Supplementary Online Content

Tap WD, Wagner AJ, Schöffski P, et al; ANNOUNCE investigators. Effect of doxorubicin plus olaratumab vs doxorubicin plus placebo on survival in patients with advanced soft tissue sarcomas: the ANNOUNCE randomized clinical trial. *JAMA*. doi:10.1001/jama.2020.1707

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. List of Prespecified Secondary Endpoints

Secondary Endpoint
Progression-free survival
Objective response rate (complete response + partial response)
Disease control rate (complete response + partial response + stable disease)
Patient-reported outcomes assessed by 3 scales European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 version 3.0 (EORTC-QLQ-C30) Brief Pain Inventory Short Form Modified (mBPI-sf) EQ-5D-5L
Duration of disease control
Safety and tolerability
Pharmacokinetics
Immunogenicity

eTable 2. List of Prespecified Subgroups for Overall Survival Analysis

OS and PFS HR for treatment effect (with 95% CI) will be estimated using an unstratified Cox PH model for each of the following subgroups (defined based on eCRF data):

- number of prior systemic therapies for advanced/metastatic disease (0 vs ≥1)
- prior systemic treatment in the neo-adjuvant or adjuvant setting (yes vs no)
- Histology (LMS vs LPS vs undifferentiated pleomorphic sarcoma vs other STS subtypes)
- LMS primary site (uterine vs non-uterine)
- ECOG performance status (0 vs 1)
- region (North America vs Europe vs ROW)
- disease stage at randomization (metastatic disease vs only locally advanced disease)
- liver lesions (presence at baseline vs absence at baseline)
- lung lesions (presence at baseline vs absence at baseline)
- sex (females vs males)
- age (<65 years vs ≥65 years)
- weight (above and below median)
- duration of disease since diagnosis (above and below median)
- grade of STS at diagnosis (1/low vs 2/intermediate vs 3/high)
- albumin level (above and below 35 g/dL)
- ALT (above and below median)
- bone lesions (presence at baseline vs absence at baseline)
- prior radiation therapy (none vs any)
- duration of most recent prior systemic therapy (above and below median)
- hemoglobin (above and below median)
- platelets (above and below 350 µliters)
- leukocytes (above and below 10,000 µliters)
- PDGFRα status (positive and negative)

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; HR, hazard ratio; LMS, leiomyosarcoma; LPS, liposarcoma; OS, overall survival; PFS, progression-free survival; PDGFR, platelet-derived growth factor; PH, proportional hazards; ROW, rest of world; STS, soft tissue sarcoma.

eTable 3. Baseline Pathological Diagnosis and Histopathological Grade

Initial Pathological Diagnosis, n (%)	Doxorubicin + Olaratumab (N = 258)	Doxorubicin + Placebo (N = 251)
Adipocytic tumors	48 (18.6)	43 (17.1)
Dedifferentiated liposarcoma	24 (9.3)	17 (6.8)
Liposarcoma NOS	4 (1.6)	1 (0.4)
Myxoid liposarcoma	10 (3.9)	11 (4.4)
Pleomorphic liposarcoma	3 (1.2)	3 (1.2)
Well differentiated liposarcoma	7 (2.7)	11 (4.4)
Fibroblastic/myofibroblastic tumors	14 (5.4)	18 (7.2)
Fibrosarcoma	4 (1.6)	6 (2.4)
Low-grade fibromyxoid sarcoma	1 (0.4)	0 (0.0)
Malignant solitary fibrous tumor	5 (1.9)	4 (1.6)
Myxofibrosarcoma	4 (1.6)	8 (3.2)
Fibrohistiocytic tumor and undifferentitiated/unclassified sarcoma	34 (13.2)	30 (12.0)
Undifferentiated epithelioid sarcoma	2 (0.8)	1 (0.4)
Undifferentiated pleomorphic sarcoma	21 (8.1)	19 (7.6)
Undifferentiated sarcoma NOS	4 (1.6)	3 (1.2)
Undifferentiated spindle cell sarcoma	7 (2.7)	7 (2.8)
Nerve sheath tumors and tumors of uncertain differentiation	20 (7.8)	21 (8.4)
Alveolar soft-part sarcoma	1 (0.4)	0 (0.0)
Clear cell sarcoma of soft tissue	3 (1.2)	2 (0.8)
Epithelioid malignant nerve sheath tumor	1 (0.4)	0 (0.0)
Epithelioid sarcoma	2 (0.8)	1 (0.4)
Extraskeletal myxoid chondrosarcoma	2 (0.8)	0 (0.0)
Malignant peripheral nerve sheath tumor	6 (2.3)	9 (3.6)
Pecoma NOS, malignant	0 (0.0)	1 (0.4)
Synovial cell sarcoma	5 (1.9)	8 (3.2)
Skeletal-muscle tumors	4 (1.6)	5 (2.0)
Pleomorphic rhabdomyosarcoma	3 (1.2)	1 (0.4)
Spindle cell/sclerosing rhabdomyosarcoma	1 (0.4)	4 (1.6)
Smooth-muscle tumors	119 (46.1)	115 (45.8)
Leiomyosarcoma	119 (46.1)	115 (45.8)
Uterine	46 (38.7)	48 (41.7)
Non-uterine	73 (61.3)	67 (58.3)
Vascular and pericytic (perivascular) tumors	10 (3.9)	12 (4.8)
Angiosarcoma of soft tissue	10 (3.9)	9 (3.6)
Epithelioid hemangioendothelioma	0 (0.0)	3 (1.2)
Lymphoma[a]	1 (0.4)	0 (0.0)

