Abstract #601
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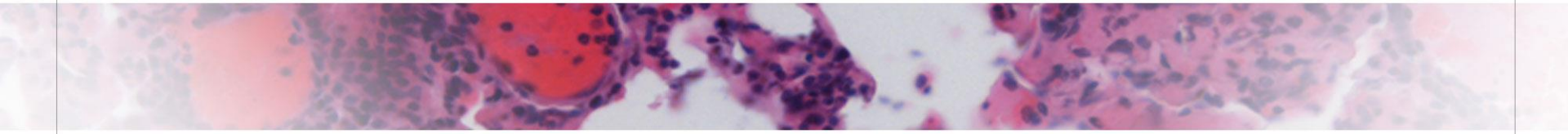

Results From REACH1, a Single-Cohort Phase 2 Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-vs-Host Disease

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Introduction

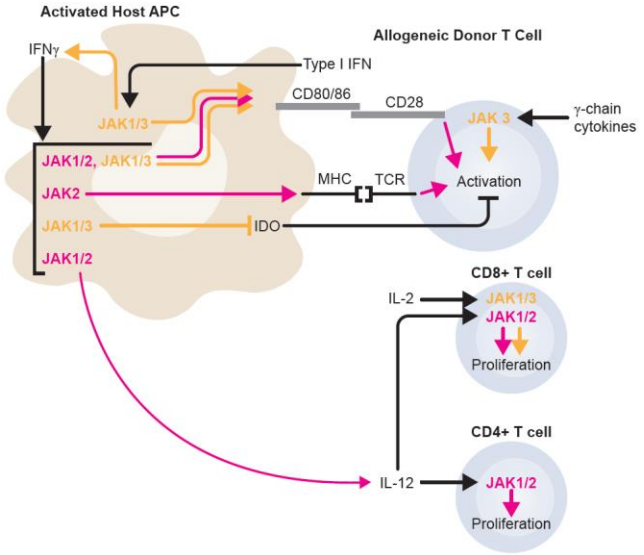
- Development of acute graft-versus-host disease (aGVHD) is a risk factor for non-relapse mortality following allogeneic hematopoietic cell transplantation (HCT)[1]
- Systemic corticosteroids are recommended first-line treatment for aGVHD, but <50% of patients achieve sustained responses[2,3]
- Outcomes are poor for patients refractory to steroid treatment[3]
  - Response rates to subsequent treatments vary (~30%–70%)[4-6]
  - 1-year non-relapse mortality rates remain high (~60%–80%)[4-6]
- There are no approved therapies for steroid-refractory aGVHD

1. Baron F, et al. *Leukemia*. 2012;26(12):2462-2468; 2. Major-Monfried H, et al. *Blood*. 2018;131(25):2846-2855; 3. Garnett C, et al. *Ther Adv Hematol*. 2013;4(6):366-378; 4. von Dalowski F, et al. *Stem Cells*. 2016;34(2):357-366; 5. Shapira MY, et al. *Bone Marrow Transplant*. 2017;52(10):1416-1422; 6. Pidala J, et al. *Bone Marrow Transplant*. 2010;45(5):919-924.

Study Rationale

- JAKs are intracellular tyrosine kinases involved in the development and function of immune cells implicated in GVHD pathogenesis[1]
- Ruxolitinib is an oral, selective inhibitor of JAK1/JAK2 signaling[2]
- Ruxolitinib reduced aGVHD severity and improved survival while preserving the graft-vs-leukemia effect in murine models[3-6]
- Retrospective studies showed benefit from salvage therapy with ruxolitinib in patients with steroid-refractory aGVHD[7,8]

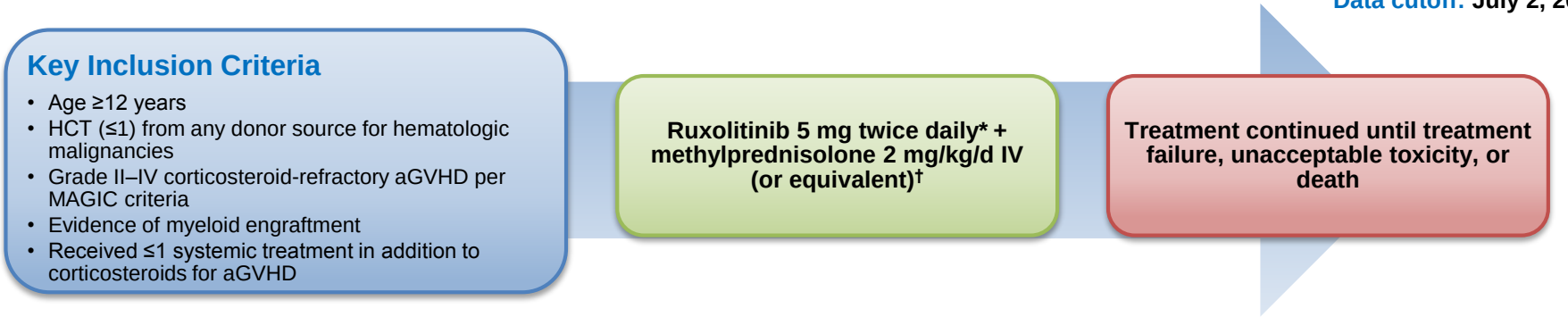
Role of JAK Signaling in Donor T-Cell Activation[1]



