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Preliminary results from a phase 2 EFTISARC-NEO trial of neoadjuvant soluble LAG-3 protein eftilagimod alpha, pembrolizumab, and concurrent radiotherapy in patients with resectable soft tissue sarcoma

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BACKGROUND

- Surgery is the mainstay of treatment of primary localized soft tissue sarcoma (STS), while in patients (pts) with high-grade localized STS of the extremity/trunk, radiation therapy (RTH) is added to reduce local recurrence.
- Combining immunotherapy (ITH) with RTH may be a promising strategy for synergistic enhancement of treatment efficacy.
- Eftilagimod alpha (efti) is a dimeric soluble recombinant LAG-3 protein and MHC Class II agonist stimulating antigen-presenting cells (APCs). The LAG-3 - MHC II interaction controls the signalling between T cells and APCs, which are responsible for the adaptive immune response. Combining efti with anti-PD-1 antibody pembrolizumab can enhance its antitumor activity.
- We hypothesize that adding combined ITH to RT prior to surgical resection would be safe and improve pathologic response compared to historical cohorts of pts with localized STS treated with RT alone.
- The percentage of hyalinization and fibrosis, as a surrogate of pathological response, appears to be most closely correlated with treatment outcome.

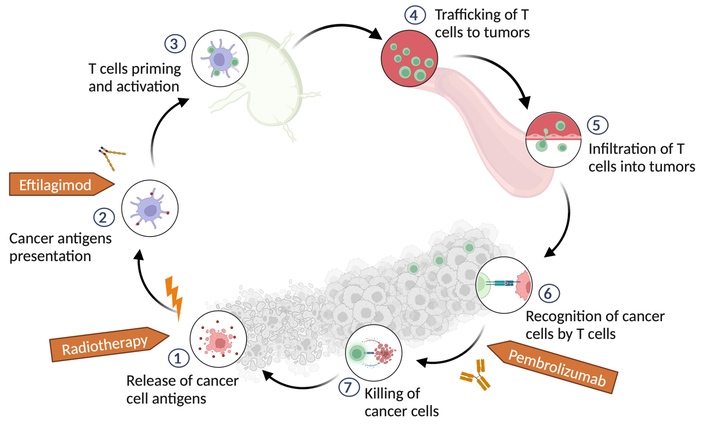

Fig. 1. Rationale for combining eftilagimod, pembrolizumab and radiotherapy based on cancer-immune cycle.

MATERIALS AND METHODS

- Single-arm single-center phase II study
- NCT06128863
- Planned enrollment – 40 patients
- Recruitment period: June 2023 – ongoing (planned completion 12/2024)

Key Inclusion Criteria
- ≥ 18 years of age
- ECOG 0 or 1
- Primary or locally recurrent deep-seated extremities, girdles and/or superficial trunk (thoracic or abdominal wall) tumor
- Histologic diagnosis of undifferentiated pleomorphic sarcoma (UPS), myxofibrosarcoma, dedifferentiated liposarcoma (DDLPS), myxoid and round cell liposarcoma (MRCLPS), epithelioid sarcoma (ES), angiosarcoma (AS), soft tissue sarcoma NOS
  - Amended on 28 Mar 2024 to allow of STS except for Ewing Sarcoma, alveolar and embryonal rhabdomyosarcoma
- Grade 2 or 3 tumors according FNCLCC
- Size of the primary tumor >5 cm or locally recurrent of any size;
- No distant metastases
- No Previous treatment with eftilagimod alpha, anti-PD-1 or anti-PD-L1
- No Prior radiotherapy to tumor-involved sites

Primary Endpoint :
- The primary efficacy endpoint is a percent tumor hyalinization as a marker of response to treatment assessed at the time of surgical resection.
H0 - 15% (based on historical data for radiotherapy alone from Schaefer M. et al.), H1 – 35%

