Defining “Response” in Prostate Cancer Immunotherapy

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Prostate Cancer Clinical States

- Pre-chemotherapy
- Post-chemotherapy

(Scher et al, JCO 2008)
Randomized Phase III Trial of Sipuleucel-T (Provenge) Targeting PAP

(D9901)

Asymptomatic Metastatic CRPC (N = 127)

- Placebo Q 2wks x 3 (N = 45)
- Provenge Q 2 wks x 3 (N = 82)
- Provenge Q 2 wks x 3
- Off Study

Primary endpoint: Time to Disease Progression
- Radiographic, Clinical or Pain
- Not PSA

Secondary endpoint: Overall Survival
Sipuleucel-T is associated with an improvement only in overall survival

(Log-rank $P = .052$
HR = 1.45, 95% CI, 0.99 to 2.11
Median: 11.7 weeks
Placebo ($n = 45$)
Median: 10.0 weeks)

(Log-rank $P = .010$
HR = 1.71, 95% CI, 1.13 to 2.58
Median benefit: 4.5 months
Survival Time (months))

(Small et al. JCO 24, 2006)
PROSTVAC: A PSA-targeted viral vaccine

Week 0 2 4 8 12 16 20

Prime
rV-PSA-Tricom $1\times10^9$PFU
GM-CSF 100mcg x 3 D

Boost
rF-PSA-Tricom $1\times10^9$PFU
GM-CSF 100mcg x 3 D

Platform: Pox viruses
Antigen: PSA
PSA-3 epitope

Tricom:LFA-3 (CD58)
ICAM-1 (CD54)
B7.1 (CD80)
Randomized Phase II Study of a Vaccine Targeting PSA

Asymptomatic or Minimally Symptomatic Metastatic Castrate Resistant Prostate Cancer (N=125)

- PROSTVAC-VF Tricom + GM-CSF
- Empty Vector + placebo

2:1

Primary endpoint: Progression Free Survival
Secondary endpoint: Overall Survival

Progression
Treated at physician discretion

Survival
Treated at physician discretion and/or Salvage Protocol

Therion BCBN

(Kantoff et al. JCO 2010)
PROSTVAC treatment is associated with an improvement only in overall survival

(Kantoff et al. JCO 2010)
Prostate Cancer Immunotherapy 2010

- Sipuleucel-T treatment is associated with an improvement in overall survival in patients with CRPC.
  - No improvement in PFS
- Prostvac treatment is associated with a similar improvement in overall survival.
  - No improvement in PFS
  - Phase 3 planned

Why do we see improvements in overall survival without altering time to progression?
Clinical Endpoints

- PSA doubling time, velocity
- PSA reduction by 50%
- Pain, quality of life
- Time to event
  - Time to progression (TTP)
  - Time to skeletal event
  - Progression free survival (PFS)
  - Overall survival (OS)
Challenges in defining clinical response for prostate cancer

- Slow growing tumor
  - Overall survival as an endpoint can take a long time
- Serologic markers: PSA
  - Easy to follow and are often used to guide treatment
  - May not correlate with clinical response
- Bone tropism for metastasis
  - Bone scans are difficult to measureable
  - Difficult to show a response
  - Most patients do not have measureable disease
- No established surrogate for overall survival
Bone Flare with Abiraterone

Baseline
PSA 41.7
Multifocal

Month 4
PSA 4.52
Progression in lesions

Month 7
PSA 4.27
Stable/sl improvement

(Shah et al. GU ASCO 2010)
Prostate Cancer Clinical Trials Working Group 2 (PCWG2)

- Treat for a minimum of 12 wks
- PSA
  - % change from baseline @ 12wks or at any time
  - Time to PSA progression (25% rise from nadir)
- Soft Tissue/Measureable disease
  - RESCIST with caveats
- Bone
  - New lesions must be seen on a confirmatory scan ≥ 6 weeks later
12 week window to tolerate early progression

(Scher et al. JCO 2004)
Defining immune responses

- Immune markers
  - Modulation of immune cell frequency and phenotype
    - APC
    - T cells (activation markers, icos, cytokines)
    - Tregs
  - Antigen specific immune responses
    - Proliferation
    - Cytokine production (IFNγ, polyfunctional, …)
  - Profiling of antigen specific responses
Prostatic acid phosphatase (PAP) is immunogenic in a murine model

Vaccinate rats with recombinant vaccinia virus expressing human PAP

1 month

3 months

(Fong et al., JI 1997)
Neoadjuvant Sipuleucel-T

- Primary endpoint: CD3+ T cells by IHC
- Secondary endpoints:
  - T cell subset infiltration by IHC
  - Antigen-specific T cell responses, pre vs. post induction
  - Antigen-specific T cell responses, pre vs. post boost/no boost
CTLA-4 Blockade: Phase 1 Trial

- First-in-man trial conducted in CRPC
- Single dose of Ipilimumab @ 3 mg/kg
- 14% PSA response rate
- Rash only treatment associated adverse event

(Small, et al., Clin Can Res, 2007)
Phase I Combination Trial of Ipilimumab and GM-CSF

- Metastatic CRPC
- Fixed GM-CSF dose (250 mcg/m2/d sc D1-14)
- Escalating anti-CTLA4 antibody dose

Anti-CTLA4 Infusion
GM-CSF sc days 1-14

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Clinical Responses

(Fong et al, Can Res 2009)
Array-Based Screening of Antigen-Specific Responses

Treatment can induce immune responses to NY-ESO-1

(Fong et al, Can Res 2009)
# Clinical and Antibody Responses

(Fong et al, Can Res 2009)

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Profiling of IgG responses with protein arrays

- 8000+ human proteins
- Expressed in baculovirus
- Hybridize with patient sera
- Detect bound IgG by fluorescence
Conclusions

■ Overall survival remains the definitive outcome for defining clinical efficacy in prostate cancer, but is not be feasible for early trial development.

■ Immunotherapies that induce clinical responses in prostate cancer provide the opportunity to help redefine meaningful immune “responses.”

■ Clinical endpoints (PCWG2) that allow for early progression are being used in prostate cancer trials.

■ Immune correlates need to be validated in larger trials (with clinical benefit) including Phase 3 trials that are followed for overall survival.
Where do we go from here?

- Introduce mechanistic studies into phase I, II, III trials (cryopreserve samples).
- Exploratory studies to examine the associations between the clinical endpoints and correlative studies may use time to progression and response criteria understanding their caveats.
- Validate associations between clinical (esp. overall survival) and immune responses in subsequent studies.
- Circulating tumor cell measurement (Veridex) currently being looked at in abiraterone and MDV3100 trials – stay tuned…
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