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# A randomized phase II study of durvalumab and tremelimumab compared to doxorubicin in patients with advanced or metastatic soft tissue sarcoma

LBA90: MEDISARC, AIO-STS-0415

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# DECLARATION OF INTERESTS

Viktor Grünwald

**Invited speaker:** Amgen, Astellas, AstraZeneca, BMS, EISAI, Ipsen, Janssen-Cilag, Merck, MSD, Novartis, Pfizer

**Advisory Board:** Apogepha, , BMS, Cureteq, Debiopharm, EISAI, EUSAPharm, Merck, MSD, Oncorena, PCI Biotech, Pfizer, Roche

**Stocks:** AstraZeneca, BMS, MSD, Seagen

**Research Grants**: BMS, Ipsen, MSD, Pfizer

**Travel support:** Ipsen, Janssen-Cilag, Merck, Pfizer

# Background

- Soft tissue sarcomas (STS) are rare tumors and exhibit substantial histological diversity.
- Anthracycline-based chemotherapy is the standard of care (SOC) in treatment-naïve patients with advanced or metastatic STS.
- Treatment efficacy remained poor and expected median Overall Survival (OS) for treated patients is 13-20 months[1-3].
- Immune checkpoint inhibitors (ICI) have demonstrated principle anti-tumor activity in patients with pretreated STS[3-6].
- We hypothesized that the dual checkpoint blockade with the PD-L1 inhibitor durvalumab (DUR) and CTLA-4 inhibitor tremelimumab (TREM) will improve OS in patients with STS compared to the SOC (doxorubicin).
- We tested the activity of ICI combination therapy vs. doxorubicin in chemo-sensitive STS subtypes.

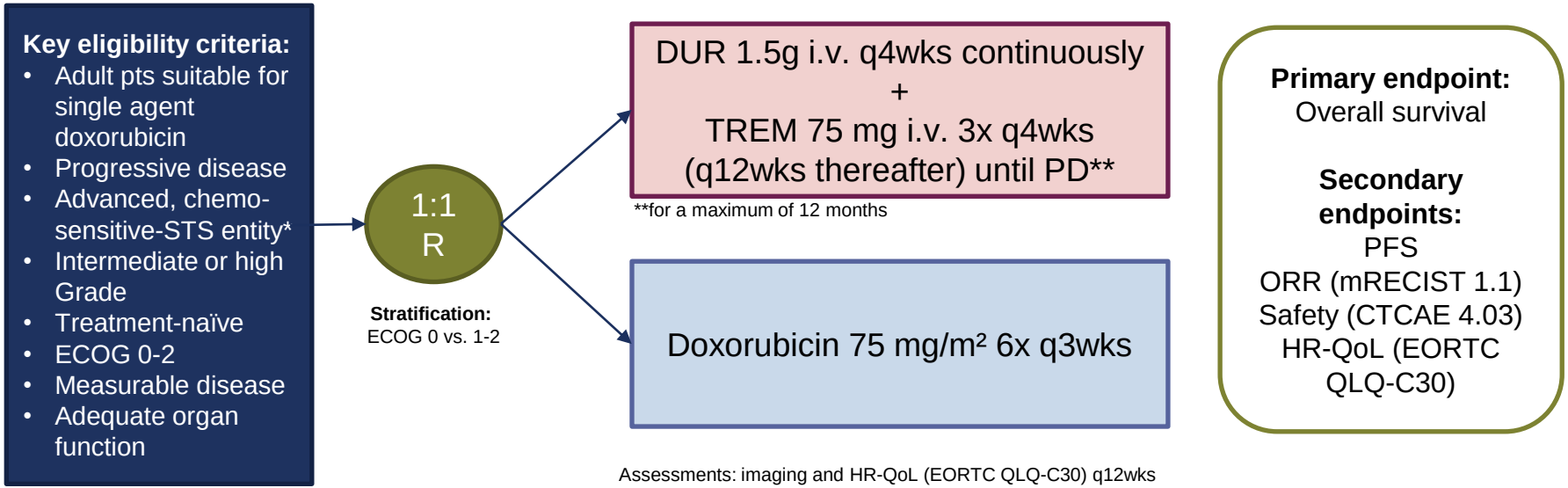
1. Paoluzzi et al. (2016). Clinical Sarcoma Research, 6(1), 24. http://doi.org/10.1186/s13569-016-0064-0. 2. Demetri et al. (2016). Journal Clinical Oncology, 34(8), 786–793. http://doi.org/10.1200/JCO.2015.62.4734. 3. Tap et al. JAMA 2020; 323 (13): 1266-76. 4. D'Anegelo et al. Lancet Oncol 2018 Mar;19(3):416-426. doi: 10.1016/S1470-2045(18)30006-8. 5. Tawbi et al. Lancet Oncol 2017 Nov;18(11):1493-1501. doi: 10.1016/S1470-2045(17)30624-1. 6. Somaiah et al. Lancet Oncol 2022 Sep;23(9):1156-1166. doi: 10.1016/S1470-2045(22)00392-8