1. Schroeder MA, et al. *Biol Blood Marrow Transplant*. 2018;24(6):1125-1134; 2. Quintás-Cardama A, et al. *Blood*. 2010;115(15):3109-3117; 3. Spoerl S, et al. *Blood*. 2014;123(24):3832-3842; 4. Choi J, et al. *PLoS One*. 2014;9(10):e109799; 5. Carniti C, et al. *Clin Cancer Res*. 2015;21(16):3740-3749; 6. Choi J, et al. *Blood*. 2012;120(19):4093-4103; 7. Zeiser R, et al. *Leukemia*. 2015;29(10):2062-2068; 8. Assouan D, et al. *Br J Haematol*. 2018;181(5):687-689.

REACH1 Study Design: Open-Label, Single-Cohort, Multicenter, Phase 2 Study (NCT02953678)

Data cutoff: **July 2, 2018**



Endpoints

Primary: Overall response rate (ORR; complete, very good, or partial response) at Day 28
Secondary: Duration of response at 6 months (key secondary endpoint), non-relapse mortality, malignancy relapse rate, overall survival, safety
Exploratory: Corticosteroid use

Steroid-Refractory Criteria

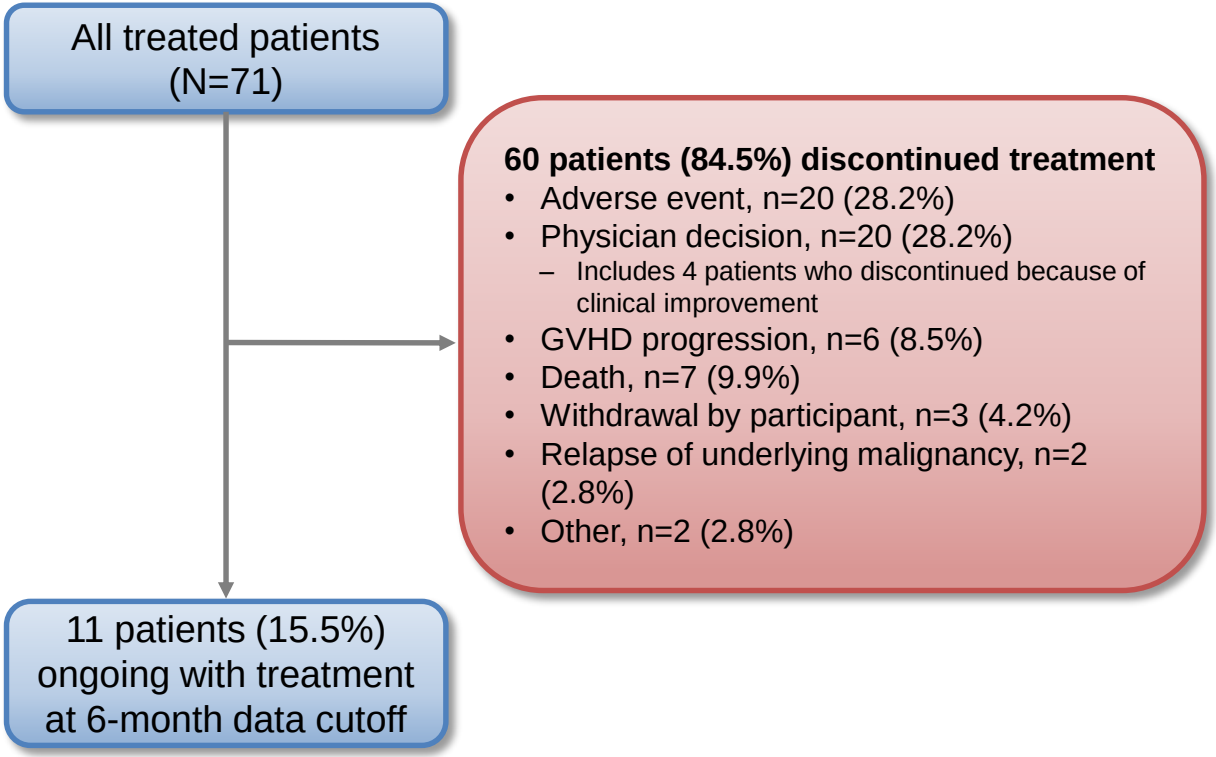
- Progressive aGVHD after 3 days of primary treatment (methylprednisolone ≥2 mg/kg/d or equivalent)
- aGVHD that had not improved after 7 days of primary treatment (methylprednisolone ≥2 mg/kg/d or equivalent)
- Development of new aGVHD after prior therapy with methylprednisolone ≥1 mg/kg/d for treatment of skin or skin plus upper GI aGVHD
- Inability to tolerate corticosteroid taper

* Patients received a starting dose of ruxolitinib 5 mg twice daily with optional increase to 10 mg twice daily in the absence of cytopenias. † Corticosteroids were tapered, as appropriate.

