SPECIAL ISSUE: **PCOC® MEETING RECAP**

1995 • 2018 23 YEARS
RESEARCH & LEADERSHIP

AJMC®
THE AMERICAN JOURNAL OF MANAGED CARE®

Evidence-Based ONCOLOGY™

FEBRUARY 2018
VOL. 24 • NO. 3

6TH ANNUAL PATIENT-CENTERED ONCOLOGY CARE® 2017 | NOV 16-17, 2017 | LOEWS HOTEL, PHILADELPHIA, PA

HIGHLIGHTS FROM THE MEETING

- How the FDA is responding to the 21st Century Cures Act's mandate to seize the reins in drug development, **SP76**.
- Putting the patient's voice alongside clinical measures in data collection to bring better outcomes, **SP80**.
- Michael Kolodziej, MD, tells oncologists they can "save oncology" by taking ownership of cost control, **SP82**.
- What it takes to bring CMS' Oncology Care Model to a large, multi-site practice, **SP87**.
- Why navigators have become the "heroes" of oncology care, and why payer are embracing their role, **SP99**.
- About our faculty, **SP68**.

AJMC® Managed Markets Network®

The Institute for Value-Based Medicine®

COMMUNITY ONCOLOGY ALLIANCE COA

SUPPORTING YOUR PATIENTS FROM THE START

We're committed to providing streamlined services for your patients. That's why we created KISQALI Care, a comprehensive support program that assists eligible patients throughout their treatment with KISQALI® (ribociclib).

---

1 FREE Treatment Cycle of KISQALI and/or FEMARA
All patients can receive a free 1-treatment cycle supply of KISQALI and/or FEMARA® (letrozole) (including generic letrozole).*

KISQALI 5-Treatment Cycle Access Program
Patients with commercial insurance who are still waiting for their coverage to take effect for KISQALI may be eligible for an additional supply of medication that could continue for up to 5 treatment cycles.†

KISQALI Care Patient Navigator
Eligible patients will be connected with a dedicated navigator who can help them understand insurance coverage, identify potentially available financial resources, and schedule routine monitoring tests through the KISQALI Care @ Home Monitoring program.

* This offer is available for patients with a valid prescription for KISQALI and/or FEMARA (including generic letrozole), including for patients who have not been prescribed KISQALI or another Novartis product.

† Limitations apply. Eligible patients must have commercial insurance, a completed Service Request Form, and be experiencing a delay in obtaining coverage for KISQALI. Program is not available to patients whose medications are reimbursed in whole or in part by Medicare, Medicaid, Tricare, or any other federal or state program. No purchase necessary. Participation is not a guarantee of insurance coverage. Once coverage is approved, patients will no longer be eligible. Novartis Pharmaceuticals Corporation reserves the right to rescind, revoke, or amend this Program without notice.

INDICATION

KISQALI® (ribociclib) is indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

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

IMPORTANT SAFETY INFORMATION

QT interval prolongation. KISQALI has been shown to prolong the QT interval in a concentration-dependent manner, with estimated mean increase in QTc interval exceeding 20 ms (22.9 ms [90% CI: 21.6-24.1]) at the mean steady-state C_{max} following administration at the 600-mg once-daily dose. In MONALEESA-2, one patient (0.3%) had >500 msec postbaseline QTcF value (average of triplicate), and 9 of 329 patients (3.0%) had a >60 msec increase from baseline in QTcF intervals (average of triplicate). These electrocardiogram (ECG) changes occurred within the first 4 weeks of treatment

KISQALI CARE
patient support

KISQALI and/or FEMARA $0 Co-Pay

Patients may be eligible for immediate co-pay savings on their next prescription‡:

- Commercially insured patients pay $0 per month
- Novartis will pay the remaining co-pay, up to $15,000 per calendar year, per product
- This offer is available for patients with a valid prescription for KISQALI and/or FEMARA (including generic letrozole), including for patients who have not been prescribed KISQALI or another Novartis product

Convenient ECG Monitoring

- **KISQALI Care @ Home Monitoring** allows eligible patients to receive their ECG monitoring and bloodwork performed by an experienced medical professional in the comfort of their own homes§
- **KISQALI Care In-Office Monitoring** can provide you with ECG testing equipment so you can perform monitoring right in your office

‡ Limitations apply. Patient must have commercial insurance. Offer is not valid under Medicare, Medicaid, or any other federal or state program. Novartis reserves the right to rescind, revoke, or amend this program without notice. For full terms and conditions, visit www.CoPay.NovartisOncology.com or call 1-877-577-7756.

§ Limitations apply. KISQALI Care @ Home Monitoring is not available to patients with Medicare, Medicaid, or any other federal or state program, or residents of Michigan, Minnesota, or Rhode Island. Novartis reserves the right to terminate or modify this program at any time.

For more information, visit www.KISQALI.com/Access.

IMPORTANT SAFETY INFORMATION (continued)

and were reversible with dose interruption. There were no reported cases of torsades de pointes. Syncope occurred in 9 patients (2.7%) in the KISQALI + letrozole arm vs 3 patients (0.9%) in the placebo + letrozole arm. In the KISQALI + letrozole treatment arm, there was 1 (0.3%) sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation.

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values <450 msec. Repeat ECG at approximately Day 14 of the first cycle, at the beginning of the second cycle, and as clinically indicated. Monitor serum electrolytes (including potassium, calcium, phosphorus, and magnesium) prior to the initiation of treatment, at the beginning of each of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting therapy with KISQALI.

KISQALI® ribociclib 200 mg tablets

IMPORTANT SAFETY INFORMATION (continued)

Avoid the use of KISQALI® (ribociclib) in patients who already have or who are at significant risk of developing QTc prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong the QTc interval and/or strong CYP3A inhibitors, as this may lead to prolongation of the QTcF interval. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation.

Hepatobiliary toxicity. In MONALEESA-2, increases in transaminases were observed. Grade 3 or 4 increases in alanine aminotransferase (ALT) (10% vs 1%) and aspartate aminotransferase (AST) (7% vs 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had grade ≥3 ALT/AST elevation, the median time to onset was 57 days for the KISQALI + letrozole treatment group. The median time to resolution to grade ≤2 was 24 days in the KISQALI + letrozole treatment group.

Concurrent elevations in ALT or AST >3 times the upper limit of normal (ULN) and total bilirubin >2 times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 4 patients (1%) in MONALEESA-2, and all patients recovered after discontinuation of KISQALI.

Perform liver function tests (LFTs) before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation. Recommendations for patients who have elevated AST/ALT grade ≥3 at baseline have not been established.

Neutropenia. In MONALEESA-2, neutropenia was the most frequently reported adverse reaction (AR) (75%), and a grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 60% of patients receiving KISQALI + letrozole. Among the patients who had grade 2, 3, or 4 neutropenia, the median time to grade ≥2 was 16 days. The median time to resolution of grade ≥3 (to normalization or grade <3) was 15 days in the KISQALI + letrozole treatment group. Febrile neutropenia was reported in 1.5% of patients receiving KISQALI and letrozole. Treatment discontinuation due to neutropenia was 0.9%.

Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction, or discontinuation.

Embryofetal toxicity. Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of KISQALI to pregnant rats and rabbits during organogenesis caused embryofetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose.

Adverse reactions. The most common ARs reported in the KISQALI + letrozole arm vs letrozole arm (incidence ≥20%) were neutropenia (75% vs 5%), nausea (52% vs 29%), fatigue (37% vs 30%), diarrhea (35% vs 22%), leukopenia (33% vs 1%), alopecia (33% vs 16%), vomiting (29% vs 16%), constipation (25% vs 19%), headache (22% vs 19%), and back pain (20% vs 18%). The most common grade 3/4 ARs (reported at a frequency >2%) were neutropenia (60% vs 1%), leukopenia (21% vs <1%), abnormal LFTs (10% vs 2%), lymphopenia (7% vs 1%), and vomiting (4% vs 1%), respectively.

Laboratory abnormalities. The most common laboratory abnormalities occurring in patients receiving KISQALI + letrozole vs letrozole arm (all grades, incidence ≥20%) were leukocyte count decrease (93% vs 29%), neutrophil count decrease (93% vs 24%), hemoglobin decrease (57% vs 26%), lymphocyte count decrease (51% vs 22%), ALT increase (46% vs 36%), AST increase (44% vs 32%), platelet count decrease (29% vs 6%), and creatinine increase (20% vs 6%). The most common grade 3/4 laboratory abnormalities (incidence >2%) were neutrophil count decrease (60% vs <2%), leukocyte count decrease (34% vs <2%), lymphocyte count decrease (14% vs 4%), ALT increase (10% vs 1%), AST increase (7% vs 2%), and phosphorus decrease (6% vs 1%), respectively.

NOVARTIS

KISQALI® ribociclib 200 mg tablets

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

9/17

KIS-1173592

KISQALI® (ribociclib) tablets, for oral use
Initial U.S. Approval: 2017

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

1 INDICATIONS AND USAGE

KISQALI® is indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 QT Interval Prolongation

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner, with estimated mean increase in QTc interval exceeding 20 ms (22.9 ms (90% CI: 21.6, 24.1)) at the mean steady-state C_{max} following administration at 600 mg once daily dose *[see Clinical Pharmacology (12.2) in the full prescribing information]*. In Study 1 (MONALEESA-2), one patient (0.3%) had >500 msec post-baseline QTcF value (average of triplicate), and nine patients out of 329 patients (3%) had a >60 msec increase from baseline in QTcF intervals (average of triplicate). These ECG changes occurred within the first four weeks of treatment and were reversible with dose interruption. There were no reported cases of Torsades de Pointes. Syncope occurred in 9 patients (2.7%) in the KISQALI plus letrozole arm versus 3 (0.9%) in placebo plus letrozole arm. On the KISQALI plus letrozole treatment arm, there was one (0.3%) sudden death in a patient with Grade 3 hypokalemia and Grade 2 QT prolongation *[see Adverse Reactions (6)]*.

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values less than 450 msec. Repeat ECG at approximately Day 14 of the first cycle and the beginning of the second cycle, and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorous and magnesium) prior to the initiation of treatment, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting KISQALI therapy *[see Dosage and Administration (2.2) in the full prescribing information]*.

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QTc prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong QTc interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 4 *[see Dosage and Administration (2.2) in the full prescribing information and Drug Interactions (7.4)]*.

5.2 Hepatobiliary Toxicity

In Study 1, increases in transaminases were observed. Grade 3 or 4 increases in ALT (10% versus 1%) and AST (7% versus 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had Grade ≥ 3 ALT/AST elevation, the median time-to-onset was 57 days for the KISQALI plus letrozole treatment group. The median time to resolution to Grade ≤ 2 was 24 days in the KISQALI plus letrozole treatment group.

Concurrent elevations in ALT or AST greater than three times the ULN and total bilirubin greater than two times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 4 (1%) patients in Study 1 and all patients recovered after discontinuation of KISQALI.

Perform LFTs before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated *[see Dosage and Administration (2.2) in the full prescribing information]*.

Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation as described in Table 3 (Dose Modification and Management for Hepatobiliary Toxicity) *[see Dosage and Administration (2.2) in the full prescribing information]*. Recommendations for patients who have elevated AST/ALT Grade ≥ 3 at baseline have not been established.

5.3 Neutropenia

In Study 1, neutropenia was the most frequently reported adverse reaction (75%) and a Grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 60% of patients receiving KISQALI plus letrozole. Among the patients who had Grade 2, 3, or 4 neutropenia, the median time to Grade ≥ 2 neutropenia was 16 days. The median time to resolution of Grade ≥ 3 (to normalization or Grade < 3) was 15 days in the KISQALI plus letrozole treatment group. Febrile neutropenia was reported in 1.5% of patients receiving KISQALI and letrozole. Treatment discontinuation due to neutropenia was 0.9%.

Perform CBC before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.

Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction or discontinuation as described in Table 2 *[see Dosage and Administration (2.2) in the full prescribing information]*.

5.4 Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ribociclib to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose *[see Use in Specific Population (8.1, 8.3) and Clinical Pharmacology (12.1) in the full prescribing information]*.

6 ADVERSE REACTIONS

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

- QT Interval Prolongation *[see Warnings and Precautions (5.1)]*
- Hepatobiliary Toxicity *[see Warnings and Precautions (5.2)]*
- Neutropenia *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trial Experience

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

The safety data reported below are based on Study 1 (MONALEESA-2), a clinical study of 668 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole. The median duration of exposure to KISQALI plus letrozole was 13 months with 58% of patients exposed for ≥ 12 months.

Dose reductions due to adverse reactions (ARs) occurred in 45% of patients receiving KISQALI plus letrozole and in 3% of patients receiving placebo plus letrozole. Permanent discontinuations due to ARs were reported in 7% of patients receiving KISQALI plus letrozole and 2% in patients receiving placebo plus letrozole. The most common ARs leading to treatment discontinuation of KISQALI in patients receiving KISQALI plus letrozole were ALT increased (4%), AST increased (3%), vomiting (2%). Antiemetics and antidiarrhea medications were used to manage symptoms as clinically indicated.

On-treatment deaths, regardless of causality, were reported in three cases (0.9%) of KISQALI plus letrozole treated patients vs. one case (0.3%) of placebo plus letrozole treated patients. Causes of death on KISQALI plus letrozole included one case each of the following: progressive disease, death (cause unknown), and sudden death (in the setting of Grade 3 hypokalemia and Grade 2 QT prolongation).

The most common ARs (reported at a frequency ≥ 20%) were neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache and back pain.

The most common Grade 3/4 ARs (reported at a frequency > 2%) were neutropenia, leukopenia, abnormal liver function tests, lymphopenia, and vomiting.

ARs and laboratory abnormalities occurring in patients in Study 1 are listed in Table 6 and Table 7, respectively.

Table 6: Adverse Reactions Occurring in ≥ 10% and ≥ 2% higher than Placebo Arm in Study 1 (All Grades)

	KISQALI + letrozole N=334			Placebo + letrozole N=330		
Adverse drug reactions	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Infections and Infestations						
Urinary tract infection	11	1	0	8	0	0
Blood and lymphatic system disorders						
Neutropenia	75	50	10	5	1	0
Leukopenia	33	20	1	1	<1	0
Anemia	18	1	<1	5	1	0
Lymphopenia	11	6	1	2	1	0
Metabolism and nutrition disorders						
Decreased appetite	19	2	0	15	<1	0
Nervous system disorders						
Headache	22	<1	0	19	<1	0
Insomnia	12	<1	0	9	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea	12	1	0	9	1	0
Musculoskeletal and connective tissue disorders						
Back pain	20	2	0	18	<1	0
Gastrointestinal disorders						
Nausea	52	2	0	29	1	0
Diarrhea	35	1	0	22	1	0
Vomiting	29	4	0	16	1	0
Constipation	25	1	0	19	0	0
Stomatitis	12	<1	0	7	0	0
Abdominal pain	11	1	0	8	0	0
Skin and subcutaneous tissue disorders						
Alopecia	33	0	0	16	0	0
Rash	17	1	0	8	0	0
Pruritus	14	1	0	6	0	0
General disorders and administration site conditions						
Fatigue	37	2	<1	30	1	0
Pyrexia	13	<1	0	6	0	0
Edema peripheral	12	0	0	10	0	0
Investigations						
Abnormal liver function tests[1]	18	8	2	6	2	0

Grading according to CTCAE 4.03 (Common Terminology Criteria for Adverse Events)
[1]abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased

Table 7: Laboratory Abnormalities Occurring in ≥ 10% of Patients in Study 1

	KISQALI + letrozole N=334			Placebo + letrozole N=330		
Laboratory parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
HEMATOLOGY						
Leukocyte count decreased	93	31	3	29	1	< 1
Neutrophil count decreased	93	49	11	24	1	< 1
Hemoglobin decreased	57	2	0	26	1	0
Lymphocyte count decreased	51	12	2	22	3	1
Platelet count decreased	29	1	< 1	6	0	< 1

(continued)

Table 7: Laboratory Abnormalities Occurring in ≥ 10% of Patients in Study 1

	KISQALI + letrozole N=334			Placebo + letrozole N=330		
Laboratory parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
CHEMISTRY						
Alanine aminotransferase increased	46	8	2	36	1	0
Aspartate aminotransferase increased	44	6	1	32	2	0
Creatinine increased	20	1	0	6	0	0
Phosphorous decreased	13	5	1	4	1	0
Potassium decreased	11	1	1	7	1	0

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Ribociclib Plasma Concentrations

CYP3A4 Inhibitors

Coadministration of a strong CYP3A4 inhibitor (ritonavir) increased ribociclib exposure in healthy subjects by 3.2-fold *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Avoid concomitant use of strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, and voriconazole) and consider alternative concomitant medications with less potential for CYP3A inhibition.

If coadministration of KISQALI with a strong CYP3A inhibitor cannot be avoided, reduce the dose of KISQALI to 400 mg once daily *[see Dosage and Administration (2.2) in the full prescribing information]*.

Instruct patients to avoid pomegranates or pomegranate juice, grapefruit, all of which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to ribociclib *[see Patient Counseling Information (17) in the full prescribing information]*.

7.2 Drugs That May Decrease Ribociclib Plasma Concentrations

CYP3A4 Inducers

Coadministration of a strong CYP3A4 inducer (rifampin) decreased the plasma exposure of ribociclib in healthy subjects by 89% *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Avoid concomitant use of strong CYP3A inducers and consider an alternate concomitant medication with no or minimal potential to induce CYP3A (e.g., phenytoin, rifampin, carbamazepine and St John's Wort (Hypericum perforatum)).

7.3 Effect of KISQALI on Other Drugs

CYP3A substrates with narrow therapeutic index

Coadministration of midazolam (a sensitive CYP3A4 substrate) with multiple doses of KISQALI (400 mg) increased the midazolam exposure by 3.8-fold in healthy subjects, compared with administration of midazolam alone *[see Clinical Pharmacology (12.3) in the full prescribing information]*. KISQALI given at the clinically relevant dose of 600 mg is predicted to increase the midazolam AUC by 5.2-fold. Therefore, caution is recommended when KISQALI is administered with CYP3A substrates with a narrow therapeutic index. The dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

7.4 Drugs That Prolong the QT Interval

Avoid coadministration of KISQALI with medicinal products with a known potential to prolong QT such as antiarrhythmic medicines (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol), and other drugs that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and ondansetron (i.v)) *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3) in the full prescribing information]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in the full prescribing information]*.

