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MEETING SUMMARY
ESMO 2020, Milan, Italy

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SARCOMA UPDATE
FEBRUARY 2020

DISCLAIMER

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SUMMARY OF *THE CHALLENGING IMMUNO LANDSCAPE OF SARCOMA AND GIST* SESSION

IMMUNOTHERAPY IN STS AND GIST

BACKGROUND: IMMUNOTHERAPY IN STS AND GIST

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Immunotherapies appear to have less efficacy in STS and GIST than other cancer subtypes, due to prevalence of 'cold' TMEs in many subtypes

Improved efficacy in high immune subclass sarcomas is in line with this concept[1]

The use of combination check-point therapies (PD-1 and CTLA-4) may improve efficacy, as in other cancer types[2]

Priming of tumours from a cold to hot immune state using mixed therapy combinations may further improve efficacy[3]

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; GIST, gastrointestinal stromal tumours; PD-1, programmed cell death protein 1; STS, soft-tissue sarcoma; TME, tumour microenvironment.

1. Petitprez F, et al. Nature. 2020;577:556-560; 2. Singh AS, et al. Journal of Clinical Oncology 2018;36 (suppl_4):55-55; 3. Martin Broto J, et al. Annals of Oncology 2019;30 (suppl_5):v683-v709.

SINGLE-AGENT CHECK POINT INHIBITORS
EFFICACY IN ADVANCED STS

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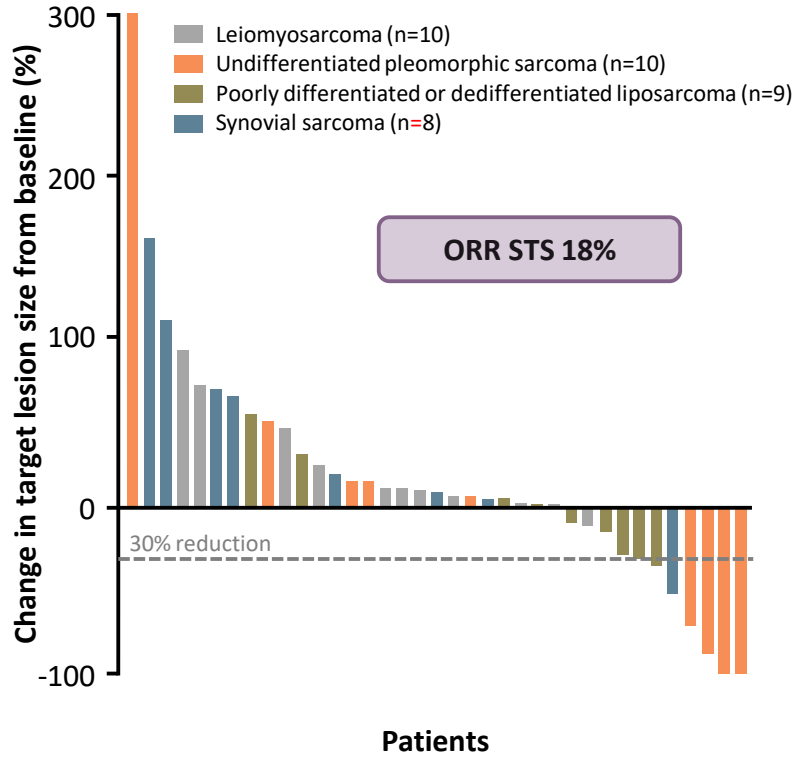
18%

Pembrolizumab ORR was 18% in patients with metastatic or locally advanced sarcoma who had received up to three previous lines of therapy

SARC028 study suggests pembrolizumab may have efficacy in:

- undifferentiated pleomorphic sarcoma
- poorly differentiated/dedifferentiated liposarcoma

Best percentage change in size of target lesions



ORR, overall response rate; STS, soft-tissue sarcoma.

Tawbi HA, et al. Lancet Oncol. 2017;18:1493-1501; Florou V, et al. J Immunother Cancer. 2019;7:213.

