# Retrospective observational studies in ultra-rare sarcomas: a consensus paper from the Connective Tissue Oncology Society (CTOS) community of experts on the minimum requirements for the evaluation of activity of systemic treatments

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# Retrospective observational studies in ultra-rare sarcomas: a consensus paper from the Connective Tissue Oncology Society (CTOS) community of experts on the minimum requirements for the evaluation of activity of systemic treatments

**Abstract**

**Background.** In ultrarare sarcomas (URS) the conduction of prospective, randomized trials is challenging. Data from retrospective observational studies (ROS) may represent the best evidence available. ROS implicit limitations led to poor acceptance by the scientific community and regulatory authorities. In this context, an expert panel from the Connective Tissue Oncology Society (CTOS), agreed on the need to establish a set of minimum requirements for conducting high-quality ROS on the activity of systemic therapies in URS.

**Methods.** Representatives from >25 worldwide sarcoma reference centres met in November 2020 and identified a list of topics summarizing the main issues encountered in ROS on URS. An online survey on these topics was distributed to the panel; results were summarized by descriptive statistics and discussed during a second meeting (November 2021).

**Results.** Topics identified by the panel included the use of ROS results as external control data, the criteria for contributing centers selection, modalities for ensuring a correct pathological diagnosis and radiologic assessment, consistency of surveillance policies across centers, study end-points, risk of data duplication, results publication. Based on the answers to the survey (55 of 62 invited experts) and discussion the panel agreed on 18 statements summarizing principles of recommended practice.

**Conclusions.** These recommendations will be disseminated by CTOS across the sarcoma community and incorporated in future ROS on URS, to maximize their quality and favor their use as control data when results from prospective studies are unavailable. These recommendations could help the optimal conduction of ROS also in other rare tumors.

**Key words.** Ultra-rare sarcoma, sarcoma, retrospective study, observational study, methodology, consensus.

## Introduction

In 2020, a multidisciplinary group of experts from the global sarcoma community, under the umbrella of the Connective Tissue Oncology Society (CTOS), reached a consensus on the definition of ultra-rare sarcomas (URS), established as sarcoma types with an incidence of ≤1/1,000,000 people/year [1]. The proposal of a threshold for defining URS was mainly intended to identify those sarcomas felt to be particularly challenging from a research and development standpoint, due to their rarity. As a consequence of the definition, a list of ultra-rare soft tissue sarcomas (55 types) and bone sarcomas (22 types) was produced based on histopathologic and, in some cases, molecular diagnostic criteria, according to the WHO classification and with the commitment of the group to update the list regularly [1,2]. As a whole, URS currently constitute approximately 20% of all sarcomas.

Informative prospective data on the natural history and treatment outcome in each URS type are often limited or unavailable, which is a major impediment to understanding the disease and proving the utility of new therapies. There are major challenges in the design and conduct of prospective, multinational, controlled clinical trials in such exceedingly rare diseases. In this setting, reliable and consistent results from retrospective studies could serve a uniquely important role as potential synthetic control data against which to evaluate treatment outcomes from new therapeutic approaches. Variations in presentation, risks of recurrence and/or metastatic spread, prognosis, and sensitivity or resistance to therapeutic modalities are important to define so as to narrow confidence intervals and to make non-randomized data useful and reliable.

Many experts across the global sarcoma community have developed international collaborative research projects over the past years to collect and analyze retrospective data in URS on the activity and tolerability of therapeutic agents available in the clinical practice,

to build evidence supporting the design of clinical studies on new systemic compounds, and to provide data to be considered for external comparison [3-8].

Retrospective observational studies (ROS) may represent the best evidence available for URS, although their implicit limitations led to poor acceptance by the general scientific community and regulatory authorities. Commonly noted criticisms of retrospective data in rare diseases focus on the potential for selection bias, possible lack of generalizability, heterogeneity in measurements of treatment outcomes, diagnostic uncertainty, and other possible confounding factors related to clinical assessments [9].

Against this background, the same community of sarcoma experts met virtually in November 2020 and November 2021 and agreed on the need to establish a set of minimum requirements for planning and conducting high-quality retrospective studies on the activity of systemic therapies in URS, in order to minimize their limitations and maximize their utility in further research and development efforts. This manuscript reports the rationale and results of these consensus meetings.

