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***L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA***

**20 - 21 APRILE  
2023 ROMA**

**THE HIVE HOTEL**

Via Torino, 6

**THE  
OXFORD DEBATE  
EDITION**



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**Le terapie locoregionali dovrebbero essere sempre associate alla terapia sistemica nella malattia oligometastatica**

**CONTRO**

**Martina Pagliuca, MD**

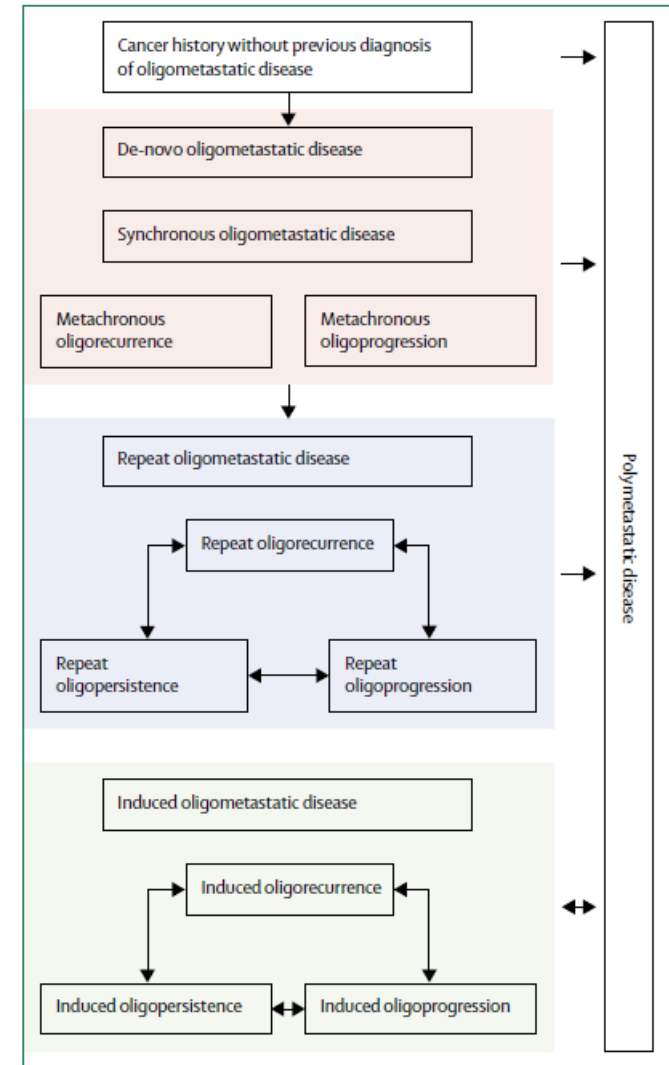
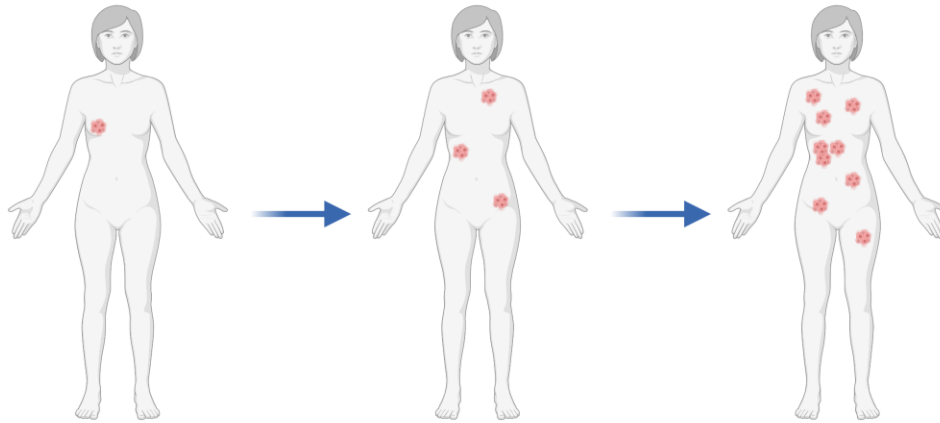
Gustave Roussy Cancer Center, Villejuif  
Scuola Superiore Meridionale, Napoli

# Contesto

**Oligometastatic disease** is defined as low volume metastatic disease with limited number and size of metastatic lesions (up to 5 and not necessarily in the same organ), potentially amenable for local treatment, aimed at achieving a complete remission status.

Expert opinion/ 78%  
n/a

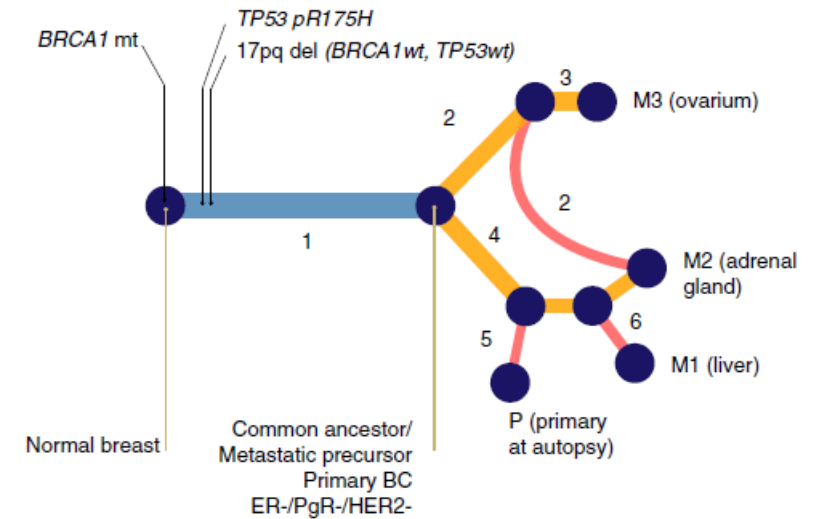
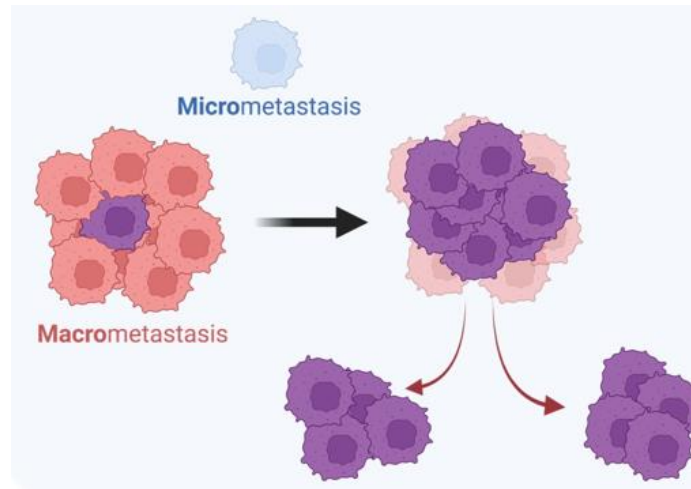
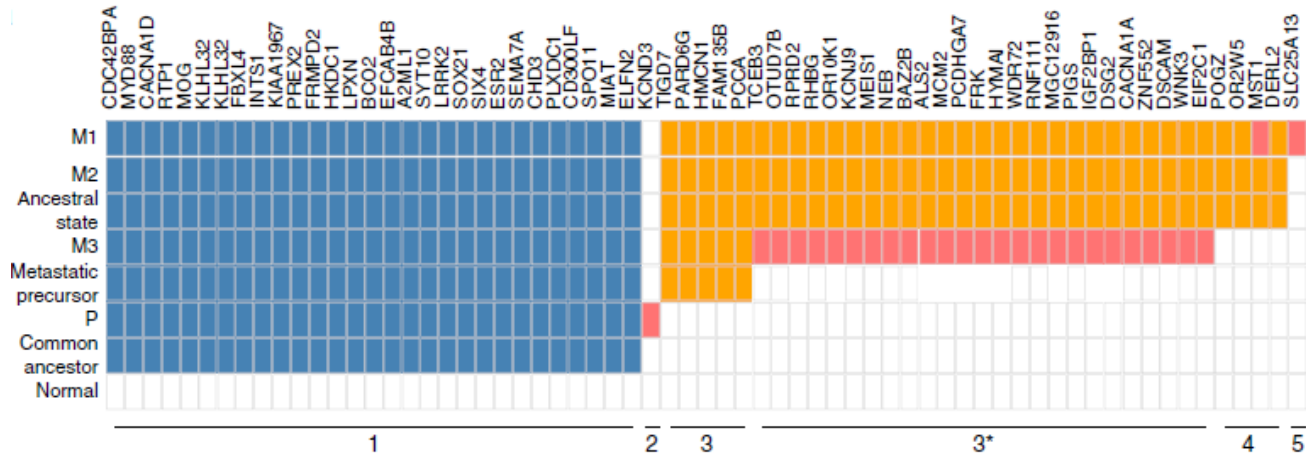
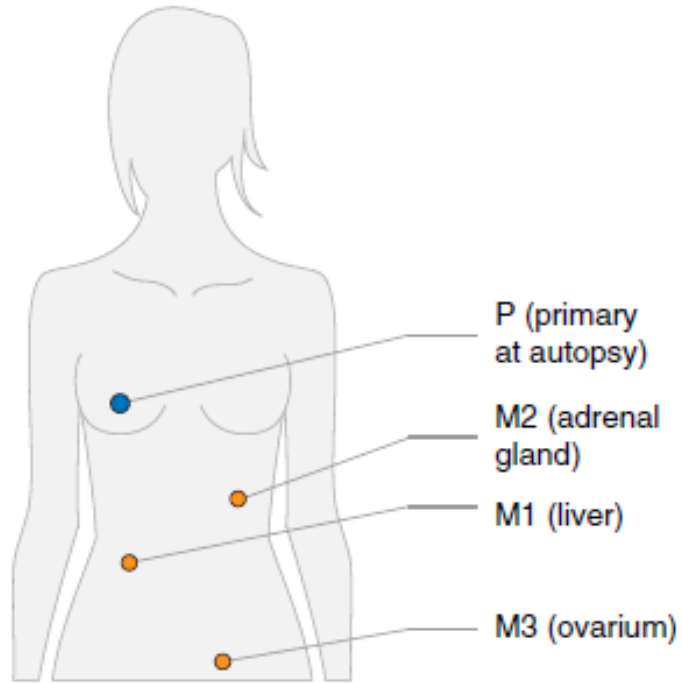
Malattia Oligometastatica



