Incyte

Ruxolitinib for the Treatment of Chronic Graft-Versus-Host Disease

Data highlights of ruxolitinib in chronic GVHD

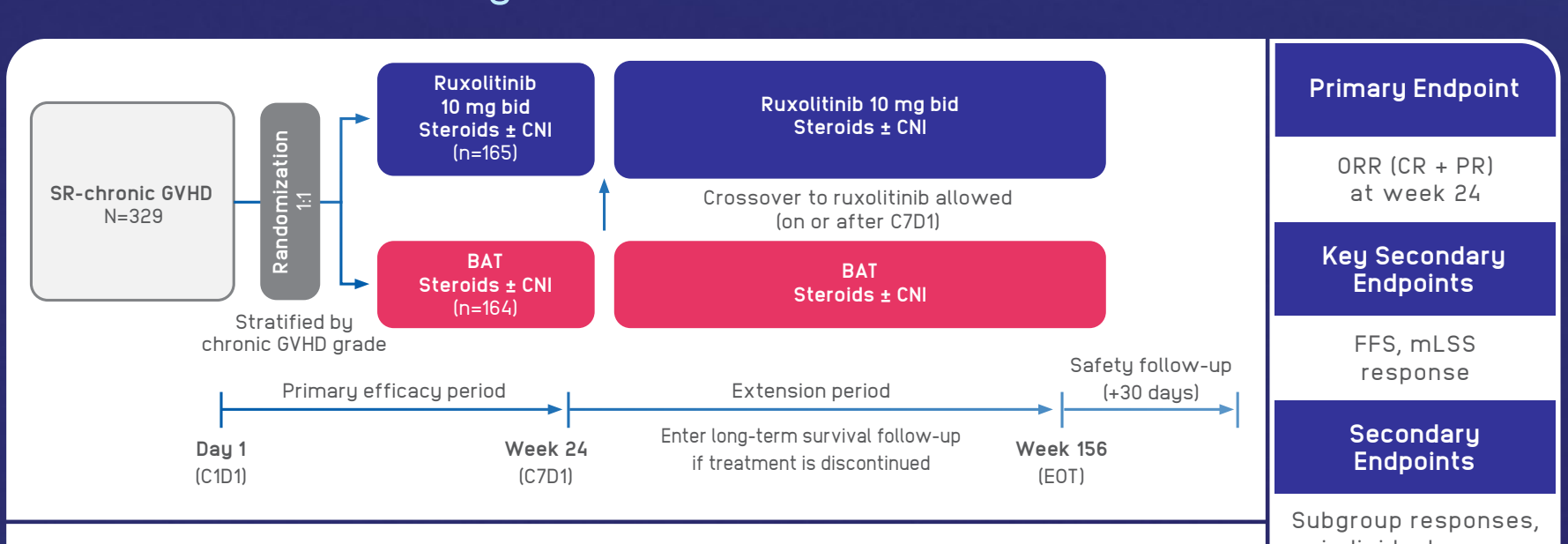
Ruxolitinib Indication and Dosing

Indication[1]	Dosing[1]
Ruxolitinib is indicated for chronic GVHD after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years of age and older	Recommended starting dose: **10 mg** orally twice daily

GVHD, graft-versus-host disease.

REACH3 Overview: Efficacy and Safety[2]

A phase 3, randomized, prospective, multicenter, open-label trial in steroid-refractory chronic GVHD[2]



BAT Medications: ECP, Low-dose MTX, MMF, Sirolimus, Everolimus, Infliximab, Rituximab, Pentostatin, Imatinib, Ibrutinib

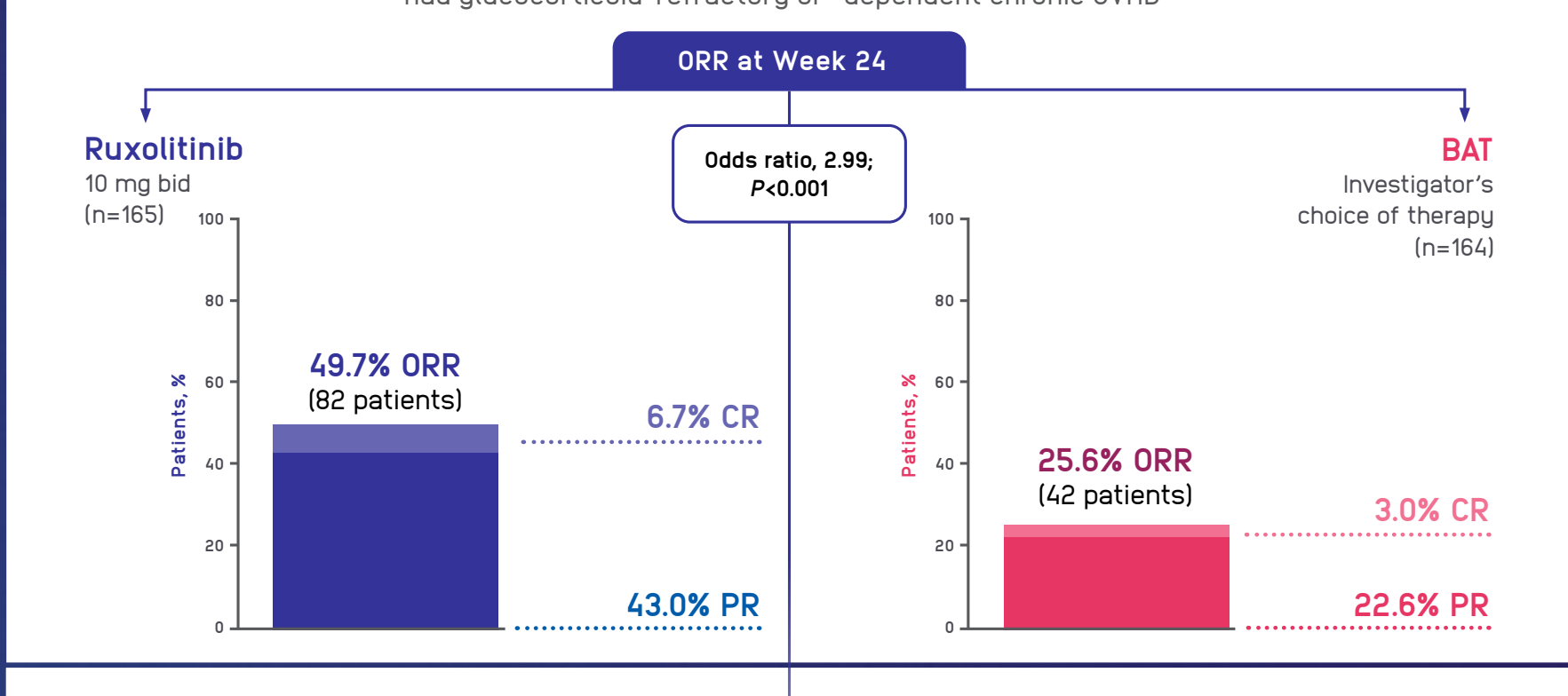
Primary Endpoint: ORR (CR + PR) at week 24

