SPECIAL ISSUE: **ASCO MEETING RECAP**

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HIGHLIGHTS FROM THE MEETING

- Biomarkers Important for PD-1/PD-L1 Treatments in Lung Cancer, **SP299**.
- Importance of a Healthy Lifestyle in Colorectal Cancer, **SP308**.
- Stakeholders Look at Changing Clinical Trial Design and Using Real-World Data, **SP316**.
- Preparing Oncologists to Meet the MACRA Challenge, **SP325**.
- Safety and Efficacy Studies of Biosimilars, **SP327-SP333**.
- The Financial Burden of Cancer Care and Cost Effectiveness Studies, **SP334-336**.

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COMMUNITY ONCOLOGY ALLIANCE COA

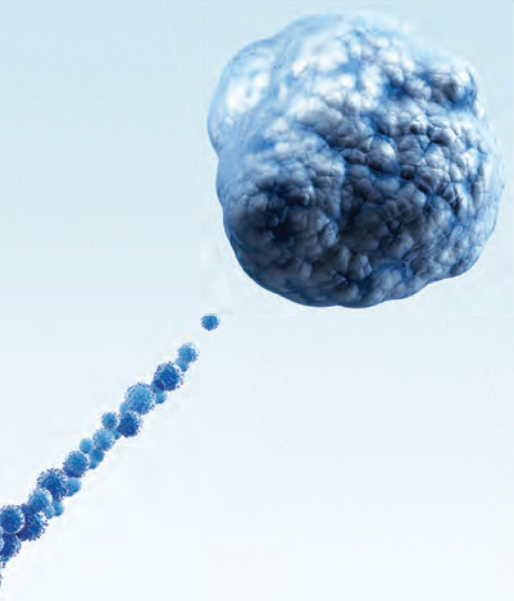
TARGET PD-L1 BLOCKADE

Indication

IMFINZI is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.



IMFINZI™
durvalumab
Injection for Intravenous Use 50 mg/mL

Enable the immune system.

RECOGNIZE. **RESPOND.**

Efficacy

- 17.0% ORR among all patients (2.7% complete response, 14.3% partial response; n=182)[1]
  - – 26.3% ORR among PD-L1 high expressers (n=95)[1]
  - – 4.1% ORR among PD-L1 low/no expressers (n=73)[1]
- 24.3% ORR demonstrated among patients who received only prior neoadjuvant or adjuvant therapy[1]
- Median time to response was 6 weeks[2]
  - – Based on a secondary endpoint in a single-arm trial
- Median duration of response not yet reached[1]

Safety

- Serious potentially fatal risks were seen with IMFINZI; serious adverse reactions occurred in 46% of patients[1]
- The most common Grade 3 or 4 adverse reactions were fatigue (6%), urinary tract infection (4%), musculoskeletal pain (4%), and abdominal pain (3%)[1]
- The most common adverse reactions were fatigue (39%), musculoskeletal pain (24%), constipation (21%), decreased appetite (19%), and nausea (16%)[1]
- Few discontinuations due to adverse events (3.3%)[1]

ORR=objective response rate.
ORR determined by blinded independent central review (BICR) of target lesion diameter according to RECIST v1.1 criteria.

Choose IMFINZI following platinum-based therapy for your patients with locally advanced or metastatic urothelial carcinoma. Visit IMFINZI.com/hcp

Important Safety Information

There are no contraindications for IMFINZI™ (durvalumab).

Monitor patients for clinical signs and symptoms of immune-mediated pneumonitis, hepatitis, colitis or diarrhea, endocrinopathies, nephritis, rash or dermatitis, other immune-mediated adverse reactions, and infection. Please refer to the full Prescribing Information for important dose management information specific to adverse reactions.

Please see Important Safety Information on next page.

Important Safety Information (continued)

Immune-Mediated Pneumonitis

In the combined safety database (n=1414), immune-mediated pneumonitis occurred in 32 patients (2.3%), including 1 fatal case (0.1%) and 6 Grade 3–4 cases (0.4%). In Study 1 (n=182), 1 patient (0.5%) died from immune-mediated pneumonitis. Monitor patients for signs and symptoms of pneumonitis and evaluate with radiographic imaging when suspected. Administer corticosteroids for ≥Grade 2 pneumonitis. Withhold IMFINZI for Grade 2 pneumonitis; permanently discontinue for Grade 3–4 pneumonitis.

Immune-Mediated Hepatitis

In the combined safety database (n=1414), immune-mediated hepatitis occurred in 16 patients (1.1%), including 1 fatal case (<0.1%) and 9 Grade 3 cases (0.6%). Grade 3–4 elevations in ALT occurred in 40/1342 patients (3.0%), AST in 58/1336 patients (4.3%), and total bilirubin in 37/1341 patients (2.8%). In Study 1 (n=182), 1 patient (0.5%) died from immune-mediated hepatitis, and 2 patients (1.1%) experienced immune-mediated hepatitis, including 1 Grade 3 case (0.5%). Monitor patients for abnormal liver tests in each cycle during treatment with IMFINZI. Administer corticosteroids and withhold IMFINZI for Grade 2–3 ALT or AST >3–5X ULN or ≤8X ULN or total bilirubin >1.5–3X ULN or ≤5X ULN. Permanently discontinue IMFINZI in patients with Grade 3 ALT or AST >8X ULN or total bilirubin >5X ULN, or in patients with concurrent ALT or AST >3X ULN and total bilirubin >2X ULN with no other cause.

Immune-Mediated Colitis

In the combined safety database (n=1414), immune-mediated colitis or diarrhea occurred in 18 patients (1.3%), including 1 Grade 4 case (<0.1%) and 4 Grade 3 cases (0.3%). In Study 1 (n=182), 23 patients (12.6%) experienced colitis or diarrhea, including 2 Grade 3–4 cases (1.1%). Monitor patients for signs and symptoms of colitis or diarrhea. Administer corticosteroids for ≥Grade 2 colitis or diarrhea. Withhold IMFINZI for Grade 2 colitis or diarrhea; permanently discontinue for Grade 3–4 colitis or diarrhea.

Immune-Mediated Endocrinopathies

- Immune-mediated thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus and hypophysitis/hypopituitarism have occurred with IMFINZI. Monitor patients for clinical signs and symptoms of endocrinopathies. For Grade 2–4 endocrinopathies (except hypothyroidism) withhold dose until clinically stable and offer symptomatic management for hyperthyroidism. For Grade 2–4 hypothyroidism, initiate thyroid hormone replacement as needed
- Thyroid disorders—In the combined safety database (n=1414), immune-mediated hypothyroidism and hyperthyroidism occurred in 136 patients (9.6%) and 81 patients (5.7%), respectively. Thyroiditis occurred in 10 patients (0.7%), including 1 Grade 3 case (<0.1%) in a patient who had a myocardial infarction. In 9 patients with thyroiditis, transient hyperthyroidism preceded hypothyroidism. Treatment with a beta-blocker and/or thioamide was administered for hyperthyroidism in five of these patients. In Study 1 (n=182), Grade 1–2 hypothyroidism or thyroiditis occurred in 10 patients (5.5%). Grade 1–2 hyperthyroidism or thyroiditis leading to hyperthyroidism occurred in 9 patients (4.9%). Monitor patients for abnormal thyroid function tests prior to and periodically during treatment
- Immune-mediated adrenal insufficiency—In the combined safety database (n=1414), immune-mediated adrenal insufficiency occurred in 13 patients (0.9%), including 2 Grade 3 cases (0.1%). In Study 1 (n=182), Grade 1 adrenal insufficiency occurred in 1 patient (0.5%). Administer corticosteroids and hormone replacement as clinically indicated
- Type 1 diabetes mellitus—In the combined safety database (n=1414), new onset type 1 diabetes mellitus without an alternative etiology occurred in 1 patient (<0.1%). For type 1 diabetes mellitus, initiate insulin as indicated and withhold IMFINZI until clinically stable
- Hypophysitis—In the combined safety database (n=1414), hypopituitarism leading to adrenal insufficiency and diabetes insipidus occurred in 1 patient (<0.1%). Administer corticosteroids and hormone replacement as clinically indicated

Other Immune-Mediated Adverse Reactions

- IMFINZI has caused immune-mediated rash. Other immune-related adverse reactions, including aseptic meningitis, hemolytic anemia, immune thrombocytopenic purpura, myocarditis, myositis, nephritis, and ocular inflammatory toxicity including uveitis and keratitis, have occurred in ≤1.0% of patients treated with IMFINZI

- Immune-mediated rash or dermatitis—In the combined safety database (n=1414), immune-mediated rash or dermatitis occurred in 220 patients (15.6%) and 4 patients (0.3%) developed vitiligo. In Study 1 (n=182), 20 patients (11.0%) developed rash, including 1 Grade 3 case (0.5%). Patients should be monitored for signs and symptoms of rash or dermatitis. Administer corticosteroids if indicated. Withhold IMFINZI for Grade 3 rash or dermatitis or Grade 2 rash or dermatitis lasting >1 week. Permanently discontinue IMFINZI in patients with Grade 4 rash or dermatitis
- Immune thrombocytopenic purpura—In the combined safety database (n=1414), 1 fatal case (<0.1%) of immune thrombocytopenic purpura occurred. Monitor patients for signs and symptoms of immune thrombocytopenic purpura
- Nephritis—In the combined safety database (n=1414), immune-mediated nephritis occurred in 3 patients (0.2%), including 2 Grade 3 cases (0.1%). Monitor patients for abnormal renal function tests prior to and during each cycle of IMFINZI. Administer corticosteroids for ≥Grade 2 nephritis (creatinine >1.5X ULN). Withhold IMFINZI for Grade 2 nephritis; permanently discontinue for ≥Grade 3 nephritis (creatinine >3X ULN)

Infection

Severe infections, including sepsis, necrotizing fasciitis, and osteomyelitis, occurred in patients receiving IMFINZI. In the combined safety database (n=1414), infections occurred in 531 patients (37.6%). In Study 1 (n=182), infections occurred in 54 patients (29.7%). 11 patients (6.0%) experienced Grade 3–4 infection and 5 patients (2.7%) were experiencing infection at the time of death. 8 patients (4.4%) experienced urinary tract infection, the most common ≥Grade 3 infection. Monitor patients for signs and symptoms of infection and treat with anti-infectives for suspected or confirmed infections. Withhold IMFINZI for ≥Grade 3 infection.

Infusion-Related Reactions

In the combined safety database (n=1414), severe infusion-related reactions occurred in 26 patients (1.8%). In Study 1 (n=182), infusion-related reactions occurred in 3 patients (1.6%). There were 5 Grade 3 (0.4%) and no Grade 4 or 5 reactions. Patients should be monitored for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion for Grade 1–2 infusion-related reactions and permanently discontinue for Grade 3–4 infusion-related reactions.

Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman. There are no data on the use of IMFINZI in pregnant women. Advise pregnant women of the potential risk to a fetus and advise women of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of IMFINZI.

Nursing Mothers

There is no information regarding the presence of IMFINZI in human milk; however, because of the potential for adverse reactions in breastfed infants from IMFINZI, advise a lactating woman not to breastfeed during treatment and for at least 3 months after the last dose.

Most Common Adverse Reactions

- The most common adverse reactions (≥15%) were fatigue (39%), musculoskeletal pain (24%), constipation (21%), decreased appetite (19%), nausea (16%), peripheral edema (15%), and urinary tract infection (15%). The most common Grade 3 or 4 adverse reactions (≥3%) were fatigue, urinary tract infection, musculoskeletal pain, abdominal pain, dehydration, and general physical health deterioration
- Adverse reactions leading to discontinuation of IMFINZI occurred in 3.3% of patients. Serious adverse reactions occurred in 46% of patients. The most frequent serious adverse reactions (>2%) were acute kidney injury (4.9%), urinary tract infection (4.4%), musculoskeletal pain (4.4%), liver injury (3.3%), general physical health deterioration (3.3%), sepsis, abdominal pain, and pyrexia/tumor associated fever (2.7% each)

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

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

References: 1. IMFINZI [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.
2. Data on File, REF-7270, AstraZeneca Pharmaceuticals LP.

AstraZeneca

IMFINZI™
durvalumab
Injection for Intravenous Use 50 mg/mL

IMFINZI™ (durvalumab) injection, for intravenous use
Initial U.S. Approval: 2017

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

INDICATIONS AND USAGE

IMFINZI is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy.
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials *[see Clinical Studies (14.1) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

Recommended Dosing

The recommended dose of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

Dose Modifications

No dose reductions are recommended. Withhold and/or discontinue IMFINZI to manage adverse reactions as described in Table 1.

Table 1. Recommended Treatment Modifications for IMFINZI

Adverse Reactions	Severity[a]	IMFINZI Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified
Pneumonitis *[see Warnings and Precautions (5.1)]*	Grade 2	Withhold dose[b]	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	Initial dose of 1 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by a taper
Hepatitis *[see Warnings and Precautions (5.2)]*	Grade 2 ALT or AST >3-5xULN or total bilirubin >1.5-3xULN	Withhold dose[b]	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 ALT or AST ≤8xULN or total bilirubin ≤5xULN		
	Grade 3 ALT or AST >8xULN or total bilirubin >5xULN	Permanently discontinue	
	Concurrent ALT or AST >3xULN and total bilirubin >2xULN with no other cause		
Colitis or diarrhea *[see Warnings and Precautions (5.3)]*	Grade 2	Withhold dose[b]	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	
Hypothyroidism *[see Warnings and Precautions (5.4)]*	Grade 2-4		Initiate thyroid hormone replacement as clinically indicated
Hyperthyroidism *[see Warnings and Precautions (5.4)]*	Grade 2-4	Withhold dose until clinically stable	Symptomatic management
Adrenal insufficiency, Hypophysitis/Hypopituitarism *[see Warnings and Precautions (5.4)]*	Grade 2-4	Withhold dose until clinically stable	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Type 1 Diabetes Mellitus *[see Warnings and Precautions (5.4)]*	Grade 2-4	Withhold dose until clinically stable	Initiate treatment with insulin as clinically indicated
Nephritis *[see Warnings and Precautions (5.5)]*	Grade 2 Creatinine >1.5-3x ULN	Withhold dose[b]	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 Creatinine >3-6x ULN	Permanently discontinue	
	Grade 4 Creatinine >6x ULN		
Rash or dermatitis *[see Warnings and Precautions (5.5)]*	Grade 2 for >1 week	Withhold dose[b]	Consider initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3		
	Grade 4	Permanently discontinue	
Infection *[see Warnings and Precautions (5.6)]*	Grade 3 or 4	Withhold dose	Symptomatic management; treat with anti-infectives for suspected or confirmed infections
Infusion-related reactions *[see Warnings and Precautions (5.7)]*	Grade 1 or 2	Interrupt or slow the rate of infusion	Consider pre-medications with subsequent doses
	Grade 3 or 4	Permanently discontinue	
Other	Grade 3	Withhold dose[b]	Symptomatic management
	Grade 4	Permanently discontinue	Consider initial dose of 1 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by taper

[a] Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.
[b] Based on severity of the adverse reactions, IMFINZI should be withheld and corticosteroids administered. Consider increasing dose of corticosteroids and/or other systemic immunosuppressants if there is worsening or no improvement. Corticosteroid taper should be initiated when adverse reaction improves to < Grade 1 and should be continued over at least 1 month. For adverse reactions that do not result in permanent discontinuation, resume treatment when adverse reaction returns to ≤ Grade 1 and the corticosteroid dose has been reduced to <10 mg prednisone or equivalent per day.

Preparation and Administration

Preparation

- Visually inspect drug product for particulate matter and discoloration. IMFINZI is clear to opalescent, colorless to slightly yellow solution, free from visible particles. Discard the vial if the solution is cloudy, discolored, or visible particles are observed.
- Do not shake the vial.
- Withdraw the required volume from the vial(s) of IMFINZI and transfer into an intravenous bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. Do not shake the solution. The final concentration of the diluted solution should be between 1 mg/mL and 15 mg/mL.
- Discard partially used or empty vials of IMFINZI.

Storage of Infusion Solution

IMFINZI does not contain a preservative.

Administer infusion solution immediately once prepared. If infusion solution is not administered immediately and needs to be stored, the total time from vial puncture to the start of the administration should not exceed:

- 24 hours in a refrigerator at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature up to 25°C (77°F)

Do not freeze.

Do not shake.

Administration

- Administer infusion solution intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.
- Do not co-administer other drugs through the same infusion line.

DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/2.4mL (50 mg/mL) and 500 mg/10mL (50 mg/mL) clear to opalescent, colorless to slightly yellow solution in a single-dose vial.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease occurred in patients receiving IMFINZI. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and manage with treatment modifications and corticosteroids *[see Dosage and Administration (2.2) in the full Prescribing Information]*.

In Study 1 (n=182), one patient (0.5%) died from immune-mediated pneumonitis. In the combined safety database (n=1414), of patients treated with IMFINZI 10 mg/kg every 2 weeks, immune-mediated pneumonitis occurred in 32 (2.3%) patients including fatal pneumonitis in one (0.1%) patient and Grade 3-4 in six (0.4%) patients. The median time to onset was 55.5 days (range: 24-423 days). Seventeen (1.2%) patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was interrupted in 12 patients and discontinued in five (0.4%) patients. Resolution occurred in 18 (1.3%) patients.

Immune-Mediated Hepatitis

Immune-mediated hepatitis occurred in patients receiving IMFINZI. Monitor patients for abnormal liver tests each cycle during treatment with IMFINZI. Manage immune-mediated hepatitis with treatment modifications and corticosteroids *[see Dosage and Administration (2.2) in the full Prescribing Information]*.

In Study 1, one (0.5%) patient died from immune-mediated hepatitis. An additional two (1.1%) patients experienced immune-mediated hepatitis, including Grade 3 in one (0.5%) patient. In the combined safety database, immune-mediated hepatitis occurred in 16 (1.1%) patients including fatal hepatitis in one (<0.1%) patient and Grade 3 in nine (0.6%) patients. The median time to onset was 51.5 days (range: 15-312 days). Twelve (0.8%) of the 16 patients received high-dose corticosteroid treatment. One patient also received mycophenolate treatment. IMFINZI was interrupted in five (0.3%) patients and discontinued in three (0.2%) patients. Resolution occurred in nine (0.6%) patients. In the combined safety database, Grade 3 or 4 elevations in ALT occurred in 40/1342 (3.0%) of patients, AST in 58/1336 (4.3%), and total bilirubin in 37/1341 (2.8%) of patients.

Immune-Mediated Colitis

Immune-mediated colitis or diarrhea occurred in patients receiving IMFINZI. Monitor patients for signs and symptoms of colitis or diarrhea and manage with treatment modifications, anti-diarrheal agents, and corticosteroids *[see Dosage and Administration (2.2) in the full Prescribing Information]*.

In Study 1, colitis or diarrhea occurred in 23 (12.6%) patients including Grade 3 or 4 diarrhea in two (1.1%) patients. No patients in Study 1 received systemic corticosteroids or immunosuppressants for diarrhea or colitis. In the combined safety database, immune-mediated colitis or diarrhea occurred in 18 (1.3%) patients including Grade 4 in one (<0.1%) and Grade 3 in four (0.3%) patients. The median time to onset was 73 days (range: 13-345 days). Of these patients, one (<0.1%) had Grade 4 and four (0.3%) had Grade 3 immune-mediated colitis or diarrhea. Ten (0.7%) of the 18 patients received high-dose corticosteroid treatment. Two (0.1%) patients received non-steroidal immunosuppressants. IMFINZI was interrupted in five (0.4%) patients and discontinued in six (0.4%) patients. Resolution occurred in 11 (0.8%) patients.

Immune-Mediated Endocrinopathies

Immune-related thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus and hypophysitis/hypopituitarism have occurred in patients receiving IMFINZI. Monitor patients for clinical signs and symptoms of endocrinopathies.

Thyroid Disorders

Monitor thyroid function prior to and periodically during treatment with IMFINZI. Asymptomatic patients with abnormal thyroid function tests can receive IMFINZI. Manage patients with abnormal thyroid function tests with hormone replacement (if indicated) and treatment modifications *[see Dosage and Administration (2.2) in the full Prescribing Information]*.

In the Study 1, hypothyroidism or thyroiditis leading to hypothyroidism occurred in ten (5.5%) patients. All patients had Grade 1-2 hypothyroidism. The median time to first onset was 42 days (range: 15-239). Thyroid stimulating hormone (TSH) was elevated and above the patient's baseline in 25 (15.3%) of 163 patients with a follow-up measurement.

In Study 1, hyperthyroidism or thyroiditis leading to hyperthyroidism occurred in nine (4.9%) patients. All patients had Grade 1-2 hyperthyroidism. The median time to first onset was 43 days (range: 14-71). Thyroid stimulating hormone (TSH) was decreased and below the patient's baseline in 26 (16%) of 163 patients with a follow-up measurement.

In the combined safety database, hypothyroidism occurred in 136 (9.6%) patients, while hyperthyroidism occurred in 81 (5.7%) patients. Thyroiditis occurred in ten patients, including Grade 3 in one patient who had a myocardial infarction. In nine patients with thyroiditis, transient hyperthyroidism preceded hypothyroidism. Treatment with a beta-blocker and/or thioamide was administered for hyperthyroidism in five of these patients.

Adrenal Insufficiency

Monitor patients for clinical signs and symptoms of adrenal insufficiency. Administer corticosteroids and hormone replacement as clinically indicated *[see Dosage and Administration (2.2) in the full Prescribing Information]*.

In Study 1, adrenal insufficiency occurred in one (0.5%) patient (Grade 1). In the combined safety database, adrenal insufficiency occurred in 13 (0.9%) patients, including Grade 3 in two (0.1%) patients. Seven (0.5%) of these patients were treated with systemic corticosteroids.

Type 1 Diabetes Mellitus

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate insulin for type 1 diabetes mellitus and manage patients with treatment modifications *[see Dosage and Administration (2.2) in the full Prescribing Information]*. New onset type 1 diabetes mellitus without an alternative etiology occurred in one patient (<0.1%) in the combined safety database.

Hypophysitis

Monitor for signs and symptoms of hypophysitis or hypopituitarism. Administer corticosteroids and hormone replacement as clinically indicated *[see Dosage and Administration (2.2) in the full Prescribing Information]*. Hypopituitarism leading to adrenal insufficiency and diabetes insipidus occurred in one patient (<0.1%) in the combined safety database.

Other Immune-Mediated Adverse Reactions

IMFINZI has caused immune-mediated rash. Other immune-related adverse reactions, including aseptic meningitis, hemolytic anemia, immune thrombocytopenic purpura, myocarditis, myositis, nephritis, and ocular inflammatory toxicity including uveitis and keratitis, have occurred in ≤1.0% of patients treated with IMFINZI.

Immune-mediated Rash

Monitor for signs and symptoms of rash *[see Dosage and Administration (2.2) in the full Prescribing Information]*. In Study 1, 20 (11.0%) of patients developed rash including Grade 3 rash in one (0.5%) patient. In the combined safety database, 220 (15.6%) patients developed rash and four (0.3%) patients developed vitiligo. Systemic corticosteroids were administered in 17 (1.2%) patients. The rash resolved in 133 (9.4%) patients.

Immune Thrombocytopenic Purpura

Monitor patients for signs and symptoms of immune thrombocytopenic purpura *[see Dosage and Administration (2.2) in the full Prescribing Information]*. In the combined safety database, immune thrombocytopenic purpura led to death in one (<0.1%) patient. The patient received high-dose corticosteroids, human immunoglobulin, and rituximab.

Nephritis

Monitor patients for abnormal renal function tests prior to and each cycle during treatment with IMFINZI and manage with treatment modifications and corticosteroids *[see Dosage and Administration (2.2) in the full Prescribing Information]*. In Study 1, one patient received systemic corticosteroids for immune-mediated nephritis. In the combined safety database, immune-mediated nephritis occurred in three (0.2%) patients including Grade 3 in two (0.1%) patients. All three patients received high-dose corticosteroids treatment. IMFINZI was discontinued in all three patients. Resolution occurred in all three patients.

Infection

Severe infections, including sepsis, necrotizing fasciitis, and osteomyelitis, occurred in patients receiving IMFINZI. Monitor patients for signs and symptoms of infection and treat with anti-infectives for suspected or confirmed infections. Withhold IMFINZI for ≥Grade 3 infection *[see Dosage and Administration (2.2) and Adverse Reactions (6.1) in the full Prescribing Information]*.

In Study 1, infections occurred in 54 (29.7%) patients. Grade 3 or 4 infection occurred in eleven (6.0%) patients, while five (2.7%) patients were experiencing infection at the time of death. Urinary tract infections were the most common cause of Grade 3 or higher infection, occurring in eight (4.4%) patients. In the combined safety database, infections occurred in 531 (37.6%) patients.

Infusion-Related Reactions

Severe infusion-related reactions have been reported in patients receiving IMFINZI. Monitor for signs and symptoms of an infusion-related reaction. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Permanently discontinue IMFINZI in patients with Grade 3 or 4 infusion reactions *[see Dosage and Administration (2.2) in the full Prescribing Information]*.

Infusion related reactions occurred in three (1.6%) patients in Study 1 and 26 (1.8%) patients in the combined safety database. There were five (0.4%) Grade 3 and no Grade 4 or 5 reactions. Four (0.3%) patients developed urticaria within 48 hours of dosing.

Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of durvalumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased premature delivery, fetal loss and premature neonatal death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMFINZI and for at least 3 months after the last dose of IMFINZI *[see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

ADVERSE REACTIONS

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

- Immune-Mediated Pneumonitis *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.
- Immune-Mediated Hepatitis *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.
- Immune-Mediated Colitis *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.
- Immune-Mediated Endocrinopathies *[see Warnings and Precautions (5.4) in the full Prescribing Information]*.
- Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.5) in the full Prescribing Information]*.
- Infection *[see Warnings and Precautions (5.6) in the full Prescribing Information]*.
- Infusion-Related Reactions *[see Warnings and Precautions (5.7) in the full Prescribing Information]*.

