Case example from PUSH: LGFMS/SEF and immunotherapy

EMA/EORTC Soft Tissue and Bone Sarcoma Group Joint Workshop

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Dana-Farber Cancer Institute

Disclosures*

Consulting/Honoraria:

Aadi Bioscience, BioAtla, Boehringer-Ingelheim, Cogent Biosciences, Daiichi Sankyo, Deciphera Pharmaceuticals, Eli Lilly, InhibRx, Kymera Therapeutics, PharmaEssentia, Servier

Research Support to My Institution:

Aadi Bioscience, Boehringer-Ingelheim, Cogent Biosciences, Daiichi Sankyo, Deciphera Pharmaceuticals, Eli Lilly, Foghorn Therapeutics, Rain Therapeutics

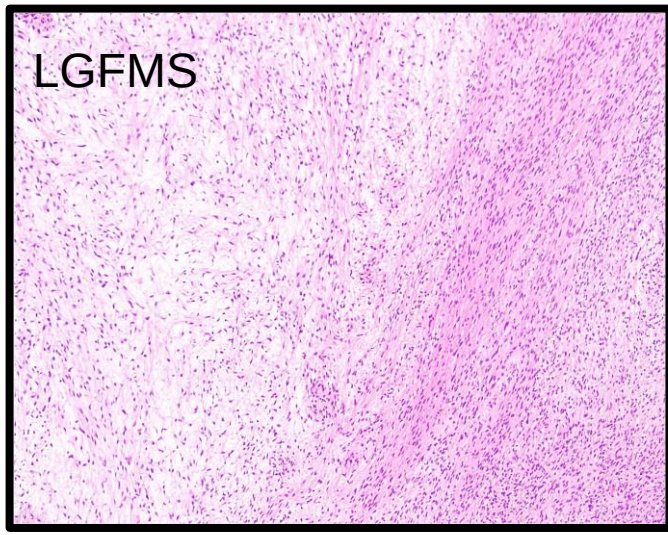
Board of Directors (uncompensated):

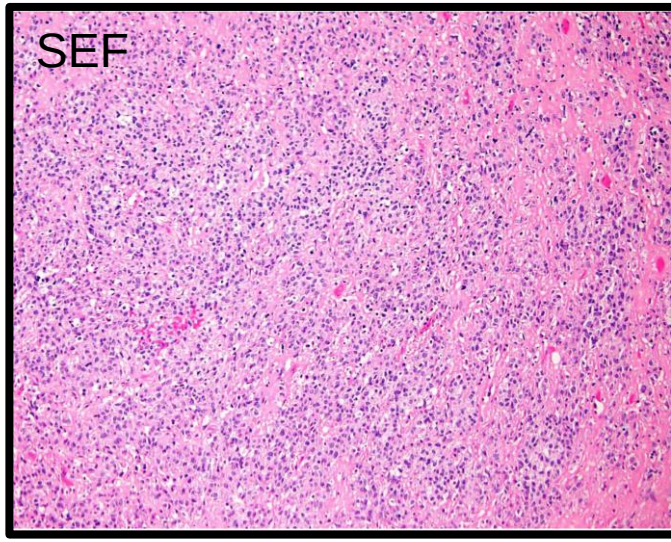
Sarcoma Alliance for Research through Collaboration (SARC)

* Last 2 years

Low-grade Fibromyxoid Sarcoma (LGFMS) and Sclerosing Epithelioid Fibrosarcoma (SEF)

- Distinct **ultra-rare sarcomas** that share morphologic, immunohistochemical, and molecular features
- LGFMS: low-grade sarcoma, young adults
  - MUC4 expression
  - *FUS::CREB3L2* in 90% of tumors
- SEF: older patients, high metastatic rate
  - MUC4 expression
  - *EWSR1::CREB3L1* in 60% of tumors
- As with other ultra-rare sarcomas, randomized studies are not feasible
- Three prior retrospective series (N=31, 12, and 10)





Stacchiotti et al. (2021) Cancer 127:2934-2942
Blay JY et al. (2024) Eur J Cancer 196:113454

https://www.pathologyoutlines.com/topic/softtissuelgfibromyxoid.html
https://www.pathologyoutlines.com/topic/softtissuesclerosingepithelioidfibrosarcoma.html

Two Collaborative Retrospective Studies

- NETSARC+ series
  - All prevalent patients in 26 NETSARC+ centers in France since 2010
  - 330 total patients
  - Limited number treated with systemic therapy
  - Anthracyclines highest response rate
  - From metastases, median PFS 18 months, median OS 43 months (SEF) and 65 months (LGFMS)

- Ultra-Rare Sarcoma Working Group/PUSH series
  - Patients treated at 28 centers in Europe, North America, South America, Asia, and Australia since 2000
  - 395 patients, 101 with metastatic disease, meeting defined entry criteria and treated with systemic therapy
    - 32 LGFMS, 50 SEF, 18 hybrid
  - Anthracyclines longest PFS in hybrid disease; pazopanib in LGFMS and SEF
  - 5/9 patients with SEF treated with **immunotherapy** observed to have prolonged stable disease

Blay JY et al. (2024) Eur J Cancer 196:113454
Giani C et al. (in review)

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- Defined criteria for retrospective series
- Historical reference group – with caveats
- Hypothesis generating

Prospective Interventional Study

- Defined patient population
- Small sample size
- Defined intervention
- Defined assessments
- Prospectively collected endpoints

- How to assess single arm study if no objective shrinkage of tumor?
- Can we use an external "control" group?

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- Hypothesis generating

Prospective Observational Study

- Defined patient population
- Slightly larger sample size
- Undefined intervention
- Defined assessments (SOC)
- Prospectively collected endpoints (SOC)

Prospective Interventional Study

- Defined patient population
- Small sample size
- Defined intervention
- Defined assessments
- Prospectively collected endpoints

- How to assess single arm study if no objective shrinkage of tumor?
- Can we use an external "control" group?

Questions for Discussion:

1. Are prospectively collected data (as in a “registry”), outside of a defined clinical intervention, helpful in providing context for a comparative patient population?

2. Are there opportunities for meetings with the EMA and FDA to collaboratively develop feasible frameworks for collection of data from prospective observational studies, to be used to help support interpretation of single arm interventional studies in ultra-rare diseases?

Thank you!

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Cancer Institute