News in the medical management of prostate cancer

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Potential predictive biomarker for prostate cancer
Background

- Androgen receptor signaling is a pivotal driver of prostate cancer
- PSA is a good marker of androgen signaling activity
- Prostate cancer response to castration is near universal
- Progression following therapy is also universal and nearly always associated with rising PSA
- Response to additional hormonal interventions are frequent
  - Androgen receptor antagonists: bicalutamide, flutamide, nilutamide, enzalutamide
  - Androgen synthesis inhibitors: ketoconazole, aminoglutethamide, adrenalectomy, abiraterone
  - Estrogens
- The newer agents (abiraterone, enzalutamide) are more potent and more active
- Progression after more and more hormonal therapy lines is nearly always associated with rising PSA
Abiraterone Acetate: An Androgen Biosynthesis Inhibitor

Abiraterone improved OS and radiographic PFS in patients with mCRPC post-docetaxel\textsuperscript{1,2}

![Chemical pathway diagram](image)

Androgens

DHEA: dehydroepiandrosterone; DHT: dihydrotestosterone; OS: overall survival; PFS: progression-free survival.

Enzalutamide: An Androgen Receptor Inhibitor

Enzalutamide improved OS and radiographic PFS in patients with mCRPC post-docetaxel

So which should go first?

- There are no clear data
- Toxicity
  - Abiraterone: liver dysfunction, fluid retention, hyperglycemia
  - Enzalutamide: seizures, fatigue
AR-V7: An Important Possible Mechanism of Resistance

- Most abundant AR-spliced variant
- Constitutively active and cannot be blocked by LBD-targeting drugs
- Expression increased around 20-fold in CRPC
  - Still minority compared to FL-AR

**FL-AR**

**AR-V7**

FL-AR: full-length AR; LBD: ligand-binding domain.

http://www.peerviewpress.com/o1/d59
Splice variants of the estrogen and androgen receptors have been known for years now. More recently they are recognized in the androgen receptor, but previously they were noted in the estrogen receptor.

These are generally truncated androgen receptors with a ligand binding domain. The area of the androgen receptor that binds to either testosterone or dihydrotestosterone is deleted. So you have a molecule and an androgen receptor variant that is capable of binding to DNA and potentially stimulating androgen binding sites in DNA and having ligand-independent activity.

AR-V7 is an important AR splice variant that is expressed at approximately 20-fold higher levels in patients with CRPC than in those without. Detection of AR-V7 may be associated with primary and acquired resistance to enzalutamide and abiraterone.
AR-V7

- If a splice variant was detectable in circulating tumor cells in these individuals, the likelihood of them responding to abiraterone or enzalutamide was almost zero. In one case it was zero. The numbers were small, but it was a very potent, negative predictor of response to these agents.
- On the other hand, if the individual didn't have that AR-V7 variant, the likelihood of responding was actually higher than might be predicted, so this could be the first biomarker for distinguishing those individuals who respond to these secondary androgen-signaling agents.
- Researchers found that men with advanced prostate cancer and detection of androgen receptor splice variant-7 (AR-V7) respond to chemotherapy just as well as men who lack the variant.
AR-V7

- Seven of the 17 men in the trial who carried the AR-V7 variant and received chemotherapy experienced a 50% reduction in their prostate-specific antigen (PSA) level.

- In comparing men with (n = 17) and without (n = 20) the gene variant, there was no statistical difference in how much patients' PSA levels declined, how long it took for their cancers to progress or their overall survival. All men received docetaxel or cabazitaxel.

- When some patients take either enzalutamide or abiraterone, the drug stops working, and their cancer grows and spreads. The incidence of AR-V7 among these patients may be as high as 30% to 40%.

- The researchers also detected what they say is an intriguing change among seven of the patients in the study who were AR-V7-positive at the start of their chemotherapy. During the course of that treatment, they converted to AR-V7-negative.

