Ruolo della Radioterapia nelle pazienti con malattia oligometastatica

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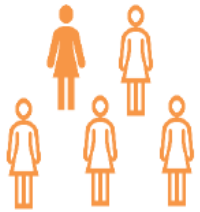
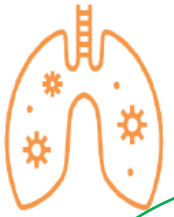
Oligometastases in Breast Cancer



- **5-10%** of patients present with metastatic disease
- **20% of patients** with localized disease **will develop metastases** within 5 years of their initial diagnosis



- Disease tends to reoccur at previously known sites of metastasis
- **Oligometastatic** breast cancer accounts for **20% of metastatic breast cancer** patients

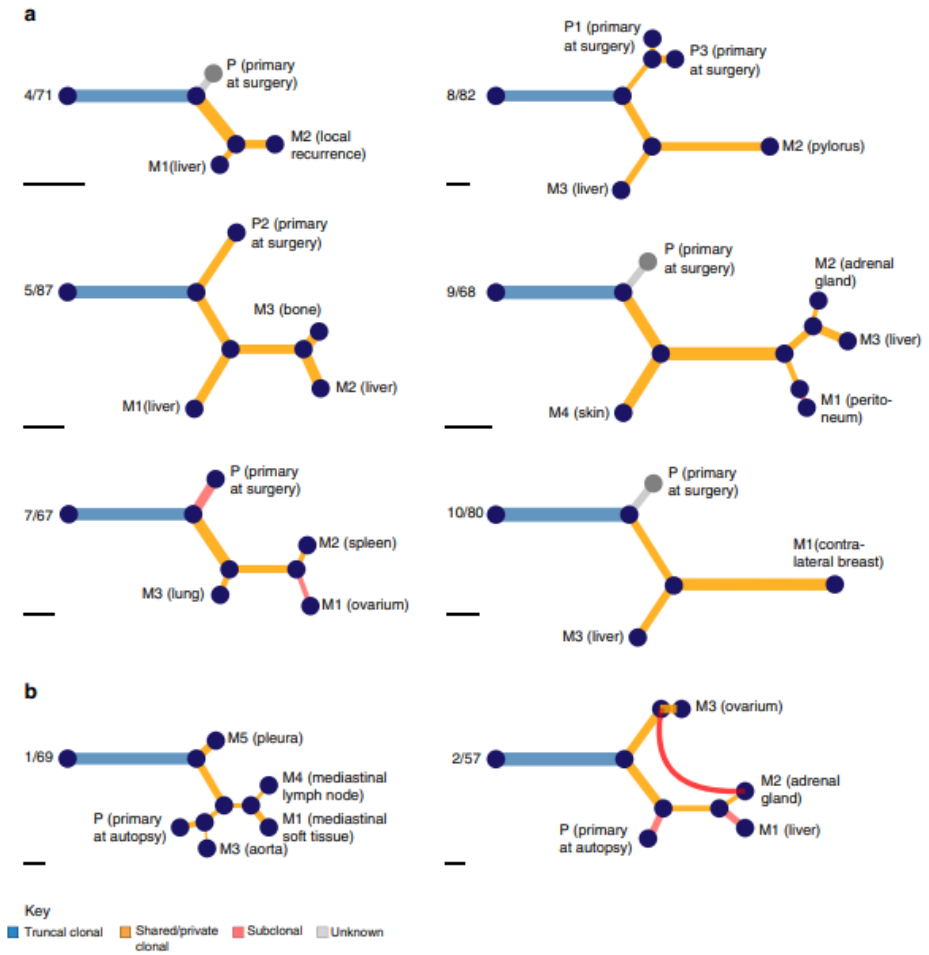
Terao M, et al. Transl Cancer Res 2020

MDT in BC patients: theoretical benefits…

- **Increase local control** to prevent symptoms and maintain quality of life
- Ablate all visible metastases **to prolong PFS**
- Reduce tumor burden **to prolong OS**
- Ablate resistant clones **to prolong systemic therapy efficacy**
- **Delay further disease progression** to delay the need to start systemic therapy
- **Synergize with systemic therapies** to improve outcomes

Breast Cancer phylogenetic trees representing metastatic progression

and tumor heterogeneity…



1. In some patients, all distant metastases cluster on a branch separate from their primary lesion. Clonal frequency analyses of somatic mutations show that the metastases have a monoclonal origin and descend from a common 'metastatic precursor‘

2. Alternatively, multiple metastatic lesions are seeded from different clones present within the primary tumour

Only two modes of disease progression in BC?

