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

Anna Maria Frezza, Medical Oncologist, Fondazione IRCCS Istituto Nazionale Tumori, Milan

Judith V.M.G. Bovée, Pathologist, Leiden University Medical Center, Leiden

EMA
EUROPEAN MEDICINES AGENCY

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

PUSH
PLATFORM

Declaration of interest

- AMF declares institutional research funding from Advenchen Laboratories, Amgen Dompé, AROG Pharmaceuticals, Ayala Pharmaceuticals, Bayer, Blueprint Medicines, Boehriger Ingelheim, Daiichi Sankyo, Deciphera, Eisai, Eli Lilly, Epizyme Inc, Foghorn Therapeutics Inc., Glaxo, Hutchison MediPharma Limited, Inhibrx, Inc., Karyopharm Pharmaceuticals, Novartis, Pfizer, PharmaMar, PTC Therapeutics, Rain Oncology, SpringWorks Therapeutics

- JB declares consultancy fees from Boehringer Ingelheim and Inhibrx research funding from Tracon pharmaceuticals

WHY
do we need retrospective studies in URS?

22 ultra-rare bone sarcomas

56 ultra-rare soft tissue sarcomas

78 ultra-rare sarcomas

24 prospective studies

> phase II
9 URS (bone and soft tissue)
no drug approval in the EU

23 retrospective studies

collaborative
> 50 patients
21 URS (bone and soft tissue)

Stacchiotti S, et al. Cancer. 2021 Aug 15;127(16):2934-2942.

Retrospective studies in URS

few examples…

Entity: **ASPS**
Patients: 44
Timeframe: 2007 - 2016
Centres: 14
Countries: EU, US, Japan

2018, Stacchiotti S et al, The Oncologist

Entity: **EHE**
Patients: 77
Timeframe: 2000 - 2020
Centres: 20
Countries: EU, US, Australia, Japan

2021, Frezza AM et al, Cancer Med

Entity: **epithelioid sarcoma**
Patients: 115 (INI1 -)
Timeframe: 1990-2016
Centres: 17
Countries: EU, US, Japan

2018, Frezza AM et al, JAMA Oncol

Entity: **CCS**
Patients: 115 (EWSR1 fusion +)
Timeframe: 1985 - 2021
Centres: 10
Countries: EU, Australia

2022, Smrke A et al, ESMO Open

Entity: **intimal sarcoma**
Patients: 72 (MDM2 +)
Timeframe: 2001 - 2018
Centres: 17
Countries: EU, US, Japan

2019, Frezza AM et al, Cancer

Entity: **SEF and LGMFS**
Patients: 395
Centres: 28
Countries: EU, US, Asia, Australia

