Jakafi® (ruxolitinib) in Graft-Versus-Host Disease

MSL-RUX-US-0003 09/24

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Notice Slide

- Some information contained in this presentation may not be included in the approved Prescribing Information for JAKAFI. This presentation is not intended to offer recommendations for any administration, indication, dosage, or other use for JAKAFI in a manner inconsistent with the approved Prescribing Information.

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Indications and Usage

- JAKAFI®(ruxolitinib) is indicated for treatment of:
  - Intermediate or high-risk MF, including primary MF, post-PV MF, and post-essential thrombocythemia MF in adults
  - PV in adults who have had an inadequate response to or are intolerant of hydroxyurea
  - SR-aGVHD in adult and pediatric patients 12 years and older
  - cGVHD after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older
- Please see the Full Prescribing Information, including Warnings & Precautions, and Patient Information for JAKAFI

MF, myelofibrosis; PV, polycythemia vera.

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

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GVHD Disease State

GVHD Is an Immune-Mediated Complication of Allo-HSCT

- Allo-HSCT offers a potential cure for patients with hematologic malignancies[1,2]
- GVHD is a major complication associated with allo-HSCT[3]
- GVHD occurs when donor immune cells recognize and attack host tissues[1]

aGVHD[1]

- Strong inflammatory component with tissue damage
- Mediated by donor T cells[4]
- Primarily affects the skin, gut, and liver

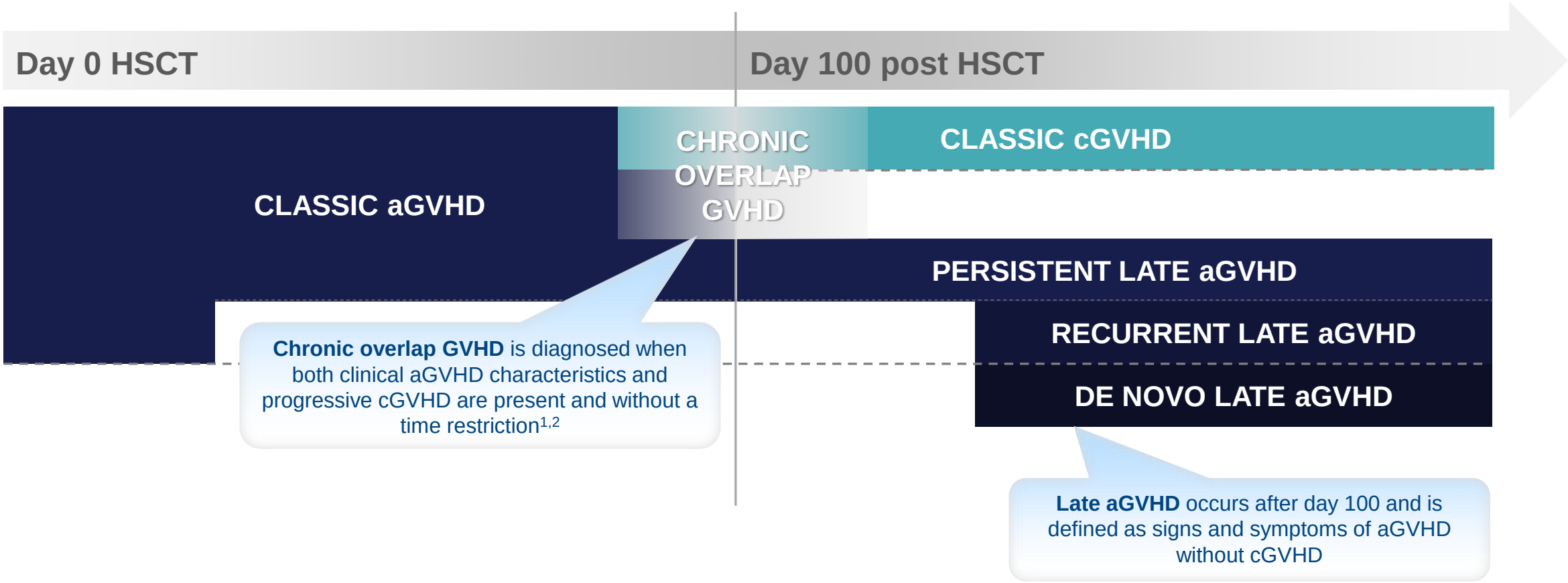
cGVHD[1]

- Displays autoimmune and fibrotic features
- Mediated primarily by T cells, B cells, and macrophages[4,5]
- Mainly affects oral and ocular mucosal surfaces and the skin, gut, liver, lungs, and kidneys

allo-HSCT, allogeneic hematopoietic stem cell transplantation.

1. Blazar BR, et al. *Nat Rev Immunol*. 2012;12:443-458. 2. Spoerl S, et al. *Blood.* 2014;123:3832-3842. 3. Ferrara JLM, et al. *Lancet*. 2009;373:1550-1561. 4. Cutler CS. *Blood*. 2017;129:22-29. 5. McDonald-Hyman C, et al. *Sci Transl Med*. 2015;7:280-282.

Classification of GVHD



aGVHD and cGVHD are considered distinct clinical syndromes without a time restriction[1]

Note: Box sizes do not reflect relative prevalence or incidence.
Figure adapted from Lee SJ. *Blood*. 2017;129:30-37.
HSCT, hemopoietic stem cell transplant.
1. Lee SJ. *Blood*. 2017;129:30-37. 2. Filipovich AH, et al. *Biol Blood Marrow Transplant*. 2005;11:945-956.

SR-aGVHD: Ruxolitinib Efficacy and Safety

REACH1: Phase 2, Single-Cohort, Open-Label Study of Ruxolitinib in SR-aGVHD[1]

SR-aGVHD: N=71
(n=49 refractory to steroids alone[a])[2]

→ Ruxolitinib 5 mg bid[b] + steroids

→ Day 28 ORR

→ Overall survival

Eligibility

- Age ≥12 years
- Grade 2-4 aGVHD per MAGIC
- SR-aGVHD:
  - PD after 3 days of primary treatment[c]
  - NR after 7 days of primary treatment[c]
  - Development of new aGVHD after prior therapy[d] for treatment of skin, or skin plus upper GI GVHD
  - Taper intolerant
- Evidence of myeloid engraftment
- Excluded if active infection, severe organ failure, or disease relapse

Click for MAGIC Guidelines for Staging and Grading aGVHD

Primary endpoint

- ORR at day 28[e]

Secondary/exploratory endpoints

- Key secondary: DOR at 6 months
- DOR, NRM, MR, FFS, OS
- cGVHD incidence
- Safety
- Discontinuation of steroids/IS
- Graft failure
- PK
- Biomarkers

[a] There were 49 patients with aGVHD refractory to steroids alone; this patient population is included in the Jakafi PI. 12 patients were excluded as they received 2 or more prior anti-GVHD therapies, and 10 patients were excluded as they did not receive an adequate amount of corticosteroids[2]. [b] Escalate to 10 mg bid after 3 days if no cytopenias. [c] Methylprednisolone ≥2 mg/kg/d or prednisone equivalent. [d] Methylprednisolone ≥1 mg/kg/d. [e] Defined as the proportion of patients demonstrating a CR, VGPR, or PR according to CIBMTR criteria.

bid, twice daily; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete response; DOR, duration of response; FFS, failure-free survival; GI, gastrointestinal; IS, immunosuppressants; MAGIC, Mount Sinai Acute GVHD International Consortium; MR, malignancy relapse; NR, no response; NRM, nonrelapse mortality; ORR, overall response rate; OS, overall survival; PD, progressive disease; PK, pharmacokinetics; PR, partial response; VGPR, very good partial response.

1. Jagasia M, et al. *Blood*. 2020;135:1739-1749. 2. Incyte Corporation. News release. Accessed Oct 2021. https://investor.incyte.com/press-releases/press-releases/2019/FDA-Approves-Jakafi-ruxolitinib-for-the-Treatment-of-Patients-with-Acute-Graft-Versus-Host-Disease/default.aspx.

REACH1: Baseline Characteristics

Patients With GVHD Refractory to Steroids Alone (n=49)

Characteristic[1]	Refractory to steroids alone (n=49)
Median age, y (range)	57 (18-72)
Male, %	47
Ethnicity: Hispanic, %	14
Race: Caucasian, %	92
aGVHD grade, %	
II	27
III	55
IV	18
Visceral GVHD, %	84
Graft source, n (%)[2]	
Bone marrow	9 (18)
PBSCs	39 (80)
Cord blood	1 (2)

Click for REACH1 Dosing

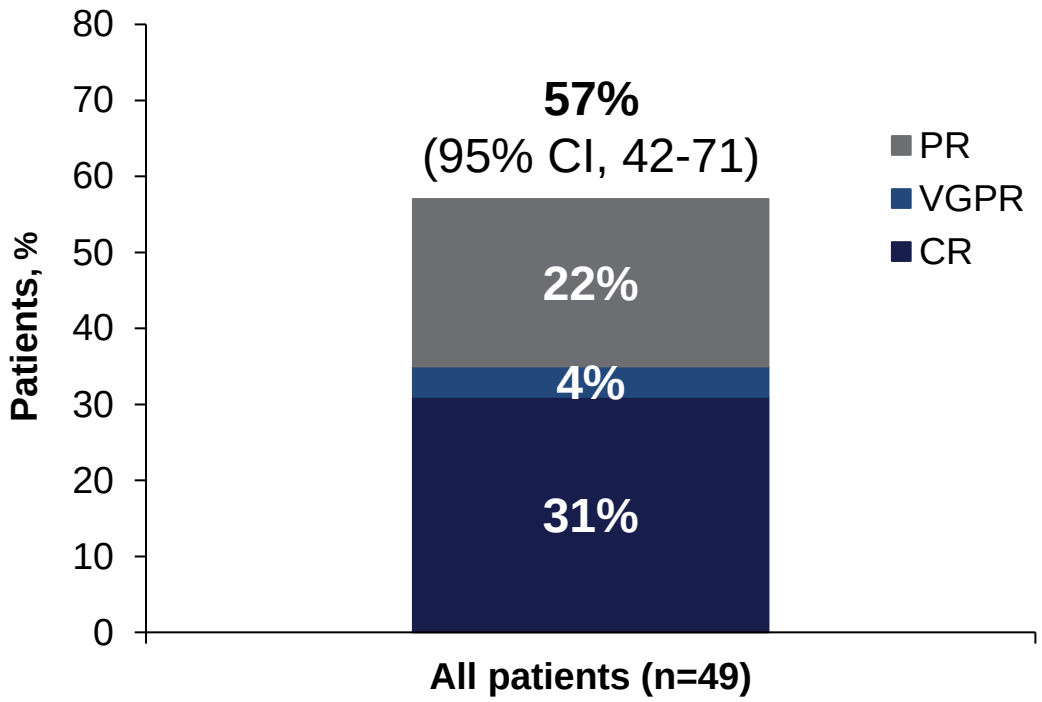
Click for REACH1 Baseline Characteristics: Patients With SR-GVHD

PBSC, peripheral blood stem cell; y, years.

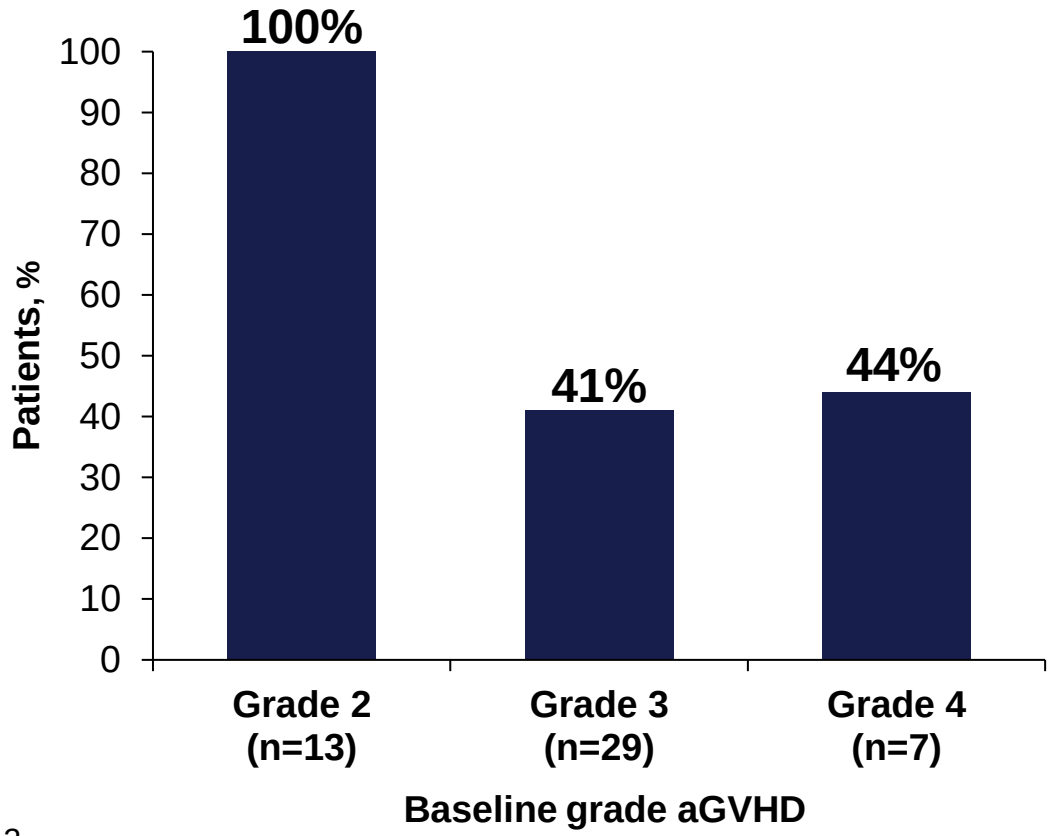
1. Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation. 2. Data on file, Incyte Corporation.

