Perspectives on Oligometastatic and Oligoprogresive Prostate Cancer
Disclosures

- **Janssen Cilag** (honoraria, advisory board, speaker)
- **Astellas Pharma** (honoraria, advisory board, speaker)
- **IPSEN** (honoraria, advisory board)
...oligomeanings

Terminology

Oligo-metastases
- synchronous
- metachronous

Oligo-recurrence
- regional
- systemic

Oligo-persistance

Oligo-progression
primary in place

primary previously treated

induced by prior systemic therapy
mCSPC with OS as Primary Endpoint

<table>
<thead>
<tr>
<th>Study; Total No. (enrollment period)</th>
<th>Experimental Treatment</th>
<th>Treatment Arm</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>GETUG-AFU15; 385 (Oct 2004 to Dec 2008)</td>
<td>Docetaxel</td>
<td>0.88 (0.68-1.14); ( P = .3 )</td>
<td></td>
</tr>
<tr>
<td>CHAARTED; 790 (July 2006 to July 2012)</td>
<td>Docetaxel</td>
<td>0.72 (0.59-0.86); ( P = .001 )</td>
<td></td>
</tr>
<tr>
<td>STAMPEDE-C; 1,817 (Oct 2005 to Mar 2013)</td>
<td>Docetaxel</td>
<td>0.72 (0.59-0.86); ( P = .005 )</td>
<td></td>
</tr>
<tr>
<td>STAMPEDE-A; 1,002 (Nov 2011 to Jan 2014)</td>
<td>Abiraterone</td>
<td>0.72 (0.59-0.86); ( P &lt; .001 )</td>
<td></td>
</tr>
<tr>
<td>LATITUDE; 1,192 (Feb 2012 to Jan 2014)</td>
<td>Enzalutamide</td>
<td>0.66 (0.56-0.78); ( P &lt; .0001 )</td>
<td></td>
</tr>
<tr>
<td>ENZAMET; 730 (Mar 2013 to Feb 2014)</td>
<td>Enzalutamide</td>
<td>0.67 (0.52-0.86); ( P = .002 )</td>
<td></td>
</tr>
<tr>
<td>TITAN; 1,074 (July 2013 to Feb 2015)</td>
<td>Apalutamide</td>
<td>0.67 (0.51-0.89); ( P = .005 )</td>
<td></td>
</tr>
</tbody>
</table>

Practice-changing trials
...but

The benefit of the combination of DOC or ARTA is uncertain

- in patients with low volume disease* (GETUG-AFU15 and CHAARTED trials)
- in older patients* (≥ 70-75 yrs): in the STAMPEDE, ENZAMET, LATITUDE, and TITAN trials

*the 95% CI for the OS HRs crossed 1
Evidences supporting the role of local treatment in mCSPC
Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

Overall survival: metastatic burden subgroup analysis

HR: 0.68 (95% CI 0.52-0.90), p=0.007
3 year OS (%): SOC = 73%
SOC+RT = 81%

HR: 1.07 (95% CI 0.90-1.28), p=0.420
3 year OS (%): SOC = 54%
SOC+RT = 53%
Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

<table>
<thead>
<tr>
<th>Metastatic burden</th>
<th>Control Deaths/N</th>
<th>Radiotherapy Deaths/N</th>
<th>Interaction p value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low burden</td>
<td>116/409</td>
<td>90/410</td>
<td>0.0098</td>
<td>0.68 (0.52–0.90)</td>
</tr>
<tr>
<td>High burden</td>
<td>252/567</td>
<td>257/553</td>
<td></td>
<td>1.07 (0.90–1.28)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiotherapy schedule</th>
<th>Control Deaths/N</th>
<th>Radiotherapy Deaths/N</th>
<th>Interaction p value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly</td>
<td>179/482</td>
<td>182/497</td>
<td>0.27</td>
<td>1.01 (0.82–1.25)</td>
</tr>
<tr>
<td>Daily</td>
<td>212/547</td>
<td>188/535</td>
<td></td>
<td>0.86 (0.71–1.05)</td>
</tr>
</tbody>
</table>
Oligometastatic state and “Disease Burden”

- **“Low-volume”** (CHAARTED)
  - **Exclusion**: Either of the following: (a) ≥4 bone mets on bone scan, with ≥1 outside the vertebral bodies or pelvis or (b) visceral mets

- **“Low-risk”** (LATITUDE)
  - **Exclusion**: Any two of the following: (a) ≥3 bone mets on bone scan, (b) Gleason score ≥8, or (c) Visceral mets

Kyriakopolous et al. JCO 2018  
Hoyle et al. Eur Urol 2019
Is Low Volume/Low Risk = Oligometastatic?

