SPECIAL ISSUE: **ASCO 2020 MEETING RECAP**

AJMC®
THE AMERICAN JOURNAL OF MANAGED CARE®

25 YEARS
RESEARCH & LEADERSHIP

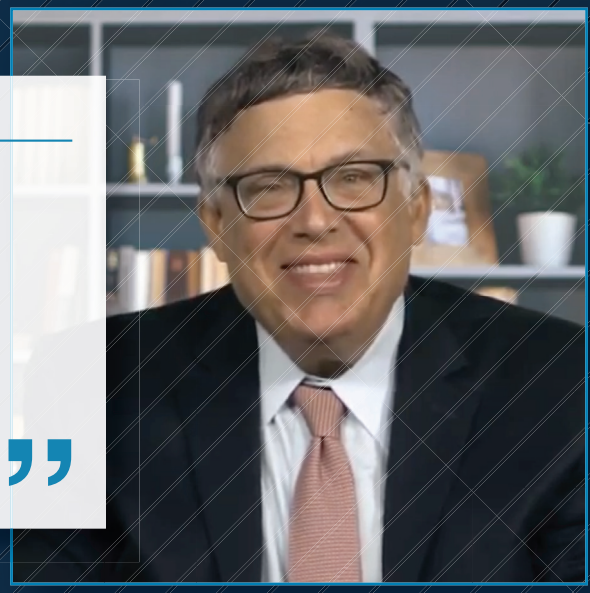
Evidence-Based ONCOLOGY™

JULY 2020
VOL. 26 • NO. 6

THE ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY | MAY 29-31, 2020 | ASCO VIRTUAL 2020

> **This is important. The longer you take the drug, the better your responses become.**
>
> Constantine Tam, MBBS, MD
> Peter McCallum Cancer Centre; Victoria, Australia

> **Collectively, these data support the use of osimertinib as an appropriate treatment in the long-term adjuvant setting....Looking ahead, future considerations for ADAURA include investigation of local versus distant recurrence; sites of disease recurrence, including incidence of [central nervous system] metastases; subsequent therapy; and quality of life.**
>
> Roy S. Herbst, MD, PhD
> Yale Cancer Center and Smilow Cancer Hospital



> **We know that not only is [next-generation sequencing] testing better, but it's more effective and more likely to identify rare mutations and single alterations.**
>
> Melissa L. Johnson, MD
> Sarah Cannon Research Institute

HIGHLIGHTS FROM THE MEETING

- COVID-19 COULD TRIGGER FIRST RISE IN CANCER DEATHS IN DECADES, **SP178**.
- PEMBROLIZUMAB AS FIRST-LINE TREATMENT FOR CERTAIN PATIENTS WITH COLORECTAL CANCER, **SP180**.
- OSIMERTINIB AFTER NSCLC SURGERY KEEPS CANCER AT BAY FOR PATIENTS WITH KEY MUTATION, **SP181**.
- UPDATED RESULTS GIVE ZANUBRUTINIB EDGE OVER IBRUTINIB IN SOME PATIENTS WITH WM, **SP182**.
- ACCESS AND COUNSELING NEEDED IN GENETIC TESTING, **SP187**.
- POSITIVE SIGNS FOR AMG 510, INHIBITOR OF *KRAS* MUTATION, **SP193**.

AJMC® Managed Markets Network®
ACCC Association of Community Cancer Centers
AJMC® The Institute for Value-Based Medicine®
Community Oncology Alliance®

In HR+, HER2– MBC

Is Verzenio® (abemaciclib) an option for your patient?

Rapid progression

Primary resistance

recurred on adjuvant ET at 22 months [1,2,4†]

Metastases beyond the bone

Visceral metastases

liver metastases[1,3,5‡]

Discover an option for HR+, HER2- MBC patients at verzenio.com/hcp

Verzenio + AI (ITT PFS analysis: HR=0.540 [95% CI: 0.418-0.698]; N=493): treatment-free interval <36 months (exploratory PFS analysis: HR=0.441 [95% CI: 0.241-0.805]; n=76) and liver metastases (exploratory PFS analysis: HR=0.477 [95% CI: 0.272-0.837]; n=78). Verzenio + fulvestrant (ITT PFS analysis: HR=0.553 [95% CI: 0.449-0.681]; N=669): primary resistance (preplanned PFS analysis: HR=0.454 [95% CI: 0.306-0.674]; n=169) and visceral disease (preplanned PFS analysis: HR=0.481 [95% CI: 0.369-0.627]; n=373). The analyses were not adjusted for multiplicity and the study was not powered to test the effect of Verzenio + AI/fulvestrant among subgroups. Verzenio single-agent (ITT ORR analysis: 19.7% [95% CI: 13.3-27.5]): progression on or after ET and prior chemotherapy in the metastatic setting and visceral disease.
For additional information and full trial design, see verzenio.com/hcp/efficacy.

Verzenio is indicated for the treatment of hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced or metastatic breast cancer (MBC)[1]:

- In **combination with fulvestrant** for women with disease progression following endocrine therapy
- In **combination with an aromatase inhibitor (AI)** for postmenopausal women as initial endocrine-based therapy
- As a **single agent** for adult patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting

Select Important Safety Information

Diarrhea occurred in 81% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 90% of patients receiving Verzenio alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 20% of patients receiving Verzenio alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

Diarrhea incidence was greatest during the first month of Verzenio dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow-up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue Verzenio until toxicity resolves to ≤Grade 1, and then resume Verzenio at the next lower dose.

Neutropenia occurred in 41% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 37% of patients receiving Verzenio alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 27% of patients receiving Verzenio alone in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1, was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days.

Monitor complete blood counts prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in <1% of patients exposed to Verzenio in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Severe, life-threatening, or fatal **interstitial lung disease (ILD) and/or pneumonitis** can occur in patients treated with Verzenio and other CDK4/6 inhibitors.

†Primary resistance is defined as relapse while on the first 2 years of adjuvant ET, or progressive disease within the first 6 months of first-line endocrine therapy for MBC.[2]
‡Visceral disease was defined as lesions on an internal organ or in the third space and could have included lung, liver, pleural, or peritoneal metastatic involvement.[6]

CI=confidence interval; ET=endocrine therapy; HR=hazard ratio; ITT=intent-to-treat; ORR=objective response rate; PFS=progression-free survival.

Select Important Safety Information (cont'd)

Across clinical trials (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of Verzenio-treated patients had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations.

Dose interruption or dose reduction is recommended in patients who develop persistent or recurrent Grade 2 ILD/pneumonitis. Permanently discontinue Verzenio in all patients with grade 3 or 4 ILD/pneumonitis.

Grade ≥3 increases in **alanine aminotransferase (ALT)** (6% versus 2%) and **aspartate aminotransferase (AST)** (3% versus 1%) were reported in the Verzenio and placebo arms, respectively, in MONARCH 3. Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the Verzenio and placebo arms respectively, in MONARCH 2.

In MONARCH 3, for patients receiving Verzenio plus an aromatase inhibitor with Grade ≥3 increases in ALT or AST, median time to onset was 61 and 71 days, respectively, and median time to resolution to Grade <3 was 14 and 15 days, respectively. In MONARCH 2, for patients receiving Verzenio plus fulvestrant with Grade ≥3 increases in ALT or AST, median time to onset was 57 and 185 days, respectively, and median time to resolution to Grade <3 was 14 and 13 days, respectively.

For assessment of potential **hepatotoxicity,** monitor liver function tests (LFTs) prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation

Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo in MONARCH 3. Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus fulvestrant in MONARCH 2 as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Verzenio can cause **fetal harm** when administered to a pregnant woman based on findings from animal studies and the mechanism of action. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for at least 3 weeks after the last dose. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential.

Please see Select Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.

everyday
Verzenio®
abemaciclib
50 | 100 | 150 | 200 mg tablets
twice a day

Discover an option for HR+, HER2- MBC patients at

verzenio.com/hcp

Select Important Safety Information (cont'd)

The **most common adverse reactions (all grades, ≥10%)** observed in **MONARCH 3 for Verzenio plus anastrozole or letrozole** and **≥2% higher than placebo plus anastrozole or letrozole vs placebo plus anastrozole or letrozole** were diarrhea (81% vs 30%), neutropenia (41% vs 2%), fatigue (40% vs 32%), infections (39% vs 29%), nausea (39% vs 20%), abdominal pain (29% vs 12%), vomiting (28% vs 12%), anemia (28% vs 5%), alopecia (27% vs 11%), decreased appetite (24% vs 9%), leukopenia (21% vs 2%), creatinine increased (19% vs 4%), constipation (16% vs 12%), ALT increased (16% vs 7%), AST increased (15% vs 7%), rash (14% vs 5%), pruritus (13% vs 9%), cough (13% vs 9%), dyspnea (12% vs 6%), dizziness (11% vs 9%), weight decreased (10% vs 3%), influenza-like illness (10% vs 8%), and thrombocytopenia (10% vs 2%).

The **most common adverse reactions (all grades, ≥10%)** observed in **MONARCH 2 for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant vs placebo plus fulvestrant** were diarrhea (86% vs 25%), neutropenia (46% vs 4%), fatigue (46% vs 32%), nausea (45% vs 23%), infections (43% vs 25%), abdominal pain (35% vs 16%), anemia (29% vs 4%), leukopenia (28% vs 2%), decreased appetite (27% vs 12%), vomiting (26% vs 10%), headache (20% vs 15%), dysgeusia (18% vs 3%), thrombocytopenia (16% vs 3%), alopecia (16% vs 2%), stomatitis (15% vs 10%), ALT increased (13% vs 5%), pruritus (13% vs 6%), cough (13% vs 11%), dizziness (12% vs 6%), AST increased (12% vs 7%), peripheral edema (12% vs 7%), creatinine increased (12% vs <1%), rash (11% vs 4%), pyrexia (11% vs 6%), and weight decreased (10% vs 2%).

The **most common adverse reactions (all grades, ≥10%)** observed in **MONARCH 1** with Verzenio were diarrhea (90%), fatigue (65%), nausea (64%), decreased appetite (45%), abdominal pain (39%), neutropenia (37%), vomiting (35%), infections (31%), anemia (25%), thrombocytopenia (20%), headache (20%), cough (19%), leukopenia (17%), constipation (17%), arthralgia (15%), dry mouth (14%), weight decreased (14%), stomatitis (14%), creatinine increased (13%), alopecia (12%), dysgeusia (12%), pyrexia (11%), dizziness (11%), and dehydration (10%).

The **most frequently reported ≥5% Grade 3 or 4 adverse reactions** that occurred in the Verzenio arm vs the placebo arm of **MONARCH 3** were neutropenia (22% vs 2%), diarrhea (9% vs 1%), leukopenia (8% vs <1%), ALT increased (7% vs 2%), and anemia (6% vs 1%).

The **most frequently reported ≥5% Grade 3 or 4 adverse reactions** that occurred in the Verzenio arm vs the placebo arm of **MONARCH 2** were neutropenia (27% vs 2%), diarrhea (13% vs <1%), leukopenia (9% vs 0%), anemia (7% vs 1%), and infections (6% vs 3%).

The **most frequently reported ≥5% Grade 3 or 4 adverse reactions** from **MONARCH 1** with Verzenio were neutropenia (24%), diarrhea (20%), fatigue (13%), infections (7%), leukopenia (6%), anemia (5%), and nausea (5%).

Lab abnormalities (all grades; Grade 3 or 4) for **MONARCH 3 in ≥10% for Verzenio plus anastrozole or letrozole and ≥2% higher than placebo plus anastrozole or letrozole vs placebo plus anastrozole or letrozole** were increased serum creatinine (98% vs 84%; 2% vs 0%), decreased white blood cells (82% vs 27%; 13% vs <1%), anemia (82% vs 28%; 2% vs 0%), decreased neutrophil count (80% vs 21%; 22% vs 3%), decreased lymphocyte count (53% vs 26%; 8% vs 2%), decreased platelet count (36% vs 12%; 2% vs <1%), increased ALT (48% vs 25%; 7% vs 2%), and increased AST (37% vs 23%; 4% vs <1%).

Lab abnormalities (all grades; Grade 3 or 4) for **MONARCH 2 in ≥10% for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant vs placebo plus fulvestrant** were increased serum creatinine (98% vs 74%; 1% vs 0%), decreased white blood cells (90% vs 33%; 23% vs 1%), decreased neutrophil count (87% vs 30%; 33% vs 4%), anemia (84% vs 33%; 3% vs <1%), decreased lymphocyte count (63% vs 32%; 12% vs 2%), decreased platelet count (53% vs 15%; 2% vs 0%), increased ALT (41% vs 32%; 5% vs 1%), and increased AST (37% vs 25%; 4% vs 4%).

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 1 with Verzenio were increased serum creatinine (98%; <1%), decreased white blood cells (91%; 28%), decreased neutrophil count (88%; 27%), anemia (68%; 0%), decreased lymphocyte count (42%; 14%), decreased platelet count (41%; 2%), increased ALT (31%; 3%), and increased AST (30%; 4%).

Strong and moderate CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity. Avoid concomitant use of the strong CYP3A inhibitor ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold. In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the Verzenio dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the Verzenio dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking Verzenio discontinues a strong CYP3A inhibitor, increase the Verzenio dose (after 3 to 5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the Verzenio dose in 50 mg decrements. Patients should avoid grapefruit products.

Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents. Coadministration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity.

With severe hepatic impairment (Child-Pugh Class C), reduce the Verzenio dosing frequency to once daily. The pharmacokinetics of Verzenio in patients with **severe renal impairment** (CLcr <30 mL/min), end stage renal disease, or in patients on dialysis **is unknown.** No dosage adjustments are necessary in patients with mild or moderate hepatic (Child-Pugh A or B) and/or renal impairment (CLcr ≥30-89 mL/min).

AL HCP ISI 17SEP2019

Please see Brief Summary of full Prescribing Information for Verzenio on the following pages.

References:

1. Verzenio [package insert]. Indianapolis, IN: Eli Lilly and Company; 2019.
2. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2– advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol.* 2017;35:2875-2884.
3. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer.* 2019;5:5. https://www.nature.com/articles/s41523-018-0097-z. Published January 17, 2019. Accessed March 14, 2019.
4. Cardoso F, Costa A, Senkus E, et al. 3rd ESO–ESMO international consensus guidelines for advanced breast cancer (ABC 3). *Breast.* 2017;31:244-259.
5. Gerratana L, Fanotto V, Bonotto M, et al. Pattern of metastasis and outcome in patients with breast cancer. *Clin Exp Metastasis.* 2015;32:125-133.
6. Data on file. Lilly USA, LLC. ONC20171128a.

everyday

Verzenio®

abemaciclib

50 | 100 | 150 | 200 mg tablets

twice a day

Lilly

VERZENIO® (abemaciclib) tablets, for oral use
Initial U.S. Approval: 2017

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

INDICATIONS AND USAGE

VERZENIO® (abemaciclib) is indicated:

- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.
- in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Diarrhea

Diarrhea occurred in 81% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and 90% of patients receiving VERZENIO alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and in 20% of patients receiving VERZENIO alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

Diarrhea incidence was greatest during the first month of VERZENIO dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue VERZENIO until toxicity resolves to ≤Grade 1, and then resume VERZENIO at the next lower dose.

Neutropenia

Neutropenia occurred in 41% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and 37% of patients receiving VERZENIO alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and in 27% of patients receiving VERZENIO in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1 was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days.

Monitor complete blood counts prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in <1% of patients exposed to VERZENIO in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, or fatal lung disease (ILD) and/or pneumonitis can occur in patients treated with VERZENIO and other CDK 4/6 inhibitors. Across clinical trials (MONARCH 1, MONARCH 2, and MONARCH 3), 3.3% of VERZENIO-treated patients had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations.

Dose interruption or dose reduction is recommended for patients who develop persistent or recurrent Grade 2 ILD/pneumonitis. Permanently discontinue VERZENIO in all patients with Grade 3 or 4 ILD or pneumonitis.

Hepatotoxicity

In MONARCH 3, Grade ≥3 increases in ALT (6% versus 2%) and AST (3% versus 1%) were reported in the VERZENIO and placebo arms, respectively. In MONARCH 2, Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the VERZENIO and placebo arms, respectively.

In MONARCH 3, for patients receiving VERZENIO plus an aromatase inhibitor with Grade ≥3 ALT increased, median time to onset was 61 days, and median time to resolution to Grade <3 was 14 days. In MONARCH 2, for patients receiving VERZENIO plus fulvestrant with Grade ≥3 ALT increased, median time to onset was 57 days, and median time to resolution to Grade <3 was 14 days. In MONARCH 3, for patients receiving VERZENIO plus an aromatase inhibitor with Grade ≥3 AST increased, median time to onset was 71 days, and median time to resolution was 15 days. In MONARCH 2, for patients receiving VERZENIO plus fulvestrant with Grade ≥3 AST increased, median time to onset was 185 days, and median time to resolution was 13 days.

Monitor liver function tests (LFTs) prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation.

Venous Thromboembolism

In MONARCH 3, venous thromboembolic events were reported in 5% of patients treated with VERZENIO plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo. In MONARCH 2, venous thromboembolic events were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported.

Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with VERZENIO and for at least 3 weeks after the last dose.

ADVERSE REACTIONS

Clinical Studies 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.

