Should Docetaxel be Standard of Care for Patients with Metastatic Hormone Sensitive Prostatic Cancer: Pros

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Management of advanced prostate cancer (PCa): Current options available

- **Metastatic castration-sensitive PCa**
  - LHRH agonists
  - Anti-androgens
  - LHRH antagonists
  - Docetaxel* (not licenced)

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

- **mCRPC post-docetaxel**
  - Cabazitaxel
  - Abiraterone
  - Enzalutamide
  - Radium-223

*CRPC: castration-resistant prostate cancer; LHRH: luteinising hormone-releasing hormone
*Sweeney C et al. J Clin Oncol 2014;32 (June 20 suppl):abstract LBA2– Docetaxel is not licenced in this population
<table>
<thead>
<tr>
<th>First Author</th>
<th>No. of Pts</th>
<th>Treatment Arms</th>
<th>Median PFS (m)</th>
<th>Median OS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy, 1976-1980</td>
<td>246</td>
<td>A: DES/orch; B: DES+CTX; C: CTX+Estramustine</td>
<td>Not reported</td>
<td>23 months in all arms</td>
</tr>
<tr>
<td>Murphy 1980-1983</td>
<td>319</td>
<td>A: DES/orch B: DES/orch+CTX+Dox C: Estramustine</td>
<td>15 months in all arms</td>
<td>33 months in all arms</td>
</tr>
<tr>
<td>Osborne 1982-1986</td>
<td>143</td>
<td>A: Flut/orch B: Flut/orch+epirubicin</td>
<td>A: 15 B: 18 (P=0.8)</td>
<td>A: 25.6 B: 22.0 (P=0.55)</td>
</tr>
<tr>
<td>Pummer 1983-1991</td>
<td>145</td>
<td>A: Orchieotomy B: Orch+estramustine</td>
<td>A: 12 B: 22 (P=&lt;0.02)</td>
<td>A: 18 B: 30 (P=0.12)</td>
</tr>
<tr>
<td>Janknegt 1989-1990</td>
<td>419</td>
<td>A: Orchieotomy B: Orch+Mitomycin C</td>
<td>A: 17 B: 24 (P=0.3)</td>
<td>A: 24 B: 27 (NS)</td>
</tr>
<tr>
<td>Boel, 1988-1991</td>
<td>148</td>
<td>A: Orchieotomy B: Orch+Mitomycin C</td>
<td>A: 29 B: 26 (P=0.64)</td>
<td>A: 31 B: 31 (NS)</td>
</tr>
<tr>
<td>De Reijke 1990-1995</td>
<td>189</td>
<td>A: Orchieotomy B: Orch+Mitomycin C</td>
<td>A: 12 B: 12 (P=0.67)</td>
<td>A: 26 B: 22 (P=0.04)</td>
</tr>
<tr>
<td>Kuriyama 1990-1992</td>
<td>136</td>
<td>A: DES or Orchieotomy B: DES or Orch + UFT</td>
<td>A: 30 B: 72 (P=0.06)</td>
<td>A: 67 B: &gt;96 (P=0.13)</td>
</tr>
<tr>
<td>Noguchi 1995-1998</td>
<td>51</td>
<td>A: LHRH + FLT; B: LHRH + estramustine</td>
<td>A: 14.6 B: 25.4(P=0.03)</td>
<td>A: 30 B: 30 (NS)</td>
</tr>
<tr>
<td>Millikan 1996-2003</td>
<td>286</td>
<td>A: LHRH or Orch B: LHRH/Orch + ketoc + Dox+vinb+estramustine</td>
<td>A: 24 B: 35 (P=0.39)</td>
<td>A: 64 B: 72(P=0.41)</td>
</tr>
<tr>
<td>Smith (SWOG) 2001-2005</td>
<td>35 (High risk)</td>
<td>CAD + Palcitxel, VP-16 +Estramustine</td>
<td>13</td>
<td>38</td>
</tr>
</tbody>
</table>
"Traditional" use of chemotherapy for CRPC

Survival in TAX-327 Study

- Docetaxel 3wkly
- Mitoxantrone 3 wkly

Median = 16.5 months
Median = 18.9 months (p=0.009)

HR=0.76 (0.62-0.94)
Early Chemo+ADT: The debate

Pro
- Attack de-novo testosterone independent clones early - allow ADT to keep PrCa in remission longer
- Some patients at the time of progression are too frail for chemo.

