



EMA AND EORTC SOFT TISSUE AND BONE SARCOMA FOLLOW UP
WORKSHOP

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

24 May 2024

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

1. Introduction

The European Medicines Agency (EMA) and the European Organisation of Research and Treatment of Cancer (EORTC) organised a workshop on soft tissue and bone sarcoma on 12th January 2024 which specifically addressed the question on how to develop new treatments in ultra-rare sarcomas, as a model for ultrarare tumours. This workshop brought together academia, learned societies, patients, non-profit organisations, and medicines regulators to explore clinical and scientific aspects related to the development of medicines for ultra-rare cancers focusing on methodological aspects of clinical studies, repurposing medicines, and the use of real-world data.

This second workshop, held on 24th May 2024, was organised to engage in a more in-depth discussion of certain aspects of the issues raised and discussed at the January workshop. Specifically, the workshop covered topics such as how to support an adequate development of medicines for ultra-rare cancers and discuss lessons learned by considering specific examples.

2. Purpose of the Workshop

The aims of the workshop were to:

1. Discuss how to develop and support an ecosystem for ultra-rare cancers, using ultra-rare sarcomas as a model;
2. Review and discuss lessons learned by considering specific ultra-rare sarcoma examples;
3. Continue to facilitate, expand and deepen the global collaboration and interactions among relevant stakeholders established during the January workshop;
4. Make material progress towards establishing regular, open meetings between the adult sarcoma community and regulatory agencies, including but not limited to the EMA and FDA, to work side by side in considering and resolving all issues associated with the development of new approaches.

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 the 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 for further consideration by participants, including EMA and FDA.

3. Purpose of the Workshop

The workshop was organised in the following sessions:

1. Welcome

Chair of the Committee for Medicinal Products for Human Use (CHMP) of EMA

2. Introduction and meeting objectives

Appointed EMA and EORTC STBSG Joint Chairs of the Workshop

3. Session 1: Support an ecosystem for ultra rare cancers from diagnosis to treatment

Invited speakers (see session report below)

4. Panel Discussion

All speakers with additional panellists and open forum for questions

5. Session 2: Practical cases: what have we learned??

Invited speakers (see session report below)

6. Panel Discussion

All speakers with additional panellists and open forum for questions

7. 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. This report should not be understood as the official views of The EMA or its scientific committees.*

3.1. Welcome

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

Harald Enzmann (HE) welcomed everybody to the joint EMA and EORTC workshop and was particularly pleased that the workshop could be organised so soon after the last workshop in January. He noted that the subject of the workshop was particularly important as it went further than both ultra-rare sarcomas and indeed oncology, as many of the fundamental issues that would be discussed would apply to very many ultra-rare diseases.

HE then moved to address the issue of marketing authorisations for very rare diseases and promising products. The workshop would focus on the procedures and processes of the EMA for ultra-rare diseases. The gold standard for the EMA, statistically significant results in two randomised controlled trials with clinically relevant endpoints, are unlikely to be practical for ultra-rare conditions. However, the EMA does want to find a way forward for promising new treatments. Ways to meet the needs of patients need to be found. Regulators need to ask: do we have the right tools, or do we need to use the tools we have in a different way, or do we need to create and find new tools to support the regulatory decisions? Because regulators absolutely do want to find ways to make promising new products and treatments available.

HE went on to note that 'promising' for patients and clinicians means having access to something they would like to use. However, for regulatory decision makers, this is not the evidence required. Usually, regulators are looking for data to support a clinical trial authorisation, and for academia and companies to secure investment and financing of the trial. However, even if a new drug is promising for academic groups, it may still not be possible to get industry support. This is not a criticism, or attributing blame, but is in fact just the reality because industry has strong obligations to their shareholders that may override any obligations to other stakeholders, based on the low probability of a return on investment.

HE hoped that the workshop would start to look beyond the problems, and begin the process of drafting solutions by starting discussions about ways forward, either from scratch or using actual positive examples to facilitate such discussions. The EMA wanted to help.

HE stated that the EMA was happy that so many were participating in the workshop, and was again pleased that it was taking place so soon after the January event. He thanked the organisers for their hard work in coordinating the workshop, and closed by wishing all participants for fruitful discussions for the day.

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

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

Pierre Demolis (PD), thanked HE for his positive words. PD noted that in his opinion the important word for the day was 'dialogue'. He also hoped that after further positive exchanges that the discussions would lead to real progress, making new medicines available to patients as these are the people that matter. The EMA agrees with the objective of getting new medicines to patients of ultra-rare diseases, and confirmed that later in the workshop he would be presenting more details on how the EMA can help.

PD then wanted to address the role of stakeholders, and particularly the clinicians, patients and regulators at the level of the marketing authorisation, on the subject of funding, recognising that drug repurposing, where the drug is already approved, may involve costs that are limited, due to the very low number of patients, when compared to the importance and need for these drugs. On this matter the EMA is keen to help, open to and supports these discussions. PD confirmed as an example that the General Director of the EMA, Emer Cooke, had provided her strong personal support for this significant initiative. Overall, the EMA would be supportive, and PD believed that at the end of the day participants would return home with good solutions for organising the EMA's support so that it was as open, efficient and available.

PD thanked everybody for being present and participating in the discussions between stakeholders that would be an important part of making progress, and closed his short introduction with a warm welcome to all present before handing over to S. Stacchiotti to speak on behalf of EORTC.

Silvia Stacchiotti (SST), also thanked the EMA and EORTC for organising and coordinating the workshop. Particular thanks were extended to Pierre Demolis, Francesco Pignatti (FP) and Caroline Voltz (CV) and their colleagues for all they had done to organise the workshop.

SST noted that this workshop had followed the previous discussions about how to improve access to active drugs for patients with ultra-rare sarcomas, and also noted that the issues that would be addressed were not unique to ultra-rare sarcomas but largely applied also to all ultra-rare diseases, regardless of their type.

SST observed that that several partners from different stakeholders were present for the workshop. In addition to EORTC, there were patients and patient-advocates who were taking part to represent all ultra-rare cancer patients. SST noted that clinicians from outside Europe were taking part, with USA clinicians physically present for which she was very grateful. This is important as ultra-rare diseases need global involvement of patients and clinicians if we are to gather the data and undertake the studies that will be necessary. SST was also pleased to see regulatory parties participating, including the FDA, who will also be key to the process. Finally not-for-profit groups like the Anticancer Fund were present, all of whom had a large part to play in finding solutions for all rare diseases. Other participants were taking part online from around the globe. It was clear that global involvement was imperative for ultra-rare diseases and that progress could not be achieved without them taking part.

SST agreed with PD that it is important to identify and refine opportunities to streamline processes. She also noted that while it was not the objective of the day to address specific drugs and specific diseases, such cases would be used as examples to illuminate the issues faced.

She closed by noting that this type of workshop was suggested during the pilot project initiated by the EMA to look at drug repurposing for ultra-rare diseases. It was an excellent example of how dialogue can lead to progress, and in fact may be the only way to move forward. She hoped that the group could ultimately help the global patient community, and asked all present to use their hearts and heads to deliver the progress those patients badly needed.

PD thanked SST for her introductory remarks and then introduced Mr Pantziarka who would summarise the results of the previous workshop in January

Summary of the last workshop and objectives

(Pan Pantziarka, The Anticancer Fund)

Pan Pantziarka (PP) started by listing areas of agreement. Ultra-rare sarcomas are seen as an exemplar of all ultra rare diseases. Challenges include a lack of natural history data; difficulty in accruing enough patients for clinical trials; low commercial interest, and a lack of biological knowledge, especially where there are high degrees of disease heterogeneity. It was also accepted that clinicians and academics may only have limited knowledge of regulatory pathways for drug approval, and that these pathways are better suited to common diseases. Programmes like ACCELERATE can help, while future legislative changes in Europe will be important.

Areas of challenge focused on integration of non-traditional data streams into regulatory processes. Strengthening non-randomised data collection and the need to build an agile collaborative environment were also addressed.

PP tabled the day's agenda with specific focus on the two discussion sessions. He closed by noting the high unmet needs of patients and the need therefore for quick and rigorous joint action, hoping the workshop would be a positive next step.

PD thanked PP for this presentation before passing the floor to R. Herold (RH) and Winan Van Houdt (WVH), moderators of Session 1.

