Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

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List of Participating REACH3 Investigators

Investigator	Trial Site Name	Trial Site Country
David Ritchie	Royal Melbourne Hospital	Australia
Nada Hamad	St Vincent's Health Network, Kinghorn Cancer Centre	Australia
Johannes Clausen	Ordensklinikum Linz Elisabethinen	Austria
Margit Mitterbauer	Universitaetsklinik fuer Innere Medizin I	Austria
Hildegard Greinix	Universitatsklinik fur Innere Medizin	Austria
Hélène Schoemans	Gasthuisberg University Hospital	Belgium
Dimitri Breems	ZNA Stuivenberg	Belgium
Penka Ganeva	National Specialized Hospital for Active Treatment of Hematological Diseases	Bulgaria
Dennis Kim	Princess Margaret Cancer Centre	Canada
Brian Leber	The Juravinski Cancer Centre	Canada
Jennifer White	Vancouver General Hospital	Canada
Pavel Zak	Faculty Hospital Hradec Kralove	Czech Republic
Veronika Valkova	Institute of Hematology and Blood Transfusion	Czech Republic
Brian Thomas Kornblit	Rigshospitalet	Denmark
Ibrahim Yakoub Agha	CHU de Lille	France
Jean-Baptiste Mear	CHU de Rennes	France
Marie-Therese Rubio	CHRU de Nancy Hôpital Brabois	France
Gerard Socié	Hôpital Saint-Louis	France
Anne Laplace	Hôpitaux Universitaires de Strasbourg	France
Mohamad Mohty	Hôpital Saint-Antoine	France
Anne Huynh	IUCT Oncopole CHU	France
Herrad Baurmann	Helios Kliniken GmbH Berlin Buch	Germany

Guido Kobbe	Universitaetsklinikum Düsseldorf	Germany
Tobias Holderried	Universitaetsklinikum Bonn	Germany
Jan Moritz Middeke	Universitaetsklinikum Dresden	Germany
Julia Winkler	Universitaetsklinikum Erlangen Nürnberg	Germany
Klaus Daniel Stachel	Universitaetsklinikum Erlangen Nürnberg	Germany
Gesine Bug	Universitaetsklinikum Frankfurt	Germany
Robert Zeiser	Universitaetsklinikum Freiburg	Germany
Francis Ayuketang Ayuk	Universitaetsklinikum Hamburg Eppendorf	Germany
Inken Hilgendorf	Universitaetsklinikum Jena Klinik für Innere Medizin II, Abteilung für Hämatologie und Internistische Onkologie	Germany
Udo Holtick	Universitaetsklinikum Koeln	Germany
Georg-Nikolaus Franke	Universitaetsklinikum Leipzig AoR	Germany
Eva Wagner	Universitaetsklinikum Mainz	Germany
Stefan Klein	Universitaetsklinikum Mannheim	Germany
Matthias Stelljes	Universitaetsklinikum Muenster	Germany
Natalie Schub	Universitaetsklinikum Schleswig Holstein Campus Kiel	Germany
Goetz Grigoleit	Universitaetsklinikum Wuerzburg	Germany
Achilleas Anagnostopoulos	General Hospital of Thessaloniki “George Papanikolaou”	Greece
Panagiotis Tsirigotis	University General Hospital ATTIKON	Greece
Alexandros Spyridonidis	University General Hospital of Patra Panagia I Voitheia	Greece
Dinesh Bhurani	Rajiv Gandhi Cancer Institute and Research Centre	India
Shashikant Apte	Sahyadri Speciality Hospital	India

Moshe Yeshurun	Rabin Medical Center Petah-Tikva, Tel-Aviv University	Israel
Tsila Zuckerman	Rambam Health Care Campus Technion	Israel
Ron Ram	Tel Aviv Sourasky Medical Center Ichilov	Israel
Franca Fagioli	Az Osp Città della Salute e Scienza-PO Infant Regina Margherita	Italy
Domenico Russo	ASST degli Spedali Civili di Brescia Univ degli Studi	Italy
Maria Caterina Micò	ASST Papa Giovanni XXIII	Italy
Francesca Bonifazi	Az Osp di Bologna Policl S Orsola Malpighi Univ degli Studi	Italy
Lucia Prezioso	Az Osp Universitaria di Parma Univ degli Studi	Italy
Francesca Patriarca	Az Osp - Universit Santa Maria della Misericordia di Udine	Italy
Maurizio Musso	Casa di Cura di Alta Spec La Maddalena Dip Onc III livel	Italy
Paolo Corradini	Fondazione IRCCS Istituto Nazionale dei Tumori	Italy
Angelo Michele Carella	IRCCS Casa Sollievo della Sofferenza	Italy
Stefania Bramanti	IRCCS Istituto Clinico Humanitas	Italy
Franco Locatelli	IRCCS Ospedale Pediatrico Bambino Gesù	Italy
Francesca Gualandi	Ospedale Policlinico San Martino IRCCS	Italy
Fabio Ciceri	Ospedale San Raffaele IRCCS S R L	Italy
Attilio Olivieri	Ospedali Riuniti di Ancona	Italy
Luisa Giaccone	P O Molinette AO Citta della Salute e della Scienza Torino	Italy
Takanori Teshima	Hokkaido University Hospital	Japan

Masaya Okada	Hyogo College of Medicine Hospital	Japan
Koichi Miyamura	Japanese Red Cross Nagoya Daiichi Hospital	Japan
Masahiro Ashizawa	Jichi Medical University Hospital	Japan
Takehiko Mori	Keio University Hospital	Japan
Takayuki Ishikawa	Kobe City Medical Center General Hospital	Japan
Tadakazu Kondo	Kyoto University Hospital	Japan
Koji Kato	Kyushu University Hospital	Japan
Yoshinobu Maeda	Okayama University Hospital	Japan
Hirohisa Nakamae	Osaka City University Hospital	Japan
Kentaro Fukushima	Osaka University Hospital	Japan
Takashi Ikeda	Shizuoka Cancer Center	Japan
Yasushi Onishi	Tohoku University Hospital	Japan
Kiyoshi Ando	Tokai University Hospital	Japan
Noriko Doki	Tokyo Metropolitan Komagome Hospital	Japan
Shuichi Taniguchi	Toranomon Hospital	Japan
Husam AbuJazar	King Hussein Cancer Center	Jordan
Sung-Soo Yoon	Seoul National University Hospital	Korea, Republic of
C. J. M. Halkes	Leids Universitair Medisch Centrum	Netherlands
J. H. E. Kuball	University Medical Center Utrecht (UMCU)	Netherlands
Tobias Gedde-Dahl	Oslo Universitetssykehus HF Rikshospitalet	Norway
Sebastian Giebel	Centrum Onkologii Instytut; Oddzial w Gliwicach	Poland
Jan Zaucha	UCK Klinika Hematologii i Transplantologii	Poland
Tomasz Wrobel	Uniwersytecki Szpital Kliniczny	Poland
Isabelina Ferreira	Instituto Português de Oncologia de Lisboa Francisco Gentil (IPOLFG)	Portugal
Elena Parovichnikova	Hematological Scientific Center of RAMS	Russia

Ivan Moiseev	St Petersburg State Medical University n.a. Pavlov	Russia
Shahrukh Hashmi	King Faisal Specialist Hospital and Research Center Riyadh	Saudi Arabia
Sonia Gonzalez Perez	Hospital Clinico Universitario de Santiago	Spain
Carlos Vallejo	Hospital de Donostia	Spain
Isabel Sanchez Ortega	Hospital Durans I Reynals ICO	Spain
Valle Gómez	Hospital Universitario de la Princesa	Spain
Lucia Del Corral	Hospital Universitario de Salamanca	Spain
Maria del Mar Perera Alvarez	Hospital Universitario Doctor Negrin	Spain
Andres Sanchez Salinas	Hospital Universitario Virgen Arrixaca	Spain
Jose Antonio Perez Simon	Hospital Virgen del Rocio	Spain
Krista Vath	Sahlgrenska Universitetssjukhuset	Sweden
Joerg Halter	Universitaetsspital Basel	Switzerland
Antonia Mueller	Universitaetsspital Zuerich - Klinik fur Haematologie	Switzerland
Ant Uzay	Acıbadem Atakent Hospital	Turkey
Sinem Civriz Bozdag	Ankara University Medical Faculty	Turkey
Erdal Kurtoglu	Antalya Training and Research Hospital	Turkey
Fevzi Altuntas	Dr Abdurrahman Yurtarslan Ankara Onkoloji Training and Research	Turkey
Hakan Goker	Hacettepe University Medical Faculty	Turkey
Hugues De Lavallade	Kings College Hospital NHS Foundation Trust	United Kingdom
Fiona Dignan	Manchester Royal Infirmary	United Kingdom
David Irvine	Queen Elizabeth University Hospital	United Kingdom
Ronjon Chakraverty	University College Hospital London	United Kingdom