Patient Disposition

At the 6-month data cutoff (July 2, 2018):

- 71 patients received ≥1 dose of ruxolitinib
- Most patients (69/71) initiated ruxolitinib at 5 mg twice daily
  - At Day 28, 46.5% of patients (20/43) who were still receiving ruxolitinib received 10 mg twice daily



Patient Demographics

Demographic characteristics	Total (N=71)
Age, median (range), y	58 (18–73)
Female, n (%)	36 (50.7)
White race, n (%)	66 (93.0)
Graft source, n (%)	
PBSC	57 (80.3)
Bone marrow	13 (18.3)
Umbilical cord blood	1 (1.4)
Underlying malignancy, n (%)	
AML	20 (28.2)
MDS	20 (28.2)
Lymphoma	9 (12.7)
ALL	8 (11.3)
CLL	3 (4.2)
Other	11 (15.5)

Patient Baseline aGVHD Characteristics

Transplant/aGVHD Characteristics	Total (N=71)
Steroid-refractory criteria, n (%)	
aGVHD that progressed after 3 days of primary treatment	19 (26.8)
aGVHD that had not improved after 7 days of treatment	30 (42.3)
Development of aGVHD in another organ in patients who previously received corticosteroids for skin or skin plus upper GI aGVHD	8 (11.3)
Inability to tolerate corticosteroid taper	14 (19.7)

Transplant/aGVHD Characteristics	Total (N=71)
MAGIC grade, n (%)	
II	23 (32.4)
III	34 (47.9)
IV	14 (19.7)
CMV serostatus,* n (%)	
D+/R+	24 (33.8)
D+/R–	7 (9.9)
D–/R+	16 (22.5)
D–/R–	23 (32.4)

D, donor; R, recipient (patient)
*Donor serostatus was missing from 1 patient (patient was positive).

- 6 patients (8.5%) each had a medical history of CMV infection or CMV viremia

Overall Response at Day 28 and at Any Time

- Responses were observed irrespective of aGVHD grade at enrollment

Response at Day 28, n (%)	Grade II (n=23)	Grade III (n=34)	Grade IV (n=14)	Total (N=71)
CR	11 (47.8)	7 (20.6)	1 (7.1)	**19 (26.8)**
VGPR	4 (17.4)	2 (5.9)	1 (7.1)	**7 (9.9)**
PR	4 (17.4)	5 (14.7)	4 (28.6)	**13 (18.3)**
Overall response rate **95% CI**	**19 (82.6)** **61.2–95.0**	**14 (41.2)** **24.6–59.3**	**6 (42.9)** **17.7–71.1**	**39 (54.9)** **42.7–66.8**

- 52 patients (73.2%) demonstrated a response at any time during treatment (CR, 56.3%)

Overall Response at Day 28 by Steroid-Refractory Criteria

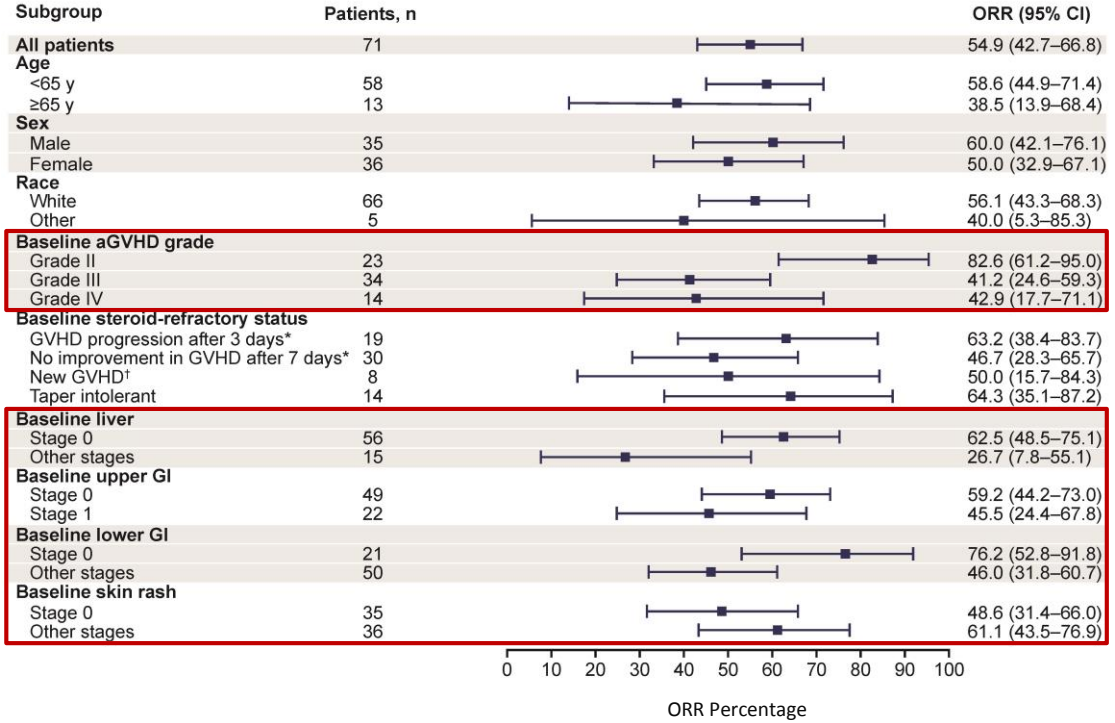
- Responses were observed irrespective of steroid-refractory criteria

