The many faces of advanced stage prostate cancer

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Dresden University of Technology
Epidemiology
Prostate cancer incidence and mortality worldwide

Australia/NZ
Western Europe

Incidence
Mortality

per 100.000 (age standardized)

Jemal et al., CA Cancer J Clin 2011
Male life expectancy, example: Germany

- 1991: 70
- 2006: 76
- 2007: 77

www.gbe-bund.de
### Proportion diagnosed with prostate cancer by age range in the US

<table>
<thead>
<tr>
<th>Age [years]</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>35–44</td>
<td>0.6 %</td>
</tr>
<tr>
<td>45–54</td>
<td>9.1 %</td>
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<tr>
<td>55–64</td>
<td>30.7 %</td>
</tr>
<tr>
<td>65–74</td>
<td>35.3 %</td>
</tr>
<tr>
<td>75–84</td>
<td>19.9 %</td>
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<tr>
<td>85+</td>
<td>4.4 %</td>
</tr>
</tbody>
</table>

Brawley et al., World J Urol 2012
Castration resistant prostate cancer: epidemiology

63,440 new CaP cases/year in Germany

10-20% become castration resistant*

ca. 6-12,000 new CRPC cases/year in Germany (12,134 deaths)

*Krebs in Deutschland 2012: www.rki.de
*Kirby et al., Int J Clin Pract 2011
Local treatment for advanced disease?
66 years, 8/8 coed Gleason score 8, PSA 221 ng/ml, cT2-3, bone scan negative.

SV invasion

Median lobe

peritoneal surface

pT3b, pN1 (7/21), L1, V0, Pn1, R1
Local therapy for advanced prostate cancer?
Metaanalysis: early vs. deferred hormonal therapy plus RT/RPE

### Overall survival

| Study     | Events / Patients | Statistics (O–E) | Var. | HR & CI (Immediate) | HR & CI (Deferred) | | 1–HR | % ± SD |
|-----------|-------------------|------------------|------|---------------------|-------------------|---|-----------------|
| VACURG—I M0 | 217 / 266          | 228 / 261        | −7.6 | 111.3               |                   |   | 0.25            |
| VACURG—I M1 | 196 / 203          | 210 / 223        | 2.5  | 101.5               |                   |   | 0.50            |
| MRC PR03   | 434 / 469          | 498 / 468        | −24.9| 218                 |                   |   | 1.00            |
| EORTC 30846| 96 / 119           | 97 / 115         | −9.6 | 47.9                |                   |   | 2.00            |
| EORTC 30891| 257 / 492          | 284 / 493        | −29.5| 134.1               |                   |   | 4.00            |
| SAKK       | 87 / 96            | 85 / 92          | −0.4 | 41.9                |                   |   |                 |
| **Total**  | **1287 / 1645**    | **1342 / 1652**  | **−69.5** | **654.7**          |                   |   | **10% ± 4 reduction** |

Test for heterogeneity
Chi—square = 4.46, df = 5; p > 0.1

*95% CI everywhere

Verhagen et al., Eur Urol 2010
High-risk CaP: survival, competing risk analysis
(SEER, n = 404 604, T2c or Gleason score 8–10)

Abdollah et al., Eur Urol 2010
**pN+: High survival rates after RPE**

Risk factors: Gleason score 8+, 3+ positive nodes, age 70+ (n=193)

Froehner, Wirth et al., Urol Int 2012
Positive lymph nodes: role of adjuvant hormonal therapy (n=122)

- 1-2 LK+ (Dresden, n=148)
- 3 LK+ (Dresden, n=45)

Schumacher, Studer et al., Eur Urol 2008 versus Froehner, Wirth et al., Urol Int 2012
## Adjuvant radiotherapy after RPE: S3-guideline 2011

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation for adjuvant RTX</th>
</tr>
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<tbody>
<tr>
<td>pT2R1</td>
<td>option</td>
</tr>
<tr>
<td>pT3R0 with risk factors (SV+...)</td>
<td>option</td>
</tr>
<tr>
<td>pT3R1</td>
<td>standard</td>
</tr>
</tbody>
</table>

*alternative option in all category: percutaneous RTX for PSA-rise from defined zero value*

