Novel Therapeutics in Prostate Cancer

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Are novel therapeutics needed in prostate cancer?

- ~32,000 deaths per year from castration resistant prostate cancer (CRPC)
- Chemotherapy has demonstrated a survival benefit and palliative role—but always room for improvement
- Targeted therapy possibly provides a more favorable therapeutic index, with less toxicity and more specificity

Novel therapeutics in prostate cancer: science versus sales

- Many novel therapeutics may be cytostatic agents
- Demonstrating efficacy may be most likely
  - in combination with known active agents
  - in clinical situations of minimal disease burden
- However, a primary registration endpoint is survival, best measured in situations of maximal disease burden

Novel therapeutics in prostate cancer: science versus sales

- Shorter time to endpoint
- Decreasing tumor burden

<table>
<thead>
<tr>
<th>Disease state</th>
<th>Median survival</th>
<th>Disease burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sx. metastatic HRPC</td>
<td>6 - 12 months</td>
<td>very extensive</td>
</tr>
<tr>
<td>Ax. metastatic HRPC</td>
<td>12 - 20 months</td>
<td>extensive</td>
</tr>
<tr>
<td>Non-metastatic HRPC (PSA only)</td>
<td>3 - 5 years</td>
<td>moderate</td>
</tr>
<tr>
<td>Serologic progression after RP, XRT</td>
<td>5 -15 years</td>
<td>minimal</td>
</tr>
</tbody>
</table>

Do you test a drug in minimal disease where it is more likely to work but less likely to be approved, or in maximal disease state, where it is less likely to work but more likely to be approved?
Novel therapeutics in prostate cancer

- New ways of using chemotherapy
- Immunotherapy
- Novel adrenal androgen inhibition
- Angiogenesis
- Cell-cycle, cell-division
- Signal-transduction
- Pro-apoptotic
- Differentiating agents

Chemotherapy and prostate cancer: TAX327, SWOG 9916

Tax 327 Primary Objective: Overall Survival

- **Docetaxel 3 wkly**
- **Docetaxel 1 wkly**
- **Mitoxantrone**

<table>
<thead>
<tr>
<th>Survival (mos)</th>
<th>Hazard ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel 3 wkly</td>
<td>18.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Docetaxel 1 wkly</td>
<td>16.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>


SWOG 9916-Overall survival

- **U + E**: 338
- **M + P**: 336
- **# of Deaths**: 235
- **Median in Months**: 17.5
- **HR**: 0.80 (95% CI 0.67, 0.97), p = 0.01
Pre-Prostatectomy Chemo/hormonal Therapy: Rationale

Based on pre-treatment disease characteristics, the likelihood that a patient with localized prostate cancer will fail definitive local therapy can be determined.

These patients may benefit from more extended local therapy or from systemic treatment.

Precedent exists in other solid tumors where the standard of care will include some combination of surgery +/- radiation +/- chemotherapy +/- hormonal therapy.

Neo-Adjuvant Chemo-hormonal therapy prior to radical prostatectomy

<table>
<thead>
<tr>
<th>6 cycles of chemohormonal therapy</th>
<th>Surgical Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel 75 mg/m² IV every 21 days</td>
<td>Staging pelvic lymphadectomy</td>
</tr>
<tr>
<td>LHRH agonist therapy (18-24 weeks)</td>
<td>Radical prostatectomy (within 60 days of end-chemo)</td>
</tr>
</tbody>
</table>

Surgical Intervention
Staging pelvic lymphadectomy
Radical prostatectomy

Endpoints: 3 yr bPFS
Secondary endpoints: PCSS, OS, time to local recurrence and metastases, toxicity, diet/lifestyle, RNA/SNP, proteomics

CALGB 90203: Entry Criteria

Clinical Stage T1-3a, Nx Prostate Cancer
No evidence of metastatic disease
Pre-operative (Kattan) nomogram probability of < 60% bPFS at 5 years after surgery

OR

Gleason sum 8, 9, 10
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Immunotherapy: Targeting the Dendritic Cell/T-Cell Interface

B7, MHC – Ag, APC, TCR, CD3, CD28

Ipilimumab inhibits CTLA-4

Provenge replaces GM-CSF

GM-CSF stimulates Provenge

Systemic GM-CSF and HRPC

PSA: 0.1 1 2 3 6 8 9 10 12 16 30 45 70 110

Clinical Stage: T1c T1ab T2a T2b T2c T3a

Biopsy Gleason Grade: ≤2+3 ≤3+3 ≥4+1

Total Points: 0 10 20 30 40 50 60 70 80 90 100

60 Month Rec. Free Prob.: .96 .93 .9 .85 .8 .7 .6 .5 .4 .3 .2 .1 .05

Preoperative Nomogram for Prostate Cancer Recurrence

Points

<table>
<thead>
<tr>
<th>PSA</th>
<th>0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Points</td>
<td>0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150</td>
</tr>
<tr>
<td>Clinical Stage</td>
<td>T1a T1b T1c T2a T2b T2c T3a</td>
</tr>
<tr>
<td>Biopsy Gleason Grade</td>
<td>≤2+2 ≤2+3 ≤3+3 ≥4+1</td>
</tr>
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<td>Total Points</td>
<td>0 10 20 30 40 50 60 70 80 90 100</td>
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60 Month Rec. Free Prob.

