La gestione della paziente con carcinoma mammario metastatico-II

La malattia oligometastatica: definizione e trattamento

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Oligometastatic BC:
Clinical definition

- Although not recommended by guidelines, many patients undergo **“spontaneous” intensive follow up**
- As a consequence, a significant proportion of patients is diagnosed with **asymptomatic metastases and limited metastatic burden** (up to 20%)
- Improved imaging has been paralleled by an **increased availability of locoregional treatments** (radiofrequency, stereotactic radiotherapy, vertebroplasty, minimally invasive surgery)[1-5]
- **Patients’ expectations are high**

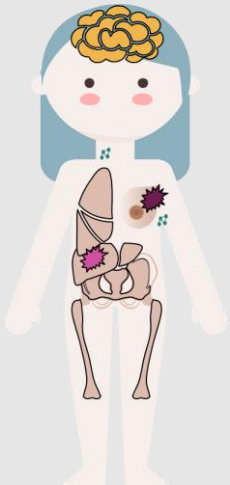
1. Friedel et al, Eur J Cardiothorac Surg 2002; 2. Abbott et al, Surgery 2012; 3. Milano et al, Radiother Oncol 2019; 4. Trovo et al, Radiother Oncol 2018; 5. Scorsetti et al, Br J Radiol 2015

Oligometastatic BC:
Clinical definition

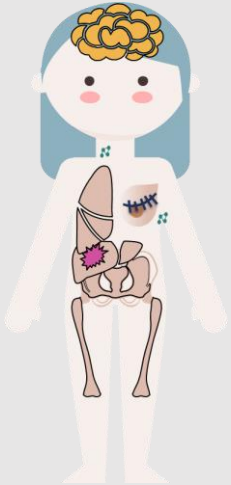
Generically, oligometastatic disease refers to MBC presenting or recurring with limited metastatic disease

Various definitions have been proposed based on the number and/or size of the metastatic lesions

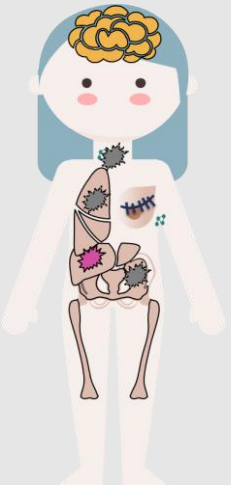
Most adopted definition: **up to five lesions in total, not necessarily in the same site/organ. Importantly, all lesions should be potentially amenable to local treatment.**



Synchronous (or de novo) oligometastatic disease
oligometastatic disease at initial presentation



Oligorecurrence
identification of metachronous oligometastases subsequent to definitive management of a non-metastatic tumor



Induced oligometastases
widespread metastatic disease is converted to oligometastases after systemic therapy eradicates most visible metastases

Gennari et al, Ann Oncol 2021; Cardoso F, et al *Ann Oncol;* Guckenberger M, et al, *Lancet Oncol.* 2020; Hellman S, et al *J Clin Oncol.* 1995.

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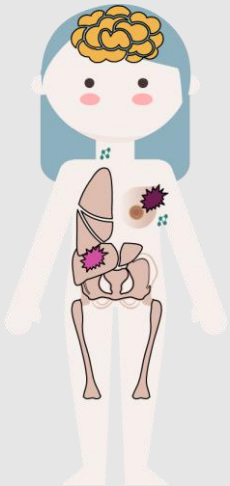

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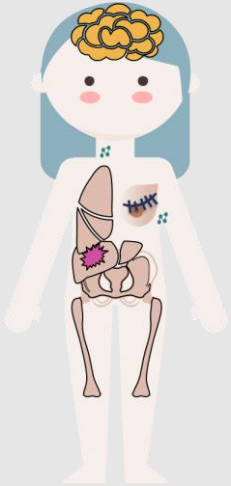

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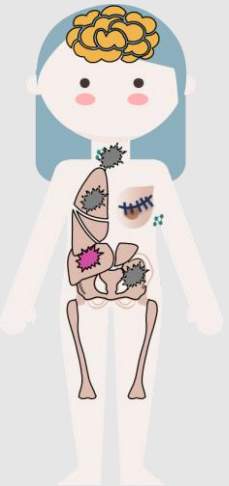

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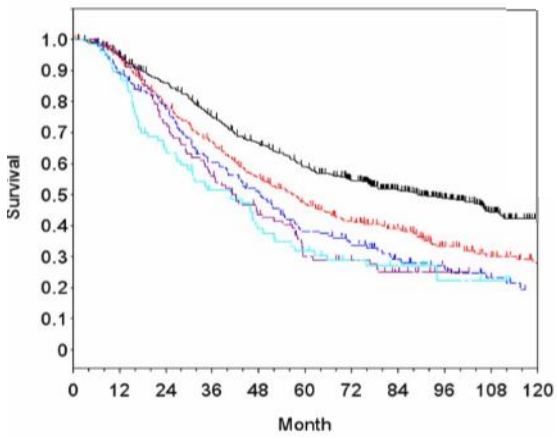
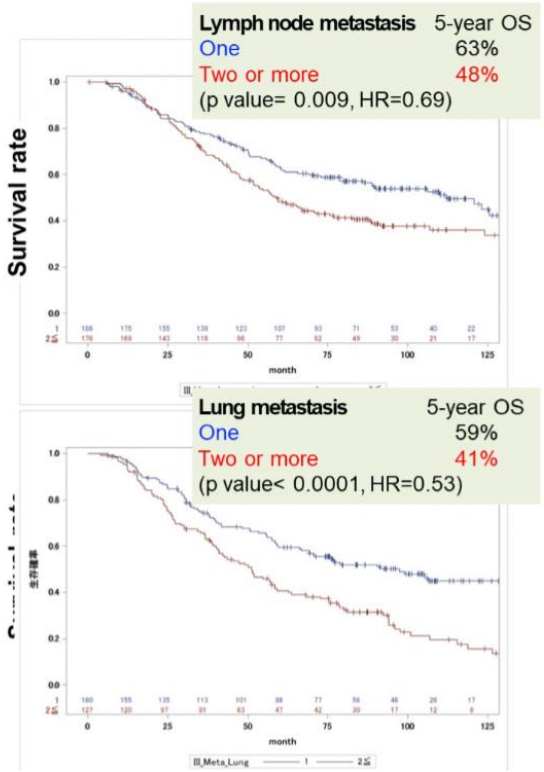
Prognostic factors for pts with OM-BC

OLIGO-BC1 study experience (n=1200)



