The novel PARP1-selective inhibitor AZD5305 has reduced haematological toxicity when compared to PARP1/2 inhibitors in pre-clinical models

Sonja J. Gill1, Ruth Macdonald1, Carmen Pin1, Rob Collins1, Emilyanne Leonard1, Gareth Maglennon1, Andy Pike2, Peter Cotton1, Glen Hawthorn1, Jordan Pugh1, Rebecca Sargeant1, Daniel Sutton1, James Atkinson1, Stewart Jones1, Sarah Chinery1, Mark Anderton1.

Clinical Pharmacology and Safety Sciences, R&D, AstraZeneca, Cambridge, UK1, DMPK, Oncology R&D, AstraZeneca, Cambridge, UK2

Introduction

• PARP1/2 inhibitor-driven haematotoxicity limits their ability to be combined with chemotherapies that cause overlapping bone marrow toxicities (e.g. anemia, neutropenia, thrombocytopenia).

• AZD5305 is a novel PARP inhibitor that selectively inhibits and traps PARP1 (#296, #1272) and is efficacious both as monotherapy and in combination with standard of care chemotherapy in in vivo pre-clinical models (#1270).

• Here we aimed to investigate the haematotoxicity profile of AZD5305, both as monotherapy and in chemotherapy combinations in rat pre-clinical models.

Results – Monotherapy Haematotoxicity

Figure 1. Haematological profiling of AZD5305 at predicted clinical efficacious exposures in rat pre-clinical models.

Results – Combination Haematotoxicity

Figure 2. Haematological assessment of AZD5305 and olaparib in combination with carboplatin in rat pre-clinical models. (A) Peripheral reticulocytes recover rapidly in the presence of continuous AZD5305, but not in the presence of continuous olaparib. (B) Olaparib+carboplatin, but not AZD5305+carboplatin, causes sustained suppression of erythroid precursor cells and (C) bone marrow hypocellularity.

Figure 3. Assessment of AZD5305 and olaparib in combination with carboplatin in a two-cycle dosing schedule that more closely mimics clinical dose and schedule. (A) AZD5305+carboplatin causes less toxicity on red blood cells due to a more rapid recovery in both cycles. (B) AZD5305 and olaparib cause similar exacerbation of carboplatin-induced platelet effects.

Conclusions

• Monotherapy AZD5305 does not cause haematotoxicity at predicted clinically efficacious exposures in rat pre-clinical models.

• In combination with carboplatin, continuous dosing of AZD5305 causes comparable exacerbation of platelet effects and a more rapid recovery of red cell parameters in comparison with olaparib, which has the most benign haematological profile of current clinical PARP1/2 inhibitors.

References

1. Pilié et al. Clinic Cancer Res. 2019

Supported by

AstraZeneca

Presented at the AACR 2021 Annual Meeting, Virtual Meeting, 10-15th April 2021