Multi-arm trial in localized osteosarcoma: moving from a dream to reality

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Context

- Chemotherapy and surgery achieve a **5-year event-free survival of 60-70% in localized osteosarcoma** (OS).
- **Little progress has been made since the 80s** (Fig) & **few randomized trials** with a survival endpoint in localized OS are ongoing (Map).

Osteosarcoma 5-year Overall Survival per Decade
From Allison 2012 Sarcoma (US data)

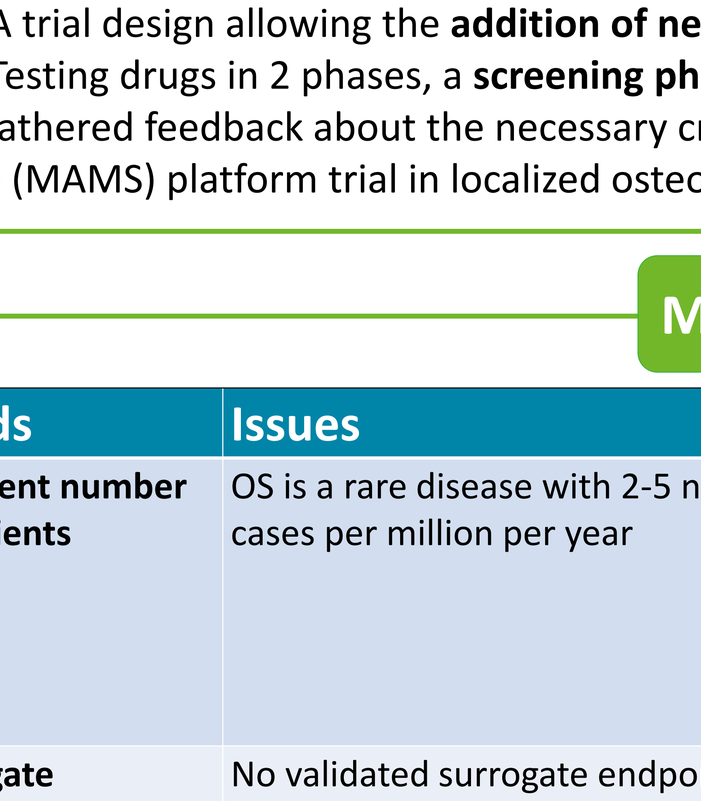
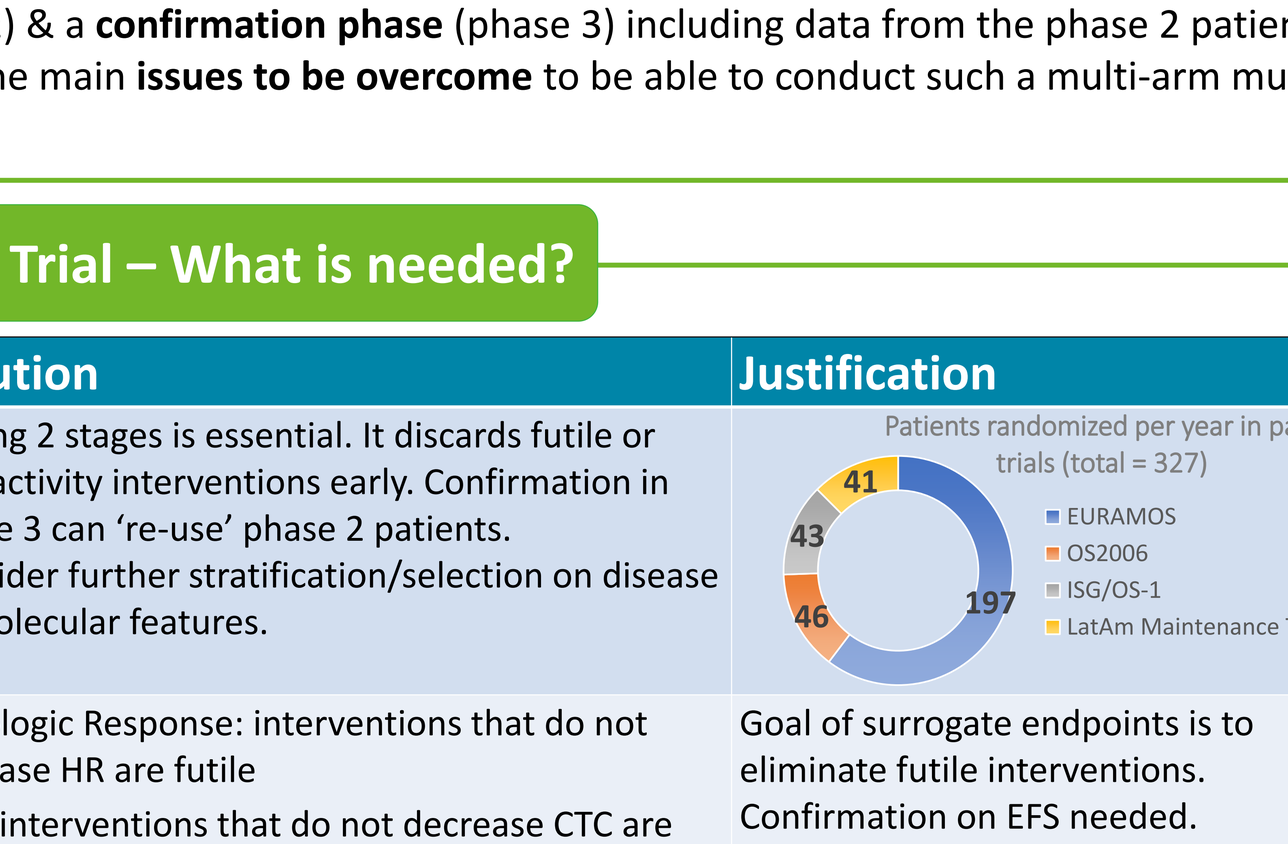


