Changing Landscape for Radiation in High-risk Prostate Cancer

Eric Vigneault MD, MSc
COI Disclosure

- Advisory Board Abbvie
- Speaker/sponsorship Sanofi
Changing Landscape for Radiation in High-risk Prostate Cancer:

- Describe the different radiotherapy treatment modalities and their applications in high-risk prostate cancer
- Discuss the role of brachytherapy in high-risk prostate cancer
Changing Landscape for Radiation in High-risk Prostate Cancer:

- Describe the role of LHRHs in radiotherapy treatments in high-risk prostate cancer with durations of treatment.
- Identify the potential opportunities to optimize LHRHs usage in radiotherapy treatment for high-risk prostate cancer in combination with other systemic therapy.
### RT in High Risk PCA: We are Armed with Data

<table>
<thead>
<tr>
<th>Radical RT</th>
<th>Adjuvant/Salvage RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 8531, RTOG 8610, RTOG 9202, RTOG 0924, EORTC 22863, EORTC 22961, TRUOG96 01, SPCG-7, Intergroup T94-0110, ASCENDE-RT, DART 01/05, STAMPEDE, PCS IV</td>
<td>EORTC 22911, SWOG 58794, ARO 96-02, RTOG 0534, RTOG 96-01, EORTC 22043, RTOG 0621, GETUG AFU16, GETUG 17, RADICALS, RAVES</td>
</tr>
</tbody>
</table>
RT + Adjuvant ADT

phase III:
EORTC 22863 et 2296, RTOG 9202, 8531
<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion</th>
<th>n</th>
<th>randomization</th>
<th>Results at 10 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 8531</td>
<td>cT3 or N1 (30%)</td>
<td>945</td>
<td>RT alone 70 Gy (HT at relapse) vs RT + HT (upfront for life)</td>
<td>OS 49 vs 39% CSS 84 vs 78% DM 24 vs 39% (mainly in GS 7-10)</td>
</tr>
<tr>
<td>RTOG 9202</td>
<td>T2c-T4 APS &lt; 150</td>
<td>1554</td>
<td>RT 70 Gy + HT 4 mo +/− adjuvant HT 24 mo</td>
<td>DSS 84 vs 89% DM 23 vs 15% BF 68 vs 52% OS 32 vs 45% (GS 8-10)</td>
</tr>
<tr>
<td>Bolla 1</td>
<td>T1-2 G3 T3-4 N0-1</td>
<td>412</td>
<td>RT 70 Gy +/− HT 36 mo</td>
<td>OS 58 vs 40% CSS 89 vs 69%</td>
</tr>
<tr>
<td>Bolla 2</td>
<td>pN1-2 ou T2c-T4</td>
<td>970</td>
<td>RT 70 Gy + 6 mo HT +/− 30 mo HT</td>
<td>Treatment non equivalent</td>
</tr>
</tbody>
</table>

Modified slides from William Foster, MD
20 y Long term Update RTOG 9202

- Compared to STAD, LTAD improves
  - Disease Free Survival
  - Local Progression
  - Disatnt Metastasis
  - bNED Survival
  - Disease Specific Survival

- For LATD 10% risk reduction, 3% absolute OS difference NS
High risk prostate cancer treated with pelvic radiotherapy and 36 vs 18 months of androgen blockade: results of a phase III randomized trial

Abdenour Nabid1, Nathalie Carrier1, André-Guy Martin2, Jean-Paul Bahary3, Luis Souhami4, Marie Duclos4, François Vincent5, Sylvie Vass6, Boris Bahoric7, Robert Archambault8, Céline Lemaire9

1 Centre Hospitalier Universitaire de Sherbrooke, CA, 2 Centre Hospitalier Universitaire de Québec, CA, 3 Centre Hospitalier Universitaire de Montréal, CA, 4 Centre Universitaire de Santé McGill, CA, 5 Centre Hospitalier Régional de Trois-Rivières, CA, 6 Centre de Santé et Services Sociaux de Chicoutimi, CA, 7 Hôpital Général Juif de Montréal, CA, 8 Hôpital de Gatineau, CA, 9 Hôpital Maisonneuve-Rosemont de Montréal, CA
Randomization from October 2000 to January 2008

**Arm 1**: AB* 36 months + RT**
(n=310) Bicalutamide 50 mg id x 1 month
Goserelin 10.8 mg q 3 months x 12

**Arm 2**: AB* 18 months + RT**
(n=320) Bicalutamide 50 mg id x 1 month
Goserelin 10.8 mg q 3 months x 6

* AB: Neo-adjuvant (4 months), concomitant and adjuvant to RT
** RT: Pelvis 44 Gy - 4 ½ weeks, prostate 70 Gy - 7 weeks

Median follow-up : 77 months
Overall Survival

HR: 1.15 (0.83-1.59), p=0.398
Disease specific survival

HR: 1.13 (0.61-2.08), p=0.153

97.6 (95.9-99.4)
96.4 (94.2-98.6)
p=0.473

87.2 (81.0-93.3)
87.2 (80.9-93.6)
p=0.838
Conclusion

In localized high risk prostate cancer:

- androgen blockade duration can be safely reduced from 36 to 18 months;
- androgen blockade delivered during 18 months could represent a threshold effect with no further gain;
- duration of side effects and treatment costs can be significantly reduced.