There are no available human data informing the drug-associated risk. In animal reproduction studies, administration of ribociclib to pregnant animals during organogenesis resulted in increased incidences of postimplantation loss and reduced fetal weights in rats and increased incidences of fetal abnormalities in rabbits at exposures 0.6 or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC *[see Data]*. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ribociclib up to 1000 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis.

In rats, 300 mg/kg/day resulted in reduced maternal body weight gain and reduced fetal weights accompanied by skeletal changes related to the lower fetal weights. There were no significant effects on embryo-fetal viability or fetal morphology at 50 or 300 mg/kg/day.

In rabbits at doses ≥ 30 mg/kg/day, there were adverse effects on embryo-fetal development including increased incidences of fetal abnormalities (malformations and external, visceral and skeletal variants) and fetal growth (lower fetal weights). These findings included reduced/small lung lobes, additional vessel on the descending aorta, additional vessel on the aortic arch, small eyes, diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes, reduced/small accessory lung lobe, extra/rudimentary 13th ribs, misshapen hyoid bone, bent hyoid bone alae, and reduced number of phalanges in the pollex. There was no evidence of increased incidence of embryo-fetal mortality. There was no maternal toxicity observed at 30 mg/kg/day.

At 300 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal systemic exposures (AUC) were approximately 0.6 and 1.5 times, respectively, the exposure in patients at the highest recommended dose of 600 mg/day.

8.2 Lactation

Risk Summary

It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breastfed infant or on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse reactions in breastfed infants from KISQALI, advise lactating women not to breastfeed while taking KISQALI and for at least 3 weeks after the last dose.

Data

In lactating rats administered a single dose of 50 mg/kg, exposure to ribociclib was 3.56-fold higher in milk compared to maternal plasma.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, KISQALI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Females of reproductive potential should have a pregnancy test prior to starting treatment with KISQALI.

Contraception

Females

Based on animal studies, KISQALI 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 (methods that result in less than 1% pregnancy rates) during treatment with KISQALI and for at least 3 weeks after the last dose.

Infertility

Males

Based on animal studies, KISQALI may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1) in the full prescribing information]*.

8.4 Pediatric Use

The safety and efficacy of KISQALI in pediatric patients has not been established.

8.5 Geriatric Use

Of 334 patients who received KISQALI in Study 1, 150 patients (45%) were ≥65 years of age and 35 patients (11%) were ≥75 years of age. No overall differences in safety or effectiveness of KISQALI were observed between these patients and younger patients.

8.6 Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A). A reduced starting dose of 400 mg is recommended in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) *[see Dosage and Administration (2.2) in the full prescribing information]*. Based on a pharmacokinetic trial in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.50 for C_{max}; 1.32 for AUC_{inf}) and severe (GMR: 1.34 for C_{max}; 1.29 for AUC_{inf}) hepatic impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

10 OVERDOSAGE

There are no known cases of overdose with KISQALI. General symptomatic and supportive measures should be initiated in all cases of overdose where necessary.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2017-26
March 2017

www.ajmc.com/about/ebo
EBOncology

SPECIAL ISSUE / PCOC® MEETING RECAP

FEBRUARY 2018
VOLUME 24 • ISSUE 3

Top, from left, A. Mark Fendrick, MD, and Michael E. Chernew, PhD, co-editors-in-chief of *The American Journal of Managed Care*®, present the Seema S. Sonnad Emerging Leader in Managed Care Research Award to Ilana Graetz, PhD, of the University of Tennessee Health Sciences Center. Henry Glick, PhD, at right, joined the presentation of the award named in honor of his late wife, who was the journal's associate editor when she died in 2015.

Attendees at Patient-Centered Oncology Care®

CONTRIBUTORS

SURABHI DANGI-GARIMELLA, PHD, MARY CAFFREY, ALISON RODRIGUEZ
EVENT PHOTOGRAPHY BY AMANDA J. COX

AJMC®
THE AMERICAN JOURNAL OF MANAGED CARE®

PUBLICATION STAFF

SENIOR VICE PRESIDENT, MANAGED MARKETS
Jeff Prescott, PharmD

ASSOCIATE EDITORIAL DIRECTOR
Surabhi Dangi-Garimella, PhD

MANAGING EDITOR
Mary K. Caffrey

COPY CHIEF
Jennifer Potash

COPY EDITORS
Maggie Shaw
Rachelle Laliberte

DESIGNER
Brianna Gibb

SALES & MARKETING

DIRECTOR OF SALES
Gilbert Hernandez

ASSOCIATE
James Pastena

NATIONAL ACCOUNTS

OPERATIONS & FINANCE

CIRCULATION DIRECTOR
Jon Severn

VICE PRESIDENT OF FINANCE
Leah Babitz, CPA

ACCOUNTANT
Katherine Wyckoff

CORPORATE OFFICERS

CHAIRMAN AND CEO
Mike Hennessy, Sr

VICE CHAIRMAN
Jack Lepping

PRESIDENT
Mike Hennessy, Jr

CHIEF OPERATING OFFICER
Steve Viviano

CHIEF FINANCIAL OFFICER
Neil Glasser, CPA/CFE

CHIEF MARKETING OFFICER
Warren Dardine

VICE PRESIDENT OF EDITORIAL SERVICES AND PRODUCTION
Kerrie Keegan

CHIEF DIGITAL STRATEGY OFFICER
Steve Ennen

VICE PRESIDENT, DIGITAL MEDIA
Jung Kim

CHIEF CREATIVE OFFICER
Jeff Brown

DIRECTOR OF HUMAN RESOURCES
Shari Lundenberg

Scan here to visit AJMC.COM.

Michael J. Hennessy Associates, Inc.

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

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

FROM THE CHAIRMAN

Putting the Patient at Every Decision Point in Cancer Care


MIKE HENNESSY, SR

WE PRESENT THIS SPECIAL ISSUE OF *Evidence-Based Oncology*™ (*EBO*™), a recap of our 6th annual Patient-Centered Oncology Care® (PCOC®) meeting held November 16-17, 2017. For the first time we met in Philadelphia, Pennsylvania, home of the Sidney Kimmel Cancer Center at Thomas Jefferson University, where many of our meeting attendees work to save lives each day. We are indebted to our meeting moderator, Margaret O'Grady, RN, MSN, OCN, FAAMA, who is the administrative director for the oncology service line at Abington-Jefferson Health in Abington, Pennsylvania. She previously served as director of nursing at the Kimmel Cancer Center.

The idea of miracle drugs for cancer has gained steam in the past year, with new options in checkpoint inhibitors and the approval of the first chimeric antigen receptor (CAR) T-cell therapies. But miracles for whom? With price tags far above what most Americans pay for their homes, the prospect of extending life where hope was lost, of curing the incurable, comes with new questions and trade-offs. Who pays? What happens if the miracle drug doesn't work? How willing are patients to deal with adverse effects? Whose job is it to have this conversation? What do health systems do if doctors who can conquer the most difficult algorithm can't deal with these discussions?

Healthcare is far from solving all of these problems. But as our conversations at PCOC® showed, we are doing a better job of recognizing them and we are taking steps to put the patient's voice into the decision-making process. Groups such as the Cancer Support Community are systematically gathering data to tell us what patients with cancer think and feel and helping us identify the gaps in doctor–patient communication. We learned from Kathleen Lokay of Via Oncology how clinical care pathways are incorporating patient preferences into the decision points for treatment. We heard from Lalan Wilfong, MD, of Texas Oncology about how the practice identifies which physicians succeed at helping patients make choices about palliative and end-of-life care and which ones are blind to weaknesses in this area.

From the very first speaker, FDA's Frank Weichold, MD, PhD, who presented a shift in thinking at the regulatory level, to the patient advocates who closed the session, what came through at PCOC® was the need for stakeholders to be active participants. No one—especially patients—should feel locked into the assignments of the past, nor should any one party wait for solutions to come from somewhere else. The best answers to drug prices and access, data transparency and sharing, and solutions that start with patients will come from tearing down the barriers within the care delivery structure. And that's just what PCOC® does. It provides a forum for conversations among physicians, payers, patients, pharmacists, technology developers, administrators, and policy leaders to hear from one another.

A meeting like this requires months of planning, and we thank Joseph Alvarnas, MD, our meeting chair and the editor-in-chief of *EBO*™, for leading the development of our most successful meeting yet.

Until next year,
Mike Hennessy, Sr
CHAIRMAN AND CEO

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

THURSDAY, NOVEMBER 16, 2017

2:00 PM	**REGISTRATION**
2:30 PM - 2:40 PM	**Opening Remarks & Introduction to Poster Competition**
Session 1: Regulation **Moderator:** Margaret O'Grady, RN, MSN, OCN, FAAMA	
2:40 PM - 3:10 PM	**Presentation: Driving Medical Innovation by Advancing Regulatory Science** Frank F. Weichold, MD, PhD
3:10 PM - 3:50 PM	**Panel: Under New Management: The FDA in 2018** Roger Brito, DO; Mark Fleury, PhD; Frank F. Weichold, MD, PhD
3:50 PM - 4:30 PM	**Panel: Right to Try Law and FDA's Expanded Access Program** W. Kevin Kelly, DO; Marjorie A. Speers, PhD; Diana Zuckerman, PhD
4:30 PM - 4:40 PM	**BREAK**
Session 2: Digital Technology **Moderator:** Margaret O'Grady, RN, MSN, OCN, FAAMA	
4:40 PM - 5:10 PM	**Presentation: Real-World Impact of Digital Decision-Support Solutions** Kathleen Lokay
5:10 PM - 5:50 PM	**Panel: Impact of Digital Data Collection and Utilization on Quality Assessment** Joseph Alvarnas, MD; Torrie K. Fields, MPH, Kathleen Lokay; Viraj Narayanan
5:50 PM - 6:30 PM	**Panel: Digital Support to Improve Performance and Outcomes** Brenton Fargnoli, MD; Felice H. LePar, MD, MPH; Jonathan Hirsch, MSc; Spencer Hoover
6:30 PM - 7:00 PM	**Keynote Presentation** Michael Kolodziej, MD
7:00 PM - 10:00 PM	**Seema S. Sonnad Emerging Leader in Managed Care Research Award Reception & Dinner**

FRIDAY, NOVEMBER 17, 2017

8:00 AM	**REGISTRATION & BREAKFAST**
Session 3: Value **Moderator:** Margaret O'Grady, RN, MSN, OCN, FAAMA	
8:30 AM - 9:00 AM	**Presentation: Learnings From the OCM, Year 1** Lalan Wilfong, MD
9:00 AM - 9:40 AM	**Panel: Impact of Novel Therapies on Oncology Stakeholders** Bruce Feinberg, DO; Thomas Graf, MD; Kashyap Patel, MD; Kavita Patel, MD, MA
9:40 AM - 10:20 AM	**Panel: Adopting Real-World Evidence and Value Into a Payment Model** Jason Harris; Ian Manners, MBA; Lalan Wilfong, MD
10:20 AM - 10:30 AM	**BREAK**
Session 4: Patient-Cenetered Care **Moderator:** Margaret O'Grady, RN, MSN, OCN, FAAMA	
10:30 AM - 11:00 AM	**Presentation: Collecting the Right Data for Patient-Focused Drug Development** Joanne Buzaglo, PhD
11:00 AM - 11:40 AM	**Panel: Impact of NPs/APs and Navigators on Patient Care** Roger Brito, DO; Bo Gamble; Karon Martyn, MSN, ANP-BC, AOCNP; Marie Kelly Pressler, RN, MSN, OCN; Nicole Taglione
11:40 AM - 12:20 PM	**Panel: Teamwork in Care Transitions** Michael Diaz, MD; Rose Gerber; Rebekah Gilbert, RN, BSN, OCN; Stacey McCullough, PharmD
12:20 PM - 12:30 PM	**Announcement of Poster Session Winner & Closing Remarks** Margaret O'Grady, RN, MSN, OCN, FAAMA

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, CA

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 Transplant Program, where he helped found the program. Dr Alvarnas subsequently worked 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/Hematopoietic Cell Transplantation at City of Hope, where he also serves as the director of Value-Based Analytics for the institution. He is the national co-chair for 2 Bone 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*®.

MODERATOR

Margaret O'Grady, RN, MSN, OCN, FAAMA
Administrative Director, Oncology Service Line
Abington Memorial Hospital
Jefferson Health System
Philadelphia, PA

Margaret "Peg" O'Grady is currently the administrative director of the Abington-Jefferson Health System's Rosenfeld Cancer Center. She oversees inpatient and outpatient oncology service, including a robust research relationship with the Sydney Kimmel Cancer Center. Peg was previously the director of nursing for the Sydney Kimmel Cancer Center Medical Oncology division. She has significant expertise in oncology care coordination, having also worked at the Fox Chase Cancer Center as the senior director of the first cancer center network in the United States—The Fox Chase Partners Program—supporting development of 30-plus institutions' cancer centers. She is the past president of the Pennsylvania Society of Oncology and Hematology, the statewide American Society of Clinical Oncology group, and is the past president of the American Academy of Medical Administrators. Her research interests are in health outcomes, transition of care, and navigation having published in breast and colorectal navigation processes.

ADDITIONAL RESOURCES

AJMC TV

Dr Brenton Fargnoli Discusses the Creation of a Learning Health System

MORE AT:
ajmc.com/link/2842.

Verzenio™
abemaciclib
50 | 100 | 150 | 200 mg tablets

NOW **APPROVED**

Visit **verzenio.com/hcp** to learn more

Lilly

FACULTY

KEYNOTE SPEAKER

Michael Kolodziej, MD

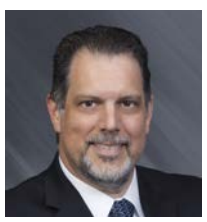
Vice President and Chief Innovation Officer
ADVI Health
Washington, DC

Michael Kolodziej, MD, is the vice president and chief innovation officer of ADVI Health, Inc. He focuses on supporting innovative alternative payment programs, including the Oncology Care Model and private payer initiatives, on behalf of life science, payer, and provider organizations in the United States and globally. He has published more than 50 medical journal articles, abstracts, and book chapters. He specializes in hematology and medical oncology and is board certified in internal medicine, medical oncology, and hematology by the American Board of Internal Medicine. Dr Kolodziej previously served as national medical director at Flatiron Health and Aetna Inc.

FACULTY

Jim Almas, MD

MolDX Medical Director
Palmetto GBA
Columbia, SC



Roger A. Brito, DO

Senior Medical Director, Oncology Solutions
Aetna Inc
Boynton Beach, FL

Joanne Buzaglo, PhD

Senior Vice President, Research & Training
Cancer Support Community
Philadelphia, PA

Michael Diaz, MD

Director of Patient Advocacy
Florida Cancer Specialists & Research Institute
Medical Co-Chair
Community Oncology Alliance Patient Advocacy Network
St. Petersburg, FL

Brenton Fargnoli, MD

Medical Director, Value-Based Care
Director, Product Marketing & Strategy
Flatiron Health
New York, NY

Bruce Feinberg, DO

Vice President and Chief Medical Officer
Cardinal Health Specialty Solutions
Dublin, OH

Torrie K. Fields, MPH

Senior Program Manager,
Advanced Illness & Palliative Care
Blue Shield of California
San Francisco, CA

Mark E. Fleury, PhD

Principal, Policy Development, Emerging Science
American Cancer Society Cancer Action Network, Inc (ACS CAN)
Washington, DC

Bo Gamble

Director of Strategic Planning Initiatives
Community Oncology Alliance
Goldsboro, NC

Rose Gerber

Director of Patient Advocacy & Education
Community Oncology Alliance
Washington, DC

Rebekah Gilbert, RN, BSN, OCN

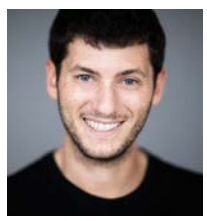
Nurse
Hematology Oncology Associates of Central New York (HOACNY)
Syracuse, NY

Thomas Graf, MD

Vice President and Chief Medical Officer
Horizon Blue Cross Blue Shield of New Jersey
Newark, NJ

Jason Harris

Manager of Public Policy
National Health Council
Washington, DC



Jonathan Hirsch, MSc

President and Founder
Syapse
Palo Alto, CA

Spencer Hoover
System Vice President and Executive Director
Henry Ford Cancer Institute
Detroit, MI

W. Kevin Kelly, DO
Professor, Medical Oncology and Urology
Director, Division of Solid Tumor Oncology
Sidney Kimmel Medical College at Thomas Jefferson University
Associate Director of Clinical Research
Leader, Prostate Cancer Program
Sidney Kimmel Cancer Center
Philadelphia, PA

Michael Kolodziej, MD
Keynote Speaker
Vice President and Chief Innovation Officer
ADVI Health
Washington, DC

Felice H. LePar, MD, MPH
Abington Hematology/Oncology Associates
Willow Grove, PA

Kathleen Lokay
President and Chief Executive Officer
Via Oncology
Pittsburgh, PA

Ian Manners, MBA
Founder and Chief Executive Officer
Vivor
New York, NY

Karon Martyn, MSN, ANP-BC, AOCNP
Nurse Practitioner
Abington Hospital - Jefferson Health
Abington, PA

Stacey McCullough, PharmD
Senior Vice President, Pharmacy
Tennessee Oncology, PLLC
Nashville, TN

Viraj Narayanan
Director, Life Sciences
Cota Healthcare
New York, NY

Kashyap Patel, MD
Medical Oncologist
Managing Partner and CEO
Carolina Blood and Cancer Care
Rock Hill, SC

Kavita Patel, MD, MA
Nonresident Senior Fellow
The Brookings Institute
Co-Founder
Tuple Health
Washington, DC

Marie Kelly Pressler, RN, MSN, OCN
Nurse Navigator
GI, Head and Neck Neurology
Abington Jefferson Health
Abington, PA

Marjorie A. Speers, PhD
Executive Director
WCG Foundation, Inc.
Atlanta, GA

Nicole Taglione
Oncology Financial Navigator
Saint Agnes Cancer Institute
Baltimore, MD

Frank F. Weichold, MD, PhD
Director, Critical Path and Regulatory Science Initiatives
Office of Regulatory Science and Innovation (ORSI)Office of the Chief Scientist (OCS)
Office of the Commissioner (OC)
Food and Drug Administration
Washington, DC

Lalan Wilfong, MD
Medical Director Quality Programs
Texas Oncology
Dallas, TX

Diana Zuckerman, PhD
President
National Center for Health Research
Cancer Prevention and Treatment Fund
Washington, DC

