VEGFR-3 SIGNATURE EXPRESSION BY HISTOLOGY TO CLASSIFY PATIENT POPULATION FOR THE SELECTIVE VEGFR-3 INHIBITOR EVT801

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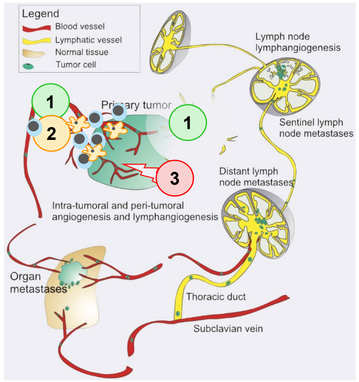
EVT801: A differentiating anti-tumor approach

Targeting tumor angiogenesis with the selective VEGFR-3 inhibitor EVT801 in combination with cancer immunotherapy
Cancer Research Communications (2022) 2 (11): 1504–1519.

1. Inhibition of tumor escape & metastasis
- Stabilization of tumor vasculature
- Inhibition of lymphangiogenesis
- Reduction of tumor hypoxia

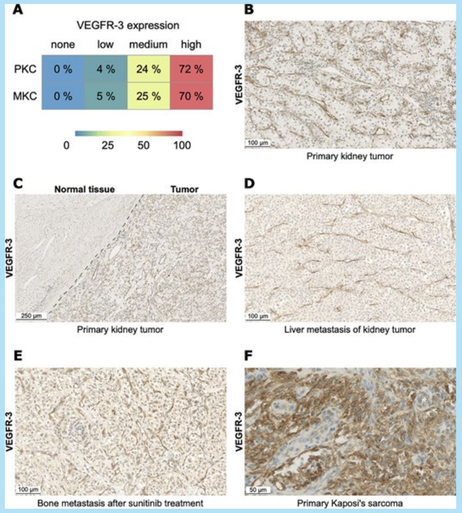
2. Enhanced anti-tumor immunity*
- No impact on T- cells viability
- Decrease in immunosuppressive cells
- Enhanced effector cell infiltration

3. Tumor killing
- Direct effect on VEGFR-3$^+$ tumor cells from endothelial origin



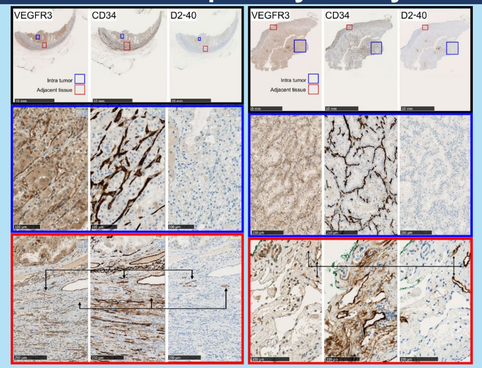
Iyer RV et al. Dose-Dependent Sorafenib-Induced Immunosuppression Is Associated with Aberrant NFAT Activation and Expression of PD-1 in T Cells. Cancers (Basel). 2019;11(5):681. doi:10.3390/cancers11050681

VEGFR-3 expression in kidney cancer cohorts



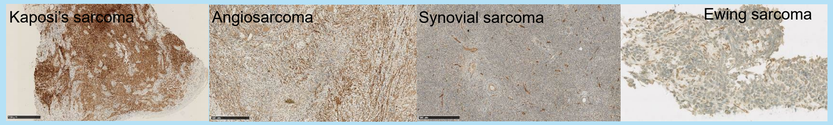
A, Level of VEGFR-3 expression in 29 primary kidney cancer (PKC) samples and 23 metastatic kidney cancer (MKC) samples. **B**, Representative IHC image of VEGFR-3 expression in PKC. **C**, Representative IHC image of VEGFR-3 expression in PKC and normal adjacent tissue. **D**, Representative IHC image of VEGFR-3 expression in liver metastasis of kidney tumor. **E** : Representative IHC image of VEGFR-3 expression in bone metastasis after treatment with sunitinib. **F**: Representative IHC image of VEGFR-3 expression in primary Kaposi's sarcoma

Expression of vascular marker CD34, lymphatic marker D2-40 and VEGFR-3 in primary kidney tumors.



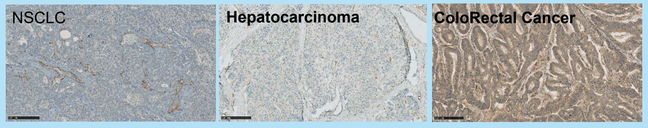
Consecutive slices of the same tumor were stained for VEGFR-3, CD34 and D2-40. VEGFR-3 was expressed in CD34-positive vessels in the tumor and in the normal adjacent tissue, whereas D2-40 staining was mainly observed in normal adjacent tissue. Black arrows indicate lymphatic vessels.