# Statistical considerations

- Median OS for doxorubicin was considered 12.8 months and 2-year-OS rate 30% (Judson et al. 2014).
- Durvalumab + tremelimumab were considered promising if 2-year OS rate was 49% (hazard ratio of 0.6)
- 1-sided logrank test with an overall sample size of N=100 subjects (1:1 randomized) achieved 80.2% power with an alpha=0.1 significance level to detect a hazard ratio of HR=0.6 when the proportion surviving (2-year OS rate) in the control group is 0.3 and the proportion surving in the experimental treatment group is 0.49 (2-year OS rate).
- Type I error rate was set to 0.1 due to rare incidence of STS and to reduce the number of exposed patients
- Events for final analyses required was 70

# Study Design

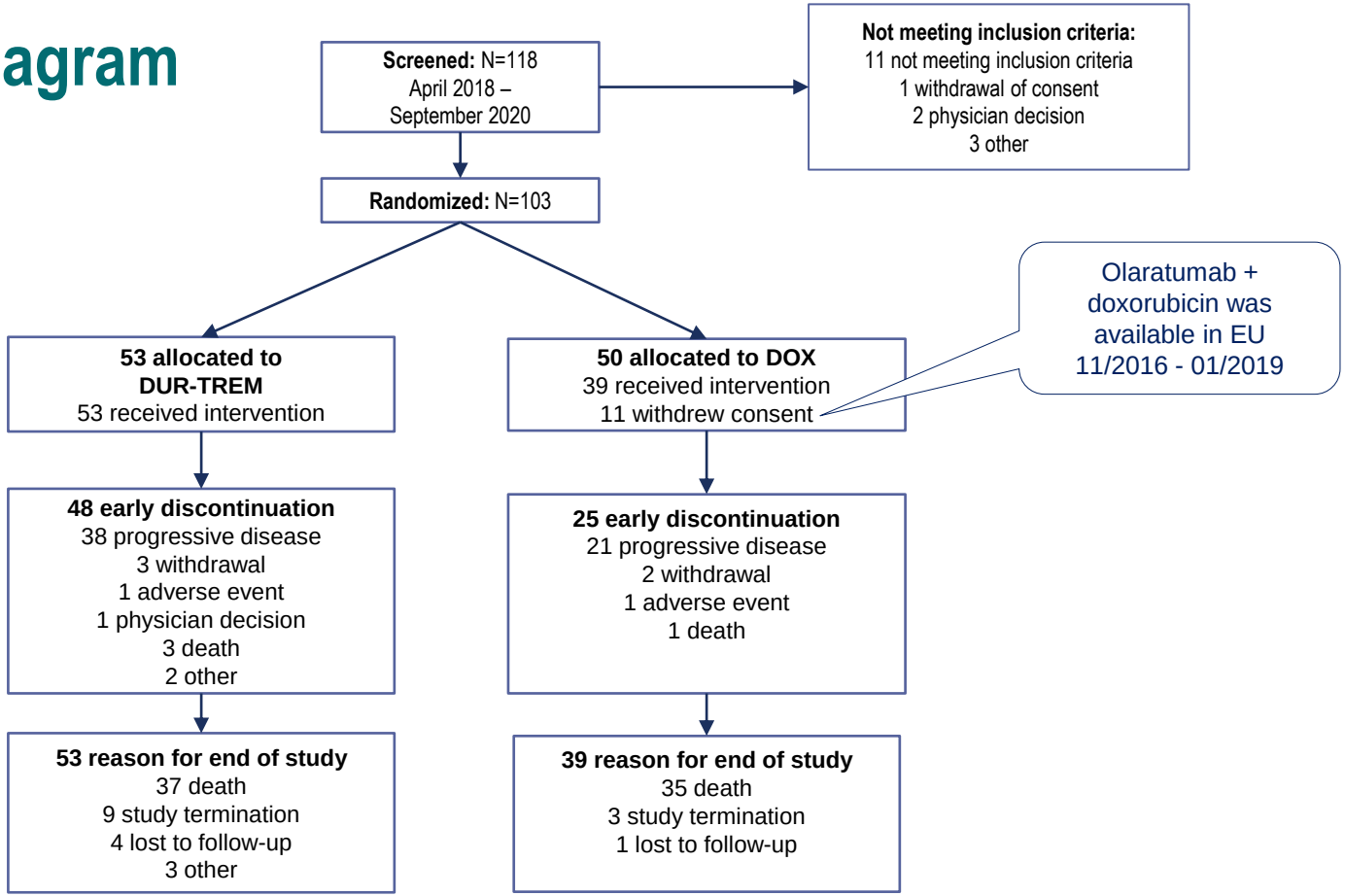
## MEDISARC – a randomized phase II trial




