SPECIAL ISSUE: PRECISION MEDICINE

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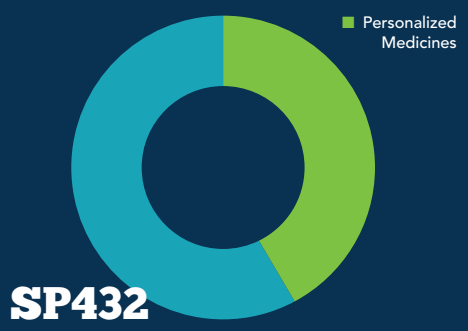
ALSO IN THIS ISSUE



PRECISION MEDICINE, FROM A COMMUNITY ONCOLOGY PERSPECTIVE

Barry Kaplan, MD, PhD, president, Queens Medical Associates, speaks to the importance of targeted treatments and the need for payers to keep pace. He also highlights challenges with these treatments, such as the need for maintenance therapy (SP409).

INTERVIEW WITH SYAPSE CEO

A conversation with Ken Tarkoff, CEO of the health information technology company Syapse, on how their digital platform helps ease workflow burdens and allows connectivity for oncology care providers (SP410).

CANCERLINQ'S COLLABORATIONS

Kevin Fitzpatrick, CancerLinQ's CEO, describes collaborations established by the organization with multiple groups associated with the business of healthcare, including the National Cancer Institute and the FDA, to improve cancer care outcomes for patients (SP412).

MEDICAL WORLD NEWS

Changes to the 340B program, potential for vision loss with immunotherapies, and more: updates from the medical world (SP415).

DIGITAL HEALTH

Implementing an Oncology Precision Medicine Clinic in a Large Community Health System

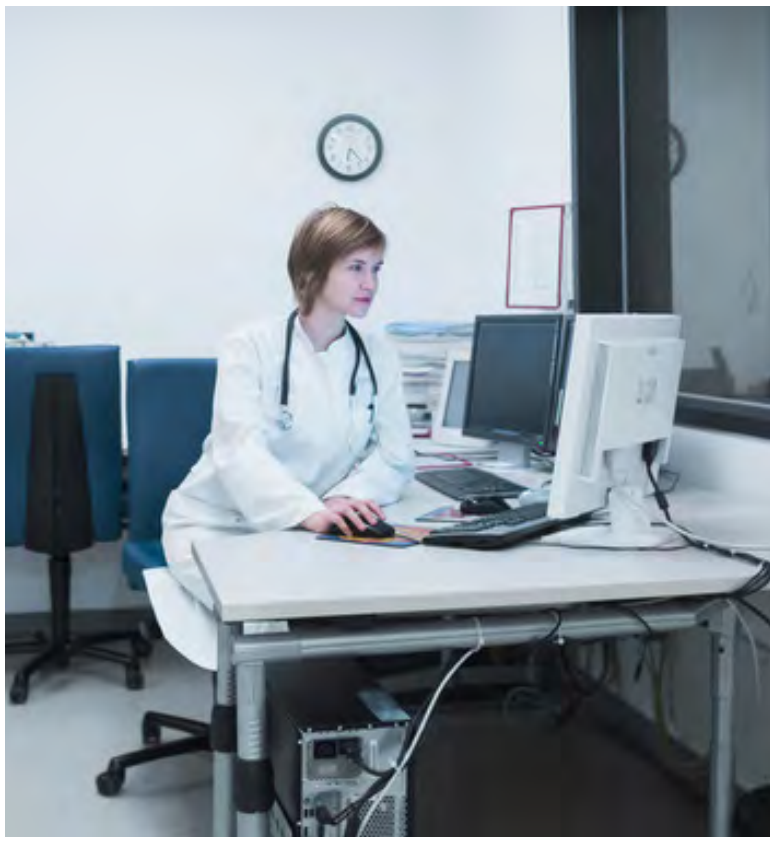
Michael A. Thompson, MD, PhD; Jennifer J. Godden, PharmD; Scott M. Weissman, MS, CGC; Deborah Wham, MS, CGC; Amanda Wilson, MD; Antony Ruggeri, MD; Michael P. Mullane, MD; and James L. Weese, MD, FACS

What Is Precision Medicine?

Precision medicine (PM) has various definitions, and several terms are used in association with it, including personalized medicine, genomic medicine, and individualized medicine. Delivered based on our understanding of molecular alterations to cancer cells, examples of individualized (or personalized) therapy include targets and inhibitors of the epidermal growth factor receptor, anaplastic lymphoma kinase, human epidermal growth factor receptor 2, and other molecular targets. An early, and likely the best, example is the use of imatinib to treat chronic myelogenous leukemia.

In his editorial, "Can We Define and Reach Precise Goals for Precision Medicine in Cancer Care?"[1] Howard West notes, "Despite the

CONTINUED ON SP425



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GENETIC COUNSELING

Genetic Counselors Save Costs Across the Genetic Testing Spectrum

Joy Larsen Haidle, MS, CGC; Darci L. Sternen, MS, CGC; Jane A. Dickerson, PhD; Amelia Mroch, MS, CGC; Denise F. Needham, MS, CGC; Christine M. Riordan, MS, CGC; and Michele C. Kieke, PhD, MS, CGC

GENETIC COUNSELORS (GCs) serve in many roles across the healthcare spectrum, in settings as diverse as a hospital or clinic, laboratory, community health center, government entity, and insurance company. Increasingly, GCs are providing test utilization management (UM) services for a variety of stakeholders involved in genetic testing processes, including patients, ordering institutions, testing laboratories, and payers. UM services aim to ensure that the most appropriate, cost-effective testing is ordered for *all* patients.

The core skills of GCs are becoming even more important in the clinical testing landscape as genetic testing continues to rapidly evolve and expand, primarily due to the advent of next-generation sequencing. These core skills include being knowledgeable about genetics, a strong communicator, a problem solver, self-sufficient, familiar with the inner workings of the healthcare system, and a team player.[1]

CONTINUED ON SP428

PATIENT PERSPECTIVE

Patient Engagement Is Mandatory at Our Table

Bonnie J. Addario and Daryl Pritchard, PhD

PRECISION MEDICINE ENTAILS the consideration of individual patient characteristics so that doctors, working directly with patients, can develop the best treatment plans for them as early in their care as possible. Treatment strategies should consider the whole person, including their age, medical history, ethnicity, biological characteristics, and other factors. This involves using technologies such as diagnostic tests, molecular profiling platforms, and therapies that directly target disease-causing genetic mutations.

CONTINUED ON SP431

AJMC® Managed Markets Network®

The Institute for Value-Based Medicine®

COA Community Oncology Alliance

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

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)

first 4 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 + 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

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 (frequency ≥20%) were neutropenia (75%), nausea (52%), fatigue (37%), diarrhea (35%), leukopenia (33%), alopecia (33%), vomiting (29%), constipation (25%), headache (22%), and back pain (20%). The most common grade 3/4 ARs (reported at a frequency >2%) were neutropenia (60%), leukopenia (21%), abnormal LFTs (10%), lymphopenia (7%), and vomiting (4%).

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

NOVARTIS

KISQALI® ribociclib

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

KIS-1164263

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
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 13^{th} 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.

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SPECIAL ISSUE/Precision Medicine
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Michael J. Hennessy Associates, Inc.

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

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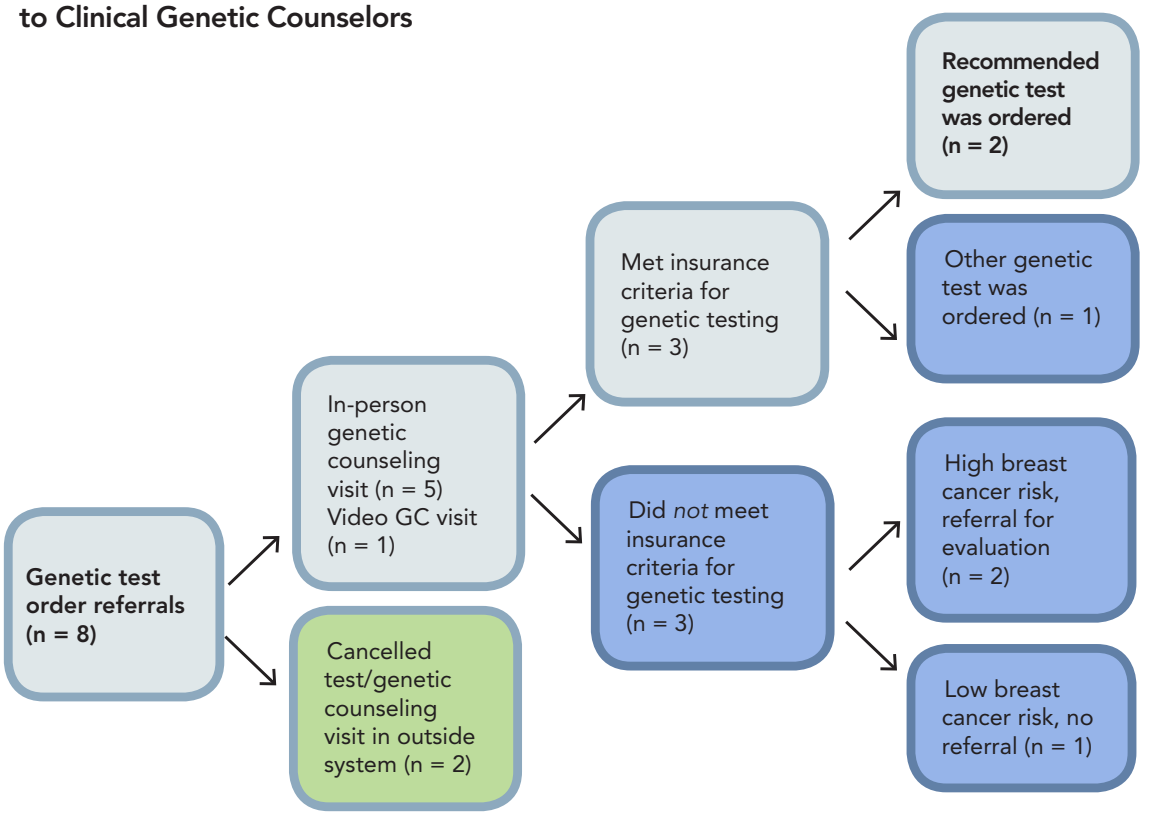
SP430

Workflow for Routing *BRCA1* and *BRCA2* Genetic Test Orders to Clinical Genetic Counselors



FEATURES

INSIDE THE ISSUE

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EBOncology

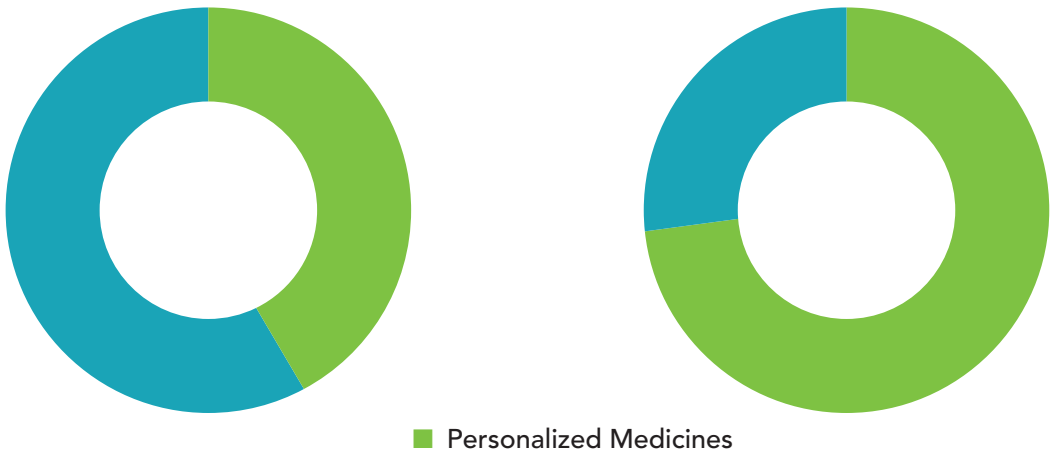
AUGUST 2017, VOLUME 23, ISSUE 10

SP432

Drug Development Pipelines Have Seen a Rapid Increase in the Number of Targeted Treatments

42% of All Drugs in Development Are Personalized Medicines

73% of Oncology Drugs in Development Are Personalized Medicines



Biopharmaceutical companies nearly doubled their research and development investment in personalized medicines over the past 5 years and expect to increase their investment by an additional third in the next 5 years. Biopharmaceutical researchers also predict a 69% increase in the number of personalized medicines in development over the next 5 years.

FROM THE CHAIRMAN

Precision Medicine Is the Way Forward, But We Need Means to Pay for It


MIKE HENNESSY, SR

IT SEEMS LOGICAL, given our immense store of knowledge on the varieties of cancer and their biologies, that precision medicine—which combines personalized and molecular medicine—should be the right way forward for most patients diagnosed with cancer. However, patients often face standard chemotherapy-based regimens rather than targeted or personalized treatments, which can be compounded by multiple factors.

In this issue of *Evidence-Based Oncology*™, we invited care providers from a large community health system, genetic counselors (GCs) working across several institutions, a patient advocacy group, a community oncologist, a healthcare technology platform developer, and an organization that helps link health data, to define precision care.

Aurora Health Care, in Milwaukee, Wisconsin, has implemented software developed by health information technology (IT) provider Syapse to integrate molecular data into the hospital's electronic health record to accommodate precision medicine findings. The authors discuss the important role played by their oncology precision medicine (OPM) clinic and describe how they implemented workflow changes for the OPM's success.

GCs serve a variety of roles across the healthcare spectrum, including test utilization management, which aims to select the most appropriate, cost-effective genetic testing for all patients. GCs from various institutions, including cancer centers, a diagnostic laboratory, and a benefit management company, describe their institutional findings using *BRCA* testing as an example. The data show that utilizing the expertise of GCs resulted in reduced test order errors, improved patient outcomes, and significant cost savings to the healthcare system.

From the patient's perspective, personalized medicine has the power to present them with the best treatment plan based on the results of diagnostic testing. In their article, Bonnie J. Addario and Daryl Pritchard, PhD, describe the advantages of empowering patients to be more engaged in their healthcare and encouraging their input in various aspects of healthcare, including clinical trial design and the development of clinical pathways.

Finally, issues with data connectivity and the existence of silos remains a significant problem for our healthcare system, and the American Society of Clinical Oncology has developed CancerLinQ, a health IT platform that is source-agnostic with respect to aggregating and analyzing real-world cancer care data. According to Kevin Fitzpatrick, CancerLinQ's CEO, the platform can "evaluate quality of care in real time, offer insights from de-identified health information based on millions of data points, and visualize patients' medical histories in novel ways." In his article, Fitzpatrick describes several partnerships initiated by CancerLinQ that include the FDA; the National Cancer Institute's Surveillance, Epidemiology, and End Results Program; and the National Comprehensive Cancer Network, all in an effort to improve outcomes for patients diagnosed with, and being treated for, cancer.

We hope you find this issue interesting and useful within your space. Don't forget to visit **ajmc.com** for regular healthcare updates and to follow our Peer Exchange™ and Insights™ offerings. ◆

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

Specialty physicians shouldn't have to decide between seeing enough patients to sustain financial health and making sure those patients receive quality care. With preferred contracting and specialty pharmacy services for more products, as well as technologies and business consulting to improve operations, practices don't have to choose. It takes quantity and quality to deliver specialty care to communities. It takes AmerisourceBergen.

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FROM THE EDITOR-IN-CHIEF

From "Magic Bullets" to Precision Medicine—Ensuring More Patient-Centered Cancer Care

IN 1998, THE ESTEEMED JOURNALIST, Seymour Hersh, wrote about a new, revolutionary anticancer technology (now known as antiangiogenic agents):

Within a year, if all goes well, the first cancer patient will be injected with two new drugs that can eradicate any type of cancer, with no obvious side effects and no drug resistance…in mice.[1]

Although the article was quick to point out that many promising discoveries are tempered by the reality of more limited activity when used to actually treat people with cancer, in the article, Hersh went so far as to quote a Nobel laureate who gushed that "Judah (the leading scientist in studying the new technology) is going to cure cancer in two years."[1] However, over the past 2 decades, the impact of antiangiogenic agents on cancer survival outcomes has been far more limited than what the initial enthusiasm suggested.

For decades, the popular press has oversold the transformational nature of new, anticancer therapeutics. Interferons and other drugs have been lauded on the cover of *Time* magazine and other popular publications as the "magic bullets" that would end the devastating impact of a cancer diagnosis. While the pace of anticancer drug discovery and innovation has accelerated beyond anyone's wildest dreams, we have yet to discover "magic." There is not a single drug that is the cure for all cancers, and in all likelihood, there will never be. The search for a cure has instead focused upon better understanding the genomic, molecular, proteomic, and transcriptomic mutations/variations that form the biological underpinnings of the breadth of cancers. Instead of finding cures by identifying an underlying simplicity, we have instead embraced the mind-numbing mechanistic complexity of navigating cancer biology.


JOSEPH ALVARNAS, MD

This era of "precision medicine" feels decidedly different than prior eras in cancer discovery. The hubris of talking about "magic bullets" has given way to a humility about understanding that a set of diseases like non–small cell lung cancer may represent a dozen or more genomic variants that present distinct opportunities for targeted therapeutic interventions. The work of deciphering the human genome and proteome have finally provided us with a set of tools that make cancer, in its many avatars, knowable and more potentially curable.

Inasmuch as the opportunities presented by the "precision medicine" paradigm are countless, the challenges posed to our patients and our healthcare delivery system, by this paradigm shift, are numerous. How can patients effectively grasp their healthcare choices when the pace of innovation creates changes in the standard of care at a rate nearly impossible to process? How can medical oncologists and hematologists outside of academic "innovation" centers become effective stewards of an increasingly complex armamentarium of anticancer drugs and the molecular diagnostic tools required to use them effectively? How do we create a value-based, economically sustainable system of delivering these care solutions to patients on a population basis? Given the extraordinary cost of the new, targeted anticancer agents, how can we deliver these care solutions without bankrupting either our patients or our healthcare system?

Beyond the extraordinary scientific challenges of understanding the molecular underpinnings of cancer, we are at a time when we need to create a better system for delivering these therapeutics that more effectively engages the multitude of healthcare stakeholders (patients, physicians, government, healthcare payers, medical groups, pharmacy benefits managers, and pharma) in the sustainable pursuit of value-centric care.

In this edition of *Evidence-Based Oncology*™, we begin what promises to be the long process of bringing these challenges and their solutions to life. Michael A. Thompson, MD, PhD, and colleagues explore the challenges and opportunities of implementing an oncology precision medicine clinic in a large community health setting. Joy Larsen Haidle, MS, and colleagues describe the value-enhancements that genetic counselors can bring to the genetic testing of cancer patients. Bonnie J. Addario and Daryl Pritchard, PhD, explore the importance of patient engagement in ensuring the relevance and sustainability of precision medicine solutions for patients with cancer.

In the shift from the search for "magic bullets" to the precision medicine model of cancer care, it is finally possible to foresee a growing, highly targeted, highly complex armamentarium of anticancer agents that will change patients' lives for the better. It is essential, however, to develop a scalable system that can deliver these (undoubtedly expensive) care solutions in a patient-centered, economically sustainable way. ◆

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Letter to the Editors

To the Editors:

RIND AND EMONDS' RECENT ARTICLE, "ICER's Value Assessment Framework: Capturing the Patient Experience,"[1] provides an overview of Institute for Clinical and Economic Review (ICER)'s enhanced focus on value from the patient's perspective. The National Health Council (NHC) wholeheartedly supports engaging the patient community (patients, caregivers, advocates, and advocacy groups) to bring the patient voice to all value assessment efforts. ICER is to be commended for improvements implemented in its approach; however, we believe there is still a great deal of work to be done to truly establish robust health technology assessment strategies and tactics for meaningfully engaging the patient community. We have been and will continue to work with ICER and other value framework developers to achieve this goal.