2023, Giani C. et al, CTOS

Entity: **IMT**
Patients: 38
Timeframe: 1996 - 2018
Centres: 9
Countries: EU

2020, Baldi GG et al, The Oncologist

2024: **adult-type RMS**

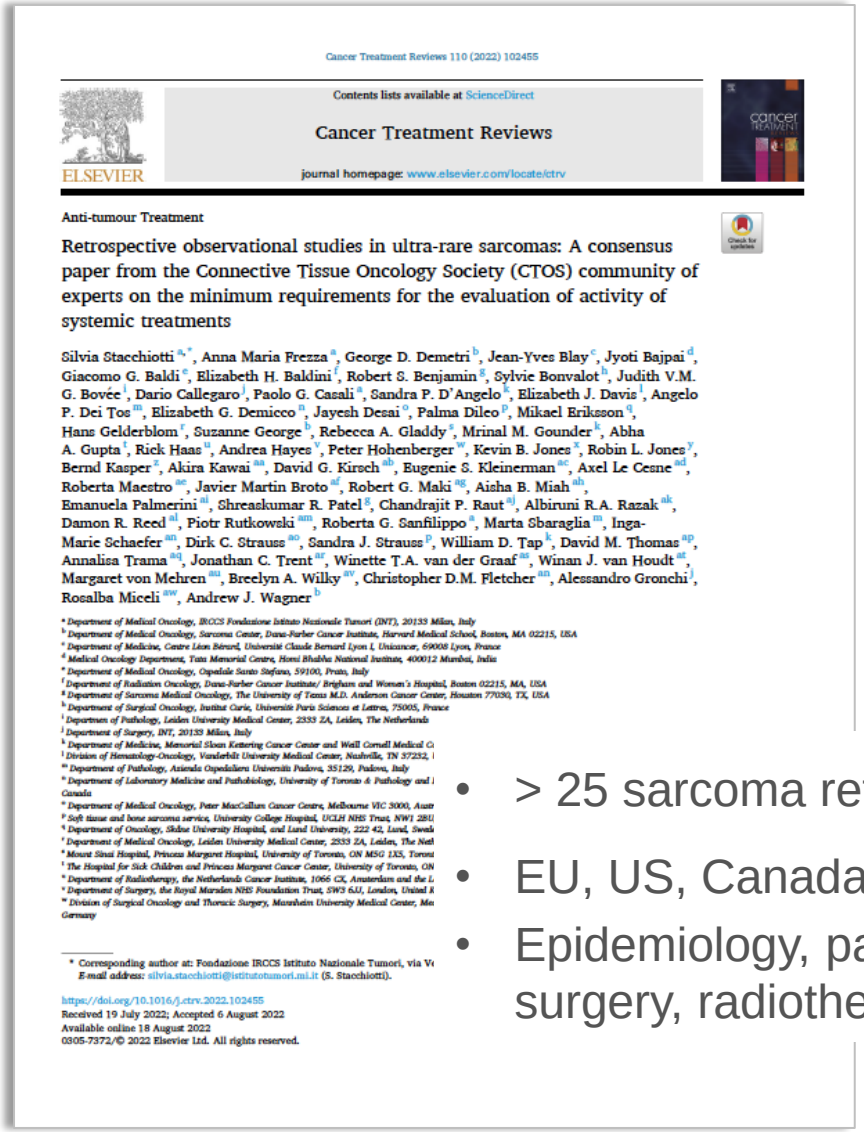
WHY do we need retrospective studies?

Build evidence on medical therapies!

- Inform clinical practice
- Prompt development of new clinical studies
- Serve as external control in single-arm prospective studies
- Support regulatory approval of new therapeutics

LIMITATIONS & CHALLENGES

HOW did we optimise the process?



Cancer Treatment Reviews 110 (2022) 102455

Contents lists available at ScienceDirect

Cancer Treatment Reviews

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

Anti-tumour Treatment

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

Silvia Stacchiotti [a,*], Anna Maria Frezza [a], George D. Demetri [b], Jean-Yves Blay [c], Jyoti Bajpai [d], Giacomo G. Baldi [e], Elizabeth H. Baldini [f], Robert S. Benjamin [g], Sylvie Bonvalot [h], Judith V.M. G. Bovée [i], Dario Callegaro [j], Paolo G. Casali [a], Sandra P. D'Angelo [k], Elizabeth J. Davis [l], Angelo P. Dei Tos [m], Elizabeth G. Demicco [n], Jayesh Desai [o], Palma Dileo [p], Mikael Eriksson [q], Hans Gelderblom [r], Suzanne George [b], Rebecca A. Gladdy [s], Mrinal M. Gounder [k], Abha A. Gupta [t], Rick Haas [u], Andrea Hayes [v], Peter Hohenberger [w], Kevin B. Jones [x], Robin L. Jones [y], Bernd Kasper [z], Akira Kawai [aa], David G. Kirsch [ab], Eugenie S. Kleinerman [ac], Axel Le Cesne [ad], Roberta Maestro [ae], Javier Martin Broto [af], Robert G. Maki [ag], Aisha B. Miah [ah], Emanuela Palmerini [ai], Shreaskumar R. Patel [g], Chandrajit P. Raut [aj], Albiruni R.A. Razak [ak], Damon R. Reed [al], Piotr Rutkowski [am], Roberta G. Sanfilippo [a], Marta Sbaraglia [m], Inga-Marie Schaefer [an], Dirk C. Strauss [ao], Sandra J. Strauss [p], William D. Tap [k], David M. Thomas [ap], Annalisa Trama [aq], Jonathan C. Trent [ar], Winette T.A. van der Graaf [as], Winan J. van Houdt [at], Margaret von Mehren [au], Breelyn A. Wilky [av], Christopher D.M. Fletcher [an], Alessandro Gronchi [j], Rosalba Miceli [aw], Andrew J. Wagner [b]

