ESMO SUMMIT AFRICA 2018

14 Years of progress in Prostate Cancer Standards of Care and new targets

Ronald de Wit
CONFLICT OF INTEREST DISCLOSURE

Sub-title

Sanofi
Roche
Merck
Lilly
14 years of progress in the Management of Prostate Cancer

- mCRPC; 2011 paradigm shift
  - Novel AR targeted agents
  - pre-chemotherapy

- mHSPC; recent paradigm shift
  - Docetaxel in addition to ADT
  - in men presenting with M1 disease

- mHSPC; latest shift addition of abiraterone to ADT
TAX 327 (Sanofi-Aventis)
Transatlantic phase 3 study 2004

Primary endpoint
OS 
(N=1006)

Randomisation
1:1

Docetaxel 75 mg/m² q3 wks + Prednisone 5 mg 2dd

Docetaxel 30 mg/m² weekly 5 of 6 weeks + Prednisone 5 mg 2dd

Mitoxantrone 12 mg/m² q3 wks + Prednisone 5 mg 2dd
Improved median survival by 2.9 months: BUT

- as compared with alternative effective treatment (mitoxantrone)
- despite 30% crossover
- despite imperfect design
  (first PSA evaluation at 6 weeks)

Randomised Phase II study in Asiatic patients (n=229) (conducted as TAX327)

Docetaxel (75mg/m2)/pred vs M/pred; N= 229mCRPC
OS benefit 8 months (21.9 versus 13.7 months, HR 0.63)

Ti Zou et al, Plos one 2015
Docetaxel standard 1st line chemotherapy in mCRPC

- 9 Phase 3 trials of docetaxel + agent have failed to improve OS
- Phase 3 docetaxel +/- lenalidomide (MAINSAIL) worse OS in exp arm, ascribed to fewer cycles and more frequent docetaxel dose reductions*

- Posthoc analysis of MAINSAIL; in MVA number of docetaxel cycles had independent prognostic importance for OS; 8 was better than 6, 10 was better than 6 or 8* (in TAX 327 med N of cycles achieved 9.6)

- Number of cycles of docetaxel/dose in mCRPC is important

* Petrylak et al Lancet Onc 2015, ** de Morree et al JAMA Onc 2016
# Phase III clinical trials in mCRPC

<table>
<thead>
<tr>
<th>Study</th>
<th>Agents</th>
<th>N</th>
<th>Indication</th>
<th>HR</th>
<th>Δ OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX-327</td>
<td>Docetaxel/P vs mito/P</td>
<td>1006</td>
<td>mCRPC</td>
<td>0.76</td>
<td>+2.9</td>
</tr>
<tr>
<td>IMPACT</td>
<td>Sipuleucel-T vs pbo</td>
<td>512</td>
<td>mCRPC (pre-Doc)</td>
<td>0.78</td>
<td>+4.1</td>
</tr>
<tr>
<td>COU-AA-302</td>
<td>Abiraterone/P vs P</td>
<td>1088</td>
<td>mCRPC (pre-Doc)</td>
<td>0.81</td>
<td>+4.4</td>
</tr>
<tr>
<td>COU-AA-301</td>
<td>Abiraterone/P vs P</td>
<td>1195</td>
<td>mCRPC (post-Doc)</td>
<td>0.74</td>
<td>+4.6</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>Enzalutamide vs pbo</td>
<td>1717</td>
<td>mCRPC (pre-Doc)</td>
<td>0.71</td>
<td>+4.0</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>Enzalutamide vs pbo (or P)</td>
<td>1199</td>
<td>mCRPC (post-Doc)</td>
<td>0.63</td>
<td>+4.8</td>
</tr>
<tr>
<td>TROPIC</td>
<td>Cabazitaxel/P vs mito/P</td>
<td>755</td>
<td>mCRPC (post-Doc)</td>
<td>0.70</td>
<td>+2.4</td>
</tr>
<tr>
<td>ALSYMCPA</td>
<td>Radium-223 vs pbo</td>
<td>921</td>
<td>mCRPC</td>
<td>0.70</td>
<td>+2.8</td>
</tr>
</tbody>
</table>
Optimal choice and sequence of current agents undefined

- Most trials conducted in parallel pre-or post doce
- Optimal sequence of drugs undefined
- OS benefit likely smaller in subsequent lines of treatment; is there any benefit to be expected in 3rd or even 4th line?
  
