Optimizing survival in senior adults with prostate cancer
Disclosures

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Management of prostate cancer in senior adults: A call to action

Matti Aapro
Genolier, Switzerland
Disclosures

• Lecturer/Meeting Participant/Advisory Board Member
  – Sanofi
  – Janssen
  – Astellas
  – Bayer
  – Millennium
  – Takeda
Proportion of population aged 60 years or older in 2002

United Nations. Population Division
Department of Economic and Social Affairs Population Ageing 2002
Proportion of population aged 60 years or older in 2050

United Nations. Population Division
Department of Economic and Social Affairs. Population Ageing. 2050
Median life expectancy is increasing in older men (US 1950-2009)

Life expectancy in older men: a large variability reflecting health status variability

‘Fit’ 70-year old man = median life expectancy of 18 years

Walter LC et al. JAMA 2001;285:2750-6
Prostate cancer: key facts

• Most frequently diagnosed cancer in men in Europe and USA\textsuperscript{1-2}

• Third most common cause of death from cancer in men in European Union in 2008 (after lung and colorectal cancers)\textsuperscript{1}

• Second most common cause of death from cancer in men in USA and UK\textsuperscript{1-2}

Most PCa deaths occur in older men (SEER 2007-2011)

National Cancer Institute website (www.cancer.gov)
Older men have higher risk prostate cancer (SEER 1998-2007)

Skosyrev E et al. Cancer 2012;118:3062-70
Older men have a higher risk of dying due to PCa (SEER 1998-2007)

Death due to PCa

Cumulative incidence

Years from prostate cancer diagnosis

Skosyrev E et al. Cancer 2012;118:3062-70
High PCa mortality in older men with Gleason 8-10 managed conservatively*

*Observation or androgen deprivation therapy (immediate or deferred)

Albertsen P et al. JAMA 2005;291:2095-2101
A few older men with high risk localized PCa receive curative therapy (CaPSURE)

*CAPRA score: 0-2 (low), 3-5 (medium), 6-10 (high)

RP: radical prostatectomy; EBRT: external-beam radiation therapy; Brachy: brachytherapy
Age remains the major predictor of curative treatment non-receipt for localized prostate cancer: a population-based study

• Irish National Registry:
  – 5456 men with localized PCa from 2002 to 2008

• After adjustment (stage, Gleason, Charlson index, socio-demographic factors), age is the main reason of treatment non-receipt
  – Risk of NOT having curative therapy X 5 in men aged 70-79 vs 60–69 years (OR 5.5, 95% CI 4.7-6.9)

Camargo Cancela M et al. BJC 2013; 109, 272–279
A few older men receive chemotherapy

2677 deaths from PCa from the Prostate Cancer database and in-patient drug registry (SALT database) between 05/2009 & 12/2010


CRPC=castration-resistant prostate cancer; PCa=prostate cancer
A few older men receive chemotherapy

2677 deaths from PCa from the Prostate Cancer database and in-patient drug registry (SALT database) between 05/2009 & 12/2010


CRPC=castration-resistant prostate cancer; PCa=prostate cancer
PCa management in older men: need for an accurate risk assessment

Risk of death due to other cause: health status +++
- Comorbidities
- Dependence
- Nutritional status

Risk of death due to PCa: tumour aggressiveness
- Gleason score+++ 
- Serum PSA
- Tumour stage
A call to action

- Older men have more aggressive tumours
- Older men have a significant risk of dying of PCa
- Only a minority of older men with high risk localized disease receive curative therapy
- Only a minority with advanced disease receive chemotherapy

Treatment decisions should be based on health status, not chronological age
Metastatic prostate cancer
A heterogeneous disease

Nicolas Mottet
Saint-Etienne
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Disclosures

Nicolas Mottet has consulting agreements with:

- Astellas
- BMS
- Ferring
- Ipsen
- Janssen
- Millennium
- Novartis
- Pierre Fabre
- Sanofi
Metastatic prostate cancer

• First treatment step:
  – Androgen suppression (whatever the modality)
  – Almost constant response . . .
    but already heterogeneous
**Metastatic prostate cancer**
A heterogeneous disease

### SWOG 8894* - Prognostic factors for OS

<table>
<thead>
<tr>
<th>PROGNOSTIC GROUPS</th>
<th>GOOD</th>
<th>INTERMEDIATE</th>
<th>POOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial bone metastasis and/or nodes</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendicular bone or visceral mets</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Performance status &lt;1</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Performance status ≥1</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Gleason score &lt; 8</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason score ≥ 8</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PSA &lt; 65 ng/ml</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>PSA ≥ 65 ng/ml</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*Randomized prospective trial comparing orchietomy ± flutamide in 1286 patients with metastatic prostate cancer


OS: Overall survival
SWOG 8894* - OS by prognostic groups

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Events</th>
<th>Median OS (mths)</th>
<th>5 year estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>244</td>
<td>132</td>
<td>54</td>
<td>46%</td>
</tr>
<tr>
<td>Group 2</td>
<td>134</td>
<td>100</td>
<td>30</td>
<td>25%</td>
</tr>
<tr>
<td>Group 3</td>
<td>178</td>
<td>153</td>
<td>21</td>
<td>14%</td>
</tr>
</tbody>
</table>

OS: Overall survival
PSA response
Another simple predictive factor

SWOG 9346* - Prognostic value of PSA response

<table>
<thead>
<tr>
<th>PSA value after 7-mth ADT</th>
<th>N</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;4 ng/ml</td>
<td>383</td>
<td>13 mths</td>
</tr>
<tr>
<td>0.2 to 4 ng/ml</td>
<td>360</td>
<td>44 mths</td>
</tr>
<tr>
<td>&lt;0.2 ng/ml</td>
<td>602</td>
<td>75 mths</td>
</tr>
</tbody>
</table>

*Phase III randomized prospective trial comparing intermittent versus continuous ADT in patients with metastatic PCa and having a PSA ≤ 4 ng/ml after 7-mth ADT


PCa: prostate cancer; mth: month; ADT: Androgen deprivation therapy
# New drugs improving survival

<table>
<thead>
<tr>
<th>Drug Comparison</th>
<th>N patients</th>
<th>Relative reduction in risk of death, %</th>
<th>HR (95% CI; P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone/P vs pbo/P (post-Docetaxel)¹</td>
<td>1088</td>
<td>26</td>
<td>0.74 (0.64–0.86; P &lt; 0.001)</td>
</tr>
<tr>
<td>Abiraterone/P vs pbo/P (pre-Docetaxel)²</td>
<td>1195</td>
<td>19</td>
<td>0.81 (0.70-0.93; P = 0.0033)</td>
</tr>
<tr>
<td>Enzalutamide vs pbo (post-Docetaxel)³</td>
<td>1199</td>
<td>37</td>
<td>0.63 (0.53–0.75; P &lt; 0.0001)</td>
</tr>
<tr>
<td>Enzalutamide vs pbo (pre-Docetaxel)⁴</td>
<td>1717</td>
<td>29</td>
<td>0.71 (0.60–0.84; P &lt;0.0001)</td>
</tr>
<tr>
<td>Docetaxel/P vs mitoxantrone/P⁵</td>
<td>1006</td>
<td>24</td>
<td>0.76 (0.62–0.94; P = 0.009)</td>
</tr>
<tr>
<td>Cabazitaxel/P vs mitoxantrone/P (post-Docetaxel)⁶</td>
<td>755</td>
<td>30</td>
<td>0.70 (0.59–0.83; P &lt; 0.0001)</td>
</tr>
<tr>
<td>Sipuleucel-T vs. pbo (pre-Docetaxel)⁷</td>
<td>512</td>
<td>22</td>
<td>0.78 (0.61–0.98; P = 0.03)</td>
</tr>
<tr>
<td>Radium-223 vs. pbo (post-docetaxel or unfit for chemo)⁸</td>
<td>921</td>
<td>31</td>
<td>0.70 (0.58–0.83; P &lt; 0.001)</td>
</tr>
</tbody>
</table>

*P: prednisone; q3w: every 3 weeks; Pbo: placebo; chemo: chemotherapy*

mCRPC: EAU 2014 guidelines

- mCRPC
  - Good performance status 0 or 1
    - Mildly symptomatic or asymptomatic men with no evidence of visceral metastasis
      - Abiraterone
      - Sipuleucel T
      - Enzalutamide
      - ? Docetaxel
    - Men with evidence of progressive disease
      - Docetaxel
      - Alpharadin
  - PS 2+
  - Symptomatic bone metastasis
    - Alpharadin
- Asymptomatic Monitoring Anti-androgens