Guckenberger et al, Lancer Oncology, 2020; Cardoso et al, Ann Oncol, 2021; BioReDer.com

# Terapia locoregionale del tumore primario nella malattia metastatica *de novo*

# Razionale biologico



Brown et al, Nature Comm, 2017  
Gupta, ASCO 2022

# Tata Memorial Hospital trial

- Arruolamento 2005-2012
- N=716; 350 randomizzati dopo terapia sistemica (6 cicli)
- Scarsa risposta alla terapia sistemica (PD o SD) era criterio d'esclusione
- Non somministrata terapia target
- Endpoint primario: OS

	Locoregional treatment group (n=173)	No locoregional treatment group (n=177)
<b>Age (years)</b>		
Median	48	48
<b>Site of metastasis</b>		
Bone	50 (29%)	50 (28%)
Visceral	75 (43%)	77 (44%)
Bone and visceral	48 (28%)	50 (28%)
<b>Number of metastases</b>		
≤3	44 (25%)	45 (26%)
>3	129 (75%)	132 (74%)
<b>Oestrogen receptor or progesterone receptor</b>		
Negative	71 (41%)	71 (40%)
Positive	102 (59%)	106 (60%)
<b>Menopausal status†</b>		
Pre and peri	74 (43%)	88 (50%)
Post	99 (57%)	89 (50%)
<b>HER2 status</b>		
Negative (including 1+)	124 (72%)	108 (61%)
Positive (3+)	45 (26%)	62 (35%)
Not known or equivocal (2+)	4 (2%)	7 (4%)

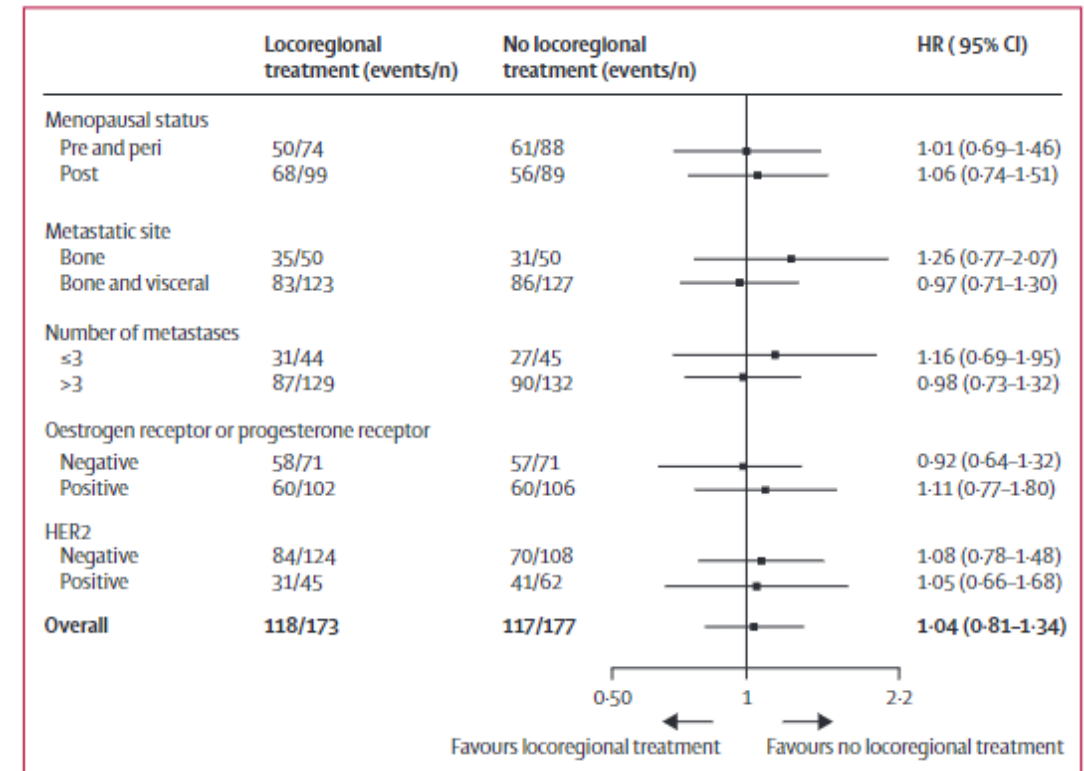
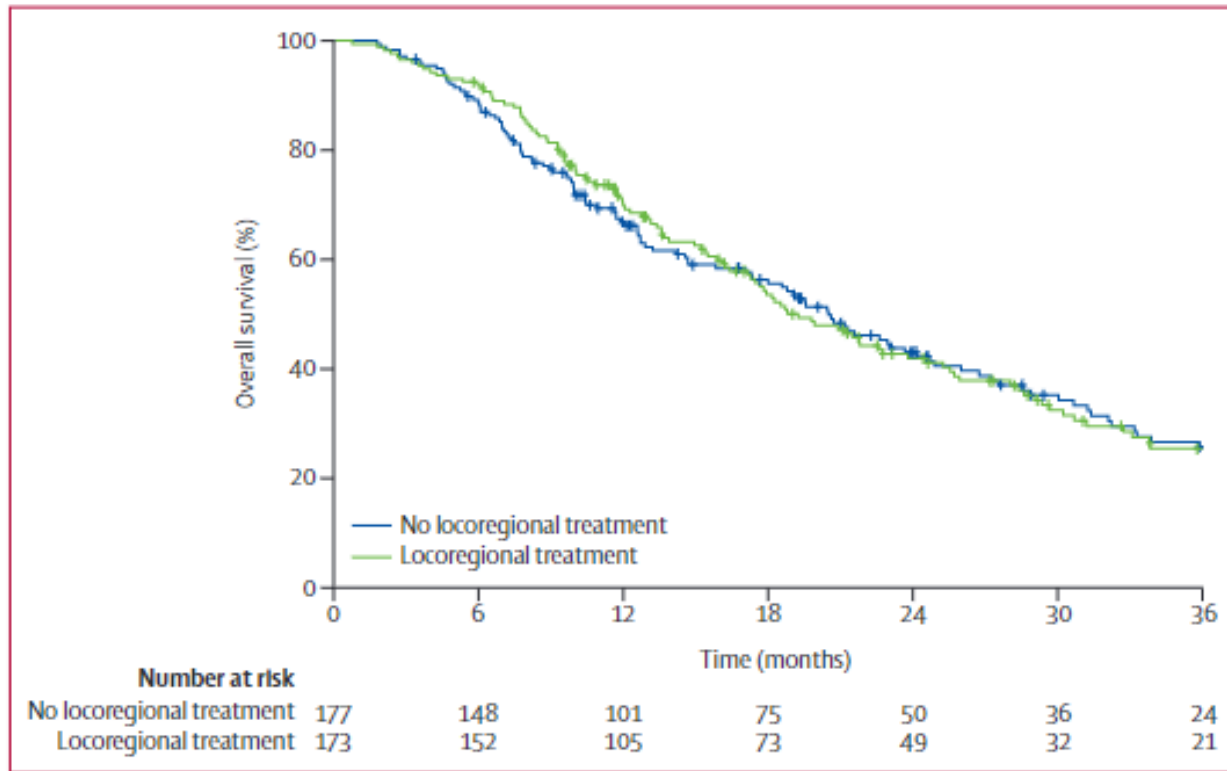
Data are n (%) unless stated otherwise. †Perimenopausal: history of no menstruation up to one preceding year; postmenopausal: cessation of menstrual cycles for more than 1 year.

