Small molecule in combination with Immune Checkpoint therapies

Positive immunomodulation by specific VEGFR3 inhibition

Pierre Fons[1], Michaël Esquerré[1], Gaëlle Badet[1], Pauline Barron[1], Jérémy Kagan[1], Antoine Alam[2], Jérôme Meneyrol[1], Isabelle Blanc[2], Roselyne Broussy[1], Florence Gaujarengues[1], Frédérique Dol[1], Pascal Cardon[1], Michael Paillasse[1], Joanna Lisztwan[1], Françoise Bono[1], Mark Whittaker[1]

[1]Evotec, Toulouse, France; [2]Sanofi, Lyon, France

Abstract #3970

Project Overview

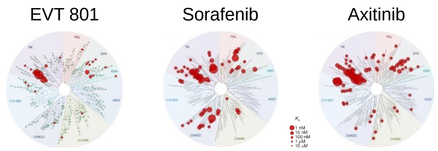
Drug concept	Develop a small molecule for cancer immunotherapy that targets immunosuppressive cell trafficking to increase ICT response rate
Target class	EVT801 is a specific inhibitor of the tyrosine kinase VEGFR3
Project status	Drug candidate / 1 year from phase I
Targeted indication	Combination with immune checkpoint therapies for non-responder patients
Administration	Oral administration

Drug candidate profile

- **High level of selectivity**
- **Nano-molar range affinity/activity**
- **Good activity on VEGFR3⁺ cells**
- **Efficacy on tumours mouse model**

VEGFR3 / FLT4

EVT801 is highly selective

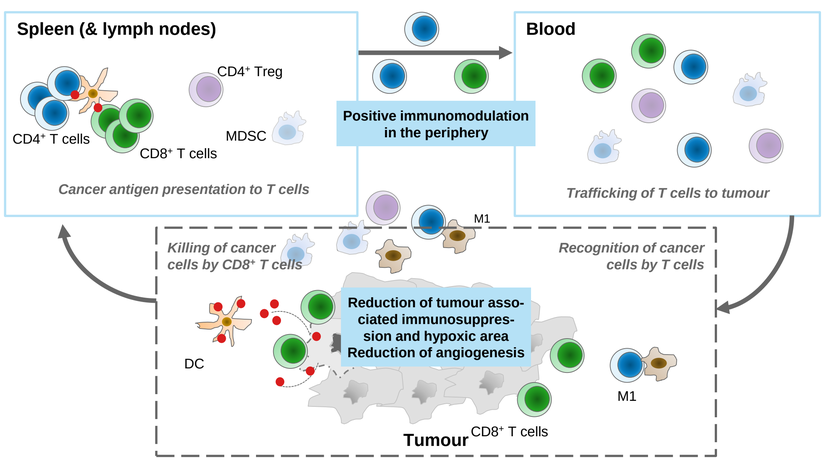


Supportive *in vivo* activity

- Full tumour control on DEN-induced tumour model
- Intermediate tumour control on VEGFR3⁻ tumours with VEGFR3⁺ TME

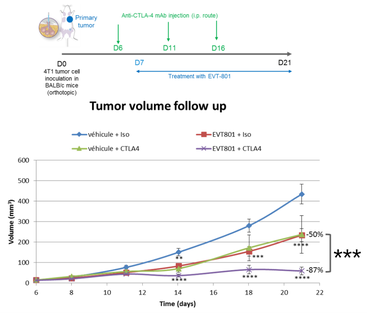
Immuno-modulatory effects that we are seeking:

Optimal potential to synergize with immune check point inhibitors



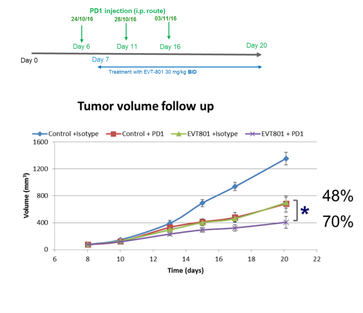
Increased efficacy of combinations with ICTs