Primary resistance and new AR-targeted agents

Abiraterone Acetate\(^1\)

Enzalutamide\(^2\)

Around 20% primary resistant patients


AR: Androgen Receptor
Mechanisms of castration resistance

*Might be AR dependent / AR independent*

**AR dependent**
- **Ligand-dependant** activation of AR signalling
  - Persistent androgens in tumour
  - AR amplification
  - AR mutations
- **Ligand-independent** activation of AR signalling
  - RB suppressor proteins
  - AR splice variants
  - AR co-activators / repressors
  - Epigenetic modifications

**AR independent**
- Disruption of android receptor expression
- Inhibition of apoptosis (BCL2)
- EMT (via E-cadherin)
- Micro-environmental changes
- Prostate cancer stem cells

*Zong Y & Goldstein AS. Nature Rev 2013; 10: 90-98*

*AR: Androgen Receptor; EMT: Epithelial-Mesenchymal Transition; RB: Retinoblastoma*
CRPC: the place of the AR

AR splice variants (ARv)

- ADT induces constitutively active splice variants$^{1-2}$
- ARv567 (43%) & ARv7 (24%) are the most prevalent$^3$:
  - May contribute to resistance to enzalutamide$^4$ & abiraterone$^5$
  - Taxanes inhibit nuclear translocation of ARv567, not ARv7$^6$

AR: androgen receptor
AR-FL: Full-length androgen receptor
NTD: N-Terminal domain
DBD: DNA-Binding domain
LBD: Ligand-Binding domain
U: Unique N- or C-terminal sequence

ARv7 and resistance to enzalutamide and abiraterone

### Enzalutamide cohort (n=31)

- **Prevalence**
  - AR-V7(+): 12/31 = 38.7%
  - AR-V7 (-): 19/31 = 61.3%

### Abiraterone cohort (n=31)

- **Prevalence**
  - AR-V7(+): 6/31 = 19.4%
  - AR-V7 (-): 25/31 = 80.6%

62 US patients prospectively enrolled to receive enzalutamide (n=31) or abiraterone (n=31)

Antonarakis E et al. NEJM 2014;371:1028-38
Retinoblastoma tumor-suppressor protein

- Retinoblastoma (RB) prevents tumor growth by suppressing G1-S cell cycle progression.

- **Loss of RB function in 25-50% of prostate cancers**

- RB loss/inactivation:
  - Promotes lethal tumor phenotypes
  - Induces cell proliferation upon ADT or AR antagonist
  - Sensitivity to taxanes and Topo2 inhibitors

The PI3K/AKT signaling pathway & PTEN

- Genomic alterations in PI3K signalling are common:
  - 40% of primary PCa
  - 70% of metastatic Pca

- Mostly through loss of PTEN:
  - Enhances AKT activity
  - Blocks signal for apoptosis

- In PCa: PTEN loss associated with increased metastases


*PTEN: phosphatase and tensin homolog; PI3K: phosphoinositide 3-kinase; AR: androgen receptor*
Glucocorticoid receptor (GR) overexpression

- GR expression associated with clinical resistance to enzalutamide
- Activation of GR by dexamethasone sufficient to confer enzalutamide resistance, whereas a GR antagonist restored sensitivity
- GR bypasses enzalutamide-mediated AR blockade without the need for any restored AR function
- Acute AR inhibition resulted in GR upregulation in a subset of prostate cancer cells


DHT: dihydrotestosterone
Epithelial-Mesenchymal-Transition (EMT)

- ↑N-cadherin associated with EMT ➔ cancer invasion & mets$^{1-2}$
- Ectopic N-cadherin expression in nonmetastatic, androgen-dependent PCa models induces CRPC, invasion and mets$^3$
- ↑N-cadherin detected in PCa biopsies 3 months after ADT and is associated with CRPC, Gleason score and metastasis$^4$
- ↑N-cadherin associated with ↓(or loss) of AR expression$^5$
- EMT genes $ZEB1$ and $TWIST1$ also upregulated in human PCa specimens following ADT$^5$

Prostate Cancer Stem Cells (CSCs)

- Strong evidence supports their existence
- Properties:
  - Castration-resistance
  - Tissue-regeneration
  - Self-renewal
  - Low or lack AR expression
- Likely to survive in low androgen conditions and initiate tumor growth upon acquisition of new genetic or epigenetic event

<table>
<thead>
<tr>
<th></th>
<th>PASC</th>
<th>TA</th>
<th>Intermediate</th>
<th>Luminal Secretory</th>
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<tbody>
<tr>
<td><strong>Renewal Capacity</strong></td>
<td>++++</td>
<td>++</td>
<td>+</td>
<td>-</td>
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<tr>
<td><strong>PSA</strong></td>
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<tr>
<td>mRNA</td>
<td></td>
<td></td>
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<td>+++</td>
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<tr>
<td>Protein</td>
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<td>+++</td>
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<tr>
<td><strong>AR</strong></td>
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<tr>
<td>mRNA</td>
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<td>+</td>
<td>+++</td>
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<tr>
<td>Protein</td>
<td></td>
<td></td>
<td></td>
<td>+++</td>
</tr>
</tbody>
</table>

Adapted from Tombal. B. Eur J Cancer 2011; 47: S179-188

*PASC: prostate adult stem cells; TA: transit amplifying cell*
Resistance to castration: 2 theories

Adaptation

Clonal Selection

Tombal. B. Eur J Cancer 2011; 47: S179-188
Clonal origin of PCa

- 47-year old diagnosed with Gleason 8 PCa
- Died 17 years later due to mCRPC
- Genetic analysis of mets and primary: *lethal clone arose from a small low grade focus present at diagnosis and harbouring PTEN and p53 mutations*


*PCa: prostate cancer; mCRPC: metastatic castration-resistant prostate cancer*
Primary lesion & mets may differ

Prostate

High AR staining

Lymph node metastasis

Low AR staining

Fleischmann A. Prostate 2011; 71: 453-460
Co-existence of AR positive and AR negative tumour cells in a same patient

AR negative cells

AR positive cells

Beltran H. Cancer discovery 2011; 1: 487-495
AR: androgen receptor
mCRPC: heterogeneous genetic findings

Molecular characterization of CTCs. CK (green) and CD45 (red) immunofluorescence and PTEN, ERG break-apart, and AR FISH.

<table>
<thead>
<tr>
<th>Pan-CK + CD45 IF</th>
<th>PTEN FISH</th>
<th>ERG “break-apart” FISH</th>
<th>AR FISH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Panel A</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patient 66</td>
<td>Event 476</td>
<td>Event 736</td>
<td>Event 963</td>
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<td><strong>Panel B</strong></td>
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<td>Patient 7</td>
<td>Event 135</td>
<td>Event 267</td>
<td>Event 416</td>
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<tr>
<td><strong>Panel C</strong></td>
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<td>Patient 26</td>
<td>Event 13</td>
<td>Event 236</td>
<td>Event 505</td>
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<td><strong>Panel D</strong></td>
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<tr>
<td>Patient 71</td>
<td>Event 73</td>
<td>Event 106</td>
<td>Event 423</td>
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</tbody>
</table>

CTC: circulating tumour cells; AR: androgen receptor
AR-negative progression with abiraterone

- 75-year old, previously progressed on ADT, bicalutamide & dexamethasone
- Prostate biopsy: AR-positive cancer
- Develops AR-negative liver metastasis with abiraterone despite good PSA response


**ADT:** adrogendeprivation therapy
Patient in AFFIRM trial (enzalutamide vs. placebo) PSA drop from >600nm/mL to 3.5 ng/ml at 3 months - ↓ size of lymph nodes

Courtesy of B. Tombal and F. Lecouvet, CUSL, UCL, Brussels
Patient in AFFIRM trial (enzalutamide vs. placebo)
3 months: ↓ lymph nodes, but NEW BONE METS
Month 6: still in AFFIRM - PSA 4.1 ng/ml, further ↓ lymph nodes

Courtesy of B. Tombal and F. Lecouvet, CUSL, UCL, Brussels
Month 6: Still in AFFIRM - PSA 4.1 ng/ml, ↑ bone mets

Courtesy of B. Tombal and F. Lecouvet, CUSL, UCL, Brussels
Prostate cancers are heterogeneous

- It is a reality from the beginning

- **Cross resistance** between drugs, a reality?

