EORTC GUCG 2238 “DE-ESCALATE”
INTERMITTENT ANDROGEN DEPRIVATION THERAPY IN THE ERA OF ANDROGEN RECEPTOR PATHWAY INHIBITORS; A PHASE 3 PRAGMATIC RANDOMISED TRIAL

An EORTC, UNICANCER, GETUG, CTI consortium Trial

Bertrand TOMBAL on March 26, 2024
The historical standard of care treatment for metastatic hormone naïve prostate cancer (mHNPC) is androgen deprivation therapy (ADT). ADT increases OS with the price of chronic side effects, including a decreased libido, accelerated cognitive decline, increased bone loss leading to frailty fractures, and an increased risk of cardiovascular disease. Consensus and guidelines recognize that ADT can be administered intermittently (iADT) in patients with a significant PSA response after 6 to 8 months of treatment. The goal of iADT is to preserve OS benefits while improving QoL and reducing resource engagement.
• 3,040 patients with HSM1PC pts with performance status (PS) 0-2, PSA ≥ 5 ng/ml were treated with 7 months (m) of goserelin + bicalutamide.
• After 7 m of CAD, 1535 eligible pts achieved PSA ≤4.0
• HR for death IAD 1.10, 90% CI: 0.99 to 1.23
Treatment of Prostate Cancer With Intermittent Versus Continuous Androgen Deprivation: A Systematic Review of Randomized Trials

Advanced Prostate Cancer Treated with Intermittent or Continuous ADT in the Randomised FinnProstate Study VII: Quality of Life and Adverse Effect.


Differences in QoL between IAD and CAD. Expressed by the 0.5 standard deviation rule in the domains of activity limitation, physical capacity, sexual functioning, and sexuality. Lower scores indicate better health in activity limitation, physical capacity, and sexuality; higher scores indicate better sexual functioning.
ADT as the standard of care treatment of metastatic PCa

• Then came four AR pathway inhibitors (ARPI): abiraterone, apalutamide, enzalutamide, and darolutamide.
• Seven trials on 8921 patients have now established ADT + ARPI as the new standard of care…
• BUT, the concept of intermittent treatment was lost in the translation.

ADT: androgen deprivation therapy;
## Early intensification strategy in mHNPC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Study</th>
<th>n</th>
<th>HR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone /P</td>
<td>LATITUDE</td>
<td>1199</td>
<td>0.62 (0.51 - 0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>STAMPEDE ITT</td>
<td>1917</td>
<td>0.63 (0.52 - 0.76)</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>PEACE 1 ITT</td>
<td>1172</td>
<td>0.82 (0.69-0.98)</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>PEACE 1 Docetaxel</td>
<td>710</td>
<td>0.75 (0.59-0.95)</td>
<td>0.017</td>
</tr>
<tr>
<td>Apalutamide</td>
<td>Titan</td>
<td>1052</td>
<td>0.65 (0.53 - 0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>ENZAMET</td>
<td>1125</td>
<td>0.67 (0.52 - 0.86)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>ARCHES</td>
<td>1150</td>
<td>0.70 (0.58-0.84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Darolutamide</td>
<td>ARASENS Docetaxel</td>
<td>1306</td>
<td>0.68 (0.57-0.80)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Trials used continuous administration until progression, with no intermittent regimens.
- 20-30% long-term Grade 3-4 TEAE
- Cost increased from 15k to 150k per patient.
- No study so far has looked at a de-escalation, intermittent setting.

ITT: Intent to treat; HR: hazard ratio; CI: confidence interval
ADT+ ARPI: long-term increase in side-effects

- significantly increased risk of CV events (RR = 1.71; 95% CI 1.29-2.27) and grade 3-4 HTA (RR = 1.53; 95% CI 1.19-1.97)\(^1\)
- increased risk of falls and fractures grade ≥3 fall (RR, 1.6; 95% CI, 1.27-2.08; P < 0.001); all-grade fracture (RR, 1.59; 95% CI, 1.35-1.89; P < 0.001); and likely grade ≥ 3 fracture (RR, 1.71; 95% CI, 1.12-2.63; P = 0.01) \(^2\).
- increased risk of cognitive toxic effects (risk ratio (RR) 2.10; 95%CI 1.30-3.38; P = 0.002) and fatigue (RR 1.34; 95% CI 1.16-1.54; P < .001)\(^3\)

ADT: androgen deprivation therapy, ARPI: AR pathway inhibitors; CV: cardiovascular; HTA: hypertension

Then came four AR pathway inhibitors (ARPI): abiraterone, apalutamide, enzalutamide, and darolutamide.

Seven trials on 8921 patients have now established ADT + ARPI as the new standard of care...

However, the concept of intermittent treatment was lost in the translation.

Although:

- There is an increased risk of side effects.
- ADT+ ARpI significantly increases the proportion of patients with a profound PSA response, hence the proportion of patients that would be candidates for an intermittent approach.

ADT: androgen deprivation therapy;
Absolute PSA value after ADT is a strong independent predictor of survival in new metastatic PCa: data from SWOG Trial 9346 (INT-0162).

- 50% of the patients reached a PSA ≤ 0.2 ng/ml.
- Median OS 75 months.
DE-ESCALATE Intermittent ADT in the era of AR pathway inhibitors; a phase 3 pragmatic randomized trial (EORTC 2238)

mHNPC: metastatic hormone naïve prostate cancer; PSA ≤ 0.2 ng/dl after 6 to 12 months of ADT + ARPI

Docetaxel

Stratification
- ADT + ARPI
- ADT+ ARPI+ radiotherapy
- ADT+ ARPI+ chemotherapy

Endpoints:
Co-Primary (hierarchical):
1. proportion of patients without iADT treatment at one year
2. Overall survival at 3 years
Secondary
- Overall survival
- Time to next systemic prostate cancer therapy
- Proportion of patient having received next systemic prostate cancer therapy at 24, 36 and 52 months.
- Toxicity with CTCAE v5
- Quality of life with QLQ-C30/PR-25
- Health economics parameters (e.g. Incremental cost effectiveness ratio)

Progression (defined as investigator decision to start next OS prolonging drug)

Death

Subsequent 2nd, 3rd, 4th line

Randomized 2:1

✓ Treatment reinitiate at investigator discretion
✓ Suspended at 6 months if PSA< reached

PSA ≤0.1 vs >0.1 - ≤ 0.2 ng/dl

Randomized 2:1

MAB

MAB

MAB

EORTC

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The future of cancer therapy
EORTC 2238  
Study Objectives

Main objective
• The primary goal of de-escalation is to investigate whether using an intermittent regime results in a similar OS to continuous treatment.

Secondary objective(s)
• Assess Toxicity profile with iADT  
• Assess the impact on QoL with iADT  
• Assess the impact on treatment resources of using an intermittent schedule
Explanatory vs. pragmatic trials

**Explanatory trials**

- Can the treatment work if it is applied under ideal circumstances?
- Treatment efficacy

**Pragmatic trials**

- Will the treatment work if it is applied in real-world clinical practice?
- Treatment effectiveness

EORTC 2238

• Hurdles:
• There is no interest from a company, purely academic support (Horizon).
• The trial is feasible only in a pragmatic low-intervention scheme.
• Although it compares two historical SOCs, CTIS perceives the study as interventional, hence “killing” the pragmatism.
• Identical frameworks for developing a new drug and optimizing its use.
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