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How to foster new treatment development in ultra-rare tumours? Joint EMA-EORTC multi-stakeholder workshops on ultra-rare sarcomas as a model for rare cancers

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ABSTRACT

Ultra-rare sarcomas (URS) and ultra-rare cancers (URC) represent a unique challenge in oncology due to their rarity, heterogeneity, and the severe unmet clinical needs of affected patients. In 2024, the European Medicines Agency (EMA) and the European Organisation for Research and Treatment of Cancer (EORTC) convened two multi-stakeholder workshops, bringing together regulators, clinicians, researchers, and patient advocates. These workshops aimed to explore innovative strategies for treatment development and establish a framework for future collaboration.

Key issues were discussed, including the scarcity of biological and clinical data, major barriers in conducting randomized trials, and limited pharmaceutical investment. A key outcome was the unanimous commitment of all stakeholders, including regulatory agencies such as EMA and the U.S. FDA, to work together towards pragmatic solutions. Participants recognized the necessity of flexible regulatory approaches, alternative trial designs, and meaningful endpoints tailored to ultra-rare conditions. The workshops also highlighted the importance of global collaboration, early regulatory engagement, and leveraging existing mechanisms like orphan drug designation and conditional approvals.

The discussions emphasized that while scientific rigor must be upheld, regulatory frameworks must adapt to the specific challenges posed by URS. Stakeholders pledged to maintain open dialogue, share expertise, and develop innovative infrastructures to accelerate progress.

This collaborative commitment marks a critical step forward in addressing the high unmet needs of URS. By fostering a unified effort among diverse stakeholders, the workshops established a model for advancing treatments in other URC, prioritizing patient outcomes while navigating the complexities of drug development for these challenging diseases.

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 two workshops, on 12 January 2024 and 24 May 2024, to discuss issues relating to the development of new treatments for ultra-rare sarcomas (URS) and ultra-rare cancers generally.

These workshops included participants from academia, clinical practice, patients, non-profit organisations, and medicines regulators to explore questions related to the development of treatments for URS as a use case for ultra-rare cancers.

Specifically, the aims of the workshops were to:

- Highlight the unique challenges that ultra-rare cancers face, and the perception of risk of regulatory failure and associated costs that impede engagement of investors and industry in new drug development.
- Describe the high unmet medical needs of URS and ultra-rare cancers.
- Discuss the development of treatments in the rarest cancer types, using URS as a model.
- Increase global collaboration.
- Help recognise the need for changes to regulatory approaches and understanding of available regulatory pathways.
- Discuss appropriate forms of data generation and study design to accommodate the rarity of the disease.
- Develop a framework for regular meetings between URS stakeholders and regulatory agencies to foster collaboration on innovative approaches and clinical studies for ultra-rare cancers.

Of note, while rare cancers are defined in Europe as malignancies with an incidence of $< 6/100{,}000$ individuals/year, there is not a uniform definition for "very rare cancers", with the exception of very rare pediatric cancers, defined as pediatric malignancies with an incidence of $< 2/1{,}000{,}000$ individuals/year [1], and URS, recently identified as sarcomas with an incidence of $\leq 1/1{,}000{,}000$ individuals/year [2]. The cut-offs identify histological types so rare that conducting traditional randomized studies becomes significantly challenging for developing new treatments as compared more common malignancies. Therefore, even in the absence of a formal definition, these workshops were conducted with reference to all ultra-rare tumours, including sarcomas, with an incidence of approximately $\leq 1/1{,}000{,}000$ individuals/year as these diseases share similar challenges in the development of, and access to new treatments.

The workshops were a joint collaboration between the EMA, the United States (US) Food and Drug Administration (FDA), and stakeholders from and invited by the EORTC STBSG. This manuscript presents a thematic report from the meetings in which guiding principles and consensus understandings were established.

