SPECIAL ISSUE: **PCOC 2018 MEETING RECAP**

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HIGHLIGHTS FROM THE MEETING

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

The first and only CAR-T cell therapy approved for 2 distinct patient populations

KYMRIAH®
(tisagenlecleucel) Suspension for IV infusion

The ONLY CAR-T cell therapy approved for the treatment of:

Patients up to 25 years of age with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (ALL)*

AND

adults with r/r diffuse large B-cell lymphoma (DLBCL)†

Visit **KYMRIAH-hcp.com** or call **KYMRIAH CARES™** at **1-844-4KYMRIAH** (1-844-459-6742) to learn more about KYMRIAH, including treatment center locations, coverage support, and patient assistance.

INDICATIONS

KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

*Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

†Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma.

IMPORTANT SAFETY INFORMATION FOR KYMRIAH® (tisagenlecleucel)

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab, or tocilizumab and corticosteroids**
- **Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed**
- **KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS**

Please see additional Important Safety Information and Brief Summary of Prescribing Information for KYMRIAH, including Boxed WARNING, on the following pages.

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions

Cytokine Release Syndrome: CRS, including fatal or life-threatening reactions, occurred following treatment with KYMRIAH. CRS occurred in 54 (79%) of the 68 patients with r/r ALL and 78 (74%) of the 106 patients with r/r DLBCL receiving KYMRIAH, including ≥ grade 3 (Penn Grading System) in 49% of patients with r/r ALL and in 23% of patients with r/r DLBCL. The median time to onset was 3 days (range: 1-51), and in only 2 patients was onset after Day 10. The median time to resolution was 8 days (range: 1-36).

Of the 54 patients with r/r ALL who had CRS, 27 (50%) received tocilizumab; 7 (13%) received 2 doses of tocilizumab, 3 (6%) received 3 doses of tocilizumab and 14 (26%) received addition of corticosteroids (eg, methylprednisolone). Of the 78 patients with r/r DLBCL who had CRS, 16 (21%) received systemic tocilizumab or corticosteroids. Six (8%) received a single dose of tocilizumab, 10 (13%) received 2 doses of tocilizumab, and 10 (13%) received corticosteroids in addition to tocilizumab. Two patients with r/r DLBCL received corticosteroids for CRS without concomitant tocilizumab, and 2 patients received corticosteroids for persistent neurotoxicity after resolution of CRS.

Five deaths occurred within 30 days of KYMRIAH infusion. One patient with r/r ALL died with CRS and progressive leukemia, and 1 patient had resolving CRS with abdominal compartment syndrome, coagulopathy, and renal failure when an intracranial hemorrhage occurred. Of the 3 patients with r/r DLBCL who died within 30 days of infusion, all had history of CRS in the setting of stable to progressive underlying disease, 1 of whom developed bowel necrosis. Among patients with CRS, key manifestations included fever (92% r/r ALL and r/r DLBCL), hypotension (67% r/r ALL; 47% r/r DLBCL), hypoxia (20% r/r ALL; 35% r/r DLBCL), and tachycardia (30% r/r ALL; 14% r/r DLBCL). CRS may be associated with hepatic, renal, and cardiac dysfunction, and coagulopathy.

Delay KYMRIAH infusion after lymphodepleting chemotherapy if patient has unresolved serious adverse reactions from preceding chemotherapies, active uncontrolled infection, active graft vs host disease, or worsening of leukemia burden.

Ensure 2 doses of tocilizumab are available on-site prior to KYMRIAH infusion. Monitor patients for signs or symptoms of CRS 2-3 times during the first week, then for at least 4 weeks after treatment. Counsel patients to remain within proximity of the health care facility for at least 4 weeks following infusion and seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, immediately evaluate the patient for hospitalization and institute treatment with supportive care, tocilizumab, and/or corticosteroids as indicated.

Risk factors for severe CRS in the r/r ALL population are high pre-infusion tumor burden (>50% blasts in bone marrow), uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infections, and/or inflammatory processes. Risk factors for developing severe CRS in r/r DLBCL are unknown.

Neurological Toxicities: Neurological toxicities, including severe or life-threatening reactions, occurred in 49 (72%) of the 68 patients with r/r ALL and 62 (58%) of the 106 patients with r/r DLBCL following treatment with KYMRIAH, including ≥ grade 3 in 21% of patients with r/r ALL and 18% of patients with r/r DLBCL. Among patients who had a neurological toxicity, 88% occurred within 8 weeks following KYMRIAH infusion. Median time to the first event was 6 days from infusion (range: 1-359), and the median duration was 6 days for patients with r/r ALL and 14 days for patients with r/r DLBCL. Resolution occurred within 3 weeks in 79% of patients with r/r ALL and 61% of patients with r/r DLBCL. Encephalopathy lasting up to 50 days was noted. The onset of neurological toxicity can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

The most common neurological toxicities observed with KYMRIAH included headache (37% r/r ALL; 21% r/r DLBCL), encephalopathy (34% r/r ALL; 16% r/r DLBCL), delirium (21% r/r ALL; 6% r/r DLBCL), anxiety (13% r/r ALL; 9% r/r DLBCL), sleep disorders (10% r/r ALL; 9% r/r DLBCL), dizziness (6% r/r ALL; 11% r/r DLBCL), tremor (9% r/r ALL; 7% r/r DLBCL), and peripheral neuropathy (4% r/r ALL; 8% r/r DLBCL). Other manifestations included seizures, mutism, and aphasia.

Monitor patients for neurological events, specifically 2-3 times during the first week following KYMRIAH infusion, and exclude other causes for neurological symptoms. Provide supportive care as needed for KYMRIAH-associated neurological events.

KYMRIAH REMS to Mitigate CRS and Neurological Toxicities: Because of the risk of CRS and neurological toxicities, KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS. Further information is available at www.kymriah-rems.com or 1-844-4KYMRIAH (1-844-459-6742).

Hypersensitivity Reactions: Allergic reactions may occur with KYMRIAH. Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide or dextran 40 in KYMRIAH.

Serious Infections: Infections, including life-threatening or fatal infections, occurred in 95 (55%) of 174 patients with r/r ALL or with r/r DLBCL after KYMRIAH infusion. Fifty-eight patients (33%) experienced grade ≥3 infections, including fatal infections in 2 patients (3%) with r/r ALL and 1 patient (1%) with r/r DLBCL. Prior to KYMRIAH infusion, infection prophylaxis should follow local guidelines. Patients with active uncontrolled infection should not start KYMRIAH treatment until the infection is resolved. Monitor patients for signs and symptoms of infection after treatment with KYMRIAH and treat appropriately.

IMPORTANT SAFETY INFORMATION (continued)

Serious Infections (continued): Febrile neutropenia (≥ grade 3) was also observed in 37% of patients with r/r ALL and 17% of patients with r/r DLBCL after KYMRIAH infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before cell collection for manufacturing.

Prolonged Cytopenias: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and KYMRIAH infusion. In patients with r/r ALL, ≥ grade 3 cytopenias not resolved by Day 28 following KYMRIAH treatment included neutropenia (40%) and thrombocytopenia (27%) among 52 responding patients. At 56 days following KYMRIAH, 17% and 12% of responding patients had ≥ grade 3 neutropenia or thrombocytopenia respectively. In patients with r/r DLBCL, grade ≥3 cytopenias not resolved by Day 28 following KYMRIAH treatment included thrombocytopenia (40%) and neutropenia (25%) among 106 treated patients. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after KYMRIAH infusion or until CRS has resolved.

Hypogammaglobulinemia: Hypogammaglobulinemia and agammaglobulinemia (IgG) related to B-cell aplasia can occur in patients with a complete remission after KYMRIAH infusion. Hypogammaglobulinemia was reported in 43% of patients with r/r ALL and 14% of patients with r/r DLBCL. Monitor immunoglobulin levels after treatment with KYMRIAH and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement standard guidelines.

The safety of immunization with live viral vaccines during or following KYMRIAH treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during KYMRIAH treatment, and until immune recovery following treatment with KYMRIAH.

Pregnant women who have received KYMRIAH may have hypogammaglobulinemia. Assess immunoglobulin levels in newborns of mothers treated with KYMRIAH.

Secondary Malignancies: Patients treated with KYMRIAH may develop secondary malignancies or recurrence of their cancer. Monitor lifelong for secondary malignancies. If a secondary malignancy occurs, call 1-844-4KYMRIAH to obtain instructions on patient samples to collect for testing.

Effects on Ability to Drive and Use Machines: Due to the potential for neurological events, including altered mental status or seizures, patients receiving KYMRIAH are at risk for altered or decreased consciousness or coordination in the 8 weeks following infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

Drug Interactions

HIV and the lentivirus used to make KYMRIAH have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests (NATs) may yield false positive results in patients who have received KYMRIAH.

Pregnancy, Lactation, Females and Males of Reproductive Potential

No data are available of KYMRIAH use in pregnant or lactating women. Therefore, KYMRIAH is not recommended for women who are pregnant or breastfeeding. Pregnancy after KYMRIAH administration should be discussed with the treating physician. Pregnancy status of females of reproductive potential should be verified with a pregnancy test prior to starting treatment with KYMRIAH. Report pregnancies to Novartis Pharmaceuticals Corporation at 1-888-669-6682.

Adverse Reactions

The most common adverse reactions (>20%) reported in patients with r/r ALL were cytokine release syndrome, hypogammaglobulinemia, infections-pathogen unspecified, pyrexia, decreased appetite, headache, encephalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting, viral infectious disorders, hypoxia, fatigue, acute kidney injury, edema, cough, and delirium.

The most common adverse reactions (>20%) reported in patients with r/r DLBCL were cytokine release syndrome, infections-pathogen unspecified, pyrexia, diarrhea, nausea, fatigue, hypotension, edema, and headache.

Please see additional Important Safety Information and Brief Summary of Prescribing Information for KYMRIAH, including Boxed WARNING, on the following pages.

NOVARTIS

KYMRIAH® (tisagenlecleucel) Suspension for IV infusion

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Printed in USA 10/18 KYD-1198765

KYMRIAH™ (tisagenlecleucel) suspension for intravenous infusion
Initial U.S. Approval: 2017

BRIEF SUMMARY: Please see package insert for full prescribing information.

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids *[see Dosage and Administration (2.3, 2.4) in the full prescribing information, Warnings and Precautions (5.1)]*.**
- **Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed *[see Warnings and Precautions (5.2)]*.**
- **KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS *[see Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

1.1 Pediatric and Young Adult Relapsed or Refractory (r/r) B-cell Acute Lymphoblastic Leukemia (ALL)

Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

1.2 Adult Relapsed or Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL)

Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome (CRS)

CRS, including fatal or life-threatening reactions, occurred following treatment with KYMRIAH. CRS occurred in 54 (79%) of the 68 pediatric and young adult patients with r/r ALL and 78 (74%) of the 106 adult patients with r/r DLBCL receiving KYMRIAH, including ≥ Grade 3 (Penn grading system[1]) in 49% of patients with r/r ALL and in 23% of patients with r/r DLBCL. The median time to onset was 3 days (range: 1-51), and in only two patients was onset after Day 10. The median time to resolution of CRS was 8 days (range: 1-36).

Of the 54 patients with r/r ALL who had CRS, 27 (50%) received tocilizumab. Seven (13%) patients received two doses of tocilizumab, 3 (6%) patients received three doses of tocilizumab, and 14 (26%) patients received addition of corticosteroids (e.g., methylprednisolone). Of the 78 patients with r/r DLBCL who had CRS, 16 (21%) received systemic tocilizumab or corticosteroids. Six (8%) patients received a single dose of tocilizumab, 10 (13%) patients received two doses of tocilizumab, and 10 (13%) patients received corticosteroids in addition to tocilizumab. Two patients with r/r DLBCL received corticosteroids for CRS without concomitant tocilizumab, and two patients received corticosteroids for persistent neurotoxicity after resolution of CRS.

Five deaths occurred within 30 days of KYMRIAH infusion. One patient with r/r ALL died with CRS and progressive leukemia, and one patient had resolving CRS with abdominal compartment syndrome, coagulopathy, and renal failure when an intracranial hemorrhage occurred. Of the 3 r/r DLBCL patients who died within 30 days of infusion, all had CRS in the setting of stable to progressive underlying disease, one of whom developed bowel necrosis. Among patients with CRS, key manifestations include fever (92% in r/r ALL and r/r DLBCL), hypotension (67% in r/r ALL; 47% in r/r DLBCL), hypoxia (20% in r/r ALL; 35% in r/r DLBCL) and tachycardia (30% in r/r ALL; 14% in r/r DLBCL). CRS may be associated with hepatic, renal, and cardiac dysfunction, and coagulopathy.

Delay the infusion of KYMRIAH after lymphodepleting chemotherapy if the patient has unresolved serious adverse reactions from preceding chemotherapies (including pulmonary toxicity, cardiac toxicity, or hypotension), active uncontrolled infection, active graft versus host disease (GVHD), or worsening of leukemia burden *[see Dosage and Administration (2.3) in the full prescribing information]*.

Ensure that two doses of tocilizumab are available on site prior to infusion of KYMRIAH. Monitor patients for signs or symptoms of CRS for at least 4 weeks after treatment with KYMRIAH. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time *[see Patient Counseling Information (17) in the full prescribing information]*. At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab and/or corticosteroids as indicated *[see Dosage and Administration (2.3, 2.4) in the full prescribing information]*.

Risk factors for severe CRS in the pediatric and young adult r/r B-cell ALL population are high pre-infusion tumor burden (greater than 50% blasts in bone marrow), uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infections, and/or inflammatory processes. Risk factors for developing severe CRS in adult r/r DLBCL are not known.

5.2 Neurological Toxicities

Neurological toxicities including severe or life-threatening reactions, occurred in 49 (72%) of the 68 patients with r/r ALL and 62 (58%) of the 106 patients with r/r DLBCL following treatment with KYMRIAH, including ≥ Grade 3 in 21% of patients with r/r ALL and 18% of patients with r/r DLBCL. Among patients who had a neurological toxicity, 88% occurred within 8 weeks following KYMRIAH infusion.

Median time to the first event was 6 days from infusion (range: 1-359), and the median duration was 6 days for patients with r/r ALL and 14 days for patients with r/r DLBCL. Resolution occurred within 3 weeks in 79% of patients with r/r ALL and 61% of patients with r/r DLBCL. Encephalopathy lasting up to 50 days was noted.

The onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS.

The most common neurological toxicities observed with KYMRIAH include headache (37% in r/r ALL; 21% in r/r DLBCL), encephalopathy (34% in r/r ALL; 16% in r/r DLBCL), delirium (21% in r/r ALL; 6% in r/r DLBCL), anxiety (13% in r/r ALL; 9% in r/r DLBCL), sleep disorders (10% in r/r ALL; 9% in r/r DLBCL), dizziness (6% in r/r ALL; 11% in r/r DLBCL), tremor (9% in r/r ALL; 7% r/r DLBCL) and peripheral neuropathy (4% in r/r ALL; 8% in r/r DLBCL). Other manifestations included seizures, mutism and aphasia.

Monitor patients for neurological events and exclude other causes for neurological symptoms. Provide supportive care as needed for KYMRIAH-associated neurological events.

5.3 KYMRIAH REMS to Mitigate Cytokine Release Syndrome and Neurological Toxicities

Because of the risk of CRS and neurological toxicities, KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS *[see Boxed Warning, Warnings and Precautions (5.1, 5.2)]*. The required components of the KYMRIAH REMS are:

- Healthcare facilities that dispense and administer KYMRIAH must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for administration within 2 hours after KYMRIAH infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer KYMRIAH are trained about the management of CRS and neurological toxicities.

Further information is available at www.kymriah-rems.com or 1-844-4KYMRIAH.

5.4 Hypersensitivity Reactions

Allergic reactions may occur with infusion of KYMRIAH. Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) or dextran 40 in KYMRIAH.

5.5 Serious Infections

Infections, including life-threatening or fatal infections, occurred in 95 (55%) of 174 patients with r/r ALL or r/r DLBCL after KYMRIAH infusion. Fifty eight patients (33%) experienced Grade ≥ 3 infections, including fatal infections in 2 patients (3%) with r/r ALL and 1 patient (1%) with r/r DLBCL. Prior to KYMRIAH infusion, infection prophylaxis should follow local guidelines. Patients with active uncontrolled infection should not start KYMRIAH treatment until the infection is resolved. Monitor patients for signs and symptoms of infection after treatment with KYMRIAH and treat appropriately *[see Dosage and Administration (2.3) in the full prescribing information]*.

Febrile neutropenia (≥ Grade 3) was also observed in 37% of patients with r/r ALL and 17% of patients with r/r DLBCL after KYMRIAH infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated.

Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells.

Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

5.6 Prolonged Cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and KYMRIAH infusion.

In the ELIANA study (Study 1), ≥ Grade 3 cytopenias not resolved by Day 28 following KYMRIAH treatment included neutropenia (40%), and thrombocytopenia (27%) among 52 responding patients. At 56 days following KYMRIAH, 17% and 12% of responding patients had ≥ Grade 3 neutropenia or thrombocytopenia respectively.

In the JULIET study (Study 2), ≥ Grade 3 cytopenias not resolved by Day 28 following KYMRIAH treatment included thrombocytopenia (40%) and neutropenia (25%) among 106 treated patients.

Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after KYMRIAH infusion or until CRS has resolved.

5.7 Hypogammaglobulinemia

Hypogammaglobulinemia and agammaglobulinemia (IgG) related to B-cell aplasia can occur in patients with a complete remission (CR) after KYMRIAH infusion.