Treatment impact on quality of life is now under analysis with 9638 questionnaires (EORTC 30 + PR.25) answered over more than 12 years.
Failure-Free Survival and Radiotherapy in Patients With Newly Diagnosed Nonmetastatic Prostate Cancer:

Data From Patients in the Control Arm of the STAMPEDE Trial

Nicholas D. James, BSc, MBBS, PhD, FRCP, FRCR, Melissa R. Spears, MSc, BSc, Noel W. Clarke, MBBS, FRCS(Eng), ChM(Manch), FRCS(Urol), David P. Dearnaley, MA, MB, BChir, MD, FRCP, FRC, Malcolm D. Mason, MD, FRCP, FRCR, FSB, Christopher C. Parker, BA, BM, BChir, MD, Alastair W. S. Ritchie, MD, FRCSEd, J. Martin Russell, BSc, MB, ChB, MRCP(UK), FRCR, FRCPSG, Francesca Schiavone, PhD, Gerhardt Attard, MD, PhD, Johann S. de Bono, MBChB, MSc, PhD, FRCP, FMedSci, Alison Birtle, MB, BS, MRCP, FRCR, MD, Daniel S. Engeler, MD, Tony Elliott, BSc, MSc, PhD, MBChB, MRCP, FRCR, David Matheson, BSc, PGCE, DipEd, MEd, PhD, FRSA, FHEA, Joe O’Sullivan, MD, FRCR, FFRRCSI, FRCPI, Delia Pudney, MBChB, Narayanan Srihari, MB, BS, Jan Wallace, MB, ChB, FRCR, Jim Barber, MA, DM, FRCR, MRCP, Isabel Syndikus, MD, Mahesh K. B. Parmar, DPhil, MSc, BSc, and Matthew R. Sydes, MSc, CStat
At a Glance

- This research describes the prognosis of men with newly diagnosed, nonmetastatic (M0) prostate cancer and considers the effect of radiotherapy on failure-free survival by nodal involvement (N0 vs N+).
- We hypothesized that radiotherapy was associated with better prognosis in men with M0 prostate cancer, regardless of nodal involvement.
- Survival for men with high-risk M0 disease was higher than anticipated at study inception, with 80% still alive at 5 years.
- Failure-free survival outcomes favored planned use of radiotherapy for patients with both N0M0 (hazard ratio, 0.33 [95% CI, 0.18-0.61]; consistent with previous reported randomized trials) and N+M0 disease (hazard ratio, 0.48 [95% CI, 0.29-0.79]).
- Radiotherapy was tolerable and the toxic effects profile was as expected.
Figure 2. Failure-Free Survival for Reported Radical Radiotherapy Status, in N0M0 and N+M0 Subcohorts
Table 3

Results in Context With Data From Previously Published Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Data Type</th>
<th>Population</th>
<th>Deaths, No./Patients, No.</th>
<th>Radiotherapy Effect, HR (95% CI)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Treatment Groups</th>
<th>Estimates</th>
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</thead>
<tbody>
<tr>
<td>Comparative Data</td>
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<tr>
<td>SPCG-7&lt;sup&gt;e&lt;/sup&gt; 2009</td>
<td>R</td>
<td>Low risk, N0M0</td>
<td>116/875</td>
<td>0.16 (0.12-0.20)</td>
<td>ADT only</td>
<td>10-y PSA-FS, 61%</td>
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<tr>
<td></td>
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<td>10-y PSA-FS, 74%</td>
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<td></td>
<td></td>
<td></td>
<td>10-y OS, 70%</td>
</tr>
<tr>
<td>NCIC PR 3/MRC PR07&lt;sup&gt;f&lt;/sup&gt; 2011/2015</td>
<td>R</td>
<td>N0M0</td>
<td>465/1205</td>
<td>0.31 (0.25-0.39)</td>
<td>ADT only</td>
<td>10-y PFS, 46%</td>
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<td></td>
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<td></td>
<td></td>
<td>10-y OS, 49%</td>
</tr>
<tr>
<td>National Cancer Database&lt;sup&gt;g&lt;/sup&gt; 2015</td>
<td>NR</td>
<td>High-risk M0</td>
<td>7636&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.50 (0.37-0.67)</td>
<td>ADT only</td>
<td>Not given, 5-y OS, 53%</td>
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<td></td>
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<td></td>
<td>Not given, 5-y OS, 72%</td>
</tr>
<tr>
<td>STAMPEDE, 2015&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NR</td>
<td>N0M0</td>
<td>18/180</td>
<td>0.25 (0.13-0.49)</td>
<td>ADT only</td>
<td>5-y FFS, 38%</td>
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<tr>
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<td>5-y OS, 86%</td>
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<tr>
<td>STAMPEDE, 2015&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NR</td>
<td>N1M0</td>
<td>22/177</td>
<td>0.35 (0.19-0.65)</td>
<td>ADT only</td>
<td>5-y FFS, 39%</td>
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<td>5-y OS, 82%</td>
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<td>Reference Data</td>
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<tr>
<td>GETUG-01&lt;sup&gt;h&lt;/sup&gt; 2007</td>
<td>R</td>
<td>N0M0</td>
<td>36/352</td>
<td>Not relevant</td>
<td>RT to prostate</td>
<td>5-y PFS, 66%</td>
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<td>5-y OS, 87%</td>
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<td>5-y PFS, 65%</td>
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<td></td>
<td></td>
<td></td>
<td>5-y OS, 88%</td>
</tr>
<tr>
<td>GETUG-12&lt;sup&gt;i&lt;/sup&gt; 2015</td>
<td>NR</td>
<td>High-risk M0</td>
<td>49/206</td>
<td>Not relevant</td>
<td>ADT with or without RT</td>
<td>8-y RFS, 50%</td>
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<td></td>
<td>8-y OS, 83%</td>
</tr>
<tr>
<td>STAMPEDE, 2015&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NR</td>
<td>Newly diagnosed M0</td>
<td>40/721</td>
<td>Not relevant</td>
<td>ADT with or without RT</td>
<td>5-y FFS, 53%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>5-y OS, 80%</td>
</tr>
</tbody>
</table>

