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European Organisation for Research and Treatment of Cancer
The future of cancer therapy

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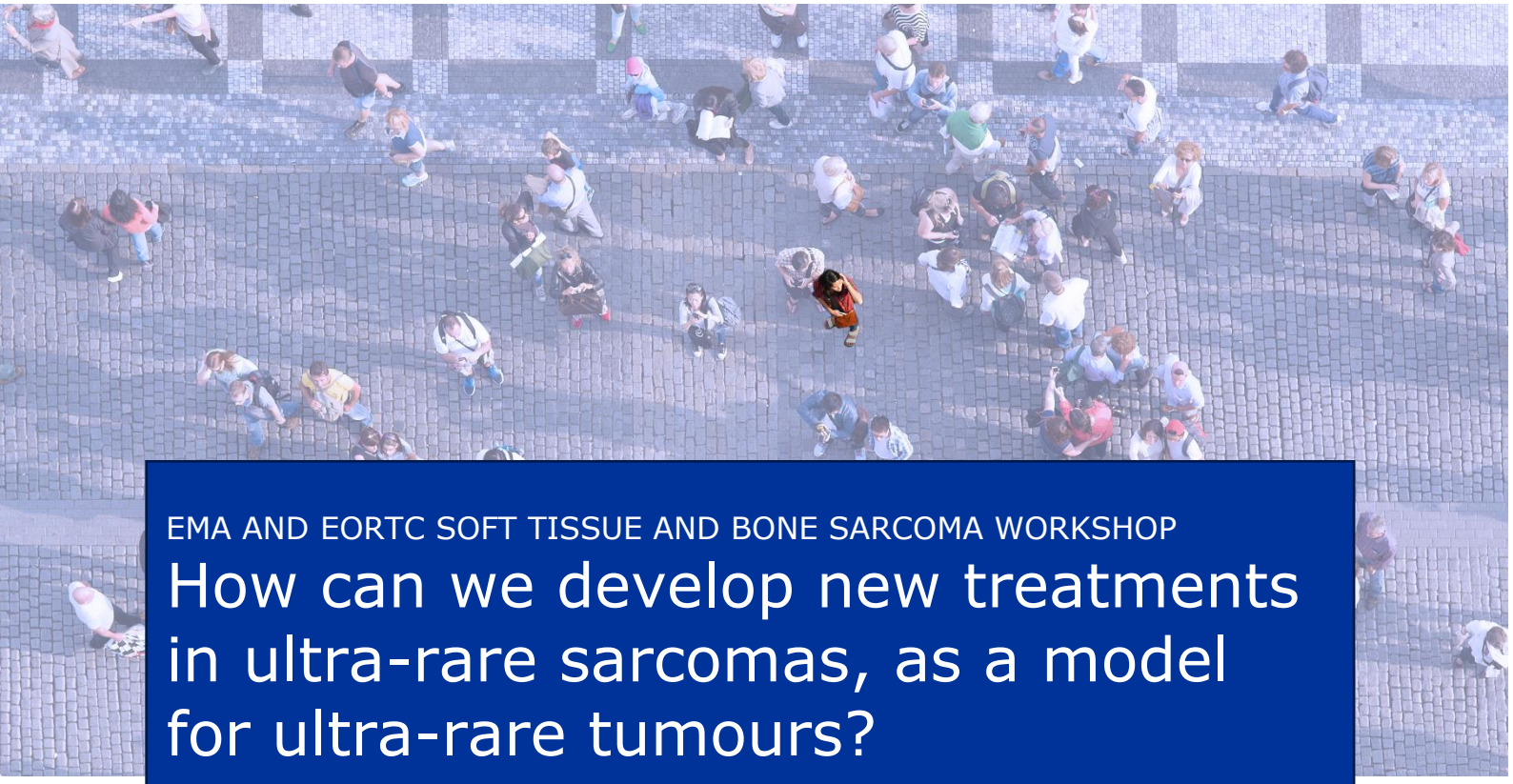

EMA AND EORTC SOFT TISSUE AND BONE SARCOMA WORKSHOP

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

12 January 2024

Meeting report of the joint EMA/EORTC workshop on soft tissue and bone sarcoma workshop

1. Introduction

The European Medicines Agency (EMA) and the Soft Tissue and Bone Sarcoma Group (STBSG) of the European Organisation of Research and Treatment of Cancer (EORTC) organised a workshop to address the question on how to develop new treatments in ultra-rare sarcomas, as a model for ultra-rare tumours. This workshop brought together academia, learned societies, patients, non-profit organisation, and medicines regulators to explore clinical and scientific aspects related to the development of treatments for ultra-rare cancers focusing on methodological aspects of prospective interventional clinical studies (such as the use of master protocols) in ultra-rare tumours, repurposing medicines, and the use of data derived from retrospective studies, prospective observational studies and prospective registries to support the design of prospective clinical studies in these indications and provide real world data as comparison.

