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Abstract#1015

For researchers:



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

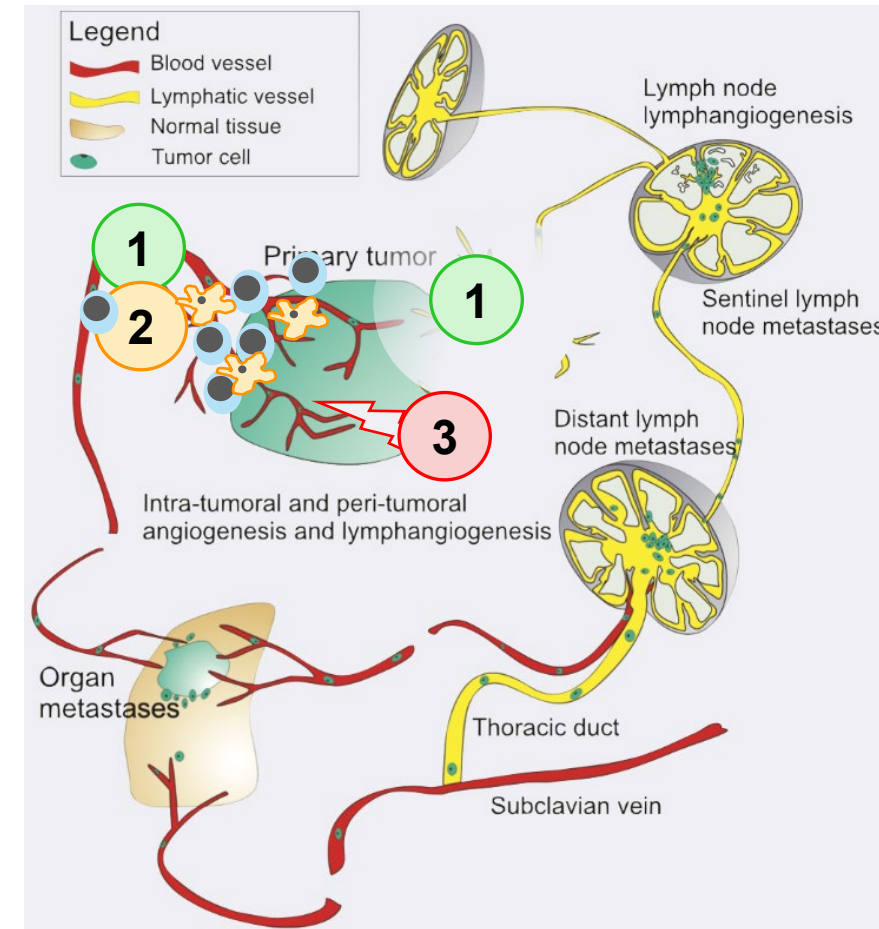
- Stabilization of tumor vasculature
- Inhibition of lymphangiogenesis
- Reduction of tumor hypoxia

