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PRACTICAL, PEER-REVIEWED PERSPECTIVES

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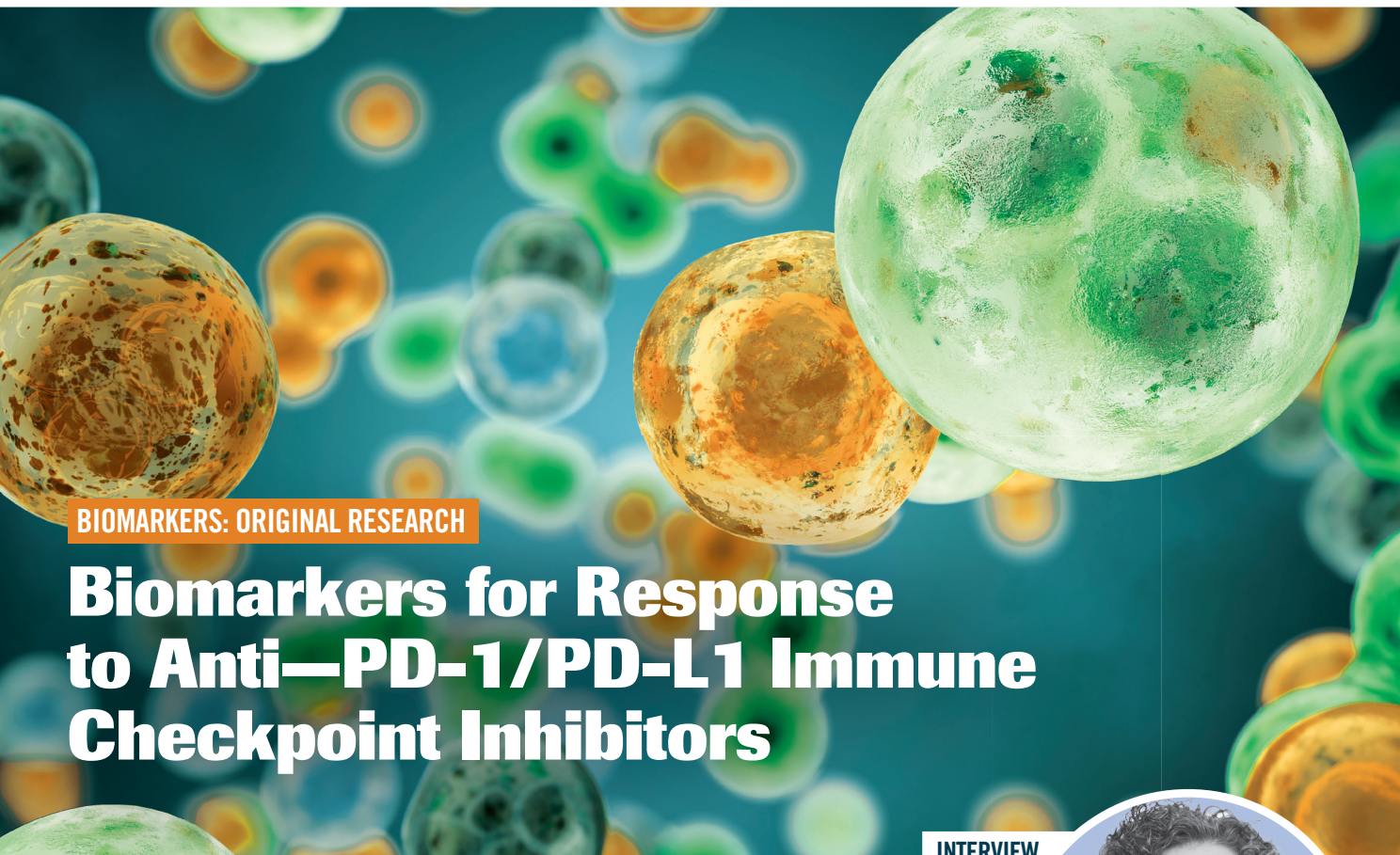


BIOMARKERS: ORIGINAL RESEARCH

Biomarkers for Response to Anti—PD-1/PD-L1 Immune Checkpoint Inhibitors

INTERVIEW

Multidisciplinary Care Is Imperative to the Future of Breast Cancer Treatment

JOYCE O'SHAUGHNESSY, MD

In adult and pediatric patients 12 years and older

Intervene With Jakafi at the *First Sign* of Initial Systemic Treatment Failure for cGVHD

Timely Diagnosis and Early Intervention Are Critical to Prevent Potentially Irreversible Organ Damage[1]

Jakafi® (ruxolitinib) is indicated for treatment of chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

REACH3 Primary Endpoint: ORR at Week 24

49.7% (82/165) with Jakafi vs 25.6% (42/164) with BAT (OR: 2.99; 95% CI, 1.86-4.80; *P*<0.0001)[2,3*†]

ORR through Week 24

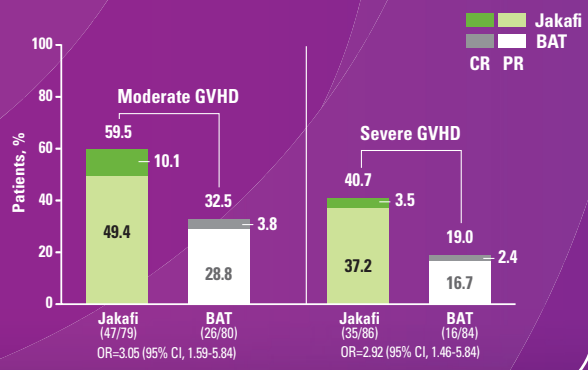
70% (116/165) with Jakafi vs 57% (94/164) with BAT[4‡]

- In the Jakafi Prescribing Information, efficacy was based on ORR through week 24 (Cycle 7 Day 1)[4]

*Overall response rate was defined as the proportion of patients with complete or partial response, according to 2014 NIH consensus criteria, at Week 24.[2]
†One-sided *P* value, odds ratio, and 95% CI were calculated using stratified Cochran-Mantel-Haenszel test, stratifying for moderate and severe cGVHD.[2]
‡Defined as proportion of patients who achieved complete or partial response, according to 2014 NIH response criteria, through Week 24 (Cycle 7 Day 1).[4]

Overall Response Rates Were Higher With Jakafi in Patients With Moderate Disease Severity at Week 24 vs BAT[3]

REACH3 Subgroup Analysis: ORR by Baseline Disease Severity at Week 24[3,5]



BAT=best available therapy; BID=twice daily; CI=confidence interval; CR=complete response; HSCT=hematopoietic stem cell transplant; GI=gastrointestinal; OR=odds ratio; ORR=overall response rate; PR=partial response.

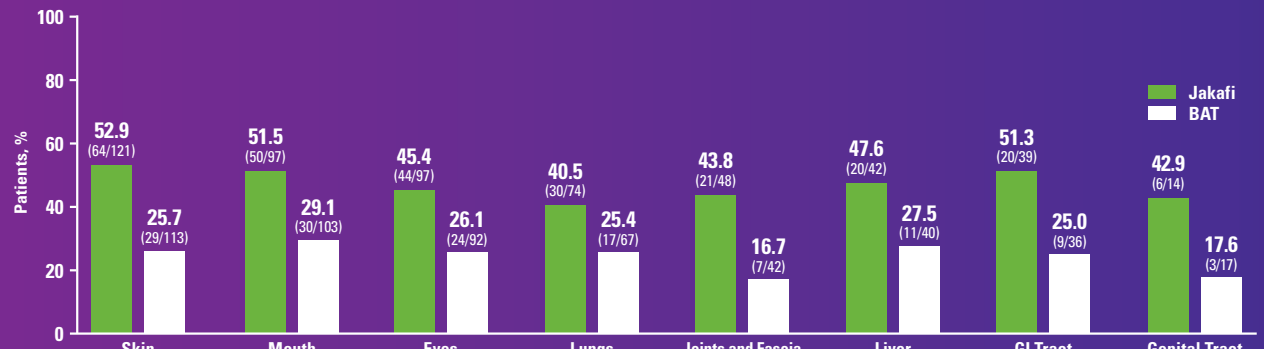
IMPORTANT SAFETY INFORMATION

- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC <0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate
- Herpes zoster infection has been reported in patients receiving Jakafi. Advise patients about early signs and symptoms of herpes zoster and to seek early treatment. Herpes simplex virus reactivation and/or dissemination has been reported in patients receiving Jakafi. Monitor patients for the development of herpes simplex infections. If a patient develops evidence of dissemination of herpes simplex, consider interrupting treatment with Jakafi; patients should be promptly treated and monitored according to clinical guidelines
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers (NMSC) including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia

Overall Response Rates Were Higher With Jakafi at Week 24 Regardless of Organs Involved at Baseline vs BAT[3]

Jakafi® ruxolitinib (tablets)
5mg • 10mg • 15mg • 20mg • 25mg

REACH3 Subgroup Analysis: ORR at Week 24 by Baseline Organ Involvement[3,a]



[a]Patients with >1 affected organ were counted in each organ subgroup. Organ involvement was defined as organ score ≥1 based on the cGVHD staging criteria.[3,6]

REACH3 was a randomized, open-label, multicenter, phase 3 study of Jakafi vs BAT in patients with steroid-refractory cGVHD (N=329).[1,2§‖¶] The starting dose for Jakafi was 10 mg BID. Crossover from BAT to Jakafi was permitted on or after Week 24 if patients progressed, had a mixed or unchanged response, developed toxicity to BAT, or experienced a cGVHD flare.[1]

[§]Patients included in the study were 12 years and older, had undergone allogeneic HSCT from any donor source/type, and had evident myeloid and platelet engraftment.[4]

[‖]BATs included ibrutinib, extracorporeal photopheresis, low-dose methotrexate, mycophenolate mofetil, rituximab, everolimus, sirolimus, imatinib, infliximab, or pentostatin.[4]

[¶]Steroid-refractory disease was defined as lack of response or disease progression after ≥1 week of prednisone 1 mg/kg/day, disease persistence without improvement after ≥4 weeks of prednisone >0.5 mg/kg/day or 1 mg/kg every other day, or increase in prednisone dose to >0.25 mg/kg/day after 2 unsuccessful attempts to taper the dose.[3,5]

Intervene with Jakafi in your appropriate patients with cGVHD.

Learn more at hcp.Jakafi.com

- Another JAK-inhibitor has increased the risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, and stroke (compared to those treated with tumor TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur
- Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. In patients with myelofibrosis (MF) and polycythemia vera (PV) treated with Jakafi in clinical trials, the rates of thromboembolic events were similar in Jakafi and control treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately
- Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi, particularly in patients with a known secondary malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers
- In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and diarrhea. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence >50%) were infections (pathogen not specified) and edema. In chronic graft-versus-host disease, the most common nonhematologic adverse reactions (incidence >20%) were infections (pathogen not specified) and viral infections
- Avoid concomitant use with fluconazole doses greater than 200 mg. Dose modifications may be required when administering Jakafi with fluconazole doses of 200 mg or less, or with strong CYP3A4 inhibitors, or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for 2 weeks after the final dose

Please see Brief Summary of Full Prescribing Information for Jakafi on the following pages.

References: 1. Lee SJ, Flower MED. Recognizing and managing chronic graft-versus-host disease. *Am Soc Hematol.* 2008;(1):134-141. **2.** Zeiser R, Polverelli N, Ram R, et al; for the REACH3 Investigators. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med.* 2021;385(3):228-238. **3.** Zeiser R, Polverelli N, Ram R, et al; for the REACH3 Investigators. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med.* 2021;385(3) (suppl):1-49. **4.** Jakafi [package insert]. Wilmington, DE: Incyte Corporation. **5.** Data on file. Incyte Corporation. Wilmington, DE. **6.** Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant.* 2015;21(3):389-401.e1.

Jakafi®
ruxolitinib (tablets)
5mg • 10mg • 15mg • 20mg • 25mg

BRIEF SUMMARY: For Full Prescribing Information, see package insert.

INDICATIONS AND USAGE: Myelofibrosis Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults. **Polycythemia Vera** Jakafi is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea. **Acute Graft-Versus-Host Disease** Jakafi is indicated for treatment of steroid-refractory acute graft-versus-host disease (aGVHD) in adult and pediatric patients 12 years and older. **Chronic Graft-Versus-Host Disease** Jakafi is indicated for treatment of chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS: Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia *[see Adverse Reactions (6.1) in Full Prescribing Information]*. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary *[see Dosage and Administration (2) in Full Prescribing Information]*. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5×10^9/L) was generally reversible by withholding Jakafi until recovery. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated *[see Dosage and Administration (2) in Full Prescribing Information]*. **Risk of Infection** Serious bacterial, mycobacterial, fungal and viral infections have occurred *[see Adverse Reactions (6.1) in Full Prescribing Information]*. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines. *Tuberculosis* Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. *Progressive Multifocal Leukoencephalopathy* Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate. *Herpes Zoster and Herpes Simplex* Herpes zoster infection has been reported in patients receiving Jakafi *[see Adverse Reactions (6.1) in Full Prescribing Information]*. Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected. Herpes simplex virus reactivation and/or dissemination has been reported in patients receiving Jakafi *[see Adverse Reactions (6.2) in Full Prescribing Information]*. Monitor patients for the development of herpes simplex infections. If a patient develops evidence of dissemination of herpes simplex, consider interrupting treatment with Jakafi; patients should be promptly treated and monitored according to clinical guidelines. *Hepatitis B* Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. **Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi** Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia *[see Dosage and Administration (2.8) in Full Prescribing Information]*, consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. **Non-Melanoma Skin Cancer (NMSC)** Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. **Lipid Elevations** Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides *[see Adverse Reactions (6.1) in Full Prescribing Information]*. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia. **Major Adverse Cardiovascular Events (MACE)** Another JAK-inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. **Thrombosis** Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. In patients with MF and PV treated with Jakafi in clinical trials, the rates of thromboembolic events were similar in Jakafi and control treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately. **Secondary Malignancies** Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi, particularly in patients with a known secondary malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers. **ADVERSE REACTIONS:** The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia *[see Warnings and Precautions (5.1) in Full Prescribing Information]* • Risk of Infection *[see Warnings and Precautions (5.2) in Full Prescribing Information]* • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi *[see Warnings and Precautions (5.3) in Full Prescribing Information]* • Non-Melanoma Skin Cancer *[see Warnings and Precautions (5.4) in Full Prescribing Information]* • Lipid Elevations *[see Warnings and Precautions (5.5) in Full Prescribing Information]* • Major Adverse Cardiovascular Events (MACE) *[see Warnings and Precautions (5.6) in Full Prescribing Information]* • Thrombosis *[see Warnings and Precautions (5.7) in Full Prescribing Information]* • Secondary Malignancies *[see Warnings and Precautions (5.8) in Full Prescribing Information]*. **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. **Myelofibrosis** The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 $\times 10^9$/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 $\times 10^9$/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia *[see Table 2]*. Thrombocytopenia, anemia and neutropenia are dose-related effects. The three most frequent nonhematologic adverse reactions were bruising, dizziness and headache *[see Table 1]*. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common nonhematologic adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 1: Myelofibrosis: Nonhematologic Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

	Jakafi (N=155)			Placebo (N=151)		
Adverse Reactions	**All Grades[a] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Bruising[b]	23	< 1	0	15	0	0
Dizziness[c]	18	< 1	0	7	0	0
Headache	15	0	0	5	0	0
Urinary Tract Infections[d]	9	0	0	5	< 1	< 1
Weight Gain[e]	7	< 1	0	1	< 1	0
Flatulence	5	0	0	< 1	0	0
Herpes Zoster[f]	2	0	0	< 1	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura
[c] includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis
[d] includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present
[e] includes weight increased, abnormal weight gain
[f] includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Reactions: Anemia In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (< 1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2

in patients treated with Jakafi and 1.7 in placebo treated patients. **Thrombocytopenia** In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50×10^9/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in < 1% of patients receiving Jakafi and < 1% of patients receiving control regimens. Patients with a platelet count of 100×10^9/L to 200×10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200×10^9/L (17% versus 7%). **Neutropenia** In the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study[a]

	Jakafi (N=155)			Placebo (N=151)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Thrombocytopenia	70	9	4	31	1	0
Anemia	96	34	11	87	16	3
Neutropenia	19	5	2	4	< 1	1

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-Controlled Study • 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. • 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was < 1% for Jakafi with no Grade 3 or 4 AST elevations. • 17% of patients treated with Jakafi and < 1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was < 1% for Jakafi with no Grade 3 or 4 cholesterol elevations.

