Maria Sklodowska-Curie
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Pembrolizumab in combination with eftilagimod alpha and radiotherapy in neoadjuvant treatment of patients with soft tissue sarcomas - EFTISARC-NEO trial

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BACKGROUND

- Surgery is the mainstay of treatment of primary localized soft tissue sarcoma (STS). However, despite optimal surgical resection, disease recurrence is common.
- In patients (pts) with high-grade localised STS of the extremity/trunk, and tumor size > 5cm, radiation therapy (RT) is added to reduce local recurrence. Adjuvant/neoadjuvant AI ChT may be used to improve survival, but its efficacy is limited to pts with poor prognosis
- Recently, immunotherapy (ITH) has been widely studied in pts with metastatic STS, however response rates are modest - its efficacy and impact on tumor microenvironment remain unclear
- Combining ITH with RTH may be a promising strategy for synergistic enhancement of treatment efficacy and the use of such a combination in the preoperative setting provides a unique opportunity to derive biological information related to tumor response.
- As anti-PD1 therapy is not sufficiently effective in many cancers, novel compounds such as eftilagimod alpha (efti) are being tested in combination with ITH to stimulate antigen-presenting cells and boost the immune response.
- Efti is a dimeric soluble recombinant LAG-3 protein. In contrast to antagonist anti-LAG-3 antibodies, Efti is an agonist stimulating antigen-presenting cells (APCs) via MHC II. The LAG-3 - MHC II interaction controls the signalling between T cells and APCs, which are responsible for the adaptive immune response (Fig. 1, 2)
- Anti-PD-1, such as pembrolizumab, addresses part of the immune escape mechanism i.e., the tumor-induced T cell downregulation. On the other hand, the capacity of immune cells to recognize tumor cells and prime an effector response can be increased by APC activators providing support for the combination of these two drug classes (Fig. 3)

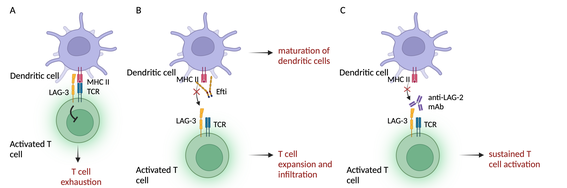

Fig. 1. Role of LAG-3 in physiological situation (A), mechanism of action of soluble LAG-3 protoein eftilagimod. (efti) (B) or anti-LAG-3 monoclonal antibody (C).

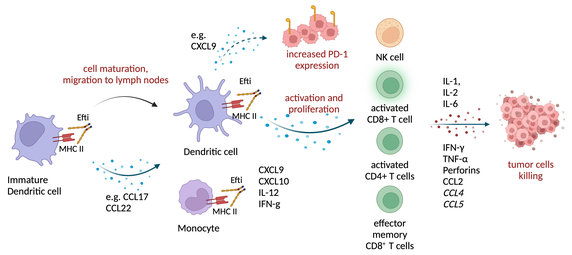

Fig. 2. Mechanism of action of soluble LAG-3 protein – eftilagimod alpha

- 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 hyalinisation and fibrosis, as a surrogate of pathological response, appears to be most closely correlated with treatment outcome.

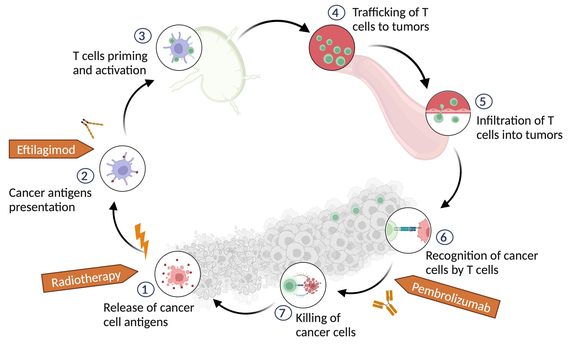

Fig. 3. Rationale for combining eftilagimod alpha, pembrolizumab and radiotherapy based on cancer-immune cycle.

STUDY ENDPOINTS

Primary:
- 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 Schaefer M. et al.), H1 – 35%

Secondary:
- Incidence of adverse events graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
- Number of patients completing neoadjuvant treatment and having a curative surgery according to the protocol
- 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

Exploratory:
- To evaluate changes in the composition of tumor microenvironment, including immune infiltrates, before and after neoadjuvant treatment
- To evaluate correlations between changes of immune-related biomarkers in the tumor or blood with response to therapy and patients' survival
- To compare changes in tumor microenvironment caused by neoadjuvant radiotherapy and immunotherapy with pembrolizumab and eftilagimod with changes related to other modalities (radiotherapy alone, radiotherapy with chemotherapy in neoadjuvant settings, or immunotherapy +/- other agents in advanced settings).

