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Ultra-rare sarcoma:

major challenges and opportunities the patient perspective

(representing the global ultra-rare sarcoma patient community)

Declaration of Interests

Hugh Leonard and Josh Sommer

The EHE Rare Cancer Charity (UK) and the Chordoma Foundation are wholly independent patient advocacy organisations. The speakers have no conflicts of interest

The content of this presentation contains discussion of the challenges faced by ultra rare sarcomas. These are provided in general terms for clarity and discussion. In doing so, we are not, either directly or indirectly, criticising or highlighting any group, community, organisation, facility of individual. We are simply high-lighting the challenges faced.

Patients' Perspectives

Perspectives:

- Ultra-rare sarcomas are not rare to those who have them –they are frightening and life threatening
- They expect the same focus on their disease as every other cancer patient
- Commercial potential should not dictate outcome – their lives are not of lower value!
- The regulators' role is to ensure that safe and efficacious drugs get approved as quickly as possible

Expectations:

- All parties in the sarcoma collaboration will work together to find better treatments
- Rare-sarcoma challenges will not be a barrier to progress - they demand that we find solutions
- Procedures developed from common diseases will not be allowed to act as a barrier to progress – find alternatives
- Ultimately, if they do not survive, it has not been because people did not try!

Ready to help:

- Patients and their advocates are ready to contribute in any way they can to make progress
  - Biobanking, registries, studies, clinical trials – patients are supremely motivated to help and participate
- Small patient numbers when coordinated can provide huge drive and momentum

Multiple Challenges

Ultra-rare sarcomas face many challenges:

Typically, no disease-specific patient coordination or disease-specific patient advocacy groups

- Incentives driven by costs or patient numbers are hugely diluted
- Interest and support from governments, pharma, researchers, funders etc is also diluted

Paucity of treatment options:

- Limited disease knowledge and experience, history, studies, registries etc and those that do exist are small
- Most ultra-rare sarcomas have no disease-specific systemic treatments approved
  - Drugs available under broad disease classifications (eg ‘soft tissue sarcomas’) are unlikely to work
- The urgent need for new treatments cannot therefore be over-stated but:
  - Limited profitability and numbers means a lower tolerance for costs and risk
  - Re-purposing and repositioning of drugs becomes a critical path to better treatment options
  - Systems and procedures largely driven by experience with common diseases – not fit for purpose for ultra-rare sarcomas

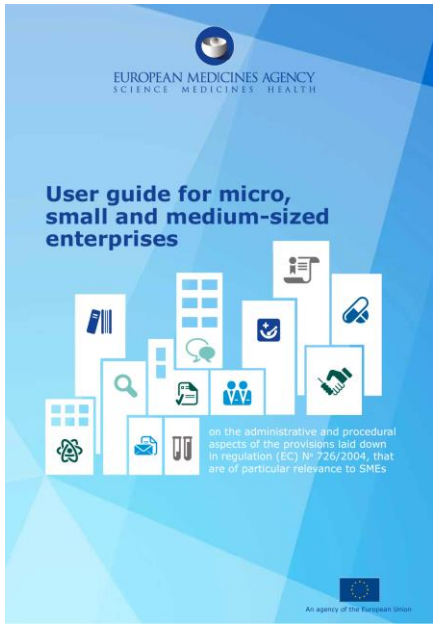
Chordoma experience

- Increased understanding of disease biology is pointing to multiple opportunities for repurposing, repositioning or new drug development
- Uncertainty about requirements for regulatory approval can impact investment at all stages of development for chordoma
- Small populations and lack of approved/effective therapies → necessitates small trials, alternate to RCT
- Slow growth, long natural history, limited budgets → precludes OS endpoint
- Matrix-rich, acellular tumor unlikely to shrink significantly, proximity to critical structures very sensitive to small changes in tumor size → necessitates alternative to RECIST ORR
- Patient preferences indicate prioritization of prolonged QoL → suggests extended PFS and/or PRO could be more meaningful than RECIST ORR
- EMA and FDA have signalled an openness to consider endpoints other than RECIST ORR (e.g. PFS and QoL endpoints);
- We now need to agree specific guidance as to the level of evidence needed for these endpoints to be used to avoid the risk of this being seen as a barrier for investigators and companies to design and invest in trials

