Ruolo della Radioterapia nelle pazienti con malattia oligometastatica

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Metastases directed Therapy (***MDT***) in Oligometastatic Breast Cancer

Claudio accusa Ero di Marcus Stone
William Shakespeare

Much Ado About Nothing?

Until now…

Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial

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TABLE 1. Baseline Characteristics

Characteristic	Arm, No. (%) Control (n = 33)	SABR (n = 66)
Median age, years (IQR)	69 (64-75)	67 (59-74)
Sex		
Male	19 (58)	40 (61)
Female	14 (42)	26 (39)
Site of original primary tumor		
Breast	5 (15)	13 (20)
Colorectal	9 (27)	9 (14)
Lung	6 (18)	12 (18)
Prostate	2 (6)	14 (21)
Other	11 (33)	18 (27)

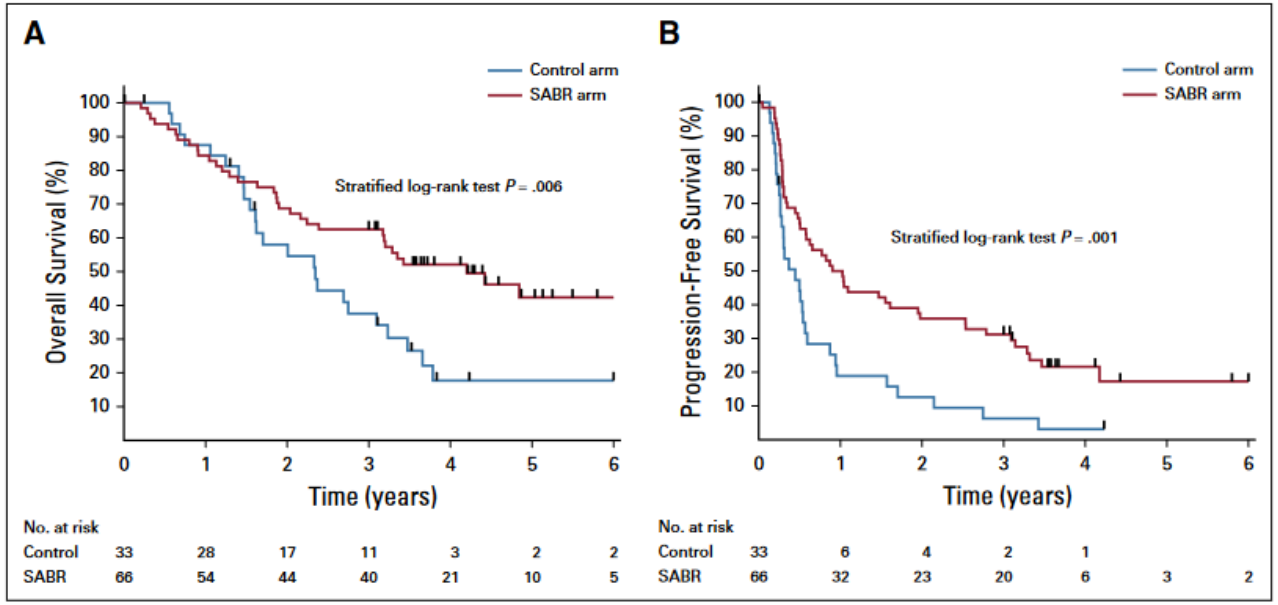

FIG 2. Kaplan-Meier plots for (A) overall survival and (B) progression-free survival. SABR, stereotactic ablative radiotherapy.

SABR achieved 22-month median OS benefit in patients with a controlled primary tumor and 1-5 oligometastases

Palma et al. JCO 2020

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INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY · BIOLOGY · PHYSICS
ASTRO

Stereotactic Radiation for the Comprehensive Treatment of Oligometastases (SABR-COMET): Extended Long-Term Outcomes

Stephen Harrow, MBChB, PhD • David A. Palma, MD, PhD • Robert Olson, MD, MSc • ...
X. Melody Qu, MD, MPH • Andrew Warner, MSc • Suresh Senan, MBBS, PhD • Show all authors

- ✓ **8-year OS was 27.2% in the SABR arm versus 13.6%** in the control arm (hazard ratio, 0.50; 95% confidence interval, 0.30-0.84; *P* = .008)
- ✓ Patients in the SABR arm were less likely to require cytotoxic chemotherapy (33.3% vs 54.6%, respectively, *P* = .043)
- ✓ Even with SABR, many patients progress with new metastases, likely be- cause of the presence of occult micrometastatic disease at presentation…but **some can receive salvage therapy with repeat SABR**

Harrow et al. IJROBP 2022

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Representative Reports of ***MDT*** in Oligometastatic Breast Cancer

Author	Histology	Metastatic sites	Design	No. of metastases	No. of patients	Intervention	Outcomes	Results
David *et al.*[27]	BC	Bone	Prospective trial	⩽3	15	SABR	2-year distant PFS	67%
Trovo *et al.*[28]	BC	Mixed	Prospective trial, single arm, phase II	1 (50%) 2–3 (50%)	54	SABR/IMRT	1-year PFS 2-year PFS 2-year OS	75% 53% 95%
Chalkidou *et al.*[29]	Mixed (BC 5.5%)	Mixed	Prospective trial, single arm, observational	1 (75%) 2 (20%) 3 (5%)	1422	SABR	2-year OS (BC)	83%
Klement *et al.*[30]	Mixed (BC 12%)	Liver	Retrospective	NA	363	SABR	2-year tumor control probability (BC)	88%
Milano *et al.*[31]	Mixed (BC 32%)	Mixed	Prospective trial, single arm	1 (31%) 2 (26%) 3 (23%) 4–5 (20%)	121	SABR	6-year OS (BC)	47%

