Immunotherapy and new agents in CRPC

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Disclosure

• Participation to advisory boards/honorarium for: Astellas, Astrazeneca, Bayer, Curevac, Janssen, Orion, Sanofi
Autologous Cellular Immunotherapy With Sipuleucel-T

The precise mechanism of action of sipuleucel-T is not known.

PAP-GM-CSF, Prostatic acid phosphatase-granulocyte-macrophage-colony-stimulating factor
A first « negative-positive » trial

**Figure 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)

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: Impact Phase 3 trial

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)
  - 1:1 ratio
  - Single-dose, bone-directed RT (8 GY)
  - Patients stratified by investigator site, alkaline phosphatase, hemoglobin, and ECOG PS

**N=399**
- Ipilimumab (10 mg/kg) Wks 1, 4, 7, 10
- Treatment until disease progression or intolerable toxicity

**N=400**
- Placebo Wks 1, 4, 7, 10
- Placebo Every 12 wks

- **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=0.0530</td>
<td></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>

Proportion Alive

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>399 362 306 260 228 195 155 131 106 85 69 52 37 24 15 9 4 3 1 0 0</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>400 376 332 281 222 184 138 106 77 65 47 36 26 16 12 6 2 1 0 0</td>
<td></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>
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><strong>70.65 → 11.1 → 1.18 → 0.11 → 0.08</strong></td>
<td>Yes (lymph)</td>
<td>PR</td>
<td>present</td>
</tr>
<tr>
<td>2</td>
<td>October 2015</td>
<td><strong>46.09 → 41.22 → 12.99 → 9.89 → 0.02</strong></td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>January 2016</td>
<td><strong>2502.75 → 1.25 → 0.07 →0.01 → &lt;0.01</strong></td>
<td>Yes (liver)</td>
<td>PR</td>
<td>absent</td>
</tr>
<tr>
<td>4</td>
<td>March 2016</td>
<td><strong>82.43 → 17.34 → 0.38 → 0.01</strong></td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>5</td>
<td>June 2016</td>
<td><strong>250 → 88.69 → 5.1 → 0.43 → 0.18</strong></td>
<td>Yes (liver)</td>
<td>PR</td>
<td>pending</td>
</tr>
</tbody>
</table>

Graff JN, ESMO 2016
Pembrolizumab in CRPC: Keynote 0-28

Best Change From Baseline in Tumor Size
Per RECIST v1.1, Investigator Review

Hansen A, ESMO 2016
Immunotherapy in mCRPC: Pembro activity in a minority independent of PD-L1

**KEYNOTE-199**
Change from baseline in sum of target lesions, cohorts 1 + 2

<table>
<thead>
<tr>
<th>Change from baseline, %</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>−1 to −100</td>
<td>36</td>
</tr>
<tr>
<td>−30 to −100</td>
<td>10</td>
</tr>
<tr>
<td>0 to +100</td>
<td>64</td>
</tr>
<tr>
<td>0 to +19</td>
<td>33</td>
</tr>
</tbody>
</table>

**Response rate:** ≤ 10%

**KEYNOTE-365: Pembro + Olaparib**
Change from baseline in sum of target lesions, cohorts 1 + 2

- 11/28 (39%) experienced reduction in tumor burden
- 8/28 (29%) experienced reduction ≥30%

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PD-1 Blockade in Tumors with Mismatch-Repair Deficiency


3% of prostate cancers with MMR mutations
CRPC progressing after Enzalutamide
Lymph node biopsy shows:
- MYC amplification
- TMPRSS2-ERG
- MSH2, MSH6 mutations
Baseline 6/18/16

Post-Atezolizumab 8/16/16: -40%

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 Navonil 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?

N-terminal targeted drugs?

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

Abiraterone
Targeting the Akt and the AR pathways

**Ipatasertib**
- **PI3KCA**
- **Akt**
- **mTORC1/2**

**Abiraterone**
- **RTK (HER2/3)**
- **PTEN**
- **PI3KCA**

**Pathway Details**
- Synthesis adrenal testicular tumor
- Androgen precursors
- Androgens

**Target Genes**
- AR target genes
**Abiraterone +/- Ipatasertib (Akt inhibitor): PFS**

**PTEN loss**

HR, \(^a\) 0.39 (0.22-0.70)

- 400 mg Ipat + Abi
  - Median 11.5 mo

- Pbo + Abi
  - Median 4.6 mo

**PTEN non-loss**

HR, \(^a\) 0.84 (0.51-1.37)

- 400 mg Ipat + Abi
  - Median 7.5 mo

- Pbo + Abi
  - Median 5.6 mo
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

Repair pathway:
- Base Excision Repair
- Homologous Recombination Repair
- Non-Homologous End Joining
- Nucleotide Excision Repair and Translesion Synthesis
- MisMatch Repair