eTable 3. Baseline Pathological Diagnosis and Histopathological Grade (continued)

Initial Pathological Diagnosis, n (%)	Doxorubicin + Olaratumab (N = 258)	Doxorubicin + Placebo (N = 251)
Other	9 (3.5)	7 (2.8)
Clear cell sarcoma of soft tissue	1 (0.4)	0 (0.0)
Endometrial stromal sarcoma	4 (1.6)	1 (0.4)
Giant cell tumor of tendon sheath	0 (0.0)	1 (0.4)
Hemangiopericytoma	0 (0.0)	1 (0.4)
Neurofibrosarcoma	0 (0.0)	1 (0.4)
Phyllodes tumor	1 (0.4)	0 (0.0)
Soft tissue sarcoma	2 (0.8)	2 (0.8)
Undifferentiated sarcoma	0 (0.0)	1 (0.4)
Histopathological Diagnosis Grade, n (%)		
Low grade	16 (6.2)	28 (11.2)
Intermediated grade	60 (23.3)	47 (18.7)
High grade	130 (50.4)	128 (51.0)
Uninterpretable	48 (18.6)	45 (17.9)
Not done	4 (1.6)	3 (1.2)

[a]Lymphoma is not a subtype of soft tissue sarcoma. Enrollment of this patient was a protocol violation.
Abbreviation: NOS, not otherwise specified.

eTable 4. Best Overall Response in the Total Soft Tissue Sarcoma Population

	Doxorubicin + Olaratumab		Doxorubicin + Placebo			
	n (%)	**95% CI**	**n (%)**	**95% CI**	**OR (95% CI)**	**p-value**
Best overall response						
Complete response (CR)	2 (0.8)	0.0–1.8	1 (0.4)	0.0–1.2	—	—
Partial response (PR)	34 (13.2)	9.1–17.3	45 (17.9)	13.2–22.7	—	—
Stable disease (SD)	138 (53.5)	47.4–59.6	144 (57.4)	51.3–63.5	—	—
Progressive disease (PD)	70 (27.1)	21.7–32.6	52 (20.7)	15.7–25.7	—	—
Non-evaluable	14 (5.4)	2.7–8.2	9 (3.6)	1.3–5.9	—	—
Overall response rate (CR/PR)	36 (14.0)	9.7–18.2	46 (18.3)	13.5–23.1	0.7 (0.4–1.2)	0.1837
Disease control rate (CR/PR/SD)	174 (67.4)	61.7–73.2	190 (75.7)	70.4–81.0	0.7 (0.5–1.0)	0.0595

Abbreviation: OR, odds ratio.