*confirmed PSA > 0,2 ng/ml

Wirth et al.: Interdisciplinary S3 guideline on diagnostics and treatment of prostate cancer  
http://www.aezq.de/edocs/pdf/info/s3-leitlinie-prostatakarzinom
Castration resistant prostate cancer
Castration resistant CaP - definition

- Castrate level testosterone (<1.7 nmol/L*)
- 3 consecutive PSA rises, 1 week apart, resulting in two 50% increases over the nadir, PSA >2 ng/mL
- Antiandrogen withdrawal for ≥4 wk (flutamide) and for ≥6 wk (bicalutamide)
- PSA progression despite consecutive hormonal manipulations

*Normal: 6.25 - 26.28

EAU-Guideline 2013
Cabazitaxel vs. mitoxantrone second line for HRPCA

(n=755)

De Bono et al., Lancet 2010
Abiraterone after docetaxel failure (n=1195)

Median survival 14.8 vs. 10.9 months; HR 0.65; 95% CI: 0.54-0.77; p<0.001
Enzalutamide after docetaxel failure
Overall survival 18.4 vs. 13.6 months

Scher et al., NEJM 2012
Abiraterone before chemotherapy
radiological progression free survival

Ryan et al., NEJM 2012

Progression free (%)

Time to progression or death (months)

AA + P (median, Monate): NR
Placebo + P (median, Monate): 8,3
HR (95% CI): 0,43 (0,35-0,52)
p-Wert: < 0,0001
Abiraterone before chemotherapy

Overall survival

AA + P (median, Monate): NR
Placebo + P (median, Monate): 27,2
HR (95% CI): 0,75 (0,61-0,93)
p-Wert: 0,01

Ryan et al., NEJM 2012
Sipuleucel-T (Provenge®) in CRPC (n=512)

Costs: $93,000/Zyklus

4.1 months

Kantoff et al., NEJM 2010
Treatment of bone metastases

Denosumab added as an additional option.
Denosumab vs. zoledronate to prevent skeleton related events in CRPC (n=1904)

Fizazi et al., Lancet 2011
Denosumab vs. zoledronate in CRPC: survival (n=1904)

Median months (95% CI):
- Denosumab: 19.4 (18.1–21.7)
- Zoledronic acid: 19.8 (18.1–20.9)

HR 1.03 (95% CI 0.91–1.17; p=0.65)
Denosumab vs. placebo to prevent bone metastases in CRPC (n=1432)

Symptomatic bone mets.

HR 0.67 (95% CI 0.49–0.92), p=0.01

Overall survival

HR 1.01 (95% CI 0.85–1.20), p=0.91

Smith et al., Lancet 2012
FDA panel votes against Amgen's Xgeva for prostate cancer

February 8, 2012 | 2:36 p.m.

Washington— A panel of cancer experts voted against a new use for Amgen Inc.’s Xgeva in prostate cancer on Wednesday, saying the drug’s ability to slow the spread of the disease did not translate into meaningful benefits for patients.

The Food and Drug Administration's cancer drug panel voted 12 to 1 that the benefits of the drug did not outweigh its risks, which included bone disease in about 6% of patients. The FDA is not required to follow the group’s advice, although it often does.
Sipuleucel-T (Provenge®) for CRPC (n=512)

Costs: $93,000/cycle

4.1 months

Kantoff et al., NEJM 2010
Radium-223 (Alpharadin)

ALSYMPCA trial: design

921 men with CRPC & bone metastases (≥ 2 hot spots)
No known visceral mets.
Post-docetaxel or “unfit”
Randomised: 2:1

Alpharadin 50 kBq/kg bw
6 IV doses
Best supportive care

Placebo 6 IV doses
Best supportive care

Primary endpoint:
• OS

Secondary endpoints:
• TTPP
• TTP in total-ALP
• Safety
• HRQoL

Stratifications:
Total ALP: < 220 U/L vs. ≥ 220 U/L
Bisphosphonate use: Yes vs. No
Prior docetaxel: Yes vs. No

Radium-223 (Alpharadin) vs. placebo for symptomatic bone metastases

ALSYMPCA trial, overall survival (n=921)

A Overall Survival

Hazard ratio, 0.70 (95% CI, 0.58–0.83)
P<0.001

Radium-223 (median overall survival, 14.9 mo)
Placebo (median overall survival, 11.3 mo)