2. Purpose of the Workshop

The aims of the workshop were to:

- Discuss the needs and points to consider for developing treatments in rarest cancer types using ultra-rare sarcomas as a model;
- Facilitate interactions among relevant stakeholders aiming at global collaboration;
- Explore a framework for regular meetings between the adult sarcoma community and regulatory agencies, in particular EMA and FDA, to work side by side in the development of new approaches and clinical studies tailored for this purpose.

The workshop was a joint collaboration between EMA and its relevant working parties, the US FDA, and stakeholders from and invited by the EORTC STBSG. P. Demolis (EMA) and S. Stacchiotti (EORTC STBSG) were the appointed joint chairs of the Workshop.

This meeting report captures the main points of discussions and main conclusions from the workshop. Particularly, it summarises the presentations and discussions that took place at the workshop. It is not an action plan but it contains points for follow-up as identified by workshop participants to be further considered together with EMA and FDA.

3. Workshop Report

The workshop was organised in the following sessions:

- **Welcome**
  Chair of the Committee for Medicinal Products for Human Use (CHMP) of EMA
- **Introduction and meeting objectives**
  Appointed EMA and EORTC STBSG Joint Chairs of the Workshop
- **Session 1: Background**
  Invited speakers (see session report below)
- **Session 2: How to establish a framework for ultra rare sarcomas?**
  Invited speakers (see session report below)
- **Panel Discussion**
  All speakers with additional panellists and open forum for questions
- **Closing Remarks**
  Appointed EMA and EORTC STBSG Joint Chairs of the Workshop

Guidance to the reader: *This report summarises the key aspects which were discussed during each session of the workshop. Abstracts and panel discussions are summarised under each session.*

3.1. Welcome

Rapporteur: Harald Enzmann (Chair of the Committee for Medicinal Products for Human Use (CHMP) of EMA)

H. Enzmann welcomed everybody to the workshop and noted that the days topic was broader than just ultra-rare sarcomas. He noted that there is a gap in clinical care between practice, expectations, and regulation. On the clinical side there is great awareness of the unmet clinical need to treat patients with severe conditions, which is a very patient-centric approach, while on the regulatory side there is a legal and regulatory framework that must be complied with. The regulatory framework has been developed over many decades, with 'standard' diseases in mind, and this framework may not be suitable for more frequently complex scenarios of (very) rare diseases. There are 'back doors, such as the exceptional circumstances pathway, which are a possible way forward, but there is an obvious gap between what we want and what we can do on both sides. This workshop is the start of a longer process involving an exchange of knowledge to better understand what we do; why we do it; how we do it; how we might do things differently; how we can get closer together and start decreasing 'the gap'. We need to start finding better ways to use data, to not just say "we cannot" but think what is conceivable, what is feasible and what can be done. For clinicians, scientists and investigators, the need is to gain a better understanding of the regulatory framework and processes – then together we can act meaningfully within this framework-. It is hoped that the workshop would be a positive process for everybody taking part where views and information can be exchanged and at the end of the day there will be clear and actionable next steps, so that we can go beyond talking and see real progress.

3.2. Introduction to the EMA and EORTC STBSG multi-stakeholder workshop on soft tissue and bone sarcoma

Pierre Demolis (EMA) and Silvia Stacchiotti (EORTC STBSG) - Joint Chairs of the Workshop

Dr. Demolis, agreed that the days topic would extend beyond ultra-rare sarcomas but felt that ultra-rare sarcomas provided a good model to discuss what we do with the orphan diseases with high needs and complexity. This would need flexibility, a change in processes, and models would need to be adapted, all of which would be discussed during the day. The workshop was not a collection of scientific advice, nor would solutions be found, but will allow the start of building on ideas and finding solutions.

Dr. Demolis presented the European 'landscape'. The organisation of the EMA was summarised including its executive bodies, committees (of which COMP was noted as being of particular interest as it is responsible for orphan legislation and its application within Europe), working parties, and 8 scientific advisory groups. The EMA also has access to around 4,000 European experts via the multiple relationships the EMA has with National Competent Authorities. and has relationships with around 50 national regulatory authorities worldwide through The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The EMA also works closely with external partners including other regulators, such as the FDA who were welcomed to the workshop, and with other partners in the oncology sphere like EORTC as this brings together regulators and experts which is important in addressing oncology needs. The specific roles of the EMA Oncology Working Party and the Oncology European Specialised Expert Community were presented. A summary of the broad range of EMA tools available for innovation and drug development and approval were presented, several of which could be directly applicable to severe orphan

diseases such as ultra-rare sarcomas. In relation to the EMA's Scientific Advice procedures, these may be too rigid and therefore not appropriate to support ultra-rare sarcomas. Greater flexibility had in fact been discussed by the EMA just the day before. The EMA have the tools, but changes are required and the development and regulatory model need to be adapted. This was a main theme of the workshop.