BC, breast cancer; IMRT, intensity-modulated radiation therapy; mOS, median overall survival; mPFS, median progression-free survival; OS,

Prognostic Factors in Oligometastatic Breast Cancer

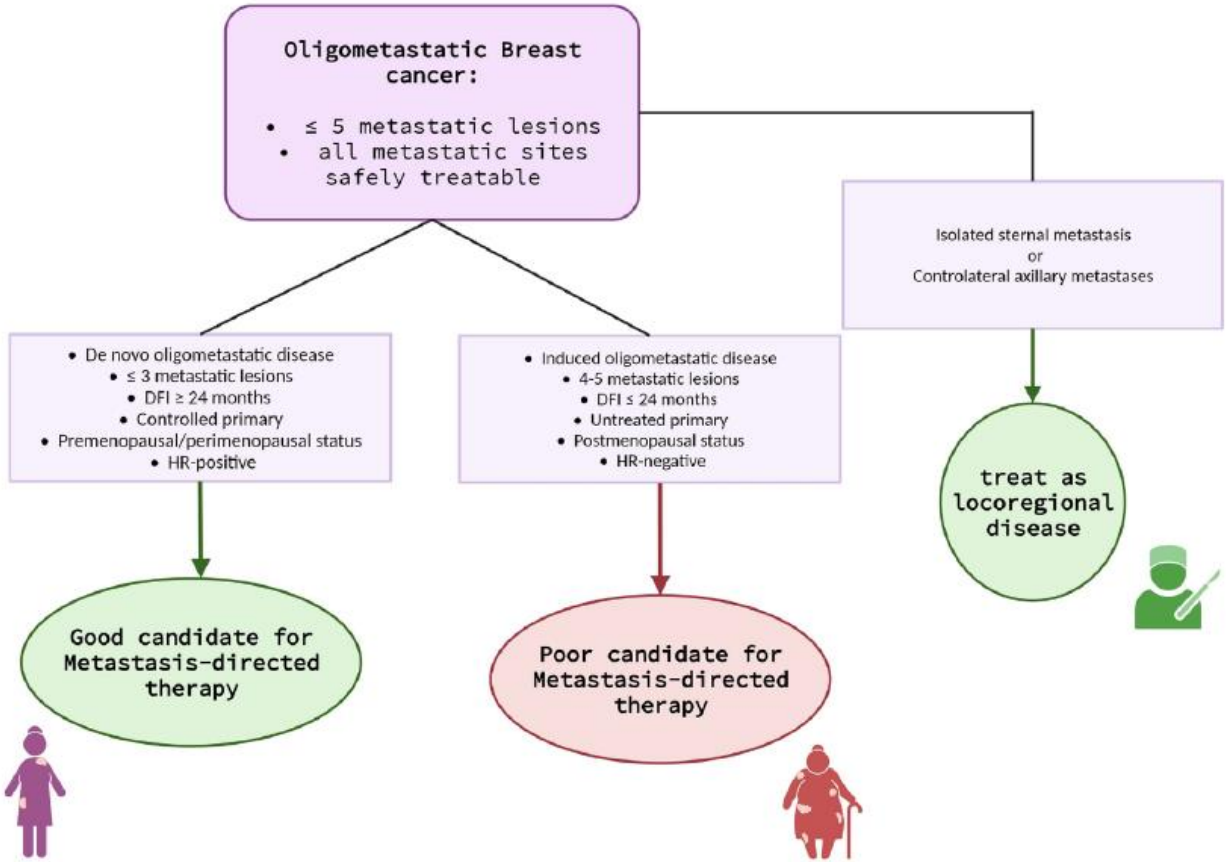

Figure 2. OMBC patients' selection for metastasis-directed therapy based on prognostic and predictive factors.
OMBC, oligometastatic breast cancer.

Merloni F et al. Therapeutic Advances in Medical Oncology 2023
Shen et at. Ann Surg Oncol 2013
Moossdorff M et al. Eur J Surg Oncol 2015