- “The clinical significance of this is unknown, but one hypothesis is that some of these patients could possibly become re-sensitised to enzalutamide or abiraterone”
AR-V7 Detection From CTCs and Subsequent Response to Abiraterone

**Best PSA Response (% Change)**

- AR-V7 Negative: 17/25 = 68.0% (95% CI, 46-85%)
- AR-V7 Positive: 0/6 = 0% (95% CI, 0-46%)

* Increase of more than 100% in best PSA response.
† Patients who had previously received enzalutamide.

CTC: circulating tumor cell.

http://www.peerviewpress.com/01/d59
AR-V7 Detection From CTCs and Subsequent Response to Enzalutamide

**Bar Graph**

- **Y-axis:** Best PSA Response (% Change)
- **X-axis:** Patients
- **Legend:**
  - AR-V7 Negative
  - AR-V7 Positive
- **Stats:**
  - AR-V7 Negative: 10/19 = 52.6% (95% CI, 29–76%)
  - AR-V7 Positive: 0/12 = 0% (95% CI, 0–26%)

**Note:**
- Increase of more than 100% in best PSA response.
- Patients who had previously received abiraterone.

**Log-log Survival Curves**

- **X-axis:** Time, mo
- **Y-axis:** PSA PFS and PFS
- **Legend:**
  - AR-V7 Negative
  - AR-V7 Positive
- **Stats:**
  - HR: 7.4 (95% CI, 2.7–20.6) Log-rank P < .001
  - HR: 8.5 (95% CI, 2.8–25.4) Log-rank P < .001

**Table:**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>AR-V7 Negative</th>
<th>AR-V7 Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19</td>
<td>12</td>
</tr>
</tbody>
</table>


http://www.peerviewpress.com/o1/d59
AR-V7 Summary

- AR-V7 warrants further evaluation as a potential predictive biomarker
  - May be associated with both primary and acquired resistance
  - May have potential to select patients who may not benefit from AR-targeted therapy
  - May help guide sequencing of therapy
  - AR-V7 predictive potential prior to docetaxel should be explored
  - A prospective, randomized trial is necessary to validate AR-V7 as a predictive biomarker
Chemotherapy
New role for Docetaxel
Background

- The survival of men with metastatic disease who progress following ADT continues to improve.
- Before 2004, the median survival was less than 36 months, but it is now more than 5 years, thanks to new therapies approved.
- The standard of care for nearly 10 years has been to initiate ADT for men with metastatic disease followed by docetaxel when the disease became castration-resistant.
So Where Does Chemotherapy Fit In? E3805 – CHAARTED Treatment

Stratification
- Extent of Mets: High vs Low
- Age: ≥70 vs <70 y
- ECOG PS: 0-1 vs 2
- CAB >30 days: Yes vs No
- SRE Prevention: Yes vs No
- Prior Adjuvant ADT: ≤12 vs > 12 mo

Randomize

ARM A:
- ADT + Docetaxel 75 mg/m² every 21 days for maximum 6 cycles
- Evaluate Q3W while receiving docetaxel and at week 24 then every 12 weeks

ARM B:
- ADT Alone
- Evaluate every 12 weeks

Follow for TTP and OS
- Chemotherapy at investigator’s discretion at progression

- Primary Endpoint: OS
- ADT allowed up to 120 days prior to randomization
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication, but no daily prednisone

Selected results from CHAARTED Courtesy of Christopher Sweeney, MBBS.

http://www.peerviewpress.com/o1/d59
CHAARTED Trial: ADT and 6 Cycles of Docetaxel Significantly Improved OS Versus ADT Alone in Men with Hormone Sensitive Prostate Cancer

Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): An ECOG-led phase III randomized trial. (Sweeney et al. abstract LBA2)

STUDY DESIGN AND PATIENTS
A randomized phase III trial to test whether docetaxel added at the time of starting androgen deprivation therapy for hormone naïve metastatic prostate cancer will prolong OS.

