Immunotherapy and new agents in CRPC

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Disclosure

• Participation to advisory boards/honorarium for: Astellas, Astrazeneca, Bayer, Curevac, Janssen, Orion, Sanofi
The precise mechanism of action of sipuleucel-T is not known.
A first « negative-positive » trial

Fig 3. Final overall survival (intent-to-treat population). HR, hazard ratio.

Small EJ, J Clin Oncol 2009; 24: 3089-94
IMPACT: Phase III Trial of Sipuleucel-T

Asymptomatic or Minimally Symptomatic Metastatic CRPC (N=512)

2:1

Sipuleucel-T Q2 weeks x 3

CONTROL* Q2 weeks x 3

Treated at Physician Discretion (N=341)

Cryopreserved Immunotherapy† (n=109)

Treated at Physician Discretion

No Immunotherapy (n=62)

Primary endpoint: Overall survival
Secondary endpoint: Time to objective disease progression

†64% of patients in the control group, following progression, crossed over to receive autologous immunotherapy made from cryopreserved cells.

Sipuleucel-T: not available outside the US

Checkpoint inhibitors in CRPC

- CTLA-4
- PD1/PD-L1
Activating receptor
Inhibitory receptor

Immune checkpoints
Ipilimumab phase III trial “043”: Study Design

- **Screening**:
  - Post-docetaxel CRPC (N=799)

- **Single-dose, bone-directed RT (8 GY)**

- **Allocation**: 1:1

- **Ipilimumab (10 mg/kg)**
  - Wks 1, 4, 7, 10
  - Every 12 wks

- **Placebo**
  - Wks 1, 4, 7, 10
  - Every 12 wks

- **N=399**
- **N=400**

Patients stratified by investigator site, alkaline phosphatase, hemoglobin, and ECOG PS

- Treatment until disease progression or intolerable toxicity

- **Primary endpoint**: overall survival (OS)
- **Secondary endpoints**: progression-free survival, safety
- **Exploratory endpoint**: PSA response rate
Ipilimumab + RXT to bone: Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab (N=399)</th>
<th>Placebo (N=400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (95% CI)</td>
<td>11.2 (9.5-12.7)</td>
<td>10.0 (8.3-11.0)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.85 (0.72-1.00)</td>
<td></td>
</tr>
<tr>
<td>Stratified log-rank P</td>
<td>0.0530</td>
<td></td>
</tr>
<tr>
<td>1-yr OS rate</td>
<td>47%</td>
<td>40%</td>
</tr>
<tr>
<td>2-yr OS rate</td>
<td>26%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Kwon E, Lancet Oncol 2014; 15: 700-12
Results: Updated OS

- n=799
- Primary endpoint= OS

<table>
<thead>
<tr>
<th></th>
<th>Ipi (n=399)</th>
<th>Pbo (n=400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>11.2 (9.6–12.6)</td>
<td>10.0 (8.4–11.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.84 (0.72–0.98)</td>
<td></td>
</tr>
<tr>
<td>Stratified log-rank*</td>
<td>P=0.03</td>
<td></td>
</tr>
<tr>
<td>1-yr OS rate</td>
<td>47%</td>
<td>41%</td>
</tr>
<tr>
<td>2-yr OS rate</td>
<td>25%</td>
<td>17%</td>
</tr>
<tr>
<td>3-yr OS rate**</td>
<td>12%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Fizazi K et al., ESMO 2014

Ipilimumab post-docetaxel phase III trial
Long-lasting complete response after Ipilimumab in CRPC

2011:
mCRPC progressing post-docetaxel
Pain requiring opioids
Ipilimumab + RXT to 1 bone lesion

2019:
No detectable disease at 8 years+

Cabel L, J Immunother Cancer 2017; 5: 31
# Pembrolizumab + continuous Enzalutamide in Enzalutamide-progressing CRPC

<table>
<thead>
<tr>
<th>Responder</th>
<th>Cycle 1</th>
<th>PSA (ng/ml) every 3-weeks and nadir</th>
<th>Measurable Disease at Baseline</th>
<th>Best Radiologic Response</th>
<th>MSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>April 2015</td>
<td>70.65 → 11.1 → 1.18 → 0.11 → 0.08</td>
<td>Yes (lymph) PR present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>October 2015</td>
<td>46.09 → 41.22 → 12.99 → 9.89 → 0.02</td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>January 2016</td>
<td>2502.75 → 1.25 → 0.07 → 0.01 → &lt;0.01</td>
<td>Yes (liver) PR absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>March 2016</td>
<td>82.43 → 17.34 → 0.1 → 0.01</td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>5</td>
<td>June 2016</td>
<td>250 → 88.69 → 5.1 → 0.43 → 0.18*</td>
<td>Yes (liver) PR pending</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Graff JN, ESMO 2016
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

5% of prostate cancers with MMR mutations?
CRPC progressing after Enzalutamide
Lymph node biopsy shows:
- MYC amplification
- TMPRSS2-ERG
- MSH2, MSH6 mutations

