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Ruxolitinib vs Best Available Therapy in Patients With Steroid-Refractory/Steroid-Dependent Chronic Graft-vs-Host Disease: Primary Findings From the Phase 3, Randomized REACH3 Study

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on behalf of the REACH3 Study Group

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Speaker Disclosures

- Honoraria from Novartis, Mallinckrodt Pharmaceuticals, and Incyte

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Introduction

- cGVHD occurs in approximately 30% to 70% of patients who undergo alloSCT[1] and is a leading cause of nonrelapse mortality and morbidity[2,3]
- Standard first-line therapy consists of systemic steroids; however, approximately 50% of patients become steroid refractory or dependent[4,5]
- No standard second-line treatment has been defined, and there have been no successful, large-scale, randomized studies in this setting

alloSCT, allogeneic stem cell transplant; cGVHD, chronic graft-vs-host disease.

1. Arora M, et al. *Biol Blood Marrow Transplant*. 2016;22:449-455. 2. Lee SJ, et al. *Blood.* 2002;100:2697-2702. 3. Zeiser R, Blazar BR. *N Engl J Med*. 2017;377:2565-2579. 4. Axt L, et al. *Bone Marrow Transplant*. 2019;54:1805-1814. 5. Jaglowski SM, Devine SM. *Curr Opin Hematol*. 2014;21:141-147.

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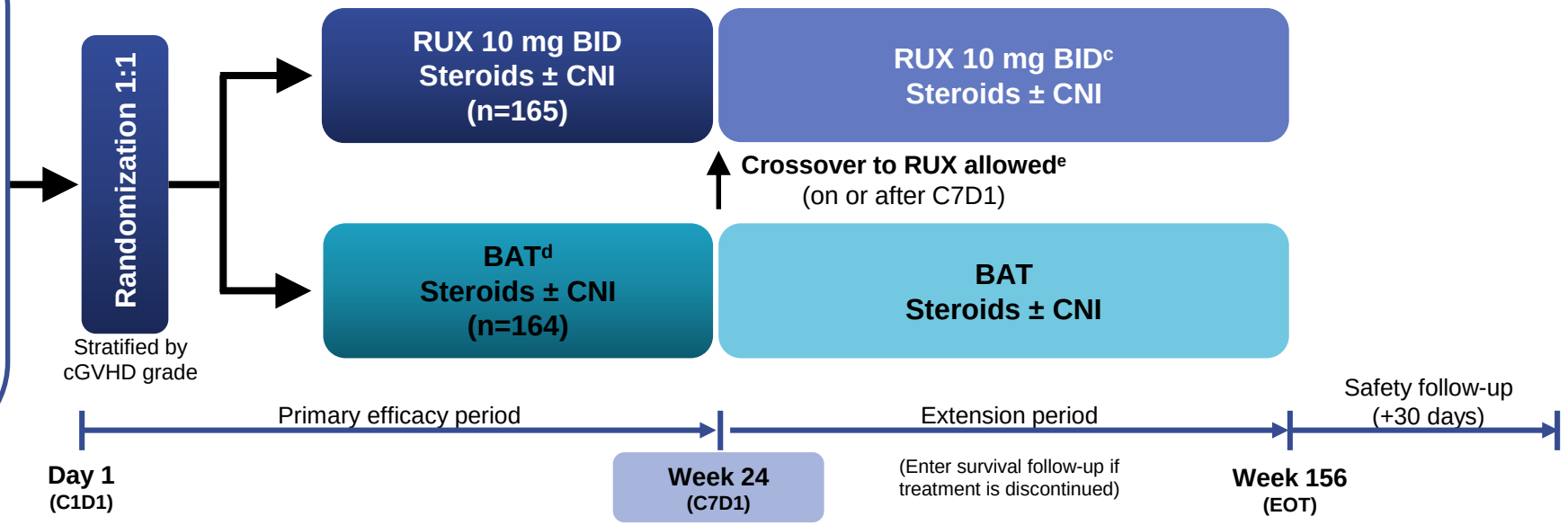
REACH3 (NCT03112603): a Phase 3, Randomized Study