ERCC1 XP proteins
DNA-PK
ATR
ATM
MLH, MSH, MTH1*, etc
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

Cumulative Survival

- **Non-carriers**
  - Median PFS: 28.2 months
  - CI-95%: (24.1-32.3)

- **Carriers**
  - Median PFS: 18.6 months
  - CI-95%: (10.6-26.6)

Log-rank p = 0.04

- **Non-BRCA2**
  - Median PFS: 28.0 months
  - CI-95%: (24.1-32.1)

- **BRCA2**
  - Median PFS: 13.2 months
  - CI-95%: (3.5-22.9)

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 (BRCA-2)
- 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)

### 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]</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)*</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>

*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)

[Graph showing best change from baseline in sum of target lesions]

ESMO 2018
Niraparib in HRD+ CRPC

Response by RECIST

PSA

Smith M, ASCO GU 2019
PROfound STUDY DESIGN

**Primary Endpoint**
Radiographic progression-free survival (rPFS) in Cohort A (RECIST 1.1 & PCWG3 by BICR)

**Key Secondary Endpoints**
- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in Cohort A
- Overall survival (OS) in Cohort A

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

**Stratification factors**
- Previous taxane
- Measurable disease

**Cohort A:**
BRCA1, BRCA2 or ATM
N=245

**Cohort B:**
Other alterations
N=142

2:1 randomization
Open-label

Upon BICR progression, physician’s choice patients were allowed to cross over to olaparib

- **Olaparib 300 mg bid**
  - n=162
  - Physician’s choice‡
    - n=83

- **Olaparib 300 mg bid**
  - n=94
  - Physician’s choice‡
    - n=48

*An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test
Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and/or RAD54L in their tumor tissue

‡Physician’s choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid])
BICR, blinded independent central review

Hussain M, N Engl J Med 2019
Primary endpoint
rPFS BY BICR IN PATIENTS WITH ALTERATIONS IN BRCA1, BRCA2, OR ATM (COHORT A)

Time from randomization (months)

Probability of rPFS

No. at risk

<table>
<thead>
<tr>
<th>Month</th>
<th>Olaparib</th>
<th>Physician's choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>162</td>
<td>83</td>
</tr>
<tr>
<td>1</td>
<td>149</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>126</td>
<td>47</td>
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<tr>
<td>3</td>
<td>116</td>
<td>44</td>
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<td>4</td>
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<td>5</td>
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<td>6</td>
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<td>9</td>
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<td>6</td>
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<tr>
<td>10</td>
<td>42</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>37</td>
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<td>12</td>
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<td>19</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>21</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Events (%)

- Olaparib (N=162): 106 (65.4)
- Physician's choice (N=83): 68 (81.9)

Median rPFS (months)

- Olaparib: 7.39
- Physician's choice: 3.55

Hazard ratio (95% CI)

- 0.34 (0.25, 0.47)
- P<0.0001

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Key secondary endpoint

PROFOUND: CONFIRMED ORR IN COHORT A

Confirmed ORR was assessed in patients with measurable disease by BICR using RECIST v1.1 and PCWG3

Confirmed ORR

Odds ratio: 20.86 (95% CI 4.18, 379.18); P<0.0001

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Key secondary endpoint

TIME TO PAIN PROGRESSION* IN COHORT A

Time since randomization (months)

No. at risk

Olaparib (N=162)

Physician's choice (N=83)

Events (%) 21 (13.0) 14 (16.9)

Median TTPP (months) NR 9.92

Hazard ratio (95% CI) 0.44 (0.22, 0.91)

P=0.0192

*Based on the Brief Pain Inventory-Short Form (BPI –SF) worst pain [Item 3] and opioid use
For the overall population (Cohorts A+B), median time to pain progression was NR in either arm (HR 0.64 [95% CI 0.35, 1.21])
NR, Not reached

Hussain M, N Engl J Med 2019
Key secondary endpoint

rPFS BY BICR IN THE OVERALL POPULATION (COHORTS A+B)

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>Olaparib (N=256)</th>
<th>Physician's choice (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median rPFS (months)</td>
<td>5.82</td>
<td>3.52</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.49 (0.38, 0.63)</td>
<td>( P&lt;0.0001 )</td>
</tr>
</tbody>
</table>

Hussain M, N Engl J Med 2019
PROFOUND: INTERIM* OVERALL SURVIVAL

Cohort A

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (N=162)</th>
<th>Physician's choice (N=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>18.50</td>
<td>15.11</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.64 (0.43, 0.97)</td>
<td>P=0.0173†</td>
</tr>
</tbody>
</table>

Of the physician's choice arm patients who progressed, 80.6% in Cohort A and 84.6% in Cohort B crossed over to olaparib

