Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

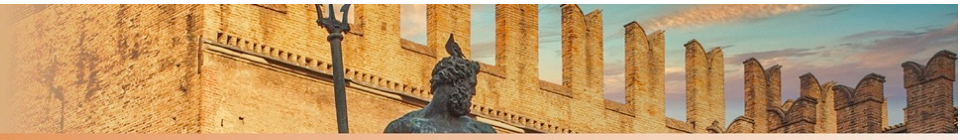
La moderna terapia sistemica nella malattia oligometastatica

Ugo De Giorgi

IRCCS IRST Meldola - Board AIOM

Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

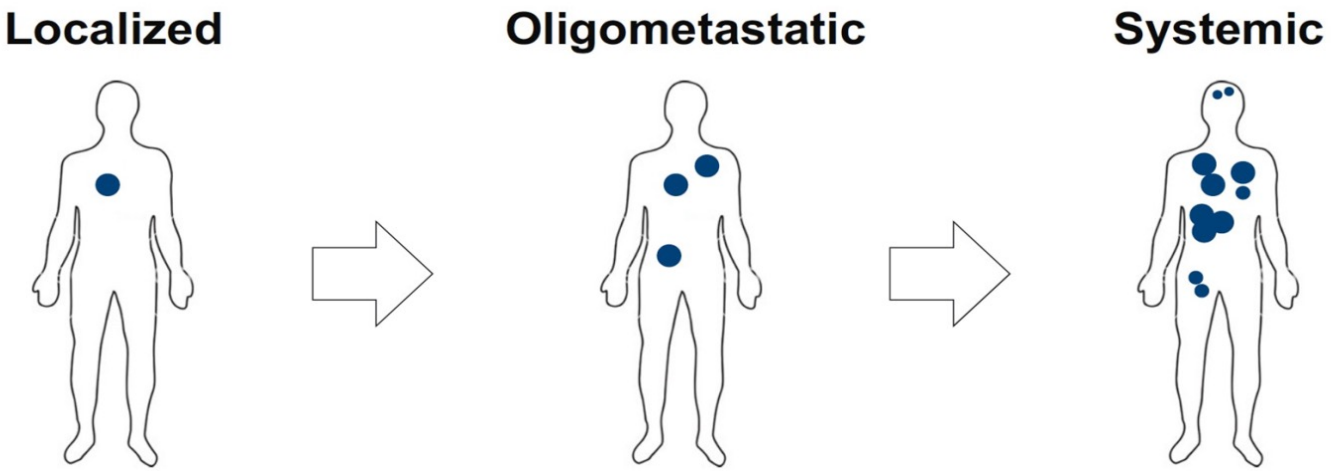


DICHIARAZIONE

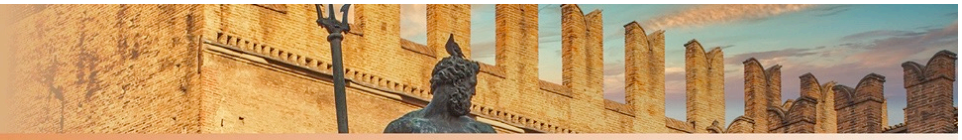
- Ai sensi dell'art. 76 sul Conflitto di Interessi, pag. 34 dell'Accordo Stato-Regione del 2 febbraio 2017, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:
  - consultant/advisory board member for Astellas, Atrazeneca, Bayer, BMS, Ipsen, Janssen, Merck, MSD, Novartis, Pharmamar, Pfizer, Roche;
  - travel support from BMS, Ipsen, Janssen and Pfizer;
  - research funding from AstraZeneca, Roche and Sanofi (Inst).