	Steroid-Refractory Criteria			
Response, n (%)	**aGVHD Progression After 3 Days* (n=19)**	**No Improvement in aGVHD After 7 Days* (n=30)**	**New aGVHD† (n=8)**	**Taper Intolerant (n=14)**
CR	7 (36.8)	6 (20.0)	1 (12.5)	5 (35.7)
VGPR	4 (21.1)	1 (3.3)	1 (12.5)	1 (7.1)
PR	1 (5.3)	7 (23.3)	2 (25.0)	3 (21.4)
Overall response rate 95% CI	**12 (63.2) 38.4–83.7**	**14 (46.7) 28.3–65.7**	**4 (50.0) 15.7–84.3**	**9 (64.3) 35.1–87.2**

* Following primary treatment with methylprednisolone ≥2 mg/kg/d.
† In another organ in patients who previously received corticosteroids (≥1 mg/kg/d methylprednisolone) for skin or skin plus upper GI aGVHD.

Subgroup Analysis of Day 28 Response

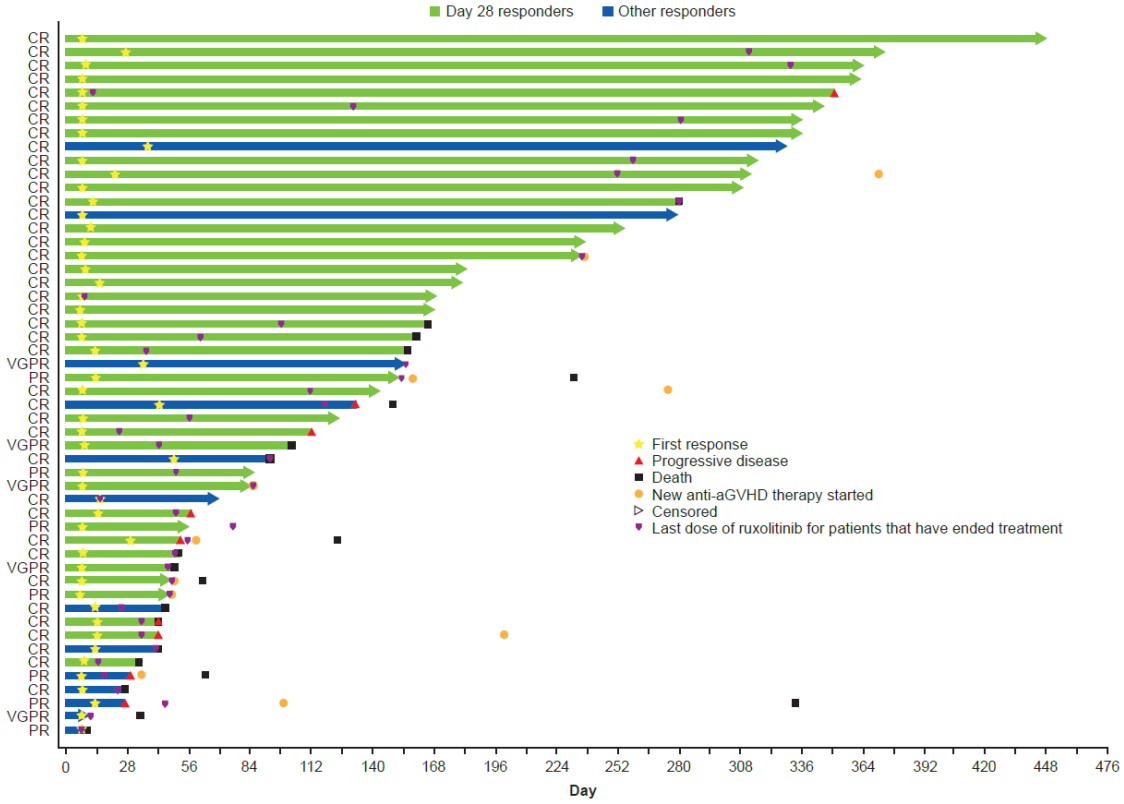
- aGVHD grade at time of enrollment was the only variable associated with response to treatment, although responses were seen across all grades
- Responses were observed across all organ systems
  - In patients with 1 organ involved, 22 patients (62.9%) responded
  - In patients with ≥2 organs involved, 17 patients (47.2%) responded
- Responses were observed regardless of demographic variables