Methods

This is a summary of the meetings jointly organised by EMA and the EORTC STBSG, in January and May 2024, hosted by the EMA in Amsterdam, the Netherlands. The meetings, titled "*How can we develop new treatments in URS, as a model for ultra-rare tumours?*", were chaired by P. Demolis (EMA) and S. Stacchiotti (EORTC STBSG). Agendas are available in the Supplementary Data 1 and 2. Full reports and recordings are available on the EMA website (Workshop 1: https://www.ema.europa.eu/en/events/ema-eortc-multi-stakeholder-workshop-soft-tissue-bone-sarcoma; Workshop 2: https://www.ema.europa.eu/en/events/follow-ema-eortc-multi-stakeholder-workshop-soft-tissue-bone-sarcoma).

The workshops were conducted in a hybrid format, allowed virtual public participation and involved stakeholders invited by EMA and EORTC. Participants represented sarcoma research and care in EU and US in recognition of the need for extended geographical involvement due to the rarity of the diseases being discussed. Specialists participating represented pathology, epidemiology and statistics, surgery,

radiotherapy, medical and pediatric oncology, and palliative care. Additional attendees included patient representatives, not-for-profit organisations, and regulators.

Presentations were followed by open discussion and addressed the following topics:

- Regulatory structures, programs and capabilities;
- Challenges and opportunities from the patients' perspective;
- Challenges in gathering and evaluating data and generating regulatory quality evidence;
- Benefits of an integrated Special Authorisations Program;
- Different forms of data capture, including retrospective data, clinical registries and childhood cancer data initiatives;
- Drug repurposing and rare cancer drug development;
- Several presentations focused on specific ultra-rare tumour types to illustrate over-arching challenges and potential solutions to develop new treatments. Presentations were not intended to address drug development in any specific ultra-rare cancer type.

The open discussion included many contributions from the meeting participants, including online participants, in addition to the panellists and speakers.

Challenges in developing new or repurposed therapies for URS and ultra-rare cancers

During the workshops, there was a high degree of concordance of the key challenges in developing treatments for ultra-rare cancers from all stakeholders, including:

- Limited data on the biology, natural history and patient experience for the majority of ultra-rare cancers.
- Extreme difficulty in accruing a sufficient number of patients to clinical trials and higher costs, limiting the feasibility of randomised studies, required to meet regulatory approval standards.
- Limited clinician and academic experience with regulatory processes and unclear requirements. Low pharmaceutical interest and investment due to small market size, and challenges in meeting evidence standards for approval and reimbursement.
- The need for flexibility beyond traditional endpoints such as overall response rate (ORR) and duration of response (DOR) by Response Evaluation Criteria in Solid Tumours (RECIST) for evaluating treatment benefit and exploration of alternative endpoints to better capture meaningful clinical outcomes.

These challenges apply to all ultra-rare cancers including sarcomas where > 75 different tumour types have an incidence of < 1 case/1,000,000 individuals/year [2]. While URS account for 20 % of all patients diagnosed with sarcoma [2], < 10 active systemic drugs (i.e., active ingredients) are currently approved and available in the European Union (EU) and in the US for their treatment, representing a substantial unmet clinical need [3]. Yet, meeting this need can be hampered by rigorous evidence standards and frameworks developed over many decades in more common diseases which may not be suitable for ultra-rare conditions.

EMA and FDA confirmed they are committed to addressing these challenges. P Demolis from EMA presented several specific tools available for this purpose, illustrated in Fig. 1, including the Innovation Task Force (ITF); orphan drug designation; scientific advice; Priority Medicines (PRIME), and marketing authorisation under exceptional circumstances as well as conditional market authorisation.

The established use of EMA's tools for drug development was recognised, but regulatory processes must be adapted to their unique challenges.