*For patients with metastatic **EGFR T790M** mutation-positive NSCLC, as detected by an FDA-approved test, at progression on or after TKI therapy*

TAGRISSO® (osimertinib)

PROVIDED BREAKTHROUGH PROGRESSION-FREE SURVIVAL VS DOUBLET CHEMOTHERAPY

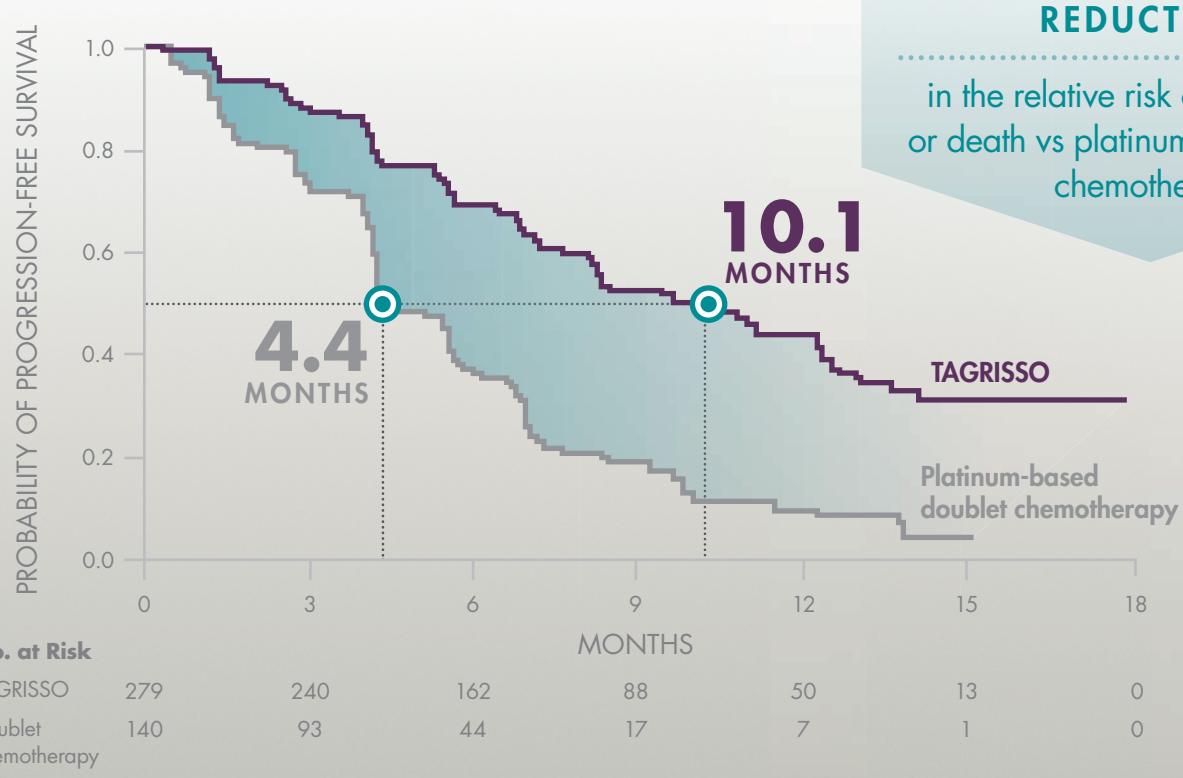
An impressive 10.1 months of median PFS compared to 4.4 months with doublet chemotherapy[1]

- In a Phase III, randomized, open-label, head-to-head clinical trial of 419 patients, TAGRISSO outperformed doublet chemotherapy (pemetrexed plus carboplatin or cisplatin)[1]

PROGRESSION-FREE SURVIVAL*

HR=0.30 | (95% CI: 0.23, 0.41) $p<0.001$

70%
REDUCTION
in the relative risk of progression or death vs platinum-based doublet chemotherapy



No. at Risk

TAGRISSO	279	240	162	88	50	13	0
Doublet chemotherapy	140	93	44	17	7	1	0

- TAGRISSO also demonstrated double the confirmed objective response rate compared to doublet chemotherapy (65% vs 29%)[1]
- A BICR assessment of CNS efficacy by RECIST v1.1 was conducted in the subgroup of 46/419 (11%) patients identified to have measurable CNS lesions on a baseline brain scan[1]
  - An ORR of 57% was seen in the TAGRISSO group and 25% in the doublet chemotherapy group[1]

**As determined by investigator assessment (IA).*

See more results from the AURA3 head-to-head study at **TAGRISSOhcp.com**

TAGRISSO®
osimertinib

IMPORTANT SAFETY INFORMATION

- There are no contraindications for TAGRISSO
- Interstitial Lung Disease (ILD)/Pneumonitis occurred in 3.5% and was fatal in 0.6% of 833 TAGRISSO-treated patients. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms 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 833 TAGRISSO-treated patients, 0.7% of patients were found to have a QTc > 500 msec, and 2.9% of patients had an increase from baseline QTc > 60 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia
- Cardiomyopathy occurred in 1.9% and was fatal in 0.1% of 833 TAGRISSO-treated patients. Left Ventricular Ejection Fraction (LVEF) decline ≥ 10% and a drop to < 50% occurred in 4% of 655 TAGRISSO-treated patients. Conduct cardiac monitoring, including an 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 or persistent, asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue TAGRISSO
- Keratitis was reported in 0.7% of 833 TAGRISSO-treated patients 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
- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during TAGRISSO treatment 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
- The most common adverse reactions (≥20%) in patients treated with TAGRISSO were diarrhea (41%), rash (34%), dry skin (23%), nail toxicity (22%), and fatigue (22%)

INDICATION

TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor therapy.

Please see Brief Summary of complete Prescribing Information on adjacent pages.

Reference: 1. TAGRISSO [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.

AstraZeneca

TAGRISSO® (osimertinib) tablets, for oral use
Brief Summary of Prescribing Information.
For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

DOSAGE AND ADMINISTRATION

Patient Selection

Confirm the presence of a T790M EGFR mutation in tumor or plasma specimens prior to initiation of treatment with TAGRISSO *[see Indications and Usage (1) and Clinical Studies (14) in full Prescribing Information]*. Testing for the presence of the mutation in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If this mutation is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing. Information on FDA-approved tests for the detection of T790M mutations is available at http://www.fda.gov/companiondiagnostics.

Recommended Dosage Regimen

The recommended dose 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 Modification

Adverse Reactions

Table 1. Recommended Dose Modifications for TAGRISSO

Target Organ	Adverse Reaction[a]	Dose 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 or asymptomatic left ventricular dysfunction that persists ≥ 4 weeks	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 coadministering 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 full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

The following information for ILD/ Pneumonitis, QTc Interval Prolongation, Cardiomyopathy and Keratitis reflects exposure to TAGRISSO in 833 patients with EGFR T790M mutation-positive non-small cell lung cancer (NSCLC) who received TAGRISSO at the recommended dose of 80 mg once daily in AURA3 (n=279), AURA Extension (n=201), AURA2 (n=210), and an expansion cohort in the first-in-human trial of osimertinib (AURA1, n=143).

Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis occurred in 3.5% (n=29) of TAGRISSO-treated patients (n=833); 0.6% (n=5) 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 full Prescribing Information]*.

QTc Interval Prolongation

Heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 833 patients treated with TAGRISSO in clinical trials, 0.7% (n=6) were found to have a QTc greater than 500 msec, and 2.9% of patients (n=24) had an increase from baseline QTc greater than 60 msec *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. No QTc-related arrhythmias were reported.

Clinical trials of TAGRISSO did not enroll patients with baseline QTc of greater than 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 full Prescribing Information]*.

Cardiomyopathy

Across clinical trials, cardiomyopathy (defined as cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 1.9% (n=16) of 833 TAGRISSO-treated patients: 0.1% (n=1) of cases were fatal.

Left Ventricular Ejection Fraction (LVEF) decline greater than or equal to 10% and a drop to less than 50% occurred in 4.0% (26/655) of patients who had baseline and at least one follow-up LVEF assessment.

Conduct cardiac monitoring, including an 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 or persistent, asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue TAGRISSO *[see Dosage and Administration (2.4) in full Prescribing Information]*.

Keratitis

Keratitis was reported in 0.7% (n=6) of 833 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 human 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 in patients at the 80 mg dose level.

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) and Clinical Pharmacology (12.3) in 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 full Prescribing Information]*
QTc Interval Prolongation *[see Warnings and Precautions (5.2) in full Prescribing Information]*
Cardiomyopathy *[see Warnings and Precautions (5.3) in full Prescribing Information]*
Keratitis *[see Warnings and Precautions (5.4) in 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 described below reflect exposure to TAGRISSO (80 mg daily) in patients with EGFR T790M mutation-positive metastatic NSCLC in an open-label, randomized, active-controlled trial (AURA3, n=279) and in two single arm trials, AURA Extension (n=201) and AURA2 (n=210). 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 trial enrollment.

AURA3 Trial

The safety of TAGRISSO was evaluated in AURA3, a multicenter international open label randomized (2:1) controlled trial conducted in 419 patients with unresectable or metastatic EGFR T790M mutation-positive NSCLC who had progressive disease following first line EGFR TKI treatment. A total of 279 patients received TAGRISSO 80 mg orally once daily until intolerance to therapy, disease progression, or investigator determination that the patient was no longer benefiting from treatment. A total of 136 patients received pemetrexed plus either carboplatin or cisplatin every three weeks for up to 6 cycles; patients without disease progression after 4 cycles of chemotherapy could continue maintenance pemetrexed until disease progression, unacceptable toxicity, or investigator determination that the patient was no longer benefiting from treatment. Left Ventricular Ejection Fraction (LVEF) was evaluated at screening and every 12 weeks. The median duration of treatment was 8.1 months for patients treated with TAGRISSO and 4.2 months for chemotherapy-treated patients. The trial population characteristics were: median age 62 years, age less than 65 (58%), female (64%), Asian (65%), never smokers (68%), and ECOG PS 0 or 1 (100%).

The most common adverse reactions (≥20%) in patients treated with TAGRISSO were diarrhea (41%), rash (34%), dry skin (23%), nail toxicity (22%), and fatigue (22%). Serious adverse reactions were reported in 18% of patients treated with TAGRISSO and 26% in the chemotherapy group. No single serious adverse reaction was reported in 2% or more patients treated with TAGRISSO. One patient (0.4%) treated with TAGRISSO experienced a fatal adverse reaction (ILD/pneumonitis).

Dose reductions occurred in 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 (1.8%), neutropenia (1.1%), and diarrhea (1.1%). Adverse reactions resulting in permanent discontinuation of TAGRISSO occurred in 7% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3%).

Tables 2 and 3 summarize common adverse reactions and laboratory abnormalities which occurred in TAGRISSO-treated patients in AURA3. AURA3 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 AURA3

Adverse Reaction	TAGRISSO (N=279)		Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=136)	
	All Grades[a] (%)	Grade 3/4[a] (%)	All Grades[a] (%)	Grade 3/4[a] (%)
Gastrointestinal disorders				
Diarrhea	41	1.1	11	1.5
Nausea	16	0.7	49	3.7
Stomatitis	15	0	15	1.5
Constipation	14	0	35	0
Vomiting	11	0.4	20	2.2
Skin disorders				
Rash[b]	34	0.7	5.9	0
Dry skin[c]	23	0	4.4	0
Nail toxicity[d]	22	0	1.5	0
Pruritus[e]	13	0	5.1	0
Metabolism and Nutrition Disorders				
Decreased appetite	18	1.1	36	2.9
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	14	0
Musculoskeletal and Connective Tissue Disorders				
Back pain	10	0.4	9	0.7
General Disorders and Administration Site Conditions				
Fatigue[f]	22	1.8	40	5.1

* NCI CTCAE v4.0.
[a] No grade 4 events were reported.
[b] Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, folliculitis, acne, dermatitis and acneform dermatitis.
[c] Includes dry skin, eczema, skin fissures, xerosis.
[d] Includes nail disorders, nail bed disorders, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail ridging, nail toxicity, onychoclasis, onycholysis, onychomadesis, paronychia.
[e] Includes pruritus, pruritus generalized, eyelid pruritus.
[f] Includes fatigue, asthenia.

Table 3. Common Laboratory Abnormalities (>20% for all NCI CTCAE Grades) in AURA3

Laboratory Abnormality	TAGRISSO (N=279)		Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=131[a])	
	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 (%)
Leukopenia	61	1.1	75	5.3
Lymphopenia	63	8.2	61	9.9
Thrombocytopenia	46	0.7	48	7.4
Neutropenia	27	2.2	49	12

[a] Based on the number of patients with available follow-up laboratory data

AURA Extension and AURA2 Trials

The safety of TAGRISSO was evaluated in two single arm trials, AURA Extension (n=201) and AURA2 (n=210). A total of 411 patients with EGFR 790M mutation-positive NSLC who received one or more prior EGFR therapies including an EGFR TKI were treated with TAGRISSO (80 mg daily). The majority of patients were heavily pretreated. Prior to enrollment, 68% of patients had received at least 2 prior treatment regimens, 46% had received 3 or more prior lines of therapy, and 63% had received prior platinum-based chemotherapy.

Median duration of exposure to TAGRISSO was 7.7 months (range: <0.1 to 11.6 months). The toxicity profile of TAGRISSO observed in the AURA Extension and AURA2 trials was generally consistent with the toxicity profile observed in the AURA3 trial. Four patients (1%) treated with TAGRISSO developed fatal adverse reactions of ILD/pneumonitis. Discontinuation of therapy due to adverse reactions occurred in 5.6% of patients treated with TAGRISSO. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis.

DRUG INTERACTIONS

Effect of Other Drugs on Osimertinib

Strong CYP3A Inducers

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

Avoid coadministering TAGRISSO with strong CYP3A inducers (e.g., phenytoin, rifampin, carbamazepine, St. John's Wort) [note: effect of St. John's Wort varies widely and is preparation-dependent]. Increase the TAGRISSO dosage when coadministering with a strong CYP3A4 inducer if concurrent use is unavoidable *[see Dosage and Administration (2.4) in 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

Coadministering TAGRISSO with a BCRP substrate increased the exposure of the BCRP substrate compared to administering the BCRP substrate alone *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Increased BCRP substrate exposure may increase the risk of exposure-related toxicity.

Monitor for adverse reactions of the BCRP substrate (e.g., rosuvastatin, sulfasalazine, topotecan), unless otherwise instructed in its approved labeling, when coadministered with TAGRISSO.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action, 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 human 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 in patients at the recommended dose of 80 mg), 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 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 full Prescribing Information]*. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise a lactating woman not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Contraception

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 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 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 full Prescribing Information]*.

Pediatric Use

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

Geriatric Use

Three hundred and forty-six (42%) of the 833 patients in AURA3 (n=279), AURA Extension (n=201), AURA2 (n=210), and an expansion cohort in the first-in-human trial of osimertinib (AURA1, n=143) 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 (9.8% versus 6.8%) and more frequent dose modifications for adverse reactions (10.1% versus 6.0%) in patients 65 years or older as compared to those younger than 65 years.

Renal Impairment

No dose adjustment is recommended in patients with mild, [creatinine clearance (CLcr) 60-89 mL/min, as estimated by the Cockcroft Gault method (C-G)] moderate, (CLcr 30-59 mL/min, as estimated by C-G) or severe (CLcr 15-29 mL/min) renal impairment. There is no recommended dose of TAGRISSO for patients with end-stage renal disease *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

No dose adjustment is recommended in patients with mild hepatic impairment [total bilirubin less than or equal to upper limit of normal (ULN) and AST greater than ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST] or moderate hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST). There is no recommended dose for TAGRISSO for patients with severe hepatic impairment *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

Iss. 03/17 3338005 4/17

FDA Moves to Era of Active Participant in Drug Development

Mary Caffrey

THE HEADLINES OF THE 21ST CENTURY Cures Act said it provided $6.4 billion for scientific research for cancer, Alzheimer disease, and opioid addiction, as well as steps to speed drug development, including new approval pathways for certain devices and biologics.[1,2]

But beyond that, said the FDA's Frank Weichold, MD, PhD, of the Office of the Commissioner and the Office of the Chief Scientist, the Cures Act brings a new way of thinking about the agency's role: For decades, most regulation was a reaction to some tragedy or weakness in existing rules. Cures ushers in an era of the FDA as a partner in drug development, Weichold said, as he kicked off Patient-Centered Oncology Care®, held November 16 and 17, 2017, in Philadelphia, Pennsylvania.

Speaking before a gathering of *The American Journal of Managed Care*®, Weichold explained how the FDA has created a culture of regulatory science and that the Cures Act brings the next step. Regulatory science is not "an attempt to regulate science," he said, but an effort to guarantee that rulemaking for drugs, foods, and consumer products under the agency's purview follows a process that ensures safety and quality under standards that are consistent and not based on unexpected whims. The less evidence there is, the more individual judgment creeps into the process, Weichold explained.

With the Cures Act, drug development will be simultaneously more evidence driven and patient centered. "It makes the FDA an active participant in drug development, and it requires us to focus more on patient-focused drug development using novel innovative trial designs, applying real-world evidence, and create drug development tools to speed this up," Weichold said. Clinical trials as we know them are "essentially disconnected from the real word," he noted, and that sometimes results in real-world outcomes that don't match what happened in studies—to say nothing of the high research costs.

Frank Weichold, MD, PhD, of the FDA Office of the Commissioner and the Office of the Chief Scientist, tells listeners at Patient-Centered Oncology Care® how the agency is taking a more proactive role in drug development.

FDA Commissioner Scott Gottlieb, MD, supports the use of computer modeling in the drug development process, Weichold said, as well as adaptive and novel trial designs that are already in use. But this requires good data—and Weichold said there's much to be done to get data out of silos and to encourage sharing to create algorithms that can speed medical decisions, with fewer errors.

"We are on an inflection point when it comes to the reductionist position and thinking in a holistic world, and what's between is a lot of data," he said.

Knowledge and data sharing isn't where it should be, Weichold said, and "we need better communication, and we need better transparency opportunities" that are not a burden for investigators. Yet he said every person in the room could likely think of an example of a hospital administrator or rule maker who prevented data sharing.

The 21st Century Cures Act calls on regulators to "get engaged," Weichold said, and facilitate sharing by creating frameworks to make it happen. Because when it happens, patients will benefit, he said.

