Pilot study of NKTR-214 plus nivolumab in patients with metastatic high grade sarcomas

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Background

On-going need for more durable, effective and less toxic therapies

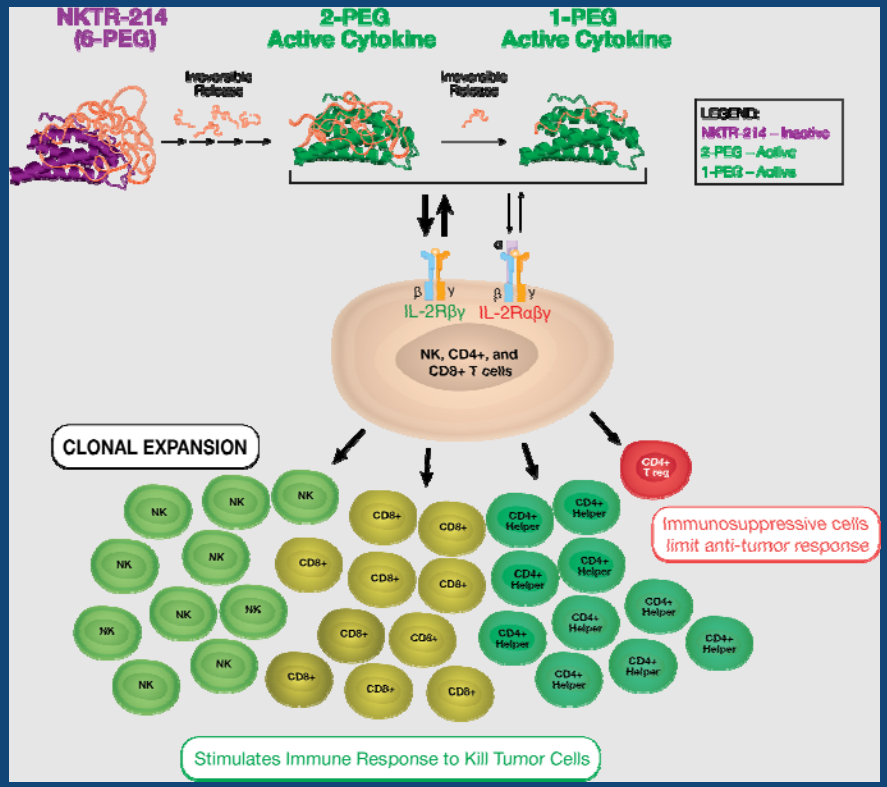
Immuno-oncology remains a promising approach

Checkpoint inhibitors have demonstrated modest efficacy in certain sarcoma histological subtypes[1]

NKTR-214 + nivolumab is tolerable, safe and efficacious in multiple malignancies[2]

1. Tawbi H et al. Lancet Oncology 2017, D'Angelo et al. Lancet Oncology 2018, Wilkey B et al. Lancet Oncology 2019
2. Diab et al. SITC 2018, Siefker-Radtke et al. ASCO GU 2019, Hurwitz et al. ASCO 2019

