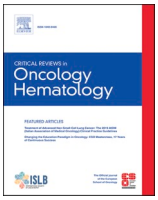
Critical Reviews in Oncology / Hematology 216 (2025) 104960

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc



Extended molecular profiling in mesenchymal tumors: a consensus paper from the Italian Sarcoma Group

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https://doi.org/10.1016/j.critrevonc.2025.104960
Received 18 May 2025; Received in revised form 18 September 2025; Accepted 19 September 2025
Available online 23 September 2025

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ARTICLE INFO

Keywords:
Next generation sequencing
Massive parallel sequencing
Sarcoma
Bone tumors
GIST

ABSTRACT

Extended molecular profiling using massive parallel sequencing (MPS) technologies, commonly referred to as next-generation sequencing (NGS), has revolutionized cancer diagnosis and treatment, including in bone and soft tissue sarcomas (BSTS). This heterogeneous group of mesenchymal tumors presents a complex spectrum of genetic alterations, such as chromosomal rearrangements, point mutations, and copy number variations. Unlike carcinomas, where driver mutations are often well defined, the role of specific genomic signatures in dictating BSTS prognosis and therapy response remains to be fully elucidated. Despite its promise, the adoption of MPS/NGS in BSTS is limited by variability in testing access, turnaround times, specimen quality, costs, and data interpretation. Although identified alterations are often not yet directly targetable, they provide critical insights that can refine diagnosis, enable better patient stratification, and guide treatment strategies. To optimize the use of MPS/NGS in BSTS, harmonization and multidisciplinary collaboration within molecular tumor boards (MTBs) are essential. With this aim, the Italian Sarcoma Group ETS (ISG) convened a consensus meeting to establish best practices for integrating MPS/NGS into everyday clinical care. ISG experts developed ten consensus statements: the first five address the role of extended molecular profiling in BSTS diagnostics, while the others offer guidance on MPS/NGS use and interpretation when searching for potentially actionable targets in the treatment of advanced disease. Furthermore, collaboration with the National Rare Cancer Network to offer expert consultation and systematically correlate MPS/NGS findings with clinical outcomes for BSTS cases undergoing extended molecular profiling will be critical to advancing precision medicine in this field.

1. Introduction

Extended molecular profiling using short-read based massive parallel sequencing technologies (MPS), commonly known as next-generation sequencing (NGS), has dramatically improved our understanding of cancer molecular heterogeneity. These deeper insights into the different molecular underpinnings of various malignancies has revolutionized the landscape of cancer diagnostics and therapeutics bringing innovative molecularly driven treatments in the field of oncology, including in bone and soft tissue sarcomas (BSTS) (Mosele et al., 2024; WHO, 2020; Gronchi et al., 2021; Strauss et al., 2021; Casali et al., 2022; Sosinsky et al., 2024). This large group of mesenchymal tumors encompasses over 80 distinct, genomically heterogeneous histologic types (WHO, 2020). Traditionally, limited treatment options and limited activity of conventional treatments made sarcoma clinical management particularly challenging (Gronchi et al., 2021; Strauss et al., 2021; Casali et al., 2022; Judson et al., 2014; D'Ambrosio et al., 2020; Pautier et al., 2024; Demetri et al., 2015). Advances in MPS/NGS have fostered personalized medicine also in these rare tumors, offering insights into sarcoma biology that improved diagnosis, patients' stratification, and – in selected cases – informed targeted therapies and tailored treatments (Gronchi et al., 2021; Strauss et al., 2021; Casali et al., 2022; Gounder et al., 2022a; Nacev et al., 2022; Schöffski et al., 2018; van der Graaf et al., 2012).

The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the use of NGS recommend integrating this tool into clinical workflows not only for diagnosis and therapeutic decision but also for monitoring treatment response and disease progression (Mosele et al., 2024). For rare and challenging tumors like BSTS, MPS/NGS can play a pivotal role in guiding treatment choices, despite the currently approved targeted therapies in this field remain very limited. Mosele et al., (2024); Gronchi et al., (2021); Strauss et al., (2021); Casali et al.,

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(2022).

Unlike carcinomas, where driver mutations are mostly well-characterized, (Midha et al., 2015; Salama et al., 2020; Pant et al., 2023; Demetri et al., 2022; Subbiah et al., 2020; Marcus et al., 2019; Hyman et al., 2018; Hendriks et al., 2023; Smyth et al., 2020; Li et al., 2024) BSTS may exhibit a complex interplay of genetic alterations, including chromosomal rearrangements, point mutations, and copy number alterations (Mosele et al., 2024; WHO, 2020; Sosinsky et al., 2024; Gounder et al., 2022a; Nacev et al., 2022; Jour et al., 2014; Lucchesi et al., 2018). The ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) classification system provides a framework to categorize the detected molecular alterations and their relevance as actionable targets (Mateo et al., 2018). This resource helps clinicians prioritize treatment options or consider clinical trial enrollment based on the molecular profile. Nonetheless, the criteria developed for the ESCAT classification might not perfectly serve the needs of patients affected by rare cancers, including BSTS where the clinical application of MPS/NGS has shown conflicting results, demanding caution in interpreting the clinical relevance of MPS/NGS findings in individual BSTS patients, although increasing clinical evidences support its wider use (Mosele et al., 2024; Gronchi et al., 2021; Strauss et al., 2021; Casali et al., 2022; Sosinsky et al., 2024; Gounder et al., 2022a; Schöffski et al., 2018; Jour et al., 2014; Gounder et al., 2022b, 2023; Casali, 2012; Wagner et al., 2021, 2010; Cote et al., 2018; Lee et al., 2017; Brčić et al., 2021; elizabeth.demicco@sinaihealthsystem.ca CGARNEa, Network CGAR, 2017; Vanni et al., 2023; Carmagnani Pestana et al., 2023; Tsimberidou et al., 2021; Pestana and Serrano, 2022; Vanoli et al., 2024; Trédan et al., 2025). For instance, NTRK-rearranged sarcomas, characterized by neurotrophic tyrosine receptor kinase (NTRK) gene fusions, though exceedingly rare, have shown remarkable responses to TRK inhibitors (Demetri et al., 2022; Brčić et al., 2021; Hong et al., 2019; Suurmeijer et al., 2019; Demetri et al., 2020; Kao et al., 2020; Dieckmann et al., 2021; Palmerini et al., 2023a; Laetsch et al., 2024). Conversely, other subtypes such as MDM2-amplified liposarcomas, exhibited varying responses to MDM2 antagonists despite the target is almost invariably present in these tumors (Lucchesi et al., 2018; Gounder et al., 2023; Dei Tos et al., 1997; Haupt et al., 1997; Ray-Coquard et al., 2012a; Wagner et al., 2017; de Jonge et al., 2017; Fang et al., 2019; Assi et al., 2020; Gluck et al., 2020; Frezza et al., 2020; Wang et al., 2021; LoRusso et al., 2023). Similarly, treatments against potentially relevant targets like HER2, although expressed also in some BSTS, did not show the same practice-changing results observed in epithelial tumors (Ebb et al., 2012; Ahmed et al., 2015). These discrepancies underscore the complexity of sarcoma genomics and highlight the need for a better integration of MPS/NGS into clinical practice. Indeed, MPS/NGS alone cannot answer all clinical questions, and its clinical utility lies not only in identifying potential targets but also in assuring that the detected alterations influence clinical decision-making and outcomes (Mosele et al., 2024; WHO, 2020; Swanton, 2012; Racanelli et al., 2020; Tsuda et al., 2020; Dermawan et al., 2024)

The incorporation of MPS/NGS into clinical trials for BSTS has been limited so far, though it has partially expanded treatment possibilities especially in basket trials or early-phase studies (Mosele et al., 2024).

