



UPDATES IN SOFT TISSUE SARCOMA

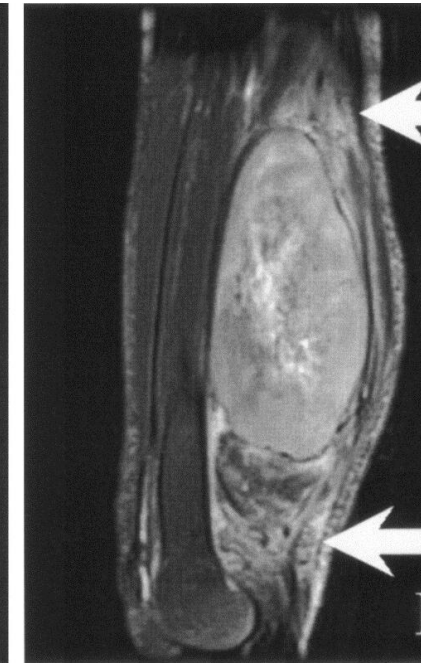
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Disclosure of Conflicts of Interest

- John Rieth, MD has no relevant financial relationships to disclose.

Soft-Tissue Sarcoma

- Very diverse family of tumors derived from primitive mesenchymal stem cells
- Chemotherapy resistant
- Radiation resistant (except for myxoid liposarcoma)
- Frequently immunologically resistant (with exceptions)
- Metastatic disease is generally incurable



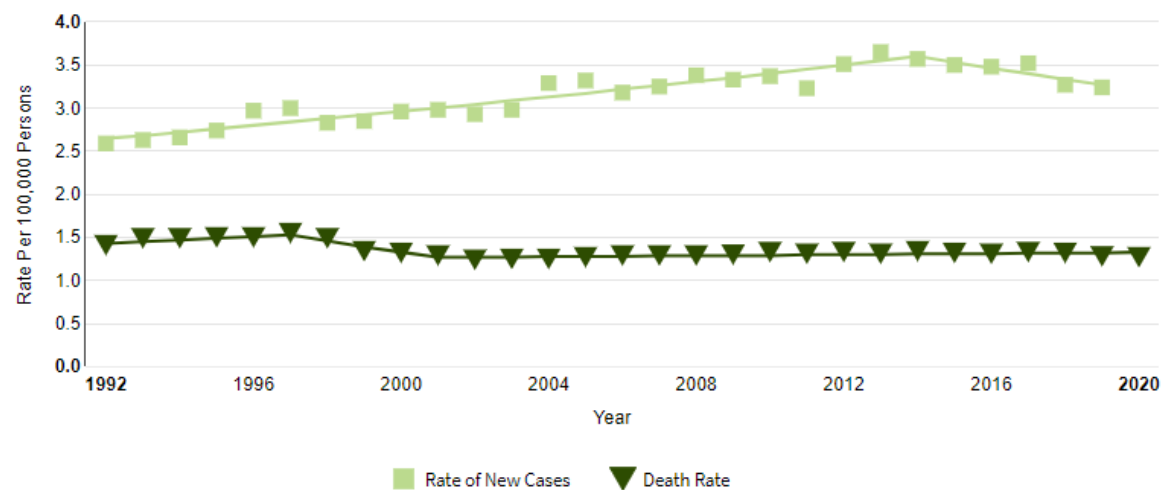
White, Lawrence M., et al. "Histologic assessment of peritumoral edema in soft tissue sarcoma." *International Journal of Radiation Oncology* Biology* Physics* 61.5 (2005): 1439-1445.

At a Glance

Estimated New Cases in 2022	13,190
% of All New Cancer Cases	0.7%

Estimated Deaths in 2022	5,130
% of All Cancer Deaths	0.8%

5-Year Relative Survival
65.4%
2012-2018

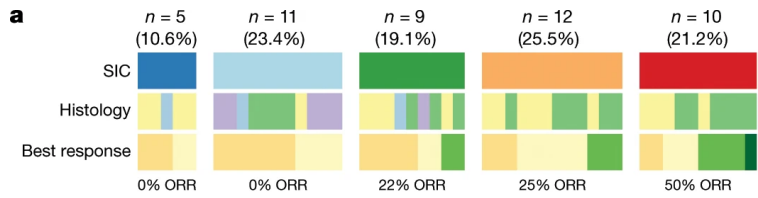


New cases come from SEER 12. Deaths come from U.S. Mortality.