Hypogammaglobulinemia was reported in 43% of patients treated with KYMRIAH for r/r ALL and 14% of patients with r/r DLBCL *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Monitor immunoglobulin levels after treatment with KYMRIAH and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement standard guidelines.

Immunization with Live Vaccine

The safety of immunization with live viral vaccines during or following KYMRIAH treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during KYMRIAH treatment, and until immune recovery following treatment with KYMRIAH.

Pregnant women who have received KYMRIAH may have hypogammaglobulinemia. Assess immunoglobulin levels in newborns of mothers treated with KYMRIAH.

5.8 Secondary Malignancies

Patients treated with KYMRIAH may develop secondary malignancies or recurrence of their cancer. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Novartis Pharmaceuticals Corporation at 1-844-4KYMRIAH to obtain instructions on patient samples to collect for testing.

5.9 Effects on Ability to Drive and Use Machines

Due to the potential for neurological events, including altered mental status or seizures, patients receiving KYMRIAH are at risk for altered or decreased consciousness or coordination in the 8 weeks following KYMRIAH infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Cytokine Release Syndrome *[see Warnings and Precautions (5.1)]*
- Neurological Toxicities *[see Warnings and Precautions (5.2)]*
- Infections and Febrile Neutropenia *[see Warnings and Precautions (5.5)]*
- Prolonged Cytopenias *[see Warnings and Precautions (5.6)]*
- Hypogammaglobulinemia *[see Warnings and Precautions (5.7)]*

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 safety data described in the WARNINGS AND PRECAUTIONS and in this section reflect exposure to KYMRIAH in two non-randomized, single-arm studies in which 68 pediatric and young adult patients with relapsed/refractory (r/r) B-cell ALL (ELIANA Study) and 106 adults with r/r diffuse large B-cell lymphoma (JULIET Study) received a single dose of CAR-positive viable T cells.

Pediatric and Young Adult r/r B-cell Acute Lymphoblastic Leukemia (ALL) (up to 25 years of age)
Based on a recommended dose which was weight-based, all 68 patients in the ELIANA study (Study 1) received a single intravenous dose of KYMRIAH *[see Clinical Studies (14.1) in the full prescribing information]*. The most common adverse reactions (> 20%) were cytokine release syndrome (79%), hypogammaglobulinemia (43%), infections-pathogen unspecified (41%), pyrexia (40%), decreased appetite (37%), headache (37%), encephalopathy (34%), hypotension (31%), bleeding episodes (31%), tachycardia (26%), nausea (26%), diarrhea (26%), vomiting (26%), viral infectious disorders (26%), hypoxia (24%), fatigue (25%), acute kidney injury (24%), edema (21%), cough (21%), and delirium (21%).

The adverse reactions with greater or equal to 10% incidence for any Grade are summarized in Table 2.

Table 2. Selected Adverse Reactions Anytime After Infusion (≥ 10%) Following Treatment with KYMRIAH in Pediatric and Young Adult r/r B-cell ALL (N = 68)

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
Blood and lymphatic system disorders		
Febrile Neutropenia	37	37
Cardiac disorders		
[a]Tachycardia	26	4
Gastrointestinal disorders		
Nausea	26	3
Diarrhea	26	1
Vomiting	26	1
Constipation	18	0
[b]Abdominal pain	16	3
General disorders and administration site conditions		
Pyrexia	40	15
[c]Fatigue	25	0
[d]Edema	21	1
Chills	10	0
[e]Pain	18	3
Immune system disorders		
Cytokine release syndrome	79	49
[f]Hypogammaglobulinemia	43	7
Infections and infestations		
Infections-pathogen unspecified	41	16
Viral infectious disorders	26	18
Bacterial infectious disorders	19	13
Fungal infectious disorders	13	7
Investigations		
International normalized ratio increased	13	0
Metabolism and nutrition disorders		
Decreased appetite	37	15
Fluid overload	10	7
Musculoskeletal and connective tissue disorders		
Myalgia	15	0
Arthralgia	12	1
Back pain	10	3
Nervous system disorders		
[g]Headache	37	3
[h]Encephalopathy	34	10
Psychiatric disorders		
[i]Delirium	21	4
Anxiety	13	3
[j]Sleep disorders	10	0
Renal and urinary disorders		
[k]Acute kidney injury	24	15
Respiratory, thoracic and mediastinal disorders		
Hypoxia	24	18
[l]Cough	21	0
[m]Dyspnea	16	12
Pulmonary edema	16	10
Tachypnea	12	6
Pleural effusion	10	4
Nasal congestion	10	0
Skin and subcutaneous tissue disorders		
[n]Rash	16	1
Vascular disorders		
Hypotension	31	22
Hypertension	19	6

[a]*Tachycardia includes tachycardia and sinus tachycardia.*
[b]*Abdominal pain includes abdominal pain, abdominal pain upper.*
[c]*Fatigue includes fatigue and malaise.*
[d]*Edema includes face edema, generalised edema, localised edema, edema peripheral.*
[e]*Pain includes pain and pain in the extremity.*
[f]*Hypogammaglobulinemia includes hypogammaglobulinemia, immunoglobulins decreased, blood immunoglobulin G decreased, blood immunoglobulin A decreased, blood immunoglobulin M decreased.*
[g]*Headache includes headache and migraine.*
[h]*Encephalopathy includes encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, somnolence, and automatism.*
[i]*Delirium includes delirium, agitation, hallucination, hallucination visual, irritability, restlessness.*
[j]*Sleep disorders includes sleep disorder, insomnia and nightmare.*
[k]*Acute kidney injury includes acute kidney injury, anuria, azotemia, renal failure, renal tubular dysfunction, renal tubular necrosis, and blood creatinine increased.*
[l]*Cough includes cough and productive cough.*
[m]*Dyspnea includes dyspnea and respiratory distress, respiratory failure.*
[n]*Rash includes rash, rash maculo-papular, rash papular, and rash pruritic.*

Additional important adverse reactions that did not meet the threshold criteria for inclusion in Table 2 were:
Blood and lymphatic system disorders: disseminated intravascular coagulation (9%), histiocytosis lymphocytic hemophagocytosis (7%), coagulopathy (6%), Grade 3 and Grade 4 hypofibrinogenemia with Grade 3 and 4 CRS (16%)
Cardiac Disorders: cardiac arrest (4%), cardiac failure (7%)
Gastrointestinal disorders: abdominal compartment syndrome (1%)
General disorders and administration site conditions: multiple organ dysfunction syndrome (3%)
Immune system disorders: graft versus host disease (1%)
Investigations: activated partial thromboplastin time prolonged (6%)
Nervous System: tremor (9%), dizziness (6%), seizure (3%), speech disorder[a] (3%), motor dysfunction[b] (1%)
Respiratory, thoracic, and mediastinal disorders: respiratory distress (6%), respiratory failure (6%), acute respiratory distress syndrome (4%), oropharyngeal pain (6%)
Metabolism and nutrition disorders: tumor lysis syndrome (6%)
Vascular disorders: capillary leak syndrome (3%), thrombosis (3%)
Eye disorders: Visual impairment (3%)

[a]*Speech disorder includes aphasia and dysarthria.*
[b]*Motor dysfunction includes muscle spasms.*

Laboratory Abnormalities

Selected laboratory abnormalities worsening from baseline Grade 0-2 to Grade 3-4 are shown in Table 3.

Table 3. Selected Other Laboratory Abnormalities Worsening (> 10%) from Baseline Grade 0-2 to Grade 3-4 Following Treatment with KYMRIAH in Pediatric and Young Adult r/r B-cell ALL based on CTCAE[a] (N = 68)

Laboratory Abnormality	Grade 3 or 4 (%)
Increased Aspartate Aminotransferase	28
Hypokalemia	27
Increased Alanine Aminotransferase	21
Increased bilirubin	21
Hypophosphatemia	19

[a]CTCAE = Common Terminology Criteria for Adverse Events version 4.03

All patients experienced neutropenia, anemia and thrombocytopenia. See Table 4 for the incidences of ≥ Grade 3 prolonged thrombocytopenia and prolonged neutropenia in responding patients.

Table 4. Prolonged Cytopenias Following Treatment with KYMRIAH in Pediatric and Young Adult r/r B-cell ALL

Prolonged Cytopenia	N = 52 (%)	N = 52 (%)
	Day 28	Day 56
Prolonged neutropenia[a]	40	17
Prolonged thrombocytopenia[a]	27	12

[a] ≥ Grade 3 observed within 14 days after Day 28 or Day 56 in responding patients

Adult r/r Diffuse Large B-cell Lymphoma (DLBCL)
In the JULIET study (Study 2) 106 adults with r/r DLBCL received a single intravenous dose of KYMRIAH *[see Clinical Studies (14.2) in the full prescribing information]*. The most common adverse reactions (incidence > 20%) were cytokine release syndrome, infections-pathogen unspecified, diarrhea, nausea, pyrexia, fatigue, hypotension, edema and headache.

The study population characteristics were: median age of 56 years (range: 22 to 76 years), 79% DLBCL; a median of 3 prior lines of therapy (range: 1-6), 49% had a prior autologous hematopoietic stem cell transplantation, and 33% had received prior radiation therapy. Ninety-nine patients (93%) received lymphodepleting chemotherapy prior to KYMRIAH, that included fludarabine (n = 77) or bendamustine (n = 22).

The adverse reactions with greater than or equal to 10% incidence for any Grade are summarized in Table 5 below.

Table 5. Selected Adverse Reactions Anytime After Infusion Reported in ≥ 10% Following Treatment with KYMRIAH in Adult r/r DLBCL (N = 106)

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
Blood and lymphatic system disorders		
Febrile Neutropenia	17	17
Cardiac disorders		
[a]Tachycardia	13	3
Gastrointestinal disorders		
Diarrhea	31	1
Nausea	27	1
Constipation	16	1
General disorders and administration site conditions		
Pyrexia	34	6
[b]Fatigue	26	7
[c]Edema	23	2
[d]Pain	15	3
Chills	13	0
Immune system disorders		
Cytokine release syndrome	74	23
[e]Hypogammaglobulinemia	14	4

(continued)

Table 5. Selected Adverse Reactions Anytime After Infusion Reported in ≥ 10% Following Treatment with KYMRIAH in Adult r/r DLBCL (N = 106)

Adverse Reaction	All Grades (%)	Grades 3 or Higher (%)
Infections and infestations		
Infections-pathogen unspecified	42	25
Investigations		
Weight decreased	11	3
Metabolism and nutrition disorders		
Decreased appetite	12	4
Musculoskeletal and connective tissue disorders		
Arthralgia	10	0
Nervous system disorders		
[f]Headache	21	0
[g]Encephalopathy	16	11
[h]Dizziness	11	1
Renal and Urinary Disorders		
[i]Acute kidney injury	17	6
Respiratory, thoracic and mediastinal disorders		
[j]Cough	19	0
[k]Dyspnea	18	6
Vascular disorders		
[l]Hypotension	26	8

[a]*Tachycardia includes tachycardia and sinus tachycardia.*
[b]*Fatigue includes fatigue and malaise.*
[c]*Edema includes face edema, generalised edema, localized edema, edema peripheral, peripheral swelling.*
[d]*Pain includes pain and pain in the extremity.*
[e]*Hypogammaglobulinemia includes blood immunoglobulin G decreased, immunoglobulins decreased and hypogammaglobulinemia.*
[f]*Headache includes headache and migraine.*
[g]*Encephalopathy includes encephalopathy, cognitive disorder, confusional state, disturbance in attention, lethargy, mental status changes, somnolence, memory impairment, metabolic encephalopathy and thinking abnormal.*
[h]*Dizziness includes dizziness, presyncope, and syncope.*
[i]*Acute kidney injury includes acute kidney injury and blood creatinine increased.*
[j]*Cough includes cough, productive cough, and upper-airway cough syndrome.*
[k]*Dyspnea includes dyspnea, dyspnea exertional, respiratory distress, and respiratory failure.*
[l]*Hypotension includes hypotension and orthostatic hypotension.*

Additional important adverse reactions that did not meet the threshold criteria for inclusion in Table 5 were*:*

Blood and lymphatic system disorders: disseminated intravascular coagulation (3%), pancytopenia (2%), histiocytosis hematophagic (1%)

Cardiac Disorders: arrhythmia[a] (6%)

Gastrointestinal disorders: vomiting (9%), abdominal pain[b] (9%), anal incontinence (1%)

General disorders and administration site conditions: asthenia (7%), multiple organ dysfunction syndrome (3%)

Infections and infestations: fungal infectious disorders (9%), viral infectious disorders (9%), bacterial infectious disorders (9%)

Musculoskeletal and connective tissue disorders: myalgia (7%), back pain (6%)

Nervous System: peripheral neuropathy[c] (8%), motor dysfunction[d] (6%), speech disorder[e] (3%), seizure[f] (3%), ischemic cerebral infarction (1%), tremor (7%), ataxia (2%)

Psychiatric disorders: anxiety (9%), delirium[g] (6%), sleep disorders[h] (9%)

Respiratory, thoracic, and mediastinal disorders: hypoxia (8%), oropharyngeal pain[i] (8%), pleural effusion (5%) pulmonary edema[j] (3%)

Metabolism and nutrition disorders: fluid overload (3%), tumor lysis syndrome (1%)

Vascular disorders: thrombosis[k] (7%), hypertension (2%), capillary leak syndrome (1%)

Skin and subcutaneous tissue disorders: rash[l] (8%), dermatitis[m] (4%)

Eye disorders: visual impairment[n] (7%)

[a]*Arrhythmia includes atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles.*
[b]*Abdominal pain includes abdominal pain and abdominal pain upper.*
[c]*Peripheral Neuropathy includes paraethesia,hypoaesthesia, hyperaesthesia,peripheral sensory neuropathy, and neuropathy peripheral.*
[d]*Motor dysfunction includes muscle spasms, muscle twitching, myoclonus and myopathy.*
[e]*Speech disorder includes speech disorder, aphasia.*
[f]*Seizure includes PTs seizure and status epilepticus.*
[g]*Delirium includes delirium, agitation, and irritability.*
[h]*Sleep disorders includes sleep disorder, insomnia and nightmare.*
[i]*Oropharyngeal pain includes oral pain and oropharyngeal pain.*
[j]*Pulmonary edema includes acute pulmonary edema and pulmonary edema.*
[k]*Thrombosis includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis, and venous thrombosis.*
[l]*Rash includes rash, rash maculo-papular, rash papular and rash pruritic.*
[m]*Dermatitis includes dermatitis, dermatitis acneiform and dermatitis contact.*
[n]*Visual impairment includes vision blurred and visual impairment.*

Laboratory Abnormalities

Selected laboratory abnormalities worsening from baseline Grade 0-2 to Grade 3-4 are shown in Table 6.

Table 6. Grade 3 or 4 Laboratory Abnormalities occurring in > 10% of Patients Following KYMRIAH Infusion in Adult r/r DLBCL Patients Based on CTCAE[a] N = 106

Laboratory Parameter	Grade 3 or 4 (%)
Hematology	
Lymphopenia	94
Neutropenia	81
Leukopenia	77
Anemia	58
Thrombocytopenia	54
Biochemistry	
Hypophosphatemia	24
Hypokalemia	12
Hyponatremia	11

[a]CTCAE = Common Terminology Criteria for Adverse Events version 4.03

6.2 Immunogenicity

In clinical studies, humoral immunogenicity of KYMRIAH was measured by determination of anti-murine CAR19 antibodies (anti-mCAR19) in serum pre- and post-administration. The majority of patients, 86% in ELIANA (Study 1) and 91.4% in JULIET (Study 2) tested positive for pre-dose anti-mCAR19 antibodies prior to KYMRIAH infusion; Treatment induced anti-mCAR19 antibodies were detected in 5% of the patients in JULIET. However, the preexisting and treatment-induced antibodies were not associated with an impact on clinical response and did not have an impact on the initial expansion and persistence of KYMRIAH. Persistence of KYMRIAH was similar between patients with positive post-infusion anti-mCAR19 antibodies compared with patients with negative post-infusion anti-mCAR19 antibodies. There is no evidence that the presence of pre-existing and treatment-induced anti-mCAR19 antibodies impact the safety or effectiveness of KYMRIAH.

T cell immunogenicity responses were not observed in adult r/r DLBCL patients.

7 DRUG INTERACTIONS

HIV and the lentivirus used to make KYMRIAH have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid test (NATs) tests may yield false-positive results in patients who have received KYMRIAH.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with KYMRIAH use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with KYMRIAH to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if KYMRIAH has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, KYMRIAH is not recommended for women who are pregnant, and pregnancy after KYMRIAH administration should be discussed with the treating physician. Report pregnancies to Novartis Pharmaceuticals Corporation at 1-888-669-6682.

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.

8.2 Lactation

Risk Summary

There is no information regarding the presence of KYMRIAH in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KYMRIAH and any potential adverse effects on the breastfed infant from KYMRIAH or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with KYMRIAH.

Contraception

See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with KYMRIAH.

Infertility

There are no data on the effect of KYMRIAH on fertility.

8.4 Pediatric Use

The safety and efficacy of KYMRIAH have been established in pediatric patients with r/r B-cell ALL. Use of KYMRIAH is supported by a single-arm trial *[see Clinical Studies (14.1) in the full prescribing information]* that included 52 pediatric patients with r/r B-cell precursor ALL in the following age groups: 33 children (age 3 years to less than 12 years) and 19 adolescents (age 12 years to less than 17 years). No differences in efficacy or safety were observed between the different age subgroups or in comparison to the young adults in the trial.