REACH1: ORR at Day 28 (n=49)

Primary Endpoint: ORR at Day 28[1]



Subgroup Analysis: ORR at Day 28 by Baseline aGVHD Grade[1]



- Among day 28 responders, 54% (15/28) achieved a CR[2]

Click for REACH1 Efficacy Data by Ruxolitinib Dose

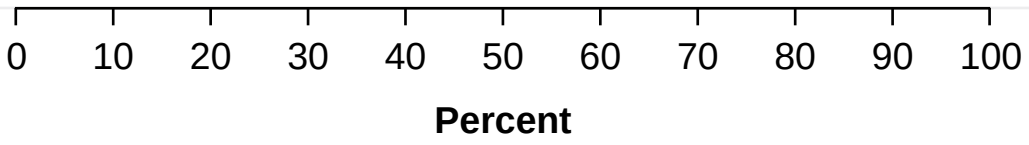
CI, confidence interval.

1. Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation. 2. Data on file, Incyte Corporation.

REACH1: ORR at Day 28 by Organ Involvement (n=49)

Subgroup Analysis

Subgroup	Number of Patients	ORR at Day 28 (95% CI)
All patients	**49**	**57 (42, 71)**
1 organ involved	22	73 (50, 89)
≥2 organs involved	27	44 (26, 65)
Liver, stage 1-4	11	27 (6, 61)
Upper GI, stage 1	16	31 (11, 59)
Lower GI, stage 1-4	36	50 (33, 67)
Skin, stage 1-4	26	62 (41, 80)



Data on file, Incyte Corporation.

REACH1: Duration of Response (n=49)

Secondary Endpoint

The median DOR was calculated using 2 methods, which define disease progression differently:

- **Method 1** – calculated from day 28 until: 1) need for new aGVHD treatment, *or* 2) death, *or* 3) worsening in any organ by one stage compared to prior response assessment (disease progression)
  - Median DOR: **16 days** (95% CI: 9, 83)
- **Method 2** – calculated from day 28 until: 1) need for new aGVHD treatment, *or* 2) death, *or* 3) increase in steroid dose from baseline (disease progression)
  - Median DOR: **173 days** (95% CI: 66, NE)

	Start of DOR assessment	Events for end of DOR				Median DOR (95% CI)
	Day 28 response	Death	Salvage therapy for aGVHD	Change in organ stage[a]	Increase in steroid dose[b]	
Method 1	✓	✓	✓	✓		16 days (9, 83)
Method 2	✓	✓	✓		✓	173 days (66, NE)

[a] Progression was defined as worsening by 1 stage in any organ without improvement in other organs in comparison to prior response assessment. [b] Increase from baseline dose.
NE, not established.
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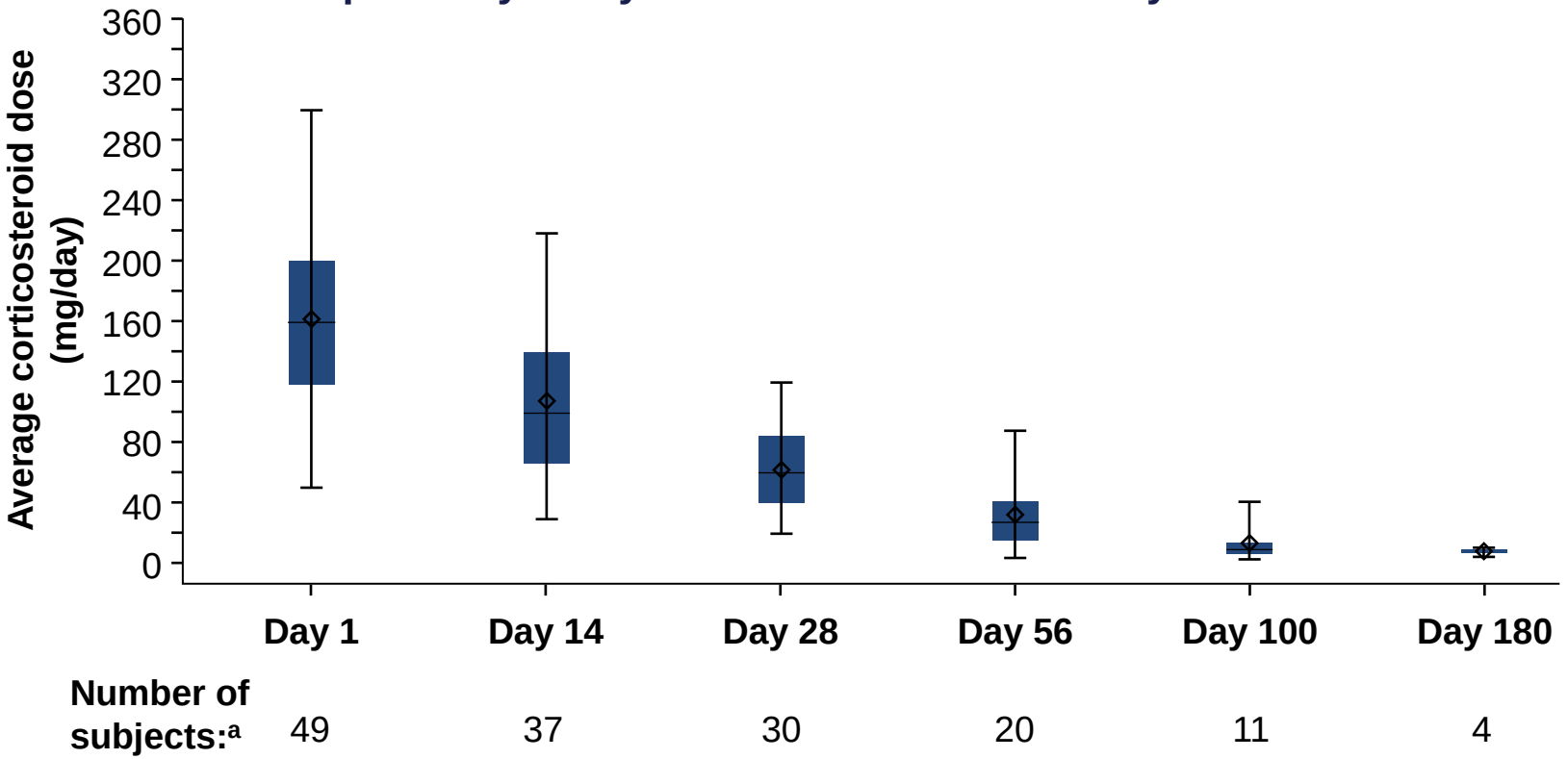
REACH1: Efficacy Data

Exploratory Analysis: Reduction in On-Study Steroid Dose

- 47% of patients remaining on ruxolitinib were able to reduce their steroid dose by ≥50% at day 28[1]

Exploratory Analysis: Reduction in On-Study Steroid Dose[2]



Patients Who Reduced Steroid Dose ≥50%[2,b]	
Day	**n/N (%)**
Day 14	6/37 (16%)
Day 28	14/30 (47%)
Day 56	18/20 (90%)
Day 100	11/11 (100%)

[a] For days 14, 28, 56, 100, and 180, average CS dose (mg/day) = total CS dose (mg) for the week ending on the specified study day 7[2]. CS dose (mg) = methylprednisolone dose (mg)×1.25 + prednisone dose (mg)[2]. [b] Percentage of patients still receiving Jakafi and CS who had a ≥50% decrease in CS dose relative to initial dose.[2]
CS, corticosteroid.

1. Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation. 2. Data on file, Incyte Corporation.

REACH1: Nonhematologic Adverse Reactions Occurring in ≥15% of Patients[a]

Infections:[b] site-/organ-specific (eg, urinary tract, lung)

Bacterial infections: organism-specific (eg, *clostridium difficile*)

Viral infections: organism-specific (eg, CMV, BK virus)

	Ruxolitinib (N=71)	
Adverse Reactions, %	**All Grades[c]**	**Grade 3-4**
Infections	55	41
Edema	51	13
Hemorrhage	49	20
Fatigue	37	14
Bacterial infections	32	28
Dyspnea	32	7
Viral infections	31	14
Thrombosis	25	11
Diarrhea	24	7
Rash	23	3
Headache	21	4
Hypertension	20	13
Dizziness	16	0

- There were no fatal adverse reactions to ruxolitinib treatment
- Adverse reactions resulting in treatment discontinuation occurred in 31% of patients
  - The most common adverse reaction leading to treatment discontinuation was infection (10%)

[a] At the time of the 3-month data cutoff. [b] Fungal infections occurred in fewer than 15% of patients and are not listed in this table. [c] National Cancer Institute CTCAE, version 4.03.
CMV, cytomegalovirus; CTCAE, Common Terminology Criteria for Adverse Events.
Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

REACH1: Selected Laboratory Abnormalities Worsening From Baseline

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

[a] National Cancer Institute CTCAE, version 4.03.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

REACH1: Data Summary

- In the single-cohort, open-label REACH1 study, 71 patients with aGVHD were treated with ruxolitinib
  - Median duration of treatment with ruxolitinib was 46 days (range, 4-382 days)
  - In total, 49 patients were refractory to corticosteroids alone
- Efficacy for patients refractory to steroids alone (n=49):
  - 57% of patients achieved an overall response at day 28[a]
  - Median duration of response[b] was 16 days (95% CI, 9-83)
  - Median time from day 28 response to death or need for new therapy for aGVHD was 173 days (95% CI, 66-NE)
  - 47% of patients remaining on ruxolitinib were able to reduce their steroid dose by ≥50% at day 28
- Safety (N=71)
  - The most frequent nonhematologic adverse reactions were infections and edema (incidence >50%)
  - Treatment discontinuation due to adverse reactions occurred in 31% of patients
    - The most common adverse reaction leading to treatment discontinuation was infection (10%)
  - Anemia, thrombocytopenia, and neutropenia were the most common hematologic adverse reactions (incidence >50%)

[a] Patients with response at day 28±2 days on/prior to start of new anti-GVHD therapy. [b] Day 28 response to progression, new salvage therapy for aGVHD, or death from any cause.

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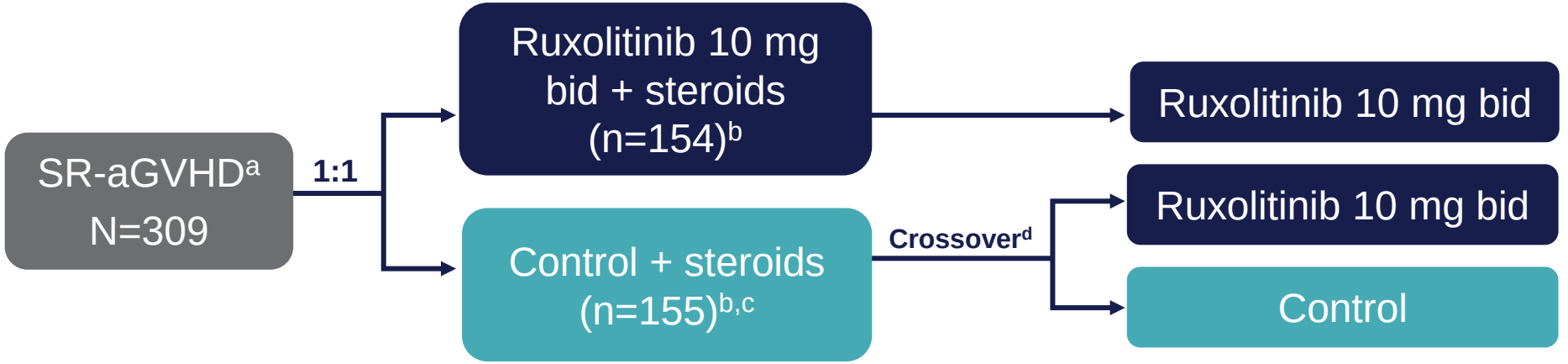
REACH2: Phase 3, Open-Label, Randomized Study of Ruxolitinib vs Control in SR-aGVHD[1]



Control[2,c]
ECP (27%)
MMF (17%)
Etanercept (15%)
ATG (13%)
Infliximab (11%)
MSC (10%)
Low-dose MTX (3%)
Sirolimus (2%)
Everolimus (1%)

Primary endpoint

- ORR (CR + PR) at day 28

Secondary endpoints

- Key secondary: durable ORR at Day 56
- Duration of response
- FFS
- Overall survival
- Disease relapse
- Non-relapse mortality
- Cumulative steroid use
- Safety

REACH2 is not included in the Jakafi prescribing information.