Clinical Trials Experience

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

The safety data described in Table 2 reflect exposure to IMFINZI in 182 patients with locally advanced or metastatic urothelial carcinoma in Study 1 whose disease has progressed during or after one standard platinum-based regimen. Patients received 10 mg/kg IMFINZI via intravenous infusion every 2 weeks *[see Clinical Studies (14.1) in the full Prescribing Information]*. The median duration of exposure was 10.2 weeks (range: 0.14, 52.4).

Thirty-one percent (31%) of patients had a drug delay or interruption for an adverse reaction. The most common (>2%) were liver injury (4.9%), urinary tract infection (3.3%), acute kidney injury (3.3%), and musculoskeletal pain (2.7%).

The most common adverse reactions (≥15%) were fatigue (39%), musculoskeletal pain (24%), constipation (21%), decreased appetite (19%), nausea (16%), peripheral edema (15%) and urinary tract infection (15%). The most common Grade 3 or 4 adverse reactions (≥3%) were fatigue, urinary tract infection, musculoskeletal pain, abdominal pain, dehydration, and general physical health deterioration.

Eight patients (4.4%) who were treated with IMFINZI experienced Grade 5 adverse events of cardiorespiratory arrest, general physical health deterioration, sepsis, ileus, pneumonitis, or immune-mediated hepatitis. Three additional patients were experiencing infection and disease progression at the time of death. IMFINZI was discontinued for adverse reactions in 3.3% of patients. Serious adverse reactions occurred in 46% of patients. The most frequent serious adverse reactions (>2%) were acute kidney injury (4.9%), urinary tract infection (4.4%), musculoskeletal pain (4.4%), liver injury (3.3%), general physical health deterioration (3.3%), sepsis, abdominal pain, pyrexia/tumor associated fever (2.7% each).

Immune-mediated adverse reactions requiring systemic corticosteroids or hormone replacement therapy occurred in 8.2% (15/182) patients, including 5.5% (10/182) patients who required systemic corticosteroid therapy and 2.7% (5/182) patients who required only hormone replacement therapy. Seven patients (3.8%) received an oral prednisone dose equivalent to ≥40 mg daily for an immune-mediated adverse reaction *[see Warnings and Precautions (5) in the full Prescribing Information]*.

Table 2 summarizes the adverse reactions that occurred in ≥10% of patients, while Table 3 summarizes the Grade 3 - 4 selected laboratory abnormalities that occurred in ≥1% of patients treated with IMFINZI in Study 1.

Table 2. Adverse Reactions in ≥10% of Patients in UC Cohort Study 1

	IMFINZI N=182	
Adverse Reaction	All Grades (%)	Grades 3 - 4 (%)
All Adverse Reactions	96	43
Gastrointestinal Disorders		
Constipation	21	1
Nausea	16	2
Abdominal pain[1]	14	3
Diarrhea/Colitis	13	1
General Disorders and Administration		
Fatigue[2]	39	6
Peripheral edema[3]	15	2
Pyrexia/Tumor associated fever	14	1
Infections		
Urinary tract infection[4]	15	4
Metabolism and Nutrition Disorders		
Decreased appetite/Hypophagia	19	1
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[5]	24	4
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea/Exertional Dyspnea	13	2
Cough/Productive Cough	10	0
Skin and Subcutaneous Tissue Disorders		
Rash[6]	11	1

[1] Includes abdominal pain upper, abdominal pain lower and flank pain
[2] Includes asthenia, lethargy, and malaise
[3] Includes edema, localized edema, edema peripheral, lymphedema, peripheral swelling, scrotal edema, and scrotal swelling
[4] Includes cystitis, candiduria and urosepsis
[5] Includes back pain, musculoskeletal chest pain, musculoskeletal pain and discomfort, myalgia, and neck pain
[6] Includes dermatitis, dermatitis acneiform, dermatitis psoriasiform, psoriasis, rash maculo-papular, rash pruritic, rash papular, rash pustular, skin toxicity, eczema, erythema, erythema multiforme, rash erythematous, acne, and lichen planus

Table 3. Grade 3-4 Laboratory Abnormalities Worsened from Baseline Occurring in ≥1% Patients in UC Cohort Study 1

Laboratory Test	Grade 3 - 4 %
Hyponatremia	12
Lymphopenia	11
Anemia	8
Increased alkaline phosphatase	4
Hypermagnesemia	4
Hypercalcemia	3
Hyperglycemia	3
Increased AST	2
Increased ALT	1
Hyperbilirubinemia	1
Increased creatinine	1
Neutropenia	1
Hyperkalemia	1
Hypokalemia	1
Hypoalbuminemia	1

Immunogenicity

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

Due to the limitations in assay performance, the incidence of antibody development in patients receiving IMFINZI has not been adequately determined. Of 1124 patients who were treated with IMFINZI 10 mg/kg every 2 weeks and evaluable for the presence of anti-drug antibodies (ADAs), 3.3% patients tested positive for treatment-emergent ADAs. The clinical significance of anti-durvalumab antibodies is unknown.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk summary

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in the full Prescribing Information]*. There are no data on the use of IMFINZI in pregnant women.

In animal reproduction studies, administration of durvalumab to pregnant cynomolgus monkeys from the confirmation of pregnancy through delivery resulted in increased premature delivery, fetal loss and premature neonatal death *(see Data)*. Human immunoglobulin G1 (IgG1) is known to cross the placental barrier; therefore, durvalumab has the potential to be transmitted from the mother to the developing fetus. Apprise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

As reported in the literature, the PD-1/PD-L1 pathway plays a central role in preserving pregnancy by maintaining maternal immune tolerance to the fetus. In mouse allogeneic pregnancy models, disruption of PD-L1 signaling was shown to result in an increase in fetal loss. The effects of durvalumab on prenatal and postnatal development were evaluated in reproduction studies in cynomolgus monkeys. Durvalumab was administered from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the clinical dose of 10 mg/kg of durvalumab (based on AUC). Administration of durvalumab resulted in premature delivery, fetal loss (abortion and stillbirth) and increase in neonatal deaths. Durvalumab was detected in infant serum on postpartum Day 1, indicating the presence of placental transfer of durvalumab. Based on its mechanism of action, fetal exposure to durvalumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice.

Lactation

Risk Summary

There is no information regarding the presence of durvalumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG1 is excreted in human milk. Durvalumab was present in the milk of lactating cynomolgus monkeys and was associated with premature neonatal death *(see Data)*.

Because of the potential for adverse reactions in breastfed infants from durvalumab, advise a lactating woman not to breastfeed during treatment with IMFINZI and for at least 3 months after the last dose.

Data

In lactating cynomolgus monkeys, durvalumab was present in breast milk at about 0.15% of maternal serum concentrations after administration of durvalumab from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the clinical dose of 10 mg/kg of durvalumab (based on AUC). Administration of durvalumab resulted in premature neonatal death.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action, IMFINZI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Advise females of reproductive potential to use effective contraception during treatment with IMFINZI, and for at least 3 months following the last dose of IMFINZI.

Pediatric Use

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

Geriatric Use

Of the 182 patients treated with IMFINZI, 112 patients were 65 years or older and 34 patients were 75 years or older. The overall response rate in patients 65 years or older was 15.2% (17/112) and was 11.8% (4/34) in patients 75 years or older. Grade 3 or 4 adverse reactions occurred in 38% (42/112) of patients 65 years or older and 35% (12/34) of patients 75 years or older. Study results in patients ≥ 65 years of age and particularly in those ≥ 75 years of age should be viewed with caution given the small number of patients.

OVERDOSAGE

There is no information on overdose with IMFINZI.

PATIENT COUNSELING INFORMATION

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

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of IMFINZI, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis or type 1 diabetes mellitus *[see Warnings and Precautions (5.4) in the full Prescribing Information]*.
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of rash, nephritis, aseptic meningitis, thrombocytopenic purpura, myocarditis, hemolytic anemia, myositis, uveitis and keratitis *[see Warnings and Precautions (5.5) in the full Prescribing Information]*.
- Infection: Advise patients to contact their healthcare provider immediately for infection *[see Warnings and Precautions (5.6) in the full Prescribing Information]*.
- Infusion-Related Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.7) in the full Prescribing Information]*.
- Embryo-Fetal Toxicity: Advise females of reproductive potential that IMFINZI can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

  Advise females of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of IMFINZI *[see Use in Specific Populations (8.3) in the full Prescribing Information]*.
- Lactation: Advise female patients not to breastfeed while taking IMFINZI and for at least 3 months after the last dose *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.2) in the full Prescribing Information]*.

Manufactured for:
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SPECIAL ISSUE / ASCO MEETING RECAP
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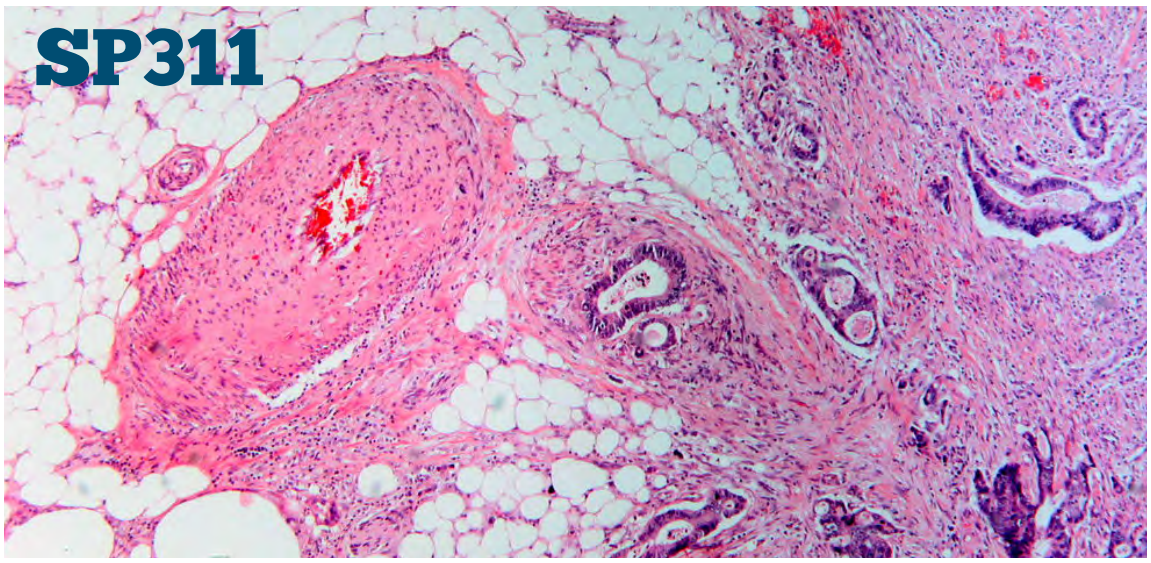
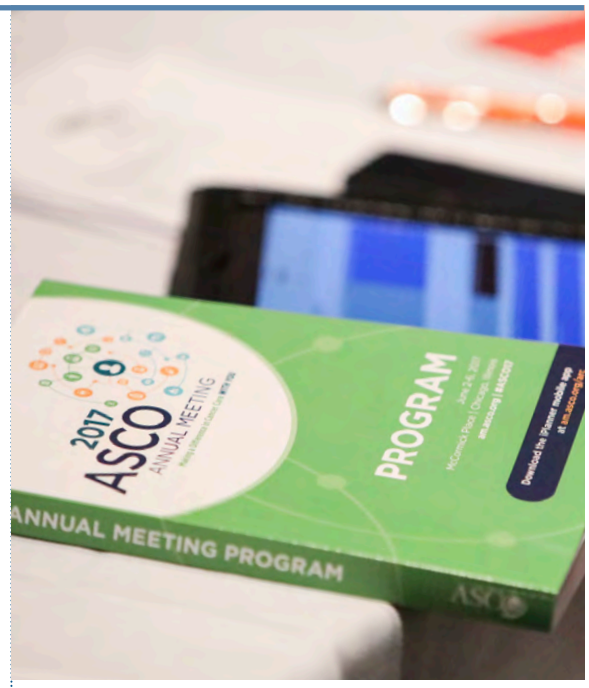


TUMOR INVASION INTO VEIN IN A CASE OF COLORECTAL CANCER, HE 1.

INSIDE THE ISSUE



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Clinical Updates, Value, and Cost of Care: Highlights From ASCO17

MIKE HENNESSY, SR

ONCOLOGISTS, RESEARCH SCIENTISTS, drug developers, and students arrive in Chicago each year to share their knowledge, provide yearly updates, and reenergize their focus for the coming year at the annual meeting of the American Society of Clinical Oncology.

A very interesting discussion on using real-world data in oncology took place on day 1. Participants—which included a payer, an oncologist, and an FDA representative—highlighted the value presented by real-world evidence from randomized clinical trials (RCTs), which often require data collection over several years before the evidence can be implemented in the clinic, by which time the information could be obsolete. Sean Khozin, MD, MPH, who represented the FDA, explained that RCTs have poor generalizability because there is no "median or average patient." So, treatments based on the median outcome of a trial will not help us maximize the potential of precision oncology.

This year's annual meeting had a special session on state-of-the-art uses for immunotherapy in non–small cell lung cancer.

As physician practices continue to grapple with quality and reporting requirements to meet payer movement toward value-based care, physicians well versed in the concept of a medical home model shared their experiences and provided advice on how physician practices can successfully meet mandates of CMS' Quality Payment Program (QPP). The discussion ranged from how to effectively implement changes within your practice to risk-sharing options offered under QPP.

Immunotherapy, particularly treatment with the programmed death-1 inhibitors and the programmed death-ligand 1 inhibitors, has seen tremendous progress over the past 5 years. With the number of agents and their various indications, this year's annual meeting had a special session on state-of-the-art uses for immunotherapy in non–small cell lung cancer, with an emphasis on managing toxicities and efficacy in specific subpopulations. Additionally, the meeting also had significant research updates for clinical practice across a variety of therapeutic areas, including oral cancer, colorectal cancer, lung cancer, and multiple myeloma. We have covered some of these developments in this special issue.

We hope that this special issue provides a good overview of the annual meeting, and we thank you for your readership. To receive updates on conferences and events held by *The American Journal of Managed Care®*, visit ajmc.com/conferences. ◆

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

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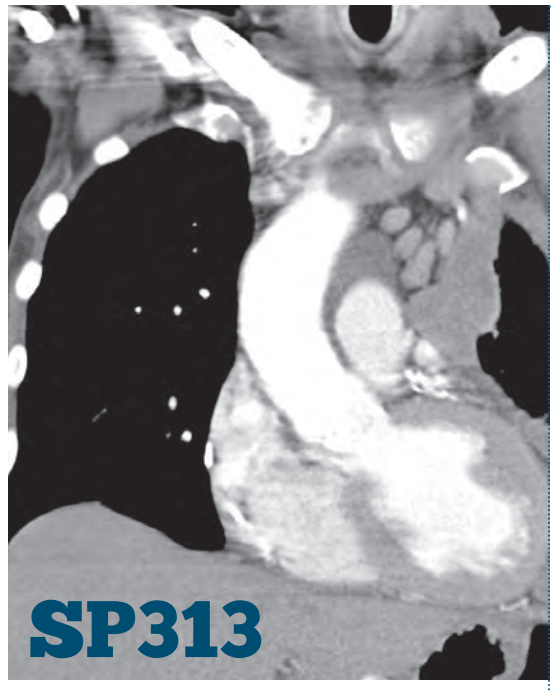
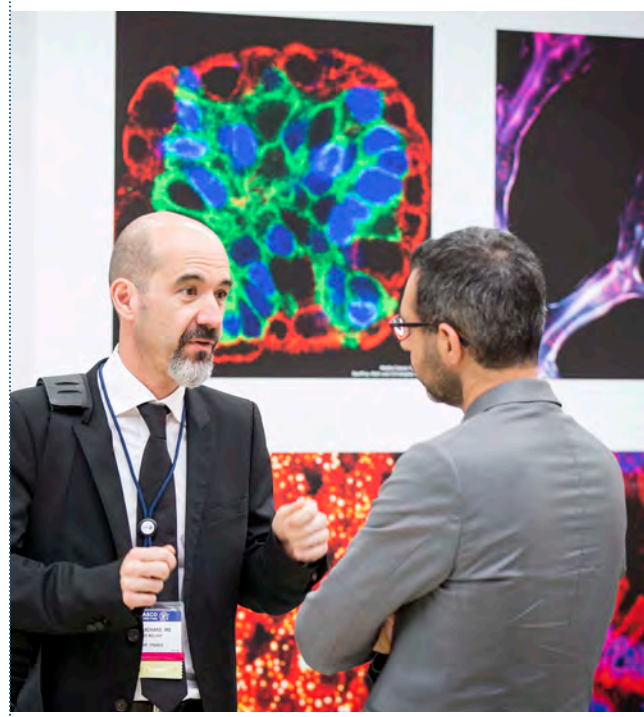


CT SCAN SHOWING A LEFT-SIDED MESOTHELIOMA WITH AN ENLARGED MEDIASTINAL LYMPH NODE



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Daratumumab With Standard Regimen Improves PFS, ORR Independent of Cytogenetic Risk in Multiple Myeloma

Surabhi Dangi-Garimella, PhD

IN AUGUST 2016, daratumumab (Darzalex) was granted breakthrough designation status as second-line treatment for use in combination with either lenalidomide (Revlimid) and dexamethasone (DRd regimen, POLLUX trial) or bortezomib (Velcade) and dexamethasone (DVd regimen, CASTOR trial) for patients with relapsed refractory multiple myeloma (RRMM) who have received at least 1 prior therapy.[1] Updated trial results at the 2017 Annual Meeting of the American Society of Clinical Oncology,[2] showed the combinations prolonged progression-free survival (PFS) and improved the depth of response, independent of the patients' cytogenetic risk.

Daratumumab is a human monoclonal antibody that targets CD38, a receptor overexpressed in multiple myeloma, resulting in complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis. The authors examined their efficacy in patients with RRMM with standard or high cytogenetic risk status.

Bone marrow aspirates for patients who participated in the open-label, multicenter, active-controlled, randomized POLLUX and CASTOR studies were collected at screening and assessed via next-generation sequencing (NGS). Patients with high-risk cytogenetics included those who had at least 1 of the following translocations or deletions: t(4;14), t(14;16), or del17p. Patients at standard risk were negative for these abnormalities.

While 311 patient samples were analyzed via NGS from the POLLUX trial, 353 were from the CASTOR trial. At a median follow-up of 25.4 months, 65% of patients receiving DRd in the intention-to-treat population (POLLUX) had a median PFS of 24 months, compared with 41% of the control Revlimid-treated (Rd) population who had a median PFS of 17.5 months (HR, 0.41; 95% CI, 0.31-0.53; $P<.0001$). Of patients who had received 1 prior line of therapy, median PFS was not reached in 79% of the cohort receiving DRd; it was 19.6 months in 40% receiving Rd (HR, 0.39; 95% CI, 0.26-0.58; $P<.0001$).

At the end of a 19.4-month follow-up period (CASTOR trial), 49% of patients receiving DVd had a median PFS of 18.7 months compared with 8% patients treated with Velcade (Vd) who had a median PFS of 7.1 months (HR, 0.31; 95% CI, 0.24-0.39; $P<.0001$). In patients who had received 1 prior line of therapy, a median PFS was not reached in 60% of patients in the DVd arm compared with a median PFS of 7.9 months in 12% of patients in the Vd arm (HR, 0.19; 95% CI, 0.12-0.29; $P<.0001$).

Cytogenetic risk analysis in patients in the POLLUX study showed DRd improved median PFS to 22.6 months in the high-risk patient population compared with 18.2 months in the Rd arm (HR, 0.53; 95% CI, 0.25 to 1.13; $P = .0021$). Median PFS was not reached in the standard-risk patients treated with DRd compared with 18.5 months in those receiving Rd (HR, 0.30; 95% CI, 0.20-0.47; $P<.0001$). Median PFS for high-risk patients in the CASTOR study was 11.2 months in the DVd arm and 7.2 months in the Vd arm (HR, 0.45; 95% CI, 0.25-0.80; $P = .0053$). In standard-risk patients, daratumumab improved median PFS to 19.6 months, against 7.9 months with Vd (HR, 0.26; 95% CI, 0.18-0.37; $P<.0001$).

The authors concluded that daratumumab included in standard-of-care regimens in RRMM prolongs PFS and improves the depth of response regardless of cytogenetic risk. Longer-term survival results are awaited for both trials. ◆

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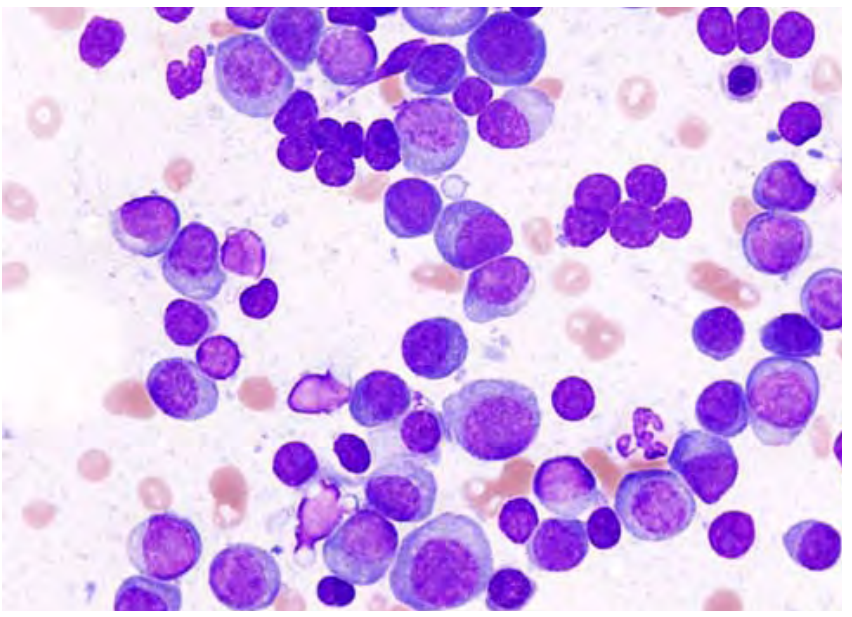
Phase 1 Study Results at ASCO Support First-Line Use of Daratumumab in Multiple Myeloma

Surabhi Dangi-Garimella, PhD

A COMBINATION OF PROTEASOME inhibitors and immunomodulatory drugs in the standard of care has improved outcomes in patients with multiple myeloma over the past 10 years. However, these patients can relapse even after complete remission in first-line indications. A phase 1 study, presented at the 2017 Annual Meeting of the American Society of Clinical Oncology, found that using daratumumab, an antibody that binds and inhibits the CD38 receptor, can improve patient response to treatment.

The trial enrolled newly diagnosed patients, regardless of transplantation eligibility. Patients were administered daratumumab at 16 mg/kg weekly for cycles 1 and 2, every other week for cycles 3 to 6, and once in 4 weeks thereafter. Carfilzomib was administered on days 1, 8, and 15 of each 28-day cycle (20 mg/m^2 on day 1 of cycle 1 and 36 mg/m^2 or 70 mg/m^2 based on tolerability of first dose), for most of the 13 cycles, or treatment was discontinued for allogenic stem cell transplant. The treatment also included 25-mg lenalidomide given on days 1 to 21 and dexamethasone 20 to 40 mg weekly. The primary endpoint for this very early phase trial was tolerability.



MULTIPLE MYELOMA MG STAIN

Twenty-two patients received a median of 8 (range, 1-10) treatment cycles and were followed for a median of 7.4 months (range, 4.0-9.3). Six patients (27%) discontinued treatment, with serious adverse events (AEs) observed in 46% of patients, 14% of which were thought to be related to daratumumab. Grade 3/4 treatment-emergent AEs (TEAE) were observed in 18 (82%) patients: lymphopenia (50%) and neutropenia (23%) were most common. No grade 5 TEAEs were reported.

The authors concluded that daratumumab with carfilzomib and lenalidomide was well tolerated, consistent with results previously reported for carfilzomib plus lenalidomide, with no additional toxicity observed. They claimed that daratumumab can be a feasible option for induction therapy in newly diagnosed patients with multiple myeloma. No grade 3/4 toxicities were noted. The treatment was highly effective, with a 100% overall response rate as well as a 100% 6-month progression-free survival. The depth of response improved with treatment duration. ◆

REFERENCE

Jakubowiak AJ, Chari A, Lonial S, et al. Daratumumab (DARA) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) in patients (pts) with newly diagnosed multiple myeloma (MMY1001): an open-label, phase 1b study. *J Clin Oncol.* 2017;35(suppl; abst 8000).

The **new permanent J-code for DARZALEX® (daratumumab)** is effective as of January 1, 2017.[1]

J9145	Injection, daratumumab, 10 mg

- J9145 will replace miscellaneous and/or temporary codes that were previously used across various sites of care*
- J9145 applies to commercial and Medicare patients in both hospital outpatient and physician's office settings[1]

Please note, the fact that a drug, device, procedure, or service is assigned an HCPCS† code and a payment rate does not imply coverage by the Medicare program. An HCPCS code and a payment rate indicate only how the product, procedure, or service may be paid if covered by the program. Fiscal Intermediaries/Medicare Administrative Contractors determine whether a drug, device, procedure, or other service meets all program requirements for coverage.[2]

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For more information please visit www.darzalexhcp.com

Indication

DARZALEX® is a CD38-directed cytolytic antibody indicated:

- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy
- as monotherapy, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

Important Safety Information

Warnings and precautions include: infusion reactions, interference with serological testing, neutropenia, thrombocytopenia, and interference with determination of complete response

- In patients who received Darzalex® in combination with lenalidomide and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: neutropenia (92%), thrombocytopenia (73%), upper respiratory tract infection (65%), infusion reactions (48%), diarrhea (43%), fatigue (35%), cough (30%), muscle spasms (26%), nausea (24%), dyspnea (21%) and pyrexia (20%). The overall incidence of serious adverse reactions was 49%. Serious adverse reactions were: pneumonia (12%), upper respiratory tract infection (7%), influenza (3%) and pyrexia (3%).
- In patients who received Darzalex® in combination with bortezomib and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: thrombocytopenia (90%), neutropenia (58%), peripheral sensory neuropathy (47%), infusion reactions (45%), upper respiratory tract infection (44%), diarrhea (32%), cough (27%), peripheral edema (22%), and dyspnea (21%). The overall incidence of serious adverse reactions was 42%. Serious adverse reactions were: upper respiratory tract infection (5%), diarrhea (2%) and atrial fibrillation (2%).