In 2016, in an effort to increase and improve patient engagement in value assessment, the NHC launched a value initiative to support its patient-advocate membership,[2] which includes:

- A value model rubric[3] to clarify what constitutes patient-centeredness and engagement;
- A get-ready checklist[4] to guide patient groups in engagement;
- A value workgroup to provide networking and information sharing through voluntary meetings of patient-organization staff who have worked with value framework developers;
- A qualitative study to provide insights on patients' definitions of value; and
- A health economics educational program to inform the patient community on basic economic and value-assessment terms and principles.

All value framework developers need to remember that patient partnership, transparency, and inclusiveness are critical. Proactive patient-engagement opportunities are a must. ICER's Patient Participation Guide outlines only reactive opportunities for patients—reactive opportunities represent a limited scope of engagement. In our comment letter[5] to ICER on its proposed process changes, we encouraged developing proactive opportunities through which the patient community can partner to shape the questions, protocol, etc. We know ICER offers these opportunities, but the processes are unclear. ICER and all other framework developers are encouraged to create and disseminate transparent patient-engagement processes describing how patients can be engaged proactively as partners, as early as possible, start to finish, and how input is gathered and incorporated.

Collecting patient data on preferred outcomes and preferences is necessary—but not sufficient. These data must be fairly considered in value assessment. ICER and other framework developers' emphasis on clinical trial data means clinical endpoints may differ from, and outweigh, the outcomes most important to patients.

All value framework developers need to remember that patient partnership, transparency, and inclusiveness are critical. Proactive patient-engagement opportunities are a must.

It is vital for independent appraisal committees that make the critical voting decisions on a value assessment, to have the knowledge and context expertise of the relevant specific disease or disability. NHC believes that a robust patient engagement strategy ensures these committees have the relevant condition-specific expertise of patients.[5]

To reiterate, the NHC wholeheartedly supports ICER's efforts to incorporate the patient voice, as highlighted in Rind and Emond's article. We look forward to continuous collaboration with ICER to enhance the incorporation of the patient voice throughout the entire value assessment and framework development process.[6] ◆

Sincerely,

Eleanor M. Perfetto, PhD, MS
Senior Vice President, Strategic Initiatives
1730 M Street NW, Suite 500
Washington, DC 20036-4561
202-973-0546

E-mail: eperfetto@NHCouncil.org

PERFETTO

Eleanor M. Perfetto, PhD, MS, is senior vice president, Strategic Initiatives, The National Health Council.

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ERBITUX®
CETUXIMAB

Injection for Intravenous Infusion
100 mg/50 mL & 200 mg/100 mL vials

There is only one.

ERBITUX, the only EGFR inhibitor approved to treat both mCRC and SCCHN.[1]

ERBITUX indications for metastatic colorectal cancer (mCRC)

- ERBITUX is indicated for the treatment of *KRAS* wild-type, epidermal growth factor receptor (EGFR)-expressing mCRC as determined by FDA-approved tests for this use:
  - —In combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment
  - —In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy
  - —As a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan

Limitation of Use: ERBITUX is not indicated for treatment of *RAS*-mutant colorectal cancer or when the results of the *RAS* mutation tests are unknown.

WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST

Infusion Reactions:

Serious infusion reactions occurred with the administration of ERBITUX in approximately 3% of patients in clinical trials, with fatal outcome reported in less than 1 in 1000. Immediately interrupt and permanently discontinue ERBITUX infusion for serious infusion reactions.

Cardiopulmonary Arrest:

Cardiopulmonary arrest and/or sudden death occurred in 2% of patients with squamous cell carcinoma of the head and neck treated in a clinical trial with ERBITUX and radiation therapy and in 3% of patients with squamous cell carcinoma of the head and neck treated in a clinical trial with European Union (EU)-approved cetuximab in combination with platinum-based therapy with 5-fluorouracil (5-FU). Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after ERBITUX administration.

Please see Important Safety Information, including Boxed Warnings regarding infusion reactions and cardiopulmonary arrest, and Brief Summary of Prescribing Information for ERBITUX on the following pages.

Over 10 years of ERBITUX experience

ERBITUX (cetuximab)* is the only EGFR inhibitor FDA approved for the treatment of mCRC and SCCHN[1-9] and is supported by over 10 years of post-approval experience.

2004

FDA approval
For treatment of EGFR-expressing mCRC in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy and as a single agent for the treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy[2,3]

2006

FDA approval
For initial treatment of locally or regionally advanced SCCHN in combination with radiation therapy[2,4]

For the treatment of patients with recurrent metastatic SCCHN as a single agent for whom prior platinum-based therapy has failed[2,5]

2007

FDA approval
For the treatment of patients with EGFR-expressing mCRC as a single agent after failure of both irinotecan- and oxaliplatin-based regimens[2,6]

2009

Label updated
Limitation of use in *KRAS* (exon 2) mutant CRC tumors[2]

2011

FDA approval
For first-line treatment of patients with recurrent locoregional disease or metastatic SCCHN in combination with platinum-based therapy with 5-FU[2,7]

2012

FDA approval
For first-line treatment of patients with *KRAS* wild-type, EGFR-expressing mCRC as determined by FDA-approved tests for this use in combination with FOLFIRI[2,8,9]

2015

Label updated
Limitation of Use expanded to include patients with mCRC harboring mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of *KRAS* or *NRAS*[2]

ERBITUX indications for squamous cell carcinoma of the head and neck (SCCHN)

- ERBITUX, in combination with radiation therapy, is indicated for the initial treatment of locally or regionally advanced SCCHN
- ERBITUX is indicated in combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional disease or metastatic SCCHN
- ERBITUX, as a single agent, is indicated for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed

The first FDA approval for ERBITUX in mCRC was in 2004. The first FDA approval for ERBITUX in SCCHN was in 2006.

*Cetuximab includes both US-licensed ERBITUX and EU-approved cetuximab. ERBITUX provides approximately 22% higher exposure relative to the EU-approved cetuximab. These pharmacokinetic data, together with the results of the clinical studies, establish the efficacy of ERBITUX at the recommended dose in the FDA-approved indications.

5-FU=5-fluorouracil; CRC=colorectal cancer; EU=European Union.

SELECT IMPORTANT SAFETY INFORMATION

Pulmonary Toxicity

- Interstitial lung disease (ILD), which was fatal in one case, occurred in 4 of 1570 (<0.5%) patients receiving ERBITUX in Studies 1, 3, and 6, as well as other studies, in colorectal cancer and head and neck cancer. Interrupt ERBITUX for acute onset or worsening of pulmonary symptoms. Permanently discontinue ERBITUX for confirmed ILD

IMPORTANT SAFETY INFORMATION FOR ERBITUX® (cetuximab)

WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST

Infusion Reactions

- **Grade 3/4 infusion reactions occurred in approximately 3% of patients receiving ERBITUX® (cetuximab) in clinical trials, with fatal outcome reported in less than 1 in 1000**
  - **—Serious infusion reactions, requiring medical intervention and immediate, permanent discontinuation of ERBITUX, included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest**
  - **—Immediately interrupt and permanently discontinue ERBITUX infusion for serious infusion reactions**
- **Approximately 90% of the severe infusion reactions were associated with the first infusion of ERBITUX despite premedication with antihistamines**
  - **—Caution must be exercised with every ERBITUX infusion, as there were patients who experienced their first severe infusion reaction during later infusions**
  - **—Monitor patients for 1 hour following ERBITUX infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (eg, epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Longer observation periods may be required in patients who require treatment for infusion reactions**

Cardiopulmonary Arrest

- **Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients with squamous cell carcinoma of the head and neck treated with radiation therapy and ERBITUX, as compared to none of 212 patients treated with radiation therapy alone. In 3 patients with prior history of coronary artery disease, death occurred 27, 32, and 43 days after the last dose of ERBITUX. One patient with no prior history of coronary artery disease died one day after the last dose of ERBITUX. Fatal cardiac disorders and/or sudden death occurred in 7 (3%) of the 219 patients with squamous cell carcinoma of the head and neck treated with platinum-based therapy with 5-fluorouracil (5-FU) and European Union (EU)-approved cetuximab as compared to 4 (2%) of the 215 patients treated with chemotherapy alone. Five of these 7 patients in the chemotherapy plus cetuximab arm received concomitant cisplatin and 2 patients received concomitant carboplatin. All 4 patients in the chemotherapy-alone arm received cisplatin**
  - **—Carefully consider the use of ERBITUX in combination with radiation therapy or platinum-based therapy with 5-FU in head and neck cancer patients with a history of coronary artery disease, congestive heart failure, or arrhythmias in light of these risks**
  - **—Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium during and after ERBITUX therapy**

Pulmonary Toxicity

- Interstitial lung disease (ILD), which was fatal in one case, occurred in 4 of 1570 (<0.5%) patients receiving ERBITUX in Studies 1, 3, and 6, as well as other studies, in colorectal cancer and head and neck cancer. Interrupt ERBITUX for acute onset or worsening of pulmonary symptoms. Permanently discontinue ERBITUX for confirmed ILD

Dermatologic Toxicities

- In clinical studies of ERBITUX, dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (eg, *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis, occurred in patients receiving ERBITUX therapy
  - —Acneiform rash occurred in 76-88% of 1373 patients receiving ERBITUX in Studies 1, 3, 5, and 6. Severe acneiform rash occurred in 1-17% of patients. Acneiform rash usually developed within the first 2 weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days
  - —Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has also been observed in patients treated with ERBITUX. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis)
  - —Monitor patients receiving ERBITUX for dermatologic toxicities and infectious sequelae
  - —Sun exposure may exacerbate these effects

ERBITUX Plus Radiation Therapy and Cisplatin

- In a controlled study, 940 patients with locally advanced SCCHN were randomized 1:1 to receive either ERBITUX in combination with radiation therapy and cisplatin or radiation therapy and cisplatin alone. The addition of ERBITUX resulted in an increase in the incidence of Grade 3-4 mucositis, radiation recall syndrome, acneiform rash, cardiac events, and electrolyte disturbances compared to radiation and cisplatin alone
- Adverse reactions with fatal outcome were reported in 20 patients (4.4%) in the ERBITUX combination arm and 14 patients (3.0%) in the control arm
- Nine patients in the ERBITUX arm (2.0%) experienced myocardial ischemia compared to 4 patients (0.9%) in the control arm
- The addition of ERBITUX to radiation and cisplatin did not improve progression-free survival (the primary endpoint)

Electrolyte Depletion

- Hypomagnesemia occurred in 55% of 365 patients receiving ERBITUX in Study 5 and two other clinical trials in colorectal cancer and head and neck cancer, respectively, and was severe (NCI CTC grades 3 & 4) in 6-17%. In Study 2, the addition of EU-approved cetuximab to cisplatin and 5-FU resulted in an increased incidence of hypomagnesemia (14% vs 6%) and of grade 3-4 hypomagnesemia (7% vs 2%) compared to cisplatin and 5-FU alone. In contrast, the incidences of hypomagnesemia were similar for those who received cetuximab, carboplatin, and 5-FU compared to carboplatin and 5-FU (4% vs 4%). No patient experienced grade 3-4 hypomagnesemia in either arm in the carboplatin subgroup. The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of ERBITUX therapy
  - —Monitor patients periodically for hypomagnesemia, hypocalcemia, and hypokalemia, during, and for at least 8 weeks following the completion of, ERBITUX therapy
  - —Replete electrolytes as necessary

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IMPORTANT SAFETY INFORMATION FOR ERBITUX® (CONTINUED)

Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with *RAS*-Mutant mCRC

- ERBITUX is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either *KRAS* or *NRAS*
- Based on retrospective subset analyses of *RAS*-mutant and wild-type populations across several randomized clinical trials of anti-EGFR-directed monoclonal antibodies, including Study 4, use of cetuximab in patients with *RAS* mutations resulted in no clinical benefit with treatment related toxicity

Late Radiation Toxicities

- The overall incidence of late radiation toxicities (any grade) was higher with ERBITUX in combination with radiation therapy compared with radiation therapy alone. The following sites were affected: salivary glands (65% vs 56%), larynx (52% vs 36%), subcutaneous tissue (49% vs 45%), mucous membranes (48% vs 39%), esophagus (44% vs 35%), and skin (42% vs 33%) in the ERBITUX and radiation versus radiation-alone arms, respectively
  - —The incidence of grade 3 or 4 late radiation toxicities was similar between the radiation therapy alone and the ERBITUX plus radiation therapy arms

Pregnancy and Nursing

- In women of childbearing potential and men, appropriate contraceptive measures must be used during treatment with ERBITUX and for 6 months following the last dose of ERBITUX. ERBITUX may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women. ERBITUX should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus
- It is not known whether ERBITUX is secreted in human milk. IgG antibodies, such as ERBITUX, can be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ERBITUX, a decision should be made whether to discontinue nursing or to discontinue ERBITUX, taking into account the importance of ERBITUX to the mother. If nursing is interrupted, based on the mean half-life of cetuximab, nursing should not be resumed earlier than 60 days following the last dose of ERBITUX

Adverse Reactions

- The most **serious adverse reactions** associated with ERBITUX are infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus
- The most common adverse reactions associated with ERBITUX (incidence ≥25%) across all studies were cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection
- The most frequent adverse reactions seen in patients with carcinomas of the head and neck receiving ERBITUX in combination with radiation therapy (n=208) versus radiation alone (n=212) (incidence ≥50%) were acneiform rash (87% vs 10%), radiation dermatitis (86% vs 90%), weight loss (84% vs 72%), and asthenia (56% vs 49%). The most common grade 3/4 adverse reactions for ERBITUX in combination with radiation therapy (≥10%) versus radiation alone included: radiation dermatitis (23% vs 18%), acneiform rash (17% vs 1%), and weight loss (11% vs 7%)
- The most frequent adverse reactions seen in patients with carcinomas of the head and neck receiving EU-approved cetuximab in combination with platinum-based therapy with 5-FU (CT) (n=219) versus CT alone (n=215) (incidence ≥40%) were acneiform rash (70% vs 2%), nausea (54% vs 47%), and infection (44% vs 27%). The most common grade 3/4 adverse reactions for cetuximab in combination with CT (≥10%) versus CT alone included: infection (11% vs 8%). Since U.S.-licensed ERBITUX provides approximately 22% higher exposure relative to the EU-approved cetuximab, the data provided above may underestimate the incidence and severity of adverse reactions anticipated with ERBITUX for this indication. However, the tolerability of the recommended dose is supported by safety data from additional studies of ERBITUX
- The most frequent adverse reactions seen in patients with *KRAS* wild-type, EGFR-expressing metastatic colorectal cancer treated with EU-approved cetuximab + FOLFIRI (n=317) versus FOLFIRI alone (n=350) (incidence ≥50%) were acne-like rash (86% vs 13%) and diarrhea (66% vs 60%). The most common grade 3/4 adverse reactions (≥10%) included: neutropenia (31% vs 24%), acne-like rash (18% vs <1%), and diarrhea (16% vs 10%). U.S.-licensed ERBITUX provides approximately 22% higher exposure to cetuximab relative to the EU-approved cetuximab. The data provided above are consistent in incidence and severity of adverse reactions with those seen for ERBITUX in this indication. The tolerability of the recommended dose is supported by safety data from additional studies of ERBITUX
- The most frequent adverse reactions seen in patients with *KRAS* wild-type, EGFR-expressing metastatic colorectal cancer treated with ERBITUX + best supportive care (BSC) (n=118) versus BSC alone (n=124) (incidence ≥50%) were rash/desquamation (95% vs 21%), fatigue (91% vs 79%), nausea (64% vs 50%), dry skin (57% vs 15%), pain-other (59% vs 37%), and constipation (53% vs 38%). The most common grade 3/4 adverse reactions (≥10%) included: fatigue (31% vs 29%), pain-other (18% vs 10%), rash/desquamation (16% vs 1%), dyspnea (16% vs 13%), other-gastrointestinal (12% vs 5%), and infection without neutropenia (11% vs 5%)
- The most frequent adverse reactions seen in patients with EGFR-expressing metastatic colorectal cancer (n=354) treated with ERBITUX plus irinotecan in clinical trials (incidence ≥50%) were acneiform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common grade 3/4 adverse reactions (≥10%) included: diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneiform rash (14%)

Please see Brief Summary of Prescribing Information for ERBITUX, including Boxed Warnings regarding infusion reactions and cardiopulmonary arrest, on following pages.

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ERBITUX® CETUXIMAB
INJECTION FOR INTRAVENOUS INFUSION
100 MG/50 ML & 200 MG/100 ML VIALS

Lilly

Erbitux® (cetuximab)
injection, for intravenous infusion
Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST

Infusion Reactions: Serious infusion reactions occurred with the administration of Erbitux in approximately 3% of patients in clinical trials, with fatal outcome reported in less than 1 in 1000. [See *Warnings and Precautions, Adverse Reactions*.] Immediately interrupt and permanently discontinue Erbitux infusion for serious infusion reactions. [See *Dosage and Administration (2.4)* in Full Prescribing Information, *Warnings and Precautions*.]

Cardiopulmonary Arrest: Cardiopulmonary arrest and/or sudden death occurred in 2% of patients with squamous cell carcinoma of the head and neck treated with Erbitux and radiation therapy in Study 1 and in 3% of patients with squamous cell carcinoma of the head and neck treated with European Union (EU)-approved cetuximab in combination with platinum-based therapy with 5-fluorouracil (5-FU) in Study 2. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux administration. [See *Warnings and Precautions, Clinical Studies (14.1)* in Full Prescribing Information.]

INDICATIONS AND USAGE

Squamous Cell Carcinoma of the Head and Neck (SCCHN): Erbitux® (cetuximab) is indicated in combination with radiation therapy for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck. [See *Clinical Studies (14.1)* in Full Prescribing Information.]

Erbitux is indicated in combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck. [See *Clinical Studies (14.1)* in Full Prescribing Information.]

Erbitux, as a single agent, is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed. [See *Clinical Studies (14.1)* in Full Prescribing Information.]

***K-Ras* Wild-type, EGFR-expressing Colorectal Cancer**: Erbitux is indicated for the treatment of *K-Ras* wild-type, epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by FDA-approved tests for this use [see *Dosage and Administration (2.2)* in Full Prescribing Information, *Warnings and Precautions, Clinical Studies (14.2)* in Full Prescribing Information]:

- in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan. [See *Warnings and Precautions, Clinical Pharmacology (12.1)* in Full Prescribing Information*, Clinical Studies (14.2)* in Full Prescribing Information.]

Limitation of Use: Erbitux is not indicated for treatment of *Ras*-mutant colorectal cancer or when the results of the *Ras* mutation tests are unknown [see *Warnings and Precautions, Clinical Studies (14.2)* in Full Prescribing Information].

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion Reactions: Serious infusion reactions, requiring medical intervention and immediate, permanent discontinuation of Erbitux included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. Severe (NCI CTC Grades 3 and 4) infusion reactions occurred in 2–5% of 1373 patients in Studies 1, 3, 5, and 6 receiving Erbitux, with fatal outcome in 1 patient. [See *Clinical Studies (14.1, 14.2)* in Full Prescribing Information.]

Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines.

Monitor patients for 1 hour following Erbitux infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (eg, epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Monitor longer to confirm resolution of the event in patients requiring treatment for infusion reactions.

Immediately and permanently discontinue Erbitux in patients with serious infusion reactions. [See *Boxed Warning, Dosage and Administration (2.4)* in Full Prescribing Information.]

Cardiopulmonary Arrest: Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated with radiation therapy and Erbitux as compared to none of 212 patients treated with radiation therapy alone in Study 1. Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of Erbitux. One patient with no prior history of coronary artery disease died one day after the last dose of Erbitux. In Study 2, fatal cardiac disorders and/or sudden death occurred in 7 (3%) of 219 patients treated with EU-approved cetuximab and platinum-based therapy with 5-FU as compared to 4 (2%) of 215 patients treated with chemotherapy alone. Five of these 7 patients in the chemotherapy plus cetuximab arm received concomitant cisplatin and 2 patients received concomitant carboplatin. All 4 patients in the chemotherapy-alone arm received cisplatin. Carefully consider use of Erbitux in combination with radiation therapy or platinum-based therapy with 5-FU in head and neck cancer patients with a history of coronary artery disease, congestive heart failure, or arrhythmias in light of these risks. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux. [See *Boxed Warning, Warnings and Precautions*.]