[a] Department of Medical Oncology, IRCCS Fondazione Istituto Nazionale Tumori (INT), 20133 Milan, Italy
[b] Department of Medical Oncology, Sarcoma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02215, USA
[c] Department of Medicine, Centre Léon Bérard, Université Claude Bernard Lyon I, Unicancer, 69008 Lyon, France
[d] Medical Oncology Department, Tata Memorial Centre, Homi Bhabha National Institute, 400012 Mumbai, India
[e] Department of Medical Oncology, Ospedale Santo Stefano, 59100, Prato, Italy
[f] Department of Radiation Oncology, Dana-Farber Cancer Institute/ Brigham and Women's Hospital, Boston 02215, MA, USA
[g] Department of Sarcoma Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston 77030, TX, USA
[h] Department of Surgical Oncology, Institut Curie, Université Paris Sciences et Lettres, 75005, France
[i] Departmen of Pathology, Leiden University Medical Center, 2333 ZA, Leiden, The Netherlands
[j] Department of Surgery, INT, 20133 Milan, Italy
[k] Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical C
[l] Division of Hematology-Oncology, Vanderbilt University Medical Center, Nashville, TN 37232,
[m] Department of Pathology, Azienda Ospedaliera Università Padova, 35128, Padova, Italy
[n] Department of Laboratory Medicine and Pathobiology, University of Toronto & Pathology and
Canada
[o] Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne VIC 3000, Aust
[p] Soft tissue and bone sarcoma service, University College Hospital, UCLH NHS Trust, NW1 2BU
[q] Department of Oncology, Skåne University Hospital, and Lund University, 222 42, Lund, Swed
[r] Department of Medical Oncology, Leiden University Medical Center, 2333 ZA, Leiden, The Net
[s] Mount Sinai Hospital, Princess Margaret Hospital, University of Toronto, ON M5G 1X5, Toron
[t] The Hospital for Sick Children and Princess Margaret Cancer Center, University of Toronto, ON
[u] Department of Radiotherapy, the Netherlands Cancer Institute, 1066 CX, Amsterdam and the L
[v] Department of Surgery, the Royal Marsden NHS Foundation Trust, SW3 6JJ, London, United K
[w] Division of Surgical Oncology and Thoracic Surgery, Mannheim University Medical Center, Me
Germany

* Corresponding author at: Fondazione IRCCS Istituto Nazionale Tumori, via Vo
E-mail address: silvia.stacchiotti@istitutotumori.mi.it (S. Stacchiotti).

https://doi.org/10.1016/j.ctrv.2022.102455
Received 19 July 2022; Accepted 6 August 2022
Available online 18 August 2022
0305-7372/

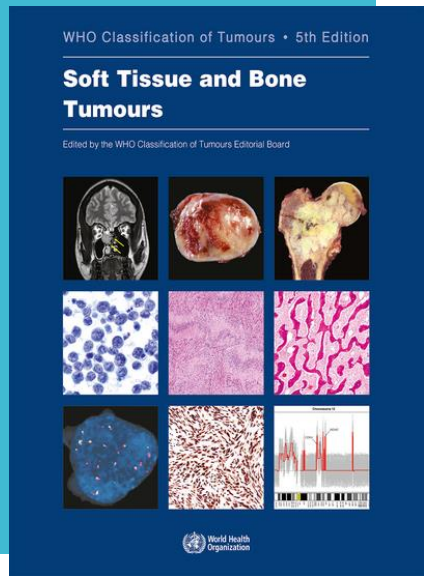
- > 25 sarcoma reference centres
- EU, US, Canada, Asia and Australia
- Epidemiology, pathology, molecular biology, radiology, surgery, radiotherapy, medical oncology, biostatistics

HOW did we optimise the process?