The safety and efficacy of KYMRIAH in pediatric patients with relapsed or refractory DLBCL has not been established.

8.5 Geriatric Use

The safety and effectiveness of KYMRIAH have not been established in geriatric patients with r/r B-cell ALL. Clinical studies of KYMRIAH did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

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SPECIAL ISSUE / PCOC MEETING RECAP

FEBRUARY 2019
VOLUME 25 • ISSUE 3

Top: Panelists discuss the latest updates in oncology care. Bottom left: Joseph Alvarnas, MD, moderates a session during the meeting. Bottom right: Barbara McAneny, MD, delivers the keynote address.

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FROM THE CHAIRMAN

Keeping Patients and Providers on the Same Page

EACH YEAR, PATIENT-CENTERED ONCOLOGY CARE® (PCOC) meeting drills down on all we are learning about delivering the right care to the right patient at the right time. It is clear that we can do more than ever for patients; it is equally clear that the challenge of figuring out how to pay for it all vexes the brightest minds in healthcare. Oncologists are being pushed to the limit as they tire of documentation and forms and endless, contradictory directives from Medicare. Our keynote speaker, American Medical Association President Barbara L. McAneny, MD, described a new payment model, which shows that oncologists are willing to take on risk for the care elements they can control—if there is recognition that drug costs are beyond their control. Our meeting chair, *Evidence-Based Oncology*™ Editor-in-Chief Joseph Alvarnas, MD, summed it up when he said that the field had to find a way to take care of patients without keeping doctors awake until 11 PM every night.

One key is realizing that doctors need not make every decision. Patients can and should make key decisions about their own care, after being informed about the pros and cons—and costs—of their options. The rise of the patient navigator–who may or may not be a clinical provider, depending on the stage of care–is perhaps the most important development in cancer care over the past decade. Case management—which keeps the patient connected to social workers, nutritionists, pharmacists, and even a person who can provide a ride—connects the dots and can keep the patient from sliding into depression or landing in the emergency department. It can help ensure that patients and families get the chance to discuss what they want from treatment and, more important, what they don't want. As Lani Alison, MS-HCQ, RN, of Regional Cancer Care Associates, describes in this issue, getting some oncologists to let go of the "treat, treat, treat" mentality can be an uphill battle, but it can be done with the right mix of measurement and competition.

This quest to eliminate the outliers also means greater use of pathways, which push both academic centers and community physicians toward the latest developments in cancer care. At PCOC, we heard how alliances of community practices use pathways as they join together to reap economies of scale and challenge each other to bring patients the very best. This gives patients care that is close to home without sacrificing quality. It gives the patient and the provider what each wants: independence and the chance for the best outcome.

We hope you enjoy this special issue that captures the best from our seventh annual gathering of PCOC. As always, thank you for reading.

Until next year,
Mike Hennessy, Sr
CHAIRMAN AND CHIEF EXECUTIVE OFFICER

EDITORIAL MISSION

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

AGENDA

FRIDAY, NOVEMBER 16, 2018

8:00 AM - 8:30 AM	**REGISTRATION & BREAKFAST**
8:30 AM - 9:00 AM	**Welcome and Keynote Speaker** Joseph Alvarnas, MD Barbara L. McAneny, MD
9:00 AM - 9:40 AM	**Panel: Lessons Learned From OCM Data Reporting** Joseph Alvarnas, MD (moderator) Aaron Lyss, MBA Charles Saunders, MD Kashyap Patel, MD Rene Frick
9:40 AM - 10:20 AM	**Panel: Advancing Oncology Value-Based Payment Models** Joseph Alvarnas, MD (moderator) James Helstrom, MD, MBA Marcus Neubauer, MD Michael Ruiz de Somocurcio, MBA Samuel Young, MD, MBA, CPE
10:20 AM - 10:40 AM	**BREAK**
10:40 AM - 11:20 AM	**Presentation: Integration Across Oncology Setting for Quality Reporting–QCCA Case Study** Barry Russo
11:20 AM - 12:00 PM	**Panel: Innovation in Clinical Pathways Design and Implementation** Joseph Alvarnas, MD (moderator) Robert Daly, MD, MBA Edward S. Kim, MD Lawrence N. Shulman, MD Blaise N. Polite, MD, MPP, FASCO
12:00 PM - 1:00 PM	**Seema S. Sonnad Emerging Leader in Managed Care Research Award Luncheon**
1:00 PM - 1:30 PM	**Presentation: CAR-T and Gene Therapy Treatment and Management–A Provider and Patient Perspective** Brian Koffman, MDCM, DCFP, DABFM, MS Ed
1:30 PM - 2:10 PM	**Panel: Pharmacy Role in Patient Care Pathway and Management of Oral Therapies** Michael J. Reff, MBA, RPh, (moderator) Howard Cohen, MS, BSPharm, FASHP Neil Nebughr, RPh Eileen Peng, PharmD Allison Trawinski, PharmD, MBA
2:10 PM - 2:30 PM	**BREAK**
2:30 PM - 3:10 PM	**Panel: Advancing Care Management** Rose Gerber (moderator) Lani Alison, MS-HCQ, RN Wes Hall Beth Wittmer, RN, OCN
3:10 PM - 4:00 PM	**Panel: Future of Oncology Value-Based Care** Christian Downs, JD, MJHA Michael Kolodziej, MD, FACP Brian Loy, MD Barbara L. McAneny, MD
4:00 PM - 4:10 PM	**CLOSING REMARKS AND ADJOURNMENT**

FACULTY

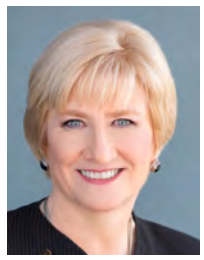
MEETING CHAIR

Joseph Alvarnas, MD

Director of Value-Based Analytics
Director of Clinical Quality, Alpha Clinic
Associate Professor, Department of Hematology and Hematopoietic Cell Transplantation
City of Hope
Duarte, California

Joseph Alvarnas, MD, attended medical school at the University of California, San Francisco. He completed internal medicine training and fellowships in hematology and hematopoietic cell transplantation at Stanford University Medical Center. He worked at the City of Hope–Banner Bone Marrow Transplant Program, which he helped found. Dr Alvarnas subsequently served as director of the Hematopoietic Stem Cell Processing Laboratory and chair of the Quality Committee for the transplant program. He is currently an associate clinical professor in the Department of Hematology and Hematopoietic Cell Transplantation at City of Hope, where he also serves as the institution's director of Value-Based Analytics. He is the national cochair for 2 Blood and Marrow Transplant Clinical Trials Network clinical trials studying stem cell transplantation in patients infected with HIV. Dr Alvarnas serves on the American Society of Hematology (ASH) Committee on Practice and as an ASH liaison to the Committee on Quality. He is editor-in-chief *of Evidence-Based Oncology*™, a publication of *The American Journal of Managed Care*®.

KEYNOTE



Barbara L. McAneny, MD

President of the American Medical Association
Chicago, Illinois
Barbara McAneny, MD, is a board-certified medical oncologist/hematologist from Albuquerque, New Mexico, and in June 2018 became the 173rd president of the American Medical Association (AMA). She has been a member of the association's board of trustees since June 2010, serving as chair in 2015–2016.

Barbara McAneny, MD, is a fellow and former member of the board of directors of the American Society of Clinical Oncology (ASCO) and a past president of the New Mexico Medical Society, the Greater Albuquerque Medical Association, and the New Mexico chapter of the American College of Physicians. She has served as a member of the Community Oncology Alliance Board of Trustees and on the board of directors of the Cancer Center Business Summit. In 2002, she was the delegate to the AMA from ASCO and was elected to the AMA Council on Medical Service in 2003, which she chaired in 2009-2010.

Dr McAneny also cofounded New Mexico Oncology Hematology Consultants Ltd in 1987. A managing partner since 1999, she built New Mexico Cancer Center as the state's first physician-owned multidisciplinary cancer center, which has clinics in Albuquerque and Gallup. She also founded the New Mexico Cancer Center Foundation, which provides grants to assist patients with nonmedical expenses.

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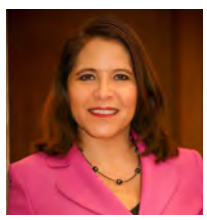

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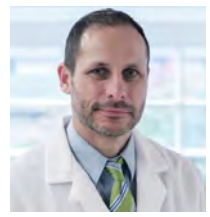

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From left: Michael Ruiz de Somocurcio, MBA; James Helstrom, MD, MBA; Marcus Neubauer, MD; and Samuel Young, MD, MBA, CPE, discuss advancing oncology care by utilizing clinical pathways.

Top: Barbara McAneny, MD, delivers the keynote address. Bottom: Joseph Alvarnas, MD, welcomes attendees.

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AMA's McAneny Calls for Real-time Oncology Payment Model Led by Physicians

Mary Caffrey

AMERICA'S HEALTHCARE SYSTEM COSTS too much, not just for patients who become ill but also for medical students who must pay for their own training and oncology practices trying to navigate payment models that ask them to take on risk associated with the eye-popping costs of cancer drugs.

The major alternative payment model (APM) put forth by Medicare, the Oncology Care Model (OCM),[1] doesn't tell practices how they are doing until after the fact. This puts practices at risk for things beyond their control, said Barbara McAneny, MD, a New Mexico oncologist/hematologist who is the current president of the American Medical Association (AMA).[2]

McAneny shared her diagnosis for the current crisis in US healthcare, as well as a prescription—a new real-time oncology payment model led by physicians—in her keynote address to attendees at Patient-Centered Oncology Care® (PCOC) 2018, the annual meeting presented by *The American Journal of Managed Care®*, which took place November 16, 2018, at Sofitel Philadelphia, in Pennsylvania.

Healthcare has reached a crisis point because payers are controlling the process and doctors are being driven away by administrative burdens and burnout, McAneny said. Medical education is extremely expensive, and young doctors enter professional life burdened with $200,000 or more in debt that limits their options. "We can't afford to train someone for 10 to 12 years and then drive them crazy so they quit," she said.

Yet, that's what's happening to so many physicians, and it's contributing to physician shortages. "It used to be we had to push doctors out the door at age 70," McAneny said. Now, too many get into their 50s and have had enough of the documentation burdens that today's electronic health systems demand. As PCOC Chairman Joseph Alvarnas, MD, of City of Hope, would ask later in the day, "How do we get to a future that isn't built on people working until midnight?"

McAneny became well known for developing the COME HOME model at her New Mexico practice,[3] which saved $2100 annually per patient by prioritizing triage protocols, clinical pathways, same-day appointments, and better patient education—all with the goal of keeping patients out of the emergency department and avoiding hospital stays. "We created savings through the things that the doctors can control," she said.

The OCM does much of this, but it adds features McAneny does not like. Although the model keeps people out of the hospital, it adds documentation that she finds burdensome.

"My [electronic medical record] is really good at managing patients one at a time," but it is not as good at population health, she said.

But the bigger challenge is the way the model handles drug costs. McAneny said Medicare "lowballs" these costs, and the Indian Health Service, which covers many of her patients, is even worse.

Oncologists are put in the position of taking on risk and becoming miniature insurers, when they don't have actuaries or reserves to predict who will come through the door, much less to absorb losses. As a result, more and more independent physician practices are being bought up by hospitals, which doubles the cost of care.

And who is making money? McAneny showed a slide that reported Anthem Blue Cross and Blue Shield reporting a record profit.[4]

"Everybody is familiar with these stories, with what's going on in oncology with the site-of-service differential," she said, referring to reimbursements for care at a hospital versus a community oncology clinic. "It has to change. This cannot go on."

Barbara McAneny, MD, president of the American Medical Association, told attendees that physicians need the ability to gain contol over healthcare costs.

If nothing changes, McAneny said, healthcare costs will crowd out everything else in the federal budget, and that will not be acceptable or sustainable. She pointed out incongruities in federal policy that will pay to amputate a foot for someone with diabetes but bankrupt a person who needed insulin that could have prevented that complication.

"What patients want is not healthcare, but health," she said.

The AMA is pushing for changes that give physicians more control over healthcare, from rethinking medical education to putting doctors at the center of healthcare delivery. To that end, McAneny noted that CMS' emphasis on the Medicare Shared Savings Program (MSSP), delivered through accountable care organizations, has never quite achieved what she managed to do with COME HOME.

Instead of $2100 in savings per patient, MSSP puts physicians through enormous expense and inconvenience to achieve $313.7 million in savings for CMS. "That's a lot if you won the lottery but not if you're running Medicare—$36 per patient is 1 office visit," McAneny said.

In cancer care, McAneny and a coalition of oncology practices, called the National Cancer Care Alliance, have stepped forward with a different APM called MASON (Making Accountable Sustainable Oncology Networks),[5] which seeks to create real-time quality measurement so that practices can respond to outliers and problems right away, not months or years after the fact.

The model "creates an accurate cost target that will be a valuable tool for optimizing patient management while avoiding actuarial risks of adverse patient clinical characteristics," the proposal states. "Practices will be at risk only for factors they can control, thereby avoiding damage to the oncology care delivery infrastructure across the country." The model will incorporate the multiple data points that bombard physicians today and allow for personalization based on patient characteristics.

At the time of PCOC, McAneny was preparing to present the model to the Physician-Focused Payment Model Technical Advisory Committee (PTAC), which is empowered to approve doctor-driven payment models. On December 11, 2018, PTAC approved MASON by a 7-0 vote.[6] But thus far, CMS has not approved any APMs that have been through PTAC.

If MASON succeeds, it will be a step toward letting physicians return to their core mission, McAneny said. "We need doctors and hospitals to take care of patients." ◆

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Keeping Ahead of the Curve in the Transition to Oncology Value-Based Payment

Christina Mattina

AT A SESSION OF Patient-Centered Oncology Care® panelists shared their views on the future of oncology value-based payment models and how they, as payers and providers, can help advance these models.

Moderator Joseph Alvarnas, MD, started the discussion by acknowledging how keynote speaker Barbara McAneny, MD, had laid out a framework of challenges in balancing value and sustainability with better outcomes and patient experience. He asked the panel about the definition of *value-based care*, which he called "part platitude, part wastebasket."

Although value-based care is "a hodgepodge of models," explained Samuel Young, MD, MBA, CPE, senior medical director, Medicare Florida Blue, its core intent is to improve patient health outcomes and quality of life for patients at lower cost. Marcus Neubauer, MD, chief medical officer, The US Oncology Network, agreed with that assessment and added that value-based care arose because the current fee-for-service system is unsustainably expensive. Neubauer sees CMS as the major catalyst for the conversion to the alternative of value-based care and said that The US Oncology Network supports being part of that transition.

Circling back to the meeting's theme, Michael Ruiz de Somocurcio, MBA, vice president, payer and provider collaboration at New Jersey–based Regional Cancer Care Associates, said that value must have the patient front and center because improving quality of care is not simply about checking a box. Fortunately, taking patient-centered steps like keeping patients out of the hospital has a ripple effect that improves care quality and lowers costs.

Complicating the matter is that the goal of improved outcome is defined differently for each patient, added James Helstrom, MD, MBA, chief medical officer, Fox Chase Cancer Center. Cancer type and stage will determine whether a patient is concerned with quality of life or is just trying to attain survival. Young agreed that there needs to be a condition-specific approach to measuring cost and quality.

Another issue, according to Young, is that incentives are misaligned from the patient, payer, and provider perspectives. Commercial plans have members who frequently change jobs and plans, meaning they may not reap long-term financial benefits after paying the up-front cost of a treatment, but they still want providers to act in the best interest of their patients.

Doing the right thing for patients is what actually led physicians in The US Oncology Network to become interested in value-based care before it became "trendy," said Neubauer. They recognize they have a responsibility to manage cost of care and are taking steps to do so, leading him to conclude that any efforts to change culture must be physician led.

Helstrom agreed about the importance of provider-led change, saying that edicts from administrators automatically engender resistance. He suggested that by keeping costs out of the discussion and simply encouraging administrators to do the right thing clinically, cost reductions would typically follow. Ruiz de Somocurcio added that value-based changes must also fit within physicians' workflow and should optimally be supported by hiring nurses, social workers, or patient navigators to alleviate physician burden.

Another "tremendous hurdle" to broader adoption of value-based care is full data exchange and transparency, said Young, which is hindered by the limitations of electronic health records. Having fully transparent 2-way data exchange will not only allow physicians to compare their cost and quality metrics with their colleagues', allowing their competitive natures to drive improvement, but also would enable consumers to choose their providers on objective performance measures instead of word of mouth.

A discussion about value in cancer care could not omit drug prices, as Alvarnas mentioned the expensive new treatments that are resulting in better outcomes but also skyrocketing costs. Neubauer explained the role of providers in controlling drug costs; although they cannot promise payers that they will not use checkpoint inhibitors, they can commit to using them responsibly and identifying patients who are not likely to benefit.

Ruiz de Somocurcio offered a different perspective, saying that a focus on other low-hanging fruits is more likely to yield savings than uncontrollable drug costs. His organization is looking into the use of new biosimilars but is also identifying cost-cutting methods like reducing emergency department visits, performing office-based imaging instead of hospital-based scans, and using pathways to reduce variation in care.

Bringing the conversation back to the theme of the meeting, Alvarnas asked how the panelists work toward including patient goals in the value equation. Neubauer explained that his system has implemented treatment plans to formally outline a road map before starting treatment so patients and care providers can refer to it.

