PRIMARY ENDPOINT AND TRANSLATIONAL CORRELATES FROM EFTISARC-NEO: PHASE II TRIAL OF NEOADJUVANT EFTILAGIMOD ALFA (EFTI), PEMBROLIZUMAB AND RADIOTHERAPY IN PATIENTS WITH RESECTABLE SOFT TISSUE SARCOMA

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30th Anniversary

2025 ANNUAL MEETING

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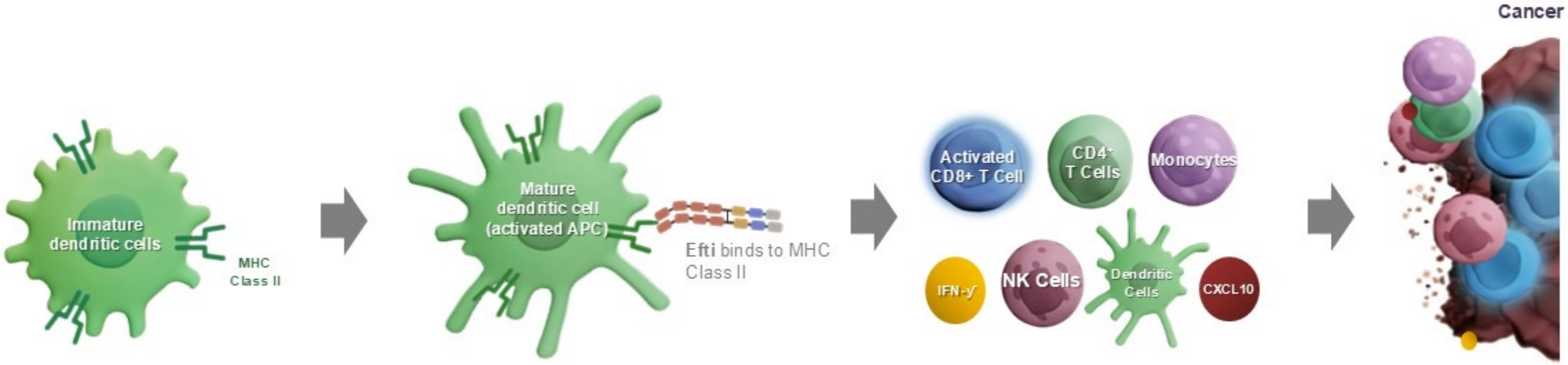
Eftilagimod alfa – mode of action

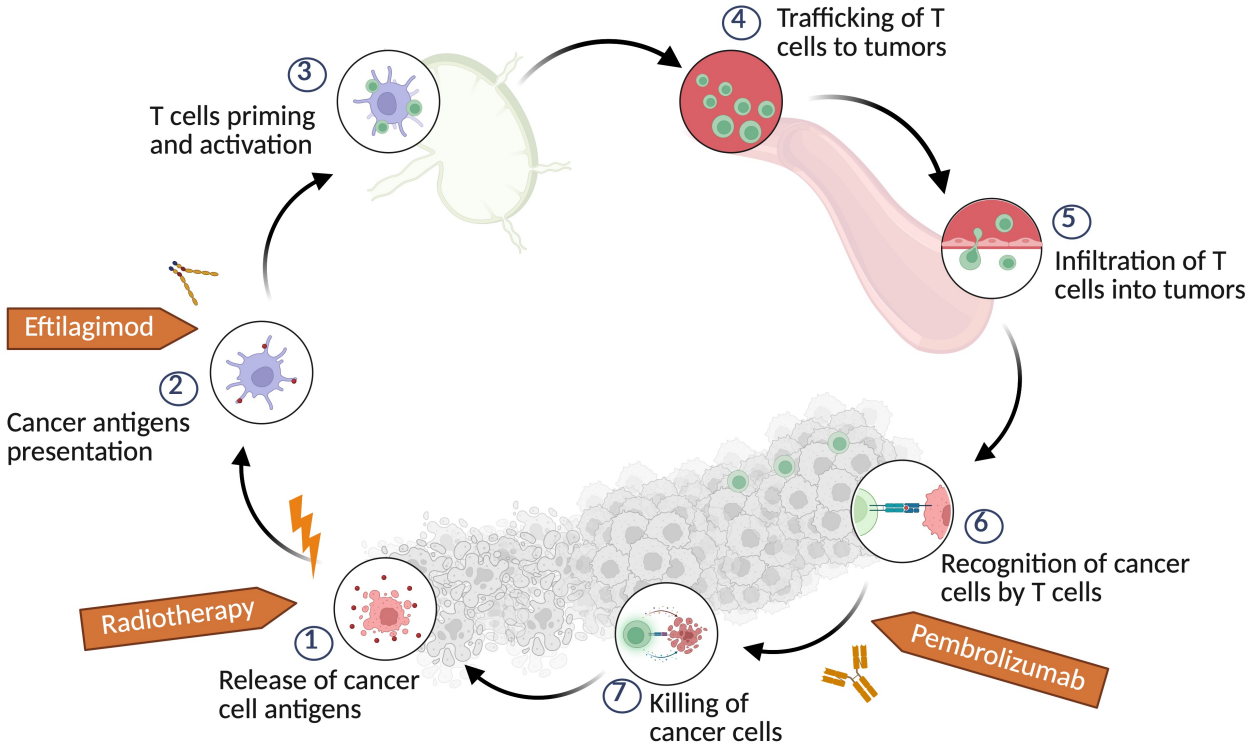
- Eftilagimod alfa (efti) is a dimeric soluble recombinant LAG-3 protein and MHC Class II agonist stimulating antigen-presenting cells (APCs).

