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mBCa: Management of oligoprogressive disease

Patients with bone metastases

Robbe Van den Begin, MD, PhD

Deputy head of clinic
Radiation oncology
Jules Bordet Institute, Brussels, Belgium

DECLARATION OF INTERESTS

Robbe Van den Begin

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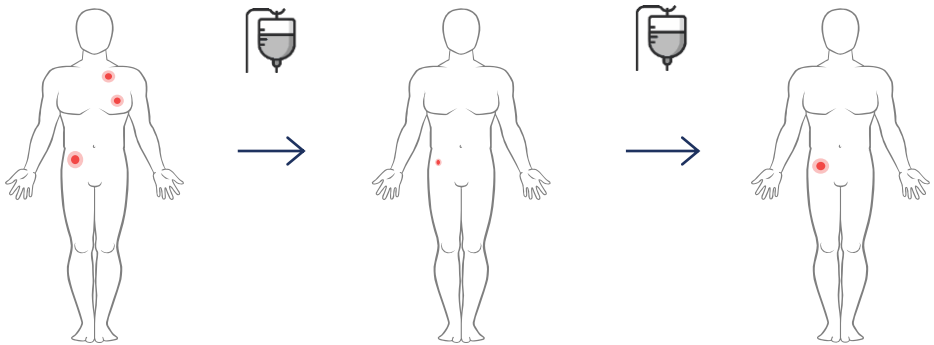
Oligoprogression: concept

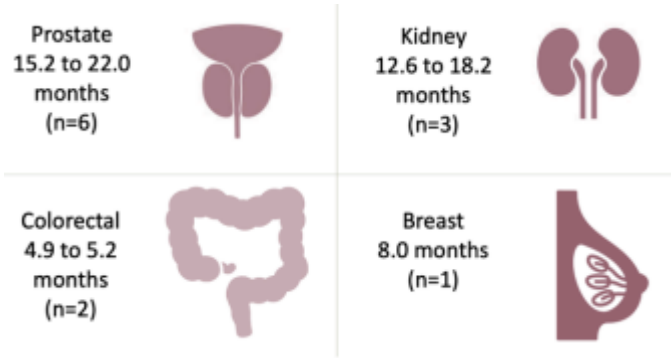
- The prognosis of several types of metastatic breast cancer has greatly improved with novel targeted and hormonal therapies (CDK4/6-inhibitors + hormonal therapy, HER2-targeted agents, anti-HER2 antibody-drug conjugates)
- Disease heterogeneity between metastases: Under systemic therapy, isolated deposits of resistant clones may arise, inducing so-called oligoprogressive disease (OPD) (≠ oligometastatic disease).
- Does local therapy of ALL oligoprogressive lesions allow to extend the benefit of the systemic line?
- Interesting for ongoing therapies with good QOL



Local therapy for oligoprogression

Encouraging outcomes, most studies focus on:

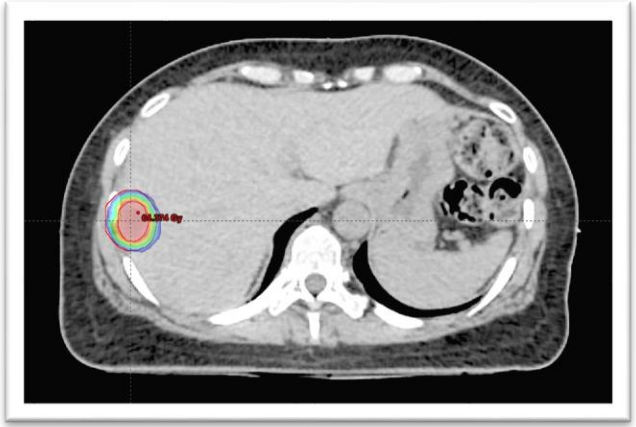
- Non-small cell lung cancer → Local treatment is proposed in ESMO guidelines for oligoprogression on TKI
- Prostate cancer
- Renal cancer
- Mixed primary tumors