MONARCH 3: VERZENIO in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) as Initial Endocrine-Based Therapy

Postmenopausal Women with HR-positive, HER2-negative locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting

MONARCH 3 was a study of 488 women receiving VERZENIO plus an aromatase inhibitor or placebo plus an aromatase inhibitor. Patients were randomly assigned to receive 150 mg of VERZENIO or placebo orally twice daily, plus physician's choice of anastrozole or letrozole once daily. Median duration of treatment was 15.1 months for the VERZENIO arm and 13.9 months for the placebo arm. Median dose compliance was 98% for the VERZENIO arm and 99% for the placebo arm.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving VERZENIO plus anastrozole or letrozole. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. VERZENIO dose reductions due to diarrhea of any grade occurred in 13% of patients receiving VERZENIO plus an aromatase inhibitor compared to 2% of patients receiving placebo plus an aromatase inhibitor. VERZENIO dose reductions due to neutropenia of any grade occurred in 11% of patients receiving VERZENIO plus an aromatase inhibitor compared to 0.6% of patients receiving placebo plus an aromatase inhibitor.

Permanent treatment discontinuation due to an adverse event was reported in 13% of patients receiving VERZENIO plus an aromatase inhibitor and in 3% placebo plus an aromatase inhibitor. Adverse reactions leading to permanent discontinuation for patients receiving VERZENIO plus an aromatase inhibitor were diarrhea (2%), ALT increased (2%), infection (1%), venous thromboembolic events (VTE) (1%), neutropenia (0.9%), renal impairment (0.9%), AST increased (0.6%), dyspnea (0.6%), pulmonary fibrosis (0.6%) and anemia, rash, weight decreased and thrombocytopenia (each 0.3%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 11 cases (3%) of VERZENIO plus an aromatase inhibitor treated patients versus 3 cases (2%) of placebo plus an aromatase inhibitor treated patients. Causes of death for patients receiving VERZENIO plus an aromatase inhibitor included: 3 (1%) patient deaths due to underlying disease, 3 (0.9%) due to lung infection, 3 (0.9%) due to VTE event, 1 (0.3%) due to pneumonitis, and 1 (0.3%) due to cerebral infarction.

The most common adverse reactions reported (≥20%) in the VERZENIO arm and ≥2% than the placebo arm were diarrhea, neutropenia, fatigue, infections, nausea, abdominal pain, anemia, vomiting, alopecia, decreased appetite, and leukopenia (Table 1). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, increased ALT, and anemia. Diarrhea incidence was greatest during the first month of VERZENIO dosing. The median time to onset of the first diarrhea event was 8 days, and the median durations of diarrhea for Grades 2 and for Grade 3 were 11 days and 8 days, respectively. Most diarrhea events recovered or resolved (88%) with supportive treatment and/or dose reductions. Nineteen percent of patients with diarrhea required a dose omission and 13% required a dose reduction. The median time to the first dose reduction due to diarrhea was 38 days.

Table 1: Adverse Reactions ≥10% of Patients Receiving VERZENIO Plus Anastrozole or Letrozole and ≥2% Higher Than Placebo Plus Anastrozole or Letrozole in MONARCH 3

	VERZENIO plus Anastrozole or Letrozole N=327			Placebo plus Anastrozole or Letrozole N=161		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	81	9	0	30	1	0
Nausea	39	<1	0	20	1	0
Abdominal pain	29	1	0	12	1	0
Vomiting	28	1	0	12	2	0
Constipation	16	<1	0	12	0	0
Infections and Infestations						
Infections[a]	39	4	<1	29	2	<1
Blood and Lymphatic System Disorders						
Neutropenia	41	20	2	2	<1	<1
Anemia	28	6	0	5	1	0
Leukopenia	21	7	<1	2	0	<1
Thrombocytopenia	10	2	<1	2	<1	0
General Disorders and Administration Site Conditions						
Fatigue	40	2	0	32	0	0
Influenza like illness	10	0	0	8	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	27	0	0	11	0	0
Rash	14	<1	0	5	0	0
Pruritus	13	0	0	9	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	24	1	0	9	<1	0
Investigations						
Blood creatinine increased	19	2	0	4	0	0
Alanine aminotransferase increased	16	6	<1	7	2	0
Aspartate aminotransferase increased	15	3	0	7	1	0
Weight decreased	10	<1	0	3	<1	0

Table 1: Adverse Reactions ≥10% of Patients Receiving VERZENIO Plus Anastrozole or Letrozole and ≥2% Higher Than Placebo Plus Anastrozole or Letrozole in MONARCH 3 (Cont.)

	VERZENIO plus Anastrozole or Letrozole N=327			Placebo plus Anastrozole or Letrozole N=161		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Respiratory, Thoracic, and Mediastinal Disorders						
Cough	13	0	0	9	0	0
Dyspnea	12	<1	<1	6	<1	0
Nervous System Disorders						
Dizziness	11	<1	0	9	0	0

[a] Includes all reported preferred terms that are part of the Infections and Infestations system organ class. Most common infections (>1%) include upper respiratory tract infection, lung infection, and pharyngitis.

Additional adverse reactions in MONARCH 3 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, and pelvic venous thrombosis), which were reported in 5% of patients treated with VERZENIO plus anastrozole or letrozole as compared to 0.6% of patients treated with anastrozole or letrozole plus placebo.

Table 2: Laboratory Abnormalities ≥10% in Patients Receiving VERZENIO Plus Anastrozole or Letrozole and ≥2% Higher Than Placebo Plus Anastrozole or Letrozole in MONARCH 3

	VERZENIO plus Anastrozole or Letrozole N=327			Placebo plus Anastrozole or Letrozole N=161		
Laboratory Abnormality	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Creatinine increased	98	2	0	84	0	0
White blood cell decreased	82	13	0	27	<1	0
Anemia	82	2	0	28	0	0
Neutrophil count decreased	80	19	3	21	3	0
Lymphocyte count decreased	53	7	<1	26	2	0
Platelet count decreased	36	1	<1	12	<1	0
Alanine aminotransferase increased	48	6	<1	25	2	0
Aspartate aminotransferase increased	37	4	0	23	<1	0

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. Across the clinical studies, increases in serum creatinine (mean increase, 0.2-0.3 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

MONARCH 2: VERZENIO in Combination with Fulvestrant

Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy

The safety of VERZENIO (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to VERZENIO in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of VERZENIO plus fulvestrant in MONARCH 2.

Median duration of treatment was 12 months for patients receiving VERZENIO plus fulvestrant and 8 months for patients receiving placebo plus fulvestrant.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving VERZENIO plus fulvestrant. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. VERZENIO dose reductions due to diarrhea of any grade occurred in 19% of patients receiving VERZENIO plus fulvestrant compared to 0.4% of patients receiving placebo and fulvestrant. VERZENIO dose reductions due to neutropenia of any grade occurred in 10% of patients receiving VERZENIO plus fulvestrant compared to no patients receiving placebo plus fulvestrant.

Permanent study treatment discontinuation due to an adverse event was reported in 9% of patients receiving VERZENIO plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Adverse reactions leading to permanent discontinuation for patients receiving VERZENIO plus fulvestrant were infection (2%), diarrhea (1%), hepatotoxicity (1%), fatigue (0.7%), nausea (0.2%), abdominal pain (0.2%), acute kidney injury (0.2%), and cerebral infarction (0.2%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 18 cases (4%) of VERZENIO plus fulvestrant treated patients versus 10 cases (5%) of placebo plus fulvestrant treated patients. Causes of death for patients receiving VERZENIO plus fulvestrant included: 7 (2%) patient deaths due to underlying disease, 4 (0.9%) due to sepsis, 2 (0.5%) due to pneumonitis, 2 (0.5%) due to hepatotoxicity, and one (0.2%) due to cerebral infarction.

The most common adverse reactions reported (≥20%) in the VERZENIO arm were diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache (Table 3). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, anemia, and infections.

Table 3: Adverse Reactions ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

	VERZENIO plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	86	13	0	25	<1	0
Nausea	45	3	0	23	1	0
Abdominal Pain[a]	35	2	0	16	1	0
Vomiting	26	<1	0	10	2	0
Stomatitis	15	<1	0	10	0	0
Infections and Infestations						
Infections[b]	43	5	<1	25	3	<1
Blood and Lymphatic System Disorders						
Neutropenia[c]	46	24	3	4	1	<1
Anemia[d]	29	7	<1	4	1	0

Table 3: Adverse Reactions ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2 (Cont.)

	VERZENIO plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Blood and Lymphatic System Disorders (Cont.)						
Leukopenia[e]	28	9	<1	2	0	0
Thrombocytopenia[f]	16	2	1	3	0	<1
General Disorders and Administration Site Conditions						
Fatigue[g]	46	3	0	32	<1	0
Edema peripheral	12	0	0	7	0	0
Pyrexia	11	<1	<1	6	<1	0
Metabolism and Nutrition Disorders						
Decreased appetite	27	1	0	12	<1	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	13	0	0	11	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	16	0	0	2	0	0
Pruritus	13	0	0	6	0	0
Rash	11	1	0	4	0	0
Nervous System Disorders						
Headache	20	1	0	15	<1	0
Dysgeusia	18	0	0	3	0	0
Dizziness	12	1	0	6	0	0
Investigations						
Alanine aminotransferase increased	13	4	<1	5	2	0
Aspartate aminotransferase increased	12	2	0	7	3	0
Creatinine increased	12	<1	0	<1	0	0
Weight decreased	10	<1	0	2	<1	0

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness.

[b] Includes upper respiratory tract infection, urinary tract infection, lung infection, pharyngitis, conjunctivitis, sinusitis, vaginal infection, sepsis.

[c] Includes neutropenia, neutrophil count decreased.

[d] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.

[e] Includes leukopenia, white blood cell count decreased.

[f] Includes platelet count decreased, thrombocytopenia.

[g] Includes asthenia, fatigue.

Additional adverse reactions in MONARCH 2 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior vena cava), which were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo.

Table 4: Laboratory Abnormalities ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

	VERZENIO plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Creatinine increased	98	1	0	74	0	0
White blood cell decreased	90	23	<1	33	<1	0
Neutrophil count decreased	87	29	4	30	4	<1
Anemia	84	3	0	33	<1	0
Lymphocyte count decreased	63	12	<1	32	2	0
Platelet count decreased	53	<1	1	15	0	0
Alanine aminotransferase increased	41	4	<1	32	1	0
Aspartate aminotransferase increased	37	4	0	25	4	<1

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. In clinical studies, increases in serum creatinine (mean increase, 0.2 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated glomerular filtration rate (GFR), which are not based on creatinine, may be considered to determine whether renal function is impaired.

VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)

Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting

Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in 132 women with measurable HR+, HER2- metastatic breast cancer. Patients received 200 mg VERZENIO orally twice daily until development of progressive disease or unmanageable toxicity. Median duration of treatment was 4.5 months.

Ten patients (8%) discontinued study treatment from adverse reactions due to (1 patient each) abdominal pain, arterial thrombosis, aspartate aminotransferase (AST) increased, blood creatinine increased, chronic kidney disease, diarrhea, ECG QT prolonged, fatigue, hip fracture, and lymphopenia. Forty-nine percent of patients had dose reductions due to an adverse reaction. The most frequent adverse reactions that led to dose reductions were diarrhea (20%), neutropenia (11%), and fatigue (9%).

Deaths due to adverse events during treatment or during the 30-day follow up were reported in 2% of patients. Cause of death in these patients was due to infection (2 patients) or pneumonitis (1 patient).

The most common reported adverse reactions (≥20%) were diarrhea, fatigue, nausea, decreased appetite, abdominal pain, neutropenia, vomiting, infections, anemia, headache, and thrombocytopenia (Table 5). Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib.

Table 5: Adverse Reactions (≥10% of Patients) in MONARCH 1

	VERZENIO N=132		
	All Grades %	**Grade 3 %**	**Grade 4 %**
Gastrointestinal Disorders			
Diarrhea	90	20	0
Nausea	64	5	0
Abdominal pain	39	2	0
Vomiting	35	2	0
Constipation	17	<1	0
Dry mouth	14	0	0
Stomatitis	14	0	0
Infections and Infestations			
Infections	31	5	2
General Disorders and Administration Site Conditions			
Fatigue[a]	65	13	0
Pyrexia	11	0	0
Blood and Lymphatic System Disorders			
Neutropenia[b]	37	19	5
Anemia[c]	25	5	0
Thrombocytopenia[d]	20	4	0
Leukopenia[e]	17	5	<1
Metabolism and Nutrition Disorders			
Decreased appetite	45	3	0
Dehydration	10	2	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	19	0	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	15	0	0
Nervous System Disorders			
Headache	20	0	0
Dysgeusia	12	0	0
Dizziness	11	0	0
Skin and Subcutaneous Tissue Disorders			
Alopecia	12	0	0
Investigations			
Creatinine increased	13	<1	0
Weight decreased	14	0	0

[a] Includes asthenia, fatigue.
[b] Includes neutropenia, neutrophil count decreased.
[c] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.
[d] Includes platelet count decreased, thrombocytopenia.
[e] Includes leukopenia, white blood cell count decreased.

Table 6: Laboratory Abnormalities for Patients Receiving VERZENIO in MONARCH 1

	VERZENIO N=132		
	All Grades %	**Grade 3 %**	**Grade 4 %**
Creatinine increased	98	<1	0
White blood cell decreased	91	28	0
Neutrophil count decreased	88	22	5
Anemia	68	0	0
Lymphocyte count decreased	42	13	<1
Platelet count decreased	41	2	0
ALT increased	31	3	0
AST increased	30	4	0

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. In clinical studies, increases in serum creatinine (mean increase, 0.3 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

DRUG INTERACTIONS

Effect of Other Drugs on VERZENIO

CYP3A Inhibitors

Strong and moderate CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.

Ketoconazole

Avoid concomitant use of ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold.

Other Strong CYP3A Inhibitors

In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the VERZENIO dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the VERZENIO dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking VERZENIO discontinues a strong CYP3A inhibitor, increase the VERZENIO dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. Patients should avoid grapefruit products.

Moderate CYP3A Inhibitors

With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the VERZENIO dose in 50 mg decrements, if necessary.

Strong and Moderate CYP3A Inducers

Coadministration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. In animal reproduction studies, administration of abemaciclib during organogenesis was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on AUC at the maximum recommended human dose (*see* Data). Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data

Animal Data

In an embryo-fetal development study, pregnant rats received oral doses of abemaciclib up to 15 mg/kg/day during the period of organogenesis. Doses ≥4 mg/kg/day caused decreased fetal body weights and increased incidence of cardiovascular and skeletal malformations and variations. These findings included absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sternebra, bipartite ossification of thoracic centrum, and rudimentary or nodulated ribs. At 4 mg/kg/day in rats, the maternal systemic exposures were approximately equal to the human exposure (AUC) at the recommended dose.

Lactation

Risk Summary

There are no data on the presence of abemaciclib in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed infants from VERZENIO, advise lactating women not to breastfeed during VERZENIO treatment and for at least 3 weeks after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, VERZENIO can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with VERZENIO.

Contraception

Females

VERZENIO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during VERZENIO treatment and for at least 3 weeks after the last dose.

Infertility

Males

Based on findings in animals, VERZENIO may impair fertility in males of reproductive potential.

Pediatric Use

The safety and effectiveness of VERZENIO have not been established in pediatric patients.

Geriatric Use

Of the 900 patients who received VERZENIO in MONARCH 1, MONARCH 2, and MONARCH 3, 38% were 65 years of age or older and 10% were 75 years of age or older. The most common adverse reactions (≥5%) Grade 3 or 4 in patients ≥65 years of age across MONARCH 1, 2, and 3 were neutropenia, diarrhea, fatigue, nausea, dehydration, leukopenia, anemia, infections, and ALT increased. No overall differences in safety or effectiveness of VERZENIO were observed between these patients and younger patients.

Renal Impairment

No dosage adjustment is required for patients with mild or moderate renal impairment (CLcr ≥30-89 mL/min, estimated by Cockcroft-Gault [C-G]). The pharmacokinetics of abemaciclib in patients with severe renal impairment (CLcr <30 mL/min, C-G), end stage renal disease, or in patients on dialysis is unknown.

Hepatic Impairment

No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B). Reduce the dosing frequency when administering VERZENIO to patients with severe hepatic impairment (Child-Pugh C).

OVERDOSAGE

There is no known antidote for VERZENIO. The treatment of overdose of VERZENIO should consist of general supportive measures.

Rx only.

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

Lilly

Eli Lilly and Company, Indianapolis, IN 46285, USA

AL HCP BS 19SEP2019

VERZENIO® (abemaciclib) tablets, for oral use AL HCP BS 19SEP2019

FROM THE CHAIRMAN

A Virtual Meeting Brings Practice-Changing Results

GOING IN, THE BIGGEST QUESTION about the 2020 Annual Meeting of the American Society of Clinical Oncology (ASCO), held May 29-31, 2020, was whether it would come off as planned. Yes, the coronavirus disease 2019 (COVID-19) had already forced many scientific and trade meetings to switch to online platforms, but ASCO would offer a different test. Could a meeting that brings 40,000 people each year to Chicago's McCormick Place—for the science, for the networking, for what's next—offer the same depth through a computer screen?

There were plenty of bumps. ASCO's technology was overwhelmed the first day, and miscues over whether session starts were listed in accordance with Central Daylight Time threw some participants off schedule. But once it got down to business, ASCO had important science and important lessons. If its major messages hold, future meetings will bring new challenges and opportunities:

ASCO HAS TALKED ABOUT DISPARITIES IN CANCER CARE FOR SOME TIME, BUT COVID-19 ADDS ANOTHER DIMENSION. The message that patient survival depends on whether the person has coverage or assistance in navigating the treatment process came through across many sessions. ASCO President Howard A. "Skip" Burris III, MD, summed this up when he said that better patient care will occur only in the setting of "access to care, access to clinical trials, and access to information."

COVID-19 WILL EXPOSE EXISTING DISPARITIES AND CREATE NEW ONES. Many Americans will lose access to health coverage, put off screenings, or find other reasons to ignore the signals that cancer is present—until their disease has progressed. Experts predict a flood of late-stage diagnoses by fall, and the National Cancer Institute Director Norman E. "Ned" Sharpless, MD, predicted that the decades-long progress in lowering cancer mortality will come to a halt.

