PP02.05

Presented at the
7th International Chronic Graft-versus-Host Disease Symposium
Vancouver, BC, Canada • October 16–17, 2024

Evaluation of Clinical Trial Efficacy Endpoints in Chronic Graft-Versus-Host Disease

John Galvin, MD, MS, MPH,[1] Chuan Tian, PhD,[1] Britnie Thomas, PhD,[1] Valkal Bhatt, PharmD[1]

[1]Incyte Corporation, Wilmington, DE, USA

Introduction

- The overall response rate (ORR) within 6 months of treatment is an endpoint accepted by regulatory agencies to determine the clinical benefit of new therapies for the treatment of chronic graft-versus-host disease (cGVHD)[1]
  - However, due to the number of approved therapies for cGVHD, this endpoint may not help to differentiate the efficacy of existing and new therapies
- An endpoint that includes clinically relevant response assessments and the durability of those responses is important
  - Failure-free survival (FFS) is an established composite endpoint for cGVHD
  - However, composite endpoints can be difficult to interpret,[2] and heterogeneity in the clinical definitions among various clinical trials can complicate the assessment of therapeutic benefit
- There is a need for further review of acceptable endpoints and the timing of these assessments in cGVHD studies

Objective

- To identify the breadth and characteristics of clinical trial efficacy endpoints in pivotal cGVHD studies and compare them with efficacy assessments for regulatory approval

Methods

- Primary publications of pivotal clinical trials for newer cGVHD treatments were summarized for study endpoints and definitions, and compared with regulatory endpoints included in the US prescribing information
- Composite endpoints in these studies were identified for further discussion

Results

Pivotal Clinical Trial Endpoints

- Efficacy endpoints from AGAVE-201 (randomized phase 2 study for axatilimab), ROCKstar (randomized phase 2 study for belumosudil), REACH3 (randomized phase 3 study for ruxolitinib), and a phase 1b/2 study for ibrutinib are summarized in **Table 1**

Table 1. Study Population and Efficacy Endpoints Included in Pivotal cGVHD Studies

Drug (study)	Prior cGVHD systemic therapies	Primary endpoint of study	Endpoints for US regulatory approval (year)*	Other efficacy endpoints
Axatilimab (AGAVE-201)[4]	≥2	ORR through Cycle 7 Day 1†	ORR through Cycle 7 Day 1 (2024)[5]	mLSS‡; DOR; FFS; OS; organ-specific responses†; TTR; CS dose reductions
Belumosudil (ROCKstar)[6]	2–5	Best ORR at any time†	ORR through Cycle 7 Day 1 (2021)[7]	mLSS‡; DOR; FFS; OS; organ-specific responses†; TTR; CS dose reductions
Ruxolitinib (REACH3)[8]	1	ORR at Week 24†	ORR through Cycle 7 Day 1 (2021)[9,§]	mLSS‡; DOR; FFS; OS; organ-specific responses†; change in CS dose over time
Ibrutinib (Phase 1b/2 study [NCT02195869])[10]	≥1	Best ORR at any time†	Best ORR at any time; SRR at any time (2017)[11]	LSS‡; SRR ≥20 weeks; change in CS dose over time

cGVHD, chronic graft-versus-host disease; CS, corticosteroid; DOR, duration of response; FFS, failure-free survival; LSS, Lee Symptom Scale; mLSS, modified Lee Symptom Scale; NIH, National Institutes of Health; ORR, overall response rate; OS, overall survival; SRR, sustained response rate; TTR, time to response.
Composite endpoints are underlined.
* Efficacy endpoints included in the US prescribing information for approved products and year of first cGVHD approval.
† Partial or complete response by the NIH 2014 cGVHD consensus criteria.
‡ ≥7-point improvement from baseline.
§ Included as a secondary endpoint in the REACH3 study.

- Notably, REACH3 included ORR at Week 24 as a primary endpoint; the other pivotal cGVHD studies included ORR through Cycle 7 Day 1, which does not assess response durability
  - Although all these studies evaluated ORR through approximately 6 months of therapy, it is unknown what length of time would be sufficient to assess clinical activity in highly morbid forms of cGVHD comprehensively
- Partial responses by the National Institutes of Health (NIH) cGVHD consensus criteria are common; NIH responses may not fully capture true cGVHD improvement, which includes improvements in functional status and associated improvements in symptom burden
- Due to the relative clinical nature and subjectivity of response assessment based on both functional and objective improvements, central review is not feasible, which may result in inconsistent assessment of patient responses[3]
- FFS was included as a composite endpoint in most trials

