Ongoing trials that might change the standard of care in mCRPC

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COI

✔ Off-label use of drugs, devices, or other agents: none
✔ Data from IRB-approved human research is presented: is not

<table>
<thead>
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<th>I have the following financial interests or relationships to disclose:</th>
<th>Disclosure code</th>
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<td>Sanofi</td>
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<td>Janssen</td>
<td>C, L</td>
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<td>Ferring</td>
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<td>Bayer</td>
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Natural history of prostate cancer (PCa)

Initial diagnosis PCa

- > 95% localized
- prostatectomy (RPE)
- radiotherapy (RTX)
- HIFU
- active surveillance
- ca. 30% recurrence
- 1/3 cure
- 70% cure

< 5% metastasized hormonnaiv

2/3 progression

Salvage-RPE
Salvage-RTX

Metastatic castration-resistant PCa (mCRPC)
Evolvement of metastatic PCa till 2004

- metastatic hormone-sensitive PCa
  - response 24-36 mo.

- metastatic castration-resistant PCa

ADT

- survival 12 mo.
- best supportive care
- palliative chemotherapy
- death

Tumor burden
Evolvement of metastatic PCa nowadays

**metastatic hormone-sensitive PCa**
- **response** 33-36 mo.

**metastatic castration-resistant PCa**

**best supportive care**
- survival 30-35 mo.

**sequential use of emerging systemic agents**

**tumor burden**

**death**

**ADT + docetaxel**
- survival 58-60 Monate

**ADT + abiraterone**
- death risk reduction 39%
Systemic treatment of mCRPC

modified from Crawford et al, Urol Oncol, 2017
Changing paradigm

✓ initially mCPRC-approved drugs increasingly used in mHSPC (and nmCRPC)
✓ many trials currently ongoing in mHSPC – value of drug combinations/sequencing?
✓ availability/cost-effectiveness of emerging agents in mHSPC/nmCRPC?
✓ definition of CRPC still valid and clinically relevant in the future?
Agenda

✓ androgen receptor signaling inhibitors
✓ chemotherapy
✓ immuno-oncological agents
✓ radiopharmaceuticals
✓ targeting tumors with DNA-repair defects
✓ targeting small molecules
Hormonal treatment: drug classes

modified from Bambury et al, Urol Oncol, 2016
Hormonal treatment: abi/enza sequencing

- NCT02125357
- Phase 2 RCT
- Treatment naïve mCRPC
- Eligible for treatment with AA or ENZ
- N = 202

Randomise 1:1

Plasma and whole blood

Progression 1

- AA 1000 mg
- P 10 mg
- ENZ 160 mg

Progression 2

- ENZ 160 mg
- AA 1000 mg
- P 10 mg

Primary objective
- Response and TTPP after 2nd line therapy

Secondary objectives
- TTP/TTPP with 1st line therapy
- PSA decline from baseline
- Correlation with deep targeted sequencing of cfDNA
- OS

Chi et al, J Clin Oncol suppl, 2017
Crossover trial: TT2PP, TT2P and OS

<table>
<thead>
<tr>
<th>PSA response after 3 mo.</th>
<th>2nd line Abiraterone + P</th>
<th>2nd line Enzalutamide</th>
<th>P-value</th>
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<tbody>
<tr>
<td></td>
<td>N= 71</td>
<td>N= 65</td>
<td></td>
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<tr>
<td>PSA decline ≥ 30%</td>
<td>4 (6%)</td>
<td>28 (43%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PSA decline ≥ 50%</td>
<td>3 (4%)</td>
<td>20 (31%)</td>
<td>&lt; 0.001</td>
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- TT2PP+TT2P+OS: no difference

Khalaf D, Abstract 5015; ASCO 2018
Hormonal treatment:
abiraterone + enzalutamide combined

- NCT01949337
- phase 3
- open-label
- **mCRPC**
- chemo-naive pts.
- estimated n=1224

