Prostate Cancer Clinical Trial

Overview:
What is New?

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Clinical trials are research studies in which people help doctors find ways to improve health and cancer care. Each study tries to answer scientific questions and to find better ways to prevent, diagnose, or treat cancer.

A clinical trial is one of the final stages of a long and careful cancer research process. Studies are done with cancer patients to find out whether promising approaches to cancer prevention, diagnosis, and treatment are safe and effective.
What are the different types of clinical trials?

1. Treatment Trials
2. Prevention Trials
3. Screening Trials
4. Quality of Life Trials

What are the phases of clinical trials?

1. Phase I
2. Phase II
3. Phase III
4. Phase IV
"3-10% with newly diagnosed cancer patients are treated on clinical trials"
# Novel Agents in CRPC

## Class of agent

<table>
<thead>
<tr>
<th>Agent</th>
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<tbody>
<tr>
<td>$17\alpha$ hydrolase/17, 20 lyase inhibitor</td>
<td>Abiraterone</td>
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<tr>
<td>Anti-angiogenic/immunomodulatory</td>
<td>CC4047, Lenalidomide, thalidomide</td>
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<tr>
<td>Anti-CTLA4 antibody</td>
<td>Ipilimumab</td>
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<td>Anti-II-6 antibody</td>
<td>CNTO 95</td>
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<td>Anti-insulin-like GFR antibody</td>
<td>IMC-A12</td>
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<td>Anti-integrin anti-body</td>
<td>CNTO 95</td>
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<tr>
<td>Anti-PSMA immunoconjugate</td>
<td>MLN2704, 177 Lu-J591</td>
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<td>Anti-prostate stem cell antibody</td>
<td>AGS-PSCA</td>
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<tr>
<td>Anti-VEGF</td>
<td>Bevacizumab</td>
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<td>Cytotoxic agent</td>
<td>ABT-751, abraxane, E7389, GMO-paclitaxel, Irofulven, Paclitaxel poliglumex, Pemetrexed, Trabectin, Vinfluvine, Epothilones, Satraplatin</td>
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<tr>
<td>EGFR antibodies\TKI</td>
<td>Pertuzumab, Cetuximab, Erlotinib, Gefitinib, Lapatinib</td>
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<td>GMP phospodiesterase inhibitor</td>
<td>Exisulind</td>
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<td>HSP-90 inhibitor</td>
<td>17-AAG</td>
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<td>HDACi</td>
<td>LBH589, Romidepsin, Valproic acid, Vorinostat, Belinostat</td>
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<tr>
<td>Integrin receptor antagonist</td>
<td>Cilengitide</td>
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<td>M-TOR inhibitor</td>
<td>RAD-001</td>
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<tr>
<td>Multi-targeted TKI</td>
<td>Sunitinib, Sorafenib, CEP 701</td>
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<tr>
<td>Pro-apoptotic agent</td>
<td>AT-101</td>
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<tr>
<td>Proteosome Inhibitor</td>
<td>Bortezomib</td>
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<tr>
<td>Signal Transduction inhibitor</td>
<td>PCK-3145</td>
</tr>
<tr>
<td>Survivin suppressant</td>
<td>YM155</td>
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Seed and Soil Hypothesis
Seed and Soil Hypothesis

Prostate Cancer Cells
“Seeds”
Personalizing Treatment for Patients
“New methods to evaluate the “Seed”

Tumor Microenvironment

“Soil”

Prostate Cancer Cells

“Seeds”
Increased intra-tumoral Testosterone in Advanced Prostate Cancer

Testosterone and dihydrotestosterone occur in recurrent prostate cancer at sufficient levels to activate the androgen receptor.