**Table 1:** Baseline characteristics of the intention-to-treat population

Badwe et al, Lancet Oncol, 2015



# Tata Memorial Hospital trial



FU mediano: 23 mesi

OS mediana 19.2 mesi LR vs 20.5 mesi No LR  
 (HR 1.04; p=0.79)

Badwe et al, Lancet Oncol, 2015

# Turkish MF07-01 trial

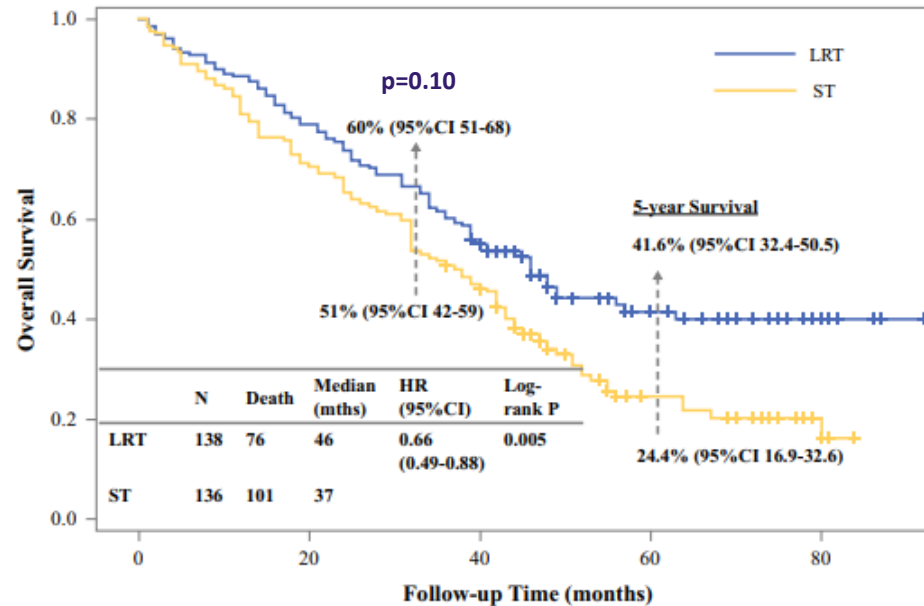
- Arruolamento 2008-2012
- N=274
- Terapia locoregionale upfront nel braccio trattamento multimodale
- Endpoint primario: 3y-OS

	LRT (n = 138) n (%)	ST (n = 136) n (%)
Mean age (years)	51.8 ± 12.6	51.5 ± 13.6
Mean BMI (kg/m <sup>2</sup> )	27.6 ± 5.2	27.8 ± 6.0
Mean follow-up (months)	40.5 ± 22.0	35.8 ± 21.7
Median follow-up (25, 75%)	41.0 (24, 54)	37 (18, 49)
Tumor size (%)		
T1	12 (8.7)	11 (8.1)
T2	72 (52.2)	58 (42.7)
T3	30 (21.7)	30 (22.1)
T4	24 (17.4)	37 (27.2)
Histologic grade (%)		
1	6 (4.4)	10 (9.6)
2	55 (39.9)	33 (31.7)
3	77 (55.8)	61 (58.9)
Tumor type (%)		
Invasive ductal	110 (79.7)	115 (84.6)
Invasive lobular	15 (10.9)	13 (9.6)
Mixed tumor type	13 (9.4)	8 (5.8)
ER/PR(+) (%) <sup>a</sup>	118 (85.5)	97 (71.8)
HER2/neu(+) (%) <sup>b</sup>	42 (30.4)	42 (31.1)
Triple-negative (%)	10 (7.3)	23 (17.4)
Treatment (%)		
BCS + axillary evaluation	36 (26)	–
M + axillary evaluation	102 (74)	–
SLNB <sup>c</sup>	23 (17)	–
ALND	128 (92.8)	–
Positive LN	123 (89.1)	–
Intervention to metastasis	35 (25)	48 (35)
Anthracycline-based CT	127 (92.0)	120 (89)
Bisphosphonates	37 (26.8)	32 (23.5)
Metastasis site (%)		
Bone only	71 (51)	55 (40)
Bone + others	33 (24)	37 (27)
Others (no bone)	34 (25)	44 (32)
Solitary/multiple metastasis (%)		
Solitary bone	33 (34)	20 (24)
Multiple bone	38 (39)	35 (41)
Solitary pulmonary or liver	13 (13)	15 (18)
Multiple pulmonary or liver	13 (13)	15 (18)