1. Ensuring the quality of pathological diagnosis
2. Selection criteria for contributing centres
3. Radiological assessment of disease response and progression
4. Consistency in the frequency of disease monitoring across centres
5. Endpoint selection
6. Avoidance of data duplication
7. Results publication

Stacchiotti et al, Cancer Treat Rev. 2022 Nov;110:102455.

Challenges in sarcoma pathological diagnosis



- Sarcomas are rare
- >150 different bone and soft tissue tumor types
- ~20% of sarcomas are ultrarare
- 78 ultrarare sarcoma types
- Concordance rates after pathology revision: 56-73%
  - 16-35% minor discrepancy
  - 8-11% major discrepancy (benign / malignant, different diagnosis) leading to management change

Sarcoma 2009, Ann Oncol 2012

How do we ensure the **quality of the pathological diagnosis** in retrospective studies?

- Pathological diagnosis should be confirmed by an **expert sarcoma pathologist** in a sarcoma reference centre
- Upfront: **consensus about essential diagnostic criteria for the URS subtype of the study** (based on WHO):
  - Morphology
  - Immunohistochemistry
  - Molecular alterations
- Centralized pathology review, preferably digitally, for difficult cases
- All uncertain / questionable cases should be excluded

HOW did we optimise the process?

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 - 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 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.	- 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.

Stacchiotti et al, Cancer Treat Rev. 2022 Nov;110:102455.

HOW did we optimise the process?

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.	- 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.
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. - 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.	- 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).

Stacchiotti et al, Cancer Treat Rev. 2022 Nov;110:102455.

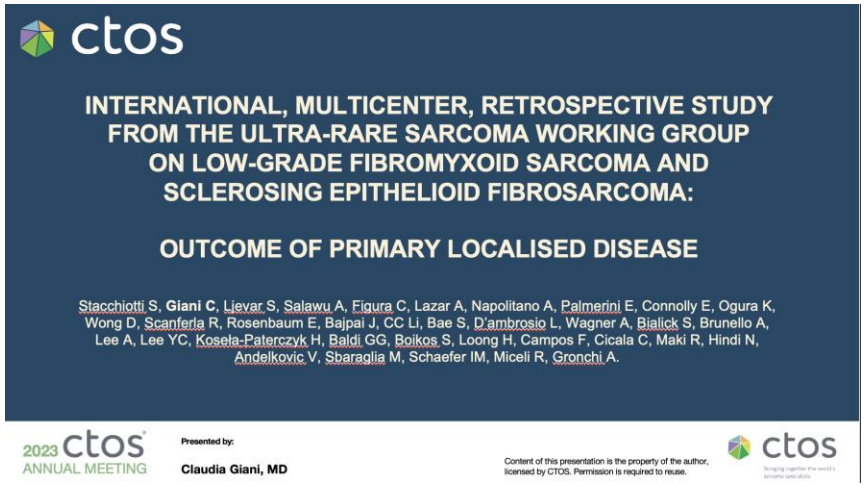
HOW did we optimise the process?

Consistency in the frequency of disease monitoring across centers	- All eligible patients should be included in the study. - 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 - 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 - 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

Stacchiotti et al, Cancer Treat Rev. 2022 Nov;110:102455.

