EUROPEAN HEMATOLOGY ASSOCIATION

EHA25 VIRTUAL

GRAVITAS-301: A Randomized, Double-Blind Phase 3 Study of Itacitinib or Placebo in Combination With Corticosteroids for Initial Treatment of Patients With Acute Graft-Versus-Host Disease

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Background

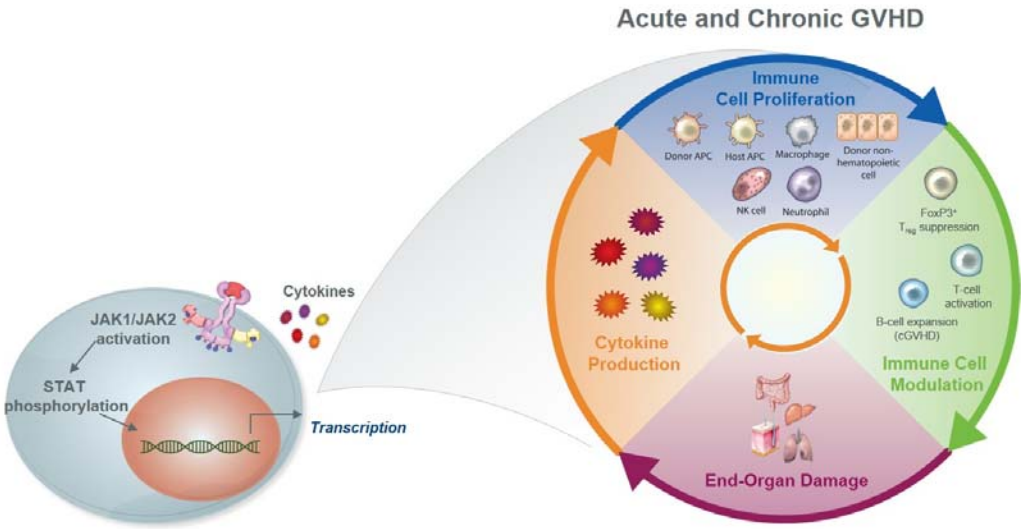
- Allogeneic HCT is the only potentially curative treatment option for several advanced hematologic malignancies and nonmalignant diseases[1,2]
- Approximately 30% to 60% of patients undergoing HCT develop grade ≥II acute GVHD,[3,4] a substantial cause of morbidity and mortality, and a major obstacle to successful HCT outcomes[5]
- Corticosteroids are standard of care for initial acute GVHD therapy; however, 35% to 60% of patients become refractory to treatment, and prolonged systemic exposure is associated with toxicity and morbidity[6-8]
- Novel treatment strategies targeting key pathogenic mechanisms underlying acute GVHD pathogenesis may improve outcomes for a large proportion of patients[9]

GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation.

1. Magenau J and Couriel DR. *Curr Oncol Rep*. 2013;15:436-444; 2. D'Souza A and Fretham C. CIBMTR Summary Slides. 2019. Available at: https://www.cibmtr.org; 3. Greco R, et al. *Front Immunol*. 2019;10:2319; 4. Jagasia M, et al. *Blood*. 2012;119(1):296-307; 5. Holtan SG, et al. *Blood*. 2015;125(8):1333-1338; 6. Axt L, et al. *Bone Marrow Transplant*. 2019;54:1805-1814; 7. Major-Monfried H, et al. *Blood*. 2018;131(25):2846-2855; 8. Bacigalupo A, et al. *Haematologica*. 2017;102(12):2125-2133; 9. Zeiser R. *Br J Haematol*. 2019;187:563-572.

Study Rationale

- JAKs contribute to GVHD pathogenesis by mediating intracellular signaling of pro-inflammatory cytokine receptors[1]
- Itacitinib is a potent, selective JAK1 inhibitor that was well tolerated and showed preliminary efficacy in a phase 1 study of patients with corticosteroid-refractory or -naive acute GVHD[2]



APC, antigen-presenting cell; cGVHD, chronic GVHD; GVHD, graft-versus-host disease; JAK, Janus kinase; NK, natural killer; STAT, signal transducer and activator of transcription; Treg, regulatory T cell.

1. Schroeder MA, et al. *Biol Blood Marrow Transplant*. 2018;24(6):1125-1134; 2. Schroeder MA, et al. *Blood Adv*. 2020;4(8):1656-1669.