**Do not lose the opportunity for cabazitaxel**

- Need for biomarkers for response on taxanes and AR targeted agents
Primary resistance to AR-targeted agents

Radiological PFS

Abiraterone\(^1\) (COU-AA-301)

- Primary resistance
  - 1 out of 3 patients

Enzalutamide\(^2\) (AFFIRM)

- Primary resistance
  - 1 out of 4 patients

Primary end-point of COU-AA-301 and AFFIRM was overall survival


PFS: progression-free survival
CTC characterization – AR-V7
< Hopkins Group> (Adna test platform)

AR Proteins

<table>
<thead>
<tr>
<th>AR (variant 1)</th>
<th>NTD</th>
<th>DBD</th>
<th>Hinge</th>
<th>LBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR3/AR-V7</td>
<td>NTD</td>
<td>DBD</td>
<td>U</td>
<td></td>
</tr>
</tbody>
</table>

Should patients with AR-V7\text{pos} CTCs be treated with AR-independent treatments? cabazitaxel?
AR-V7 in Cabazitaxel treated patients
Erasmus MC Group

Do AR-V7-positive patients benefit from cabazitaxel given its presumptive AR-independent mechanisms of action?

7.5 mL blood in EDTA tube before cycle 1 and 3
CellSearch enrichment, Lysis, RNA isolation, RT-qPCR

- CTC response
  - Decline to or stable <5 CTC
  - Overall 44%
  - N = 51
    - 50% versus 36%, P = 0.40
AR-V7 in Cabazitaxel treated patients
Erasmus MC Group

- No difference in PFS and OS
Optimal choice and sequence of current agents undefined

- Most trials conducted in parallel pre-or post doce
- Optimal sequence of drugs undefined
- OS benefit likely smaller in subsequent lines of treatment; is there any benefit to be expected in 3rd or even 4th line?
- Need for biomarkers for response on taxanes and AR targeted agents
- Cross resistance between agents
Cross resistance between taxanes and AR-targeted agents in vivo model of CRPC with acquired resistance to enzalutamide

Van Soest, de Wit et al. Eur Urol 2014
Impaired Efficacy of Docetaxel Post-Abiraterone?

[2-5] trials are retrospective studies

<table>
<thead>
<tr>
<th></th>
<th>VENICE(^1) n=612</th>
<th>De Bono(^2) n=35</th>
<th>Schweizer(^3) n=95</th>
<th>Azad(^4) n=86</th>
<th>De Bono(^5) (COU-AA-302) n=261</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOC therapy line</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Visceral mets</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>↓ PSA ≥50%</td>
<td>63.5(%)</td>
<td>25.7(%)</td>
<td>63.0(%)</td>
<td>38.0(%)</td>
<td>35.0(%)</td>
</tr>
<tr>
<td>Median PSA-PFS (mths)</td>
<td>8.1</td>
<td>4.6</td>
<td>6.7</td>
<td>4.1</td>
<td>4.0</td>
</tr>
<tr>
<td>OS, median (mths)</td>
<td>21.2</td>
<td>12.5</td>
<td>-</td>
<td>-</td>
<td>11.7</td>
</tr>
</tbody>
</table>

Cabazitaxel Remains Active in Patients Progressing With an AR-Targeted Agent

Progression-Free Survival

Overall Survival

Prospective, randomized phase 2 study of cabazitaxel ± budesonide

Poor response to abiraterone in patients progressing on enzalutamide?

<table>
<thead>
<tr>
<th></th>
<th>Loriot(^1) ((n=38))</th>
<th>Noonan(^2) ((n=30))</th>
<th>COU-AA-301(^3) ((n=797))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Enzalutamide</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Median PFS, mths</td>
<td>2.7</td>
<td>3.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Median OS, mths</td>
<td>7.2</td>
<td>11.8</td>
<td>14.8</td>
</tr>
<tr>
<td>↓PSA ≥50%*</td>
<td>8%</td>
<td>3%</td>
<td>29%</td>
</tr>
</tbody>
</table>

[1-2] trials are retrospective studies conducted in 38 and 30 patients, respectively
*Confirmed by a second value

OS: Overall survival; PFS: Progression-free survival
1st line taxane phase III study; FIRSTANA (ASCO 2016)

mCRPC and no prior chemotherapy
N = 1,168 pts

159 centers worldwide

CBZ 20 + PRED
Cabazitaxel 20 mg/m² Q3W
+ prednisone 10 mg/d
n = 389

CBZ 25 + PRED
Cabazitaxel 25 mg/m² Q3W
+ prednisone 10 mg/d
n = 388

DOC + PRED
Docetaxel 75 mg/m² Q3W
+ prednisone 10 mg/d
n = 391
FIRSTANA: Overall Survival