Polycythemia Vera In a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy *[see Clinical Studies (14.2) in Full Prescribing Information]*. The most frequent adverse reaction was anemia. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi. Table 3 presents the most frequent nonhematologic adverse reactions occurring up to Week 32.

Table 3: Polycythemia Vera: Nonhematologic Adverse Reactions Occurring in ≥ 5% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

	Jakafi (N=110)		Best Available Therapy (N=111)	
Adverse Reactions	**All Grades[a] (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Diarrhea	15	0	7	< 1
Dizziness[b]	15	0	13	0
Dyspnea[c]	13	3	4	0
Muscle Spasms	12	< 1	5	0
Constipation	8	0	3	0
Herpes Zoster[d]	6	< 1	0	0
Nausea	6	0	4	0
Weight Gain[e]	6	0	< 1	0
Urinary Tract Infections[f]	6	0	3	0
Hypertension	5	< 1	3	< 1

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes dizziness and vertigo
[c] includes dyspnea and dyspnea exertional
[d] includes herpes zoster and post-herpetic neuralgia
[e] includes weight increased and abnormal weight gain
[f] includes urinary tract infection and cystitis

Clinically relevant laboratory abnormalities are shown in Table 4.

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment[a]

	Jakafi (N=110)			Best Available Therapy (N=111)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Hematology						
Anemia	72	< 1	< 1	58	0	0
Thrombocytopenia	27	5	< 1	24	3	< 1
Neutropenia	3	0	< 1	10	< 1	0
Chemistry						
Hypercholesterolemia	35	0	0	8	0	0
Elevated ALT	25	< 1	0	16	0	0
Elevated AST	23	0	0	23	< 1	0
Hypertriglyceridemia	15	0	0	13	0	0

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Acute Graft-Versus-Host Disease In a single-arm, open-label study, 71 adults (ages 18-73 years) were treated with Jakafi for aGVHD failing treatment with steroids with or without other immunosuppressive drugs *[see Clinical Studies (14.3) in Full Prescribing Information]*. The median duration of treatment with Jakafi was 46 days (range, 4-382 days). There were no fatal adverse reactions to Jakafi. An adverse reaction resulting in treatment discontinuation occurred in 31% of patients. The most common adverse reaction leading to treatment discontinuation was infection (10%). Table 5 shows the adverse reactions other than laboratory abnormalities.

Table 5: Acute Graft-Versus-Host Disease: Nonhematologic Adverse Reactions Occurring in ≥ 15% of Patients in the Open-Label, Single-Cohort Study

	Jakafi (N=71)	
Adverse Reactions[a]	**All Grades[b] (%)**	**Grade 3-4 (%)**
Infections (pathogen not specified)	55	41
Edema	51	13
Hemorrhage	49	20
Fatigue	37	14
Bacterial infections	32	28
Dyspnea	32	7
Viral infections	31	14
Thrombosis	25	11
Diarrhea	24	7
Rash	23	3
Headache	21	4
Hypertension	20	13
Dizziness	16	0

[a] Selected laboratory abnormalities are listed in Table 6 below
[b] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03

Selected laboratory abnormalities during treatment with Jakafi are shown in Table 6.

Table 6: Acute Graft-Versus-Host Disease: Selected Laboratory Abnormalities Worsening from Baseline in the Open-Label, Single Cohort Study

	Jakafi (N=71)	
	Worst grade during treatment	
Laboratory Parameter	**All Grades[a] (%)**	**Grade 3-4 (%)**
Hematology		
Anemia	75	45
Thrombocytopenia	75	61
Neutropenia	58	40
Chemistry		
Elevated ALT	48	8
Elevated AST	48	6
Hypertriglyceridemia	11	1

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

Chronic Graft-Versus-Host Disease In a Phase 3, randomized, open-label, multi-center study, 165 patients were treated with Jakafi and 158 patients were treated with best available therapy for cGVHD failing treatment with steroids with or without other immunosuppressive drugs *[see Clinical Studies (14.4) in Full Prescribing Information]*; sixty-five patients crossed over from best available therapy to treatment with Jakafi, for a total of 230 patients treated with Jakafi. The median duration of exposure to Jakafi for the study was 49.7 weeks (range, 0.7 to 144.9 weeks) in the Jakafi arm. One hundred and nine (47%) patients were on Jakafi for at least 1 year. There were five fatal adverse reactions to Jakafi, including 1 from toxic epidermal necrolysis and 4 from neutropenia, anemia and/or thrombocytopenia. An adverse reaction resulting in treatment discontinuation occurred in 18% of patients treated with Jakafi. An adverse reaction resulting in dose modification occurred in 27%, and an adverse reaction resulting in treatment interruption occurred in 23%. The most common hematologic adverse reactions (incidence > 35%) are anemia and thrombocytopenia. The most common nonhematologic adverse reactions (incidence ≥ 20%) are infections (pathogen not specified) and viral infection. Table 7 presents the most frequent nonlaboratory adverse reactions occurring up to Cycle 7 Day 1 of randomized treatment.

Table 7: Chronic Graft-Versus-Host Disease: All-Grade (≥ 10%) and Grades 3-5 (≥ 3%) Nonlaboratory Adverse Reactions Occurring in Patients in the Open-Label, Active-controlled Study up to Cycle 7 Day 1 of Randomized Treatment

	Jakafi (N = 165)		Best Available Therapy (N = 158)	
Adverse Reactions[b]	**All Grades[a] (%)**	**Grade ≥ 3 (%)**	**All Grades (%)**	**Grade ≥ 3 (%)**
Infections and infestations				
Infections (pathogen not specified)	45	15	44	16
Viral infections	28	5	23	5
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	18	1	13	0
General disorders and administration site conditions				
Pyrexia	16	2	9	1
Fatigue	13	1	10	2
Edema	10	1	12	1
Vascular disorders				
Hypertension	16	5	13	7
Hemorrhage	12	2	15	2
Respiratory, thoracic and mediastinal disorders				
Cough	13	0	8	0
Dyspnea	11	1	8	1
Gastrointestinal disorders				
Nausea	12	0	13	2
Diarrhea	10	1	13	1

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03
[b] Grouped terms that are composites of applicable adverse reaction terms.

Clinically relevant laboratory abnormalities are shown in Table 8.

Table 8: Chronic Graft-Versus-Host Disease: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Cycle 7 Day 1 of Randomized Treatment[a]

	Jakafi (N = 165)		Best Available Therapy (N = 158)	
Laboratory Test	**All Grades[b] (%)**	**Grade ≥ 3 (%)**	**All Grades (%)**	**Grade ≥ 3 (%)**
Hematology				
Anemia	82	13	75	8
Neutropenia	27	12	23	9
Thrombocytopenia	58	20	54	17

	Jakafi (N = 165)		Best Available Therapy (N = 158)	
Laboratory Test	**All Grades[b] (%)**	**Grade ≥ 3 (%)**	**All Grades (%)**	**Grade ≥ 3 (%)**
Chemistry				
Hypercholesterolemia	88	10	85	8
Elevated AST	65	5	54	6
Elevated ALT	73	11	71	16
Gamma glutamyltransferase increased	81	42	75	38
Creatinine increased	47	1	40	2
Elevated lipase	38	12	30	9
Elevated amylase	35	8	25	4

[a] Presented values are worst Grade values regardless of baseline

[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of Jakafi. 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: • Infections and Infestations: Herpes simplex virus reactivation and/or dissemination.

DRUG INTERACTIONS: Effect of Other Drugs on Jakafi: Fluconazole Concomitant use of Jakafi with fluconazole increases ruxolitinib exposure *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*, which may increase the risk of exposure-related adverse reactions. Avoid concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily. Reduce the Jakafi dosage when used concomitantly with fluconazole doses of less than or equal to 200 mg *[see Dosage and Administration (2.6) in Full Prescribing Information]*. **Strong CYP3A4 Inhibitors** Concomitant use of Jakafi with strong CYP3A4 inhibitors increases ruxolitinib exposure *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*, which may increase the risk of exposure-related adverse reactions. Reduce the Jakafi dosage when used concomitantly with strong CYP3A4 inhibitors except in patients with aGVHD or cGVHD *[see Dosage and Administration (2.6) in Full Prescribing Information]*. **Strong CYP3A4 Inducers** Concomitant use of Jakafi with strong CYP3A4 inducers may decrease ruxolitinib exposure *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*, which may reduce efficacy of Jakafi. Monitor patients frequently and adjust the Jakafi dose based on safety and efficacy *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS: Pregnancy: Risk Summary When pregnant rats and rabbits were administered ruxolitinib during the period of organogenesis adverse developmental outcomes occurred at doses associated with maternal toxicity *(see Data)*. There are no studies with the use of Jakafi in pregnant women to inform drug-associated risks. The background risk of major birth defects and miscarriage for the indicated populations is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk in the U.S. general population of major birth defects is 2% to 4% and miscarriage is 15% to 20% of clinically recognized pregnancies. **Data** *Animal Data* Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations. Adverse developmental outcomes, such as decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). **Lactation: Risk Summary** No data are available regarding the presence of ruxolitinib in human milk, the effects on the breast fed child, or the effects on milk production. Ruxolitinib and/or its metabolites were present in the milk of lactating rats *(see Data)*. Because many drugs are present in human milk and because of the potential for thrombocytopenia and anemia shown for Jakafi in human studies, discontinue breastfeeding during treatment with Jakafi and for two weeks after the final dose. **Data** *Animal Data* Lactating rats were administered a single dose of [^{14}C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13-fold the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma. **Pediatric Use:** Myelofibrosis The safety and effectiveness of Jakafi for treatment of myelofibrosis in pediatric patients have not been established. Polycythemia Vera The safety and effectiveness of Jakafi for treatment of polycythemia vera in pediatric patients have not been established. Acute Graft-Versus-Host Disease The safety and effectiveness of Jakafi for treatment of steroid-refractory aGVHD has been established for treatment of pediatric patients 12 years and older. Use of Jakafi in pediatric patients with steroid-refractory aGVHD is supported by evidence from adequate and well-controlled trials of Jakafi in adults *[see Clinical Studies (14.3) in Full Prescribing Information]* and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of steroid-refractory aGVHD has not been established in pediatric patients younger than 12 years old. Chronic Graft-Versus-Host Disease The safety and effectiveness of Jakafi for treatment of cGVHD after failure of one or two lines of systemic therapy has been established for treatment of pediatric patients 12 years and older. Use of Jakafi in pediatric patients with cGVHD after failure of one or two lines of systemic therapy is supported by evidence from adequate and well-controlled trials of Jakafi in adults and adolescents *[see Clinical Studies (14.4) in Full Prescribing Information]* and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of cGVHD has not been established in pediatric patients younger than 12 years old. Other Myeloproliferative Neoplasms, Leukemias, and Solid Tumors The safety and effectiveness of ruxolitinib were assessed but not established in a single-arm trial (NCT01164163) in patients with relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms. The patients included 18 children (age 2 to < 12 years) and 14 adolescents (age 12 to < 17 years). Overall, 19% of patients received more than one cycle. No new safety signals were observed in pediatric patients in this trial. The safety and effectiveness of ruxolitinib in combination with chemotherapy for treatment of high-risk, de novo CRLF2 rearranged or JAK pathway–mutant Ph-like acute lymphoblastic leukemia (ALL) were assessed but not established in a single-arm trial (NCT02723994). The patients included 2 infants (age < 2 years), 42 children (age 2 to < 12 years) and 62 adolescents (age 12 to < 17 years). No new safety signals were observed in pediatric patients in this trial. Juvenile Animal Toxicity Data Administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at exposures that are at least 27% the clinical exposure at the maximum recommended dose of 25 mg twice daily. **Geriatric Use:** Of the total number of patients with MF in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. Clinical studies of Jakafi in patients with aGVHD did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Of the total number of patients with cGVHD treated with Jakafi in clinical trials, 11% were 65 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. **Renal Impairment:** Total exposure of ruxolitinib and its active metabolites increased with moderate (CLcr 30 to 59 mL/min) and severe (CLcr 15 to 29 mL/min) renal impairment, and ESRD (CLcr less than 15 mL/min) on dialysis *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Modify Jakafi dosage as recommended *[see Dosage and Administration (2.7) in Full Prescribing Information]*. **Hepatic Impairment:** Exposure of ruxolitinib increased with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Reduce Jakafi dosage as recommended in patients with MF or PV with hepatic impairment *[see Dosage and Administration (2.7) in Full Prescribing Information]*. Reduce Jakafi dosage as recommended for patients with Stage 4 liver aGVHD. Monitor blood counts more frequently for toxicity and modify the Jakafi dosage for adverse reactions if they occur for patients with Score 3 liver cGVHD *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3) in Full Prescribing Information]*. **OVERDOSAGE:** There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of Jakafi.

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MAY 2023 ▪ VOL. 37 ▪ NO. 5

OUR BOARD MEMBERS HAVE BEEN BUSY! TAKE A LOOK TO SEE WHAT THEY HAVE BEEN UP TO.

María T. Bourlon, MD, MS
Clinical Quandaries Series Editor
Bourlon was recently awarded the 2023 International Women Who Conquer Cancer Mentorship Award from the American Society of Clinical Oncology (ASCO). This award was designed to recognize female leaders in oncology who are also mentors to others in the field. The ceremony will take place during the 2023 ASCO Annual Meeting.

Jason S. Starr, DO
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Rafael Fonseca, MD
@Rfonsi1

Starr and Fonseca, both from the Mayo Clinic, have accepted positions as social media editorial board members for CancerNetwork® and the journal *ONCOLOGY*. They will be hosting and facilitating different social events with their colleagues. Areas of focus are breaking research, recent FDA approvals, and conferences. Interested in this new initiative? Contact us today!