- Activating APCs with efti leads to a broad immune response to fight cancer, including increases in activated T cells (CD4/CD8) and other important immune cells/cytokines.



Cancer immunity cycle – rationale for EFTISARC-NEO trial

- We hypothesize that adding combined immunotherapy to radiotherapy prior to surgical resection would be safe and improve pathologic response compared to historical cohorts of patients treated with radiotherapy alone.
- The percentage of hyalinization and fibrosis, as a surrogate of pathological response, appears to be most closely correlated with treatment outcome.



Study design

Key eligibility criteria

- ≥ 18 years of age
- ECOG PS 0 or 1
- Primary or locally recurrent, deep-seated tumor of extremities, girdles and/or superficial tumor of the trunk
- Histologic diagnosis of STS except for Ewing Sarcoma, alveolar/embryonal RMS
- Grade 2 or 3 tumors according FNCLCC
- Primary tumor >5 cm or locally recurrent of any size;
- No distant metastases
- No previous treatment with efti, anti-PD-1/PD-L1

Primary endpoint

- The percentage of tumor hyalinization and fibrosis assessed at the time of surgical resection

Secondary endpoints

- Safety
- Disease-free survival time (DFS), Locoregional disease-free survival (LRFS), Distant metastasis-free survival (DMFS), Overall survival time (OS)
- Radiologic response rate
- Quality of life