Nevertheless, it was also highlighted that a lowering of standards is seen as a particular risk. Scientific standards, methods and quality of data should not be compromised, even in extremely rare diseases, and adequate efforts should be made to generate the required evidence. Randomised clinical trials remain the gold standard, and developers should aspire for this level of certainty in rare cancer populations when

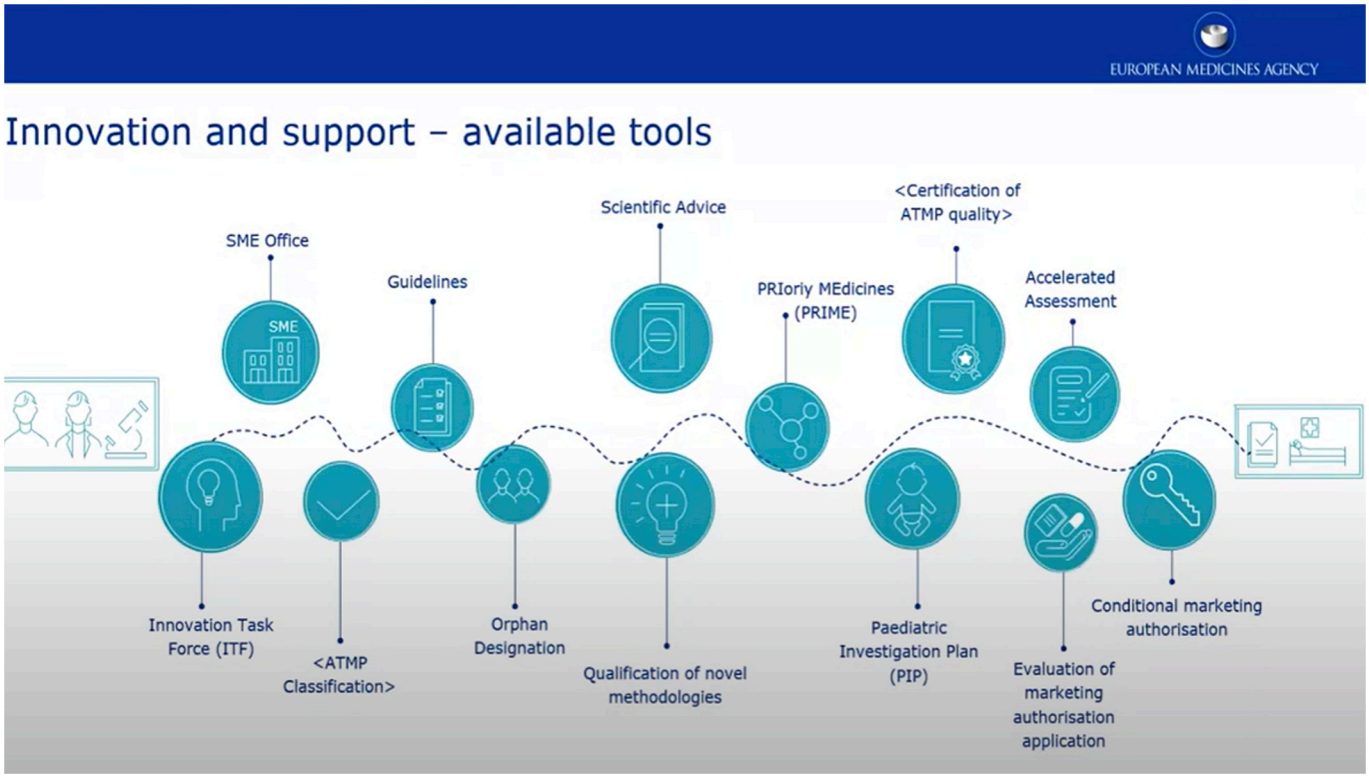

Fig. 1. Tools available at the European Medicines Agency (EMA) to support the development of medicines for rare and challenging conditions.

possible. However, there was a general and shared agreement that for ultra-rare diseases undertaking randomised trials is challenging regarding hypothesis-based generation, assessment of clinical benefit and recruitment. Participants confirmed that from a regulatory perspective, alternative forms of evidence can be considered, including uncontrolled prospective studies and retrospective data, provided an acceptable level of quality evidence can be achieved while recognising that this will result in a higher level of uncertainty. The issue of what level of data will be considered acceptable was raised and it was agreed that this is difficult to generally define in advance and needs to be assessed on a case-by-case basis depending on the specific trial under consideration. Ultimately it was recognised that the prospective collection of observational data, and the prospective definition of use of observational data, both provide superior data with less uncertainty than retrospectively defined uses of data. However, retrospective data and non-parallel controlled studies, although having several intrinsic limitations, can support evidence generation. In certain cases—such as when high-quality data are provided with robust analyses, and demonstration of large treatment effect sizes—retrospective studies can still provide valuable evidence and can also be useful in designing clinical studies or defining historical control groups.