NKTR-214

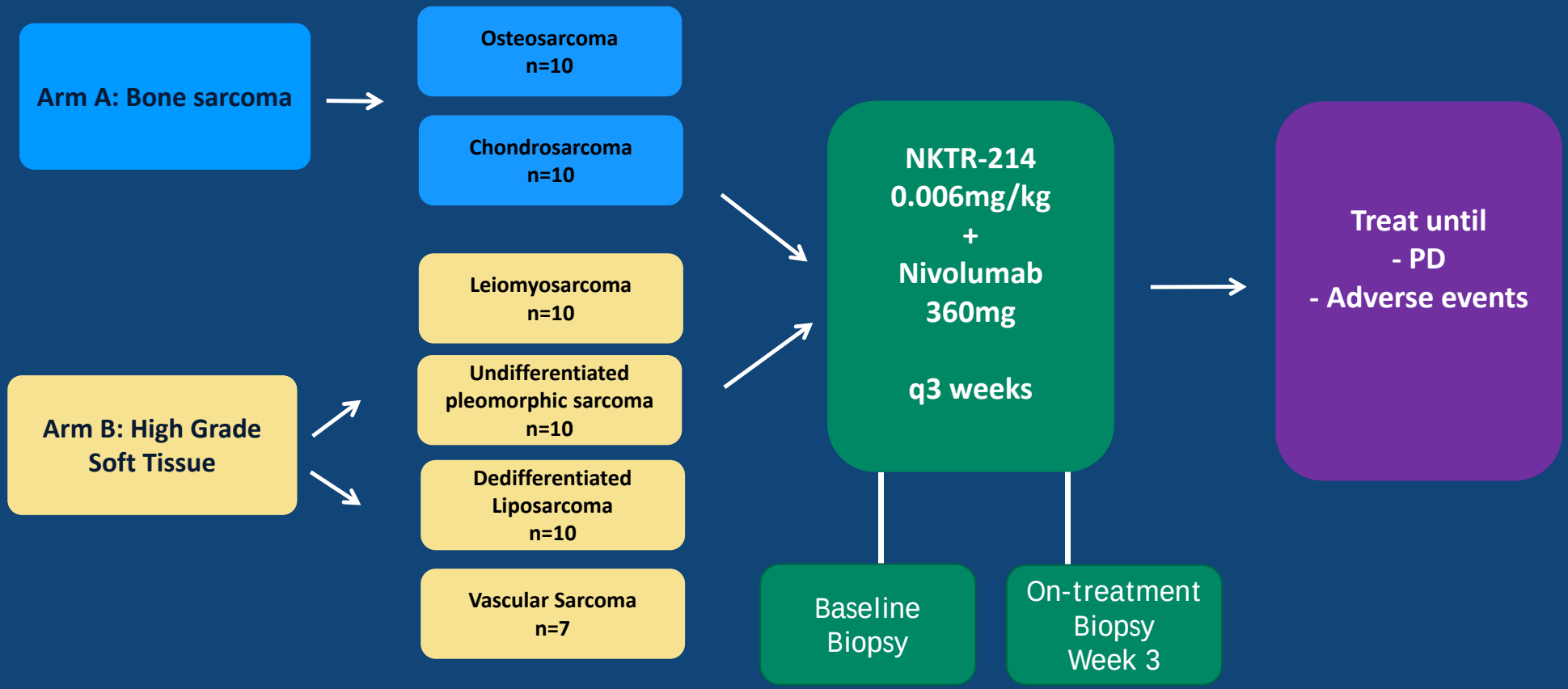


First in class CD122-preferential IL-2 pathway agonist

Prodrug design favors signaling towards the CD122 receptor (IL-2Rβγ complex)

Activates and expands natural killer and CD8+ T cells

Study Design: NKTR-214 + nivolumab in metastatic, high grade sarcomas



Study Objectives

Primary objective

- To evaluate the confirmed response rate within each specific histologic cohort

Secondary objectives

- To evaluate adverse event rates (NCI CTCAE v4.0) within each treatment arm.
- To evaluate duration of response, clinical benefit rate, progression-free survival (PFS), and overall survival (OS) within each treatment arm.

Exploratory objectives

- PD-L1 expression
- Characterization of tumor infiltrating lymphocyte by IHC
- Whole exome sequencing
- RNA seq

Statistical Plan

A sample size of 10 patients is planned for each histological cohort

If 2 or more confirmed responses are observed among the 10 patients in an arm, the drug combination will be claimed to be positive and worthy of further study

This decision rule is associated with a 9% type I error rate and 9% type II error rate

Key eligibility

Inclusion Criteria	Exclusion Criteria
Advanced or unresectable sarcoma	Active brain metastases
≥1 Prior Treatment	Autoimmune disease requiring steroids
Measurable disease by RECIST 1.1	Unstable angina
ECOG 0-1	
Age ≥ 12	

Patient characteristics

	Osteosarcoma n=10	Chondrosarcoma n=10	Leiomyosarcoma n=10	Liposarcoma n=10	Undifferentiated pleomorphic sarcoma n=10	Vascular Sarcoma n=7	Total n=57
Age (Mean, Range)	54, (14-76)	55, (35-76)	55, (48-80)	56, (40-77)	63, (55-74)	48, (27-65)	**52, (14-80)**
Male	6 (60%)	6 (60%)	2 (20%)	5 (50%)	8 (80%)	2 (28%)	**29 (51%)**
ECOG PS 0	5 (50%)	5 (50%)	7 (70%)	8 (80%)	8 (80%)	6 (85%)	**39 (68%)**
≥ 3 priors lines	6 (60%)	2 (20%)	7 (70%)	5 (50%)	5 (50%)	3 (43%)	**28 (49%)**
Avg # of Days on prior therapy	77	80	91	79	93	193	**102**

