early data suggests that there’s not going to be kind of a silver bullet for most patients in terms of overcoming resistance.

A lot of the focus now is trying to figure out how we can extend the efficacy of [MET inhibitors] with combination therapies up front. The logical [next step is to] look at [tepotinib] in combination with existing treatments. For example, combination with chemotherapy, [or] combinations with other targeted therapies might be of interest. There’s ongoing development with MET antibodies, which we initially had looked at a decade ago but that failed to generate an efficacy signal in randomized phase 3 data. But we’re beginning to [revisit that] as it relates to targeting MET exon 14 skipping.

REFERENCE
PIVOTAL CLINICAL TRIAL

VISION (NCT02864992) was a phase 2, multicenter, nonrandomized, open-label, multicohort trial that evaluated efficacy and safety of tepotinib in 152 adult patients with advanced or metastatic NSCLC with MET exon 14 skipping alterations; patients with EGFR-activating mutations or ALK rearrangements were excluded. Patients received tepotinib at 450 mg orally once daily until disease progression or unacceptable toxicity.

BASELINE PATIENT CHARACTERISTICS

Median age (years, range) 73 (41-94) N = 152

ECOG performance status at baseline

Number of prior therapies for advanced NSCLC

Histopathological classification

COMMONLY REPORTED ADVERSE EFFECTS IN THE VISION TRIAL

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Tepotinib (N = 255)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
</tr>
<tr>
<td>Edema</td>
<td>70%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27%</td>
</tr>
<tr>
<td>Nausea</td>
<td>27%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>24%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>20%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>16%</td>
</tr>
<tr>
<td>Constipation</td>
<td>16%</td>
</tr>
<tr>
<td>Cough</td>
<td>15%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11%</td>
</tr>
</tbody>
</table>

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: Monitor liver function tests. Withhold, dose reduce, or permanently discontinue tepotinib based on severity.
- Embryo-fetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception.

REFERENCES


NSCLC NOS, non–small cell cancer not otherwise specified.
NOVEL THERAPEUTIC STRATEGIES ARE poised to expand in adjuvant settings for patients with early-stage disease facing recurrence risks in the treatment paradigms for a range of tumor types after positive data from large phase 3 clinical trials were highlighted at the 2021 American Society of Clinical Oncology Annual Meeting (ASCO 2021).

The new findings establish an earlier role for therapies introduced for metastatic disease, but experts say that uptake in clinical practice will depend upon the perceived benefits of adjuvant treatment compared with the toxicities and the costs of additional therapy.

From a clinical standpoint, ASCO 2021 featured results of studies showing that adjuvant therapy could enhance disease-free survival (DFS) vs placebo or best supportive care for subsets of patients with breast, lung, and renal cell carcinoma. Key findings were reported from these studies (TABLE 1–4):

- **OlympiA** (NCT02032823)—The PARP inhibitor olaparib (Lynparza) significantly improved 3-year invasive DFS to 85.9% compared with 77.1% with placebo in patients with HER2-negative breast cancer harboring a germline *BRCA1/2* mutation that was deemed high risk after primary local treatment and neoadjuvant or adjuvant therapy.1

- **IMpower010** (NCT02486718)—Atezolizumab (Tecentriq), a PD-L1 immune checkpoint inhibitor, demonstrated a 34% reduction in the risk of disease recurrence or death (HR, 0.66; 95% CI, 0.50-0.88) compared with best supportive care (BSC) among patients with resected PD-L1-positive stage II to IIIA non–small cell lung cancer (NSCLC).2

- **KEYNOTE-564** (NCT03142334)—Pembrolizumab (Keytruda), a PD-1 inhibitor, showed a 24-month estimated DFS rate of 77.3% compared with 68.1% with placebo in patients with clear-cell renal cell carcinoma (RCC) categorized as intermediate high risk or high risk after nephrectomy. Investigators also observed a preliminary trend toward an overall survival (OS) benefit of 96.6% with pembrolizumab vs 93.5% with placebo.3

The emphasis on the adjuvant setting underscores the importance of developing therapies that can improve outcomes for patients who face a high residual risk of recurrence after primary treatment, according to Julie R. Gralow, MD, FACP, FASCO, chief medical officer and executive vice president of ASCO. “This is a population [for which] for many cancers, we don't have a high likelihood of cure,” Gralow said in an interview with OncologyLive®. “We’re looking for something that can add benefit. We’re also testing risk vs benefit.”

In that regard, negative results from an adjuvant therapy trial in cervical cancer were highlighted along with positive adjuvant data during the conference’s plenary session. Findings from the international phase 3 OUTBACK trial (ACTRN12610000732088) demonstrated that administering chemotherapy to patients with locally advanced cervical cancer following standard cisplatin-based chemoradiation resulted in similar progression-free survival without improving OS at 5 years (HR, 0.91; 95% CI, 0.70-1.18).4

“It’s not often that we pick a negative trial to put in the plenary session, but because this group of patients with locally advanced cervical cancer has a rate of high relapse… [clinicians] have been adding chemotherapy thinking more must be better,” Gralow said. “It’s important to show chemotherapy
isn’t the answer. Now we need to think outside the box.”

Overall, the expansion of adjuvant therapies is indicative of the trend toward individualizing treatment, according to Erika P. Hamilton, MD, director of the breast cancer and gynecologic cancer research program at Sarah Cannon Research Institute of Tennesse Oncology in Nashville. “I think this is really kind of the next wave of personalized medicine,” she said in an OncLive® NewsNetwork: On Location interview.

**DFS SERVES AS END POINT**

The findings that form the underpinnings of the OlympiA, IMpower010, and KEYNOTE-564 trials hinge on DFS, an end point that the FDA and clinical guidelines recognize. The FDA has approved the use of DFS as an end point for accelerated and traditional adjuvant therapy approvals for stage III NSCLC and following complete resection for 6 solid tumor types: colon, colorectal, and breast cancer; RCC; melanoma; and gastrointestinal stromal tumor.5

Nevertheless, the development of therapies in the adjuvant setting has proceeded comparatively slowly. In an analysis published in *JAMA Network Open* in April 2020, investigators identified 69 agents that the FDA approved or the National Comprehensive Cancer Network guidelines recommended for use in the metastatic setting for patients with NSCLC, breast, and colon cancers as of May 15, 2019, compared with 25 therapies for adjuvant use. For drugs approved or recommended in both settings, the mean delay in moving a therapy from the metastatic to the adjuvant setting was 10 years (SD, 7.5).6

Challenges to developing adjuvant therapy include identifying the patient population likely to benefit, recruiting enough patients for meaningful comparisons, and determining whether the improvement in outcomes justifies the added toxicity, Gralow said.

Meanwhile, the extent to which adjuvant approaches are embraced in clinical practice may vary. Oncologists who treat patients with breast cancer, for whom investigators pioneered the use of adjuvant strategies in the 1970s,7 are familiar with such approaches whereas those who specialize in other malignancies may not be. “If it’s a cancer type [with which] most patients do well and cure is highly likely, it’s going to take a lot to convince [oncologists] to add something more. I think we’ve had a lot of dialogue in this meeting on exactly how we relate to our patients and [explain] what their actual risk of recurrence is,” Gralow said.

A decision to recommend adjuvant therapy is “all about precision medicine,” she continued. “You have to understand the cancer, you have to understand features of the patient. And then you have to look at the features of the therapy. They all have to come together for [adjuvant therapy] to make sense. That’s where I think we’re going.”

**OLAPARIB IN BREAST CANCER**

In OlympiA, investigators recruited 1836 patients with HER2-negative breast cancer who had high-risk stage II or III disease or failed to achieve a pathologic complete response to neoadjuvant chemotherapy and whose tumors had a germline BRCA1/2 mutation. All participants except 2 in the placebo arm underwent primary surgery (either a mastectomy or conservative surgery) with adjuvant (50%) or neoadjuvant (50%) chemotherapy. Investigators randomized participants to receive either olaparib at 300 mg twice daily or placebo for 1 year.1

In the intent-to-treat (ITT) population, olaparib therapy resulted in an absolute difference in the 3-year invasive DFS rate of 8.8% (95% CI, 4.5%-13.0%), which translated into a 42% reduction in the risk of disease recurrence or death (HR, 0.58; 99.5% CI, 0.41-0.82; *P* < .0001). Treatment with olaparib also improved distant DFS vs placebo (HR, 0.57; 99.5% CI, 0.39-0.83; *P* < .0001).

**TABLE. Select Adjuvant Therapy Phase 3 Trial Findings Presented at ASCO 2021**4

<table>
<thead>
<tr>
<th>Study description</th>
<th>Patient population</th>
<th>Primary findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OlympiA (NCT02302823): BRCA1/2-mutant, HER2-negative early breast cancer</strong></td>
<td>TNBC: ≥ pT2 or ≥ pN1 disease prior to ACT or non-pCR after NACT; Hormone receptor–positive: ≥4 positive nodes prior to ACT or non-pCR and CPS&amp;EG score ≥ 3 after NACT</td>
<td>Invasive DFS at 3 years: 85.9% vs 77.1% (HR, 0.58; 99.5% CI, 0.41-0.82; <em>P</em> &lt; .0001)</td>
</tr>
<tr>
<td>IMpower010 (NCT02486718): early-stage NSCLC</td>
<td>Compl etely resected stage IB-IIIA NSCLC; stage IB tumors ≥4 cm</td>
<td></td>
</tr>
<tr>
<td><strong>KEYNOTE-564 (NCT03142334): resected RCC</strong></td>
<td>Clear cell RCC, nephrectomy ≤ 12 weeks prior to randomization; no prior systemic therapy</td>
<td>24-month DFS rate: 77.3% vs 68.1%* Median DFS: NR vs 35.3 months (HR, 0.68; 95% CI, 0.50-0.88; <em>P</em> = .004)</td>
</tr>
<tr>
<td>OUTBACK (ACTRN12610000732088): locally advanced cervical cancer</td>
<td>Concurrent CRT vs concurrent CRT plus ACT (919)*</td>
<td>Cervical cancer suitable for curative intent CRT; FIGO 2008 stage IB1+LN, IB2, II, IIB, IVA</td>
</tr>
</tbody>
</table>

---

*Act, adjuvant chemotherapy; BSC, best supportive care; CPS, clinical and pathological stage; CRT, chemoradiation therapy; DFS, disease-free survival; EG, estrogen receptor status and histologic grade; FIGO, International Federation of Gynecology and Obstetrics; ITT, intention to treat; NACT, neoadjuvant chemotherapy; NE, not estimable; NR, not reached; NSCLC, non–small cell lung cancer; OS, overall survival; pCR, pathologic complete response; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

*PD-L1 staining on ≥ 1 of tumor cells.

*Not statistically significant per trial protocol.

*DFS per investigator.

*Negative trial for adjuvant therapy.

**Erika P. Hamilton, MD**

Vol. 22 | No. 13 | JULY 2021
Notably, investigators also observed a trend toward improved OS in the olaparib arm, with a 92.0% rate vs 88.3% with placebo (stratified HR, 0.68; 99.5% CI, 0.44-1.05; P = .024). However, the OS was not statistically significant given the median follow-up of only 2.5 years and a prespecified threshold of P < .01. Blinded follow-up continues.

In terms of tolerability, the incidence of all-grade adverse events (AEs) was greater with olaparib than placebo, including for nausea (57% vs 23%, respectively), fatigue (40% vs 27%), and anemia (23% vs 4%). However, olaparib did not increase the incidence of serious AEs compared with placebo (8.7% vs 8.4%, respectively), or AEs of special interest (3.3% vs 5.1%, respectively).

The findings mark the first time that results were reported for adjuvant PARP inhibition in this population, investigators said. The trial “changes care for women who have a possibility of having a germline mutation,” Judy E. Garber, MD, MPH, a leading OlympiA investigator, said in an interview. “These treatments should be different” for these patients.

“It does mean we have to think more about how to manage genetic testing in our patients at high risk,” added Garber, chief of the Division for Cancer Genetics and Prevention and Susan F. Smith Chair at Dana-Farber Cancer Institute in Boston, Massachusetts. “[For] those patients who would have been eligible for the trial, we should be thinking, is this someone who might have a mutation. That means people have to devise ways to get genetic testing done.”

BRCA testing is not routinely conducted for patients with early-stage breast cancer but “there will certainly be a push” to expand testing in this setting as a result of the OlympiA findings, according to Cathy Su, PhD, a consultant in oncology and specialty therapeutics at Kantar Health, a research and analytical company in New York, New York.9

Expanded testing and adjuvant olaparib therapy has the potential to affect a large pool of patients. Overall, more than 475,000 patients with early-stage HER2-negative breast cancer will be treated this year with neoadjuvant or adjuvant therapies in the United States and other G8 countries, according to Kantar.9

“The cost of these drugs will affect how well they are adopted in the wealthy countries as well as the poorer countries,” Garber observed. “It would be a shame to show that the drugs are effective and not be able to make them available.”

To Hamilton and Garber, the OlympiA findings are part of a continuing expansion of adjuvant therapies for patients with breast cancer.

“We are learning in breast cancer care that adding additional adjuvant therapies is a really good way to right-size therapy for our patients,” Hamilton said. “Probably a great example of this was the KATHERINE data [NCT01772472]. We had some lukewarm results in the HER2 [population] but KATHERINE came along with a great trial design, taking those patients who were high risk based on the fact that they did not have a pathologic complete response to good therapy, and we saw an 11% improvement in DFS when we added T-DM1 [ado-trastuzumab emtansine; Kadcyla].2 OlympiA is the same. It’s taking patients who have a known predictor here, the germline BRCA mutation, and offering them an additional therapy for improvement.”

“Adjuvant therapy is the treatment that transformed breast cancer from a more often fatal disease to a potentially curable one,” Garber observed. “But the responsibility in adjuvant therapy is to identify those patients who will most benefit from the intervention and to target therapies appropriately, to forgo toxic treatments in patients who don’t need them. Fortunately, we’re at the place in breast cancer where that’s the tension—we’re trying to match more aggressive treatments in patients who need them and to back off more toxic treatments in patients who can do without them. That’s a good place to be. That says you have success.”

ATEZOLIZUMAB IN NSCLC

In NSCLC, adjuvant platinum-based chemotherapy has been integrated into the treatment paradigm for patients with completely resected stage IB to IIIA disease for more than 15 years, demonstrating a 4% to 5% OS improvement over observation.2 In December 2020, the FDA approved osimertinib (Tagrisso) as adjuvant therapy after tumor resection for patients with NSCLC that harbors EGFR exon 19 deletions or exon 21 L858R mutations after the third-generation EGFR inhibitor showed a substantial improvement in median DFS over placebo (HR, 0.17; 95% CI, 0.12-0.23; P < .0001) in the ADJURA trial (NCT02511106).10

Meanwhile, the PD-L1 inhibitor durvalumab (Imfinzi) has emerged as an adjuvant option for unresectable stage III disease following its February 2018 approval for patients whose cancer has not progressed after concurrent platinum-based chemoradiation.11

In IMpower010, investigators sought to expand the benefits of immunotherapy to patients with stage IB to IIIA disease who had undergone complete tumor resection followed by chemotherapy with cisplatin plus pemetrexed (Alimta), gemcitabine, docetaxel, or vinorelbine for 1 to 4 cycles. Following those treatments, 1005 patients were then randomized to receive either atezolizumab at 1200 mg every 21 days for 16 or BSC. Participates were stratified by PD-L1 expression status at study entry. Primary end points were DFS in patients with stage II to IIIA disease with PD-L1 expression on 1% or more of tumor cells; all randomized patients in the stage II to IIIA cohort; and the ITT population with stage IB to IIIA disease.2

After a median follow-up of 32.8 months, atezolizumab therapy proved most effective for participants with stage II to IIIA disease with PD-L1 expression of 1% or more on tumor cells. The median DFS was not estimable (NE; 95% CI, 36.1-NE) among participants in this cohort (n = 248) compared with 35.3 months (95% CI, 29.0-NE) for those who received BSC (n = 228), which translated to an HR of 0.66 (95% CI, 0.49-0.87; P = .004). For all randomized patients with stage II to IIIA disease, the HR was 0.79 (95% CI, 0.64-0.96; P = .02). In the ITT population, the DFS did not cross the threshold for statistical significance (HR, 0.81; 95% CI-0.67-0.99; P = .04).