Eligibility

- Age ≥12 years
- SR/D cGVHD (moderate or severe), defined as:
  - Lack of response or disease progression after prednisone ≥1 mg/kg/day[a] for ≥1 week ***or***
  - Disease persistence without improvement with prednisone >0.5 mg/kg/day or 1 mg/kg/every other day[a] for ≥4 weeks ***or***
  - Increase in prednisone dose to >0.25 mg/kg/day[a] after 2 unsuccessful attempts to taper the dose
- Evident myeloid and platelet engraftment[b]



Primary endpoint: overall response rate (ORR; complete response + partial response) at week 24 using NIH consensus criteria for response[1]

Key secondary endpoints:

- Failure-free survival (FFS)
- Modified Lee Symptom Scale (mLSS) response at week 24

BAT, best available therapy; BID, twice daily; C, cycle; cGVHD, chronic graft-vs-host disease; CNI, calcineurin inhibitor; D, day; EOT, end of treatment; NIH, National Institutes of Health; RUX, ruxolitinib; SR/D, steroid refractory or dependent. [a] Or prednisone equivalent. [b] Absolute neutrophil count >1×10^9/L and platelet count >25×10^9/L. [c] RUX tapering was permitted after C7D1 for responding patients. [d] Chosen by the investigator at randomization and could include extracorporeal photopheresis, low-dose methotrexate, mycophenolate mofetil, everolimus, sirolimus, infliximab, rituximab, pentostatin, imatinib, or ibrutinib. [e] On or after C7D1, patients randomized to BAT who progressed, had a mixed or unchanged response, developed toxicity to BAT, or experienced a cGVHD flare could cross over from BAT to RUX.

1. Lee SJ, et al. *Biol Blood Marrow Transplant*. 2015;21:984-999.

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Baseline Characteristics

Patient characteristics at baseline were well balanced between both treatment arms

Characteristic	RUX (n=165)	BAT (n=164)
Age, median (range), years	49.0 (13.0-73.0)	50.0 (12.0-76.0)
12 to <18 years, n (%)	**4 (2.4)**	**8 (4.9)**
18 to 65 years, n (%)	143 (86.7)	134 (81.7)
>65 years, n (%)	18 (10.9)	22 (13.4)
Male, n (%)	109 (66.1)	92 (56.1)
cGVHD severity, n (%)		
Mild[a]	0	1 (0.6)
Moderate	**68 (41.2)**	**73 (44.5)**
Severe	**97 (58.8)**	**90 (54.9)**
Refractory/dependent criteria, n (%)		
Lack of response or disease progression after prednisone ≥1 mg/kg/day for ≥1 week	62 (37.6)	73 (44.5)
Disease persistence without improvement with prednisone >0.5 mg/kg/day or 1 mg/kg/every other day for ≥4 weeks	58 (35.2)	42 (25.6)
Increase in prednisone dose to >0.25 mg/kg/day after 2 unsuccessful attempts to taper the dose (steroid dependency)	45 (27.3)	49 (29.9)
Total mLSS score, median (range)	18.67 (0-79.6)[b]	18.54 (0.7-54.4)[c]

BAT, best available therapy; cGVHD, chronic graft-vs-host disease; mLSS, modified Lee Symptom Scale; RUX, ruxolitinib.
[a] Protocol deviation. [b] n=149. [c] n=141.

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Baseline Characteristics (cont)

Patient characteristics at baseline were well balanced between both treatment arms

Characteristic	RUX (n=165)	BAT (n=164)
Time from cGVHD onset to randomization, median (range), weeks	24.9 (1.0-288.1)	21.4 (1.4-278.1)
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)
Donor/recipient CMV status, n (%)		
Negative/negative	51 (30.9)	45 (27.4)
Negative/positive	30 (18.2)	28 (17.1)
Positive/negative	16 (9.7)	17 (10.4)
Positive/positive	67 (40.6)	73 (44.5)
Unknown[b]	1 (0.6)	1 (0.6)

BAT, best available therapy; cGVHD, chronic graft-vs-host disease; CMV, cytomegalovirus; RUX, ruxolitinib.
[a] Some patients underwent >1 transplant. [b] Data not available for donor and/or recipient (patient).

