GU MALIGNANCIES

Bruce J. Roth, M.D.
Clinical Trials: Medivation, Oncogenix

PROSTATE CANCER

1) Alpharadin (Ra223) in CRPC with bone metastases
2) Enzalutamide (MDV-3100) in CRPC and prior docetaxel
3) Abiraterone in chemo-naïve CRPC
4) Intermittent androgen deprivation in androgen-sensitive PCa
UPDATED ANALYSIS OF THE PHASE III, DOUBLE-BLIND, RANDOMIZED MULTINATIONAL STUDY OF RADIUM-223 CHLORIDE IN CASTRATION-RESISTANT PROSTATE CANCER (CRPC) PATIENTS WITH BONE METASTASES (ALSYMPCA)

Parker C, et al.
LBA4512

ALPHA PARTICLES AS RADIOPHARMACEUTICALS

- Differ from beta particles in terms of energy, tissue range, linear-energy transfer, and number of DNA hits needed to kill a cell
- Deliver and intense and highly localized radiation dose (range 2-10 cell diameters)
- Double-stranded DNA breaks (does not require cycling cells)
- Less irradiation of healthy bone marrow
Calcium-mimetic, forms complexes with hydroxyapatite, incorporated into bony matrix

Preferential uptake in areas of new bone formation, targeting tumor cells in close proximity to areas of new bone growth surrounding metastases

Path length of only 40 – 100 μm

Half-life of 11.4 days
**ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III**

**Patients**
- Symptomatic CRPC
- \( \geq 2 \) bone mets
- No visceral mets
- Post-docetaxel or doxetaxel unfit

**Stratification**
- Total ALP
  - \( < 220 \) vs \( \geq 220 \)
- Bisphosphonate Y/N
- Prior docetaxel Y/N

**Treatment**
- Radium-223 (50 kBq/kg) + Best standard of care
- Placebo + Best standard of care

**N = 922**

**ALSYMPCA: ENDPOINTS**

- **Primary** – overall survival
- **Secondary**
  - Time to first SRE
  - Time to alk phos progression
  - Total alk phos response
  - Total alk phos normalization
  - Time to PSA progression
  - QOL
  - Safety
### ALSYMPCA Updated Analysis

#### Patient Demographics and Baseline Characteristics (ITT N = 921)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Radium-223 n = 614</th>
<th>Placebo n = 307</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>70.2</td>
<td>70.8</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>575 (94)</td>
<td>290 (95)</td>
</tr>
<tr>
<td>Baseline ECOG score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1</td>
<td>536 (87)</td>
<td>265 (86)</td>
</tr>
<tr>
<td>2</td>
<td>76 (12)</td>
<td>40 (13)</td>
</tr>
<tr>
<td>Extent of disease, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 metastases</td>
<td>100 (16)</td>
<td>38 (12)</td>
</tr>
<tr>
<td>6–20 metastases</td>
<td>262 (43)</td>
<td>147 (48)</td>
</tr>
<tr>
<td>&gt; 20 metastases/superscan</td>
<td>249 (41)</td>
<td>121 (40)</td>
</tr>
<tr>
<td>WHO ladder, cancer pain index ≥ 2, n (%)</td>
<td>345 (56)</td>
<td>168 (55)</td>
</tr>
</tbody>
</table>

#### Median OS

- **Radium-223, n = 614**: Median OS: 14.9 months
- **Placebo, n = 307**: Median OS: 11.3 months

**HR = 0.695**

95% CI, 0.581, 0.832

**P = 0.00007**
**ALSYMPCA Updated Analysis**

**OS by Stratification Variables: Prior Docetaxel Use**

- **Prior docetaxel use**
  - HR = 0.710, 95% CI, 0.565, 0.891, \( P = 0.00307 \)

- **NO prior docetaxel use**
  - HR = 0.745, 95% CI, 0.562, 0.987, \( P = 0.03932 \)

**ALSYMPCA Updated Analysis**

**OS by Stratification Variables: Bisphosphonate Use**

- **Current bisphosphonate use**
  - HR = 0.699, 95% CI, 0.525, 0.931, \( P = 0.01378 \)

- **NO current bisphosphonate use**
  - HR = 0.736, 95% CI, 0.587, 0.923, \( P = 0.00775 \)
**ALSYMPCA Updated Analysis**

