The QuEST for an effective immunotherapy for Prostate Cancer

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I have the following financial relationships to disclose:

The NCI has a Cooperative Research and Development Agreement (CRADA) with a number of pharma partners including Bavarian Nordic, ImmunityBio, Incyte, EMD Serono and has a clinical trial agreement (for biologics) with BMS. The CRADAs provide drug and may provide resources for co-development in clinical trials.

- and -

I will discuss the following off label use and/or investigational use in my presentation:

Ipilimumab
Nivolumab
Cancer Immunity Cyclical Evolution (E⁸)

1. Emit antigen
2. Engage
3. Expand
4. Expedition
5. Excursion
6. Establish ID
7. Enable

Blood vessel
Lymph node
Tumor

Modified from Chen and Mellman, *Immunity* 2013
Cancer Immunity Cyclical Evolution ($E^8$)

1. Emit antigen
2. Engage
3. Expand
4. Expedition
5. Excursion
6. Establish ID
7. Enable

Vaccine
CAR-T
Bispecific Ab
Prostvac increases intra/peritumoral immune infiltrate in patients with localized prostate cancer undergoing radical prostatectomy (NCT02153918) (n=27)

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Priming Vaccination s.c.</th>
<th>Booster Vaccination s.c.</th>
<th>Booster Vaccination s.c.</th>
<th>Booster Vaccination s.c.</th>
<th>RP</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>Day 1</td>
<td>Day 15</td>
<td>Day 29</td>
<td>Day 57</td>
<td>64</td>
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</tbody>
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≥ 2X ↑ CD4 Infiltrate  
≥ 2X ↑ CD8 Infiltrate

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
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<tbody>
<tr>
<td>No Peripheral IR</td>
<td>3</td>
<td>9</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Peripheral IR</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td>8</td>
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<tr>
<td>Total</td>
<td>17/24</td>
<td>14/24</td>
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</tr>
</tbody>
</table>

RNA expression profiles consistent with an activated immune response post vaccine

Houssein et al., JITC 2020
Importance of PD-1/PD-L1 blockade
Cancer Immunity Cyclical Evolution

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Blood vessel
Lymph node
Tumor

Modified from Chen and Mellman, *Immunity* 2013

Vaccine

PD1i
Experimental algorithm for immunotherapy for mCRPC

Biomarker (MSI-H; TMB)

~5% Positive

~95% Negative

+ PD-1 or PD-L1 inhibitor

Possible activity

No activity

Pembrolizumab

~50% response

FDA Approved

Madan and Gulley Nature Rev. Urology, 2018
Prostvac (+ Ipilimumab) + Nivolumab (NCT02933255)

- Eligibility (n=12)
  - mCRPC
  - No prior chemotherapy

- Treatment
  - Prostvac Vaccine
  - Immune checkpoints
    - Ipilimumab 1 mg/kg
    - Nivolumab 240 mg
Anti-PD1

Prostvac

Nivolumab

CR

4 years!
Prostvac + Nivo (+ipi)
Multi-layered immunosuppression

- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune suppression, thereby restoring the capacity of T cells to eradicate the tumor
QuEST-1 (Quick Efficacy Seeking Trial)
Ongoing study (QuEST1)

- CRPC
- ORR / sustained PSA ↓

Redman et al., *JITC* Sept 2018
Spider Plot

Change in Size of Tumor

Time

bigger

smaller
Bintrafusp alfa in HPV Associated Malignancies

- ORR was 18/59 (31%)
- Total Clinical Response rate (included 3 delayed responses) was 21/59 (36%)

*Includes 2 patients with SCC rectal tumors, 1 patient (each) with neuroendocrine cervical, vaginal, and vulvar tumors from study 012.
Targeting Brachyury

- Brachyury (TBXT)
  - Overexpressed in tumor vs. normal tissue
  - Involved in EMT / drug resistance / cellular plasticity
  - Expression associated with NE markers and PTEN loss in prostate cancer
  - T-cells specific for brachyury can kill brachyury expressing cells in an MHC restricted manner

Pinto et al, Clin Ca Res 2014
Well tolerated (no DLT)

28 of 34 (82%) patients developed brachyury-specific CD4 and/or CD8 T-cell responses after vaccination
N-803

- Improved affinity for IL2/15R-β (CD122) expressing immune cells (NKs and T cells)
- Longer serum half-life than native IL15 (25 h vs. 40 min) in mice

**Increased NK function on a per-cell basis**

**Anti-metastatic activity**

- Balb/C mice injected with IL-15/IL15RA-Fc (1ug/IP). Purified NK cell activity tested on day 3.
- 4T1 tumor bearing Balb/C mice injected with IL-15/IL15RA-Fc (1ug/IP) on day 7. Tumor metastases counted on day 26. Dependent on CD8 and NK cells

Kim et al, Oncotarget, 2016
Best PSA Responses

Redman...Gulley, ESMO 2020

- 24 weeks
- 31 weeks
- 27+ weeks
- 41+ weeks
- 11+ weeks
- 49+ weeks

Prior Abiraterone/Enzalutamide
Prior Chemotherapy + Abiraterone/Enzalutamide
Patient 34

Prior Treatment
- Sipuleucel-T
- Enzalutamide
- Radium-223 + Niraparib (Trial)
- Adenoviral vaccine targeting PSA, MUC1, Brachyury

Baseline

~1 Year On Treatment

PSA

% Change in PSA from Baseline

Weeks on Treatment

steroids

Patient 34
Conclusions

- Immunotherapy can be powerful, and can lead to complete responses which are durable
- Despite the impressive results seen in subsets patients in some cancer, unselected patients with prostate cancer rarely have objective responses to current immunotherapy monotherapy
- In order to harness the potential power of immunotherapy in prostate cancer, one must address the critical elements that are necessary for an immune response
- Approaches that (a) stimulate a relevant immune response, (b) expand number and function of those immune cells and (c) facilitate functionality in the TME may be essential for “immune deserts” like mCRPC.
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Patients and their Families