*Fibrosarcoma, Pleomorphic high grade sarcoma, Leiomyosarcoma, Liposarcoma (myxoid liposarcoma, dedifferentiated liposarcoma, pleomorphic liposarcoma), Malignant glomus tumor, Rhabdomyosarcoma, alveolar or pleomorphic, Vascular sarcoma (angiosarcoma), Synovial sarcoma, High-grade sarcoma, not otherwise specified (NOS), Malignant peripheral nerve sheath tumors.

ORR: objective response rate. HR-QoL: health-related quality of life. R: randomization. PFS: Progression free survival. DUR: Durvalumab. TREM: Tremelimumab

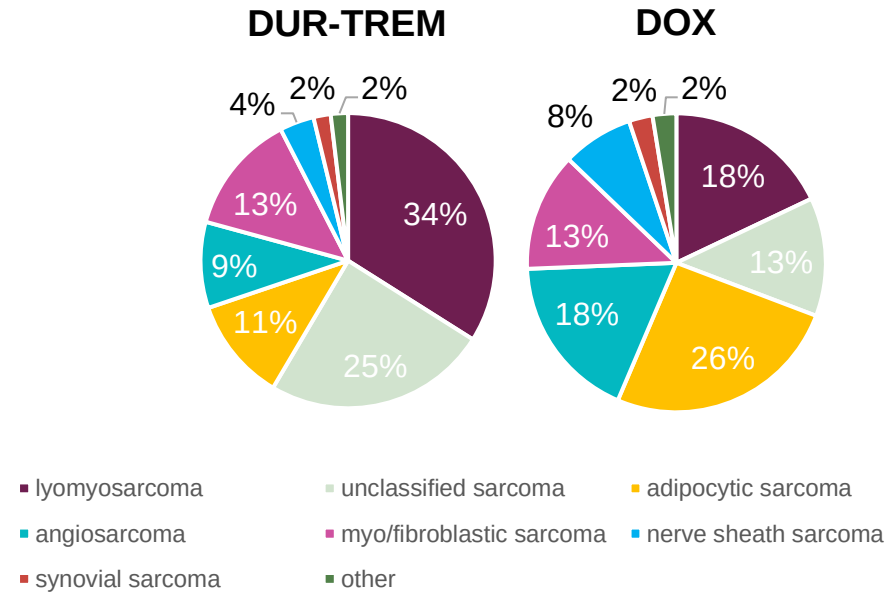
# CONSORT Diagram



# Patient characteristics

| | DUR-TREM (n=53) | DOX (n=39) |
|---|---|---|
| **Median age (range)** | 61.0 (23-82) | 62.0 (35-82) |
| **Gender, n (%)** | | |
| Male | 25 (47.2) | 17 (43.6) |
| Female | 28 (52.8) | 22 (56.4) |
| **Ethnicity, n (%)** | | |
| Caucasian | 53 (100) | 38 (97.4) |
| Other | 0 (0.0) | 1 (2.6) |
| **ECOG, n (%)** | | |
| 0-1 | 51 (96.2) | 38 (97.4) |
| 2 | 2 (3.8) | 1 (2.6) |
| **Grading, n (%)** | | |
| Grade 2 | 20 (37.7) | 16 (41.0) |
| Grade 3 | 33 (62.3) | 23 (59.0) |