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

<table>
<thead>
<tr>
<th>STRATIFICATION</th>
<th>ADT + Doc (N=397)</th>
<th>ADT alone (N=393)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>Range</td>
<td>36-88</td>
<td>39-91</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>344</td>
<td>330</td>
</tr>
<tr>
<td>Other</td>
<td>44</td>
<td>48</td>
</tr>
<tr>
<td>Unknown</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>276</td>
<td>272</td>
</tr>
<tr>
<td>1</td>
<td>114</td>
<td>114</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Volume of Mets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>134</td>
<td>142</td>
</tr>
<tr>
<td>High</td>
<td>263</td>
<td>251</td>
</tr>
<tr>
<td>Gleason Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>96</td>
<td>82</td>
</tr>
<tr>
<td>8-10</td>
<td>240</td>
<td>240</td>
</tr>
<tr>
<td>Unknown</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>PSA (ng/mL) at time of ADT start</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>56.0</td>
<td>50.5</td>
</tr>
<tr>
<td>Range</td>
<td>0.4-8540.1</td>
<td>0.1-8056.0</td>
</tr>
</tbody>
</table>
CHARTED Trial: ADT and 6 Cycles of Docetaxel Significantly Improved OS Versus ADT Alone in Men with Hormone Sensitive Prostate Cancer (Cont’d)

**Efficacy**

- **Primary endpoint:** median OS, ADT + D 57.6 vs 44.0 mos for ADT alone; HR=0.61 (95% CI, 0.47-0.80) P=0.0006.
- **OS by high volume:** 49.2 vs 32.2 mos (HR=0.60 (95% CI 0.45-0.81)) P=0.0006.
- **OS by low volume:** NR vs NR(HR=0.63 (95% CI 0.34-1.17) P=0.1398.

**Secondary Endpoints**

<table>
<thead>
<tr>
<th>Secondary Endpoints</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>19.8</td>
<td>&lt;0.0001</td>
<td>0.49 (0.37-0.65)</td>
</tr>
</tbody>
</table>

**Safety**

<table>
<thead>
<tr>
<th>Non-hematologic (%)</th>
<th>ADT + Docetaxel</th>
<th>N=397</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Colitis/Diarrhea</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Neuropathy-motor</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Neuropathy-sensory</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sudden death</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

**Hematologic (%)**

| Anemia | 1 | <1 | - |
| Thrombocytopenia | - | <1 | - |
| Neutropenia | 3 | 9 | - |
| Febrile Neutropenia | 4 | 2 | - |
| Infection w/ gr3-4 neutropenia | 1 | <1 | - |

**Total % of patients with worst grade heme and non-heme toxicity**

| 17 | 12 | 1 pt |

**Key Take Away**

The combination of standard ADT and 6 cycles of docetaxel significantly improved overall survival compared to standard ADT alone in men with hormone sensitive prostate cancer. 6 cycles of docetaxel in addition to ADT represents an appropriate option for men with metastatic prostate cancer commencing ADT who are suitable for docetaxel therapy. The benefit in patients with a high volume of metastases is clear and justifies the treatment burden; longer follow-up is required for patients with low volume metastatic disease.
Primary Endpoint: Overall Survival

HR: 0.61 (0.47-0.80)
P = .0003
Median OS
ADT + D: 57.6 mo
ADT alone: 44.0 mo

Overall Survival By Extent of Metastatic Disease at Start of ADT

For high-volume metastatic disease, there is a 17-month improvement in median OS from 32.2 months to 49.2 months.