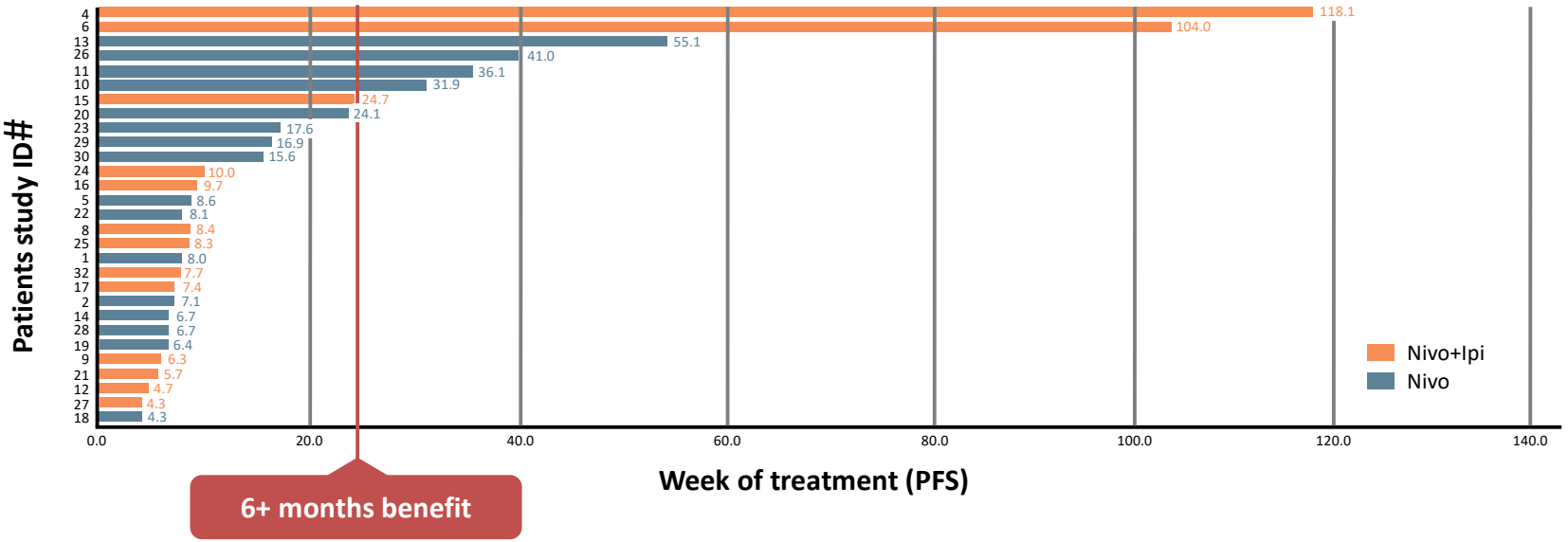
COMBINATION THERAPIES MAY IMPROVE EFFICACY OF CHECKPOINT INHIBITORS

PD-1 AND CTLA-4

Nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor):

- Efficacy in advanced GIST

Progression-free survival of patients over time



CT, chemotherapy; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; Ipi, ipilimumab; GIST, gastrointestinal stromal tumours; Nivo, nivolumab; PD-1, programmed cell death protein 1; PFS, progression-free survival; RT, radiotherapy.

Singh AS, et al. Journal of Clinical Oncology 2018;36 (suppl_4):55-55.

IMMUNE PRIMING WITH COMBINATION THERAPIES

PRIMING OF THE IMMUNE SYSTEM MAY IMPROVE EFFICACY OF CHECKPOINT INHIBITORS

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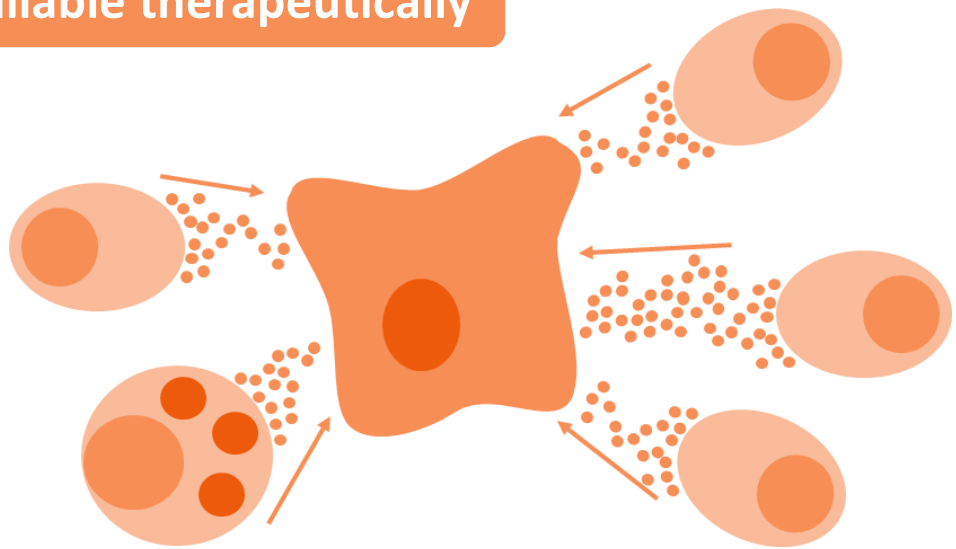
IFN-α:

- Promotes CD4+ T-cell response
- Leads to increase in NK cells, NKT cells, CD8+ T-cells; CD4+ T-cells
  - Lineages which promote anti-tumour IFN-ϒ

Pegylated IFN-α is available therapeutically



Adapted with permission from Prof. Jon Trent.

CD, cluster of differentiation; IFN, interferon; NK, natural killer.

Chen LL, et al. Cancer Immunol Immunother. 2012;61:1113-24.

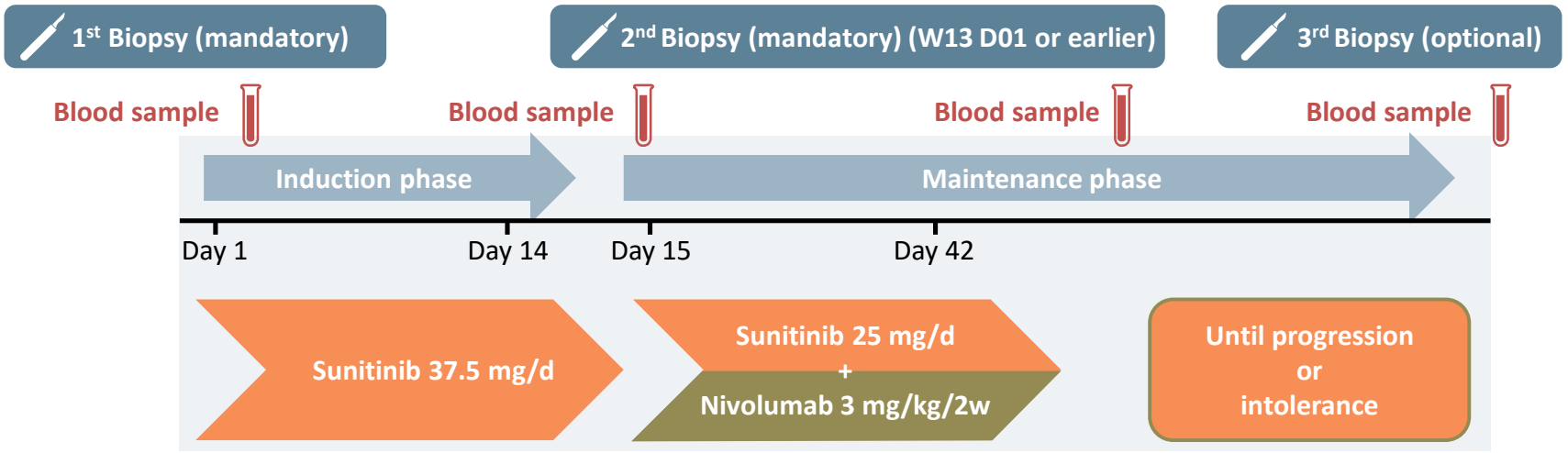
ANTI-ANGIOGENIC AND PD-1 COMBINATIONS

SUNITINIB + NIVOLUMAB: IMMUNOSARC STUDY DESIGN

VEGF promotes growth of tumour blood vessels and is also immunosuppressive[1]

Anti-VEGF sunitinib may allow maturation of DCs which promote T-cell activation in parallel with check-point inhibition[1]

IMMUNOSARC study design[2]



DC, dendritic cell; PD-1, programmed cell death protein 1; VEGF, vascular endothelial growth factor.

