AR Targeting in Non-CRPC
Can we do better?

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Premise

• AR Targeting is moving “left” from mCRPC to:
  – Nonmet CRPC
  – serologic relapse to:
    – adjuvant.

• Enhanced potency may give the opportunity to delay, avoid or shorten castration.

• Attention to the reduced toxicity and enhanced QOL is key.
The direction of progress is to the left.
If Rx is going to last for years how can we continue to push efficacy and simultaneously reduce toxicity?
Do we target the ligand, the receptor or both?

Receptor events:
- AR Amplification and Mutation
- AR Splice Variants

Pre-Receptor Events:
- Adrenal Androgen Production
- And Polymorphisms
- Intracrine Androgen Production

Ryan, Tindall Journal of Clinical Oncology 2011
SPARTAN Phase 3 RCT in Non-Metastatic CRPC

Registration Study for Apalutamide

- M0 (central imaging)
- Rising PSA despite medical or surgical ADT
- PSADT ≤10 mos
- T <50 ng/dL

Randomization

ARN-509 + ADT

Placebo + ADT

- Primary Endpoint: MFS
- Key Secondary Endpoint: OS
- Other Secondary Endpoints:
  - TT symptomatic progression
  - TT Chemo
  - rPFS
  - TT mets
  - PROs
  - Safety
  - Pop PK
  - QT sub-study

Global Principal Investigators: Matthew Smith and Eric Small
Latitude: >20% death within 2 years.
AR directed therapy does not benefit all…

HR (95% CI) = 0.62 (0.51-0.76); p < 0.001
OS rate at 3 years: 66% vs 49%, favoring Abiraterone

From Fizazi et al, ASCO 2017
Do the Known Mechanisms of Abiraterone Resistance in Metastatic CRPC Apply in the post Latitude Patient?

Abiraterone

COU 301 (DeBono)
COU 302 (Ryan)

Disease Burden

- **FISH ANALYSIS**
  - AR probe
  - Centromere probe

- **IHC ANALYSIS**
  - AR Stain

- **H & E STAINING**
  - Rx-associated Small Cell/Neuroendocrine Prostate Cancer

Data from West Coast Prostate Cancer Dream Team

courtesy: Eric J Small, MD
Is the fear of “Inducing” more aggressive post AR Disease Warranted??

Post Abi/Enza: Non-Adeno is common and has a poor prognosis....in CRPC

Histology of 124 Evaluable Biopsies
74% were “pure” with a single histologic subtype (*isolated by LCM)
Remainder (26%) were comprised of mixed populations

<table>
<thead>
<tr>
<th>Histological Features</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdenoCA + IAC separate clusters</td>
<td>11</td>
</tr>
<tr>
<td>IAC + SCNC separate clusters</td>
<td>4</td>
</tr>
<tr>
<td>AdenoCA + SCNC separate clusters</td>
<td>1</td>
</tr>
<tr>
<td>Non-adenoCA cytology with adenoCA architecture</td>
<td>11</td>
</tr>
</tbody>
</table>

Overall survival as function of biopsy pathology
Grouping IAC and SCNC

Log rank P = 0.006
ENZAMET

Hypothesis: Earlier use of enzalutamide will increase the longevity of men commencing ADT for hormone sensitive metastatic prostate cancer

Eligibility
Metastatic prostate cancer
Adequate organ function
Starting 1st line ADT

Stratification
Volume of disease
Anti-resorptive therapy
Comorbidities
Study Site

(Docetaxel use -Amendment pending)

1,100 participants
2 years accrual + 3.5 years minimum additional follow-up
80% power to detect 25% reduction in the hazard of death from any cause, assuming an OS rate at 3 years of 65% in the control group

Endpoints
Overall survival (primary)
PSA progression free survival
Clinical progression free survival
Health related quality of life
Adverse events
Incremental cost-effectiveness

Enzalutamide 160mg/daily + LHRHA (or orchidectomy) until progression

Non-Steroidal Anti-Androgen* + LHRHA (or orchidectomy) until progression

1:1

*Conventional Non-Steroidal Anti-Androgens: bicalutamide 50mg daily, nilutamide 150mg daily, or flutamide 250mg tid
Select Enzalutamide Prostate Clinical Studies

For example, surgery, radiotherapy.