No. at Risk
Radium-223 614 578 504 369 274 178 105 60 41 18 7 1 0 0 0
Placebo 307 288 228 157 103 67 39 24 14 7 4 2 1 0 0

Parker et al., NEJM 2013
62 years, 08/2006 PCA metastatic to bone, PSA 422 ng/ml, metastasis left hip

- Start hormonal therapy

- PSA NADIR 31 ng/ml

- from 08/2007 Docetaxel Chemotherapy, 10 cycles until 03/2008

- PSA 01/2008: 11.9 ng/ml

- 02/2010: PSA 63, Start clinical study with antibody against Integrines
62 years, 08/2006 PCA metastatic to bone, PSA 422 ng/ml, metastasis left hip

- Study until 11/2010
- consecutive PSA-rise until 282 ng/ml
- no progressive pain, no progressive bone metastasis
- from 01/2011 again therapy with docetaxel
- 9 cycles: PSA 06/2011 83.7 ng/ml
- Stop Chemo, PSA 09/2011, 40 ng/ml (NADIR)
62 years, 08/2006 PCA metastatic to bone, PSA 422 ng/ml, metastasis left hip

- from 01/2012 Abiraterone with PSA 90 ng/ml
- 04/2012 PSA 171 ng/ml, from 04/2012 Cabazitaxel
- 10 cycles Cabazitaxel until 10/2012
- PSA 11/2012: 19 ng/ml (Nadir)
- PSA 04/2013 127 ng/ml
- Bone scan: progressive bone metastases
- Start Enzalutamide 03/2014
Future developments: new drugs
Testosterone metabolism, androgen receptor signalling and interaction of MDV3100

Androgen receptor

Intranuclear translocation

DNA binding of AR complex

Recruiting of activating co-proteins

Androgen receptor

Cholesterol

DHT

HSP

5α-Reduktase

TOK-001

Abirateron
Ketokonazol
TAK-700
TOK-001

Hoden

NNR

MDV3100

© Dr. M. Sergon, UKD

Tran et al., Science 2009

Ohlmann et al., Urologe 2011
Future developments: earlier treatment
Castration Resistant Prostate Cancer (CRPC): progression while on androgen deprivation therapy

Non-metastatic CRPC

Metastatic, hormone-naïve

Metastatic CRPC

Pre-doc

With doc

Post-doc

Abiraterone MDV3100 TAK-700

Zoledronic acid

Docetaxel

Abiraterone MDV3100 TAK-700

Abiraterone Cabazitaxel

© 2011 American Association for Cancer Research

Massard and Fizazi, Clin Cancer Res 2011
Androgen signalling blockade
Androgen synthesis blockade

CRPC

Zoledronate
Denosumab
Sipuleucel-T, Ipilimumab ...
Radium-223

Docetaxel
Cabazitaxel
Patient history

- 42 y, academic
- 2/10 Zyl. Gleason 3+4=7, cT1c, PSA 7.9 ng/ml
- Reference pathologist: Gleason 3+5=8
- No comorbidity
CT: normal
Options

- a) Nerve-sparing RPE
- b) EBRTX
- c) Brachytherapy
- d) Active Surveillance
<table>
<thead>
<tr>
<th>Current Model</th>
<th>Historical Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extent of Disease Probability</strong></td>
<td><strong>Extent of Disease Probability</strong></td>
</tr>
<tr>
<td>Indolent Cancer</td>
<td>Indolent Cancer</td>
</tr>
<tr>
<td>Organ Confined Disease</td>
<td>Organ Confined Disease</td>
</tr>
<tr>
<td>Extracapsular Extension</td>
<td>Extracapsular Extension</td>
</tr>
<tr>
<td>Seminal Vesicle Invasion</td>
<td>Seminal Vesicle Invasion</td>
</tr>
<tr>
<td>Lymph Node Involvement</td>
<td>Lymph Node Involvement</td>
</tr>
<tr>
<td><strong>Primary Treatment Outcome</strong></td>
<td><strong>Primary Treatment Outcome</strong></td>
</tr>
<tr>
<td>Progression Free Probability after</td>
<td>Progression Free Probability after</td>
</tr>
<tr>
<td>Radical Prostatectomy</td>
<td>Radical Prostatectomy</td>
</tr>
<tr>
<td>5 Year</td>
<td>5 Year</td>
</tr>
<tr>
<td>92%</td>
<td>80%</td>
</tr>
<tr>
<td>10 Year</td>
<td>10 Year</td>
</tr>
<tr>
<td>88%</td>
<td>N/A</td>
</tr>
<tr>
<td>Probability of Cancer-Specific Survival</td>
<td>Probability of Cancer-Specific Survival</td>
</tr>
<tr>
<td>10 Year</td>
<td>10 Year</td>
</tr>
<tr>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>15 Year</td>
<td>15 Year</td>
</tr>
<tr>
<td>99%</td>
<td>99%</td>
</tr>
</tbody>
</table>
Therapieempfehlung

