ATP128 vaccine with ezabenlimab promotes antigen-specific immune responses in stage IV colorectal cancer in the KISIMA-01 Phase 1b trial

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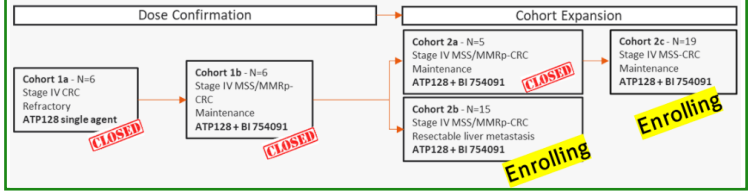
Background

KISIMA™ is a vaccine platform based on a single chimeric fusion protein, containing a proprietary cell-penetrating peptide (CPP) for antigen delivery, a proprietary Toll-like receptor (TLR)-peptide agonist with self-adjuvant properties and a modulable multi-antigenic domain (Mad). ATP128 vaccine targets 3 antigens: carcinoembryonic antigen (CEA), Survivin and Achaete-scute complex homolog 2 (ASCL2); it is used in combination with a PD-1 inhibitor in the treatment of MSS/MMR proficient stage IV colorectal cancer (CRC) patients, after first line of standard of care therapy or as perioperative administration in patients with resectable liver metastases.

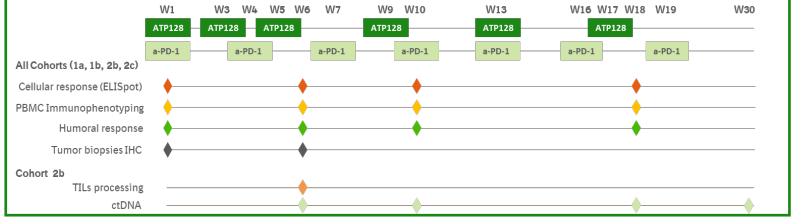
Methods

KISIMA-01 (NCT04046445) is an open-label, multi-center Phase 1b trial to investigate the safety, tolerability and immunogenicity of ATP128 alone or in combination with the anti-PD-1 antibody ezabenlimab (BI 754091) in patients with stage IV CRC. ATP128 is given SC q2w for the first 3 immunizations (prime) and q4w for the last 3 immunizations (boost). Ezabenlimab is administered q3w starting with the first ATP128 administration. Blood and tissue samples are collected before, during and after ATP128 treatment to monitor the induction of a tumor associated antigen-specific immune response (ELISpot) and immune-related changes in the peripheral blood and in the tumor microenvironment by immunohistochemistry (IHC) and flow cytometry.

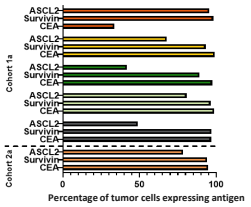
Clinical study design



Translational program



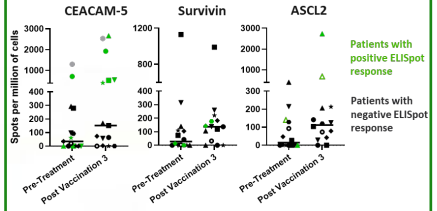
Vaccine antigen expression by tumor cells



Six out of 6 evaluated patients are positive for the expression of the 3 tumor-associated antigens of ATP128 vaccine.

Slices from FFPE liver metastasis biopsies of the patients (1 color/patient) before treatment were stained by IHC for CEACAM-5 and survivin and by RNAscope for ASCL2.

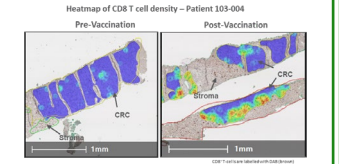
Peripheral immune response

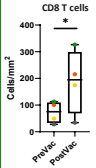


8 out of 15 (53%) evaluated patients treated with ATP128 alone or with ezabenlimab showed T-cell response against at least 1 vaccine antigen monitored by ELISpot post *in vitro* stimulation (all cohorts).

IFN-γ ELISpot analyses of PBMCs from patients before treatment and after the 3rd vaccination. Of note, one patient had a T cell response against 2 antigens (CEACAM-5 and ASCL2, green close triangle).

CD8 T cell infiltration within the tumor

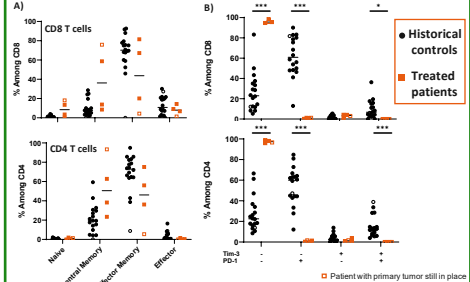




Significant increase in CD8 T cells infiltration into the tumor parenchyma after 3 ATP128 administrations in patients with paired biopsies (cohort 1a).

Slices from FFPE liver metastasis biopsies of the patients before and after 3 vaccinations with ATP128 were stained by IHC for CD8 T cells.

Quality of T cells infiltrated within the tumor



Improved quality of infiltrated T cells:

A) 2-fold increase in proportion of central memory T cells; B) impressive decrease of the % of cells positive for exhaustion markers in ATP128/ezabenlimab treated patients (Cohort 2b).

Tumor infiltrating leukocytes were isolated and analyzed by flow cytometry by comparing untreated (historical controls) and ATP128/ezabenlimab-treated patients.

Conclusion

Data from this ongoing study indicate:

1) an induction of ATP128-specific immune response in the peripheral circulation.

2) an increase of tumor-infiltrating T cells into liver metastases, with an improved quality (more central memory prone and less exhausted phenotype).

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