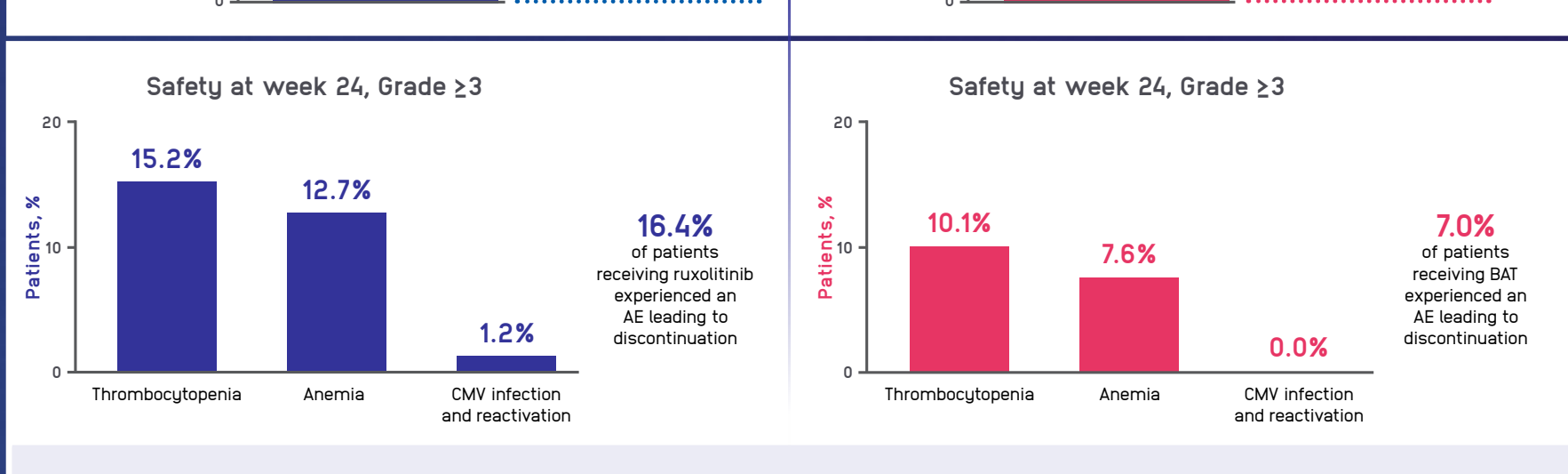
Key Secondary Endpoints: FFS, mLSS response

Secondary Endpoints: Subgroup responses, individual organ response, NRM, BOR, DOR, OS, QOL, CS reduction, safety

Primary Analysis Summary[2,3]

329 patients had undergone allogeneic stem cell transplantation and had glucocorticoid-refractory or -dependent chronic GVHD





Median dose intensity of ruxolitinib (interquartile range): 19.6 mg/day (4.8-20.5)

Adverse Events up to Week 24 in ≥8% of Patients Treated with Ruxolitinib[2]

Adverse Event	Ruxolitinib (n=165) Any grade	Ruxolitinib (n=165) Grade ≥3	BAT (n=150) Any grade	BAT (n=150) Grade ≥3
	Number of patients (%)			
Any	161 (97.6)	94 (57.0)	145 (91.8)	91 (57.6)
Hematologic event				
Anemia	48 (29.1)	21 (12.7)	20 (12.7)	12 (7.6)
Thrombocytopenia	35 (21.2)	25 (15.2)	23 (14.6)	16 (10.1)
Neutropenia	18 (10.9)	14 (8.5)	8 (5.1)	6 (3.8)
Gastrointestinal event				
Diarrhea	17 (10.3)	1 (0.6)	21 (13.3)	2 (1.3)
Nausea	15 (9.1)	0	16 (10.1)	2 (1.3)
Infection				
Pneumonia	18 (10.9)	14 (8.5)	20 (12.7)	15 (9.5)
Upper respiratory tract infection	14 (8.5)	0	13 (8.2)	2 (1.3)
Laboratory abnormality				
Alanine aminotransferase increased	25 (15.2)	7 (4.2)	7 (4.4)	0
Creatinine increased	23 (13.9)	0	7 (4.4)	1 (0.6)
Aspartate aminotransferase increased	16 (9.7)	3 (1.8)	4 (2.5)	1 (0.6)
Hypertriglyceridemia	16 (9.7)	8 (4.8)	13 (8.2)	6 (3.8)
γ-glutamytransferase increased	15 (9.1)	11 (6.7)	5 (3.2)	3 (1.9)
Other				
Hypertension	26 (15.8)	8 (4.8)	20 (12.7)	11 (7.0)
Pyrexia	26 (15.8)	3 (1.8)	15 (9.5)	2 (1.3)
Cough	17 (10.3)	0	11 (7.0)	0
Fatigue	17 (10.3)	1 (0.6)	12 (7.6)	3 (1.9)
Dyspnea	16 (9.7)	3 (1.8)	10 (6.3)	2 (1.3)
Headache	14 (8.5)	2 (1.2)	12 (7.6)	1 (0.6)