Julius Hackethal
Keine Angst vor Krebs
1 year later

- 3/12 Zyl. Gleason 3+4=7, cT1c,
- PSA 12.3 ng/ml
### Current Model

<table>
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<tr>
<td>Indolent Cancer</td>
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</table>

<table>
<thead>
<tr>
<th>Primary Treatment Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression Free Probability after Radical Prostatectomy</td>
</tr>
<tr>
<td>5 Year</td>
</tr>
<tr>
<td>10 Year</td>
</tr>
<tr>
<td>Probability of Cancer-Specific Survival</td>
</tr>
<tr>
<td>10 Year</td>
</tr>
<tr>
<td>15 Year</td>
</tr>
</tbody>
</table>

### Historical Model

<table>
<thead>
<tr>
<th>Extent of Disease Probability</th>
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<tbody>
<tr>
<td>Indolent Cancer</td>
</tr>
<tr>
<td>Organ Confined Disease</td>
</tr>
<tr>
<td>Extracapsular Extension</td>
</tr>
<tr>
<td>Seminal Vesicle Invasion</td>
</tr>
<tr>
<td>Lymph Node Involvement</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Treatment Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression Free Probability after Radical Prostatectomy</td>
</tr>
<tr>
<td>5 Year</td>
</tr>
<tr>
<td>10 Year</td>
</tr>
</tbody>
</table>
Radium 223 case studies part 4: combination therapy

Manfred Wirth

University Hospital Carl Gustav Carus Dresden and Technical University of Dresden, Dresden, Germany
Case

- 78 year old male
- Diagnosis of PCA metastatic to bone 06/2011
- Gleason score 4+5=9
- Since 06/2011 complete androgen blockade with Busereline and Bicalutamide
- Since 08/2011 Zoledronic acid 4 weekly
- After progression to castrate resistance 4 cycles of Docetaxel 1012/2012
- Since 01/2013 Abiraterone 1000 mg daily
- 10/2013 stop Bicalutamide
Overall PSA - Kinetics

Start Abiraterone
Case – PSA during Ra-223

- PSA after start of Ra-223 parallel to Abiraterone:
Case II – Ra-223 and Abiraterone

- No significant AE‘s
- No progressive pain
- No opioid medication

- No liver toxicity, no bone marrow toxicity

- Conclusion: In this case no AE‘s with both medications
- Therapy oncologically effective regarding PSA response and Performance status
Radium 223 case studies part 4: combination therapy

Manfred Wirth

University Hospital Carl Gustav Carus Dresden and Technical University of Dresden, Dresden, Germany
Case

• 65 year old male at diagnosis
• 11/2011: PSA 65 ng/ml, Gleason 5+5=10
• Androgen deprivation therapy
  – 05/2012: PSA Nadir 0.34 ng/ml
• CRPC
  – 09/2012: PSA 20.5 ng/ml
  – Na-F-PET 10/2012: multiple bone metastases
• Initiation of Docetaxel 12 cycles until 05/2013
  – PSA Nadir 1.6 ng/ml
  – PSA 05/2013: 14.9 ng/ml
Case

- Docetaxel-therapy and further course:
  - 07/2013: PSA 34.5 ng/ml
  - Pain lumbar spine
  - Planning of Ra-223
  - First dose 30/09/2013
## Case – PSA, Medication and LFT