## Material and Methods

A first virtual consensus meeting was organised under the umbrella of CTOS (November 18th, 2020) to discuss the minimum requirements to conduct ROS on the activity of systemic agents in URS, with the final goal of facilitating the most appropriate development and approval of novel therapeutics for patients with URS. Representatives from >25 sarcoma reference centers (SRCs) in the EU, USA, Canada, Asia, and Australia, covering all disciplines involved in the research and care of sarcoma patients (epidemiology, pathology, molecular biology, radiology, surgery, radiotherapy, medical oncology, biostatistics) were present.

In May 2021, an online survey entitled ”*URS: minimum requirements for evaluation of the activity of systemic treatments*”, covering the main issues encountered over the years while running ROS, was distributed to the multidisciplinary panel of experts (Supp. Figure 1). The topics covered by the survey included:

- use of results derived from ROS as external control data when a randomized study is not feasible
- criteria for the identification of centers which should be allowed to contribute data (including suggestions for investigator training at such centers)
- pathological diagnosis and its reliability (in the presence and absence of an available molecular diagnostic marker)
- modalities for retrospective radiologic assessment
- consistency in follow-up timing and procedures across contributing centers
- study end-points
- risk of data duplication
- result publication

The survey data were summarized by descriptive statistics.

Finally, a second virtual consensus meeting was organized during the 2021 CTOS Annual Meeting, held virtually on November 10th. The results of the survey were presented and, following discussion, the CTOS panel of experts agreed on a statement for each of the below mentioned points.

## Results

At the meeting November 18th, 2020, the panel of experts agreed on the need to define the minimum requirements to standardize the planning and conduct of ROS on the activity of systemic agents in URS. The aim was to improve as much as possible the quality of such studies with the final goal of facilitating the optimal development and approval of novel therapeutics for patients with these diseases.

Of 62 experts invited to participate in the survey, 55 answered the questionnaire. Following the survey and the final discussion, the group eventually agreed on 18 statements summarizing principles of recommended practice in conducting ROS on systemic agents in URS. Each field of discussion and the consensus recommendations are listed below and summarized in Table 1**.**

1. *Use of results of ROS as control data in URS*

93% (53/55) of participants in the survey agreed on the importance of being able to rely upon results from high-quality, pre-defined ROS as control data in assessing outcomes for URS. During the final discussion, no critical issues were raised on this item.

Recommendation: For URS (i.e sarcomas with an incidence ≤1/1,000,000/year), it is our community's aspirational goal to use results from high-quality, pre-defined ROS as control data when data from prospective randomized or non-randomized studies are unavailable in these patient groups.

2. *Selection criteria for contributing centers*

90% (49/55) participants in the survey agreed that selection criteria for contributing centers were required. Training of investigators was also viewed as a critical component supporting the surrogate quality measure of "center selection".

The panel agreed that for ROS of medical therapies in URS, it is critical to find the right balance between the competing needs of expanding patient samples as much as possible to provide meaningful results, and ensuring collection of high-quality data through the involvement of SRCs/networks with expertise in the disease management.

Without universally established criteria for the designation of a SRC, and considering the differences in terms of established networks especially across the EU, USA and Canada, the panel agreed that selection based on volume (at least 100 new sarcoma cases discussed at the multidisciplinary tumor board per year) and the availability of a dedicated sarcoma multidisciplinary team made of physicians from different disciplines with specific training in sarcoma could be reasonably applied to identify contributing institutions. These criteria are currently used both within the European Reference Network on Rare Adult Solid Cancers (EURACAN) and by the United Kingdom National Institute of Health and Care Excellence (NICE) for designation of SRCs. Furthermore, in those countries where there is a formally established national sarcoma network [e.g. Italian Rare Cancer Network (Italy); NETSARC (France); GEIS (Spain), GISG and network of accredited sarcoma centers (Germany), etc.], often linked to the European Reference Networks (ERNs) or, more in general, to reference centers as defined above, cases managed within the network by spoke centers in collaboration with national hubs could contribute to the series with the aim of including additional valuable information. The overall number of patients receiving treatment within the network but outside SRCs should be annotated in the manuscript when reporting the results. While it is recognized that the patients referred to SRC in some countries may represent a biased population, we anticipate that there will be greater diagnostic accuracy and sarcoma-oriented surgical, radiation, and medical treatment which will add greater confidence in outcome assessments.