Emi Caywood	Nemours/Alfred I. duPont Hospital for Children	United States
Murali Kodali	Arizona Cancer Center	United States
Malgorzata McMasters	Beth Israel Deaconess Medical Center/ Harvard Medical School	United States
Ali Haris	City of Hope National Medical Center	United States
Betty Hamilton	Cleveland Clinic	United States
Mitchell Horwitz	Duke University Medical Center	United States
Joseph Pidala	H. Lee Moffitt Cancer Center and Research Institute, Inc.	United States
John Edwards	Indiana Blood and Marrow Institute	United States
Michael Grunwald	Levine Cancer Institute, Carolinas Healthcare System	United States
Patrick Stiff	Loyola University Medical Center/Cardinal Bernardin Cancer Center	United States
Reshma Ramlal	Markey Cancer Center	United States
Zachariah DeFilipp	Massachusetts General Hospital	United States
Amin Alousi	MD Anderson Cancer Center	United States
Nirav Shah	Medical College of Wisconsin, Inc.	United States
Miguel Perales	Memorial Sloan Kettering Cancer Center	United States
Anne Renteria	Mount Sinai School of Medicine	United States
Jennifer Choi	Northwestern University	United States
Samantha Jaglowski	Ohio State University Wexner Medical Center	United States
Essell James	Oncology Hematology Care, Inc	United States
Mary Flowers	Seattle Cancer Care Alliance	United States
Aric Hall	The University of Wisconsin	United States
Salmon Fazal	The Western Pennsylvania Hospital	United States

Leland Metheny	University Hospitals Cleveland - Seidman Cancer Center	United States
Gary Schiller	University of California, Los Angeles	United States
Dimitrios Tzachanis	University of California, San Diego	United States
Andrew Artz	University of Chicago Medical Center, Hematology & Oncology	United States
Nosha Farhadfar	University of Florida	United States
Damiano Rondelli	University of Illinois at Chicago	United States
Sunil Abhyankar	University of Kansas Medical Center	United States
Jan Cerny	University of Massachusetts Medical School	United States
Vijaya Bhatt	University of Nebraska Medical Center	United States
William Wood	University of North Carolina	United States
Carrie Yuen	University of Oklahoma Health Sciences Center	United States
Mary Ellen Martin	University of Pennsylvania - Abramson Cancer Center	United States
Annie Im	University of Pittsburgh Cancer Institute	United States
George Yaghmour	USC/Kenneth Norris Comprehensive Cancer Center	United States
Madhuri Vusirikala	UT Southwestern Medical Center	United States
Madan Jagasia	Vanderbilt Institute for Clinical and Translational Research	United States
Dianna Howard	Wake Forest Baptist Health	United States
Stuart Seropian	Yale Cancer Center	United States

Data Monitoring Committee

An independent data monitoring committee (DMC) was added based on health authority feedback. The DMC reviewed safety on a regular basis and was requested to recommend whether the study should continue with or without modification or should be stopped or if additional data were required for review. The DMC reviewed the full closed DMC report, particularly the distribution of safety events (serious adverse events [AEs], deaths, and graft failures) between treatment arms. The DMC was also responsible for reviewing efficacy and safety data during the conduct of the interim analyses as defined in the protocol and DMC charter. The DMC reviewed interim analysis results, with the request to inform the sponsor only if all three endpoints were positive; the DMC recommended continuing the study as planned. The results of the interim analysis were generated by an external contract research organization and provided to the DMC by an independent external statistician. The sponsors had no access to the interim results.

DMC members

Prof Dr med Daniel Wolff (DMC chairperson)
Department of Internal Medicine III
University Hospital of Regensburg
Regensburg, Germany

Dr Richard T. Maziarz, MD (hematologist)
Center for Hematologic Malignancies
Oregon Health & Science University
Portland, OR, USA

Dr Claudia Schmoor, PhD (DMC biostatistician)
Clinical Trials Unit, Faculty of Medicine and Medical Center
University Medical Center Freiburg
Freiburg, Germany

Supplementary Methods

Patients

Patients had undergone allogeneic stem cell transplantation from any donor source using bone marrow, peripheral blood stem cells, or cord blood and had evident myeloid and platelet engraftment: absolute neutrophil count >1×10^9/L and platelet count >25×10^9/L. Patients were receiving systemic or topical glucocorticoids for the treatment of chronic graft-versus-host disease (cGVHD) for a duration of <12 months prior to cycle 1 day 1 and had a confirmed diagnosis of glucocorticoid-refractory or -dependent cGVHD defined per 2014 National Institutes of Health (NIH) consensus criteria[1] as:

- A lack of response or disease progression after administration of minimum prednisone 1 mg/kg/day for ≥1 week (or equivalent) *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 equivalent) *or*
- Increase to prednisone dose to >0.25 mg/kg/day after two unsuccessful attempts to taper the dose (or equivalent)

Statistical Analysis

Statistical tests of the primary and the two key secondary endpoints at the interim analysis and the primary analysis were performed according to an overall hierarchical testing procedure[2] in a two-look group sequential study design to hold the overall one-sided family-wise error rate of alpha=0.025. Per study protocol, the testing sequence for key secondary endpoints differed for US (modified Lee Symptom Scale [mLSS] tested before failure-free survival [FFS]) and non-US (FFS tested before mLSS).

- Interim analysis (N=196): significance level for one-sided test as per the predefined alpha-spending function was alpha=0.01176
- Primary analysis (N=329): significance level for one-sided test is alpha=0.01858 (remaining alpha, if not rejected at interim analysis)

- *P* values for the primary analysis are given for descriptive purposes if significance was already achieved at the interim analysis

The overall one-sided type I error for the primary and both key secondary endpoints was preserved by the overall hierarchical testing procedure. Using this procedure allowed testing of all three endpoints at the interim and the primary analysis, maintaining the overall family-wise one-sided error of alpha=0.025 (**Figure S2**).[2]

When reviewing interim data, the DMC compared one-sided *P* values to the targeted efficacy boundary for the interim analysis. Accordingly, the nonrejected hypotheses were retested for the 329 patients in the primary analysis, again using one-sided tests as per study protocol. The same alpha was used for all three endpoints.

Treatment Assignment

Prior to dosing, all patients who fulfilled all inclusion/exclusion criteria were randomized via interactive response technology (IRT) to one of the treatment arms. The investigator or their delegate called or logged on to the IRT and confirmed that the patient fulfilled all the inclusion/exclusion criteria. The IRT assigned a randomization number to the patient, which was used to link the patient to a treatment arm and specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number was not communicated to the caller.

Change in BAT

Addition or initiation of a new systemic therapy in the best available therapy (BAT) arm was allowed only after documented lack of response, intolerable toxicity, or cGVHD flare and was considered a treatment failure for both the primary and key secondary objectives. At the study visit in which the patient met the criteria for disease progression, intolerable toxicity, or cGVHD flare treatment failure, addition or initiation of a new systemic BAT treatment was allowed. However, if mixed response or no response was

assessed, the response was confirmed prior to the addition or change of therapy. This confirmation could not occur prior to 1 week or later than 4 weeks after the initial assessment.

Ruxolitinib Dose Modifications

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated to allow patients to continue the study treatment. Please refer to the protocol for a summary of these modifications. A standardized dosing paradigm was used to determine dose adjustments for safety and efficacy so that each patient's dose was titrated to the most appropriate dose. Patients who had a dose reduction to manage toxicity could resume treatment at the previous dose if hematologic/nonhematologic parameters met the required threshold (please refer to the protocol for recommended thresholds).

Dose Reduction Steps[a]

Starting Dose Level 0	**Dose Level 1**	**Dose Level 2**
10 mg BID	5 mg BID	5 mg QD[b]

BID, twice daily; QD, once daily.

[a] Dose reduction should be based on the worst toxicity demonstrated at the last dose.

[b] Dose reduction to <5 mg total daily dose is not allowed.

Dose Reescalation Steps[a]

Current Dose	**First Dose Escalation**	**Second Dose Escalation**
5 mg QD	5 mg BID	10 mg BID
5 mg BID	10 mg BID	–

BID, twice daily; QD, once daily.

[a] Dose increases may not exceed 10 mg BID, in increments of 5 mg and may not occur more often than every 2 weeks.