Con
- ADT will take cells out of cycle and be less responsive to cytotoxics
- Some patients respond for a long time and never need chemotherapy
Timing of chemotherapy – ADT vs ADT + Docetaxel

• Trials
  - CHAARTED – M1 (Predominantly high risk)
  - GETUG-15 – M1
  - STAMPEDE – M1 and High risk M0
  - GETUG-12 – High risk M0
  - RTOG 0521 – High risk M0
Learning Objectives

1. Clinical trial results that have only been published in abstract form and presented at Scientific Meetings should be interpreted cautiously.

2. The outcomes observed in a population of men who met protocol specific criteria and deemed “fit for chemotherapy” can not be extrapolated to all men at the same point in the disease.

   “High volume disease” as defined includes a broad range of disease extent and prognoses.

3. “Early adoption” has risks, and physicians are cautioned on the use of approaches where the true risk/benefit ratio can not be explained.

4. Delaying progression may be beneficial but does not assure a survival benefit.

5. A range of systemic options are now available for men with metastatic prostate cancer, but at present we do not know the optimal timing or sequence to use them to maximize benefit for an individual patient.

Presented By Howard Scher at 2015 ASCO Annual Meeting
All of This Changed After the CHAARTED Presentation in the 2014 ASCO Plenary Session

The final clinical interpretation was very positive:

6 cycles of docetaxel in addition to ADT represents an appropriate option.

The benefit in patients with a high volume of metastasis is clear and justifies the treatment burden.

Christopher Sweeney, ASCO, 2014
Role of chemotherapy for hormone-naïve PC

Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial

Gwenaëlle Gravis, Karim Fizazi, Florence Joly, Stéphane Oudard, Franck Piriou, Benjamin Esterni, Igor Latorzeff, Remy Delva, Ivan Krakowski,

Lancet Oncol 2013; 14: 149-58

31/05/2015
GETUG-15

PFS (biochemical)

OS

Gwenaelle, Lancet Oncol 2013
E3805 CHAARTED Treatment

STRATIFICATION
- Extent of Mets: High vs Low
- Age: ≥ 70 vs < 70yo
- ECOG PS: 0-1 vs 2
- CAB: >30 days vs Yes vs No
- SIRE Prevention: Yes vs No
- Prior Adjuvant ADT: <12 vs >12 months

RANDOMIZE

ARM A:
- ADT + Docetaxel 75mg/m2 every 21 days for maximum 6 cycles

ARM B:
- ADT (androgen deprivation therapy alone)

Evaluate every 3 weeks while receiving docetaxel and at week 24 then every 12 weeks

Evaluate every 12 weeks

Follow for time to progression and overall survival

Chemotherapy at investigator's discretion at progression

- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

Presented By Christopher Sweeney at 2014 ASCO Annual Meeting
Primary endpoint: Overall survival

HR=0.61 (0.47-0.80) p=0.0003
Median OS:
ADT + D: 57.6 months
ADT alone: 44.0 months

Presented By Christopher Sweeney at 2014 ASCO Annual Meeting
## Secondary Endpoint

<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>ADT + Doc (N=397)</th>
<th>ADT alone (N=393)</th>
<th>P-value</th>
<th>Hazard Ratio (95% CI*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA &lt;0.2 ng/mL at 6 months</td>
<td>27.5%</td>
<td>14.0%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>PSA &lt;0.2 ng/mL at 12 months</td>
<td>22.7%</td>
<td>11.7%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Median time to CRPC - biochemical, symptoms, or radiographic (months)</td>
<td>20.7</td>
<td>14.7</td>
<td>&lt;0.0001</td>
<td>0.56 (0.44, 0.70)</td>
</tr>
<tr>
<td>Median time to clinical progression - symptoms or radiographic (months)</td>
<td>32.7</td>
<td>11.8</td>
<td>&lt;0.0001</td>
<td>0.49 (0.37, 0.65)</td>
</tr>
</tbody>
</table>

*CI: confidence intervals
The Top Line Results: No Survival Benefit in GETUG15 and a Significant One in CHAARTED

**GETUG15**

- Median OS: ADT + D: 58.9 [50.8-69.1]
- ADT alone: 54.2 [44.2-NR]
- HR: 1.01 [0.7-1.4]
- p=0.95

**CHAARTED**

- Median OS: ADT + D: 57.6 mos.
- ADT alone: 44.0 mos.
- HR: 0.61 (0.47, 0.80)
- P=0.003

