Immunotherapy for Prostate Cancer

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Sipuleucel-T: Autologous APC Cultured with PAP-cytokine Fusion Protein

Recombinant Prostatic Acid Phosphatase (PAP) antigen combines with resting antigen presenting cell (APC)

APC takes up the antigen

Antigen is processed and presented on surface of the APC

Fully activated, the APC is now sipuleucel-T

T-cells proliferate and attack cancer cells

Sipuleucel-T activates T-cells in the body

INFUSE PATIENT

The precise mechanism of sipuleucel-T in prostate cancer has not been established.
IMPACT Overall Survival
Intent-to-Treat Population

P = 0.032 (Cox model)
HR = 0.775 [95% CI: 0.614, 0.979]
Median Survival Benefit = 4.1 months

Placebo (n = 171)
Median Survival: 21.7 months

Sipuleucel-T (n = 341)
Median Survival: 25.8 months
Optimal timing for treatment of metastatic castration-resistant prostate cancer (mCRPC): sequencing and identifying parameters of early progression with sipuleucel-T

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Patients in the lowest PSA quartile had greatest OS benefit with sipuleucel-T

<table>
<thead>
<tr>
<th>Baseline PSA ng/mL</th>
<th>≤22.1 (n=128)</th>
<th>&gt;22.1 to 50.1 (n=128)</th>
<th>&gt;50.1 to 134.1 (n=128)</th>
<th>&gt;134.1 (n=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>Sipuleucel-T</td>
<td>41.3</td>
<td>27.1</td>
<td>20.4</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>28.3</td>
<td>20.1</td>
<td>15.0</td>
</tr>
<tr>
<td>Difference, months</td>
<td></td>
<td>13.0</td>
<td>7.1</td>
<td>5.4</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td>0.51</td>
<td>0.74</td>
<td>0.81</td>
</tr>
</tbody>
</table>

• Although all PSA quartile groups in IMPACT showed a benefit from sipuleucel-T treatment, those in the lowest PSA quartile benefitted the most in terms of OS

• The magnitude of treatment effect in patients in the lowest quartile appeared to be greater than those in the highest quartile (13.0 vs. 2.8 months median OS benefit, respectively)

Analysis of Three Randomized Trials, Time to Disease Related Pain

12 month pain free (39% vs. 19%)

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D9902A</td>
<td>1.392 (0.652, 2.973)</td>
<td>0.390</td>
</tr>
<tr>
<td>Integrated</td>
<td>0.844 (0.635, 1.122)</td>
<td>0.241</td>
</tr>
</tbody>
</table>

From Cox regression model with treatment as independent variable

Log-rank test

Analyses stratified by study

Event-free Probability

12 month pain free (39% vs. 19%)
Abstract # 5047 A randomized phase II trial of sipuleucel-T with concurrent or sequential abiraterone acetate (AA) plus prednisone (P) in metastatic castrate-resistant prostate cancer (mCRPC).

Eric Jay Small, Raymond S. Lance, Charles H. Redfern, Frederick E. Millard, Thomas A. Gardner, Lawrence Ivan Karsh, Nancy Ann Dawson, Candice McCoy, Andrew Stubbs, Todd DeVries, Corazon P. dela Rosa, Nadeem A. Sheikh, Neal D. Shore
Study Design

- Ongoing, randomized, open-label, phase 2 study in mCRPC patients
- Interim analysis includes 31 patients in the concurrent arm and 32 patients in the sequential arm who have completed sipuleucel-T treatment
- Baseline patient characteristics of the 2 arms were well matched
Sipuleucel-T Product Characteristics: Comparable in Concurrent and Sequential Arms

- Both arms showed APC activation was substantially greater at the second and third infusions, indicative of a prime boost effect.

