A Pilot Study of Omalizumab to Treat Oxaliplatin-Induced Hypersensitivity Reaction

Ajai Chari, MD, Talks Diversity in Multiple Myeloma Research

Hematologic Malignancies: Review
Current Frontline Treatment of Multiple Myeloma

Review: Psycho-Oncology
Caring for Patients With Serious Mental Illness: Guide for the Oncology Clinician

CAR T-Cell Therapy: CME
Caring for Patients on CAR T-Cell Therapy in the Inpatient Versus Outpatient Setting
She needs a treatment shown to reduce risk of recurrence in high-risk early breast cancer (EBC)\(^1\)

The first FDA-approved addition to adjuvant ET in nearly 2 decades\(^1\)-\(^9\)

ET=endocrine therapy, HER2=human epidermal growth factor receptor 2-negative, HR=hormone receptor-positive.
INDICATION

VERZENIO® (abemaciclib) is indicated in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% as determined by an FDA-approved test.¹

SELECT IMPORTANT SAFETY INFORMATION

Severe diarrhea associated with dehydration and infection occurred in patients treated with Verzenio. Across four clinical trials in 3691 patients, diarrhea occurred in 81 to 90% of patients who received Verzenio. Grade 3 diarrhea occurred in 8 to 20% of patients receiving Verzenio. Most patients experienced diarrhea during the first month of Verzenio treatment. The median time to onset of the first diarrhea event ranged from 6 to 8 days; and the median duration of Grade 2 and Grade 3 diarrhea ranged from 6 to 11 days and 5 to 8 days, respectively. Across trials, 19 to 26% of patients with diarrhea required a Verzenio dose interruption and 13 to 23% required a dose reduction.

Instruct patients to start antidiarrheal therapy, such as loperamide, at the first sign of loose stools, 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, including febrile neutropenia and fatal neutropenic sepsis, occurred in patients treated with Verzenio. Across four clinical trials in 3691 patients, neutropenia occurred in 37 to 46% of patients receiving Verzenio. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 19 to 32% of patients receiving Verzenio. Across trials, the median time to first episode of Grade ≥3 neutropenia ranged from 29 to 33 days, and the median duration of Grade ≥3 neutropenia ranged from 11 to 16 days. Febrile neutropenia has been reported in <1% of patients exposed to Verzenio across trials. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

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.

Severe, life-threatening, or fatal interstitial lung disease (ILD) or pneumonitis can occur in patients treated with Verzenio and other CDK4/6 inhibitors. In Verzenio-treated patients in EBC (monarchE), 3% of patients experienced ILD or pneumonitis of any grade: 0.4% were Grade 3 or 4 and there was one fatality (0.1%). In Verzenio-treated patients in MBC (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of Verzenio-treated patients had ILD or pneumonitis of any grade: 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD or pneumonitis have been observed in the postmarketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD or 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 or pneumonitis. Permanently discontinue Verzenio in all patients with Grade 3 or 4 ILD or pneumonitis.

TAKE HOPE FURTHER

Please see Select Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.
Verzenio: FDA-APPROVED for patients with HR+, HER2-, node-positive EBC at high risk of recurrence and a Ki-67 score $\geq 20\%^{1-3}$

**APPROVAL BASED ON RESULTS IN PATIENTS WITH THE INDICATED CLINICAL AND PATHOLOGICAL RISK FACTORS (n=2,003)$^1$**

Consider Verzenio for your patients with

**NODE-POSITIVE DISEASE**

4+ nodes OR 1-3 nodes with Grade 3 disease or tumor size $\geq 5$ cm

monarchE was a phase III clinical trial that enrolled 5,637 peri- and postmenopausal adult women and men with HR+, HER2-, node-positive EBC at high risk of recurrence. High risk was defined as 4+ positive nodes, or 1-3 positive nodes with Grade 3 disease or tumor size $\geq 5$ cm (central Ki-67 testing was conducted retrospectively for patients with untreated breast tissue samples), or 1-3 positive nodes with Ki-67 $\geq 20\%$. All patients completed primary treatment prior to 1:1 randomization to receive either 150-mg, twice-daily Verzenio plus SoC ET or SoC ET alone for 2 years. ET continued through 5-10 years as clinically indicated. The primary endpoint was IDFS.$^{1,2}$

**SELECT IMPORTANT SAFETY INFORMATION (cont’d)**

Grade $\geq 3$ increases in alanine aminotransferase (ALT) (2 to 6%) and aspartate aminotransferase (AST) (2 to 3%) were reported in patients receiving Verzenio. Across three clinical trials in 3559 patients (monarchE, MONARCH 2, MONARCH 3), the median time to onset of Grade $\geq 3$ ALT increases ranged from 57 to 87 days and the median time to resolution to Grade $<3$ was 13 to 14 days. The median time to onset of Grade $\geq 3$ AST increases ranged from 71 to 185 days and the median time to resolution to Grade $<3$ ranged from 11 to 15 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 any Grade 3 or 4 hepatic transaminase elevation.

Please see Select Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.
In patients with HR+, HER2−, node-positive EBC at high risk of recurrence and a Ki-67 score ≥20% (n=2,003)

**Verzenio:** The only CDK4 & 6 inhibitor to reduce risk of recurrence in combination with ET ¹,⁷⁻⁹

**At 3 years, Verzenio reduced the risk of recurrence by more than a third**¹

86.1% of patients remained recurrence-free with Verzenio plus ET vs 79.0% with ET alone.¹

The number of events at the time of analysis was 104 with Verzenio plus ET vs 158 with ET alone.¹

OS was immature. A total of 95 (4.7%) patients had died. Long-term follow-up is planned.¹,²

This post hoc efficacy analysis was performed at a median follow-up of 27.1 months. Additional exploratory analyses were performed at this time; efficacy results for the subpopulation with high-risk clinicopathological features and Ki-67 ≥20% are provided.³

*Statistical significance was achieved for this subpopulation earlier at the final IDFS analysis. The result in this post hoc analysis cannot be interpreted as statistically significant.¹

**SELECT IMPORTANT SAFETY INFORMATION (cont’d)**

Venous thromboembolic events (VTE) were reported in 2 to 5% of patients across three clinical trials in 3559 patients treated with Verzenio (monarchE, MONARCH 2, MONARCH 3). VTE included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. In clinical trials, deaths due to VTE have been reported in patients treated with Verzenio.

Verzenio has not been studied in patients with early breast cancer who had a history of VTE. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. Dose interruption is recommended for EBC patients with any grade VTE and for MBC patients with a Grade 3 or 4 VTE.

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 3 weeks after the last dose. Advise MBC patients with a Grade 3 or 4 VTE.

Verzenio can impair fertility in males of reproductive potential. There are no data on the presence of Verzenio in human milk or its effects on the breastfeeding 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.
SELECT IMPORTANT SAFETY INFORMATION (cont’d)

The most common adverse reactions (all grades, ≥10%) observed in monarchE for Verzenio plus tamoxifen or an aromatase inhibitor vs tamoxifen or an aromatase inhibitor, with a difference between arms of ≥2%, were diarrhea (84% vs 9%), infections (51% vs 39%), neutropenia (46% vs 6%), fatigue (41% vs 18%), leukopenia (38% vs 7%), nausea (30% vs 9%), anemia (24% vs 4%), headache (20% vs 15%), vomiting (18% vs 4.6%), stomatitis (14% vs 5%), lymphopenia (14% vs 3%), thrombocytopenia (13% vs 2%), decreased appetite (12% vs 2.4%), ALT increased (12% vs 6%), AST increased (12% vs 5%), dizziness (11% vs 7%), rash (11% vs 4.5%), and alopecia (11% vs 2.7%).

The most frequently reported ≥5% Grade 3 or 4 adverse reaction that occurred in the Verzenio arm vs the tamoxifen or an aromatase inhibitor arm of monarchE were neutropenia (19.6% vs 1%), leukopenia (11% vs <1%), diarrhea (8% vs 0.2%), and lymphopenia (5% vs <1%).

Lab abnormalities (all grades; Grade 3 or 4) for monarchE in ≥10% for Verzenio plus tamoxifen or an aromatase inhibitor with a difference between arms of ≥2% were increased serum creatinine (99% vs 91%; 5% vs <1%), decreased white blood cells (89% vs 28%; 19.1% vs 1.1%), decreased neutrophil count (84% vs 23%; 18.7% vs 1.9%), anemia (68% vs 17%; 1% vs 1%), decreased lymphocyte count (59% vs 24%; 13.2% vs 2.5%), decreased platelet count (37% vs 10%; 9% vs <1%), increased ALT (37% vs 24%; 2.6% vs 1.2%), increased AST (31% vs 18%; 1.6% vs 9%), and hypokalemia (11% vs 3.8%; 1.3% vs 0.2%).

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 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 C), reduce the Verzenio dosing frequency to once daily. The pharmacokinetics of Verzenio in patients with severe renal impairment (CrCl <30 mL/min), end stage renal disease, or in patients on dialysis is unknown. No dosages adjustments are necessary in patients with mild or moderate hepatic (Child-Pugh A or B) and/or renal impairment (CrCl ≥30-<80 mL/min).

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

AL HCP IS_l_ME 12OCT2021


PP-AL-US-3237 03/2022 ©Lilly USA, LLC 2022. All rights reserved. Verzenio® is a registered trademark owned or licensed by Eli Lilly and Company, its subsidiaries or affiliates.
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 endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% as determined by an FDA-approved test.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS
Diarrhea
Severe diarrhea associated with dehydration and infection occurred in patients treated with VERZENIO. Across four clinical trials in 3691 patients, diarrhea occurred in 81% to 90% of patients who received VERZENIO. Grade 3 diarrhea occurred in 6% to 20% of patients receiving VERZENIO. Most patients experienced diarrhea during the first month of VERZENIO treatment. The median time to onset of the first diarrhea event ranged from 6 to 8 days; and the median duration of Grade 2 and Grade 3 diarrhea ranged from 6 to 11 days and 5 to 8 days, respectively. Across trials, 19% to 26% of patients with diarrhea required a VERZENIO dose interruption and 13% to 23% required a dose reduction.

Instruct patients to start antidiarrheal therapy such as loperamide at the first sign of loose stools, 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, including febrile neutropenia and fatal neutropenic sepsis, occurred in patients treated with VERZENIO. Across four clinical trials in 3691 patients, neutropenia occurred in a 37% to 46% of patients receiving VERZENIO. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 19% to 32% of patients receiving VERZENIO. Across trials, the median time to the first episode of Grade ≥3 neutropenia ranged from 29 days to 33 days, and the median duration of Grade ≥3 neutropenia ranged from 11 days to 16 days.

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

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.

Interstitial Lung Disease (ILD) or Pneumonitis
Severe, life-threatening, or fatal interstitial lung disease (ILD) or pneumonitis can occur in patients treated with VERZENIO and other CDK4/6 inhibitors. In VERZENIO-treated patients in early breast cancer (monarchE, N=2791), 3% of patients experienced ILD or pneumonitis of any grade: 0.4% were Grade 3 or 4 and there was one fatality (0.1%). In VERZENIO-treated patients in advanced or metastatic breast cancer (N=900) (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of VERZENIO-treated patients had ILD or pneumonitis of any grade: 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD or pneumonitis have been observed in the postmarketing setting, with fatalities reported.

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

VERZENIO® (abemaciclib) tablets, for oral use

Hepatotoxicity
Grade ≥3 ALT (2% to 6%) and AST (2% to 3%) were reported in patients receiving VERZENIO. Across three clinical trials in 3559 patients (monarchE, MONARCH 2, MONARCH 3), the median time to onset of Grade ≥3 ALT increases ranged from 57 to 87 days and the median time to resolution to Grade <3 was 13 to 14 days. The median time to onset of Grade ≥3 AST increases ranged from 71 to 165 days and the median time to resolution to Grade <3 ranged from 11 to 15 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 ALT or AST elevation.

Venous Thromboembolism
Across three clinical trials in 3559 patients (monarchE, MONARCH 2, MONARCH 3), venous thromboembolic events were reported in 2% to 5% of patients treated with VERZENIO. 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. In clinical trials, deaths due to venous thromboembolism have been reported in patients treated with VERZENIO.

VERZENIO has not been studied in patients with early breast cancer who had a history of venous thromboembolism. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. Dose interruption is recommended for early breast cancer patients with any grade venous thromboembolic event and for advanced or metastatic breast cancer patients with a Grade 3 or 4 venous thromboembolic event.

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 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.

The safety population described in the Warnings and Precautions reflect exposure to VERZENIO in 3691 patients from four clinical trials: monarchE, MONARCH 1, MONARCH 2, and MONARCH 3. The safety population includes exposure to VERZENIO as a single agent at 200 mg twice daily in 132 patients in MONARCH 1 and to VERZENIO at 150 mg twice daily in 3559 patients administered in combination with fulvestrant, tamoxifen, or an aromatase inhibitor in monarchE, MONARCH 2, and MONARCH 3. The median duration of exposure ranged from 4.5 months in MONARCH 1 to 24 months in monarchE. The most common adverse reactions (incidence ≥20%) across clinical trials were: diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, alopecia, and thrombocytopenia.

Early Breast Cancer
monarchE/VERZENIO in Combination with Tamoxifen or an Aromatase Inhibitor as Adjuvant Treatment
Adult patients with HR-positive, HER2-negative, node-positive early breast cancer at a high risk of recurrence

The safety of VERZENIO was evaluated in monarchE, a study of 5591 adult patients receiving VERZENIO plus endocrine therapy (tamoxifen or an aromatase inhibitor) or endocrine VERZENIO® (abemaciclib) tablets, for oral use

AL HCP BS_MonE 12OCT2021

AL HCP BS_MonE 12OCT2021
therapy (tamoxifen or an aromatase inhibitor) alone. Patients were randomly assigned to receive 150 mg of VERZENIO orally, twice daily, plus tamoxifen or an aromatase inhibitor, or tamoxifen or an aromatase inhibitor, for two years or until discontinuation criteria were met. The median duration of VERZENIO treatment was 24 months.

The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, leukopenia, diarrhea, and lymphopenia.

Fatality adverse reactions occurred in 0.8% of patients who received VERZENIO plus endocrine therapy (tamoxifen or an aromatase inhibitor), including: cardiac failure (0.1%), cardiac arrest, myocardial infarction, ventricular fibrillation, cerebral hemorrhage, cerebrovascular accident, pneumonia, hypotension, hypoxia, diarrhea and mesenteric artery thrombosis (0.03% each).

Permanent VERZENIO treatment discontinuation due to an adverse reaction was reported in 19% of patients receiving VERZENIO, plus tamoxifen or an aromatase inhibitor. Of the patients receiving tamoxifen or an aromatase inhibitor, 1% permanently discontinued due to an adverse reaction. The most common adverse reactions leading to VERZENIO discontinuations were diarrhea (5%), fatigue (2%), and neutropenia (0.9%).

Dose interruption of VERZENIO due to an adverse reaction occurred in 62% of patients receiving VERZENIO plus tamoxifen or aromatase inhibitors. Adverse reactions leading to VERZENIO dose interruptions in ≥5% of patients were diarrhea (20%), neutropenia (16%), leukopenia (7%), and fatigue (5%).

Dose reductions of VERZENIO due to an adverse reaction occurred in 44% of patients receiving VERZENIO plus tamoxifen or aromatase inhibitors. Adverse reactions leading to VERZENIO dose reductions in ≥5% were diarrhea (17%), neutropenia (8%), and fatigue (5%).

The most common adverse reactions reported (≥20%) in the VERZENIO, plus tamoxifen or an aromatase inhibitor arm and ≥2% higher than the tamoxifen or an aromatase inhibitor arm were: diarrhea, infections, neutropenia, fatigue, leukopenia, nausea, anemia, and headache. Adverse reactions are shown in Table 1 and laboratory abnormalities are shown in Table 2.

The most relevant adverse reactions in <10% of patients who received VERZENIO in combination with tamoxifen or an aromatase inhibitor in monarchE include:

- Pruritus-9%
- Dyspepsia-8%
- Nail disorder-6% (includes nail bed disorder, nail bed inflammation, nail discoloration, nail disorder, nail dystrophy, nail pigmentation, nail shedding, nail toxicity, onychalgia, onycholysis, onychomadesis)
- Lactic acidosis increased-6%
- Dyspepsia-5%
- Interstitial lung disease (ILD)/pneumonitis-3% (includes pneumonitis, radiation pneumonitis, interstitial lung disease, pulmonary fibrosis, organizing pneumonia, radiation fibrosis – lung, lung opacity, sarcoidosis)
- Venous thromboembolic events (VTEs)-3% (includes catheter site thrombosis, cerebral venous thrombosis, deep vein thrombosis, device related thrombosis, embolism, hepatic vein thrombosis, jugular vein occlusion, jugular vein thrombosis, ovarian vein thrombosis, portal vein thrombosis, pulmonary embolism, subclavian vein thrombosis, venous thrombus limb)

**Table 1: Adverse Reactions (≥10%) of Patients Receiving VERZENIO Plus Tamoxifen or an Aromatase Inhibitor (with a Difference between Arms of ≥2%) in monarchE**

<table>
<thead>
<tr>
<th></th>
<th>VERZENIO Plus Tamoxifen or an Aromatase Inhibitor</th>
<th>Tamoxifen or an Aromatase Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Grades</strong></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>84</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>0.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>0.5</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>14</td>
<td>0.1</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Infections</td>
<td>51</td>
<td>4.9</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>41</td>
<td>2.9</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Headache</td>
<td>20</td>
<td>0.3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>0.1</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>0.6</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Rash</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>Alopeia</td>
<td>11</td>
<td>0.0</td>
</tr>
</tbody>
</table>

- Includes asthma, fatigue.
- Includes exfoliative rash, mucocutaneous rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash papular, rash papulosquamous, rash pruritic, rash vesicular, vulvovaginal rash.

**Table 2: Laboratory Abnormalities (≥10%) in Patients Receiving VERZENIO Plus Tamoxifen or an Aromatase Inhibitor (with a Difference between Arms of ≥2%) in monarchE**

<table>
<thead>
<tr>
<th></th>
<th>VERZENIO Plus Tamoxifen or an Aromatase Inhibitor</th>
<th>Tamoxifen or an Aromatase Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=2791</td>
<td>N=2800</td>
</tr>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>99</td>
<td>0.5</td>
</tr>
<tr>
<td>White blood cell</td>
<td>89</td>
<td>19</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>84</td>
<td>18</td>
</tr>
<tr>
<td>Anemia</td>
<td>68</td>
<td>1.0</td>
</tr>
<tr>
<td>Lymphocytopena count</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>Platelet count</td>
<td>37</td>
<td>0.7</td>
</tr>
<tr>
<td>Alamine aminotransferase increased</td>
<td>37</td>
<td>2.5</td>
</tr>
<tr>
<td>Aspartate</td>
<td>31</td>
<td>1.5</td>
</tr>
<tr>
<td>Hyposkemia</td>
<td>11</td>
<td>1.2</td>
</tr>
</tbody>
</table>

**DRUG INTERACTIONS**

**Effect of Other Drugs on VERZENIO**

- **CYP3A4 Inhibitors**
  
  Strong and moderate CYP3A4 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 sternum, 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 3 weeks after the last dose.

**Females and Males of Reproductive Potential**

Based on animal studies, VERZENIO can cause fetal harm when administered to a pregnant woman.

**Pregnancy Testing**

Verify pregnancy status in females of reproductive potential prior to initiating treatment with VERZENIO.

**Contraception**

**Females**

Advise females of reproductive potential to use effective contraception during VERZENIO treatment and for 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.
PUBLISHER’S NOTE
Editorial Advisory Board Updates and Call for Papers

LETTER TO THE READERS
Platinum Hypersensitivity Reaction (HSR): An Ongoing Problem in Cancer Treatment
Howard S. Hochster, MD

Visit CancerNetwork.com, home of the journal ONCOLOGY® and a web destination for oncologists seeking expert peer perspectives, podcasts, and other clinically practical features.

PODCAST
Oncology Peer Review On-the-Go: Academic Promotion and Oncology Drug Development
Cancernetwork.com/podcast_7.22

VIDEO
Shubham Pant, MD, on the Future of Treatment of Pancreatic Cancer With Targeted Therapies
Cancernetwork.com/Pant_7.22

FDA APPROVAL
FDA Grants Accelerated Approval to Dabrafenib Plus Trametinib for BRAF V600E+ Tumor-Agnostic Indication
Cancernetwork.com/approval_7.22

Check out our e-newsletter for the latest in oncology.
SCAN TO SUBSCRIBE.
HEMATOLOGIC MALIGNANCIES: INTERVIEW
412 Ajai Chari, MD, Talks Diversity in Multiple Myeloma Research

HEMATOLOGIC MALIGNANCIES: REVIEW
430 Current Frontline Treatment of Multiple Myeloma
Sarah A. Holstein, MD, PhD

PEER PERSPECTIVE:Kimberley R. Doucette, MD, MSC; and David H. Vesole, MD, PhD

REVIEW: PSYCHO-ONCOLOGY
450 Caring for Patients With Serious Mental Illness: Guide for the Oncology Clinician
Veronica B. Decker, DNP, MBA, APRN, PMH CNS-BC; Zoe E. Nelson, BA; Amy Corveleyn, MSW; Priya K. Gopalan, MD, MPH; and Kelly Irwin, MD, MPH

PEER PERSPECTIVE:Sheila Lahijani, MD, FACLP

RAPID REPORTER®
460 ONCOLOGY® Reviews Key Presentations From the 2022 American Society of Clinical Oncology Annual Meeting

MEDICAL ECONOMICS®
465 Tracking Success to Improve Your Practice

CAR T-CELL THERAPY: CME
466 Caring for Patients on CAR T-Cell Therapy in the Inpatient Versus Outpatient Setting
Charise Gleason, MSN, NP-BC, AOCNP

CancerNetwork®, home of the journal ONCOLOGY®, partners with leading national cancer centers and organizations to bring multidisciplinary oncology providers clinical take-aways for application in today's time-constrained practice environment.
ONCOLOGY® and its website, CancerNetwork.com, provide oncologists with the practical, timely, clinical information they need to deliver the highest level of care to their patients. Expert authors and peer review ensure the quality of ONCOLOGY® and CancerNetwork.com’s articles and features. Focused discussions capture key clinical take-aways for application in today’s time-constrained practice environment.

EDITORIAL ADVISORY BOARD

MISSION STATEMENT

EDITORS-IN-CHIEF

Julie M. Vose, MD, MBA
Onah, NE
Howard S. Hochster, MD
New Brunswick, NJ

EDITORIAL BOARD

TUMOR CHAIRS

BREAST CANCER
Sara A. Hurvitz, MD, Los Angeles, CA
GENITOURINARY CANCER
Robert A. Figlin, MD, Los Angeles, CA
GASTROINTESTINAL CANCER
Tanios S. Berek-Saab, MD, Phoenix, AZ
HEAD AND NECK CANCER
Eric J. Sherman, MD, New York, NY
HEMATOLOGIC MALIGNANCIES
C. Ola Landgren, MD, PhD, Miami, Fl
THORACIC MALIGNANCIES
Hossein Borghaei, DO, MS, Philadelphia, PA

BOARD MEMBERS

BREAST CANCER
William J. Gradishar, MD, FACCP, Chicago, IL
Tari King, MD, Boston, MA
Stephen M. Schleichter, MD, MBA, Lebanon, TN
Vereen Stearns, MD, Baltimore, MD
Melindu L. Teji, MD, Palo Alto, CA
CANCER SURVIVORSHIP
Matthew J. Matalan, MD, MS, New York, NY
COLORECTAL/GASTROINTESTINAL CANCER
Edward Chu, MD, Pittsburgh, PA
Mehmet Sikten Copur, MD, FACCP, Omaha, NE
Daniel Haller, MD, Philadelphia, PA
John L. Marshall, MD, Washington, DC
Shubham Pant, MD, Houston, TX
Matthew B. Yurgelun, MD, Boston, MA
GENITOURINARY CANCER
L. Michael Glöde, MD, FACCP, Denver, CO
Paul Mathew, MD, Boston, MA
Elisabeth Heath, MD, FACCP, Detroit, MI
Bobby Liaw, MD, New York, NY
GYNECOLOGIC ONCOLOGY
Mario M. Leitao Jr, MD, New York, NY
Ritu Salani, MD, Los Angeles, CA
HEAD AND NECK CANCER
Apar K. Ganju, MD, MS, FACP, Omaha, NE
HEALTH ECONOMICS
Nora Janjan, MD, MPH, MBA, Dallas, TX
HEMATOLOGIC MALIGNANCIES
Danielle M. Brandner, MD, Durham, NC
Christopher R. Flowers, MD, Houston, TX
Steven T. Rosen, MD, Duarte, CA
Naval D. Duvet, MD, Houston, TX
Eshah L. Atallah, MD, Misakiue, WI
INFECTIOUS DISEASE
Genoveta Papadopoulou, MD, New York, NY
INTEGRATIVE ONCOLOGY
Ting Bao, MD, New York, NY
Linda Carlson, PhD, RPsych, Calgary, Alberta, Canada
LUNG CANCER
David S. Ettinger, MD, Baltimore, MD
James L. Mulschene, MD, Chicago, IL
Edward S. Kim, MD, Duarte, CA
Jennifer W. Carlisle, MD, Atlanta, GA
MELANOMA
Richard D. Carvajal, MD, New York, NY
Jason Luke, MD, FACCP, Pittsburgh, PA
NEURO-ONCOLOGY
David A. Reardon, MD, Boston, MA
Stuart A. Grossman, MD, Baltimore, MD
Nicole A. Shonka, MD, Omaha, NE
PEDIATRIC ONCOLOGY
David G. Poplack, MD, Houston, TX
Richard A. Drachman, MD, New Brunswick, NJ
PROSTATE CANCER
Tomasz M. Beer, MD, Portland, OR
E. David Crawford, MD, Denver, CO
Judd W. Mould, MD, FACS, Durham, NC
PSYCHO-ONCOLOGY
Daniel C. McFarland, DO, New York, NY
Michelle Ribba, MD, Ann Arbor, MI
RADIATION ONCOLOGY
Louis Potters, MD, FACP, Hempstead, NY
James B. Yu, MD, MHS, New Haven, CT
SARCINA
Kenneth Cardona, MD, FACS, Atlanta, GA
SURGICAL ONCOLOGY
Burton L. Eisenberg, MD, Newport Beach, CA

INTERESTED IN SUBMITTING TO ONCOLOGY®?
Please contact CancerNetwork@mjhlifesciences.com for submission guidelines.
EDITORIAL ADVISORY BOARD UPDATES

ONCOLOGY® is pleased to spotlight some important updates from our Editorial Advisory Board members.

In May, William J. Gradishar, MD, Betsy Bramsen Professor of Breast Oncology and chief of hematology and oncology in the Department of Medicine at Northwestern University’s Feinberg School of Medicine in Chicago, Illinois, was awarded the 2022 Rodger Winn Award by the National Comprehensive Cancer Network (NCCN). The award’s namesake is the medical oncologist who oversaw the development of the first generation of NCCN Guidelines. Gradishar is the current chair of the NCCN Guidelines Panel for Breast Cancer.

Edward Chu, MD, MMS, and colleagues have partnered with the Price Family Foundation to research novel cancer therapies for historically underserved populations in the Bronx. Chu is a professor in the departments of oncology, medicine (oncology & hematology), and molecular pharmacology and director of the Albert Einstein Cancer Center at Montefiore Medicine New York.

In June, Melinda L. Telli, MD, was among a group of investigators awarded funds from the Susan G. Komen Foundation. Telli is an associate professor of medicine (oncology) in the Division of Medical Oncology at Stanford University School of Medicine, director of the Stanford Cancer Institute’s Breast Cancer Program, and associate director of the Stanford Women’s Cancer Center. This year, the Susan G. Komen Foundation awarded $21.7 million to 48 new research projects across 26 different academic medical institutions.

For more about the Editorial Advisory Board, visit cancernetwork.com/editorial-board

CALL FOR PAPERS

ONCOLOGY® is seeking to expand its coverage of original peer-reviewed research articles and is now encouraging authors to submit high-quality original manuscripts about clinical trials and investigations. Areas of particular interest include, but are not limited to, gastrointestinal, breast, gynecologic, genitourinary, and lung cancers as well as hematologic malignancies.

Authors wishing to submit their original research manuscripts are encouraged to review the ONCOLOGY® author guidelines for formatting and other requirements prior to submission. Manuscripts for consideration should be submitted to https://mc.manuscriptcentral.com/oncology.
Platinum Hypersensitivity Reaction (HSR): An Ongoing Problem in Cancer Treatment

Howard S. Hochster, MD

In this issue of ONCOLOGY®, Stacey Stein, MD, and colleagues report on the use of anti-immunoglobulin E (IgE) antibodies (omalizumab; Xolair) for the successful treatment of oxaliplatin hypersensitivity reaction (HSR; see pages 414-419). In the spirit of full disclosure, I am the senior author on this paper and originated the idea of using omalizumab for platinum HSR about 10 years ago. This is based on the known biology of platinum hypersensitivity, which is mediated by IgE.