The term "oligometastatic" was coined by **Hellman and Weichselbaum** in 1995

… an **intermediate state** between loco-regional and widespread disease in which the full metastatic biological potential is not expressed and circulating tumor cells has metastasized in limited sites…



Hellman & Weichselbaum JCO 1995



Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document

Yolande Lievens [a,*], Matthias Guckenberger [b], Daniel Gomez [c], Morten Hoyer [d], Puneeth Iyengar [e], Isabelle Kindts [f], Alejandra Méndez Romero [g], Daan Nevens [h], David Palma [i], Catherine Park [j], Umberto Ricardi [k], Marta Scorsetti [l], James Yu [m], Wendy A. Woodward [c]

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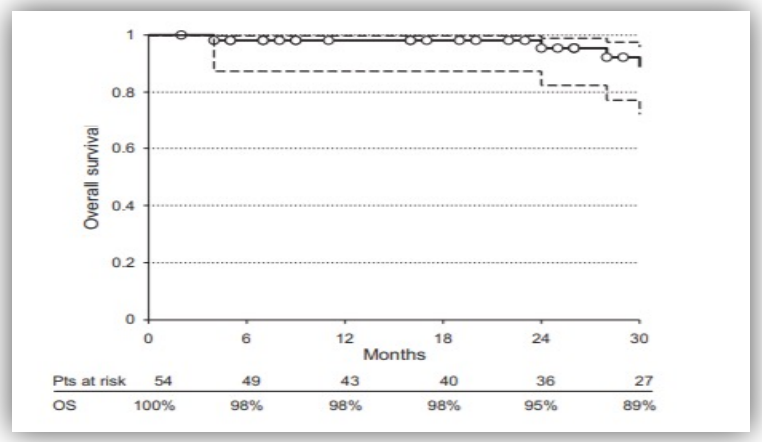
- A threshold of **1-5 metastatic lesions**
- All lesions must be **safely treatable** with local therapy
- Oligometastatic state must be assessed with **high resolution imaging**

Lievens et al, Radiother Oncol 2020

AGGRESSIVE MULTIDISCIPLINARY APPROACH: Systemic therapy plus ablative radiotherapy **can be beneficial**?

- **Phase II Italian** trial: 54 oligometastatic **Breast cancer** patients with **less than 6 lesions** treated with Stereotactic ablative body radiotherapy (**SABR**) or fractionated intensity modulated radiotherapy (**IMRT**)

