Anti-CTLA-4 Therapy in Prostate Cancer

NASPCC Symposium on Immuno-Oncology in Prostate Cancer: Current and Future Trends

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Disclosures

• **Consulting or Advisory Role:** Amgen, Apricity Health, AstraZeneca, Bayer, Bristol-Myers Squibb, Cancer Expert Now, Dava Oncology, Dendreon, Exelixis, Janssen Oncology, Javelin Oncology, Kahr Bio, and MD Education Limited

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• **Joint Scientific Committee:** Janssen Oncology, Polaris

• I will be discussing non-FDA approved indications during my presentation.
Immunosuppressive Cold Prostate Tumor Microenvironment

Allison JP, Sharma P and Subudhi SK
MD Anderson Cancer Center Immunotherapy Platform

Do immune checkpoint therapies work in prostate cancer?
FDA-Approved Immune Checkpoint Therapies

Pembrolizumab Induced Radiographic Responses in a Subset of Metastatic Prostate Cancer


<table>
<thead>
<tr>
<th>Response</th>
<th>PD-L1 Positive n = 133</th>
<th>PD-L1 Negative n = 66</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response (CR)</strong></td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Partial Response (PR)</strong></td>
<td>5 (4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td><strong>SD ≥ 6 months</strong></td>
<td>10 (8)</td>
<td>10 (15)</td>
</tr>
</tbody>
</table>

Ipilimumab Did Not Improve Overall Survival (OS) in Patients with Metastatic Prostate Cancer


Subset of Patients Derive Durable Benefit from Ipilimumab

Fizazi K et al., *Eur Urol*, 2020.
Can we identify the subset of patients with metastatic prostate cancer who benefit from anti-CTLA-4?
Clinical Outcomes in Patients with Metastatic Prostate Cancer After Ipilimumab

Clinical Trial Schema (NCT02113657)

Ipilimumab Enhanced T Cell Responses Against Prostate Cancer Mutant Neoantigens for Patient #7

<table>
<thead>
<tr>
<th># Somatic Mutations</th>
<th># Non-Synonymous Mutations</th>
<th># Expressed Non-Synonymous Mutations</th>
<th># Neoantigens Detected by ELISPOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>122</td>
<td>13</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Peptide Name</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>rho guanine nucleotide exchange factor 37 (WT)</td>
<td>H-GYVPSFLARARSPV LNGWSLPS-OH</td>
</tr>
<tr>
<td>rho guanine nucleotide exchange factor 37 (MUT)</td>
<td>H-GYVPSFLARAWSPV LNGWSLPS-OH</td>
</tr>
</tbody>
</table>

Transcriptional Signatures of T Cell Effector Cells/Functions were Associated with Favorable Outcomes

Increased Density of Effector T Cells was Associated with Favorable Outcomes

Conclusions

- Low TMB prostate tumors can have high density of effector T cells and/or IFN-γ response signature
- These biomarkers may select for patients benefiting from ipilimumab
- Ipilimumab enhanced systemic antigen-specific T cell responses
What prevents anti-CTLA-4 from being more effective in prostate cancer?
Anti-CTLA-4 Increased Immune Infiltration Within the Primary Prostate Tumor Microenvironment

Increased Tumor-Infiltrating T Cells were Insufficient Due to Adaptive Resistance (Upregulation of PD-L1 and VISTA)

Differentially-Expressed Genes

Total DEGs  
N = 850

Immune DEGs  
N = 41

Pre-treatment  
Post-treatment  
(Immune cells)  
(Tumor cells)

PD-L1

VISTA

Ipilimumab Increased PD-L1 Expression on CD8, CD68, and Prostate Tumor Cells

Concurrent Targeting of the CTLA-4 and PD-(L)1 Pathways Improved Survival in a Murine Model of Prostate Cancer
Conclusions

• Ipilimumab induced upregulation of PD-L1/VISTA within the TME

• PD-L1/VISTA have different mechanisms of inhibiting T cell functions
  • Myeloid cells expressing PD-L1 or VISTA suppress T cell functions

• Targeting both CTLA-4 and PD-1 improved outcomes in a preclinical model of prostate cancer
Can we improve clinical responses by co-targeting the CTLA-4 and PD-(L)1 pathways?
Study Design for CheckMate 650 in Prostate Cancer

Open-label, multicenter, phase 2 study (NCT02985957)

Patients with mCRPC
- Ongoing ADT confirmed by testosterone level ≤1.73 nmol/L (50 ng/dL)
- ECOG performance status ≤1

Cohort 1: Asymptomatic or minimally symptomatic patients who progressed after ≥1 second-generation hormone therapy and had not received chemotherapy in the mCRPC setting (N = 45)*