# Investigator Sponsored Research / COOP Study
Serologic Relapse:

Cure  Prevent  Delay  Over Treat
Serologic Relapse: ARN-002 Study: Apalutamide vs LHRH vs combination in Serologic Relapse

**ACCRUAL COMPLETE**

N = 90

- Prior radical prostatectomy w/RT or RT
- Biochemically relapsed disease with PSADT <= 9 months
- No metastases (abdominal/pelvic nodes < 2 cm allowed)
- No prior ADT for biochemical relapse
- No ADT within 9 months of study entry

Randomize 1:1:1

Arm A: Leuprolide

Arm B: Apalutamide

Arm C: Leuprolide Apalutamide

Primary Endpoint: QOL

Serologic Relapse

Is AR Targeting alone good enough in disease control but better in QOL?

12 months

Rahul Aggarwal PI
Increased Intensity  ---  Brief Duration

A Phase 3 Study of Androgen Annihilation in High-Risk Biochemically Relapsed Prostate Cancer

Sponsor: Alliance Foundation
AFT-19
IND #: 131441

Study Chair: Rahul Aggarwal
Correlative Chair: Akash Patnaik

Primary Statistician: Susan Halabi
PROs/Quality of Life: Ron Chen
AFT-19 Phase III Study of Triple Potent AR blockage

N = 504 patients

Prior radical prostatectomy
Biochemically relapsed disease with PSADT <= 9 months
No metastases (abdominal/pelvic nodes < 2 cm allowed)
No prior ADT for biochemical relapse
No ADT within 9 months of study entry

Stratified by:
PSA doubling time (< 3 mos vs 3-9 mos)

Randomize 1:1:1

Arm A: Degarelix

Arm B: Degarelix + Apalutamide

Arm C: Degarelix + Apalutamide + Abi/Pred

Follow up for PSA Progression
Long term follow up for time to CRPC, metastasis-free survival and overall survival

12 months
Primary endpoint:

- Median PSA progression-free survival in all randomized pts (ITT population)
  - On-treatment: Rising PSA confirmed on repeat measurement and absolute value > 25% + 2 ng/ml above nadir/baseline
  - In-follow up: PSA > 0.2 ng/mL confirmed by repeat measurement

Secondary endpoints:

- Median PSA progression-free survival in T-evaluable population
  - T-evaluable defined as recovery of serum T to > 50 ng/dL with follow up PSA measurements sufficient for evaluation
- 36 month PSA progression-free survival rate
- Quality of life (on treatment and in follow up)
- Median time to T recovery to > 50 ng/dL
- Median time to castration-resistance
  - PSA increase > 25% and more than 2 ng/mL above nadir with concomitant T < 50 ng/dL
- Median metastasis-free survival
- Median overall survival
Sample Size Justification

• N = 504 patients (168 pts/arm)
• 205 PFS events required for each comparison
• Study power 85%
• 2 interim analyses at 50% (~30 months) and 75% (~38 months) of PFS events
• Overall (interim + final analysis) 2 sided alpha = 0.025 for each pair-wise comparison
  • Triplet versus control
  • Doublet versus control
Can we do it without Castration?

As patients live longer, ADT Side effects impact QOL (and DOL?) more.....

ADT And Dementia (of all types)

Nead et al

*JAMA Oncology*  Published online October 13, 2016
Level One Evidence
Targeting the AR alone can impact survival.

