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

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2. MD Anderson Cancer Center
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\(^2\)

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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

Arm A: Bone sarcoma
- Osteosarcoma n=10
- Chondrosarcoma n=10

Arm B: High Grade Soft Tissue
- Leiomyosarcoma n=10
- Undifferentiated pleomorphic sarcoma n=10
- Dedifferentiated Liposarcoma n=10
- Vascular Sarcoma n=7

NKTR-214 0.006mg/kg + Nivolumab 360mg q3 weeks

Baseline Biopsy
On-treatment Biopsy Week 3

Treat until - PD - Adverse events
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

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>Advanced or unresectable sarcoma</td>
<td>Active brain metastases</td>
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<tr>
<td>≥1 Prior Treatment</td>
<td>Autoimmune disease requiring steroids</td>
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<td>Measurable disease by RECIST 1.1</td>
<td>Unstable angina</td>
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<tr>
<td>ECOG 0-1</td>
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<tr>
<td>Age ≥ 12</td>
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</table>
### Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Osteosarcoma n=10</th>
<th>Chondrosarcoma n=10</th>
<th>Leiomyosarcoma n=10</th>
<th>Liposarcoma n=10</th>
<th>Undifferentiated pleomorphic sarcoma n=10</th>
<th>Vascular Sarcoma n=7</th>
<th>Total n=57</th>
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<tbody>
<tr>
<td>Age (Mean, Range)</td>
<td>54, (14-76)</td>
<td>55, (35-76)</td>
<td>55, (48-80)</td>
<td>56, (40-77)</td>
<td>63, (55-74)</td>
<td>48, (27-65)</td>
<td>52, (14-80)</td>
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<tr>
<td>Male</td>
<td>6 (60%)</td>
<td>6 (60%)</td>
<td>2 (20%)</td>
<td>5 (50%)</td>
<td>8 (80%)</td>
<td>2 (28%)</td>
<td>29 (51%)</td>
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<tr>
<td>ECOG PS 0</td>
<td>5 (50%)</td>
<td>5 (50%)</td>
<td>7 (70%)</td>
<td>8 (80%)</td>
<td>8 (80%)</td>
<td>6 (85%)</td>
<td>39 (68%)</td>
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<tr>
<td>≥ 3 priors lines</td>
<td>6 (60%)</td>
<td>2 (20%)</td>
<td>7 (70%)</td>
<td>5 (50%)</td>
<td>5 (50%)</td>
<td>3 (43%)</td>
<td>28 (49%)</td>
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<tr>
<td>Avg # of Days on prior therapy</td>
<td>77</td>
<td>80</td>
<td>91</td>
<td>79</td>
<td>93</td>
<td>193</td>
<td>102</td>
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<tr>
<td>Treatment Related Grade 1-2 in &gt;10%</td>
<td>Treatment Related Grade 3</td>
<td>16 (28%)</td>
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<td>Flu like symptoms 40 (70.2%)</td>
<td>Pneumonitis 2 (3.5%)</td>
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<tr>
<td>Fatigue 33 (57.9%)</td>
<td>Hypotension 2 (3.5%)</td>
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<td>Rash 29 (50.1%)</td>
<td>Abdominal pain 1 (1.8%)</td>
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<td>Pruritus 18 (31.6%)</td>
<td>Acute Kidney Injury 1 (1.8%)</td>
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<td>Anemia 14 (24.6%)</td>
<td>Anemia 1 (1.8%)</td>
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<td>Myalgia 14 (24.6%)</td>
<td>Arthritis 1 (1.8%)</td>
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<td>ALT increased 13 (22.8%)</td>
<td>AST increased 1 (1.8%)</td>
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<td>Nausea 13 (22.8%)</td>
<td>Hypophosphatemia 1 (1.8%)</td>
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<td>Arthralgia 12 (21.1%)</td>
<td>Lipase increased 1 (1.8%)</td>
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<tr>
<td>AST increased 12 (21.1%)</td>
<td>Myalgia 1 (1.8%)</td>
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<td>Cough 8 (14.0%)</td>
<td>Neutrophil count decreased 1 (1.8%)</td>
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<td>Diarrhea 8 (14.0%)</td>
<td>Parotitis 1 (1.8%)</td>
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<td>Hypotension 8 (14.0%)</td>
<td>Serum amylase increased 1 (1.8%)</td>
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<td>Vomiting 7 (12.3%)</td>
<td>Diarrhea 1 (1.8%)</td>
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<td>Anorexia 6 (10.5%)</td>
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<td>Platelet count decreased 6 (10.5%)</td>
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Patients who discontinued due to a TRAE 3 (5.2%)

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

<table>
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<tr>
<th>Gene</th>
<th>UPS</th>
<th>LMS</th>
<th>Chondrosarcoma</th>
<th>DDLPS</th>
<th>OS</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
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<td>CDK4/MDM2/STAT6</td>
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<td>NCOR1/MAPK4</td>
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- Cohort
- Best Response
- TP53
- CDK4/MDM2/STAT6
- NCOR1/MAPK4
- RB1
- IDH2
- IDH1
- TERT
- NF1
- CDKN2A
- ATRX

Amplification
Homozogous Deletion
Oncogenic Truncating Mutation
Truncating Mutation
Oncogenic Missense Mutation
Missense Mutation
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
Acknowledgments

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