eTable 5. Best Overall Response in the Leiomyosarcoma Population

	Doxorubicin + Olaratumab		Doxorubicin + Placebo			
	n (%)	**95% CI**	**n (%)**	**95% CI**	**OR (95% CI)**	**p-value**
Best overall response						
Complete response (CR)	1 (0.8)	(0.0–2.5)	0 (0)	(N/A)	—	—
Partial response (PR)	15 (12.6)	(6.6–18.6)	26 (22.6)	(15.0–30.3)	—	—
Stable disease (SD)	59 (49.6)	(40.6–58.6)	69 (60.0)	(51.0–69.0)	—	—
Progressive disease (PD)	40 (33.6)	(25.1–42.1)	17 (14.8)	(8.3–21.3)	—	—
Non-evaluable	4 (3.4)	(0.1–6.6)	3 (2.6)	(0.0–5.5)	—	—
Overall response rate (CR/PR)	16 (13.4)	(7.3–19.6)	26 (22.6)	(15.0–30.3)	0.5 (0.3–1.1)	0.0890
Disease control rate (CR/PR/SD)	75 (63.0)	(54.4–71.7)	95 (82.6)	(75.7–89.5)	0.4 (0.2–0.7)	0.0011

Abbreviation: OR, odds ratio.

eTable 6. Post-discontinuation Therapy in the Total Soft Tissue Sarcoma Population

Post-discontinuation therapy, n (%)	Doxorubicin + Olaratumab (N = 258)	Doxorubicin + Placebo (N = 251)
Surgical procedure	32 (12.4)	28 (11.2)
Radiotherapy	39 (15.1)	70 (27.9)
Systemic therapy		
Overall	178 (69.0)	169 (67.3)
Anastrozole	0 (0.0)	1 (0.4)
Anlotinib	1 (0.4)	0 (0.0)
Bevacizumab	0 (0.0)	1 (0.4)
Brentuximab Vedotin	1 (0.4)	0 (0.0)
Cabozantinib	1 (0.4)	0 (0.0)
Carboplatin	2 (0.8)	1 (0.4)
Chemotherapeutics	1 (0.4)	0 (0.0)
Cisplatin	6 (2.3)	4 (1.6)
Cyclophosphamide	10 (3.9)	8 (3.2)
Dacarbazine	31 (12.0)	35 (13.9)
Denosumab	2 (0.8)	2 (0.8)
Dexamethasone	0 (0.0)	2 (0.8)
Dexrazoxane	1 (0.4)	0 (0.0)
Docetaxel	40 (15.5)	48 (19.1)
Docetaxel plus gemcitabine	0 (0.0)	1 (0.4)
Doxorubicin	10 (3.9)	17 (6.8)
Durvalumab	1 (0.4)	1 (0.4)
Efatutazone	0 (0.0)	1 (0.4)
Epirubicin	0 (0.0)	1 (0.4)
Eribulin	18 (7.0)	24 (9.6)
Etoposide	7 (2.7)	10 (4.0)
Everolimus	2 (0.8)	1 (0.4)
Faz 053	1 (0.4)	0 (0.0)
Gemcitabine	72 (27.9)	82 (32.7)
Ifosfamide	25 (9.7)	26 (10.4)
Investigational Drug	8 (3.1)	6 (2.4)
Ipilimumab	3 (1.2)	2 (0.8)

eTable 6. Post-discontinuation Therapy in the Total Soft Tissue Sarcoma Population (continued)