VEGFR-3 expression in soft tissue sarcoma cohorts



Cohort	N° of cases	VEGFR-3 intensity on tumor blood vessels*			
		No	Low	Medium	high
Kaposi's sarcomas	53	0%	0%	0%	**100%**
(Lymph) angiosarcomas	7	10%	0%	0%	**90%**
Synovial sarcomas	6	0%	0%	**15%**	**85%**
Pleiomorphic liposarcomas	6	0%	0%	**15%**	**85%**
Pleiomorphic sarcomas	20	0%	**5%**	**40%**	**55%**
Ewing sarcomas	3	0%	0%	**33%**	**66%**
Solitary fibrous tumor	8	13%	0%	**87%**	0%

VEGFR3 expression has been validated in multiple indications including non small cell lung cancer, hepatocarcinoma and colorectal cancer



EVT801 in Phase I clinical trial KZA-0801-101

Clinical trial design

A Phase I, First-in-Human, Open-Label Study to Assess the Safety, Tolerability, and Pharmacokinetics of EVT801 in Patients with Advanced Solid Tumors

Sponsor: Kazia Therapeutics Ltd
Product : EVT801
EudraCT: 2021-002483-47 / NCT: NCT05114668

Clinical sites (France):
IUCT-Oncopole, Toulouse - PI : Dr Gomez-Roca
Centre Léon Bérard, Lyon – PI : Dr Philippe Cassier

STAGE 1 (Ongoing) - Monotherapy Dose Escalation, n ≤ 48

Dose Cohort 1 EVT801 monotherapy → Dose Cohort 2 EVT801 monotherapy → Dose Cohort 3 EVT801 monotherapy → Dose Cohort 8 EVT801 monotherapy

- Mixed population of advanced solid tumors
- Single-patient cohorts initially, expand to 3+3 when toxicity is encountered
- ***Dose escalation*** up to 8 cohorts :
  50mgQD→100mgQD→100mgBID→200mgBID→400mgBID→500mgBID→600mgBID→800mgBID

MTD RP2D →

STAGE 2 - Biomarker / PD Expansion Cohort
n = 12
- 6-patients PD Cohort in Soft Tissue Sarcoma
- 6-patients PD Cohort in Renal Cell Carcinoma

STAGE 3 (Optional)
IO Combination Dose Escalation
Solid tumors
n ≤ 36
Dose Cohort 1 EVT801 + ICI combination
Dose Cohort 2 EVT801+ ICI combination

Biomarker strategy

Patient stratification based on VEGFR-3 expression on tumoral tissues
(pre and post treatment)
- VEGFR-3 expression by IHC and IF
  Duplexes VEGFR-3/CA9/CD8/CD31/PD-L1
- VEGFR-3 + AntiPD1 Ab-resistance mRNA signature

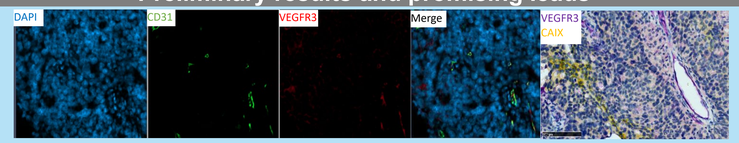
PD biomarkers *(C1D1 & C2D1)*
- Immunomonitoring
  Based on CD8$^+$ T-cells/MDSC ratio
- Protein signature
  Chemokines involved in angiogenesis and inflammation

Unbiased biomarkers *(C1D1 & C2D1)*
Total RNA sequencing

Resting blood samples *(C1D1 & C2D1)*:
- Frozen whole blood
- Frozen plasma
- Frozen PBMCs

Safety biomarkers *(several timepoints)*
Blood pressure measurement

Preliminary results and promising leads



3 high grade serous ovarian carcinoma patients included in the phase I clinical trial exhibited a strong VEGFR3 expression associated with a significant tumor regression in one patient

Conclusion

- EVT801 presents a more selective and less toxic profile than two major approved inhibitors of VEGFRs *(i.e.*, sorafenib and pazopanib).
- In monotherapy, EVT801 showed a potent antitumor effect in tumors with VEGFR-3–positive microenvironment in preclinical models
- EVT801 will be evaluated as single agent in patients with kidney cancer and soft tissue sarcomas. Combination with cancer immunotherapies would come next.

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