Median OS, months (95% CI)

- DOC + PRED: 24.3 (22.18–27.60)
- CBZ 20 + PRED: 24.5 (21.75–27.20)
- CBZ 25 + PRED: 25.2 (22.90–26.97)

CBZ 20 vs DOC
HR: 1.009 (0.85–1.197)
P = 0.9967

CBZ 25 vs DOC
HR: 0.97 (0.819–1.16)
P = 0.7574
## FIRSTANA: Prior Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>DOC + PRED N = 391</th>
<th>CBZ 20 + PRED N = 389</th>
<th>CBZ 25 + PRED N = 388</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormonal therapy, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 regimen</td>
<td>150 (38.4)</td>
<td>147 (37.8)</td>
<td>143 (36.9)</td>
</tr>
<tr>
<td>2 regimens</td>
<td>105 (26.9)</td>
<td>87 (22.4)</td>
<td>108 (27.8)</td>
</tr>
<tr>
<td>≥ 3 regimens</td>
<td>127 (32.5)</td>
<td>145 (37.3)</td>
<td>132 (34.0)</td>
</tr>
<tr>
<td><strong>Radical prostatectomy, n (%)</strong></td>
<td>85 (21.7)</td>
<td>99 (25.4)</td>
<td>78 (20.1)</td>
</tr>
<tr>
<td><strong>Radiation, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curative</td>
<td>133 (34.0)</td>
<td>150 (38.6)</td>
<td>120 (30.9)</td>
</tr>
<tr>
<td>Palliative</td>
<td>62 (15.9)</td>
<td>73 (18.8)</td>
<td>74 (19.1)</td>
</tr>
<tr>
<td><strong>Next-generation AR-targeted agents, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>3 (0.8)</td>
<td>4 (1.0)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Abiraterone acetate</td>
<td>8 (2.0)</td>
<td>2 (0.5)</td>
<td>3 (0.8)</td>
</tr>
</tbody>
</table>
1st line taxane in mCRPC

- Cabazitaxel 20mg and 25mg show a similar OS benefit as Docetaxel in a non resistant population (<2% of patients treated with prior ABI or ENZA)

- 1st line efficacy of Cabazitaxel as compared to Docetaxel in patients progressing after ABI or ENZA is not known

If there is no benefit after 3 cycles of doce in post-abi/enza setting consider to switch to cabazitaxel (20mg /m2)
14 years of progress in the Management of Prostate Cancer

- **mCRPC;** 2011 paradigm shift
  - novel AR targeted agents
  - pre-chemotherapy

- **mHSPC;** recent paradigm shift
  - docetaxel in addition to ADT
  - in men presenting with M1 disease

- **mHSPC;** latest shift addition of abiraterone to ADT
Combination of ADT and taxanes

CHAARTED (M1)

Phase III randomized trial in 790 men with metastastic hormone-naïve PCa

STAMPEDE (M0/M1)

Phase III randomized trial in M0/M1 patients with hormone-naïve PCa

DOC: Docetaxel

2James N et al. Lancet. 2015, December
GETUG 15 in metastatic hormone-sensitive PCa
Activity of subsequent therapies

Modest PSA response and PFS in patients initially treated with ADT+DOC and rechallenged with DOC at disease progression

Lavaud P et al. J Clin Oncol 2016; 34 (suppl); abstract 5080
Short response to first ADT may predict poor response to Enzalutamide (Oudard, ESMO discussant 2017)

Retrospective cohort of 173 patients, including 57 treated with enzalutamide in AFFIRM trial

**PSA decrease ≥ 50%**

- P<0.001
- 8% < 12 mo
- 58% ≥ 12 mo

**TTCRPC:** time to castration resistance; **PFS:** progression-free survival

**PFS**

- TTCRPC ≥12 months
- TTCRPC <12 months
- HR: 0.58 (95% CI: 0.42-0.82)
- Median PFS: 5.8 mo vs 2.8 mo
- Log-rank P =0.002

OS in Patients who Discontinued Prior Docetaxel due to Disease Progression

- Median OS was 13.8 months in the cabazitaxel/prednisone group vs. 10.9 months in the mitoxantrone /prednisone group
  - HR 0.70 (0.57-0.87)

![Graph showing survival probabilities and hazard ratio](image-url)
Post CHAARTED/STAMPEDE (doce) treatment