1. Yang J, et al. Front Immunol. 2018;9:978; 2. Martin Broto J, et al. Annals of Oncology 2019;30 (suppl_5):v683-v709.

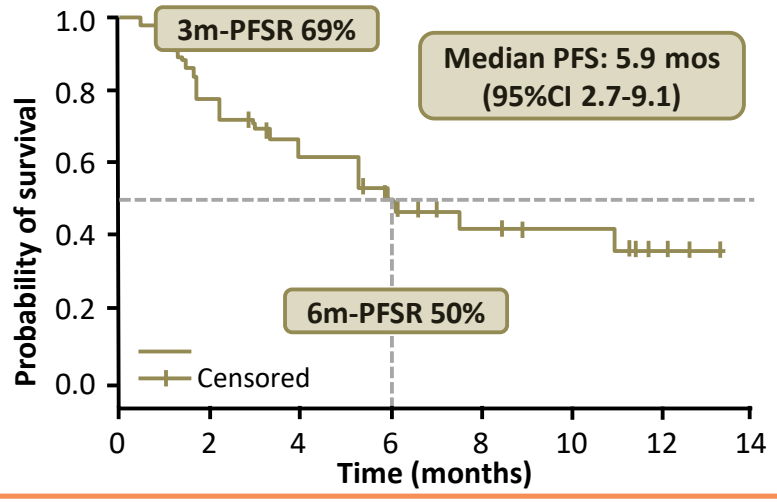
ANTI-ANGIOGENIC AND PD-1 COMBINATIONS

SUNITINIB + NIVOLUMAB: IMMUNOSARC EFFICACY

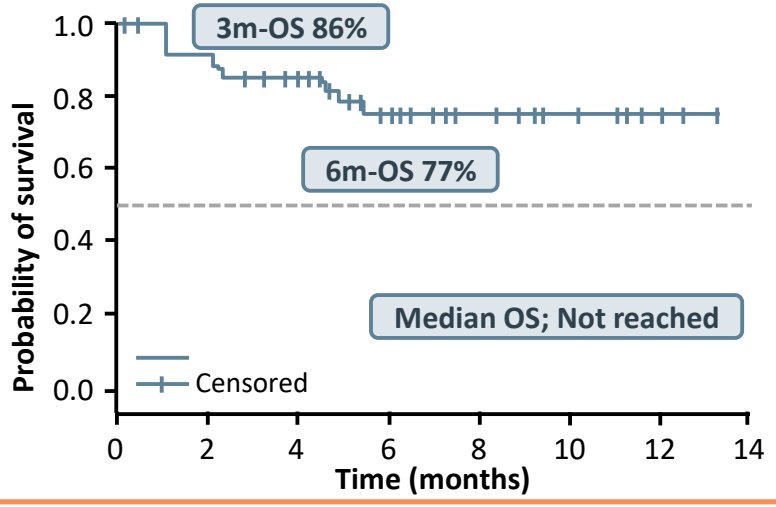
IMMUNOSARC efficacy showed impressive activity in patients with pre-treated progressing sarcoma

Response*	N = 46
CR	1 (2%)
PR	4 (9%)
SD	28 (61%)
PD	13 (28%)

Progression-free survival



Overall survival



*RECIST data as reported at the ESMO Sarcoma and GIST Symposium 2020.

CI, confidence intervalCR, complete response; mo, month; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PFS, progression-free survival; PFSR, progression-free survival rate; PR, partial response; RECIST, response evaluation criteria in solid tumors, SD, stable disease.

Martin Broto J, et al. Annals of Oncology 2019;30 (suppl_5):v683-v709.