In terms of toxicities, investigators found that the safety profile of atezolizumab was consistent with prior studies of the drug in more advanced disease settings. The incidence of grade 3/4 AEs was 21.8% in the atezolizumab arm and 11.5% in
the BSC group. In all, 67.7% of those who received immunotherapy experienced treatment-related AEs (TRAEs), including 7.5% with serious TRAEs. There were 8 deaths among patients who received atezolizumab, including 4 attributable to TRAEs, compared with 3 deaths on the BSC arm. Grade 5 events in the atezolizumab population included interstitial lung disease, multiple organ dysfunction syndrome, myocarditis, and acute cardiac failure.

The findings show that “atezolizumab may be considered a practice-changing adjuvant treatment option for patients with resected PD-L1-expressing stage II to IIIA non-small cell lung cancer,” lead study author Heather Wakelee, MD, a professor of medicine at Stanford University Medical Center in California, said in presenting the results.

The study will continue for DFS and OS analyses in the ITT population, Wakelee said. At the time of her presentation, OS data were immature and not formally tested, although early findings favor atezolizumab therapy in the PD-L1-positive stage II to IIIA population.

The IMpower010 findings are “compelling,” Edward S. Kim, MD, MBA, said in an OncLive® NewsNetwork: On Location interview. “We all have this gut feeling that if we can do something more that has some benefit, we will help folks,” said Kim, physician in chief of City of Hope Orange County and vice physician in chief of City of Hope National Medical Center in California. “We largely learned from colon cancer and breast cancer that longer-term biologic-type therapy may help and we do see that in this study. This study will change how we approach lung cancer, especially those surgically resected, curative-intent patients.”

The results may hold the potential for a narrow adjuvant indication for atezolizumab, according to Stephanie Hawthorne, vice president of oncology and specialty therapeutics at Kantar Health. The agent currently is approved in several first-line and recurrent settings for patients with metastatic NSCLC.

Looking forward, Hawthorne noted that investigators are testing adjuvant immunotherapy for NSCLC in several other large clinical trials. “IMpower 010 is the first to report positive results in the postsurgical setting,” she said. “Learnings from this trial, especially how the oncology community and regulatory bodies perceive this level of evidence, is going to provide critical insights for the pharma industry that is also working to develop in this space.”

For his part, Kim feels that the emphasis on early-stage settings that IMpower010 exemplifies represents “movement in the right direction.”

“We need to be receptive to allowing these types of therapies to be studied and to be approved quickly for patients,” he said. “We all want there to be safety—that absolutely has to be the case—but this is why we do informed consent, this is why we talk to the patients. Accelerating these drugs is even more important in a curative-intent population because these are patients that we’re trying to keep their disease away and this way we build long-term survivors.”

**PEMBROLIZUMAB FOR RCC**

Although locoregional RCC is typically treated with curative-intent nephrectomy, nearly half of patients eventually experience disease recurrence, according to Toni K. Choueiri, MD, lead author of the KEYNOTE-564 study. “Currently, there is no globally accepted standard-of-care therapy to delay disease progression after surgery,” Choueiri said in presenting the findings at ASCO 2021. “Cytokines and VEGF-targeted agents have not shown much consistent benefit in this setting.”

For KEYNOTE-564, investigators recruited patients with clear cell RCC who had undergone nephrectomy within 12 weeks of randomization without prior systemic therapy. In all, 994 patients were randomized to receive pembrolizumab at 200 mg every 3 weeks for approximately 1 year or placebo. Stratification factors included stage M0 cancer vs M1 with no evidence of disease (NED). The pembrolizumab and placebo arms were well-balanced for disease risk categories, respectively, for M0 intermediate-high risk (86.1% vs 86.9%), M0 high risk (8.1% vs 7.2%), and M1 NED (5.8% vs 5.8%).

Investigator-assessed DFS was the primary end point of the trial. At 24 months, the DFS rate was 77.3% for patients who received pembrolizumab compared with 68.1% for those who had placebo, for an HR favoring immunotherapy of 0.68 (95% CI, 0.53-0.87; P = .0010). The median DFS was not reached in either arm.

“The difference with pembrolizumab vs placebo was statistically significant,” said Choueiri, director of the Lank Center for Genitourinary Oncology at Dana-Farber and the Jerome and Nancy Kohlberg Professor of Medicine at Harvard Medical School in Boston. “The curve split early on, with an estimated difference in DFS rate of about 10% for pembrolizumab vs placebo at the key time points of 12 and 24 months.”

Interim OS results also favored pembrolizumab (HR, 0.54; 95% CI, 0.30-0.96; P = .0164), although only about 25% of events needed for analysis had occurred at the time of data cutoff.

In terms of safety, Choueiri said AEs with pembrolizumab fit the known profile for the drug and were manageable. TRAEs were higher with pembrolizumab compared with placebo for frequently observed events including fatigue (20.3% vs 14.3%, respectively), pruritus (18.6% vs 11.5%), hypothyroidism (17.6% vs 2.6%), and diarrhea (15.8% vs 10.3%). Grade 3 to 5 TRAEs also were more prevalent with pembrolizumab (18.9% vs 1.2%).

Putting the results into context for patients with the malignancy, Choueiri added a personal observation.

“The first randomized controlled trial, to my knowledge, of adjuvant immunotherapy in renal cell cancer was with interferon,” he said. “And this was presented at the 1992 ASCO meeting. At that time, I wasn’t done with high school. Now 29 years later, finally, finally, we have a positive adjuvant study in renal cell cancer, a positive adjuvant study of immunotherapy with pembrolizumab. It took a whole generation to achieve this goal.”

For a full list of references, see the article at OncLive.com.
IN A WORLD FILLED WITH COVID-19...

CIN CAN STRIKE AT ANY MOMENT

It's time to take a crucial new look at CIN, the dire consequences of leaving patients unprotected, and how the COVID-19 pandemic is changing guidelines as well as your approach to providing the best standard of care.

TO LEARN MORE, VISIT CINRisk.com

With the ongoing threat of chemotherapy-induced neutropenia (CIN), the COVID-19 pandemic is making oncologists and their care teams revisit their approach as they use aggressive regimens to treat their patients with cancer. Along with this, current treatment guidelines are now recommending the expanded prophylactic use of granulocyte-colony stimulating factors (G-CSFs) to intermediate-risk cancer patients as well.1

When your patients are left unprotected, particularly in Cycle 1,2 CIN may lead to life-threatening events, such as fever, infection, and hospitalization3–severely disrupting the predictability of your treatment plan.

These chemotherapy delays and decreases can ultimately impact outcomes and decrease overall survival.4-6

References:
With the ongoing threat of chemotherapy-induced neutropenia (CIN), the COVID-19 pandemic is making oncologists and their care teams revisit their approach as they use aggressive regimens to treat their patients with cancer. Along with this, current treatment guidelines are now recommending the expanded prophylactic use of granulocyte-colony stimulating factors (G-CSFs) to intermediate-risk cancer patients as well.¹

When your patients are left unprotected, particularly in Cycle 1,² CIN may lead to life-threatening events, such as fever, infection, and hospitalization³—severely disrupting the predictability of your treatment plan. These chemotherapy delays and decreases can ultimately impact outcomes and decrease overall survival.⁴⁻⁶

References:
Shorter Duration of Adjuvant Trastuzumab Shows Long-Term Survival Benefit in Select HER2+ Early Breast Cancer

by HAYLEY VIRGIL

UPDATED SURVIVAL DATA FROM the phase 3 Short-HER trial (NCT00629278) presented during the European Society for Medical Oncology Breast Cancer 2021 Virtual Congress confirm the promising long-term results obtained with 9 weeks of adjuvant trastuzumab (Herceptin) in patients with HER2-positive early breast cancer who have low and intermediate risk factors. The noninferiority data present a more optimized duration of treatment for highly representative population of patients seen most in clinical practice.1

After a median follow-up of 8.7 years, patients who had received 1 year of trastuzumab (n = 626) had a 5-year disease-free survival (DFS) rate of 87.9% vs 85.8% in those who received trastuzumab for 9 weeks (n = 627; HR, 1.09; 90% CI, 0.88-1.35). Patients had a 5-year overall survival (OS) rate of 95.1% in both arms, respectively.

“Athough 1 year of trastuzumab remains a standard, de-escalation of treatment is a reasonable option for a large proportion of a real-world population of [patients with] HER2-positive early breast cancer,” PierFranco Conte, MD, said in a presentation on the findings. Conte is a professor of oncology at the University of Padova, Italy, and director of the Division of Medical Oncology 2 at the Istituto Oncologico Veneto in Padova.

Investigators enrolled patients with HER2-positive, node positive, or high-risk node-negative disease. Patients were stratified as low risk (primary tumor [pT] < 2cm and pN0), intermediate risk (pT < 2cm and 1 to 3 pN+, or pT > 2cm and 1 to 3 pN+, or pT > 2cm and 0 to 3 pN+) or high risk (any pT and 4+ pN+). In total, these groups represented 37.5%, 47.1%, and 15.4% of the total population, respectively.

Patients were randomized to receive either 1 year (long arm) or 9 weeks (short arm) of trastuzumab plus chemotherapy. In the long arm, the chemotherapy regimen was 4 courses of doxorubicin or epirubicin plus cyclophosphamide, followed by 4 courses of a taxane and trastuzumab, starting with an 8-mg/kg loading dose followed by 6 mg/kg every 3 weeks.

The short-arm chemotherapy regimen consisted of 3 courses of docetaxel combined with 9 weeks of weekly trastuzumab, starting with a 4-mg/kg loading dose followed by 2 mg/kg weekly. Once complete, patients were administered 3 courses of fluorouracil, epirubicin hydrochloride, and cyclophosphamide every 3 weeks.

Additional stratification factors included hormone receptor status and nodal status. Conte noted that patients who were 65 years or older received docetaxel at 80 mg/m² dose of docetaxel and 11% of patients who received the longer duration of trastuzumab were given paclitaxel at 175 mg/m² during the study treatment.

The overall patient population (N = 1253) had a median age of 55 years (range, 25-78), and 64.0% were postmenopausal. At baseline, 40.6% of patients had stage I disease, 43.8% had stage II disease, and 15.2% had stage III disease. More than half of patients were node negative (53.5%), 30.7% of patients had 1 to 3 positive nodes, and 15.8% had at least 4 positive nodes. Additionally, 68.2% of patients had hormone receptor–positive status, defined as staining on at least 10% of tumor cells.

Short-HER PRIMARY ANALYSIS MISSES MARK

The superiority of combining 1 year of
trastuzumab with adjuvant chemotherapy over chemotherapy alone in patients with HER2-positive early breast cancer was previously demonstrated in results of both the phase 3 HERA trial (NCT00045032) and a joint analysis of OS data from the National Surgical Adjuvant Breast and Bowel Project B31 (NCT00004067) and the North Central Cancer Treatment Group N9831 (NCT00005970) trials. In November 2006, trastuzumab was approved by the FDA as an adjuvant therapy for patients with HER2-positive, node-positive breast cancer as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel.1

"It was very clear at the time that the choice of a 1-year duration of trastuzumab administration was based empirically and that a similar degree of benefit had already been reported with the small FinHER study [International Standard Randomised Controlled Trial number, ISRCTN 76560285] with 9 weeks of trastuzumab," Conte said. The Short-HER trial was conducted across 82 investigational sites in Italy and had a recruitment period that ran from December 2007 to October 2013. It was designed to assess the noninferiority of shorter trastuzumab to October 2013. It was designed to assess the noninferiority of shorter trastuzumab with respect to DFS and OS outcomes with respect to risk category in the updated analysis (TABLE). At median follow-up of 8.7 months, 237 events and 109 deaths had occurred.1

"The high-risk group clearly has worse outcomes in terms of both DFS and OS, whereas both low- and intermediate-risk groups had very good DFS and OS estimates," Conte said. Patients classified as low/intermediate risk on the basis of [tumor] size and nodal status represent 84.6% of the Short-HER study population. In this patient population, long-term DFS and OS outcomes in terms of both DFS and OS are superimposable between the 2 treatment arms."

Specifically, investigators reported a 5-year DFS rate of 91% in both treatment arms for patients in the low-risk group (HR, 0.91; 90% CI, 0.60-1.38). In the intermediate-risk group, those who were treated with the longer duration of trastuzumab had a 5-year DFS rate of 88% vs 89% with the shorter duration (HR, 0.88; 95% CI, 0.63-1.21); the 5-year DFS rates in the high-risk group for the longer and shorter treatment durations were 82% and 64%, respectively (HR, 2.06; 90% CI, 1.36-3.13).1 Additionally, the 5-year OS rate for patients in the low-risk group who received the longer duration of treatment was 97% vs 99% with the shorter duration (HR, 0.57; 90% CI, 0.27-1.13). In the intermediate-risk group, these rates were 96% and 95%, respectively (HR, 1.14; 90% CI, 0.68-1.89) and were 95% and 91%, respectively, in the high-risk group (HR, 1.09; 0.75-1.359). Investigators also reported 9-year OS rates for the short and long arms at 90% and 91%, respectively (HR, 1.18, 90% CI, 0.86-1.62). Conte concluded the presentation by stating that response rates with 9 weeks of trastuzumab support the use of the short regimen as an option for patients with limited access to trastuzumab and for those with low- or intermediate-risk disease.

**TABLE.** Short-HER Long-Term Results by Risk Categories1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shorta (n = 233)</td>
<td>Longb (n = 234)</td>
<td>Short (n = 291)</td>
</tr>
<tr>
<td>5-year DFS rate</td>
<td>91%</td>
<td>91%</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td>HR, 0.91 (90% CI, 0.60-1.38)</td>
<td>HR, 0.88 (90% CI, 0.63-1.21)</td>
<td>HR, 0.97 (90% CI, 0.68-1.41)</td>
</tr>
<tr>
<td>5-year OS rate</td>
<td>99%</td>
<td>97%</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>HR, 0.57 (90% CI, 0.27-1.13)</td>
<td>HR, 1.14 (90% CI, 0.68-1.89)</td>
<td>HR, 1.09 (90% CI, 0.75-1.359)</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; OS, overall survival.

*Short is defined as 9-week trastuzumab.

*Long is defined as 1-year trastuzumab.

Ribociclib/Endocrine Therapy Improves OS Regardless of Age in Advanced HR+/HER2- Breast Cancer

by CAROLINE SEYMOUR

RESULTS OF AN EXPLORATORY analysis of patients enrolled in the phase 3 MONALEESA-7 trial (NCT02278120) showed that ribociclib (Kisqali) plus endocrine therapy improved overall survival (OS) and postprogression outcomes in pre- or perimenopausal patients with hormone receptor–positive, HER2-negative advanced breast cancer irrespective of age.

In patients 39 years or younger, median OS was 51.3 months with ribociclib/endocrine therapy vs 40.5 months with placebo/endocrine therapy, translating to a 35% reduction in the risk of death with the CDK4/6 inhibitor (HR, 0.651; 95% CI, 0.431-0.983). The 4-year OS rates were 56.2% vs 34.4%, respectively.

In patients aged 40 years or older, the median OS was 58.8 months with ribociclib/endocrine therapy vs 51.7 months with placebo/endocrine therapy, translating to a 19% reduction in the risk of death with the CDK4/6 inhibitor (HR, 0.810; 95% CI, 0.617-1.065). The 4-year OS rates were 61.1% vs 55.9%, respectively (TABLE).

"Ribociclib plus endocrine therapy prolonged OS and improved post-progression outcomes in pre- or perimenopausal patients with hormone receptor–positive, HER2-negative advanced breast cancer regardless of age," Yen-Shen Lu, MD, PhD, said in a virtual presentation of the data during the European Society for Medical Oncology Breast Cancer 2021 Virtual Congress. Lu is a clinical associate professor in the Department of Internal Medicine at the National Taiwan University College of Medicine in Taipei. He is also division chief of Medical Oncology in the Department of Oncology at the National Taiwan University Hospital.

Younger patients with hormone receptor–positive, HER2-negative advanced breast cancer typically have more aggressive disease and worse prognosis than older patients. Specifically, patients younger than 40 years have higher breast cancer mortality than those 40 years or older. Therefore, investigators conducted an exploratory analysis to evaluate the effect of age on the efficacy and safety of ribociclib/endocrine therapy vs placebo/endocrine therapy in the MONALEESA-7 trial.

Prior results from the MONALEESA-7 trial showed a significant improvement in progression-free survival (PFS), OS, and quality of life with the combination of ribociclib and endocrine therapy vs placebo plus endocrine therapy. Moreover, an exploratory analysis performed with a median follow-up of 53.5 months demonstrated sustained OS with ribociclib/endocrine therapy vs placebo/endocrine therapy in the overall population. The median OS was 58.7 months vs 48.0 months, respectively (HR, 0.76; 95% CI, 0.61-0.96).