FIGURE 1: Osteosarcoma 5-year overall survival.

Location & number of randomized trials in localized osteosarcoma of interventions aiming at improving survival (as of 5 Nov 2018)



- To **accelerate the pace of clinical research in localized osteosarcoma**, we proposed the establishment of a **trial infrastructure (platform)** which combines two concepts:
  - A trial design allowing the **addition of new arms and the removal of arms for futility**;
  - Testing drugs in 2 phases, a **screening phase** (phase 2) & a **confirmation phase** (phase 3) including data from the phase 2 patients.
- We gathered feedback about the necessary criteria and the main **issues to be overcome** to be able to conduct such a multi-arm multi-stage (MAMS) platform trial in localized osteosarcoma.

Multi-Arm Trial – What is needed?

Needs	Issues	Solution	Justification
Sufficient number of patients	OS is a rare disease with 2-5 new cases per million per year	Having 2 stages is essential. It discards futile or low-activity interventions early. Confirmation in phase 3 can 're-use' phase 2 patients. Consider further stratification/selection on disease or molecular features.	
Surrogate endpoint(s)	No validated surrogate endpoint.	Histologic Response: interventions that do not increase HR are futile CTC: interventions that do not decrease CTC are futile	Goal of surrogate endpoints is to eliminate futile interventions. Confirmation on EFS needed.
Interventions with good risk/benefit ratio	1- 60-70% patients are cured with current treatment. Additional benefit is relatively low. Risk should be low.	Only select high-risk patients. E.g. during neoadjuvant chemo, test experimental treatment in poor responders on early PET	Results from small studies suggest PET can predict histologic response to neoadjuvant chemo.
	2- There is a limited number of low risk interventions	Low risk interventions exist (Poster Bouche ASCO 2018).	Dossiers compiled for sirolimus, ATRA & decitabine with data in pediatrics & rationale in OS.
Large collaboration / network	International collaboration is hard	Set up international collaboration. Patient advocates, foundations & governments may coordinate this effort.	EURAMOS ran 2 phase 3 trials. Other countries ran phase 3 trials (France, Italy, Japan, LatAm, China …)
Large funding	Rare, pediatric, academic, international, pragmatic… all 'bad' points to get large funding	Major funding schemes exist in both the US & Europe. Solid government-funded trial infrastructure already exist in many countries	Past trials & efforts (EURAMOS). Large efforts in Ewing (Euro-Ewing) or in rhabomyosarcoma (Far-RMS)

Conclusion

- Further improvement in EFS is needed in patients with localized osteosarcoma. **A long-term research plan is required**.
- A **stable but flexible clinical trial infrastructure** is possible. Most issues are manageable.
- A **first concept** to screen new interventions could be **to test low risk modifications of current neoadjuvant chemotherapy in poor responders on PET** after 1 or 2 cycles. Prospective confirmation that PET predicts HR may first be needed.
- The **Anticancer Fund is gathering feedback and input** for setting up this ambitious effort.