Conflicts of Interest Disclosure

Alan Horwich

I have no personal conflicts of interest relating to prostate cancer.
1 Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
C. Parker, S. Gillessen, A. Heidenreich & A. Horwich, on behalf of the ESMO Guidelines Committee
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MANAGEMENT OF PROSTATE CANCER

Treatment “windows”

Subclinical
Localised
PSA only recurrence

Asymptomatic metastases
Symptomatic metastases
Castration resistant
Post docetaxel

Palliative care

20 years
Issues in the diagnosis of prostate cancer

• Screening
  o Interpretation of “benefit vs cost” in European trial

• Is PSA a good tumour marker?
  o Does it help selection for biopsy or treatment?

• Role of staging techniques
  o Lymphadenectomy, Choline PET, PSMA-PET?
Issues in the management of early prostate cancer

• Who needs an attempt at curative treatment?
  o Often indolent cancer in an elderly population

• Outcomes of different radical treatments.
  o Radiotherapy, Brachytherapy, Prostatectomy

• Current therapeutic developments
  o Robotic surgery; IMRT, Dose Escalation.
  o Focal therapies
NCCN: National Comprehensive Cancer Network

www.nccn.org

Recurrence risk

• Low: T1/T2a and Gleason 2-6 and PSA<10
• Intermediate: T2b/c or Gleason 7 or PSA 10 - 20
• High: T3a or Gleason 8-10 or PSA >20
• Very High: T3b/T4

*Patients with multiple adverse factors may be shifted into the next higher risk group
20-Year Outcomes Following Conservative Management of Clinically Localized Prostate Cancer

Watchful Waiting

Prostate Ca

Other causes

Cumulative mortality

Albertsen, P. C. et al. JAMA 2005;293
Issues in metastatic prostate cancer

- When to start treatment
  - Should we use “palliative” treatments before any symptoms?

- Sequence of drugs
  - When to bring in cytotoxics

- Role/timing of new agents
  - Abiraterone, Enzalutamide, Radium-223, Cabazitaxel,
Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

C. Parker¹, S. Gillessen², A. Heidenreich³ & A. Horwich⁴, on behalf of the ESMO Guidelines Committee

¹Royal Marsden Hospital, Sutton, UK; ²Department of Oncology/Hematology, Kantonsspital St Gallen, St Gallen, Switzerland; ³Department of Urology, Uniklinik RWTH Aachen, Aachen, Germany; ⁴Institute of Cancer Research, Sutton, UK

management of advanced/metastatic disease

recommendations

- Continuous ADT is recommended as first-line treatment of metastatic, hormone-naïve disease [I, A].
- Men starting ADT should be informed that regular exercise reduces fatigue and improves quality of life [31] [I, A].
- ADT plus docetaxel is recommended as first-line treatment of metastatic, hormone-naïve disease in men fit enough for chemotherapy [I, A].
Androgen Deprivation in M1 Disease

- 917 men with M1 disease treated 2005-2014 in the control arm (androgen deprivation)
- Median FFS 11.2 months (IQR 5.1-28.8 months)
- Median overall survival 42.1 months (IQR 22.7-90.7 months)
HR: 1.10, 90% CI 0.99-1.23
This CI does not exclude a 20% detriment so IAD is not recommended
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ADT Androgen deprivation therapy
Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial

- 385 M1 hormone-naïve: randomised 2004-2008 (median FU 50 months).
- No difference in overall survival (59 months vs 54)

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Gravis G, Fizazi K et al 2013.
Lancet Oncol
Chemo-hormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

CHAARTED Trial

790 M1 patients, 2006-2012
6x docetaxel at 75mg/m2

Median Overall Survival 57 months vs 44

HR similar over all subgroups

*Sweeney* et al 2015  NEJM 373: 737-46
Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

2962 men randomised in 4 treatment groups:

1184 men Standard of Care (SOC)
593 men SOC plus zoledronic acid (2 years)
592 men SOC plus docetaxel x6
593 men SOC plus zoledronic acid plus docetaxel

PATIENTS

<table>
<thead>
<tr>
<th>M1</th>
<th>1817</th>
<th>61%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N+/x</td>
<td>448</td>
<td>15%</td>
</tr>
<tr>
<td>N0M0</td>
<td>697</td>
<td>24%</td>
</tr>
</tbody>
</table>

James et al. Lancet 2015, Open access
STAMPEDE Results

Zoledronate results are the same than CALGB 90212; Smith et al 2014

FFS Failure-free survival
OS Overall survival

James et al. Lancet 2015,

HR 0.76
P<0.005
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Treatment of castrate-resistant prostate cancer

Recommendations

- Abiraterone or enzalutamide are recommended for asymptomatic/mildly symptomatic men with chemotherapy-naïve metastatic CRPC [I, A].
- Radium-223 is recommended for men with bone-predominant, symptomatic metastatic CRPC without visceral metastases [I, A].
- Docetaxel is recommended for men with metastatic CRPC [I, A].
- Sipuleucel-T is an option in asymptomatic/mildly symptomatic patients with chemotherapy-naïve metastatic CRPC [II, B].
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- Sipuleucel-T is an option in asymptomatic/mildly symptomatic patients with chemotherapy-naïve metastatic CRPC [II, B].