<table>
<thead>
<tr>
<th>Cumulative Characteristic, median (range)</th>
<th>Concurrent Arm (n=31)</th>
<th>Sequential Arm (n=32)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC activation(^a)</td>
<td>36.4 (5.9-65.6)</td>
<td>40.7 (15.1-62.5)</td>
<td>.342</td>
</tr>
<tr>
<td>APC count (x 10(^9))</td>
<td>1.8 (0.2-5.0)</td>
<td>1.5 (0.5-4.0)</td>
<td>.456</td>
</tr>
<tr>
<td>TNC count (x 10(^9))</td>
<td>8.3 (0.5-24.2)</td>
<td>10.3 (3.3-24.4)</td>
<td>.370</td>
</tr>
</tbody>
</table>

Abbreviations: APC, antigen presenting cell (large CD54-positive cells); TNC, total nucleated cell.
\(^a\) APC activation was defined as upregulation of CD54 expression on APCs, and expressed as a ratio of the average number of CD54 molecules on cells post-vs pre-culture with PA2024.
APC Activation: Comparable in Concurrent and Sequential Arms

- APC activation was defined as upregulation of CD54 expression on APCs, and expressed as a ratio of the average number of CD54 molecules on cells post- versus pre-culture with PA2024.
Ab Response: Comparable in Concurrent and Sequential Arms

Serum IgG-IgM levels were measured with ELISA. Results reported are the mean of triplicates and expressed as the reciprocal of the dilution yielding an optical density equivalent to assay background.

### PA2024

<table>
<thead>
<tr>
<th>Week</th>
<th>Concurrent Arm (n=12)</th>
<th>Sequential Arm (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### PAP

<table>
<thead>
<tr>
<th>Week</th>
<th>Concurrent Arm (n=12)</th>
<th>Sequential Arm (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**P-values**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>PA2024</th>
<th>PAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6 vs Week 0</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Concurrent vs Sequential</td>
<td>.300</td>
<td>.336</td>
</tr>
</tbody>
</table>
T-Cell Proliferation: Comparable in Concurrent and Sequential Arms

- T-cell proliferation was measured with 3H-thymidine incorporation following incubation with PA2024 or PAP, and expressed as a stimulation index (3H-thymidine incorporation in the presence of antigen divided by 3H-thymidine incorporation with media alone).

<table>
<thead>
<tr>
<th>Comparison</th>
<th>PA2024</th>
<th>PAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6 vs Week 0</td>
<td>&lt;.001</td>
<td>.940</td>
</tr>
<tr>
<td>Concurrent vs Sequential</td>
<td>.559</td>
<td>.984</td>
</tr>
</tbody>
</table>
Memory T-Cell Counts: Comparable in Concurrent and Sequential Arms

- IFNγ ELISPOT assay results reported are the median of triplicates per 3x10^5 PBMCs; background (PBMCs incubated with media only) IFN-γ spots were subtracted.
Immune Activation Was Similar Between Arms

- No significant difference in TNC counts, APC counts, and CD54 upregulation between the groups

* = p<.05, for APC count in arm 2 between wk0 vs wk2 or wk4
Randomized Phase II trial of Sipuleucel T + MDV3100

- Chemotherapy naïve
- Visceral disease permitted
- No prior ketoconazole/abiraterone

**Randomize**

- Sipuleucel T x 3 doses
- MDV 3100 1600 mg concomitantly

**Randomize**

- Sipuleucel T x 3 doses
- MDV 3100 after completion of Sipeuleucel T
The initial vaccine may target one antigen only
A broader antitumor immune response may be initiated through tumor antigen spreading (e.g., immune response to additional antigens)

Adapted from Gulley JL. *Hum Vaccin Immunother.* 2013;9(1):1-3.

PSMA, prostate-specific membrane antigen; PSCA, prostate stem cell antigen; MUC-1, mucin-1.

Abbas AK, Lichtman AH. *Basic Immunology.* 3rd ed. 2011.
Full List of Prostate Cancer Antigens Tested