<table>
<thead>
<tr>
<th>Date</th>
<th>PSA (ng/ml)</th>
<th>Ra 223</th>
<th>Abiraterone (mg/24h)</th>
<th>ASAT (µmol/s*l)</th>
<th>ALAT (µmol/s*l)</th>
</tr>
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<tbody>
<tr>
<td>30/09/2013</td>
<td>83.02</td>
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<td>-</td>
<td>0.43</td>
<td>0.35</td>
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<tr>
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<td>196.84</td>
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<td>0.46</td>
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<td>27/11/2013</td>
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<td>0.45</td>
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<td>30/12/2013</td>
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<td>29/01/2014</td>
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<td>0.88</td>
<td>0.35</td>
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<tr>
<td>27/02/2014</td>
<td>3443.16</td>
<td>-</td>
<td>1000</td>
<td>0.37</td>
<td>0.5</td>
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# Adverse events

<table>
<thead>
<tr>
<th>Cycle</th>
<th>AE 1 (Treatment)</th>
<th>AE 2 (Treatment)</th>
<th>AE 3 (Treatment)</th>
<th>AE 4 (Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Pain right hip (Metamizol, Tilidine)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Fatigue</td>
<td>Flu/ Cold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Fatigue</td>
<td>Pain/ cramps both thighs</td>
<td>Weight loss 4kg</td>
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</tbody>
</table>
Serious Adverse Events

- **30/01/2014 – 05/02/2014**
  - Fever
  - Exsiccosis
  - Hypokalemia
  - Anemia – Transfusion, 2 Units of Packed red blood cells

- **17/02/2014 – 22/02/2014**
  - Fever
  - Exsiccosis
  - Borderline Hypokalemia
## Case – PSA, Medication, Hb and Potassium

<table>
<thead>
<tr>
<th>Date</th>
<th>PSA (ng/ml)</th>
<th>Ra 223</th>
<th>Abiraterone (mg/24h)</th>
<th>Hb (mmol/l)</th>
<th>Potassium (mmol/l)</th>
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</thead>
<tbody>
<tr>
<td>30/09/2013</td>
<td>83.02</td>
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<td>-</td>
<td>7.5</td>
<td>4.05</td>
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<td>1000</td>
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<td>4.5</td>
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<td>7.0</td>
<td>4.8</td>
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<td>1000</td>
<td>6.1</td>
<td>4.5</td>
</tr>
<tr>
<td>30/01/2014</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SAE)</td>
<td></td>
<td></td>
<td>1000</td>
<td>4.9</td>
<td>2.92</td>
</tr>
<tr>
<td>17/02/2014</td>
<td>2539.33</td>
<td>-</td>
<td>1000</td>
<td>6.5</td>
<td>3.51</td>
</tr>
<tr>
<td>(SAE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27/02/2014</td>
<td>3443.16</td>
<td>-</td>
<td>1000</td>
<td>6.0</td>
<td>3.51</td>
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## Phase 3 ALSYMPCA: adverse events

<table>
<thead>
<tr>
<th></th>
<th>All grades</th>
<th>Grades 3 or 4</th>
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<tbody>
<tr>
<td></td>
<td>Radium 223 (n=600)</td>
<td>Placebo (n=301)</td>
</tr>
<tr>
<td><strong>Haematological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>187 (31)</td>
<td>92 (31)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30 (5)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69 (12)</td>
<td>17 (6)</td>
</tr>
<tr>
<td><strong>Non-haematological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>300 (50)</td>
<td>187 (62)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>151 (25)</td>
<td>45 (15)</td>
</tr>
<tr>
<td>Nausea</td>
<td>213 (36)</td>
<td>104 (35)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>111 (18)</td>
<td>41 (14)</td>
</tr>
<tr>
<td>Constipation</td>
<td>108 (18)</td>
<td>64 (21)</td>
</tr>
</tbody>
</table>

Data are n (%)  
Summary

• Combination therapy feasible
• No additional significant adverse events than expected
• Liver function stable
• Notable: Serious adverse events
  – Hypokalemia: probably related to Abiraterone, could have been aggravated by Ra 223 though no typical side effects of Ra 223
  – Anemia: caused by progressive tumor in bone, but possibly related to Ra 223
• Oncologic efficacy of combination Ra 223 with abiraterone in this case not convincing
  – PSA rise
  – Deterioration of clinical state
• More data needed, observational studies?
Thank you for your attention!

www.uniklinikum-dresden.de