Tapering Guidelines

Tapering of glucocorticoids, calcineurin inhibitors (CNIs), and ruxolitinib will follow two steps: first taper systemic glucocorticoids following documented complete response (CR) or partial response (PR) and follow with taper of CNI/ruxolitinib. The taper of glucocorticoids should be attempted at the time of documented CR or PR. However, the taper of ruxolitinib and CNI should not be attempted until the patient is off glucocorticoids *and* has completed the assessments for cycle 7 day 1. Ruxolitinib may not be tapered prior to cycle 7 day 1 for patients initially randomized to the ruxolitinib arm.

During the treatment period in both the ruxolitinib and BAT arms, immunosuppression taper guidelines are:

- Glucocorticoids: Every effort should be made to use the minimum dose of glucocorticoid that is sufficient to control cGVHD manifestations. It is recommended that a taper of glucocorticoids should be attempted approximately 2 weeks after achieving a CR. If a flare should occur during the taper, treatment should continue for at least 3 months prior to attempting to resume the taper
- CNI (cyclosporine or tacrolimus): Once off systemic glucocorticoids and a CR or PR has been documented, starting at cycle 7 day 1 a 25% dose reduction per month is allowed, or to be tapered per institutional practice
- Ruxolitinib: Once off systemic glucocorticoids and a CR or PR has been documented, a 50% dose reduction every 2 months (56 days) can be initiated starting at cycle 7 day 1. Initial dose reduction is to 5 mg orally twice daily. If sustained cGVHD response is observed (ie, no worsening of cGVHD signs and symptoms), the dose is further tapered by a second 50% reduction to 5 mg orally once a day for an additional 2 months (56 days) prior to cessation

Efficacy Assessments

Global and organ-specific cGVHD clinician assessments were performed at baseline, cycle 1 day 15, cycle 2 day 1, and then every 28 days until cycle 7 day 1 according to the NIH consensus criteria.[1] Following cycle 7 day 1, response will be assessed on cycle 9 day 1 and every 12 weeks thereafter.

Complete response was defined as complete resolution of all signs and symptoms of cGVHD in all evaluable organs without additional therapies. A partial response was defined as an improvement in at least one organ (eg, improvement of at least one point on a 4- to 7-point scale, or an improvement of at least two points on a 10- to 12-point scale) without progression in other organs or sites or addition/initiation of new systemic treatment. A lack of response was defined as unchanged, mixed response, or progression:

- Progression: worsening of at least one organ and no improvement (CR or PR) in any other organ
- Mixed response: CR or PR in at least one organ accompanied by progression in another organ
- Unchanged response: stable disease or absence of improvement in any organ involved by cGVHD

A cGVHD flare was defined as any increase in symptoms during taper of any immunosuppressive therapy for cGVHD after an initial response (CR or PR). A cGVHD flare was not considered a treatment failure unless severity required addition and/or change of another systemic immunosuppressive treatment. cGVHD recurrence was the return of cGVHD symptoms after tapering off study treatment due to response. Following completion of a taper of systemic therapy, if worsening of cGVHD symptoms occurred, the patient could resume treatment for cGVHD as per local institutional practice. However, this was documented as a recurrence of cGVHD.

Subgroup Analyses of ORR

Subgroup analyses comparing the odds ratios (ruxolitinib vs BAT) of the overall response rate (ORR) by demographics, cGVHD disease history, transplant-related history, and organ involvement were conducted. Estimation of the odds ratios and 95% CIs was performed using Cochrane-Mantel-Haenszel methods.

Response by Organ Involvement

Response by organ was determined based on the NIH guidelines for response assessment in cGVHD.[3] The involvement of each organ was assessed at baseline, and response was assessed at week 24. Baseline organ involvement for response assessments was determined at randomization/treatment start using the criteria established by Lee and colleagues.[3] Therefore, baseline organ involvement for response assessments may differ from the organ involvement reported as part of patient characteristics at baseline, which in this study was determined using NIH staging criteria.[4]

Modified LSS

The Lee Symptom Scale (LSS)[5] is a 30-item, seven-domain, self-administered symptom scale that has been considered the most reliable instrument for detecting changes in cGVHD symptom status and has been recommended for use in cGVHD clinical trials by the 2005 and 2014 NIH consensus conferences. Patients with cGVHD report on symptom "bother" over the previous month on a 5-point Likert scale, with subscales ranging from 0 to 100 (higher scores indicating worse symptoms). A difference of 6 to 7 points has been suggested as an indicator of clinically meaningful changes. REACH3 used a modified version of the assessment (mLSS) to address feedback from health authorities, which recommended focusing on the outcome of symptom severity rather than symptom bother and shortening the recall period from 1 month to 1 week. Modifications were using a 7-day recall window instead of a month,[6] changing "bothered" to "severity," and altering the response options. The modified survey asked patients the following question: "Please let us know **how severe** any of the following problems have been in the past **week**." (original question: "Please let us know whether you have been bothered by any of the following problems in the past month. Not at all, Slightly, Moderately, Quite a Bit, Extremely"). Patients instead reported severity of symptoms on a 5-point Likert scale: did not have this problem, mild, moderate, severe, or very severe.

Patient-Reported Outcomes

To measure symptoms and quality of life of patients affected by cGVHD and potential changes over time, the following patient-reported outcome instruments were administered:

1. The mLSS: consists of 30 items in seven subscales (skin, eye, mouth, lung, nutrition, energy, and psychological) (*see previous section*).

2. The Functional Assessment of Cancer Therapy–Bone Marrow Transplant v4.0: a 50-item self-reported questionnaire that measures the effect of a therapy on domains including physical, functional, social/family, and emotional well-being, together with additional concerns relevant for bone marrow transplant patients.[7]

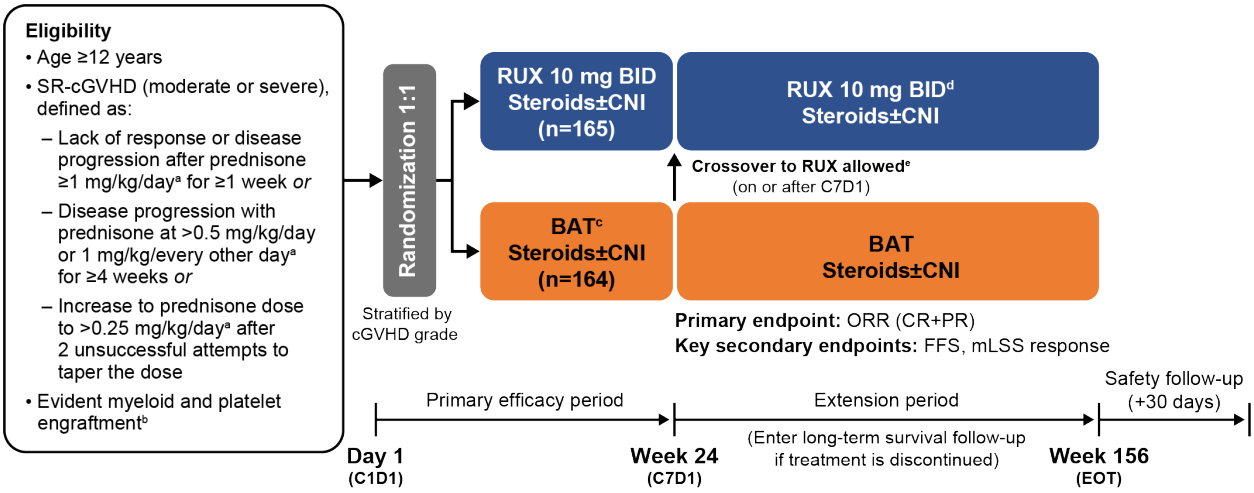
3. The EQ-5D-5L: a descriptive classification consisting of five dimensions of health: mobility, self-care, usual activities, anxiety/depression, and pain/discomfort.[8] The five-level version uses a 5-point Likert scale that was published in 2011.[9]

4. The Patient Global Impression of Change: a single-item measure of overall change in cGVHD symptoms since starting the study medication.