Repeated exposure to platinum results in HSR in a fairly high proportion of those exposed. This is well known from platinum battery workers who after 1 to 2 years of continued exposure begin to develop significant allergies. The issue of platinum HSR in the treatment of cancer has been present since cisplatin was first introduced. It is well documented that platinum HSRs result from prolonged intermittent exposure to these drugs, or after a break, and at the time of retreatment. Gynecologic oncologists have been dealing with this when retreating ovarian cancer, mainly using carboplatin; they have developed a number of means of managing adverse reactions, including subcutaneous drug testing, prolonged and gradual dosing increments to help bind the platinum slowly before triggering HSR, and even admissions to intensive care units for treating such patients with “desensitization.”

The problem of oxaliplatin HSR has also been around since the agent’s introduction in the 1990s. It is documented that up to 40% of patients treated with oxaliplatin for advanced disease are taken off treatment without progression, and 20% of patients in the adjuvant setting do not complete 6 months of treatment.1 These patients typically stop the drug due to cumulative neurotoxicity or other events, mainly related to myelosuppression. Treatment with FOLFOX after progression on other drugs, can lead to responses once more, as we have seen in other scenarios. However, we frequently find that the first dose of FOLFOX retreatment is tolerated well, but the second or third treatment results in an amnestic response of the immune system to the platinum and causes a significant HSR.

Omalizumab is an anti-IgE antibody approved for treatment of asthma and urticaria.2 It has documented use for allergic reactions to peanuts and has also been used for drug reactions, particularly in chemotherapy. It can block IgE activation of mast cells, prevent HSRs, and reverse ongoing HSR by releasing IgE binding. As noted in the review article by Bumbacea et al,2 current experience is limited to only 1 or 2 prospective trials for chemotherapy HSR, including the Stein article published here, which is the largest experience to date. Other publications are case reports. Pharmaceutical sponsors have shown little interest in supporting large trials, but the problem of oxaliplatin HSR is significant: If patients were not discontinued from oxaliplatin retreatment for HSR, they might continue to benefit from treatment. In our study of 9 patients treated prospectively with biweekly omalizumab, 8 of 9 patients reached the primary end point of receiving 2 cycles of treatment and reaching the next scan, and 5 of 9 were able to achieve disease control for a median of 6 months. This new and more biologic approach to HSR has promise and should be further tested in multicenter trials.

REFERENCES
EMBRACE
SUPERIOR SURVIVAL
WITH PROVEN SAFETY

TUKYSA + trastuzumab + capecitabine vs placebo + trastuzumab + capecitabine

- Median PFS: 7.8 months (95% CI: 7.5–9.6) vs 5.6 months (95% CI: 4.2–7.1); HR = 0.54 (95% CI: 0.42–0.71); P <0.00001 (primary endpoint)

More than 2 years median overall survival at follow-up analysis

- Primary analysis‡: 21.9 months (95% CI: 18.3–31.0) vs 17.4 months (95% CI: 13.6–19.9); HR = 0.66 (95% CI: 0.50–0.87); P = 0.0048 (secondary endpoint)

- Follow-up analysis§: 24.7 months (95% CI: 21.6–28.9) vs 19.2 months (95% CI: 16.4–21.4); HR = 0.73 (95% CI: 0.59–0.90); median follow-up: 29.6 months

Follow-up OS analysis: Results of this prespecified exploratory analysis are descriptive but not conclusive, are not controlled for type 1 error, and should be interpreted with caution.

Safe and well tolerated

- The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash

- 6% of patients discontinued TUKYSA due to adverse reactions vs 3% with placebo

**Indication**

TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

**Select Important Safety Information**

- The Prescribing Information for TUKYSA contains warnings and precautions for diarrhea, hepatotoxicity, and embryo-fetal toxicity, some of which may be severe
- The most common serious adverse reactions in ≥2% of patients who received TUKYSA were diarrhea, vomiting, nausea, abdominal pain, and seizure

**Study design:** HER2CLIMB was a randomized (2:1) trial of TUKYSA or placebo each in combination with trastuzumab and capecitabine in 612 patients with HER2+ MBC, previously treated with trastuzumab, pertuzumab, and T-DM1. Primary endpoint was PFS per BICR in the first 480 patients enrolled. Secondary endpoints included OS. A prespecified exploratory analysis was included to evaluate OS at ~2 years. Please see additional study design on the following page.

*Data from the first 480 patients.

**CIC0722_407-411_Seagen-Tukysa.indd   407**
In combination with trastuzumab + capecitabine

TUKYSA ACHIEVED A MEDIAN OVERALL SURVIVAL OF MORE THAN 2 YEARS AT FOLLOW-UP ANALYSIS\(^2\)*

OS in the total population (N = 612)\(^2\)

**Warning and Precautions**

**Important Safety Information**

**Warnings and Precautions**

- **Diarrhea:** TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of anti-diarrheal treatment was not required on HER2CLIMB.

  If diarrhea occurs, administer anti-diarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Hepatotoxicity:** TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5×ULN, 6% had an AST increase >5×ULN, and 1.5% had a bilirubin increase >3×ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% of patients.

  Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Embryo-Fetal Toxicity:** TUKYSA can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during TUKYSA treatment and for at least 1 week after the last dose.

**Adverse Reactions**

Serious adverse reactions occurred in 26% of patients who received TUKYSA; those occurring in ≥2% of patients were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions led to treatment discontinuation in 6% of patients who received TUKYSA; those occurring in ≥1% of patients included Grade ≥3 laboratory abnormalities reported in ≥5% of patients who received TUKYSA (8%) and diarrhea (6%). The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

**Lab Abnormalities**

In HER2CLIMB, Grade ≥3 laboratory abnormalities reported in ≥5% of patients who received TUKYSA were decreased phosphate, increased ALT, decreased potassium, and increased AST.
The most common adverse reactions (≥20%) were diarrhea, PPE, nausea, fatigue, vomiting, decreased appetite, stomatitis, headache, AST increased, anemia, ALT increased, and blood bilirubin increased.

<table>
<thead>
<tr>
<th>TEAEs Grade ≥3</th>
<th>TEAEs leading to death</th>
</tr>
</thead>
<tbody>
<tr>
<td>61% (245/404) in the TUKYSA arm vs 51% (101/197) in the control arm</td>
<td>2% (8/404) in the TUKYSA arm vs 3% (6/197) in the control arm</td>
</tr>
</tbody>
</table>

The rate of discontinuation due to adverse reactions for the TUKYSA arm remained consistent with the primary analysis²,³,⁴

<table>
<thead>
<tr>
<th>PRIMARY ANALYSIS³</th>
<th>FOLLOW-UP ANALYSIS²</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUKYSA 6% vs PLACEBO 3%</td>
<td>TUKYSA 6% vs PLACEBO 4%</td>
</tr>
</tbody>
</table>

The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

**Drug Interactions**
- **Strong CYP3A/Moderate CYP2C8 Inducers**: Concomitant use may decrease TUKYSA activity. Avoid concomitant use of TUKYSA.
- **Strong or Moderate CYP2C8 Inhibitors**: Concomitant use of TUKYSA with a strong CYP2C8 inhibitor may increase the risk of TUKYSA toxicity; avoid concomitant use. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.
- **CYP3A Substrates**: Concomitant use may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage.

- **P-gp Substrates**: Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicity.

**Use in Specific Populations**
- **Lactation**: Advise women not to breastfeed while taking TUKYSA and for at least 1 week after the last dose.
- **Renal Impairment**: Use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (ClCr < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.
- **Hepatic Impairment**: Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment.

Please see Brief Summary of Prescribing Information on adjacent pages.
Permanently discontinue TUKYSA in patients unable to tolerate 150 mg orally twice daily.

Table 1: Recommended TUKYSA Dose Reductions for Adverse Reactions

<table>
<thead>
<tr>
<th>Severity</th>
<th>TUKYSA Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 without anti-diarrheal treatment</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Grade 2 bilirubin (&gt;1.5 to 3 × ULN) Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 ALT or AST (&gt;5 to 10 × ULN) OR Grade 3 bilirubin (&gt;3 to 10 × ULN)</td>
<td>Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 4 ALT or AST (&gt;20 × ULN) OR Grade 4 bilirubin (&gt;10 × ULN)</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td>ALT or AST &gt;3 × ULN AND Bilirubin &gt;2 × ULN</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
</tbody>
</table>

Permanent discontinuation of TUKYSA is not recommended in patients unable to tolerate 150 mg orally twice daily.

Table 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td>Grade 3 without anti-diarrheal treatment</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 with anti-diarrheal treatment</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Grade 2 bilirubin (&gt;1.5 to 3 × ULN) Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 ALT or AST (&gt;5 to 10 × ULN) OR Grade 3 bilirubin (&gt;3 to 10 × ULN)</td>
<td>Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 4 ALT or AST (&gt;20 × ULN) OR Grade 4 bilirubin (&gt;10 × ULN)</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td>ALT or AST &gt;3 × ULN AND Bilirubin &gt;2 × ULN</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
</tbody>
</table>

1. Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.
2. Abbreviations: ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

WARNINGs AND PRECAUTIONs

Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 diarrhea and 0.5% with Grade 4 diarrhea. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. The median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to dose reductions of TUKYSA in 6% of patients and discontinuation of TUKYSA in 1% of patients. Prophylactic use of anti-diarrheal treatment was not required on HER2CLIMB, if diarrhea occurs, administer anti-diarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Hepatotoxicity: TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 × ULN, 6% had an AST increase >5 × ULN, and 1.5% had a bilirubin increase >3 × ULN (Grade ≥3). Hepatotoxicity led to dose reduction of TUKYSA in 8% of patients and discontinuation of TUKYSA in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis caused embryofetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. TUKYSA is used in combination with trastuzumab and capcitabine. Refer to the Full Prescribing Information of trastuzumab and capcitabine for pregnancy and contraception information.

ADVERSE REACTIONS

Clinical Trials Experience

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

HER2-Positive Metastatic Breast Cancer (HER2CLIMB)

The safety of TUKYSA in combination with trastuzumab and capcitabine was evaluated in HER2CLIMB. Patients received either TUKYSA 300 mg twice daily plus trastuzumab and capcitabine (n=404) or placebo plus trastuzumab and capcitabine (n=197). The median duration of treatment was 5.6 months (range: 3 days, 2.9 years) for the TUKYSA arm. Serious adverse reactions occurred in 26% of patients who received TUKYSA. Serious adverse reactions in ≥2% of patients who received TUKYSA were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions leading to treatment discontinuation occurred in 6% of patients who received TUKYSA. Adverse reactions leading to treatment discontinuation of TUKYSA in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions leading to dose reduction occurred in 21% of patients who received TUKYSA. Adverse reactions leading to dose reduction of TUKYSA in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

Table 3: Adverse Reactions (≥10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB (All Grades)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capcitabine (N = 404)</th>
<th>Placebo + Trastuzumab + Capcitabine (N = 197)</th>
<th>Grade (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>81</td>
<td>53</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>58</td>
<td>44</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>36</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>32</td>
<td>21</td>
<td>0.5</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>63</td>
<td>53</td>
<td>9</td>
</tr>
<tr>
<td>Rash</td>
<td>20</td>
<td>15</td>
<td>0.5</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>42</td>
<td>24</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Table 4: Adverse Reactions (≥10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB (All Grades)
DRUG INTERACTIONS

Effects of Other Drugs on TUKYSA

Strong CYP3A Inducers or Moderate CYP2C8 Inducers: Concomitant use of TUKYSA with a strong CYP3A or moderate CYP2C8 inducer decreased tucatinib plasma concentrations, which may reduce TUKYSA activity. Avoid concomitant use of TUKYSA with a strong CYP3A inducer or a moderate CYP2C8 inducer.

Strong or Moderate CYP2C8 Inhibitors: Concomitant use of TUKYSA with a strong CYP3A21 or moderate CYP2C8 inhibitor increased tucatinib plasma concentrations, which may increase the risk of TUKYSA toxicity. Avoid concomitant use of TUKYSA with a strong CYP2C8 inhibitor. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

Effects of TUKYSA on Other Drugs

CYP3A Substrates: Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

P-glycoprotein (P-gp) Substrates: Concomitant use of TUKYSA with a P-gp substrate increased the plasma concentrations of P-gp substrate, which may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy information. Based on findings in animals and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. There are no available human data on TUKYSA use in pregnant women to inform a drug-associated risk.

In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

Lactation

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capcitabine for lactation information. There are no data on the presence of tucatinib or its metabolites in human or animal milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with TUKYSA and for at least 1 week after the last dose.

Females and Males of Reproductive Potential

TUKYSA can cause fetal harm when administered to a pregnant woman. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capcitabine for contraception and infertility information.

Females and Males of Reproductive Potential

Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating treatment with TUKYSA.

Contraception:

Females: Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.

Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.

Infertility: Based on findings from animal studies, TUKYSA may impair male and female fertility.

Pediatric Use: The safety and effectiveness of TUKYSA in pediatric patients have not been established.

Geriatric Use: In HER2CLIMB, 82 patients who received TUKYSA were ≥ 65 years, of whom 8 patients were ≥ 75 years. The incidence of serious adverse reactions in those receiving TUKYSA was 34% in patients ≥ 65 years compared to 24% in patients < 65 years. The most frequent serious adverse reactions in patients who received TUKYSA and ≥ 65 years were diarrhea (9%), vomiting (6%), and nausea (5%). There were no observed overall differences in the effectiveness of TUKYSA in patients ≥ 65 years compared to younger patients. There were too few patients ≥ 75 years to assess differences in effectiveness or safety.

Renal Impairment: The use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (Ccr ≤ 30 mL/min) estimated by Cockcroft-Gault Equation, because capcitabine is contraindicated in patients with severe renal impairment. Refer to the Full Prescribing Information of capecitabine for additional information in severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [CrCl] 30 to 89 mL/min).

Hepatic Impairment: Tucatinib exposure is increased in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment. No dose adjustment for TUKYSA is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Seagen

TUKYSA and its logo, and Seagen and  are US registered trademarks of Seagen Inc. ©2021 Seagen Inc., Bothell, WA 98021 All rights reserved Printed in USA REF:51251(1) 4/20
INTERVIEW

MEET OUR EXPERT

Ajai Chari, MD, Talks Diversity in Multiple Myeloma Research

“What is more gratifying than people who are alive in complete remission for years?...The therapeutics are so effective and the symptoms of myeloma can be so rapidly reversed. It’s really gratifying.”

Novel treatment regimens are prolonging life in patients with multiple myeloma, both those who are eligible and ineligible for transplant. However, as new research results emerge, clinicians are learning to manage the real-world considerations associated with these therapies, from effects on the immune system to concerns surrounding therapy sequencing.

Ajai Chari, MD, spoke with ONCOLOGY® about the rapidly evolving field of multiple myeloma. He began by discussing how he first became interested in this therapeutic area and why it is so rewarding to work with these patients each day.

Chari also specifically explained the need for diversity among patients with multiple myeloma who are enrolled on clinical trials. In addition, he spoke about how COVID-19 can severely impact and impair the immune systems of patients with multiple myeloma who are undergoing treatment.

Q: Why did you get into the oncology field?
CHARI: No one in my family has ever been a physician. I didn’t know what I was getting into. When I got to medical school, I enjoyed it, I enjoyed internal medicine, but my eyes lit up in oncology. It was a combination of amazing relationships with patients—the depths and continuity of relationships you get from patients with cancer is unprecedented—and the intellectual stimulation. The challenge of the complexity of the care is exciting. There are so many unanswered questions, and so, from an intellectual perspective, there’s so much research to be done.

What drew me to myeloma was, first, that the diagnostic testing can be so complicated. It’s almost like a scientific equivalent of a Wordle because you have to understand the light chains, the urine proteins, and the imaging of the marrow; there are a lot of data to integrate. I find it interesting that no 2 patients are the same. What drives me is the medicine, and I feel like we should be providing the same care that we would to our loved ones. When that is your benchmark, we get amazing results. What’s more gratifying than people who are alive in complete remission for years beyond what we originally thought? For the newly diagnosed patients, you have patients who are bedridden or bed-bound, who within a few months are back to their previous quality of life because the therapeutics are so effective and the symptoms of myeloma can be so rapidly reversed. It’s really gratifying.

Q: What challenges do community oncologists face with the introduction of new therapies?
CHARI: With the T-cell redirection therapies come a steep learning curve and the management of cytokine release syndrome [CRS]. It needs to be recognized and treated properly, and it’s an interdisciplinary effort. It starts with the nurses; we need them to know if the patient is having a fever or if they’re
Can you discuss your recent paper on the effects of COVID-19 on patients with multiple myeloma?

**CHARI:** I was the lead author [analyzing] a global data set; it was a very collaborative effort looking at COVID-19 outcomes in late 2020. We found that the risk factors for worse outcomes in myeloma were older age, renal failure, higher-risk myeloma, and uncontrolled myeloma.

Interestingly, at that point, we didn’t find any differences [due to myeloma] treatment. Now, subsequent work from our institution has shown that treatments can [indeed] affect vaccine responses to particular BCMA-directed therapy, and that C38 antibody therapy doesn’t [allow] response to COVID-19 vaccines. Those patients should be getting booster shots, and [they should receive] the COVID-19 therapeutics [if they contract the virus], because of their impaired immune system. In some ways, myeloma is a canary in the coal mine, because our patients [may have] immunoparesis, [meaning] their plasma cells don’t work. We have unfortunately seen adverse outcomes from COVID-19. The outcomes [in general] have gotten much better with the vaccine therapeutics, but we’re [still] in the trenches with COVID-19.

What are some unmet needs in myeloma, specifically for those who are older or frail?

**CHARI:** Our youngest patient at Mount Sinai was diagnosed when he was aged 18 years and our oldest is [aged more than] 100 years, so it’s a very heterogeneous disease. You can’t have a one-size-fits-all [approach] because there’s no way that somebody [aged more than] 80 [years] will be able to tolerate therapy just as well as somebody who’s in their 20s or 30s. People come to the table as they get older with more medical problems, and [these can] affect not only their overall lifespan but also their tolerance to therapies and [adverse effects]. The problem with older patients is that they don’t always get to the unteenth line of therapy. Sometimes you get [only] 1 or 2 [attempts to reach the best outcome possible].

One of the biggest advancements for that population is the regimen of daratumumab [Darzalex], lenalidomide [Revlimid], and dexamethasone, from the MAIA study [NCT02252172]. In that study at current follow-up, the remission duration for newly diagnosed patients with a median age of 73 years is more than 4 years. These are not patients who are getting transplanted; they’re just getting this cocktail of drugs. That’s tremendous progress and an improvement in survival as well. We still need more therapies for this population because the truly frail and elderly aren’t necessarily coming to academic medical centers. They’re being treated in the community. One of the limitations of myeloma research, and oncology research in general, is that the patients in clinical trials don’t capture the real world. We have huge gaps in outcomes between study-eligible [patients] and real-world patients. To narrow that gap, academia, pharmaceutical companies, the FDA, nonprofits, and patient advocacy groups need to work together collaboratively. We need to collectively work together to change these very restrictive eligibility criteria and try to make [study eligibility] more permissive and real-world friendly.

**REFERENCES**


A Pilot Study of Omalizumab to Treat Oxaliplatin-Induced Hypersensitivity Reaction

Stacey Stein, MD1; Kirsten Dooley, BS, APRN2; Nataliya V. Uboha, MD, PhD3; and Howard S. Hochster, MD4,5

ABSTRACT

Background: Oxaliplatin hypersensitivity reactions (HSRs) are immunoglobulin E (IgE)-mediated and prevent maximum benefit from this drug. This study was designed to determine whether oxaliplatin HSRs could be prevented or reduced with omalizumab (Xolair), an anti-IgE antibody.

Patients/Methods: This was a single-arm prospective pilot study. Patients receiving oxaliplatin-based chemotherapy for gastrointestinal cancers who were experiencing grade 1/2 HSRs were eligible. Patients received omalizumab 300 mg subcutaneously every 2 weeks, alternating with oxaliplatin-based chemotherapy. Nine patients enrolled. The primary end point was reduction of repeat HSR over the next 2 cycles. The sample size of 12 patients would achieve 79% power to detect a decrease from HSR rate of 70% (the null hypothesis) to 35% using a 1-sided binomial test. The study would be considered positive if fewer than 6 HSR events over 2 cycles occurred on omalizumab.

Results: Nine patients received 58 cycles of omalizumab. The mean number of treatments was 6 (range, 1-12). Eight of 9 patients (88%) completed 2 or more cycles and 7 (78%) completed 4 or more cycles; the overall rate of HSR was 12%. Five of 7 evaluable patients had stable disease, including 1 with near partial response.

Conclusions: Omalizumab reduces or abrogates oxaliplatin HSRs and allows months of additional therapy with apparent clinical benefit.

Keywords: gastrointestinal malignancies, oxaliplatin, hypersensitivity reaction, omalizumab

Introduction

Oxaliplatin is a third-generation platinum alkylating agent that has demonstrated efficacy against a variety of tumor types, both in adjuvant and metastatic regimens.1-8 Oxaliplatin is widely used in treatment of gastrointestinal (GI) cancers, including the FOLFIRI regimen (folic acid, fluorouracil [5FU], and irinotecan), and oxaliplatin for colorectal cancer and gastrointestinal cancer and the FOLFIRINOX regimen (leucovorin calcium, 5FU, irinotecan hydrochloride, and oxaliplatin) for pancreatic cancer. Unfortunately, oxaliplatin use is limited by the development of drug-related neuropathy and drug hypersensitivity reaction (HSR). The incidence of oxaliplatin-induced HSRs is 10% to 19%, emerging after a median of 7 cycles of continuous treatment or on the second cycle after reintroduction.7-11 When HSRs occur, there is no clear protocol for selecting which patients should be rechallenged with oxaliplatin and how best to rechallenge. Patients who develop HSR while they are still deriving benefit from oxaliplatin therapy may have a worse prognosis than those who do not need to discontinue oxaliplatin. HSRs to chemotherapeutic agents have been defined as unforeseen reactions that are inconsistent with a treatment’s known toxicities. Oxaliplatin-
induced HSR has been reported to occur with an overall incidence of 10% to 19%. The most common symptoms of HSRs include flushing, urticarial rash, and dyspnea without bronchospasm. Grade 3/4 reactions—which, according to Common Terminology Criteria for Adverse Events (CTCAE) version 4, involve symptomatic bronchospasm with or without urticarial rash, edema/angioedema, and hypotension requiring urgent intervention—are rare, occurring in 1.6% of patients receiving platinum-based chemotherapy. They have been described in case reports. Patients with a personal history of allergies to environmental factors or other drugs appear to be at increased risk to develop HSRs to platinum agents. There are also reports that a link may exist between the type and number of metastatic sites and the risk for HSR. In addition, young women may be at great risk for HSR.

Several desensitization protocols are in the literature for continued oxaliplatin use in patients with HSR. The protocols usually involve administering gradually increasing oxaliplatin concentrations at increasing rates of infusion until the full therapeutic dose is given. These protocols are complicated, time consuming, and labor intensive, potentially involving hospitalization and specially trained nursing staff. In addition, the protocol is not truly a desensitization and needs to be repeated with every subsequent oxaliplatin infusion. Often histamine 1 (H₁) antagonists and steroids are given as premedication prior to each infusion.

Omalizumab (Xolair) is a recombinant humanized monoclonal anti-immunoglobulin E (IgE) antibody that is approved as an add-on therapy for moderate to severe persistent allergic asthma. Omalizumab binds soluble IgE, thus preventing IgE from binding to the high-affinity receptor on mast cells and basophils. This then leads to downregulation of the high-affinity IgE receptor on the surfaces of these cells and precludes their activation. Omalizumab has been used for a variety of indications, including moderate to severe allergic asthma, asthma with concurrent parasitic infections, seasonal and perennial allergic rhinitis, atopic dermatitis, food allergies, and chronic idiopathic urticaria. Safety, efficacy, and dose response of omalizumab was evaluated in 10 phase 1/2 studies. The exact mechanism of how oxaliplatin causes HSR is unknown; it may be that it occurs via an IgE-dependent activation of mast cells and basophils with subsequent release of preformed inflammatory mediators. This results in itching, chest pain, rash, and, rarely, anaphylaxis. These symptoms usually occur during or shortly after the drug infusion. Therefore, we hypothesized that omalizumab could be a therapeutic tool to prevent HSRs to oxaliplatin and could allow for the continued use of an effective chemotherapy drug.

**HIGHLIGHTS**

- Patients with gastrointestinal cancers frequently receive oxaliplatin as part of effective regimens.
- Oxaliplatin-induced hypersensitivity reactions (HSRs) occur with an incidence of 10% to 19%.
- This pilot study showed a positive signal for using omalizumab to reduce oxaliplatin HSRs and warrants a randomized study.

**Methods**

The study was conceived in 2013 and a letter of intent for the protocol was approved by Genentech on September 4, 2014. The study was approved by the Yale University institutional review board on November 13, 2014, and activated for accrual on April 27, 2015. Genentech provided omalizumab as an investigational agent and partial financial support for the trial.

**Patient Selection**

Eligible subjects had a clinically evident oxaliplatin-induced HSR (defined as symptoms of flushing, urticaria, pruritus, rash, and/or dyspnea without bronchospasm emerging during or shortly after infusion) while undergoing treatment with an oxaliplatin-containing regimen for GI cancer. Patients who enrolled had metastatic GI malignancies and were receiving either the FOLFOX, FOLFOXIRI (folinic acid, 5FU, oxaliplatin, irinotecan), or FOLFIRINOX chemotherapy regimen. Eligible patients were required to have at least stable disease or response to the regimen. Any line of therapy was included. Patients had an ECOG performance status of 0 to 2. Patients who had a severe reaction to oxaliplatin, defined as hemodynamic instability, significant respiratory symptoms, or potential airway compromise, were excluded from participation. Patients with a history of HSR to omalizumab were also excluded.

**Treatment**

Omalizumab (300 mg subcutaneously) was administered in clinic every 2 weeks during the duration of chemotherapy. The first injection was given at least 7 days after the development of the initial reaction and at least 7 days before the next scheduled oxaliplatin dose. Once anti-IgE therapy was initiated, regular doses of oxaliplatin were administered at a usual infusion rate (2 hours). Patients who had previously received oxaliplatin at a slower infusion rate, or
at increasing concentrations, were allowed to continue with their prior infusion plan. All patients received cetirizine and dexamethasone 8 mg the evening before and morning of treatment. They then received dexamethasone 20 mg as premedication in the clinic. In the event of minor reactions, oxaliplatin infusion duration was allowed to be increased. Subjects were evaluated during and after oxaliplatin infusion for the development of clinically evident HSRs.

Rescue medications were available for all patients during their chemotherapy infusion as per institutional guidelines. Patients were closely monitored for HSRs during treatment and any adverse events were graded per CTCAE guidelines. Grade 1 is defined as cutaneous signs with transient flushing or rash and drug fever above 100.4 °F. Grade 2 reactions include cutaneous effects, arterial hypotension (defined as 30% or greater decrease in blood pressure) with unexplained tachycardia. Grade 3 is symptomatic bronchospasm with or without urticarial rash, allergy-related edema, or angioedema hypotension. Grade 4 reaction is defined by cardiac or respiratory arrest.

If a subject developed a recurrent grade 1/2 HSR to oxaliplatin during the first scheduled oxaliplatin infusion while on the study, they were allowed to continue on the study and received subsequent oxaliplatin infusion at a regular rate given that their symptoms were adequately controlled with rescue medication or infusion rate adjustment.

Subjects who developed recurrent grade 2 HSR to oxaliplatin during the second or later oxaliplatin infusion were discontinued from the study and omalizumab was deemed to be not effective. Subjects who developed grade 3 or 4 HSR at any point during the trial were taken off the study, and no further oxaliplatin was administered.

Patients received imaging every 8 weeks. Patients had an end-of-treatment

### TABLE 1. Patient Demographics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Prior cycles of oxaliplatin</th>
<th>No. of lines of prior therapy</th>
<th>Prior rechallenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>52</td>
<td>26</td>
<td>3</td>
<td>Dose decreased</td>
</tr>
<tr>
<td>2/6*</td>
<td>F</td>
<td>66</td>
<td>11</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>63</td>
<td>11</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>76</td>
<td>24</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>39</td>
<td>9</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>62</td>
<td>6</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>70</td>
<td>11</td>
<td>2</td>
<td>Rechallenged with H₁/H₂ blockers and steroids with HSR</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>63</td>
<td>6</td>
<td>1</td>
<td>Rechallenged with H₁/H₂ blockers and steroids with HSR, then dilutional desensitization with premedication and HSR</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>73</td>
<td>3</td>
<td>3</td>
<td>Rechallenged with desensitization</td>
</tr>
</tbody>
</table>

HSR, hypersensitivity reaction.

*Patient 2 and patient 6 are the same person.
visit within 7 days of completing therapy and then had a 28-day posttreatment follow-up visit for toxicity assessment.

**Statistics**
We estimated that a maximum of 30% of patients treated with premedication and slower infusion rate alone would not have a HSR during the next 2 oxaliplatin infusions (in other words, at least 70% would react again). We hypothesized that the use of omalizumab would reduce this rate by half—that the HSR rate in the subsequent 2 cycles would be less than 35%. The study was designed to enroll 12 patients. This sample size would have achieved 79% power to detect a decrease from a HSR rate of 70% (the null hypothesis) to 35% using a 1-sided binomial test. Based on this estimation, if fewer than 6 HSR events occurred over the next 2 cycles on omalizumab, the drug would be considered worthy of further study.

