2022 | Issue 1

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Influenza A - 96.0% (95% CI: 94.4% - 97.2%)
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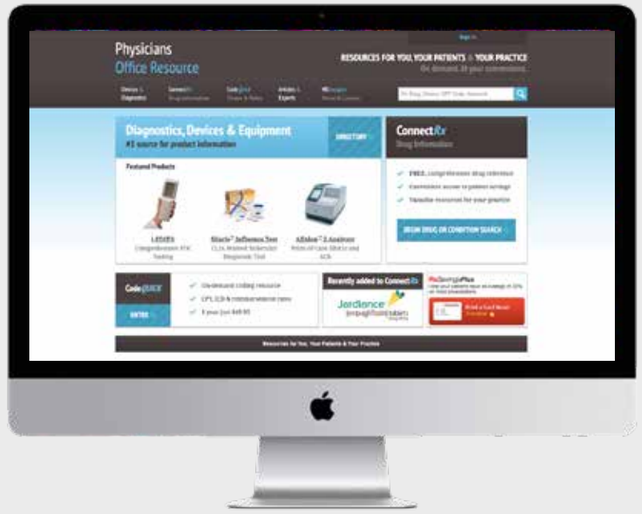
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HOW CAN YOU PREVENT ANTIMICROBIAL RESISTANCE?

In 2019, the World Health Organization declared antibacterial resistance one of the top 10 threats to global health.

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IDENTIFYING MIS-C WITH RISK PREDICTION MODEL

While children often recover quickly from COVID-19, with the emergence of the highly contagious omicron variant, cases and hospitalizations are on the rise.



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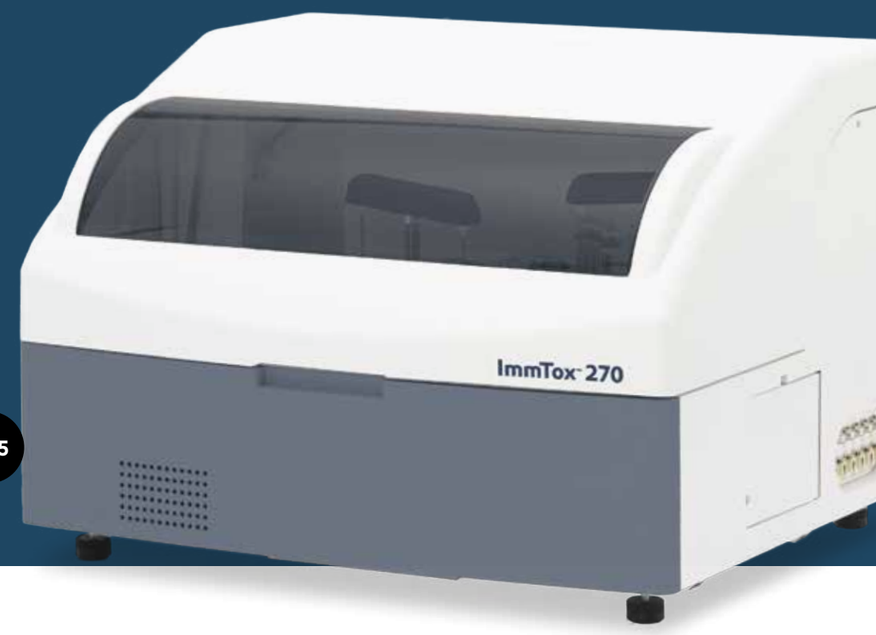
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COVID-19 TESTING

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BD VERITOR™ PLUS SYSTEM

From BD Veritor™

The BD Veritor™ Plus System is a portable, easy-to-use, testing solution for SARS-COV-2*, Flu A+ B and other respiratory tract infections that delivers results in 15 minutes or less. It features two analysis modes that adapt to your workflow, online education tools, and optional reporting capabilities including the BD Synapsys™ Informatics Solution—making it the point-of-care diagnostic tool you won't want to be without.

*EUA authorized by FDA

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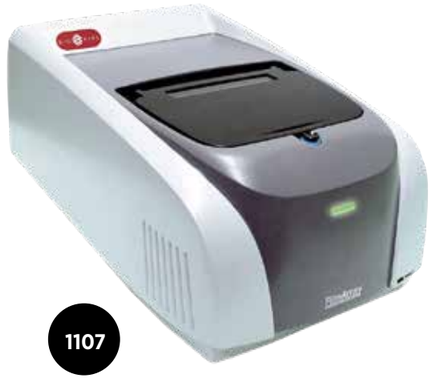
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From BioFire

SARS-CoV-2 is everyone's top suspect, but many other respiratory bugs can cause similar, overlapping symptoms. In your clinic, you can test for 19 common respiratory pathogens, including SARS- CoV-2, with the BioFire RP2.1-EZ Panel (EUA)[1]—now available under an FDA Emergency Use Authorization. Syndromic testing means all it takes is one test and just 45 minutes to round up SARS-CoV-2—and all the other usual respiratory suspects.

1. This test is not FDA cleared or approved. This test has been authorized by FDA under an EUA for use by authorized laboratories.

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1107



1108

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This point-of-care (POC) designated test is one of the top-used amongst our customers.

Features/Benefits:
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This test is not FDA cleared or approved. This test has been authorized by FDA under an EUA for use by authorized laboratories.

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NOW APPROVED FOR ADULT PATIENTS WITH WALDENSTRÖM'S MACROGLOBULINEMIA (WM)[1]



24-hour inhibition of BTK was maintained at 100% in PBMCs and 94% to 100% in lymph nodes when taken at the recommended total daily dose of 320 mg. The clinical significance of 100% inhibition has not been established.[1,2]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage
Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 3.4% of patients treated with BRUKINSA monotherapy. Hemorrhage events of any grade occurred in 35% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhag Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections
Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 27% of patients, most commonly pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (26%), thrombocytopenia (11%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy. Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia occurred in 3.6% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose or discontinue treatment as warranted. Treat using growth factor or transfusions, as needed.

Second Primary Malignancies
Second primary malignancies, including non-skin carcinoma, have occurred in 14% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 8% of patients. Other second primary malignancies included malignant solid tumors (4.0%), melanoma (1.7%) and hematologic malignancies (1.2%). Advise patients to use sun protection, and monitor patients for the development of second primary malignancies.

Cardiac Arrhythmias
Atrial fibrillation and atrial flutter were reported in 3.2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension and acute infections may be at increased risk. Grade 3 or higher events were reported in 1.1% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Embryo-Fetal Toxicity
Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for 1 week after the last dose. Advise men to avoid fathering a child during treatment and for 1 week after the last dose.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

ADVERSE REACTIONS

The most common adverse reactions, including laboratory abnormalities, in ≥ 30% of patients who received BRUKINSA (N=847) included decreased neutrophil count (54%), upper respiratory tract infection (47%), decreased platelet count (41%), hemorrhage (35%), decreased lymphocyte count (31%), rash (31%) and musculoskeletal pain (30%).

DRUG INTERACTIONS

CYP3A Inhibitors: When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For co-administration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid co-administration with moderate or strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment: The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

Please see Brief Summary of full Prescribing Information on following pages.

THE BTK INHIBITOR THAT DELIVERS POWERFUL AND CONSISTENT RESPONSES

BRUKINSA® (zanubrutinib) is a kinase inhibitor indicated for the treatment of adult patients with Waldenström's macroglobulinemia.

BRUKINSA > Ibrutinib

The first and only head-to-head trial of BTK inhibitors in WM

A global, randomized Phase 3 trial in WM across a range of patients*[1]

- Treatment-naïve
- Relapsed/refractory
- *MYD88^{MUT} (CXCR4^{WT}, CXCR4^{WHIM})*
- *MYD88^{WT}*

Powerful Responses Across WM Patients

While the primary endpoint of superiority did not reach statistical significance, numerically higher VGPR/CR rates were achieved in the BRUKINSA treatment arm.[1]

All patients[1]
IWWM-6 criteria† (Cohort 1)

BRUKINSA (n=102)	Ibrutinib (n=99)
78% CR+VGPR+PR‡ (95% CI: 68, 85)	78% CR+VGPR+PR (95% CI: 68, 86)
16% VGPR/CR‡	7% VGPR/CR
62% PR	71% PR

All patients[1]
Modified IWWM-6 criteria† (Cohort 1)

BRUKINSA (n=102)	Ibrutinib (n=99)
78% CR+VGPR+PR‡ (95% CI: 68, 85)	78% CR+VGPR+PR (95% CI: 68, 86)
28% VGPR/CR‡	19% VGPR/CR
49% PR	59% PR

Median follow-up time was 19.4 months.[3]

The prespecified efficacy outcome measure of VGPR/CR was assessed by IRC.[1]

Safety in WM is consistent with the established BRUKINSA profile[1]

Serious adverse reactions, including fatal events, have occurred with BRUKINSA, including hemorrhage, infections, cytopenias, second primary malignancies, and cardiac arrhythmias. The most common adverse reactions (≥30%) include neutrophil count decreased, upper respiratory tract infection, platelet count decreased, hemorrhage, lymphocyte count decreased, rash, and musculoskeletal pain.

*Patients were enrolled from the United States, Europe, and Australia/New Zealand.
†IWWM-6 criteria (Owen et al, 2013) requires complete resolution of extramedullary disease (EMD) if present at baseline for VGPR to be assessed. Modified IWWM-6 criteria (Treon, 2015) requires a reduction in EMD if present at baseline for VGPR to be assessed.[4,5]
‡There were no CRs in either treatment arm.

BTK=Bruton's tyrosine kinase; CI=confidence interval; CR=complete response; IRC=independent review committee; IWWM-6=6th International Workshop on Waldenström's Macroglobulinemia; MUT=mutated; ORR=overall response rate; PBMCs=peripheral blood mononuclear cells; PR=partial response; VGPR=very good partial response; WHIM=WHIM syndrome-like somatic mutation; WT=wild type.

References: 1. BRUKINSA. Package insert. BeiGene, Ltd; 2021. **2.** Tam C, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood*. 2019;134(11):851-859. **3.** Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood*. 2020;136(18):2038-2050. **4.** Owen RG, Kyle RA, Stone MJ, et al. Response assessment in Waldenström macroglobulinemia: update from the VIth International Workshop. *Br J Haematol*. 2013;160(2):171-176. **5.** Treon SP. How I treat Waldenström macroglobulinemia. *Blood*. 2015;126(6):721-732.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION
FOR BRUKINSA® (zanubrutinib)
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

BRUKINSA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.2 Waldenström's Macroglobulinemia

BRUKINSA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

1.3 Marginal Zone Lymphoma

BRUKINSA is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 3.4% of patients treated with BRUKINSA monotherapy. Hemorrhage events of any grade, excluding purpura and petechiae, occurred in 35% of patients.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 27% of patients, most commonly pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (26%), thrombocytopenia (11%) and anemia (8%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy *[see Adverse Reactions (6.1)]*. Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia occurred in 3.6% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dosage and Administration (2.4)]*. Treat using growth factor or transfusions, as needed.

5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 14% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 8% of patients. Other second primary malignancies included malignant solid tumors (4.0%), melanoma (1.7%) and hematologic malignancies (1.2%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

5.5 Cardiac Arrhythmias

Atrial fibrillation and atrial flutter were reported in 3.2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension and acute infections may be at increased risk. Grade 3 or higher events were reported in 1.1% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate *[see Dosage and Administration (2.4)]*.

5.6 Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for 1 week after the last dose. Advise men to avoid fathering a child during treatment and for 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

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

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.4)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

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

The data in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA in seven clinical trials, administered as a single agent at 160 mg twice daily in 730 patients, at 320 mg once daily in 105 patients, and at 40 mg to 160 mg once daily (0.125 to 0.5 times the recommended dosage) in 12 patients. Among 847 patients receiving BRUKINSA, 73% were exposed for at least 1 year, 57% were exposed for at least 2 years and 26% were exposed for at least 3 years.

In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in ≥ 30% of patients included neutrophil count decreased (54%), upper respiratory tract infection (47%), platelet count decreased (41%), hemorrhage (35%), lymphocyte count decreased (31%), rash (31%) and musculoskeletal pain (30%).

Mantle Cell Lymphoma (MCL)

The safety of BRUKINSA was evaluated in 118 patients with MCL who received at least one prior therapy in two single-arm clinical trials, BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02343120] *[see Clinical Studies (14.1)]*. The median age of patients who received BRUKINSA in studies BGB-3111-206 and BGB-3111-AU-003 was 62 years (range: 34 to 86), 75% were male, 75% were Asian, 21% were White, and 94% had an ECOG performance status of 0 to 1. Patients had a median of 2 prior lines of therapy (range: 1 to 4). The BGB-3111-206 trial required a platelet count ≥ 75 x 10^9/L and an absolute neutrophil count ≥ 1 x 10^9/L independent of growth factor support, hepatic enzymes ≤ 2.5 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. The BGB-3111-AU-003 trial required a platelet count ≥ 50 x 10^9/L and an absolute neutrophil count ≥ 1 x 10^9/L independent of growth factor support, hepatic enzymes ≤ 3 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. Both trials required a CLcr ≥ 30 mL/min. Both trials excluded patients with prior allogeneic hematopoietic stem cell transplant, exposure to a BTK inhibitor, known infection with HIV and serologic evidence of active hepatitis B or hepatitis C infection and patients requiring strong CYP3A inhibitors or strong CYP3A inducers. Patients received BRUKINSA 160 mg twice daily or 320 mg once daily. Among patients receiving BRUKINSA, 79% were exposed for 6 months or longer, and 68% were exposed for greater than one year.

Fatal events within 30 days of the last dose of BRUKINSA occurred in 8 (7%) of 118 patients with MCL. Fatal cases included pneumonia in 2 patients and cerebral hemorrhage in one patient.

Serious adverse reactions were reported in 36 patients (31%). The most frequent serious adverse reactions that occurred were pneumonia (11%) and hemorrhage (5%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

Table 3 summarizes the adverse reactions in BGB-3111-206 and BGB-3111-AU-003.