Post-discontinuation therapy, n (%)	Doxorubicin + Olaratumab (N = 258)	Doxorubicin + Placebo (N = 251)
Irinotecan	2 (0.8)	0 (0.0)
Liposomal Doxorubicin	1 (0.4)	0 (0.0)
Lurbinectedin	2 (0.8)	0 (0.0)
Megestrol	0 (0.0)	1 (0.4)
Mesna	4 (1.6)	4 (1.6)
Mitomycin	1 (0.4)	0 (0.0)
Naloxegol	0 (0.0)	1 (0.4)
Nintedanib	1 (0.4)	1 (0.4)
Nivolumab	8 (3.1)	4 (1.6)
Olaparib	1 (0.4)	0 (0.0)
Olaratumab	1 (0.4)	1 (0.4)
Paclitaxel	8 (3.1)	5 (2.0)
Palbociclib	1 (0.4)	1 (0.4)
Pazopanib	55 (21.3)	57 (22.7)
Pembrolizumab	4 (1.6)	4 (1.6)
Placebo	0 (0.0)	1 (0.4)
Prasterone	0 (0.0)	1 (0.4)
Prednisolone	1 (0.4)	0 (0.0)
Ribociclib	1 (0.4)	0 (0.0)
Selinexor	0 (0.0)	2 (0.8)
Sirolimus	0 (0.0)	1 (0.4)
Sunitinib	4 (1.6)	1 (0.4)
Temozolomide	2 (0.8)	0 (0.0)
Topotecan	1 (0.4)	2 (0.8)
Trabectedin	65 (25.2)	67 (26.7)
Trofosfamide	0 (0.0)	1 (0.4)
Vincristine	1 (0.4)	2 (0.8)
Vinorelbine	0 (0.0)	1 (0.4)
Vorinostat	0 (0.0)	2 (0.8)
Zoledronic Acid	2 (0.8)	1 (0.4)

eTable 7. Overall Survival by Treatment and PDGFR Status (Positive/Negative) in the Total Soft Tissue Sarcoma Population

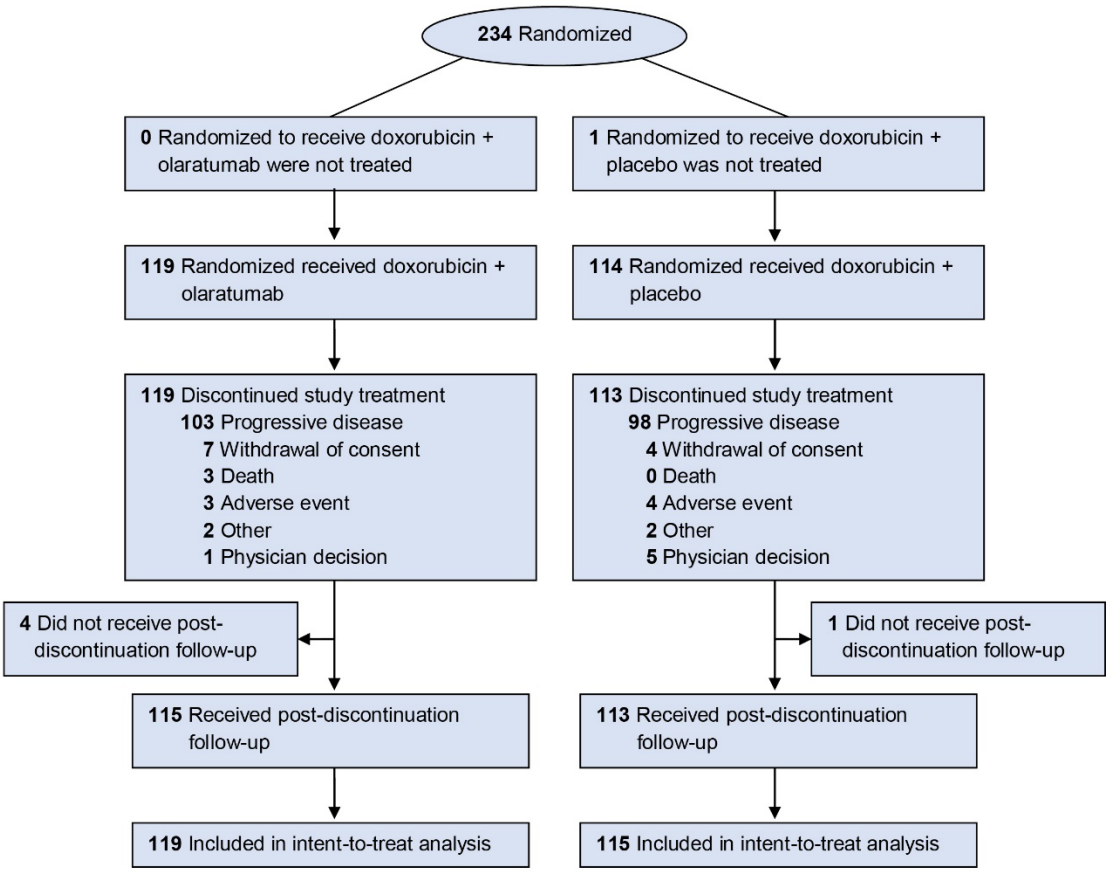
PDGFR IHC Status[b] (+ or –)	N	Doxorubicin + Olaratumab[a] mOS, months	n	Doxorubicin + Placebo[a] mOS, months	n	Stratified HR (95% CI)
PDGFR-α (+)	267	17.2	133	19.1	134	1.09 (0.81–1.47)
PDGFR-α (–)	195	23.6	95	21.9	100	0.93 (0.65–1.34)
PDGFR-β (+)	323	18.8	163	19.9	160	1.10 (0.84–1.44)
PDGFR-β (–)	141	28.3	66	20.6	75	0.85 (0.54–1.33)
PDGFR-α (–) and PDGFR-β (–)	97	28.5	43	20.6	54	0.79 (0.46–1.37)
PDGFR-α (–) and PDGFR-β (+)	97	20.8	51	22.9	46	1.07 (0.65–1.75)
PDGFR-α (+) and PDGFR-β (–)	42	14.4	22	19.5	20	1.03 (0.45–2.36)
PDGFR-α (+) and PDGFR-β (+)	222	17.2	110	19.1	112	1.11 (0.81–1.54)