Despite the promise of MPS/NGS, several challenges still need to be addressed in BSTS: significant variability in the implementation of genomic testing across institutions, with discrepancies in turnaround time, tools (including technical issues related to the platform itself), BSTS specimens (bone vs soft tissue, fresh vs paraffin embedded, decalcified vs non-decalcified), (Green et al., 2024) cost-effectiveness, budget availability, and data interpretation (Mosele et al., 2024; WHO, 2020; Swanton, 2012; Racanelli et al., 2020; Tsuda et al., 2020; Dermawan et al., 2024). Additionally, ethical concerns about data privacy and unequal access to precision oncology remain partially unresolved. Therefore, it is critical to develop robust guidelines and/or consensus statements that advocate for standardizing and harmonizing genomic testing in BSTS.

This requires a multidisciplinary approach, involving oncologists, pathologists, molecular biologists, genetic counselors, computer scientists, bioethicists, and pediatricians/pediatric oncologists (in case of pediatric BSTS) within a molecular tumor board (MTB). Collaboration among these specialists will be essential to develop frameworks that enable equitable access to precision medicine for all sarcoma patients (Mosele et al., 2024; Tsimberidou et al., 2023).

In summary, while the clinical utility of wide MPS/NGS use in BSTS is still under debate, it has the potential to enhance diagnosis, drive treatment choices, and ultimately improve patients' outcomes. As sequencing technologies become more affordable and accessible, developing a consensus on the role and use of MPS/NGS in the clinical ground is mandatory to move from an artisanal and poorly reproducible approach to a shared and more harmonized set of rules.

2. Methodology

Aiming to harmonize the approach to MPS/NGS, a consensus meeting of the Italian Sarcoma Group ETS (ISG) took place in Rome on April 13, 2024. The present work reports the consensus stemmed from the meeting and subsequent discussion among a representative of the Italian community of experts belonging to the ISG representing a wide range of specialties, including pathology, molecular biology, adult and pediatric medical oncology, surgery, radiation oncology, radiology, clinical trials and data management, and patient advocacy.

A second consensus meeting was held on January 23, 2025, in Milan, to further refine the statements and the manuscript content, and achieve final consensus where all statements had a level of agreement $\geq$ 90 %. After this second meeting the final version of the consensus was circulated, revised and approved by all contributing authors. Fig. 1 depicts the workflow for the development of the consensus. Details regarding the literature review process are available as supplementary material.

The primary objective of this work is to provide a reference to assist healthcare professionals in the daily clinical management of patients with BSTS and to increase appropriateness in MPS/NGS use. Although it may promote harmonization and improve the quality also of MPS/NGS conducted for clinical or preclinical research, the document should not be intended for that purpose.

Fig. 2 summarizes the ten statements on the use of extended molecular profiling in BSTS.

2.1. MPS/NGS use in the diagnosis of BSTS

2.1.1. Statement 1

BSTS diagnosis is challenged by their histological and molecular heterogeneity with discrepancies between local and centralized assessments reported in up to 40 % of cases (Gronchi et al., 2021; Ray-Coquard et al., 2012b). This highlights the need for centralized pathological review in BSTS.

ESMO and NCCN guidelines advocate for multidisciplinary teams and centralized pathology assessments to reduce diagnostic misinterpretation (Gronchi et al., 2021; Strauss et al., 2021; Casali et al., 2022; NCCN, n.d.). Integration of clinical and radiological data is key for the diagnosis of BSTS providing crucial contexts for interpreting molecular and pathological results. Pathological reports should follow the International Collaboration on Cancer Reporting (ICCR) guidelines (Dei Tos et al., 2023). Furthermore, the need of expert sarcoma pathologists' evaluation is crucial not only for traditional histological assessment but it also plays a key role in guiding the use of molecular testing and selecting the most informative tissue. Indeed, centralized reviews ensure that molecular testing is appropriately integrated into robust diagnostic workflows.

The final decision to perform a centralized review for a specific case remains with the treating clinician and/or the local pathologist, although it should be highlighted that adopting this practice can significantly enhance diagnostic accuracy and improve patient

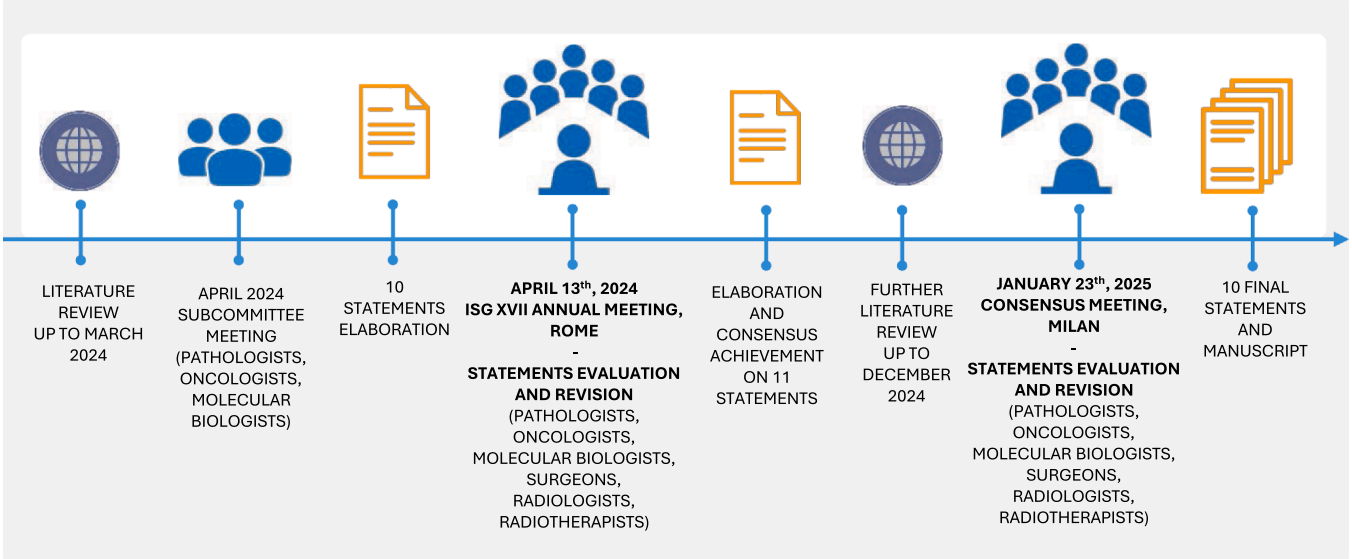

Fig. 1. Schematic representation of the methodology used for statements elaboration. To prepare for the consensus meeting, a smaller working group –comprising pathologists, medical oncologists, and molecular biologists (LDA, MS, AM, MR, GG, RM, APDT)– conducted a thorough review of the existing literature and proposed an initial set of ten statements. During the meeting, the community of experts engaged in an open and collaborative discussion regarding the ten proposed statements. Each statement was evaluated and refined as needed until a consensus was reached among the participants on a total of ten statements (one out of the ten initial statements was split into two different statements, resulting in a total of eleven statements, which were later revised and reduced back to ten). Following this meeting, a further revision of the literature was performed, and the updated version of the statements and the draft manuscript were prepared and shared among the same ISG experts. A second consensus meeting was held on January 23, 2025, in Milan, to further refine the statements and the manuscript content, and achieve final consensus. All final statements had a level of agreement $\geq$ 90 %.

outcomes (Gronchi et al., 2021; Strauss et al., 2021; Casali et al., 2022; NCCN, n.d.).