Num. of metastatic sites	
One,	59%
Two,	47%
Three,	38%
Four,	30%
Five,	32%

Disease burden

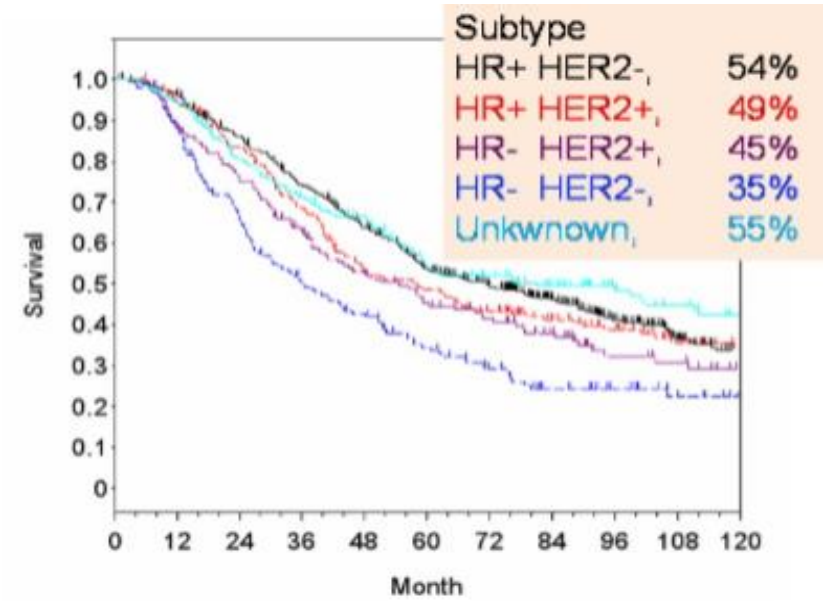


Ueno et al ASCO 2020, Wang et al ASCO 2021

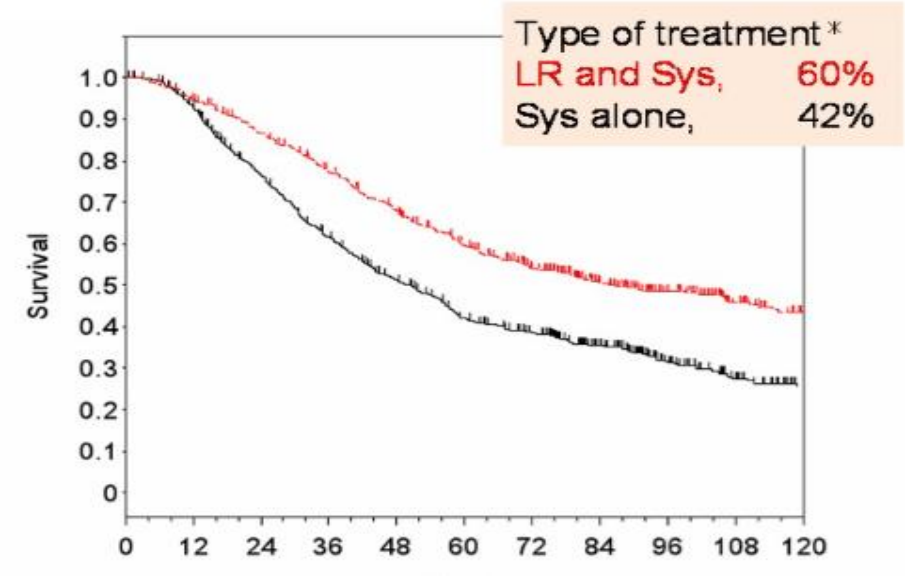
Prognostic factors for pts with OM-BC

OLIGO-BC1 study experience (n=1200)

Biology



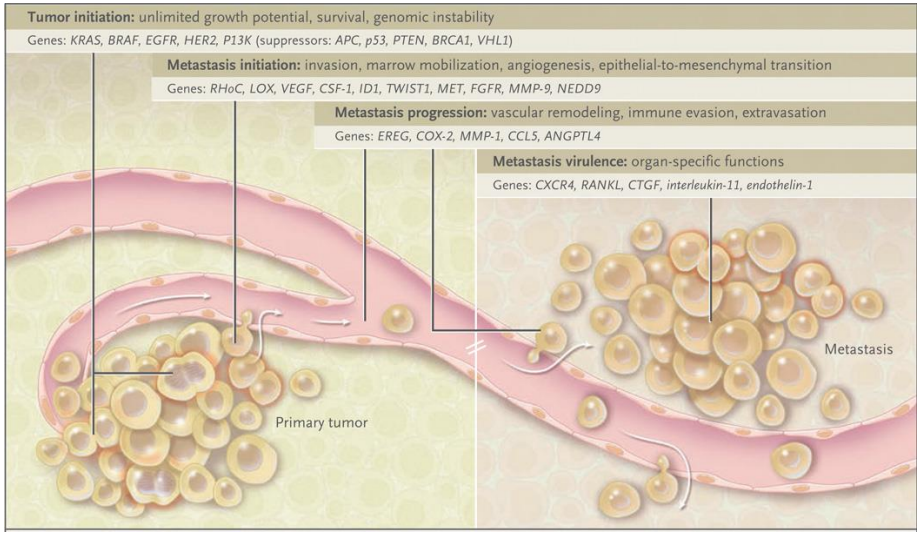
Type of treatment



Ueno et al ASCO 2020, Wang et al ASCO 2021

Oligometastatic BC:
Biological substrate supporting the rational for curative intent

- **It is increasingly appreciated that OM-BC cancer differs from multi-metastatic disease in prognosis → High-propensity of OM-BC to obtain long-term remission**
- **New biological and clinical concept**
    - Intermediate biological state of **restricted metastatic capacity**
    - **Transitional state** of dissemination



Oligometastatic phenotype may reflect a low malignant potential

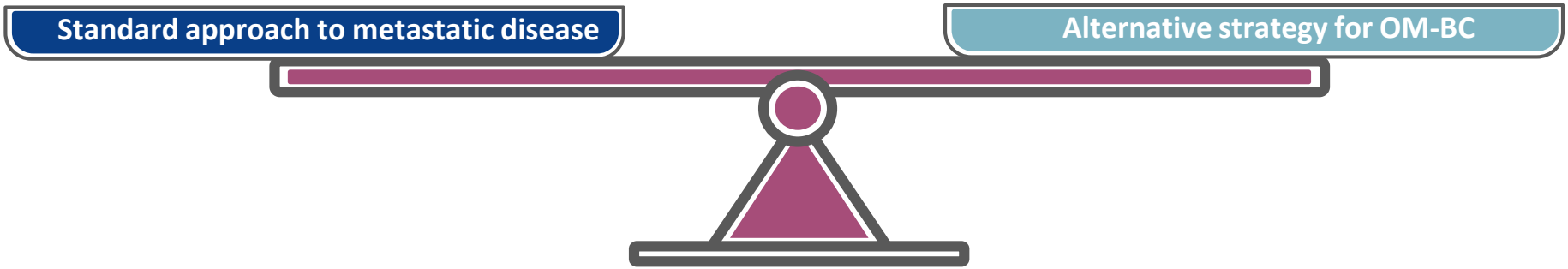
Weichselbaum and Hellmann, JCO 1995 and NRCO 2011; Greenberg et al JCO 1996; Chiang et al, NEJM 2008

Oligometastatic BC:
Biological substrate supporting the rational for curative intent

OLIGOMETASTATIC DISEASE

Disease chronicization, symptomatic control, quality of life, survival prolongation. Local treatment with palliative intent.