Diseases with high unmet medical needs, which is often the case for rare cancers, can also be considered for marketing authorisation under exceptional circumstances or conditional approval in EU, a provision that allows a decision on the basis of non-comprehensive clinical data provided certain requirements in terms of unmet need and subsequent evidence generation, are met.

Early and frequent engagement with regulators is crucial to developing evidence-generating plans that addresses the need to provide sufficient evidence of safety and effectiveness to support regulatory decision-making, while at the same time meeting the needs of patients. Proactive data collection and adherence to scientific and regulatory guidance can expedite approvals. By anticipating scientific and regulatory requirements, applicants can generate data proactively and deliver quality results sooner. Participants confirmed the existence of regulatory agencies' procedures for advice and interaction with academia to engage in ongoing conversations with applicant companies and academia to facilitate this process and ultimately benefit patients.

From the patients' perspective, urgency is crucial in the search for effective treatments. Patients with URS are fighting progressive diseases today with very few efficacious treatments available, necessitating prioritisation of ways to deliver active drugs more quickly. Limited pharmaceutical investments, treatment accessibility inequalities across regions, particularly within EU, and challenges with using RECIST for certain sarcomas were emphasised. However patient communities are highly motivated and seek tailored processes to address their specific needs and generate sufficient evidence for an acceptable benefit/risk balance. Drug repurposing, assessing approved drugs for new indications, is a promising pathway to treatment options where none exist.

Methodology & evidence generation in ultra-rare cancers

Scientific methodology and data-related questions were central concerns of nearly all speakers and meeting moderators emphasising the need to balance rigorous standards with the urgency of making progress despite limited patients and high uncertainty.

Trial designs

The primary goal of drug evaluation is assessing the benefit/risk balance for the drug, alongside uncertainty, which in combination can support a marketing application. Robust evidence is primarily derived from prospective randomized trial data and it is acknowledged that there are methodological limitations which exist for single-arm trials or observational studies.

One of the main challenges is how to best characterize the intended and unintended effects of therapy when randomisation isn't feasible and robust controls do not exist. Pre-specification of trial parameters, appropriate endpoints and adherence to protocol is crucial for minimising biases and ensuring consistency, transparency, and reliability of outcomes. Obtaining patients' baseline data and medical history, including prior treatment, is also important. Participants highlighted the need for methodological innovation and novel trial designs to address these issues concretely. A number of designs were mentioned as potentially applicable in the context of ultra-rare cancers, including non-randomised controls, hybrid designs, and trials within cohorts (e.g., TwICs). Prospective high-quality registries, with high-quality data capture and adequate cohort size, are valuable for many trial designs and support treatment development for ultra-rare tumours. Prospective registries can inform natural history of diseases, and generate evidence from off-label drug use useful for drug repurposing efforts. Alternative designs should be developed in an early phase, with close collaboration between regulators, researchers/clinicians and patients. The level of scientific rigor required and how this is generated must be assessed case-by-case, considering the complexity involved. Evaluating all available data for URS requires flexibility beyond traditional designs. Stakeholders must be open to adapt past practices and newer methodologies.

Data sources

Stakeholders agreed that processes for evaluating treatments in ultra-rare cancers should be developed or refined to consider all available data, providing guidance on their utility. Clinical scientists and regulators must align on acceptable standards to inform future study designs.