Table 3: Adverse Reactions (≥ 10%) in Patients Receiving BRUKINSA in BGB-3111-206 and BGB-3111-AU-003 Trials

Body System	Adverse Reaction	Percent of Patients (N=118)	
		All Grades %	Grade 3 or Higher %
Blood and lymphatic system disorders	Neutropenia and Neutrophil count decreased	38	15
	Thrombocytopenia and Platelet count decreased	27	5
	Leukopenia and White blood count decreased	25	5
	Anemia and Hemoglobin decreased	14	8
Infections and infestations	Upper respiratory tract infection[¶]	39	0
	Pneumonia[§]	15	10^
	Urinary tract infection	11	0.8
Skin and subcutaneous tissue disorders	Rash[ll]	36	0
	Bruising*	14	0
Gastrointestinal disorders	Diarrhea	23	0.8
	Constipation	13	0
Vascular disorders	Hypertension	12	3.4
	Hemorrhage†	11	3.4^
Musculoskeletal and connective tissue disorders	Musculoskeletal pain‡	14	3.4
Metabolism and nutrition disorders	Hypokalemia	14	1.7
Respiratory, thoracic and mediastinal disorders	Cough	12	0

^ Includes fatal adverse reaction.
* Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis.
† Hemorrhage includes all related terms containing hemorrhage, hematoma.
‡ Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis.
§ Pneumonia includes pneumonia, pneumonia fungal, pneumonia cryptococcal, pneumonia streptococcal, atypical pneumonia, lung infection, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection viral.
ll Rash includes all related terms containing rash.
¶ Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract infection viral.

Other clinically significant adverse reactions that occurred in < 10% of patients with mantle cell lymphoma include major hemorrhage (defined as ≥ Grade 3 hemorrhage or CNS hemorrhage of any grade) (5%), hyperuricemia (6%) and headache (4.2%).

Table 4: Selected Laboratory Abnormalities* (> 20%) in Patients with MCL in Studies BGB-3111-206 and BGB-3111-AU-003

Laboratory Parameter	Percent of Patients (N=118)	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	45	20
Platelets decreased	40	7
Hemoglobin decreased	27	6
Lymphocytosis†	41	16
Chemistry abnormalities		
Blood uric acid increased	29	2.6
ALT increased	28	0.9
Bilirubin increased	24	0.9

* Based on laboratory measurements.
† Asymptomatic lymphocytosis is a known effect of BTK inhibition.

Waldenström's Macroglobulinemia (WM)

The safety of BRUKINSA was investigated in two cohorts of Study BGB-3111-302 (ASPEN). Cohort 1 included 199 patients with MYD88 mutation *($MYD88^{MUT}$)* WM, randomized to and treated with either BRUKINSA (101 patients) or ibrutinib (98 patients). The trial also included a non-randomized arm, Cohort 2, with 26 wild type MYD88 *($MYD88^{WT}$)* WM patients and 2 patients with unknown MYD88 status *[see Clinical Studies (14.2)]*.

Among patients who received BRUKINSA, 93% were exposed for 6 months or longer, and 89% were exposed for greater than 1 year.

In Cohort 1 of the ASPEN study safety population (N=101), the median age of patients who received BRUKINSA was 70 years (45-87 years old); 67% were male, 86% were White, 4% were Asian and 10% were not reported (unknown race). In Cohort 2 of the ASPEN study safety population (N=28), the median age of patients who received BRUKINSA was 72 (39-87 years old); 50% were male, 96% were White and 4% were not reported (unknown race).

In Cohort 1, serious adverse reactions occurred in 44% of patients who received BRUKINSA. Serious adverse reactions in > 2% of patients included influenza (3%), pneumonia (4%), neutropenia and neutrophil count decreased (3%), hemorrhage (4%), pyrexia (3%) and febrile neutropenia (3%). In Cohort 2, serious adverse reactions occurred in 39% of patients. Serious adverse reactions in > 2 patients included pneumonia (14%).

Permanent discontinuation of BRUKINSA due to an adverse reaction occurred in 2% of patients in Cohort 1 and included hemorrhage (1 patient), neutropenia and neutrophil count decreased (1 patient); in Cohort 2, permanent discontinuation of BRUKINSA due to an adverse reaction occurred in 7% of patients and included subdural hemorrhage (1 patient) and diarrhea (1 patient).

Dosage interruptions of BRUKINSA due to an adverse reaction occurred in 32% of patients in Cohort 1 and in 29% in Cohort 2. Adverse reactions which required dosage interruption in > 2% of patients included neutropenia, vomiting, hemorrhage, thrombocytopenia and pneumonia in Cohort 1. Adverse reactions leading to dosage interruption in > 2 patients in Cohort 2 included pneumonia and pyrexia.

Dose reductions of BRUKINSA due to an adverse reaction occurred in 11% of patients in Cohort 1 and in 7% in Cohort 2. Adverse reactions which required dose reductions in > 2% of patients included neutropenia in Cohort 1. Adverse reaction leading to dose reduction occurred in 2 patients in Cohort 2 (each with one event: diarrhea and pneumonia).

Table 5 summarizes the adverse reactions in Cohort 1 in ASPEN.

Table 5: Adverse Reactions (≥ 10%) Occurring in Patients with WM Who Received BRUKINSA in Cohort 1

Body System	Adverse Reaction	BRUKINSA (N=101)		Ibrutinib (N=98)	
		All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection[¶]	44	0	40	2
	Pneumonia[§]	12	4	26	10
	Urinary tract infection	11	0	13	2
Gastrointestinal disorders	Diarrhea	22	3	34	2
	Nausea	18	0	13	1
	Constipation	16	0	7	0
	Vomiting	12	0	14	1
General disorders and administration site conditions	Fatigue[#]	31	1	25	1
	Pyrexia	16	4	13	2
	Edema peripheral	12	0	20	0
Skin and subcutaneous tissue disorders	Bruising*	20	0	34	0
	Rash[ll]	29	0	32	0
	Pruritus	11	1	6	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[‡]	45	9	39	1
	Muscle spasms	10	0	28	1
Nervous system disorders	Headache	18	1	14	1
	Dizziness	13	1	12	0
Respiratory, thoracic and mediastinal disorders	Cough	16	0	18	0
	Dyspnea	14	0	7	0
Vascular disorders	Hemorrhage†	42	4	43	9
	Hypertension	14	9	19	14

* Bruising includes all related terms containing "bruise," "contusion," or "ecchymosis."
† Hemorrhage includes epistaxis, hematuria, conjunctival hemorrhage, hematoma, rectal hemorrhage, periorbital hemorrhage, mouth hemorrhage, post procedural hemorrhage, hemoptysis, skin hemorrhage, hemorrhoidal hemorrhage, ear hemorrhage, eye hemorrhage, hemorrhagic diathesis, periorbital hematoma, subdural hemorrhage, wound hemorrhage, gastric hemorrhage, lower gastrointestinal hemorrhage, spontaneous hematoma, traumatic hematoma, traumatic intracranial hemorrhage, tumor hemorrhage, retinal hemorrhage, hematochezia, diarrhea hemorrhagic, hemorrhage, melena, post procedural hematoma, subdural hematoma, anal hemorrhage, hemorrhagic disorder, pericardial hemorrhage, postmenopausal hemorrhage, stoma site hemorrhage, subarachnoid hemorrhage.
# Fatigue includes asthenia, fatigue, lethargy.
‡ Musculoskeletal pain includes back pain, arthralgia, pain in extremity, musculoskeletal pain, myalgia, bone pain, spinal pain, musculoskeletal chest pain, neck pain, arthritis, musculoskeletal discomfort.
§ Pneumonia includes lower respiratory tract infection, lung infiltration, pneumonia, pneumonia aspiration, pneumonia viral.
ll Rash includes all related terms rash, maculo-papular rash, erythema, rash erythematous, drug eruption, dermatitis allergic, dermatitis atopic, rash pruritic, dermatitis, photodermatosis, dermatitis acneiform, stasis dermatitis, vasculitic rash, eyelid rash, urticaria, skin toxicity.
¶ Upper respiratory tract infection includes upper respiratory tract infection, laryngitis, nasopharyngitis, sinusitis, rhinitis, viral upper respiratory tract infection, pharyngitis, rhinovirus infection, upper respiratory tract congestion.

Clinically relevant adverse reactions in < 10% of patients who received BRUKINSA included localized infection, atrial fibrillation or atrial flutter and hematuria.

Table 6 summarizes the laboratory abnormalities in ASPEN.

Table 6: Select Laboratory Abnormalities* (≥ 20%) That Worsened from Baseline in Patients with WM Who Received BRUKINSA in Cohort 1

Laboratory Abnormality	BRUKINSA[1]		Ibrutinib[1]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic Abnormalities				
Neutrophils decreased	50	24	34	9
Platelets decreased	35	8	39	5
Hemoglobin decreased	20	7	20	7
Chemistry Abnormalities				
Bilirubin increased	12	1.0	33	1.0
Calcium decreased	27	2.0	26	0
Creatinine increased	31	1.0	21	1.0
Glucose increased	45	2.3	33	2.3
Potassium increased	24	2.0	12	0
Urate increased	16	3.2	34	6
Phosphate decreased	20	3.1	18	0

* Based on laboratory measurements.
[1] The denominator used to calculate the rate varied from 86 to 101 based on the number of patients with a baseline value and at least one post-treatment value.

Marginal Zone Lymphoma

The safety of BRUKINSA was evaluated in 88 patients with previously treated MZL in two single-arm clinical studies, BGB-3111-214 and BGB-3111-AU-003 *[see Clinical Studies (14.3)]*. The trials required an absolute neutrophil count ≥ 1 x 10^9/L, platelet count ≥ 50 or ≥ 75 x 10^9/L and adequate hepatic function and excluded patients requiring a strong CYP3A inhibitor or inducer. Patients received BRUKINSA 160 mg twice daily (97%) or 320 mg once daily (3%). The median age in both studies combined was 70 years (range: 37 to 95), 52% were male, 64% were Caucasian and 19% were Asian. Most patients (92%) had an ECOG performance status of 0 to 1. Eighty percent received BRUKINSA for 6 months or longer, and 67% received treatment for more than one year.

Two fatal adverse reactions (2.3%) occurred within 30 days of the last dose of BRUKINSA, including myocardial infarction and a Covid-19 related death.

Serious adverse reactions occurred in 40% of patients. The most frequent serious adverse reactions were pyrexia (8%) and pneumonia (7%).

Adverse reactions lead to treatment discontinuation in 6% of patients, dose reduction in 2.3%, and dose interruption in 34%. The leading cause of dose modification was respiratory tract infections (13%).

Table 7 summarizes selected adverse reactions in BGB-3111-214 and BGB-3111-AU-003.

Table 7: Adverse Reactions Occurring in ≥ 10% Patients with MZL Who Received BRUKINSA

Body System	Adverse Reaction	BRUKINSA (N=88)	
		All Grades %	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infections[a]	26	3.4
	Urinary tract infection[b]	11	2.3
	Pneumonia[c†]	10	6
Gastrointestinal disorders	Diarrhea[d]	25	3.4
	Abdominal pain[e]	14	2.3
	Nausea	13	0
Skin and subcutaneous tissue disorders	Bruising[f]	24	0
	Rash[g]	21	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[h]	27	1.1
Vascular disorders	Hemorrhage[i]	23	1.1
General disorders	Fatigue[j]	21	2.3
Respiratory, thoracic and mediastinal disorders	Cough[k]	10	0

* Includes 2 fatal events of COVID-19 pneumonia.
[a] Upper respiratory tract infections includes upper respiratory tract infection, nasopharyngitis, sinusitis, tonsillitis, rhinitis, viral upper respiratory tract infection.
[b] Urinary tract infection includes urinary tract infection, cystitis, Escherichia urinary tract infection, pyelonephritis, cystitis.
[c] Pneumonia includes COVID-19 pneumonia, pneumonia, bronchopulmonary aspergillosis, lower respiratory tract infection, organizing pneumonia.
[d] Diarrhea includes diarrhea and diarrhea hemorrhagic.
[e] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort.
[f] Bruising includes contusion, ecchymosis, increased tendency to bruise, post procedural contusion.
[g] Rash includes rash, rash maculo-papular, rash pruritic, dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, drug reaction with eosinophilia and systemic symptoms, erythema, photosensitivity reaction, rash erythematous, rash papular, seborrheic dermatitis.
[h] Musculoskeletal pain includes back pain, arthralgia, musculoskeletal pain, myalgia, pain in extremity, musculoskeletal chest pain, bone pain, musculoskeletal discomfort, neck pain.
[i] Hemorrhage includes epistaxis, hematuria, hemorrhoidal hemorrhage, hematoma, hemoptysis, conjunctival hemorrhage, diarrhea hemorrhagic, hemorrhage urinary tract, mouth hemorrhage, pulmonary hematoma, subcutaneous hematoma, gingival bleeding, melena, upper gastrointestinal hemorrhage.
[j] Fatigue includes fatigue, lethargy, asthenia.
[k] Cough includes cough and productive cough.

Clinically relevant adverse reactions in < 10% of patients who received BRUKINSA included peripheral neuropathy, second primary malignancies, dizziness, edema, headache, petechiae, purpura and atrial fibrillation or flutter.

Table 8 summarizes selected laboratory abnormalities.

Table 8: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with MZL

Laboratory Abnormality[1]	BRUKINSA	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	43	15
Platelets decreased	33	10
Lymphocytes decreased	32	8
Hemoglobin decreased	26	6
Chemistry abnormalities		
Glucose increased	54	4.6
Creatinine increased	34	1.1
Phosphate decreased	27	2.3
Calcium decreased	23	0
ALT increased	22	1.1

The denominator used to calculate the rate varied from 87 to 88 based on the number of patients with a baseline value and at least one post-treatment value.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 9: Drug Interactions that Affect Zanubrutinib

Moderate and Strong CYP3A Inhibitors	
Clinical Impact	• Co-administration with a moderate or strong CYP3A inhibitor increases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may increase the risk of BRUKINSA toxicities.
Prevention or management	• Reduce BRUKINSA dosage when co-administered with moderate or strong CYP3A inhibitors *[see Dosage and Administration (2.3)]*.
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Co-administration with a moderate or strong CYP3A inducer decreases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may reduce BRUKINSA efficacy.
Prevention or management	• Avoid co-administration of BRUKINSA with moderate or strong CYP3A inducers *[see Dosage and Administration (2.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women. There are no available data on BRUKINSA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of zanubrutinib to pregnant rats during the period of organogenesis was associated with fetal heart malformation at approximately 5-fold human exposures *(see Data)*. Women should be advised to avoid pregnancy while taking BRUKINSA. If BRUKINSA is used during pregnancy, or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Embryo-fetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose of 160 mg twice daily.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 32 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre- and post-natal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g., cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for two weeks following the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA therapy.