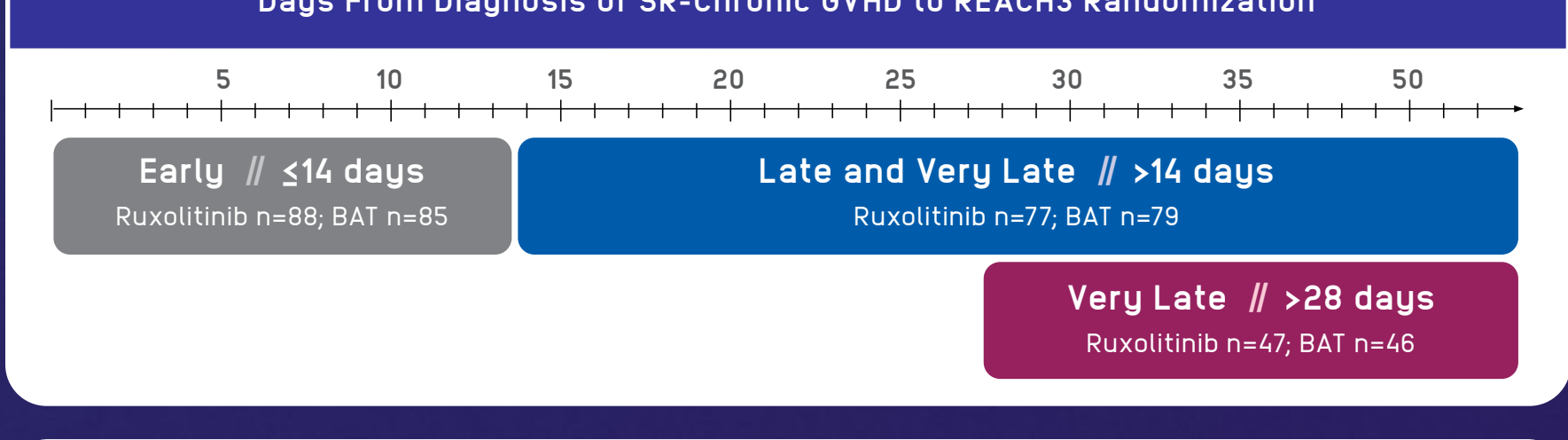
AE, adverse event; BAT, best available therapy; bid, twice daily; BOR, best overall response; C1D1, Cycle 1 Day 1; C7D1, cycle 7 day 1; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CR, complete response; CS, corticosteroids; DOR, duration of response; ECP, extracorporeal photopheresis; EOT, end of treatment period; FFS, failure-free survival; mLSS, modified Lee Symptom Scale; MMF, mycophenolate mofetil; MTX, methotrexate; NRM, non-relapse mortality; ORR, overall response rate; OS, overall survival; PR, partial response; QOL, quality of life; SR, steroid refractory.

Early vs Late Treatment

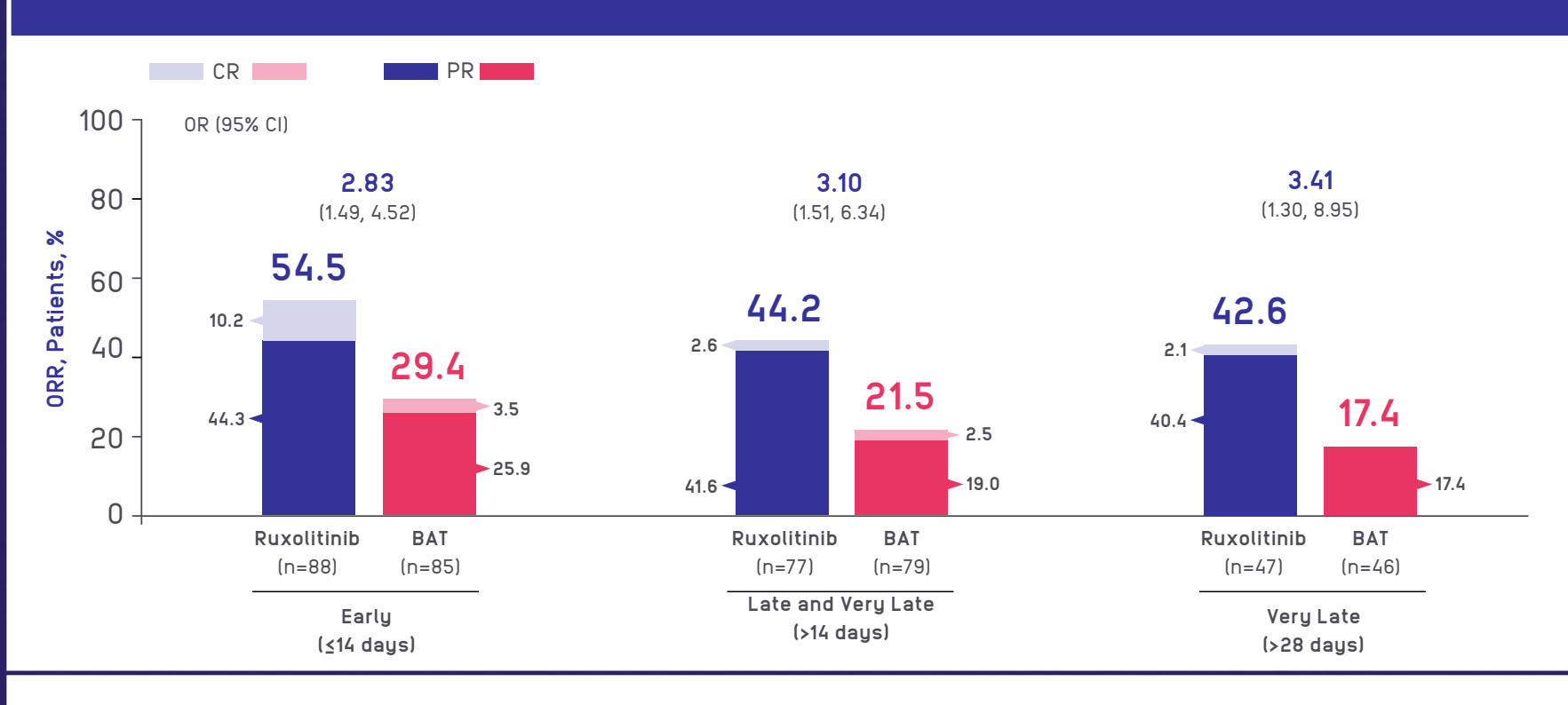
Impact of the timing of ruxolitinib initiation on efficacy[4]

