EMA & EORTC Soft Tissue and Bone Sarcoma Follow-up Workshop

How can we develop new treatments in ultra-rare sarcomas, as a model for ultra-rare tumours?

Repurposing: case example of sirolimus in epithelioid hemangioendothelioma

Denise Robinson
Executive Director, The EHE Foundation

24 May 2024

EMA Drug Repurposing Pilot Initiative

- Regulators
- Academia / Clinicians
- Not-for-profit Orgs
- Patients / Advocates
- MAH ✗

recognition of new indications for well-established, authorised medicines that are adequately supported by data when MAH does not take lead in applying for a new therapeutic use for the medicine (off protection)

- ✓ preclinical data
- ✓ safety data
- ✓ retrospective data
- ✓ clinical efficacy data
- ✓ real world data

Objectives Constrained by Absence of MAH ✗

THE EHE FOUNDATION

Repurposing Challenges for URS Patients

Existing drug(s) can meet urgent medical needs but are not available.

Lives are on the line!

Drug developer has no incentives or interest, absent profits.

Current regulatory processes are a hinderance to drug development for small, ultra-rare populations.

No organization is accountable to ensure that approved medicines are used to treat every person/disease they possibly can.

How Can We Improve the Situation?

What data can we use? What study designs are suitable? What roles can patients play?

Epithelioid Hemangioendothelioma (EHE)

- Ultra rare sarcoma (URS), <1/1million, globally dispersed population, heterogenous disease
- Highly variable presentations: indolent - highly aggressive, few prognostic indicators
- ~ 180 new cases in EU/ yr. (Lau *et al.*, 2011; de Pinieux *et al.*, 2021; Silvia Stacchiotti, Frezza, *et al.*, 2021)
  - >50% present requiring systemic therapy - too few patients for traditional treatment trials
  - Industry has little interest – simply too few patients + challenges of a highly variable disease

Drug repurposing is critical to bringing treatments to URS patients

- ➢ unmet medical needs require an appropriate plan of action
- ➢ URS can not conform to common cancer research – all supporting evidence & expert clinician-scientists must have a higher value in repurposed/URS treatment development

THE EHE FOUNDATION

Evidence for Sirolimus in EHE

Existing Support:

- ✓ Retrospective Data
- ✓ Case Reports
- ✓ Clinical Trials

Data In Progress:

- ❖ EURACAN Observational Prospective Clinical Registry
- ❖ Prospective Observational Study

What other data is needed?

Study	Design	# of EHE patients	Response
Efficacy of rapamycin for refractory hemangioendothelioma in Maffucci's syndrome (Riou et al., 2012)	Case report	1	Partial response (PR) lasting 16 months.
Phase I studies of sirolimus alone or in combination with pharmacokinetic modulators in advanced cancer patients (Cohen et al., 2012)	3 Phase I trials (NCT00707135, NCT00708591, NCT00375245)	1	In this series of trials, the only partial response by RECIST observed was in an EHE patient. At report, PR was maintained >3 years after enrolment.
Activity of sirolimus in patients with progressive EHE: A case-series analysis within the Italian Rare Cancer Network (Silvia Stacchiotti, Simeone, et al., 2021)	Retrospective study	38	RECIST responses in 37 evaluable patients were a PR in 4 patients, stable disease in 28 (76.5%) patients, and disease progression in 5 patients.
Indications and Limitations of Sirolimus in the treatment of vascular anomalies-insights from a retrospective case series (Karastaneva et al., 2022)	Retrospective study	1	Patient had an initial objective response and has been receiving sirolimus for >5 years, with a continued PR without any treatment-related complications.
A retrospective review of the use of Sirolimus for pediatric Patients with EHE (Engel et al., 2020)	Retrospective study	6	4 of 6 patients demonstrating partial response or disease stabilization.

Of 46 evaluable EHE patients, 39 (85%) have positive response to sirolimus – no other drug has demonstrated this effect.

THE EHE FOUNDATION

Experts Consensus on Sirolimus

>80 multi-disciplinary experts, with patient and advocacy representatives aimed to define evidence-based best practices for optimal approach to primary and metastatic EHE.

