Safety and Tolerability of AZD0466 as Monotherapy for Patients with Advanced Hematological Malignancies. Preliminary Results from an Ongoing Phase I/II Trial

Shuikha Arslan,1 Shaun Fleming,2 Nitin Jain,3 Giovanni Martinelli,4 Anthony Stein,5 James S Blachly,6 Ashish Bajel,7 Antonio Curti,8 Giovanni Marconi,9 Giulia Fabbrini,7 Yotvat Marmor7, Shrini Sharma7, Nairouz Elgeioushi7, Giovanni Martinelli8,9,10, Anthony Stein7
1City of Hope National Medical Center, Duarte, CA, USA; 2The Adelaide, Melbourne, VIC, Australia; 3MD Anderson Cancer Center, Houston, TX, USA; 4IRCIS Institute Romagnole per il Studio del Tumore Oncio Amatoli; 5Mediol, Italy; 6Gene Family Center for Leukemia Research, City of Hope National Medical Center, Duarte, CA, USA; 7The Ohio State University James Comprehensive Cancer Center, Columbus, OH, USA; 8Peter MacCallum Cancer Centre and The Royal Melbourne Hospital, Melbourne, VIC, Australia; 9IRCIS Asociación Universidad de la República, Instituto de Oncología "Seràgnoli", Bologna, Italy; 10Oncology R&D, AstraZeneca, Boston, MA, USA; 11Oncology R&D, AstraZeneca, South San Francisco, CA, USA; 12Oncology R&D, AstraZeneca, Gothenburg, MD, USA; 13Oncology R&D, AstraZeneca, Cambridge, UK; 14OncoMed, Welwyn Garden City, UK.

Introduction
- Anti-proliferative effects of the Bcl-2 family (e.g., Bcl-2 and Bcl-xL) are critical for tumor survival and maintenance of the antiapoptotic phenotype.
- The Bcl-2 inhibitor venetoclax has benefit in patients with acute myeloid leukemia (AML), but resistance often develops due to upregulation of anti-apoptotic proteins such as Bcl-xL.
- Dual inhibition of Bcl-2 and Bcl-xL has potential for broader activity than is observed with venetoclax.
- AZD0466 is a novel drug-dimer conjugate, where the Bcl-2/Bcl-xL dual inhibitor AZD4362 is covalently conjugated to Staphylococcal clavatin's clinically validated DP527 dendrimer platform and gradually released by hydrolisis. Drug conjugation with the dimer reduces the lag phase from peak plasma levels to direct induction of apoptosis at similar levels, reducing the potential for off-target toxicity associated with Bcl-2 inhibition.
- AZD0466 has shown preclinical efficacy in solid and hematological malignancies.
- Preliminary results from a first-in-human study (NCT0424320) in patients with advanced solid malignancies indicated that AZD0466 is well tolerated, with no dose-limiting toxicities (DLTs) reported.

Methods
- **Study design**
  - MM/BL (drug only)/AFTER: BCR-ABL1 in acute Leukemia; NCT04885549 is a modified multi-arm randomized phase 1 trial.
  - Module 1, Part A is a dose-escalation study of AZD0466 monotherapy in patients who meet the following eligibility criteria:
    - Age ≥18 years
    - No active central nervous system involvement
    - No history of prior chemotherapy with venetoclax.
    - Hematological improvement in patients with intermediate and higher risk MDS

- **Safety and tolerability of AZD0466 in patients with advanced hematological malignancies.**

- **Results**
  - A summary of adverse events (AEs) is shown in Table 3.
  - No DLTs, treatment-related serious AEs, treatment-related deaths, or AEs leading to treatment discontinuation were observed in this trial as of September 24, 2022.

- **Conclusions**
  - AZD0466 monotherapy is well tolerated, with no DLTs and no discontinuations due to treatment-related AEs observed in this trial as of September 24, 2022.
  - The trial continues to enroll and further dose escalation is planned.