TRIAL DESIGN

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;
- One of the following histologies
  - undifferentiated pleomorphic sarcoma (UPS),
  - myxofibrosarcoma,
  - dedifferentiated liposarcoma (DDLPS),
  - myxoid and round cell liposarcoma (MRCLPS),
  - epithelioid sarcoma (ES)
  - angiosarcoma (AS),
  - soft tissue sarcoma NOS.
- Grade 2 or 3 tumors according FNCLCC;
- Size of the primary tumor >5 cm or locally recurrent of any size;
- Measurable disease based on RECIST 1.1;
- No previous systemic treatment for sarcoma;

Key Exclusion Criteria
- Distant metastases
- Previous treatment with eftilagimod alpha, anty-PD-1 or anty-PD-L1;
- Prior radiotherapy to tumor-involved sites;
- Subjects with active, known or suspected autoimmune disease or inflammatory bowel disease, which might impair the subject's tolerance of trial treatment.

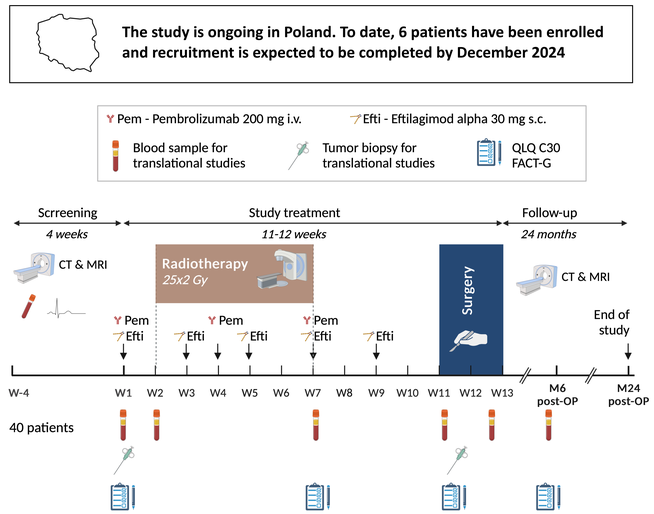

Fig. 4. EFTISARC-NEO trial design

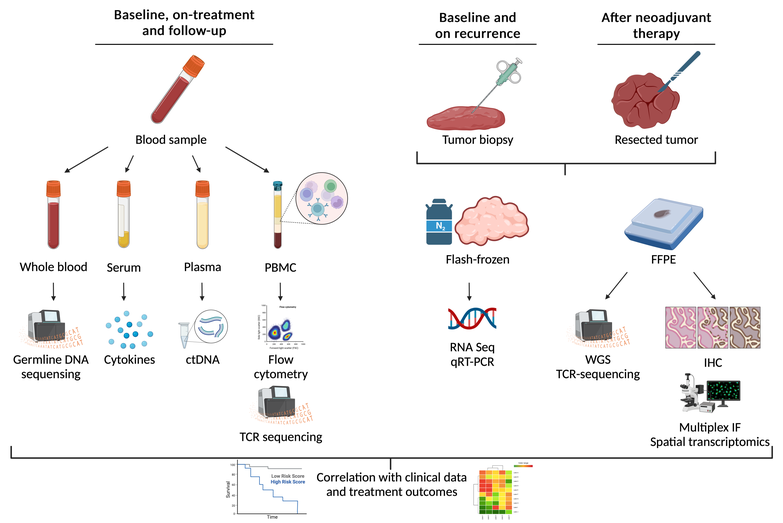

Fig. 5. Design of translation studies within EFTISARC-NEO trial.

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DISCLOSURES

Katarzyna Kozak: Speaker honoraria – BMS, MSD, Novartis, Pierre Fabre, Sanofi; advisory board - BMS, MSD; **Pawel 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 Kopec** declare no conflicts of interests; **Piotr Rutkowski:** Speaker honoraria – BMS, Merck, MSD, Novartis, Pierre Fabre, Sanofi; advisory board - Blueprint

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Immutep has provided eftilagimod alpha.

immutep LAG-3 IMMUNOTHERAPY

MEDICAL RESEARCH AGENCY

SCAN ME

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