Mohler et al., Clin Cancer Res. 10(2):440-8, 2004
Testosterone | DHT

Increased Androgen Level

Prostate Cancer Cell
Increased Androgen Level

Testosterone|DHT

Prostate Cancer Cell

Novel therapies

Increased Androgen Level
Abiraterone Acetate (CB7630)

- CYP17 is key to androgenic steroid synthesis
- Oral, selective inhibitor of CYP17
  - one enzyme, dual function
    - 17α-hydroxylase
    - C17,20-lyase
- Inhibits testosterone production in testis, adrenal glands and prostate

MW = 391.55

3β-Acetoxy-17-(3-pyridyl)androsa-5,16-diene
Activity of Abiraterone in patients that the tumors growing despite treatment with multiple hormone therapies: Maximum Decline in PSA

Ryan et al Proc ASCO 2007
1. Engineered for activity in prostate cancer cells that overexpress the androgen receptor (AR).

2. Binds the AR more potently than bicalutamide.

3. Unlike bicalutamide, MDV3100 inhibits nuclear translocation of the AR and its binding to DNA.

4. Induces apoptosis in prostate cancer cells.

Scher et al. ASCO 2009
Patients that failed hormone therapy
PSA Change from Baseline- MDV3100

Chemotherapy-Naïve (N=65)

62% (40/65) >50% Decline

Post-Chemotherapy (N=75)

51% (38/75) >50% Decline
New Tumor Blood Vessels to the Cancer
“Angiogenesis”

Prostate Cancer
VEGF: The Key Mediator to New Blood Vessel Growth (Angiogenesis)

Environmental factors (Hypoxia, pH)
Growth factors (EGF, bFGF, PDGF, IGF-1, IL-1α, IL-6)

HIF-1α

Endothelial cell activation

Docetaxel

VEGF

Binding and activation of VEGF receptor

Survival
Proliferation
Migration

ANGIOGENESIS

Genes involved in tumorigenesis (p53, p73, src, ras, vHL, Bcr-Abl)
Avastin™ (bevacizumab)

- Recombinant humanized monoclonal IgG1 antibody\(^1\)
- Recognizes all isoforms of VEGF\(^2\)
- Estimated half-life is approximately 20 days (range, 11-50 days)\(^1\)
- Approved for the use in multiple cancers
- Improves survival in many cancer

Atrasentan: A Selective Endothelin-A Receptor Antagonist (important for tumors to grow in the bone)

Orally bioavailable
Once daily dosing
1800 x more selective for ET_A than ET_B

Targeting the Tumor and Its “Soil”

- Tumor (seed)
- Angiogenesis Inhibitors-Bevacizumab
- Endothelium-A Atrasentan

OR

Micro-environment (soil)

Docetaxel
Immunotherapy

“Vaccine”

- Sipuleucel-T (Provenge)
- G-VAX
- Prostvac-VF-Tricom

Turns on the Immune system

- CTLA-4 (Ipilimumab)
- Anti-PD-1
Immune System

1. The B cell finds an antigen which matches its receptors.
2. It waits until it is activated by a helper T cell.
3. Then the B cell divides to produce plasma and memory cells.
4. Plasma cells produce antibodies that attach to the current type of invader.
5. “Eater cells,” prefer intruders marked with antibodies, and “eat” loads of them.
6. If the same intruder invades again, memory cells help the immune system to activate much faster.
Immunotherapy

Sipuleucel-T (Provenge®) Manufacturing Process

Day 1
Leukapheresis

Apheresis Center

Day 2-3
Sipuleucel-T is manufactured

Dendreon

Day 3-4
Patient is infused

Doctor's Office

COMPLETE COURSE OF THERAPY:
3 CYCLES

Stimulate with artificial APCs

Isolate mixed T-cell population

Patient blood sample

Inject back into patient

Tumor-specific T-cells expand

Immune system attacks tumor
Provenge: Overall Survival:
Primary Endpoint Intent-to-Treat Population

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

Sipuleucel-T (n = 341)
Median Survival: 25.8 Mos.