Recommendation: - Given the risk of misdiagnosis and practice variability, it was considered that data homogeneity might be optimized by focusing on

SRCs (i.e., centers with at least 100 new sarcoma patients per year discussed at multidisciplinary tumor boards by experts with specific training in sarcoma) as the primary source of data collection for ROS on medical therapies in URS.

- In those countries where a formalized national network for sarcoma care is in place, the inclusion of cases co-managed with national spokes should be allowed, provided that the critical steps of a patient's pathway (i.e. diagnosis, primary surgery, establishment of treatment plan, <radiological assessment of treatment response) took place at, or were shared with, a SRC.

3. *Ensuring the quality of pathological diagnosis*

98% (54/55) of participants in the survey agreed on the need of expert pathological review for all cases included in the series.

The group agreed that, in principle, centralizing the pathological review in few SRCs with particular expertise in the URS type that is the subject of the study would represent the ideal strategy to ensure the correct inclusion of patients. However, this may not be always feasible due to the lack of resources and logistic challenges, especially when multiple worldwide institutions are involved. In this case, internal review of all contributed cases should be regarded as appropriate as each contributing center or network will have an in-house expert sarcoma pathologist, consistent with Recommendation 2. Since even across SRCs there can be a degree of variability in pathological expertise, the pathologists joining the meeting agreed to establish a dedicated working group to define, ahead of any new retrospective effort, essential diagnostic criteria for the sarcoma under study, to be shared with all contributing centers, and available for centralized review of those complex cases not fully

matching these criteria. Digital pathology was recommended although it presently might not represent a feasible strategy for the review of all cases, due to the heterogeneous degree of implementation across countries. As approximately 50% of URS types are characterized by pathognomonic genomic alterations (e.g. mutations, gene-fusions) [2] the panel agreed that, when applicable, their assessment by either immunohistochemistry (IHC) or molecular testing should be performed to support the diagnosis.

Recommendations:
- Pathologic diagnosis of all cases included in the study should be confirmed by an expert sarcoma pathologist within a SRC/network
- Ahead of starting the study, dedicated sarcoma pathologists should provide consensus on the morphological, immunohistochemical, and molecular diagnostic requirements for the specific URS type which is object of the study, based on the latest WHO diagnostic criteria.
- For difficult cases (including those not matching the pre-established pathological requirements), centralized pathological review in selected sarcoma centers, with specific expertise in that specific sarcoma type, is advisable. Digital pathology could be considered in order to minimize the need of material transfer.
- When required for diagnosis, evaluation of characteristic IHC or molecular markers should be performed.
- All uncertain/questionable cases should be excluded by the analysis to avoid contamination of the data set.

*4. Radiological assessment of response and disease progression*

The survey showed consensus (55/55, 100%) on the need of radiological review in SRCs, based on imaging and not on radiological reports alone. Radiologic review should be done

by radiologists with specific experience in the sarcoma type under study. As for pathology review, consideration should be given to centralization of images if within the constraints of resources and logistical challenges.

Radiological evaluation of progressive disease prior to treatment start and treatment response in retrospective studies were among the most challenging items of discussion, as 1) it is not possible to properly apply pre-established radiological criteria retrospectively (e.g. RECIST, WHO, Choi) in patients treated outside of clinical trials, 2) retrieving images performed outside the SRC is often not feasible, 3) there can be variations in timing and modality of disease assessment across centers. On this background, the group agreed that the assessment of radiological response and of radiologic progression before treatment start should be reviewed by a radiologist in collaboration with a clinician of each participating sarcoma expert center and defined simply as response (R), stable disease (S) and progressive disease (P) according to radiologist's overall judgment without following pre-established metrics (e.g. RECIST 1.1).

The clinical progression of disease prior to treatment start should be taken into account, valued, and reported even in the absence of objective radiological progression. We acknowledge that this kind of radiological assessment might imply issues in replicability across centers, but specific efforts aiming to estimate the possible impact of this inter-observer variability will be put in place.

Recommendation: - The radiological assessment of response to systemic treatments and of progression prior to treatment start should be performed in SRCs and should not be based on radiological or medical reports, but on retrospective review of radiological images performed by a radiologist trained in the assessment of the URS subject of the study.

- Radiological assessment should define response (R), stable disease (S) and progressive disease (P) according to the radiologist's determination without following pre-established metrics (e.g. RECIST), which cannot be applied retrospectively.