In the exploratory analysis, baseline characteristics were generally well-balanced between patients under age 40 and those 40 years or older with no notable differences between the cohorts, Lu said.

Additional findings indicated that PFS2, defined as the time from randomization to tumor progression on next-line treatment or death from any cause, favored ribociclib/endocrine therapy vs placebo/endocrine therapy in patients younger than 40 and those 40 years or older. In the former group, the median PFS2 was 46.0 months with ribociclib/endocrine therapy vs 25.5 months with placebo/endocrine therapy (HR, 0.588; 95% CI, 0.401-0.862). In the latter group, the median PFS2 was 43.6 months with ribociclib/endocrine therapy vs 32.7 months with placebo/endocrine therapy (HR, 0.705; 95% CI, 0.555-0.894).

Further, the time to first chemotherapy was delayed with ribociclib/endocrine therapy vs placebo/endocrine therapy across both age subgroups. In patients younger than 40, the median time to first chemotherapy was 50.2 months vs 36.8 months, respectively (HR, 0.693; 95% CI, 0.534-0.898).

The addition of ribociclib to endocrine therapy also prolonged chemotherapy-free survival in both age subgroups. In the younger cohort, the median chemotherapy-free survival was 46.5 months with ribociclib/endocrine therapy vs 22.7 months with placebo/endocrine therapy (HR, 0.582; 95% CI, 0.431-0.983). In the older cohort, the median chemotherapy-free survival was 41.5 months vs 27.6 months, respectively (HR, 0.679; 95% CI, 0.541-0.852).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age &lt;40 years</th>
<th>Age ≥40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribociclib + ET (n = 237)</td>
<td>Placebo + ET (n = 249)</td>
<td>Ribociclib + ET (n = 98)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>58.8</td>
<td>51.3</td>
</tr>
<tr>
<td>HR, 0.651 (95% CI, 0.431-0.983)</td>
<td>HR, 0.810 (95% CI, 0.617-1.065)</td>
<td></td>
</tr>
<tr>
<td>4-year OS rate</td>
<td>56.2%</td>
<td>34.4%</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>43.6</td>
<td>25.5</td>
</tr>
<tr>
<td>HR, 0.549 (95% CI, 0.416-1.011)</td>
<td>HR, 0.705 (95% CI, 0.555-0.894)</td>
<td></td>
</tr>
<tr>
<td>TTC, months</td>
<td>38.6</td>
<td>36.6</td>
</tr>
<tr>
<td>HR, 0.693 (95% CI, 0.534-0.898)</td>
<td>HR, 0.679 (95% CI, 0.541-0.852)</td>
<td></td>
</tr>
</tbody>
</table>

ET, endocrine therapy; OS, overall survival; PFS, progression-free survival; TTC, time to first chemotherapy.

---

**TABLE Subgroup Analysis of MONALEESA-7 Trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age &lt;40 years</th>
<th>Age ≥40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribociclib + ET (n = 237)</td>
<td>Placebo + ET (n = 249)</td>
<td>Ribociclib + ET (n = 98)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>58.8</td>
<td>51.3</td>
</tr>
<tr>
<td>HR, 0.651 (95% CI, 0.431-0.983)</td>
<td>HR, 0.810 (95% CI, 0.617-1.065)</td>
<td></td>
</tr>
<tr>
<td>4-year OS rate</td>
<td>56.2%</td>
<td>34.4%</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>43.6</td>
<td>25.5</td>
</tr>
<tr>
<td>HR, 0.549 (95% CI, 0.416-1.011)</td>
<td>HR, 0.705 (95% CI, 0.555-0.894)</td>
<td></td>
</tr>
<tr>
<td>TTC, months</td>
<td>38.6</td>
<td>36.6</td>
</tr>
<tr>
<td>HR, 0.693 (95% CI, 0.534-0.898)</td>
<td>HR, 0.679 (95% CI, 0.541-0.852)</td>
<td></td>
</tr>
</tbody>
</table>
Atezolizumab Plus Carboplatin Induces Early Efficacy Signals in Invasive Lobular Breast Carcinoma

by JESSICA HERGERT

TREATMENT WITH ATEZOLIZUMAB (TECENTRIQ) plus carboplatin demonstrated early clinical activity in patients with metastatic invasive lobular carcinoma (ILC) of the breast, with slight trends toward increased clinical benefit in patients with triple-negative ILC (TN-ILC) and responders with higher PD-L1 expression. Initial findings of the nonrandomized phase 2 GELATO trial (NCT03147040) were presented during the European Society for Medical Oncology Breast Cancer 2021 Virtual Congress.

The median progression-free survival (PFS) was 14.6 weeks (95% CI, 9.0-20.1) with atezolizumab plus carboplatin in evaluable patients with ILC (n = 23). At 24 weeks, 4 patients were free of progression, meeting the primary end point of the trial’s first stage.

Notably, 4 of the 6 patients who derived any clinical benefit from atezolizumab plus chemotherapy had TN-ILC, and 3 each had PD-L1-negative disease (< 1%) and PD-L1-positive disease (≥ 1%) per evaluation with the Ventana PD-L1 (SP142) assay. Moreover, 11 patients with PD-L1-negative disease had progressive disease vs 2 patients with PD-L1-positive disease. As such, the percentage of patients with clinical benefit was 21% in the PD-L1-negative group vs 60% in the PD-L1-positive group (Fisher exact test, P = .26), suggesting that higher PD-L1 expression may correlate with increased clinical benefit.

In a discussion of the rationale for the trial, Leonie Voorwerk, a coauthor of the study abstract and PhD student at the Netherlands Cancer Institute in Amsterdam, said that limited treatment options are available to treat patients with ILC who develop resistance to endocrine therapy.

ILC is the most common special histological subtype of breast cancer and is distinct from breast cancers of no special type. ILC is characterized by loss of E-cadherin, and metastases most commonly occur in the peritoneum, gastrointestinal tract, and bones. Approximately 90% of ILC cases highly express the estrogen receptor (ER).

Additionally, although checkpoint inhibitors have demonstrated modest benefit in patients with metastatic ER-positive breast cancer, the utility of checkpoint inhibitors is not known in ILC, Voorwerk explained.

Treatment discontinuations due to adverse effects with ribociclib/endocrine therapy and placebo/endocrine therapy, respectively, occurred in 5.1% vs 3.4% of patients younger than 40 and 4.6% vs 3.6% of patients 40 years or older.

“The safety findings were similar in both groups compared with those of the overall population, and there were no notable safety differences between the age subgroups,” Lu said.

For a full list of references, see the article at bit.ly/3qpd2Jk.
“Based on translational and clinical research, we believe that there are 3 reasons that there is a strong rationale for checkpoint blockade together with platinum in ILC,” Voorwerk said.

Translational and preclinical research suggest that a subset of ILCs highly express immune-related genes, as well as tumor infiltrating lymphocytes and PD-L1. In vitro data indicate that immune-related ILC could be sensitive to platinum-based therapy. Moreover, a mouse model for ILC demonstrated synergy with platinum-based therapy and checkpoint inhibitors.

 “[GELATO] is the first clinical immunotherapy trial executed exclusively in metastatic ILC. We show a clear efficacy signal of PD-L1 blockade in combination with carboplatin in metastatic ILC,” the study’s authors wrote.

In the study, patients were treated with 12 cycles of weekly carboplatin plus 1200 mg of atezolizumab every 3 weeks starting at cycle 3 of platinum-based therapy. Atezolizumab was continued until disease progression or unacceptable toxicity.

Patients underwent a metastatic lesion biopsy and blood sampling 2 weeks prior to treatment, as well as during week 0 and week 6 of treatment. Eligible patients had to have metastatic ILC with negative or aberrant E-cadherin. In cases of ER-positive disease, patients had to be resistant to endocrine therapy.

PFS at 6 months served as the primary end point of the study, and overall response rate (ORR), 12-month PFS rate, overall survival, and safety served as key secondary end points.

The study utilized a Simon’s 2-stage design. Of the patients enrolled in stage 1 of the trial, at least 3 patients needed to be progression free at 6 months.

Overall, 37 patients were screened for enrollment. Of these patients, 11 were not registered because of biopsy failure or unavailable lesions (n = 5), no clear ILC diagnosis (n = 4), or rapid clinical progression (n = 2). Of the 26 patients registered, 3 patients did not receive atezolizumab because of rapid clinical progression after 1 cycle of carboplatin (n = 1), heart failure from preexisting cardiomyopathy after 1 cycle of carboplatin (n = 1), or rapid lactate dehydrogenase increase before starting carboplatin (n = 1).

Overall, 23 patients received at least 1 cycle of atezolizumab. As of January 2021, 2 patients were receiving ongoing atezolizumab maintenance and 1 patient was receiving ongoing atezolizumab plus carboplatin.

Baseline patient characteristics were as expected for this patient population, Voorwerk said. Patients had a median age of 60 years (range, 45-69) and the majority had ER-positive ILC (n = 18; 79%) followed by TN-ILC (n = 5; 22%). No patients had HER2-positive disease.

Most patients (n = 18; 78%) had visceral metastasis and 1 to 2 metastatic sites (n = 12; 52%). More than half of patients (n = 15; 65%) had prior neoadjuvant or adjuvant chemotherapy, and 52% (n = 12) had 1 or 2 prior lines of palliative chemotherapy.

The majority of patients (n = 16; 70%) had previous exposure to CDK4/6 inhibitors. Most patients (n = 13; 57%) had a prior disease-free interval of less than 5 years.

Patients received a median of 9 cycles of carboplatin (range, 3-12) and a median of 5 cycles of atezolizumab (range, 1-13).

Additional results from 21 evaluable patients showed that treatment with atezolizumab plus carboplatin elicited an ORR of 19% (95% CI, 5%-42%). No patients achieved a complete response, 4 (19%) achieved a partial response, and 2 (10%) had stable disease lasting longer than 6 months. The majority of patients (n = 15; 71%) experienced progressive disease. This translated to a clinical benefit rate of 29% (95% CI, 11%-52%).

The median duration of response was 12 weeks with the addition of atezolizumab (95% CI, 7.1-not reached).

Baseline stromal tumor infiltrating lymphocytes and stromal CD8+ counts were not found to be associated with clinical benefit in patients with ILC based on assessment of metastatic lesions.

“Further translational research is needed to provide a rationale for new strategies to improve checkpoint blockade in lobular breast cancer,” Voorwerk concluded.

**REFERENCE**


**FIGURE.** Best Overall Response in GELATO Trial

![Diagram showing response rates](image-url)
Follow @OncLive to have the latest oncology updates at your fingertips.

- Receive alerts on the latest updates and news in oncology
- Get live conference coverage
- Find out about upcoming events

Get constant updates from your favorite all-access resource for oncology by following @OncLive on Twitter today!
Novel Combination May Break Outcomes Stalemate in Pancreatic Cancer

by BRITTANY LOVELY

THERAPEUTIC BREAKTHROUGHS FOR PATIENTS with metastatic pancreatic cancer have eluded investigators for decades, with chemotherapeutic combination strategies serving as the insurmountable standard of care. Investigators are seeking to overcome the stagnation and fill an unmet need for improved survival benefit in this patient population with devimistat, a novel agent designed to target the mitochondrial tricarboxylic acid (TCA) cycle in the phase 3 AVENGER 500 trial (NCT03504423).1

“It has been 2 decades since the first drug [for patients with pancreatic cancer] was approved by the FDA—gemcitabine—and since then our progress in pancreatic cancer has been really very unsatisfactory,” said Philip A. Philip, MD, PhD, in an interview with OncologyLive®. “After 2 decades or so, we have only 2 regimens that we use: one is the gemcitabine and Abraxane [nab-paclitaxel] and the other one is a triplet called FOLFIRINOX [leucovorin, 5-fluorouracil, irinotecan hydrochloride, and oxaliplatin].” Philip is a professor of hematology-oncology at Wayne State University School of Medicine and leader of the Gastrointestinal and Neuroendocrine Oncology Multidisciplinary Team at Barbara Ann Karmanos Cancer Institute in Detroit, Michigan.

BUILDING ON THE STANDARD OF CARE

FOLFIRINOX as well as the combination of gemcitabine and nab-paclitaxel are the 2 preferred regimens for patients with metastatic pancreatic cancer. However, survival benefits have been limited to those with good performance status, including Eastern Cooperative Oncology Group performance status of 0 to 1, good biliary drainage, and adequate nutritional intake.2

FOLFIRINOX bested single-agent gemcitabine and demonstrated its efficacy in data from the phase 3 PRODIGE trial (NCT00112658). At a median follow-up of 26.6 months, the median overall survival (OS) was 11.1 months (95% CI, 9.0-13.1) in the FOLFIRINOX arm vs 6.8 months (95% CI, 5.5-7.6) in the gemcitabine arm (HR, 0.57; 95% CI, 0.45-0.73; P < .001).3 Further, OS rates were 75.9%, 48.4%, and 18.6%, at 6, 12, and 18 months, respectively, in the FOLFIRINOX arm compared with 66% in the gemcitabine arm (HR, 0.47; 95% CI, 0.30-0.70; P < .001).3

Additional toxicity associated with FOLFIRINOX are of concern as investigators look to add therapeutics that have their own AEs, the regimen out performed gemcitabine alone in regard to quality of life. At 6-month follow-up, 31% of patients in the FOLFIRINOX arm had definitive decrease in Global Health Status and Quality of Life scale scores compared with 66% in the gemcitabine arm (HR, 0.47; 95% CI, 0.30-0.70; P < .001).3

However, improvements in survival data compared with less toxic regimens have left the chemotherapeutic combination uncontested in its spot as the standard for those with good performance, leaving investigators to set their sights on less toxic combination regimens to move the needle.

Devimistat is an intravenous small molecular dual inhibitor of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, 2 of the major reregulated control points.

FIGURE. AVENGER 500 Trial Adds Devimistat to Improve Outcomes in Pancreatic Cancer

End Points
Primary • OS
Select secondary • PFS • DOR • ORR

*Devimistat is defined as oxaliplatin at 65 mg/m² given as a 2-hour IV infusion; florouracil at 400 mg/m² given as a 90-minute infusion immediately after oxaliplatin, and concurrently with irinotecan at 140 mg/m² given as a 90-minute IV infusion via a Y-connector; fluorouracil at 400 mg/m² as a bolus followed by a 46-hour infusion at 2400 mg/m², starting immediately after completion of oxaliplatin and irinotecan.

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Histologically or cytologically confirmed metastatic stage IV adenocarcinoma of the pancreas</td>
</tr>
<tr>
<td>• No prior treatments for stage IV pancreatic adenocarcinoma</td>
</tr>
<tr>
<td>• Prior adjuvant or neoadjuvant treatment is allowed provided it has been completed &gt;6 months prior to disease recurrence</td>
</tr>
<tr>
<td>• ECOG performance status: 0-1</td>
</tr>
<tr>
<td>• Male and female patients aged 18 to 75 years</td>
</tr>
<tr>
<td>• Measurable disease determined using RECIST v1.1 criteria</td>
</tr>
<tr>
<td>• Expected survival &gt; 3 months</td>
</tr>
</tbody>
</table>

PRODIGE showed incidence of grade 3/4 neutropenia in 45.7% of patients treated with FOLFIRINOX (n = 171) vs 21% in those treated with gemcitabine monotherapy (n = 171; P < .001).3 Despite the higher incidence of AEs, the regimen out performed gemcitabine alone in regard to quality of life. At 6-month follow-up, 31% of patients in the FOLFIRINOX arm had definitive decrease in Global Health Status and Quality of Life scale scores compared with 66% in the gemcitabine arm (HR, 0.47; 95% CI, 0.30-0.70; P < .001).3
that input carbon into the TCA cycle of cancer cells.\textsuperscript{4,5}

In the phase 1 dose-escalation study (NCT01835041), 18 patients with pancreatic cancer received the agent in combination with a modified FOLFIRINOX regimen at the maximum-tolerated dose. Results showed that 61% of patients had an objective response to the treatment, the median OS was 19.9 months, and the median PFS was 9.9 months. Three patients had a reported complete response to treatment (17%).

