Biochemical failure post-local treatment for prostate cancer

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Disclosure

Participation to advisory boards/honorarium for: Amgen, Astellas, Astrazeneca, Bayer, Clovis, Curevac, Essa, Genentech, Janssen, MSD, Orion, Sanofi
Biochemical relapses

• Définition:
  – PSA > 0,2 ng/mL after prostatectomy
  – PSA rise > 2 ng/mL beyond the nadir after radiotherapy

• Frequent, associated with anxiety

• Bone scan and CT scan not recommended
• Role of next generation imaging? (WB MRI, PET-choline, PET-PSMA) PSA > 0.5-2 ng/mL
PSMA-Pet: detection of 17 lymph nodes with diameter below the morphological detection limit; Median 0.46mm; Max 0.66; Min 0.32

**a**

- Little radioactivity in the bladder
- Cleavage of the tracer in the kidneys
- Renal storage of the chelator

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Giesel et al., Clinical Genitourinary Cancer 2017
Prostate-specific antigen (PSA) recurrence after radical prostatectomy

<table>
<thead>
<tr>
<th>Prostate-specific antigen (PSA) recurrence after radical prostatectomy</th>
<th>LE</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform imaging only if the outcome will influence subsequent treatment decisions.</td>
<td></td>
<td>Strong</td>
</tr>
<tr>
<td>If the PSA level is ≥ 1 ng/mL, perform a prostate-specific membrane antigen positron emission tomography computed tomography (PSMA PET/CT), if available, or a choline PET/CT imaging otherwise.</td>
<td>2b</td>
<td>Weak</td>
</tr>
</tbody>
</table>
What Is the Natural History of Patients Who Relapse After Local Therapy?

- 304 men relapsed after surgery
- No hormones until (+) bone scan
- Time to PSA rise, Gleason, PSADT were predictors of survival

Specific Survival by time from RP to PSA relapse

Specific Survival by Gleason score


![Graph showing specific survival by pathological Gleason score.](Image)
Specific Survival by PSA doubling time (PSADT)

Should a second local treatment be used in case of PSA relapse?
Predicting the Outcome of Salvage Radiation Therapy for Recurrent Prostate Cancer After Radical Prostatectomy


**A**

- Proportion Free of Progression
- Time From Salvage Radiotherapy End (months)
- No. of patients at risk:
  - 1,540
  - 749
  - 392
  - 146
  - 58

40% at 5y

**B**

- Proportion Free of Progression
- Time From Salvage Radiotherapy End (months)
- PSA categories:
  - PSA <0.5
  - PSA 0.51-1.0
  - PSA 1.01-1.5
  - PSA >1.5

J Clin Oncol 35:2035-2041, 2007
Should we used salvage ADT in men with PSA relapses?
Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial

Gillian M Duchesne, Henry H Woo, Julie K Bassett, Steven J Bowe, Catherine D’Este, Mark Frydenberg, Madeleine King, Leo Ledwich, Andrew Loblaw, Shawn Malone, Jeremy Millar, Roger Milne, Rosemary G Smith, Nigel Spry, Martin Stockler, Rodney A Syme*, Keen Hun Tai, Sandra Turner

- **293 men:**
  - 261 with a rising PSA post-local treatment
  - 32 not candidate for local treatment

- **Superiority trial** (hypothesis=immediate is better)
  
  Immediate ADT

  \[ \text{R} \]

  Differed ADT (delay of at least 2 years)
Early vs differed ADT

Median follow-up: 5 years

Overall Survival (Primary)   Time to prostate cancer complication

HR=0.55; p=0.05

Duchesne GM, Lancet Oncol 2016
Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial


- 743 men with pT2-4 post-RP, PSA 0.2-2 ng/mL
- Superiority trial

RXT 66 Gy

R

RXT 66 Gy + Goserelin 10.8 x 2
Relapse-free survival

Radiotherapy alone vs Radiotherapy plus goserelin
Hazard ratio 0.50 (95% CI 0.38-0.66)
Stratified log-rank test: p<0.0001

Number at risk:
- Radiotherapy plus goserelin: 363, 360, 349, 342, 319, 298, 285, 269, 236, 185, 111, 87, 46, 24, 5

Carrie C, Lancet Oncol 2016; 17: 747-56
RXT +/- Bicalutamide for rising PSA post-Prostatectomy: OS

3 trials supporting earlier use of ADT in biochemical failures post-local treatment.