- In patients with metastatic CRPC in the post-docetaxel setting, abiraterone, enzalutamide, cabazitaxel and radium-223 (in those without visceral disease) are recommended options [I, A].
Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial

Penson et al 2016
Enzalutamide post-docetaxel

AFFIRM Trial. Scher et al 2012
### Selected AEs in COU-301 (Abiraterone) and AFFIRM (Enza)

#### COU-301

<table>
<thead>
<tr>
<th>Adverse event (AE)</th>
<th>AA + P</th>
<th>PL + P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Fluid retention or edema</td>
<td>31%</td>
<td>2%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>17%</td>
<td>3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10%</td>
<td>%</td>
</tr>
<tr>
<td>Cardiac disorders*</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>LFT abnormalities</td>
<td>10%</td>
<td>3%</td>
</tr>
</tbody>
</table>

#### AFFIRM

<table>
<thead>
<tr>
<th>Adverse event (AE)</th>
<th>Enzalutamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>34%</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>12%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>21%</td>
<td>1%</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>LFT Abnormalities*</td>
<td>8%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Seizure</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

AA Abiraterone acetate
P Prednisone
PL Placebo
Radium-223: ALSYMPCA Trial

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)

Time to First Symptomatic Skeletal Event

- Hazard ratio, 0.66 (95% CI, 0.52–0.83)
- P<0.001
- Radium-223 (median time to first symptomatic skeletal event, 15.6 mo)
- Placebo (median time to first symptomatic skeletal event, 9.8 mo)

## Phase III CRPC Trials Showing OS Benefit

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prior Therapy</th>
<th>Symptom Improvement/Delay</th>
<th>Control</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel</strong></td>
<td>Chemo-naïve</td>
<td>+</td>
<td>Mitox</td>
<td>2.4, 0.76</td>
</tr>
<tr>
<td><strong>Sipuleucel-T</strong></td>
<td>+/- chemo</td>
<td>-</td>
<td>Placebo</td>
<td>4.1, 0.78</td>
</tr>
<tr>
<td><strong>Cabazitaxel</strong></td>
<td>Post-docetaxel</td>
<td>+/-</td>
<td>Mitox</td>
<td>2.4, 0.70</td>
</tr>
<tr>
<td><strong>Abiraterone</strong></td>
<td>Post-docetaxel</td>
<td>+</td>
<td>Prednisone</td>
<td>4.6, 0.74</td>
</tr>
<tr>
<td><strong>Enzalutamide</strong></td>
<td>Post-docetaxel</td>
<td>+</td>
<td>Placebo</td>
<td>4.8, 0.63</td>
</tr>
<tr>
<td><strong>Radium-223</strong></td>
<td>+/- chemo</td>
<td>+</td>
<td>Placebo</td>
<td>3.6, 0.70</td>
</tr>
<tr>
<td><strong>Abiraterone</strong></td>
<td>Chemo-naïve</td>
<td>+</td>
<td>Prednisone</td>
<td>4.4, 0.81</td>
</tr>
<tr>
<td><strong>Enzalutamide</strong></td>
<td>Chemo-naïve</td>
<td>+</td>
<td>Placebo</td>
<td>2, 0.70</td>
</tr>
</tbody>
</table>
The optimal sequence or combination of these agents (abiraterone, enzalutamide, radium-223, docetaxel and Sipuleucel-T) is unknown. In practice, sequencing decisions will be made in the light of the distribution, extent and pace of disease, co-morbidities, patient preferences and drug availability.
Role of radiotherapy to the primary in patients with metastases? (EXPERIMENTAL!)

Mouse models of metastasis.
Factors secreted by the primary tumors (e.g., VEGF-A, PIGF, PSAP) are thought to mobilize bone marrow–derived cells that are subsequently attracted to premetastatic sites. The cells of this “premetastatic niche” then release factors that can attract disseminating tumor cells.
6. STAMPEDE FROM 2014

[Diagram showing trial arms and timelines from 2006 to 2021.]

- SOC
- SOC + zoledronic acid
- SOC + docetaxel
- SOC + celecoxib
- SOC + zoledronic acid + docetaxel
- SOC + zoledronic acid + celecoxib
- SOC + (abi)*
- SOC + M1/RT (M1)
- SOC + (enze + abi)**

Accrual - past, Accrual - future, Follow-up.

July 2014: Third new comparison.
Advanced Hormone-naïve Prostate Cancer 2017

- STAMPEDE M1 trial of RT to the primary due to report
- STAMPEDE Abi trial due to report
- Stampede Abi+Enza trial competed recruitment
- Stampede Metformin trial initiated
Prostate Cancer Guidelines

The field is intensively researched. Guidelines need to be up-to-date.

ESMO Guidelines are available online at 
http://www.esmo.org/Guidelines/Genitourinary-Cancers/Cancer-of-the-Prostate

E-updates are added regularly either when standard practice changes or when a medicinal product gains European Medicines Agency approval.

New EMA approvals are also scored with the ESMO MCBS Magnitude of Clinical Benefit Scale