Androgen Deprivation Therapy (ADT) and other hormonal treatments

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- **Institutional financial interests:** AAA International; Active Biotech; Astellas; Bayer; Bristol-Myers Squibb; Clovis; CureVac; Ferring; Innocrin; Janssen; Menarini Silicon Biosystems; Orion; Roche; Sanofi; Tolero Pharmaceuticals

- **Non-financial interests:** Amgen; Aranda; Astellas; Bayer; ESSA; Janssen; Menarini Silicon Biosystems; Nectar; ProteoMediX; Sanofi

- Co-inventor on patent application (WO 2009138392 A1) for a method for biomarker discovery (granted in China, Europe, Japan and the US)

- Deputy of the ESMO guidelines committee for GU cancers, member of the EAU guideline panel for prostate cancer, past chair of the EORTC GU group; Member of the STAMPEDE trial management group
Development of castration-resistance

Upon initiation of ADT
- Testosterone reduced to very low levels in blood (<1.7nmol/l)
- PSA decline
- Some cancer cells die, others “hibernate”
Castration-resistance

Mechanisms of resistance to ADT
- Adrenal androgens
- Paracrine/Intracrine androgen production
- AR amplification
- AR mutations

• ADT is continued to keep testicular testosterone suppressed
Definition of Castration-Resistance

Progression of disease by PSA or radiographic progression despite ADT with adequately suppressed testosterone (< 50ng/dl or 1.7nmol/l)

• Consecutive rises: Rising PSA has to be confirmed!

• Testosterone level needs to be measured

• Perform Imaging
Prostate Cancer: Castration resistant (CRPC)

Localised Prostate Cancer

Advanced Prostate Cancer: Castration-sensitive/naive

Advanced Prostate Cancer: Castration-resistant

M0: By imaging no evidence of metastases
M1: Metastases detected by imaging

Local Therapy (RT/OP) or Active Surveillance

Salvage Therapy

PSA Rise

De Novo M1

ADT

M0

ADT + Docetaxel

M1

ADT + Abiraterone

ADT + Radiotherapy to the primary

ADT +/- AR-antagonist

1st-line

2nd-line

3rd-line

mCRPC treatments with OS benefit:
- Abiraterone
- Cabazitaxel
- Docetaxel
- Enzalutamide
- Radium-223
- Sipuleucel-T

ADT: Androgen Deprivation Therapy
M0: By imaging no evidence of metastases
M1: Metastases detected by imaging
Approved systemic therapies for mCRPC

1. Docetaxel + P* vs Mitoxantrone + P*
   NEJM 2004
   19.2 vs 16.3m**

2. Cabazitaxel + P* vs Mitoxantrone + P*
   LANCET 2010
   **15.1 vs 12.7

1. Enzalutamide vs Placebo
   NEJM 2014
   **32.4 vs 30.2

1. Abiraterone + P* vs Placebo + P*
   NEJM 2013
   **34.7 vs 30.3

2. Abiraterone + P* vs Placebo + P*
   NEJM 2011
   **15.8 vs 11.2

2. Enzalutamide vs Placebo
   NEJM 2012
   **18.4 vs 13.6

Radium-223 vs Best standard of care
   NEJM 2013
   **14.9 vs 11.3

1. or 2.

***Zoledronate vs Placebo*** JNCI 2004; 16 vs 10.5m

***Denosumab vs Zoledronate*** LANCET 2011; 20.7 vs 17.1m

***Time to first skeletal event***
Several agents approved for mCRPC, but optimal sequence is unclear

- None of these mCRPC trials compared the new agent with current «standard» therapy
- None of the trials has included patients with ADT plus docetaxel or plus abiraterone in the castration-sensitive setting
First Line Therapy mCRPC

Options of Standard of Care (according to Phase III trials)

Abiraterone/Prednisone (COU-302): Asymptomatic, mildly symptomatic; no visceral metastases

Docetaxel/Prednison (TAX-327)

Enzalutamide (PREVAIL): Asymptomatic, mildly symptomatic

Radium-223 (ALSYMPCA): Symptomatic, no lymph node bulk, no visceral metastases
Sequencing: Factors to help treatment decisions

• Patient history (symptomatic versus non-symptomatic), co-medication, co-morbidities, clinical exam

• What treatment in castration-sensitive setting (ADT alone or ADT plus), duration of response to this therapy

• Staging
  • Blood counts, renal and liver function, ALP, LDH...
  • PSA value, PSA-DT
  • Imaging: CT Chest and Abdomen, Bone scan, MRI long spine

• Patient preference!
What is your preferred first line option in a fit, asymptomatic patient with mCRPC who is progressing after ADT alone?