Exploratory endpoints

- Biologic correlates from tumor tissue and peripheral blood

Study treatment

Eftilagimod alfa
30 mg sc Q2W
x 5 doses

+

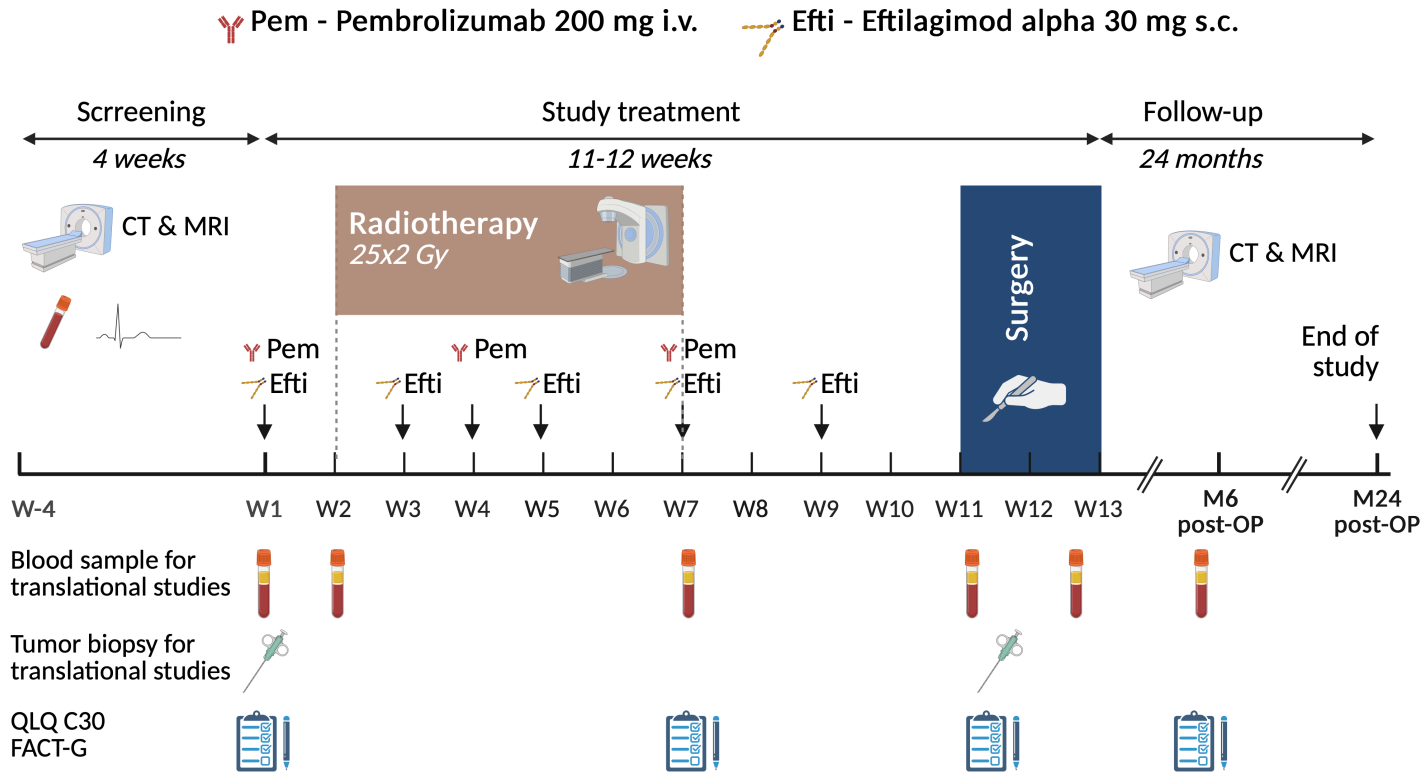
Pembrolizumab
200 mg iv Q3W
x 3 cycles

+

Radiation therapy
25 x 2 Gy

→

Surgery
(within
5-6 weeks after
radiation therapy)



Statistical design

- Historical data from retrospective analyses indicate that the median percentage of fibrosis and hyalinization following preoperative radiotherapy is approximately **15% (H0)** *(Schaefer M. et al. Int J Radiat Oncol Biol Phys 2017)*
- With the addition of pembrolizumab and efti, we expect to increase this median to **35% (H1)**

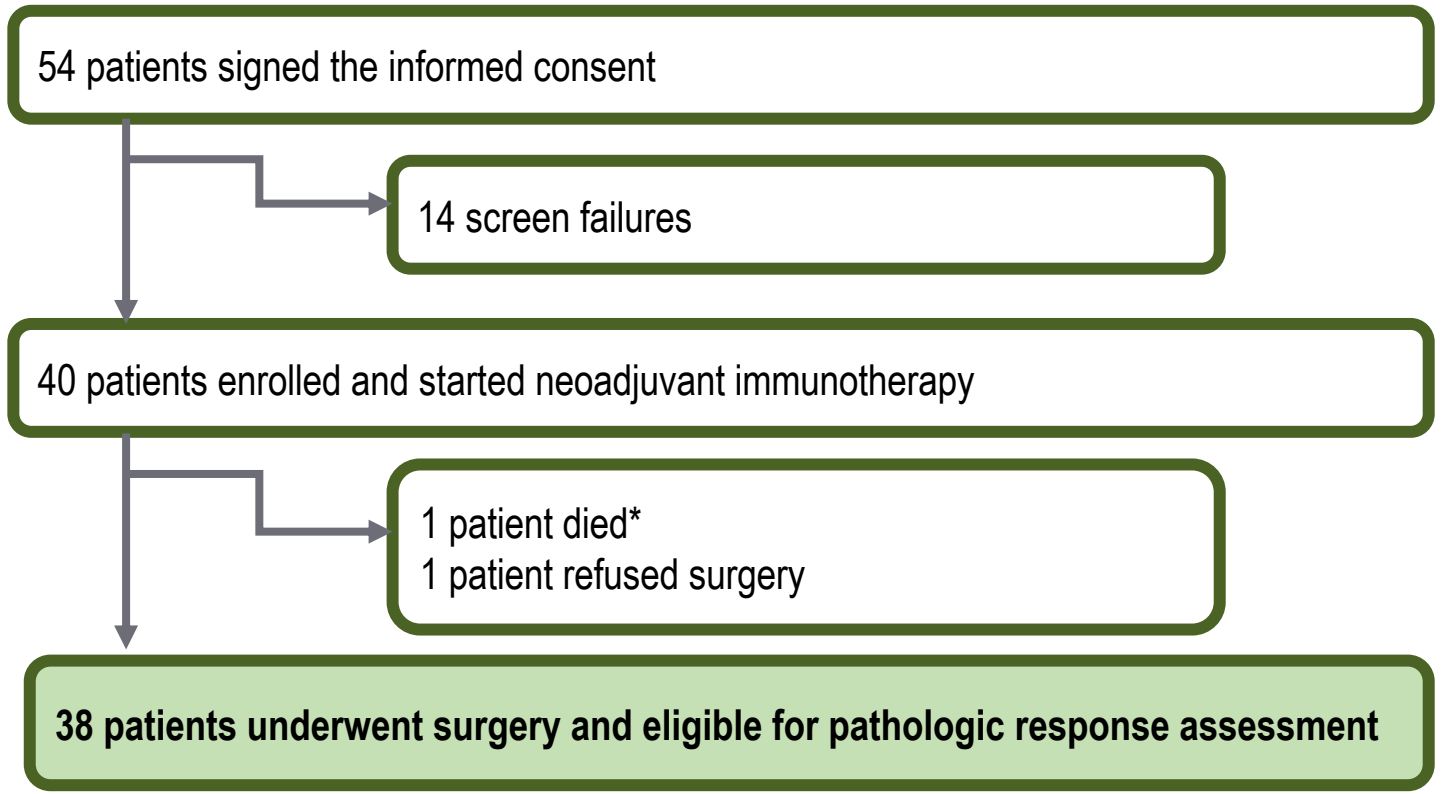
- The sample size calculations are based on the Wilcoxon signed-rank test.

