The effect of apalutamide on mCSPC compared to other androgen receptor signaling inhibitors: network MA of RCTs

Chung-Ang University
Se Young CHOI
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Background

• CSPC

The term "castration-sensitive" is used to define patients who have not been treated with ADT and those who are not on ADT at the time of progression.

The NCCN Prostate Cancer Panel uses the term "castration-sensitive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of RT provided they have recovered testicular function.
Background

- Key RCT studies in mCSPC

2015: CHAARTED study
- Docetaxel + ADT vs ADT alone

2017: LATITUDE study
- Abiraterone + Prednisone + ADT vs Placebo + ADT

2019: TITAN study
- Apalutamide + ADT vs Placebo + ADT

2019: ENZAMET study
- Enzalutamide + ADT vs 1st generation ARIs + ADT

2019: ARCHES study
- Enzalutamide + ADT vs Placebo + ADT

2022: PEACE-1 study
- Abiraterone / Darolutamide + docetaxel + ADT vs Placebo + docetaxel + ADT

Background

- Proposed mechanism of action (Docetaxel)

  - Microtubule inhibitor
Background

- Proposed mechanism of action (Abiraterone)
  - selective and irreversible inhibition of cytochrome P450 17A1 (CYP17A1)
Background

- Proposed mechanism of action (enzalutamide, apalutamide, darolutamide)
- Non-steroidal, potent AR inhibitor which acts by blocking critical steps in the AR signaling pathway
Background

- GETUG-AFU 15 (2013; n=385)
- Docetaxel + ADT vs ADT
- Pri. End point: OS

Background

- CHAARTED (2015; n=790)
  - Docetaxel+ADT vs ADT
  - Pri. End point: OS

High vol: visceral meta or ≥4 Bone meta with vertebral body & pelvis with ≥ 1 beyond vertebral body & pelvis

![Graphs showing survival rates for patients with high-volume disease](image)

**Table:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel + ADT</td>
<td>14m↑</td>
</tr>
<tr>
<td>ADT alone</td>
<td>17m↑</td>
</tr>
</tbody>
</table>

Background

- **STAMPEDE (2016; n=1776 Arm A vs Arm C)**
- **Docetaxel+ADT vs ADT**
- **High risk (T3/4, PSA≥40ng/ml or GS 8-10), N+, M+**
- **Pri. End point: OS**

### SOC vs SOC+Doc

<table>
<thead>
<tr>
<th>Metastasis status</th>
<th>SOC</th>
<th>SOC+Doc</th>
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</thead>
<tbody>
<tr>
<td>M0</td>
<td>65/460</td>
<td>31/230</td>
</tr>
<tr>
<td>M1</td>
<td>350/724</td>
<td>144/362</td>
</tr>
</tbody>
</table>

- Long-term results: M1 only

Background

- **STAMPEDE (2017; n=1917 Arm A vs Arm G)**
- **Abiraterone+ADT vs ADT**
- **High risk (T3/4, PSA≥40ng/ml or GS 8-10), N+, M+**
- **Pri. End point: OS**

![Graphs and tables showing survival analysis and outcomes](image)

- **HR: 0.60 (0.50 to 0.71)**
- **P-value: 0.000000003**
- **Median survival (years): SOC=3.8, SOC+AAP=6.6**
- **Events: SOC=329, SOC+AAP=244**

![Survival curve graph with marked time points](image)

**2017 (M1 only)**
- **HR: 0.61 (0.49 to 0.75)**

**Proportion surviving**
- **SOC+AAP**: Red line
- **SOC**: Grey line

**Survival time**
- **14m↑**
- **26m↑**
Background

- **LATITUDE (2017; n=1199)**
- **Abiraterone+ADT vs ADT**
- **High risk mCSPC**
- **Pri. End point: OS & rPFS**

![Graph showing survival rates with and without treatment]

- Hazard ratio 0.66 (95% CI 0.56-0.78); p<0.0001
- **53.3 m** for Abiraterone acetate and prednisone plus ADT
- **36.5 m** for Placebos plus ADT
- **17m↑**

High risk: GS≥8, ≥3 lesions on BS, Visceral meta

<table>
<thead>
<tr>
<th>Number at risk (number censored)</th>
<th>Abiraterone acetate and prednisone plus ADT</th>
<th>Placebos plus ADT</th>
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</thead>
<tbody>
<tr>
<td>597 (14)</td>
<td>586 (23)</td>
<td>529 (34)</td>
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<td>529 (34)</td>
<td>479 (34)</td>
<td>425 (42)</td>
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<td>425 (42)</td>
<td>389 (46)</td>
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<td>124 (205)</td>
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<tr>
<td>124 (205)</td>
<td>40 (282)</td>
<td>3 (322)</td>
</tr>
</tbody>
</table>