DUR-TREM: Durvalumab + Tremelimumab; DOX: Doxorubicin



# Objective response rate

## Investigator-based best overall response

2 leiomyo
1 angio
1 unclassified
1 fibroblastic

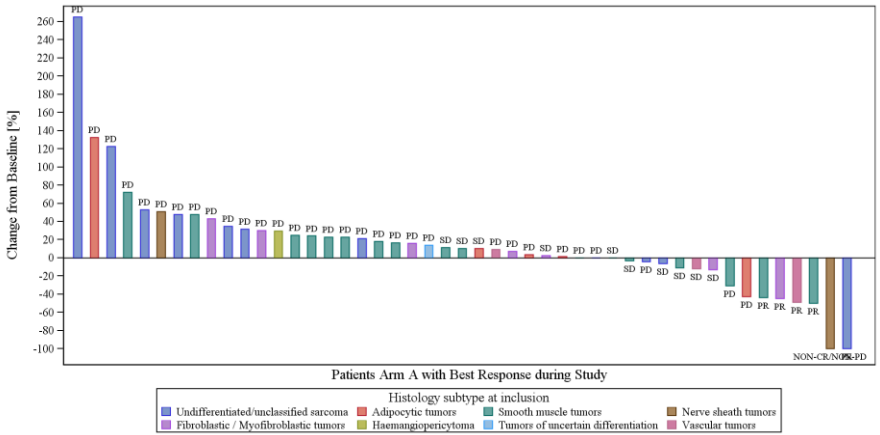
2 adipocytic
1 leiomyo
1 angio
1 synovial

| | DUR-TREM (n=53) | DOX (n=39) |
|---|---|---|
| **Objective response rate, n (%)** | 5 (9.4) | 5 (12.8) |
| **95% CI** | 3.1-20.7 | 4.3-27.4 |
| **Complete response, n (%)** | 0 (0) | 1 (2.6) |
| **Partial response, n (%)** | 5 (9.4) | 4 (10.3) |
| **Stable disease, n (%)** | 10 (18.9) | 12 (30.8) |
| **Progressive disease, n (%)** | 31 (58.5) | 19 (48.7) |
| not evaluable | 1 (1.9) | 0 (0) |