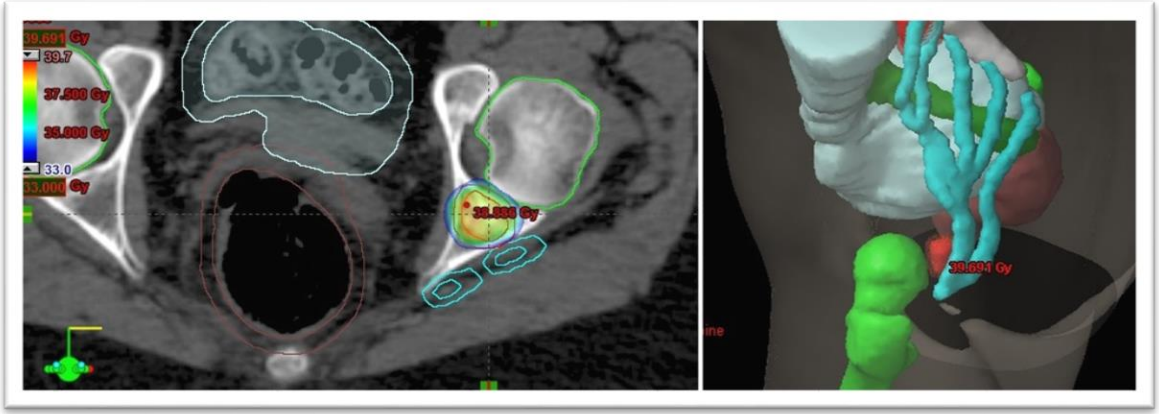


Median time to change in systemic therapy
Tan et al. Radiotherapy and Oncology 2024

Stereotactic Body Radiotherapy (SBRT/SABR)

- Short series of external radiotherapy
- High precision
- High dose per fraction
- Yields high local control
- Well-tolerated, rarely high-grade toxicity





SBRT for bone (spine) metastases

Guninski et al. Radiother Oncol 2024

Study	Events	Total	Weight (common)	Weight (random)	IV, Fixed + Random, 95% CI
Gerszten et al. 2005	50	50	11.9%	16.5%	1.000 [0.929; 1.000]
Gerszten et al. 2006	77	77	18.2%	17.6%	1.000 [0.953; 1.000]
Ahmed et al. 2011	59	66	15.6%	17.2%	0.894 [0.794; 0.956]
Garg et al. 2012	54	61	14.4%	17.0%	0.885 [0.778; 0.953]
Wang et al. 2012	128	149	35.1%	18.7%	0.859 [0.793; 0.911]
Ito et al. 2019	17	20	4.8%	13.1%	0.850 [0.621; 0.968]
Total (common effect, 95% CI)		**423**	**100.0%**	--	**0.932 [0.905; 0.956]**
Total (random effect, 95% CI)			--	**100.0%**	**0.938 [0.855; 0.990]**

Heterogeneity: $Tau^2 = 0.0227$; $Chi^2 = 35.32$, df = 5 ($P < 0.01$); $I^2 = 86\%$

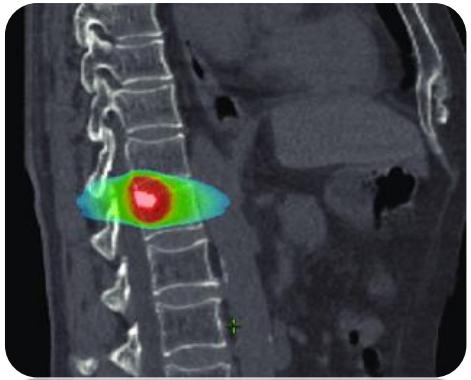
IV, Fixed + Random, 95% CI

0 0.2 0.4 0.6 0.8 1

1-year local control

Local control

C



Study	Events	Total	Weight (common)	Weight (random)	IV, Fixed + Random, 95% CI
Gerszten et al. 2005	0	50	4.2%	7.5%	0.000 [0.000; 0.071]
Gerszten et al. 2006	0	77	6.5%	7.9%	0.000 [0.000; 0.047]
Ahmed et al. 2011	1	66	5.6%	7.8%	0.015 [0.000; 0.082]
Garg et al. 2012	13	61	5.2%	7.7%	0.213 [0.119; 0.337]
Wang et al. 2012	0	149	12.5%	8.2%	0.000 [0.000; 0.024]
Mantel et al. 2019	10	56	4.7%	7.6%	0.179 [0.089; 0.304]
Ito et al. 2019	2	20	1.7%	6.3%	0.100 [0.012; 0.317]
Ning et al. 2019	7	52	4.4%	7.6%	0.135 [0.056; 0.258]
Zeng et al. 2021	59	267	22.4%	8.4%	0.221 [0.173; 0.276]
Sahgal et al. 2021	13	114	9.6%	8.1%	0.114 [0.062; 0.187]
Guckenberger et al. 2021	12	57	4.8%	7.7%	0.211 [0.114; 0.339]
Sprave et al. 2018	2	27	2.3%	6.8%	0.074 [0.009; 0.243]
Ryu et al. 2023	37	191	16.0%	8.3%	0.194 [0.140; 0.257]
Total (common effect, 95% CI)		**1187**	**100.0%**	--	**0.102 [0.085; 0.121]**
Total (random effect, 95% CI)			--	**100.0%**	**0.088 [0.035; 0.158]**