2. Enhanced anti-tumor immunity*

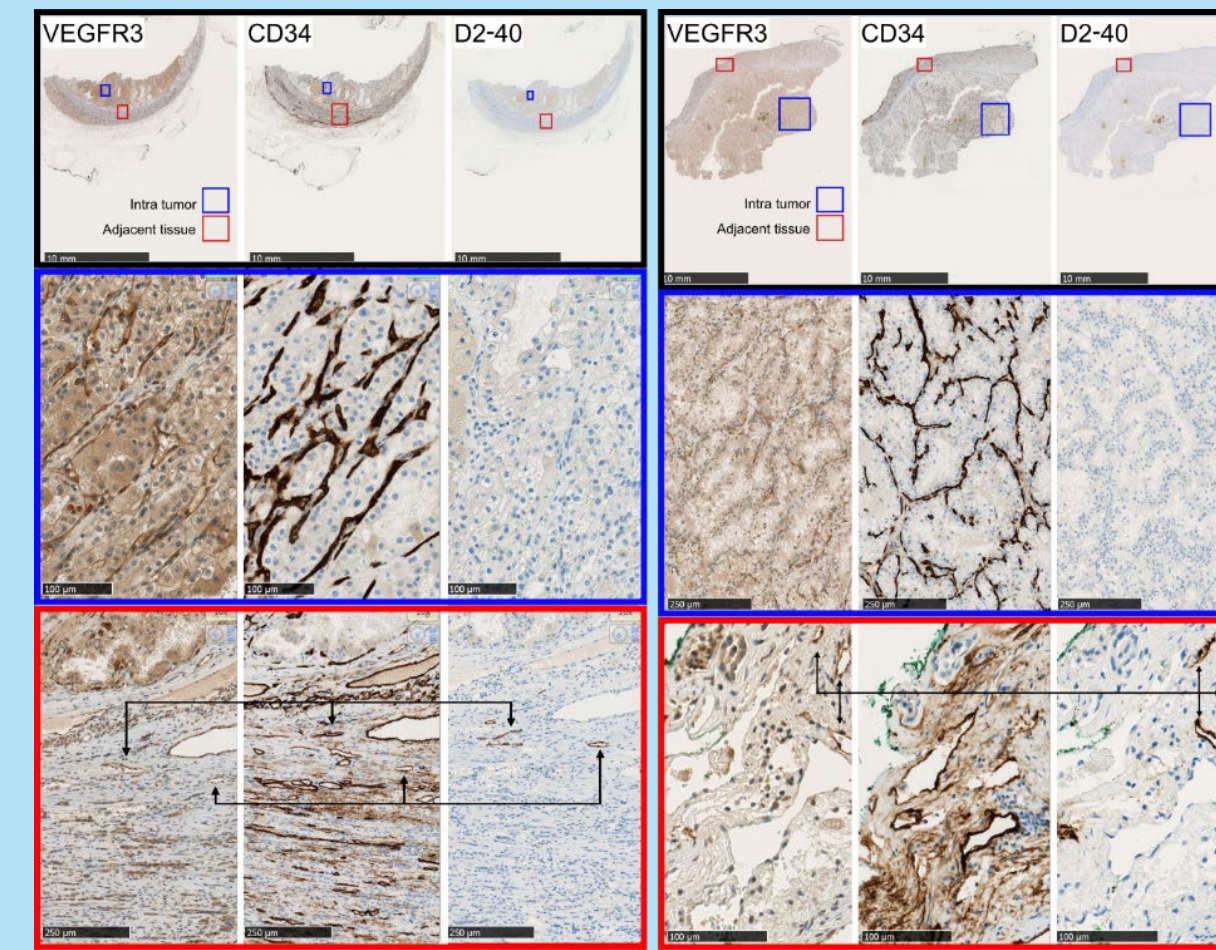
- No impact on T- cells viability
- Decrease in immunosuppressive cells
- Enhanced effector cell infiltration

3. Tumor killing

- Direct effect on VEGFR-3⁺ tumor cells from endothelial origin

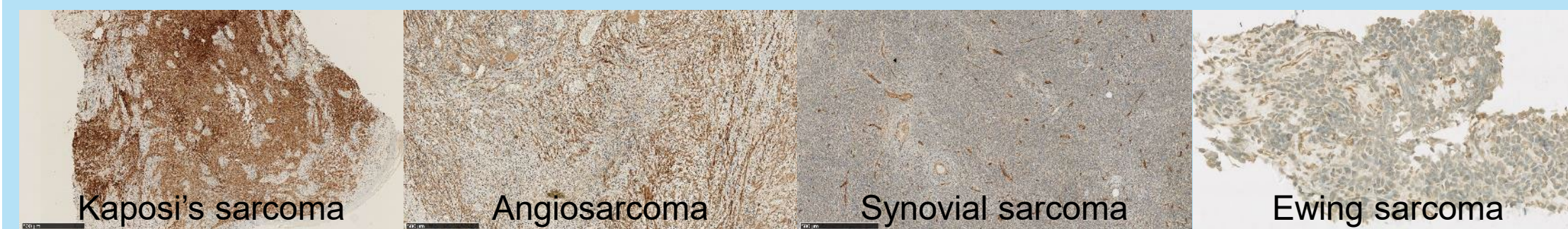


Expression of vascular marker CD34, lymphatic marker D2-40 and VEGFR-3 in primary kidney tumors.