- The "one drug fits all" policy neither applicable nor acceptable
  - Mode of administration / side effects different
  - Predicting factors for individual drug efficacy?
Tailoring therapy in advanced prostate cancer

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Georges Pompidou Hospital
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Paris, France
Disclosures

• Stéphane Oudard has consulting agreements with:
  – Bayer
  – GSK
  – Janssen
  – Keocyt
  – Novartis
  – Pfizer
  – Roche
  – Sanofi
  – Takeda
Targets of therapies in advanced PCa

- **Cell trafficking**
  - *Taxanes*

- **Ligand depletion**
  - *Abiraterone*

- **Bone targeting**
  - *Radium-223*

- **AR targeting**
  - *Enzalutamide*

- **Immunotherapy**
  - *Sipuleucel-T*

And more to come ....

*docetaxel, cabazitaxel; AR: androgen receptor*
Management of metastatic hormone-sensitive PCa

- Metastatic hormone-sensitive PC
  - LHRH agonists
  - Anti-androgens
  - LHRH antagonists
  - Docetaxel* (not licenced)

*CHAARTED. C. Sweeney et al. ASCO 2014 (abstract BA2) – Docetaxel is not licenced in this population
**E3805 – CHAARTED study**

- **ARM A (n=397)**
  - ADT + Docetaxel* for 6 cycles

- **ARM B (n=393)**
  - ADT

Follow for time to progression and overall survival

Chemotherapy at investigator’s discretion at progression

- Open-label, multicenter, phase III trial conducted in US
- Standard dexamethasone premedication **but no daily prednisone**

Docetaxel in combination with prednisone is indicated for the treatment of or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer


*Mets: Metastases; PS: Performance Status; SRE: Skeletal Related Events; CAB: Complete Androgen Blockade; docetaxel (75mg/m2 every 21 days; ADT: Androgen Deprivation Therapy*
Key eligibility criteria

• High volume metastatic disease:
  – visceral metastases
  and/or
  – 4 or more bone metastases (with at least 1 beyond pelvis and vertebral column)

• At study initiation, only patients with high volume disease were to be accrued
  – Study amendment to allow patients with low volume to be enrolled, with stratification on disease volume

ADT: androgen deprivation therapy;
Primary endpoint: overall survival

Overall survival

Sweeney C et al. J Clin Oncol 2014;32(June 20 suppl):abstract LBA2
ADT: androgen deprivation therapy; DOC: docetaxel; OS: overall survival; mths: months
ADT + Docetaxel benefited all subgroups

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>790</td>
<td>0.61</td>
<td>(0.47-0.80)</td>
</tr>
<tr>
<td>Age &lt;70</td>
<td>612</td>
<td>0.68</td>
<td>(0.50-0.91)</td>
</tr>
<tr>
<td>Age ≥70</td>
<td>178</td>
<td>0.43</td>
<td>(0.23-0.78)</td>
</tr>
<tr>
<td>Low-volume disease</td>
<td>276</td>
<td>0.63</td>
<td>(0.34-1.17)</td>
</tr>
<tr>
<td>High-volume disease</td>
<td>514</td>
<td>0.60</td>
<td>(0.45-0.81)</td>
</tr>
<tr>
<td>Visceral mets ± bone mets (BM)</td>
<td>125</td>
<td>0.48</td>
<td>(0.23-0.99)</td>
</tr>
<tr>
<td>High volume (BM only)</td>
<td>387</td>
<td>0.65</td>
<td>(0.46-0.91)</td>
</tr>
<tr>
<td>Race - white</td>
<td>674</td>
<td>0.62</td>
<td>(0.47-0.83)</td>
</tr>
<tr>
<td>Race - other</td>
<td>92</td>
<td>0.53</td>
<td>(0.17-1.60)</td>
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<tr>
<td>Gleason score &lt;8</td>
<td>220</td>
<td>0.41</td>
<td>(0.21-0.80)</td>
</tr>
<tr>
<td>Gleason score ≥8</td>
<td>480</td>
<td>0.60</td>
<td>(0.43-0.84)</td>
</tr>
<tr>
<td>Prior local therapy - no</td>
<td>575</td>
<td>0.66</td>
<td>(0.50-0.89)</td>
</tr>
<tr>
<td>Prior local therapy - yes</td>
<td>214</td>
<td>0.55</td>
<td>(0.23-1.31)</td>
</tr>
<tr>
<td>CAB &gt;30 days - no</td>
<td>459</td>
<td>0.69</td>
<td>(0.49-0.99)</td>
</tr>
<tr>
<td>CAB &gt;30 days - yes</td>
<td>331</td>
<td>0.52</td>
<td>(0.34-0.79)</td>
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<tr>
<td>SRE - no</td>
<td>443</td>
<td>0.58</td>
<td>(0.34-0.79)</td>
</tr>
<tr>
<td>SRE - yes</td>
<td>347</td>
<td>0.65</td>
<td>(0.45-0.96)</td>
</tr>
</tbody>
</table>

Sweeney C et al. J Clin Oncol 2014;32(June 20 suppl):abstract LBA2

ADT: androgen deprivation therapy; DOC: Docetaxel 75mg/m2; Mets: metastases;
CAB: Complete Androgen Blockade
## Therapy beyond progression

<table>
<thead>
<tr>
<th></th>
<th>ADT + DOC (N=397)</th>
<th>ADT alone (N=393)</th>
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</thead>
<tbody>
<tr>
<td><strong>Biochem, symptom, radiographic PD</strong></td>
<td>145</td>
<td></td>
</tr>
<tr>
<td><strong>Symptom or radiographic PD</strong></td>
<td>93</td>
<td></td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td></td>
<td>129</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>Mitoxantrone and/or platinum</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>Abiraterone/enzalutamide</td>
<td>92</td>
<td>79</td>
</tr>
<tr>
<td>Antiandrogen/ketoconazole</td>
<td>87</td>
<td>99</td>
</tr>
<tr>
<td>Sipuleucel</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>54</td>
<td>67</td>
</tr>
</tbody>
</table>

74% received docetaxel at progression in ADT arm

*Sweeney C et al. J Clin Oncol 2014;32(June 20 suppl):abstract LBA2
ADT: androgen deprivation therapy; DOC: Docetaxel 75mg/m2; Mets: metastases; CAB: Complete Androgen Blockade*
Conclusion

• Adding 6 cycles of docetaxel to ADT significantly improves OS in patients with metastatic PCa
• Patients with high volume disease should be offered combination of docetaxel + ADT upfront
• Patients with low volume disease with long life expectancy should also be considered
• Ongoing clinical trials for non-metastatic high risk cancers have become critical to determine just how early chemotherapy should be used

ADT: androgen deprivation therapy; PCa: prostate cancer
Management of mCRPC in first-line

Metastatic castrate-sensitive PC
- LHRH agonists
- Anti-androgens
- LHRH antagonists
- Docetaxel* (not licenced)

Metastatic CRPC 1st line
- Docetaxel
- Sipuleucel-T
- Abiraterone
- Enzalutamide (US)
- Radium-223

*CHAARTED. C. Sweeney et al. ASCO 2014 (abstract BA2) – Docetaxel is not licenced in this population
# Phase III clinical trials in first-line mCRPC

<table>
<thead>
<tr>
<th>Study</th>
<th>Agents</th>
<th>N</th>
<th>Indication</th>
<th>HR</th>
<th>Δ OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX-327¹</td>
<td>Docetaxel/P vs mito/P</td>
<td>1006</td>
<td>mCRPC</td>
<td>0.76</td>
<td>+2.9</td>
</tr>
<tr>
<td>IMPACT²</td>
<td>Sipuleucel-T vs pbo</td>
<td>512</td>
<td>mCRPC (pre-Doc) No visceral mets</td>
<td>0.78</td>
<td>+4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No/mild symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COU-AA-302³</td>
<td>Abiraterone/P vs P</td>
<td>1088</td>
<td>mCRPC (pre-Doc) No visceral mets</td>
<td>0.81</td>
<td>+4.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No/mild symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PREVAIL⁴</td>
<td>Enzalutamide vs pbo</td>
<td>1717</td>
<td>mCRPC (pre-Doc) No/mild symptoms</td>
<td>0.71</td>
<td>+2.2 (est)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALSYMPCA⁸</td>
<td>Radium-223 vs pbo</td>
<td>921</td>
<td>mCRPC (unfit for Doc) No visceral mets</td>
<td>0.70</td>
<td>+2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Painful bone mets</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADT: Androgen Deprivation Therapy; P: Prednisone; Pbo: Placebo; Mito: Mitoxantrone; Doc: Docetaxel; CRPC: Castration-Resistant Prostate Cancer

Docetaxel (TAX 327)
Survival not influenced by age

Hazard ratio in favour of
Docetaxel+P  Mitoxantrone+P

ITT
Age < 65 years
Age ≥ 65 years
Age ≥ 75 years

Pain: no
Pain: yes
KPS ≥ 80
KPS ≤ 70

• Among men ≥75 years, 3-weekly Docetaxel+P resulted in more dose reductions than weekly schedule (22% versus 8%, p = 0.007) but tolerability was otherwise comparable.