3.3. Session 1: Support an ecosystem for ultra rare cancers from diagnosis to treatment:

Moderators: Ralf Herold (EMA): Winan Van Houdt (EORTC)

RH was delighted and excited to be able to introduce the first session of the day where he hoped that excellent dialogue would help get to the solutions that were needed to meet the objectives of the workshop. Without further delay, RH introduced the first speaker of the session.

Presentations:

Patient involvement – hospital cohorts and mobilising the patient community

(Hugh Leonard, EHE Rare Cancer Charity)

Hugh Leonard (HL) started by summarising the typical position of ultra-rare patient cohorts in hospitals. He noted that, due to tiny numbers of patients, some hospitals would have no or just one or two patients, leaving patients isolated and alone. Typically, clinicians and hospitals would likely follow a general treatment procedure, but this would result in a number of differences in the type and nature of treatments and the collection and recording of data. Such data, if collated retrospectively, was then hard to assess and seen as poor quality by regulators. HL then presented a 'dream' scenario where hospitals all rigorously followed a detailed treatment protocol, collating appropriate data in the same way. This data would be more prospective in nature when collated and so likely to be more valuable in supporting an application for drug approvals.

HL next moved on to the issue of mobilising patient communities, and presented a summary history of the EHE worldwide community. Started in 2013 with a Facebook page in the USA, patient enrolment grew quickly. This created not only support for patients themselves but a growing voice with which to engage

in advocacy activities and demand change. Foundations in the USA, UK and Australia were established in 2015, with Canadian and Italian groups following. The patient community had continued to grow, raising substantial research funding. HL showed the research impact with one dedicated EHE research team in 2015 but with 26 research projects either completed or progressing today. HL listed key deliverables from this research including greater understanding of the biology of EHE; development of multiple disease models; the setting up of large scale observational studies and registries; a global patient registry; establishment of US and UK biobanks; drug screening; and patient support and involvement in all of these projects. All of these achievements added up to real momentum in moving the knowledge and treatment of EHE forward.

HL summarised the benefits that a mobilised patient group can bring, and why such groups are such powerful partners. He also listed the reasonable expectations of those patients, such as being listened to and included; not allowing inappropriate standard practices to be a barrier to progress; nor the rarity of their disease and lack of drug revenue potential. Ultimately, patients wanted their issues to be dealt with as a matter of urgency, a key word high-lighted by HL.

HL closed by asking attendees if they had the collective ambition to deliver what patients need, as in reality, a lack of ambition is the only thing that could stop the group reaching its goals. If it did have the ambition needed, then the challenge is to develop a new drug approval pathway for ultra rare diseases.

Identifying new drugs in ultra-rare indications and off label use

(Robin Jones, Royal Marsden, London, UK)

Robin Jones (RJ) noted that for patients with advanced EHE unable to access off-label sirolimus there is clear unmet need, as these patients have no effective systemic therapy. The EHE community believes that the data from the prospective study combined with the retrospective data should be acceptable to support the extension of the indication to include this ultra-rare cancer. The safety profile of sirolimus is well known, and the retrospective data in adult advanced EHE patients with disease progression (Stacchiotti et al, 2021) showed that most (28/37 - 76%) participants benefited from sirolimus with 24 RECIST stable disease and 4 partial responses recorded. The characteristics of this retrospective data collection [namely: 1) retrieved from a network of excellence; 2) all cases with radiological progression before starting sirolimus; 3) pathological diagnosis confirmed by an expert sarcoma pathologist; 4) sirolimus administered under the same sarcoma-experienced clinical team and following the same procedures and radiologic assessment intervals; 5) inclusion of all consecutive patients with systemic and progressive disease requiring systemic treatment with no biased selection based on disease presentation] render the data of good quality, although retrospective.

Importantly, the belief in the efficacy of sirolimus in EHE is shared by the community of experts in the treatment of sarcomas, as also stated in the ESMO guidelines for treatment of soft tissue sarcomas (A Gronchi et al., 2021) and in the consensus document on the optimal treatment strategy for EHE patients drafted by the community of experts and EHE patient representatives (S Stacchiotti et al., 2021). In these guidelines, sirolimus is proposed as first line treatment for EHE patients affected by advanced and progressive disease. In addition, the EHE patient community reported outcomes described in this submission provide further strong support for this indication.

Although the precise mechanism of action of sirolimus in EHE is still under investigation, preclinical data available from EHE cell lines and PDX mice models have confirmed the antitumor effect of sirolimus in EHE and, in particular, its superiority to anthracyclines (Stacchiotti S, Simeone N, Lo Vullo S, et al.

Activity of sirolimus in patients with Progressive Epithelioid Hemangioendothelioma (EHE): a case-series analysis within the Italian Rare Cancer Network. Cancer 2021; 127:569-576.

Frezza AM, Ravi V, Lo Vullo S, et al. Systemic therapies in advanced epithelioid haemangioendothelioma:

a retrospective international case series from the World Sarcoma Network and a review of literature. Cancer Med 2021; 10:2645-2659)

Case example from PUSH: LGFMS/SEF and immunotherapy

(Andrew Wagner, DFCI, Boston, US)

Andrew Wagner (AW) started his talk on low-grade fibromyxoid sarcoma (LGFMS) and sclerosing epithelioid fibrosarcoma (SEF) with an introduction to both of these ultra-rare sarcomas, and confirmation of the limited data comprising three prior retrospective series.

AW then presented results from two large collaborative retrospective studies, one based in France (330 patients) and one multinational (395 patients). Results of both studies were summarised.

AW next discussed a framework for studying ultra-rare sarcomas, citing the CTOS consensus paper on the minimum requirements for the evaluation of activity of systemic treatments, and how this paper assisted in defining criteria for a retrospective series using an historical reference group and generating hypotheses. AW then went on to explain how the paper helped define a prospective interventional study and a prospective observational study, and posed questions as to how to assess a single arm study if there is no objective of shrinkage, and whether an external 'control' group could be useful.

AW closed with two questions. The first was whether prospectively collected data outside of a defined clinical intervention can be useful in providing the context for a comparative patient population; and are there opportunities to meet with the EMA and FDA to collaboratively develop feasible frameworks for collection of data from prospective observational studies to help support interpretation of single arm interventional studies in ultra-rare diseases?

What could the development of medicines in ultra rare indication look like?

(Pierre Demolis, chair of the Oncology Working Party and SAWP vice chair, EMA)

PD started by noting that he was quite reassured by the previous speakers as they had all addressed issues that needed to be discussed and agreed, but in reality were all aligned. The goal of the workshop was not to act as a collection of Scientific Advices, but would indeed look at specific examples to help us define the more general areas and points that need to be resolved. Nor was it setting out to draft new guidelines to address these exceptional cases as it is impossible to have a guideline for every case. So, parties often approach the EMA to ask in fact how they might deviate from the guidelines in their exceptional situation.

So, if the EMA cannot offer a guideline or scientific advice, what can it offer? In this case the EMA can offer general organisation principles. PD explained that in the case of EHE and sirolimus approval, academia had approached the EMA using a fairly standard scientific advice procedure. The EMA colleagues involved had quickly realised however that this would not work. EMA staff met to discuss and develop a process in which the applicant would be invited to informal meetings to transform the normal short, very rigid exchanges into a longer term, less rigid process to allow the development of a better, more appropriate procedure suitable for such an exceptional disease. This was in fact the start of considering that for every ultra-rare disease, there is a different challenge, even though some elements may be common. The example of diseases where disease stability might be the best outcome was noted and was an example of an issue that needs to be addressed through dialogue. However, if such dialogue is not taking place, then the issue will not be addressed.

PD outlined the tools that are currently available to help these exceptional cases. These include the innovation taskforce (ITF), scientific advice or protocol assistance, specific legislation and procedures

such as those for orphan diseases, and PRIME designation. So, it is important to make people aware of the available support which already exists. The ITF is usually the entry door for academic groups. Protocol assistance should be sought and does not provide regular exchange. A nice project that might be agreed through the workshop discussions could be to develop a new toolbox with all these tools included and available for anybody who needs to engage in an open dialogue. The EMA were therefore prepared to consider the development of a 'widely-open' tool box which could be very useful.

In this process, clinicians, academics and patients can bring real data, clinical experience and scientific evaluation to these discussions, all of which will be valuable and for which the regulators. Bringing these data and coordination forward would be very useful.

PD then summarised his discussion by pinpointing key words. These were flexibility; adaptability, dialogue exchanges; a wide open toolbox; experience; observations; science; and real issues. All of these different attributes are in our collective hands and each party needs to bring the attributes they have to the group to make it possible to deliver our overall objectives.