From the consensus paper to study design and development:

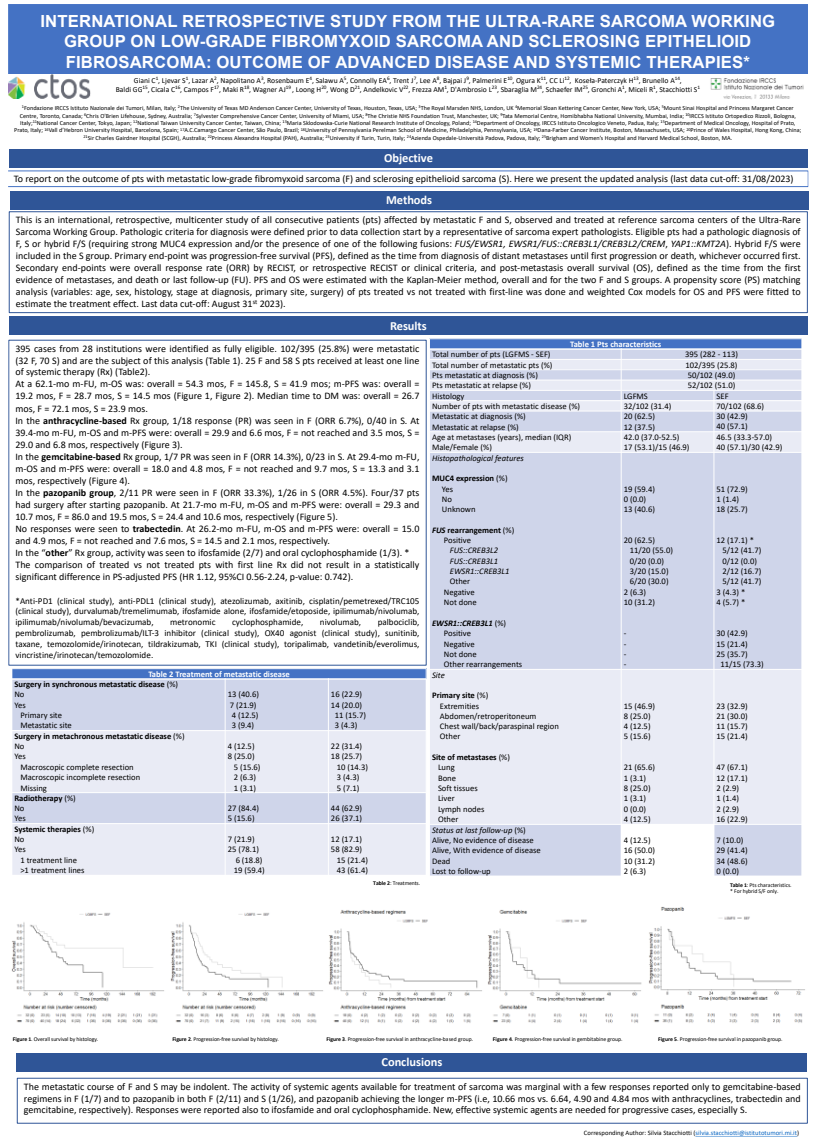
the SEF/LGFMS retrospective collection experience



Entity: **SEF/LGFMS**

Patients: 395

Timeframe: 2000-2022



INTERNATIONAL RETROSPECTIVE STUDY FROM THE ULTRA-RARE SARCOMA WORKING GROUP ON LOW-GRADE FIBROMYXOID SARCOMA AND SCLEROSING EPITHELIOID FIBROSARCOMA: OUTCOME OF ADVANCED DISEASE AND SYSTEMIC THERAPIES*

ctos

Giani C[1], Ljevar S[1], Lazar A[2], Napolitano A[3], Rosenbaum E[4], Salawu A[5], Connolly EA[6], Trent J[7], Lee A[8], Bajpai J[9], Palmerini E[10], Ogura K[11], CC Li[12], Kosela-Paterczyk H[13], Brunello A[14], Baldi GG[15], Cicala C[16], Campos F[17], Maki R[18], Wagner AJ[19], Loong H[20], Wong D[21], Andelkovic V[22], Frezza AM[3], D'Ambrosio L[23], Sbaraglia M[24], Schaefer IM[25], Gronchi A[1], Miceli R[3], Stacchiotti S[1]

Fondazione IRCCS Istituto Nazionale dei Tumori

Objective

To report on the outcome of pts with metastatic low-grade fibromyxoid sarcoma (F) and sclerosing epithelioid sarcoma (S). Here we present the updated analysis (last data cut-off: 31/08/2023)