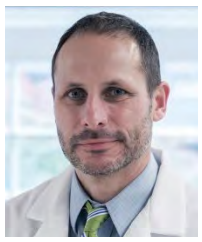
"In our transition to value-based care, I've seen patient experience improve," Neubauer attested.

From the payer perspective, Young explained that as a custodian of members' health data, his organization has launched data platforms that give patients a "virtual care community" that ties together patients' life plans with opinions from their family members, social workers, and other stakeholders, allowing the care provider to access all of that input and bring it into the care discussion.

"Ultimately, this falls on us to bring together all these information sources so that everyone can see what's best for the patient," he said.

When Alvarnas asked the panelists to provide their final thoughts, each of them agreed that the shift to value is not going away. Ruiz de Somocurcio emphasized that value is here to stay, giving the example of the mandatory radiation oncology bundles announced by HHS Secretary Alex Azar on November 8, 2018.[1] In terms of the larger shift toward value, Ruiz de Somocurcio said, "you don't want to be last in line when that happens, so it's time to do it now." ◆

ALVARNAS



HELSTROM

YOUNG

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Learning to Manage Data and Code for Comorbidities Is Critical for OCM Success

Laura Joszt

SAUNDERS

LYSS

FRICK

PATEL

DATA IS OF CRITICAL IMPORTANCE in the Oncology Care Model (OCM)—and CMS shares a lot of data with participating practices—but managing that data and using it to improve performance can be challenging, according to panelists at Patient-Centered Oncology Care®.

Typically, data can be difficult to access and integrate, explained Charles Saunders, MD, chief executive officer (CEO) of Integra Connect. He explained that some electronic health record (EHR) systems are better than others at giving up data, but most systems are not very good at all. Sometimes this is because EHR vendors are purposefully uncooperative and do not want to share information, but EHRs also were not built with data sharing in mind.

Saunders said that most practices do not have any experience in managing or understanding Medicare data, which is fairly high in quality. Aaron Lyss, MBA, director, value-based care, Tenessee Oncology, added that managing data is one of the areas in which his organization has probably made the most progress.

"The volume of claims data that we get through OCM is certainly at the outset daunting, like drinking from a firehose, but over time it's become an incredible asset to our organization," explained Lyss.

Seeing and managing the claims data has given Tenessee Oncology a better understanding of policy issues of payment models and given the practice more confidence in participating in these models, Lyss said.

René Frick, senior director, network innovations and partnerships, BlueCross BlueShield of South Carolina (BCBSSC), noted that her company has a lot of claims information but that the payer is trying to integrate with practices to get clinical data and view the full picture of care. Another challenge is that even when the payer provides practices with data they seek, those practices do not always know what to do with the information to improve care.

BCBSSC has 8 practices participating in OCM, including Carolina Blood and Cancer Care (CBCC), where Kashyap Patel, MD, is the CEO.

One of the things BCBSSC has found is that patients are going outside their regular practices to the emergency department (ED). According to Patel, CBCC has been focusing on reducing ED visits, hospitalizations, and number of days in the hospital. Frick added that these are areas BCBSSC is looking at with most of its practices, because they are aspects the practices can control. These were some of the low-hanging fruits that CBCC focused on, and now it is focused on indexing comorbidities.

Recording morbidities and Hierarchical Condition Category (HCC) codes is crucial for success in OCM, explained Saunders. CMS sets the practice target price based on a risk model that includes HCC coding, but oncologists tend to undercode patients. Integra's analysis found that in 27% of cases, oncologists were recording just 1 HCC code or comorbidity and that in 17% of cases, there were no HCC codes or comorbidities at all.

"That means in over 40% of the cases, it's either 0 or 1, and for a [patient with] lung cancer who's between the ages of 65 and 85, you know that's not realistic," Saunders said. "That means that their target price is set inappropriately low, so it's not surprising they can't achieve that target price."

Patel said that his practice created small laminated cards that list the common comorbidities and HCC codes, and each physician was given multiple cards to keep in their coat pocket, at their house, in their office, and anywhere else. But it remains a challenge, he admitted. Every week, physicians in the practice meet and improve but will then start to forget to record the comorbidities.

Doing a better job of coding is one of the many cultural changes required in OCM, the panelists agreed.

"I think the behavior change in physicians has been a challenge," Patel said. "I have to say my team is very well organized, very cooperative…but, including me, we have [been] programmed [and] we have to decondition ourselves and, really, recondition to look at this value-based care."

At Tenessee Oncology, the practices show the physicians how they are all performing so there is transparency in the organization. For physicians who want to improve their performance, one-on-one meetings are available, Lyss explained.

"It's kind of old-fashioned, but I think it's worked well," Lyss said.

Although Saunders acknowledged the cultural transformation that the practices represented on the panel had undergone, he noted that such transformation has been variable across the country. He outlined the difference between 1 practice with more than 200 oncologists that had been able to invest in infrastructure to achieve success and compared it with a smaller practice that did not have that capability and was so busy taking care of patients that the physicians could not become experts in Medicare or the model.

However, he also highlighted the differences Integra has seen between community-based and health system–based practices.

"Surprisingly, or maybe not surprisingly, the community-based ones are doing a better job of controlling the costs than the hospital-based ones," Saunders said. "And we see ones [in which] there is a big difference between those that use organized care pathways [and] ones that don't."

The panelists concluded by discussing what is next in the OCM, which is scheduled to eventually shift to 2-sided risk. Originally, the model called for 20% downside risk, which is the stop-loss limit, but CMS recently brought the risk down to 8%. Although that is better for practices, Lyss said it was the difference between "completely absurd to 50% as absurd but still absurd."

That said, Tenessee Oncology has been meeting frequently since CMS announced the change, and the practice believes that the economics of the new arrangement look better not just for Tenessee Oncology but for many of the practices. The organization has figured out that if it just matches its current performance, it will stand to do better in the 2-sided risk arrangement.

However, for many practices, the stop-loss adjustment is not enough, Saunders acknowledged.

"It's still a level where if you really think your practice is going to get anywhere near that stop-loss, you're not going to do that 2-sided risk arrangement," he concluded. "It's just a nonstarter." ◆

Lessons From a Texas Oncology Practice Within an Integrated Network

Mary Caffrey

IN THE ERA OF value-based care, community oncology practices are challenged to develop the infrastructure for quality reporting practices. How can practices do this and stay independent?

For 19 oncology practices across 17 states, the solution comes from being part of a clinically integrated network (CIN). The Quality Cancer Care Alliance (QCCA), which began with conversations in 2014, formally became a CIN in February 2018.[1]

At Patient-Centered Oncology Care®, the chief executive officer of a QCCA member practice, Barry Russo of the Center for Cancer and Blood Disorders in North Texas, described how this geographically diverse group of practices had come together around a common set of values, recognizing the need to work together to achieve the scale needed for CMS quality reporting programs.

The idea of a "super group," Russo explained, would allow these practices to join forces for benchmarking, to share best practices, and to be served by committees covering education, data sharing, purchasing, research, quality, and value-based care.

"Each member is at a different phase of maturity in quality reporting," he said, which presents challenges but is also part of the point—for community oncology practices to survive, they must learn from others.

When members of the super group pull together data from across the network, "they are working to have the kind of data they need, and the business intelligence to foster a value-based environment," said Russo.

One thing the QCCA collectively does is unravel contracts with electronic health record vendors that make it difficult or impossible for practices to get back their own data in a usable way for quality reporting purposes. "How do you not have access to your own clinical data? Believe it or not, there is a lot of this out there," Russo said.

The QCCA also helps practices get both clinical data and claims data, which can inform a practice about a few different things. "In our practice, we noticed that patients with COPD [chronic obstructive pulmonary disease] had a lot of hospitalizations," said Russo. In following up on these patients through the claims data, Russo and his colleagues realized "many of these people weren't being seen by a pulmonologist."

So, if these patients had breathing problems, "they just went to the emergency department [ED]."

Once the practice identified the 35% of their patients with COPD who were not seeing a pulmonologist, they made an effort to make referrals. The practice did the same for patients with congestive heart failure—the oncologists referred these patients to a cardiologist. "We wouldn't have that information without the claims data," Russo said.

FROM EARLY LESSONS, TO A LEGAL FRAMEWORK

Russo said most practices have had little or no experience with value-based care. "We needed to do a lot of education on what that meant," he said. Launching quality reporting initiatives can be "time-consuming and costly, especially if the practice hasn't invested in that at all."

In some cases, technical hurdles were the challenge, but in others, there were emotional decisions, such as moving the entire network to a single group purchasing organization to save money on drugs. "These were emotional decisions at the grassroots levels of the practice, and the hurdles are often huge," he said.

It became clear that that the legal structure of the CIN was essential. And that meant agreeing to defined initiatives: clinical pathways, triage pathways, data integration, research, analytics, quality benchmarks, and value-based programs such as risk assessment and member match, the latter being a tool to account for members who are in the ED or the hospital.

For Russo's Center for Cancer and Blood Disorders, using clinical pathways was not much of a leap, as the practice had implemented pathways 13 years ago. "In today's world, it surprises me that there are practices that have not implemented pathways," he said.

A key step, however, was moving triage out of the chemotherapy area and putting it in administration. The practice had to create incentives to keep patients out of the ED so that triage became a quality indicator and did not consist simply of answering the phone.

DATA INTEGRATION AND PILOTS

So, what is the CIN accomplishing? Russo outlined several milestones:

- Most members use a common set of **triage pathways**; the rest have scheduled implementation.
- **Clinical pathway** compliance is mandatory across the CIN, as this is a key quality indicator.
- Today, 90% of the member practices contribute to **data integration** for benchmarking and enrollment in future clinical trials. This has allowed talks with a manufacturer for a value-based contract for a specific drug.
- **Pilot programs** are under way for an artificial intelligence risk assessment tool that will include special pricing for members of the CIN. Practices that are in the CIN and also enrolled in the Oncology Care Model (OCM) through CMS are taking part in a Member Match pilot that identifies attributed patients who show up in the ED.

The risk assessment tool builds predictive models, including information that may seem to have little to do with a patient's medical history—such as tax data—but is proving to be 100% correct in predicting which patients will be readmitted and highly predictive (89%) on which ones will be diagnosed with depression.The QCCA is still evaluating vendors for analytic and actuarial support, to offer the predictive tools needed for practices to take on risk, Russo said.


RUSSO

He spoke of the need to deal directly with employers, who are increasingly cost-conscious. "Seventy percent of the market is self-funded," he said. "Many of them have purchased second opinion programs specifically related to cancer … but many programs have low utilization." Once patients enter a facility certified by the National Cancer Institute, where costs are higher, "they never leave." Employers are asking if there are ways through value-based care "where the cost structure may be a little more reasonable," noted Russo. Through the CIN, the practices of QCCA get the volume of data across a large geographic landscape and the support of established vendors for analytic support, the ability to take on 2-sided risk in the OCM, and perhaps the ability to join with another CIN while publishing meaningful data.

He said the CIN offers his practice the chance to stay independent while still "getting bigger" from the standpoint of having services at scale. Sharing information means knowing right away when new drugs come out, what a payer's policy is, or how a patient's genomic fingerprint affects what kind of therapy they should have. The physician can have this information immediately.

The bottom line, Russo said, is that "all this stuff has to happen at the point of care." ◆

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Using Clinical Pathways to Improve Quality of Care, Prepare for Value-Based Future

Jaime Rosenberg

DALY

SHULMAN

KIM

POLITE

DURING A SESSION AT Patient-Centered Oncology Care® panelists drew on their own experiences of utilization and innovation of clinical pathways and pushed back against criticisms about the systems.

Clinical pathways are not "cookie-cutter medicine," said Robert Daly, MD, MBA, medical oncologist, Memorial Sloan Kettering Cancer Center, who explained that the idea behind pathways is not that they will cover all patients, but that they will be able to guide decision making for most of them. Daly added that many pathway vendors have different levels within the pathway that account for nuances and comorbidities, and this allows physicians to make alterations to the treatment plan.

"I don't really see it as cookie-cutter medicine; I see it more as advancing quality of care by better understanding what is the best treatment for those patients at that particular point in time and understanding that not all patients will be able to go along those pathways," he said.

According to Lawrence N. Shulman, MD, deputy director, clinical services, Abramson Cancer Center, University of Pennsylvania, clinical pathways have also been criticized as another unfunded mandate that creates more work for overburdened faculty. But, he said, the faculty at the University of Pennsylvania Health System have embraced their clinical pathways, which members of the hospital system created themselves.

With the belief that the main goal of the clinical pathways process is to change the culture of healthcare delivery, the hospital system brought faculty members together to dig in to why they treat certain diseases the way they do. The faculty also reviewed recent literature.

Similarly, Levine Cancer Institute, part of Carolinas HealthCare System, also developed its own pathway system with input from the faculty. Meeting once a month, the faculty update the pathways and determine which practices are preferred and which are acceptable based on the parameters of the patient, explained Edward S. Kim, MD, chair, solid tumor oncology, Levine Cancer Institute.

Edward S. Kim, MD, of Levine Cancer Institute, second from left, makes a point during the panel discussion.

An important aspect of the pathway system is that it's nimble, Kim said. This allows for new drug and treatment information to be added quickly and seamlessly. He used the example of when there was a shortage of the chemotherapy etoposide. The faculty were able to quickly remove the drug from the pathway system so that a physician didn't order it and then find out it was not available.

The University of Chicago Medicine uses Via Oncology's commercial system, an acquired third-party vendor-implemented system, which lets physicians dip a toe into the water of pathways while also allowing for some customization, said Blase N. Polite, MD, MPP, associate director, Center for Clinical Cancer Genetics, assistant professor of medicine, University of Chicago.

All panelists agreed that the pathway systems brought attention to the heterogeneity of care happening among doctors and allowed for collaboration and consensus going forward. "I think what we've emphasized is, with growing networks, it's unconscionable for us to put the University of Chicago brand in place in a suburb of Chicago, and then people come there and don't get the same care" as in the city, said Polite. "It's also a way of protecting and customizing your brand."

Both Shulman and Kim pointed to their pathway systems as being empowerment tools for their healthcare system, particularly for physicians at community cancer centers. "At most of the community hospitals, our oncologists are general oncologists, and it's hard for them to keep up in all the different diseases of the patients they treat, so the pathways have really been invaluable," said Shulman.

The clinical pathways systems also allow community practices to offer precision medicine, said Kim. Within the Levine Cancer Institute's clinical pathway system, there is an approved genomic test for solid tumors that allows any physician in the healthcare system to order the test.

In response to a question asking how to change physician culture from "all of us do this differently" to adherence to the pathways, Daly said that in an institution, it is essential to identify who the thought leaders are and get their buy-in. Once the leaders start using the pathway to improve care, it will disseminate, he said. If you rush the implementation without the buy-in, he warned, you risk the stability of the project.

Switching gears to alternative payment models (APMs), the panelists agreed that clinical pathways have the potential to prepare healthcare systems for a risk-bearing future.

"I'm a big fan of the value-based pathway concept," said Polite. "Where pathways are right now, I think they're in their infancy. But I do believe that they have the potential to be our answer to the drug utilization issue for all the APMs we've been discussing, because once you start incorporating value into it, you're seeing that this is going to be the number-1 thing on the pathway because of what it does in terms of the total cost of care, efficacy, and toxicity, and you start driving decisions that way."

He added that if CMS' Center for Medicare & Medicaid Innovation wants healthcare systems to take on 2-sided risk, drugs need to be taken out of the model, and if drugs are taken out of the model, there needs to be an alternative: holding physicians accountable for utilization with pathways. ◆

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Pharmacists Address Ways to Monitor Patients, Redue Waste Through Medically Integrated Pharmacy Model

Christina Mattina

REFF

TRAWINSKI

NEBUGHR

PENG

COHEN

PHARMACISTS REPRESENTING DIVERSE HEALTH systems discussed their role in the transition to a medically integrated pharmacy model for oral cancer therapies at a session of Patient-Centered Oncology Care® 2018.

Moderator Michael J. Reff, MBA, RPh, executive director and founder, National Community Oncology Dispensing Association, began by noting the geographical and system-level diversity the 4 panelists represented. He asked each person to discuss examples of progress and benefits of the medically integrated pharmacy model within their health systems, focusing on management of oral therapies for cancer.

Allison Trawinski, PharmD, MBA, specialty pharmacy manager and PGY1 community residency director, University of Rochester (UR) Medical Center, explained that integrating 6 clinical pharmacists integrated the clinic leads to more personalized services. Each patient has 1 dedicated pharmacist and 1 dedicated pharmacy technician, so patients know exactly who to go to when they need help.

For Neil Nebughr, RPh, previously at Utah Cancer Specialists, now associate director, Market Acces and Strategic Accounts at Sanofi, marker of success is simple: getting patients their medications. The practice sees 50% to 60% of the cases at its 9 locations, making it Utah's largest independent oncology practice. It has worked with regional payers to help accomplish the goal of patient access.

Eileen Peng, PharmD, pharmacy manager and director, pharmacy services at Regional Cancer Care Associates, described how the community-based oncology organization created a collaborative pharmacy team to work with care providers, triage nurses, and patients to ensure safe, effective treatment.

According to Howard Cohen, MS, BSPharm, FASHP, director, oncology pharmacy, Smilow Cancer Hospital at Yale New Haven Health, the transition to a medically integrated pharmacy model came about when the academic health center realized it needed to better support its patients after discharge and throughout the entire care continuum.