S. Stacchiotti, thanked the attendees and stakeholders for their participation. She described the background to the workshop and the decision of the EMA and EORTC STBSG to work together more closely to fight discrimination against ultra-rare tumours. The process started in 2020, thanks to two initiatives launched by EMA (the innovation task force and repurposing pilot) that clarified the need to optimise study designs and make the best use of available data to improve patients' affected by extremely rare sarcomas. Ultra-rare sarcomas are those with an incidence of less than or equal to 1 per 1 million inhabitants per year (CTOS definition). The list of 78 such sarcomas was provided, with 56 being soft tissue and 22 being bone related. Conducting randomized studies in these diseases is challenging. The list of the drugs specifically available for treatment of ultra-rare sarcomas in EU is 4 agents (for 3 indications) and in US 8 agents (for 7 indications). The importance of understanding what regulators require and accept as support for drug approval in the case of these rare diseases is paramount. The PUSH (Pushing Ultra-Rare Sarcoma Towards Hope) initiative, started in 2023, was introduced. PUSH is a global initiative from the sarcoma community in collaboration with multiple stakeholders including patient representatives and non-for-profit organisations. The objective of the global consortium is to maximize the knowledge that is gained from each patient, make the best use of all available data and support developing new treatments to improve outcome and quality of life. PUSH includes the development of a platform to conduct prospective clinical trials called PUSH-IT. The community would like to develop this platform alongside the regulatory agencies.

3.3. Session 1: Background:

EMA regulatory framework for rare disease

Ralf Herold, Head of work stream Regulatory Science and Academia, EMA.

In paediatric cancers large scale international and intercontinental trials have been undertaken involving thousands of participants. The ACCELERATE initiative is an example of a successful multi-stakeholder programme to assist with paediatric diseases. Support programmes available within EMA including the PRIME scheme, orphan designations, and conditional marketing authorisations, together with a summary of the benefits these programmes delivered are available. The importance of collaborations and partnering offers was also highlighted, and examples include the EU PEARL and EATRIS programmes. These programmes help to deliver tools, develop recommendations, and give access to experts. New developments in 2023 involving trials and clinical practice were then presented, including four initiatives of ICH and two of EMA. New initiatives for 2024 were including expanding Academia briefing offers for not-for-profit developers and innovators, something that could be directly applicable to the subject of the workshop. An overview of how the EMA seeks to support stakeholders was presented. It was noted that the EMA wants to engage on projects and development of new tools; to be responsive to queries, and occasionally be proactive. The lowering of standards is a particular risk, and a summary of the necessary high-level criteria that needed to be met was provided. The EMA would not lower its standards and that that appropriate clinical standards and methods, even in rare diseases, should show that sufficient efforts have been made to bring forward credible evidence.

Ultra-rare sarcomas: major challenges and opportunities – the patient perspective

Hugh Leonard, Chair of Trustees, The EHE Rare Cancer Charity, UK, and J.Sommer, Executive Director Chordoma Foundation, US.

H. Leonard thanked the EMA, FDA, and all participants for giving their time to discuss what were important issues. Both were speaking on behalf of all patients with ultra-rare sarcomas not just for their specific disease areas. Ultra-rare diseases are not rare to this who have them. Patients expect that the same focus and questions applied to more common cancers apply to their ultra-rare conditions. Neither the rarity of their diseases nor the lower profit potential they present should be accepted as reasons for lack of attention. The patient communities are hugely motivated to assist in any way they can. Challenges are largely driven once by extremely low patient numbers. The urgent need for new drugs and treatments could not be over-stated, yet the lower tolerance of drug development companies to risk and cost due to smaller profit margins acts an impediment. The importance of drug repurposing was stressed, as was the need to find appropriate procedures for their approval.

J. Sommer noted that in Chordoma, a greater understanding of the biology of the disease was developing all the time and this led to greater potential for drug repurposing, positioning and development. However, uncertainty of regulatory requirements for drug approval could act as an impediment to investment. Challenges faced included small patient populations limiting trial size and design; the nature of the diseases requiring the consideration of different endpoints as standard RECIST criteria may not be appropriate, with possible alternatives relating to QoL being noted. Regulatory bodies could help address these issues by providing more specific guidance relating to the pathway to drug approvals for ultra-rare sarcomas. It was recognised that these sarcomas are different, but guidance relating to groups with common types of tumours could be considered.

H. Leonard high-lighted that many of the types of procedure and guidance that could be of assistance is recognised. The case of the EMA's Guide for SMEs was an example. The benefits of SME procedures would be directly beneficial to academia/patient-advocacy led groups. Experience from the 2023 Pilot Programme showed good progress in several areas, but key issue remained unresolved, partly due to the rigid and prescriptive nature of communications. One example of an alternative structure, possibly delivering faster and clearer communications, was described.

There is a growing awareness that more needs to be done for ultra-rare sarcomas, but while the direction of travel is good, the pace of change is too slow. This requires all stakeholders to work harder to find solutions. In particular, the presenters asked if all parties could work together to establish an open and ongoing dialogue that will enable the solutions needed for ultra-rare sarcomas to be found?