Pulmonary Toxicity: Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients receiving Erbitux in Studies 1, 3, and 6, as well as other studies, in colorectal cancer and head and neck cancer. Interrupt Erbitux for acute onset or worsening of pulmonary symptoms. Permanently discontinue Erbitux for confirmed ILD.

Dermatologic Toxicity: Dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis occurred in patients receiving Erbitux therapy. Acneiform rash occurred in 76–88% of 1373 patients receiving Erbitux in Studies 1, 3, 5, and 6. Severe acneiform rash occurred in 1–17% of patients.

Acneiform rash usually developed within the first two weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has also been observed in patients treated with Erbitux. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis). Monitor patients receiving Erbitux for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during Erbitux therapy. [See *Dosage and Administration (2.4)* in Full Prescribing Information.]

Use of Erbitux in Combination With Radiation and Cisplatin: In a controlled study, 940 patients with locally advanced SCCHN were randomized 1:1 to receive either Erbitux in combination with radiation therapy and cisplatin or radiation therapy and cisplatin alone. The addition of Erbitux resulted in an increase in the incidence of Grade 3–4 mucositis, radiation recall syndrome, acneiform rash, cardiac events, and electrolyte disturbances compared to radiation and cisplatin alone. Adverse reactions with fatal outcome were reported in 20 patients (4.4%) in the Erbitux (cetuximab) combination arm and 14 patients (3.0%) in the control arm. Nine patients in the Erbitux arm (2.0%) experienced myocardial ischemia compared to 4 patients (0.9%) in the control arm. The main efficacy outcome of the study was progression-free survival (PFS). The addition of Erbitux to radiation and cisplatin did not improve PFS.

Hypomagnesemia and Electrolyte Abnormalities: In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of 365 patients receiving Erbitux in Study 5 and two other clinical trials in colorectal cancer and head and neck cancer, respectively, and was severe (NCI CTC Grades 3 and 4) in 6–17%.

In Study 2, where EU-approved cetuximab was administered in combination with platinum-based therapy, the addition of cetuximab to cisplatin and 5-FU resulted in an increased incidence of hypomagnesemia (14% vs. 6%) and of Grade 3–4 hypomagnesemia (7% vs. 2%) compared to cisplatin and 5-FU alone. In contrast, the incidences of hypomagnesemia were similar for those who received cetuximab, carboplatin, and 5-FU compared to carboplatin and 5-FU (4% vs. 4%). No patient experienced Grade 3–4 hypomagnesemia in either arm in the carboplatin subgroup.

The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of Erbitux. Periodically monitor patients for hypomagnesemia, hypocalcemia, and hypokalemia, during and for at least 8 weeks following the completion of Erbitux. Replete electrolytes as necessary.

Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with *Ras*-Mutant mCRC
Erbitux is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either *K-Ras* or *N-Ras* and hereafter is referred to as "*Ras.*"

Retrospective subset analyses of *Ras*-mutant and wild-type populations across several randomized clinical trials including Study 4 were conducted to investigate the role of *Ras* mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies. Use of cetuximab in patients with *Ras* mutations resulted in no clinical benefit with treatment related toxicity. [See *Indications and Usage*, and *Clinical Pharmacology (12.1)* and *Clinical Studies (14.2)* in Full Prescribing Information.]

Epidermal Growth Factor Receptor (EGFR) Expression and Response: Because expression of EGFR has been detected in nearly all SCCHN tumor specimens, patients enrolled in the head and neck cancer clinical studies were not required to have immunohistochemical evidence of EGFR tumor expression prior to study entry.

Patients enrolled in the colorectal cancer clinical studies were required to have immunohistochemical evidence of EGFR tumor expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ test kit. Specimens were scored based on the percentage of cells expressing EGFR and intensity (barely/faint, weak-to-moderate, and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

ADVERSE REACTIONS

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

- Infusion reactions [See *Boxed Warning, Warnings and Precautions*.]
- Cardiopulmonary arrest [See *Boxed Warning, Warnings and Precautions*.]
- Pulmonary toxicity [See *Warnings and Precautions*.]
- Dermatologic toxicity [See *Warnings and Precautions*.]
- Hypomagnesemia and Electrolyte Abnormalities [See *Warnings and Precautions*.]

The most common adverse reactions in Erbitux clinical trials (incidence ≥25%) include cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.

The most serious adverse reactions with Erbitux are infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus.

Across Studies 1, 3, 5, and 6, Erbitux was discontinued in 3–10% of patients because of adverse reactions.

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

The data below reflect exposure to Erbitux in 1373 patients with SCCHN or colorectal cancer in randomized Phase 3 (Studies 1 and 5) or Phase 2 (Studies 3 and 6) trials treated at the recommended dose and schedule for medians of 7 to 14 weeks. [See *Clinical Studies (14)* in Full Prescribing Information.]

Infusion reactions: Infusion reactions, which included pyrexia, chills, rigors, dyspnea, bronchospasm, angioedema, urticaria, hypertension, and hypotension occurred in 15–21% of patients across studies. Grades 3 and 4 infusion reactions occurred in 2–5% of patients; infusion reactions were fatal in 1 patient.

Infections: The incidence of infection was variable across studies, ranging from 13–35%. Sepsis occurred in 1–4% of patients.

Renal: Renal failure occurred in 1% of patients with colorectal cancer.

Squamous Cell Carcinoma of the Head and Neck

Erbitux in Combination with Radiation Therapy—Table 1 contains selected adverse reactions in 420 patients receiving radiation therapy either alone or with Erbitux for locally or regionally advanced SCCHN in Study 1. Erbitux was administered at the recommended dose and schedule (400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly). Patients received a median of 8 infusions (range 1–11).

Table 1: Incidence of Selected Adverse Reactions (≥10%) in Patients with Locoregionally Advanced SCCHN

Body System Preferred Term	Erbitux plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1–4	Grades 3 and 4	Grades 1–4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia	56	4	49	5
Fever[a]	29	1	13	1
Headache	19	<1	8	<1
Infusion Reaction[b]	15	3	2	0
Infection	13	1	9	1
Chills[a]	16	0	5	0
Digestive				
Nausea	49	2	37	2
Emesis	29	2	23	4
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolic/Nutritional				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8

Erbitux® (cetuximab) injection,
for intravenous infusion CE HCP BS 18OCT2016

Table 1: Incidence of Selected Adverse Reactions (≥10%) in Patients with Locoregionally Advanced SCCHN (Cont.)

Body System Preferred Term	Erbitux plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1–4	Grades 3 and 4	Grades 1–4	Grades 3 and 4
	% of Patients			
Metabolic/Nutritional (Cont.)				
Alanine Transaminase, high[c]	43	2	21	1
Aspartate Transaminase, high[c]	38	1	24	1
Alkaline Phosphatase, high[c]	33	<1	24	0
Respiratory				
Pharyngitis	26	3	19	4
Skin/Appendages				
Acneiform Rash[d]	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

[a] Includes cases also reported as infusion reaction. [b] Infusion reaction is defined as any reaction described at any time during the clinical study as "allergic reaction" or "anaphylactoid reaction," or any reaction occurring on the first day of dosing described as "allergic reaction," "anaphylactoid reaction," "fever," "chills," "chills and fever," or "dyspnea." [c] Based on laboratory measurements, not on reported adverse reactions, the number of subjects with tested samples varied from 205–206 for Erbitux plus radiation arm; 209–210 for radiation alone. [d] Acneiform rash is defined as any reaction described as "acne," "rash," "maculopapular rash," "pustular rash," "dry skin," or "exfoliative dermatitis."

The incidence and severity of mucositis, stomatitis, and xerostomia were similar in both arms of the study.

Late Radiation Toxicity—The overall incidence of late radiation toxicities (any grade) was higher in Erbitux in combination with radiation therapy compared with radiation therapy alone. The following sites were affected: salivary glands (65% versus 56%), larynx (52% versus 36%), subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus (44% versus 35%), skin (42% versus 33%). The incidence of Grade 3 or 4 late radiation toxicities was similar between the radiation therapy alone and the Erbitux plus radiation treatment groups.

Study 2: EU-Approved Cetuximab in Combination with Platinum-based Therapy with 5-Fluorouracil—Study 2 used EU-approved cetuximab. Since U.S.-licensed Erbitux provides approximately 22% higher exposure relative to the EU-approved cetuximab, the data provided below may underestimate the incidence and severity of adverse reactions anticipated with Erbitux for this indication. However, the tolerability of the recommended dose is supported by safety data from additional studies of Erbitux [see *Clinical Pharmacology (12.3)* in Full Prescribing Information].

Table 2 contains selected adverse reactions in 434 patients with recurrent locoregional disease or metastatic SCCHN receiving EU-approved cetuximab in combination with platinum-based therapy with 5-FU or platinum-based therapy with 5-FU alone in Study 2. Cetuximab was administered at 400 mg/m^2 for the initial dose, followed by 250 mg/m^2 weekly. Patients received a median of 17 infusions (range 1–89).

Table 2: Incidence of Selected Adverse Reactions (≥10%) in Patients with Recurrent Locoregional Disease of Metastatic SCCHN

System Organ Class Preferred Term	EU-Approved Cetuximab plus Platinum-based Therapy with 5-FU (n=219)		Platinum-based Therapy with 5-FU Alone (n=215)	
	Grades 1–4	Grades 3 and 4	Grades 1–4	Grades 3 and 4
	% of Patients			
Eye Disorders				
Conjunctivitis	10	0	0	0
Gastrointestinal Disorders				
Nausea	54	4	47	4
Diarrhea	26	5	16	1
General Disorders and Administration Site Conditions				
Pyrexia	22	0	13	1
Infusion Reaction[a]	10	2	<1	0
Infections and infestations				
Infection[b]	44	11	27	8
Metabolism and Nutrition Disorders				
Anorexia	25	5	14	1
Hypocalcemia	12	4	5	1
Hypokalemia	12	7	7	5
Hypomagnesemia	11	5	5	1
Skin and Subcutaneous Tissue Disorders				
Acneiform rash[c]	70	9	2	0
Rash	28	5	2	0
Acne	22	2	0	0
Dermatitis Acneiform	15	2	0	0
Dry skin	14	0	<1	0
Alopecia	12	0	7	0

[a] Infusion reaction defined as any event of "anaphylactic reaction," "hypersensitivity," "fever and/or chills," "dyspnea," or "pyrexia" on the first day of dosing. [b] Infection — this term excludes sepsis-related reactions which are presented separately. [c] Acneiform rash defined as any reaction described as "acne," "dermatitis acneiform," "dry skin," "exfoliative rash," "rash," "rash erythematous," "rash macular," "rash papular," or "rash pustular." Chemotherapy = cisplatin + 5-fluorouracil or carboplatin + 5-fluorouracil

For cardiac disorders, approximately 9% of subjects in both the EU-approved cetuximab plus chemotherapy and chemotherapy-only treatment arms in Study 2 experienced a cardiac event. The majority of these events occurred in patients who received cisplatin/5-FU, with or without cetuximab as follows: 11% and 12% in patients who received cisplatin/5-FU with or without cetuximab, respectively, and 6% or 4% in patients who received carboplatin/5-FU with or without cetuximab, respectively. In both arms, the incidence of cardiovascular events was higher in the cisplatin with 5-FU containing subgroup. Death attributed to cardiovascular event or sudden death was reported in 3% of the patients in the cetuximab plus platinum-based therapy with 5-FU arm and 2% in the platinum-based chemotherapy with 5-FU alone arm.

Colorectal Cancer

Study 4: EU-Approved Cetuximab in Combination with FOLFIRI—Study 4 used EU-approved cetuximab. U.S.-licensed Erbitux (cetuximab) provides approximately 22% higher exposure to cetuximab relative to the EU-approved cetuximab. The data provided below for Study 4 is consistent in incidence and severity of adverse reactions with those seen for Erbitux in this indication. The tolerability of the recommended dose is supported by safety data from additional studies of Erbitux [see *Clinical Pharmacology (12.3)* in Full Prescribing Information].

Table 3 contains selected adverse reactions in 667 patients with *K-Ras* wild-type, EGFR-expressing, metastatic colorectal cancer receiving EU-approved cetuximab plus FOLFIRI or FOLFIRI alone in Study 4 [see *Warnings and Precautions*]. Cetuximab was administered at the recommended dose and schedule (400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly). Patients received a median of 26 infusions (range 1–224).

Table 3: Incidence of Selected Adverse Reactions Occurring in ≥10% of Patients with *K-Ras* Wild-type and EGFR-expressing, Metastatic Colorectal Cancer[a]

Body System Preferred Term	EU-Approved Cetuximab plus FOLFIRI (n=317)		FOLFIRI Alone (n=350)	
	Grades 1–4[b]	Grades 3 and 4	Grades 1–4	Grades 3 and 4
	% of Patients			
Blood and Lymphatic System Disorders				
Neutropenia	49	31	42	24
Eye Disorders				
Conjunctivitis	18	<1	3	0
Gastrointestinal Disorders				
Diarrhea	66	16	60	10
Stomatitis	31	3	19	1
Dyspepsia	16	0	9	0
General Disorders and Administration Site Conditions				
Infusion-related Reaction[c]	14	2	<1	0
Pyrexia	26	1	14	1
Infections and Infestations				
Paronychia	20	4	<1	0
Investigations				
Weight Decreased	15	1	9	1
Metabolism and Nutrition Disorders				
Anorexia	30	3	23	2
Skin and Subcutaneous Tissue Disorders				
Acne-like rash[d]	86	18	13	<1
Rash	44	9	4	0
Dermatitis Acneiform	26	5	<1	0
Dry Skin	22	0	4	0
Acne	14	2	0	0
Pruritus	14	0	3	0
Palmar-plantar Erythrodysesthesia Syndrome	19	4	4	<1
Skin Fissures	19	2	1	0

[a] Adverse reactions occurring in at least 10% of Erbitux combination arm with a frequency of at least 5% greater than that seen in the FOLFIRI arm. [b] Adverse reactions were graded using the NCI CTC, V 2.0. [c] Infusion related reaction is defined as any event meeting the medical concepts of allergy/anaphylaxis at any time during the clinical study or any event occurring on the first day of dosing and meeting the medical concepts of dyspnea and fever or by the following events using MedDRA preferred terms: "acute myocardial infarction," "angina pectoris," "angioedema," "autonomic seizure," "blood pressure abnormal," "blood pressure decreased," "blood pressure increased," "cardiac failure," "cardiopulmonary failure," "cardiovascular insufficiency," "clonus," "convulsion," "coronary no-reflow phenomenon," "epilepsy," "hypertension," "hypertensive crisis," "hypertensive emergency," "hypotension," "infusion related reaction," "loss of consciousness," "myocardial infarction," "myocardial ischaemia," "prinzmetal angina," "shock," " sudden death," "syncope," or "systolic hypertension." [d] Acne-like rash is defined by the events using MedDRA preferred terms and included "acne," "acne pustular," "butterfly rash," "dermatitis acneiform," "drug rash with eosinophilia and systemic symptoms," "dry skin," "erythema," "exfoliative rash," "folliculitis," "genital rash," "mucocutaneous rash," "pruritus," "rash," " rash erythematous," "rash follicular," "rash generalized," "rash macular," "rash maculopapular," "rash maculovesicular," "rash morbilliform," "rash papular," "rash papulosquamous," "rash pruritic," "rash pustular," "rash rubelliform," "rash scarlatiniform," "rash vesicular," "skin exfoliation," "skin hyperpigmentation," "skin plaque," "telangiectasia," or "xerosis."

Erbitux Monotherapy—Table 4 contains selected adverse reactions in 242 patients with *K-Ras* wild-type, EGFR-expressing, metastatic colorectal cancer who received best supportive care (BSC) alone or with Erbitux in Study 5 [see *Warnings and Precautions*]. Erbitux was administered at the recommended dose and schedule (400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly). Patients received a median of 17 infusions (range 1–51).

Table 4: Incidence of Selected Adverse Reactions Occurring in ≥10% of Patients with *K-Ras* Wild-type, EGFR-expressing, Metastatic Colorectal Cancer Treated with Erbitux (cetuximab) Monotherapy[a]

Body System Preferred Term	Erbitux plus BSC (n=118)		BSC Alone (n=124)	
	Grades 1–4[b]	Grades 3 and 4	Grades 1–4	Grades 3 and 4
	% of Patients			
Dermatology/Skin				
Rash/Desquamation	95	16	21	1
Dry Skin	57	0	15	0
Pruritus	47	2	11	0
Other-Dermatology	35	0	7	2
Nail Changes	31	0	4	0
Constitutional Symptoms				
Fatigue	91	31	79	29
Fever	25	3	16	0
Infusion Reactions[c]	18	3	0	0
Rigors, Chills	16	1	3	0

Table 4: Incidence of Selected Adverse Reactions Occurring in ≥10% of Patients with *K-Ras* Wild-type, EGFR-expressing, Metastatic Colorectal Cancer Treated with Erbitux (cetuximab) Monotherapy[a] (Cont.)

Body System Preferred Term	Erbitux plus BSC (n=118)		BSC Alone (n=124)	
	Grades 1–4[b]	Grades 3 and 4	Grades 1–4	Grades 3 and 4
	% of Patients			
Pain				
Pain-Other	59	18	37	10
Headache	38	2	11	0
Bone Pain	15	4	8	2
Pulmonary				
Dyspnea	49	16	44	13
Cough	30	2	19	2
Gastrointestinal				
Nausea	64	6	50	6
Constipation	53	3	38	3
Diarrhea	42	2	23	2
Vomiting	40	5	26	5
Stomatitis	32	1	10	0
Other-Gastrointestinal	22	12	16	5
Dehydration	13	5	3	0
Mouth Dryness	12	0	6	0
Taste Disturbance	10	0	5	0
Infection				
Infection without neutropenia	38	11	19	5
Musculoskeletal				
Arthralgia	14	3	6	0
Neurology				
Neuropathy-sensory	45	1	38	2
Insomnia	27	0	13	0
Confusion	18	6	10	2
Anxiety	14	1	5	1
Depression	14	0	5	0

[a]Adverse reactions occurring in at least 10% of Erbitux plus BSC arm with a frequency at least 5% greater than that seen in the BSC alone arm. [b] Adverse reactions were graded using the NCI CTC, V 2.0. [c] Infusion reaction is defined as any event (chills, rigors, dyspnea, tachycardia, bronchospasm, chest tightness, swelling, urticaria, hypotension, flushing, rash, hypertension, nausea, angioedema, pain, sweating, tremors, shaking, drug fever, or other hypersensitivity reaction) recorded by the investigator as infusion-related.

Erbitux in Combination with Irinotecan—The most frequently reported adverse reactions in 354 patients treated with Erbitux plus irinotecan in clinical trials were acneiform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common Grades 3–4 adverse reactions included diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneiform rash (14%).

Immunogenicity: As with all therapeutic proteins, there is potential for immunogenicity. An ELISA methodology was used to characterize the incidence of anti-cetuximab antibodies. In total, 105 Erbitux-treated patients with at least one post-baseline blood sample (≥4 weeks post first administration) were assessed for the development of anti-cetuximab binding antibodies and the incidence of treatment-emergent anti-cetuximab binding antibodies was <5%.

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

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

- Aseptic meningitis
- Mucosal inflammation
- Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis, life-threatening and fatal bullous mucocutaneous disease

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C — There are no adequate and well-controlled studies of Erbitux (cetuximab) in pregnant women. Based on animal models, EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Human IgG is known to cross the placental barrier; therefore, Erbitux may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women. Erbitux should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnant cynomolgus monkeys were treated weekly with 0.4 to 4 times the recommended human dose of cetuximab (based on body surface area) during the period of organogenesis (gestation day [GD] 20–48). Cetuximab was detected in the amniotic fluid and in the serum of embryos from treated dams at GD 49. No fetal malformations or other teratogenic effects occurred in offspring. However, significant increases in embryolethality and abortions occurred at doses of approximately 1.6 to 4 times the recommended human dose of cetuximab (based on total body surface area).