- Empirical power estimates were derived using Monte Carlo simulations, assuming a two-sided test with $\alpha = 0.05$ and a target power of 90%.

- With **planned enrollment of 40 patients**, the simulations indicate an **empirical power of 91%** to detect the improvement from 15% to 35%
  - if 36 patients complete the treatment (10% failure rate) – an **empirical power of 88%**

Patients disposition

From July 2023 to January 2025, a total of 40 patients were enrolled in the study



*due to SAE not related to therapy

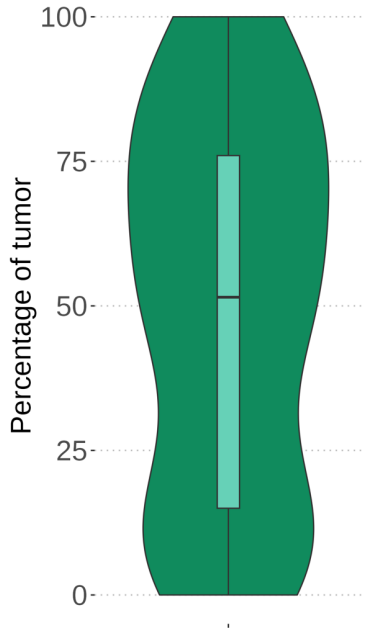
Baseline Patient Characteristics

Characteristics		Patients, n=40
Median age, years (range)		54.5 (34-77)
Female, n (%)		16 (40.0)
Median tumor size, cm (IQR)		8.8 (6.7-10.9)
Recurrent tumor, n (%)		11 (27.5)
Tumor location, n (%)	Lower extremity Upper extremity Trunk	28 (70.0) 10 (25.0) 2 (5.0)
Grade, n (%)	2 3	24 (60.0) 16 (40.0)
Subtype, n (%)	Myxofibrosarcoma Undifferentiated pleomorphic sarcoma Myxoid liposarcoma Dedifferentiated liposarcoma Malignant peripheral nerve sheath tumor Other*	16 (40.0) 10 (25.0) 5 (12.5) 2 (5.0) 2 (5.0) 5 (12.5)

** 1 each: sarcoma not otherwise specified, synovial sarcoma, myxoid leiomyosarcoma, epithelioid sarcoma with TMEM123-YAP1 fusion, myxoinflammatory fibroblastic sarcoma*