Nat Commun. 2017 Apr 20:8:14944

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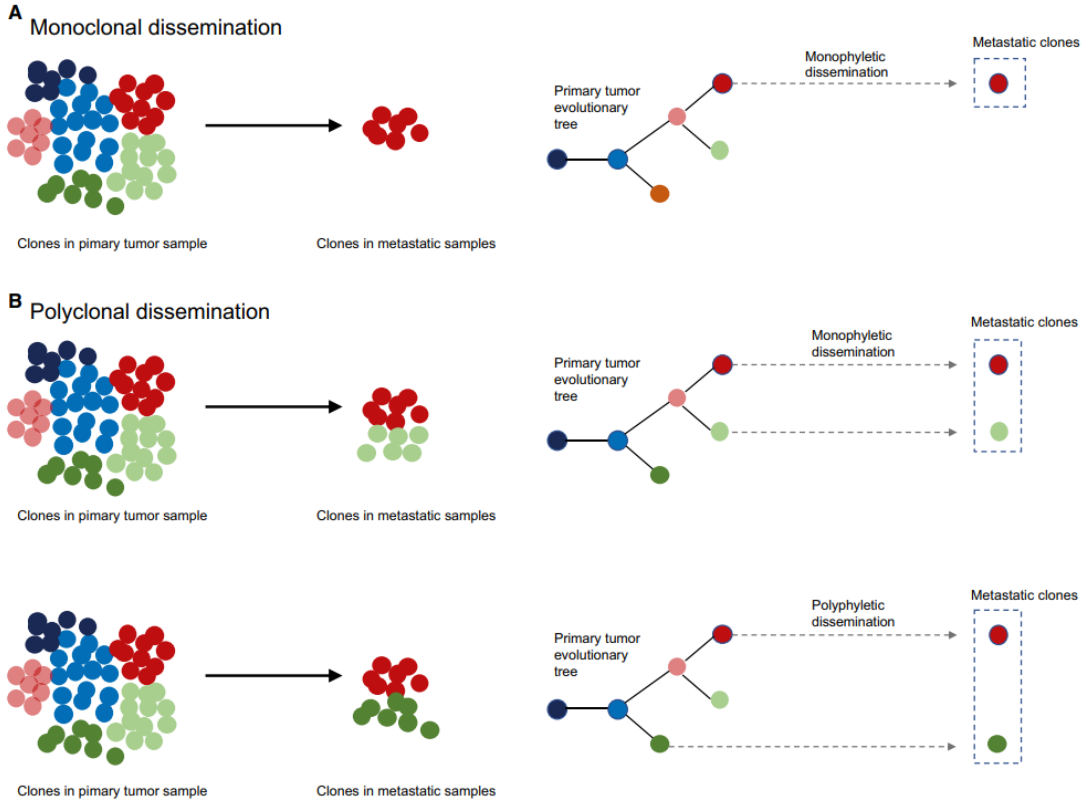
Cancer Genome Evolutionary Trajectories in Metastasis



Metastatic lesions acquire new genomic alterations spontaneously and under selective pressure from therapies

Nat Commun. 2017 Apr 20:8:14944

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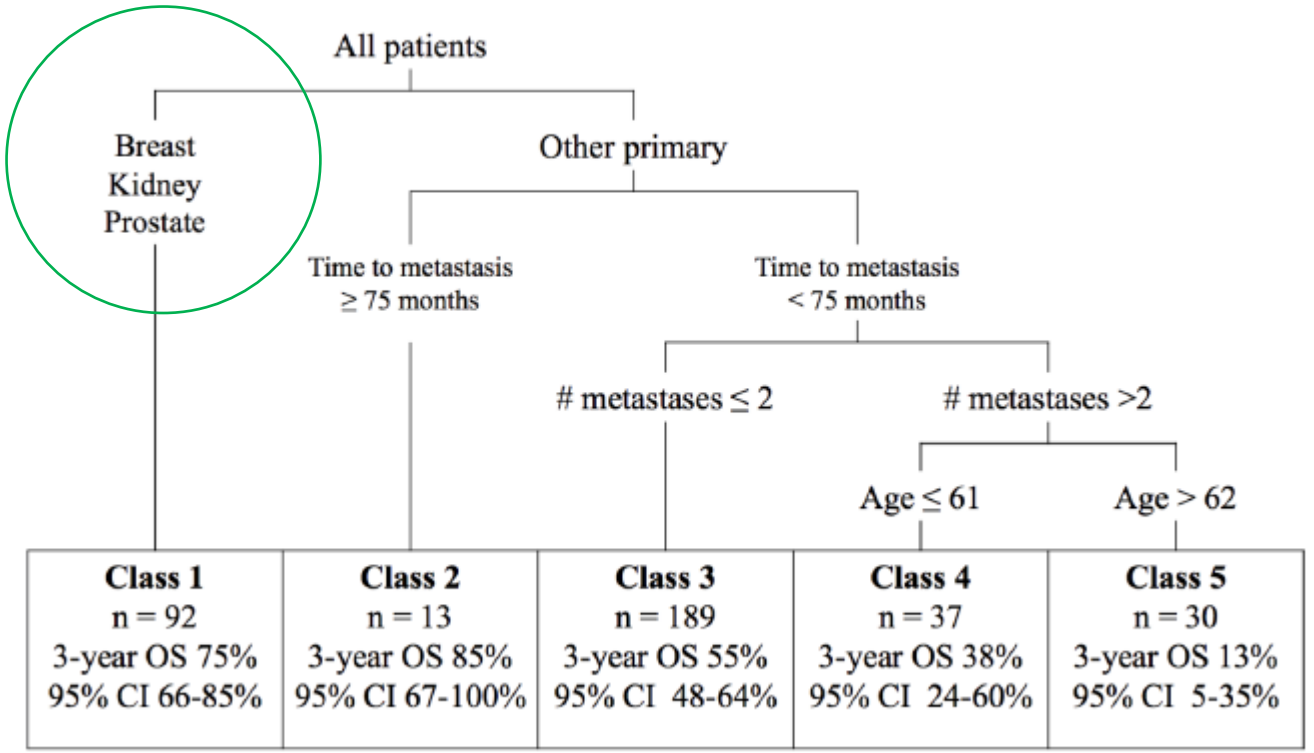
Classification for long-term survival in oligometastatic patients treated with ablative radiotherapy: A multi-institutional pooled analysis