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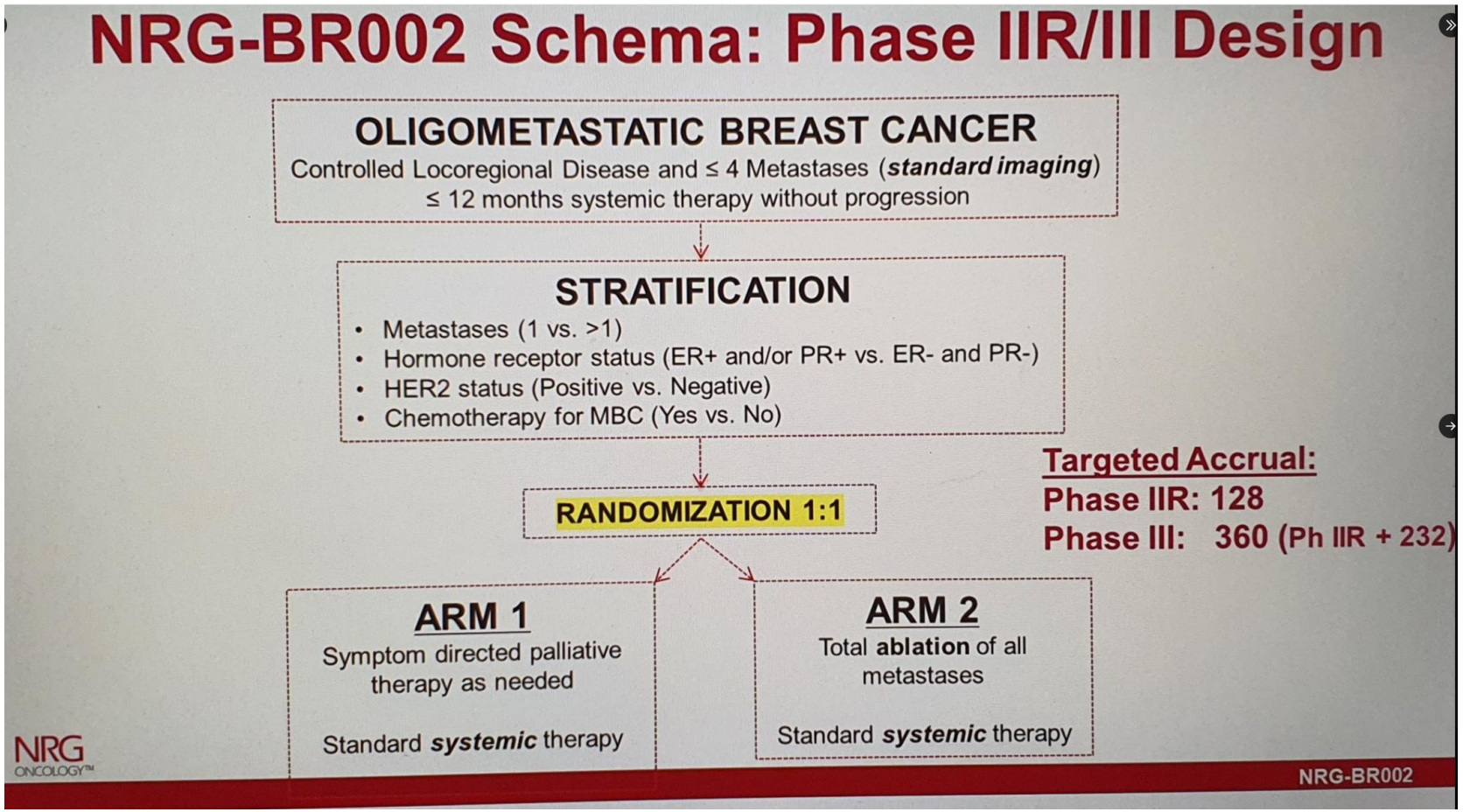
EBM Reports of ***MDT*** in Oligometastatic Breast Cancer: The NRG-BR002



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EBM Reports of ***MDT*** in Oligometastatic Breast Cancer: The NRG-BR002

Patient and Tumor Characteristics

	Standard of Care (n=65)	Standard of Care + Ablation (n=60)	Total (n=125)
Age (years)			
Median	53	55.5	54
Performance Status (Zubrod)			
0	41 (63%)	41 (68%)	82 (66%)
1	24 (37%)	19 (32%)	43 (34%)
Patient Metastasis Count			
1	39 (60%)	36 (60%)	75 (60%)
>1	26 (40%)	24 (40%)	50 (40%)
Hormone Receptor/HER2 Status			
ER and PR-; HER2-	5 (8%)	5 (8%)	10 (8%)
ER and PR-; HER2+	2 (3%)	1 (2%)	3 (2%)
ER and/or PR+; HER2+	6 (9%)	7 (12%)	13 (10%)
ER and/or PR+; HER2-	52 (80%)	47 (78%)	99 (79%)
Metastatic Timing			
Synchronous	12 (18%)	15 (25%)	27 (22%)
Not synchronous	52 (80%)	45 (75%)	97(78%)
Pending	1 (2%)	0 (0%)	1 (1%)

NRG ONCOLOGY™

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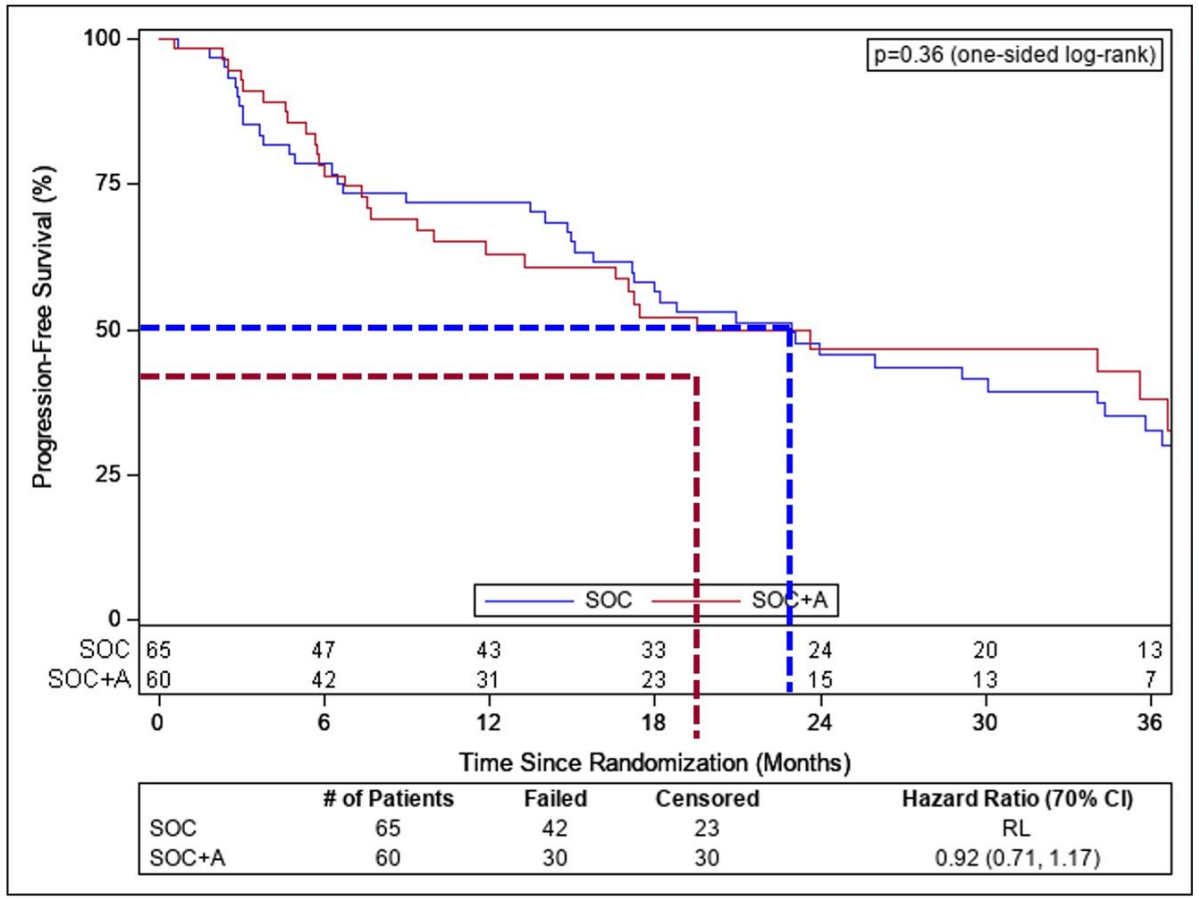
EBM Reports of ***MDT*** in Oligometastatic Breast Cancer: The NRG-BR002