Methods

This is an international, retrospective, multicenter study of all consecutive patients (pts) affected by metastatic F and S, observed and treated at reference sarcoma centers of the Ultra-Rare Sarcoma Working Group. Pathologic criteria for diagnosis were defined prior to data collection start by a representative of sarcoma expert pathologists. Eligible pts had a pathologic diagnosis of F, S or hybrid F/S (requiring strong MUC4 expression and/or the presence of one of the following fusions: *FUS/EWSR1, EWSR1/FUS::CREB3L1/CREB3L2/CREM, YAP1::KMT2A*). Hybrid F/S were included in the S group. Primary end-point was progression-free survival (PFS), defined as the time from diagnosis of distant metastases until first progression or death, whichever occurred first. Secondary end-points were overall response rate (ORR) by RECIST, or retrospective RECIST or clinical criteria, and post-metastasis overall survival (OS), defined as the time from the first evidence of metastases, and death or last follow-up (FU). PFS and OS were estimated with the Kaplan-Meier method, overall and for the two F and S groups. A propensity score (PS) matching analysis (variables: age, sex, histology, stage at diagnosis, primary site, surgery) of pts treated vs not treated with first-line was done and weighted Cox models for OS and PFS were fitted to estimate the treatment effect. Last data cut-off: August 31° 2023).

Results

395 cases from 28 institutions were identified as fully eligible. 102/395 (25.8%) were metastatic (32 F, 70 S) and are the subject of this analysis (Table 1). 25 F and 58 S pts received at least one line of systemic therapy (Rx) (Table2).

At a 62.1-mo m-FU, m-OS was: overall = 54.3 mos, F = 145.8, S = 41.9 mos; m-PFS was: overall = 19.2 mos, F = 28.7 mos, S = 14.5 mos (Figure 1, Figure 2). Median time to DM was: overall = 26.7 mos, F = 72.1 mos, S = 23.9 mos.

In the **anthracycline-based** Rx group, 1/18 response (PR) was seen in F (ORR 6.7%), 0/40 in S. At 39.4-mo m-FU, m-OS and m-PFS were: overall = 29.9 and 6.6 mos, F = not reached and 3.5 mos, S = 29.0 and 6.8 mos, respectively (Figure 3).

In the **gemcitabine-based** Rx group, 1/7 PR was seen in F (ORR 14.3%), 0/23 in S. At 29.4-mo m-FU, m-OS and m-PFS were: overall = 18.0 and 4.8 mos, F = not reached and 9.7 mos, S = 13.3 and 3.1 mos, respectively (Figure 4).

In the **pazopanib group**, 2/11 PR were seen in F (ORR 33.3%), 1/26 in S (ORR 4.5%). Four/37 pts had surgery after starting pazopanib. At 21.7-mo m-FU, m-OS and m-PFS were: overall = 29.3 and 10.7 mos, F = 86.0 and 19.5 mos, S = 24.4 and 10.6 mos, respectively (Figure 5).

No responses were seen to **trabectedin**. At 26.2-mo m-FU, m-OS and m-PFS were: overall = 15.0 and 4.9 mos, F = not reached and 7.6 mos, S = 14.5 and 2.1 mos, respectively.

In the "**other**" Rx group, activity was seen to ifosfamide (2/7) and oral cyclophosphamide (1/3). *

The comparison of treated vs not treated pts with first line Rx did not result in a statistically significant difference in PS-adjusted PFS (HR 1.12, 95%CI 0.56-2.24, p-value: 0.742).

*Anti-PD1 (clinical study), anti-PDL1 (clinical study), atezolizumab, avitinib, cisplatin/pemetrexed/TRC105 (clinical study), durvalumab/tremelimumab, ifosfamide alone, ifosfamide/etoposide, ipilimumab/nivolumab, ipilimumab/nivolumab/bevacizumab, metronomic cyclophosphamide, nivolumab, palbociclib, pembrolizumab, pembrolizumab/ILT-3 inhibitor (clinical study), OX40 agonist (clinical study), sunitinib, taxane, temozolomide/irinotecan, tildrakizumab, TKI (clinical study), toripalimab, vandetinib/everolimus, vincristine/irinotecan/temozolomide.