But PD noted that while the EMA could and would be flexible, this could not be at the expense of standards which could seriously damage the regulatory system. Flexibility relates to the approach taken, and may require the regulator to tailor their requirements to the reality of the situation faced so that outcomes are possible but remain acceptable. He was convinced that acceptable solutions existed and that by working together they could be found.

Ultimately the regulators would come back to the evaluation of uncertainties of the benefits and risks, with the latter being as limited as possible and justifying the marketing authorisation. In this context, the EMA in most cases, but not all, view retrospective data as being unreliable in providing the necessary level of evidence, but do accept that this data can contribute to the overall assessment. PD noted the natural history of the disease as a good example, where it may be shown that disease stabilisation never occurs naturally, then disease stabilisation after treatment may be seen as a positive benefit. This type of exceptional situation needs to be the subject of dialogue as it will never appear in a guideline due to its exceptional character.

Overall, the 'need' starts with patients and clinicians; the need of patients for a new drug and the need of clinicians to be able to provide meaningful care. This in turn creates a need to collate appropriate data, ideally prospective if possible, but this will happen outside the regulatory process and may be derived from off-label use which may in turn deliver the initial evidence needed. PD then noted that the French Compassionate Use Programmes presented at the January workshop had been informative and could deliver useful prospective data. Indeed, the EMA were considering if this could also be encouraged at the level of individual European States?

PD closed by again stating that he believed solutions could be found if we work together with openness, flexibility, help and cooperation. This would be to the benefit of the regulators and the patient communities. He encouraged applicants to bring forward acceptable plans with heterogeneity removed as much as possible, together with the best and clearest evidence package leading to the positive outcome we all want.

3.4. Panel Discussion

(Moderators: Ralf Herold (EMA), Winan Van Houdt and Silvia Stacchiotti (EORTC))

All speakers with additional panellists:

- *Martha Donoghue, associate Director of Paediatric Oncology and Rare Cancers, FDA*
- *Nicole Scobie, Accelerate*
- *Kit Roes, chair of the Methodology working Party, EMA*

WVH opened the panel discussion by noting that there had been some excellent points made by the different speakers, and in particular the need for a 'change of approach'. He wondered however what the real priorities were and asked each speaker in one word to state what they felt the priority was. HL said 'urgency'; RJ agreed with urgency, but also felt 'use and quality of all data' needed to be addressed; AW said 'yes' to using all data but posed the question "How do we do that?" and explained why defining requirements and procedures in advance may be essential if we are to deal with all ultra-rare diseases.

SST noted that as we had agreed not to focus on specific diseases, then in more general terms what clinicians and patients can provide is the network, collaboration, willingness to help and some infrastructure to collect the data. SST felt that PD's comments about the wide-open toolbox was a great opportunity to talk about types of data collection. SST noted that PD had ended his presentation by talking about compassionate use programmes. So was it possible to discuss with the EMA and the FDA what type of data is required to support a compassionate use programme which could then lead to data to support the approval of the drug? Also, what type of data could be collected in a prospective observational study of an ultra-rare tumour, again to ensure the data can support a regulatory process? Finally, SST noted that the sarcoma community were continuing to assess retrospective data and this would also be very useful to discuss with the EMA to ensure we are doing this in the best manner from a regulatory perspective. How might we meet and discuss these issues with the EMA to understand how to improve so as to make the best use of the data?

PD noted that speaking of real-world evidence or other forms of data may be misleading. The key issue is understanding the difference between prospective and retrospective. It is not the case that retrospective is always unacceptable and prospective is a magic solution. In this context he noted that regulation involves the testing of a hypothesis, and it is normally prospective data that is used to achieve this. Clinical trials are part of this process, but real-world data may also be a useful component.

Kit Roes (KR) asked what it was that we should be focused on? Data was one focus. We also need to evaluate the benefit/risk balance, and levels of uncertainty with which we ultimately need to be comfortable. KR noted that the challenge from a methodological point of view is that we are good at articulating and quantifying these issues if we have prospective randomised trial data with a type 1 error control. However, we are less good as we move away from randomised trials to a prospective observational study with maybe a small clinical trial, or we have prospective observational data combined with a single arm trial. These are in fact different designs and we therefore need to articulate the uncertainty for less straight forward situations, but will allow us to evaluate all available data. KR also noted that our classical thinking was to define a single endpoint and simply test if this is met. However, in the current discussions, we need to try and establish processes and procedures that will take into account all available data rather than focus on one single endpoint.

These trials are in reality partly learning and partly confirmation because we are dealing with diseases that we don't know that much about. And what is acceptable to the regulator? To understand this we need a broad review with open and honest communication and discussion about the uncertainties involved rather than a simple 'yes/no' answer to the question "what is acceptable?".

RH thought these were all important points and wondered, moving away from issues of specific content, what we needed to do to deliver and progress. We had spoken about patients, and clinicians and toolboxes. RH now wanted to focus on what needed to be in the toolbox, and invited Martha Donoghue and then Paolo Foggi to comment on how we might facilitate and help the group get to discussions that will address and inform the quality and content of the data collected.

Martha Donoghue (MD) thanked RH for the question and noted that it is a very big question with multiple ways to progress the conversations and dialogue, looking at both the big picture relating to drug development for ultra-rare cancers as a whole, trying to agree areas of agreement between stakeholders, but also the necessary sequential, detailed, focused discussions such as common data elements, data sharing, and the overarching principles relating to real world data and evidence such as compassionate-use trial data.

MD noted that we would also need more detailed discussions relating to a specific drug development which would need to be highly contextualised, considering the tools that are most appropriate in a given disease context, as well as looking at the biology of the cancer and the unmet medical need. We will also need to consider the scientific information supporting the potential mechanism of action of a drug. MD noted that there are ways to coordinate and progress these discussions but they are highly complex and often require more than one meeting to reach agreement.

MD noted that in all these discussions, the FDA believes that gathering the data prospectively ahead of the decision is preferred, rather than trying to collect and package old data which can work, but introduces significant challenges and can waste time. So having clear, frequent and early communications is vital. It may also be useful to look at ultra-rare cases where drug approvals were achieved, and see what lessons can be learnt, but we need to recognise that this is often due to specific characteristics of the disease. In summary, we need to engage in detailed discussions in each case, understand patient unmet needs and build coherent plans. We have mechanisms in place to do this but need to find ways to leverage them to best seek the outcome we desire.

RH thanked MD for her contribution, particularly noting the words “sequential detailed discussions” and biology of the cancer, the “unmet medical need” and the available information available supporting the “mechanism of action” which point to the need for an evidence generation plan that combines these elements and facilitates the discussions from different perspectives. Indications on how to do this may come from previous success cases which need to be considered to see if they can help guide us to a successful way forward.

Paolo Foggi (PF) suggested that off-label use is a good place to start with a need to produce the highest quality evidence possible. PF’s main message was that no single element of data should be lost and all data needs to be combined. The question was also raised as to how to assess single arm studies if no objective shrinkage of tumours is present. This requires us to do some contextualisation and discuss how we can use single arm trials. This is key as there are many examples, even in ultra-rare sarcomas, where single arm trials were sufficient. It is easy when you have a response rate, but what if we don’t have this? Here the key is the data, possibly a collection of prospective data, or a collection of data with an accuracy and quality that matches regulatory expectation. This is something we can collaborate on broadly, and not just in single types of sarcoma, recognising their heterogeneous nature. Indeed, there are guidelines on how registries or the collection of real-world data should be carried out to provide the information we want to see in terms of overall data quality. So, a dialogue on the data required and how this can be used in a specific situation, including possible external controls, is important.

WVH thanked PF, and wanted to amplify PF’s point that no data should be lost. WVH then asked Denis Lacombe for the vision on data collection from the EORTC perspective.

Denis Lacombe (DL) started by noting that it is necessary to re-engineer everything as with ultra-rare cancers we are facing different challenges. Based on the morning’s discussions, DL had tried to capture what needed to be re-engineered, but observed that as academics, sometime the needs of the downstream stakeholders are not fully understood.

