



The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Elenestinib, an Investigational, Next Generation KIT D816V Inhibitor, Reduces Mast Cell Burden, Improves Symptoms, and Has a Favorable Safety Profile in Patients with Indolent Systemic Mastocytosis: Analysis of the Harbor Trial

Tsewang Tashi, MD¹, Olivier Hermine, MD PhD², Mariana Castells, MD PhD³, Mar Guilarte, MD PhD⁴, Vito Sabato, MD PhD⁵, Marcus Maurer, MD⁶, Jens Panse, MD⁷, Ivan Alvarez-Twose, MD PhD⁸, Renata Cabral, MD⁹, Robert Bird, MBBS¹⁰, Stéphane Barete, MD PhD¹¹, Laurence Bouillet, MD PhD¹², Maud Hermans, MD PhD¹³, Paul Van Daele, MD PhD¹⁴, David González-De-Olano, MD PhD¹⁵, Elizabeth A. Griffiths, MD¹⁶, Joseph Jurcic, MD¹⁷, Ingunn Dybedal, MD PhD¹⁸, Gandhi Laurent Damaj, MD PhD¹⁹, Philippe Schafhausen²⁰, Chiara Elena, MD²¹, Tse-Chieh Teh, MD PhD²², Pankit Vachhani, MD²³, Caroline Labe, BA²⁴, Saranya Venugopal, MS, MPharm²⁴, Kevin He, PhD²⁴, Javier Muñoz-González, PhD²⁵, Ben Lampson, MD PhD²⁴, Robyn Scherber, MD²⁴, Prithviraj Bose, MD²⁶, Clive Grattan, MD²⁷, Thanai Pongdee, MD²⁸, Tracy I. George, MD²⁹, Cristina Bulai Livideanu³⁰

¹ University of Utah, Huntsman Cancer Institute, Salt Lake City, UT

² Département d'hématologie, CEREMAST, Hôpital Necker-Enfants Malades, APHP et Institut Imagine, Paris, France

³ Department of Medicine, Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, Boston, MA

⁴ Hospital Universitari Vall d'Hebron, Institut de Recerca (VHIR), Barcelona, Spain

⁵ Department of Immunology, Allergology and Rheumatology, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium

⁶ Charité - Universitätsmedizin Berlin and Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology Hindenburgdamm, Berlin, Germany

⁷ University Hospital Aachen, Medical Faculty, RWTH Aachen University, Aachen, Germany

⁸ Institute of Mastocytosis Studies of Castilla-La Mancha (CLMast), Virgen del Valle Hospital, Toledo, Spain

⁹ Centro Hospitalar Universitário do Porto and ICBAS-School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal

¹⁰ Princess Alexandra Hospital, Woolloongabba, Australia

¹¹ AP-HP, Pitié-salpêtrière Hospital, University Pierre & Mari, Paris, France

¹² CHU Grenoble Alpes, Grenoble, France

¹³ Department of Allergology and Clinical Immunology Section of Clinical Immunology, Internal Medicine, Erasmus MC University Medical Centre, Rotterdam, Netherlands

¹⁴ Erasmus Medical Center, Rotterdam, Netherlands

¹⁵ University Hospital Ramón y Cajal, IRYCIS, Madrid, Spain

¹⁶ Roswell Park Comprehensive Cancer Center, Buffalo, NY

¹⁷ Columbia University Medical Center, New York, NY

¹⁸ Oslo University Hospital, Rikshospitalet, Oslo, Norway

¹⁹ Hematology Institute, University Of Caen Normandie Hospital Center, Caen, France

²⁰ University Medical Center Hamburg-Eppendorf, Hamburg, Germany

²¹ Department of Molecular Medicine & Department of Hematology and Oncology, University of Pavia, Pavia, Italy

²² Alfred Hospital, Melbourne, Australia

²³ University of Alabama at Birmingham, Birmingham, AL

²⁴ Blueprint Medicines Corporation, Cambridge, MA

²⁵ Blueprint Medicines Corporation, Zug, Switzerland

²⁶ The University of Texas MD Anderson Cancer Center, Houston, TX

²⁷ St John's Institute of Dermatology, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom

²⁸ Division of Allergic Diseases, Mayo Clinic, Rochester, MN

²⁹ ARUP Laboratories, University of Utah School of Medicine, Salt Lake City, UT

³⁰ Department of Dermatology, CEREMAST Toulouse, CHU Toulouse, Toulouse, France

Introduction

Indolent systemic mastocytosis (ISM) is a rare clonal mast cell disease driven by the *KIT* D816V mutation in nearly all patients. Patients with ISM can present with debilitating acute and chronic cutaneous, gastrointestinal, neurocognitive, and systemic symptoms caused by the release of inflammatory mediators from abnormal mast cells. In some patients, symptoms are not adequately controlled with best supportive care (BSC) medications. Elenestinib (BLU-263) is a novel, investigational, oral, next-generation tyrosine kinase inhibitor that potently and selectively inhibits *KIT* D816V with limited central nervous system penetration and pharmacokinetics (PK) that support once daily dosing. HARBOR (NCT04910685) is a randomized, double-blind, placebo-controlled, phase 2/3 study assessing efficacy and safety of elenestinib in patients with ISM.

Methods

Eligible adult patients with ISM, confirmed following central review of bone marrow (BM) pathology, clinical, and laboratory findings per World Health Organization criteria and a moderate-to-severe symptom score based on minimum mean total symptom score (TSS) of the ISM-Symptom Assessment Form (ISM-SAF©2018), were stratified by baseline serum tryptase (<20 ng/mL vs ≥ 20 ng/mL) and randomly assigned 3:1 to elenestinib 25 mg, 50 mg, or 100 mg once daily + BSC ("elenestinib") or placebo + BSC ("placebo"). The primary objective of Part 1 was to determine the recommended dose based on safety, PK, and pharmacodynamics. Secondary endpoints included changes in biomarkers of disease burden (serum tryptase, *KIT* D816V variant allele fraction [VAF], and BM mast cells) and ISM-SAF TSS. Three additional open-label PK groups enrolled patients at 50 mg, 75 mg, and 100 mg to further characterize PK and safety.

Results

As of data cutoff on July 3, 2023, a total of 122 patients with ISM have received their assigned treatment in Part 1 of the study; 39 were blinded and randomized to elenestinib or placebo, and 83 were treated with open-label elenestinib in the PK groups (21 patients at 50 mg, 34 patients at 75 mg, and 28 patients at 100 mg). Baseline demographics were similar to those reported for the general ISM population.

After 12 weeks of therapy, symptom improvement was observed for all dose cohorts, and symptom reduction by TSS was greater for patients on elenestinib versus placebo in the blinded portion of Part 1. Patients receiving elenestinib at 25 mg, 50 mg, and 100 mg doses showed reduction (mean percent) from baseline for tryptase (-15.4%, -50.9%, and -68.4% vs 3.3%, respectively) and *KIT* D816VVAF (-37.5%, -70.3%, and -77.0% vs -2.5%, respectively) as compared to placebo. Similar reductions in TSS and disease-related biomarkers were observed in the open-label PK cohorts.

After a median treatment duration of 35.3 weeks, elenestinib was well-tolerated at all dose levels. There were no treatment-related serious adverse events and no treatment-related adverse events that led to drug discontinuation.

Conclusion

Elenestinib at all tested doses demonstrated beneficial effects on disease-related symptoms and biomarkers of mast cell burden in this large and maturing cohort of patients with ISM with a moderate-to-severe symptom burden. Elenestinib was well tolerated across all dose levels with a promising early benefit-risk profile in ISM. These preliminary findings will inform dosing for the planned Part 2 of HARBOR, which will examine elenestinib versus placebo in a randomized, blinded, placebo-controlled setting.