GENETIC TESTING IS CENTRAL TO CANCER CARE—BUT ACCESS TO COUNSELING IS STILL A HURDLE. Almost all the major scientific announcements involved uses of a therapy to target cancers with specific mutations. Thus, genetic testing—and increasingly, next-generation sequencing—has never been more important. But the supply of counselors is still a problem, and even the advance of telehealth hasn't made counseling universal. Thus, the risk of overtreatment or inappropriate treatment remains.

THERAPIES FOR SOME HARD-TO-TREAT CANCERS ARE ARRIVING—OR ARE CLOSER THAN EVER. Results for AstraZeneca's osimertinib after surgery in some patients with non–small cell lung cancer are practice-changing, and early data from the AMG 510 clinical trial show that the ability to target *KRAS* seems within reach. Pembrolizumab broke more ground in colorectal cancer.

The challenges ahead are great. Sharpless and manufacturers report lower enrollment in clinical trials, and current studies will miss data collection points. The FDA will have to decide how to view evidence in these changed circumstances, as the need for therapy will increase. Although some value-based models are on hold, the need for a long-term move away from fee-for-service has never been more apparent.

Fortunately, we have seen plenty of innovation come from these difficult times, and we expect the rest of 2020 will bring even more. One thing we know: Next year, we hope to see you all in person. ◆

Sincerely,
Mike Hennessy, Sr
Chairman and Founder

EDITORIAL MISSION

To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in cancer care.

AJMC®
THE AMERICAN JOURNAL OF MANAGED CARE®

2 Clarke Drive, Suite 100
Cranbury, NJ 08512 • (609) 716-7777

The American Journal of Managed Care® ISSN 1088-0224 (print) & ISSN 1936-2692 (online) is published monthly by Managed Care & Healthcare Communications, LLC, 2 Clarke Drive, Suite 100, Cranbury, NJ 08512.

www.ajmc.com/about/ebo
EBOncology

SPECIAL ISSUE /ASCO Recap
JULY 2020
VOLUME 26, ISSUE 6

A session on genetic testing in cancer care highlighted evidence that testing is critical for selecting the right therapy, but bypassing genetic counseling isn't the best idea.

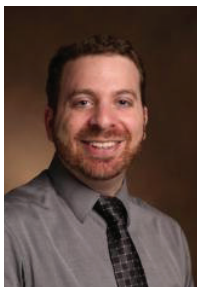
ADAURA trial results showcasing osimertinib after NSCLC surgery and CITYSCAPE, involving an anti-TIGIT antibody, highlight the rising number of treatments for lung cancer.

BLOOD SAMPLE PHOTO: DANIEL STONE / NCI / IN PUBLIC DOMAIN. LUNG CANCER © ERAXION / ISTOCK

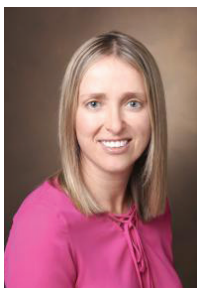
NCI's Sharpless: COVID-19 Could Halt Streak of US Cancer Mortality Gains

Mary Caffrey and Peter Wehrwein

SHARPLESS
Norman E. "Ned" Sharpless, MD, director, National Cancer Institute



WARNER
Jeremy L. Warner, MD, MS, associate professor of medicine, Vanderbilt University Medical Center



HORN
Leora Horn, MD, MSc, Ingram Associate Professor of Cancer Research; director, thoracic oncology, Vanderbilt University Medical Center

MONTHS OF DEFERRED SCREENINGS or delayed treatments due to coronavirus disease 2019 (COVID-19) could reverse the US streak in improved cancer mortality that has lasted more than 25 years, said Norman E. "Ned" Sharpless, MD, director of the National Cancer Institute (NCI), during the American Society of Clinical Oncology (ASCO) 2020 Annual Meeting, presented in a virtual format due to the pandemic.

Sharpless, who served briefly as acting FDA commissioner in 2019, opened the virtual session on "Cancer and COVID-19" with a sober assessment of COVID-19's effects on both clinical care and cancer research.

His talk preceded presentations on some of the earliest findings about the effects of COVID-19 on cancer: It appears that patients treated with chemotherapy for lung or thoracic cancer shortly before being diagnosed with COVID-19 face a higher risk of death, and so do patients with cancer who take the combination of hydroxychloroquine (HCQ) and azithromycin.

> **"We need to know as much about the impact of COVID-19 on cancer patients in Montana as we do about those in New York."**
>
> —Norman E. "Ned" Sharpless, MD, director, National Cancer Institute

The separate data sets help shape an emerging picture of what patients with cancer face under COVID-19: They are more likely to be older or have underlying health problems, which are known to make the virus more deadly.

And, as explained by Jeremy L. Warner, MD, MS, an associate professor of medicine at Vanderbilt University Medical Center, patients may be immunosuppressed, from the treatment or the disease itself, and have more frequent contact with the health care system than people without cancer.

Deferred Care Will Come at a Price

The decision to preserve hospital and clinical capacity was "necessary and important" as COVID-19 peaked this spring, Sharpless said, "But all this deferred care—it's going to have costs for patients with cancer," he noted. "It may mean more cancer suffering outcomes for our patients. What we don't know yet is the scale of these bad outcomes."

Each year, Sharpless said, NCI works with the American Cancer Society and others to publish an annual report on the state of cancer, and the declining mortality rates have become an annual "shot in the arm" for cancer researchers. "My fear is that diminished cancer care will produce a negative impact on these cancer statistics of relevance to the public health. And we expect to see these trends play out over several years," he said. "We cannot escape this reality."

Research is taking a hit, too, as patient accruals in NCI trials have fallen off pace, and Sharpless said he had heard similar reports about industry-sponsored trials. What has filled the gap somewhat, he said, are aggressive efforts to start trials to understand COVID-19's effect on patients with cancer. He highlighted 2 groups presenting results during the ASCO meeting, as well as registries set up by ASCO and the American Society of Hematology.

On May 21, 2020, NCI launched the COVID-19 in Cancer Patients Study[1] that will enroll 2000 patients with cancer who are diagnosed with COVID-19. "We aim to conduct the study at more than 1000 sites," Sharpless said. "We need to know as much about the impact of COVID-19 on cancer patients in Montana as we do about those in New York."

He asked, rhetorically, "What have you learned about the impact of the virus on patients across racial and ethnic groups?"

Sharpless pointed out that the NCI effort "is not a registry" but a trial approved by an institutional review board; investigators will seek patient consent to collect samples, analyze biomarkers, and develop germline sequencing of patients.

Patients who participate will be required to have regular health care visits, during which the facility will collect blood samples and copies of routine imaging scans for up to 2 years. "It's important to note that participation in this study will not require additional visits to the hospital or other facilities," Sharpless said. "Much of the data will be collected electronically and some of the tests will be part of the patient's routine care."

Results From TERAVOLT

Prior smoking history or lung damage are among the characteristics that put patients with thoracic cancer at particular risk from COVID-19, according to insights gleaned from 400 patients' records in the Thoracic cancERs international coVid 19 cOLlaboraTion (TERAVOLT) registry.[2] Thoracic cancers include lung tumors, mesothelioma, carcinoid tumors, and thymic neoplasms.

According to the researchers, use of chemotherapy within 3 months of a COVID-19 diagnosis turned out to have a particularly strong association with early death: a 64% increased risk of dying from the virus. The effect of chemotherapy was seen whether or not patients also had other therapies, such as immunotherapy, which showed up as a potential risk factor in an earlier study.[3]

Of the 400 patients, 144 died: 79.4% (n = 112) from COVID-19, 10.6% (n = 15) from cancer, and the rest from other causes. Treatments with anticoagulants and corticosteroids were also linked to increased death risk, adding to existing concerns about the use of corticosteroids for patients with chronic disease. More data will be needed to draw any firm conclusions about the use of anticoagulants.

Lead author Leora Horn, MD, MSc, commented on the speed with which the research effort has taken shape. "In less than a week, we had a study enrolling patients," said Horn, who is the Ingram Associate Professor of Cancer Research and the director of the thoracic oncology program at Vanderbilt University Medical Center. "We have seen clinical trials being funded, approved, and enrolling patients within weeks, when it can often take months or years to get approval for a trial."

Cancer and the Cocktail

Cancer patients with COVID-19 who were treated with both HCQ and azithromycin were 3 times more likely to die during the 30 days after they were diagnosed with COVID-19, according to

findings[4] presented by Warner, lead author of the study from the COVID-19 and Cancer Consortium, which launched its registry March 15.

Warner cautioned that the association is of "uncertain validity" and may stem from residual confounding. "For example," he said, "patients receiving this combination were more likely to have severe disease or more likely to be hospitalized."

The researchers also reported that neither drug was associated with an added mortality risk when taken alone.

After some statistical adjustments, the researchers found that patients with worsening cancer were 5 times more likely to have died within 30 days of their COVID-19 diagnosis than patients in remission or with no evidence of disease.

Of the 928 people with cancer and COVID-19 who were included in the study, 121 (13%) died within 30 days of their COVID-19 diagnosis, according to findings that Warner presented. The written abstract, submitted earlier to meet ASCO deadlines, had slightly different numbers: 1108 cases and 106 deaths, or 10.4% of the total cases.

In their analysis of the cases and deaths, the researchers found that factors associated with a 30-day mortality risk including worsening, progressing, or active cancer; older age; male sex; and being a former smoker.

Only 3 of the 121 deaths that Warner discussed in his video presentation were of people with no comorbidities. Of the 466 who were hospitalized, 106 died. ◆

REFERENCES

1. NCI COVID-19 in Cancer Patients Study (NCCAPS). National Cancer Institute. May 21, 2020. Accessed May 30, 2020. https://www.cancer.gov/research/key-initiatives/covid-19/coronavirus-research-initiatives/nccaps
2. Horn L, Whisenant JG, Torri V, et al. Thoracic Cancers International COVID-19 Collaboration (TERAVOLT): impact of type of cancer therapy and COVID therapy on survival. *J Clin Oncol.* 2020;38(18 suppl; abstr LBA111). doi:10.1200/JCO.2020.38.18_suppl.LBA111
3. Dai M, Liu D, Liu M, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. *Cancer Discov.* 2020;10(6):783-791. doi:10.1158/2159-8290.CD-20-0422
4. Warner JL, Rubinstein S, Grivas P, et al. Clinical impact of COVID-19 on patients with cancer: data from the COVID-19 and Cancer Consortium (CCC19). *J Clin Oncol.* 2020;38(18 suppl; abstr LBA110). doi:10.1200/JCO.2020.38.18_suppl.LBA110

Burris: United With Our Patients, We Accelerate Progress Together

Maggie L. Shaw

VIRTUAL FOR THE FIRST TIME EVER, the annual meeting of the American Society of Clinical Oncology (ASCO) kicked off its sessions with an address from outgoing president Howard A. "Skip" Burris III, MD, who will next assume the position of chair of ASCO's Board of Directors.

"Our patients are the reasons we do what we do. They are the reason we do the work. It's been a joy for me to have such a diverse job," said Burris, who is also president of clinical operations, chief medical officer, and executive director of drug development at Sarah Cannon Research Institute. Additionally, he is a member of the board of directors of Conquer Cancer: The ASCO Foundation.

Burris, a 1981 graduate of the United States Military Academy at West Point who served with the Army Corps of Engineers, chose the 2-pronged theme for his year-long presidential term to be "Unite and Conquer: Accelerating Progress Together."

"Uniting and conquering" and "accelerating progress" are goals that can be addressed, and accomplished, through a multidisciplinary team approach to cancer care, believes Burris. He views this approach as essential to every patient's spectrum of care, with the patient squarely at the center. The approach pairs well with the ASCO mission, which is conquering cancer through the latest research and education, as well as promoting the importance of quality patient care. Burris returned to the mission time and again, sharing highlights from the past year while noting how far the field of oncology still has to go to improve the quality of cancer care through education, research, and advocacy—principles that underlie ASCO's mission.

"We've had advancements, but we need to go faster," Burris pointed out, stressing the importance of advancing therapies for better patient outcomes by addressing obstacles to patients' care. "Access to care, access to clinical trials, and access to information are really key."

Burris highlighted ASCO CancerLinQ, an initiative that is aggregating big data from clinicians across the country, analyzing the findings. The entire cancer community will have access to CancerLinQ. Burris also described ASCO's push to transform care delivery, and in doing so he broached an issue that continues to trouble many: patients' inability to access care because of financial reasons. ASCO is helping to address this barrier to health care through its Patient-Centered Oncology Payment Program, an alternative payment model meant to ensure access to high-quality and high-value care.

Last fall, Burris noted, ASCO volunteers held more than 160 meetings, advocating to Congress on behalf of the Bipartisan Clinical Treatment Act, which would require Medicaid to cover the routine costs that come with being in a clinical trial, including doctor visits and lab studies. The act is meant to open up access of patients, especially underrepresented minorities, to potential treatment advances. It would be a victory for ASCO and for patients with cancer, Burris stressed.

Burris noted how his 30-plus years as a clinical researcher, clinical oncologist, leader of people—there are more than 1000 now at Sarah Cannon—military experience, and dual passions of cancer drug development and phase 1 clinical trials have opened his eyes to so much high-quality work that is going on both in the United States and around the world. It's given him a great sense of faith and confidence in the future of the field to see so many people pulling together to try to improve cancer care.

"We are strongest together. We are united in our mission to reduce the global burden of cancer," Burris said. "We need all of you serving on our committees and task forces, connecting and collaborating, to solve the complex problems of cancer care. Together we are a powerhouse." ◆

BURRIS

ASCO President Howard A. "Skip" Burris III, MD, is the chief medical officer and executive director, drug development, Sarah Cannon Research Institute

Pembrolizumab as First-Line Treatment Doubles PFS in Certain Patients With Colorectal Cancer

Mary Caffrey

ANDRÉ
Thierry André, MD, professor of medical oncology, Sorbonne Université and Hôpital Saint Antoine, Paris

OVERMAN
Michael Overman, MD, professor, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center

USING BIOMARKERS TO CONNECT the right patients with the right treatment at the right time is the mantra for deciding when to use immunotherapy in cancer care. Results presented virtually at the American Society of Clinical Oncology (ASCO) 2020 Annual Meeting proved that point for certain patients with metastatic colorectal cancer (mCRC).

The interim analysis of the phase 3 KEYNOTE-177 trial, presented during ASCO's plenary session on May 31, showed that using pembrolizumab as a first-line therapy in mCRC patients with specific genetic mutations—microsatellite instability high/mismatch repair deficient (MSI-H/dMMR) tumors—doubled progression-free survival (PFS) compared with chemotherapy (16.5 vs 8.2 months).[1]

FDA approval for pembrolizumab in this setting came less than a month later, on June 29, 2020, as *Evidence-Based Oncology*™ went to press.[2]

"These results should change clinical practice....It is critical that we test all colorectal cancer patients for mismatch repair or microsatellite status."

—Michael Overman, MD,
professor, Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center

Lead study author Thierry André, MD, professor of medical oncology, the Sorbonne Université and Hôpital Saint Antoine in Paris, said during the plenary session that the results would change clinical practice. "No medical treatment has shown such an improvement," he noted.

"Pembrolizumab works in nonrandomized studies in this group of patients with advanced disease," André said. "This randomized study demonstrates a huge benefit in first-line [treatment] with pembrolizumab and should be the new standard of care."

Michael Overman, MD, of the University of Texas MD Anderson Cancer Center, a discussant for KEYNOTE-177, agreed. "These results should change clinical practice," he said, noting that the type of tumors being treated in the study are particularly good candidates for immunotherapy. Going forward, Overman said, "It is critical that we test all colorectal cancer patients for mismatch repair or microsatellite status."

The only caveat, Overman explained, might involve patients for whom near-term survival is the highest priority, because results show that the benefit of immunotherapy over chemotherapy does not start to appear until about the 6-month mark.

About 5% of mCRC patients' tumors are MSI-H/dMMR, and these patients do not fare as well with conventional chemotherapy. Pembrolizumab's effectiveness when this mutation is present is well recognized, and it led to FDA's first tissue-agnostic approval in 2017.[3]

"These data represent another step forward for biomarker-driven studies," André said.

The data cutoff for the interim analysis was February 19, 2020; at that time, the study included 307 mCRC patients with MSI-H/dMMR. Patients were randomized to receive first-line pembrolizumab for up to 2 years, or the investigator's choice of 6 different standard chemotherapy regimens. Primary end points were PFS and overall survival (OS), while secondary end points included objective response rate (ORR) and safety.

An independent data monitoring committee had previously found statistically significant and clinically meaningful improvement, and it called for the trial to continue without changes to the second co-primary end point of OS.[4]

Patients in the chemotherapy group who progressed were allowed to cross over into the pembrolizumab group.

Results

At 12 months, PFS was 55.3% with pembrolizumab vs 37.3% with chemotherapy; at 24 months, PFS was 48.3% with pembrolizumab vs 18.6% with chemotherapy.

The ORR, a measure of how much patients' tumors shrank, was also better for the patients treated with pembrolizumab: 43.8% compared with 33.1% for chemotherapy. The data also show:

- 11% of the pembrolizumab patients had a complete response, meaning no detectable cancer, compared with 3.9% treated with chemotherapy
- 32.7% of the pembrolizumab patients had a partial response, compared with 29.2% in the chemotherapy group
- 30.9% taking pembrolizumab had stable disease, compared with 42.2% in the chemotherapy group.
- 83% in the pembrolizumab group had responses lasting longer than 2 years, compared with 35% in the chemotherapy group.