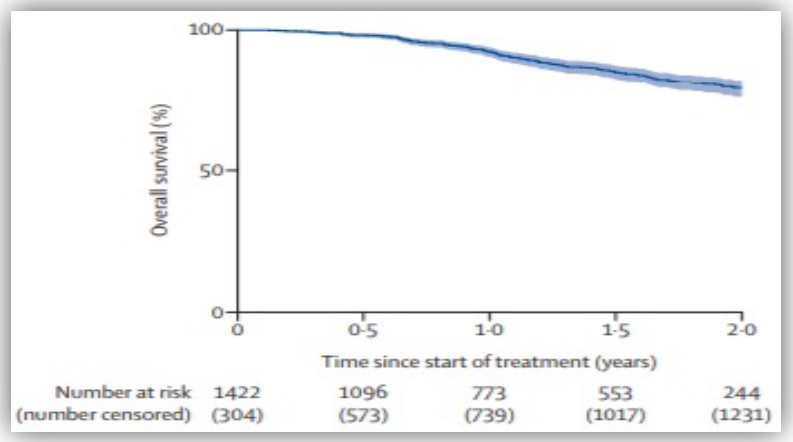
Two-year OS was 95 %



Trovo et al, Radiother Oncol 2018

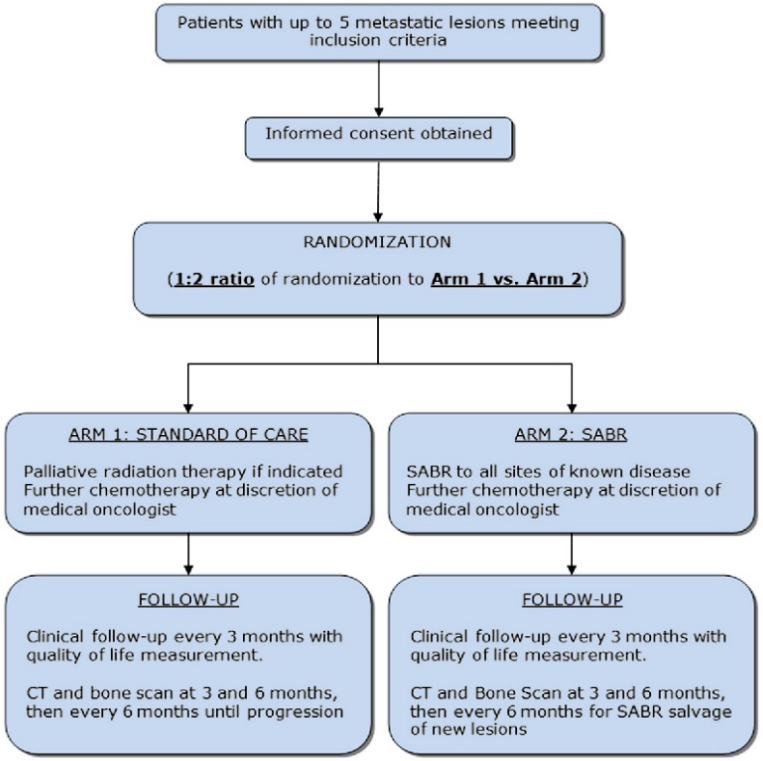
- Recent **prospective observational** study: **1422** patients with **1-3 metastatic lesions** treated with SABR
  Mixed histology (28.6% prostate cancer)

Two-year OS of 79%



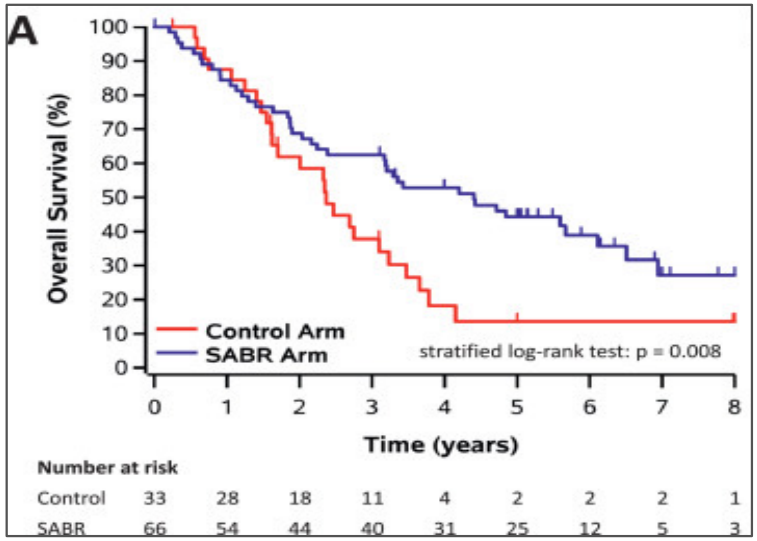
Chalkidou et al, Lancet Oncol 2021

SABR-COMET TRIAL: Extended Long-Term Outcomes



99 Randomized Patients (mixed histology)
1-3 metastatic lesions (91%)
4-5 metastatic lesions (9%)

lung (n = 18), breast (n = 18), colon (n = 18), prostate (n = 16), and other (n = 29)



8-year OS

27.2% in the **SABR** arm
VS
13.6% in the **control arm**
(HR 0.50; P = .008)

Harrow et al, Int J Rad Onc, 2022

- Retrospective or prospective non-randomized studies
- Oligometastatic definition heterogeneity among studies
- Outdated imaging for staging
- Outdated systemic therapy (dual HER-2 blockade therapy, CDK 4/6 inhibitors, immune checkpoint inhibitors …)

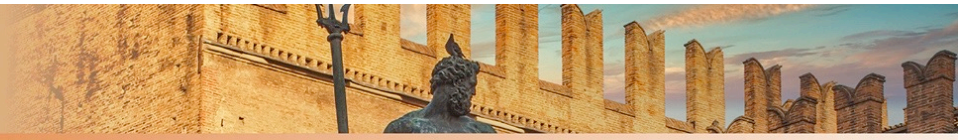
The use of aggressive multidisciplinary approach has **great variability** between different Hospital Departments and is often considered for **palliative purposes** rather than curative intent, but we can not miss the **opportunity to achieve long survival**

