Poster 3909

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Patient-Reported Outcomes Among Patients With Steroid-Refractory or -Dependent Chronic Graft-vs-Host Disease Randomized to Ruxolitinib vs Best Available Therapy

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CONCLUSIONS

- In REACH3, ruxolitinib treatment led to greater improvements in both physician-assessed cGVHD outcomes and PROs compared with BAT
  - Unlike in the BAT arm, symptom burden decreased rapidly in the ruxolitinib arm, with continuing improvement observed over time
- An organ response at week 24 in eye, skin, mouth, or lung was predictive of a decrease from baseline in the respective mLSS subscale score at week 24
- Patients were more likely to report a feeling of improvement in their symptoms when treated with ruxolitinib vs BAT, as assessed by PGIS and PGIC
- Importantly, the patient experience of organ-specific symptom improvements was consistent with physician-assessed objective organ responses, both of which were greater with ruxolitinib than with BAT

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INTRODUCTION

- The Janus kinase (JAK) 1/JAK2 inhibitor ruxolitinib was recently approved in the US for the treatment of patients aged ≥12 years with chronic graft-vs-host disease (cGVHD) who have failed 1 or 2 lines of systemic therapy[1]
  - This US Food and Drug Administration approval was based on data from the randomized phase 3 trial REACH3 (NCT03112603), which evaluated ruxolitinib (N=165) vs best available therapy (BAT; N=164) in patients with steroid-refractory/-dependent (SR/D) cGVHD[2]
- In comparison with BAT, ruxolitinib demonstrated superiority in the primary and key secondary endpoints[2]
  - Significantly higher overall response rate at week 24 (primary endpoint; 49.7% vs 25.6%; *P*<0.001) and greater best overall response at any time up to week 24 (76.4% vs 60.4%)
  - Longer median failure-free survival (key secondary endpoint; not reached vs 5.7 months; *P*<0.001)
  - Greater improvement in symptoms at week 24, as measured by the cGVHD-specific modified Lee Symptom Scale (mLSS) (key secondary endpoint; 24.2% vs 11.0%; *P*=0.001)
- Due to the considerable effect that cGVHD has on patient quality of life (QOL), patient-reported outcomes (PROs) are an important component for determining the full measure of a drug's efficacy and are recommended for collection by the National Institutes of Health (NIH) consensus criteria for clinical trials in cGVHD[3]
- Here we present an in-depth analysis of the impact of ruxolitinib vs BAT on various PROs in patients with SR/D cGVHD in the REACH3 study (data cutoff: May 8, 2020)

METHODS

- REACH3 is an open-label, randomized (1:1), multicenter phase 3 trial of ruxolitinib 10 mg twice daily with steroids ± calcineurin inhibitors vs BAT (chosen by investigator from 10 options; see **Supplementary Material**)[2]
- 329 eligible patients (aged ≥12 years with moderate or severe SR/D cGVHD according to the NIH consensus criteria[3]) received randomized treatment for ≥6 cycles (28 days/cycle)
- The LSS is a validated, cGVHD-specific, 30-item, self-administered survey ranging from 0 (no symptoms) to 100 (worst symptoms) with 1 summary score and 7 subscales (skin, mouth, eye, lung, energy, nutrition, psychological)[4]
  - In REACH3, the LSS was modified (ie, mLSS) so that patients reported on symptom severity rather than "bother" and had a recall period of 1 week instead of 1 month[2]
  - Response was defined as a ≥7-point reduction from baseline in the summary symptom score at week 24
  - mLSS response rate at week 24, including response by baseline cGVHD severity and overall response, was analyzed by the intention-to-treat principle; mLSS data at week 24 were available for 55.8% of ruxolitinib patients (92/165) and 53.0% of BAT patients (87/164)
  - mLSS response rate at week 24 by steroid dose (<7.5 mg/day vs ≥7.5 mg/day) was determined for patients with evaluable biweekly steroid exposure data between day 155 and day ≤168 (ruxolitinib, n=118; BAT, n=116)
    - <7.5 mg/day was considered a physiological dose, which is generally associated with fewer adverse events[5]
- Additional secondary objectives included evaluation of Functional Assessment of Cancer Therapy–Bone Marrow Transplantation (FACT-BMT) and 5-level EQ-5D (EQ-5D-5L) scores. Exploratory objectives included evaluation of Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) scores
  - FACT-BMT is a multidimensional, cancer-specific QOL instrument
  - EQ-5D-5L is a utility measurement comprised of 5 domains, each with 5 severity levels
  - PGIS is a 5-point scale ranging from "no symptoms" to "very severe symptoms," and PGIC is a 7-point scale ranging from "very much better" to "very much worse." For this study, patients used these tools to rate their perceived change in cGVHD symptoms over the past week (PGIS) and since starting study treatment (PGIC)
  - All of these nonspecific PROs were analyzed in patients with evaluable data at the specified time point
- Individual organ responses were supportive analyses of the primary endpoint
- Linear regression analysis was performed to determine whether organ response in eye, skin, mouth, or lung at week 24 predicted change from baseline in the respective mLSS subscale score at week 24 after adjusting for treatment and baseline mLSS subscale score
- PROs were collected at baseline and every 4 weeks through week 24 or until treatment failure or discontinuation from the main study period
- *P* values were calculated only for primary and key secondary endpoints
- Odds ratios (ORs) and 95% CIs were calculated using the Cochran-Mantel-Haenszel test stratified according to baseline cGVHD severity