- For pts > 12 months response duration on ADT, reasonable option AR-targeted therapy (subsequent line would be cabazitaxel)

- For pts < 12 months response duration on ADT most logical choice would appear cabazitaxel
Study design of LATITUDE

Patients
- Newly diagnosed adult men with high-risk mHNPC

Stratification factors
- Presence of visceral disease (yes/no)
- ECOG PS (0, 1 vs 2)

Randomized 1:1

ADT + Abiraterone acetate 1000 mg QD + Prednisone 5 mg QD (n = 597)

ADT + placebos (n = 602)

Efficacy end points
Co-primary:
- OS
- rPFS
Secondary: time to
- pain progression
- PSA progression
- next symptomatic skeletal event
- chemotherapy
- subsequent PC therapy

High-risk defined as meeting at least 2 of 3 high-risk criteria:
- Gleason score of ≥ 8
- Presence of ≥ 3 lesions on bone scan
- Presence of measurable visceral lesion

Presented by: Karim Fizazi
LATITUDE: Co-primary End Points

38% Risk Reduction for Death

53% Risk Reduction for rPFS

STAMPEDE – ABI+ADT vs ADT in newly diagnosed locally advanced or metastatic Pca (ASCO 2017)

Phase 3 randomized trial in newly diagnosed M0/M1 prostate cancer.  
Primary end-point: OS  
**FFS: failure free survival**

*James ND et al. NEJM 2017; 377: 338-51*
In 2018 Multiple Choices and Sequences

- mHSPC  early taxane /late taxane
- mHSPC  early abi/late abi/enza
- mCRPC  abi/enza pre- or post taxane
- mCRPC  Radium 223 pre- or post taxane

- Even after 4 lines considerable number of mCRPC patients wish to receive systemic therapies
- New avenues: 
  - Immunotherapy
  - Molecular targeted therapies
Precision medicine in mCRPC

- Molecular targeted treatment is based on pathways
- Best known example in PC is DNA repair deficiency as a target for PARP inhibitors (10-15% of PC pts)*

- Requires Biopsy material from metastatic lesion
- or Liquid Biopsy (CTCs or ctDNA)

Antitumor Activity of Olaparib and Association with Defects in DNA-Repair Genes, According to Biomarker Status.
Gene Mutations and splice variants

- Enriched in metastatic setting, especially in pretreated patients
  - Biopsies cumbersome, sometimes impossible
  - Invasive
- Difficult to repeat during treatment
## CTCs vs cell-free tumor DNA (ctDNA)

<table>
<thead>
<tr>
<th>CTCs</th>
<th>cfDNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact tumor cell in the circulation</td>
<td>cell-free in the circulation</td>
</tr>
<tr>
<td>DNA, RNA and protein</td>
<td>DNA only</td>
</tr>
<tr>
<td>Detectable in 30-40% of mCRPC patients</td>
<td>Detectable in 60% of mCRPC patients</td>
</tr>
<tr>
<td>More complex processing (EpCAM-based enrichment)</td>
<td>Easy processing (plasma isolation)</td>
</tr>
</tbody>
</table>
PTEN is a tumor suppressor protein

Negative regulator of PI3Kinase

PTEN loss results in activation of the PI3K/AKT/mTOR pathway causing promotion of tumor growth, cell survival and resistance to therapy

Cross-talk between AR and PI3K-AKT signaling, rationale for concurrent inhibition of both pathways

Phase 1 study in biopsy proven (fresh/archived material) PTEN deficient mCRPC patients
Phase I Study of GSK2636771, a Phosphoinositide 3-kinase (PI3K)β Inhibitor with Enzalutamide in mCRPC pts Failing Enzalutamide

Rescigno et al (RMH)

- GSK2636771 is a selective inhibitor of PI3Kβ that inhibits the growth of PTEN-deficient tumor cells in preclinical models.