**CEACAM7**: carcinoembryonic antigen-related cell adhesion molecule 7

**CTAG2 (NY-ESO-2/LAGE-1)**: cancer/testis antigen 2

**GLUD1**: glutamate dehydrogenase 1 (mitochondrial)

**GSTK1**: glutathione S-transferase kappa 1

**HSPA2**: heat shock 70kDa protein 2

**MAP4**: microtubule-associated protein 4

**MRPL12**: mitochondrial ribosomal protein L12

**NY-ESO-1 CTAG1B**: cancer/testis antigen 1B

**PAPD7**: PAP-associated domain-containing 7

**PARK7**: oncogene DJ1; protein DJ-1

**PSA/KLK3**: prostate-specific antigen

**PSCA**: prostate stem cell antigen

**PSMA**: prostate-specific membrane antigen

**SOX2**: SRY (sex-determining region Y)-box 2

**SSX2**: synovial sarcoma, X breakpoint 2

**STEAP/STEAP1**: six transmembrane epithelial antigen of the prostate 1

**SURVIVIN/BIRC5**: baculoviral IAP repeat-containing 5a

**TARP1**: T-cell alternate reading frame protein 1

**TPA/PLAT**: plasminogen activator, tissue

**TSGA10**: cancer/testis antigen 79; testis-specific gene 10

**TSGK6**: cancer/testis antigen 72; testis-specific serine kinase 6

**UPA/PLAU**: plasminogen activator, urokinase
Clinical Evidence of Epitope Spreading With Sipuleucel-T Treatment

Positive Ab Counts Against PCa Antigens Are Increased Post-Treatment in Sipuleucel-T–Treated Patients (n=30 from IMPACT)

Ab, antibody.

Phase 3 Study of Ipilimumab in Post-Docetaxel mCRPC (CA184-043): Study Design*¹

- Primary endpoint: overall survival (OS)
- Secondary endpoints: progression-free survival (PFS), safety
- Exploratory endpoint: prostate-specific antigen (PSA) response rate

*N=399

Ipilimumab (10 mg/kg)
Wks 1, 4, 7, 10

Every 12 wks

N=400

Placebo
Wks 1, 4, 7, 10

Treatment until disease progression or intolerable toxicity

*ClinicalTrials.gov Identifier: NCT00861614.
ALP=alkaline phosphatase; ECOG=Eastern Cooperative Oncology Group; RT=radiotherapy.
Phase 3 Study of Ipilimumab in Post-Docetaxel mCRPC (CA184-043)

Primary Endpoint: OS (Intent to Treat [ITT] Population)

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab (n=399)</th>
<th>Placebo (n=400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>11.2 (9.5-12.7)</td>
<td>10.0 (8.3-11.0)</td>
</tr>
<tr>
<td>HR (95% CI):</td>
<td>0.85 (0.72-1.00)</td>
<td></td>
</tr>
<tr>
<td>Stratified log-rank P</td>
<td>0.0530</td>
<td></td>
</tr>
</tbody>
</table>

Safety

- Adverse event (AE) profile was consistent with that previously reported for ipilimumab*
  - The most frequent severe immune-related AEs were diarrhea and colitis

*See poster presentation at this meeting: Beer et al. Abstract ID: 52.
## Overall Survival: Prespecified Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Deaths/No. Randomized (Ipilimumab vs Placebo)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>138/215 vs 172/234</td>
<td>0.81 (0.64, 1.01)</td>
</tr>
<tr>
<td>≥70</td>
<td>131/184 vs 133/166</td>
<td>0.88 (0.69, 1.13)</td>
</tr>
<tr>
<td><strong>ECOG status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>98/167 vs 123/168</td>
<td>0.72 (0.55, 0.94)</td>
</tr>
<tr>
<td>1</td>
<td>171/232 vs 182/232</td>
<td>0.94 (0.76, 1.16)</td>
</tr>
<tr>
<td><strong>ALP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.5 x ULN</td>
<td>142/243 vs 166/243</td>
<td>0.78 (0.62, 0.97)</td>
</tr>
<tr>
<td>≥1.5 x ULN</td>
<td>127/156 vs 139/157</td>
<td>0.95 (0.75, 1.21)</td>
</tr>
<tr>
<td><strong>Gleason score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7</td>
<td>111/174 vs 140/190</td>
<td>0.86 (0.67, 1.11)</td>
</tr>
<tr>
<td>&gt;7</td>
<td>134/191 vs 149/186</td>
<td>0.76 (0.60, 0.96)</td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Visceral metastases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>205/326 vs 237/325</td>
<td>0.82 (0.68, 0.99)</td>
</tr>
<tr>
<td>No</td>
<td>52/58 vs 50/53</td>
<td>1.00 (0.69, 1.47)</td>
</tr>
<tr>
<td><strong>Hemoglobin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;11 g/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥11 g/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA/Canada</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-USA/Canada</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Average daily worst pain at baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>98/111 vs 103/113</td>
<td>0.98 (0.74, 1.29)</td>
</tr>
<tr>
<td>≥4</td>
<td>171/288 vs 202/287</td>
<td>0.79 (0.64, 0.97)</td>
</tr>
</tbody>
</table>