Primary endpoint – pathologic response

Hyalinization and fibrosis



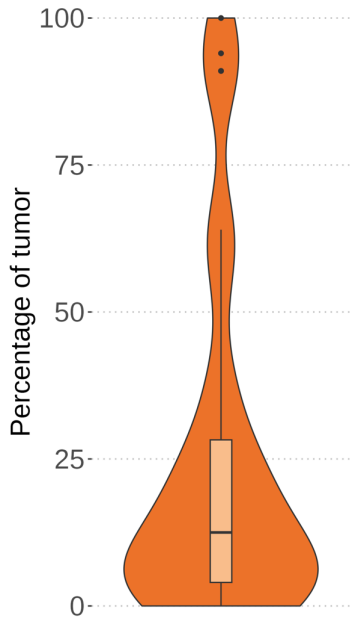
Median 51.5%

IQR 15.0-76.0

p<0.001*

*compared to historical data and using statistical assumptions

Viable tumor cells



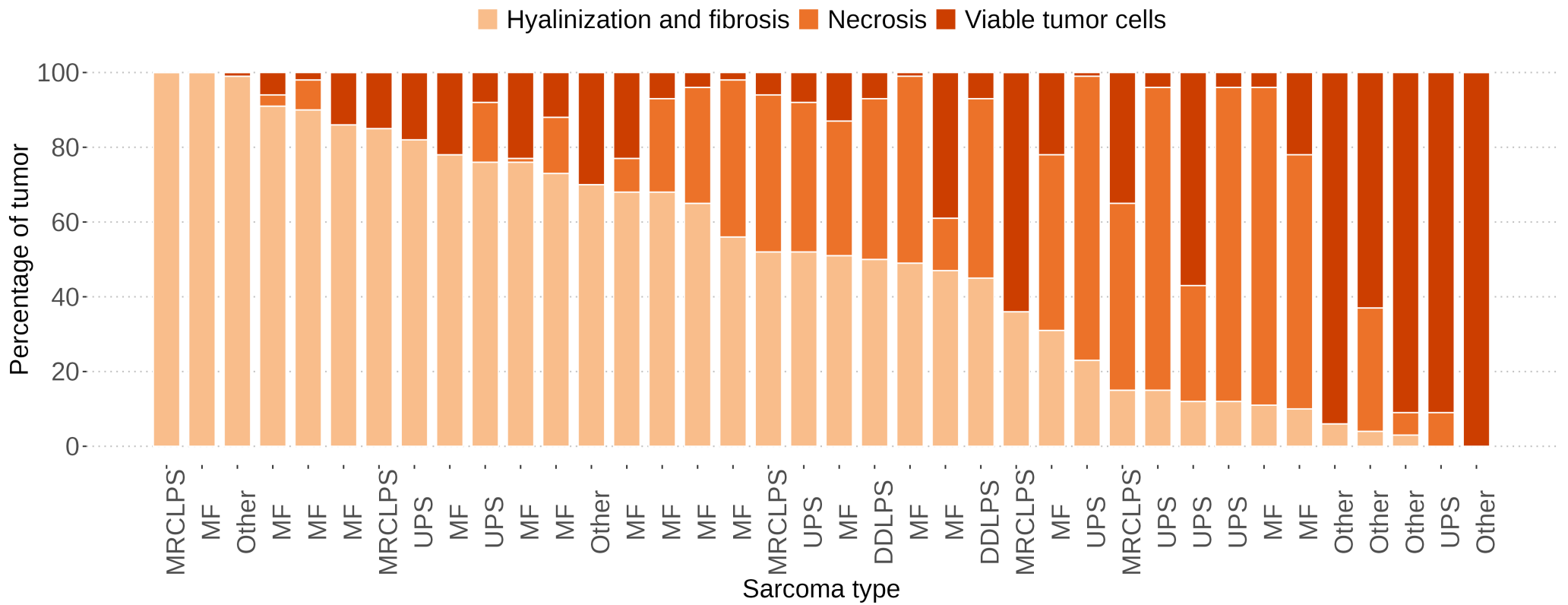
Median 12.5%

IQR 4.5-30.0

Data cut-off: May 10, 2025

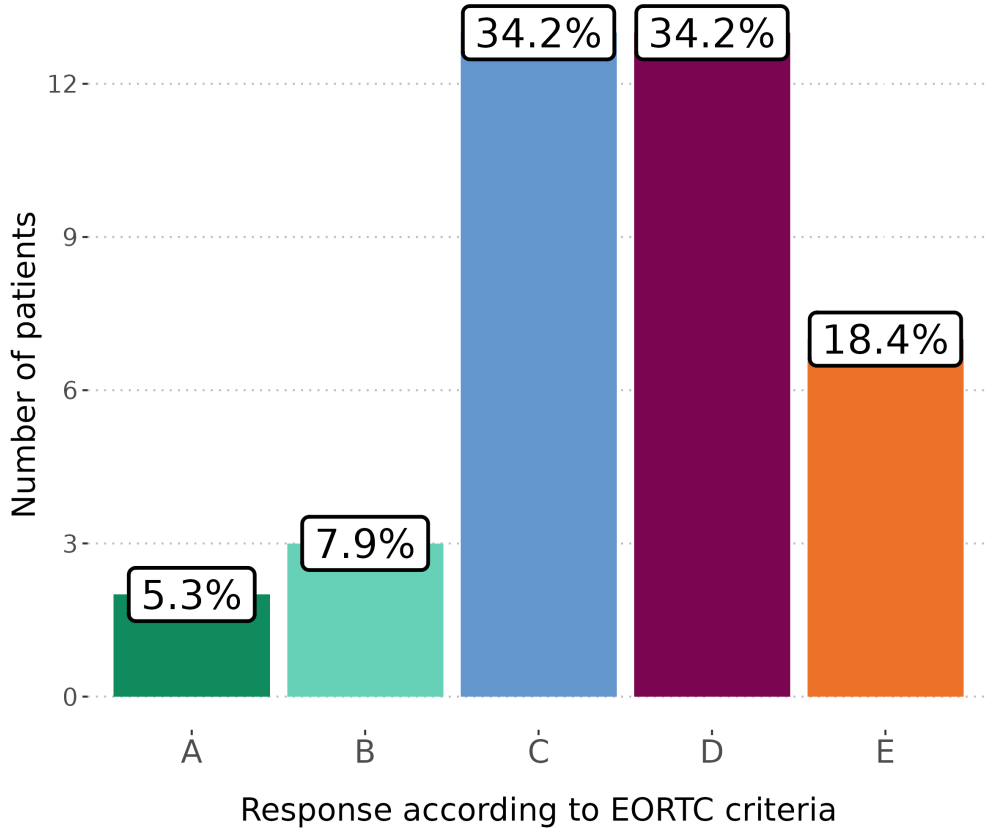
Study treatment increased percentage of tumor hyalinization and fibrosis, meeting the primary endpoint