Hong JC et al. PlosONE 2018

Oligometastases in Breast Cancer

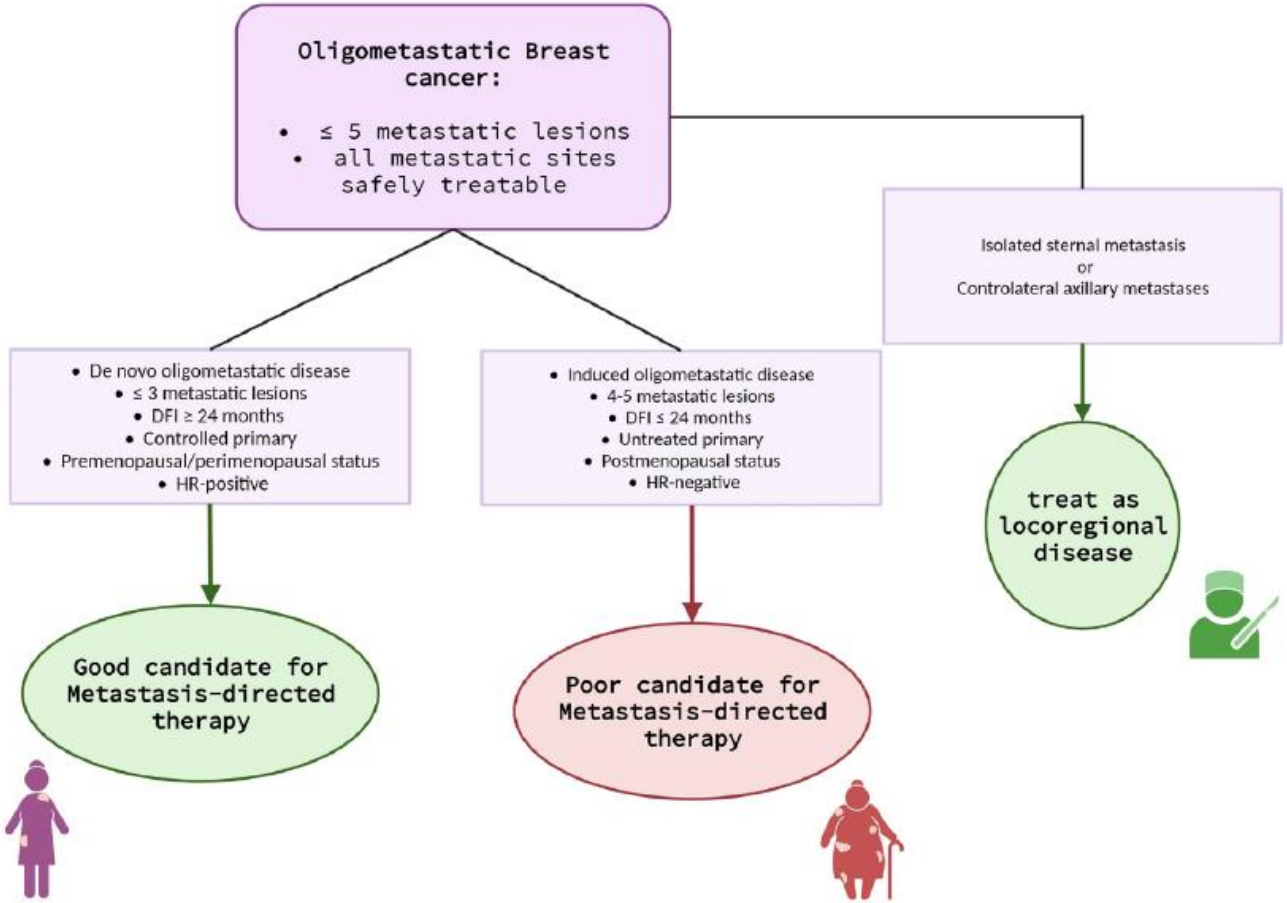


Figure 2. OMBC patients' selection for metastasis-directed therapy based on prognostic and predictive factors.
OMBC, oligometastatic breast cancer.

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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OXFORD

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Article

Characterization of Oligometastatic Disease in a Real-World Nationwide Cohort of 3447 Patients With de Novo Metastatic Breast Cancer

Tessa G. Steenbruggen, MD,[1] Michael Schaapveld, PhD,[2] Hugo M. Horlings, MD, PhD,[3] Joyce Sanders, MD, PhD,[3] Sander J. Hogewoning, MSc,[4] Esther H. Lips, PhD,[5] Marie-Jeanne T. Vrancken Peeters, MD, PhD,[6] Niels F. Kok, MD, PhD,[6] Terry Wiersma, MD,[7] Laura Esserman, MD, PhD[8] Laura J. van 't Veer, PhD,[9] Sabine C. Linn, MD, PhD,[1,10] Sabine Siesling, PhD,[4,11] Gabe S. Sonke, MD, PhD[1,12,*]

Table 1. Association of number of metastases with overall survival

Cutoff oligo	No. (%)[a]	10-y overall survival estimate[b]	Adjusted HR (95% CI)[c]	P
1 metastasis	269 (8.6)	17.1%	0.70 (0.52 to 0.96)	.03
2-3 metastases	248 (7.9)	12.5%	0.63 (0.45 to 0.89)	.009
4-5 metastases	95 (3.0)	7.4%	0.91 (0.60 to 1.37)	.65
>5 metastases	2528 (80.1)	3.2%	Referent	

[a]Numbers are based on the weighted cohort; the number of metastases was available for 3140 out of 3447 MBC patients. CI = confidence interval; HR = hazard ratio.
[b]Ten-year overall survival estimates are based on an univariable model.
[c]Hazard ratios are adjusted for age at diagnosis of MBC, breast cancer subtype, single-organ metastases, bone, liver, lung, and central nervous system metastases. The 95% confidence interval is based on robust standard errors.