http://www.peerviewpress.com/o1/d59
# ADT + Docetaxel Benefited All Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>780</td>
<td>0.61 (0.47-0.80)</td>
</tr>
<tr>
<td>Age &lt;70 y</td>
<td>612</td>
<td>0.68 (0.50-0.91)</td>
</tr>
<tr>
<td>Age ≥70 y</td>
<td>178</td>
<td>0.43 (0.23-0.78)</td>
</tr>
<tr>
<td>Low Volume Disease</td>
<td>276</td>
<td>0.63 (0.34-1.17)</td>
</tr>
<tr>
<td>High Volume Disease</td>
<td>514</td>
<td>0.60 (0.45-0.81)</td>
</tr>
<tr>
<td>Visc Mts ± BM</td>
<td>125</td>
<td>0.48 (0.23-0.99)</td>
</tr>
<tr>
<td>High-volume (BM only)</td>
<td>387</td>
<td>0.65 (0.46-0.91)</td>
</tr>
<tr>
<td>Race - White</td>
<td>674</td>
<td>0.62 (0.47-0.83)</td>
</tr>
<tr>
<td>Race - Other</td>
<td>92</td>
<td>0.53 (0.17-1.60)</td>
</tr>
<tr>
<td>Gleason Score &lt;8</td>
<td>220</td>
<td>0.41 (0.21-0.80)</td>
</tr>
<tr>
<td>Gleason Score ≥8</td>
<td>480</td>
<td>0.60 (0.43-0.84)</td>
</tr>
<tr>
<td>Prior Local Therapy - No</td>
<td>575</td>
<td>0.66 (0.50-0.89)</td>
</tr>
<tr>
<td>Prior Local Therapy - Yes</td>
<td>214</td>
<td>0.55 (0.23-1.31)</td>
</tr>
<tr>
<td>CAB &gt;30 Days - No</td>
<td>459</td>
<td>0.69 (0.49-0.99)</td>
</tr>
<tr>
<td>CAB &gt;30 Days - Yes</td>
<td>331</td>
<td>0.52 (0.34-0.79)</td>
</tr>
<tr>
<td>SRE - No</td>
<td>443</td>
<td>0.58 (0.40-0.84)</td>
</tr>
<tr>
<td>SRE - Yes</td>
<td>347</td>
<td>0.65 (0.45-0.98)</td>
</tr>
</tbody>
</table>

Adding docetaxel to standard androgen ablation therapy (ie, testosterone suppression) extended survival by more than 1 year in men with newly diagnosed metastatic hormone-sensitive prostate cancer in the phase III E3805 trial, funded by the National Institutes of Health.

As reported at the ASCO Annual Meeting in Chicago 2014, the survival benefit was observed mainly in men with more extensive metastatic disease.
From 2006 to 2012, E3805 enrolled 790 men with newly diagnosed metastatic prostate cancer and randomized them to androgen-deprivation therapy alone vs androgen-deprivation therapy plus six cycles of docetaxel. Of this cohort, 397 were randomized within 4 months of starting ADT to receive docetaxel 75 mg/m² every 3 weeks for 6 cycles.

In the study, about 64% of the patients had high-risk disease.

In accordance with the current standard of care, the 129 patients who progressed on ADT alone were eventually given docetaxel.
Median overall survival was significantly improved with the addition of docetaxel to androgen-deprivation therapy: 57.6 months vs 44 months for androgen-deprivation therapy alone \( (P = .0003) \), representing a 39% reduction in risk of death at every time point assessed. This is an almost unprecedented improvement in survival.

The combination, compared with ADT alone, was particularly effective in the 520 men with high-volume disease, where the increase in survival was 17 months (median overall survival, 49.2 vs to 32.2 months; HR, 0.60; \( P = .0006 \)).

The number of patients who had a significant and major suppression of their prostate-specific antigen (PSA) level was doubled with the combination, "both at the 6-month mark and the 12-month mark".

Median time to progression (developing castrate-resistant prostate cancer) — an elevation in PSA level, new symptoms, or worsening scans — was significantly longer with the combination than with ADT alone (20.7 vs 14.7 months; \( P < .001 \)), as was median time to the harder end point of clinical progression (32.7 vs 19.8 months; \( P < .001 \)).
CHAARTED

- Overall, 28% of patients had grade 3 or 4 events related to treatment.
- The main toxicities associated with docetaxel were febrile neutropenia (6%); sensory neuropathy (1%) and motor neuropathy (1%); and 1 of the 397 patients who received early docetaxel died due to treatment.
In this randomised, open-label, phase 3 study, we enrolled patients in 29 centres in France and one in Belgium. Eligible patients were older than 18 years and had histologically confirmed adenocarcinoma of the prostate and radiologically proven metastatic disease; a Karnofsky score of at least 70%; a life expectancy of at least 3 months; and adequate hepatic, haematological, and renal function.