Adverse Events

Severe events, grade 3 or above, were less common among patients in the pembrolizumab group: 22%, compared with 66% in the chemotherapy group. The most common toxicities in the immunotherapy group were colitis and hepatitis, while the most frequent chemotherapy-related toxicities were diarrhea, neutropenia, fatigue, nausea, stomatitis, alopecia, and neurotoxicity. ◆

Merck funded the study.

REFERENCES

1. André T, Shiu K-K, Kim TW, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer: the phase 3, KEYNOTE-177 study. *J Clin Oncol.* 2020;38(18 suppl; abstr LBA4). doi:10.1200/JCO.2020.38.18_suppl.LBA4
2. Caffrey M. Pembrolizumab approved for first-line treatment of patients with colorectal cance and key mutations. *The American Journal of Managed Care*® website. www.ajmc.com/newsroom/pembrolizumab-approved-for-firstline-treatment-of-patients-with-colorectal-cancer-and-key-mutations. Published and accessed June 29, 2020.
3. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. FDA. May 23, 2017. Updated May 30, 2017. Accessed June 6, 2020. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pembrolizumab-first-tissuesite-agnostic-indication
4. Merck announces KEYTRUDA (pembrolizumab) significantly improved progression-free survival as first-line treatment for advanced microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer. News release. Merck; April 2, 2020. Accessed June 6, 2020. https://investors.merck.com/news/press-release-details/2020/Merck-Announces-KEYTRUDA-pembrolizumab-Significantly-Improved-Progression-Free-Survival-as-First-Line-Treatment-for-Advanced-Microsatellite-Instability-High-MSI-H-or-Mismatch-Repair-Deficient-dMMR-Colorectal-Cancer/default.aspx

Osimertinib After NSCLC Surgery Keeps Cancer at Bay for Patients With Key Mutation

Mary Caffrey

OSIMERTINIB, ALREADY THE FIRST CHOICE to treat patients with advanced *EGFR*-mutated non–small cell lung cancer (NSCLC), should become the treatment of choice for patients with this mutation who are treated after surgery for early-stage, localized disease, according to the lead investigator who outlined results virtually at the American Society of Clinical Oncology Annual Meeting.[1]

A remarkable 90% of the patients with stage II or stage IIIA NSCLC who received the targeted therapy osimertinib after surgery were alive after 2 years without cancer recurring, compared with 44% of those patients who received placebo, according to findings presented during the May 31, 2020, plenary session. In patients at these stages, the risk of death or recurrence was reduced by 83%. Median disease-free survival (DFS) for osimertinib was not reached (NR) while for placebo, it was 20.4 months (HR, 0.17; 95% CI, 0.12-0.23; $P < .0001$).

The full study, called ADAURA, was unblinded in April after the overwhelming efficacy became evident.[2] AstraZeneca, maker of osimertinib (Tagrisso), a third-generation *EGFR* tyrosine kinase inhibitor, sponsored the study.

Roy S. Herbst, MD, PhD, the lead study author and chief of medical oncology at Yale Cancer Center and Smilow Cancer Hospital, called the trial a "home run" and said the results clearly pointed to giving osimertinib to patients earlier in course of treatment.

"Collectively, these data support the use of osimertinib as an appropriate treatment in the long-term adjuvant setting," Herbst said, with safety and tolerability being important considerations. "Looking ahead, future considerations for ADAURA include investigation of local versus distant recurrence; sites of disease recurrence, including incidence of [central nervous system] metastases; subsequent therapy; and quality of life."

Among the overall study population, which covered 682 patients with disease ranging from stage IB to IIIA, treatment with osimertinib reduced the risk of death or recurrence by 79% compared with placebo. Overall, DFS at the 2-year mark was 89% with osimertinib vs 53% for placebo.

Of note, Herbst pointed to data showing that patients who had adjuvant chemotherapy alongside osimertinib fared about the same as those who did not. Among patients who received chemotherapy, the median DFS for osimertinib was NR, compared with 22.1 months for those on placebo (HR, 0.18; 95% CI, 0.11-0.29). Among those without chemotherapy, median DFS for osimertinib was NR, compared with 33.1 months for placebo (HR, 0.23; 95% CI, 0.13-0.38).

Data for overall survival are not yet mature, and both Herbst and a discussant, David Spigel, MD, chief scientific officer of the Sarah Cannon Research Institute, acknowledged that this might be challenging to evaluate going forward, now that the trial has been unblinded.

Other questions remain, including what happens after 3 years, when patients would be scheduled to stop taking the daily 80-mg tablets. Still, Spigel said if asked the question he hears in the clinic—which treatment would he give a family member?—he would choose osimertinib.

The results have important implications for managed care. Currently, patients with stage IB to stage III NSCLC who have surgery to remove the tumor typically have chemotherapy, but Herbst said rates of recurrence are high: Cancer returns in about half of patients with stage IB disease, and rates are higher at later stages.

In addition, the ability to more effectively treat patients with early-stage *EGFR*-mutated NSCLC tumors raises new questions about the need to screen more patients for lung cancer—and catch more cancers at earlier stages.

Spigel said it is unclear at this point whether osimertinib is eliminating disease or "simply controlling and deferring disease that cannot be eradicated." But the safety and tolerability of the targeted therapy are important, given a planned 3-year treatment course. And, he said, the results were consistent across subgroups.

Paradigm Shift?

Adrian Kilcoyne, MD, MBA, MPH, AstraZeneca's vice president for US Medical Affairs and Health Economics Outcomes Research in Oncology, said the results should be paradigm shifting.

"What we've been able to demonstrate is compelling," Kilcoyne said. Any time a study is stopped early the results are important, but ADAURA "is important in a number of ways."

"One, it's telling us that if you hit [the disease] early, you can have very compelling results in lung cancer," Kilcoyne said. "Second, in some of these patients, while they all had surgery, not all of them had adjuvant chemotherapy—half didn't—and regardless of that, you're seeing a significant benefit.

"It may drive people to want to identify disease earlier, which is really important, too."

When asked if the results might reopen discussion about current US Preventive Services Task Force guidelines on who should be screened for lung cancer,[3] Kilcoyne said, "You've asked the million dollar question."

Current guidelines are based on a mix of factors that include a person's age, smoking history, and how long ago they quit smoking. Some study results suggest that the guidelines do not cast a wide enough net, but a CDC study found earlier this year that even under the current standards, very few people eligible for screening are tested.

"We're at a point where we just can't just focus on smoking," Kilcoyne expressed. "I think we should look at screening in a far more broad way. It's not just screening patients who would have been smoking, how many pack years, age, etc.…How we screen is going to be incredibly important. We need to embrace newer technology" that takes a personalized medicine approach.[4] ◆

HERBST

Roy S. Herbst, MD, PhD, chief of medical oncology, Yale Cancer Center and Smilow Cancer Hospital

SPIGEL

David Spigel, MD, chief scientific officer, Sarah Cannon Research Institute

KILCOYNE

Adrian Kilcoyne, MD, MBA, MPH, vice president, US Medical Affairs and Health Economics Outcomes Research for Oncology, AstraZeneca

REFERENCES

1. Herbst RS, Tsuboi M, John T, et al. Osimertinib as adjuvant therapy in patients (pts) with stage IB-IIIA EGFR mutation positive (EGFRm) NSCLC after complete tumor resection: ADAURA. *J Clin Oncol*. 2020;38(18 suppl; abstr LBA5). doi:10.1200/JCO.2020.38.18_suppl.LBA5
2. Tagrisso phase III ADAURA trial will be unblinded early after overwhelming efficacy in the adjuvant treatment of patients with *EGFR*-mutated lung cancer. News release. AstraZeneca; April 10, 2020. Accessed June 6, 2020. https://www.astrazeneca.com/media-centre/press-releases/2020/tagrisso-phase-iii-adaura-trial-will-be-unblinded-early-after-overwhelming-efficacy-in-the-adjuvant-treatment-of-patients-with-egfr-mutated-lung-cancer.html
3. Richards TB, Soman A, Thomas CC, et al. Screening for lung cancer—10 states, 2017. *MMWR Morb Mortal Wkly Rep*. 2020;69(8):201-206. doi:10.15585/mmwr.mm6908a1
4. Francis Crick Institute. New lung cancer trial will use personalized monitoring to help predict relapse. Technology Networks. May 26, 2020. Accessed June 6, 2020. https://www.technologynetworks.com/tn/news/new-lung-cancer-trial-will-use-personalized-monitoring-to-help-predict-relapse-335275

Zanubrutinib Pulls Away From Ibrutinib in Update, Shows Durable Responses in WM Patients Lacking Key Mutation

Mary Caffrey

TAM

Constantine Tam, MD, MBBS, clinical hematologist and professor, Peter McCallum Cancer Centre; Victoria, Australia

ZANUBRUTINIB, THE BRUTON TYROSINE KINASE (BTK) inhibitor approved by the FDA to treat mantle cell lymphoma, showed a clear advantage over its competitor in new data presented virtually on May 29, 2020, during the American Society of Clinical Oncology (ASCO) 2020 Annual Meeting.

The BTK inhibitor also produced meaningful and durable responses in certain patients with Waldenström macroglobulinemia (WM), even though they lacked a key mutation that has signaled successful treatment, according to updated results of the ASPEN trial.[1]

MYD88 mutations are present in 95% of patients with WM, a rare form of lymphoma, and BTK inhibitors have been effective in treating WM patients who have them. Prior research showed poorer response rates and shorter progression-free survival (PFS) among those who lack the mutations. Complicating matters is the fact that diagnosing mutations in WM can be tricky.

In an interview, lead investigator Constantine Tam, MBBS, MD, said while ASPEN did not initially meet its end point, after an extra 5 months of data collection, the difference between zanubrutinib and ibrutinib became more evident. "This is important," Tam said. "The longer you take the drug, the better your responses become."

Results from ASPEN released in December 2019, and updated at ASCO,[2] compared zanubrutinib with ibrutinib in WM patients with the *MYD88* mutation. Early reactions were mixed. Some analysts noted that the ASPEN trial missed the goal of doubling ibrutinib's rate of complete or very good partial responses, but others pointed to the fact that data showed zanubrutinib numerically outperformed ibrutinib, with 28.9% of relapsed or refractory patients achieving this mark, compared with 19.8% for ibrutinib. Results for all patients, including those starting treatment, were comparable—28.4% vs 19.2%.

In an interview, lead investigator Constantine Tam, MBBS, MD, a clinical hematologist and professor at the Peter MacCallum Cancer Centre in Victoria, Australia, noted there were "some imbalances" in the randomization; more patients in the zanubrutinib arm were older than 75 years and more were anemic.

Updated Data at ASCO

ASPEN did more follow-up in January, accruing another 5 months of data. "This is important," Tam said during the interview. "The longer you take the drug, the better your responses become." So, while the study technically did not meet its end point, Tam said the lines separating zanubrutinib and ibrutinib have diverged since the first results were announced. Data presented online May 29, 2020, showed the following[3]:

- Complete response plus very good partial response as assessed by investigators for zanubrutinib was 30.4% compared with 18.2% for ibrutinib (exploratory analysis; 2-sided descriptive $P = .0302$).
- Adverse events (AEs): Compared with ibrutinib, zanubrutinib had less atrial fibrillation/flutter of any grade (3.0% vs 18.4%), bleeding of any grade (50.5% vs 60.2%), major hemorrhage (5.9% vs 10.2%), diarrhea (21.8% vs 32.7%), and hypertension (12.9% vs 20.4%). Patients taking zanubrutinib did have more neutropenia (31.7% vs 15.3%).
- Rates of grade ≥3 neutropenia were higher in the zanubrutinib arm (22.8% vs 8.2% for ibrutinib); however, rates of infection were comparable among patients in both arms (any grade: 69.3% vs 71.4%; grade ≥3: 18.8% vs 23.5%).
- No additional patients stopped treatment due to AEs in the zanubrutinib arm, compared with 5 patients in the ibrutinib arm (4.0% vs 14.3%). Neither arm had additional patients with an AE leading to death (1.0% vs 4.1%).

Data From Patients Without Key Mutation

The data presented in December did not include patients without *MYD88* mutations. At enrollment in ASPEN, patients were assigned to cohorts based on mutation status. Data presented at ASCO covered 28 patients, including 26 who were WM with *MYD88* wild type, enrolled in the cohort for patients lacking the mutation. Their median age was 72 years; 5 were not previously treated and 23 were relapsed/refractory. With a median follow-up of 17.9 months, results were the following:

- Two patients stopped treatment due to adverse events.
- Six patients experienced disease progression.
- The overall response rate (ORR) was 80.8%.
- The ORR featured a major response rate of 50.0%, including a very good partial response rate of 26.9%.
- PFS event-free rate at 12 months was 72.4%.
- Common AEs were diarrhea, anemia, contusion, pyrexia, and upper respiratory tract infection.

Importance of Safety Data

The early ASPEN results showed that zanubrutinib produced fewer serious AEs and fewer AEs that led to discontinuation. Patients taking zanubrutinib were also significantly less likely to experience atrial fibrillation (2.0% vs 15.3%), hypertension (10.9% vs 17.3%), or major bleeding (5.9% vs 9.2%). Those taking zanubrutinib did experience more neutropenia (29.7% vs 13.3%).

But overall, do the results point to zanubrutinib for certain groups of patients with WM?

"At the moment, there aren't a whole lot of data about which patients get these other vascular [AEs]," Tam said. ASPEN did not set out to study examine which drug was better for patients who have hypertension or related risk factors, and Tam noted the event rates were fairly low.

However, Tam said, "One may come away from the study and say, 'Well, those patients who potentially have a history of hypertension or have a history of atrial fibrillation—or have an abnormal electrocardiogram or abnormal echocardiogram—maybe they're the ones who would be better off on [zanubrutinib] compared with ibrutinib.'"

When asked if this second-generation BTK inhibitor would produce fewer cardiac AEs, Tam said, "We think it's [related to] how clean the targeting is." The updated data presented at ASCO showed even greater differences between the 2 drugs in toxicity and atrial fibrillation, he said.

"It is nice to have a drug that is fairly clean," Tam said. Zanubrutinib does have to be taken twice a day, but there is no fasting requirement. "From [an AE] profile, it's worth it," he said.

Zanubrutinib, sold in the United States as Brukinsa by BeiGene, last year received the first FDA approval from data gathered mostly in China. ◆

REFERENCES

1. Garcia-Sanz R, Dimopoulos MA, Lee H-P, et al. Updated results of the ASPEN trial from a cohort of patients with *MYD88* wild-type (*MYD88*^{WT}) Waldenström macroglobulinemia (WM). *J Clin Oncol.* 2020;38(15 suppl; abstr e20056). doi:10.1200/JCO.2020.38.15_suppl.e20056
2. Tam CSL, Opat S, D'Sa S, et al. ASPEN: results of a phase III randomized trial of zanubrutinib versus ibrutinib for patients with Waldenström macroglobulinemia (WM). *J Clin Oncol.* 2020;38(15 suppl; abstr 8007). doi:10.1200/JCO.2020.38.15_suppl.8007
3. BeiGene presents updated head to head results from phase 3 trial of zanubrutinib vs. ibrutinib in patients with Waldenström's macroglobulinemia at the 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program. News release. BeiGene; May 29, 2020. Accessed May 29, 2020. http://ir.beigene.com/news-releases/news-release-details/beigene-presents-updated-head-head-results-phase-3-trial?loc=US

Taking Aim at TIGIT: A New Immunotherapy Approach to Non–Small Cell Lung Cancer

Maggie L. Shaw and Mary Caffrey

THE 2020 ANNUAL MEETING of the American Society of Clinical Oncology (ASCO) featured the first results from CITYSCAPE, a trial involving a novel immunotherapy approach in non–small cell lung cancer. This phase 2 trial is the first to combine the immunotherapy tiragolumab with atezolizumab (Tecentriq), the monoclonal antibody that targets PD-L1.

Tiragolumab offers a brand-new way to fight cancer: It binds to TIGIT, an immune checkpoint protein present on some T cells and also some natural killer cells. Like the better-known protein PD-L1, TIGIT plays a role in immune suppression, and blocking both the PD-L1 and TIGIT pathways at once could create a powerful tumor-fighting regimen:

- Results after 6 months of follow-up presented at ASCO show that the combination met both co-primary end points among patients with high levels of PD-L1. In an exploratory analysis among 135 randomized patients with tumor proportion score ≥50%, those taking the combination (n = 67) compared with those taking atezolizumab alone (n = 68) showed clinically meaningful improvement in objective response rate (ORR), 66% vs 24%, respectively, as well as a 70% reduction in the risk of disease worsening or death after 6 months.
- Median progression-free survival (PFS) for those taking the combination was not reached vs 4.1 months for patients taking atezolizumab alone (HR, 0.30; 95% CI, 0.15-0.61).
- After an additional 6 months of follow-up since the primary analysis, improvement in ORR and median PFS was maintained in the intent-to-treat population taking the combination.
- In the intent-to-treat population, the improvement in ORR was 37% for the combination compared with 21% for atezolizumab alone, and median PFS was 5.6 months vs 3.9 months, respectively (HR, 0.58; 95% CI, 0.38-0.89).
- The updated results showed no new or delayed safety events; grade 3 or above treatment-related adverse events (AEs) occurred in 14.9% of those taking the combination, compared with 19.1% of those taking atezolizumab alone. AEs of grade 3 or above for any cause were 48% for the combination and 44% for atezolizumab alone.

In a statement emailed to *Evidence-Based Oncology*™, a Genentech spokesperson said its scientists discovered TIGIT while researching innovative approaches to harnessing a patient's immune system to fight cancer. "Tiragolumab is our novel cancer immunotherapy designed to bind to TIGIT," the statement said. "Although TIGIT is expressed on immune cells in multiple tumor types, it is highly expressed in lung cancer."