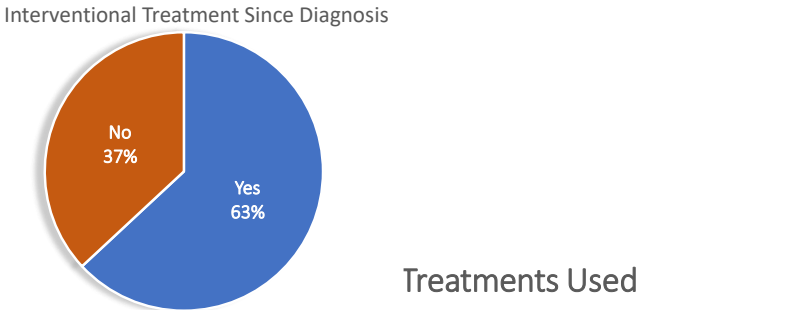
Leveraging the data – conclusions and consensus published in 2021:

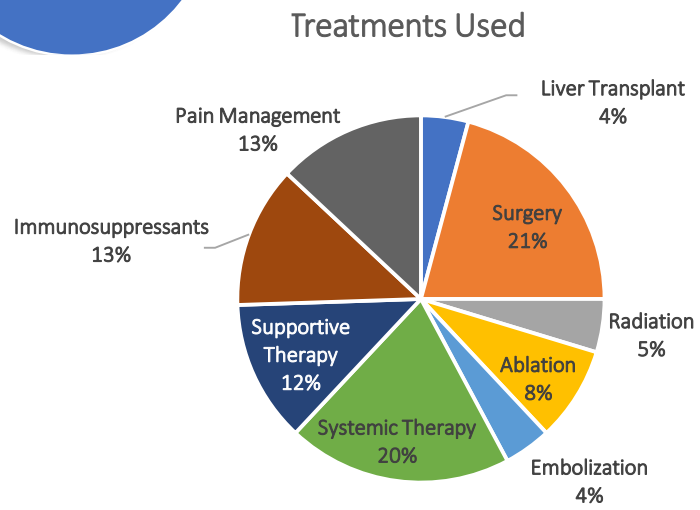
- patients with metastatic disease and unequivocal evidence of disease progression and/or worsening of symptoms and/or organ dysfunction are candidates for systemic treatment
- highest clinical activity has been reported for mTOR inhibitors, with a PFS and OS in the range of 1 year and 2 years, respectively, and approximately 10% of patients having even longer PFS
- mTOR inhibitors, such as sirolimus, represent the preferred treatment options for patients with advanced and moderately progressive disease

THE EHE FOUNDATION

EHE Global Patient Registry: Provides Patients' Experiences

220 Participants - Baseline Treatments Reported





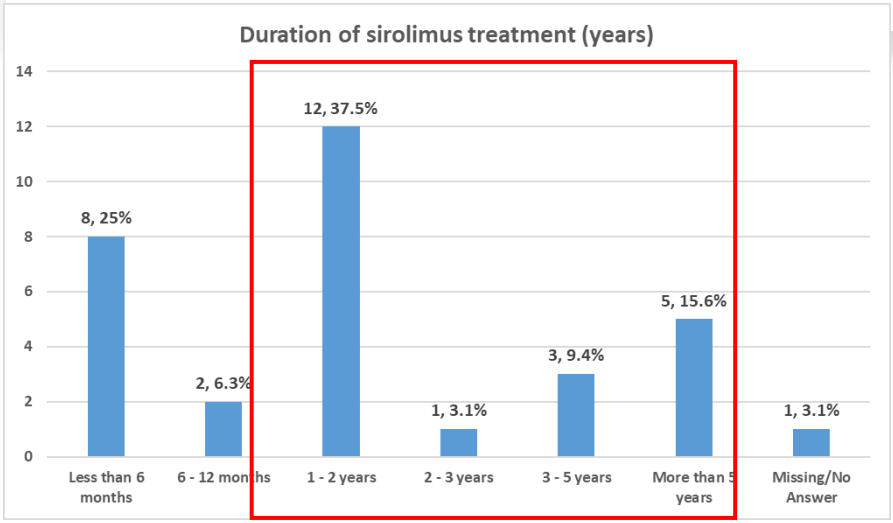
Distribution of Participants by Country			
Australia	6.3%	Netherlands	1.1%
Belarus	0.5%	Poland	1.6%
Canada	9.5%	Portugal	0.5%
Chile	0.5%	Romania	1.1%
Czech Republic	0.5%	Serbia	0.5%
Denmark	0.5%	South Africa	0.5%
Estonia	0.5%	Spain	1.1%
France	1.1%	Switzerland	0.5%
Germany	2.1%	Taiwan	0.5%
Greece	1.1%	Thailand	0.5%
Italy	5.3%	United Kingdom	7.9%
Japan	0.5%	United States	55.8%