GRAVITAS-301 Study Design

First-line acute GVHD (N=439)

Patients stratified by high vs standard risk

Eligibility:
- Age ≥18 years
- Received allogeneic HCT for hematologic malignancy
- Developed grades II–IV acute GVHD per MAGIC criteria
- Evidence of myeloid engraftment
- ≤2 days of corticosteroids for GVHD

Exclusion criteria:
- >1 allogeneic HCT
- Active infection or severe organ failure
- Prior receipt of JAK inhibitor
- Evidence of malignancy relapse or GVHD overlap syndrome

1:1

Itacitinib 200 mg QD + Corticosteroids*

Placebo + Corticosteroids*

End of treatment → **Overall survival**

Primary endpoint:
- ORR (CR, VGPR, or PR) at Day 28

Select secondary/exploratory endpoints:
- Key secondary: 6-month NRM
- Duration of response
- Overall survival
- Failure-free survival
- Steroid use
- Chronic GVHD incidence
- Safety

* Methylprednisolone 2 mg/kg/d, prednisone equivalent, or an appropriate dose per local treatment guidelines.
CR, complete response; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; JAK, Janus kinase; MAGIC, Mt. Sinai Acute GVHD International Consortium; NRM, nonrelapse mortality; ORR, overall response rate; PR, partial response; QD, once daily; VGPR, very good partial response.

GRAVITAS-301 Statistical Assumptions

- A sample size of 414 patients was calculated to allow for the detection of an absolute improvement in ORR at Day 28 of 16% (ie, 72% vs 56%) with 90% statistical power (1-sided alpha of 0.025)
  - The assumed ORR of 56% was based on a standard-risk/high-risk ratio of 0.50/0.50 with a stratum-specific response rate of 68% and 44%, respectively[1]

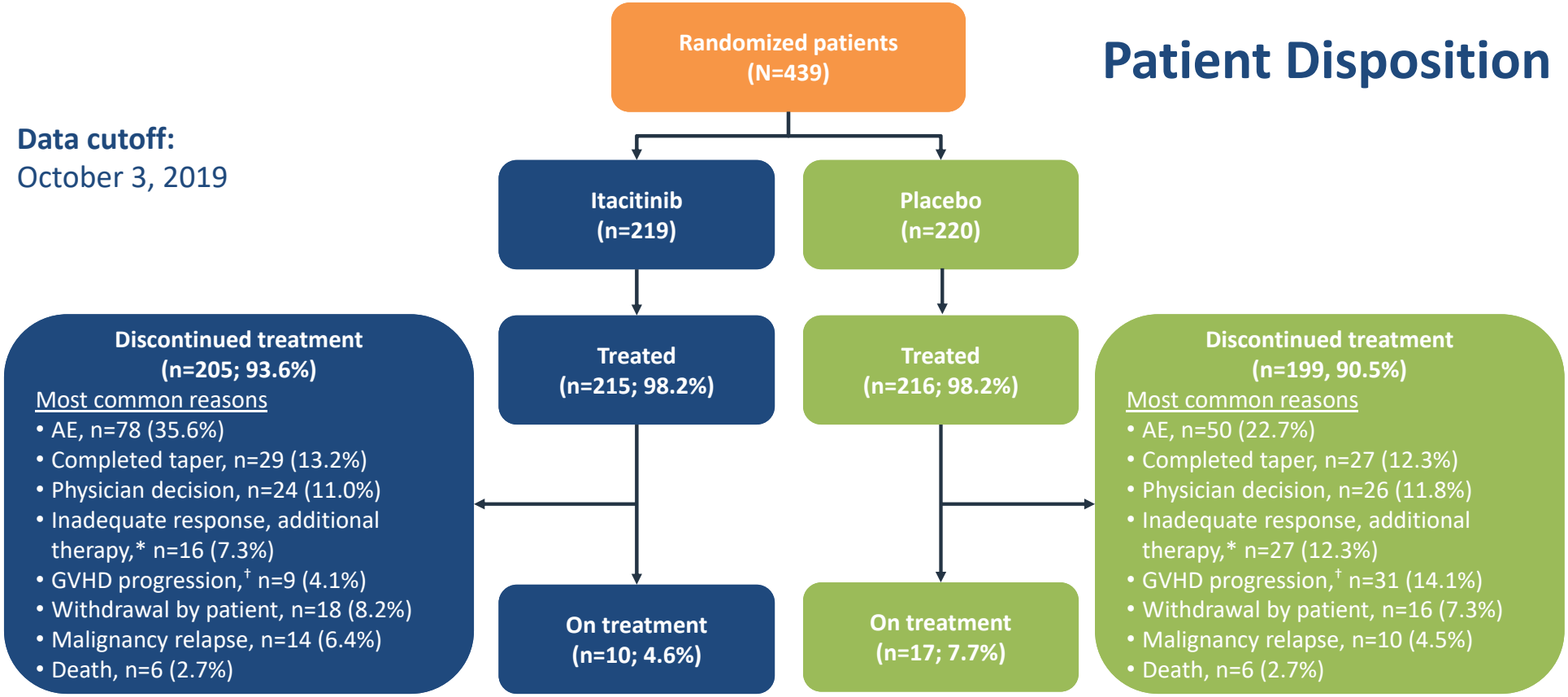
- The sample size of 414 patients would allow for the detection of an absolute difference in NRM at Month 6 of 13.2% (ie, 19.2% vs 33%) with 83% power (1-sided alpha of 0.025)