Achieve STAGE IV NED to attempt curability

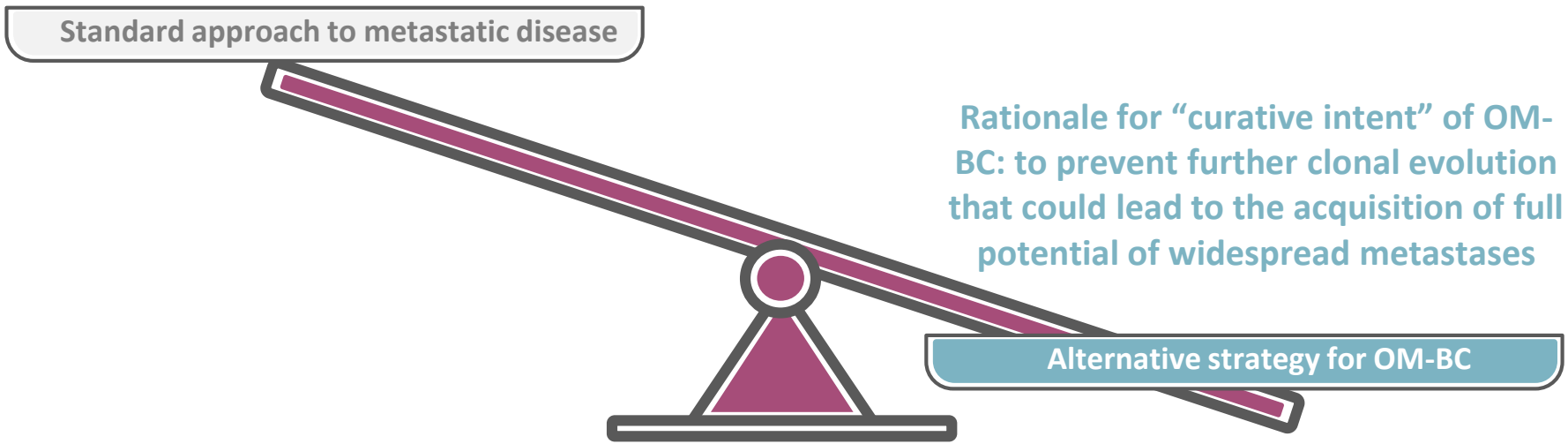


The clinical challenge in these scenarios is to understand whether treatment should follow a palliative approach or be escalated to pursue complete and sustained remission (curative approach)

Weichselbaum and Hellmann, JCO 1995 and NRCO 2011

Oligometastatic BC:
Biological substrate supporting the rational for curative intent

OLIGOMETASTATIC DISEASE

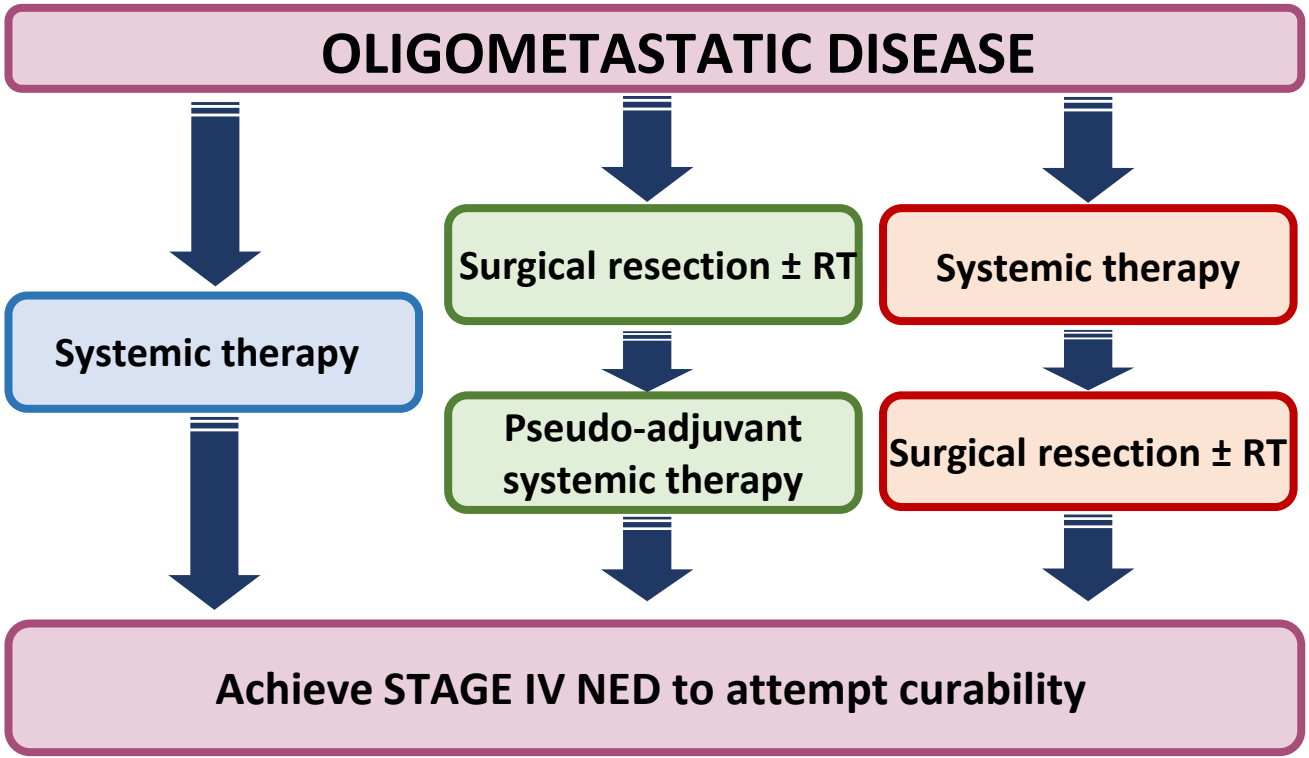


Rationale for “curative intent” of OM-BC: to prevent further clonal evolution that could lead to the acquisition of full potential of widespread metastases