Disclosures Tashi: *Blueprint Medicines Corporation, PharmaEssentia:* Membership on an entity's Board of Directors or advisory committees; *Blueprint Medicines Corporation:* Other: PI on several clinical trials including PIONEER. **Hermine:** *AB Science, BMS/Celgene, Alexion, Novartis, and Inatherys:* Research Funding; *AB Science:* Consultancy, Other: Shareholder.

Castells: *Current Allergy and Asthma Reports:* Membership on an entity's Board of Directors or advisory committees; *ABAI:* Membership on an entity's Board of Directors or advisory committees; *UptoDate:* Honoraria, Other: Receives authors fees; *Blueprint:* Consultancy, Other: PI on several Blueprint clinical trials. **Guilarte:** *Blueprint Medicines Corporation:* Consultancy.

Sabato: *Institutional:* Other: Institution has received research funding from Blueprint Medicines Corporation for clinical trials.; *Blueprint Medicines Corporation, Novartis, and Cogent:* Honoraria, Other: Honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events. **Maurer:** *Allakos, Amgen, AstraZeneca, Bayer, Blueprint Medicines Corporation, Celldex, Dr. Pflieger, FAES, Genentech, GI Innovation, GSK, Innate Pharma, Kyowa Kirin, Lilly, Merkle Recordati, Moxie, Novartis, Regeneron, Roche, Sanofi, Third Harmonic Bio, UCB, and Ur:* Honoraria, Research Funding. **Panase:** *MSD:* Consultancy; *Boehringer Ingelheim:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *F. Hoffmann-La Roche Ltd.:* Membership on an entity's Board of Directors or advisory committees, Other: Third party writing assistance by Akshaya Srinivasan, PhD, of MediTech Media Ltd and funded by F. Hoffmann-La Roche Ltd, , Speakers Bureau; *BMS:* Consultancy; *Alexion, AstraZeneca Rare Disease:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Sanofi Ltd:* Consultancy; *Samsung Bioepis:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *SOBI:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Pfizer:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Novartis:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Blueprint Medicines:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Apellis Pharmaceuticals, Inc.:* Consultancy; *Amgen:* Consultancy. **Alvarez-Twose:** *Blueprint Medicines Corporation:* Other: Advisory Board or Speaker Fees, Research Funding; *Novartis:* Other: Advisory Board or Speaker Fees. **Bird:** *Principia (Sanofi):* Research Funding; *Rigel:* Research Funding; *Amgen:* Speakers Bureau. **Barete:** *Blueprint Medicines Corporation:* Consultancy, Other: Fees for symposium and scientific boards; financial support for clinical trials; *AbbVie:* Other: Fees; *Leo Pharma Laboratories:* Other: Fees. **Bouillet:** *Takeda, Biocryst, Behring, Blueprint Medicines Corporation, Novartis:* Consultancy, Other: Advisory Role; *Takeda, Behring, Biocryst, Blueprint*