ANTI-ANGIOGENIC AND PD-1 COMBINATIONS

AXITINIB + PEMBROLIZUMAB: PHASE 2 STUDY DESIGN

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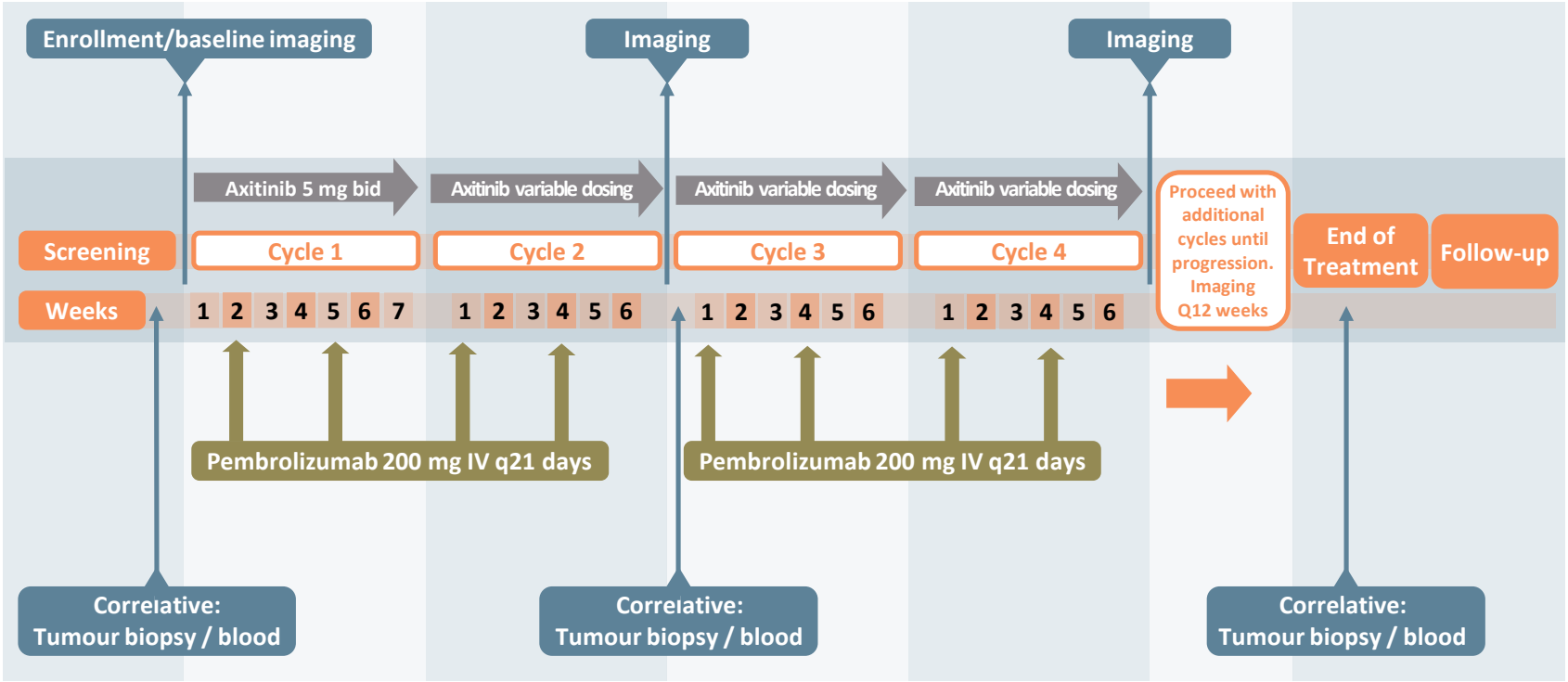
Study design: NCT02636725



BID, twice daily; IV, intravenous; PD-1, programmed cell death protein 1.

Wilky BA, et al. Lancet Oncol. 2019;20:837-848.