**Median follow up:** 83 months

**Median follow up:** 29 months

Gravis et al. GU ASCO, 2015

Sweeney et al. ASCO, 2014

Presented By Howard Scher at 2015 ASCO Annual Meeting
Key Differences: GETUG15 Used More Docetaxel and Had Longer Follow-Up While CHAARTED Was Larger With More High Volume Patients

<table>
<thead>
<tr>
<th></th>
<th>GETUG-15</th>
<th>CHAARTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total enrolled</td>
<td>385</td>
<td>790</td>
</tr>
<tr>
<td>De novo metastatic</td>
<td>75%</td>
<td>71%</td>
</tr>
<tr>
<td>Initiation of ADT</td>
<td>2 months or less</td>
<td>4 months or less</td>
</tr>
<tr>
<td>Deaths</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td># of Docetaxel Cycles</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Follow-up</td>
<td>83 months</td>
<td>29 months</td>
</tr>
<tr>
<td>High Volume</td>
<td>48% (193)</td>
<td>65% (514)</td>
</tr>
</tbody>
</table>

Presented By Howard Scher at 2015 ASCO Annual Meeting
The Greatest Benefit in CHAARTED Was in Patients With High Volume Disease

High Volume:
4 or More Bone Lesions,
1 Beyond the Axial Skeleton
or Visceral Spread

Low Volume

Sweeney et al. ASCO, 2014 and ESMO, 2014
Applying The CHAARTED Disease Extent Metrics To GETUG15 Did Not Change The Outcome and the Absolute Survival Difference is Small

GETUG15

High Volume

Median OS
ADT + D: 39 [28-52.6]
ADT alone: 35.1 [29.9-44.2]
HR: 0.8 [0.6-1.2]
p=0.35

Low Volume

Gravis et al. GU ASCO, 2015

Median OS
ADT + D: 83.1 [69.5-NR]
ADT alone: NR [61.8-NR]
HR: 1.0 [0.6-1.5]
p=0.87

Sweeney et al. ASCO, 2014 and ESMO, 2014

Median OS:
ADT + D: 49.2 months
ADT alone: 32.2 months
HR: 0.60 (0.45-0.81)
p=0.0005

Median OS:
ADT + D: Not reached
ADT alone: Not reached
HR: 0.63 (0.34-1.17)
p=0.1398

Presented By Howard Scher at 2015 ASCO Annual Meeting
Both Studies Showed a Significant Improvement in Time to Progression, a Survival Benefit Was Only Seen in CHAARTED

**GETUG15**
- Median TTP: ADT: 9.2 [8.3-12.2]
- ADT + D: 15.2 [12-21.2]
- HR (95% CI): 0.6 [0.5-0.8]
- P = 0.0021

**CHAARTED**
- Median time to CRPC: ADT + D: 16.4 months
- ADT alone: 9.1 months
- P = 0.0001
- HR: 0.52 (95% CI: 0.40-0.67)

Gravis et al. GU ASCO, 2015

Sweeney et al. ASCO, 2014 and ESMO, 2014

Presented By Howard Scher at 2015 ASCO Annual Meeting
The ADT+D Arm in **CHAARTED** Received 25% More Courses of a Life Prolonging Therapy and 50% More Taxane than the ADT+D Arm in GETUG

<table>
<thead>
<tr>
<th></th>
<th>GETUG-15</th>
<th>CHAARTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADT + D</td>
<td>192</td>
<td>397</td>
</tr>
<tr>
<td>ADT</td>
<td>193</td>
<td>393</td>
</tr>
<tr>
<td>Total Enrolled</td>
<td><strong>142 (74%)</strong></td>
<td><strong>145 (36%)</strong></td>
</tr>
<tr>
<td>Total Failed</td>
<td><strong>146 (81%)</strong></td>
<td><strong>174 (44%)</strong></td>
</tr>
</tbody>
</table>

Courses Life Prolonging Rx.  
- ADT + D: 277 (144%)  \( \text{Ratio} = \frac{277}{142} = 1.94 \)  
- ADT: 150 (78%)  \( \text{Ratio} = \frac{150}{146} = 1.02 \)  
- Total: 603 (151%)  \( \text{Ratio} = \frac{603}{255} = 2.37 \)

Taxane Only  
- ADT + D: 489 (123%)  \( \text{Ratio} = \frac{489}{277} = 1.76 \)  
- ADT: 122 (63%)  \( \text{Ratio} = \frac{122}{150} = 0.81 \)  
- Total: 158 (40%)  \( \text{Ratio} = \frac{158}{489} = 0.32 \)

Presented By Howard Scher at 2015 ASCO Annual Meeting
CHAARTED Vs GETUG
Prostate cancer drug 'extends lives'

Early treatment with a chemotherapy drug extends the lives of patients with advanced prostate cancer by nearly two years, a major study shows.