Contraception

Females

BRUKINSA can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with BRUKINSA and for 1 week following the last dose of BRUKINSA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise men to avoid fathering a child while receiving BRUKINSA and for 1 week following the last dose of BRUKINSA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 847 patients in clinical studies with BRUKINSA, 53% were ≥ 65 years of age, and 20% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between younger and older patients.

8.6 Renal Impairment

No dosage modification is recommended in patients with mild, moderate, or severe renal impairment (CLcr ≥ 15 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients on dialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment *[see Dosage and Administration (2.2)]*. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for BRUKINSA adverse reactions in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

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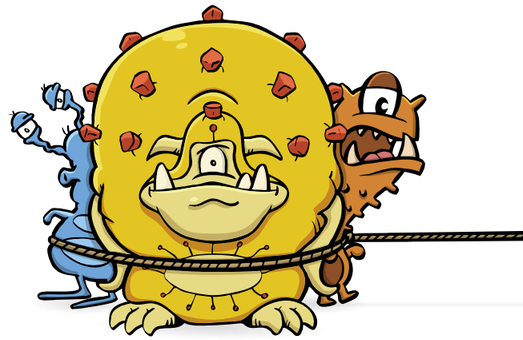
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1115

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PLANNING FOR NEW INSTRUMENTS AND NEW TESTS

BY IRWIN Z. ROTHENBERG, MBA, MS, CLS(ASCP), TECHNICAL WRITER /QUALITY ADVISOR, COLA RESOURCES, INC.

Whether planning a new, start-up laboratory operation, or performing an analysis of current testing, (providing input for decisions on whether or not to purchase new or replacement instruments, or add or delete tests), it is important to do a realistic assessment not only of what you want to offer your ordering physicians, but what you can realistically offer. The laboratory's test menu should be aligned as closely as possible with physician expectations and needs, as well as the laboratory's operational capabilities.

By strengthening relationships with ordering physicians, laboratories can more accurately forecast future service needs and make the best decisions as to test menu, instrumentation, and staffing, including which tests to outsource or maintain in-house[10].

Begin this process by:
Reviewing Basic Information about the Current / Proposed Laboratory Operation

The first step in the planning process for adding new tests and new instrumentation begins with asking the following baseline questions regarding the present or proposed laboratory operation:

- What is your present test menu? Present instrumentation? Present staffing levels?
- What medical specialties are represented by your ordering physicians? (an important determinant of what tests will be requested, as well as patient demographics)
- Do you anticipate changes in the number of client physicians served? New specialties added? New populations served?
- What are your current or anticipated test volumes / demand for specific tests?
- What is the complexity of testing already performed or planned? (waived vs. non-waived, with attendant regulatory requirements, including personnel)
- What are your present hours of operation with attendant staffing levels / type and volume of testing performed per shift / commitment for turn-around times?
- What are your anticipated operating and capital budgets? (important determinant for changes to instrumentation and level of automation; as well as staffing expertise)
- Is adequate workspace available to accommodate all phases of new patient testing from specimen collection to test result reporting?

The answers to these questions provide guidance for any changes to the test menu, which will be a driver for decisions on whether to acquire new or replacement instruments.

The next step forward is to perform a Cost/Benefit analysis of your present operation, and of the proposed changes to the test systems to determine economic and logistical feasibility.

Determine the Feasibility of Adding New Tests:
Perform a Cost / Benefit Analysis[1]

It is by taking into account the internal as well as external factors in the laboratory environment, that the decisions made will have the best chance of success.

Below are items to consider for your cost/benefit analysis:
- Instrument capacity for current or proposed test menu (is it "right-sized" for test volume and level of staffing)
- Instrument cost (purchase or lease)
- Reagent cost (are you obligated to purchase reagents from a particular manufacturer?)
- Reagent life (expiration dates: days, weeks, months before/after opening packages)

- Storage requirements for reagents (do you need to buy a new refrigerator or freezer?)
- Frequency and expense of Quality Controls, Calibration, and Maintenance
- Tests run singly or in batch-mode
- Comparison of in-house testing with reference laboratory charges and turn-around time
- Complexity of present and proposed testing.
- Staffing requirements: number, training expenses; qualifications and experience beyond present staffing; continuing education
- Proficiency Testing requirements
- Facility space, ventilation, electrical needs; hazardous disposal requirements
- Time and involvement of the Lab Director, and the Technical Consultant
- Document storage requirements / LIS capability
- Adjusting the front office staffing to handle additional pre and post analytical paperwork and communications

Additional strategies to determine the appropriateness of testing offered, and the instrumentation needed[2].

- Analyze test mix and outsource demanded but low-volume tests. Only outsource these tests if you can provide the test results a lower cost and with a better turnaround time.

- Project test demand and costs to determine which tests to perform in house. Conversely, analysis of send-out volumes may indicate opportunities to bring certain tests in-house.

- Partner with reference laboratories. Reference laboratories can provide valuable support in the form of financial analysis, methodology assessment, and provision of clinical samples to help make in-source-versus-outsource decisions and to establish and increase on-site test volumes.

Consider external factors as well[3]

Consider what is going on in the laboratory industry today, noting trends both locally and across the country and seeing if these factors may affect your laboratory:

- What will be the impact of changes in reimbursement / payment mechanisms?

- What is the current market for your laboratory services? Estimating market size and location is a critical component to determine market opportunity. These estimates will drive financial outcomes.

- If you are part of an organization that has adopted the concept of value-based medical care, and it now part of an Accountable Care Organization (ACO), or accepts "bundled payments", your expenses will come under increased pressure to be held down and minimized. You may be encouraged to outsource more than originally planned.

- The well-documented staffing shortage may be a factor in your area; consider your local situation if planning to increase testing, add shifts, and new pre-analytic services.

Of course, providing the highest level of service for your patients may justify costs associated with the above considerations, but it is vital to ensure that your instrumentation can handle the changes in projected demand in terms of test volume capacity, variety of tests offered, operating times and staffing. This may require considering more automation. Automation has long been regarded as an important means for clinical laboratories to achieve greater operational efficiency, test accuracy, method standardization, total data handling and reduced turnaround time; in short, an improved quality of patient care.

The development of new generations of automated stand-alone and bench top equipment has made automation a more viable option for labs of all sizes—and in many cases, a necessary option for labs seeking to remain competitive in today's marketplace[4].

Steps in Determining the Right Automation for Your Laboratory[5]

A. Questions to ask when deciding how much automation is needed

The amount of automation needed depends on the type and size of your laboratory. If all you are looking for is increased throughput and you don't really have to deal with diverse assays and readouts, then you might want to think about modular components. So, with a few nonintegrated pieces of equipment, you can get the throughput you need without a huge investment, or additional space required.

B. Set priorities for automation based on realistic budget limitations

Once you have taken care of the above, and determined your needs, start getting quotes on systems needed. Budget negotiations will begin, with sets of reality checks on what is doable and what is not. Decisions should be based on priorities set in advance.

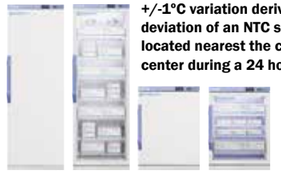
C. A few more points to remember

Always choose a vendor who can provide prompt, affordable service to minimize any downtime. Remember the data management involved. There are different sets of tools for data processing, data mining and data visualization, and you need to think about how you are going to track and analyze this data. Finally, create an infrastructure that can be easily modified or expanded for other applications.

VACCINE FREEZERS and REFRIGERATORS

- Built-in readout for current & high/low temperature
- Audible & visual high/low temperature alarms
- Optimized efficient performance for stable temperature
- Eco-friendly natural refrigerants for a greener footprint

Solid & Glass Door Refrigerators From 1 to 15 Cu.ft.



+/-1°C variation derived from the maximum deviation of an NTC sensor in a 1 oz. vial located nearest the champer geometric center during a 24 hour test period

1123

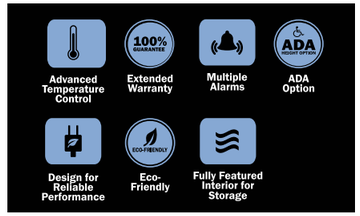
Refrigerators & Freezers From 23 to 49 Cu.ft.



Refrigeration designed and purpose-built for pharmacy, medication, and vaccination applications to support meeting CDC/VFC vaccine storage guidelines

Advanced Temperature Control & Durable Performance

- Intelligent microprocessor digital temperature controller
- Adjustable operating control range from +2 to +8°C
- Digital display of the min/max temperature in Celsius or Fahrenheit
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- Optimized forced air cooling for excellent stability & uniformity with rapid recovery
- Open door and high/low temperature alarms
- Factory installed lock conveniently located towards the top of each unit
- Adjustable shelving can be spaced in ½" intervals for flexible storage



Pharma-Vac Refrigerators

Accucold	Capacity	Height	Width	Depth	Door	PRICE
ARS1PV	1 cu.ft.	21.5"	17.5"	19.5"	White	$936.00
ARG1PV	1 cu.ft.	21.5"	17.5"	20"	Glass	$949.00
ARS3PV	3 cu.ft.	33.75"	18.5"	19"	White	$1,089.00
ARG3PV	3 cu.ft.	33.75"	18.5"	19.5"	Glass	$1,102.00
ARS6PV	6 cu.ft.	32.5"	23.5"	24.5"	White	$1,235.00
ARG6PV	6 cu.ft.	32.5"	23.5"	25"	Glass	$1,266.00
ARS8PV	8 cu.ft.	50"	23.38"	24.5"	White	$1,654.00
ARG8PV	8 cu.ft.	50"	23.38"	25"	Glass	$1,667.00
ARS12PV	12 cu.ft.	61.75"	23.38"	24.5"	White	$2,139.00
ARG12PV	12 cu.ft.	61.75"	23.38"	25"	Glass	$2,152.00
ARS15PV	15 cu.ft.	72"	23.5"	24.5"	White	$2,321.00
ARG15PV	15 cu.ft.	72"	23.5"	25"	Glass	$2,334.00

models with data loggers are available

Pharma-Lab Refrigerators

Accucold	Capacity	Height	Width	Depth	Door	PRICE
ARS23ML	23 cu.ft.	83.75	27.5	31	(1) Stainless	$2,789.00
ARG23ML	23 cu.ft.	83.75	27.5	31	(1) Glass	$3,114.00
ARS49ML	49 cu.ft.	83.75	55.25	31	(2) Stainless	$4,674.00
ARG49ML	49 cu.ft.	83.75	55.25	31	(2) Glass	$5,031.00

Pharma-Lab Freezers

Accucold	Capacity	Height	Width	Depth	Door	PRICE
AFS23ML	23 cu.ft.	83.75	27.5	31	(1) Stainless	$3,205.00
AFS49ML	49 cu.ft.	83.75	55.25	31	(2) Stainless	$5,194.00

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Choosing the Right Sized Unit

Below are a few handy steps for determining the ideal Accucold refrigerator size for your clinic:

1 Estimate the maximum number of doses of publicly-provided vaccine and privately purchased vaccine that will be in your refrigerator.

Refrigerator: Add the number of doses on hand (current inventory) from your last order form.

Public Vaccine		_____
Private Vaccine	+	_____
Total doses	=	_____
Multiply (max inventory)		x 1.25
Maximum doses	=	_____

2 Match your maximum doses with the minimum cubic feet needed to safely store your vaccine

Max. Doses	Minimum Cubic Ft.
2,000+ doses	may need more than one refrigerator
1000-2000	40 cu.ft
900-1000	36 cu.ft
801-900	21-23 cu.ft
701-800	17-19.5 cu.ft
400-700	11-16.7 cu.ft
100-399	4.9-6.1 cu.ft

For product application suggestions or recommendations please feel free to contact our product specialists to discuss your options at:

877-646-3300

Medical Device Depot Inc.

www.medicaldevicedepot.com

D. Plan for downtime for routine maintenance and equipment breakdown

E. Consider purchasing a service contract[6]
A service contract can include many services beyond a general warranty, such as software updates, calibration, certification, preventative maintenance, priority service, and/or additional discounts on upgrades. Service contracts can be costly, and you can either discuss options with colleagues or make your own informed decision. Several reasons why you may choose to purchase a service contract could include reduced hassles if your equipment breaks, faster/priority repairs and a predictable expense in your budget. If a piece of equipment is critical to your work, you use it frequently, and major repairs are very expensive, a service contract may be worthwhile. In terms of budget, you will know exactly what you are going to pay in advance and will not be blindsided with a major "surprise" expense.

Recognize the strategic importance of physician / laboratory relationships

One of the ways that laboratories can use their resources more effectively is to strengthen their relationships with physicians. These relationships are vital as strategic assets, and, as the demands on physicians continue to multiply, they will increasingly rely on their laboratory partners for diagnostic support. Physicians increasingly seek a diagnostic resource that can meet all of their testing needs[7].

Laboratories are discovering that they are well positioned to provide medical guidance and direction for clinicians who are trying to maneuver their way through the increasingly complex world of laboratory testing.

To efficiently manage laboratory test utilization requires both ensuring adequate utilization of needed tests in some patients and discouraging superfluous tests in other patients[8].

An important step in this process is to work with client physicians on a program of proper test utilization to encourage the most efficient and relevant use of the testing offered.

The key role of competent management in accomplishing these goals[9]

Effective laboratory planning requires competent management. It is through the application of management skills that you can implement change with minimal disruption.

Competent laboratory management includes effective communication with the staff; providing key information and direction for the continuing future development of the laboratory; and encouraging involvement in the development of strategic plans.

Successful management can motivate staff to provide feedback about their workload; instruments and kits used; make suggestions for improvement of, and changes to, their test menu; and provide information about interactions with other offices, departments, physicians, and patients. These types of information play an important role when developing strategies for cost containment, automation, growth, re-alignment, and even repositioning of the lab in the community.