"Essentially, to enter the right data once and use it many times is something that we have to accomplish," Weichold said. Regulators can help health systems address privacy and safety concerns, but "we have to change the culture," he added.

He pointed out examples from the FDA's Oncology Center of Excellence, which collaborated with the Harvard Business School to develop master trial protocols; he also discussed the I-SPY 2 breast cancer trial, which follows an adaptive design that takes the response times from patients as they move through the trial to make treatment decisions for future patients.[3]

Data sharing is key in developing better biomarkers, Weichold said, which the I-SPY trials and other analyses have shown can be used as surrogate end points, to help bring drugs to market fast and identify positive responders. He cited work by Laura Esserman, MD, MBA, at the University of California at San Francisco in the I-SPY trials, which has shown how trials can work with real-time feedback.

Data and technology alone are not enough, however. "We have most of the things that it takes to have a continuous collaborative and transparent system, including data exchange, data liberation, [and] data markets, if you want to call it that way," he said. "But what we need is to build trust and build relationships, and as such, it all hinges on the people—people who are also depending on the FDA."

Who are the final collaborators? Patients. "We need to include patients in a different way—make them co-researchers, codevelopers—and leverage the tools that we have in our advanced age of technology."

"And with that," he concluded, "we will have better outcomes, better performance, and, perhaps, happier people." ◆

REFERENCES

1. 21st Century Cures Act. FDA website. fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/21stCenturyCuresAct/default.htm. Updated September 14, 2017.
2. DeBonis M. Congress passes 21st Century Cures Act, boosting research and easing drug approvals. *Washington Post*. December 7, 2016. washingtonpost.com/news/powerpost/wp/2016/12/07/congress-passes-21st-century-cures-act-boosting-research-and-easing-drug-approvals/?utm_term=.aade676a9585. Accessed January 4, 2018.
3. The I-SPY trials. ispytrials.org/home. Accessed January 4, 2018.

Building a Culture of Transparency Is Key to FDA in 2018, Experts Say

Alison Rodriguez

THE FDA'S ROLE IN ESTABLISHING THE standards and regulations for public health would benefit from increased transparency, according to stakeholders who included a representative from the agency. The group was part of a panel that appeared on the first day of Patient-Centered Oncology Care®, presented November 16 and 17, 2017, in Philadelphia, Pennsylvania, by *The American Journal of Managed Care®*.

Panelists included Roger Brito, DO, senior medical director of Oncology Solutions at Aetna; Mark Fleury, PhD, principal of policy development at the American Cancer Society Cancer Action Network; and Frank F. Weichold, MD, PhD, director for Critical Path and Regulatory Science, Office of Regulatory Science and Innovation, Office of Chief Scientist, in the Office of Commissioner of FDA.

Brito discussed expanding the oncology footprint at Aetna through potentially collaborating with the FDA to increase data-sharing transparency; this would benefit clinical trials and pilot studies. Brito explained that such transparency could be achieved through top-down engagement not only with providers but also with Aetna members. "I think it's an exciting time to be in healthcare. I think we need to collaborate, include the patients, include pharmaceutical industries, [the] FDA, [the] healthcare company," he said.

Referring to the cost of care, Brito emphasized that transparency will allow all stakeholders to know about different therapies and treatments earlier in the pipeline, which will improve the cost-containing measures among therapeutics.

Weichold also explained that transparency is necessary to identify areas of improvement between the drug regulators and the patients. He expressed the need for building a new culture in which all stakeholders are contributing resources. "We need to be able to engage the stakeholders and include experts, not just opinion leaders but actual experts that can, through scientific means, define opportunities for solutions," he said.

Weichold noted that increased transparency could be achieved through embracing the opportunities that technology provides. For example, he mentioned the app HUGO, which gives physicians easy access to patient records. Weichold also noted the significance for high-quality data and access to such data—a component that the United States could adopt from European models.

Fleury discussed the role of advocacy organizations in working to bring people together and sparking policy conversations among groups of stakeholders. He offered a recent example of a pediatric cancer drug that had biological, regulatory, and financial factors that were different from those of a drug developed for adults; stakeholders came together to reach a common understanding of the problem.

"I THINK WE NEED TO COLLABORATE, INCLUDE THE PATIENTS, INCLUDE THE PHARMACEUTICAL INDUSTRIES, [THE] FDA, [THE] HEALTHCARE COMPANY."

—Roger Brito, DO

The FDA faces an ongoing challenge of deciding whether the benefits outweigh the risks for the average patient for a condition—although all patients are different, Fleury said. Therefore, he explained, the system is moving toward gathering the patient's experience and perspective so the FDA does not have to make decisions based on the "average" patient.

Additionally, Fleury noted the importance of providing education to individual patients while ensuring that they trust their physician, as part of building the new culture. "I do think there's an important role to make sure that we inform the system and create a system that makes sure that they are getting the best possible care and not rely on that patient on day 1 knowing everything that they should ask and everything that they could do," Fleury said.

Although many changes to the care system are needed, the experts all agreed on the progress that has been made, and they believe progress will continue to be made by the FDA in 2018.

"The agency, I can tell you, from its leadership but also in particular from its staff, [is] very much interested and feels a high level of responsibility and also a sense of public service to make significant contributions to that," Weichold said. ◆

From left, Roger Brito, DO, of Aetna; Mark Fleury, PhD, of the American Cancer Society Cancer Action Network; and Frank Weichold, MD, PhD, of FDA, join moderator Margaret "Peg" O'Grady, RN, MSN, OCN, FAAMA, for a discussion of FDA's efforts to build a culture of transparency.

Weighing the Merits of Right-to-Try Laws and FDA's Expanded Access Program

Alison Rodriguez and Mary Caffrey

KELLY

SPEERS

ZUCKERMAN

JUST A MONTH BEFORE ATTENDEES gathered in Philadelphia, Pennsylvania, for the annual meeting of Patient-Centered Oncology Care®, legislators in the state's capital of Harrisburg made it the 38th to pass a right-to-try law. That was 6 states in 2017 alone.[1] Championed by conservative groups like the Goldwater Institute as well as Vice President Mike Pence,[2] the laws sound good on their face: they can connect terminally ill patients with experimental treatments; even opponents say the idea of giving dying patients "one last chance" is hard to oppose.

But as panelists discussed during the session presented by *The American Journal of Managed Care®*, these state laws are not necessarily good for patients or long-term drug development, and there is a better alternative: the FDA's newly streamlined Expanded Access program, which allows patients to gain access to investigational therapies in a more regulated way, with greater accountability. Thus, there is great concern about a proposed federal right-to-try legislation, including a version that has passed the United States Senate.

The panel featured W. Kevin Kelly, DO, director of the Division of Solid Tumor Oncology at the Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia; Marjorie A. Speers, PhD, executive director for the WCG Foundation; and Diana Zuckerman, PhD, president of the National Center for Health Research, board member of the Reagan-Udall Foundation.

As Speers explained, the Expanded Access program began decades ago during the AIDS crisis, when patients demanded protocols be established for those not enrolled in a clinical trial who wanted to try a potentially life-saving medication when nothing else was available. Once FDA approves a request, the patient's doctor supervises administration of the drug as an extension of an ongoing clinical trial, with significant reporting requirements. The modern proliferation of right-to-try laws has occurred even though FDA has streamlined its process and increased its approval of individual Expanded Access applications, from 1200 to 1500 in recent years, she said. "There has been a lot of attention and pressure on the FDA to make more of these drugs available," Speers said. "And much of that has been through social media."

Zuckerman said that so far, state-level right-to-try laws have not had a significant effect, but the proposed version of a federal law could do harm by letting patients obtain drugs independent of the FDA. The Senate version was amended so that drug makers are not required to sell investigational drugs to patients outside of clinical trials, but if they do, they must report adverse events to the FDA.[2] Typically, patients receiving investigational drugs while they are going through FDA approval can only be charged for the drug's manufacturing cost, and patients usually receive them for free. Zimmerman said an early version of the bill did not cap sale prices, but the bill that passed the Senate only allows pharmaceutical companies to charge manufacturing costs.[2] Still, if patients obtain drugs this way, there are far fewer requirements than there are currently under the FDA's Expanded Access program.[3]

And this appears to be central to the appeal: Right-to-try laws purport to cut the FDA out of the picture, connecting patients directly with pharmaceutical companies to reduce burdens on patients and physicians, if drugs have cleared phase 1 safety hurdles. But some see this as a threat to the drug development process; FDA's Expanded Access requires at least some evidence of efficacy in addition to phase 1 results.

Speers discussed the 3 categories of use under the FDA's Expanded Access program. Applications can be submitted for (1) individual patients, (2) intermediate-size patient populations, (3) wider treatment use ahead of distribution after approval.

Because this process includes patients with life-threatening diseases, Speers noted that the FDA has ensured transparency in the process of accessing the necessary experimental drugs. Therefore, a patient must complete an application, and a specific judgment about the individual patient is made by the FDA. The agency also can also review the requests with a clinical trial's Institutional Review Board.

Speers also discussed the accessibility of experimental medications for patients through the Expanded Access program. Some of the issues raised through the expansion of right-to-try laws concern the low number of patients who take part in clinical trials—it's only about 10%.

"There are things that we can do to move trials along more quickly, and it's across a whole range of things: recruitment, data, and design, and what's required as a standard to make the decision. That's I think where we want our emphasis to be, and for this to be a smaller program but remove those barriers that can be removed from it," she said.

Kelly, a clinician, emphasized the importance of safety when evaluating patients for investigational drugs, considering that many clinicians would not have experience in administering these drugs.

"Can we get more expansion protocols to expand to more patients, [and] decrease the eligibility criteria, so we can treat these patients on a study [by] physicians who actually know how to use the drugs?" Kelly asked.

Still, he has seen both sides of the issue. "I spent several years at the FDA on the advisory committee, so I know the safety issue that they grapple with," he said. "But being on the front line, it's a lot different. I have patients coming to me to all the time asking me about investigational drugs. Some are appropriate, some are not … And it's a lot of education that the patients actually need to understand what is their disease, what are the treatments, and what is a reality."

The rise of checkpoint inhibitors offers a great example, he said, in that there are significant toxicities involved—if a physician has never seen them he or she might not know how to handle them. To expand access and knowledge among clinicians, collaborative databases should be developed so data can be shared among a large range of individuals.

Zuckerman also noted the importance of physicians and patients reporting the serious adverse events from individual patient uses of investigational drugs. In the Expanded Access program, physicians administer the drugs on behalf of the FDA and there are significant reporting requirements, which demands accountability, according to Zuckerman.

"I think we really should focus on education for physicians who want to use an investigational drug through Expanded Access," she said.

Despite the risks and challenges involved in administering these investigational drugs, Zuckerman said there are ways to streamline the application and monitoring process, so that safety can still be the highest priority while making it easier for patients and physicians to participate.

Each panelist expressed the issues and potentially negative effects of the federal right-to-try laws. Each concluded by offering an ideal system that would address the different concerns. Zuckerman proposed a simpler system that makes it easier for patients, Speers proposed limiting the use of expanded access until after a drug has been approved by the FDA but before it is on the market, and Kelly proposed a patient-centric system that provides patients with a direct source for information. ◆

REFERENCES

1. Pennsylvania becomes the 38th state to pass right to try. Goldwater Institute website. goldwaterinstitute.org/article/pennsylvania-becomes-38th-state-to-pass-right-to-try/. Published October 13, 2017. Accessed January 16, 2018.
2. Karlin-Smith S, Kim SM. Senate approves 'right-to-try' drug bill. Politico. www.politico.com/story/2017/08/03/senate-right-to-try-drug-bill-241293. Published August 3, 2017. Accessed January 16, 2018.
3. FDA Expanded Access (Compassionate Use). FDA website. fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm. Updated January 4, 2018. Accessed January 16, 2018.

Via Oncology's Lokay on Real-World Impact of Digital Decision-Support Solutions

Alison Rodriguez

CLINICAL CARE PATHWAYS HAVE COME a long way, according to Kathleen Lokay, the president and CEO of Via Oncology, who discussed the real-world impact of digital decision-support solutions at Patient-Centered Oncology Care® in Philadelphia, Pennsylvania. The meeting was held November 16-17, 2017, presented by *The American Journal of Managed Care®*.

Lokay emphasized the importance of content in treatment pathways. She explained that treatment pathways typically start out small, with tracks for only a few diseases, and then evolve to incorporate different phases of care, like symptom management, workup, or surveillance.

At Via Oncology, Lokay said the evolving pathway model builds accountability among physicians by forcing them to consider the patient perspective in pathway development. This is accomplished through a committee system, with 36 panels that meet throughout the year to adapt and update pathways.

The 3 pathway determinants Lokay discussed in her presentation include:

- **Efficacy**: If one treatment represents the clear choice, it becomes the pathway.
- **Toxicity**: If efficacy between different treatments is comparable, the pathway calls for treatments with less toxicity to improve quality of life and reduce hospitalization and emergency department visits.
- **Cost**: Only if efficacy and toxicity are comparable will the pathway choose the lower cost treatment for the payer.

Lokay also discussed the need for multiple options that accommodate different patient preferences in the pathway. "Even though we haven't changed the construct about how we develop the pathways, we've had to get smarter about giving more information if [patients] need it and creating situations where maybe the pathway even actually has a recommendation for a financial toxicity situation that would take you away from the single best and take you to something that has sort of that economic trade-off for the patient," Lokay stated.

Despite the efforts and evolution of the pathway, real-world evidence has not yet been incorporated—but it could be added at a later point. "I always have trouble saying that phrase, 'real-world evidence.' And partially that's because what we really need to be able to do is make sure that that real-world evidence has the same kind of voracity that the published trial data do," Lokay explained. "But I think, until it rises to that level to actually make pathway decisions on treatment recommendations based on that, we're just not there yet."

She noted that pathways need to have a way of remaining up-to-date. She mentioned iKnowMed, which customizes and regularly updates the pathway so it can be easily shared. The output can then be used by the physicians to make treatment decisions.

The electronic health record (EHR) is also critical to decision support, according to Lokay. Integrating the EHR with the pathway decision-support software, like iKnowMed, would produce a high level of connectivity and common set of content for physicians to use. Additionally, making sure information from the most recent clinical trial results finds its way into pathways is critical, as this ensures the content of the pathway provides value to decisions.

Lokay separated the players involved into 3 categories: precision medicine support companies and big data companies, those that create services for payers, and those that are trying to create their own pathways.

At the conclusion of the presentation, when asked about the provider versus the payer pathway, Kathy discussed the content and software parts of the pathways. She overall predicts that pathways will expand into more areas of oncology and evolve as multidisciplinary pathways.

"So, the content is really not the issue that we find. What we find the rub in is that the physicians will use our pathway and then their team will still have to use the software to submit data for the other pathway…The problem is how to keep up with that because our pathways are changing, their pathways are changing, [and] they're changing at different points in time," Lokay said. "It is a real challenge." ◆

During her remarks, Via Oncology President and CEO Kathleen Lokay explained how customed technology and integration with electronic health records helps keep clinical care pathways up-to-date.

Panel Addresses Impact of Digital Data Collection and Utilization on Quality Assessment

Alison Rodriguez

THE USE OF DIGITAL DATA has become a prominent aspect in medicine as technology continues to advance. A panel at the Patient-Centered Oncology Care® meeting held in Philadelphia, Pennsylvania, November 16 and 17, 2017, explored the impact of digital data on different aspects of healthcare. *The American Journal of Managed Care®* presented the meeting.

The panel featured Torrie K. Fields, MPH, senior program manager for Advanced Illness and Palliative Care at Blue Shield of California; Viraj Narayanan, director of Life Sciences at Cota; and Kathleen Lokay, president and CEO of Via Oncology.

"ONE OF THE REALLY BIG OPPORTUNITIES IS TO USE EVIDENCE AND PATHWAYS [AND] TO UNDERSTAND HOW INDIVIDUAL DECISIONS ARE BEING MADE, SO WE HAVE THE RIGHT SOLUTION ARCHITECTURE IN PLACE."

—Viraj Narayanan

Fields said Blue Shield uses digital data to allow for greater flexibility in treatment pathways for those with serious illnesses. She emphasized the need to ensure that oncologists and patients are communicating and fully understand their treatment options. The 2 things to consider when assessing quality and utilization are understanding variance and considering the patient perspective.

"Spending that time to evaluate what a patient needs and also what the impact is on that family—and making sure that you're not only thinking about survivorship planning but you're also thinking about pain and symptoms—and measuring pain and symptoms in a systemic way [are] important," Fields noted.

Fields also discussed minimizing risks in decision making, symptoms, and variability to ensure quality care. Blue Shield of California benchmarks practices against one another to compare them; however, those that have the highest quality rise to the top rather than those that focus on cost—therefore, quality becomes the higher priority.

Narayanan explained that Cota is able to extract data from electronic health records and organize the information to create an asset for the oncologist—providing the oncologist with all the essential data on the patient and the options for subsequent treatments. Furthermore, the Cota Nodal Address is a stratification tool that takes the patient information and labels it with a digital code. With this code, the system works to identify similar patients in the country and considers the treatments they are receiving and their outcomes. Narayanan emphasized the importance of looking at these real-world outcomes and identifying points of variance.

"So, what we're hoping to accomplish, and what our mission is, [is] to optimize care for every individual patient while reducing the total cost of care for the population," Narayanan stated.

Lokay discussed the process of ensuring quality in different treatment pathways. She explained that every decision is put into software that is fully transparent for the physicians who use the pathways. Therefore, they can provide immediate feedback if they disagree with the decision that a committee made about the treatment. Lokay called this the self-policing model.

She also noted the risks of real-world evidence, which must be controlled in order to avoid incorrect answers. Narayanan further explained that real-world evidence is not "clean data;" using it requires adhering to the right standards to make decisions from that information.

"I think one of the really big opportunities is to use evidence and pathways [and] understand how individual decisions are being made so we have the right solution architecture in place," Narayanan stated.

Narayanan noted the patient-reported outcomes tool that measures how treatment decisions are affected by the feeling of the patient. The voice of the patient will continue to be emphasized in the future as a supplement to the data, Narayanan explained. Although tools that can combine such information are difficult and costly to administer, they are something to consider as provider partnerships scale up.