Ultra-rare tumours major challenges and opportunities: the EORTC perspective

Denis Lacombe, EORTC Chief Executive Officer, Brussels, Belgium.

Randomised clinical trials are the best tool we have and that there was no reason not to offer the same level of certainty to rare cancer patients as for other cancer patients when possible. Trial design depends on the question being asked and cannot overcome poor understanding of disease biology. Key challenges include limited access and recruitment of patients; limited or no support from the commercial sector; reduced support from independent funders; a fragmented approach from academia; and a lack of flexibility within regulations. CREATE (Cross-Tumoral Phase II study with Crizotinib (MEK/ALK alterations)) is an example of a clinical trial successfully undertaken for a group of ultra-rare sarcomas. This was a Phase II non-randomised trial using standard end-points and long term follow-up.

The ARCAGEN-SPECTA study and STRASS 2-STREXIT phase III study are also examples of how progress can be made. The ARCAGEN-SPECTA study completed the molecular profiling of 918 patients of 991 recruited (92.6%) affected by any kind of rare cancers from 14 European countries and ultimately delivered therapy recommendations to 456 patients based on the clinically relevant molecular alterations identified from the molecular profiling. The STRASS 2-STREXIT2 study is ongoing and is comparing neoadjuvant chemotherapy followed by surgery versus surgery alone for patients with High-Risk Retroperitoneal

leiomyosarcoma and liposarcoma. Finally, as a conclusion to the challenges faced, a matrix of requirements to optimise the overall understanding of ultra-rare sarcomas and deliver new treatments was presented, broken down into three core areas, namely: (i) feasibility and assessment; (ii) data access, and (iii) partnerships.

How do we get the best of the 2 worlds: observational and interventional for (ultra) rare cancers? Possible ways to optimise existing solutions include: re-engineering the partnership between existing infrastructures and solutions (registries with interventional trials); optimising existing clinical research solutions and infrastructures; re-designing regulatory solutions to allow agile interactions between observational and interventional solutions; and co-creating solutions for moving the field forward by federating expertise (epidemiology, methodology, clinical trials, outcome research etc…).

Concluding, three core questions are posed: (i) how could we create an ecosystem for (ultra) rare cancers where the efficiency is better than the sum of its parts?; (ii) What could be the optimal datasets (design and end-points) which can be suitable for approval and access?; and (iii) How to structure the work of academic research in regulatory decision making and stimulate access to relevant new agents.

Generating the right data: randomized or not; observational or prospective?

Kit Roes, Chair of the EMA Methodology Working Party & Professor of Biostatistics, Radboud UMC.

How do we address the intended and unintended effects of therapy? Adverse effects are unintended and usually not associated with the indication, with observational evidence being strong. Randomised clinical trials deliver standardisation and quality of data, and allow the causes of effect to be identified and a proper estimate of variability / uncertainty. Single arm trials are self-standing, with the primary research question in the protocol aiming to be answered without integration of control data. The limited ability of single-arm trials to verify causality of treatment effects was addressed with key concepts the isolation of treatment effect, choice of endpoints and estimation of the treatment effect discussed. The importance of pre-specification of trial parameters and adherence to study protocols is essential when single-arm trial data is submitted as pivotal evidence, with assessment needing to comply with ICH E9 confirmatory trials standards.

Different designs of clinical trials were then presented, including non-randomised controls, hybrid designs, and trials within cohorts (TwICs), with relevant papers listed for each. The benefits of TWICs, as platform-based trials including randomisation, were high-lighted. While not an ultra-rare sarcoma, the case of ALS demonstrates how a hybrid trial design (randomised clinical trial plus registry) may increase efficiency. Disease description, trial design and eligibility criteria, results and the matching to external controls were all presented, with the hybrid design ultimately potentially allowing the trial to be terminated earlier.

Randomisation to the extent possible, and inclusion of adequate control groups in prospective designs is vital. A critical factor is to maintain the high level of scientific rigor that is associated with randomised clinical trials. It is also recognised that prospective high-quality registries and cohorts are of high value for many trial designs. In the case of ultra-rare sarcomas, the need to develop a framework and criteria to assess the relative credibility and uncertainty of more complex and innovative trial designs is crucial. Open and early discussion of alternative designs with regulators is important, rather than seeking general acceptability of a specific proposal once developed.

Lessons learned from the compassionate use program:

Valérie DENUX Director Europe & Innovation. ANSM.

The Special Authorisations Program, a framework established in France in July 2021, accelerates access to drugs for patients in need. The program includes three key compassionate use programs for drugs that are not yet fully approved and available for general prescription.

