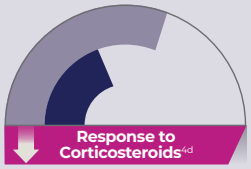
Critical Need for Novel First-Line Treatment Approaches to Prevent aGVHD Progression

40% of allo-HCT recipients with aGVHD will progress to a higher grade of aGVHD, which increases the risk of mortality, morbidity, and reduced response to steroids[1a]

P<0.05

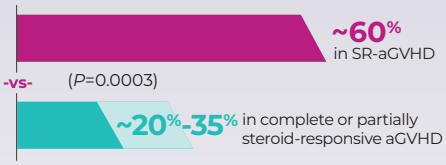


P=0.003

Suboptimal efficacy in first-line SoC corticosteroids for aGVHD significantly increases the risk of progressing to higher grades of aGVHD or to steroid-refractory aGVHD (SR-aGVHD)[1a,5,6]

Progression to SR-aGVHD is associated with more severe clinical consequences, worsened outcomes, and increased treatment burden for patients, compared with steroid-responsive aGVHD

INCREASED RATES OF NRM



At 2 years after initial treatment[7e]

INCREASED MORTALITY

80% higher risk of mortality in SR-aGVHD compared with steroid-responsive aGVHD (HR, 1.8; 95% CI, 1.2-2.8; *P*=0.01)[8f]

INCREASED cGVHD RISK

Patients with SR-aGVHD are 50% more likely to develop cGVHD compared with patients with steroid-responsive aGVHD (HR, 1.5; 95% CI, 1.0-2.4; *P*=0.06)[8f]

- **Patients with SR-aGVHD are more likely to have progressive onset cGVHD** vs patients with steroid-responsive aGVHD[9g]

INCREASED IMMUNOSUPPRESSIVE BURDEN & COMPLICATIONS

Up to ~36% of patients with SR-aGVHD may be subject to **corticosteroid dose escalations**, leading to **increased risk of treatment-related complications**[1a,10]

Complications associated with corticosteroid use include[10,11h,12]:

- Infection
- Diabetes/Hyperglycemia
- Hypertension
- Bone and muscle complications (eg, avascular necrosis)
- Gastrointestinal complications

INCREASED OPPORTUNISTIC INFECTIONS

2.49 SR-aGVHD **-vs-** **1.24** steroid-responsive

Patients with SR-aGVHD have more episodes of infections (bacterial, viral, fungal) per 100 patient-days over the first year post transplantation[13i]

Patients with SR-aGVHD commonly experience severe bacterial infections (61%), which contribute to a 4-year infection-related mortality of 46%[14j]

SUBOPTIMAL TREATMENT OPTIONS AVAILABLE

34% of patients may completely respond to the SR-aGVHD SoC, with 95% of patients expected to experience at least 1 TEAE and 78% to experience Grade ≥3 TEAEs.[6,15k]

The development of novel first-line treatment strategies to improve efficacy, response, and reduce aGVHD severity is critical to helping mitigate the risk of progression to SR-aGVHD, where outcomes are poorer and treatment is more challenging[1a,8f,15k]

aGVHD=acute GVHD; allo=allogeneic; cGVHD=chronic GVHD; CI=confidence interval; CIBMTR=Center for International Blood and Marrow Transplant Research; GVHD=graft-versus-host disease; HCT=hematopoietic cell transplantation; NRM=non-relapse mortality; SoC=standard of care; SR-aGVHD=steroid-refractory aGVHD; TEAE=treatment-emergent adverse event.

*3-year overall survival reported from the 2006-2012 cohort.[2]

[a]A multicenter, retrospective chart review of 475 pediatric and adult patients who developed Grade II-IV aGVHD after receiving an allo-HCT between January 1, 2014, and June 30, 2016, from 11 large transplant centers in the United States to examine the clinical courses, treatments, hospitalization rates, and outcomes of patients who developed aGVHD after HCT and before the approval of ruxolitinib.[1]

[b]A large CIBMTR registry retrospective analysis of 2905 patients who received an allo-HCT between 1999 and 2012, and developed Grade II-IV aGVHD to determine whether survival outcome after a diagnosis of aGVHD has improved significantly over time.[2]

[c]A retrospective study of 44 pediatric and adult patients who developed intestinal aGVHD after an HCT from January 2010 to December 2012, at the 307th Hospital of Chinese People's Liberation Army in Beijing, China, to examine the relationship between intestinal aGVHD and intestinal infection after allo-HCT.[3]

[d]A retrospective evaluation of prospective clinical trials data from the University of Texas M.D. Anderson Cancer Center, between January 1998 and September 2002, examining predictors of corticosteroid failure in 287 consecutive patients who underwent allo-HCT.[4]

[e]A retrospective study of 303 consecutive, relapse-free, adult patients who received systemic steroid treatment for Grade IIb-IV aGVHD after a first allo-HCT at the Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance, between 2000 and 2005, to evaluate short-term response endpoints for aGVHD.[7]

[f]A retrospective cohort study of 1143 consecutive pediatric and adult patients who received their first allo-HCT from the University of Minnesota, between 2008 and 2016, to assess the incidence, risk factors, and clinical outcomes of patients with aGVHD who were steroid-sensitive, steroid-dependent, or SR after initial steroid therapy.[8]

[g]A retrospective cohort study of 784 consecutive pediatric and adult patients who received their first allo-HCT from the University of Minnesota, between 2008 and 2016, to assess the incidence, risk factors, and clinical outcomes of patients with cGVHD after a previous diagnosis of steroid-sensitive, steroid-dependent, or SR-aGVHD compared to those with no history of aGVHD.[9]

[h]An open-label, multicenter, phase 3, randomized study (EUDTRACT N 2008-000413-29) that compared no treatment versus treatment with methylprednisolone in 171 pediatric and adult patients with Grade I aGVHD to examine disease progression.[11]

[i]A retrospective analysis of 1143 consecutive pediatric and adult patients who received their first allo-HCT from the University of Minnesota, between 2008 and 2016, to examine infectious complications based on steroid responsiveness for 1 year following transplantation in patients with aGVHD versus those without aGVHD.[13]

[j]A retrospective study of 127 adult patients who developed Grade II-IV SR-aGVHD after allo-HCT at the Hospitals Sant Pau and Vall d'Hebrón while on corticosteroids, and subsequently received salvage treatment to analyze the occurrence, risk factors, and impact on long-term outcomes of severe infections in patients with SR-aGVHD.[14]

[k]A multicenter, randomized, open-label, phase 3 trial that assigned 309 pediatric and adult patients with SR-aGVHD to receive ruxolitinib or "best available care" between April 12, 2017, and May 30, 2019, to compare the efficacy and safety of ruxolitinib with the "best available care."[15]

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