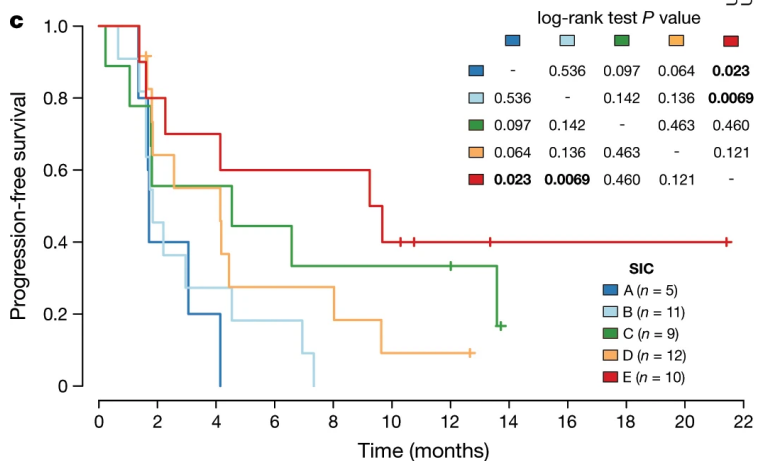
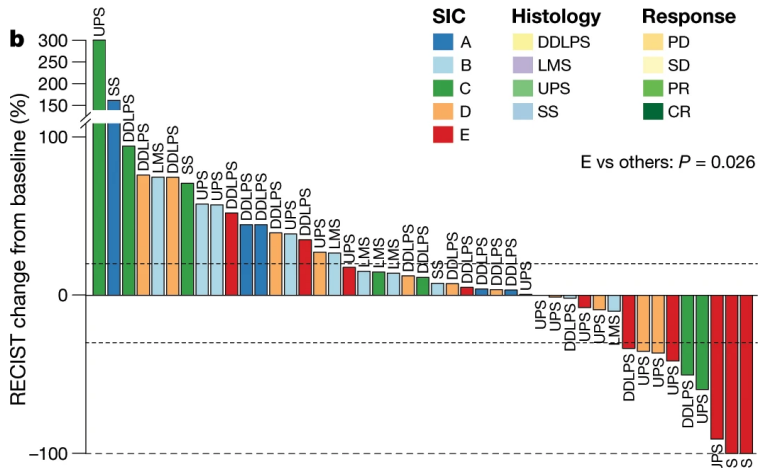
All Races, Both Sexes. Rates are Age-Adjusted.

Modeled trend lines were calculated from the underlying rates using the [Joinpoint Trend Analysis Software](#).

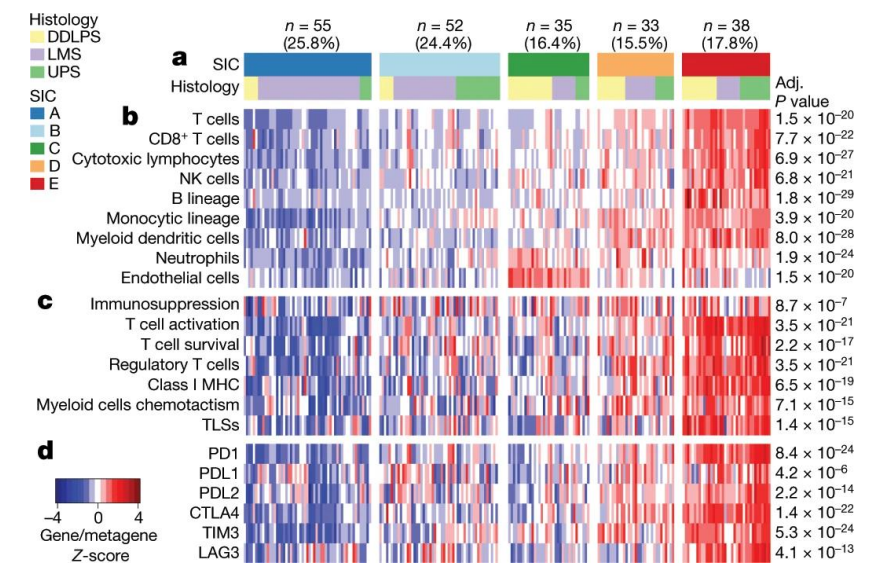
New cases are also referred to as incident cases in other publications. Rates of new cases are also referred to as incidence rates.