Of note, safety data for the combination regimen demonstrated that it was well tolerated, with expected adverse effects (AEs) including thrombocytopenia, anemia, and lymphopenia. For the 18 patients evaluated at the maximum-tolerated dose, the most common grade 3/4 AEs were hypokalemia (33%), diarrhea (28%), and abdominal pain (22%). Seventeen patients experienced sensorial neuropathy (94%), which investigators reported was managed with dose de-escalation or discontinuation. No patients experienced grade 5 AEs.

“The metabolism of the cancer cell is not the same as [it is in] the normal cell, so we’re trying to really exploit that differential between the normal cell and the cancer cell,” Philip said. “Devimistat [inhibits] a couple of enzymes in the TCA cycle, and these are enzymes critical to the way that the cancer cells generate energy.” Philip added that the mechanism of action of devimistat also allows it to affect the metabolism of the cancer cells without causing much harm to normal cells.

Leveraging the data collected in the phase 1 study, investigators of the AVENGER 500 trial will randomize individuals 1:1 to evaluate the efficacy of FOLFIRINOX compared with the combination of devimistat plus a modified FOLFIRINOX regimen (FIGURE\textsuperscript{5}). Those randomized to the experimental arm will receive devimistat 500 mg/m\textsuperscript{2} on days 1 and 3 of a 14-day cycle; the modified FOLFIRINOX regimen comprises the standard dose and schedule of 5-fluorouracil and leucovorin and uses reduced doses of oxaliplatin (65 mg/m\textsuperscript{2}) and irinotecan (140 mg/m\textsuperscript{2}).

The control arm uses the standard regimen: leucovorin (400 mg/m\textsuperscript{2}), 5-fluorouracil (400 mg/m\textsuperscript{2} as a bolus followed by 2400 mg/m\textsuperscript{2} as a 46-hour infusion), oxaliplatin (85 mg/m\textsuperscript{2}), and irinotecan (180 mg/m\textsuperscript{2}). The trial has met its target enrollment of 500 patients.\textsuperscript{7}

“One thing which was surprising to me as an investigator and surprising to everyone who was involved in the trial is that despite COVID-19 hitting in the spring of 2020, the trial continued to accrue very fast,” Philip said. “It just gives you the idea that individuals are desperate to find something, and patients [with pancreatic cancer] are desperate to be on a clinical trial because that is a potential benefit for them.”

Another result of the fast accrual was the opportunity to adjust the trial design to use OS as the primary end point rather than PFS. The change was made in June 2021.\textsuperscript{6}

“With the number of patients who were accrued, we will have enough events go into [waiting for the data on] overall survival. Ultimately, overall survival is what matters to patients and what matters also to the FDA in the long run, in terms of having a drug approved,” Philip said. The sponsor of the trial, Raphael Pharmaceuticals, in consultation with statisticians and the study steering committee, has decided to wait for the more meaningful outcome data.

“It was a function of the trial growing very fast. And when that happens, you might as well just wait a bit longer in your analysis and get to the end point that everyone wants to know [about],” Philip added.

In addition to PFS, secondary end points include duration of response and overall response rate.\textsuperscript{3} The treatment phase will consist of a minimum of 12 cycles of therapy in responding patients with acceptable tolerance and include predosing tests, AE assessment, and a radiology scan for the measurement of overall response every 8 weeks. In the follow-up phase, investigators will assess patients every 2 months for OS and PFS until death.\textsuperscript{6}

**FULFILLING AN UNMET NEED**

In November 2020, devimistat received fast track designation from the FDA.\textsuperscript{7} Data from the AVENGER 500 trial will, hopefully, pave a path forward for the full approval of devimistat.

The agent is also under investigation with the alternative standard-of-care option for patients with metastatic pancreatic cancer, gemcitabine plus nab-paclitaxel. In data from a phase 1 trial (NCT03435289), presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program, the combination elicited an objective response rate of 50% among 20 evaluable patients. Specifically, the addition of devimistat elicited a 5% complete response rate and a 45% partial response rate. Forty percent of patients had stable disease and the remaining 10% experienced disease progression.\textsuperscript{8}

“There is a high unmet need [for these patients],” Philip said. “Pancreatic cancer really falls behind almost all other cancers in terms of effective drug therapies because most patients with pancreatic cancer present with advanced disease requiring systemic treatment.

“Even the minority, less than 20%, who may present with localized disease that can be removed by surgery, still require chemotherapy to clean up the micrometastatic disease, which most of them have. Even then, unfortunately, after having radical surgery and additional chemotherapy, patients will ultimately succumb to their disease because of recurrence. [This patient population] requires effective systemic treatment that we do not currently have.”

“I’m looking forward to seeing how the results shake out because it would be nice to see some improvements for these patients,” Philip noted. ■

---

\textsuperscript{4}Philip added that the input carbon into the TCA cycle of cancer cells.

\textsuperscript{5}In the phase 1 dose-escalation study (NCT01835041), 18 patients with pancreatic cancer received the agent in combination with a modified FOLFIRINOX regimen at the maximum-tolerated dose. Results showed that 61% of patients had an objective response to the treatment, the median OS was 19.9 months, and the median PFS was 9.9 months. Three patients had a reported complete response to treatment (17%).

\textsuperscript{6}Of note, safety data for the combination regimen demonstrated that it was well tolerated, with expected adverse effects (AEs) including thrombocytopenia, anemia, and lymphopenia. For the 18 patients evaluated at the maximum-tolerated dose, the most common grade 3/4 AEs were hypokalemia (33%), diarrhea (28%), and abdominal pain (22%). Seventeen patients experienced sensorial neuropathy (94%), which investigators reported was managed with dose de-escalation or discontinuation. No patients experienced grade 5 AEs.

““The metabolism of the cancer cell is not the same as [it is in] the normal cell, so we’re trying to really exploit that differential between the normal cell and the cancer cell,” Philip said. “Devimistat [inhibits] a couple of enzymes in the TCA cycle, and these are enzymes critical to the way that the cancer cells generate energy.” Philip added that the mechanism of action of devimistat also allows it to affect the metabolism of the cancer cells without causing much harm to normal cells.

Leveraging the data collected in the phase 1 study, investigators of the AVENGER 500 trial will randomize individuals 1:1 to evaluate the efficacy of FOLFIRINOX compared with the combination of devimistat plus a modified FOLFIRINOX regimen (FIGURE\textsuperscript{5}). Those randomized to the experimental arm will receive devimistat 500 mg/m\textsuperscript{2} on days 1 and 3 of a 14-day cycle; the modified FOLFIRINOX regimen comprises the standard dose and schedule of 5-fluorouracil and leucovorin and uses reduced doses of oxaliplatin (65 mg/m\textsuperscript{2}) and irinotecan (140 mg/m\textsuperscript{2}).

The control arm uses the standard regimen: leucovorin (400 mg/m\textsuperscript{2}), 5-fluorouracil (400 mg/m\textsuperscript{2} as a bolus followed by 2400 mg/m\textsuperscript{2} as a 46-hour infusion), oxaliplatin (85 mg/m\textsuperscript{2}), and irinotecan (180 mg/m\textsuperscript{2}). The trial has met its target enrollment of 500 patients.\textsuperscript{7}

“One thing which was surprising to me as an investigator and surprising to everyone who was involved in the trial is that despite COVID-19 hitting in the spring of 2020, the trial continued to accrue very fast,” Philip said. “It just gives you the idea that individuals are desperate to find something, and patients [with pancreatic cancer] are desperate to be on a clinical trial because that is a potential benefit for them.”

Another result of the fast accrual was the opportunity to adjust the trial design to use OS as the primary end point rather than PFS. The change was made in June 2021.\textsuperscript{6}

““With the number of patients who were accrued, we will have enough events go into [waiting for the data on] overall survival. Ultimately, overall survival is what matters to patients and what matters also to the FDA in the long run, in terms of having a drug approved,” Philip said. The sponsor of the trial, Raphael Pharmaceuticals, in consultation with statisticians and the study steering committee, has decided to wait for the more meaningful outcome data.

“It was a function of the trial growing very fast. And when that happens, you might as well just wait a bit longer in your analysis and get to the end point that everyone wants to know [about],” Philip added.

In addition to PFS, secondary end points include duration of response and overall response rate.\textsuperscript{3} The treatment phase will consist of a minimum of 12 cycles of therapy in responding patients with acceptable tolerance and include predosing tests, AE assessment, and a radiology scan for the measurement of overall response every 8 weeks. In the follow-up phase, investigators will assess patients every 2 months for OS and PFS until death.\textsuperscript{6}

**FULFILLING AN UNMET NEED**

In November 2020, devimistat received fast track designation from the FDA.\textsuperscript{7} Data from the AVENGER 500 trial will, hopefully, pave a path forward for the full approval of devimistat.

The agent is also under investigation with the alternative standard-of-care option for patients with metastatic pancreatic cancer, gemcitabine plus nab-paclitaxel. In data from a phase 1 trial (NCT03435289), presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program, the combination elicited an objective response rate of 50% among 20 evaluable patients. Specifically, the addition of devimistat elicited a 5% complete response rate and a 45% partial response rate. Forty percent of patients had stable disease and the remaining 10% experienced disease progression.\textsuperscript{8}

““There is a high unmet need [for these patients],” Philip said. “Pancreatic cancer really falls behind almost all other cancers in terms of effective drug therapies because most patients with pancreatic cancer present with advanced disease requiring systemic treatment.

“Even the minority, less than 20%, who may present with localized disease that can be removed by surgery, still require chemotherapy to clean up the micrometastatic disease, which most of them have. Even then, unfortunately, after having radical surgery and additional chemotherapy, patients will ultimately succumb to their disease because of recurrence. [This patient population] requires effective systemic treatment that we do not currently have.”

“I’m looking forward to seeing how the results shake out because it would be nice to see some improvements for these patients,” Philip noted. ■
Bring early-stage breast cancer into focus.
**closer look**

**TEST** for biomarkers, such as BRCA, HR, and HER2, at diagnosis.

**ADAPT** your treatment approach for curative intent, based on biomarker results.

[TakeACloserLookBC.com](http://www.TakeACloserLookBC.com)

©2021 AstraZeneca. All rights reserved. US-51502 4/21
Talazoparib Likely to Induce Response in mCRPC With tDDR Alterations

by JASON BRODERICK

PATIENTS WITH HEAVILY PRETREATED metastatic castration-resistant prostate cancer (mCRPC) who have germline and/or homozgous tumor DNA damage response (tDDR) alterations have been shown to have a higher likelihood of responding to treatment with talazoparib (Talzenna), according to data from a retrospective ad hoc exploratory subgroup analysis of a phase 2 trial presented during the American Association for Cancer Research Virtual Annual Meeting 2021.1

The open-label, international TALAPRO-1 trial (NCT03148795) examined single-agent oral talazoparib at 1 mg daily in patients with mCRPC previously treated with taxane-based chemotherapy, as well as abiraterone acetate (Zytiga)/prednisone, enzalutamide (Xtandi), or both hormonal agents. All patients had at least 1 homologous recombination repair (HRR) gene alteration from a panel of 11 genes (HRR11) likely to sensitize their tumor to PARP inhibition: ATM, ATR, BRCA1, BRCA2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, and RAD51C.

The data cutoff was September 4, 2020, and the primary end point was objective response rate (ORR) by blinded independent central review. The study met its primary end point as the final analysis showed that among 104 patients in the efficacy population the ORR was 29.8% (n = 31).

“The strongest antitumor effect was observed in patients with BRCA1 alterations, with a confirmed ORR of 45.9% and a median radiographic progression-free survival of 11.2 months,” said Johann S. de Bono, MBChB, PhD, MSc, FRCP, FMedSci, a professor in experimental cancer medicine and director of the Drug Development Unit at The Institute of Cancer Research and The Royal Marsden National Health Services Foundation Trust, in London, England.

Talazoparib also induced objective responses in patients with non-BRCA1 HRR gene alterations, including those with PALB2 and ATM alterations.

“Both the antitumor activity and tolerability were promising [with talazoparib] for this heavily pretreated population of patients with mCRPC,” de Bono said.

Regarding the ad hoc analyses presented, de Bono said, “We explored the importance of germline vs somatic origin and the zygosity of these DNA repair defects [in association with] response. Characterization of alteration origin was based on a comparison of DNA sequences from matched tumor and saliva samples.”

FoundationOne CDx was used to sequence tumor tissue samples, and Ambry Genetics’ CustomNext-Cancer panel was used to test saliva. The somatic-germline-zygosity (SGZ) computational algorithm established by Sun et al2 was used to predict zygosity.

“Both the characterization of origin and zygosity prediction were limited to short variants. The analysis was focused on the HRR-altered measurable disease population, defined as patients who had measurable soft-tissue disease at screening and a DNA-repair gene defect presumed to directly or indirectly sensitize [the tumor] to PARP inhibition as assessed in the HRR11 core gene panel and [who] had received at least 1 dose of talazoparib,” de Bono explained.

The assessment of tumor alterations by origin showed that 25 were germline, 43 were somatic, and 33 were unknown or not evaluable.

“BRCA2 and ATM were the most commonly altered genes. The BRCA2 alterations were evenly split between germline and somatic, at 13 vs 19, respectively. In contrast, the ATM alterations tended to be somatic in origin,” de Bono said.

Among 25 patients with germline alterations, the ORR was 28% (n = 7), comprising 1 CR and 6 PRs. An additional 10 patients had stable disease (SD), 6 patients had progressive disease (PD), and 2 patients were not evaluable.

The ORR was 25.6% (n = 11) among 43 patients with somatic mutations; this included 3 CRs and 8 PRs. Another 16 patients reached SD, 9 had PD, and 5 were not evaluable. Two patients were categorized by the investigators as “non-CR/non-PD.”

“ORRs were similar for germline and somatic alterations,” de Bono said.

In the subpopulation of 13 patients with germline BRCA2 alterations, the ORR was 53.8% (n = 7), comprising 1 CR and 6 PRs. An additional 5 patients had SD and 1 patient was not evaluable.

The ORR was 36.8% (n = 7) among 19 patients with somatic BRCA2 alterations; this included 2 CRs and 5 PRs. Another 6 patients reached SD, 2 patients had non-CR/non-PD, 2 patients had PD, and 2 patients were not evaluable.

“As expected, for the BRCA2-altered tumors we saw the highest ORR, independent of germline vs somatic origin,” de Bono said.

The assessment of the prevalence of tumor alterations by zygosity across all HRR11

“Based on analysis of short variants, tumors exhibiting homozgous tDDR alterations were more likely to respond to talazoparib than those with heterozygous tDDR alterations.”

—JOHANN S. DE BONO, MBChB, PhD, MSc, FRCP, FMedSci
Alterations found that 30 were homozygous, 30 were heterozygous, and 13 were not evaluable.

Among 30 patients with homozygous alterations, the ORR was 40% (n = 12), comprising 3 CRs and 9 PRs. An additional 9 patients had SD, 2 patients had non-CR/non-PD, 6 patients had PD, and 1 patient was not evaluable.

The ORR was 13.3% (n = 4) among the 30 patients with heterozygous alterations; this included 1 CR and 3 PRs. Another 12 patients reached SD, 10 had PD, and 4 patients were not evaluable.

“The ORR was significantly higher for homozygous alterations. Interestingly, the short variants not evaluable for SGZ prediction (n = 32) exhibited an ORR (40.6%) similar to homozygous alterations, although the interpretation of these data is unclear,” de Bono said.

Regarding zygosity in the BRCA2 subgroup, alterations were primarily homozygous; there were 18 homozygous and 9 heterozygous alterations. This breakdown contrasted with some of the other variants, such as CHEK2, in which the alterations were mainly heterozygous.

In the 18-patient BRCA2 homozygous group, the ORR was 50% (n = 9), comprising 2 CRs and 7 PRs. An additional 5 patients had SD, 2 had non-CR/non-PD, 1 had PD, and 1 patient was not evaluable.

Among the 9 patients with BRCA2 with heterozygous alterations, the ORR was 44.4% (n = 4), comprising 1 CR and 3 PRs. Another 2 patients reached SD, 1 had PD, and 2 patients were not evaluable.

“The ORR was higher for patients with BRCA2, independent of detectable zygosity. The difference in response by zygosity observed in the BRCA2 subset and the larger HRR panel does suggest a higher ORR for homozygous loss across the DNA repair genes and may reflect differences in zygosity distribution between the genes. For example, we saw 1 homozygous, 6 heterozygous, and 3 nonevaluable alterations for CHEK2,” de Bono explained.