They were randomly assigned to receive to ADT (orchiectomy or luteinising hormone-releasing hormone agonists, alone or combined with non-steroidal antiandrogens) alone or in combination with docetaxel (75 mg/m(2) intravenously on the first day of each 21-day cycle; up to nine cycles). Patients were randomised in a 1:1 ratio.

The primary endpoint was overall survival.

192 patients were randomly allocated to receive ADT plus docetaxel and 193 to receive ADT alone.

Median follow-up was 50 months

Median overall survival was 58.9 months (95% CI 50.8-69.1) in the group given ADT plus docetaxel and 54.2 months (42.2-not reached) in that given ADT alone (hazard ratio 1.01, 95% CI 0.75-1.36).

72 serious adverse events were reported in the group given ADT plus docetaxel, of which the most frequent were neutropenia (40 [21%]), febrile neutropenia (six [3%]), abnormal liver function tests (three [2%]), and neutropenia with infection (two [1%]).

Four treatment-related deaths occurred in the ADT plus docetaxel group (two of which were neutropenia-related), after which the data monitoring committee recommended treatment with granulocyte colony-stimulating factor. After this recommendation, no further treatment-related deaths occurred. No serious adverse events were reported in the ADT alone group.

Docetaxel should not be used as part of first-line treatment for patients with non-castrate metastatic prostate cancer.
Dr. Gravis was involved in the GETUG-AFU 15 study, which is the "major challenge" to the new E3805 results. It examined the same treatments in the same patient population and found no benefit to early docetaxel.

However, GETUG-AFU 15 was much smaller than E3805, and "the number of patients in the ADT-only arm who received subsequent docetaxel for disease progression was 31% in E3805 and 62% in GETUG-15," Dr. Gravis reported.

GETUG-AFU 15 also had much fewer high-volume patients.

"For these reasons, I think that GETUG-AFU 15 does not refute the fact that high-volume patients benefit from chemotherapy. If anything, it confirms that low-risk or low-volume patients should not get chemotherapy until there is better evidence".

Docetaxel and/or Zoledronic Acid for Hormone-Naïve Prostate Cancer: First Survival Results From STAMPEDE

Abstract #5001

Trial Activity: Original Research Arms

STAMPEDE: Initiation

- A: Standard-of-care (SOC) = ADT (+/- RT)
- B: SOC + zoledronic acid
- C: SOC + docetaxel
- D: SOC + celecoxib
- E: SOC + zoledronic acid + docetaxel
- F: SOC + zoledronic acid + celecoxib

STAMPEDE

- Number of patients: 2962
  - A - Standard of care (SOC) – 1184
  - B - SOC + zoledronic acid – 593
  - C – SOC + docetaxel – 592
  - E – SOC + docetaxel + zoledronic acid - 593
The new results come from an analysis of nearly 3000 patients from the British STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial.

Men with newly diagnosed advanced prostate cancer who were starting on androgen-deprivation therapy (ADT) lived on average for 10 months longer when docetaxel was given together with the hormone therapy.

Patients with metastatic disease benefited most profoundly, with a median survival benefit of 21 months.
This is the second study to show that adding chemotherapy up front can improve survival.

This latest trial from the United Kingdom is larger than both of these previous studies, and had a broader patient population, involving about 1800 men with metastatic disease and 1200 with high-risk nonmetastatic prostate cancer.

The STAMPEDE study is an ongoing study with a multistage, multigroup design, which can be modified to drop therapies proven to be ineffective, add new therapies to be evaluated, and also can adapt to changes in the standard of care. For instance, while the trial was in progress, radiation was added to the standard of care of ADT for certain patients.