# Effect of Antiandrogen Therapy with Bicalutamide on 12-Year Overall Survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients (%)</th>
<th>Bicalutamide Group 12-yr overall survival rate (%)</th>
<th>Placebo Group 12-yr overall survival rate (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>760 (100.0)</td>
<td>76.3</td>
<td>71.3</td>
<td>0.77 (0.59–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–6</td>
<td>214 (28.2)</td>
<td>79.5</td>
<td>79.2</td>
<td>0.95 (0.57–1.59)</td>
<td>0.84</td>
</tr>
<tr>
<td>7</td>
<td>413 (54.5)</td>
<td>78.5</td>
<td>70.9</td>
<td>0.69 (0.49–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>8–10</td>
<td>131 (17.3)</td>
<td>63.9</td>
<td>58.4</td>
<td>0.76 (0.44–1.30)</td>
<td>0.32</td>
</tr>
<tr>
<td>PSA level at trial entry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.7 ng/ml</td>
<td>405 (53.3)</td>
<td>76.8</td>
<td>80.7</td>
<td>1.13 (0.77–1.65)</td>
<td>0.53</td>
</tr>
<tr>
<td>0.7–1.5 ng/ml</td>
<td>237 (31.2)</td>
<td>77.0</td>
<td>67.5</td>
<td>0.61 (0.39–0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>&gt;1.5 ng/ml</td>
<td>118 (15.5)</td>
<td>73.5</td>
<td>48.9</td>
<td>0.45 (0.25–0.81)</td>
<td>0.007</td>
</tr>
<tr>
<td>Positive surgical margin</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>191 (25.1)</td>
<td>73.5</td>
<td>72.9</td>
<td>0.87 (0.53–1.41)</td>
<td>0.56</td>
</tr>
<tr>
<td>Yes</td>
<td>569 (74.9)</td>
<td>77.3</td>
<td>70.7</td>
<td>0.73 (0.54–0.98)</td>
<td>0.04</td>
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Androgen Receptor (AR) Pathway and Prostate Cancer

A Randomized, Double-blind, Placebo Controlled Phase III Study of ODM-201 Versus Placebo in Addition to Standard Androgen Deprivation Therapy and Docetaxel in Patients With Metastatic Hormone Sensitive Prostate Cancer.

**Registration Study for Darolutamide**

- **M1 Prostate cancer**

**Randomization**

- **Primary Endpoint: OS**

- **Darolutamide + Docetaxel + ADT**

- **Docetaxel + ADT**

*Accruing*
The molecular subtypes of prostate cancer are similar to those of breast cancer.

Breast Cancer Cohort (232 patients, Parker et al, JCO)

Prostate Cancer Cohort (1567 patients)

Validated on another 6300 patients with prostate cancer!! Zhao et al, JAMA Oncology 2017
Luminal B prostate cancers have worse outcomes compared to Luminal A or Basal.
Cohorts for Matching  
N=780

2:1 matching on ADT  
Covariates: Gleason, PSA, RT, LNI, ECE, SVI, SM

Final Matched Cohort  
N=315

Predict response to post-operative ADT

Luminal B prostate cancers exhibit the greatest response to androgen deprivation

Zhao et al, JAMA Oncology 2017
Eligibility
PSA recurrent post-RP with PSA ≥0.1 and ≤1.0 ng/mL and at least one of the following risk features:

- Gleason score 4+3 or greater
- Persistent PSA elevation after RP
- Pathologic pT3 disease

Stratification
1. One vs. multiple risk features
2. Molecular subtype (Luminal B vs non-Luminal B)

Randomize

Arm 1
Salvage RT + 6 months of placebo

Arm 2
Salvage RT + 6 months of apalutamide

NRG 1614 trial schema:

Trial PIs: F Feng & D Spratt

Luminal A, B and Basal: The next step: Molecular stratification
ERADICATE: ECOG Study in Development

Study Design – Phase II/III

**Screen**
(2 parts)
1. Exclude low risk
2. Identify high risk

- CAPRA-S ≥ 3
- Decipher

**Decipher ≥ 0.6**
- Randomize
  - ADT x 18 mo
  - ADT+Enza x 18 mo

**Decipher <0.6**
- Not followed

**Endpoint**
- 5 year Metastasis Free Survival

* Can administer adjuvant XRT at any time during the initial 12 months.

Alicia Morgans PI
Summary

• AR Targeting is moving “left” from mCRPC to:
  – Nonmet CRPC
  – serologic relapse to:
  – adjuvant.

• Enhanced potency may give the opportunity to delay, avoid or shorten castration.

• Attention to the reduced toxicity and enhanced QOL is key.