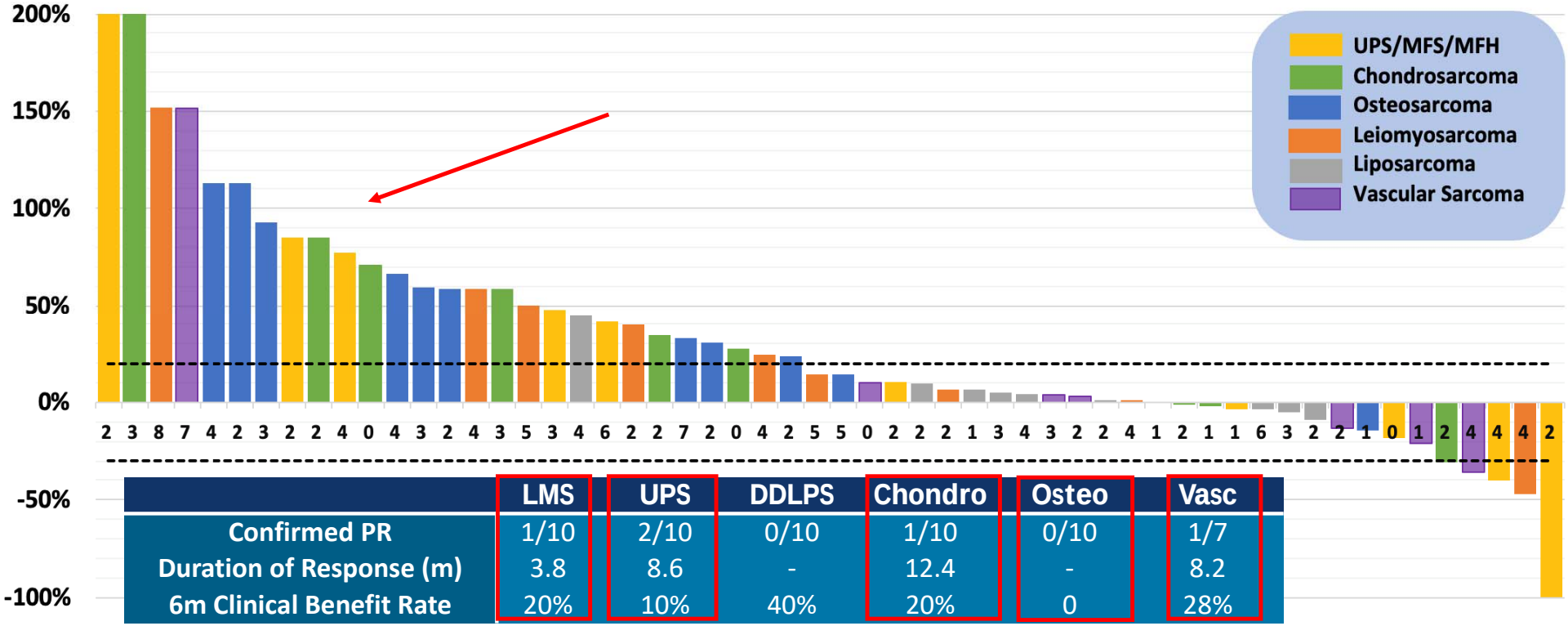
Treatment related adverse events

Treatment Related Grade 1-2 in >10%	
Flu like symptoms	40 (70.2%)
Fatigue	33 (57.9%)
Rash	29 (50.1%)
Pruritus	18 (31.6%)
Anemia	14 (24.6%)
Myalgia	14 (24.6%)
ALT increased	13 (22.8%)
Nausea	13 (22.8%)
Arthralgia	12 (21.1%)
AST increased	12 (21.1%)
Cough	8 (14.0%)
Diarrhea	8 (14.0%)
Hypotension	8 (14.0%)
Vomiting	7 (12.3%)
Anorexia	6 (10.5%)
Platelet count decreased	6 (10.5%)
Patients who discontinued due to a TRAE	**3 (5.2%)**

Treatment Related Grade 3	16 (28%)
Pneumonitis	2 (3.5%)
Hypotension	2 (3.5%)
Abdominal pain	1 (1.8%)
Acute Kidney Injury	1 (1.8%)
Anemia	1 (1.8%)
Arthritis	1 (1.8%)
AST increased	1 (1.8%)
Hypophosphatemia	1 (1.8%)
Lipase increased	1 (1.8%)
Myalgia	1 (1.8%)
Neutrophil count decreased	1 (1.8%)
Parotitis	1 (1.8%)
Serum amylase increased	1 (1.8%)
Diarrhea	1 (1.8%)

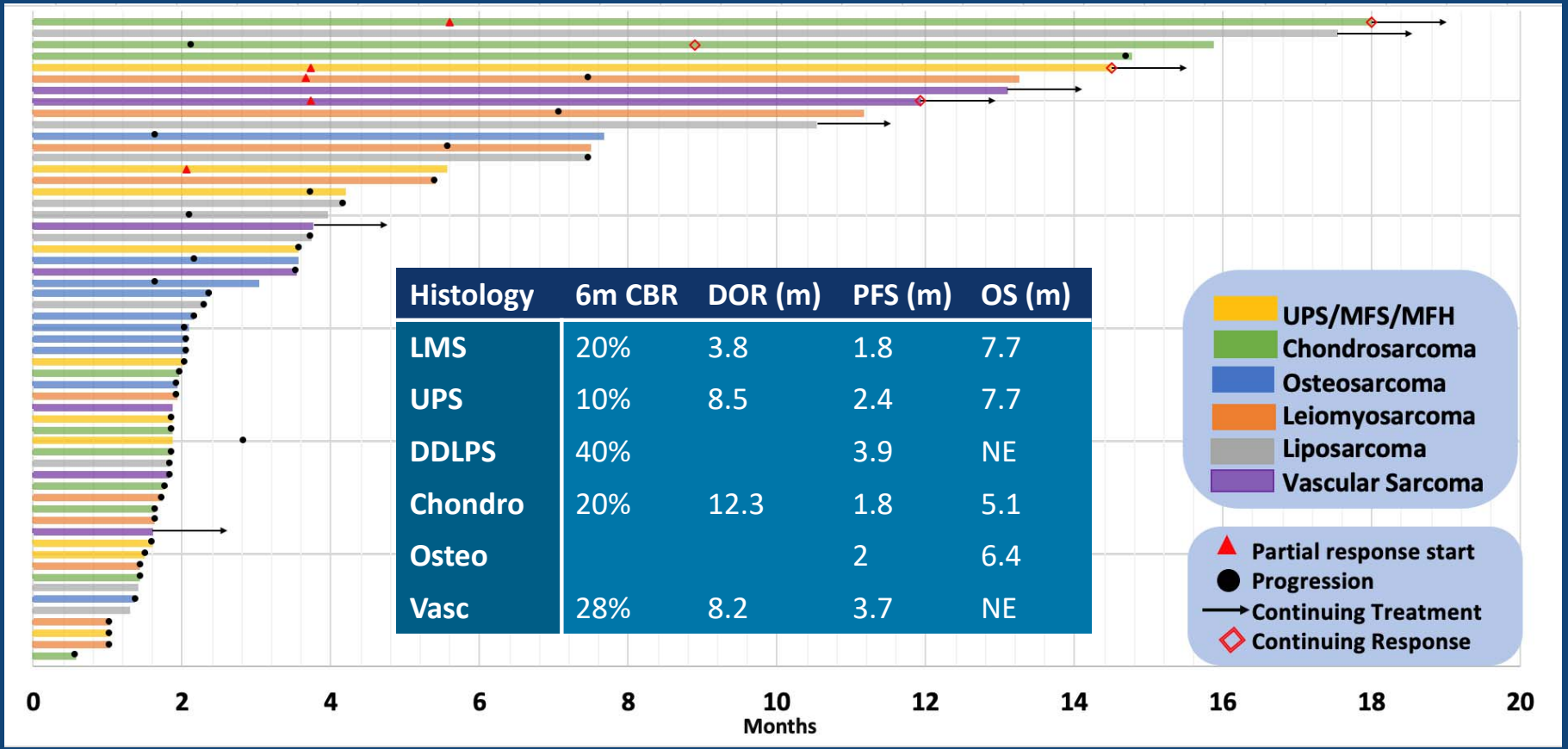
*** 1 patient with G4 respiratory failure**
*** 3 episodes G4 asymptomatic elevated amylase/lipase**