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The Painful Problem of Biosimilars in the Clinic

Just this week I ordered erythropoietin for a patient with chemotherapy-induced anemia. It was obvious, and the treatment was completely indicated. However, my electronic medical records order set had it listed as epoetin alfa (Procrit), so it took many hours and emails to eventually get epoetin alfa-epbx (Retacrit) approved by his insurance.

Why the major hassle for the use of biosimilar drugs (**Table**)? Why can't we just order erythropoietin, filgrastim (Neupogen), bevacizumab (Avastin), or trastuzumab (Herceptin) and receive approval for any of the biosimilars?

The approval process for biosimilars is a result of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), a part of Obamacare. This congressional act was meant to parallel the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Amendments, for generic drugs, but sadly, the FDA has inadvertently undermined this process and created a lot of pain in the clinic.

The Hatch-Waxman Amendments created an important pathway for generic drugs, which allowed compounds of an identical chemical structure and bioequivalence to be approved without clinical trials. However, with the advent of "biologic" compounds that are not synthesized, but rather harvested from cell cultures, the drugs would never be chemically identical. Note: Even original brand compounds are not identical to themselves after a few years due to biological "drift"!

Therefore, the BPCI Act created an alternative pathway for biologically manufactured macromolecules to be considered "biosimilar." If the drug acts on the same target and is considered "highly similar with no meaningful clinical differences," it can be approved as a biosimilar. The preponderance of data required is preclinical, with laboratory analyses and binding assays, for example. In addition, one clinical trial is required to demonstrate the equivalent clinical activity to the originator molecule. If the agent is approved based on 1 trial, the biosimilar receives all the FDA-approved use indications that apply to the originator.

Then there is the problem of further FDA regulation. The FDA has legitimate concerns about monitoring the clinical activity and toxicity of these biosimilars through the "pharmacovigilance" program. To better track these varied biosimilars, the FDA issued a guidance in 2017 requiring all biologics to append the generic name with a 4-letter suffix, which should be random and of no meaning. This would allow better tracking of any problems with a particular biosimilar from a certain manufacturer.

However, by requiring the suffix, the FDA created a usage nightmare. Each biosimilar has its own identity today as a "branded biosimilar" (eg, for bevacizumab, Avastin is the originator and bevacizumab-awwb [Mvasi], bevacizumab-bvzr [Zirabev], and bevacizumab-maly [Alymsys] are all biosimilars). In addition, each of these drugs has its own J-code for billing. As a result, it becomes a game of ordering a biosimilar, insurance denying, and then trying to guess which one they will cover for payment. We have to reorder the drug with the correct biosimilar for which the insurer will pay. This is undesirable in a number of ways: (1) causes confusion in ordering the proper biosimilar, (2) is a waste of time for approvals and correction of orders, (3) requires additional pharmacy space and effort to stock multiple biosimilars because we cannot predict which one will be reimbursed, and (4) results in a lack of real competition between biosimilars, resulting in less competition and price reduction.

The need for pharmacovigilance should be balanced against the downstream pain experienced every day in the clinic. The drugs can be traced by manufacturer and lot number without suffixes and branded biosimilars (as with generic drugs). This is a case of "belt and suspenders," and the belt is way too tight!

We should also note that clinicians have no scientific basis for preferring 1 approved biosimilar over another. We do not see the data on approvals and have to look hard to even find the manufacturer. To date, no biosimilar product has failed to live up to expectations as a drug compared with the originator drug, yet we experience the pain of prescribing biosimilars daily in the clinic. ■

TABLE. **FDA-Approved Oncology Drug Biosimilars as of April 2023**

Biosimilar	Approval	Reference product	Manufacturer
Bevacizumab-awwb (Mvasi)	September 2017	Bevacizumab (Avastin)	Amgen Inc
Bevacizumab-bvzr (Zirabev)	June 2019	Bevacizumab (Avastin)	Pfizer Inc
Bevacizumab-maly (Alymsys)	April 2022	Bevacizumab (Avastin)	Amneal Pharmaceuticals, Inc
Bevacizumab-adcd (Vegzelma)	September 2022	Bevacizumab (Avastin)	Celltrion USA
Epoetin alfa-epbx (Retacrit)	May 2018	Epoetin alfa (Epogen)	Hospira, Inc
Trastuzumab-dkst (Ogivri)	December 2017	Trastuzumab (Herceptin)	Mylan GmbH
Trastuzumab-pkrb (Herzuma)	December 2018	Trastuzumab (Herceptin)	Celltrion, Inc/Teva Pharmaceutical Industries Ltd
Trastuzumab-dttb (Ontruzant)	January 2019	Trastuzumab (Herceptin)	Merck Sharp & Dohme Corp/Samsung Bioepis Co, Ltd
Trastuzumab-qyyp (Trazimera)	March 2019	Trastuzumab (Herceptin)	Pfizer Inc
Trastuzumab-anns (Kanjinti)	June 2019	Trastuzumab (Herceptin)	Amgen Inc/Allergan plc
Filgrastim-sndz (Zarxio)	March 2015	Filgrastim (Neupogen)	Sandoz Inc
Filgrastim-aafi (Nivestym)	July 2018	Filgrastim (Neupogen)	Hospira, Inc
Filgrastim-ayow (Releuko)	February 2022	Filgrastim (Neupogen)	Kashiv Biosciences LLC/ Amneal Biosciences, LLC
Pegfilgrastim-jmdb (Fulphila)	June 2018	Pegfilgrastim (Neulasta)	Mylan Pharmaceuticals Inc
Pegfilgrastim-cbqv (Udenyca)	November 2018	Pegfilgrastim (Neulasta)	Coherus BioSciences, Inc
Pegfilgrastim-bmez (Ziextenzo)	November 2019	Pegfilgrastim (Neulasta)	Sandoz Inc
Pegfilgrastim-apgf (Nyvepria)	June 2020	Pegfilgrastim (Neulasta)	Pfizer Inc
Pegfilgrastim-pbbk (Fylnetra)	May 2022	Pegfilgrastim (Neulasta)	Amneal Pharmaceuticals LLC
Pegfilgrastim-fpgk (Stimufend)	September 2022	Pegfilgrastim (Neulasta)	Fresenius Kabi
Rituximab-abbs (Truxima)	November 2018	Rituximab (Rituxan)	Celltrion, Inc/Teva Pharmaceuticals USA, Inc
Rituximab-pvvr (Ruxience)	July 2019	Rituximab (Rituxan)	Pfizer Inc
Rituximab-arrx (Riabni)	December 2020	Rituximab (Rituxan)	Amgen, Inc

MEET OUR EXPERT

Joyce O'Shaughnessy, MD, the Celebrating Women Chair in Breast Cancer Research at Baylor University Medical Center and director of the Breast Cancer Research Program at Texas Oncology, US Oncology, in Dallas, Texas. She is also the program chair for the 22nd Annual International Congress on the Future of Breast Cancer® East hosted by Physician's Education Resource®, LLC (PER®).

Multidisciplinary Care Is Imperative to the Future of Breast Cancer Treatment

"Sometimes we have to advocate, but mostly we have to hire experts in our practice who can access these agents through free assistance programs, partial assistance, co-pay assistance, etc. That is an effort, a big part of the infrastructure and practices, to be able to access therapies."

Prior to the *22nd Annual* International Congress on the Future of Breast Cancer East, *ONCOLOGY* spoke with Joyce O'Shaughnessy, MD, regarding the importance of multidisciplinary cancer-focused treatments for patients with breast cancer.

O'Shaughnessy also spoke about how insurance can be a barrier to patients receiving the care they need and touched upon why she enjoys this meeting so much and how it brings together expert opinions in the industry.

Q: How important is multidisciplinary care in the breast cancer space?

O'SHAUGHNESSY: As I always tell my patients, breast cancer treatment and management [are] always 2 parts. You've got to take optimal care of the local regional area, the breast itself, and the surrounding lymph node beds. You've got to get control of the disease; you never want to see it back again. You also have to have restoration; you [have] to have reconstruction. In some cases, not everybody needs that. That's very important to be done [for] the patient's health and overall well-being, but [it is] critically important for breast cancer control.

Then you have your systemic management. What [are] the chances that the breast cancer has already metastasized? Or in the case of metastatic disease, managing overt disease, there are still multidisciplinary issues around who could still benefit from the [surgical] management of the primary [site of disease]. How could patients benefit from radiation management of the primary [site of disease] as well as palliative radiation approaches or surgical approaches [for] the patient with metastatic disease? We've always got dual goals, local regional management or management of a particularly morbid sight of metastatic disease, as well as general systemic management.

Q: When do you decide to bring the entire multidisciplinary team into the picture?

O'SHAUGHNESSY: Patients will usually see surgical and medical oncologists immediately after diagnosis, particularly if they have stage II or III disease. For stage I disease, patients may simply begin with the surgeon, [who will] then bring the medical oncologist and the radiation oncologist in if the patient clearly needs to go to surgery first. Otherwise, though, the surgeon will reach out to the radiation oncologist and medical oncologist to get their consultation sooner than later. Most of us have weekly tumor boards, [during which] we will get a multidisciplinary discussion of patients, either all patients or controversial patients [for whom] you need to hear, "OK, there are some different options here. What should we do? What [does] the team think is the best approach for this patient?"

Q: What are some barriers to optimal care in this space?

O'SHAUGHNESSY: Most patients have insurance, either federal insurance, insurance to exchange, Medicaid, government insurance, Medicare, or commercial insurance. Within the world of insured patients, barriers [include] how fast we can get the patients in and [seen and treated]. All of us in our practices are very aware that we all generally have internal goals of seeing a new patient within a week to have that initial diagnosis. The other barrier is access to therapies—expensive therapies, systemic therapies, and sometimes needed radiation therapy approaches such as proton beam radiation therapy. In most of our practices, experts work with third-party payers to access care, but also these issues of co-pay assistance are a very big deal. Some of these are very costly therapies. Sometimes we have to advocate for coverage.

For example, scalp cooling is a very important quality-of-life issue [that] patients with breast cancer or any cancer [are interested in] because getting [certain types of] therapy causes alopecia. Scalp cooling is something that we need to advocate [for] more because there's growing partial coverage for that; it just needs to be expanded and increased. This is important for patients to be able to access in the scheme of things, and the cost is not very much compared with the therapies we're giving to people. Sometimes we have to advocate, but mostly we have to hire experts in our practice who can access these agents through free assistance programs, partial assistance, co-pay assistance, etc. That is an effort, a big part of the infrastructure and practices, to be able to access therapies.

For uninsured patients, generally there are safety net facilities that patients can be treated [at]. Up in the Dallas–Fort Worth metroplex, we have several public hospitals that are our safety net programs, and then these facilities help patients access what they're entitled to, for example, Medicaid. A lot of people are entitled to Medicaid; they just need some help accessing it. Our practice will do that as well. For patients that are clearly Medicaid eligible, they don't have insurance, we'll help them get that. We will make sure that we direct them to insurance and exchanges and help them upgrade their insurance options. This is a very big issue, and practices have experts in this. For patients that simply need the care provided by the county, all over the country, there's access through the public hospital system.

Q: What do you enjoy most about this conference that makes you want to keep attending?

O'SHAUGHNESSY: I love the data. I love the science. I need and benefit from hearing the data presented by expert faculty who have pulled together the new data, but importantly, put it in the context of the existing data. I need to rehear the new data multiple times and in context, and then I also like hearing the debate [portion]. I like hearing multiple expert opinions in 1 setting around a particular case or a particular controversial management scenario. Not surprisingly, the surgeons don't always agree with the radiation oncologist in terms of approach. I like to hear a difference of opinion. [What's] valuable for me is hearing it again in the context and then hearing it vetted, as well as seeing how other people feel this should be applied to practice. ■

An Arthroscopic Approach for the Intralesional Curettage of Giant Cell Tumor of the Distal Femur: A Case Report

Hans Kristian Nugraha, MD, SpOT[1]; I Gede Eka Wiratnaya, MD, PhD, SpOT(K)[1]; and Putu Astawa, MD, MSc, PhD, SpOT(K)[1]

ABSTRACT

As a locally aggressive primary benign tumor, giant cell tumor of bone (GCTB) presents a challenge to surgeons, as it often recurs regardless of surgical resection. This report describes a case of GCTB of the distal femur in a man, aged 39 years, treated with intralesional curettage through an arthroscopic approach. A 360° view of the tumor cavity can be achieved with the help of an arthroscope, which can help complete intralesional curettage and minimize possible larger approach-related complications. The result is favorable in terms of functional outcome and recurrence after 1-year follow-up.

Introduction

Surgeons face a challenge with giant cell tumor of bone (GCTB), as it has a tendency to recur even after surgical resection. Some previous studies showed that the recurrence rate of this pathology could reach 90%, regardless of surgical treatments. Treatments vary; they include intralesional curettage, wide excision, bone grafting, adjuvant addition, and prosthetic replacement. Intralesional curettage is preferred in many cases of GCTB; however, an arthroscopic approach is rarely chosen nor reported in the literature.[1,2] In this case report, we present a 39-year-old man with GCTB of the distal femur who underwent an arthroscopic intralesional curettage. Our findings indicate a positive functional outcome and low risk of recurrence.

Case Presentation

A man, aged 39 years, came to our outpatient clinic with the chief complaint of pain in his left thigh for the previous 6 months. The pain occurred mainly with activity (eg, gardening, climbing stairs), and improved with rest. The pain was accompanied by a slow-growing lump on his left knee. One month prior to his visit, the patient had almost fallen and had used his left leg as a support to prevent himself from falling. Since then, he felt that his left knee was swollen and he had prolonged difficulty in walking. The swelling on his left knee had diminished over time, but the pain had remained. He reported no weight loss, fever, nocturnal pain, or fatigue. At presentation, the patient used 2 crutches to help him in his daily activities, including work. The patient is employed in a public health department and his knee issues were disrupting his proper job performance.