The multigroup design of the trial also allowed the researchers to test whether adding the bone-targeting drug zoledronic acid (Zometa, Novartis) provided any extra benefit. The results show that it does not.
STAMPEDE

- The results presented by Dr James and colleagues at the meeting come from an analysis of 2962 men with newly diagnosed advanced prostate cancer. About 60% had metastatic disease, the rest had high-risk locally advanced nonmetastatic disease (either node-positive, or with two of three of the following risk factors: stage T3/T4, PSA ≥ 40 ng/mL, or Gleason sum score of 8–10).

- All of these men received standard of care, which was at least 3 years of ADT, with radiation for patients who were suitable. In addition, some men also received docetaxel for six cycles, zoledronic acid for 2 years, or both docetaxel and zoledronic acid.
After a median follow-up of 42 months, 948 men had died. The addition of docetaxel significantly improved median overall survival to 77 months, compared with 67 months for ADT alone. For the subgroup of patients with metastatic disease, the survival benefit was even greater, with median overall survival of 65 vs 43 months on ADT alone. For this group of men with newly diagnosed metastatic prostate cancer, docetaxel upfront should become routine practice. However, in the other subgroup of patients with advanced but not metastatic disease, the difference in survival was not statistically significant, but these survival data are still immature. However, docetaxel prolonged the event-free survival by "a substantial amount," and so it should also be considered in this group.
Zoledronic Acid: Failure-Free Survival

SOC 750 FFS events
SOC + ZA 371 FFS events
HR (95%CI) 0.93 (0.82, 1.05)
$P$ value 0.26

Non-PH $P$ value = .99

Restricted mean FFS time
SOC 35.2m
SOC+Doc 36.9m
Diff (95%CI) 1.7m (-0.8, 4.2m)

Zoledronic Acid: Survival

Median OS (95% CI)
SOC  67m (60, 91m)
SOC+ZA  80m (70, NR)

SOC  405 deaths
SOC+ZA  197 deaths

HR (95%CI)  0.93 (0.79, 1.11)
P value  .44

Non-PH P value = .83

Restricted mean OS time
SOC  58.5m
SOC+Doc  59.5m
Diff (95%CI)  1.0m (-1.4, 3.4m)

Docetaxel: Failure-Free Survival

SOC 750 FFS events
SOC+Doc 371 FFS events

HR (95% CI) 0.62 (0.54, 0.70)
P value <.000000001*

Non-PH P value = .0002

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

*exact P value .000000000002014

Docetaxel: Survival

SOC 405 deaths
SOC+Doc 165 deaths

HR (95%CI) 0.76
(0.63, 0.91)

P value 0.003

Non-PH P value = .51

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

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-PH P value**: .23

**Median OS (95% CI)**:
- SOC: 43m (24, 88m)
- 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)

Zoledronic Acid + Docetaxel: Failure-Free Survival

SOC  750 FFS events
SOC+ZA+Doc  371 FFS events

HR (95%CI)  0.62
(0.54, 0.71)
P value  <.0000000001

Non-PH P value = <.0000000001

Restricted mean FFS time
SOC  35.3m
SOC+ZA+Doc  43.5m
Diff (95%CI)  8.2m (5.5, 11.1m)

Zoledronic Acid + Docetaxel: Survival

SOC: 405 deaths
SOC+ZA+Doc: 181 deaths

HR (95% CI): 0.81 (0.68, 0.97)
P value: 0.02

Non-PH P value: 0.40

Restricted mean OS time
SOC: 58.4m
SOC+Doc: 61.5m
Diff (95% CI): 3.4m (0.5, 6.2m)

STAMPEDE

- There was an increase in toxicity with the addition of docetaxel. Grade 3/4 toxicity was reported by 30% of patients in the standard of care group, by 50% of patients who also took docetaxel, by 32% of patients who also took zoledronic acid, and by 50% of patients who also took both docetaxel and zoledronic acid.