Soran et al, Ann Surg Oncol, 2018

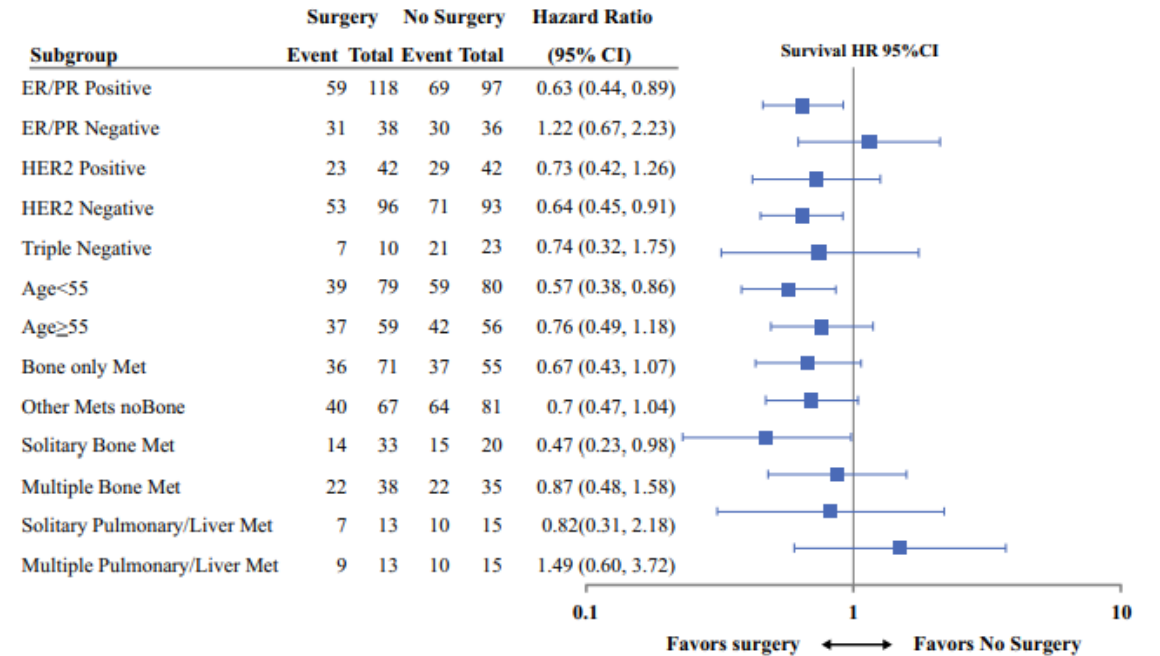


# Turkish MF07-01 trial



### Number at Risk

LRT	138	109	75	27	6
ST	136	97	63	17	5



No differenza in 3y-OS (endpoint primario)  
5y-OS superiore nel braccio LRT

Soran et al, Ann Surg Oncol, 2018

# ECOG E2108 trial

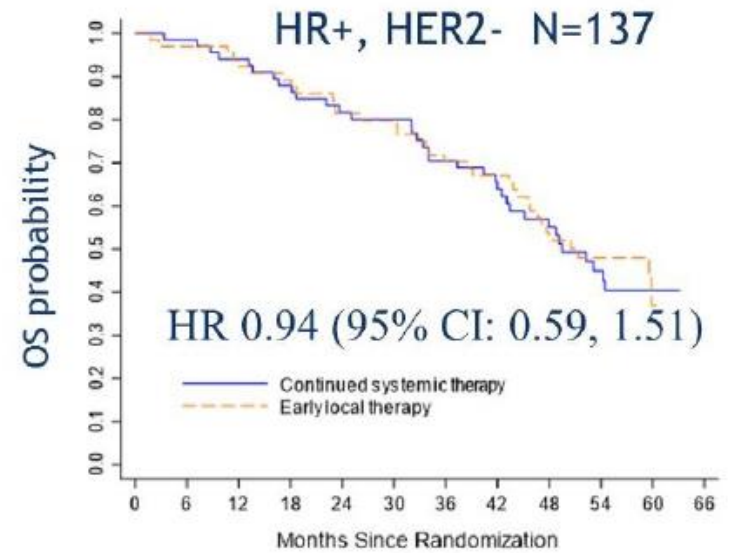
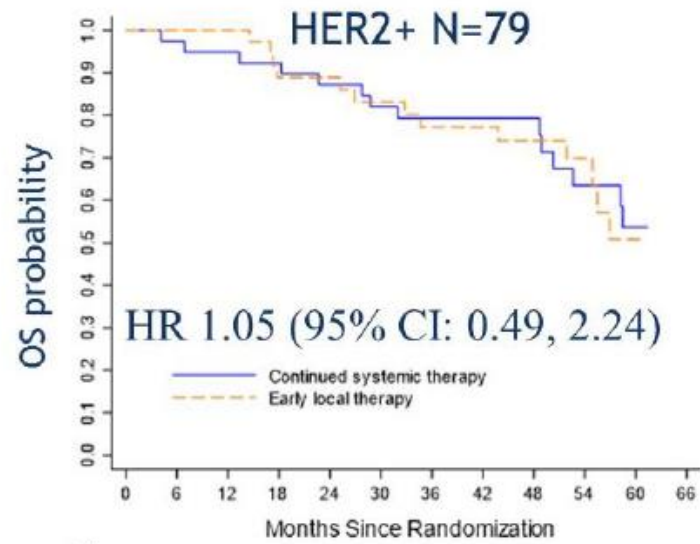
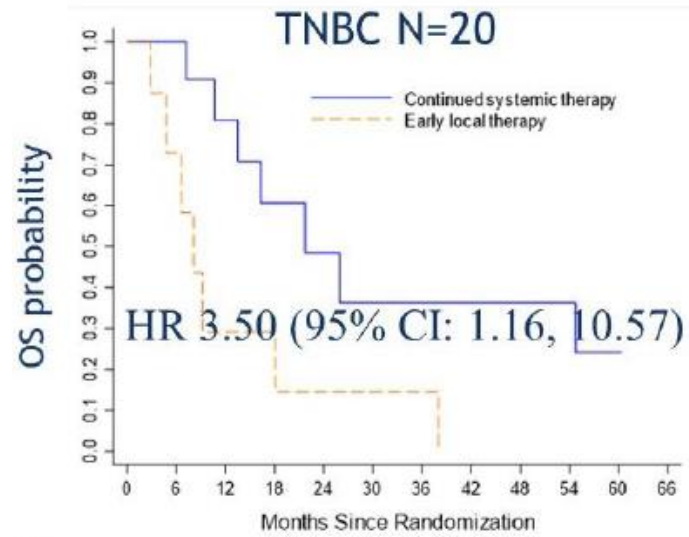
- Arruolamento 2011-2015
- N=368; 256 randomizzati
- Randomizzati pazienti senza evidenza di progressione dopo 4-8 mesi di terapia sistemica
- Endpoint primario: OS

	Randomized (n=256)
Metastatic sites	
visceral only	30 (11.9%)
bone only	95 (37.7%)
soft tissue only	7 (2.8%)
multiple sites	120 (47.6%)
missing	4
Oligometastasis*	
Yes	41 (16.3%)
No	211 (83.7%)
Missing	4
Breast cancer subtype	
HR+/HER2-	146 (59.6%)
HR-/HER2-	20 (8.2%)
HR-/HER2+	79 (32.2%)
missing	11

\* ≤3 lesioni in un singolo organo

Khan et al. J Clin Oncol 2022  
Mittendorf, ESMO 2022

# ECOG E2108 trial



FU mediano: 53 mesi

Khan et al. J Clin Oncol 2022  
Mittendorf, ESMO 2022

# POSITIVE trial

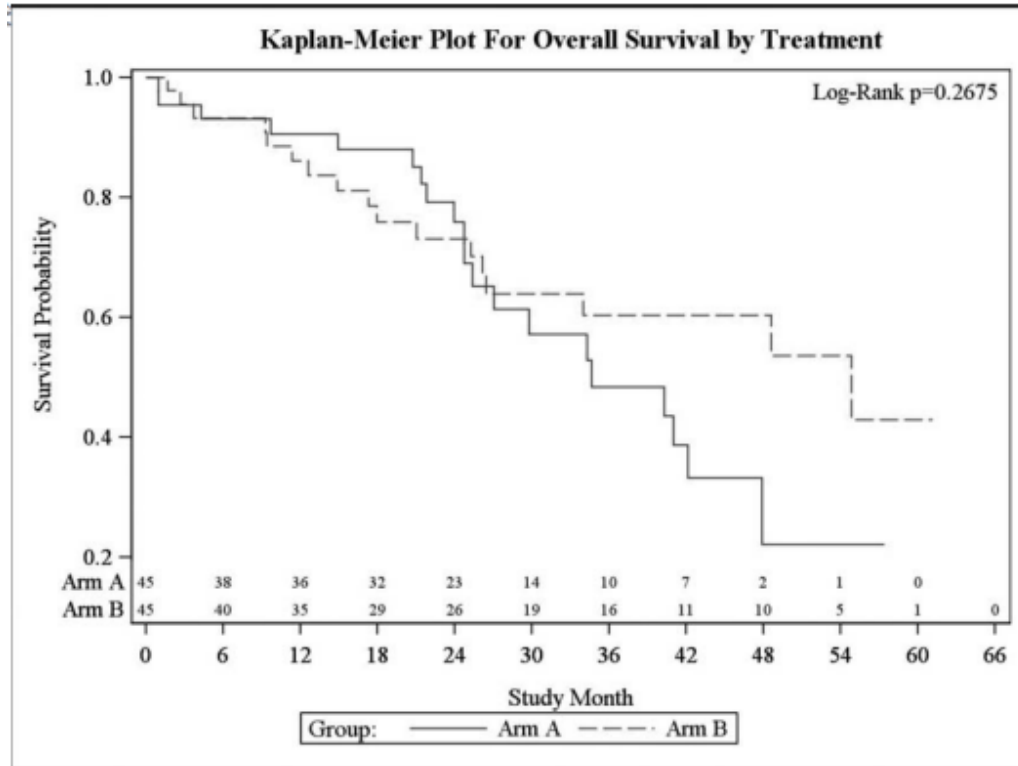
- Arruolamento 2011-2015
- N=90 (pianificato 254)
- Terapia locoregionale upfront nel braccio trattamento multimodale
- Endpoint primario: OS