Summarizing his discussion, de Bono said, “Based on this retrospective ad hoc exploratory analysis in this heavily pretreated mCRPC population, patients with diverse tDDR alterations demonstrated responses to talazoparib monotherapy.

“Based on analysis of short variants, tumors exhibiting homozygous tDDR alterations were more likely to respond to talazoparib than those with heterozygous tDDR alterations. Potential explanations include gene-specific imbalances in zygosity of alterations and/or sensitivity to talazoparib, but further investigation in a larger data set is needed,” de Bono said. ■

For a full list of references, see the article at bit.ly/3daAk07.

Thank you for your nominations for the 2021 Class of Giants of Cancer Care®

The newest class of Giants will be announced in mid-September of 2021 and will be honored at an awards ceremony on November 4, 2021.

For more information visit giantsofcancercare.com
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.

RET= rearranged during transfection.

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 8%. 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

**Metastatic RET Fusion-Positive NSCLC**

<table>
<thead>
<tr>
<th>Treatment naïve (n=39)</th>
<th>Previously treated with platinum chemotherapy (n=105)</th>
</tr>
</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;1,5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Responses in intracranial lesions were observed in 10 of 11 previously treated patients with measurable brain metastases**<sup>1</sup> No patients received radiation therapy to the brain within 2 months prior to study entry<sup>1</sup>

**Advanced or Metastatic RET Fusion-Positive Thyroid Cancer (Non-MTC)**

<table>
<thead>
<tr>
<th>Systemic therapy naïve&lt;sup&gt;1&lt;/sup&gt; (n=8)</th>
<th>Previously treated&lt;sup&gt;1&lt;/sup&gt; (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>100% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>79% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<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: 76, NE); median follow-up: 17.5 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Advanced or Metastatic RET-Mutant MTC**

<table>
<thead>
<tr>
<th>Cabozantinib/vandetanib treatment naïve (n=88)</th>
<th>Cabozantinib/vandetanib treatment previously treated with cabozantinib and/or vandetanib (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>73% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>69% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<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> was 22.0 months</td>
<td><strong>Median DoR</strong> not yet reached</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, 1.1); 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.

---

*Primary tumor histologies included papillary thyroid cancer, poorly differentiated thyroid cancer, anaplastic thyroid cancer, and Hurthle cell thyroid cancer<sup>2</sup> Patients previously treated with platinum-based chemotherapy and with measurable CNS lesions at baseline according to IRB assessment.<sup>1</sup> Patients in this cohort received no prior systemic therapy other than radioactive iodine (RAI)<sup>1</sup> Patients in this cohort received a prior systemic therapy (including sorafenib, lenvatinib, or both) other than RAI.<sup>1</sup> The efficacy of Retevmo was evaluated in 55 patients with RET-mutant advanced MTC who were previously treated with cabozantinib or vandetanib enrolled into a cohort of LIBRETTO-001.<sup>1</sup> Patients with advanced or metastatic RET fusion-positive NSCLC who had progressed on platinum-based chemotherapy and those without prior systemic therapy were enrolled in separate cohorts<sup>1</sup> Non-medullary thyroid cancers (non-MTC) by histology included papillary (n=31), poorly differentiated (n=4), anaplastic (n=2), and Hurthle cell (n=1)<sup>1</sup> Other tumors included pancreatic cancer (n=7), colon cancer (n=5), and adrenal gland carcinoma (n=1).<sup>1</sup> Number of patients included in the initial efficacy analysis. Efficacy was based on patients who had at least 6 months of follow-up.<sup>1</sup> Efficacy was evaluated in 105 adult patients with metastatic RET fusion-positive NSCLC who were previously treated with platinum chemotherapy enrolled into a cohort of LIBRETTO-001. At 105 patients received systemic therapy, 18 of the 105 patients received prior anti-PD-1/PD-L1 therapy, and 50 of the 105 patients received a prior multikinase inhibitor (MKI).<sup>1</sup> Patients with RET-mutant NSCLC and RET-mutant thyroid cancer (non-MTC) were not enrolled in the trial since RET is not the driver of tumor growth in these cancers.<sup>1</sup> BID=twice daily; CI=confidence interval; CNS=central nervous system; CR=complete response; DIF=duration of response; NE=not estimable; ORR=objective response rate; PO=orally; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

Retevmo<sup>®</sup> is a registered trademark owned or licensed by Eli Lilly and Company, its subsidiaries, or affiliates.

PP-SE-US-0397 11/2020 © Lilly USA, LLC 2020. All rights reserved.
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 bradycardia, torsades de pointes, 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 transaminis. 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 (51%; 8%), ALT increased (45%; 9%), increased total cholesterol (31%; 0.1%), increased sodium (27%; 7%), decreased magnesium (24%; 0.6%), increased potassium (24%; 1.2%), increased bilirubin (23%; 2%), 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 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).

Concomitant use of strong and moderate CYP3A inhibitors 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 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 CYP2C8 and CYP3A substrates increases their plasma concentrations which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of Retevmo with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 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 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 [CrCl] ≥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.

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

References:

IMPORTANT SAFETY INFORMATION FOR RETEVMO® (selpercatinib 40 mg, 80 mg capsules) (CONT'D)
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-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 are radioactive iodine-refractory (if radioactive iodine is appropriate)

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 8%. 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
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. Withhold, 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 80 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/tachyarrhythmias, 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 CYP3A4 inhibitors or drugs known to prolong QTc interval. Withhold and 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 23% of patients treated with RETEVMO including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheoectomy 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 1.6%. 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.

Table 1 summarizes the adverse reactions in LIBRETTO-001.

Table 1: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVMO (n=702)</th>
<th>RETEVMO™ (selpercatinib) capsules, for oral use</th>
<th>SE HCP BS 08MAY2020</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
<td>Grades 3-4 (%)</td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>39</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea²</td>
<td>37</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain²</td>
<td>23</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>35</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

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 was approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryopathy 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.
### Table 1: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001 (Cont.)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVMO (n=702)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
</tr>
<tr>
<td>Edema</td>
<td>33</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>27</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
</tr>
<tr>
<td>Dryness</td>
<td>16</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>17</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System</strong></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>15</td>
</tr>
</tbody>
</table>

1. Diarrhea includes diarrhea, defecation urgency, frequent bowel movements, and anal incontinence.
2. Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain.
3. Fatigue includes fatigue, asthenia, malaise.
4. Edema includes edema, edema peripheral, face edema, eye edema, eyelid edema, generalized edema, localized edema, lymph edema, scrotal edema, peripheral swelling, scrotal swelling.
5. Headache includes headache, sinus headache, tension headache.
6. Includes cough, productive cough.
7. Includes dyspnea, dyspnea exertional, dyspnea at rest.
8. Hemorrhage includes epistaxis, hematuria, hemoptysis, contusion, rectal hemorrhage, vaginal hemorrhage, ecchymosis, hematocheia, petechiae, traumatic hemotoma, anal hemorrhage, blood blister, blood urine present, cerebral hemorrhage, gastric hemorrhage, hemorrhage intracranial, spontaneous hemotoma, abdominal wall hemotoma, angina bulla hemorrhagica, diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival bleeding, hematemesis, hemorrhagic anemia, intrabdominal hemorrhage, lower gastrointestinal hemorrhage, melema, mouth hemorrhage, occult blood positive, pelvic hemotoma, perihepatic hemotoma, pharyngeal hemorrhage, pulmonary contusion, purpura, retroperitoneal hemotoma, subarachnoid hemorrhage, subdermal hemorrhage, upper gastrointestinal hemorrhage, vessel puncture site hemotoma.
9. Only includes a grade 3 adverse reaction.

Clinically relevant adverse reactions in ≥15% of patients who received RETEVMO include hypothyroidism (9%).

### Table 2: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RETEVMO1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>51</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>44</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>42</td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>41</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>37</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>36</td>
</tr>
<tr>
<td>Increased total cholesterol</td>
<td>31</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>24</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>24</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>23</td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>22</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>43</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>33</td>
</tr>
</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.

**Increased Creatinine**

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 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 CYP3A4 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 CYP3A4 inhibitors with RETEVMO. If concomitant use of strong or moderate CYP3A4 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 CYP3A4 inducer decreases selpercatinib plasma concentrations, which may reduce RETEVMO anti-tumor activity. Avoid coadministration of strong or moderate CYP3A4 inducers with RETEVMO.

**Effects of RETEVMO on Other Drugs**

**CYP2C8 and CYP3A Substrates**

RETREVIMO™ (selpercatinib) capsules are a moderate inhibitor of CYP2C8 and a weak CYP3A inhibitor. Concomitant use of RETEVMO with CYP2C8 and CYP3A substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of RETEVMO with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

**Drugs that Prolong QT Interval**

RETREVIMO 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 physeal 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 physeal 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 [CLcr] ≥30 mL/min, estimated by Cockcroft-Gault). The recommended dosage has not been established for patients with severe renal impairment (CLcr <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
Copyright ©2020, Eli Lilly and Company. All rights reserved.

SE HCP BS 08MAY2020

RETEVMO™ (selpercatinib) capsules, for oral use
New Toolkit Aims to Help Employers Address Cancer Treatment

by KYLE DOHERTY

THE NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) has launched a digital initiative to provide strategic approaches specifically geared toward employers who need to navigate a diagnosis of cancer among their staff. The NCCN Employer Toolkit, which launched on June 2, is a free online resource that contains information such as basic medical definitions as well as suggestions on how to help employees estimate and plan for out-of-pocket costs.1

“Cancer is a very complicated disease, and it affects much more than just the patient,” Warren Smedley, vice president of The Kinetix Group and a consultant for the NCCN Employer Advisory Board, said in an interview with OncologyLive. “[A diagnosis of cancer] affects a lot of people around the patient, including their employer. We set out to create some guidelines [by pulling] together a group of experts to provide those resources specifically to employers because a lot of the care decisions are made based on the structure of a benefit plan. We wanted to make sure that employers had information that would help them structure their benefit plans and structure the information that is made available to their employees and the constituents that may be impacted by a diagnosis of cancer.”

The new toolkit was conceived by the NCCN, which originally created and offered a less-comprehensive version that existed in a physical binder, offline, in 2013. The NCCN’s Employer Advisory Board solicited input from an advisory group to help with the composition process, beginning in 2017. The advisory group included physicians, benefits managers, employer advocacy groups, and representatives from the regional sectors of the Business Group On Health.

The toolkit is structured around 6 guiding principles:

1. strive to deliver the highest-quality, highest-value care to plan members and their families;
2. emphasize patient-centered care designed to exceed the expectations of plan members;
3. promote the most appropriate, value-based use of health care resources;
4. encourage the selection of care providers with proven high quality-care;
5. endeavor to minimize the complexities and barriers to accessing high-quality care; and
6. empower plan members to become more engaged in improving their health.

“We want to strive for value, strive for quality, and strive to be patient centric,” Smedley said. “We created these as very high-level guiding principles to begin that discussion and then drill down as deep as we want to go within that, but [it’s important to have] a great launching point for these discussions and for a general understanding that everybody can agree on. We started very high level [when developing the toolkit].”

Each principle contains a subsection listing with employer strategies, links to resources, and tactics specific to each guiding topic. The toolkit touches on a variety of topics related to assisting employers with navigating treatment-plan decisions and initial care-centric conversations, such as clinical trial enrollment and mental health support.

“There are recommendations that are specifically things that employers can do to provide support, information, and direction.
to their plan members,” Smedley said. “Then there are recommendations for [employers] to give to their insurance company, third party administrator, or whoever is actually administering the claims for them to make sure that the plan understands how they want the [care of their] employees [to be handled].”

For example, the first principle—strive to deliver the highest-quality, highest-value care plan to members and their families—breaks the recommendations down into employer strategies and tactics and carrier strategies and tactics. The former provides guidance on the employer-employee relationship, outlining items to support the employee as they navigate the early stages of their cancer diagnosis and treatment. The toolkit recommends providing patient-friendly care guidelines and educational resources as well as establishing clear, written questions for employees to ask their care providers that will prepare them to manage through. There are lots of great resources that are available through NCCN member institutions, advocacy groups, and others,” Smedley said. “We designed this with the idea that you can dig as deep as you’d like. For example, if you’re a well-seasoned senior benefits manager for a large employer, you might not need all the basic stuff. You would want to drill down deeper to the plan language information or something else. But if you are early in your career or experience and you need help understanding definitions, concepts, and so on, we have that as well. We tried to design it in a way that would meet the most needs of the most people.”

Focusing on the initiation of coverage selection for employees, guidance from the NCCN suggests that employers work with their carriers to provide plan members with access to support services and resources necessary to implement an approved care plan. These include coverage of survivorship care, palliative care, and hospice and end-of-life care.

Further, the principles emphasize the importance of minimizing the complexities and barriers to high-quality care. Two key recommendations from the toolkit include ensuring that coverage is provided for care coordination and patient navigation services and, on a more personal level, providing accommodations that allow employees to continue working as much as and for as long as it is appropriate.

“The more and more of the burden of care is being pushed to the employee/patient themselves,” Smedley said. “That gets complicated. Employers need these guidelines, which we will continue to add resources to, to help their plan members, patients, employees, and their loved ones manage through.”

Smedley noted the need for the toolkit to be malleable because hundreds of new therapies are in the pipeline and an increasing amount of cancer care is being pushed to the outpatient setting. The NCCN plans to continue to evolve the toolkit over time to reflect the latest trends and innovations in cancer care and continue to advance their mission of providing access to high-quality, affordable care to patients.

“Employers need more resources, and this toolkit needs to continue to expand with additional resources and additional partner organizations that would be able to provide actual hands-on resources to help patients in distress,” he said.

**REFERENCES**


Reducing Burnout Requires an Organizational Response

by JEFF BENDIX

EFFORTS TO ADDRESS PHYSICIAN burnout typically focus either on addressing systemic factors, such as electronic health records and loss of individual autonomy, or on implementing changes focused on helping individuals cope with workplace stress through coaching and mindfulness tools. A new study suggests that reducing burnout requires an organizational-level response that focuses on creating of a medical practice culture that value qualities such as teamwork, open communication, and process improvement.

The study was published in the June issue of Health Affairs. The authors surveyed more than 5000 physicians and advanced practice clinicians at 715 small- to medium-sized practices taking part in the Agency for Healthcare Research and Quality’s EvidenceNOW trial from 2015 to 2017. They measured burnout levels among individual respondents using the Maslach Burnout Inventory. The survey also included questions regarding adaptive reserve—the capacity for organizational learning and development as measured by characteristics such as teamwork, work environment, and leadership.

Practices fell into 1 of 2 categories—zero-burnout or high-burnout practices—with the former having no practice members reporting burnout and the latter with at least 40% of members reporting burnout. Top-line results demonstrated the following:

- **Burnout correlates with practice size:** Solo practices fell into the zero-burnout category more frequently at 30.8% vs 10.6% in the high-burnout category. Conversely, among practices with 6 to 10 clinicians, 7.5% of respondents were in the zero-burnout category compared with 17% in the high-burnout grouping.

- **Practice ownership is an important factor in burnout:** 53% of clinician-owned practices fell into the zero-burnout category and 37% were in the high-burnout category; 19% of practices owned by a hospital, health system, or health maintenance organization were zero burnout and 37% were high burnout.

- **Patient volume does not significantly affect differences in burnout levels:** At practices where clinicians saw 20 or fewer patients per day, 62% were in the zero-burnout vs 66% that were in the high-burnout category. At practices where clinicians saw more than 20 patients, 28% were zero burnout and 32% were high burnout.

In a finding that may have implications for the movement to value-based care, 29% of practices participating in an accountable care organization (ACO) were in the zero-burnout category compared with 53% in the high-burnout category. A spokesperson for the National Association of ACOs called the study sample “biased,” noting that it also controls for other transformational practice activities such as patient-centered medical home recognition and participation in meaningful use.

Looking at zero-burnout practices overall, the authors noted that a common trait is a strong practice culture “in which teamwork, communication, psychological safety, mindfulness of others, facilitative leadership, and understanding that people make and can learn from mistakes are among the key attributes.”

**REFERENCE**


Connect with OncLive®

Follow us

facebook.com/onclive
twitter.com/onclive
youtube.com/onclive

Are you subscribed?

Get the latest breaking news, specialty coverage and conference coverage straight to your inbox and/or mailbox.

