Abstract #2753

Translation to the clinic of EVT801: A novel immune-oncology agent for expanding patient population responding to immune checkpoint therapies

Selective inhibitor of VEGFR3 for patients resistant to immune checkpoint inhibitors: Clinical translation activities

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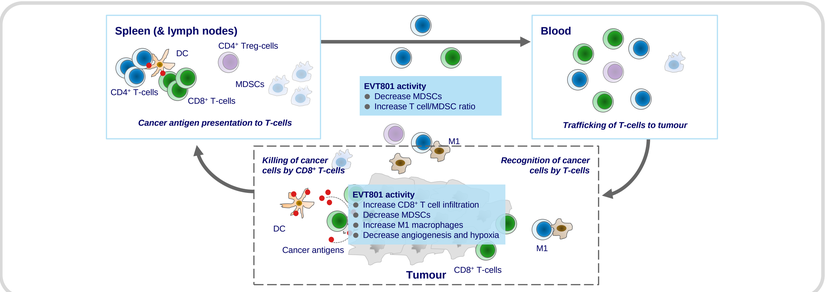
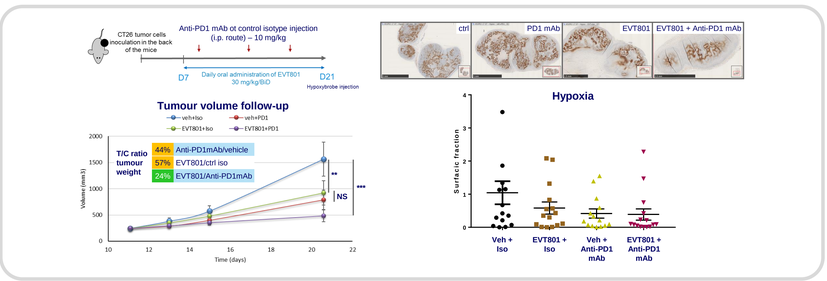
Overview

Drug concept	● Develop a small molecule for cancer immunotherapy that targets immunosuppressive cell trafficking to increase ICT response rate
Target class	● EVT801 is a selective inhibitor of the VEGFR3 tyrosine kinase
Project status	● EVT801 is currently in late preclinical development and is anticipated to be Phase 1 ready in Q3 2018
Targeted indication	● **Combination with immune checkpoint therapies for non-responder patients** with VEGFR3$^+$ microenvironment
Gateway indication	● Solid tumours with VEGFR3$^+$ microenvironment and/or Kaposi's sarcoma as orphan disease
Administration	● Oral administration
Biomarkers	● Patient stratification: VEGFR3 expression on TME & circulating MDSCs quantification ● PD biomarker: ERK/AKT phosphorylation & gene signature ● Biomarker of activity: Gene signature & circulating immune-cells quantification

EVT801 MoA in immuno-oncology



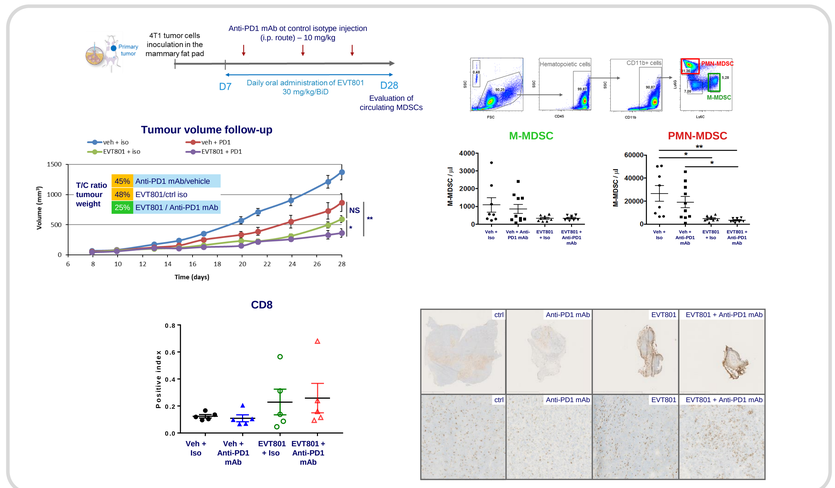
EVT801 and combination with anti-PD1 mAb: Acting on hypoxia to control tumour outgrowth