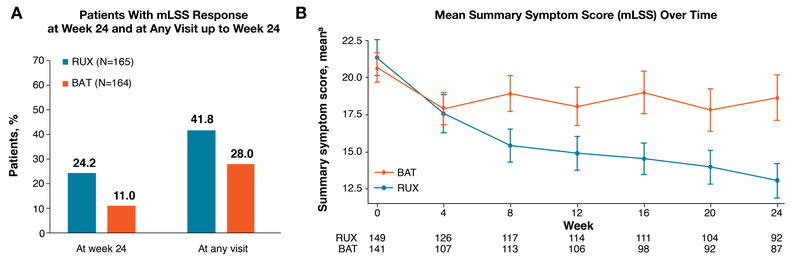
RESULTS

Patients

- Baseline characteristics, including symptom burden, were balanced between arms (**Supplementary Material**)

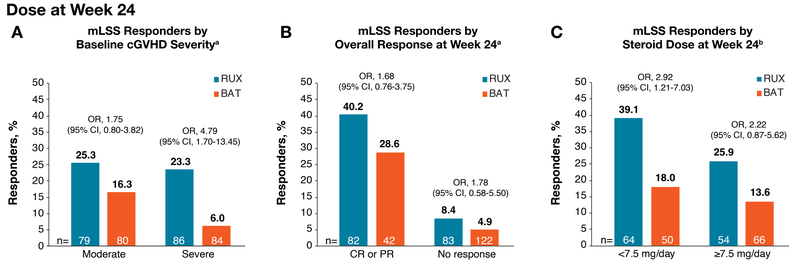
mLSS response

Figure 1. mLSS Response and Mean Summary Symptom Score Over Time



[a] Mean summary symptom scores are shown for patients with data available at each time point.

Figure 2. mLSS Responders by Baseline cGVHD Severity, Overall Response at Week 24, and Steroid Dose at Week 24

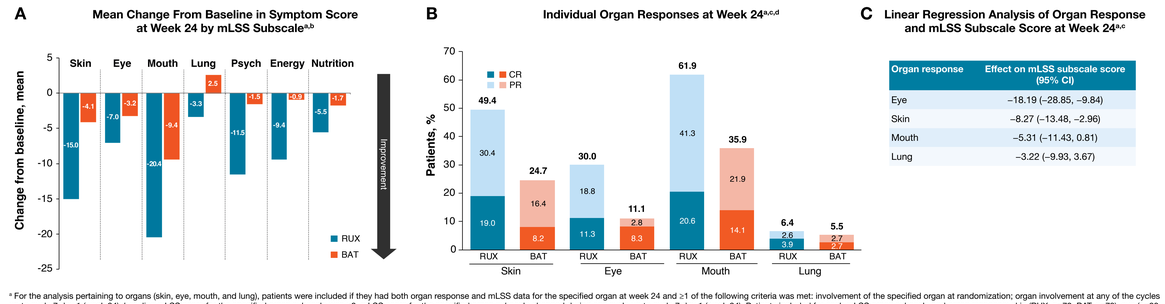


Patients with change to or addition of new systemic cGVHD treatment were counted as nonresponders (mLSS) irrespective of the summary symptom score value.
[a] The analysis shown was done per the intention-to-treat principle. Ninety-two patients in the RUX arm and 87 patients in the BAT arm had valid summary symptom scores at week 24. [b] The patient populations shown had steroid exposure data for study interval day 155 to day ≤168. Of these patients, 89 in the RUX arm and 83 in the BAT arm had valid summary symptom scores at week 24.