Chordoma experience cont'd

- Regulatory agencies could increase feasibility and reduce risk of clinical development — and, thereby, unlock significant investment — by providing specific guidance regarding path(s) to approval for ultra-rare sarcomas
- Specific questions that need to be addressed collaboratively:
  - What endpoints other than RECIST ORR can serve as the basis for approval with a small, single arm trial and under what circumstances?
  - What constitutes suitable external/historical control(s)?
  - What magnitude of benefit is required?
- Can guidance be generated for all ultra-rare sarcomas, certain groups of similar tumors, or must guidance be on a disease by disease basis?
- We welcome the opportunity to work with regulators to develop such guidance. You can rely on us to facilitate crucial patient input.

Opportunities - key principles already exist



- **Objective:** "…to overcome the main financial and administrative hurdles associated with pre-marketing procedures, particularly scientific advice, marketing authorisation application and inspection procedures…"
- **Role:** "…to offer assistance to SMEs who, due to lack of experience with the centralised authorisation procedure or lack of familiarity with the Agency and its procedures, may otherwise experience difficulties with the development and marketing of their new medicinal products."
- **Assistance:** "Regulatory, administrative and procedural assistance from the Agency's SME office including SME briefing meetings."
- **Fees:** Fee reductions, exemptions and/or deferrals."
- **Dialogue:** The SME office offers SME briefing meetings, which provide a platform for a company to discuss its planned regulatory strategy.

These SME incentives are all directly applicable and beneficial to non-corporate groups seeking approvals for repurposing of existing drugs for ultra-rare sarcomas

These incentives help address the cost and risk issues for ultra-rare diseases

- How do we make these incentives available to ultra-rare sarcomas
- We all need to work to ensure that profit does not dictate access to treatment
- Again, ultra-rare sarcomas need a different approach

Opportunities - can we do better?

The 2023 pilot process

Achieved:

- Initial scientific advice procedure completed
- Exceptional circumstances application (ECA) indicated
- Hybrid application identified
- Benefits of orphan drug status high-lighted
- Indication that pharma involvement is necessary

Limitations:

- Still not clear if and what additional data is required
- Largely limited to email communications
- Written questions and answers can be unclear
- Limited ability to discuss and agree key points
- Relatively slow and laborious
- Cannot access SME process benefits

A possible alternative?

- EMA review applicant dossier and decide on merit to progress?
- If positive, initiate face to face working group meeting(s)

- Discuss and reach preliminary agreement on:
  - Validity and presentation of existing data
  - Application pathway – Exceptional circumstances?
  - Design and magnitude of additional data required
  - ‘SME’ access to help with risk and cost

- Initiate ongoing programme with ‘SME’ support/advice
- Exceptional circumstances application prepared
- Pharma engaged with clarity on process, costs and risk

Open and regular dialogue
Clarity on requirements at all stages
A collaborative process finding solutions
Applicant does all the work

Moving forward

- Awareness of ultra-rare sarcomas is growing and with it a realisation that more needs to be done
  - The EMA's drug repurposing pilot scheme is just one example of this
  - Legislative changes are being looked at to try and facilitate drug approvals (eg EU Art 48)
  - Patient advocates are mobilising – they can help and desperately want to
- For ultra-rare sarcoma patients, the direction of travel is good, but the speed of change is not
- If we are going to deliver on patient expectations, everybody in this room needs to work together
- Can we establish open and ongoing dialogue that will enable us to find the solutions needed for ultra-rare sarcomas, and answer key questions?
  - What endpoints other than RECIST ORR can serve as the basis for approval with a small, single arm trial and under what circumstances?
  - What constitutes suitable external/historical control(s)?
  - What magnitude of benefit is required?