[a] Randomization occurred according to baseline aGVHD grade. [b] Standard supportive therapy (including growth factors, anti-infective medication, transfusion support, and other standard supportive care measures) was allowed in both treatment groups in addition to the continued use of calcineurin inhibitors and glucocorticoids. [c] Control was chosen by the investigator at the time of randomization. [d] Crossover to ruxolitinib therapy was permitted if patients did not have a response at day 28 or if they had a loss of response and received additional systemic therapy and did not have signs of cGVHD.

ATG, antithymocyte globulin; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; MSC, mesenchymal stromal cells; MTX, methotrexate.

1. Zeiser R, et al. *N Engl J Med*. 2020;382:1800-1810. 2. Data on File. Incyte Corporation.

REACH2: Key Eligibility Criteria

Steroid refractory[a] defined as:

- Progressive disease after 3 days of primary treatment, or
- No response after 7 days of primary treatment, or
- Treatment failure during primary treatment taper or inability to taper

Inclusion criteria

- Age ≥12 years
- Recipients of allo-HSCT
- Grade 2-4 SR-aGVHD

Exclusion criteria

- Disease relapse
- Active, uncontrolled infection
- Previously received more than one treatment for SR-aGVHD
- Previously received JAKi therapy for any indication after initiation of allo-HSCT conditioning

[a] High-dose systemic glucocorticoid therapy with or without calcineurin inhibitors.

Zeiser R, et al. *N Engl J Med*. 2020;382:1800-1810.

REACH2: Baseline Characteristics

Characteristic[a]	Ruxolitinib 10 mg bid (n=154)	Control (n=155)
Median age, y (range)	52.5 (12-73)	54.0 (13-71)
Male, n (%)	92 (60)	91 (59)
Race: Caucasian, n (%)	111 (72)	102 (66)
aGVHD grade, n (%)		
II	50 (32.5)	54 (34.8)
III	68 (44.2)	68 (43.9)
IV	30 (19.5)	32 (20.6)
SR criteria, n (%)		
Progression after 3 days	35 (22.7)	43 (27.7)
Response failure after 7 days	72 (46.8)	63 (40.6)
Failure to steroid taper	47 (30.5)	49 (31.6)

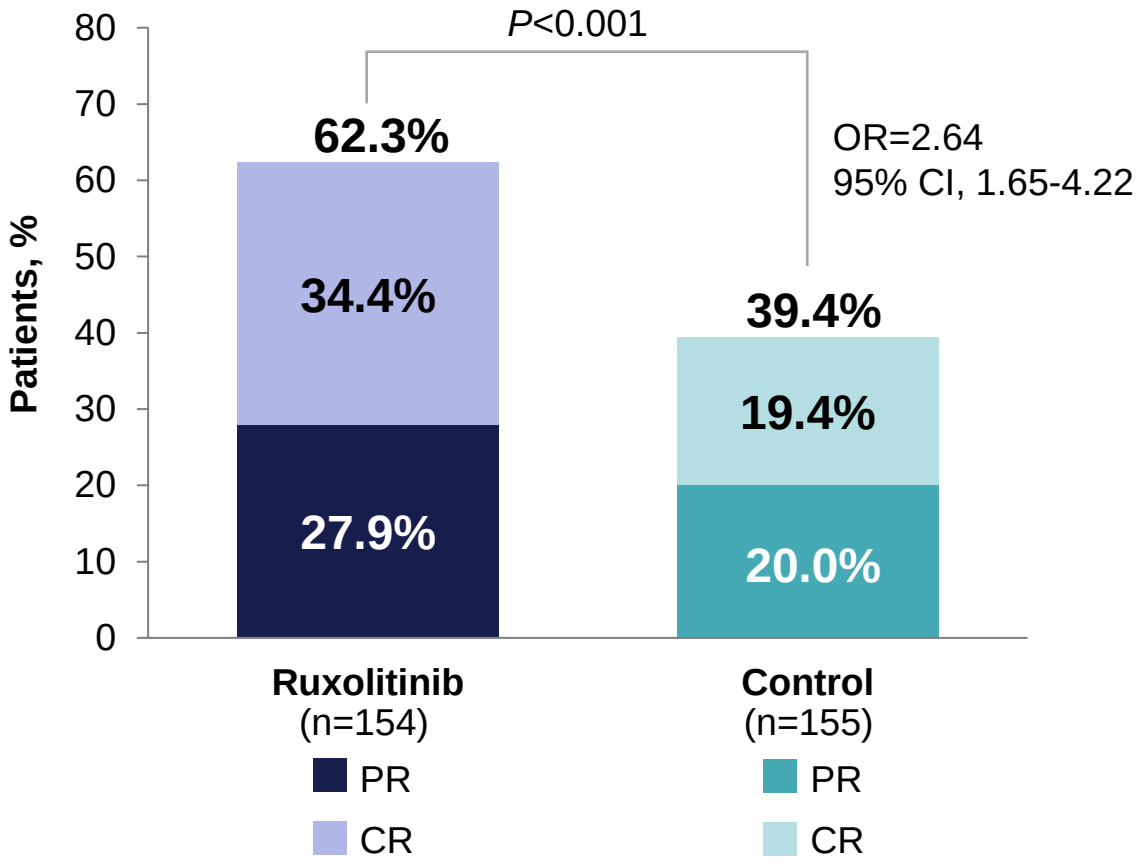
[a] Baseline characteristics were well balanced between the 2 groups.
SR, steroid refractory.
Zeiser R, et al. *N Engl J Med*. 2020;382:1800-1810.

REACH2: Baseline Characteristics

Characteristic	Ruxolitinib 10 mg bid (n=154)	Control (n=155)
Primary malignancy, n (%)		
Acute leukemia/MDS[a]	113 (73.4)	111 (71.6)
Non-Hodgkin lymphoma	9 (5.8)	19 (12.3)
Hodgkin lymphoma	6 (3.9)	2 (1.3)
Other[b]	19 (12.3)	15 (9.7)
Stem cell type, n (%)		
PBSCs	134 (87.0)	118 (76.1)
Bone marrow	19 (12.3)	30 (19.4)
Single cord blood	1 (0.6)	7 (4.5)

[a] Includes acute lymphoblastic leukemia, acute myelogenous leukemia, MDS, and other acute leukemias. [b] Includes chronic myelogenous leukemia, excess blasts from Fanconi syndrome, multiple myeloma, and other leukemias/malignant disease.
MDS, myelodysplastic syndrome.
Zeiser R, et al. *N Engl J Med*. 2020;382:1800-1810.

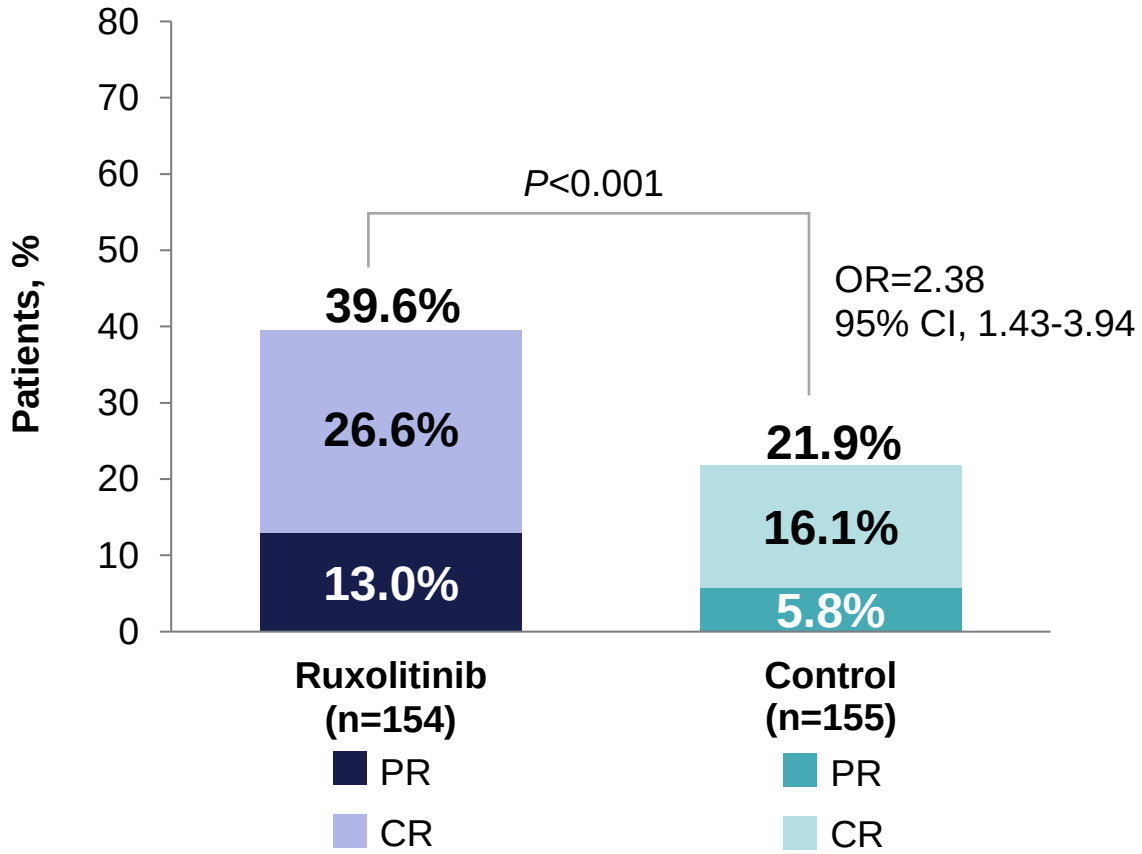
REACH2 Primary Endpoint: ORR at Day 28



OR, odds ratio.

Zeiser R, et al. *N Engl J Med*. 2020;382:1800-1810.

REACH 2 Key Secondary Endpoint: Durable Overall Response at Day 56



Discontinued steroids by day 56

21% of patients (n=32) receiving ruxolitinib

14% of patients (n=21) receiving control

[a] Patients who responded at day 28 and maintained response at day 56.

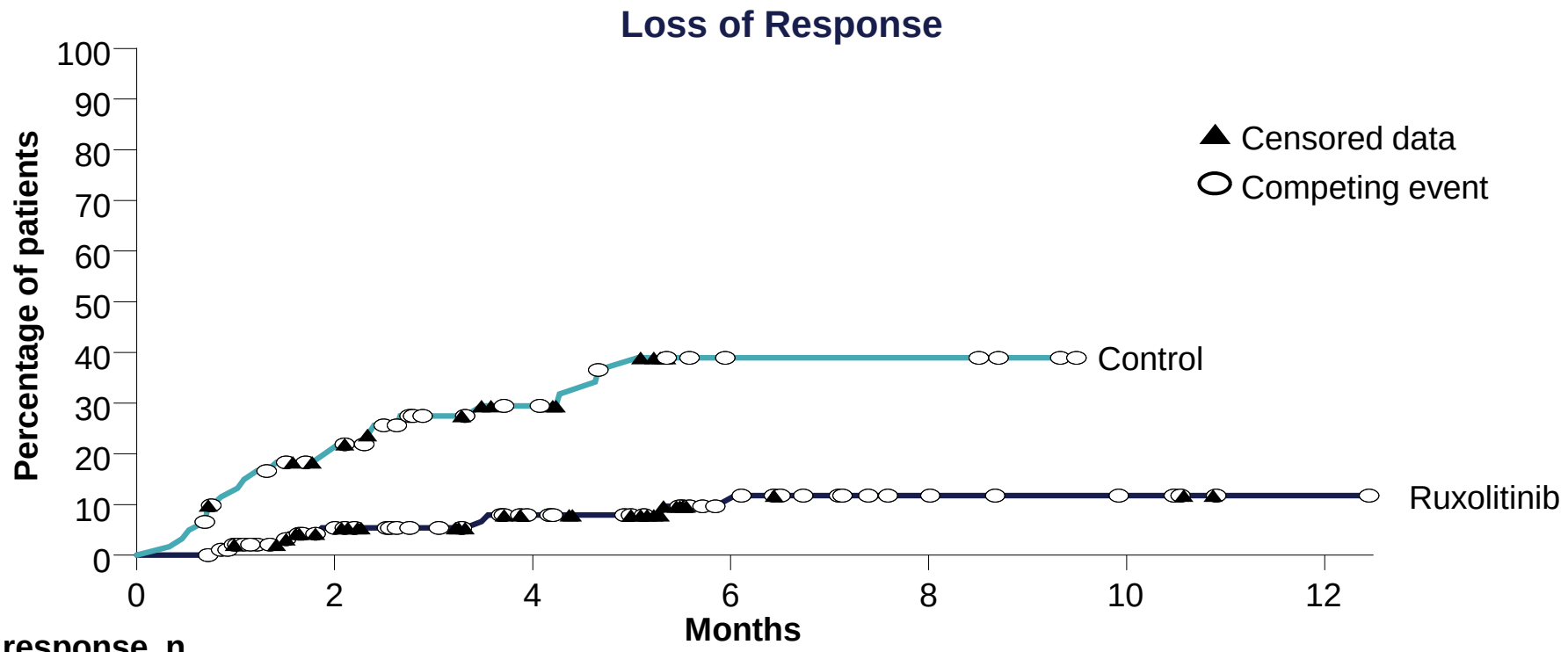
Zeiser R, et al. *N Engl J Med*. 2020;382:1800-1810.