- In the assessment of radiologic progressive disease prior to treatment start, clinical progression should be also taken into consideration, valued, reported, and provided on a time scale (possibly depending on the type sarcoma).

5. *Consistency in the frequency of disease monitoring across centers*

Variability in the timing of disease monitoring across sites can influence retrospective assessment of outcome measures such as progression free survival (PFS). The proposal that the typical frequency of disease monitoring at each institution should not influence patient inclusion, but should be assessed through a dedicated survey to be circulated across contributing institutions was the one that found the most consensus (47% [26/55]) among survey participants.

The results of this survey will have to be reported/disclosed in the manuscript, and will need to be considered when judging the study results (i.e., depending on the magnitude of observed differences in study end-points). Starting from the survey results, dedicated simulation studies will be performed to assess the magnitude of distortion introduced by the different monitoring across institutions, and will be reported in the manuscript.

Recommendation: - All eligible patients should be included in the study, to minimize ascertainment bias.

- A survey across contributing institutions should be circulated to assess the institutional approach for evaluation of the disease status of patients

with the specific sarcoma type. The outcome of the survey should be reported in the final paper.

6. *End-point selection*

The survey showed that the preferred option (46%, 25/54) was to use overall response rate (ORR) (following a response assessment methodology as defined above), PFS, and overall survival (OS) as the most reliable endpoints. In addition, PFS at 6 months is felt to be another reasonably robust and simple endpoint when immune-agents are investigated, as new data have pointed out that PFS at 6 months correlates with survival in immunotherapy trials, while ORR does not [10].

During the live discussion, a further endpoint was discussed as an alternative in this setting, which is time to next treatment. However, the group felt overall that this endpoint should be used with caution as patients might continue on the same treatment beyond radiological progression due to clinical benefit and/or absence of other therapeutic options.

Also, although recognizing the importance of additional data on toxicity or quality of life, the majority of participants in the survey (53%, 29/55) felt that no additional data can be reliably and consistently collected in a retrospective setting, with the possible exception of severe adverse events (i.e. grade 4 and 5) recorded while on treatment, and details of additional local treatment strategies (e.g. radiotherapy and surgery).

Recommendation: - ORR, PFS, PFS at 6 months and OS are the most reasonable endpoints to be used in ROS on the activity of medical therapies in URS.

- An effort should be made to collect data on severe adverse events recorded while on treatment and details on additional local treatment strategies.

*7. Avoidance of data duplication*

One of the main issues while running multicenter ROS includes the risk of data duplication. This risk can imply both the possibility of the same patient being reported in multiple retrospective series, or the possibility that data of the same patient, treated or evaluated at multiple institutions, may be reported twice or more in the same series.

There was general agreement that reporting the same patient/series of patients in more than one ROS can be acceptable providing that it is clearly disclosed.

More challenging is how to avoid duplication of data from the same patient, treated at multiple institutions, in the same series/retrospective study. To limit this risk, it is advisable 1) to allow data entry for a specific patient only by the center which administered the treatment, and 2) ask explicitly in the data collection spreadsheet if the patient was treated in different centers (and which) to identify cases which might be at risk of duplication. Finally, many of the respondents to the survey (21/43, 48%) suggested to use demographic data to highlight possibly duplicated cases and send a specific query to the contributing institutions for a cross-check.

Recommendation: - The inclusion of the same patient(s) in multiple series is acceptable as long as this is clearly disclosed and described in the paper.

- To avoid duplication of data from the same patient, it is advisable to 1) allow data entry of a specific patient only to the centes which administered the treatment, 2) include an item in the data collection spreadsheet asking if the patient was treated in different centers (and

which), and 3) use demographic data to cross-check and highlight possibly duplicated cases.

8. *Results publication*

There was a general consensus (98%, 54/55) supporting the importance of reporting all results, including negative studies.

Recommendations: - All results, including negative results, should be published.

Table 2 lists the distinguishing quality features, their links with the survey questions and the statements set out in the results section, together with some additional items that that should be addressed by ROS in order to produce reliable evidence.

## Discussion

Improving the quality of care and outcome of patients affected by sarcomas and other rare cancers requires global collaborative efforts to increase the knowledge about each tumor type and help design prospective clinical studies that focus specifically on each uniquely different and rare tumor entity. Indeed, connective tissue tumors represent not a single disease but consist of >150 distinct entities [2]. The study of sarcomas is particularly challenging in URS. Under the umbrella of CTOS, a representative group of the global sarcoma community began working together in 2019 to facilitate clinical research specifically in the context of URS.