• Both Docetaxel schedules were associated with more favorable efficacy than mitoxantrone

P: prednisone
## Phase 3 trial - Bi-weekly vs 3-weekly docetaxel in mCRPC

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel bi-weekly + P (n=170)</th>
<th>Docetaxel 3-weekly + P (n=169)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTTF (median)</td>
<td>5.6 mo</td>
<td>4.9 mo</td>
<td>0.014</td>
</tr>
<tr>
<td>OS (median)</td>
<td><strong>19.5 mo</strong></td>
<td>17 mo</td>
<td>0.021</td>
</tr>
<tr>
<td>PSA response</td>
<td>49%</td>
<td>42%</td>
<td>0.49</td>
</tr>
<tr>
<td>Best clinical response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CR or PR</td>
<td>23%</td>
<td>22%</td>
<td>0.95</td>
</tr>
<tr>
<td>- Stable</td>
<td>46%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>- Progression</td>
<td>8%</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>

### Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel bi-weekly + P (n=170)</th>
<th>Docetaxel 3-weekly + P (n=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA response</td>
<td>49%</td>
<td>42%</td>
</tr>
<tr>
<td>Best clinical response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CR or PR</td>
<td>23%</td>
<td>22%</td>
</tr>
<tr>
<td>- Stable</td>
<td>46%</td>
<td>46%</td>
</tr>
<tr>
<td>- Progression</td>
<td>8%</td>
<td>11%</td>
</tr>
</tbody>
</table>

### Grade ≥ 3 toxicities

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel bi-weekly + P (n=170)</th>
<th>Docetaxel 3-weekly + P (n=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Neutropenia</td>
<td>36%</td>
<td>53%</td>
</tr>
<tr>
<td>- Leucopenia</td>
<td>13%</td>
<td>29%</td>
</tr>
<tr>
<td>- Anemia</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>- Thrombocytopenia</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>- Febrile neutropenia</td>
<td><strong>4%</strong></td>
<td><strong>14%</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel bi-weekly + P (n=170)</th>
<th>Docetaxel 3-weekly + P (n=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-hematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Fatigue</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>- Infection without neutropenia</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>- Neutropenic infection</td>
<td>6%</td>
<td>24%</td>
</tr>
<tr>
<td>- ↑ALP</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>- Diarrhea</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>- Nausea</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>


*mCRPC: metastatic castrate-resistant prostate cancer; TTTF: Time to Treatment Failure; OS: overall survival; ALP: Alkaline phosphatase*
# Abiraterone (COU-AA-302)
## Survival not influenced by age

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1088</td>
<td>0.79</td>
<td>(0.66-0.95)</td>
</tr>
<tr>
<td>Baseline ECOG 0</td>
<td>830</td>
<td>0.76</td>
<td>(0.60-0.95)</td>
</tr>
<tr>
<td>Baseline ECOG 1</td>
<td>258</td>
<td>0.89</td>
<td>(0.62-1.26)</td>
</tr>
<tr>
<td>Baseline BPI 0-1</td>
<td>716</td>
<td>0.74</td>
<td>(0.57-0.94)</td>
</tr>
<tr>
<td>Baseline BPI 2-3</td>
<td>276</td>
<td>0.94</td>
<td>(0.68-1.31)</td>
</tr>
<tr>
<td>Bone mets only at entry: YES</td>
<td>479</td>
<td>0.70</td>
<td>(0.51-0.95)</td>
</tr>
<tr>
<td>Bone mets only at entry: NO</td>
<td>609</td>
<td>0.86</td>
<td>(0.68-1.10)</td>
</tr>
<tr>
<td>Age &lt;65 yrs</td>
<td>290</td>
<td>0.82</td>
<td>(0.56-1.20)</td>
</tr>
<tr>
<td>Age ≥65 yrs</td>
<td>798</td>
<td>0.78</td>
<td>(0.63-0.97)</td>
</tr>
<tr>
<td>Age ≥75 yrs</td>
<td>350</td>
<td>0.74</td>
<td>(0.55-1.00)</td>
</tr>
<tr>
<td>Baseline PSA above median: YES</td>
<td>542</td>
<td>0.78</td>
<td>(0.61-0.99)</td>
</tr>
<tr>
<td>Baseline PSA above median: NO</td>
<td>564</td>
<td>0.78</td>
<td>(0.58-1.06)</td>
</tr>
<tr>
<td>Baseline LDH above median: YES</td>
<td>537</td>
<td>0.68</td>
<td>(0.53-0.87)</td>
</tr>
<tr>
<td>Baseline LDH above median: NO</td>
<td>551</td>
<td>0.93</td>
<td>(0.69-1.24)</td>
</tr>
<tr>
<td>Baseline ALK-P above median: YES</td>
<td>535</td>
<td>0.86</td>
<td>(0.67-1.10)</td>
</tr>
<tr>
<td>Baseline ALK-P above median: NO</td>
<td>553</td>
<td>0.67</td>
<td>(0.50-0.91)</td>
</tr>
<tr>
<td>Region: NA</td>
<td>572</td>
<td>0.72</td>
<td>(0.55-0.94)</td>
</tr>
<tr>
<td>Region: Other</td>
<td>516</td>
<td>0.89</td>
<td>(0.68-1.17)</td>
</tr>
</tbody>
</table>

*Abbreviations: BPI: Brief Pain Inventory; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; ALK: alkaline phosphatase; OS: overall survival; PSA: prostate-specific antigen*
# Enzalutamide (PREVAIL)

**Survival not influenced by age**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1717</td>
<td>0.71</td>
<td>(0.60-0.84)</td>
</tr>
<tr>
<td>Baseline ECOG 0</td>
<td>1169</td>
<td>0.70</td>
<td>(0.56-0.87)</td>
</tr>
<tr>
<td>Baseline ECOG 1</td>
<td>548</td>
<td>0.69</td>
<td>(0.53-0.90)</td>
</tr>
<tr>
<td><strong>Age &lt;75 yr</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;75 yr</td>
<td>1108</td>
<td>0.77</td>
<td>(0.62-0.96)</td>
</tr>
<tr>
<td>Age ≥ 75 yrs</td>
<td>609</td>
<td>0.60</td>
<td>(0.47-0.79)</td>
</tr>
<tr>
<td>Geographic region – North America</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geographic region – Europe</td>
<td>426</td>
<td>0.83</td>
<td>(0.60-1.16)</td>
</tr>
<tr>
<td>Geographic region – Rest of world</td>
<td>911</td>
<td>0.68</td>
<td>(0.54-0.86)</td>
</tr>
<tr>
<td>Visceral disease (lung and/or liver) at screening: YES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral disease (lung and/or liver) at screening: NO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Gleason score at diagnosis ≤7</td>
<td>799</td>
<td>0.66</td>
<td>(0.51-0.85)</td>
</tr>
<tr>
<td>Total Gleason score at diagnosis ≥8</td>
<td>847</td>
<td>0.77</td>
<td>(0.60-0.97)</td>
</tr>
<tr>
<td>Type of progression at study entry: PSA only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of progression at study entry: Radiological ± PSAy</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline PSA value (ng/mL) ≤ median (49.60)</td>
<td>860</td>
<td>0.78</td>
<td>(0.58-1.05)</td>
</tr>
<tr>
<td>Baseline PSA value (ng/mL) &gt; median (49.60)</td>
<td>856</td>
<td>0.61</td>
<td>(0.49-0.75)</td>
</tr>
<tr>
<td>Baseline LDH value (U/L) ≤ median (185)</td>
<td>866</td>
<td>0.57</td>
<td>(0.43-0.76)</td>
</tr>
<tr>
<td>Baseline LDH value (U/L) &gt; median (185)</td>
<td>849</td>
<td>0.80</td>
<td>(0.65-0.99)</td>
</tr>
</tbody>
</table>