All parties agreed that retrospective data play a crucial role in evidence generation to support medical product development, by informing and supporting hypotheses. Even with maximal efforts for prospective data collection (e.g., as part of usual care), retrospective data remain a valuable source. Clinicians highlighted efforts in the sarcoma community to improve and maximise the quality of retrospective data. As an example that could be expanded to other groups as well, the sarcoma community has produced a consensus paper that lists the minimum criteria for conducting high-quality retrospective observational studies and optimising retrospective data collection in URS, including year of diagnosis, confirmed pathological diagnosis by expert pathologists, centralised review for challenging cases, and consistent radiological assessments across centres [4]. Study optimisation should also consider excluding uncertain or questionable cases from the analysis, appropriate end-point selection and evaluation; the avoidance of duplication of data; and publishing all – including negative – results. An example is a 2022–2023 retrospective study on two ultra-rare sarcomas, namely sclerosing epithelioid fibrosarcoma and low-grade fibromyxoid sarcoma, involving 395 patients treated over 20 years at 28 centres, illustrating the long timelines required for sufficient data in such cases [5,6]. Throughout this entire period, clinical decisions of systemic treatment for patients with these ultra-rare sarcomas could only be guided by limited data, primarily from very small series including fewer than 10 patients [7]. It is hard to reconcile such time scales with the "urgency" imperative expressed and acknowledged by workshop participants.

In the case of URS where randomised trials are unfeasible, data collection via prospective registries was also agreed to be a major data source. The EURACAN registry is one example. The four key objectives for each disease included in the registry are to describe natural history, evaluate factors that influence prognosis, assess treatment effectiveness, measure quality of care. The registry includes biological samples and imaging data. Comprehensive data elements have been developed using international standards and data dictionaries. Quality assurance will focus on conformance (using agreed formats), completeness (no missing elements), and plausibility (the data should be reliable). Governance is outlined in a public document clarifying the rules and procedures to

access and manage the registry data, and is centrally managed. The EURACAN rare head and neck cancers, and sarcoma, including epithelioid hemangioendothelioma (EHE) registries are currently open [8].

Compassionate Use Programs can also generate valuable prospective data while providing patients access to drugs under similar treatment protocols. Such programs should include capture of outcomes data from patients, which may be considered by regulators to assess the benefit/risk for new indications and to complement limited data available from prospective clinical studies. An example is the Special Access established in France in July 2021 [https://www.insideeulifesciences.com/2021/07/06/new-early-access-and-off-label-use-rules-in-france/].

Data from patient associations can supplement clinical evidence, capturing lived experiences and perspectives [9]. These data may be collected within patient registries or surveys and may or may not provide the same rigor as clinical data; however, they are valuable in assessing the treatment accessibility, acceptability and effectiveness from the voice of the patient.

Endpoints

Overall survival (OS) or progression-free survival (PFS) investigated in randomised trials are the most convincing endpoints to assess the efficacy of a new treatment. Where randomised trials are not feasible and single-arm trials are run, ORR and DOR using standard radiological criteria is usually preferred. However, regulators pointed out that there is no one-size-fits-all answer when considering efficacy endpoints. A combination of endpoints rather than a single endpoint may help in the understanding of effectiveness. What degree of response can be assumed to be clinically meaningful varies by situations, and while complete tumour regression (i.e. complete responses), higher ORR, and longer response durations are preferred, even low response rates with clinical outcome assessment measures demonstrating patient benefit may help establish effectiveness. For instance, endpoints such as disease stability and its duration may also be relevant, as they can indicate sustained control over disease progression and contribute to evaluating treatment success when information on disease's natural history is known. Importantly, regulators confirmed their support for the scientific community assessing new approaches or endpoints better suited to reflect treatment efficacy for rare diseases and meet urgent unmet patients' needs.

Formal regulatory feedback on new approaches may also be sought through formal meetings with regulatory authorities and other established regulatory frameworks.