Docetaxel is normally given after hormone treatment has failed.

But results, to be presented at the American Society of Clinical Oncology, will show earlier treatment can extend life expectancy from 43 to 65 months.

‘Game-changing’

Cancer Research UK said the results were "important" and "show that it should be given earlier in a man’s treatment”.

Dr Ian Eremin, the director of research at Prostate Cancer UK, said: "The findings of this trial are potentially game-changing - we can’t wait to see the full results.

"Chemotherapy is currently one of the last-resort treatments for advanced prostate cancers.

"If it is shown to have a much greater impact on survival when prescribed earlier and alongside hormone therapy, that’s incredibly exciting, and we would want to see this brought in to the clinic so it can benefit men without delay.”
Inclusion criteria

**Newly-diagnosed**
- Metastatic
- Node-Positive
- ≥2 of: Stage T3/4
  - PSA ≥ 40ng/ml
  - Gleason 8-10

**All patients**
- Fit for all protocol treatment
- Fit for follow-up
- WHO performance status 0-2
- Written informed consent

**Relapsing after previous RP or RT with ≥1 of:**
- PSA ≥ 4ng/ml and rising with doubling time < 6m
- PSA ≥ 20ng/ml
- Node-positive
- Metastatic

**Full criteria**
www.stampedtrial.org
Accrual

Comparison
Open: Oct-2005
Closed: Mar-2013
Accrual: 2962

Number of patients
1184 A Standard-of-care (SOC)
593  B SOC + zoledronic acid
592  C SOC + docetaxel
593  E SOC + zoledronic acid + docetaxel
Docetaxel: Failure-free survival

SOC: 750 FFS events
SOC+Doc: 371 FFS events

HR (95% CI): 0.62 (0.54, 0.70)
P-value: <0.0000000001*

Non-PH p-value: 0.0002

Restricted mean FFS time:
SOC: 35.3m
SOC+Doc: 44.4m
Diff (95% CI): 9.1m (6.3, 11.9m)

*exact p-value 0.0000000000002014
Docetaxel: Survival

Median OS (95% CI)
SOC 67m (60, 91m)
SOC+Doc 77m (70, NR)

HR (95%CI) 0.76 (0.63, 0.91)
P-value 0.003

Non-PR p-value 0.51

Restricted mean OS time
SOC 58.8m
SOC+Doc 63.4m
Diff (95%CI) 4.6m (1.8, 7.3m)
Docetaxel: Survival – M1 Patients

- SOC: 343 deaths
- SOC+Doc: 134 deaths
- HR (95%CI): 0.73 (0.59, 0.89)
- P-value: 0.002

Non-Philpago p-value: 0.23

Median OS (95% CI)
- SOC: 43m (24, 83m)
- SOC+Doc: 65m (27, NR)

Restricted mean OS time
- SOC: 49.3m
- SOC+Doc: 56.1m
- Diff (95%CI): 6.8m (2.8, 11.0m)
# Effect of docetaxel by metastases at entry

## Failure free Survival

<table>
<thead>
<tr>
<th>Mets status</th>
<th>FFS</th>
<th>No.</th>
<th>Haz. Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>229</td>
<td>689</td>
<td>0.57 (0.42, 0.76)</td>
</tr>
<tr>
<td>M1</td>
<td>832</td>
<td>1087</td>
<td>0.62 (0.54, 0.73)</td>
</tr>
<tr>
<td>Overall</td>
<td>1061</td>
<td>1776</td>
<td>0.62 (0.54, 0.70)</td>
</tr>
</tbody>
</table>

## Survival

<table>
<thead>
<tr>
<th>Mets status</th>
<th>OS</th>
<th>No.</th>
<th>Haz. Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>93</td>
<td>689</td>
<td>1.01 (0.65, 1.56)</td>
</tr>
<tr>
<td>M1</td>
<td>477</td>
<td>1087</td>
<td>0.73 (0.59, 0.89)</td>
</tr>
<tr>
<td>Overall</td>
<td>570</td>
<td>1776</td>
<td>0.76 (0.63, 0.91)</td>
</tr>
</tbody>
</table>
# Grade 3+ adverse events at 1 year

