Can We Combine Novel Agents in the Management of Advanced Prostate Cancer

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Combination Therapy

- Oncologists are at times creatures of habit
  - Combination therapy
    - Non-overlapping mechanism
    - Non-overlapping toxicity
    - Additive/synergistic benefit

- In the world of cytotoxics
  - If one is good, more is better (not always)

- Combination therapy with novel agents
  - Not always easy
    - RCC: Sunitinib + bevacizumab
Complete Biochemical (Prostate-specific Antigen) Response to Sipuleucel-T With Enzalutamide in Castration-resistant Prostate Cancer: A Case Report With Implications for Future Research

- 69 year old with mcrpc on phase I study of enzalutamide
- Obtains significant psa response (undetectable), improved bone scan, duration of biochemical response 14 months
- At time of psa progression, treated with sipuleucel-t (remained on enzalutamide/LHRH)
- Six months post, undetectable PSA, maintained x 1 year without radiographic change

Combination Therapy in metastatic CRPC: Current Status

- T suppression
  - + second line hormonal therapy
  - + sipuleucel-T
  - + docetaxel, + bone targeted agents
  - + radiotherapy
MDV3100 effects on androgen receptor (AR) signaling and bone marrow testosterone concentration modulation: A preliminary report

- 47 pts with progressive metastatic CRPC, treated with MDV3100 underwent serial BM bx
- Mean plasma T rose from 0.041 ng/ml range (0.00-0.1) to 0.066 (range 0.00-0.18) in 40 evaluable pts
- Higher pretreatment BM and plasma T are associated with PSA response

MDV3100 effects on androgen receptor (AR) signaling and bone marrow testosterone concentration modulation: A preliminary report

- Findings support the hypothesis that MDV3100 efficacy in CRPC is attributed to potent AR inhibition
- MDV3100 increases BM T and decreases nuclear AR
- Abiraterone acetate decreases T and increases AR copy number
- Taken together these data suggest evaluation of these two androgen signaling inhibitors in combination will work synergistically

A Study to Determine Safety and Tolerability of Enzalutamide (MDV3100) in Combination With Abiraterone Acetate in Bone Metastatic Castration-Resistant Prostate Cancer Patients

- Phase II trial of mCRPC patients (prior chemotherapy allowed)
- N=60
- ClinicalTrials.gov Identifier: NCT01650194
Proposed Intergroup Phase III Trial

Patients with metastatic castration-resistant prostate cancer

- Enzalutamide
- Enzalutamide + Abiraterone/Prednisone
- Abiraterone/Prednisone
Trial Endpoints: FDA/CMS and the rest of us

- Things would be a lot easier if PSA was a true intermediate endpoint: it’s not
- Prostate cancer is a bone tropic disease, true measurable disease in only 20-30% of patients
- Overall survival is a hard endpoint
  - It’s worked as a regulatory endpoint till now, but…
Trial Endpoints: FDA/CMS and the rest of us

- Pre/Post docetaxel enabled a start point for survival studies
- Both abiraterone and enzalutamide demonstrated survival in post chemotherapy setting
  - Abiraterone approved on rPFS endpoint
- Given the number of new agents approved, all impacting survival, is reliance on a survival endpoint going forward viable?
Clinical States In Prostate Cancer

Organ Confined

Locally Advanced Disease

Rising PSA Hormone Naive

Rising PSA Castrate

Metastatic Disease (De novo)

Metastases Castrate Resistant Asymptomatic

Metastases Castrate Resistant Symptomatic

Metastases Castrate Resistant Post Docetaxel Post Abiraterone

Metastases Castrate Resistant Post Cabazitaxel

Sipuleucel-T

Cabazitaxel

Radium 223

Enzalutamide

Abiraterone

Denosumab

Zolendronic Acid

Combination and or Sequential Therapy for CRPC: Challenges

- Current reimbursement paradigm, is slowly but inexorably coming to an end
- Compendium listing of drugs will be nice, but will increasingly miss the point
- In a world of ACO’s, medical homes and contracts for populations we need to think about VALUE in addition to science/clinical results
Metastases Castrate Resistant Asymptomatic

Sipuleucel-T

Metastases Castrate Resistant Symptomatic

Sipuleucel-T

Enzalutamide + Abiraterone

Followed by Abiraterone at disease progression (PSA/radiographic)

Phase I/II underway
Phase III proposed

Likely only empirical data will be available re: sequence
No comparative data re: time to PSA progression/radiographic progression etc
Bone Targeted Agents

- Enzalutamide + Abiraterone

- Denosumab
- Zolendronic Acid

- Radium 223

- Enzalutamide with Abiraterone at disease progression

- Metastases Castrate Resistant Asymptomatic

- Metastases Castrate Resistant Symptomatic
Impact of enzalutamide, an androgen receptor signaling inhibitor, on time to first skeletal related event (SRE) and pain in the phase 3 AFFIRM study

- Enzalutamide significantly delayed time to first SRE
  - 16.7 months with enzalutamide versus 13.3 months with placebo
  - Equates to a 31% reduction in risk of SRE ($P = .0001$)

- Fewer patients experienced EBRT to bone
  - 20% for enzalutamide versus 25% for placebo
  - Spinal cord compression 6% (Enza) versus 8% (Placebo)
  - 4% in each group experienced pathological fracture

Fizazi, K, et al. European Society for Medical Oncology Congress, 2012; Vienna, Austria. Abstract 896O
Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial

- In the overall population, median time to occurrence of first skeletal-related event was significantly longer with abiraterone acetate and prednisone than with prednisone only (25 months vs 20.3 months p=0.0001)

- In patients with clinically significant pain at baseline abiraterone acetate and prednisone resulted in significantly more palliation 45.0% vs 28.8% p=0.0005) pain intensity than did prednisone only

Bone Targeted Agents

Enzalutamide + Abiraterone

Enzalutamide with Abiraterone at disease progression

Metastases Castrate Resistant Asymptomatic

Metastases Castrate Resistant Symptomatic

Denosumab
Zolendronic Acid

ADDITIVE?
SYNERGISTIC?
ALSYMPCA Time to First Skeletal-Related Event

HR 0.610; 95% CI, 0.461-0.807
\( P = 0.00046 \)

Radium-223, \( n = 541 \)
Median: 13.6 months

Placebo, \( n = 268 \)
Median: 8.4 months

Parker C. J Clin Oncol 30, 2012 (suppl; LBA 4512)
Radium 223 Combination Therapy

- Excellent toxicity profile
- Unique mechanism of action
- Combination studies with AR targeted agents
  - Issues of other bone targeted therapy when combined with two potent agents that decrease SRE/impact survival
- Combination with immunomodulatory agents
Near Term Questions for Combination Therapy

- Can more potent AR targeted therapy cure patients with minimal disease state disease
  - The adjuvant breast paradigm
  - Lyase inhibitor + next generation AR antagonist
- Locally advanced prostate cancer s/p combined modality therapy
- Cost effective/ value based care questions
“In the history of the world no one has ever washed a rented car”

Lawrence Summers, Ph.D.