- However, the researchers say the adverse effects were "manageable," and add that very few patients discontinued because of them.
Conclusions:

- Docetaxel improves survival for hormone-naive prostate cancer patients
- 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 for 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
A Phase III Protocol of Androgen Suppression (AS) and Radiotherapy (RT) Versus AS and RT Followed by Chemotherapy With Docetaxel and Prednisone for Localized, High-Risk Prostate Cancer (NRG Oncology/RTOG 0521)

Abstract #LBA5002

### RTOG 0521

#### High risk

<table>
<thead>
<tr>
<th>Stage</th>
<th>Gleason score</th>
<th>Prostate-specific antigen (PSA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any T stage</td>
<td>≥9</td>
<td>&lt;150</td>
</tr>
<tr>
<td>T2</td>
<td>7-8</td>
<td>≥20-150</td>
</tr>
<tr>
<td>≥T2</td>
<td>8</td>
<td>&lt;20</td>
</tr>
</tbody>
</table>

**Randomize**

- **Arm 1**
  - Androgen suppression (24 months) +
  - External RT (8 weeks)

- **Arm 2**
  - Androgen suppression (24 months) +
  - External RT (8 weeks) +
  - Docetaxel beginning 4 weeks after RT (6 cycles)

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RTOG 0521

- RTOG 0521 enrolled 563 patients (mean age, 66 years) with high-risk localized prostate cancer. Patients were randomly assigned to receive standard therapy, which consisted of 24 months of androgen suppression and 8 weeks of external radiotherapy, or standard therapy plus chemotherapy, which consisted of six 21-day cycles of docetaxel plus prednisone starting 28 days after radiotherapy.
- Primary endpoint was overall survival. After a median follow-up of approximately 6 years, the 4-year overall survival rate was significantly higher in the chemotherapy group (93% vs 89%; \( P = .04; \) HR, 0.70, although this did not meet the prestated HR goal of 0.49).
- Other endpoints such as distant metastasis and disease-free survival were also significantly better in the chemotherapy group compared with the control group.
- Although there were more deaths in the control group, the causes of death were "strange" noted Dr Tannock.
- There were seven more prostate cancer deaths in the control group, but this was counter-balanced by six deaths in the experimental group resulting from toxicity or unknown causes compared with none in the control group.
Overall Survival

4 yr OS  93% vs. 89%
HR 0.70 (90%CI: 0.51-0.98)

Biochemical Failure

6 year BF  74% vs. 66%
HR 0.81 (95%CI: 0.58-1.11)

Disease-Free Survival

6 yr DFS 65% vs. 55%
HR 0.76 (95%CI: 0.58-0.99)

Distant Metastasis at Any Time

- AS + RT: Fail 41, Total 281
- AS + RT + CT: Fail 26, Total 282

$P$ value = .05

## Cause of death

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Androgen Suppression + Radiotherapy (n = 59)</th>
<th>Androgen Suppression + Radiotherapy + Chemotherapy (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death resulting from cancer under study</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Death resulting from protocol treatment</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Death resulting from other cause</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Death resulting from secondary primary</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Unknown cause of death</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>
Adverse events definitely, probably or possibly related to treatment

<table>
<thead>
<tr>
<th>Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADT + RT (%)</td>
<td>17</td>
<td>53</td>
<td>21</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ADT + RT + CT (%)</td>
<td>3</td>
<td>29</td>
<td>38</td>
<td>26</td>
<td>1</td>
</tr>
</tbody>
</table>
In a French phase III trial (GETUG 12) reported in *The Lancet Oncology*, Fizazi et al found that the addition of docetaxel and estramustine (Emcyt) to androgen-deprivation therapy (ADT) improved relapse-free survival among patients with high-risk localized prostate cancer.

In the open-label trial, 413 patients with treatment-naive disease and at least one risk factor (stage T3-T4, Gleason score $\geq 8$, prostate-specific antigen [PSA] concentration $> 20$ ng/mL, or pathologic node-positive disease) underwent staging pelvic lymph node dissection and were randomized to ADT (goserelin 10.8 mg every 3 months for 3 years) plus four cycles of docetaxel 70 mg/m$^2$ on day 2 and estramustine 10 mg/kg/d on days 1 to 5 every 3 weeks ($n = 207$) or ADT alone ($n = 206$). Local treatment was administered at 3 months.

The primary endpoint was relapse-free survival in the intention-to-treat population. Follow-up for other endpoints is ongoing.