Perspectives and experiences from ultra-rare Sarcomas

Several examples were discussed to draw learnings from the experiences

Among others, the EMA pilot program in drug repurposing was mentioned as an extremely useful project, promoting interaction among parties, sharing problems, highlighting common needs and desires to find solutions that allow access to active drugs for indications where no drugs were previously approved [10]. The repurposing pilot was an EMA initiative that explored issues in repurposing generic medications for new indications, including cancers. For ultra-rare cancers, an example was the URS EHE, for which the candidate drug is sirolimus. The scientific advice process, involving clinicians from the EORTC STBSG, researchers, not-for-profit organizations and patient advocates explored issues around data and suitable endpoints for a disease where available data are only retrospective, randomisation is unfeasible, and standard radiologic criteria, such as RECIST, fail to capture response to treatment and patient's benefit. Indeed, RECIST focuses on changes in tumour size as the main indicator of treatment activity. However, many cancer therapies, e.g. immunotherapies and targeted treatments, show beneficial effects without significant tumour shrinkage. Since the mid-2000 s, examples like GISTs treated with imatinib showed that response criteria like Choi, which account for densitometric changes, correlate with outcomes more effectively than RECIST [11,12]. In URS like EHE, disease progression and treatment response are often marked by serosal effusions or symptom changes that reflect disease behaviour more accurately than alterations in solid lesion size. These aspects are not captured by RECIST, making it inadequate for accurately assessing treatment response. The pilot program fostered engagement among all partners, enhancing academia and patients' understanding of the regulatory pathway, and guiding data collection to complement available evidence.

Under the currently EU regulatory framework, only a marketing authorisation holder (MAH) can apply for a label extension for a new indication. In other words, even with favourable regulatory evaluation, label extension is impossible without MAH action. This may change in the future in light of proposed changes to the pharmaceutical legislation in the EU [13], particularly article 48 of the new EU Regulation, which allows not-for-profit entities to submit non-clinical and clinical evidence for new indications addressing unmet needs. A favourable opinion would oblige the MAH to submit a variation to update product information.

The willingness of the MAH to cooperate was critical for FDA approval of nab-sirolimus for the URS perivascular epithelioid cell tumour (PEComa). The development of nab-sirolimus in PEComa demonstrated the feasibility of approving a drug for an ultra-rare malignancy via a single-arm Phase II study involving "only" 31 patients. In this case, the fact that the traditional dimensional endpoint, i.e. RECIST ORR, was considered suitable for evaluating the benefit of the treatment in this specific tumour type was a major point [14]. This was possible, among various factors, thanks to the precise definition of the mechanism of action/target of the drug under investigation, it aligns with the genomic alteration of the disease, the high proportion of objective dimensional responses, as well as the availability of data on the natural history of the disease, particularly about PEComa aggressiveness without therapy and conventional sarcoma treatment inefficacy. However, RECIST limitations are evident in tumours like EHE, where responses involve stabilization or symptomatic relief without significant dimensional regression.

Even though the story of a single patient can provide valuable insights into ultra-rare diseases, the National Cancer Institute (NCI) experience teaches that the natural history of a disease cannot be fully characterized based on a single case; yet the building of meaningful cohorts is both resource and time intensive. Focusing on selected 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 the NCI Childhood Cancer Data Initiative and recognition that that a national/international effort is required to enable enrolment of adequate numbers of participants to more rapidly, efficiently, and consistently study multiple rare cancers.

Many issues that apply to URS are common to developing pediatric oncology medications. Experiences of the ACCELERATE program, particularly the Pediatric Strategy Forums (PSF), are relevant to advancing new drug development and serve as a model [15]. ACCELERATE is an international, multi-stakeholder, not-for-profit organisation promoting drug development for childhood cancers [16]. PSFs are multi-stakeholder meetings, in a pre-competitive setting, with open dialog and dedicated to a specific childhood cancer or class of compounds. Meetings include representatives from patient advocacy, clinicians, researchers, industry, and regulators (mainly the EMA and FDA). Notably, regulators are active organisers and participants, not simply observers, although no formal regulatory opinion or advice is provided at these forums. All stakeholders are equal partners, and a high-level of trust exists – the motto is "no blame, no shame". Regulator involvement is a key factor for success. The PSF aim is to share information among stakeholders, evaluate the science, and inform pediatric cancer drug development. There have been 12 PSFs to date, and while competing interests from different stakeholders exist, the meetings have been

positive with a high-level of collaboration. Metrics indicate PSFs have positively impacted pediatric cancer drug development [15].