Ruxolitinib provides clinical benefit compared with BAT regardless of the time elapsed between onset of SR-chronic GVHD and treatment initiation

Days From Diagnosis of SR-Chronic GVHD to REACH3 Randomization



Greater ORR at Week 24 With Ruxolitinib vs BAT

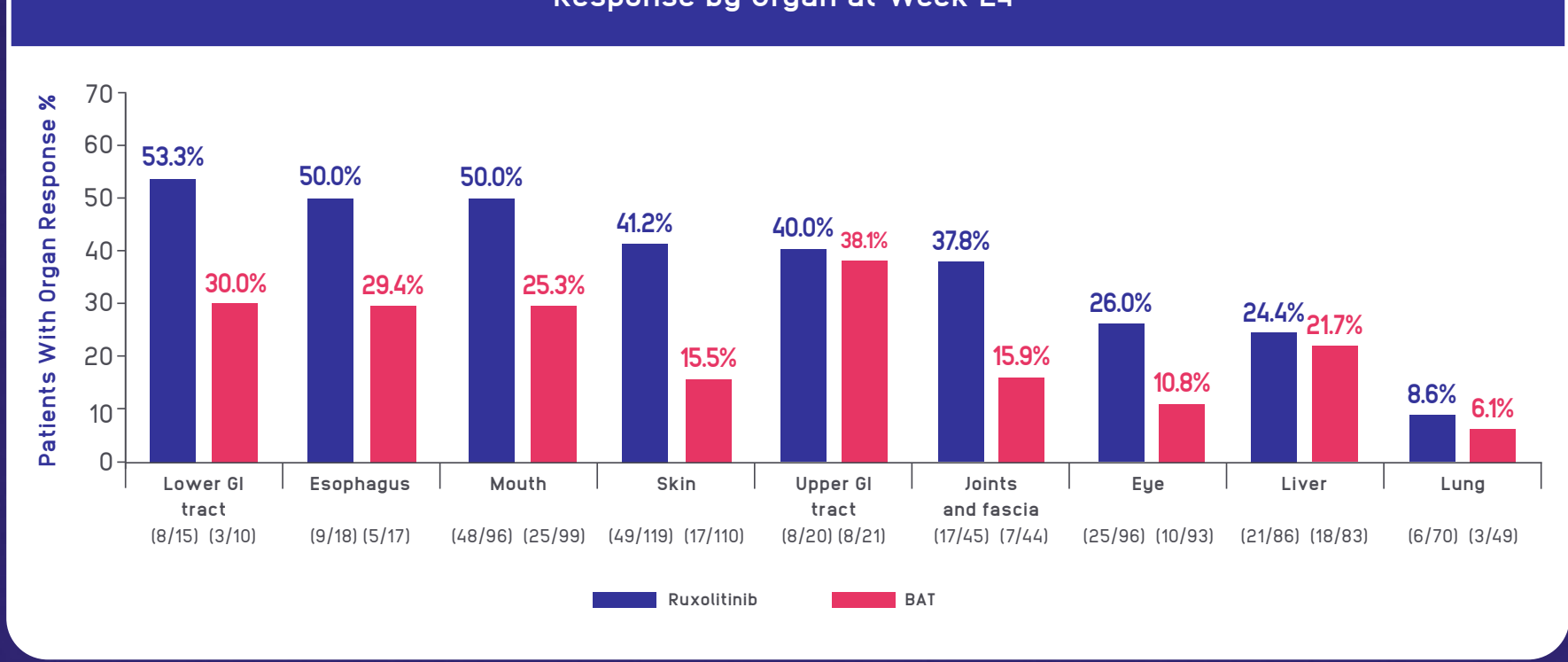


- Week 24 ORR was higher with ruxolitinib vs BAT in all 3 time-to-treatment subgroups
- Ruxolitinib provides clinical benefit compared with BAT regardless of the time elapsed between onset of SR-chronic GVHD and treatment initiation

OR, odds ratio.