"We're dealing with hazardous medications," Cohen said, referring to oral oncology therapies, "so we have to provide the same level of vigilance for those patients even though they're transitioning from care to the home."

When Reff asked about efforts to "go beyond the first fill" by extending continuity of care via a medically integrated pharmacy model, most of the panelists mentioned that the model helped them review each order and monitor each patient. Eventually, the pharmacists focused on following pathways based on clinical circumstances, not just filling prescriptions for the sake of filling them. They also described how medical integration allowed prescribers to quickly adapt dosing regimens to address any toxicities that might arise.

The experts stressed the importance of receiving buy-in from all stakeholders, including pharmacists, payers, and drugmakers. Trawinski described how the pharmacists in her system took the lead on creating treatment plans for the new and improved care pathways, which helped standardize care, and Nebughr said that the state pharmacy board and retail pharmacists came on board with the model because they saw that it resulted in high-quality care and filled an important need.

For Peng, information from the electronic health record (EHR) was crucial in getting payers to buy in to the integrated model. By showing payers data on how the pharmacists stopped unnecessary fills for patients on medication holidays or adjusted regimens for those who experienced toxicity, they proved to payers that "being able to give patients the best and the most appropriate treatment, safe treatment, improved outcomes," she said.

"These are tremendous examples of leading institutions that are promoting this medically integrated pharmacy team model," Reff said. "The benefits transcend all of the stakeholders but are centered solely on the patient." By having the right systems and people in place to prevent unnecessary fills, he said, "you remove the cost and the toxicities, and you're promoting a better collaborative relationship with the payers or employers."

He asked the panelists to describe the major challenges they face with the integrated model and how these might change as cancer therapies evolve. According to Trawinski, the biggest barrier is access to medication, but the UR program has a leg up on the competition in the eyes of drug manufacturers: "[It's] important to them that we have a fast turnaround time, that we have a lower abandonment rate, and that we're able to manage [adverse] effects a lot faster and easier than the mail-order pharmacies."

The discussion also covered the challenge of financial toxicity and obtaining assistance for patients, especially in light of diminishing foundation support. None of the panelists had easy solutions for this issue; Peng noted that her staff spends more time getting financial support than providing clinical services. Nebughr said that Utah Cancer Specialists has doubled the number of employees who help with obtaining financial assistance. However, he said, a benefit of the medically integrated pharmacy model is that if a patient cannot afford a certain medication, their provider will be informed right away and can choose an alternative therapy.

Cohen reported that capturing prescriptions is a challenge for organizations that are spread out across a state, but being medically integrated and having a single EHR helps address that challenge. After creating a pathway for oral chemotherapy treatment plans, Smilow Cancer Hospital implemented a system that automatically sends each prescription order to a basket, after which they are reviewed by a clinical oncology pharmacist for clinical appropriateness and then sent to their specialty pharmacy.

"In doing this, we're able to capture those prescriptions, and we're able to monitor those patients whether the patient gets that prescription filled or not at our site," he explained.

Reff summarized, based on the panelists' stories, that if a pharmacy wants to become medically integrated, it must leverage the power of the EHR—otherwise, it's no better than any other pharmacy. Leveraging that internal power, he said, is "critical to elevating our collective games to tell a story of quality and value." ◆

The Doctor as Patient: Life During and After CAR T-Cell Therapy

Mary Caffrey

FOR 38 YEARS, Brian Koffman, MDCM, DCFP, DABFM, MS Ed, was a family physician—caring for patients young and old, rich and poor, and, as he wrote in his blog, "those with poor health choices and health fanatics, many omnivores and a few fellow vegans, professional athletes, weekend warriors, and couch potatoes."[1]

For nearly 4 years, he wore a second hat—that of chief medical officer and executive vice president of the nonprofit CLL Society.[2] It's a job he never expected to have but one he embraced after founding the group following his own diagnosis with chronic lymphocytic leukemia (CLL) in 2005. In December 2018, Koffman gave up private practice to focus on the CLL Society full-time.

A month prior, he shared with the audience at Patient-Centered Oncology Care® what it was like to be a doctor who was also a patient, and no ordinary one at that. Koffman was the 37th of 40 patients in a clinical trial at the Fred Hutchinson Cancer Research Center in Seattle, Washington, where he received treatment with an experimental chimeric antigen receptor (CAR) T-cell therapy developed there in collaboration with Juno Therapeutics (since acquired by Celgene and, in turn, Bristol-Myers Squibb).[3,4]

KOFFMAN

For Koffman, CAR T-cell therapy has meant a complete change of fortune. "I had every bad marker in CLL," he said, outlining his journey with a very aggressive form of cancer, including a trial and ultimate failure on ibrutinib. "If you look at the data, I'm supposed to have been dead 10 years ago."

Koffman likened both the process of getting treatment and its effects to "the worst flu you could get."

When the treatment is first administered, it seems very "anticlimactic," he said. But then, the waiting begins, and patients know they are anticipating the flu-like symptoms to appear to show that the cancer cells are being attacked.

Things can turn ugly quickly, Koffman said. He stayed in a hotel near Fred Hutchinson and was hospitalized twice, and his wife intervened when the cognitive effects left him unable to make decisions. Admittedly, for a physician, that was tough.

He doesn't sugar-coat the ordeal that CAR T-cell treatment is, but afterward, "I was in the deepest remission you could possibly get," he said.

"Does that mean I'm cured? We don't know."

Because the inflammatory response of the therapy, cytokine release syndrome (CRS), can be so severe, patients receive cardiac and psychological screening before the expensive therapy is administered (approved products cost as much as $475,000 for just 1 dose of the treatment). A caregiver is required; Koffman's wife saw him through stretches where he experienced neurotoxicity so severe, "I [believed I] was in some museum in [Washington State's] Olympic peninsula, talking to monks in caves."

Therapies are now available to reverse some of the harshest effects of CRS, Koffman explained. Also, he said, scientists now understand that they can tone down the blast of T cells that patients receive without losing the treatment's effect. "There used to be some hesitance," he said. "There is less hesitancy now. You don't want to lose the patient to save the cure."

At one point, Koffman developed an arthritic condition and had to go through physical therapy to regain his strength. But it was worth it.

"CAR T-cell therapy is not a wimpy therapy," he said. "The adverse events I wouldn't wish on anybody, but they're almost always reversible." And, unlike with transplants, there is almost no graft-to-host response.

Physicians are making progress in stratifying who will have the harshest CRS responses and learning to prevent them (results of studies presented in December 2018 at the American Society of Hematology meeting showed that using ibrutinib with CAR T-cell therapy can mitigate reactions).[5] As his life returned to normal, Koffman turned his attention to sharing his experience with other physicians and patients. He even served as a coauthor on an article about his own case.[6] Through the CLL Society, he travels to meet with patient groups and has set up a program by which patients who don't live near a major academic center can consult with experts remotely.

He has spoken with officials at CMS, where reimbursement for CAR T-cell therapy remains unresolved and means some children in Medicaid with acute lymphoblastic leukemia cannot gain access to treatment.

Koffman discusses his experience as both a doctor and a patient with cancer.

Right now, "hospitals are losing money doing this therapy," he said. "This [therapy] is game-changing. Prices will come down as more people enter the market." ◆

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6. Chung SH, Hughes G, Koffman B, Turtle CJ, Maloney DG, Acharya UH. Not so crystal clear: observations from a case of crystalline arthritis with cytokine release syndrome (CRS) after chimeric antigen receptor (CAR)-T cell therapy [published online October 5, 2018]. *Bone Marrow Transplant.* doi: 10.1038/s41409-018-0357-4.

*For the treatment of refractory mCRC,**

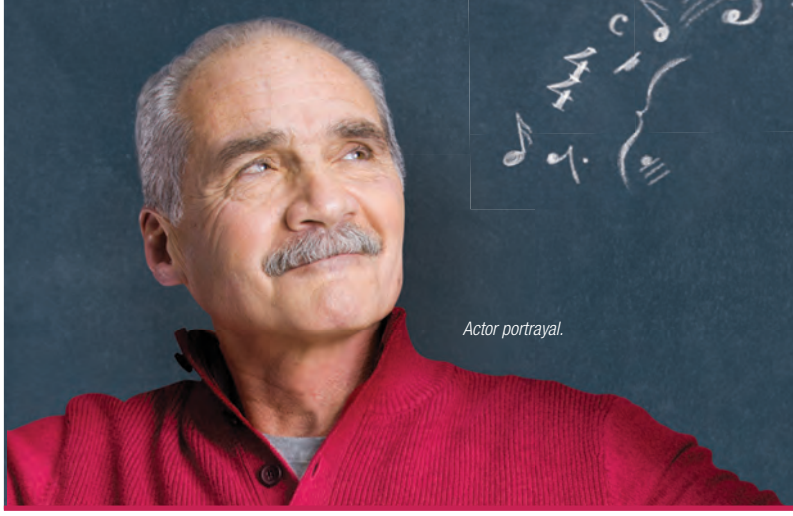
The pursuit of more moments

The first and only oral oncolytic combination tablet, *LONSURF® (trifluridine and tipiracil) tablets deliver extended overall survival (OS)† and a demonstrated safety profile[1]*

LONSURF is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild type, an anti-EGFR therapy.[1]

2 tablet strengths available for personalized dosing[1]:
- *15 mg trifluridine/6.14 mg tipiracil tablet*
- *20 mg trifluridine/8.19 mg tipiracil tablet*

*Metastatic colorectal cancer.
†Median OS (95% CI): 7.1 months (6.5-7.8) for LONSURF vs 5.3 months (4.6-6.0) for placebo (HR=0.68 [95% CI: 0.58-0.81]; *P*<0.001). Number (%) of deaths was 364 (68) for LONSURF and 210 (79) for placebo.



Actor portrayal.

Lonsurf®
(trifluridine and tipiracil) tablets

Learn more at LONSURFhcp.com/data

Selected Important Safety Information

Severe Myelosuppression: LONSURF caused severe and life-threatening myelosuppression (Grade 3-4). Obtain complete blood counts prior to initiation and on day 15 of each treatment cycle and monitor for signs of infection. Increase frequency of blood counts, adjust dosage, and/or withhold LONSURF as clinically indicated.

Please see additional Important Safety Information below and brief summary of Prescribing Information on following pages.

Important Safety Information

WARNINGS AND PRECAUTIONS

Severe Myelosuppression: In Study 1, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%), and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/mm^3. Upon recovery, resume LONSURF at a reduced dose as clinically indicated.

Embryo-Fetal Toxicity: LONSURF can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF.

USE IN SPECIFIC POPULATIONS

Lactation: It is not known whether LONSURF or its metabolites are present in human milk. There are no data to assess the effects of LONSURF or its metabolites on the breast-fed infant or the effects on milk production. Because of the potential for serious adverse reactions in breast-fed infants, advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose.

Male Contraception: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose.

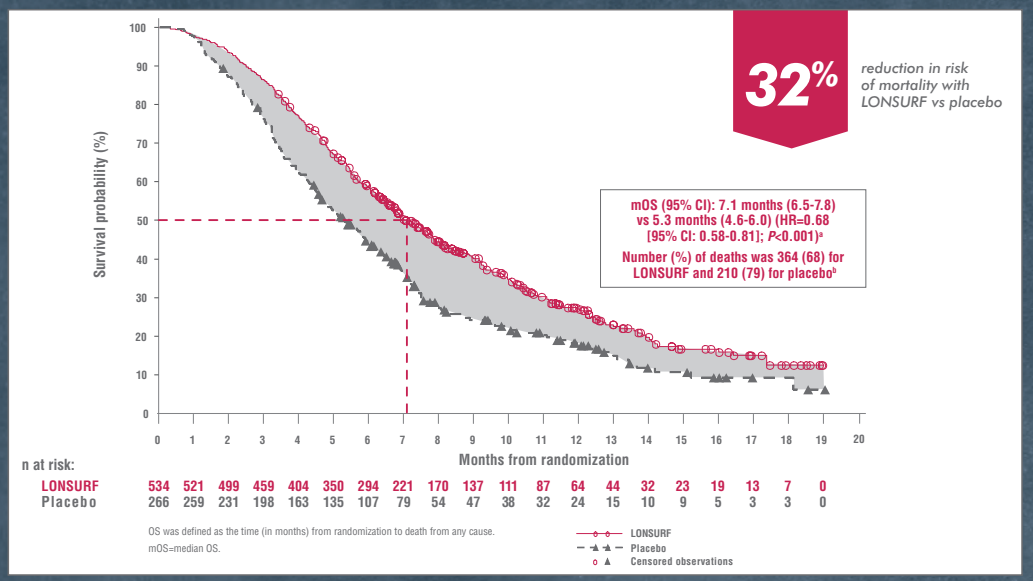
Geriatric Use: Patients 65 years of age or over who received LONSURF had a higher incidence of the following compared to patients younger than 65 years: Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anemia (26% vs 12%), and Grade 3 or 4 thrombocytopenia (9% vs 2%).

Hepatic Impairment: Patients with severe hepatic impairment (total bilirubin greater than 3 times ULN and any AST) were not studied. No adjustment to the starting dose of LONSURF is recommended for patients with mild hepatic impairment. Do not initiate LONSURF in patients with baseline moderate or severe (total bilirubin greater than 1.5 times ULN and any AST) hepatic impairment.

Renal Impairment: In Study 1, patients with moderate renal impairment (CLcr=30 to 59 mL/min, n=47) had a higher incidence (difference of at least 5%) of ≥Grade 3 adverse events, serious adverse events, and dose delays and reductions compared to patients with normal renal function (CLcr ≥90 mL/min, n=306) or patients with mild renal impairment (CLcr=60 to 89 mL/min, n=178).

Patients with moderate renal impairment may require dose modifications for increased toxicity. Patients with severe renal impairment were not studied.

LONSURF provided statistically significant improvement in OS[1,2]



- *6-month OS rate:*
  58% for LONSURF vs 44% for placebo[3]
- *1-year OS rate:*
  27% for LONSURF vs 18% for placebo[3]

[a] Kaplan-Meier estimates.
[b] Prespecified study endpoint.

- *In the RECOURSE‡ trial, 89% of the planned dose was received by patients in the LONSURF group vs 94% in the placebo group[3]*
- *The recommended starting dose of LONSURF is 35 mg/m² up to a maximum of 80 mg/dose (based on the trifluridine component) administered orally twice daily within 1 hour of completion of morning and evening meals on days 1 through 5 and days 8 through 12 of each 28-day cycle until disease progression or unacceptable toxicity*
- *53% of patients treated with LONSURF experienced a dose delay due to an adverse event (AE)[3]*
- *3.6% of patients discontinued LONSURF due to an AE and 13.7% required a dose reduction[1]*
  – The most common AEs leading to a dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea
- *The most frequently observed AEs or laboratory abnormalities (≥10%) in patients receiving LONSURF were anemia (77% vs 33% with placebo), neutropenia (67% vs 1%), asthenia/fatigue (52% vs 35%), nausea (48% vs 24%), thrombocytopenia (42% vs 8%), decreased appetite (39% vs 29%), diarrhea (32% vs 12%), vomiting (28% vs 14%), abdominal pain (21% vs 18%), and pyrexia (19% vs 14%)[1]*

STUDY DESIGN[1-3]

- *RECOURSE was a randomized, double-blind, placebo-controlled phase 3 study.§ All patients were ≥18 years of age, had Eastern Cooperative Oncology Group performance status of 0 or 1, and had received at least 2 prior regimens of standard chemotherapy and were refractory to or were failing all of the following within 3 months: fluoropyrimidine, irinotecan and oxaliplatin; an anti-VEGF biological therapy; and an anti-EGFR therapy (if RAS wild type)*
- *The primary efficacy endpoint was OS*

‡ **Re**fractory **Co**lo**re**ctal Cancer **S**tudy (Study 1).[2]
§ Treatment arms were LONSURF plus best supportive care vs placebo plus best supportive care.[1]

ADVERSE REACTIONS

Most Common Adverse Drug Reactions in Patients Treated With LONSURF (≥5%): The most common adverse drug reactions in LONSURF-treated patients vs placebo-treated patients with refractory mCRC, respectively, were asthenia/fatigue (52% vs 35%), nausea (48% vs 24%), decreased appetite (39% vs 29%), diarrhea (32% vs 12%), vomiting (28% vs 14%), abdominal pain (21% vs 18%), pyrexia (19% vs 14%), stomatitis (8% vs 6%), dysgeusia (7% vs 2%), and alopecia (7% vs 1%).

Additional Important Adverse Drug Reactions: The following occurred more frequently in LONSURF-treated patients compared to placebo: infections (27% vs 15%) and pulmonary emboli (2% vs 0%).

The most commonly reported infections which occurred more frequently in LONSURF-treated patients were nasopharyngitis (4% vs 2%) and urinary tract infections (4% vs 2%).

Interstitial lung disease (0.2%), including fatalities, has been reported in clinical studies and clinical practice settings in Asia.

Laboratory Test Abnormalities in Patients Treated With LONSURF: Laboratory test abnormalities in LONSURF-treated patients vs placebo-treated patients with refractory mCRC, respectively, were anemia (77% vs 33%), neutropenia (67% vs 1%), and thrombocytopenia (42% vs 8%).

Please see brief summary of Prescribing Information on following pages.

References: 1. LONSURF [package insert]. Princeton, NJ: Taiho Oncology, Inc.; 2017 . **2.** Data on file. Taiho Oncology, Inc., Princeton, NJ. **3.** Mayer RJ, Van Cutsem E, Falcone A, et al; for the RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med.* 2015;372(20):1909-1919.