Weichselbaum and Hellmann, JCO 1995 and NRCO 2011

OM-BC management

Possible approaches



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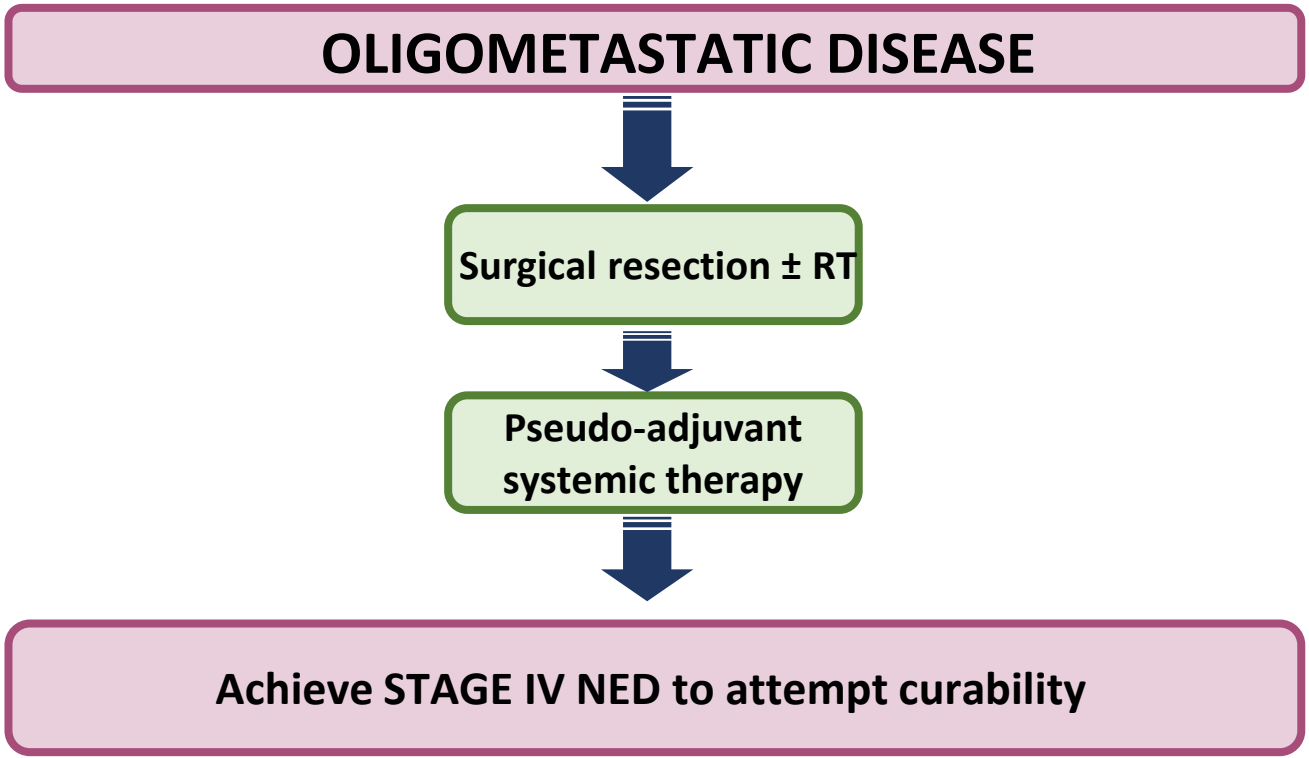
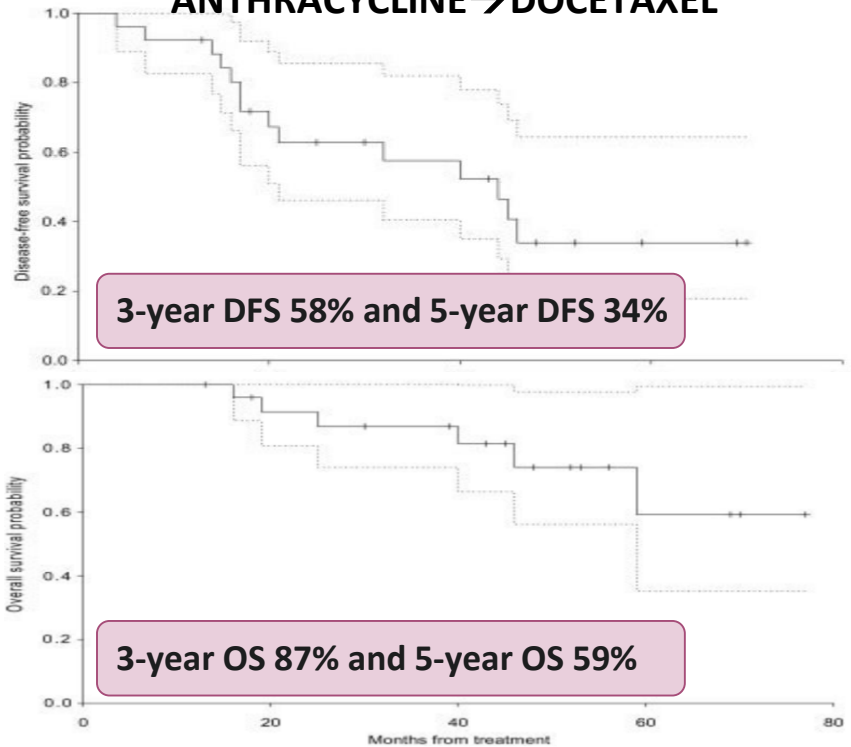


OM-recurrence: «pseudo-adjuvant» systemic treatment

Stage IV NED BC after locoregional treatment of isolated recurrence

OM-BC patients due to isolated recurrence → local treatment with curative intent → stage IV NED treated in 3 ANTHRACYCLINE trials (n=259) and 1 ANHTRACYCLINE→TAXANE trial (n=26). ER+ patients could receive ET