**Results**
Nine patients enrolled on the study, 8 with colon cancer and 1 with gastric cancer. Demographic characteristics are summarized in Table 1. Patient age ranged from 39 to 76 years. One patient was enrolled in the study twice for repeat oxaliplatin rechallenge (enrolled as both patient 2 and 6). Prior to starting omalizumab, 5 patients had not been rechallenged after their initial HSR. One patient had received attenuated oxaliplatin dosing prior to enrollment on this study. Two patients had received premedications with H1 and H2 blockers and with steroids to prevent repeat HSR prior to study enrollment. One patient had received dilutional desensitization with repeat HSR prior to enrolling on the study.

Patients had received between 3 and 26 prior oxaliplatin-containing treatment cycles. Five subjects were able to receive 8 or more additional cycles of oxaliplatin on study (8, 8, 8, 9, and 12; Figure 1). Five patients came off treatment due to disease progression (after cycles 4, 8, 8, 9, and 12). One patient came off study secondary to patient choice (after 8 cycles). Two patients came off study secondary to oxaliplatin HSR (both after cycle 1 on study). One patient received 12 cycles and came off for progression of disease; they went back on the study approximately 7 months later but had an HSR to the first dose of oxaliplatin upon second study entry. The patient with gastric cancer received 5 chemotherapy cycles on study but had to stop treatment secondary to peripheral neuropathy. Omalizumab injections were well tolerated in all patients with no adverse events, including HSR or local skin reaction (Table 2).

Patient 7 did not have evaluable disease. The rest of the patients had stable disease (SD) by RECIST 1.1 criteria, including patient 3, who had a 28.12% decrease in tumor size. Progression-free survival (PFS; range, 3.8-15.4 months) and overall survival (OS; range, 4.5-25.2 months) ranged significantly among patients (Figure 2).

### TABLE 2. Adverse Events and Cycles on Study

<table>
<thead>
<tr>
<th>Patient</th>
<th>Adverse events</th>
<th>IRRs on study</th>
<th>Reason for coming off study</th>
<th>Cycles on study (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>Grade 2 IRR with cycle 1</td>
<td>Grade 2 reaction with cycle 1</td>
<td>1</td>
</tr>
<tr>
<td>2*</td>
<td>Grade 3 neutropenia Grade 3 thrombocytopenia</td>
<td>No IRR</td>
<td>Treatment changed after 12 cycles on study</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>Grade 3 hypophosphatemia Grade 3 neutropenia</td>
<td>No IRR</td>
<td>Patient choice for treatment break</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>Grade 2 peripheral neuropathy</td>
<td>No IRR</td>
<td>Peripheral neuropathy after cycle 2</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Grade 3 abdominal pain</td>
<td>No IRR</td>
<td>POD</td>
<td>4</td>
</tr>
<tr>
<td>6*</td>
<td>Grade 3 IRR</td>
<td>Grade 3 IRR after cycle 1</td>
<td>Grade 3 oxaliplatin reaction after cycle 1</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Grade 3 neutropenia Grade 2 neutropenia Grade 3 headache</td>
<td>No IRR</td>
<td>Grade 2 peripheral neuropathy (then developed leptomeningeal disease)</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>Grade 2 IRR with cycle 6</td>
<td>Grade 2 IRR with cycle 6</td>
<td>POD after cycle 8</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>None</td>
<td>No IRR</td>
<td>POD after cycle 9</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>Grade 3 hyponatremia at end-of-treatment visit</td>
<td>No IRR</td>
<td>POD after cycle 8</td>
<td>8</td>
</tr>
</tbody>
</table>

IRR, infusion-related reaction; POD, progression of disease.

*Patient 2 and patient 6 are the same person.
Patients’ IgE levels were checked once, at baseline, and ranged from 20 IU/ml to 224 IU/ml. There was no clear correlation between IgE levels and ability to continue on treatment. However, formal conclusions cannot be drawn given the limited number of subjects in the study.

**Discussion**

The treatment of metastatic GI cancers largely involves chemotherapy. Oxaliplatin is a mainstay of treatment and is typically given in combination with a fluoropyrimidine antimetabolite (5FU or capecitabine) with the further addition of oxaliplatin or irinotecan. Immune therapy has demonstrated effectiveness only in patients with DNA mismatch repair–deficient/microsatellite instability–high tumors, which account for approximately 4% of patients with metastatic colorectal cancer. Therefore, it remains important for each patient to be able to maximize the benefit from each approved chemotherapy regimen. Patients are often removed from treatment with oxaliplatin secondary to either peripheral neuropathy or HSR. Given that 10% to 19% of patients receiving oxaliplatin eventually develop HSR, an intervention that could allow for continued treatment with oxaliplatin despite HSR has the potential to improve survival for these patients.

Omalizumab has been shown to be beneficial for patient groups with IgE-mediated allergic reactions including peanut allergies, severe persistent allergic asthma, and chronic idiopathic urticaria. Oxaliplatin HSRs are believed to be IgE mediated, and therefore there was rationale to see if administering omalizumab prior to oxaliplatin could abrogate HSRs.

This pilot study evaluated the role of omalizumab for its potential to treat HSR. We were able to treat patients for up to 12 cycles successfully by giving omalizumab the week before oxaliplatin infusion. The study met the primary end point, in that 89% of patients (8/9) were able to successfully receive at least additional cycles without HSR. In addition, 6 patients were able to receive 8 or more additional cycles of treatment. Given the small number of patients in this study, we can only hypothesize that an effective treatment for oxaliplatin HSRs will improve OS for these patients; however, omalizumab clearly appeared to offer a modest clinical benefit to most patients, affording prolonged disease control, and just 1 patient showed progressive disease by RECIST 1.1 while on study. The PFS and OS outcomes for these patients were variable, which likely reflects the fact that patients had had 1 to 3 lines of prior therapy; therefore, they did not compose a uniform group for this assessment.

Limitations of this study include that it did not finish accrual due to slow enrollment and enrolled just 9 unique patients. However, by the time the ninth patient enrolled, the study had already met its primary end point by having only 2 discontinuations secondary to HSR. Also, IgE levels were drawn only at baseline, making it impossible to know for sure that IgE levels were actually decreased with administration of omalizumab.
Patients with a history of oxaliplatin hypersensitivity were able to receive additional cycles of oxaliplatin when they received omalizumab prior to treatment. Given that this study met its primary clinical end point despite a smaller than planned sample size, the results warrant a larger randomized study of the use of omalizumab in preventing recurrent oxaliplatin HSR in patients with GI malignancies; this is in development. In a larger study, we will be able to evaluate the benefit of continuing oxaliplatin in the setting of prior allergic reaction; the tolerance of additional oxaliplatin among all subjects; and the correlation of baseline IgE levels with IgE levels influenced by omalizumab administration. ■

DISCLOSURES: HSH has consulted for AstraZeneca, Bayer, Genentech, and Natera Inc; and has equity in Compass Therapeutics and Processa; SS has consulted for AstraZeneca, Genentech, Ipsen, Inmav Inc, and QED Therapeutics; NVU has consulted for AstraZeneca, BostonGene, Incyte, Helsinn Healthcare SA, QED Therapeutics, and Taiho Oncology, Inc.; has received research funding from EMD Serono, Ipsen, and Taiho Oncology, Inc.; and has long position holdings in Exact Sciences and Natera Inc.

AUTHOR AFFILIATIONS:
1. Yale School of Medicine, New Haven, CT
2. Yale Cancer Center, New Haven, CT
3. University of Wisconsin School of Medicine and Public Health, Madison, WI
4. Rutgers Cancer Institute, New Brunswick, NJ
5. RWJ Barnabas Health, New Brunswick, NJ

REFERENCES
In the treatment of newly diagnosed, transplant-ineligible multiple myeloma:

**ADD TO THE MOMENTUM WITH DARZALEX® + Rd IN FRONTLINE**

Reach for a treatment that significantly extended progression-free survival vs Rd alone in a clinical trial.

**IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE**

**DARZALEX® AND DARZALEX FASPRO®: CONTRAINDICATIONS**

DARZALEX® and DARZALEX FASPRO® are contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase (for DARZALEX FASPRO®), or any of the components of the formulations.

**DARZALEX®: Infusion-Related Reactions**

DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening, and fatal outcomes have been reported. In clinical trials (monotherapy and combination: N=2066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma.

Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting, and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision.

When DARZALEX® dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX®, the incidence of infusion-related reactions was 11% for the first infusion following ASCT.

Infusion-related reactions occurring at re-initiation of DARZALEX® following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4: <1%) with those reported in previous studies at Week 2 or subsequent infusions. In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days, ie, 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX® infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute expedited medical management as needed.

**IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE**
Powerful efficacy to start the treatment journey\(^1,4\)
After a median \(~30\) months\(^*\) of follow-up, mPFS was not reached with DARZALEX\(^*\) + Rd vs \(31.9\) months with Rd alone.\(^1,4\)
- \(70.6\%\) of patients had not progressed with Rd vs \(55.6\%\) of patients in the Rd group (DRd: \(95\%\) CI, \(65.0\)–\(75.4\); Rd: \(95\%\) CI, \(49.5\)–\(61.3\)).\(^3\)
- \(44\%\) reduction in the risk of disease progression or death with Rd vs Rd alone (HR\(=0.56\); \(95\%\) CI, \(0.43\)–\(0.73\); \(P<0.0001\)).

Demonstrated safety profile (median treatment duration of \(25.3\) months\(^1\))
- The most common adverse reactions (\(\geq 20\%\)) were upper respiratory infection, neutropenia, IRRs, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia.
- Serious adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd 1%).

MAIA Study Design: A phase 3 global, randomized, open-label study, compared treatment with DRd (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma. Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was PFS.\(^1\)

Efficacy results in long-term follow-up\(^2,3\)
At median ~5 years (56 months\(^*\)) of follow-up, mPFS was not reached with DRd vs 34.4 months with Rd alone.\(^2\)
- \(53\%\) of patients had not progressed after ~5 years of treatment with DRd vs 29% with Rd alone (DRd: \(95\%\) CI, \(47\)–\(58\); Rd: \(95\%\) CI, \(23\)–\(35\)).\(^1\)
- \(47\%\) reduction in the risk of disease progression or death with DRd vs Rd alone (HR\(=0.53\); \(95\%\) CI, \(0.43\)–\(0.66\)).

These ~5-year analyses were not adjusted for multiplicity and are not included in the current Prescribing Information.

Safety results in long-term follow-up (median treatment duration of \(47.5\) months\(^2\))
At median ~5 years of follow-up\(^3,3\):
- Most frequent TEAEs\(^\#\) \(\geq 30\%\) were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, anorexia, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms.
- Grade 3/4 infections were \(41\%\) for DRd vs \(29\%\) for Rd.
- Grade 3/4 TEAEs\(^\#\) \(\geq 10\%\) were neutropenia (54% for DRd vs \(37\%\) for Rd), pneumonia (19% vs \(11\%\)), anemia (17% vs \(22\%\)), lymphopenia (16% vs \(11\%\)), hypokalemia (13% vs 10%), leukopenia (12% vs \(6\%\)), and cataaract (11% vs 11%).

These ~5-year analyses are not included in the current Prescribing Information.

\(^1\)Confidence interval. DRd=DARZALEX\(^*\) (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio. IRR=Injection-related reaction; mPFS=Median progression-free survival; PFS=Progression-free survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.
\(^2\)Range: 0.0–41.4 months. \(^4\)Kaplan-Meier estimate.
\(^3\)Range: 0.03–69.52 months. \(^5\)TEAEs are defined as any adverse event (AE) that occurs after start of the first study treatment through 30 days after the last study treatment; or the day prior to start of subsequent antimalyeloma therapy, whichever is earlier; or any AE that is considered drug related (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug related by the investigator.

\(^4\)To reduce the risk of delayed infusion-related reactions, administer appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion. To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX\(^*\) infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX\(^*\) infusion. If ocular symptoms occur, interrupt DARZALEX\(^*\) infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX\(^*\).

**DARZALEX FASPRO\(^*\): Hypersensitivity and Other Administration Reactions**
Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO\(^*\). Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO\(^*\).

Systemic Reactions
In a pooled safety population of 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO\(^*\) as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 1%), systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX FASPRO\(^*\) administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO\(^*\). Consider administering **IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE**
In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, headache, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, upper respiratory tract infection, peripheral sensory neuropathy, constipation, pneumonia, and peripheral edema. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

INDICATIONS
DARZALEX® (daratumumab) is indicated for the treatment of adult patients with multiple myeloma:

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

DARZALEX® and DARZALEX FASPRO®: Neutropenia and Thrombocytopenia
Daratumumab and DARZALEX® may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX® or DARZALEX FASPRO® until recovery of neutrophils or for recovery of platelets.

In lower body weight patients receiving DARZALEX® FASPRO®, higher rates of Grade 3-4 neutropenia were observed.

DARZALEX® and DARZALEX FASPRO®: Interference With Determination of Complete Response
Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO antigens in the patient’s serum. The determination of a patient’s ABO antigens may be affected.

Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs is undetected on blood bank tests. The determination of ABO antigens in patient serum is affected.

Thrombocytopenia
Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO antigens in the patient’s serum. The determination of a patient’s ABO antigens may be affected.


Please see Brief Summary of full Prescribing Information for DARZALEX® and DARZALEX FASPRO® on adjacent pages.

cp-248517v3

References:
DARZALEX® (daratumumab) injection, for intravenous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE
DARZALEX is indicated for the treatment of adult patients with multiple myeloma:
• in combination with lenalidomide and dexamethasone in newly diagnosed patients
• as a single agent for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

CONTRAINDICATIONS
DARZALEX is contraindicated in patients with a history of severe hypersensitivity (e.g., anaphylactic reaction) to daratumumab or any of the components of the formulation [see Warnings and Precautions].

WARNINGS AND PRECAUTIONS
Infusion-Related Reactions
DARZALEX can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening and fatal outcomes have been reported (see Adverse Reactions).

In clinical trials (monotherapy and combination: N=2,066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 5% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 7, 4, and 3 hours respectively. Nearly all reactions occurred during infusion or within 4 hours of completing the infusion. DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion-related reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including chorioid effusion, acute myopia, and acute angle closure glaucoma. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision [see Adverse Reactions].

When DARZALEX dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption for ASCT.

Infusion-related reactions occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4:<1%) with those reported in previous studies at Week 2 or subsequent infusions.

In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion [see Dosage and Administration (2.3) in Full Prescribing Information]. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion [see Dosage and Administration (2.4) in Full Prescribing Information].

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX infusions [see Dosage and Administration (2.3) in Full Prescribing Information]. Patients with a history of chronic obstructive pulmonary disease associated with increased post-infusion medications to manage respiratory complications. Consider prescribing short-and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease [see Dosage and Administration (2.3) in Full Prescribing Information].

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX infusion. If ocular symptoms occur, interrupt DARZALEX infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX.

Interference with Serological Testing
Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum [see References].

The determination of a patient’s ABO and Rh blood type are not impacted [see Drug Interactions]. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX [see Dosage and Administration (2.1) in Full Prescribing Information].

Neutropenia
DARZALEX may increase neutropenia induced by background therapy [see Adverse Reactions].

Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX until recovery of neutrophils.

Thrombocytopenia
DARZALEX may increase thrombocytopenia induced by background therapy [see Adverse Reactions].

Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX until recovery of platelets.

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

Embryo-Fetal Toxicity
Based on the mechanism of action, DARZALEX can cause fetal harm when administered to a pregnant woman. DARZALEX may cause deprivation of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose [see Use in Specific Populations].

The combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
• Infusion-related reactions [see Warning and Precautions].
• Neutropenia [see Warning and Precautions].
• Thrombocytopenia [see Warning and Precautions].

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

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 2,459 patients with multiple myeloma including 2,303 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. In this pooled safety population, the most common adverse reactions (≥20%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia.

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant
Combination Treatment with Lenalidomide and Dexamethasone (DRd) The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in MAIA [see Clinical Studies (14.1) in Full Prescribing Information]. Adverse reactions described in Table 1 reflect exposure to DARZALEX for a median treatment duration of 25.3 months (range: 0.1 to 40.4 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 21.3 months (range: 0.03 to 40.64 months) for lenalidomide-dexamethasone (Rd). Serious adverse reactions with a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%) and dehydration (DRd 2% vs Rd <1%).
Table 1: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in MAIA

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>DRd (N=364)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>Rd (N=365)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>57</td>
<td>7</td>
<td>46</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>41</td>
<td>1</td>
<td>&lt;1</td>
<td>36</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>32</td>
<td>1</td>
<td>0</td>
<td>23</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>Upper respiratory tract infectionb</td>
<td>52</td>
<td>2</td>
<td>&lt;1</td>
<td>36</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>Bronchitisa</td>
<td>29</td>
<td>3</td>
<td>0</td>
<td>21</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pneumoniac</td>
<td>26</td>
<td>14</td>
<td>1</td>
<td>14</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>16</td>
<td>2</td>
<td>0</td>
<td>16</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Infusion-related reactionsd</td>
<td>41</td>
<td>2</td>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Peripheral edemaa</td>
<td>41</td>
<td>2</td>
<td>0</td>
<td>33</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>40</td>
<td>8</td>
<td>0</td>
<td>28</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>32</td>
<td>4</td>
<td>0</td>
<td>25</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>23</td>
<td>2</td>
<td>0</td>
<td>18</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td>34</td>
<td>3</td>
<td>&lt;1</td>
<td>26</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>29</td>
<td>1</td>
<td>0</td>
<td>22</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspneaa</td>
<td>32</td>
<td>3</td>
<td>&lt;1</td>
<td>20</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Coughb</td>
<td>30</td>
<td>&lt;1</td>
<td>0</td>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Peripheral sensory neuropathy</td>
<td>24</td>
<td>1</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>19</td>
<td>1</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Paresthesia</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>22</td>
<td>1</td>
<td>0</td>
<td>15</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
<td>14</td>
<td>6</td>
<td>1</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hypocalcemia</td>
<td>14</td>
<td>1</td>
<td>&lt;1</td>
<td>11</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertensiona</td>
<td>13</td>
<td>8</td>
<td>&lt;1</td>
<td>7</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

a Acute sinusitis, Bacterial rhinitis, Laryngitis, Metapneumovirus infection, Nasopharyngitis, Oropharyngeal candidiasis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Tracheitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection
b Bronchiolitis, Bronchitis, Bronchitis viral, Respiratory syncytial virus bronchiolitis, Tracheobronchitis
c Atypical pneumonia, Bronchopulmonary aspergillosis, Lung infection, Pneumocystis jiroveci infection, Pneumocystis jiroveci pneumonia, Pneumonia, Pneumonia aspiration, Pneumonia pneumococcal, Pneumonia viral, Pulmonary mycosis
d Infusion-related reaction includes terms determined by investigators to be related to infusion
e Generalized edema, Gravitational edema, Edema, Peripheral edema, Peripheral swelling
f Dyspnea, Dyspnea exertional
g Cough, Productive cough
h Blood pressure increased, Hypertension
i Hypersensitivity

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRd (N=364)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>Rd (N=365)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Leukopenia</td>
<td>90</td>
<td>30</td>
<td>5</td>
<td>82</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>91</td>
<td>39</td>
<td>17</td>
<td>77</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
<td>84</td>
<td>41</td>
<td>11</td>
<td>75</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>67</td>
<td>6</td>
<td>3</td>
<td>58</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>47</td>
<td>13</td>
<td>0</td>
<td>57</td>
<td>24</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in POLLUX (see Clinical Studies (14.2) in Full Prescribing Information). Adverse reactions described in Table 3 reflect exposure to DARZALEX for a median treatment duration of 13.1 months (range: 0 to 20.7 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 12.3 months (range: 0.2 to 20.1 months) for lenalidomide-dexamethasone (Rd).

Serious adverse reactions occurred in 49% of patients in the DRd arm compared with 42% in the Rd arm. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 12% vs Rd 10%), upper respiratory tract infection (DRd 7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

Table 3: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in POLLUX

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRd (N=283)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>Rd (N=281)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Leukopenia</td>
<td>65</td>
<td>6</td>
<td>&lt;1</td>
<td>51</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>35</td>
<td>8</td>
<td>&lt;1</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
<td>20</td>
<td>2</td>
<td>0</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>43</td>
<td>5</td>
<td>0</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>24</td>
<td>1</td>
<td>0</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspneaa</td>
<td>30</td>
<td>3</td>
<td>0</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Coughb</td>
<td>21</td>
<td>3</td>
<td>&lt;1</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spasms</td>
<td>26</td>
<td>1</td>
<td>0</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

a upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection
b Infusion-related reaction includes terms determined by investigators to be related to infusion
c cough, productive cough, allergic cough
d dyspnea, Dyspnea exertional

Laboratory abnormalities worsening during treatment from baseline listed in Table 4.
On page 125 of the document, the following natural text is provided:

**DRUG INTERACTIONS**

**Effects of Daratumumab on Laboratory Tests**

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding [see References] or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

**Interference with Serum Protein Electrophoresis and Immunofixation Tests**

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Daratumumab can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models [see Data]. There are no available data on the use of DARZALEX in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

**Clinical Considerations**

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematology evaluation is completed.

**Data**

**Animal Data**

Mice that were genetically modified to eliminate all CD38 expression (CD38−/−) have demonstrated depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematology evaluation is completed.

**Lactation**

**Risk Summary**

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

**Females and Males of Reproductive Potential**

**Use in Specific Populations**

**Pregnancy**

The combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide, refer to the lenalidomide, pomalidomide, or thalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

**Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX**

<table>
<thead>
<tr>
<th></th>
<th>D-Rd (N=373)</th>
<th>D-VPd (N=369)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, R= lenalidomide-dexamethasone.

**Herpes Zoster Virus Reactivation**

Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the combination therapy studies, herpes zoster was reported in 2-5% of patients receiving DARZALEX.

**Infections**

Grade 3 or 4 infections were reported as follows:

- where carfilzomib 20/56 mg/m2 was administered twice-weekly
- where carfilzomib 20/70 mg/m2 was administered once-weekly

Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In active controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients.

Fatal infections (Grade 5) were reported as follows:

- Relapsed/refractory patient studies: D-Vd: 1%, Vd: 2%; D-Rd: 2%; Rd: 1%; D-Pd: 2%; D-Kd: 5%; D-Kd: 3%; D-Dk: 0%
- where carfilzomib 20/56 mg/m2 was administered twice-weekly
- where carfilzomib 20/70 mg/m2 was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; D-Rd: 2%; Rd: 2%; D-Vd: 0%; Vd: 0%

Fetal infections were generally infrequent and balanced between the DARZALEX containing regimens and active control arms. Fetal infections were primarily due to pneumonia and sepsis.

**Hepatitis B Virus Reactivation**

Hepatitis B virus reactivation has been reported in less than 1% of patients (including fatal cases) treated with DARZALEX in clinical trials.

**Other Clinical Trials Experience**

The following adverse reactions have been reported following administration of daratumumab and hyaluronidase for subcutaneous injection:

**Neurological System disorders: Syncope**

**Immunogenicity**

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products may be misleading.

In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, none of the 111 evaluable monotherapy patients, and 2 of the 1,383 evaluable combination therapy patients, tested positive for anti-daratumumab antibodies. One patient administered DARZALEX as combination therapy, developed transient neutralizing antibodies against daratumumab. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

**Postmarketing Experience**

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

**Immunological disorders: Anaphylactic reaction, IRR (including deaths)**

**Gastrointestinal disorders: Pancreatitis**

**Infections:** Cytomegalovirus, Listeriosis
Contraception
Advise females of reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose. Additionally, refer to the lenalidomide, pomalidomide, or thalidomide labeling for additional recommendations for contraception.

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

Geriatric Use
Of the 2,459 patients who received DARZALEX at the recommended dose, 38% were 65 to 74 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. The incidence of serious adverse reactions was higher in older than in younger patients [see Adverse Reactions]. Among patients with relapsed and refractory multiple myeloma (n=1,213), the serious adverse reactions that occurred more frequently in patients 65 years and older were pneumonia and sepsis. Within the DKd group in CANDOR, fatal adverse reactions occurred in 14% of patients 65 years and older compared to 6% of patients less than 65 years. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the serious adverse reaction that occurred more frequently in patients 75 years and older was pneumonia.

REFERENCES

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

Infusion-Related Reactions
Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion-related reactions: itchy, runny or blocked nose; fever, chills, nausea, vomiting, throat irritation, cough, headache, dizziness or lightheadedness, tachycardia, chest discomfort, wheezing, shortness of breath or difficulty breathing, itching, and blurred vision [see Warnings and Precautions].

Neutropenia
Advise patients to contact their healthcare provider if they have a fever [see Warnings and Precautions].

Thrombocytopenia
Advise patients to contact their healthcare provider if they notice signs of bruising or bleeding [see Warnings and Precautions].

Interference with Laboratory Tests
Advise patients to inform their healthcare providers, including personnel at blood transfusion centers that they are taking DARZALEX, in the event of a planned transfusion [see Warnings and Precautions].

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

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

Embryo-Fetal Toxicity
Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions, Use in Specific Populations].

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX and for 3 months after the last dose [see Use in Specific Populations].

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

Hereditary Fructose Intolerance (HFI)
DARZALEX contains sorbitol. Advise patients with HFI of the risks related to sorbitol [see Description (11) in Full Prescribing Information].

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
U.S. License Number 1864
© 2015-2021 Janssen Pharmaceutical Companies

cp-271933v2
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE
DARZALEX FASPRO® is indicated for the treatment of adult patients with multiple myeloma:

• in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

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

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions
Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO® (see Adverse Reactions).

Systemic Reactions
In a pooled safety population of 888 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=183) who received DARZALEX FASPRO® as monotherapy or as part of a combination therapy, 9% of patients experienced a systemic administration-related reaction (Grade 2-3, Grade 3 1%). Systemic administration-related reactions occurred in 6% of patients with the first injection, 10% for the second injection, and cumulatively 11% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 12 (8%) occurred on the day of DARZALEX FASPRO® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions include hypoxia, dyspnea, hypertension, and tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids [see Dosage and Administration (2.5) in Full Prescribing Information]. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO®. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO® depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions [see Dosage and Administration (2.5) in Full Prescribing Information].

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX FASPRO® and seek immediate ophthalmologic evaluation prior to restarting DARZALEX FASPRO®.

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO®. Monitor for local reactions and consider symptomatic management.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis
Severe or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO® in combination with bortezomib, cyclophosphamide and dexamethasone [see Adverse Reactions]. Severe cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class III or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIB or IV disease were not studied.

Monitor patients for cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

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

Embryo-Fetal Toxicity
Based on the mechanism of action, DARZALEX FASPRO® can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO® and for 3 months after the last dose [see Use in Specific Populations].

The combination of DARZALEX FASPRO® with lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide or pomalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Interference with Serological Testing
Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Anti-globulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum [see References (15)]. The determination of a patient’s ABO and Rh blood type are not impacted [see Drug Interactions].

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

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

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

• Hypersensitivity and Other Administration Reactions [see Warnings and Precautions].
• Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis [see Warnings and Precautions].
• Neutropenia [see Warnings and Precautions].
• Thrombocytopenia [see Warnings and Precautions].

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

Refractory Multiple Myeloma

In combination with Lenalidomide and Dexamethasone

The safety of DARZALEX FASPRO® with lenalidomide and dexamethasone was evaluated in a single-arm cohort of PLEIADES [see Clinical Studies (14.2) in Full Prescribing Information]. Patients received DARZALEX FASPRO® 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=85) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

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

Permanent discontinuation of DARZALEX FASPRO® due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO®. Serious adverse reactions in >5% of patients included pneumonia, influenza and diarrhea. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO® in more than 1 patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO®. Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased. The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasm, constipation, pyrexia, pneumonia, and dyspnea.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO® in PLEIADES.

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

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

Table 1. Clinical Trials Experience: Adverse Reactions

| Adverse Reaction | Grade 3/4 | Grade 1/2 | N=85
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>69%</td>
<td>31%</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>36%</td>
<td>64%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>19%</td>
<td>81%</td>
</tr>
<tr>
<td>Influenza</td>
<td>19%</td>
<td>81%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18%</td>
<td>82%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13%</td>
<td>87%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>13%</td>
<td>87%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35%</td>
<td>65%</td>
</tr>
<tr>
<td>Constipation</td>
<td>37%</td>
<td>63%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td>Pneumonia+influenza</td>
<td>19%</td>
<td>81%</td>
</tr>
<tr>
<td>Pneumonia+dyspnea</td>
<td>19%</td>
<td>81%</td>
</tr>
<tr>
<td>Pneumonia+diarrhea</td>
<td>19%</td>
<td>81%</td>
</tr>
<tr>
<td>Thrombocytopenia+influenza</td>
<td>12%</td>
<td>88%</td>
</tr>
</tbody>
</table>
Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO® with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>Pyrexia*</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection*</td>
<td>43</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Bronchitis*</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Cough*</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

* Fatigue includes asthenia, and fatigue.
* Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
* Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
* Bronchitis includes bronchitis viral.
* Dyspnea includes dyspnea, and dyspnea exertional.
* Cough includes cough, and productive cough.

Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with lenalidomide and dexamethasone included:
- **Musculoskeletal and connective tissue disorders**: arthralgia, musculoskeletal chest pain
- **Nervous system disorders**: dizziness, headache, paresthesia
- **Skin and subcutaneous tissue disorders**: rash, pruritus
- **Gastrointestinal disorders**: abdominal pain
- **Infections**: influenza, sepsis, herpes zoster
- **Metabolism and nutrition disorders**: decreased appetite
- **Cardiac disorders**: atrial fibrillation
- **General disorders and administration site conditions**: chills, infusion reaction, injection site reaction
- **Vascular disorders**: hypertension, hypertension

Table 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO in PLEIADES.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leucocytes</td>
<td>94</td>
<td>34</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82</td>
<td>58</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>85</td>
<td>34</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>89</td>
<td>52</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
<td>8</td>
</tr>
</tbody>
</table>

* Denominator is based on the safety population treated with DARZALEX FASPRO-Rd (N=65).
Clinical Considerations

Fetal/Neonatal Adverse Reactions
Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab in utero until a hematologic evaluation is completed.

Data

Animal Data
DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryofetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously during organogenesis, which is 45 times higher than the human dose.

There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 980,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Lactation

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

Data

Animal Data
No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryofetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Females and Males of Reproductive Potential
DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations].

Pregnancy Testing
With the combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide, refer to the lenalidomide, thalidomide or pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception
Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose [see Warnings and Precautions].

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

Geriatric Use
Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 37% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness of DARZALEX FASPRO have been observed between patients ≥65 years of age and younger patients. Adverse reactions that occurred at a higher frequency (≥2% difference) in patients ≥65 years of age included fatigue, pyrexia, peripheral edema, urinary tract infection, diarrhea, constipation, vomiting, dyspnea, cough, and hyperglycemia. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included neutropenia, thrombocytopenia, diarrhea, anemia, COVID-19, ischemic colitis, deep vein thrombosis, general physical health deterioration, pulmonary embolism, and urinary tract infection.

Of the 193 patients who received DARZALEX FASPRO as part of a combination therapy for light chain (AL) amyloidosis, 35% were ≥75 years of age, and 10% were ≥75 years of age or older. Clinical studies of DARZALEX FASPRO as part of a combination therapy for patients with light chain (AL) amyloidosis did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs from that of younger patients. Adverse reactions that occurred at a higher frequency in patients ≥65 years of age were peripheral edema, asthma, pneumonia and hypotension.

No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients [see Clinical Pharmacology (12.3) in Full Prescribing Information].

REFERENCES

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

Hypersensitivity and Other Administration Reactions
Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing, and blurred vision [see Warnings and Precautions].

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis
Advise patients to immediately contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions [see Warnings and Precautions].

Neutropenia
Advise patients to contact their healthcare provider if they have a fever [see Warnings and Precautions].

Thrombocytopenia
Advise patients to contact their healthcare provider if they have bruising or bleeding [see Warnings and Precautions].

Embryo-Fetal Toxicity
Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions, Use in Specific Populations].

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO and for 3 months after the last dose [see Use in Specific Populations].

Advise patients that lenalidomide, thalidomide and pomalidomide have the potential to cause fetal harm and have specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program [see Use in Specific Populations].

Interference with Laboratory Tests
Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion [see Warnings and Precautions].

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

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

Product of Switzerland
Manufactured by: Janssen Biotech, Inc.
Horsham, PA 19044
U.S. License Number 1884
© 2021 Janssen Pharmaceutical Companies cp-267881v2
Current Frontline Treatment of Multiple Myeloma

Sarah A. Holstein, MD, PhD

ABSTRACT
Treatment paradigms for management of newly diagnosed (ND) multiple myeloma have been evolving over the past 20 years as a consequence of the development of immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies. While recent studies have continued to confirm the progression-free survival benefit of consolidation with upfront autologous stem cell transplant in those considered transplant eligible (TE), the line between induction strategies for TE and transplant-ineligible (TI) patients has blurred, based on studies evaluating both populations. Here, we present an overview of the data guiding current treatment approaches in the ND setting and discuss areas of ongoing investigation, including the role of quadruplet combination therapies in TE patients, the optimal strategies for frail TI patients, and management of high-risk disease.

Introduction
The past 20 years have seen the development of immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies (mAbs), which have dramatically reshaped the treatment paradigms for newly diagnosed (ND) multiple myeloma (MM). While consolidation with high-dose melphalan and autologous stem cell transplant (ASCT) remains a standard of care (SOC) for patients who are considered to be transplant eligible (TE), the use of alkylating agents and other traditional cytotoxic agents has decreased dramatically. Effective triplet and even quadruplet combination therapies consisting of IMiDs, PIs, and/or mAbs can induce very deep responses, including achievement of minimal residual disease (MRD) negativity. These advances in therapies have led to considerable prolongation of survival times, although frail transplant-ineligible (TI) patients or patients with high-risk disease features continue to represent populations with inferior survival outcomes. In this review, we present an overview of the data that guide current treatment approaches for NDMM as well as the evolving strategies that may lead to future standards of care.
\[ \beta_{-}\text{microglobulin, and LDH, as well as evaluation of key high-risk cytogenetic abnormalities observed from the FISH analysis of the bone marrow aspirate (including del}(17p), [t}(4;14), \text{and } [t}(14;16)].\]

Several options for whole-body imaging exist, including low-dose whole-body CT (LDWBCT), whole-body PET/CT, and whole-body MRI imaging.\(^2\) In both the International Myeloma Working Group and the National Comprehensive Cancer Network guidelines, the initial choices for imaging modality in the setting of suspected MM include either LDWBCT or PET/CT, with axial or whole-body MRI performed in the setting of negative or inconclusive testing.\(^3\) In the setting of known or suspected extramedullary involvement, PET/CT is the preferred imaging modality. These imaging modalities have replaced conventional skeletal surveys; the latter, while widely available, offer comparatively poor sensitivity. For example, in one head-to-head comparison between skeletal survey and LDWBCT, 25% of patients with negative skeletal surveys had lytic lesions on LDWBCT.\(^4\)

**Molecular Testing**

Current staging and risk stratification systems primarily rely on information obtained from the CD138-selected FISH panel, which, at minimum, should evaluate for the presence of del(13), del(17p), t(4;14), t(11;14), t(14;16), and t(14;20), and for gain/amplification of 1q21 and del(1p). The frequency of these cytogenetic abnormalities is shown in Table 1. Within this panel, the “traditional” high-risk abnormalities have included del(17p), t(4;14), t(14;16), and t(14;20). Increasing evidence supports that 1q abnormalities, particularly amplification (>4 copies) or in combination with other high-risk abnormalities, should also be considered a high-risk abnormality.\(^5\) “Double-hit” biallelic inactivation of TP53 (eg, del(17p) in one allele plus mutation in the other allele) appears to be associated with the highest risk, although a recent publication demonstrated that del(17p) by itself is also associated with poor outcomes.\(^6\)\(^7\)

A number of gene signatures associated with standard- or high-risk disease have been reported over the years, and while the different panels have been demonstrated to identify different risk groups, these panels generally do not share any overlapping genes across the signatures.\(^8\) Thus, consensus has not been reached in the field regarding the optimal gene expression profiling (GEP) panel to utilize, and therefore this testing is not considered SOC.

**Stratification for Treatment Selection**

**TRANSPLANT ELIGIBILITY.** For many patients, recommendations for initial treatment still hinge on whether the patient is considered to be eligible for high-dose therapy and ASCT. However, there is increasing overlap in the induction strategies used in the transplant-eligible (TE) and transplant-ineligible (TI) groups, and multiple studies have demonstrated the feasibility and efficacy of ASCT in older adults.\(^9\)\(^-\)\(^11\) While ASCT candidacy is still sometimes in the eye of the beholder (namely, the transplant physician), several key factors that lead to ineligibility include poor performance status, liver cirrhosis, and heart failure (New York Heart Association functional status Class III/IV). Unfortunately, many patients who are potentially TE are never referred to an ASCT center for evaluation.\(^12\)\(^-\)\(^15\)

The line between TI and TE has also been blurred by the study design of several recent cooperative group phase 3 studies. In these, ND patients could either be TE who chose not to go through an upfront ASCT or TI (Table 2). As previously discussed,\(^16\) it can be difficult to apply the results of these studies (eg, SWOG S0777, ECOG E1A11) to the more typical TI patient seen in practice, who is often older with more comorbidities. For instance, in the SWOG S0777 study (NCT00644228), 68% of the enrolled population were noted to have intent to pursue ASCT. Thus, while this trial is often used to support the assertion that lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone (RVD) is an SOC in the TI population, in actuality this study primarily enrolled a TE population who chose not to undergo upfront ASCT. In addition, the region of the world in which a trial was conducted is important, because age cutoffs for transplant eligibility may differ by nation. For example, in the MAIA trial (NCT02252172; discussed further below), which helped establish the combination of daratumumab, (Dara; Darzalex), lenalidomide, and dexamethasone (Dara-Rd) as an SOC for TI patients, more than half of the enrolled subjects were aged less than 75 years\(^17\) and thus may have been considered TE in the United States.

---

**TABLE 1. Frequencies of Cytogenetic Abnormalities in Multiple Myeloma**\(^9\)

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperdiploidy</td>
<td>50</td>
</tr>
<tr>
<td>Gain 1q</td>
<td>40</td>
</tr>
<tr>
<td>IGH translocation</td>
<td></td>
</tr>
<tr>
<td>t(11;14)</td>
<td>17</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>15</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>5</td>
</tr>
<tr>
<td>t(6;14)</td>
<td>2</td>
</tr>
<tr>
<td>t(14;20)</td>
<td>1</td>
</tr>
<tr>
<td>Deletions</td>
<td></td>
</tr>
<tr>
<td>13q</td>
<td>45</td>
</tr>
<tr>
<td>1p</td>
<td>30</td>
</tr>
<tr>
<td>6q</td>
<td>33</td>
</tr>
<tr>
<td>8p</td>
<td>25</td>
</tr>
<tr>
<td>14q</td>
<td>38</td>
</tr>
<tr>
<td>16q</td>
<td>35</td>
</tr>
<tr>
<td>17p</td>
<td>10</td>
</tr>
</tbody>
</table>
# Summary of Recent Randomized Phase 2 or 3 Studies in Patients With Newly Diagnosed Multiple Myeloma

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligible age (yrs)</th>
<th>TE or TI</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG 0777[^1,^2]</td>
<td>≥18</td>
<td>TE (without plan for upfront) and TI</td>
<td>Rvd × 8 → Rd vs Rd</td>
</tr>
<tr>
<td>ECOG E1A11[^3]</td>
<td>≥18</td>
<td>TE (without plan for upfront) and TI</td>
<td>KRd × 9 vs Rvd × 12 (R maintenance for both groups)</td>
</tr>
<tr>
<td>SWOG-1211</td>
<td>≥18</td>
<td>TE (without plan for upfront) and TI</td>
<td>RVd × 8 → RVd maintenance vs Elo-Rvd × 8 → Elo-Rvd maintenance</td>
</tr>
<tr>
<td>MAIA[^4,^5]</td>
<td>≥18</td>
<td>TI</td>
<td>Dara-R vs Rd</td>
</tr>
<tr>
<td>TOURMALINE-MM2[^6]</td>
<td>≥65 (or TI due to comorbidities)</td>
<td>TI</td>
<td>IRd × 18 → IR vs Rd × 18 → R</td>
</tr>
<tr>
<td>ALCYONE[^7,^8]</td>
<td>≥65 (or TI due to comorbidities)</td>
<td>TI</td>
<td>Dara-VMP × 9 → Dara vs VMP × 9</td>
</tr>
<tr>
<td>CLARION[^9]</td>
<td>≥18</td>
<td>TI</td>
<td>KMP × 9 vs VMP × 9</td>
</tr>
<tr>
<td>KEYNOTE-185[^10]</td>
<td>≥18</td>
<td>TI</td>
<td>Pembrol-Rd vs Rd</td>
</tr>
<tr>
<td>GRIFFIN[^11,^12]</td>
<td>≤70</td>
<td>TE</td>
<td>Dara-RVd × 4 → ASCT → Dara-RVd × 2 → Dara-R</td>
</tr>
<tr>
<td>CASSIOPEIA[^13]</td>
<td>≤70</td>
<td>TE</td>
<td>RVd × 4 → ASCT → RVd × 2 → R</td>
</tr>
<tr>
<td>GMMG-HD6[^14]</td>
<td>≤70</td>
<td>TE</td>
<td>RVd × 4 → ASCT → Elo-RVd × 2 → Elo-R</td>
</tr>
<tr>
<td>FORTE[^15]</td>
<td>≤65</td>
<td>TE</td>
<td>RVd × 3 → ASCT → RVd × 2 → R</td>
</tr>
<tr>
<td>IFM 2009[^16]</td>
<td>≤65</td>
<td>TE</td>
<td>RVd × 3 → ASCT → RVd × 2 → R</td>
</tr>
<tr>
<td>DFCI 2009[^17]</td>
<td>≤65</td>
<td>TE</td>
<td>RVd × 3 → ASCT → RVd × 2 → R</td>
</tr>
</tbody>
</table>

ASCT, autologous stem cell transplant; C, cyclophosphamide; Dara, daratumumab; d, dexamethasone; Elo, elotuzumab; I, ixazomib; K, carfilzomib; M, melphalan; mo, month; NR, not reached; OS, overall survival; P, prednisone; Pembro, pembrolizumab; PFS, progression-free survival; R, lenalidomide; T, thalidomide; TE, transplant eligible; TI, transplant ineligible; upfront, upfront ASCT; V, bortezomib; yr, year.

---

[^1]: IFM 2009[^16]; 5-yr: 79% vs 81% (P = .988; HR, 0.998; 95% CI, 0.790-1.261; P for KRd-ASCT vs KRd-12, 0.998; HR, 1.10; 95% CI, 0.73-1.65; P = .0008).
[^2]: SWOG 0777[^1,^2]; 5-yr: 66.2% vs 67.2% (P = .159; HR, 0.742; 96% CI, 0.594-0.928; P = .003).
[^3]: ECOG E1A11[^3]; 5-yr: 72 (31%) vs 80% (32%) vs 65 (33%) yrs (P = .90; HR, 0.83; 95% CI, 0.676-1.018).
[^4]: MAIA[^4,^5]; 5-yr: 63 (43%) vs 65 (32%) yrs (P = .74; HR, 1.22; 95% CI, 0.67-2.22; P = .43).
[^5]: MAIA[^4,^5]; 4-yr: 66.2% vs 67.2% (P = .97; HR, 0.998; 95% CI, 0.790-1.261; P for KRd-ASCT vs KRd-12, 0.998; HR, 1.10; 95% CI, 0.73-1.65; P = .0008).
[^6]: TOURMALINE-MM2[^6]; 5-yr: 75 yrs (HR, 0.709; 96% CI, 0.543-0.926; P = .0114).
[^7]: ALCYONE[^7,^8]; 5-yr: 75 yrs (HR, 0.53; 95% CI, 0.43-0.66; P < .0001).
[^8]: ALCYONE[^7,^8]; 5-yr: 67.5 yrs vs 63.6 yrs (P < .001; HR, 1.53; 95% CI, 1.23-1.91; P = .0008).
[^9]: CLARION[^9]; 5-yr: 67.5 yrs vs 63.6 yrs (P < .001; HR, 1.53; 95% CI, 1.23-1.91; P = .0008).
[^10]: KEYNOTE-185[^10]; 5-yr: 75 yrs (HR, 0.968; 95% CI, 0.697-1.344; P = .90).
[^11]: GRIFFIN[^11,^12]; 5-yr: 67.5 yrs vs 63.6 yrs (P < .001; HR, 1.53; 95% CI, 1.23-1.91; P = .0008).
[^12]: GRIFFIN[^11,^12]; 3-yr: 66.2% vs 67.2% (P = .43; HR, 1.22; 95% CI, 0.67-2.22; P = .43).
[^13]: CASSIOPEIA[^13]; 3-yr: 75 yrs (HR, 0.83; 95% CI, 0.676-1.018; P = .90).
[^14]: GMMG-HD6[^14]; 3-yr: 75 yrs (HR, 0.99; 95% CI, 0.83-1.16; P > .99).
[^15]: FORTE[^15]; 3-yr: 75 yrs (HR, 0.99; 95% CI, 0.83-1.16; P > .99).
[^16]: IFM 2009[^16]; 3-yr: 75 yrs (HR, 0.99; 95% CI, 0.83-1.16; P > .99).
[^17]: DFCI 2009[^17]; 3-yr: 75 yrs (HR, 0.99; 95% CI, 0.83-1.16; P > .99).
### TABLE 2. Summary of Recent Randomized Phase 2 or 3 Studies in Patients With Newly Diagnosed Multiple Myeloma

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligible age (yrs)</th>
<th>Treatment</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG E1A1135 IFM 2009 40 FORTE 38 GMMG-HD6 79 CASSIOPEIA 45 GRIFFIN 46,47 KEYNOTE-185 66 CLARION 67 ALCYONE 68,69 TOURMALINE-MM2 65 MAIA17,64 SWOG-1211</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligible age (yrs)</th>
<th>Treatment</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG E1A1135 IFM 2009 40 FORTE 38 GMMG-HD6 79 CASSIOPEIA 45 GRIFFIN 46,47 KEYNOTE-185 66 CLARION 67 ALCYONE 68,69 TOURMALINE-MM2 65 MAIA17,64 SWOG-1211</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Median age (yrs) PFS OS

<table>
<thead>
<tr>
<th>Median age (yrs)</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>63 (43% ≥65 yrs)</td>
<td>Median: 41 vs 29 mos (HR, 0.742; 96% CI, 0.594-0.928; P = .003)</td>
<td>Median: NR vs 69 mos (HR, 0.709; 96% CI, 0.543-0.926; P = .0114)</td>
</tr>
<tr>
<td>65 (32% ≥70 yrs)</td>
<td>34.6 vs 34.4 mos (HR, 1.04; 95% CI, 0.83-1.3; P = .74)</td>
<td>Median: NR in either arm (HR, 0.98; 96% CI, 0.71-1.36; P = .92)</td>
</tr>
<tr>
<td>66 (24% ≥70 yrs)</td>
<td>33.6 vs 31.5 mos (HR, 0.968; 80% CI, 0.697-1.344; P = .90)</td>
<td>Median: NR vs 68 mos (HR, 1.279; 80% CI, 0.819-2.000; P = .48)</td>
</tr>
<tr>
<td>73 (44% ≥75 yrs)</td>
<td>Median: NR vs 34.4 mos (HR, 0.55; 95% CI, 0.43-0.66; P &lt; .0001)</td>
<td>Median: NR in either arm (HR, 0.66; 95% CI, 0.52-0.86; P = .0013)</td>
</tr>
<tr>
<td>73-74 (43%-44% ≥75yrs)</td>
<td>Median: 35.3 vs 21.8 mos (HR, 0.83; 95% CI, 0.676-1.018; P = .073)</td>
<td>Median: NR in either arm (HR, 0.998; 95% CI, 0.790-1.261; P = .988)</td>
</tr>
<tr>
<td>71 (30% ≥75 yrs)</td>
<td>Median: 36.4 vs 19.3 mos (HR, 0.42; 95% CI, 0.34-0.41; P &lt; .0001)</td>
<td>Median: NR in either arm (HR, 0.80; 95% CI, 0.46-0.80; P = .0003)</td>
</tr>
<tr>
<td>72 (31% ≥75 yrs)</td>
<td>Median: 22.3 vs 21.1 mos (HR, 0.906; 95% CI, 0.746-1.101; P = .150)</td>
<td>Median: NR in either arm (HR, 1.08; 95% CI, 0.82-1.43)</td>
</tr>
<tr>
<td>74 (31%-32% ≥80 yrs)</td>
<td>6-mo: 82% vs 85% (HR, 1.22; 95% CI, 0.67-2.22; P = .75)</td>
<td>Median NR in either arm (HR, 2.06; 95% CI, 0.89-4.55; P = .97)</td>
</tr>
<tr>
<td>60 (27% ≥65 yrs)</td>
<td>3-yr: 88.9% vs 81.2% (HR, 0.46; 95% CI, 0.21-1.01)</td>
<td>3 yr: 92.6% vs 92.2% (HR, 0.90; 95% CI, 0.32-2.57)</td>
</tr>
<tr>
<td>58</td>
<td>Median: NR in either arm (HR, 0.47; 95% CI, 0.33-0.67; P &lt; .0001)</td>
<td>Median: NR in either arm (HR, 0.43; 95% CI, 0.23-0.80)</td>
</tr>
<tr>
<td>59</td>
<td>3-yr: 68.8% vs 68.5% vs 66.2% vs 67.2% (P = .86)</td>
<td>3-yr: 89.4% vs 89.1% vs 92.5% vs 89.7% (P = .43)</td>
</tr>
<tr>
<td>57 (39% ≥60 yrs)</td>
<td>3-yr: 68.8% vs 68.5% vs 66.2% vs 67.2% (P = .86)</td>
<td>4-yr: 86% (KRd-ASCT) vs 85% (KRd-12) (HR, 1.16; 95% CI, 0.80-1.68; P = .24)</td>
</tr>
<tr>
<td>59-60</td>
<td>Median: 50 vs 36 mos (HR, 0.65; 95% CI, 0.53-0.80; P &lt; .001)</td>
<td>4-yr: 81% vs 82% (KRd-12) vs 76% (Kd-ASCT) (HR, 1.16; 95% CI, 0.80-1.68; P = .87)</td>
</tr>
<tr>
<td>55-57</td>
<td>Median: 46.2 vs 67.5 mos (HR, 1.53; 95% CI, 1.23-1.91; P &lt; .001)</td>
<td>5-yr: 79% vs 81% (HR, 1.10; 95% CI, 0.73-1.65; P &gt; .99)</td>
</tr>
</tbody>
</table>
FRAILTY-BASED ASSESSMENT. A growing body of literature supports the use of geriatric and frailty assessment in determining treatment strategies for older adults who are being considered for ASCT as well as those who are considered TL. Frailty status has been shown to be a predictor of mortality in patients with MM. Multiple different frailty indices have been developed, including the International Myeloma Working Group (IMWG) Frailty Index, the Revised Myeloma Comorbidity Index, the Simplified Frailty Scale, and the UK Myeloma Research Alliance (UKMRA) Myeloma Risk Profile. The IMWG Frailty Index encompasses patient age, the Katz Activity of Daily Living scale, the Lawton Instrumental Activity of Daily Living scale, and the Charlson Comorbidity Index (CCI) score. The Revised Myeloma Comorbidity Index incorporates age, renal function, lung function, Karnofsky performance status, frailty (as determined by the Fried definition), and disease cytogenetics. The Simplified Frailty Scale includes age, ECOG status, and CCF score; the UKMRA Myeloma Risk Profile includes age, World Health Organization performance status, ISS, and C-reactive protein.

To date, the majority of the literature derives from post hoc analysis of clinical trials or large database reviews, and there is no consensus about the best available instrument to assess frailty. The Hovon 143 phase 2 study, which evaluated an induction strategy of daratumumab, ixazomib (Ninlaro), and dexamethasone, was of interest as having 2 or more high-risk features to have ultra–high-risk disease, defined inclusively enrolled patients considered for frail patients—who more accurately represent the real-world population of patients seen in practice—are needed.

CYTOGENETIC RISK. Another potential stratification for treatment selection involves standard-risk vs high-risk disease. However, in the era of triplet/quadruplet induction regimens, few data suggest that one specific induction strategy has superior outcomes over others for patients with high-risk disease. This is primarily because the majority of randomized phase 2/3 studies have relied on underpowered subgroup analyses to compare standard vs high-risk groups, and typically, patients with high-risk disease are underrepresented. This problem has been further exacerbated by differing definitions of high-risk disease (eg, whether 1q abnormalities are included, differing cut-offs for positivity, or exclusion of primary plasma cell leukemia) across studies.

The ENDURANCE trial (NCT01863550; ECOG E1A11) randomized patients to RVd vs carfilzomib (Kyprolis), lenalidomide, and dexamethasone (KRd) induction (without upfront ASCT) (Table 2). This study excluded patients with del(17p), t(14;16), t(14;20), LDH greater than 2 times the upper limit of normal (ULN), or greater than 20% circulating plasma cells. There was no difference in the primary end point (PFS) between the 2 treatment arms. Furthermore, subgroup analysis of the patients with t(4;14) did not reveal benefit for KRd over RVd (HR, 1.16; 95% CI, 0.54-2.47). In contrast, the SWOG-1211 study (NCT016686719) enrolled all of the high-risk patients who had been excluded from the ENDURANCE trial (high-risk GEP, t(14;16), t(14;20), del(17p), amp(1q), primary plasma cell leukemia, or LDH >2x ULN). In this study, which again did not include upfront ASCT, patients were randomized to elotuzumab (Empliciti) plus RVd vs RVd induction. This study failed to demonstrate benefit of adding elotuzumab to the backbone of RVd induction in patients with high-risk MM. The UK OPTIMUM/MUKnine trial (NCT03188172) exclusively enrolled patients considered to have ultra–high-risk disease, defined as having 2 or more high-risk features (t[4;14], t[14;16], t[14;20], gain[1q], del[1p], del[17p], gene expression SKY92 profiling, or >20% circulating plasma cells). This study was designed as a digital comparator-arm trial in which enrolled subjects were compared with molecularly matched patients from the National Cancer Research Institute Myeloma XI/XI+ trial (NCT01554852). A superior 18-month PFS rate (the primary end point) was observed with the UK OPTIMUM/MUKnine treatment strategy (involving a 5-drug induction regimen, transplant, and intensive
consolidation/maintenance strategies) compared with that achieved by the molecularly matched participants from the previous Myeloma XI trial: 81.7% vs 65.9%, respectively. 37 It is hoped that ongoing phase 3 studies comparing quadruplets vs triplets (eg, PERSEUS [NCT03710603], GMMG HD7 [NCT03617731]) will provide more information regarding the potential benefit of quadruplets in patients with high-risk disease.

**Therapy Selection**

**TRANSPLANT ELIGIBLE.** In the TE setting, induction therapy consisting of lenalidomide, a PI (either bortezomib or carfilzomib), and dexamethasone is established as SOC (Figure). A direct comparison of RVd and KRd induction followed by ASCT has not been conducted. As noted above, no difference in PFS (comparing RVd vs KRd) was observed in the ENDURANCE study; however, this study did not include consolidation with ASCT or most categories of high-risk disease. 38 While prospective randomized data are lacking for the comparison of RVd vs the combination of bortezomib, cyclophosphamide, and dexamethasone (VCd), some trial results have demonstrated the superiority of bortezomib, thalidomide, and dexamethasone (VTd) over VCd (IFM2013-04; NCT01971658) as well as KRd over carfilzomib, cyclophosphamide, and dexamethasone (FORTE; NCT02203643). 38,39

The IFM/DFCI2009 (NCT01191060) and FORTE trials demonstrated superior PFS rates for the inclusion of upfront ASCT as consolidation following RVd (IFM/DFCI2009) or KRd (FORTE) induction. 38,40,41 None of these studies have demonstrated superior overall survival (OS) outcomes with inclusion of upfront ASCT, but given the increasing number of salvage therapies available and the overall trend for longer duration of survival in this patient population, it is becoming increasingly difficult to demonstrate OS benefit in the upfront setting.

As shown in Table 2 and Table 3, many recent and/or ongoing randomized studies have included post-ASCT consolidation with multiagent therapy prior to transitioning to maintenance...
therapy. Whether these cycles of post-ASCT consolidation contribute significantly to the long-term outcomes of these treatment strategies is not clear. The BMT CTN 0702 trial (NCT01109004) randomized patients who had completed induction therapy to 1 of 3 arms: single ASCT, tandem ASCT, or single ASCT followed by 4 cycles of RVd consolidation. All 3 arms then went on to receive lenalidomide maintenance. No differences in either PFS or OS outcomes were observed across the 3 arms, suggesting that single ASCT followed by lenalidomide maintenance was an SOC. The EMN02/HOVON 95 MM trial (NCT01208766) compared post-VCd induction therapy of the combination of bortezomib, melphalan, and prednisone (VMP) vs ASCT (1 or 2 transplants). A second randomization involved additional consolidation with either 2 cycles of RVd or nothing, followed by lenalidomide maintenance in both arms. As a whole, a superior PFS rate was observed for those receiving RVd consolidation (59.3% vs 42.9%; HR, 0.81; 95% CI, 0.68-0.96; P = .016). However, upon closer examination of the subset of patients who received ASCT, one observes that the trend toward superior PFS with RVd consolidation did not quite reach statistical significance (HR, 0.83; 95% CI, 0.66-1.03). Of note, no patients in the EMN02/HOVON 95 MM trial received lenalidomide with induction, whereas 56% of patients in the BMT CTN 0702 trial received RVd induction and 10% received lenalidomide and dexamethasone (Rd) induction. Overall, outside the context of a clinical trial, patients commonly proceed directly from ASCT to maintenance therapy, bypassing multiagent consolidation.