PSA doubling time to help decision making?

| Patients at Risk | Placebo+RT | 376 372 368 359 350 332 319 307 294 280 262 240 203 130 71 25 |
|------------------|------------|------------------|------------------|------------------|
|                  | AAT+RT     | 384 382 376 368 362 347 337 326 308 294 280 259 223 151 78 32     |
Intermittent vs Continuous ADT for PSA relapses: The NCIC trial

n= 1386 with PSA progression after RXT (primary or salvage) PSA > 3

Continuous ADT

Intermittent ADT

Intermittent ADT:
- 8 months ADT
- Stopped if PSA < 4
- Recycled when PSA > 10

I-ADT better for physical function, fatigue, urinary problems, hot flashes, libido, and erectile function

Crook J, N Engl J Med 2012; 367
Should we used:

- pelvic radiation
- salvage ADT

in men with PSA relapses?
### NRG Oncology/RTOG 0534/SPPORT Trial Design

<table>
<thead>
<tr>
<th>STRATEGIZE</th>
<th>RANDOMIZE</th>
</tr>
</thead>
</table>
| **SV Involvement** | **Arm 1: PBRT Alone**  
1. No  
2. Yes |
| Prostatectomy Gleason Score | **Arm 2: PBRT + STAD**  
1. Gleason ≤ 7  
2. Gleason 8-9  
**Arm 3: PLNRT + PBRT + STAD**  
1. PSA ≥ 0.1 and ≤ 1.0 ng/mL  
2. PSA > 1.0 and < 2.0 ng/mL  
**Pathology Stage**  
1. pT2 and margin negative  
2. All others |

Primary endpoint: FFP at 5 years

Failure defined as first occurrence of:
- PSA ≥ Nadir+2 ng/mL
- Clinical progression (local, regional or distant)
- Death due to any cause

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SV = seminal vesicle; RT = radiation therapy; PBRT = prostate bed RT; PLNRT = pelvic lymph node RT; STAD = neoadjuvant and concurrent short-term androgen deprivation

Pollack I, ASTRO 2018
FFP: All eligible patients (1,792)

Arm 1: PBRT Alone; 71%
Arm 2: PBRT + STAD; 81%
Arm 3: PLNRT+PBRT+STAD; 87%

5 yr Rate Comparison
Arm 3 vs Arm 1: p<0.0001
Arm 2 vs Arm 1: p<0.0001
Arm 3 vs Arm 2: p=0.0039

HRs and 97.5% CIs
3 vs 1: 0.45 (0.34-0.61)
2 vs 1: 0.62 (0.47-0.82)
3 vs 2: 0.71 (0.52-0.98)

Pollack I, ASTRO 2018
Freedom from distant metastasis: All eligible patients

Metastasis seen in 108 Pts

Arm and 5 year Rate
- Arm 1: PBRT Alone; 91.7%
- Arm 2: PBRT + STAD; 94.4%
- Arm 3: PLNRT+PBRT+STAD; 95.2%

5 yr Rate Comparison
- Arm 3 vs Arm 1: p=0.014
- Arm 2 vs Arm 1: p=0.05
- Arm 3 vs Arm 2: p=0.28

HRs and 97.5% CIs
- 3 vs 1: 0.52 (0.30-0.92)
- 2 vs 1: 0.81 (0.49-1.33)
- 3 vs 2: 0.64 (0.36-1.14)

No statistically significant differences in OS

Pollack I, ASTRO 2018
Conclusion: Biochemical failures

- Long delay between PSA relapse and clinical symptoms
- Prognostic factors, mostly:
  - Gleason $\geq 8$
  - PSA doubling time $< 9$ mo
- Conventional imaging useless
- Pet-PSMA likely to change the game (local relapses, oligo-mets)
Conclusion: Treatment of Biochemical failure

- Radiotherapy (prostate bed + pelvis) and short-term ADT likely to become standard of care post-RP

- If relapse post-RXT, intermittent ADT as standard treatment if short PSA DT?

- All indications to be balanced with co-morbidities and life expectancy
CRPC M0: Definition

• A man with prostate cancer:
  – Who often had a previous local treatment
  – PSA relapse and then received ADT (or ADT together with primary local Tx)
  – Who is now progressing by PSA while on ADT

• No detectable metastases on conventional imaging (bone scan, CT scan)

• Testosterone at castrated levels
High-risk nmCRPC patients, at risk of metastases or death, can be readily identified

![Graphs showing time to bone metastases or death by PSA level and PSADT](Smith MR, et al. J Clin Oncol. 2005;23:2918-25.)
High-risk nmCRPC is a deadly cancer

All patients had PSA ≥ 8 and/or PSADT ≤ 10 months at baseline.

OS, overall survival

PROSPER/SPARTAN/ARAMIS Study Design: in High-Risk M0 CRPC

Similar trials with Enzalutamide (Prosper), Apalutamide (Spartan) and Darolutamide (Aramis)

Estimated Enrollment: 1,200-1,500
- M0 CRPC
- PSA doubling time of ≤10 months
- ECOG PS 0-1

Primary endpoints:
- Metastasis-free survival

Key secondary endpoints:
- OS
- Time to first SSE
- Time to initiation of first cytotoxic chemo
- Time to pain progression
Background: next-generation androgen receptor inhibitors

- Darolutamide is structurally distinct from apalutamide and enzalutamide
- Low blood–brain barrier penetration\(^1,2\)
- This could result in less CNS toxicity and improved tolerability


SPARTAN and PROSPER: primary endpoint – MFS

**SPARTAN**
- 72% reduction of distant progression or death
- Median MFS: APA 40.5 vs PBO 16.2 months
- 24-month additional MFS benefit