Endnotes

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2 R. Saunders and A. Westerink. Sidebar: The Strategic Value of laboratory Outreach. Nov 1, 2014. http://www.hfma.org/Content.aspx?id=25853

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6 K Huey. Starting a New Lab: How to Develop a Budget and Buy Equipment. American Physiological Society (APS). http://www.the-aps.org/mm/Careers/Mentor/Managing-a-Lab-and-Personnel/Early-Career-Professionals/Setting-Up-a-Laboratory/Developing-a-Budget-and-Buying-Equipment

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8 Dr. Curtis Hanson and Elizabeth Plumhoff. MAYO CLINIC: Test Utilization and the Clinical Laboratory. May 2012. http://www.mayomedicallaboratories.com/articles/communique/2012/05.html

9 How To become A Good Lab Manager by Elizabeth Sandquist. ASBMB Today. October 2013.
10 R. Saunders and A. Westerink. Sidebar: The Strategic Value of laboratory Outreach. Nov 1, 2014. http://www.hfma.org/Content.aspx?id=25853

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Accurate—Lab-accurate results for a wide range of tests.*
Versatile—Comprehensive CLIA-waived menu available.
Simple—Intuitive function to improve operational efficiency.
Convenient—Have test results during office visit, increasing patient satisfaction.

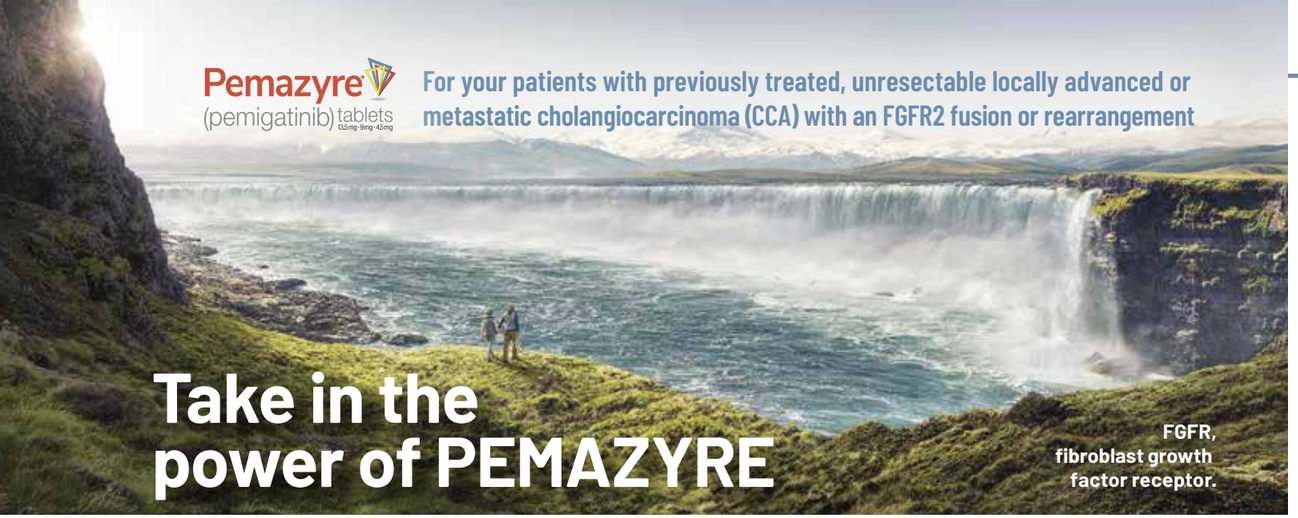
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*2016 Proficiency Testing Results, American Proficiency Institute, www.api-pt.com [*Piccolo Xpress*]. See cartridge information at www.pointofcare.abbott [*i-STAT*].

***i-STAT* Part No:** 04J60-20 Waived Kit, 04J48-50 Moderately Complex Kit, 06F20-20 Waived Analyzer, 04P75-03 Moderately Complex Analyzer
***Piccolo Xpress* Part No:** 07P05-50 *Piccolo Xpress* with 3YR Serv, 07P05-51 *Piccolo Xpress* with 5YR Serv

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INDICATIONS AND USAGE

PEMAZYRE is the first FDA-approved therapy for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

The major efficacy outcomes were evaluated in 107 patients with an FGFR2 fusion or non-fusion rearrangement* in a multicenter, open-label, single-arm study of 146 total patients with locally advanced unresectable or metastatic cholangiocarcinoma who had received ≥1 previous line of systemic therapy.[1,†]

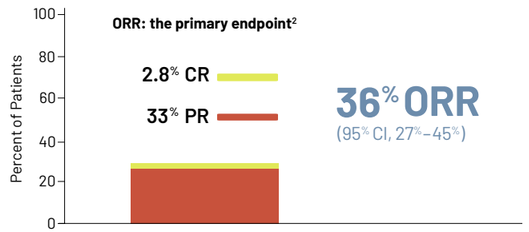
Patients receiving PEMAZYRE achieved durable responses

Median DoR was **9.1** months[1,‡]

Patients with DoR:

- **≥6 months: 63% (n=24)**
- **≥12 months: 18% (n=7)**

Clinical response rates of PEMAZYRE[1]



Efficacy evaluable population (N=107)

Note: Data are from IRC per RECIST v1.1, and CR and PR are confirmed.

*Determined by a clinical trial assay performed at a central laboratory.

†Patients received PEMAZYRE in 21-day cycles at a dosage of 13.5 mg orally once daily for 14 consecutive days, followed by 7 days off therapy, until disease progression or unacceptable toxicity occurred. The major efficacy outcome measures were ORR and DoR, as determined by IRC according to RECIST v1.1.

‡95% CI, 6.0-14.5 months and was calculated using the Brookmeyer and Crowley's method.[1]

CI, confidence interval; DoR, duration of response; IRC, independent review committee; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Molecular profiling is necessary to detect FGFR2 fusions or rearrangements

A next-generation sequencing assay, such as FoundationOne® CDx, meets the following criteria to detect FGFR2 fusions[3-6]:

- Specifically detects FGFR2 fusions (distinct from FGFR2 mutations)
- Detects FGFR2 fusions with a wide range of fusion partners (whether known or unknown)

Learn more about testing and treating your appropriate patients.
Visit **hcp.PEMAZYRE.com**

IMPORTANT SAFETY INFORMATION

Ocular Toxicity

Retinal Pigment Epithelial Detachment (RPED): PEMAZYRE can cause RPED, which may cause symptoms such as blurred vision, visual floaters, or photopsia. Clinical trials of PEMAZYRE did not conduct routine monitoring including optical coherence tomography (OCT) to detect asymptomatic RPED; therefore, the incidence of asymptomatic RPED with PEMAZYRE is unknown.

Among 466 patients who received PEMAZYRE across clinical trials, RPED occurred in 6% of patients, including Grade 3-4 RPED in 0.6%. The median time to first onset of RPED was 62 days. RPED led to dose interruption of PEMAZYRE in 1.7% of patients, and dose reduction and permanent discontinuation in 0.4% and in 0.4% of patients, respectively. RPED resolved

continued

Please see Important Safety Information for PEMAZYRE continued on the adjacent page.

IMPORTANT SAFETY INFORMATION (CONTINUED)

or improved to Grade 1 levels in 87.5% of patients who required dosage modification of PEMAZYRE for RPED.

Perform a comprehensive ophthalmological examination including OCT prior to initiation of PEMAZYRE and every 2 months for the first 6 months and every 3 months thereafter during treatment. For onset of visual symptoms, refer patients for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of PEMAZYRE. Modify the dose or permanently discontinue PEMAZYRE as recommended in the prescribing information for PEMAZYRE.

Dry Eye: Among 466 patients who received PEMAZYRE across clinical trials, dry eye occurred in 27% of patients, including Grade 3-4 in 0.6% of patients. Treat patients with ocular demulcents as needed.

Hyperphosphatemia and Soft Tissue Mineralization

PEMAZYRE can cause hyperphosphatemia leading to soft tissue mineralization, cutaneous calcification, calcinosis, and non-uremic calciphylaxis. Increases in phosphate levels are a pharmacodynamic effect of PEMAZYRE. Among 466 patients who received PEMAZYRE across clinical trials, hyperphosphatemia was reported in 92% of patients based on laboratory values above the upper limit of normal. The median time to onset of hyperphosphatemia was 8 days (range 1-169). Phosphate lowering therapy was required in 29% of patients receiving PEMAZYRE.

Monitor for hyperphosphatemia and initiate a low phosphate diet when serum phosphate level is >5.5 mg/dL. For serum phosphate levels >7 mg/dL, initiate phosphate lowering therapy and withhold, reduce the dose, or permanently discontinue PEMAZYRE based on duration and severity of hyperphosphatemia as recommended in the prescribing information.

Embryo-Fetal Toxicity

Based on findings in an animal study and its mechanism of action, PEMAZYRE can cause fetal harm when administered to a pregnant woman. Oral administration of pemigatinib to pregnant rats during the period of organogenesis caused fetal malformations, fetal growth retardation, and embryo-fetal death at maternal exposures lower than the human exposure based on area under the curve (AUC) at the clinical dose of 13.5 mg.

Advise pregnant women of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with PEMAZYRE and for 1 week after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with PEMAZYRE and for 1 week after the final dose.

Adverse Reactions

Serious adverse reactions occurred in 45% of patients receiving PEMAZYRE. Serious adverse reactions in ≥2% of patients who received PEMAZYRE included abdominal pain, pyrexia, cholangitis, pleural effusion, acute kidney injury, cholangitis infective, failure to thrive, hypercalcemia, hyponatremia, small intestinal obstruction, and urinary tract infection. Fatal adverse reactions occurred in 4.1% of patients, including failure to thrive, bile duct obstruction, cholangitis, sepsis, and pleural effusion.

Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received PEMAZYRE. Adverse reactions requiring permanent discontinuation in ≥1% of patients included intestinal obstruction and acute kidney injury.

Dosage interruptions due to an adverse reaction occurred in 43% of patients who received PEMAZYRE. Adverse reactions requiring dosage interruption in ≥1% of patients included stomatitis, palmar-plantar erythrodysesthesia syndrome, arthralgia, fatigue, abdominal pain, AST increased, asthenia, pyrexia, ALT increased, cholangitis, small intestinal obstruction, alkaline phosphatase increased, diarrhea, hyperbilirubinemia, electrocardiogram QT prolonged, decreased appetite, dehydration, hypercalcemia, hyperphosphatemia, hypophosphatemia, back pain, pain in extremity, syncope, acute kidney injury, onychomadesis, and hypotension.

Dose reductions due to an adverse reaction occurred in 14% of patients who received PEMAZYRE. Adverse reactions requiring dosage reductions in ≥1% of patients who received PEMAZYRE included stomatitis, arthralgia, palmar-plantar erythrodysesthesia syndrome, asthenia, and onychomadesis.

Clinically relevant adverse reactions occurring in ≤10% of patients included fractures (2.1%). In all patients treated with pemigatinib, 1.3% experienced pathologic fractures (which included patients with and without cholangiocarcinoma [N=466]). Soft tissue mineralization, including cutaneous calcification, calcinosis, and non-uremic calciphylaxis associated with hyperphosphatemia were observed with PEMAZYRE treatment.

Within the first 21-day cycle of PEMAZYRE dosing, serum creatinine increased (mean increase of 0.2 mg/dL) and reached steady state by Day 8, and then decreased during the 7 days off therapy. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

The most common adverse reactions (incidence ≥20%) were hyperphosphatemia (60%), alopecia (49%), diarrhea (47%), nail toxicity (43%), fatigue (42%), dysgeusia (40%), nausea (40%), constipation (35%), stomatitis (35%), dry eye (35%), dry mouth (34%), decreased appetite (33%), vomiting (27%), arthralgia (25%), abdominal pain (23%), hypophosphatemia (23%), back pain (20%), and dry skin (20%).

Drug Interactions

Avoid concomitant use of strong and moderate CYP3A inhibitors with PEMAZYRE. Reduce the dose of PEMAZYRE if concomitant use with a strong or moderate CYP3A inhibitor cannot be avoided. Avoid concomitant use of strong and moderate CYP3A inducers with PEMAZYRE.

Special Populations

Advise lactating women not to breastfeed during treatment with PEMAZYRE and for 1 week after the final dose.

Reduce the recommended dose of PEMAZYRE for patients with severe renal impairment as described in the prescribing information.

Reduce the recommended dose of PEMAZYRE for patients with severe hepatic impairment as described in the prescribing information.

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

References: 1. PEMAZYRE (pemigatinib) Prescribing Information. Incyte Corporation. **2.** Abou-Alfa GK, Sahai V, Hollebecque A, et al. *Lancet Oncol.* 2020;21(5):671-684. **3.** Lowery MA, Ptashkin R, Jordan E, et al. *Clin Cancer Res.* 2018;24(17):4154-4161. **4.** Javle MM, Murugesan K, Shroff RT, et al. *J Clin Oncol.* 2019;37(15 suppl):4087. **5.** Hollebecque A, de Bono JS, Plummer R, et al. *Ann Oncol.* 2019;30(suppl 1):mdz029. **6.** Frampton GM, Fichtenholtz A, Otto GA, et al. *Nat Biotechnol.* 2013;31(11):1023-1031.