Enza 160 mg + Abi 1g + Pred 5mg QD

Enza 160 mg QD

- pEP: OS
- selected sEP: rPFS, PSA response, ORR
- estimated study completion 12/2019
Hormonal treatment: apalutamide

greater potency and less CNS penetration than enza

- phase 3 RCT
- n=1207, 2:1
- nmCRPC (N1 allowed)
- PSADT ≤ 10 mo.
- primary EP: MFS

Smith et al, NEJM, 2018
Hormonal treatment: apalutamide + abiraterone combined

- NCT02257736
- phase 3
- double-blind
- mCRPC
- chemo-naive pts.
- estimated n=960

- pEP: rPFS
- selected sEP: OS, TTPP
- estimated study completion 8/2021

Apa 240 mg QD + Abi 1g QD + Pred 5mg BD
PB + Abi 1g QD + Pred 5mg BD
Hormonal treatment: darolutamide

low CNS penetration

- phase 2
- open-label
- n=110
- mCRPC

- primary EP: PSA$_{50}$ response at 12 wks.
Hormonal treatment: darolutamid

- NCT02200614
- phase 3
- quadruple masking

- nmCRPC
- PSADT ≤ 10 mo.
- estimated n=1500

ARAMIS

- Dar 1200 mg QD

PB

- pEP: MFS
- selected sEP: OS, Time to SSE, TTPP
- estimated study completion 6/2020
Hormonal treatment: darolutamade

- NCT02933801
- phase 2
- quadruple masking

- mCRPC
  - maintainence in stable disease after ARSIs and taxane
  - estimated n=88

- selected sEP: TTP, OS, PSA response
- estimated study completion 12/2020

Dar 1200 mg QD
PB
Hormonal treatment: seviteronel

no exogenous steroids required

- NCT02445976
- phase 2
- open-label
- mCRPC
  - progression on ARSIs
  - estimated n=197

SEV 450 mg QD

- pEP: PSA_{50} response, TTRP
- selected sEP: ORR
- estimated study completion 12/2018
Hormonal treatment: bipolar androgen therapy

- pilot study
- n=16
- mCRPC
- 3 cycles /28 d
- primary EP: PSA response, radiographic response

Schweizer et al, Sci Transl Med, 2015
Hormonal treatment: bipolar androgen therapy

- NCT02286921
- phase 2
- open-label

- **asym. mCRPC**
  - progression on abiraterone
  - estimated n=180

**TRANSFORMER**

- BAT (T 400 mg IM E4W)
- ENZA 160 mg QD

- pEP: rPFS
- selected sEP: ORR, Time to PSA progression
- estimated study completion 12/2018
Hormonal treatment: bipolar androgen therapy

- NCT02090114
- phase 2
- open-label

- mCRPC
  - progression on abi or enza or ADT
  - estimated n=90

- pEP: PSA response rate to BAT/re-challenge
- selected sEP: ORR, Time to PSA progression
- estimated study completion 4/2019

RESTORE

BAT (T 400 mg IM E4W)

progression

re-treatment with the same drug
Chemotherapy: cabazitaxel vs. abi/enza

- NCT02254785
- phase 2
- open-label
- **poor prognosis** mCRPC (e.g. liver mets, CRPC development <12 mo. etc.)
- estimated n=120

**CABAZITAXEL 25 mg/m2 E3W**

**ENZA 160 mg QD or ABI 1000 mg QD**

- pEP: clinical benefit rate
- selected sEP: OS, PFS
- estimated study completion 5/2020
Chemotherapy: cabazitaxel vs. abi/enza

- NCT02485691
- phase 3
- open-label

**mCRPC**
- pre-treated with Doc, progression ≤12 mo. on ABI or ENZA
- estimated n=324

**CABAZITAXEL 25 mg/m2 E3W**
- CABAZITAXEL 25 mg/m2 E3W

**ENZA 160 mg QD or ABI 1000 mg QD**
- ENZA 160 mg QD or ABI 1000 mg QD

- pEP: rPFS
- selected sEP: OS, PFS
- estimated study completion 8/2019
Immune checkpoint inhibitors: removing the brakes