**Favor Ipilimumab**

95% CI: 0.79 to 0.85

**Favor Placebo**

95% CI: 0.85 to 1.11

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*Stratification factors.
Note: Also evaluated were race, prior cancer vaccines, bisphosphonate use, No. bone metastases, No. bone regions with metastases, and pain (none vs minimal).
LDH=lactate dehydrogenase; ULN=upper limit of normal.

PDL-1 Expression in Prostate cancer

• Hormone sensitive radical prostatectomy specimens express high levels of PDL-1 52.2% of cases (Gevensleben et al Clin Cancer Res 2016)

• Patients progressing on enzalutamide have significantly increased PDL-1/2 dendritic cells in blood compared to those progressing on treatment. (Bishop et al. Oncotarget, 2016)

• Nivolumab treatment in men with CRPC demonstrated no objective responses in 17 patients; 2 patients who had tissue stained for PDL-1 demonstrated no immunoreactivity (Topalian NEJM2012)

• 3/20 samples (15%) had focal areas of PD-L1 positivity, although in only two of the three positive samples was plasma membrane staining clearly observed on malignant epithelial cell. (Martin et al. Prostate Cancer and Prostatic Disease 2015)
## Responding Patients: Pembrolizumab in Prostate Cancer

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Date of cycle 1</th>
<th>PSA (ng/ml) baseline to nadir</th>
<th>Measurable Disease at Baseline</th>
<th>Best Radiologic Response</th>
<th>MSI</th>
<th>Prior Treatment for mCRPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>April 2015</td>
<td>70.65 → 0.08</td>
<td>Yes</td>
<td>PR</td>
<td>present</td>
<td>abi, enz</td>
</tr>
<tr>
<td>7</td>
<td>October 2015</td>
<td>46.09 → 0.02</td>
<td>No</td>
<td>N/A</td>
<td>n/a</td>
<td>abi, enz</td>
</tr>
<tr>
<td>10</td>
<td>January 2016</td>
<td>2502.75 → &lt;0.01</td>
<td>Yes</td>
<td>PR</td>
<td>absent</td>
<td>enz</td>
</tr>
</tbody>
</table>

* All responding patients remain on study.

PR – partial response; N/A – not applicable (i.e. no baseline biopsy done); MSI – microsatellite instability; abi – abiraterone; enz – enzalutamide
Programmed death-1 blockade in mismatch repair deficient cancer independent of tumor histology.

• 29 patients were enrolled and treated on this study, including the following histologies: (endometrial: 9; pancreatic: 4; ampullary: 4; biliary: 3; small bowel: 3; gastric: 3; thyroid: 1; prostate: 1)

• The one prostate cancer patient demonstrated an objective response.

Diaz LA et al. J Clin Oncol 34, 2016 (suppl; abstr 3003)
Avelumab in CRPC

• Avelumab 10 mg/kg Q 2 weeks
• 18 pts, median age 67, median PSA17, 3 prior docetaxel, 4 pts sipueleucel T, 3pts Prostvac
• 7 pts had SD>24 weeks; 6 PD after first evaluation, reconfirmed 12 weeks later

Fakherjahani et al Proc ASCO GU 2017
Durvalumab (D) + Olaparib (O) in CRPC

- D 1500 mg iv Q28 days; O 300 mg po Q12 hours
- 6 pts, all had prior abiraterone or enzalutamide; median PSA 258; 1/6 had a BRCA germ line mutation
- 4/6 had a >50% PSA decline, 1PR by RECIST
Ongoing Trials

• Atezolizumab Phase I
• Atezolizumab + Radium 223
• Enzalutamide +/- Atezolizumab
Conclusions

- Treatment with immune therapy should be used early in the course of CRPC
- PSA declines may not be seen in patients treated with immune therapy