"We think that a big part of the future is making sure that we're embedding that voice of the patient in combination with the clinical data as much as we can. And that's not with payer data but directly with the patient. We think that if we can start to see that, then we can see, especially in end-of-life circumstances, for example, there might be some light shed on what are the best decisions that can be made for patients," Narayanan concluded. ◆

Torrie K. Fields, MPH, of Blue Shield of California, center, makes a point in a discussion with Viraj Narayanan of Cota Healthcare, Kathleen Lokay, and Margaret "Peg" O'Grady, RN, MSN, OCN, FAAMA.

Digital Support to Improve Performance Outcomes

Alison Rodriguez

AS TECHNOLOGY ADVANCES, the hope is that the healthcare system can translate improvements into better outcomes for patients. A panel at the Patient-Centered Oncology Care® meeting presented November 16-17, 2017, by *The American Journal of Managed Care*® in Philadelphia, Pennsylvania, examined the ways in which digital support can make this happen.

The panel included Brenton Fargnoli, MD, medical director for value-based care and director of product and marketing strategies at Flatiron Health, New York, New York; Felice H. LePar, MD, MPH, medical oncologist at Abington Hematology Oncology Associates in Willow Grove, Pennsylvania; Jonathan Hirsch, president and founder of Syapse in Palo Alto, California; and Spencer Hoover, assistant vice president and executive director for the Henry Ford Cancer Institute in Detroit, Michigan.

"I THINK THAT THE POINT IS—ESPECIALLY FOR SMALL PRACTICES, RELATIVELY SMALL PRACTICES LIKE OURS—WE NEED SUPPORT."

—Felice H. LePar, MD, MPH

Hoover emphasized the importance of clinical trials at Henry Ford. A systematized integration of data can be used to prescreen patients and put them on trials faster. Hirsch explained that Syapse has created a standard for molecular data interoperability so that there are consistent data to compare—something that is needed for clinical trials. Now there is a clinical trial matching solution, and those who are providing the recommendations know more about the patient, which helps prevent different interpretations of eligibility criteria.

"What we've started doing more recently is not just trying to work directly with the sponsor to get them to structure the criteria in a computable format that can be compared against the medical record data, but really working on the up-front optimization so that the eligibility criteria can reflect, in particular, what we see in the community health systems that we work with," Hirsch explained.

Hirsch also expressed how Syapse is able to achieve integration from different health systems. He explained how despite the competitiveness among health systems, they integrate and share information through Syapse. Therefore, data can be taken from the health systems to make outcome and quality measurements.

Fargnoli discussed the importance of data being available to both large health systems and to community oncology practices. He emphasized an integrated system in which data are entered as a natural part of the workflow and captured at the point of care—and analyzed to determine the quality measurements.

"Of course, and I'm a physician myself, we don't always enter things in structured fields. And so, for that on the back end, we provide data completeness work lists for the teams to say these data points are specifically missing for these patients and to go through and ensure that those get completed, so you can get a whole picture, a complete picture across," Fargnoli said.

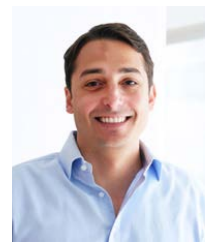
LePar explained how digital data can analyze and account for small pieces of patient information that cannot be accounted for in another way. When the data are digital, they can be organized into codes that provide and store information in a simpler way.

"I think the point of that is—especially for small practices, relatively small practices like ours—we need the support. That would be something that would be impossible to do just by paper, and really that it's an iterative process, that there are hidden complexities in things that on their face seem very simple," LePar said.

When discussing palliative care, Hoover noted Henry Ford's in-house care pathway initiative that works to tie together the patient care experience and engagement with all aspects of the health system. This is a start for addressing palliative care templates, however. Hoover emphasized the need for the industry as a whole to work on palliative medicine and its integration into the health system.

Furthermore, Fargnoli explained that having certain requirements, like the 13-point care plan, can be a reminder in the oncology care model and should be worked into a care plan and that these specific plans could act as a standard template in electronic medical records.

In conclusion, all panelists noted the benefits and progress that technology and digital data have made, but there is still more that can be done in the future to increase their benefits. ◆



FARGNOLI

From left, Jonathan Hirsch, MSc, of Syapse; Felice H. LePar, MD, MPH, of Abington Hematology-Oncology; and Spencer Hoover of Henry Ford Cancer Institute.

Oncologists Can Save Oncology if They Take Ownership of Costs, Kolodziej Says

Mary Caffrey

IF ONCOLOGISTS ARE TO BRING INNOVATIVE treatments to the patients who most need them, they must confront their own role in escalating costs—and take ownership of the solutions, said a leading oncologist who has worn the hat of payer and technology leader.

"If oncology is going to get fixed, oncologists need to fix it," said Michael Kolodziej, MD, ADVI's vice president and chief innovation officer, who has worked recently for Flatiron Health and spent 3 years at Aetna. Kolodziej was the keynote speaker at Patient-Centered Oncology Care®, the annual meeting that brings together stakeholders across cancer care, presented by *The American Journal of Managed Care*®. The meeting took place November 16 and 17, 2017, at Loews Philadelphia Hotel in Pennsylvania.

Is the cost of cancer drugs a problem? Of course, Kolodziej said. But the decisions oncologists make are a big reason that US cancer care costs are on track to rise 27% to $157.77 billion by 2020 from where they were in 2010.[1]

Kolodziej pointed to 3 pressure points: the cost of chemotherapy, poor end-of-life care (EOL), and unnecessary hospitalizations and emergency department visits. Oncologists can do more to impact all 3 by using patient-centered medical homes, embracing clinical care pathways, and encouraging better palliative and EOL care.

For all the innovation in cancer care, oncologists have hit a crossroads. Kolodziej showed a photo of the gas lines in the 1970s and likened oncologists to the Detroit, Michigan, auto industry of that era: Refusing to change is not an option, he said.

He then featured a slide of Kymriah, the first approved chimeric antigen receptor (CAR) T-cell therapy, developed just a few blocks from the meeting site at Penn Medicine.[2] For pediatric patients with acute lymphoblastic leukemia (ALL), Kolodziej said, "this is transformative."

He described the old way of thinking: "The doctor might say, 'Why don't I just give it to everybody with ALL?' It's not that the doctor is wrong. It's just that the game has changed." Kolodziej understands that thought process. "We come from a time when we had so few therapeutic choices and were willing to try anything," he said.

But today, oncologists have many choices—and that's part of the problem, he said. Unnecessary variation helps drive up costs, leading to the rise of clinical pathways to guide care based on the best evidence available.

For oncologists who don't like pathways, Kolodziej was blunt: Quit complaining.

And rein it in even further, he said: "Stop complaining about pharmaceutical companies that are just trying to get a return on their investment."

Embracing change will give oncologists the ability to connect the right patients with CAR T-cell therapy, even though "it costs more than most of your houses," he said.

Team-based care, early use of palliative care, and better use of EOL care not only reduce hospitalization and save money but also lead to better experiences for patients, Kolodziej said.

Despite all the advances in cancer care, some patients will not be cured, and oncologists must help these patients manage their disease so they have the best quality of life for as long as possible. That may mean having different conservations from those in the past.

Oncologist Michael Kolodziej, MD, who has been both a provider and payer in his career, is now the vice president and chief innovation officer for ADVI.

Although patients typically won't bring up EOL care when they are first diagnosed, they know what they don't want. In 2010, 28% of cancer patients spent time in the intensive care unit (ICU) in the last month of life.[3] Although oncologists might be unsure about what patients want, Kolodziej said, "none of them said, 'I'd really like to spend time in the ICU before I die.'"

Kolodziej then reviewed evidence from the COME HOME project[4] and other efforts to reduce costs, noting evidence from the University of Alabama at Birmingham that found pairing patients with lay navigators dramatically reduced costs.[5]

Some oncologists might not like pathways or medical homes or be reluctant to promote good end-of-life care, but the arrival of changing reimbursement structures and Medicare's Oncology Care Model will compel change. "Every one of these practices is going to be doing this math," Kolodziej said. ◆

REFERENCES

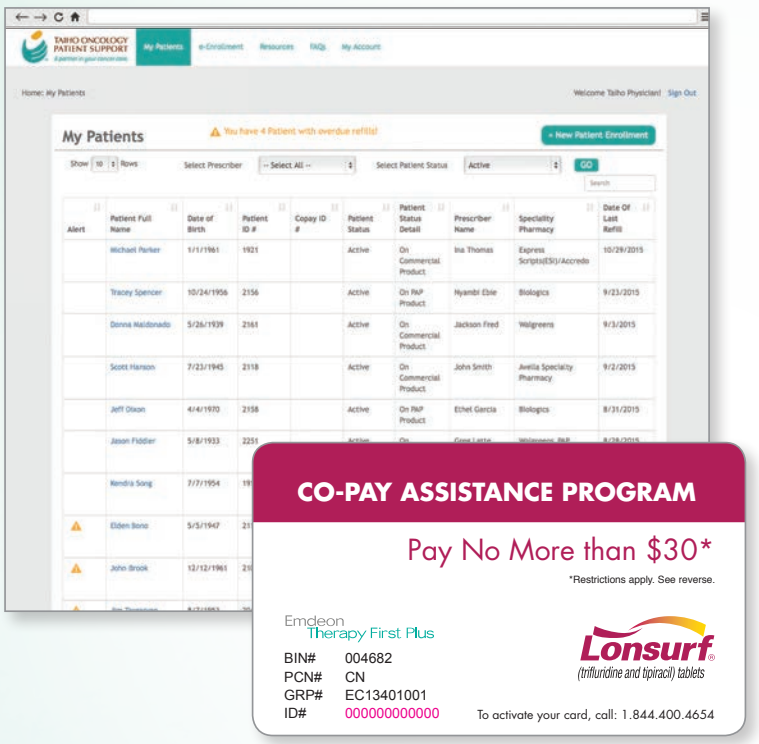
1. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst.* 2011;103(2):117-128. doi.org/10.1093/jnci/djq495.
2. FDA approves personalized cellular therapy for advanced leukemia developed by University of Pennsylvania and Children's Hospital of Philadelphia [press release]. Philadelphia, PA: Penn Medicine; August 30, 2017. pennmedicine.org/news/news-releases/2017/august/fda-approves-personalized-cellular-therapy-for-advanced-leukemia. Accessed December 11, 2017.
3. Goodman DC, Morden NE, Chang CH, Fisher ES, Wennberg JE. Trends in cancer care near the of life. The Dartmouth Atlas of Health Care website. www.dartmouthatlas.org/downloads/reports/Cancer_brief_090413.pdf. Published September 4, 2013. Accessed November 16, 2017.
4. Colligan EM, Ewald E, Ruiz S, Spafford M, Cross-Barnet C, Parashuram S. Innovative oncology care models improve end-of-life quality, reduce utilization and spending. Health Aff (*Millwood*). 2017;36(3):433-440. doi: 10.1377/hlthaff.2016.1303.
5. Rocque GB, Pisu M, Jackson BE, et al. Resource use and Medicare costs during lay navigation for geriatric patients with cancer. *JAMA Oncol.* 2017;3(6):817-825. doi: 10.1001/jamaoncol.2016.6307.

TAIHO ONCOLOGY PATIENT SUPPORT

A partner in your cancer care.

Getting Patients Access to Treatment Can Be Challenging—**WE CAN HELP**

Taiho Oncology Patient Support complements the care you provide by offering customizable services that help with access and reimbursement for LONSURF® (trifluridine and tipiracil). We strive to make this critical step in your patients' treatment as simple as possible.



- **Benefit Investigations**
- **Prior Authorization and Appeals Assistance**
- **Specialty Pharmacy Rx Coordination**
- **Co-pay Support**
- **Patient Assistance Program**
- **Alternate Funding Support**
- **Personalized Nurse Support 24/7**
- **Online Provider Portal**

Enrollment is easy and convenient, both online and by phone

To learn more, visit
www.TaihoPatientSupport.com
and access the provider portal

Call our Resource Center toll free at
(844) TAIHO-4U [844-824-4648]
Monday through Friday, 8 AM – 8 PM ET

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

Lonsurf® (trifluridine and tipiracil) tablets

TAIHO ONCOLOGY

Lonsurf®
(trifluridine and tipiracil) tablets

Indication

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.

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.

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 breast-feed during treatment with LONSURF and for 1 day following the final dose.

Male Contraception: 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: Grade 3 or 4 neutropenia and thrombocytopenia and Grade 3 anemia occurred more commonly in patients 65 years or older who received LONSURF.

Renal Impairment: Patients with moderate renal impairment may require dose modifications for increased toxicity. No patients with severe renal impairment were enrolled in Study 1.

Hepatic Impairment: Patients with moderate or severe hepatic impairment were not enrolled in Study 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%).

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 the following pages.

Learn more at LONSURFhcp.com

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
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-treatment 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.

7 DRUG INTERACTIONS
No pharmacokinetic drug-drug interaction studies have been conducted with LONSURF.

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 trifuridine/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

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of LONSURF. No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin (TB) 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). Patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment were not enrolled in Study 1. *[*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 dose 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. No patients with severe renal impairment (CLcr < 30 mL/min) were enrolled in Study 1. *[*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)]*

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.

What Implementing the OCM Looks Like in a Large Practice

Mary Caffrey

MOVING AWAY FROM A FEE-FOR-SERVICE (FFS) reimbursement model to one that rewards value is no small undertaking for a busy practice. As the second day of Patient-Centered Oncology Care® opened on November 17, 2017, moderator Margaret O'Grady, RN, MSN, OCN, FAAMA, administrative director of the Oncology Service Line at Abington Memorial Hospital, Jefferson Health System, said it's important to see the best practice methodologies.

In cancer care, that means understanding how practices are adapting to the Oncology Care Model (OCM), which is now in the second year of its 5-year run under the Center for Medicare and Medicaid Innovation.[1] Lalan Wilfong, MD, medical director for quality programs at Texas Oncology, shared how adapting to the OCM caused Texas Oncology to dig deeper into what it did well, where it could improve, and where variation and excess staffing had crept in, given that the 420-physician practice had grown through acquisitions.

Wilfong outlined the OCM basics: the model operates in 6-month episodes, which can be repeated, with Medicare paying a services fee for qualifying patients as well as shared savings. Wilfong went through the required OCM elements:

- 24/7 patient access
- Use of electronic health records
- Using data for quality improvement
- Offering core functions of patient navigation
- Documenting a care plan, based on nationally recognized clinical guidelines
- Use of quality metrics for shared savings and claims-based metrics
- Documentation of care for pain, depression screening, and certain medications.

When Texas Oncology first signed on for OCM, Wilfong said some responded, "What are you doing to me?" But others embraced it.

"What this forced us to do, for the very first time in our practice, it forced us to sit down and think about how we take care of our patients. We always thought we did a good job," he said. The practice was growing, but oncology was changing so quickly. "What we never really thought through was, 'Are we doing this well? Are we taking care of our patients well?'"

The number of OCM requirements forces the practice physicians to meet frequently to make sure they are meeting them, a process that has led to many changes that have helped patients, Wilfong said, offering several examples:

24/7 access. Texas Oncology's physicians always took calls, but what did this requirement really mean? How did it correlate with reducing hospital admission and emergency department (ED) visits? The practice gained access to its CMS data feed to see which patients were ending up in the hospital, and followed that up with 2 things: it set a goal of reducing hospital admissions by 5%, and it said nurses could not refer patients to the ED without a physician's order. "We hold our physicians accountable for their hospitalization rates. We share that widely in our organization," Wilfong said.

"Most physicians are fairly anal-retentive people. They were used to being the A+ student in their classes," he said. "When I give them a score card that shows that they're red, not green, they don't tend to like that very much."

Texas Oncology also redeployed nursing staff to return calls from high-risk patients within 30 minutes, and it set aside appointment slots at each site that can only be used for urgent care—and these are consistently 90% filled.

Data for quality improvement. Gaining access to CMS data showed it made more sense for nurses to contact patients on day 3 of chemotherapy instead of day 2, which is when steroids were still having an effect. "We're working on a high-risk identification protocol with increasing clinic visits and increasing proactive nursing phone calls," Wilfong said.

The practice is also using data to optimize its antiemetics protocol for chemotherapy-induced vomiting, which calls on pharmacists to adjust the antiemetics based on the risk of each regimen. In a pilot of this effort, only 2 of 300 patients had a nausea grade of 5 or more on the Likert scale of 1-10.

Improving end-of-life care. The OCM process revealed a need for major improvements. "It surprised me, when we looked at our baseline numbers, how poorly our practice was doing at end-of-life (EOL) care," Wilfong said. The doctors thought they were doing well, but the metrics showed something else: a need for better conversations, fewer hospitalizations near the end of life, and less chemotherapy.

It was a big challenge. "It's hard to tell a physician who's been practicing for 20 years that they [are failing] at end-of-life care," Wilfong said. "They don't like to hear it, and everybody kind of knows it. All the nurses talk about it behind their backs."

Identifying those physicians who excel at EOL conversations and arranging for them to mentor those who need improvement is hard, and a work in progress. "I would love to tell you we have this fixed, but we don't. But we are improving."

Texas Oncology is using a program, My Choices My Wishes, to help physicians talk to patients, and building a culture of shared decision making. It's producing results: a high percentage of those who go through the program complete an advanced directive. Among patients with an advanced directive, 76% die in hospice, with a median length of stay of 21 days compared with those who went through the program who did not do advanced directives, a group in which 61% died in hospice and had an average length of stay of 12.5 days.

Care plans along national guidelines. The compensation changes under OCM took Texas Oncology from 83% compliance with clinical pathways to 90%, a level that Wilfong says "is a perfect number to me."

When physicians want to treat patients off a pathway, their decision requires medical review, a step that dramatically controls drug spending. "What I tell doctors all the time is that if you're doing something, you should be able to stand up in a group of your peers and at least half of them agree with you. And if you can't convince at least [half of] the people that what you're doing is right, then you probably shouldn't be doing it in the first place," he said.

OCM raises the specter of taking on the taboo topic in oncology care. "Drug margins are a revenue source for oncology practices, and we've got to start talking about this if we're ever going to be able to get a handle on our drug spend," Wilfong said.

When practices have some patients in FFS and others in value-based reimbursement programs, it gets complicated administratively but ethically, too. "This is something…we have to get a handle on in oncology practices in order to be able to succeed in value-based programs in the future," he said. ◆

WILFONG

REFERENCE

1. Oncology Care Model Fact Sheet. CMS website. www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2016-Fact-sheets-items/2016-06-29.html. Published June 29, 2016. Accessed January 7, 2018.