Responses in multiple subtypes



	LMS	UPS	DDLPS	Chondro	Osteo	Vasc
Confirmed PR	1/10	2/10	0/10	1/10	0/10	1/7
Duration of Response (m)	3.8	8.6	-	12.4	-	8.2
6m Clinical Benefit Rate	20%	10%	40%	20%	0	28%

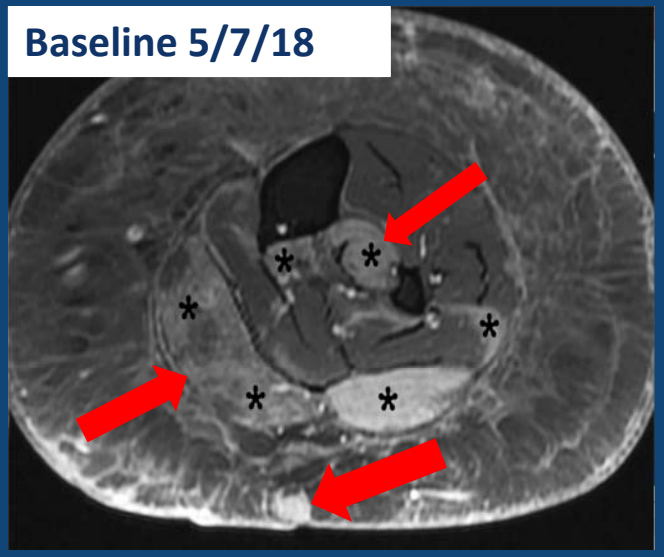
Responses were durable as well as prolonged stable disease in numerous subtypes



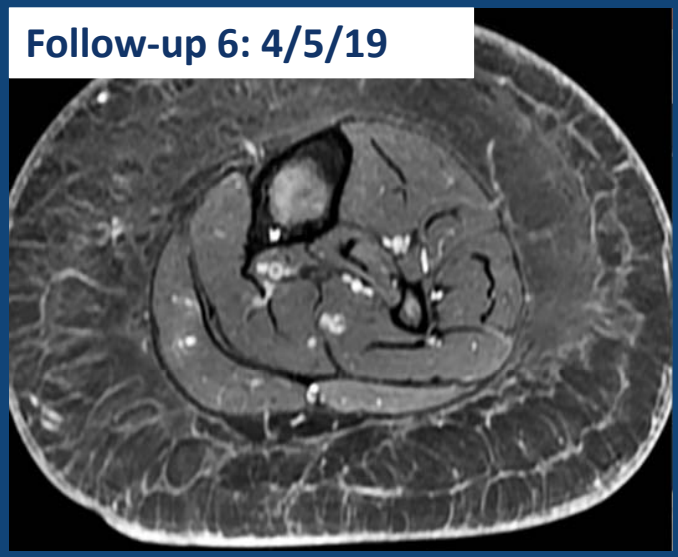
66 yo woman w Stewart Treves angiosarcoma, prior therapies included liposomal doxorubicin, paclitaxel, gemcitabine/vinorelbine, ILI TNF and pazopanib. Started on protocol 5/18/18, remains on study w PR