DL outlined the requirements from his perspective. Firstly, there needed to be reorganisation at the level of each organisation regarding the data that needs to be collected, and observed from the regulatory position that it was necessary to focus on prospective data and forget about retrospective data. Secondly, we need to address the methodology of the research, with data needing to be of regulatory quality to attract pharma involvement. These requirements require infrastructure that cannot be created from scratch. In reality we need to use existing infrastructure of which there are already several solutions available with capacity to accommodate these requirements. Without using these systems the urgent need of patients cannot be met. DL strongly advised against the idea of creating new infrastructure from scratch. Having said this, DL noted that from existing EORTC systems it is possible to create agnostic infrastructure to accommodate some of the challenges identified, and then customised for use with specific drug situations. DL felt these would be his key points and without addressing these there was a likelihood that we would not deliver what was required. However, our starting point should focus on using the systems already developed.

SST then asked the EMA participants what they thought was the best way to move the workshops forward. Was it for example sensible to use an example disease with real retrospective data and preliminary ideas on drugs that might work, and propose a prospective observational collection of data, and collectively discuss this without pharma in the room as pharma may be currently doubtful as to the likelihood of such data securing a positive outcome from regulators? So, we need to work on the methodology and quality of data to be collected. Or do we focus on a more general discussion of methodology? SST noted that in her view, an actual example made such discussions more meaningful, although she recognised that such a discussion would not cover all ultra-rare sarcomas. However, it is a starting point. So how do discuss using the open toolbox as described by PD which is an opportunity that nobody present wants to miss.

SST noted that some speakers had already identified examples where clinicians had outlined their readiness to progress with data collection and were looking for guidance from regulators to help them build a workable strategy. The immediate question was how do we take this forward; how do we ensure that the opportunity is not lost?

PD noted that EHE and repurposing on the drug sirolimus was a good example where we had already initiated an open dialogue and are looking at possible ways forward. PD felt that this was the right model. This had led to a very adaptive consultation between stakeholders trying to find the best solution through continuous dialogue to generate a plan for development of a data package that could be acceptable to CHMP for positive discussion. As to the question of whether this would be enough for all situations, PD confirmed that he would need to consult with other involved members and groups within the EMA, and consider whether access through an alternative process such as ITF was more appropriate. PD however felt it was the EMA's responsibility to ensure that when approached by any rare disease situation, they must adapt to the specific case and not stick rigidly to any formal procedure. PD noted that the EMA was already discussing for rare situations how they will adapt procedures to respond proactively and flexibly to the development observed to ensure that they can make clear the tools that are available to assist the applicant. So the entry could be a repurposing approach or any other approach, and in this case it might be a good idea as soon as such an approach is identified, then the EMA will build a team and make them available for discussion and adapting the rigid structures and providing the flexibility to address the needs. PD noted that one such case was in process, and having a second one would be useful, highlighting differences and how the procedures can accommodate them. PD noted the many groups in the EMA that might be involved and felt it was important to keep all options open, and to ensure that options were not dropped just because they were not mentioned in an existing procedure.

PF agreed that using concrete examples was a good way forward and asked that data collection platforms should be included within such discussions, asking what data we need and what will it be used for? In addition, we need to consider what data we can collect in real life which can be very important. Questions as to what data is collected, how it is collected, and how does it fit with regulatory requirements all need to be considered. Ultimately, can we get alignment between the regulator and those in the field who are collecting the data.

PD asked that we start these conversations, noting that during the January workshop, the French compassionate use programme had been presented. PD wondered if the EMA could provide advice to European Commission to promote and encourage member states to adopt such a programme, if affordable. In this way, patient data across Europe for patients accessing the same drug and treated under the same protocol could provide valuable prospective real world data to support use of the drug. PD wants to investigate taking such an idea forward, a suggestion strongly supported by WVH and many others in the room.

KR also commented that from a methodological perspective, such discussions are often positive when using actual examples, while the actual structure of the discussions is perhaps less important. The mindset of those entering these discussions is also important, not sticking rigidly to past practice, but genuinely being prepared to consider what must change. So, the challenge is partly structure but also partly how do we frame our discussions for successful treatments for ultra rare cancers and so flexibility and understanding needs to happen on both sides.

HE agreed with all the points tabled, but wanted to note that there is no way to avoid the requirement at the end of the process for a positive opinion from the regulator. To achieve this it will be important to get early buy-in from the CHMP members. While the regulator will of course look at the data provided, we need to recognise that the regulator needs to be consistent. In this context, and in a spirit of fairness, it will be important to look at historical practice and not deviate from this unless there are very clear, justifiable reasons. We want to avoid a situation where the data supports a different decision compared to the past, but this is difficult as there has been no preparation or announcement of such a change and CHMP members therefore feel bound to the previous practice. HE stressed that he was not suggesting this was a barrier. Instead, recognising that CHMP will be critical to this process, he was suggesting that they are engaged early to ensure they are kept abreast of developments and are comfortable with these. It is important that such engagement is used early in the process. HE noted that there are mechanisms for doing this. The CHMP meets every month and discusses the most interesting issues being dealt with by Scientific Advice. This could be a useful mechanism to keep CHMP informed.

PD agreed and noted that there are two established procedures for such engagement, one being an update process with the CHMP, as outlined by HE, and the other is part of PRIME, where a member of CHMP is involved from the start of a development and carries responsibility for ensuring compatibility and consistency with regulatory requirements. One of these two systems, or both, could be used to ensure that CHMP are involved early.

RH summarised by noting that discussions could progress both on general basis but also looking at specific cases. RH lastly wanted to confirm that the EMA is very supportive of not-for-profit developers. RH noted that clinical researchers and regulators can and are engaged in dialogue, but the process requires more than just this. Firstly, there is also a need for clinical researchers to engage expertise and professional services around, for example, technology transfer and even regulatory engagement and support. The EMA see these services growing which represents a growing change to the overall regulatory landscape which needs to be leveraged. Such skills may already exist within universities for example. Applicants need to consider sourcing these skills, and an important and early example is seeking advice on the development of a strategy and/or regulatory plan and how the process works. Secondly, it is important to build methodology and expertise into the project. This maturing of the

methodological thinking will be important and allows the regulatory process to build on the integrated methodological advice having looked into the challenges and options. This will also help develop an evidence-generation plan that will allow discussion of not just a study, but the purpose, the background which will give real perspective and will anticipate the critical thinking that has been discussed during the morning. In summary the evidence generation plan is important as it can form a vehicle for facilitating the discussions. The EMA will help by asking the right questions from the regulatory perspective. This may sound circular, but the EMA experience is that this process allows the EMA to identify areas of difficulty in advance which can then be thoroughly discussed.

WVH thanked all the participants for their lively contributions. He recognised the excellent discussions, noted that tools to help do exist, but also wanted to again stress the need for urgency as delays can cost lives. WVH looked forward to the afternoon discussion that will look at some of the many issues faced including all aspects of data collection and harmonisation, across both different diseases but also across different regulators. The workshop was then adjourned for lunch.

3.5. Session 2: Practical cases: what have we learned??

Moderators: Caroline Voltz (EMA), Denis Lacombe (EORTC)

Caroline Voltz (CV) welcomed everybody to the second session of presentations. She noted that this session would focus on specific examples and it was hoped that these would lead to an interesting discussion at the close of the day. CV then introduced the first speaker.

Presentations:

What is important for patients in addition to RECIST and overall survival?

(Gerard van Oortmerssen, SPAGN)

Gerard van Oortmerssen (GVO) presented data from a SPAGN study on the wishes of patients relating to research and advocacy. The study showed that patients wanted more research, especially on different subtypes, and more emphasis on quality of life. In the case of ultra-rare subtypes, clinical trials were often patients' last hopes. Patients' unmet needs including new treatments, repurposing of drugs, other criteria than just RECIST, and overall survival, again with quality of life, were seen as an important factors.

GVO went on to address the PROs that were assessed and the challenges of measuring and interpreting these outcomes. The benefits of using the internet and smartphones in opening up longitudinal data collection was highlighted, together with the power of mobilising patients to take action together, leading to registries, biobanks and greater collaboration between patients and researchers. Examples of such groups were given, including GIST, Chordoma and EHE.

GVO then tabled the results of an analysis of a GIST patient Facebook using AI. Results relating to side effects, and their comparison to trial-reported data (avapritinib) were presented with good correlations achieved.

GVO concluded that trials were important for ultra-rare sarcomas, but it was important to consider criteria other than RECIST. Patient reported outcomes (PROs) also have an important role to play, highlighting the importance of collaboration between patients and researchers.