Heterogeneity: $Tau^2 = 0.0330$; $Chi^2 = 150.66$, df = 12 ($P < 0.01$); $I^2 = 92\%$

IV, Fixed + Random, 95% CI

0 0.2 0.4 0.6 0.8 1

Fracture rate

Vertebral fracture

D

Study	Events	Total	Weight (common)	Weight (random)	IV, Fixed + Random, 95% CI
Gerszten et al. 2005	0	50	5.5%	5.5%	0.000 [0.000; 0.071]
Gerszten et al. 2006	0	77	8.4%	8.4%	0.000 [0.000; 0.047]
Ahmed et al. 2011	0	66	7.2%	7.2%	0.000 [0.000; 0.054]
Garg et al. 2012	0	61	6.6%	6.6%	0.000 [0.000; 0.059]
Wang et al. 2012	0	149	16.1%	16.1%	0.000 [0.000; 0.024]
Mantel et al. 2019	0	56	6.1%	6.1%	0.000 [0.000; 0.064]
Ito et al. 2019	0	20	2.2%	2.2%	0.000 [0.000; 0.168]
Ning et al. 2019	2	52	5.7%	5.7%	0.038 [0.005; 0.132]
Sahgal et al. 2021	0	114	12.4%	12.4%	0.000 [0.000; 0.032]
Guckenberger et al. 2021	0	57	6.2%	6.2%	0.000 [0.000; 0.063]
Sprave et al. 2018	0	27	3.0%	3.0%	0.000 [0.000; 0.128]
Ryu et al. 2023	0	191	20.7%	20.7%	0.000 [0.000; 0.019]
Total (common effect, 95% CI)		**920**	**100.0%**	--	**0.000 [0.000; 0.002]**
Total (random effect, 95% CI)			--	**100.0%**	**0.000 [0.000; 0.002]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 6.33$, df = 11 ($P = 0.85$); $I^2 = 0\%$

IV, Fixed + Random, 95% CI

0 0.2 0.4 0.6 0.8 1

radiation induced myelopathy

Myelopathy

E

Studies on local therapy for oligoprogressive (bone) metastases in breast cancer

- Oligoprogressive breast cancer: domain in exploration
- No series on bone metastases only
- Small studies (depend on academic research)

Nicosia et al.

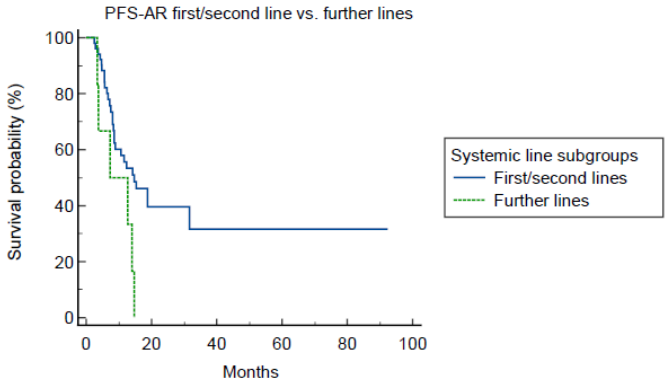
- Retrospective analysis from two institutions.
- 1-5 oligoprogressive lesions under 1st or 2nd line systemic treatment
- Primary endpoint: time to next systemic treatment (NEST).
- N=79 patients, 153 metastases treated with SBRT (35% bone metastases).
- **Luminal A (39%), luminal B (37%),** HER-2 rich (15.5%), triple negative (8.5%).
- Systemic therapy was changed in case of polymetastatic progression (>5 progressive lesions) or new oligoprogression < 6months. Repeated SBRT for new oligoprogression was possible ± change of systemic therapy
- Median follow-up 24 months.
- **Median NEST 8 months** (range: 7-10).
- PFS: NA. Median "**time to polymetastatic conversion": 10 months**.