REACH2: DOR With Ruxolitinib Compared With Control

Estimated cumulative incidence of loss of response at 6 months

10% with ruxolitinib (95% CI, 4-17)

39% with control (95% CI, 26-52)

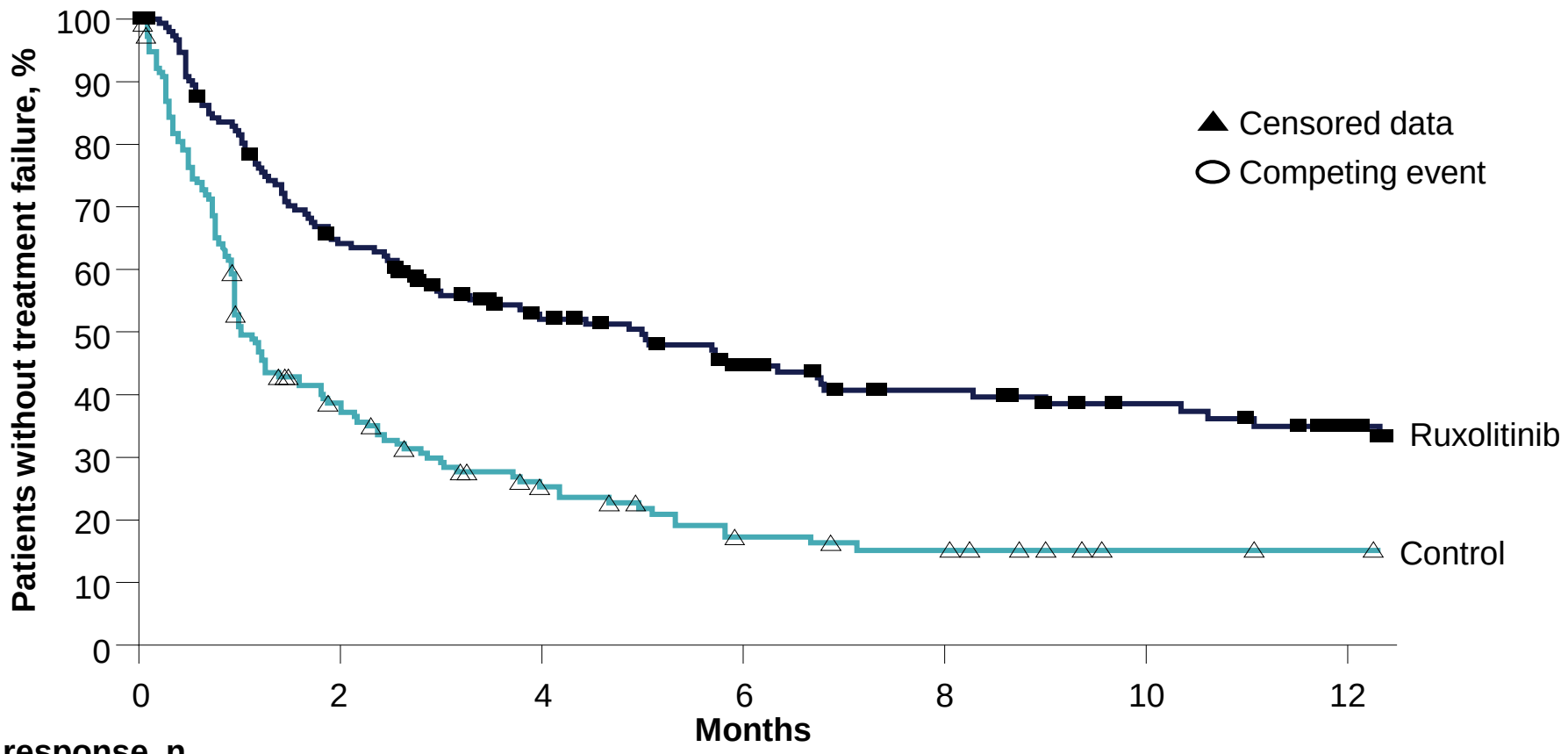


Patients with response, n							
Ruxolitinib	96	71	47	20	10	7	2
Control	61	40	21	4	4	0	0
Cumulative number of competing events							
Ruxolitinib	0	13	26	37	45	48	51
Control	0	5	14	19	19	23	—

Zeiser R, et al. *N Engl J Med*. 2020;382:1800-1810.

REACH2: Median FFS With Ruxolitinib Compared With Control

Median FFS[a]
5 months with ruxolitinib
1 month with control
(HR, 0.46; 95% CI, 0.35-0.60)



Patients with response, n

Ruxolitinib	154	95	67	50	39	32	23
Control	155	54	30	18	15	9	8

[a] Relapse or progression of hematologic disease, non–relapse-related death, or addition of new systemic therapy for aGVHD.
HR, hazard ratio.
Zeiser R, et al. *N Engl J Med*. 2020;382:1800-1810.

REACH2: AEs Occurring in ≥12% of Patients Up to Day 28 (Safety Population)

AE, n (%)	Ruxolitinib (n=152)		Control (n=150)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Thrombocytopenia	50 (33)	41 (27)	27 (18)	23 (15)
Anemia	46 (30)	33 (22)	42 (28)	28 (19)
CMV[a]	39 (26)	11 (7)	31 (21)	12 (8)
Peripheral edema	28 (18)	2 (1)	26 (17)	1 (1)
Platelet count decreased	26 (17)	22 (14)	21 (14)	20 (13)
Neutropenia	24 (16)	20 (13)	19 (13)	14 (9)
Hypokalemia	20 (13)	9 (6)	25 (17)	9 (6)
Hypomagnesemia	15 (10)	0	20 (13)	1 (1)

- Serious AEs occurred in 57 patients (38%) receiving ruxolitinib and in 51 (34%) receiving control
- AEs led to treatment discontinuation in 17 patients (11%) receiving ruxolitinib and 7 (5%) receiving control

[a] A distinction between CMV infection and reactivation was not made in this study.
AE, adverse event.
Zeiser R, et al. *N Engl J Med*. 2020;382:1800-1810.

REACH2: Rate of Infection Up to Day 28 (Safety Population)

Infection, n (%)	Ruxolitinib (n=152)[a]		Control (n=150)[b]	
	Any Grade	Grade 3	Any Grade	Grade 3
Number of patients with at least 1 event	93 (61.2)	34 (22.4)	82 (54.7)	28 (18.7)
Fungal infections	13 (8.6)	7 (4.6)	6 (4.0)	3 (2.0)
Viral infections	65 (42.8)	13 (8.6)	50 (33.3)	12 (8.0)
Bacterial infections	45 (29.6)	18 (11.8)	48 (32.0)	13 (8.7)

[a] In the ruxolitinib group, there were also 13 infections categorized as “unknown” (grade 3: 4) and 4 categorized as “other” (grade 3: 0). [b] In the Control group, there were also 8 infections categorized as “unknown” (grade 3: 4) and 1 as “other” (grade 3: 0).

Zeiser R, et al. *N Engl J Med*. 2020;382:1800-1810.

REACH2: Causes of Death

Mortality, n (%)	Ruxolitinib 10 mg bid (n=154)	Control (n=155)
Death at data cutoff	**72 (47)**	**77 (51)**
Attributed to aGVHD	34 (22)	37 (25)
Disease progression		
Neoplasms	8 (5)	8 (5)
Multiple organ dysfunction syndrome	3 (2)	1 (1)
Sepsis	4 (3)	3 (2)
Septic shock	3 (2)	3 (2)

Zeiser R, et al. *N Engl J Med*. 2020;382:1800-1810.

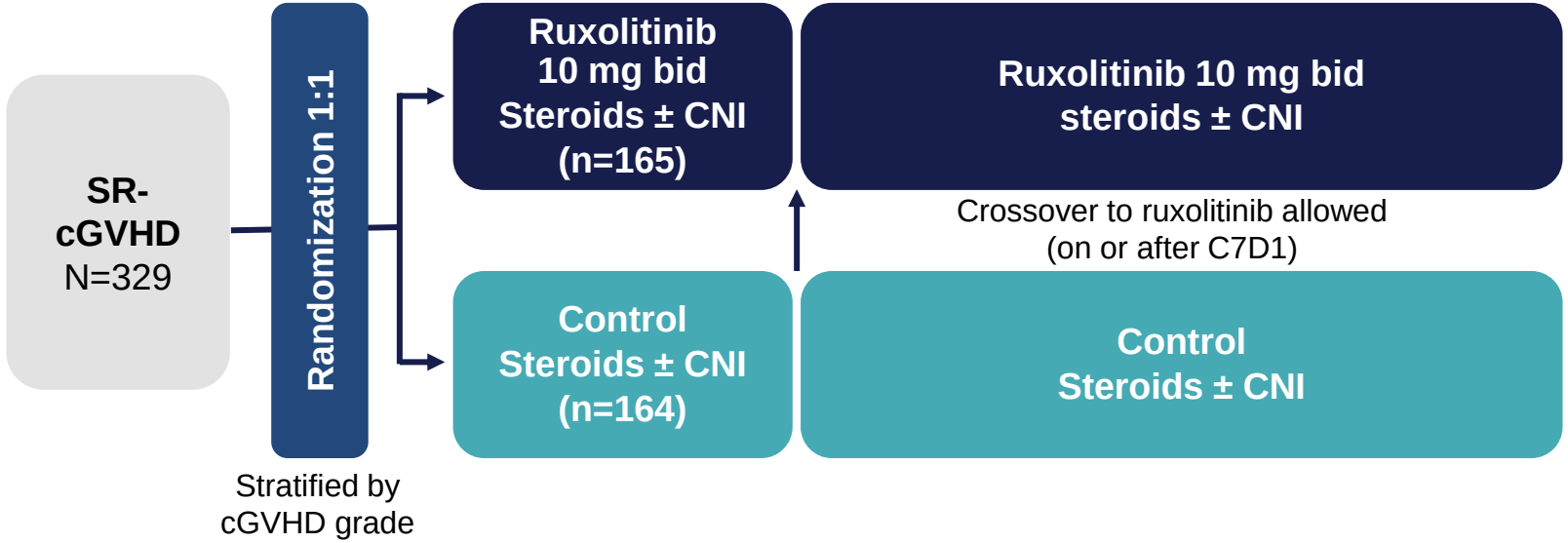
REACH2 Summary

- Among patients with grade 2 to 4 SR-aGVHD, ruxolitinib was associated with a significantly higher ORR at day 28 compared with control (62.3% vs 39.4%, respectively; *P*<0.001)
  - Ruxolitinib was also associated with a greater DOR at day 56 when compared with control (39.6% vs 21.9%, respectively; *P*<0.001)
  - DOR and FFS were both longer with ruxolitinib than with control
- The most common AEs up to day 28 were thrombocytopenia, anemia, and CMV
- Rate of infection was similar between ruxolitinib and control, with infection of grade 3 severity occurring in 22% and 19% of patients, respectively
- In both groups, the main causes of death were related to progression of either aGVHD or relapse of primary disease

Zeiser R, et al. *N Engl J Med*. 2020;382:1800-1810.

cGVHD: Ruxolitinib Efficacy and Safety

REACH3: Phase 3, Open-Label, Randomized Study of Ruxolitinib vs Control in SR-cGVHD



Control
ECP (35%)
MMF (22%)
Ibrutinib (17%)
MTX (6%)
Imatinib (5%)
Sirolimus (4%)
Rituximab (4%)
Everolimus (3%)
Infliximab (3%)
Pentostatin (0%)

Primary endpoint
- ORR (CR + PR) at week 24 (C7D1)

Key secondary endpoints
- FFS
- mLSS response

Secondary and exploratory endpoints
- Subgroup OR
- Individual organ response
- NRM
- BOR
- DOR
- QOL
- CS reduction
- Safety

BOR, best overall response; CNI, calcineurin inhibitor; C7D1, cycle 7, day 1; mLSS, modified Lee Symptom Scale; QOL, quality of life.