Please see Full Important Safety Information on next page and Brief Summary of Full Prescribing Information on adjacent page.

References: 1. Department of Health and Human Services: Centers for Medicare & Medicaid Services. Federal Register: Rules and Regulations. November 2, 2016; 81(219): 79562-7989.
2. Medicare National Coverage Determinations Manual. Centers for Medicare & Medicaid Services (CMS); May 16, 2016.

*Please check with individual payers and carriers for specific documentation and guidance when billing for a new drug.

†Healthcare Common Procedure Coding System.

DARZALEX®
(daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

Important Safety Information

CONTRAINDICATIONS - None

WARNINGS AND PRECAUTIONS

Infusion Reactions

- DARZALEX® can cause severe infusion reactions. Approximately half of all patients experienced a reaction, most during the first infusion. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing an infusion. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension.
- Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt infusion for reactions of any severity and institute medical management as needed. Permanently discontinue therapy for life-threatening (Grade 4) reactions. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.
- To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Interference with Serological Testing

- Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX®. Type and screen patients prior to starting DARZALEX®.

Neutropenia

- DARZALEX® may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX® dose delay may be required to allow recovery of neutrophils. No dose reduction of DARZALEX® is recommended. Consider supportive care with growth factors.

Thrombocytopenia

- DARZALEX® may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. DARZALEX® dose delay may be required to allow recovery of platelets. No dose reduction of DARZALEX® is recommended. Consider supportive care with transfusions.

Interference with Determination of Complete Response

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

Adverse Reactions

- In patients who received DARZALEX® in combination with lenalidomide and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: neutropenia (92%), thrombocytopenia (73%), upper respiratory tract infection (65%), infusion reactions (48%), diarrhea (43%), fatigue (35%), cough (30%), muscle spasms (26%), nausea (24%), dyspnea (21%) and pyrexia (20%). The overall incidence of serious adverse reactions was 49%. Serious adverse reactions were pneumonia (12%), upper respiratory tract infection (7%), influenza (3%) and pyrexia (3%).
- In patients who received DARZALEX® in combination with bortezomib and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: thrombocytopenia (90%), neutropenia (58%), peripheral sensory neuropathy (47%), infusion reactions (45%), upper respiratory tract infection (44%), diarrhea (32%), cough (27%), peripheral edema (22%), and dyspnea (21%). The overall incidence of serious adverse reactions was 42%. Serious adverse reactions were upper respiratory tract infection (5%), diarrhea (2%) and atrial fibrillation (2%).

DRUG INTERACTIONS

Effect of Other Drugs on Daratumumab

- The coadministration of lenalidomide or bortezomib with DARZALEX® did not affect the pharmacokinetics of daratumumab.

Effect of Daratumumab on Other Drugs

- The coadministration of DARZALEX® with bortezomib did not affect the pharmacokinetics of bortezomib.

Please see Brief Summary of Full Prescribing Information on adjacent page.

janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

 1/17 065184-170106

DARZALEX®
(daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

DARZALEX® (daratumumab) injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

DARZALEX is indicated:

- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.
- as monotherapy, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion Reactions

DARZALEX can cause severe infusion reactions. Approximately half of all patients experienced a reaction, most during the first infusion.

Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension *[see Adverse Reactions].*

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy for life-threatening (Grade 4) reactions. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion *[see Dosage and Administration (2.1) in Full Prescribing Information].*

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following DARZALEX infusions *[see Dosage and Administration (2.2) in Full Prescribing Information].* Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum[1] *[see References].* The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions].*

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX.

Neutropenia

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

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX dose delay may be required to allow recovery of neutrophils. No dose reduction of DARZALEX is recommended. Consider supportive care with growth factors.

Thrombocytopenia

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

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. DARZALEX dose delay may be required to allow recovery of platelets. No dose reduction of DARZALEX is recommended. Consider supportive care with transfusions.

Interference with Determination of Complete Response

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

ADVERSE REACTIONS

The following serious adverse reactions are also described elsewhere in the labeling:

- Infusion reactions *[see Warning and Precautions].*
- Neutropenia *[see Warning and Precautions].*
- Thrombocytopenia *[see Warning and Precautions].*

Adverse Reactions in Clinical Trials

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

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 717 patients with multiple myeloma including 526 patients from two Phase 3 active-controlled trials who received DARZALEX in combination with either lenalidomide (DRd, n=283; Study 3) or bortezomib (DVd, n=243; Study 4) and four open-label, clinical trials in which patients received DARZALEX either in combination with lenalidomide (n=35), or as monotherapy (n=156).

Combination Treatment with Lenalidomide

Adverse reactions described in Table 1 reflect exposure to DARZALEX (DRd arm) for a median treatment duration of 13.1 months (range: 0 to 20.7 months) and median treatment duration of 12.3 months (range: 0.2 to 20.1 months) for the lenalidomide group (Rd) in Study 3. The most frequent adverse reactions (≥20%) were infusion reactions, diarrhea, nausea, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, cough and dyspnea. The overall incidence of serious adverse reactions was 49% for the DRd group compared with 42% for the Rd group. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (12% vs Rd 10%), upper respiratory tract infection (7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

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

Table 1: Adverse reactions reported in ≥ 10% of patients and with at least a 5% frequency greater in the DRd arm in Study 3

Adverse Reaction	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Infusion reactions[a]	48	5	0	0	0	0
Gastrointestinal disorders						
Diarrhea	43	5	0	25	3	0
Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
General disorders and administration site conditions						
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[b]	65	6	< 1	51	4	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	30	0	0	15	0	0
Dyspnea[d]	21	3	< 1	12	1	0

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

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.

[b] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment from baseline listed in Table 2.

Table 2: Treatment-emergent hematology laboratory abnormalities in Study 3

	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Anemia	52	13	0	57	19	0
Thrombocytopenia	73	7	6	67	10	5
Neutropenia	92	36	17	87	32	8
Lymphopenia	95	42	10	87	32	6

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

Combination Treatment with Bortezomib

Adverse reactions described in Table 3 reflect exposure to DARZALEX (DVd arm) for a median treatment duration of 6.5 months (range: 0 to 14.8 months) and median treatment duration of 5.2 months (range: 0.2 to 8.0 months) for the bortezomib group (Vd) in Study 4. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, peripheral edema, upper respiratory tract infection, peripheral sensory neuropathy, cough and dyspnea. The overall incidence of serious adverse reactions was 42% for the DVd group compared with 34% for the Vd group. Serious adverse reactions with at least a 2% greater incidence in the DVd arm compared to the Vd arm were upper respiratory tract infection (DVd 5% vs Vd 2%), diarrhea and atrial fibrillation (DVd 2% vs Vd 0% for each).

Adverse reactions resulted in discontinuations for 7% (n=18) of patients in the DVd arm versus 9% (n=22) in the Vd arm.

Table 3: Adverse reactions reported in ≥ 10% of patients and with at least a 5% frequency greater in the DVd arm Study 4

Adverse Reaction	DVd (N=243) %			Vd (N=237) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Infusion reactions[a]	45	9	0	0	0	0
Gastrointestinal disorders						
Diarrhea	32	3	< 1	22	1	0
Vomiting	11	0	0	4	0	0
General disorders and administration site conditions						
Edema peripheral[b]	22	1	0	13	0	0
Pyrexia	16	1	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[c]	44	6	0	30	3	< 1
Nervous system disorders						
Peripheral sensory neuropathy	47	5	0	38	6	< 1
Respiratory, thoracic and mediastinal disorders						
Cough[d]	27	0	0	14	0	0
Dyspnea[e]	21	4	0	11	1	0

Key: D=daratumumab, Vd=bortezomib-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.
[b] edema peripheral, edema, generalized edema, peripheral swelling
[c] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection
[d] cough, productive cough, allergic cough
[e] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment are listed in Table 4.

Table 4: Treatment-emergent hematology laboratory abnormalities in Study 4

	DVd (N=243) %			Vd (N=237) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anemia	48	13	0	56	14	0
Thrombocytopenia	90	28	19	85	22	13
Neutropenia	58	12	3	40	5	<1
Lymphopenia	89	41	7	81	24	3

Key: D=Daratumumab, Vd=bortezomib-dexamethasone.

Monotherapy

The safety data reflect exposure to DARZALEX in 156 adult patients with relapsed and refractory multiple myeloma treated with DARZALEX at 16 mg/kg in three open-label, clinical trials. The median duration of exposure was 3.3 months (range: 0.03 to 20.04 months). Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%).

Adverse reactions resulted in treatment delay for 24 (15%) patients, most frequently for infections. Adverse reactions resulted in discontinuations for 6 (4%) patients.

Adverse reactions occurring in at least 10% of patients are presented in Table 5. Table 6 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥10%.

Table 5: Adverse reactions with incidence ≥10% in patients with multiple myeloma treated with DARZALEX 16 mg/kg

	DARZALEX 16 mg/kg N=156		
	Incidence (%)		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Infusion reaction[a]	48	3	0
General disorders and administration site conditions			
Fatigue	39	2	0
Pyrexia	21	1	0
Chills	10	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	21	0	0
Nasal congestion	17	0	0
Dyspnea	15	1	0
Musculoskeletal and connective tissue disorders			
Back pain	23	2	0
Arthralgia	17	0	0
Pain in extremity	15	1	0
Musculoskeletal chest pain	12	1	0
Infections and infestations			
Upper respiratory tract infection	20	1	0
Nasopharyngitis	15	0	0
Pneumonia[b]	11	6	0
Gastrointestinal disorders			
Nausea	27	0	0
Diarrhea	16	1	0
Constipation	15	0	0
Vomiting	14	0	0
Metabolism and nutrition disorders			
Decreased appetite	15	1	0
Nervous system disorders			
Headache	12	1	0
Vascular disorders			
Hypertension	10	5	0

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see below.
[b] Pneumonia also includes the terms streptococcal pneumonia and lobar pneumonia.

Table 6: Treatment emergent Grade 3-4 laboratory abnormalities (≥10%)

	Daratumumab 16 mg/kg (N=156)		
	All Grade (%)	Grade 3 (%)	Grade 4 (%)
Anemia	45	19	0
Thrombocytopenia	48	10	8
Neutropenia	60	17	3
Lymphopenia	72	30	10

Infusion Reactions

In clinical trials (monotherapy and combination treatments; N=717) the incidence of any grade infusion reactions was 46% with the first infusion of DARZALEX, 2% with the second infusion, and 4% with subsequent infusions. Less than 1% of patients had a Grade 3 infusion reaction with second or subsequent infusions.

The median time to onset of a reaction was 1.5 hours (range: 0.02 to 72.8 hours). The incidence of infusion modification due to reactions was 41%. Median durations of infusion for the 1st, 2nd and subsequent infusions were 7.0, 4.3, and 3.5 hours respectively.

Severe (Grade 3) infusion reactions included bronchospasm, dyspnea, laryngeal edema, pulmonary edema, hypoxia, and hypertension. Other adverse infusion reactions (any Grade, ≥5%) were nasal congestion, cough, chills, throat irritation and vomiting.

Herpes Zoster Virus Reactivation

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

DRd and Rd groups respectively (Study 3) and in 5% versus 3% in the DVd and Vd groups respectively (Study 4).

Infections

In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported with DARZALEX combinations and background therapies (DVd: 21%, Vd: 19%; DRd: 28%, Rd: 23%). Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. Discontinuations from treatment were reported in 3% versus 2% of patients in the DRd and Rd groups respectively and 4% versus 3% of patients in the DVd and Vd groups respectively. Fatal infections were reported in 0.8% to 2% of patients across studies, primarily due to pneumonia and sepsis.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, none of the 111 evaluable monotherapy patients, and 1 (0.4%) of the 234 combination therapy patients, tested positive for anti-daratumumab antibodies. This patient administered DARZALEX as combination therapy, developed transient neutralizing antibodies against daratumumab. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to daratumumab with the incidence of antibodies to other products may be misleading.

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding[1] *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

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

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no human data to inform a risk with use of DARZALEX during pregnancy. Animal studies have not been conducted. However, there are clinical considerations *[see Clinical Considerations].* 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.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. In cynomolgus monkeys exposed during pregnancy to other monoclonal antibodies that affect leukocyte populations, infant monkeys had a reversible reduction in leukocytes.

DARZALEX® (daratumumab) injection

Lactation

Risk Summary

There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for DARZALEX and any potential adverse effects on the breast-fed child from DARZALEX or from the underlying maternal condition.

Females and Males of Reproductive Potential

Contraception

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of DARZALEX treatment.

Pediatric Use

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

Geriatric Use

Of the 156 patients that received DARZALEX monotherapy at the recommended dose, 45% were 65 years of age or older, and 10% were 75 years of age or older. Of 561 patients that received DARZALEX with various combination therapies, 40% were 65 to 75 years of age, and 9% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients *[see Clinical Studies (14) in Full Prescribing Information].*

OVERDOSAGE

The dose of DARZALEX at which severe toxicity occurs is not known.

In the event of an overdose, monitor patients for any signs or symptoms of adverse effects and provide appropriate supportive treatment.

REFERENCES

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

PATIENT COUNSELING INFORMATION

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

Infusion Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion reactions:

- itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing *[see Warnings and Precautions and Adverse Reactions].*

Neutropenia

- Advise patients that if they have a fever, they should contact their healthcare professional *[see Warnings and Precautions and Adverse Reactions].*

Thrombocytopenia

- Advise patients to inform their healthcare professional if they notice signs of bruising or bleeding *[see Warnings and Precautions and Adverse Reactions].*

Interference with Laboratory Tests

Advise patients to inform healthcare providers including blood transfusion centers/personnel that they are taking DARZALEX, in the event of a planned transfusion *[see Warnings and Precautions and Drug Interactions].*

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

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Janssen Biotech, Inc.
Horsham, PA 19044
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063322-161115

Daratumumab-Based Combination Effective in Relapsed/Refractory Multiple Myeloma, Short PFS in Heavily Pretreated Patients

MANAGING HEAVILY PRETREATED, often less fit, patients with relapsed/refractory multiple myeloma (RRMM) is a challenge in routine practice, as illustrated by the fact progression-free survival (PFS) remains short, particularly in quadruple-refractory patients, although daratumumab-based combination therapies are proven effective. This conclusion, based on results of a single-center study, was presented during a poster session at the 2017 American Society of Clinical Oncology Annual Meeting.

Daratumumab-based combination therapies with bortezomib/lenalidomide/pomalidomide, and dexamethasone have shown exceptional activity in patients with RRMM in clinical trials. However, since the approval of daratumumab in 2015, experience outside of trials is limited.

Patients with RRMM who were seen at Mayo Clinic, Rochester, Minnesota, from 2015 to 2016, were reviewed. Those who received at least 1cycle of daratumumab-based combination therapies were included. Time-to-event analyses were performed from the date of starting daratumumab-based combination therapy, and common terminology criteria for adverse events v4.0 were used to grade toxicities. Of 130 patients, 59% were male, the median age at daratumumab-based combination therapy initiation was 67 years (range, 43-93), and the Eastern Cooperative Oncology Group performance score was ≥2 in 29% of patients.

Patients were classified as melanoma Stratification for Multiple and Risk-adapted Therapy (mSMART) high (22%), intermediate (22%), or standard (56%) risk. The median time from diagnosis to initiation of daratumumab-based combination therapy was 51.3 months (range, 5-156), and the median number of prior therapies was 4 (range, 1-14).

Daratumumab-based combination therapies are effective in relapsed/refractory multiple myeloma, but progression-free survival remains short, especially in quadruple-refractory patients.

Fourteen percent of patients were refractory to prior daratumumab monotherapy. Fifty-three (41%), 34 (26%), and 25 (19%) received daratumumab/pomalidomide/dexamethasone, daratumumab/lenalidomide/dexamethasone, and daratumumab/bortezomib/dexamethasone, respectively. Eighteen (14%) patients received "other" daratumumab-based combination therapies, according to the abstract.

Median time to first response (at least a partial response) was 3.1 months (95% CI, 2.1-4.6), with an overall response rate of 46% (complete response, 2%; *very good partial response,* 18%; and partial response, 26%). Seventeen percent of enrollees experienced a minimal response, with a clinical benefit rate of 62%.

The median estimated follow-up from initiation of daratumumab-based combination therapy was 5.5 months (95% CI, 4.2-6.1), the median duration of response was 6.1 months (95% CI, 5.1-not reached), median PFS was 5.5 (95% CI, 4.1-7.8) months, and the median time to next therapy was 5.9 months (95% CI, 4.6-9.4).

The Median PFS durations for daratumumab/pomalidomide/dexamethasone, daratumumab/lenalidomide/dexamethasone, daratumumab/bortezomib/dexamethasone, and other daratumumab-based combination therapy was 4.6 (95% CI, 2.7-not reached), 7.8 (95% CI, 5-not reached), 3.9 (95% CI, 2.1-not reached), and 3.9 (95% CI, 2.8-8.2) months, respectively ($P = .3$).

Median PFS for quadruple-refractory (n = 28) multiple myeloma (MM) was 2.8 (95% CI, 2.2-5.3) versus 5.9 (95% CI, 4.9-not reached) months ($P<.01$).

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Median overall survival from the start of daratumumab-based combination therapy was not reached (95% CI, 11.4 months-not reached). Grade 3 or higher hematological toxicities were seen in 42% of patients. Other toxicities included infections (37%), fatigue (31%), infusion reactions (16%), and diarrhea (10%).

The investigators concluded that daratumumab-based combination therapies are effective in RRMM, but PFS remains short, particularly in quadruple-refractory patients. These suboptimal outcomes illustrate the challenges encountered in managing heavily pretreated, and often less fit, patients in routine practice.

Daratumumab (Darzalex) is the first CD38-directed cytolytic antibody indicated[2,3]:

- In combination with lenalidomide and dexamethasone or bortezomib and dexamethasone for the treatment of patients with MM who have received at least 1 prior therapy (approved for this indication in 2016)
- In combination with pomalidomide and dexamethasone for the treatment of patients with MM who have received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor (approved for this indication in 2016)
- As monotherapy, for the treatment of patients with MM who have received at least 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent (approved for this indication in 2015)

Daratumumab was designated as a breakthrough therapy for the second and third indications above. The antibody is believed to induce tumor cell death through multiple immune-mediated mechanisms of action, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis, as well as through apoptosis, in which a series of molecular steps in a cell lead to its death. A subset of myeloid-derived suppressor cells, CD38+ regulatory T cells, and CD38+ B cells were decreased by daratumumab.[2,3]

REFERENCES

1. Lakshman A, Abeykoon JP, Kumar S, et al. Daratumumab-based combination therapies (DCT) in heavily-pretreated patients (pts) with relapsed and/or refractory multiple myeloma (RRMM). *J Clin Oncol.* 2017;35(suppl; abstract 8038).

2. Darzalex (daratumumab). Darzalex website. darzalexhcp.com. Revised June 2017. Accessed June 30, 2017.

3. Darzalex (daratumumab) approved by U.S. FDA in combination with two standard of care regimens for the treatment of patients with multiple myeloma who have received at least one prior therapy [press release]. Horsham, PA: Janssen Biotech Inc; November 21, 2016. jnj.com/media-center/press-releases/darzalex-daratumumab-approved-by-us-fda-in-combination-with-two-standard-of-care-regimens-for-the-treatment-of-patients-with-multiple-myeloma-who-have-received-at-least-one-prior-therapy. Accessed June 30, 2017.

Patient Selection Vital in Ensuring Improved Response to PD-1, PD-L1 Inhibitors in NSCLC

Surabhi Dangi-Garimella, PhD

A LATE AFTERNOON extended education session on day 1 of the 2017 American Society of Clinical Oncology Annual Meeting in Chicago became a discussion on state-of-the-art uses for immunotherapy in the management of non–small cell lung cancer (NSCLC). Oncologists shared their experiences with managing toxicities from immunotherapy and discussed the role of immunotherapy in specific patient populations.

Edward B. Garon, MD, director of the Thoracic Oncology Program and associate professor of medicine, David Geffen School of Medicine at University of California Los Angeles, spoke about using checkpoint inhibitors, primarily programmed death-1 (PD-1) inhibitors, in first-line therapy and sequencing these agents.

Garon discussed results from Keynote-024,[1] a phase 3 randomized controlled trial that compared pembrolizumab as frontline therapy with platinum-based chemotherapy in patients diagnosed with programmed death ligand-1 (PD-L1)–expressing advanced NSCLC (50% PD-L1 expression threshold). The primary study endpoint was progression-free survival (PFS). Despite patients who crossed over from pembrolizumab to chemotherapy, overall survival (OS) improved.

Checkmate-026,[2] which had a similar study design, compared first-line single-agent nivolumab versus chemotherapy. Crossover was allowed, and PFS was the primary endpoint. The main difference was that the PD-L1 expression cut-off was set at 5%, which encompasses a much broader patient population. Nivolumab, however, failed in the frontline setting compared with chemotherapy. "OS was not different in the 2 arms," Garon said.

He lined up a series of differences to explain the differential results:

- Failure of the randomized trial mechanism. The data showed that women were less likely to be on the nivolumab arm, as were patients with more than 50% PD-L1.
- Difference in efficacy
- Difference in the patient cohort:

    a. The most common clinical difference was the difference in radiotherapy. The Checkmate trial, Garon said, used a higher dose of radiation. "However, a single-institution study has shown that patients who may have received prior radiation may have done better."
    b. Use of PD-L1 expression. Selection of 50% cutoff for PD-L1 expression was used to select patients for pembrolizumab, as opposed to 5% for nivolumab.

Garon also highlighted a tumor's mutation burden: "[The] higher the mutation burden, [the] greater the benefit," he said. The take-home messages from his presentation were:

- Patients with staining in at least 50% of their tumor cells should be eligible for frontline pembrolizumab.
- Those with staining in less than half of their tumor cells should receive standard chemotherapy as frontline treatment.
- Adding nonselected therapy for each group remains a topic of debate

Melissa Lynne Johnson, MD, associate director of lung cancer research, Sarah Cannon Research Institute, addressed the conundrum of choosing a suitable immunotherapy agent. She explained that PD-1 and PD-L1 inhibitors are monoclonal antibodies. The interesting thing is that different PD-1 inhibitors bind different faces of the PD-L1 protein. "They also block different protein-protein interactions," which might result in differences in patient responses based on which drug is administered. Variability also arises from immunoglobulin G isotypes and antibody-dependent cell-mediated cytotoxicity (ADCC). "Avelumab is the only immunotherapy drug that has retained its ADCC function compared with nivolumab, durvalumab, pembrolizumab, and atezolizumab," Johnson said.

The PD-L1 assay used to assess protein expression also adds to the variability. Patient adverse events (AEs) associated with the treatment have varied, Johnson said: they have hovered around 76% for nivolumab, much higher than pembrolizumab (67.5%), atezolizumab (65%), durvalumab (60.6%), and avelumab (67%).

DANIEL F. HAYES, MD, FACP, FASCO, PRESIDENT, AMERICAN SOCIETY OF CLINICAL ONCOLOGY, DELIVERS HIS PRESIDENTIAL ADDRESS.

Compared with docetaxel for nonsquamous NSCLC, survival data in the second-line setting show that the median OS is 12.2 months for nivolumab, 10.4 months with pembrolizumab compared with 8.5 months, and 13.8 months for atezolizumab compared with 9.6 months. In the first-line setting, however, nivolumab has lagged behind pembrolizumab, Johnson showed. The median PFS for nivolumab is 4.2 months and 5.9 months for chemotherapy. Pembrolizumab has a median PFS of 10.3 months. The median OS for nivolumab is 14.4 months, and it has not yet been reached for pembrolizumab.

JOHNSON

Johnson emphasized that cost versus convenience is another question that both physicians and patients are concerned with. Nivolumab is administered every 2 weeks (both 240 and 3 mg/kg doses) and costs about $21,990 for a 6-week treatment, while pembrolizumab is administered once in 3 weeks (both 240 and 2 mg/kg doses) and costs about $21,662 over 6 weeks. She proposed evaluating these agents over a long treatment interval to lower costs and the inconvenience to patients of frequent administration.

Johnson summarized her presentation by saying that in the first-line setting, understanding the role of the tumor microenvironment might help understand the differences in patient response, as will identifying additional biomarkers. "Until then, [the] dosing schedule and cost will continue to play a significant part in oncologists' decision making." ◆

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An Early Stage Safety, Efficacy Study for Atezolizumab Plus Daratumumab in Advanced NSCLC

Surabhi Dangi-Garimella, PhD

AN EARLY STAGE INTERNATIONAL clinical trial is actively enrolling patients with relapsed, advanced or metastatic non–small cell lung cancer (NSCLC) to evaluate response to a combination of atezolizumab, the programmed death-ligand 1 (PD-L1) inhibitor, and daratumumab, an anti-CD38 antibody. A study at the 2017 Annual Meeting of the American Society of Clinical Oncology detailed the trial design for the phase 1b/2 study.[1]

Daratumumab is approved for the treatment of relapsed/refractory multiple myeloma (RRMM).[2] The therapy produces deep clinical responses in RRMM and induces T-cell expansion through reduction of immune suppressive cells. Atezolizumab was approved last year for metastatic NSCLC that failed to respond to platinum-based therapy,[3] following a review of data from the OAK and POPLAR trials.