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

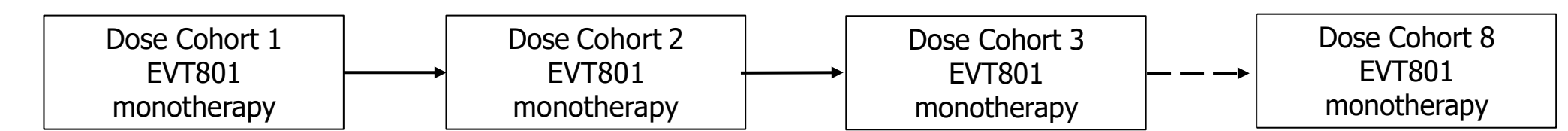
Clinical trial design

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

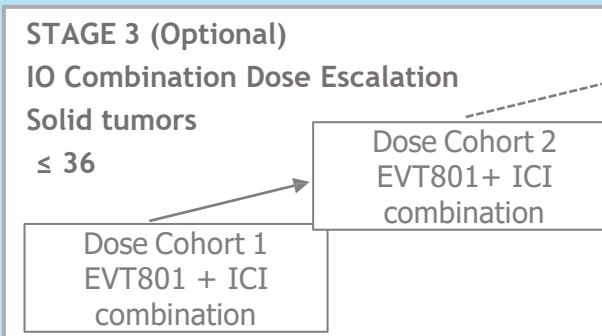
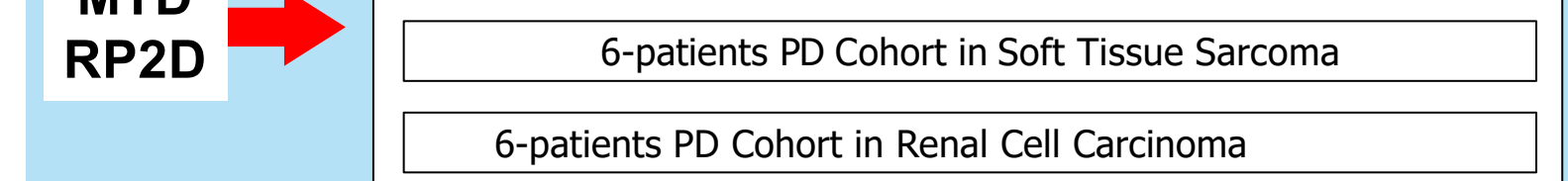
Clinical sites (France):
 IUCT-Oncopole, Toulouse - PI : Dr Gomez-Roca
 Centre Léon Bérard, Lyon - PI : Dr Philippe Cassier