1. Abiraterone Acetate/Pred
2. Enzalutamide
3. Docetaxel
4. Radium-223
5. Other
What is your preferred first line option in a symptomatic patient with mCRPC who is progressing after ADT alone?

1. Abiraterone Acetate/Pred
2. Enzalutamide
3. Docetaxel
4. Radium-223
5. Other
First-line mCRPC Therapy after ADT alone

- Docetaxel
- Abiraterone
- Enzalutamide
- Radium-223

Trials

Table 6 – Sequencing of metastatic castration-resistant prostate cancer (mCRPC) first-line options

<table>
<thead>
<tr>
<th>What is your preferred first-line mCRPC treatment option:</th>
<th>Abiraterone or enzalutamide (%)</th>
<th>Cabazitaxel (%)</th>
<th>Docetaxel (%)</th>
<th>Platinum-based chemotherapy (%)</th>
<th>Radium-223 (%)</th>
<th>Sipuleucel-T (%)</th>
<th>No preferred option (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the majority of asymptomatic men who did not receive docetaxel in the castration-naive setting?</td>
<td>86</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>In the majority of symptomatic men who did not receive docetaxel in the castration-naive setting?</td>
<td>52</td>
<td>0</td>
<td>46</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Gillessen S et al, Eur Urol 2017
First-line mCRPC Therapy after ADT plus docetaxel

ADT + Docetaxel

Docetaxel
Cabazitaxel
Abiraterone
Enzalutamide
Radium-223

Trials

Tumor - Volume (PSA)

Table 6 - Sequencing of metastatic castration-resistant prostate cancer (mCRPC) first-line options

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<th>No preferred option (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the majority of asymptomatic men who did receive docetaxel in the castration-naive setting?</td>
<td>90</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>In the majority of symptomatic men who did receive docetaxel in the castration-naive setting?</td>
<td>73</td>
<td>19</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Gillessen S et al, Eur Urol 2017
First-line mCRPC after ADT + Docetaxel

245 patients from GETUG-15 (Upfront ADT vs ADT + 9x Docetaxel)
Retrospective analysis

<table>
<thead>
<tr>
<th>Docetaxel for</th>
<th>PSA Decline ≥ 50%</th>
<th>ADT alone (n=80)</th>
<th>ADT plus Docetaxel (n=29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPC</td>
<td></td>
<td>38%</td>
<td>20%</td>
<td>0.14</td>
</tr>
<tr>
<td>CRPC</td>
<td>Biochem. PFS</td>
<td>6m</td>
<td>4.1m</td>
<td></td>
</tr>
</tbody>
</table>

Lavaud et al, Eur Urol 2018
First-line mCRPC after ADT + Abiraterone/P (or Enza/Apa)

No prospective data about activity of the substances after ADT plus Abiraterone/P or novel AR antagonist

- Activity of enzalutamide after abiraterone (and vice versa) likely to be low

- In case of oligoprogression on ADT plus Abiraterone → Local Therapy?