On physical examination, we found swelling over the left knee, without venectasia or shiny skin. Palpation confirmed the existence of a painful lump sized 8.5 × 8 cm at the lateral side of the left distal femur, fixed with an ill-defined border and solid consistency. The pulse of the femoral and popliteal arteries was still palpable, with normal capillary refill time and sensation. However, the active range of motion (ROM) of the left knee was limited, especially in flexion. The active ROM of the distal leg was within normal limits

FIGURE 1. **Clinical Picture of the Patient, Presenting With a Lump Over His Left Knee**

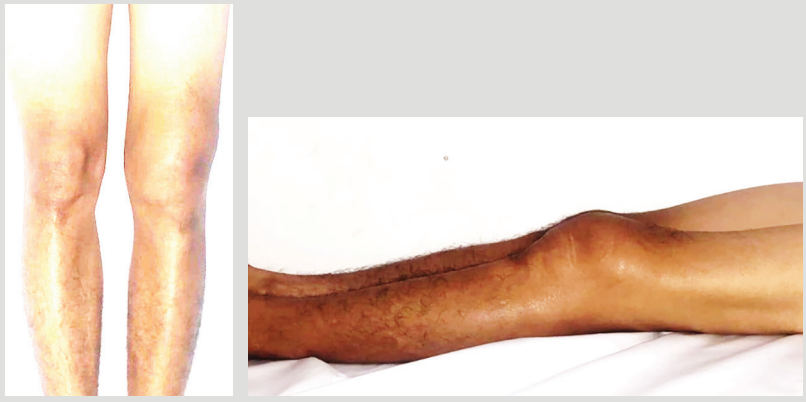
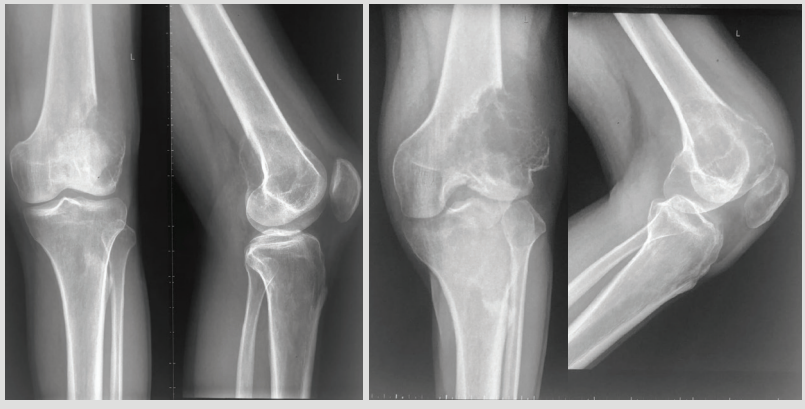


FIGURE 2. **Plain Radiographs Taken Prior to Surgery (first image taken 1 month prior to the second)**



(**Figure 1**). A plain x-ray demonstrated a lytic destructive lesion of the lateral condyle femur (**Figure 2**).

From the clinical and radiological examination, the patient was suspected to have GCTB of the left distal femur. We, therefore, decided to do an arthroscope-assisted fixation of the fracture and intralesional curettage of the GCTB.

During the surgery, the patient was positioned supine, with the knee in 90° flexion. An incision was made for lateral portal insertion, at the soft spot above the joint line 2 cm lateral to the patellar tendon. The hematoma was drained, and an anteromedial portal was established with an outside-in technique. The joint was then irrigated with copious amounts of saline solution. A guide wire was passed from the lateral femoral condyle using a 6.5-mm drill bit. The presence of a mass on the lateral condyle of the femur was confirmed, and a sample taken for frozen section examination demonstrated a histological result in accordance with GCTB. A lateral longitudinal incision was made on the distal femur, extending up to expose the tumor. The fascia was incised to expose the lateral femoral condyle. Curettage and ablation were performed arthroscopically. A cortical window measuring 2 × 2 cm was made with an intact periosteal hinge. A 30° arthroscope with a light source was introduced through the cortical window. After the introduction of the scope, the light source cable was rotated to provide a 360° visualization of the tumor cavity. The surrounding structure of the cortical window was covered with a sterile mop to avoid spillage of the tumor cells or of irrigation fluid in the surrounding tissue. A small curette, 4.5-mm shaver tip, and high-speed burr were interchangeably used to curette the GCTB cavity. The end point of curettage was the visualization of the normal cortical bone through the arthroscope. During the curettage, copious amounts of normal saline were used for irrigation of the cavity. After curettage, the cavity was filled with polymethyl methacrylate cement. A distal femoral locking plate with 5 holes and 8 screws was then installed with the minimally invasive plate osteosynthesis (MIPO) technique. After hemostasis was achieved, the incision was closed in layers over a drain. The operation procedure and radiograph after the procedure are shown in **Figure 3** and **Figure 4**.

Knee ROM exercises were started immediately postoperatively, as tolerated. The patient was advised to walk with 2 crutches and to not bear weight for 4 weeks, before gradually increasing weight according to his pain tolerance. He was asked to return for outpatient follow-up every month for the initial 6 months. After 1 year of follow-up, the patient has full ROM and has demonstrated no sign of recurrence on serial radiography and a satisfactory functional outcome; he has returned

to his occupational and daily activities (**Figure 5** and **Figure 6**).

Discussion

GCTB was first described by Cooper and Travers in 1818 and is characterized histologically by a multinucleated giant cell tumor with a background of mononuclear stromal cells. GCTB occurs mainly (80%) in patients aged 20 to 40 years; fewer than 3% of cases occur in patients younger than 14 years, and only 13% in patients older than 50 years.[3,4] GCTB accounts for 5% of all primary bone tumors and 20% of benign skeletal tumors. The 3 most common locations are the distal femur, proximal tibia, and distal radius, making it one of the differential diagnoses for radiographic lytic bone lesions in the metaphyseal-epiphyseal area of long bones.[4,5]

Traditionally, GCTB has been treated surgically with curettage and placement of cement (polymethyl methacrylate). As most GCTBs are benign and located near a joint, some orthopedic surgeons favor an intralesional approach that preserves the anatomy of the bone during resection. However, because the local behavior of GCTBs can be

FIGURE 3. **Intraoperative Pictures During Arthroscopic Curettage and Ablation**

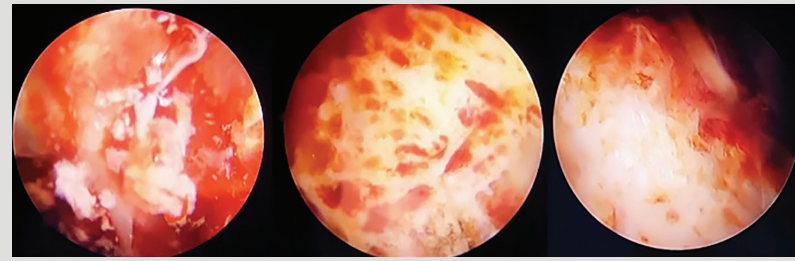


FIGURE 4. **Postoperative Radiological Picture of Left Knee**

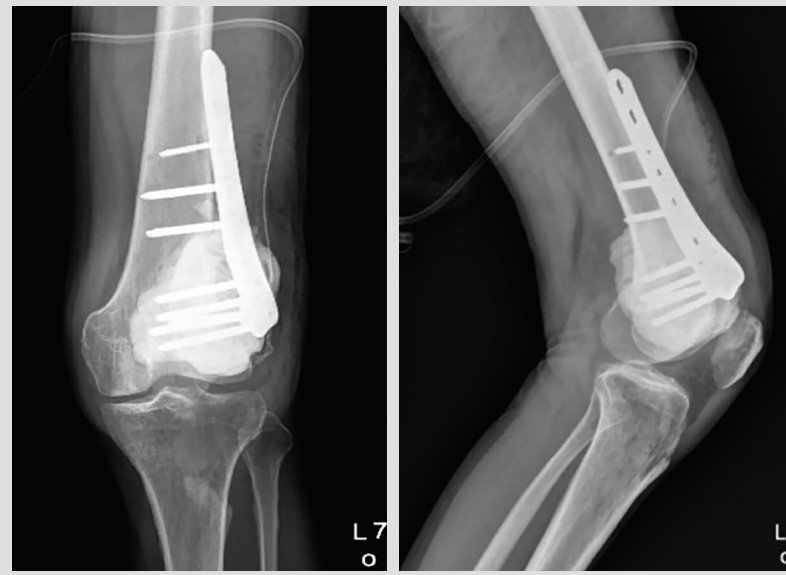
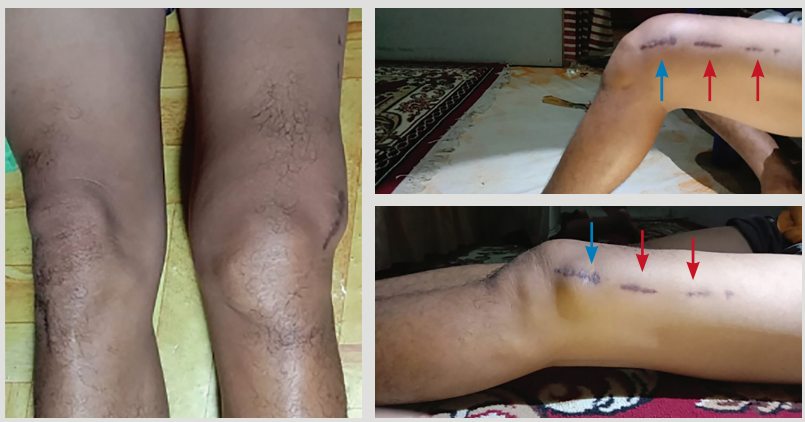
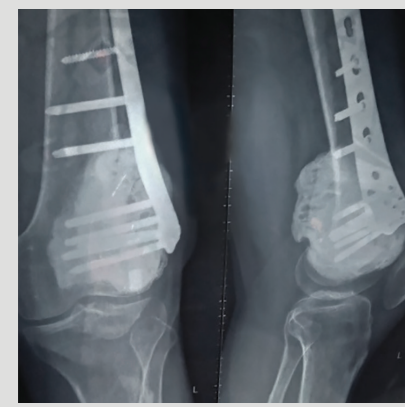


FIGURE 5. **One-Year Follow-up Clinical Condition, Showing No Sign of Recurrence and Improved Functional Outcome**



Blue arrow, scar for arthroscopic window; red arrow, scar for minimally invasive plate osteosynthesis.

FIGURE 6. **One-Year Follow-up Plain X-ray, Showing the Implants in Good Position and No Sign of Recurrence**



aggressive and the risk of local recurrence is substantial, other surgeons advocate wide resection and reconstruction for these grade 3 lesions, with the goal of preventing local recurrence and preserving joint function.[6]

The intralesional curettage method of treatment is associated with a risk of recurrence of approximately 16% to 45%, higher than that of wide resection and reconstruction. Local adjuvant therapy has been shown to help prevent recurrence,[7] and some orthopedic surgeons argue that the skillfulness of the tumor removal rather than the use of adjuvant modalities is what determines the risk of recurrence. In addition, patients with extensive, aggressive, and/or incompletely-resected GCTBs are not candidates for intralesional curettage—they require wide excision and curettage.[8-10] An arthroscopic approach, as in the case described here, is a challenge for surgeons, considering the proximity of the tumor to the joint and the possible injury of surrounding structures due to minimally invasive exposure. The bone cement was applied to fill the bone defect as a reconstructive measure and to decrease the possibility of recurrence. Fixation using plate and screw was also performed via the MIPO technique to minimize surgical trauma to the surrounding soft tissue and restrict the associated inflammation.

Extraarticular endoscopic resection of bone tumors was introduced in 1995 to treat chondroblastoma of the femoral head.[11,12] Arthroscopic removal of GCTB was first reported later, in 2015, by Kekatpure et al at a distal femur location; results were satisfactory and no recurrence was seen at 1-year follow-up.[13] An arthroscopic approach for such pathology has some advantages, including the ability to visualize the tumor directly, and in detail, as well as the opportunity to evaluate and subsequently repair possible cartilage defects. The minimal incision also allows the lesion to heal faster with minimal blood loss, lower risk of infection, and shorter length of hospital stay. However, there are some potential drawbacks: The use of block bone graft, in this case, was not feasible due to the minimal size of the portals, and bone cement should always be used cautiously, as it might damage the arthroscopy set. These potential drawbacks can be minimized when an experienced surgeon performs the procedure.[2,13]

At 1-year follow-up, this patient has a satisfactory range of movement and no sign of recurrence on serial radiography. The pain is diminished, and he has returned to his normal daily activities. Nonetheless, annual long-term follow-up is still required to detect any possible recurrence or metastasis.

Conclusions

Intralesional curettage with an arthroscopic approach for GCTB of the distal femur with the addition of bone cement and MIPO fixation shows a favorable outcome in terms of pain control, functional outcome, and recurrence at 1-year follow-up. ■

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CONSENT

Written informed consent was obtained from the patient for being included in the study and its publication.

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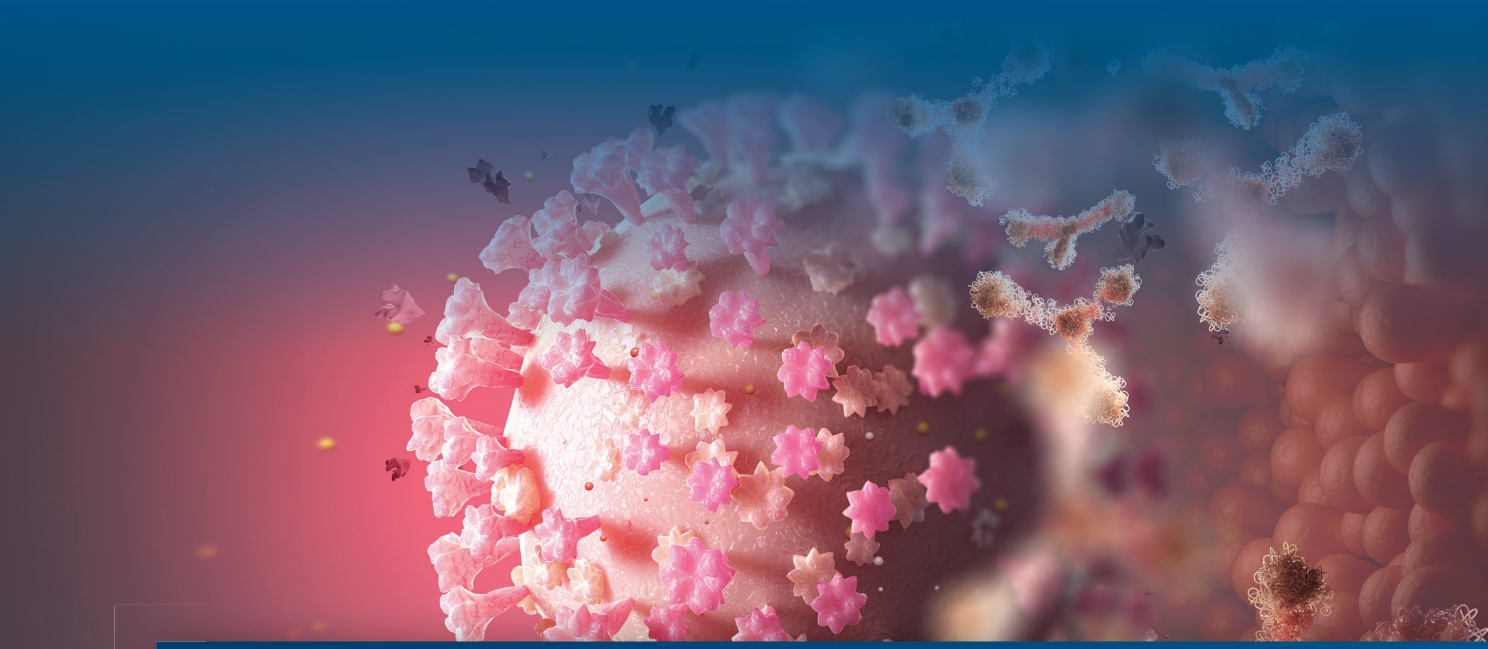

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Biomarkers for Response to Anti–PD-1/Anti–PD-L1 Immune Checkpoint Inhibitors: A Large Meta-Analysis

Arshiya Mariam, BS[1]; Suneel Kamath, MD[2]; Kimberly Schveder, MS[3]; Howard L. McLeod, PharmD[4]; Daniel M. Rotroff, PhD[5]

ABSTRACT

BACKGROUND: Immune checkpoint inhibitors (ICIs) that block PD-1/PD-L1 have consistently demonstrated durable clinical activity across multiple histologies but have low overall response rates for many cancers—indicating that too few patients benefit from ICIs. Many studies have explored potential predictive biomarkers (eg, PD-1/PD-L1 expression, tumor mutational burden [TMB]), no consensus biomarker has been identified.