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Patient Disposition[a]

More RUX than BAT patients remained on treatment at the primary analysis

	RUX (n=165)	BAT (n=164)
Patients randomized, n (%)	165 (100)	164 (100)
Not treated	0	6 (3.7)[b]
Ongoing treatment	**83 (50.3)**	**42 (25.6)**
Discontinued treatment	**82 (49.7)**	**122 (74.4)**
Reason for discontinuation, n (%)		
Adverse event	**28 (17.0)**	**8 (4.9)**
Lack of efficacy	**24 (14.5)**	**70 (42.7)**
Disease relapse	9 (5.5)	7 (4.3)
Death	8 (4.8)	7 (4.3)
Failure to meet protocol continuation criteria	4 (2.4)	5 (3.0)
Physician decision	**4 (2.4)**	**14 (8.5)**
Patient/guardian decision	**4 (2.4)**	**11 (6.7)**
Loss to follow-up	1 (0.6)	0
Crossover to RUX, n (%)	**–**	**61 (37.2)**

BAT, best available therapy; RUX, ruxolitinib.

[a] Data cutoff: May 8, 2020. Reasons for discontinuation were also reported for patients who were not treated. [b] Patients did not receive BAT due to logistic reasons (n=3) and use of prohibited medications (n=3).

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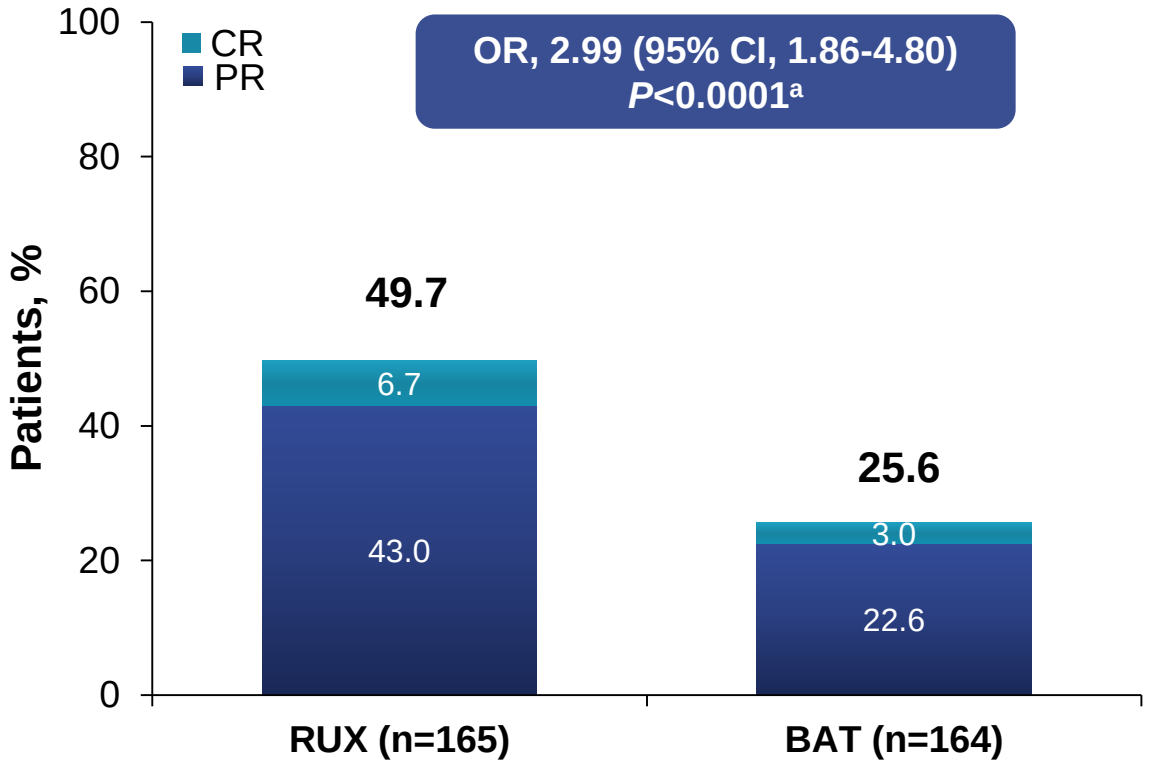
Overall Response Rate at Week 24