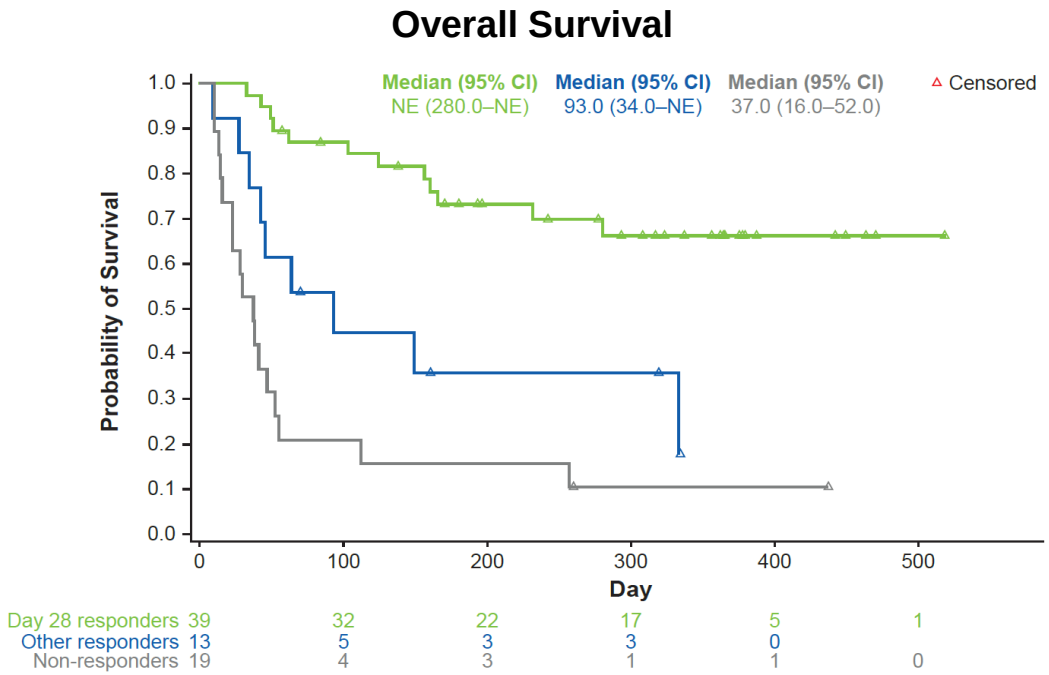
* Following primary treatment with methylprednisolone ≥2 mg/kg/d.
† In another organ in patients who previously received corticosteroids (≥1 mg/kg/d methylprednisolone) for skin or skin plus upper GI aGVHD.

Duration of Response

- Median time to first response for all responders was 7 days
- Median duration of response was 345 days for both Day 28 responders (lower limit, 159 days) and for other responders (lower limit, 106 days)
- Event-free probability estimates for Day 28 responders at 3 and 6 months were 81.6% and 65.2%, respectively