2.1.2. Statement 2

Whenever indicated, MPS/NGS analyses should complement BSTS diagnosis but cannot substitute an expert pathologist. Indeed, despite several works highlighted the potential role of MPS/NGS in reassigning the diagnosis in about 10 % of sarcoma patients, in the majority of these cases the same results could be achieved in an easier, faster, and cheaper way by simple immunohistochemistry (IHC) or fluorescent in-situ hybridization (FISH) (Gounder et al., 2022a; Nacev et al., 2022; Öfverholm et al., 2024). When evaluating the best technique to be used in a specific case, it should be considered that MPS/NGS, polymerase chain reaction (PCR), and Sanger sequencing represent bulk analysis, while FISH is an in-situ assessment. MPS/NGS becomes more advantageous when a broader panel is required. In this case a parallelized approach might be cost- and time-effective and might reduce the tumor tissue needed for the analysis. Furthermore, extended molecular profiling can be particularly useful when the specific pathological entity is doubtful or ambiguous, and in these cases MPS/NGS is recommended (Gronchi et al., 2021; Strauss et al., 2021; Casali et al., 2022).

However, relying solely on MPS/NGS can lead to misdiagnosis of several BSTS harboring the same pathognomonic genomic alteration (mainly chromosomal translocations) but having a completely different clinical behavior. For example, the *EWSR1* gene, which may fuse with various partner genes, is commonly associated with Ewing sarcoma but also with other sarcomas as clear cell sarcoma or a nearly benign disease like angiomatoid fibrous histiocytoma (WHO, 2020; Delattre et al., 1992; Antonescu et al., 2006; Wang et al., 2009; Kao et al., 2017; Dermawan et al., 2022). This promiscuity challenges the interpretation of genomic profiles, leading to potential misdiagnoses and incorrect treatment if morphology and IHC are not carefully evaluated (Scarpa et al., 2017).

Moreover, the challenge lies in discriminating which genomic variants truly drive the neoplastic aggressiveness and which are simply "bystanders" (Swanton, 2012).

This complexity necessitates the involvement of specialized sarcoma pathologists and molecular biologists who can help in identifying clinically relevant findings and avoid misclassification. Additionally, multidisciplinary approaches, incorporating input from clinical oncologists, pathologists, molecular biologists, radiologists, and geneticists within a MTB can improve the workflow from diagnosis to treatment, enhancing patient care.

2.1.3. Statement 3

MPS/NGS reports should follow ESMO recommendations on clinical reporting of genomic test results for solid cancers (van de Haar et al., 2024).

Accordingly, one critical aspect that pathologists must emphasize in their reports is the viable tumor fraction present in the sample sent for bulk molecular/genomic analysis as it affects interpretation of genetic alterations and helps distinguish true tumor signals from background noise.

In addition to ESMO document, ISG experts recommend reporting the presence of immune infiltrate, particularly when it exceeds 30 % of the sample. Indeed, when high levels of immune infiltrate are present, clonal hematopoiesis can pose challenges in the interpretation of MPS/NGS results (Weeks and Ebert, 2023; Zink et al., 2017). Somatic mutations carried by hematopoietic progenitors/stem cells can result in altered profiles that may be mistakenly attributed to the tumor itself (Coombs et al., 2018). ISG experts agreed that reporting the presence or absence of significant immune infiltrate is sufficient to help pathologists and molecular biologists in interpreting the results of MPS/NGS.

Reports should clearly detail the specific panels used, genes or alterations analyzed (whole gene, hot spot, customized, et cetera), target coverage, software versions, and the version of the human reference genome released by the Genome Reference Consortium. Variant of allele frequency (VAF) should be included in the reports and very low VAFs should be interpreted with caution (i.e., the clinical relevance of a VAF $<$1 % is left to be demonstrated provided the tumor tissue has been correctly selected) (van de Haar et al., 2024). These data can improve reproducibility and allow for better comparison between different

Fig. 2. Graphic statements summary.

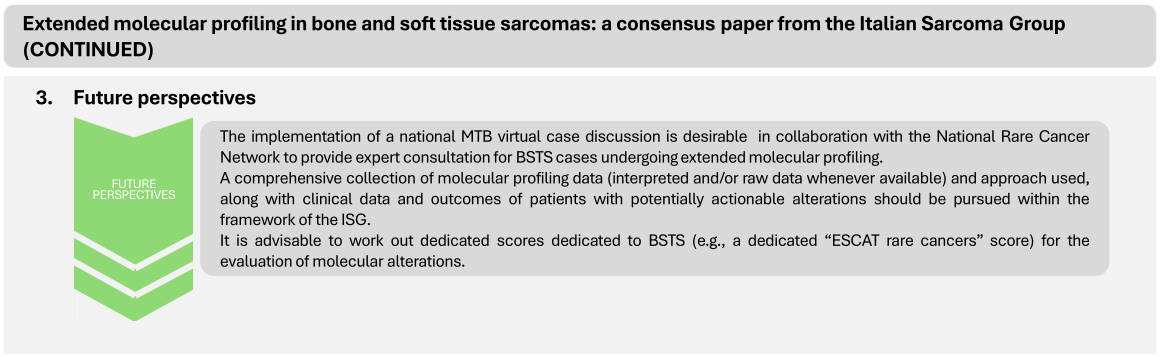

Fig. 2. (*continued*).

STATEMENT 1

Pathological diagnosis in mesenchymal tumors is based on morphological, immunophenotypic, and, whenever needed, molecular analyses, and should be done by an expert sarcoma pathologist. Integration with clinical and radiological data is crucial. The pathological report should follow ICCR guidelines.

STATEMENT 2

Indication to molecular/genomic testing for diagnosis (including targeted MPS/NGS) and selection of the tissue sample to be analyzed should be done by expert sarcoma pathologists. Interpretation of the results should be done by pathologists and molecular biologists with adequate experience in sarcomas and integrated with morphological immunophenotypic characteristics. Molecular/genomic testing is recommended when the specific pathological entity is doubtful or ambiguous.

reports. Pathologists should also disclose potential limitations in the interpretation of the data due to impaired sample adequacy for the specific test used (Mosele et al., 2024; van de Haar et al., 2024). Conducting MPS/NGS on poor-quality samples is discouraged, and any factors that could potentially compromise the interpretation of results must be clearly documented in the final report (Mosele et al., 2024; van de Haar et al., 2024).

2.1.4. Statement 4

Standard DNA-based MPS/NGS is effective in detecting point mutations and small indels but can miss key molecular alterations in sarcomas, particularly chromosomal translocations which represent hallmark features in many BSTS subtypes (Mosele et al., 2024; Casolino et al., 2024; Li et al., 2017; Jennings et al., 2017). Standard DNA sequencing typically focuses on coding regions and may not adequately capture structural variations such as translocations or larger chromosomal abnormalities, low-frequency variants, complex rearrangements, presence of multiple fusion transcripts, gene amplifications or the involvement of non-coding regions (Mosele et al., 2024; WHO, 2020; Racanelli et al., 2020; Casolino et al., 2024; Li et al., 2017; Jennings et al., 2017).

