NEW AVENUES IN MCRPC;

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DISCLOSURE SLIDE

- Consultancy,
  Sanofi, Merck, Lilly, Bayer, Janssen, Roche, Clovis

- Speaker fees
  Sanofi, Merck

- Institutional financial interests,
  Sanofi, Bayer
In 2018 Multiple drugs and sequences

- mHSPC  early taxane /late taxane /early abi/late abi
- mCRPC  abi/enza (ART) predoce/ postdoce/pre/postcaba
- mCRPC  Radium 223 post ART pre/ post taxane
- >Even after 4 lines many mCRPC patients opt to receive systemic therapies
- >New avenues: PSMA guided therapy
  Molecular targeted therapies
  Immunotherapy
177 Lu-PSMA targeted therapy in Prostate Cancer

- Prostate-specific membrane antigen PSMA; transmembrane protein expressed in aggressive variants of PC
- Upregulated by ADT and second generation ART
- Radioconjugated PSMA antagonists, such as 68 Ga and 177Lu-PSMA
  Bound to the cell membrane the PSMA ligands are internalised and the beta particles (68 Ga, 177 Lu) or alpha particles (actinium-225) exert a toxic effect on tumor DNA
- No randomised data!!
- How promising are the existing data actually?
177 Lu-PSMA targeted therapy in mCRPC
ASCO 2018 Interim analysis phase II trial

- 50 Patients with PSMA –avid mCRPC who had progressed after conventional therapies (abi/enza and docetaxel)
- Up to 4 cycles of LU-PSMA every 6 weeks
- Primary endpoint PSA 50% decline rate
  >PSA 50% decline obtained in 31/50 (62%)
  >Median OS 12 months

Sandhu et al ASCO 2018 (recent full paper smaller cohort Hofman et al, Lancet Oncol 2018, 19, 825-33)
Lutetium-177 PSMA in mCRPC interim results (ASCO 2018)

RESULTS: PSMA PET/CT before and after

REFERENCES:
1 Hofman MS, Violet J, Hicks RJ et al, Lancet Oncology 2018
https://doi.org/10.1016/s1470-2045(18)30198-0
177 Lu-PSMA targeted therapy in mCRPC
Interim results phase II trial (ASCO 2018)

> Median OS 12 months
  • Prior treatment abi/enza 90%
  • Prior docetaxel 84%
  • Prior docetaxel plus cabazitaxel 48%
  • *Thus 52% of patients had not received cabazitaxel*

Sandhu et al ASCO 2018
177 Lu-PSMA targeted therapy in mCRPC
Clinical Experience 100 pts (ESMO 2018)

> Median OS 12.9 months
• Prior treatment abi/enza 89%
• Prior docetaxel 83%
• Prior docetaxel plus cabazitaxel 20%
• Thus 80% of patients had not received cabazitaxel

Tauber et al Universitäts Klinikum Munich (ESMO 2018 poster 831)
177 Lu-PSMA targeted therapy in mCRPC Clinical Experience 100 pts (ESMO 2018)

> Adverse events

- Myelotoxicity gr 1-2 ; 27%, gr 3-4 ; 9%
- Dry mouth gr 1-2 ; 24%
- Fatigue gr 1-2 ; 20%
- Loss of appetite gr 1-2 ; 10%
- Gastrointestinal gr 1-2 ; 11%

Tauber et al. ESMO 2018
How does 177 Lu-PSMA targeted therapy compare with standard 2\textsuperscript{nd} /3\textsuperscript{rd} line cabazitaxel

- Is a median OS of 12 months promising in a cohort of patients of whom 52-80% of patients had not received cabazitaxel?

- If not, why are PSMA PET scans so dramatically improved and current OS data less impressive?
OS data 2nd/3rd line cabazitaxel
ASCO 2018 Caffo et al

1099pts;
-398 pts receiving caba 2nd line
median OS 20 mo
-512 pts receiving caba 3rd line
median OS 12.5 mo
Survival outcomes from observational studies on sequential use of agents in mCRPC

- Is a median OS of 12 months promising in a cohort of patients of whom 52% of patients had not received cabazitaxel?