Daratumumab induces T-cell expansion through a reduction of immune suppressive cells.

With the current study, the authors hypothesize that a combination of daratumumab and atezolizumab may improve clinical responses in previously-treated patients with NSCLC by enhancing anti-tumor T-cell responses facilitated by checkpoint inhibition. The early stage study has been designed to assess the anti-tumor activity and safety profile of the combination compared with atezolizumab alone in the above patient population.

Patient eligibility criteria, in addition to being older than 18 years, having an Eastern Cooperative Oncology Group status ≤1, and stage IIIb or IV advanced NSCLC, include:

- Known PD-L1 status
- No mutations in *ALK*, *EGFR*, and *ROS1*
- No prior treatment with daratumumab or other CD-30 therapies
- No prior treatment with CD137 agonists, immune-checkpoint inhibitors, and anti–PD-L1 therapies
- No active or untreated metastases to the central nervous system

The run-in safety cohort of 6 patients will receive 1200-mg intravenous (IV) atezolizumab in combination with 16-mg/kg IV daratumumab. The trial will be expanded to include 90 patients (randomly assigned to the 2 arms) if less than 2 patients experience dose-limiting toxicity. The atezolizumab arm will receive the drug on day 1 of every 21-day cycle; the combination arm will receive atezolizumab on day 2 of cycle 1 and day 1 of every 21-day cycle after that, along with daratumumab once weekly for cycles 1 to 3 and on day 1 of every 21-day cycle thereafter. Crossover is allowed if patients progress.

The primary endpoint is overall response rate. Secondary outcomes include safety, duration of response, clinical benefit rate (≥16 weeks duration), progression-free survival, overall survival, and pharmacokinetics and immunogenicity of the daratumumab-atezolizumab combination. ◆

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LDH Levels Could Predict irAEs Associated With Checkpoint Inhibition and Radiotherapy in Lung Cancer

Surabhi Dangi-Garimella, PhD

A STUDY PRESENTED BY researchers from Massachusetts General Hospital (MGH), which queried the effect of thoracic radiotherapy and immune checkpoint inhibition on the risk of pneumonitis or immune-related adverse events (irAEs), found that radiotherapy did not increase patient risk for pneumonitis. Additionally, the study, presented as a poster, found that elevated expression of lactate dehydrogenase (LDH) could be a predictor of grade 2 or higher irAEs.[1]

The newer immune checkpoint inhibitors have been documented to cause unique irAEs, which can result in patients dropping out of a treatment schedule.[2] Although an increased risk of pneumonitis is a known effect of thoracic radiotherapy, the authors of the current study were interested in evaluating the effect of the combination treatment on the risk of pneumonitis or other irAEs. The study also examined the importance of serum LDH in predicting irAEs associated with the immune checkpoint treatment.

Clinicopathological and response data on 164 patients who received treatment for metastatic lung cancer (95% non–small cell lung cancer and 5% small cell lung cancer) at MGH between 2013 and 2016, were retrospectively analyzed. Patient data included at least a 1-month follow-up, except in cases of rapid death from an irAE (n = 4); cohorts were formed based on receipt of thoracic radiotherapy.

Seventy-three patients received thoracic radiotherapy and 91 did not. Baseline characteristics such as age, gender, smoking status, supplemental oxygen requirement, median number of chemotherapy lines prior to immune checkpoint treatment (1 vs 1, respectively), median cycles of immune checkpoint treatment (5 vs 3), and median follow-up after immune checkpoint treatment initiation (8 months vs 7 months) were similar in the 2 cohorts.

Lactate dehydrogenase may be a negative predictor of grade 2 and higher immune-related adverse events.

The study found that the rates of grade 2 and higher irAEs (18.1 vs 14.4%; $P = .67$), all-grade pneumonitis (8.2 vs 5.5%; $P = .54$), and grade 2 and higher pneumonitis (4.1 vs 3.3%; $P = 1$) were not significantly different between the radiotherapy versus no radiotherapy cohorts, respectively. There was no difference between the mean thoracic radiotherapy dose either, between those patients who developed pneumonitis and those who did not (55.8 vs 55.9 Gy). About 85% of patients received the radiotherapy for a median 8.6 months before checkpoint inhibitor treatment. Of the 7 patients (10%) who had concurrent treatment, none developed symptomatic pneumonitis. Notably, patients with grade 2 and higher irAEs (n = 26) had significantly higher mean serum LDH before initiation of the checkpoint inhibitor treatment than patients who did not (283 IU/L vs 214 IU/L; ref 98 to 192 IU/L; $P = .03$).

The authors concluded that thoracic radiotherapy in patients with lung cancer who received immune checkpoint treatment was not associated with increased risk of pneumonitis and that LDH may be a negative predictive biomarker for grade 2 and higher irAEs. ◆

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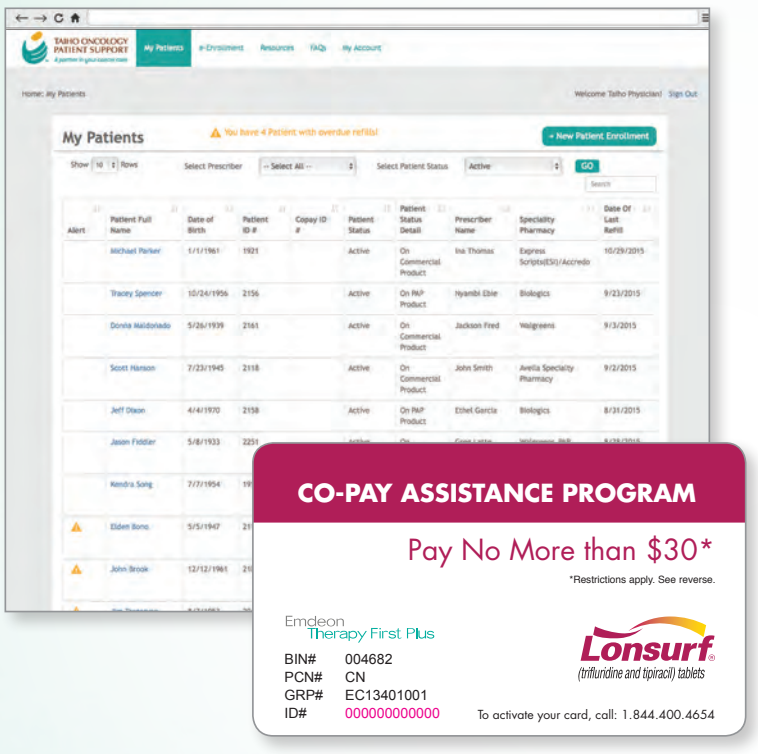

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Please see Important Safety Information and brief summary of Prescribing Information on the following pages.

Lonsurf® (trifluridine and tipiracil) tablets

TAIHO ONCOLOGY

Lonsurf®
(trifluridine and tipiracil) tablets

Indication

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

Important Safety Information

WARNINGS AND PRECAUTIONS

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

Hepatic Impairment: Patients with moderate or severe hepatic impairment were not enrolled in Study 1.

ADVERSE REACTIONS

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

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

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

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

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

Learn more at LONSURFhcp.com

TAIHO ONCOLOGY

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

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

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

4 CONTRAINDICATIONS
None.

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

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

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

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

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

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

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

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

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

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

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

Table 2 Laboratory Test Abnormalities

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

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

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

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

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

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

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

Data

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

8.3 Females and Males of Reproductive Potential

Contraception

Females

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

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

Males

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

8.4 Pediatric Use

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

Animal Data

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

8.5 Geriatric Use

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

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

8.6 Hepatic Impairment

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of LONSURF. No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin (TB) less than or equal to the upper limit of normal (ULN) and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST). Patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment were not enrolled in Study 1. *[*see *Clinical Pharmacology (12.3) in the full Prescribing Information]*

8.7 Renal Impairment

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

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

No dose adjustment to the starting dose of LONSURF is recommended in patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min); however patients with moderate renal impairment may require dose modification for increased toxicity. No patients with severe renal impairment (CLcr < 30 mL/min) were enrolled in Study 1. *[*see *Clinical Pharmacology (12.3) in the full Prescribing Information]*

8.8 Ethnicity

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

10 OVERDOSAGE

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

There is no known antidote for LONSURF overdosage.

17 PATIENT COUNSELING INFORMATION

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

Severe Myelosuppression:

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

Gastrointestinal toxicity:

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

Administration Instructions:

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

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

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

Embryo-Fetal Toxicity:

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

Lactation:

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

TAIHO ONCOLOGY, INC.

Alectinib May Be a New Standard of Care for Treatment-Naïve *ALK*-Positive NSCLC

AJMC Staff

ALECTINIB HAS SHOWN SUPERIOR efficacy and favorable tolerability compared with crizotinib in the primary results of the global phase 3 ALEX study in patients with treatment-naïve advanced anaplastic lymphoma kinase (*ALK*)-positive non–small cell lung cancer (NSCLC). This outcome was reported as a late-breaking abstract at the 2017 American Society of Clinical Oncology Annual Meeting.

Alectinib, a tyrosine kinase inhibitor that targets *ALK,* has shown robust efficacy in crizotinib-naïve/resistant *ALK*-positive NSCLC. Results of the J-ALEX trial demonstrated the superiority of alectinib 300 mg twice daily versus crizotinib in Japanese patients with crizotinib-naïve *ALK*-positive NSCLC (hazard ratio [HR] for progression-free survival [PFS,] 0.34; *P* <.0001).[1]

Primary results of the ALEX study of first-line alectinib, 600 mg twice daily, versus crizotinib in advanced *ALK*-positive NSCLC were reported. ALEX was an open-label, randomized, multicenter phase 3 trial that began in 2014 and was completed in 2017. The date for final data to be collected for analysis of PFS, the primary outcome measure, which was assessed every 8 weeks up to 33 months, was February 9, 2017.[2] The primary endpoint was investigator-assessed PFS according to Response Evaluation Criteria in Solid Tumors v1.1. Systematic central nervous system (CNS) imaging was performed in all patients.

Patients with stage 3B/4 *ALK*-positive NSCLC, as determined by central immunohistochemical testing, were enrolled in the study. Eligible patients scored 0-2 in Eastern Cooperative Group Performance Status and had received no prior systemic therapy for advanced NSCLC. Those with asymptomatic CNS metastases were eligible to participate. Patients (n = 303) were randomized 1:1 to alectinib 600 mg or crizotinib 250 mg, twice daily. Secondary endpoints included independent review committee–assessed PFS, independent review committee–assessed time to CNS progression, objective response rate (ORR), overall survival (OS), and safety.

At the primary data cut-off in February 2017, alectinib had demonstrated statistically significant superiority over crizotinib, having reduced risk of disease progression or death by 53% (HR, 0.47; 95% CI, 0.34-0.65; *P* <.0001). Median PFS for alectinib had not been reached (95% CI, 17.7-not estimable) versus 11.1 months for crizotinib (95% CI, 9.1-13.1). Key secondary endpoints showed superiority for alectinib versus crizotinib, respectively:

- HR for independent review committee–assessed PFS: 0.50 (95% CI, 0.36-70; *P*<.0001)
- Median PFS: 25.7 (95% CI, 19.9-not estimable) versus 10.4 (95% CI, 7.7-14.6) months
- Time to CNS progression, cause-specific HR of CNS progression: 0.16 (95% CI, 0.10-0.28; *P* <.0001)
- Investigator-assessed ORR: 83% (95% CI, 76%-89%) versus 76% (95% CI, 68%-82%; *P* = .09
- OS based on 25% events: HR, 0.76 (95% CI, 0.48-1.20; *P* = .24)

Grade 3/4 adverse events (AEs) were less frequent with alectinib than with crizotinib: 41% versus 50%, respectively. Fatal AEs occurred in 3% versus 5% of patients, respectively. Rates of AEs leading to discontinuation, dose reduction, and interruption were lower with alectinib.

The researchers concluded that alectinib showed superior efficacy and favorable tolerability compared with crizotinib and that the ALEX results support alectinib as a new standard of care for treatment-naïve *ALK*-positive NSCLC.

Alectinib (Alecensa) was approved in 2015 and is indicated for patients with *ALK*-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib. This indication was granted under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent on verification and description of clinical benefit in a confirmatory trial.[3,4]

A PACKED POSTER HALL AT THE ANNUAL MEETING.

The FDA designated the alectinib application as a breakthrough therapy and granted it priority review status. These distinct programs are intended to facilitate and expedite the development and review of certain new drugs in light of their potential to benefit patients with serious or life-threatening conditions.[3] Alectinib was also designated an orphan drug, a designation that provides incentives such as tax credits, user-fee waivers, and eligibility for exclusivity to assist and encourage the development of drugs for rare diseases.[3]

Alectinib is taken orally twice daily with food until disease progression or unacceptable toxicity.[4] ◆

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Dacomitinib a New First-Line Option for Advanced *EGFR* Mutation–Positive NSCLC

AJMC Staff

ARCHER 1050, the first phase 3 head-to-head study of epithelial growth factor receptor (EGFR) tyrosine kinase inhibition, has produced results that demonstrate statistically significant and clinically meaningful improvement with dacomitinib compared with gefitinib (Iressa) as first-line therapy for non–small cell lung cancer (NSCLC) with *EGFR*-activating mutations. These results were reported as a late-breaking abstract at the 2017 American Society of Clinical Oncology Annual Meeting.

Data collection for ARCHER 1050, which began in 2013, will be completed in July 2017, with an anticipated study completion date of September 2017. Collection of data for analysis of the primary outcome measure of progression-free survival (PFS) is 18 months after the anticipated first visit by the last subject.[1]

As reported by Jänne et al in 2014, dacomitinib is a second-generation EGFR tyrosine kinase inhibitor (TKI) with encouraging clinical activity as first-line therapy in patients with *EGFR*-activating mutation–positive advanced NSCLC.[2] NSCLC accounts for approximately 85% of cases of lung »

cancer and remains difficult to treat, particularly in the metastatic setting. Approximately 75% of patients are diagnosed late with metastatic disease,[3] and the 5-year disease survival rate is only 5%.[4]

EGFR mutations occur in 10% to 20% of nonsquamous NSCLC tumors overall and 35% to 55% of nonsquamous NSCLC tumors in Asian populations.[5,6] Patients with *EGFR*-mutant NSCLC generally experience a PFS of 9 to 13 months when treated with gefitinib or erlotinib (Tarceva), both EGFR TKIs. These treatments, along with afatinib (Gilotrif) are the only targeted therapies available to patients with *EGFR*-mutant NSCLC.[7] However, resistance issues with these agents have resulted in the need for more effective EGFR inhibitors.[2]

Dacomitinib is a covalent pan-human EGFR inhibitor that has shown clinical activity in patients previously treated with gefitinib or erlotinib.[2] An oral, once-daily drug, dacomitinib inhibits HER1/EGFR, HER2, and HER4 irreversibly by binding covalently to the receptor tyrosine kinase domains and preventing autophosphorylation, thereby inhibiting downstream signaling and leading to inhibition of tumor growth and apoptosis.

ARCHER 1050 is the first randomized phase 3 trial that compares dacomitinib with gefitinib as first-line therapy and is being conducted at sites across Asia and Europe. Patients with newly diagnosed stage 3B/4 recurrent NSCLC harboring an *EGFR*-activating mutation are randomized 1:1 to dacomitinib 45 mg orally every day or gefitinib 250 mg orally every day. Stratification is by race and subtype of *EGFR* mutation.

The primary endpoint of PFS is determined per blinded independent review analyzed by the Kaplan-Meier method, with log-rank test and Cox model. Secondary endpoints include overall survival (OS), objective response rate (ORR), duration of response, PFS per investigator, time to treatment failure, restricted mean survival time for PFS, safety, and patient-reported outcomes.

The intent-to-treat population included 452 patients with well-balanced baseline characteristics between arms. ORR, per independent review committee, has been similar between arms: 75% (95% CI, 69%-80%) for dacomitinib and 72% (95% CI, 65%-77%; $P = .39$); OS data is not yet mature.

The most commonly reported grade 3 adverse events with dacomitinib have been dermatitis acneiform (13.7%) and diarrhea (8.4%); with gefitinib, alanine aminotransferase (8.5%). No new safety signals have been identified.

The investigators concluded that the results of ARCHER 1050 have demonstrated statistically significant and clinically meaningful improvement in the efficacy of dacomitinib overgefitinib as first-line therapy for NSCLC with *EGFR*-activating mutations. The side effect profile has been manageable.

Lead investigator Tony Mok, MD, of the Chinese University of Hong Kong, said, "We changed the treatment paradigm for *EGFR*-positive lung cancer a few years ago when targeted therapy replaced chemotherapy. This study shows that dacomitinib may be an even more effective treatment for these patients. However, patients should be aware of the need to deal with potential side effects when making treatment decisions." ◆

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Androgen Deprivation, With or Without Radiotherapy, New Standard of Care in High-Risk Prostate Cancer

AJMC Staff

A CLINICALLY AND STATISTICALLY significant effect on overall survival (OS) and failure-free survival (FFS) from the addition of abiraterone at the start of androgen deprivation therapy (ADT) in men with high-risk prostate cancer was reported as a late-breaking abstract at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting. Abiraterone has shown a survival advantage in men with castration-refractory prostate cancer. The investigators queried whether abiraterone would exert an effect earlier in the disease.

Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE), a randomized controlled trial that employs a multi-arm, multistage platform design, was initiated in 2005 and will complete data collection for analysis of the primary outcome measures in September 2017. Patients with high-risk, locally advanced, or metastatic prostate cancer starting long-term androgen deprivation therapy are being recruited. The first comparative survival data were reported at ASCO.

The primary outcome measures include the safety of ADT alone versus ADT in combination with enzalutamide and abiraterone and/or radiotherapy to the prostate (and previously celecoxib, zoledronic acid, docetaxel, and abiraterone alone) in patients with locally advanced or metastatic prostate cancer, FFS, and OS.[1] The study will determine which treatment is cost-effective. More than 5000 patients have participated and answers have become available over 7 to 12 years.[1]

The standard of care was ADT for ≥2 years. Radiotherapy was mandated for men with N0M0 disease and encouraged for those with N+M0. Stratified randomization allocated patients 1:1 to standard of care or standard of care with abiraterone (1000 mg) and prednisolone (5 mg) daily. Treatment duration depended on stage and intent to administer radical radiotherapy. In patients not receiving radiotherapy or with M1 disease, treatment continued until progression as determined by prostate specific antigen (PSA) level, imaging, and clinical determination. Otherwise, treatment continued until the earlier of 2 years or all types of progression.

Among the 1917 patients, randomized from 2011 to 2014, the median age was 67 years, 52% were metastatic, 20% had N+/XM0 disease, 28% had N0M0 disease, and the median PSA was 53 ng/mL. Over 40-months of median follow-up, 262 deaths occurred in the control arm (82% from prostate cancer).

For standard of care plus abiraterone versus standard of care alone, the adjusted hazard ratio (HR) was 0.63 (95% CI, 0.52-0.76; $P = .115\ 10^{-7}$; 184 deaths), with 3-year OS improved from 76% to 83%. A total of 535 FFS events occurred in the control arm. The adjusted HR was 0.29 (95% CI, 0.25 - 0.34; $P = .377\ \ 10^{-63}$, 248 FFS events) for standard of care plus abiraterone versus standard of care alone.

Grade 3 adverse events (AEs) were noted in 29% and 3% of patients who received standard of care alone versus standard of care plus abiraterone, respectively; grade 4 AEs in 41% and 5% of patients, respectively; and grade 5 AEs in 3% and 9% of patients, respectively (1% and 2%, respectively, related to the drug,).

The researchers concluded that the addition of abiraterone at the start of ADT resulted in a clinically and statistically significant effect on OS and FFS, with a manageable increase in toxicity. ADT with or without radiotherapy has been shown to be a new standard of care in men with high-risk prostate cancer.

Abiraterone acetate is a selective, irreversible inhibitor of CYP17. Androgen depletion with CYP17 inhibition plus ADT is more effective than surgical castration or gonadotropin releasing hormone analogues alone.[2] ◆

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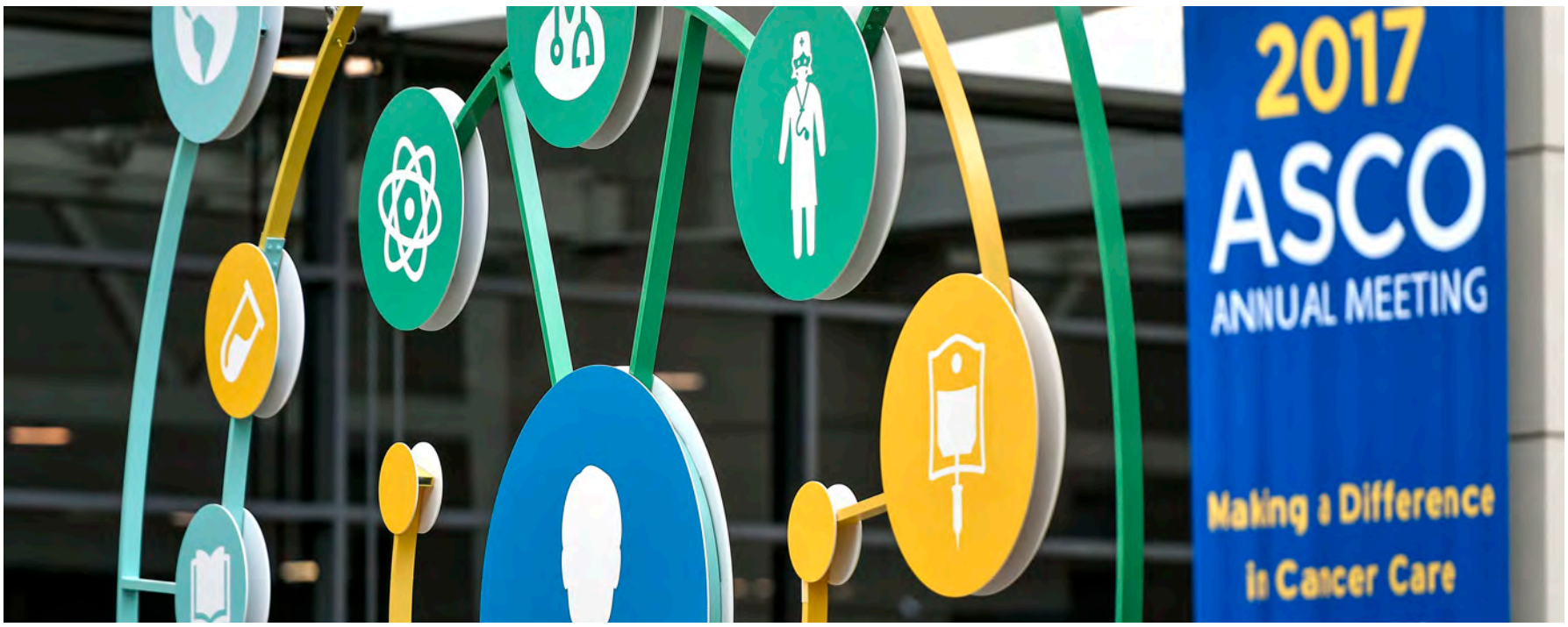

THE MEETING EMPHASIZED THE IMPORTANCE OF CARE COLLABORATION.

Trabectedin and Lurbinectedin Effective in *BRCA2*-Associated Metastatic Breast Cancer

AJMC Staff

AN INTERIM ANALYSIS OF TWO phase 2 trials has found that trabectedin and lurinectedin demonstrated remarkable activity as single agents in *BRCA2*-associated metastatic breast cancer, with 33% clinical response with trabectedin and 61% with lurbinectedin. Results of the analysis were reported in a poster session at the 2017 American Society of Clinical Oncology Annual Meeting.[1]

BRCA1- and *BRCA2*-associated breast cancers share homologous recombination deficiency, but also play independent and potentially actionable roles. Novel drugs with innovative mechanisms of action, which lack cross-resistance with other commonly used agents, are needed for treating this subgroup of patients with metastatic breast cancer.

Trabectedin and its analog, lurbinectedin, have demonstrated activity in *BRCA1*- and *BRCA*2-associated metastatic breast cancer. The present study sought to determine any difference in activity between these agents in *BRCA1* vs *BRCA2* mutation carriers. Both, safety and efficacy of single-agent trabectedin and lurbinectedin were analyzed in two separate phase 2 trials.

Trabectedin (Yondelis) is a multimodal, synthetically produced antitumor agent, originally derived from the sea squirt, *Ecteinascidia turbinata*. The drug exerts its activity by targeting the transcriptional machinery and impairing DNA repair. It is approved in close to 80 countries in North America, Europe, South America, and Asia for advanced soft tissue sarcomas as a single agent and for relapsed ovarian cancer in combination with doxorubicin hydrochloride liposome injection in the European Union.[2]

Lurbinectedin (Zepsyre) is an inhibitor of RNA polymerase II—an essential component of the transcription process that is overactivated in tumors with transcription addiction. The antitumor efficacy of lurbinectedin is being investigated in various types of solid tumors, including platinum-resistant ovarian cancer (phase 3 trial), *BRCA1*- and *BRCA2*-associated metastatic breast cancer (phase 2 trial), and small-cell lung cancer (phase 3 trial).[2]

Eighty-eight patients were evaluated in the present trial: 34 received trabectedin and 54 lurbinectedin. The median age was 46 years and 43 years, respectively. Patients who received trabectedin had received a median (range) of 4 (1-10) lines of chemotherapy. Those who received lurbinectedin had received 2 (0-5) lines. Trabectedin was given at a dose of 1.3 mg/m^2 on day 1, every 3 weeks. The 7 mg full dose of lurbinectedin was given at 3.5 mg/m^2 on day 1, every 3 weeks.