Alternative techniques, such as RNA sequencing or specialized genomic assays like FISH, reverse transcription PCR (RT-PCR), whole-genome sequencing (WGS), or array comparative genomic

STATEMENT 3

MPS/NGS reports must follow ESMO recommendations on clinical reporting of genomic test results for solid cancers.

The information on viable tumor fraction for samples sent for bulk molecular/genomic analysis must be reported by pathologists. The presence of immune infiltrate (especially if high, *e.g.* >30% of total sample sent for analysis) is strongly recommended to be reported to improve interpretation of the results and to avoid misleading information due to clonal hematopoiesis.

Panels, specific analyzed genes/alterations, coverage of the targets, software' versions, and the version of the human GRC reference genome used for the analysis should be specified in the final molecular report. Potential limitations in analysis interpretation due to paucity or low quality of analyzed nucleic acid should be highlighted at the beginning of the molecular report.

hybridization (aCGH), which are better suited for detecting these larger genetic rearrangements, are often necessary to fully characterize these alterations and provide a comprehensive molecular profile. Therefore, it is essential to employ MPS/NGS techniques able to identify BSTS pathognomonic genetic alterations, like RNA-based panels (WHO, 2020; Racanelli et al., 2020; Zago Baltazar et al., 2024; Atiq et al., 2025; Hofvander et al., 2015). As the field continuously evolves, no tool-specific recommendation can be provided. Furthermore, new techniques like methylation profiling and proteomics are entering the field, which might open new avenues for improving our understanding of BSTS heterogeneity, particularly among poorly defined entities (elizabeth.demicco@sinaihealthsystem.ca CGARNEa, Network CGAR, 2017; Burns et al., 2023; Tang et al., 2024; Koelsche et al., 2021).

MPS/NGS testing must be conducted in laboratories adhering to rigorous external quality assurance programs to ensure accuracy and reproducibility (Mosele et al., 2024; van de Haar et al., 2024; Jennings et al., 2017; Dubbink et al., 2014). The institution of an external quality program for molecular diagnostics in BSTS is strongly advised.

2.1.5. Statement 5

The community of experts recognize that in some BSTS entities, the direct application of extensive molecular profiling by means of MPS/NGS might be cost and time-effective given the need of evaluating multiple alterations and/or due to the absence of pathognomonic morphological or IHC features.

After thorough discussion, the community of experts agreed to the following list of scenarios where parallelized molecular approaches like MPS/NGS targeted panels may be particularly useful:

- Undifferentiated round cell sarcomas; (Strauss et al., 2021; Palmerini et al., 2023b; Watson et al., 2018; Antonescu et al., 2017; Sbaraglia et al., 2020)
- Spindle-cell sarcoma not otherwise specified (NOS), in particular those featuring the co-expression of CD34 and S100; (WHO, 2020; Suurmeijer et al., 2019; Demetri et al., 2020; Kao et al., 2020; Dieckmann et al., 2021)
- Types of sarcomas where molecular alterations have a prognostic or predictive impact (e.g., non-pleomorphic rhabdomyosarcoma, ALK-negative IMT); (WHO, 2020; Parham and Barr, 2013; Agaram et al., 2019)
- Quadruple wild type gastrointestinal stromal tumors (GISTs) (Gasparotto et al., 2017; Rossi et al., 2018; Pantaleo et al., 2015)
- The specific pathological entity is doubtful or ambiguous (e.g., myoepithelioma) (WHO, 2020; Gronchi et al., 2021; Strauss et al., 2021).

It should be highlighted that, whenever available, other testing like IHC or ISH/FISH can be used as a simpler and cheaper alternative to MPS/NGS techniques (Rossi et al., 2018; Lasota et al., 2024; Orlando et al., 2023; Schaefer et al., 2018; Scapa et al., 2021; Righi et al., 2022). It is worth to underline that IHC techniques can identify the presence or absence of target expression, which may indicate genetic alterations. However, they cannot determine whether a sample is mutated or translocated unless specific antibodies against the fusion products of molecular alterations are employed.

RNA-based targeted panels are generally regarded as the most effective MPS/NGS techniques, whereas DNA-based targeted panels can be used as an alternative to Sanger-based sequencing in presence of BSTS with specific DNA alterations like the majority of gastrointestinal stromal tumors, desmoids, chondrosarcomas, PEComas, and others. In GISTs lacking abnormalities in *KIT*, *PDGFRA*, *SDH*, or *RAS* signaling pathways (the so-called quadruple wild-type GISTs), the panel of experts recommends performing extended molecular profiling, including the assessment of alterations in the neurofibromatosis type 1 (*NF1*) gene (Gasparotto et al., 2017; Rossi et al., 2018; Pantaleo et al., 2015).

Deletions can be often seen by means of FISH or IHC if an appropriate antibody is available.

Of note, DNA-based NGS panels can also identify mutational signatures, as UV-induced mutational signatures. This analysis might be considered for complex differential diagnoses between undifferentiated melanomas or spindle cell carcinomas and sarcomas. However, it should be noted that specific sarcoma entities might similarly harbor UV-induced mutational signatures, *e.g.*, cutaneous angiosarcoma (Ike et al., 2024; Painter et al., 2020), atypical fibroxanthoma (Dei Tos et al., 1994), atypical dermatofibrosarcoma (Dei Tos et al., 1994), and pleomorphic dermal sarcomas (Griewank et al., 2018). As indicated in Statement 2, the pathologists will take the final decision on the most appropriate molecular testing to complement diagnosis and address clinical questions.

Finally, the panel of experts recommends that any MPS/NGS results inconsistent with the morphology, phenotypic characteristics and/or clinical behavior of the disease should not automatically change the diagnosis but should be evaluated in the context of the overall clinical picture.

Conversely, negative results from MPS/NGS cannot completely exclude a specific pathologic entity in case the diagnosis is strongly supported by clinical characteristics, IHC, and morphology. In these cases, the panel of expert suggest considering reanalyzing the data (including raw data whenever available) given the potential limitations of epithelial cancers-dedicated software used for MPS/NGS analysis in the BSTS field. As an alternative approach, a different method of detection might be considered.

2.2. Statement MPS/NGS to identify therapeutic targets in mesenchymal tumors

2.2.1. Statement 6

The following considerations should start from the assumption that previous statements have been satisfied for what concern the diagnostic process.

The rapidly advancing field of precision medicine has increased reliance on extensive genomic profiling to identify potentially actionable targets in various tumors, including BSTS. Indeed, MPS/NGS can be used not only for diagnostic purposes but also to detect molecular alterations that might inform treatment decisions (Mosele et al., 2024). However, in the field of BSTS its use beyond standard protocols should be carefully evaluated within a MTB. Economic constraints should be balanced against the often-modest likelihood of discovering truly actionable alterations in BSTS. MTB have emerged as a useful tool in the management of complex malignancies and are particularly relevant in rare tumors, as BSTS. The involvement of BSTS experts – including pediatricians and pediatric oncologists for pediatric cases – within the

STATEMENT 4

Whenever indicated beyond standard analyses, extensive molecular/genomic testing should encompass techniques able to identify sarcoma pathognomonic genetic alterations. External quality assurance programs are mandatory for laboratories performing molecular pathology assessments.

STATEMENT 5

MPS/NGS targeted panels may be particularly useful in the following situations:

- **Undifferentiated round cell sarcomas;**
- **Spindle-cell sarcoma not otherwise specified (NOS), in particular those featuring the co-expression of CD34 and S100;**
- **The molecular alterations have a prognostic/predictive impact (e.g., non-pleomorphic rhabdomyosarcoma, ALK negative IMT);**
- **Quadruple wild type GIST;**
- **The specific pathological entity is doubtful or ambiguous (e.g., myoepithelioma).**

MPS/NGS results need to be interpreted along with morphology and phenotypic characteristics and/or clinical behavior.