Panel Explores Impact of Novel Therapies on Oncology Stakeholders

Alison Rodriguez

IN BOTH CLINICAL IMPACT AND COST, novel therapies play a significant role for all oncology stakeholders, and experts discussed that impact during Patient-Centered Oncology Care® in Philadelphia, Pennsylvania. The meeting was presented November 16-17, 2017, by *The American Journal of Managed Care*®.

The panel featured Bruce Feinberg, DO, chief medical officer at Cardinal Health; Thomas Graf, MD, vice president and chief medical officer at Horizon Blue Cross Blue Shield of New Jersey; Kashyap Patel, MD, a medical oncologist and CEO of Carolina Blood and Cancer Center in Rock Hill, South Carolina; and Kavita Patel, MD, MA, a nonresident senior fellow with The Brookings Institute and co-founder of Tuple Health in Washington, DC.

Dr Kavita Patel explained Medicare's Novel Therapy Adjustment Factor, which is used to avoid penalizing doctors who are being reimbursed through alternative payment models (APMs) if they prescribe a novel therapy. She then explained the 3 issues involved with Medicare's Oncology Care Model (OCM):

- What constitutes a novel therapy?
- How do we really know what to make of a utilization rate when we don't really have comparison groups?
- How do the novel therapies apply to the APMs?

Dr Kashyap Patel said that for him, novel therapies are promising, but they come with many complications. He attributed this to the higher cost of care, not only for the cost of therapy itself but also due to the additional time patients must spend with a caregiver. "So, along with trying to reduce hospitalization, plugging numbers into the OCM portal, [and] reporting quality parameters, it's making things a little harder right now, and we'll see how it goes over the next 2 to 3 years. But definitely, the novel therapies [have] promise but also [have] complicated the implementation of value-based care in real day-to-day life," Dr Kashyap Patel said.

Feinberg discussed the Center for Medicare and Medicaid Innovation's (CMMI) role in novel therapies. He questioned whether CMMI will help align the different stakeholders' opinions of novel therapies in order to lead to further advancements.

Graf noted the current significance of the term "value" in healthcare and the fact that the meaning differs for every stakeholder. He offered the "episodes approach" for managing costs and quality in oncology. In this approach, multiple bundles would be available for patients and allow them to be stratified so the cost can be assessed.

"But it's really about the rest of the care that's critically important and it's going to determine the outcome for the patients," Graf explained. "If we can ideally match the patient and their medical needs with the level of resource we deploy, we're going to minimize the huge increase in costs."

Furthermore, Feinberg emphasized the need for transparency among stakeholders in order to manage costs and to better understand why other stakeholders make certain care choices. Graf agreed with this concept, while highlighting that trust is required among organizations and patients to produce a successful model of care. Dr Kavita Patel also noted the need for transparency, but called for a "realistic on-ramping for people"—meaning a better understanding of certain healthcare processes among stakeholders.

Said Graf, "If we keep the patients first, and we figure out how to push the money around in the back, we'll be OK. And so, I think you need a flexible, open, willing payer that's ready to experiment, that's willing to understand." With that, "It's a great model."

Dr Kashyap Patel demonstrated the need for transparency by discussing the use of chimeric antigen receptor (CAR) T-cell therapy. He explained that major stakeholders have no way of being prepared for 2-sided risk in the current OCM, especially without any level of transparency. Therefore, 1-sided risk is more comfortable to consider with CAR T-cell therapy because the outcome of the patient would not be compromised.

"So, it's about really an exploration, and we're sort of thinking about it the same way we think about transplant, which is, look, we're going to go in, we know it's going to be expensive, [but] we're going to figure it out together," Graf said in response. "And you need to make a rational margin, we need to pay a reasonable amount, and, if we all agree to that, we can be okay. But, yeah, taking risk when there's that many unknowns would be crazy."

The panelists agreed that these types of conversations are important and need to continue around novel therapies in order to produce improvement and changes in healthcare. ◆

From left, Kavita Patel, MD, MA, of Tuple Health; Kashyap Patel, MD, of Carolina Blood and Cancer Center; Bruce Feinberg, DO, of Cardinal Health; and Thomas Graf, MD, of Horizon Blue Cross Blue Shield of New Jersey, discuss the impact of novel therapies with moderator Margaret "Peg" O'Grady, RN, MSN, OCN, FAAMA.

Adopting Real-World Evidence and Value Into a Payment Model

Alison Rodriguez

From left, Jason Harris, MBA, of the National Health Council; Lalan Wilfong, MD, of Texas Oncology; and Ian Manners, MBA, of Vivor discuss the role of real-world evidence with moderator Margaret "Peg" O'Grady, RN, MSN, OCN, FAAMA.

DOES REAL-WORLD EVIDENCE have a place in increasing the value of care? A panel took on that question during a discussion on the second day of Patient-Centered Oncology Care® in Philadelphia, Pennsylvania. The meeting was presented November 16-17, 2017, by *The American Journal of Managed Care®*.

The panel included Lalan Wilfong, MD, oncologist at Texas Oncology; Ian Manners, MBA, founder and CEO of Vivor; and Jason Harris, manager of public policy at the National Health Council (NHC), who discussed the role of real-world evidence in the healthcare field.

Harris said the NHC pursues patient engagement both directly and indirectly. The council speaks with patient groups to learn their priorities, but it also has the capacity to draw data from patient registries to learn what learn what patients value. This data can then be used by payers or the FDA to improve overall value for patients.

Wilfong noted that his team is focusing on improving the patient experience, specifically when calling a doctor's office, through the information gathered from patient satisfaction surveys. He also said that his organization is working to hold other organizations and individual sites within Texas Oncology, which is a multisite practice, accountable for change management and increased engagement at a local level.

Additionally, Wilfong described the challenges involving patient decisions that call for balancing financial considerations without limiting what is needed for good care. "They don't want to fully engage us in those conversations because they're afraid that we will limit their care if we realize how financially struggling it is for them," Wilfong said. "Many times, we don't realize that, as providers, until it's too late, until you see not just the patient but the family struggling to make ends meet. And that's a problem. No matter how you have those conversations, there's still a disconnect between us and the patient about those needs."

Manners' software company Vivor acts as a financial platform that helps providers find resources that are underused for patients, like assistance from pharmaceutical companies or nonprofit foundations. The company finds solutions for providers to help their patients afford treatments, Manners explained. He emphasized that it is part of a provider's responsibility to consider the patient's financial experience.

Manner also discussed a trial that Vivor is conducting to see if providing patients with financial resource information at the point-of-care would reduce out-of-pocket (OOP) costs. "[At] least they can start there, explain what the patient's out-of-pocket costs are going to be as they go through a treatment plan, and then bring up the other issues, [such as, 'How is this going to affect your work? Is it going to change the insurance that you can afford?'" Manner noted.

The panelists agreed that when it comes to cancer treatment, most individuals are willing to spend whatever it takes for the best treatment and doctors, but according to Wilfong, their ability to make a choice is eliminated. Furthermore, Harris emphasized the importance of accountability when considering the limited choices for cancer treatment, especially for those that are uninsured and underinsured.

"When it comes to looking for positive outcomes, health outcomes [come] first, of course, but when we say this pathway, this treatment plan, was the best one based on real-world evidence, we need to account for the patient's financial experience as well," explained Manner. "And we need to start doing that by first collecting the data on it."

In reference to the Oncology Care Model (OCM), Manners considers it to be vague and open to interpretation. He called for a more specific financial plan through the OCM that would help patients understand insurance benefits and OOP costs.

Overall, the panelists emphasized the importance of providing patients with the necessary resources and to work on minimizing the disconnect between physicians and patients, especially when it involves treatment costs.

"So, where we're at right now is sometimes there's a big disconnect between the different stakeholders and what that value means to that patient sitting in front of you," Wilfong said. "Many payers are having their own pathways that may be discordant from our pathways for various reasons. And so, we're having those discussions more." ◆

Using Data on Patients' Cancer Experiences to Change Payment Paradigms

Mary Caffrey

BUZAGLO

SCIENCE IS YIELDING MORE OPTIONS than ever to treat cancer. That's the good news.

The bad news is that as cancer care becomes more complex, so do choices for patients and their families. How much does a wonder drug help patients if they can't afford it or if the adverse effects (AEs) make quality of life poor or if it forces them to spend down retirement savings or puts the family home in foreclosure?

These are the real challenges facing patients that are now being studied and measured by the Cancer Support Community, according to Joanne Buzaglo, PhD, senior vice president of the group's Research and Training Institute.

Buzaglo noted that the idea of "value" in cancer care has gained attention in recent years. The American Society of Clinical Oncology, the National Comprehensive Cancer Network, and Peter Bach, MD, MAPP, of Memorial Sloan Kettering Cancer Center have all developed value frameworks.[1] But simply looking at a drug's cost compared with how much it extends a person's life misses the mark if the patient's perspective is left out.

The Research and Training Institute works to collect that patient perspective through its Cancer Experience Registry that develops data that can lead to system change. Buzaglo described how the registry collects information on patient demographics, cancer-related distress, symptom management, AEs, and the clinical trial experience and how cancer affects a person's ability to work. Of great importance, it collects information on financial toxicity and shared decision making and planning.

"BY UNDERSTANDING HOW PATIENTS DEFINE VALUE, WE CAN IDENTIFY STRATEGIES TO BETTER ENGAGE THE PATIENT IN VALUE-BASED CANCER CARE."

—Joanne Buzaglo, PhD

She shared data on the top 10 concerns among cancer patients in the registry, which included eating and nutrition (62%), remaining physically active (55%), worrying about the future (53%), feeling too tired (50%), and having sleep problems (46%). Nearly half of cancer survivors (47%) are at risk for clinically significant levels of depression.

What causes this? Communication gaps with the healthcare team don't help, Buzaglo said:

- 1 in 3 patients said their healthcare team did not explain short-term AEs
- 52% received guidance on long-term side effects of treatment, which means nearly half did not
- 14% did not share AEs and symptoms

What is value? The term is in the eye of the stakeholder, Buzaglo said, and the patient's view is often missing. "By understanding how patients define value, we can identify strategies to better engage the patient in value-based cancer care," she said.

The institute asked patients, "When considering your cancer experience, how would you define value?" and the results led to 2 reports: findings on 769 patients with metastatic breast cancer (MBC) and comparative findings in MBC and breast cancer.

It turns out that value not only means different things to different people, but sometimes that meaning has nothing to do with a patient's health: When making treatment decisions, 93% of patients consider quality of life, 79% consider length of life, and 74% consider the impact a decision has on their family. And although patients are increasingly involved in decisions (66% said they were very involved), less than half (46%) felt they had sufficient knowledge to make good choices and only 38% felt fully prepared.

Impact on finances. Buzaglo and her team's research also showed that while three-quarters of patients said they knew what clinical trials are, 80% said they were uncomfortable being randomly assigned to a treatment andnd 77% say their insurance would not cover the cost of treatment.

The financial burden of cancer care weighs on patients: 58% of registry patients said it had significantly affected them and 37% were experiencing anxiety. Yet the topic of financial burdens presents the greatest communication gap between the care team and patients: 73% said they had not discussed their financial concerns with their healthcare providers, but they were making significant trade-offs or cutting corners on care:

- 30% had depleted their savings
- 13% had applied for or used public assistance
- 17% put off a complementary appointment, such as one to a physical therapist
- 11% postponed doctors' appointments
- 11% postponed filling prescriptions
- 5% had taken an extra job while undergoing cancer treatment to pay medical costs

Cancer support source. Buzaglo said this Web-based program was created by the Cancer Support Community, incorporating its research findings into a screening tool to evaluate distress and make referrals to improve quality of life and health outcomes and help patients deal with the cost of care.

A new tool called VOICE (Value Outcomes in the Cancer Experience) is being tested with patients identified in the cancer registry. VOICE would be focused on the future and what patients want to achieve with their treatment.

Buzaglo posed these questions: What if patients were screened for the outcomes that were important to them? What if healthcare professionals were paid for properly informing patients?

Finally, she asked, what if reimbursement was tied not to giving patients drugs, but to giving them the outcomes they sought? ◆

REFERENCE

1. Peer Exchange: 2016 Oncology Stakeholders Summit. *Am J Manag Care*. 2016. ajmc.com/journals/evidence-based-oncology/2016/peer-exchange-spring-2016-oncology-stakeholders-summit. Published May 10, 2016. Accessed January 9, 2018.

ADDITIONAL RESOURCES

curetoday.com

Tapur Study Aims To Give Strength Back To Patients With Ovarian Cancer

MORE AT:
ajmc.com/link/2843.

In first-line treatment of
unresectable or metastatic melanoma

GIVE YOUR PATIENTS A KEY TO **SUPERIOR OVERALL SURVIVAL**

The first anti–PD-1 to achieve superior overall survival (OS) vs ipilimumab in a 2-year analysis[1]

- 32% reduction in the risk of death with KEYTRUDA vs ipilimumab.[1]
  - With KEYTRUDA 10 mg/kg every 3 weeks; HR=0.68; 95% CI, 0.53–0.86; *P*<0.001.

PD-1 = programmed death receptor-1; HR = hazard ratio; CI = confidence interval.

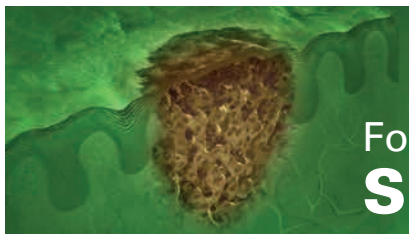
KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma.

SELECTED SAFETY INFORMATION

- KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Pneumonitis occurred in 94 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 1 (0.8%), 2 (1.3%), 3 (0.9%), 4 (0.3%), and 5 (0.1%) pneumonitis, and occurred more frequently in patients with a history of prior thoracic radiation (6.9%) compared to those without (2.9%). Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected pneumonitis with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 or recurrent Grade 2 pneumonitis.

Please read the additional Selected Safety Information on the following pages and the adjacent Brief Summary of the Prescribing Information.

KEYTRUDA®
(pembrolizumab) Injection 100 mg



For first-line use in patients with advanced melanoma

SUPERIOR OVERALL SURVIVAL vs ipilimumab

55% 2-year overall survival rate with KEYTRUDA vs 43% with ipilimumab[1,a]

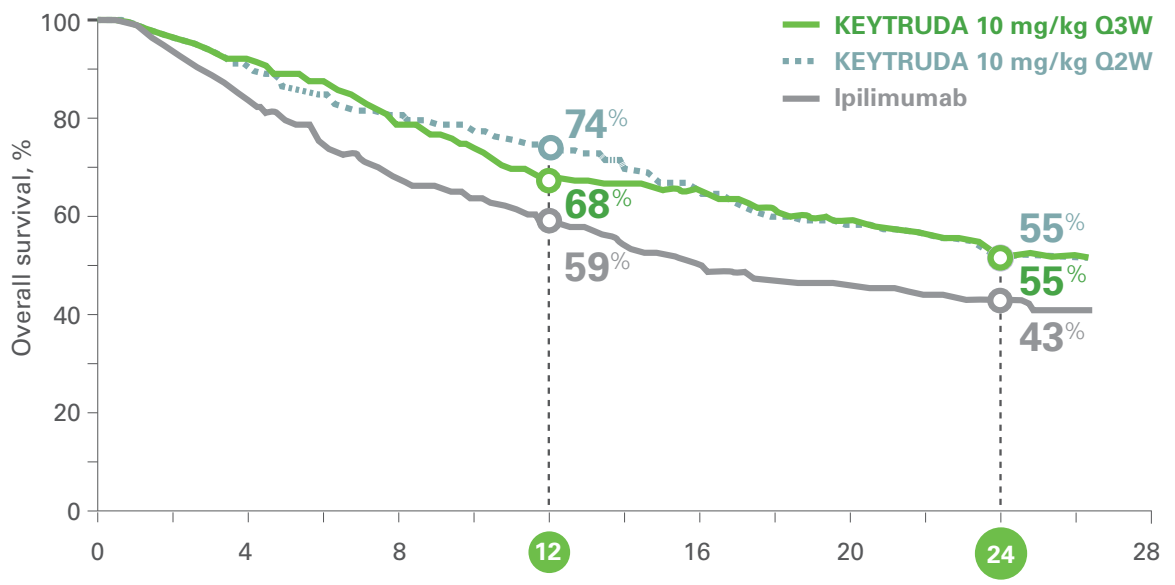
Kaplan-Meier Estimates of Overall Survival[1,b]

MEDIAN

OS

NOT REACHED

WITH KEYTRUDA[1]



Number at risk								
KEYTRUDA Q3W	277	251	215	184	174	156	43	0
KEYTRUDA Q2W	279	249	221	202	176	156	44	0
Ipilimumab	278	213	170	145	122	110	28	0

[a]KEYTRUDA 10 mg/kg Q3W.

[b]Results were similar in the 2 treatment arms for KEYTRUDA.

- Median OS not reached with KEYTRUDA 10 mg/kg Q3W (95% CI, 23.5 months–NR) or with KEYTRUDA 10 mg/kg Q2W (22.1 months–NR). Median OS was 16.0 months with ipilimumab (95% CI, 13.5–22.0).[1]
- Significant improvement in OS (HR=0.68; *P*<0.001) with KEYTRUDA 10 mg/kg Q3W (95% CI, 0.53–0.86) and KEYTRUDA 10 mg/kg Q2W (95% CI, 0.53–0.87) vs ipilimumab.[1]
  - Number of deaths observed in each arm: 119/277 (43%) and 122/279 (44%) with KEYTRUDA 10 mg/kg Q3W and Q2W, respectively, and 142/278 (51%) with ipilimumab.[1]

Q3W = every 3 weeks; Q2W = every 2 weeks; NR = not reached.