<table>
<thead>
<tr>
<th>LATITUDE: FU 30.4m</th>
<th>ADT + Abi</th>
<th>ADT + Placebo</th>
<th>STAMPEDE: FU 40m</th>
<th>ADT</th>
<th>ADT + Abi</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel</strong></td>
<td><strong>106 (34)</strong></td>
<td>187 (40)</td>
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<td>200 (37%)</td>
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<td>Enzalutamide</td>
<td>30 (10)</td>
<td>76 (16)</td>
<td>Enzalutamide</td>
<td>138 (26%)</td>
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<td>AA-P</td>
<td>10 (3)</td>
<td>53 (11)</td>
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<td>120 (22%)</td>
<td>8 (3%)</td>
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<tr>
<td>Cabazitaxel</td>
<td>11 (4)</td>
<td>30 (6)</td>
<td>Radium-223</td>
<td>24 (5%)</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>Radium-223</td>
<td>11 (4)</td>
<td>27 (6)</td>
<td>Cabazitaxel</td>
<td>28 (5%)</td>
<td>15 (6%)</td>
</tr>
</tbody>
</table>

Fizazi K et al, NEJM 2017  James N et al, NEJM 2017
Second Line mCRPC after Docetaxel

Options of Standard of Care (according to Phase III trials)

Abiraterone/Prednisone (COU-301)

Cabazitaxel/Prednison (TROPIC and PROSELICA)

Enzalutamide (AFFIRM)

Radium-223 (ALSYMPCA): Symptomatic, no lymph node bulk, no visceral metastases
Second Line mCRPC after Enzalutamide or Abiraterone/P

More frequent situation, but no large prospective, randomised Phase III trials published yet!
Abiraterone/P after Enzalutamide

PLATO Trial (n= 509)

Enzalutamide

PSA Progression after initial response

Enzalutamide + Abiraterone/P
PSA Response
0.8%

Abiraterone/P + Placebo
PSA Response
2.5%

• Prospective data in selected Patients (PSA responders to Enzalutamide)

• Confirms retrospective data that showed only minimal activity of Abiraterone/P after Enzalutamide

Attard G et al ASCO 2017; Attard G et al J Clin Oncol 2018
Enzalutamide after Abiraterone/P

Multicentre, single-arm, open-label study
214 men with mCRPC and PD after ≥24 wk Abiraterone
- 145 chemotherapy-naïve
- 69 post chemotherapy

Median duration of therapy with Enza 5.7m
Median rPFS 8.1m
mOS not reached
PSA Decline ≥50%: 27% (48 of 181)
- pre-chemo: 28%
- post-chemo: 26%

De Bono et al, Eur Urol 2017
Docetaxel after Abiraterone in COU-302

N=100
PSA response rate: 40%

De Bono et al, Eur Urol 2016
3rd line: CARD trial

Eligibility criteria: PD ≤ 12 months on prior alternative ART

1. Enzalutamide OR Abiraterone + P

2. Docetaxel + P ≥ 3 cycles

3. Cabazitaxel (25 mg/m² Q3W) + Prednisone + G-CSF

De Wit et al, NEJM 2019
Efficacy

Radiographic FS (Primary Endpoint)

Median radiographic PFS, months (95% CI)

- Cabazitaxel: 8.0 (5.7 – 9.2)
- ART: 3.7 (2.8 – 5.1)

HR: 0.54 (0.40 – 0.73)

p < 0.001

Kaplan-Meier estimate

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Cabazitaxel</th>
<th>ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>129</td>
<td>126</td>
</tr>
<tr>
<td>3</td>
<td>91</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>41</td>
<td>22</td>
</tr>
<tr>
<td>12</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>24</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

De Wit R et al LBA13 ESMO 2019; De Wit et al NEJM 2019
Efficacy

PSA, Tumor and Pain responses

Confirmed PSA response

- **Cabazitaxel (N = 115)**: 35.7% (n = 41)
- **ART (N = 111)**: 13.5% (n = 15)

Objective tumor response

- **Cabazitaxel (N = 63)**: 36.5% (n = 23)
- **ART (N = 52)**: 11.5% (n = 6)

Pain response

- **Cabazitaxel (N = 111)**: 45.0% (n = 50)
- **ART (N = 109)**: 19.3% (n = 21)

Response definitions:

- **PSA**: PSA reduction $\geq 50\%$ from baseline, confirmed by a second value at least three weeks later.
- **Tumor**: Complete or partial responses according to RECIST 1.1 criteria.
- **Pain**: Decrease $\geq 30\%$ from baseline in average BPI-SF pain intensity score at 2 consecutive evaluations $\geq 3$ weeks apart without increase in analgesic usage score.