...NO!

Low metastatic burden disease is sometimes known as oligometastatic. Although this term is widely used, it is imprecise and potentially misleading because it implies only a small number of metastases. Patients with low metastatic burden disease, according to the CHAARTED definition, may have an unlimited number of metastases provided they are confined to lymph nodes and the axial skeleton.
Association of Bone Metastatic Burden With Survival Benefit From Prostate Radiotherapy in Patients With Newly Diagnosed Metastatic Prostate Cancer
A Secondary Analysis of a Randomized Clinical Trial
Median PSA = 142 ng/ml; 67% of patients had > 5 bone metastases

Boevè et al. Eur Urol. 2018
New Metastatic Burden Classification (with Conventional Imaging)

- **Low-burden**
  - NRLN or ≤ 3 or fewer bone metastases ± NRLN regardless of axial or extra axial location and without any visceral metastasis

- **High-burden**
  - All the others
Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (SABR-COMET): Study protocol for a randomized phase II trial

David A Palma1, Cornells J A Haasbeek2, George B Rodrigues3, Max Dahele3, Michael Lock1, Brian Yaremko1, Robert Olson3, Mitchell Liu3, Jason Panarotto4, Gwendolyn H M J Griffioen2, Stewart Gaede1, Ben Slotman2 and Suresh Senan2

INCLUSION CRITERIA:

- Controlled primary tumor
- Up to 3 mts in any organ/system
- Total number of mts ≤5
- Life expectancy > 6 months
- No CT 4 weeks prior, during or 2 weeks after RT

20% prostate cancer patients

Palma et al. BMC Cancer 2012, 12:305
## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=99)</th>
<th>Control Arm (n=33)</th>
<th>SABR Arm (n=66)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Metastases – n(%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.591</td>
</tr>
<tr>
<td>1</td>
<td>42 (42.4)</td>
<td>12 (36.4)</td>
<td>30 (45.5)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>32 (32.3)</td>
<td>13 (39.4)</td>
<td>19 (28.8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>18 (18.2)</td>
<td>6 (18.2)</td>
<td>12 (18.2)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 (4.0)</td>
<td>2 (6.1)</td>
<td>2 (3.0)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3 (3.0)</td>
<td>0 (0.0)</td>
<td>3 (4.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Location of Metastases – n(%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.181</td>
</tr>
<tr>
<td>Adrenal</td>
<td>9 (4.7)</td>
<td>2 (3.1)</td>
<td>7 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>65 (34.0)</td>
<td>20 (31.3)</td>
<td>45 (35.4)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>19 (10.0)</td>
<td>3 (4.7)</td>
<td>16 (12.6)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>89 (46.6)</td>
<td>34 (53.1)</td>
<td>55 (43.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (4.7)</td>
<td>5 (7.8)</td>
<td>4 (3.2)</td>
<td></td>
</tr>
</tbody>
</table>
Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial

Median follow up: 51 months
Open Issues

• RT and abiraterone together? No concerning safety interaction from the STAMPEDE

• Any benefit in treating metastatic sites? The next arm of STAMPEDE (arm M) randomizes patients to systemic therapy and RT to the primary ± metastasis-directed therapy
BIOLOGIA E TRATTAMENTO RADIANTE CURATIVO DELLA MALATTIA OLIGOMETASTATICA

De novo or Synchronous  
primary in place

Oligorecurrent or Metachronous  
primary previously treated

Oligoprogressive CSPC or CRPC  
induced by prior systemic therapy
• The benefit of the combination of DOC or ARTA is uncertain in the subset of men developing metastatic disease after initial local treatment*

*the 95% CI for the OS HRs crossed 1 (GETUG-AFU15, CHAARTED and ENZAMET)
• 75% of patients with recurrence after primary therapy have ≤3 involved sites*