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Pemazyre® (pemigatinib) tablets 13.5mg•9mg•4.5mg

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

INDICATIONS AND USAGE PEMAZYRE is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test *[see Dosage and Administration (2.1) in Full Prescribing Information]*. This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14.1) in Full Prescribing Information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Ocular Toxicity Retinal Pigment Epithelial Detachment (RPED) PEMAZYRE can cause RPED, which may cause symptoms such as blurred vision, visual floaters, or photopsia. Clinical trials of PEMAZYRE did not conduct routine monitoring including optical coherence tomography (OCT) to detect asymptomatic RPED; therefore, the incidence of asymptomatic RPED with PEMAZYRE is unknown. Among 466 patients who received PEMAZYRE across clinical trials, RPED occurred in 6% of patients, including Grade 3-4 RPED in 0.6%. The median time to first onset of RPED was 62 days. RPED led to dose interruption of PEMAZYRE in 1.7% of patients, and dose reduction and permanent discontinuation in 0.4% and in 0.4% of patients, respectively. RPED resolved or improved to Grade 1 levels in 87.5% of patients who required dosage modification of PEMAZYRE for RPED. Perform a comprehensive ophthalmological examination including OCT prior to initiation of PEMAZYRE and every 2 months for the first 6 months and every 3 months thereafter during treatment. For onset of visual symptoms, refer patients for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of PEMAZYRE. Modify the dose or permanently discontinue PEMAZYRE as recommended *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Dry Eye Among 466 patients who received PEMAZYRE across clinical trials, dry eye occurred in 27% of patients, including Grade 3-4 in 0.6% of patients. Treat patients with ocular demulcents as needed. **Hyperphosphatemia and Soft Tissue Mineralization** PEMAZYRE can cause hyperphosphatemia leading to soft tissue mineralization, cutaneous calcification, calcinosis, and non-uremic calciphylaxis. Increases in phosphate levels are a pharmacodynamic effect of PEMAZYRE *[see Clinical Pharmacology (12.2) in Full Prescribing Information]*. Among 466 patients who received PEMAZYRE across clinical trials, hyperphosphatemia was reported in 92% of patients based on laboratory values above the upper limit of normal. The median time to onset of hyperphosphatemia was 8 days (range 1-169). Phosphate lowering therapy was required in 29% of patients receiving PEMAZYRE. Monitor for hyperphosphatemia and initiate a low phosphate diet when serum phosphate level is > 5.5 mg/dL. For serum phosphate levels > 7 mg/dL, initiate phosphate lowering therapy and withhold, reduce the dose, or permanently discontinue PEMAZYRE based on duration and severity of hyperphosphatemia *[see Dosage and Administration (2.3) in Full Prescribing Information]*. **Embryo-Fetal Toxicity** Based on findings in an animal study and its mechanism of action, PEMAZYRE can cause fetal harm when administered to a pregnant woman. Oral administration of pemigatinib to pregnant rats during the period of organogenesis caused fetal malformations, fetal growth retardation, and embryo-fetal death at maternal exposures lower than the human exposure based on area under the curve (AUC) at the clinical dose of 13.5 mg. Advise pregnant women of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with PEMAZYRE and for 1 week after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with PEMAZYRE and for 1 week after the final dose *[see Use in Specific Populations (8.1, 8.3) in Full Prescribing Information]*. **ADVERSE REACTIONS** The following adverse reactions are discussed elsewhere in the labeling: • Ocular Toxicity *[see Warnings and Precautions (5.1) in Full Prescribing Information]* • Hyperphosphatemia and Soft Tissue Mineralization *[see Warnings and Precautions (5.2) in Full Prescribing Information]*. **Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of PEMAZYRE was evaluated in FIGHT-202, which included 146 patients with previously treated, locally advanced or metastatic cholangiocarcinoma *[see Clinical Studies (14.1) in Full Prescribing Information]*. Patients were treated orally with PEMAZYRE 13.5 mg once daily for 14 days on followed by 7 days off therapy until disease progression or unacceptable toxicity. The median duration of treatment was 181 days (range: 7 to 730 days). The median age of PEMAZYRE-treated patients was 59 years (range 26-78), 58% were females, and 71% were White. Serious adverse reactions occurred in 45% of patients receiving PEMAZYRE. Serious adverse reactions in ≥ 2% of patients who received PEMAZYRE included abdominal pain, pyrexia, cholangitis, pleural effusion, acute kidney injury, cholangitis infective, failure to thrive, hypercalcemia, hyponatremia, small intestinal obstruction, and urinary tract infection. Fatal adverse reactions occurred in 4.1% of patients, including failure to thrive, bile duct obstruction, cholangitis, sepsis, and pleural effusion. Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received PEMAZYRE. Adverse reactions requiring permanent discontinuation in ≥ 1% of patients included intestinal obstruction and acute kidney injury. Dosage interruptions due to an adverse reaction occurred in 43% of patients who received PEMAZYRE. Adverse reactions requiring dosage interruption in ≥ 1% of patients included stomatitis, palmar-plantar erythrodysesthesia syndrome, arthralgia, fatigue, abdominal pain, AST increased, asthenia, pyrexia, ALT increased, cholangitis, small intestinal obstruction, alkaline phosphatase increased, diarrhea, hyperbilirubinemia, electrocardiogram QT prolonged, decreased appetite, dehydration, hypercalcemia, hyperphosphatemia, hypophosphatemia, back pain, pain in extremity, syncope, acute kidney injury, onychomadesis, and hypotension. Dose reductions due to an adverse reaction occurred in 14% of patients who received PEMAZYRE. Adverse reactions requiring dosage reductions in ≥ 1% of patients who received PEMAZYRE included stomatitis, arthralgia, palmar-plantar erythrodysesthesia syndrome, asthenia, and onychomadesis. Table 1 summarizes the adverse reactions in FIGHT-202. Table 2 summarizes laboratory abnormalities in FIGHT-202.

Table 1: Adverse Reactions (≥ 15%) in Patients Receiving PEMAZYRE in FIGHT-202

	PEMAZYRE N=146	
Adverse Reaction	**All Grades[a] (%)**	**Grades ≥ 3* (%)**
Metabolism and nutrition disorders		
Hyperphosphatemia[b]	60	0
Decreased appetite	33	1.4
Hypophosphatemia[c]	23	12
Dehydration	15	3.4
Skin and subcutaneous tissue disorders		
Alopecia	49	0
Nail toxicity[d]	43	2.1
Dry skin	20	0.7
Palmar-plantar erythrodysesthesia syndrome	15	4.1
Gastrointestinal disorders		
Diarrhea	47	2.7
Nausea	40	2.1
Constipation	35	0.7
Stomatitis	35	5
Dry mouth	34	0
Vomiting	27	1.4
Abdominal pain	23	4.8
General disorders		
Fatigue	42	4.8
Edema peripheral	18	0.7
Nervous system disorders		
Dysgeusia	40	0
Headache	16	0
Eye disorders		
Dry eye[e]	35	0.7
Musculoskeletal and connective tissue disorders		
Arthralgia	25	6
Back pain	20	2.7
Pain in extremity	19	2.1

Table 1 continued above.

Table 1 continued.

	PEMAZYRE N=146	
Adverse Reaction	**All Grades[a] (%)**	**Grades ≥ 3* (%)**
Infections and infestations		
Urinary tract infection	16	2.7
Investigations		
Weight loss	16	2.1

*Only Grades 3 – 4 were identified.
[a] Graded per NCI CTCAE 4.03.
[b] Includes hyperphosphatemia and blood phosphorous increased; graded based on clinical severity and medical interventions taken according to the "investigations-other, specify" category in NCI CTCAE v4.03.
[c] Includes hypophosphatemia and blood phosphorous decreased.
[d] Includes nail toxicity, nail disorder, nail discoloration, nail dystrophy, nail hypertrophy, nail ridging, nail infection, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, and paronychia.
[e] Includes dry eye, keratitis, lacrimation increased, pinguecula, and punctate keratitis.

Clinically relevant adverse reactions occurring in ≤ 10% of patients included fractures (2.1%). In all patients treated with pemigatinib, 1.3% experienced pathologic fractures (which included patients with and without cholangiocarcinoma [N=466]). Soft tissue mineralization, including cutaneous calcification, calcinosis, and non-uremic calciphylaxis associated with hyperphosphatemia were observed with PEMAZYRE treatment.

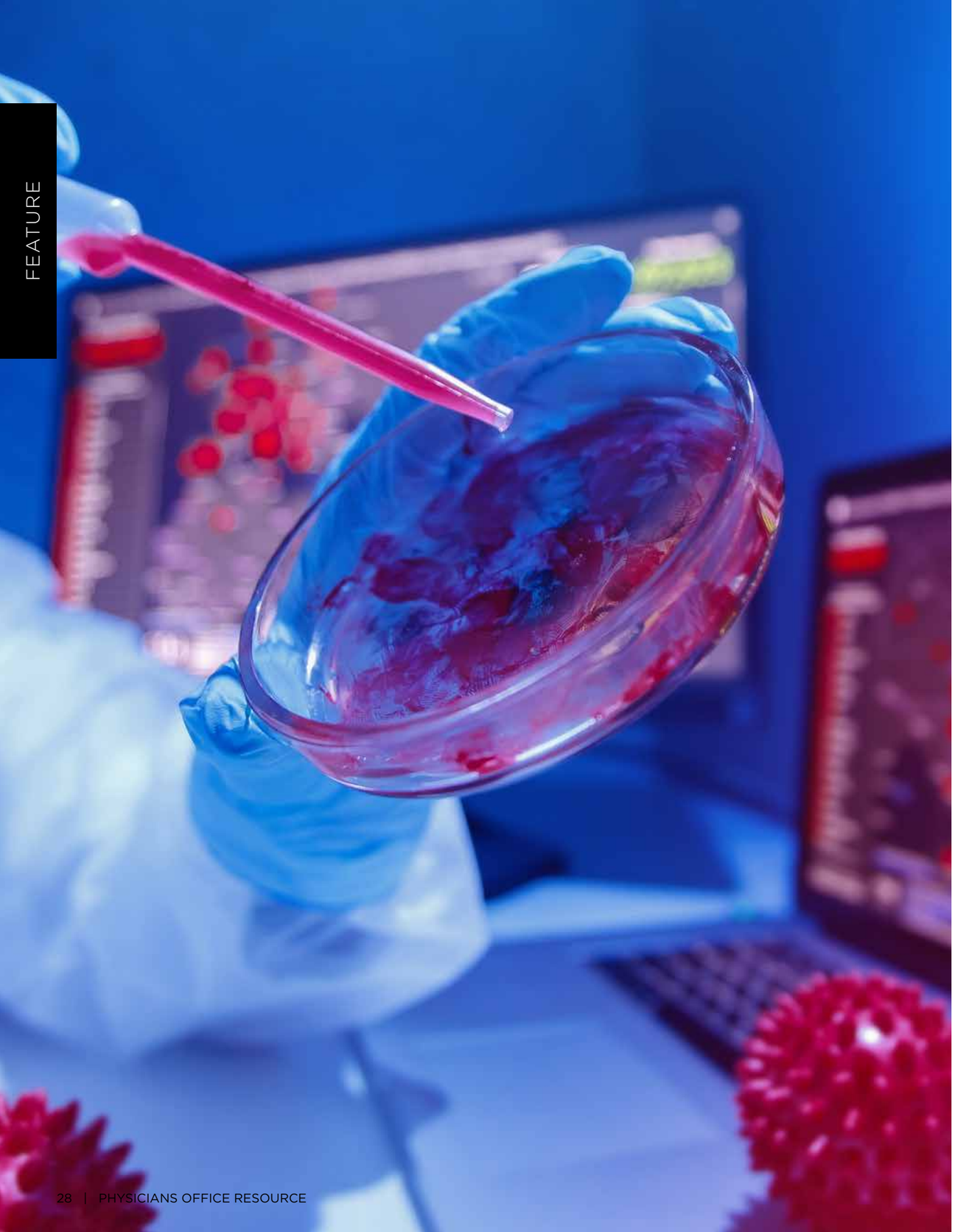
Table 2: Select Laboratory Abnormalities (≥ 10%) Worsening from Baseline in Patients Receiving PEMAZYRE in FIGHT-202

	PEMAZYRE[a] N=146	
Laboratory Abnormality	**All Grades[b] (%)**	**Grades ≥ 3 (%)**
Hematology		
Decreased hemoglobin	43	6
Decreased lymphocytes	36	8
Decreased platelets	28	3.4
Increased leukocytes	27	0.7
Decreased leukocytes	18	1.4
Chemistry		
Increased phosphate[c]	94	0
Decreased phosphate	68	38
Increased alanine aminotransferase	43	4.1
Increased aspartate aminotransferase	43	6
Increased calcium	43	4.1
Increased alkaline phosphatase	41	11
Increased creatinine[d]	41	1.4
Decreased sodium	39	12
Increased glucose	36	0.7
Decreased albumin	34	0
Increased urate	30	10
Increased bilirubin	26	6
Decreased potassium	26	5
Decreased calcium	17	2.7
Increased potassium	12	2.1
Decreased glucose	11	1.4

[a] The denominator used to calculate the rate varied from 142-146 based on the number of patients with a baseline value and at least one post-treatment value.
[b] Graded per NCI CTCAE 4.03.
[c] Based on CTCAE 5.0 grading.
[d] Graded based on comparison to upper limit of normal.

Increased Creatinine Within the first 21-day cycle of PEMAZYRE dosing, serum creatinine increased (mean increase of 0.2 mg/dL) and reached steady state by Day 8, and then decreased during the 7 days off therapy. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. **DRUG INTERACTIONS Effect of Other Drugs on PEMAZYRE** Strong and Moderate CYP3A Inducers Concomitant use of PEMAZYRE with a strong or moderate CYP3A inducer decreases pemigatinib plasma concentrations, *[see Clinical Pharmacology (12.3) in Full Prescribing Information]* which may reduce the efficacy of PEMAZYRE. Avoid concomitant use of strong and moderate CYP3A inducers with PEMAZYRE. Strong and Moderate CYP3A Inhibitors Concomitant use of a strong or moderate CYP3A inhibitor with PEMAZYRE increases pemigatinib plasma concentrations, *[see Clinical Pharmacology (12.3) in Full Prescribing Information]* which may increase the incidence and severity of adverse reactions. Avoid concomitant use of strong and moderate CYP3A inhibitors with PEMAZYRE. Reduce PEMAZYRE dosage if concomitant use of strong and moderate CYP3A inhibitors cannot be avoided *[see Dosage and Administration (2.4) in Full Prescribing Information]*. **USE IN SPECIFIC POPULATIONS Pregnancy** Risk Summary Based on findings in an animal study and its mechanism of action, PEMAZYRE can cause fetal harm or loss of pregnancy when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in Full Prescribing Information]*. There are no available data on the use of PEMAZYRE in pregnant women. Oral administration of pemigatinib to pregnant rats during the period of organogenesis at maternal plasma exposures below the human exposure at the clinical dose of 13.5 mg resulted in fetal malformations, fetal growth retardation, and embryo-fetal death (*see Data*). Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Data *Animal Data* Once daily oral administration of pemigatinib to pregnant rats during the period of organogenesis resulted in 100% embryofetal mortality due to post-implantation loss at doses ≥ 0.3 mg/kg (approximately 0.6 times the human exposure based on AUC at the clinical dose of 13.5 mg). Fetal survival was unaffected at 0.1 mg/kg per day; however, once daily oral administration of pemigatinib at the 0.1 mg/kg dose level (approximately 0.2 times the human exposure based on AUC at the clinical dose of 13.5 mg) resulted in reduced mean fetal body weight and an increase in fetal skeletal and visceral malformations, major blood vessel variations, and reduced ossification. **Lactation** Risk Summary There are no data on the presence of pemigatinib or its metabolites in human milk or their effects on either the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children from PEMAZYRE, advise women not to breastfeed during treatment and for 1 week after the final dose. **Females and Males of Reproductive Potential** Pregnancy Testing Verify pregnancy status of females of reproductive potential prior to initiating PEMAZYRE *[see Use in Specific Populations (8.1) in Full Prescribing Information]*. Contraception PEMAZYRE can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1) in Full Prescribing Information]*. **Females** Advise females of reproductive potential to use effective contraception during treatment with PEMAZYRE and for 1 week after the final dose. **Males** Advise males with female partners of reproductive potential to use effective contraception during treatment with PEMAZYRE and for 1 week after the final dose. **Pediatric Use** The safety and effectiveness of PEMAZYRE have not been established in pediatric patients. Animal Toxicity Data In 4- or 13-week repeat-dose toxicology studies in rats and non-human primates, animals displayed toxicities in bone and teeth at pemigatinib exposures lower than the human exposure at the clinical dose of 13.5 mg. Physeal and cartilage dysplasia were present in multiple bones in both species, and tooth (incisor) abnormalities (complete loss of ameloblasts with associated secondary changes) occurred in rats. Six weeks after cessation of dosing, these findings did not show complete evidence of recovery, and additional tooth-related findings (mal-aligned, whitened, broken, and trimmed/thinned incisors) developed in the 13-week study. **Geriatric Use** In FIGHT-202, 32% of patients were 65 years and older, and 8% of patients were 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients. **Renal Impairment** Reduce the recommended dosage of PEMAZYRE for patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2, estimated by Modification of Diet in Renal Disease [MDRD] equation) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information]*. No dosage adjustment is recommended for patients with mild or moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2). No dosage adjustment is recommended for patients with end-stage renal disease (eGFR < 15 mL/min/1.73 m^2) who are receiving intermittent hemodialysis. *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. **Hepatic Impairment** Reduce the recommended dosage of PEMAZYRE for patients with severe hepatic impairment (total bilirubin > 3 × ULN with any AST) *[see Dosage and Administration (2.6) and Clinical Pharmacology (12.3) in Full Prescribing Information]*. No dosage adjustment is recommended for patients with mild (total bilirubin > upper limit of normal [ULN] to 1.5 × ULN or AST > ULN) or moderate (total bilirubin >1.5–3 × ULN with any AST) hepatic impairment *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

