Predictive response biomarkers from a Phase I clinical trial of a SIRPalpha inhibitor, BI 765063, stand-alone and in combination with ezabenlimab, a PD-1 inhibitor, in patients with advanced solid tumors

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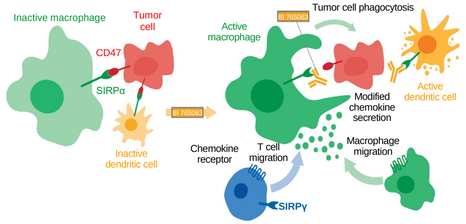
Introduction

- BI 765063 is a first-in-class, humanized IgG4 monoclonal antibody that binds selectively to the V1 allele of signal regulatory protein α (SIRPα) blocking the SIRPα/cluster of differentiation 47 (CD47) "don't eat me" pathway[1,2]
- SIRPα is expressed by myeloid cells: macrophages (inhibition of tumor cell phagocytosis) and myeloid-derived suppressor cells (MDSCs; control of immature suppressive state).[3] Therefore, the inhibition of SIRPα by BI 765063 could lead to substantial modification of the tumor microenvironment (TME)
- In the Phase I trial (NCT03990233), BI 765063 alone or in combination with ezabenlimab (programmed cell death protein-1 [PD-1] inhibitor) was well tolerated, and showed preliminary efficacy in patients with advanced solid tumors[4]
- Here we report predictive efficacy biomarkers of BI 765063 from the monotherapy and ezabenlimab combination escalation cohorts



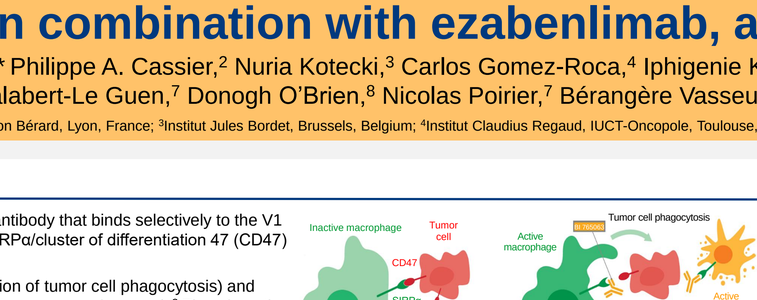
BI 765063 (anti-SIRPα) mechanism of action

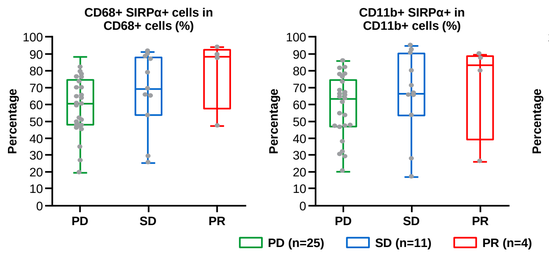
Methods and patient population

- Open-label, multicenter Phase I trial in patients genetically SIRPα V1/V1 homozygous or V1/V2 heterozygous with advanced solid tumors who had failed/were ineligible for standard therapy, treated with 0.02–36 mg/kg BI 765063 (monotherapy) or 18/24 mg/kg + 240 mg ezabenlimab (combination; all intravenously every 3 weeks)
- A total of 68 patients (monotherapy: n=50; combination: n=18) have been enrolled. The most frequent tumor types were: colorectal (n=13); ovarian (n=10); endometrial carcinoma (n=5); non-small cell lung cancer (n=4); melanoma (n=4); kidney (n=4); and breast (n=2)
- Tumor biopsies were collected before treatment and 2 weeks after the first infusion
- The TME was analyzed using a Brightplex® immunohistochemistry (IHC) panel comprised of CD68+ macrophages expressing SIRPα, CD11b+ myeloid cells expressing SIRPα, CD8 T-cells, PD-L1 and CD47 markers. NanoString tumor profiling used a PanCancer IO360 panel

Clinical efficacy and predictive biomarkers

- Disease control rate (DCR; defined as the sum of complete response [CR], partial response [PR], and stable disease [SD]) in escalation with anti-SIRPα BI 765063 monotherapy was 35% by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) and 40% by immuneRECIST (iRECIST), including one ongoing PR (>2.5 years) in hepatocellular carcinoma (HCC)
- DCR in escalation combination with ezabenlimab was 50% by RECIST 1.1 and 56% by iRECIST, including a total of four PRs: ongoing in HCC (n=1, >2 years), in microsatellite stable (MSS) endometrial cancer (n=2), and in MSS colorectal cancer (n=1)