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Fizazi et al. Lancet Oncol. 2019
Background

- TITAN (2019; n=1052)
- Apalutamide + ADT vs ADT
- Prior docetaxel: permitted
- Pri. End point: OS & rPFS
Background

- ARCHES (2019; n=1050)
- Enzalutamide+ADT vs ADT
- Prior docetaxel: permitted
- Pri. End point: rPFS

Final analysis: OS
Background

- ENZAMET (2019; n=1125)
  - Enzalutamide+ADT vs ADT+NSAA (bicalutamide, nilutamide, flutamide)
  - Prior docetaxel: permitted
  - Pri. End point: OS

Second analysis: OS

![Graph showing overall survival](image)
Background

- PEACE-1 (2022; n=1173)
  - Abiraterone + Docetaxel + ADT vs Docetaxel + ADT
  - Pri. End point: OS & rPFS
Background

- ARASENS (2022; n=1306)
- Darolutamide+Docetaxel+ADT vs Docetaxel+ADT
- Pri. End point: OS
Background

- CHART (2022; n=654)
  - Rezvnilutamide vs Bicalutamide+ADT
  - Pri. End point: OS, rPFS
  - preclinical study showed that rezvnilutamide has a significantly lower penetration rate across the BBB than enzalutamide, reducing risk of seizures

Gu et al. Lancet Onc. 2022

High vol: visceral meta or ≥4 Bone meta with vertebral body & pelvis with ≥ 1 beyond vertebral body & pelvis
### Background

- **Apalutamide**

- 식약청 허가 (2020.12, 인정비금여) → 암질환심의위원회 (2022, 급여 신청중)

<table>
<thead>
<tr>
<th>구분</th>
<th>품목</th>
<th>제약사</th>
<th>효능·효과</th>
<th>심의 결과</th>
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</thead>
<tbody>
<tr>
<td>요 양급여 결정사항</td>
<td>너링스점 (네라티널델레실)</td>
<td>(주)비양크</td>
<td>조기 유방암의 현장 보조치료</td>
<td>급여기준 미실정</td>
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<td></td>
<td>피크레이징 (알펜리십)</td>
<td>한국노바타스 (주)</td>
<td>진행성 또는 전이성 유방암</td>
<td>급여기준 미실정</td>
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<tr>
<td></td>
<td>업리다점 (아플루타미드)</td>
<td>(주)한국안센</td>
<td>호르몬 반응성 전이성 전립선암(mHSPC)</td>
<td>급여기준 미실정</td>
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<table>
<thead>
<tr>
<th>품목</th>
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<tbody>
<tr>
<td>Apalutamide</td>
<td>정상</td>
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### 분쟁정보

<table>
<thead>
<tr>
<th>국제 지재권 분쟁</th>
</tr>
</thead>
</table>

- IP Daily
- IP 분쟁동향


<table>
<thead>
<tr>
<th>분쟁경과</th>
<th>소취하</th>
</tr>
</thead>
</table>

| 산업분류 | 희석바이오 > 의약품 |

| 계열제품 | Enzalutamide 캡슐, 40 mg, Xtandi®(Xtandi®)의 일반 버전 |

특허 반대가 J&J의 전립선암 프로판체로 괴롭힐 수 있다.
Proposal

- Purpose
  - mCSPC: various medicine → selection guideline
Proposal

- Outcome measurement
  - Overall survival (OS)
  - Progression free survival (PFS)
Proposal

- Expected results

- Flowchart

Records identified through database searching (n = 404)

Records after duplicates removed (n = 207)

Title and abstract screened (n = 207)

Full-text articles assessed for eligibility (n = 19)

Studies included in qualitative synthesis (n = 9)

Records excluded (n = 188)
Title excluded: (n = 71)
Abstract excluded: (n = 117)
• Review article: 46
• Animal study: 8
• Not RCT: 13
• No English: 1
• Duplicate study subject: 9
• Maintenance therapy: 9
• Additional treatments: 21
• No standard dose: 10

Full-text article excluded (n = 10)
• Animal study: 2
• Not RCT: 2
• Maintenance therapy: 1
• Additional treatments: 3
• No standard dose: 2
Proposal

- Expected results
- Risk of bias assessment
### Expected results

**Summary table**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of patients</th>
<th>Age</th>
<th>PSA</th>
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<tbody>
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<td>Treatment</td>
<td>Control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Proposal

- Expected results
- Network plot
Proposal

- Expected results
- Forest plot
Proposal

- Expected results
  - Ranking analysis (Surface under the cumulative ranking score, SUCRA)
Summary

- **Background**
  - Many medicines are available in mCSPC in Korea

- **Proposal**
  - Meta-analysis about mCSPC RCTs may be helpful for the selection of the medicines
Thank you