Scan the QR code or visit OncLive.com
NOW APPROVED

FIND OUT MORE AT
PEPAXTOHCP.COM

© 2021 Oncopeptides, Inc. 02/21 US--2000024
Defining Oligometastatic Gastroesophageal Cancer May Provide Clarity for Treatment Advances

by Nataliya V. Uboha, MD, PhD

The Concept of Oligometastatic Disease, which refers to a disease state with limited metastatic burden, is not novel and was introduced more than 25 years ago. Aggressive treatment of oligometastatic disease can significantly extend survival in a number of tumor types. Resection of isolated brain metastases has been accepted as a standard approach across tumor types and the resection of liver metastases is an accepted practice during the treatment of oligometastatic colorectal cancer. However, debate continues as to how to define oligometastatic disease and whether it represents a unique stage between limited-stage and widely metastatic disease.

Recently, an increased interest in oligometastatic states has been fueled by both the development of highly effective noninvasive ablation approaches as well as improvements to systemic therapy. Stereotactic radiotherapy (SBRT) and hypofractionated ablative radiation therapy, which provide ablative doses of radiation with low toxicities, can result in excellent local tumor control and have the potential to eradicate any residual treatment-resistant disease. At the same time, improved systemic therapies can better control micrometastatic disease. For example, it has been demonstrated in preclinical models that immunotherapy, a part of systemic therapy, can potentially synergize with radiation therapy (XRT).

The phase 2 SABR-COMET trial (NCT01446744) was the first prospective randomized study to evaluate whether an aggressive approach to the oligometastatic state using high doses of XRT could improve survival. Patients with metastatic cancers of various primary sites (N = 99) who had at most 5 metastatic lesions were randomized in a 2:1 fashion to an ablative approach with SBRT (n = 66) vs standard treatments (n = 33) after a period of systemic therapy. The impressive trial results included a median overall survival (OS) of 50 months (95% CI, 29-83) in the SBRT group vs 28 months (95% CI, 18-39) in the control cohort (HR, 0.47; 95% CI, 0.27-0.81; \( P = .006 \)). It remains to be determined whether these results are applicable to all cancers; however, they certainly warrant further investigation of this approach in a disease-specific setting.

Defining the Oligometastatic State

Esophageal and gastric adenocarcinoma (EGA) is a major health problem worldwide. In Western countries, lower gastroesophageal adenocarcinoma, which frequently involves the gastroesophageal junction, is the most common site of occurrence and histological subtype of gastroesophageal cancer and the incidence of this cancer in both male and female patients is on the rise. Stage IV disease is almost universally fatal, with 5-year survival rates of less than 5%. Recently, we have seen a significant rise in the incidence of this disease in younger adults aged less than 50 years, in whom it is frequently diagnosed in advanced stages.

Systemic therapy plays a critical role in the management of metastatic EGA. However, even with recent advances in care, OS for stage IV disease remains less than 1.5 years. Possibly, a subset of patients with EGA are undertreated with current strategies and benefit from more aggressive locoregional therapies in the course of their disease.

There are no standard treatments or definitions of oligometastatic EGA. Multiple literature reports suggest that a subset of patients with EGA who have a limited burden of metastatic disease may benefit from more aggressive management. Surgical resection of oligometastatic disease has been attempted at multiple institutions with promising efficacy results.

Review Data and Ongoing Trials

Results of a systematic review of literature published from 1990 to 2015, as well as a pooled analysis on the role of hepatic metastasis resection across 39 studies that included 480 patients, demonstrated a 5-year OS rate of 27%. A retrospective study of national series in England with propensity-matched analysis identified 78 patients with EGA and liver resection; in these patients, the 5-year OS rate was 38.5%. These outcomes compare favorably with what we typically observe in patients with stage IV EGA who are treated with standard systemic therapy alone. However, significant limitations exist with retrospective and single-institution data, and these results should be interpreted with caution.

Recently, a phase 2 prospective trial conducted in Europe—AIO-FLOT3 (NCT00849615)—evaluated surgical...
resection in patients with limited-stage gastric cancer. The results demonstrated a median OS of 31.3 months in patients with oligometastatic EGA who were able to undergo resection after induction chemotherapy. Based on these promising results, European investigators are examining whether surgical debulking of oligometastatic disease improves outcomes for patients in the randomized phase 3 trial RENAISSANCE (AIO-FLOT5; NCT02578368). Patients with protocol-defined oligometastatic disease will receive 2 months of induction chemotherapy (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; FLOT) and will then be randomized to resection of all metastases followed by continuation of FLOT vs continuation of FLOT alone.

There are also promising data for consolidative XRT for patients with EGA, including results of a case series from The University of Texas MD Anderson Cancer Center. The series described 101 long-term survivors with oligometastatic EGA who received consolidative radiation therapy to all sites of disease during their treatment continuum. Using radiation therapy provides a number of advantages over resection in this setting, including shorter interruptions in systemic therapy and less associated morbidity.

The ongoing phase 3 trial EA2183 (NCT04248452) is the first prospective study to determine the benefits of aggressive nonsurgical debulking of oligometastatic EGA. Patients with 3 or fewer metastases are treated with induction systemic therapy, and those who do not have progression after 4 months of treatment are then randomized 2:1 to either consolidative XRT to all sites of disease or continuation of systemic therapy. The primary end point of this study is OS. This trial is actively enrolling patients in multiple United States sites. Investigators are in the process of updating study protocol to allow nivolumab (Opdivo) in addition to chemotherapy. This amendment follows the FDA approval of first-line nivolumab for patients with EGA based on the results of the phase 3 CheckMate 649 study (NCT02872116). EA2813 is an instrumental study that has a potential to prolong OS and change the standard of care in a subset of patients with EGA.

At this time, the definition of and approach to oligometastatic EGA remain to be determined. Oligometastatic state in any disease is more than just a number of metastatic sites seen on scans. Tumor biology is critical for oligometastatic designation. Ongoing research with novel biomarkers, including circulating tumor cell and circulating tumor DNA, will likely be instrumental in refining oligometastatic classification in the future, and ongoing studies, such as EA2183 and AIO-FLOT35, are essential for studying oligometastatic EGA in a prospective scientific manner.

**REFERENCES**

12. Kaya DM, Wang X, Harada K, et al. 101 long-term survivors with oligometastatic designation. Ongoing research with novel biomarkers, including circulating tumor cell and circulating tumor DNA, will likely be instrumental in refining oligometastatic classification in the future, and ongoing studies, such as EA2183 and AIO-FLOT35, are essential for studying oligometastatic EGA in a prospective scientific manner.

**Partner Perspectives**
The Rapid Readout video programs feature insights from top experts on noteworthy research findings presented at major conferences.

Objective response rate (independent review)

---

**Copanlisib/Rituximab Combination Demonstrates Superiority Across iNHL**

by **KYLE DOHERTY**

**COPANLISIB (ALIQOPA) PLUS RITUXIMAB** (Rituxan) exhibited a manageable safety profile and superior efficacy in patients with relapsed indolent non-Hodgkin lymphoma (iNHL) compared with rituximab plus placebo, according to Tycel J. Phillips, MD.

Phillips, a clinical associate professor at the University of Michigan Rogel Cancer Center in Ann Arbor, discussed data from the ongoing CHRONOS-3 study (NCT02367040), which examined the combination of copanlisib and rituximab vs placebo plus rituximab in patients with relapsed iNHL, as part of an OncLive® Rapid Readout program. Results from the trial were originally presented at the American Association for Cancer Research Annual Meeting 2021.

The median progression-free survival (PFS) for patients with iNHL treated with copanlisib plus rituximab (n = 307) was 21.5 months (95% CI, 17.8-33.0) compared with 13.8 months (95% CI, 10.2-17.5) for the 151 patients in the rituximab plus placebo cohort (HR, 0.52; 95% CI, 0.39-0.68; P < .0001).

The median duration of treatment was 8.3 months (range, 0.2-54.0) and 10.8 months (range, 0.2-46.6) in the copanlisib and rituximab and the rituximab plus placebo groups, respectively.

“Given that this study was mainly done in patients in a second-line setting, it does appear in this situation that copanlisib plus rituximab is a viable option for this patient population,” Phillips explained. “Ideally, the key to if this moves into the mainstream will be the duration of response of this treatment and, [specifically,] how durable some of the complete remissions are in this patient population. As of now, with the data we have, that information has not been extrapolated.”

Copanlisib, a selective, potent, intravenous (IV) pan-class I PI3K inhibitor, is approved as monotherapy for the treatment of patients with relapsed follicular lymphoma (FL) who have received at least 2 systemic therapies.

Copanlisib has predominant on-target activity against the PI3K-α and PI3K-σ isoforms. Rituximab monotherapy is recognized as a standard of care for patients with relapsed iNHL and a long remission after prior rituximab-based therapy, or for those who are unwilling to have or unfit for treatment with chemotherapy.

CHRONOS-3 is a randomized, double-blinded, placebo-controlled, phase 3 study enrolling a total of 458 adult patients with indolent B-cell lymphoma. Patients included were those with relapsed disease following a previous rituximab, rituximab biosimilar, or anti-CD20 monoclonal antibody-containing regimen. Study participants also had to be progression and treatment free for at least 12 months since the previous...
rituximab-containing regimen or at least 6 months for patients who were unwilling or unfit to receive chemotherapy.

Patients were randomized 2:1 in favor of the experimental arm. In the copanlisib plus rituximab arm, patients received 1V copanlisib at a dose of 60 mg on days 1, 8, and 15 of a 28-day cycle. Rituximab was given at a dose of 375 mg/m² on days 1, 8, 15, and 22 during cycle 1, and on day 1 of cycles 3, 5, 7, and 9.

The dose scheduled was mirrored in the control arm, with placebo taking the place of copanlisib. Treatment in both arms continued until disease progression or intolerance. Additionally, the investigators conducted a safety follow-up, active follow-up, and survival follow-up in both cohorts.

The primary end point of the study was PFS by central review. Secondary end points included objective response rate (ORR), duration of response (DOR), and safety, and tertiary endpoints include pharmacokinetics and biomarkers.

In the experimental group, 59.9% of patients presented with FL, 21.5% with marginal zone lymphoma (MZL), 11.4% with small lymphocytic lymphoma (SLL), and 7.2% with lymphoplasmacytic lymphoma (LPL) or Waldenström macroglobulinemia (WM) lymphoma. In the control group, 60.3% had FL, 19.2% had MZL, 9.9% were those with SLL, and 10.6% were those with LPL or WM.

Patients treated with copanlisib plus rituximab underwent dose reduction at a rate of 27% compared with 6.8% in the control group. Further, 75.2% and 56.8% of patients experienced dose interruptions or delays in the experimental and control arms, respectively. Treatment discontinuation was reported for 31.9% of patients in the experimental arm vs 8.2% in the control arm because of adverse events.

Subgroup data, stratified by histology, were also presented (Table). Patients with FL in the experimental arm had a median PFS of 14.2 months (95% CI, 10.9-20.5), compared with 5.7 months (95% CI, 3.5-11.0) in the control arm (HR, 0.24; 95% CI, 0.11-0.53; P < .0001). The largest difference in PFS was in patients with LPL or WM: 33.4 months (95% CI, 15.5-NE) in the experimental arm vs 7.6 months (95% CI, 1.7-16.6) in the control arm (HR, 0.44; 95% CI, 0.16-1.23; P = .054).

Overall, copanlisib plus rituximab elicited an ORR of 81%, with 34% of responders experiencing a complete response (CR). Patients treated with placebo and rituximab had an ORR of 48% and a 15% CR rate. At a median follow-up of 20.0 months, the median DOR was 20.4 months (range, 17.0-30.8) and 17.3 months (range, 11.8-25.3) in the experimental and control groups, respectively.

“A key point to this study, when looking at the benefits, is the safety profile,” Phillips said. “All patients in the [experimental arm of the] study had some treatment-emergent adverse event [TEAE].”

Common TEAEs included hyperglycemia, hypertension, and diarrhea. Hyperglycemia of any grade occurred in 69.4% of patients in the experimental group, with grade 3 occurring at a rate of 48.2% and grade 4 at a rate of 8.1%. In the control arm, hyperglycemia was experienced at any grade by 23.3% of patients and at grade 3 in 8.2%, with no patients having grade 4. Hypertension of any grade was seen in 49.2% of the experimental group vs 19.2% in the control group. Diarrhea of any grade occurred at a rate of 33.6% in the experimental cohort, compared with 9.6% in the control arm.

Pneumonitis was an AE of interest in the study. A total of 6.8% of patients in the experimental arm experienced pneumonitis of any grade; 2.0% of these were grade 3 events and 0.7% were grade 4. Patients in the control arm had pneumonitis of any grade at a rate of 1.4%, with 0.7% of these being grade 3 and no patients having grade 4 events.

In terms of TEAEs of any grade that led to discontinuation, 31.3% occurred in the experimental arm and 8.2% were seen in the control arm. Common TEAEs of any grade leading to discontinuation on the experimental side were pneumonitis (6.2%), hyperglycemia (2.6%), interstitial lung disease (1.3%), and pneumocystis jirovecii pneumonia (1.3%).

“Overall, this is a very good start,” Phillips said. “We are opening the window for this sort of treatment. As was demonstrated in this study, it does appear that the addition of rituximab did not add any new safety information or concerns when given with copanlisib. This was something we had not seen with a majority of the delta inhibitors, which have specifically all been given as single agents.”

### Table. Primary End Point Results in the CHRONOS-3 Trial

<table>
<thead>
<tr>
<th>Histology</th>
<th>Copanlisib + rituximab</th>
<th>Placebo + rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>Median PFS, months (95% CI)</td>
<td></td>
</tr>
<tr>
<td>INHL</td>
<td>21.5 (18.8-33.0)</td>
<td>13.8 (10.2-17.5)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.52; 95% CI, 0.39-0.68; P &lt; .0001</td>
<td></td>
</tr>
<tr>
<td>FL</td>
<td>22.0 (17.8-33.1)</td>
<td>18.7 (10.2-21.1)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.58; 95% CI, 0.40-0.83; P = .001</td>
<td></td>
</tr>
<tr>
<td>MZL</td>
<td>22.1 (13.8-NE)</td>
<td>11.5 (5.6-16.3)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.48; 95% CI, 0.25-0.92; P = .012</td>
<td></td>
</tr>
<tr>
<td>SLL</td>
<td>14.2 (10.9-20.5)</td>
<td>5.7 (3.5-11.0)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.24; 95% CI, 0.11-0.53; P &lt; .0001</td>
<td></td>
</tr>
<tr>
<td>LPL/WM</td>
<td>33.4 (15.5-NE)</td>
<td>7.6 (1.7-16.6)</td>
</tr>
<tr>
<td></td>
<td>HR, 0.44; 95% CI, 0.16-1.23; P = .054</td>
<td></td>
</tr>
</tbody>
</table>

**FL**, follicular lymphoma; **INHL**, indolent non-Hodgkin lymphoma; **LPL/WM**, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; **MZL**, marginal zone lymphoma; **NE**, not estimable; **PFS**, progression-free survival; **SLL**, small lymphocytic lymphoma

---

**REFERENCE**

Emerging Immune Checkpoint Research Focuses on CD137

by JANE DE LARTIGUE, PhD

DURING THE PAST DECADE, a growing number of immune checkpoint inhibitors targeting inhibitory PD-1/PD-L1 receptors that keep T-cell activity in check gained FDA approval to treat a wide range of cancer types. Their stimulatory counterparts also emerged as sought-after anticancer targets but have proved much more challenging to manipulate therapeutically.\(^1,2\)

Based on the same premise of reigniting an antitumor immune response, development of agonist antibodies targeting stimulatory T-cell receptors has lagged, hampered by severe toxicity and limited efficacy.\(^2\)

Nevertheless, efforts to develop drugs that target these receptors continue. One facet of this research focuses on drugs targeting CD137 (4-1BB), an inducible costimulatory receptor expressed on the surface of activated T cells but absent from resting T cells.\(^2\)

In early clinical trials, the first generation of CD137 agonists exemplified the difficulty of targeting this receptor. Urelumab (BMS-663513) caused liver inflammation at effective doses, and utomilumab (PF-05082566) elicited few responses.\(^2\) Both drugs remain under study as part of combination regimens.

Meanwhile, as investigators seek to understand toxicity issues with this therapeutic approach, a new generation of agents is emerging (TABLE). Investigators are pursuing novel designs to target CD137 agonism conditionally to avoid systemic toxicity.\(^3\)

Bispecific antibodies that simultaneously target tumor-associated antigens (TAAs) in addition to CD137 represent a prominent alternative strategy. These include agents such as cinrebafusp alfa (PRS-343), a first-in-class CD137 x HER2 bispecific fusion protein, and drugs targeting CD137 plus PD-L1. Another approach involves trispecific antibodies.

