Intermittent versus Continuous Androgen Deprivation in Hormone Sensitive Metastatic Prostate Cancer Patients: Results of SWOG 9346 (INT-0162) an International Phase III Trial


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Background

• Continuous androgen deprivation (CAD) is the standard for patients with metastatic hormone sensitive prostate cancer.

• Despite a high response rate most patients will progress to castration resistance.

• The historic median survival is 2.5-3 years.\textsuperscript{1,2}

• Scientific data indicate that progression to castration resistance is an adaptive process secondary to AD via androgen receptor dependent and independent mechanisms.\textsuperscript{3}

Background & Rational for Intermittent Therapy

• Preclinical data in an androgen-dependent tumor model:
  • Progression on AD was associated with a 500-fold increase in the proportion of androgen-independent stem cells.¹
  • Apoptosis could be re-induced with intermittent androgen deprivation (IAD).²
  • IAD prolonged (almost tripled) the mean time to androgen-independence.²

• Early clinical trials indicated that IAD is feasible and may be associated with improvement in quality of life.³-⁶

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*
Step 1: Induction Registration

Key Eligibility Criteria

- Newly diagnosed metastatic prostate cancer.
- PSA ≥ 5 ng/ml prior to initiation of AD.
- Prior neoadjuvant or adjuvant hormone therapy or prior finasteride was allowed with some restrictions.
- Signed IRB approved informed consent.
Stratification factors:

• Performance Status: 0 - 1 vs. 2

• Extent of Disease:
  – Minimal: Spine, pelvis &/or Lymph nodes vs.
  – Extensive: Ribs, long bones and / or visceral organs (Liver, lung)

• Prior hormone therapy:
  – Neoadjuvant therapy vs. finasteride vs. neither
Study Design

STEP 1
Induction Registration
Newly diagnosed metastatic prostate cancer & a PSA ≥ 5 ng/mL

Induction AD = Goserelin + Bicalutamide × 7 months

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

STEP 2
Randomly Assign

Continuous AD
Intermittent AD

Discontinue AD, monthly PSAs. Resume AD based on pre-specified criteria
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.
S9346 Study Information


Step 1: Induction Registrations: 3040 pts (90 ineligible)

Step 2: Randomization to CAD vs. IAD: 1535 eligible pts (projected 50% randomized)

IAD 770 eligible patients

CAD 765 eligible patients

PRESENTED BY: Maha Hussain, MD, FACP
S9346 Study Information

**N=3040**

**Accrual by Cooperative Group**
- SWOG: 39%
- ECOG: 20%
- EORTC: 14%
- CALGB: 14%
- NCIC: 8%
- Other/Multi: 2%
- Unknown (EORTC): 2%

**Race**
- White: 63%
- Black: 21%
- Other/Multi: 14%
- Unknown (EORTC): 2%
### Patients Characteristics at Randomization (Step 2)

<table>
<thead>
<tr>
<th></th>
<th>IAD (N=770)</th>
<th>CAD (N=765)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>70 (39, 97)</td>
<td>70 (39, 92)</td>
</tr>
<tr>
<td><strong>PSA (ng/ml) at Randomization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 0.2</td>
<td>35.4%</td>
<td>34.9%</td>
</tr>
<tr>
<td>0.3 – 4.0</td>
<td>64.6%</td>
<td>65.1%</td>
</tr>
<tr>
<td><strong>Performance Status:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 vs. 2</td>
<td>96%, 4%</td>
<td>96%, 4%</td>
</tr>
<tr>
<td><strong>Disease Extent:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive</td>
<td>49%</td>
<td>47%</td>
</tr>
<tr>
<td>Minimal</td>
<td>51%</td>
<td>53%</td>
</tr>
<tr>
<td><strong>Visceral Disease:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>7.1%</td>
<td>6.3%</td>
</tr>
<tr>
<td><strong>Prior hormone therapy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>87%</td>
<td>88%</td>
</tr>
<tr>
<td>Neoadjuvant, Finasteride</td>
<td>12%, 1%</td>
<td>11%, 1%</td>
</tr>
<tr>
<td><strong>Bone Pain:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>28%</td>
<td>26%</td>
</tr>
<tr>
<td><strong>Gleason score:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td>23%</td>
<td>25%</td>
</tr>
<tr>
<td>7</td>
<td>50%</td>
<td>48%</td>
</tr>
<tr>
<td>8-10</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>(31% missing)</td>
<td></td>
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</tr>
</tbody>
</table>
IAD Arm: Time on Study & Receiving Treatment
(Only Patients Who are Off Protocol Treatment)

<table>
<thead>
<tr>
<th></th>
<th>Time on Study*</th>
<th>% of time “on study” patient is receiving CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients</strong> (N=618)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (25%,75%)</td>
<td>19 (10,38)</td>
<td>47% (23%, 69%)</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Extensive Disease</strong> (N=319)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (25%,75%)</td>
<td>17 (10,34)</td>
<td>51% (25%, 73%)</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Minimal Disease</strong> (N=299)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (25%,75%)</td>
<td>21 (9, 38)</td>
<td>47% (22%, 64%)</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Time on study: from randomization to “Off Study” notification
### Adverse Events with a Grade 4 Reported*

<table>
<thead>
<tr>
<th>AE Category</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>8</td>
<td>3</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Flu-like Symptoms</td>
<td>18</td>
<td>2</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>4</td>
<td>0</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Liver</td>
<td>7</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>9</td>
<td>2</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Neurologic</td>
<td>15</td>
<td>1</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Pain</td>
<td>26</td>
<td>1</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Renal/Bladder</td>
<td>11</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>Max Grade Any AE</strong></td>
<td><strong>203</strong></td>
<td><strong>11</strong></td>
<td><strong>224</strong></td>
<td><strong>15</strong></td>
</tr>
</tbody>
</table>

* Treatment attribution: possible, probable, or definite, **No Grade 5 reported**
Overall Survival: Intermittent Therapy is Inferior Compared to Continuous Therapy

**At Risk**
- Continuous: 765
- Intermittent: 770

**Death**
- Continuous: 422
- Intermittent: 455

**Median in Years**
- Continuous: 5.8
- Intermittent: 5.1

**7 yr Survival**
- Continuous: 42%
- Intermittent: 38%

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

**Presented By**: Maha Hussain, MD, FACP
Evaluating Homogeneity of Treatment Effect Across Subsets of Patients

Extensive disease
Minimal disease
Bone pain
No bone pain
PSA at Randomization ≤ 0.2 ng/ml
PSA at Randomization 0.3 - 4.0 ng/ml
Overall

* test of factor x treatment interaction

favors intermittent
favors continuous

p=0.08*
p=0.26*
p=0.94*
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)

**Presented by:** Maha Hussain, MD, FACP
Overall Survival for Patients with Minimal Disease by Treatment Arm

Continuous therapy
- At Risk: 403
- Death: 205
- Median in Years: 7.1

Intermittent therapy
- At Risk: 389
- Death: 226
- Median in Years: 5.2

HR: 1.23, 95% CI (1.02, 1.49) p=0.034

At risk
- Intermittent: 143
- Continuous: 194

Years from Randomization
- Intermittent: 35
- Continuous: 30

PRESENTED BY: Maha Hussain, MD, FACP
Conclusions

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.
Acknowledgments

• All patients and their families

• All contributing SWOG, ECOG, CALGB, NCIC & EORTC investigators and research teams

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