Nicosia, Clinical & Experimental Metastasis 2022

Marazzi et al.

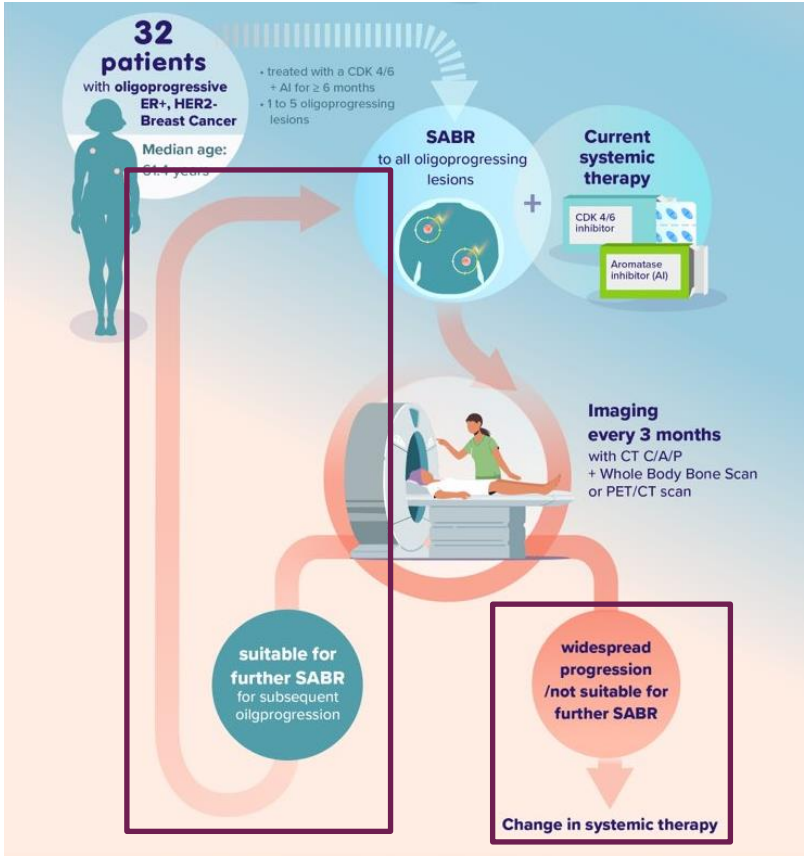
- Retrospective series
- 1-3 oligoprogressive sites treated with RT, without alteration of systemic therapy
- n=59 patients (39% bone metastases)
- Luminal A (10%), **luminal B (42%), HER2+ (41%)**, triple negative (7%
- 66% first line systemic therapy, 24% second line
- **PFS: 13 months** (95% CI 8.5–18.8 months).
  - 11 months (95% CI 8–31.6) for bone metastases

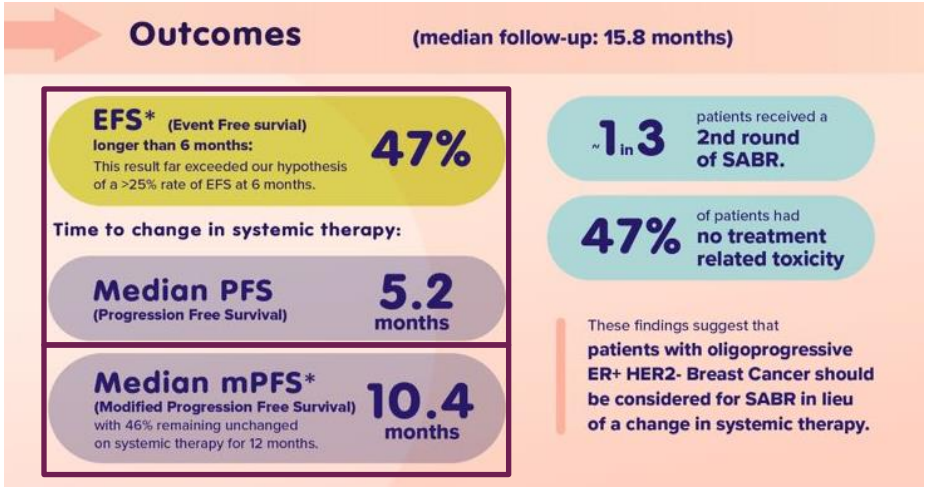
  Significant difference (p=0,03):
  - Patients under first and second-line: 14.7 months (95% CI 8.5–31.6)
  - Subsequent lines: 7.3 months (95% CI 3.4–14.7)
- **81%** was still on the **same systemic therapy at 6 months** post RT