Cabazitaxel data presented at ASCO 2018*
1099pts;
398 pts receiving caba 2nd line median OS 20 mo
512 pts receiving caba 3rd line median OS 12.5 mo

* Caffo et al ASCO 2018
177 Lu-PSMA targeted therapy in Prostate Cancer

- If OS 12 months, why are scans so notably improved but current OS data modest at best?

> Hypothesis: If PC contains both PSMA positive (scan avid) and PSMA negative clones, 177 Lu-PSMA may be targeting only part of the disease (escape of the negative clones)?
EC1169 is a PSMA-targeted small molecule drug conjugate constructed of a PSMA targeted ligand and a potent microtubule inhibitor.

- Phase 1 study
  - EC1169 well tolerated and resulted in AlkPhos/LD declines (not PSA)
  - 35/40 pts had CTCs
  - 43% of pts had both PSMA + and –ve CTCs; intrapatient heterogeneity (late stage?)

Morris et al ESMO 2017 (poster 793)
Phase 1 study of the PSMA targeted drug conjugate EC1169 in pts with mCRPC

43% of patients with CTCs had PSMA positive CTCs but also had CTCs that were not PSMA positive

This has implication for all PSMA targeted therapies, including radio conjugates

Really need phase III trials
False negative PSMA-PET scan

Noto et al al; Clin Nucl Med 43, June 2018
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)

Defects in DNA repair genes associated with PARP inhibitor sensitivity

- 49 heavily pretreated mCRPC men
- PARP inhibitor (olaparib 400 mg BID)
- Genomic signature of PARP inhibitor sensitivity in 16/49 (33%)
  - BRCA2, ATM, BRCA1, PALB2, CHEK2, FANCA, HDAC2
  - Response to PARP in 14/16

Genomic data on prostate cancer

Cell, Volume 161, Issue 5, 21 May 2015, Pages 1215–1228
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**

- Safety:
  - Assess safety and tolerability
  - Determine recommended combination dose for Phase II trials
- Efficacy:
  - Non-disease progression at 12 weeks

**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
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 Mutations and splice variants

Enriched in metastatic setting, especially in pretreated patients

- Biopsies cumbersome, sometimes impossible
- Invasive
- Difficult to repeat during treatment

Liquid biopsies
## CTCs vs cell-free tumor DNA (ctDNA)

<table>
<thead>
<tr>
<th>CTCs</th>
<th>cfDNA</th>
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<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>

NO prime time for clinic (yet)
CIRCUS study <ErasmusMC Group>

CPCT-02 study

- Biopsy
- DNA isolation
- DNA sequencing
- SV selection

CRPC patient
- PSMA scan

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

Graphs showing data analysis and responses.
CPCT: Dutch Collab. study WGS 197pts
Future studies and hopefully treatment will be increasingly biology directed!

Remainder at this time: ART and taxanes
Olaparib Combined With Abiraterone in Patients With Metastatic Castration-Resistant Prostate Cancer: A Randomized Phase II Trial

Noel Clarke,1 Pawel Wiechno,2 Boris Alekseev,3 Nuria Sala,4 Robert Jones,5 Ivo Kocak,6 Vincenzo Emanuele Chiuri,7 Jacek Jassem,8 Aude Fléchon,9 Charles Redfern,10 Carsten Goessl,11 Joseph Burgents,11 Robert Kozarski,12 Darren Hodgson,13 Fred Saad14

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ClinicalTrials.gov identifier: NCT01972217. This study was sponsored by AstraZeneca
Rationale: synergy between olaparib and abiraterone

Proposed hypotheses

Olaparib monotherapy
- PARP inhibition blocks DNA repair pathways in cells harboring HRR defects