These novel agents are in the early stages of clinical development, but promising initial data demonstrate favorable safety profiles while hinting at potential antitumor efficacy.\(^3\)

CHALLENGES OF TARGETING CD137

As the main effectors of the antitumor immune response, T cells have been a central focus of cancer immunotherapy.\(^1\) CD137, a member of the tumor necrosis factor receptor superfamily, generates stimulatory signals that help regulate T-cell activation, thus promoting T-cell proliferation, survival, and effector functions.\(^2\)

Investigators designing chimeric antigen receptor (CAR) T-cell therapies have successfully developed constructs that incorporate the intracellular domain of CD137. CARs with a 4-1BB domain, as it is frequently described in CAR therapies, differentiate into central memory T cells and are associated with fewer toxicities than agents that use CD28 costimulatory domains.\(^4\)

The story has been different for attempts to leverage CD137 as a drug target in its own right. Agonist antibodies targeting CD137 have been pursued for nearly 20 years, culminating in the development of the first-generation drugs urelumab and utomilumab.\(^2,3\)

Urelumab is a fully human IgG1 agonist antibody\(^5\) for which clinical development began in 2005 with 2 trials evaluating its safety and efficacy as monotherapy (NCT00309023, NCT00612664) in patients with advanced solid tumors and melanoma, respectively. All trials were halted in 2008 following 2 hepatotoxicity-related deaths.\(^6\)

Subsequent analyses demonstrated that liver toxicity was dose dependent–severe transaminitis was associated with doses of 1 mg/kg or greater – and was likely a result of on-target effects of urelumab on liver Kupffer cells.\(^7\)

Clinical development resumed in 2012, with trials evaluating urelumab monotherapy at reduced doses below 1 mg/kg and as part of various combination regimens.\(^8,9\) Unfortunately, the reduced doses abolished single-agent activity,\(^9\) with the exception of limited responses among patients with non-Hodgkin lymphoma (NHL). Objective response rates (ORRs) of 6%, 12%, and 17% were observed in patients with diffuse large B-cell lymphoma, follicular lymphoma (FL), and other B-cell lymphomas, respectively (NCT01471210). The ORR was 35% among patients with FL treated with a combination of urelumab and rituximab (Rituxan) and 10% for participants with diffuse large B-cell lymphoma (NCT01775631).\(^5\)

Utomilumab is a fully human IgG2-based antibody with weaker CD137 agonist activity than urelumab.\(^10\) As a result, it is well tolerated up to a dose of 10 mg/kg; however, the trade-off is limited activity both as a single agent and in combination with other anticancer agents. In trials treating patients with solid tumors, utomilumab monotherapy led to an ORR of 3.8% (NCT01307267)\(^1\) and utomilumab in combination with the CCR4 antagonist mogamulizumab-kpc4 (Poteligeo) produced an ORR of 4.2% (NCT02444793).\(^10\)

The combination of utomilumab and OX40 agonist PF-8600 in 30 patients with melanoma and non-small cell lung cancer

---


**The Network**

**CD137 Signaling Has Stimulatory Effect**

by JANE DE LARTIGUE, PhD

**T CELLS ARE THE central mediators of the adaptive immune response. To protect healthy tissues from their potent cytotoxic effects, the amplitude and duration of T-cell activation are tightly controlled through integration of multiple signaling inputs.**

The primary signal is delivered through the binding of the T-cell receptor (TCR) on the T-cell surface to foreign or altered self-antigens displayed on major histocompatibility complex 1 molecules on the surface of antigen-presenting cells (APCs). This is followed by a second, antigen-independent signal generated by interactions between numerous other receptors and their ligands on the surface of T cells and APCs. These secondary signals can be either stimulatory or inhibitory, and the receptors that transduce them have been dubbed immune checkpoints in recognition of their central role in maintaining T-cell–mediated immune homeostasis (FIGURE).2-4

Most costimulatory receptors belong to either the immunoglobulin or tumor necrosis factor receptor (TNFR) superfamilies of proteins. The best known among them, the constitutively expressed receptor CD28, belongs to the former.3

---

**FIGURE. An Overview of Immune Checkpoints**

CD137 and its ligand CD137L play a stimulatory role in the immune system and, along with other ligand-receptor pairs, are among the immune checkpoints targeted in drug discovery efforts.

Ag, antigen; APC, antigen-presenting cells; MHC, major histocompatibility complex; TCR, T-cell receptor.

---

**REFERENCES**


---

**The Network**

**CD137 Signaling Has Stimulatory Effect**

The TNFR superfamily receptors include CD137, also known as 4-1BB or TNFRSF9, which was first identified in the late 1980s. Unlike CD28, CD137 is not constitutively expressed, but its expression is transiently induced within 24 hours of TCR engagement, peaking at 2 to 3 days.5-7

CD137 has a single known ligand, CD137L (4-1BBL), which is expressed on APCs. CD137L exists as a trimer and, when it binds to CD137, it induces clustering of the receptor that is essential for its activity. CD137 has no intrinsic enzymatic activity; instead, upon activation, it recruits TNF receptor–associated factors (TRAFs), adaptor proteins that then help assemble other proteins into the CD137 signalosome to promote downstream signaling.5-7

These downstream signals include the NFκB, PI3K, and MAPK pathways, which drive T-cell proliferation, and antiapoptotic pathways that promote T-cell survival. In addition, CD137 signaling enhances T-cell effector functions (cytokine production and cytotoxicity) and favors memory T-cell differentiation.5-7

Although CD137 is expressed on the surface of both CD4+ and CD8+ T cells as well as regulatory T cells (Tregs), evidence suggests that its primary effects are on CD8+ T cells, in contrast to CD28, which most strongly affects CD4-positive T cells. The functional role of CD137 on CD4+ T cells and Tregs is still poorly understood.5-7

CD137 is also expressed on a range of other immune cells, including natural killer cells, monocytes, dendritic cells, and B cells. Although CD137 expression on tumor cells has also been reported for various types of malignancies, the significance of this expression remains unknown.5-7
TABLE. Ongoing Clinical Development of CD137-Targeted Drugs

<table>
<thead>
<tr>
<th>Agent (developer)</th>
<th>Tumor types</th>
<th>Phase(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD137 agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Utomilumab (PF-05082566) (Pfizer)</td>
<td>TNBC, oropharyngeal cancer, ovarian cancer, DLBCL/MCL, HER2+ breast cancer, CRC</td>
<td>1-2</td>
</tr>
<tr>
<td>Urelumb (BMS-663513) (Bristol Myers Squibb)</td>
<td>MIBC, pancreatic cancer</td>
<td>1/2-2</td>
</tr>
<tr>
<td><strong>Conditional CD137 agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGEN2373 (Agenus)</td>
<td>Advanced solid tumors</td>
<td>1</td>
</tr>
<tr>
<td>ADG106 (Adagene Ltd)</td>
<td>Advanced solid tumors/NHL</td>
<td>1/2</td>
</tr>
<tr>
<td>ATOR-1017 (Alligator Bioscience)</td>
<td>Advanced solid tumors</td>
<td>1</td>
</tr>
<tr>
<td>LVG6051 (Lygven Biopharma)</td>
<td>Advanced malignancies</td>
<td>1</td>
</tr>
<tr>
<td><strong>Bispecific antibodies with targets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cinrebafuspa alfa (PRS-343) (Pieris Pharmaceuticals)</td>
<td>HER2+ solid tumors</td>
<td>1</td>
</tr>
<tr>
<td>FS120 (CD137 x OX40) (F-star Beta Ltd)</td>
<td>Advanced solid tumors</td>
<td>1</td>
</tr>
<tr>
<td>FS222 (CD137 x PD-L1) (F-star Beta Ltd)</td>
<td>Advanced solid tumors</td>
<td>1</td>
</tr>
<tr>
<td>MCLA-145 (CD137 x PD-L1) (Merus)</td>
<td>Advanced malignancies</td>
<td>1</td>
</tr>
<tr>
<td>RO7122990 (CD137 x FAP) (Roche)</td>
<td>Metastatic CRC</td>
<td>1/2</td>
</tr>
<tr>
<td>RO7227166 (CD137 x CD19) (Roche)</td>
<td>Relapsed/refractory NHL</td>
<td>1</td>
</tr>
<tr>
<td>INBRX-195 (CD137 x PD-L1) (Inhibrx)</td>
<td>Advanced thoracic tumors/solid tumors</td>
<td>1/2-1</td>
</tr>
<tr>
<td>ABL503 (CD137 x PD-L1) (ABL Bio)</td>
<td>Advanced solid tumors</td>
<td>1</td>
</tr>
<tr>
<td><strong>Trispecific antibodies with targets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB307 (CD137 x PSMA x HSA) (Crescendo Biologics)</td>
<td>Advanced PSMA+ solid tumors</td>
<td>1</td>
</tr>
<tr>
<td>NM21-1480 (CD137 x PD-L1 x HSA) (Numab Therapeutics)</td>
<td>CD137 x PD-L1 x HSA trispecific</td>
<td>11/2</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; DLBCL, diffuse large B-cell lymphoma; FAP, fibroblast activation protein; HSA, human serum albumin; MCL, mantle cell lymphoma; MIBC, muscle-invasive bladder cancer; NHL, non-Hodgkin lymphoma; PSMA, prostate-specific membrane antigen; TNBC, triple-negative breast cancer.

*Trials registered on ClinicalTrials.gov.

(NSCLC) elicited only 1 partial response (NCT02315066).12 The combination of utomilumab and pembrolizumab (Keytruda) was more promising, with an ORR of 26%, including 2 complete responses (CRs), in patients with advanced solid tumors (NCT02179918).13

Clinical trials of both drugs are ongoing, with a focus on combination therapies. In results from another cohort of the phase 1 clinical trial (NCT01307267), the combination of utomilumab and rituximab in patients with relapsed/refractory NHL demonstrated an ORR of 21.2%, including 4 CRs, with a median duration of response of 20.3 months. Most utomilumab treatment-related adverse events (TRAEs) were grade 1 or 2 in severity; most common was fatigue. There was 1 grade 3 increase in alanine aminotransferase at a dose of 2.4 mg/kg.14

Meanwhile, urelumab in combination with nivolumab (Opdivo) and GVAX (an allogeneic cancer vaccine comprising pancreatic tumor cells that express granulocyte-macrophage colony-stimulating factor) is being evaluated as neoadjuvant or adjuvant therapy in patients with resectable pancreatic ductal adenocarcinoma in 1 arm of a phase 1/2 trial (NCT02451982).

Preliminary results presented at the 35th Annual Meeting of the Society for Immunotherapy of Cancer in 2020 demonstrated a pathologic complete response rate of 30% among 10 evaluable patients, with 9 of them remaining disease free after a median follow-up of 1 year. The combination was well tolerated, with nausea the most common AE attributed to urelumab.15

**CONDITIONAL AGONISTS**

A swath of next-generation CD137 agonists that recently entered clinical development is designed to overcome the limitations of the first-generation drugs.3 Intrinsic agonistic strength, immunoglobulin isotype, and interactions with Fcγ receptors (FγRs) have been found to be critical to the relative safety and efficacy of CD137 antibodies. Thus, investigators have been tinkering with these properties to optimize CD137 agonist design.1,16

Notably, conditional CD137 agonists have been designed to be dependent on FγR cross-linking so that they will stimulate CD137 signaling only in the context of ongoing immune cell activation. The theory is that high concentrations of endogenous IgG circulating in blood and in highly vascularized tissues such as the liver will block the agonist function of these antibodies by competing for binding to FγRs. The agonist activity of the antibodies will be targeted to the tumor microenvironment, where both CD137 and FγRs are strongly expressed.16-21

AGEN2373 is a fully human, non-ligand-blocking, IgG1-based antibody that binds to cysteine-rich domain (CRD) IV on CD137 as opposed to urelumab, which binds to CRD I, and utomilumab, to CRD II and III.16,22 Results from an ongoing first-in-human study in patients with advanced solid tumors (NCT04121676) were recently presented at the 2021 American Society of Clinical Oncology Annual Meeting (ASCO 2021).
Nearly 5 years

What could this data mean for your patients?

Find out at KISQALI-hcp.com
Patients (N = 19) were treated with AGEN2373 monotherapy at escalating doses from 0.03 to 2 mg/kg every 4 weeks. The best response, prolonged disease stabilization, was seen in 5 patients. There were no dose-limiting toxicities and no grade 2 or higher drug-related increases in transaminase or bilirubin levels. The most common TRAEs were fatigue and nausea.22

ADG106 is a fully human, ligand-blocking, IgG4-based antibody, which was engineered on Adagene’s NEObody platform.18 Results from ongoing phase 1 clinical trials (single-center, NCT03802955; multicenter, NCT03707093) in patients with advanced solid tumors and/or relapsed/refractory NHL were presented at ASCO 2021. As of November 2020, the disease control rate (DCR) across these trials was 56%, and ADG106 displayed a favorable safety profile.23 According to an earlier analysis of the single-center trial, the most common treatment-emergent AEs were arthralgia, decreased appetite, diarrhea, hypothyroidism, and vomiting, which were predominantly grade 1 or 2.24

Investigators also identified a potential biomarker that correlated with response to ADG106; 3 of the 4 biomarker-positive patients experienced greater than 30% tumor shrinkage at doses of 3 mg/kg or 5 mg/kg.25 A phase 2 trial of ADG106 being planned will select for patients with this biomarker, the identity of which has not been publicly revealed.25

Alligator Bioscience is developing ATOR-1017, a fully human, IgG4-based ligand-blocking antibody that binds to CRD II, the natural ligand-binding domain of CD137.21,26 In an ongoing first-in-human trial of ATOR-1017 monotherapy in patients with advanced solid tumors (NCT04144842), 12 patients had been enrolled as of January 2021 (at doses of 0.38, 1.5, 5, 15, 40, and 100 mg). Preliminary results demonstrated a best response of stable disease (SD). TRAEs were predominantly grade 1 or 2 and included chest pain, headache, pyrexia, upper abdominal pain, mouth ulceration, nausea, leukopenia, neutropenia, cytokine release syndrome, arthralgia, neck pain, and rash.27

LVGN6051, another conditional agonist of CD137 that Lyvgen Biopharma is developing, is unique in that its Fc domain has been engineered to selectively bind to FcγRIIB, the sole inhibitory FcγR.28 FcγR engagement by a therapeutic antibody triggers dual effects: clustering of the antibody’s receptor target and activation of the antibody’s cytotoxic effector functions. Although the latter outcome can be advantageous in certain circumstances, with agonist antibodies these effector functions can eliminate the T cells that express the costimulatory receptor, inadvertently reducing the antibody’s antitumor efficacy. However, FcγRIIB mediates CD137 clustering without inducing cytotoxicity and thus avoids this off-target effect.29

As of January 2021, 16 patients had been enrolled in an ongoing first-in-human clinical trial of LVGN6051 as monotherapy or in combination with pembrolizumab for the treatment of advanced cancers (NCT04130542). Seven patients treated with monotherapy achieved SD, with the longest duration greater than 8 months. More than 10% tumor reduction was observed in patients with melanoma and neuroendocrine tumors. One patient with metastatic head and neck cancer treated with combination therapy had an immune partial response (PR) that lasted more than 6 months.20

MULTISPECIFIC ANTIBODIES
A prominent alternative strategy for leveraging CD137 is the development of bi- and trispecific antibodies, which engage a TAA in addition to CD137. This is another way to potentially achieve conditional stimulation of CD137 at the tumor site, as the drug should be activated only where CD137 and the TAA are simultaneously expressed.23

An array of multispecific antibodies targeting numerous TAs is in the early stages of clinical development. Pieris Pharmaceuticals is developing cirebafusp alfa, a bispecific fusion protein composed of a HER2 antibody and a CD137-binding Antibulin. Antibulin is recombinant human proteins derived from a group of transport proteins called lipocalins. Small, stable, and modular, Antibulin are being tested as an alternative to antibodies.29

In a phase 1 trial in patients with HER2-positive solid tumors (NCT03330561), cirebafusp alfa was administered at doses ranging from 0.0005 to 8 mg/kg every 2 or 3 weeks. Among 19 response-evaluable patients treated at the active dose range of 2.5 mg/kg and above, the DCR was 58%, with confirmed PRs in 11% of patients. The most common TRAEs were fatigue, chills, and diarrhea.30

Genmab and BioNTech are jointly developing GEN1042 and GEN1046, CD137 agonist antibodies that simultaneously target CD40 and PD-L1, respectively.31 According to preliminary data from the ongoing first-in-human trial of GEN1046 (NCT03917381) in patients with advanced solid tumors (N = 61 as of June 2020), the DCR was 65.6%, with SD or PRs observed in patients with triple-negative breast cancer, ovarian cancer, and NSCLC. The most common TRAEs included transaminase elevation, hypothyroidism, and fatigue.32

Roche is testing its bispecific antibody-like fusion proteins R07122290 and R07227166 in phase 1 clinical trials. Both agents target CD137; in addition, R07122290 binds to fibroblast activation protein alpha, which is highly expressed on cancer-associated fibroblasts in many tumors, whereas R07227166’s secondary target is CD19. R07122290 is being evaluated in a European-based 3-part first-in-human clinical trial as a single agent and in combination with atezolizumab (Tecentriq) in patients with advanced solid tumors (Eudra CT number: 2017-003961-83). Results from the dose-escalation portion of the trial (parts A and B) were presented at the European Society for Medical Oncology Virtual Congress 2020. In part A, 62 patients were treated with monotherapy doses ranging from 5 to 2000 mg; in part B, 39 patients received R07122290 at doses ranging from 45 to 2000 mg in combination with atezolizumab 1200 mg.