5. The Patient Global Impression of Severity: a single-item measure of overall cGVHD symptom severity in the past week.

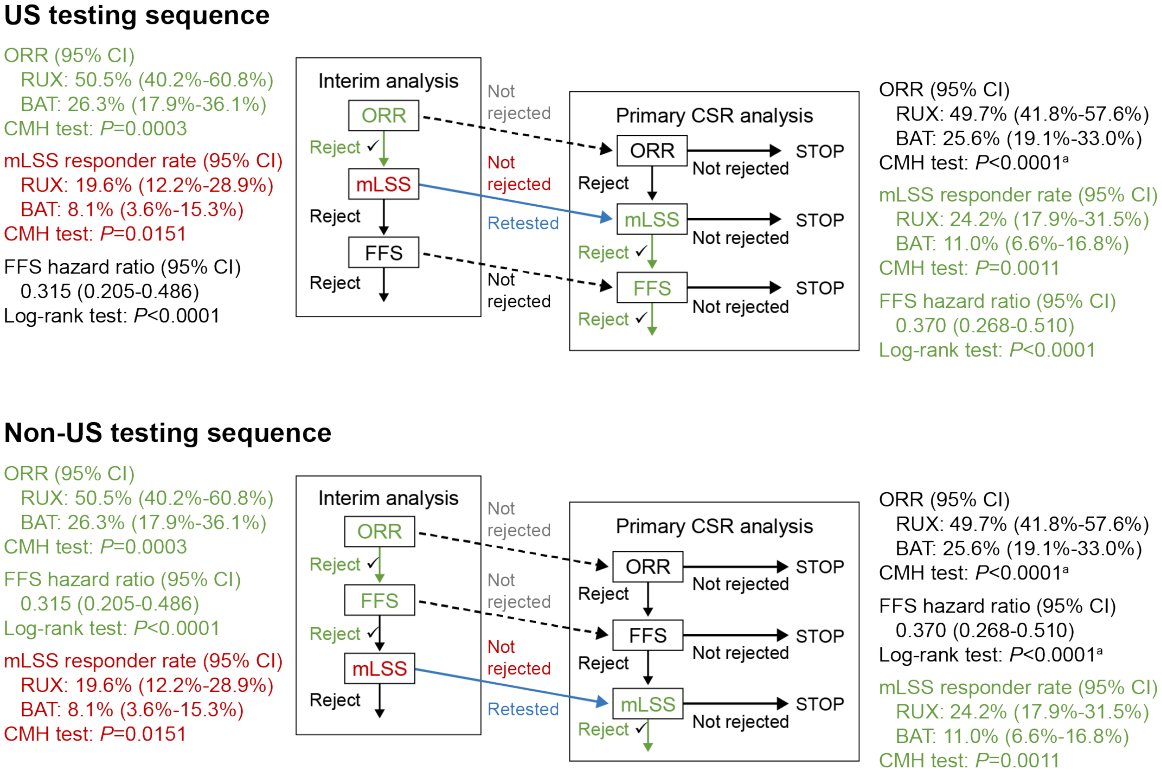
Supplementary Figures and Tables

Figure S1. Study Design.



BAT, best available therapy; BID, twice daily; C, cycle; cGVHD, chronic graft-versus-host disease; CNI, calcineurin inhibitor; CR, complete response; D, day; EOT, end of treatment period; FFS, failure-free survival; mLSS, modified Lee Symptom Scale; NRM, nonrelapse mortality; ORR, overall response rate; PR, partial response; RUX, ruxolitinib; SR, steroid refractory/dependent. [a] Or prednisone equivalent. [b] Absolute neutrophil count >1000/mm^3 and platelet count ≥25,000/mm^3. [c] Chosen by the investigator at randomization and could include extracorporeal photopheresis, low-dose methotrexate, mycophenolate mofetil, everolimus, sirolimus, infliximab, rituximab, pentostatin, imatinib, or ibrutinib. [d] RUX tapering was permitted after C7D1 for responding patients. [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 were allowed to cross over from BAT to ruxolitinib.

Figure S2. Results of the Hierarchical Testing Procedure.



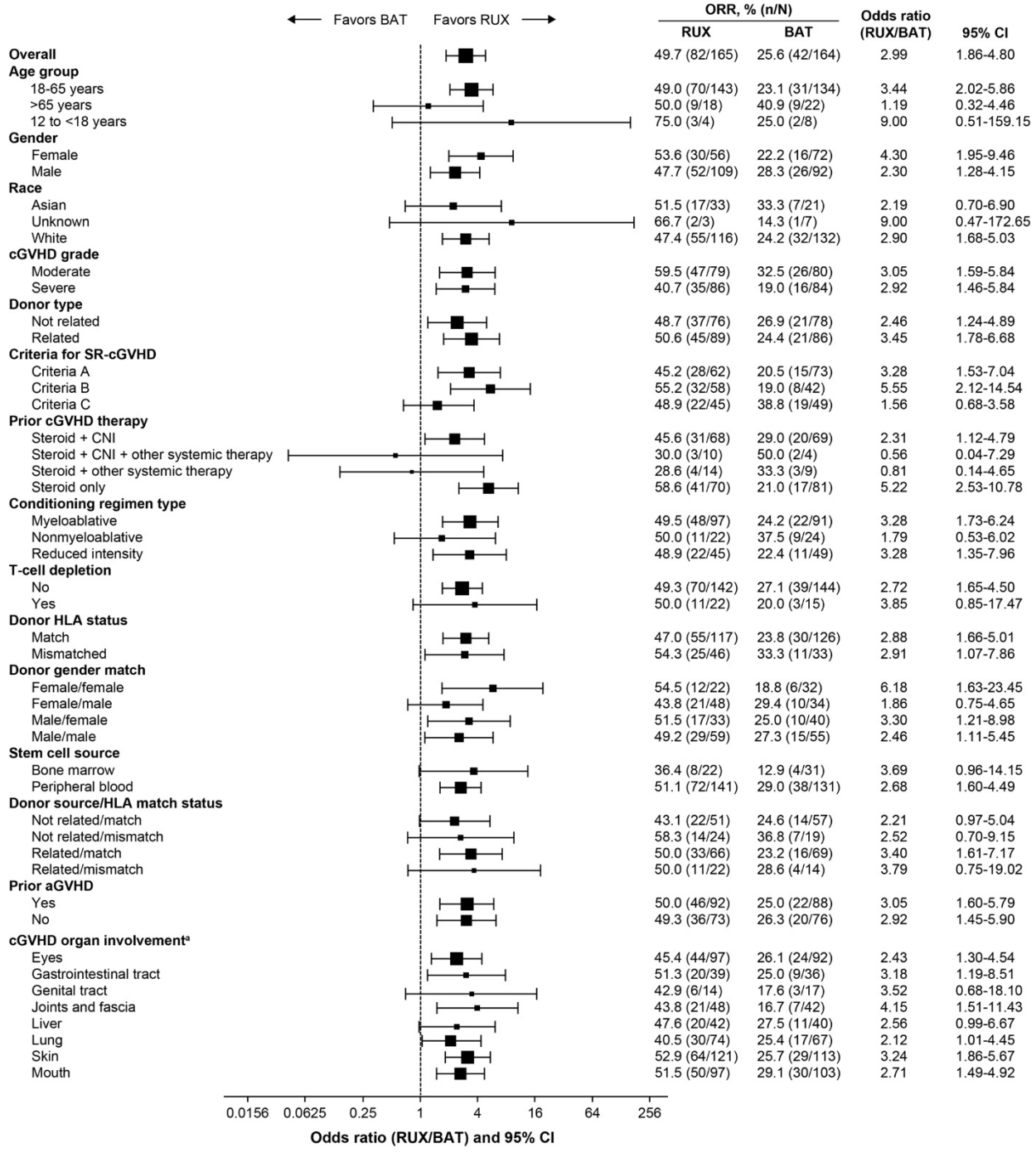
An efficacy interim analysis (IA) was planned to be performed when 194 patients (60% of the targeted 324 patients) completed the cycle 7 day 1 visit or discontinued early from the study and data of assessments were available. Following a two-look group sequential design, a rho-spending function with parameter rho=1.5 was used as the alpha-spending function.

The IA included 196 patients (60.5% of 324); the significance boundary based on the alpha-spending function was alpha=0.01176 and was used for all three endpoints in the overall hierarchical testing procedure. Hypotheses that were not rejected at the IA were retested at the primary analysis by using the remaining alpha (=0.01858) according to the group sequential methodology.

BAT, best available therapy; CMH, Cochran-Mantel-Haenszel; FFS, failure-free survival; mLSS, modified Lee Symptom Scale; ORR, overall response rate; RUX, ruxolitinib.

[a] *P* values given for descriptive purposes; significance was achieved at IA.

Figure S3. ORR at Week 24 by Patient Subgroups.