Whenever available and appropriate, other techniques such as IHC or ISH/FISH can be used as alternatives to MPS/NGS. In presence of a high clinical suspicion of a specific pathologic entity/molecular alteration with negative results from in silico/bioinformatics analysis, it is strongly suggested to consider to reanalyze data (manually or with other software) because of potential limitations of the used software working pipeline. Alternatively, consider the use of a different method of detection.

MTB, along with collaboration with multidisciplinary BSTS boards, is crucial. These collaborative discussions allow for a more nuanced understanding of the patient's clinical context and the potential implications of genomic findings. Several studies clearly highlight that the multidisciplinary approach in a reference center can improve decision-making, leading to better patient outcomes, especially in rare diseases such as BSTS (Blay et al., 2017, 2019, 2024; Westphalen et al., 2025).

The panel of experts agreed that patients to be candidate to MPS/NGS looking for potentially actionable mutations should be identified by MTB with experience in BSTS management (Pishvaian et al., 2019). Ideally, these patients should be in adequate clinical conditions, already treated with best standard treatments for their disease and with a reasonable life expectancy (3–6 months). However, since life expectancy is often hard to estimate in BSTS, given the usual absence cachexia and the persistence of good clinical conditions even with high disease burden, the panel of experts suggests focusing on the risk/benefit balance of the potential treatment, and advices to avoid giving unrealistic expectations to patients and advocates for taking this decision within the sarcoma MTB (Pishvaian et al., 2019; Shirdarreh et al., 2021).

While MPS/NGS can unlock new diagnostic/therapeutic opportunities and is generally considered worthwhile, its cost can challenge routine implementation (Mosele et al., 2024; Trédan et al., 2025; Casolino et al., 2024; Pritchard et al., 2022; Hsiao et al., 2020; Colomer et al., 2023; Zavala et al., 2021). Nonetheless, a decrease in costs over the years is expected making these analyses more sustainable in the near future.

Beyond economic constraints, it is essential for patients and providers to engage in informed discussions regarding the potential benefits and limitations of MPS/NGS. Patients must be aware that, while genomic profiling may uncover alterations that could potentially lead to targeted therapies outside standard treatments, several works reported that only a small proportion of identified mutations are truly actionable, and many of these treatments remain investigational in BSTS (Mosele et al., 2024; Gronchi et al., 2021; Strauss et al., 2021; Gounder et al., 2022a; Nacev et al., 2022; Mateo et al., 2018). Clinical trials represent the ideal framework where to test these therapeutic approaches, but their availability for BSTS patients remains limited and targeted treatments might be accessible only off-label or within expanded access programs. Therefore, patients must be informed of these challenges as part of the decision-making process surrounding MPS/NGS, ensuring they have realistic expectations regarding access to potential treatments and their activity.

The story of *NTRK* translocations in solid tumors, including BSTS, stands alone in this field (Demetri et al., 2020). Indeed, the search of *NTRK* translocations should be part of the diagnostic process whenever indicated as reported in previous statements. Spindle-cell sarcoma NOS featuring the co-expression of CD34 and S100 are enriched in kinase-altered mesenchymal neoplasm, which encompass tyrosine (mainly NTRK) or serine-threonine fusions or point mutations that are potentially targetable by kinase inhibitors (WHO, 2020; Suurmeijer et al., 2019; Demetri et al., 2020; Kao et al., 2020; Dieckmann et al., 2021). *NTRK* translocations are usually searched by means of multi-genes targeted sequencing that often encompass other potential therapeutic targets that are derived from more common epithelial cancers (Trédan et al., 2025; Casolino et al., 2024). By chance, these panels can result in detecting the presence of potentially targetable molecular alterations in one of the tested genes, though their therapeutic relevance is still to be demonstrated in the majority of BSTS cases but can also foster novel therapeutic options.

By instance, according to ESCAT classification, NTRK1/2/3 fusions, RET, FGFR1/2/3 fusions/mutations, BRFAV600E mutations, microsatellite instability-high (MSI-H), and tumor mutation burden-high (TMB-H) are designated as ESCAT tier IC tumor-agnostic targets based mainly on the clinical outcomes observed in basket trials (Mateo et al., 2018). In some cases, tumor-specific prospective trials have been run leading to the categorization of some of these targets into ESCAT tier IA or IB in the respective drug-alteration match (Mosele et al., 2024; Mateo et al., 2018; Botticelli et al., 2024). These alterations, though exceedingly rare, can be found also in BSTS but the ESCAT classification is not currently mirrored by Regulatory Agencies' approval in Europe with the notable exception of NTRK inhibitors.

2.2.2. *Statement 7*

Whenever MPS/NGS testing is planned to search for potentially actionable targets, the panel of experts recommends using the most recent available archival tumor sample or to consider a re-biopsy. Re-biopsy is warranted when archival samples are old, not representative of the actual tumor (e.g., several treatments occurred in between), or derived from primary tumors rather than metastatic lesions. Indeed, tumor heterogeneity is a well-recognized challenge in the field of solid tumors and clinicians should consider the clonal evolution of the disease (Mosele et al., 2024; Swanton, 2012; Gerlinger et al., 2012).

Therefore, in case of multiple metastases, the panel of experts recommends prioritizing a biopsy of the most aggressive lesion to inform treatment decisions targeting the most threatening site.

In case this is not feasible, or if the metastatic sites exhibit homogeneous behavior, the biopsy of the lesion that is easiest and safest to reach is recommended.

Currently available data in BSTS cannot yet support the use of liquid

STATEMENT 6

The decision to use extensive genomic profiling for searching potentially "actionable" targets beyond standard treatment should be taken within a MTB with the involvement of experts in BSTS management and in collaboration with multidisciplinary BSTS boards, provided that all the standards regarding the correct diagnostic workup are met.

The use of extended molecular profiling to search for potentially "actionable" targets should be pursued provided the patient is informed of the overall actual chance of identifying truly actionable alterations in BSTS and is aware that access to potentially active drugs may be challenged by the limited availability of clinical trials for BSTS and the constraints related to prescriptive restrictions under the national healthcare system.

Participation into clinical trials should be strongly encouraged.

STATEMENT 7

When planning to test for potentially actionable targets, it is strongly recommended to use the most recent archival tumor sample or to consider a new biopsy whenever feasible. In cases with multiple lesions, it is suggested to biopsy the most aggressive lesion. If not feasible, targeting the lesion that is easiest and most accessible for biopsy is considered the best option.

biopsy to search for potentially actionable targets outside clinical trials, neither in GIST, although this scenario may change in the near future.

2.3. Statement Performing MPS/NGS in mesenchymal tumors: the perspective of ESCAT

2.3.1. Statement 8

The ESCAT classification system ranked molecular alterations according to the expected clinical impact of their targeting and the robustness of data supporting the use of the drug of interest.

This classification is linked to the ESMO Magnitude of Clinical Benefit Scale (MCBS), a validated tool to assess the magnitude of clinical benefit of new cancer therapies (Cherny et al., 2017).