NRM, nonrelapse mortality; ORR, overall response rate.

1. MacMillan ML, et al. *Biol Blood Marrow Transplant*. 2015;21(4):761-767.

Patient Disposition

Data cutoff:
October 3, 2019



AE, adverse event; GVHD, graft-versus-host disease; MAGIC, Mt. Sinai Acute GVHD International Consortium.
* Inadequate response requiring additional therapy was defined as investigator determination that response was suboptimal and decision to switch to another therapy (or increase corticosteroids to a dose higher than the Day 1 dose), although MAGIC criteria for GVHD progression were not met. † GVHD progression was defined as a worsening of GVHD meeting MAGIC criteria for progression.

Demographics and Baseline Disease Characteristics

Demographic Characteristics	Itacitinib (n=219)	Placebo (n=220)
Age, median (range), y	58.0 (18-78)	58.0 (19-77)
<65 y, n (%)	166 (75.8)	170 (77.3)
≥65 y, n (%)	53 (24.2)	50 (22.7)
Male, n (%)	137 (62.6)	129 (58.6)
Race, n (%)		
White	196 (89.5)	194 (88.2)
Black/African American	8 (3.7)	5 (2.3)
Asian	4 (1.8)	4 (1.8)
Other*	10 (4.6)	13 (5.9)
Missing	1 (0.5)	4 (1.8)
Region, n (%)		
North America	93 (42.5)	93 (42.3)
Western Europe	110 (50.2)	107 (48.6)
Rest of world	16 (7.3)	20 (9.1)

Disease Characteristics	Itacitinib (n=219)	Placebo (n=220)
MAGIC grade, n (%)		
0	2 (0.9)	1 (0.5)
1	2 (0.9)	5 (2.3)
2	154 (70.3)	149 (67.7)
3	51 (23.3)	51 (23.2)
4	5 (2.3)	10 (4.5)
Missing	5 (2.3)	4 (1.8)
GVHD risk, n (%)		
Standard	168 (76.7)	164 (74.5)
High	51 (23.3)	56 (25.5)

GVHD, graft-versus-host disease; MAGIC, Mt. Sinai Acute GVHD International Consortium.
* Includes American-Indian/Alaska native, native Hawaiian/Pacific Islander, and “other.”

Primary Endpoint: Overall Response Rate at Day 28

Post Hoc Analysis: Day 28 Response by Risk Status

– The study did not meet its primary endpoint of improved Day 28 ORR with itacitinib vs placebo

	Itacitinib (n=219)	Placebo (n=220)	Odds Ratio (95% CI); *P* Value
Day 28 ORR, n (%) [95% CI]	162 (74.0) [67.6-79.7]	146 (66.4) [59.7-72.6]	1.45 (0.959-2.204); *P*=0.0782
CR	116 (53.0)	89 (40.5)	
VGPR	27 (12.3)	33 (15.0)	
PR	19 (8.7)	24 (10.9)	