Organ Specific Outcomes

Response by Organ at Week 24[2]



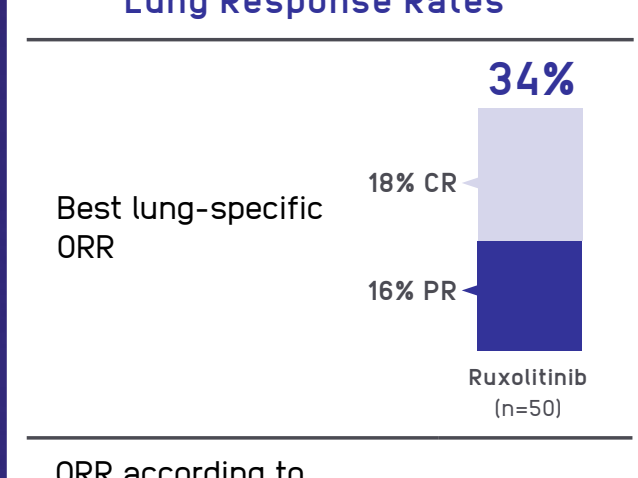
Ruxolitinib in patients with bronchiolitis obliterans syndrome[2,5]

BOS results from an immunological attack of the small airways, leading to fibrotic narrowing of the respiratory bronchioles and subsequent obliteration

- In REACH3, **74 participants receiving ruxolitinib had lung involvement at baseline,** including NIH lung score of 2 (n=24) or 3 (n=14)
- At week 24, the lung-specific response rate was 8.6% (6/70)

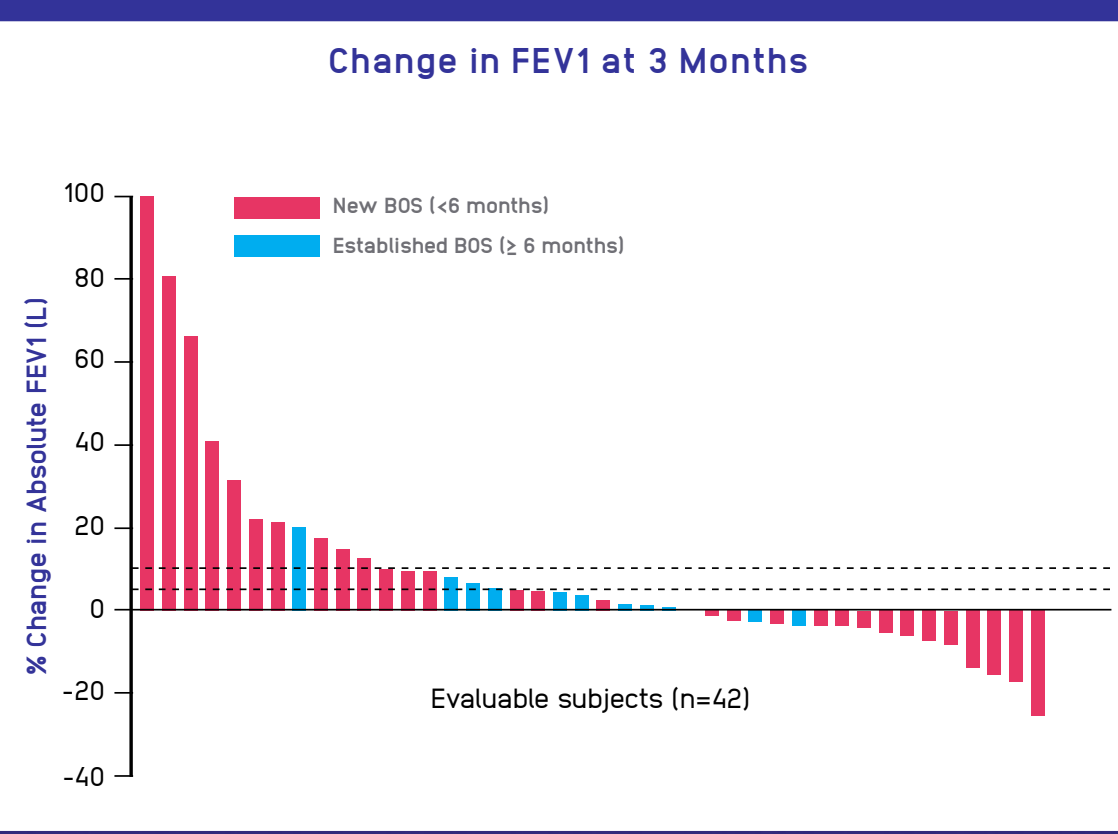
Ruxolitinib (10 mg bid) was investigated in a phase 2 multicenter study of patients who developed bronchiolitis obliterans syndrome after allogeneic HCT[5]

Lung Response Rates



ORR according to baseline NIH lung score[a]	
1	44%
2	16%
3	57%

Change in FEV1 at 3 Months



- Among the 42 evaluable patients, those with **newly diagnosed BOS** experienced dynamic early changes in FEV1 (11 subjects with ≥10% increase, 8 subjects with ≥5% decrease) after 3 28-day cycles of ruxolitinib
- Those with **established BOS** experienced stable disease (1 subject with ≥10% increase, no subjects with ≥5% decrease)

Phase 2 study of ruxolitinib for the treatment of SR sclerotic chronic GVHD[6]

Sclerotic chronic GVHD is a highly morbid form of chronic GVHD, often refractory to treatment and associated with significant decline in the patients' QOL

Ruxolitinib (10 mg bid for 6 months) was investigated in a single-arm phase 2 multicenter study in adult patients with sclerotic chronic GVHD