According to ESMO recommendation, ESCAT tier I (ESCAT_1) alterations should be considered standard of care. In the field of BSTS, with the notable exception of GISTs, there are very few molecular alterations that can be classified as ESCAT_1 and ready for clinical use. The most notable example of ESCAT_1 alteration in the field of BSTS is represented by first-generation NTRK inhibitors (e.g., larotrectinib and entrectinib) that showed a huge clinical benefit in sarcomas harboring NTRK fusions.

Despite their recognized clinical relevance, the possibility of targeting ESCAT_1 alterations in BSTS deals with differences in agnostic drugs approval across European Countries and the US, posing accessibility issues. For instance, while tumors with deficient mismatch repair (dMMR)/MSI-H benefit from immune checkpoint inhibitors (ICIs) regardless of tumor type, ICIs are not registered for the treatment of BSTS harboring of dMMR/MSI-H. Although this is a rare situation detected in less than 1 % of BSTS, (Gounder et al., 2022a; Nacev et al., 2022; Poumeaud et al., 2024) it raises relevant clinical and ethical

Table 1A
ESCAT_1 alterations in mesenchymal tumors.

Sarcoma type	Gene	Alteration	Estimated prevalence	Matched therapy	ESCAT I sub-tier (evidence)	Key reference(s)
GIST	*KIT*	mutation/ insertion/ deletion/ indel	~85 %	imatinib and other anti-KIT TKIs	I-A	(Dematteo et al., 2009; Joensuu et al., 2012, 2020)
GIST	*PDGFRA non-D842V*	mutation/ insertion/ deletion/ indel	10–15 %	imatinib and other anti-PDGFRA TKIs	I-A	(Dematteo et al., 2009; Joensuu et al., 2012, 2020)
Tenosynovial giant cell tumor (TGCT)	*CSF1*	rearrangements	~75 %	pexidartinib vimseltinib	I-A	(Wagner et al., 2025; Gelderblom et al., 2024)
GIST	*PDGFRA* D842V	missense mutations	5–7 %	avapritinib	I-B	(Heinrich et al., 2020)
Inflammatory myofibroblastic tumor	*ALK*	rearrangements	50–60 %	crizotinib	I-B	(Schöffski et al., 2018, 2021)
Dermatofibrosarcoma protuberans	*COL1A1–PDGFB* fusion (PDGFRB pathway)	rearrangements	100 %	imatinib	I-B	(Rutkowski et al., 2010)
PEComa	*TSC1/2*	mutations/ deletions	> 80 %	nab-sirolimus	I-B	(Wagner et al., 2024)
Epithelioid sarcoma	*SMARCB1*	deletions or mutations	90 %	tazemetostat	I-B	(Gounder et al., 2020)*

TKI, tyrosine kinase inhibitor.

* This study was a phase II basket study which enrolled predominantly epithelioid sarcoma patients. So, the ESCAT tier for tazemetostat in epitheliod sarcoma is usually attributed as I-B despite the study was originally a basket trial.

questions for clinicians and healthcare providers. Indeed, access to ICIs in routine clinical practice for these patients might strongly differ across institutions, potentially leading to inequitable treatment opportunities.

In cases of dMMR/MSI-H and other ESCAT_1 drug-alteration matches that are not available in clinical practice, clinical trials represent the preferred option and should be strongly encouraged. However, when clinical trials are not feasible or not available, the panel of experts recommends discussing alternative strategies with the patient, such as off-label drug use or expanded access programs.Table 1A

2.3.2. Statement 9

ESCAT tier II (ESCAT_2) identifies investigational targets that likely define a patient population that benefits from a targeted drug, though the robustness of the evidence is less than that for ESCAT_1 alterations and additional confirmatory data are in principle needed. ESCAT_2 alterations are generally considered enough to justify treatment with a drug-alteration match, preferably in the context of prospective data collection, either within a registry or a prospective clinical trial. An example of ESCAT_2 in BSTS is the targeting of IDH1 mutations with ivosidenib in IDH1 mutated advanced conventional chondrosarcoma (Tap et al., 2020).

ESCAT tier III (ESCAT_3) refers to the so-called "hypothetical targets". This subgroup refers to alteration-drug match suspected to improve outcomes based on clinical trials in other tumor types or cancers with similar molecular alterations. Examples of ESCAT_3 alterations in BSTS can be BRCA1/2 mutations or high tumor mutational burden (TMB). For these alterations, robust prospective data in BSTS are lacking, but given their high predictive impact in several tumor types, it is presumable that the presence of these alterations can predict activity of a specific alteration-drug match also in BSTS. By instance, NCCN guidelines support the use of ICIs in TMB-high tumors following an agnostic approach (NCCN,).

In BSTS, and especially in ultra-rare BSTS, the possibility to generate data from prospective randomized clinical trials is challenged by several factors, including their rarity and the limited interest of pharmaceutical companies (Stacchiotti et al., 2021). Therefore, given the few therapeutic options in BSTS and the limited activity of second- and further-line therapies, the panel of experts considers that ESCAT_2 and ESCAT_3 alterations can justify the treatment of patients with a drug-alteration match, provided an adequate risk-benefit ratio is preserved (Vanoli et al., 2024; Westphalen et al., 2024). In particular for ESCAT_3 alterations, the panel of experts advice that a drug-alteration match should be preferably supported by preclinical evidence of actionability of the proposed target. Furthermore, in case of uncertainty, a multidisciplinary discussion involving molecular biologists, pathologists, and clinicians familiar with BSTS management is recommended. Ongoing research could better define the therapeutic potential of ESCAT_2 and ESCAT_3 alterations in the future. As the field of precision oncology continues to advance, further delineation of these alterations and their associated therapies will be critical in improving outcomes for patients with BSTS.

Given the peculiarity of drug development process for pediatric population, the robustness of clinical evidence in pediatric BSTS patients might be further reduced. Thus, identified molecular alterations should be discussed in MTBs that include pediatricians or pediatric oncologists with a strong expertise in precision medicine approach and pediatric drug development.

2.3.3. Statement 10

According to ESMO recommendations on clinical reporting of genomic test results for solid cancers it is suggested to report biological/functional interpretation of the identified variants using the classification system for functional relevance based on 5 different classes: benign, likely benign, variant of unknown significance (VUS), likely pathogenic, and pathogenic (Richards et al., 2015).

The ESMO recommendations advised reporting pathogenic and likely pathogenic variants along with their clinical actionability. On the opposite, authors suggested not to report benign and likely-benign variants to avoid misinterpretations; VUS can be included provided they are listed in a separate section to avoid the risk of overinterpretation.

The same approach can be applied to BSTS, with the only exception of a different and more strict recommendation for VUS. Indeed, given BSTS rarity and the limited evidence available on the relevance of molecular/genomic alterations detected by means of MPS/NGS, the panel of experts suggests to always report VUS in the pathological report. The detection of VUS presents both challenges and opportunities in the management of BSTS and the panel of experts believe that reporting all VUS results comprehensively may have implications for both patient care and treatment strategies. Indeed, a detected variant can be labelled as VUS until it is reported and reclassified in one of the other categories. The rarity of BSTS mandates not to miss potentially relevant data. VUS should be periodically re-evaluated according to growing evidence coming from the literature and the available worldwide databases.

In line with ESMO recommendations, VUS should be listed in a different part of the report.

Given the limited treatment options and the need to avoid missing potentially relevant therapeutic opportunities, it is strongly recommended that cases involving VUS in potentially actionable targets or genes associated with hereditary syndromes be discussed within an MTB (Tsimberidou et al., 2023). This MTB should include specific expertise in managing BSTS, with the involvement of BSTS experts and pediatricians or pediatric oncologists for pediatric cases, as well as experts in molecular biology and genetics.