- The **Individual Compassionate Use Program (AAC)** is assessed on an individual case-by-case basis. Eligibility criteria, assessed by indication, were presented as well as through the Early Access Program (see below). Key elements of the AAC are available on the ANSM website. Details and statistics of all 2023 authorisations and oncology-specific authorisations under the AAC were provided, with more than 900 authorisations granted for paediatric cancer patients in 2023.
- The **Early Access Program (AAP)** utilises patient cohort evaluation. The AAP involves five different cohorts that are the effective eligibility criteria for the program and are evaluated by indication. Both hospital and general practitioners can include their patients in a cohort if they meet the conditions described in the Protocol for Therapeutic Use (PTU). Program statistics for the AAP were provided for the 180 decisions over the past two years which included 125 new products. On average, patients have access 11 months earlier to drugs through the early access system with clinical benefit before a price is published in one of the corridor countries.
- The **Compassionate Prescription Program (CPC)** involves off-label use of drugs that have not received a marketing authorisation from the appropriate regulators for the disease being considered. Four eligibility criteria for the CPC program were presented, with the program providing accelerated access to new indications. Again, both hospitals and general practitioners can prescribe CPC eligible treatments off-label so long as they meet the conditions specified in the PTU. A flow diagram of the CPC decisions was provided, recognising the likely 'drug repurposing' opportunity at the end of the process. The importance of reliable data collection to help in designing confirmatory clinical studies or trials in support of the repurposing process was high-lighted.

3.4. Session 2: How to establish a framework for ultra-rare sarcomas

How to collect retrospective data for the development of new treatment in ultra-rare sarcoma

Anna Maria Frezza, Medical Oncologist, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy;
J.V.M.G. Bovée, Pathologist, Leiden University Medical Center, Leiden, The Netherlands.

Dr Frezza asked why do we need retrospective studies in ultra-rare sarcomas? Analysis has identified 24 sarcoma prospective studies that were at least phase II of which only 9 were ultra-rare sarcomas. No drugs have been approved in the EU based on these studies. In addition, there were 23 retrospective studies that were collaborative and had more than 50 patients enrolled, of which 21 were ultra-rare sarcomas Retrospective studies are required to build evidence of medical therapies. In doing this they will inform clinical practice, encourage development of new clinical studies, can serve as external controls in single-arm prospective studies, and support regulatory approval of new therapeutics.

Dr Bovée explained that correct pathological diagnosis is particularly difficult in ultra-rare sarcomas and provided statistics relating to the diagnostic changes after pathological review and revision from initial diagnosis. Key criteria include pathological diagnosis being confirmed by an expert sarcoma pathologist in a sarcoma reference centre; agreement of essential diagnostic criteria for the URS subtype of the study; centralised pathology review for difficult cases; and the exclusion of all uncertain or questionable cases.

Accepting that retrospective studies are required, the next question is how these can be optimised. The importance of involving recognised sarcoma reference centres is essential. To maximise study optimisation other key factors are: (1) ensuring the quality of pathological diagnosis; (2) selection criteria for contributing centres; (3) radiological assessment of disease response and progression; (4) consistency in the frequency of disease monitoring across centres; (5) end-point selection; (6) avoidance of data duplication; and (7) results publication.

Dr Frezza presented an overview of the experience of the retrospective data collection relating to Sclerosing Epithelioid Fibrosarcoma and Low-Grade Fibromyxoid Sarcoma (SEF/LGFMS) undertaken from 2002 to 2022, involving 395 patients from 28 sarcoma reference centres, and which will be published in 2024. Lessons learned in this process will be incorporated into a new platform called PUSH, to ensure the efficient capture of quality data which could be used to support regulatory applications for ultra-rare sarcomas

Repurposing of old drugs in new ultra-rare indications: example of Sirolimus in EHE

Pan Pantziarka, Programme Director Drug Repurposing, Anti-Cancer Fund, Belgium; S. Marreaud, Clinical Trial and Development Lead, EORTC, Brussels, Belgium.

P. Pantziarka presented a schematic of key factors supporting sirolimus being active against epithelioid haemangioendothelioma (EHE). There is an unmet medical need for an effective treatment of the disease and a clear scientific rationale for its safe use repurposing of sirolimus for the treatment of EHE.

S. Marreaud outlined key facts in support of sirolimus, a recognised mTOR inhibitor, as a treatment for EHE. The molecular hallmark of EHE, oncogenic fusions involving YAP or TAZ, are involved in activation of mTOR complex 1. It was also noted that preclinical data regarding the comparative activity of doxorubicin (a drug approved for soft tissue sarcoma) and sirolimus in EHE, showed that sirolimus induced an 80% tumour volume inhibition while the effect of doxorubicin was negligible. In terms of clinical data, there is no prospective data available at the current time, although a prospective registry study involving Italy and the UK is on-going. Retrospective data includes an Italian study with 38 patients (including 13 with serosal effusion) with progressive disease at baseline. No Grade 4-5 toxicity was observed.