Systemic Tx & Immunosuppressants Used	
Agent	# ppl report
Sirolimus	22
Pazopanib (Votrient)	9
Gemcitabine	6
Paclitaxel	6
Docetaxel	5
Bevacizumab	3
Doxorubicin	3
Trametinib (Mekinist)	3
Doxorubicin Liposomal (Doxil)	2
Taclitaxel (Taxol)	2
Sunitinib	2
Levatinib	2
Sorafenib	2
Everolimus	2
Carboplatin	1
Erubulin	1
Interferon alfa	1
Ifosfamide	1
Nivolumab	1
Temozolomide	1
Thalidomide	1
Vincristine	1

Patient-reported data from 25 countries; data analysis will help understand patients' reported outcomes

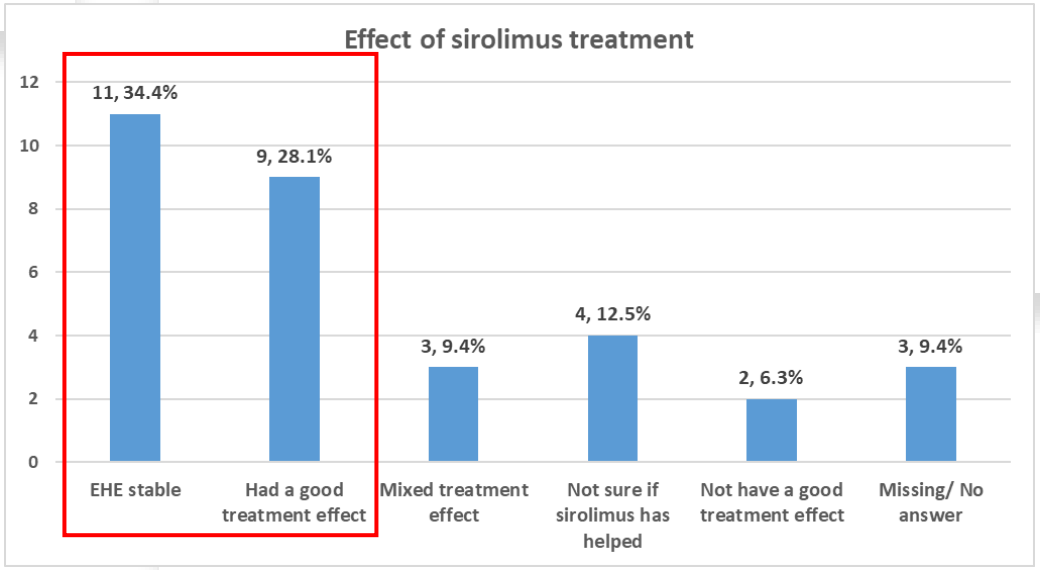
THE EHE FOUNDATION

Patients' Perspectives on Sirolimus for EHE



32 EHE patients reported treatment (non LT pts)

- 5/32 (16%) duration >5 yrs
- 16/32 (50%) duration 1-5 yrs
- *66% of patients have duration >1 yr. with treatments exceeding 5 years – no other reports have met this duration (PFS relevant)*