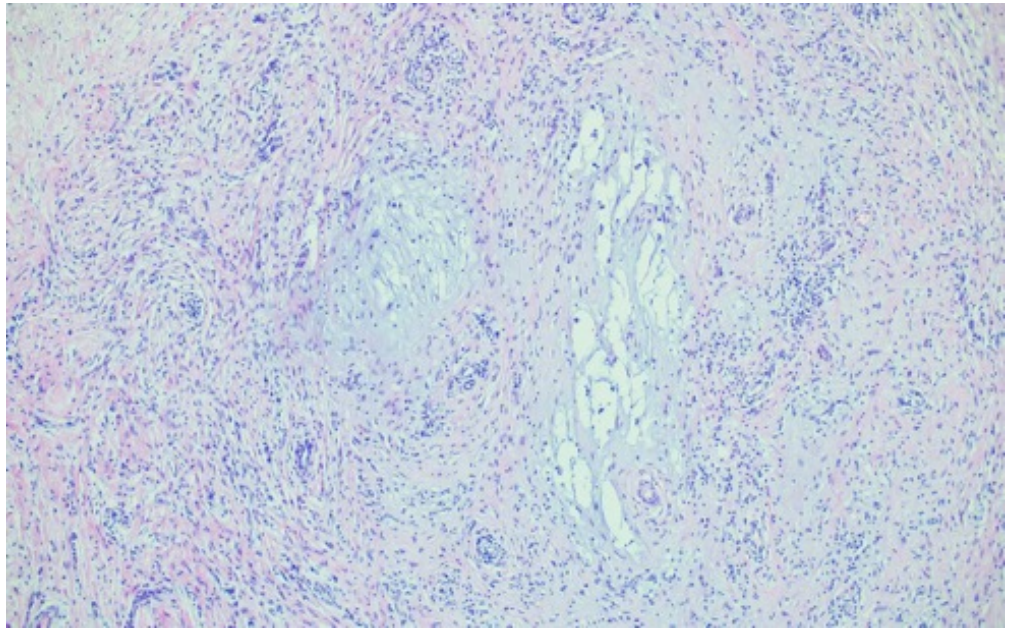
Primary endpoint – pathologic response



Study treatment increased percentage of tumor hyalinization and fibrosis across sarcoma subtypes

Pathologic response according to EORTC STBSG criteria





Example of fibrosis in a patient with myxofibrosarcoma and complete pathologic response

