EORTC
European Organisation for Research and Treatment of Cancer

Clinical research for Ultra Rare cancers: Challenges and Opportunities for Clinical Research

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- I have no Conflict of Interest

Disclaimer

- I am a proponent of randomised clinical trials
  - This does not mean necessarily phase III
  - Randomisation can occur in real life and be pragmatic
  - The rarer, the more we should randomise
- There is no reason not to offer the same level of certainty to rare cancer patients as for frequent cancer patients whenever possible
- The design depends on the question
- No design will overcome a poor understanding of the underlying biology
- One should understand the limits of designs and what can be claimed for

Challenges

- Access to patients/ recruitment: informative registries, epidemiology, natural history etc..
- Commercial sector: very limited to no interest
- Independent funders: mitigated support
- Academia: fragmentation of initiatives, lack of cohesive approach
- Regulations: lack of flexibility to access to patients
- Methodology: how best to approach for high level evidence
- Translational research opportunities

Starting from existing CT examples i.e CREATE

- CREATE: Cross-Tumoral Phase II study with Crizotinib (MEK/ALK alterations)
  - Inflammatory Myofibroblastic Tumors
  - Papillary Renal Cell Carcinoma
  - Alveolar Soft Part Sarcoma
  - Clear Cell Sarcoma
  - Anaplastic Large cell Lymphoma
  - Alveolar Rhabdomyosarcoma
- Basket trial- classical Phase II design with standards end-points and long term follow up – non randomized
- IMT as an example: 55 months-35 patients-13 sites: could we do better?

Building from tangible solutions / access (I)

- ARCAGEN-SPECTA: Molecular profiling of 991 prospectively recruited rare cancers patients in EUROPE: First results of ARCAGEN – an EORTC-SPECTA and EURACAN study
  - 3.5 years, 991 patients, 10 different tumor types,14 countries in Europe, 918 molecular profile (92.60% success rate), median turn-around time of 13.25 days [range 11.5-17].
  - Clinically relevant molecular alterations identified in 606 patients (66%): TP53 (28.5% of all enrolled patients), CDKN2A/B (16.8%), KRAS (9.2%). The TMB was above 10 for 53 patients (5.3%) and 9 MSI-high patients were identified.
  - 456 patients (46%) received a therapy recommendation based on the molecular analysis: 63 (6.8%) patients for an already approved treatment (ESCAT 1A); 232 (25.3%) for an off-label use of an approved treatment in another indication with similar molecular alteration (ESCAT IC, II or III); and 161 (17.5%) for a clinical trial.

- EORTC –EURACAN partnership: but it was an observational cohort

Building from tangible solutions / methodology (II)

- STRASS 2-STREXIT: A randomized phase III study of neoadjuvant chemotherapy followed by surgery versus surgery alone for patients with High Risk RetroPeritoneal Sarcoma (STRASS 2)
  - To compare the outcome of these patients with the outcome of an observational cohort of patients (STREXIT 2) eligible for but not randomized into STRASS 2 to see how the outcome of the randomized patients compares with real-life, clinical practice data
  - A specific focus on QoL
  - On-going, supported by EU grant
  - A global trial (US, Australia..)

What do we optimally need?

Feasibility & assessment

- Natural history of rare cancer patients (longitudinal follow-up)
- Hypothesis generation for new therapeutic directions
- Rapidly conduct interventional/ non interventional CTs, TWICs..
- Bench marking of therapeutic interventions
- Recruitment access through limited number of highly specialised centres

Data access

- High quality/ versatile access to genomic solutions
- Capacity for highly reliable synthetic /control arms
- Clinical and translational research across rare entities
- Quality control solutions for clinical, biological and imaging data
- Support data sharing exercises

Partnerships

- Global programs with other programs outside the EU
- Interaction with the commercial sector: operational and strategic
- Interaction with regulators and HTA/payers: policy

Opportunities

How do we get the best of the 2 worlds observational and interventional for (ultra) rare cancers?

Optimising existing solutions for ultra-rare cancers

- Need to re-engineer partnership between existing infrastructures and solutions (registries with interventional trials)
- Deploy existing registries to receive clinical trials: EURACAN
- Optimise existing clinical research solutions and infrastructures
- Re-design regulatory solutions for agile interactions between observational and interventional solutions
- Develop methodology such as TWICs, quality standards for external controls, decentralized trials…
- Co-creation of solutions for moving the field forward by federating expertise (epidemiology, methodology, clinical trials, outcome research etc…)

Possible relevant questions?

1. How could we create an ecosystem for (ultra) rare cancers where the efficiency is better than the sum of its parts?
2. What could be the optimal datasets (design and end-points) which can be suitable for approval and access?
3. How to structure the work of academic research in regulatory decision making and stimulate access to relevant new agents?