	Arm A Surgical Therapy n = 45 (%)	Arm B No Surgical Therapy n = 45 (%)	P
Age groups			
<50	7 (16)	6 (13)	0.9021
50-59	9 (20)	10 (22)	
60-69	14 (31)	14 (31)	
70-79	14 (31)	12 (27)	
≥80	1 (2)	3 (7)	
Menopausal status			
Perimenopausal	0	1 (2.2)	1.0000
Postmenopausal	39 (87)	39 (87)	
Premenopausal	6 (13)	5 (11)	
T-stage			
cT1	10 (22)	7 (16)	0.0498
cT2	8 (18)	26 (58)	
cT3	10 (22)	3 (7)	
cT4	8 (18)	8 (18)	
Unknown	3 (7)	1 (2)	
N-stage			
cN0	10 (22)	10 (22)	0.4261
cN1	20 (44)	21 (47)	
cN2	7 (16)	2 (4)	
cN3	4 (9)	2 (4)	
Unknown	4 (9)	10 (22)	
IHC subtype			
Luminal A	22 (49)	24 (53)	0.8181
Luminal B	6 (13)	6 (13)	
HER2 enriched	12 (27)	8 (18)	
Triple negative	4 (9)	4 (9)	
Unknown	1 (2)	3 (7)	
Metastasis location			
Bone only	18 (49)	16 (36)	0.8281
Visceral ± bone	27 (60)	29 (64)	

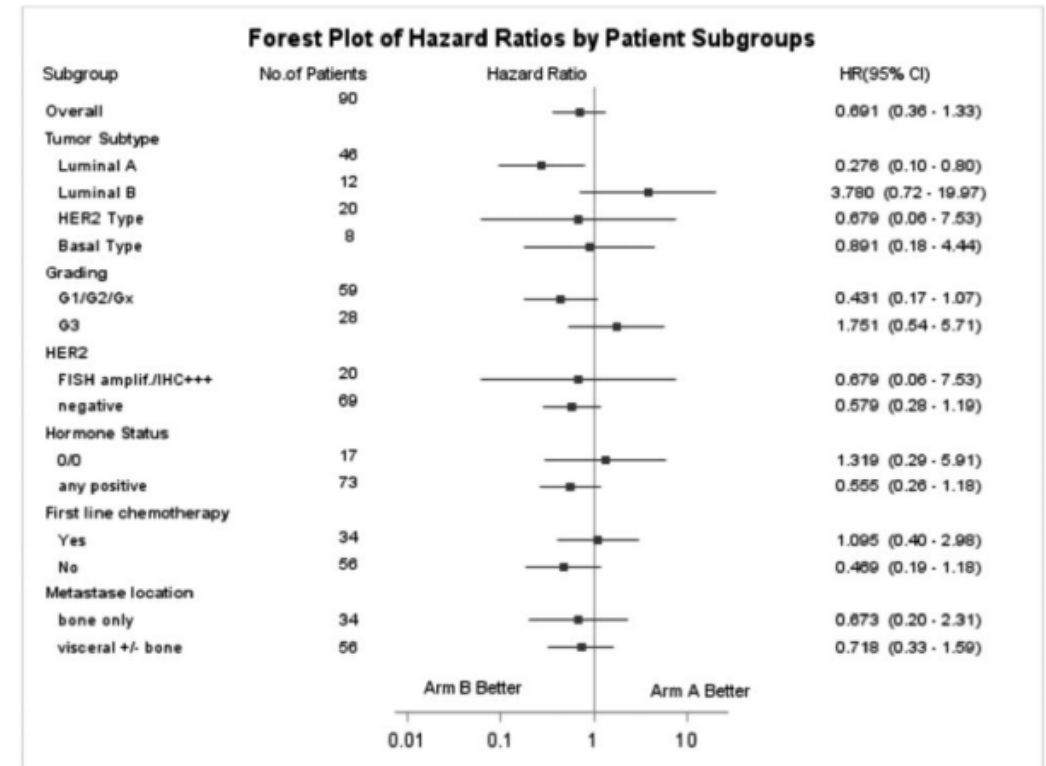
Fitzal et al, Ann Surg, 2019



# POSITIVE trial

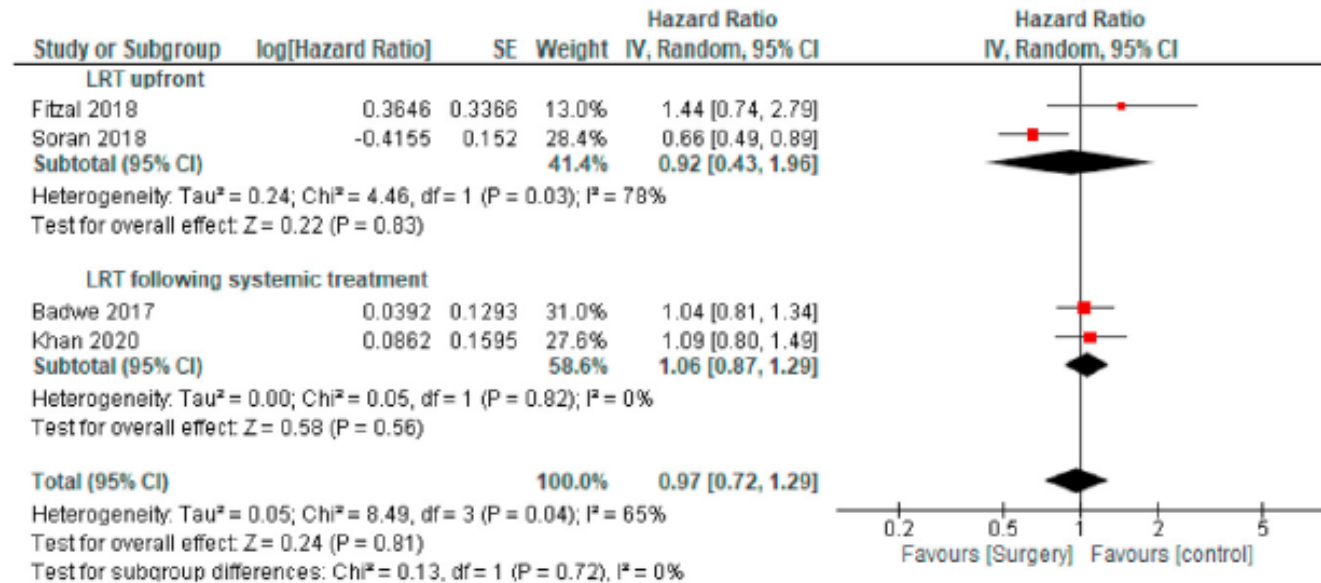


Arm A: chirurgia upfront  
FU mediano: 37.5 mesi



Fitzal et al, Ann Surg, 2019

# Meta-analisi RCT



Nessuna analisi di sottogruppo (biologia tumorale o sede di metastasi) ha mostrato un beneficio della terapia locoregionale del tumore primitivo rispetto alla sola terapia sistemica standard.