**OS by Stratification Variables:**

Baseline ALP

<table>
<thead>
<tr>
<th>Total ALP &lt; 220 U/L</th>
<th>Total ALP ≥ 220 U/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR = 0.825</td>
<td>HR = 0.619</td>
</tr>
<tr>
<td>95% CI, 0.635, 1.072</td>
<td>95% CI, 0.486, 0.788</td>
</tr>
<tr>
<td>P = 0.14945</td>
<td>P = 0.00009</td>
</tr>
</tbody>
</table>

**Radium-223, n = 348**
Median: 17.0 months

**Placebo, n = 169**
Median: 15.8 months

HR = 0.825
95% CI, 0.635, 1.072
P = 0.14945

Radium-223, n = 266
Median: 11.4 months

Placebo, n = 138
Median: 8.1 months

HR = 0.619
95% CI, 0.486, 0.788
P = 0.00009

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**ALSYMPCA Updated Analysis**

**Time To First SRE**

<table>
<thead>
<tr>
<th>Radium-223, n = 614</th>
<th>Placebo, n = 307</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR = 0.64</td>
<td></td>
</tr>
<tr>
<td>95% CI, 0.52, 0.78</td>
<td></td>
</tr>
<tr>
<td>P &lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

**Radium-223**
Median: 12.2 months

**Placebo**
Median: 6.7 months

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*Provisional data*
**ALSYMPCA Updated Analysis**

**AEs of Interest**

<table>
<thead>
<tr>
<th>Patients with AEs n, (%)</th>
<th>Radium-223 n = 600</th>
<th>Placebo n = 301</th>
<th>Radium-223 n = 600</th>
<th>Placebo n = 301</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>187 (31)</td>
<td>92 (31)</td>
<td>77 (13)</td>
<td>39 (13)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30 (5)</td>
<td>3 (1)</td>
<td>13 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69 (12)</td>
<td>17 (6)</td>
<td>38 (6)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Non-Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>300 (50)</td>
<td>187 (62)</td>
<td>125 (21)</td>
<td>77 (26)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151 (25)</td>
<td>45 (15)</td>
<td>9 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>213 (36)</td>
<td>104 (35)</td>
<td>10 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>111 (19)</td>
<td>41 (14)</td>
<td>10 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>108 (18)</td>
<td>64 (21)</td>
<td>6 (1)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

**CONCLUSIONS:**

**(Author’s)**

- Radium-223 compared with placebo in CRPC patients with bone metastases:
  - Significantly prolonged median OS by 3.6 months (HR = 0.695; \( P = 0.00007 \))
    - 30.5% reduction in risk of death
  - Significantly prolonged median time to first SRE by 5.5 months (HR = 0.64; \( P < 0.0001 \))

- Further follow-up in all randomized patients continues to show highly favorable safety profile

Radium-223, a first-in-class alpha-emitter, may provide a new standard of care for the treatment of CRPC patients with bone metastases
CONCLUSIONS: (Mine)

- What “standard of care” is this replacing?
  - samarium? cabazitaxel? bisphosphonates? denosumab?
- Let’s wait for additional info
  - Peer-reviewed publication
  - ODAC deliberation
  - Package insert
- That being said, this is a first-in class compound with unexpectedly good results

PHASE III TRIAL (AFFIRM) OF ENZALUTAMIDE (MDV3100), AN ANDROGEN RECEPTOR SIGNALING INHIBITOR: PRIMARY, SECONDARY, AND QUALITY–OF–LIFE ENDPOINT RESULTS

De Bono J, et al.
LBA 4519
ANTIANDROGENS


ADDITION OF AN ANTIANDROGEN

Adrenal/Paracrine Synthesis

Testosterone

DNA binding

cell nucleus

Androgen Receptors

bicalutamide
SECOND-GENERATION ANTIANDROGEN

Adrenal/Paracrine Synthesis

Testosterone

DNA binding

cell nucleus

Androgen Receptors

Waterfall Plot of Best Percent PSA Change from Baseline

Chemotherapy-Naive (N=65)       Post-Chemotherapy (N=75)

<table>
<thead>
<tr>
<th>Change %</th>
<th>Count (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% Decline</td>
<td>62% (40/65)</td>
</tr>
<tr>
<td>≥50% Decline</td>
<td>51% (38/75)</td>
</tr>
</tbody>
</table>
Patient Population: 1199 patients with progressive CRPC Failed docetaxel chemotherapy