P. Pantziarka presented a schematic summarising the 2023 repurposing pilot experience There are two potential ways forward to repurposing. The first is to collect prospective data, agreed via a scientific advice process, and hence to a label extension (type II variation). The second pathway recognises that the collation of a full data package is not possible and would therefore engage with the EMA's Exceptional Circumstances procedures. A key obstacle in both pathways is the absence of the Marketing Authorisation Holder (MAH) for the existing approved form of sirolimus. The need for an MAH to be engaged and to make the application remains a major impediment to drug approvals for ultra-rare sarcomas as the profit potential of these drugs is low, and there is little commercial interest from MAHs.

For this reason, the forthcoming European pharmaceutical legislative changes, and in particular the proposed Article 48 allowing academic/patient advocacy led applications, are seen as critical.

Prospective studies in ultra-rare sarcomas: nab-sirolimus in PEComa as an example

Andrew Wagner, Associate Professor, Medicine, Harvard Medical School and Senior Physician, Adult Oncology, Dana-Farber Cancer Institute, Boston, US.

Dr Wagner gave a high-level description of Perivascular Epithelioid Cell Tumors (PEComa), together with an explanation of how the disease interrupts the mTOR signalling pathway. Similarities of PEComa to LAM/AML and reported activation of the mTOR pathway led to the off-label use of mTOR inhibitors to treat

patients with advanced disease. A number of papers reported the treatment of PEComa with mTOR inhibitors, including sirolimus and temsirolimus, between 2010 and 2014.

A prospective study of nab-sirolimus in malignant PEComa was carried out between April 2016 and November 2018. This phase II, single arm, prospective trial was the first ever prospective clinical trial in this disease, involving 31 patients with advanced disease across 9 trial sites in the USA. Results from the trial showed both maximum target tumour reduction (%) and change in target tumour measurements (%).

Key factors that had led to the trial being successful and the efficacy of the drug being demonstrated. Firstly, the trial involved both a commonly altered pathway and a tolerable drug; secondly the associated pharmacological company was willing to conduct the study in this ultra-rare disease; and thirdly the activity of nab-sirolimus was demonstrated by significant tumour shrinkage. However, it was recognised that in ultra-rare sarcoma trials with other drugs, it was likely that tumour size reduction would not occur, and instead the target responses sought would be the control and stabilisation of tumours and/or symptoms.

Prospective registries

Annalisa Trama, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy.

The EURACAN Registry will initially focus on three of categories of cancer: sarcoma, head and neck cancers, and rare thoracic cancers. There are four key objectives for reach disease are: (i) to describe the natural history; (ii) to evaluate factors that influence prognosis; (iii) to assess treatments effectiveness; and (iv) to measure indicators of quality of care. The Registry will also collect information on the storage of biological samples and imaging at the participating centres. Comprehensive data elements have been developed using international standards, data dictionaries and will also integrate data from available databases and existing alliances, examples of which were presented. Registry quality assurance will focus on conformance (using agreed formats), completeness (no missing elements), and plausibility (the data should be believable). The difference between centralised and federated registries was also explained with preference being for a federated structure for this large scale, multi-institutional project involving multiple European states. Key factors to maximise quality assurance in the federated structure were outlined at both the health care provider level and the centralised management and project coordination level.

Governance is outlined in a public document clarifying the rules and procedures to access and manage the registry data. Data access rules are of particular importance High-level GDPR requirements were also noted with recognition that these may be country specific. The importance of data privacy and the role that federated learning, a machine learning technique that trains an algorithm across multiple decentralized devices or servers holding local data samples, without exchanging them, were high-lighted. It was confirmed that the EURACAN EHE registry is now open.

A prospective master protocol / platform to conduct international multicentric single-arm studies in ultra-rare sarcomas including real world data for external comparisons

Lorenzo D'Ambrosio, Department of Oncology, San Luigi di Orbassano, Turin, Italy; Gautier Bouche, Anti-Cancer Fund, Belgium; Rosalba Miceli, Director of Biostatistics for Clinical Research Unit at Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

The global aim of the PUSH (Pushing Ultra-rare Sarcomas towards Hope) platform is to maximize the knowledge gained from every single ultra-rare sarcoma patient to support developing new treatments and improve outcomes and quality of life. Listeners were reminded of the challenges created by the rarity and heterogeneity of ultra-rare sarcomas, and the global need to find solutions.

The PUSH platform needs to be faster, more agile, attractive to participants and able to accommodate multiple different arms and structures. The master protocol which is being developed, will provide a common framework and governance, include pre-defined design hypotheses and address issues such as ethics, data management and IT issues. Lying underneath the Master Protocol will be one or more PUSH-IT (PUSH international trial) studies, which may or may not be histotype-specific. The PUSH platform can ultimately deliver a wide range of different studies, including investigational, natural history, and observational studies.

Specific issues that face ultra-rare sarcomas were highlighted. These include the likelihood that expected ORR results may be low, so that there is an urgent need to exploit all available data to improve evaluation of drug activity. There is a need to identify and define appropriate external control groups. Examples of how control groups might be structured were presented for a multi-centred global platform such as PUSH. Different sources of control data were also listed and included data from patients, genomic and molecular data, academic chart reviews, previous trials and real-world data. Examples of two study structures were then presented. The first involved an investigational prospective, open-label phase 2 trial with an external control made up of prospectively collected data in the same population treated as per normal standard of care. The second was a small scale randomised clinical trial with both specialised design and statistical analysis structured for a specific disease.