N, patients evaluable for PSA, tumor or pain response.

De Wit R et al LBA13 ESMO 2019
Combination Therapies in mCRPC

All combinations with docetaxel failed in Phase III trials:

- Oblimersen
- DN-101
- Bevacizumab
- VEGF-Trap
- Lenalidomide
- Atrasentan
- Zibotentan
- GVAX
- Dasatinib
- Custirsen
Combination Therapies in mCRPC

Radium-223 plus Abiraterone/P versus Abiraterone/P alone: Failed (more fractures, more deaths)

Abiraterone/P plus Enzalutamide vs Enza: No significant difference in OS

*Smith M et al Lancet Oncol 2019*

*Morris M et al ASCO 2019*
Several survival prolonging treatment options, “optimal” sequence unclear
• Situation more complex with advent of combination therapies for mCSPC
• Most experts are using Abi/P or Enza as first-line for men with mCRPC
• Do not rely on PSA alone for treatment decisions in men with mCRPC: Imaging!
• Do not change treatment because of early “increase” in bone lesions alone
• Majority of patients who are fit for chemotherapy should be offered docetaxel and also one of the novel endocrine agents at some stage of their disease
• Third line treatment in patients who received docetaxel plus and also a novel endocrine agent (PD within 1 year) and who are fit: Cabazitaxel!
Take home messages for mCRPC II

- Abi/P after Enza low activity, Enza after Abi/P modest activity in selected pts
- Combination therapies not successful until now for mCRPC
- We need more validated predictive markers
  - DNA repair defects in mCRPC offer an opportunity for treatment selection!
  - Tracking AR aberrations (and loss of RB1, p53 and PTEN?) could improve selection of patients for AR targeting
- New options on the horizon: Next talk!
Thank you very much for your attention!
Direct comparison: FIRSTANA

A

Overall Survival (%)

C20 v D75
HR 1.01 (0.85 to 1.20)
Log-rank $P = .997$

C25 v D75
HR 0.97 (0.82 to 1.16)
Log-rank $P = .757$

Time (months)

B

Progression-Free Survival (%)

C20 v D75
HR 1.06 (0.91 to 1.24)
Log-rank $P = .422$

C25 v D75
HR 0.99 (0.85 to 1.15)
Log-rank $P = .804$

Time (months)

No. at Risk

C20
389 356 319 296 234 192 133 49 19 3 0
C25
388 345 325 296 239 197 138 70 28 5 0
D75
391 366 336 307 243 192 133 57 18 3 0

No. at Risk

C20
389 145 83 39 15 6 2 0
C25
388 149 94 48 19 5 1 0
D75
391 152 83 37 16 8 3 0

Oudard S et al, J Clin Oncol 2017
Save the date
Advanced Prostate Cancer Consensus Conference
(APCCC 2019)
Basel 29-31 August 2019
Combination Therapies in mCRPC

Radium-223 plus Abiraterone/P versus Abiraterone/P alone: Failed (more fractures, more deaths)

Abiraterone added to Enzalutamide not effective:

Attard G et al J Clin Oncol 2018
In daily practice:

- Staging: Always before start of a new therapy
- Monitoring: Risk-adapted

Scher et al, J Clin Oncol 2016
First-line mCRPC after ADT + Docetaxel

What to do if rapid progression after ADT plus docetaxel?

Table 6 - Sequencing of metastatic castration-resistant prostate cancer (mCRPC) first-line options

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</thead>
<tbody>
<tr>
<td>In the majority of asymptomatic men who received chemo-hormonal therapy and who progressed within ≤6 mo after completion of docetaxel in the castration-naive setting?</td>
<td>77</td>
<td>17</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>In the majority of symptomatic men who received chemo-hormonal therapy and who progressed within ≤6 mo after completion of docetaxel in the castration-naive setting?</td>
<td>57</td>
<td>27</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Gillessen S et al, Eur Urol 2017
What is your preferred first line option in a fir, asymptomatic patient with mCRPC who is progressing after ADT plus Abiraterone?