Reinhorn et al, The Breast, 2021

# Trial randomizzati

	Tata Memorial trial	Turkish trial	POSYTIVE trial	ECOG-2108 trial
FU mediano (mesi)	23	40	37.5	53
Pazienti	350	274	90	256
Pre-menopausa	46%	58%	13%	36%
Malattia oligometastatica (≤3 met)	25%	ND	ND	16.3%
Trattamento upfront	Terapia sistemica	Chirurgia	Chirurgia	Terapia sistemica
HR+	60%	79%	64%	60%
HER2+	30%	31%	22%	32%
TN	ND	12%	9%	8%
Malattia viscerale	71%	54%	62%	65%
Sola malattia ossea	28%	47%	36%	38%
Risultati	No OS diff	No 3y-OS diff 5y-OS > nel braccio terapia LR+S	No OS diff	No OS diff

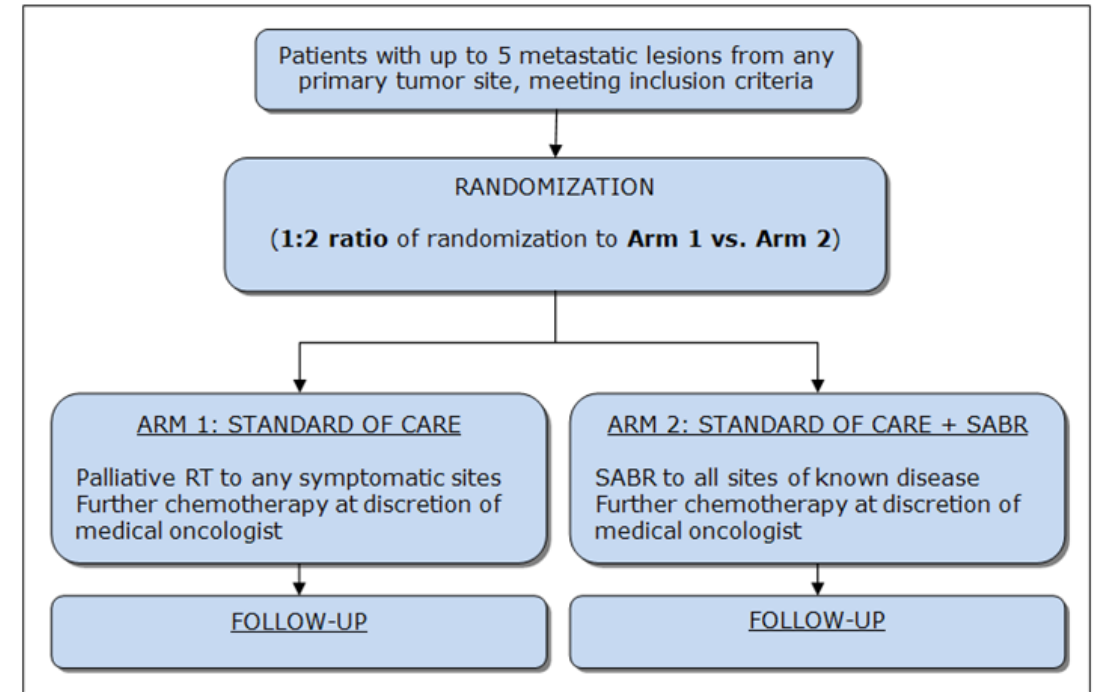
Badwe et al, Lancet Oncol, 2015; Soran et al, Ann Surg Oncol, 2018; Khan et al. J Clin Oncol 2022; Fitzal et al, Ann Surg, 2019

# Terapia locoregionale delle metastasi nella malattia oligometastatica



# SABR-COMET

- Studio di fase II randomizzato
- Arruolamento 2012-2016
- N=99
- Histology agnostic trial
- Endpoint primario: OS
- ECOG: 0-1
- Criteri di inclusione principali:
  - Fino a 5 siti metastatici
  - Trattamento definitivo del tumore primitivo (almeno 3 mesi prima della randomizzazione senza evidenza di progressione)
  - Tutte le metastasi trattabili con SABR



Palma et al, Lancet 2019

# SABR-COMET

Characteristic	Control arm (n = 33)	SABR arm (n = 66)
Age, median (IQR)	69 (64, 75)	67 (59, 74)
Sex, n (%)		
Male	19 (58)	40 (61)
Female	14 (42)	26 (39)
Site of original primary tumor, n (%)		
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)
Time from diagnosis of primary tumor to randomization (y), median (IQR)	2.3 (1.3, 4.5)	2.4 (1.6, 5.3)

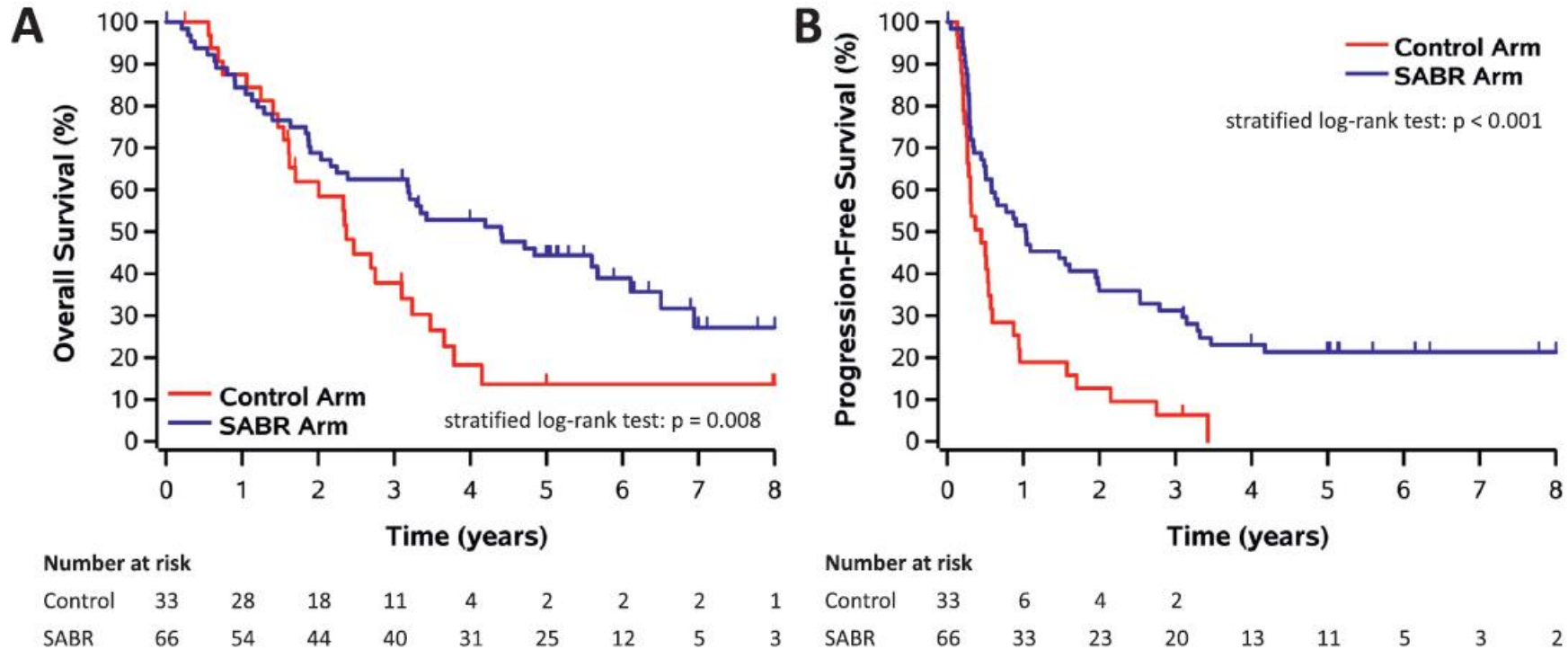
Number of metastases, n (%)		
1	12 (36)	30 (46)
2	13 (40)	19 (29)
3	6 (18)	12 (18)
4	2 (6)	2 (3)
5	0 (0)	3 (5)
Location of metastases (n = 191 lesions), n (%)		
Adrenal	2 (3)	7 (6)
Bone	20 (31)	45 (35)
Liver	3 (5)	16 (13)
Lung	34 (53)	55 (43)
Other*	5 (8)	4 (3)
<i>Abbreviation:</i> IQR = interquartile range. * "Other" includes brain (n = 4 lesions), lymph nodes (n = 4 lesions), and pararenal (n = 1 lesion).		