SELECTED SAFETY INFORMATION (*continued*)

- KEYTRUDA can cause immune-mediated colitis. Colitis occurred in 48 (1.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.4%), 3 (1.1%), and 4 (<0.1%) colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for Grade 2 or 3; permanently discontinue KEYTRUDA for Grade 4 colitis.
- KEYTRUDA can cause immune-mediated hepatitis. Hepatitis occurred in 19 (0.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.4%), and 4 (<0.1%) hepatitis. Monitor patients for changes in liver function. Administer corticosteroids for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA.
- KEYTRUDA can cause hypophysitis. Hypophysitis occurred in 17 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.2%), 3 (0.3%), and 4 (<0.1%) hypophysitis. Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for Grade 2; withhold or discontinue for Grade 3 or 4 hypophysitis.
- KEYTRUDA can cause thyroid disorders, including hyperthyroidism, hypothyroidism, and thyroiditis. Hyperthyroidism occurred in 96 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.8%) and 3 (0.1%) hyperthyroidism. Hypothyroidism occurred in 237 (8.5%) of 2799 patients receiving KEYTRUDA, including Grade 2 (6.2%) and 3 (0.1%) hypothyroidism. Thyroiditis occurred in 16 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.3%) thyroiditis. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Superior progression-free survival (PFS) vs ipilimumab (1-year analysis)

- 42% reduction in the risk of disease progression or death with KEYTRUDA 10 mg/kg Q3W vs ipilimumab (HR=0.58; 95% CI, 0.47–0.72; *P*<0.001) and with KEYTRUDA Q2W vs ipilimumab (HR=0.58; 95% CI, 0.46–0.72; *P*<0.001).
  - Results based on 502 events: 157/277 (57%) and 157/279 (56%) with KEYTRUDA 10 mg/kg Q3W and Q2W, respectively, and 188/278 (68%) with ipilimumab.
- Median PFS was 4.1 months (95% CI, 2.9–6.9), 5.5 months (95% CI, 3.4–6.9), and 2.8 months (95% CI, 2.8–2.9) with KEYTRUDA 10 mg/kg Q3W, KEYTRUDA 10 mg/kg Q2W, and ipilimumab, respectively.

Nearly 3 times higher overall response rate (ORR) vs ipilimumab (1-year analysis)[c]

- 33% (n=91/277; 95% CI, 27–39) and 34% (n=94/279; 95% CI, 28-40) of patients responded to KEYTRUDA 10 mg/kg Q3W and Q2W, respectively, vs 12% with ipilimumab (n=278; 95% CI, 8-16).[d]
  - 6% complete response rate and 27% partial response rate with KEYTRUDA 10 mg/kg Q3W.
  - 5% complete response rate and 29% partial response rate with KEYTRUDA 10 mg/kg Q2W.
  - 1% complete response rate and 10% partial response rate with ipilimumab.
- Among the 91 patients randomized to KEYTRUDA 10 mg/kg Q3W with an objective response, response durations ranged from 1.4+ to 8.1+ months.
- Among the 94 patients randomized to KEYTRUDA 10 mg/kg Q2W with an objective response, response durations ranged from 1.4+ to 8.2 months.

[c]KEYTRUDA 10 mg/kg Q3W.
[d]Percentages have been rounded to the nearest integer.

KEYNOTE-006 study design[2]: Open-label, multicenter, randomized, active-controlled phase 3 trial that included patients with unresectable or metastatic melanoma with progression of disease, no prior ipilimumab, and no more than 1 prior systemic treatment for metastatic melanoma. Patients with BRAF V600E mutation–positive melanoma were not required to have received prior BRAF inhibitor therapy. Patients were randomized to receive KEYTRUDA 10 mg/kg over 30 minutes Q3W (n=277) or Q2W (n=279), or 4 cycles of ipilimumab 3 mg/kg over 90 minutes Q3W (n=278). Patients were treated with KEYTRUDA until disease progression or unacceptable toxicity. Patients with disease progression could receive additional doses of treatment unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. The primary end points were OS and PFS as assessed by blinded independent central review using Response Evaluation Criteria In Solid Tumors (RECIST 1.1). The secondary end points were ORR and duration of response.

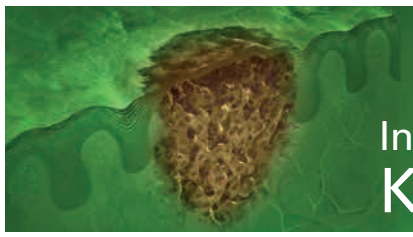
SELECTED SAFETY INFORMATION (*continued*)

Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for Grade 3 or 4 hyperthyroidism.

- KEYTRUDA can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which have been reported in 6 (0.2%) of 2799 patients. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA and administer antihyperglycemics in patients with severe hyperglycemia.
- KEYTRUDA can cause immune-mediated nephritis. Nephritis occurred in 9 (0.3%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.1%), and 4 (<0.1%) nephritis. Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 nephritis.
- Immune-mediated rashes, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor patients for suspected severe skin reactions and based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA.
- KEYTRUDA can cause other clinically important immune-mediated adverse reactions. These immune-mediated reactions may occur in any organ system. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month.

Please read the additional Selected Safety Information on the following page and the adjacent Brief Summary of Prescribing Information.

KEYTRUDA®
(pembrolizumab) Injection 100 mg



In first-line treatment of advanced melanoma

KEYTRUDA: **Q3W FIXED DOSE**

200-mg fixed dose for unresectable or metastatic melanoma administered intravenously	over **30 minutes**	every **3 weeks**

...until disease progression or unacceptable toxicity.

Across 4 clinical trials, the rate of each reported Grade 3 and Grade 4 immune-mediated adverse reaction was ≤1.4% (N=2,799)

SELECTED SAFETY INFORMATION (*continued*)

Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume KEYTRUDA when the adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue KEYTRUDA for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

- The following clinically significant immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients: arthritis (1.5%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma. In addition, myelitis and myocarditis were reported in other clinical trials, including classical Hodgkin lymphoma, and postmarketing use.
- Solid organ transplant rejection has been reported in postmarketing use of KEYTRUDA. Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with KEYTRUDA vs the risk of possible organ rejection in these patients.
- KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients. Monitor patients for signs and symptoms of infusion-related reactions, including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For Grade 3 or 4 reactions, stop infusion and permanently discontinue KEYTRUDA.
- In clinical trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of these patients with a PD-1 or PD-L1 blocking antibody in this combination is not recommended outside of controlled clinical trials.
- Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. If used during pregnancy, or if the patient becomes pregnant during treatment, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose of KEYTRUDA.
- In KEYNOTE-006, KEYTRUDA was discontinued due to adverse reactions in 9% of 555 patients with advanced melanoma; adverse reactions leading to discontinuation in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). The most common adverse reactions with KEYTRUDA vs ipilimumab were fatigue (28% vs 28%), diarrhea (26% with KEYTRUDA), rash (24% vs 23%), and nausea (21% with KEYTRUDA). Corresponding incidence rates are listed for ipilimumab only for those adverse reactions that occurred at the same or lower rate than with KEYTRUDA.

Please read the additional Selected Safety Information and the adjacent Brief Summary of Prescribing Information.

References: 1. Data available on request from Merck, Professional Services-DAP, WP1-27, PO Box 4, West Point, PA 19486-0004. Please specify information package ONCO-1208197-0005. **2.** Robert C, Schachter J, Long GV, et al; for the KEYNOTE-006 investigators. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med.* 2015;372(26):2521–2532.

MERCK

Merck Oncology

ONCO-1220987-0002 01/18 **keytruda.com**

KEYTRUDA® (pembrolizumab) Injection 100 mg

Brief Summary of the Prescribing Information for
KEYTRUDA® (pembrolizumab) for injection, for intravenous use
KEYTRUDA® (pembrolizumab) injection, for intravenous use

INDICATIONS AND USAGE

KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Immune-Mediated Pneumonitis: KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis.

Pneumonitis occurred in 94 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 1 (0.8%), Grade 2 (1.3%), Grade 3 (0.9%), Grade 4 (0.3%), and Grade 5 (0.1%) pneumonitis. The median time to onset was 3.3 months (range: 2 days to 19.3 months), and the median duration was 1.5 months (range: 1 day to 17.2+ months). Sixty-three (67%) of the 94 patients received systemic corticosteroids, with 50 of the 63 receiving high-dose corticosteroids for a median duration of 8 days (range: 1 day to 10.1 months) followed by a corticosteroid taper. Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.9%) than in patients who did not receive prior thoracic radiation (2.9%). Pneumonitis led to discontinuation of KEYTRUDA in 36 (1.3%) patients. Pneumonitis resolved in 55 (59%) of the 94 patients.

Immune-Mediated Colitis: KEYTRUDA can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater colitis. Withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis.

Colitis occurred in 48 (1.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.4%), Grade 3 (1.1%), and Grade 4 (<0.1%) colitis. The median time to onset was 3.5 months (range: 10 days to 16.2 months), and the median duration was 1.3 months (range: 1 day to 8.7+ months). Thirty-three (69%) of the 48 patients received systemic corticosteroids, with 27 of the 33 requiring high-dose corticosteroids for a median duration of 7 days (range: 1 day to 5.3 months) followed by a corticosteroid taper. Colitis led to discontinuation of KEYTRUDA in 15 (0.5%) patients. Colitis resolved in 41 (85%) of the 48 patients.

Immune-Mediated Hepatitis: KEYTRUDA can cause immune-mediated hepatitis. Monitor patients for changes in liver function. Administer corticosteroids (initial dose of 0.5 to 1 mg/kg/day [for Grade 2 hepatitis] and 1 to 2 mg/kg/day [for Grade 3 or greater hepatitis] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA.

Hepatitis occurred in 19 (0.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), Grade 3 (0.4%), and Grade 4 (<0.1%) hepatitis. The median time to onset was 1.3 months (range: 8 days to 21.4 months), and the median duration was 1.8 months (range: 8 days to 20.9+ months). Thirteen (68%) of the 19 patients received systemic corticosteroids, with 12 of the 13 receiving high-dose corticosteroids for a median duration of 5 days (range: 1 to 26 days) followed by a corticosteroid taper. Hepatitis led to discontinuation of KEYTRUDA in 6 (0.2%) patients. Hepatitis resolved in 15 (79%) of the 19 patients.

Immune-Mediated Endocrinopathies

Hypophysitis

KEYTRUDA can cause hypophysitis. Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for moderate (Grade 2) hypophysitis and withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hypophysitis.

Hypophysitis occurred in 17 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.2%), Grade 3 (0.3%), and Grade 4 (<0.1%) hypophysitis. The median time to onset was 3.7 months (range: 1 day to 11.9 months), and the median duration was 4.7 months (range: 8+ days to 12.7+ months). Sixteen (94%) of the 17 patients received systemic corticosteroids, with 6 of the 16 receiving high-dose corticosteroids. Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.1%) patients. Hypophysitis resolved in 7 (41%) of the 17 patients.

Thyroid Disorders

KEYTRUDA can cause thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism.

Hyperthyroidism occurred in 96 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.8%) and Grade 3 (0.1%) hyperthyroidism. The median time to onset was 1.4 months (range: 1 day to 21.9 months), and the median duration was 2.1 months (range: 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 (74%) of the 96 patients.

Hypothyroidism occurred in 237 (8.5%) of 2799 patients receiving KEYTRUDA, including Grade 2 (6.2%) and Grade 3 (0.1%) hypothyroidism. The median time to onset was 3.5 months (range: 1 day to 18.9 months), and the median duration was not reached (range: 2 days to 27.7+ months). Hypothyroidism led to discontinuation of KEYTRUDA in 1 (<0.1%) patient. Hypothyroidism resolved in 48 (20%) of the 237 patients. The incidence of new or worsening hypothyroidism was higher in patients with HNSCC occurring in 28 (15%) of 192 patients receiving KEYTRUDA, including Grade 3 (0.5%) hypothyroidism. Of these 28 patients, 15 had no prior history of hypothyroidism.

Thyroiditis occurred in 16 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.3%) thyroiditis. The median time of onset was 1.2 months (range: 0.5 to 3.5 months).

Type 1 Diabetes mellitus

KEYTRUDA can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA and administer anti-hyperglycemics in patients with severe hyperglycemia.

Immune-Mediated Nephritis and Renal Dysfunction: KEYTRUDA can cause immune-mediated nephritis. Monitor patients for changes in renal function. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater nephritis. Withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis.

Nephritis occurred in 9 (0.3%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), Grade 3 (0.1%), and Grade 4 (<0.1%) nephritis. The median time to onset was 5.1 months (range: 12 days to 12.8 months), and the median duration was 3.3 months (range: 12 days to 8.9+ months). Eight (89%) of the 9 patients received systemic corticosteroids, with 7 of the 8 receiving high-dose corticosteroids for a median duration of 15 days (range: 3 days to 4.0 months) followed by a corticosteroid taper. Nephritis led to discontinuation of KEYTRUDA in 3 (0.1%) patients. Nephritis resolved in 5 (56%) of the 9 patients.

Immune-Mediated Skin Adverse Reactions: Immune-mediated rashes, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA.

Other Immune-Mediated Adverse Reactions: KEYTRUDA can cause other clinically important immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume KEYTRUDA when the immune-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue KEYTRUDA for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients treated with KEYTRUDA: arthritis (1.5%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma. In addition, myelitis and myocarditis were reported in other clinical trials, including cHL, and post-marketing use.

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with KEYTRUDA. Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with KEYTRUDA versus the risk of possible organ rejection in these patients.

Infusion-Related Reactions: KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue KEYTRUDA.

Increased Mortality in Patients with Multiple Myeloma when KEYTRUDA is Added to a Thalidomide Analogue and Dexamethasone: In two randomized clinical trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Embryofetal Toxicity: Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment with KEYTRUDA and for 4 months after the last dose of KEYTRUDA.

ADVERSE REACTIONS

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

- Immune-mediated pneumonitis.
- Immune-mediated colitis.
- Immune-mediated hepatitis.
- Immune-mediated endocrinopathies.
- Immune-mediated nephritis and renal dysfunction.
- Immune-mediated skin adverse reactions.
- Other immune-mediated adverse reactions.
- Infusion-related reactions.

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

The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to KEYTRUDA in 2799 patients in three randomized, open-label, active-controlled clinical trials (KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010), which enrolled 912 patients with melanoma and 682 patients with NSCLC, and one single-arm trial (KEYNOTE-001) which enrolled 655 patients with melanoma and 550 patients with NSCLC. In addition, these data reflect exposure to KEYTRUDA in a non-randomized, open-label, multi-cohort trial (KEYNOTE-012) which enrolled 192 patients with HNSCC and 241 cHL patients in two non-randomized, open-label trials (KEYNOTE-013 and KEYNOTE-087). Across all studies, KEYTRUDA was administered at doses of 2 mg/kg intravenously every 3 weeks, 10 mg/kg intravenously every 2 weeks, 10 mg/kg intravenously every 3 weeks, or 200 mg intravenously every 3 weeks. Among the 2799 patients, 41% were exposed for 6 months or more and 21% were exposed for 12 months or more.

The data described in this section were obtained in five randomized, open-label, active-controlled clinical trials (KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, KEYNOTE-021, and KEYNOTE-045) in which KEYTRUDA was administered to 912 patients with melanoma, 741 patients with NSCLC, and 542 patients with urothelial carcinoma, and four non-randomized, open-label trials (KEYNOTE-012, KEYNOTE-087, KEYNOTE-052 and KEYNOTE-059) in which KEYTRUDA was administered to 192 patients with HNSCC, 210 patients with cHL, 370 patients with urothelial carcinoma, and 259 patients with gastric cancer. In these trials, KEYTRUDA was administered at 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks.

Brief Summary of the Prescribing Information for
KEYTRUDA® (pembrolizumab) for injection, for intravenous use
KEYTRUDA® (pembrolizumab) injection, for intravenous use (*continued*)

Melanoma

Ipilimumab-Naive Melanoma

The safety of KEYTRUDA for the treatment of patients with unresectable or metastatic melanoma who had not received prior ipilimumab and who had received no more than one prior systemic therapy was investigated in Study KEYNOTE-006. KEYNOTE-006 was a multicenter, open-label, active-controlled trial where patients were randomized (1:1:1) and received KEYTRUDA 10 mg/kg every 2 weeks (n=278) or KEYTRUDA 10 mg/kg every 3 weeks (n=277) until disease progression or unacceptable toxicity or ipilimumab 3 mg/kg every 3 weeks for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity (n=256). Patients with autoimmune disease, a medical condition that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or active infection requiring therapy, including HIV or hepatitis B or C, were ineligible.

The median duration of exposure was 5.6 months (range: 1 day to 11.0 months) for KEYTRUDA and similar in both treatment arms. Fifty-one and 46% of patients received KEYTRUDA 10 mg/kg every 2 or 3 weeks, respectively, for ≥6 months. No patients in either arm received treatment for more than one year.

The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 32% had an elevated lactate dehydrogenase (LDH) value at baseline, 65% had M1c stage disease, 9% with history of brain metastasis, and approximately 36% had been previously treated with systemic therapy which included a BRAF inhibitor (15%), chemotherapy (13%), and immunotherapy (6%).

In KEYNOTE-006, the adverse reaction profile was similar for the every 2 week and every 3 week schedule, therefore summary safety results are provided in a pooled analysis (n=555) of both KEYTRUDA arms. Adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 9% of patients. Adverse reactions leading to discontinuation of KEYTRUDA in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). The most common adverse reactions (reported in at least 20% of patients) were fatigue and diarrhea. Table 1 and Table 2 summarize the incidence of selected adverse reactions and laboratory abnormalities that occurred in patients receiving KEYTRUDA.

Table 1: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-006

	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab n=256	
Adverse Reaction	**All Grades† (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General Disorders and Administration Site Conditions				
Fatigue	28	0.9	28	3.1
Skin and Subcutaneous Tissue Disorders				
Rash‡	24	0.2	23	1.2
Vitiligo§	13	0	2	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	18	0.4	10	1.2
Back pain	12	0.9	7	0.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	7	0.4
Dyspnea	11	0.9	7	0.8
Metabolism and Nutrition Disorders				
Decreased appetite	16	0.5	14	0.8
Nervous System Disorders				
Headache	14	0.2	14	0.8

*Adverse reactions occurring at same or higher incidence than in the ipilimumab arm

†Graded per NCI CTCAE v4.0

‡Includes rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and exfoliative rash.

§Includes skin hypopigmentation

Other clinically important adverse reactions occurring in ≥10% of patients receiving KEYTRUDA were diarrhea (26%), nausea (21%), and pruritus (17%).

Table 2: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-006

	KEYTRUDA 10 mg/kg every 2 or 3 weeks		Ipilimumab	
Laboratory Test†	**All Grades‡ %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Chemistry				
Hyperglycemia	45	4.2	45	3.8
Hypertriglyceridemia	43	2.6	31	1.1
Hyponatremia	28	4.6	26	7
Increased AST	27	2.6	25	2.5
Hypercholesterolemia	20	1.2	13	0
Hematology				
Anemia	35	3.8	33	4.0
Lymphopenia	33	7	25	6

*Laboratory abnormalities occurring at same or higher incidence than in ipilimumab arm

†Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (520 to 546 patients) and ipilimumab (237 to 247 patients); hypertriglyceridemia: KEYTRUDA n=429 and ipilimumab n=183; hypercholesterolemia: KEYTRUDA n=484 and ipilimumab n=205.