Use of real word data to complement prospective studies: case example in alveolar soft part sarcoma and epithelioid sarcoma

(William Tap, MSKCC, New York, US)

William Tap (WT) started with a summary of a large scale early clinical trial involving 6 drugs, 40+ disease entities, 80-99 sites worldwide, and over 2,000 randomised participants. WT explained why the trial ultimately failed to produce useable data. Issues with hindsight included poor trial design and outcomes, lack of contemporary data sets and accurate historical controls, a poor scientific rationale, lack of biomarkers and pharmacodynamics.

WT then asked how things had improved, and provided a summary of the Ultra-Rare Sarcoma Working Group (URSWG) Consensus Paper on 'Incidence Threshold and the List of Entities', with a table of key challenges relating to the understanding of ultra-rare sarcomas. WT then walked the group through two examples: epithelioid sarcoma and alveolar soft part sarcoma. In each case, data was presented to show the effect of different drugs on each of these two diseases, and how these results had led to FDA approvals. WT also posed the question as to how the example of these results can help us and what can be learnt from people being treated with these drugs.

WT then addressed discovery and innovation in drug development and patient care in rare cancers. He outlined the need for comprehensive development strategies and listed 6 key factors including understanding the clear clinical application; defining the natural history and best treatment outcomes; understanding the biology and outcomes; and the need to build collaborative networks. WT presented the extensive French sarcoma structure and the new PUSH platform as two examples of collaborative networks. In the case of PUSH, WT presented the hierarchy and structure of data sources and their collation for different forms of study, and as an example of how global data and patient access can lead to significant progress.

Developing new criteria for response assessment: Case example of epithelioid haemangioendothelioma

(Lorenzo D'Ambrosio, University of Turin, Turin, Italy)

Lorenzo D'Ambrosio (LDA) explained that his presentation was founded on the stated aim to improve response assessment in rare tumours where RECIST 1.1 do not mirror clinical treatment and effect and randomised clinical trials are unfeasible. As an example, LDA showed images of two patients (one GIST treated with imatinib and one EHE treated with sirolimus) who had shown excellent response to their treatments, highlighting the fact that imatinib changed the history of GIST treatment but sirolimus is not registered for the treatment of advanced EHE.

LDA moved on to show summaries of past case series of EHE patients and the resultant activity of sirolimus, and provided a simple diagram to show how RECIST worked clearly when there was significant tumour growth or shrinkage, but was inadequate in cases where there was little or no change to tumour size. Variations of RECIST 1.1 were then tabled as examples of how clinicians had tried to improve RECIST 1.1 in several clinical situations (e.g., to evaluate response to immunotherapy).

LDA then moved on to explain why response assessment in soft tissue sarcomas is challenging, where tumour shrinkage may not occur, and tumours may become fibrotic, cystic or myxoid without significant change in size. It was suggested that these poor response definitions may partially explain why predictive factors for response and survival in sarcomas are still poorly defined and need to be improved.

LDA then presented response assessment examples in GIST where shrinkage was not evident but patient survival was shown to increase. He also presented a flow diagram showing how sirolimus was identified as having activity in advanced EHE, yet challenges to prove this were faced due to standard RECIST 1.1 criteria not being effective for this disease/drug combination, despite clear clinical benefit.

LDA next addressed the challenges of introducing new response criteria and provided a table summarising 'End point validation criteria'. Actual patient examples were used to amplify the points being

made. The challenges presented by advanced EHE involving the pleural lining and pleural effusion were highlighted, together with suggested ways to measure the quantity of pleural effusion as a possible criterion for showing clinical benefit in such cases.

LDA then presented new response criteria, called RESCOrE (Response Evaluation by Symptomatic Change and Outcomes Reporting), which have been developed for EHE assessment (RESCOrE criteria are presented in Annex 1 to this report). Definitions for complete response, partial response, stable disease and progressive disease were shown. Radiographic images were then shown to illustrate the differences between RESCOrE and RECIST 1.1. LDA also presented new RESCOrE pain criteria (see Annex 2) and RESCOrE quality of life assessments which are both being developed to be used to complementary assess drug activity in EHE. The previously presented 'End point validation criteria' were then reintroduced to show how RESCOrE met all the stated requirements.

LDA completed his presentation by asking the EMA: (i) if the new RESCOrE criteria were acceptable for evaluating drug activity in EHE; and (ii) could regular meetings and scientific advice be scheduled to discuss new response assessment criteria in ultra-rare tumours where RECIST 1.1 is shown to be inadequate.

Repurposing: case example of sirolimus in epithelioid haemangioendothelioma

(Denise Robinson, The EHE Foundation, US)

Denise Robinson (DR) started her presentation with a summary of the EMA's Drug Repurposing Pilot Scheme that was introduced to assist in situations where there is a new indication for well-established drugs that have adequate data to support their use but are lacking support from the Marketing Authorisation Holder. In addition, the importance of drug repurposing, and challenges were also summarised.

Posing the question 'How Can We Improve the Situation?', DR started with a brief description of EHE, provided statistics of European patient numbers making randomised trials almost impossible, and why drug repurposing is a critical pathway for new drug approval for ultra rare diseases. DR then provided a summary of published retrospective data, case reports and clinical trials, all of which supported sirolimus as a medicine that is effective in treating EHE. She also reminded the group that mTOR inhibitors like sirolimus had been recognised and recommended as the front-line drug for EHE in the *ESMO* paper "Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts".

The utilization and importance of sirolimus to treat EHE was also illustrated. DR shared unpublished data from the EHE Global Patient Registry showing sirolimus as the most reported systemic agent used. Additionally, DR presented key results from a 2023 global survey, published in *Frontiers in Oncology*, of patients' perspectives on sirolimus for EHE, noting that the data strongly supported Stable Disease as a response to the drug, together with significant improvement in Progression Free Survival. DR then summarised key points that supported the approval of the repurposing of the drug. In particular, she noted that patients of ultra-rare diseases should not face barriers of commercialism and impractical study designs when there are clear and present opportunities to observe treatments in real world settings.

DR concluded her presentation by tabling several key steps and procedures that would assist in delivering the broad stakeholder collaboration required to achieve a positive outcome. These included recognising the limitations of small patient numbers; giving greater weight to the expertise of clinicians; involving all stakeholders; and defining and agreeing a plan to fully involve ultra-rare patients and their real-world data. By adopting such plans, we can meet the real and significant unmet needs of patients.

Engaging companies in academic trials of Ultra Rare Tumours – Hopes and hurdles

(Gauthier Bouche, Anticancer Fund)

Gauthier Bouche (GB) started his presentation by summarising the past six approvals of medicines for ultra-rare sarcomas, clarifying if these approvals were the first marketing authorisation or repurposing, and whether the approval had been granted by the EMA and/or the FDA. This was followed by a summary of reasons why approvals of such drugs are so rare, focusing on the rarity of the disease, the absence of drug manufacturers' interest and limitations for academic led trials within current regulatory processes.

GB next provided a flow chart of the different pathways for drug repurposing approval, with the first issue being whether the data for such an application is generated by the marketing authorisation holder (MAH) or an academic group. GB walked through a presentation of each of the pathways in the flow chart. He observed that MAH interest at the data-generation stage for ultra-rare diseases mirrored the diseases themselves, in that such early interest was also ultra-rare. Cases where an MAH takes up the application after data generation by an academic group are also ultra-rare, but two examples were given. Next, GB noted that the lack of MAH interest in submitting an application even if the data has been generated by an academic group was a major impediment to getting approval for the repurposing of a drug. He also noted however that this was not an uncommon situation for ultra-rare diseases and was in fact the default when generic products are proposed. Four current examples of drugs and the associated diseases, that are facing this situation were given. In these situations, the only route to access the drug is off-label prescription.

GB then addressed the issue of the different timepoints for MAH and academic engagement, shown as 'early', 'late' leading to a type 2 variation, and 'very late' resulting in the academic group seeking the approval prior to engaging with the MAH, although his route currently would only be available in the EU after legislative change (Article 48).

'Early' engagement is obviously the best outcome, and GB provide examples of where this had been successful, such as the University College London and Astra-Zeneca collaboration. The benefits of strategic forums, streamlining trials, and the role of trial funders were all high-lighted as important aspects of encouraging early engagement.

The 'late' pathway was shown to have direct incentives for MAHs but significant and complex issues still need to be addressed. These include the due diligence and agreement with the data owner, liability issues, and potential loss due to the opportunity cost of engaging in such an application, and resultant mandated lowering of pricing when the label extension is provided and the drug is marketed for this use.

In the case of the 'very late' pathway, this would require the academic group to be able to make the application. This currently is not possible in the EU but may become so if the legislative changes being discussed are adopted.