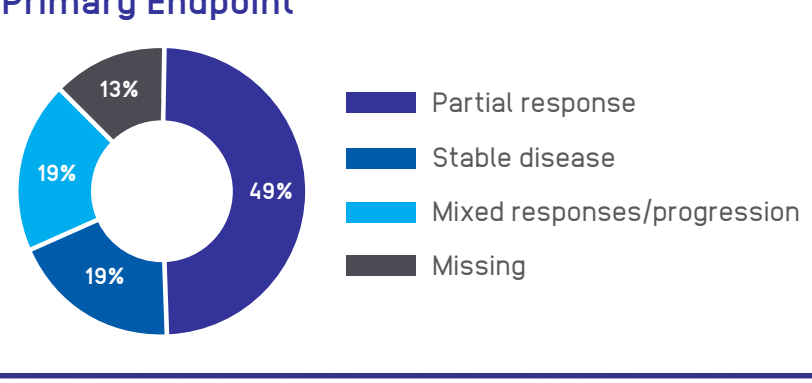
Enrolled Patients

47 patients with chronic GVHD

- Median time from chronic GVHD diagnosis: 48 months
- 2% mild, 13% moderate, 85% severe
- Mean of 3 prior lines of treatment

Skin and Joint Responses at 6 Months[b]

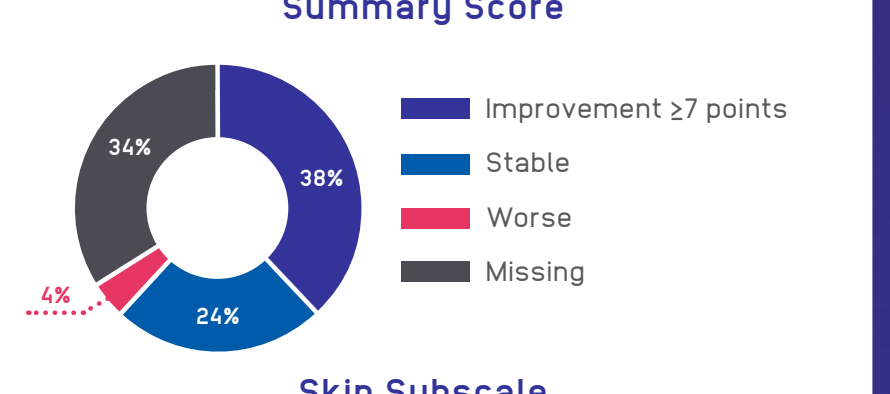
Primary Endpoint



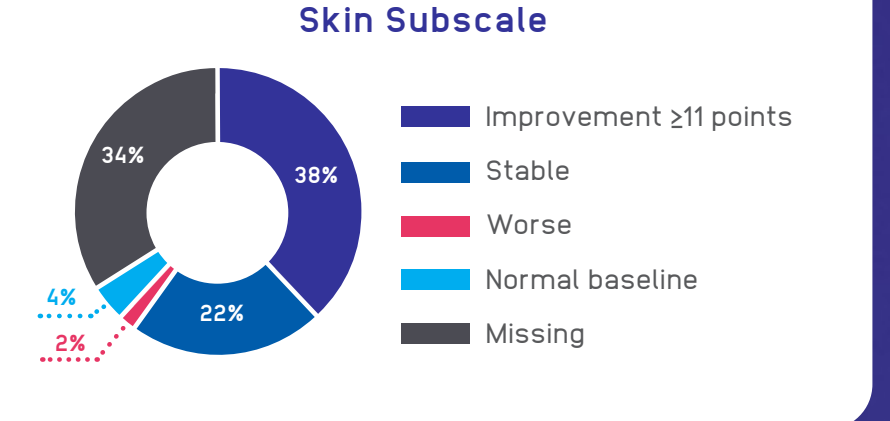
Overall chronic GVHD response at 6 months: 47%

PRO: Lee Symptom Scale

Summary Score



Skin Subscale



[a] NIH lung score is defined as 1 for mild symptoms (eg, shortness of breath after climbing one flight of steps), 2 for moderate symptoms (eg, shortness of breath after walking on flat ground), and 3 for severe symptoms (eg, shortness of breath at rest; requiring oxygen). [b] Skin responses were defined as a decrease in NIH skin score by ≥1 point. Joint responses were defined as a decrease in NIH Joint and Fascia Score by ≥1 point, or increase in P-ROM score by ≥1 point. Overall chronic GVHD response was defined as improvement in ≥1 organ/site without progression in any other organ/site.

BOS, bronchiolitis obliterans syndrome; FEV1, forced expiratory volume in 1 second; GI, gastrointestinal; HCT, hematopoietic cell transplantation; NIH, National Institutes of Health; PRO, patient-reported outcome.

Cytopenias in REACH3

Incidence of cytopenias in REACH3[2,3]

AE, n (%)	Ruxolitinib (n=165) Any grade	Ruxolitinib (n=165) Grade ≥3	BAT (n=158) Any grade	BAT (n=158) Grade ≥3
Anemia	48 (29)	21 (13)	20 (13)	12 (8)
Thrombocytopenia[a]	35 (21)	25 (15)	23 (15)	16 (10)
Neutropenia	18 (11)	14 (9)	8 (5)	6 (4)

Despite cytopenias, patients achieved close to the maximal dose of ruxolitinib (10 mg bid) at the study endpoint (week 24)

Median dose intensity of ruxolitinib: 19.6 mg/day (4.8-20.5)

Cytopenias improved over time as patients received treatment for chronic GVHD

Hematologic events up to cycle 7 day 1 requiring dose modification/interruption[3]

AE, n (%)	Ruxolitinib (n=165) Any grade	Ruxolitinib (n=165) Grade ≥3	BAT (n=158) Any grade	BAT (n=158) Grade ≥3
No. of patients ≥1 event	62 (37.6)	38 (23.0)	26 (16.5)	12 (7.6)
Blood and lymphatic system disorders	23 (13.9)	14 (8.5)	6 (3.8)	5 (3.2)
Anemia	13 (7.9)	5 (3.0)	1 (0.6)	1 (0.6)
Neutropenia	8 (4.8)	7 (4.2)	2 (1.3)	2 (1.3)
Thrombocytopenia	6 (3.6)	6 (3.6)	2 (1.3)	1 (0.6)
Febrile neutropenia	4 (2.4)	4 (2.4)	1 (0.6)	1 (0.6)
Leukopenia	3 (1.8)	3 (1.8)	0	0
Lymphopenia	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)
Pancytopenia	0	0	2 (1.3)	2 (1.3)

Clinically relevant low blood counts were defined as platelets <30x10⁹ cells/L, hemoglobin <8 g/dL, white blood cells <5x10⁹ cells/L, and absolute neutrophil count <1x10⁹ cells/L.