Primary Endpoint: Overall Survival

Randomized 2:1

Enzalutamide 160 mg daily n = 800
Placebo n = 399

OVERALL SURVIVAL

HR = 0.631 (0.529, 0.752) P < 0.0001
37% reduction in risk of death

Enzalutamide: 18.4 months (95% CI: 17.3, NYR)
Placebo: 13.6 months (95% CI: 11.3, 15.8)

Survival, %

Duration of Overall Survival, Months

Enzalutamide 800 775 701 627 400 211 72 7 0
Placebo 399 376 317 263 167 81 33 3 0
SECONDARY ENDPOINTS

- PSA response
  - ≥ 50%: E - 54%; P - 2% (p < 0.0001)
  - > 90%: E - 25%; P - 1% (p < 0.0001)

- PSA PFS
  - E – 8.3 mths; P – 3.0 mths (HR 0.248, p < 0.0001)

- RECIST Response
  - CR + PR: E – 28.9%; P – 3.8% (p < 0.0001)

SECONDARY ENDPOINTS (cont.)

- Radiographic PFS
  - E – 8.3 mths; P – 2.9 mths (HR 0.404, p < 0.0001)

- Time to First SRE
  - E – 16.7 mths; P – 13.3 mths (HR 0.621, p < 0.0001)

- QOL Responses (FACT-P) (10-pt increase in score)
  - E – 43.2%; P – 18.3% (p < 0.0001)
### Adverse Events of Special Interest

<table>
<thead>
<tr>
<th></th>
<th>All Grades</th>
<th>Grade ≥ 3 Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enzalutamide (n = 800)</td>
<td>Placebo (n = 399)</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>33.6%</td>
<td>29.1%</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td>6.1%</td>
<td>7.5%</td>
</tr>
<tr>
<td><strong>Myocardial Infarction</strong></td>
<td>0.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>LFT Abnormalities</strong></td>
<td>1.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td><strong>Seizure</strong></td>
<td>0.6%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

### Seizure Cases

<table>
<thead>
<tr>
<th>CASE</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time on Study</strong></td>
<td>2 months</td>
<td>10 months</td>
<td>2 months</td>
<td>5 months</td>
<td>10 months</td>
</tr>
<tr>
<td><strong>On study drug?</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Off trial drug for 26 days</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Seizure type</strong></td>
<td>Focal onset</td>
<td>Generalized</td>
<td>Complex partial status</td>
<td>Focal onset</td>
<td>Unknown, fall not witnessed</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Potential confounding factors</strong></td>
<td>Large 5 x 4 cm temporal lobe brain metastases</td>
<td>IV Lidocaine inadvertently given just before seizure*</td>
<td>Atrophy and leukoariosis on MRI brain; no else</td>
<td>Multiple CNS metastases: Eye, meninges, cerebellar</td>
<td>Alcohol excess; started on haloperidol 7 days prior</td>
</tr>
</tbody>
</table>

*40 mg IV lidocaine (lignocaine); patient also on Na+ channel modulator: propafenone (flecainide like antidysrhythmic).
**CONCLUSIONS**

- Enzalutamide, a once a day oral Androgen Receptor Signaling Inhibitor, is well tolerated and prolongs survival in men with CRPC by almost 5 months.

- Enzalutamide improved secondary measures of antitumor activity including health-related quality of life, response, time to SRE and time to disease progression.

- The androgen receptor remains a valid therapeutic target for treating CRPC following chemotherapy.

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**ENZALUTAMIDE – FUTURE DIRECTIONS**

- FDA approved 8/31/2012

- Pre-chemotherapy phase III trial has completed accrual – results likely available in 2013

- STRIVE – phase III enzalutamide versus bicalutamide as second-line hormonal therapy (both non-metastatic and metastatic) just opening to accrual
INTERIM ANALYSIS RESULTS OF COU-AA-302, A RANDOMIZED PHASE III STUDY OF ABIRATERONE ACETATE IN CHEMOTHERAPY-NAÏVE PATIENTS WITH METASTATIC, CASTRATION-RESISTANT PROSTATE CANCER