Overall Survival

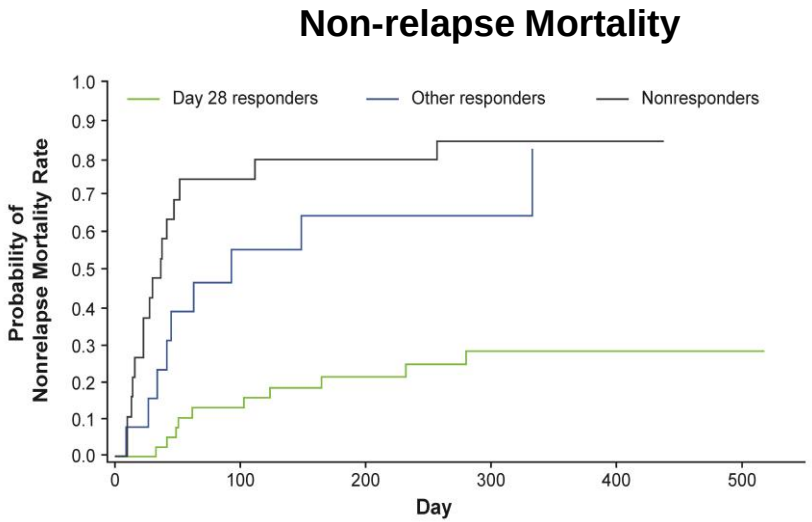


Cumulative Incidence (95% CI)	Overall Survival		
	Day 28 Responders (n=39)	Other Responders (n=13)	Non-responders (n=19)
6 months	73.2% (55.9%–84.6%)	35.9% (11.7%–61.3%)	15.8% (3.9%–34.9%)
9 months	69.9% (52.0%–82.2%)	35.9% (11.7%–61.3%)	10.5% (1.8%–28.4%)
12 months	66.2% (47.8%–79.4%)	NE (NE–NE)	10.5% (1.8%–28.4%)

- Among all patients, median (95% CI) overall survival was 232.0 (93.0–NE) days

NE, not evaluable.

Non-relapse Mortality Rate

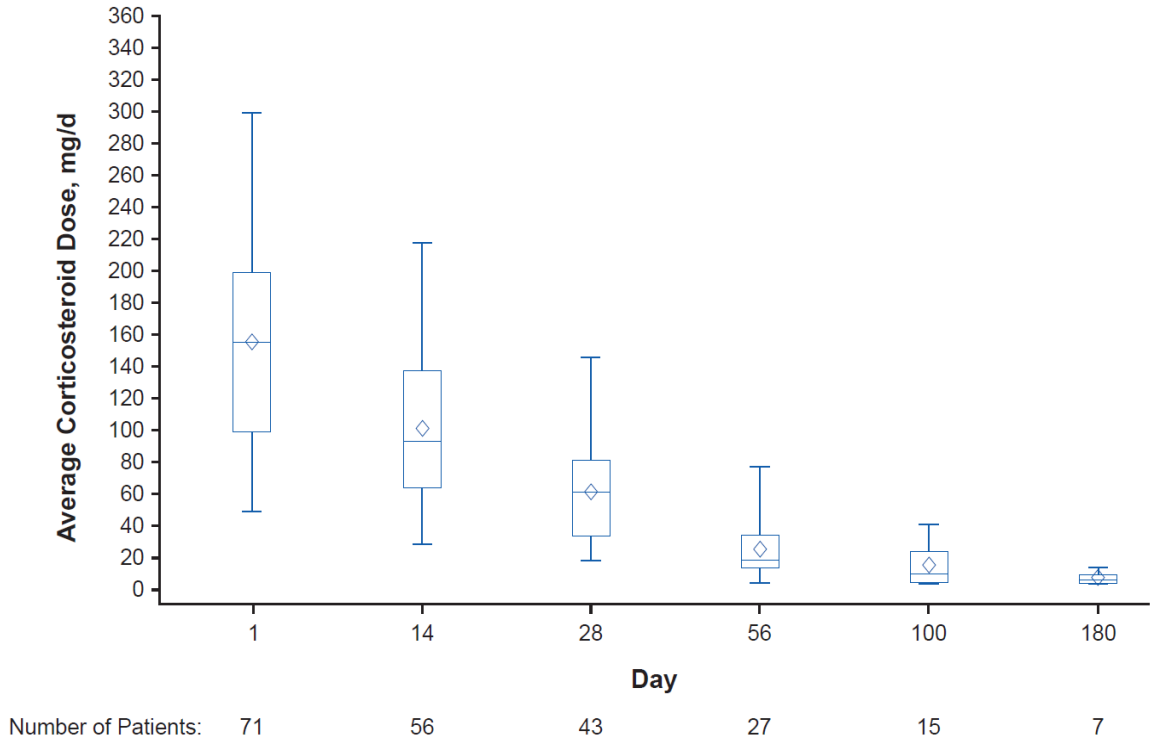


Cumulative Incidence (95% CI)	Non-relapse Mortality			
	Day 28 Responders (n=39)	Other Responders (n=13)	Non-responders (n=19)	Total (N=71)
6 months	21.2% (9.9%–35.2%)	64.1% (31.5%–84.3%)	78.9% (53.2%–91.5%)	44.4% (32.5%–55.7%)
9 months	24.5% (12.1%–39.2%)	64.1% (31.5%–84.3%)	84.2% (58.7%–94.6%)	48.2% (35.8%–59.5%)
12 months	28.2% (14.5%–43.6%)	--	84.2% (58.7%–94.6%)	52.9% (39.6%–64.5%)

- 4 patients had a relapse of their underlying malignancy: AML, n=2 (both fatal); MDS, n=1; plasma cell leukemia, n=1 (fatal)

Corticosteroid Use

- At Day 28, 43 patients were on ruxolitinib and corticosteroid treatment; among these patients, 55.8% (24/43) had a ≥50% reduction from baseline in corticosteroid dose
- Median corticosteroid dose* was 156.3 mg/d at Day 1 and 62.5 mg/d at Day 28



* Corticosteroid dose (mg) = methylprednisolone dose (mg) × 1.25 + prednisone dose (mg).