Clinical Results
Metastases-directed-therapy in Oligometastatic Breast Cancer

AUTHOR	DISEASE	SITE	DESIGN of trial	N^ lesions	N^ patients	Technique	ENDPOINTS	%
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,

Radiotherapy and Oncology 164 (2021) 245–250

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic Review

Stereotactic body radiotherapy to treat breast cancer oligometastases: A systematic review with meta-analysis

Gustavo A. Viani [a,b,*], Andre G. Gouveia [b,c], Alexander V. Louie [d], Martin Korzeniowski [e], Juliana F. Pavoni [f], Ana Carolina Hamamura [a], Fabio Y. Moraes [b,e]

[a] Ribeirão Preto Medical School, Department of Medical Imagings, Hematology and Oncology of University of São Paulo (FMRP-USP), Ribeirão Preto; [b] Latin America Cooperative Oncology Group (LACOG), Porto Alegre; [c] Radiation Oncology Department - Americas Centro de Oncologia Integrado, Rio de Janeiro, Brazil; [d] Department of Radiation Oncology, Odette Cancer Center, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada.; [e] Department of Oncology - Division of Radiation Oncology, Kingston General Hospital, Queen's University, Kingston, Canada; [f] Faculty of Philosophy, Letters and Natural Sciences, University of São Paulo, Ribeirão Preto, Brazil

Table 1
Characteristics of studies included.

Author	Milano	Scorsetti	Trovo	Onal	David	Milano 1	Milano 2	Weykamp	Li	Tan	Weitjunga
Design	R	R	P	R	P	P	P	R	R	R	R
Patients	40	33	54	22	15	36	12	46	10	120	79
Lesions	85	43	92	29	19	83	21	58	10	193	103
Age (median)	55	57	57	55	61	60	44	55	54	55	56
Number of mets (median)	≤5	≤5	≤5	≤3	≤3	≤5	≤5	≤3	≤5	≤5	≤5
Site of mets	Mixed	Mixed	Mixed	Mixed	Bone only	Mixed	Bone only	Mixed	Bone only	Mixed	Mixed
KPS (median)	>70	>70	>70	>70	>70	>70	>70	>70	>70	>70	>70
Number of sites (median)	2	2	2	1	1	1	1	1	2	1	1
ER/PR%	63	70	80	77	73	56	92	76	80	83	84
Her-2 (+) %	NR	48	20	32	20	NR	NR	20	20	17	10
RT technique	VMAT	VMAT	IMRT	IMRT	IMRT	NR	NR	IMRT	3DRT	3DRT/IMRT	IMRT
SBRT total dose Gy/fractions (median)	NR	75/3fx	36/3fx	54/3 fx	20/1fx	50/10fx	50/10fx	28/3fx	20/1fx	NR	BED >60 Gy4
Follow-up (median) months	56	24	30	18	24	52	52	21	32	50	50

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Table 2
Metaregression analysis of patients, tumor and treatment parameters for overall survival and local control at 2 years.

Variable	*B*	*P*
Overall Survival at 2 years		
Bone only	0.20	0.01
Prospective design	0.18	0.001
%ER/PR	0.005	0.230
%HER-2 (+)	−0.007	0.105
≤ 3 sites	0.08	0.491
BEDGy10	−0.002	0.212
Local Control at 2 years		
Bone only	0.05	0.297
Prospective design	0.009	0.210
%ER/PR	0.05	0.001
%HER-2 (+)	0.001	0.978
≤ 3 sites	−0.009	0.858
BEDGy10	−0.001	0.802