Placebo (n = 171)
Median Survival: 21.7 Mos.
PROSTVAC-VF (PV) comprises 2 recombinant viral vectors (Vaccinia and Fowlpox), each encoding transgenes for prostate specific antigen (PSA) and 3 immune costimulatory molecules (B7.1, ICAM-1, and LFA3: TRICOM).

Kantoff et al; ASCO 2009: Abstract #5013
VITAL-2: G-VAX trial: Survival

(GVAX: 2 lines of whole prostate tumor cells modified to constantly produce GM-CSF)

GVAX/docetaxel:
- 67 deaths
- Median OS 12.2 m

Pred/docetaxel:
- 47 deaths
- Median OS 14.1 m

HR 1.7 (95% CI: 1.15, 2.53)

P = 0.0076

Small et al., ASCO GU Symposium 2009; Abst 7
Blocking CTLA-4 Increases Immune Responses

1. Co-stimulation via CD28 ligation transduces T cell activating signals

2. CTLA-4 ligation on activated T cells down-regulates T cell responses

3. Blocking CTLA-4 ligation enhances T cell responses
Novel Prostate Therapies

Ansamycins (17-AAG)
TK Inhibitors (ZD1839, OSI774)
Mono Abs (C225, Herceptin, 2c4)

FTI (BMS 214662)
Ansamycins
PD98059
Proteasome inhibitors (PS341)

Grb2/Shc
Sos
Ras

PTEN
AKT
Bad
BCL-2

PI3K
 LY294002

Src
PD173855/PD179483)

Src
PD173855/PD179483)

FTI (BMS 214662)

PI3K
 LY294002

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GU Clinical Research Program
Clinical Trial Status

Localized Prostate Cancer

Rising PSA

Non-Castrate Metastatic

Castrate Metastatic

High Risk Disease:
• PH III: CALGB 90203: AD + Doc + RP vs RP
• RTOG 0521: AD + XRT +/- Docetaxel

High Risk Disease:
• PH II AD + Bevac.
Low\Inter. Risk Disease
Phenoxodiol

1st Line
• Ph III CALGB 90202

2nd Line
• Phenoxodiol
• COU-AA-302
• Lu-J591 + Keto

First Line
• Ph III CALGB 90202

2nd Line
• Phenoxodiol
• COU-AA-302
• Lu-J591 + Keto

1st Line
• PH III: Doc +/- Aflibercept.
• PH II Docetaxel + metronic cytoxan
• Mito + IMC-A12 or IMC-1121
• MDV3100

3rd Line therapy
• Lu-J591 + Docetaxel
• Anti-PD-1

Protocol being written
Protocol written-pending receipt
Protocol written-pending submission
Protocol under Institution review
Protocol activated
Nanoparticles for Diagnosis and Therapy

Features of technology:
• Constructed entirely from FDA-approved materials
• Versatility:
  • Encapsulate agents of any type or size
  • Encapsulate multiple agents
  • Surface modification, through high density surface attachment sites
  • Proven in multiple animal models, in oral and injected dosages

Saltzman and Hoimes
Personalizing Treatment for Patients
“Seed and Soil”
Thank You
Targets for Prostate Cancer Therapy

1. Growth factors
2. Growth factor receptors
3. Adaptor proteins
4. Docking proteins/binding proteins
5. Guanine nucleotide exchange factors
6. Phosphatases and phospholipases
7. Signaling kinases
8. Ribosomes
9. Transcription factors
10. Histones
11. DNA
12. Microtubules
ET-1 Pathway Dysregulation in Cancer

- Normal cell: 
  - $\text{ET}_B$ receptors predominate
  - NEP active
  - ET-1 degraded

- Cancer cell: 
  - $\text{ET}_A$ receptor expression upregulated
  - $\text{ET}_B$ receptor expression downregulated
  - NEP activity decreased

Neutral endopeptidase 24.11 (NEP)
MLN2704

MLN591 (aka J591)

Drug maytansinoid-1 (DM1)
Tumor Localization: Bone (25 mg dose)

J591 Scan

Bone Scan
Gene gun technology