**References**

Beer TM et al. NEJM 2014; 371:424-334 (appendix)

BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; OS: overall survival; PSA: prostate-specific antigen
Management of mCRPC post-docetaxel

Metastatic castrate-sensitive PC
- LHRH agonists
- Anti-androgens
- LHRH antagonists
- Docetaxel* (not licenced)

Metastatic CRPC 1st line
- Docetaxel
- Sipuleucel-T
- Abiraterone
- Enzalutamide (US)
- Radium-223

Metastatic CRPC post-docetaxel
- Cabazitaxel
- Abiraterone
- Enzalutamide
- Radium-223

*CHAARTED. C. Sweeney et al. ASCO 2014 (abstract BA2) – Docetaxel is not licenced in this population
# Phase III clinical trials in mCRPC post-docetaxel

<table>
<thead>
<tr>
<th>Study</th>
<th>Agents</th>
<th>N</th>
<th>Indication</th>
<th>HR</th>
<th>Δ OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TROPIC²</td>
<td>Cabazitaxel/P vs mito/P</td>
<td>755</td>
<td>mCRPC (post-Doc)</td>
<td>0.70</td>
<td>+2.4</td>
</tr>
<tr>
<td>COU-AA-301²</td>
<td>Abiraterone/P vs P</td>
<td>1195</td>
<td>mCRPC (post-Doc)</td>
<td>0.74</td>
<td>+4.6</td>
</tr>
<tr>
<td>AFFIRM³</td>
<td>Enzalutamide vs pbo (or P)</td>
<td>1199</td>
<td>mCRPC (post-Doc)</td>
<td>0.63</td>
<td>+4.8</td>
</tr>
<tr>
<td>ALSYMPCA⁴</td>
<td>Radium-223 vs pbo</td>
<td>921</td>
<td>mCRPC (post-Doc or unfit for Doc)</td>
<td>0.70</td>
<td>+2.8</td>
</tr>
</tbody>
</table>

ADT: Androgen Deprivation Therapy; P: Prednisone; Pbo: Placebo; Mito: Mitoxantrone; Doc: Docetaxel; CRPC: Castration-Resistant Prostate Cancer

# Cabazitaxel (TROPIC): Survival not influenced by age

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Favors CABA+P</th>
<th>Favors MITO+P</th>
<th>HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>All randomized patients</td>
<td>755</td>
<td></td>
<td></td>
<td>0.70 (0.59–0.83)</td>
</tr>
<tr>
<td>ECOG status: 0,1</td>
<td>694</td>
<td></td>
<td></td>
<td>0.68 (0.57–0.82)</td>
</tr>
<tr>
<td>ECOG status: 2</td>
<td>61</td>
<td></td>
<td></td>
<td>0.81 (0.48–1.38)</td>
</tr>
<tr>
<td>Measurable disease: no</td>
<td>350</td>
<td></td>
<td></td>
<td>0.72 (0.55–0.93)</td>
</tr>
<tr>
<td>Measurable disease: yes</td>
<td>405</td>
<td></td>
<td></td>
<td>0.68 (0.54–0.85)</td>
</tr>
<tr>
<td>Number of previous ...</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of previous chemotherapies: 1</td>
<td>528</td>
<td></td>
<td></td>
<td>0.67 (0.55–0.83)</td>
</tr>
<tr>
<td>Number of previous chemotherapies: ≥2</td>
<td>227</td>
<td></td>
<td></td>
<td>0.75 (0.55–1.02)</td>
</tr>
<tr>
<td>Age&lt;65 years</td>
<td>295</td>
<td></td>
<td></td>
<td>0.81 (0.61–1.08)</td>
</tr>
<tr>
<td>Age≥65 years</td>
<td>460</td>
<td></td>
<td></td>
<td>0.62 (0.50–0.78)</td>
</tr>
<tr>
<td>Pain at baseline: no</td>
<td>314</td>
<td></td>
<td></td>
<td>0.57 (0.43–0.77)</td>
</tr>
<tr>
<td>Pain at baseline: yes</td>
<td>310</td>
<td></td>
<td></td>
<td>0.76 (0.59–0.98)</td>
</tr>
<tr>
<td>Rising PSA at baseline: no</td>
<td>159</td>
<td></td>
<td></td>
<td>0.88 (0.61–1.26)</td>
</tr>
<tr>
<td>Rising PSA at baseline: yes</td>
<td>583</td>
<td></td>
<td></td>
<td>0.65 (0.53–0.80)</td>
</tr>
<tr>
<td>Progression during docetaxel treatment</td>
<td>219</td>
<td></td>
<td></td>
<td>0.65 (0.47–0.90)</td>
</tr>
<tr>
<td>Progression &lt;3 months after docetaxel</td>
<td>339</td>
<td></td>
<td></td>
<td>0.70 (0.55–0.91)</td>
</tr>
<tr>
<td>Progression ≥3 months after docetaxel</td>
<td>192</td>
<td></td>
<td></td>
<td>0.75 (0.51–1.11)</td>
</tr>
</tbody>
</table>

de Bono et al. Lancet 2010;376:1147–54
ECOG: Eastern Cooperative Oncology Group; CABA+P: cabazitaxel+prednisone; MITO+P: mitoxantrone + prednisone
# Cabazitaxel (European compassionate use program) - Safety in senior adults

<table>
<thead>
<tr>
<th></th>
<th>&lt;70 years (n=238)</th>
<th>70-74 years (n=100)</th>
<th>75+ years (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N cycles, median (range)</td>
<td>4 (1-16)</td>
<td>4 (1-12)</td>
<td>4 (1-11)</td>
</tr>
<tr>
<td>Dose delay for drug-related AE</td>
<td>4.3%</td>
<td>13.0%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Dose reduction for any cause</td>
<td>18.5%</td>
<td>16.0%</td>
<td>15.9%</td>
</tr>
<tr>
<td>G-CSF primary prophylaxis (C1)</td>
<td>39.2%</td>
<td>46.1%</td>
<td>50.3%</td>
</tr>
</tbody>
</table>

## Hematological, grade ≥3

- Neutropenia                         | 15.0%             | 16.7%               | 23.4%            |
- Leucopenia                          | 6.2%              | 8.3%                | 9.7%             |
- Anemia                              | 5.0%              | 4.4%                | 4.1%             |
- Febrile neutropenia                 | 5.2%              | 5.6%                | 5.5%             |
- Neutropenic sepsis                  | 1.0%              | 1.6%                | 1.4%             |

## Non-hematological, grade ≥3

- Fatigue                             | 4.0%              | 3.3%                | 5.5%             |
- Asthenia                            | 1.4%              | 4.4%                | 5.5%             |
- Diarrhea                            | 3.3%              | 1.7%                | 2.8%             |
- Nausea                              | 0%                | 0.6%                | 3.4%             |
- Vomiting                            | 1.0%              | 1.1%                | 2.1%             |
- Hematuria                           | 0.5%              | 2.8%                | 1.4%             |
- Peripheral neuropathy               | 0%                | 0%                  | 0.7%             |
- Nail disorders                      | 0%                | 0%                  | 0%               |

Heidenreich A et al. Eur J Cancer 2014; 50; 1090-99
## Specific considerations for senior adults with VERY advanced disease

### Cabazitaxel*1
- Higher risk of **febrile neutropenia** (7.5 vs 1.3%)
  - Consider primary prophylaxis with G-CSF in high risk patients4

- Higher risk of **diarrhea** (6.5 vs 0.3% grade ≥3)
  - Rehydration with antiemetics and antidiarrheals as needed

### Abiraterone*2
- Hypokalemia, hypertension & fluid retention due to **mineralocorticoid excess**
  - Use with caution in patients with CV diseases

- Risk of **adrenocortical insufficiency**
  - Caution if interruption of daily steroids and/or infection or stress

- Risk of **hepatotoxicity**
  - Monitor liver function

### Enzalutamide3
- Higher risk of **fatigue** (34% vs 29%)
  - Assess functional status
  - Physical exercise

- Risk of **seizures** (0.9%)
  - Caution if history of seizure, brain injury, cerebral vascular accident, brain mets

- Higher risk of **hot flushes** (20 vs 10%)

- Higher risk of **falls** (4.6 vs 1.3%)

---

Product information: 1. cabazitaxel, 2. abiraterone, 3. enzalutamide; 4. EORTC guidelines Aapro M et al. EJC 2011; 47: 8-32 - CV: cardiovascular; G-CSF: granulocyte colony-stimulating factor; * administered with prednisone
Which drug for which patient?
Primary resistance to AR-targeted agents

Radiological PFS

Abiraterone\(^1\) (COU-AA-301)

Enzalutamide\(^2\) (AFFIRM)

Primary resistance
1 out of 3 patients

Primary resistance
1 out of 4 patients

Primary end-point of COU-AA-301 and AFFIRM was overall survival


PFS: progression-free survival
Who are the non responders to abiraterone?