Nursing Mothers: It is not known whether Erbitux is secreted in human milk. IgG antibodies, such as Erbitux, can be excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Erbitux, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If nursing is interrupted, based on the mean half-life of cetuximab [see *Clinical Pharmacology (12.3)* in Full Prescribing Information], nursing should not be resumed earlier than 60 days following the last dose of Erbitux.

Pediatric Use: The safety and effectiveness of Erbitux in pediatric patients have not been established. The pharmacokinetics of cetuximab, in combination with irinotecan, were evaluated in pediatric patients with refractory solid tumors in an open-label, single-arm, dose-finding study. Erbitux was administered once-weekly, at doses up to 250 mg/m^2, to 27 patients ranging from 1 to 12 years old; and in 19 patients ranging from 13 to 18 years old. No new safety signals were identified in pediatric patients. The pharmacokinetic profiles of cetuximab between the two age groups were similar at the 75 and 150 mg/m^2 single dose levels. The volume of the distribution appeared to be independent of dose and approximated the vascular space of 2–3 L/m^2. Following a single dose of 250 mg/m^2, the geometric mean $AUC_{0\text{-}inf}$ (CV%) value was 17.7 mg•h/mL (34%) in the younger age group (1–12 years, n=9) and 13.4 mg•h/mL (38%) in the adolescent group (13–18 years, n=6). The mean half-life of cetuximab was 110 hours (range 69 to 188 hours) for the younger age group, and 82 hours (range 55 to 117 hours) for the adolescent age group.

Geriatric Use: Of the 1662 patients who received Erbitux with irinotecan, FOLFIRI or Erbitux monotherapy in six studies of advanced colorectal cancer, 588 patients were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

Clinical studies of Erbitux conducted in patients with head and neck cancer did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects.

OVERDOSAGE

The maximum single dose of Erbitux administered is 1000 mg/m^2 in one patient. No adverse events were reported for this patient.

PHARMACOKINETICS

A drug interaction study was performed in which Erbitux was administered in combination with irinotecan. There was no evidence of any pharmacokinetic interactions between Erbitux and irinotecan.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to test cetuximab for carcinogenic potential, and no mutagenic or clastogenic potential of cetuximab was observed in the *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test. Menstrual cyclicity was impaired in female cynomolgus monkeys receiving weekly doses of 0.4 to 4 times the human dose of cetuximab (based on total body surface area). Cetuximab-treated animals exhibited increased incidences of irregular or absent cycles, as compared to control animals. These effects were initially noted beginning week 25 of cetuximab treatment and continued through the 6-week recovery period. In this same study, there were no effects of cetuximab treatment on measured male fertility parameters (ie, serum testosterone levels and analysis of sperm counts, viability, and motility) as compared to control male monkeys. It is not known if cetuximab can impair fertility in humans.

Animal Pharmacology and/or Toxicology: In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument. At the highest dose level, the epithelial mucosa of the nasal passage, esophagus, and tongue were similarly affected, and degenerative changes in the renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of the animals at the highest dose level beginning after approximately 13 weeks of treatment.

PATIENT COUNSELING INFORMATION

Advise patients:

- To report signs and symptoms of infusion reactions such as fever, chills, or breathing problems.
- Of the potential risks of using Erbitux during pregnancy or nursing and of the need to use adequate contraception in both males and females during and for 6 months following the last dose of Erbitux therapy.
- That nursing is not recommended during, and for 2 months following the last dose of Erbitux therapy.
- To limit sun exposure (use sunscreen, wear hats) while receiving and for 2 months following the last dose of Erbitux.

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

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PROVIDER PERSPECTIVE

Targeted Therapies: One Practice's Story

Barry Kaplan, MD, PhD

QUEENS MEDICAL ASSOCIATES
CENTER FOR CANCER AND BLOOD DISORDERS

CANCER CARE HAS EVOLVED from surgery as the only treatment option to broad-spectrum chemotherapy, more precise chemotherapy, and combination chemotherapy. We have arrived at the next phase of this ongoing evolution: targeted therapy.

Patients who would previously have received traditional chemotherapy are now benefitting from targeted therapy, used alone or in conjunction with traditional chemotherapy. In addition, those for whom traditional chemotherapy was not successful or not a good treatment option, can now be successfully treated with targeted therapy if they meet the eligibility criteria. The results can be dramatic.

Who Is a Candidate?

Only an estimated 7% to 8% of all patients with cancer are candidates for targeted therapies. Inclusion criteria are determined, not by the type of cancer, but by the presence of specific gene mutations.

The first classic illness to be treated with targeted therapy was chronic myeloid leukemia (CML), a disease in which nearly all patients express the *BCR-ABL* fusion gene, making them candidates for targeted therapies such as imatinib (Gleevec), dasatinib (Sprycel), nilotinib (Tasigna), and ponatinib (Iclusig). Remissions lasted for years and some patients may even have been cured. For other cancer types, however, a patient's tumor tissue must be tested to determine whether an appropriate target is present.

Genetic Testing

Genetic tests for targeted cancer therapy detect mutations in the DNA of cancer cells. For the most part, these mutations are not inherited, but develop in the cancer. Knowing whether the cancer has a particular mutation can help guide the type of treatment a patient should receive, as the presence or absence of certain mutations (predictive biomarkers) is often predictive of who may benefit from these agents versus who is not likely to respond. As these targeted cancer drugs are expensive and generally only work in patients whose cancer has the "target," genetic testing prior to treatment initiation is necessary to match the treatment with patients and the cancer types likely to benefit from them. Genetic testing, while readily available in larger cities, may not be available in smaller cities and rural areas. Medicare, Medicaid, and private payers typically cover the testing.

Targeted Therapy: Successes and Problems

Prognosis

There are more and more data demonstrating that matching patients to targeted therapies based on the unique molecular profile of the patient's disease leads to improved outcomes across a variety of key measures, including overall survival. The successes are obvious. Not so obvious are the nonmedical problems.

Cost of Drugs

The drugs prescribed in targeted therapy treatment are often prohibitively expensive. Monthly averages of $5000 to $10,000 and annual totals over $100,000 are common. Orphan drugs, which are used to treat "rare" diseases, can cost $300,000 or more per year, however. Some patients will need to take these expensive drugs for the rest of their lives. Although many patients turn to patient assistance programs and foundations for help with drug costs, the availability of these mechanisms for covering drug costs is decreasing. The increased use of targeted therapies and the ever-rising drug costs make the current system unsustainable. If patients are to survive, reform is vital.

Payers Keeping Pace

Payers often find it difficult to keep pace with the rapid developments within the field of targeted therapies and the new treatments that gain FDA approval. In 2016 alone, 6 new drugs were approved for treating cancer and approved entities were granted 15 new indications. So far, in 2017, there are 8 new entities and 12 new indications for current entities. Payers—both national and local—need more time and education to assimilate new drugs and treatment protocols into the predetermination, approval, and claim processing systems, and manufacturers must do more to educate payers at all levels on the value proposition of new agents. It is unfair to place this burden on oncologists.

Oncologists are increasingly being asked to carry the burden of no, low, or slow pay for rapidly deployed new agents or face the moral dilemma of refraining from offering the potential best option to their patients. One possible solution is to change current regulations that prohibit manufacturers from initiating the payer education process prior to the FDA approval of their drug. This would give payers more time to learn about the specific treatment and make decisions for formulary inclusion and payment policies. Manufacturers should also give extended dating on payment for costly targeted therapies, potentially until reimbursement by insurers, to reduce the financial burden on community oncologists.

Future Challenges

There is no doubt that targeted therapies are allowing patients to live longer. The results can be dramatic, especially those seen, to date, in patients with lung cancer, myeloma, and CML. It is unclear how many more indications research will discover that can be treated with the various targeted therapies. The next hurdle will be determining if maintenance treatment provides continuous disease-free survival once the cancer is in remission. Currently, it is difficult to know when or if to stop treatment. Yet, there is no good data to guide oncologists. Once a patient is in remission, many oncologists (including me) will stop treatment for 1 to 3 months under careful and continued monitoring. After that respite, re-staging will indicate if active treatment should resume.

In the 40-plus years that I have been treating patients with cancer, now is the most wonderful time. I see patients who 3 years ago would not have survived, myeloma patients surviving 8 years after diagnosis when a few years ago they would have survived for only 3 years, and patients with stage IV non–small cell lung cancer surpassing the previously dismal 5-year survival rates. The drugs and targeted treatments that are available today could mean these outcomes may soon become the norm. ◆

KAPLAN

Barry Kaplan, MD, PhD, is clinical associate professor, Weill Medical College of Cornell University; and president, Queens Medical Associates.

AUTHOR INFORMATION

Barry Kaplan, MD, PhD, is a practicing, board-certified oncologist/hematologist; clinical associate professor, Weill Medical College of Cornell University; and president, Queens Medical Associates.

ADDRESS FOR CORRESPONDENCE

Barry Kaplan, MD, PhD
President, Queens Medical Associates
176-60 Union Turnpike, Suite 360
Fresh Meadows, NY 11366

Q&A With Syapse CEO Ken Tarkoff

Surabhi Dangi-Garimella, PhD

TARKOFF

Ken Tarkoff is CEO, Syapse.

HEALTH INFORMATION TECHNOLOGY (HIT) industry veteran Ken Tarkoff, formerly the COO of RelayHealth, joined HIT company Syapse in March 2017 as CEO. *Evidence-Based Oncology*™ (*EBO*™) spoke with Tarkoff as he took up this new role.

***EBO*™: Can you provide an overview of Syapse and the services that the company provides to healthcare systems?**

TARKOFF: Our focus is on improving outcomes for cancer patients. We are, at the highest level, doing what we can to improve outcomes. More specifically, the solution we bring to the marketplace is we are a provider-driven network business, where we are providing workflow solutions to our customers to enable them to provide precision medicine in their cancer care areas within their organization.

The product capabilities we bring are a combination of: first, collecting the clinical and molecular data and aggregating that in a visual workflow that allows providers and their staff a longitudinal view of the patient's tumor and their history. We also provide them with additional workflow that gives them access to see similar patients, both within their enterprise and beyond their enterprise, and [grant access to] additional participants within the Syapse network, so they can see common treatments and documentation of outcomes for that [treatment] process.

We also offer, in the network component of our business, a sharing component that allows each of our customers the opportunity to do data exchange. We are also providing more value to the ecosystem as our provider customers are trying to address many of the challenges in getting their patients on a specific therapy and working with other parties in the ecosystem—clinical trial players, pharmaceutical companies and others—to streamline the process and to lower the administrative burden for the providers to get their patients on those therapies.

***EBO*™: What are the most critical health system requirements to deliver precision treatment to patients with cancer?**

TARKOFF: I'd break this into 2 parts: first, the biggest problem is [getting] appropriate testing for the patient and understanding that in the context of the other clinical information that you have available. So, we see inconsistent behavior among our oncology customers. There's different levels of understanding on when it's appropriate to order a test: how you can actually get this information and make it easy to understand and get feedback from others on when best to use these therapies.

Second, underneath all that, one of the reasons why this is complex is that the reimbursement market for these services and this testing is in its early stages and is not well defined. This obviously creates more complexities for the provider organizations and health systems to understand how to deliver more personalized care to the patient when you are trying to navigate all these complexities.

***EBO*™: What are some of the challenges faced while assimilating patient clinical history, which may live within EHRs of disparate clinics or health systems?**

TARKOFF: From my background—prior to joining Syapse, I came from the clinical data and interoperability world where we were focused around health information exchange [HIE]—I'd say that the first part that we are trying to address is the part where someone is from within the system. You need to be able to treat that patient in the community to be able to get access to molecular test data and clinical data to be able to combine them for patient benefit. The issue you raise adds an additional complexity, with a patient who had gone to multiple locations. How you are able to provide care for that patient? That's a more complex problem.

One way we could be tackling that is that if they are a common Syapse customer, we'd be able to get them the information, but we are not yet solving the problem of aggregating patient information from multiple health systems. That is a real problem, but we are not tackling that first. We are trying to help health systems deliver community oncology care, so they have the necessary information available to deliver a more personalized experience, [considering] the complexity of information that they have coming their way. I think, at least within the HIE market, we are ways away from having that type of data access.

***EBO*™: How does your decision support platform stay updated on the latest clinical developments and treatment guidelines?**

TARKOFF: We enable clinical decision support. We are not in the business of providing clinical decision support; it varies by customers. Some customers are more prescriptive, other customers leave it open and only want to share the information on what is happening within their network as a way to guide their behavior.

***EBO*™: Can health systems use the Syapse platforms to gather quality of care and outcomes data?**

TARKOFF: We do capture that information. Today, it's available as reports, and that's one of the areas of focus over the next year. A big part of the next year is not only deploying our customers' oncologist and realizing their value, but also building off that feedback loop. At this stage, what we are doing is capturing that information and allowing them to query it. Within the next year, we will be looking at the insight on how these decisions are being made; that's not a big focus for us this year. This year, we are focused on capturing the information for our patients and making them realize the value of the information that we are helping them capture [through our platform].

***EBO*™: Can you describe some of your ongoing collaborations?**

TARKOFF: We have a lot of things we are doing with Providence [a health system]. We are starting to look at the ways in which they are delivering precision medicine and working with them on some additional product enhancement to support their experiences as they have been delivering that care in their markets. Catholic Health Initiatives and Dignity Health are new customers of ours, and there are a number of different strategic initiatives with them that we are planning on rolling out later this year.

We have started to work with some payer associations and a pharma company to help them get patients on to therapies by removing some administrative burdens. We are capturing some information from providers for payers so that they can track that and use it for specific guidance for reimbursement purposes. So, we have a number of initiatives that we plan to announce later this year.

***EBO*™: Has Syapse been working with independent community practices?**

TARKOFF: We would love to work with independent practices, but the problem is the complexity of how you get to them—building the interoperability and getting all the price points right for standalone practices. So, we are looking at other partnerships that will get us through to the independents that are not associated with any health systems. We are, however, a little away from signing up 1-doc practices. The complexity of the technology integration as well as the training and implementation, in terms of the price point for a single-doc practice, we are not at the retail level, we are more at the health system level.

I'd love to be able to offer a consumer-level retail offering, but I don't think we are there yet. ◆

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The Newest Members of CancerLinQ's Community—FDA and NCI

Kevin Fitzpatrick

FITZPATRICK

Kevin Fitzpatrick is CEO, CancerLinQ LLC.

REAL-WORLD EVIDENCE HAS far-reaching potential to transform cancer care if we are able to appropriately gather, analyze, and learn from it. Millions of patients receive a diagnosis each year, yet most insights that drive improvements in cancer care and treatment have come from a tiny subset of the patient population. Traditionally, the cancer community has not been able to tap into 97% of this group because these individuals are not involved in standard clinical trials.[1] This system must be revolutionized.

With this in mind, the American Society of Clinical Oncology (ASCO) is leading the development of CancerLinQ, a health information technology (IT) platform designed to harness big data for a single purpose: to rapidly improve the quality of care for people with cancer. CancerLinQ powerfully aggregates and analyzes real-world cancer care data from almost any electronic record source and has the tools to evaluate quality of care in real time, offer insights from de-identified health information based on millions of data points, and visualize patients' medical histories in novel ways—all to enable the cancer community to more effectively understand what is taking place with patients in the real-world setting.

This is an ambitious undertaking—and one that we cannot do alone. At the June 2016 ASCO Annual Meeting, we announced that CancerLinQ was up and running and rapidly expanding, with participants ranging from small private practices to some of the nation's leading cancer centers.[2] As of June 2017, the rapidly expanding CancerLinQ network included a growing number of patient records amassed from more than 90 oncology practices and institutions from 40 states and the District of Columbia. This makes CancerLinQ one the largest and most robust sources of real-world evidence in oncology. Participants range from small private practices to large academic institutions, from safety net hospitals to integrated delivery networks and the nation's leading cancer centers.

The FDA and the National Cancer Institute are invited to participate in the CancerLinQ Oncology Leadership Council, the official body of strategic advisors comprising member representatives from CancerLinQ's official partner organizations and advisory groups.

This year, our guiding theme for our ever-growing CancerLinQ database has been "CancerLinQ is community." We have spent the past year cultivating strategic alliances and formalizing a series of collaborative initiatives that accelerate the expansion of CancerLinQ's reach and impact across the broader healthcare community. Not only do we have a growing network of oncology practices and providers, but CancerLinQ is proud to partner with entities across the public, private, and not-for-profit sectors that care about our mission to improve care for every patient.

The power of partnership is of paramount importance to us, and our goal is to continue to convene collaborators across the oncology community. We encourage efforts that make resources more accessible so that providers can make informed and timely decisions while caring for patients. Welcoming ideas and support from all types of stakeholders, we have forward-thinking leaders and organizations joining us as change agents. Together, we are a community movement of committed, collaborative partners from across the healthcare ecosystem working to improve the quality of cancer care for every patient.

Developed by CancerLinQ LLC, the health IT platform provides ASCO members an opportunity to improve quality of care, and every collaboration represents another positive step in that direction. The idea is that each new entity furthers CancerLinQ's capacity to improve patient care and helps us collectively accelerate outcomes that are larger and more effective than what any one of us can achieve alone.

NCI

CancerLinQ LLC recently launched its very first partnerships with federal agencies. In June 2017, a partnership was announced between CancerLinQ LLC and the National Cancer Institute (NCI)[3] to bring an exchange of information between CancerLinQ-participating oncology practices and NCI's Surveillance, Epidemiology, and End Results (SEER) program, one of the primary sources of data on cancer incidence and survival in the United States. The goal is to provide oncologists easy access to valuable population-level cancer data while strengthening the nation's cancer surveillance efforts through a national data-sharing collaboration.

The new partnership includes 2 major phases. Initially, NCI and CancerLinQ will incorporate national SEER data on patients diagnosed with cancer into CancerLinQ's core quality improvement and data-sharing platform. SEER is composed of 18 central cancer registries, which currently cover approximately 30% of the US population and include de-identified, population-level data on:

- Patient demographics
- Cancer diagnosis, including tumor morphology and stage at diagnosis
- First course of treatment
- Laboratory data
- Follow-up for vital status

The integrated access to SEER data in an easy-to-visualize format will allow CancerLinQ participants to view and draw comparisons between regional- and national-level SEER data and their own practice data, enhancing their ability to inform clinical care and decision making for their patients.

In a second phase, NCI and CancerLinQ will pilot a system for care providers in select geographic regions to quickly and seamlessly upload and transmit their practice data to the SEER program directly through the CancerLinQ portal. In the United States, healthcare facilities and providers who diagnose or treat patients with cancer are legally mandated by each state to report cancer case information to their respective cancer registries. This data-sharing effort holds the promise to make legally mandated cancer surveillance reporting activities more timely, efficient, and complete, while enhancing the richness of SEER databases for population-level research with longitudinal, real-world data and insights from CancerLinQ.