Combination with anti-CTLA-4 mAb

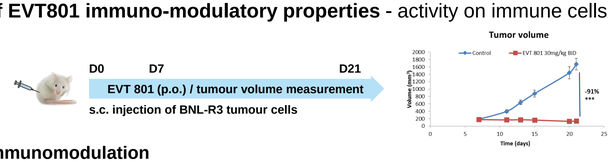


Mean ±sem
Dunnett's test

Combination with anti-PD-1 mAb

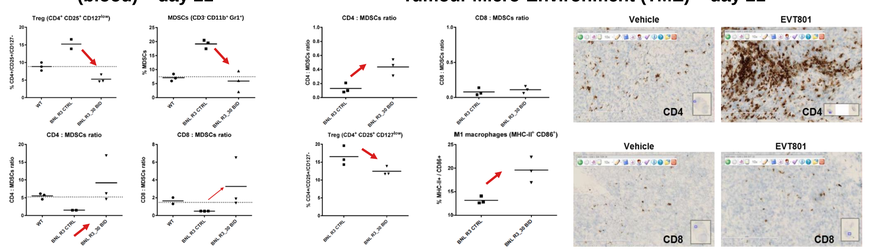


Validation of EVT801 immuno-modulatory properties - activity on immune cells

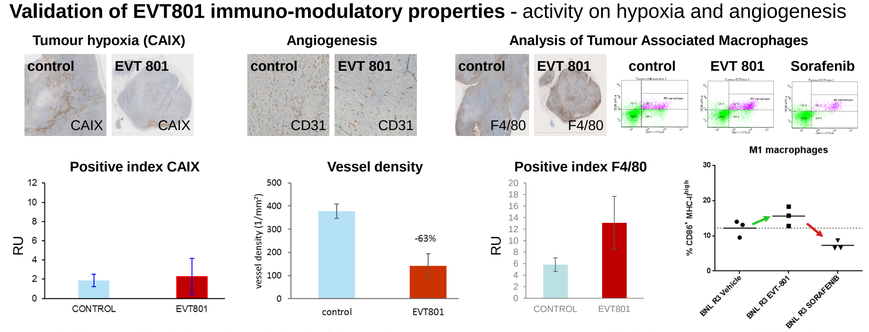


Peripheral Immunomodulation (blood) – day 21

Tumour Micro-Environment (TME) – day 21



Validation of EVT801 immuno-modulatory properties - activity on hypoxia and angiogenesis



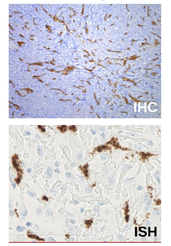
Labelling quantification is performed using Definiens software

Each dot represents an individual mouse

Clinical Translation: biomarkers of stratification and activity

Patient stratification	VEGFR3 is expressed on 40-80% of the tumor microenvironment Specific cohorts are under investigation
Biomarkers of activity in tumor	Signaling pathway
Biomarkers of activity in blood	Collaboration with University Cancer institute of Toulouse for specific markers in patients receiving ICT

VEGFR3 expression in HNSCC patient



Conclusion

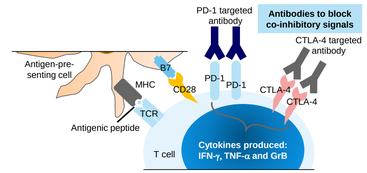
Sustained tumour blood vessel normalization

- **Decrease of angiogenesis**
- Less Necrotic and Hypoxic tumours

Decrease of tumour-associated immunosuppression

- Blood
  - Decrease of immunosuppressive cells: MDSCs
  - Increase of T cell: MDSCs ratio
- Tumour
  - Increase of CD4⁺ TILs
  - Decrease of CD45⁺ PD-L1⁺ cells
  - Increase of M1 macrophages

Blockade of regulatory pathway in T cells



Enhancement of antitumor immunity and activity on tumour microenvironment:
Potential to induce durable clinical responses

Efficacy

- Nanomolar activity on functional cellular assays
- Strong anticancer effects in clinically relevant models
- Greater efficacy expected in human (lower IC_{50} and clearance)

Selectivity

- ~10 fold less potent on VEGFR2 which is the only off-target

MoA

- Long lasting anticancer effect
- Sustained vessel normalization
- Reduction of immunosuppression associated to tumour immunity
- Sustained specific and memory T-cell responses without exhaustion

First in Man Phase I clinical trial

- Expected in 2018

Safety

- *In vitro* safety profile of EVT801 is compatible with progression into preclinical development
- Therapeutic index above 10 according to rat DRF and monkey MTD
- 4-week rat and monkey studies pending

EVT801 has the potential to enlarge patient population sensitive to immune check point inhibitors

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Corporate Headquarters: Evotec AG, Manfred Eigen Campus, Essener Bogen 7, 22419 Hamburg, Germany **Email:** info@evotec.com **Web:** www.evotec.com