**Primary objectives**

<table>
<thead>
<tr>
<th>Safety:</th>
<th>Efficacy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Assess safety and tolerability</td>
<td>• Non-disease progression at 12 weeks</td>
</tr>
<tr>
<td>• Determine recommended combination dose for Phase II trials</td>
<td></td>
</tr>
</tbody>
</table>

**Secondary objectives**

- Evaluate the clinical activity of oral GSK2636771 + enzalutamide in the treatment of PTEN-deficient mCRPC
- Determine the effect of GSK2636771 on PK characteristics of enzalutamide
- Determine the effect of enzalutamide on PK characteristics of GSK2636771

**Inclusion Criteria**

- ≥18 years old, male
- Diagnosed with mCRPC
- Tested PTEN-deficient by IHC
- Testosterone ≤50 ng/dL
- ECOG: 0 or 1
- Progression on enzalutamide
- Has not been without prior enzalutamide for >30 days

**Part 1: Dose Escalation**

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalutamide (160 mg) + GSK2636771</td>
<td>200 mg</td>
<td>300 mg</td>
</tr>
</tbody>
</table>

**Part 2: Dose Expansion**

Up to 20 subjects recruited per dose level

**Primary Outcomes**

- Safety and tolerability
- Non-disease progression at 12 weeks
GSK2636771 (PI3Kβ Inhibitor) with Enzalutamide in mCRPC; 28 patients enrolled

- Cmax and AUC of GSK2636771 and enzalutamide in combo were comparable with monotherapy
- No safety issues
- One PR (200 mg GSK2636771) and continued treatment for 35 weeks
Gene expression profiling
ESMO 2015 (Vancouver Group)

- Remaining RNA from CellSearch-enriched CTCs
- RT-qPCR
  - Panel of prostate-associated genes
  - CTC-specific
- Predict treatment response/resistance?
  - Cabazitaxel
  - Abiraterone/Enzalutamide
- Changes in gene expression during cabazitaxel?

Genomic analysis of ctDNA in plasma of mCRPC patients

Waterfall plot of maximum % PSA change from baseline stratified by AR gene status during treatment with enzalutamide

Azad et al. (Vancouver Group) Clin Cancer Res 2015
CIRCUS study <ErasmusMC Group>

**CPCT-02 study**
- Biopsy
- DNA isolation
- DNA sequencing
- SV selection

**CIRCUS study**
- Temporal measurements
- Plasma
- Urine
- ctDNA isolation
- dPCR
- Therapy response

CRPC patient

PSMA scan
Solid Cancers; mutational load

Alexandrov et al Nature 2013
†Membranous PD-L1 expression in ≥1% of tumor or stromal cells using a prototype immunohistochemistry assay and 22C3 antibody (Merck). § Clinically stable patients were allowed to remain on pembrolizumab until progressive disease was confirmed on a second scan performed ≥4 weeks later. Patients who experienced progression after discontinuing pembrolizumab were eligible for up to 1 year of additional treatment if no other anticancer therapy was received.

†Response assessment: Every 8 weeks for the first 6 months; every 12 weeks thereafter
Primary end points: ORR per RECIST v1.1 and safety
Secondary end points: PFS, OS, duration of response
KN365 - Prostate Umbrella Trial to Study Combinations with Pembrolizumab

Goal:
- Signal generation: test and identify combinations with additive or synergistic effect
- Broaden patient population (test without regard to PDL-1 status, improve BMx)
- Adaptive design to test promising combinations

Stage IV mCRPC
- RECIST Measurable or Non-measurable disease
- Enroll without respect to PDL-1 status
- Primary Endpoint PSA response
  - Evaluate: Serum PDL1, Prostate PDL1 NS, NGS

1st wave of combinations
- A: Pembro + Olaparib post docetaxel
- B: Pembro+ docetaxel post abi or enza
- C: Pembro + enzalutamide post Abi

2nd wave of combinations
- D: Pembro +
- E: Pembro +
- F: Pembro +

N=50-70/cohort
Conclusions

- Docetaxel remains important taxane in mCRPC, efficacy likely impaired in post AR treatment setting
- Cross-resistance between AR–targeted treatments, do not loose the opportunity to use cabazixel
- Benefit of docetaxel in addition to ADT is robust in setting of mHSPC, evidence strongest in high-volume disease setting
- Benefit of adding abiraterone in addition to ADT in mHSPC, next talk….
Conclusions

- ctDNA and biopsies (and CTCs) allow to identify genomic aberrations and may play an increasing role in precision medicine.
- To date, findings need to be prospectively validated, with the exception of DNA repair deficiency as a target for PARP inhibitors.

- Current aberrations of interest;
  - RB (cell cycle)
  - BRCA/ATM (DNA repair)
  - PTEN (PI3K/AKT signalling)
  - AR mutations and splice variants (testosterone)
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Martijn Lolkema
Robert van Soest
Ron Mathijssen
Wytske van Weerden
Guido Jenster
Ronald de Wit

All recruiting physicians and research nurses

Patients and their families