Overall: 21% ORR



SARCOMA RESPONSE TO IMMUNOTHERAPY



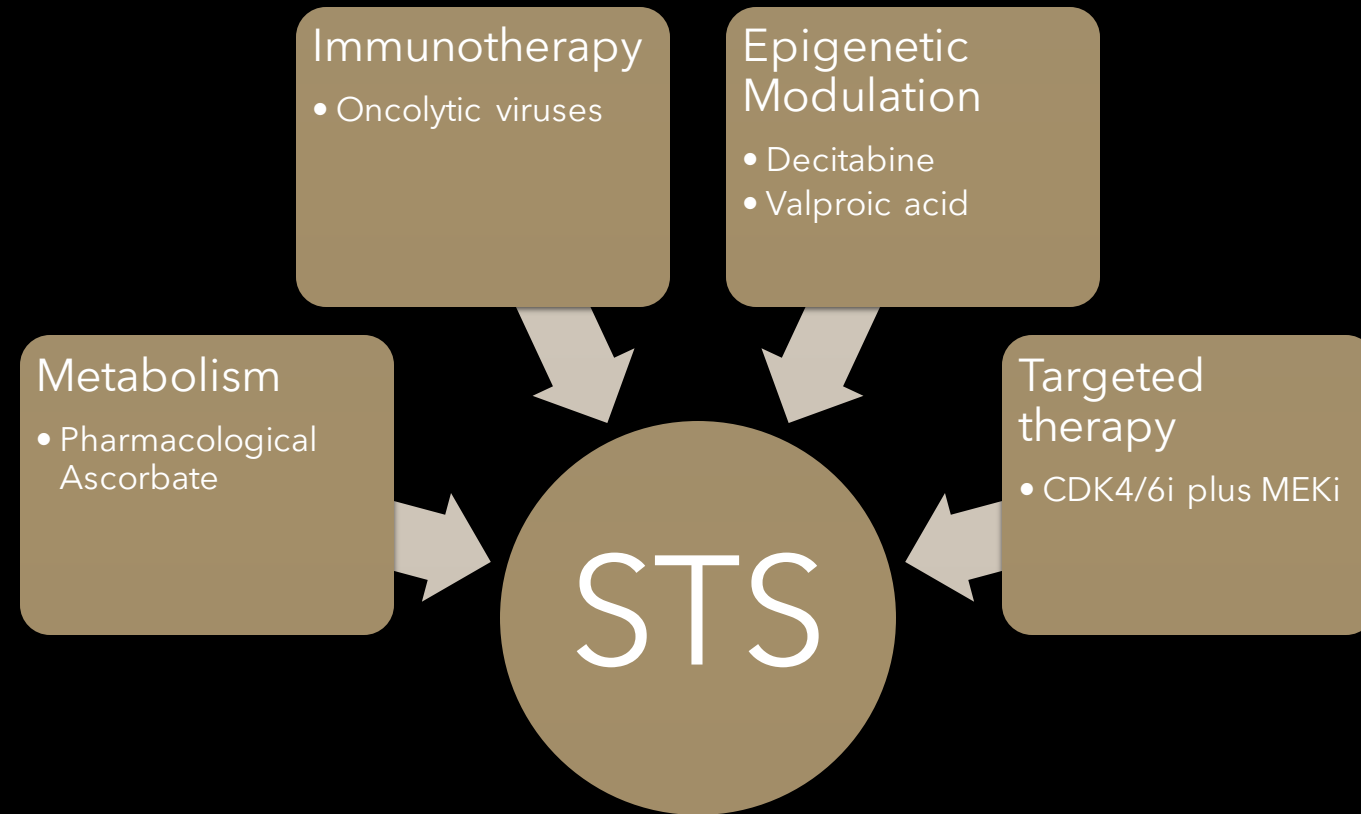
Neoadjuvant Treatment in Soft-Tissue Sarcoma