Ryan, CJ et al
LBA 4518

SOURCES OF ANDROGEN FOR THE PROSTATE CANCER CELL

- Testicle
- Adrenal
- Intracrine

Androgen synthesis inhibition
Androgen Synthesis Pathway

Phase III Registration Trial of Abiraterone Acetate in Post-Chemotherapy Setting

- **Abiraterone 1000 mg daily**
- **Prednisone 10 mg daily**

Randomization 2:1

- **Placebo daily**
- **Prednisone 10 mg daily**

**Primary Endpoint:** 25% survival increase (12 – 15 mos)

**Secondary Endpoints:** TT PSA progression, PFS, PSA response rate
Phase III Abiraterone Post-Chemotherapy – Results

- 1195 pts (abiraterone 797: placebo 398); median f/u 12.8 mths: data unblinded at interim analysis
- OS: abiraterone 14.8 mths: placebo 10.9 mths (HR .65 (95% CI 0.54 - 0.77; P<0.001)
- TT PSA progression: abi 10.2 v placebo 6.6 mths
- PFS: abi 5.6 v placebo 3.6 mths
- PSA RR: abi 29% v placebo 6% (P< 0.001)


Overall Study Design of COU-AA-302

- Patients
  - Progressive chemo-naïve mCRPC patients (Planned N = 1088)
  - Asymptomatic or mildly symptomatic

- Efficacy end points
  - Co-Primary:
    - rPFS by central review
    - OS
  - Secondary:
    - Time to opiate use (cancer-related pain)
    - Time to initiation of chemotherapy
    - Time to ECOG-PS deterioration
    - TTPP

- 1:1 RANDOMIZED

- AA 1000 mg daily Prednisone 5 mg BID (Actual n = 546)
- Placebo daily Prednisone 5 mg BID (Actual n = 542)

- Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada
- Stratification by ECOG performance status 0 vs 1
COU–AA–302: rPFS Definition

- Progressive disease (PD) by bone scan: Adapted from Consensus Criteria\(^1\)
  - Blinded central radiologist review
  - \(< 12\) weeks after randomization
    - \(\geq 2\) new bone lesions plus \(2\) additional at confirmation ("2+2")
  - \(\geq 12\) weeks after randomization
    - \(\geq 2\) new bone lesions with subsequent confirmation
- PD (soft tissue lesions) by CT or MRI by modified RECIST criteria
- Death from any cause


Statistically Significant Improvement in rPFS Primary End Point

<table>
<thead>
<tr>
<th></th>
<th>AA + P (median, mos): NR</th>
<th>PL + P (median, mos): 8.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>0.43 (0.35–0.52)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Data cutoff 12/20/2010. NR, not reached; PL, placebo.
Pre-specified significance level by O'Brien-Fleming Boundary = 0.0008.

Data cutoff 12/20/2011.

Pre-specified significance level by O'Brien-Fleming Boundary = 0.0008.

Serologic and Clinical Responses

<table>
<thead>
<tr>
<th>PSA decline ≥50%</th>
<th>AA + P (n = 546)</th>
<th>Placebo + P (n = 542)</th>
<th>RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>62%</td>
<td>24%</td>
<td>NA</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

RECIST: Defined objective response

| Complete response | 11% | 4%  |
| Partial response  | 25% | 12% |
| Stable disease    | 61% | 69% |
| Progressive disease | 2%  | 15% |

2.273 (1.591, 3.247) <0.0001
Statistically Significant Improvement in All Secondary End Points

<table>
<thead>
<tr>
<th></th>
<th>AA + P</th>
<th>Placebo + P</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to opiate use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cancer related pain)</td>
<td>NR</td>
<td>23.7</td>
<td>0.69 (0.57, 0.83)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Time to chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>initiation</td>
<td>25.2</td>
<td>16.8</td>
<td>0.58 (0.49, 0.69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Time to ECOG PS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>deterioration</td>
<td>12.3</td>
<td>10.9</td>
<td>0.82 (0.71, 0.94)</td>
<td>0.0053</td>
</tr>
<tr>
<td><strong>Time to PSA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>progression</td>
<td>11.1</td>
<td>5.6</td>
<td>0.49 (0.42, 0.57)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Note: All secondary end points remain significant after adjusting for multiplicity testing.

Patient Reported Outcomes favored AA + P vs Placebo + P.
Full data to be reported.

Data cut off 12/20/2011.

Summary

- In patients with asymptomatic and mildly symptomatic, chemotherapy-naive mCRPC, treatment with abiraterone acetate plus prednisone:
  - Delays disease progression
  - Increases survival
  - Extends time with minimal or no symptoms
  - No new important safety signals
  - Granted accelerated review for expanded indication by FDA
Continuous androgen deprivation is the standard approach to advanced disease.

Preclinical data suggested that intermittent therapy might prolong the time to development of castrate resistant state.