Lonsurf®
(trifluridine and tipiracil) tablets

Change the refractory mCRC story

TAIHO ONCOLOGY

LONSURF (trifluridine and tipiracil) tablets, for oral use
Initial U.S. Approval: 2015

Brief Summary of Prescribing Information
For complete Prescribing Information consult official package insert.

1 INDICATIONS AND USAGE
LONSURF is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Severe Myelosuppression
In Study 1, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%) and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on Day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/mm^3. Upon recovery resume LONSURF at a reduced dose. *[see Dosage and Administration (2.2) in the full Prescribing Information]*

5.2 Embryo-Fetal Toxicity
Based on animal studies and its mechanism of action, LONSURF can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dose levels resulting in exposures lower than those achieved at the recommended dose of 35 mg/m^2 twice daily.

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF. *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1) in the full Prescribing Information]*

6 ADVERSE REACTIONS
The following serious adverse reactions are discussed in detail in other sections of the labeling:

- Severe Myelosuppression *[see Warnings and Precautions (5.1)]*

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 data described below are from Study 1, a randomized (2:1), double-blind, placebo-controlled trial in which 533 patients (median age 63 years; 61% men; 57% White, 35% Asian, 1% Black) with previously treated metastatic colorectal cancer received LONSURF as a single agent at a dose of 35 mg/m^2/dose administered twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. The mean duration of LONSURF therapy was 12.7 weeks.

The most common adverse drug reactions or laboratory abnormalities (all Grades and greater than or equal to 10% in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

In Study 1, 3.6% of patients discontinued LONSURF for an adverse event and 13.7% of patients required a dose reduction. The most common adverse reactions leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

Table 1 Per Patient Incidence of Adverse Drug Reactions (≥5%) in Study 1 Occurring More Commonly (>2%) than in Patients Receiving Placebo.

Adverse Reactions	LONSURF (N=533)		Placebo (N=265)	
	All Grades	Grades 3-4*	All Grades	Grades 3-4*
Gastrointestinal disorders				
Nausea	48%	2%	24%	1%
Diarrhea	32%	3%	12%	<1%
Vomiting	28%	2%	14%	<1%
Abdominal pain	21%	2%	18%	4%
Stomatitis	8%	<1%	6%	0%
General disorders and administration site conditions				
Asthenia/fatigue	52%	7%	35%	9%
Pyrexia	19%	1%	14%	<1%
Metabolism and nutrition disorders				
Decreased appetite	39%	4%	29%	5%
Nervous system disorders				
Dysgeusia	7%	0%	2%	0%
Skin and subcutaneous tissue disorders				
Alopecia	7%	0%	1%	0%

*No Grade 4 definition for nausea, abdominal pain, or fatigue in National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

Table 2 Laboratory Test Abnormalities

Laboratory Parameter	LONSURF (N=533*)			Placebo (N=265*)		
	Grade†			Grade†		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic system disorders						
Anemia‡	77	18	N/A#	33	3	N/A
Neutropenia	67	27	11	1	0	0
Thrombocytopenia	42	5	1	8	<1	<1

*% based on number of patients with post-baseline samples, which may be less than 533 (LONSURF) or 265 (placebo)
† Common Terminology Criteria for Adverse Events (CTCAE), v4.03
‡ Anemia: No Grade 4 definition for these laboratory parameters in CTCAE, v4.03
# One Grade 4 anemia adverse reaction based on clinical criteria was reported

In Study 1, infections occurred more frequently in LONSURF-treated patients (27%) compared to those receiving placebo (15%). The most commonly reported infections which occurred more frequently in LONSURF-treated patients were nasopharyngitis (4% versus 2%), and urinary tract infections (4% versus 2%).

In Study 1, pulmonary emboli occurred more frequently in LONSURF-treated patients (2%) compared to no patients on placebo.

Additional Clinical Experience
Interstitial lung disease was reported in fifteen (0.2%) patients, three of which were fatal, among approximately 7,000 patients exposed to LONSURF in clinical studies and clinical practice settings in Asia.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on animal data and its mechanism of action, LONSURF can cause fetal harm. LONSURF caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to exposures at the recommended dose in humans. [see *Data*] There are no available data on LONSURF exposure in pregnant women. 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

Trifluridine/tipiracil was administered orally once daily to female rats during organogenesis at dose levels of 15, 50, and 150 mg/kg [trifluridine (FTD) equivalent]. Decreased fetal weight was observed at FTD doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily). At the FTD dose of 150 mg/kg (approximately 0.92 times the FTD exposure at the clinical dose of 35 mg/m^2 twice daily) embryolethality and structural anomalies (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels, and skeletal anomalies) were observed.

8.2 Lactation

Risk Summary

It is not known whether LONSURF or its metabolites are present in human milk. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk. There are no data to assess the effects of LONSURF or its metabolites on the breastfed infant or the effects on milk production. Because of the potential for serious adverse reactions in breastfeeding infants, advise women not to breastfeed during treatment with LONSURF and for one day following the final dose.

Data

Radioactivity was excreted in the milk of nursing rats dosed with trifluridine/tipiracil containing ^{14}C-FTD or ^{14}C-tipiracil (TPI). Levels of FTD-derived radioactivity were as high as approximately 50% of the exposure in maternal plasma an hour after dosing with trifluridine/tipiracil and were approximately the same as those in maternal plasma for up to 12 hours following dosing. Exposure to TPI-derived radioactivity was higher in milk than in maternal plasma beginning 2 hours after dosing and continuing for at least 12 hours following administration of trifluridine/tipiracil.

8.3 Females and Males of Reproductive Potential

Contraception

Females

LONSURF can cause fetal harm when administered to a pregnant woman. *[see Use in Specific Populations (8.1)]*

Advise females of reproductive potential to use effective contraception during treatment.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose. *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*

8.4 Pediatric Use

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

Animal Data

Dental toxicity including whitening, breakage, and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in rats treated with trifluridine/tipiracil at doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily).

8.5 Geriatric Use

In Study 1, 533 patients received LONSURF; 44% were 65 years of age or over, while 7% were 75 and over. No overall differences in effectiveness were observed in patients 65 or older versus younger patients, and no adjustment is recommended for the starting dose of LONSURF based on age.

Patients 65 years of age or older who received LONSURF had a higher incidence of the following compared to patients younger than 65 years: Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anemia (26% vs 12%, and Grade 3 or 4 thrombocytopenia (9% vs 2%).

8.6 Hepatic Impairment

In a pharmacokinetic trial comparing 10 patients with mild hepatic impairment (total bilirubin less than or equal to the upper limit of normal (ULN) and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST) and 6 patients with moderate hepatic impairment (total bilirubin greater than 1.5 to 3 times ULN and any AST) to 8 patients with normal hepatic function, no clinically important differences in the mean exposures of trifluridine and tipiracil were observed. Five of 6 patients with moderate hepatic impairment experienced Grade 3 or 4 increased bilirubin levels. Patients with severe hepatic impairment (total bilirubin greater than 3 times ULN and any AST) were not studied. No adjustment to the starting dose of LONSURF is recommended for patients with mild hepatic impairment. Do not initiate LONSURF in patients with baseline moderate or severe (total bilirubin greater than 1.5 times ULN and any AST) hepatic impairment. *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*

8.7 Renal Impairment

No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of LONSURF.

In Study 1, patients with moderate renal impairment (CLcr = 30 to 59 mL/min, n= 47) had a higher incidence (difference of at least 5%) of ≥ Grade 3 adverse events, serious adverse events, and dose delays and reductions compared to patients with normal renal function (CLcr ≥ 90 mL/min, n= 306) or patients with mild renal impairment (CLcr = 60 to 89 mL/min, n= 178).

No adjustment to the starting dose of LONSURF is recommended in patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min); however patients with moderate renal impairment may require dose modification for increased toxicity. Patients with severe renal impairment (CLcr < 30 mL/min) were not studied. *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*

8.8 Ethnicity

There were no clinically meaningful differences in Study 1 between Western and Asian subgroups with respect to overall incidence of adverse events or ≥ Grade 3 adverse events in either the LONSURF or placebo groups.

10 OVERDOSAGE

The highest dose of LONSURF administered in clinical studies was 180 mg/m^2 per day.

There is no known antidote for LONSURF overdosage.

17 PATIENT COUNSELING INFORMATION

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

Severe Myelosuppression:

Advise the patient to immediately contact their healthcare provider if they experience signs or symptoms of infection and advise patients to keep all appointments for blood tests. *[see Warnings and Precautions (5.1)]*

Gastrointestinal toxicity:

Advise patients to contact their healthcare provider for severe or persistent nausea, vomiting, diarrhea, or abdominal pain. *[see Adverse Reactions (6.1)]*

Administration Instructions:

Advise the patient that LONSURF is available in two strengths and they may receive both strength tablets to provide the prescribed dose. Advise the patient of the importance of reading prescription labels carefully and taking the appropriate number of tablets.

Advise the patient to take LONSURF within 1 hour after eating their morning and evening meals. *[see Dosage and Administration (2.1) in the full Prescribing Information]*

Advise the patient that anyone else who handles their medication should wear gloves. *[see References (15) in the full Prescribing Information]*

Embryo-Fetal Toxicity:

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF. *[see Warnings and Precautions (5.2)* and *Use in Specific Populations (8.3) in the full Prescribing Information]*

Lactation:

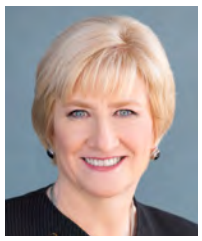
Advise women not to breastfeed during treatment with LONSURF and for one day following the final dose. *[see Use in Specific Populations (8.2)]*

TAIHO ONCOLOGY, INC.

Barriers to the Future of Oncology Value-Based Care Are Complex but Can Be Overcome

Christina Mattina

ALVARNAS



MCANENY

KOLODZIEJ

LOY

DOWNS

AT THE 2018 MEETING of Patient-Centered Oncology Care®, panelists looked to the future and offered predictions on the path of oncology value-based care.

Moderator Joseph Alvarnas, MD, of City of Hope began by listing some words and phrases that stood out to him, representing important ideas during the day's presentations: *practice transformation, data, risk, scalability, patient experience, burdens versus rewards*. "If we're going to create a future system that makes sense, we've got to address all these things at some level," he said, "or we end up with a system that's not even a partial fix to the issues we face today, much less those that will come tomorrow."

He turned to the conference's keynote speaker, Barbara L. McAneny, MD, president, American Medical Association, for her thoughts on the first element of practice transformation and where she foresees it heading.

Foremost on her mind, she said, was the "alarming" trend of oncology practice acquisitions by health systems, plans, or investors that are more focused on profits than on patient care. This threatens the sustainability of independent practices, which she considers the most high-quality, cost-effective site of service. On a more specific level, McAneny spoke of the need for CMS and other payers to understand that "transformation takes time and money and a significant amount of effort" and that more patience might be warranted when evaluating restructuring efforts.

Alvarnas picked up on something McAneny mentioned—"there is a cost to getting this right that involves investment"—and asked panelist Michael Kolodziej, MD, FACP, vice president and chief innovation officer, ADVI Health LLC, how to bring physicians into the transformation without imposing unbearably high costs of time and burden on them.

Kolodziej offered that it's important to "recognize that technology has to be an enabling tool, as opposed to an impediment." He said that this became especially clear to him as he heard the grievances of his wife, who is an oncologist, when her practice migrated to a new electronic health record (EHR) system. He also spoke of a need to standardize processes—beyond EHR systems—to improve care and "use technology and data to understand the optimal way to treat each individual patient."

He added that he thinks these efforts will largely be funded by the private sector, not by physicians, and that reaching the goals of value-based oncology will require some big changes, both in terms of payment models and the amount of attention it gets in Washington, DC. Most of the focus is on drug prices, Kolodziej said, not more specific issues, such as the unintended consequences of a Competitive Acquisition Program, which could be an alternative to the buy-and-bill system of acquiring Medicare Part B drugs in cancer care.

For a different perspective on the investments needed to provoke transformation, the conversation turned to Brian Loy, MD, physician lead, oncology, laboratory, and personalized medicine, Humana. He explained that as a payer placing bets on solutions to a problem, he sees opportunities for a variety of stakeholders, including employer groups, to assign themselves roles and determine how to pay for new models of care. Otherwise, he said, it's like "delivering furniture to someone's new house when they're still pouring the foundation."

As the only nonphysician on the panel, Christian Downs, JD, MJHA, executive director, Association of Community Cancer Centers, offered his view on the barriers to success under the Oncology Care Model (OCM). Considering the tremendous amount of work invested by the Center for Medicare & Medicaid Innovation to launch and maintain the model, as well as the time put in by physicians responding to OCM requirements, he is not convinced that improvements in experience have been worth this amount of effort, he said. In addition, he sees the need for reforms that cut across disciplines and look at the total cost of cancer care instead of breaking costs down by specialty.

Another barrier, according to McAneny, is the head-spinning rate of change in value-based care models like the OCM. "People invest in this, and they create relationships with payers and with other physicians, and they restructure their practice, and then before we even have time to see whether it's going to work, we are already rearranging it to the next flavor of what the value-based care will be," she said. "We need to have the ability to have some time to actually see if something works before we change the rules of the game the next time around."

It's also a challenge for physician practices to balance the demands of Medicare and commercial payers. "Everyone has different quality measures, different pathways, different values. We have to get some consistency, because otherwise physicians feel like they have 50 people shouting their priorities at them every day," McAneny said.

In discussing how to fix these problems, Kolodziej called CMS "the natural convener" because it has the bulk of patients and drives much of the healthcare conversation, but he worried that the lessons learned and potential achievements would be drowned out by political considerations. Loy added that many of the steps toward improvement in oncology consume time and resources and require finesse, such as shared decision making, patient value discussions, and advanced care planning.

Circling back to the discussion about burdens on physicians, Downs voiced concerns about rates of burnout and stress on physicians in cancer care workforce. With every new payment model announced, he said, he fears that more older oncologists will lean toward retirement and more medical school students will choose other specialties.

Alvarnas proposed a hypothetical for Kolodziej: If he could magically transform himself into CMS Administrator Seema Verma or HHS Secretary Alex Azar, what would he do? Though Kolodziej quipped that he's not interested in that hypothetical, he offered a suggestion of increasing transparency and dialogue between healthcare delivery professionals on the front lines and the decision makers within the federal agencies and commercial payers. He also said that CMS should sit down with the tech industry more than it already has in its efforts to regulate telemedicine and health information technology.

"We're not going to get anywhere unless we can really adopt a collaborative approach to this," Kolodziej warned, and he reminded all stakeholders to keep in mind the goal of giving the best care possible no matter where a patient lives. "Irrespective of how sophisticated the doctor is in that area or what kind of support the hospital system is given, irrespective of all that stuff,

Panelists from left: Christian Downs, JD, MJHA; Bryan Loy, MD; Michael Kolodziej, MD, FACP; Barbara McAneny, MD; and Joseph Alvarnas, MD, discuss the future of cancer care.

we want to make sure that we don't have a 2-tier delivery system."

Finally, Alvarnas asked the panelists to channel their inner psychic and predict if these issues will have been solved 10 years from now. Downs thought that things will have improved, although not achieved perfection, helped in part by the technology that is being developed now "from a data standpoint, particularly around social determinants of health and risk stratification," he said.

Loy concurred that social determinants of health are an important frontier that will be more fully explored, and he posited that the healthcare system must find sustainable ways to finance new technologies.

Kolodziej's answer was succinct and not entirely optimistic: "We will deliver much better, much more personalized care to our patients irrespective of where they live, but we will still not know how to pay for that care."

In McAneny's view of the future, as we cope with the current funding crisis, we will see "the pendulum swinging back from aggregation into some disaggregation, so that we recognize that healthcare is local and that we build new structures" for sharing data and best practices.

"I'm an oncologist, so I'm an optimist," she concluded. "I think that we will pull it together and come up with a system where we're delivering healthcare to everybody at an affordable manner, because we have to, and we will have tried everything else first."

Alvarnas concluded the session by thanking the panelists and tying their discussion back to the name of the conference.

"What was so inspirational is that the conference is called the Patient-Centered Oncology Care® event, and when we talk about social determinants of health and delivering care closer to home in a way that engenders forming relationships with patients that are delivered in the pursuit of wellness and well-being and healing, as opposed to maintaining a chronicity of disease, that really seems to be the crux of where we're trying to go through these conversations." ◆

What Oncology Care Management Means to Providers, Patients

Mary Caffrey

CARE MANAGEMENT IS RELATIVELY new in cancer treatment, but it quickly became the heart of value-based care and a core requirement of CMS' Oncology Care Model (OCM). As a panelist at Patient-Centered Oncology Care® (PCOC) described it, care management calls on practices to deal with "everything in between" the physician appointments, including nutrition counseling, dealing with depression, and getting connected with a survivorship program.

Rose Gerber, cancer survivor and director, patient advocacy, Community Oncology Alliance, chaired the panel, which featured providers and a patient with stomach cancer now on his seventh treatment.

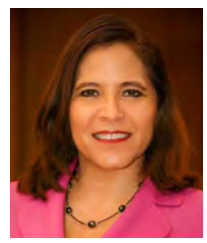
Gerber asked a series of what she called "bundled questions" to Beth Wittmer, RN, OCN, senior manager, care management program, Florida Cancer Specialists (FCS), starting with the most basic: What is care management? She followed with: What does being in care management mean to the patient? How are patients contacted? In the era of the OCM, what are the requirements? And has the OCM created savings?