FDA

CancerLinQ LLC also announced a long-term partnership with the FDA[4] to harness cancer patient information and big data analytics to examine the real-world use of emerging and newly approved cancer therapies. Real-world data from CancerLinQ will be used to

EVIDENCE PARTNERSHIPS

FIGURE. CancerLinQ's Partner Organizations

OUR PARTNERS	OUR GOALS
American Academy of PAs (AAPA)	To draw on the expertise of PAs, who are on the front lines in providing and improving patient care
American Society for Radiation Oncology (ASTRO)	To bring the expertise of radiation oncologists into CancerLinQ and use their insights to improve care for patients receiving radiation therapy
AstraZeneca	To create curated CancerLinQ Discovery™ datasets that researchers can use to answer questions about the treatment of common cancers
Cancer Informatics for Cancer Centers (CI4CC)	To harness the expertise of the nation's informaticists and data scientists in the development of CancerLinQ
College of American Pathologists (CAP)	To enhance CancerLinQ with the expertise of leaders in cancer pathology and laboratory science
U.S. Food and Drug Administration (FDA)	To study the real-world use of newly approved cancer treatments to inform regulatory decision-making strategies and frameworks
Hematology/Oncology Pharmacy Association (HOPA)	To leverage the expertise of pharmacists as key members of the care team to optimize the safe and effective use of drugs for cancer care
National Cancer Institute (NCI)	To place population-level cancer care data at oncologists' fingertips and strengthen national cancer surveillance efforts
National Comprehensive Cancer Network (NCCN)	To link CancerLinQ subscribers to NCCN's evidence-based guidance on the use of cancer drugs and biologics
Oncology Nursing Society (ONS)	To incorporate insights from nursing professionals as key members of the care team and provide on-the-ground support to CancerLinQ-participating practices
Society of Gynecologic Oncology (SGO)	To improve women's oncology care with guidance and insights from the leading experts on gynecologic cancers

In the past year, CancerLinQ LLC has forged strategic partnerships with organizations representing the full spectrum of cancer care. With each new partnership, we are building CancerLinQ into a community that learns together and shares insights to improve outcomes for all people with cancer.
NCCN indicates National Comprehensive Cancer Network; PA, physician assistant.

expand the knowledge base about patterns of care across all cancer types and therapies, accelerate development of novel insights that could otherwise be challenging to obtain through standard research initiatives and data collection means, and inform future FDA regulatory strategy, frameworks, and decision-making processes.

Initially, the FDA and CancerLinQ project will focus on treatments for advanced melanoma, aiming to characterize the real-world experience of these patients, inform the clinical use of approved therapies, and provide data-driven guidance for future FDA regulatory review of targeted drugs and immunotherapies. The partnership will address some of the most important and talked-about advances of the last decade, including checkpoint inhibitors, the groundbreaking class of immunotherapies, and several molecularly targeted therapies. Although these treatments have collectively transformed care for advanced melanoma and extended many patients' lives, questions remain about their use and adoption in real-world settings. For example, relatively little is known about the specific benefits and risks of immune checkpoint inhibitors in elderly patients or those with serious health problems because such patients are often excluded from participation in studies due to the strict criteria of most clinical trials.

CancerLinQ and FDA investigators will explore a variety of issues related to the use of newly approved therapies, including the optimal sequence of treatments, the impact of comorbidities on treatment tolerability and cancer outcomes, and the experience with immunotherapy combinations versus single agents. They will share their learnings with the cancer community to help guide the use of these treatments as well as inform the development of future clinical trials and other innovative approaches for the care delivery system. The FDA may also apply the findings to future drug reviews or labeling refinements.

Under this new partnership, the FDA will be able to utilize CancerLinQ LLC's latest offering, CancerLinQ Discovery—anonymized, statistically de-identified, fit-for-purpose clinical data sets derived from the rapidly expanding CancerLinQ platform—to support hypothesis-based research. Physicians, researchers, and analysts in oncology may submit requests to the CancerLinQ Discovery Research & Publications Committee to explore insights on cancer care questions they intend to use in creating new clinical knowledge for improving patient outcomes. In November 2016, AstraZeneca joined CancerLinQ Discovery as a founding enterprise partner.[5] »

EVIDENCE PARTNERSHIPS

The CancerLinQ Oncology Leadership Council meets at the American Society of Clinical Oncology's Annual Meeting 2017 in Chicago, June 1–5.

Back row (left to right): Susannah Koontz, PharmD, BCOP, FHOPA, president, Hematology/Oncology Pharmacy Association and principal, Koontz Oncology Consulting LLC; Hallie Brewer, CA-AM, director of strategic alliances and operations, College of American Pathologists; Sameer R. Keole, MD, Oncology Leadership Council chairperson, American Society of Radiation Oncology, and assistant professor of radiation oncology, Mayo Clinic; Robert S. Miller, MD, FACP, FASCO, vice president, American Society of Clinical Oncology, and medical director, CancerLinQ; Sean Khozin, MD, MPH, associate director (acting), FDA Oncology Center of Excellence, and founder, INFORMED; Richard C. Friedberg, MD, PhD, FCAP, College of American Pathologists, and chair, Department of Pathology, Baystate Health; Sorena Nadaf, MS, MMI, senior vice president, chief informatics officer, Cancer Informatics for Cancer Centers and senior vice president, chief informatics officer, City of Hope Comprehensive Cancer Center; and Pierre M. Dési, MPH, CAE, chief executive officer, Society of Gynecologic Oncology.

Front row (left to right): Lynne Penberthy, MD, MPH, National Cancer Institute, associate director, Surveillance Research Program (SEER); Amy Seung, PharmD, BCOP, member, Hematology/Oncology Pharmacy Association and senior director, Clinical Development, AssistRx; Michele McCorkle, MSN, RN, chief strategy officer, Oncology Nursing Society; Kevin Fitzpatrick, chief executive officer, CancerLinQ LLC; Michele Galioto, MSN, RN, assistant chief clinical officer, Oncology Nursing Society; Summer Dewdney, MD, Society of Gynecologic Oncology, and assistant professor of gynecologic oncology, Rush University Medical Center; and Jennifer L. Wong, MPP, chief, Strategic Alliances, CancerLinQ LLC. Not pictured: Daniel Pace, CHCP, chief strategy officer/vice president, Education and Research, American Academy of PAs.

FDA and NCI are also invited to participate in the CancerLinQ Oncology Leadership Council (OLC), the official body of strategic advisors comprising member representatives from CancerLinQ's official partner organizations and advisory groups (**see photo**). This is the first time that a coalition of this nature has been created and convened. As we create this community of learning in cancer, these foundational partners of CancerLinQ offer us incredible thought leadership and represent the importance of a team-based approach to delivering high quality care. The OLC embodies our commitment to value via the voices and expertise of the many stakeholders that span the care continuum, all of whom impact key decision points in a patient care. The OLC includes professional medical specialty societies that are CancerLinQ LLC partners, such as the American Academy of Physician Assistants,[6] American Society for Radiation Oncology,[7] Cancer Informatics for Cancer Centers,[8] College of American Pathologists,[9] Hematology/Oncology Pharmacy Association,[10] Oncology Nursing Society,[11] and Society of Gynecologic Oncology.[12]

In late May, CancerLinQ LLC announced a collaboration with the National Comprehensive Cancer Network (NCCN)[13] to provide a link to the NCCN website for easy access to the NCCN Drugs & Biologics Compendium (NCCN Compendium) within CancerLinQ. For a fee, CancerLinQ participants can access the NCCN Compendium, which will provide evidence-based guidance regarding appropriate uses of drugs and biologics in patients with cancer. The compendium includes recommendations on the appropriate use of drugs and biologics to support decision making for patients with cancer that are derived from relevant NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) along with their clinical context, route of administration, recommended use, and NCCN category of evidence. In addition to NCCN Guidelines-specific indication and use, NCCN adds relevant information, such as pharmacologic class, relevant classification codes, and FDA indication, to the searchable database.

CancerLinQ, the only effort of its kind being driven by a nonprofit organization, leverages the combined expertise of more than 40,000 of the world's leading oncologists who make up ASCO's membership. We are humbled by the level of engagement thus far and look forward to continuing the acceleration and expansion of CancerLinQ's community in the coming years. ◆

ADDRESS FOR CORRESPONDENCE

Kevin Fitzpatrick
CEO
CancerLinQ LLC
American Society of Clinical Oncology
2318 Mill Rd.
Alexandria, VA 22314

E-mail: kevin.fitzpatrick@cancerlinq.org

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PHOTO COURTESY OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY

CMS Proposes Payment Rate Change for 340B Program

Laura Joszt

REFORM MAY BE COMING TO the controversial 340B Drug Discount Program, a federal program that requires drug companies to provide discounts to hospitals, clinics, and covered entities that include freestanding cancer centers.

In January 2017, the Health Resources and Services Administration (HRSA) within HHS finalized a rule that would set the 340B ceiling price and allow HRSA to fine manufacturers up to $5000 for each incident of knowing and intentionally overcharging 340B hospitals for drugs »

purchased through the program. However, the rule was pulled back by the Trump administration.

Now, the new administration has proposed its own change to the payment rate for certain Medicare Part B drugs purchased by hospitals through the 340B program. According to CMS Administrator Seema Verma, "The proposed rule takes a critical step toward fulfilling President Trump's promise to lower the cost of drugs, particularly for Medicare beneficiaries."[1]


VACIRCA

The proposal gained immediate support from the Community Oncology Alliance (COA), which has previously called out abuses taking place in the 340B program. The program was created with good intentions, COA has argued, but it has morphed into an opportunity for hospitals to make tremendous profits by buying deeply discounted drugs and selling them to patients at full price.

"Community oncology practices across the country will tell you that hospitals have been strong-arming them to sell or close because of the tremendous profits they make from the 340B program and higher billing rates," said Jeff Vacirca, MD, president of COA and CEO of NY Cancer and Blood Specialists on Long Island, NY, in a statement.[2]

"Community oncology practices across the country will tell you that hospitals have been strong-arming them to sell or close because of the tremendous profits they make from the 340B program and higher billing rates."

—Jeff Vacirca, MD

The proposal would implement a new payment methodology for Medicare Part B reimbursement for 340B drugs, which would cut reimbursement by close to 30%: entities would be allowed to purchase discounted 340B drugs at the average sales price (ASP) minus 22.5% rather than the ASP plus 6%. The Medicare Payment Advisory Commission estimated that this was the average minimum discount that eligible hospitals could receive for drugs purchased through the 340B program.

The comment period for the rule will be open through September 11, 2017, and the proposed rule will take effect January 1, 2018.

"We applaud HHS Secretary Price and CMS Administrator Verma for taking this bold step in curtailing hospital abuse of the 340B program and further addressing site payment parity," said Ted Okon, MBA, executive director of COA. "These proposals represent a good first step, but the administration and Congress must take additional steps to address the alarming consolidation of cancer care that is fueling drug prices and driving up costs for seniors and taxpayers." ◆

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Rural America's High Cancer Mortality Rates Point to Growing Disparities

Christina Mattina

A RECENT ANALYSIS OF CANCER incidence and mortality rates across America found that while those in rural counties are less likely to get cancer, cancer-related mortality rates are higher than in more populous areas and this disparity is increasing over time.

The surveillance study, conducted by CDC researchers, was published in the *Morbidity and Mortality Weekly Report*.[1] It used data from several national registries to calculate average annual age-adjusted incidence and death rates in 4 types of counties:

- Nonmetropolitan rural
- Nonmetropolitan urban
- Metropolitan with population <1 million
- Metropolitan with population ≥1 million

It also compared the trends in these rates in recent years among counties classified as nonmetropolitan or metropolitan. From 2004 to 2013, the incidence rates of cancers at all sites was lower in rural counties than in the other county types, but rural residents had higher rates of developing lung, colorectal, and cervical cancers. Overall incidence rates in nonmetropolitan counties decreased by about 0.8% per year during this period, while they decreased in metropolitan counties by 1% annually.

Cancer death rates were higher in nonmetropolitan rural counties than the others during 2011 to 2015. Although cancer mortality decreased nationwide from 2006 to 2015, death rates showed a steeper decline in metropolitan counties than in nonmetropolitan counties (1.6% decrease vs 1.0% decrease per year, respectively). To explain the findings, the researchers referenced prior studies showing that rural residents are more likely to have risk factors for cancer, such as cigarette smoking or obesity, and may have more difficulty accessing screening due to higher uninsurance rates.

"While geography alone can't predict your risk of cancer, it can impact prevention, diagnosis, and treatment opportunities—and that's a significant public health problem in the United States," said Anne Schuchat, MD, acting director of the CDC, in a press release.[2] "Many cancer cases and deaths are preventable, and with targeted public health efforts and interventions, we can close the growing cancer gap between rural and urban Americans."

According to the study results, these interventions will need to use "evidence-based strategies to improve health-related behaviors, use of vaccinations that prevent infections with cancer-causing viruses, and use of cancer screening tests" among rural residents in particular.

A blog post by Robert T. Croyle, PhD, of the National Cancer Institute (NCI), explored the potential next steps toward reducing cancer disparities in light of both the CDC study and a recent NCI commentary that discussed the issue.[3] He called for stronger outreach to rural community organizations and for a better understanding of the racial demographics in rural areas. Croyle also noted that the NCI will host a meeting in May 2018 to collaborate with researchers on potential solutions to reduce rural disparities.

"In the meantime, NCI will continue to work with the cancer community and others to refine and reinvigorate our cancer control efforts in rural areas across the country," he concluded. ◆

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FDA Considers Label Changes for Some Immunotherapies Due to Potential Vision Loss

Alison Rodriguez

THE FDA IS CONSIDERING ADDING the risk of ocular inflammatory conditions to labels for 3 immune checkpoint inhibitors due to sight-threatening complications. The drugs that could have label changes include Bristol-Myers Squibb's Yervoy (ipilimumab) and Opdivo (nivolumab) and Merck's Keytruda (pembrolizumab). The 3 labels currently list uveitis, a type of eye inflammation, as a potential immune-mediated adverse reaction, but the FDA's postmarketing reviews have found further complications including retinal detachment and vision loss.[1]

Ocular inflammation resulting in vision loss was also observed in a study that treated metastatic melanoma with ipilimumab. The study involved a male patient that was diagnosed with melanoma that progressed during treatment. Eventually, he participated in a clinical trial for ipilimumab and received 3mg/kg every 3 weeks for 3 doses.[2]

Following treatment, he experienced adverse effects (AEs), including a rash and diarrhea, which were treated with supportive therapy, and headaches that were resolved with steroids. However, 4 months after the initial treatment, the participant experienced acute vision loss in his left eye, followed by vision loss in his right eye after 5 months.

"High-dose steroid therapy stabilized the right eye vision, but the left eye vision never improved after initial presentation, again supporting a probable vascular cause for the left eye visual loss," the study noted. "This may or may not have been secondary to an inflammatory/immune-mediated process (ie, local thrombosis related to inflammation/vasculitis)."

Furthermore, the steroids taken by the patient to treat the AEs from the ipilimumab treatment caused further complications. The FDA is considering labeling changes to emphasize the risks of these complications.

"Regulatory discussions are ongoing regarding PD-1 pathway–blocking antibodies in attempts to improve the consistency and effectiveness of the information regarding immune-mediated AEs provided in the labels," explained Tralisa Colby, an FDA public affairs specialist, in a statement to *Regulatory Focus*. "Those labeling changes may include additional characterization of ocular inflammatory conditions; however, the current term, uveitis, should convey the severity and potential ocular complications to oncology physicians."[3] ◆

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FDA Advisory Committee Confirms Support for Biosimilars to Trastuzumab, Bevacizumab

Surabhi Dangi-Garimella, PhD

A 17-0 VOTE IN FAVOR of the Amgen/Allergan bevacizumab biosimilar candidate, ABP 215, and a 16-0 vote in favor of Mylan's trastuzumab biosimilar candidate, MYL-1401O were the final tiles following voting by the FDA's Oncologic Drugs Advisory Committee (ODAC) on the 2 pioneer biosimilar candidates for cancer treatment.

Both of the reference drugs, trastuzumab (Herceptin) and bevacizumab (Avastin), are manufactured by Roche and are blockbusters in their own right: together they brought in $5.6 billion in sales in 2016.[1] Bevacizumab is indicated for the treatment of patients with unresectable, locally advanced, recurrent or metastatic nonsquamous non–small cell lung cancer (NSCLC), metastatic carcinoma of the colon or rectum, metastatic renal cell carcinoma, and other region-specific indications. Trastuzumab is indicated for the treatment of HER2-positive breast cancer following surgery, for metastatic disease, and for gastric cancer.

In a briefing document released prior to the meeting, the ODAC committee members stated that the "totality of evidence" submitted by Amgen showed that the lung cancer data can be extrapolated to other indications of bevacizumab.

In a briefing document released prior to the meeting, the ODAC committee members stated that the "totality of evidence" submitted by Amgen showed that the lung cancer data can be extrapolated to other indications of bevacizumab. This was following evaluation of phase 3 data from the company, which showed the biosimilar candidate had similar safety and immunogenicity as the reference product in patients with NSCLC. However, a few ODAC members did raise concerns over extrapolating data from studies conducted in a single disease to multiple indications.

In a release prior to the beginning of the day's proceedings, David Nicholson, chief R&D officer at Allergan, said, "ABP 215 is the first product of our collaboration with Amgen to reach this important milestone. If approved, ABP 215 has the potential to provide another high-quality treatment option for cancer patients and pave the way for additional high-quality oncology biosimilars from Allergan and Amgen."[2]

ABP 215 has a Biosimilar User Fee Act date of September 14, while the date for MYL-1401O is September 3. ◆

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Is Complete Lymph Node Dissection Essential in Melanoma?

Surabhi Dangi-Garimella, PhD

SENTINEL LYMPH NODE BIOPSY in patients with diagnosed melanoma helps establish the spread of the disease beyond the cancer site. However, according to findings from a 63-center international study, complete lymph node excision may not be essential for to improve melanoma outcomes.

Relatively rare, but significantly deadly, melanoma makes up less than 1% of skin cancers although it is responsible for a majority of skin cancer-related deaths; almost 10,000 deaths are projected for 2017.[1] Sentinel lymph nodes are routinely surgically removed because they are the closest draining lymph nodes where melanoma is known to spread. Standard treatment involves removing all nearby lymph nodes, which can sometimes trigger complications.

"They can have repeat hospitalizations for infections in their extremities. They can have life-limiting, painful swelling where they can't do the activities they like to do or wear their usual clothing. It's a significant, real problem for patients who are affected," explained[2] study author Tawnya L. Bowles, MD.


BOWLES

For the present study, the Multicenter Selective Lymphadenectomy Trial II, published in the *New England Journal of Medicine*, more than 3500 patients across 63 centers around the world, including the Intermountain Medical Center and the Huntsman Cancer Institute in Salt Lake City, were recruited;1939 patients had an abnormal lymph-node biopsy.[3] Patients were randomly assigned to standard of care and had complete lymph-node dissection (dissection group) or nodal observation with ultrasonography (observation group). Ultrasounds were scheduled at every 4 months for the first 2 years, followed by every 6 months over the next 3 years. The primary trial endpoints included disease-free survival (DFS) and cumulative rate of nonsentinel-node metastases.

"Checking [the sentinel] lymph node is really important, but many patients can be spared taking out the others."

—Tawnya L. Bowles, MD

The study found that complete lymph node dissection was not associated with increased melanoma-specific survival, based on data from an intent-to-treat analysis or 1755 in the per-protocol analysis, the authors write. The mean 3-year rate of melanoma-specific survival was similar between the dissection group (86%±1.3%) and the observation group (86%±1.2%; $P = .42$), as observed following a median follow-up of 43 months. DFS, however, was higher in the dissection group (68%±1.7%) than in the observation group (63%±1.7%; $P = .05$) at 3 years.

Nonsentinelnode metastases were a strong independent predictor of recurrence in 11.5% of patients (HR, 1.78; $P = .005$). "If the sentinel node biopsy hadn't been done, the tumor present in the lymph node would have grown and progressed," said Bowles. "Checking that lymph node is really important, but many patients can be spared taking out the others."

She also pointed out the importance of immune therapy in these patients, especially in the context of distant metastases, which is the most common reason for mortality among patients with melanoma. The question is, would outcomes be different in patients treated with immunotherapies, such as nivolumab or pembrolizumab, who do not have their lymph nodes removed? ◆

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Neratinib Approved as Extended Adjuvant Breast Cancer Treatment, Carries Diarrhea Risk

Christina Mattina

THE FDA HAS APPROVED neratinib (Nerlynx) for the extended adjuvant treatment of some forms of breast cancer, but recommends taking precautions against the common side effect of diarrhea.