The ORRs were 3.6% in part A and 18.4% in part B. AEs were generally mild to moderate in both parts. Grade 3 and higher AEs included asthenia, increased aspartate aminotransferase levels, and pneumonia in part A and pneumonia, pneumonitis, neutropenia, and lymphocytopenia in part B. The maximum-tolerated dose was not reached.33

For a full list of references, see the article at OncLive.com.
MOLECULAR CHARACTERIZATION OF ENDOMETRIAL tumors has resulted in a boom of investigative efforts aimed at ushering in a new era of tailored therapeutic regimens for patients with these malignancies. Although radiation and chemotherapy have been the cornerstone of treatment for patients with advanced or recurrent endometrial cancer, knowledge of these tumors’ molecular signature has led to a plethora of clinical trials examining the accuracy of these predicative characteristics. “We can be curing more patients while limiting toxic therapies and providing better quality of life and less long-term morbidity; that’s because of molecular signature,” David M. O’Malley, MD, said during a recent OncLive Peer Exchange®.

A panel of gynecologic oncology experts discussed some of the molecular characteristics that have thus far been identified and what these might mean for prognosis and treatment decision-making. They also shared their insights on the promising ongoing phase 3 trials that are examining a variety of adjuvant and maintenance approaches as well as highlighted novel targets of interest. “We are amid a very impressive moment for the treatment of endometrial cancer. We’re moving forward,” Nicoletta Colombo, MD, PhD, said.

TO WATCH THE ENTIRE ONSLIVE PEER EXCHANGE® DISCUSSION, SCAN THE QR CODE OR VISIT, bit.ly/3Snhhmg.

Personalized Medicine Is Gaining Momentum in Advanced Endometrial Cancer
by CHRISTINA T. LOGUIDICE

Using Molecular Features to Guide Adjuvant Therapy Selection

In 2013, the Cancer Genome Atlas Research Network published the results of an integrated genomic, transcriptomic, and proteomic characterization of nearly 400 endometrial carcinomas using array- and sequencing-based technologies. This analysis identified 4 new tumor types: POLE ultramutated, microsatellite instability (MSI) hypermutated, copy-number low, and copy-number high. The molecular characterization data indicate that 25% of tumors classified as high-grade endometrioid by pathologists had a molecular phenotype similar to uterine serous carcinomas, including frequent TP53 mutations and extensive somatic copy number alterations. Based on these findings, investigators concluded that treating copy number–altered endometrioid tumors with chemotherapy rather than adjuvant radiotherapy should be considered and assessed in clinical trials.

Results of the PORTEC-3 trial (NCT00411138), which assessed adjuvant chemotherapy vs radiotherapy alone for patients with high-risk endometrial cancer, demonstrated that adjuvant chemotherapy did not improve 5-year overall survival (OS). Applying The Cancer Genome Atlas molecular classification findings, investigators conducted a retrospective analysis of tissue samples from more than 400 participants enrolled in PORTEC-3 and results signaled that response to treatment varies significantly based on tumors’ molecular profile.
“In particular, the patients with POLE mutations have a good prognosis; they probably don’t need any adjuvant treatment,” Domenica Lorusso, MD, PhD, said. “On the contrary, the tumors with TP53 mutations have a worse prognosis and seem to benefit with chemotherapy. The intermediate prognosis is that the mismatch repair-deficient [dMMR] population seems not to have such a good response to chemotherapy when we combine chemotherapy plus radiation treatment. These patients would require another kind of treatment, such as I/O [immuno-oncology] therapy. The last group—the group with no specific molecular characteristics—gained a little benefit from chemotherapy.” She added that these data have helped investigators design “a new generation of clinical trials that use this information to guide adjuvant treatment.”

One example is the PORTEC-4a trial (NCT03469674), a multicenter, international, phase 3 randomized trial of molecular-integrated risk profile-based adjuvant treatment vs standard adjuvant vaginal brachytherapy.4 “PORTEC-4a is very interesting because it divides patients into 3 groups based on molecular characteristics: low-risk, intermediate-risk, and high-risk,” Lorusso said. “The study doesn’t offer any treatment—no radiation—to the low-risk group while offering radiation treatment only to the intermediate- and high-risk groups.”

Lorusso noted that while PORTEC-4a is the first trial to use molecular characteristics of patient tumors to guide adjuvant treatment, similar trials are also in development, including the international RAINBO trials program, which comprises 4 trials.5 These trials will select and compare adjuvant treatments based on molecular group for patients with high-risk and advanced-stage endometrial cancer into 1 of 4 subgroups: TP53-mutant, dMMR, no specific molecular profile, and POLE-mutant. “Patients with tumors that have TP53 mutations will receive chemotherapy and then PARP inhibitors for 2 years. Those with dMMR tumors will receive radiation treatment and then immunotherapy for 1 year. Those with MMSP [malignant melanoma of soft parts] tumors will receive radiation treatment and hormonal treatment, with adjuvant chemotherapy as maintenance. Those with POLE-mutant tumors do not receive adjuvant treatment; it’s a completely different way to approach treating endometrial cancer,” Lorusso said.

Bradley J. Monk, MD, highlighted an exciting large international trial in this space, the phase 3 KEYNOTE-B21 trial (NCT04634877), which is expecting to enroll almost 1000 participants.4 “It’s basically taking patients with newly diagnosed endometrial cancer with positive nodes—including patients with TP53 mutations—and treating them with chemotherapy and adding a placebo or pembrolizumab [Keytruda]. Radiation is elective,” he said.

“The most important step forward in endometrial cancer treatment is molecular profiling,” Lorusso said. “We’ll use this information to guide our treatments: surgical treatment, possibly medical treatment, advanced disease treatment. We performed [molecular profiling] more than in the treatment of other tumors, [such as] ovarian and cervical cancers. Endometrial cancer treatment is a step ahead of all the others in terms of the ecological malignancies.”

**PHASE 3 TRIALS FOR ADVANCED OR RECURRENT ENDOMETRIAL CANCER**

The panelists proceeded to share their thoughts several ongoing phase 3 clinical trials that have the potential to reshape the endometrial cancer treatment landscape in the next few years. They discussed trials that are combining a single-agent checkpoint inhibitor with other treatments to try to improve efficacy, such as VEGF inhibitors (KEYNOTE-775; NCT03517449) or chemotherapy (RUBY [NCT03981796]; NRG-GY018 [NCT03914612]; AtTEnd [NCT03603184]). They also reviewed several maintenance strategies under investigation, including the use of PARP inhibitors in the DUO-E trial (NCT04269200) as well as selinexor (Xpovio) in the ENGOT-ENS/SIENDO trial (NCT03555422).

**KEYNOTE-775**

Investigators are evaluating lenvatinib (Lenvima) plus pembrolizumab vs physician’s choice as a first-line treatment for patients with advanced endometrial cancer (stage III or stage IV) in the KEYNOTE-775 trial.7 “Patients will be randomized 1:1 to lenvatinib at 20 mg orally once daily plus pembrolizumab at 200 mg every 3 weeks vs the standard paclitaxel-carboplatin IV [intra- venous] every 3 weeks,” Vicky Makker, MD, explained. “The study has a dual primary end points of PFS [progression-free survival] and OS.”

The first data from this pivotal trial were reported by Makker at the Society of Gynecologic Oncology 2021 Virtual Annual Meeting on Women’s Cancer in March.8 After a median follow-up of 12.2 months for patients receiving lenvatinib plus pembrolizumab (n = 411) and 10.7 months for those receiving physician’s choice of treatment (n = 416), lenvatinib plus pembrolizumab showed statistically significant and clinically meaningful improvements in PFS, OS, and overall response rate (ORR) vs physician’s choice of treatment, regardless of patients’ MMR status, thereby meeting its primary and secondary end points (Table).8.9 Among the patients who responded, the duration of response (DOR) among all-comers was 14.4 months in the lenvatinib/pembrolizumab arm compared with 5.7 months in the physician’s choice arm, whereas the DOR in the mismatch repair-proficient cohort was 9.2 months vs 5.7 months, respectively.9 “I was a little skeptical [of this regimen] until I saw the results of KEYNOTE-775,” Monk said. “Whoa—this whole idea of a chemotherapy-free regimen, which is what the study is, is so exciting.” Based on these data, the FDA granted priority review to the supplemental biologics application for the combination in May.10

**RUBY, NRG-GY018, AtTEnd Trials**

RUBY, NRG-GY018, and AtTEnd are seeking to answer the question of whether an I/O approach in combination with
chemotherapy has a clinical benefit in patients with advanced or recurrent endometrial cancer.\(^{11,13}\) \[These] trials include the same populations more or less,” Columbo said. “[Individuals] are stratified according to their MSI status, but all-comers are included.” Each of the trials will evaluate PFS as its primary end point.

RUBY is assessing the addition of dostarlimab (Jemperli) to paclitaxel and carboplatin in women with recurrent or primary advanced endometrial cancer.\(^{14}\) On April 22, 2021, the FDA granted accelerated approval to dostarlimab for adult patients with dMMR-recurrent or advanced endometrial cancer that progressed on or after a platinum-containing regimen.\(^{14}\) Approval was based on data from the GARNET trial (NCT02715284), a multicenter, multicohort, open-label trial that included patients with a variety of advanced solid tumors, including 71 with dMMR recurrent or advanced endometrial cancer. The confirmed ORR was 42.3% in this cohort, with a 12.7% complete response rate and a 29.6% partial response rate. The median DOR was not reached, with a 12.7% complete response rate and a 29.6% partial response rate. The median DOR was not reached, with a 12.7% complete response rate and a 29.6% partial response rate.

Further, the ArtEnd is assessing the addition of atezolizumab (Tecentriq) to paclitaxel and carboplatin in women with advanced or recurrent endometrial cancer with dual primary end points of PFS and OS.\(^{15}\) Investigators plan to enroll 550 patients with an estimated completion date of December 2023.

DUO-E Trial
“[Investigators are] also looking at a carboplatin-paclitaxel backbone with durvalumab (Imfinzi) followed by durvalumab maintenance plus or minus olaparib [after first-line treatment of advanced or recurrent endometrial cancer],” O’Malley said. DUO-E is a randomized, double-blind, placebo-controlled trial that is anticipated to enroll approximately 700 patients.\(^{15}\) The primary outcome measure is PFS. The estimated study completion date is March 2025.

In addition to DUO-E, Monk noted that part 2 of the RUBY trial and the RAINBO trials program will also examine the use of PARP inhibitors, which will help to answer the question of whether these agents may play a role in treating patients with endometrial cancer. Lorusso said she suspects these agents will eventually play a greater role, particularly for patients with \(TP53\) mutations. “We will see the results of these trials, and then we will better define when to use them in the algorithm of treatment—if we should use them in the adjuvant setting or in the first-line metastatic setting,” she said.

### TABLE. Preliminary Findings From the KEYNOTE-775\(^{8,9}\)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All-comers (pMMR and dMMR)</th>
<th>pMMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lenvatinib/pembrolizumab (n = 411)</td>
<td>Physician’s choice (n = 416)</td>
</tr>
<tr>
<td><strong>Primary end points</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>18.3 (15.2-20.5)</td>
<td>11.4 (10.5-12.9)</td>
</tr>
<tr>
<td>HR, 0.62; 95% CI, 0.51-0.75; (P\leq0.0001)</td>
<td>HR, 0.68; 95% CI, 0.56-0.84; (P&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>7.2 (5.7-7.6)</td>
<td>3.8 (3.6-4.2)</td>
</tr>
<tr>
<td>HR, 0.56; 95% CI, 0.47-0.66; (P&lt;0.0001)</td>
<td>HR, 0.60; 95% CI, 0.50-0.72; (P&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>31.9% (27.4%-36.6%)</td>
<td>14.7% (11.4%-18.4%)</td>
</tr>
<tr>
<td>CR, %</td>
<td>6.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>PR, %</td>
<td>25.3%</td>
<td>12.0%</td>
</tr>
<tr>
<td>Median DOR, months (range)</td>
<td>14.4 (1.6-23.7)</td>
<td>5.7 (0.0-24.2)</td>
</tr>
</tbody>
</table>

\(CR\), complete response; \(dMMR\), mismatch repair–deficient; \(DOR\), duration of response; \(ORR\), objective response rate; \(OS\), overall survival; \(pMMR\), mismatch repair–proficient; \(PR\), partial response.
partial response following this treatment.\textsuperscript{16} “Selinexor is a novel oral selective inhibitor of nuclear export,” Makker said. “Essentially, “Selinexor is a novel oral selective inhibitor with a CDK4/6 inhibitor, which was discussed is the combination of an aromatase inhibitor and a CDK4/6 inhibitor, which has shown activity across a number of other hematologic malignancies and solid tumors. It has shown some efficacy treating endometrial cancers that have been previously treated,” she said.

ENGOT-EN3/SIENDO is anticipated to enroll 248 participants, and the estimated study completion date is March 2023.\textsuperscript{16} The primary outcome measure is investigator-assessed PFS.

**NOVEL TARGETS OF INTEREST**

“There’s emerging evidence that WEE1 inhibition might be effective in treating serous cancer,” Monk said. One agent targeting this pathway is adavosertib, which O’Malley said showed promising results in a small study that included 34 patients.\textsuperscript{18} “[There was] a response rate of 29%, with a duration of response of 9 months,” he said. “[Individuals] had to have 1 regimen of prior systemic chemotherapy, but it’s very interesting because this was an extremely heavily pretreated group of patients with [a median of] 3 prior regimens—3 prior regimens with a response rate of 29% in these patients with serous cancers. That’s a very impressive response.”

Another novel approach the panelists discussed is the combination of an aromatase inhibitor with a CDK4/6 inhibitor, which was explored in the phase 2 ENGOT-EN3-NSGO/PALÉO trial (NCT02730429).\textsuperscript{19} “There was a strong proof of concept suggesting that when we combine the aromatase inhibitor—in this case, letrozole—with palbociclib [Ibrance], a CDK4/6 inhibitor,” Lorusso said.

“We were able to increase response rates and PFS with respect to letrozole alone. Particularly, [data from] the subgroup analysis suggests that the benefit is higher in patients who were pretreated with hormonal treatment. We are designing the phase 3 confirmatory trial, and if these results are to be confirmed in the future, we may have this combination to treat all receptor-positive tumors,” she said.

She noted that a large percentage of patients had to discontinue treatment because of toxicity, but that the trial participants were older and had several comorbidities, which was a contributing factor that is being taken into consideration for the phase 3 trial. Additionally, although aromatase inhibitors plus CDK4/6 inhibitors have been shown to shrink tumors in breast cancer, this is not the case with endometrial cancer. Instead, this combination appears to keep disease stable. ■

**REFERENCES**


NOW APPROVED!

Zynlonta™
loncastuximab tesirine-lpyl
for injection, for intravenous use

Visit zynlontahcp.com to learn about:

Prescribing Information
Dosing and administration
Resources for healthcare professionals
Access and support for patients

ZYNLONTA is a trademark of ADC Therapeutics SA.
US-Comm-LTX-00002. April 2021
© 2021 ADC Therapeutics SA. All rights reserved.