Baseline 5/7/18

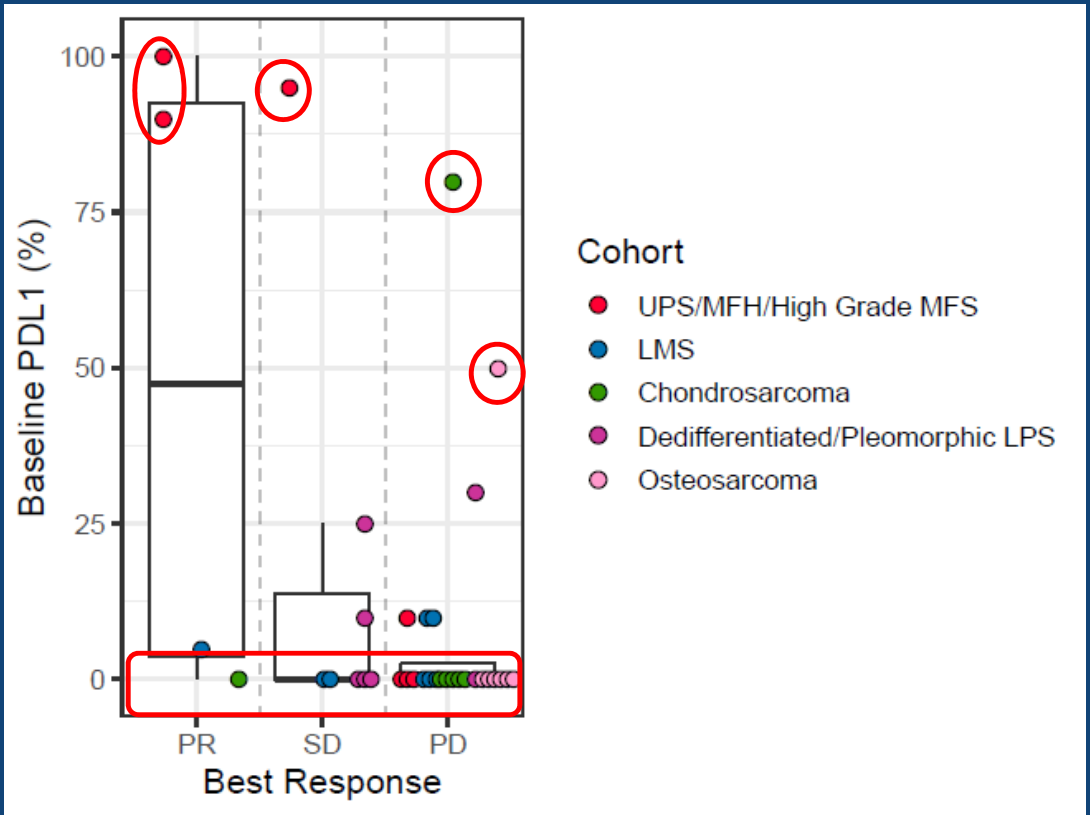
Baseline 5/7/18



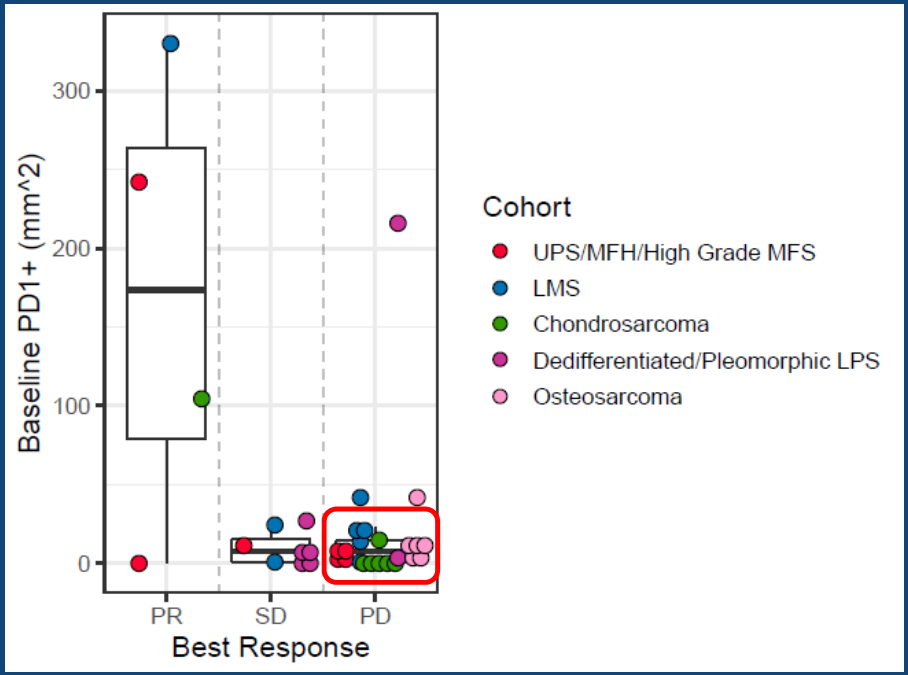
Follow-up 6: 4/5/19

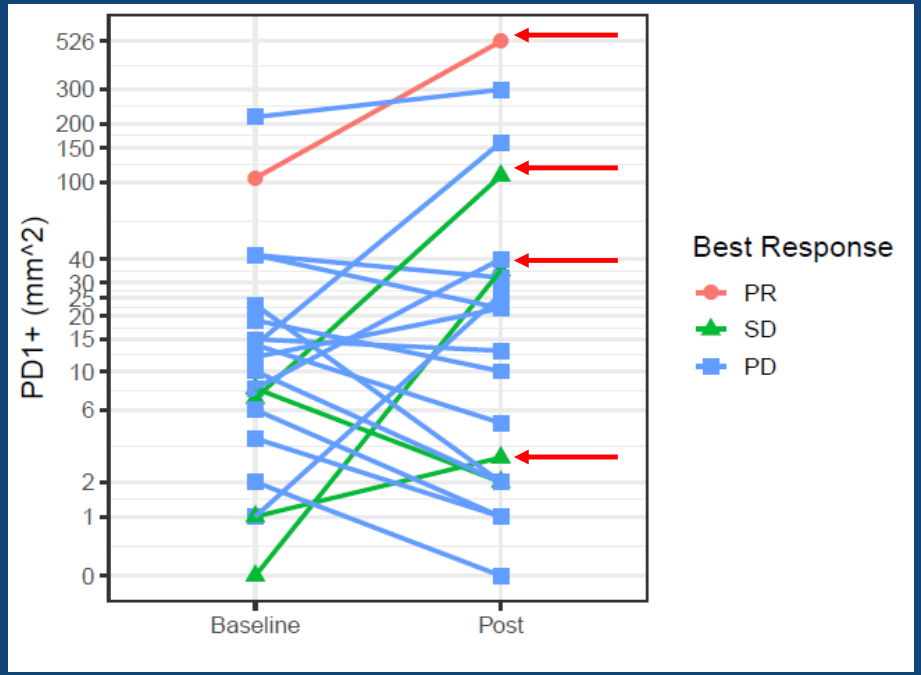


