European Society for Medical Oncology (ESMO) Congress 2025

Proffered Paper Oral Presentation

EFTISARC-NEO: A phase II study of neoadjuvant eftilagimod alpha, pembrolizumab and radiotherapy in patients with resectable soft tissue sarcoma

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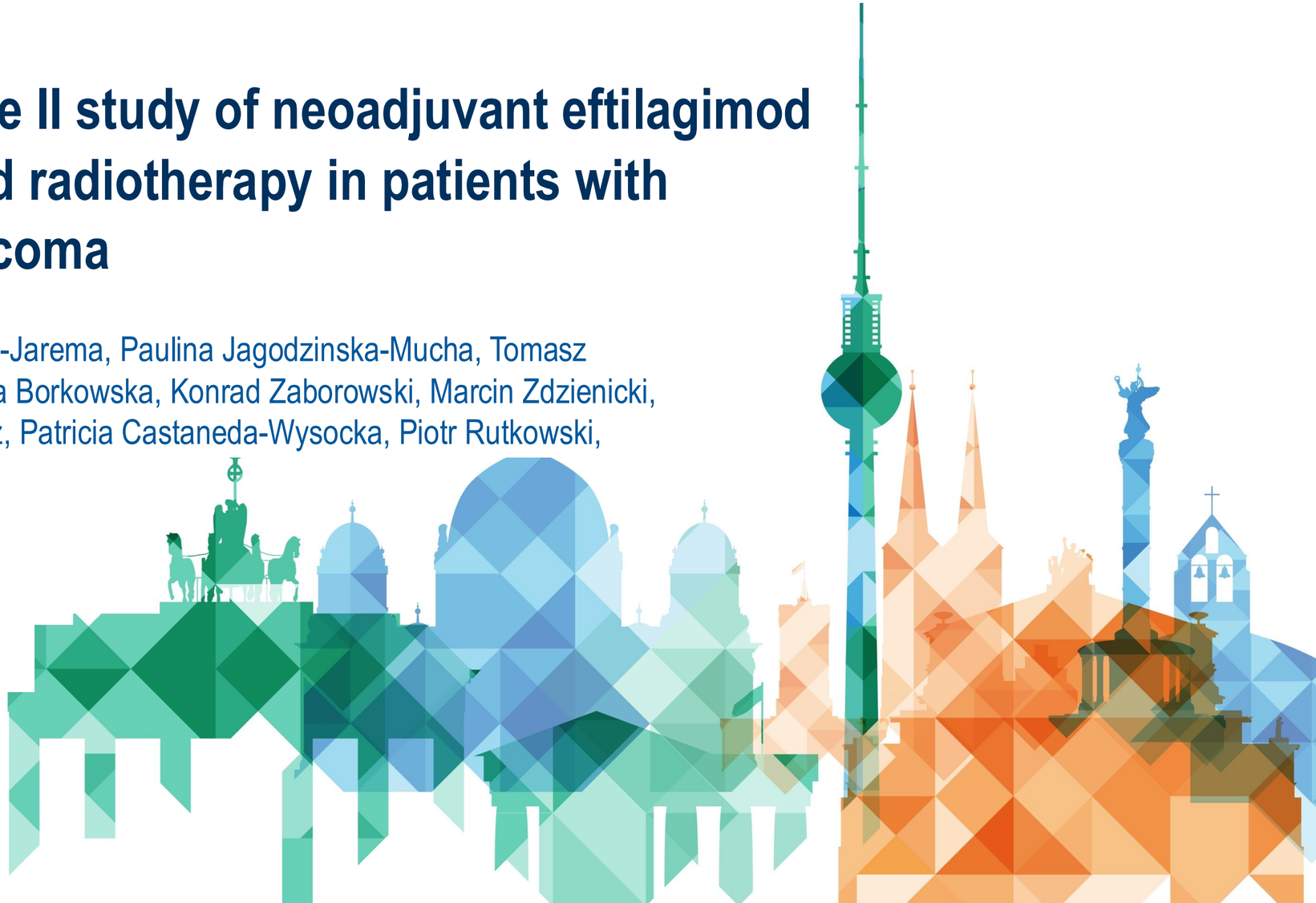

Declaration of interests

- Consultancy, speaker fees/honoraria —Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, Genesis
- The study is funded by the Polish Medical Research Agency
- Immutep has provided eftilagimod alpha

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Background

- Surgery is the mainstay of treatment of primary localized soft tissue sarcoma (STS), while for patients with high-grade localized STS of the extremity/trunk, radiation therapy (RT) is added to reduce local recurrence

- Immunotherapy alone has limited activity in patients diagnosed with metastatic soft tissue sarcoma (ORR 18%, Tawbi et al. *Lancet Oncology* 2017)

- The efficacy of immunotherapy appears to be enhanced when it is administered at the earlier stages of the disease and combined with radiation therapy (Roland et al. *Nature Cancer* 2024, Movery et al. *Lancet* 2024)