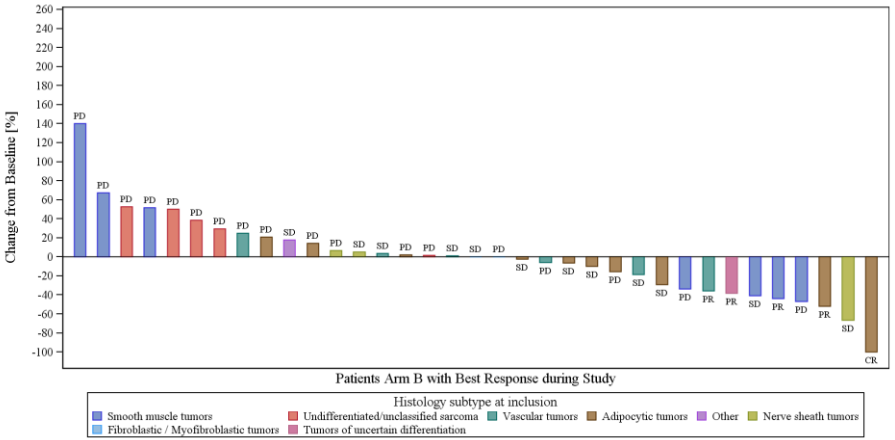
# Waterfall plot

## Sum of target lesion diameter provided as change from baseline

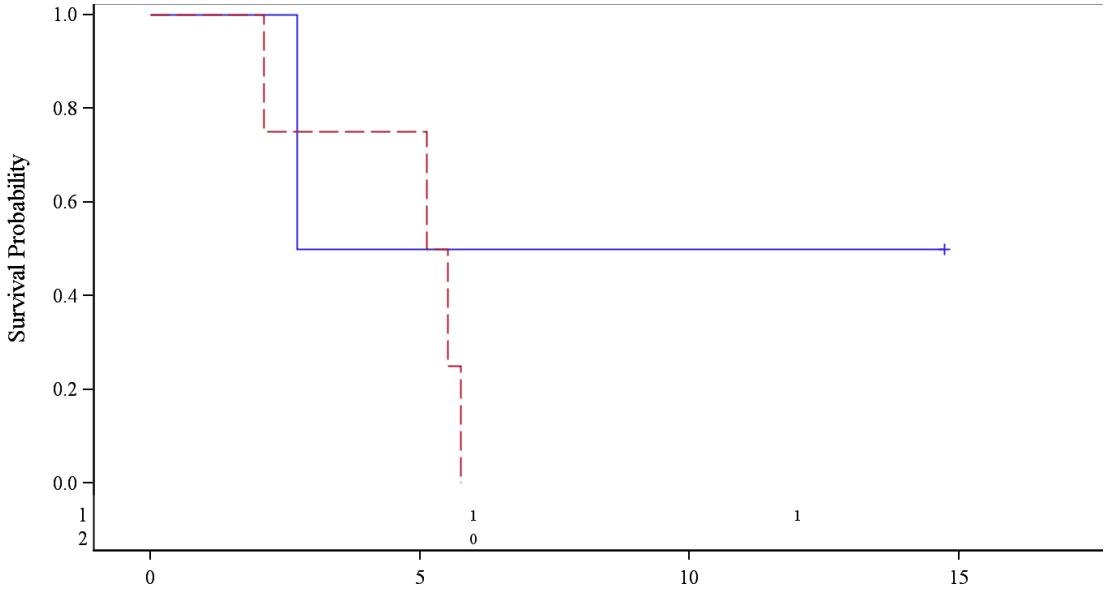
**DUR-TREM**




**DOX**



# Duration of response



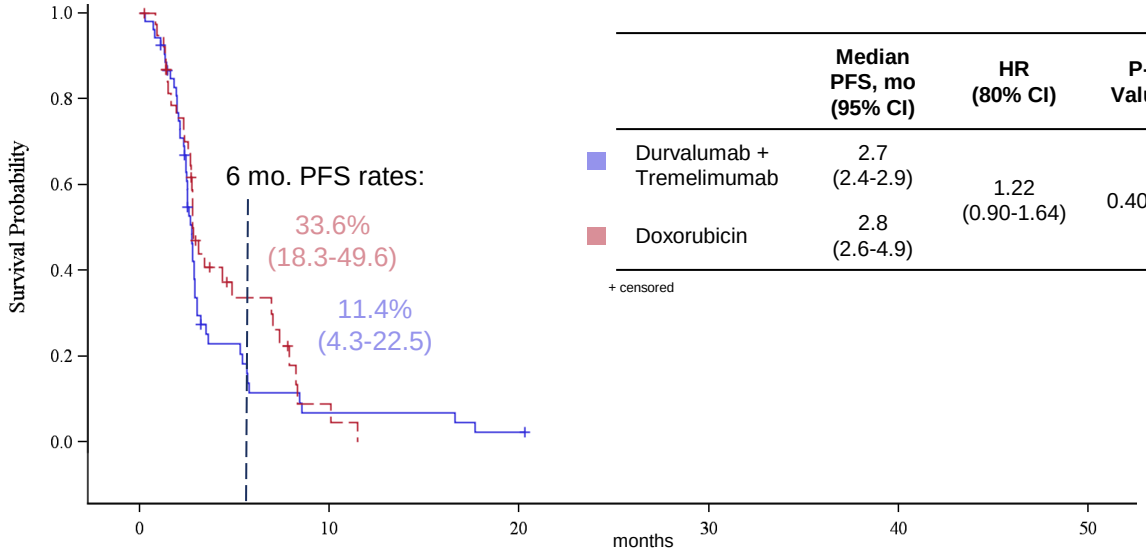

| | Median DoR, mo (95% CI) | P-Value |
|---|---|---|
| Durvalumab + Tremelimumab | NC (2.4-NC) | 0.4407 |
| Doxorubicin | 5.3 (2.1-5.8) | |