Randomized controlled trials (RCTs) remain the most trusted and reliable source of information regarding safety and efficacy in development of new therapeutics. However, considering the number of patients that are needed to carry out well-powered RCT, these are generally not feasible in a reasonable timeframe in URS except for the unusual case of a new therapeutic agent with an enormously large effect size on outcomes. For development of the majority of useful therapeutics, other strategies are needed to collect reliable clinical information in a systematic manner. Often, an interventional, prospective uncontrolled study is the only feasible option. If so, external controls are needed to compare the new treatment with a standard of care. Thus, reliable external control data representative of the standard of care may be precious for the design and analysis of uncontrolled clinical trials, to obtain benchmark estimates (e.g. response frequency, median disease-free, PFS, OS). Ideally, external controls should be incorporated in the protocol of such uncontrolled studies, to evaluate the experimental treatment, or even to support an early closure of the study when the experimental treatment is ineffective [11]. Such external controls may well be captured through clinical registries [12[. These are indeed dedicated efforts to prospectively record all

consecutive cases meeting specified inclusion criteria within a cancer institution, a cancer network, a collaborative research group, etc. Of course, these registries can be exploited also as a source of data to explore the real-world effectiveness of treatments whose efficacy was already studied through RCT. As a matter of fact, however, multi-institutional ROS have been instrumental in building evidence on the activity of medical therapies in several URS, leading to the availability of results which are used to inform clinical practice [3-8]. This consensus meeting was the first attempt to provide guidelines and structure regarding ROS in URS to develop qualitatively valid sources of reliable evidence, while acknowledging and overcoming their widely recognized limitations. The consensus group agreed that these results should be considered as a source of external control data in single-arm prospective studies of specific URS entities. However, to obtain high-quality data to be used in supporting the development and regulatory approval of novel therapeutics for URS when RCT are not feasible, it was felt necessary to define a set of minimum requirements to increase the quality of these ROS and to standardize as much as possible the collection of data within the sarcoma community, while maintaining the feasibility of their acquisition. Such requirements may be crucial to drive future ROS as well as the construction of prospective clinical registries.

The consensus meetings addressed 8 different topics and results of the discussion were summarized in 18 statements (Table 1). A high level of agreement (≥90%) was reached in the group about the need of selecting the centers participating in data collection, ensuring the quality of pathological diagnosis and radiologic response assessment, and reporting all results, including the negative ones. Conversely, an extensive discussion was required to agree on criteria to define a center as a sarcoma center of expertise, alternative strategies to overcome the need for centralization, both for pathological and radiological review, with the goal of balancing the need for collecting high-quality data while keeping this kind of effort

feasible despite legal constraints, such as those regulating privacy and material transfer, and the absence of dedicated funding.

Similarly, other challenging items included the identification of mechanisms to lower the risk of data duplication and limit the impact of consistency in the frequency of disease monitoring across centers on results. The discussion led to the proposal of complementary solutions, including the need of 1) establishing a pathological workgroup dedicated to URS to define minimal diagnostic criteria for the sarcoma under study, 2) exploiting new approaches such as digital pathology for complex cases, 3) developing a simplified way to retrospectively evaluate disease response which is consistent with everyday clinical practice, and 4) improving data accuracy to avoid data duplication (see “Results” section for details).

The group focused on ROS in URS, addressing the main constraints/issues that are specifically related to the rarity of these entities. In this manuscript, we did not cover other aspects that are relevant to the conduct of high-quality ROS in general, independently from disease incidence, but that certainly also apply to URS, or other methodological approaches for using external data. These statements can be taken from previously published guidelines and checklists such as, for instance, those developed by the ISPOR Task Force on Retrospective Databases [13]. The ISPOR checklist highlights the importance of 1) a clear definition of the study population (i.e. description of inclusion and exclusion criteria), 2) a definition for censoring (time limits placed at the beginning or end of the study period may potentially distort the selection and generalizability of the results), 3) assessment of data reliability and validity, 4) application of methods of linkages among data sources and different centers (which should be described, by identifying and annotating any problems that could affect data validity or study findings). These aspects should be taken into consideration also when ROS are conducted in URS. The ISPOR checklist also underlines the value of an appropriate definition of control group and reduction of imbalance in potential