Carlo et al, Nat Rev Urol, 2016
Immune checkpoint inhibitors: mutational burden

- less active CTLs
- many T-regs
- modest PD-L1 expression

✓ combination with other drugs/IOs to boost immunogenic microenvironment and enhance tumor immune recognition

Chalmers et al, Genome Med, 2017
Immune checkpoint inhibitors: ipilimumab

- phase 3 study
- n=799
- mCRPC / ≥1 bone met
- progression after DOC
- bone-directed RT +/- ipilimumab
- primary EP: OS

Kwon et al, Lancet Oncol, 2014
Immune checkpoint inhibitors: ipilimumab

- phase 3 study
- n=598
- asym./min. sym. mCRPC, no visceral mets
- chemo naive
- primary EP: OS

**HR 1.11 (ns)**
- mOS 28.7 vs. 29.7 mo.

**HR 0.67 (s)**
- mPFS 5.6 vs. 3.8 mo.

*Beer et al, J Clin Oncol, 2017*
Immune checkpoint inhibitors: ipilimumab

CheckMate 650

- NCT02985957
- phase 2
- open-label

- mCRPC
  - progression on ARSIs or taxanes
  - estimated n=90

- pEP: rPFS, ORR
- selected sEP: OS, rcPFS
- estimated study completion 3/2022

IPI + NIVOLUMAB
Immune checkpoint inhibitors: tremelimumab

- NCT03204812
- phase 2
- open-label
- **asym./min. sym. mCRPC**
  - chemonaive
  - estimated n=27

- pEP: rPFS, ORR
- selected sEP: OS, rcPFS
- estimated study completion 7/2020
**Immune checkpoint inhibitors: atezolizumab**

- NCT03016312
- phase 3
- open-label

- **mCRPC**
  - progression on ARSIs
  - failure/ineligibility of taxane
  - estimated n=730

**Imbassador 250**

- **ATEZOLIZUMAB 1200 mg E3W + ENZA 160 mg QD**

- **ENZA 160 mg QD**

- **pEP: OS**
- **selected sEP: TTSSE, TTPP**
- **estimated study completion 7/2022**
Immune checkpoint inhibitors: pembrolizumab

- NCT02787005
- phase 2
- open-label

**mCRPC**
- pre-treated with Doc/ARSI (C1-3)
- progression on enza (C4-5)
- estimated n=370

**KEYNOTE 199**

- PEMBRO 200 mg E3W
- PEMBRO
- PEMBRO + ENZA

**PD-L1+/measurable D**
**PD-L1-/measurable D**
**bone mets + non-meas. D**
**RECIST 1.1 meas. D**
**bone mets only/mainly**

- pEP: ORR
- selected sEP: DCR, PSARR
- estimated study completion 7/2020
Immune checkpoint inhibitors: pembrolizumab

- NCT02861573
- phase 2
- open label
- mCRPC
- estimated n=180

KEYNOTE 365

- PEMBRO + OLAPARIB
- PEMBRO + DOCETAXEL
- PEMBRO + ENZA

- pEP: PSA_{50} response
- selected sEP: ORR, DCR
- estimated study completion 4/2020
Immunooncological agents: DCVAC/PCa

- NCT02111577
- phase 3
- triple blinding

- mCRPC
- estimated n=1170

pEP: OS
- selected sEP: rPFS, duration of PSA response
- estimated study completion 6/2019
Immunooncological agents: sipuleucel-T

- NCT02463799
- phase 2
- open label
- asym./min. sym. bmCRPC
- estimated n=34

• pEP: immune response
• selected sEP: TTPSAP, TTRP, TTCP
• estimated study completion 12/2020
Radiopharmaceuticals: radium-223 and lutetium-177