CITYSCAPE coauthor Melissa L. Johnson, MD, associate director for lung cancer research at the Sarah Cannon Research Institute and a partner at Tennessee Oncology, explained that TIGIT works similarly to PD-L1, in that it can blunt the immune response. "So, in a similar way to how blocking PD-1 or PD-L1 works, when you block TIGIT with the anti-TIGIT antibody," she said, "you can restore the antitumor response and activate the inflammatory cells to fight the cancer."

JOHNSON

Melissa L. Johnson, MD, associate director for lung cancer research, Sarah Cannon Research Institute

"In the past, we have done hotspot panels or isolated analyte testing for single mutations. We know that not only is NGS testing better, but it's more effective and more likely to identify rare mutations and single alterations. It's also more cost-effective to do it that way, as opposed to piecemeal testing, 1 mutation at a time. It has led to many, many different therapy options for our patients that we otherwise wouldn't know about."

—Melissa L. Johnson, MD,
associate director for lung cancer research,
Sarah Cannon Research Institute

The new combination "may be useful for patients and doctors who are looking for a chemotherapy-free option," Johnson said. There is work directed toward exploring TIGIT as a second biomarker, but "right now, it appears to be expressed in many of the same cells as PD-L1."

According to the statement from Genentech, "Both TIGIT and PD-L1 play an important role in immune suppression, and by blocking both pathways simultaneously we hope to deepen patient responses to immunotherapy and broaden the number of people who may benefit. »

"Identifying the right treatment for the right patient is very important, especially as each person's cancer is different. We're investigating the predictive and prognostic value of PD-L1 as a biomarker for tiragolumab, as well the potential roles of TIGIT and poliovirus receptor, in clinical trials. We will look for further insights as part of our late-stage program."

Johnson said the heart of her research involves the hunt for new compounds that can help patients who have developed resistance "to the standard FDA-approved agents."

Johnson discussed the findings within the context of the advances in lung cancer since her arrival at Sarah Cannon in 2014. "Thinking back over the last 5 years, I think some of the biggest gains in lung cancer research include the recognition of the importance of our immune system for the care of patients with lung cancer," she said. "Now all patients with lung cancer will receive immunotherapy as part of their first line of treatment in the metastatic setting, and that wasn't happening 5 years ago."

Physicians—and patients—now have multiple options for PD-1 and PD-L1 inhibitors, not just from a single company but several, Johnson added. "We have learned so much because of the cumulative knowledge and wisdom gained across all those trials," she said.

The second major advance, Johnson described, has been the recognition of the importance of molecular profiling, in the form of next-generation sequencing (NGS). Ideally, she said, this occurs in the first-line setting before treatment is given. "In the past, we have done hotspot panels or isolated analyte testing for single mutations. We know that not only is NGS testing better, but it's more effective and more likely to identify rare mutations and unique alterations. It's also more cost-effective to do it that way, as opposed to piecemeal testing, 1 mutation at a time. It has led to many, many different therapy options for our patients that we wouldn't otherwise know about."

A third major advance is the way clinical trials are conducted. "Five years ago, we were still trying to compare each new therapy with platinum-based chemotherapy for lung cancer patients," Johnson explained. "We now know that if you can design trials with selection for particular mutations up front, and you can show a benefit north of 50% in terms of response rates, then you have an active drug."

The ability to combine data sets from many small subsets of patients, across lung and other tumor types, has allowed not only for advances that lead to new drug approvals, pointed out Johnson, but advances "in the way that we take care of patients." ◆

REFERENCE

Rodriguez-Abreu D, Johnson ML, Hussein MA, et al. Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first-line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE). *J Clin Oncol.* 2020;38(15 suppl; abstr 9503). doi:10.1200/JCO.2020.38.15_suppl.9503

MURANO Shows Worse Outcomes in R/R CLL When Venetoclax Is Stopped Early

Mary Caffrey

WHEN THE FIRST RESULTS from MURANO were published in the *New England Journal of Medicine* in 2018,[1] they showed that the combination of venetoclax (Venclexta) with rituximab produced superior progression-free survival (PFS) in patients with relapsed or refractory chronic lymphocytic leukemia, compared with bendamustine/rituximab, if patients took venetoclax for 2 years.

Unfortunately, a significant number of the patients who begin taking venetoclax interrupt their treatment course or stop it completely. A fresh look at the MURANO data, released May 29 at the American Society of Clinical Oncology (ASCO) 2020 Annual Meeting,[2] shows the poor outcomes that result when patients halt treatment for good. The data highlight the need to manage doses carefully to avoid toxicity.

MURANO data on discontinuation of venetoclax, featured in a poster released on May 29, 2020, were part of a Virtual ASCO 2020 highlights session on hematologic malignancies.

Venetoclax, taken by mouth, inhibits BCL-2, a key protein that regulates cell death. The protein is overexpressed in several blood cancers and can make them resistant to chemotherapy.

The poster's data show that among the 194 patients in the venetoclax–rituximab arm of MURANO through May 8, 2019, 54 patients, or 28%, stopped the drug completely for the following reasons:

- adverse events (AEs): 29
- disease progression: 12
- study withdrawal: 5
- physician decision: 3
- death: 2
- other: 2
- nonadherance: 1

The median time on venetoclax before stopping due to AEs was 11.3 months (range, 0.5-24.6); for disease progression, it was 17.1 months (range, 4.6-25.1). According to the trial results, "greater cumulative exposure" to venetoclax significantly reduced the risk of either a PFS or overall survival (OS) event (PFS: HR, 0.93; 95% CI, 0.88-0.99; $P = .0168$; and OS: HR, 0.85; 95% CI, 0.79-0.92; $P < .0001$).

A table included in the abstract gave statistics for patients who discontinued venetoclax for any reason (PFS: HR, 5.98; 95% CI, 3.31-10.82; $P < .0001$) and for those who discontinued due to AEs (PFS: HR, 5.82; 95% CI, 2.39-11.57; $P < .0001$).

Treatment interruption for AEs was seen in 134 of the 194 patients, mostly due to neutropenia (84/194, or 43%). The median time of treatment interruption was relatively short at 9 days, and short interruptions did not affect PFS or OS.

The authors reported, "These data highlight the importance of effective control of toxicity to realize the full benefit of [venetoclax/rituximab] treatment."

The key to management of venetoclax has been the development of the 5-week dose-escalation schedule, as well as dosing adjustments, both of which help prevent tumor lysis syndrome (TLS). Data reported in 2019 by the American Association of Cancer Research on 297 patients "provide insights into current use of venetoclax in clinical practice, including TLS rates observed.…We identified opportunities for improved adherence to TLS risk stratification and prophylaxis, which may improve safety."[3] ◆

Genentech and AbbVie supported the study.

REFERENCES

1. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 2018;378(12):1107-1120. doi:10.1056/NEJMoa1713976
2. Mato AR, Sharman JP, Biondo J, et al. Impact of premature venetoclax (ven) discontinuation/interruption on outcomes in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): phase III MURANO study results. *J Clin Oncol.* 2020;38(15 suppl; abstr 8028). doi:10.1200/JCO.2020.38.15_suppl.8028
3. Roeker LE, Fox CP, Eyre TA, et al. Tumor lysis, adverse events, and dose adjustments in 297 venetoclax-treated CLL patients in routine clinical practice. *Clin Cancer Res.* 2019;25(14):4264-4270. doi:10.1158/1078-0432.CCR-19-0361

Janssen's Wildgust Breaks Down Bispecific Antibodies in Development for Non–Small Cell Lung Cancer and Multiple Myeloma

Interview by Maggie L. Shaw

WILDGUST

Mark Wildgust, PhD, vice president, Global Medical Affairs/Oncology, Janssen

BISPECIFIC ANTIBODIES RECEIVED plenty of attention at last year's meeting of the American Society of Hematology, and the momentum continued in late May during the virtual annual meeting of the American Society Society of Clinical Oncology (ASCO). As the name suggests, these therapies are manufactured proteins that can bind to 2 separate antigens at the same time, bringing extra power to the fight against cancer.

During ASCO, Janssen presented results from the CHRYSALIS study on amivantimab,[1] a bispecific antibody being developed to treat non–small cell lung cancer (NSCLC). The pharma giant, along with its parent company, Johnson & Johnson (J&J), had previously received a breakthrough therapy designation in December for teclistamab, another bispecific antibody indicated for potential treatment of multiple myeloma.[2]

Mark Wildgust, PhD, vice president of Global Medical Affairs/Oncology at Janssen, who leads a team of scientists and physicians developing new, targeted therapies for oncologic and hematologic conditions, expounded on the similarities and differences of these 2 novel dual-targeted therapies with *Evidence-Based Oncology*™ (*EBO*).

Wildgust explained that intervening earlier in the premalignant setting is a primary goal. To that end, Janssen has 6 bispecific antibodies in development—all first-in-class therapies. He also touched upon medication affordability, noting that availability and regulatory approval are moot points if a drug is not accessible, because although it is proven safe and effective, patients can't benefit from a treatment if they can't get it.

This interview has been edited slightly for clarity.

EBO: Two bispecific antibodies in development, amivantamab for NSCLC and teclistamab for multiple myeloma, have some similarities, but one is being developed for a solid tumor and the other for hematologic cancer. Can you discuss the similarities and differences?

WILDGUST: Both are built on the same duobody platform, which is what we call it. Bispecifics are essentially monoclonal antibodies that bind to 2 different targets—that's why we call them bispecific. The method by which we make them is the same, but they are actually quite distinctly different.

Let's take teclistamab. We actually create 2 individual antibodies: 1 targets CD3 and 1 targets BCMA. We then break those apart and glue them back together so that they can basically target CD3 and BCMA. So, that's teclistamab.

Now, the same process is used for making amivantamab as well: 1 [antibody] targets *EGFR* and 1 targets c-MET. We break these 2 antibodies apart and glue them back together and create that single bispecific. So, the similarities kind of end there.

Then we get into the differences. Teclistamab binds to BCMA. BCMA is essentially an antigen target that's almost ubiquitously expressed on myeloma cells. Then you have CD3. Why CD3? CD3 is essentially picking up T cells, which express CD3. The BCMA-CD3 teclistamab is really what we would call a T-cell redirector. It essentially picks up the T cell on the monoclonal antibody and then it binds to the BCMA antigen that's expressed on the myeloma cells. And so, you're essentially bringing the T cell to the cancer cell to kill it. So, that's how teclistamab works. Amivantamab, though, targets *EGFR* and c-Met, so it's not redirecting T cells. With amivantamab you're targeting 2 distinct antigen targets. And then there's a variety of immune-type mechanisms by which binding of *EGFR* or binding of c-Met separately kills the cancer cell.

Why should you target *EGFR* and why should you target c-Met? When you think about NSCLC, there are those cases that are driven by driver mutations and those that are not. Those that are driven by driver mutations are things like *EGFR*, ALK, ROS, RON—and *EGFR* is quite distinct as a driver mutation. Lots of different compounds are out there for *EGFR*-expressing NSCLC, like gefitinib and erlotinib [Tarceva] and osimertinib. But we've learned over the last 10-plus years that in many *EGFR* lung cancers, one primary mechanism of resistance is through c-Met.

So, the idea of targeting *EGFR* and c-Met is that potentially, you can target both the driver of the cancer and the resistance mutation, too.

Now, there's another element about *EGFR*/c-Met that's unique as well. The different kinase inhibitors I just mentioned—like osimertinib and gefitinib and Tarceva—target *EGFR* from an intracellular perspective, and amivantamab targets it in an extracellular manner.

So why does that matter?

When you think about lung cancer and exon 20 insertion, why don't the classical *EGFR* inhibitors work in that space? They don't work because they don't have the ability to bind within the conformational pocket. By targeting the receptor from an extracellular perspective, you don't have that issue. We know that about 10% of *EGFR* lung cancers are of the exon 20 insertion type. They currently have no standard of care. By targeting *EGFR* extracellularly, we can target that and potentially address something where current *EGFR* inhibitors don't work.

So, similarities, but quite a few more differences.

EBO: Are these therapies meant to be curative?

WILDGUST: That's a good question. Let's take multiple myeloma for a second, a highly complex, heterogeneous disease. Once patients become refractory, we know that their overall survival is quite poor. I think in the refractory setting it's very unlikely that we will give patients cure, but what we're really trying to do is achieve really deep, durable responses, for as many patients as possible, with the idea that if we can get deep, durable responses, we can give them a meaningful amount of time.

In the relapse setting, I think that it's about harnessing the immune system, harnessing those T cells to be able to try to target those cancer cells. As we learn more about teclistamab, I think the question will be, how can we use it to build curative-type regimens? One of our focuses at J&J and Janssen is to develop individual molecules or compounds, but at the same time, we're very much interested in building curative regimens. So, I think for teclistamab in its current setting, unfortunately, I don't think there is the potential for cure, mostly because of the disease complexity and heterogeneous nature. I think that teclistamab has the potential to be part of a regimen for cure in the earliest setting, and that's certainly something that we will explore. »

Now, in terms of amivantamab, there are a couple of places to think about it. The first is where we just got the breakthrough designation, for patients with the exon 20 insertion. A patient with lung cancer who has an *EGFR* exon 20 insertion unfortunately has a survival of probably about a year and a half. Their outcomes are very poor.

I don't think it's really about cure, but more about trying to build regimens right now that can give patients more time. For patients with exon 20 insertion, for patients who have progressed after initial therapy—that's where the breakthrough designation is for amivantamab. Once a patient has had initial therapy and progresses with exon 20, their median life expectancy is probably less than a year. What we're trying to do now is give them more time. That's the goal.

Ultimately, we would love to get to cure, and that's part of our overall initiative. We actually have an ongoing lung cancer initiative across J&J; we brought the 3 different parts of the company together to look at how we can intervene earlier in the premalignant setting and premalignant stage. That's the place where we can think, potentially, about cure for some of these patients, and that's part of our overall approach in terms of disease intervention.

EBO: Especially for lung cancer, because it's so often diagnosed in such a late stage that by the time it's caught, it has metastasized.

WILDGUST: Unfortunately, most patients are caught at stage IV because it's relatively asymptomatic. Most patients might have a cough. It may seem like they have something that seems quite benign, so unfortunately, most patients get caught late. More than 1.8 million patients die a year from lung cancer worldwide,[3] and the median life expectancy for a patient with newly diagnosed stage IV lung cancer is less than 2 years.

You saw some of the quite exciting data that came out at ASCO on one of the other compounds, looking at a checkpoint inhibitor in chemotherapy, and we're heralding the outcomes of that.

But we're talking about moving survival by a couple of months. Median survival is still less than 2 years, right? For *EGFR*-driven disease, the outcomes are a little bit better, but still, the outcomes are very poor. We've got a long way to go to help patients with lung cancer....

You asked me about cure. We're trying to give patients more time by advancing new, innovative therapies. You talked about teclistamab and amivantamab; we have 6 different bispecifics in the clinic. All of them are brand-new, first-in-class therapies, and we're hopeful that these can help advance care for patients.

EBO: For teclistamab, what biologic process underlies the effectiveness for patients with hematologic malignancies who have not responded to prior therapies or have relapsed disease?

WILDGUST: We know that the T cells in patients with multiple myeloma are still very active. So even in the patient who has been multiply treated or is refractory, we're trying to harness the killing [power] of those T cells and redirect them to be able to kill the cancer cells. And because we know that BCMA is so widely expressed, we can target the antigen, that BCMA, and redirect the T cell there.

Then the question is going to be, are those responses durable? When you look at the teclistamab data, in particular—and we're still in that dose-finding and dose-escalation phase with teclistamab, but also already at the 270 mcg/kg dose—we're seeing two-thirds of patients responding. If we look broadly across the patients there, we're seeing patients who are having not only responses, but durable responses. So, 16 of 21 patients in that trial—with time, we will report the data—still haven't progressed.

When you talk about biological processes that underlie the effectiveness, I think the key question is, what causes resistance? Is it the T cell becoming exhausted? And if that's the case, can we use checkpoint inhibitors to overcome that? Or is it the immunosuppressive effect of the bone marrow niche? Or is it loss of the receptor target? Did BCMA go away? Did the target go away?

"If a patient has a very aggressive myeloma, you can't wait for the number of days it takes for that T cell to be sent off, to make a CAR T, and come back. Among the benefits of the bispecific [antibodies] is that it's on the shelf; it's available straightaway for that patient who walks through the door."

—Mark Wildgust, PhD,
vice president, Global Medical Affairs/Oncology,
Janssen

We're going to learn more about that in terms of patients who progress, and then from there, we can start to identify how we can better optimize care for these patients, using these T-cell–oriented or T-cell–redirecting types of compounds.

EBO: Is teclistamab being studied in patients who have relapsed on chimeric antigen receptor (CAR) T-cell therapy?

WILSGUST: Not yet, because we're still in that dose-finding/dose-escalation phase, trying to understand what the right dose is. I think it is an outstanding clinical question. Could you target a patient who's had a CAR T with a bispecific? I think there are 2 parts of that question.

The first is, do they have the same antigen target? If you think about a BCMA CAR T and a BCMA bispecific, there's a question of, is that the right thing to do? Because we don't know why patients might have progressed on the BCMA-targeted therapy. Maybe it wasn't the loss of that BCMA antigen, and if that's the case, then targeting it with another BCMA-targeting agent probably doesn't make sense. But if it's actually something different, then there may still be potential to do that.

Now, if you have a CAR T and a bispecific that target different antigens, I think that's an entirely different question, and I think the answer is, yes, you probably could use them one after another. That's because you're really then talking about a different target versus anything else.

EBO: Does amivantamab, which targets activating and resistant *EGFR* and MET mutations and amplifications in NSCLC, have potential in other solid tumor cancers?