Zeiser R, et al. *N Engl J Med.* 2021;385:228-238.

REACH3: Key Eligibility Criteria

Steroid-refractory or -dependent cGVHD defined per 2014 NIH consensus criteria[1,2]

- Lack of response or disease progression after prednisone[a] ≥1 mg/kg/day for ≥1 week, or
- Disease persistence without improvement despite continued treatment with prednisone at >0.5 mg/kg/day or 1 mg/kg/every other day for ≥4 weeks, or
- Increase in prednisone dose to >0.25 mg/kg/day after 2 unsuccessful attempts to taper the dose

Inclusion criteria[1]

- Age ≥12 years
- Recipients of allogeneic stem cell transplantation
- Moderate or severe glucocorticoid-refractory or -dependent cGVHD
- Previous treatment with JAKi therapy for aGVHD if treatment had resulted in CR or PR and if they had discontinued JAKi treatment ≤8 weeks before receiving the first dose of ruxolitinib or control therapy
- Evident myeloid and platelet engraftment[b]

Exclusion criteria[1]

- Previous treatment with ≥2 systemic therapies for cGVHD in addition to glucocorticoids, with or without calcineurin inhibitors
- Relapse of the primary cancer
- Graft loss within 6 months before treatment initiation
- Active, uncontrolled infection

[a] Or prednisone equivalent. [b] ANC>1,000/mm^3 and platelet count ≥25,000/mm^3.
ANC, absolute neutrophil count; NIH, National Institutes of Health.
1. Zeiser R, et al. *N Engl J Med.* 2021;385:228-238. 2. Martin PJ, et al. *Biol Blood Marrow Transplant.* 2015;21:1343-1359.

REACH3: Baseline Demographics

Characteristic	Ruxolitinib n=165	Control n=164
Median age, (range), y	49 (13-73)	50 (12-76)
Age 12 to <18 y, n (%)	4 (2)	8 (5)
Age >65 y, n (%)	18 (11)	22 (13)
Male, n (%)	109 (66)	92 (56)
Race, n (%)		
White	116 (70)	132 (81)
Black	2 (1)	0
Asian	33 (20)	21 (13)
Other	9 (5.5)	4 (2.4)
Unknown	3 (1.8)	7 (4.3)
Primary malignancy, n (%)		
Leukemia/MDS	121 (73.3)	122 (74.4)
Lymphoma (Hodgkin/NHL)	26 (15.8)	33 (20.1)
Myeloproliferative neoplasm	9 (5.5)	5 (3)
Nonmalignant disease	8 (4.8)	2 (1.2)
Other	1 (0.6)	2 (1.2)

NHL, non-Hodgkin lymphoma.

Zeiser R, et al. *N Engl J Med.* 2021;385:228-238.

REACH3: Transplant Characteristics

Characteristic	Ruxolitinib n=165	Control n=164
Stem cell source, n (%)		
Peripheral blood	141 (85.5)	131 (79.9)
Bone marrow	22 (13.3)	31 (18.9)
Single cord blood	2 (1.2)	2 (1.2)
Donor type, n (%)[a]		
Related	91 (54.5)	87 (52.1)
Unrelated	76 (45.5)	80 (47.9)
Prior aGVHD, n (%)		
Any	92 (55.8)	88 (53.7)
Grade I	25 (15.2)	30 (18.3)
Grade II	53 (32.1)	43 (26.2)
Grade III	14 (8.5)	12 (7.3)
Grade IV	0	3 (1.8)
SR-aGVHD	18 (10.9)	17 (10.4)

[a] Some patients underwent more than 1 transplant.

Zeiser R, et al. *N Engl J Med.* 2021;385:228-238.

REACH3: GVHD Characteristics

Characteristic	Ruxolitinib n=165	Control n=164
Median (range) corticosteroid dose at baseline (PE mg/kg)[1,a]	0.29 (0.01-1.81)	0.26 (0.06-1.21)
Prior therapy[1]		
Failed first-line steroids alone	115 (70)	125 (76)
Failed first-line combination including steroids	42 (25)	30 (18)
Failed 2 lines of therapy	6 (4)	8 (5)
No prior treatment for cGVHD	2 (1)	1 (1)
Refractory/dependent criteria[2], n (%)		
No response or disease progression after steroids[b]	62 (37.6)	73 (44.5)
Disease persistence despite continued treatment with steroids[c]	58 (35.2)	42 (25.6)
Prednisone dose increase after 2 unsuccessful taper attempts[d]	45 (27.3)	49 (29.9)

[a] PE milligrams/kilogram. [b] Lack of response or disease progression after prednisone ≥1 mg/kg/day for ≥1 week. [c] Disease persistence without improvement despite continued treatment with prednisone at >0.5 mg/kg/day or 1 mg/kg/every other day for ≥4 weeks. [d] Increase in prednisone dose to >0.25 mg/kg/day after 2 unsuccessful attempts to taper the dose.
PE, prednisone equivalent.

1. Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation. 2. Zeiser R, et al. *N Engl J Med.* 2021;385:228-238.

REACH3: Disease Characteristics

Characteristic	Ruxolitinib n=165	Control n=164
Median time from transplant to randomization[1], (range), wk	69.4 (4.1-372.0)	63.21 (7.4-1427.7)
Median time from cGVHD onset to randomization[1], (range), wk	24.9 (1.0-288.1)	21.4 (1.4-278.1)
cGVHD severity at initial diagnosis[2], n (%)		
Mild	33 (20)	41 (25)
Moderate	77 (46.7)	77 (47)
Severe	53 (32.1)	45 (27.4)
Unknown	1 (0.6)	0
Missing	1 (0.6)	1 (0.6)
cGVHD severity at study entry, n (%) [1,a]		
Mild	1 (0.6)	1 (0.6)
Moderate	67 (40.6)	74 (45.15)
Severe	97 (58.8)	89 (54.3)
≥4 organs involved[3], n (%)	67 (41)	63 (38)
Median (range) mLSS score[1]	19 (0-80)	18 (1-54)

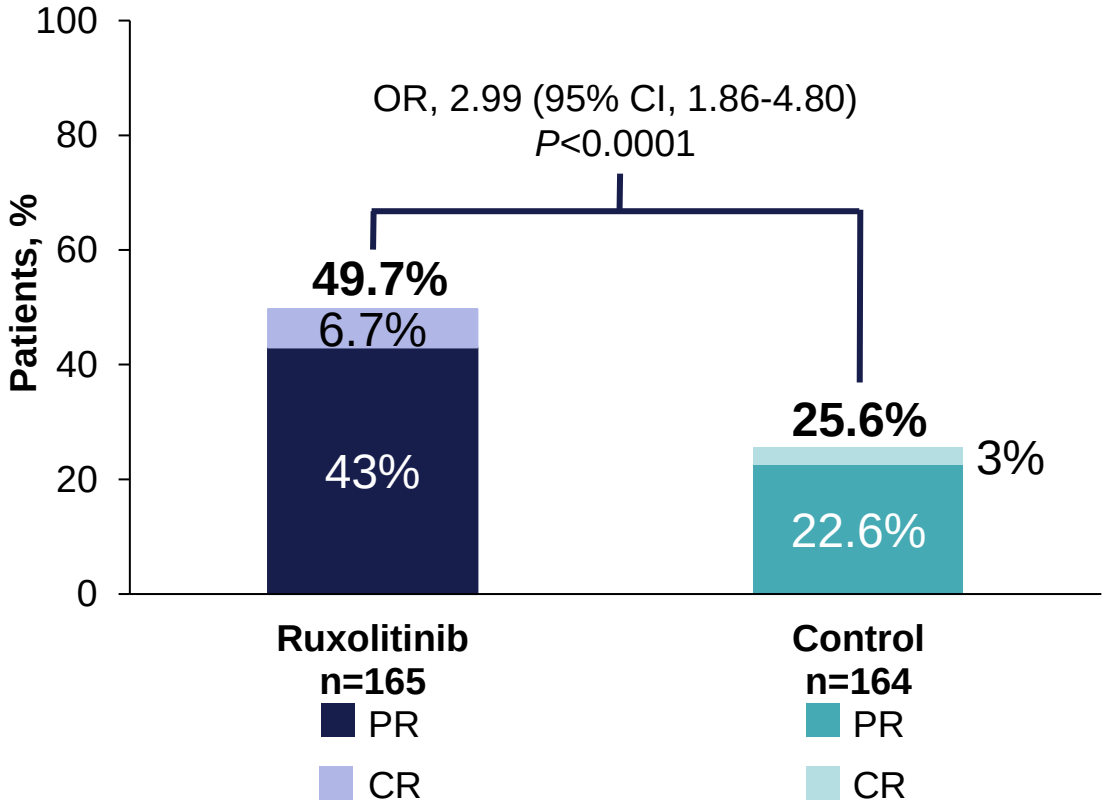
[a] Severity was graded according to NIH consensus staging criteria at screening. Enrollment of patients with mild glucocorticoid-refractory or -dependent cGVHD was considered a protocol deviation.[1,4]

wk, week.

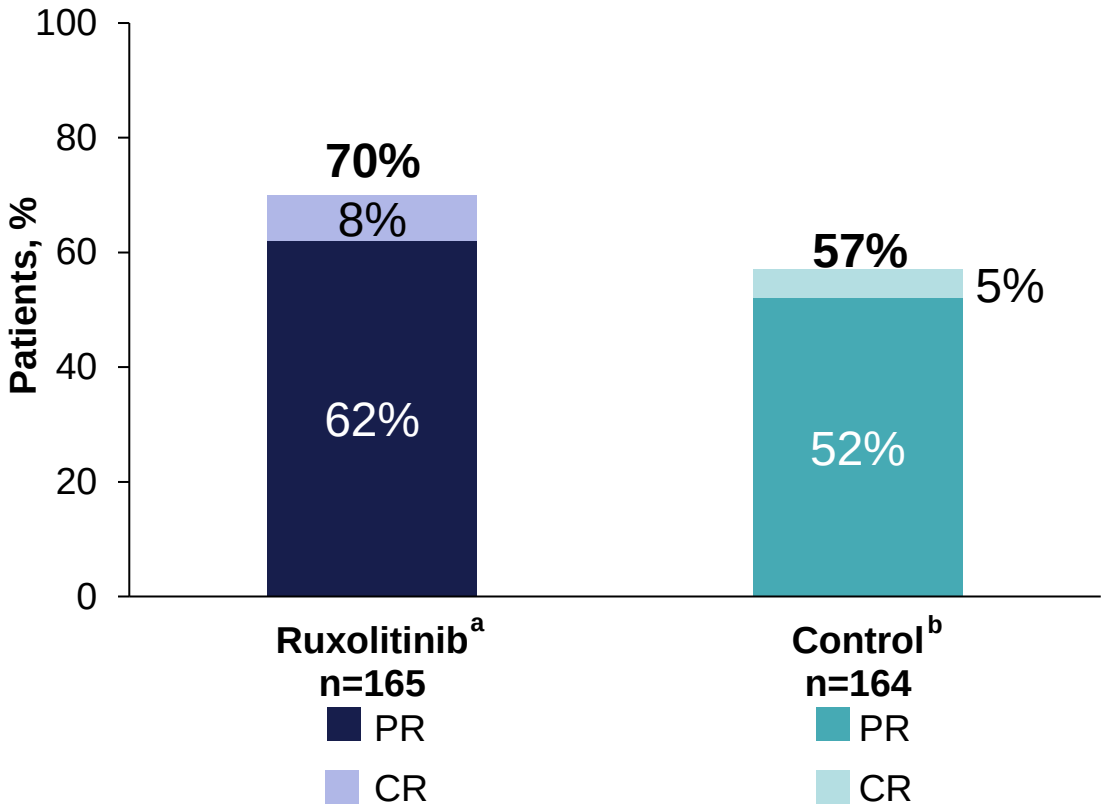
1. Zeiser R, et al. *N Engl J Med.* 2021;385:228-238. 2. Data on file, Incyte Corporation. 3. Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation. 4. Jagasia MH, et al. *Biol Blood Marrow Transplant*. 2015;21:389-401.e1.