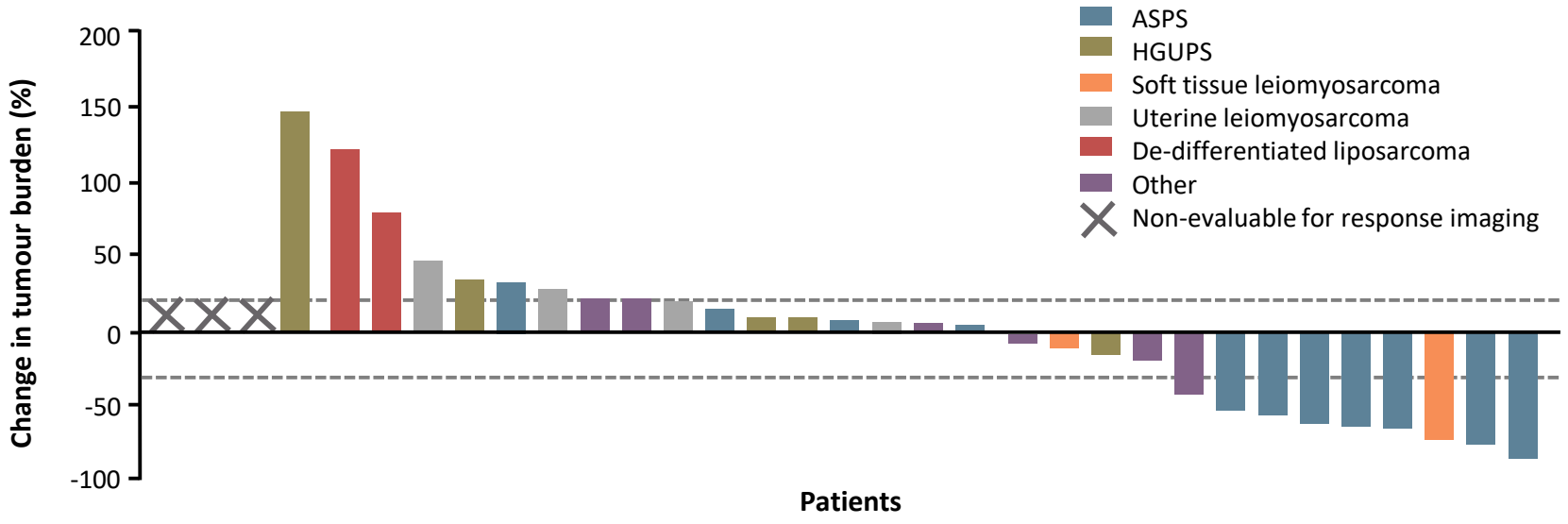
ANTI-ANGIOGENIC AND PD-1 COMBINATIONS

AXITINIB + PEMBROLIZUMAB: EFFICACY

- Anti-VEGF axitinib and pembrolizumab have shown preliminary efficacy in advanced sarcomas, including GIST
  - RR was > 50% in ASPS

Response	N = 32
CR	0 (0%)
PR	8 (25%)
SD	9 (28%)
PD	15 (47%)

Efficacy: change in tumour burden



ASPS, alveolar soft part sarcoma; CR, complete response; GIST, gastrointestinal stromal tumours; HGUPS, high-grade undifferentiated pleomorphic sarcoma; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; RR, response rate; SD, stable disease; VEGF, vascular endothelial growth factor.

Wilky BA, et al. Lancet Oncol. 2019;20:837-848.

T-VEC ONCOLYTIC VIRUS THERAPY
MECHANISM AND STUDY DESIGN

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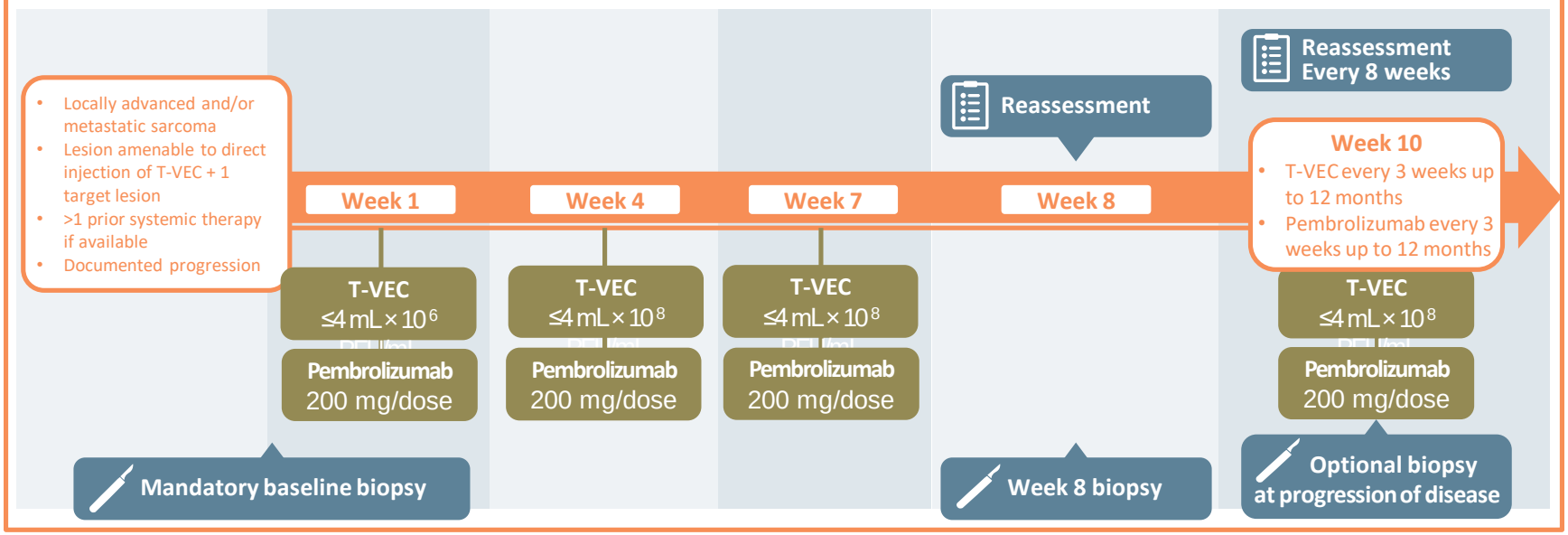
Oncolytic T-VEC has dual local and systemic effects:[1]

- Local viral replication in tumour cells leads to oncolysis
- Systemic release of antigens due to cell lysis leads to immune recruitment

Study design[2]



PFU, plaque-forming units; T-VEC, talimogene laherparepvec.