**PROSPER**
- 71% reduction of distant progression or death
- Median MFS: ENZA 36.6 vs PBO 14.7 months
- 22-month additional MFS benefit

SPARTAN and PROSPER secondary endpoint: OS

SPARTAN¹ (Median follow-up: 2 years)

HR (95% CI): 0.70 (0.47–1.04)  
p = 0.07

- 30% risk reduction of death (HR 0.70; p = 0.07)
- Median OS: APA NR vs PBO 39 months

PROSPER²

HR (95% CI): 0.80 (0.58–1.09)  
p = 0.1519

- 20% risk reduction of death (HR 0.80; p = 0.15)
- Median OS: ENZA NR vs PBO NR

SPARTAN and PROSPER: AEs of interest

<table>
<thead>
<tr>
<th></th>
<th>SPARTAN(^1)</th>
<th>PROSPER(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>APA (n = 803)</td>
<td>PBO (n = 398)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE reporting every 4 weeks</td>
<td>AE reporting every 4 months</td>
<td></td>
</tr>
<tr>
<td><strong>AEs (all grades), %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>30.4</td>
<td>21.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24.8</td>
<td>19.8</td>
</tr>
<tr>
<td>Rash</td>
<td>23.8</td>
<td>5.5</td>
</tr>
<tr>
<td>Falls</td>
<td>15.6</td>
<td>9.0</td>
</tr>
<tr>
<td>Mental impairment disorders</td>
<td>5.1</td>
<td>3.0</td>
</tr>
<tr>
<td>Fractures</td>
<td>11.7</td>
<td>6.5</td>
</tr>
<tr>
<td><strong>AEs (grade 3 and 4 only), %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14.3</td>
<td>11.8</td>
</tr>
<tr>
<td>Rash</td>
<td>5.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Falls</td>
<td>1.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Mental impairment disorders</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Seizures</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Major CV event</td>
<td>1(^a)</td>
<td>1(^a)</td>
</tr>
<tr>
<td>AEs leading to discontinuation, %</td>
<td>11.0</td>
<td>7.0</td>
</tr>
<tr>
<td>AEs leading to death, n (%)</td>
<td>10 (1.2)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

\(^a\)Adverse events. AEs in SPARTAN were measured to 28 days after the end of regimen.
AE, adverse event; CV cardiovascular.

Primary endpoint: Metastasis-free survival
59% risk reduction of distant metastases or death

Presented by: Karim Fizazi

Darolutamide: 40.4 months (median)
Placebo: 18.4 months (median)

HR 0.41 (95% CI 0.34–0.50)
P<0.0001

Median follow-up time at primary analysis was 17.9 months
Secondary endpoint: Time to pain progression (BPI-SF)
35% risk reduction of increase in pain

Survival Probability

Survival Probability

95% CI 0.53–0.79
P<0.0001

Darolutamide: 40.3 months (median)
Placebo: 25.4 months (median)

HR 0.65 (95% CI 0.53–0.79)
P<0.0001

BPI-SF, Brief Pain Inventory – Short Form; CI, confidence interval; HR, hazard ratio.

Presented by: Karim Fizazi
Secondary endpoint: Overall survival

29% risk reduction of death

Darolutamide: median not reached
Placebo: median not reached

HR 0.71 (95% CI 0.50–0.99)
P=0.0452
## TEAEs of interest

<table>
<thead>
<tr>
<th>Adverse event, all grades, n (%)</th>
<th>Darolutamide (N = 954)</th>
<th>Placebo (N = 554)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue/asthenic conditions</td>
<td>151 (15.8)</td>
<td>63 (11.4)</td>
</tr>
<tr>
<td>Dizziness (including vertigo)</td>
<td>43 (4.5)</td>
<td>22 (4.0)</td>
</tr>
<tr>
<td>Cognitive disorder</td>
<td>4 (0.4)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>5 (0.5)</td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>Seizure (any event)</td>
<td>2 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>40 (4.2)</td>
<td>20 (3.6)</td>
</tr>
<tr>
<td>Falls (including accident)</td>
<td>40 (4.2)</td>
<td>26 (4.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>63 (6.6)</td>
<td>29 (5.2)</td>
</tr>
<tr>
<td>Coronary artery disorders</td>
<td>31 (3.2)</td>
<td>14 (2.5)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>18 (1.9)</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>Rash</td>
<td>28 (2.9)</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>Weight decreased (any event)</td>
<td>34 (3.6)</td>
<td>12 (2.2)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2 (0.2)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

**TEAEs of interest**

Presented by: Karim Fizazi

**Presented at:** 2019 Genitourinary Cancers Symposium | #GU19

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Conclusion: M0 CRPC

- Quite rare situation, unmet need
- Even rarer if next generation imaging is used
- 3 agents (Darolutamide, Enzalutamide, Apalutamide):
  - Clear and meaningful improvement of MFS
  - Remarkable safety profile with Darolutamide
  - Clear suggestion that clinical endpoints are improved (Pain progression, OS)
  - Cost-effectiveness?