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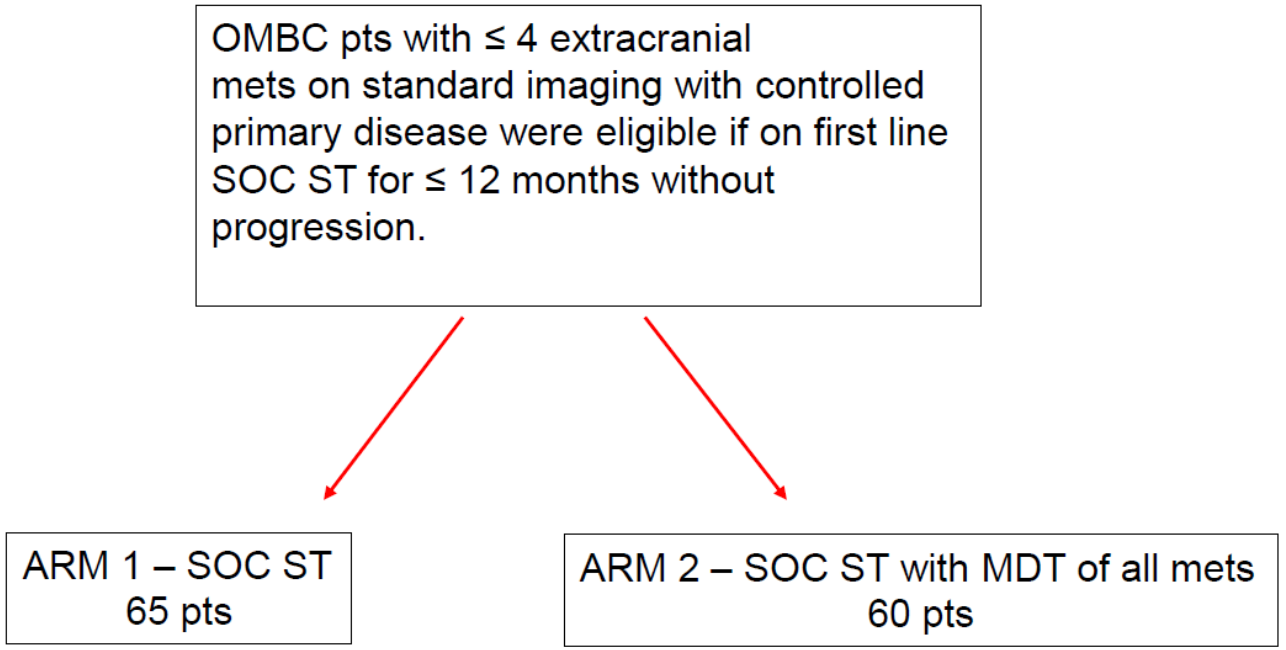
NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) for newly oligometastatic breast cancer (NCT02364557).



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NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) for newly oligometastatic breast cancer (NCT02364557).

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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NRG-BR002: A phase IIR/III trial of standard of care systemic therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical resection (SR) for newly oligometastatic breast cancer (NCT02364557).

- **Median PFS**: 23 vs 19.5 months
- **24 and 36-mo PFS:** 45.7% and 32.8% vs 46.8 and 38.1; HR (70% CI): 0.92 (0.71, 1.17); 1-sided log-rank p = 0.36.
- **Median OS** was not reached
- **36-mo OS**: 71.8% vs 68.9% (2-sided log-rank p = 0.54).
- There were **no grade 5 treatment-related adverse events** (AEs), 1 grade 4 AE in ARM 1, and 9.7% and 5.3% grade 3 AEs in ARMS 1 and 2, respectively.

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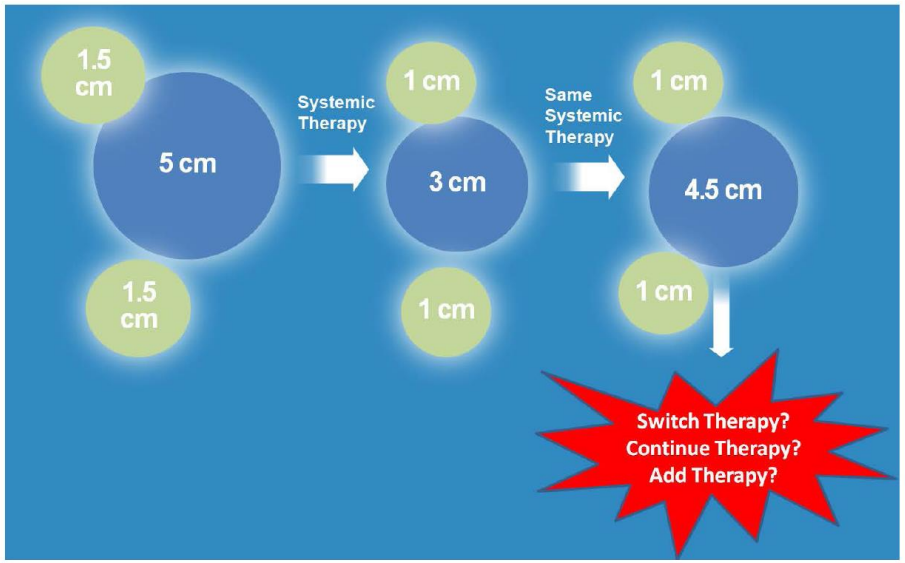
CONCERNS regarding NRG-BR002 trial

- 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??
- Median PFS in the arm receiving only systemic therapy was better than expected compared to previous evidence in the literature
- 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

We need a better understanding of OMBC **biology** to fine our results

What about oligoprogressive disease or induced oligometastases?