[a] Includes events recorded as thrombocytopenia and decreased platelet count.

No., number.

Drug-Drug Interactions

Dose modification guidelines for concomitant use of ruxolitinib with strong CYP3A4 inhibitors or fluconazole[1,a]

Ruxolitinib Dose Modification[1,3]

For patients receiving	
Fluconazole doses >200 mg	Avoid concomitant use of ruxolitinib
Fluconazole doses ≤200 mg	Use the following dosage modifications: • 5 mg ruxolitinib qd for patients with acute GVHD • 5 mg ruxolitinib bid for patients with chronic GVHD
Other CYP3A4 inhibitors	• Monitor blood counts more frequently for toxicity • Modify the ruxolitinib dosage for adverse reactions, if they occur

No empiric dose adjustments needed with voriconazole or posaconazole

REACH3 post hoc analysis: Effects of concomitant azoles on ruxolitinib treatment in patients with chronic GVHD

More than two-thirds of patients in REACH3 received concomitant azoles[7]

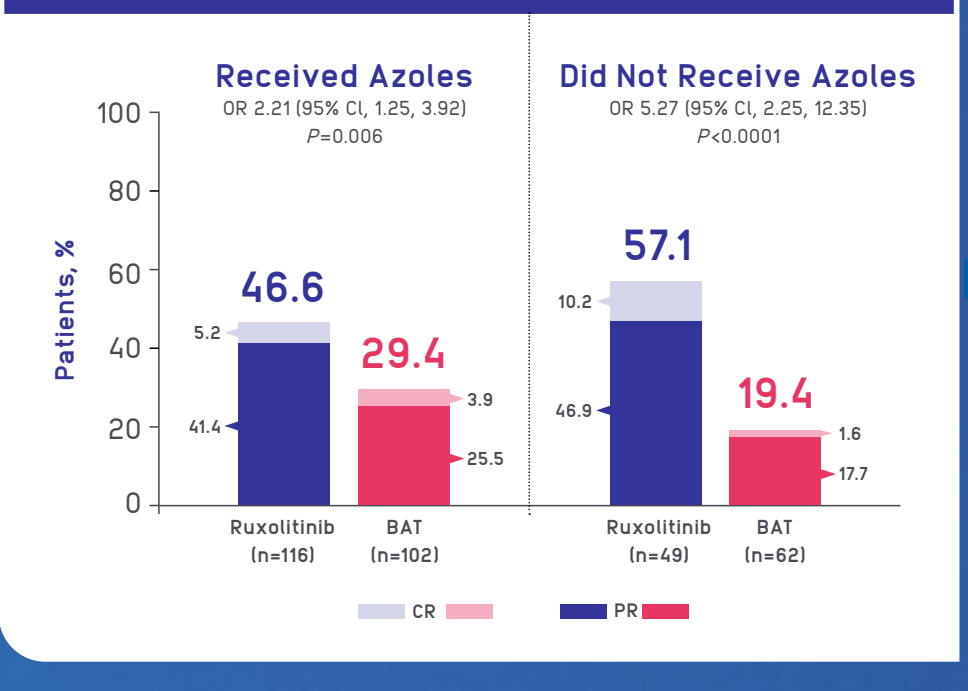
Safety Analysis Set (N=323)[8]

Azole Received[b], %	Ruxolitinib (n=165)	BAT (n=158)
Posaconazole	29.1	34.2
Fluconazole[c]	24.8	24.7
Voriconazole	23.0	12.7
Isavuconazole[d]	3.6	4.4

Efficacy and safety for REACH3 patients receiving concomitant azoles

ORR with ruxolitinib vs BAT according to receipt of concomitant azoles[7]

ORR at Week 24



Week 24 ORR was significantly higher with ruxolitinib vs BAT in patients who received azoles as well as those who did not

Incidence of cytopenias in patients treated with ruxolitinib and BAT by azole subgroup[7]

	Ruxolitinib (n=165) With Azoles (n=116)	Ruxolitinib (n=165) Without Azoles (n=49)	BAT (n=158) With Azoles (n=102)	BAT (n=158) Without Azoles (n=56)
Cytopenia at baseline, n (%)	16 (13.8)	8 (16.3)	23 (22.5)	10 (17.9)
WBC <5x10⁹ cell/L	15 (12.9)	6 (12.2)	19 (18.6)	10 (17.9)
Platelets <30x10⁹ cells/L	2 (1.7)	1 (2.0)	5 (4.9)	0
Hemoglobin <8 g/dL	1 (0.9)	0	0	0
ANC <1x10⁹ cells/L	2 (1.7)	3 (6.1)	2 (2.0)	0
Cytopenia up to week 24, n (%)	74 (63.8)	31 (63.3)	56 (54.9)	25 (44.6)
WBC <5x10⁹ cell/L	70 (60.3)	28 (57.1)	51 (50.0)	23 (41.1)
Platelets <30x10⁹ cells/L	14 (12.1)	3 (6.1)	11 (10.8)	3 (5.4)
Hemoglobin <8 g/dL	17 (14.7)	5 (10.2)	9 (8.8)	4 (7.1)
ANC <1x10⁹ cells/L	15 (12.9)	8 (16.3)	14 (13.7)	3 (5.4)

Development of cytopenias at week 24 was similar for patients who received ruxolitinib with azoles vs without azoles

Mean and median ruxolitinib dose intensity up to week 24 were similar in patients with vs without concomitant administration of azoles

The mean dose of ruxolitinib (10 mg orally twice daily) was generally well tolerated when administered with concomitant azoles

[a] Fluconazole 100-400 mg qd (a moderate CYP3A4 and CYP2C9 inhibitor) increases steady-state ruxolitinib AUC by approximately 100-300%. [b] Patients may have been exposed to more than one azole during the follow-up period. [c] Includes fluconazole and fosfluconazole. [d] Includes isavuconazole and isavuconazonium sulfate.