confounding factors between treated and control patients (when the attempt is to undertake a comparative study). Another important contribution to the discussion on how to strengthen the reporting of observational studies is the STROBE statement, born from an international collaborative initiative of epidemiologists, methodologists, statisticians, researchers, and journal editors [14]. The STROBE statement indicates how follow-up quality (type of assessment and length) and completeness are critical to determine the accuracy of statistical estimates and correlate directly with accuracy of study findings. Ideally, cancer study findings should be based on complete follow-up information, which is often impractical in ROS. Thus, it is important to systematically declare how complete follow-up is, since otherwise the study validity cannot be judged [15]. In addition, patients in retrospective series should ideally be consecutive and a denominator of the total number of observed patients relative to the number from which data were obtained should be provided. Finally, the consensus meeting did not discuss how to incorporate a control group and other statistical considerations on optimal study design in conceiving and reporting ROS on systemic treatment in URS. These more technical topics are already discussed in other papers such as by Rehman et al., a review on the use of external data in the design and analysis of clinical trials in the context of glioblastoma which (similar to URS) involves considerable challenges in drug development [16] and will be the focus of a future group meeting.

The recommendations presented in this manuscript will not be able to prevent all criticisms about retrospective data raising issues such as selection bias, lack of generalizability, heterogeneity of measurements of treatment outcomes, and other possible confounding factors related to clinical assessments [9], However, they are mainly meant to apply to the use of observational data as external controls for prospective interventional non-randomized studies, i.e, to generate external observational evidence to improve the analysis of

interventional single-arm prospective clinical trials, upon which to possibly base new agent approvals. Sometimes, approvals may be based on real-world evidence (RWE) alone, but this will mainly be the case when the magnitude of benefit of a new agent is exceptional. We also believe that a major effort to build prospective clinical registries may be crucial for future drug development in ultra-rare cancers, as registries can prospectively standardize procedures to capture data and their format (17). An effort to create a prospective clinical registry on sarcomas and other rare adult solid cancers has been launched, for example, in an ERN such as EURACAN, first focusing on ultra-rare cancers.

CTOS and all the members of this group are committed to incorporating all the recommendations presented here in future ROS it will carry out in URS and disseminate them across the community of sarcoma investigators, practicing clinicians, and patients, families, and advocates. In addition, several principles stated in the manuscript would apply also to ROS on URS not specifically addressing the role of medical treatments. Indeed, the value of observational evidence in ultra-rare cancers goes much beyond the investigation of new anti-cancer agents. Many times, even the natural history of such cancers is poorly known, and the value of observational retrospective or prospective RWE is enormous, especially if a significant number of consecutive cases within a given setting can be collected. This paper may indeed serve as a backbone to further discuss research methodology in URS.

## Tables

**Table 1.** Summary of recommendations on the minimum requirements to conduct valuable retrospective studies on the activity of systemic treatments in ultra-rare sarcomas

| Item | Recommendations |
|---|---|
| **Use of results of retrospective studies as control data in ultra-rare sarcomas** | - For URS (i.e. sarcomas with an incidence ≤1/1,000,000), it is our community's aspirational goal to use results from high-quality, pre-defined retrospective studies as control data when data from prospective randomized or non-randomized studies are unavailable in these patient groups. |
| **Selection criteria for contributing centers** | - Given the risk of misdiagnosis and practice variability, it was considered that data homogeneity might be optimized by focusing on sarcoma reference centers (SRCs) (i.e., centers with at least 100 new sarcoma patients per year discussed at multidisciplinary tumor boards by experts with specific training in sarcoma) as the primary source of data collection for retrospective studies on medical therapies in URS.<br>- In those countries where a formalized national network for sarcoma care is in place, the inclusion of cases co-managed with national spokes should be allowed, provided that the critical steps of a patient's pathway (i.e. diagnosis, primary surgery, establishment of treatment plan, radiological assessment of treatment response) took place at, or were shared with, a SRC. |
| **Ensuring the quality of pathological diagnosis** | - Pathologic diagnosis of all cases included in the study should be confirmed by a expert sarcoma pathologist within a SRC/ network<br>- Ahead of starting the study, dedicated sarcoma pathologists should provide consensus on the morphological, immunohistochemical, and molecular diagnostic requirements for the specific URS type which is object of the study, based on the latest WHO diagnostic criteria.<br>- For difficult cases (including those not fully matching the pre-established pathological requirements), centralized pathological review in selected sarcoma centers, with specific expertise in that specific sarcoma type, is advisable. Digital pathology could be considered in order to minimize the need of material transfer.<br>- When required for diagnosis, evaluation of characteristic IHC or molecular markers should be performed.<br>- All uncertain / questionable cases should be excluded by the analysis to avoid contamination of the data set. |