+ censored

NC: not calculable

# Progression free survival

## All treated patients

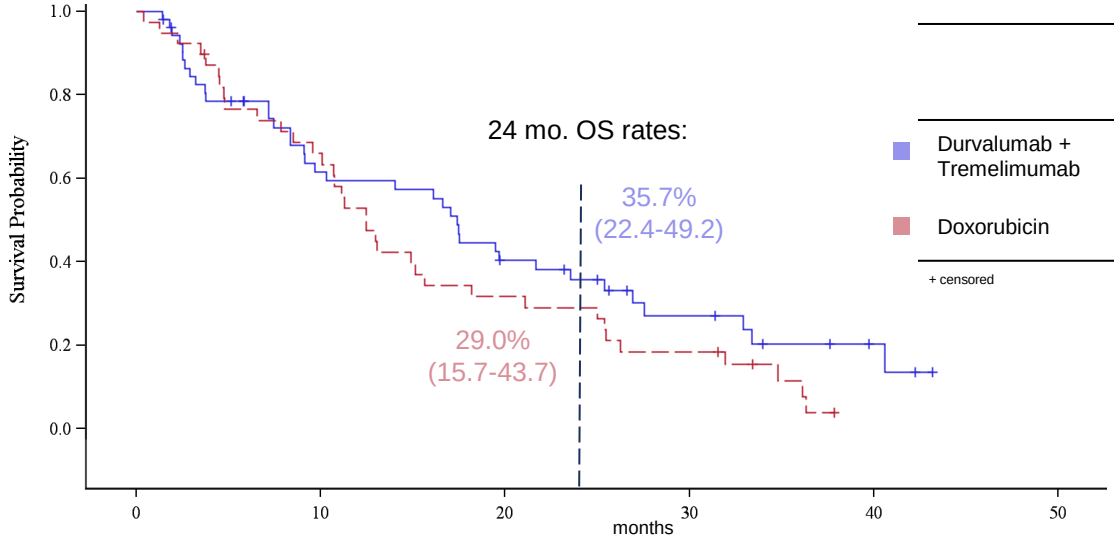



| | Median PFS, mo (95% CI) | HR (80% CI) | P-Value |
|---|---|---|---|
| Durvalumab + Tremelimumab | 2.7 (2.4-2.9) | 1.22 (0.90-1.64) | 0.4049 |
| Doxorubicin | 2.8 (2.6-4.9) | | |

+ censored

# Overall survival

## All treated patients




| | Median OS, mo (95% CI) | HR (80% CI) | P-Value |
|---|---|---|---|
| Durvalumab + Tremelimumab | 17.4 (9.1-23.5) | 0.73 (0.54-0.99) | 0.1851 |
| Doxorubicin | 12.5 (9.6-15.6) | | |