	SOC (65 pts)	SOC+A (60 pts)
24-month estimate (70% CI)	45.7% (38.9%, 52.5%)	46.8% (39.2%, 54.3%)
36-month estimate (70% CI)	32.8% (26.0%, 39.5%)	38.1% (29.7%, 46.6%)
mPFS		
Design	10.5 months	19 months
Observed	23 months	19.5 months

HR [SOC+A/SOC] (70% CI): 0.92 (0.71, 1.17)

Median Follow-up = 35 months
(min-max: 0.03-62.74)

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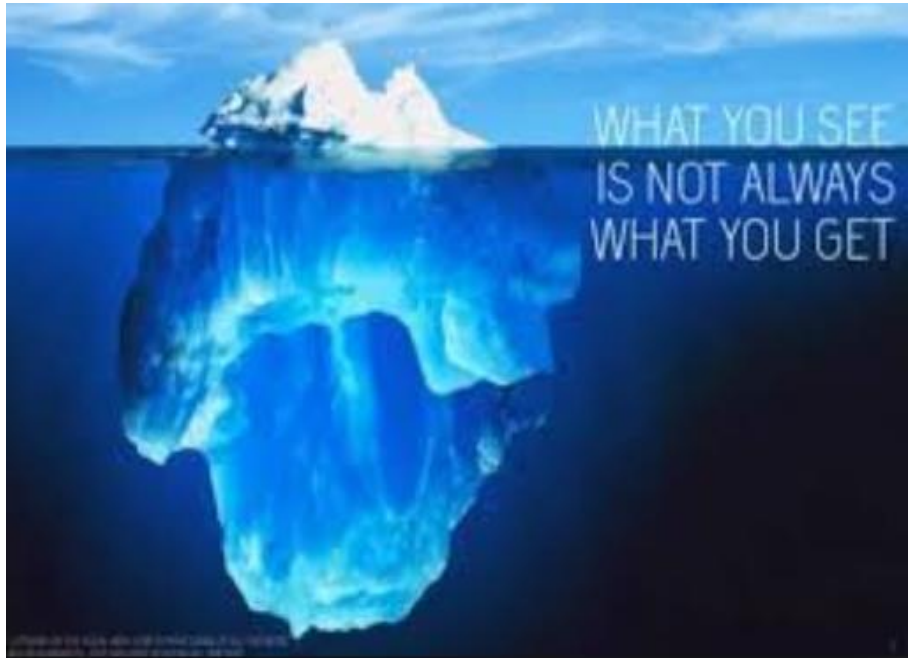
CONCERNS regarding NRG-BR002 trial

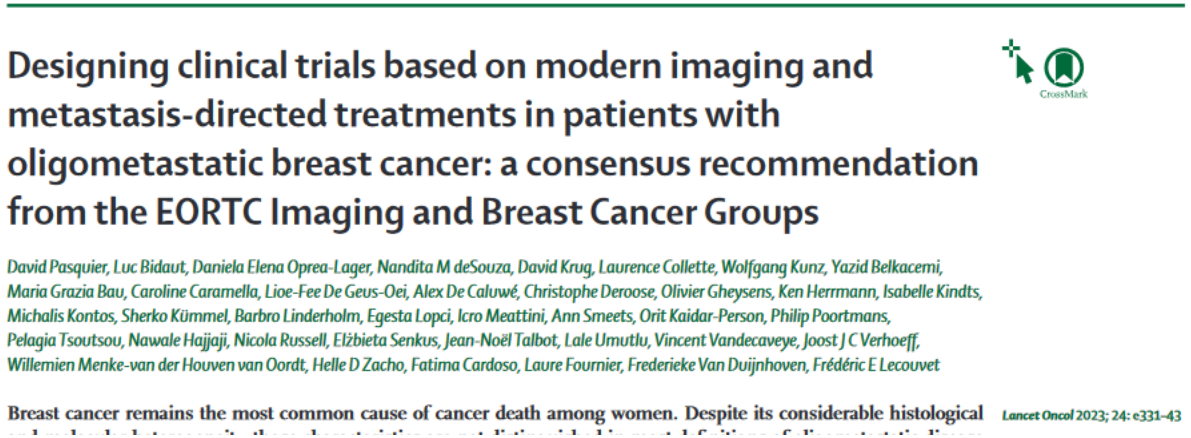
- ❑ **NRG-BR002 has targeted recurrent and de-novo oligometastatic BC without specifying the duration of chemotherapy prior to SBRT (pts could been enrolled within 12 months) neither standardizing the timing of SBRT**
- ❑ **Heterogeneity in SBRT schedules: biological effect of 30Gy/single session is the same of 45Gy/5 fractions??**
- ❑ **It was remarkable that Authors designed the study with an estimated PFS in the ablation arm of 19 months, and it was absolutely spot-on with an observed PFS of 19.5 months. But it also turns out that *Authors grossly underestimated how well patients did on just systemic therapy alone***
- ❑ **Insufficient regulation of the regimen for systemic therapy, (ii) inaccurate timing of the start of PFS and (iii) problems with the procedure for diagnosing oligometastases**