PEMAZYRE is a registered trademark of Incyte Corporation.
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HOW CAN YOU PREVENT ANTIMICROBIAL RESISTANCE?

BY SEKISUI DIAGNOSTICS

In 2019, the World Health Organization declared antibacterial resistance one of the top 10 threats to global health.

As deadly as it has already proven to be, COVID-19 could result in even more health-related disruptions in the future. Several studies estimate that 70% to 97% of hospitalized patients with COVID-19 received antibiotic therapy. Here's the problem: Increased antibiotic usage accelerates antibiotic resistance.

The irony is, SARS-CoV-2 is a virus with respiratory symptoms, and no antibiotic is yet available against it. Inappropriate prescribing could have been avoided with diagnostic testing for influenza, Respiratory Syncytial Virus, group A strep, etc., prior to prescription and treatment. COVID-19 pandemic reminds us of the value of infectious diseases diagnostics. Even though economic value of infectious diseases diagnostics is not always easily quantifiable, diagnostics play a valuable and critical role in effective patient care. Diagnostics helps to determine the disease etiology, influence treatment modalities, and enable public health surveillance. Moreover, advances in Point-Of-Care (POC) testing have further improved patient care.

Antimicrobial resistance

Microbes are survivors. To paraphrase German philosopher Friedrich Nietzsche, what doesn't kill them makes them stronger. When exposed to conditions that inhibit growth, such as antibiotics, microbes make changes that help them survive. Those that acquire resistance can multiply rapidly and spread the resistance to other microbes.

Per Rodney Rohde, PhD, professor, and chair for the Clinical Laboratory Science (CLS) Program in the College of Health Professions at Texas State University, COVID-19 pandemic can worsen the threat posed by antimicrobial resistance.

In 2019, the World Health Organization declared antibacterial resistance one of the top 10 threats to global health. Left unchecked, drug-resistant diseases could cause 10 million deaths each year by 2050, warns the UN Ad hoc Interagency Coordinating Group on Antimicrobial Resistance.

In the United States, antibiotic-resistant bacteria and fungi cause more than 2.8 million infections and 35,000 deaths each year— nearly twice as many annual deaths from antibiotic resistance as reported in 2013. The Centers for Disease Control and Prevention's 2019 AR Threats Report includes two new urgent threats: drug-resistant Candida auris and Carbapenem-resistant Acinetobacter. These were added to three identified in 2013: Carbapenem-resistant Enterobacteriaceae (CRE), Neisseria gonorrhoeae, and Clostridioides difficile.

Enter COVID-19

COVID has exacerbated the threat. In 2020, the World Health Organization reported on a study that showed that while 72% of COVID-19 patients received antibiotics, only 8% demonstrated bacterial or fungal co-infections. WHO also reported that early in the pandemic, azithromycin was widely used with hydroxychloroquine in the mistaken belief it could quell the virus. Azithromycin has since been shown to have no effect on SARS-CoV-2.

Another factor exacerbating antibiotic resistance has been the upswing in telehealth during the pandemic. Studies have shown that antibiotics are prescribed for a broader set of symptoms in the absence of physical examinations or laboratory tests -- e.g., telehealth.

Hospital admissions increase the risk of healthcare-associated infections and the transmission of multidrug-resistant organisms. Disruptions to health services during the pandemic also led to interruptions to treatments, such as for tuberculosis and human immunodeficiency virus, which can lead to selection for drug resistance. Similarly, disruptions to vaccination services increase the risk of infection, potentially leading to an overuse of antimicrobials.

The widespread use of biocidal agents for environmental and personal disinfection represents another threat. Low-level exposure to biocidal agents can select for drug-resistant strains and enhance the risk of cross-resistance to antibiotics, particularly those that treat Gram-negative bacteria.

What now?

Outsmarting microbes will never be easy. After all, they've been at it for a long time. Researchers believe that Enterococci bacteria – which cause thousands of multidrug-resistant infections in patients each year – were carried onto land in the guts of the world's first terrestrial animals 425 million years ago. Still, efforts are being made to slow down the growth of antibiotic resistance. For the duration of the current pandemic, the World Health Organization recommends:

1. Training health workers to identify signs and symptoms of severe COVID-19 and those of bacterial or fungal disease; evaluate the need for medical devices that increase the chances of health care-associated infections; and implement strict infection prevention and control measures.

2. Ensuring the regular supply of quality-assured antimicrobials, including antiretroviral and tuberculosis drugs, and vaccines.

3. Reducing the turnaround time of COVID-19 testing by improving testing methods and expanding testing facilities, especially for presumed patients, to reduce the urge to initiate antibiotics.

4. Exercising caution in the use of biocides for environmental and personal disinfection, and prioritizing biocidal agents with a low selection pressure for antibiotic resistance.

In the long run

Government agencies, academic institutions, and non-profit and industry groups around the world are sharing their expertise and aligning clinical trials and resources to tackle the growing problem. For example, the Antibacterial Resistance Leadership Group, funded by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) is collaborating with groups in 19 countries and has initiated more than 40 clinical studies at 130 sites.

In 2019, the UN Interagency Coordination Group on Antimicrobial Resistance recommended countries support awareness programs for prudent use of antimicrobials by professionals in human, animal and plant health; invest in research and development for new technologies to combat antimicrobial resistance; and urgently phase out the use of critically important antimicrobials as growth promoters in agriculture.

In 2020, NIAID proposed a four-pronged approach to the challenge:

- Support research into promising therapeutics. For example, the Institute is funding research projects to develop models to predict the potency of therapeutics based on an understanding of how molecules enter and leave Gram-negative pathogens.

- Optimize existing antibiotics, that is, developing regimens of older antibiotics to more effectively treat infections and suppress the emergence of resistance.

- Develop microbiome-based approaches. For example, NIAID scientists collaborated with researchers in Thai land on a project that showed that Bacillus -- a "good" bacterium commonly found in probiotic digestive supplements -- helps eliminate Staphylococcus aureus.

- Explore phage therapy. Bacteriophages (phages) are viruses that selectively infect and kill bacteria. Phage therapy has been used to treat patients with severe, multi-drug-resistant infections under compassionate use conditions with promising results. However, knowledge gaps have hindered its development in the U.S.

Diagnostics an essential component

The need for antibiotic stewardship programs has never been more urgent. The UK's National Institute for Health and Care Excellence (NICE) defines such programs as "an organizational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness." They emphasize education and training about antimicrobial resistance, providing regular feedback to prescribers, and integrating audits into existing quality improvement programs.

In the U.S., the National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020-2025 recognizes the importance of rapid and innovative diagnostics as a tool to ensure appropriate antimicrobial use. Specifically, the authors call for researchers to:

- Develop new or enhance existing diagnostics that use isolates and primary samples to determine the presence, severity, or antimicrobial susceptibility or resistance of bacterial or fungal infections and to identify appropriate treatment.

- Stimulate research to better understand the appropriate use of diagnostics to determine the presence, severity, or antimicrobial susceptibility or resistance of bacterial or fungal infections in human and veterinary care.

- Develop evidence-based guidance to promote the appropriate use of new diagnostics and to improve the use of existing diagnostics that determine the presence, severity, or antimicrobial susceptibility or resistance of bacterial or fungal infections in human clinical care.

To summarize

- Detect, respond to, and contain emerging resistance

- Prevent and stop spread of resistant infections in health care and community settings.

- Improve antibiotic use.

In addition to the above, Point-of-Care (POC) testing can play a crucial role in antibiotic stewardship.

A study in a UK hospital demonstrated that a point-of-care test (POCT) for viral respiratory infections reduced the number of inappropriate hospital admissions and antibiotic prescriptions. With advancement in POC testing and conscious efforts towards antibiotic stewardship we can prevent antimicrobial resistance.

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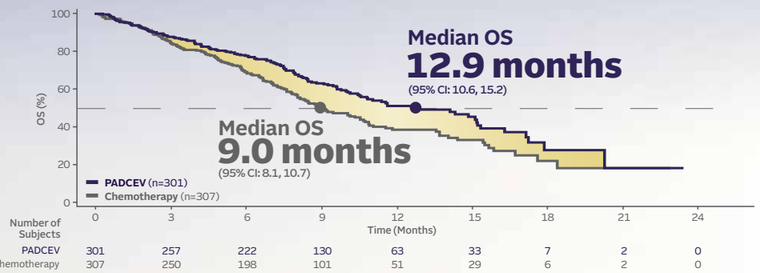
IN POST-PLATINUM, POST–PD-(L)1 la/mUC PATIENTS

SET A COURSE FOR LONGER SURVIVAL[1]

In the EV-301* trial

PADCEV® SIGNIFICANTLY IMPROVED OS vs CHEMOTHERAPY[1]

MAJOR EFFICACY OUTCOME MEASURE: OS†



30% reduction in the risk of death vs chemotherapy (N=608; HR=0.70; 95% CI: 0.56, 0.89; *P*=0.0014)

*The EV-301 trial evaluated PADCEV vs investigator's-choice chemotherapy in a randomized, multicenter, phase 3 trial of 608 patients with locally advanced or metastatic urothelial cancer who had previously received platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor. Patients were randomized 1:1 to either 1.25 mg/kg of PADCEV via IV infusion over 30 minutes on days 1, 8, and 15 of every 28-day cycle, or docetaxel at 75 mg/m^2, paclitaxel at 175 mg/m^2, or vinflunine at 320 mg/m^2 on day 1 of every 21-day cycle. For both arms, treatment continued until radiographic disease progression or unacceptable toxicity.[1,2]

†Based on log-rank test. Stratification factors were ECOG PS, region and liver metastasis.[1]

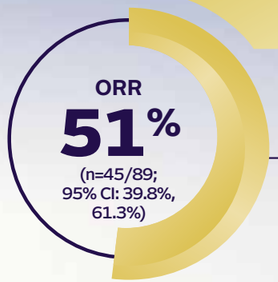
IN CISPLATIN-INELIGIBLE, POST–PD-(L)1 la/mUC PATIENTS

SET A COURSE FOR RESPONSE[1]

In the EV-201‡ trial (Cohort 2)

PADCEV DELIVERED CLINICALLY MEANINGFUL RESPONSE[1,3]

MAJOR EFFICACY OUTCOME MEASURE: CONFIRMED ORR BY BICR[1,3,4]



CR: 22% (n=20/89)

PR: 28% (n=25/89)

Major efficacy outcome measure: Median DOR§‖ was 13.8 months with PADCEV (95% CI: 6.4, NE)[1]

‡The EV-201 trial (Cohort 2) was a single-arm, multicenter trial of 89 patients with locally advanced or metastatic urothelial cancer who had previously received a PD-1 or PD-L1 inhibitor and were cisplatin ineligible. Patients received 1.25 mg/kg of PADCEV via IV infusion over 30 minutes on days 1, 8, and 15 of every 28-day cycle and continued to receive treatment until disease progression or unacceptable toxicity. The major efficacy outcome measures, confirmed ORR and DOR, were assessed by BICR using RECIST v1.1. ORR consisted of confirmed CR and PR. CR was defined as the disappearance of all target and nontarget lesions. PR was defined as a ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Median duration of follow-up was 13.4 months.[1,4,5]

§Kaplan-Meier estimate of duration of response, defined as the time from first response to date of progression or death due to any cause, was assessed by BICR.[4,6]

‖Based on patients (n=45) with a response by BICR.[1]

IMPORTANT SAFETY INFORMATION

BOXED WARNING: SERIOUS SKIN REACTIONS

- **PADCEV can cause severe and fatal cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which occurred predominantly during the first cycle of treatment, but may occur later.**
- **Closely monitor patients for skin reactions.**
- **Immediately withhold PADCEV and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.**
- **Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions.**

INDICATION

PADCEV is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who:

- have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy, or
- are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.