REACH3 Primary Endpoint: ORR

ORR at Week 24[1]



ORR Through Week 24[2]



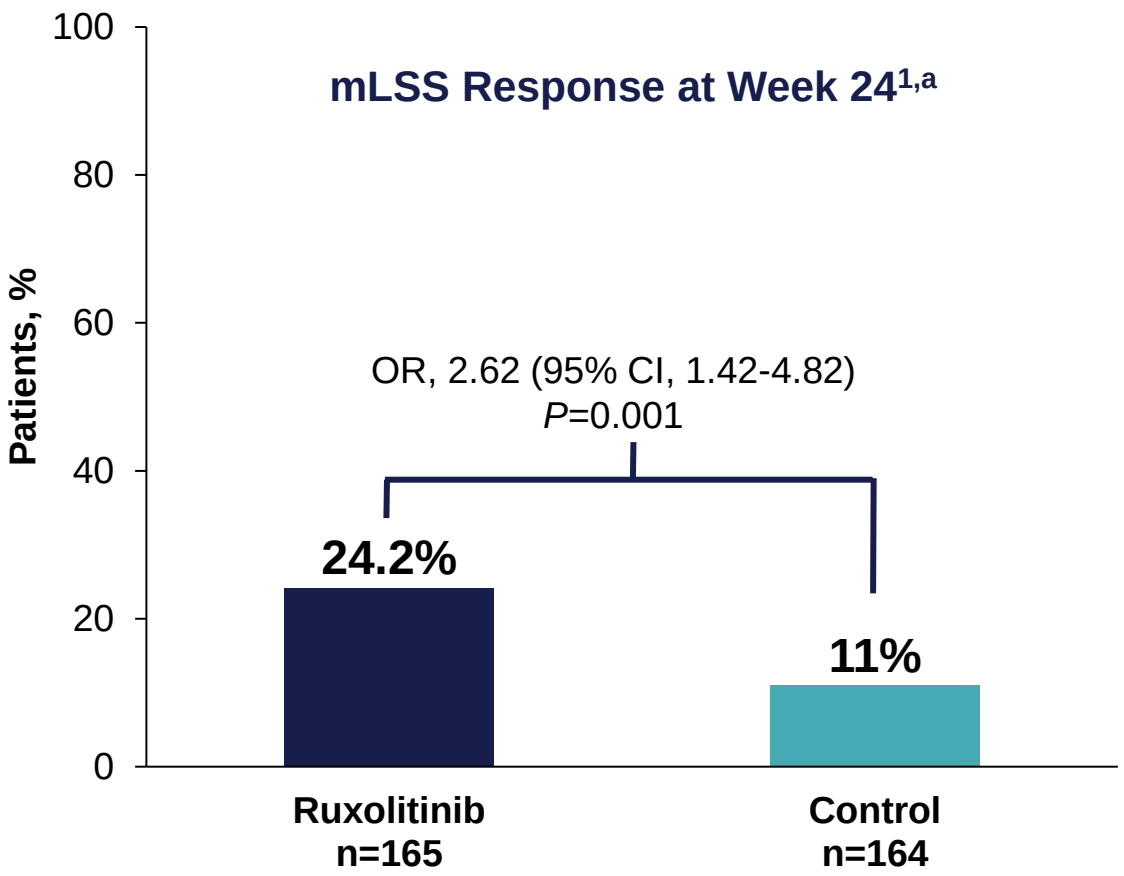
Median time to first response[2]

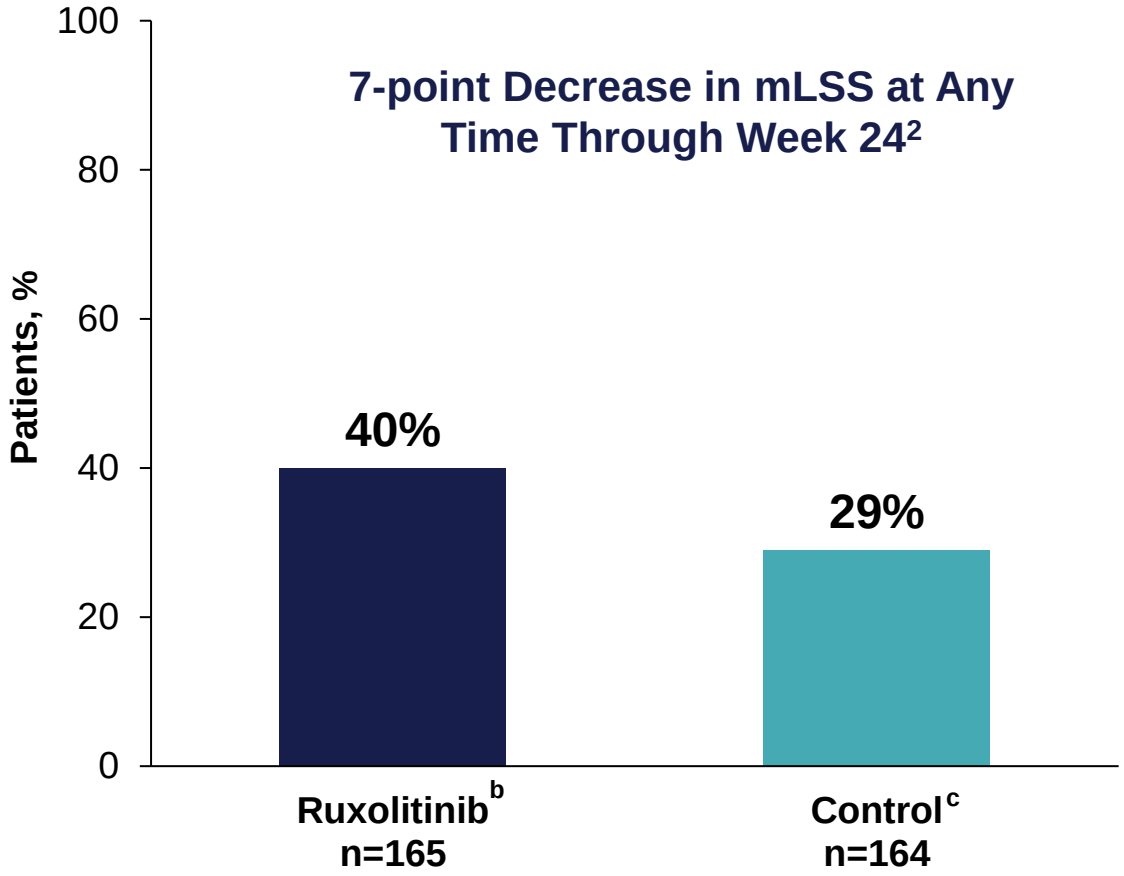
3 weeks (range, 2-24) with ruxolitinib
4 weeks (range, 2-25) with control

[a] 95% CI, 63-77%. [b] 95% CI, 49-65.

1. Zeiser R, et al. *N Engl J Med.* 2021;385:228-238. 2. Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

REACH3 Key Secondary Endpoint: mLSS Response

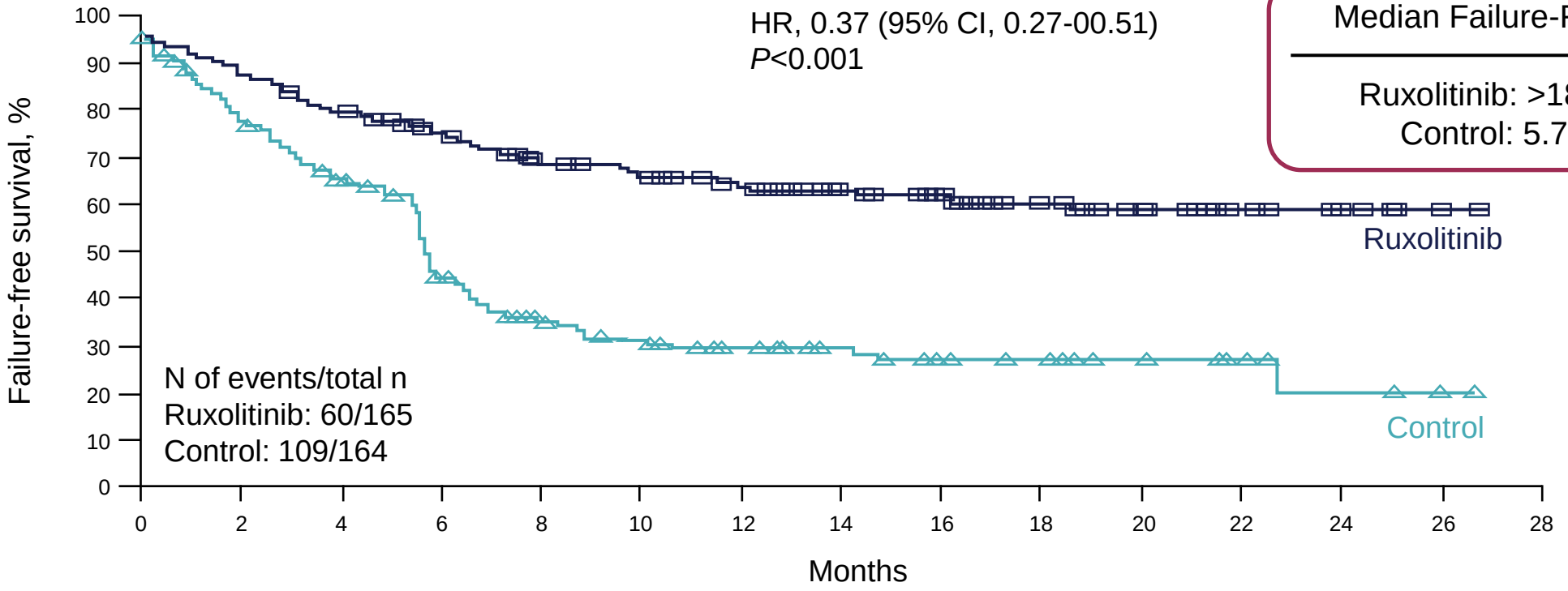




[a] mLSS defined as a ≥7-point reduction from baseline in total symptom score on the scale, which measures the symptoms of cGVHD on a scale of 0 to 100, with higher scores indicating worse symptoms. [b] 95% CI, 32-48. [c] 95% CI, 22-36.

1. Zeiser R, et al. *N Engl J Med.* 2021;385:228-238. 2. JAKAFI® (ruxolitinib). Prescribing Information. Incyte Corporation.

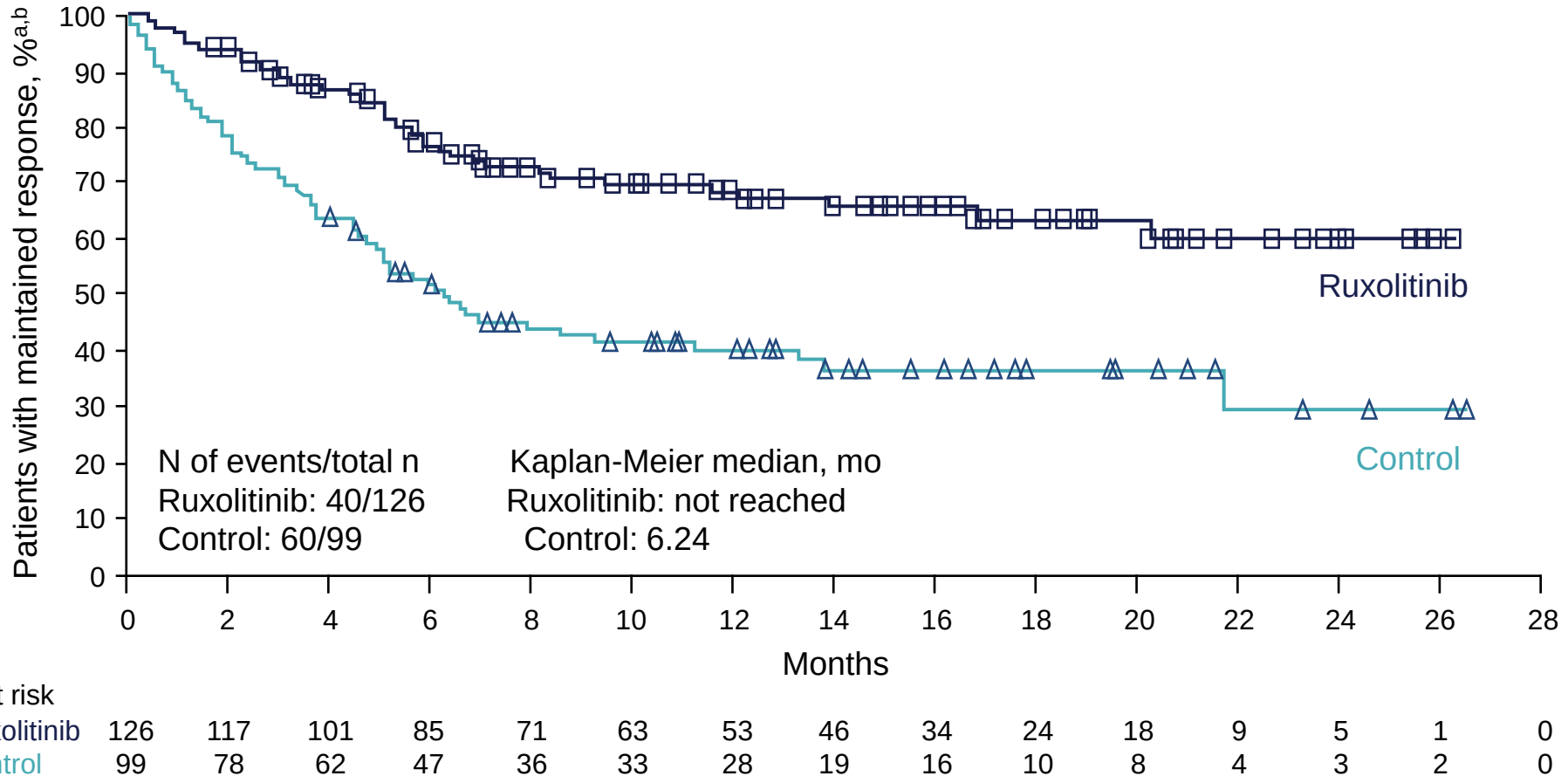
REACH3 Key Secondary Endpoint: FFS at Week 24



N at risk															
Ruxolitinib	165	145	130	115	92	87	76	58	49	37	27	15	9	4	0
Control	164	123	100	64	45	39	31	23	17	15	9	6	3	1	0

Zeiser R, et al. *N Engl J Med.* 2021;385:228-238.