3/4 Partial responders with >5% PD-L1 expression



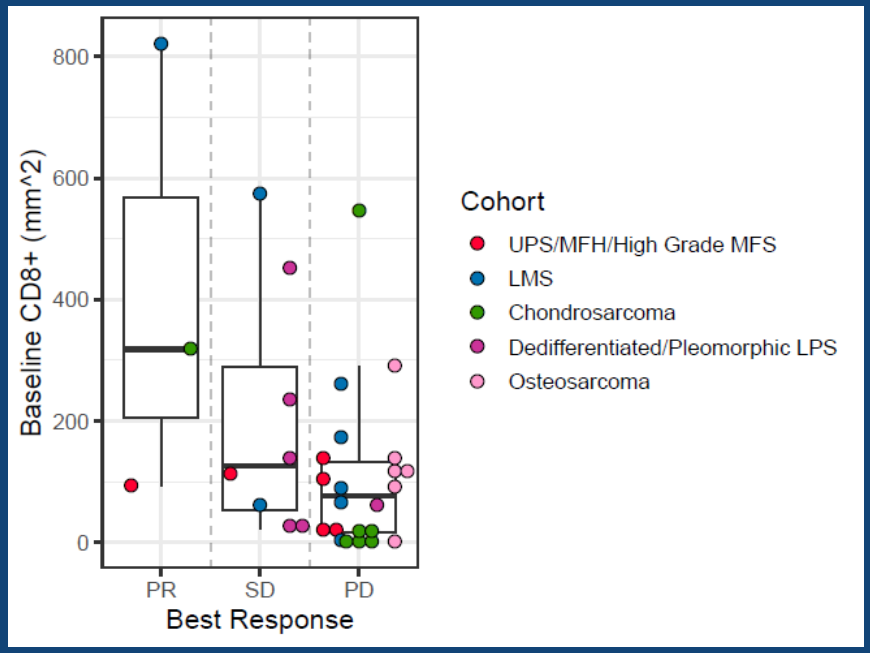
Baseline PD-1+ Cells and Increase in PD-1+ Cells Trend with Benefit