METHODS: This meta-analysis combined predictive accuracy metrics for various biomarkers, across multiple cancer types, to determine which biomarkers are most accurate for predicting ICI response. Data from 18,792 patients from 100 peer-reviewed studies that evaluated putative biomarkers for response to anti–PD-1/anti-PD-L1 treatment were meta-analyzed using bivariate linear mixed models. Biomarker performance was assessed based on the global area under the receiver operating characteristic curve (AUC) and 95% bootstrap confidence intervals.

RESULTS: PD-L1 immunohistochemistry, TMB, and multimodal biomarkers discriminated responders and nonresponders better than random assignment (AUCs >.50). Excluding multimodal biomarkers, these biomarkers correctly classified at least 50% of the responders (sensitivity 95% CIs, >.50). Notably, variation in biomarker performance was observed across cancer types.

CONCLUSIONS: Although some biomarkers consistently performed better, heterogeneity in performance was observed across cancer types, and additional research is needed to identify highly accurate and precise biomarkers for widespread clinical use.

PERSPECTIVE

Ben Kong, PharmD, BCPS, on Biomarkers and Response to Immune Checkpoint Inhibitors on page 216

Introduction

Immune checkpoint inhibitors (ICIs) are becoming a cornerstone of cancer therapy across multiple histologies.[1,2] ICIs that block PD-1 or PD-L1 are at the forefront of ICI clinical implementation. These therapies reactivate the immune response to tumor cells by inhibiting the interaction of PD-L1 and PD-1, and multiple studies have demonstrated their clinical benefit over standard treatments.[3-7] Although ICIs show evidence of durable clinical benefit for individuals who respond, the objective response rate (ORR) to anti–PD-1/anti–PD-L1 therapies is approximately 24% (95% CI, 21%-28%).[2] Approximately 16% (95% CI, 12%-21%) of patients also experience significant toxicity, including colitis and endocrine organ dysfunction.[2] It is critical that biomarkers for ICIs are robustly predictive to better guide clinical decision-making.

Many studies have explored whether PD-L1 or PD-1 protein expression,[8-11] tumor mutational burden (TMB),[12-16] and, more recently, immune-mediated adverse events[17] (imAEs) and the microbiome signature,[18-20] can discriminate

between responders and nonresponders to anti–PD-1/anti–PD-L1 immunotherapies. The results from these studies are often inconsistent. For example, Bellmunt et al reported that a PD-L1 expression threshold above 10% discriminated against patients with urothelial bladder cancer,[21] whereas Massard et al reported a threshold of 25% for the same cancer type.[22] Differences in patient populations, sample collection and processing, technology platforms, biomarker thresholds, and the specific ICI used all contribute to high variability across studies. In addition to methodological differences, many studies also have limited sample sizes that may impact statistical power for discovering biomarkers. Although most reviews qualitatively condense information across studies, biomarker performances are not always summarized in a quantitative manner.[23,24] Meta-analysis is an approach to developing consensus important clinical questions from previously published literature, and it provides an opportunity to obtain relevant statistical summaries for potential ICI biomarkers.[2] An additional benefit of meta-analyses is that biomarkers can be concurrently evaluated across different treatments, threshold values, and cancer types. Here, we conducted the largest meta-analysis of predictive biomarkers for ICI therapy to date, including 100 peer-reviewed studies with data from 18,792 patients. We also investigated whether some emerging biomarkers, such as the microbiome signature or imAEs, show promise for clinical utility. Furthermore, we implemented a robust statistical approach that went beyond reporting which biomarkers displayed the highest predictive accuracy. The objective of this study is to provide a comprehensive evaluation of the current state of predictive utility for the most common biomarkers, and some emerging ones, for ICI treatment response.

Methods

Literature Search and Inclusion Criteria

PubMed and Google Scholar were searched for peer-reviewed manuscripts and conference abstracts focused on anti–PD-1/anti–PD-L1 therapies and biomarkers. Keywords used to search included: "anti–PD-1/anti–PD-L1 therapies and tumor mutational burden," "anti–PD-1/anti–PD-L1 therapies and AEs," "anti–PD-1/anti–PD-L1 therapies and biomarkers," and "biomarkers for immune checkpoint inhibitors." Studies were selected based on the availability of summary-level or patient-level data on clinical outcomes and predictive biomarkers. PRISMA 2020 checklist detailing the quality assessment for including studies in the meta-analysis is provided in **Supplementary File 1**.

Data

For each study, the title, publication year, treatment, type of cancer, biomarker, and clinical outcome details were documented by 3 separate reviewers (**Supplementary File 2**). Any discrepancies in collected data were reviewed by all reviewers and reconciled by consensus. ORR was considered the primary clinical outcome, and clinical benefit (CB) was used if ORR was not available. Responses were determined using RECIST, immune-related response criteria, or modified RECIST[3,25] by investigator assessment or independent review. If a response was evaluated using multiple tumor criteria or by multiple assessors, the means of data were rounded to the nearest integer. The thresholds for biomarker activity were accepted as defined in each study.

The following metrics for biomarker performance were calculated: sensitivity, specificity, false positive rate, and false negative rate (**Supplementary Table 1**). Each of these metrics can be calculated from a 2 × 2 contingency table, where counts of individuals meeting the criterion for having a positive or negative result for a biomarker and having a positive or negative result for the clinical outcome can be tabulated. Only studies that provided either individual counts for each cell in the 2 × 2 table or the necessary individual-level information to complete the 2 × 2 table were included. Studies that did not propose a threshold or cutoff value for the biomarker were excluded unless participant-level data were available from which a 2 × 2 table could be developed.

Biomarkers

Across all included studies, 9 classes of biomarkers were investigated (**Supplementary Table 2**). The 3 most frequently observed biomarkers were PD-L1 protein expression, TMB, and multimodal biomarkers. Interest in AEs and the microbiome signature as potential biomarkers has emerged more recently. Specific details regarding each of the 9 biomarker classes are described below.

PD-L1 protein expression. PD-L1 protein expression measured on tumor cells, immune cells, or both, was included. Each study provided an expression threshold that was used to evaluate observed clinical responses. Patients with PD-L1 expression greater than the threshold were expected to be more likely to respond to treatment. PD-L1 expression was further divided into (1) immunohistochemistry (IHC) and (2) multiplex immunohistochemistry/immunofluorescence (mIHC/IF) assays.

TMB. TMB refers to the number of somatic DNA mutations across the tumor genome. Since the early TMB studies, many variations of this biomarker have been studied. TMB has been quantified based on nonsynonymous single nucleotide variants,[26,27] frameshift mutations,[28] and circulating tumor DNA,[29] and studies calculating TMB from whole exome or whole genome sequencing were included. Median TMB was a commonly

reported threshold for assessing response to ICIs. The TMB threshold defined by the authors of each study was used for this analysis, except for that of Hugo et al,[27] which did not report a threshold; here, the authors used the median TMB. For all studies, TMB was evaluated to determine if being above the threshold was indicative of an increased likelihood of response to treatment.

T cell–related gene signatures (TGSs). Four studies evaluated sets of gene expression for association with response to treatment. Wang et al developed an epithelial-mesenchymal transition–related gene expression correlated with T-cell infiltration and predictive of response to treatment.[30] Other gene expressions related to T-cell inflammation were calculated from total RNA and mRNA. PD-L1 and CXCL9 were commonly included genes.[31,32]

CD8+. CD8+ tumor-infiltrating lymphocytes are involved in the immune response to the tumor and have been linked to improved overall survival in esophageal cancer[33] and urothelial cancer.[30] Of the 3 studies included in the analysis, results from 2 studies reported improved ORRs and prolonged overall survival with higher CD8+ infiltration.[30,33]

Microbiome signature. Three studies investigated the relationship between microbiome signature and ICI response. Individuals with gut and oral commensal microbiome signatures that promote antitumor immunity have been shown to benefit more from ICI treatments than others.[20,34] Conversely, downregulation of these microbiome signatures by antibiotics has been linked to worse treatment responses.[18] Commensal bacterial species implicated in response included *Akkermansia muciniphila*, *Bifidobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium*.[20] The predictive thresholds established by the authors for these studies were utilized for this analysis.

AEs of special interest and imAEs. Unlike other biomarkers, which are assessed prior to treatment initiation, adverse events of special interest (AESIs) and imAEs are observed after the administration of ICIs but prior to the determination of clinical response. AESIs comprised a variety of events including autoimmune events, rash, and diarrhea. imAEs were defined as AESIs that required treatment with systemic or topical corticosteroids.[17] These data were previously reported in Maher et al, which combined data from 7 trials submitted to the FDA,[17] and we previously reported the discriminatory potential for these biomarkers.[35] AESIs and imAEs were evaluated to determine if their occurrence was indicative of an increased likelihood of response to treatment.

Multimodal biomarkers. The discriminatory potential of biomarker combinations has been investigated in a few studies that collectively investigated 3 cancer types: melanoma, non–small cell lung cancer (NSCLC), and head and neck cancer.[31,36] The following combinations of multimodal biomarkers are presented here: (1) TMB and PD-L1 IHC (4 studies), (2) TMB and TGS (1 study), and (3) PD-L1 IHC and PD-1 IHC (1 study).

International Metastatic RCC Database Consortium (IMDC) risk score. This scoring method is used to predict prognosis and recommend first-line therapies for patients with renal cell carcinoma (RCC) only.[37,38] Disease is categorized as favorable, intermediate, and poor risk based on the presence of 0, 1 to 2, and 3 or more risk factors, respectively.

Statistical Analysis

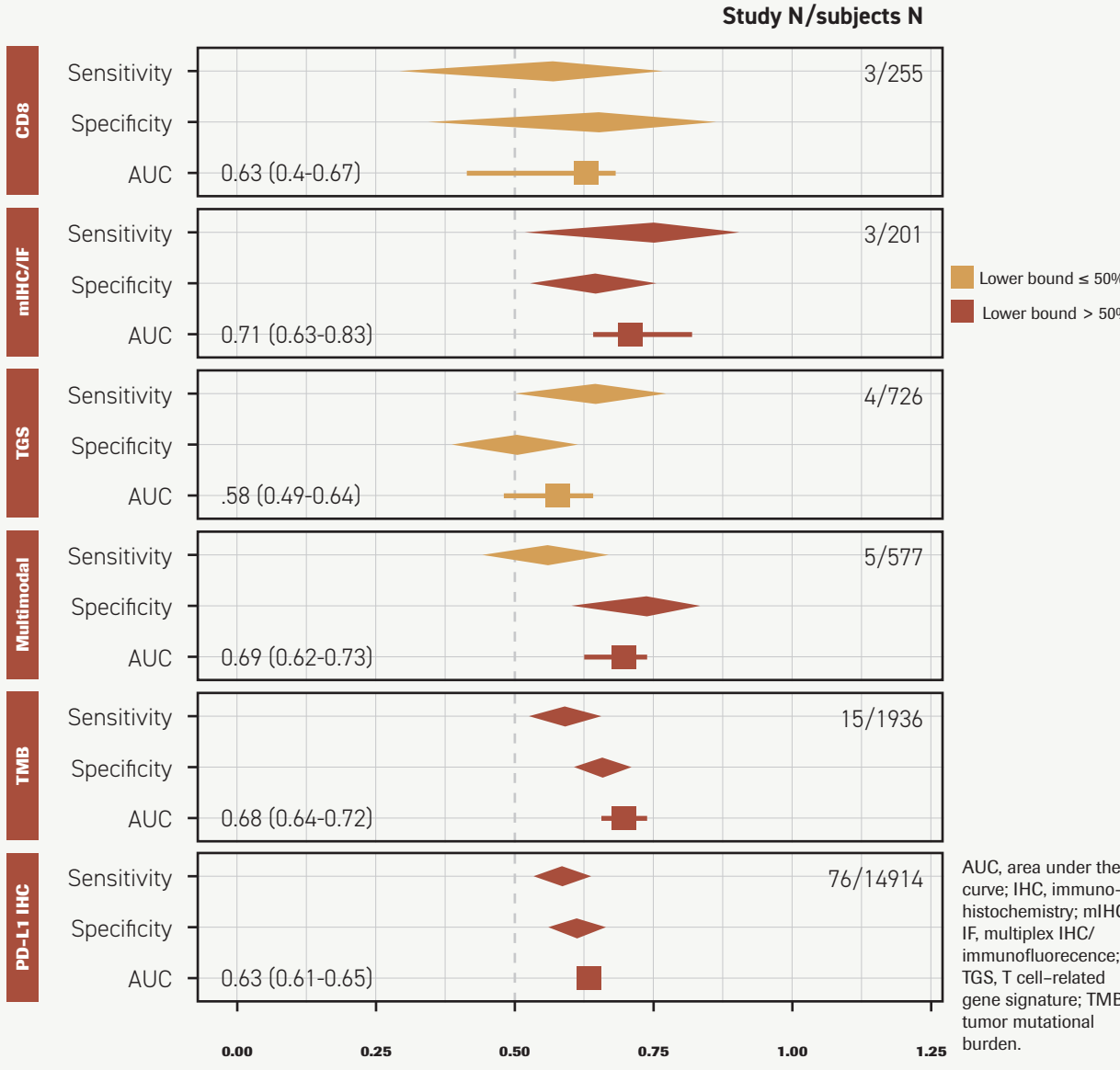
Meta-analysis

Biomarker performance metrics (Supplementary Table 1) were calculated for each study, and various groups were meta-analyzed for comparison using the R package, *mada*.[39] Meta-analyses were conducted to determine (1) discriminatory potential for each biomarker across multiple cancer types, and (2) discriminatory potential for each biomarker for each cancer type. Binary test outcomes, such as sensitivity and specificity, rely on a threshold for determining the optimal test performance. This threshold often creates a tradeoff between certain values, and simply averaging values across studies with different thresholds can confound results.[40] To address this, we implemented the summary-receiving operating characteristic curve approach,[41,42] which performs bivariate analyses using a linear mixed effects model. We separately evaluated specificity and sensitivity. A minimum of 3 studies, or 500 patients, were required to perform each meta-analysis. For biomarkers that did not meet this inclusion criterion, the results of the individuals are described for context, but they were not meta-analyzed. If a study reported multiple thresholds for the same biomarker, only the results of the threshold with the greatest balance accuracy were included in the meta-analysis. The area under the curve (AUC) estimate was calculated from the extrapolated bivariate models. CIs for AUCs were estimated based on 10,000 bootstrap iterations.[43]

Results

After performing quality control, 100 of 197 studies published from 2010 to 2021 met the inclusion criteria. ORR and CB were reported in 85% and 8% of studies, respectively. The descriptive statistics for the studies are provided in **Supplementary Figure 1**. The most frequent cancer types in the data set were NSCLC (29.5%) and melanoma (22.1%) (Supplementary Table 2). The most frequently investigated biomarker was PD-L1 expression (76%) **Supplementary Table 3**). Below, we present the overall characterization of each biomarker followed by the meta-analysis

FIGURE 1. **Diagnostic Accuracy Metrics of Biomarkers Analyzed Across All Cancer Types**



AUC, area under the curve; IHC, immunohistochemistry; mIHC/IF, multiplex IHC/immunofluorecence; TGS, T cell–related gene signature; TMB, tumor mutational burden.