…problems with the procedure for diagnosing oligometastases

CONVENTIONAL IMAGING

METABOLIC/NEXT GENERATION IMAGING?





Designing clinical trials based on modern imaging and metastasis-directed treatments in patients with oligometastatic breast cancer: a consensus recommendation from the EORTC Imaging and Breast Cancer Groups

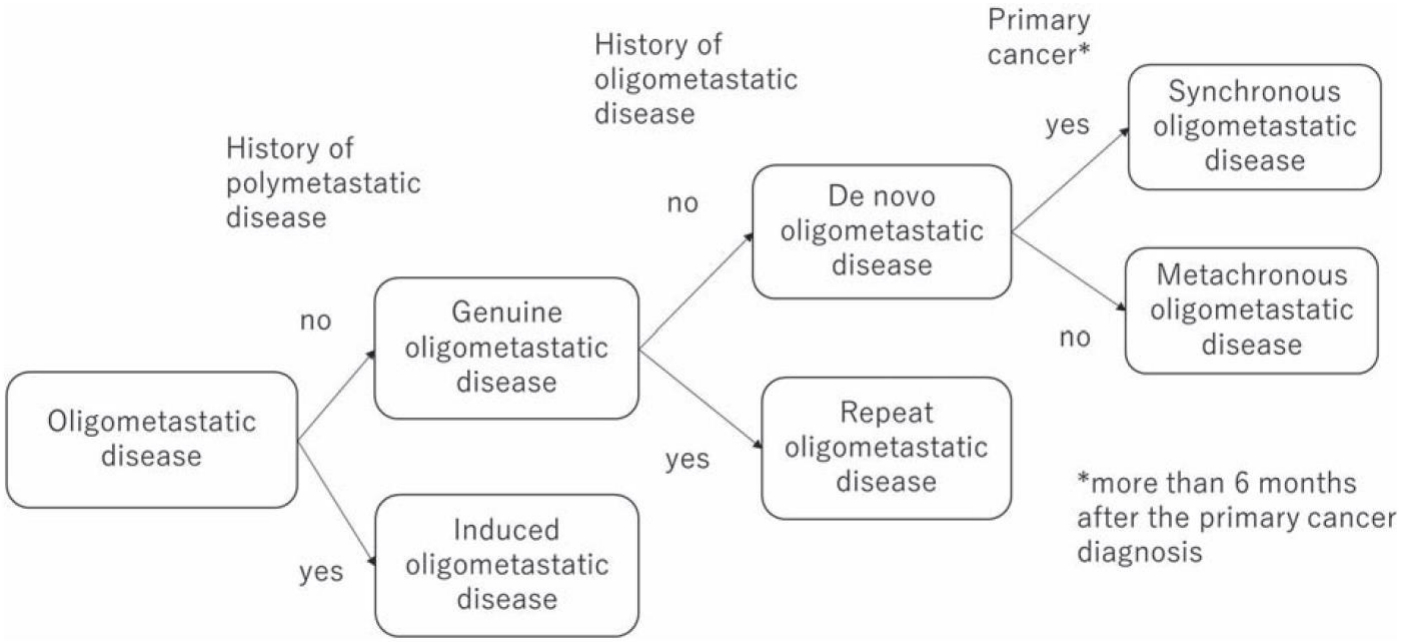
David Pasquier, Luc Bidaut, Daniela Elena Oprea-Lager, Nandita M deSouza, David Krug, Laurence Collette, Wolfgang Kunz, Yazid Belkacemi, Maria Grazia Bau, Caroline Caramella, Lioe-Fee De Geus-Oei, Alex De Caluwé, Christophe Deroose, Olivier Gheysens, Ken Herrmann, Isabelle Kindts, Michalis Kontos, Sherko Kümmel, Barbro Linderholm, Egesta Lopci, Icro Meattini, Ann Smeets, Orit Kaidar-Person, Philip Poortmans, Pelagia Tsoutsou, Nawale Hajjaji, Nicola Russell, Elżbieta Senkus, Jean-Noël Talbot, Lale Umutlu, Vincent Vandecaveye, Joost J C Verhoeff, Willemien Menke-van der Houven van Oordt, Helle D Zacho, Fatima Cardoso, Laure Fournier, Frederieke Van Duijnhoven, Frédéric E Lecouvet

Breast cancer remains the most common cause of cancer death among women. Despite its considerable histological

Lancet Oncol 2023; 24: e331–43

- Delphi questionnaire aimed at offering consensus recommendations
- The main recommendations are the introduction of modern imaging methods in metastatic screening for an earlier diagnosis of oligometastatic breast cancer and the development of prospective trials also considering the histological and molecular complexity of breast cancer
- Strategies for the randomisation of imaging methods and therapeutic approaches in different subsets of patients are also addressed

New classification of Oligometastatic Breast Cancer: what about oligoprogressive disease or induced oligometastases?