Bruland et al, Clin Cancer Res, 2006
Simone et al, Clin Cancer Res, 2013
Radiopharmaceuticals: radium-223

- NCT02194842
- phase 3
- open label
- asym./min. sym. mCRPC
- estimated n=560

PEACE III

ENZA + Ra-223

ENZA

- pEP: rPFS
- selected sEP: OS, TSS
- estimated study completion 4/2021
Radiopharmaceuticals: lutetium-177

- phase 2 study
- n=47
- mCRPC
- single dose
- primary EP: RR

PSA decline in 59.6%

Tagawa et al, Clin Cancer Res, 2013
Radiopharmaceuticals: lutetium-177

- NCT03042312
- phase 2
- open label

- mCRPC
- positive PSMA-PET/CT
- estimated n=200

- pEP: PSA$_{50}$ at week 12
- selected sEP: PFS, PSA decline
- estimated study completion 4/2019

Lu177-PSMA-617 dose 1
E8W up to 4 cycles

Lu177-PSMA-617 dose 2
E8W up to 4 cycles
DNA repair defects: frequency

PARP inhibitors and platin-based protocols reasonable

Frequency of germline mutations in DNA-repair genes:

- Localized PCA (EAC, CGA) 2.7-4.6%
- M+ PCA 11.8%

DNA repair defects: olaparib

- phase 2 study
- n=16/50 with DNA repair gene mutations
- mCRPC
- primary EP: response rate

14/16 – response to olaparib

DNA repair defects: olaparib

- NCT02987543
- phase 3
- open-label

**mCRPC**
- DNA-repair gene mutations
- progression on ARSIs
- estimated n=340

**PROfound**

- OLAPARIB 300 mg BD
- ENZA 160 mg QD or ABI 1000 mg QD

- pEP: rPFS
- selected sEP: ORR, TTPP, OS
- estimated study completion 2/2021
DNA repair defects: rucaparib

- NCT02975934
- phase 3
- open-label

**mCRPC**
- DNA-repair gene mutations
- progression on ARSIs
- estimated n=400

**TRITON3**

**RUCAPARIB**

**ENZA 160 mg QD or ABI 1000 mg QD or DOCETAXEL**

- pEP: rPFS
- selected sEP: ORR, TTPsaP, OS
- estimated study completion 4/2022
DNA repair defects: carboplatin

- phase 2 study
- n=160
- mCRPC
- primary EP: PFS

Figure 2. Median PFS. A, Overall population B, Men with or without AVPC-C.

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Event</th>
<th>Median PFS (95%CI)(Months)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>CAB</td>
<td>79</td>
<td>74</td>
<td>4.59 (3.51, 5.81)</td>
<td>0.004</td>
</tr>
<tr>
<td>CAB/CARB</td>
<td>81</td>
<td>74</td>
<td>7.4 (5.57, 8.28)</td>
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</tr>
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Aparicio et al, J Clin Oncol suppl, 2017
DNA repair defects: carboplatin

- NCT02985021
- phase 2
- open-label

- **mCRPC**
  - DNA-repair gene mutations
  - prior treatment with ARSIs or Doc
  - estimated n=35

- DOC 60 mg/qm + CARBO AUC5

- pEP: PSA$_{50}$ response
- selected sEP: response, TTP
- estimated study completion 12/2022
Targeting small molecules: akt

- proliferation
- differentiation

- cell growth
- proliferation
- survival

- cross-talk

- tyrosine kinase receptor
- PI3K
- mTOR
Targeting small molecules: akt

- NCT03072238
- phase 3
- double blind

- **mCRPC**
  - progression on ARSIs
  - estimated n=850

**IPATential 150**

- IPATASERTIB 400 mg QD + ABI 1000 mg QD
- PB+ ABI 1000 mg QD

- pEP: rPFS
- selected sEP: ORR, TTPP, OS
- estimated study completion 8/2023
SUCCESS

Stay tuned!
תודה על תשומת הלב