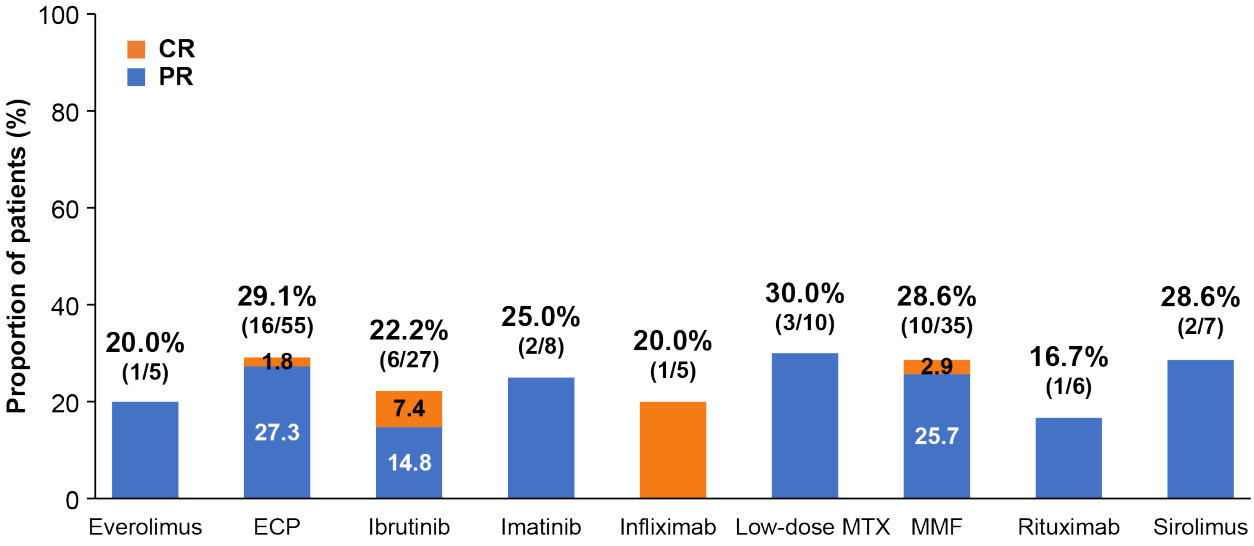


aGVHD, acute graft-versus-host disease; BAT, best available therapy; cGVHD, chronic graft-versus-host disease; HLA, human leukocyte antigen; ORR, overall response rate; RUX, ruxolitinib; SR-cGVHD, steroid-refractory/dependent chronic graft-versus-host disease.

X-axis values are represented in natural log scale. Dotted line shows no effect point. The area of the box indicates the weight of the subgroup, measured by the size of the subpopulation.

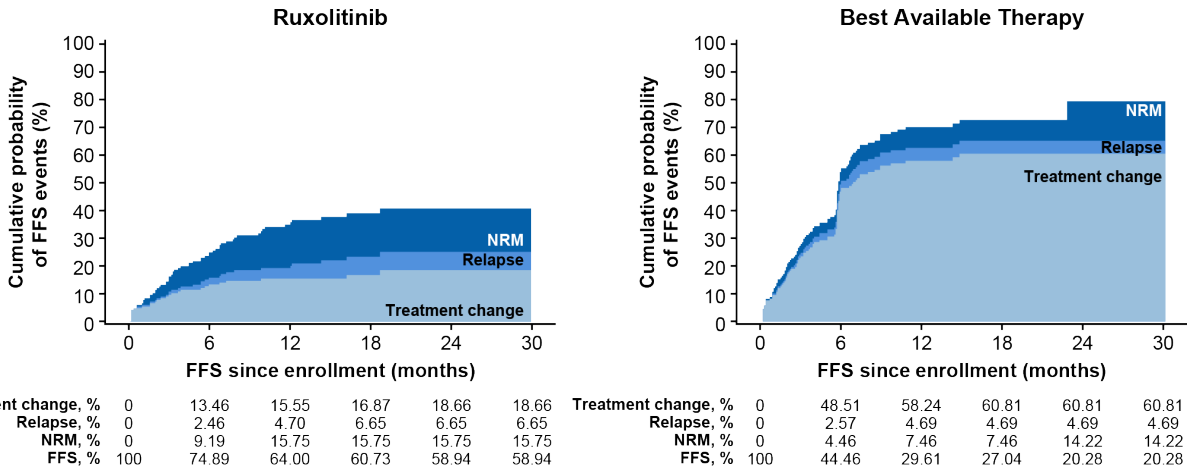
[a] Organ involvement defined as organ score ≥1 based on the cGVHD staging criteria (Jagasia MH, et al. *Biol Blood Marrow Transplant*. 2015).[4] Patients with >1 affected organ were counted in each organ subgroup.

Figure S4. Overall Response Rates by Individual BAT.



BAT, best available therapy; CR, complete response; ECP, extracorporeal photopheresis; MMF, mycophenolate mofetil; MTX, methotrexate; PR, partial response.

Figure S5. Failure-Free Survival by Treatment Arm.



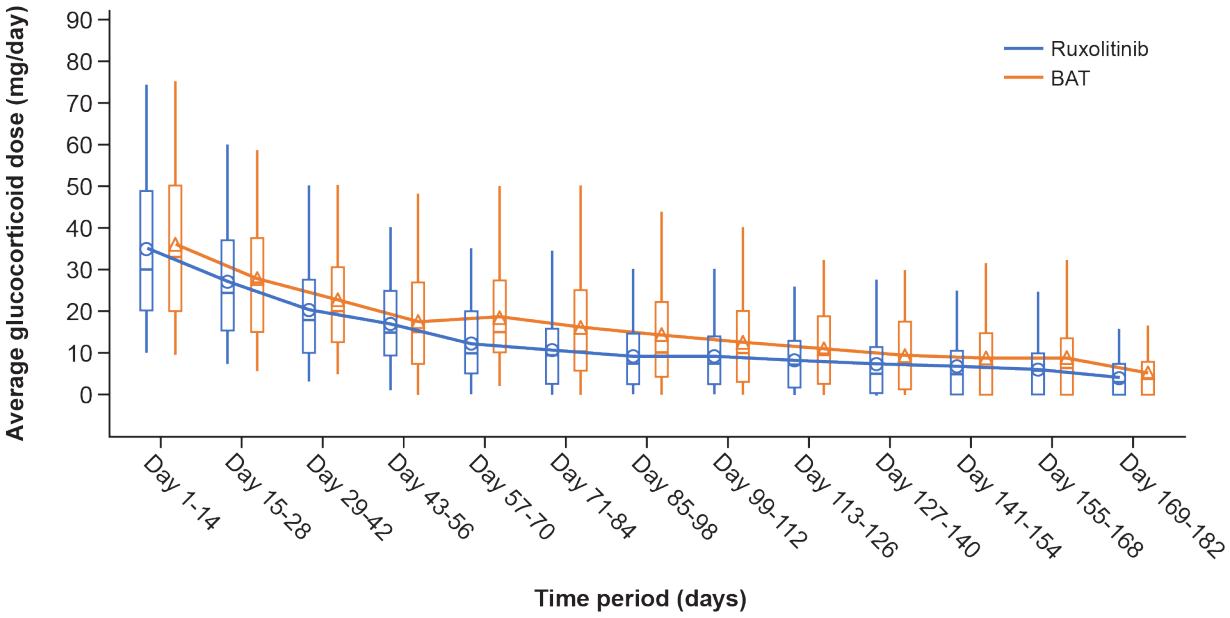
Treatment change, %	0	13.46	15.55	16.87	18.66	18.66
Relapse, %	0	2.46	4.70	6.65	6.65	6.65
NRM, %	0	9.19	15.75	15.75	15.75	15.75
FFS, %	100	74.89	64.00	60.73	58.94	58.94

Treatment change, %	0	48.51	58.24	60.81	60.81	60.81
Relapse, %	0	2.57	4.69	4.69	4.69	4.69
NRM, %	0	4.46	7.46	7.46	14.22	14.22
FFS, %	100	44.46	29.61	27.04	20.28	20.28

FFS, failure-free survival; NRM, nonrelapse mortality. Cumulative incidences used to obtain the contribution of each event type considering the two others as competing events. FFS is the time to the earliest of the three events (eg, death after treatment change is not counted). FFS obtained by 100% minus the rate for NRM, relapse, and treatment change.