Medicines Corporation, Novartis: Other: Travel and Accommodation Expenses. **Van Daele:** Novartis: Other: Speaking Fees. **Griffiths:** Taiho Oncology: Consultancy; Abbvie: Consultancy; Bristol Myers Squibb: Consultancy, Research Funding; Genentech, Inc.: Consultancy, Research Funding; Apellis Pharmaceuticals: Consultancy, Research Funding; Alexion Pharmaceuticals: Consultancy, Research Funding; S. Karger Publishing: Honoraria; Artis Ventures: Membership on an entity's Board of Directors or advisory committees; Picnic Health: Membership on an entity's Board of Directors or advisory committees; MediCom Worldwide, Inc.: Honoraria; NextCure, Inc: Research Funding; American Society of Hematology: Honoraria; Celldex Therapeutics: Research Funding; CTI Biopharma: Consultancy; Vera and Joseph Dresner Foundation: Membership on an entity's Board of Directors or advisory committees; Astex Pharmaceuticals: Research Funding; Partner Therapeutics: Consultancy; Blueprint Medicines, Inc: Research Funding; AstraZeneca Rare Disease: Consultancy, Research Funding; MDS International Foundation: Honoraria; Medscape: Honoraria; AAMDSIF: Honoraria; Novartis: Consultancy, Research Funding; Physicians Educational Resource: Honoraria; Takeda Oncology: Consultancy. **Jurcic:** Gilead/Forty Seven: Research Funding; Rigel Pharmaceuticals: Consultancy; AbbVie: Research Funding; Ionis Pharmaceuticals: Research Funding; Seattle Genetics: Research Funding; Blueprint Medicines: Research Funding; Syros Pharmaceuticals: Membership on an entity's Board of Directors or advisory committees; Forma Therapeutics: Research Funding; Bristol Myers Squibb: Consultancy, Research Funding; Sumitomo Pharma: Research Funding. **Dybedal:** Novartis: Other: Advisory Board Fees. **Damaj:** Takeda, Blueprint Medicines Corporation, and Thermo Fisher: Consultancy, Other: Advisory Role; Takeda, AbbVie and Pfizer: Other: Travel and Accommodation Expenses. **Schafhausen:** Alexion: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel and accommodation support; AOP Orphan: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel and accommodation support; Blueprint Medicines Corporation: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel and accommodation support; BMS/Celgene: Consultancy, Honoraria, Other: Travel and accommodation support; Merck Serono: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel and accommodation support; MSD: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel and accommodation support; Novartis: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel and accommodation support; Pfizer: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel and accommodation support; Roche: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel and accommodation support; Sobi: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel and accommodation support. **Elena:** Blueprint Medicines Corporation, Cogent and Gilead: Other: Advisory Board Fees. **Vachhani:** Incyte, CTI BioPharma Corp, Blueprint Medicines: Speakers Bureau; Abbvie, Amgen, Blueprint Medicines, Cogent Biosciences, Incyte, CTI BioPharma Corp, Daiichi Sankyo, GlaxoSmith Kline, Karyopharm, Novartis, Pfizer, Genentech, Inc., Servier, Stemline, MorphoSys, LAVA therapeutics: Honoraria. **Labe:** Blueprint Medicines Corporation: Current Employment. **Venugopal:** Blueprint Medicines Corporation: Current Employment, Current equity holder in publicly-traded company. **He:** Blueprint Medicines Corporation: Current Employment, Current equity holder in publicly-traded company. **Muñoz-González:** Blueprint Medicines Corporation: Current Employment, Current equity holder in publicly-traded company. **Lampson:** Blueprint Medicines Corporation: Current Employment, Current equity holder in publicly-traded company. **Scherber:** Blueprint Medicines Corporation: Current Employment, Current equity holder in publicly-traded company. **Bose:** GSK, Novartis, Karyopharm, AbbVie, Pharma Essentia, Jubilant, Morphic: Honoraria; Kartos, Telios, Ionis, Disc, Janssen, Geron: Research Funding; Incyte, BMS, CTI, Morphosys, Blueprint, Cogent, Sumitomo: Honoraria, Research Funding. **Grattan:** Blueprint Medicines Corporation, AB Science: Other: Study Steering Committee; Celltrion, Sanofi: Consultancy. **Pongdee:** AstraZeneca: Research Funding; Blueprint Medicines Corporation: Research Funding; Sanofi: Research Funding; GlaxoSmithKline: Research Funding. **George:** Blueprint Medicines Corporation: Consultancy, Membership on an entity's Board of Directors or advisory committees; Celgene/BMS: Consultancy, Membership on an entity's Board of Directors or advisory committees; Cogent Biosciences: Consultancy, Membership on an entity's Board of Directors or advisory committees; Incyte Corporation: Consultancy, Membership on an entity's Board of Directors or advisory committees; ARUP Laboratories: Current Employment. **Livideanu:** Novartis: Research Funding; Blueprint Medicines Corporation: Membership on an entity's Board of Directors or advisory committees; Lilly, Novartis, UCB: Consultancy; ABSscience: Membership on an entity's Board of Directors or advisory committees.

<https://doi.org/10.1182/blood-2023-188904>