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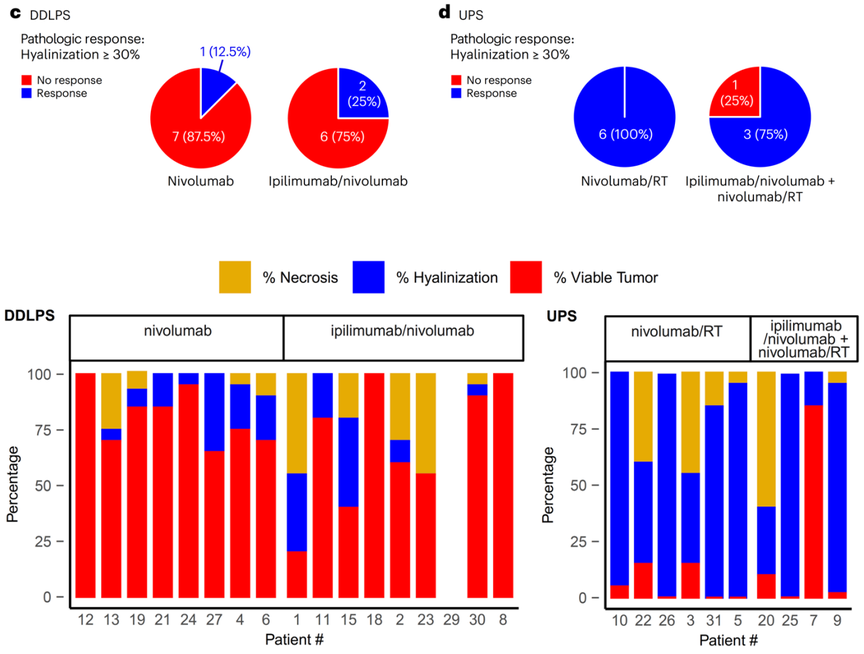
Immunotherapy for resectable soft tissue sarcoma

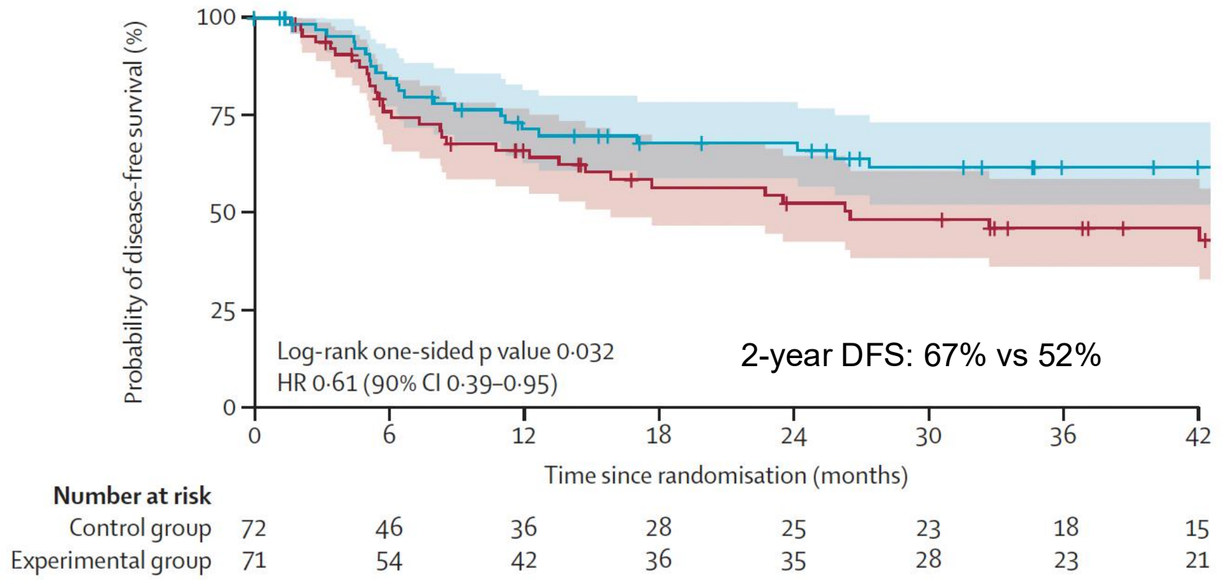
Article https://doi.org/10.1038/s43018-024-00726-z

A randomized, non-comparative phase 2 study of neoadjuvant immune-checkpoint blockade in retroperitoneal dedifferentiated liposarcoma and extremity/truncal undifferentiated pleomorphic sarcoma



Roland et al. Nature Cancer 2024

Safety and efficacy of pembrolizumab, radiation therapy, and surgery versus radiation therapy and surgery for stage III soft tissue sarcoma of the extremity (SU2C-SARC032): an open-label, randomised clinical trial



Movery et al. Lancet 2024

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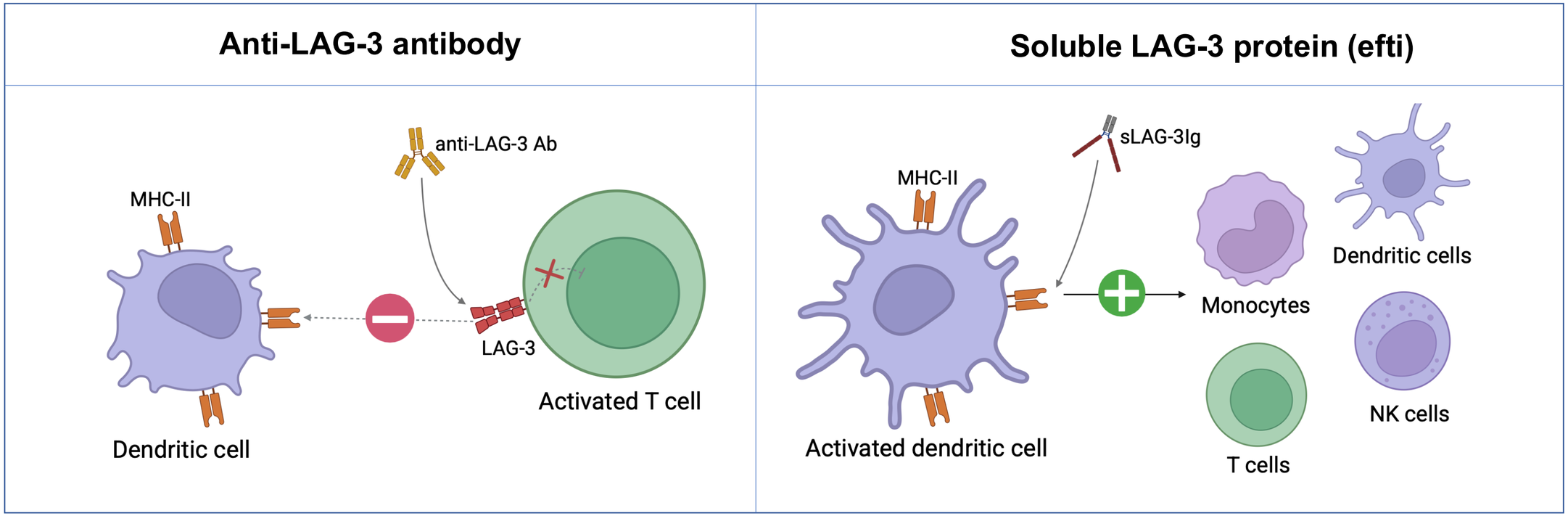
Eftilagimod alpha – mode of action