WARNINGS AND PRECAUTIONS

Skin reactions Severe cutaneous adverse reactions, including fatal cases of SJS or TEN, occurred in patients treated with PADCEV. SJS and TEN occurred predominantly during the first cycle of treatment but may occur later. Skin reactions occurred in 55% of the 680 patients treated with PADCEV in clinical trials. Twenty-three percent (23%) of patients had maculo-papular rash and 33% had pruritus. Grade 3-4 skin reactions occurred in 13% of patients, including maculo-papular rash, rash erythematous, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), dermatitis bullous, dermatitis exfoliative, and palmar-plantar erythrodysesthesia. In clinical trials, the median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 6.4). Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV (n=59), 24% of patients restarting at the same dose and 16% of patients restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV in 2.6% of patients. Monitor patients closely throughout treatment for skin reactions. Consider topical corticosteroids and antihistamines, as clinically indicated. Withhold PADCEV and refer for specialized care for suspected SJS or TEN or for severe (Grade 3) skin reactions. Permanently discontinue PADCEV in patients with confirmed SJS or TEN, or for Grade 4 or recurrent Grade 3 skin reactions.

Hyperglycemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with PADCEV. Patients with baseline hemoglobin A1C ≥8% were excluded from clinical trials. In clinical trials, 14% of the 680 patients treated with PADCEV developed hyperglycemia; 7% of patients developed Grade 3-4 hyperglycemia. The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. Five percent (5%) of patients required initiation of insulin therapy for treatment of hyperglycemia. The median time to onset of hyperglycemia was 0.6 months (range: 0.1 to 20.3). Hyperglycemia led to discontinuation of PADCEV in 0.6% of patients. Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia. If blood glucose is elevated (>250 mg/dL), withhold PADCEV.

Pneumonitis Severe, life-threatening or fatal pneumonitis occurred in patients treated with PADCEV. In clinical trials, 3.1% of the 680 patients treated with PADCEV had pneumonitis of any grade and 0.7% had Grade 3-4. In clinical trials, the median time to onset of pneumonitis was 2.9 months (range: 0.6 to 6). Monitor patients for signs and symptoms indicative of pneumonitis, such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Evaluate and exclude infectious, neoplastic and other causes for such signs and symptoms through appropriate investigations. Withhold PADCEV for patients who develop persistent or recurrent Grade 2 pneumonitis and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis.

Peripheral neuropathy (PN) occurred in 52% of the 680 patients treated with PADCEV in clinical trials, including 39% with sensory neuropathy, 7% with muscular weakness and 6% with motor neuropathy; 4% experienced Grade 3-4 reactions. PN occurred in patients treated with PADCEV with or without pre-existing PN. The median time to onset of Grade ≥2 PN was 4.6 months (range: 0.1 to 15.8 months). Neuropathy led to treatment discontinuation in 5% of patients. Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when PN occurs. Permanently discontinue PADCEV in patients who develop Grade ≥3 PN.

Ocular disorders were reported in 40% of the 384 patients treated with PADCEV in clinical trials in which ophthalmologic exams were scheduled. The majority of these events involved the cornea and included events associated with dry eye such as keratitis, blurred vision, increased lacrimation, conjunctivitis, limbal stem cell deficiency, and keratopathy. Dry eye symptoms occurred in 34% of patients, and blurred vision occurred in 13% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.6 months (range: 0 to 19.1 months). Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.

Infusion site extravasation Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 680 patients, 1.6% of patients experienced skin and soft tissue reactions, including 0.3% who experienced Grade 3-4 reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2-7 days after extravasation and resolved within 1-4 weeks of peak. Two patients (0.3%) developed

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WARNINGS AND PRECAUTIONS

Skin reactions Severe cutaneous adverse reactions, including fatal cases of SJS or TEN, occurred in patients treated with PADCEV. SJS and TEN occurred predominantly during the first cycle of treatment but may occur later. Skin reactions occurred in 55% of the 680 patients treated with PADCEV in clinical trials. Twenty-three percent (23%) of patients had maculo-papular rash and 33% had pruritus. Grade 3-4 skin reactions occurred in 13% of patients, including maculo-papular rash, rash erythematous, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), dermatitis bullous, dermatitis exfoliative, and palmar-plantar erythrodysesthesia. In clinical trials, the median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 6.4). Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV (n=59), 24% of patients restarting at the same dose and 16% of patients restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV in 2.6% of patients. Monitor patients closely throughout treatment for skin reactions. Consider topical corticosteroids and antihistamines, as clinically indicated. Withhold PADCEV and refer for specialized care for suspected SJS or TEN or for severe (Grade 3) skin reactions. Permanently discontinue PADCEV in patients with confirmed SJS or TEN, or for Grade 4 or recurrent Grade 3 skin reactions.

Hyperglycemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with PADCEV. Patients with baseline hemoglobin A1C ≥8% were excluded from clinical trials. In clinical trials, 14% of the 680 patients treated with PADCEV developed hyperglycemia; 7% of patients developed Grade 3-4 hyperglycemia. The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. Five percent (5%) of patients required initiation of insulin therapy for treatment of hyperglycemia. The median time to onset of hyperglycemia was 0.6 months (range: 0.1 to 20.3). Hyperglycemia led to discontinuation of PADCEV in 0.6% of patients. Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia. If blood glucose is elevated (>250 mg/dL), withhold PADCEV.

Pneumonitis Severe, life-threatening or fatal pneumonitis occurred in patients treated with PADCEV. In clinical trials, 3.1% of the 680 patients treated with PADCEV had pneumonitis of any grade and 0.7% had Grade 3-4. In clinical trials, the median time to onset of pneumonitis was 2.9 months (range: 0.6 to 6). Monitor patients for signs and symptoms indicative of pneumonitis, such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Evaluate and exclude infectious, neoplastic and other causes for such signs and symptoms through appropriate investigations. Withhold PADCEV for patients who develop persistent or recurrent Grade 2 pneumonitis and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis.

Peripheral neuropathy (PN) occurred in 52% of the 680 patients treated with PADCEV in clinical trials, including 39% with sensory neuropathy, 7% with muscular weakness and 6% with motor neuropathy; 4% experienced Grade 3-4 reactions. PN occurred in patients treated with PADCEV with or without pre-existing PN. The median time to onset of Grade ≥2 PN was 4.6 months (range: 0.1 to 15.8 months). Neuropathy led to treatment discontinuation in 5% of patients. Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when PN occurs. Permanently discontinue PADCEV in patients who develop Grade ≥3 PN.

Ocular disorders were reported in 40% of the 384 patients treated with PADCEV in clinical trials in which ophthalmologic exams were scheduled. The majority of these events involved the cornea and included events associated with dry eye such as keratitis, blurred vision, increased lacrimation, conjunctivitis, limbal stem cell deficiency, and keratopathy. Dry eye symptoms occurred in 34% of patients, and blurred vision occurred in 13% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.6 months (range: 0 to 19.1 months). Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.

Infusion site extravasation Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 680 patients, 1.6% of patients experienced skin and soft tissue reactions, including 0.3% who experienced Grade 3-4 reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2-7 days after extravasation and resolved within 1-4 weeks of peak. Two patients (0.3%) developed

PADCEV®
enfortumab vedotin-ejfv
Injection for IV infusion 20 mg & 30 mg vials

PADCEV® (enfortumab vedotin-ejfv) for injection, for intravenous use

The following is a brief summary of the full Prescribing Information. **Please see the package insert for full prescribing information including BOXED WARNING.**

WARNING: SERIOUS SKIN REACTIONS

- **PADCEV can cause severe and fatal cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which occurred predominantly during the first cycle of treatment, but may occur later.**
- **Closely monitor patients for skin reactions.**
- **Immediately withhold PADCEV and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.**
- **Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions**

INDICATIONS AND USAGE

PADCEV® is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who:

- have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy, or
- are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dose of PADCEV is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥ 100 kg) administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Dose Modifications

Table 1. Dose Modifications

Adverse Reaction	Severity*	Dose Modification*
Skin Reactions	Suspected SJS or TEN	Immediately withhold, consult a specialist to confirm the diagnosis. If not SJS/TEN, see Grade 3 skin reactions.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions	Permanently discontinue.
	Grade 3 (severe) skin reactions	Withhold until Grade ≤ 1, then resume treatment at the same dose level or consider dose reduction by one dose level.
Hyperglycemia	Blood glucose > 250 mg/dL	Withhold until elevated blood glucose has improved to ≤ 250 mg/dL, then resume treatment at the same dose level.
Pneumonitis	Grade 2	Withhold until Grade ≤ 1 for persistent or recurrent Grade 2 pneumonitis, consider dose reduction by one dose level.
	Grade ≥ 3	Permanently discontinue.
Peripheral Neuropathy	Grade 2	Withhold until Grade ≤ 1, then resume treatment at the same dose level (if first occurrence). For a recurrence, withhold until Grade ≤ 1, then resume treatment reduced by one dose level.
	Grade ≥ 3	Permanently discontinue.
Other nonhematologic toxicity	Grade 3	Withhold until Grade ≤ 1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Permanently discontinue.
Hematologic toxicity	Grade 3, or Grade 2 thrombocytopenia	Withhold until Grade ≤ 1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Withhold until Grade ≤ 1, then reduce dose by one dose level or discontinue treatment.

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

Table 2. Recommended Dose Reduction Schedule

Dose Level	
Starting dose	1.25 mg/kg up to 125 mg
First dose reduction	1.0 mg/kg up to 100 mg
Second dose reduction	0.75 mg/kg up to 75 mg
Third dose reduction	0.5 mg/kg up to 50 mg

WARNINGS AND PRECAUTIONS

Skin Reactions

Severe cutaneous adverse reactions, including fatal cases of SJS or TEN occurred in patients treated with PADCEV. SJS and TEN occurred predominantly during the first cycle of treatment but may occur later.

Skin reactions occurred in 55% of the 680 patients treated with PADCEV in clinical trials. Twenty-three percent (23%) of patients had maculopapular rash and 33% had pruritus. Grade 3-4 skin reactions occurred in 13% of patients, including maculo-papular rash, rash erythematous, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), dermatitis bullous, dermatitis exfoliative, and palmar-plantar erythrodysesthesia. In clinical trials, the median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 6.4 months). Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV (n=59), 24% of patients restarting at the same dose and 16% of patients restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV in 2.6% of patients.

Monitor patients closely throughout treatment for skin reactions. Consider topical corticosteroids and antihistamines, as clinically indicated.

Withhold PADCEV and refer for specialized care for suspected SJS, TEN or for severe (Grade 3) skin reactions.

Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions.

Hyperglycemia

Hyperglycemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with PADCEV.

Patients with baseline hemoglobin A1C ≥ 8% were excluded from clinical trials. In clinical trials, 14% of the 680 patients treated with PADCEV developed hyperglycemia; 7% of patients developed Grade 3-4 hyperglycemia. The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. Five percent (5%) of patients required initiation of insulin therapy for treatment of hyperglycemia. The median time to onset of hyperglycemia was 0.6 months (range: 0.1 to 20.3 months). Hyperglycemia led to discontinuation of PADCEV in 0.6% of patients.

Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia.

If blood glucose is elevated (> 250 mg/dL), withhold PADCEV.

Pneumonitis

Severe, life-threatening or fatal pneumonitis occurred in patients treated with PADCEV. In clinical trials, 3.1% of the 680 patients treated with PADCEV had pneumonitis of any grade and 0.7% had Grade 3-4. In clinical trials, the median time to onset of pneumonitis was 2.9 months (range: 0.6 to 6 months).

Monitor patients for signs and symptoms indicative of pneumonitis such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Evaluate and exclude infectious, neoplastic and other causes for such signs and symptoms through appropriate investigations.

Withhold PADCEV for patients who develop persistent or recurrent Grade 2 pneumonitis and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis.

Peripheral Neuropathy

Peripheral neuropathy occurred in 52% of the 680 patients treated with PADCEV in clinical trials including 39% with sensory neuropathy, 7% with muscular weakness and 6% with motor neuropathy; 4% experienced Grade 3-4 reactions. Peripheral neuropathy occurred in patients treated with PADCEV with or without preexisting peripheral neuropathy. The median time to onset of Grade ≥ 2 peripheral neuropathy was 4.6 months (range: 0.1 to 15.8 months). Neuropathy led to treatment discontinuation in 5% of patients.

Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when peripheral neuropathy occurs.

Permanently discontinue PADCEV in patients who develop Grade ≥ 3 peripheral neuropathy.

Ocular Disorders

Ocular disorders were reported in 40% of the 384 patients treated with PADCEV in clinical trials in which ophthalmologic exams were scheduled. The majority of these events involved the cornea and included events associated with dry eye such as keratitis, blurred vision, increased lacrimation, conjunctivitis, limbal stem cell deficiency, and keratopathy.

Dry eye symptoms occurred in 34% of patients, and blurred vision occurred in 13% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.6 months (range: 0 to 19.1 months). Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.

Infusion Site Extravasation

Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 680 patients, 1.6% of patients experienced skin and soft tissue reactions, including 0.3% who experienced Grade 3-4 reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2-7 days after extravasation and resolved within 1-4 weeks of peak. Two patients (0.3%) developed extravasation reactions with secondary cellulitis, bullae, or exfoliation. Ensure adequate venous access prior to starting PADCEV and monitor for possible extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.

Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of enfortumab vedotin-ejfv to pregnant rats during the period of organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures approximately similar to the clinical exposures at the recommended human dose of 1.25 mg/kg.

Advise patients of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with PADCEV and for 2 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

ADVERSE REACTIONS

Clinical Trial Experience

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

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to PADCEV as a single agent at 1.25 mg/kg in 680 patients in EV-301, EV-201, EV-101 (NCT02091999), and EV-102 (NCT03070990). Ocular disorders reflect 384 patients in EV-201, EV-101, and EV-102. Among 680 patients receiving PADCEV, 36% were exposed for ≥ 6 months, and 9% were exposed for ≥ 12 months. In this pooled population, the most common (≥ 20%) adverse reactions, including laboratory abnormalities, were rash, aspartate aminotransferase increased, glucose increased, creatinine increased, fatigue, peripheral neuropathy, lymphocytes decreased, alopecia, decreased appetite, hemoglobin decreased, diarrhea, sodium decreased, nausea, pruritus, phosphate decreased, dysgeusia, alanine aminotransferase increased, anemia, albumin decreased, neutrophils decreased, urate increased, lipase increased, platelets decreased, weight decreased and dry skin.

The data described in the following sections reflect exposure to PADCEV from an open-label, randomized, study (EV-301); and Cohort 1 and Cohort 2 of an open-label, single arm, two cohort study (EV-201). Patients received PADCEV 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Previously Treated Locally Advanced or Metastatic Urothelial Cancer

EV-301

The safety of PADCEV was evaluated in EV-301 in patients with locally advanced or metastatic urothelial cancer (n=296) who received at least one dose of PADCEV 1.25 mg/kg and who were previously treated with a PD-1 or PD-L1 inhibitor and a platinum-based chemotherapy. Routine ophthalmologic exams were not conducted in EV-301. The median duration of exposure to PADCEV was 5 months (range: 0.5 to 19.4 months).