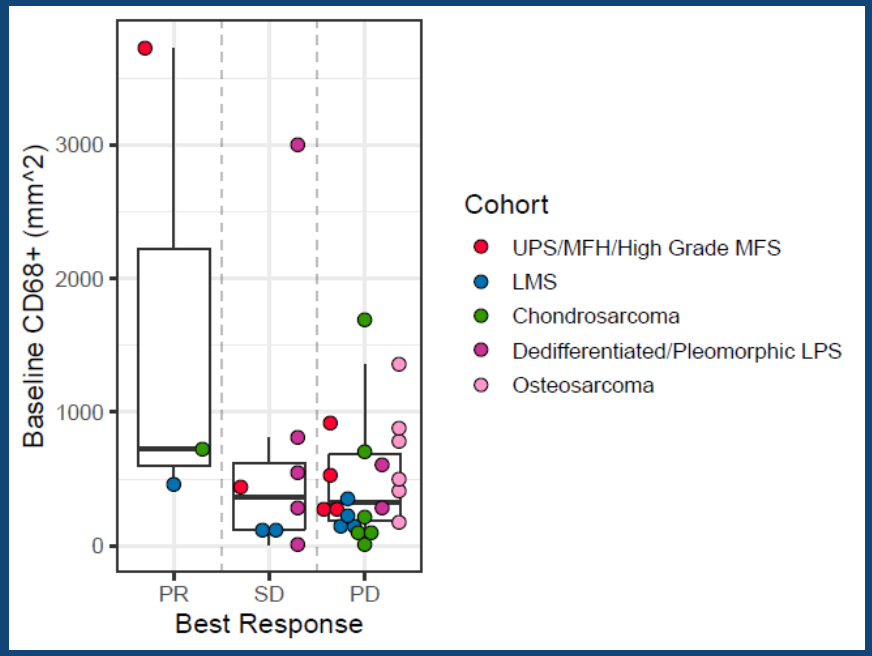


Post treatment biopsy only available for 1 PR patient

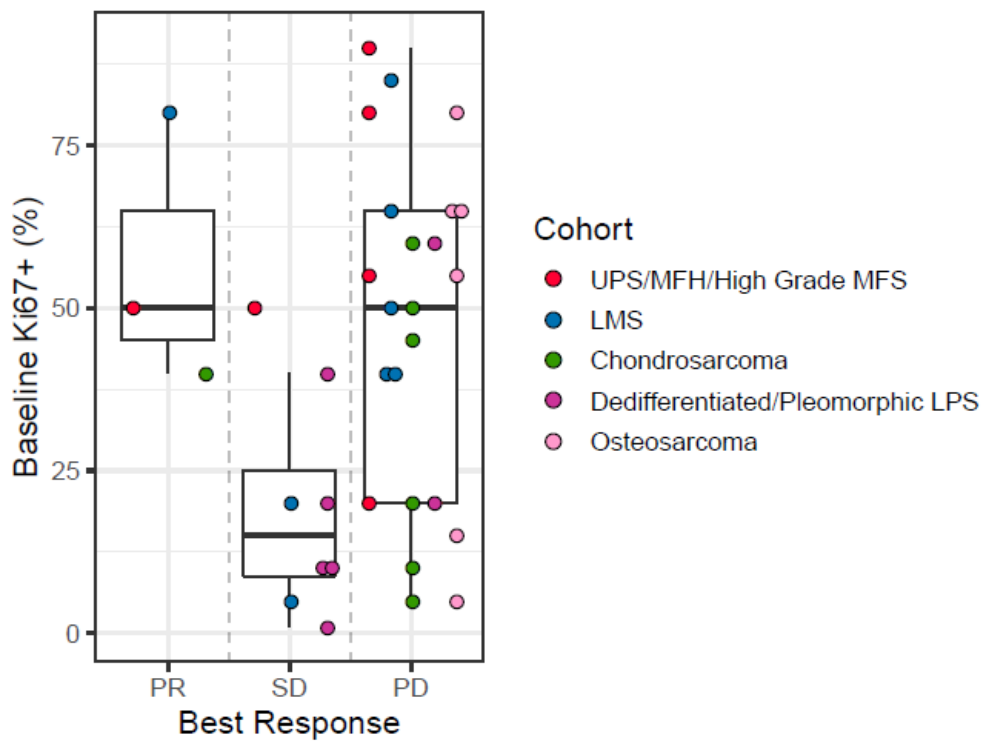
Higher baseline CD8 towards benefit



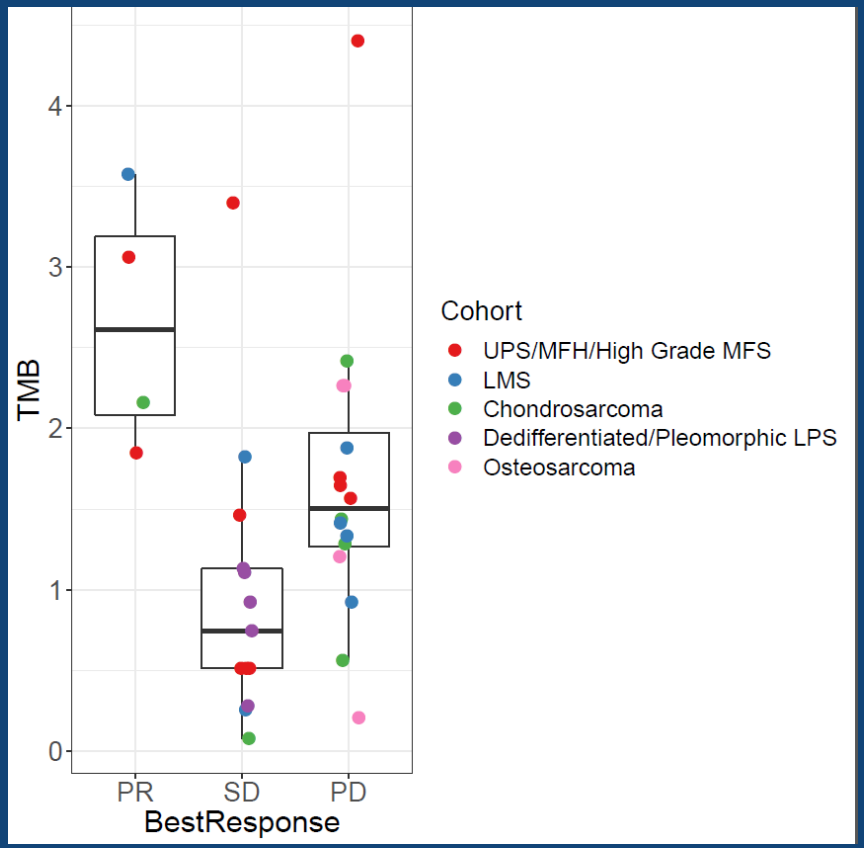
Baseline CD68 levels were markedly higher than CD8 levels