GB concluded his talk with some final thoughts. Patients and funders of academic trails need to be demanding and ensure their voices are heard. Academia needs to focus on approval as the key goal, and not fame or career progression. Prioritisation, timing, collaboration and clarity about expectations are all important, and academia needs to educate itself about regulatory processes and procedures. The role of companies is also key in terms of helping to make a data package as strong as possible. The corporate and social responsibility benefits of assisting with ultra-rare cancers should also be amplified. Finally, the benefits of ultra-rare tumour strategic forums needs to be further evaluated and tested.

3.6. Panel Discussion

(Moderators: Caroline Voltz (EMA): Denis Lacombe (EORTC))

All speakers with additional panellist:

- *Kit Roes, chair of the Methodology working Party, EMA)*

CV started the session by highlighting some of the key points raised by the today's speakers, as follows:

- It is important to have a clear plan as to how an application to a regulator will be structured and to organise activities and data capture accordingly;
- Identifying patients is key, and once identified, patients' baseline data, medical history including baseline treatment reported should be captured. This can be accessed using e.g. the Health Information Exchange Act in the US and the European Health Data Space in EU, through patients themselves, maybe mobilised through social media;
- An evidence generation plan is important understanding the rationale (pharmacology level), capturing what has already been done, and what additional data needs to be collected and why. Both patient advocates as well as science can help provide good data;
- We need to understand the mechanism of action, and the best endpoints need to be recognised, with patient reported outcomes (PROs) being a useful source of initial information and safety evaluation (with follow-up of patients using digital tools)
- Urgency of delivery is important for patients therefore the use of compassionate use programme represent a clear advantage. The French programme was presented at the 1st workshop and an European wide with International program would be extremely helpful;
- Standards for data collection need to be considered. Prospective data with a standardised protocol should be considered, including where possible some randomisation. This data collection needs to be appropriate for the best endpoints that will be used, and might include different forms of endpoint such as RESCORE. Quality of life also needs to be considered;
- There is a need for an Innovation Task Force approach that can advise academics as well as looking at new tools to collect and evaluate data, while also adapting existing processes and procedures. We need to recognise, including through collaboration with other regulators, that endpoints need to be defined before any trial or study to which they apply, starts. These may be both indication and disease specific; and
- Obtaining early involvement and feedback from regulators may be seen as positive by industry and so may also help academics secure funding from industry. The EMA is ready to assist and share information to facilitate partnerships and encourage progress.

DL also wanted to comment at the start of the session and noted that RJ had talked about off-label use and the value of both prospective and retrospective data. DL hoped that in two years' time, for example, the issue of retrospective data will be behind us as all data will have been collected prospectively. So, we are talking about changing the 'evaluation paradigm'. In DL's opinion this raised the question as to what the 'battlefield' is? DL wanted to repeat his message of the morning and again suggested that it was important to embrace everything, and noted that the EURACAN structure and groups like EORTC had systems and solutions that could add value, and achieve many of the things discussed during the day. He noted that the EU likes to build on existing infrastructure, adding significant value while reducing costs. It is not sensible to build systems and infrastructure in isolation.

MD was invited to comment from the FDA's perspective. MD noted that she was aligned with previous comments. There was a clear urgency to address the unmet needs of patients with ultra-rare disease, ideally using prospective data. Data sources from off-label use may potentially be used, but these different data sources would require coordination and we need to focus on how to better aggregate and

use such data. MD was not an expert on EURACAN but thought its systems could be useful. She noted that the NCI in the US may have similar infrastructure. Overall, the FDA was keen to work with the development of any appropriate infrastructure as every bit of patient data is important for ultra-rare diseases. With regards to prospective vs retrospective data, MD noted that prospective data was the preferred option for the FDA, but that retrospective data would be considered in support of prospective data, provided it was analysed in a prospective and unbiased fashion. However, the ideal is to collect data in real time so that it is as contemporaneous as possible and as useful as possible for regulatory purposes.

SST asked if she could once again speak about the value of retrospective data? It is essential with ultra-rare diseases to consider every data that is available. This is critical to avoid discriminating against new entities. SST noted that new entities are regularly identified in sarcomas for which there may be very little if any prospective data available, so we need to make the best and most rigorous use of all data. So, it is essential that we all work together, with each party 'putting on the table' their capabilities, resources and willingness to work together. At the same time, we need to recognise that there are different types of condition. Some have been known for a long time, their natural history is known; effective drugs and their mechanisms of activity are known; and in these cases we can focus strongly on prospective data. But other conditions are new, or almost new, where we need to generate hypotheses about what type of prospective data we need to collect by looking at the retrospective data we have. It is important that we therefore collectively agree the criteria for collecting all the data needed with workable quality criteria that applies to all kinds of data that can be collected – translational data, retrospective data, observational prospective data, prospective registries, and interventional prospective studies. The last of these is of course the best but is not always feasible for the reasons discussed. A patient that is diagnosed with an entity today needs a treatment today, and not in 10 years' time. Maybe in ten years we can build a prospective data collection and we will be able to offer better treatments, and new drugs, but for patients today we need to agree and align on the data we need to collect and we all need to be open to using all the data available in the best way we can for our patients.

AW agreed and noted two examples where the initial signals of possible active drugs were identified in 2010 but those drugs were only recently approved, over 10 years later. These were cases where industry was not interested in assisting, so it has taken over ten years to eventually get approval for the drugs that patients desperately needed. The key question is whether such delays are justified simply because prospective data is a requirement and where the refusal to consider retrospective data results in years without progress. RJ strongly agreed and said this was why using the totality of data was critical.

WT wanted to note that the FDA had been a fabulous partner, both in terms of getting drugs approved but also through the open dialogue that they engaged with. WT was keen to engage with the FDA to discuss further the overall current data collection thinking that is ongoing within academia, to try and ensure that the regulator is part of the process. MD repeated her earlier points, namely that quality of patient data is key, and so the FDA far prefers prospective data, but retrospective data would be considered, but how it is used and what conclusions can be drawn would depend on the specifics of the case. Being able to access the granularity of the data and understand what it means for each patient is very important. Being involved early in the process is therefore key to ensure that the data being collected has the best chance of supporting an application. This includes collection of data through registries etc, where the FDA have robust mechanisms for helping and supporting such data capture, including data sources and data elements. MD closed by welcoming contact from stakeholders who wanted support or had questions.

PP noted that there had been some excellent discussions with positive suggestions on the way forward, addressing many topics such as maximising the use of data so that we leave no data behind in the same way that we leave no patient behind. Sources of data and how these can be optimised had been discussed. The fundamental question was how to make these discussions more concrete because dealing

with these issues in an ad hoc manner is a way to ensure that progress is not made. Was it possible to formalise this dialogue so that we can discuss these matters regularly with a time table for deliverables? There are many issues 'on the table' and discussion could take years without coming to any concrete solutions. Given the urgency that has been agreed by all parties today, what could be done to make this process more organised with real deliverables.

PD returned to the issue of prospective versus retrospective data, and wanted to be clear that nobody was saying retrospective data should be ignored. All data needed to be included in an appropriate manner. It would indeed be a pity if any data is neglected. Sometimes data quality would be poor and not very useful, but it must all be considered. Retrospective data can be interesting for the reasons outlined by SST. It can inform on the natural history of the disease, the activity, or the mechanism of action. Nobody was saying that retrospective data can be ignored. But in the not-best-case scenarios, where retrospective data suggests a drug may do something but it is unclear if improvement of some symptoms is of benefit to the patient, then more data would be required and this must be prospective. On this point it appears there is agreement and we already have some results because we have opened an appropriate dialogue as shown in the case of sirolimus for EHE which is a form of pilot discussion. In addition, we have heard of different endpoints that may be more reliable for a given indication. PD noted that the EMA has a process known as the Qualification Procedure that is part of Scientific Advice, and this allows discussion of new proposed endpoints which an applicant believes are valid for a specific indication. So, for example, whether the volume of pleura effusion can be used in EHE can be discussed. So, these tools are available. These are good examples and PD stressed that people should not return home, disappointed and thinking nothing has changed. The EMA is open to consider these matters. This is not a guarantee that the CHMP will approve everything. They may still feel the data is not sufficient for a marketing authorisation, even after all the discussions, but they will do their best to favour the positive issues whenever possible. The EMA will not neglect or ignore any information and can offer collaboration and dialogue to build a system that can be used in similar situations to offer the best opportunity for a positive issue, for the best of the patients, and in a timely manner. The EMA has many processes, and is in good agreement with the FDA, and holds monthly calls to review key issues relating to cancer to ensure that such alignment continues, or understand reasons why not.