FCS had an advantage when the OCM began, Wittmer said, because it had already launched its care management program. FCS separated care management from the nurses who took care of patients in the clinic and created a dedicated staff for this purpose, including nonclinical staff who handle some of the intake tasks.

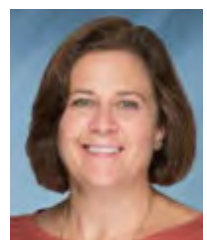
"You know [patients treated in the clinic] are going to be sick in 3 days, but you don't have time to make those calls," she said, because a new round of patients has arrived for treatment.

Care management now has its own team and its own protocol. "Our biggest goal is that we are proactive in our care," Wittmer said.

Gerber asked if patients appreciate the phone calls, and Wittmer acknowledged that not all do. Patients get calls when they start treatment and at intervals based on where they are in their care. Patients who are starting a third or fourth course of treatment may say, "I've got this," but that reaction is preferable to having too many patients show up in the emergency



GERBER



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department, Wittmer said. Care management is also integrated with FCS' pharmacy to improve adherence to oral oncolytics.

FCS has adjusted its protocols along the way. Wittmer said the required language in the OCM letter to patients can be confusing and disruptive, and it made some think the initial care management phone call was Medicare fraud. FCS now sends out a welcome packet. "As with anything new, you go through some bumps and bruises," Wittmer said.

When patients are set up in care management, they are told that it is available 24/7, which is a requirement of the OCM. Ultimately, this works for seniors, Wittmer said. To physicians in the room, she said, "Patients don't like calling you … but they have no problem calling a nurse."

Lani Alison, MS-HCQ, RN, vice president, clinical affairs at Regional Cancer Care Associates (RCCA), faced a tall order when she took on implementing the OCM across more than 30 locations in 3 states. "We changed the culture of the organization," Alison said.

It was Alison's task to help the oncologists understand the metrics and get at the heart of the question: "What makes the patient go to the emergency room?" Even though it might differ among locations, the answer mattered, because it helped RCCA fix issues and meet the terms of its value-based contracts. Better coordination with primary care physicians became essential. "We live and die from referrals from primary care physicians," Alison said, and RCCA had to know more about these patients and existing comorbidities. "You are in for the total cost of care if your patients die of a heart attack or [one] gets hit by a bus—we're still responsible. We have to make care coordination part of our DNA."

Most of the RCCA locations are in New Jersey, which historically has ranked near the top among states for Medicare spending at the end of life.[1] RCCA has put a significant focus on survivorship and palliative care planning so that patients have discussions early on about how their values and religious beliefs should guide their care. Survivorship "has become a hallmark of our daily practice," Alison said.

RCCA has tried to dig deep into understanding how a small group of patients accounts for a disproportionate share of the costs, Alison said: "We've created our own risk stratification," paying special attention to how social determinants of health affect care and outcomes.

The good news, she said, is that once oncologists understand the metrics and where they rank among their peers, they want to improve. "Oncologists are [like] really frustrated NFL players. They are competitive," she said.

Like other practices, RCCA finds the greatest challenge is the rising cost of cancer therapies. The oncologists do point this out, Alison said, noting that there are some outliers "who are still wired to treat, treat, treat."

But slowly, as the nurse navigators and other team members are working at the top of their licenses, care management is making a difference in the bottom line.

Gerber next introduced Wes Hall, a 75-year-old patient at FCS who has taken part in clinical trials on and off since receiving a diagnosis of stage IV stomach cancer in 2013. Hall is an example of patient who has formed a close relationship with a primary oncologist "that he has a lot of faith in," she said.

Hall shared how far cancer care has come since he was growing up, when a diagnosis meant "exploratory surgery," he said: "They closed you up and sent you home, and that was it."

He went through his litany of treatments, from radiation to targeted therapy to immunotherapy, which have kept him alive but caused adverse effects, including severe neuropathy and gastrointestinal effects. But he values his bonds with his oncologist and the staff. He said he can get hydration whenever he needs it, and when his cancer progresses on a clinical trial, he is referred back to his primary team at FCS and can get in within a day.

Last year was rough for Hall. He spoke with *Evidence-Based Oncology*™ in early February 2018 after learning that treatment on a clinical trial had failed.[2] For most of his cancer journey, scans showed lesions only on his stomach or liver, but in May they appeared on his scapula, lymph nodes, femur, and colon. Radiation and another round of treatment reduced his tumor markers significantly, and scans showed some shrinkage, but Hall lost 33 pounds in 12 weeks.

To participate in the panel, Hall had to work with his oncologist to regain some strength. "Just 2 things bother me. The residual neuropathy [and what it suggests]—I haven't been drinking, but it just looks like it."

He also gets frustrated that when he takes part in a clinical trial, the protocol requires that he leave the trial with the smallest progression, even if he is feeling better.

Hall shared what he called a few pieces of trivia: Through October 2018, his insurance company had been billed $1.274 million for his care, and his co-payments are 34% of his total income.

"I have a very good relationship with the people that I work with," Hall said. "You've got to keep a good attitude that you're going to make it." ◆

From left: Beth Wittmer, RN, OCN; Lani Alison, MS-HCQ, RN, Wes Hall; and Rose Gerber discuss oncology care from the patient perspective.

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Produced by Laura Joszt

Brian Koffman, MDCM, DCFP, DABFM, MS Ed, Medical Director, CLL Society

As someone treated with chimeric antigen receptor (CAR) T cells, what do you do regarding follow-up? What is your physician keeping an eye out for?

Since CAR T is a new therapy, and the first genetic therapy that's been approved in the United States by the FDA, I'm being followed for 15 years. Which I'm very happy about, because if I'm being followed for 15 years, that will mean I'm 82 years old, so it means I've lived 15 years with this.

I'm being followed to see are there any undiscovered adverse events that we don't know about. It is gene therapy, I have foreign genes in my body, that's why it's a chimera—a mix of 2 different creatures in me. So I have foreign protein in me. Is this going to cause a problem? Other gene therapies have been disastrous in the past. So far with CAR T things have gone well. But is there something that's going to pop up 5 years from now, 10 years from now? We really don't know the answer to that. So that's one thing that I'm being looked at for.

The other thing is how persistent are the CAR T cells themselves? There's not clarity on how important that is in terms of the duration of the response. So, some people lose their CAR Ts and they still have very durable responses and other people have persistent CAR Ts, but the cancer comes back.

And that leads to the other big question: Do I remain in a complete response? Or is the cancer creeping back again? That's the main thing that they want. So, in CLL [chronic lymphocytic leukemia], the responses have tended to be quite durable for most patients. But in other blood cancers, sometimes people get a deep response—MRD [minimal residual disease] undetectable—but the disease can be back again in 6 months. So I think that those are the things that they're looking for.

Plus, the usual kind of things. Am I getting more infections? Am I getting anemic? Am I getting problems with my platelets? Things like that. The follow-up isn't too onerous. I essentially get a physical exam and blood work once a year.

What have been the benefits and the challenges of being treated with CAR T therapy?

CAR T therapy is very early in its development. So, making a decision to jump into CAR T therapy has inherent risks associated with it. But I decided the risks were worth the potential benefits, which would be an extremely durable response. There are a number of concerns about that. The first is that we don't know yet how to predict who is going to respond well to CAR T. We also don't know who is going to get quite toxic from CAR T. These things are not yet predictable, although they're working on it.

The other thing is, except really for a handful—and I'm talking a couple of patients—we don't have much data beyond 2 years out. The bulk of people have been treated in the last 2 years, so the 2-year data [are] encouraging. And there's a handful of patients who are 5, 6, 7 years out [who] are doing well, but I wish there were hundreds of patients, and I wish they were 30 years out and I could see that data. That's another issue.

When you enter CAR T therapy, there's this ironic twist, and that is you're hoping that you're going to get sick, because the sickness means that when these CAR Ts, which have been re-engineered to attack your cancer—they're serial killers—they're going in and killing off your cancer cells. And you get pretty darn sick when all this killing is going on in your bone marrow and in your blood and your lymph nodes are shrinking and your spleen. And this is called cytokine release syndrome. Cytokines are these enzymes that are released when there's an inflammatory process going on, and it's like the worst flu that you ever had, and most people need to be hospitalized for this. And you're kind of hoping that you get it, but not get it too bad, because if you don't get it—that doesn't mean the CAR Ts aren't working—but generally, you have to get a little bit of the cytokine release to get the benefit of the CAR Ts.

It's very strange to get a therapy that you hope you get sick with, because that means that it's working. Having said that, and I was extraordinarily sick, I had a really bad time, but I got what I came for. When I was restaged, this cancer, which was 60% of my bone marrow, was gone to the best testing of something called MRD undetectable, or minimal residual disease undetectable, down to 1 in 100,000 or maybe 1 in 1 million cells. They could not find it anywhere in my blood or my bone marrow.

Beth Wittmer, RN, OCN, Manager of Care Management at Florida Cancer Specialists and Research Institute

How are patients educated on the risk of neutropenia when they're treated for cancer?

Any patient coming to Florida Cancer Specialists does education prior to starting or on the day of starting their chemotherapy, but there are many that are oral patients that maybe don't ever go into a treatment room.

So, our care management department helps manage all of those patients, and with that, we talk about the side effects of chemotherapy, with neutropenia being one of the most potentially lethal to them. So we talk about those precautions and we sort of have templates built, as well as patients calling in after hours, and we have a neutropenia protocol that we follow as well.

Are there strategies to treat patients quickly in the office before they have to go to the emergency department (ED) if they have neutropenia?

And that's our goal: to try to keep them out of the ED. So, one, being proactive in calling the patient. If they finish the treatment, so this is from the care management perspective, the nurse is calling the patient to see how they're doing, what kind of adverse effects they're having. Fever, of course, is the number 1 sign to watch for with neutropenia.

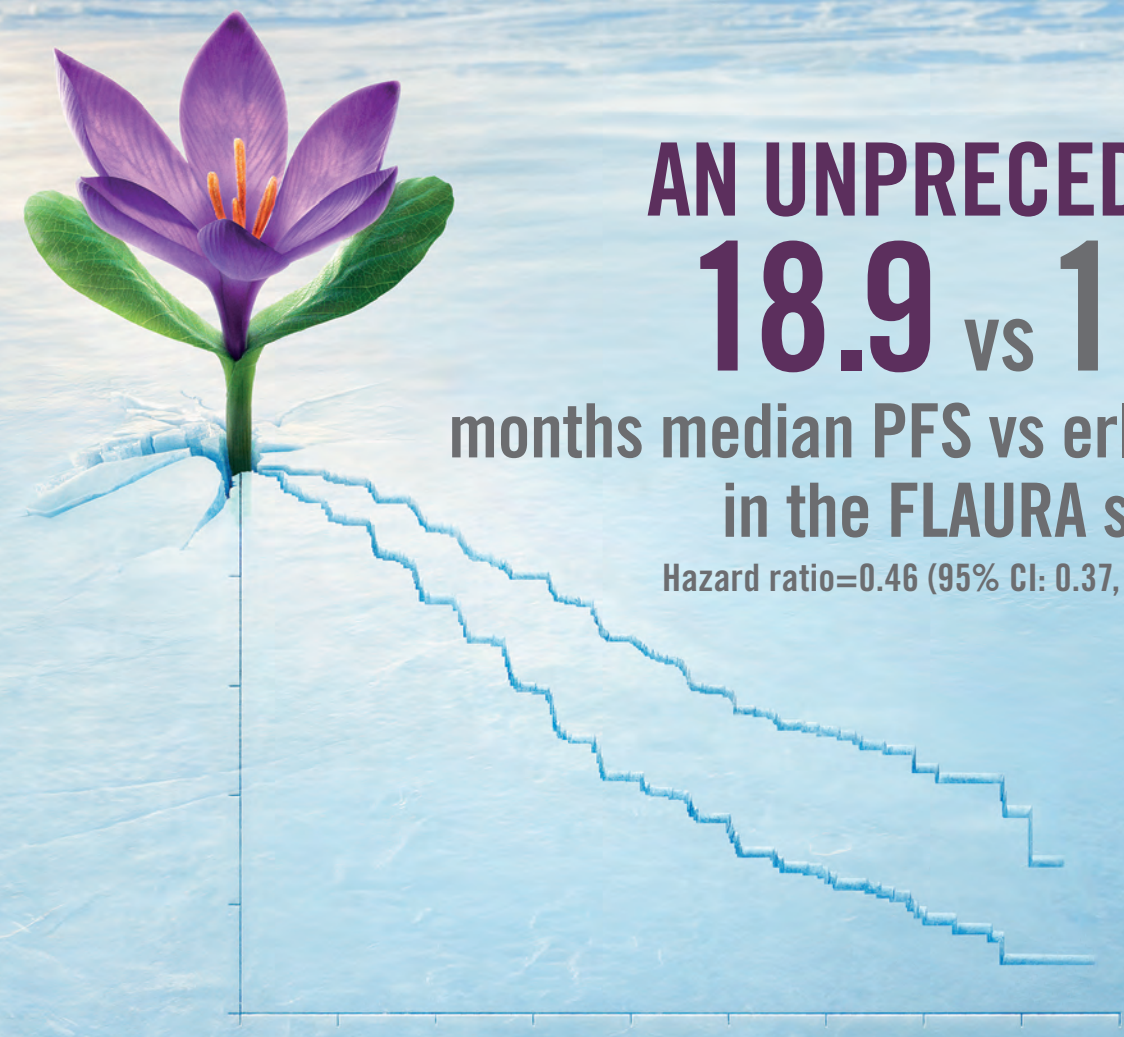
And as their white cells drop, their neutrophils drop. Neutrophils are your front line of fighting off an infection. So if you don't have the neutrophils there, the body's response is different. It doesn't say, "Hey, guys, we need your help from the macrophages and everybody else to come in and help surround the infection."

Also, educating on foods that they should avoid: raw foods; raw vegetables, especially salad; berries, because they're a little harder to wash, they can carry bacteria that normally our gut can handle, but someone who's neutropenic can't.

So just making them aware of what to be cautious about. Check your temperature and report any symptoms that you're having. And then, if we can, we take them in to see the physician, into our own clinics, if we can help that. Either bringing them in for potentially reviewing their [complete blood count] again, putting them prophylactically on antibiotics. Sometimes those are done [intravenously] in the clinic, as well. ◆

FOR THE TREATMENT OF METASTATIC EGFRm NSCLC

FIRST-LINE TAGRISSO® DELIVERED



AN UNPRECEDENTED

18.9 vs 10.2

months median PFS vs erlotinib/gefitinib in the FLAURA study

Hazard ratio=0.46 (95% CI: 0.37, 0.57), *P*<0.0001

Randomized, double-blind, active-controlled trial in 556 patients with metastatic EGFRm NSCLC who had not received prior systemic treatment for advanced disease. Patients were randomized 1:1 to either TAGRISSO (n=279; 80 mg orally, once daily) or EGFR TKI comparator (n=277; gefitinib 250 mg or erlotinib 150 mg, once daily). Crossover was allowed for patients in the EGFR TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation. Patients with CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was PFS based on investigator assessment (according to RECIST v.1.1). Secondary endpoints included OS, ORR, and DOR.[1,2]

INDICATION

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

SELECT SAFETY INFORMATION

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1142 TAGRISSO-treated patients in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec. No QTc-related arrhythmias were reported.

AstraZeneca

GROUNDBREAKING EFFICACY

DOSING

First-line TAGRISSO offers convenient, once-daily dosing, with or without food[1]

ALL SUBGROUPS

Delivered consistent PFS results across all subgroups, including patients with or without CNS metastases[2]

NCCN CATEGORY 1 RECOMMENDED

First-line osimertinib (TAGRISSO) is a National Comprehensive Cancer Network® (NCCN®) Category 1* option[3]

*Category 1 means NCCN has uniform consensus based upon high-level evidence.[3]

SELECT SAFETY INFORMATION

Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia

- Cardiomyopathy occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO
- Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist
- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose
- Most common adverse reactions (≥20%) were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue and decreased appetite

Abbreviations: CNS, central nervous system; DOR, duration of response; EGFRm, epidermal growth factor receptor mutation-positive; NSCLC, non-small cell lung cancer; ORR, overall response rates; OS, Overall Survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TKI, tyrosine kinase inhibitor.

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Please see Brief Summary of Prescribing Information on adjacent pages.

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TAGRISSO®
osimertinib

TAGRISSO® (osimertinib) tablets, for oral use

Brief Summary of Prescribing Information.
For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

First-line Treatment of EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

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

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients for the first-line treatment of metastatic EGFR-positive NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor or plasma specimens *[see Clinical Studies (14) in the full Prescribing Information]*. If these mutations are not detected in a plasma specimen, test tumor tissue if feasible.

Information on FDA-approved tests for the detection of EGFR mutations is available at http://www.fda.gov/companiondiagnostics.

Recommended Dosage Regimen

The recommended dosage of TAGRISSO is 80 mg tablet once a day until disease progression or unacceptable toxicity. TAGRISSO can be taken with or without food.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

Administration to Patients Who Have Difficulty Swallowing Solids

Disperse tablet in 60 mL (2 ounces) of non-carbonated water only. Stir until tablet is dispersed into small pieces (the tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL to 240 mL (4 to 8 ounces) of water and immediately drink.

If administration via nasogastric tube is required, disperse the tablet as above in 15 mL of non-carbonated water, and then use an additional 15 mL of water to transfer any residues to the syringe. The resulting 30 mL liquid should be administered as per the nasogastric tube instructions with appropriate water flushes (approximately 30 mL).