REACH3: DOR[1,a,b]



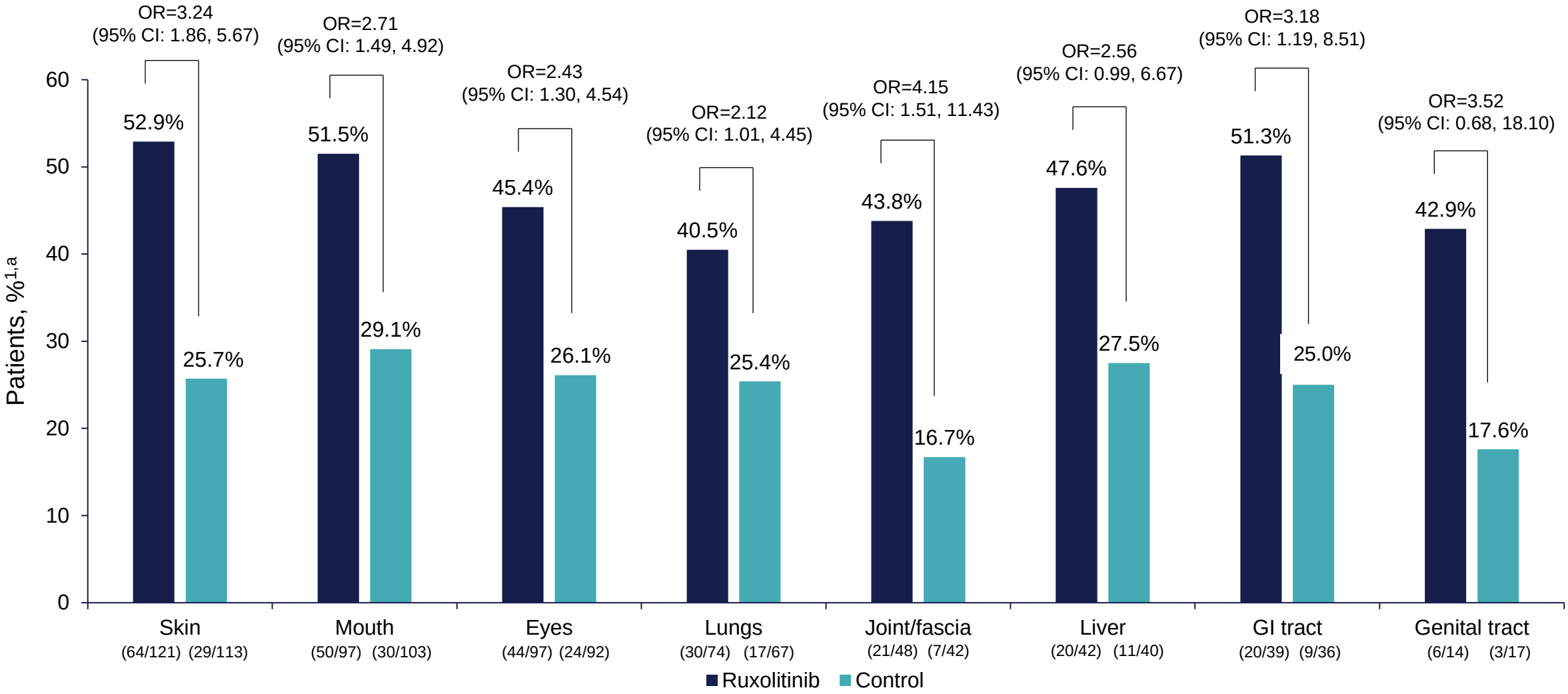
Median DOR[2,c]
4.2 months (95% CI, 3.2-6.7) with ruxolitinib
2.1 months (95% CI, 1.6-3.2) with control[2]

Median time from first response to death or new systemic therapies for cGVHD
25 months (95% CI, 16.8-NE) with ruxolitinib
5.6 months (95% CI, 4.1-7.8) with control[2]

[a] The comparisons for DOR are based on the subgroup of patients who had a CR or PR at any time up to week 24. [b] DOR to treatment was measured as the time from first documented CR or PR. [c] Median DOR was calculated from first response to progression, death, or new system therapies for cGVHD.

1. Zeiser R, et al. *N Engl J Med.* 2021;385:228-238. 2. JAKAFI® (ruxolitinib). Prescribing Information. Incyte Corporation.

REACH3: ORR by Organ Involvement



Patients with >1 affected organ were counted in each organ subgroup.

[a] Organ involvement defined as organ score ≥1 based on the cGVHD staging criteria.[2]

1. Zeiser R, et al. *N Engl J Med.* 2021;385:228-238. 2. Jagasia MH, et al. *Biol Blood Marrow Transplant.* 2015;21:389-401.e1.

REACH3: All Grade (≥10%) and Grades 3-5 (≥3%) Nonlaboratory Adverse Reactions up to Week 24

AE	Ruxolitinib n=165		Control n=158	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grades ≥3 (%)
Infections and infestations				
Infection (pathogen not specified)	45	15	44	16
Viral infection	28	5	23	5
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	18	1	13	0
General disorders and administration site conditions				
Pyrexia	16	2	9	1
Fatigue	13	1	10	2
Edema	10	1	12	1

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

REACH3: All Grade (≥10%) and Grades 3-5 (≥3%) Nonlaboratory Adverse Reactions up to Week 24 (cont)

AE[a]	Ruxolitinib n=165		Control n=158	
	All Grades[b] (%)	Grade ≥3 (%)	All Grades (%)	Grades ≥3 (%)
Vascular disorders				
Hypertension	16	5	13	7
Hemorrhage	12	2	15	2
Respiratory, thoracic, and mediastinal disorders				
Cough	13	0	8	0
Dyspnea	11	1	8	1
Gastrointestinal disorders				
Nausea	12	0	13	2
Diarrhea	10	1	13	1

[a] Grouped terms that are composites of applicable adverse reactions terms. [b] National Cancer Institute CTCAE, version 4.03.
Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

REACH3: Selected Laboratory Abnormalities up to Week 24

Laboratory Test[a]	Ruxolitinib n=165		Control n=158	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grades ≥3 (%)
Hematology				
Anemia	82	13	75	8
Neutropenia	27	12	23	9
Thrombocytopenia	58	20	54	17
Chemistry				
Hypercholesterolemia	88	10	85	8
Elevated AST	65	5	54	6
Elevated ALT	73	11	71	16
GGT increased	81	42	75	38
Creatinine increased	47	1	40	2
Elevated lipase	38	12	30	9
Elevated amylase	35	8	25	4

[a] Presented values are worst grade values regardless of baseline.
GGT, gamma glutamyltransferase.
Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

REACH3: CMV Infection

CMV Infection (Safety Set), n (%)	Ruxolitinib n=165		Control n=158	
	At C7D1	At Data Cutoff	At C7D1	At Data Cutoff
Patients with ≥1 event	15 (9.1)	16 (9.7)	17 (10.8)	18 (11.4)
CMV infection reactivation	9 (5.5)	9 (5.5)	13 (8.2)	14 (8.9)
CMV infection	2 (1.2)	2 (1.2)	2 (1.3)	2 (1.3)
CMV test positive	2 (1.2)	3 (1.8)	2 (1.3)	2 (1.3)
CMV enteritis	1 (0.6)	1 (0.6)	0	0
CMV viremia	1 (0.6)	1 (0.6)	2 (1.3)	2 (1.3)
Cytomegaloviral pneumonia	1 (0.6)	1 (0.6)	2 (1.3)	2 (1.3)

Data on file, Incyte Corporation.

REACH3: Summary

- Among patients with SR-aGVHD, ruxolitinib was associated with a significantly higher ORR at week 24 compared with control (49.7% vs 25.6%, respectively; *P*<0.0001) and higher ORR through week 24 (70% vs 57%, respectively)[1,2]
  - Ruxolitinib was also associated with higher mLSS response at week 24 compared with control (24.2% vs 11%, *P*=0.001)[2]
  - Median time from first response to death or new systemic therapies for cGVHD was 25 months with ruxolitinib and 5.6 months with control[1]
  - Median duration of response was 4.2 months with ruxolitinib and 2.1 months with control[1]
- The most common grade 3 and higher AEs across both groups were cytopenias, infection, increased GGT, hypercholesterolemia, elevated AST, elevated ALT[1]
- Rate of infection was similar between ruxolitinib and control, with infection of grade ≥3 severity occurring in 19% and 18% of patients, respectively[2]

1. Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation. 2. Zeiser R, et al. *N Engl J Med.* 2021;385:228-238.

Ruxolitinib Dosing in GVHD

Ruxolitinib Dosing in aGVHD

- Recommended starting dose: 5 mg bid

Dose increases

- Consider increasing the dose to 10 mg bid after at least 3 days of treatment if the ANC and platelet counts are not decreased by 50% or more relative to the first day of dosing with ruxolitinib

Tapering of ruxolitinib

- Consider tapering ruxolitinib after 6 months of treatment in patients with response who have discontinued therapeutic doses of corticosteroids
- Taper ruxolitinib by 1 dose level approximately every 8 weeks (10 mg bid to 5 mg bid to 5 mg qd)
- If aGVHD signs or symptoms recur during or after the taper of ruxolitinib, consider retreatment

Monitoring

- Monitor complete blood counts, including platelet count and ANC, and bilirubin prior to initiating therapy, every 2-4 weeks until doses are stabilized, and then as indicated clinically

qd, once a day.
Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Dose Modification Guidelines for Patients With aGVHD

By Laboratory Parameter

Laboratory Parameter	Dosing Recommendations
Clinically significant thrombocytopenia after supportive measures	• Reduce dose by 1 level. When platelets recover to previous values, dosing may return to prior dose level
ANC <1x10^9/L considered related to ruxolitinib	• Hold ruxolitinib for up to 14 days; resume at 1 dose level lower upon recovery
Total bilirubin elevation, no liver GVHD	• **3-5xULN:** continue ruxolitinib at 1 dose level lower until recovery • **>5-10xULN:** hold ruxolitinib for up to 14 days until bilirubin ≤1.5xULN; resume at current dose upon recovery • **Total bilirubin >10xULN:** hold ruxolitinib for up to 14 days until bilirubin ≤1.5xULN; resume at 1 dose level lower upon recovery
Total bilirubin elevation, liver GVHD	• **>3xULN:** continue ruxolitinib at 1 dose level lower until recovery

ULN, upper limit of normal.