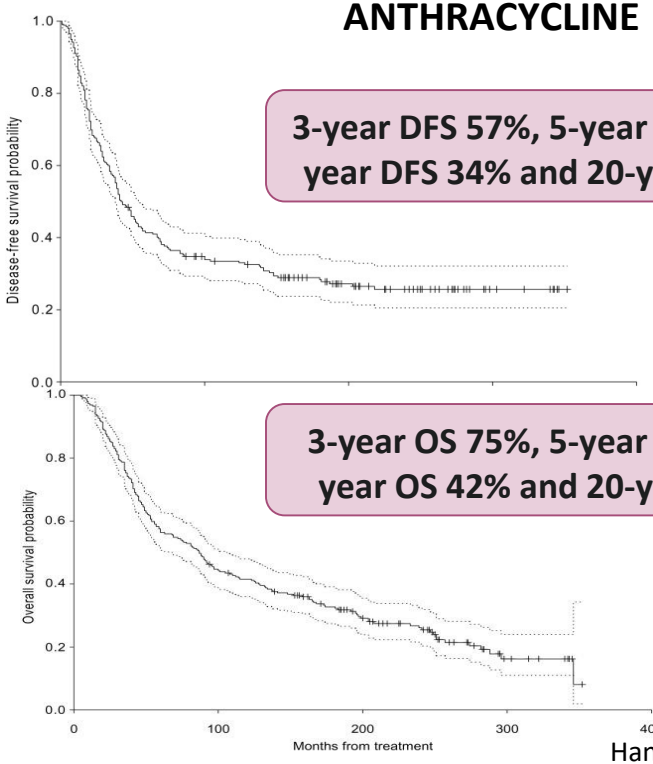
ANTHRACYCLINE→DOCETAXEL



3-year DFS 58% and 5-year DFS 34%

3-year OS 87% and 5-year OS 59%

ANTHRACYCLINE



3-year DFS 57%, 5-year DFS 41%, 10-year DFS 34% and 20-year DFS 26%

3-year OS 75%, 5-year OS 56%, 10-year OS 42% and 20-year OS 26%

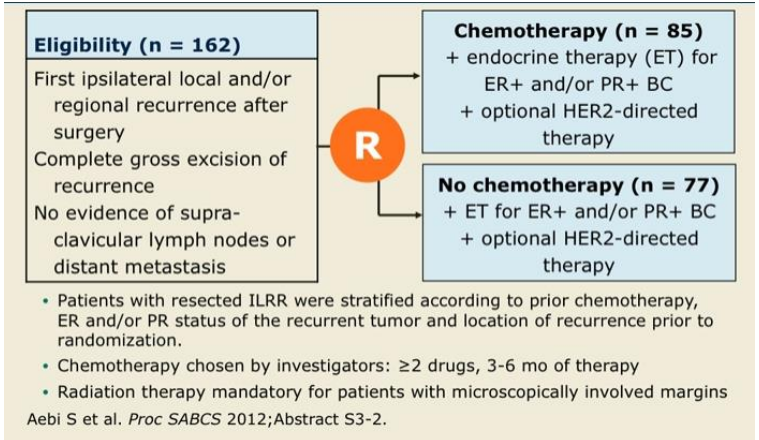
Hanrahan E, Cancer 2005

OM-recurrence: «pseudo-adjuvant» systemic treatment

Isolated locoregional recurrence

Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial

Chemotherapy as **A**djuvant for **LO**cally **R**ecurrent Breast Cancer



Primary endpoint DFS: invasive local, regional, or distant recurrence, appearance of a second primary tumour, or death from any cause.

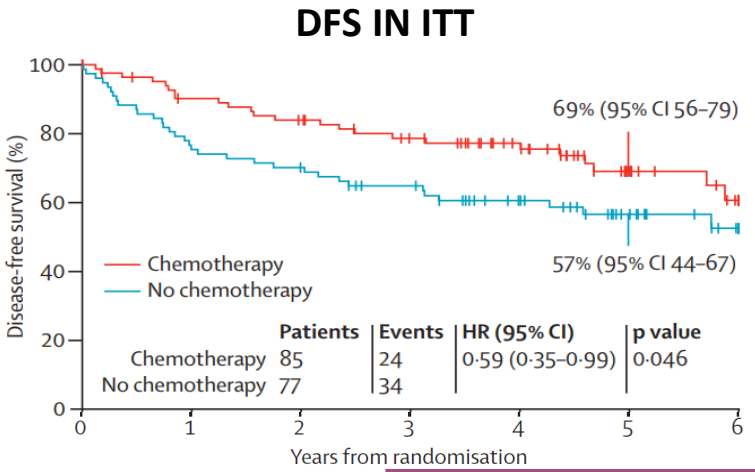
Time from primary surgery to ILRR surgery	median 12 years (range ≈3yy - ≈10yy)
ILRR location	• Breast in 55% • Mastectomy scar/chest wall 32-33% • Regional lymph-nodes 12-13%

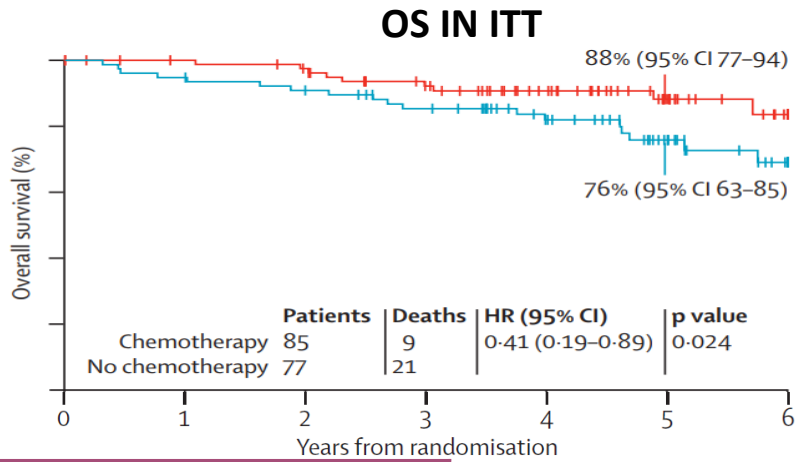
Mono-CT 29%	**Poly-CT 65%**
• Taxane 19%	• Anthra-based 45%
• Capecitabine 11%	• Tax-based 15%

Aebi et al, Lancet Oncol 2014; Wapnir et al JCO 2018

OM-recurrence: «pseudo-adjuvant» systemic treatment

Isolated locoregional recurrence





DFS event	CT, n	NO CT, n
Second local or regional	**6**	**9**
Distant	**15**	**22**
Soft tissue	0	2
Bone	8	5
Viscera	7	15
Contralateral	**1**	**1**
Second non-breast	**1**	**0**
Death without previous recurrence	**1**	**0**
Death cause ukn	**0**	**2**

Aebi et al, Lancet Oncol 2014

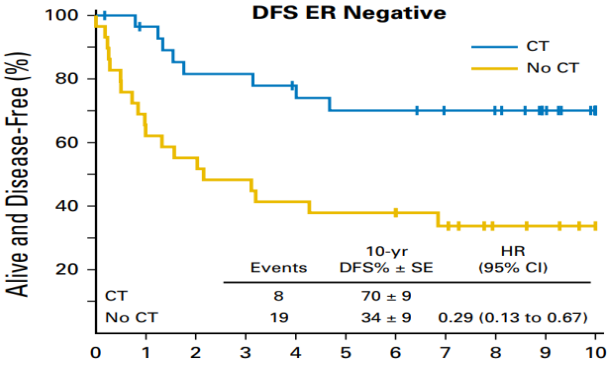
OM-recurrence: «pseudo-adjuvant» systemic treatment