Table 1B
ESCAT_1 alterations in mesenchymal tumors for which matched treatment with agnostic approach is available.

Sarcoma type	Gene	Alteration	Estimated prevalence	Matched therapy	ESCAT I subtier (evidence)	Key reference(s)
NTRK fusion–positive sarcomas (including infantile fibrosarcoma; ultra-rare)	*NTRK1/2/3*	rearrangements	100 % (entity defined based on the presence of the alteration)	Larotrectinib; Entrectinib	I-C (tumor-agnostic)	(Demetri et al., 2022, 2020; Dieckmann et al., 2021; Kummar et al., 2023)
MSI-H / dMMR sarcomas (rare across histologies)	Mismatch repair deficiency → MSI-H	-	As above	Pembrolizumab (tumor-agnostic)	I-C (tumor-agnostic)	(Marcus et al., 2019; Poumeaud et al., 2024)
RET-rearranged sarcomas (ultra-rare)	*RET*	rearrangements	As above	Selpercatinib	I-C (tumor-agnostic)	(Subbiah et al., 2022)
TMB> 10	TMB> 10	-	As above	Nivolumab - Ipilimumab	I-C (tumor-agnostic)	(Okuma et al., 2023; Schenker et al., 2024)
BRAF V600E-mutant sarcomas (ultra-rare)	BRAF V600E mutation	missense mutations	As above	Dabrafenib + Trametinib (tumor-agnostic)	I-C (tumor-agnostic)	(Gouda and Subbiah, 2023)

TMB, tumor mutational burden

Table 2
Main ESCAT_2 and ESCAT_3 alterations in mesenchymal neoplasias.

Sarcoma type	Gene	Alteration	Estimated prevalence	Matched therapy	ESCAT I sub-tier (evidence)	Key reference(s)
Conventional chondrosarcoma	*IDH1*	mutations	38–40 %	Ivosidenib	II-B	(Tap et al., 2020, 2025)
Dedifferentiated liposarcoma (DDLPS)	*CDK4*	amplification	90 %	abemaciclib palbociclib	II-B	(Dickson et al., 2016; Gleason et al., 2024)
Inflammatory myofibroblastic tumor	*ROS1*	rearrangements	5–10 %	Crizotinib	II-B/III-A	(Mai et al., 2019; Comandini et al., 2021; Schoot et al., 2023)
Leiomyosarcoma (mostly uterine, uLMS)	*BRCA1/2*	Deletions, mutations (*particularly BRCA2 homozygous deletions (5 %) in uLMS*	5–10 %	PARPi	II-B/III-A	(Rao et al., 2025; Ingham et al., 2023)
Histiocytic sarcomas	MAPK pathway alterations	Mostly activating missense mutations	50–60 %	trametinib	II-B/III-A	(Kemps et al., 2024; Gounder et al., 2018)

Many of these data came to case series or case reports or a few prospective studies. In these cases, ESCAT tier II-B/III-A was attributed according to available evidences.
MAPK: Mitogen-Activated Protein Kinase

STATEMENT 8

Targeting ESCAT_1 alterations, including tumor-agnostic alterations, should be prioritized in clinical practice whenever feasible. When routine access to a specific drug-alteration match is not available, participation in clinical trials should be strongly encouraged or alternative strategies should be discussed with the patients, such as off-label use or expanded access programs.

STATEMENT 9

Evidence classified as ESCAT_2 or ESCAT_3 can be considered sufficient for BSTS given the rarity of many histotypes and molecular alterations encountered. The same considerations as for ESCAT_1 alterations should be taken into account, albeit with a higher degree of uncertainty. These drug-alteration matches should be preferably corroborated by preclinical evidence supporting their pathogenic role.

In case the MTB is not available at a local level, the cases should be referred to an external MTB with adequate expertise in BSTS after obtaining the appropriate informed consent (ICF) from the patient. This multidisciplinary approach ensures that the patient receives comprehensive insights into the potential implications of the VUS, guiding the development of tailored therapeutic strategies whenever needed.

3. Statement future perspectives

Extended molecular profiling may further enhance complexity of mesenchymal tumor management. To address potential limitations at the local level and improve collaboration across institutions leveraging shared expertise and resources, the implementation of a national MTB virtual case discussion is desirable in collaboration with the National Rare Cancer Network to provide expert consultation for BSTS cases undergoing extended molecular profiling. This will require a dedicated ICF signature by the patient. Beyond improving MPS/NGS data interpretation, this collaborative effort may also help to harmonize treatment approaches at a national level.

In this field, the ESCAT classification support MPS/NGS analyses interpretation (Mosele et al., 2024; Mateo et al., 2018). However, evidence and suggestions are mainly derived from epithelial tumors that share little or nothing with mesenchymal neoplasms from the biological point of view. Therefore, the true clinical applicability of MPS/NGS findings to BSTS based on other tumor data remains a matter of discussion. The panel recommends the prospective, comprehensive collection of extended molecular profiling results (interpreted and/or raw data whenever available) along with clinical data and outcomes of patients affected by BSTS. This initiative should be pursued within the framework of the ISG and might be instrumental to shed light on observed findings. Such a registry would advance knowledge, inform treatment guidelines, and support innovative, data-driven approaches to

STATEMENT 10

VUS identified through MPS/NGS analyses must be always reported and listed in a separate section. It is recommended that the patient is evaluated by an MTB with expertise in BSTS management. In case a MTB experienced in BSTS is not available at the same institution, the case should be discussed – after dedicated ICF signature – within an external MTB, or experts in BSTS clinical management and molecular biology / genetics should be invited to MTB discussion.

improve patient care. Additionally, these data could pave the way to the creation of a dedicated score (e.g., an "ESCAT rare cancers" score) to evaluate alterations in BSTS and other rare cancers, aiding clinicians in prioritizing actionable mutations and therapeutic options, particularly for ultra-rare sarcomas.

4. Conclusions

As the field continues to evolve, a better understanding of the implications of detecting specific genomic alterations in BSTS will be essential to improve diagnosis and treatment outcomes and to guide the development of more effective targeted therapies tailored to each patient. In this context, enrolling patients in clinical trials is of paramount importance to shed light on the biological relevance of identified molecular alterations (driver/passenger).

Leveraging these powerful tools might open new avenues also for the diagnosis/treatment of BSTS patients who, with few exceptions, have been left behind by the personalized medicine revolution that characterized more common epithelial tumors in the last years.

Optimizing the use of molecular analyses must be accompanied by two parallel efforts: first, systematically collecting and correlating molecular data with clinical outcomes to expand our understanding of BSTS biology and treatment; second, addressing disparities in care by improving access to potentially effective, biologically supported therapies for BSTS patients.

Funding

This work was supported in part by co-funding from the European Union, EU4H-2023-JA-3-IBA-Joint Action JANE 2, GA 101183265, Joint Action on Networks of Expertise (to Roberta Maestro).

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FUTURE PERSPECTIVES

The implementation of a national MTB virtual case discussion is desirable in collaboration with the National Rare Cancer Network to provide expert consultation for BSTS cases undergoing extended molecular profiling.

A comprehensive collection of molecular profiling data (interpreted and/or raw data whenever available) and approach used, along with clinical data and outcomes of patients with potentially actionable alterations should be pursued within the framework of the ISG.

It is advisable to work out dedicated scores dedicated to BSTS (e.g., a dedicated "ESCAT rare cancers" score) for the evaluation of molecular alterations.