The primary endpoint was met: ORR was significantly higher with RUX



Characteristic	RUX (n=165)	BAT (n=164)
Responders, n (%)		
Complete response	**11 (6.7)**	**5 (3.0)**
Partial response	**71 (43.0)**	**37 (22.6)**
Nonresponders, n (%)		
Unchanged response	9 (5.5)	15 (9.1)
Mixed response	10 (6.1)	17 (10.4)
Progression	4 (2.4)	21 (12.8)
Other[b]	5 (3.0)	9 (5.5)
Unknown[c]	55 (33.3)	60 (36.6)

BAT, best available therapy; cGVHD, chronic graft-vs-host disease; CR, complete response; OR, odds ratio; ORR, overall response rate; PR, partial response; RUX, ruxolitinib.

[a] Descriptive *P* value at the primary analysis as the efficacy boundary was crossed at the interim analysis (N=196; ORR was 50.5% with RUX and 26.3% with BAT; *P*=0.0003). One-sided *P* value, odds ratio, and 95% CI were calculated using a stratified Cochran-Mantel-Haenszel test with strata of moderate vs severe cGVHD. [b] Other: patients with additional systemic therapies along with CR/PR per investigator assessment.

[c] Considered to be nonresponders due to death, early discontinuation, or missing data.

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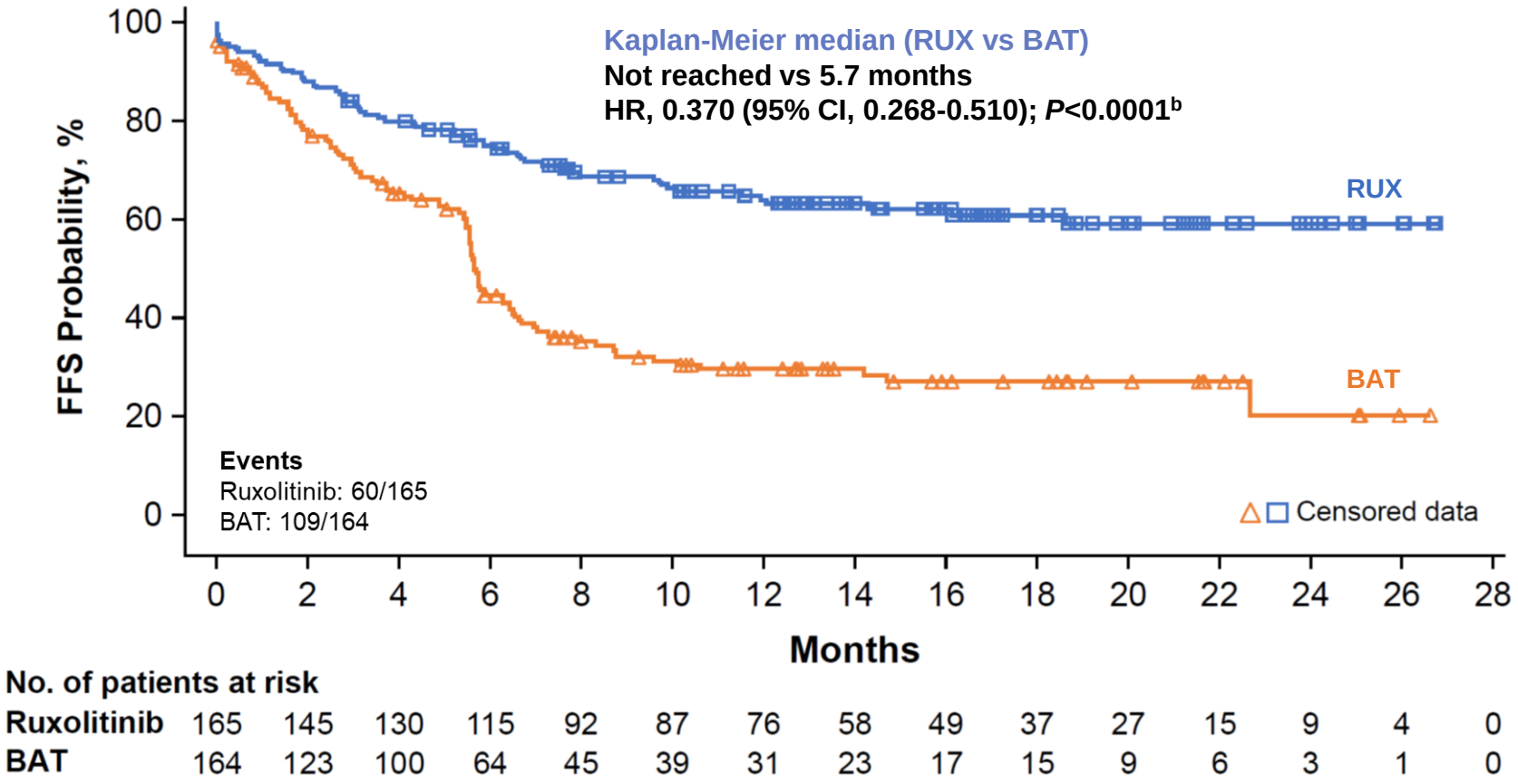
Failure-Free Survival at Week 24[a]