- 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 signaling between T cells and APCs, which are responsible for the adaptive immune response.



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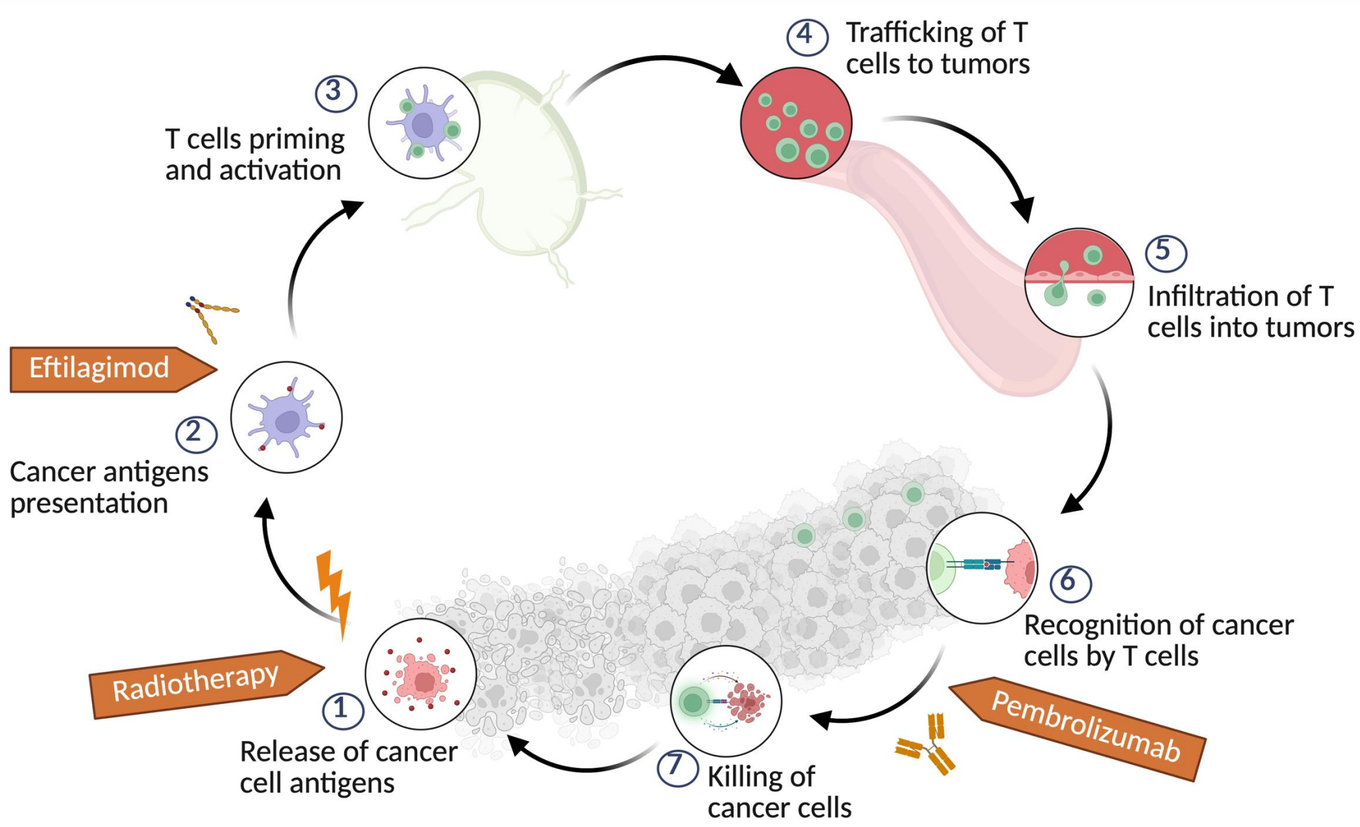
Cancer immunity cycle – rationale for EFTISARC-NEO trial

- We hypothesize that adding combined immunotherapy (ITH) to RT prior to surgical resection would be safe and improve pathologic response compared to historical cohorts of patients 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.