Abbreviations: FFS, failure-free survival; HR, hazard ratio; M0, nonmetastatic; N+, node positive; N0, node negative; NR, nonrandomized; OS, overall survival; PFS, progression-free survival; R, randomized; RT, radiotherapy.

<sup>d</sup>Effect on progression unless otherwise stated.

<sup>e</sup>PR07 had no mandatory nodal staging.

<sup>f</sup>Patients matched by propensity scoring; number of deaths unknown; no analysis on progression.

<sup>g</sup>Data presented within this article.
RT + ADT + Chemo in High Risk

RTOG 9902, 0521, STAMPEDE
Clinical Investigation

A Phase 3 Trial of 2 Years of Androgen Suppression and Radiation Therapy With or Without Adjuvant Chemotherapy for High-Risk Prostate Cancer: Final Results of Radiation Therapy Oncology Group Phase 3 Randomized Trial NRG Oncology RTOG 9902

Seth A. Rosenthal, MD,* Daniel Hunt, PhD,† A. Oliver Sartor, MD,‡ Kenneth J. Pienta, MD,§ Leonard Gomella, MD,‖ David Grignon, MD,¶ Raghu Rajan, MD, # Kevin J. Kerlin, MD,** Christopher U. Jones, MD,* † † Michael Dobelbower, MD, ‡ ‡ William U. Shipley, MD, §§ Kenneth Zeitzer, MD, ‖‖ Daniel A. Hamstra, MD, PhD, ¶¶ Viroon Donavanik, MD, ## Marvin Rotman, MD, *** Alan C. Hartford, MD, † † † Jeffrey Michalski, MD, † † † † Michael Seider, MD, † † † † † Harold Kim, MD, † † † † † † Deborah A. Kuban, MD, ¶¶¶ Jennifer Moughan, MS, † and Howard Sandler, MD † † † † †
Fig. 2. Radiation Therapy Oncology Group 9902. Overall survival by treatment arm for all randomized patients (n=397). Abbreviations: AS = androgen suppression; CT = chemotherapy; HR = hazard ratio; RT = radiation therapy. (CT) with paclitaxel, estramustine, and oral etoposide.
A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521).


J Clin Oncol 33, 2015 (suppl; abstr LBA5002)
Background: High-risk, localized prostate cancer (PCa) patients have a relatively poor prognosis. We hypothesized that the addition of adjuvant docetaxel and prednisone to long-term (24 month) AS and radiation therapy (RT) would improve overall survival (OS).

Methods: RTOG 0521 opened December 2005 and closed August 2009 with targeted accrual of 600 cases. It was designed to detect improvement in 4-year OS from 86% to 93% with a 51% hazard reduction (HR = 0.49). Under a 0.05 1-sided type I error and 90% power, at least 78 deaths were required to analyze the OS endpoint. Patients had 1) Gleason (G1) 7-8, any T-stage, and PSA > 20, or 2) G1 8, ≥ T2, any PSA, or 3) G1 9-10, any T-stage, any PSA. All had PSA ≤ 150. RT dose was 75.6 Gy. CT consisted of 6, 21-day cycles of docetaxel + prednisone starting 28 days after RT.
Conclusions: For high-risk, localized PCa, adjuvant CT improved the OS from 89% to 93% at 4 years. Toxicity was acceptable. This trial was designed with a short OS assessment period and additional follow-up is warranted to determine the long-term benefit of CT to the current standard of care of long-term AS+RT.
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

Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Melissa R Spears, Alastair W S Ritchie, Christopher C Parker, J Martin Russell, Gerhardt Attard, Johann de Bono, William Cross, Rob J Jones, George Thalmann, Claire Armos, David Matheson, Robin Millman, Myooma Alzouabi, Sharon Beesley, Alison J Birtle, Susannah Brock, Richard Cathomas, Prabir Chakraborti, Simon Chowdhury, Audrey Cook, Tony Elliott, Joanna Gale, Stephanie Gibbs, John D Graham, John Hetherington, Robert Hughes, Robert Loing, Fiona McKinna, Duncan B McLaren, Joe M O'Sullivan, Omi Parikh, Clive Peedell, Andrew Protheroe, Angus J Robinson, Narayanan Sripriy, Rajaguru Srinivasan, John Staffurth, Santhanam Sundar, Shaun Tolan, David Tsang, John Wagstaff, Mahesh K B Parmar, for the STAMPEDE investigators*