| | |
|---|---|
| **Radiological assessment of response and disease progression** | - The radiological assessment of response to systemic treatments and of disease progression prior to treatment start should be performed in SRCs and should not be based on radiological or medical reports, but on the retrospective review of radiological images performed by a radiologist trained in the assessment of the specific URS which is the subject of the study.<br>- Radiological assessment should define response (R), stable disease (S) and progressive disease (P) according to the radiologist's determination without following pre-established metrics, which cannot be applied retrospectively.<br>- In the assessment of radiologic progressive disease prior to treatment start, clinical progression should be also taken into consideration, valued, reported, and provided on a time scale (possibly depending on the type sarcoma). |
| **Consistency in the frequency of disease monitoring across centers** | - All eligible patients should be included in the study.<br>- A survey across contributing institutions should be circulated to assess the institutional approach for evaluation of the disease status of patients with the specific sarcoma type. The outcome of the survey should be reported in the final paper |
| **Endpoint selection** | - ORR, PFS, PFS at 6 months and OS are the most reasonable endpoints to be used in retrospective studies on the activity of medical therapies in URS<br>- An effort should be made to collect data on severe adverse events recorded while on treatment and details on additional local treatment strategies |
| **Avoidance of data duplication** | - The inclusion of the same patient(s) in multiple series is acceptable as long as this is clearly disclosed and described in the paper<br>- To avoid duplication of data from the same patient, treated at multiple institutions, within one series it is advisable to 1) allow data entry of a specific patient only to the center which administered the treatment, 2) include an item in the data collection spreadsheet asking if the patient was treated in different centers (and which), and 3) use demographic data to cross-check and highlight possibly duplicated cases. |
| **Results publication** | - All results, including negative results, should be published |

**Table 2** Quality features of observational retrospective studies on medical therapies in ultra-rare sarcomas in relation to the survey questions and CTOS community of experts' recommendations.

| Quality elements | Details | Survey question | Recommendation |
|---|---|---|---|
| **Protocol** | Study hypotheses should be clearly formulated. | Q1 | XX.1 |
| | Establish participating centers, setting, location, recruitment period. | Q2 | XX.2 |
| | Establish eligibility criteria. | Q6 | XX.5 |
| | Establish appropriate study design and select an adequately sized sample | | |
| **Data** | Use reliable and verifiable data sources (paper/electronic medical records, laboratory and imaging data, etc). | Q3, Q4, Q5, Q6, Q9, Q11 | XX.3, XX.4 |
| | Ensure consistency of disease monitoring frequency across centers. | Q7 | |
| | Avoid data duplications (patients reported by multiple centers) | Q10 | XX.7 |
| | Minimize missing data on patient/disease characteristics, and treatment(s) | | |
| | Collect all relevant information on possible baseline confounding factors (potentially influencing treatment choice and/or | | |

| | | | |
|---|---|---|---|
| | unequally distributed between treated patients and controls. | | |
| **Outcomes / end-points** | Establish the outcomes of interest and the minimum accepted criteria to ascertain them. | Q5, Q8 | XX.4, XX.6 |
| | Verify that similar criteria were applied to ascertain outcome in treated and control patients (information bias mimization). | | |
| **Follow-up** | Update data (survival, local relapse, distant metastasis), minimize lost to follow-up. | Q7 | |
| | Similar follow-up procedures in treated and control patients | | |
| | Ascertain (if possible) that any differential loss to follow up between treated and controls was not related to outcome. | | |
| **Statistical methods /analysis** | Apply appropriate statistical methods to compare treated and controls, e.g. taking into account for confounding factors. | | |
| | Deal with missing data (e.g. sensitivity analysis). | | |
| **Publication** | All results, including negative results, should be published. | Q12 | XX.8 |

**Supplementary Figure 1** Online survey circulated In May 2021 across the members of the consensus panel, entitled: ”Ultra-rare sarcomas: minimum requirements for evaluation of the activity of systemic treatments”.

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