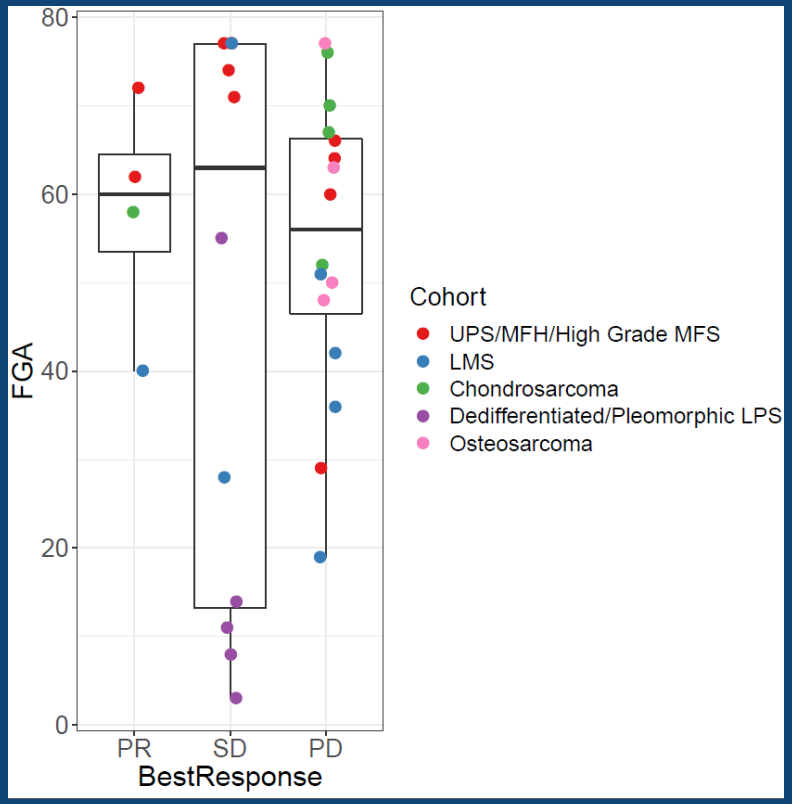
High Baseline Median Ki-67% trends towards lack of benefit



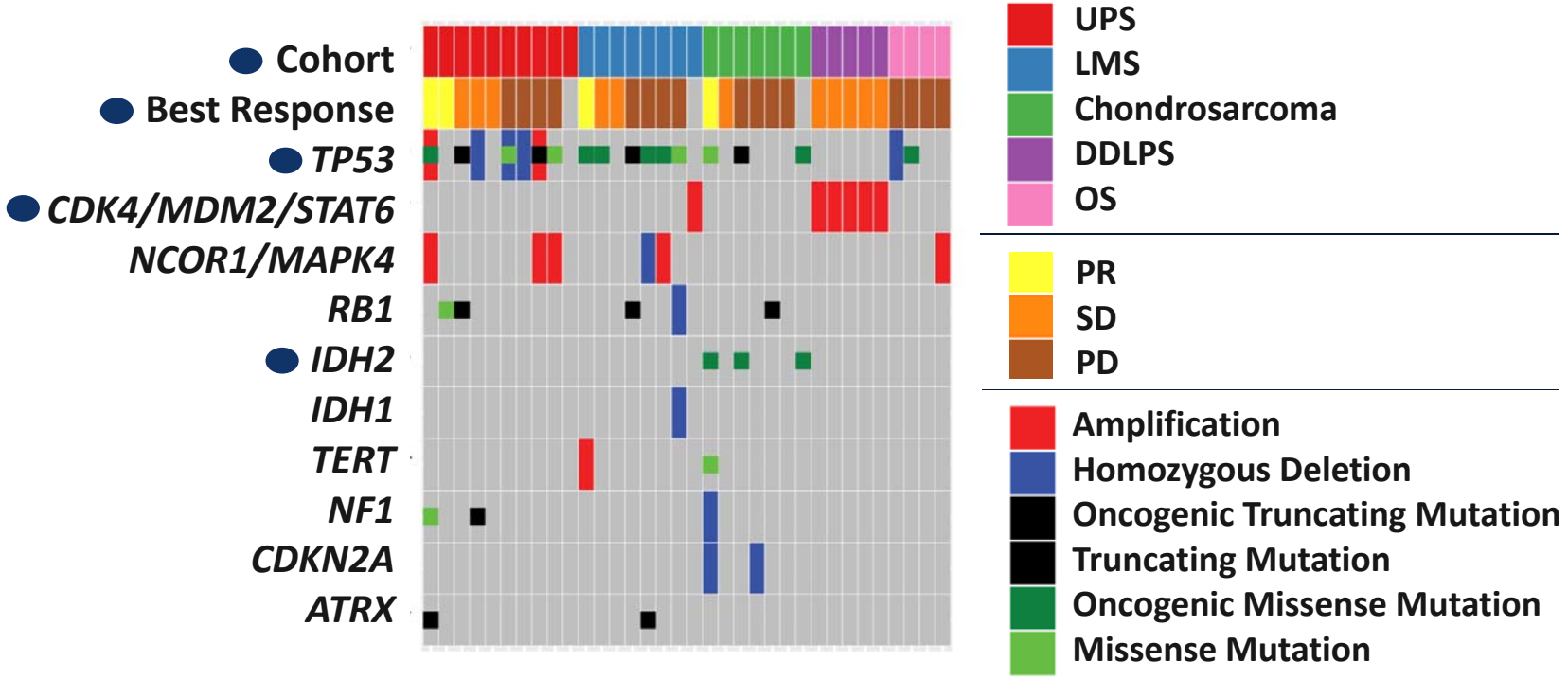
Higher TMB trend towards benefit



No difference in benefit based on fraction altered genome



Most common genomic alterations typical of sarcoma population



Conclusion

Nivolumab + NKTR-214 was safe and tolerable

Primary study endpoint met in UPS, prolonged responses in LMS, dedifferentiated chondrosarcoma, angiosarcoma, and prolonged disease stability in LPS

Trend towards improved responses in tumors with high PD1 expression, increased immune infiltrates, lower ki67 and high TMB

PD-L1 expression found in 3/4 patients with durable PR

Evidence of clinical activity in heavily pretreated, refractory patients warrants consideration of further study in a treatment naïve setting in certain subtypes

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Patients and their families

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