Abbreviations: +, positive; –, negative; HR, hazard ratio; IHC, immunohistochemistry; mOS, median overall survival; N, total number of patients from both treatment groups; n, number of patients within treatment group; PDGFR, platelet-derived growth factor receptor. [a]The number of patients included in the prespecified PDGFR-α analysis were 228 (olaratumab) and 234 (placebo). The number of patients included in the post hoc PDGFR-β analysis were 229 (olaratumab) and 235 (placebo).[b]PDGFR-α tumor status was determined with a rabbit monoclonal antibody (Cell Signaling Technology clone D13C6) specific for PDGFR-α without cross-reactivity to PDGFR-β. PDGFR-β tumor status was determined with a mouse monoclonal antibody (Cell Signaling Technology clone 2B3) proven to be specific for PDGFR-β with no cross-reactivity for PDGFR-α. The status for PDGFR-α and PDGFR-β was provided as a dichotomous variable with “positive” and “negative” expression, where a “positive” result showed ≥10% of the tumor as demonstrating at least weak but specific membranous expression (1+ on a 0, 1+, 2+, 3+ scale of staining intensity). “Negative” corresponded to expression that did not meet these criteria.

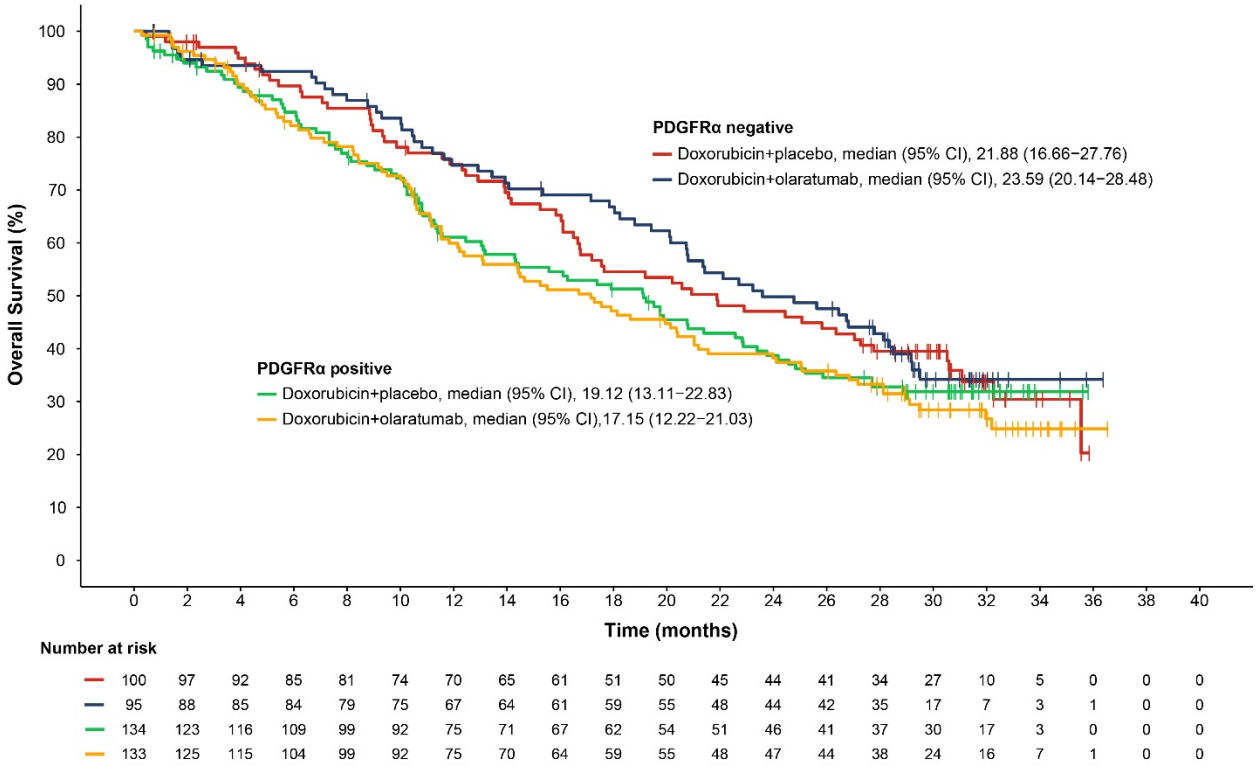
eTable 8. Summary of Abnormal Left Ventricular Ejection Fraction Results Over Time

	Doxorubicin + Olaratumab (N = 257)	Doxorubicin + Placebo (N = 249)
Baseline, n	254	244
<50%, n (%)	0 (0.0)	0 (0.0)