Background

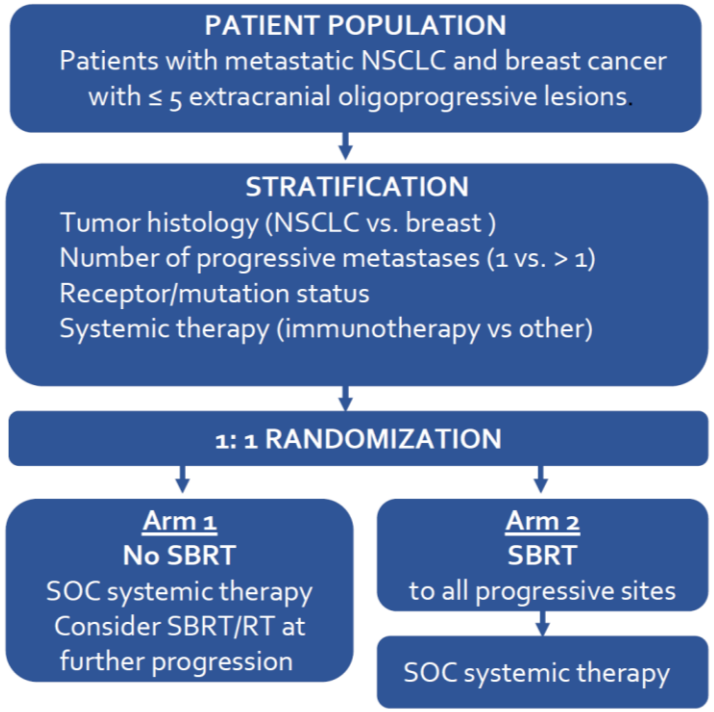


- **Second-line systemic therapy**
  - Non-small-cell lung cancer (NSCLC)
    - PDL-1 positive: Pembrolizumab; PFS= 4 months (Lancet 2016)
    - After platinum: Ramucirumab + Docetaxel; PFS = 4.5 months (Lancet 2014)
    - After first-line EGFR-TKI: Osimertinib; PFS = 10.1 months (NEJM 2017)
    - After 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

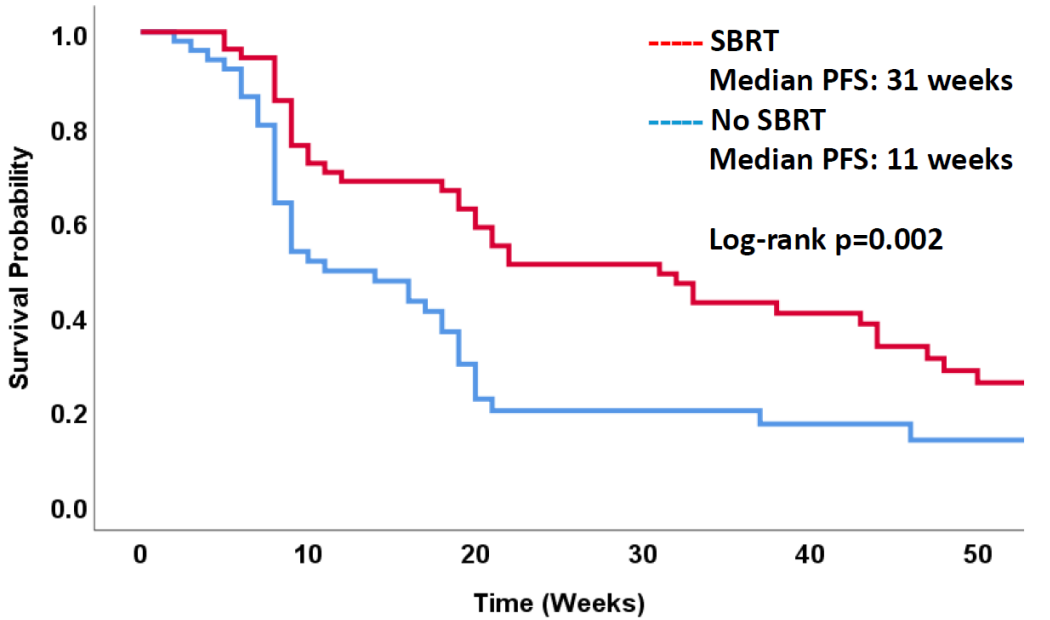
Method

- **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.

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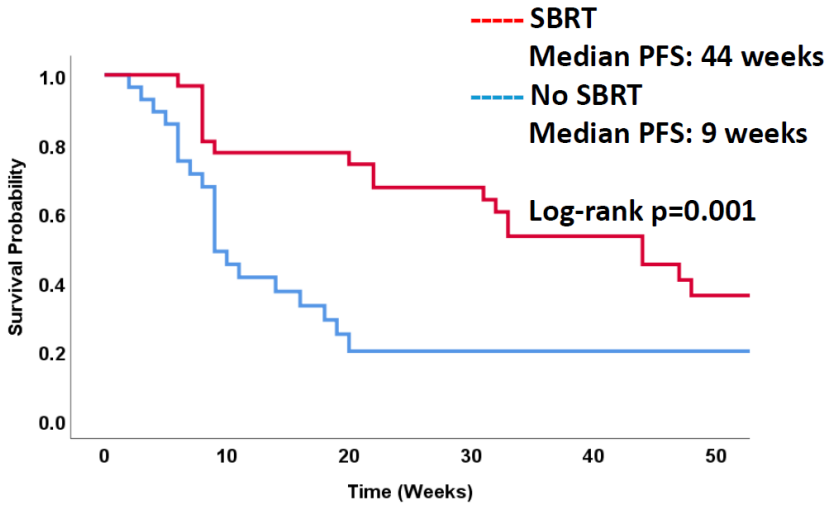
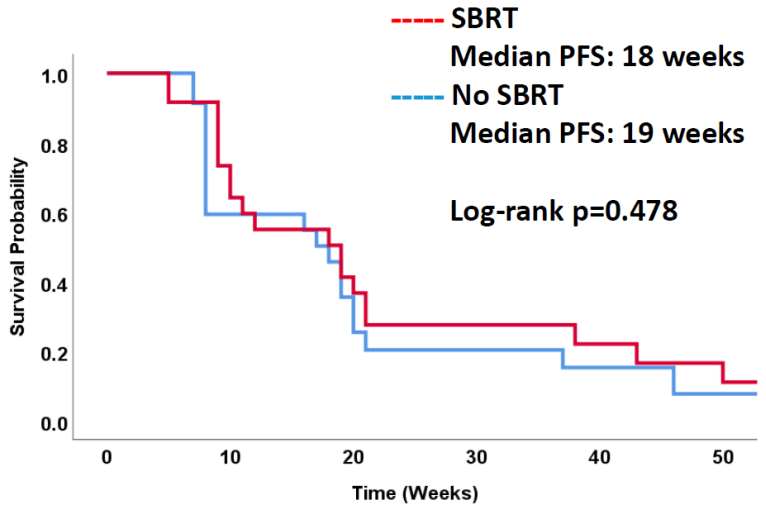
Results – PFS by Primary Disease Sites