Median FFS was longer with RUX than with BAT



BAT, best available therapy; cGVHD, chronic graft-vs-host disease; FFS, failure-free survival; HR, hazard ratio; RUX, ruxolitinib.

[a] Defined as time to recurrence of the underlying disease, start of new systemic treatment for cGVHD, or death, whichever was earliest. [b] Descriptive *P* value at the primary analysis (non-US testing sequence only) as the efficacy boundary was crossed at the interim analysis (N=196; HR, 0.315 [95% CI, 0.205-0.486]; *P*<0.0001). For US testing sequence, the hypothesis was retested at the primary analysis following the overall hierarchical testing procedure.

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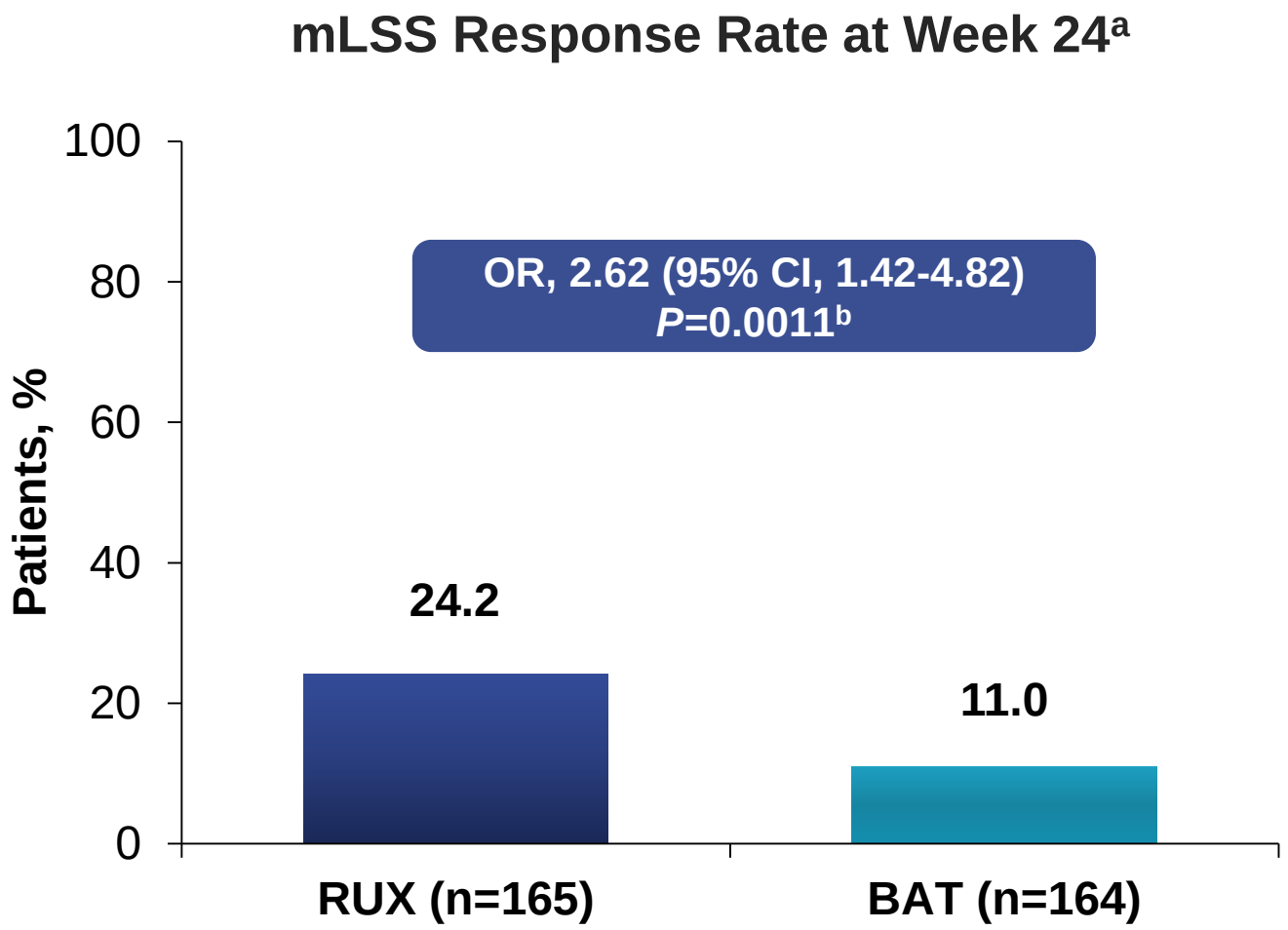
mLSS Response

