EUROPEAN HEMATOLOGY ASSOCIATION

EHA2021 VIRTUAL

S235

# IBRUTINIB VS PLACEBO IN COMBINATION WITH CORTICOSTEROIDS IN PATIENTS WITH NEW-ONSET CHRONIC GRAFT-VERSUS-HOST DISEASE (CGVHD): RESULTS FROM THE RANDOMIZED, DOUBLE-BLIND PHASE 3 INTEGRATE STUDY

Topic: 22. Stem cell transplantation - Clinical

Keywords: Chronic graft-versus-host | Ibrutinib | Phase III | Prednisone

David Miklos[1], Mohammad Abu Zaid[2], Julian P. Cooney[3], Jörn Albring[4], Mary Flowers[5], Alan P. Skarbnik[6], Ibrahim Yakoub-Agha[7], Bor-Sheng Ko[8], Benedetto Bruno[9], Edmund K. Waller[10], Jean Yared[11], Sang Kyun Sohn[12], Claude-Eric Bulabois[13], Takanori Teshima[14], David Jacobsohn[15], Hildegard Greinix[16], Ahmad Mokatrin[17], Yihua Lee[17], Justin Wahlstrom[17], Lori Styles[17], Gerard Socie[18]

[1] Stanford University School of Medicine, Stanford, CA, United States
[2] Melvin and Bren Simon Cancer Center (IUSCC), Indiana University, Indianapolis, IN, United States
[3] Harry Perkins Medical Research Institute, Fiona Stanley Hospital, Murdoch, Australia
[4] University of Muenster, Muenster, Germany
[5] Fred Hutchinson Cancer Research Center, Seattle, WA, United States
[6] John Theurer Cancer Center, Hackensack, NJ, United States
[7] CHU de Lille, Univ Lille, INSERM U1386, Infinite, 59000 Lille, France
[8] National Taiwan University Hospital, Taipei, Taiwan, Province of China
[9] A.O.U. Citta della Salute e della Scienza di Torino, Torino, Italy
[10] Emory University, Winship Cancer Institute, Atlanta, GA, United States
[11] University of Maryland, Greenebaum Comprehensive Cancer Center, Baltimore, MD, United States
[12] Kyungpook National University Hospital, Daegu, Korea, Republic Of
[13] CHU Grenoble Alpes, La Tronche, France
[14] Hokkaido University Hospital, Sapporo, Japan
[15] The Children's Research Institute, Washington, DC, United States
[16] Medical University of Graz, Graz, Austria
[17] Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA, United States
[18] AP-HP, Hopital St. Louis and University of Paris, Paris, France

**Background:** Approximately 34% of patients (pts) who develop cGVHD after hematopoietic cell transplant require systemic treatment. Many pts experience recurrent cGVHD or become refractory to standard of care first-line corticosteroids. Ibrutinib (ibr) has demonstrated sustained efficacy and safety in cGVHD and is currently the only therapy approved in the United States for adults with cGVHD after failure of ≥1 line of systemic therapy.

**Aims:** We present the efficacy and safety results from the randomized, double-blind, placebo-controlled phase 3 iNTEGRATE study (PCYC-1140; NCT02959944) of ibr plus corticosteroids in previously untreated pts with cGVHD.