Angelo Paolo Dei Tos: conceptualization, investigation, methodology, original draft writing, supervision, visualization.

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Declaration of Competing Interest

All authors reported no conflict of interest (COI) for the present work.

Outside the submitted work the following authors reported potential COIs:

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Advisory role: PSI CRO Italy, Boerhinger Ingelheim, GSK, Eisai Co Ltd, and AstraZeneca

Meeting participation: PharmaMar, Gentili, and Amgen Inc

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Grant (institutional): PharmaMar

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Grants and personal fees from PharmaMar, grants from Novartis, and personal consulting fees from Lilly, Pfizer, Bayer, and Eisai.

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Consulting fees: Eli Lilly, Pharmamar

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Travel grants: Istituto Gentili, Pharmamar, Eli Lilly

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Essentia, Rain Therapeutics, Regeneron, Servier.

Institutional financial interests: Abbisko, Advenchen, Bayer, Boehringer, Daiichi Sankyo, Deciphera, Eisai, Epizyme, Foghorn, Glaxo Smith Kline, Hutchinson, Inhibrix, Ipsen, Karyopharm, Novartis, Pharmamar, RainThera, Springworks

Acknowledgements

The Authors would like to acknowledge Laura Abate-Daga and Giuseppe Bianchi for their crucial role for the organization and logistics coordination of both online and in-person meetings during which the consensus document was prepared.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2025.104960.

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Andrei Ivanescu — Patient advocate and president of EHE Italy, the association for the study and research of epithelioid hemangioendothelioma, a rare cancer. The association promotes awareness, education, and dissemination of knowledge about this disease.

Gianluca Ignazzi — Biologist with a master's degree in "Data Management in Oncology." He is currently Clinical Trial Unit Lead at the Italian Sarcoma Group, Milan.

Lorena Incorvaia — Medical oncologist and associate professor at the University of Palermo. She conducts clinical and translational research in sarcomas.

Alessandra Linari — Pathologist at Città della Salute e della Scienza Hospital, Turin, with extensive experience in bone and soft tissue sarcomas, which are her primary focus.

Roberto Luksch — Pediatric oncohematologist at the National Cancer Institute, Milan. He conducts clinical and translational research in sarcomas.

Andrea Marrari — Medical oncologist at Policlinico di Milano. He is involved in the clinical management of soft tissue and bone sarcomas.

Alessandro Mazzocca — Medical oncologist at Campus Biomedico, Rome, focusing on sarcoma clinical and translational research.

Giuseppe Maria Milano — Pediatric oncohematologist at Bambino Gesù Hospital, Rome. He conducts clinical and translational research in sarcomas affecting children, adolescents, and young adults, and leads several research initiatives in the field.

Carlo Morosi — Radiologist and Head of the Radiology Division at the National Cancer Institute, Milan. His work focuses on bone and soft tissue sarcomas, including clinical research.

Margherita Nannini — Medical oncologist and associate professor at the University of Bologna. She works at Sant'Orsola-Malpighi Polyclinic, Bologna, and is focused on clinical and translational sarcoma research, particularly GIST.

Pierina Navarria — Radiation oncologist and Associate Chief in the Radiotherapy and Radiosurgery Department at Humanitas Cancer Center, Rozzano, Milan. She is an expert in the radiotherapy of bone and soft tissue sarcomas.

Elena Palassini — Medical oncologist at the National Cancer Institute, Milan, focusing on clinical and translational research in bone and soft tissue sarcomas.

Emanuela Palmerini — Medical oncologist currently appointed as Research Professor of Sarcoma at the Miller School of Medicine, joining the Medical Oncology team and the Sarcoma Sylvester Comprehensive Cancer Center, previously oncologist and researcher at Istituto Ortopedico Rizzoli, Bologna, focusing on bone sarcoma clinical care and research

Fiammetta Paloschi — Patient advocate and Vice-President of the Italian GIST Foundation ETS, a patient association aimed at raising public awareness and improving the diagnosis and therapy of patients with GIST.

Maria Abbondanza Pantaleo — Medical oncologist and associate professor at the University of Bologna. She works at Sant'Orsola-Malpighi Polyclinic and is dedicated to the treatment and research of sarcomas, particularly gastrointestinal stromal tumors (GIST).

Sandro Pasquali — Head of Molecular Pharmacology Unit and surgical oncologist at National Cancer Institute in Milan, focusing on translational research and patient-relevant sarcoma models

Valeria Pavese — Medical oncologist at Cardinal Massaia Hospital, Asti. During her residency, she focused on research and treatment of sarcomas.

Enrico Pozzo — Radiation oncologist at Humanitas Cancer Center, Rozzano, Milan. He is dedicated to sarcoma treatment and preclinical radiotherapy research.

Vittorio Quagliuolo - Head of Oncologic Surgery, Humanitas Cancer Center, Rozzano, Milan, leading expert in sarcoma surgery.

Michela Quirino — Medical oncologist at Gemelli Hospital, Rome, focusing on sarcoma treatment.

Roberta Sanfilippo — Medical oncologist at the National Cancer Institute, Milan, focusing on clinical and translational research, especially in liposarcomas and leiomyosarcomas.

Federica Santoro — Pathologist at Città della Salute e della Scienza Hospital, Turin, focusing on bone and soft tissue sarcomas.

Katia Scotlandi — Biologist and Director of the Experimental Oncology Laboratory at the Rizzoli Orthopedic Institute, Bologna. She coordinates translational research activities in bone sarcomas and is head of the ACC (Alleanza Contro il Cancro) Sarcoma Working Group.

Massimo Serra — Biologist and Head of the Pharmacogenomics and Pharmacogenetics Unit at the Rizzoli Orthopedic Institute, Bologna, focusing on sarcomas.

Elisabetta Setola — Medical oncologist at the European Institute of Oncology (IEO), Milan. Her work is dedicated to patients with bone and soft tissue sarcomas.

Sabino Strippoli — Medical oncologist at the "Giovanni Paolo II" Cancer Institute, Bari, focusing on bone and soft tissue sarcomas.

Salvatore Tafuto — Medical oncologist at the National Cancer Institute of Naples, focusing on bone and soft tissue sarcomas.

Elisa Tirtei — Pediatric oncohematologist and researcher at Regina Margherita Children's Hospital, AOU Città della Salute e della Scienza, Turin.

Silvia Vanni — Biologist with a PhD in Functional and Structural Genomics, she is a researcher at IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, focusing on sarcoma research and preclinical models.

Bruno Vincenzi — Medical oncologist and Full Professor at Campus Biomedico University Hospital, Rome, focusing on sarcoma clinical and translational research. He is also Director of the Hematology Residency Program.

Roberta Maestro — Biologist and Director of the Functional Oncogenetics and Oncogenomics Unit at CRO Aviano, IRCCS. Her research is focused on sarcomas and the application of -omic technologies in this rare tumor field.

Angelo Paolo Dei Tos — Head of Pathology Department and Full Professor at the University of Padua; vice-dean at the University of Padua; CTOS past president; member of the WHO Classification Group, his research in sarcoma pathology has significantly contributed to shape sarcoma research and diagnosis.

Silvia Stacchiotti — President of Italian Sarcoma Group, president of CTOS, secretary of the EORTC Soft Tissue and Bone Sarcoma, oncologist at National Cancer Institute, Milan. Her clinical and research work has significantly contributed to shape sarcoma research and clinical practice and focuses on sarcomas and GISTs, including the coordination of rare cancer networks.