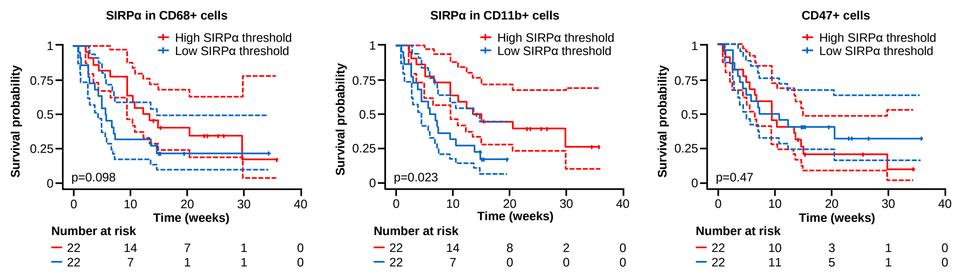


- Patients from the escalation STEP-1 arms were pooled and stratified into two groups (high/low) depending on the expression of CD47 and SIRPα based on IHC results
- Comparison of patient best response showed that baseline tumor SIRPα+ expression in CD68+ macrophages and in CD11b+ myeloid cells was higher in patients with PR versus those with progressive disease (PD)

Impact of predictive biomarkers on overall survival

- A high percentage of CD68+ SIRPα+ macrophages among total CD68+ macrophages in the TME showed a trend for better overall survival (OS), but did not reach statistical significance
- A high percentage of CD11b+ SIRPα+ myeloid cells among total CD11b+ myeloid cells at baseline significantly correlated with better OS (p=0.023)
- CD47 tumor expression did not correlate with OS

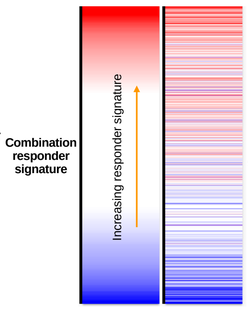
OS in patients, stratified by CD68/CD11b/CD47



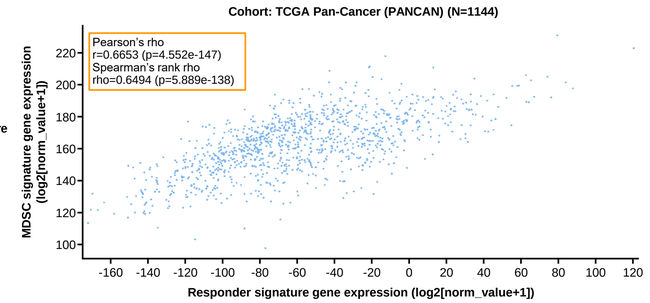
Biomarker	Median for threshold (%)
CD68+ SIRPα+	64.9
CD11b+ SIRPα+	65.3
CD47+ tumor cells	54.9

There is a strong correlation between the combination responder and MDSC signatures

- The Cancer Immunome Database provides results of comprehensive immunogenomic analyses of next generation sequencing data for 20 solid cancers from The Cancer Genome Atlas (TCGA) and other data sources
- The responder signature based on the top deregulated genes in responders versus non-responders at baseline was devised to sort relevant TCGA cohorts, and showed strong positive correlation with TME MDSC infiltration (p≤0.0001)



Other significative correlations were observed for activated CD8 cytotoxic T lymphocytes, B cells and macrophages



Key findings and conclusions

- High levels of CD11b+ SIRPα+ myeloid cells in TME at baseline, but not CD47 tumor expression, correlates with longer OS in patients treated with anti-SIRPα, BI 765063
- The MDSC signature in the TME at baseline correlates with clinical response and survival
- MDSCs expressing SIRPα in the TME may represent a predictive efficacy biomarker

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Presented at the American Association for Cancer Research (AACR) Congress, Orlando, FL, USA, April 14–19, 2023

This trial was funded by OSE Immunotherapeutics and Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version. The authors did not receive payment related to the development of the poster. Acknowledgement: HalioDx (Marseille, France), now part of Veracyte, for the IHC and NanoString analysis. Medical writing support for the development of this poster, under the direction of the authors, was provided by Steven Kirkham, PhD, of Ashfield MedComms, an Inizio Company, and funded by Boehringer Ingelheim