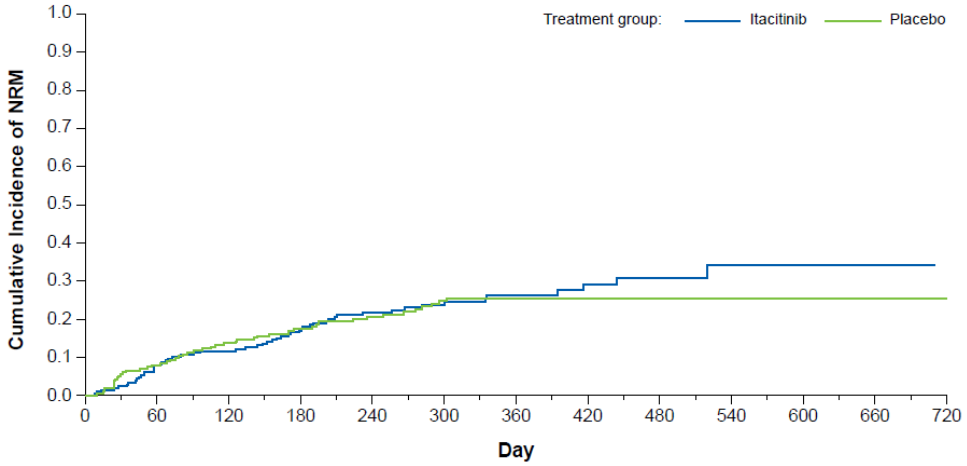
– In a post hoc analysis of CR rates stratified by GVHD risk status, itacitinib was associated with significantly improved CR vs placebo

	Standard Risk		High Risk	
	Itacitinib (n=162)	Placebo (n=163)	Itacitinib (n=57)	Placebo (n=57)
Day 28 ORR, n (%)	127 (78.4)	114 (69.9)	35 (61.4)	32 (56.1)
Odds ratio (95% CI); P value	1.56 (0.94-2.58); *P*=0.082		1.24 (0.59-2.62); *P*=0.570	
Day 28 CR, n (%)	92 (56.8)	69 (42.3)	24 (42.1)	20 (35.1)
Odds ratio (95% CI); *P* value	1.66 (1.14-2.44); *P*=0.008			

CR, complete response; GVHD, graft-versus-host disease; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

Malignancy Relapse and Nonrelapse Mortality

- Malignancy relapse occurred in 27 (12.4%) patients randomized to itacitinib and 24 (10.9%) randomized to placebo
  - Death owing to malignancy relapse occurred in 10 (4.6%) and 16 (7.3%) patients, respectively
- There was no difference in terms of NRM between the treatment groups

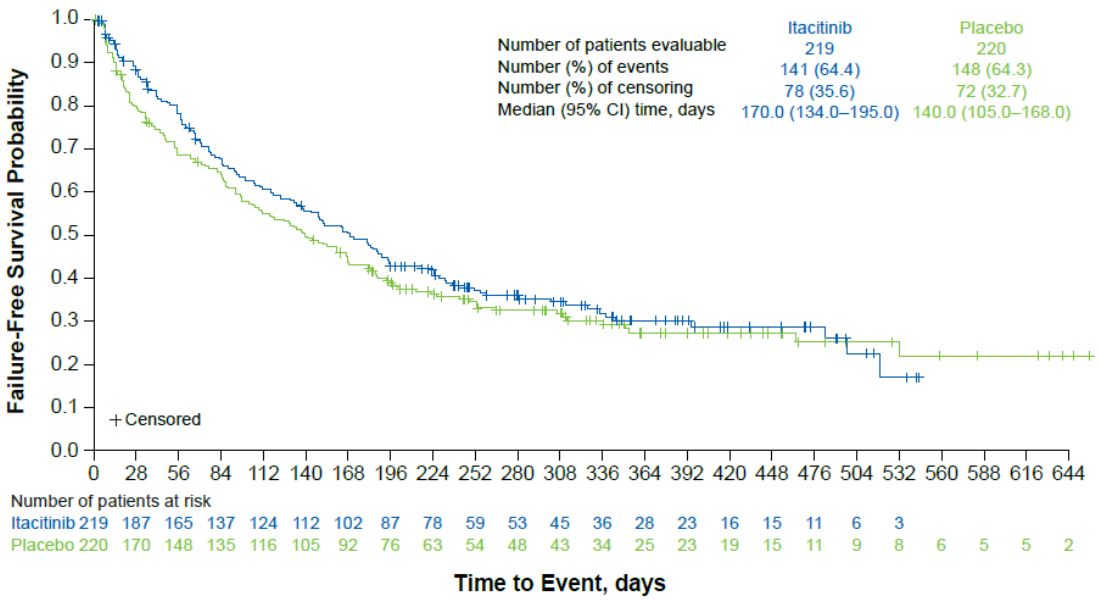


6-Month NRM	Itacitinib (n=197)	Placebo (n=196)
NRM, n (%) [95% CI]	36 (18.3) [13-24]	37 (18.9) [14-25]
	P=0.7952	
Standard risk, n (%)	n=144	n=146
	20 (13.9)	19 (13.0)
High risk, n (%)	n=54	n=50
	17 (31.5)	18 (36.0)