EORTC/ESTRO classification of Oligometastatic disease

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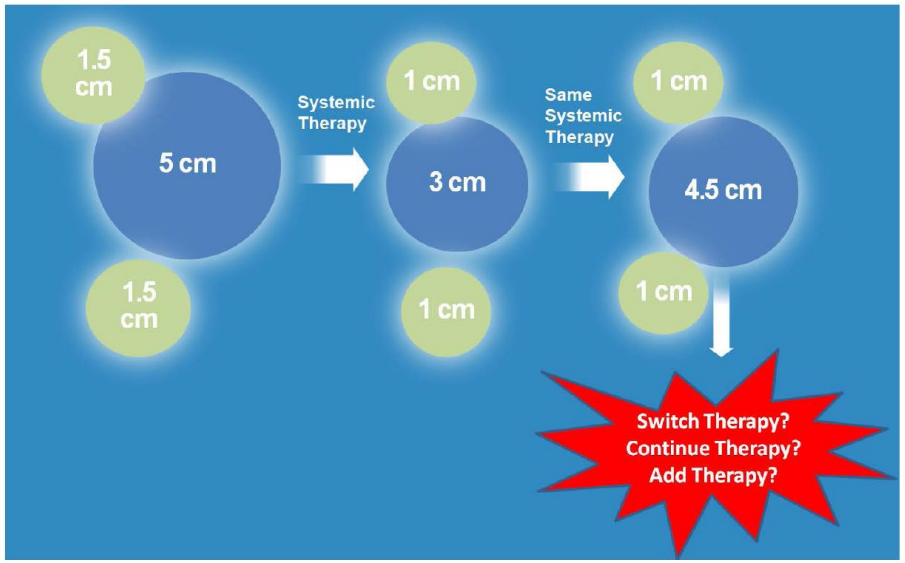
What about oligoprogressive disease or induced oligometastases?

Background

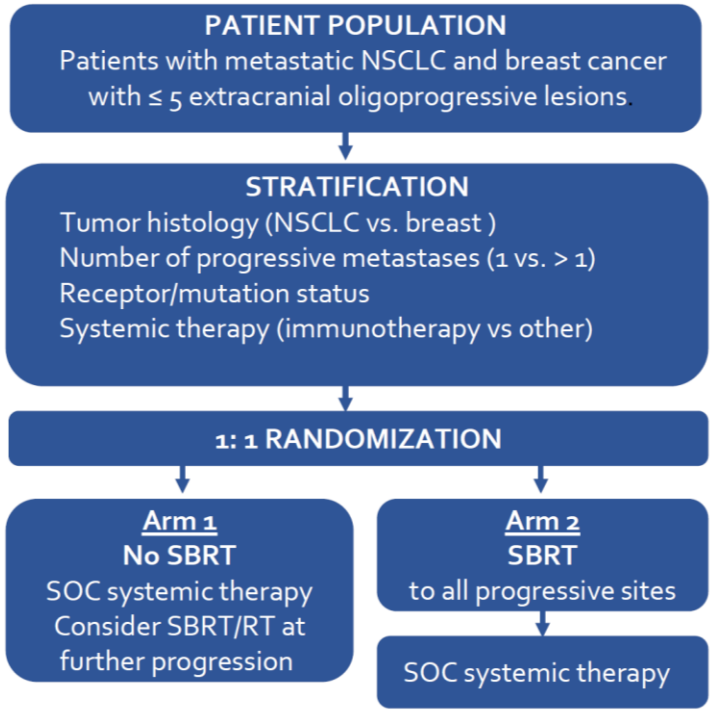


- **Second-line systemic therapy**
  - Non-small-cell lung cancer (NSCLC)
    - PDL-1 positive: Pembrolizumab; PFS= 4 months (Lancet 2016)
    - After platinum: Ramucirumab + Docetaxel; PFS = 4.5 months (Lancet 2014)
    - After first-line EGFR-TKI: Osimertinib; PFS = 10.1 months (NEJM 2017)
    - After Osimertinib: No standard
  - Breast
    - ER+ after first-line ET: Fulvestrant + CDK4/6 inhibitor; PFS = 9.5-20.5 months
    - TNBC after first-line: No standard; PFS = 2.3-5.6 months