Stop enzalutamide

Atezolizumab

Courtesy of Christophe Massard
Inactivation of CDK12 Delineates a Distinct Immunogenic Class of Advanced Prostate Cancer

Yi-Mi Wu,1,2,20 Marcin Cieślak,1,2,20 Robert J. Lonigro,1 Pankaj Vats,1 Melissa A. Reimers,3 Xuhong Cao,1 Yu Ning,1 Lisha Wang,1 Lakshmi P. Kunju,1,2,4 Navoni de Sarkar,5 Elisabeth I. Heath,6,7 Jonathan Chou,8 Felix Y. Feng,8,9,10,11 Peter S. Nelson,5,12,13 Johann S. de Bono,14,15 Weiping Zou,1,2,16 Bruce Montgomery,12,17 Ajjai Alva,1,3 PCF/SU2C International Prostate Cancer Dream Team, Dan R. Robinson,1,2,* and Arul M. Chinnaiyan1,2,4,18,19,21,*
**Ipilimumab + Nivolumab:**
**Association of HRD, DDR, and TMB With rPFS**

- Enhanced rPFS benefit was observed in patients with HRD+ or DDR+ tumors
- High TMB (above the median) was associated with prolonged rPFS vs low TMB (below the median) ($P<0.0001$)
Conclusion: Immunotherapy

• Immunotherapy has demonstrated effect on overall survival in prostate cancer (Sipuleucel-T: not available in Europe)

• New approaches ongoing:
  – CTLA4 (Ipilimumab): PFS met, not OS
  – PD-1/PD-L1: Preliminary activity
« Other » targets and drugs
Genomics and new targets in CRPC

Robinson, Cell 2015
AR splice variants: N-term targeted drugs?

Splice variant -> AR constitutively active (no need for androgens)
Shut the hormones down?

Abiraterone
Targeting the Akt and the AR pathways

AR target genes

Abiraterone

androgen precursors

synthesis adrenal testicular tumor

androgens

RTK (HER2/3)

PIK3CA

PI3CA

PI3P

mTORC1/2

Ipatasertib

Akt

PTEN

AR
Abiraterone +/- Ipatasertib (Akt inhibitor): PFS

**PTEN loss**

- **400 mg Ipat + Abi**
  - Median 11.5 mo
  - HR,\(^a\) 0.39 (0.22-0.70)

- **Pbo + Abi**
  - Median 4.6 mo

**PTEN non-loss**

- **400 mg Ipat + Abi**
  - Median 7.5 mo
  - HR,\(^a\) 0.84 (0.51-1.37)

- **Pbo + Abi**
  - Median 5.6 mo

\(^a\) Unstratified HR; 90% CI.
DNA damage repair defect

**Type of damage:**
- Single-strand breaks (SSBs)
- Double-strand breaks (DSBs)
- Bulky adducts (e.g., from platinum and UV)
- Nucleotide mutations, substitutions, deletions, insertions

**Repair targets:**
- APE1 PARP
- ATR
- ATM
- DNA-PK
- ERCC1
- XP proteins
- Polymerases (ERCC1, etc.)
- MLH, MSH, MTH1*, etc.

**Repair pathway:**
- Base Excision Repair
- Homologous Recombination Repair
- Non-Homologous End Joining
- Nucleotide Excision Repair and TransLesion Synthesis
- MisMatch Repair
BRCA-related synthetic lethality with PARP inhibition

DNA repair and prostate cancer

Germline DNA repair mutations:
- 12% in men with M1 prostate cancer
- 5% in men with localized CaP
- 3% general population

Somatic DNA repair mutations:
- 10% in men with mCRPC?

Pritchard CC, NEJM 2016: 375: 443-53
Robinson D, Cell 2015; 162: 454
Time from ADT initiation to mCRPC by germline DDR status

<table>
<thead>
<tr>
<th>Group</th>
<th>Median PFS (months)</th>
<th>CI-95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-carriers</td>
<td>28.2</td>
<td>(24.1-32.3)</td>
</tr>
<tr>
<td>Carriers</td>
<td>18.6</td>
<td>(10.6-26.6)</td>
</tr>
</tbody>
</table>

Log-rank p = 0.04

<table>
<thead>
<tr>
<th>Group</th>
<th>Median PFS (months)</th>
<th>CI-95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-BRCA2</td>
<td>28.0</td>
<td>(24.1-32.1)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>13.2</td>
<td>(3.5-22.9)</td>
</tr>
</tbody>
</table>

Log-rank p = 0.05

n=419 mCRPC pts DDR+= 9.1%

Castro E, ESMO 2017
DNA repair defects and CRPC

- Not only young men
- Not only those with a family history
- Worse prognosis
- Likely maintained sensitivity to current drugs, although of less duration:
  - Taxanes
  - AR targeted drugs
Olaparib: activity is predicted by DRD gene mutations