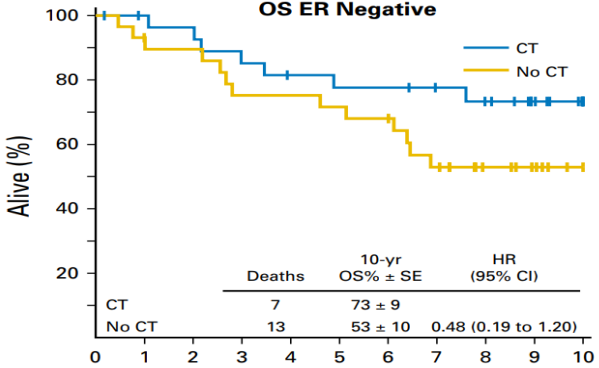
Isolated locoregional recurrence

DFS according to ER status

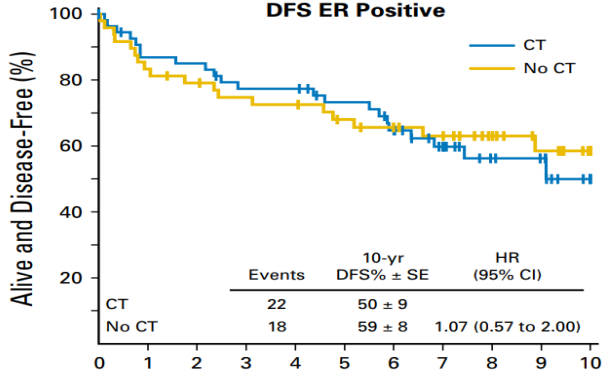
OS according to ER status

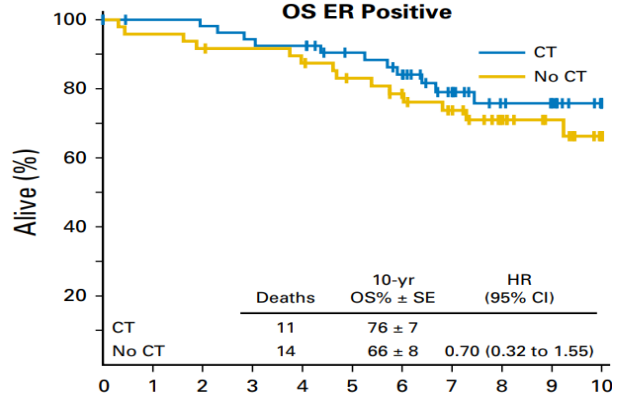
ER-





ER+



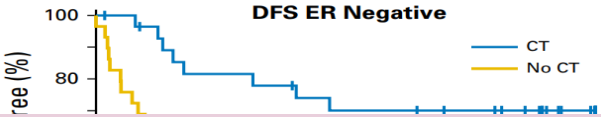


Wapnir et al
JCO 2018

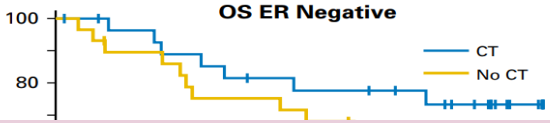
OM-recurrence: «pseudo-adjuvant» systemic treatment

Isolated locoregional recurrence

DFS according to ER status

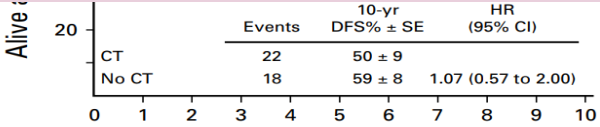


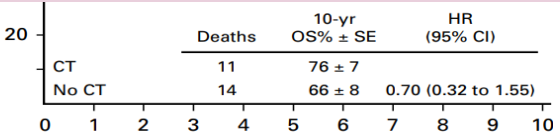
OS according to ER status



Important considerations:

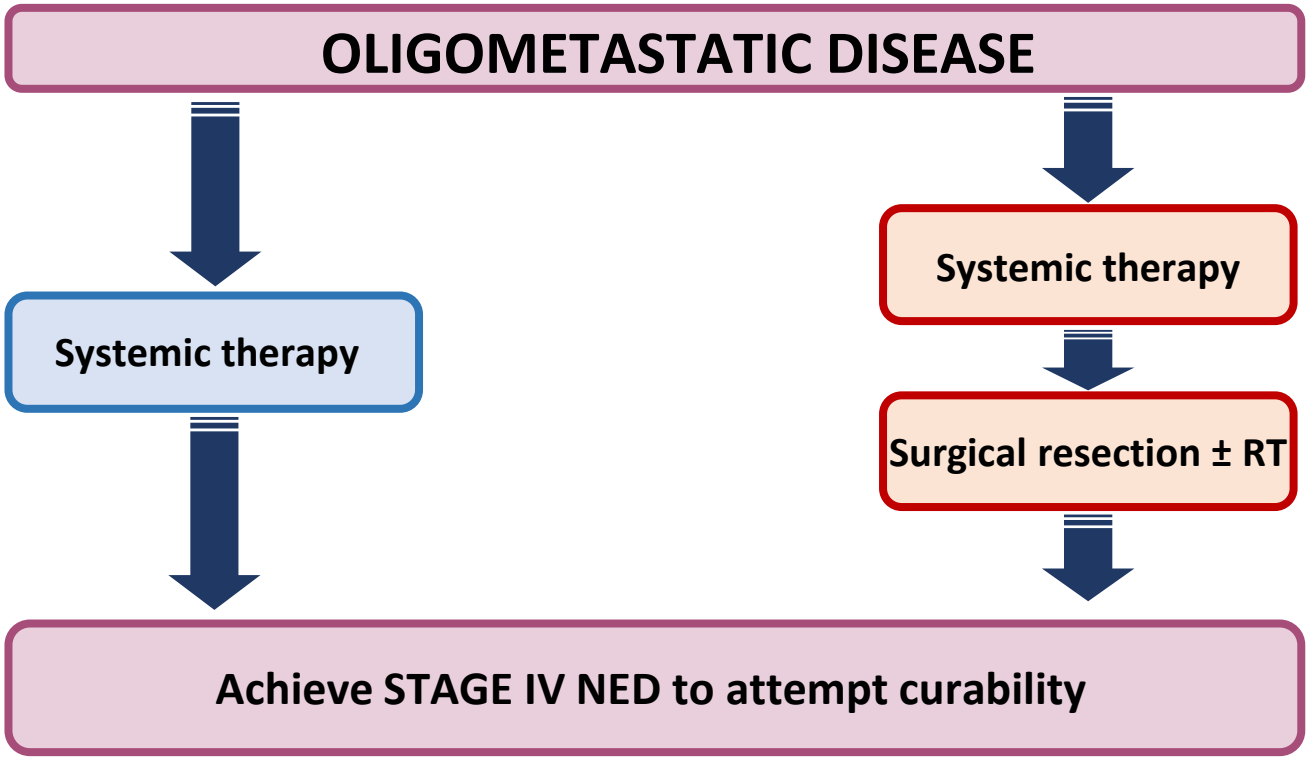
- **ER+ patients** received **ENDOCRINE THERAPY in both arms**.
  - It would be interesting to estimate the value of genomic tests (ILRR excluded from TailorX, RxPonder, Mindact)
- The different outcomes based on treatment allocation according to ER status were more striking when cohorts were examined according to **ILRR ER status** rather that primary BC ER status.