PD then noted that the paediatric ACCELERATE programme had succeeded in bringing stakeholders together including industry. One note of caution with ultra-rare diseases is that competition between industry players can fragment the patient community into small groups where studies are less informative. In these cases, keeping studies focused on the full and larger patient cohort is preferred, collecting better evidence for a single development. This is not in the control of the regulators, so PD asked for help from the clinicians and patients to try and ensure that patient engagement is not driven by competition, or the desire for more scientific papers, but with the focus being the delivery of the best development possible for the patients. This would be excellent and much appreciated, and is very important.

MD liked what PD had said and concurred with the points he made. The need to avoid small duplicate studies was important as these often failed and the answers being sought could have been more easily achieved with a coordinated approach. MD also wanted to respond to PP's question about concrete actions. She agreed that breaking the process down into concrete steps and questions created clarity and made responding easier, particularly when dealing with complex issues.

KR wanted to go back to the discussion of prospective and retrospective data, and felt that perhaps the better discussion was how do we achieve the necessary level of scientific rigor into our decision making, and how do we get the level of uncertainty down to a level we are comfortable with? We can then look at how the data is collected. For prospective and retrospective data, it is totally different if for a single-arm trial, we define prospectively, even before the trial has started, how we intend to use any relevant data from outside the trial, compared to adding pre-existing data alongside the trial data, and then developing

a story as to how the data is used. In the latter case the uncertainties are almost impossible to address, whereas in the former case the uncertainties can be addressed. It is therefore very important as part of any data discussion to agree what the prospective research questions are that we want to address and how we intend to use the data that exists and the data that will be prospectively collected. KR felt that this sort of thinking was crucial because staying fixed on the gold standard randomised trial will result in getting stuck and not being able to move forward. KR noted that some questions cannot be answered retrospectively. Considering novel endpoints, these cannot usually be assessed using retrospective data, but that same data may be very influential in moving forward. Finally, with regard to the Qualification Procedure for assessing novel endpoints, KR noted that the traditional pathway requires an independent validation of these endpoints, but that may not be possible due to the rarity of the disease. We may therefore need to prospectively define a very good standard on how these endpoints are defined and how the data is collected, so that we will have to assess the trial and the relevant endpoints once we have the data. This could be on the agenda in discussions of how we intend to change our thinking on endpoints in such a rare disease setting, as the traditional idea of having two years to evaluate an endpoint before introducing it into trials that may take another two years may not be appropriate in light of the urgency.

CV agreed and again confirmed that the EMA is open to dialogue and more flexible meeting structures.

PF agreed with KR's comments. He also suggested that it would be sensible to look at specific cases, the data that is available, and use existing procedures to undertake concrete discussions and try to identify what can be taken forward for a marketing authorisation and also what is missing. It would also be good with regard to planning and a desire to have high quality prospective data, to find alignment on the broad, longer-term scope. PF recognised that there are some 'hot issues' on the table, with some drugs looking positive and urgent patient needs, so suggested we engage and use these examples to see what can be achieved, together with the FDA.

Regarding data, RH noted that in general the EMA goes from observation to general recommendation. If we think of existing retrospective data, this could be a specific registry that is highly dedicated and curated, and is in the hands of the researchers where it can be tailored and refined. Here the regulators will ask how this can be generalised. On the other hand, we have automated data and electronic health records (EHRs) etc which offer more data but the regulator may ask if there is even a ICD-10 code for EHE? This is probably unlikely as you don't have an ICD10 in the EHRs. So how can these issues be addressed, together with the clinical support decisions that will be prospectively relevant and is outside the reach of the regulators? The second point relates to having a plan as to how to merge all this evidence and bring it forward as a case for a medicine or the natural history and this can be discussed in a scientific advice. So, the practical suggestion is that we have general discussions on overarching topics and then case-specific discussions, and we need to see how this can be organised and enriched perhaps with manufacturers insights and science, leading to scientific advice and then use of the scientific advice to take the next regulatory steps. So, in summary, the elements are common discussions, break-out discussions, scientific advices and then taking the results forward. RH confirmed that the EMA is happy to conduct several of these meetings both this year and next year.

HL agreed with the need not to run parallel patient processes, but also thought this applied to the current regulatory discussions. These were seen as very positive but the idea of repeating the entire process with regulators in the UK, Canada, Australia and other key areas was neither sensible nor attractive. He noted that the involvement of multiple regulators would also be potentially attractive to industry as they would recognise the chance to make material progress with a single process. CV agreed and confirmed that their monthly regulator calls were not just with the FDA, but other regulators too.

GB asked MD if a process like ACCELERATE could work for ultra rare diseases? MD noted that that the ACCELERATE programme is unique and is more focused on generating discussion between all stakeholders; a 'meeting of minds'. It is not decisional, but regulators, for example, will take the results

of the discussions back into their decision-making processes. Importantly it also generates questions about paediatric studies for the entire group that can lead to projects and workstreams that are taken forward in a working group format, addressing issues that are perhaps obstructing drug development for example. MD felt that a similar system may have some benefit for ultra-rare diseases as part of a more multi-dimensional solution.

LDA supported the views expressed by KR. LDA then wondered, from a regulatory perspective, if new criteria such as RESCORE might be considered even if they cannot be validated using standard procedures? In reality, for new criteria in ultra-rare sarcomas, it is likely that we will have to rely on clinical observations and the biological rationale behind the criteria. This may not be answered today but is important to understand if we are to consider developing such new assessment criteria.

PD noted that an endpoint can be agreed for a given clinical development when it is believed to be a suitable endpoint for this drug in this disease, and in a scientific advice, but will be restricted to this one drug/disease combination. In the case of 'Qualification' as previously mentioned, this was for an endpoint that could be used beyond the specific development. In other words, general qualification of an endpoint is not acceptable if based on a single disease but may be possible if there are indications across other diseases.

FP expressed admiration for both patients and clinicians and their bravery in developing drugs for these complex treatment situations. He noted that PD had stated that response of the disease may on occasions be a criterion that is sufficient to approve a drug for a disease. He also noted KR's point that uncertainty is not an absolute regulatory threshold but is something that we need to manage and decide collectively if it is acceptable when we see the data. If we combine these two points, then perhaps if the clinician and patients tell the regulator, then they can design criteria that are clinically meaningful and tell us how the drug is working and how the patients are benefitting, and this does not require complex randomised trials as we trust the response when we see it that it is meaningful. Regulators are open to look at this and that is an important step forward. FP suggested to PD and FR that if there is a clear message from the community that there is clinical relevance and value to a response, should we be asking for surrogate validation? We should be able to value this in the benefit risk assessment. This is an important issue to take forward with the oncology working party and guidelines. FP also noted HL's comment that rare cancers are not rare to those who have them, they are just a frightening disease. FP suggested that we need to retitle the workshop as in reality it is not about ultra-rare diseases, but in fact any disease for which there is a very high unmet need. So, these discussions and what we are seeking to achieve have an even wider application including any situations where we have a disease without an approved treatment but where there is also a meaningful response that patients and clinicians believe can be interpreted.

MD valued the questions about endpoints. In terms of validating new criteria to support evidence of efficacy, MD noted the importance of continued discussions and encouraged all parties to engage with regulators as early as possible so that they could be involved and also include fellow regulators. The FDA is ready to consider new endpoints, but these need to be contextualised and understood. For example, will they be primary endpoints or just for additional supportive validation? There is more than one way to validate endpoints and discussing how this is done is important. MD noted that the FDA recently deviated from their standard practice when they granted accelerated approval to a drug based on an endpoint that included 'minor' responses in addition to 'partial' and 'complete' responses, based on information provided in the application suggesting that partial responses provided a benefit to patients.

DR endorsed the view point that studies should attempt to include all patients. From the EHE experience there was no justification for ignoring anyone. It is important to ensure that with modern technology issues such as losing patients due to limited places of contact do not occur. CV agreed and also noted the

importance again of maximising numbers and avoiding competitive processes that divide the patient community.