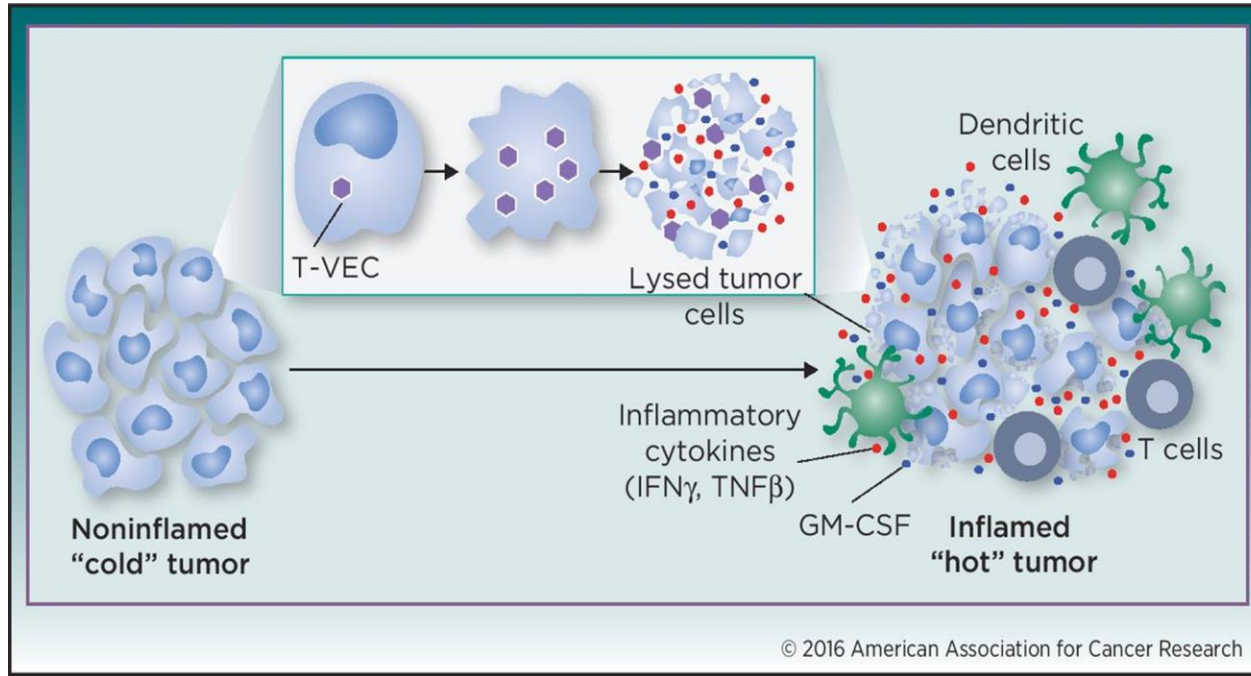
- Neoadjuvant treatment: medical and/or radiation treatment prior to surgical resection
- Adjuvant treatment: medical and/or radiation treatment post surgical resection
- EORTC 62931: Adjuvant doxorubicin and ifosfamide with no relapse free or overall survival benefit
- SARC32: Neoadjuvant + adjuvant pembrolizumab with XRT for undifferentiated pleomorphic sarcoma (and other names for UPS), results pending
- Neoadjuvant Ascorbate with concurrent radiotherapy: At UIHC, did not meet endpoints (no increase in rate of greater than 95% pathological necrosis), but did demonstrate an association between immune cells in the resected tumor and peripheral blood at end of treatment, ascorbate treatment associated with increase activated CD8 T-cells

Adjuvant vs Neoadjuvant Radiotherapy for Soft-Tissue Sarcoma

- Different side effect profiles
- Neoadjuvant radiotherapy with increased acute wound complications
- Adjuvant radiotherapy with increase late side effects and decrease limb functioning
- Neoadjuvant is generally preferred, due to relative sparing of the normal tissues
- Adjuvant radiotherapy may be offered in elderly symptomatic patients