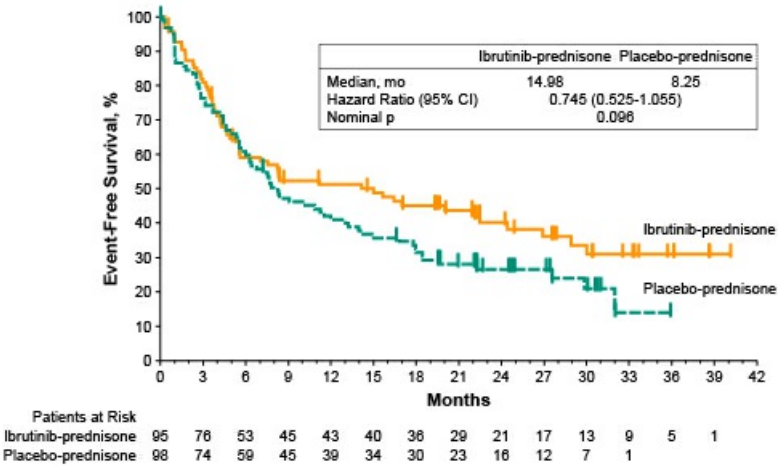
**Methods:** Eligible pts (aged ≥12 y) had newly diagnosed moderate/severe cGVHD, required systemic corticosteroid therapy, and had no prior systemic treatment for cGVHD. Pts were randomized 1:1 to receive ibr 420 mg/d or placebo (pbo) in combination with prednisone (pred) starting at 1 mg/kg/d. The primary endpoint was response rate (complete or partial response) at 48 wks per the 2014 NIH Consensus Development Project Criteria. Other endpoints included event-free survival (EFS; ie, survival without cGVHD progression, malignancy relapse, or start of subsequent cGVHD therapy), duration of response (DOR), time to withdrawal of corticosteroids and immunosuppressants (except ibr/pbo), improvement of Lee cGVHD Symptom Scale score, overall survival (OS), and safety.

**Results:** In total, 95 pts received ibr-pred and 98 received pbo-pred. Baseline pt characteristics were well balanced between treatment arms. Median time on treatment was 5.4 mo and 6.4 mo for ibr-pred and pbo-pred arms, respectively; median follow-up was 25 mo for both arms. At the time of the primary analysis, 41% (39/95) of pts treated with ibr-pred had a response at 48 wk vs 37% (36/98) of pts receiving pbo-pred ($p$=0.54). Though the

primary endpoint of the study was not statistically significant, ibr-pred resulted in clinically meaningful improvements in several other key endpoints, prompting evaluation of these endpoints with a longer follow up (reported *p*-values are nominal). With extended follow up, median DOR was 16 mo with ibr-pred vs 10 mo with pbo-pred ($p$=0.12). Median EFS was 15 mo with ibr-pred and 8 mo with pbo-pred (hazard ratio 0.75 [95% CI: 0.53-1.1]; $p$=0.1; **Figure**). 48% vs 39% ($p$=0.15) of pts receiving ibr-pred vs pbo-pred withdrew corticosteroids, and 38% vs 28% ($p$=0.08) withdrew immunosuppressants. 40% of pts in the ibr-pred arm experienced an improvement in overall Lee cGVHD Symptom Scale score vs 29% in the pbo-pred arm ($p$=0.09). Median OS was not reached in either arm; 22% (21/95) of pts in the ibr-pred arm and 19% (19/98) in the pbo-pred arm died from any cause. 49% (46/94) of pts in the ibr-pred arm and 46% (44/96) in the pbo-pred arm experienced a grade ≥3 serious adverse event (AE); 22% (21/94) and 25% (24/96), respectively, experienced an AE leading to discontinuation of study drug.

**Image:**

**Figure. EFS with ibr-pred vs pbo-pred in pts with moderate/severe cGVHD.**




**Summary/Conclusion:** In this randomized, pbo-controlled trial of ibr in combination with corticosteroids for NIH-defined moderate/severe cGVHD, the primary endpoint did not meet statistical significance. However, numerical trends of improved clinical outcomes in the ibr-pred arm were noted, including longer DOR and EFS and improved patient-reported outcomes. Safety was consistent with the known profiles of ibr and pred and was similar between treatment arms. The positive trends observed in other important clinical endpoints along with no additional safety trends and concerns suggest that ibr may have value in some previously untreated pts with cGVHD.



**Abstract Book Citations:** Authors, Title, HemaSphere, 2021;5:(S2):pages. Abstract Book, DOI: http://dx.doi.org/10.1097/HS9.0000000000000566