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

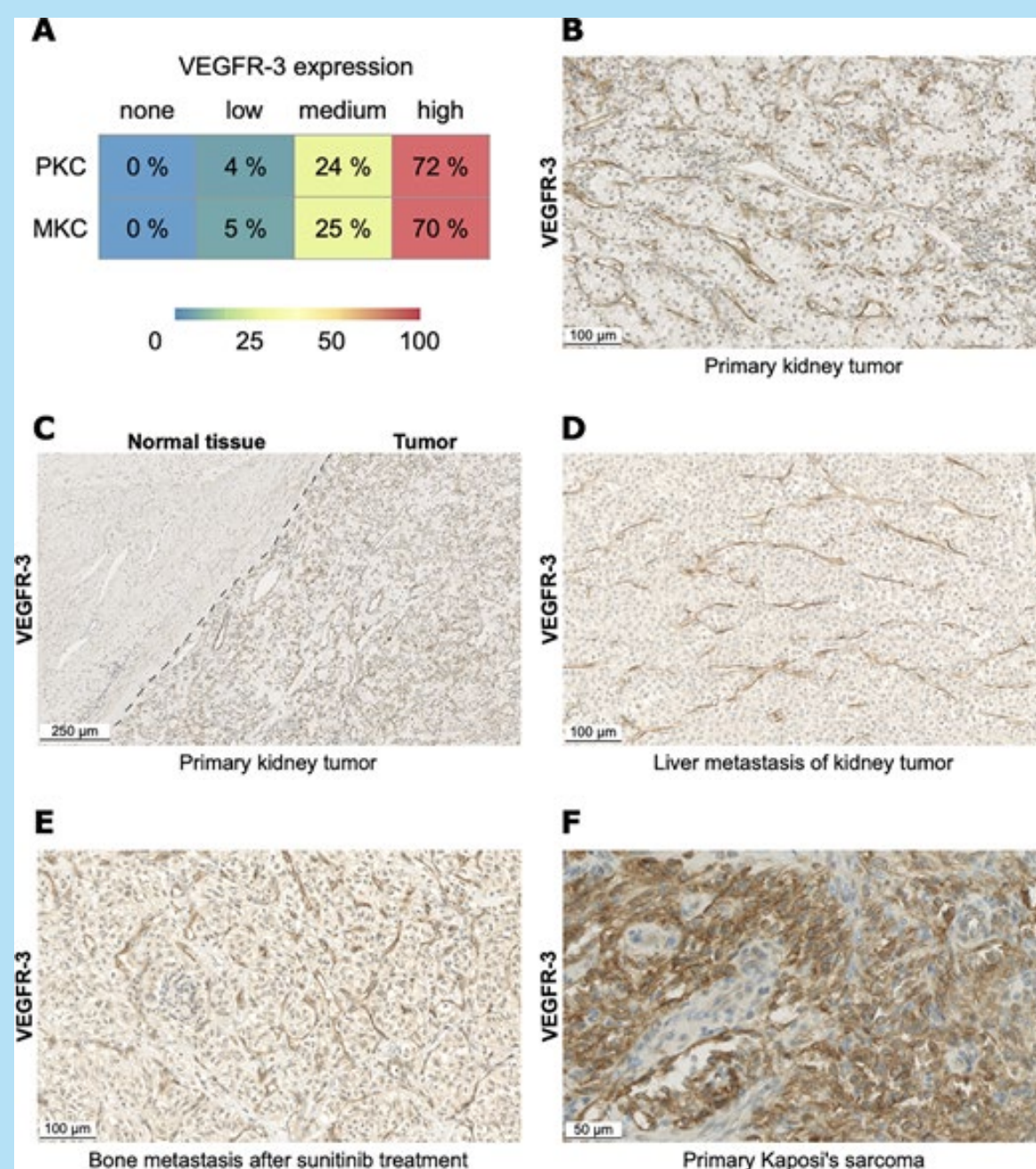


- Mixed population of advanced solid tumors
- Single-patient cohorts initially, expand to 3+3 when toxicity is encountered
- **Dose escalation** up to 8 cohorts :
 50mgQD→100mgQD→100mgBID→200mgBID→400mgBID→500mgBID→600mgBID→800mgBID

STAGE 2 - Biomarker / PD Expansion Cohort n = 12



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

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

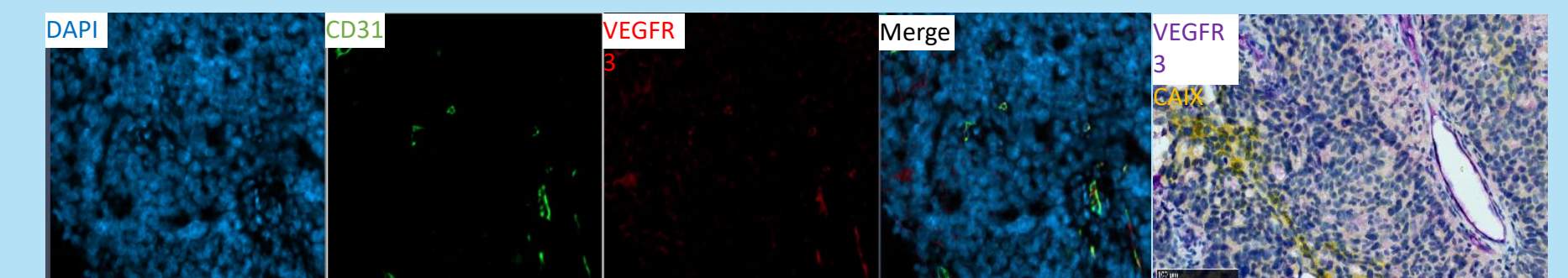
Resting blood samples (C1D1 & C2D1):

- 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.