EUROPEAN HEMATOLOGY ASSOCIATION

EHA2021 VIRTUAL

S168

SABATOLIMAB PLUS HYPOMETHYLATING AGENTS (HMAS) IN PATIENTS (PTS) WITH HIGH-/VERY HIGH-RISK MYELODYSPLASTIC SYNDROME (HR/VHR-MDS) AND ACUTE MYELOID LEUKEMIA (AML): SUBGROUP ANALYSIS OF A PHASE 1 STUDY

Topic: 10. Myelodysplastic syndromes - Clinical

Keywords: Acute myeloid leukemia, Clinical trial, Immunotherapy, Myelodysplasia

Andrew Wei[1], Jordi Esteve[2], Kimmo Porkka[3], Steve Knapper[4], Elie Traer[5], Sebastian Scholl[6], Guillermo Garcia-Manero[7], Norbert Vey[8], Martin Wermke[9], Jeroen Janssen[10], Rupa Narayan[11], Sun Loo[12], Natalia Tovar[2], Mika Kontro[3], Oliver Ottmann[4], Purushotham Naidu[13], Sema Kurtulus[14], Elena Orlando[14], Nidhi Patel[14], Jessica Makofske[14], Fei Ma[13], Na Zhang[14], Anisa Mohammed[13], Mikael L. Rinne[14], Uma Borate[5], Andrew M. Brunner[11]

[1] The Alfred Hospital and Monash University, Melbourne, Australia
[2] Hospital Clínic, Barcelona, Spain
[3] Department of Hematology, Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland
[4] Cardiff University, Cardiff, United Kingdom
[5] Oregon Health & Science University, Portland, United States
[6] University Hospital Jena, Jena, Germany
[7] MD Anderson Cancer Center, Houston, United States
[8] Institut Paoli-Calmettes, Marseille, France
[9] University Hospital Dresden, Dresden, Germany
[10] Amsterdam University Medical Centers, location VUmc, Amsterdam, Netherlands
[11] Massachusetts General Hospital, Boston, United States
[12] The Alfred Hospital, Melbourne, Australia
[13] Novartis Pharmaceuticals Corporation, East Hanover, United States
[14] Novartis Institutes for BioMedical Research, Cambridge, United States

Background:

Novel therapies providing improved and durable outcomes with a favorable safety profile are needed in higher-risk MDS and AML. Sabatolimab (MBG453) is a novel immuno-myeloid therapy targeting TIM-3, an immune regulator expressed on immune and myeloid leukemic cells but not on normal hematopoietic stem cells. In a Ph 1b study (NCT03066648), sabatolimab+HMA showed promising overall response rates in pts with HR/vHR-MDS (64%) and newly diagnosed (ND)-AML (41%). Response durability was encouraging, with an estimated 84% and 79% still in response after 6 mo. Treatment-emergent AE profile was consistent with that reported for HMA alone (Brunner ASH 2020).

Aims:

To further explore safety/tolerability, efficacy in pt subgroups, and biomarkers with sabatolimab+HMA.

Methods:

Study design/eligibility criteria have been reported. Pts with HR/vHR-MDS (per IPSS-R) or ND-AML who were HMA-naïve and ineligible for intensive chemotherapy received sabatolimab (1-2 infusions/mo) + decitabine or azacitidine. Primary objectives were safety/tolerability; secondary objectives included PK and preliminary efficacy. Data cutoff 22 Sep 2020; updated data will be presented.

Results:

To explore sabatolimab+HMA safety/tolerability, sabatolimab dose interruption (>7 d delay), reduction, and discontinuation due to AE/death were assessed in 89 pts with HR/vHR-MDS (n=41) and ND-AML (n=48). Of 89 pts, 36 (40%) had sabatolimab dose interruption, 1 (1%) had sabatolimab dose reduction, 2 (2%) had dose interruption and reduction, 5 (6%) discontinued, and 3 (3%) had dose interruption and discontinued. Dose interruption rate in

first 2 cycles was low (21% [19/89]). Of 8 discontinuations, 4 were due to AE (1/4 related to study treatment) and 4 to death. Of 22 pts with gr 4 neutropenia/thrombocytopenia at baseline (BL), 4 (18%) had dose interruption, 2 (9%) discontinued, 1 (5%) had dose interruption and discontinued, and none had dose reduction.

In analyses of remission rates (CR+mCR/CRi+PR) by BL factors, response was independent of BM blast burden in pts with HR/vHR-MDS or ND-AML. Remission rates were similar in pts ≥75 and 65-74 y: 50% (6/12) and 65% (11/17) with HR/vHR-MDS and 42% (8/19) for both groups with ND-AML. Response durability in pts ≥75 and 65-74 y was encouraging: an estimated 83% and 86% with HR/vHR-MDS and 69% and 88% with ND-AML remained in remission after 6 mo. In pts with *TP53* mutation or pts with ≥1 mutation conferring ELN high risk (*TP53*, *RUNX1*, *ASXL1*), respectively, remission rates were 55% (6/11; 4/6 in remission >200 d) and 59% (13/22; 8/13 in remission >200 d) for HR/vHR-MDS and 25% (1/4; in remission 129 d) and 50% (6/12; 2/6 in remission >200 d) for ND-AML. 6/7 responders with *TP53* mutation had complex karyotype.

Biomarker analyses identified IL-1β, a proinflammatory cytokine reported to promote expansion of AML progenitor cells, as one of the most differentially expressed genes in BM of responders vs nonresponders to sabatolimab+HMA, with expression levels inversely correlated with remission. Single-cell RNA sequencing showed sabatolimab+HMA downregulated IL-1β in blast cells but, consistent with prior observations in TIM-3 deficient pts, it upregulated IL-1β in myeloid cells.

Summary/Conclusion:

Sabatolimab+HMA showed favorable tolerability in MDS/AML, including in pts with gr 4 cytopenias at BL. Promising remission rates were seen irrespective of BL blast burden and in older pts and pts with adverse risk mutation. This supports development of sabatolimab+HMA in the STIMULUS trial program in MDS/AML.

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