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.**

STUDY PROTOCOL Open Access

Stereotactic radiotherapy for oligoprogressive ER-positive breast cancer (AVATAR)

Reem Alomran[1,2], Michelle White[3], Melissa Bruce[1], Mathias Bressel[1], Susan Roache[1], Lama Karroum[1], Gerard G. Hanna[1,4], Shankar Siva[1,4], Shom Goel[1] and Steven David[1,3*]

Estimated study duration

It is anticipated that 32 eligible patients will be recruited over 2 years. All participants will be followed until death or study completion. The study will be considered closed after all patients had a minimum of 2 years of follow-up or died. It is anticipated that this study will run for approximately 4 years. Participants who do not commence SRT within 28 days of enrolment will be replaced until 32 patients commence SRT.

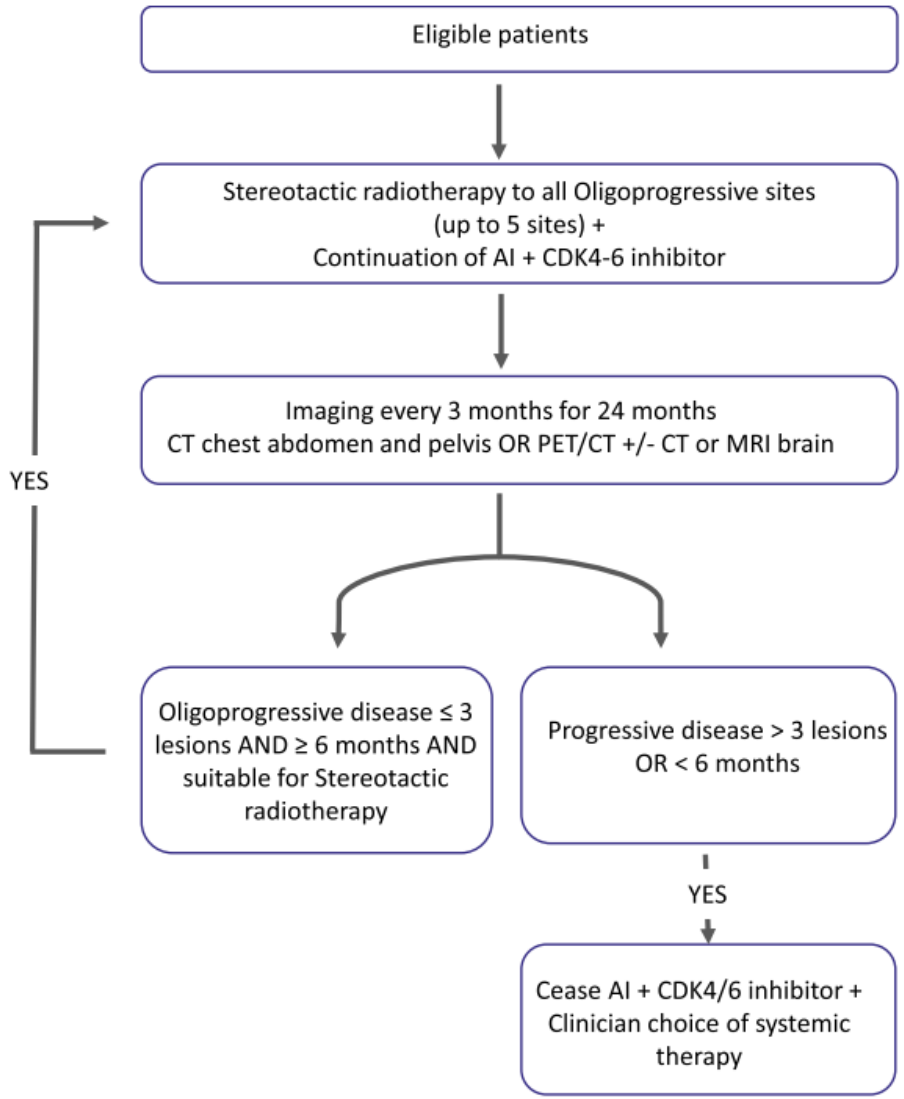
Primary objective

The primary objective of this study is to describe the time to change in systemic therapy after SRT in patients with ER-positive HER2-negative advanced breast cancer receiving an AI in combination with a CDK 4/6 inhibitor who have up to 5 sites of OPD.