1. Enzalutamide
2. Docetaxel
3. Radium-223
4. Other
### When to switch treatment: Defining Progression

#### Generally 2 out of 3 criteria should be fulfilled:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Cave!</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. PSA Progression</strong></td>
<td>• Easily done, but….</td>
</tr>
<tr>
<td></td>
<td>• Can rise in the first 9-12 weeks of a new treatment, PSA rise on Radium-223 very common</td>
</tr>
<tr>
<td></td>
<td>• Not reliable in very advanced disease</td>
</tr>
<tr>
<td></td>
<td>• PSA can be low in relation to tumour volume (aggressive variants!)</td>
</tr>
<tr>
<td><strong>2. Radiographic progression</strong></td>
<td>• 90% of patients with advanced prostate cancer have bone metastases</td>
</tr>
<tr>
<td></td>
<td>• Flare on bone scintigraphy very common</td>
</tr>
<tr>
<td></td>
<td>• Increasing sclerosis on CT scans often miss-interpreted as progression</td>
</tr>
<tr>
<td></td>
<td>• Epidural tumour difficult to appreciate on CT</td>
</tr>
<tr>
<td></td>
<td>• Malignant superscan not uncommon in advanced disease</td>
</tr>
<tr>
<td><strong>3. Clinical Progression</strong></td>
<td>• Bone pain in elderly patients with advanced prostate cancer can also have other causes (e.g. degenerative disease, osteoporosis…)</td>
</tr>
</tbody>
</table>

*Scher et al, J Clin Oncol 2016; Gillessen et al, Ann Oncol 2015*
Progression of disease in the presence of falling PSA

Log PSA decline on docetaxel-based chemotherapy (red arrows: CT scan timepoints)

<table>
<thead>
<tr>
<th></th>
<th>H&amp;E</th>
<th>AR IHC</th>
<th>PSA IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver metastasis</td>
<td>![H&amp;E Image]</td>
<td>![AR IHC Image]</td>
<td>![PSA IHC Image]</td>
</tr>
</tbody>
</table>

CT 23/07/2012

CT 09/10/2012

Pezaro et al, Eur Urol 2014
First-line mCRPC after ADT + Abiraterone/P

No prospective data about activity of the substances after ADT plus Abiraterone/P

• Activity of enzalutamide likely to be low

• In case of oligoprogression on ADT plus Abiraterone → Local Therapy?

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<tr>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STAMPEDE: FU 40m</th>
<th>ADT</th>
<th>ADT + Abi</th>
</tr>
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<tbody>
<tr>
<td>Docetaxel</td>
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Fizazi K et al, NEJM 2017

James N et al, NEJM 2017
Take home messages for mCRPC

• Several survival prolonging treatment options
• “Optimal” sequence of therapies unclear
• Situation more complex with the advent of combination therapies for mCSPC
• Most experts are using Abi/P or Enza as first-line for men with mCRPC
• Abiraterone after Enzalutamide low activity, Enzalutamide after Abiraterone modest activity in selected patients
Take home messages for mCRPC II

• Do not rely on PSA alone for treatment decisions in men with mCRPC
• Do not change treatment because of early “increase” in bone lesions alone
• In case of neurological symptoms: MRI long spine!
• Combination therapies not successful until now
• No validated predictive markers yet
• New options on the horizon: PARP inhibition, 177-Lu-PSMA therapy...
First-line mCRPC after ADT + Abiraterone/P

ADT + Abiraterone/P

Tumor - Volume (PSA)