Composite Endpoints

- Although composite endpoints have been included in pivotal cGVHD studies, there can be heterogeneity in definitions across studies
  - Progression, which is included in multiple composite endpoints, may be of limited clinical relevance and has a poor correlation with global clinician and patient-reported assessments
    - The definition is often based on progression from nadir and, thus, does not account for the responses that patients achieve from baseline
- Key considerations for select composite endpoints for cGVHD are shown in **Table 2**

Table 2. Summary of Composite Endpoints

Endpoint	Examples of definitions*	Key considerations
DOR	Time from first response to cGVHD progression, start of new cGVHD therapy, or death	• Only accounts for outcomes in patients with a clinical response • Does not evaluate responses within individual organs or evaluate the extent of disease progression • Response assessments can have heterogeneity if completed by different investigators
EFS	Time to cGVHD progression, relapse of underlying disease, start of new cGVHD therapy, or death	• No standardized, validated definition of events has been established for cGVHD • Does not evaluate responses within individual organs or evaluate the extent of disease progression
FFS	Time to addition of systemic immunosuppressive therapy for cGVHD, relapse of underlying malignancy, or death	• Does not evaluate responses within individual organs or evaluate the extent of disease progression

cGVHD, chronic graft-versus-host disease; CR, complete response; DOR, duration of response; EFS, event-free survival; FFS, failure-free survival.
* Definitions can vary across different studies.

Patient-Reported Outcomes for cGVHD

- All pivotal studies for cGVHD included the Lee Symptom Scale or the modified version (LSS/mLSS) assessments to capture patient-reported improvements in cGVHD symptoms
  - Although these assessment tools are standard in cGVHD studies, they are not validated to assess organ-specific symptom improvements and may not fully capture the disease burden with cGVHD
  - Additionally, patient-reported assessments are not used in real-world practice, so it is difficult to interpret the real-world effectiveness of these tools
  - There is a need for the development of additional tools for assessing the burden of cGVHD
- In a recent analysis, there was a poor correlation between patient-reported outcomes and clinical responses, suggesting that patient-reported outcomes provide additional critical insight into clinical benefit[12]
- THRIVE (NCT05919511) is an observational study that will evaluate multiple patient-reported outcome assessments among patients with allogeneic hematopoietic stem cell transplantation to characterize the disease burden among those who develop cGVHD[13]

Conclusions

- **Current clinical and patient-reported assessments for cGVHD have important limitations**
- **Careful selection of composite endpoints is critical for cGVHD studies; further work is needed to develop composite endpoints that are clinically relevant and consistently implemented across studies**
- **Expert evaluation and additional discussion of completed and ongoing cGVHD studies are needed to inform the design of future clinical trials for cGVHD**

Disclosures

JG, CT, BT, and VB are employees and shareholders of Incyte Corporation.

Acknowledgments

Medical writing support was provided by Valerie Kinchen, PhD, from The Curry Rockefeller Group, LLC, a Citrus Health Group, Inc., company (Chicago, IL), and was funded by Incyte Corporation (Wilmington, DE) and Syndax Pharmaceuticals, Inc (Waltham, MA).

References

1. Food and Drug Administration. Graft-versus-host diseases: developing drugs, biological products, and certain devices for prevention or treatment. 2023. Food and Drug Administration. Accessed September 20, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/graft-versus-host-diseases-developing-drugs-biological-products-and-certain-devices-prevention-or. **2.** Baracaldo-Santamaria D, et al. *J Clin Med*. 2023;12(13). **3.** Dello Russo C and Navarra P. *Front Pharmacol*. 2022;13:858354. **4.** Wolff D, et al. *N Engl J Med*. 2024;391(11):1002-1014. **5.** NIKTIMVO™ (axatilimab-csfr). Full Prescribing Information. Incyte Corporation; 2024. **6.** Cutler C, et al. *Blood*. 2021;138(22):2278-2289. **7.** REZUROCK® (belumosudil). Full Prescribing Information. Kadmon Pharmaceuticals; 2024. **8.** Zeiser R, et al. *N Engl J Med*. 2021;385(3):228-238. **9.** JAKAFI® (ruxolitinib). Full Prescribing Information. Incyte Corporation; 2023. **10.** Miklos D, et al. *Blood*. 2017;130(21):2243-2250. **11.** IMBRUVICA® (ibrutinib). Full Prescribing Information. Janssen Biotech, Inc.; 2024. **12.** Im A, et al. Haematologica. 2024;109(1):143-150. **13.** Ponce DM, et al. *Blood*. 2023;142(suppl 1):7035.

To download a copy of this poster, scan code.