SST noted that the end of the day was approaching and wanted to suggest that, at the next workshop in the autumn, PUSH would be presented more fully using specific examples. However, SST suggested it would be good to have industry involvement, but SST wanted to check if anybody felt that this could be seen as a conflict of interest, although it was clearly not possible to develop or repurpose drugs without the appropriate companies being involved. SST asked if anybody had any ideas regarding getting industry players to come to the meetings, and engage in something like the repurposing process. FP agreed that this was essential, and an area where the EMA would be able to provide an appropriate framework for such discussions and so this should not be seen as a limitation.

DL thanked all participants for taking part in such a lively discussions, and handed over to PD and SST for closing comments.

4. Closing Remarks:

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

PD started by thanking everybody for their participation and was very pleased that the day had been very productive, with all parties understanding each other better and better. In summary, he felt that all parties want safe and effective drugs to be available as soon as possible. In the case of rare disease, the rarity is a reason 'to do much', and not 'to do nothing'!

PD noted that to make progress it is essential that all stakeholders work together. We have to accept that we won't always agree but we should all do our best to get patients what they need. PD confirmed that the EMA would adapt where necessary. He also noted that the process was easier for the regulators as they just considered the data presented. It was the applicant groups that had the far harder task of collecting the data. But PD assured the group that regulators would remain flexible, available and would act with good will. The EMA is ready to establish new processes, ready to consider retrospective data, and is ready to agree new endpoints where appropriate. In fact this is something that is already done at CHMP and in the Scientific Advice process when the classical approach does not work. The EMA can also help with industry involvement and will not 'ask for the moon'. In short, PD was confident that agreement can be found as everybody appeared to be on the same page within a 'great meeting'.

SST thanked PD, FP and everybody else at the EMA and FDA again for all their hard work, and everybody else who had contributed to a great day with great discussion. SST confirmed that the EORTC group would prepare a manuscript that would summarise both this workshop and the previous workshop held in January, and felt that this would be good for industry too. She committed to agreeing the day for the next meeting and to prepare further contributions. With that said, SST thanked all the patients and other participants for their hard work and wished everybody a safe trip home.

Finally, Gerry Finey, a sarcoma patient of several years, wanted to express his encouragement at the motivation and enthusiasm of everybody present for the very important topics discussed, and for giving him the opportunity to be present and to contribute.

REFERENCES

1. Stacchiotti S, Miah AB, Frezza AM, Messiou C, Morosi C, Caraceni A, et al. Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts. Vol. 6, *ESMO Open*. 2021.
2. Frezza AM, Napolitano A, Miceli R, Badalamenti G, Brunello A, Buonomenna C, et al. Clinical prognostic factors in advanced epithelioid haemangioendothelioma: a retrospective case series analysis within the Italian Rare Cancers Network. *ESMO Open*. 2021;6(2).
3. Rosenbaum E, Jadeja B, Xu B, Zhang L, Agaram NP, Travis W, et al. Prognostic stratification of clinical and molecular epithelioid hemangioendothelioma subsets. *Modern Pathology*. 2020;33(4).
4. Lau K, Massad M, Pollak C, Rubin C, Yeh J, Wang J, et al. Clinical patterns and outcome in epithelioid hemangioendothelioma with or without pulmonary involvement: Insights from an internet registry in the study of a rare cancer. *Chest*. 2011;140(5).
5. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin JC, Pujol S, et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magn Reson Imaging*. 2012;30(9).
6. 3DSlicer [Internet]. [cited May 17, 2024]. Available at: <https://www.slicer.org/>
7. Orsatti G, Morosi C, Giraudo C, Varotto A, Crimi F, Bonzini M, et al. Pediatric rhabdomyosarcomas: Three-dimensional radiological assessments after induction chemotherapy predict survival better than one-dimensional and two-dimensional measurements. *Cancers (Basel)*. 2020;12(12).
8. RESCORE RADIOLOGIC ASSESSMENT CRITERIA (Response Evaluation by Symptomatic Change and Outcomes Reporting)
9. PAIN ASSESSMENT CRITERIA
10. Caraceni A, Portenoy RK; a working group of the IASP Task Force on Cancer Pain. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. *Pain*. 1999 Sep;82(3):263-274. doi: 10.1016/S0304-3959(99)00073-1. PMID: 10488677.
11. Portenoy RK, Ahmed E. Cancer Pain Syndromes. *Hematol Oncol Clin North Am*. 2018 Jun;32(3):371-386. doi: 10.1016/j.hoc.2018.01.002. Epub 2018 Mar 22. PMID: 29729775.
12. Perrot S, Cohen M, Barke A, Korwisi B, Rief W, Treede RD; IASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: chronic secondary musculoskeletal pain. *Pain*. 2019 Jan;160(1):77-82. doi: 10.1097/j.pain.0000000000001389. PMID: 30586074.
13. Caraceni A. Evaluation and assessment of cancer pain and cancer pain treatment. *Acta Anaesthesiol Scand*. 2001 Oct;45(9):1067-75. doi: 10.1034/j.1399-6576.2001.450903.x. PMID: 11683654.
14. Caraceni A, Martini C, Zecca E, Portenoy RK, Ashby MA, Hawson G, Jackson KA, Lickiss N, Muirden N, Pisasale M, Moulin D, Schulz VN, Rico Pazo MA, Serrano JA, Andersen H, Henriksen HT, Mejholm I, Sjogren P, Heiskanen T, Kalso E, Pere P, Poyhia R, Vuorinen E, Tigerstedt I, Ruismaki P, Bertolino M, Larue F, Ranchere JY, Hege-Scheuing G, Bowdler I, Helbing F, Kostner E, Radbruch L, Kastrinaki K, Shah S, Vijayaram S, Sharma KS, Devi PS, Jain PN, Ramamani PV, Beny A, Brunelli C, Maltoni M, Mercadante S, Plancarte R, Schug S, Engstrand P, Ovalle AF, Wang X, Alves MF, Abrunhosa MR, Sun WZ, Zhang L, Gazizov A, Vaisman M, Rudoy S, Gomez Sancho M, Vila P, Trelis J, Chaudakshetrin P, Koh ML, Van Dongen RT, Vielvoye-Kerkmeier A, Boswell MV, Elliott T, Hargus E, Lutz L; Working Group of an IASP Task Force on Cancer Pain. Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. *Palliat Med*. 2004 Apr;18(3):177-83. doi: 10.1191/0269216304pm890oa. PMID: 15198130.
15. Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain*. 1995 May;61(2):277-284. doi: 10.1016/0304-3959(94)00178-H. PMID: 7659438.
16. Harris K, Li K, Flynn C, Chow E. Worst, average or current pain in the Brief Pain Inventory: which should be used to calculate the response to palliative radiotherapy in patients with bone metastases?

Clin Oncol (R Coll Radiol). 2007 Sep;19(7):523-7. doi: 10.1016/j.clon.2007.04.007. Epub 2007 Jun 12. PMID: 17566723.

17. Atkinson TM, Mendoza TR, Sit L, Passik S, Scher HI, Cleeland C, Basch E. The Brief Pain Inventory and its "pain at its worst in the last 24 hours" item: clinical trial endpoint considerations. *Pain Med*. 2010 Mar;11(3):337-46. doi: 10.1111/j.1526-4637.2009.00774.x. Epub 2010 Jan 15. PMID: 20030743; PMCID: PMC3806650.
18. Farrar, J. T. , Young, J. P. , LaMoreaux, L. , Werth, J. L. & Poole, M. R. (2001). *Pain*, 94 (2), 149-158. doi: 10.1016/S0304-3959(01)00349-9.
19. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, von Stein T, White RE, Witter J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008 Feb;9(2):105-21. doi: 10.1016/j.jpain.2007.09.005. Epub 2007 Dec 11. PMID: 18055266.
20. Corli O, Montanari M, Greco MT, Brunelli C, Kaasa S, Caraceni A, Apolone G. How to evaluate the effect of pain treatments in cancer patients: results from a longitudinal outcomes and endpoint Italian cohort study. *Eur J Pain*. 2013 Jul;17(6):858-66. doi: 10.1002/j.1532-2149.2012.00257.x. Epub 2012 Dec 5. PMID: 23213042.
21. Buckley MM, Brogden RN. Ketorolac. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. *Drugs*. 1990 Jan;39(1):86-109. doi: 0.2165/00003495-199039010-00008. PMID: 2178916.
22. Patrignani P, Patrono C. Cyclooxygenase inhibitors: From pharmacology to clinical read-outs. *Biochim Biophys Acta*. 2015 Apr;1851(4):422-32. doi: 10.1016/j.bbalip.2014.09.016. Epub 2014 Sep 28. PMID: 25263946.