Serious adverse reactions occurred in 47% of patients treated with PADCEV. The most common serious adverse reactions (≥ 2%) were urinary tract infection, acute kidney injury (7% each) and pneumonia (5%). Fatal adverse reactions occurred in 3% of patients, including multiorgan dysfunction (1.0%), hepatic dysfunction, septic shock, hyperglycemia, pneumonitis and pelvic abscess (0.3% each).

Adverse reactions leading to discontinuation occurred in 17% of patients; the most common adverse reactions (≥ 2%) leading to discontinuation were peripheral neuropathy (5%) and rash (4%).

Adverse reactions leading to dose interruption occurred in 61% of patients; the most common adverse reactions (≥ 4%) leading to dose interruption were peripheral neuropathy (23%), rash (11%) and fatigue (9%).

Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions (≥ 2%) leading to dose reduction were peripheral neuropathy (10%), rash (8%), decreased appetite (3%) and fatigue (3%).

Table 3 summarizes the most common (≥ 15%) adverse reactions in EV-301.

Table 3. Adverse Reactions (≥ 15%) in Patients Treated with PADCEV in EV-301

Adverse Reaction	PADCEV n=296		Chemotherapy n=291	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Skin and subcutaneous tissue disorders				
Rash[1]	54	14	20	0.3
Alopecia	47	0	38	0
Pruritus	34	2	7	0
Dry skin	17	0	4	0
General disorders and administration site conditions				
Fatigue[2]	50	9	40	7
Pyrexia[3]	22	2	14	0
Nervous system disorders				
Peripheral neuropathy[4]	50	5	34	3
Dysgeusia[5]	26	0	8	0
Metabolism and nutrition disorders				
Decreased appetite	41	5	27	2
Gastrointestinal disorders				
Diarrhea[6]	35	4	23	2
Nausea	30	1	25	2
Constipation	28	1	25	2
Abdominal Pain[7]	20	1	14	3
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain[8]	25	2	35	5
Eye Disorders				
Dry eye[9]	24	0.7	6	0.3
Blood and lymphatic system disorders				
Anemia	20	6	30	12
Infections and infestations				
Urinary Tract Infection[10]	17	6	13	3
Vascular disorders				
Hemorrhage[11]	17	3	13	2
Investigations				
Weight decreased	16	0.3	7	0

[1]Includes: blister, blood blister, conjunctivitis, dermatitis, dermatitis bullous, drug eruption, eczema, erythema, erythema multiforme, exfoliative rash, intertrigo, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, skin irritation, skin exfoliation, stomatitis.

[2]Includes: fatigue, asthenia

[3]Includes: pyrexia, hyperthermia, hyperpyrexia, body temperature increased

[4]Includes: burning sensation, demyelinating polyneuropathy, dysesthesia, hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peroneal nerve palsy, peripheral sensory neuropathy, gait disturbance, polyneuropathy, sensory loss

[5]Includes: dysgeusia, ageusia, hypogeusia

[6]Includes: diarrhea, colitis, enterocolitis

[7]Includes: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, hepatic pain, abdominal tenderness, gastrointestinal pain

[8]Includes: myalgia, arthralgia, back pain, bone pain, pain in extremity, musculoskeletal pain, arthritis, neck pain, non-cardiac chest pain, musculoskeletal chest pain, spinal pain, musculoskeletal stiffness, musculoskeletal discomfort

[9]Includes: blepharitis, conjunctivitis, dry eye, eye irritation, keratitis, keratopathy, lacrimation increased, Meibomian gland dysfunction, ocular discomfort, punctate keratitis

[10]Includes: urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal, streptococcal urinary tract infection, escherichia urinary tract infection, pyelonephritis acute, escherichia pyelonephritis, urinary tract infection fungal, cystitis, urinary tract infection staphylococcal, urinary tract infection pseudomonal

[11]Includes: hematuria, rectal hemorrhage, gastrointestinal hemorrhage, epistaxis, upper gastrointestinal hemorrhage, tumor hemorrhage, hemoptysis, vaginal hemorrhage, anal hemorrhage, hemorrhagic stroke, urethral hemorrhage, infusion site hemorrhage, conjunctival hemorrhage, hemorrhagic ascites, hemorrhoidal hemorrhage

Clinically relevant adverse reactions (< 15%) include vomiting (14%), aspartate aminotransferase increased (12%), hyperglycemia (10%), alanine aminotransferase increased (9%), dry eye (6%) and infusion site extravasation (0.7%).

EV-201, Cohort 2

The safety of PADCEV was evaluated in EV-201, Cohort 2 in patients with locally advanced or metastatic urothelial cancer (n=89) who received at least one dose of PADCEV 1.25 mg/kg and had prior treatment with a PD-1 or PD-L1 inhibitor and were not eligible for cisplatin-based chemotherapy. The median duration of exposure was 5.98 months (range: 0.3 to 24.6 months).

Serious adverse reactions occurred in 39% of patients treated with PADCEV. The most common serious adverse reactions (≥ 3%) were pneumonia, sepsis and diarrhea (5% each). Fatal adverse reactions occurred in 8% of patients, including acute kidney injury (2.2%), metabolic acidosis, sepsis, multiorgan dysfunction, pneumonia and pneumonitis (1.1% each).

Adverse reactions leading to discontinuation occurred in 20% of patients; the most common adverse reaction (≥ 2%) leading to discontinuation was peripheral neuropathy (7%).

Adverse reactions leading to dose interruption occurred in 60% of patients; the most common adverse reactions (≥ 3%) leading to dose interruption were peripheral neuropathy (19%), rash (9%), fatigue (8%), diarrhea (5%), aspartate aminotransferase increased (3%) and hyperglycemia (3%).

Adverse reactions leading to dose reduction occurred in 49% of patients; the most common adverse reactions (≥ 3%) leading to dose reduction were peripheral neuropathy (19%), rash (11%) and fatigue (7%).

Table 4 summarizes the All Grades and Grade 3-4 adverse reactions reported in patients in EV-201, Cohort 2.

Table 4. Adverse Reactions ≥ 15% (All Grades) or ≥ 5% (Grades 3-4) in Patients Treated with PADCEV in EV-201, Cohort 2

Adverse Reaction	PADCEV n=89	
	All Grades (%)	Grades 3-4 (%)
Skin and subcutaneous tissue disorders		
Rash[1]	66	17
Alopecia	53	0
Pruritus	35	3
Dry skin	19	1
Nervous system disorders		
Peripheral neuropathy[2]	58	8
Dysgeusia[3]	29	0
General disorders and administration site conditions		
Fatigue[4]	48	11
Metabolism and nutrition disorders		
Decreased appetite	40	6
Hyperglycemia	16	9
Blood and lymphatic disorders		
Anemia	38	11
Gastrointestinal disorders		
Diarrhea[5]	36	8
Nausea	30	1
Investigations		
Weight decreased	35	1
Eye disorders		
Dry eye[6]	30	0

[1]Includes: blister, conjunctivitis, dermatitis bullous, dermatitis exfoliative generalized, eczema, erythema, erythema multiforme, intertrigo, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash vesicular, skin exfoliation, stomatitis

[2]Includes: demyelinating polyneuropathy, gait disturbance, hypoesthesia, motor dysfunction, muscle atrophy, muscular weakness, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peroneal nerve palsy, peripheral sensory neuropathy

[3]Includes: dysgeusia, ageusia, hypogeusia

[4]Includes: fatigue, asthenia

[5]Includes: diarrhea, colitis, enterocolitis

[6]Includes: blepharitis, conjunctivitis, dry eye, eye irritation, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, Meibomian gland dysfunction, ocular discomfort, punctate keratitis, tear break up time decreased

Clinically relevant adverse reactions (<15%) include vomiting (13%), aspartate aminotransferase increased (12%), alanine aminotransferase increased (10%) and infusion site extravasation (1%).

Immunogenicity

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

Following administration of PADCEV 1.25 mg/kg; 16/590 (2.7%) patients tested positive for anti-therapeutic antibody (ATA) against enfortumab vedotin-ejfv at one or more post-baseline time points. Due to the limited number of patients with ATA against enfortumab vedotin-ejfv, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy, safety or pharmacokinetics.

DRUG INTERACTIONS

Effects of Other Drugs on PADCEV

Dual P-gp and Strong CYP3A4 Inhibitors

Concomitant use with dual P-gp and strong CYP3A4 inhibitors may increase unconjugated MMAE exposure which may increase the incidence or severity of PADCEV toxicities. Closely monitor patients for signs of toxicity when PADCEV is given concomitantly with dual P-gp and strong CYP3A4 inhibitors.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. There are no available human data on PADCEV use in pregnant women to inform a drug-associated risk. In an animal reproduction study, administration of enfortumab vedotin-ejfv to pregnant rats during organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures approximately similar to the exposures at the recommended human dose of 1.25 mg/kg. Advise patients of the potential risk to the fetus.

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

Lactation

Risk Summary

There are no data on the presence of enfortumab vedotin-ejfv in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women not to breastfeed during treatment with PADCEV and for at least 3 weeks after the last dose.

Females and Males of Reproductive Potential

Pregnancy testing

Verify pregnancy status in females of reproductive potential prior to initiating PADCEV treatment.

Contraception

Females

PADCEV can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during PADCEV treatment and for 2 months after the last dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

Infertility

Males

Based on findings from animal studies, PADCEV may impair male fertility.

Pediatric Use

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

Geriatric Use

Of the 680 patients treated with PADCEV in clinical trials, 440 (65%) were 65 years or older and 168 (25%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Hepatic Impairment

Avoid the use of PADCEV in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 x ULN and AST any). PADCEV has only been studied in a limited number of patients with moderate hepatic impairment (n=3) and has not been evaluated in patients with severe hepatic impairment. In another ADC that contains MMAE, the frequency of ≥ Grade 3 adverse reactions and deaths was greater in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment compared to patients with normal hepatic function. No adjustment in the starting dose is required when administering PADCEV to patients with mild hepatic impairment (total bilirubin 1 to 1.5 × ULN and AST any, or total bilirubin ≤ ULN and AST >ULN).

Renal Impairment

No dose adjustment is required in patients with mild (CrCL > 60-90 mL/min), moderate (CrCL 30-60 mL/min) or severe (CrCL < 30 mL/min) renal impairment.

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081-0282-PM 07/21



IDENTIFYING MIS-C WITH RISK PREDICTION MODEL

BY PHYSICIANS OFFICE RESOURCE

While children often recover quickly from COVID-19, with the emergence of the highly contagious omicron variant, cases and hospitalizations are on the rise. With the rise in COVID-19 cases, brings on another concern, MIS-C.

What is MIS-C?

According to the CDC, "Multisystem inflammatory syndrome in children (MIS-C) is a condition where different body parts can become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs." Scientists aren't quite sure what causes MIS-C; however they do know that many children with MIS-C have had COVID-19. The CDC continues, "MIS-C can be serious, even deadly, but most children who were diagnosed with this condition have gotten better with medical care."1

MIS-C often comes as a surprise to parents and clinicians

MIS-C often comes as a surprise to parents and clinicians as some who develop this serious condition never showed signs or symptoms of COVID-19 and symptoms of MIS-C often do not arise until two to six weeks after COVID-19 infection.

as some who develop this serious condition never showed signs or symptoms of COVID-19 and symptoms of MIS-C often do not arise until two to six weeks after COVID-19 infection.

While MIS-C is rare, there have been almost 6,500 cases and 55 deaths over the last year. Experts expect that number to increase this year as we battle against the highly contagious omicron variant, especially within children younger than 5 who are unable to receive the vaccine.

Can MIS-C be Prevented?

Much is still being learned about MIS-C and its relationship to COVID-19, however according to a new report from the CDC, the "estimated effectiveness of 2 doses of Pfizer-BioNTech vaccine against MIS-C was 91% [in patients aged 12-18]. Among critically ill MIS-C case patients requiring life support, all were unvaccinated."2

MIS-C Prediction Model

Late last year, a team of medical scientists and investigators from Vanderbilt University and John Hopkins presented a risk prediction model at the annual meeting of the American College of Rheumatology. The model utilizes clinical, laboratory, and cardiac feature to help identify MIS-C cases within 24 hours of observed symptoms. Identifying MIS-C is difficult because MIS-C shares features common with infectious and inflammatory syndromes. Therefore, having a prediction model could be verry valuable to clinicians needing to identify these cases quickly and accurately.4

The four predictors in the model included:

- **Hypotension** (defined as requiring fluid resuscitation, vasopressor support or blood pressure less than 10th percentile for age, height, and sex).
- **Abdominal Pain**
- **Rash**
- **Serum Sodium**

To develop this prediction model, investigators used retrospective chart data of children less than 20 years old that were evaluated for MIS-C at Vanderbilt Children's Hospital during the pandemic. While in the care of the hospital, clinicians collected a set of standardized clinical, lab, and cardiac characteristics. In all the trial population included 127 children admitted to the Vanderbilt hospital that were evaluated for MIS-C. Utilizing the retrospective chart data of the 127 children evaluated for MIS-C, 45 cases of MIS-C were confirmed versus 82 non-cases.

Matthew Clark, MD, RhMSUS and lead investigator on the study said, "We used early clinical and laboratory features to inform the design of a clinical diagnostic prediction model with excellent discrimination to assist clinicians in distinguishing patients with MIS-C from those without… We plan to test this model with external and prospective validation."3

Sources

1. https://www.cdc.gov/mis/mis-c.html

2. https://www.cdc.gov/mmwr/volumes/71/wr/mm7102e1.htm

3. https://acrabstracts.org/abstract/a-prediction-model-to-distinguish-patients-with-multisystem-inflammatory-syndrome-in-children/

4. https://www.hcplive.com/view/risk-prediction-model-identify-pediatric-mis-c-cases

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1 Neuro-Cognitive Testing 1139

- Medicare mandates yearly cognitive assessment
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2 ANS Testing (can be combined with SUDOMOTOR into 1 full system) 1140

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3 SudoMotor Testing 1141

(can be combined with ANS into 1 full system)

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