Lancet 2016; 387: 1163-77
Figure 1: Trial profile
SOC-only=standard of care only. SOC+ZA=standard of care plus zoledronic acid. SOC+Doc=standard of care plus docetaxel. SOC+ZA+Doc=standard of care plus zoledronic acid and docetaxel.
Figure 2: Failure-free and overall survival

Figure shows Kaplan-Meier curves and flexible parametric models fitted to the data. Number at risk (events) shows the number of individuals at risk (ie, the number who were event free) at each timepoint, with parentheses showing the number of individuals who developed events in the period between each timepoint. SOC-only = standard of care only, SOC + ZA = standard of care plus zoledronic acid, SOC + Doc = standard of care plus docetaxel, SOC + ZA + Doc = standard of care plus zoledronic acid and docetaxel.
<table>
<thead>
<tr>
<th>Safety population</th>
<th>Standard of care (n=1184)</th>
<th>Standard of care plus zoledronic acid (n=593)</th>
<th>Standard of care plus docetaxel (n=592)</th>
<th>Standard of care plus zoledronic acid and docetaxel (n=593)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients included in analysis*</td>
<td>1228</td>
<td>608</td>
<td>550</td>
<td>516</td>
</tr>
<tr>
<td>Grade 1-5 adverse event</td>
<td>1213 (99%)</td>
<td>604 (99%)</td>
<td>550 (100%)</td>
<td>515 (100%)</td>
</tr>
<tr>
<td>Grade 3-5 adverse event</td>
<td>399 (32%)</td>
<td>157 (31%)</td>
<td>288 (52%)</td>
<td>269 (52%)</td>
</tr>
<tr>
<td>Grade 5 adverse event</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Most frequent adverse events reported as grade 3-5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine disorder (including impotence, hot flushes)</td>
<td>145 (12%)</td>
<td>74 (12%)</td>
<td>57 (10%)</td>
<td>64 (12%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>15 (1%)</td>
<td>5 (&lt;1%)</td>
<td>84 (15%)</td>
<td>74 (14%)</td>
</tr>
<tr>
<td>Neutropenia (neutrophils)</td>
<td>6 (0%)</td>
<td>3 (&lt;1%)</td>
<td>66 (12%)</td>
<td>62 (12%)</td>
</tr>
<tr>
<td>General disorder (including lethargy, fever, asthenia)</td>
<td>46 (4%)</td>
<td>28 (5%)</td>
<td>34 (7%)</td>
<td>56 (11%)</td>
</tr>
<tr>
<td>Musculoskeletal (including bone pain, generalised pain)</td>
<td>69 (6%)</td>
<td>35 (6%)</td>
<td>32 (6%)</td>
<td>44 (9%)</td>
</tr>
<tr>
<td>Gastrointestinal disorder (including diarrhoea, abdominal pain, constipation, vomiting)</td>
<td>36 (3%)</td>
<td>19 (3%)</td>
<td>45 (8%)</td>
<td>37 (7%)</td>
</tr>
<tr>
<td>Renal (including renal impairment, urinary-tract infection)</td>
<td>71 (6%)</td>
<td>30 (5%)</td>
<td>23 (4%)</td>
<td>25 (5%)</td>
</tr>
<tr>
<td>Notable adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory disorder (including dyspnoea, upper respiratory-tract infection)</td>
<td>27 (2%)</td>
<td>13 (2%)</td>
<td>29 (5%)</td>
<td>23 (4%)</td>
</tr>
<tr>
<td>Cardiac disorder (including hypertension, myocardial infarction)</td>
<td>35 (3%)</td>
<td>19 (3%)</td>
<td>16 (3%)</td>
<td>19 (4%)</td>
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<tr>
<td>Osteonecrosis of the jaw</td>
<td>0 (0%)</td>
<td>10 (2%)</td>
<td>0 (0%)</td>
<td>21 (4%)</td>
</tr>
<tr>
<td>Nervous system other (including peripheral neuropathy)</td>
<td>20 (2%)</td>
<td>8 (1%)</td>
<td>19 (3%)</td>
<td>19 (4%)</td>
</tr>
<tr>
<td>Nail changes</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>5 (1%)</td>
<td>4 (1%)</td>
</tr>
</tbody>
</table>

ITT population

<table>
<thead>
<tr>
<th>Number of patients included in analysis†</th>
<th>Standard of care (n=1173)</th>
<th>Standard of care plus zoledronic acid (n=587)</th>
<th>Standard of care plus docetaxel (n=579)</th>
<th>Standard of care plus zoledronic acid and docetaxel (n=563)</th>
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</thead>
<tbody>
<tr>
<td>Grade 1-5 adverse event</td>
<td>1160 (99%)</td>
<td>583 (99%)</td>
<td>577 (100%)</td>
<td>562 (100%)</td>
</tr>
<tr>
<td>Grade 3-5 adverse event</td>
<td>375 (32%)</td>
<td>184 (31%)</td>
<td>298 (51%)</td>
<td>296 (53%)</td>
</tr>
<tr>
<td>Grade 5 adverse event</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

Grade 5 adverse events were not necessarily treatment-related; similarly treatment-related deaths were not always grade 5 adverse events. ITT=intention-to-treat. *Analysis by actual treatment initiated (irrespective of assigned study arm) in patients who underwent adverse event assessment. †Analysis by assigned study arm in patients who underwent adverse event assessment.

