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DIGITAL SPATIAL PROFILING OF PAIRED TUMOR BIOPSIES REVEALS INDOLEAMINE 2,3-DIOXYGENASE (IDO)1 AS A POTENTIAL RESISTANCE MECHANISM FOR A TUMOR-TARGETED 4-1BB AGONIST IN PATIENTS WITH SOLID TUMORS

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¹Tamara Tanos, ¹Christian Heichinger, ¹Sabine Wilson, ²Marta Canamero, ¹Mariana Bustamante, ¹Chiahuey Ooi, ¹Irina Klamann, ¹Bruno Gomes, ¹Maurizio Ceppi*, ¹Maurizio Ceppi. ¹Roche Innovation Center Basel, Basel, Switzerland; ²Roche Innovation Center Munich, Penzberg, Germany

Background We previously described the capacity of RO7122290 (RO) - a FAP-targeted 4-1BB bispecific antibody - to induce CD8+ T cell infiltration and activation in the tumor (Moreno V. et al, SITC 2020). Aiming to compare pharmacodynamic (PD) changes in tumor nests and stroma, paired tumor biopsies from patients treated with RO (Part A) and RO + atezolizumab (Part B) were analysed by digital spatial profiling (DSP, Nanostring).

Methods Seven paired (baseline and on-treatment) FFPE tumor tissue biopsies (three from Part A, four from Part B) obtained from an ongoing Phase 1/1b trial (EUDRACT 2017-003961-83) were assessed for mRNA and protein expression. Biopsies were taken from six different tumor types at different RO doses. Up to twelve Regions of Interest (ROIs) were collected per slide and the morphology markers PanCK, CD8, CD3 and DAPI were applied. The ROIs were further annotated in tumor nests and stroma segments based on PanCK staining. The immune-oncology 58-plex protein and 78-plex mRNA expression panels (Nanostring) were used to profile all samples. Data were normalized according to Nanostring guidelines and filtered based on relevance (absolute log₂ fold change > 1) and significance (FDR < 0.05, p-value).

Results The level of CD8+ T cell infiltration measured by spatial profiling correlated with the level measured by IHC, in both tumor nests and stroma. The activation markers 4-1BB and PD-1 were upregulated, confirming the PD effect already measured by mRNA sequencing. We also identified novel protein markers - CD40, PD-L1 and IDO1 - being upregulated after treatment. Spatial regulation differed among the markers with 4-1BB, PD-1 and CD40 upregulated only in the stroma, PD-L1 and IDO1 upregulated in the tumor nests and in the stroma. IDO1 induction is particularly relevant, since this protein is known to attenuate 4-1BB-mediated effector responses. Conventional IHC analysis performed on 14 paired biopsies confirmed IDO1 being upregulated in 11 out of 14 cases and revealed dendritic cells, macrophages and stromal cells to express IDO1. Importantly, IDO1 upregulation was observed in both Part A (3 out of 3) and Part B (8 out of 11).

Conclusions Spatial profiling allowed us to identify key markers that are spatially regulated after treatment and to gain new insights on the MoA of RO. The induction of IDO1 by RO confirms the dual immunoregulatory nature of 4-1BB signaling and highlights IDO1 as a potential resistance mechanism for RO in the clinical setting, both as single agent and in combination with atezolizumab.

Trial Registration EUDRACT Number: 2017-003961-83; Protocol Number: BP40087

REFERENCES

1. Moreno V. et al, Pharmacodynamic assessment of a novel FAP-targeted 4-1BB agonist, administered as single agent and in combination with atezolizumab to patients with advanced solid tumors, Nov 1 2020, Journal for Immunotherapy of Cancer, presented at SITC 2020