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Incidence</th>
<th>Rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOC</td>
<td>71/732</td>
<td>9.7%</td>
<td>(7.6% to 11.8%)</td>
</tr>
<tr>
<td>SOC+ZA</td>
<td>40/377</td>
<td>10.6%</td>
<td>(7.5% to 13.7%)</td>
</tr>
<tr>
<td>SOC+Doc</td>
<td>44/437</td>
<td>10.1%</td>
<td>(7.2% to 12.9%)</td>
</tr>
<tr>
<td>SOC+ZA+Doc</td>
<td>51/450</td>
<td>11.3%</td>
<td>(8.4% to 14.3%)</td>
</tr>
</tbody>
</table>

Early peak in toxicity during chemotherapy seems to settle by 1 year.
Conclusions

- Docetaxel improves survival for hormone-naive prostate cancer
- Zoledronic acid does not improve survival
- Adding both improves survival but offers no obvious benefit over adding just docetaxel
- Multi-arm, multi-stage trials are practicable and efficient

- Docetaxel should be:
  - Considered for routine practice in suitable men with newly-diagnosed metastatic disease
  - Considered for selected men with high-risk non-metastatic disease in view of substantial prolongation of failure-free survival
How similar are the men participating in these studies?

<table>
<thead>
<tr>
<th></th>
<th>Median age</th>
<th>% with mets at presentation</th>
<th>% high risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GETUG-15</td>
<td>64</td>
<td>71%</td>
<td>52%</td>
</tr>
<tr>
<td>CHAARTED</td>
<td>63</td>
<td>75%</td>
<td>65%</td>
</tr>
<tr>
<td>STAMPEDE</td>
<td>65</td>
<td>Most of them</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*high-volume” disease was defined as visceral metastases and/or ≥4 bone metastases with at least one metastasis beyond the pelvis or vertebral column.

These trials do **NOT** represent men with slowly progressive disease who develop metastases several years after diagnosis (+/- local treatment).
Forest plot of overall survival for the 3 studies
(thanks to Dr Eitan Amir)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAARTED</td>
<td>30.3%</td>
<td>0.61 [0.47, 0.80]</td>
</tr>
<tr>
<td>GETUG-15</td>
<td>30.8%</td>
<td>0.90 [0.70, 1.18]</td>
</tr>
<tr>
<td>STAMPEDE</td>
<td>38.9%</td>
<td>0.73 [0.59, 0.89]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>100.0%</td>
<td>0.74 [0.60, 0.90]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 4.26$, df = 2, $P = 0.12$
Test for overall effect: $Z = 2.92$, $P = 0.003$

* weight by inverse variance

Presented By Ian Tannock at 2015 ASCO Annual Meeting
RECOMMENDATION #1

Men with high-risk metastatic prostate cancer, especially those presenting with metastases at or soon after diagnosis, who are judged fit to receive chemotherapy, should be offered 6 cycles of docetaxel in addition to ADT.
Role of chemotherapy for localized high-risk PC (M0) after radiation therapy

Overall Survival

4 yr OS: 93% vs. 89%
HR 0.70 (90% CI: 0.51-0.98)
Given that only RTOG-0521 reports a difference in overall survival (93% vs 89%, p=0.04 one-sided)....

....is this sufficient evidence to recommend docetaxel +ADT after radiotherapy for men with M0 disease?
Should we consider these results a practice change: **YES in mHSPC**

- Two large randomized trials have shown a robust and clinically meaningful survival benefit by the addition of docetaxel to ADT in men with mHSPC (13.6&15 months survival benefit in CHRRTED and STAMPEDE in metastatic population)

- The metaanalysis in the LANCET ONCOLGY including 3 main studies with different populations with absolute benefit of 9% at 4 years in patients with mHSPC,mixed populations with low risk group in 50% in the french trial(GETUG-15)

- For localized disease patients the median survival is not reached

- **Failure Free survival was statistically significant in both M0&M1 groups in STAMPEDE trial**

RECOMMENDATION #2
Men with localized M0 prostate cancer who are to receive local treatment with radiotherapy should NOT be offered docetaxel in addition to ADT

This opinion might change with longer follow-up of the GETUG-12, STAMPEDE and RTOG 0521 trials
How times have changed!

A Reevaluation of Nonhormonal Cytotoxic Chemotherapy in the Treatment of Prostatic Carcinoma

By Mario A. Eisenberger, Richard Simon, Peter J. O'Dwyer, Robert E. Wittes, and Michael A. Friedman


Is There Evidence That Chemotherapy Is of Benefit to Patients With Carcinoma of the Prostate?

By Ian F. Tannock


The evolution of medical oncology for prostate cancer

No role for you

30 years later

Oh yes there is
Thank you for your Attention