Cohort 2: Patients who progressed after cytotoxic chemotherapy in the mCRPC setting (N = 45)*

NIVO 1 mg/kg IV + IPI 3 mg/kg IV Q3W for up to 4 doses
- Treatment continued until progression or unacceptable toxicity
- Treatment beyond progression was permitted b

NIVO 480 mg IV Q4W

Co-primary endpoints:
- Investigator-assessed ORR (per RECIST 1.1)
- rPFS (per PCWG2 criteria)

Secondary endpoints:
- OS
- Safety

Exploratory endpoints:
- PSA response rate
- Correlation of biomarkers (PD-L1, HRD, DDR, TMB) with efficacy

## Treatment Exposure and Patient Disposition

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort 1 (N = 45)</th>
<th>Cohort 2 (N = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median follow-up, months</strong></td>
<td>11.9</td>
<td>13.5</td>
</tr>
<tr>
<td><strong>Treatment exposure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration of therapy, months (range)</td>
<td>2.1 (0–13.6+)</td>
<td>1.4 (0–17.2+)</td>
</tr>
<tr>
<td>Combination doses received, median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIVO</td>
<td>3.0 (1–4)</td>
<td>3.0 (1–4)</td>
</tr>
<tr>
<td>IPI</td>
<td>3.0 (1–4)</td>
<td>3.0 (1–4)</td>
</tr>
<tr>
<td>Patients receiving 4 combination doses, n (%)</td>
<td>15 (33.3)</td>
<td>11 (24.4)</td>
</tr>
<tr>
<td>NIVO maintenance doses received, median (range)</td>
<td>n = 14</td>
<td>n = 9</td>
</tr>
<tr>
<td></td>
<td>2.0 (1–11)</td>
<td>2.0 (1–15)</td>
</tr>
<tr>
<td><strong>On study treatment, n (%)</strong></td>
<td>2 (4.4)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td><strong>Reasons for treatment discontinuation, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression</td>
<td>15 (33.3)</td>
<td>20 (44.4)</td>
</tr>
<tr>
<td>Study drug toxicity</td>
<td>23 (51.1)</td>
<td>20 (44.4)</td>
</tr>
<tr>
<td>Adverse event unrelated to study drug</td>
<td>1 (2.2)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Patient withdrew consent</td>
<td>2 (4.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other/not reported</td>
<td>2 (4.4)</td>
<td>3 (6.7)</td>
</tr>
</tbody>
</table>

+ Indicates a censored value.

Clinical Response Outcomes for Nivolumab Plus Ipilimumab

Objective response (measurable disease only)a

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (N = 32)</th>
<th>Cohort 2 (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, n (%)</td>
<td></td>
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</tr>
<tr>
<td>95% CI</td>
<td>11.5–43.4</td>
<td>2.1–26.5</td>
</tr>
<tr>
<td>Confirmed ORR, n (%)</td>
<td>8 (25.0)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>13 (40.6)</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>9 (28.1)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>2 (6.3)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Complete response</td>
<td>2 (6.3)b</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Partial response</td>
<td>6 (18.8)c</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13 (40.6)</td>
<td>11 (36.7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>9 (28.1)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>2 (6.3)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Disease control rate, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 (46.9)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Median time to response, months (Q1–Q3)</td>
<td>1.9 (1.9–2.8)</td>
<td>2.1 (1.9–7.4)</td>
</tr>
</tbody>
</table>

• Objective response was ongoing in 5/8 responders in cohort 1 and all 3 responders in cohort 2

Duration of Responses for Patients with Objective Responses

<table>
<thead>
<tr>
<th>OBJECTIVE RESPONDERS</th>
<th>PD-L1</th>
<th>HRD</th>
<th>DDR</th>
<th>TMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing objective response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off treatment</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Responder at MD Anderson

PSA (ng/mL)

Months
### Expanded Phase 2 Clinical Trial

**Screening Phase**
- Metastatic CRPC treated with prior docetaxel-containing regimen
- Tissue/plasma required for retrospective BM testing
- ECOG PS 0-1

**Treatment Phase**
(N = approximately 315)

- **Arm D1 (n= 90)**
  - Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg Q3W up to 4 cycles,
  - then Nivolumab 480 mg Q4W

- **Arm D2 (n= 90)**
  - Nivolumab 1 mg/kg Q3W (8 doses)+ Ipilimumab 3 mg/kg Q6W (4 doses) of Ipilimumab, then Nivolumab 480 mg Q4W