AUC, area under the curve.

More Information

For more information about ruxolitinib in chronic GVHD, please see the links below:

- **Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease** — Zeiser R, et al. *N Engl J Med.* 2021;385:228-238. LEARN MORE
- **A Phase II Multicenter Trial of Ruxolitinib to Treat Bronchiolitis Obliterans Syndrome after Allogeneic Hematopoietic Cell Transplantation** — DeFilipp Z, et al. ASH 2023. Abstract 775. LEARN MORE
- **Ruxolitinib for Treatment of Steroid Refractory Sclerotic Chronic Graft-Versus-Host Disease (cGVHD): Results of a Multicenter Phase II Trial** — Bhatt VR, et al. *Blood.* 2022. 140 (Supplement 1): 1379–1380. LEARN MORE
- **Effects of Concomitant Azoles on Ruxolitinib Treatment in Patients with Chronic Graft-Versus-Host Disease: A Post Hoc Analysis from the Randomized Phase 3 REACH3 Study** — Mahmoudjafari Z, et al. Transplantation & Cellular Therapy Meeting of ASTCT and CIBMTR 2024. Poster 386. LEARN MORE
- **Impact of Cytopenias and Early Versus Late Treatment With Ruxolitinib in Patients With Steroid-Refractory Acute or Chronic Graft-Versus-Host Disease** — Mahmoudjafari Z, et al. *Bone Marrow Transplant.* 2024 Nov 6. doi: 10.1038/s41409-024-02445-6. Online ahead of print. LEARN MORE

For more information, please see the Full Prescribing Information.

1. Jakafi (ruxolitinib). Prescribing Information. Incyte Corporation; January 2023. 2. Zeiser R, et al. *N Engl J Med.* 2021;385:228-238. 3. Data on File. Incyte Corporation. 4. Mahmoudjafari Z, et al. *Bone Marrow Transplant.* 2024 Nov 6. doi: 10.1038/s41409-024-02445-6. Online ahead of print. 5. DeFilipp Z, et al. ASH 2023. Abstract 775. 6. Bhatt VR, et al. *Blood.* 2022. 140 (Supplement 1): 1379–1380. 7. Mahmoudjafari Z, et al. Transplantation & Cellular Therapy Meeting of ASTCT and CIBMTR 2024. Poster 386. 8. Kintsch E, et al. Hematology/Oncology Pharmacy Association Annual Conference 2024. Poster 65.

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Warnings, Precautions, and Specific Populations

Thrombocytopenia, Anemia and Neutropenia

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC less than 0.5 × 10^9/L) was generally reversible by withholding Jakafi until recovery
- Perform a pre-treatment complete blood count and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated

CBC, complete blood count.

Risk of Infection

- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines

Tuberculosis

- Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly
- Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed
- For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination

PML

- PML has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate

Herpes Zoster and Herpes Simplex

- Herpes zoster infection has been reported in patients receiving Jakafi
- Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected
- Herpes simplex virus reactivation and/or dissemination has been reported in patients receiving Jakafi. Monitor patients for the development of herpes simplex infections. If a patient develops evidence of dissemination of herpes simplex, consider interrupting treatment with Jakafi; patients should be promptly treated and monitored according to clinical guidelines

Hepatitis B

- Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines

HBV, hepatitis B virus; PML, progressive multifocal leukoencephalopathy.

Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi

- Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia, consider tapering the dose of Jakafi gradually rather than discontinuing abruptly

DIC, disseminated intravascular coagulation; MF, myelofibrosis.

NMSC

- NMSCs including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations

NMSC, non-melanoma skin cancer.

Lipid Elevations

- Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia

MACE

- Another JAK-inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated
- Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur

MACE, major adverse cardiovascular event.

Thrombosis

- Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. In patients with MF and PV treated with Jakafi in clinical trials, the rates of thromboembolic events were similar in Jakafi and control treated patients
- Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately

TNF, tumor necrosis factor.

Secondary Malignancies

- Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients who are current or past smokers are at additional increased risk
- Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi, particularly in patients with a known secondary malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers

TNF, tumor necrosis factor.

Pregnancy and Lactation

- There are no studies with the use of Jakafi in pregnant women to inform drug-associated risks
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus
- Advise women not to breastfeed during treatment with Jakafi and for at least 2 weeks after the final dose

Pediatric Use

- The safety and effectiveness of Jakafi for treatment of chronic GVHD or acute GVHD has not been established in pediatric patients younger than 12 years old

Renal Impairment

- Total exposure of ruxolitinib and its active metabolites increased with moderate and severe renal impairment, and end stage renal disease on dialysis
- Modify Jakafi dosage as recommended

Hepatic Impairment

- Exposure of ruxolitinib increased with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment
- Reduce Jakafi dosage as recommended for patients with Stage 4 liver acute GVHD
- Monitor blood counts more frequently for toxicity and modify the Jakafi dosage for adverse reactions if they occur for patients with Score 3 liver chronic GVHD

Geriatric Use

- Clinical studies of Jakafi in patients with acute GVHD did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects
- Of the total number of patients with chronic GVHD treated with Jakafi in clinical trials, 11% were 65 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients

Jakafi (ruxolitinib). Prescribing Information. Incyte Corporation; January 2023.