Clinical responses were seen in the 2 trials and were higher in *BRCA2* than in *BRCA1* carriers (trabectedin 33% vs 9% and lurbinectedin 61% vs 26%, respectively). The main adverse event was myelosuppression (grade 3/4 neutropenia/thrombocytopenia/febrile neutropenia: trabectedin, 62.1%/24.3%/10.8%, lurbinectedin, 66.7%/20.4%/20.4%).

Nonhematological toxicity was mostly grade 1/2 fatigue, nausea/vomiting, and high transaminases. Grade 3/4 nonhematological toxicity was reported in 40.5% of patients who received trabectedin and 18.5% of those who received lurbinectedin.

The trial of lurbinectedin began in 2012 and final data for analysis of the primary outcome measure will be collected in December 2018. The primary outcome measure is overall response rate over a minimum of 10-12 months if results are negative and up to 26 to28 months if targeted enrollment is completed.[2]

Overall response rate is defined as the percentage of patients with confirmed response (complete or partial response per Response Evaluation Criteria in Solid Tumors v1.1.).[3] Secondary outcome measures are progression-free survival (PFS) and overall survival (OS) over 36 months.

PFS is defined as the duration from first infusion to progressive disease, death due to any cause, or last tumor evaluation. OS rate at 1 year is defined as the estimated probability of patients to remain alive at 1 year. OS is defined as the duration from first infusion to death or last contact.[3]

The investigators concluded that trabectedin and lurbinectedin demonstrated remarkable activity as single agents against *BRCA2*-associated metastatic breast cancer in this interim analysis. The finding warrants further investigation. A potential mechanistic rationale is the role of lurbinectedin and that of *BRCA2* in transcription. Safety was acceptable and manageable in both studies. ◆

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CLINICAL / ORAL CANCER

HPV Vaccination May Lower Prevalence of Oropharyngeal Cancers in Young Adults

Surabhi Dangi-Garimella, PhD

ONE OF THE FASTEST GROWING CANCERS among young men in the United States, the incidence of human papilloma virus (HPV)-positive oropharyngeal cancer can be reduced with a prophylactic vaccine. These are the findings of a collaborative study that was presented at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago.

Data from the National Health and Nutrition Examination Survey (NHANES) found that for the period between 2011 and 2014, the prevalence of oral HPV was 7.3% for adults aged 18 to 69 years, while high-risk HPV came in at 4%. The absence of any specific disease symptoms makes it difficult to identify infected individuals and, thereby, easier to transmit the disease.

HPV vaccines are recommended for cancer prevention. The CDC updated its vaccination recommendations late in 2016, stating that 11- to 12-year-old children should be administered 2 doses of the 9-valent HPV vaccine 6 months apart and adolescents and young adults, 15 years and older, should receive 3 doses. The recommendation subsequently gained support from 69 National Cancer Institute–designated cancer centers.[1]

Maura L. Gillison, MD, PhD, a head and neck medical oncologist and molecular epidemiologist at The Ohio State University and study co-author, said during a pre-meeting press cast organized by ASCO that there have not been any trials evaluating whether currently approved vaccines can prevent HPV infections, especially in the younger population. The objective, therefore, "was to evaluate the impact of HPV vaccination on oral HPV infections among young adults in the United States," she said.

"The HPV vaccine may reduce oral HPV infections. However, clinical trials would be needed to demonstrate a cause-effect relation between vaccination and the extent of oral HPV infections."

-Maura L. Gillison, MD, PhD

For their present study,[2] the authors used data from the NHANES study to retrospectively analyze the impact of a prophylactic vaccination on the incidence of oral HPV infections among US men and women between 18 and 33 years of age (n = 2627). The exposure was the receipt of 1 or more doses (self-reported) of 4 vaccine types—16, 18, 6, and 11—or not. The authors also examined the percent reduction in infection prevalence among vaccinated individuals and the population-level effectiveness of vaccination.

The authors found that 18.3% of the study cohort reported receiving at least 1 dose of an HPV vaccine prior to age 26. This included 29.2% of women and 6.9% of men. Oral HPV 16/18/6/11 infections were significantly lower in the vaccinated population (0.11%) compared with unvaccinated individuals (1.61%; $P = .008$). The impact was even more dramatic among men: 0.0% versus 2.1% ($P = .007$) in the vaccinated versus the unvaccinated population, respectively. On the other hand, the prevalence of nonvaccine HPV was similar between the 2 populations overall (3.98% versus 4.74%; $P = .24$), the authors noted. Based on their analysis, the authors estimated an 88% overall reduction in vaccine-type infections and a 100% reduction among young adult men, the authors concluded.

"The HPV vaccine may reduce oral HPV infections," Gillison said. "However, clinical trials would be required to demonstrate a cause-effect relation between vaccination and the extent of oral HPV infections." ◆

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CLINICAL / COLORECTAL CANCER

Physical Activity, Healthy Diet Improve Survival in Colorectal Cancer: Study at ASCO

Surabhi Dangi-Garimella, PhD

A COLLABORATIVE STUDY, conducted at various cancer institutions across the United States, evaluated the impact of following the 2012 American Cancer Society Nutrition and Physical Activity Guidelines[1] for Cancer Survivors and concluded that patients with colon cancer who had a healthy body weight, who engaged in physical activity, and ate a healthy diet had longer overall (OS) and disease-free survival (DFS). Results from the 7-year median follow-up were presented at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago.[2]

More than 1.3 million individuals in the United States have been diagnosed with colorectal cancer (CRC). With the ACS' release of its guidelines for CRC survivors, the authors were curious to find out if they improved outcomes among patients who adhered to them. The prospective study included 992 patients with stage III colon cancer who received adjuvant chemotherapy between 1999 and 2001. Researchers assessed lifestyle twice and assigned a score, known as the McCullough score, that quantified patient adherence to the guidelines (**Table**) in the context of their body mass index, physical activity, and a diet of vegetables, whole grains, and red or processed meats. While alcohol was included in the guideline for cancer prevention, it was not included in the survivor guide. However, the authors included it in calculating the McCullough score.

TABLE. Healthy Lifestyle Recommendations

Recommendation	Score
Achieve and maintain a healthy body weight	0: BMI ≥30 kg/m² (obese)
	1: BMI ≥25 to <30 kg/m² (overweight)
	2: 0: BMI 18.5 to < 25 kg/m² (normal weight)
Regular physical activity	0: <8.75 MET-hours/week
	1: 8.75- <17.5 MET-hours/week
	2: ≥17.5 MET-hours/week
Dietary pattern high in vegetables, fruits, and whole grains; low in red and processed meat	0: 0-2 diet points
	1: 3-6 diet points
	2: 7-9 diet points
Alcohol, up to 1/day (women) or 2/day (men)	0: >1/day 9w, >2/day (men)
	1: nondrinker
	2: up to 1/day (women), 2/day (men)

BMI indicates body mass index; MET, metabolic equivalent of task.

The study documented 335 recurrences and 299 deaths (43 without recurrence) during the follow-up period. Patients who scored between 5 and 6 points (91; 9%) had a 42% lower risk of death (HR, 0.58; 95% CI, 0.34-0.99) compared with those who scored between 0 and 1 (262; 26%). The higher-scoring group of patients also had a better DFS (HR, 0.69; 95% CI, 0.45-1.06) compared with their lower-scoring counterparts. Including alcohol intake in the score further reduced the hazard if the patients were moderate consumers.

Based on their results, the authors concluded that patients with CRC with higher lifestyle scores had a lower risk of death. Meaning, those who had a healthy body weight; engaged in regular physical activity; ate a diet rich in fruits, vegetables, whole grains, and low in processed and red meats; and drank small to moderate amounts of alcohol had longer DFS and OS compared with those patients who did not. ◆

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For prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of chemotherapy

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Indication

AKYNZEO is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. AKYNZEO is an oral fixed combination of palonosetron and netupitant: palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.

Important Safety Information

Warnings and Precautions

- Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other 5-HT_3 receptor antagonists
- Serotonin syndrome has been reported with 5-HT_3 receptor antagonists alone but particularly with concomitant use of serotonergic drugs. Serotonin syndrome can be life threatening. Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms. Patients should be monitored for the emergence of serotonin syndrome, and if symptoms occur, discontinue AKYNZEO and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if AKYNZEO is used concomitantly with other serotonergic drugs

Adverse Reactions

- Most common adverse reactions: headache, asthenia, dyspepsia, fatigue, constipation and erythema

Drug Interactions

- Use with caution in patients receiving concomitant medications primarily metabolized by CYP3A4. The plasma concentrations of CYP3A4 substrates can increase when co-administered with AKYNZEO. The inhibitory effect on CYP3A4 can last for multiple days
  - — Dexamethasone doses should be reduced when given with AKYNZEO. A two-fold increase in the systemic exposure of dexamethasone was observed 4 days after single dose of netupitant
  - — Consider the potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) when administering with AKYNZEO. When administered with netupitant, the systemic exposure to midazolam was significantly increased
- Avoid concomitant use of AKYNZEO in patients on chronic use of a strong CYP3A4 inducer such as rifampin as this may decrease the efficacy of AKYNZEO

Use in Specific Populations

- Avoid use of AKYNZEO in patients with severe hepatic impairment, severe renal impairment, or end-stage renal disease

Please see brief summary of Full Prescribing Information on the following page.
To report SUSPECTED ADVERSE REACTIONS, contact Helsinn at 1-855-541-3498 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

*Multicenter, randomized, double-blind, double-dummy, parallel-group study. Primary endpoint: complete response (no emesis and no use of rescue medication) in the overall phase (0-120 hours). Patients received cisplatin (≥50 mg/m^2 either alone or in combination with other chemotherapy agents). Randomization: AKYNZEO plus oral dexamethasone (dex) 12 mg on Day 1, followed by oral dex 8 mg once daily on Days 2-4, or oral palonosetron 0.5 mg plus oral dex 20 mg on Day 1, followed by oral dex 8 mg twice daily on Days 2-4.[1,3]

CINV=chemotherapy-induced nausea and vomiting.

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HELSINN

AKYNZEO® (netupitant and palonosetron) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

DOSAGE AND ADMINISTRATION

Highly Emetogenic Chemotherapy, including Cisplatin Based Chemotherapy

The recommended dosage in adults is one capsule of AKYNZEO administered approximately 1 hour prior to the start of chemotherapy with dexamethasone 12 mg administered orally 30 minutes prior to chemotherapy on day 1 and 8 mg orally once daily on days 2 to 4.

Anthracyclines and Cyclophosphamide Based Chemotherapy and Chemotherapy Not Considered Highly Emetogenic

The recommended dosage in adults is one capsule of AKYNZEO approximately 1 hour prior to the start of chemotherapy with dexamethasone 12 mg administered orally 30 minutes prior to chemotherapy on day 1. Administration of dexamethasone on days 2 to 4 is not necessary.

AKYNZEO can be taken with or without food.

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other 5-HT_3 receptor antagonists.

Serotonin Syndrome: The development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT_3 receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT_3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of AKYNZEO and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue AKYNZEO and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if AKYNZEO is used concomitantly with other serotonergic drugs.

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 overall safety of AKYNZEO was evaluated in 1538 cancer patients and healthy volunteers in clinical trials. The data described below reflect exposure to AKYNZEO in 1169 cancer patients, receiving at least one cycle of cancer chemotherapy in 3 active-controlled trials, including 782 exposed to AKYNZEO for at least 4 cycles and 321 exposed for at least 6 cycles, up to a maximum of 12 cycles of chemotherapy. The median age was 55, 79% were female, 83% were White, 13% were Asian, and 4% were Hispanic. All patients received a single oral dose of AKYNZEO 1 hour prior to the start of each chemotherapy cycle. In all studies, dexamethasone was co-administered with AKYNZEO.

Cisplatin Based Highly Emetogenic Chemotherapy: In a single-cycle study of patients receiving cisplatin-based highly emetogenic chemotherapy, 136 patients were treated with AKYNZEO. Table 1 shows adverse reactions defined as adverse events reported at an incidence of at least 3% and for which the AKYNZEO rate exceeded palonosetron alone.

Table 1: Adverse Reactions Occurring in ≥3% of Cancer Patients Receiving AKYNZEO and Cisplatin Based Highly Emetogenic Chemotherapy (Cycle 1)

Adverse Reactions	AKYNZEO netupitant 300 mg/ palonosetron 0.5 mg (N=136)	Palonosetron 0.5 mg (N=136)
Dyspepsia	4%	2%
Fatigue	4%	2%
Constipation	3%	1%
Erythema	3%	2%

Anthracyclines and Cyclophosphamide Based Chemotherapy: In a study of patients receiving anthracycline and cyclophosphamide based chemotherapy, 725 patients were treated with AKYNZEO during Cycle 1, and 635 of these patients continued for up to 8 cycles in a multiple-cycle extension. Table 2 shows adverse reactions defined as adverse events reported at an incidence of at least 3% and for which the AKYNZEO rate exceeded palonosetron alone during Cycle 1. The adverse reaction profile in subsequent cycles was similar to that observed in Cycle 1.

Table 2: Adverse Reactions Occurring in ≥3% of Cancer Patients Receiving AKYNZEO and Anthracyclines and Cyclophosphamide Based Chemotherapy (Cycle 1)

Adverse Reactions	AKYNZEO netupitant 300 mg/ palonosetron 0.5 mg (N=725)	Palonosetron 0.5 mg (N=725)
Headache	9%	7%
Asthenia	8%	7%
Fatigue	7%	5%

In addition to the adverse reactions shown above, there were reports of concomitant elevations of transaminases > 3 x ULN and total bilirubin in both arms of the two trials that compared AKYNZEO to oral palonosetron, and the frequency of these elevations was comparable between treatment groups. See Table 3.

Table 3: Liver Function Laboratory Abnormalities

Laboratory Changes	AKYNZEO netupitant 300 mg/palonosetron 0.5 mg (N=861)	Palonosetron 0.5 mg (N=861)
AST > 3 x ULN and/or ALT > 3 x ULN with Total Bilirubin > ULN	3 (0.3%)	5 (0.6%)
AST > 10 x ULN and/or ALT > 10 x ULN with Total Bilirubin > ULN	–	2 (0.2%)
AST > 3 x ULN and/or ALT > 3 x ULN with Total Bilirubin ≥ 2 x ULN	1 (0.1%)	1 (0.1%)

In a multi-cycle safety study of 412 patients, the safety profile of AKYNZEO (n = 308) was comparable to aprepitant and palonosetron (n = 104) in patients undergoing initial and repeat cycles (median 5 cycles, range of 1-14 cycles) of chemotherapy, including carboplatin, cisplatin, oxaliplatin, and doxorubicin regimens. There were no reports of concomitant elevations of transaminases > 3 x ULN and total bilirubin in this study in either arm.

In a randomized, clinical non-inferiority study, that compared oral palonosetron 0.5 mg to intravenous palonosetron 0.25 mg in cancer patients scheduled to receive highly emetogenic cisplatin (≥70 mg/m^2) based chemotherapy, there were two patients (0.5%; 2/369) in the intravenous palonosetron arm who had concomitant elevations of transaminases and total bilirubin. Neither experienced transaminase elevations of > 10 x ULN.

DRUG INTERACTIONS

Effects of AKYNZEO on other drugs

Interaction with CYP3A4 substrates:

Netupitant, a component of AKYNZEO is a moderate inhibitor of CYP3A4.

AKYNZEO should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. The plasma concentrations of CYP3A4 substrates can increase when co-administered with AKYNZEO. The inhibitory effect on CYP3A4 can last for multiple days.

Dexamethasone: A two-fold increase in the systemic exposure of dexamethasone was observed 4 days after single dose of netupitant. The duration of the effect was not studied beyond 4 days. Administer a reduced dose of dexamethasone with AKYNZEO.

Midazolam: When administered with netupitant, the systemic exposure to midazolam was significantly increased. Consider the potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) when administering these drugs with AKYNZEO.

Interaction with chemotherapeutic agents: The systemic exposure of chemotherapy agents metabolized by CYP3A4 can increase when administered with AKYNZEO. Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. Caution and monitoring for chemotherapeutic related adverse reactions are advised in patients receiving chemotherapy agents metabolized primarily by CYP3A4.

Interaction with oral contraceptives: Clinically significant effect of AKYNZEO on the efficacy of the oral contraceptive containing levonorgestrel and ethinyl estradiol is unlikely.

Effects of other drugs on AKYNZEO

Netupitant, a component of AKYNZEO is mainly metabolized by CYP3A4.

In vitro metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron.

CYP3A4 Inducers: Avoid concomitant use of AKYNZEO in patients who are chronically using a strong CYP3A4 inducer such as rifampin. A strong CYP3A inducer can decrease the efficacy of AKYNZEO by substantially reducing plasma concentrations of the netupitant component.

CYP3A4 Inhibitors: Concomitant use of AKYNZEO with a strong CYP3A4 inhibitor (e.g., ketoconazole) can significantly increase the systemic exposure to the netupitant component of AKYNZEO. However, no dosage adjustment is necessary for single dose administration of AKYNZEO.

Serotonergic Drugs: Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT_3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs)

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Risk Summary: Adequate and well-controlled studies with AKYNZEO have not been conducted in pregnant women. In animal reproduction studies, no effects on embryo-fetal development were observed following daily administration of netupitant in pregnant rats during the period of organogenesis at doses up to 3.7 times the human AUC (area under the plasma concentration-time curve) at the recommended single human dose to be given with each cycle of chemotherapy. However, a dose-dependent increase in adverse effects on embryo-fetal development was observed following daily administration of netupitant in pregnant rabbits during the period of organogenesis with doses at least 0.2 times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy. Daily administration of netupitant in rats up to 3.7 times the human AUC at the recommended human dose during organogenesis through lactation produced no adverse effects in the offspring. In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed following oral administration during the period of organogenesis at doses up to 921 and 1841 times the recommended human oral dose in rats and rabbits, respectively. AKYNZEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data: Daily administration of up to 30 mg/kg netupitant in rats (3.7 times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy) during the period of organogenesis produced no effects on embryo-fetal development. However, an increased incidence of external and skeletal abnormalities in rabbit fetuses was observed following daily administration of netupitant in rabbits at 10 mg/kg/day and higher (0.2 times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy) during the period of organogenesis. These abnormalities included positional abnormalities in the limbs and paws, and fused sternebrae. Reduction in fetal rabbit weight occurred at 30 mg/kg/day. Maternal toxicity in rabbits (i.e. loss of bodyweight during the treatment period) was also observed at 30 mg/kg/day. Daily administration of up to 30 mg/kg netupitant (3.7 times the human AUC at the recommended human dose) in rats during organogenesis through lactation produced no adverse effects in the offspring.

In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed in pregnant rats given oral doses up to 60 mg/kg/day (921 times the recommended human oral dose based on body surface area) or pregnant rabbits given oral doses up to 60 mg/kg/day (1841 times the recommended human oral dose based on body surface area) during the period of organogenesis.

Nursing Mothers: It is not known whether AKYNZEO is present in human milk. Because many drugs are present in human milk and because of the potential for tumorigenicity shown for palonosetron in the rat carcinogenicity study, 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.

Pediatric Use: Safety and effectiveness in patients below the age of 18 years have not been established.

Geriatric Use: Of the 1169 adult cancer patients treated with AKYNZEO in clinical studies, 18% were aged 65 and over, while 2% were aged 75 years and over. The nature and frequency of adverse reactions were similar in elderly and younger patients. Exploratory analyses of the impact of age on efficacy were performed in the two trials that compared AKYNZEO to palonosetron. In Study 1 in patients treated with cisplatin chemotherapy, among the patients less than age 65 years, 115 were treated with AKYNZEO and 116 were treated with palonosetron alone. Among the patients 65 years or older, 20 were treated with AKYNZEO and 20 were treated with palonosetron alone. The difference in Complete Response (CR) rates between AKYNZEO and palonosetron alone was similar between the two age groups in both the acute and delayed phases. In Study 2 in patients treated with anthracyclines plus cyclophosphamide chemotherapy, among the patients less than age 65 years, 608 were treated with AKYNZEO and 602 were treated with palonosetron alone. Among the patients 65 years or older, 116 were treated with AKYNZEO and 123 were treated with palonosetron alone. The difference in CR rates between AKYNZEO and palonosetron alone (4% in <65 years and 2% in ≥65 years) was similar between the two age groups in the acute phase. In the delayed phase, the difference in CR rates between AKYNZEO and palonosetron alone (9% in <65 years and 1% in ≥ 65 years) was numerically higher in patients <65 years. This difference between age groups in the delayed phase of Study 2 may be explained, in part, by higher CR in the delayed phase associated with palonosetron alone in the older age group (81%) relative to the younger patients treated with palonosetron alone (67%).

In general, use caution when dosing elderly patients as they have a greater frequency of decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy.

Hepatic Impairment: No dosage adjustment for AKYNZEO is necessary for patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 8). Limited data are available with AKYNZEO in patients with severe hepatic impairment (Child-Pugh score >9)/ Avoid use of AKYNZEO in patients with severe hepatic impairment.

Renal Impairment: No dosage adjustment for AKYNZEO is necessary in patients with mild to moderate renal impairment. The pharmacokinetics and safety of netupitant has not been studied in patients with severe renal impairment, although severe renal impairment did not substantially affect pharmacokinetics of palonosetron. The pharmacokinetics for netupitant and palonosetron was not studied in patients with end-stage renal disease requiring hemodialysis.

OVERDOSAGE: No specific information is available on the treatment of overdosage with AKYNZEO. In the event of overdose, AKYNZEO should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of AKYNZEO, drug-induced emesis may not be effective. Dialysis studies have not been performed; due to the large volume of distribution, dialysis is unlikely to be an effective treatment for AKYNZEO overdose.

A total of 33 adult cancer patients were administered oral palonosetron at a dose of 90 µg/kg (equivalent to 6 mg fixed dose), as part of a dose ranging study. This is approximately 12 times the recommended oral dose of 0.5 mg palonosetron. This dose group had a similar incidence of adverse events compared to the other dose groups and no dose response effects were observed. The highest dose of netupitant administered to 1169 cancer patients was 300 mg. The highest dose of netupitant administered to 49 healthy subjects was 600 mg. A similar incidence of adverse events was observed when compared to lower doses of netupitant in the respective populations of cancer patients and healthy subjects.

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HELSINN

Three Months of Oxaliplatin-Based Adjuvant Therapy Noninferior to 6 Months in Stage III Colon Cancer

AJMC Staff

In a prospective pooled analysis of 6 phase 3 trials investigating the duration of adjuvant oxaliplatin-based therapy (3 vs 6 months) for patients with stage III colon cancer, noninferiority was not established for the overall cohort, but noninferiority of 3 versus 6 months oxaliplatin-based adjuvant therapy was supported for capecitabine plus oxaliplatin (XELOX). This outcome from the International Duration Evaluation of Adjuvant chemotherapy (IDEA) collaboration was reported in a plenary session at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting.[1]

Since 2004, 6 months of oxaliplatin-based treatment has been the standard of care as adjuvant therapy for stage III colon cancer. Oxaliplatin is associated with cumulative neurotoxicity, so a shorter duration of adjuvant therapy could spare patients toxicity and lead to substantial reductions in health expenditure.

A prospective, preplanned pooled analysis of 6 concurrently conducted randomized phase 3 trials conducted in North America, Europe, and Asia was performed to evaluate the noninferiority of 3 versus 6 months of adjuvant 5-fluorouracil and oxaliplatin (FOLFOX/XELOX).

The primary endpoint was disease-free survival (DFS), defined as time from enrollment to relapse, second colorectal cancer, and death from all causes. Noninferiority was to be declared if the 2-sided 95% confidence interval (CI) for hazard ratio (HR) for DFS (3 vs 6 months) was below 1.12. Noninferiority was examined within regimen and stage subgroups as planned.

The analysis included 12,834 patients from 12 countries, accrued from 2007 to 2015. Axel Grothey, MD, of Mayo Clinic Cancer Center, Rochester, Minnesota, said, "We needed this large number of patients to answer the study question, but at the time this study began in 2007 it was not possible to run one study of that size anywhere in the world. With more than 12,834 patients, this is the largest collaboration of its kind in oncology."[1]

Stage distribution was:
- 13% T1-T2
- 66% T3
- 21% T4
- 28% N2

Forty percent of patients received XELOX. Grade ≥3 neurotoxicity was higher in the 6- than in the 3-month arm (16% vs 3% FOLFOX, 9% vs 3% XELOX, $P<.0001$).

After a median follow-up of 39 months, 3263 DFS events were observed. Overall, the 3-year DFS rate was 74.6% (3 months) and 75.5% (6 months), with estimated HR for DFS of 1.07 (95% CI, 1.00-1.15).

HRs for 3- versus 6-month DFS were 1.16 (95% CI 1.06 - 1.26) and 0.95 (95% CI, 0.85-1.06) for FOLFOX- and XELOX-treated patients, respectively. HRs for 3- vs 6-month DFS were 1.01 (95% CI, 0.90-1.12) in T1-3 N1 and 1.12 (95% CI, 1.03-1.23) for T4 or N2 patients.

A central side effect of oxaliplatin is nerve damage, which can result in permanent numbness, tingling, and pain. The longer a patient receives oxaliplatin, the higher the risk of severe and long-lasting nerve damage. Nerve damage (numbness/tingling of the hands and feet) was substantially less common in patients receiving a 3-month course of chemotherapy versus a 6-month month course (15% vs 45% with FOLFOX and 17% vs 48% with XELOX).

"Many side effects of chemotherapy, such as hair loss, go away over time, but nerve damage is a side effect some patients have to deal with for the rest of their lives," said Grothey.[2]

The investigators concluded that, while noninferiority was not established for the overall cohort, noninferiority of 3 versus 6 months of oxaliplatin-based adjuvant therapy was supported for XELOX. Each IDEA trial treated varying proportions of patients with XELOX (0%-75%), so the interaction among regimens likely produced the differential outcomes observed between individual studies.

Certain substages (T1-3 N1) also showed noninferiority for 3 versus 6 months. The data provide a framework for discussions on risks and benefits of individualized approaches to adjuvant therapy.