Novel Approaches to Treatment



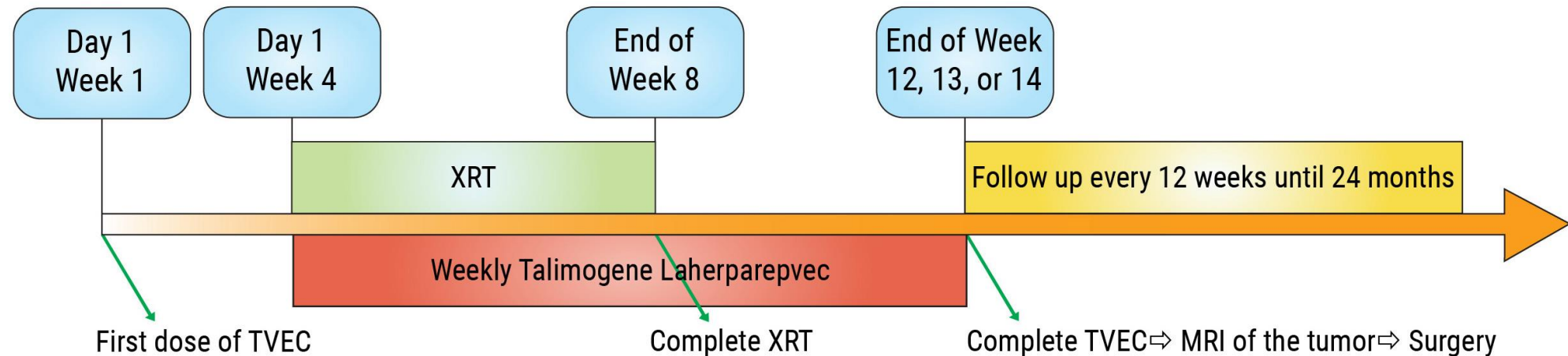


TVEC – ONCOLYTIC VIRUS

NEOADJUVANT INTRATUMORAL HIGH DOSE TALIMOGENE LAHERPAREPVEC (TVEC) WITH CONCURRENT RADIATION IN HIGH-RISK EXTREMITY AND TRUNK SOFT-TISSUE SARCOMAS

- TVEC is currently approved for the treatment of melanoma, and we hypothesized that this could have benefit in soft-tissue sarcoma by direct infection and GM-CSF generation
- Used 8 mL dosing
- A total of 6 patients with high risk (grade greater than 2) were treated with TVEC with EBRT followed by surgical resection, 50 Gy in 25 Fx

TVEC AND RADIOOTHERAPY AS NEOADJUVANT TREATMENT FOR STS, PILOT STUDY



Monga V, Miller BJ, Tanas M, *et al* Intratumoral talimogene laherparepvec injection with concurrent preoperative radiation in patients with locally advanced soft-tissue sarcoma of the trunk and extremities: phase IB/II trial *Journal for ImmunoTherapy of Cancer* 2021;9:e003119

Objectives

- Primary Objectives
 - Safety and tolerability of TVEC (8 mL 10^8 PFU/mL dosing) + EBRT as defined by incidence of dose-limiting toxicities
 - Determine efficacy as determined by post treatment tumor necrosis >95%
- Secondary Objectives
 - Overall response rate as per RECIST
 - Time to progression (local or metastatic) at 2 years from last enrollment
 - Overall Survival at 5 years

TVEC 8 mL Phase 1b Results

Myxoid liposarcoma, grade 2

95% necrosis

Undifferentiated sarcoma NOS, grade 2

100% necrosis

Undifferentiated pleomorphic sarcoma, grade 2

57% necrosis (developed lung metastases within 3 months of surgery)

Dedifferentiated liposarcoma, grade 2

27% necrosis (developed mets to soft tissue and lung within 3 months of completion of surgery)