1. Harrington KJ, et al. Onco Targets Ther. 2017;10 3867-3880; 2. Kelly CM, et al. JAMA Oncol. 2020;doi: 10.1001/jamaoncol.2019.6152. [Epub ahead of print].

ONCOLYTIC AND PD-1 COMBINATIONS
T-VEC + PEMBROLIZUMAB

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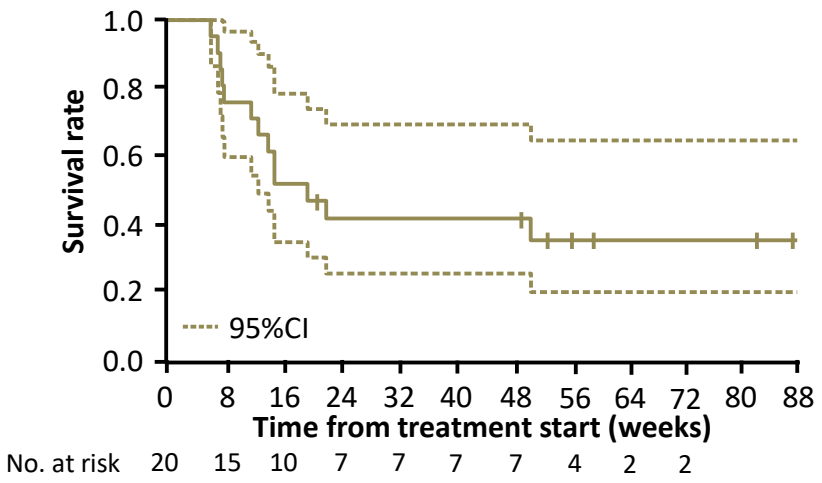
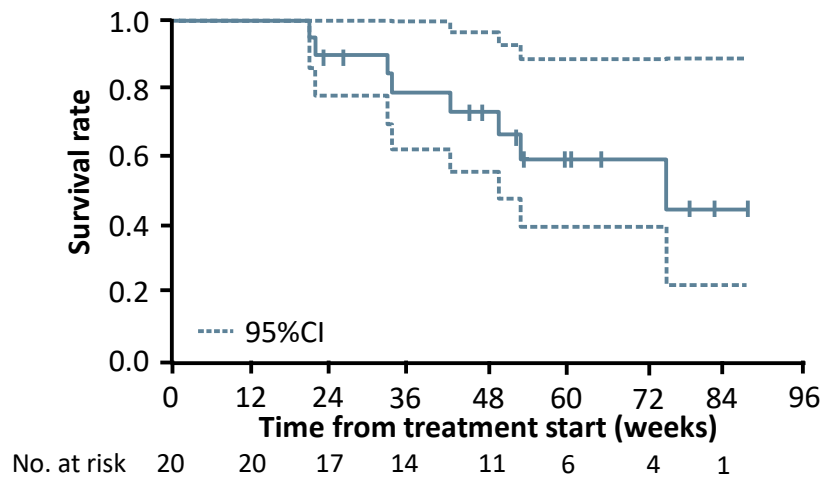
- Immune recruitment due to T-VEC induced lysis may aid immune checkpoint activity
- T-VEC in combination with pembrolizumab showed promising results in mixed STS subtypes

Progression-free survival



Overall survival



PD-1, programmed cell death protein 1; STS, soft-tissue sarcoma; T-VEC, talimogene laherparepvec.

Kelly CM, et al. JAMA Oncol. 2020;doi: 10.1001/jamaoncol.2019.6152. [Epub ahead of print].

SUMMARY

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There have been a number of major advances recently in immunotherapy

Single-agent activity is apparent in cutaneous angiosarcoma

Combination regimens with immune check point inhibitors appear to be superior to single agents

We may require triplet immunotherapy combinations in order to recruit, activate and retain memory of the immune system in order to eradicate STS and GIST

GIST, gastrointestinal stromal tumours; STS, soft-tissue sarcoma.

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