Grothey a, "Our findings could apply to about 400,000 colon cancer patients worldwide every year. For 60% of these patients, who are at lower risk for cancer recurrence, 3 months of chemotherapy will likely become the new standard of care. Patients with higher-risk colon cancer, however, should discuss these results with their doctor to determine whether a shorter course of therapy would be right for them, taking into account their preference, age, and ability to tolerate chemotherapy."[2]

"Aside from nerve damage, longer chemotherapy also means more diarrhea and fatigue, more doctor appointments, blood draws, and time away from work and social interactions," he added.[2]

ASCO Expert Nancy Baxter, MD, PhD, of St. Michael's Hospital in Toronto, Canada, remarked, **"**This is extremely important work that will affect the lives of many of my patients, and will allow us to provide a more personalized approach to our patients with colon cancer. Though addressing the question, 'can we give less treatment?' is of major importance to patients and their doctors, it is rare to see this type of study. Given that these questions are unlikely to be of interest to the pharmaceutical industry, federal support for these trials is critical."[2]

She added, "In this case, less is more. We are now able to spare many patients with colon cancer unnecessary side effects of an additional 3 months of chemotherapy without compromising results. The study is an excellent example of how existing treatments can be refined to work even better for patients."[2] ◆

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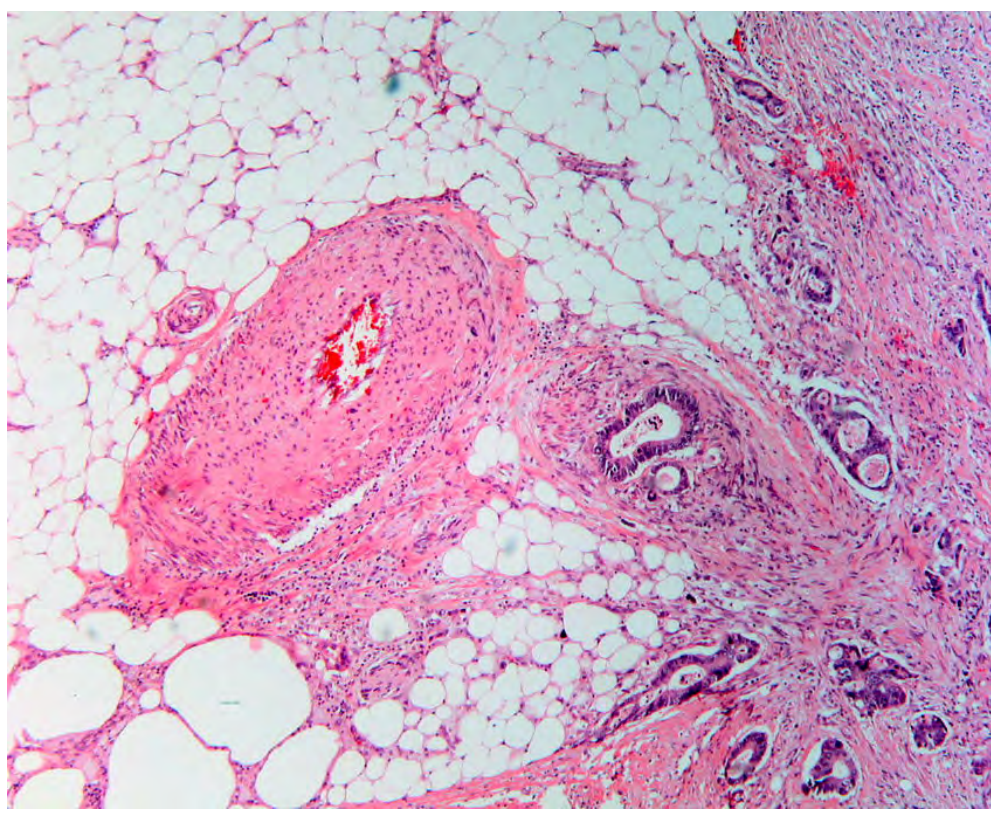

TUMOR INVASION INTO VEIN IN A CASE OF COLORECTAL CANCER, HE 1.

2017 ASCO ANNUAL MEETING: MAKING A DIFFERENCE IN CANCER CARE WITH YOU.

Fas Biomarker Can Predict Response to Second-Line Therapy for Advanced Soft Tissue Sarcoma

AJMC Staff

FAS BIOMARKER DETECTION HAS shown value in predicting progression-free and overall survival (PFS and OS) after trabectedin administration to patients with advanced soft tissue sarcoma. This outcome of a study performed by the Grupo Español de Investigación en Sarcomas (GEIS) was reported in a poster session at the 2017 American Society of Clinical Oncology Annual Meeting.[1]

Several second-line options are available for advanced soft tissue sarcoma as gemcitabine combinations or trabectedin, pazopanib, eribulin, or olaratumab plus doxorubicin in cases where anthracycline administration is still possible. The lack of predictive biomarkers, however, hinders rational selection of the best sequence of second-line therapies. GEIS demonstrated the prognostic value of Fas detection in first-line treatment of advanced soft tissue sarcoma in 2016.[2]

The 2016 randomized, open-label phase 2 trial compared trabectedin plus doxorubicin versus doxorubicin alone as first-line treatment of advanced soft tissue sarcomas. The trial was stopped early because risk reduction for the main endpoint was <9.64% in the experimental arm.[2]

Trabectedin (Yondelis) is a multimodal, synthetically produced antitumor agent, originally derived from the sea squirt, Ecteinascidia turbinata. The drug exerts its activity by targeting the transcriptional machinery and impairing DNA repair. It is approved in close to 80 countries in North America, Europe, South America, and Asia for advanced soft tissue sarcomas as a single-agent and for relapsed ovarian cancer in combination with doxorubicin HCl liposome injection in the European Union.[3]

Translational research, however, was performed to correlate expression of apoptotic and DNA repair genes with clinical outcome. Fas and p53 were shown to be prognostic factors for progression-free survival (7.0 months in cases of Fas positivity and p53 negativity; 3.4 months in cases of Fas positivity and p53 positivity or Fas negativity and p53 negativity; and 0.7 months in cases of Fas and p53 positivity; *P*<.001). Fas and p53 were also shown to be prognostic factors for OS.[2]

The present study analyzed the predictive role of Fas detection in various second-line therapies. Major relevant selection criteria were having received trabectedin second-line or beyond for advanced soft tissue sarcoma or progressive disease after at least 1 previous line of therapy for advanced soft tissue sarcoma.

A tissue microarray was set up for Fas staining and 2 expert, blinded pathologists reviewed and classified cases as negative, weak, or strong. Kaplan-Meier estimations were used for time-to-event variables and the log-rank test was used to compare groups.

A series of 198 patients met selection criteria. Metastases at diagnosis occurred in 46 (24%) patients, and median time to metastases was 18.8 months (range, 16.3-21.3). The line previous to trabectedin consisted of gemcitabine combination in 83 patients (42%), doxorubicin-based therapy in 65 (33%), and others in 50 (25%). Median PFS for previous and trabectedin lines were 3.5 (range, 2.8-4.2) and 3.4 (range, 2.8-4) months, respectively.

Fas positivity was associated with significantly longer PFS for the previous trabectedin line: 4.1 (range, 1.5-6.7) versus 3.0 (range, 2.5-3.5) months, *P* = .01. Fas positivity was associated with shorter PFS for the trabectedin line (2.5 [range, 2.2-2.8] vs 3.7 [range, 2.7-4.8] months, *P* = .028).

Trabectedin (Yondelis), derived from a sea squirt, targets the transcriptional machinery and impairs DNA repair.

These results were more notable in cases of liposarcomas: 7.0 (3.6-10.5) versus 4.3 (1.9-6.6) months, *P* = .017, in the previous line and 2.4 (range, 2.2 -2.6) versus 6.5 (range, 3.8-9.3) months, *P* <.001 in the trabectedin line.

From the time of trabectedin administration, Fas positivity was associated with significantly shorter OS, especially in liposarcomas: 11.9 (range, 5.2-18.7) months versus 21.7 (range, 12.7-30.8) months, *P* = .002. The researchers concluded that Fas is a valuable biomarker in predicting PFS and OS after trabectedin administration in patients with advanced soft tissue sarcoma. The various prognostic roles of Fas detection across distinct lines and its relevance in liposarcomas deserve further attention.

GEIS is a scientific society founded in 1994 to meet a need for cooperation in the medical treatment of soft tissue sarcoma. The group is composed of professionals from more than 60 medical centers across Spain, including oncologists, surgeons, pediatricians, oncologic radiation therapy specialists, pathologists, and molecular researchers.[4] ◆

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Nivolumab, Alone or With Ipilimumab, Met the Disease Control Rate in Malignant Pleural Mesothelioma

AJMC Staff

IN AN INTERIM ANALYSIS of the Intergroupe Francophone de Cancérologie Thoracique (IFCT) 1501 MAPS2 randomized phase 2 trial of second- or third-line nivolumab, with or without ipilimumab, in patients with second- or third-line malignant pleural mesothelioma, both arms met the primary endpoint of disease control rate (DCR) at 12 weeks. This interim outcome was reported as a late-breaking abstract at the 2017 American Society of Clinical Oncology Annual Meeting.[1]

No treatment is recommended in patients with malignant pleural mesothelioma whose disease progresses after first-line pemetrexed-platinum doublet. The DCR is <30% with all drugs tested in second-line setting.

Preliminary results suggested the possible activity of anti-programmed death 1 (PD-1) monoclonal antibodies in the second or third line, as opposed to single agent anti-cytotoxic T-lymphocyte-associated protein *4* (CTLA-4) monoclonal antibodies. Anti–PD-1 monoclonal antibody efficacy, therefore, deserves confirmation. However, the efficacy of combining an anti–PD-1 and an anti–CTLA-4 monoclonal antibody is unknown in malignant pleural mesothelioma.

The investigators of this study set out to test the hypothesis that inhibition of immune PD-1 with or without CTLA-4 checkpoint inhibition would delay tumor progression in patients with unresectable malignant pleural mesothelioma whose disease progresses after 1 or 2 lines of chemotherapy, including at least first-line pemetrexed and platinum. They also hypothesized that quality of life (QOL) would not be significantly altered with this treatment.[2]

Arnaud Scherpereel, MD, PhD, of the University Hospital (CHU) of Lille, France, stated: "For too long, patients with mesothelioma have been underserved in terms of treatment options compared with other types of cancers. The encouraging results of the previous IFCT trial, reported at the ASCO 2015 annual meeting, showed that when bevacizumab was used with the current standard-of-care combination of pemetrexed and cisplatin, it improved survival in patients with mesothelioma. Unfortunately, all patients in that study experienced disease progression."[3,4]

The multicenter, randomized noncomparative, phase 2 IFCT-1501 MAPS2 trial began in 2016. Final data for the primary outcome measure of CT-assessed DCR at 12 weeks were collected in May 2017. The study is estimated to be completed in December 2018.[2]

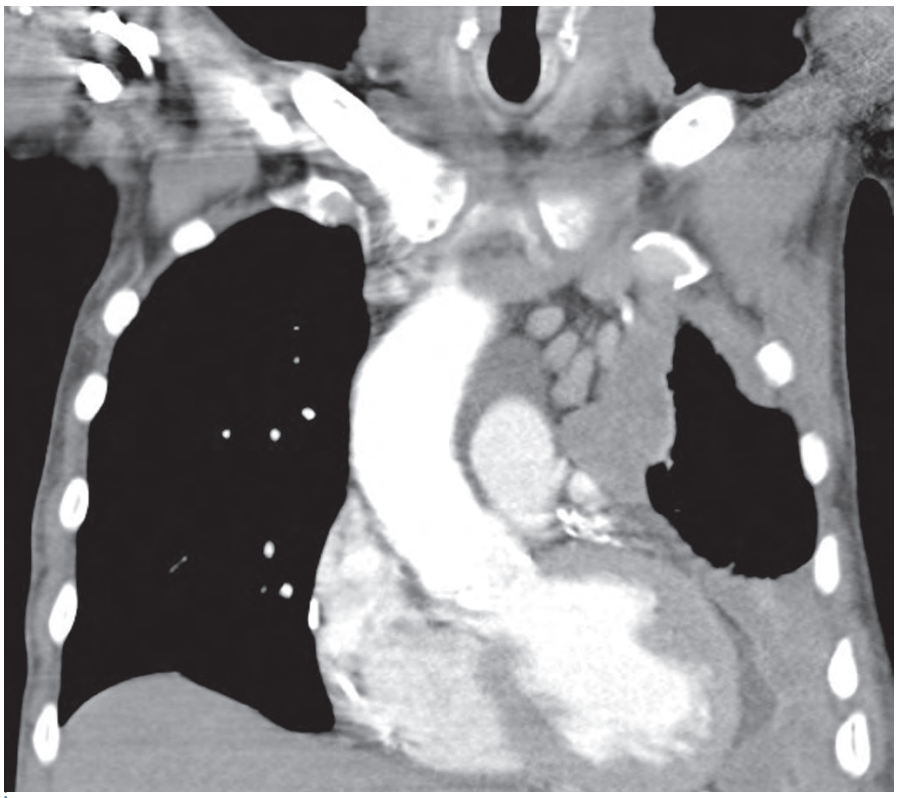
Eligible patients were older than age 18 years and their performance status was 0-1. They had histologically proven, measurable malignant pleural mesothelioma that relapsed after 1 or 2 prior lines including pemetrexed/platinum doublet.

Patients were randomized 1:1 to nivolumab 3 mg/kg of body weight, once every 2 weeks (q2w), or nivolumab 3 mg per kilogram of body weight q2w and ipilimumab 1 mg/kg of body weight once every 6 weeks, until progression or unacceptable toxicity. Nivolumab was administered intravenously over 60 minutes. Ipilimumab was administered intravenously over 90 minutes.

The primary endpoint was DCR as assessed by CT scanning at 12 weeks by blinded independent central review. Tumors were assessed according to modified Response Evaluation Criteria in Solid Tumors v1.1 for mesothelioma.

Secondary outcome measures were the following at 12 weeks:[2]

- The number of participants with treatment-related adverse events as assessed by Common Terminology Criteria for Adverse Events v4.0
- Progression-free survival
- Overall survival
- QOL, as measured by the Lawrence County School System scale
- Prognostic impact of exploratory blood biomarkers and the quantity in blood of numerous biomarkers



CT SCAN SHOWING A LEFT SIDED MESOTHELIOMA WITH AN ENLARGED MEDIASTINAL LYMPH NODE

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A total of 125 patients were enrolled in 21 centers in 2016. Eighty percent were male, median age was 71.8 (range, 32.5-88.1) years, 62.4% rated as performance status 1, 83.2% had epithelioid disease, and 69.6% had received 1 previous line of treatment. Seventy percent of patients received ≥3 cycles of either treatment.

The 12-week-DCR, assessed by blinded independent central review, in the first 108 eligible patients was 42.6% (95% CI, 29.4%-55.8%) with nivolumab (n = 23/54), and 51.9% (95% CI, 38.5%-65.2%) with nivolumab plus ipilimumab (n = 28/54). The overall response rate was 16.7% (95% CI, 6.7%-26.6%) with nivolumab (n = 9/54), and 25.9% (95% CI, 14.2%-37.6%) with nivolumab plus ipilimumab (n = 14/54).

All grade 3/4 toxicities were slightly increased in the combination arm (86.9%/16.4%) versus nivolumab alone (77.8%/9.5%) and 3 treatment-related deaths were observed in the combination arm (1 metabolic encephalopathy, 1 fulminant hepatitis, and 1 acute renal failure).

The investigators concluded that both second- or third-line nivolumab and nivolumab plus ipilimumab met their endpoint in patients with second- or third-line malignant pleural mesothelioma. The results suggest that immunotherapy may provide new options for these patients.

Scherpereel said, "The results of the IFCT-1501 MAPS-2 study, showing the efficacy and safety of nivolumab alone or in combination with ipilimumab, are promising, and additional research is needed for patients with relapsed mesothelioma."[3] ◆

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Ibrutinib vs No Consolidation Are Being Compared Following Autologous HSCT in IRONCLAD Trial

AJMC Staff

RELAPSED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) in the rituximab era portends a poor prognosis: only approximately 25% of patients achieve long-term disease control following second-line therapy and autologous hematopoietic stem cell transplantation (auto HSCT). Further, patients with the relapsed/refractory activated–B-cell (ABC) subtype have a poorer prognosis at diagnosis than those with germinal center disease and are overrepresented at relapse.

A poster session at the 2017 American Society of Clinical Oncology Annual Meeting presented the trial details of IRONCLAD, a randomized phase 3 study of ibrutinib versus no consolidation following auto HSCT for ABC subtype DLBCL.[1] The trial began in 2016 and final data collection for evaluation of the primary outcome measure, superior 24-month progression-free survival (PFS), will be in 2020.[2]

IRONCLAD is targeting disease pathobiology at the time of auto HCT in an effort to improve outcomes in ABC-DLBCL. Ibrutinib possesses a safety profile that allows it to be combined with cytotoxic chemotherapy and confers single-agent activity with a 37% response rate in patients with relapsed/refractory ABC-DLBCL. The intergroup, randomized, placebo-controlled, phase 3 study combines ibrutinib or placebo with high-dose chemotherapy during conditioning with auto HCT and for the following 12 months. Patients with relapsed/refractory DLBCL undergo tissue resection and these samples are submitted centrally for real-time review and subtype assignment.

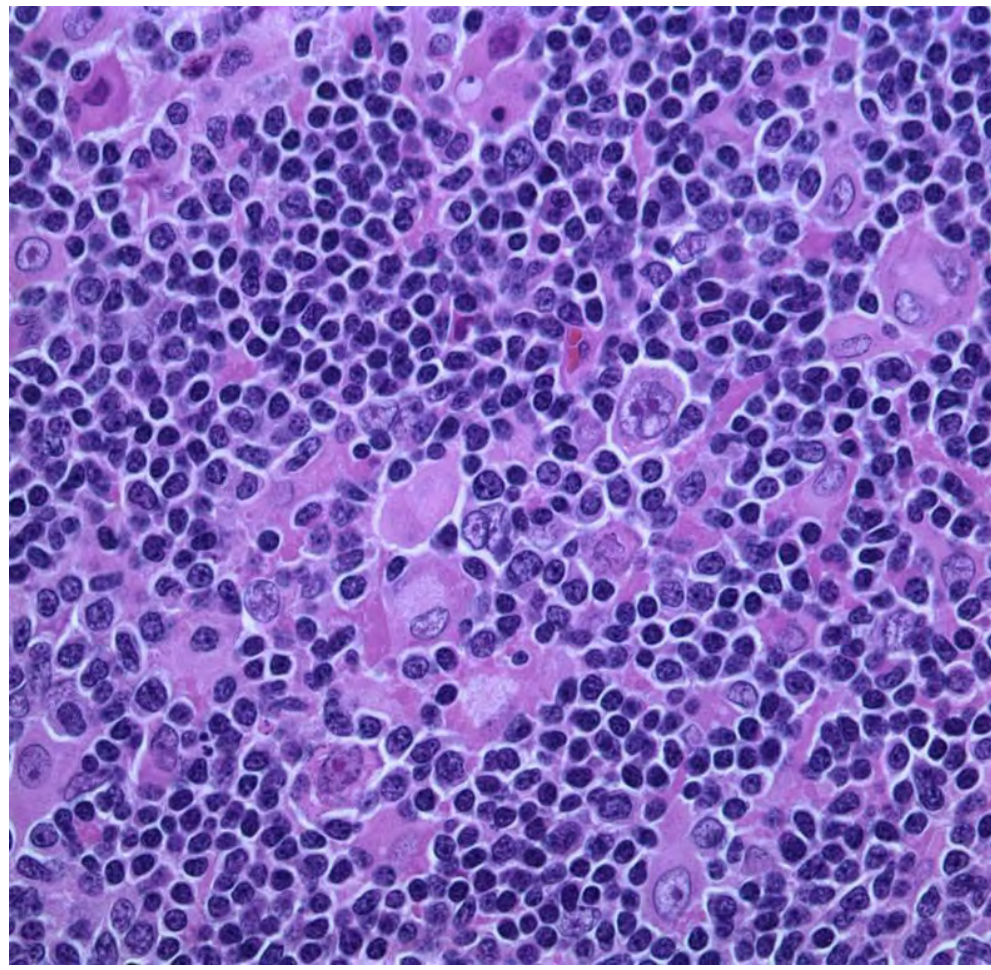
IRONCLAD is a phase 3 study of ibrutinib versus no consolidation following auto hematopoietic stem cell transplantation in patients with diffuse large B-cell lymphoma.

Eligibility criteria include no more than 3 prior regimens, no active central nervous system involvement, no need for long-term anticoagulation, and no progression with prior ibrutinib therapy. Patients with chemosensitive ABC-DLBCL are randomized to ibrutinib 560 mg or placebo with carmustine, etoposide, cytarabine, and melphalan (BEAM) or cyclophosphamide, BCNU (carmustine), and VP-16 (CBV) chemotherapy until day 0. After engraftment, patients receive ibrutinib 560 mg daily or placebo for 12 additional cycles. Patients with progressive disease on placebo will be eligible to cross over to ibrutinib monotherapy. An initial safety cohort of 6 patients is being enrolled to evaluate the tolerability of ibrutinib with concurrent BEAM and CBV therapy.

As previously stated, the primary endpoint is superior 2-year PFS (Ha/H0 67% versus 50%). Secondary endpoints include time to count recovery, posttransplant response rates, overall survival (OS), PFS, and the incidence of secondary malignancies. PFS is defined as the proportion of patients who are alive and progression-free 2 years from randomization, using the Lugano classification.[2]

Secondary outcome measures include:[2]

- The incidence of hematologic toxicity of ibrutinib therapy in up to 60 months, summarized using contingency tables
- The incidence of secondary malignancies in up to 60 months
- The incidence of secondary malignancies, summarized using contingency tables
- OS from randomization to death from any cause, assessed up to 60 months
- For each arm, the distribution of OS will be estimated using the Kaplan-Meier method and will be compared between the 2 arms using the log-rank test and Cox regression method, adjusting for known predictors.
- PFS, from registration to disease progression or death, whichever comes first, in up to 60 months



HODGKIN LYMPHOMA, NODULAR LYMPHOCYTE PREDOMINANT - HIGH POWER VIEW - H&E

- For each arm, the distribution of PFS will be estimated using the Kaplan-Meier method. PFS will be compared between the 2 arms using the log-rank test and Cox regression method, adjusting for known predictors.
- Response rate using the Lugano classification in up to 60 months. The metabolic response proportion following auto HCT will be compared between the 2 arms using the Chi-squared test
- Time to hematopoietic engraftment (platelet count ≥20,000/mcL following nadir) from the first day of 1 week without platelet transfusion, assessed up to 60 months
- Treatment-related mortality for up to 60 months, summarized using contingency tables

The prognostic and predictive role of a pretransplant fludeoxyglucose PET scan in the setting of ibrutinib or placebo therapy, the role of emergent B-cell antigen receptor pathway mutations, double-hit genetics, and pharmacogenetic determinants of treatment outcome and toxicities will be assessed in correlative studies. A total of 296 patients are expected to accrue over 4 years.

IRONCLAD is being undertaken by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), which was established to help meet a critical need for multi-institutional clinical trials that focus directly on improving survival for patients undergoing hematopoietic cell transplantation. Since 2001, the BMT CTN has opened more than 30 multi-institutional phase 2 and 3 trials, involved more than 100 transplant centers, and enrolled thousands of patients.[3]

BMT CTN is funded through the National Institutes of Health. ◆

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THE ANNUAL MEETING DRAWS OVER 30,000 GLOBAL ONCOLOGY PROFESSIONALS.

Web-Based Patient Reporting of Symptoms Shown to Improve Survival in Patients With Metastatic Solid Tumors

AJMC Staff

PATIENTS RECEIVING ROUTINE outpatient chemotherapy for metastatic solid tumors who self-reported 12 common symptoms via tablet computers experienced an overall survival (OS) benefit over those who received usual care. This outcome was reported at a plenary session at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting.[1]

In 2016, Ethan Basch, MD, and his team at Memorial Sloan Kettering Cancer Center reported significant benefits in quality of life, patient satisfaction, and emergency department (ED) use outcomes in their large single-center randomized controlled comparison of Web-based symptom monitoring with patient-reported outcomes (PROs) vs usual care in patients receiving chemotherapy for metastatic solid tumors.[2] Basch's research group, now at the Lineberger Comprehensive Cancer Center of the University of North Carolina, presented OS results of this trial at ASCO.

"The improvement in survival we saw may seem modest, but it is greater than the effect of many targeted cancer drugs for metastatic cancer."

–Ethan Basch, MD

Patients were randomized to self-report 12 common symptoms including appetite loss, difficulty breathing, fatigue, hot flashes, nausea, and pain. Patients graded them on a 5-point scale. The web-based tool, Symptom Tracking And Reporting or (STAR), was developed for research purposes and is not commercially available.

Patients reported symptoms remotely from home or at the doctor's office during oncology or chemotherapy visits, using tablet computers or computer kiosks. The intervention group included patients with little prior experience using the internet.

Treating physicians received symptom printouts at visits and nurses received e-mail alerts when participants reported severe or worsening symptoms. OS was tabulated based on medical records and Social Security Death Index data, estimated using the Kaplan-Meier method, and compared using a log-rank test and Cox proportional hazards regression that adjusted for age, sex, race, educational level, and cancer type.

Between 2007 and 2011, 766 patients with a median age of 61 (range 26-91 years) years were randomized—86% were white, 58% female, and 22% had less than a high school education. Cancer types included genitourinary (32%), gynecologic (23%), breast (19%), and lung cancer (26%).