- .96
- .93
- .9
- .85
- .8
- .7
- .6
- .5
- .4
- .3
- .2
- .1
- .05

GM-CSF Started

Small Clin Canc Res 1999
Neoadjuvant GM-CSF study: Phase I/II

GM-CSF SQ daily for Phase I cohorts:
- 2 weeks - done
- 3 weeks - done
- 4 weeks - ONGOING
- 5 weeks
- 6 patients per level

RP within 3 days of stopping GM-CSF

ENDPOINTS:
- Primary:
  - Safety/tolerability, tissue infiltration of APCs into prostate (5-fold increase = response)
- Secondary:
  - PB immune response (T-cell subsets), pre and post RP, PSA changes, surgical outcomes, primary tumor response

RESULTS (Fong et al. ASCO 2008)

Safety: elevated WBC observed (30K); tolerated well

Compared with untreated RP tissue, neoadjuvant GM-CSF led to:
- Increased interstitial DC (CD1a+)
- Increased expression activation marker (CD83/86)

To early to comment re clinical effects

Immunotherapy: Targeting the Dendritic Cell/T-Cell Interface

- APC
  - MHC - Ag
  - B7
  - CTLA-4
  - CD28

- T Cell
  - TCR
  - CD3
  - CD28

Ipilimumab inhibits
CTLA-4 Blockade: Phase 1 Trial

First-in-man trial conducted in CRPC at UCSF
Single dose of ipilimumab @ 3 mg/kg
14% PSA Response Rate. Good PK, no sig AE

Clinical effects of GM-CSF/ipilimumab therapy

- 50% (3/6) of patients on highest dose level had a PSA response
- 1 patient at highest dose level had measurable disease, with a partial response in liver metastases
- There appears to be a threshold effect or dose-response relationship with no responses seen at lower dose levels
GM-Ipi Clinical Responses

Pretreatment

Post-treatment

Immunotherapy: Targeting the Dendritic Cell/T-Cell Interface

APC

MHC – Ag

B7

CTLA-4

TCR

CD3

B7

CD28

T Cell

D9901: randomized phase III trial of Provenge® in CRPC

Provenge®

Every 2 weeks x 3

(N = 82)

Placebo

Every 2 weeks x 3

(N = 45)

Small EJ et al. JCO 2006

Immunotherapy: Sipuleucel-T, Provenge®

Prostatic acid phosphatase (PAP)-GM-CSF

Antigen-loaded precursor APC

In vivo

Antigen-presenting cell

Antigen

Precursor

APC

T cells attack tumor cells

T cell activation

In vivo

Provenge

Replaces

Immunotherapy: Sipuleucel-T, Provenge®
**D9901: randomized phase III trial of Provenge® in CRPC**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. patients</th>
<th>Deaths</th>
<th>Alive at 36 mos</th>
<th>Median survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provenge®</td>
<td>82</td>
<td>54</td>
<td>28 (34%)</td>
<td>25.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>45</td>
<td>40</td>
<td>5 (11%)</td>
<td>21.4</td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>--</td>
<td>0.0046</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Original primary endpoint:**
- Time to progression

**Off-study:**
- Provenge®: Every 2 weeks x 3
- Placebo: Every 2 weeks x 3

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**Neoadjuvant Sipuleucel-T (Provenge®) study: Phase II**

- Provenge® Q4 weeks x 3 doses
- No booster
- 9 weeks post-RP

**ENDPOINTS:**
- Primary: CD3+ T-cell infiltration
- Secondary: T-cell tissue and PB subsets, antigen-specific T-cell responses, PSA and primary tumor response

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Is Progressive Cancer after ADT Truly “Hormone Resistant?”

What are mechanisms for persistence of AR signaling?

Potential Mechanisms of Androgen Independence


The Hypothalamic-Pituitary-Gonadal Axis

Hypothalamus

Hypothalamic-Pituitary-Gonadal Axis

Abiraterone Acetate, a 17 alpha hydroxylase C17,20-Lyase inhibitor in Castration Resistant Prostate Cancer (CRPC).
Abiraterone Acetate - Overall Phase I Trial
PSA Decline Proportion

>50% decline @ 12 weeks
16/30 (53%) (95% CI 34%-72%)

Phase I data - Effect of Prior Ketoconazole?