Secondary objective

The secondary objectives of this study are to describe:

1. Overall survival (OS)
2. Progression free survival (PFS).
3. Treatment related toxicity.



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The hypothesis was that SBRT to the OP lesions would delay a change in systemic therapy by ≥ 6 months in > 25% of patients and the study would be considered meaningful if ≥ 25% of patients remained event free and on endocrine therapy and CDK4/6 inhibitor for ≥ 6 months.

The study was considered positive as 47% of patients (15/32) remained on endocrine therapy+CKD4/6 inhibitor for ≥ 6 months

AVATAR trial was presented at the American Society for Radiation Oncology 2023 annual meeting

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

Table 3 Ongoing prospective trials of MDT for oligometastatic and oligoprogressive breast cancer

Trial	Phase	Study completion	Primary endpoint	Tumor histology	# of metastasis allowed	Local tx
Oligometastasis						
STEREO-SEIN (NCT02089100)	III	2023	PFS	Breast (HR+/any HER2)	5	SBRT
CLEAR (NCT03750396)	II, single arm	2025	PFS	Breast (HR+/HER2-)	2	Surgery, SBRT, RFA
EXTEND (NCT03599765)	II, single arm	2025	PFS	Various	5	SBRT
LARA (NCT04698252)	II, randomized	2031	PFS	Breast (HR+/HER2-)	4	Surgery, SBRT, RFA
OMIT (NCT04413409)	III	2025	OS	Various	3	Surgery
SABR-COMET-10 (NCT03721341)	III	2029	OS	Various	10	SBRT
OLGIOMA (NCT04495309)	III	2025	PFS	Various	5	SBRT
TAORMINA (NCT05377047)	III	2027	OS	Various	5	SBRT
Oligoprogression						
AVATAR (ACTRN 12620001212943)	II, single arm	2024	Time to change of sys tx	Breast (HR+/HER2-)	5	SBRT
EXTEND (NCT03599765)	II, single arm	2025	PFS	Various	5	SBRT
COSMO (NCT05301881)	II, single arm	2040	PFS	Various	2	Surgery, SBRT, RFA

tx treatment, *PFS* progression-free survival, *OS* overall survival, *sys tx* systemic treatment, *HR* hormone-receptor, *HER2* HER2/neu, *SBRT* stereotactic body radiotherapy, *RFA* radiofrequency ablation

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

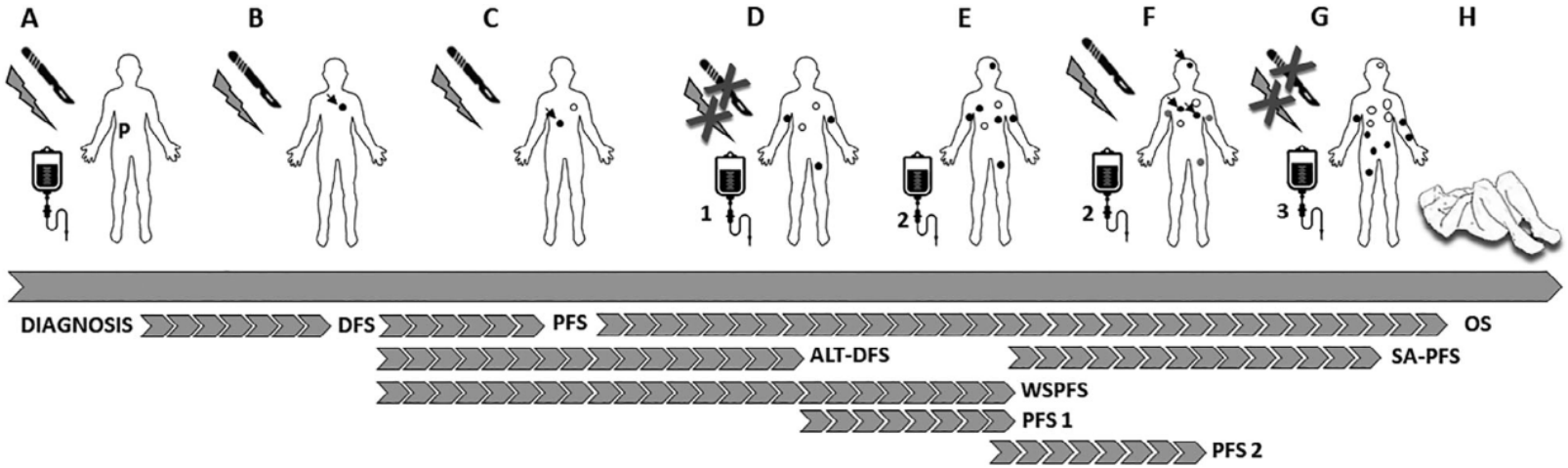

Figure 1. Natural history of oligometastatic disease considering integration of ablative local treatments (ALT). **(A)**: Multimodal management of primary tumor (P). **(B)**: Oligometastatic relapse consisting of a viable metastasis (black dot) treated with surgical or radiation ALT. **(C)**: Stable 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

Who is the real OMBC patient?

Easily accessible

Difficult availability

- Clinical
- Imaging
- Genetic/epigenetic

Less informative

Highly informative

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

MDT in BC patients: theoretical benefits…

- ✓ Reducing tumor heterogeneity

- ✓ Extending the current line of systemic therapy (thereby reducing cost or toxicity to patients no longer requiring the immediate switch to a less effective next-line therapy)

- ✓ Potentially improving PFS and/or OS