A recent initiative has been developed with similar aims to ACCELERATE for the URS global community. The PUSH (Pushing Ultra-rare Sarcomas towards Hope) project (http://www.push-platform.org/) aims to maximize the knowledge gained from every single patient with URS to support new treatment development and improve outcomes and quality of life. PUSH aims to deliver a wide range of study designs, both retrospective and prospective, including investigational, and observational studies for multiple URS types. Key issues include incorporating real-word data (including retrospective and prospective observational registries and/or studies), developing response criteria to record drug activity when standard response criteria are not appropriate, and suitable control arms for interventional studies exploiting the role of external comparisons. The plan is to develop this platform as extensively as possible in collaboration with regulatory agencies, in order to generate evidence to effectively supports the approval of new treatments.

Areas for future development

Over the two workshops, broad agreement was reached on many important issues, summarised as follow:

1. Patients with URS, and ultra-rare cancer in general, face severe and urgent unmet need for new treatments due to their rarity, complexity and severity;
2. Regulators recognise the challenges of ultra-rare cancers and commit to exploring new flexible, adaptive regulatory processes and procedures, and to engaging in proactive dialogue, and supporting treatment development where feasible;
3. Academics and patient advocates of ultra-rare cancers are exploring the development of new infrastructure to allow efficient global engagement of clinicians and patients with such diseases, including access to regulatory understanding and skills through appropriate regulatory involvement;
4. Randomised trials are preferred but challenging for small populations such as those represented by ultra-rare sarcomas. Notwithstanding their inherent limitations, there is a need to consider alternative types of data. These can include clinical trials with non-randomised controls, prospective observational studies (with or without concurrent control data) and retrospective data. Depending on the evidence and decision setting, the totality of data may be sufficient to support regulatory decisions, despite the larger uncertainties involved;
5. Lowering scientific standards should be avoided. However proactive discussion between, and careful use of decision-making by, all parties that adequately manages uncertainties can be useful in situations of high unmet needs where comprehensive clinical data are not available;
6. Applicants and regulators, are encouraged to develop an evidence generation plan to fully assess all available data, agree if additional data are required, and how these should be collected. In particular, the approach to prospective evidence generation and careful consideration and balance of feasibility, uncertainties and data quality should occur with early and iterative engagement among all stakeholders;
7. Regulators are prepared to consider appropriate endpoints for ultra-rare cancers, where such endpoints can be shown to be indicative of a treatment effect and enable an understanding of whether and how the product benefits patients. Such endpoints may be disease-specific and may allow a robust assessment of efficacy, in the right decision framework;
8. All data and analysis with its uncertainty will lead to the evaluation of a benefit/risk relationship for which stakeholders ultimately need to be comfortable with for the approval of a marketing authorisation;
9. All stakeholders agreed that solutions are more likely to be found if they work together with openness, flexibility, and in a cooperative way, sharing their expertise and resources, to the extent possible and appropriate;
10. Engaging industry/MAHs is crucial, requiring strategies to motivate industry and foster effective collaboration.

Discussion

The need for regulators, clinicians, and patients to collaborate on addressing barriers and challenges to medicinal product development for patients with URS for all ultra-rare tumours and conditions, was unanimously agreed upon. Interaction needs to be adaptable, regular, and innovative. Current approaches, like scientific advice and orphan drug designation, might not always be sufficient for all scenarios.

Investigators and regulators need consensus on which endpoints are most informative; how to make the most of additional data sources outside clinical trials; how to best collect prospective data; how to integrate registry data; and to design prospective collection to meet scientific standards and regulatory requirements. The workshops conducted so far have been considered a useful and most welcome starting point by all participants, with a consensus to continue organizing further workshops in the coming months to foster dialogue and address divergences proactively.