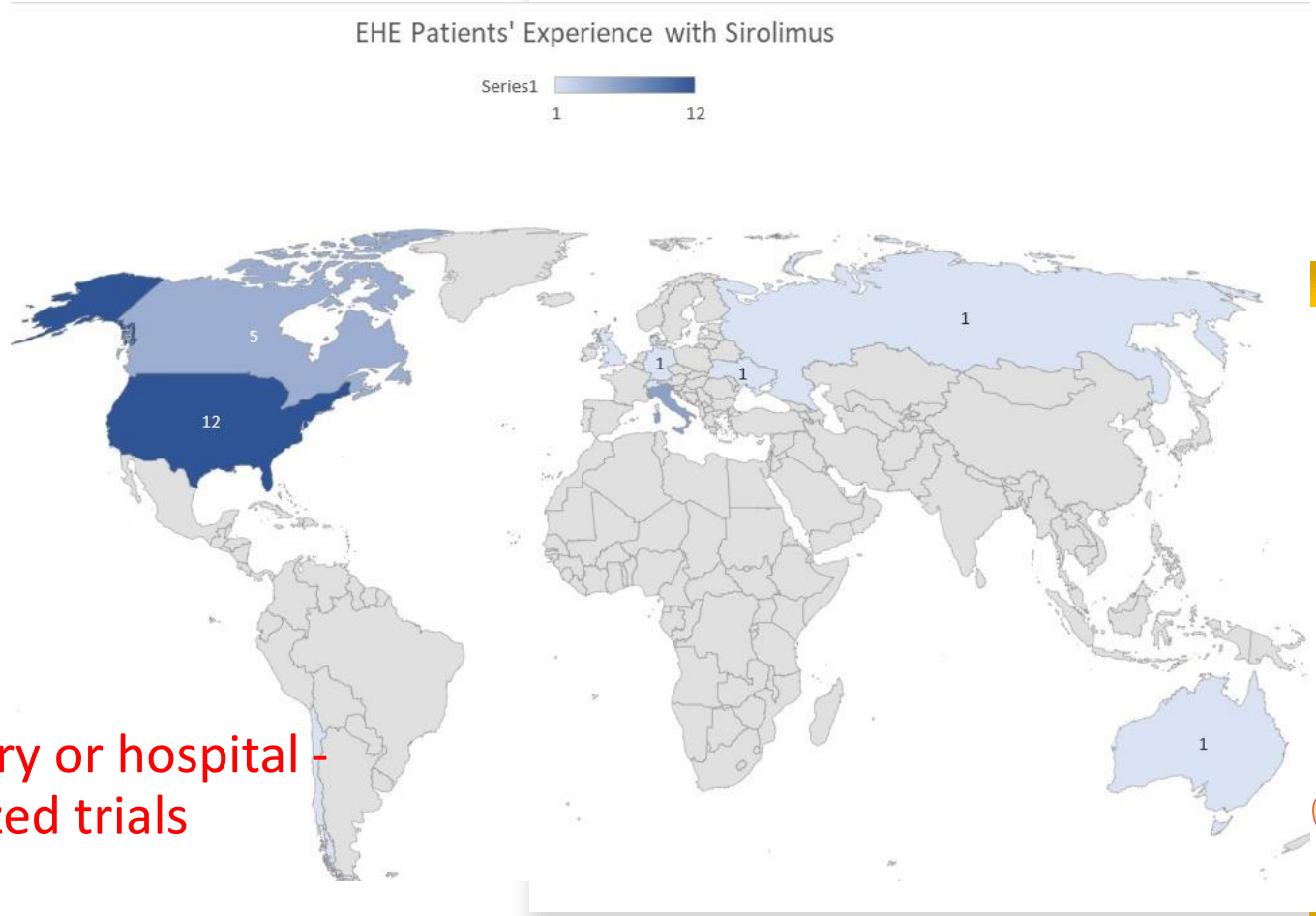
- 11/32 (34%) disease stabilization
- 9/32 (28%) tumours shrank or stopped growing
- *62% of patients report positive response to sirolimus – no other treatment has reportedly achieved this in EHE (SD relevant)*

Robinson, et. al., Front. Oncol., 2024

THE EHE FOUNDATION

Patients' Reported Use of Sirolimus by Region

Country	No. Pts.
Australia	1
Canada	5
Chile	1
Denmark	1
Germany	1
Israel	1
Italy	6
Russia	1
Switzerland	1
Ukraine	1
United Kingdom	1
USA	12
Total	**32**



Too few patients in any one country or hospital - impossible to undertake randomized trials

THE EHE FOUNDATION

Is Sirolimus for EHE a Good Case, Representing URS?

Can we align on the types of data needed?

Case for Repurposing Sirolimus in EHE

- A **majority of patients report achieving disease stability or re-establishing stability**, tumour shrinkage, and/or reduction or alleviation of disease-related symptoms – **in some cases over years of time**.
- Expert clinicians agree that **stabilising EHE is currently the primary target for treatment** of progressive disease.
- Patients and clinicians accept that sirolimus will not work for all EHE cases – ***every person it can help matters***.
- **Toxicity of the drug is fully understood** as it is widely used in other indications.
- **Sirolimus for EHE** would provide the first (and only) disease-specific approved systemic therapy option **meeting urgent unmet needs and improving more patients' lives**.

Patients diagnosed with an incurable, ultra-rare cancer without treatments should not face barriers of commercialism and impractical study designs when clear and present opportunities exist to observe treatment in real-world settings.

THE EHE FOUNDATION

How Can We Be Successful Together?

- **Accept limitations of URS disease populations** – use all available, reliable data to bring treatments to patients
- **Elevate the opinion of expert clinician-scientists** for URS therapeutic development
- **Illuminate patients' participation in academic research** – removes challenges in URS drug development
- **Establish an inclusive process requiring all stakeholders**: patients' advocates, clinician-scientists, MAHs, regulators – compel all to participate, or at minimum observe
- **Define a plan appropriate to URS** populations to collect and use real-world evidence:
  - To give approval where data exists – ***harness evidence, meaningfully improve patients' lives***
  - To define pathway to approval where data is sufficiently lacking

THE EHE FOUNDATION

On behalf of EHE patients and all patients with ultra-rare cancers,

Thank you!

THE EHE FOUNDATION