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Study design

Key eligibility criteria

- ≥ 18 years of age
- ECOG PS 0 or 1
- Primary or locally recurrent deep-seated extremities, girdles and/or superficial trunk tumor
- 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

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Study treatment

Eftilagimod alpha
30 mg sc Q2W
x 5 doses

+

Pembrolizumab
200 mg iv Q3W
x 3 cycles

+

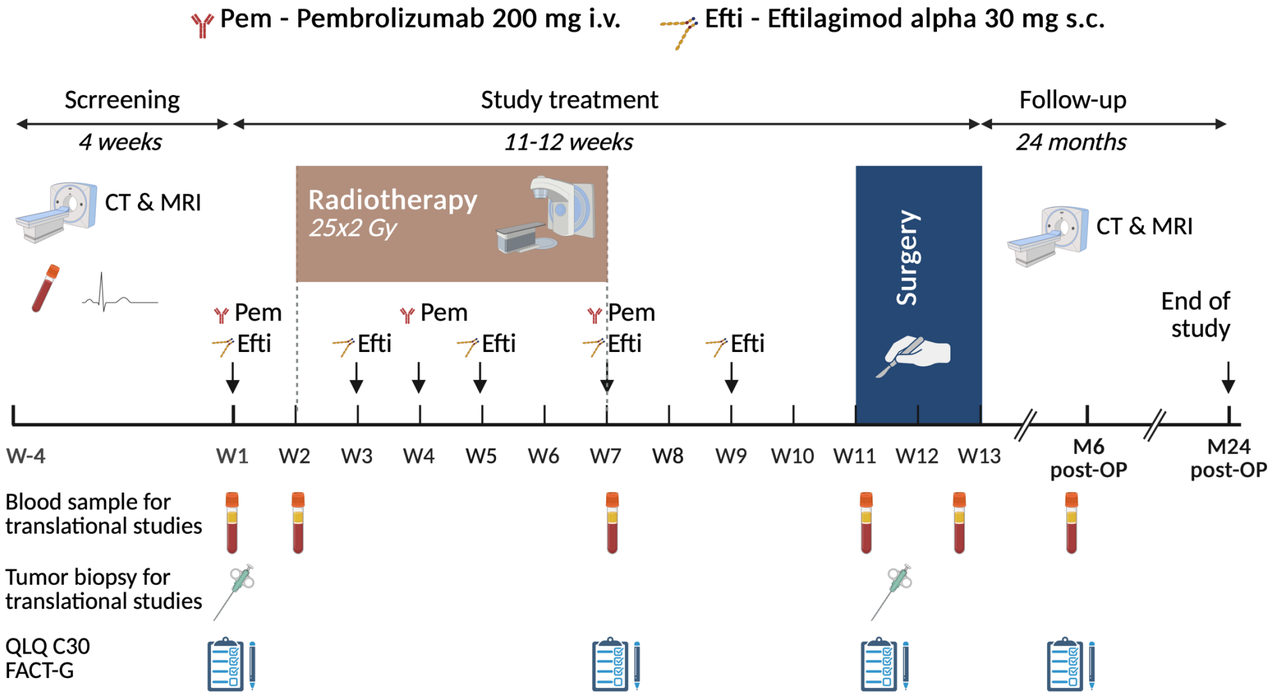
Radiation therapy
25 x 2 Gy

→

Surgery
(within
5-6 weeks
after
radiation
therapy)

→

Follow-up



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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 all patients complete the treatment
  - An empirical power of 88% to detect the improvement from 15% to 35% if 36 patients complete the treatment (10% failure rate)

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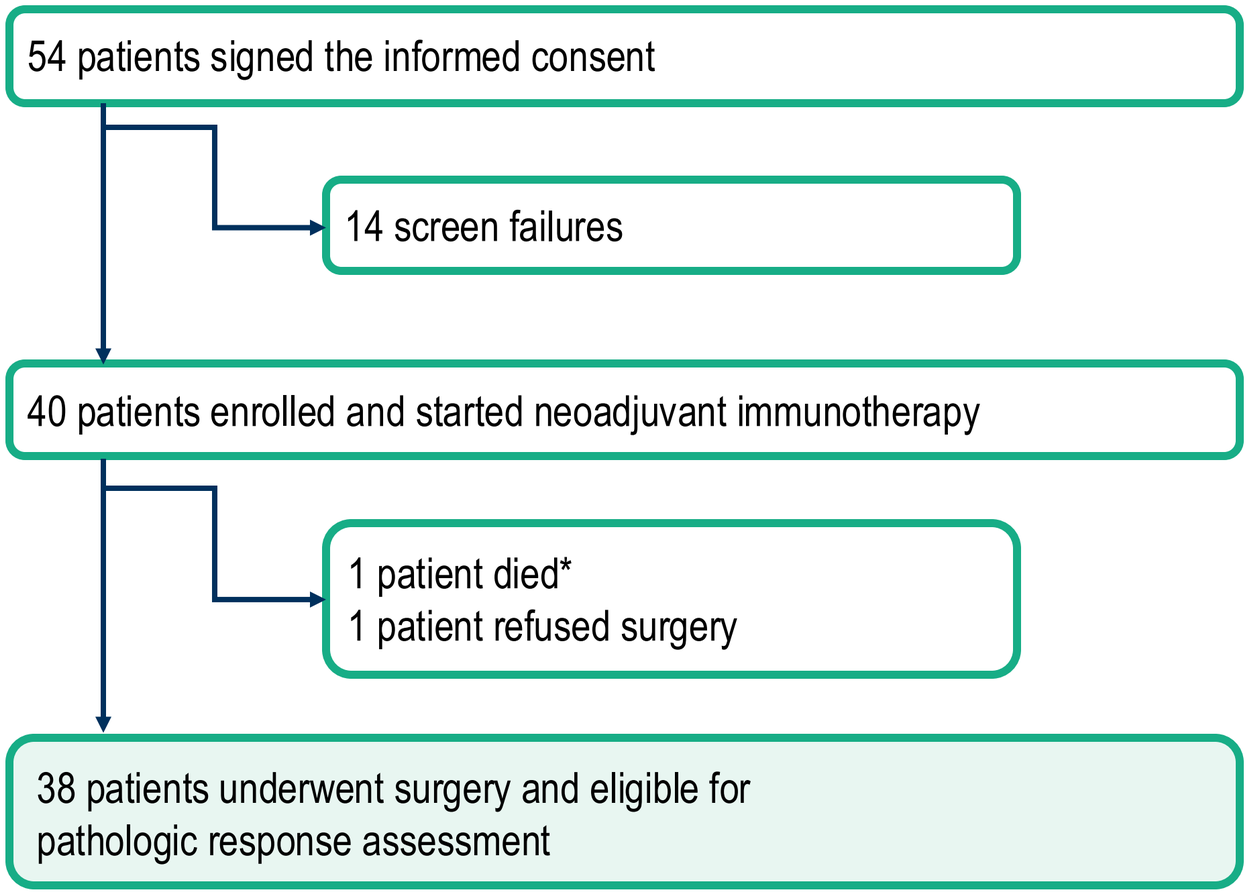
Patients disposition flow diagram