Future collaboration should aim to be flexible, open, collaborative and focus on developing a ‘toolbox’ of mechanisms and processes that could be applied to solve problems in an expeditious manner. This toolbox could support upholding scientific standards while accepting that limitations and uncertainties can be considered in clinical and regulatory decisions, given the characteristics of URS and ultra-rare cancers with limited potential for fully powered randomised trials. Higher uncertainty can be considered and may be acceptable in the particular situation of ultra-rare indications with no approved treatments. Such a collaboration would focus on general issues and not supplant existing tools such as scientific advice, which could still be used to answer questions on specific cases. Non-generalizable solutions must be found for specific critical issues unique to each ultra-rare tumour, optimizing practical approaches to balance scientific standards and uncertainty management, appropriate for each decision setting. Development approaches must involve all relevant stakeholders and decision makers to maximise efficiency.

Future workshops should actively involve pharmaceutical companies alongside the CHMP to maximize the potential for positive outcomes from this initiative. Indeed, these first two workshops were organised without the active participation of pharmaceutical companies, although the meetings were open to everyone to join virtually. This choice was based on the need for academia to initiate the discussion while minimizing the perception of a conflict of interest regarding specific drugs or treatments. However, involving pharmaceutical companies was recognized by many contributors as crucial, enhancing understanding of all perspectives in developing treatments for ultra-rare cancers and fostering innovative solutions [17]. There was indeed a strong hope that the ongoing discussion may help make development of treatment for ultra-rare cancers more attractive to the pharmaceutical industry, by:

a. Dispelling misperceptions and misinterpretation of regulatory and scientific expectations, which are often more pragmatic than is commonly understood from the experience with non-rare cancers;
b. Reducing the regulatory uncertainties through early, clear communication and agreement on the evidence package needed to assess the safety and effectiveness of an investigational medical product, including the potential for additional evidence generation in the post-marketing setting for continued marketing authorisation, and a

clear understanding of how risks are going to be managed in clinical practice;
c. Lowering any barriers for communication between stakeholders and enhancing constructive cooperation during development, as and where appropriate, to complement the existing procedures for advice and consultation;
d. Identifying new opportunities and incentives for pharmaceutical companies to play a key role in identifying issues and addressing these public health challenges.

On this matter the decision was taken to consider inviting pharma representatives to participate actively in future meetings.

It is envisaged that the participants representing academia, patient-advocates, not-for-profit foundations and regulators will work together to discuss and reach agreement on topics for the next workshop, possibly using specific use cases to guide the discussion. They will include:

1. Possible working structures to efficiently discuss specific cases through to the final marketing authorisation application.
2. The availability and involvement of expert advice, often missing from academic/advocate groups, to provide broad advisory and infrastructure support should be recognised. Such services should be engaged to assist in streamlining the application and engagement process, to maximise the probability of delivering a successful application.
3. Discussion of possible infrastructure to optimize the collection and sharing of data and how these might optimise results, and ensure the early involvement of key groups, such as regulatory agencies.
4. Strategies to maximise the engagement of pharmaceutical companies, including reducing costs and uncertainty, and increase the likelihood of successful drug applications.
5. Using a disease/drug specific case to help identify ways to improve and optimise delivery and evaluation of available data; identification of new data required; generation of an evidence generation plan; evaluation of appropriate endpoints and response assessment criteria; and the involvement of pharma and regulators throughout the process.

Conclusion

There is strong agreement among all partners involved, particularly participants from regulatory agencies, EORTC STBSG, and the entire sarcoma community, that it is time to build a global and multidisciplinary and multisectoral collaboration aimed at advancing and optimising the development of new treatments for sarcomas, and in general for other ultra-rare cancers, to address high unmet medical needs. Success of this undertaking depends on regular and close collaboration among all involved stakeholders. Establishing a regular forum for discussion and collaboration is essential for making progress, and all parties are committed to continuing the work already begun.

Disclaimer

The views expressed in this article are the personal views of the author(s) and should not be understood or quoted as being made on behalf of, or reflecting, the position of the regulatory agency/agencies or organisations with which the authors are employed/affiliated.

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Appendix A. Supplementary data

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