CURB trial: oligoprogressive BC

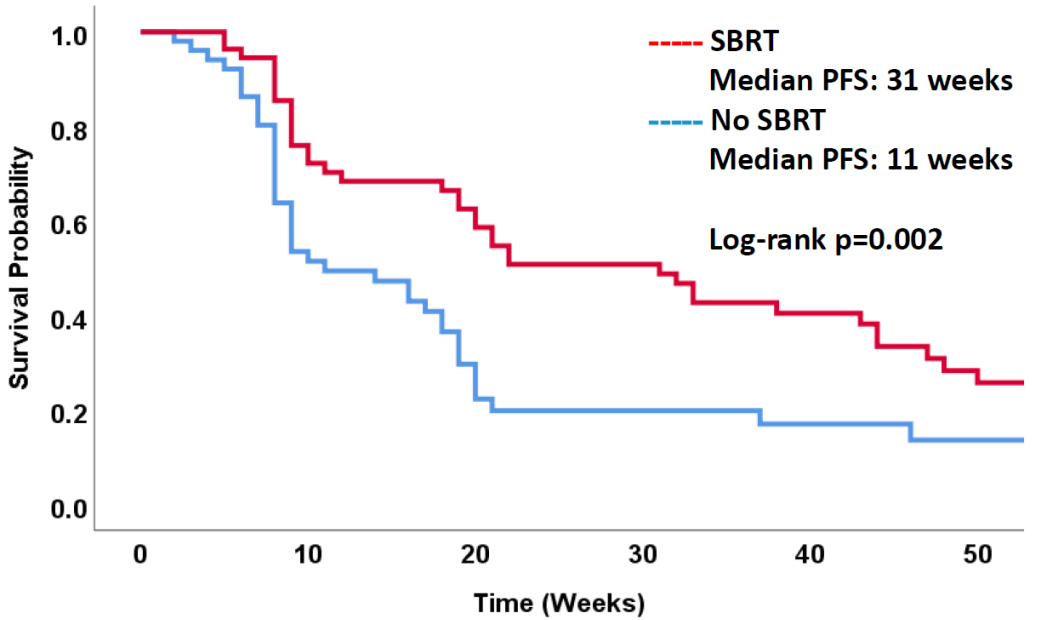
Method

- **Primary objective:**
  - Progression-free survival
- **Accrual goal:**
  - 160 (80 each arm)
  - Current accrual: 106/160
- **Study timeline:**
  - Serial follow up imaging up to 52 weeks



CURB trial: oligoprogressive BC

Results – Progression-Free Survival (Entire Cohort)



Number at risk						
SBRT	55	39	30	25	18	10
No SBRT	51	25	11	7	6	4

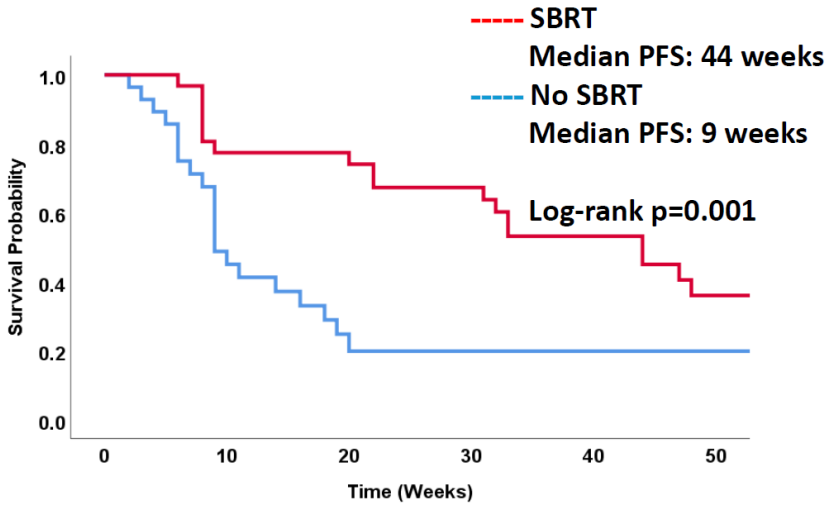
Median follow up: 45 weeks; 58 weeks for living patients.

78 of 106 patients further progressed.

39 of 106 (37%) died.

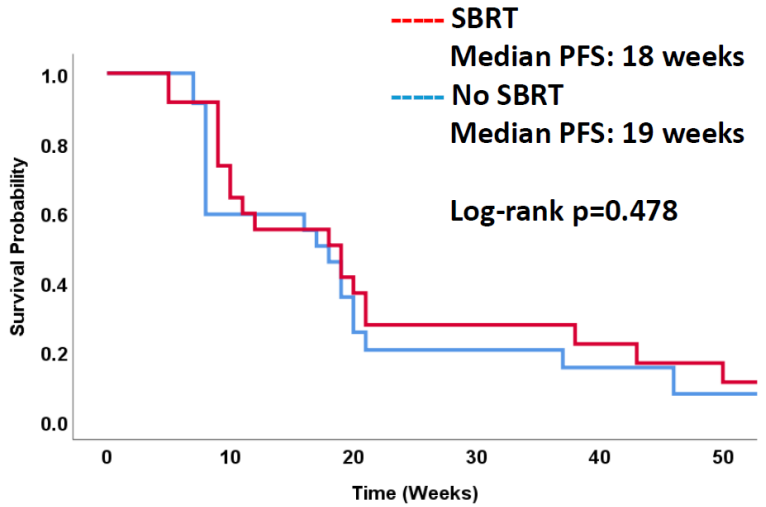
Results – PFS by Primary Disease Sites

Lung (40 of 59 progressed)



Number at risk						
SBRT	31	24	22	19	14	8
No SBRT	28	12	4	3	3	3

Breast (38 of 47 progressed)



Number at risk						
SBRT	24	15	8	6	4	2
No SBRT	23	13	6	4	3	1

Conclusions

- **In this pre-planned interim analysis, we demonstrated the benefit of SBRT to sites of oligoprogression on overall PFS, meeting the primary endpoint.**
  - The difference was driven by the substantial response in NSCLC cohort.
    - Median PFS = 44 weeks, longer than many further lines of systemic therapy.
  - No benefit of SBRT seen in the breast cohort.
    - Most breast patients developed new lesions upon further progression.
- **SBRT to oligoprogression had acceptable toxicity profiles.**
- **The mechanism of the differential benefits between NSCLC and breast cohorts merits further evaluation.**

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IS **PFS** THE PROPER ENDPOINT IN OLIGOMETASTATIC BC?