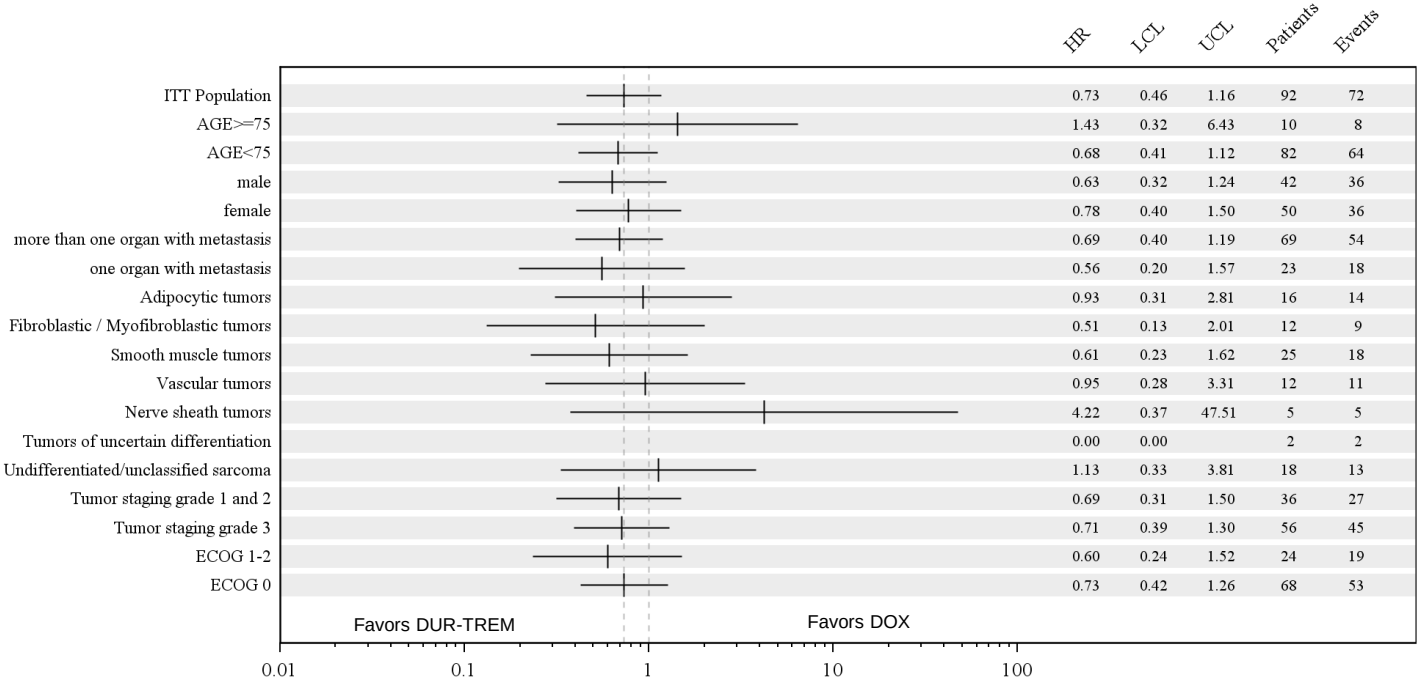
+ censored

| | | | | | | |
|---|---|---|---|---|---|---|
| DUR-TREM | 53 | 37 | 28 | 21 | 15 | 5 |
| DOX | 39 | 29 | 20 | 13 | 11 | 3 |

Median Follow-up:
DUR-TREM: 34.0 mo. (25.6-42.2)
DOX: 37.9 mo. (31.5-37.9)