Docetaxel
Cabazitaxel
Enzalutamide
Radium-223 Trials

?
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>C20 (n = 369)</th>
<th>All Grades</th>
<th>Grade ≥ 3</th>
<th>All Grades</th>
<th>Grade ≥ 3</th>
<th>All Grades</th>
<th>Grade ≥ 3</th>
<th>All Grades</th>
<th>Grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>364 (95.3)</td>
<td>152 (41.2)</td>
<td>376 (96.2)</td>
<td>235 (60.1)</td>
<td>376 (97.2)</td>
<td>178 (46.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>127 (34.4)</td>
<td>106 (28.7)</td>
<td>187 (47.8)</td>
<td>166 (42.5)</td>
<td>126 (32.6)</td>
<td>110 (28.4)</td>
<td></td>
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<td>Any TEAE leading to treatment discontinuation</td>
<td>90 (25.1)</td>
<td>47 (12.7)</td>
<td>124 (31.7)</td>
<td>79 (20.2)</td>
<td>131 (33.9)</td>
<td>59 (15.2)</td>
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<tr>
<td>Diarrhea</td>
<td>120 (32.5)</td>
<td>13 (3.5)</td>
<td>195 (49.9)</td>
<td>22 (5.6)</td>
<td>143 (37.0)</td>
<td>9 (2.3)</td>
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<td>Nausea</td>
<td>93 (25.2)</td>
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<td>126 (32.2)</td>
<td>4 (1.0)</td>
<td>88 (22.7)</td>
<td>3 (0.8)</td>
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<td>Fatigue</td>
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<td>126 (32.0)</td>
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<td>112 (28.9)</td>
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<td>Hematuria</td>
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<td>98 (25.1)</td>
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<td>1 (0.3)</td>
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<td>Asthenia</td>
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<td>90 (23.0)</td>
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<td>94 (24.3)</td>
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<td>Constipation</td>
<td>92 (24.9)</td>
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<td>79 (20.0)</td>
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<td>70 (18.1)</td>
<td>4 (1.0)</td>
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<tr>
<td>Vomiting</td>
<td>44 (11.9)</td>
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<td>77 (19.7)</td>
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<td>45 (11.6)</td>
<td>3 (0.8)</td>
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<td>Decreased appetite</td>
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<td>74 (19.1)</td>
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<td>Dysgeusia</td>
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<td>59 (15.1)</td>
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<td>70 (18.1)</td>
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<tr>
<td>Back pain</td>
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<td>55 (14.1)</td>
<td>5 (1.3)</td>
<td>52 (13.4)</td>
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<td>Alopecia</td>
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<td>51 (13.0)</td>
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<td>151 (39.0)</td>
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<tr>
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<td>9 (2.4)</td>
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<td>47 (12.0)</td>
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<td>32 (8.3)</td>
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<td>Arthralgia</td>
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<td>4 (1.0)</td>
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<td>Weight decreased</td>
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<td>19 (4.9)</td>
<td>1 (0.3)</td>
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<tr>
<td>Urinary tract infection</td>
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<td>37 (9.5)</td>
<td>8 (2.0)</td>
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<td>3 (0.8)</td>
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<tr>
<td>Neutropenia</td>
<td>14 (3.8)</td>
<td>8 (2.2)</td>
<td>35 (9.0)</td>
<td>29 (7.4)</td>
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<td>Dizziness</td>
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<td>25 (6.5)</td>
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<tr>
<td>Cough</td>
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<td>34 (8.7)</td>
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<td>38 (9.8)</td>
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<tr>
<td>Abdominal pain</td>
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<td>1 (0.3)</td>
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<tr>
<td>Dyspepsia</td>
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<td>1 (0.3)</td>
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<td>5 (1.3)</td>
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<td>1 (0.3)</td>
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<tr>
<td>Pyrexia</td>
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<td>Edema peripheral</td>
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<tr>
<td>Bone pain</td>
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<td>4 (1.0)</td>
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<td>6 (1.6)</td>
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<tr>
<td>Incorrect dose administered</td>
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<tr>
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<tr>
<td>Stomatitis</td>
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<tr>
<td>Neutropenic infection</td>
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<td>5 (1.4)</td>
<td>24 (6.1)</td>
<td>23 (5.9)</td>
<td>19 (4.9)</td>
<td>16 (4.1)</td>
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<td>Myalgia</td>
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<tr>
<td>Dysuria</td>
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<td>Insomnia</td>
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<td>Blood creatinine increased</td>
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<tr>
<td>Pain in extremity</td>
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<td>4 (1.0)</td>
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<td>Epistaxis</td>
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<td>15 (3.8)</td>
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<td>25 (6.5)</td>
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<td>Muscle spasms</td>
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<td>Hypertension</td>
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<td>Laceration increased</td>
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<td>Nail disorder</td>
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<td>35 (9.0)</td>
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