The development of the PUSH Platform is ongoing with a focus on: (i) exploiting all its potential; (ii) maximizing the knowledge gained from each patient; (iii) looking for innovative approaches; and (iv) providing a starting point for other rare tumours.

NCI childhood Cancer Data Initiatives

Brigitte Widemann, Chief of the NCI Center for Cancer Research Pediatric Oncology Branch and special Advisor on Childhood Cancer to the NCI Director, US

Dr Widemann started with a definition of rare cancer as one with < 15cases per 100,000 people/year. This encompasses 25% of adult cancers and all pediatric cancers. Very rare cancers are defined as < 2 cases per million of population. Overall, based on accepted definitions of ultra-rare cancers (CTOS and Orphanet) there are at least 222 ultra-rare tumours of which around 60 have characteristic molecular alterations, including fusions and disease-causing germline or somatic mutations.

MyPART (My Pediatric and Adult Rare Tumor Network) is focused on rare solid tumours affecting children, teens, and young adults (<39 years old). A summary of the MyPART Natural History Study of Rare Solid Tumours was presented, including its objectives, participants, and key deliverables. MyPART also recognises that to make progress a national/international effort is needed. Multiple examples of actions taken and partnerships developed such an international effort were presented.

Other NCI/NIH initiatives include the NIH Rare Tumour Clinics, and a phase II trial in SMARCB1 or SMARCA4 deficient tumours.

Rare tumor experience shows that advocacy and rare tumor expertise are critical in managing these diseases. Disease insights cannot be gained through single patients, yet the building of meaningful cohorts is both resource and time intensive. Focusing on select tumour types is needed to accrue sufficient patient numbers, while partnerships with all stakeholders will be critical to accelerate progress in rare tumours. This has led to NCI Childhood Cancer Data Initiative realisation and vision that a national/international effort will allow enrolling adequate numbers of participants to more rapidly, efficiently, and consistently study multiple rare cancers. Further examples of initiatives to deliver such a vision were presented, including the CCDI Molecular Characterization Initiative (MCI), and the CCDI-Coordinated Rare Pediatric/AYA Tumor Study.

The NCI's "Champions" initiative is an example where Disease Champions across the USA, together with advocacy and research partnerships can focus on disease-specific data collection. International collaborations include the NCI-European Union collaboration bringing together the EU Beating Cancer Plan and the NCI Cancer Moonshot / National Cancer Plan.

In conclusion, the NCI/CCDI is working to create the foundational infrastructure for data collection and sharing to benefit pediatric and AYA cancer patients.

FDA Perspectives on Rare Cancer Drug Development

Caitlin Tydings, MD Clinical Reviewer, Division of Oncology 3 Oncology Center of Excellence

Using the NCI definition of fewer than 15 cases per 100k/year, 25% of adult cancers are rare. Recent approvals of drugs for sarcomas show 11 approvals over the past ten years. Common challenges to such approvals include low patient numbers and wide geographical dispersion resulting in limited access to molecular testing. The natural history of these heterogenous diseases is often poorly understood, and there are significant challenges to randomisation of trials and difficulty in assessing response.

The Oncology Center of Excellence (OCE) has initiated a number of programs to address these challenges.

The **Rare Cancer Program** seeks to leverage multiple OCE projects to address the challenges of developing new treatments for cancers that affect a small number of patients. Through collaboration the Program seeks to decrease obstacles, harness scientific knowledge, and strengthen coordination.

Project Catalyst fosters early-stage oncology product innovation and development, facilitating scientific discussion, education, guidance, and regulatory engagement. The Project focuses on academic life science incubators and accelerators as well as small pharmaceutical companies, with access to regulatory expertise and guidance.

Project Pragmatica promotes functional efficiency and patient centricity. It also strives to integrate aspects of clinical trials with real-world routine clinical practice.

The **Oncology Real World Evidence Program** was established to advance the appropriate use of real-world evidence in oncology product development to facilitate patient-centred regulatory decision-making.

Project Significant provides a platform to participate, discuss, and advance the science of oncology trial designs while promoting non-product specific scientific discussions on design and analysis of cancer clinical trials, and so fostering broad stakeholder collaboration.

Project Orbis is a multi-national collaborative review program where an FDA review provides for independent multi-disciplinary assessment including full review of datasets. Current participants include the USA, Australia, Brazil, Canada, Israel, Singapore, Switzerland, and United Kingdom.

Opportunities for international collaboration were also outlined.

The development of drugs to treat rare cancers can be challenging, typically requiring more frequent and earlier multidisciplinary engagement with the FDA. A global approach including broad stakeholder engagement and collaboration is also critical.