NRM, nonrelapse mortality.

Failure-Free Survival

Failure-Free Survival*	Itacitinib (n=219)	Placebo (n=220)
Median follow-up, d	148	130
Failure event, n (%)	141 (64.4)	148 (67.3)
Initiate new GVHD therapy	61 (27.9)	65 (29.5)
Chronic GVHD	30 (13.7)	49 (22.3)
Relapse of underlying hematologic disease	24 (11.0)	14 (6.4)
Death (not malignancy relapse)	26 (11.9)	17 (7.7)
Death (malignancy relapse)	0	2 (0.9)
Death (unknown reason)	0	1 (0.5)
Event-free probability estimates, % (95% CI)		
6 months	49 (42-56)	43 (36-49)
1 year	30 (23-37)	27 (21-34)
Time to failure, median (range), d	148.0 (1-546)	129.5 (1-658)
	P=0.3560	

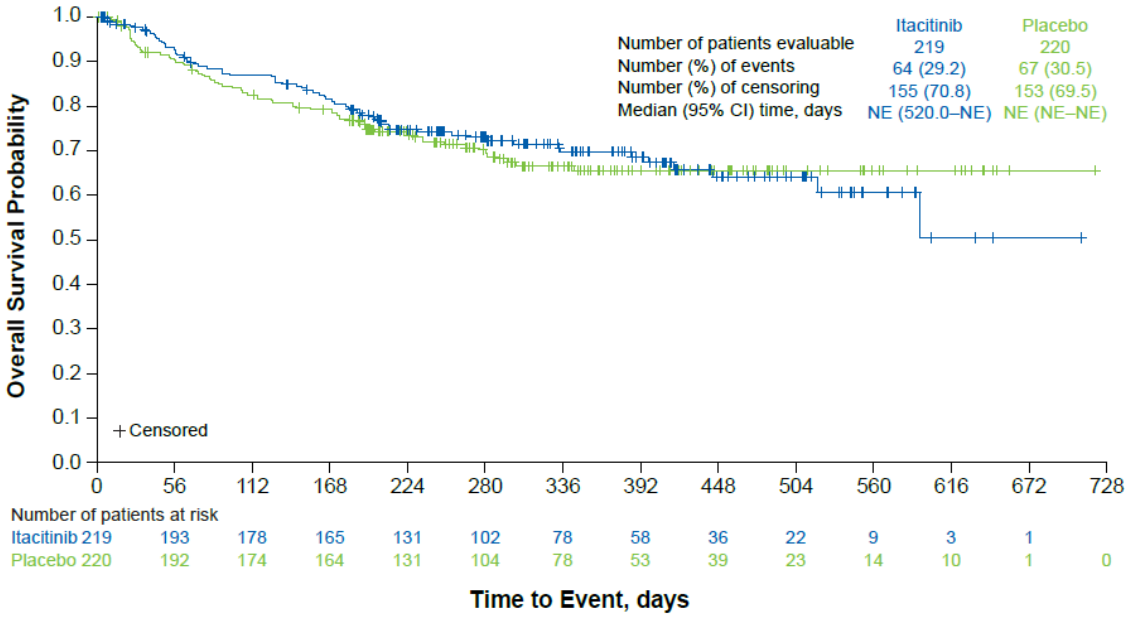


GVHD, graft-versus-host disease.

* Failure-free survival was defined as the time that a patient had not relapsed, required no additional acute GVHD therapy, demonstrated no signs or symptoms of chronic GVHD, and was still alive. Patients with no such event were censored at the date of study withdrawal or last contact.