Smaller clinical trials have confirmed a better QOL for patients receiving intermittent therapy, but have been underpowered to conclude anything regarding overall survival.
S9346 (INT-0162): Objectives

Primary
- Determine if survival with IAD is Not Inferior to survival with CAD.
- QOL*: To compare 3 treatment-specific symptoms (Impotence, Libido, Energy/Vitality) and physical and emotional functioning between arms

Secondary:
- More general QOL measures
- PSA dynamics between arms, and correlations with other endpoints

*Moinpour et-al, Abstract #4571 describes results for QOL

ELIGIBILITY AND STRATIFICATION

- Eligibility
  - Newly diagnosed metastatic prostate cancer
  - PSA ≥ 5 ng/ml
  - PS 0-2

- Stratification
  - PS (0-1 v 2)
  - Extent of disease
    - Minimal (spine, pelvis +/- nodal disease)
    - Extensive (ribs, long bones +/- visceral disease)

- Prior hormonal tx
  - neoadjuvant therapy v finsteride v neither
Study Design

**STEP 1**

Induction Registration

- Newly diagnosed metastatic prostate cancer & a PSA ≥ 5 ng/mL

- Induction AD = Goserelin + Bicalutamide X 7 months

**STEP 2**

Randomly Assign

- Continuous AD
- Intermittent AD

If PSA ≤ 4 ng/mL on months 6&7 (PSA normalization criteria)

- Discontinue AD, monthly PSAs. Resume AD based on pre-specified criteria

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IAD Arm: Subsequent Therapy Cycles

- Therapy was reinitiated when PSA increased to 20 ng/ml (or returned to baseline for patients who had pre-registration baseline value < 20 ng/ml) or for symptoms.

- If the PSA after another 7 months induction course met the PSA normalization criterion then the patients started another observation period.

- If the PSA at either months 6 or 7th of an induction course was greater than 4 ng/ml then the patients received continuous therapy until progression.
Statistical Methods

- **Primary outcome**: Survival post-randomization
  - Hypothesis: “IAD is NOT inferior to CAD”

- **Design specifications**:
  - Survival with IAD is not inferior if the 95% confidence interval for the hazard ratio (IAD vs. CAD) excludes 1.2, $\alpha=0.05$, power=90%, adjusting for stratification factors in proportional hazards model.

- **Assumptions**: post-randomization median survival for CAD = 3 years:
  - Sample size: 1500 eligible, randomized patients
  - accrual: 6.25 yrs. + 2 additional yrs. of follow-up.
### Overall Survival: Intermittent Therapy is Inferior Compared to Continuous Therapy

**Continuous therapy**
- At Risk: 765
- Death: 422
- Median in Years: 5.8
- 7 yr Survival: 42%

**Intermittent therapy**
- At Risk: 770
- Death: 455
- Median in Years: 5.1
- 7 yr Survival: 38%

**HR: 1.09 95% CI (0.95, 1.24)**

### Overall Survival for Patients with Extensive Disease by Treatment Arm

**Continuous therapy**
- At Risk: 362
- Death: 217
- Median in Years: 4.4
- 7 Year Survival: 33%

**Intermittent therapy**
- At Risk: 381
- Death: 229
- Median in Years: 5.0
- 7 Year Survival: 33%

**HR: 0.96 95% CI (0.80, 1.16)**
In this international phase III trial in patients with metastatic hormone sensitive prostate cancer:

1. IAD was inferior to CAD based on our pre-specified definition of survival comparability [HR: 1.09, 95% CI (0.95, 1.24)]. Therefore, CAD continues to be the standard of care.

2. In a secondary analysis:
   - IAD was not-inferior to CAD in patients with extensive disease. [HR: 0.96 95% CI (0.80, 1.16)].
   - IAD was inferior in patients with minimal disease & CAD was statistically significantly superior [HR: 1.23, 95% CI (1.02, 1.49), p=0.034].
   - These observations suggest inherent biological differences and warrant further mechanistic evaluation.
Huge debate at the meeting regarding the definitions of minimal v extensive metastatic disease

Even bigger debate regarding the statistical implications of a therapy being “not non-inferior”

**AXIOM #1**

- If the results of a trial validate your pre-existing bias, then you are willing to overlook some statistical aberrations
- If the results are contrary to your bias, then you attack the statistics unmercifully
Interruption androgen deprivation is absolutely superior in terms of QOL.

But, the assumption that survival is equivalent with this approach is not supported by this trial.

A patient may still choose IAD based on QOL issues, but the survival differences observed in this study need to be discussed with the patient.