Patients treated with RUX had greater improvements in symptoms



BAT, best available therapy; mLSS, modified Lee Symptom Scale; OR, odds ratio; RUX, ruxolitinib.

[a] mLSS response was defined as a ≥7-point reduction from baseline in the total symptom score. [b] Statistically significant at the primary analysis. At the interim analysis (N=196), patients receiving RUX had a numerically but not significantly higher mLSS responder rate (19.6% vs 8.1%; OR, 2.80; *P*=0.0151) than those receiving BAT.

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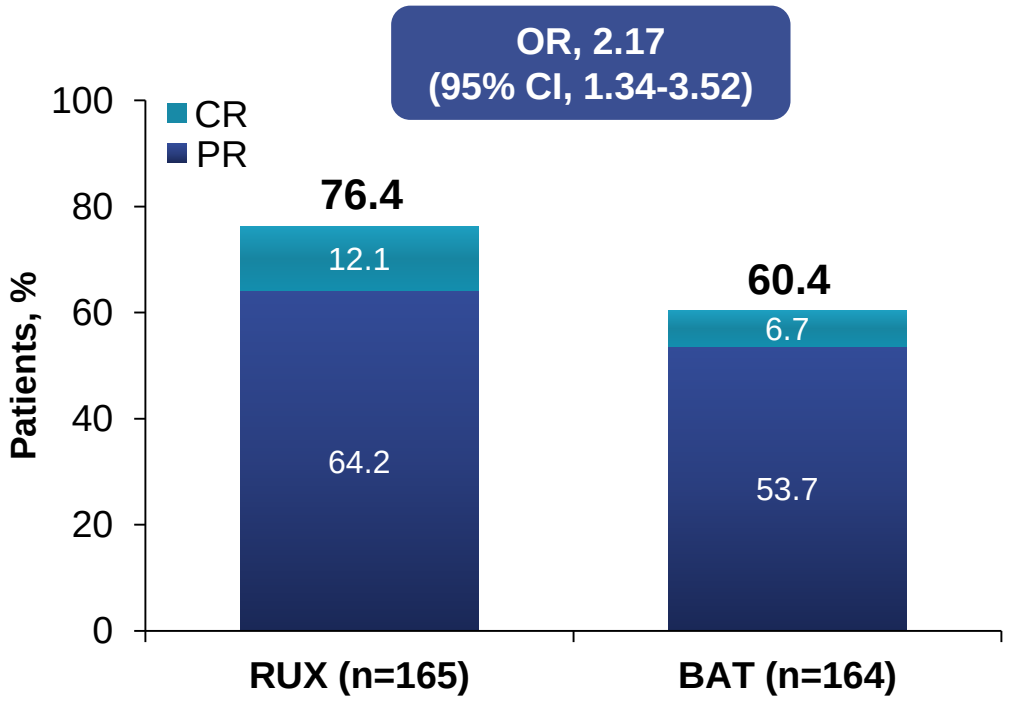
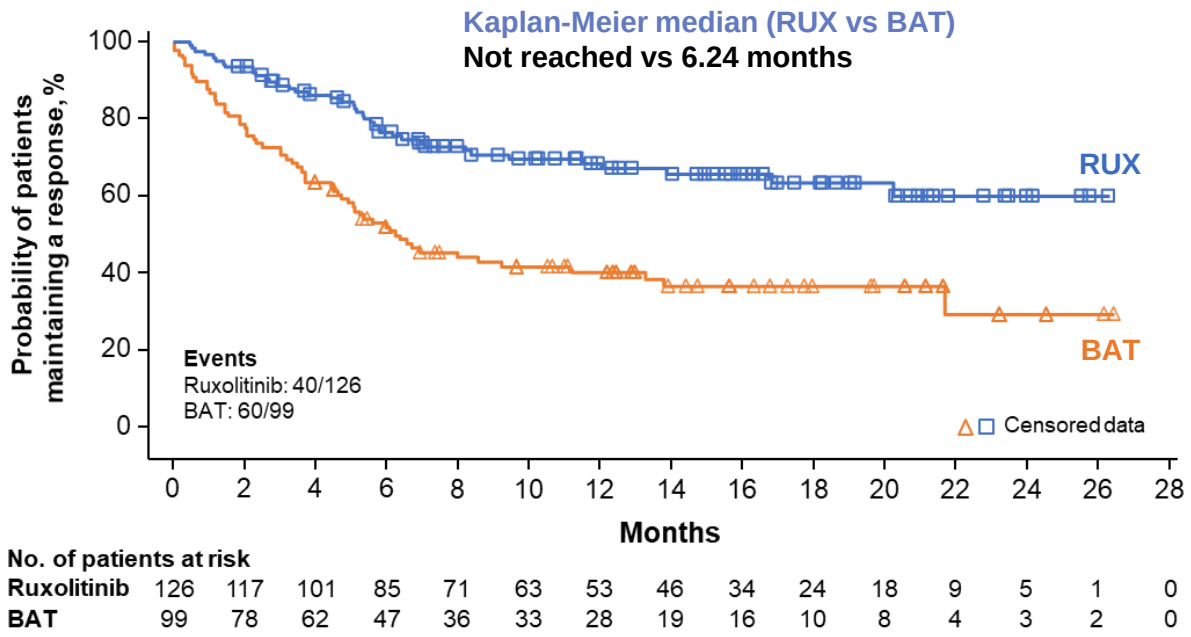
Best Overall Response[a]

Best overall response rate was higher with RUX than with BAT

Best Overall Response



Duration of Response



- **Median duration of best overall response was 6.24 months in the BAT arm but was not reached in the RUX** arm

BAT, best available therapy; CR, complete response; OR, odds ratio; PR, partial response; RUX, ruxolitinib.
[a] Among patients who achieved a CR or PR at any time up to week 24. Duration of response from first documented PR or CR.

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Safety up to Week 24[a]

Rates of AEs were similar between treatment arms

	RUX (n=165)	BAT (n=158)
Duration of exposure up to study cutoff, median (range), weeks[b]	41.3 (0.7-127.3)	24.1 (0.6-108.4)
Any-grade AEs, n (%)	161 (97.6)	145 (91.8)
Grade ≥3 AEs, n (%)	94 (57.0)	91 (57.6)
Serious AEs, n (%)	55 (33.3)	58 (36.7)
AEs leading to dose modification, n (%)	62 (37.6)	26 (16.5)
AEs leading to discontinuation, n (%)	27 (16.4)	11 (7.0)
Deaths, n (%)[c] Up to data cutoff	31 (18.8)	27 (16.5)

AE, adverse event; BAT, best available therapy; cGVHD, chronic graft-vs-host disease; RUX, ruxolitinib.