Table 5: Worst adverse event (grade) reported over entire time on trial

Lancet 2016; 387: 1163-77
In conclusion, we have shown improved survival across a population of men commencing first-line long-term hormone therapy through the addition of docetaxel chemotherapy but not by adding zoledronic acid. Therefore, zoledronic acid should not become part of standard of care. Standard of care should be updated to include docetaxel chemotherapy in suitable patients with metastatic disease, and docetaxel may be considered for men with high-risk non-metastatic prostate cancer with or without radiotherapy.
Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data

Claire L Vale*, Sarah Burdett*, Larysa H M Rydzewska, Laurence Albiges, Noel W Clarke, David Fisher, Karim Fizazi, Gwenaelle Gravis, Nicholas D James, Malcolm D Mason, Mahesh K B Parmar, Christopher J Sweeney, Matthew R Sydes, Bertrand Tombal, Jayne F Tierney, for the STOPCaP Steering Group

Lancet Oncol 2016; 17: 243–56
Figure 1: Study flow chart

CRPC = castrate-resistant prostate cancer. *One trial (STAMPEDE)* is eligible to be included in both docetaxel and bisphosphonate comparisons.
<table>
<thead>
<tr>
<th>Docetaxel trials</th>
<th>Accrual period</th>
<th>Number of patients</th>
<th>Control</th>
<th>Treatment</th>
<th>Metastatic status</th>
<th>Median age (range)</th>
<th>Gleason score of 8–10 (%)</th>
<th>Performance status of 0–1 (%)</th>
<th>Median follow-up (survival)</th>
<th>Treatment on progression (control group only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GETUG-12/06</td>
<td>November 2002–December 2006</td>
<td>413</td>
<td>ADT (gonadlaxis 10-8 mg every 3 months for 3 years)</td>
<td>ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles) plus estramustine</td>
<td>M0</td>
<td>63 (46–77)</td>
<td>42%</td>
<td>Unknown</td>
<td>7 years, 6 months</td>
<td>Not reported</td>
</tr>
<tr>
<td>TAX 3502</td>
<td>December 2005–September 2007</td>
<td>228</td>
<td>ADT (leuprolide 22.5 mg every 3 months for 18 months)</td>
<td>ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles)</td>
<td>M0</td>
<td>61.9*</td>
<td>52%</td>
<td>Unknown</td>
<td>3 years, 3 months</td>
<td>Not reported</td>
</tr>
<tr>
<td>RTOG 0521</td>
<td>December, 2005–August, 2009</td>
<td>612</td>
<td>ADT (LHRH agonist plus oral anti-androgen plus RT)</td>
<td>ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles) plus prednisone</td>
<td>M0</td>
<td>66 (unknown)</td>
<td>84%</td>
<td>Unknown</td>
<td>6 years</td>
<td>Not reported</td>
</tr>
<tr>
<td>STAMPEDE (standard of care with or without docetaxel)</td>
<td>September, 2005–March, 2013</td>
<td>1776</td>
<td>ADT (plus radiotherapy for M0 patients)</td>
<td>ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles) plus prednisone</td>
<td>M0 and M1</td>
<td>65 (40–82)</td>
<td>70%</td>
<td>99%</td>
<td>3 years, 6 months</td>
<td>40% received docetaxel (49% received life-extending treatments)</td>
</tr>
<tr>
<td>STAMPEDE (standard of care plus zolendronic acid with or without docetaxel)</td>
<td>September, 2005–March, 2013</td>
<td>1186</td>
<td>ADT (plus radiotherapy for M0 patients) plus zolendronic acid (4 mg every 3–4 weeks for 2 years)</td>
<td>ADT (plus radiotherapy for M0 patients) + zolendronic acid (4 mg for 3–4 weeks for 2 years) plus docetaxel (75 mg/m² every 3 weeks for six cycles)</td>
<td>M0 and M1</td>
<td>66 (42–84)</td>
<td>71%</td>
<td>99%</td>
<td>3 years, 6 months</td>
<td>36% received docetaxel (45% received life-extending treatments)</td>
</tr>
<tr>
<td>GETUG-15/06</td>
<td>October, 2004–December, 2008</td>
<td>385</td>
<td>ADT (LHRH agonist or surgical castration or combined androgen blockade)</td>
<td>ADT plus docetaxel (75 mg/m² every 3 weeks for up to nine cycles)</td>
<td>M1</td>
<td>63.5 (57–70)</td>
<td>56%</td>
<td>100%</td>
<td>6 years, 11 months</td>
<td>62% received docetaxel</td>
</tr>
<tr>
<td>CHAARTED</td>
<td>July, 2006–November, 2012</td>
<td>790</td>
<td>ADT (LHRH agonist or LHRH antagonist) or surgical castration</td>
<td>ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles)</td>
<td>M1</td>
<td>64 (36–91)</td>
<td>61%</td>
<td>98%</td>
<td>2 years, 5 months</td>
<td>147 (51%) of 287 men received docetaxel (104 of 287 men received abiraterone or enzalutamide)</td>
</tr>
<tr>