Who are the NON responders? (defined as patients treated for ≤4 months)

Bone marrow biopsy:
- Intense AR nuclear expression
- CYP17 expression

Open-label phase II study of 62 mCRPC patients treated with abiraterone + prednisone. Transilial bone marrow biopsies before treatment, at 8 wks and at end of study

Who are the non-responders to enzalutamide?

Open-label phase II study of 60 patients with bone mCRPC treated with enzalutamide. Transilial bone marrow biopsies before treatment, at 8 wks and at end of treatment.

Efstathiou E et al. Eur Urol 2014 (epub ahead of print)

Mths: months; wk: weeks
Combination of AR-targeted agents does not overcome primary resistance

Abiraterone/P¹

Enzalutamide²

Enzalutamide + abiraterone/P³

PSA Change (%)

↓ PSA ≥30%: 61% (34/56)
↓ PSA ≥50%: 50% (28/56)
↓ PSA ≥90%: 16% (9/56)

↓ PSA ≥30%: 55% (30/55)
↓ PSA ≥50%: 50% (25/55)
↓ PSA ≥90%: 20% (11/55)

↓ PSA ≥30%: 83.6% (41/49)
↓ PSA ≥50%: 75.5% (37/49)
↓ PSA ≥90%: 44.9% (22/49)

27%  29%  12%

3 different open-label phase II study of 60 patients with bone mCRPC treated with abiraterone acetate plus prednisone (P), enzalutamide, or combination of both.

Transilial bone marrow biopsies before treatment, at 8 wks and at end of treatment.

3. Efstatthiou E et al. J Clin Oncol 2014; 32 (suppl); abstract 5000
May duration of response to first ADT help to guide treatment choice?

Retrospective analysis in 153 mCRPC patients treated with cabazitaxel plus prednisone. 2nd ADT included anti-androgens, DES, estramustine, ketoconazole, abiraterone, enzalutamide.

Optimal management of mCRPC: highlights from a European Expert Consensus Panel

Short duration of response (<1 year) to first-line ADT could be used as an indicator of increased risk for primary resistance to AR-targeted agents

![Bar chart showing the percentage of voting experts (21 EU experts) for different responses:]

- **AGREE**: 86%
- **DISAGREE**: 14%
- **ABSTAIN**: 0%

21 EU experts
Strong consensus

ADT: androgen deprivation therapy
Extended metastatic spread and high NLR prognostic & predict poor response to ABI

PSA response ≥ 50%

<table>
<thead>
<tr>
<th>Condition</th>
<th>Restricted mets &amp; NLR≤5</th>
<th>Other cases</th>
<th>Extended** mets &amp; NLR&gt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with PSA decrease ≥50%</td>
<td>58%</td>
<td>50%</td>
<td>36%</td>
</tr>
<tr>
<td>PSA response ≥ 50%</td>
<td>37%</td>
<td>30%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Overall survival

<table>
<thead>
<tr>
<th>Condition</th>
<th>Princess Margaret (test cohort, n=116)</th>
<th>Royal Mardsen (validation cohort, n=250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restricted mets &amp; NLR≤5</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Other cases</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Extended** mets &amp; NLR&gt;5</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

NLR: neutrophil/lymphocyte ratio


*Bone mets only or lymph node mets only; **visceral mets alone or combined with bone or lymph nodes
NLR and activity of docetaxel

VENICE (1224 patients)
- dNLR ≥2 & duration of 1st ADT are prognostic for OS (MVA analysis)

<table>
<thead>
<tr>
<th></th>
<th>HR (CI 95%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≥ median)</td>
<td>1.24 (1.06-1.44)</td>
<td>0.006</td>
</tr>
<tr>
<td>ALP (≥ median)</td>
<td>1.65 (1.41-1.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of initial ADT (&lt; median)</td>
<td>1.41 (1.21-1.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>dNLR (≥ median)</td>
<td>1.29 (1.44-1.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin (&lt;median)</td>
<td>1.45 (1.24-1.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain at baseline (PPI ≥2)</td>
<td>1.56 (1.33-1.82)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TAX327 (1006 patients)
- OS benefit particularly marked for high dNLR vs mitoxantrone

<table>
<thead>
<tr>
<th></th>
<th>dNLR &lt;2</th>
<th>dNLR ≥2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOC (n=156)</td>
<td>20.8</td>
<td>18.6</td>
</tr>
<tr>
<td>M (n=181)</td>
<td>17.4</td>
<td>13.1</td>
</tr>
<tr>
<td>DOC (n=176)</td>
<td>17.4</td>
<td>13.1</td>
</tr>
<tr>
<td>M (n=155)</td>
<td>13.1</td>
<td></td>
</tr>
</tbody>
</table>

Median OS Difference HR [95% CI]
2.2 mths 0.80 [0.59-1.09] 0.72 [0.54-0.95]
4.3 mths

- Confirmed PSA decrease ≥50% with docetaxel:
  - dNLR <2: 70%
  - dNLR ≥2: 55%

*Posthoc analyses

Van Soest R et al. ESMO 2014 (poster P786)
dNLR: derived neutrophil lymphocyte ratio; ALP: Alkaline Phosphatase; M: mitoxantrone
ARv7 and resistance to Abi or Enza
PSA response rate

**Enzalutamide**

- **AR-V7 positive: 0%** (95% CI: 0–26%)
- **AR-V7 negative: 52.6%** (95% CI: 29–76%)

62 US patients prospectively enrolled to receive enzalutamide (n=31) or abiraterone (n=31)
Antonarakis et al. NEJM 2014 (epub ahead of print on 4 Sept)

**Abiraterone**

- **AR-V7 positive: 0%** (95% CI: 0–46%)
- **AR-V7 negative: 68.0%** (95% CI: 46–85%)

p=0.004
Docetaxel refractory patients

Cabazitaxel

- Retrospective review of 186 mCRPC patients
- 33 (17.7%) docetaxel refractory*
- Multivariate analysis: better OS if DOC → CABA → ABI or ENZ

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st therapy post-DOC (ABI or ENZ vs CABA)</td>
<td>3.22</td>
<td>0.02</td>
</tr>
<tr>
<td>2nd therapy post-DOC (ABI or ENZ vs CABA)</td>
<td>0.36</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Abiraterone

- Retrospective study of 44 patients with mCRPC
- Treated with docetaxel → ABI
- 7/44 patients docetaxel refractory
- No PSA, radiological or clinical response to ABI


mCRPC: metastatic castration-resistant prostate cancer; ABI: abiraterone; ENZ: Enzalutamide; CABA: cabazitaxel; DOC: Docetaxel

*DOC refractoriness defined as disease progression occurring within 3 mths from DOC initiation and after adequate exposure to DOC (ie cumulative dose of ≥225 mg/m2).
Cross-resistance between these new therapies?
## Poor response to abiraterone in patients progressing on enzalutamide?

<table>
<thead>
<tr>
<th></th>
<th>Loriot(^1) (n=38)</th>
<th>Noonan(^2) (n=30)</th>
<th>COU-AA-301(^3) (n=797)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Enzalutamide</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Median PFS, mths</td>
<td>2.7</td>
<td>3.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Median OS, mths</td>
<td><strong>7.2</strong></td>
<td><strong>11.8</strong></td>
<td>14.8</td>
</tr>
<tr>
<td>↓ PSA ≥50%*</td>
<td>8%</td>
<td>3%</td>
<td>29%</td>
</tr>
</tbody>
</table>

[1-2] trials are retrospective studies conducted in 38 and 30 patients, respectively

*Confirmed by a second value

---


*OS: Overall survival; PFS: Progression-free survival*
### Poor response to enzalutamide in patients progressing on abiraterone?