- **Arm D3 (n= 45)**
  - Ipilimumab 3 mg/kg Q3W up to 4 cycles

- **Arm D4 (n= 90)**
  - Cabazitaxel 25mg/m² Q3W + Prednisone 10mg PO D1-D21

**Follow-up Phase**
- Treat until PD, or unacceptable toxicity or up to a maximum treatment of 2 years
- Treat until PD, or unacceptable toxicity or maximum of 4 cycles
- Treat until PD, or unacceptable toxicity or maximum of 10 cycles

**Randomization** 2:2:1:2
**Stratification:** measurable vs non-measurable disease

**Follow-up**
- Follow-up Visit 1 & Visit 2
- Survival Follow-up
Conclusions

• Combining anti-CTLA-4 and anti-PD-1 may improve clinical outcomes in a subset of patients

• Need to explore dose/schedule to potentially mitigate toxicities

• New rational combinations will be needed to provide clinical benefit for a greater number of patients
Prostate Cancer Bone Metastases were Associated with Poorer Survival

<table>
<thead>
<tr>
<th></th>
<th>Lymph Node Only</th>
<th>Bone Only</th>
<th>Bone + Lymph Node</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Men</td>
<td>6.4</td>
<td>42.9</td>
<td>29.8</td>
</tr>
<tr>
<td>Overall Survival (Months)</td>
<td>31.6</td>
<td>21.3</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Halabi, S et al., *J Clin Oncol*, 2016.
How effective is concurrently targeting the CTLA-4 and PD-(L)1 pathways in patients with mCRPC to the bones?
Durvalumab + Tremelimumab in mCRPC to the Bones

Concurrent Treatment

Durvalumab (1500 mg)

Tremelimumab (75 mg)

Maintenance

Durvalumab (1500 mg)

Bone Marrow Collections

NCT03204812 (N=26)

Subudhi SK, Siddiqui B et al., *manuscript in review*
**Efficacy Outcomes**

**PSA PFS**

Median PSA PFS: **0.9 months**
(95% CI: 0.9-1.8)

**Radiographic PFS**

Median rPFS: **3.7 months**
(95% CI: 1.9-5.7)

**Overall Survival**

Median OS: **28.1 months**
(95% CI: 14.5 – NR)

Subudhi SK, Siddiqui B et al., *manuscript in review*
# Summary of Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients with Response Information</td>
<td>25 (100)</td>
</tr>
<tr>
<td>PSA Response*</td>
<td>3 (12)</td>
</tr>
<tr>
<td>ORR</td>
<td>0 (0)</td>
</tr>
<tr>
<td>DCR</td>
<td>6 (24)</td>
</tr>
<tr>
<td>CR</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PR</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SD</td>
<td>6 (24)</td>
</tr>
<tr>
<td>PSA PFS – Months, Median (CI)</td>
<td>0.9 (0.9 - 1.8)</td>
</tr>
<tr>
<td>rPFS – Months, Median (CI)</td>
<td>3.7 (1.9 - 5.7)</td>
</tr>
<tr>
<td>OS – Months, Median (CI)</td>
<td>28.1 (14.5 – NR)</td>
</tr>
</tbody>
</table>

12 month OS (Standard Error) 96% (4%)

24 month OS (Standard Error) 54% (10%)

Subudhi SK, Siddiqui B et al., *manuscript in review*
Macrophage/Neutrophil Transcriptional Signatures Upregulated Within the Bone Tumor Microenvironment

Subudhi SK, Siddiqui B et al., manuscript in review
Targets of Immunosuppressive Myeloid Cells Within the Bone Tumor Microenvironment

Subudhi SK, Siddiqui B et al., manuscript in review
Conclusions

• Combining anti-CTLA-4 and anti-PD-L1 was safe and tolerable

• Concurrently targeting immunosuppressive myeloid cells may improve clinical benefit for a greater number of patients
Are there clinically effective ways to target immunosuppressive myeloid cells?
Therapeutic Approaches for Targeting Immunosuppressive Myeloid Cells

- Immune checkpoints (PD-L1, VISTA)
- Cytokines / Chemokines (IL-8, IL-23)
- Tyrosine kinase pathways (VEGFR2, AXL, PTEN/PI3K)
- Metabolic pathways (adenosine, arginine)
Adenosine Pathway Expression Correlates with Unfavorable Survival in Prostate Cancer

Subudhi SK et al., ESMO 2020.
Radiographic PFS: Docetaxel + anti-PD-1 + Adenosine Receptor Antagonist
Conclusions

• Targeting the adenosine pathway may improve outcomes with immune checkpoint based-combinations
Moving Forward

• Rational sequential/combinatorial strategies:
  – Increase T cell infiltration
  – Target immune checkpoints
  – Modulating immunosuppressive cells
  – Influence of other factors (e.g., metabolism, hypoxia, microbiome, epigenetics, etc.)

• Improve patient selection
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Patients

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