Novel Endpoints in the Appraisal of Ablative Local Treatments of Oligometastatic Cancer

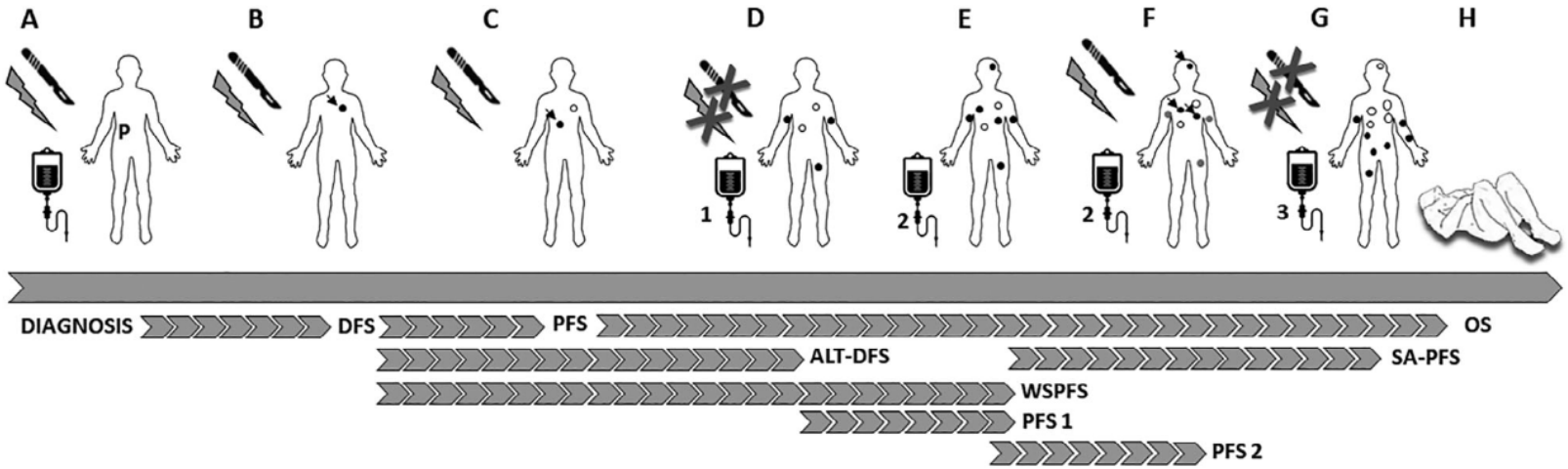

Figure 1. Natural history of oligometastatic disease considering integration of ablative local treatments (ALT). **(A)**: Multimodal management of primary tumor (P). **(B)**: Oligometastatic relapse consisting of a viable metastasis (black dot) treated with surgical or radiation ALT. **(C)**: Stable remission of the ALT-treated metastasis (white dot) and second course of ALT to novel active metastases (black dot). **(D)**: Stable remission of the ALT-treated metastases and onset of 3 metastases not amenable to ALT to all disease sites (black dots), resulting in first-line systemic therapy initiation. **(E)**: Polymetastatic conversion, requiring second-line systemic therapy. **(F)**: Oligoprogression consisting of 3 oligoprogressive metastases (black dots) treated with ALT and stable remaining disease (grey dots), resulting in second-line systemic therapy continuation. **(G)**: Polymetastatic progression (black dots) under second-line systemic therapy, not amenable to ALTs and initiation of third-line systemic therapy. **(H)**: Death.
Abbreviations: ALT-DFS, ablative local treatments-disease-free survival; DFS, disease-free survival; OS, overall survival; PFS, progression-free survival; PFS-1, progression-free survival with first line systemic therapy; PFS-2, progression-free survival with second line systemic therapy; SA-PFS, systemic therapy plus-adjusted progression-free survival; WSPFS, widespread progression-free survival.

Loi M et al. Oncologist 2021

Breast Care

Review Article

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St. Gallen/Vienna 2023: Optimization of Treatment for Patients with Primary Breast Cancer – A Brief Summary of the Consensus Discussion

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Oligometastatic Disease

A case was presented with a patient who has been diagnosed with ER-negative HER2-positive breast cancer, and staging scans disclose a 4 cm tumor in the breast, positive axillary LN, and an isolated pulmonary nodule. With primary docetaxel-trastuzumab-pertuzumab combination therapy, a complete clinical response was achieved. The majority of the panelists would proceed with local therapy (in total 86%); however, 10% would perform surgery only, 8% would perform radiotherapy only, and 68% would consequently do both surgery and radiotherapy. There were also votes for no local therapy (14%). Accompanying discussions indicated that the majority of panelists voted for "pushing the boundaries of cure" under favorable circumstances of oligometastatic disease.

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Future efforts to identify specific subsets who may benefit from SBRT to oligometastases are likely to continue…

Table 3. Select accruing/closed trials in metastatic breast cancer.

	Premise	Inclusion criteria	Study design
OLIGOMA	The addition of MDT with RT to systemic therapy in oligometastatic breast cancer improves PFS and QOL	Metastatic breast cancer with ⩽5 metastases (includes intra-cranial)	Randomized to systemic therapy *versus* systemic therapy + MDT with RT
JCOG1017/PRIM-BC	Systemic therapy + primary tumor resection in *de novo* metastatic breast cancer is superior to systemic therapy alone	*De novo* metastatic breast cancer treated with 3 months of primary systemic therapy	Randomized to continuation of systemic therapy *versus* primary tumor resection + systemic therapy

MDT, metastasis-directed therapy; PFS, progression-free survival; QOL, quality of life; RT, radiotherapy.

Conclusion AND Unmet points

- ❑ What's the clinically relevant endpoint in MDT?
- ❑ Optimal timing of MDT: Should we treat metastases upfront, or should we prioritize systemic therapy and subsequently consider MDT?
- ❑ How long should we wait to initiate MDT?

Based on current data, these questions remain unanswered, and ongoing trials seem not designed to solve this issue