Marazzi J. Pers. Med. 2024

The AVATAR trial





1st or 2nd line therapy with CDK4/6i for > 6 months, 71% Bone metastases

Event-free Survival (EFS) included:

- Any change in systemic therapy
- Any progression within 6 months
- Progression in more than 3 lesions

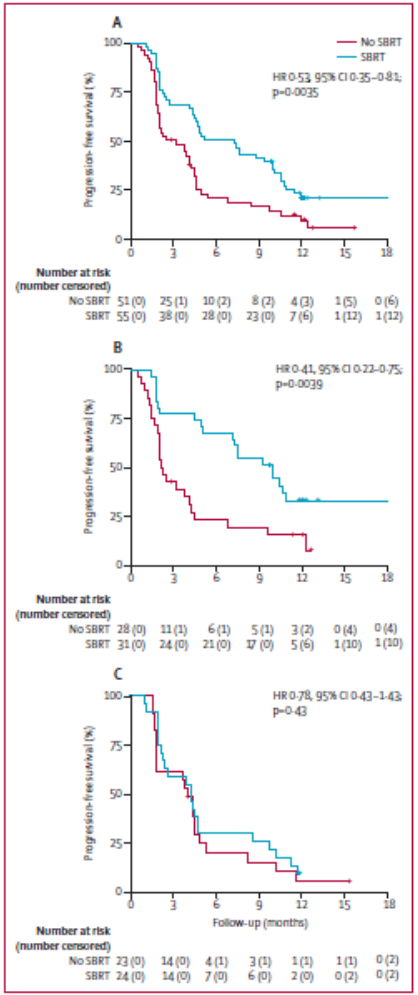
mPFS : any progression not amenable to SBRT at the clinicians discretion (~NEST)

Abstract ASTRO 2023, David et al. IJROBP 2023

The CURB trial

A phase 2, open-label, randomised controlled trial of SBRT

- Oligoprogressive metastatic breast cancer or non-small-cell lung cancer (NSCLC)
- 1-5 progressive lesions
- SOC ± SBRT (SOC: decision to switch systemic therapy left to the discretion of the treating physician)
- Primary endpoint: PFS
- **N=106: 47 breast cancer**, 59 NSCLC. **45% bone metastases**.
- **34% TNBC**
- Accrual closed early after meeting primary endpoint:
  - Overall: Median PFS: 7,2 months for SBRT versus 3,2 months for SOC (HR 0·53, 95% CI 0·35–0·81; p=0·0035)
  - Preplanned subgroup analysis: No difference for breast cancer patients (**4,4 months vs 4,2 months**; HR 0·78, 0·43–1·43; p=0·43).
  - Local control: 100%. 16% of patients had G2+ toxicity linked to SBRT.



Tsai Lancet 2023

The CURB trial

Differences between BCa and NSCLC cohorts

- Only due to difference in primary tumor?
- BCa patients: Longer interval since metastatic diagnosis than for NSCLC (29 months *vs* 18 months; p=0·0009).
- BCa patients: higher number of previous systemic therapies (49% of patients already received 4 lines or more) than patients with NSCLC (8%)
- More patients with brain metastases (26% vs. 16%)
- More total sites of metastasis

- Hypothesis: Accrual for BCa happened later in the disease course, with more resistant disease and less effective therapies available.

Tsai Lancet 2023

Oligoprogression in breast cancer

Selected studies (all SBRT)