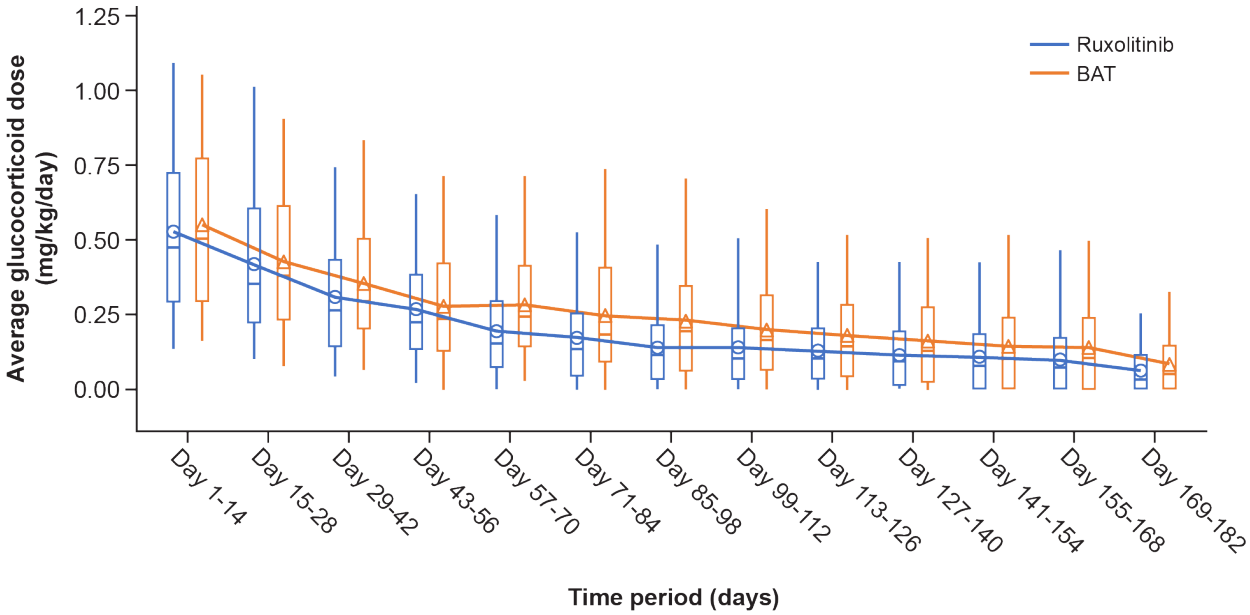
Figure S6. Glucocorticoid Dose Over Time up to Week 24.

A. Average Biweekly Glucocorticoid Dosing[a,b]



No. of patients													
Ruxolitinib	159	158	157	153	150	146	141	132	127	125	120	118	116
BAT	153	152	148	146	142	138	137	134	130	123	120	116	89

B. Average Biweekly Weight-Normalized Standardized Glucocorticoid Dosing.[a,b]



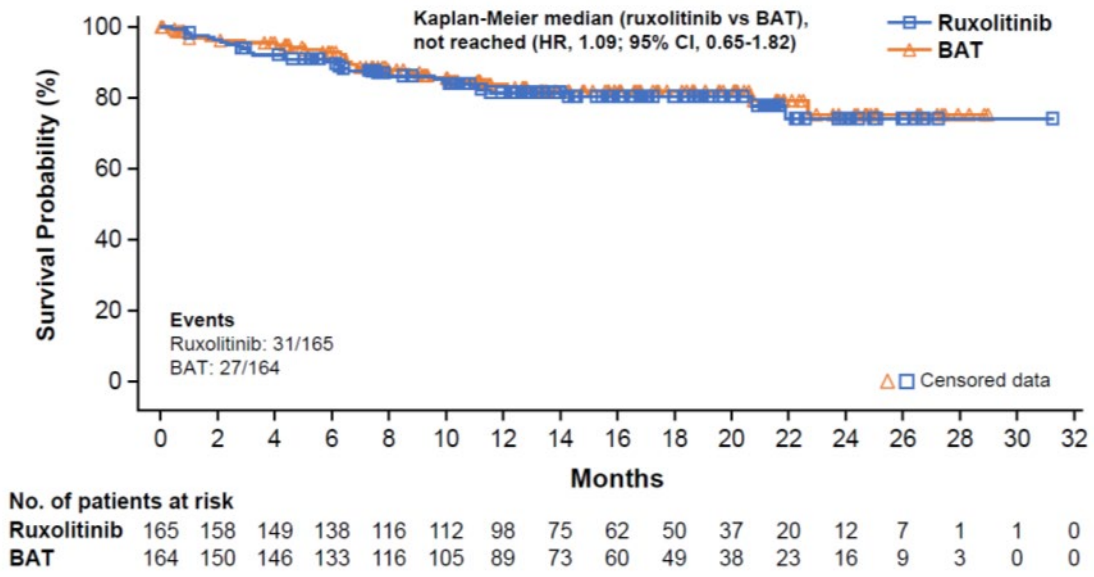
No. of patients													
Ruxolitinib	159	158	157	153	150	146	141	132	127	125	120	118	116
BAT	152	151	147	145	141	137	136	133	129	122	119	115	88

BAT, best available therapy.

[a] Patients who are completely tapered off steroids and are ongoing will be counted as having steroid dose=0 mg/kg/day until the end of the main treatment period or the restart of treatment with systemic steroids. Plot shows boxes (25th-75th percentiles) with median as horizontal line. The dots in the boxes and joint lines represent the mean values. Whiskers (vertical lines) extend to the 10th to 90th percentiles. Values outside this range are not displayed.

[b] Dose of methylprednisolone was converted to prednisone equivalent.

Figure S7. Kaplan-Meier Estimate of Overall Survival.



BAT, best available therapy; HR, hazard ratio.

Table S1. Patient Demographics and Baseline Clinical Characteristics.

Demographic variable	Ruxolitinib (n=165)	BAT (n=164)
Age, years		
Median (range)	49.0 (13.0-73.0)	50.0 (12.0-76.0)
12 to <18, n (%)	4 (2.4)	8 (4.9)
18 to 65, n (%)	143 (86.7)	134 (81.7)
>65, n (%)	18 (10.9)	22 (13.4)
Gender, n (%)		
Male	109 (66.1)	92 (56.1)
Female	56 (33.9)	72 (43.9)
Race, n (%)		
White	116 (70.3)	132 (80.5)
Black	2 (1.2)	0
Asian	33 (20.0)	21 (12.8)
Other	9 (5.5)	4 (2.4)
Unknown	3 (1.8)	7 (4.3)
Weight, mean (SD), kg	68.5 (18.3)	67.9 (16.7)
Height, mean (SD), cm	169.7 (9.8)	169.4 (10.1)
Body mass index, mean (SD), kg/m^2	23.4 (5.4)	23.5 (4.9)
Prior aGVHD, n (%)	92 (55.8)	88 (53.7%)
cGVHD severity, n (%)[a]		
Mild	1 (0.6)	1 (0.6)
Moderate	67 (40.6)	74 (45.1)
Severe	97 (58.8)	89 (54.3)

Time from transplant to randomization, median (range), weeks	69.4 (4.1-372.0)	63.21 (7.4-1427.7)
Time from cGVHD onset to randomization, median (range), weeks	24.9 (1.0-288.1)	21.4 (1.4-278.1)
CMV serological status, n (%)		
Positive	97 (58.8)	102 (62.2)
Negative	68 (41.2)	62 (37.8)
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)
T-cell depleted graft, n (%)		
Yes	22 (13.2)	16 (9.6)
No	144 (86.2)	146 (87.4)
Missing	1 (0.6)	5 (3.0)
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)
Donor type, n (%)[c]		
Related	91 (54.5)	87 (52.1)
Unrelated	76 (45.5)	80 (47.9)
Prior systemic therapy for cGVHD or glucocorticoid-refractory/dependent cGVHD, n (%)[d]		

Glucocorticoid only	70 (42.4)	81 (49.4)
Glucocorticoid+CNI	68 (41.2)	69 (42.1)
Glucocorticoid+CNI+other systemic therapy	10 (6.1)	4 (2.4)
Glucocorticoid+other systemic therapy	14 (8.5)	9 (5.5)
Missing	3 (1.8)	1 (0.6)
Primary diagnosis classification of underlying disease, n (%)		
Leukemia/MDS	121 (73.3)	122 (74.4)
Lymphoproliferative disorder	26 (15.8)	33 (20.1)
Myeloproliferative neoplasm	9 (5.5)	5 (3.0)
Sickle cell disease	1 (0.6)	0
Severe aplastic anemia	5 (3.0)	1 (0.6)
Thalassemia	1 (0.6)	0
Inherited metabolic disorder	1 (0.6)	1 (0.6)
Other	1 (0.6)	2 (1.2)
SR-cGVHD diagnostic criteria, n (%)		
Any SR criteria met	165 (100)	164 (100)
Lack of response or disease progression after prednisone ≥1 mg/kg/day	62 (37.6)	73 (44.5)
Disease persistence without improvement despite continued treatment with prednisone	58 (35.2)	42 (25.6)