<td>Blisphosphonate trials</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROS²</td>
<td>June, 1994-December, 1997</td>
<td>508</td>
<td>Local standard practice (radiotherapy or hormone therapy or both) plus placebo</td>
<td>Local standard practice plus zoledronic acid (5 mg every 4 times daily)</td>
<td>M0</td>
<td>69.5 (49-87)</td>
<td>Unknown</td>
<td>97%</td>
<td>12 years</td>
<td>Not reported</td>
</tr>
<tr>
<td>RADAR²</td>
<td>October, 2003-August, 2007</td>
<td>1071</td>
<td>ADT (leuprolin 22.5 mg for either 6 months or 18 months)</td>
<td>ADT plus zoledronic acid (4 mg every 3 months for 18 months)</td>
<td>M0</td>
<td>68.8 (62-73.3)</td>
<td>35%</td>
<td>100%</td>
<td>7 years, 5 months</td>
<td>Secondary therapeutic intervention was needed in 78 men in the short-term androgen suppression group, and 61 men in the intermediate-term androgen suppression group; nature of treatment not reported</td>
</tr>
<tr>
<td>ZEUS³</td>
<td>June, 2004-August, 2007</td>
<td>1433</td>
<td>ADT</td>
<td>ADT plus zoledronic acid (4 mg every 3 months for up to 4 years)</td>
<td>M0</td>
<td>67 (44-87)</td>
<td>62%</td>
<td>100%</td>
<td>4 years, 9 months</td>
<td>Not reported</td>
</tr>
<tr>
<td>STAMPEDE (standard of care with or without zoledronic acid)⁴</td>
<td>September, 2005-March, 2013</td>
<td>1777</td>
<td>ADT (plus radiotherapy for M0 patients)</td>
<td>ADT (plus radiotherapy for M0 patients) plus zoledronic acid (4 mg every 3-4 weeks for 9 years)</td>
<td>M0 and M1</td>
<td>66 (41-82)</td>
<td>69%</td>
<td>99%</td>
<td>3 years, 7 months</td>
<td>40% received docetaxel (45% received life-extending treatments)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Accrual period</th>
<th>Number of patients</th>
<th>Control</th>
<th>Treatment</th>
<th>Metastatic status</th>
<th>Median age (range)</th>
<th>Gleason score of 8-10 (%)</th>
<th>Performance status of 0-1 (%)</th>
<th>Median follow-up (survival)</th>
<th>Treatment on progression (control group only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAMPEDE (standard of care plus docetaxel with or without zoledronic acid)⁴</td>
<td>November, 2005-March, 2013</td>
<td>1185</td>
<td>ADT (plus radiotherapy for M0 patients) + docetaxel (75 mg/m²/3 wks/5 cycles)</td>
<td>ADT (plus radiotherapy for M0 patients) plus docetaxel (75 mg/m² every 3 weeks for six cycles) plus zoledronic acid (4 mg every 3-4 weeks for 2 years)</td>
<td>M0 and M1</td>
<td>66 (40-84)</td>
<td>73%</td>
<td>99%</td>
<td>3 years, 7 months</td>
</tr>
<tr>
<td>PROS²</td>
<td>June, 1994-July, 1998</td>
<td>311</td>
<td>Local standard practice-radiotherapy or hormone therapy or both plus placebo</td>
<td>Local standard practice plus zoledronate (520 mg four times daily)</td>
<td>M1</td>
<td>71 (47-88)</td>
<td>Unknown</td>
<td>94%</td>
<td>11 years, 6 months</td>
</tr>
<tr>
<td>CALGB 90202⁴</td>
<td>June, 2004-April, 2012</td>
<td>645</td>
<td>ADT-bilateral orchiectomy, GnRH agonist or GnRH antagonist (and zoledronic acid plus placebo)</td>
<td>ADT plus zoledronic acid (4 mg intravenous every 4 weeks)</td>
<td>M1</td>
<td>66.3 (60-73)</td>
<td>58%</td>
<td>97%</td>
<td>2 years</td>
</tr>
</tbody>
</table>

ADT = androgen deprivation therapy. LH/RH = luteinising hormone-releasing hormone. PSA = prostate specific antigen. *This value is the mean (no SD was available)

Table 1: Characteristics of studies included in the systematic review and meta-analysis
Figure 2: Effect of addition of docetaxel to standard of care on survival and failure-free survival

(A) Effect of the addition of docetaxel on survival in men with M1 disease. (B) Effect of the addition of docetaxel on survival in men with M0 disease. (C) Effect of the addition of docetaxel on failure-free survival in men with M0 disease. (D) Effect of the addition of docetaxel on failure-free survival in men with M0 disease. NA= event numbers by group not available. SOC= standard of care.
Meta-analysis Conclusion

**Interpretation** The addition of docetaxel to standard of care should be considered standard care for men with M1 hormone-sensitive prostate cancer who are starting treatment for the first time. More evidence on the effects of docetaxel on survival is needed in the M0 disease setting. No evidence exists to suggest that zoledronic acid improves survival in men with M1 or M0 disease, and any potential benefit is probably small.

