Clinical pharmacology of AZD4635 (A2ARi): Integration of PK data from cancer patients (CP) and healthy volunteer (HV) clinical trials to provide dosing recommendations

Ganesh Moorthy1, Gayle Pageau Pouliot2, Lorraine Graham3, Chris Wilks2, Tinnu Sarvotham2, Patrick Mitchell4, Lindsey Jung4, Yan Li1, Wenlin Shao2, Ganesh Mugundu1

1 Clinical and Quantitative Pharmacology, Clinical Pharmacology and Safety Sciences, R&D, AstraZeneca; 2 Early Oncology, Oncology R&D, AstraZeneca; 3 Pharmaceutical Sciences, R&D, AstraZeneca; 4 Early Oncology Statistics, R&D Oncology

Methods

• PK parameters including maximum plasma concentration (Cmax) and area under the plasma concentration-time curve from zero time to infinity (AUC) were calculated by non-compartmental analysis methods using Phoenix WinNonlin software (v8.0).
• Formal statistical analyses were performed on the PK parameters to assess relative bioavailability, food effect and impact of pH on AZD4635 PK.

Results

Phase 1 Study in CP:
• AZD4635 exposure at 75 and 100 mg were above the invitro IC50 for A2AR inhibition through out the dosing interval (Figure 2).
• AZD4635 NS rapidly appeared in plasma after single or multiple oral administration with median tmax of 1 h and declined in a biphasic manner with a t1/2 of 13.13 h (mean, 100 mg QD).

Clinical Pharmacology Study in HV:
• Peak (Cmax) and overall (AUC) exposure of AZD4635 were approximately 27% and 10% higher, respectively, for CF relative to NS.
• High fat meal resulted 12% decrease in AUC and 56% reduction in Cmax (Figure 3 & 4).
• PPI (Lansoprazole) coadministration resulted in similar AUC and Cmax suggesting minimal impact of pH changes.

Conclusions

• Based on totality of exposure and safety data from ongoing Phase I study in CP at various doses of AZD4635 NS, and data from HV study for both NS and CF, a dose of 75 mg CF has been proposed for further clinical investigations.
• As food can mitigate gastrointestinal toxicities, and there was a lack of significant effect on AUC, the current fasting restrictions have been relaxed to allow patients to receive AZD4635 with or without food.
• No impact of PPI allows for better compliance as the target patient population may also be receiving gastric modifiers (e.g. antacids, H2 antagonists, PPIs).

References

Acknowledgements
This study was sponsored by AstraZeneca. We thank the patients and their caregivers, as well as the investigators and site staff, who participated in this study.