Overall Survival

Overall Survival	Itacitinib (n=219)	Placebo (n=220)
Median follow-up, d	267	
Deaths, n (%)	64 (29.2)	67 (30.5)
Event-free probability estimates (95% CI)		
6 months	80% (74-85)	77% (71-82)
1 year	70% (62-76)	66% (58-72)
Time to death, median (range), d	273.0 (1-710)	266.5 (1-720)
	P=0.7414	



NE, not evaluable.

Other Efficacy Endpoints

Corticosteroid Use

– Median (range) duration of steroid use was 47.0 (2–310) days in the itacitinib group and 44.0 (1–591) days in the placebo group

Time to Response and Duration of Response

	Itacitinib (n=219)	Placebo (n=220)
Time to first response, median (range), d	8.0 (5-55)	8.0 (5-41)
Duration of response, median (range), d	180.0 (1-587)	174.0 (1-633)
Estimate of 6-month response durability (95% CI)	83% (76-88)	83% (76-89)

Most Common TEAEs

(≥20% Any Grade or >5% Grade ≥3 in Either Group)

TEAEs	Itacitinib (n=215)		Placebo (n=216)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE, n (%)	208 (96.7)	185 (86.0)	214 (99.1)	178 (82.4)
Thrombocytopenia/platelet count decreased	107 (49.8)	78 (36.3)	93 (43.1)	68 (31.5)
CMV infections	80 (37.2)	18 (8.4)	68 (31.5)	16 (7.4)
Anemia	64 (29.8)	40 (18.6)	54 (25.0)	26 (12.0)
Neutropenia/neutrophil count decreased	56 (26.0)	49 (22.8)	56 (25.9)	45 (20.8)
Peripheral edema	54 (25.1)	4 (1.9)	52 (24.1)	1 (0.5)
Hyperglycemia	50 (23.3)	26 (12.1)	52 (24.1)	28 (13.0)
Diarrhea	48 (22.3)	14 (6.5)	53 (24.5)	22 (10.2)
Pyrexia	48 (22.3)	11 (5.1)	36 (16.7)	8 (3.2)
Hypertension	46 (21.4)	17 (7.9)	31 (14.4)	14 (6.5)
Hypokalemia	42 (19.5)	10 (4.7)	35 (16.2)	11 (5.1)
Hypertriglyceridemia	32 (14.9)	21 (9.8)	27 (12.5)	9 (4.2)
ALT increased	31 (14.4)	15 (7.0)	21 (9.7)	4 (1.9)
Pneumonia	14 (6.5)	11 (5.1)	21 (9.7)	15 (6.9)
Febrile neutropenia	11 (5.1)	11 (5.1)	14 (6.5)	13 (6.0)

– Fungal infections were reported in 22 patients (10.2%; grade ≥3, n=5 [2.3%]) and 23 patients (10.6%; grade ≥3, n=7 [3.2%]) in the itacitinib and placebo treatment groups, respectively

ALT, alanine aminotransferase; CMV, cytomegalovirus; TEAE, treatment-emergent adverse event.

Fatal Adverse Events

Fatal TEAEs	Itacitinib (n=215)	Placebo (n=216)
Fatal TEAEs, n (%)	22 (10.2)	29 (13.4)
Fatal TEAEs by system organ class,* n (%)		
Infections and infestations	13 (6.0)	13 (6.0)
Sepsis	3 (1.4)	3 (1.4)
Septic shock	1 (0.5)	3 (1.4)
Pneumonia	0	2 (0.9)
Immune system disorders	2 (0.9)	7 (3.2)
Acute GVHD	0	2 (0.9)
GVHD	1 (0.5)	2 (0.9)
GVHD in GI tract	1 (0.5)	2 (0.9)
Neoplasms† (benign, malignant, and unspecified)	2 (0.9)	5 (2.3)

Fatal TEAEs (cont'd)	Itacitinib (n=215)	Placebo (n=216)
Fatal TEAEs by system organ class,* n (%)		
Respiratory, thoracic, and mediastinal disorders	3 (1.4)	3 (1.4)
Respiratory failure	1 (0.5)	2 (0.9)
Hepatobiliary disorders	2 (0.9)	1 (0.5)
Blood and lymphatic disorders	0	2 (0.9)
GI disorders	2 (0.9)	0
General disorders and administration site conditions	1 (0.5)	1 (0.5)
Nervous system disorders	1 (0.5)	1 (0.5)
Cardiac disorders	0	1 (0.5)
Renal and urinary disorders	1 (0.5)	0

GI, gastrointestinal; GVHD, graft-versus-host disease; TEAE, treatment-emergent adverse event.
* Preferred terms are provided below the system organ class categories for TEAEs reported in ≥2 patients in either group. † Malignancy relapse in all cases.