WILDGUST: We know that *EGFR* is expressed in other cancers as well, and so is MET. And so, as part of our development plan, we will look at other cancers where *EGFR* and MET are potential drivers. I think the biggest unmet need is in NSCLC. As I mentioned earlier, patients with exon 20–expressing and *EGFR*-expressing lung cancer don't respond to traditional *EGFR*-targeting agents. The outcomes for those patients are particularly poor. But dual targeting of *EGFR* and MET is particularly interesting because we know MET is a resistance pathway for *EGFR*. But discretely, there are other cancers that are MET driven, *EGFR* driven, and we will absolutely be thinking about exploring those other tumor types, looking at amivantamab.

EBO: In results for amivantamab presented at ASCO, the overall median progression-free survival (PFS) of 8.3 and 8.6 months, clinical benefit rates of 67% and 72%, and their ranges, were comparable between all patients and those who received previous platinum-based chemotherapy, respectively. How much of a survival advantage is amivantamab really providing?

WILDGUST: CHRYSALIS is a single-arm exploratory cohort study. The idea was that we wanted to take the recommended phase 2 dose and then explore that in a cohort of patients who are exon 20. We're not comparing it with something else, so I can't tell you if it did improve survival. But the median survival is less than 12 months for a patient with exon 20 insertion who has progressed after prior therapy, so we know the outcomes for these patients are poor.

The PFS data that we reported were about 8.5 months, but those data are still actually quite immature. There's a lot of censoring there, because the follow-up is quite short. We still need to learn more about the PFS for those patients. But to see a PFS of between 8 and 9 months in this group of patients, when the median survival is 12 months, is very promising. It seems like [amivantamab] is providing real benefit, because the median PFS for these patients would normally be a couple of months. The data look exciting and promising.

I think that's why the FDA gave us a breakthrough designation for this therapy. One, because there are no currently approved therapies out there. And second, because there's a high unmet medical need. Again, the data look very, very promising, and better than anything else out there at this point.

EBO: Do bispecific antibodies have other advantages?

WILDGUST: When we talked about amivantamab, we talked about targeting a receptor in a different way. That's an advantage. But when you think about teclistamab, you have to think about it in terms of what

other types of therapies are out there. You almost have to think about teclistamab as a bispecific and a CAR T. And, first of all, when we think about teclistamab and the CAR T, what are some of the differences?

First of all, we don't see grade 3 or grade 4 cytokine release syndrome for teclistamab, and I think that's particularly important. We see very low rates of neurotoxicity. But one of the things about CAR T cells is that you have to collect the patient's T cells through apheresis, send them away, and have [the product] manufactured and come back. So, if a patient has a very aggressive myeloma, you can't wait for the number of days it takes for that T cell to be sent off, to make a CAR T, and come back. Among of the benefits of the bispecific is that it's on the shelf; it's available straightaway for that patient who walks through the door.

It seems like teclistamab has a very good safety profile, which means it looks like a good option for patients in that regard. It doesn't have the grade 3, grade 4, rates of neutropenia, anemia, and thrombocytopenia that you might see with CAR T therapy. I think there are advantages of them versus other similar targeting types of agents, like CAR Ts, which I think is good as well.

But the other advantage of a bispecific, particularly one like teclistamab, is that it's taking those T cells that we know are active and redirecting them against the cancer. The advantage of something like amivantamab is that it's dual-targeting. The potential to target both pathways is important, particularly as we know that c-MET is a resistance escape pathway for *EGFR*.

This is a good example of how you start to think about, how do I use my tools? How do I use the different types of tools to target the cancer and to try to provide meaningful responses and benefit for patients?

EBO: While these therapies are still very early in the study phase, are there general financial models that Janssen or J&J is discussing with payers to ensure that this treatment can reach patients?

WILDGUST: I think at the end of the day, not necessarily with these specifically, our overall goal is to make our medicines accessible and affordable for patients of our health care systems. That's the key. While we strive to develop innovative therapies that are transformative, the only medicines that really deliver value are those that patients can access. We work really hard with different health care systems around the world, and different governments and different stakeholders, to try to make our medicines available through coverage, through reimbursement. And as part of our development process, we engage with different payers to try to understand how we can bring these medicines to patients, looking at different ways in which we can negotiate price or different agreement methods so that we can provide access.

At the end of the day, if you have a drug that's available, but not accessible, then the regulatory approval really doesn't count for anything, whether it's safe or effective, because unless that patient can get it, they can't receive the benefit. So we take that very seriously. And whenever we develop medicines, we're not only thinking about regulatory approval, we're also thinking about making sure that we can provide access. And that means access through payers as well. ◆

REFERENCES

1. Study of JNJ-61186372, a human bispecific *EGFR* and cMet antibody, in participants with advanced non-small cell lung cancer (CHRYSALIS). ClinicalTrials.gov. Updated June 2, 2020. Accessed June 8, 2020. https://clinicaltrials.gov/ct2/show/NCT02609776
2. Park K, John T, Kim S-W, et al. Amivantamab (JNJ-61186372), an anti-*EGFR*-MET bispecific antibody, in patients with *EGFR* exon 20 insertion (exon20ins)-mutated non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2020;38(15 suppl; abstr 9512). doi:10.1200/JCO.2020.38.15_suppl.9512
3. Lung cancer. The Cancer Atlas. canceratlas.cancer.org/the-burden/lung-cancer/. Accessed June 22, 2020.

Genetic Testing Can Guide Treatment, but Access and Counseling Are Essential, Results Say

Mary Caffrey

ADVANCES IN GENETIC TESTING increasingly connect cancer patients with treatments that work—and help them avoid those that won't. But providers have a responsibility to make sure they are ordering the right tests and using the results correctly, said Erin Hofstatter, MD, associate professor adjunct and co-director of the Cancer Genetics and Prevention Program at Yale School of Medicine.

Getting the full picture means patients should have access to genetic counselors who can evaluate individual risk, Hofstatter said during the virtual session, "Cancer Risk, Genetics, and Prevention," held May 30 during the American Society of Clinical Oncology (ASCO) 2020 Annual Meeting.

Hofstatter highlighted 4 studies that she said amplify the 3 components of using genetic testing in cancer treatment and prevention: (1) understanding the germline component of a tumor test, (2) broadening access to genetic counselors with video sessions, and (3) making sure risk assessment of each patient is accurate, so that patients do not have unnecessary surgeries.

MSK-IMPACT TRIAL. Tumor tests typically look for acquired mutations—somatic testing—to select targeted therapies. MSK-IMPACT evaluated the value, or clinical utility, of adding germline profiling, for inherited mutations, for patients with advanced cancer, through next-generation sequencing.[1] From a study population of 11,975 patients, investigators identified 2043 (17.1%) who had pathogenic or likely pathogenic germline variants, including 777 patients (6.5%) who had genes for which targeted therapies were available. Most of these were for *BRCA* mutations (n = 416) or for Lynch syndrome (n = 149). Of importance, Hofstatter said, is the share of patients with advanced disease who received a targeted therapy: The authors reported the share was 45.3% of 554 patients.

But Hofstatter noted that such findings are essentially a moving target. "If emerging genes of interest in homologous recombination repair are included, prevalence rose to 8.6%," she said.

"With the emergence of novel targeted treatments, it's important to realize that the therapeutic actionability of germline variants is likely to increase significantly over time," Hofstatter noted. Increasingly, she said, the advanced setting is where germline testing will be indicated to select a cancer treatment.

"It's important to know your test. Remember that tumor sequencing is not a substitute for control. Hence of germline »

HOFSTATTER

Erin Hofstatter, MD, associate professor adjunct and co-director, Cancer Genetics and Prevention Program, Yale School of Medicine

MD Anderson's Lu: MAGENTA Highlights Need to Use Genetic Counselors in "Most Effective Way Possible"

Peter Wehrwein

WOMEN WHO UNDERGO genetic testing for hereditary breast and ovarian cancer are often advised to speak with a genetic counselor before and after they take the test, even if the result is ultimately negative for a mutation that would indicate a greater risk.

But results presented virtually at the 2020 annual meeting of the American Society of Clinical Oncology suggest that an online educational video about genetic testing may be sufficient, and that women often don't need to speak in person with a genetic counselor in the context of this type of testing.

"We were surprised by the findings," said Karen H. Lu, MD, the study's principal investigator and chair of the Department of Gynecologic Oncology and Reproductive Medicine at the University of Texas MD Anderson Cancer Center, in an interview.

"I would hate for anyone to say, 'We don't need genetic counselors—they are not necessary,'" Lu added. "I think what [we] need to do is use them in the most effective way possible."

Lu and her colleagues presented findings from MAGENTA (Making GENetic Testing Accessible), a 4-arm study that included 3111 women with a family history of hereditary breast and ovarian cancer and another group of 711 women with a family member whose genetic test results were positive for a risk-conferring mutation.

Women enrolled in the trial watched an online educational video about genetic testing. Lu explained that women in the control arm of the study then spoke with a genetic counselor by telephone before and after they took the genetic test, which was an at-home "spit kit" test that involves collecting saliva sample for DNA testing. (The MAGENTA study website describes it as "the study of genetic testing from your living room.")

Others arms of the study included genetic counseling only before the genetic test, only after, and no genetic counseling either before or after.

However, if the test came back positive for a risk-conferring mutation, genetic counseling was given regardless of which arm of the study the woman was in. Among the participants who completed testing, 173 (7.2%) had a positive test.

LU

The primary outcome was "cancer risk distress" at 3 months. Lu and her colleagues measured distress among the women in 3 groups with more limited genetic counseling—including the group that didn't receive any counseling if their results were negative. These results were noninferior to those of the group that received counseling before and after the test, the scenario which Lu described as the current standard of care.

Analysis of data on secondary end points such as anxiety, depression and "decisional regret" painted a similar picture of no difference among the 4 arms. However, test completion was highest in the no-counseling arm (86.4%) and lowest in the control arm (60.6%).

Lu said genetic counselors provide "a wonderful service" to patients, but she added that there aren't enough of them, particularly as testing becomes more prevalent and the results become more instrumental in making treatment decisions. She said the most effective way to use counselors may be to focus their efforts on people who test positive for risk-conferring mutations and those with a strong family history of cancer.

The overarching concern is making genetic testing more accessible, so women at high risk are identified and monitored or treated early, said Lu. "As a whole, [the results] really show that this type of testing—which is available commercially—can be used," she said ◆

testing, and it should be considered separately to achieve the best results," Hofstatter reminded.

IMPROVING ACCESS. Despite broader availability of germline testing, uptake is poor. For instance, only about 2% of Lynch syndrome carriers have been identified, Hofstatter said. Lack of knowledge, cost, inconvenience, and a shortage of genetic counselors—some payers require a counseling session before testing—have all been barriers.

Two studies presented during ASCO examined whether there was any disadvantage for patients if counselors met with them via telemedicine—a method that has taken off in recent months due to the coronavirus 2019 pandemic. The ProGen study, led by Huma Q. Rana, MD, of Dana-Farber Cancer Institute, was a randomized trial that compared the effectiveness of video visits with traditional genetic counseling among men diagnosed with prostate cancer.[2] The study reported high uptake by both groups: 88% of the eligible men in the traditional counseling group agreed to be tested, compared with 93% of those eligible in the video group. Testing completion rates were 99% in both groups who agreed to be tested, and according to initial survey results, patients in both groups were equally satisfied with the process. Over 2 years, 604 patients were tested and pathogenic variants were identified in 79 of them (13.2%).

However, Hofstatter noted that ProGen took place in a highly controlled setting. What, she wondered, would be the result in a study that reflected real-world conditions? For this answer, she turned to the MAGENTA study,[3] which recruited many of its participants over social media. The study aimed to learn whether pre- and posttest genetic counseling is needed to best guide genetic testing for women at risk of hereditary breast and ovarian cancer. All counseling took place online. Of 3822 patients randomized, 3111 were placed in a family-history cohort and 711 in a cascade cohort, where someone in the family was known to have a mutation. Among those completing genetic testing, 173 participants (7.2%) had a mutation in a breast or ovarian gene; this included 114 patients (5.7%) in the family history cohort and 59 (14.2%) in the cascade cohort.

Hofstatter explained the results, which focused on distress level among patients: It was lowest among those who had neither pre- nor posttest counseling. Overall, 318 participants (18%) had high levels of distress, and there was little difference whether their test was ultimately positive or negative.

Both studies, Hofstatter said, "demonstrate high uptake rates with pretest video education, and they truly represent new models of genetic counseling, breaking down barriers and improving accessibility to testing.

"And it would be very tempting," Hofstatter continued, "to have our major take-home message being that pretest counseling is really [superfluous]—that 'Less is more,' or at least that no counseling 'is just as good.' [Some could say,] 'Let's get rid of the [counselors] altogether.'" However, "test completion or uptake of testing cannot be our only goal," she said. "Truly, it's what you do with the information from testing that counts. Certainly uptake, satisfaction, distress, and intention-to-share are essential."

PROMPT TRIAL. For a view of how information is used, Hofstatter turned to the PROMPT study, which examined how many women completed oophorectomy based on results of multipanel genetic testing. While the results included some self-reported statements from the patients, the findings highlight the concerns payers have had about genetic testing without proper counseling or education for providers: The testing may lead to unnecessary or even harmful procedures.

Of the 1566 women in the PROMPT registry who reported having oophorectomy, 487 (30.7%) reported having cancer treatment and 432 reported benign disease (27.6%). Another 186 (12.8%) reported pathogenic variants associated with risk of ovarian cancer. The majority of women had no

family history of ovarian cancer, and most of the women having surgery were not yet aged 50 years. The study found that 10% to 15% of the women who had surgery had a pathogenic variant or a variant of unknown significance, and thus were reporting having a procedure without a clear indication.[4]

The study, Hofstatter said, "serves as a cautionary tale, especially when we're thinking about omitting or limiting the availability of genetic counseling as part of genetic testing." Increased access to testing—a good goal—in combination with less counseling would invite "the inevitable potential for misinformation and possible mismanagement."

A provider may have good intentions in streamlining the process, but Hofstatter said treatment management decisions "must be based on accurate risk assessment. And certainly, with less availability and less use of genetic counselors, the burden is going to be increasingly on the provider to make sure that they understand the implications of testing results." ◆

REFERENCES

1. Stadler ZK, Maio A, Kemel Y, et al. Targeted therapy based on germline analysis of tumor-normal sequencing (MSK-IMPACT) in a pan-cancer population. *J Clin Oncol.* 2020;38(15 suppl; abstr 1500). doi:10.1200/JCO.2020.38.15_suppl.1500
2. Rana HQ, Stopfer JE, Petrucelli N, et al. A randomized controlled trial of video-education or in-person genetic counseling for men with prostate cancer (ProGen). *J Clin Oncol.* 2020;38(15 suppl; abstr 1507). doi:10.1200/JCO.2020.38.15_suppl.1507
3. Swisher EM, Rayes N, Bowen D, et al. Results from MAGENTA: a national randomized four-arm noninferiority trial evaluating pre- and post-test genetic counseling during online testing for breast and ovarian cancer genetic risk. *J Clin Oncol.* 2020;38(15 suppl; abstr 1506). doi:10.1200/JCO.2020.38.15_suppl.1506
4. Domchek SM, Brower J, Symecko H, et al. Uptake of oophorectomy in women with findings on multigene panel testing: results from the Prospective Registry of Multiplex Testing (PROMPT). *J Clin Oncol.* 2020;38(15 suppl; abstr 1508). doi:10.1200/JCO.2020.38.15_suppl.1508

Study Shows How NGS, Precision Medicine Benefited Patients at Community Cancer Clinic

Allison Inserro

IN ONCOLOGY, PRECISION MEDICINE is already well established, with targeted therapies approved based on the patient's genetic makeup or genetic variants of their tumor. Now, a combination of precision medicine, next-generation sequencing (NGS), and diagnostics is making its way into community cancer clinics. Study outcomes revealed during the American Society of Clinical Oncology 2020 Virtual Scientific Program analyzed NGS testing results in a community cancer care clinic in coordination with a precision medicine program.

With decreasing costs—of NGS to identify both germline and somatic pathogenic variants, and of other technological advancements—there is a critical need for curation and interpretation of these results, the study authors noted, as clinicians often order the tests simultaneously.

The retrospective review examined germline NGS results from patients who were seen since 2001 by the Hereditary Cancer Program at Hoag Family Cancer Institute in Newport Beach, California. Researchers also compared those who had both positive genetic testing results for germline and somatic variants and those who had tumor molecular profiling.

The cancer program saw a total of 8239 patients; of those, 6100 had germline testing done, and approximately 50% had multigene panel testing (MGPT).

Results showed that 15% of the patients with germline testing had a pathogenic or likely pathogenic mutation. Of those patients with positive results, 71% had breast or ovarian cancer, while 29% had other cancer types.

The researchers also analyzed NGS results for 713 tumors tested in 1 year through a commercial laboratory. All cases were subject to the authors' secondary annotation. That analysis resulted in additional recommendations in 40% of cases, beyond what was in the commercial report. The secondary annotations also provided additional clinical trial options in 30% of cases.

The cancer clinic had also begun a new program in the past year that led to the researchers examining tumor profiling results for indications of possible germline mutations. By analyzing those results, the authors said they made recommendations for genetic counseling in 91 cases (12.8%).

The results show the importance of genetic counseling and MGPT in a community setting in patients with personal and/or family histories of cancer, the authors wrote.