Harrow et al, Int J Radiation Oncol Biol Phys 2022

# SABR-COMET

Median OS was 28 months (control) vs. 53 months (SABR)  
 PFS: 5.4 months (control) vs. 12 months (SABR)

FU mediano  
 68 mesi



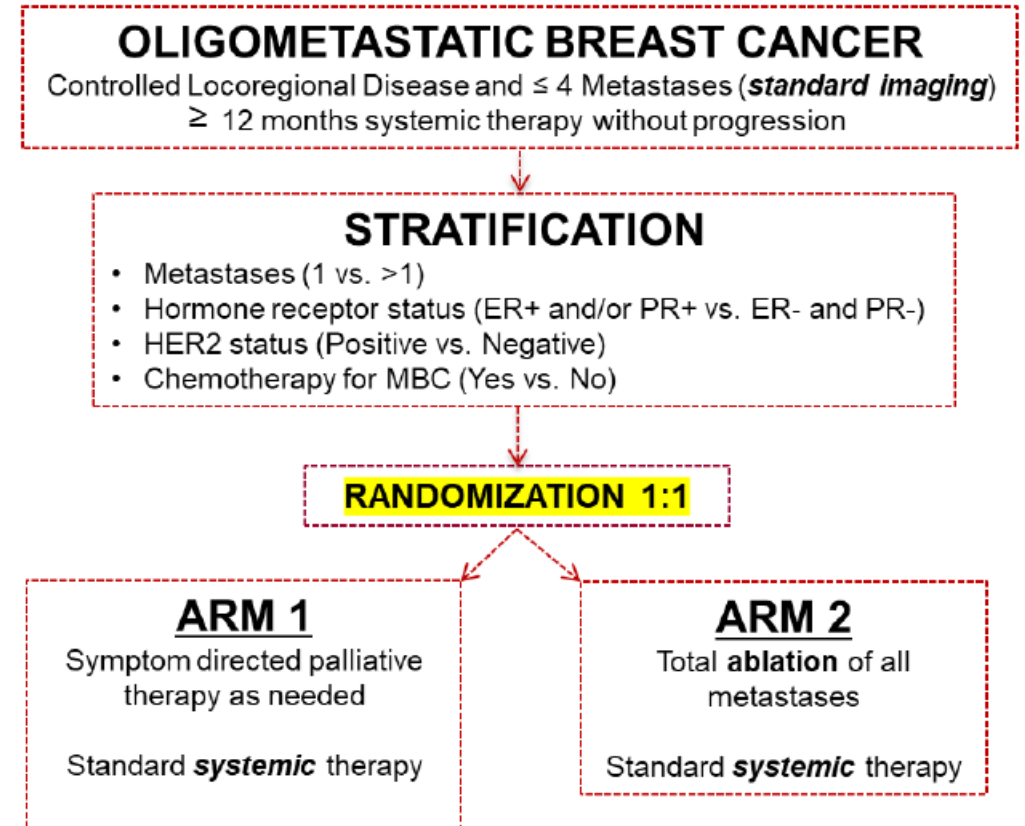
BC: OS HR 0.77 (95% CI 0.21, 2.88); PFS HR 0.53 (95% CI 0.18, 1.59)

3 morti correlate al trattamento nel braccio SABR (N= 66, 4.5%)

Harrow et al, Int J Radiation Oncol Biol Phys 2022

# NRG-BR002

- Studio di fase II/III randomizzato
- N=125
- Pazienti con carcinoma mammario oligometastatico
- Endpoint primario: PFS
- ECOG: 0-2
- Criteri di inclusione principali:
  - Fino a 4 siti metastatici ( $\leq 5$  cm)
  - Malattia controllata (terapia sistemica  $\leq 12$  mesi senza evidenza di progressione)
  - Tutte le metastasi trattabili con terapia locoregionale (SBRT/resezione)



Chmura, ASCO 2022



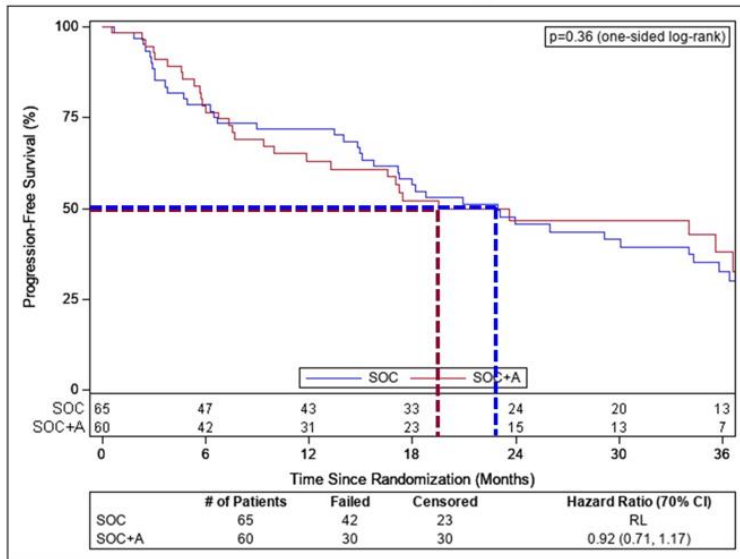
# NRG-BR002

	Standard of Care (n=65)	Standard of Care + Ablation (n=60)	Total (n=125)
<b>Age (years)</b>			
Median	53	55.5	54
<b>Performance Status (Zubrod)</b>			
0	41 (63%)	41 (68%)	82 (66%)
1	24 (37%)	19 (32%)	43 (34%)
<b>Patient Metastasis Count</b>			
1	39 (60%)	36 (60%)	75 (60%)
>1	26 (40%)	24 (40%)	50 (40%)
<b>Hormone Receptor/HER2 Status</b>			
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%)
<b>Metastatic Timing</b>			
Synchronous	12 (18%)	15 (25%)	27 (22%)
Not synchronous	52 (80%)	45 (75%)	97 (78%)
Pending	1 (2%)	0 (0%)	1 (1%)

	Standard of Care (n=65)	Standard of Care + Ablation (n=60)	Total (n=125)
<b>Ablation</b>			
SBRT/SABR		56 (93%)	
Surgery		1 (2%)	
No protocol treatment		3 (5%)	
<b>Systemic Therapy (1<sup>st</sup> Follow up)</b>			
Chemotherapy	18 (28%)	16 (27%)	34 (27%)
Hormonal	54 (83%)	41 (68%)	95 (76%)
Biologic	48 (74%)	36 (60%)	84 (67%)
Bone Protective	21 (32%)	9 (15%)	30 (24%)
No protocol treatment	3 (5%)	3 (5%)	6 (5%)