Olaparib + abiraterone
- PARP involved in androgen-receptor dependent transcription
- Abiraterone-induced HRR deficiency

Synergy

Antitumor activity

HRR, homologous recombination repair; PARP, poly (ADP ribose) polymerase

Presented By Noel Clarke at 2018 ASCO Annual Meeting
**Trial design**

- mCRPC
- Prior treatment with docetaxel for mCRPC
- ≤2 prior lines of chemotherapy
- No prior 2nd-generation antihormonal agents

**Randomized 1:1 Double-blind**

- Olaparib tablets 300 mg bid + abiraterone* 1000 mg od
- Placebo + abiraterone* 1000 mg od

**Primary endpoint:**
- Radiologic progression-free survival (investigator-assessed; RECIST 1.1, PCWG2)

**Secondary endpoints:**
- rPFS by HRRm status
- Time to second progression (PFS2)
- Overall survival (OS)
- Objective response rate (ORR)
- CTC-conversion rate
- Safety and tolerability
- Times to first and second subsequent therapies (TFST/TSST)
- Health-related quality of life (HRQoL)

*Prednisone/prednisolone (5 mg) was administered alongside abiraterone as indicated, bid, twice daily; CTC, circulating tumor cell; HRRm, homologous recombination repair gene mutation; mCRPC, metastatic castration-resistant prostate cancer; od, once daily; PCWG, Prostate Cancer Working Group; RECIST, Response Evaluation Criteria in Solid Tumors; rPFS, radiographic progression-free survival.

Presented By Noel Clarke at 2018 ASCO Annual Meeting
rPFS by HRR mutation status

**HRRm**
- Events, n (%)
  - Olap + Abl (n=11)
    - 8 (73)
    - 17.8
    - HR 0.74
    - 95% CI 0.26, 2.12
  - Abi (n=10)
    - 7 (70)
    - 6.5

**HRRpc**
- Olap + Abl (n=45)
  - 30 (67)
  - 13.1
  - HR 0.67
  - 95% CI 0.40, 1.13
- Abi (n=41)
  - 30 (73)
  - 6.4

**HRRwt**
- Olap + Abl (n=15)
  - 8 (53)
  - 15.0
  - HR 0.52
- Abi (n=20)
  - 17 (85)
  - 9.7
  - 95% CI 0.24, 1.15

*80/86 patients HRRwt by plasma and/or germline testing
HRRpc, HRR partially characterized; HRRwt, HRR wild-type

Presented By Noel Clarke at 2018 ASCO Annual Meeting
Olaparib with abiraterone

- Olaparib with abiraterone provided a significant rPFS benefit in mCRPC patients who had previously received docetaxel, compared with abi alone
- Benefit was seen independent of HRR mutation status
- Combination resulted in increase incidence of adverse events
- A phase III study based on these results is needed
KEYNOTE-199: Pembrolizumab For Post-Docetaxel Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Johann S. de Bono, Jeffrey Goh, Kristiina Ojamaa, Marine Gross-Goupil, Josep Piulats, Charles G. Drake, Christopher J. Holmes, Haiyan Wu, Ping Qiu, Christian Poehlein, Emmanuel S. Antonarakis

1Royal Marsden and The Institute of Cancer Research, London, UK; 2Royal Brisbane & Women’s Hospital, Herston, and University of Queensland, St. Lucia, QLD, Australia; 3East Tallinn Central Hospital, Tallinn, Estonia; 4Institut Bergonié, Bordeaux, France; 5Instituto Catalan de Oncologia, Hospital Duran i Reynals, Hospital de Llobregat, Barcelona, Spain; 6Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY, USA; 7Case Western Reserve University Hospitals Seidman Cancer Center, Cleveland, OH, USA; 8MSD China, Beijing, China; 9Merck & Co., Inc., Kenilworth, NJ, USA; 10Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA

Presented By Johann De Bono at 2018 ASCO Annual Meeting
KEYNOTE-199: Pembrolizumab For Post-Docetaxel Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Study Design

- mCRPC
- ≥1 prior targeted endocrine therapy
- 1-2 prior chemotherapy regimens, including docetaxel
- ECOG PS 0-2
- Measurable disease per RECIST v1.1
- mCRPC
- ≥1 prior targeted endocrine therapy
- 1-2 prior chemotherapy regimens, including docetaxel
- ECOG PS 0-2
- Bone mets with no measurable disease per RECIST v1.1
- Any PD-L1 status

Cohort 1: PD-L1 positive N=131
Cohort 2: PD-L1 negative N=67
Cohort 3 N=60

Presented By Douglas McNeel at 2018 ASCO Annual Meeting
Overall Conclusions:

- Biomarker work ongoing, but suggests that DNA repair defects may be associated with antitumor activity
- Low number of responses overall makes interpretation difficult

<table>
<thead>
<tr>
<th></th>
<th>BRCA1/2 or ATM</th>
<th>Other DDR Genes*</th>
<th>Negative</th>
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<tbody>
<tr>
<td></td>
<td>n = 19</td>
<td>n = 10</td>
<td>n = 124</td>
</tr>
<tr>
<td>RECIST v1.1</td>
<td>2 (11%)</td>
<td>0</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>ORR</td>
<td></td>
<td></td>
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<tr>
<td>DCR (any duration)</td>
<td>2 (11%)</td>
<td>0</td>
<td>2 (2%)</td>
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<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
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<tr>
<td>PR</td>
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<td>SD (any duration)</td>
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<td>2 (20%)</td>
<td>10 (12%)</td>
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<tr>
<td>NonCR/nonPD</td>
<td>1 (5%)</td>
<td>0</td>
<td>7 (6%)</td>
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<tr>
<td>PD</td>
<td>12 (63%)</td>
<td>5 (50%)</td>
<td>80 (65%)</td>
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<tr>
<td>NE or missing</td>
<td>2 (11%)</td>
<td>3 (30%)</td>
<td>15 (12%)</td>
</tr>
<tr>
<td>PSA responders</td>
<td>2 (11%)</td>
<td>1 (10%)</td>
<td>4 (3%)</td>
</tr>
</tbody>
</table>

- This could be important, since the rate of HRRm is likely higher than microsatellite instability

Presented By Douglas McNeel at 2018 ASCO Annual Meeting
Why Are Mutations So Important?

- Pembrolizumab blocks PD-1/PDL-1 interaction
- Activation of T cells causes PD-1 upregulation
- With stronger activation signal, greater and more persistent PD-1 expression
- Opportunities:
  - Mutations – higher affinity, tumor-specific epitopes
  - Combine PD-1 blockade with other agents that activate T cells

Zahm (2017) Canc Imm Res 5:630

Presented By Douglas McNeel at 2018 ASCO Annual Meeting
Immunogenic mCRPC subtypes by WGS, 197 patients, poster Mehra et al

Tumor mutational load varies between CRPC subtypes

- 7.7% have highTMB (>10 mutations/Mb), of which 6.7% have a highTMB /MSI signature and 1% with BRCA inactivation
- 11.7% of patients have BRCAness signature (BRCA2 biallelic inactivation)
- 6.7% of patients have CDK12 biallelic inactivation and focal tandem duplication signature

WGS identifies hTMB, BRCAness and focal tandem duplications in ~25% of patients with mCRPC. Patients with MSI and BRCAness have significant higher TMB compared to those with CDK12 biallelic inactivation and other molecular signatures
Management of mCRPC

- 14 years of progress
- Many new agents, some remaining questions about sequence
- New avenues that need to be tested in well designed Phase III trials
- Future studies will be increasingly biology directed
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Wytske van Weerden  
Guido Jenster  
Ronald de Wit

All recruiting physicians and research nurses  
Patients and their families