Physicians at the center have an increased understanding of the clinical utility of molecular testing, which benefits patients, the authors said. ◆

REFERENCE

Darabi S, Braxton DR, Homer J, et al. Precision medicine, genetics and genomics in a community cancer clinic. *J Clin Oncol.* 2020;38(15 suppl; abstr e13511). doi:10.1200/JCO.2020.38.15_suppl.e13511

Biosimilars May Help Bridge the Transition From Fee-for-Service to Value-Based Care

Healthcare Providers Are Feeling the Burden of Rising Costs

Financial challenges remain the #1 concern of hospital executives according to the 2018 American College of Healthcare Executives' annual survey.[1] Similarly, oncology practices face significant financial strain, which has resulted in over 1600 community oncology practice closures, hospital acquisitions, and corporate mergers in the past decade.[2]

One way to alleviate this burden is through utilizing opportunities to recognize cost savings. For example, hospitals may be able to leverage cost savings to reallocate funds for other important projects not funded by Medicare or commercial payers. In addition, this may lead to better management of hospital budgets to optimize care and a positive budget impact on drug spend for hospital inpatients.[3]

The Healthcare Industry Is Feeling the Effects of the Shift to Value-Based Care

In recent years, there has been a significant transition in focus from fee-for-service to value-based care. The goal of a value-based care system is to encourage clinicians to provide quality and efficient care, as well as improved outcomes at a lower cost.[4]

There have been several actions in the market place to recognize this shift to value-based care. For example, the Centers for Medicare & Medicaid Services (CMS) has created value-based care programs that reward providers with incentives for lowering costs and improving the quality of care they provide to Medicare beneficiaries. An example of this type of market reform is the development of a voluntary pilot program called the Oncology Care Model (OCM), which is designed to test the effects of improved care coordination, greater access to practitioners, and appropriate clinical care on both health outcomes and the cost of care for patients receiving chemotherapy.[5] Another type of market reform that was recently announced, the Patient-Centered Oncology Payment (PCOP) model, offers a way to expand on the OCM experience and represents an additional step towards innovation.[6]

This shift from fee-for-service to value-based care is playing a significant role in how practices and providers are viewing the cost of care.[8]

IN LIGHT OF THESE MARKET TRENDS

87% **of community oncologists surveyed are thinking differently about drug choices as a result of value-based care.[9]**

In order to manage appropriate utilization and take more risk, it will be crucial to assess the expense side of the equation as well.[10]

As the industry shifts to value-based reimbursement models, healthcare systems will continue to realize the need for solutions that advance health initiatives and support quality care objectives in the future.[7]

References:

1. American College of Healthcare Executives. Top issues confronting hospitals in 2018. https://www.ache.org/learning-center/research/about-the-field/top-issues-confronting-hospitals/top-issues-confrontinghospitals-in-2018. Accessed November 1, 2019. **2.** Chartis Oncology Solutions. Optimizing your oncology practice: real-world approaches that produce results. https://www.chartisforum.com/wp-content/uploads/2018/12/Oncology-WP-2018_FINAL-12-14.pdf. Published May 14, 2019. Accessed November 1, 2019. **3.** Data on file. Pfizer Inc., New York, NY. **4.** Bean M. Two-sided risk is coming – here's how healthcare providers can prepare. https://www.beckershospitalreview.com/payer-issues/two-sided-risk-is-coming-here-s-how-healthcareproviders-can-prepare.html. Published October 2, 2017. Accessed November 1, 2019. **5.** Centers for Medicare & Medicaid Services. OCM performance-based payment methodology. https://innovation.cms.gov/Files/x/ocm-pp3be-yond-pymmeth.pdf. Published December 17, 2018. Accessed December 1, 2019. **6.** ASCO. ASCO launches new payment reform model to transform cancer care delivery and enhance the quality of patient care. https://www.asco.org/about-asco/press-center/news-releases/asco-launches-new-payment-reform-model-transform-cancer-care. Published November 26, 2019. Accessed December 5, 2019. **7.** Walker T. The future of value-based care. Managed Healthcare Executive. https://www.managedhealthcareexecutive.com/news/future-value-based-care. Published November 1, 2019. Accessed December 5, 2019. **8.** The Deloitte Center for Health Solutions. The great consolidation: the potential for rapid consolidation of health systems. https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-scienceshealth-care/us-lshc-great-consolidation-111214.pdf. Published 2014. Accessed November 1, 2019. **9.** IntegraConnect. How is value-based care changing cancer treatment decisions? http://campaign.integraconnect.com/vbc-oncology-survey. Accessed December 1, 2019. **10.** HealthLeaders. Value-based care is ripping into health system profits. https://www.healthleadersmedia.com/finance/value-based-care-ripping-health-system-profits. Accessed December 2, 2019. **11.** Centers for Disease Control and Prevention. Understanding value-based insurance design. https://www.cdc.gov/nccdphp/dch/pdfs/Value_Based_Ins_Design.pdf. Accessed July 15, 2019. **12.** NEJM Catalyst. New Marketplace Survey. Transitioning payment models: fee-for-service to value-based care. https://catalyst.nejm.org/transitioning-fee-for-service-value-based-care/. Accessed December 3, 2019. **13.** Community Oncology Alliance. COA biosimilars position statement. https://www.communityoncology.org/biosimilars-community-oncology-alliance-position-statement/. Accessed on December 3, 2019. **14.** Patel KB, Arantes LH Jr, Tang WY, et al. The role of biosimilars in value-based oncology care. *Cancer Manag Res.* 2018;10:4591-4602. **15.** Strober BE, Armour K, Romiti R, et al. Biopharmaceuticals and biosimilars in psoriasis: what the dermatologist needs to know. *J Am Acad Dermatol.* 2012;66(2):317-322. **16.** Scheinberg MA, Kay J. The advent of biosimilar therapies in rheumatology—"O brave new world." *Nat Rev Rheumatol.* 2012;8(7):430-436. **17.** Henry D, Taylor C. Pharmacoeconomics of cancer therapies: considerations with the introduction of biosimilars. *Semin Oncol.* 2014;41(suppl 3):S13-S20. **18.** US Food and Drug Administration (FDA). Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Silver Spring, MD: FDA; April 2015.

Unlocking the Potential of Biosimilars

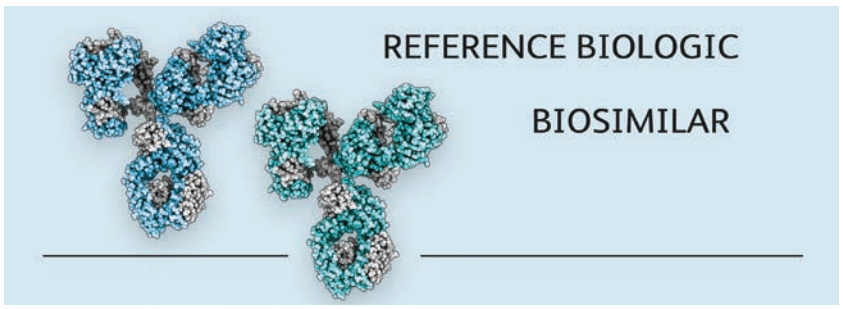
Given the growing costs of cancer care, delivering value while maintaining efficacy and safety is a pivotal issue in today's healthcare environment. Biosimilars may help address this issue by providing additional treatment options, at a potentially lower cost, while providing highly similar safety and efficacy to their reference biologic.[11-13] They may potentially better position providers for emerging value-based care initiatives from payers and employers through availability of lower-cost treatment options resulting in reduced drug spend. In addition, biosimilars may help meet established cost targets and position for future risk-sharing for OCM practices.[13-14]

Biosimilars May Prove Fundamental to the Future of Oncology Care, as We Shift to Value-Based Care as a Solution to Contain Costs[15-17]

- By potentially reducing costs and helping decrease financial risk in an emerging value-based environment, biosimilars may be able to unlock resources that can be reinvested in improving patient care
- Biosimilars may potentially offer a variety of therapeutic options at a lower cost, as well as savings and efficiencies for the healthcare system
- Demonstrating the ability to lower costs for high volume, costly therapies may prove beneficial with practice discussions with payers

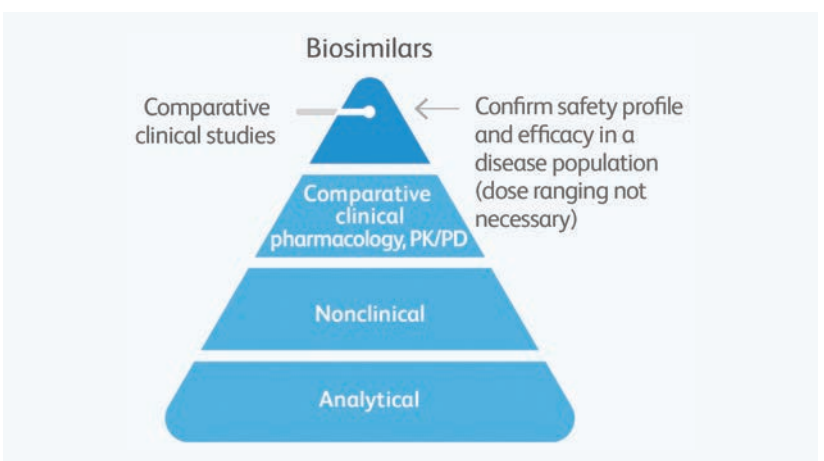
Introduction to Biosimilars

- A biosimilar is a biologic medicine that is highly similar to a reference biologic, with no clinically meaningful differences in terms of safety, purity, and potency[18]
- As potential alternatives to reference biologics, biosimilars may potentially expand treatment options and lower costs to meet the growing demand for biologic therapies



Development and Approval of Biosimilars

Extensive analytical, clinical, and nonclinical studies are part of biosimilar development[18]



The FDA approval process evaluates the totality of evidence to help ensure biosimilar quality, efficacy, and safety[18]

- A comparative clinical study is typically required to confirm no clinically meaningful differences between the 2 products
- Comparative human pharmacokinetic/pharmacodynamic (PK/PD) studies and clinical immunogenicity assessment are expected
- Nonclinical testing to evaluate the toxicity and safety profiles of the biosimilar is required
- Robust analytical testing, including comparative structural and functional characterization, is performed

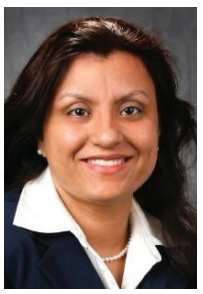
For more information, please visit PfizerBiosimilars.com

Pfizer Oncology

RESEARCH REPORT

How Does Cardiotoxicity Present Itself in Patients With Cancer?

Maggie L. Shaw



ISMAIL-KHAN

Roohi Ismail-Khan, MD, MSc, medical oncologist and co-director, cardio-oncology program, H. Lee Moffitt Cancer Center

A TRIO OF ABSTRACTS presented at this year's annual meeting of the American Society of Clinical Oncology focused on cardiotoxic effects of cancer treatment and how cardiac disease remains a barrier to effective cancer therapy among patients with cancer and survivors.

"There's a 3-pronged approach in cardio-oncology. We describe short-term and delayed cardiotoxic effects of cancer treatments," noted Roohi Ismail-Khan, MD, MSc, medical oncologist and co-director of the cardio-oncology program at H. Lee Moffitt Cancer Center.[1] "We explain strategies for screening and monitoring of cancer patients for cardiovascular toxicity before, during, and after cancer treatment. And lastly, we would like to outline a multidisciplinary approach between cardiologists and oncologists to manage cardio-oncology patients using recommendations and optimizing survivorship outcomes."

Five-year survival rates noticeably improved across a variety of cancers between 1971 and 2011, Khan pointed out. Among the cancers with the most significant improvements are prostate, non-Hodgkin lymphoma, and leukemia. However, longer survival times mean that late-term adverse effects are becoming more common. These include cardiovascular disease (CVD), especially among patients with early-stage breast cancer who are beginning to die more from CVD than the cancer itself.

Cardiotoxicity

The first 2 abstracts that Ismail-Khan presented[1] focused on results from the Pathways Heart Study,[2,3] from the National Cancer Institute and Kaiser Permanente Northern California (KPNC), which is examining CVD and its risk factors among women with breast cancer, women with no history of the disease, and survivors. Patient data came from KPNC electronic health records for all cases of invasive breast cancer diagnosed from 2005 to 2013.

CVD was classified as major (eg, ischemic heart disease, heart failure, cardiomyopathy, stroke) or other (eg, arrhythmia, cardiac arrest, valvular disease, etc). In addition to statistical analyses, subgroup analyses looked at differences among patients who received chemotherapy, radiation, and hormonal therapy.

There were 14,942 women in the breast cancer cohort and 74,702 in the control group (no breast cancer), with an average age of 62 years and an average body mass index of 28.3 kg/m^2 at diagnosis. The average follow-up was 7 years.

The overall results show an increased risk of both hypertension and diabetes:

- Hypertension: HR, 1.18 (95% CI, 1.13-1.24)
- Diabetes: HR, 1.25 (95% CI, 1.18-1.33)

Treatment for breast cancer with chemotherapy, left-sided radiation therapy, and endocrine therapy was also shown to increase the risk of cardiotoxic effects. In particular, chemotherapy increased the risk of heart failure and cardiomyopathy.

Ismail-Khan noted, however, that other factors influence these outcomes in patients with cancer, and these include genetics, cancer type, and lifestyle factors.

Exercise

The third abstract[4] Ismail-Khan presented focused on using exercise to improve heart health among patients with testicular, breast, and colon cancers as well as non-Hodgkin lymphoma (NHL) who have undergone treatment. They were randomized to a 24-week exercise intervention either during chemotherapy (n = 131) or when it finished (n = 135). The primary outcome was the effect on peak oxygen uptake (VO_2 peak), adjusted for baseline values at diagnosis (T0), with additional measures taken after chemotherapy (T1), post-exercise intervention (T2), and 1-year post-exercise intervention (T3).

The average ages of the patients were 33 years for testicular cancer, 52 years for breast cancer, and 64 years for both colon cancer and NHL.

Although both groups benefited, the results showed that the early-exercise cohort fared significantly better, with less of a decline in their VO^2 peak and quality of life. The early exercisers also had less overall general ($P = .002$) and physical fatigue ($P < .0001$) at the first time point.

> **"We explain strategies for screening and monitoring of cancer patients for cardiovascular toxicity before, during, and after cancer treatment. And lastly, we would like to outline a multidisciplinary approach between cardiologists and oncologists to manage [patients]."**
>
> —Roohi Ismail-Khan, MD, medical oncologist and co-director, cardio-oncology program, H. Lee Moffitt Cancer Center

At the second time point, VO^2 peak ($P = .9$), quality of life ($P = .7$), general fatigue ($P = .3$), and physical fatigue ($P = .7$) were comparable between early and postchemotherapy groups.

A supervised exercise program is best, Ismail-Khan noted, but "the earlier we introduce exercise in our chemotherapy adjuvant patients, the better.

"These cardio-oncology studies are looking at modifying multiple areas, so we can have better outcomes for our cancer survivors," Ismail-Khan concluded. "When I see my patients, I tell them, 'While we are curing your cancer, we don't want to increase your risk of dying from yet another disease. So, while we are curing your cancer, we have to concentrate on preventing heart disease at the same time.'" ◆

REFERENCES

1. Ismail-Khan R. To the heart of the matter: understanding and improving cardiovascular health in cancer. Presented at: ASCO20 Virtual; May 29-31, 2020. Accessed May 29, 2020. https://meetinglibrary.asco.org/record/188934/video
2. Greenlee H, Iribarren C, Neugebauer, et al. Risk of cardiovascular disease in women with and without a history of breast cancer: the Pathways Heart study. Presented at: ASCO20 Virtual; May 29-31, 2020. Accessed May 29, 2020. https://meetinglibrary.asco.org/record/188171/abstract
3. Kwan ML, Iribarren C, Neugebauer R, et al. Onset of cardiovascular disease risk factors in women with and without a history of breast cancer: the Pathways Heart study. Presented at: ASCO20 Virtual; May 29-31, 2020. Accessed May 29, 2020. https://meetinglibrary.asco.org/record/188346/abstract
4. van der Schoot GGF, Ormel HL, Westerink N-DL, et al. Effect of a tailored exercise intervention during or after chemotherapy on cardiovascular morbidity in cancer patients. Presented at: ASCO20 Virtual; May 29-31, 2020. Accessed May 29, 2020. https://meetinglibrary.asco.org/record/187836/abstract

Coverage by Mary Caffrey

More Positive Signs for AMG 510, Inhibitor of *KRAS* Mutation That Stymied Scientists for Decades

THE 2020 ANNUAL MEETING of the American Society of Clinical Oncology (ASCO) featured updates on AMG 510, the first-in-class small-molecule inhibitor of the *KRAS* p.G12C mutation, which is implicated in multiple solid tumor cancers including 13% of non–small cell lung cancers (NSCLCs).[1]

Identified more than 30 years ago, *KRAS* is one of the most frequently mutated oncogenes, but over the years, it was considered "undruggable" because the protein lacked surfaces where a small molecule could bind to impede its function. One type of *KRAS* mutation, called *KRAS* G12C, stood out: by itself, it accounted for 44% of *KRAS* mutations.[1] But in recent years, researchers at Amgen found a work-around for this problem. As outlined in *Nature* last fall,[2] they isolated the novel histidine 95 groove, which offered a way for molecules to selectively and irreversibly bind to *KRAS* G12C.