A major unanswered question in the TE setting is the potential role of mAb therapy as an addition to the backbone of IMiD/Pd/dexamethasone induction; many recent and ongoing studies are addressing this knowledge gap (Tables 2 and 3). For instance, the CASSIOPEIA IA trial (NCT02341383), a randomized phase 3 study, evaluated the addition of daratumumab to the backbone of VTd induction/consolidation (Table 2). While the study met its primary end point (median PFS not reached in either arm; HR, 0.47; 95% CI, 0.33-0.67; P < .0001), resulting in the FDA approval of Darasa-VTd, it has not been practice-changing in the United States given the use of thalidomide. Of more interest have been the studies evaluating the addition of mAb therapy to RVd or KRd backbones. Griffin (NCT02874742), a randomized phase 2 trial, compared RVd induction, ASCT, RVd consolidation, and R maintenance with Dara-RVd induction, ASCT, Dara-RVd consolidation, and Dara-R maintenance. The study met its primary end point of stringent complete response (sCR) rate post consolidation (42.4% vs 32.0%; odds ratio [OR], 1.57; 95% CI, 0.87-2.82; 1-sided P = .068 with a prespecified 1-sided α of 0.10). However, the 24-month PFS rates were similar (95.8% vs 89.8%). With longer follow-up, the PFS curves have had more separation, not yet meeting statistical significance (3-year PFS rate, 88.9% vs 81.2%; HR, 0.46; 95% CI, 0.21-1.01). Higher rates of grade 3/4 neutropenia, thrombocytopenia, and upper respiratory tract infections were observed in the daratumumab-containing group. The ongoing phase 3 PERSEUS study (Table 3), which has a similar design (with the exception of the maintenance portion), is powered to evaluate PFS as the primary end point and should therefore provide more substantive evidence for the use of Dara-RVd as an induction strategy. The phase 3 GMMG-HD7 trial evaluated ixazomib (Ixa; Sarcilisa), another anti-CD38 mAb, in the context of RVd induction. This study was designed to evaluate the achievement of MRD negativity (at 10−6 sensitivity using flow cytometry) post induction therapy as the primary end point. A statistically significant improvement in rates of MRD negativity post induction was observed for the Isa-RVd arm (50.1%) vs the RVd arm (33.6%) (OR, 1.83; 95% CI, 1.34-2.51; P < .001). No data regarding PFS outcomes have been reported thus far. Several single-arm studies have evaluated Dara-KRd induction (with or without ASCT) and reported high rates of MRD negativity. As neither SCR nor rates of MRD negativity have been confirmed as surrogate end points for PFS or OS, further follow-up is required from ongoing studies to determine whether initial achievement of deeper response rates in the setting of quadruplet therapies translates to superior long-term outcomes.

An in-depth discussion of maintenance is outside the scope of this review and is discussed more extensively elsewhere. However, the current SOC, established through four randomized phase 3 studies, is the use of single-agent lenalidomide maintenance therapy. These studies demonstrated significant PFS benefit with lenalidomide maintenance (compared with placebo or observation) and in aggregate also showed superior OS outcomes. Current unanswered questions include whether addition of mAb therapy to the backbone of lenalidomide maintenance improves outcomes, whether maintenance must be continued indefinitely to achieve optimal long-term outcomes, and whether a response-adapted approach using MRD negativity can be utilized to determine maintenance intensity and duration.

**TRANSPANT INELIGIBLE.** Many of the randomized studies conducted over the past decade have built upon the backbone of continuous Rd induction, which had previously been established as an SOC by the FIRST trial (NCT00689936). As noted above, SWOG S0777 randomized patients to RVd vs Rd induction in the absence of ASCT, but the minority of enrolled subjects were considered TI. This study demonstrated superior PFS.
**TABLE 3. Ongoing Randomized Phase 3 Studies in NDMM**

<table>
<thead>
<tr>
<th>Study</th>
<th>ASCT candidacy requirement at entry</th>
<th>Induction regimens</th>
<th>Primary end point</th>
<th>Study scheme details</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03742297</td>
<td>TI</td>
<td>VMP→ Rd vs KRd +/- Dara → Dara-R</td>
<td>CR rate</td>
<td>Induction therapy followed by maintenance (Rd or Dara-R)</td>
</tr>
<tr>
<td>NCT03993912 (IFM2017-03)</td>
<td>TI (frail)</td>
<td>Dara-R vs Rd</td>
<td>PFS</td>
<td>Continuous treatment until progression</td>
</tr>
<tr>
<td>NCT04751877 (IFM2020-05)</td>
<td>TI (nonfrail)</td>
<td>Isa-RVd vs Isa-Rd</td>
<td>Rate of MRD negativity rate at 18 mos ($10^{-5}$)</td>
<td></td>
</tr>
<tr>
<td>NCT04096066</td>
<td>TI</td>
<td>KRd vs Rd</td>
<td>MRD negativity and PFS</td>
<td>In the KRd arm, if ≥ VGPR within first year and in sustained MRD-negativity ($10^{-5}$) after 1 and 2 years, then K is stopped and Rd is continued</td>
</tr>
<tr>
<td>NCT03720041 (Myeloma XIV, FiTNESS)</td>
<td>TI</td>
<td>IRd (reactive vs adaptive dosing)</td>
<td>Early treatment cessation rate</td>
<td>First randomization based on frailty scoring. Second randomization to R/placebo vs R/I maintenance</td>
</tr>
<tr>
<td>NCT03652064 (CEPHEUS)</td>
<td>TE (without plan for upfront) and TI</td>
<td>Dara-RVd vs RVd</td>
<td>MRD negativity</td>
<td>Induction (8 cycles), maintenance (Rd vs Dara-Rd) until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td>NCT04566328 (EQUATE)</td>
<td>TE (without plan for upfront) and TI</td>
<td>Dara-Rd vs Dara-RVd</td>
<td>OS</td>
<td>Dara-Rd induction, MRD testing, randomization to DRd vs Dara-RVd × 9, followed by Dara-R until progression</td>
</tr>
<tr>
<td>NCT03710603 (PERSEUS)</td>
<td>TE</td>
<td>Dara-RVd vs RVd</td>
<td>PFS</td>
<td>Induction (4 cycles), ASCT, consolidation (2 cycles), maintenance (R or Dara-R) until disease progression or unacceptable toxicity. Duration of Dara based on MRD.</td>
</tr>
<tr>
<td>NCT03617731 (GMMG-HD7)</td>
<td>TE</td>
<td>Isa-RVd vs RVd</td>
<td>MRD negativity after induction; PFS from second randomization</td>
<td>Induction (three 42-day cycles), ASCT (x 2 if not in CR after first), 2nd randomization to Isa-R vs R maintenance</td>
</tr>
<tr>
<td>NCT04483739 (IsKia)</td>
<td>TE</td>
<td>Isa-KRd vs KRd</td>
<td>MRD negativity post ASCT</td>
<td>Induction (4 cycles), ASCT, consolidation (4 cycles plus 12 “light” cycles), R maintenance</td>
</tr>
<tr>
<td>NCT04923893 (CAR TITUDE-5)</td>
<td>TE (without plan for upfront) and TI</td>
<td>RVd→Rd vs RVd→ciltacabtagene autoleucel</td>
<td>PFS</td>
<td>8 cycles of RVd prior to Rd vs CAR T-cell therapy</td>
</tr>
<tr>
<td>NCT05257083 (CAR TITUDE-6)</td>
<td>TE</td>
<td>Dara-RVd/ASCT/Dara-RVd vs Dara-RVd/ciltacabtagene autoleucel</td>
<td>PFS and sustained MRD negativity ($10^{-5}$ for at least 12 mos)</td>
<td>Both arms receive R maintenance for up to 2 years</td>
</tr>
</tbody>
</table>

ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; CR, complete response; Dara, daratumumab; d, dexamethasone, Elo, elotuzumab; I, ixazomib; Isa, isatuximab; K, carfilzomib; mos, months; M, melphalan; MRD, minimal residual disease; OS, overall survival; P, prednisone; PFS, progression-free survival; R, lenalidomide; TE, transplant eligible; TI, transplant ineligible; V, bortezomib; VGPR, very good partial response.
Recent Advancements and Future Directions in Frontline Treatment of Multiple Myeloma

Kimberley R. Doucette, MD, MSC; and David H. Vesole, MD, PhD

Recent advancements and OS outcomes with the triplet vs the doublet (Table 2). However, it is again worth noting that the majority of patients enrolled in this study were TE. As real-world experience has highlighted the difficulties of utilizing full-dose lenalidomide, twice-weekly bortezomib, and/or prolonged dexamethasone in more frail patients, a single-arm phase 2 study was conducted to evaluate the “RVd lite” regimen. In this study, lenalidomide was decreased to 15 mg, bortezomib was administered once weekly (subcutaneously), and dexamethasone was administered only during the induction phase. The trial consisted of 9 cycles of triplet therapy followed by 6 cycles of consolidation with lenalidomide and bortezomib. Maintenance was not dictated by the trial, but lenalidomide maintenance could be utilized per investigator discretion. Consistent

The author of “Current Frontline Treatment of Multiple Myeloma,” provides a thorough review of the current standard of care for multiple myeloma in the frontline setting. It is becoming more apparent that multiple myeloma is a heterogenous disease that requires individually tailored treatment, dependent on patient factors and biologic characteristics, including disease stage and molecular features. We have traditionally divided patients into transplant eligible vs transplant ineligible, but there are important nuances in making these determinations. The literature has varying definitions of transplant eligibility. In addition, there are restrictions on medical financial resources in some countries outside the United States, sometimes limiting accessibility to transplant options. Supportive care for autologous stem cell transplants is continuously improving, allowing us to perform successful transplants in a greater number of patients. As the FORTE trial (NCT02203643) highlights, autologous stem cell transplant remains a standard of care in multiple myeloma even in the era of novel therapies. The experience at our center, and in numerous centers across the United States, is that successful transplants can be done in fit patients aged up to 80 years or a little older, without significant morbidity and mortality. The challenge has been to increase the number of patients referred to transplant centers to optimize this treatment strategy. According to statistics compiled by the Center for International Blood and Marrow Transplant Research, less than 50% of individuals who are transplant eligible actually receive a transplant, and for members of US minority populations, this percentage is substantially lower.

Aside from chronologic age, many other factors can affect treatment options and outcomes. The authors successfully point out that geriatric and frailty assessments are becoming increasingly important in identifying optimal treatment strategies for each individual patient. Clinical trials are addressing these assessments as a more objective measure of morbidity and mortality. For non–transplant-eligible patients, equally important therapeutic advancements have been made with the triplet regimen daratumumab (Darzalex), lenalidomide (Revlimid), and dexamethasone, which was studied in the MAIA trial (NCT02252172). This trial has provided a new standard of care for frail older adults. This regimen is both tolerable and has good long-term outcomes (the most recent update shows a 53% progression-free survival [PFS] rate at 5 years). Unfortunately, despite the PFS advantage, many practitioners in the community have not yet adopted this as first-line therapy and are most commonly utilizing RVd-lite (lenalidomide, bortezomib [Velcade], and dexamethasone), a regimen with a less favorable administration schedule, increased risk of toxicity (eg, peripheral neuropathy), and shorter PFS.

A critical goal for the multiple myeloma community is to identify treatment strategies that benefit patients...
with a TI population, the median age was 73 years (range, 65-91). The reported median PFS was 35.1 months (95% CI, 30.9 to not reached). The overall feasibility of this approach was demonstrated by 64% of the patients completing the 15 cycles of induction/consolidation (with only 4% discontinuing due to toxicity) and patient-reported quality-of-life outcomes showing statistically significant improvements in physical function, future perspective, and disease symptom scores at the end of treatment compared with baseline.

MAIA, a phase 3 study comparing Dara-Rd with Rd in the ND TI setting, has established Dara-Rd as an SOC in that setting. With a median follow-up of 56.2 months, the median PFS was not reached in the Dara-Rd group, compared with 34.4 months in the Rd group with high-risk disease, because their outcomes remain poor, despite recent advances in therapy. Most outcomes for high-risk disease are focused on subgroup analyses, and they therefore lack statistical strength. As pointed out by the authors, an increasing number of trials are focusing on high-risk groups to help identify successful treatment strategies. Thus far, we have had conflicting results regarding the benefit of quadruplet therapies on outcomes in patients with high-risk disease. Additionally, this is a heterogenous group of patients with varying definitions of high-risk disease. For example, the revised International Staging System,7 the International Myeloma Work Group,8 and the Mayo Clinic’s mSmart9 all have different definitions of high risk. Regardless of which definition is utilized, optimal management of high-risk disease is a focus of active research as the field attempts to identify strategies to overcome its aggressive nature in these individuals.

As more knowledge emerges about patient outcomes with newer targeted therapies, clinicians are also learning about the importance of incorporating agents with different mechanisms of action and the role of minimal residual disease (MRD). MRD negativity, a surrogate marker of depth of response, is being incorporated as a biological end point in virtually all ongoing clinical trials. As the number of trials utilizing MRD negativity as a surrogate end point increases, we will hopefully gain deeper understanding into how to incorporate MRD data into our clinical decision making. Quadruplet therapies are likely to become standards of care as they produce deep responses with high rates of MRD negativity and prolonged PFS. These include daratumumab + RVd as examined in the GRIFFIN trial (NCT02674742),10 daratumumab + VThd (bortezomib, thalidomide, and dexamethasone) in the CASSIOPEIA trial (NCT02541383),11,12 and daratumumab + KRd (carfilzomib, lenalidomide, and dexamethasone) in the MANHATTAN13 and MASTER (NCT03224507)14 trials.

The current dogma in multiple myeloma is to continue treatment until treatment intolerance or disease progression. In contrast, the MASTER trial is utilizing an MRD-adapted treatment approach, whereby after confirmation of MRD negativity, patients will enter a treatment-free phase. This would markedly change the current treatment paradigm of continuous therapy.

Lastly, the future of upfront therapy is likely to change as more targeted therapies and novel agents are being investigated in combinations with current standard of care. These therapies and agents include antibody-drug conjugates, cereblon E3 ligase modulating drugs, and T-cell engagers such as bispecific antibodies, chimeric antigen receptor T cells, and natural killer cells. These agents are revolutionizing the relapsed/refractory therapeutic landscape and are likely to make significant impact in the upfront setting as well. The advantage of many of these agents is their safety profile; their tolerability allows more patients to be successfully treated with fewer serious adverse effects. Studying these new agents and combinations in high-risk groups will be important.

We anticipate many ongoing changes in the frontline treatment setting over the next few years, with the goals of further increasing overall survival, PFS, and, importantly, quality of life.

AUTHOR BIOS

Doucette is a medical oncologist and hematologist specializing in multiple myeloma at the Georgetown Lombardi Comprehensive Cancer Center in Washington, DC. She is an assistant professor of medicine at Georgetown University.

Vesole is director of the myeloma program at MedStar Georgetown University Hospital. He is also codirector of the myeloma division and director of myeloma research at the John Theurer Cancer Center at Hackensack University Medical Center in Hackensack, New Jersey. He is also a professor of medicine at Georgetown Lombardi Comprehensive Cancer Center and Hackensack Meridian School of Medicine.

For references visit cancernetwork.com/Doucette_7.22
The addition of a third drug to the Rd backbone has not always resulted in superior outcomes. In the phase 3 TOURMALINE-MM2 study (NCT01850524), patients were randomized to the combination of ixazomib, lenalidomide, and dexamethasone (IRd) vs Rd.61 While the median PFS of the IRd group improved numerically relative to the Rd group (35.3 vs 21.8 months), this did not meet statistical significance (HR, 0.83; 95% CI, 0.676-1.018; P = .073). No difference in OS was observed, although the median time to progression was superior in the IRd arm (45.8 vs 26.8 months; HR, 0.738; 95% CI, 0.589-0.925; P = .008). The phase 3 KEYNOTE-185 trial (NCT02579863) evaluated the addition of the immune checkpoint inhibitor pembrolizumab (Pembro; Keytruda) to the Rd backbone.61 Notably, this study, as well as several others involving combination therapy with checkpoint inhibitors and IMiDs, were halted by the FDA due to imbalances involving combination therapy with checkpoint inhibitors and IMiDs, were halted by the FDA due to imbalances.

VMP was historically an SOC induction regimen, particularly in Europe. The phase 3 CLARION study (NCT01818752) compared fixed-duration VMP induction therapy with carfilzomib, melphalan, and prednisone (KMP). No differences in PFS (the primary end point), OS, complete response, or rate of MRD negativity were observed.65 Consistent with the known AE profiles of the 2 PIs, the VMP arm was associated with higher rates of peripheral neuropathy while the KMP arm was associated with higher rates of acute renal failure and cardiac failure.67 The results of this study, as well as those of ENDURANCE,65 failed to demonstrate superiority of carfilzomib over bortezomib in the ND setting.

The phase 3 ALCYONE trial (NCT02195479) built upon the VMP backbone by adding daratumumab.64,65 Fixed-dose VMP induction followed by observation was compared with Dara-VMP induction followed by daratumumab maintenance until progression. Here, the daratumumab-containing arm had significantly improved PFS (median, 19.3 vs 13.1 months; HR, 0.53; 95% CI, 0.43-0.66; P <.0001).64 Furthermore, an OS benefit was observed (HR, 0.68; 95% CI, 0.53-0.86; P = .0013).64 Median duration of response, overall response rate, and rate of MRD negativity were all superior in the Dara-Rd arm.64

As noted above, the incorporation of anti-CD38 mAb therapy is now well established in the TI setting and likely represents a future SOC in the TE setting as well. However, there is also interest in the incorporation of other novel agents into the newly diagnosed setting, such as anti-B-cell maturation antigen (BCMA) agents, chimeric antigen receptor (CAR) T-cell therapy, the XPO1 inhibitor selinexor (Sel; Xpovio), and cereblon E3 ligase modulators (CELMoDs). The first-in-class anti-BCMA antibody-drug conjugate (ADC) belantamab mafodotin (Bela; Blenrep) is currently approved as a single agent in the heavily relapsed/refractory setting. Several ongoing studies are evaluating Bela in combination with other MM therapies in earlier lines of therapy, including in the ND setting. A phase 2 study (NCT04802356) is evaluating the combination of Bela-RVd induction followed by ASCT, Bela-RVd consolidation, and then maintenance with Bela-R (up to 2 years of Bela; lenalidomide until progression). Bela-RVd combination is also being studied in the ND TI setting (DREAMM-9, NCT04091126) in which patients receive 8 cycles of Bela-RVd followed by Bela-Rd until progression.67 During the phase 1 portion, the optimal dosing/schedule of Bela will be determined, followed by a phase 3 portion in which patients will be randomized 1:1 to Bela-RVd vs RVd. Determining a dose/schedule that minimizes the corneal toxicity associated with Bela, and thus allows long-term administration of this agent, will be critical. Also, some studies under development will incorporate novel bispecific antibody (BiAb) therapies such as teclistamab (an anti-BCMA/anti-CD3 agent) into the ND setting.

Several ongoing studies are evaluating the incorporation of BCMA-directed CAR-T-cell therapy in the ND setting. The phase 1 KarMMa-4 (NCT04196491) study involves consolidation with idecabtagene vicleucel following induction (RVd, Dara-RVd, KRd, Dara-KRd, or CyBorD allowed) in patients with high-risk disease. Maintenance therapy with lenalidomide is allowed. The phase 3 CARTITUDE-5 (NCT04923893) trial randomizes patients who are not planning upfront ASCT to either RVd induction followed by ciltacabtagene autoleucel CAR T-cell therapy or RVd induction followed by Rd. In CARTITUDE-6...
place of currently used IMiDs (Figure). These agents, with their increased potency setting (eg, NCT05177536). If NCT05199311) and post-ASCT maintenance (eg, NCT05272826, and alkylators. Several studies are in- domide (CC-92480)—the CELM- be critical, as use of this drug is often of Seli that has long-term tolerability will ra-Rd in TI patients. Establishing a dose exploring the combination of Seli-Da- lasting disease-free intervals. Conclusion Remarkable strides have been made in the treatment of NDMM in large part due to the development of IMiDs, PIs, and mAbs. Incorporation of anti-CD38 mAb therapy into the ND setting has been a significant advance for the TI population and appears poised to become an SOC in the TE setting as well (Figure). Looking ahead to the next 15 years, the hope is that incorporation of other strategies, including CAR T-cell therapy and BiAbs, will shift the treatment paradigm, potentially eradicating the disease with frontline therapy. Even if a cure remains out of reach during that timeframe, it is anticipated that incorporating novel therapies into the frontline setting will significantly improve survival outcomes. Whether these new therapies could be accompanied by prolonged treatment-free intervals, which would represent a notable shift from current treatment strategies, remains to be determined. Integral in the development of these emerging treatment paradigms will be incorporation of novel surrogate end points, such as MRD negativity, into trial design; this will not only allow earlier readouts of trials, but also help guide decision making regarding treatment de-escalation, intensification, or cessation.49,75-77

Disclosures: The author has served as a consultant for Bristol Myers Squibb/ Celgene, GSK plc, Janssen Pharmaceuticals, Oncopeptides, Pfizer, Sanofi, Secura Bio, and Takeda Pharmaceutical Company; and has received research funding from Oncopeptides.

Corresponding Author: Sarah A. Holstein, MD, PhD
Division of Oncology and Hematology
Department of Internal Medicine
University of Nebraska Medical Center
Omaha, NE 68198
Phone: 402-559-8500
Fax: 402-559-8520
Email: sarah.holstein@unmc.edu

Key references

Email: sarah.holstein@unmc.edu
Fax: 402-559-6520

University of Nebraska Medical Center
Department of Internal Medicine
Division of Oncology and Hematology

For full list of references visit cancernetwork.com/Holstein_7.22
**LOOK TO PUSH RET BACK**

with GAVRETO, the only once-daily therapy designed to selectively target RET+ mNSCLC and advanced thyroid cancers

**INDICATIONS**

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

- Adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

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

**ARROW study design**

Efficacy and safety with GAVRETO (400 mg orally once daily) were evaluated in patients with RET fusion+ mNSCLC, advanced or metastatic RET-mutant MTC, and advanced or metastatic RET fusion+ thyroid cancer in the ARROW study, a phase 1/2, single-arm, multicohort, multicenter clinical trial. All patients must have had a non-resectable RET-altered solid tumor or MTC per local assessment of tumor tissue and/or blood. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DoR), as assessed by a blinded independent central review (BICR) according to RECIST v1.1.

**IMPORTANT SAFETY INFORMATION**

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

**Hypertension** occurred in 29% of patients, including Grade 3 hypertension in 14% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue GAVRETO based on the severity.

Please see additional Important Safety Information throughout and Brief Summary of the full Prescribing Information for GAVRETO on adjacent pages.
Efficacy and safety data of GAVRETO in advanced thyroid cancers

Select baseline characteristics from the U.S. Prescribing Information (USPI)¹

**MTC: cabozantinib- and vandetanib-naïve patients (n=29):** The median age was 61 years (range: 19-81); 72% were male and 14% had a history of CNS metastases.

**MTC: previously cabozantinib- and/or vandetanib-treated patients (n=55):** The median age was 59 years (range: 25-83); 69% were male and 7% had a history of CNS metastases.

**RET fusion-positive thyroid cancer (n=9):** The median age was 61 years (range: 46-74); 67% were male and 56% had a history of CNS metastases.

For additional baseline characteristics, refer to the USPI.

**CNS=central nervous system; RECIST=Response Evaluation Criteria in Solid Tumors.**

**GAVRETO demonstrated robust and durable response in advanced or metastatic RET-mutant MTC and advanced or metastatic RET fusion+ thyroid cancer.**¹³

**Safety of GAVRETO in 138 patients with RET-altered thyroid cancers**

**The most common adverse reactions (≥15%) and Grades 3-4 laboratory abnormalities (≥2%) were:**

- **Musculoskeletal pain** (42%), constipation (41%), hypertension (40%), fatigue (38%), diarrhea (34%), edema (29%), cough (27%), rash (24%), headache (24%), pyrexia (22%), dyspnea (22%), peripheral neuropathy (20%), dizziness (19%), abdominal pain (17%), dry mouth (17%), stomatitis (17%), nausea (17%), dysgeusia (17%), and decreased appetite (15%)

- **Decreased lymphocytes** (27%), decreased neutrophils (16%), decreased hemoglobin (13%), decreased calcium (corrected) (9%), decreased phosphate (8%), increased AST (4.3%), increased ALT (3.6%), decreased platelets (2.9%), and decreased sodium (2.2%)

¹For grouped terms, please refer to the USPI.

ALT=alanine aminotransferase; AST-aspartate aminotransferase.

**IMPORTANT SAFETY INFORMATION**

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

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

Please see additional Important Safety Information throughout and Brief Summary of the full Prescribing Information for GAVRETO on adjacent pages.
Select baseline characteristics from the USPI¹
Treatment-naive (n=27): The median age was 65 years (range: 30-87); 48% were male and 37% had either a history of or current CNS metastasis.

Previously platinum-treated (n=87): The median age was 60 years (range: 28-85); 51% were male and 43% had either a history of or current CNS metastasis.

For additional baseline characteristics, refer to the USPI.

GAVRETO demonstrated robust and durable response in RET fusion+ mNSCLC patients treated with GAVRETO from the USPI¹-⁵

Treatment-naive patients (n=27)
- 70% ORR
- Median DoR (n=19): 9.0 months (6.3 months-NE)

Previously platinum-treated patients (n=87)†
- 57% ORR
- Median DoR (n=50): NE (15.2 months-NE)

- 58% of patients continued to respond to treatment at 6 months*¹
- Median time to first response was 1.9 months (range: 1.4 months-5.6 months)²

- 80% of patients continued to respond to treatment at 6 months*¹
- Median time to first response was 1.8 months (range: 1.3 months-9.1 months)²

Per initial protocol, treatment-naive patients were included if they were deemed not eligible for platinum-based chemotherapy based on investigator assessment*¹

Safety of GAVRETO in 220 patients with RET fusion+ mNSCLC
The most common adverse reactions (≥15%) and Grades 3-4 laboratory abnormalities (≥2%) were¹⁷:
- Fatigue¹ (35%), constipation (35%), musculoskeletal pain¹ (32%), hypertension¹ (28%), diarrhea¹ (24%), cough¹ (23%), pyrexia (20%), edema¹ (20%), pneumonia¹ (17%), and dry mouth (16%)
- Decreased lymphocytes (19%), decreased neutrophils (16%), decreased phosphate (11%), decreased hemoglobin (9%), decreased sodium (7%), decreased platelets (3.2%), increased AST (2.3%), and increased ALT (2.3%)

¹The safety of GAVRETO 400 mg orally once daily was evaluated in both treatment-naive and previously platinum-treated mNSCLC patients.
²For grouped terms, please refer to the USPI

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

Impaired wound healing: can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing. Withhold GAVRETO for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of GAVRETO after resolution of wound healing complications has not been established.

Please see additional Important Safety Information throughout and Brief Summary of the full Prescribing Information for GAVRETO on adjacent pages.
Exploratory follow-up analyses of treatment-naïve mNSCLC patients

These analyses include treatment-naïve patients enrolled through May 22, 2020, which include the patients from the pivotal analysis in the USPI. These results are not included in the GAVRETO labeling. As these were not prespecified analyses, data must be interpreted with caution.

### All treatment-naïve patients

**Overall Response Rate (n=68)**

- **PR: 74%**
- **CR: 6%**
- **79% ORR (95% CI: 68%-88%)**

**Duration of Response (n=54)**

- **Median DoR: Not Reached (9 months-NR)**
- **Median DoR follow-up: 7.4 months (6.4 months-9.5 months)**


### Post hoc analyses of treatment-naïve patients

Initially, the ARROW protocol included treatment-naïve patients who were not candidates for standard therapy. In July 2019, the protocol was amended to expand the eligibility criteria to include patients who were eligible for standard therapy.†

**Pre-protocol amendment (n=43)**

- **74% ORR**

**Post-protocol amendment (n=25)**

- **88% ORR**

**All responses were partial (95% CI: 69%-98%)**

**Median DoR (n=22): Not Reached (NR-NR)**

Select baseline characteristics

- **Median age: 65 years (30-87)**
- **Gender: female 44%, male 56%**
- **History of or current CNS metastases at baseline: 35%**

All other baseline characteristics were generally balanced between the pivotal data included in the USPI and exploratory follow-up populations.†

### Adverse reactions (≥15%) and Grades 3-4 laboratory abnormalities (≥2%) in RET fusion+ mNSCLC patients (n=281) were generally consistent with the pivotal data included in the USPI†

### IMPORTANT SAFETY INFORMATION

Based on findings from animal studies and its mechanism of action, GAVRETO can cause fatal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose. Advise women not to breastfeed during treatment with GAVRETO and for 1 week after the final dose.

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

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

You may report side effects to the FDA at 1-800-FDA-1088. You may also report side effects to Genentech at 1-888-835-2555.

Please see additional Important Safety Information throughout and Brief Summary of the full Prescribing Information for GAVRETO on adjacent pages.