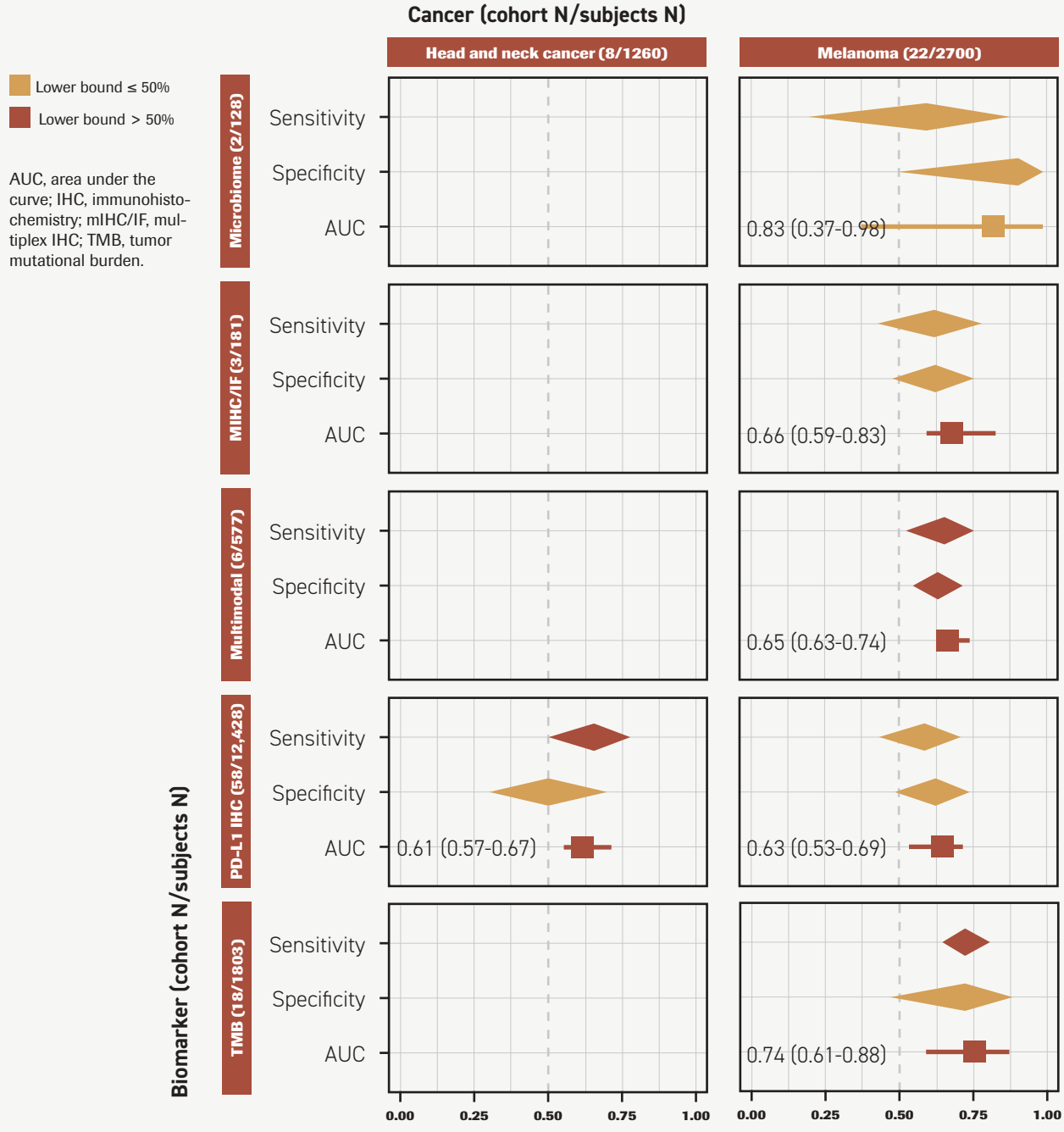
The accuracy metrics of the various types of biomarkers that met the criteria are shown. These include PD-L1 immunohistochemistry, IHC; tumor mutational burden, TMB; multimodal, T-cell–related gene signature, TGS; multiplex IHC/immunofluorescence, mIHC/IF, and CD8+ tumor-infiltrating lymphocytes, CD8+. Sensitivities and specificities were meta-analyzed using R *mada* package and are represented by the diamond shape. Area under the curve (AUC) estimates are represented by squares. The 95% CI of AUC values was obtained from bootstrap samples of the biomarker studies. Total number of studies and subjects in each meta-analysis are annotated.

results by cancer type. The meta-analysis results across all cancer types and other analyses are shown in **Supplementary Tables 4 and 5**. All of the included studies are listed in **Supplementary Table 6**.

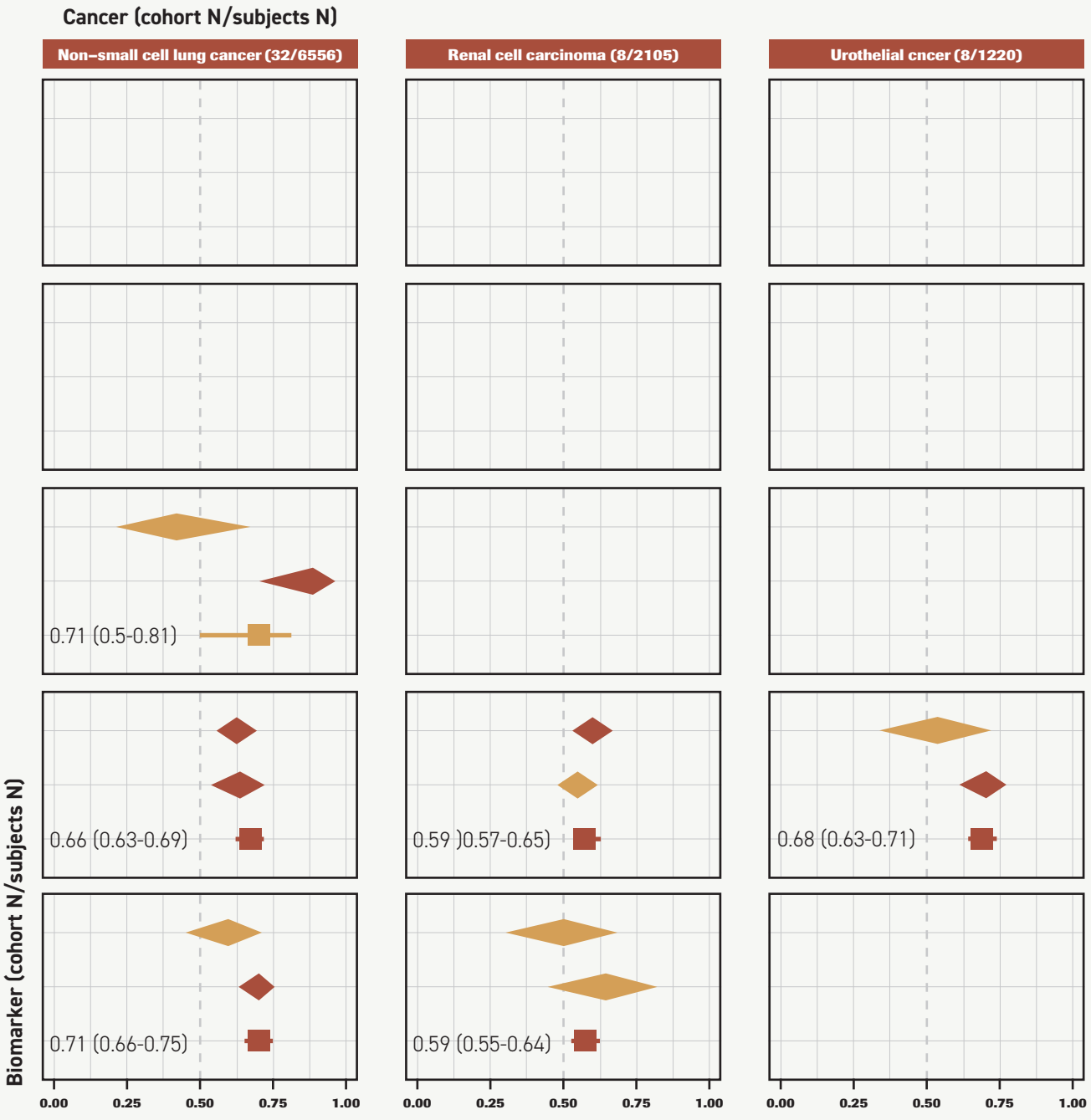
Overall Biomarker Performance

Of 9 defined classes of biomarkers, 6 met the criteria for the number of studies or samples to be meta-analyzed. AESIs/imAEs, microbiome signature, and IMDC were not meta-analyzed and were considered separately because they were investigated in 1, 2, and 2 studies, respectively. Three biomarkers—TMB,

FIGURE 2. **Diagnostic Accuracy Metrics of Biomarkers by Most Frequently Investigated Cancer Types**



The accuracy metrics of the various types of biomarkers by the 5 most frequently investigated cancer types are shown. Five biomarkers, (1) PD-L1 IHC, (2) TMB, (3) multimodal biomarker, (4) multiplex IHC/immunofluorescence, and (5) microbiome signature were meta-analyzed in at least 1 cancer type. Sensitivities and specificities were meta-analyzed using R *mada* package and are represented by the diamond shape. Area under the curve (AUC) estimates are represented by squares. The 95% CI of AUC values was obtained from bootstrapped samples



of the biomarker studies. Study-level sensitivities and specificities are shown if 3 studies were not available for the biomarker and cancer combination. Few studies (<10%) used separate discovery and validation cohorts. Cohort N is annotated by cancer type and by biomarker. It represents the total number of unique cohorts used for meta-analyses across shown cancer types for the biomarker and across shown biomarkers for the cancer type.

PERSPECTIVE BY

Ben Kong, PharmD, BCPS, Clinical Pharmacy Specialist, Oregon Health & Science University, Portland, OR

The Complexities and Art of Interpreting Biomarkers and Response to Immune Checkpoint Inhibitors

A function of immune checkpoint inhibitors, such as PD-1 and PD-L1 inhibitors, is to allow normal tissues to coexist with the immune system and avoid triggering a destructive response. When PD-1 (found on T cells) is bound to PD-L1 (found on normal tissue), it dampens T-cell activation.[1] It is now recognized that tumors can also express PD-L1, gaining the ability to escape detection and be allowed to proliferate. Thus, the role of PD-L1 as a biomarker has emerged, and there is interest in the therapeutic opportunity to block the PD-1/PD-L1 interaction.

In 2014, pembrolizumab (Keytruda) was the first PD-1 inhibitor to receive FDA approval for use in melanoma. This was further expanded in 2017 and 2020 to tumors with microsatellite instability–high status and tumor mutational burden (TMB) greater than 10 mut/Mb, respectively. Since then, other PD-1/PD-L1 inhibitors have been approved in various diseases, such as nivolumab (Opdivo), atezolizumab (Tecentriq), avelumab (Bavencio), and durvalumab (Imfinzi). When a response is seen, it tends to be durable and prolonged. Regarding immune-related adverse effects, they can affect any organ system and lead to reactions such as rash, diarrhea, endocrinopathies, musculoskeletal pain, pneumonitis, and more.

The authors of "Biomarkers for Response to Anti–PD-1/PD-L1 Immune Checkpoint Inhibitors: A Large Meta-Analysis" performed a comprehensive review of 100 studies, encompassing approximately 18,000 patients to address the role of 9 predictive biomarkers across tumor types. With a large data set available to conduct robust statistical analysis, their findings suggest that TMB, PD-L1 immunohistochemistry (IHC), and multiplex IHC/immunofluorescence were sensitive in predicting response across all tumor types, although the authors acknowledge heterogeneity in study design and limited study size. Some of the complexities and nuances may pertain to the assay and clinical interpretation of immune therapies.

Among the antibodies available to assess PD-L1 expression, 4 are associated with the clinical indication (eg, 22C3/pembrolizumab, 28-8/nivolumab, SP263/durvalumab, and SP142/atezolizumab). When interpreting PD-L1 IHC, a

PD-L1 IHC, and mIHC/IF—correctly classified at least 50% of the responders (sensitivity, 95% CIs >0.50) (**Figure 1**). Sensitivities for PD-L1 IHC (n = 76) and TMB (n = 15) were estimated to be 0.60 (95% CI, 0.55-0.64) and 0.59 (95% CI, 0.52-0.66), respectively. mIHC/IF was the most sensitive (sensitivity, 0.75; 95% CI, 0.53-0.89); however, it has been investigated only in 3 studies. mIHC/IF (AUC, 0.71; 95% CI, 0.63-0.83) closely followed by TMB (AUC, 0.68; 95% CI, 0.64-0.72) had the highest AUCs. PD-L1 IHC discriminated marginally better than random assignment, with an AUC of 0.63 (95% CI, 0.61-0.65).

Cancer-Specific Performance

NSCLC

PD-L1 IHC (29 cohorts), TMB (14 cohorts), and multimodal biomarkers (3 cohorts) were meta-analyzed. PD-L1 IHC was the most sensitive (sensitivity, 0.63; 95% CI, 0.57-0.68) and demonstrated moderate specificity (specificity, 0.63; 95% CI, 0.55-0.70). The sensitivity of TMB was slightly lower and varied more across studies (sensitivity, 0.60; 95% CI, 0.47-0.70). However, both PD-L1 IHC and TMB were consistently accurate in their classification of patients (AUCs >0.50) (**Figure 2**).