Table 1 Pts characteristics

Total number of pts (LGFMS - SEF)	395 (282 - 113)	
Total number of metastatic pts (%)	102/395 (25.8)	
Pts metastatic at diagnosis (%)	50/102 (49.0)	
Pts metastatic at relapse (%)	52/102 (51.0)	
Histology	LGFMS	SEF
Number of pts with metastatic disease (%)	32/102 (31.4)	70/102 (68.6)
Metastatic at diagnosis (%)	20 (62.5)	30 (42.9)
Metastatic at relapse (%)	12 (37.5)	40 (57.1)
Age at metastases (years), median (IQR)	42.0 (37.0-52.5)	46.5 (33.3-57.0)
Male/Female (%)	17 (53.1)/15 (46.9)	40 (57.1)/30 (42.9)
Histopathological features		
MUC4 expression (%)		
Yes	19 (59.4)	51 (72.9)
No	0 (0.0)	1 (1.4)
Unknown	13 (40.6)	18 (25.7)
***FUS* rearrangement** (%)		
Positive	20 (62.5)	12 (17.1) *
FUS::CREB3L2	11/20 (55.0)	5/12 (41.7)
FUS::CREB3L1	0/20 (0.0)	0/12 (0.0)
EWSR1::CREB3L1	3/20 (15.0)	2/12 (16.7)
Other	6/20 (30.0)	5/12 (41.7)
Negative	2 (6.3)	3 (4.3) *
Not done	10 (31.2)	4 (5.7) *
EWSR1::CREB3L1 (%)		
Positive	-	30 (42.9)
Negative	-	15 (21.4)
Not done	-	25 (35.7)
Other rearrangements	-	11/15 (73.3)
Site		
Primary site (%)		
Extremities	15 (46.9)	23 (32.9)
Abdomen/retroperitoneum	8 (25.0)	21 (30.0)
Chest wall/back/paraspinal region	4 (12.5)	11 (15.7)
Other	5 (15.6)	15 (21.4)
Site of metastases (%)		
Lung	21 (65.6)	47 (67.1)
Bone	1 (3.1)	12 (17.1)
Soft tissues	8 (25.0)	2 (2.9)
Liver	1 (3.1)	1 (1.4)
Lymph nodes	0 (0.0)	2 (2.9)
Other	4 (12.5)	16 (22.9)
Status at last follow-up (%)		
Alive, No evidence of disease	4 (12.5)	7 (10.0)
Alive, With evidence of disease	16 (50.0)	29 (41.4)
Dead	10 (31.2)	34 (48.6)
Lost to follow-up	2 (6.3)	0 (0.0)

Table 2 Treatment of metastatic disease

Surgery in synchronous metastatic disease (%)		
No	13 (40.6)	16 (22.9)
Yes	7 (21.9)	14 (20.0)
Primary site	4 (12.5)	11 (15.7)
Metastatic site	3 (9.4)	3 (4.3)
Surgery in metachronous metastatic disease (%)		
No	4 (12.5)	22 (31.4)
Yes	8 (25.0)	18 (25.7)
Macroscopic complete resection	5 (15.6)	10 (14.3)
Macroscopic incomplete resection	2 (6.3)	3 (4.3)
Missing	1 (3.1)	5 (7.1)
Radiotherapy (%)		
No	27 (84.4)	44 (62.9)
Yes	5 (15.6)	26 (37.1)
Systemic therapies (%)		
No	7 (21.9)	12 (17.1)
Yes	25 (78.1)	58 (82.9)
1 treatment line	6 (18.8)	15 (21.4)
>1 treatment lines	19 (59.4)	43 (61.4)

Table 2: Treatments.

Table 1: Pts characteristics. * For hybrid S/F only.