OM-BC management

Possible approaches



OM-recurrence: systemic treatment +/ locoregional tx.

INCLUSION CRITERIA	
# organs involved (other than primary site)	≤2
# metastatic lesions per organ	≤5
Lesion diameter	≤5 cm

1) Eligible patients received **systemic therapy**

2) In case of CR or PR **local therapy** could be performed (surgery or RT) in order to achieve or maintain a STAGE IV NED state.

- Anthra-based 30.7%
- Tax-based 65.3%
- Targeted tx 4.0%

LRT 44%
- RT 50%
- Surgery 32%

HR+ 67% | **HER2+ 17%** | **TN 21%**

Kobayashi T et al. Breast Cancer, 2012; Nagasaki et al, Breast Cancer 2021

OM-recurrence: systemic treatment +/ locoregional tx.

ORR	**93.6% (59/63 cases)**
CR/NED	**61.9% (39/63 cases)**
PR	**31.7% (20/63 cases)**

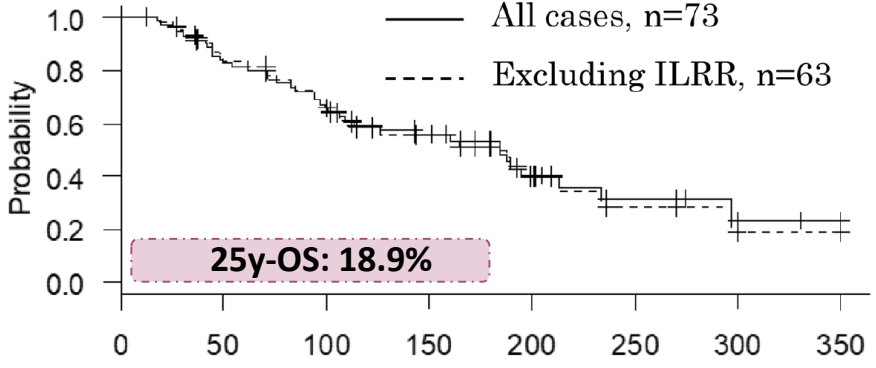
Factor associated with CR/NED:

- Single organ involvement
- ≤3 metastatic lesions per organ

Kobayashi T et al. Breast Cancer, 2012; Nagasaki et al, Breast Cancer 2021

OM-recurrence: systemic treatment +/ locoregional tx.

OS



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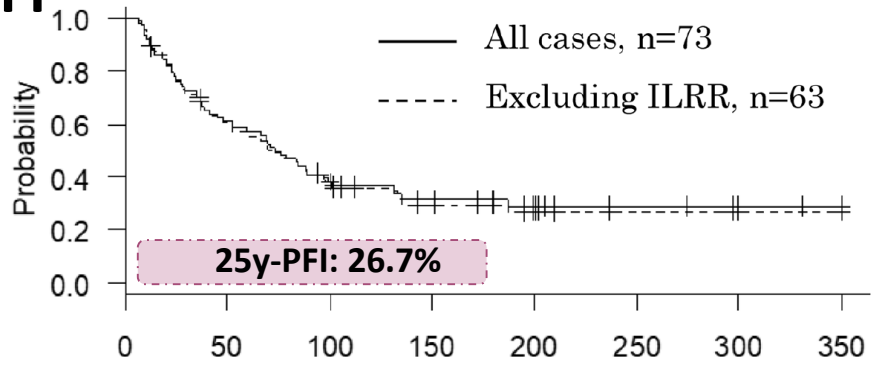


<u>LOCAL therapy</u> → NOT at multivariable analysis

Kobayashi T et al. Breast Cancer, 2012; Nagasaki et al, Breast Cancer 2021

DE-novo OM-BC primary BC locoregional treatment

Controversial issue

STUDY	POPULATION	TREATMENT ARMS	MAIN RESULTS
Tata Memorial Centre Study	716 treatment naive stage IV BC	LRT → ST vs ST **If not-resectable: induction CT prior to randomization (if responders)**	**OS: similar for the LRT and ST**
MF07-01	274 treatment naive stage IV BC	LRT → ST vs ST	**3-y OS: similar for the LRT and ST (primary endpoint)** 5-y OS: 41.6% for LRT group vs 24.4% for ST (p=0.005) **better OS: HR+/HER2-** age <55 years, bone-only solitary metastasis
ABCSG28 POSYTIVE	90 treatment naive stage IV BC	LRT → ST vs ST	**OS: similar for the LRT and ST**
ECOG-ACRIN 2108	258 stage IV BC **responding to 1° line CT**	LRT vs ST	**OS: similar for the LRT and ST.** **Worse OS for LRT vs ST in TNBC subgroup**

- Lack of stratification for biology and tumor burden.
- Systemic tx not always appropriate.
- *NOT specified if these patients had undergone local treatment for metastatic lesions* (or extremely under-represented).
- NO signal for survival improvement in OM-BC subgroup.
- Signals for detrimental effect in TN subtype, while positive impact suggested in HR+/HER2-.

BC, breast cancer; pts, patients; LRT, locoregional treatment; ST, systemic treatment;

Badwe et al Lancet Oncol 2015; Khan et al ASCO 2020; King et al ASCO 2016; Fitzal Ann Surg 2018

Proposed algorithm for OM-BC (stage IV)*

*NOT ILRR

A preliminary multidisciplinary discussion is necessary to discuss with the patient the alternative treatment strategies[1-2].