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



*due to SAE not related to therapy

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Baseline Patient Characteristics

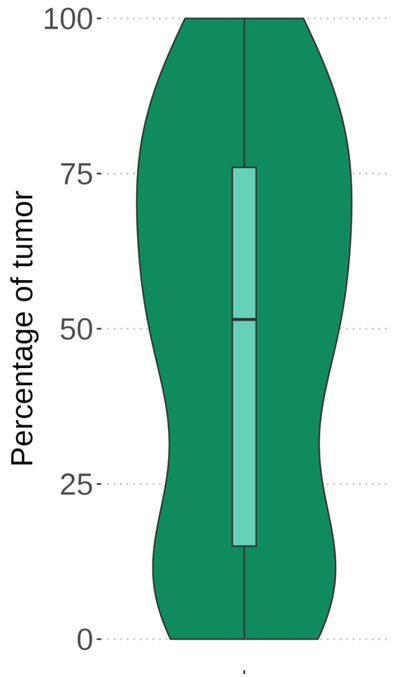
Characteristics		Patients, n=40
Median age, years (range)		54.5 (34-77)
Female, n (%)		16 (40.0)
Median tumor size, cm (IQR)		8.8 (6.7-10.9)
Recurrent tumor, n (%)		11 (27.5)
Tumor location, n (%)	Lower extremity	28 (70.0)
	Upper extremity	10 (25.0)
	Trunk	2 (5.0)
Grade, n (%)	2	24 (60.0)
	3	16 (40.0)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

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

Hyalinization and fibrosis



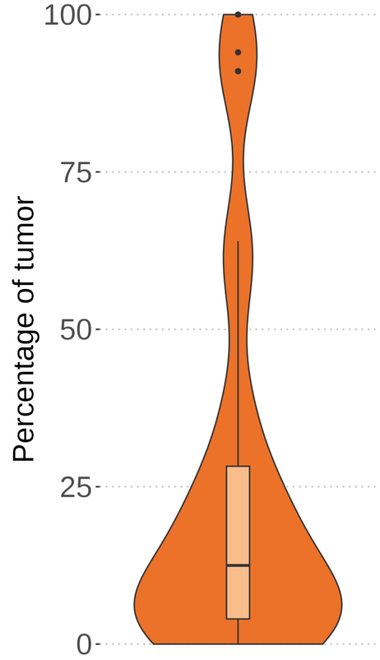
Median 51.5%

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

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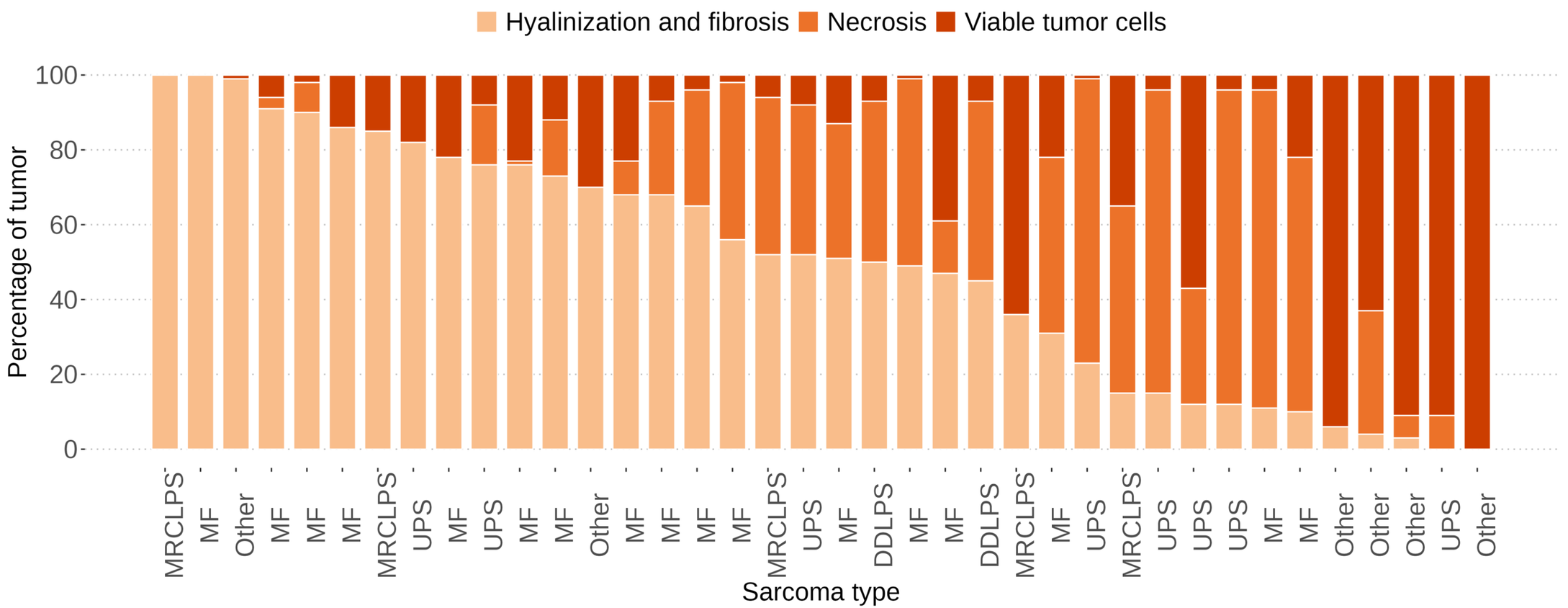
Primary endpoint – pathologic response