Following results at the 2019 ASCO Scientific Program involving AMG 510 in patients with previously treated metastatic NSCLC, the FDA granted fast-track designation to the drug for individuals with this cancer if the *KRAS* G12C mutation were present.[3]

At the 2020 ASCO Virtual Scientific Program in May, researchers presented data from CodeBreak100, involving AMG 510 in patients who had a poor colorectal cancer prognosis,[4] as well as patients with multiple tumor types other than colorectal or NSCLC.[5]

COLORECTAL CANCER. Researchers released an update of a phase 1 trial involving 42 patients with colorectal cancer, including 12 women. The median age was 57.5 years, and 19 patients had received at least 3 prior lines of therapy. Patients were tested with doses of 180, 360, 720, and 960 mg; 25 patients were selected for the expansion phase of the trial at 960 mg. As of January 8, 2020, median follow-up was 7.9 months (range, 4.2-15.9 months); 13 patients had died (31.0%), and 8 patients (19.0%) were still on treatment, with 22 (52.4%) and 8 (19.0%) on treatment for more than 3 and 6 months. Disease progression was the most common reason for stopping treatment. Of the group, 20 patients (47.6%) had treatment-related adverse events (TRAEs), and 2 (4.8%) had a grade 3 TRAE. Overall, the objective response rate (ORR) was 7.1% and the disease control rate was 76.2%. With the 960-mg dose, the ORR was 12.0% and the disease control rate was 80.0%. Three patients with partial responses had a duration of response of 1.5, 4.2, and 4.3 months, which were ongoing at the time of data cutoff.[4]

OTHER TUMOR TYPES. Other results from CodeBreak 100, reported in a separate abstract, involved mutant solid tumors in pancreatic, endometrial, bile duct, small bowel, melanoma, and other cancers. The primary end point was safety and secondary end points were pharmacokinetics and ORR. The same dose-escalation schedule was used. As of January 8, 2020, 25 patients (9 women; median age, 60 years) reported results. Of the group, 23 received the 960-mg dose, including 20 (80%) who had received at least 2 prior lines of therapy. At data cutoff on January 8, 2020, 13 patients (52.0%) were still on treatment, with 9 patients (36.0%) and 3 (12.0%) on therapy at least 3 and 6 months, respectively. Median follow-up was 4.3 months. TRAEs were seen in 9 patients, and 2 patients had grade 3 TRAEs. Of the group, 22 were followed for at least 7 weeks, including 3 partial responses, 13 with stable disease, and 6 with progressive disease.[5] ◆

REFERENCES

1. Amgen's *KRAS* G12C research could bring hope to some patients with lung, colorectal and pancreatic cancers. Amgen. Accessed June 22, 2020. www.amgen.com/media/featured-news/2019/10/amgens-kras-g12c-research-could-bring-hope-to-some-patients
2. Canon J, Rex K, Saiki AY, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature*. 2019;575:217-223. doi:10.1038/s41586-019-1694-1
3. Cortez MF, Flanagan C. Amgen slips as gene-targeting drug misses some lofty hopes. Bloomberg. September 9, 2019. Accessed June 23, 2020. www.bloomberg.com/news/articles/2019-09-08/amgen-s-gene-targeting-drug-shrank-54-of-lung-tumors-in-study
4. Fakih M, Desai J, Kuboki Y, et al. CodeBreak 100: activity of AMG 510, a novel small molecule inhibitor of $KRAS^{G12C}$, in patients with advanced colorectal cancer. *J Clin Oncol*. 2020;38:(suppl; abstr 4018). doi: 10.1200/JCO.2020.38.15_suppl.4018
5. Hong DS, Kuo J, Sacher AG, et al. CodeBreak 100: phase I study of AMG 510, a novel $KRAS^{G12C}$ inhibitor, in patients (pts) with advanced solid tumors other than non-small cell lung cancer (NSCLC) and colorectal cancer (CRC). *J Clin Oncol*. 2020;38:(suppl; abstr 3511). doi: 10.1200/JCO.2020.38.15_suppl.3511

Safety Edge Is Seen for Lurbinectedin Over Topotecan in Combined Data Set

A POOLED SAFETY ANALYSIS comparing single-agent lurbinectedin, a selective oncogenic transcription inhibitor, with topotecan, a topoisomerase I inhibitor, has found that patients using lurbinectedin had fewer hematological toxicities and were less likely to need supportive treatments, including therapies with granulocyte colony-stimulating factor.

Data presented at the American Society of Clinical Oncology evaluated data from a phase 2 basket study that featured 335 patients treated with lurbinectedin across 9 indications, including 105 patients treated for small cell lung cancer (SCLC). These results were pooled with data from the phase 3 CORAIL trial, which studied topotecan in patients with platinum-resistant ovarian cancer. The CORAIL trial included 219 patients taking lurbinectedin and 87 who took topotecan.[1]

The most common adverse events (AEs) with lurbinectedin were grade 1/2 fatigue, nausea, and vomiting. Patients taking topotecan were more likely to have treatment adjustments and serious AEs, as follows:

- dose reductions: lurbinectedin, 22.9%; topotecan, 48.3%;
- treatment delays: lurbinectedin, 25.8%; topotecan, 52.9%;
- serious AEs, grade 3 or higher: lurbinectedin, 15.0%; topotecan, 32.2%;
- discontinuations: lurbinectedin, 3.2%; topotecan, 5.7%;
- deaths: lurbinectedin, 1.3%; topotecan, 1.5%; and
- use of granulocyte colony-stimulating factor drugs: lurbinectedin, 23.8%; topotecan, 70.1%.

The investigators concluded that within the limitations of indirect comparisons, the analysis found patients taking lurbinectedin were less likely to experience hematological toxicities and treatment adjustments or discontinuations than those taking topotecan.

When the analysis was presented at the American Society of Clinical Oncology on May 29, 2020, topotecan was the only approved second-line therapy for SCLC. Since then, on June 16, the FDA granted lurbinectedin accelerated approval for second-line treatment of SCLC, based on results for the 105 patients in the basket trial.[2] Lurbinectedin, developed by PharMar and Jazz Pharmaceuticals, is sold as Zepzelca. ◆

REFERENCES

1. Leary A, Gaillard S, Vergote I, et al. Pooled safety analysis of single-agent lurbinectedin versus topotecan (Results from a randomized phase III trial CORAIL and a phase II basket trial). *J Clin Oncol* 2020;38(15): suppl; abstr 3635. doi:10.1200/JCO.2020.38.15_suppl.3635
2. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label phase 2 basket trial. *Lancet Oncol*. 2020;21(5):645-654. doi:10.1016/S1470-2045(20)30068-1

AJMC®TV interviews let you catch up on what's new and important about changes in health care, with insights from key decision makers—from the clinician, to the health plan leader, to the regulator. When every minute in your day matters, *AJMC*®TV interviews keep you informed. Access the video clips at ajmc.com/interviews.

Produced by Laura Joszt, Maggie L. Shaw, Mary Caffrey, and Briana Contreras

NOTE: this section has been edited for clarity

Tiragolumab Plus Atezolizumab Improves Objective Response in CITYSCAPE Trial

JOHNSON

Blocking TIGIT, a T-cell immunoreceptor, benefits patients with non–small cell lung cancer in that it can restore their immune system's antitumor response, leading to a greater objective response and progression-free survival, noted **MELISSA L. JOHNSON, MD**, associate director for lung cancer research at Sarah Cannon Research Institute and partner in Tennessee Oncology, in discussing the results of the CITYSCAPE trial.

At the American Society of Clinical Oncology (ASCO) meeting, you presented findings from CITYSCAPE. Can you provide some background on this trial, as well as its notable results?

CITYSCAPE is a randomized phase 2 trial. We enrolled 135 patients who were newly diagnosed with metastatic non–small cell lung cancer. They were negative for EGFR and ALK alterations, and their tumors expressed PD-L1 at least 1% or higher as tested using the Dako 22C3 assay. That assay could be done locally or centrally. Patients were randomized to receive tiragolumab, an anti-TIGIT antibody, plus atezolizumab, a PD-L1 antibody, versus placebo plus atezolizumab. The primary end points were objective response rate and progression-free survival (PFS). The trial results showed that patients who received the combination of tiragolumab plus atezolizumab had improved objective response as well as PFS compared with patients who were treated with placebo plus atezolizumab.

What particular mechanism of action of the anti-TIGIT immunotherapy is important in the lung cancer space?

TIGIT is another inhibitory checkpoint. It works similarly to PD-L1. TIGIT is expressed on immune cells, T cells, and natural killer cells, and when it binds to its ligand, PVR, on tumor cells or antigen-presenting cells, it can blunt the immune response. In a similar way to blocking PD-1 or PD-L1, when you block TIGIT with the anti-TIGIT antibody, tiragolumab, you can restore the antitumor immune response and activate inflammatory cells to fight the cancer. ◆

Understanding the Benefits of Zanubrutinib on Cardiac Effects

TAM

Compared with ibrutinib, the second-generation Bruton tyrosine kinase (BTK) inhibitor zanubrutinib appears to have more of a benefit for patients in that it is associated with less atrial fibrillation and hypertension, and fewer other cardiac effects, explained **CONSTANTINE S. TAM, MBBS, MD**, clinical hematologist, Peter MacCallum Cancer Centre in Melbourne, Australia. He discussed findings from the initial ASPEN study and updated results presented at ASCO.

What is it about the second-generation BTK inhibitors that might tend to cause less of these cardiac effects?

We think it's how clean the targeting is. We don't really know what causes hypertension and atrial fibrillation. We look at congenital BTK deficiency—humans born without BTK—and they don't really get atrial fibrillation or hypertension. So, presumably, you can dispense with BTK and be okay from a vascular point of view. We think that ibrutinib causes some of these AEs because it's not totally clean. So, it's like TEC, and EGFR, and JAK3 and a whole group of other enzymes, which are structurally related to BTK.

Now, with either zanubrutinib or acalabrutinib, you get less off-target enzyme inhibition [than with ibrutinib]. And I don't think anyone can actually put a finger on it and say, "*This* enzyme is causing it." But we just know that the cleaner it is, the better the profile.

And it wasn't just hypertension: Fibrillation and a whole multitude of other AEs, like muscle spasm, peripheral edema, pneumonitis, and pneumonia were reduced with zanubrutinib compared with ibrutinib. And I think a lot of the [cases of] sudden pneumonia were in fact pneumonitis, because there's no real reason why there should be such a big difference in infective pneumonia.

Overall, the ability to stay on a drug longer seems to favor zanubrutinib. Is that a benefit of it over ibrutinib?

Yes; the drug is easier to take. Fewer AEs, (adverse events) less dose reduction—people can stay on it for longer. Also, we actually examined the cumulative risk of atrial fibrillation and hypertension over time. You see that for zanubrutinib, essentially, most of the events happen in the first 12 months and then it sort of plateaus. Conversely, with ibrutinib, we've seen an increasing cumulative pattern. This suggests that if you are going to take one of these drugs for, let's say, 3 or 5 years, zanubrutinib may be a bit better because it has no cumulative effect on the vascular system, whereas ibrutinib appears to have one. ◆

AstraZeneca's Kilcoyne Claims Paradigm Shift in Lung Cancer Treatment

KILCOYNE

ADRIAN KILCOYNE, MD, MBA, MPH, vice president of US Medical Affairs and Health Economics Outcomes Research for Oncology at AstraZeneca, discusses a paradigm shift in lung cancer treatment due to the overwhelming efficacy of a EGFR–tyrosine kinase inhibitor (TKI) treatment.

A lot of excitement was generated by the news that ADAURA would be unblinded due to the overwhelmingly efficacy of the EGFR-TKI treatment. Can we expect the results to be paradigm shifting?

Absolutely. As you're aware, we've had some great results with osimertinib (Tagrisso) already in the metastatic setting.

So, we feel there's great promise in bringing it earlier into the disease paradigm. When we look at the ADAURA study, this is very much earlier in the longer-term curative setting; it's in the early stages, stage IB to IIIA, meaning these are the resectable populations. What we've been able to demonstrate is compelling. When any study is stopped 2 years early, that has to be done for a very good reason. As you can imagine, these data are compelling in terms of the disease-free survival benefit we're seeing, but they are important in a number of ways.

One, the data are telling us that if you hit cancer early, well, you can have very compelling results in lung cancer. This may drive people to want to identify disease earlier, which is really important, too. The second thing is that while all these patients had surgery, not all of them had adjuvant chemotherapy. Half did, half didn't, and regardless of that you're seeing significant benefit. So, in my view, there will be a paradigm shift. I think you'll see [osimertinib] will become standard of care.

Three is the question: Do you also need to give chemotherapy? And again, we don't have enough data; we have to wait for referrals, [more] data, etc. But I think those 3 areas will see very significant changes in clinical care.

Osimertinib is already approved in the United States for the frontline setting in metastatic non–small cell lung cancer. What can we expect to see in the adjuvant setting after ASCO?

So after ASCO—and I think I've touched on some of the things already said—in the frontline metastatic setting, which is late-stage, disease stage IV, we have seen great results with Tagrisso. It really has become the standard of care for all intents and purposes.…At AstraZeneca, we're very much committed to really eliminating cancer as a cause of death, and we do understand the best chance of achieving that is to treat early, [by] identifying the right patients early. This is what ADAURA is allowing us to do: treat patients early. Now if we think about the stage IBs, those are pretty early lung cancers, and right through to stage III—that's a broad group of patients. But if you look at those groups individually, we're seeing benefits in each group. So, this is incredibly compelling for physicians now to be able to treat their very early lung cancers, which would probably have a good chance of cure with just resection. Still, a huge proportion of these [surgical] patients will relapse. So, for me, this is going to be a huge change in clinical care. ◆

Video Conference Interventions Are an Invaluable Resource for Those Who Choose to Participate


DOUGLAS

Being part of a multidisciplinary team of oncologists, health care providers, caregivers, and patients benefits all members—not least the patients themselves—and telehealth-based interventions can help to foster these relationships. However, we should understand when patients do not want to involve their families in their care, noted **SARA L. DOUGLAS, PHD, RN**, the Gertrude Perkins Oliva Professor in Oncology Nursing and associate dean for research at the Frances Payne Bolton School of Nursing at Case Western Reserve University in Cleveland, Ohio.

The theme for this year's virtual meeting was "Unite and Conquer: Accelerating Progress Together." How does your poster on video conference interventions for distance caregivers of patients with cancer reflect this theme?

That's such an interesting question. To be honest, I didn't even know that was the theme of this year's conference. So, it's a very appropriate question. My answer, as I thought about it, is that I really think this study represented all of the good and the positive that come when all the members of the team unite for the benefit of the patient. In this research study, we had to rely on the oncologist and health care providers to participate and be involved, as well as the patient, the local caregiver, and the distance caregiver. By all of us sort of working together in conjunction with the researchers, we were able to test an intervention that's not only going to help the distance caregiver but will potentially help patients as well.

Did you find that people were eager to participate, or were they reticent?

All of the physicians were very interested in participating. This is one of the few intervention studies I've done where people didn't, you know, run and hide when they saw me coming, you know? They were very interested and engaged, as were other members of the health care team. Our refusal rate for participation was about 20%, which is less than what we usually see.…It was interesting that sometimes the distance caregiver didn't want to participate. Then again, sometimes, the patient didn't want them to participate.

[I couldn't help but notice something] when I would be involved in talking to a patient about whether or not they were interested in the study, and then in asking if they'd give us permission to reach out to their distance caregiver. I recognized that sometimes our family members are distant for a reason. Not all families want to be together, want to share information, etc. And so I think—although some of the health care providers were very surprised at times—when a patient did not want their extended family involved, it's very understandable. Each family unit is different, and so we did have some patients and some distance caregivers who were not interested in participating. ◆

Experimental Glioblastoma Therapy Has Promise in Treatment-Resistant Cancers


SKOLNICK

An experimental glioblastoma therapy with promising 12-month results may also have potential with other treatment-resistant cancers, according to **JEFFREY SKOLNICK, MD**, vice president of clinical development, Inovio Pharmaceuticals, Inc.

Inovio's experimental therapy, INO-5401, in combination with PD-1 checkpoint inhibitor cemiplimab, has shown promising results in glioblastoma. When can we expect to learn about 18-month findings?

We're really excited about our 18-month overall survival (OS) data. As we've just released the OS data at 12 months, we anticipate that by the end of this year, certainly fall or winter, we will have all of the data for our 18-month OS. That's really exciting to us.

If the 18-month findings are as promising as the 12-month findings, then what will the next steps be?

We're very excited to move on to a more pivotal study, for which we'll be speaking with our potential partners. With this study, we're collaborating with Regeneron and [its] cemiplimab, the PD-1 inhibitor that we are utilizing. We hope to continue those conversations with our collaborator, and we will move to designing a larger study and one that potentially will bring benefit to more patients.

Is there the potential for the combination of Inovio's experimental therapy, INO-5401, and immunotherapy to work in other treatment-resistant cancers the way you've shown it can work in glioblastoma?

It's key that INO-5401 is made up of 3 different DNA plasmids, which make up the 5401 DNA medicine. These 3 plasmids are proteins that are often overexpressed in human tumors. It is true that specifically for glioblastoma, these particular proteins are important. For example, human telomerase is often—if not almost always—overexpressed in glioblastoma.

But the same can be said for 2 other proteins: WT1, or Wilms' tumor 1, protein, as well as for prostate-specific antigen. And so together, we really do have a program that has the opportunity to be studied in many other human cancers.

Final thoughts?

First, thank you very much for allowing me to share my excitement about Inovio's therapies. I think that Inovio's DNA medicines really have the opportunity to change the way we are treating not only patients with cancer, but patients with precancerous conditions, potentially infectious diseases, as well. And we're really excited about the immunology and safety [data,] but most important, the efficacy data that we are seeing from our programs. ◆

AJMC 25 YEARS

MANAGED CARE PERSPECTIVES AT YOUR FINGERTIPS

AJMC® INSIGHTS

Participate in a unique opportunity to view lively discussions featuring peer-to-peer exchanges that provide authoritative insights, opinions, and perspectives on important issues facing today's managed care professionals.

FEATURED 2020 PROGRAMS

- BASAL CELL CARCINOMA
- INTERSTITIAL LUNG DISEASE
- MULTIPLE SCLEROSIS
- NASH (NONALCOHOLIC FATTY LIVER)
- DIABETES
- MULTIPLE MYELOMA

ONLY AT
AJMC.COM/INSIGHTS