<table>
<thead>
<tr>
<th></th>
<th>Schrader&lt;sup&gt;1&lt;/sup&gt; (n=35)</th>
<th>Bianchini&lt;sup&gt;2&lt;/sup&gt; (n=39)</th>
<th>Thomsen&lt;sup&gt;3&lt;/sup&gt; (n=24)</th>
<th>Badrising&lt;sup&gt;4&lt;/sup&gt; (n=61)</th>
<th>AFFIRM&lt;sup&gt;5&lt;/sup&gt; (n=800)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior ABI</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Partial response</td>
<td>2.9%</td>
<td>4.3%</td>
<td>-</td>
<td>-</td>
<td>29%</td>
</tr>
<tr>
<td>Median PFS, mths</td>
<td>-</td>
<td>2.8</td>
<td>-</td>
<td>3.0</td>
<td>8.3</td>
</tr>
<tr>
<td>Median OS, mths</td>
<td>7.1**</td>
<td>-</td>
<td>4.8</td>
<td>7.9</td>
<td>18.4</td>
</tr>
<tr>
<td>↓PSA ≥50%</td>
<td>28.6%</td>
<td>12.8%*</td>
<td>16.7%</td>
<td>21%</td>
<td>54%*</td>
</tr>
</tbody>
</table>

*PSA response confirmed by a second value; [1-4] trials are retrospective studies


ABI: Abiraterone, PFS: Progression-free survival; OS: overall survival
# Does abiraterone prior to docetaxel decrease efficacy of taxanes?

<table>
<thead>
<tr>
<th></th>
<th>VENICE&lt;sup&gt;1&lt;/sup&gt; DOC/Pbo n=612</th>
<th>De Bono&lt;sup&gt;2&lt;/sup&gt; ABI→DOC n=35</th>
<th>Schweizer&lt;sup&gt;3&lt;/sup&gt; DOC n=95</th>
<th>Schweizer&lt;sup&gt;3&lt;/sup&gt; ABI→DOC n=24</th>
<th>Azad&lt;sup&gt;4&lt;/sup&gt; ABI→DOC n=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOC therapy line</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>PSA decrease ≥50%</td>
<td>63.5%</td>
<td>25.7%</td>
<td>63.0%</td>
<td>38.0%</td>
<td>30.0%*</td>
</tr>
<tr>
<td>Median time to PSA progression</td>
<td>8.1 mths</td>
<td>4.6 mths</td>
<td>6.7 mths</td>
<td>4.1 mths</td>
<td>3.25 mths*</td>
</tr>
<tr>
<td>OS, median</td>
<td>21.2 mths</td>
<td>12.5 mths</td>
<td>-</td>
<td>-</td>
<td>≈12.5 mths*</td>
</tr>
</tbody>
</table>

[2-4] trials are retrospective studies


DOC: Docetaxel; OS: Overall survival
Cabazitaxel PSA response does not seem influenced by prior AR targeted agents

59 men with progressing mCRPC treated with cabazitaxel, 37 of whom had received prior abiraterone and 9 of whom had received prior enzalutamide.

Is there an optimal sequence?
Retrospective cohort of 275 consecutive patients treated with cabazitaxel

- Treatment sequences received:
  - DOC → CAB only (n=158)
  - DOC → ABI or ENZ → CAB (n=68)
  - DOC → CAB → ABI or ENZ (n=43)

- Prognostic factors of overall survival analysed by multivariate stepwise logistic regression
Prognostic factors of survival (multivariate analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (CI 95%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metastatic site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone only</td>
<td>Ref</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Visceral</strong></td>
<td><strong>2.19</strong> (1.42-3.38)</td>
<td></td>
</tr>
<tr>
<td>Bone + lymph node</td>
<td>1.43 (0.01-2.03)</td>
<td></td>
</tr>
<tr>
<td>Lymph node only</td>
<td>0.34 (0.15-0.75)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of response to 1st ADT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>Ref</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>≤ 12 months</strong></td>
<td><strong>1.66</strong> (1.19-2.32)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of active therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOC → CAB only</td>
<td>Ref</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>DOC → CAB → ART</strong></td>
<td><strong>0.33</strong> (0.20-0.54)</td>
<td></td>
</tr>
<tr>
<td><strong>DOC → ART → CAB</strong></td>
<td><strong>0.56</strong> (0.40-0.80)</td>
<td></td>
</tr>
</tbody>
</table>

Oudard S et al, ESMO 2014 (poster 789P) DOC: docetaxel; ART: androgen receptor targeted agent; CAB: cabazitaxel; ABI: abiraterone; ENZ: enzalutamide; PS: performance status; mths: months
Overall survival from initiation of next life-extending therapy post-docetaxel

Trend for better OS (p=0.06) in patients treated with DOC→CABA→ABI or ENZA

Oudard S et al, ESMO 2014 (poster 789P) DOC: docetaxel; ART: androgen receptor targeted agent; CAB: cabazitaxel; ABI: abiraterone; ENZ: enzalutamide; PS: performance status; mths: months
Clinical characteristics of patients by treatment sequence

<table>
<thead>
<tr>
<th></th>
<th>DOC → CAB (n=158)</th>
<th>DOC → CAB → ART (n=43)</th>
<th>DOC → ART → CAB (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yr)</td>
<td>69.0</td>
<td>66.0</td>
<td>68.0</td>
</tr>
<tr>
<td>Gleason 8-10 (%)</td>
<td>52.7</td>
<td>45.9</td>
<td>48.5</td>
</tr>
<tr>
<td>Duration of response to 1st ADT ≤ 12 mths (%)</td>
<td>36.7</td>
<td>18.6</td>
<td>21.6</td>
</tr>
<tr>
<td>ECOG 2 or more (%)</td>
<td>16.2</td>
<td>20.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Pain (%)</td>
<td>66.5</td>
<td>62.8</td>
<td>38.7</td>
</tr>
<tr>
<td>Hb, median (g/dL)</td>
<td>11.8</td>
<td>12.6</td>
<td>12.9</td>
</tr>
<tr>
<td>ALP, median (UI/mL)</td>
<td>140.5</td>
<td>185.0</td>
<td>96.0</td>
</tr>
<tr>
<td>PSA, median (ng/mL)</td>
<td>108.0</td>
<td>86.0</td>
<td>88.0</td>
</tr>
</tbody>
</table>

Patients treated with DOC→CAB→ABI or ENZ more likely to have poor PS and pain at initiation of first life-extending therapy post-DOC

Oudard S et al, ESMO 2014 (poster 789P) DOC: docetaxel; ART: androgen receptor targeted agent; CAB: cabazitaxel; ABI: abiraterone; ENZ: enzalutamide; PS: performance status; mths: months
Conclusions

• Docetaxel (without prednisone) plus ADT provides a major OS benefit versus ADT alone in metastatic hormone-naive PCa

• Short response to ADT in first-line (NOT duration of hormonal therapy) and high NLR seem prognostic and predictive of lower response to AR-targeted agents

• AR-V7 splice variant evaluation in CTCs is very promising but requires validation

• Survival benefit is related to the number of life-extending therapies received → do not miss the window of opportunity for chemotherapy
Updated SIOG guidelines for the management of senior adults with advanced PCa

Jean-Pierre Droz, MD, PhD.
Professor Emeritus of Medical Oncology
Claude-Bernard-Lyon University
Consultant, Centre Léon-Bérard, Lyon, France
Disclosures

Jean-Droz has consulting agreements with:

• Sanofi
SIOG recommendations for senior adults with PCa

Background for the proposal of SIOG guidelines for the management of prostate cancer in senior adults

Jean-Pierre Droz a,b,*, Lodovico Balducci c, Michel Bolla d, Mark Emberton e, John M. Fitzpatrick f, Steven Joniau g, Michael W. Kattan h, Silvio Monfardini i, Judd W. Moui j, Arash Naeim k, Hendrik van Poppel g, Fred Saad l, Cora N. Sternberg m

Management of prostate cancer in older men: recommendations of a working group of the International Society of Geriatric Oncology

Jean-Pierre Droz l, Lodovico Balducci 2, Michel Bolla 3, Mark Emberton 4, John M. Fitzpatrick 5, Steven Joniau 6, Michael W. Kattan 7, Silvio Monfardini 8, Judd W. Moui 9, Arash Naeim 10, Hendrik van Poppel 8, Fred Saad 11 and Cora N. Sternberg 12

Treatment recommendations for older men with prostate cancer should be based on:

- Health status (mainly driven by co-morbidities)
- Patient preferences

NOT Chronological age
SIOG recommendations for senior adults with PCa

- The urological approach in senior men with PCa should be the same as in younger patients
- Internationally accepted guidelines (EAU, NCCN, etc.) are valid, as well as scientifically established national guidelines