Treatment-emergent Adverse Events (≥20% of Patients)

	Total (N=71)	
Event, n (%)	**Any Grade**	**Grade 3/4**
Anemia	46 (64.8)	36 (50.7)
Hypokalemia	35 (49.3)	13 (18.3)
Edema peripheral	32 (45.1)	8 (11.3)
Platelet count decreased	32 (45.1)	28 (39.4)
Neutrophil count decreased	28 (39.4)	23 (32.4)
Muscular weakness	24 (33.8)	8 (11.3)
Dyspnea	23 (32.4)	5 (7.0)
Hypomagnesemia	23 (32.4)	2 (2.8)
Hypocalcemia	22 (31.0)	8 (11.3)
Nausea	22 (31.0)	4 (5.6)
Fatigue	21 (29.6)	10 (14.1)
WBC decreased	21 (29.6)	12 (16.9)
Diarrhea	20 (28.2)	5 (7.0)

	Total (N=71)	
Event, n (%)	**Any Grade**	**Grade 3/4**
ALT increased	18 (25.4)	4 (5.6)
Hyperglycemia	18 (25.4)	14 (19.7)
Hypophosphatemia	18 (25.4)	11 (15.5)
Vomiting	18 (25.4)	2 (2.8)
AST increased	17 (23.9)	1 (1.4)
Back pain	17 (23.9)	3 (4.2)
Acute kidney injury	16 (22.5)	5 (7.0)
Hypertension	16 (22.5)	9 (12.7)
Abdominal pain	15 (21.1)	5 (7.0)
Headache	15 (21.1)	3 (4.2)
Hypotension	15 (21.1)	10 (14.1)
Pyrexia	15 (21.1)	2 (2.8)

Treatment-emergent (Non-CMV) Infections (≥5% of Patients)

	Total (N=71)	
Event, n (%)	**Any Grade**	**Grade 3/4**
Sepsis	9 (12.7)	8 (11.3)
Bacteremia	7 (9.9)	7 (9.9)
Enterococcal infection	6 (8.5)	4 (5.6)
Urinary tract infection	6 (8.5)	3 (4.2)
Lung infection	6 (8.5)	6 (8.5)

	Total (N=71)	
Event, n (%)	**Any Grade**	**Grade 3/4**
BK virus infection	5 (7.0)	1 (1.4)
Pneumonia	5 (7.0)	5 (7.0)
Staphylococcal infection	5 (7.0)	4 (5.6)
Device-related infection	4 (5.6)	3 (4.2)
Septic shock	4 (5.6)	4 (5.6)

- Treatment-emergent infections of any grade occurred in 57 patients (80.3%); 46 patients (64.8%) had a grade 3/4 infection

CMV Events

CMV Serostatus*	CMV AEs, n (%)			
	CMV Infection	De Novo CMV Viremia	Recurrent CMV Viremia	No CMV AE
D+/R+ (n=24)	8 (33.3)	NA	3 (12.5)	13 (54.2)
D+/R– (n=7)	2 (28.6)	0	NA	5 (71.4)
D–/R+ (n=16)	0	NA	1 (6.3)	15 (93.8)
D–/R– (n=23)	0	0	NA	23 (100.0)
Total	10 (14.1)	0	4 (5.6)	56 (78.9)

* Donor serostatus was missing from 1 patient (patient was positive and did not experience any CMV AEs).

- All patients who had a CMV event (n=14) had a positive CMV donor or recipient serostatus or both at baseline
- No deaths were attributed to CMV events

Conclusions

- In this first prospective trial of ruxolitinib in steroid-refractory aGVHD, ruxolitinib treatment resulted in overall responses in 54.9% of patients at Day 28; 68% had grade III/IV disease at baseline
- The best overall response rate at any time during treatment was 73.2%
- Responses were rapid and durable, with median time to first response of 7 days and median duration of response of 345 days
- Most patients on ruxolitinib had sustained reductions in corticosteroid use over time
  - More than half of patients on ruxolitinib at Day 28 had a ≥50% reduction from baseline in corticosteroid dose
- Relapse rate of underlying malignancy was low (5.6%)
- Ruxolitinib was well tolerated, and the adverse event profile was consistent with the observed safety profiles of ruxolitinib and that of patients with steroid-refractory aGVHD