The chemotherapy and ADT alone groups were balanced for age (median 62 and 62 years), Gleason score (42% and 43% $\geq 8$), pathologic node-positive status (29% in both), and serum PSA level ($> 20$ ng/mL in 59% in both).
GETUG 12

- After a median follow-up of 8.8 years, relapse or death had occurred in 43% of patients in the ADT plus docetaxel/estramustine group, vs 54% of the ADT only group. Eight-year relapse-free survival was 62% (95% confidence interval [CI] = 55%–69%), vs 50% (95% CI = 44%–57%; adjusted hazard ratio = 0.71, \( P = .017 \)).

- Among patients who had received radiotherapy and had data available, 31 (21%) of 151 in the ADT plus chemotherapy group vs 26 (18%) of 143 in the ADT only group had grade \( \geq 2 \) long-term adverse events (\( P = .61 \)). Second cancers were observed in 13% vs 11% (\( P = .57 \)). No treatment-related deaths were reported.

- The investigators concluded: “Docetaxel-based chemotherapy improves relapse-free survival in patients with high-risk localized prostate cancer. Longer follow-up is needed to assess whether this benefit translates into improved metastasis-free survival and overall survival.”
Ian Tannock, an outstanding investigator in prostate cancer field, made a presentation regarding clinical trial design and chemotherapy—an excellent overview of the past decade of clinical trials using docetaxel earlier in the disease.

He pointed out the similarities of the three trials (including the negative GETUG-15 trial reported earlier) and noted that in spite of lack of statistical significance of GETUG-15, it favored docetaxel and that combining the data from all three trials leads to a highly significant test for overall effect of $p = 0.003$, leading him to recommend that men with high-risk metastatic disease at presentation should receive six cycles of chemotherapy as a new standard of care.

Turning to the early use of docetaxel in combination with radiotherapy and ADT in the initial curative-intent treatment as was done in RTOG 0521, he pointed to several potential pitfalls in accepting this as a standard of care. He again combined the other studies (GETUG-12 and STAMPEDE) looking at similar patients and noted that only the RTOG trial showed a difference in overall survival in spite of all three showing improvement in failure-free survival. Given the RTOG trial used a one-sided statistical analysis for finding a marginally significant ($p = 0.04$) improvement in overall survival, he concluded that “chemo delayed is toxicity delayed” and feels that at present adding docetaxel up front to ADT/radiation curative-intent treatment is not warranted.
Comments

- Perhaps the most remarkable slide he presented, however, was a look at his own institution’s experience with using docetaxel in a trial setting as opposed to routine practice. Toxicity increased and efficacy diminished, highlighting the challenges of extrapolating from the generally healthier, better staged and more closely followed patients who enter clinical trials compared to day to day experience.

- Another concern is that based on the abstract data, there is no ability to see who did or did not have access to recently emerging second- and third-line therapies.

- The main question is whether the sequencing of the novel second- and third-line therapies, such as abiraterone or enzalutamide, after initial development of metastatic castration-resistant prostate cancer then followed by chemo is better, worse, or the same as initiation of chemo–hormonal therapy earlier.

- Docetaxel has some significant toxicities and exposure to a patient population who could enjoy a long remission with hormonal therapy (without exposure to chemo and its attendant toxicities ) needs to be considered.
Conclusions

- Chemotherapy, which has traditionally been considered a treatment of last resort for prostate cancer, continues to inch closer to the therapeutic frontline, according to new research presented at the American Society of Clinical Oncology (ASCO) 2015 Annual Meeting.

- On the heels of several recent trials (CHAARTED and STAMPEDE) suggesting a role for docetaxel chemotherapy in metastatic prostate cancer, another trial — RTOG 0521 — suggests it may have even greater benefit at an earlier stage: in high-risk, localized disease.

- "This is the first study that shows a potential survival benefit to using chemotherapy in high-risk patient subset, and I think that for the right patient, the right physician, there will be justification — based on these results — for adding adjuvant docetaxel."