As an extended adjuvant treatment, neratinib is intended to be taken after initial treatment to reduce odds of the cancer returning. Specifically, it is indicated for patients whose early stage, HER2-positive breast cancer has been treated with a trastuzumab-based therapy regimen, according to an FDA press release.[1]

A randomized trial of nearly 3000 patients found that 94.2% of those who received neratinib did not experience cancer recurrence or death after 2 years compared with 91.9% of patients taking a placebo. This ability to keep cancer recurrences at bay is especially important for the 15% of patients with breast cancer whose tumors are HER2-positive, FDA officials explained.

"HER2-positive breast cancers are aggressive tumors and can spread to other parts of the body, making adjuvant therapy an important part of the treatment plan," said Richard Pazdur, MD, director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research, in the press statement. "Now, these patients have an option after initial treatment that may help keep the cancer from coming back."

The approval was accompanied by warnings of the drug's potential side effects, most notably diarrhea. More than just an unpleasant symptom, this diarrhea can be severe and cause dehydration. As such, the FDA stated that patients should take loperamide, an antidiarrheal medication sold over the counter as Imodium, for the first 56 days of treatment and as necessary thereafter. Rates of diarrhea experienced in study populations were not specified in the approval announcement, but a prior report by Advera Health found that 90% of neratinib patients in 11 clinical trials experienced diarrhea and 19% experienced serious cases, according to a September 2016 report in FiercePharma.[2]

At the time, Puma Biotechnology, which manufactures neratinib, sought to downplay these findings. Alan Auerbach, chief executive, pointed out to FiercePharma that rates of diarrhea appeared high because few of the studies used loperamide to prevent it. "When you use the Imodium, the rates come down dramatically and it completely changes the safety and tolerability profile of the drug," he said.

Puma's press statement in response to the FDA's approval of neratinib mentions diarrhea as a potentially severe side effect and provides recommendations to mitigate the risk, including taking loperamide.[3] However, the statement mainly focuses on the approval's implications for women with breast cancer and the improved peace of mind that neratinib could provide after treatment.

"Despite advances in the treatment of early-stage HER2-positive breast cancer, there remains a need for further therapeutic improvements in order to attempt to further reduce the risk of disease recurrence," said Auerbach in the press release. "We are pleased to be able to bring this new medicine to patients with breast cancer."

Neratinib, which is a tyrosine kinase inhibitor that blocks enzymes that promote cell growth, is currently being reviewed by the European Medicines Agency for sale in Europe. Neither Puma nor the FDA specified a date for when neratinib would enter the US market. ◆

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Produced by Laura Joszt

How Being a Nurse Prepared Dr Patricia Flatley Brennan to Be NLM Director

Being a nurse prior to becoming director of the National Library of Medicine (NLM) offered Patricia Flatley Brennan, RN, PhD, a greater appreciation and understanding of the need for information at the point of care and to provide patients with information to practice self-care and self-management.

How will your experiences as a practicing nurse help inform your work as the director of NLM?

My practice in nursing was in intensive care nursing and psychiatric nursing, and it provides 2 inspirations that drive my work. The first is, I understand the criticality of information at the point of care, particularly under emergency circumstances. So, it makes me very aware of the importance of having a large repository of information that is the evidence for healthcare, but also effective ways to deliver at the point of need.

The second is, through my practice in psychiatric nursing, I learned the importance of patient engagement and the importance of ensuring the participant in care had the kind of information he or she both needed to participate as a partner in care and also self-manage. So, I recognize that our resources, while they're largely built by biomedical scientists for the practice of professional care, they need to be translated and made accessible for individuals for self-care and self-management. ◆

Dr Craig Portell Highlights New and Exciting Treatments for Non-Hodgkin's Lymphoma

Craig Portell, MD, of the University of Virginia Health System, discussed some of the most exciting developments in the treatment of non-Hodgkin's lymphoma, including CAR T therapies and targeted therapies, such as venetoclax.

What is the latest in treatments for non-Hodgkin's lymphoma?

There are many new and exciting treatments for non-Hodgkin's lymphoma that are coming up. Some of them are changing the standard rituximab antibody, doing new novel ways of targeting CD20 in non-Hodgkin's lymphoma. Some of them are having very good outcomes and prolonging progression-free survival when compared to rituximab.

There's also cellular therapies, such as CAR (chimeric antigen receptor) therapy, where patients' own T cells are activated and stimulated to attack non-Hodgkin's lymphoma cells as well as other normal B cells. It's kind of a targeted way of doing an allogeneic stem cell transplant. Those are labor intensive and difficult to do, but as we move forward in the field, as it gets easier to do, I think those are going to be very promising.

Of course, we also have many small molecule targeted therapies that are becoming increasingly used in non-Hodgkin's lymphoma, including ibrutinib, idelalisib, and any of the other targeted therapies in the B-cell receptor pathway. Finally, one of the more exciting drugs in targeted therapy is venetoclax. We just recently had a publication out of *Journal of Clinical Oncology*, which showed efficacy of venetoclax, how we use it and where we use it, and monitoring for tumor lysis is very important when we move to using venetoclax more and more in non-Hodgkin's lymphoma. ◆

Dr Zirui Song: Working at the Intersection of Clinical Medicine and Health Policy

Zirui Song, MD, PhD, resident at Massachusetts General Hospital, discussed his research interests, which center on strategies to control healthcare spending while improving the quality of care. He also expressed the importance of examining health equity within the United States healthcare system.

What is the main focus of your research?

The main purpose of my work has been to evaluate strategies for controlling the growth of healthcare spending. These have involved several different approaches: those that work on prices, those that work on quantities, and those that work on the collective product of prices and quantities, which is spending.

Most of my work has centered around evaluating a global payment contract or Alternative Quality Contract, in Massachusetts. In addition, some of the related work has surrounded evaluations of Medicare payment changes for physicians and for health plans and Medicare. Largely, the broader theme is, what can policy makers do to slow the growth of healthcare spending while we try to, at the same time, improve the quality of care that patients get.

What topics would you like to explore next for your research?

I would like to continue working at the intersection of clinical medicine and health policy. I plan to continue working on evaluating policy strategies to control healthcare spending while improving care quality. The overarching goal, is to improve the value of healthcare spending in the United States, the value for the dollar that we spend, whether that be the public dollar for the Medicare or Medicaid system or the private dollar for populations under 65.

I would also like to pursue work that looks at the equity in our healthcare system, because for all of the policies that are trying to do good, one of the things that we can't forget is the equity and equality of what we do as physicians, as policy makers. ◆

Dr David Cutler Assesses the Political Odds of Drug Pricing Reform

Members of Congress from both parties may have difficulty finding a common solution to high drug prices, but President Donald Trump could be instrumental in bringing prices down if he acts on his pledges, according to David M. Cutler, PhD, of Harvard University.

The need to rein in drug prices is an area where Democrats and Republicans agree. Do you think they might be able to pass legislation addressing rising drug costs? What might it look like?

On drug costs, as with everything in healthcare, the best guess is always no change. Both sides are upset that there are people who can't afford medications, but what they would do about it is different, so the ability to compromise will be difficult.

There are things they can do about the FDA, and they're doing a little bit of that, but the other major issues about things like prices of new medications, price increases, how much you can charge people who are uninsured, things like that, I don't see a lot of agreement upon. I think the wild card here is the President, whose sympathies on this seem to lie much more with the Democrats than with the Republicans. If he decided to do something there and he was going to work with the Democrats and bring things along, he could force the issue more. I don't know whether he will. ◆

#1 PRESCRIBED THERAPY ACROSS ALL LINES OF CLL SINCE NOVEMBER 2016.*
MORE THAN 25,000 PATIENTS TREATED SINCE APPROVAL[1†]

TAKE CONTROL OF CLL/SLL WITH YOUR FIRST STEP: IMBRUVICA®

Proven results across key efficacy endpoints: PFS and OS[2]

CLL
SLL

IMBRUVICA® (ibrutinib) is a kinase inhibitor indicated for the treatment of patients with:

- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)[2]
- CLL/SLL with 17p deletion[2]

*Based on market share data from IMS as of January 2017.
†Based on IMS data February 2014 to date.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and postsurgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and nonfatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Evaluate patients for fever and infections and treat appropriately.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13% to 29%), thrombocytopenia (range, 5% to 17%), and anemia (range, 0% to 13%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA®. Monitor complete blood counts monthly.

Atrial Fibrillation - Atrial fibrillation and atrial flutter (range, 6% to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension - Hypertension (range, 6% to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new-onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®. Adjust existing antihypertensive medications and/or initiate antihypertensive treatment as appropriate.

Second Primary Malignancies - Other malignancies (range, 3% to 16%) including non-skin carcinomas (range, 1% to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2% to 13%).

Tumor Lysis Syndrome - Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (eg, high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity - Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of

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RESONATE™-2 FRONTLINE DATA

RESONATE™-2 was a multicenter, randomized 1:1, open-label, Phase 3 trial of IMBRUVICA® vs chlorambucil in frontline CLL/SLL patients ≥65 years (N=269)[2,3]
Patients with 17p deletion were not included in the RESONATE™-2 trial[3]

EXTENDED OVERALL SURVIVAL

IMBRUVICA® significantly extended OS vs chlorambucil[2]

Statistically significant reduction in risk of death[2]

56%

HR=0.44
(95% CI: 0.21, 0.92)

41% of patients crossed over to IMBRUVICA®

Estimated survival rates at 24 months

95% IMBRUVICA®
(95% CI: 89, 97)

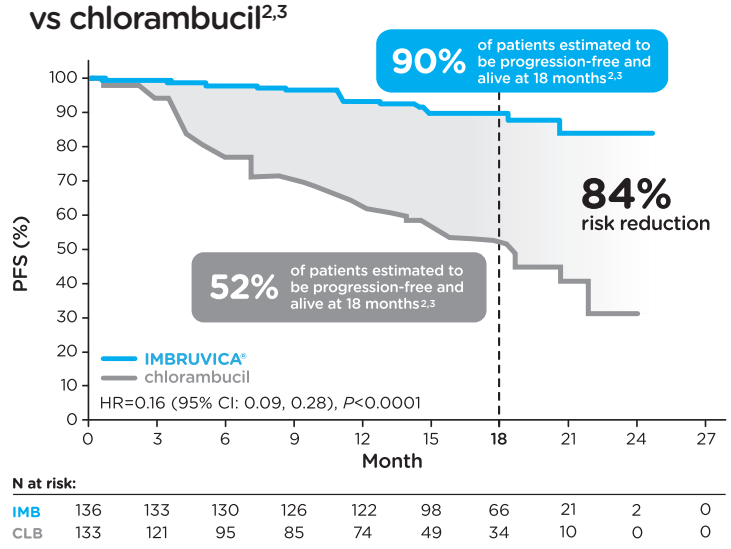
84% chlorambucil
(95% CI: 77, 90)

SECONDARY ENDPOINT: OS

- Median follow-up was 28 months[2]

PROLONGED PROGRESSION-FREE SURVIVAL

IMBRUVICA® significantly extended PFS vs chlorambucil[2,3]



PRIMARY ENDPOINT: PFS

- Median follow-up was 18 months[3]
- IMBRUVICA® median PFS not reached[2]
- Chlorambucil median PFS was 18.9 months (95% CI: 14.1, 22.0)[2]
- PFS was assessed by an IRC per revised iwCLL criteria[3]

Adverse reactions ≥20% across CLL/SLL registration studies[2]

- Neutropenia
- Thrombocytopenia
- Anemia
- Diarrhea
- Musculoskeletal pain
- Nausea
- Rash
- Bruising
- Fatigue
- Pyrexia
- Hemorrhage

therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

The most commonly occurring adverse reactions in the phase 1b/2 and phase 3 trials in patients with CLL/SLL receiving IMBRUVICA® (≥ 20%) were neutropenia (40%)*, thrombocytopenia (23%)*, anemia (21%)*, diarrhea (42%), musculoskeletal pain (31%), nausea (30%), rash (30%), bruising (29%), fatigue (26%), pyrexia (23%) and hemorrhage (20%).

*Based on adverse reactions and/or laboratory measurements (noted as platelets, neutrophils, or hemoglobin decreased).

Approximately 4%-10% of patients discontinued treatment due to adverse reactions. Most common adverse reactions leading to discontinuation were pneumonia, hemorrhage, atrial fibrillation, rash, and neutropenia (1% each).

Approximately 6% of patients had a dose reduction due to adverse reactions.

DRUG INTERACTIONS

CYP3A Inhibitors - Avoid coadministration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

CYP3A Inducers - Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment - Avoid use in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

Please see the Brief Summary on the following pages.

CI=confidence interval, CLL=chronic lymphocytic leukemia, HR=hazard ratio, IRC=Independent Review Committee, iwCLL=International Workshop on CLL, OS=overall survival, PFS=progression-free survival, SLL=small lymphocytic lymphoma.

References: 1. Data on file. Pharmacyclics LLC. **2.** IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC 2017. **3.** Burger JA, Tedeschi A, Barr PM, et al; for the RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.

To learn more, visit IMBRUVICAHCP.com

imbruvica®
(ibrutinib) 140mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

Mantle Cell Lymphoma: IMBRUVICA is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial *[see Clinical Studies (14.1) in Full Prescribing Information].*

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.2) in Full Prescribing Information].*

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion *[see Clinical Studies (14.2) in Full Prescribing Information].*

Waldenström's Macroglobulinemia: IMBRUVICA is indicated for the treatment of patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.3) in Full Prescribing Information].*

Marginal Zone Lymphoma: IMBRUVICA is indicated for the treatment of patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.

Accelerated approval was granted for this indication based on overall response rate *[see Clinical Studies (14.4) in Full Prescribing Information].* Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding *[see Clinical Studies (14) in Full Prescribing Information].*

Infections: Fatal and non-fatal infections have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 29% of patients *[see Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

Atrial Fibrillation: Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Dosage and Administration (2.3) in Full Prescribing Information].*

Hypertension: Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (range, 3 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2 to 13%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations].*

ADVERSE REACTIONS

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

- Hemorrhage *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Cytopenias *[see Warnings and Precautions]*
- Atrial Fibrillation *[see Warnings and Precautions]*
- Hypertension *[see Warnings and Precautions]*
- Second Primary Malignancies *[see Warnings and Precautions]*
- Tumor Lysis Syndrome *[see Warnings and Precautions]*

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

Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MCL (N=111)

	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial and three randomized controlled clinical trials in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1 included 51 patients with previously treated CLL/SLL, Study 2 included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, Study 3 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil and Study 4 included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1, 2, 3 and 4 in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1, 2, 3 and 4 discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1 (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

* One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL/SLL (N=51) in Study 1

	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	69	12
Neutrophils Decreased	53	26
Hemoglobin Decreased	43	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

Study 2: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in Study 2 in patients with previously treated CLL/SLL.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in Study 2

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Pyrexia	24	2	15	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

Table 6: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL/SLL in Study 2

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

* Based on laboratory measurements per IWCLL criteria.

Study 3: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in Study 3.

IMBRUVICA® (ibrutinib) capsules

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in Study 3

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye Disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular Disorders				
Hypertension*	14	4	1	0
Nervous System Disorders				
Headache	12	1	10	2

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

Study 4: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in Study 4 in patients with previously treated CLL/SLL.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in Study 4

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	55
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash*	32	4	25	1
Bruising*	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal Pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular Disorders				
Hemorrhage*	19	2	9	1
Hypertension*	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo + BR.

Waldenström's Macroglobulinemia and Marginal Zone Lymphoma: The data described below reflect exposure to IMBRUVICA in open-label clinical trials that included 63 patients with previously treated WM (Study 5) and 63 patients with previously treated MZL (Study 6).

The most commonly occurring adverse reactions in Studies 5 and 6 (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, fatigue, bruising, hemorrhage, anemia, rash, musculoskeletal pain, and nausea.

Nine percent of patients receiving IMBRUVICA across Studies 5 and 6 discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 10% of patients.

Study 5: Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study 5.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 5 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 10: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM in Study 5 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	43	13
Neutrophils Decreased	44	19
Hemoglobin Decreased	13	8

* Based on laboratory measurements.

Study 6: Adverse reactions and laboratory abnormalities described below in Tables 11 and 12 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 6.

Table 11: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with MZL in Study 6 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	43	5
	Nausea	25	0
	Dyspepsia	19	0
	Stomatitis*	17	2
	Abdominal pain	16	2
	Constipation	14	0
	Abdominal pain Upper	13	0
	Vomiting	11	2
General disorders and administrative site conditions	Fatigue	44	6
	Peripheral edema	24	2
	Pyrexia	17	2
Skin and subcutaneous tissue disorders	Bruising *	41	0
	Rash*	29	5
	Pruritus	14	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	40	3
	Arthralgia	24	2
	Muscle spasms	19	3
Infections and infestations	Upper respiratory tract infection	21	0
	Sinusitis*	19	0
	Bronchitis	11	0
	Pneumonia*	11	10
Metabolism and nutrition disorders	Decreased appetite	16	2
	Hyperuricemia	16	0
	Hypoalbuminemia	14	0
	Hypokalemia	13	0
Vascular Disorders	Hemorrhage*	30	0
	Hypertension*	14	5
Respiratory, thoracic and mediastinal disorders	Cough	22	2
	Dyspnea	21	2
Nervous system disorders	Dizziness	19	0
	Headache	13	0
Psychiatric disorders	Anxiety	16	2

The body system and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

IMBRUVICA® (ibrutinib) capsules

Table 12: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MZL in Study 6 (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	49	6
Hemoglobin Decreased	43	13
Neutrophils Decreased	22	13

* Based on laboratory measurements.

Additional Important Adverse Reactions: *Diarrhea:* Diarrhea of any grade occurred at a rate of 43% (range, 36% to 59%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 14%) and Grade 3 in 3% (range, 0 to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 10 days (range, 0 to 627), of Grade 2 was 39 days (range, 1 to 719) and of Grade 3 was 74 days (range, 3 to 627). Of the patients who reported diarrhea, 82% had complete resolution, 1% had partial improvement and 17% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 2% Grade 2). The median time to first onset was 85 days (range, 1 to 414 days). Of the patients with visual disturbance, 61% had complete resolution and 38% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 335 days).

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

Hepatobiliary disorders: hepatic failure

Respiratory disorders: interstitial lung disease

Metabolic and nutrition disorders: tumor lysis syndrome *[see Warnings & Precautions]*

Immune system disorders: anaphylactic shock, angioedema, urticaria

Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onychoclasis

DRUG INTERACTIONS

CYP3A Inhibitors: Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A (CYP3A). In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng • hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity *[see Dosage and Administration (2.4) in Full Prescribing Information].*

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A *[see Dosage and Administration (2.4), and Clinical Pharmacology (12.3) in Full Prescribing Information].*

CYP3A Inducers: Administration of IMBRUVICA with rifampin, a strong CYP3A inducer, decreased ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction *[see Clinical Pharmacology (12.3) in Full Prescribing Information].*

USE IN SPECIFIC POPULATIONS

Pregnancy: *Risk Summary:* IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including malformations *[see Data].* If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. 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.

Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Lactation: *Risk Summary:* There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

Females and Males of Reproductive Potential: *Pregnancy Testing:* Verify the pregnancy status of females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception:

Females: Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males: Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

DIGITAL HEALTH

Implementing an Oncology Precision Medicine Clinic in a Large Community Health System

Michael A. Thompson, MD, PhD; Jennifer J. Godden, PharmD; Scott M. Weissman, MS, CGC; Deborah Wham, MS, CGC; Amanda Wilson, MD; Antony Ruggeri, MD; Michael P. Mullane, MD; and James L. Weese, MD, FACS

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intoxicating appeal of an imminent future in which the majority of patients can have their cancer's molecular drivers decoded and eradicated by a customized agent or cocktail, a sober view of the evidence, particularly as derived from prospectively designed trials of personalized medicine, should lead us to fear that our current oncology community will be guilty of hubris and of overpromising, what we can deliver in a realistic time line." Part of this caution stems from results like those from the French SHIVA trial,[2] which found no progression-free survival (PFS) or overall survival benefit in patients treated based on their molecular profiling (using drugs available in France). A similar viewpoint published in *JAMA* in 2015 asked "Seven Questions for Personalized Medicine."[3]

Despite this trepidation of adopting PM as a standard-of-care treatment, there are examples of studies showing benefit. In the seminal study from Von Hoff and colleagues[4] and, more recently by Radovich et al,[5] the metric of PFS ratio—that is, PFS new (molecularly chosen drug) to PFS old (prior therapy)—has shown promise for use in individuals (n-of-one trial). Another study, by Haslem and colleagues, found a PFS hazard ratio of 0.47, showing a precision medicine benefit in the community setting.[6] Further, the PM patients had lower costs per PFS week than the control group. In addition, Schwaederle et al performed a meta-analysis of 13,203 patients with phase 1 refractory cancer in clinical trials.[7] They found that a personalized strategy was independently correlated with improved response rate (30.6% vs 4.9%; P <.0001) and prolonged median PFS (5.7 vs 2.95 months; P = .0002). Also, phase 1 clinical trials that used targeted agents without a biomarker-based selection strategy had negligible response rates.