Increase to prednisone dose to >0.25 mg/kg/day after two unsuccessful attempts to taper	45 (27.3)	49 (29.9)
Conditioning regimen, n (%)		
Myeloablative	97 (58.8)	91 (55.5)
Reduced intensity	45 (27.3)	49 (29.9)
Nonmyeloablative	22 (13.3)	24 (14.6)
Missing	1 (0.6)	0
Donor/recipient gender, n (%)		
Female/male	48 (29.1)	35 (21.3)
Female/female	22 (13.3)	32 (19.5)
Male/female	34 (20.6)	40 (24.4)
Male/male	60 (36.4)	55 (33.5)
Unknown[b]	1 (0.6)	2 (1.2)
Donor HLA match, n (%)[d]		
Matched	119 (71.3)	127 (76.0)
Mismatched	46 (27.5)	35 (21.0)
Unknown	2 (1.2)	5 (3.0)
Total HCT-specific comorbidity index score, n (%)		
0	75 (45.5)	78 (47.6)
1	21 (12.7)	20 (12.2)
2	31 (18.8)	19 (11.6)
≥3	32 (19.4)	44 (26.8)
Missing	6 (3.6)	3 (1.8)
Organ involvement, n (%)[f]		
Skin		

Any	121 (73.3)	113 (68.9)
With score ≥2	100 (60.6)	97 (59.1)
Mouth		
Any	97 (58.8)	103 (62.8)
With score ≥2	44 (26.7)	45 (27.4)
Eyes		
Any	97 (58.8)	92 (56.1)
With score ≥2	53 (32.1)	45 (27.4)
Lung		
Any	74 (44.8)	67 (40.9)
With score = 2	24 (14.5)	18 (11.0)
With score = 3	14 (8.5)	13 (7.9)
Joints and fascia		
Any	48 (29.1)	42 (25.6)
With score ≥2	26 (15.8)	20 (12.2)
Liver		
Any	42 (25.5)	40 (24.4)
With score = 2	24 (14.5)	22 (13.4)
With score = 3	2 (1.2)	3 (1.8)
Gastrointestinal		
Any	39 (23.6)	36 (22.0)
With score ≥2	15 (9.1)	17 (10.4)
Genital tract		
Any	14 (8.5)	17 (10.4)
With score ≥2	5 (3.0)	9 (5.5)
Missing	0	1 (0.6)
Initial BAT treatment, n (%)[g]		

ECP	–	55 (34.8)
MMF	–	35 (22.2)
Ibrutinib	–	27 (17.1)
Low-dose methotrexate	–	10 (6.3)
Imatinib	–	8 (5.1)
Sirolimus	–	7 (4.4)
Rituximab	–	6 (3.8)
Everolimus	–	5 (3.2)
Infliximab	–	5 (3.2)
Pentostatin	–	0
Total mLSS score, median (range)	18.67 (0-79.6)[h]	18.54 (0.7-54.4)[i]

BAT, best available therapy; cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus, ECP, extracorporeal photopheresis; HCT, hematopoietic cell transplant; HLA, human leukocyte antigen; MDS, myelodysplastic syndromes; mLSS, modified Lee Symptom Scale; MMF, mycophenolate mofetil; NIH, National Institutes of Health; SR, steroid-refractory/dependent.

[a] Based on NIH consensus staging criteria[4] at screening. Enrollment of patients with mild glucocorticoid-cGVHD was considered a protocol deviation.

[b] Data not available for donor and/or recipient (patient).

[c] Some patients received more than one transplant.

[d] Prior treatment for cGVHD as documented in the prior medication data; topical or local treatments not counted.

[e] Percentage refers to the number of donors (n=167 in each arm). Some patients received more than one transplant.

[f] Organ involvement at baseline was based on NIH consensus staging criteria[4] at screening. A score of one or greater is counted as organ involvement. Patients with missing assessments of single organs are counted as having no organ involvement for the organ assessed.

[g] Percentages are based on the number of patients treated with BAT (n=158).

[h] n=149.

[i] n=141.

Table S2. CNI Use During the Randomized Treatment Period.

Medication	Ruxolitinib (n=165)	BAT (n=158)
Any CNI	94 (57.0)	82 (51.9)
Cyclosporine	56 (33.9)	56 (35.4)
Tacrolimus	40 (24.2)	27 (17.1)

BAT, best available therapy; CNI, calcineurin inhibitor.

Data cutoff date, May 8, 2020.

Table S3. Primary and Secondary Efficacy Endpoints.

Variable	Ruxolitinib (n=165)	BAT (n=164)	*P* value
Primary endpoint[a]			
ORR, n (%)[b]	82 (49.7)	42 (25.6)	<0.0001[c]
Odds ratio (95% CI)[d]	2.99 (1.86-4.80)		–
Risk ratio (95% CI)[e]	1.93 (1.44-2.60)		–
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[f]	5 (3.0)	9 (5.5)	–
Unknown	55 (33.3)	60 (36.6)	–
Death	16 (9.7)	11 (6.7)	–
Early discontinuation	33 (20.0)	33 (20.1)	–
Missing visits	6 (3.6)	16 (9.8)	–
Key secondary endpoints[a]			
Median FFS (95% CI), months	>18.6 (18.6-not reached)[g]	5.7 (5.6-6.5)	<0.0001[h]
Hazard ratio (95% CI)	0.370 (0.268-0.510)		–
mLSS responders, n (%)	40 (24.2)	18 (11.0)	0.0011
Odds ratio (95% CI)[d]	2.62 (1.42-4.82)		–

Risk ratio (95% CI)[e]	2.19 (1.31-3.65)		–
Secondary endpoints			
Best overall response	126 (76.4)	99 (60.4)	0.0011
Odds ratio (95% CI)[d]	2.17 (1.34-3.52)		–
Risk ratio (95% CI)[e]	1.24 (1.07-1.43)		–

BAT, best available therapy; cGVHD, chronic graft-versus-host disease; FFS, failure-free survival; mLSS, modified Lee Symptom Scale; ORR, overall response rate.

[a] Tested at the interim analysis (N=196, significance level was alpha=0.01176) and the current primary analysis (N=329, significance level if not positive at the interim analysis alpha=0.01858) according to an overall hierarchical testing procedure to hold the overall one-sided family-wise error alpha=0.025. Test sequence for non-US was ORR, FFS, and mLSS; test sequence for US was ORR, mLSS, and FFS.

[b] Includes all patients who achieved a complete response or partial response.

[c] Descriptive *P* value. Efficacy boundary crossed at the interim analysis (ORR was 50.5% for ruxolitinib and 26.3% for BAT; *P*=0.0003).

[d] Calculated based on the Cochrane-Mantel-Haenszel method.

[e] Adjusted risk ratio obtained by generalized linear model using treatment arm and cGVHD severity as covariates.

[f] Patient with additional systemic therapies along with complete response/partial response per investigator assessment.

[g] At data cutoff (May 8, 2020), the median FFS was not reached in the ruxolitinib arm, but the lower bound of the 95% CI was estimated as 18.6 months.

[h] Descriptive *P* value (ex-US only). Efficacy boundary crossed at the interim analysis (hazard ratio [95% CI] was 0.315 [0.205-0.486], *P*<0.0001). For US, the *P* value gives the result of the retested hypothesis at the primary analysis, following the overall hierarchical testing procedure.

Table S4. Response by Organ at Week 24 (Cycle 7 Day 1).

	Ruxolitinib n=165		BAT n=164	
Organ	**Baseline involvement[a]**	**Organ response[b]**	**Baseline involvement[a]**	**Organ response[b]**
	n (%)	**m/n (%)**	**n (%)**	**m/n (%)**
Skin	119 (72.1)	49/119 (41.2)	110 (67.1)	17/110(15.5)
Eye	96 (58.2)	25/96 (26.0)	93 (56.7)	10/93 (10.8)
Mouth	96 (58.2)	48/96 (50.0)	99 (60.4)	25/99 (25.3)
Esophagus	18 (10.9)	9/18 (50.0)	17 (10.4)	5/17 (29.4)
Upper GI tract	20 (12.1)	8/20 (40.0)	21 (12.8)	8/21 (38.1)
Lower GI tract	15 (9.1)	8/15 (53.3)	10 (6.1)	3/10 (30.0)
Liver	86 (52.1)	21/86 (24.4)	83 (50.6)	18/83 (21.7)
Lung	70 (42.4)	6/70 (8.6)	49 (29.9)	3/49 (6.1)
Joints and fascia	45 (27.3)	17/45 (37.8)	44 (26.8)	7/44 (15.9)
Overall response	–	82 (49.7)	–	42 (25.6)

ALT, alanine aminotransferase; AP, alkaline phosphatase; BAT, best available therapy; cGVHD, chronic graft-versus-host disease; CR, complete response; FEV_1, forced expiratory volume in the first second of expiration; GI, gastrointestinal; NIH, National Institutes of Health; PR, partial response; ULN, upper limit of normal.