SYSTEMIC TREATMENT* TO DOCUMENT RESPONSE[1]
→ standard first-line treatment according to tumor biology and clinical features

**demonstrated efficacy irrespective of tumor burden[3-5]*

HR+/HER2-

CDK4/6 INH. + ENDOCRINE THERAPY

HER2+

PERTUZUMAB + TRASTUZUMAB + CT

ANTI-HER2 ADC
in case of early relapse to trastuzumab-based adjuvant tx

TRIPLE-NEGATIVE

IMMUNOTHERAPY + CT
if PD-L1+

CT if PD-L1-
(PARP inh if BRCAmut and pre-treated with anthra-tax for EBC)

LOCOREGIONAL APPROACH FEASIBLE

Consider locoregional treatment (local ablative tx to all metastatic lesions) with radical intent → stage IV NED[1]

Resume systemic treatment

Treatment cessation in case of sustained CR is still controversial and, if considered, should be thoughtfully discussed with the patient

LOCOREGIONAL APPROACH NOT FEASIBLE

Continue systemic treatment

1. Gennari et al ESMO gl, Ann Oncol 2021; 2. LG AIOM 2021; 3. Rossi et al,Cancers 2019; 4. Schmid et al, NEJM 2018; 5. Cortes et al, Lancet Oncol 2020;

Should we «force» the diagnosis of OM-BC?
The position of AIOM and ESMO guidelines

Aiom
Associazione Italiana di Oncologia Medica

Linee guida
NEOPLASIE DELLA MAMMELLA

Edizione 2021
Aggiornata a 11.11.2021

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione
ALTA	In assenza di sospetti clinici individuali o di programmi personalizzati, il cosiddetto follow up "intensivo" non dovrebbe essere raccomandato. In particolare, l'uso di indagini strumentali quali la radiografia del torace; l'ecografia addominale, la TC encefalo-torace-addome; la TC-PET con FdG; la scintigrafia ossea, come anche la determinazione dei marcatori tumorali (CEA, CA 15.3) non dovrebbero fare parte delle indagini routinarie di follow up in assenza di sospetto clinico di ripresa di malattia[26-33,37,38,40].	**Condizionata a sfavore**
COI: nessun conflitto dichiarato		

Aggiornamento: Luglio 2021

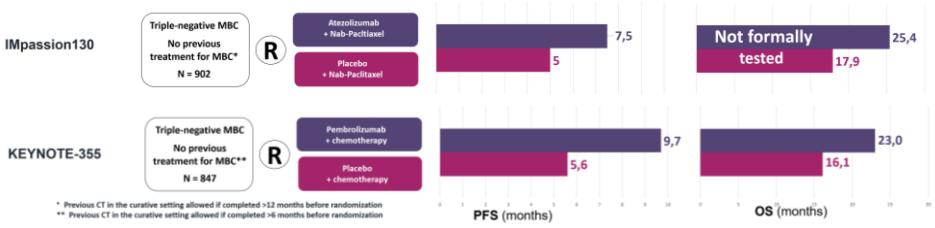
ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

- In asymptomatic patients, other laboratory or imaging tests (e.g. blood counts, routine chemistry tests, chest X-rays, bone scans, liver US exams, CT scans, FDG-PET-CT) or any tumour markers such as CA15-3 or CEA are not recommended [I, D].

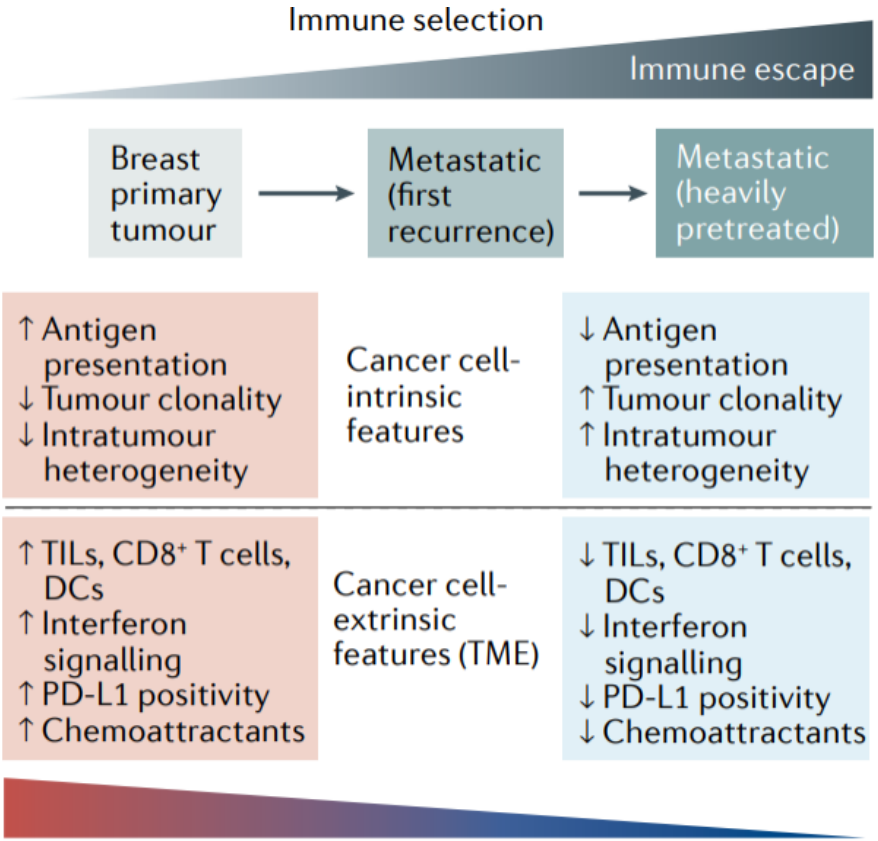
Currently, available evidence does not support the implementation of an intensive follow up for all EBC patients. However, **most data for follow-up recommendations come from an era of less sophisticated diagnostic procedures and less efficacious treatment of advanced disease**, and new trials are urgently needed to reassess this question.

Should we «force» the diagnosis of OM-BC?

Just to be provocative



Immunotherapy + CT (atezo+ nab-P / pembro + CT) are currently approved (Europe and US) as first-line treatment for PD-L1-positive TN MBC pts

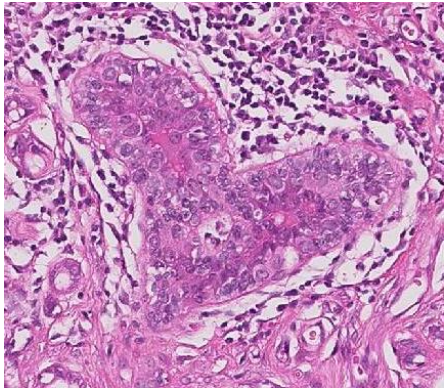


Modified from Miglietta et al, ESMO Open 2022; Bianchini et al, Nat Rev Clin Oncol 2022

Conclusions

- **In the absence of solid evidence, a multimodal approach for OM-BC can be a «risky bet» → why & when can be worth to take this bet in the interest of the patients?**
  - **An accurate case-by-case multidisciplinary discussion is required in order to evaluate the feasibility and potential value of this approach** (taking into account tumor and patient characteristics, patient preferences, availability and feasibility of effective systemic and locoregional treatments).
  - Pending results from NRG-BR002 phase II/III trial (standard of care +/- ablative therapy to all metastatic sites)
- **The entire treatment MUST be PLANNED taking into account the possibility of «cure» remembering that ABSENCE of EVIDENCE does not mean EVIDENCE of ABSENCE.**
- Future research should be addressed towards a more qualitative investigation of OM-BC, whose definition still relies on mere quantitative factors.

Grazie per l'attenzione!



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