### References

GAVRETO® (pralsetinib)
100 mg capsules, for oral use
Initial U.S. Approval: 2020
This is a brief summary of information about GAVRETO. Before prescribing, please see full Prescribing Information.

1 INDICATIONS AND USAGE
1.1 Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer
GAVRETO is indicated for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

1.2 RET-Mutant Medullary Thyroid Cancer
GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.2)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

1.3 RET Fusion-Positive Thyroid Cancer
GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.3)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

5 WARNINGS AND PRECAUTIONS
5.1 Interstitial Lung Disease/Pneumonitis
Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis has been reported with GAVRETO. Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3-4, and 0.5% with fatal reactions. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD [see Dosage and Administration (2.3)].

5.2 Hypertension
Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients [see Adverse Reactions (6.1)]. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-except-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue GAVRETO based on the severity [see Dosage and Administration (2.3)].

5.3 Hepatotoxicity
Serious hepatic adverse reactions occurred in 2.1% of patients treated for GAVRETO. Increased AST occurred in 69% of patients, including Grade 3 or 4 in 5% and increased ALT occurred in 46% of patients, including Grade 3 or 4 in 6% [see Adverse Reactions (6.1)]. The median time to first detection of clinical benefit was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years). Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity [see Dosage and Administration (2.3)].

5.4 Hemorrhagic Events
Serious, including fatal, hemorrhagic events can occur with GAVRETO. Grade ≥ 3 hemorrhagic events occurred in 2.5% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event. Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage [see Dosage and Administration (2.3)].

5.5 Tumor Lysis Syndrome
Cases of tumor lysis syndrome (TLS) have been reported in patients with medullary thyroid carcinoma receiving GAVRETO [see Adverse Reactions (6.1)]. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

5.6 Risk of Impaired Wound Healing
Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing. Withhold GAVRETO for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of GAVRETO after resolution of wound healing complications has not been established.

5.7 Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. Oral administration of GAVRETO to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in labeling:
• Intestinal Lung Disease/Pneumonitis [see Warnings and Precautions (5.1)]
• Hypertension [see Warnings and Precautions (5.2)]
• Hepatotoxicity [see Warnings and Precautions (5.3)]
• Hemorrhagic Events [see Warnings and Precautions (5.4)]
• Tumor Lysis Syndrome [see Warnings and Precautions (5.5)]
• Risk of Impaired Wound Healing [see Warnings and Precautions (5.6)]

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

The pooled safety population in the WARNINGS AND PRECAUTIONS reflect exposure to GAVRETO as a single agent at 400 mg orally once daily in 438 patients with RET-altered solid tumors, including with RET fusion-positive NSCLC (n = 220), and RET-altered thyroid cancer (n = 138), in ARROW [see Clinical Studies (14)]. Among 438 patients who received GAVRETO, 47% were exposed for 6 months or longer and 23% were exposed for greater than one year. The most common adverse reactions (≥ 25%) were constipation, hypertension, fatigue, musculoskeletal pain and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased calcium (corrected), decreased sodium, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased platelets, and increased alkaline phosphatase.

RET Fusion-Positive Non-Small Cell Lung Cancer
The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 220 patients with metastatic rearranged during translocation (RET fusion-positive) non-small cell lung cancer (NSCLC) in ARROW [see Clinical Studies (14)]. Among the 220 patients who received GAVRETO, 42% were exposed for 6 months or longer and 19% were exposed for greater than one year.

The median age was 60 years (range: 26 to 87 years); 36% were female, 6% were ≥ 70 years, and 42% were enrolled at an Asian institution. Serious adverse reactions occurred in 45% of patients who received GAVRETO. The most frequent serious adverse reaction (in ≥ 2% of patients) was pneumonia, pneumonitis, sepsis, urinary tract infection, and pyrexia. Fatal adverse reactions occurred in 5% of patients; fatal adverse reactions which occurred in ≥ 1 patient included pneumonia (n = 3) and sepsis (n = 2).
Permanent discontinuation due to an adverse reaction occurred in 15% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation which occurred in > 1 patient included pneumonitis (1.8%), pneumonia (1.8%), and sepsis (1%).

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

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

Table 4 summarizes the adverse reactions in RET Fusion-Positive NSCLC Patients in ARROW.

### Table 4: Adverse Reactions (≥ 15%) in RET Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>GAVRETO N=220</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20</td>
</tr>
<tr>
<td>Edema</td>
<td>20</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>16</td>
</tr>
<tr>
<td>Musculoskeletal Disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>32</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>28</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>23</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>17</td>
</tr>
</tbody>
</table>

1 Fatigue includes fatigue, asthenia
2 Edema includes edema peripheral, face edema, periorbital edema, eyelid edema, edema generalized, swelling
3 Diarrhea includes diarrhea, colitis, enteritis
4 Musculoskeletal pain includes back pain, myalgia, arthralgia, pain in extremity, musculoskeletal pain, neck pain, musculoskeletal chest pain, bone pain, musculoskeletal stiffness, arthritis, spinal pain
5 Hypertension includes hypertension, blood pressure increased
6 Cough includes cough, productive cough, upper-airway cough syndrome
7 Pneumonia includes pneumonia, atypical pneumonia, lung infection, pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia influenza, pneumonia streptococcal
8 Only includes a Grade 3 adverse reaction

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

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

### RET-altered Thyroid Cancer

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 138 patients with RET-altered Thyroid Cancer in ARROW (see Clinical Studies [14.2, 14.3]). Among the 138 patients who received GAVRETO, 68% were exposed for 6 months or longer, and 40% were exposed for greater than one year.

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

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

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

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

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

Table 5 summarizes the laboratory abnormalities in ARROW.

### Table 5: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in RET Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>GAVRETO N=220</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>74</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>49</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>42</td>
</tr>
<tr>
<td>Decreased calcium (corrected)</td>
<td>39</td>
</tr>
</tbody>
</table>

Table 6: Adverse Reactions (≥ 15%) in RET-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>GAVRETO N=138</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>42</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>41</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
</tr>
</tbody>
</table>

Table 5: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in RET Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW (cont’d)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>GAVRETO N=220</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>36</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>35</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>33</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>29</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>26</td>
</tr>
</tbody>
</table>

Hematology

- Decreased neutrophils: 61%
- Decreased hemoglobin: 58%
- Decreased lymphocytes: 56%
- Decreased platelets: 27%
Table 6: Adverse Reactions (≥ 15%) in RET-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW (cont’d)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>GAVRETO N=138</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain†</td>
<td>17</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>17</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>17</td>
</tr>
<tr>
<td>Nausea</td>
<td>17</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>40</td>
</tr>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td>Fatigue†</td>
<td>38</td>
</tr>
<tr>
<td>Edema†</td>
<td>29</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>24</td>
</tr>
<tr>
<td>Peripheral Neuropathy†</td>
<td>20</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>17</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Cough†</td>
<td>27</td>
</tr>
<tr>
<td>Dyspnea†</td>
<td>22</td>
</tr>
<tr>
<td>Skin and Subcutaneous</td>
<td></td>
</tr>
<tr>
<td>Rash†</td>
<td>24</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>15</td>
</tr>
</tbody>
</table>

† Musculoskeletal Pain includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
‡ Diarrhea includes colitis, diarrhea
§ Abdominal Pain includes abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness, epigastric discomfort
¶ Stomatitis includes mucosal inflammation, stomatitis, tongue ulceration
† Fatigue includes asthenia, fatigue
# Edema includes eyelid edema, face edema, edema, edema peripheral, periorbital edema
€ Headache includes headache, migraine
§ Peripheral neuropathy includes dysesthesia, hypeaesthesia, hypoaesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy
¾ Dizziness includes dizziness, dizziness postural, vertigo
oresthesia includes asepsia, dysesthesia
†† Cough includes cough, productive cough, upper-airway cough syndrome
‡‡ Dyspnea includes dyspnea, dyspnea exertional
§§ Rash includes dermatitis, dermatitis acniform, eczema, palm-palmar, erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular
* Only includes a Grade 3 adverse reaction
Clinical relevant adverse reactions in < 15% of patients who received GAVRETO included tumor lysis syndrome and increased creatine phosphokinase.

Table 7: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in RET-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>GAVRETO N=138</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>70</td>
</tr>
<tr>
<td>Increased AST</td>
<td>69</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>43</td>
</tr>
</tbody>
</table>

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

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

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on GAVRETO

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

Avoid coadministration of GAVRETO with combined P-gp and strong CYP3A inhibitors. If coadministration with a combined P-gp and strong CYP3A inhibitor cannot be avoided, reduce the GAVRETO dose [see Dosage and Administration (2.4), Clinical Pharmacology (12.3)].

Strong CYP3A Inducers
Coadministration of GAVRETO with a strong CYP3A inducer decreases pralsetinib exposure, which may decrease efficacy of GAVRETO. Avoid coadministration of GAVRETO with strong CYP3A inducers. If coadministration of GAVRETO with strong CYP3A inducers cannot be avoided, increase the GAVRETO dose [see Dosage and Administration (2.5), Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

Data
Animal Data
In an embryo-fetal development study, once daily oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in 100% post-implantation loss at dose levels ≥20 mg/kg (approximately 1.8 times the human exposure based on area under the curve [AUC] at the clinical dose of 400 mg). Post-implantation loss also occurred at the 10 mg/kg dose level (approximately 0.8 times the human exposure based
on AUC at the clinical dose of 400 mg). Once daily oral administration of pralsetinib at doses ≤ 5 mg/kg (approximately 0.2 times the human AUC at the clinical dose of 400 mg) resulted in an increase in visceral malformations and variations (absent or small kidney and ureter, absent uterine horn, malpositioned kidney or testis, retroesophageal aortic arch) and skeletal malformations and variations (vertebral and rib anomalies and reduced ossification).

### 8.2 Lactation

#### Risk Summary

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

### 8.3 Females and Males of Reproductive Potential

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

#### Pregnancy

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

#### Contraception

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

#### Females

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

#### Males

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

#### Infertility

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

### 8.4 Pediatric Use

The safety and effectiveness of GAVRETO have been established in pediatric patients aged 12 years and older for RET-mutant MTC and RET-fusion thyroid cancer. Use of GAVRETO in this age group is supported by evidence from an adequate and well-controlled study of GAVRETO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of pralsetinib (see data), that the exposure of pralsetinib is expected to be similar between adults and pediatric patients aged 12 years and older, and that the course of RET-mutant MTC and RET-fusion thyroid cancer is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)].

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

#### Animal Toxicity Data

In a 4-week repeat-dose toxicity study in non-human primates, pharyngeal dysplasia in the femur occurred at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. In rats there were findings of increased pharyngeal thickness in the femur and sternum as well as both (incisor) abnormalities (fractures, dentin matrix alteration, ameloblast/odontoblast degeneration, necrosis) in both 4- and 13-week studies at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. Recovery was not assessed in the 13-week toxicity study, but increased pharyngeal thickness in the femur and incisor degeneration did not show evidence of complete recovery in the 28-day rat study.

Monitor growth plates in adolescent patients with open growth plates. Consider interrupting or discontinuing therapy based on the severity of any growth plate abnormalities and based on an individual risk-benefit assessment.

### 8.5 Geriatric Use

Of the 438 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, 30% were 65 years or older. No overall differences in pharmacokinetics (PK), safety or efficacy were observed in comparison with younger patients.

### 8.6 Hepatic Impairment

GAVRETO has not been studied in patients with moderate hepatic impairment (total bilirubin > 1.5 to 3.0 × upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe hepatic impairment (total bilirubin > 3.0 × ULN and any AST). No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST) [see Clinical Pharmacology (12.3)].

### 17 PATIENT COUNSELING INFORMATION

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

**ILD/Pneumonitis**

Advise patients to contact their healthcare provider if they experience new or worsening respiratory symptoms [see Warnings and Precautions (5.1)].

**Hypertension**

Advise patients that they will require regular blood pressure monitoring and to contact their healthcare provider if they experience symptoms of increased blood pressure or elevated readings [see Warnings and Precautions (5.2)].

**Hepatotoxicity**

Advise patients that hepatotoxicity can occur and to immediately contact their healthcare provider for signs or symptoms of hepatotoxicity [see Warnings and Precautions (5.3)].

**Hemorrhagic Events**

Advise patients that GAVRETO may increase the risk for bleeding and to contact their healthcare provider if they experience any signs or symptoms of bleeding [see Warnings and Precautions (5.4)].

**Tumor Lysis Syndrome**

Advise patients to contact their healthcare provider promptly to report any signs and symptoms of TLS [see Warnings and Precautions (5.5)].

### Risk of Impaired Wound Healing

Advise patients that GAVRETO may impair wound healing. Advise patients that temporary interruption of GAVRETO is recommended prior to any elective surgery [see Warnings and Precautions (5.6)].

**Embryo–Fetal Toxicity**

Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.7)]. Use in Specific Populations (8.1).

Advise females of reproductive potential to use effective non-hormonal contraception during the treatment with GAVRETO and for 2 weeks after the final dose [see Use in Specific Populations (8.3)].

Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose [see Use in Specific Populations (8.3)].

**Lactation**

Advise women not to breastfeed during treatment with GAVRETO and for 1 week after the final dose [see Use in Specific Populations (8.2)].

**Infertility**

Advise males and females of reproductive potential that GAVRETO may impair fertility [see Use in Specific Populations (8.3)].

**Drug Interactions**

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions (7.1)].

**Administration**

Advise patients to take GAVRETO on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after taking GAVRETO) [see Dosage and Administration (2.2)].

Manufactured for:
Genentech, Inc.

A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

Jointly marketed by: Genentech USA, Inc. and Blueprint Medicines Corporation

© 2022 Blueprint Medicines Corporation and Genentech, Inc. All rights reserved. M-US-00012419/v2.0

GAVRETO, Blueprint Medicines, and associated logos are trademarks of Blueprint Medicines Corporation.
Challenges for Patients With Cancer and Serious Mental Illness

Advances in cancer care have resulted in improved cancer survival in the general population, but decades of evidence reveal that individuals with serious mental illness (SMI) experience poorer quality of cancer care and disproportionate cancer mortality. SMI, encompassing mental disorders such as schizophrenia, bipolar disorder, or major depressive disorder that significantly impede functioning, affects more than 13 million adults in the United States. Barriers to care for patients with SMI include late-stage cancer diagnoses at initial contact due to lower rates of cancer screening; fragmented or inadequate psychosocial care, which may result in uncontrolled psychiatric symptoms; and increased risk of medication interactions with cancer therapies. This population has higher incidence of comorbidities, smoking, obesity, and substance abuse; fewer support systems for navigating cancer care; and higher incidence of cognitive deficits that interfere with illness understanding and decision-making. Patients’ reluctance to share mental health history, deriving from traumatic experiences with discrimination, is also a common barrier and can lead to delays in psychiatric referral.

Historically, people with SMI have experienced mental health discrimination. Common misperceptions include that they are dangerous, unpredictable, uncooperative, incapable of working, and/or unable to participate in research studies. Self-stigma, the process of internalizing negative stereotypes and applying them to oneself, can also contribute to lower rates of disclosing psychiatric history and may deter help-seeking completely. In a meta-analysis, a majority of nonpsychiatric medical physicians believed that people with SMI were more dangerous than cohorts with less serious psychiatric diagnoses. Although these physicians were amenable to seeing patients with SMI, they worried about the amount of time required as well as potential nonadherence to treatment. Clinician inexperience can also contribute to delays and misdiagnoses. For example, implicit bias may occur if the clinician ascribes a patient’s physical symptoms to mental illness, which can lead to delays in specialty referrals and initiation of treatment. Structural discrimination, referring to discriminatory institutional policies or laws that inhibit opportunities for marginalized populations, can also curb oncology specialists’ investment in mental health training or accessing mental health services for their patients. Moreover, since patients with SMI have higher incidence of substance use or abuse, oncology clinicians may miss opportunities to improve cancer treatment outcomes and survivorship if they do not assess for this and refer patients to addiction experts.

Overcoming Barriers With Patients With SMI

Collaborative care approaches that integrate psychological and physical care have demonstrated clinical effectiveness and cost-effective access to care for a variety of health conditions among different populations and across practice settings. Why, then, haven’t these approaches been more widely adopted in oncology settings? The integration process may be perceived as too complex, requiring more time than oncology clinicians can devote to it without sacrificing care quality. Practical
strategies exist, however, for overcoming some of the barriers with patients with SMI, beginning with patient-provider communication.28

Establishing Rapport for Effective Communication

Patients and clinicians have recommended establishing fast rapport by using person-first language, a type of linguistic approach that focuses on the person as a unique individual and not on the person’s condition or diagnosis.29 In this approach, an individual’s medical diagnosis follows them as a human being, not the other way around: a patient with cancer rather than a cancer patient. Person-first language has been taught in most health professions programs for decades and is mandated by most scholarly journals as an important aspect of cultural competence in health care. It demonstrates the power of language to raise consciousness about and respect for all patients, and it affirms patients’ autonomy and the right to identify themselves however they choose. Despite its obvious significance, it is nonetheless infrequently used in clinical practice.30

To initiate person-first language with patients with SMI, clinicians and their staffs can show sensitivity and respect by first asking how they would like to be addressed (eg, Ms Smith, Pamela, Pam, Ms Pam). This can be followed with open-ended questions to find out about their current circumstances, hopes, fears, and possible adherence barriers, and how they feel the oncology team can be helpful. Clinicians can tailor their language, slowing their speech and using concrete terms and visual aids to explain procedures. As staff members become aware of how their perceptions of patients may impact their language and professionalism, practicing person-first thinking and language may boost their confidence in knowing how to communicate with all patients and each other as well.31 Table 1 contrasts examples of blaming and stigma-perpetuating language with corrections in person-first language.

<table>
<thead>
<tr>
<th>Table 1. Reframing Communication for Patients With Cancer and Mental Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language that comes across as blaming</td>
</tr>
<tr>
<td>Biggest complaint</td>
</tr>
<tr>
<td>Frequent fliers</td>
</tr>
<tr>
<td>Patient failed cancer treatment</td>
</tr>
<tr>
<td>Patient is difficult</td>
</tr>
<tr>
<td>No-show</td>
</tr>
<tr>
<td>What is his/her problem?</td>
</tr>
</tbody>
</table>

Language that inadvertently perpetuates stigma

| Drug addict | Person with substance use disorder |
| In drug rehab | In recovery |
| So OCD | Extremely neat and well organized |

Moody or touchy

| Off the deep end | Experiencing difficulty |
| Street person/vagrant/hobo | Without shelter/housing |

OCD, obsessive-compulsive disorder.

Trauma-Informed Care

It is important for staff to realize that many patients with SMI have had a lifetime of exposure to trauma. These experiences have left them deeply distressed or disturbed, beginning with abuse and/or neglect in their early years and continuing into adulthood.12,32,33 In a study of individuals with SMI spanning 30 years, participants reported a mean lifetime prevalence rate of 47% for physical abuse, 37% for sexual abuse, and 30% for posttraumatic stress disorder, compared with prevalence rates in the general population of 21%, 23%, and 7%, respectively.14 According to the US Substance Abuse and Mental Health Services Administration, traumatic experiences often adversely impact people in every functional sphere: physically, mentally, emotionally, socially, and spiritually.31 Common forms of trauma include familial physical and sexual violence; childhood abuse and/or neglect; neighborhood/community violence, including bullying, gang wars/shootings, robberies, and rape; and natural disasters. Types of trauma that are less understood include racism as well as other stigma-related or prejudice-related incidences; these include being ridiculed or treated differently because of one’s mental illness or disability, historical trauma (eg, genocide), and other types of long-term hardship, such as extreme poverty.36

Trauma-informed care is an approach that emphasizes sensitivity to the impact of trauma in patients’ lives. Health care professionals’ heightened sensitivity is essential for helping patients feel safe and for not inadvertently triggering
patients’ previous trauma responses while they cope with all the challenges of a cancer diagnosis and treatment. To help patients feel safe and more in control, 2 of the aims of trauma-informed care, clinicians can check for illness understanding, offer options, and empower patients as ultimate authorities who will decide what happens to their own bodies regarding treatment preferences and goals. Patients with SMI, however, may require more explanation about their cancer and treatment options, including such explanations in visual formats, as well as more time to process what has been presented to them. It may be helpful to ask patients their preferences about staff member gender and to promote continuity of care when possible. In this regard, for example, a staff member whom patients have

**Bridging the Gaps: Taking Care of the Whole Person**

Sheila Lahijani, MD, FACLP

Over the last 15 years, data have continued to emerge that highlight the large disparities in both the screening and treatment of cancer in individuals with (vs without) serious mental illness. The authors of this review effectively present practical guidance for oncology clinicians to enhance the person-centered approach to treating patients with the “double stigma,” cancer and serious mental illness. Specifically, the authors focus on the importance of a communication style that is engaging and intended to be respectful and curious. They also acknowledge the effects on clinicians of individual and systemic factors, such as cognitive biases, suboptimal distress screening and management, provider burnout, and limited access to clinical trials.

The multidisciplinary field of psycho-oncology is uniquely positioned to address and manage the challenges associated with caring for this vulnerable patient population. As psycho-oncologists, we tailor our approaches to the patient interview and exam with our knowledge of the impacts of cancer and its treatments on mental health. We can apply our armamentarium of psychotherapeutic modalities as well as our expertise in psychopharmacology to cancer care. Educational efforts and training led by us across a cancer setting can empower nonpsychiatric providers and trainees in medicine to care for patients with psychiatric symptoms and disorders, and support them as they do so.

While psycho-oncologists are not accessible in every cancer care setting, this review emphasizes that improving access to psychiatric services through other approaches, such as collaborative care and community outreach, can also improve cancer outcomes. Yet while many organizations and agencies have mandated distress screening in the cancer setting, patients with psychiatric symptoms, and specifically those with serious mental illness, may not be identified through these traditional methods. These individuals may also not disclose their psychiatric history to their oncology providers. The effects of self-stigma, as stated in this review article, can be profound, influencing health behaviors and how and when patients access medical care. Patients with cancer and serious mental illness consequently can have poorer prognoses and shorter survival times.

It is imperative to bridge these gaps in cancer care. Earlier diagnosis and treatment of cancer in patients with serious mental illness is needed. We can develop more population-based methods to assure that these patients are being identified and offered medical care in a timely and effective matter. We must thereby confront the biases in medicine about patients who suffer from psychiatric disease. While there may be higher comorbidity indices, more potential for significant drug-drug interactions, changes in decision-making capacity, and/or difficulties with adherence and coping, generalizing these associations to an individual patient can be a deterrent to providing comprehensive cancer care. We need to leverage the involvement of psycho-oncology clinicians, social workers, patient navigators, caregivers, primary care providers, chaplains, and others who can collaboratively participate in a patient’s cancer care and advocate for the
already met, trained in person-first language and trauma-informed care, can accompany them to consults for additional support, to answer questions or concerns afterward, and to provide materials to study at home when they are not under pressure. This type of additional support may be particularly helpful when cancer care requires invasive procedures, such as colonoscopies; imaging and procedures related to gastrointestinal, genitourinary, gynecologic, and breast cancers; and mask fitting prior to radiation. Oncology clinicians can invest in person-first and trauma-informed literature and workshops for themselves and staff (much of it free) that will help overcome patients’ previous experiences with discrimination and improve communication. Tailored approaches can be discussed with staff members.

patient with mental illness; that strategy can help harvest good clinical outcomes along the care continuum.

Psycho-oncologists can and do treat patients’ psychiatric distress and illness. We can and do diagnose and treat cognitive problems, such as delirium. We can and do promote health behaviors, such as intentional physical activity and sleep management. However, this can all be done more expansively and sustainably with the right prioritization of institutional efforts and allocation of funding. We need to address the insurance barriers, delays in scheduling, limited availability of mental health specialists, and provider burnout, which are but a few of the remarkably widespread problems in our medical system. Inherently, formal and informal caregivers can also suffer distress due to demands of multiple roles and unmet psychosocial needs, all of which have been amplified during the COVID-19 pandemic.

Access to mental health services in general is a pervasive problem. When an individual with serious mental illness is diagnosed with cancer, processes must be in place that facilitate the medical and psychiatric care of that individual—specifically, so that treatment is not withheld or minimally offered and that potential medical and psychiatric emergencies are not overlooked. This would not only help individual patients, but it would improve population health and the distribution of clinical services and efforts. It would also enhance our understanding of the interplay between oncologic and psychiatric disease. By having these processes in place, we can develop more effective treatments, decrease health care costs, and customize our models of care to the needs of patients who suffer from the “double stigma.” If we, as a nation, are truly aiming to provide comprehensive cancer care, we must collectively improve the care of our most vulnerable and marginalized patients.

We can lead and implement more of these endeavors and practices while we also take care of the health care providers and caregivers. In these unprecedented times, greater attention is rightfully being given to the health disparities in our medical system. In parallel, there is more recognition that health care providers and caregivers are suffering from burnout, increased workload, and fatigue. Furthermore, among the general population, physicians and nurses populate the groups at highest risk of suicide. Research has shown that long-lasting changes in health care provider wellness take place by intervening at the organizational level, which requires support from leadership.

To serve more of our most vulnerable patient populations, we must also consider the health of those who are treating them and doing the caregiving. Interventions must take place to assure that we are creating environments that are psychologically safe and that foster more self-care. By prioritizing clinician well-being, we can work toward lessening the stigma associated with seeking mental health care. We can demonstrate the importance of preventive care. We can increase the opportunity for good health behaviors, such as exercise, mindfulness, and sleep routines. By doing so, we can henceforth provide better and safer patient care.

When it comes to caring for our patients with cancer and serious mental illness, we can all work together to advocate for earlier and more effective screening, diagnosis, and treatment. We can advocate for safe practices while also encouraging the enrollment of these patients in clinical trials. We can work together to promote and enforce organizational changes to support clinicians and caregivers who are at the helm of caring for these individuals with medical and psychiatric illness. We can do better for them and for ourselves.

AUTHOR BIO
Dr. Lahijani is an associate clinical professor in the Division of Medical Psychiatry at Stanford University School of Medicine and the medical director of the Stanford Cancer Center Psychosocial Oncology Program, Palo Alto, CA.
Screening and Identification of Mental Illness

The American Society of Clinical Oncology and the Commission on Cancer mandated psychosocial distress screening as a quality care standard in 2015, but only 50% to 65% of patients with cancer are currently screened for distress. Reasons given for the slow implementation rate are lack of staff training and fragmentation between mental health and oncology care. Mental health clinics are often geographically isolated from main health care structures, with separate electronic health records (EHRs). If communication between oncology and mental health care teams exists at all, it is likely infrequent. Moreover, even if measures are used to assess patients’ distress in oncology clinics, they are not typically meant to assess SMI, so serious psychiatric disorders may be missed.

The most practical method for identifying SMI may be assessment of patients’ medications. A staff member can compile a list of commonly prescribed psychotropic medications for SMI that can be checked against patients’ reported medications or EHR medication history. In a recent international study of 13,200 primary care clinicians, only 40% in the United States reported frequently coordinating with social services, but disruptions in patients’ psychiatric care and/or failure to manage symptoms result in decreased adherence to cancer treatment and decreased quality of life and survivorship, accenting inequities in care.

If patients are taking a medication commonly prescribed to treat mental illness, clinicians can ask about patients’ prescribers, so they can be contacted right away. If patients do not list any psychotropic medications in the medical record, clinicians need to remember they may be reluctant to share their mental health history because of stigma-related experiences. Gentle questioning to find out the cause of reticence can open the door to building trust. Psychological safety enables effective communication, and person-first and trauma-informed communication strategies have been demonstrated as facilitators of psychological safety with patients, caregivers, and staffs. Additionally, not all patients have a formal diagnosis of mental illness or insight into that diagnosis. It is helpful to ask patients if they have a history of seeing a social worker or psychiatrist or if they have ever received a mental health diagnosis. If they are accompanied by a caregiver, it is also important to partner with them to obtain additional history.

Referring Patients With SMI to Clinical Trials

Historically, inequities in care for patients with SMI who have cancer have been exacerbated by lack of research. Almost 25 years ago, a National Cancer Institute Clinical Trials Program Review Group asserted there were “too many exclusion criteria in the current clinical trials system” and “entry criteria for all studies need to be simplified and broadened.” Currently, however, half of the most circulated and cited US clinical trials, including oncology trials, exclude patients with psychiatric conditions. Oncology clinicians reported that their main reasons for nonreferral of patients with SMI to trials were the patients’ possible lack of motivation to participate, inability to provide informed consent, inability to complete protocols and return for follow-up appointments; the potential for increased patient burden and compromised safety; and perceived risk and additional burden for investigators. However, when patients with SMI, including schizophrenia, are provided with more details about the study and given more time to process this information, their motivation and capacity to consent is improved. In a trial bridging cancer care and psychiatric care, patients had high rates of consent, symptoms remained stable or improved during the trial, and they were able to complete the trial.

People with SMI have also demonstrated the ability to successfully participate in remote interventions. Recently, 315 people with confirmed diagnoses of bipolar disorder, major depressive disorder, and/or schizophrenia or schizoaffective disorder were recruited from advertisements placed in large search engines, and they participated in a fully remote smartphone intervention for reducing severity of psychiatric symptoms and increasing self-esteem. Although retention was a challenge, some of the main reasons oncologists gave for not referring (eg, lack of motivation, inability to provide consent, and burden for investigators) were not encountered, and results indicated that people with SMI can be successfully recruited and treated remotely for reduced symptom severity.

