Translation to the clinic of EVT801: A novel immune-oncology agent for addressing innate-driven immunosuppression into the tumor microenvironment and expand patient population responding to immune checkpoint therapies

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Purpose: Amongst resistance mechanisms of immune checkpoint therapies (ICTs), expansion and recruitment of immunosuppressive innate cells and in particular Myeloid Derived Suppressor Cells (MDSCs) can be a major cause of resistance to Immune Checkpoint Inhibitors (ICI). Here we describe joint efforts of clinicians and researchers to translate the promising action on MDSCs of EVT801 drug candidate into the clinic.

EVT801, a highly selective VEGFR3 inhibitor, exerts intermediate activity on tumours for which VEGFR3 is only expressed in Tumour MicroEnvironment (TME), paralleled with decrease of MDSCs.

Results: To evaluate the potential to combine with ICTs, we used the 4T1 orthotopic breast cancer mouse model. We have demonstrated that EVT801 increases the therapeutic activity of an anti-PD1 antibody (Anti-PD1) on primary tumours and decreases lung metastasis compared to anti-PD1 Ab alone. Decrease of circulating MDSCs is correlated with tumour control and therapeutic efficacy. In parallel, Immuno Histo Chemistry analyses shown that EVT801 treatment increased CD8\textsuperscript{+} T-cells infiltration inside the tumour. Taken together, these results indicate that EVT801 represents an innovative drug for cancer immunotherapy that improves the frequency of response to ICI by controlling MDSC immunosuppressive activity and in turn by unleashing tumor-specific T-lymphocytes.

To translate these promising results into the clinic, we evaluated different biomarkers to properly select patients and monitor efficacy of EVT801:
- We refined an anti-PD1 resistance gene signature and correlated it with VEGFR3 pathway gene overexpression.
- We investigated VEGFR3 expression in the TME for different cancer indications. Taken together, these results will facilitate patient stratification as based on the anti-PD1 resistance gene signature associated with VEGFR3 expression in the TME.
- In non-small cell lung cancer patients, we validated that a high-level baseline of circulating MDSCs is associated with poorer survival. According to EVT801 activity in preclinical mouse model, we propose that circulating MDSC levels could be a biomarker of its activity in non-responder patients to ICI.

Conclusion: EVT801 represents a novel agent for cancer immunotherapy for non-responder patients to ICI. Patient stratification strategy, target engagement biomarker and biomarkers of activity have been identified and will enable the initiation of a planned Phase I clinical trial with EVT801.