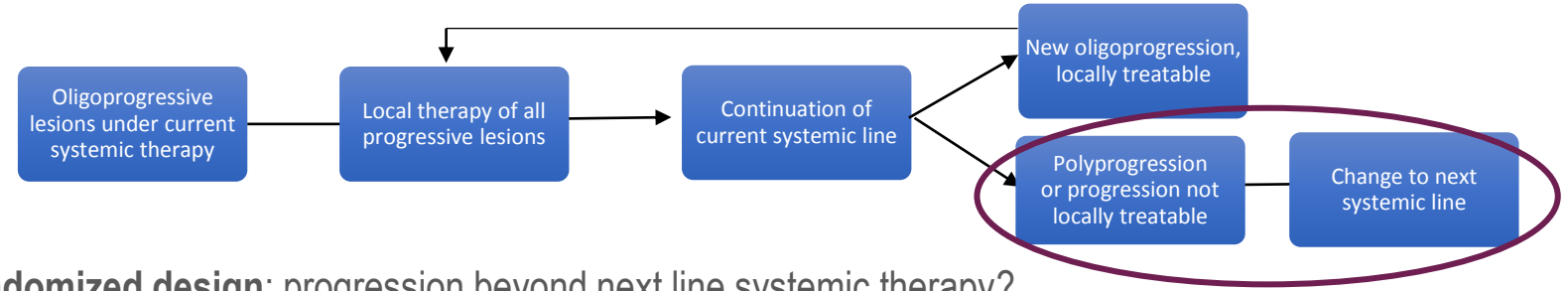
Study	N	TNBC (%)	Number of systemic lines received (median (IQR))	Systemic therapy	PFS (median, months (95% CI))	NEST-free (median, months)
Nicosia 2022	79	9%	Maximum 2	Unchanged	NA	8 (range: 7-10)
Marazzi 2024	59	7%	1-2 in 89% of pts	Unchanged	13 (8,5–18,8)	> 13 81% at 6 months
AVATAR	32	0%	Maximum 2	Unchanged	5,2	10,4
CURB (breast cohort, SOC)	23	39%	4 (2-5)	Variable	4,2 (1,8-5,5)	3,9 (2,6-6,3) (not specified per treatment arm)
CURB (breast cohort, SBRT)	24	29%	3 (2-4)	Variable	4,4 (2,5-8,7)	

For discussion

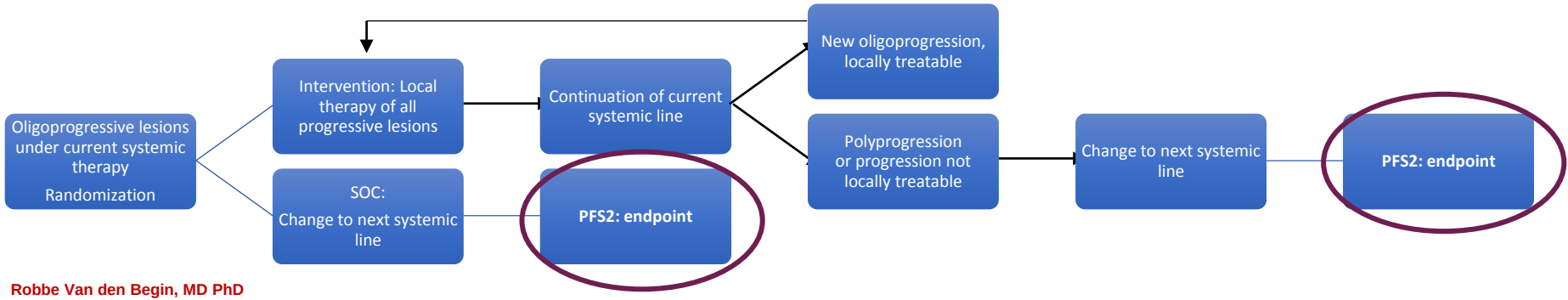
What is the most relevant endpoint to evaluate treatment of oligoprogressive disease?

Objective: defer next line of systemic therapy

Single arm design: mPFS/NEST?



Randomized design: progression beyond next line systemic therapy?



Conclusion (1)

- While there is more evidence for some other primary tumors, the oligoprogression data for breast cancer is still limited
- No studies investigated oligoprogressive bone lesions specifically
- SBRT (bone and other locations) yields high local control and limited toxicity
- Systemic results vary (PFS and NEST of 4 months to >13 months)

(2) Proposed points for future oligoprogression trials

Personal opinion

- **Selection/stratification for BCa subtype**
- **Focus on first lines of metastatic treatment**
- Extensive staging: e.g. FDG-PET-CT
- Continuation of the same systemic therapy. Permission of new local treatment in case of new oligoprogression.
- If randomized: clear control arm
- **Primary endpoint: NEST (for single arm trial); PFS after next systemic line (for a randomized trial)**
- **Report: NEST, classical PFS, modified PFS (PFS not eligible for local treatment)**
- Explore biomarkers for patient selection

- Challenge: accrual to randomized trial (e.g. STOP trial)
- Further recommandations: Tan, Vivian et al. Radiotherapy and Oncology 2024

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Thank you for your attention

robbe.vandenbegin@hubruxelles.be
X: @Van_den_Begin

European Society for Medical Oncology (ESMO)
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org