



Repurposing an old drug in a new ultra-rare indication: pilot of sirolimus in EHE

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No conflicts of interest

Pan Pantziarka

No conflicts of interest







Repurposing
Epithelioid hemangioendothelioma (EHE)



Ultra-rare disease

Unmet medical

need

 Lack of approved systemic treatment

- Mechanism of action
- ESMO consensus statement
- Off label use

Scientific rationale

- Molecular hallmark
- Preclinical and clinical data
- Prospective observational data
- Safety



Repurposing



Molecular hallmark

 The molecular hallmark of EHE, oncogenic fusions YAP/TAZ, are involved in activation of mTOR complex 1

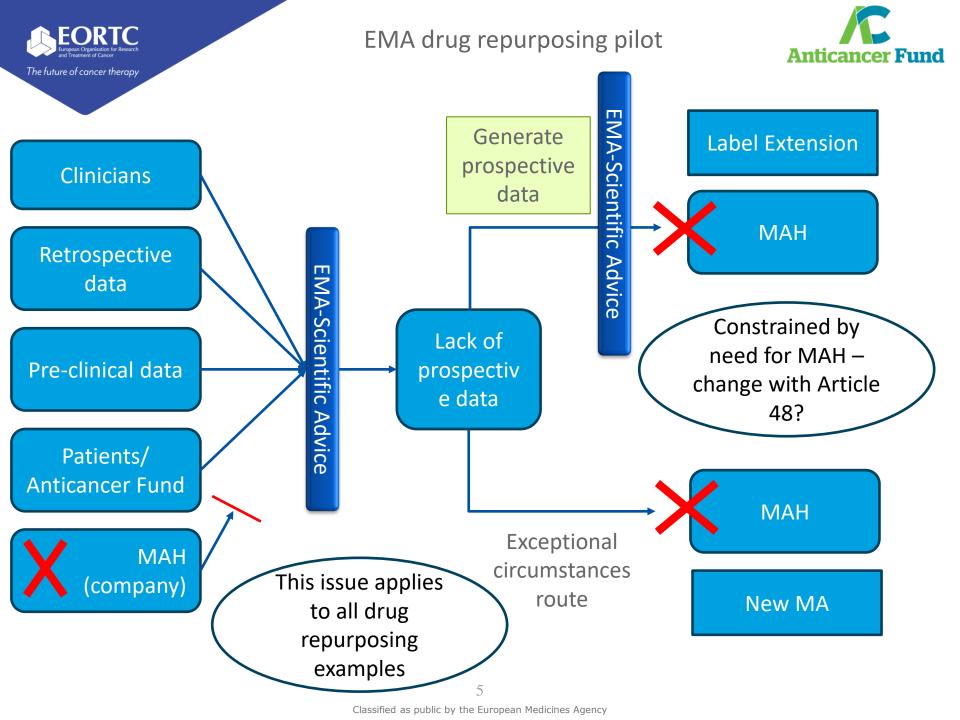
Pre-clinical data

• Preclinical data regarding the comparative activity of doxorubicin and sirolimus in an EHE, WWTR1-CAMTA1-translocated patient derived model → sirolimus induced an 80% tumor volume inhibition, negligible for doxorubicin.

Clinical data

- Prospective data: no prospective data on the activity of sirolimus/mTOR inhibitors are available at the moment. A prospective registry study (Italy and UK) is on-going.
- Retrospective Italian study with 38 pats (including 13 with serosal effusion) with PD at baseline. No Gr4-5 toxicity observed. (DOI: 10.1002/cncr.33247).

	EHE N=38	EHE pats with serosal effusion N=13
Evaluable pats	37	12
Median PFS	13 mo	4.8 mo
Median OS	18.8 mo	10.6 mo





Data Generation



Prospective data collection (registry, ongoing IT-UK)

EMA-Scientific Advice

- Prospective data required 10-15 pats (progressive disease at entry, homogenous population, strong endpoint (2nd PFS, time to next treatment))
- **Biomarker** for response (better proof of evidence)

RCT not currently feasible (heterogenous disease, tiny population)

PLATFORM
Innovative clinical
trial ideas

Regulatory involvement

Other approaches

With art 48 – label extension without MAH driving the application – solution for the general problem not just this very important example

Aim to engage MAH

Article 48 is passed

Application for label extension

Classified as public by the European Medicines Agency





Questions:

 Can we formalise requirements for prospective data collection for ultra-rare cancers?

When do we think article 48 will be effective?







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