Herein we report on the advantages of implementing an oncology precision medicine (OPM) clinic, including installation of a Syapse precision medicine data integration platform (Syapse Inc, Palo Alto, California), in a large community health system.

OPM Clinic Workflow

Oncologists throughout our healthcare system may utilize the OPM clinic in 2 ways. In some cases, providers choose to refer their patients to the OPM team to coordinate the entire process. In this scenario, the patient meets with the team at a centralized location within the healthcare system for a 60-minute initial visit during which a physician introduces the concepts of PM and molecular testing. Subsequently, a molecular test is ordered for the patient from an outside vendor, using archived tissue, or a new biopsy is performed. Once the results are available, the case is discussed by the Molecular Tumor Board (MTB), a body comprising medical oncologists, surgical oncologists, molecular pathologists, genetic counselors, pharmacists, cancer nurse navigators, and research coordinators to discuss the patient's case and formulate recommendations. The patient then returns to the OPM clinic for a second visit with one of our physicians to discuss the results and suggested treatments in detail. Ultimately, all information and recommendations are communicated to the referring oncologist for consideration during the subsequent treatment steps. The OPM team will facilitate referrals to genetic counseling, research protocol screening, or drug insurance coverage as needed.

In other cases, treating oncologists will choose to coordinate the molecular testing and associated education themselves, and send the results for discussion by the same MTB. In that scenario, although the OPM team never meets the patient in clinic, they can still offer recommendations to the treating oncologist. »

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THOMPSON


GODDEN


WEISSMAN


WHAM

Michael A. Thompson, MD, PhD, is medical director of early-phase cancer research at Aurora Research Institute.

Jennifer J. Godden, PharmD, is a specialty pharmacy coordinator, Oncology, at Aurora Research Institute.

Scott M. Weissman, MS, CGC, is a genetic counselor at Aurora Health Care.

Deborah Wham, MS, CGC, is a genetic counselor at Aurora Health Care.

Syapse

Syapse is a software product with several functionalities relevant to PM programs.[8] The most basic functionality is pulling raw molecular panel data into the electronic health record (EHR). Most molecular panel data exist in Adobe (as PDF files), with detailed descriptions and summaries; some companies also offer proprietary online portals and databases. Additionally, Syapse can be used to sort molecular data from various sources for running reports and understanding test usage and correlation with clinically relevant endpoints.

The oncology precision medicine team facilitates referrals to genetic counseling, research protocol screening, or drug insurance coverage as needed.

Additional utility may be realized by its applicability as an online real-time resource for MTBs. Syapse's Oncology Precision Network (OPeN) allows aggregated cancer genomics data to be pulled from all participating health systems. This capability could aid in understanding de-identified genotype–phenotype correlations much earlier than possible case reports or case series publications. For example, if a patient within the network with a specific tumor type, genotype, or drug treatment did or did not respond to treatment, the information will be available to the network. This may lead to faster development of clinical trials in various patient subsets. Syapse anticipates that, when fully implemented, OPeN will impact 104,000 new cancer patients per year, representing 3% of the nation's total cancer population. Based on new partners joining the network, current projections are for 780,000 total cases in 2018, and 1.1 million total historical cases by the end of 2019.

Pathologist's Role

Pathologists play a variety of roles within PM, the foremost being an intrinsic role in the diagnosis of cancer. When a pathologist is present at the time of biopsy, he or she ensures there is adequate tissue to make a diagnosis and allocates the specimen for any necessary ancillary tests, such as immunohistochemistry or flow cytometry. As more diagnoses are made on small tissue biopsies, it is important for pathologists to be judicious in their use of these ancillary tests.

Following diagnosis, pathologists are responsible for the maintenance and storage of tissue samples. When molecular analysis is ordered, the pathologist reviews whether there is enough tissue to perform such testing and selects the optimal sample to be sent either to an in-house or a specialized molecular laboratory. The pathologist can provide insights into specific diagnoses and test results and facilitate appropriate ordering for standard-of-care testing (eg, acute myeloid leukemia molecular tests) as well as testing in OPM.

Administrative Issues in an OPM Clinic

It is our belief that PM will change the entire approach to cancer treatment. In this time of upheaval in the healthcare industry, this concept must be weighed as it relates to value-based care. Molecular-based treatments, despite their potential effectiveness when used appropriately, can be very expensive on a per-case basis.

Although tumor genetic analysis has shown greater similarity among cancer types than within a specific tumor identified by organ site, most genetic tests are returned to our physicians in the form of lengthy PDF files, making it hard to incorporate results into the EHR and often difficult to retrieve after initial review.

As we looked toward developing our OPM program, we realized the importance of obtaining and accessing the molecular data in a more granular manner, such that it could be easily accessed for patient care. From an administrative perspective, we explored companies whose software met the following criteria:

1. Data can be transferred from different testing companies or labs and be accessible in the EHR
2. Data can be readily retrievable in the long term
3. Data can be easily matched to specific clinical trials
4. Results can be compared with other patients with the same molecular profile to investigate past responses to a given agent

Following a review of several providers who offer management of molecular data, we believed Syapse was the best option to accomplish these goals. Its platform is essentially source-agnostic regarding which company performed the testing, and it has the capability to analyze raw data from the molecular vendor instead of just PDF files; the data also is readily retrievable. By joining the consortium of health systems on the Syapse platform, we would be eligible to join OPeN (as described above), thereby allowing us to provide evidence-based care to our patients without a long delay. This feature is consistent with the Cancer Moonshot program organized by former Vice President Joe Biden and funded by the Cancer Care Act of 2016. For these reasons, we elected to incorporate the Syapse platform into our OPM program and institutional EHR.

We are cognizant that payers will be evaluating the value of molecular panels and molecularly guided therapy. The data from Syapse and OPeN can provide large datasets to complement studies by Haslem et al[6] in tumor panels and Trosman et al[9] in hereditary cancer panels.

Role of the Genetics Provider

An integral component of an OPM clinic is the team of genetics providers, including genetic counselors, medical geneticists, and advanced practice nurses in genetics. Next-generation sequencing (NGS) can identify germline pathogenic variants in addition to somatic pathogenic variants—studies have shown that between 3% and 16% of individuals undergoing somatic NGS harbor a germline pathogenic variant depending on the number of genes tested.[10,11] However, due to differences in variant interpretation and the lack of testing for large-copy number variations in most somatic NGS tests, some patients may have a germline pathogenic variant not identifiable on a somatic NGS tumor test.

Incorporating a genetics provider into an OPM clinic also can help educate patients about the possibility of identifying a hereditary cancer syndrome prior to initiating NGS or after a somatic NGS test is performed. Genetics providers can help determine which patients need additional germline genetic testing.

Once results are returned, the genetics provider can perform a hereditary cancer risk assessment by reviewing the patient's personal and family history within the context of the somatic NGS results. However, because sporadic cancers can have somatic pathogenic variants in common hereditary cancer syndrome genes (eg, *APC*, *BRCA1*, *BRCA2*, and *TP53*), pathogenic variants identified in these genes do not always indicate that germline genetic testing is needed.[12] If a hereditary cancer syndrome is identified, not only can it help guide therapeutic decisions (eg, use of BRCA1/2 or PARP inhibitors), but it can influence cancer screening and prevention recommendations for both the patient and family members.

Centering Care Around the Patient

In an OPM clinic, the patient is brought into the center of this OPM mechanism in a very real way. Patients who attend the clinic meet with some of the OPM team members, during which time they are interviewed and their goals assessed. The conversation also includes discussions on:

- The advantages and limitations of genomic testing on their specific tumor type
- The possibility of finding targets that may indicate treatment medications
- The possibility of finding genetic traits that run in the family, which may impact their family's risk of cancer
- The cost of genomic testing

Bringing the patient into the clinic to discuss molecular testing has numerous advantages:

Most genetic tests are returned to our physicians in the form of lengthy PDF files, making it hard to incorporate results into the electronic health record and often difficult to retrieve after initial review.

- We have time to discuss the benefits and disadvantages to help the patient understand how the process works
- It allows us to connect genomic data with the unique patient and biopsychosocial milieu
- We can expedite biopsy or blood draws to obtain DNA samples, complete paperwork for drug acquisition, and gauge insurance coverage of testing

In short, the OPM clinic takes the rather complex process out of the busy oncology clinic and provides services to both patients and oncologists, from assessing and educating to ordering testing to obtaining the appropriate medications.

Conclusions

Prior studies showing a lack of benefit from PM may reflect a need for optimized patient selection, greater understanding of systems biology, and knowledge integration through technology such as Syapse. The overall success of PM will be determined by ongoing evaluations of its value, both in individual patient terms and across health systems. ◆

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ADDRESS FOR CORRESPONDENCE

Michael A. Thompson, MD, PhD
960 N 12th St, Room 4111
Milwaukee, WI 53233

Email: Michael.A.Thompson@aurora.org

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WILSON


RUGGERI


MULLANE


WEESE

Amanda Wilson, MD, is a pathologist at Aurora Health Care.

Antony Ruggeri, MD, is a medical oncologist at Aurora Health Care.

Michael P. Mullane, MD, is a medical oncologist and medical director, Hereditary Cancer and Prevention Center, Aurora Health Care.

James L. Weese, MD, FACS, is vice president, Aurora Cancer Care.

GENETIC COUNSELING

Genetic Counselors Save Costs Across the Genetic Testing Spectrum

Joy Larsen Haidle, MS, CGC; Darci L. Sternen, MS, CGC; Jane A. Dickerson, PhD; Amelia Mroch, MS, CGC; Denise F. Needham, MS, CGC; Christine M. Riordan, MS, CGC; and Michele C. Kieke, PhD, MS, CGC

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DICKERSON


MROCH

Joy Larsen Haidle, MS,CGC, is a genetic counselor at North Memorial Health Cancer Center.

Darci L. Sternen, MS, CGC, is a laboratory genetic counselor at Seattle Children's Hospital.

Jane A. Dickerson, PhD, is the co-director of chemistry labs at Seattle Children's Hospital.

Amelia Mroch, MS, CGC, is a genetic counselor at Sanford Health.

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An estimated 70,000 genetic testing products are currently available, with about 10 reaching the market each day[2]. There are a variety of factors to consider when choosing an appropriate genetic test. **Figure 1** highlights the duties GCs take on throughout the testing process, including:

- Choosing the best test methodology
- Choosing the best person in the family to test
- Selecting the optimal testing laboratory
- Comparing test costs
- Obtaining insurance prior authorization (PA)
- Assisting with interpretation of test results

Here, we present ways in which GCs involved in test UM have helped to realize cost savings that reduced the financial burden on the healthcare system, improved patient care and satisfaction, and prevented potential patient harm in a variety of oncology-related settings. Our data demonstrate that GCs' expertise in the clinic, institutional laboratory, reference laboratory, and PA process save money across the healthcare system.

Methods

Members of the National Society of Genetic Counselors Test Utilization Subcommittee shared data collected through their institutional processes related to ordering genetic tests, tracking cost savings, and improving patient outcomes. Data contributed by each author from her respective institution were pooled and divided into 4 categories based on the GC's role: clinic, institutional laboratory (2 authors), reference laboratory, and insurance PA.

Results

Clinic. At Sanford Health, electronic health record modification routed *BRCA1* and *BRCA2* genetic test orders to clinical GCs for pre-test counseling, risk assessment, and standardized patient care. Clinical GCs reviewed the original order in the context of the patient's personal and family health histories, and determined the appropriate test before an order was placed. This pilot process was very recently implemented at the institution and, therefore, the sample size is small (n = 8) (**Figure 2**). Patients could choose from 3 appointment options: in person, over the phone, or live video. Seven (87.5%) patients had a family history of cancer, and 1 patient had a personal history of breast cancer.

Several key risk assessment points were considered:

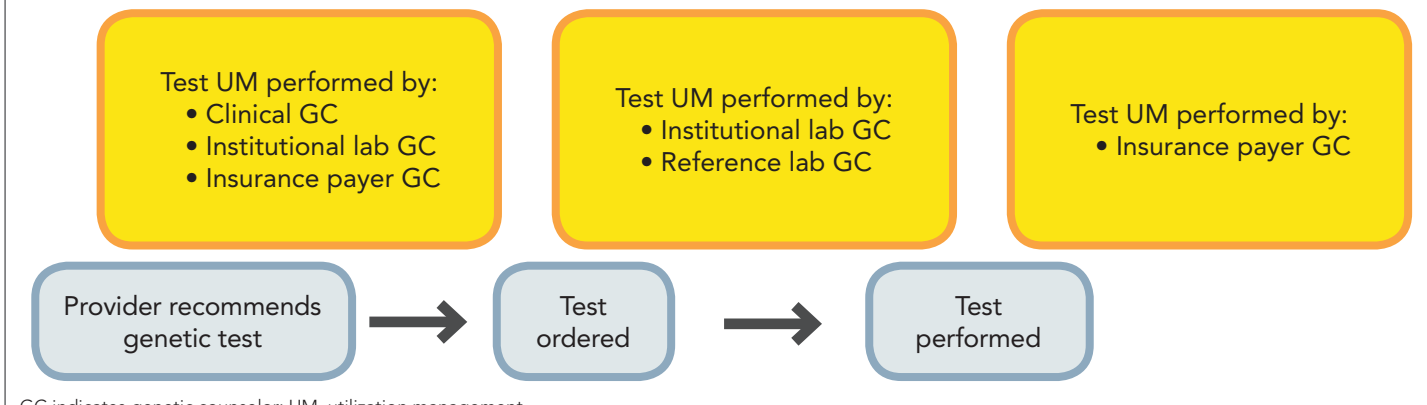
1. Is genetic testing appropriate?
2. Are *BRCA* genetic testing criteria met per insurance guidelines?
3. Is another type of genetic testing more appropriate (*eg*, known familial mutation in a non-*BRCA* gene)?
4. Based on risk assessment models and personal and/or family history, is the patient's overall breast cancer risk high or low?
5. If breast cancer risk is high, is referral to the high-risk breast clinic appropriate?

Interestingly, the recommended genetic test was appropriately ordered for only 2 of the 8 patients in the pilot study (**Figure 2**). One patient needed a different test, 2 did not meet criteria for testing and were referred to the high-risk breast cancer clinic, and 1 had a low risk for breast cancer and thus was not referred. For the remaining 2 cases, testing was cancelled and/or the patient saw a GC in another health system. These data suggest that intervention by a GC after a genetic test order is placed may help avoid unnecessary genetic testing and ensure that the optimal test is ordered.

Institutional Laboratory. At Seattle Children's Hospital, laboratory GCs reviewed 3441 genetic tests' send-out orders from hospital and ambulatory clinics over a 57-month period, resulting in a 32% test modification rate and $972,000 total cost savings (**Table**). In a subset of test send-out orders reviewed in greater detail over a 2.5-year period (n = 1393), data showed that the order error rate from non-genetics providers exceeded 5% (versus 1.7% for orders placed by genetics providers). This may reflect a lack of experience of non-genetics providers and the increasing complexity of genetic testing.

In the 1393 case subset, we determined that 42 cases (3%) were classified as an "ordering error"—defined as such because the test was not appropriate given the clinical situation. Eleven of these ordering errors may have had diagnostic implications for

FIGURE 1. Varied Roles of Genetic Counselors in Genetic Test Utilization Management



GC indicates genetic counselor; UM, utilization management.

the patients, such as risk for missed diagnosis or failure to rule out a condition in the differential diagnosis. We also found that 131 orders of the 1393 case subset (9.4%) were defined as "modified" (5.2% due to cost, 2.7% due to improvement, and 1.5% corrected). Order modification is defined as such because testing was indicated but an incorrect test was ordered. We also determined that 121 orders (8.8 %) were defined as "cancelled" (approximately 3.3% due to lack of PA, 2.2% deferred/postponed, 1.5% due to wrong test order, 1.1% due to duplication of testing, 0.4% due to cost, and 0.3% due to new information regarding the patient or available testing). In addition, 205 orders (15%) were performed as sequential diagnostic pathway with UM consultant input, which saved costs by selecting the most relevant, high-yield genes and/or test methodology first, subsequently reflexing to an additional test depending on the result of the first test.[3]

At the Regions Hospital/HealthPartners care system in Minnesota and western Wisconsin, laboratory GCs reviewed 904 genetic test send-out orders from June 2015 to May 2016, resulting in an overall 13.5% test modification/cancellation rate and a total of $263,000 in cost savings for all genetic test order requests (including orders that were not oncology-related testing) (**Table**). For the subset of oncology-related test orders tracked by one of the GCs (n = 80 cases), a total of just over $150,000 in cost savings was realized (**Table**). Approximately 9% of test orders were modified after review by, and consultation with, the GC. The laboratory GC provided consultation to the ordering provider in 45 of the 80 cases (56%), facilitated insurance PA in 33 of the 80 cases (41%), and referred 8 patients (10%) to a clinical genetics specialist.

Although GCs traditionally focus on genetic conditions caused by germline (inherited) mutations, a majority of oncology-related molecular testing involves somatic tumor profiling, which has led to a somewhat unexpected role for the laboratory GC in assisting with somatic (rather than germline) testing. In our experience at HealthPartners, the knowledge and skills of the GC are useful for both types of testing. As large gene panels continue to replace single-gene testing in the oncology setting and panel tests incorporating the detection of both germline and somatic tumor mutations become available, it will become increasingly important to involve genetics specialists in discussions related to clinically useful and appropriate testing, as well as in results interpretation.

Reference Laboratory. At Laboratory Corporation of America, laboratory GCs review test requisitions and clinical histories to confirm that the most appropriate test has been ordered. A total of 392 *BRCA1/BRCA2* targeted orders placed between December 2013 and February 2015 were reviewed. Of these, 112 (29%) were ordered by a GC and thus were subtracted from the analysis because they were assumed to be appropriate. Analysis of the adjusted total number of orders (n = 280) requested by non-genetics providers (71% of requesters) revealed that 152 orders (54%) were modified by a laboratory GC following consultation with the ordering provider. Based on the cost of the original order and the adjusted cost after testing had been modified, savings totaled approximately $148,000 (**Table**).

Data from this study support the premise that laboratory GC review of genetic test orders improves order accuracy and lowers healthcare costs by reducing unnecessary testing. Although pretest clinical genetic counseling is preferred, our study results demonstrate that laboratory GCs can fill some of the gaps in the absence of pretest genetic counseling.

Genetic counselors' expertise in the clinic, institutional laboratory, reference laboratory, and prior authorization process save money across the healthcare system.

There are diverse opportunities for GCs working in healthcare. In fact, the GC workforce is among the fastest growing healthcare professions,[4] with an estimated 72% growth of the clinical workforce over the next 10 years.[5] The current data suggest that the clinical GC workforce will likely reach an equilibrium of 1 GC per 100,000 individuals in the United States in approximately 5 years, as the growth rate has exceeded the initial estimate by 4%-5% in the first year following the workforce analysis.[5] Optimizing the utilization and efficiency of the GC workforce is a professional priority.