Oncology clinicians may believe that they are protecting their patients by not referring them for trials. Ironically, lack of research drives misperceptions about the ability of people with SMI to participate in research, and participation in trials may be needed to dispel these limiting misperceptions that lead to care inequities.

Table 2 describes types and examples of barriers that might occur with patients with SMI and practical recommendations for overcoming them.

Pulling the Team Together to Enhance Care for Patients With Mental Illness

As patients with SMI begin the challenging process of managing the demands of cancer treatment, ongoing mental health care is needed to address their complex psychological needs and help them be successful. The clinical team can brainstorm the most efficient way to tailor the existing practice for an integrated approach to increase access to the psychiatric care
### TABLE 2. Strategies to Improve Cancer Care for Patients With Serious Mental Illness

<table>
<thead>
<tr>
<th>Barriers</th>
<th>Examples</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| Patient-clinician communication is impacted by patient's history of discrimination and other kinds of trauma/abuse | Patient appears reluctant to answer questions or share information about mental health status. Patient is hesitant to engage in discussion about plan for cancer treatment. | • Develop proficiency in person-first language and trauma-informed care: warm greeting, ask patients how they want to be addressed, sit with/have no desk between clinician and patients, slow pace of speech, short sentences, concrete language, eye contact with both patients and caregivers, allow extra time for patients to consider options, ask open-ended questions about patient's strengths, hopes, fears, and how team can be helpful.  
• Ask patients who trusted allies are. Who helps with medications, transportation, insurance, activities of daily living, or other needs? Engage trusted allies to facilitate communication and make recommendations for care.  
• Have designated staff member trained in trauma-informed care available. Creating a “safe” space may be necessary for effective communication to occur. |
| Untreated psychiatric symptoms                                           | Patient presents with atypical affect and/or behavior such as unhygienic appearance, smiling inappropriately, or lack of eye contact.  
Clinician does not ask patient about medical history.  
Patient omits history of mental illness and distress assessment scores are in normal range, but patient presents with atypical affect.  
Patient has started cancer treatment but has missed multiple appointments with psychiatric provider, and psychiatric medications have not been reviewed. Patient is having uncontrolled psychiatric symptoms (eg, paranoia, major depression) or is experiencing drug interactions between psychiatric and cancer treatments. | • Increase mental health expertise:  
1. Support mental health training and cross-training in mental health and oncology for oncologists, fellows, and nurses.  
2. Increase mental health literacy, including common symptoms and facial affect or behaviors commonly associated with certain SMI, and awareness of own stigma-related perceptions regarding SMI.  
• Develop tools to aid in early recognition of SMI:  
1. MA or oncology nurse can compile list of psychotropic medications commonly used to treat SMI; consequently, check patients’ reported medications against list, and alert oncology clinician about possible SMI.  
2. If no medication for SMI is reported but patient exhibits symptoms of SMI, clinician can ask if patient has ever seen a psychiatrist or therapist, and if so, for what.  
• Contact patient’s psychotropic medication prescriber and other mental health care providers in patient’s life (eg, psychiatric nurse/social worker, counselor, therapist, patient advocate in group home) to build team to support patient and improve communication of health information.  
• Oncology nurses can help patients with tobacco cessation prior to surgery, monitor for adverse effects of chemotherapy, tailor treatment regimens to address associated nausea or anxiety (eg, olanzapine), and monitor for other symptoms.  
• Partner with pharmacist to assess medication interactions.  
• Patients with stable SMI can tolerate varenicline and are 5 times more likely to quit with vs without tobacco cessation medications.  
• Fund portion of psychiatrist’s or psychiatric NP’s time. |
| Patient does not demonstrate illness understanding or seems to lack capacity to make informed decisions | Patient declines treatment recommendations without reasonable explanation or accepts all recommendations without asking about risks and benefits. | • MA, oncology nurse, or navigator helps patients navigate the initial cancer diagnosis and may accompany them to consults to provide additional explanation/clarification afterward.  
• Slow down speech, use short sentences and concrete language, and check for understanding. Employ teach-back method to aid patient/caregiver in comprehending the illness itself and treatment options/plans.  
• If appropriate, engage caregiver/trusted ally to help explain the cancer and proposed treatment.  
• Use videos and take-home materials with video links, pictures of procedures, diagrams, and definitions of terminology. It may help the patient to review the information at home when less pressured or when additional support is present.  
• Encourage patients and caregiver to write down 3 questions before oncology visits.  
• When necessary, refer patient for formal capacity assessment to facilitate decisions about cancer treatment; capacity assessments are focused on a specific issue and can change over time. |

CWH, community health worker; ED, emergency department; MA, medical assistant; NP, nurse practitioner; OSW, oncology social worker; PCP, primary care physician; SMI, serious mental illness; TB, tumor board.
TABLE 2 CONTINUED. Strategies to Improve Cancer Care for Patients With Serious Mental Illness

<table>
<thead>
<tr>
<th>Barriers</th>
<th>Examples</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communication deficits among patient's health care teams in different systems</td>
<td>Patient's history of mental illness, including associated hospitalizations/ED visits and medication information, is not available to oncology team.</td>
<td>• Have navigator or other designated staff member function as liaison/coordinator to contact patient's psychotropic medication provider to facilitate exchange of health information, arrange a meeting, and be the patient's champion/caregiver in building a care team. This duty would typically fall to a navigator or OSW, but an oncology nurse or CWH could also manage it. If your oncology clinic does not have access to an OSW or navigator, consider training a staff member to perform duties of a health navigator (Figure 1). • Have patient sign release of health information as standard part of first visit.</td>
</tr>
<tr>
<td>Communication deficits in tumor board</td>
<td>Patient's psychosocial history, current circumstances/barriers to treatment, and preferences are omitted or minimally considered at TB. Oncology recommendations may not account for patient's values, goals, or ability to adhere to treatment.</td>
<td>• Invite patient's mental health provider, PCP, and other mental health team members (eg, provider from group home) to attend tumor board to provide current, accurate, multidimensional view of patient's treatment preferences/goals, facilitators (eg, has reliable caregiver, quit smoking), and barriers to cancer care (eg, lack of illness understanding, history of nonadherence to psychotropic medications). Alternately, have oncology team member contact mental health team member prior to TB for guidance.</td>
</tr>
<tr>
<td>Potential for diagnostic overshadowing</td>
<td>Patient has multiple comorbid medical conditions. Clinician mistakenly assumes one cluster of symptoms is related to SMI and not to another medical comorbid condition.</td>
<td>• Recognize that diagnostic overshadowing is a quality and safety issue for patients with mental illness.61 • Gain expertise in distinguishing symptoms from mental illness and cancer; maintain a broad differential diagnosis and rule out medical symptoms first. • Clinicians can ask themselves what tests they would suggest if patient did not have diagnosis of major depression, bipolar disorder, schizophrenia, etc. • Patients with SMI may have experienced previous care in which providers attributed their symptoms to mental illness rather than fully considering medical contributors.86 • Attend to nonverbal cues indicating pain or discomfort not typically associated with cancer.</td>
</tr>
<tr>
<td>Lack of research</td>
<td>Clinician may assume patients with SMI would not be able to consent to a clinical trial or that a trial would cause too much burden or stress; therefore, no referrals to clinical trials are made. Information about trials may be presented quickly and not allow time for patients and caregivers to fully consider risks and benefits.</td>
<td>• Clinicians can consider whether to refer patients with SMI to clinical trials by asking themselves this question: If I would consider referring another patient with the same type of cancer, stage, tumor type, and support structure to this clinical trial, why am I not referring this patient? • Once potential participation is broached with a patient, elicit feedback from family champion/caregiver and/or group home social worker/patient advocate/CWH, as they may play key role in patient's transportation and/or online access. Invite patients with SMI to partner with you in research, given the need for high-quality data to guide cancer treatment. • If the caregiver is amenable but the patient refuses right away, ask open-ended questions to discern reasons. Patients with SMI may need more explanation and additional time to consider, and may decide to participate if asked again (see “Referring patients with SMI to clinical trials” in main text).16,65 • Being mindful that many clinical trials exclude participation of patients with SMI, ask designated staff member to reach out to appropriate study contact regarding eligibility restrictions for patients with SMI; frequently, restrictions are poorly defined. If there are exclusionary criteria, ask to broaden eligibility criteria or clarify the rationale for the exclusion criteria.16</td>
</tr>
</tbody>
</table>

CWH, community health worker; ED, emergency department; MA, medical assistant; NP, nurse practitioner; OSW, oncology social worker; PCP, primary care physician; SMI, serious mental illness; TB, tumor board.

of care for patients with SMI60; thus, they may value rapid access to psychiatric expertise or to a consultant when needed. They may also bring their own multidisciplinary alliances to the table.61 With greater projected gaps in the psychiatric clinician workforce and greater demand for services,62 PCPs will likely play an even larger role for many patients during the survivorship period. Regardless of situation or prescribing practices, PCPs are allies who may have considerable influence with patients and caregivers, and they may offer excellent advice for building trust with and engaging patients in cancer care.

Oncology nurses and advanced practice clinicians fill key roles in a team prepared for all types of patients with comorbidities, taking the lead in identifying SMI and making referrals to psychiatric clinicians for care and assessment of patients’ decisional capacity. As experts in symptom management and tracking, oncology nurses are often the first to note changes in patients’ symptoms and/or treatment adherence barriers. They may help conduct chemotherapy teaching and tailor medication guidance for patients with SMI in collaboration with pharmacists, who should be able to help with assessment of medication interactions. Common challenges include tailoring antiemetics and decreasing the risk of mood instability when steroids are used. Nurses may also fulfill 2 important aspects of caring for patients that can build trust and adherence to cancer care: establishing tailored communication (eg, phone calls, texts) to remind patients/caregivers about appointments, and
supporting the emotional needs of caregivers, who typically keep patients on track.\textsuperscript{63,64} Caregivers routinely drive and accompany patients to appointments, and they typically pick up, administer, and monitor medications and schedules. Support is particularly important for caregivers of patients with schizophrenia or severe bipolar disorder, as these patients may have difficulty communicating about symptoms, organizing thoughts and scheduling, or lack insight regarding the urgency for treatment. When faced with the additional complexities of cancer care, caregivers are at particular risk for distress and burnout. They frequently feel helpless, inadequate, overwhelmed, and uncertain, especially when they cannot identify or access health care resources for help.\textsuperscript{65} Their emotional and physical health must thus be considered throughout the cancer care continuum.\textsuperscript{63,65} Oncology nurses and/or social workers may be able to help them cope with emotional stressors and exhaustion by offering educational resources and individual and/or family support groups. Of note, caregivers for patients with SMI are less likely to be spouses and include other family members and community mental health staff from group living environments.\textsuperscript{54}

Many cancer centers have oncology social workers (OSWs) and navigators. OSWs can also conduct psychosocial assessments to identify sources of distress, psychiatric comorbidity, and patients’ unique needs. They can make early referrals to psychiatric services and may serve as liaisons between the oncology team and mental health team to prevent disruptions in cancer care.\textsuperscript{13} As licensed professionals, they can, like oncology nurses, provide evidence-based treatments/brief therapies, follow-up, and education. Almost half (48.4\%) of caregivers, however, reported unmet service needs as their biggest stressor,\textsuperscript{66} and connecting them to support services is one of the expert skills of a navigator.

Navigators can build trust with patients and facilitate their day-to-day care, helping them deal with the complexities of the system by connecting them to services as they progress through the care continuum.\textsuperscript{67,68} Often, they serve as point persons for communication, so when patients have questions or concerns, they call the navigator. Lay navigators, who do not have formal health care training, can offer emotional support, help with coordination of appointments, and assist in addressing barriers related to social determinants of health, such as impaired health literacy or lack of transportation or childcare.\textsuperscript{69} Community health workers (CHWs) are nonclinical public health workers who possess deep knowledge of the community a patient is from. Like navigators, CHWs may serve as liaisons between patients and health care teams, providing outreach, education, and informal counseling, and they may accompany patients to oncology consults and other appointments.\textsuperscript{70}

**Tumor Boards**

Information about patients with SMI from all the people involved in their care presents a multidimensional view of these patients’ unique circumstances, barriers, facilitators, preferences, and goals, which are key considerations for developing workable treatment plans. Because tumor boards are composed largely of oncology specialists,\textsuperscript{71} it may happen that patients’ psychosocial histories, medical and psychiatric comorbidities, complex circumstances and barriers, and preferences/goals for treatment are minimally considered or omitted entirely.\textsuperscript{71} These gaps in knowledge can limit consideration of barriers to cancer care, contribute to delays in care, and in some cases, prevent patients with SMI from receiving the care they need.\textsuperscript{72} If community mental health clinicians and PCPs are invited to and attend tumor boards when their patients are being discussed, their input may help to inform proactive plans for both cancer and mental health treatment and address care barriers.

Collaborative care models use a team-based approach to integrate mental health services in primary or specialty care to increase access to integrated mental health services for patients with cancer.\textsuperscript{73,74} We recognize that, given limited time and resources, it will not be feasible for all oncology practices to implement all aspects of a collaborative care model. Therefore, we aimed to provide pragmatic recommendations that can be adapted to different practice settings, regardless of size or affiliation with larger health care systems. The **Figure** illustrates the steps an independent oncology practice can take to connect with and integrate a patient’s mental health team as part of routine cancer care. Next, we present recent developments in collaborative care approaches for patients with SMI.

**Recent Developments**

**Adapting the Collaborative Care Model for SMI and Cancer**

To date, few teams that care for people with serious medical illnesses, like cancer, are staffed with cross-trained experts in mental health care.\textsuperscript{75} The collaborative care model is a promising approach that increases access to mental health expertise and has been found to improve patients’ psychiatric symptoms in more than 70 randomized trials.\textsuperscript{54,58,76-78} However, patients with SMI and cancer have traditionally been excluded from collaborative care trials. In 2019, Irwin and colleagues piloted a person-centered collaborative care model for patients with SMI.\textsuperscript{14,79} Key components of the intervention, called Bridge, included (1) early screening, identification, and tracking of patients with SMI, (2) person-centered, team-based care, including psychiatry and social work, and (3) collaboration between the mental health intervention team and oncology to guide treatment recommendations and integrate input.
Cancer care has the potential to be a healing opportunity for patients who have been marginalized in many areas of their lives. One of the core elements of person-centered collaborative care is the creation of patient-clinician partnerships. For example, oncology clinicians can support patients’ decision-making processes and empower them to decide what happens to their bodies regarding treatment preferences and goals. Person-first language and trauma-informed care can be used to initiate and safeguard the partnership to increase patient engagement in care, and there is evidence that engagement has the potential to improve both cancer and mental health outcomes.

More research is under way that explores how person-centered collaborative care can impact health outcomes, quality of life, and patient satisfaction.

CWH, community health worker; MA, medical assistant; OSW, oncology social worker; PCP, primary care physician; SMI, serious mental illness; TB, tumor board
Another opportunity to gather information about marginalized populations is through cultivation of a population-based registry, a tool that can capture important data (eg, cancer type, stage of diagnosis at consult, physical and psychiatric comorbidities, history of screenings) and facilitate both early identification and systematic tracking. Population-based management using data available in commercial EHRs can be done by any trained team member and can be an efficient strategy to fill information gaps about a specific population and identify unmet needs. This information may be aggregated with mandated efforts for distress screening to identify a population at high risk for gaps in cancer care delivery using International Classification of Diseases, Tenth Edition codes, problem lists, or commonly prescribed medications. Our research team, for example, developed a population-based registry for screening EHRs to identify patients with both SMI and a new cancer diagnosis; such a registry can facilitate referrals for consultation and clinical trials as well as prioritize patients experiencing challenges accessing cancer care.81

Adapting the Tumor Board Model for SMI and Cancer
Virtual multidisciplinary tumor boards or conferences are gaining ground as a strategy to increase access to multispecialty cancer care for patients in underserved settings. Virtual approaches enable providers located in distant settings to share information and may help ensure appropriate dispersal of resources and access to specialty expertise, as has been demonstrated during the COVID-19 pandemic.82 These models also hold promise for integrating mental health and cancer care and may be considered for building collaborations between comprehensive cancer centers and community-based settings that serve individuals with SMI. More research is needed, however, to confirm whether virtual multidisciplinary conferences have the capacity to increase access to quality cancer care for patients with SMI.

Conclusions
In this review, we focused on supporting oncologists in their efforts to address the complex needs of patients with serious mental illness. We provided practical recommendations for overcoming barriers to cancer care and provided a simple method for identifying the population at the time of cancer diagnosis. We offered evidence-based strategies for improved patient-physician communication and partnership, methods to build illness understanding, and strategies to prepare and support patients undergoing treatment procedures. We emphasized the importance of ongoing collaborations with patients’ psychiatric providers as part of routine care, and in this vein, the relevance of inviting patients’ mental health clinicians to tumor boards for their input. We also recommended referral of patients with SMI to clinical trials to dispel misperceptions about SMI and this population’s ability to participate, and to provide critical evidence to guide cancer care delivery with potential to mitigate disparities in cancer outcomes. Finally, we discussed innovative approaches to care delivery, including adaptation of the collaborative care model and the tumor board model, for increasing access to evidence-based mental health and cancer care for a marginalized population. ■

DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

CORRESPONDING AUTHOR: Veronica B. Decker, DNP, MBA, APRN, PMHCNS-BC
University of Central Florida
12201 Research Parkway
Orlando, FL 32826
Tel: 407-823-9025 | Fax: 407-823-5675 | veronica.decker@ucf.edu

AUTHORS AFFILIATIONS:
1 University of Central Florida, Orlando, FL
2 Massachusetts General Hospital, Boston, MA
3 Massachusetts General Hospital – Cancer Center, Boston, MA
4 Orlando VA Medical Center, Orlando, FL

KEY REFERENCES

For full references list, visit cancernetwork.com/Decker_7.22
Lasofoxifene Plus Abemaciclib Induces Response in Previously Treated ER+, HER2–, ESR1+ Metastatic Breast Cancer

Results of the phase 2 ELAINEII trial (NCT04432454) indicated acceptable tolerability and a favorable risk-benefit ratio with lasofoxifene in combination with abemaciclib (Verzenio) for pre- and postmenopausal women with previously treated locally advanced or metastatic estrogen receptor (ER)–positive, HER2-negative breast cancer and an acquired ESR1 mutation.

In a group of patients who had progressed on 1 or 2 prior lines of therapy, the objective response rate (ORR) was 50% (95% CI, 29.0%-71.0%) with a 24-week clinical benefit rate (CBR) of 69.0% (95% CI, 50.8%-82.7%). The censored median progression-free survival (PFS) was 55.7 weeks (95% CI, 32.0 to not evaluable), or about 13 months.

Among patients with measurable target lesions, 9 (50%) had partial responses (PRs). The median time to PR was 169 days, with a median response duration of 164 days. Of 4 patients who had previously progressed while receiving abemaciclib, 3 had significant clinical responses: PR in 1 and stable disease in 2. Two of 3 patients who received prior fulvestrant plus alpelisib (Piqray) had clinical benefit.

The open-label, single-arm multicenter study evaluated lasofoxifene plus abemaciclib in patients aged at least 18 years with ER-positive, HER2-negative metastatic breast cancer, and an acquired ESR1 mutation at 150 mg twice daily until disease progression, toxicity, withdrawal, or death. The primary end point was safety and tolerability; secondary outcome measures included PFS, CBR, and ORR.

→ For the full article, visit CancerNetwork.com/ASCO22_breast1

Trastuzumab Deruxtecan Doubles PFS in HER2-Low Metastatic Breast Cancer

Fam-trastuzumab deruxtecan-nxki (Enhertu) can be considered a new standard-of-care option for patients with HER2-low, hormone receptor–positive metastatic breast cancer, due to improved progression-free survival (PFS) outcomes reported from the phase 3 DESTINY-Breast04 study (NCT03734029).

In the indicated patient population, trastuzumab deruxtecan, an antibody-drug conjugate, elicited a median PFS of 10.1 months (95% CI, 9.5-11.5) compared with 5.4 months (95% CI, 4.4-7.1) with chemotherapy (HR, 0.51; 95% CI, 0.40-0.64; P <.0001). The median overall survival was 23.9 months (95% CI, 20.8-24.8) with trastuzumab deruxtecan compared with 17.5 months (95% CI, 15.2-22.4) for chemotherapy (HR, 0.64; 95% CI, 0.40-0.86; P = .003).

In the study, 557 patients were randomly assigned 2:1 to receive trastuzumab deruxtecan at 5.4 mg/kg every 3 weeks (n = 373) or physician’s choice of chemotherapy at locally approved dosing (n = 184). Chemotherapy consisted of capecitabine (Xeloda; 20.1%), eribulin (Halaven; 51.1%), gemcitabine (10.3%), paclitaxel (8.2%), or nab-paclitaxel (Abraxane; 10.3%). Low expression of HER2 was defined as an immunohistochemistry score of 1+ or 2+ with a negative...
fluorescence in situ hybridization test. Overall, 88.7% of patients were hormone receptor–positive and 11.3% were hormone receptor–negative.

Fewer grade 3 or greater adverse events were reported with trastuzumab deruxtecan compared with chemotherapy, in 52.6% and 67.4% of patients, respectively.

→ For the full article, visit CancerNetwork.com/ASCO22_breast2

Sacituzumab Govitecan Bests Chemotherapy in HR+/HER2– Metastatic Breast Cancer With ET Resistance

Data from the phase 3 TROPiCS-02 trial (NCT03901339) revealed that the single-agent antibody-drug conjugate (ADC) sacituzumab govitecan-hziy (Trodelvy) led to statistically significant and clinically meaningful treatment benefit vs chemotherapy for patients with hormone receptor–positive, HER2-negative breast cancer with endocrine therapy (ET) resistance.

At a median follow-up of 10.2 months, the median progression-free survival (PFS) was 5.5 months (95% CI, 4.2-7.0) with sacituzumab govitecan vs 4.0 months (95% CI, 3.1-4.4) with investigator’s choice chemotherapy, the standard of care (SOC), equating to a 34% reduction in the risk of disease progression or death (HR, 0.66; 95% CI, 0.53-0.83; \( P < .0003 \)). The overall survival data were not mature at the time of the primary analysis; however, investigators noted a numeric trend toward improvement with the ADC vs SOC.

Specifically, at 6 months, 46% of patients who received sacituzumab govitecan (n = 272) were alive without worsening disease compared with 30% with chemotherapy (n = 271). At 12 months, the PFS rates were 21% vs 7%, respectively.

Investigators of TROPiCS-02 evaluated the safety and efficacy of sacituzumab govitecan, which targets Trop-2. For patients who develop progressive disease following sequential treatment with endocrine therapies, including CDK4/6 inhibitors, mTOR inhibitors, and PI3K inhibitors, the SOC consists of single-agent chemotherapy such as capecitabine, vinorelbine, gemcitabine, or eribulin. Because of acquired resistance, outcomes for patients who receive chemotherapy in later-line settings are not favorable, with a PFS of approximately 4 months.

→ For the full article, visit CancerNetwork.com/ASC022_breast3

LUNG CANCER

Best Responses With Pembrolizumab Monotherapy Are Observed in NSCLC With 90% or Higher PD-L1 Expression

Patients with \( EGFR/ALK \) wild-type non–small cell lung cancer (NSCLC) and a PD-L1 tumor proportion score (TPS) of 90% or more had statistically significant long-term survival benefit with first-line pembrolizumab (Keytruda) monotherapy vs those with a PD-L1 TPS of 50% to 89%, according to data from a correlative analysis.

The median progression-free survival was 6.3 months (95% CI, 4.9-10.8) in the group with a TPS of 90% or higher vs 4.7 months (95% CI, 3.8-6.1) in the group with a TPS of 50% to 89% (HR, 0.69; 95% CI, 0.55-0.86; \( P < .001 \)). The median overall survival was 29.0 months (95% CI, 21.0-45.3) in those with TPS of 90% or greater vs 17.8 months (95% CI, 15.3-20.9) with TPS 50% to 89% (HR, 0.40; 95% CI, 0.33-0.50; \( P = .0001 \)). The objective response rate in those with TPS 50% to 89% was 32.0% vs 47.9% for TPS 90% or greater (\( P = .001 \)).

Of note, a gene mutation enrichment analysis showed that certain genomic alterations were significantly enriched in tumors with a PD-L1 TPS of 50% to 89% compared with 90% or more. Mutations in \( FBXW7, STK11, KEAP1, \) and \( CTNNB1 \) were more common in the TPS 50% to 89% group. Additionally, those with TPS of 90% or greater had high rates of tumor infiltrating T cells, including CD8-positive (\( P = .04 \)) and CD8-positive/PD-1–positive (\( P = .02 \)) cells.

Patients with PD-L1 TPS of 50% or greater who received frontline pembrolizumab monotherapy for advanced NSCLC were enrolled. The groups with TPS 50% to 89% or with 90% or greater included 284 and 169 patients, respectively.

→ For the full article, visit CancerNetwork.com/ASC022_lung1

Adagrasib Induces Deep Responses, Shows Promising Efficacy in KRAS G12C–Mutated NSCLC

Adagrasib monotherapy demonstrated promising objective responses and disease control, as well as overall survival (OS), among patients with previously treated KRAS G12C–mutated non–small cell lung cancer (NSCLC), according to
ONCOLOGY®

Jul y 2022

results from cohort A of the phase 1/2 KRYSTAL-1 trial (NCT03785249).

After a median follow-up of 12.9 months, the objective response rate (ORR) was 43% (95% CI, 33.5%-52.6%) among the 112 patients with measurable disease at baseline; this included 1 complete response (CR; 1%) and 47 partial responses (PRs; 42%). There were 41 patients with stable disease (SD; 37%) and 6 with progressive disease (5%) for a disease control rate (DCR) of 80% (n = 89; 95% CI, 70.8%-86.5%). There were no differences in ORR by subgroup in exploratory analyses.

Moreover, the median time to response with the KRAS G12C inhibitor was 1.4 months (range, 0.9-7.2) and median duration of response was 8.5 months (95% CI, 6.2-13.8). As of the data cutoff, treatment was ongoing in half of patients who experienced a response (n = 24), and 33% (n = 16) had maintained their response. Lastly, the median progression-free survival (PFS) was 6.5 months (95% CI, 4.7-8.4), with 6- and 12-month PFS rates of 52% and 29%, respectively. Similarly, the median OS was 12.6 months (95% CI, 9.2-19.2), with 6- and 12-month OS rates of 71% (95% CI, 61.1%-78.3%) and 51% (95% CI, 40.9%-60.0%), respectively.

Efficacy evaluation was completed among 33 patients with treated, stable central nervous system metastases. The intracranial ORR was 33% (n = 11; 95% CI, 18%-52%), which included 5 CRs (15%) and 6 PRs (18%). There were 17 patients with SD (52%) for a DCR of 85% (n = 28; 95% CI, 68%-95%). The median intracranial PFS was 5.4 months (95% CI, 3.3-11.6).

Adding Frontline Toripalimab to Chemotherapy for NSCLC Across PD-L1 Expression Levels Leads to Survival Boost

Progression-free survival (PFS) with frontline chemotherapy in patients with EGF R or ALK wild-type advanced nonsmall cell lung cancer (NSCLC) across PD-L1 expression levels appeared to benefit from addition of toripalimab (Tuoyi), according to a biomarker analysis of the phase 3 CHOICE-01 trial (NCT03856411).

Patients with PD-L1 expressed in at least 50% of tumor cells elicited a median PFS of 8.4 months (n = 72) compared with 5.6 months with chemotherapy alone (n = 28; HR, 0.45; 95% CI, 0.27-0.78). The 12-month PFS rates for these patients were 46.4% and 20.3% in the toripalimab and placebo arms, respectively.

In patients with PD-L1 expressed in less than 50% of tumor cells, toripalimab achieved a median PFS of 8.4 months (n = 128) vs 6.7 months for placebo (n = 75; HR, 0.56; 95% CI, 0.40-0.78). The 12-month PFS rates were 39.4% and 20.8% for the toripalimab and placebo arms, respectively.

In patients with PD-L1 expressed in less than 1% of tumor cells, the median PFS for the toripalimab (n = 98) and placebo (n = 41) arms was 8.2 months and 5.6 months, respectively (HR, 0.47; 95% CI, 0.32-0.71). The 12-month PFS rates were 25.9% and 10.3% for the toripalimab and placebo arms, respectively.

For patients with an unknown PD-L1 status, toripalimab elicited a median PFS of 8.4 months (n = 11) compared with 5.5 months for placebo (n = 12; HR, 0.62; 95% CI, 0.21-1.79). The 12-month PFS rates were 37.5% and 11.4%, respectively.

CHOICE-01 was a double-blind, placebo-controlled, multicenter trial evaluating toripalimab plus chemotherapy in untreated patients with advanced squamous and nonsquamous stage IIIB and IV NSCLC. Patients were required to be treatment naive in the locally advanced or metastatic setting; to have no known EGF R or ALK mutations; and to have measurable disease per RECIST v1.1, an ECOG performance status of 0 or 1, and tumor tissue available for PD-L1 testing.