*38% maturity in Cohort A; 41% maturity in Cohort A+B; final analysis planned after ~146 deaths in Cohort A (60% maturity)
†Alpha spend at interim was 0.01; statistical significance not reached

Cohort A+B

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (N=256)</th>
<th>Physician's choice (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>17.51</td>
<td>14.26</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.67 (0.49, 0.93)</td>
<td>P=0.0063 (nominal)</td>
</tr>
</tbody>
</table>

Hussain M, N Engl J Med 2019
## Efficacy Summary by Cohort

<table>
<thead>
<tr>
<th></th>
<th>Cohort A (Olaparib/Physician’s choice)</th>
<th>Cohort B</th>
<th>Cohorts A+B</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>162/83</td>
<td>94/48</td>
<td>256/131</td>
</tr>
<tr>
<td><strong>rPFS (BICR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.34 (0.25, 0.47) P&lt;0.0001</td>
<td>0.88 (0.58, 1.36)</td>
<td>0.49 (0.38, 0.63) P&lt;0.0001</td>
</tr>
<tr>
<td><strong>rPFS (investigator-assessed)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.24 (0.17, 0.34)</td>
<td>0.60 (0.39, 0.93)</td>
<td>0.36 (0.27, 0.47)</td>
</tr>
<tr>
<td><strong>ORR (BICR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%, Olaparib vs Physician’s Choice</td>
<td>33.3 vs 2.3%</td>
<td>3.7 vs 8.3%</td>
<td>21.7 vs 4.5%</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>20.86 (4.18, 379.18) P&lt;0.0001</td>
<td>Not calculated†</td>
<td>5.93 (2.01, 25.40)</td>
</tr>
<tr>
<td><strong>OS (interim)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.64 (0.43, 0.97) P=0.0173</td>
<td>0.73 (0.45, 1.23)</td>
<td>0.67 (0.49, 0.93)</td>
</tr>
</tbody>
</table>

Denotes multiplicity-controlled endpoint

Hussain M, N Engl J Med 2019
Exploratory analyses
GENE-BY-GENE rPFS

- 7/15 genes had alteration frequencies too low for descriptive statistics (<5 patients)
- 97% of patients were randomized based on alterations in 8/15 single genes
- There is evidence of clinical activity of olaparib in patients with alterations in genes other than BRCA1 or BRCA2
- Gene-level analysis is complex and exploratory, and comparisons may be confounded by multiple factors

![Graph showing frequency and median rPFS for different genes](image)

NR, not reached

Hussain M, N Engl J Med 2019
4.3% pulmonary embolism with olaparib vs 0.8% with physician’s choice; none were fatal

No reports of myelodysplastic syndromes or acute myeloid leukemia

*Anemia (46.1%) and decreased Hb (0.4%)

Hussain M, N Engl J Med 2019
Prostate specific membrane antigen (PSMA)

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

$^{111}$In-capromab Prostascint

PSMA PET
normal biodistribution


$^{68}$Ga-PSMA-11
$^{177}$Lu-PSMA-617

- High expression in prostate cancer
- $\rightarrow$ castrate-resistant metastatic disease

- J591 antibodies
- Active centre PSMA-inhibitors
- 7E11 antibodies

Key locations for radioactivity:
- Lacrimal
- Parotid
- Submandibular
- Liver
- Spleen
- Kidney
- Small bowel (duodenum)
- Radioactive urine
THERANOSTICS

TARGETED THERAPEUTIC + DIAGNOSTIC COMPANION

177Lu-PSMA-617

Post-therapy SPECT/CT

68Ga-PSMA-11 PET/CT

Pre-therapy PET/CT

Hofman MS, ESMO 2017
177LU-PSMA-617: 1º ENDPOINT: PSA RESPONSE

PSA Response @ 12 Weeks from 1st dose

- >50% in 50%
- >80% in 27%

Best PSA Response (PCWG2 criteria)

- >50% in 57%
- >80% in 43%

Hofman MS, ESMO 2017
VISION Phase 3 trial

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

Randomized

SOC + PSMA-Lutetium

Randomized

SOC

Courtesy of K Fizazi
Next European 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)

DNA repair signature
MSI high
Cdk12-/-

Oligo-M1
SOC
SOC + RXT to mets
SOC (ADT)
SOC + Darolutamide
SOC + PARPi + IO
SOC + Lu-PSMA

Unfit
SOC
SOC + Darolutamide
SOC + Lu-PSMA

All others
SOC
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

Study sponsor: Gustave Roussy

Primary endpoint: OS (HR: 0.77)

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

PEACE-4: European Phase III Trial of Aspirin and Statin in CRPC

Study sponsor: Gustave Roussy

Funded!
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)