Backup Slides

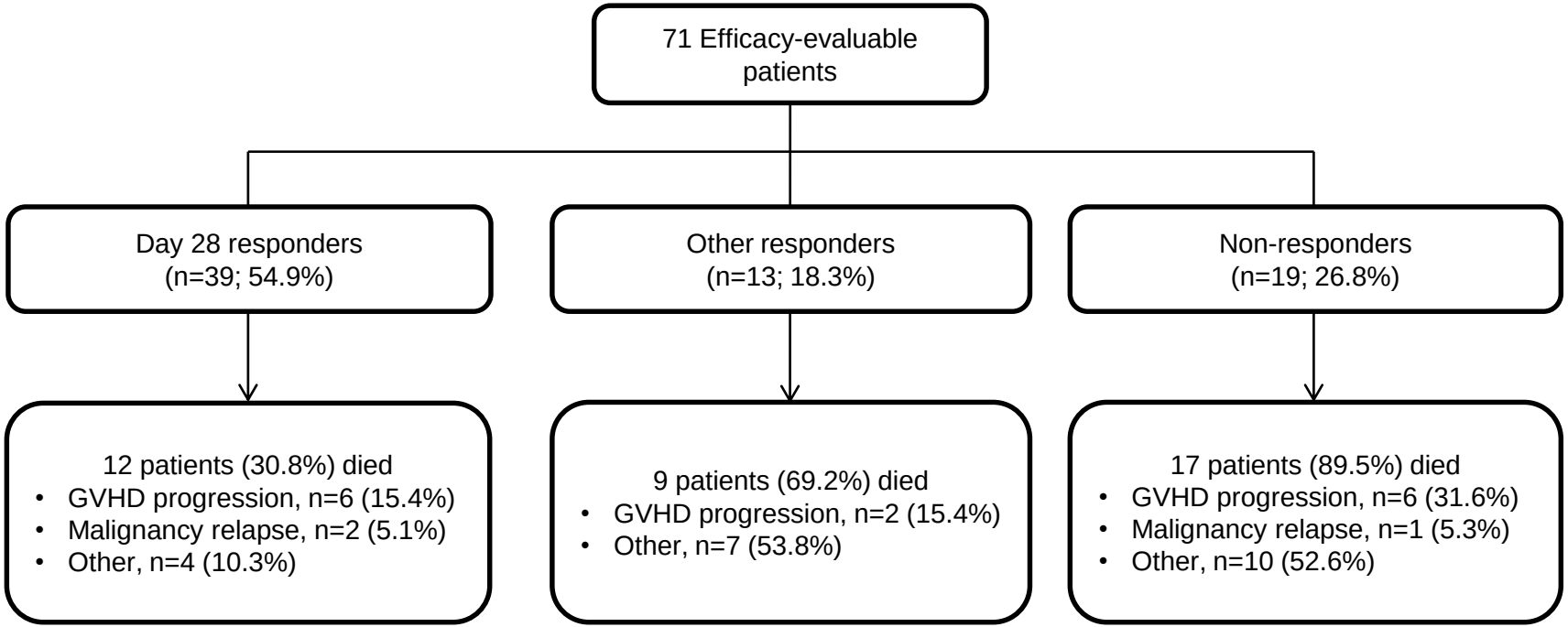
Safety: Ruxolitinib-Related TEAEs (≥5% of Patients)

- Ruxolitinib-related TEAEs of any grade occurred in 53 patients (74.6%); 46 patients (64.8%) had a grade 3/4 ruxolitinib-related TEAE
- Ruxolitinib-related treatment-emergent infections of any grade occurred in 20 patients (28.2%); 15 patients (21.1%) had a grade 3/4 ruxolitinib-related infection
  - Sepsis was the only ruxolitinib-related treatment-emergent infection occurring in ≥5% of patients (n=4; 5.6%; all grade 3/4)
- Fatal ruxolitinib-related TEAEs were sepsis and pulmonary hemorrhage (1 patient each) and were attributed to both ruxolitinib and corticosteroid treatment

Ruxolitinib-Related Hematologic TEAEs (≥5% of Patients)

	Total (N=71)	
Event, n (%)	**Any Grade**	**Grade 3/4**
Anemia	25 (35.2)	20 (28.2)
Platelet count decreased	23 (32.4)	21 (29.6)
Neutrophil count decreased	19 (26.8)	15 (21.1)
WBC count decreased	14 (19.7)	8 (11.3)
Thrombocytopenia	11 (15.5)	9 (12.7)
Lymphocyte count decreased	7 (9.9)	7 (9.9)

Causes of Death by Response Status



Overall Response at Day 28

- Responses were observed irrespective of number of organs involved

Response at Day 28, n (%)	1 Organ Involved (n=35)	≥2 Organs Involved (n=36)
CR	12 (34.3)	7 (19.4)
VGPR	5 (14.3)	2 (5.6)
PR	5 (14.3)	8 (22.2)
Overall response rate 95% CI	**22 (62.9) 44.9–78.5**	**17 (47.2) 30.4–64.5**