Droz JP et al. BJU Int. 2010;106: 462-69
**SIOG classification 2010 for advanced PCa**

**Health status groups: evaluation of chance of living**

- **Group 1** (Healthy)
  - Comorbidity (CISR-G): Grade 0, 1 and 2
  - Independent in IADL
  - No malnutrition

- **Group 2** (Vulnerable, i.e. reversible problem)
  - Comorbidity (CISR-G): at least one Grade 3
  - Dependent in ≥1 IADL
  - At risk for malnutrition

- **Group 3** (Frail, i.e. non-reversible problem)
  - Comorbidity (CISR-G): several Grade 3 or at least one Grade 4
  - Dependency: ≥1 ADL impaired
  - Severe malnutrition

- **Group 4** (Terminal illness)
  - Terminal
  - Bedridden
  - Major comorbidities
  - Cognitive impairment

**Hormonal treatment (1st and 2nd lines, antiandrogen withdrawal, bisphosphonates)**

- Standard chemotherapy
- Standard chemotherapy
- Adapted (weekly?) chemotherapy
- Symptomatic treatment

**Geriatric intervention**

Droz JP et al. BJU Int. 2010, 106: 462-69
Health status screening
Evaluation of dependence - Activities Daily Living (ADL) and Instrumental ADL (IADL)

Activity (ADL)
- Bathing
- Dressing
- Going to toilets
- Moving out of bed (continence)
- Feeding

Activity (IADL)
- Take own medicine without help
- Manage money without help
- Use telephone without help
- Go to places out of walking distance without help

1 IADL: simplified Instrumental Activities of Daily Living (Lawton, Gerontologist 1969, 9: 179)
2 ADL: index of independence in Activities of Daily Living (Katz, JAMA 1963, 185: 914)
Other components of health status

**Nutritional status**
- No weight loss (>5% body weight within last 3 months)
- Moderate malnutrition (weight loss of 5-10%)
- Severe malnutrition (weight loss ≥ 10%)

**Mental health**
- Cognitive impairment

Droz JP et al. BJU Int. 2010, 106: 462-69
## Comorbidities: simplified CIRS-G

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score 1-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>[1] Current mild problem or past significant problem</td>
</tr>
<tr>
<td>Vascular</td>
<td>[2] Moderate disability or morbidity/requires 1st line therapy</td>
</tr>
<tr>
<td>Haematopoietic</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>ENT &amp; larynx</td>
<td></td>
</tr>
<tr>
<td>Upper GI</td>
<td>[3] Severe/constant significant disability / ‘uncontrollable ‘ chronic problems</td>
</tr>
<tr>
<td>Lower GI</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>[4] Extremely severe / immediate treatment required /end organ failure /severe impairment in function</td>
</tr>
<tr>
<td>Genitourinary</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal / integument</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td>Endocrine / metabolic / breast</td>
<td></td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td></td>
</tr>
</tbody>
</table>

Droz JP et al. BJU Int. 2010, 106: 462-69
SIOG guidelines 2014
Management of prostate cancer in older patients: updated recommendations of a working group of the International Society of Geriatric Oncology

Jean-Pierre Droz, Matti Aapro, Lodovico Balducci, Helen Boyle, Thomas Van den Broeck, Paul Cathcart, Louise Dickinson, Eleni Efstathiou, Mark Emberton, John M Fitzpatrick*, Axel Heidenreich, Simon Hughes, Steven Joniau, Michael Kattan, Nicolas Mottet, Stéphane Oudard, Heather Payne, Fred Saad, Toru Sugihara

In 2010, the International Society of Geriatric Oncology (SIOG) developed treatment guidelines for men with prostate cancer who are older than 70 years old. In 2013, a new multidisciplinary SIOG working group was formed to update these recommendations. The consensus of the task force is that older men with prostate cancer should be managed according to their individual health status, not according to age. On the basis of a validated rapid health status screening instrument and simple assessment, the task force recommends that patients are classed into three groups for treatment: healthy or fit patients who should have the same treatment options as younger patients; vulnerable patients with reversible impairment who should receive standard treatment after medical intervention; and frail patients with non-reversible impairment who should receive adapted treatment.

The article is dedicated to the memory of our friend, Professor John M Fitzpatrick, deceased on 14 may 2014

## G-8 Geriatric Screening Tool

<table>
<thead>
<tr>
<th>Question</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?</td>
<td>0 = severe decrease, 1 = moderate decrease, 3 = no decrease</td>
</tr>
<tr>
<td>Weight loss during the last 3 months?</td>
<td>0 = &gt; 3kg; 1 = does not know; 2 = between 1 and 3kg; 3 = none</td>
</tr>
<tr>
<td>Mobility?</td>
<td>0 = bed or chair bound; 1 = able to get out of bed or chair but does not go out; 2 = goes out</td>
</tr>
<tr>
<td>Neuropsychological problems?</td>
<td>0 = severe dementia/depression, 1 = mild dementia, 2 = no psychological problems</td>
</tr>
<tr>
<td>BMI (weight in kg/height in m²)</td>
<td>0 = BMI &lt; 19; 1 = BMI 19 to &lt; 21; 2 = BMI 21 to &lt; 23; 3 = BMI ≥ 23</td>
</tr>
<tr>
<td>Takes more than 3 prescription drugs per day?</td>
<td>0 = yes; 1 = no</td>
</tr>
<tr>
<td>In comparison with other people of the same age, how does the patient consider his health status?</td>
<td>0 = not as good; 0.5 = does not know; 1 = as good; 2 = better</td>
</tr>
<tr>
<td>Age</td>
<td>0 = &gt; 85 yr; 1 = 80-85 yr; 2 = &lt; 80 yr</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td><strong>0-17</strong></td>
</tr>
</tbody>
</table>

Bellara CA et al. Annals Oncol 2012; 23: 2166
The G8 cut-off is 14

- >14 → favorable
- 14 or less → Comprehensive Geriatric Evaluation needed

Bellera CA et al. Annals Oncol 2012; 23: 2166-72
Strong prognostic value of G8 for OS

Prospective non interventional study in 937 men aged 70 or older

Kenis C et al, J Clin Oncol 2014; 32: 19-26
G8 Screening

>14
No geriatric assessment requested

≥14
Geriatric assessment requested

Reversible:
• Abnormal ADL: 1 or 2
• Malnutrition
• Depression
• Comorbidities CISR-G grades 1-2

Not reversible:
• Abnormal IADL
• Abnormal ADL ≥3
• Severe malnutrition
• Cognitive impairment
• Comorbidities CISR-G grades 3-4

Geriatric interventions

FIT

VULNERABLE

FRAIL
Principles of the 2014 guideline

Health status evaluation

Group 1 (Healthy)

Group 2 (Vulnerable, i.e. reversible problem)

Group 3 (Frail, i.e. non reversible problem)

Group 4 (Terminal illness)

Geriatric Screening with G-8 tool

Standard treatment as for younger patients

Standard treatment as for younger patients

Symptomatic management including adapted specific treatments

Only palliative treatment

Readaptation

Metastatic hormone-sensitive PCa Panel consensus

• ADT is the first-line treatment in hormone-sensitive metastatic PCa
• Bone mineral status evaluation and prevention of osteoporotic fracture in high-risk patients recommended
• CHAARTED* results were not yet available at the time of guideline submission

*Sweeney C et al. J Clin Oncol 2014;32(June 20 suppl):abstract LBA2
Metastatic CRPC – First-line Panel consensus

- Docetaxel (75 mg/m² q3w) is suitable for both fit and vulnerable older patients
- Docetaxel weekly or an every-2-week regimen should be considered in frail patients.
- Abiraterone is suitable in the first-line setting in asymptomatic or mildly symptomatic patients without visceral metastases
- Bone targeted drugs are indicated in the prevention of bone loss, and in the treatment of patients with bone metastases

Metastatic CRPC – Post-docetaxel Panel consensus

- Cabazitaxel, abiraterone and enzalutamide are now available for second-line therapy, but careful monitoring is needed in older patients
- The order in which these therapies should be given is a topic for further research
- Palliative treatments include radiotherapy, radiopharmaceuticals, bone-targeted therapies, surgery, and medical treatments for pain and symptoms

Take home message

• PCa in senior adults is a public health problem
• PCa evaluation in senior adults is not different from younger patients
• Efficacy of PCa treatments for localized and advanced therapies is similar in younger and older patients
• The critical issue in decision making process is to adequately estimate the risk of death due to PCa and that due to health status
• Health status warrants an evaluation
Conclusions