Study treatment increased percentage of tumor hyalinization and fibrosis



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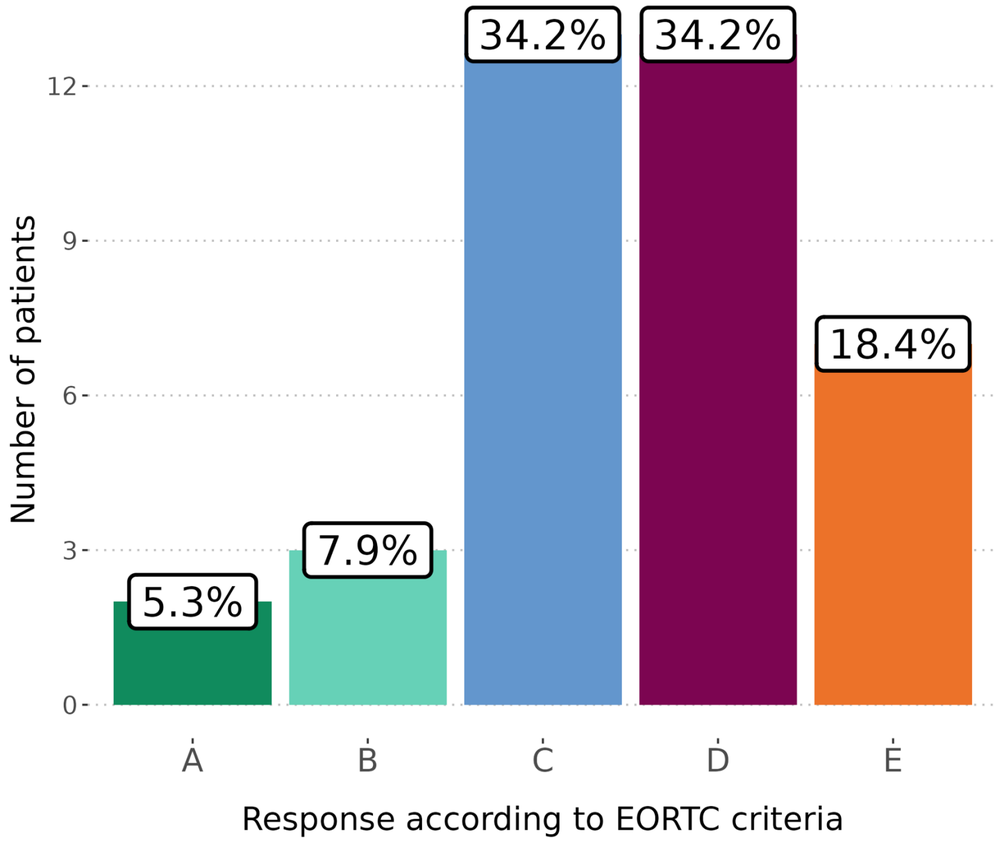
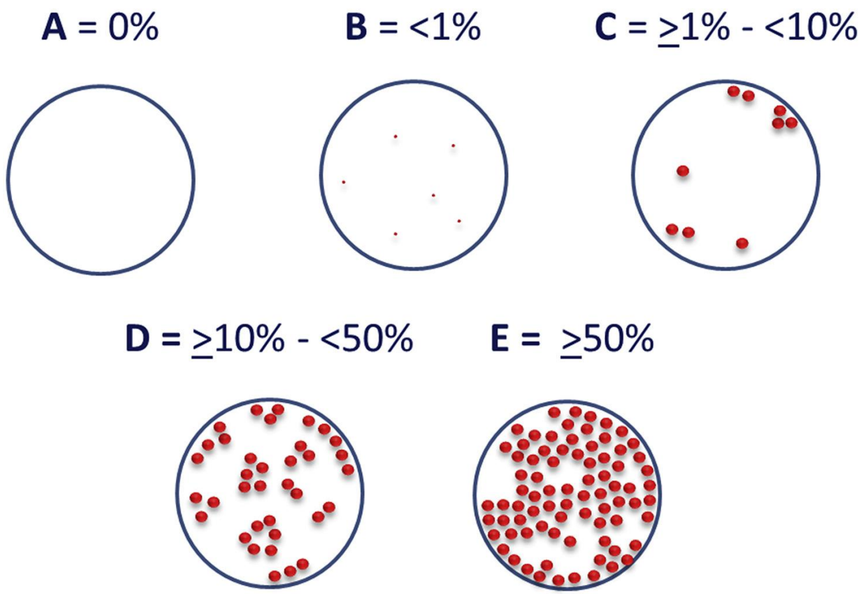
Pathologic response according to EORTC STBSG criteria