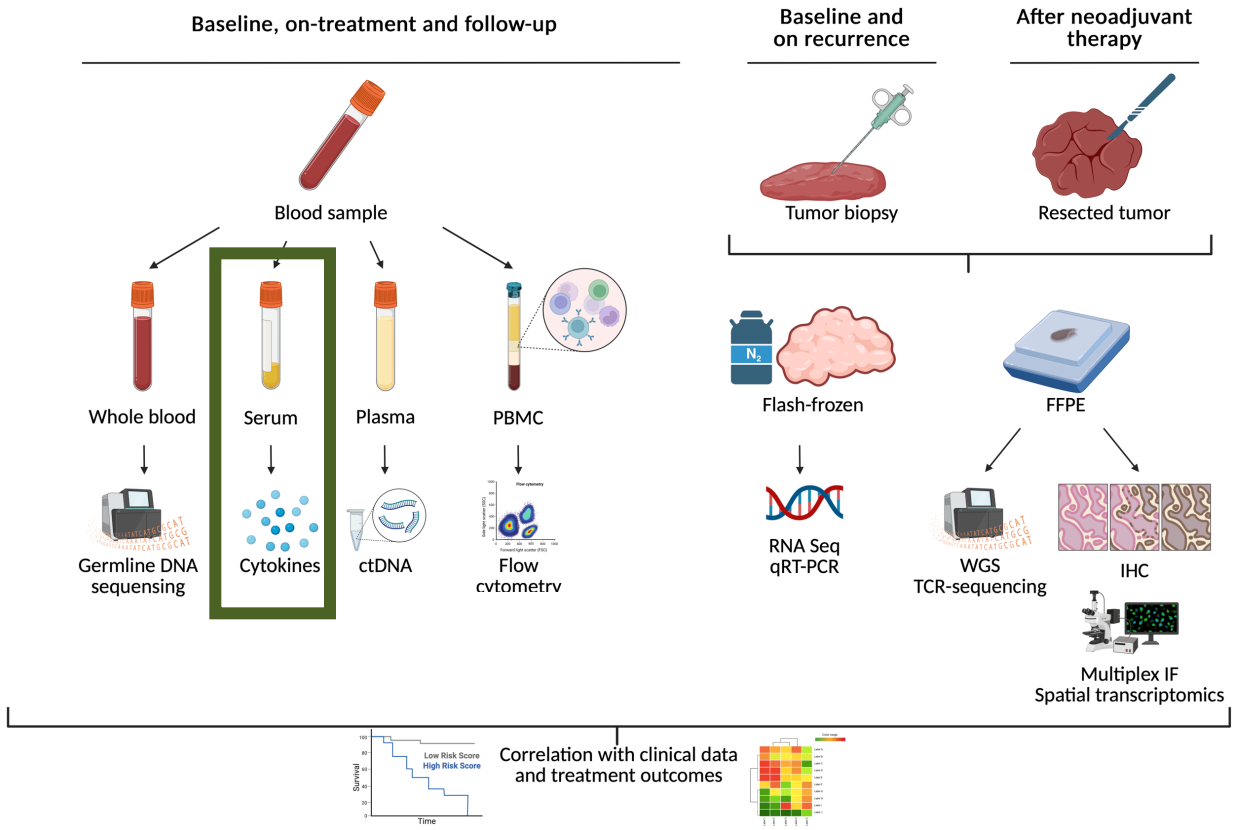
Radiologic response to neoadjuvant treatment

* One patient developed metastatic disease during neoadjuvant therapy

Response by RECIST 1.1 before surgery	% (n), n=38
Partial Response	13.2 (5)
Stable Disease	78.9 (30)
Progressive Disease	7.9 (3)
ORR	13.2 (5)
DCR	92.1 (35)