3.5. Panel Discussion:

All speakers with additional panellists:

(i) Martha Donoghue, Associate Director of Paediatric Oncology and Rare Cancers, FDA
(ii) Hugh Leonard, Chair of The EHE Rare Cancer Charity, UK

(iii) William Tap, Chief, Sarcoma Medical Oncology Service, Memorial Sloan Kettering Cancer Center, New York, US
(iv) Wim Oyen, Nuclear Medicine Physician, Arnhem, The Netherlands

The panel discussion addressed the following three key topic areas:

1. Research question and the end-points to use to establish efficacy;
    - What are optimal endpoints? Other end-points than RECIST ORR for mall SAT?
    - What magnitude of benefit is required?
    - How do we demonstrate efficacy when tumours are controlled (but do not shrink) and when randomisation is not feasible

2. Research question and the study design to use;
    - How do we improve the methodology of data collection and use high-quality, pre-defined retrospective studies as control data for non-randomized prospective studies in URS?
    - How do we get the best of the 2 worlds observational and interventional for (ultra) rare cancers?
    - What constitutes suitable external/historical control(s)?
    - How could data from registries complement studies such as those conducted in PUSH-IT and play a role in the regulatory assessment?

3. How to create a framework for developing rare cancer medicines.
    - How could we create an ecosystem for (ultra) rare cancers where the efficiency is better than the sum of its parts;
    - How to structure the work of academic research in regulatory decision making and stimulate access to relevant new agents?
    - Discuss and develop the PUSH-IT project.

Dr. Demolis noted that the first topic contained questions raised by the investigators and required a response from the regulators; the second topic required responses from all parties; and the third was for the entire audience but did require response from the regulators also.

Research questions and the endpoints to use to establish efficacy

The discussion was focused on the importance of endpoints in demonstrating efficacy and clinical benefits for rare sarcomas and how activity is assessed when tumours do not shrink. It was said that not one best endpoint exists, but that overall survival and progression-free survival are preferred in randomized trials, while response rate is reliable in cases where randomized trials are not feasible. Furthermore, in cases of no tumour shrinkage, satisfying endpoints are very much needed. Duration of response, clinical significance, and natural history of the disease are important factors to consider in assessing treatment response.

There was a general agreement on the need for regular discussions to address these issues and develop a framework for developing rare cancer medicines. EMA is interested in off-patent drug but someone must take responsibility for marketing these drugs.

A survey will be distributed to gather views on forward priorities and a report of the meeting will be prepared. Additional topics such as compassionate access to drugs and digitalization of data were raised as valid topics for future meetings.

4. Consensus and way forward

P. Demolis (EMA) and S. Stacchiotti (EORTC): Joint Chairs of the Workshop

Need for research question, endpoints and study design to use to establish efficacy

Dr Demolis confirmed the need for investigators to produce standardised high-quality collections of clinical and biological data, with the regulators assistance to be sure that this meets the regulatory requirements. This will be discussed on a case-by-case basis and the EMA have a duty to offer a forum for such discussions also on a case-by-case basis, addressing: which end-points are required; how we can rely on external data; how we can collect prospective data; is a given registry the best form; and is a prospective collection organised the way EMA would like to see it, responding to some given projects.

At the same time, the regulators will engage in discussions to find the most adaptive and flexible solutions to deliver these meetings. It cannot be the classical scientific advice procedure, and it is not the PRIME process or the ITF. EMA has some tools, but these tools must be combined to create something that cannot be as rigid as the other tools. EMA would be starting the internal discussions immediately.

Solution must be found for small and orphan conditions which are conditions that are too rare to have industry interested in them but then industry does become interested. In the case of ultra-rare sarcomas it is more than 'orphan', as industry may never be interested. Article 48 may be a solution, but we need to be creative to avoid the very disappointing result where a good question that could benefit the patients in a crucial condition, with a very poor prognosis, and the right questions have been addressed in the right development but nobody will take responsibility for putting the treatment into the market so that the solution is not available. We must find a solution. This is a longer-term project as laws don't change easily, but a solution must be found for many situations described today.

How to create a framework for developing rare cancer medicines

Dr Demolis confirmed that EMA will consult and will come forward with proposed solutions that meet stakeholders' requirements. Whatever solution is initially proposed, it will be submitted for stakeholder feedback and suggestions and approval. A survey will be issued where the priorities and suggestions of workshop participants can be indicated. This is the first step in an engagement to deliver better procedures to address the problems of academia, patients and regulators, with the priority being patients.

Dr Stacchiotti then thanked Mr Demolis for EMA's initiatives like the EMA repurposing pilot to help ultra-rare diseases. It was also excellent to have heard new ideas during the workshop about new ways to meet and discuss issues. The sarcoma community want to develop global collaborations such as PUSH at multiple levels, and will involve EMA and other regulators as appropriate, initially as an observer or advisor to help optimise what is done and take the best from the combined energy and enthusiasm of working together. Dr Stacchiotti closed by thanking all the virtual participants for their interest and input.