47% of patients had <10% of viable cells in surgical specimen

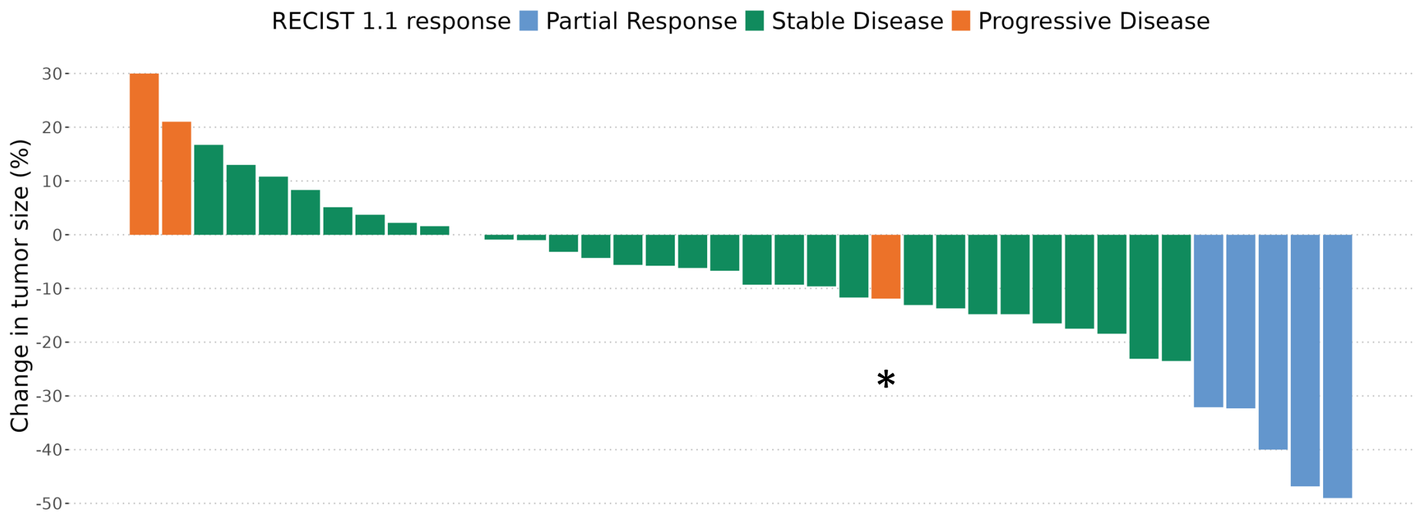




Wardelmann E. et al, EJC 2016

Radiologic response to neoadjuvant treatment

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)



* One patient developed metastatic disease during neoadjuvant therapy

DCR – disease control rate, ORR – objective response rate

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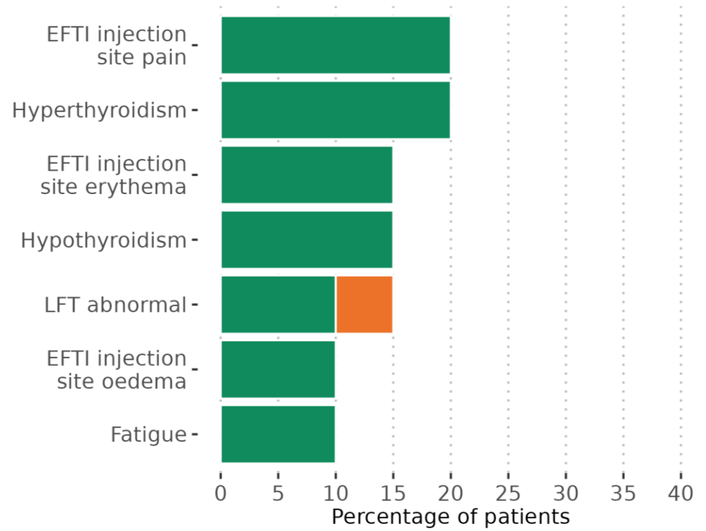
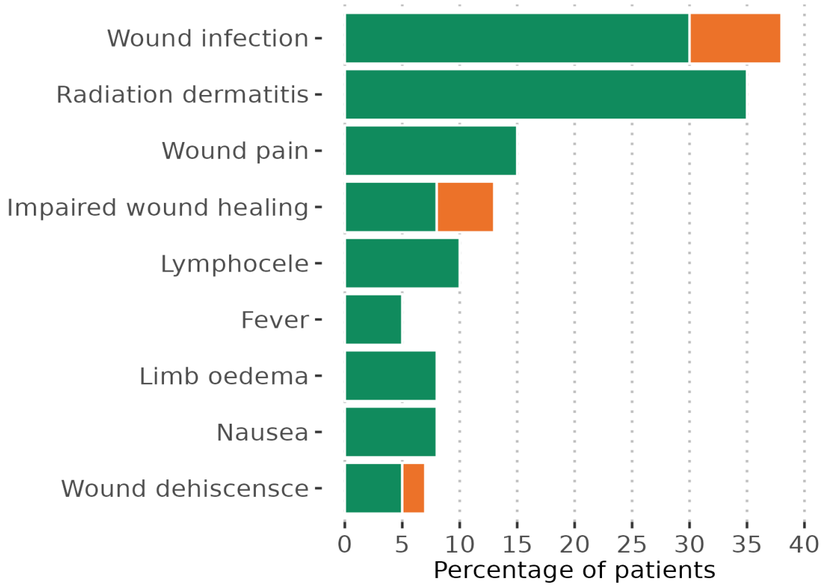
Safety overview