Dosage Modifications

Adverse Reactions

Table 1. Recommended Dosage Modifications for TAGRISSO

Target Organ	Adverse Reaction[a]	Dosage Modification
Pulmonary	Interstitial lung disease (ILD)/Pneumonitis	Permanently discontinue TAGRISSO.
Cardiac	QTc[†] interval greater than 500 msec on at least 2 separate ECGs[b]	Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume at 40 mg dose.
	QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	Permanently discontinue TAGRISSO.
	Symptomatic congestive heart failure	Permanently discontinue TAGRISSO.
Other	Adverse reaction of Grade 3 or greater severity	Withhold TAGRISSO for up to 3 weeks.
	If improvement to Grade 0-2 within 3 weeks	Resume at 80 mg or 40 mg daily.
	If no improvement within 3 weeks	Permanently discontinue TAGRISSO.

[a] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).
[b] ECGs = Electrocardiograms
[†] QTc = QT interval corrected for heart rate

Drug Interactions

Strong CYP3A4 Inducers

If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when co-administering with a strong CYP3A inducer. Resume TAGRISSO at 80 mg 3 weeks after discontinuation of the strong CYP3A4 inducer *[see Drug Interactions (7) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal.

Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed *[see Dosage and Administration (2.4) and Adverse Reactions (6) in the full Prescribing Information]*.

QTc Interval Prolongation

Heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 1142 patients treated with TAGRISSO in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. No QTc-related arrhythmias were reported.

Clinical trials of TAGRISSO did not enroll patients with baseline QTc of > 470 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Cardiomyopathy

Across clinical trials, cardiomyopathy (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal.

A decline in left ventricular ejection fraction (LVEF) ≥ 10% from baseline and to less than 50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment.

Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Keratitis

Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.

Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended clinical dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5 times those observed at the recommended dose of 80 mg once daily. Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose *[see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

ADVERSE REACTIONS

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

Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

QTc Interval Prolongation *[see Warnings and Precautions (5.2) in the full Prescribing Information]*

Cardiomyopathy *[see Warnings and Precautions (5.3) in the full Prescribing Information]*

Keratitis *[see Warnings and Precautions (5.4) in the full Prescribing Information]*

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 data in the Warnings and Precautions section reflect exposure to TAGRISSO in 1142 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)], two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study, AURA1 (n=173) *[see Warnings and Precautions (5) in the full Prescribing Information]*.

The data described below reflect exposure to TAGRISSO (80 mg daily) in 558 patients with EGFR mutation-positive, metastatic NSCLC in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)]. Patients with a history of interstitial lung disease, drug induced interstitial disease or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from enrollment in these studies.

Previously Untreated EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer

The safety of TAGRISSO was evaluated in FLAURA, a multicenter international double-blind randomized (1:1) active controlled trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC who had not received previous systemic treatment for advanced disease. The median duration of exposure to TAGRISSO was 16.2 months.

The most common adverse reactions (≥20%) in patients treated with TAGRISSO were diarrhea (58%), rash (58%), dry skin (36%), nail toxicity (35%), stomatitis (29%), and decreased appetite (20%). Serious adverse reactions were reported in 4% of patients treated with TAGRISSO; the most common serious adverse reactions (≥1%) were pneumonia (2.9%), ILD/pneumonitis (2.1%), and pulmonary embolism (1.8%). Dose reductions occurred in 2.9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (4.3%), diarrhea (2.5%), and lymphopenia (1.1%). Adverse reactions leading to permanent discontinuation occurred in 13% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3.9%).

Tables 2 and 3 summarize common adverse reactions and laboratory abnormalities which occurred in FLAURA. FLAURA was not designed to demonstrate a statistically significant reduction in adverse reaction rates for TAGRISSO, or for the control arm, for any adverse reaction listed in Tables 2 and 3.

Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA*

Adverse Reaction	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
Gastrointestinal Disorders				
Diarrhea[a]	58	2.2	57	2.5
Stomatitis	29	0.7	20	0.4
Nausea	14	0	19	0
Constipation	15	0	13	0
Vomiting	11	0	11	1.4
Skin Disorders				
Rash[b]	58	1.1	78	6.9
Dry skin[c]	36	0.4	36	1.1
Nail toxicity[d]	35	0.4	33	0.7
Pruritus[e]	17	0.4	17	0
Metabolism and Nutrition Disorders				
Decreased appetite	20	2.5	19	1.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	15	0.4
Dyspnea	13	0.4	7	1.4
Neurologic Disorders				
Headache	12	0.4	7	0
Cardiac Disorders				
Prolonged QT Interval[f]	10	2.2	4	0.7
General Disorders and Administration Site Conditions				
Fatigue[g]	21	1.4	15	1.4
Pyrexia	10	0	4	0.4
Infection and Infestation Disorders				
Upper Respiratory Tract Infection	10	0	7	0

* NCI CTCAE v4.0
[a] One grade 5 (fatal) event was reported (diarrhea) for EGFR TKI comparator
[b] Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, rash follicular, erythema, folliculitis, acne, dermatitis, dermatitis acneiform, drug eruption, skin erosion.
[c] Includes dry skin, skin fissures, xerosis, eczema, xeroderma.
[d] Includes nail bed disorder, nail bed inflammation, nail bed infection, nail discoloration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.
[e] Includes pruritus, pruritus generalized, eyelid pruritus.
[f] The frequency of "Prolonged QT Interval" represents reported adverse events in the FLAURA study. Frequencies of QTc intervals of >500 ms or >60 ms are presented in Section 5.2.
[g] Includes fatigue, asthenia.

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

Laboratory Abnormality[a,b]	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)
Hematology				
Lymphopenia	63	5.6	36	4.2
Anemia	59	0.7	47	0.4
Thrombocytopenia	51	0.7	12	0.4
Neutropenia	41	3.0	10	0
Chemistry				
Hyperglycemia[c]	37	0	31	0.5
Hypermagnesemia	30	0.7	11	0.4
Hyponatremia	26	1.1	27	1.5
Increased AST	22	1.1	43	4.1
Increased ALT	21	0.7	52	8
Hypokalemia	16	0.4	22	1.1
Hyperbilirubinemia	14	0	29	1.1

[a] NCI CTCAE v4.0
[b] Each test incidence, except for hyperglycemia, is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (TAGRISSO range: 267 - 273 and EGFR TKI comparator range: 256 - 268)
[c] Hyperglycemia is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TAGRISSO (179) and EGFR comparator (191)

DRUG INTERACTIONS

Effect of Other Drugs on Osimertinib

Strong CYP3A Inducers

Co-administering TAGRISSO with a strong CYP3A4 inducer decreased the exposure of osimertinib compared to administering TAGRISSO alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Decreased osimertinib exposure may lead to reduced efficacy.

Avoid co-administering TAGRISSO with strong CYP3A inducers. Increase the TAGRISSO dosage when co-administering with a strong CYP3A4 inducer if concurrent use is unavoidable *[see Dosage and Administration (2.4) in the full Prescribing Information]*. No dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers.

Effect of Osimertinib on Other Drugs

Co-administering TAGRISSO with a breast cancer resistant protein (BCRP) or P-glycoprotein (P-gp) substrate increased the exposure of the substrate compared to administering it alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Increased BCRP or P-gp substrate exposure may increase the risk of exposure-related toxicity.

Monitor for adverse reactions of the BCRP or P-gp substrate, unless otherwise instructed in its approved labeling, when co-administered with TAGRISSO.

Drugs That Prolong the QTc Interval

The effect of co-administering medicinal products known to prolong the QTc interval with TAGRISSO is unknown. When feasible, avoid concomitant administration of drugs known to prolong the QTc interval with known risk of Torsades de pointes. If not feasible to avoid concomitant administration of such drugs, conduct periodic ECG monitoring *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1) in the full Prescribing Information]*, TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryolethality and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended clinical dose *(see Data)*. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

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

Lactation

Risk Summary

There are no data on the presence of osimertinib or its active metabolites in human milk, the effects of osimertinib on the breastfed infant or on milk production. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise women not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

TAGRISSO can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Infertility

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. The effects on female fertility showed a trend toward reversibility. It is not known whether the effects on male fertility are reversible *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Pediatric Use

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

Geriatric Use

Forty-three percent (43%) of the 1142 patients in FLAURA (n=279), AURA3 (n=279), AURA Extension (n=201), AURA2 (n=210), and AURA1, (n=173) were 65 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (13.4% versus 9.3%) and more frequent dose modifications for adverse reactions (13.4% versus 7.6%) in patients 65 years or older as compared to those younger than 65 years.

Renal Impairment

No dose adjustment is recommended in patients with creatinine clearance (CLcr) 15 - 89 mL/min, as estimated by Cockcroft-Gault. There is no recommended dose of TAGRISSO for patients with end-stage renal disease (CLcr < 15 mL/min) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Hepatic Impairment

No dose adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh A and B or total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to 3 times ULN and any AST). There is no recommended dose for TAGRISSO for patients with severe hepatic impairment (total bilirubin between 3 to 10 times ULN and any AST) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

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Mergers, New Locations for Care, and the Oncologist

Mary Caffrey

FEINBERG

KOLODZIEJ

MACHER

SOBERMAN

BRUCE FEINBERG, DO, vice president and chief medical officer for Cardinal Health Specialty Solutions, recently chaired a discussion centered on the flurry of megamergers in healthcare: Walmart and Humana, Aetna and CVS, Cigna and Express Scripts, and Amazon and PillPack.

Panelists Michael Kolodziej, MD, FACP, an oncologist who is now vice president and chief innovation officer with ADVI Health; Dana Macher, senior vice president at Avalere Health; and Mark Soberman, MD, MBA, FACS, medical director of the Oncology Service Line and physician executive at Monocacy Health Partners, Frederick Regional Health System, discussed these developments and what they mean for cancer care delivery, in light of pressures on the oncologist at the practice level.

Kolodziej offered background on how the 1980s and 1990s brought the early waves of change to oncology, as practice management companies sought to help physician groups bring economies of scale to their business operations, as well as assist in dealing with pharmaceutical companies. The "bigger is better" concept began to prevail, even before the pressures of the 340B drug discount program—which Macher said brought a whole new set of challenges.

Soberman noted that the model changed on the pharmaceutical side as well. Research and development, once done all in-house, now occurs in small biotechs that take on the early risk before being acquired by larger companies.

The nature of today's consolidation is different, Macher said. "A lot of that was horizontal," she continued. "Now, we're looking at a very different type of consolidation…with a lot of vertical integration going on."

Goals have changed, too, Soberman said. The first wave of managed care in the 1990s was strictly about cost containment, and "there was not a lot of emphasis on outcomes and on quality of care." Health systems are now doing what the practice management companies once did: looking for ways to find savings and do things differently, even if it is not within the hospital walls.

The Shift to Quality and Vertical Integration

Today's emphasis on outcomes will manifest itself in a host of ways, from where care takes place to breaking down barriers between retail and healthcare functions. Kolodziej said payers realize there is only so much money to be made managing claims—and Macher agreed, costs themselves must come down. The difference today is that data can reveal how to do this.

"The big driver now, in terms of why it's happening more, is that we have the capability. We have the data that are driving these mergers and acquisitions," she said.

Models like Geisinger—fully integrated payer and provider systems—are pointing the way for others. Although the Department of Justice (DOJ) rejected mergers of the largest national payers—Anthem and Cigna, Aetna and Humana—because these deals would deplete choice in certain markets, the DOJ has allowed recent vertical deals to go through. The panelists generally thought the recent megamergers made sense.

Soberman called the Amazon–PillPack deal "brilliant," and Feinberg noted the obvious need for Amazon to gain pharmacy licenses in all 50 states to realize its ambitions of becoming an online pharmacy.

Kolodziej liked the merger between Walmart and Humana as it brings together a retailer that is already in the pharmacy space with a payer heavily invested in Medicare Advantage. He sees opportunities for in-store chronic disease care, where nutritionists can assist clients with healthy food shopping. Plus, Walmart is accessible in states with high rates of chronic disease. "As somebody said to me once, there are many places in America where Walmart is a heck of a lot closer than your doctor's office," he said.

Macher noted that the Express Scripts and Cigna deal made more sense after Express Scripts severed its relationship with Anthem, which is now building its own pharmacy benefit manager (PBM). Kolodziej, who previously worked for Aetna, said CVS was always the PBM of choice for that payer, so this merger makes sense. Soberman said he is watching the situation with UnitedHealth and Optum, and Feinberg agreed, adding, "I've heard rumors they're not going to be in the payer business much longer."

As these transactions unfold, Kolodziej said 2 things are essential to make them work: (1) attention to outcomes and (2) attention to cost. Soberman said large employers are finally starting to create innovative contracts around these bottom lines, and Feinberg agreed that employers "are going to be the catalyst that's going to push this forward."

Will Employers Step Forward?

Kolodziej said physicians and oncologists in particular are "intimidated" by the prospect of a merger between Aetna and CVS (the American Medical Association opposed it), because they believe it "is going to do nothing but empower the health plans to exercise increased leverage over their day-to-day life." Soberman pointed out the transaction is dwarfed by Medicare, which already has great power over the lives of physicians, and Feinberg wondered aloud what will come of the effort by Berkshire Hathaway, Amazon, and JP Morgan Chase, who have engaged Atul Gawande, MD, MPH, to design a joint venture to shake up healthcare.

However, Soberman said it is more important to pay attention to the direct contracting relationships happening between Home Depot and Cleveland Clinic for heart surgery, or MD Anderson and other employers for specialty cancer care. Feinberg was not so sure—he said employers have been pretty unwilling to directly manage costs, save for few, such as Boeing.

Although the panelists agreed the jury was still out on the venture between Berkshire, Amazon, and JP Morgan Chase, they wondered whether the midsize employers—those with 5000 to 10,000 workers who Feinberg said pay for 60% of healthcare in the United States—would ever exercise leverage over costs. Kolodziej said most rely on third-party consultants or administrators, but innovators like Amazon could change things.

Integrated Delivery Networks and the Oncology Care Model

What makes a hospital an "integrated delivery network" (IDN), and what does this mean for cancer care? Soberman said hospitals realized that they are not islands of care, and in time they may not even be the anchor. "I think oncology has been the poster child for this," he said, offering examples of how groups like the Cleveland

Clinic now organize care around a patient's disease, not "radiation oncology" or "surgery."

Feinberg asked what components are needed to be an IDN, and Macher replied that breadth of services matters. Kolodziej noted that hospital systems have been buying nursing homes, which is significant because under the Oncology Care Model (OCM), the cost of postacute care is significant—and can be hard to control. "Nobody asked the oncologist which nursing home to send the patient to because the hospitals don't care what the model says about what nursing home to use," he said. "But hospitals have caught on to this."

The discussion also noted that the IDN movement has brought about hospital closures in rural areas. The push-and-pull over how many services health systems can provide, and where, is an ongoing issue. Will there be freestanding emergency departments? Will we see more systems like Geisinger in Pennsylvania and Kaiser as it exists in California?

In oncology care, the 340B program has changed the dynamic by driving consolidation of practices into hospital systems—until recently, care in hospital-owned facilities was reimbursed at much higher rates than care in community settings.

Although 340B is not solely responsible for the change in where care occurs, Feinberg said, "There has been a significant shift in the site of care for cancer patients, where 80% of it 5 to 10 years ago was being provided in the community setting in private practice clinics, now it's half that number today. The half that's not there is being treated at a site of care, usually in a facility owned by an IDN, however we define it."

Soberman called it "unreasonable" to pay more for care in different settings, and that his health system put care in a setting where the physician fee schedule applied, because "we want to be less expensive, not more expensive."

IDNs that are not all working in concert can present challenges for practices enrolled in the OCM, Soberman said, because "it makes the medical oncologist responsible for a whole lot of things they have no control over."

Macher agreed. The OCM is transforming patient care, she said, but from a financial perspective, it still has some flaws. "There are a lot of kinks to be worked out in the [OCM] and they're working hard to do that."

Burnout in Oncology Care

Changes in reimbursement, stresses from 340B, adapting to technology, and the modern challenges of running a practice have all contributed to the loss of small 3-to-5-member oncology practices, Feinberg said, asking the panelists to comment.

"The burnout factor, interestingly, is not just a private practice phenomenon," Soberman said. "It's just the emotional toll that being a cancer care provider takes."

More must be done to improve working conditions and increase the time providers spend with patients, not on paperwork or in front of a computer. "Getting that joy of practice back in is a real challenge," he said.

Kolodziej agreed that the electronic health record is a huge problem, and Feinberg agreed that hiring a scribe does not completely eliminate the problem.

Can an IDN do a better job than the traditional practice? Feinberg focused on the term "patient engagement" and asked, what does this really mean? Macher said it can mean many things, but "the one that certainly bubbles to the top is adherence … and having the ability to engage the patient at certain points along the continuum if they're not adhering to their therapy."

IDNs excel here due to technology and care coordination. But, Feinberg said in his conversations with community oncologists, being close to patients is exactly why they are best for this role.

"I'll offer a cynical response that, at this point, most technology solutions have been embraced by the well, the worried, and the wealthy," Feinberg said, "but not by the patients who really need them."

Macher and Kolodziej said this will change as millennials move through the healthcare system, because they are heavier users of technology. "They care less that their doctor went to Harvard and more that their doctor answered their email," he said.

"I would say the world is changing, and it's going to change in ways that we cannot predict," Kolodziej said. ◆

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