***The CT26 mouse model* is a model with heterogeneity, highly dependent on hypoxia and with low MDSC frequency**

- Combination of EVT801 and anti-PD1 mAb results in a strong therapeutic activity
- Treatment with EVT801 is associated with a decrease of hypoxia

EVT801: Decreasing circulating MDSCs and increasing CD8$^+$ T-cell tumour infiltration to generate anti-tumour immunity

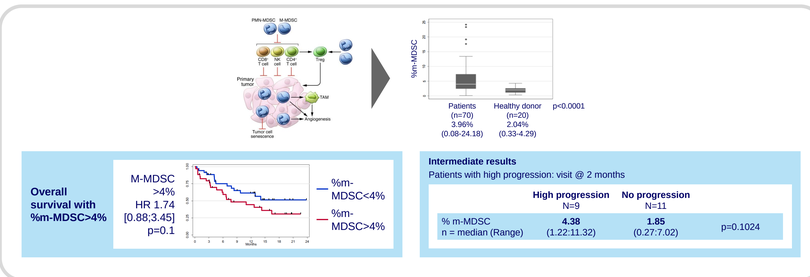


Dedicated biomarker approach developed for EVT801

- **Patient stratification**
  - VEGFR3 expression on tumour cells and in Tumour Microenvironment from biopsies
  - High level of circulating MDSCs
    - Baseline circulating myeloid-derived suppressor cells and response to anti-PD1 mAb in non-small cell lung cancer patients: Collaboration Oncopole/CRCT/Evotec (IMMUNOPREDICT trial NCT02827344)
- **Biomarker of activity/resistance**
  - **Single agent**
    - Gene signature related to resistance to PD1/VEGFR3 signalling pathways
    - Phosphorylation pathways: pERK and pAKT
  - **Combination with ICT (Immune Checkpoint Therapies)**
    - Quantification of circulating immune cells and circulating MDSCs
  - **Single agent and Combination with ICT**
    - Development of specific labelling by IHC related to EVT801 MoA for on-treatment biopsies

We are actively looking for partners for clinical development

Circulating MDSCs as stratification biomarker
IMMUNOPREDICT trial NCT02827344



- Higher level of m-MDSCs in patients decrease Overall Survival
- Intermediate results seems to show that patients with high progression @ 2 months have a strong level of m-MDSCs and could be the population of interest for EVT801, especially if VEGFR3 is expressed in tumour and/or microenvironment

VEGFR3 expression in tumour and microenvironment (in %)

Indication	HCC	HNSCC	NSCLC	Lung AC	Kaposi	CCRCC	Colon cancer
VEGFR3 expression in TME	30 to 100%	40%	100%	100%	***100% on tumour cells***	94%	30%
Access to patients eligible for Ph1a	No	Yes	+/-	+/-	Yes	Yes	Yes
Recommendation	Phase 2 combo	Ib combo	Ib combo	Ib combo	(1a) / 1b	(1a) / 1b	1a / 1b

Current ideas for clinical plan up to PoC

Phase Ia: Dose escalation

Advanced or meta-static solid tumours (CRC, CCRCC)
- Adult patients
- ECOG score 0-1
- 2 Biopsies feasible
- Blood sampling 20 ml

EVT801 → **X mg/BiD** → MTD or Y mg/BiD

+ Biomarkers exploration

→ MTD/ RP2D

Phase Ib: Dose expansion

Group 1: Single agent
VEGFR3 solid tumours, n=30 per cohort: Kaposi's sarcoma and other sarcomas

→ Support pivotal double blind PII

Group 2: Combo with ICT
(solid tumours with VEGFR3$^+$ TME)
n=30 per cohort
Cohort 1: Kidney cancer
Cohort 2: Lung cancer
Cohort 3: Solid tumours with VEGFR3$^+$ in TME

→ PoM + combo RP2D

+ Efficacy (RECIST criteria) and Biomarkers evaluation

→ Indication specific PII

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