Conclusions

- Itacitinib added to corticosteroids for the initial treatment of acute GVHD was well tolerated but did not significantly improve Day 28 ORR, 6-month NRM, or overall survival vs placebo plus corticosteroids
- Post hoc analysis showed significant association with Day 28 complete response rates; further analyses are needed to understand if this finding translates into clinical benefit
- More patients in the placebo group discontinued study treatment because of GVHD progression/inadequate response requiring additional therapy compared with the itacitinib group
- Assumptions used in powering the study may have led to over-enrollment of standard risk or grade II patients and over-performance of the placebo group

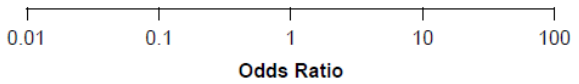
GVHD, graft-versus-host disease; NRM, nonrelapse mortality; ORR, overall response rate.

Back-up

Day 28 ORR: Subgroup Analysis

- Subgroup analyses did not reveal significant differences between treatment groups when stratified by patient demographic or baseline disease characteristic factors

Subgroup	Patients, n	Odds Ratio (95% CI)
All patients	439	1.45 (0.959–2.204)
Stratification		
Standard risk	325	1.56 (0.944–2.577)
High risk	114	1.24 (0.589–2.623)
Age		
18–65 y	336	1.49 (0.928–2.394)
≥65 y	103	1.34 (0.558–3.196)
65–74 y	98	1.25 (0.514–3.040)
75–84 y	5	(NE–NE)
MacMillan age		
18–40 y	77	0.58 (0.187–1.824)
>40 y	362	1.73 (1.094–2.733)
Sex		
Male	266	1.32 (0.772–2.249)
Female	173	1.74 (0.890–3.417)
Race		
White/Caucasian	390	1.67 (1.064–2.614)
Non-White/Caucasian	44	0.54 (0.152–1.920)
Region		
North America	186	1.08 (0.573–2.051)
Western Europe	217	1.73 (0.945–3.151)
Rest of World	36	2.15 (0.483–9.557)
HLA/donor source combined		
Matched related	113	1.28 (0.562–2.933)
Matched unrelated	169	1.43 (0.735–2.768)
Mismatched related	101	1.91 (0.784–4.664)
Mismatched unrelated	56	1.27 (0.393–4.097)
Allogeneic transplant type		
Bone marrow	59	1.47 (0.508–4.278)
Peripheral blood stem cell	372	1.50 (0.950–2.378)
Cord blood	8	(NE–NE)
Baseline aGVHD grade		
Grade I	7	(NE–NE)
Grade II	303	1.92 (1.089–3.396)
Grade III	102	1.17 (0.537–2.554)
Grade IV	15	0.56 (0.038–8.085)
Skin involvement at baseline		
Yes	296	1.81 (1.050–3.108)
No	135	0.99 (0.490–2.004)
Lower GI involvement at baseline		
Yes	184	1.28 (0.692–2.357)
No	245	1.65 (0.884–3.098)
Upper GI involvement at baseline		
Yes	132	1.52 (0.737–3.130)
No	299	1.44 (0.844–2.450)
Liver involvement at baseline		
Yes	24	0.89 (0.142–5.518)
No	407	1.49 (0.961–2.311)



GI, gastrointestinal; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; NE, not evaluable; ORR, overall response rate.

Chronic GVHD

	Itacitinib (n=219)		Placebo (n=220)	
Patients with chronic GVHD,* n (%)	42 (19.2)		59 (26.8)	
Chronic GVHD grade at onset,† n (%)				
Mild	32 (14.6)		43 (19.5)	
Moderate	8 (3.7)		13 (5.9)	
Severe	2 (0.9)		3 (1.4)	
Cumulative incidence of chronic GVHD by risk status	n	n (%)	n	n (%)
Standard	162	34 (21.0)	163	48 (29.4)
High	57	8 (14.0)	57	11 (19.3)

GVHD, graft-versus-host disease.
* Number (%) of patients experiencing chronic GVHD during the study, unadjusted for withdrawal of study medication or loss to follow-up. † When first presented to the investigator.