What are the data supporting ablative therapy in mCSPC?
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Sample size</th>
<th>Follow-up</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kneebone et al (2018)</td>
<td>Single-arm, prospective observational study</td>
<td>57 patients</td>
<td>16.0 (range: 5.0–31.0) mo</td>
<td>Median b-PFS: 11.0 mo (95% CI, 8.1–13.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bowden et al (2020)</td>
<td>SBRT, single-arm, prospective observational study, interim results</td>
<td>199 patients, 176 patients available at last FUP</td>
<td>35.1 (range: 6.5–51.3) mo, including patients lost to FUP</td>
<td>b-PFS: 41/176 (23.3%) at last FUP</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ost et al (2018)</td>
<td>Randomized (1:1), prospective</td>
<td>31 patients in both the intervention and the control group (n=62)</td>
<td>36 (IQR: 27.6–45.6) mo</td>
<td>Median b-PFS: 10.0 (80% CI, 8.0–13.0) mo</td>
<td>Median b-PFS: 6.0 (80% CI, 4.6–7.0) mo</td>
<td>b-PFS: HR, 0.53; 80% CI, 0.37–0.77; p = 0.03</td>
</tr>
<tr>
<td>Phillips et al (2020)</td>
<td>Randomized (2:1), prospective</td>
<td>36 patients in the intervention group and 18 in the control group (n=54)</td>
<td>18.8 (range: 5.8–35.5) mo</td>
<td>b-PFS at 6 mo: 1 event</td>
<td>Median b-PFS: 6.4 mo</td>
<td>b-PFS: HR, 0.31; 95% CI, 0.13–0.75; p = 0.002</td>
</tr>
<tr>
<td>PMID: 32215577</td>
<td>SBRT vs observation, interim results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP): study protocol for a randomized phase II trial

Karel Decaestecker¹, Gert De Meerleer², Filip Ameye³, Valerie Fonteyne², Bieke Lambert⁴, Steven Joniau⁵, Louke Delrue⁶, Ignace Billiet⁷, Wim Duthoy⁸, Sarah Junius⁹, Wouter Huysse⁶, Nicolaas Lumen¹ and Piet Ost*²

≤ 3 extracranial metastases on Choline PET CT

Reasons to start ADT: local progression, symptomatic progression or polymetastatic progression
Target = 0.50

HR, 0.60 (95% CI, 0.31 to 1.13); log-rank P = .11
### Table 2. Indications for Starting Androgen Deprivation Therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Surveillance (n = 31)</th>
<th>Metastasis-Directed Therapy (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not started yet</td>
<td>6 (19)</td>
<td>12 (39)</td>
</tr>
<tr>
<td>Polymetastatic progression</td>
<td>16 (55)</td>
<td>19 (61)</td>
</tr>
<tr>
<td>Local progression</td>
<td>6 (23)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Symptomatic progression</td>
<td>3 (10)*</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

NOTE. Data are presented as No. (%).
*Two patients with symptomatic progression also showed local and polymetastatic progression.
Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer
The ORIOLE Phase 2 Randomized Clinical Trial

**Population**
54 Men
Adult men with recurrent, hormone-sensitive prostate cancer and 1-3 metastases detectable by conventional imaging
Median age: 68 y

**Intervention**
36 Stereotactic radiotherapy
Stereotactic ablative radiotherapy (SABR) to all metastases

18 Observation
Observation only for 6 mo

**Findings**
Progression of disease at 6 mo was less common with SABR compared with observation (19% vs 61%; \( P = .005 \))

**Settings / Locations**
3 Radiation treatment facilities in 2 US locations

**Primary Outcome**
Progression of disease measured by any of the following: prostate-specific antigen testing, conventional imaging, symptomatic progression, androgen deprivation therapy initiation for any reason, death

Proportion of patients with progression at 6 mo
Stereotactic radiotherapy: 19%
Observation: 61%
PSMA-targeted PET-CT after randomization

45% had lesions not included in RT fields

Phillips et al. JAMA 2020
Prostate to Metastases

Metastasis to Metastases
Potential Effect of Locally Ablative Therapy
“Gotta Catch ’em All”, or Do We? Pokemet Approach to Metastatic Prostate Cancer

Declan G. Murphy a,b,c,*, Christopher I. Ginsberg y d, Bertrand Tombal e
Number of cells versus volume calculation

Assuming pure cancer cells (which we know is not true)

\[ \frac{4}{3} \pi r^3 \]

one cell - 10 \( \mu m^3 \) = volume = 500 \( \mu m^3 \)