Myxoid round cell liposarcoma, grade 2

99% necrosis

Undifferentiated pleomorphic sarcoma

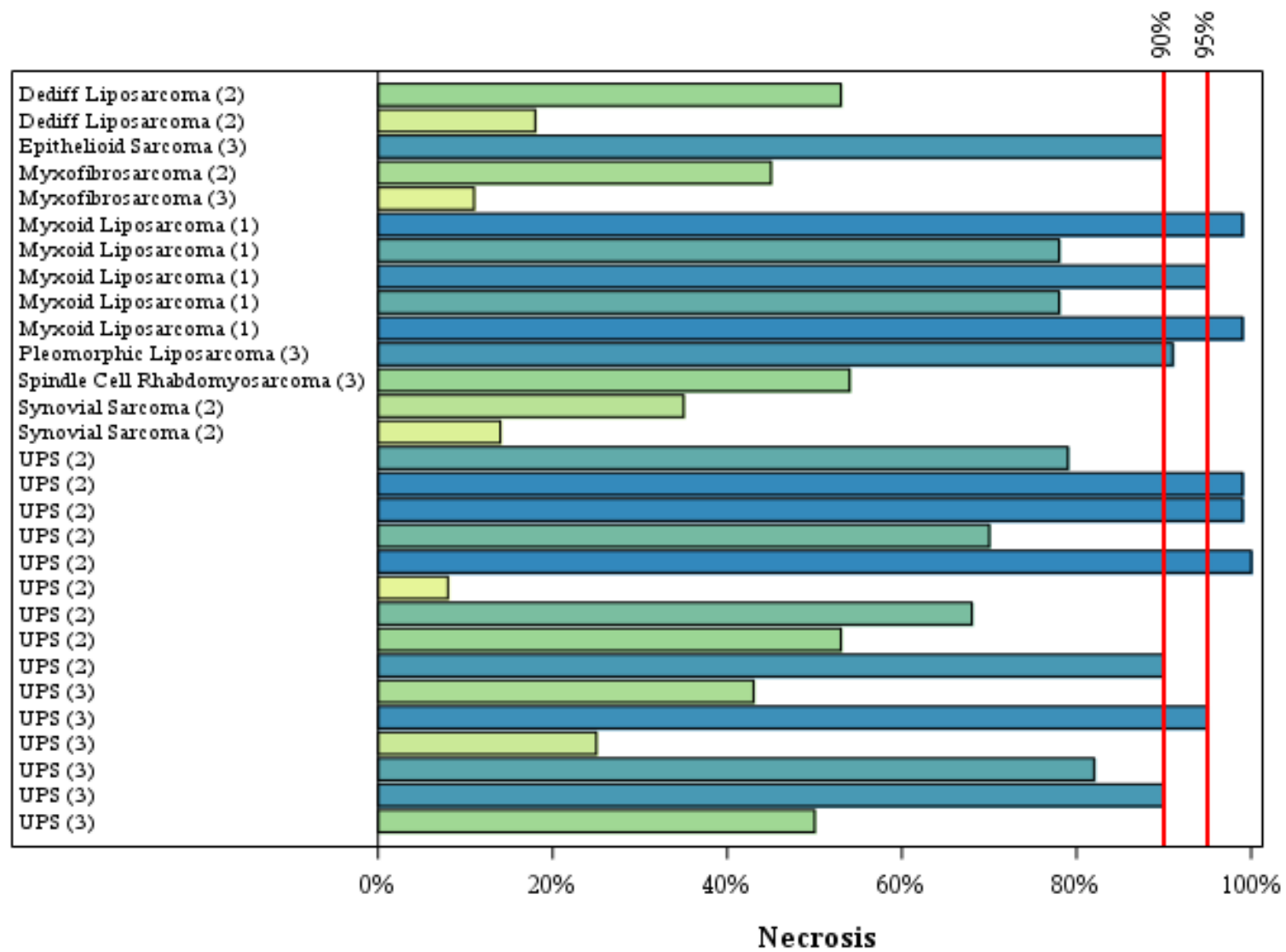
93% necrosis

Adverse events

- Grade 3 adverse events
 - fatigue in one patient (16.6%)
 - dermatitis in one patient (16.6%)
- Grade 1-2 adverse events
 - nausea in three (50.0%)
 - vomiting in two (33.3%)
 - chills in five (83.3%)
 - fatigue in four (66.7%)
 - fever in three (50.0%)
 - anorexia in two (33.3%)

Learning points of clinical trial

- Myxoliposarcoma: Has significant treatment effect with radiation regardless of other interventions
 - Added 2 additional patients with non-myxoliposarcoma histologies
- TVEC dosing? 4mL vs 8mL
- What is the significance of necrosis when assessing novel agents? What is a good surrogate for PFS and OS?
- Heterogeneity of STS makes it difficult to assess
- Hypofractionated EBRT



Learning points

- Soft-tissue sarcoma represents a large family of very diverse tumors, with different prognosis, rate of progression, sensitivity to different treatments
- Soft-tissue sarcoma is generally resistant to chemotherapy and radiotherapy
- Generally considered resistant to immunotherapy, with some exceptions (UPS, DDLPS, pleomorphic rhabdomyosarcoma)
- New treatments are needed, and are being explored
- Both adjuvant and neoadjuvant radiation can be considered for high-grade (2 or 3) sarcoma; neoadjuvant radiation is generally preferred due to lower risk of long term side effects

QUESTIONS?



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- Steve Varga
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Citations

- Monga V, Miller BJ, Tanas M, et al Intratumoral talimogene laherparepvec injection with concurrent preoperative radiation in patients with locally advanced soft-tissue sarcoma of the trunk and extremities: phase IB/II trial Journal for ImmunoTherapy of Cancer 2021;9:e003119
- Ott, Patrick A., and F. Stephen Hodi. "Talimogene Laherparepvec for the Treatment of Advanced MelanomaTalimogene Laherparepvec in Melanoma." Clinical Cancer Research 22.13 (2016): 3127-3131.
- Petitprez, Florent, et al. "B cells are associated with survival and immunotherapy response in sarcoma." Nature 577.7791 (2020): 556-560.
- White, Lawrence M., et al. "Histologic assessment of peritumoral edema in soft tissue sarcoma." International Journal of Radiation Oncology* Biology* Physics 61.5 (2005): 1439-1445.