PARP inhibitors in CRPC

• 4 compounds currently in trials (P2-3):
  – Olaparib
  – Niraparib
  – Rucaparib
  – Talazoparib
• Patient selection:
  – Tumor sample vs ctDNA?
  – Monoallelic vs Biallelic?
  – Are all gene mutations the same?
  – Germline vs somatic mutations?
Rucaparib in HRD+ mCRPC

TRITON 2: Radiological Response in Patients with Measurable Disease (N=46/85)\(^1\)

**Confirmed Investigator-Assessed ORR in Evaluable Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BRCA1/2m (n=25)</th>
<th>ATMm (n=5)</th>
<th>CDK12m (n=8)</th>
<th>Other (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%) [95% CI] (RECIST/PCWG3)</td>
<td>11 (44.0%) [24.4–65.1]</td>
<td>0 [0.0–52.2]</td>
<td>0 [0.0–36.9]</td>
<td>2 (25.0%) [3.2–65.1]</td>
</tr>
<tr>
<td>Complete response, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>11 (44.0)</td>
<td>0</td>
<td>0</td>
<td>2 (25.0)(^a)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>9 (36.0)</td>
<td>4 (80.0)</td>
<td>5 (62.5)</td>
<td>5 (62.5)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>4 (16.0)</td>
<td>1 (20.0)</td>
<td>2 (25.0)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Not evaluable, n (%)</td>
<td>1 (4.0)</td>
<td>0</td>
<td>1 (12.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) confirmed objective response by investigator assessment was also observed in 1 patient with a BRIP1 alteration and 1 patient with a FANCA alteration

Best change from baseline in sum of target lesions (n=46)

ESMO 2018
Niraparib in HRD+ CRPC

Response by RECIST

PSA

Smith M, ASCO GU 2019
PROFOUND: STUDY DESIGN

Key eligibility criteria
• mCRPC
• Disease progression on prior NHA, eg enzalutamide and/or abiraterone treatment
• Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR*

Stratification Factors
• Previous taxane
• Measurable disease

2:1 randomization
Open-label

Cohort A: BRCA1, BRCA2 or ATM
N=245

Cohort B: Other HRR alterations
N=142

Physician's choice of enza or abi†
N=83

Olaparib 300 mg bid
n=162

Physician's choice of enza or abi†
N=48

Olaparib 300 mg bid
n=94

Upon BICR progression, Physician's choice patients were eligible for crossover to olaparib

Primary endpoint:
- rPFS by BICR in Cohort A (alpha=0.05)
- Confirmed ORR in Cohort A (alpha=0.05)
- rPFS by BICR in Cohorts A+B (alpha=0.05)
- Time to pain progression in Cohort A (alpha=0.05)
- OS in Cohort A (Interim: alpha=0.01, Final: alpha=0.047)

Statistical assumption for primary endpoint: Target hazard ratio = 0.53 (assumed 9.5 vs 5 months), 95% power, 2-sided 5% alpha (60% maturity, 143 events)
Prostate specific membrane antigen (PSMA)

- **Type II transmembrane glycoprotein (FOLH1)**
- **Highly over-expressed in prostate cancer**
- ↑↑ castrate-resistant metastatic disease

177LU-PSMA-617: 1º ENDPOINT: PSA RESPONSE

PSA Response @ 12 Weeks from 1st dose

Best PSA Response (PCWG2 criteria)

>50% in 50%

>50% in 57%

>80% in 27%

>80% in 43%
VISION Phase 3 trial

- mCRPC
- Post-Abi/Enza
- Post-taxane
- Max 2 lines of chemo

Randomized

SOC + PSMA-Lutetium

SOC

Courtesy of K Fizazi
Next PEACE-6 trial in M1 CSPC

- Patients with newly diagnosed (ADT naïve) metastatic CaP
- To be discussed: pts with M1 relapse after local treatment (ADT naïve)

- Oligo-M1
- Unfit
- DNA repair signature MSI high Cdk12-/-
- All others

Randomized:

- SOC
- SOC+ RXT to mets
- SOC (ADT)
- SOC + Darolutamide
- SOC + PARPi + IO
- SOC + Lu-PSMA

Study sponsor: Unicancer
Finally, can we improve outcomes with simple, old treatments?
**PEACE-4: European Phase III Trial of Aspirin and Statin in CRPC**

**Funded!**

- Patients with “early” CRPC
- Stratification on M0 vs M1
- 1152 patients planned

Randomized Study:
- Standard of care (SOC)
- SOC + Aspirin 100 mg
- SOC + Statin
- SOC + Aspirin + Statin

Primary endpoint: OS (HR: 0.77)

Study sponsor: Gustave Roussy

Courtesy of K Fizazi
Conclusion: Targeted treatments

• AR targeting remains key (major oncogenic driver)
• DNA damage repair defect clearly emerging
• PSMA targeting clearly emerging
• PI3K/Akt/Pten targeting clinically relevant?
• Immunotherapy as a player
• Role of non-anticancer drugs? (Metformin, Aspirin, Statins)