Organ response as documented by the investigator, m is the number of patients with organ response = CR or PR and excluding those responders where the organ abnormality is due to non-cGVHD reasons. Overall response counts patients with CR or PR as per investigator.

[a] Based on NIH cGVHD response guidelines (Lee SJ, et al. *Biol Blood Marrow Transplant.* 2015).[3] Baseline involvement if respective score at cycle 1 day 1 >0, or %FEV1 <75% (lung), ALT, bilirubin or AP > ULN (liver), joints and fascia score >0.

[b] m/n shows number of responders/patients with baseline involvement excluding in m those patients with change/addition of new systemic cGVHD treatment before cycle 7 day 1

Table S5. Overall Safety up to Week 24.[a]

	Ruxolitinib (n=165)		BAT (n=158)	
Category, n (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
AEs	161 (97.6)	94 (57.0)	145 (91.8)	91 (57.6)
Treatment related	104 (63.0)	56 (33.9)	45 (28.5)	23 (14.6)
SAEs	55 (33.3)	49 (29.7)	58 (36.7)	53 (33.5)
Treatment related	27 (16.4)	25 (15.2)	16 (10.1)	12 (7.6)
Fatal SAEs	12 (7.3)	12 (7.3)	8 (5.1)	8 (5.1)
Treatment related	7 (4.2)	7 (4.2)	4 (2.5)	4 (2.5)
AEs leading to discontinuation	27 (16.4)	20 (12.1)	11 (7.0)	8 (5.1)
Treatment related	16 (9.7)	12 (7.3)	6 (3.8)	5 (3.2)
AEs leading to dose adjustment/interruption	62 (37.6)	38 (23.0)	26 (16.5)	12 (7.6)
AEs requiring additional therapy	138 (83.6)	72 (43.6)	131 (82.9)	74 (46.8)

AE, adverse event; BAT, best available therapy; SAE, serious adverse event.

[a] AEs were assessed and graded according to the Common Terminology Criteria for Adverse Events version 4.03 and were determined to be treatment related by the treating investigator.

Table S6. Serious AEs in ≥1% of Patients in Either Treatment Arm up to Week 24.[a]

Preferred term, n (%)[a]	Ruxolitinib n=165		BAT n=158	
	All grades	Grade ≥3	All grades	Grade ≥3
Any	55 (33.3)	49 (29.7)	58 (36.7)	53 (33.5)
Hematologic				
Febrile neutropenia	3 (1.8)	3 (1.8)	2 (1.3)	2 (1.3)
Pancytopenia	0	0	2 (1.3)	2 (1.3)
Gastrointestinal				
Vomiting	0	0	2 (1.3)	2 (1.3)
Diarrhea	0	0	2 (1.3)	2 (1.3)
Gastrointestinal hemorrhage	0	0	2 (1.3)	2 (1.3)
Respiratory/thoracic				
Pulmonary embolism	2 (1.2)	2 (1.2)	3 (1.9)	3 (1.9)
Respiratory failure	2 (1.2)	2 (1.2)	0	0
Renal				
Acute kidney injury	2 (1.2)	2 (1.2)	3 (1.9)	3 (1.9)
Infections				
Pneumonia	13 (7.9)	12 (7.3)	13 (8.2)	11 (7.0)
Lower respiratory tract infection	4 (2.4)	2 (1.2)	0	0
Bronchopulmonary aspergillosis	2 (1.2)	2(1.2)	4 (2.5)	3 (1.9)
Cytomegalovirus infection/reactivation	2 (1.2)	2 (1.2)	1 (0.6)	0

Pneumothorax	2 (1.2)	2 (1.2)	0	0
Sepsis	2 (1.2)	2 (1.2)	1 (0.6)	0
Septic shock	1 (0.6)	1 (0.6)	3 (1.9)	3 (1.9)
Pneumonia, bacterial	1 (0.6)	1 (0.6)	2 (1.3)	2 (1.3)
Pneumonia, cytomegaloviral	1 (0.6)	0	2 (1.3)	2 (1.3)
Upper respiratory tract infection	1 (0.6)	0	2 (1.3)	2 (1.3)
Escherichia infection	0	0	2 (1.3)	2 (1.3)
Pneumonia, pseudomonal	0	0	2 (1.3)	2 (1.3)
Other				
Back pain	2 (1.2)	1 (0.6)	0	0
Dehydration	2 (1.2)	2 (1.2)	0	0
Dyspnea	2 (1.2)	1 (0.6)	2 (1.3)	2 (1.3)
Hypotension	2 (1.2)	2 (1.2)	0	0
Pyrexia	8 (4.8)	3 (1.8)	3 (1.9)	2 (1.3)
Hypoxia	0	0	3 (1.9)	3 (1.9)
Seizure	0	0	2 (1.3)	1 (0.6)

AE, adverse event; BAT, best available therapy.

Table S7. AEs up to Week 24 Leading to Treatment Discontinuation.

Preferred term, n (%)[a]	Ruxolitinib n=165		BAT n=158	
	All grades	Grade ≥3	All grades	Grade ≥3
Hematologic				
Anemia	1 (0.6)	0	1 (0.6)	0
Neutropenia	1 (0.6)	0	1 (0.6)	1 (0.6)
Neutrophil count decreased	1 (0.6)	1 (0.6)	0	0
Thrombocytopenia[b]	0	0	2 (1.3)	1 (0.6)
Thrombotic microangiopathy	0	0	1 (0.6)	1 (0.6)
White blood cell count decreased	0	0	1 (0.6)	0
Gastrointestinal				
Ileus	1 (0.6)	1 (0.6)	0	0
Diarrhea	0	0	1 (0.6)	0
Vomiting	0	0	1 (0.6)	0
Cardiac				
Atrial flutter	1 (0.6)	1 (0.6)	0	0
Respiratory/thoracic				
Pneumothorax	2 (1.2)	1 (0.6)	0	0
Respiratory failure	1 (0.6)	1 (0.6)	0	0
Pulmonary embolism	0	0	1 (0.6)	1 (0.6)
Renal				
Acute kidney injury	1 (0.6)	1 (0.6)	0	0

Renal failure	1 (0.6)	1 (0.6)	0	0
Atypical hemolytic uremic syndrome	0	0	1 (0.6)	1 (0.6)
Vascular				
Thrombosis	1 (0.6)	0	0	0
Microangiopathy	0	0	1 (0.6)	1 (0.6)
Infections				
Pneumonia	8 (4.8)	6 (3.6)	2 (1.3)	2 (1.3)
Meningitis, viral	1 (0.6)	1 (0.6)	0	0
Pneumonia, bacterial	1 (0.6)	1 (0.6)	0	0
Sepsis	1 (0.6)	1 (0.6)	0	0
Septic shock	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)
Laboratory abnormalities				
Alanine aminotransferase increased	1 (0.6)	1 (0.6)	0	0
Neoplasms				
Posttransplant lymphoproliferative disorder	1 (0.6)	1 (0.6)	0	0
Other				
Body temperature increased	1 (0.6)	0	0	0
Brain abscess	1 (0.6)	1 (0.6)	0	0
Cushingoid	1 (0.6)	0	0	0
General physical health deterioration	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)

Pyrexia	1 (0.6)	0	0	0
Toxic epidermal necrolysis	1 (0.6)	1 (0.6)	0	0
Multiple organ dysfunction syndrome	0	0	1 (0.6)	1 (0.6)

AE, adverse event; BAT, best available therapy.

[a] A patient with multiple severity grades for an AE is counted only under the maximum grade.

[b] Includes preferred terms “thrombocytopenia” and “platelet count decreased.”

Table S8. Overview of Infections up to Week 24.[a]

Type of infection, n (%) Maximum severity grade	Ruxolitinib (n=165)	BAT (n=158)
Patients with ≥1 event	105 (63.6)	89 (56.3)
Grade 1	29 (17.6)	27 (17.1)
Grade 2	41 (24.8)	33 (20.9)
Grade 3	32 (19.4)	29 (18.4)
Missing	3 (1.8)	0
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
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)
Other unknown infections	35 (21.2)	32 (20.3)
Grade 1	9 (5.5)	9 (5.7)
Grade 2	16 (9.7)	13 (8.2)

Grade 3	7 (4.2)	9 (5.7)
Missing	3 (1.8)	1 (0.6)

BAT, best available therapy.

[a] Infections were classified by type (viral, bacterial, fungal, unknown, or other) and severity (grades 1 to 3) at the investigator's discretion by using an infection-specific grading system predictive of mortality that was developed for and validated in allogeneic stem cell transplant recipients (Cordonnier C, et al. *Transplantation*. 2006)[10] based on criteria provided in the protocol.

Supplementary References

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