The Role of Brachytherapy in High Risk PCa
Comparing Treatment Results Of PROSTATE CANCER

Prostate Cancer Results Study Group 2011

Peter Grimm, DO et al
Prostate Cancer Center of Seattle
Criteria for Inclusion of Article*

1. Patients should be separated into Low, Intermediate, and High Risk

2. Success must be determined by PSA analysis

3. All Treatment types considered: Seeds (Brachy), Surgery (Standard or Robotic), IMRT (Intensity Modulated Radiation), HIFU (High Frequency Ultrasound), CRYO (Cryo Therapy), Protons, HDR (High dose Rate Brachytherapy)

4. Article must be in a Peer Reviewed Journal
   * Expert panel consensus
### % Articles Meeting Criteria

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RP</th>
<th>EBRT/IMRT</th>
<th>Cryo</th>
<th>Brachy</th>
<th>Robot RP</th>
<th>Proton</th>
<th>HIFU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9%</td>
<td>18%</td>
<td>16%</td>
<td>31%</td>
<td>5%</td>
<td>15%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Total of 848 Treatment Articles. Some articles addressed several treatments and were counted as separate articles for each treatment.
HIGH RISK RESULTS

Weighted

Treatment Success

% PSA Progression Free

EBRT, Seeds & ADT

Brachy

EBRT

Surgery

← Years from Treatment

- Prostate Cancer Results Study Group
- Numbers within symbols refer to references
ASCENDE-RT
Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy

A Multicenter randomized Trial of Dose- Escalated External beam Radiation Therapy ( DE-EBRT) vs Low-Dose-Rate Brachytherapy (:DR-PB) boosts for Men with Unfavorable Risk Localized Prostate Cancer

W James Morris BCCA and al
ASCENDE-RT RTC

**DE-EBRT**
- 12 m ADT
  (8 m neoadjuvant)
- 46 Gy whole pelvis
- 78 Gy 3-DCRT boost

**LDR-PB arm**
- 12 m ADT
  (8 m neoadjuvant)
- 46 Gy whole pelvis
- LDR 115 Gy boost
Ascende Study

- N = 398 (6 centres, 29 RO)
- Median Fup
  - 6.5 after ADT
  - 5 y after completion
Ascende Intent to treat Biochemical Kaplan-Meier PFS

<table>
<thead>
<tr>
<th></th>
<th>DE-EBRT</th>
<th>LDR-PB</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yr</td>
<td>83.8 (±5.6)</td>
<td>88.7 (±4.8)</td>
</tr>
<tr>
<td>7 yr</td>
<td>75.0 (±7.2)</td>
<td>86.2 (±5.4)</td>
</tr>
<tr>
<td>9 yr</td>
<td>62.4 (±9.8)</td>
<td>83.3 (±6.6)</td>
</tr>
</tbody>
</table>

P < 0.05

Absolute differences
5y 4.9%
7y 11.2%
9y 20.95%
Ascende Biochemical Kaplan-Meier PFS for High Risk

DE-EBRT \quad N = 276 \quad LDR-PB

- 5 yr 83.6 (±7.0)
- 7 yr 71.9 (±9.4)
- 9 yr 58.2 (±12.8)

P = 0.05

- 5 y 85.6 (±6.4)
- 7 y 82.9 (±7.2)
- 9 y 78.0 (±9.6)

Absolute differences
5y 2%
7y 11%
9y 19.8%
Ascende Overall Survival

DE-EBRT (N=200)
- 5 yr 88.7 (±4.8)
- 7 yr 81.5 (±6.4)
- 9 yr 73.6 (±8.4)

LDR-PB (N=198)
- 5 y 91.3 (±4.4)
- 7 yr 85.7 (±5.8)
- 9 yr 77.9 (±8.2)

P = 0.29

Trial not powered for OS
Median S not reached
≈ 13 y
## Ascende 5y Cumulative late G3+ Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Toxicity</th>
<th>LDR-PB</th>
<th>DE-EBRT</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GU</td>
<td>Grade 3</td>
<td>19%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>1%</td>
<td>1%</td>
<td>0.547</td>
</tr>
<tr>
<td>GI</td>
<td>Grade 3</td>
<td>9%</td>
<td>4%</td>
<td>0.120</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>1%</td>
<td>0%</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Randomized phase II feasibility trial of image guided external beam radiotherapy with or without high dose rate brachytherapy boost in men with intermediate-risk prostate cancer (CCTG PR15/ NCT01982786)

Figure 1: Treatment schedule

Prostate Carcinoma
- Stage T2b-T2c, Gleason < 8 and PSA < 20
- Stage T1c-T2a, Gleason 7 and PSA < 20
- Stage T1c-T2c, Gleason ≤ 6 and 10 ≤ PSA < 20

