AZD4820 ONCOLYTIC VACCINIA VIRUS ENCODING IL-12 MEDIATES ANTI-TUMOR ACTIVITY THROUGH ONCOLYSIS AND TUMOR-SPECIFIC IMMUNITY

1Cheyne Kurokawa, 1Sonia Agrawal, 1Abhisek Mitra, 1Elena Galvani, 1Shannon Burke, 1Arkita Vanshine, 1Raymond Rothstein, 1Johann Foloppe, 1Nathalie Silvestre, 1Eric Quemeneur, 1Puja Sapra, 1Carl Barrett, 1Scott Hammond, 1Jason Laliberte, 1Nicholas Durham, 1Michael Oberst*, 1Maria Broggi. 1Astrazeneca, Gaithersburg, MD, United States; 2Transgene, Illkirch-Graffenstaden, France

Background While vaccinia virus (VACV) has demonstrated robust oncolytic activity, we sought to enhance therapeutic efficacy by engineering VACV to express interleukin-12 (IL-12), a potent NK and T cell activating cytokine that reprograms the tumor immune microenvironment. AZD4820 is an oncolytic VACV engineered to express IL-12 with viral thymidine kinase and ribonucleotide reductase deleted to enhance tumor cell-specific replication. We evaluated the oncolytic activity of AZD4820 and enhancement of anti-tumor immunity in combination with immune checkpoint inhibitors (ICIs).

Methods The oncolytic activity of VACV was evaluated in 47 primary patient derived xenograft (PDX) models representing 9 tumor indications. Replication, oncolytic activity, and IL-12 transgene production of AZD4820 was evaluated in cultured human tumor cell lines, normal human cells, primary human dissociated tumor cells (DTCs) and tumor tissue slice cultures (TSCs). The anti-tumor activity and mechanism of action for AZD4820 was evaluated in syngeneic rat tumor models, as well as MC38 and CT26 syngeneic mouse tumor models with or without ICI targeting PD-L1. Specific anti-tumor immunity in the CT26 model was assessed in mice treated with AZD4820 alone or in combination with anti-PD-L1 mAb by interferon-γ (IFNγ) ELISpot assays after stimulating splenocytes with tumor-specific peptides.

Results Oncolytic VACV demonstrated anti-tumor activity (disease stabilization, partial or complete responses) in 35 of 47 PDX models tested. AZD4820 was highly oncolytic in human tumor cells relative to normal cells, both in vitro (EC50 range 0.0005 to 0.86) and in vivo. To evaluate AZD4820 in human tumor samples, we showed that AZD4820 resulted in production of IL-12 in DTCs (19/19 samples) and TSCs (22/22 samples). A surrogate virus expressing murine IL-12 demonstrated anti-tumor activity in both the MC38 and CT26 syngeneic models. In the CT26 syngeneic tumor model, delivery of AZD4820 significantly upregulated IFNγ relative to control VACV-Luciferase treated mice. In this study, 6/10 mice had a complete response following treatment with AZD4820, while the control VACV-Luciferase treated mice had 0/10 complete responders. Next, we demonstrated in the CT26 tumor model that treatment with AZD4820 in combination with an anti-PD-L1 blocking antibody augmented tumor-specific T cell immunity relative to monotherapies.

Conclusions AZD4820 is an oncolytic VACV expressing IL-12 in vitro and in vivo which replicates preferentially in tumor cells compared to normal cells. A surrogate of AZD4820 demonstrated activity in pre-clinical syngeneic mouse tumor models in combination with anti-PD-L1 mAb, supporting its use in combination with ICIs in patients with cancer.