[a] Safety population: all patients who received ≥1 dose of study treatment. [b] Includes all systemic cGVHD treatments given during the main study period. [c] Most common causes of death were cGVHD (RUX, 22; BAT, 13) and infections (RUX, 2; BAT, 6).

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AEs (≥10%) up to Week 24

Cytopenias were the most common AEs in the RUX arm

Event, n (%)	RUX (n=165)[a]		BAT (n=158)[a]	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Hematologic				
Anemia	**48 (29.1)**	**21 (12.7)**	**20 (12.7)**	**12 (7.6)**
Thrombocytopenia[b]	**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				
Diarrhea	17 (10.3)	1 (0.6)	21 (13.3)	2 (1.3)
Nausea	15 (9.1)	0	16 (10.1)	2 (1.3)
Infections				
Pneumonia	18 (10.9)	14 (8.5)	20 (12.7)	15 (9.5)
Laboratory abnormalities				
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)
Hypokalemia	13 (7.9)	3 (1.8)	16 (10.1)	7 (4.4)
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)

AE, adverse event; BAT, best available therapy; RUX, ruxolitinib.

[a] Safety population: all patients who received ≥1 dose of study treatment. AEs were assessed according to the Common Terminology Criteria for Adverse Events v4.03. [b] Includes preferred terms "thrombocytopenia" and "platelet count decreased."

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Overview of Infections up to Week 24[a]

Viral infections were the most common type of infections

Type of Infection, n (%)[a]	RUX[b] (n=165)	BAT[b] (n=158)
Patients with ≥1 event	**105 (63.6)**	**89 (56.3)**
Viral infections	56 (33.9)	46 (29.1)
Grade 1	23 (13.9)	21 (13.3)
Grade 2	22 (13.3)	16 (10.1)
Grade 3	9 (5.5)	9 (5.7)
Missing	2 (1.2)	0
Bacterial infections	46 (27.9)	41 (25.9)
Grade 1	13 (7.9)	9 (5.7)
Grade 2	16 (9.7)	15 (9.5)
Grade 3	16 (9.7)	16 (10.1)
Missing	1 (0.6)	1 (0.6)
Fungal infections	19 (11.5)	9 (5.7)
Grade 1	2 (1.2)	2 (1.3)
Grade 2	5 (3.0)	4 (2.5)
Grade 3	11 (6.7)	3 (1.9)
Missing	1 (0.6)	0

- CMV infection/reactivation in 5.5% of patients treated with RUX and 8.2% of patients treated with BAT

BAT, best available therapy; CMV, cytomegalovirus; RUX, ruxolitinib.

[a] Infections were classified by type and severity (grades 1 to 3) at the investigator's discretion by using an infection-severity grading system developed for and validated in recipients of allogeneic stem cell transplant (Cordonnier C, et al. *Transplantation*. 2006;82(1):86-92). [b] Safety population: all patients who received ≥1 dose of study treatment.

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Conclusions

- This is the first successful randomized phase 3 trial in adolescent and adult patients with cGVHD with an inadequate response to steroids
- RUX demonstrated:
  - **Significantly higher ORR** at week 24 than BAT (49.7% vs 25.6%; *P*<0.0001)
  - **Significant improvement in FFS** vs BAT (HR, 0.370 [95% CI, 0.268-0.510]; *P*<0.0001)
  - **Significantly greater symptom improvement** vs BAT (mLSS responder rate: 24.2% vs 11.0%; *P*=0.0011)
  - **Higher best overall response rate** up to week 24 than BAT (76.4% vs 60.4%), with a **longer duration of response**
- The safety profile of RUX was consistent with previous observations and with what is expected in patients with cGVHD
  - The most frequent AEs in the RUX arm were anemia and thrombocytopenia
- **RUX is the first agent to demonstrate superior efficacy to BAT in a phase 3 trial of patients with cGVHD with an inadequate response to steroids**

AE, adverse event; BAT, best available therapy; cGVHD, chronic graft-vs-host disease; FFS, failure-free survival; HR, hazard ratio; mLSS, modified Lee Symptom Scale; ORR, overall response rate; RUX, ruxolitinib.

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