Baseline
Post Cycle 6

Ryan et al. Proc ASCO 2008
Conclusions

1. Abiraterone acetate demonstrates considerable activity in the pre-chemotherapy setting as a secondary hormonal therapy.

2. Consistent effects are seen on the reduction of circulating androgen levels.

3. In addition to PSA declines, objective responses are seen.

4. These response data compare favorably to prior studies in ketoconazole treated patients.

5. Phase III studies in the pre-chemotherapy setting are planned, and a post-chemotherapy study is underway.

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CALGB  
DOD Prostate Cancer Therapy  
PCF Therapy Consortium  
UCSF Prostate SPORE  
CALGB

Angiogenesis and metastatic HRPC

Baseline serum and urine VEGF levels are prognostic markers for survival

Anti-angiogenics:

CALGB 90401: docetaxel/prednisone plus bevacizumab or placebo
Bevacizumab and metastatic HRPC

- Single-agent
  Single-arm phase II (UCSF) N=14
  PSA RR: 0%

- Combined with chemotherapy
  CALGB 90006: Docetaxel/estramustine + bevacizumab
  Single-arm, multi-center phase II trial N=72

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PSA RR</th>
<th>Time to Progression</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel/estramustine/carboplatin (CALGB 9813)</td>
<td>68%</td>
<td>8.1 months</td>
<td>18 months</td>
</tr>
<tr>
<td>Docetaxel/estramustine/bevacizumab (CALGB 90006)</td>
<td>81%</td>
<td>9.7 months</td>
<td>21 months</td>
</tr>
</tbody>
</table>

CALGB 90401: Docetaxel/prednisone plus bevacizumab or placebo

- Randomized phase III study now accruing
- Docetaxel 75 mg/m² q3 week
  - Prednisone 5 mg bid
  - Placebo q3 week
- Docetaxel 15 mg/kg q3 week

Metastatic HRPC

Endpoint:
- Improvement OS from 18 to 22 mos
- 90% power, \( \alpha = 0.05 \)
- Target accrual: 1000 patients
- Correlative
  - Pre- and post-treatment VEGF levels

Novel second-line chemotherapy:

Ixabepilone/mitoxantrone/prednisone
Satraplatin (SPARC trial)

2nd-line chemotherapy for HRPC

- With FDA-approved 1st-line chemotherapy, development of 2nd-line regimens for docetaxel failures important
  - Median survival for this group of patients ~1 year
  - Need non-cross-resistant regimens that are tolerable given prior chemotherapy

References:
1. Lin, Rosenberg. Proc ASCO 2006
3. Oh. Urology 2006
2nd-line chemotherapy for HRPC

- De-facto regimen has become mitoxantrone as already FDA approved in past for palliative benefit
  - 2nd-line RR: 20% \(^1\)

- Completed phase III registration trial (SPARC)
  2nd-line satraplatin (oral platinum)/prednisone vs. prednisone/placebo (N=950)
  - Preliminary report: median PFS 11 weeks vs. 9.7 weeks, \(p<0.00001\)

Novel agents for 2nd-line chemotherapy
Epothilones: ixabepilone (BMS-247550)

- Non-taxane agents affecting tubulin polymerization with anti-tumor activity in taxane-resistant cell lines
- Bypasses multi-drug resistance (MDR) and tubulin mutation modes of resistance implicated in taxane resistance
- 1st-line (no prior chemo): PSA RR: 33-48% \(^1,2\)
- 2nd-line: PSA RR 17% \(^3\)

UCSF phase I trial: combination of ixabepilone with mitoxantrone/prednisone

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Mitoxantrone</th>
<th>Ixabepilone</th>
<th>Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>8 mg/m²</td>
<td>20 mg/m²</td>
<td>5 mg bid</td>
</tr>
<tr>
<td>II</td>
<td>8 mg/m²</td>
<td>25 mg/m²</td>
<td>5 mg bid</td>
</tr>
<tr>
<td>III</td>
<td>10 mg/m²</td>
<td>25 mg/m²</td>
<td>5 mg bid</td>
</tr>
<tr>
<td>IV</td>
<td>10 mg/m²</td>
<td>30 mg/m²</td>
<td>5 mg bid</td>
</tr>
<tr>
<td>V</td>
<td>12 mg/m²</td>
<td>30 mg/m²</td>
<td>5 mg bid</td>
</tr>
<tr>
<td>VI</td>
<td>12 mg/m²</td>
<td>35 mg/m²</td>
<td>5 mg bid</td>
</tr>
</tbody>
</table>

Multi-center, UCSF-initiated