ARM 1
- IGRT* 60 Gy in 20 fractions
  OR
  IGRT 78 Gy in 39 fractions

ARM 2
- IGRT 37.5 Gy in 15 fractions
  + HDR brachytherapy boost 15 Gy
**Table 4:** GI and GU Adverse events graded according to CTCAE V4.0

<table>
<thead>
<tr>
<th>Grade</th>
<th>IGRT (n=29)</th>
<th>IGRT + HDR (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GI (#, %)</td>
<td>GU (#, %)</td>
</tr>
<tr>
<td>1</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>5</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

IGRT: image guided radiotherapy; GI: gastrointestinal.
Adjuvant / Salvage in High Risk PCa
NRG Oncology/RTOG 9601, a phase III trial in prostate cancer patients: Anti-androgen therapy (AAT) with bicalutamide during and after salvage radiation therapy (RT) following radical prostatectomy (RP) and an elevated PSA.

William U. Shipley et al
J Clin Oncol 34, 2016 (suppl 2S; abstr 3)
RTOG 9601

**Methods:** Post-RP patients with pT3pN0 or with pT2pN0 and positive margins who had or developed elevated PSA levels from 0.2 to 4.0 ng/ml were randomized on a phase III, double-blind, trial of RT + placebo (64.8 Gy in 36 fractions of 1.8 Gy) vs. RT + AAT (24 months bicalutamide, 150 mg daily) during and after RT.

Primary end-point was overall survival.

**Results:** From 3/98 to 3/03, 761 eligible patients (median age 65) were randomized to RT + AAT (384) or RT + placebo (377). 248 patients (33%) were pT2pN0 and 513 (67%) were pT3pN0. 671 (88%) had a PSA nadir after RP of < 0.5 ng/ml. 649 (85%) had an entry PSA value of <1.6, 112 patients (15%) had an entry PSA of 1.6-4.

Median follow up was 12.6 years.

Actuarial overall survival at 10 years was 82% for RT plus AAT and 78% for RT + placebo and a hazard ratio of 0.75 (95% CI: 0.58-0.98) (2-sided p = 0.036).

12-year incidence of PC central-reviewed deaths were 2.3% for RT + AAT and 7.5% for RT + placebo (p< 0.001).

Cumulative incidence of metastatic PC at 12 years was less in the RT + AAT arm, 14% (51 patients), vs. 23% (83 patients) in the RT + placebo arm (p < 0.001).

Late grade III and IV toxicity were similar in the AAT and placebo arms. The combined grade III and IV toxicities for RT + AAT and RT + placebo were: bladder 7.0% vs. 6.7%, bowel 2.7% vs. 1.6%.

Gynecomastia differed significantly by treatment arm, 70% vs. 11%.
RTOG 9601

Conclusions: 24 months of AAT using 150mg bicalutamide daily during and after salvage RT significantly improved long term overall survival and reduced the incidence of metastatic PC and PC death.
RTOG 0534

PSA 0.2-2.0 s/p RP

RANDOM

R Prost bed 65-70 Gy
A Prost bed 65-70 Gy
N + 4-6 mos ADT
D Pelvis 45 Gy
O Prost bed 65-70 Gy
M + 4-6 mos ADT
I
Z
E
NCIC PR13

RADICALS closed to recruitment on 30th December 2016 and randomised 2840 patients to RADICALS-HD and 1396 patients to RADICALS-RT

Figure 3: Overall Summary of Trial entry, Randomisation and Treatment

RADICALS - overall design

Random prostatectomy

Assess need: Is immediate post-operative RT required?

Yes

Immediate RT

No

Immediate RT

RT timing RANDOMISATION

Salvage RT policy

Salvage RT policy

Hormone duration RANDOMISATION

RT + no HT

RT + 6mo HT

RT + 2yr HT

Monitor on trial

Monitor off trial

No rise in PSA

Rise in PSA

Hormone duration RANDOMISATION

RT + no HT

RT + 6mo HT

RT + 2yr HT

Trial follow-up

Trial follow-up

Outcome measures

Outcome measures

Outcome measures
Impact of Adjuvant Radiotherapy on Survival of Patients With Node-Positive Prostate Cancer

Firas Abdollah, R. Jeffrey Karnes, Nazareno Suardi, Cesare Cozzarini, Giorgio Gandaglia, Nicola Fossati, Damiano Vizziello, Maxine Sun, Pierre I. Karakiewicz, Mani Menon, Francesco Montorsi, and Alberto Briganti
Fig 1. A novel cancer-specific mortality (CSM) risk stratification tree based on data for 1,107 patients with pN1 prostate cancer treated with radical prostatectomy, anatomically extended pelvic lymph node dissection, and adjuvant hormonal therapy (aHT) with or without adjuvant radiotherapy (aRT). SM, surgical margins.
Conclusion

- RT + 18 m ADT appears safe
- There is a benefit to Add RT to ADT in HR PCA (N0 & N+)
- There is a benefit to use BT over EBRT in HR PCA but with increase GU toxicity
Conclusion

- There is a potential benefit to add Docetaxel to ADT and RT in HR PCA
- There is a benefit to add 2 y of Casodex to salvage EBRT post PR but with gynecomastia +++
- There is a benefit to Add RT + ADT in in selected post PR N+
Thank U

Questions