Prior to Cycle 5, n	105	96
<50%, n (%)	0 (0.0)	3 (3.1)
>10% decrease in LVEF over baseline, n (%)	22 (21.0)	22 (22.9)
<50% absolute value and/or >10% decrease in LVEF over baseline, n (%)	22 (21.0)	22 (22.9)
Prior to Cycle 7, n	78	75
<50%, n (%)	3 (3.8)	3 (4.0)
>10% decrease in LVEF over baseline, n (%)	21 (26.9)	15 (20.0)
<50% absolute value and/or >10% decrease in LVEF over baseline, n (%)	21 (26.9)	15 (20.0)
Prior to Cycle 9, n	71	87
<50%, n (%)	3 (4.2)	4 (4.6)
>10% decrease in LVEF over baseline, n (%)	24 (33.8)	25 (28.7)
<50% absolute value and/or >10% decrease in LVEF over baseline, n (%)	24 (33.8)	25 (28.7)
Any time on or after Cycle 9, n	179	171
<50%, n (%)	20 (11.2)	20 (11.7)
>10% decrease in LVEF over baseline, n (%)	79 (44.1)	77 (45.0)
<50% absolute value and/or >10% decrease in LVEF over baseline, n (%)	81 (45.3)	78 (45.6)
Lowest post-baseline, n	200	201
<50%, n (%)	23 (11.5)	25 (12.4)
>10% decrease in LVEF over baseline, n (%)	94 (47.0)	97 (48.3)
<50% absolute value and/or >10% decrease in LVEF over baseline, n (%)	96 (48.0)	98 (48.8)

Abbreviation: LVEF, left ventricular ejection fraction.



eFigure 1. Flow of Patient Disposition in the Leiomyosarcoma Population



eFigure 2. Overall Survival by PDGFRα IHC Status (Positive or Negative) in the Total Soft Tissue Sarcoma Population. Tick marks on curves denote censored observations. Abbreviations: IHC, immunohistochemistry; PDGFR, platelet-derived growth factor receptor.