Melanoma

PD-L1 IHC (15 cohorts), TMB (6 cohorts), mIHC/IF (5 cohorts), and multimodal biomarkers (4 cohorts) were meta-analyzed. Unlike NSCLC, TMB was more sensitive in melanoma (sensitivity, 0.73; 95% CI, 0.64-0.81) than PD-L1 IHC (sensitivity, 0.58; 95% CI, 0.44-0.71). It was also most accurate in classifying both responders and nonresponders (AUC, 0.74; 95% CI, 0.61-0.88). Multimodal biomarkers had moderate overall accuracy (AUC, 0.65; 95% CI, 0.63-0.74) and accurately discriminated more than 50% of responders and nonresponders. The sensitivity of mIHC/IF was similar to that of PD-L1 IHC (sensitivity, 0.62; 95% CI, 0.43-0.77). The microbiome signature was investigated only in melanoma. Gut microbiome signature and buccal microbiome signature for response were investigated in 2 studies and 1 study, respectively. Their sensitivities were low (range, 0.22-0.40) and specificities were high (range, 0.67-1.00).

number of additional factors need consideration besides the PD-L1 clone, such as the control, tissue fixation, adequate number of tumor cells, and PD-L1 scoring method (tumor proportion score, combined positive score, tumor cell/immune cell).[2,3]

The TMB captures somatic alterations within a genomic sequence, and higher values are associated with response to immune therapy. Although the standard method to determine TMB is generally derived from whole exome or genome sequencing, it is not routinely performed due to cost and turnaround. Instead, targeted panels are widely adopted and used to identify oncogenic mutations and estimate TMB. Because of the potential discrepancy, a study explored the performance of panel-based assay compared with whole exome sequencing and observed that variabilities exist among the 11 participating laboratories, leading to either underestimation or overestimation of TMB—likely due to differences in panel size and bioinformatic algorithms.[4]

The RECIST Working Group has provided guidance in defining and measuring responses to cancer therapies. Unlike traditional therapies, immune modulators tend to have a different pattern of response, which led to the development of iRECIST.[5] Specifically, immune modulators can elicit either a delayed clinical response or pseudoprogression—the latter being a phenomenon in which the initial imaging assessment may show new lesions or existing tumors that appear larger, followed by a delayed clinical response. The distinction between pseudoprogression and true progression remains a challenge, so it is currently recommended to continue treatment until the next imaging assessment.

Moving forward, a future toward standardization of analytical methods and interpretation would assist in reducing certain aspects of heterogeneity that are naturally inherent in studies. Doing so would pave the way to better understanding the predictive potential of biomarkers and identifying the patient who may benefit the most from treatment. ■

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Urothelial cancer

Only PD-L1 IHC had sufficient studies to perform meta-analysis (9 cohorts). TGS and AESIs/imAEs were both investigated in only a single cohort. PD-L1 IHC was marginally better at discriminating responders and nonresponders than random assignment (AUC, 0.68; 95% CI, 0.63-0.71) (Figure 2), with a sensitivity of 0.53 (95% CI, 0.35-0.70) and specificity of 0.70 (95% CI, 0.61-0.77). AESIs/imAEs demonstrated poor sensitivity (0.36). TGS performed poorly at discriminating responders and nonresponders (sensitivity, 0.51; specificity, 0.50).

Head and neck cancer

PD-L1 IHC was the only biomarker examined in a sufficient quantity of studies to perform a meta-analysis (8 cohorts). It detected responders with a sensitivity of 0.65 (95% CI, 0.50-0.77). The discriminatory ability of PD-L1 IHC was similar between this cancer type and others investigated (AUC, 0.61; 95% CI, 0.57-0.67). Multimodal biomarkers and TMB were each investigated in 2 cohorts. Multimodal biomarkers were consistently sensitive to at least 50% of the responders and nonresponders (sensitivities, >50%; specificities, >50%) (Figure 2).

RCC

PD-L1 IHC (7 cohorts) and TMB (6 cohorts) were meta-analyzed. Each of these biomarkers had a similar discriminatory ability; however, PD-L1 IHC was more sensitive in response prediction (0.60 vs 0.49) (Figure 2). The AUC estimates for PD-L1 IHC and TMB were 0.59 (95% CI, 0.57-0.65) and 0.59 (95% CI, 0.55-0.64), respectively (Figure 2). IMDC was investigated only in RCC, and sensitivities of favorable scores ranged between 0.28 and 0.30, with moderate to high specificities between 0.57 and 0.86 (Supplementary File 2). Sensitivity improved from 0.28 to 0.90 and specificity decreased from 0.86 to 0.24 when intermediate was used as the threshold instead of favorable.[38]

Discussion

ICIs targeting PD-1/PD-L1 have resulted in breakthrough treatments for a multitude of cancers, and the impact this class of drugs has on cancer treatment cannot be overstated. Despite the successes,

however, only 24% (95% CI, 21%-28%) of patients respond to these treatments.[2] A variety of biomarkers have been considered, but no consensus exists regarding which of these biomarkers is capable of or has the potential to be clinically useful. This broad-based meta-analysis addresses the unmet need of characterizing commonly considered biomarkers for ICI treatment response in various cancer types. Most recently, Lu et al[44] provided a characterization of biomarker performance, and we have expanded the scope of this investigation in several ways. We included more studies (100 vs 46) and, consequently, more patients (18,792 vs 8135). We also expanded the range of included biomarkers, including novel biomarkers (eg, microbiome signature and imAEs/AESIs). Methodological differences included our implementation of bivariate linear mixed models, which have been shown to provide more accurate estimates compared with estimating sensitivity and specificity separately.[44] Clinical response to ICI was defined to improve consistency across studies and consisted only of ORR, CB, and PFS (6 months).

PD-L1 IHC, TMB, and mIHC/IF were moderately sensitive to ICI response when summarized across all investigated cancer types. Consistent with Lu et al,[44] these biomarkers also had better discriminatory ability than random assignment (AUCs >0.50). Overall, TMB had better discriminatory ability than PD-L1 expression (Figure 1). Other studies have also reported that TMB better predicted response to ICI than PD-L1 IHC.[45] Although relatively few studies investigating mIHC/IF and multimodal biomarkers have been performed, our results and those presented by Lu et al[44] demonstrated that both of these biomarkers show promise that warrants additional investigation. Because mIHC/IF has been investigated only in 2 cancer types (melanoma and Merkel cell carcinoma), its performance in other cancer types is yet to be determined.

We also investigated biomarker performance across the 5 most common cancer types evaluated. PD-L1 IHC, TMB, and multimodal biomarkers were the only biomarkers meta-analyzed in more than 1 cancer type. Zhang et al reported greater response in PD-L1–positive subgroups compared with PD-L1 negative subgroups in melanoma, NSCLC, and RCC.[2] Better ORR, albeit to a smaller degree, was also observed when multiple cancer types were analyzed together.[2] In addition to PD-L1 IHC, TMB also discriminated responders and nonresponders better than a random assignment in these cancer types as well as across all cancers (AUCs > 0.50) (Figure 2). PD-L1 IHC was the only consistently sensitive biomarker in NSCLC and RCC subgroups. On the other hand, TMB and multimodal biomarkers were consistently sensitive in the melanoma subgroup (Figure 2). Multimodal biomarkers were investigated in 3 and 4 cohorts in NSCLC and melanoma, respectively. Its discriminatory ability was more consistent across studies of melanoma (AUC, 0.65; 95% CI, 0.63-0.74) compared with studies of NSCLC (AUC, 0.71; 95% CI, 0.50-0.81). While meta-analytical summaries of results account for heterogeneity among studies,[41] given the small number of studies, additional research is needed to rule out factors other than cancer type contributing to heterogeneity. In the case of PD-L1 IHC alone, tumor type, observing pathologist, assay type, and nonuniform evaluation of tumor microenvironments were reported to impact the efficacy of PD-L1 IHC.[44] It is also important to note that the thresholds used are inconsistent across studies and may not align with those currently used in clinical practice. For example, in many contexts, TMB of more than 10 mut/Mb is the approved FDA metric; however, thresholds as low as 6 mut/Mb and as high as 248 mut/Mb have been used in these studies. These studies often do not report individual-level TMB, eliminating the possibility of deriving alternative thresholds for analysis. This will be an important line of investigation in future studies, to determine an optimal threshold for TMB biomarker performance.

AEs and the microbiome signature have recently emerged as potential biomarkers. imAEs/AESIs are distinctive because they are ascertained after treatment initiation, limiting their potential use as pretreatment biomarkers. However, if determined to be effective, they could still serve as leading indicators of response, providing opportunities to modify or enhance treatment. To our knowledge, AEs, and responses to ICIs have been explored only in patients with urothelial cancer.[17] AEs and the microbiome signature were found to have low sensitivities (<0.40) for detecting responding individuals. Defining these biomarkers with a different criterion in a different cancer type, or using these in conjunction with an imprecise biomarker, may lead to improved discrimination. Matson et al reported high sensitivity and specificity using a microbiome signature in multiple cancers (Supplementary File 2). An important metric, not reported here, is the positive predictive value (PPV). PPV is a measure of the probability of the outcome given a positive biomarker result. However, PPV is influenced by the prevalence of responders and is therefore highly dependent on tumor type and many other factors. It will be important in follow-up studies that investigate specific use cases of these biomarkers to consider PPV. The results we have presented here also justify the investigation of these biomarkers in other cancer types and potentially in response prediction for other ICIs. The results of these constituent studies

should be prospectively validated in an independent cohort for prediction in the future.

Conclusions

mIHC/IF, multimodal biomarkers, TMB, and PD-L1 IHC adequately captured responders and nonresponders across all included cancer types. Between the 2 most frequently investigated biomarkers, TMB outperformed PD-L1 IHC when all cancers were combined. These 2 also adequately captured responders and nonresponders across NSCLC and melanoma. The results for multimodal biomarkers were mixed in NSCLC; however, multimodal biomarkers captured responders and nonresponders similarly to other biomarkers within melanoma and across all cancers. The performance of the biomarkers varies greatly among studies despite accounting for cancer type, and additional work will be needed to optimize these biomarkers. ■

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For references and supplemental material visit cancernetwork.com/5.23_Biomarkers

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ONCOLOGY Reviews Key Presentations From the
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RUBY Trial Supports Addition of Dostarlimab to Chemo as SOC in Endometrial Cancer

Adding dostarlimab (Jemperli) to carboplatin and paclitaxel improved progression-free survival (PFS) compared with placebo plus chemotherapy for patients with recurrent endometrial cancer regardless of whether they had mismatch–repair deficient (dMMR), microsatellite instability–high (MSI-H) disease, according to updated findings from the phase 3 RUBY trial (NCT03981796).

Results of the randomized, double-blind, multicenter phase 3 study showed that the trial met its primary end point in patients on the immune checkpoint inhibitor (ICI) plus chemotherapy treatment (n = 245) compared with patients on placebo and chemotherapy (n = 249), demonstrating a superior PFS of 36.1% (95% CI, 29.3%-42.9%) vs 18.1% (95% CI, 13%-23.9%) at 24 months, respectively (HR, 0.64; 95% CI, 0.51-0.80, $P < .001$).

Moreover, in the dMMR/MSI-H population of patients on dostarlimab and chemotherapy (n = 53), the estimated PFS at 24 months was 61.4% (95% CI, 46.3%-73.4%) compared with 15.7% (95% CI, 7.2%-27.0%) in the placebo group (n = 65) (HR, 0.28; 95% CI, 0.16-0.50; $P <.001$). In the mismatch repair proficient (MMRp)/microsatellite stable (MSS) population of patients, a PFS benefit was observed for patients in the experimental treatment group at 28.4% at 24 months vs 18.8% in the placebo group, but these results did not meet the criteria for statistical significance (HR, 0.76; 95% CI, 0.59-0.98).

Although not found to be significant, and the data still at 33% maturity, overall survival (OS) favored patients in both the overall population and dMMR/MSI-H population. At the 24-month mark, OS was 71.3% (95% CI, 64.5%-77.1%) for patients on dostarlimab compared with 56% in the placebo group (HR, 0.64%; 95% CI, 0.46-0.87; $P = .021$) whereas OS in the dMMR/MSI-H population was 83.3% on the combination therapy compared with 58.7% for patients on placebo at 24 months (HR, 0.30; 95% CI, 0.13-0.69). OS at 24 months was closer in the MMRp/MSS population at 67.7% for patients on the ICI combination vs 55.1% of patients in the placebo arm (HR, 0.73; 95% CI, 0.52-1.02).

→ **For the full article, visit** CancerNetwork.com/RUBY

Niraparib Yields Limited OS in Final Analysis for Ovarian Cancer

Treatment with niraparib (Zejula) maintenance therapy did not produce a statistically significant improvement in overall survival (OS), according to findings from an updated exploratory analysis in the phase 3 ENGOT-OV16/NOVA study (NCT01847274).

The updated OS results from the randomized, double-blind, placebo-controlled trial showed a collected survival status of 97.6% among patients involved in the trial (n = 540). The OS maturity of the data was 77.9%.

Split among the germline (g)*BRCA*-mutated cohort (n = 203) and non–g*BRCA*-mutated cohort (n = 350), median OS for niraparib and placebo was 40.9 months vs 38.1 months, respectively (HR, 0.85; 95% CI, 0.61-1.20). In comparison, the median OS with niraparib in the non–*gBRCA*-mutated

cohort was 31.0 months vs 34.8 months with placebo (HR, 1.06; 95% CI, 0.81-1.37).

Further exploratory analyses of the homologous recombination-deficient (HRD) subgroups within the non–*gBRCA*-mutated cohort showed that while there was still no significant difference in the use of niraparib over placebo, the PARP inhibitor was still favored. In the HRD group of patients who received niraparib (n = 106), the median OS was 35.6 months compared with 41.4 months in the placebo group (n = 56), with an HR of 1.29 (95% CI, 0.85-1.95).

Moreover, in the homologous recombination not determined subgroup of patients who received niraparib (n = 36), the median OS was 29.8 months vs 20.2 months for patients who received placebo (n = 18), with an HR of 0.62 (95% CI, 0.29-1.35). However, patients who were homologous recombination proficient had the same median OS of 27.9 months in both the niraparib arm (n = 92) and placebo arm (n = 42), with an HR of 0.93 (95% CI, 0.61-1.41).

Compared with the primary analysis, the safety profile of niraparib was consistent, including the incidence of grade 3 or greater adverse events like thrombocytopenia (35.7%), anemia (27%), neutropenia (20.7%), hypertension (2.2%), fatigue (2.8%), and gastrointestinal disorders.

→ **For the full article, visit** CancerNetwork.com/ENGOT-OV16

Olaparib Plus Selumetinib Shows Benefit in *RAS*-Mutated Ovarian, Endometrial Cancers

Patients with *RAS*-mutated ovarian or endometrial cancer benefited most from the recommended phase 2 dose of olaparib (Lynparza) plus selumetinib, according to results from the phase 1b dose expansion of the SOLAR trial (NCT05554328).

The recommended phase 2 dose was determined to be 300 mg of oral olaparib daily and 75 mg of oral selumetinib daily. For patients with *RAS*-aberrant ovarian cancer, 69% of patients achieved a clinical benefit, with 32% having a partial response (PR), and 37% having standard disease after 4 or more cycles.

For those with *RAS*-aberrant endometrial cancer, 59% had a clinical benefit, 35% experienced a PR, and 24% had stable disease after 4 or more cycles of treatment. Of note, of the patients who had a PR, 2 had a *BRCA* mutation.

Across all patients, efficacy data included 47% of patients who had a clinical benefit; 21% had a PR, with 3% experiencing responses during dose escalation and 19% during dose expansion. In 26% of patients, stable disease occurred, with 3% of patients experiencing response during dose escalation, and 23% in dose expansion.