DCR – disease control rate
ORR – objective response rate

Translational studies

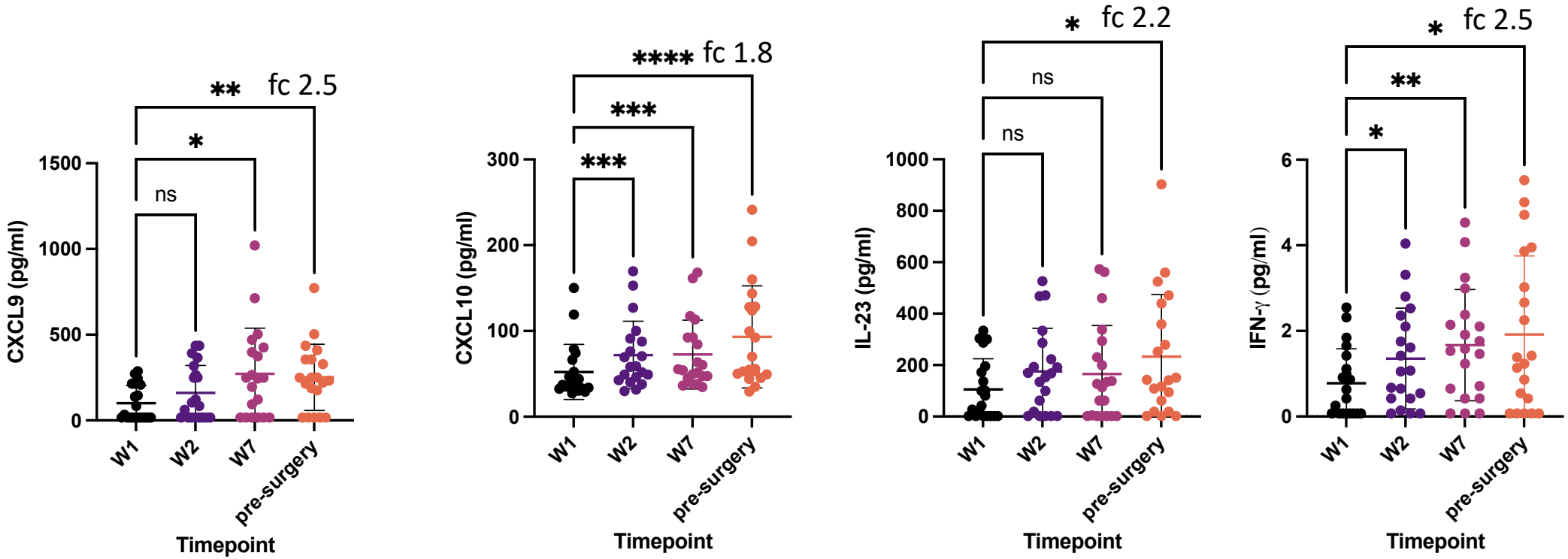


Preliminary translational results

- The first 20 patients who underwent surgery
- Cytokine profiling from serum using a multiplex Luminex assay
- Baseline, W2 (before RTH), W7 (after completion of RTH), and pre-surgery

Translational studies

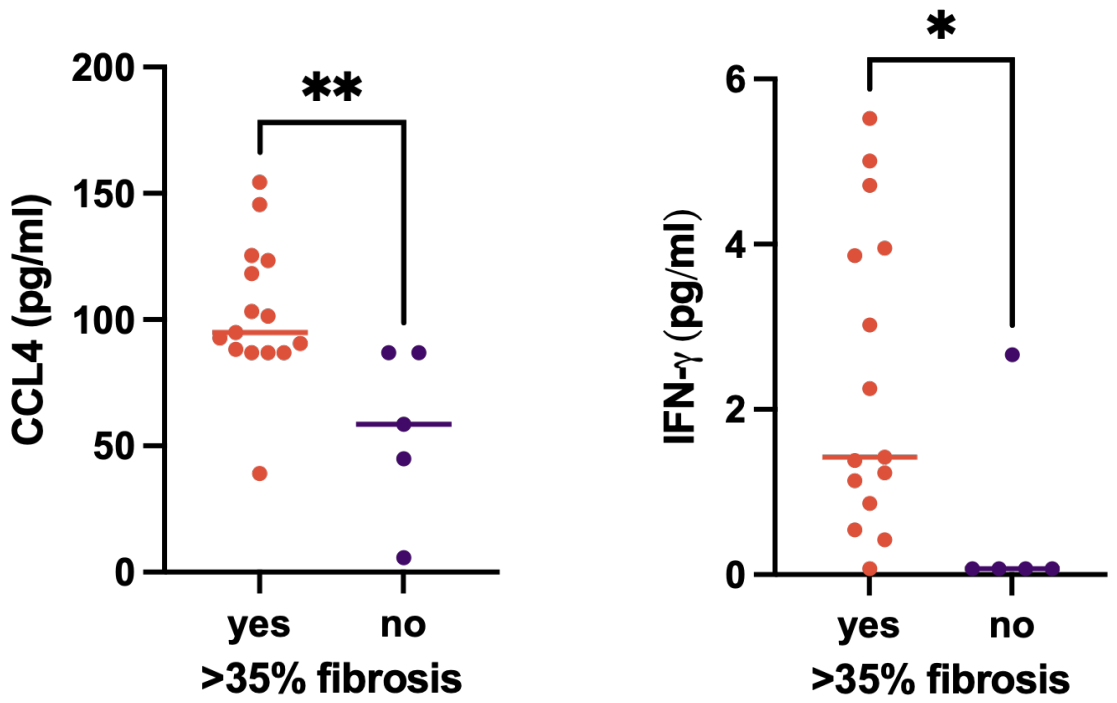
Study treatment increased the expression of serum CXCL9, CXCL10, IL-23 and IFN-γ



*one-way repeated measures ANOVA; *p<0.05, **p<0.01, *** p<0.001; ****p<0.0001*

Translational studies

Pre-surgery level of CCL4 and IFN-γ correlates with pathologic response defined as hyalinization and fibrosis >35%



Conclusions

- **The trial has met the primary endpoint, reporting high pathologic responses when combining eftilagimod alpha and pembrolizumab with radiotherapy in patients with resectable soft tissue sarcoma.**
- The study proved surgical feasibility with no delays of planned surgeries.
- Early translational data suggest a pro-inflammatory response in the peripheral blood.
- Patients with good pathologic response have higher pre-surgery level of CCL4 and IFN-γ.
- Disease-free survival and overall survival data are immature and will be presented in the future. Further correlative translational studies are ongoing.
- The combination warrants further investigation in registrational settings.

Acknowledgments

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- Immutep has provided eftilagimod alpha.

Maria Sklodowska-Curie
National Research Institute of Oncology

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