Fewer participants in the STAR arm visited the ER than those who received usual care (34% vs 41% after 1 year; $P = .02$). The 2016 analysis concluded that in adults receiving outpatient chemotherapy for advanced cancer at a large specialty cancer center, Web-based symptom reporting with automated clinician e-mail alerts resulted in better health-related QOL, fewer ED visits, fewer hospitalizations, a longer duration of palliative chemotherapy, and superior quality-adjusted survival.[2]

Survival results were assessed in 2016 after a median follow-up of 7 years. A total of 517 of 766 (67%) participants had died. Median OS in the intervention arm was 5 months longer than in the control arm (31.2 vs 26.0 months, $P = .03$). In the multivariable model, results remained statistically significant with a hazard ratio of 0.832 ($P = .04$; 95% CI, 0.696-0.995).

The investigators concluded that systematic symptom monitoring during outpatient chemotherapy using web-based PROs confers OS benefits.

These single-center results are being evaluated further in a national multicenter implementation trial. The national trial uses an updated, more user-friendly online tool that works on both personal computers and mobile devices. The study is being conducted in community practices across the United States.

"We showed that using a web-based symptom reporting system that alerts the care team about problems leads to actions that alleviate suffering and improve patient outcomes," Bach said in a statement. "The improvement in survival we saw may seem modest, but it is greater than the effect of many targeted cancer drugs for metastatic cancer. Symptom management is a central part of what oncology care teams do."[3]

ASCO Expert Harold J. Burstein, MD, PhD, FASCO, commented, "Online technologies have transformed communications in practically every aspect of our lives, and now we're seeing they're also allowing patients to take an active role in their care and get immediate access to their care provider. It is impressive that something as simple as this not only improves quality of life, but in this case, helps patients live longer. I think we will soon see more cancer centers and practices adopting this model."[3] ◆

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Physician, Regulatory, and Payer Perspectives on the Value of Real-World Data

Surabhi Dangi-Garimella, PhD

A KICKOFF SESSION ON THE first day of the 2017 American Society of Clinical Oncology Annual Meeting in Chicago turned in to a lively discussion on ensuring that the data used to inform patient care and create healthcare policies hold value. This, according to the speakers who participated on the panel, entails moving away from clinical trial data and foraging real-world data captured in health records.

The goal of the session was to identify existing and developing data sources that can be used to inform comparative effectiveness research, patient care, and healthcare policy. The presenters provided examples of questions that can be asked using these data and described how payers consider observational data alone or in conjunction with data from clinical trials.

CHEN

ROSENBERG

KHOZIN

Ronald C. Chen, MD, MPH, associate professor, Department of Radiation Oncology, University of North Carolina at Chapel Hill, was both presenter and chair of the session, and he tried to convince listeners that while randomized controlled trials (RCTs) are the industry's gold standard, they come with significant limitations. He explained that RCTs are not obsolete, that they are a significant source of information, "but there are gaps that exist, and we need to find alternatives."

Comparative effectiveness research is unbiased comparison that yields valid results. "The goal is to estimate the truth…which RCTs help with, especially when it comes to comparing the efficacy of product A versus product B," Chen said. He added that RCTs and observational data together can prove helpful to clinicians, policy makers, payers, and patients.

Although RCTs minimize confounding, there are limitations to this gold standard, Chen added, citing the Prostate Cancer Intervention Versus Observation Trial (PIVOT)[1] as a case study. The primary question that PIVOT asked was whether radical prostatectomy can save lives in men who have localized prostate cancer. Starting with a large cohort of over 13,000 men, 5000 met the trial's eligibility criteria. Of these, only a little over 700 patients were randomized between the 2 arms: radical prostatectomy and observation between 1994 and 2002; the follow-up period ended in early 2010 and the results were published in 2012. The trial found no difference in survival between the observation and the surgical intervention arms, but the data were available nearly 20 years after trial initiation.

Chen listed the following potential limitations of RCTs:

- Patients are often highly selected (younger, healthier), which begs the question: are outcomes representative of "all" patients in the real world? Generalizability is a concern. "Can decreased generalizability decrease treatment adoption?" he asked.
- Can results remain relevant, especially since RCTs usually require a long time to complete?
- Is it possible for RCTs to provide clinically relevant and timely results?
- Not every clinically important question can be addressed through an RCT.

Providing the FDA's perspective on real-world data was Sean Khozin, MD, MPH, senior medical officer at the FDA. Khozin reviewed how the FDA is using real-world evidence in the context of regulatory decision making. Despite significant strides in other areas over the past several decades, the clinical trial model remains rudimentary, he said. "There remains room for improvement in RCTs," Khozin explained. "We trust these results because they have robust internal validity." He described the structure of RCTs as a "validity imbalance," with an overcompensation of internal validity and an external validity deficit. RCTs also have poor generalizability—there is no median or average patient. "That is just a statistical concept." So, treatment decisions based on the "median" outcome of a trial will not help us maximize the potential of precision oncology.

Khozin explained that the characteristics of real-world data are mostly based on the intent of data collection: within the controlled settings of a clinical trial or in the real-world of a physician's office. "Real-world data help retrospective analysis," Khozin explained, which can be achieved using electronic health record (EHR) data that is cleaned up. EHRs have a structured (billing and lab codes, patient history and demographics) and an unstructured component (physician notes and diagnostic reports).

Speaking with *The American Journal of Managed Care®* in November 2016, Khozin said that one component of the FDA's Information Exchange and Data Transformation initiative is using real-world evidence, in the form of EHRs, to guide regulatory decisions.[2] Exclusion criteria in clinical trials can be limiting, he said, so trial data may not reflect patients being treated in the real world. "We can change the intent of data collection from research to real-world data by providing clinicians incentives to do so," Khozin said during the ASCO session. This is how pragmatic or prospective trials are defined, he added.

Khozin stated that frameworks exist for real-world data collection and that the FDA is not concerned with the original intent of data collection since there are processes in place to scrutinize the submitted information. Real-world data can be used for:

- **Pharmacovigilance.** Currently, a passive process associated with voluntary reporting of adverse events, real-world data can power an active pharmacovigilance program (eg, the FDA's Sentinel program[3] and direct EHR abstraction).
- **Benchmarking.** This process develops historical control benchmarks to inform future trial designs and provide reliable safety and efficacy data.
- **Conduct pragmatic clinical trials.** To allow for point-of-care clinical decisions, EHRs serve as vehicles for prospective clinical research at the point of care, can support randomization, are patient-centric, and may bend the cost curve.

The primary challenge with real-world data, Khozin said, is ensuring its quality and fulfilling the need to provide the right incentives at the point of care to extract clinically relevant data. "This is more an organizational issue."

Alan Rosenberg, MD, vice president of clinical pharmacy and medical policy, Anthem, spoke about how payers view nonrandomized data when making coverage determinations. "Quality, access, efficiency, [and] equity remain challenges with healthcare in our country compared with the rest of the world. This is a real issue for us as healthcare providers."

Rosenberg believes that the variation in care stems from socioeconomic and geographic differences. "However, a lot of this variation remains unexplained," he added. "We, as payers, are aware of the origins in [the] knowledge gap and also understand the cost associated with running RCTs. But we do expect well-designed trials that provide significant outcomes."At the same time, real-world adherence is typically lower than RCT adherence. So, the number-needed-to-treat in RCTs is much higher, considering adherence issues. The coversage decision process involves multiple steps:

- Examination of relevant peer-reviewed data, which are used with caveats
- Recognition that there is significant difference in the quality of nonclinical trial data
- Recognition of the difference between quantum and small incremental results
- Recognition of the difference between RCTs and developing treatment for ultrarare diseases

Rosenberg also emphasized that FDA approval is necessary, but may not be sufficient for making coverage decisions. ◆

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Do We Have Adequate Surveillance in Cancer Care?

Surabhi Dangi-Garimella, PhD

SURVIVORSHIP CARE IS IMPORTANT among patients who have undergone treatment for cancer, and follow-up can help them discuss issues that may be associated with their treatment, share their financial concerns, and, most importantly, ensure disease-free survival. A poster discussion session at the 2017 Annual Meeting of the American Society of Clinical Oncology examined retrospective surveillance data in 3 cancers: non–small cell lung cancer (NSCLC), head and neck cancer (HNC), and colorectal cancer (CRC). Katherine Van Loon, MD, MPH, from the University of California, San Francisco, led the discussion.

VAN LOON

Head and Neck Cancer

The first study,[1] conducted by researchers affiliated with multiple healthcare systems in Philadelphia, evaluated the impact of radiation therapy and a latency period on the risk of developing new primary lung cancers after HNC. The population-based study of 85,154 patients with HNC in the Surveillance, Epidemiology, and End Results (SEER) database found 4209 patients with new primary lung cancers. Compared with the no radiation group, those who received radiation therapy had a higher incidence of primary lung cancers across all latency periods: from less than 1 year of follow-up (standardized incidence ratio [SIR], 3.45 vs 2.18, respectively) to 10 to 15 years (SIR, 3.19 vs 1.88). The highest incidence for the radiation-treated group was observed in the 1-to-3-year latency period (4.57 vs 2.41).

The authors concluded that in patients with HNC, the risk of developing a new primary lung cancer is associated with radiation treatment, with the greatest risk observed within 10 years of the initial HNC diagnosis. They recommended that screening for patients who smoke should be considered, especially within 10 years of the primary HNC diagnosis.

Van Loon said that while the large sample size from the SEER data was a significant strength of the study, retrospective analysis placed limitations on the observations. Further, the predominance of squamous cell carcinoma raised questions on de-novo versus metastatic nature of the observed lung cancer. She also pointed out the lack of data on patient exposure to risk factors as a study limitation.

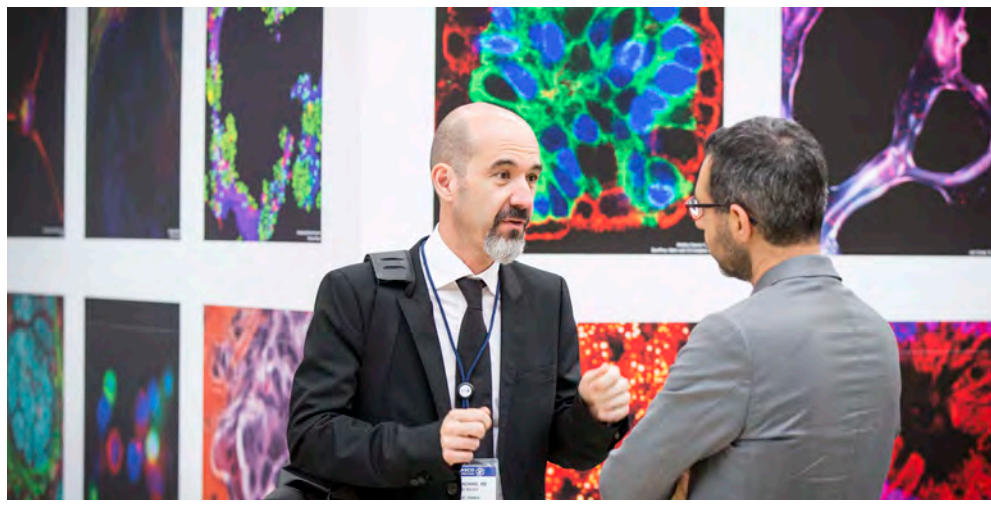
Colorectal Cancer

The next study[2] evaluated the impact of posttreatment surveillance in CRC, with the purpose being to determine if the surveillance is associated with time to recurrence detection, treatment, or overall survival (OS). The authors examined the primary records of 10,636 stage I to III patients with CRC from Commission on Cancer-accredited hospitals who were diagnosed between 2006 and 2007; data were merged with records in the National Cancer Database. A predicted and observed number of imaging and carcinoembryonic antigen (CEA) tests per patient were determined and clustered by hospital; patients were then categorized into high- or low-intensity categories.

Of the 6279 patients, those who underwent high-intensity imaging (50.6%) or CEA surveillance (51.2%) in the 3 years after CRC treatment had a mean of 2.9 imaging studies and 4.7 CEA tests. Patients with low-intensity imaging underwent a mean of 1.4 imaging studies and 1.6 CEA tests. Patients' 5-year recurrence rates were no different based on the intensity of surveillance: stage II and stage III patients who underwent high-intensity imaging and CEA testing had a slightly higher resection rate, without any improvement in the 5-year OS.

The authors concluded that higher-intensity surveillance was not associated with earlier detection of recurrent disease or improved OS. It did, however, result in a slightly higher resection rate. They went on to recommend less frequent testing for surveillance in patients with CRC.

Van Loon praised the highly annotated design and large real-world sample of patients used by the trial. "The findings add to results of [the] FACS and GILDA trials, so intensive follow-up may not improve OS for CRC survivors," she added. Questions remain about whether a subset of patients with recurrence may benefit from more intensive surveillance, she concluded.



THE ASCO ANNUAL MEETING PROVIDES OPPORTUNITY FOR NETWORKING AND COLLABORATIONS.

Lung Cancer

The final abstract[3] discussed was the receipt of recommended surveillance with imaging in survivors of early stage NSCLC. Lifelong imaging surveillance for early cancer detection is recommended in lung cancer survivors who have a high risk for recurrence and second cancers and a 5-year survival of 50%. The study authors examined the rates and determinants of regular surveillance imaging in NSCLC survivors.

Examination of the SEER-Medicare linked database identified 10,680 patients with stage I and II NSCLC diagnosed over the 10 years between 2001 and 2011 and treated with surgery. Patients were censored at the time of recurrence/second cancer, loss of insurance, or 3 months before death. In this population, receipt of computerized tomography and/or positron emission tomography imaging during the surveillance periods of 7 to 18, 19 to 30, 31 to 42, and 43 to 60 months from the date of surgery was assessed.

The study found that 79% and 40% of survivors had follow-up information until the end of the 30- and 60-month surveillance periods, respectively. With a median follow-up of 7.6 years, 71% of the survivors received imaging in the first 18 months after surgery, but only 56% and 44% of survivors continued to receive regular imaging by the 30- and 60-month of follow-up periods, respectively.

Survivors, the analysis found, were less likely to receive imaging if they were older (≥80 years), black, not married, lived in a rural location, did not receive adjuvant therapy, had stage I disease (compared with stage II), and received their diagnosis in 2006 or earlier. In adjusted analysis, survivors receiving recommended imaging up to 18 months post-surgery had improved survival compared with survivors who did not (HR, 0.86; 95% CI, 0.81-0.92). Survival benefit was also observed in survivors who had regular imaging up to 5 years from surgery (HR, 0.68; 95% CI, 0.60-0.76).

The fact that more than 50% of the lung cancer survivors did not receive recommended long-term surveillance imaging had the authors conclude that adherence to regular surveillance, even 5 years from the initial surgery, is associated with improved survival. Van Loon noted that the large cohort size was a definite plus for the study, as was the use of the SEER-Medicare linked database. The limitations of the study were that it was retrospective, was missing a population group younger than 66 years, and did not use non-Medicare sources. Additionally, 60% of patients were missing follow-up at 60 months. ◆

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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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MACRA 2.0 and Beyond: Preparing Your Practice to Meet the Quality and Reporting Challenges

Surabhi Dangi-Garimella, PhD

CMS' NEW PAYMENT MODEL, the Medicare Access and CHIP Reauthorization Act (MACRA), is now live. MACRA, which replaced the Sustainable Growth Rate formula includes 2 tracks under the Quality Payment Program (QPP)[1]: the Merit-based Incentive Payment System (MIPS) and Advanced Alternative Payment Models (APMs). At the 2017 American Society of Clinical Oncology Annual Meeting, oncologists heard from fellow experts on the best way to navigate this daunting payment reform challenge.

POLITE

MCANENY

The learning objectives of the session included the practice impact of MACRA, quality reporting and APM options under MACRA, and the impact of APMs on Medicare. Blase N. Polite, MD, MPP, associate professor of medicine, The University of Chicago, explained MIPS and APMs. "There are no fully blessed oncology payment models yet, unless you choose the 2-sided risk model offered under the Oncology Care Model (OCM)." This provided impetus for ASCO to develop its own APM, he explained.

In 2017, which is the first performance period, MIPS incorporates scores for quality, advancing care information (ACI), and improvement activities (IAs), Polite said. "Cost, unfortunately, was not included in the 2017 MIPS program score," he added, but will find a place in the 2018 scores.

Payment, Polite explained, will be based on where a practice falls along the range of low to high performers compared with the National Median Composite Score. The 2019 scores will be based on 2017 performance. A significant chunk (60%) of the score is driven by quality reporting, formerly known as the Physician Quality Reporting Score. Although the general oncology measures set includes 19 reportable measures that comprise a mix of process and outcome measures, reporting requirements mandate only 6 measures, at least 1 of which should be an outcome or a high-priority measure, Polite said. Further, each practice is expected to report on at least 50% of patients eligible for each measure in 2017, which includes Medicare and commercially insured patients.

Practices that do not participate in the Quality Payment Program in 2017 will see a negative 4% payment adjustment in 2019.

Explaining the cost reporting basics, Polite said that the per capita cost measures will be risk-adjusted by specialty. The measure set currently includes 41 episode measures, none of which are oncology-related. The measures include the cost of Medicare Part B drugs; Part D drugs have been excluded.

"CMS is still working with issues, such as defining an episode, and ASCO is working with CMS to provide feedback and help develop the reimbursement model," Polite told the audience. He went on to urge the oncologists in the room to take concrete steps to work with CMS on QPP reporting, although in 2017, CMS has allowed practices to "pick their pace." The options that are available include:

- Practices that don't participate in the QPP reporting program in 2017 will see a negative 4% payment adjustment in 2019.
- Practices that test the program and report 1 quality measure or IA, or the required ACI measures (which, Polite said should be the least a practice should do in 2017), can avoid penalties in 2019.
- Practices involved in partial MIPS reporting in 2017—meaning they report on more than 1 quality measure or IA, or more than the required ACI—can avoid penalties and be eligible for partial positive payment adjustment in 2019.
- Practices that take on full MIPS reporting in 2017 can avoid penalties and be eligible for partial positive payment adjustment and an exceptional performance bonus in 2019.

MEETING ATTENDEES CATCH UP ON THE WAY TO THEIR NEXT SESSION.

Barbara McAneny, MD, provided a historic perspective on the evolution of payment models, comparing the top-down versus the bottom-up models, which are payer-driven and provider-driven, respectively. The provider-driven model, where the practice identifies problems that lead to changes with the way payers pay for care, is more patient-centric and geared to reduce financial toxicity for patients.

"We looked at things in our clinic that we can influence, such as hospital admission, triage to manage toxicities, and avoiding sending the patients to the emergency department (ED)," McAneny said, and that resulted in the COME HOME pilot,[2] which received a CMS funding grant.

Another payment model that resulted from a collaboration between McAneny's Innovative Oncology Business Solutions and ASCO is the Patient-Centered Oncology Payment (PCOP) model. In a recent article in *The American Journal of Managed Care®*, McAneny and her coauthors explained that the PCOP model offers a chemotherapy or immunotherapy episode of care with 3 levels of reimbursement, leading from basic fee-for-service care to monthly payments to overall care bundles.[3] A practice will get a 1-time $750 payment for each new patient, a $200 monthly fee during the 6-month episode of care, and a $50 care management payment during the active monitoring phase, which can last up to 6 months after treatment ends.

The PCOP model aims to:

- Reduce avoidable readmissions
- Ensure practices follow appropriate use criteria for drugs, tests, and imaging
- Deliver higher payments than existing reimbursement margins to participating practices

The pilot, to date, has seen:

- 11 hospitalizations (4.1% monthly hospitalization rate)
- 41 triage encounters, with 18 same-day appointments and 3 ED visits avoided
- 142 active chemotherapy months, with 92.2% pathways compliance

McAneny shared her worry with the 2-sided risk offered under the OCM. Her practice ran a simulation using 290,000 episodes from COME HOME and then randomized them. "We found that our COME HOME practice, even with all its transformations and efficiencies, has only a 3% chance of making any money." The patient population is too small to meet the actuarial risk associated with these payment models.

"I am even concerned with taking 1-sided risk with these APMs," she said. "We need to talk to CMS to devise a more realistic system and develop targets that we can achieve." ◆

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POLICY

ASCO Study Finds Shift in Diagnosis Stage for Several Cancers Following ACA Implementation

Surabhi Dangi-Garimella, PhD

ANALYSIS OF DATA AVAILABLE within the National Cancer Data Base, a national hospital-based registry, showed that the diagnosis of stage I disease increased for female breast cancer, colorectal cancer (CRC), and lung cancer following implementation of the Affordable Care Act (ACA). Although early diagnosis of cervical cancer was not statistically significant, diagnosis of stage I prostate cancer saw a drop. The results were presented at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago.[1]

A shift to early-stage diagnosis for colorectal cancer and lung cancer were mainly seen in Medicaid-expansion states.

Inadequate insurance and education have previously been identified as significant determinants of increased screening rates.[2] A 2015 study, published in *The American Journal of Managed Care®*, found that individuals from lower socioeconomic or uninsured groups are least likely to use preventive screening.[3]

The current study was designed by researchers from the American Cancer Society to identify changes in stage at diagnosis following ACA implementation. The study cohort included nonelderly patients of screening-appropriate age who were diagnosed between 2013 and 2014. The prevalence of stage I disease was calculated for 5 cancer types, before (2013 Q1 to Q3) and after (2014 Q2 to Q4) the ACA.

Disease-specific distribution was as follows:

- 121,402 female breast cancer (40 to 64 years)
- 39,418 CRC (50 to 64 years)
- 11,190 cervical cancer (21 to 64 years)
- 41,436 lung cancer (55 to 64 years)
- 59,210 prostate cancer (50 to 64 years)

The analysis found a statistically significant increase in stage I disease for female breast cancer (47.8% vs 48.9%; prevalence ratio [PR] = 1.02; 95% CI, 1.01-1.03), CRC (22.8% vs 23.7%; PR = 1.04; 95% CI, 1-1.08), and lung cancer (16.6% vs 17.7%; PR = 1.06; 95% CI, 1.02-1.11) in 2014. While cervical cancer saw a nonsignificant shift to stage I disease, (47.2% vs 48.7%; PR = 1.02; 95% CI, 0.98-1.06), the percentage of stage I disease diagnosis for prostate cancer decreased (18.5% vs 17.2%; PR = 0.93; 95% CI, 0.9-0.96) in 2014.

HAN

Xuesong Han, PhD, a study co-author, explained during a press cast hosted by ASCO, that the recommendation by the US Preventive Services Task Force (USPSTF) regarding routine prostate cancer screening might have influenced the observed drop in screening rates. USPSTF's Grade D recommendation for a routine prostate-specific antigen–based screening for prostate cancer has previously been blamed for a reduction in intermediate and high-risk prostate cancer diagnoses.

During the press cast, Han shared detailed analyses based on Medicaid expansion status in the states and concluded that the shifts to early-stage diagnosis for CRC and lung cancer were mainly seen in Medicaid-expansion states, while the shift observed for female breast cancer was independent of the states' Medicaid expansion. ◆

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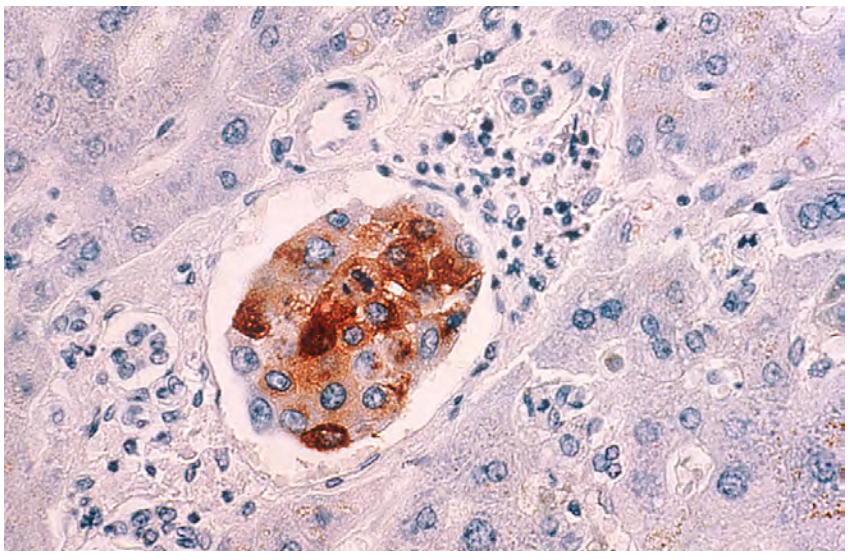
Switching Study Reports Equivalence Between Filgrastim, Biosimilar in Breast Cancer

Surabhi Dangi-Garimella, PhD

A PHASE 3, RANDOMIZED, double-blind registration study in patients with breast cancer receiving neoadjuvant myelosuppressive chemotherapy has found clinical equivalence between filgrastim and its biosimilar after switching studies. The study results were presented during a poster session at the 2017 Annual Meeting of the American Society of Clinical Oncology.

In 2016, Filgrastim EP2006 (Zarxio) became the first biosimilar approved by the FDA for commercial use in the United States.[1] The current phase 3 study compared the impact of switching the reference product with the biosimilar and the biosimilar with the reference product in the said patient population.

The 218 German patients receiving 5 µg/kg/day filgrastim over 6 chemotherapy cycles were randomized equally into 4 arms: 2 arms received only 1 product each, either the biosimilar or the reference (unswitched), and 2 arms (switched) received alternating treatments every other cycle (the biosimilar first then reference or vice versa, over cycles 1 to 6). Four patients did not receive treatment: 2 in the reference group, 1 in the switched group, and 1 in the biosimilar group.



BREAST CANCER METASTASIS TO LIVER

A total of 107 patients switched treatment, and 51 patients received the reference drug in all cycles. The incidence of febrile neutropenia (FN) was 3.4% (switched) versus 0% (reference) (95% CI, –9.65% to 4.96%). Infections occurred in 9.3% of the switched cohort compared with 9.9% in the reference cohort. Hospitalization due to FN was low, with 1 patient in cycle 6 (switched).