All patients proceeded to intended surgery without delay

Safety parameter	% (n), n=40
TRAEs	92.5 (37)
TRAEs ≥G3	20 (8)
TRAEs leading to treatment discontinuation	5 (2)
AEs related to pembro	72.5 (29)
AEs related to efti	75 (30)
AEs related to RTH	52.5 (21)
AEs related to surgery	87.5 (35)



Most common AEs related to immunotherapy



Most common AEs related to local therapy

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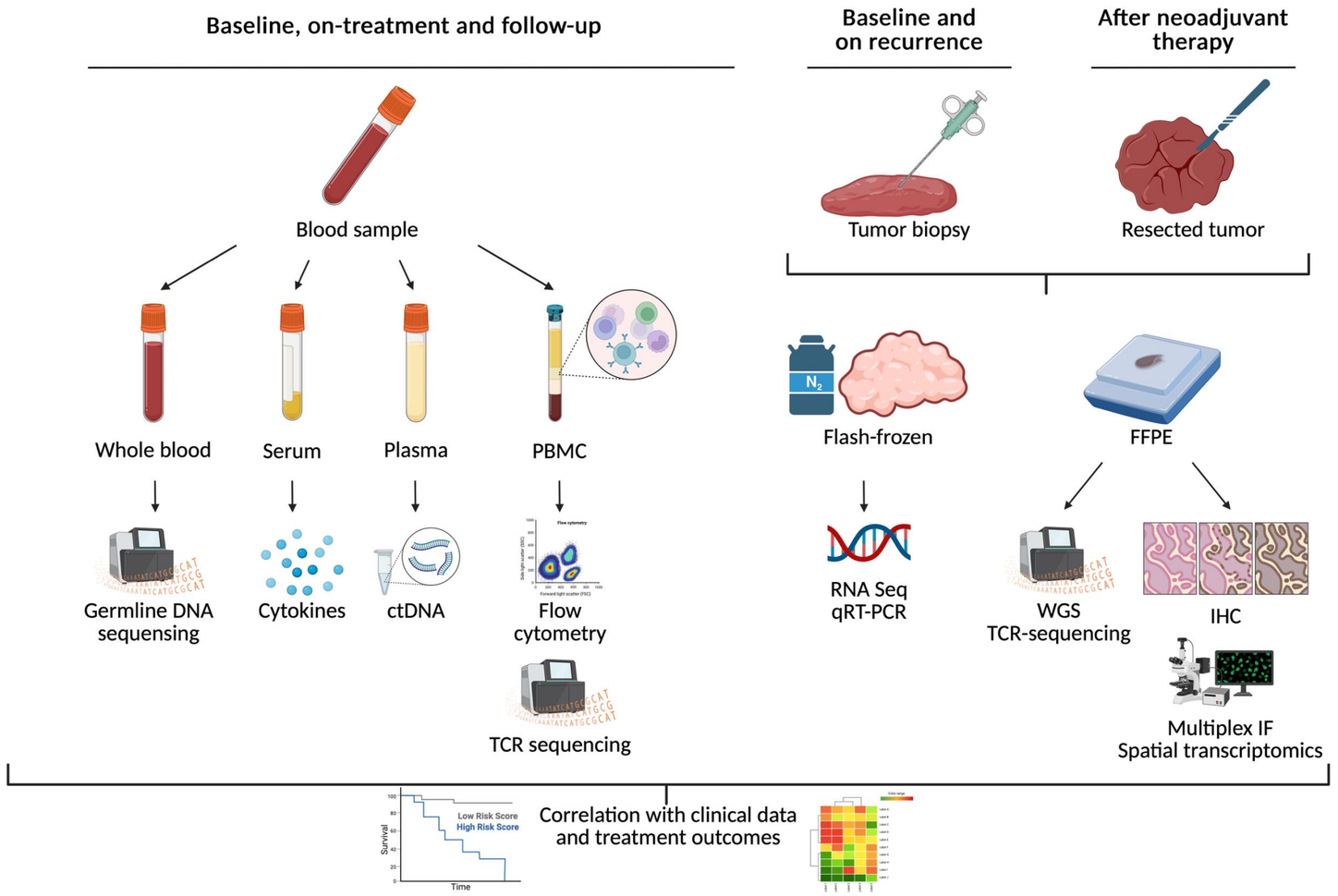
Translational studies



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Conclusions

- **The trial has met the primary endpoint, confirming the efficacy and safety of combining eftilagimod alpha and pembrolizumab with radiotherapy.**

- Study treatment provides promising pathological responses - median fibrosis 51.5%, median viable tumor cells 12.5%.
- Study proved a manageable safety profile - one grade ≥3 toxicity related to immunotherapy.
- The study proved surgical feasibility with no delays of planned surgeries.
- Disease-free survival and overall survival data are immature and will be presented in the future.
- The combination warrants further investigation in registrational settings.

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Acknowledgments

- The patients and their caregivers
- The study investigators and site staff from the Department of Soft Tissue/Bone Sarcoma and Melanoma, and the Early Phase Clinical Trials Unit

Maria Sklodowska-Curie National Research Institute of Oncology

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MEDICAL RESEARCH AGENCY

- Immutep has provided eftilagimod alpha

immutep
Empowering the Immune System

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Thank You

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