- A larger proportion of patients treated with ruxolitinib than BAT were mLSS responders (≥7-point reduction from baseline in the summary symptom score) at week 24 and at any visit up to week 24 (**Figure 1A**)
- Ruxolitinib was associated with a rapid and continued reduction in mean summary mLSS symptom score over time, whereas only an initial reduction at week 4 was seen with BAT (**Figure 1B**)
- mLSS response in the ruxolitinib arm was similar regardless of baseline cGVHD severity and consistently greater than in patients receiving BAT (**Figure 2A**). In the BAT arm, patients with severe cGVHD had a markedly lower rate of mLSS response than those with moderate cGVHD
- Among patients achieving a complete or partial cGVHD response, those treated with ruxolitinib were more likely to have an mLSS response (40.2% vs 28.6%) (**Figure 2B**). A similar trend was observed even among patients without a cGVHD response (8.4% vs 4.9%)
- The mLSS response rate was higher in patients whose steroid dose was <7.5 mg/day vs ≥7.5 mg/day at week 24 (**Figure 2C**). The highest response rates in both subgroups were among patients receiving ruxolitinib
  - Among patients with available steroid data, a greater percentage of patients treated with ruxolitinib vs BAT were receiving steroid doses <7.5 mg/day at week 24 (54.2% vs 43.1%)

Organ and mLSS response

Figure 3. Association Between Organ Response and Change in Symptom Score (mLSS)

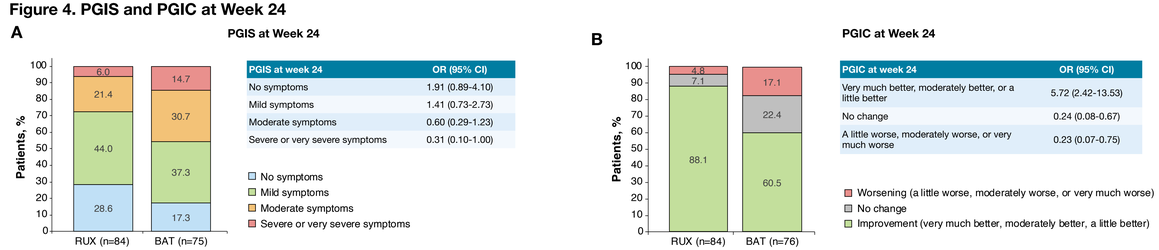


[a] For the analysis pertaining to organs (skin, eye, mouth, and lung), patients were included if they had both organ response and mLSS data for the specified organ at week 24 and ≥1 of the following criteria was met: involvement of the specified organ at randomization; organ involvement at any of the cycles up to cycle 7 day 1 (week 24); baseline mLSS score for the specified organ subscale was >0; mLSS score for the specified organ subscale changed during any cycle up to cycle 7 day 1 (week 24). Patients included for each mLSS organ subscale and organ response: skin (RUX, n=79; BAT, n=73); eye (n=80; n=72); mouth (n=63; n=64); lung (n=78; n=73). [b] For the psychological, energy, and nutrition mLSS subscales, change from baseline was calculated for all patients with available data at baseline and week 24 (RUX, n=85; BAT, n=81). [c] Organ response of CR or PR as documented by the investigator at week 24.
[d] Percentage is based on the number of patients who met the inclusion criteria for each organ as stated in footnote a.

- Greater mean reductions were observed with ruxolitinib vs BAT at week 24 across all mLSS subscales (**Figure 3A**); greater improvements in organ-specific subscales corresponded with higher objective cGVHD responses in the respective organ at week 24 in both arms (**Figure 3B**)
- As demonstrated by reductions on the psychological, energy, and nutrition subscales, overall symptom burden not directly tied to organ responses was also better with ruxolitinib than with BAT (**Figure 3A**)
- After adjusting for treatment and baseline subscale score, each of the organ-specific regression models predicted a decrease in mLSS subscale score for those who had an organ response at week 24 (**Figure 3C**)
  - However, the 95% CI included 0 for mouth and lung responders

Additional PROs

Figure 4. PGIS and PGIC at Week 24



Percentage is calculated based on the number of patients with PGIS or PGIC data at week 24 (RUX, n=84; BAT, n=75).

PGIS and PGIC

- Patients treated with ruxolitinib were more likely to report no or mild symptoms according to PGIS (**Figure 4A**) and greater symptom improvement by PGIC (**Figure 4B**) at week 24 than those who received BAT

FACT-BMT

- No difference between arms was observed in the FACT-BMT (**Supplementary Material**), suggesting that this measure is too generic to fully capture the impact of cGVHD on QOL
  - However, these findings suggest that ruxolitinib treatment is not accompanied by increased toxicity and confirm that multidimensional QOL was not reduced with ruxolitinib or BAT

EQ-5D-5L

- EQ-5D-5L scores were numerically higher with ruxolitinib than with BAT (**Supplementary Material**)

Abbreviations

BAT, best available therapy; cGVHD, chronic graft-vs-host disease; CR, complete response; mLSS, modified Lee Symptom Scale; OR, odds ratio; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PR, partial response; Psych, psychological; RUX, ruxolitinib.

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