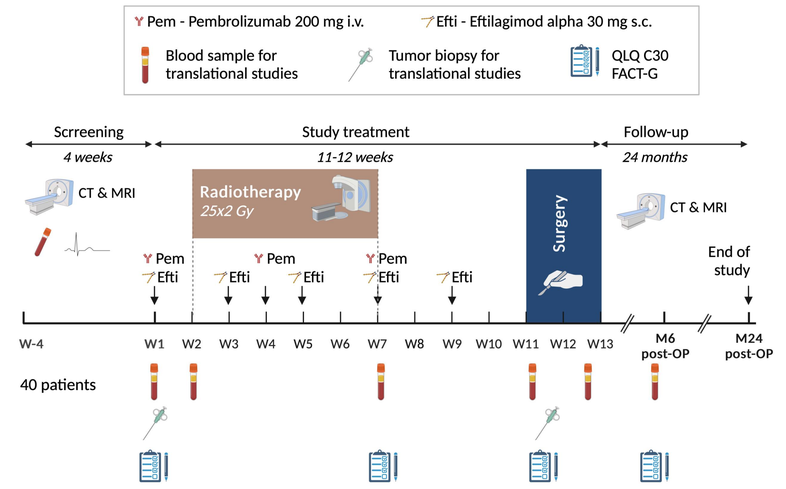

Fig. 2. EFTISARC-NEO trial procedures

Key Secondary Endpoints:
- Incidence of adverse events graded according to CTCAE version 5.0
- Disease-free survival time (DFS), Locoregional disease-free survival (LRFS), Distant metastasis-free survival (DMFS), Overall survival time (OS)
- Radiologic Response To Neoadjuvant Treatment using RECIST 1.1

Data cut-off for preliminary results: October, 20 2024 , after enrollment of 29/40 patients and with 21 patients available for primary endpoint assessment.

RESULTS

As of October 20th, 2024:

42 patients signed the informed consent
→ 11 patients not eligible; 2 patients are in screening

29 patients enrolled and started neoadjuvant immunotherapy
→ 3 patients await surgery; 3 patients continue therapy; 1 patients died*; 1 patient refused surgery

21 patients underwent surgery and are eligible for pathologic response assessment

Total enrolment planned for 40 patients
*due to SAE not related to therapy

Fig. 3. Patients disposition flow diagram

Factor		% (n) n=21
Female sex		42.9% (9)
Age (median; range)		53 (41-73) year
Tumor size (median; range)		8.8 (1.7-17) cm
Recurrent tumor		19.0% (4)
Tumor location	*lower extremity*	76.2% (16)
	upper extremity	14.3% (3)
	trunk	9.5% (2)
Subtype	*myxofibrosarcoma*	47.6% (10)
	myxoid liposarcoma	19.0% (4)
	dedifferentiated liposarcoma	9.5% (2)
	undifferentiated pleomorphic sarcoma	14.3% (3)
	leiomyosarcoma	4.8% (1)
	malignant peripheral nerve sheath tumor	4.8% (1)

Tab. 1 Patients characteristics.