‡Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were increased hypoalbuminemia (27% all Grades; 2.4% Grades 3-4), increased ALT (23% all Grades; 3.1% Grades 3-4), and increased alkaline phosphatase (21% all Grades, 2.0% Grades 3-4).

Ipilimumab-Refractory Melanoma

The safety of KEYTRUDA in patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was evaluated in Study KEYNOTE-002. KEYNOTE-002 was a multicenter, partially blinded (KEYTRUDA dose), randomized (1:1:1), active-controlled trial in which 528 patients received KEYTRUDA 2 mg/kg (n=178) or 10 mg/kg (n=179) every 3 weeks or investigator's choice of chemotherapy (n=171), consisting of dacarbazine (26%), temozolomide (25%), paclitaxel and carboplatin (25%), paclitaxel (16%), or carboplatin (8%). The trial excluded patients with autoimmune disease, severe immune-related toxicity related to ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; medical conditions that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or an active infection requiring therapy, including HIV or hepatitis B or C.

The median duration of exposure to KEYTRUDA 2 mg/kg every 3 weeks was 3.7 months (range: 1 day to 16.6 months) and to KEYTRUDA 10 mg/kg every 3 weeks was 4.8 months (range: 1 day to 16.8 months). The data described below reflect exposure to KEYTRUDA 2 mg/kg in 36% of patients exposed to KEYTRUDA for ≥6 months and in 4% of patients exposed for ≥12 months. In the KEYTRUDA 10 mg/kg arm, 41% of patients were exposed to KEYTRUDA for ≥6 months and 6% of patients were exposed to KEYTRUDA for ≥12 months.

The study population characteristics were: median age of 62 years (range: 15 to 89 years), 61% male, 98% White, 41% with an elevated LDH value at baseline, 83% with M1c stage disease, 73% received two or more prior therapies for advanced or metastatic disease (100% received ipilimumab and 25% a BRAF inhibitor), and 15% with history of brain metastasis.

In KEYNOTE-002, the adverse reaction profile was similar for the 2 mg/kg dose and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=357) of both KEYTRUDA arms. Adverse reactions resulting in permanent discontinuation occurred in 12% of patients receiving KEYTRUDA; the most common (≥1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 14% of patients; the most common (≥1%) were dyspnea (1%), diarrhea (1%), and maculo-papular rash (1%). The most common adverse reactions (reported in at least 20% of patients) of KEYTRUDA were fatigue, pruritus, rash, constipation, nausea, diarrhea, and decreased appetite.

Table 3 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

Table 3: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-002

	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks n=357		Chemotherapy† n=171	
Adverse Reaction	**All Grades‡ (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General Disorders and Administration Site Conditions				
Pyrexia	14	0.3	9	0.6
Asthenia	10	2.0	9	1.8
Skin and Subcutaneous Tissue Disorders				
Pruritus	28	0	8	0
Rash§	24	0.6	8	0
Gastrointestinal Disorders				
Constipation	22	0.3	20	2.3
Diarrhea	20	0.8	20	2.3
Abdominal pain	13	1.7	8	1.2
Respiratory, Thoracic and Mediastinal Disorders				
Cough	18	0	16	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	14	0.6	10	1.2

*Adverse reactions occurring at same or higher incidence than in chemotherapy arm

†Chemotherapy: dacarbazine, temozolomide, carboplatin plus paclitaxel, paclitaxel, or carboplatin

‡Graded per NCI CTCAE v4.0

§Includes rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, and rash pruritic

Other clinically important adverse reactions occurring in patients receiving KEYTRUDA were fatigue (43%), nausea (22%), decreased appetite (20%), vomiting (13%), and peripheral neuropathy (1.7%).

Table 4: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-002

	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks		Chemotherapy	
Laboratory Test†	**All Grades‡ %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Chemistry				
Hyperglycemia	49	6	44	6
Hypoalbuminemia	37	1.9	33	0.6
Hyponatremia	37	7	24	3.8
Hypertriglyceridemia	33	0	32	0.9
Increased Alkaline Phosphatase	26	3.1	18	1.9
Increased AST	24	2.2	16	0.6
Bicarbonate Decreased	22	0.4	13	0
Hypocalcemia	21	0.3	18	1.9
Increased ALT	21	1.8	16	0.6

*Laboratory abnormalities occurring at same or higher incidence than in chemotherapy arm.

†Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 320 to 325 patients) and chemotherapy (range: 154 to 161 patients); hypertriglyceridemia: KEYTRUDA n=247 and chemotherapy n=116; bicarbonate decreased: KEYTRUDA n=263 and chemotherapy n=123).

‡Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were anemia (44% all Grades; 10% Grades 3-4) and lymphopenia (40% all Grades; 9% Grades 3-4).

Brief Summary of the Prescribing Information for
KEYTRUDA® (pembrolizumab) for injection, for intravenous use
KEYTRUDA® (pembrolizumab) injection, for intravenous use (*continued*)

Immunogenicity: As with all therapeutic proteins, there is the potential for immunogenicity. Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks, 27 (2.1%) of 1289 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies of whom six (0.5%) patients had neutralizing antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic profile or increased infusion reactions with anti-pembrolizumab binding antibody development.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to KEYTRUDA with the incidences of antibodies to other products may be misleading.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary: Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. There are no available human data informing the risk of embryo-fetal toxicity. Apprise 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: Animal reproduction studies have not been conducted with KEYTRUDA to evaluate its effect on reproduction and fetal development, but an assessment of the effects on reproduction was provided. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering KEYTRUDA during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 knockout mice. Based on its mechanism of action, fetal exposure to pembrolizumab may increase the risk of developing immune-mediated disorders or of altering the normal immune response.

Lactation

Risk Summary: It is not known whether KEYTRUDA is excreted in human milk. No studies have been conducted to assess the impact of KEYTRUDA on milk production or its presence in breast milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with KEYTRUDA and for 4 months after the final dose.

Females and Males of Reproductive Potential

Contraception: Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for at least 4 months following the final dose.

Geriatric Use: Of 3991 patients with melanoma, NSCLC, HNSCC, cHL or urothelial carcinoma who were treated with KEYTRUDA in clinical studies, 46% were 65 years and over and 16% were 75 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

OVERDOSAGE

There is no information on overdosage with KEYTRUDA.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA, including:
  - Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath.
  - Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain.
  - Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding.
  - Hypophysitis: Advise patients to contact their healthcare provider immediately for persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes.
  - Hyperthyroidism and Hypothyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperthyroidism and hypothyroidism.
  - Type 1 Diabetes Mellitus: Advise patients to contact their healthcare provider immediately for signs or symptoms of type 1 diabetes.
  - Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.
  - Severe skin reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS or TEN.
- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions.
- Advise patients of the risk of solid organ transplant rejection and to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection.
- Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests.
- Advise females that KEYTRUDA can cause fetal harm. Instruct females of reproductive potential to use highly effective contraception during and for 4 months after the last dose of KEYTRUDA.
- Advise nursing mothers not to breastfeed while taking KEYTRUDA and for 4 months after the final dose.

For more detailed information, please read the Prescribing Information.

uspi-mk3475-iv-1711r014

Revised: 11/2017

ONCO-1220987-0002 01/18 MEL

MERCK

Nominate Today!

2018 GIANTS OF CANCER CARE®

The *Giants of Cancer Care®* Awards celebrate individuals who have achieved landmark success within the field of oncology.

Help us identify oncology specialists whose dedication has helped save, prolong, or improve the lives of patients who have received a diagnosis of cancer.

PROGRAM OVERVIEW

- Nominations are open through February 2018.
- Domestic and international nominations will be accepted. Self-nominations are permitted and encouraged.
- The *Giants of Cancer Care®* Advisory Board will vet all nominations to determine finalists in each category.
- A selection committee of 90+ oncologists will vote to determine the 2018 inductees.
- The 2018 *Giants of Cancer Care®* class will be announced in Chicago on May 31, 2018.

Recognize Greatness. Recognize a Giant of Cancer Care.

2018

To nominate, please visit:
giantsofcancercare.com/nominate

OncLive PRESENTS Giants OF Cancer Care®

cure Connections®

A valuable resource for *your* patients with cancer

Real people expressing their feelings, fears and hopes is just a click away.

To help your patients and their loved ones navigate a cancer diagnosis, recommend CURE Connections® video resources.

- Insight on managing the physical and psychological aspects of cancer
- Recommendations for networking with advocates
- Guidance on all types of treatment options
- Advice for caregivers
- Expert insight on breakthroughs in cancer detection

curetoday.com

A patient video series brought to you by cure® magazine, the premiere BPA-audited, direct-to-patient oncology publication.

BPA WORLDWIDE CONSUMER

CURE Connections® video resources target *all* types of cancers

Lung Cancer

Neuroendocrine Tumors

Breast Cancer

Prostate Cancer

Ovarian Cancer

Navigators Offer Touch Points on Patients' Cancer Journey

Mary Caffrey

FOR ALL OF THE INNOVATIONS in cancer therapy and diagnostic tools, one of the most profound advances in care may be the helping hand. The role of the nurse navigator continues to evolve, and evidence shows giving patients this source of support works.

Different aspects of the navigator and support roles were the topic of a panel on the second day of Patient-Centered Oncology Care®, the multistakeholder gathering in cancer care held in Philadelphia, Pennsylvania.

The insurer, Aetna, is incorporating nurse navigators throughout the cancer care continuum due to the "vital impact" these professionals have on patients, said Roger Brito, DO, senior medical director of Oncology Solutions at the payer. Navigators wear multiple hats and reach out immediately after a biopsy—they don't wait for the results to come back, he said. The biopsy itself is "an anxiety provoking procedure," Brito said.

"They follow our members through their cancer journey by getting them into the right treatment plan" he said. "Our philosophy is, 'You don't join us, we join you.'"

Bo Gamble, director of strategic practice initiatives for the Community Oncology Alliance, has seen the evolution of the navigator's role, especially over the last 5 years. "I've really seen it take hold," Gamble said, adding that the presence of navigators affects not only the quality of care for patients but also affects physician recruitment.

Navigators have communication skills, particularly as mediators between providers and a patient's employer, that physicians lack. "They have a magic touch," Gamble said, and are so needed that the challenge now is freeing up time for professional development.

As an oncology financial navigator for St. Agnes Cancer Institute in Ellicott City, Maryland, Nicole Taglione connects with nurse navigators at the beginning of a patient's treatment to figure out what insurance will pay and whether there is need for assistance from private foundations or drug manufacturers. "We help the patient to understand what to expect before they get the bills," she said.

Marie Kelly Pressler, RN, MSN, OCN, and Karon Martyn, MSN, ANP-BC, AOCNP, both of Abington Hospital-Jefferson Health, a hospital north of Philadelphia, discussed the sequence of their roles in a patient's care. Pressler serves at the initial point of contact and emphasized how important that is for setting the tone for the rest of the patient's experience.

"That first touchpoint is so very important for the patient," Pressler said. It's essential to communicate a sense to the patient that "I'm safe. I'm comfortable with the decision I make after this phone call."

When Pressler transitions a patient to Martyn's care, the process is very careful and deliberate. Martyn knows the patient is headed her way and assists in a shared decision-making process that she says is a far cry from the 1950s model of care where physicians did little to inquire what patients wanted.

"We make sure that treatment decisions are best for them," Martyn said, and she makes sure patients understand that things can change.

Moderator Margaret O'Grady RN, MSN, OCN, FAAMA, the administrative director for Abington Hospital-Jefferson Health Oncology Service Line, asked each member of the panel to discuss how they address acute episodes as well as the topic of palliative care—a challenging but necessary step.

Brito said the more that Aetna does to increase the "stickiness" of the relationship between the navigator and the patient, the more likely they are to prevent issues of toxicity of medication from turning into a trip to the emergency department. The growing emphasis on survivorship care, and the rising number of survivors, extends the length of these relationships.

Pressler was more direct. "The first thing is, you have to be nosy." Nurses in the infusion room, for example, must be trained to ask the patients about adverse effects. When patients say nothing is wrong, nurses must be willing to dig a little deeper. Developing that rapport will allow patients to open up and share things before they turn into big problems, as well as make the appointment with the physician more efficient.

Gamble agreed. His organization has done extensive surveys with patients about their experiences and learned, for example, that sometimes the stress level within families is so high that a patient's workplace is the only refuge. Again, he said, the navigators seem better equipped at finding out these things. "They've become the heroes in this generation." ◆

From left, Roger Brito, DO, of Aetna; Bo Gamble, of the Community Oncology Alliance; Nicole Taglione of St. Agnes Cancer Institute; Marie Kelly Pressler, RN, MSN, OCN, and Karon Martyn, MSN, ANP-BC, both of Abington-Jefferson Health, discuss patient navigation needs, including financial consulting, with questions from moderator Margaret "Peg" O'Grady, RN, MSN, OCN, FAAMA.

The Importance of Teamwork in Oncology Care Transitions

Surabhi Dangi-Garimella, PhD

DIAZ

PATIENT CARE IS A TEAM EFFORT, and this is truly evident in oncology care. A panel on the importance of clinical and nonclinical stakeholders in a patient's care trajectory brought together a diverse group convened by *The American Journal of Managed Care*® for Patient-Centered Oncology Care®, held November 16-17, 2017, in Philadelphia, Pennsylvania.

Panelists included Rose Gerber, director of patient advocacy and education, Community Oncology Alliance; Stacey McCullough, PharmD, senior vice president for pharmacy, Tennessee Oncology; Michael Diaz, MD, director of patient advocacy, Florida Cancer Specialists & Research Institute; and Rebekah Gilbert, RN, BSN, OCN, nurse practitioner, Hematology Oncology Associates of Central New York.

Gerber, a breast cancer survivor, narrated her personal experience as a patient and a survivor, which serve as her inspiration for her current role as a patient advocate and educator. Having received her diagnosis while she was raising a young family, Gerber said that she and her husband were devastated. Overwhelmed by the news, and vulnerable, Gerber and her husband were ready for her to participate in any clinical trial that was offered. "However, when I looked at the pages and pages of consent forms and disclosure forms, I was scared," she said, adding that she values the importance of clinical trials as an option for patients and firmly believes that patients should be engaged to participate in trials.

Gerber also noted that care transitions are extremely important for patients. "I never thought, 14 years later, that I'd still be actively seeing my oncologist, as I continue dealing with some of my health issues," she said, explaining that her chemotherapy (trastuzumab) and other cancer treatments increased her susceptibility to secondary health issues. So, in addition to an oncologist, a radiologist, and a surgeon, Gerber's care plan includes a cardiologist because of heart conditions developed as an adverse effect of the trastuzumab, an endocrinologist, and a neurologist. Additionally, she struggles with weight issues, which could be related to some of the treatments that were administered. "But at the center of it all has been my oncologist," Gerber said.

From left, panelists Rebekah Gilbert, RN, BSN, OCN; Stacey McCullough, PharmD; and Rose Gerber.

Gilbert said that each care team in her practice includes a patient navigator, a nurse, an advanced practitioner, and a doctor. "We huddle each morning to discuss our patients who will be visiting our clinic that day, as well as the patients who have been identified as being high risk." This keeps everyone on the team abreast of what's going on with their patients. Additionally, the clinic has a telephone triage system, with 3 dedicated nurses on call all day, who either bring in a patient or give them home-care instructions over the phone. "Very rarely do we send a patient to the ER [emergency room]," Gilbert said.

McCullough explained that, following the advent of oral oncolytics, Tennessee Oncology established an in-house retail system that operates as a specialty pharmacy. "Our healthcare system has, so far, underutilized pharmacists, but a pharmacist can definitely step in and be a part or a better partner along with nurses and physicians," she said. Pharmacists have access to the electronic health record as well as the doctor's notes. Also, when they access the system to refill prescriptions, the pharmacist can keep track of when a patient was due for a clinic visit but may have missed the appointment and can be the point of contact for the patient. "So, a pharmacist can play a more proactive role in patient care," McCullough said.

Diaz noted a very specific challenge at Florida Cancer Specialists: Consolidation has increased its size to over 100 sites across the state, with more than 200 oncologists on the team in addition to advanced practitioners. "Each site had their own model on how they operated, and we needed a process so everyone would work in a similar fashion to be able to provide all the advanced care that patients need," Diaz explained. Their 40 care coordinators have been divided into 3 teams:

- Care coordination for patients on active treatment
- Care coordination for survivorship care
- Transitional care coordination

The team that works with active patients has protocols in place so it knows how often they need to contact the patients. They also have specific questions when they reach out to these patients, in addition to routine clinic visits.

The team dedicated to survivorship coordinates care with the doctors and calls the patients to ensure they are aware of upcoming appointments.

The team that manages transitional care coordination has access to software that allows a coordinator to follow all of the information and ensure patients are taken care of during their transition out of a hospital, in case they need extra care post discharge, because they may or may not always know whether they need to get in touch with a doctor with regard to a specific concern. "So, the bulk of the care we are trying to provide to our patients is handled by our care coordinators," he said.

As a nurse navigator in her practice, Gilbert noted that she works closely with the pharmacist on patient education, especially with oral oncolytics, which is at the top of their plan. A nurse also makes follow-up phone calls with the patient at pre-determined intervals, and if there are any issues, the nurse will let the team know to follow up with the patient.

"While the patient should be at the center, I think the oncologist, the nurse, the pharmacist, and even family caregivers should be part of the patient's care team," Gerber said, aptly summarizing the discussion. ◆

Coming Soon!

HOW IMPACTFUL WILL WEARABLE TECHNOLOGY BE IN TREATMENT PROTOCOLS?

HRA® DATA DRIVEN INTELLIGENCE

A MJH MICHAEL J. HENNESSY COMPANY

HRA® is bridging the gap between drug and medical device manufacturers, payers, physicians, and patients to gauge their interactions with wearable healthcare technology, and to determine how wearables will impact the future of healthcare.

CONTACT US TO LEARN MORE ABOUT THIS LANDMARK SYNDICATED STUDY.

inquiries@hraresearch.com

609.716.7777

Creating connections.
Inspired by patients.

Commitment to patients and innovation fueled the advancement of the Celgene portfolio from hematology and oncology into inflammatory diseases. Those same principles guide our approach to making sure patients can get the essential treatments they need.

Celgene | Market Access