Figure 1. Overall survival by histology. **Figure 2**. Progression-free survival by histology. **Figure 3**. Progression-free survival in anthracycline-based group. **Figure 4**. Progression-free survival in gemcitabine group. **Figure 5**. Progression-free survival in pazopanib group.

Conclusions

The metastatic course of F and S may be indolent. The activity of systemic agents available for treatment of sarcoma was marginal with a few responses reported only to gemcitabine-based regimens in F (1/7) and to pazopanib in both F (2/11) and S (1/26), and pazopanib achieving the longer m-PFS (i.e, 10.66 mos vs. 6.64, 4.90 and 4.84 mos with anthracyclines, trabectedin and gemcitabine, respectively). Responses were reported also to ifosfamide and oral cyclophosphamide. New, effective systemic agents are needed for progressive cases, especially S.

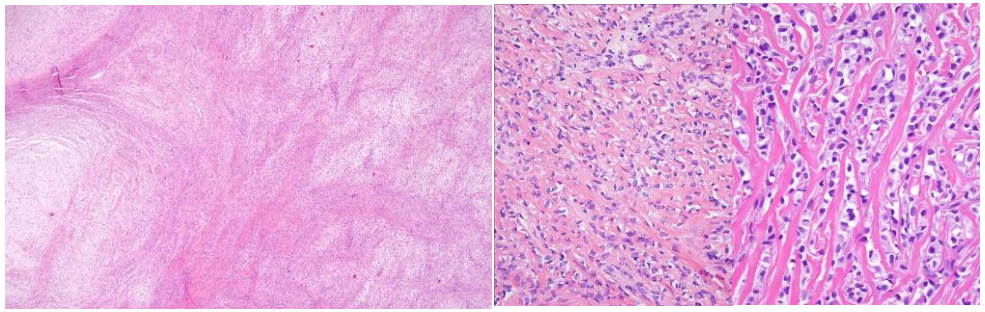
Corresponding Author: Silvia Stacchiotti (silvia.stacchiotti@istitutotumori.mi.it)

From the consensus paper to study design and development:

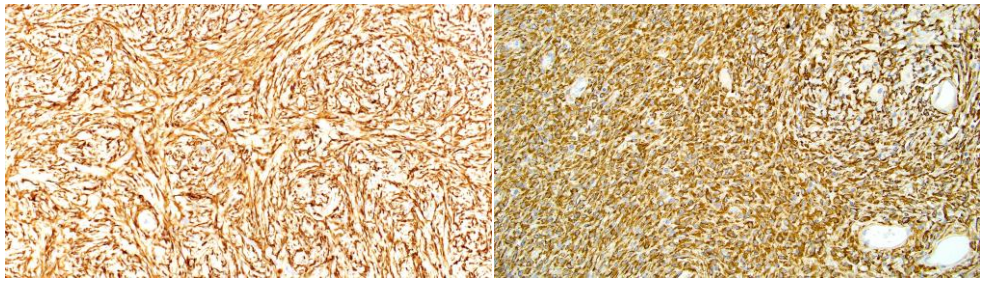
the SEF/LGFMS retrospective collection experience

Pathology diagnosis, present criteria for inclusion:

- Morphology



- Immunohistochemistry: MUC4



- If MUC4 negative or not available:
  FUS or EWSR1 fusion with CREB3L1, CREB3L2 or CREM

From the consensus paper to study design and development:

the SEF/LGFMS retrospective collection experience

• Selection criteria for contributing centres	**28 sarcoma reference centres**
• Radiological assessment	**Imaging review**
• Consistency in disease monitoring across centres	**Dedicated item in the e-CRF**
• Endpoint selection	**Primary: PFS; secondary: ORR (RECIST 1.1)**
• Avoidance of data duplication	**Quality-check through e-CRF**
• Results publication	**Q1 2024**

e-CRF fully reusable!

2024:

adult-type RMS

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.

Stacchiotti et al, Cancer Treat Rev. 2022 Nov;110:102455.

Q1 – How can we further improve the methodology of data collection and use high-quality, pre-defined retrospective studies as control data for non-randomized prospective studies in URS?