The study also looked at patients who had *RAS*-aberrant tumors and included pancreatic, lung, appendiceal, colon, and rectal cancers, as well as cholangiocarcinoma. Of 36 patients treated, 26 were evaluable. Overall, 31% experienced a clinical benefit, with 8% having a PR, both of whom had lung cancer, and 19% had stable disease after 4 or more cycles.

In patients who had PARP-resistant ovarian cancer, 15 patients were treated, and 12 were evaluable. A clinical benefit was observed in 41% of patients, 17% had a PR, both of whom had a *BRCA* mutation; and 25% had stable disease after 4 or more cycles.

→ **For the full article, visit** CancerNetwork.com/SOLAR

Lenvatinib Combo Yields Robust, Enduring Responses in Endometrial Cancer

Treatment with lenvatinib (Lenvima) plus pembrolizumab (Keytruda) resulted in deep, sustained responses in most patients with advanced endometrial cancer, according to data from the phase 3 Study 309/KEYNOTE-775 (NCT03517449).

In the all-comer population, the overall response rate (ORR) was 33.8% (95% CI, 29.3%-38.6%), which included a complete response (CR) rate of 7.5% (95% CI, 5.2%-10.5%) and a partial response rate of 26.3% (95% CI, 22.1%-30.8%); investigators confirmed a total rate of 33.8% of responses.

The median time to response (TTR) was 2.1 months (range, 1.5-23.0), and the median duration of response (DOR) was 12.9 months. Extended responses occurred in 73.7%, 51.8%, and 39.5% of patients at the 6 months or more, 12 months or more, and 24 months or more time points, respectively. Moreover, 76.3% of patients had a 50% or more reduction in tumor diameter, and 43.2% had a 75% or more reduction.

In patients who were mismatch repair proficient (pMMR), the ORR was 32.4% (95% CI, 27.5%-37.6%) and included a CR rate of 5.8% (95% CI, 3.6%-8.8%) and a partial response rate of 26.6% (95% CI, 22.0%-31.6%). Moreover, 32.4% of responses were confirmed.

The median TTR was 2.1 months (range, 1.5-23.0), and the median DOR was 9.3 months. Extended response at 6 months or more, 12 months or more, and 24 months or more, occurred in 68.9%, 44.1%, and 31.4% of patients, respectively. Additionally, 71.4% and 42.0% of patients had tumor diameter reductions of 50% or more and 75% or more, respectively. ■

→ **For the full article, visit** CancerNetwork.com/KEYNOTE-775

CONTINUING MEDICAL EDUCATION (CME)

MAPK Pathway Inhibitors Augment Treatments for Pediatric Low-Grade Gliomas

FACULTY

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- Explain the impact of genomic technologies on pediatric low-grade glioma and how interrogating tumor tissue applies to current therapeutics
- Assess modalities implemented in pediatric low-grade glioma and the goals of treatment with the rationale for why these may or may not be used
- Outline a communication approach for parents of patients with low-grade glioma concerning disease treatment and clinical trial participation

RELEASE DATE: MAY 1, 2023
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The goal of treatment in pediatric low-grade gliomas is to cure patients of the disease, which is an achievable outcome in this setting. Kenneth J. Cohen, MD, MBA, is a pediatric oncologist and the director of the pediatric neuro-oncology program at Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, Maryland. In this article, Cohen discusses the current state of therapy in pediatric low-grade gliomas, which includes his perceptions of the new FDA approval of MAPK inhibitors for this indication. Further, Dr Cohen offers his advice about communicating treatment and clinical trial options to the patient and family.

Q: What can you tell us about the biology of pediatric low-grade gliomas and the molecular drivers behind the etiology of this disease?

COHEN: What we've learned about pediatric low-grade gliomas is that they almost all fall into 1 particular signaling pathway, which is called the RAS/MAP kinase (MAPK) pathway.[1] And while there are different abnormalities within that pathway, almost without exception, most pediatric low-grade gliomas have some aberration in some portion of that pathway, which has been interesting, because it's allowed us to sort of home in on a particular approach to our planned treatment.

Q: Are there cases of pediatric low-grade glioma that arise due to a cancer predisposition?

COHEN: Yes. The notable example is children with neurofibromatosis type 1 (NF1).[2] Again, due to an abnormality in the same pathway, they are at higher risk of developing low-grade gliomas, often tumors within the optic pathway. But these all fall under that same umbrella. This is the most common cancer predisposition syndrome that leads to a risk for the development of low-grade gliomas.

Q: What kind of effect have advanced genomic technologies had on the diagnosis, tumor interrogation, or treatment selection in pediatric low-grade glioma?

COHEN: There has been an enormous impact from genomic technologies on our understanding and diagnosis of these tumors.[3] Historically, we made the diagnosis either by classic imaging features in the absence of collecting tissue or when tissue was collected, by straightforward histology and immunohistochemistry. That tended to allow us to put these tumors into the overly broad category of pediatric low-grade gliomas, but not necessarily further subdivide them into what these mutations are that are driving the tumor development in that particular child. The improvement has been that we can not only say it is a low-grade glioma broadly, but we can be much more specific about what type of low-grade glioma [is involved] and some of the molecular features that we may be able to impact directly in terms of our therapeutic choices.[4]

Q: What is the rationale for the hypothesis that pediatric low-grade gliomas become quiescent in the transition from childhood to adulthood?

COHEN: There is some excellent research, including some from my colleagues here at Johns Hopkins, which demonstrates that these tumors do eventually go through something that is called senescence, where the tumor sort of falls asleep or loses interest in ever growing again. That is driven by some other molecular features and expression of certain things, like the p16 protein.[5] There is biologic evidence that supports this behavior when examined in vitro. From the clinical side, from my past and current experience, I can't remember transitioning one of my many low-grade glioma patients to an adult neuro-oncologist. Somewhere through the course of their childhood treatment, we eventually gain control in most cases, to the point where something changes about the biology of the tumor, either because of or despite our therapies, which causes the tumor to become quiescent.

Q: Can you describe the clinical work-up approach for pediatric brain tumors that provides an accurate diagnosis to inform prognosis and therapy selection from interrogating the tissue and finding biomarkers?

COHEN: When there are findings that suggest the need for imaging the central nervous system and a mass is identified, then we begin to make that diagnosis first by an assessment of the imaging findings. Ultimately, the gold standard when feasible is to gather tissue from that patient. And how much tissue can be gathered depends on the location of the tumor. There are some places in the brain where these tumors are relatively accessible with a small likelihood of significant neurologic injury from the surgical procedure, in which case our surgeons will go and try and remove the entirety of the tumor. There are other locations in the brain where there would be an inability to do that sort of a complete resection, and we would approach it by a biopsy or trying to get a small piece of tissue.[6]

There are circumstances [for which] the risks of the surgical procedure, even a biopsy, are [believed] to be too great, and we make treatment decisions based on our understanding of the imaging features and the location. If we can get tissue, which is our goal, then that tissue will get a certain amount of molecular interrogation. And based on those findings, that will help to define the potential therapies that we might be able to apply in that particular child. That doesn't mean we are always going to do it because, in some cases, treatment beyond diagnosis isn't required.

Q: When is treatment warranted and intervention necessary?

COHEN: The minimal goal of treatment is to at least to try and to eliminate the risk of further neurologic injury related to the tumor. The maximal goal is, if there has been injury in some way, can we restore function as a consequence of treating? It depends on location and the nature of the tumor. Our decisions about treatment are driven around those 2 considerations: Would a worsening of this tumor create a significant or a higher risk for neurologic injury? Is there already significant injury that we may be able to improve upon by our treatment?

For example, in a child with neurofibromatosis, it's not uncommon to find evidence of an optic pathway, low-grade glioma in those patients.[7] Yet, they have perfect vision, and they're clinically perfectly well, and we may decide that no further treatment is warranted. In other circumstances, a child may come along and have significant visual impact, and, in that case, treatment would be warranted.

Q: For a patient in whom surgical resection is not feasible, what are the available treatment options?

COHEN: The treatment options are no different from the treatment options even in the setting of a surgical resection. The difference is that in the absence of a resection, we have to make a few guesses about the nature of that tumor and what would be the best approach to therapy. We still utilize traditional chemotherapies, newer therapies often described as targeted therapies, or radiation therapy.[6] Those really become the mainstays of our treatment options if treatment is [believed] to be necessary. In some cases, we identify a tumor that we think is a low-grade tumor incidentally, and we may not treat that patient at all or even move forward with a biopsy. It's not that the therapy choices are different with or without tissue, it's just [that] our ability to make very specific decisions about targeted therapies would be impacted by the absence of information about the molecular drivers in the absence of tissue.

Q: Can you share your thoughts on the recent approval of the BRAF V600E and MEK inhibitor combinations for the treatment of pediatric low-grade gliomas with the driving mutation, especially considering that this population is less responsive to traditional therapy?

COHEN: One of the important findings in this group of patients is that 2 of the common abnormalities in pediatric low-grade gliomas are either these *BRAF* mutations, like the V600E mutation, or the alternate mutation called a *BRAF* fusion. If you look at most children with low-grade gliomas, the majority will either have a V600E mutation or a *BRAF* fusion.[8] The experience prior to the availability of these targeted therapies was that, in general, the children [who] had a *BRAF* V600E mutation did less well, meaning that they were more likely to progress following conventional chemotherapy, or they would require multiple lines of therapy to try and gain better control of the tumor than [did] children who didn't have a *BRAF* V600E mutation.[9,10]

When BRAF inhibitors came along that specifically target the V600E mutation, it gave us an opportunity to change the natural history of that subgroup of patients.[11] And what we have seen in the recent approval of the BRAF and MEK inhibitors for this group of patients is that their outcomes are substantially improved compared to what was seen or what is seen even prospectively in patients who are getting more traditional chemotherapy regimens. We believe this is a significantly better therapy, and we anticipate it will provide better long-term control than we are able to obtain with our prior therapies.

Q: Can we predict if a patient's tumor will experience rebound growth following drug cessation or what kind of therapy follows refractory tumor growth?

COHEN: Probably not, at least not with any certainty. There's experience with these types of therapies that when you stop them, if it appears that the tumor response isn't durable, you'll begin to see evidence of progression at some point.[12] In other cases, certainly in my own practice, I have patients who have been on these therapies, and they've been stopped, and their tumors have been stable for many years since the discontinuation of that therapy.[13] But there is concern that these therapies may not be durable in all cases. Sometimes you're required to think about second-line therapies for those patients or third-line therapies, depending on where they are in their disease course.[14]

The interesting thing has been that, historically, our view about traditional chemotherapy was that if you failed that therapy, we rarely would reintroduce it in recurrence or a progression of disease. The assumption being that if those cells figured out how to live through that original therapy, they would be unlikely to be responsive in the setting of progression. Interestingly, for the targeted therapies, it appears that you can reinitiate those therapies and, in many cases, regain control of the tumor even if [the disease has] progressed following the discontinuation of those therapies. Now, the decision about when to do that depends. If someone progresses 2 weeks after we stop their therapy, we would probably [think] differently about that than a patient who maybe had disease control for a year or 2 after the therapy and then had progression. There, we might think about reintroducing the therapy.

Q: What kind of considerations exist for the long-term impacts of MAPK inhibitor therapy?

COHEN: That's the biggest question. We have 30 to 40 years of experience using traditional chemotherapy regimens like carboplatin, vincristine, and other similar therapies. So we know a great deal about those long-term toxicities, and they have very limited, long-term toxicities. We don't know the answer to that for the MAPK therapies yet, and that's simply a consequence of the fact that we haven't treated patients for as many years and for long enough necessarily to know whether there will be impact. We do know that there are specific organ toxicities that we monitor for patients who are on MAPK therapies, like certain eye findings that can be related to [an adverse] effect of these therapies. Cardiac findings we pay attention to, as well.[15]

Everything we give has certain side effects, and whether those [adverse] effects are significant or pose the risk for long-term toxicity, we do not know yet. That's obviously one of the things that makes us be a little cautious in our application of these approaches—when we don't know as much about durability, we don't know as much about long-term toxicity, and that information will come over time as there's a growing use of these therapies. In my practice, we have patients who have been on these therapies for 5 to 6 years now and appear to be quite tolerant of these therapies long term, but the jury is certainly still out on whether that will be the case over many years.

Q: What do you anticipate the near future holds regarding treatment for pediatric low-grade gliomas?

COHEN: There's a strong sense that we know the pathway that we're working to impact, and we have a growing armamentarium of therapies that are designed to impact that pathway. We are benefiting from the fact that this pathway is not unique to pediatric low-grade gliomas but is commonly a problem in many forms of both pediatric and adult cancer, which means there's lots of research occurring for other disease conditions that we may be able to borrow from.

For many children, we may move to a place where these targeted therapies will be our frontline therapy. There will be a group of patients that fail, as there is with virtually any therapy we've ever found. Then, the next line of research will be, why do they fail? What is it about this subgroup of patients that makes them fail when others do not? And do they have ways to circumvent some of these inhibitors, and can we find other inhibitors or other strategies that also impact that pathway that protect against failure or could be used in the setting of the subset of patients who aren't successfully treated? It will be a growing series of therapeutics that impact the MAPK pathway in some way, to figure out what the specific Achilles heel is for each of the patients that we take care of.

Q: How do you approach communicating treatment and clinical trial options to the patient and family?

COHEN: This is something that's part of being a pediatric oncologist, and we have really made all our successes by the fact that we have a robust clinical trials infrastructure and philosophy about the value of that approach. For every patient and family that I interact with, if we have a clinical trial that we think is relevant to the disease condition, then we sit and talk about it. We discuss the rationale for the trial, the potential merits, the risks and benefits of the proposed treatment, what we would do in the absence of the trial, and how much does it deviate from what we'd otherwise propose. All those things are considered, and then, based on that information and our ability to provide comprehensive and informed consent, parents and patients make a decision about whether the trial feels like something they'd be willing to participate in or not.

We've made all this headway in this disease area because of some very good clinical trials that have definitively shown the value of these approaches. We can still continue to improve, and we're constantly trying to chip away at our success in terms of trying to find what we can do to make that even a more successful outcome for our patients.

Q: Is there any other point that you would like to make regarding this disease?

COHEN: We are thinking about how to choose from the entire armamentarium. Radiation therapy is a therapy that is quite effective in the treatment of many types of brain tumors, including low-grade gliomas. Moving into the future, we are going to have to think about this burgeoning number of therapeutic options, given a long list of standard chemotherapeutics that may be useful and given the expanding improvements in the technology of radiation therapy. We have to think really carefully about the balance of burden to patients, the risk and benefits of each of our approaches, and the fact that, in certain circumstances, things like radiation, which has sort of fallen out of favor for the treatment of these patients, may be a very reasonable thing to consider.

This is an area where we have a growing pool of ways to approach this. There was a time when it was just chemotherapy, and if line A didn't work, we went to line B. And if line B didn't work, we went to line C. We're in a very different place therapeutically, both because of the targeted therapies and because of improved radiation technologies. As a community, we're going to have to think very carefully about how we apply each of those technologies in sensible ways without some of the antecedent bias that has gone into a lot of the decision-making historically. ■

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