1 mm tumor = 1000 \( \mu m \) = 2093 \( \mu m^3 \) / 500 = 1 million cells

2 mm tumor = 2000 \( \mu m \) = volume = 4,000,000,000 \( \mu m^3 \) / 500 = 8 million cells

3 mm tumor = 3000 \( \mu m \) = volume = 13,500,000,000 \( \mu m^3 \) / 500 = 27 million cells

10 mm tumor = 10000 \( \mu m \) = volume = 5000000000000 \( \mu m^3 \) / 500 = 1,000,000,000 = 1 billion cells
<table>
<thead>
<tr>
<th>PSA value</th>
<th>PSMA results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2-0.49 ng/mL</td>
<td>30% Positive/70% Negative</td>
</tr>
<tr>
<td>0.5-0.99 ng/mL</td>
<td>60% Positive/40% Negative</td>
</tr>
<tr>
<td>1.0-3.9 ng/mL</td>
<td>80% Positive/20% Negative</td>
</tr>
<tr>
<td>&gt; 4 ng/mL</td>
<td>90% Positive/10% Negative</td>
</tr>
</tbody>
</table>
primary in place

primary previously treated

induced by prior systemic therapy
In progression during ADT

AUA/ASTRO/SUO Guideline

ADVANCED PROSTATE CANCER: AUA/ASTRO/SUO GUIDELINE
2020

Treatment

27. In newly diagnosed mCRPC patients, clinicians should offer continued ADT with abiraterone acetate plus prednisone, docetaxel, or enzalutamide. (Strong Recommendation; Evidence Level: Grade A [abiraterone acetate plus prednisone and enzalutamide] B [docetaxel])
Can Local Ablative Radiotherapy Revert Castration-resistant Prostate Cancer to an Earlier Stage of Disease?

Fabian Lohaus, Klaus Zöphel, Steffen Löck, Manfred Wirth, Jörg Kotzerke, Mechthild Krause, Michael Baumann, Esther G.C. Troost, Tobias Hölscher
Which patients could benefit adding RT to ADT?
How long SBRT is repeatable with the aim of delaying systemic therapy?

At least ≥ 6 months between each treatment if M+ at conventional imaging

Ryan CJ et al, Lancet Oncol 2015
Beer TM et al, Eur Urol 2017
How long SBRT is repeatable with the aim of delaying systemic therapy?

CT and Bone scan negative, PET-CT positive

<table>
<thead>
<tr>
<th></th>
<th>SPARTAN</th>
<th>PROSPER</th>
<th>ARAMIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFS - Experimental arm</td>
<td>40.5 mos</td>
<td>36.6 mos</td>
<td>40.4 mos</td>
</tr>
<tr>
<td>MFS – Placebo</td>
<td>16.2 mos</td>
<td>14.7 mos</td>
<td>18.4 mos</td>
</tr>
</tbody>
</table>

More than one year between each treatment

Smith MR et al, NEJM 2018
Hussain M et al, NEJM 2018
Fizazi K et al. NEJM 2019
Consensus statements on ablative radiotherapy for oligometastatic prostate cancer: A position paper of Italian Association of Radiotherapy and Clinical Oncology (AIRO)

Statement 3.1

In an asymptomatic or minimally symptomatic oligometastatic mCRPC patient, with a PSA doubling time > 6 months, time to castration resistant phenotype > 12 months, oligometastasis detected by metabolic imaging, radiotherapy with radical intent to metastatic sites could be offered as alternative to androgen receptor target agent to differ systemic treatment

Agreement: 91%
Median: 8
New Opportunities in mCRPC

- Precision Medicine: PARPi
- Theragnostics: $^{177}$Lu-PSMA-617

In progression during DOC or ARTA
RECOMMENDATION FROM THE PROSTATE CANCER CLINICAL WORKING GROUP 3 (2016):

In cases in which multiple sites of disease continue to respond but one to two sites grow, focal therapy such as radiation or surgery could be administered to the resistant site(s) and systemic therapy continued.
median NEST-free survival of 16 mo

Berghen et al. Eur Urol. 2019
Metastasis-directed Therapy Prolongs Efficacy of Systemic Therapy and Improves Clinical Outcomes in Oligoprogressive Castration-resistant Prostate Cancer

\[ p = 0.07 \]

\[ p = 0.03 \]