Chmura, ASCO 2022  
Rivera, ESMO 2022

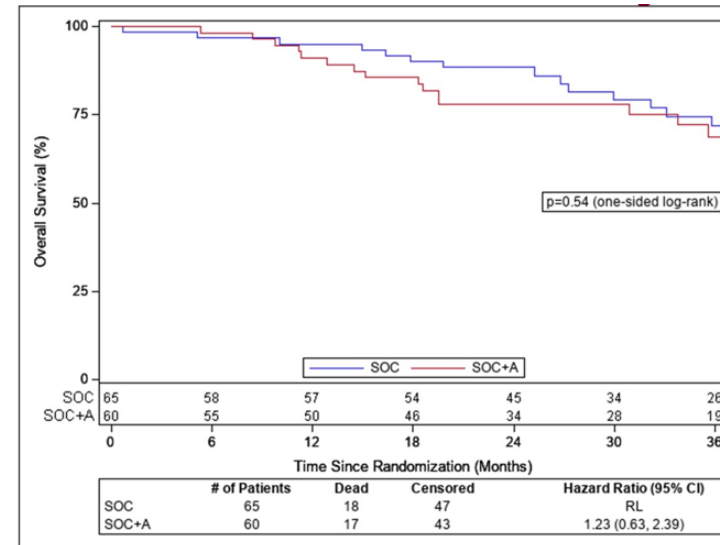
# NRG-BR002



	SOC (n=65)	SOC+A (n=60)
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)

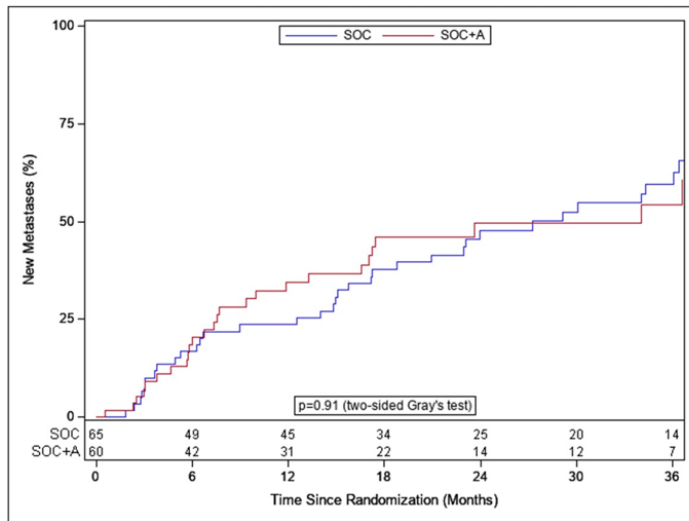


	SOC (n=65)	SOC+A (n=60)
36-month estimate (95% CI)	71.8% (58.9%, 84.7%)	68.9% (55.1%, 82.6%)

HR [SOC+A/SOC] (95% CI): 1.23 (0.63, 2.39)

Chmura, ASCO 2022

# NRG-BR002



## Analysis of first failure:

- New mets *outside* index area (Arm 1) /RT field (Arm 2)
  - Developed similarly in both arms (~40%)
- New mets *inside* index area (Arm 1) /RT field (Arm 2)
  - Fewer for SOC+A: 7% vs. 29%

## OS

Subgroup	Events/Total	Hazard Ratio (2-sided 95% CI)	2-Year Estimate (2-sided 95% CI)	
			SOC	SOC+Ablation
All patients	35/125		88.4 (80.2-96.5)	78.0 (66.9-89.0)
Age				
< 50 years	10/46		90.9 (78.9-100.0)	81.0 (64.2-97.7)
≥ 50 years	25/79		86.9 (76.2-97.6)	76.0 (61.4-90.5)
Race				
White	27/96		91.5 (83.6-99.5)	75.8 (62.7-88.9)
Non-white	8/29		76.9 (54.0-99.8)	84.6 (65.0-100.0)
Zubrod performance status				
0	21/82		86.5 (75.5-97.5)	82.5 (70.7-94.3)
1	14/43		91.3 (79.8-100.0)	64.1 (38.6-89.6)
Number of metastases				
1	19/75		97.2 (91.9-100.0)	70.2 (54.7-85.8)
>1	16/50		75.1 (57.9-92.4)	90.2 (77.3-100.0)
Hormone receptor status				
ER+ and/or PR+	27/112		90.9 (83.3-98.5)	85.9 (76.2-95.6)
ER- and PR-	8/13		60.0 (17.1-100.0)	- (-)
HER2 status				
Negative	31/109		88.7 (80.1-97.2)	76.4 (64.1-88.6)
Positive	4/16		85.7 (59.8-100.0)	87.5 (64.6-100.0)
First-line systemic chemotherapy				
Yes	22/90		90.5 (81.6-99.4)	83.0 (71.6-94.5)
No	13/35		83.3 (66.1-100.0)	61.9 (35.2-88.6)
Received Chemotherapy				
Yes	20/34		82.4 (64.2-100.0)	56.3 (31.9-80.6)
No	15/91		90.7 (82.0-99.4)	87.0 (76.4-97.6)
Received Hormonal Therapy				
Yes	23/96		92.5 (85.3-99.6)	85.1 (74.1-96.1)
No	12/29		58.3 (22.0-94.7)	57.1 (31.2-83.1)

SOC + Ablation better      SOC better

Chmura, ASCO 2022

# Trial in corso

Ongoing randomized phase II/III trials of local ablative therapy + systemic therapy in **BC**.

Identifier	Phase	Patients	End of Study	Primary Endpoint(s)	Local treatment	Number and site of metastases allowed	Tumour biology
NCT04413409 (OMIT)	Phase III randomized	172	2025	OS	Surgery	≤3 metastatic lesions, involving 1–2 organs, single lesion ≤ 5 cm	Any
NCT04495309 (OLIGOMA)	Phase III randomized	564	2025	PFS HRQoL	SBRT	Up to 5 clinically manifest metastases (maximum 3 CNS lesions)	Any
NCT04698252 (LARA)	Phase II randomized	74	2031	PFS	SBRT, surgery, RFA	1–4 bone lesions; 1–4 lung and/ or liver lesions	HR+/HER2-
NCT04424732	Phase II single arm	50	2026	PFS	SBRT	1–3 bone metastases	Any
NCT03750396 (CLEAR)	Phase II single arm	110	2025	PFS	Palliative RT, SBRT, surgery, RFA	≤2 lesions in single organ or site (lung, bone, liver, adrenal glands, nodal)	HR+/HER2-
NCT02089100 (STEREO-SEIN)	Phase III randomized	280	2023	PFS	SBRT	≤5 metastatic lesions	HR+ (HER2+/-)
NCT05301881 (COSMO)	Phase II single arm	118	2040	PFS	SBRT, surgery, RFA	Oligoprogression defined as 1–2 metastatic lesions, limited to one organ, or the primary tumour or regional nodes	Any
NCT05377047 (TAORMINA)	Phase III randomized	345	2027	OS	SBRT	1–5 lesions in 1–2 organs	Any

Miglietta et al, Cancer Treat Rev, 2022



# Take home messages

- I trial clinici randomizzati che hanno investigato il ruolo della resezione del tumore primitivo non arruolavano solo pazienti in stadio oligometastatico e non hanno dimostrato un beneficio in OS
- Alcuni trial condotti non riflettono i progressi delle terapie sistemiche (guidate dalla biologia tumorale)
- Le evidenze da RCT sul ruolo della metastasectomia sono scarse
- Non è stato dimostrato beneficio in PFS (e OS) in RCT che investigassero il ruolo della terapia locoregionale in pazienti con carcinoma mammario oligometastatico
- Definizione ottimale di malattia oligometastatica?

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**L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA**

**20 - 21 APRILE  
2023 ROMA**

**THE HIVE HOTEL**

Via Torino, 6

**Le terapie locoregionali dovrebbero essere sempre associate alla terapia sistemica nella malattia oligometastatica?**

**NO**

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**GRAZIE PER L'ATTENZIONE**

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