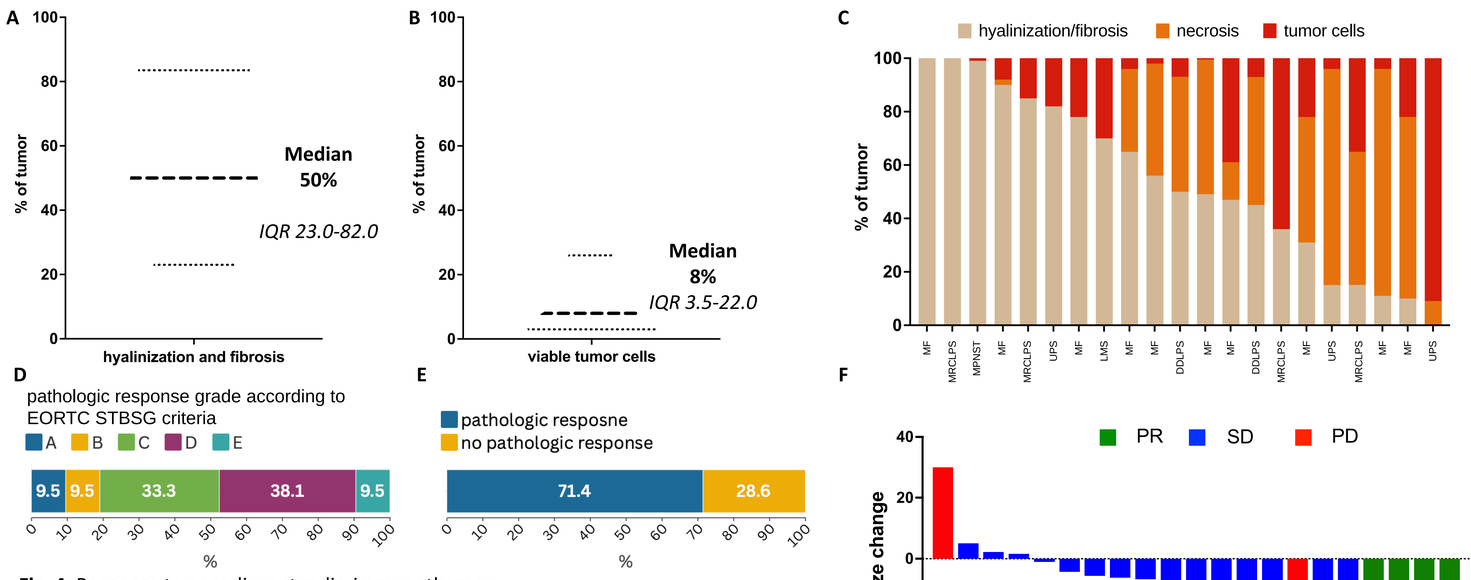

Fig. 4. Response to neoadjuvant radio-immunotherapy.
A – Hyalinization and fibrosis in surgical specimens after treatment.
B – viable tumor cells in surgical specimens after treatments.
C – the proportion of tumor components after treatment in all evaluable patients.
D – response grade according to EORTC STBSG criteria.
E - pathologic response, defined as >35% hyalinization and fibrosis.
F – radiologic response according to RECIST 1.1 criteria.

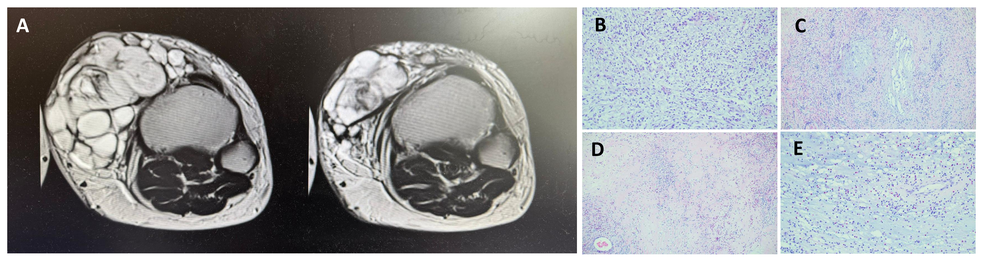

Fig. 5. Example of partial radiologic response per RECIST 1.1 (A) and complete pathologic response (B-E) in a patient with myxofibrosarcoma. B – MF before treatment; C – fibrosis; D – hyalinization; E– cell-free mucous.

CONCLUSIONS

- **Based on the preliminary analysis, combining eftilagimod alpha and pembrolizumab with radiotherapy demonstrates significant efficacy in the neoadjuvant setting in patients with resectable STS.**
  - **Median hyalinization/fibrosis was 50% (compared to historical 15% for radiotherapy alone) and median viable tumor cells was 8%.**
  - **9.5% achieved complete pathologic response, 71.4% achieved pathologic response defined as ≥ 35% of hyalinization/fibrosis and ORR was 19%.**
- **The combination is safe (no grade ≥3 toxicities related to eftilagimod alpha and pembrolizumab) and leads to higher tumor hyalinization than radiotherapy alone compared to historical data.**
- **The EFTISARC-NEO trial is currently ongoing to reach the planned enrolment of 40 patients Q1 2025.**

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DISCLOSURES

Katarzyna Kozak: Speaker honoraria – BMS, MSD, Novartis, Pierre Fabre, Sanofi; advisory board - BMS, MSD; **Paweł Sobczuk:** speaker honoraria – BMS, Swixx Biopharma, Gilead; travel grants – BMS, MSD, Novartis, Pierre Fabre; advisory board – Sandoz; Stocks owner – Celon Pharma; Board member - Polish Society of Clinical Oncology; **Tomasz Świtaj**: Speaker honoraria – BMS, MSD, Novartis, Pierre Fabre, Sanofi; travel grants – BMS, MSD, Novartis, Pierre Fabre; **Paweł Teterycz:** Speaker honoraria – BMS, MSD, Novartis, Pierre Fabre; travel grants – BMS, MSD, Novartis, Pierre Fabre; **Aneta Borkowska and Sylwia Kopeć** declare no conflicts of interests; **Piotr Rutkowski:** Speaker honoraria – BMS, Merck, MSD, Novartis, Pierre Fabre, Sanofi; advisory board - Blueprint Medicines, BMS, Merck, MSD, Philogen, Pierre Fabre, Sanofi; research funding – BMS, Pfizer.

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