Adding Frontline Toripalimab to Chemotherapy for NSCLC Across PD-L1 Expression Levels Leads to Survival Boost

In 14 patients with stage II/III mismatch repair–deficient (dMMR) locally advanced rectal cancer who participated in a phase 2 trial (NCT04165772), treatment with dostarlimab-gxly (Jemperli) yielded a 100% clinical complete response (cCR).

The median follow-up for the analysis was 6.8 months (range, 0.7-23.80), with a majority of patients achieving cCR at 6 months.

Patients received the PD-1 monoclonal antibody dostarlimab at 500 mg intravenously every 3 weeks for 6 months, equaling 9 total cycles. At baseline and through treatment, patients were closely monitored and assessed for response at 6 weeks, 3 months, and 6 months. At these key timepoints patients underwent endoscopic and digital rectal exams. Upon treatment completion at 6 months, patients then underwent...
Comprehensive radiologic and endoscopic evaluation including tumor biopsy collection and T2-weighted and diffusion-weighted MRI of the rectum, 18F-fluorodeoxyglucose PET, and CT scan of the chest, abdomen, and pelvis.

→ For the full article, visit CancerNetwork.com/ASCO22_gastro1

Circulating tumor DNA (ctDNA) status following surgery can effectively be used to avoid adjuvant chemotherapy while maintaining recurrence-free survival rates for some patients with stage II colon cancer, according to findings from the phase 2 DYNAMIC study.

In the study, patients were randomized to a ctDNA-guided treatment cohort (n = 294) or to a standard therapy group (n = 147). Those who tested negative for ctDNA in the guided cohort were given the chance to forego chemotherapy while patients who were positive for ctDNA received adjuvant chemotherapy. Overall, 15% of patients received chemotherapy in this arm compared with 28% in the standard treatment group, in which the decision was based on standard clinical factors (relative risk [RR], 1.82; 95% CI, 1.25-2.65).

Despite less treatment in the ctDNA group, the recurrence-free survival (RFS) rates were similar between arms. Those in the ctDNA-guided cohort had a 2-year RFS rate of 93.5% compared with 92.4% in the standard treatment group (95% CI, 4.1 to 6.2). The 3-year RFS rates were 91.7% and 92.4%, respectively (HR, 0.96; 95% CI, 0.51-1.82). Additionally, the study found that those with ctDNA-positive tumors experienced better outcomes when treated with an oxaliplatin-based doublet compared with a single-agent fluoropyrimidine therapy.

In the study, ctDNA analysis was completed for 99% (n = 291/294) of those in the guided arm. Two patients did not receive ctDNA-guided treatment. In this group, 45 patients were ctDNA positive, and all but 1 received chemotherapy. Chemotherapy was not administered to those with ctDNA negativity following surgery (n = 249), except for 1 patient.

There was less chemotherapy used with the ctDNA-guided approach across all patient subgroups, except for those with a lymph node yield fewer than 12 and those aged more than 70 years. The biggest differences in chemotherapy use favoring less in the ctDNA-guided group, were for patients with T4 tumors (RR, 2.57; 95% CI, 1.46-4.50), high-risk characteristics (RR, 2.14; 95% CI, 1.43-3.21), and poorly differentiated tumors (RR, 5.06; 95% CI, 1.02-25.10).

In the guided cohort, recurrence or death occurred in 6% of patients with ctDNA-negative status compared with 18% of the ctDNA-positive group. The estimated 3-year RFS rate was 92.5% in patients from the ctDNA-negative group who did not receive chemotherapy compared with 86.4% in patients with ctDNA positivity treated with chemotherapy (HR, 1.83; 95% CI, 0.79-4.27). Furthermore, there was a difference in RFS by type of chemotherapy used within the ctDNA-positive group, with a 3-year RFS rate of 92.6% for those receiving an oxaliplatin-based doublet compared with 76.0% for single-agent fluoropyrimidine therapy.

→ For the full article, visit CancerNetwork.com/ASCO22_gastro2

Lenvatinib (Lenvima) plus pembrolizumab (Keytruda) led to a 50% reduction in risk of progression or death on second-line therapy for patients with advanced renal cell carcinoma (RCC) compared with sunitinib (Sutent), according to findings from the phase 3 CLEAR trial (NCT02811861).

Investigators analyzed progression-free survival on next-line therapy (PFS2) in patients who received lenvatinib plus pembrolizumab (n = 355) and compared it with that of patients prescribed sunitinib (n = 357) in the randomized, open-label CLEAR trial. Median PFS2 was not reached for the lenvatinib/pembrolizumab cohort (95% CI, not evaluable [NE]), and it was 28.7 months in the sunitinib cohort (95% CI, 23.0-NE).

At the 24-month mark, the PFS2 rate was 72.7% (95% CI, 67.3%-77.4%) and 54.2% (95% CI, 48.4%-59.6%) in the dual-therapy and sunitinib arms, respectively. At 36 months, the PFS2 rate was 61.9% (95% CI, 53.7%-69.0%) and 42.9% (95% CI, 32.8%-52.5%) in the lenvatinib/pembrolizumab and sunitinib arms, respectively.

A total of 117 patients in the lenvatinib/pembrolizumab cohort and 206 patients in the sunitinib cohort went on to receive another therapy. Median time to next-line therapy was 12.2 months (range, 1.45-37.36) and 6.4 months (range, 0.39-28.52) in the lenvatinib/pembrolizumab and sunitinib arms, respectively.

The most common next line of therapy was anti-VEGF treatment, mainly cabozantinib (Cabometyx; 33.0% of patients in the lenvatinib/pembrolizumab cohort and 57.7%
in the sunitinib group), followed by checkpoint inhibition (30.4% and 33.6%, respectively), mTOR inhibition (8.2% and 43.1%), CTLA-4 inhibition (1.7% and 5%), and other (1.7% and 5%).

Using risk groups defined by the International mRCC Database Consortium, median PFS2 was not reached for the favorable-, intermediate-, or poor-risk groups for those on lenvatinib plus pembrolizumab, although it was 34.7 months (95% CI, 28.7-NE), 23.0 months (95% CI, 17.7-NE), and 10.2 months (95% CI, 4.2-12.2), in the sunitinib groups, respectively.

Median duration of first subsequent treatment was 5.2 months for the lenvatinib/pembrolizumab cohort (range, 0.10-31.23) and 6.8 months in the sunitinib cohort (range, 0.03-30.72).

→ For the full article, visit CancerNetwork.com/ASCO22_GU1

HEMATOLOGY

Avelumab Maintenance Yields Survival Benefit in First-Line Advanced Urothelial Carcinoma, Regardless of Second-Line Therapy

Frontline avelumab (Bavencio) maintenance yielded long-term overall survival (OS) in patients with advanced urothelial carcinoma regardless of second-line therapy, according to an exploratory analysis of the JAVELIN Bladder 100 study (NCT02603432).

Median OS was not reached in the patients still receiving avelumab; it was 19.9 months (95% CI, 18.2-23.0) in patients discontinuing avelumab and moving on to second-line treatment, and 18.2 months (95% CI, 10.0-34.4) in patients discontinuing avelumab and not receiving second-line treatment.

Earlier results of this trial demonstrated that avelumab first-line maintenance and best supportive care (BSC) significantly prolonged OS compared with BSC alone in patients with advanced urothelial carcinoma that had not progressed with first-line platinum-containing chemotherapy. In the current work, the investigators performed an exploratory analysis of outcomes in patients in the avelumab/BSC arm based on receipt of second-line treatment.

Patients in the trial had unresectable locally advanced or metastatic urothelial carcinoma that had not progressed with 4 to 6 cycles of first-line platinum-containing chemotherapy. Patients were randomized 1:1 to receive avelumab maintenance plus BSC or BSC alone after an interval of 4 to 10 weeks from the end of first-line chemotherapy. The study’s primary end point was OS.

Of the 350 patients randomized to avelumab plus BSC, 43 (12.3%) were still receiving avelumab first-line maintenance, with a median duration of treatment of 35.6 months (range, 24.5-49.7); 185 (52.9%) had discontinued treatment with avelumab and moved on to second-line treatment, with a median duration of avelumab treatment of 5.1 months (range, 0.5-44.6); and 122 (34.9%) had discontinued avelumab and did not receive second-line treatment, with a median duration of avelumab treatment of 5.0 months (range, 0.5-43.7).

In patients receiving second-line treatment, the median time from the end of avelumab maintenance to the start of second-line treatment was 1.35 months (range, 0.3-30.9). Median time from randomization to the end of second-line treatment was 11.7 months (95% CI, 9.7-13.8).

→ For the full article, visit CancerNetwork.com/ASCO22_GU2

Pacritinib Boasts Safety Profile Comparable With That of Best Available Therapy in Myelofibrosis Treatment

Pacritinib (Vonjo) had a safety profile comparable with or superior to that of best available therapy (BAT) and ruxolitinib (Jakafi), in patients with myelofibrosis, even those with platelet counts lower than 50 × 10⁹/L.

A total of 160 patients given pacritinib were included in the analysis (n = 106 from PERSIST and n = 54 from PAC203). Ninety-eight were in the BAT cohort, including 44 on ruxolitinib.

While data showed a higher rate of adverse events (AEs) for those on pacritinib vs BAT (1570 per 100 patient-years at risk, compared with 903 per 100 patient-years at risk), the rate of fatal AEs was lower. The incidence of bleeding or cardiac events was slightly lower for those given pacritinib compared with those given BAT (12 vs 22 per 100 patient-years at risk, respectively). In the pacritinib arm, no major cardiac AEs occurred, whereas 5 occurred in the BAT group. Thrombosis was similar between the 2 arms.

Infection was more prevalent in the pacritinib cohort, but fungal and viral infections happened less frequently for these patients compared with those in the BAT cohort. Additionally, herpes zoster reactivation occurred less frequently on the pacritinib arm than it did on the BAT arm (0 vs 2.4 vs 5.5 per 100 patient-years in the pacritinib, BAT, and ruxolitinib arms, respectively).

A similar rate of malignant neoplasms was seen between the 2 arms, with a statistically significant lower risk of non-
melanoma skin cancer in patients given pacritinib compared with BAT (3 vs 7 vs 11 per 100 patient-years in the pacritinib, BAT, and ruxolitinib arms, respectively).

→ For the full article, visit CancerNetwork.com/ASCO22_heme1

Feasibility of Daratumumab and Carfilzomib Quadruplet and Tandem Transplant Is Demonstrated in High-Risk Myeloma

Quadruplet induction with daratumumab (Darzalex), carfilzomib (Kyprolis), lenalidomide (Revlimid), and dexamethasone appears to be effective and feasible for patients with newly diagnosed high-risk multiple myeloma who will go on to receive tandem transplant, according to results of the phase 2 IFM 2018-04 trial (NCT03606577).

The objective response rate among evaluable patients (n = 48) was 96%, with 31% of patients having either a complete response (CR) or stringent CR and 91% having at least a very good partial response to therapy. Additionally, of those who were evaluable (n = 46), 62% achieved minimal residual disease negativity by next-generation sequencing at a threshold of 10⁻⁶.

At the time of data cut-off, treatment was ongoing in 72% of patients, 11 of whom were in consolidation, 24 of whom were on maintenance therapy, and 1 who had received their second autologous stem cell transplant. Fourteen patients (28%) discontinued therapy, due to progressive disease (n = 2), adverse events (n = 4), withdrawal (n = 2), and stem cell collection failure (n = 6).

With a median follow-up of 19.4 months, the rates of progression-free survival at 12 and 18 months were 96% and 92%, respectively. Corresponding rates of overall survival were 96% at each of the time points.

→ For the full article, visit CancerNetwork.com/ASCO22_heme2

Tracking Success to Improve Your Practice

Benchmarking is an important tool to measure successes or setbacks of a practice. Several key areas are necessary to identify these milestones, such as converting leads to claim denials, navigating a value-based care model, and tracking reimbursement.

**Clinical/Quality Benchmarks**

Measuring clinical metrics can be challenging, particularly when trying to measure patient outcomes. Physicians should utilize quality-of-life surveys or track how often patients avoid emergency room admission. In the value-based care model, physicians get paid for value they create. Primary care physicians should eliminate hospitalization or referrals to specialists, both of which can be tracked.

**Operational Benchmarks**

Operational benchmarks include such metrics as tracking how long patients wait in your office before being seen, how well your practice communicates with patients, and whether it provides options such as text, email, and phone.

In a new era of consumer-driven health care, it is necessary to look at the patient experience from the moment a practice first collects patient information, which should be a digital, simple process. Physicians should also follow up appointments with reviews through an automatic process, such as a text or email survey.

**Financial Benchmarks**

Important financial benchmarks begin before a practice sees a patient. There are many opportunities to track conversion rates of patient leads into appointments, but it does require having a website, app, or patient portal and staying on top of online reviews. It also requires attention to patients’ show rates and looking at the technology and software that could be introduced to make the process easier for the practice manager and patient.

**Equity Benchmarks**

It is important to measure equity in a practice, although it is not easy. This extends to guiding patients, who are often confused by their health care journey, in understanding everything from how to make an appointment to the costs of their care.

To read the full article, visit https://bit.ly/3NXmnb8
CONTINUING MEDICAL EDUCATION (CME)

Caring for Patients on CAR T-Cell Therapy in the Inpatient Versus Outpatient Setting

LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

• Outline the importance of patient monitoring to support the efficacy and safety of the procedure before, during, and after the CAR T therapy infusion.
• Compare the benefits and risks of inpatient vs outpatient administration of CAR T therapy.
• Discuss the role of the multidisciplinary team in the management and education of patients before, during and after CAR T therapy.

RELEASE DATE: July 1, 2022
EXPIRATION DATE: July 1, 2023

INSTRUCTIONS FOR PARTICIPATION / HOW TO RECEIVE CREDIT

1. Read this activity in its entirety.
2. Go to http://www.gotoper.com/cpcart22ivos-art to access and complete the posttest.
3. Answer the evaluation questions.
4. Request credit using the drop-down menu.
You may immediately download your certificate.

FACULTY, STAFF, AND PLANNERS’ DISCLOSURES

In accordance with ACCME Guidelines, PER® has identified and resolved all COI for faculty, staff, and planners prior to the start of this activity by using a multistep process.

Disclosures: Charise Gleason, MSN, NP-BC, AOCNP, has no relevant financial relationships with commercial interests.
The staff of PER® have no relevant financial relationships with commercial interests to disclose.

OFF-LABEL DISCLOSURE AND DISCLAIMER

This activity may or may not discuss investigational, unapproved, or off-label use of drugs. Learners are advised to consult prescribing information for any products discussed. The information provided in this activity is for accredited continuing education purposes only and is not meant to substitute for the independent clinical judgment of a healthcare professional relative to diagnostic, treatment, or management options for a specific patient’s medical condition. The opinions expressed in the content are solely those of the individual faculty members, and do not reflect those of PER® or any of the companies that provided commercial support for this activity.

This activity is funded by PER®.

ACCREDITATION/CREDIT DESIGNATION

Physicians’ Education Resource®, LLC, is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. Physicians’ Education Resource®, LLC, designates this enduring material for a maximum of 0.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
himeric antigen receptor (CAR) T-cell therapies have emerged as potent treatment options for hematological malignancies. There are currently 6 United States Food and Drug Administration (FDA)-approved CAR T-cell therapies: tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, idecabtagene vicleucel, and ciltacabtagene autoleucel.1 While these therapies have significantly improved survival outcomes and produced high rates of response and durable remission, barriers remain which restrict their access to a larger patient population. One of the main concerns that limits access is toxicity, including cytokine release syndrome (CRS) and neurological toxicity.2 Because of these toxicities, CAR T therapy is largely administered in the inpatient setting, which poses further financial and geographical restrictions. Clinical trials are therefore examining the feasibility and safety of administering CAR T therapy in the outpatient setting.1,4

Charise Gleason, MSN, NP-BC, AOCNP, is the advanced practice provider chief at Winship Cancer Institute at Emory University in Atlanta, Georgia. In this article, Ms. Gleason reviews the benefits and risks of inpatient versus outpatient administration of CAR T-cell therapy, the critical role of the close monitoring of patients undergoing CAR T-cell therapy, and the need for a multidisciplinary team to ensure optimal patient management in both the inpatient and outpatient settings.

Q: There are discussions about moving CAR T therapy infusions from the specialized centers to the outpatient setting for selected patients. Please let us know your thoughts on this possible move.

GLEASON: The more I’ve read about it, I find it very interesting. It’s definitely [moving forward] in the population of patients [with lymphoid malignancies], and it really depends a lot on the product that they’re receiving. So, looking at that time to potential cytokine release syndrome (CRS), it seems to be a big factor, and I think that [there’s] more to come on this for a very select patient population.

Q: Please outline the role of nurses in monitoring patients for adverse events before, during, and after CAR T infusion.

GLEASON: I think sometimes patients feel like, “I’m just going to go get CAR T and I’m done.” It’s targeted as a 1-and-done, but it’s such a process. We first have to determine if a patient is eligible for CAR T. And so, in that setting, you’ve got nurses working in different capacities. You’re going to have the CAR T coordinator working with the team, setting up the [patient] screening, checking their pulmonary status, their cardiac status, their liver status to make sure that they can go through this procedure. The nursing role in the clinic is still with the team monitoring patients for [adverse events] that they’re having from disease [and] from their current therapy, and really trying to get them to the point that they can go to CAR T. After that you’ve got your apheresis nurse who is in on the T-cell collection. These drugs are FDA approved, but you’re still limited on how much that company can do because you have to send [the T-cells] off. They have to reengineer them. It takes 4 to 6 weeks, and all the while you’re trying to keep your patient balanced and not progressing while they’re waiting.

The apheresis nurses are monitoring things when there are patients going through apheresis—like electrolyte imbalances, checking their calcium, checking for things like hypotension, syncopal episodes while they’re going through that process. And patients also can have nausea and vomiting, [which] has a lot to do with those calcium swings. Also, they can become diaphoretic.3 So the nurse is very important in that aspect, in choosing what type of line that [patient is] going to need.

Do they have peripheral veins that they can use for apheresis versus do they need a central line placement? All of that depends on that assessment by nursing. And then when you get to the next step, when the patient is in that bridging, it’s back to that normal role of infusion and it’s the clinic nurse who’s helping monitor for those [adverse events] while [patients] are going through their therapy.4

Before you give lymphodepleting chemotherapy, you have to assess the patient [and] make sure that they don’t have any infections. Typically, they get a nasopharyngeal swab. You do a COVID test. Now that everything’s changed since we have COVID, you don’t want to give chemotherapy and then admit a patient for CAR T and find out that they had an infection or had COVID.4

So patients are monitored throughout this time. Whether you’re doing it in the outpatient setting or the patient is getting admitted, at that point you have another set of nurses whose expertise is to monitor their patients through CAR T.4 But the reactions that you think of, or the [adverse events] when they’re actually getting their cells back, you think more about those hypersensitivity-type reactions. So, they’re monitoring for rigors, for shortness of breath, for hives—those kinds of things that would make you pause, give additional premeds. After that you start monitoring for that cytokine release syndrome and neurotoxicities and any other [adverse events] that they might have.4

When a patient then is back a little further out from their CAR T and they switch back more to clinic team management, you’ve got another set of nursing eyes looking at them, monitoring for those long-term effects of infection issues and neurotoxicities, which can go on for up to 8 weeks depending on the product.
It really takes a lot of peer coordination and a multidisciplinary approach to care for patients.4

Q: Please outline the significance of REMS programs associated with CAR T therapy.

GLEASON: REMS stands for risk evaluation and mitigation strategies.5,6 What they’re trying to do in the context of CAR T is make sure that the center has what it needs to do this safely, that the benefit outweighs the risk for the patient, and [they] have the appropriate medications to handle [the adverse events] and the potential harm that can come up—things like having the steroids on hand, having tocilizumab on hand to manage CRS.7

If you’re thinking of doing this in the outpatient setting, you have to make sure that you’re set up for all of these things, because your patients still could get admitted. You have to have availability of these things and also to quickly move them inpatient if needed.

Q: How would patients be selected for outpatient versus inpatient CAR T therapy?

GLEASON: I think it goes back to what the potential for CRS is. If you have a product, for instance, in myeloma, 1 of our CAR T products, the median time of onset for CRS is the first day, where for other products, it’s 7 days. For the lymphomas, for tisa-cel [tisagenlecleucel], for instance, the median time to CRS is 3 days.4 So you’ve got some time in there that it’s not immediate. I think that is a big thing to consider.

And then you have to look at the patient. It really is on an individual basis. If you have a patient who has a really high disease burden, that’s a patient who’s going in the hospital. They have more risk for CRS. Your [patients with] CNS lymphoma, they already may have some neurological changes. It really comes down to the individual patient and the product they’re getting and that disease burden. The other thing to consider as well is the socioeconomic support for that patient. If you don’t have that in place, these patients are closely monitored, especially that first week. They’re coming to the center multiple times, maybe even daily on the outpatient side. They have to have those resources to bring them in. They need to be close to the center. But also, they need to have that care partner at home that’s monitoring them and with them as well.

Q: Are there benefits from providing CAR T therapy in the outpatient setting for selected patients?

GLEASON: Patients always feel better when they’re at home or they’re around familiar things, even if they’re staying in an outpatient-type center or a hotel, or if the center has housing, there’s just something about being able to do what you want to do or get up, go to the kitchen—that kind of thing. From that standpoint you’re in a bubble at that point, so you’ve got to be very careful from an infection standpoint not to have a lot of other people in.

Some of these patients are young, and for these younger patients, being around their families—there’s a benefit to not having to go in the hospital. People don’t like to go to the hospital.

Q: What are the potential risks of moving CAR T infusion from specialized centers to the outpatient setting?

GLEASON: I wonder about the monitoring. I know there have been some publications looking at some new ways to monitor patients with electronic means, but do they really have the means to monitor and identify something like CRS?5 I think about infection. So [with regard to] exposure, coming back and forth to an infusion center-type setting, you’re still exposed to other people—maybe a little bit more than if you’re in your room in the hospital.

It goes with what [the patient] needs; if you don’t have that, if your caregiver really isn’t equipped to be monitoring these things or noticing subtle changes in a patient that can happen with CRS. You’ve got this pool of professionals in the hospital, and this is what they look out for. So, it just really is a question: How do we get that kind of monitoring 24 hours in the outpatient setting?

Q: What resources would be required to make outpatient infusion feasible?

GLEASON: Most centers that do this have an infusion center, so it’s just doing another type of infusion. People do outpatient [autologous] stem cell transplant. There are centers that are used to doing this. I think you need to have some sort of observation unit that can get patients quickly into the hospital. I mentioned this earlier, but if you’ve got a patient in front of you that you know needs to go to the hospital now, you’re starting to see CRS, is there a bed?

There has to be some kind of bed saved for a patient, and that’s challenging in these times. Hospitals are full and they go on diversion. I think it’s getting them to know that you can take care of them equally, whether they’re out or in and getting them in. That’s one of the big things I think about from a feasibility standpoint.

Right now, you do CAR T at mostly big academic centers that have the infrastructure to do this. And even to get referred in, these centers have their own patients, and so community patients need to be referred in sooner than later, so they already have an established relationship.

Q: What kind of results would a clinical trial comparing inpatient versus outpatient CAR T have to have in order to give you confidence in moving the therapy out of specialized centers?

GLEASON: I think having some numbers behind it and looking at how they risk
stratified to see which patients were suitable. And then of those patients, how many ended up going in the hospital? So, looking at that and then what grades of CRS or neurotoxicities did they have? We learn everything from clinical trials. [The Barbara Ann Karmanos Cancer Center] looked at their CAR T population over the period of time. It was the retrospective study that looked at diffuse large B cell lymphoma patients, and they looked at their number.\(^\text{10}\) They had 12 patients who went to CAR T. They had 6 that required hospitalizations within 30 days, and the median stay was 4 days. They had 5 patients that had CRS, all 5 of them needed tocilizumab. One patient needed steroids, and 1 patient did have neurotoxicity that was a grade one.\(^\text{10}\)

So, half their patients did okay and were in the outpatient setting. So, it’s a really small number, but I think you can learn something from that. And then there were 3 trials, the JULIET, the TRANSCEND, and the ELIANA.\(^\text{8,11}\) In the JULIET trial, 27% of those patients were in the outpatient setting and the ELIANA had 24%.\(^\text{8,12}\) So, that’s a decent amount. The TRANSCEND had 7%.\(^\text{11}\)

Some of those patients that went in the hospital again were those patients with high disease burden or CNS involvement. So, I think we do learn from this. This is in the lymphoma population or the lymphoid cancer population, but I’ll be interested to see more for instance, with myeloma patients as well, now that we’re doing more CAR T on those patients.

**Q:** How can members of the multidisciplinary team managing CAR T therapy communicate most effectively with each other and with the patient?

**GLEASON:** I think it’s important to know from the patient and caregiver standpoint, who do I need to call when I need a number where I’m getting a person. You’re going to have a team—a medical team from the day that is different from the medical team at night. I think it’s important for anybody the patient is going to come in contact with [be] well-versed on CAR T and what to do, and on the [adverse events]. And that there’s an appropriate handoff to the night team, whether it’s a physician or advanced practice provider taking that call.

So, they’re familiar with the patient that they know has had the cells and could potentially be calling and have a plan that if something’s going on, we can get them in and get them seen quickly. I think it’s all the team members knowing their role in this and being very familiar with the patients that they’re monitoring.

**Q:** What advice can you give regarding educating patients about what they can expect during CAR T therapy?

**GLEASON:** When we started doing these years ago, you’d have patients show up and they would be like, “Okay, I’m ready for my CAR T.” Your patient is kind of hanging on, and things have to really align for patients. So, I think really explaining the process to them that here’s what we’re going to do at the start, and here’s how we’re going to collect your cells while they’re off being manufactured. Here’s our plan during this period with bridging therapy. You have to then be off therapy for a period of time. Here’s the expectation of when you’re going to get lymphodepleting chemotherapy, or [adverse events] from that. Patients have a lot of questions about that and the process, why you’re getting that, the additional testing to make sure that you are not sick before you get the chemotherapy and then your cells back, and then just talking to them about that process, whether it’s on the outpatient or inpatient.

If you’re outpatient, here are all the things you’re going to need to do and be aware of and how to contact us and how frequently you’re going to need to come. If you’re going inpatient, same sort of thing: what to expect while you’re in the hospital. Patients like to know that, how long they’re going to be in there. Typically tell patients as far as CRS and what to expect—just think of it as a really bad case of the flu, that patients just feel very flukey when they get that.

And then the monitoring: what’s the expectation of monitoring after the procedure? How often are you going to need to come for visits? If you’ve been referred to us from a community practice, when are we sending you back? Things like the fact that you can’t drive for 8 weeks after this, and you really need that commitment of a care partner for that period of time because you can have those delayed neurological changes. It’s a lot. It can be very overwhelming for a patient. And typically, these are pretty sick patients that really need that next line of therapy, and so many things have to line up.
Q: How might digital health tools help in monitoring outpatients who have had CAR T therapy?

GLEASON: I think these are going to be very important. So, telemedicine really came about during COVID, and we’re all doing it now. We learned how to do it quickly, and it’s here to stay, but there’s certainly a role for this in that outpatient setting, whether it’s with a provider or your nursing team to have that where somebody is looking at you on the other end and they can see you and talk about the [adverse events] that you’re having. I think that will be a tool that would be heavily used in this.

The new devices—your Apple watch or those type of devices that monitor heart rates—they’re looking at developing tools that can detect early signs of CRS. You need these kinds of things to do this without having to send stem cells off. So, things like bispecific antibodies that might target the same thing. In myeloma, it could be BCMA for instance. Yes, there’s some competition in that. And can you get the same effect from some of these other trials? I think there’s more to come.

And so, how you use one over the other will be what we figure out later on. And with CAR T, as we do with any treatment, you start these on clinical trials in a relapse refractory population of patients heavily pretreated, and then you start moving them up. And so, what’s the effect then if you give CAR T for instance earlier versus later? And there will be more data on that based on clinical trials.

Q: Are there emerging therapies that may impact the role of CAR T-cell therapy in the management of hematologic malignancies?

GLEASON: In addition to CAR T, there are other clinical trials looking at ways to do this without having to send stem cells off. So, things like bispecific antibodies that might target the same thing. In myeloma, it could be BCMA for instance. Yes, there’s some competition in that. And can you get the same effect from some of these other trials? I think there’s more to come.

And so, how you use one over the other will be what we figure out later on. And with CAR T, as we do with any treatment, you start these on clinical trials in a relapse refractory population of patients heavily pretreated, and then you start moving them up. And so, what’s the effect then if you give CAR T for instance earlier versus later? And there will be more data on that based on clinical trials.

KEY REFERENCES

For references visit http://www.gotoper.com/cpcart22ives-art
Hear timely & informative insights from some of the leading voices in the field.

Listen: www.cancernetwork.com/resources/podcasts
A 24-hour streaming program

For Health Care Professionals, By Health Care Professionals

Season 6 is streaming now!

www.medicalworldnews.com