Deek et al. Eur Urol Oncol 2020
Metastasis-directed stereotactic radiotherapy for oligoprogresive castration-resistant prostate cancer: a multicenter study

Luca Triggiani1 · Rosario Mazzola2 · Stefano Maria Magrini1 · Gianluca Ingrosso3 · Paolo Borghetti1 · Fabio Trippa4 · Andrea Lancia3 · Beatrice Detti5 · Giulio Francollini5 · Fabio Matrone6 · Roberto Bortolus6 · Giuseppe Fanetti6 · Ernesto Maranzano4 · Francesco Pasqualetti9 · Fabiola Paia9 · Marco Lorenzo Bonu1 · Alessandro Magli10 · Alessio Bruni11 · Ercole Mazzoc11 · Ciro Franzese12 · Marta Scorsetti12,14 · Filippo Alongi1,2 · Barbara Alicja Jereczek-Fossa7,8 · Piet Ost13 · Michela Buglione1

Radiotherapy in metastatic castration resistant prostate cancer patients with oligo-progression during abiraterone-enzalutamide treatment: a mono-institutional experience

Maurizio Valeriani1, Luca Marinelli1, Serena Macrini2, Chiara Reverberi1, Anna Maria Aschelter3, Vitaliana De Sanctis1, Paolo Marchetti2, Lidia Tronnolone1 and Mattia Falchietto Osti1

Stereotactic ablative radiotherapy in castration-resistant prostate cancer patients with oligoprogression during androgen receptor-targeted therapy

G. Ingrosso1 · B. Detti2 · A. Fodor3 · S. Caini4 · S. Borghesi5 · L. Triggiani6 · F. Trippa7 · D. Russo8 · A. Bruni9 · G. Francollini5 · A. Lancia10 · L. Marinelli11 · N. Di Muzio5 · L. Livi3 · S. M. Magrini6 · E. Maranzano7 · D. Musio8 · C. Aristel1 · M. Valeriani11
Primary endpoint: postponement of the start of next-line systemic treatment (NEST)
Open Issues in Oligometastatic Disease

✓ Does MTD impact clinical outcomes in both synchronous and metachronous or progressive disease?

✓ What are valid(ated) endpoints?
  – Survival
  – Time to polymetastatic progression
  – Time to systemic therapy
Variable Definitions of Oligometastatic Disease in Representative Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Type; Sample Size, Location of Metastases</th>
<th>Imaging Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singh et al(^5)</td>
<td>R; NA; 369</td>
<td>(^{99m})Tc bone scan</td>
</tr>
<tr>
<td>Berkovic et al(^14)</td>
<td>P; SA; (\leq 3); Bone or LN</td>
<td>(^{99m})Tc bone scan, (^{18})F-FDG PET/CT, (^{11})C-choline PET/CT</td>
</tr>
<tr>
<td>Schick et al(^13)</td>
<td>P; SA; 50; (\leq 4); NR</td>
<td>(^{99m})Tc bone scan, (^{18})F-choline PET/CT, (^{11})C-acetate PET/CT</td>
</tr>
<tr>
<td>Decaestecker et al(^16)</td>
<td>P; SA; 50; (\leq 3); Bone or LN</td>
<td>(^{18})F-FDG PET/CT, (^{18})F-choline PET/CT</td>
</tr>
<tr>
<td>Jereczek-Fossa et al(^17)</td>
<td>P; SA; 69; LN</td>
<td>(^{18})F-FDG PET/CT, (^{11})C-choline PET/CT, CT</td>
</tr>
<tr>
<td>Ost et al(^18)</td>
<td>P; SA; 119; (\leq 3); Any</td>
<td>(^{18})F-FDG PET/CT, (^{18})F-choline PET/CT</td>
</tr>
<tr>
<td>Ost et al(^19)</td>
<td>P; RA; 62; (\leq 3); Any</td>
<td>(^{18})F-choline PET/CT</td>
</tr>
</tbody>
</table>

Abbreviations: FDG, 18-fluorodeoxyglucose; LN, lymph node; NA, not applicable; NR, not reported; P, prospective; R, retrospective; RA, randomized; SA, single arm.
Oligometastatic Prostate Cancer: Future Perspectives

Integration of clinical and molecular features

- Molecular imaging
- ctDNA
- Exosomes
- Seed vs. soil: Biology of tumor + metastatic niche?

Goals of care should be driven by biology