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Ruxolitinib Dosing in cGVHD

- Recommended starting dose: 10 mg bid

Dose reductions

- For dose reductions, patients who are currently receiving Jakafi 10 mg bid may have their dose reduced to 5 mg bid; patients receiving 5 mg bid may have their dose reduced to 5 mg qd
- Patients who are unable to tolerate ruxolitinib at a dose of 5 mg qd should have treatment interrupted until their clinical and/or laboratory parameters recover

Tapering of ruxolitinib

- Consider tapering ruxolitinib after 6 months of treatment in patients with response who have discontinued therapeutic doses of corticosteroids
- Taper ruxolitinib by 1 dose level approximately every 8 weeks (10 mg bid to 5 mg bid to 5 mg qd)
- If GVHD signs or symptoms recur during or after the taper of ruxolitinib, consider retreatment

Monitoring

- Monitor complete blood counts, including platelet count and ANC, and bilirubin prior to initiating therapy, every 2-4 weeks until doses are stabilized, and then as indicated clinically

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Dose Modification Guidelines for Adverse Reactions in Patients With cGVHD

Parameter	Dosing Recommendations
Platelet count <20x10^9/L	• Reduce dose by 1 level. If resolved within 7 days, dosing may return to initial dose level. If not resolved within 7 days, then maintain at 1 dose level lower
ANC <0.75x10^9/L considered related to ruxolitinib	• Reduce ruxolitinib by 1 dose level; resume at initial dose level upon recovery
ANC <0.5x10^9/L considered related to ruxolitinib	• Hold ruxolitinib for up to 14 days; resume at 1 dose level lower upon recovery. May resume initial dose level when ANC >1x10^9/L
Total bilirubin: 3-5xULN	• Continue ruxolitinib at 1 dose level lower until recovery. If resolved within 14 days, then increase by 1 dose level. If not resolved within 14 days, then maintain the decreased dose level
Total bilirubin: >5-10xULN	• Hold ruxolitinib for up to 14 days until resolved; resume at current dose upon recovery. If not resolved within 14 days, then resume at 1 dose level lower upon recovery
Total bilirubin: >10xULN	• Hold ruxolitinib for up to 14 days until resolved; resume at 1 dose level lower upon recovery. If not resolved within 14 days, discontinue
Other AEs: grade 3	• Continue ruxolitinib at 1 dose level lower until recovery
Other AEs: grade 4	• Discontinue ruxolitinib

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Dose Modification Guidelines for Patients With aGVHD and cGVHD

For Concomitant Use With Strong CYP3A4 Inhibitors or Fluconazole

- Modify the ruxolitinib dose when coadministered with strong CYP3A4 inhibitors or doses <200 mg of fluconazole
- Avoid concomitant use of ruxolitinib with fluconazole doses >200 mg qd

For Patients Coadministered Strong CYP3A4 Inhibitors or Doses ≤200 mg of Fluconazole	Starting Dose for Patients With cGVHD
Fluconazole doses ≤200 mg	• 5 mg ruxolitinib qd for patients with aGVHD • 5 mg ruxolitinib bid for patients with cGVHD
Other CYP3A4 inhibitors	• Monitor blood counts more frequently for toxicity and modify the ruxolitinib dosage for adverse reactions if they occur

CYP3A4, cytochrome P450 3A4.

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Dose Modification Guidelines for Renal and Hepatic Impairment for Patients With aGVHD and cGVHD

Impairment	Dosing Recommendations
Renal impairment	**Patients with aGVHD:** • Moderate (CL_{cr} 30-59 mL/min) or severe (CL_{cr} 15-29 mL/min): 5 mg qd • ESRD (CL_{cr} <15 mL/min) on dialysis: 5 mg once after dialysis session **Patients with cGVHD:** • Moderate (CL_{cr} 30-59 mL/min) or severe (CL_{cr} 15-29 mL/min): 5 mg bid • ESRD (CL_{cr} <15 mL/min) on dialysis: 10 mg once after dialysis session
Hepatic impairment	**Patients with aGVHD:** • Mild, moderate, or severe based on NCI criteria without liver GVHD: no dose adjustment • Stage 1, 2, or 3 liver aGVHD: no dose adjustment • Stage 4 liver aGVHD: 5 mg qd **Patients with cGVHD:** • Mild, moderate, or severe based on NCI criteria without liver GVHD: no dose adjustment • Score 1 or 2 liver cGVHD: no dose adjustment • Score 3 liver cGVHD: monitor blood counts more frequently for toxicity and modify the ruxolitinib dosage for adverse reactions if they occur

CL_{cr}, creatinine clearance; ESRD, end-stage renal disease; NCI, National Cancer Institute.

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Pharmacokinetics of Ruxolitinib[1]

Absorption

- Ruxolitinib achieves C_{max} within 1-2 hours post-dose
- Oral absorption of ruxolitinib is estimated to be at least 95%

Distribution

- Protein binding of ruxolitinib is approximately 97%, mostly to albumin

Elimination

- Mean elimination half-life is approximately 3 hours
- Mean elimination half-life of ruxolitinib and its metabolites is approximately 5.8 hours
- Ruxolitinib clearance (% coefficient of variation)
  - 11.8 L/h (63) in patients with aGVHD
  - 9.7 L/h (51) in patients with cGVHD

Metabolism

- Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9

Excretion

- Following a single oral dose of radiolabeled ruxolitinib, 74% of radioactivity was excreted in urine and 22% via feces

Click for Pharmacokinetic Modeling: Drug-Drug Interactions

C_{max}, maximum plasma concentration; CYP2A9, cytochrome P450 2C9.

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Warnings, Precautions, and Specific Populations

Summary of Warnings and Precautions

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.

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Summary of Warnings and Precautions

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

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Summary of Warnings and Precautions

Risk of Infection (cont)

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.
Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Summary of Warnings and Precautions

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

NMSC

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

DIC, disseminated intravascular coagulation; MF, myelofibrosis; NMSC, non-melanoma skin cancer.

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Summary of Warnings and Precautions

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

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Summary of Warnings and Precautions

MACE

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

Thrombosis

- Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis, 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

MACE, major adverse cardiovascular event; TNF, tumor necrosis factor.

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Summary of Warnings and Precautions

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

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Use in Specific Populations with GVHD

Pregnancy and Lactation

- There are no studies with the use of Jakafi in pregnant women to inform drug-associated risks
- 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 cGVHD or aGVHD 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 ESRD 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 aGVHD
- Monitor blood counts more frequently for toxicity and modify the Jakafi dosage for adverse reactions if they occur for patients with Score 3 liver cGVHD

Geriatric Use

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

Jakafi® (ruxolitinib). Prescribing Information. Incyte Corporation.

Appendix

REACH1: Phase 2, Single-Cohort, Open-Label Study of Ruxolitinib in SR-aGVHD[1]

MAGIC Guidelines for Staging and Grading aGVHD[1]

BACK

- MAGIC Guidelines were developed to help provide standardization in the clinical staging of aGVHD[1]

MAGIC guidelines for acute GVHD grading[1]

Stage	Skin (Active erythema only)	Liver (bilirubin)	Upper GI	Lower GI (Stool output/day)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: <500 mL/day or <3 episodes/day Child: <10 mL/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting, or anorexia	Adult: 500-999 mL/day or 3-4 episodes/day Child: 10-19.9 mL/kg/day or 4-6 episodes/day
2	Maculopapular rash 25-50% BSA	3.1-6 mg/dL	–	Adult: 1,000-1,500 mL/day or 5-7 episodes/day Child: 20-30 mL/kg/day or 7-10 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dL	–	Adult: >1,500 mL/day or >7 episodes/day Child: >30 mL/kg/day or >10 episodes/day
4	Generalized erythroderma (>50%) with bullae	>15 mg/dL	–	Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

Overall clinical grade:

Grade 0:	No stage 1-4 of any organ
Grade I:	Stage 1-2 skin without liver, upper GI, or lower GI involvement
Grade II:	Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI
Grade III:	Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI
Grade IV:	Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI

- Other guidelines for grading include IBMTR and modified Glucksberg aGVHD classification[2]

BSA, body surface area; IBMTR, International Bone Marrow Transplant Registry.

1. Harris AC, et al. *Biol Blood Marrow Transplant*. 2016;22:4-10. 2. Schoemans HM, et al. *Bone Marrow Transplant*. 2018;53:1401-1415.

REACH1: Baseline Characteristics

Patients With GVHD Refractory to Steroids Alone (n=49)

REACH1 Dosing

BACK

Ruxolitinib Dose	(n=49)[a]		(n=71)[b]	
	Day 7	Day 28	Day 7	Day 28
Total, n	46	30	67	43
5 mg bid, n (%)	17 (37.0)	9 (30.0)	28 (41.8)	13 (30.2)
10 mg bid, n (%)	27 (58.7)	14 (46.7)	35 (52.2)	20 (46.5)
Other, n (%)	2 (4.3)	7 (23.3)	4 (6.0)	10 (23.3)

[a] For day 7, other included 5 mg qd or 10 mg qd. For day 28, other included 0 mg, 5 mg qd, or 15 mg qd. [b] For day 7, other included 5 mg qd, 10 mg qd, or 15 mg qd. For day 28, other included 0 mg, 5 mg qd, or 15 mg qd.
Data on file, Incyte Corporation.

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REACH1: Baseline Characteristics

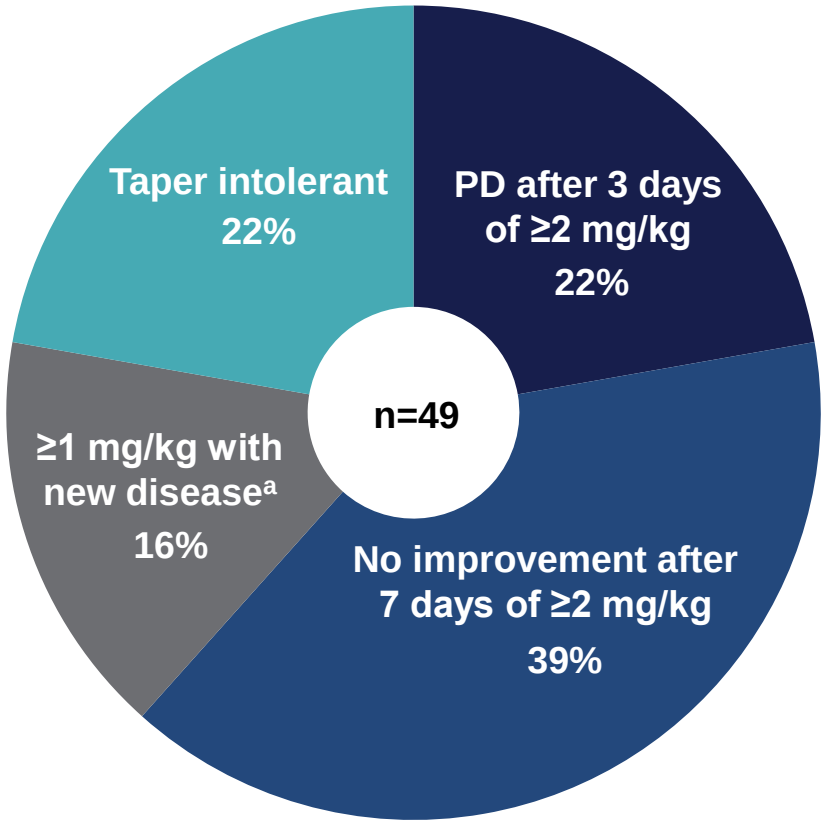
Patients With GVHD Refractory to Steroids Alone (n=49)

REACH1 Baseline Characteristics: Patients With SR-GVHD

BACK

- Definitions of SR-aGVHD[1]
  - Progression after 3 days of methylprednisolone ≥2 mg/kg/day or equivalent
  - Failure to improve after 7 days of methylprednisolone ≥2 mg/kg/day or equivalent
  - Development of new aGVHD after prior therapy with methylprednisolone ≥1 mg/kg/day for treatment of skin or skin plus upper GI aGVHD[a]
  - Inability to achieve a 50% taper of steroid dose without progression of GVHD
- Median duration of prior corticosteroid exposure at baseline was 15 days (range, 3-106)[2]

REACH1: patients with SR disease[2]



[a] Patients who previously began steroid therapy at a lower dose (≥1 mg/kg/day methylprednisolone) for treatment of skin GVHD or skin plus upper GI GVHD but developed new GVHD in another organ system.

1. Jagasia M, et al. *Blood*. 2020;135:1739-1749. 2. Data on file. Incyte Corporation.

REACH1: ORR at Day 28 (n=49)

REACH1 Efficacy Data by Ruxolitinib Dose

BACK

- Starting dose of ruxolitinib was 5 mg bid

Ruxolitinib Dose	(n=49)[a]	
	CR	PR/VGPR
Total, n	15	13
5 mg bid, n (%)	6 (40.0)	2 (15.4)
10 mg bid, n (%)	4 (26.7)	9 (69.2)
Other, n (%)	5 (33.3)	2 (15.4)

[a] Other included 0 mg or 5 mg qd.
Data on file, Incyte Corporation.

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Pharmacokinetics of Ruxolitinib[1]

Pharmacokinetic Modeling: Drug-Drug Interactions

BACK

CYP3A4 Inhibitor	Dose	AUC ratio	C_{max} ratio
Voriconazole	200 mg bid oral	2.35	1.29
	200 mg bid IV	2.52	1.29
	400 mg bid IV	2.92	1.32
Posaconazole	300 mg qd oral	1.66	1.17
	300 mg qd IV	2.05	1.25
	200 mg tid oral	1.95	1.21
	100 mg qd oral	1.27	1.08
Erythromycin	500 mg bid oral	1.84	1.22
Itraconazole	200 mg qd	2.82	1.33

AUC, area under the curve; IV, intravenous; tid, three times daily.
Data on file, Incyte Corporation.