Treatment emergent adverse events (TEAEs) related to filgrastim were reported in 42.1% of patients in the switched cohort versus 39.2% of reference patients (throughout all cycles). The most frequent TEAEs were musculoskeletal/connective tissue disorders related to filgrastim, which occurred in 35.5% (switched) compared with 39.2% (reference) (all cycles) of patients. These events included bone pain (30.8% vs 33.3%).

No neutralizing or clinically relevant antibodies against recombinant human granulocyte-colony stimulating factor were detected post dose while switching from the reference product to the biosimilar and vice versa. The authors concluded that there was no evidence of clinically meaningful differences related to efficacy, safety, or immunogenicity when patients with breast cancer were switched from reference to biosimilar filgrastim or from biosimilar to reference filgrastim. ◆

REFERENCE

1. Joszt L. FDA approves first biosimilar in US. *The American Journal of Managed Care®* website. ajmc.com/newsroom/FDA-Approves-First-Biosimilar-in-US. Published March 6, 2015. Accessed June 3, 2017.

Research Demonstrates Efficacy and Safety of Trastuzumab Biosimilar SB3

Kelly Davio

A STUDY PRESENTED AT the 2017 American Society of Clinical Oncology Annual Meeting demonstrated that SB3, a proposed biosimilar to trastuzumab (TRZ), has comparable efficacy, safety, immunogenicity, and pharmacokinetics (PKs) to the reference product based on the breast pathological complete response (bpCR). The researchers defined the bpCR rate as the primary endpoint of the study, which comprised 403 patients per arm.

The phase 3, double-blind, randomized, parallel-group, multicenter study, sponsored by Samsung Bioepis, sought to demonstrate the comparable efficacy of SB3 (which has an identical primary amino acid sequence to TRZ) and TRZ in terms of bpCR when the products are used in neoadjuvant settings in women who have either epidermal growth factor receptor 2–positive early breast cancer or locally advanced breast cancer.

Patients who were 18 to 65 years of age and newly diagnosed with stage II to III primary breast cancer received either SB3 or the reference product for 8 treatment cycles, which were given concurrently with chemotherapy. The patients then underwent surgery and a subsequent 10 cycles of either SB3 or TRZ.

Researchers concluded that SB3 and TZB had equivalent efficacy based on the ratio of bpCR rates and that SB3 was both well tolerated and comparable to TZB in safety, immunogenicity, and pharmacokinetics.

The study analyzed efficacy in a per-protocol set (PPS), comprising those who had completed neoadjuvant therapy and surgery without any prespecified major deviations from protocol, and also considered a full-analysis set to provide supportive data. Drawing upon several published TRZ studies as a guideline, the researchers set equivalence margins in the PPS at a 90% confidence interval (CI) of the ratio of bpCR rates for SB3 and TRZ, or a 95% CI of the difference between the bpCR rates for the 2 products. Secondary endpoints for the study included total pathologic complete response (tpCR), overall response rate (ORR), event-free survival, PK equivalence, immunogenicity, and safety.

The researchers found that, after adjusting results by hormone receptor status, disease stage, and region, the adjusted bpCR ratio for the PPS was 1.259 (90% CI, 1.112-1.426), a value that falls within the pre-defined margin of 0.785 to 1.546. The adjusted difference was 10.7% (95% CI, 4.13%-17.26%), with the lower margin contained within and the upper margin falling outside the predefined margin (–13% to 13%). The tpCR results were reflective of the bpCR findings, with an adjusted PPS ratio of 1.315 (90% CI, 1.137-1.520). Results for ORR also bore out bpCR results, with an adjusted ratio for the PPS at 1.055 (90% CI, 1.023-1.088).

Additionally, the study data demonstrate comparable safety between SB3 and TRZ, with neutropenia, alopecia, and nausea representing the most commonly reported adverse effects in both study arms. PK data demonstrated equivalent steady-state trough levels. Finally, immunogenicity was comparable between the 2 groups up to cycle 9 of treatment, with positive anti-drug antibody results reported for 3 patients in the group receiving SB3 and none in the group receiving TZB.

Although the report notes that complete safety and survival data will follow, the researchers concluded that SB3 and TZB had equivalent efficacy based on the ratio of bpCR rates and that SB3 was both well tolerated and comparable to TZB in safety, immunogenicity, and PKs. ◆

REFERENCE

Pivot XB, Bondarenko I, Dvorkin M, et al. A randomized, double-blind, phase III study comparing SB3 (trastuzumab biosimilar) with originator trastuzumab in patients treated by neoadjuvant therapy for HER2-positive early breast cancer. *J Clin Oncol.* 2017;35(suppl; abst 509).

#1 PRESCRIBED ORAL CLL THERAPY.*
MORE THAN 20,000 PATIENTS TREATED SINCE APPROVAL[1†]

MAKE IMBRUVICA® YOUR FIRST STEP

Approved in frontline CLL with or without 17p deletion[2]

CLL
SLL

IMBRUVICA® is a once-daily oral therapy indicated for:

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

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 therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this

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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)

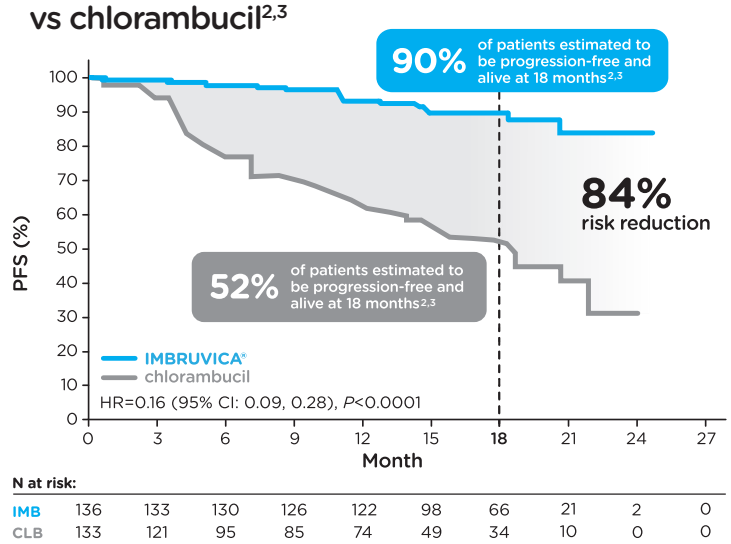
84% chlorambucil
(95% CI: 77, 90)

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

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.

*Based on market share 2016 July YTD data from IMS.
†Based on IMS data February 2014 to date.

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 leukemia.

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.

BIOSIMILARS

CT-P6, a Trastuzumab Biosimilar, Shares the Safety and Efficacy Profile of Its Reference

Kelly Davio

RESEARCH PRESENTED AT THE 2017 American Society of Clinical Oncology Annual Meeting shows that CT-P6, a proposed trastuzumab biosimilar, is safe and effective as a neoadjuvant treatment in human epidermal growth factor receptor 2–positive (HER2–positive) early breast cancer (EBC).

CT-P6, a recombinant humanized monoclonal antibody that targets HER2 that was approved by the Ministry of Food and Drug Safety, a government body in Korea, has an identical amino acid sequence and highly similar physicochemical and in vitro functional properties to trastuzumab. The results of a phase 1 trial demonstrated similar pharmacokinetics (PKs), safety, and immunogenicity between the 2 products.

This double-blind, randomized, phase 3 study sought to demonstrate the therapeutic response equivalence of CT-P6 and its reference product as determined by the pathological complete response (pCR), defined as the absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in situ. Secondary objectives for the study included obtaining additional PKs, pharmacodynamic, and safety data. The researchers also sought to evaluate additional efficacy parameters, including breast pCR (bpCR), defined as the absence of invasive cancer in the breast irrespective of ductal carcinoma in situ (DCIS) or nodal involvement; pCR without DCIS, defined as the absence of invasive cancer and in situ cancer in the breast and axillary nodes; overall response rate (ORR); and breast conservation rate.

The researchers considered 549 female patients 18 years or older who had been diagnosed with HER2–positive EBC of clinical stage I to IIIa. The patients had generally balanced demographics and disease characteristics, and were randomized at 112 centers in 22 countries. The 2 groups were treated with CT-P6 (n = 271) or the reference trastuzumab (n = 278) in combination with chemotherapy, as neoadjuvant treatment for 8 cycles, and for up to 1 year (or 10 cycles) of monotherapy as adjuvant treatment. Following neoadjuvant treatment, patients underwent surgery, at which point pathological response, PKs, and immunogenicity were assessed.

The predefined therapeutic equivalence margin for the risk ratio was 0.74 to 1.35, and the margin for the risk difference was –15% to 15%. The researchers found, with a 95% confidence interval, that the treatment risk ratio for the per-protocol set (PPS) was 0.93 (range, 0.78-1.11) and the treatment difference estimate for the PPS was –3.62% (range, –12.38% to 5.16%), both within the predefined equivalence margin. The proportion of pCR without DCIS, bpCR, and ORR were similar between the 2 treatment groups.

The study further found that serum concentrations of the treatment products, HER2-shed antigen levels, the proportion of patients who underwent breast conservation surgery, and rates of treatment-emergent adverse events (with neutropenia, anemia, and leukopenia being the most commonly reported adverse events) were similar for the 2 groups during the neoadjuvant period. None of the patients developed anti-drug antibodies during the study.

While adjuvant period data will be generated in the future, the researchers concluded that:

- CT-P6 was well tolerated.
- CT-P6 and trastuzumab are therapeutically equivalent in terms of pCR for both the PPS and the intent-to-treat set.
- CT-P6 and the reference product had similar safety profiles in the neoadjuvant period.

Secondary efficacy endpoints, as well as the results of PKs and pharmacodynamic analysis, further supported the similarity of the 2 products. ◆

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Can the 4 Ps Devise Interventions to Reduce the Financial Toxicity of Cancer?

Surabhi Dangi-Garimella, PhD

THERE IS NO ARGUING that cancer care can drain an individual's or a family's coffers. A discussion at the 2017 American Society of Clinical Oncology Annual Meeting addressed practical solutions to address the financial toxicity of cancer care and identified leads for future intervention studies aimed to prevent or reduce this burden.

The session, chaired by Yousuf Zafar, MD, MHS, associate professor of medicine, Duke University Medical Center, included the 4 Ps:

- **Pharma:** Matthew Shaulis, president, North America Oncology, Pfizer
- **Payer:** Lee N. Newcomer, MD, senior vice president, Oncology and Genetics, UnitedHealth Group
- **Physician:** Leonard Saltz, MD, chief, Gastrointestinal Oncology Service and head of the Colorectal Oncology Section, Memorial Sloan Kettering Cancer Center
- **Patient:** Shelley Fuld Nasso, MPP, chief executive officer, National Coalition for Cancer Survivorship.

Zafar asked the panelists to provide their 1 clear solution to the problem of financial toxicity in oncology—without using slides. Shaulis said that Pfizer shares the goal of improving quality of care for patients. "We need to focus and prioritize. We have to tailor market-based solutions to ensure continued innovation."

A longitudinal actuarial study conducted among cancer patients by Milliman and sponsored by Pfizer identified a 500% increase in care costs in the first month of care, mainly due to diagnosis and initial treatment, Shaulis told the audience.[1] The costs were highest for colorectal cancer and lung cancer, followed by breast cancer. "However, consistent across the numerous studies was that cancer drugs accounted for only 20% of the total cost of care."

"The burden of finances needs to be a part of the overall impact on the patient, in addition to the disease being treated."

-Shelly Fuld Nasso, MPP

From a more holistic perspective, we also should include peripheral costs, such as loss of work for the patient and caregivers, Shaulis added. "Market-based solutions are important because innovation and choice are necessary to ensure support for new medications," he added, and competition paves the path to affordable access, investment in data, and novel reimbursement mechanisms.

"As a federal or commercial insurance program, you are mandated to provide coverage to all FDA-approved drugs. So, I propose ending the mandate for providing coverage for each and every drug that is out there even if it does not provide value," said Newcomer, the payer voice in the discussion. "When you make a value decision, you are using a set of principles that others may not agree with," he said. "But with the mandate on cancer drugs, we cannot use the value quotient."

Newcomer referenced a retrospective study by UnitedHealth Group that was presented at the meeting using data from stage 4 patients with metastatic non–small cell lung cancer (mNSCLC).[2] The study found that patients treated with the 5 most commonly prescribed first-line therapies for mNSCLC have much shorter durations of therapies (52-76 days) than reported in published clinical trials, with a significant risk of hospitalization (18% to 30%) and at substantial cost ($34,971 to $108,100).

"This is an easy value decision to make, but the mandate creates a barrier," Newcomer said. He concluded that when there's competition among multiple regimens that give us the same results, we need to have the flexibility to make those value decisions.

"For me as an oncologist, my 1 solution is to know the cost of the treatment," said Saltz. "What we need is an informed discussion among stakeholders, and for that, we need everyone to have all the information.' He emphasized that he was talking about cost, not "value." Saltz believes that cost and value are not the same. "They are related. They are inversely proportional."

ATTENDEES LISTEN IN DURING A PLENARY SESSION.

However, we cannot put a number on value, and we cannot provide an accurate qualitative context to it. Saltz drove home the point that while physicians consider it their duty to provide patients an accurate estimate of toxicities and the adverse effects, discussions of the impact on patient finances "is also a part of our job. We cannot be uncomfortable about this. I'd also argue that as academicians, we could be considering costs in our trials. When we look at benefits (such as overall survival and disease-free survival), we could also include cost in the equation."

Nasso said that patients want to live their life well during and after treatment. They want to be functional, working, and understand the impact on their families during treatment. "So, the burden of finances needs to be a part of the overall impact on the patient, in addition to the disease being treated," she said.

Care planning, Nasso believes, should not be a checkbox; it should be a conduit to initiate a discussion on the topic. This should include conversations around out-of-pocket costs as well as the indirect cost of the treatment: hospital visits, work loss for self and family, etc. "Affordability should not be on the map at all, but that's where we currently are."

She emphasized the importance of a cancer care plan for the patient to revisit after their conversation with the care provider and added that the healthcare system should reimburse this process through incentives. She also urged physicians to step up and be more proactive on this front. "I'd like to see a system where we can help patients go through this process." ◆

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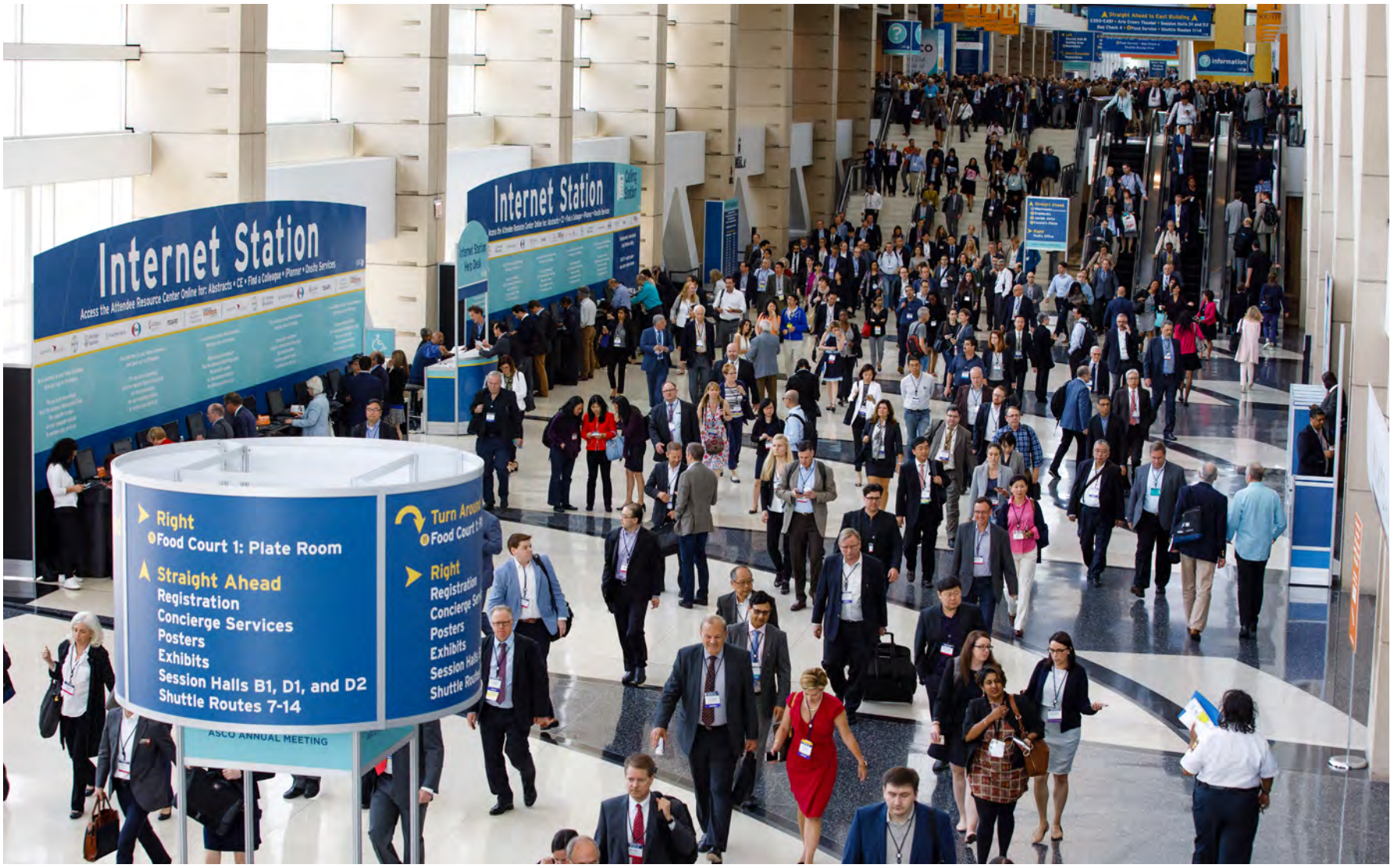

A GENERAL VIEW OF ATTENDEES AT THE ANNUAL MEETING.

Adjuvant Chemotherapy Reduces Cost, Improves Survival in NSCLC Post-Surgery

Surabhi Dangi-Garimella, PhD

A COST-EFFECTIVENESS ANALYSIS conducted by researchers at Rush University, Washington University, and St. Louis University has found that including adjuvant chemotherapy in the postsurgical treatment plan in patients with non–small cell lung cancer (NSCLC) improves survival and is cost-effective compared with surgical resection alone. The results were presented at the 2017 American Society of Clinical Oncology Annual Meeting.

Benefits of adjuvant chemotherapy in stage I non–small cell lung cancer remain controversial.

The benefits of adjuvant chemotherapy in stage I NSCLC remain controversial, as patients die from systemic relapse. Therefore, the authors of the current study evaluated the effectiveness and cost-effectiveness of adjuvant chemotherapy after surgical resection in stage IB NSCLC.

The authors conducted propensity score matching on the National Cancer Database for the period between 2004 and 2011. The Kaplan-Meier method generated conditional probabilistic incremental 1- to 5-year survival after surgical resection stratified by receipt of adjuvant chemotherapy. Medicare-allowable charges for surgical resection and adjuvant chemotherapy, and their respective complications, were used, and proportions of chemotherapeutic agents administered in real-world settings were estimated by decision modeling. The incremental cost-effectiveness ratio (ICER) was calculated over a 5-year period.

The analysis found that 3662 of 18,709 patients who met the inclusion criteria received adjuvant chemotherapy and surgical resection for stage IB NSCLC; the annual usage ranged from 15% to 27%. Propensity score matching showed an overall survival benefit of including adjuvant chemotherapy in the treatment plan over surgical resection alone (at 5 years: 68.9% vs 60.4%; $P<.001$).

The incremental cost of adjuvant chemotherapy over surgical resection alone was $11,541, and the incremental effectiveness of adjuvant chemotherapy was 0.28 life-years, with an ICER of $41,218. Using 2-way sensitivity analysis, the authors found that the combination treatment dominated for the entire range of cost and survival estimates, while with a probabilistic sensitivity analysis, the combination dominated the model above a willing-to-pay threshold of $16,000. While adjuvant chemotherapy costs could nearly double, the ICER remained under conventional thresholds. However, only 3 of the 4 common adjuvant chemotherapy regimens were cost-effective.

Based on their findings, the authors conclude that in stage IB NSCLC, surgery is insufficient to render a cure, but that including adjuvant chemotherapy in the treatment plan extends life expectancy and is cost-effective compared with surgery alone. These conclusions are valid over a range of clinically meaningful variations in cost and treatment outcomes, although a cost-conscious approach is needed when selecting an adjuvant chemotherapy regimen. ◆

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A GENERAL VIEW OF THE ANNUAL MEETING.

Brazilian Study Queries: Is NGS Cost-Effective in Advanced Lung Cancer?

Surabhi Dangi-Garimella, PhD

THE DEBATE OVER THE VALUE of using companion diagnostic tests in cancer care continues to hound providers and payers alike. Moving away from single-gene assays to gene panels, scientists are now grappling with deriving value from next-generation sequencing (NGS) as a companion diagnostic test.

NGS can sequence the entire genome or narrow down to specific areas of interest, such as the whole exome or specific genes. This is extremely important in the scenario of targeted therapy (1) to identify drugs that bring a patient response, (2) to avoid unnecessary toxicities, and (3) to reduce costs. The bottom line is proving the cost-effectiveness of NGS over other routinely used tests.

In this study, presented at the 2017 American Society of Clinical Oncology Annual Meeting, researchers from the Brazilian Cancer Foundation and the Brazilian National Cancer Institute evaluated the cost-effectiveness of a unique exam using NGS versus other routine tests, such as the ones that involve reverse transcription polymerase chain reaction and fluorescence in situ hybridization (FISH) analysis.

The target population for the study were patients with non–small cell lung cancer, adenocarcinoma, and candidates to first-line therapy, with mutations in the epidermal growth factor receptor (*EGFR*) or translocations in anaplastic lymphoma kinase (*ALK*) or *ROS-1* genes. The testing strategy followed the below pattern:

Strategy 1: Test for *EGFR* mutation: if negative, FISH analysis for *ALK*; if FISH is negative, FISH for *ROS-1*.
Strategy 2: FISH analyses for *ALK* and *ROS* are requested together.
Strategy 3: NGS for all individuals (platform includes *EGFR*, *ALK*, *ROS-1*, and other genes).

The study was analyzed from a healthcare-payer perspective based on the Brazilian private sector. Cost estimates were based on 2016 data from diagnostic companies, ANS (National Regulatory Agency= for Private Health Insurance and Plans) and AMB-CBHPM (Brazilian Medical Association). The authors found that the use of NGS increased both the cost and the rate of accurate mutations that were identified: 24% extra cases were rightly identified, and there was a simultaneous increase in treatment costs (US $800.76; 2015 purchasing power parity) attributed to the molecular testing. The incremental cost effectiveness ratio comparing NGS with sequential tests was US $3381.82 for every correct case detected. When the authors compared strategy 2 to 1, the ICER was US $937.86 for every correct case detected.

The study was founded on the effort to integrate companion diagnostics discussions on precision medicine and covered drugs in the Brazilian health system. "These findings can [subsidize] cost-effectiveness studies that incorporates subsequent treatments and survival," the authors concluded. ◆

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POSTER SESSIONS PROVIDE A WELCOME OPPORTUNITY FOR EXCHANGING RESEARCH IDEAS.

SEER-Medicare Database Analysis Notes Higher Resource Utilization Among Patients With Neuroendocrine Tumors

Surabhi Dangi-Garimella, PhD

NEUROENDOCRINE TUMORS (NETs) are diagnosed in over 12,000 people in the United States each year,[1] and survival varies by tumor type and location, among other factors.

A previous study found a significant increase in resource utilization among patients with advanced NETs, independent of the NET tumor site.[2] However, in that study, patients with pancreatic NETs had a higher rate of surgical procedures compared with those who had gastrointestinal tract or lung NETs; chemotherapy use was higher in the GI tract/lung NET population.

In the current study,[3] presented at the 2017 American Society of Clinical Oncology Annual Meeting, researchers at MD Anderson Cancer Center used data on 12,052 elderly patients diagnosed with NETs between January 2003 and December 2011 using ICD-O-3 codes from the Surveillance, Epidemiology and End Results Medicare database, with continuous Medicare Parts A and B enrollment during a 1-year period prior to NET diagnosis. Propensity score matching was used to identify a group of comparable elderly patients from a noncancer Medicare cohort as the control sample.

Potentially relevant conditions (defined as a greater than 1 indicative claim), resource utilization, and costs from patients' medical claims were documented for the 1-year period before diagnosis. To calculate resource utilization, the authors examined the number of outpatient visits, emergency department (ED) visits, and hospitalizations. Healthcare costs included inpatient, outpatient, and total costs.

The study found a higher likelihood of diarrhea (8% vs 2%), abdominal pain (37% vs 8%), irritable bowel syndrome (1.5% vs 0.6%), hypertension (72% vs 55%), heart failure (16% vs 8%), and peripheral edema (7% vs 4%) in the NET cohort compared with the non-cancer control group, respectively. Patients with NETs also had more outpatient visits (mean, 27.25 vs 18.45) and a higher percentage of ED visits (64% vs 36%) and hospitalizations (66% vs 34%).

Concurrently, patients with NETs had a significant increase in total (mean, $32,924 vs $10,048), outpatient (mean, $8869 vs 4580), and inpatient costs (mean, $24,055 vs $10,048) compared with the control cohort (all $P < .001$).

Based on their results, the authors conclude that patients with NETs incurred higher resource utilizations and costs in the year preceding the diagnosis of an NET. ◆

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1. The FDA in 2018
2. Real-world impact of digital decision-support solutions
3. Case study: health system and their technology partner
4. An update on evidence from the OCM
5. Adopting real-world evidence into a payment model
6. Patient-focused drug development
7. Teamwork in care transitions

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