Prior Authorization. PA for genetic testing is now required by many payers and is often outsourced to a medical benefits management organization such as eviCore healthcare. At eviCore, GCs perform PA case reviews by applying policies based on National Comprehensive Cancer Network[6] and US Preventive Services Task Force[7] guidelines to determine medical necessity for *BRCA1/BRCA2* genetic testing (Current Procedural Terminology codes 81211-81217). »


NEEDHAM


RIORDAN


KIEKE

Denise F. Needham, MS, CGC, is a genetic counselor and senior director, Program Development, Laboratory Management Program at eviCore Healthcare.

Christine M. Riordan, MS, CGC, is a genetic counselor at Laboratory Corporation of America.

Michele C. Kieke, PhD, MS, CGC, is a laboratory genetic counselor at Regions Hospital/HealthPartners.

TABLE. Laboratory Utilization Management Metrics for Genetic Testing

	Institutional Lab Seattle Children's Hospital (n = 3441 genetic orders, 4 yr 9 mos)	Institutional Lab HealthPartners (n = 904 cases, 12 mos)	Institutional Lab HealthPartners (n = 80 oncology-related cases, 13 mos)	Reference Lab Laboratory Corporation of America (n = 280, 14 mos)
Total cost tracked (test list price)	$5,965,000	$557,758	$166,673	
Total cost savings to institution/patient	**$972,000**	**$263,400**	**$153,292**	**$148,000**
Savings per test	**$282**	**$275**	**$2472**	**$528**
Rate of test modification	**32%**	**13.5%**	**9.3%**	**54%**
Number of consults with providers			56%	
Number of cases that included investigating patient's insurance coverage		Most orders for tests ≥$500 submitted for prior authorization	41%	
Number of referrals to genetics professionals			10%	

Yr indicates years; mos, months.

FIGURE 2. Workflow for Routing *BRCA1* and *BRCA2* Genetic Test Orders to Clinical Genetic Counselors

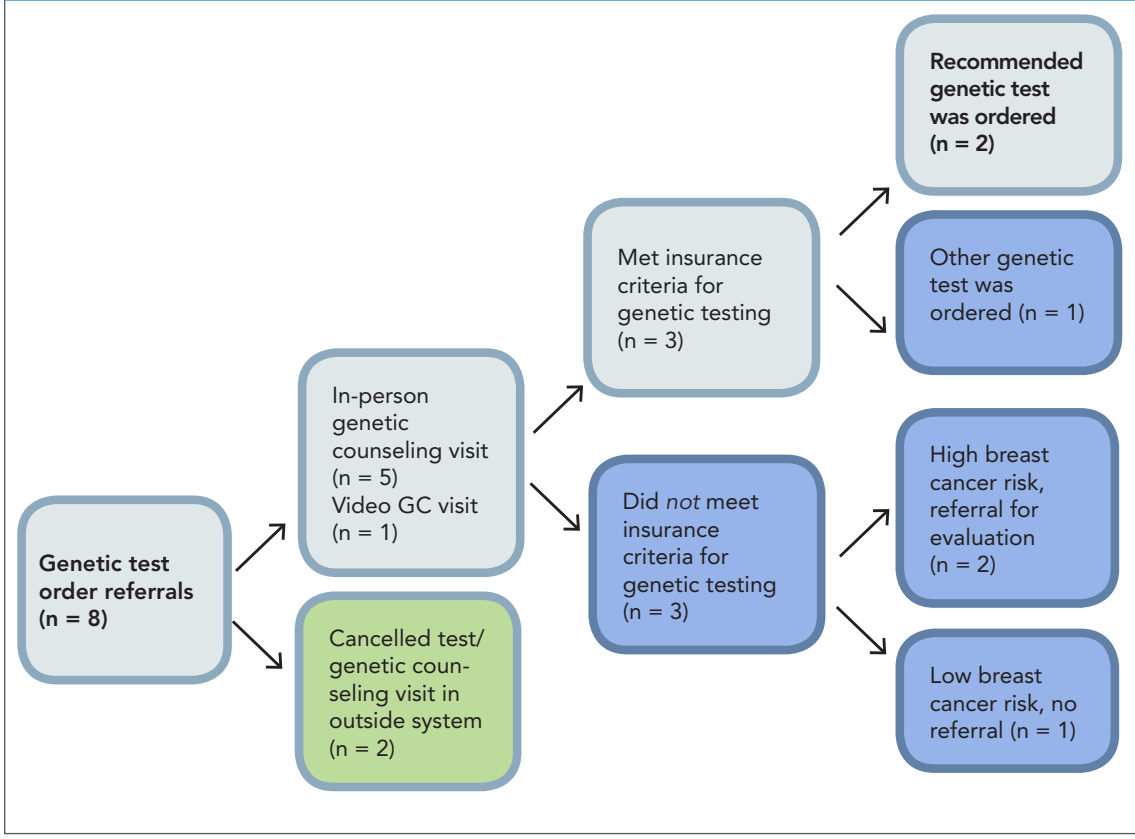
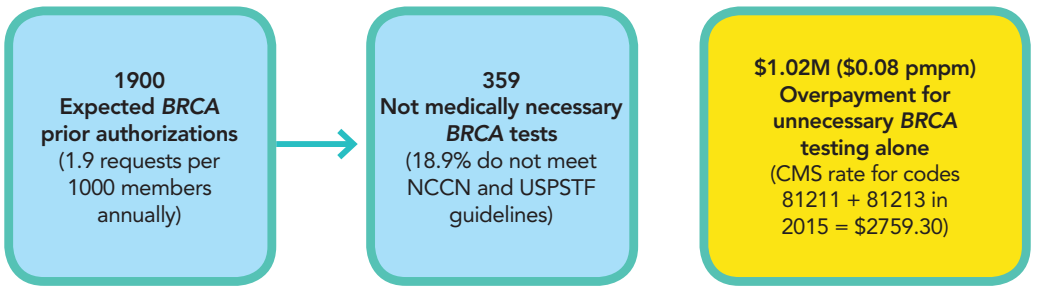


FIGURE 3. *BRCA1* and *BRCA2* Genetic Test Preauthorization: Projected Experience and Savings for a 1-Million Member Commercial Insurance Plan



NCCN indicates National Comprehensive Cancer Network; pmpm, per member per month; USPSTF, US Preventive Services Task Force.

For a subgroup of payer clients who consented to participate in research, we analyzed 1591 *BRCA1/BRCA2* cases (associated with 3465 *BRCA* procedure codes) that underwent a medical necessity review in 2015. *BRCA1/BRCA2* full gene sequencing (81211) and deletion/duplication analysis (81213) procedure codes were the most commonly requested codes. These orders included 97.5% of all *BRCA* gene codes reviewed, which themselves were part of a broader hereditary cancer syndrome gene panel in 15.3% of cases. Based on PA volume, annual *BRCA* test request utilization was 1.9 per 1000 commercial payer and Medicare members and 0.2 per 1000 Medicaid members (**Figure 3**).

In total, *BRCA1/BRCA2* genetic testing did not meet criteria in 14.6% of all cases reviewed. When evaluated by line of business, *BRCA1/BRCA2* genetic testing did not meet criteria in 18.9% of commercial cases, 12.1% of Medicaid cases, and 13.6% of Medicare cases. Overall, 22.1% of all genetic tests reviewed by GCs were found to be inappropriate, demonstrating yet another opportunity to optimize healthcare costs and to identify the most appropriate testing (or lack thereof) for all patients.

Conclusions

GCs selected the most appropriate genetic testing in clinic and performed test UM in the institutional laboratory, reference laboratory, and insurance PA process. Non-genetics providers made genetic test order errors at a significantly higher rate (twice as high for an institutional laboratory), and over half of the orders for *BRCA* genetic testing were corrected by a reference laboratory. Even though *BRCA* testing has been available for 20 years, it's still challenging for non-genetics providers to determine the optimal test and to identify the appropriate testing candidates. GCs also facilitate education of non-genetics providers in the UM process and recommend clinical referrals.

In some cases, a genetic test send-out order may be reviewed by the ordering institution, the insurance payer, and the testing laboratory. These redundancies in the UM process, from the time of test request to performance, could be addressed to improve efficiency across the test UM process, resulting in additional cost savings while also improving efficiency and access for the GC workforce. The diagnostic process for patients presenting with a potentially rare disease is inherently complex and has become more so with the rapidly expanding growth of genetic testing. Establishing UM systems in which GCs are actively involved is important for providing quality, cost-effective care to all patients. GCs are part of the healthcare team and, along with our colleagues, help to optimize patient care and save costs to the healthcare system. ◆

ADDRESS FOR CORRESPONDENCE
Joy Larsen Haidle, MS
North Memorial Health Cancer Center
3435 W. Broadway, Suite 1135
Robbinsdale, MN 55422

E-mail: joy.larsen.haidle@northmemorial.com

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PATIENT PERSPECTIVE

Patient Engagement Is Mandatory at Our Table

Bonnie J. Addario and Daryl Pritchard, PhD

continued from cover

I see the profound impact of precision medicine on patients every day. In 2006, my family and I founded the Bonnie J. Addario Lung Cancer Foundation (ALCF). We started another nonprofit, the Addario Lung Cancer Medical Institute (ALCMI), in 2008. ALCF works with patients to support research and to advocate for innovative lung cancer medicines and treatments. Both the ALCF and the ALCMI facilitate, fund, and drive research. We work with thousands of patients and their families around the globe, providing free education and support programs, connecting patients with doctors and clinical trials, and funding innovative research.

A lung cancer diagnosis is grim—only 18% of patients survive the disease. In the United States alone, 450 patients die from lung cancer every day. Lung cancer is the top cancer killer of men and women, killing almost twice as many women as any other type of cancer in the United States. Responsible for 26% of all cancer deaths, lung cancer is the second leading cause of all deaths in the country.[1]

With the rapid pace of developments in precision medicine, I am excited about the potential to shift the paradigm on how we diagnose and treat lung cancer and save lives. Furthermore, in this era of personalized medicine, we have an opportunity to vastly improve clinical trial design, thereby fostering an environment for innovation that can lead to the development of even more novel treatment strategies.

In 2016, for the third year in a row, targeted medicines and diagnostic tests accounted for more than 20% of the new molecular entities approved by the FDA (**Figure 1**).[2] A recent study sponsored by the Personalized Medicine Coalition and conducted by Tufts University found that 42% of all medicines and 73% of cancer medicines in development are potential personalized medicines (**Figure 2**).[3]

Patient Input in Clinical Trial Design

At the ALCF, we strongly believe that patients are our most important partner in clinical research. There would be no clinical research without patients participating in studies and donating their specimens. The traditional clinical trial design process overlooked patient input, which led to profound inefficiencies. Researchers often needed to scrap or redesign their clinical trials to address patient needs and circumstances. We have an opportunity at hand to vastly improve the process. Including patients in clinical trial design and giving them an opportunity to own their data provide a platform to streamline the process by getting it done right, arriving at the endpoints that matter most, and finding ways to most effectively improve health. We need processes for greater patient participation in clinical research. Now is the time to move from concept to practice, and lung cancer is a prime example of where it can work.

I advocate for the need to shift the way we look at clinical research. The current biomedical innovation paradigm, of discoveries moving from the bench to the patient, needs to shift its focus so that clinical researchers first take into consideration the patient and new discoveries move from the patient to the bench and then back to the patient. This will transform research to ensure it is patient driven and truly personalized.

Consider the example of Corey Wood. While attending the University of California, Berkeley, Corey was diagnosed with stage 4 lung cancer. A triathlete and marathon runner, she immediately began doing research about targeted therapies and genomic tests. Once her oncologists zeroed in on the rare genetic mutation that was responsible for Corey's tumor, they treated her with targeted therapy. Corey now leads the normal life of a 25-year-old thanks to precision medicine. She is passionate about furthering research in the hopes that researchers can develop more effective targeted therapies. Corey owes her life to medical research.

Still, these new and more effective targeted treatments are not useful if we cannot get them to patients. Research and innovation in personalized medicine are surging, but its adoption into clinical practice is relatively slow. In most cases, doctors do not even discuss personalized medicine at the point of care. A recent public survey showed that only 4 of 10 people are aware of personalized medicine and just 11% of patients say their doctor has discussed or recommended personalized medicine treatment options to them.[4]

Another survey found that most healthcare organizations are unprepared to implement personalized medicine[5] and some hospital systems may be placing implementation programs on hold.[6] This lag is caused by novel challenges encountered by healthcare delivery systems as they adapt to the new treatments »

ADDARIO

PRITCHARD

Bonnie J. Addario is chair, Bonnie J. Addario Lung Cancer Foundation, Addario Lung Cancer Medical Institute.

Daryl Pritchard, PhD, is vice president, Science Policy, Personalized Medicine Coalition.

FIGURE 1. More Than 20% of New Molecular Entitites Approved by FDA in Each of Past 3 Years Are Personalized Medicines

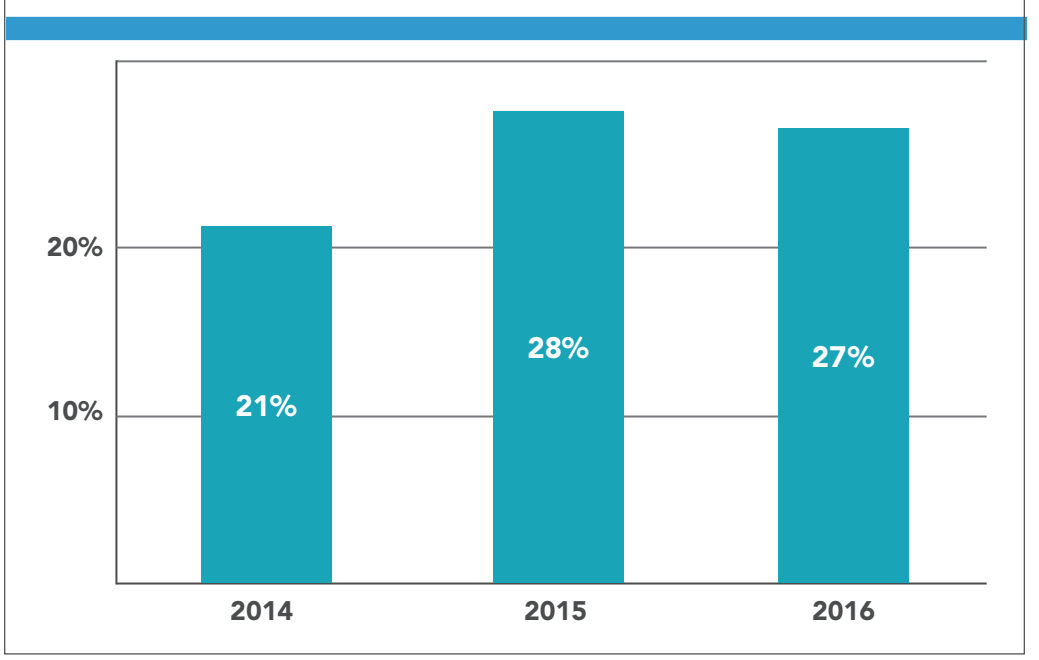
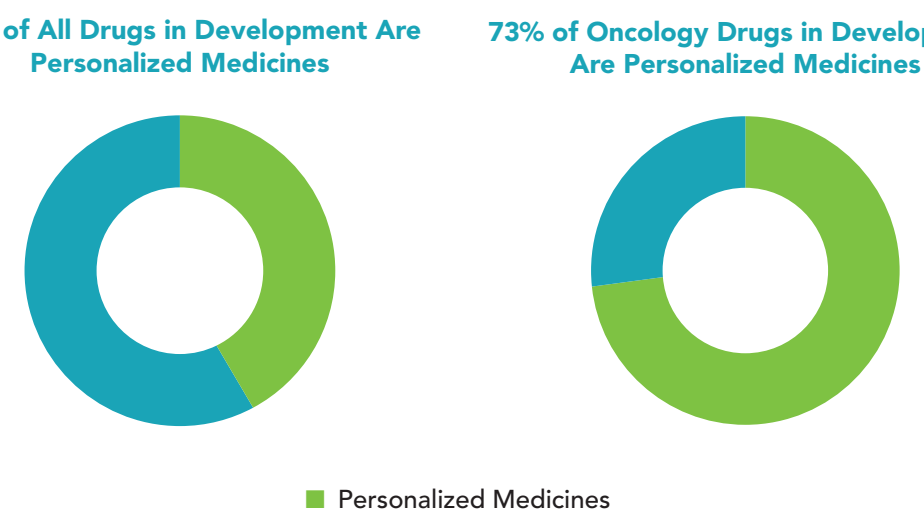


FIGURE 2. Drug Development Pipelines Have Seen a Rapid Increase in the Number of Targeted Treatments



Biopharmaceutical companies nearly doubled their research and development investment in personalized medicines over the past 5 years and expect to increase their investment by an additional third in the next 5 years. Biopharmaceutical researchers also predict a 69% increase in the number of personalized medicines in development over the next 5 years.

and practices associated with personalized care. What we lack are more patient-driven healthcare delivery approaches and processes that would ensure access to personalized medicine, including comprehensive genomic testing and multidisciplinary care.

Empowering patients to be more engaged in their healthcare through awareness programs and education on the promise of precision medicine would be a good start. The strategy should focus on:

- Patient involvement in learning about the healthcare system
- Improving patients' engagement with their physicians
- Shifting the control of individual genetic data to patients
- Encouraging patient participation in the development of treatment guidelines and clinical pathways

Support for precision medicine and patient-centered research is strong, as indicated by several recent legislative initiatives and public policies. Patient-centered directives are included in the Affordable Care Act, and the recently passed 21st Century Cures Act focuses on involving patients in research and care design. The Precision Medicine Initiative, an effort to recruit 1 million volunteers to donate their genetic information for research aimed at finding more effective ways to improve health, and the Cancer Moonshot Initiative, an effort to cut in half the time it takes to discover new personalized cancer treatments, were authorized in the 21st Century Cures Act.

These policies underscore the importance of ensuring patients are receiving the appropriate diagnostic tests and personalized treatment. Lung cancer is not one-size-fits-all. Patients who feel they are not receiving the care they need can share the information with regulators by visiting **www.mypatientrights.org**.

Patients must have a seat at the table to provide valuable data to drive faster cures. This includes ensuring that there is appropriate patient-driven trial design, clinical trial participation, diagnostic testing, endpoint determination, and data aggregation.

Implementing Changes

So, what can we do to advance personalized medicine? Patients must have a seat at the table to provide valuable data to drive faster cures. This includes ensuring that there is appropriate patient-driven trial design, clinical trial participation, diagnostic testing, endpoint determination, and data aggregation. We can change the clinical medicine research ecosystem and adapt it to be more patient-centered. This will bring new treatments forward on a shorter timeline.

We need to ensure that community hospitals and physicians are appropriately engaging patients and promoting personalized medicine. The ALCF is doing this by designating hospitals as Lung Cancer Community Centers of Excellence, where patients are assured of multidisciplinary care, tumor boards, genomic testing, and early screenings in these facilities. We can conduct clinical trials at community hospitals so that patients do not have to travel hundreds of miles to participate in one.

The ALCF just launched its patient-powered Lung Cancer Registry,[7] a place to gather and store detailed information for patients with lung cancer. The registry directly involves patients in the collection of their information, which allows medical professionals to quickly analyze data to improve patient care. By creating a centralized registry, patients, healthcare professionals, researchers, the pharmaceutical industry, and policy makers have open access to information. Programs such as these will ensure that patients are empowered to educate themselves about their disease so they can receive the best, most personalized treatments possible. ◆

ADDRESS FOR CORRESPONDENCE

Daryl Pritchard, PhD
VP, Science Policy
Personalized Medicine Coalition
1710 Rhode Island Ave., NW
Suite 700
Washington, DC 20036

E-mail: dpritchard@personalizedmedicinecoalition.org

Bonnie J. Addario
Lung Cancer Survivor and Chair
Bonnie J. Addario Lung Cancer Foundation
1100 Industrial Road #1
San Carlos, CA 94070

E-mail: bonnie@lungcancerfoundation.org

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