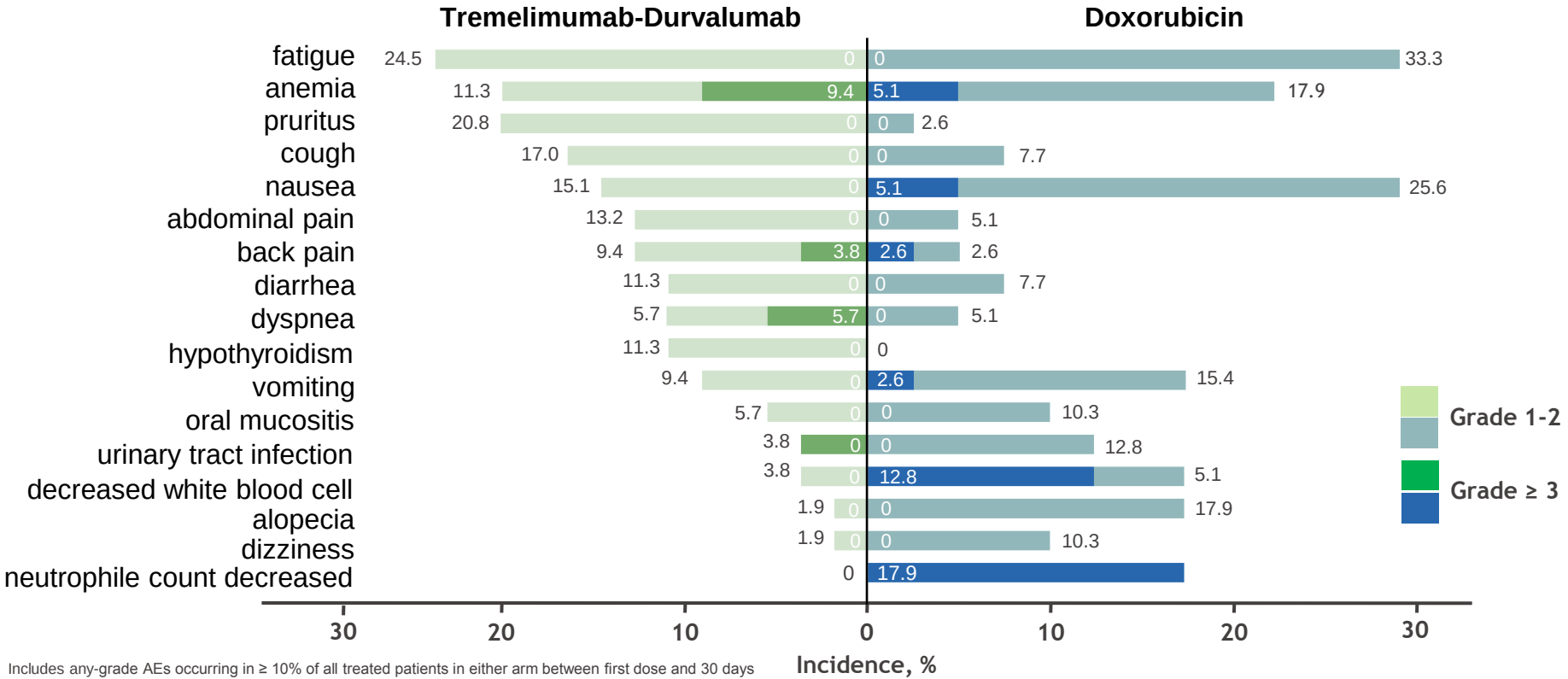
# Forrest plot

## Overall survival for different patient subgroups




HR: hazard ratio. UCL/LCL: upper/lower confidence limit

# Adverse events of any grade




Includes any-grade AEs occurring in ≥ 10% of all treated patients in either arm between first dose and 30 days after the last dose of study drug.

# Safety parameters

| | DUR-TREM (n=53) n (%) | DOX (n=39) n (%) |
|---|---|---|
| **Any grade AE** | 48 (90.6) | 35 (89.7) |
| **AE grade ≥3** | 28 (52.8) | 16 (41.0) |
| **Any SAE** | 18 (34.0) | 7 (17.9) |
| **Dose reduction** | 0 (0) | 6 (15.4) |
| **Therapy discontinuation** | 1 (2.1) | 1 (4.0) |
| **Median duration of treatment, mo (range)** | 2.8 (0-13) | 2.1 (0-4) |

The most common serious adverse events for durvalumab + tremelimumab were febrile infection and pneumonitis, both occurred twice in one patient (1.9%), respectively. For doxorubicin, some of the serious adverse events comprised constipation, back pain, pneumonia or neutrophil count decreased, all were reported only once in a singular patient (2.6%).

# Adverse events of special interest (AESI)

| | DUR-TREM (n=53) n (%) | DOX (n=39) n (%) |
|---|---|---|
| **Any grade AESI** | 18 (34.0) | 0 |
| **AESI grade ≥3** | 6 (11.3) | 0 |
| Hypothyroidism | 5 (9.4) | 0 |
| Hyperthyroidism | 4 (7.5) | 0 |
| Exanthema | 2 (3.8) | 0 |
| Dermatitis | 1 (1.9) | 0 |
| Erythema | 1 (1.9) | 0 |
| Rash | 1 (1.9) | 0 |
| Rash maculo-papular | 1 (1.9) | 0 |
| Colitis | 1 (1.9) | 0 |
| Diarrhea | 1 (1.9) | 0 |
| Pancreatitis | 1 (1.9) | 0 |
| Pneumonitis | 2 (3.8) | 0 |
| Immune hemolytic anemia | 1 (1.9) | 0 |
| Myocarditis | 1 (1.9) | 0 |
| Hepatitis | 1 (1.9) | 0 |
| Sarcoidosis | 1 (1.9) | 0 |
| Myositis | 1 (1.9) | 0 |

# Conclusions

- MEDISARC is the first study to compare immune-checkpoint-inhibitor (ICI) therapy with doxorubicin in treatment-naive sarcoma patients
- The major limitation of the study is its enrichment for chemo-sensitive soft tissue sarcoma entities
- Efficacy and safety of durvalumab + tremelimumab were comparable to that of single-agent doxorubicin
  - ORR: 9.4 vs. 12.8%; median PFS: 2.7 vs 2.8 mo. (HR 1.22; CI80%: 0.90-1.64)
  - any grade AE: 90.6% vs. 89.7%
- Overall survival showed a trend in favor of durvalumab + tremelimumab, but did not reach significance
  - Median OS 17.4 vs. 12.5 mo. (HR 0.73; CI95%: 0.54-0.99)
- Our data is encouraging and suggests further exploration of ICI-based regimen in STS

# Acknowledgements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- the academic research teams

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All authors contributed to and approved the presentation