Advanced surgery

Innovative systemic therapies

Ablative radiotherapy

- DISCUSS IN **MULTIDISCIPLINARY** TUMOR BOARD
- TREAT IN CENTERS WITH **AGGRESSIVE APPROACH EXPERTISE**



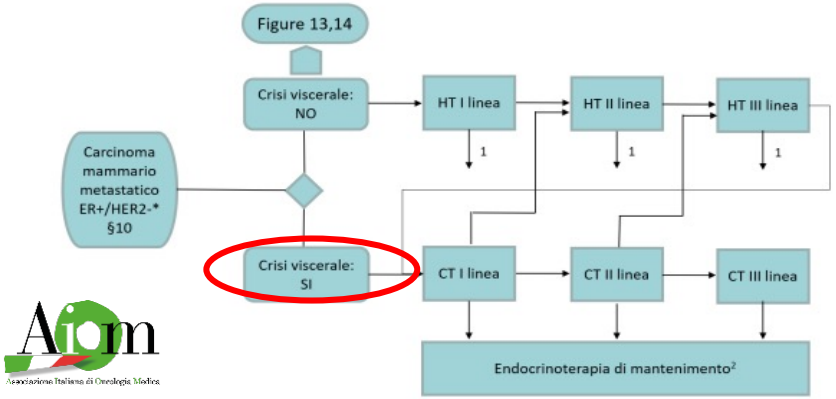
INNOVATIVE SYSTEMIC THERAPY IN …

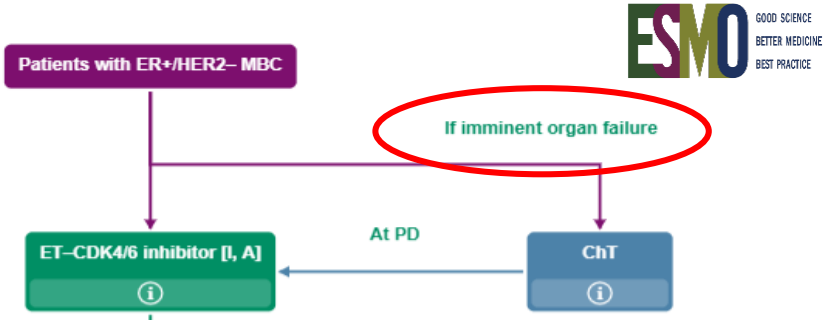
- HORMONE RECEPTOR POSITIVE/ HER2-NEGATIVE OLIGOMETASTATIC BREAST CANCER
- HER2-POSITIVE OLIGOMETASTATIC BREAST CANCER
- TRIPLE NEGATIVE OLIGOMETASTATIC BREAST CANCER

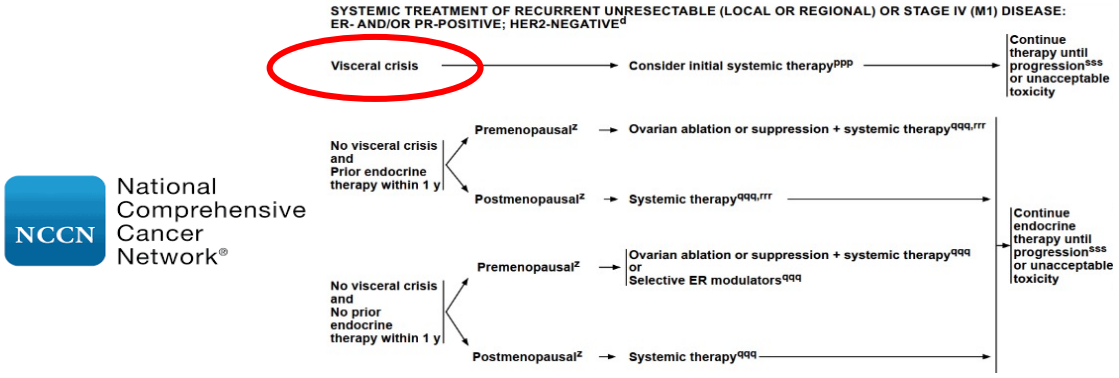
… AND …

- ANTIBODY-DRUG CONJUGATE REVOLUTION

HORMONE RECEPTOR POSITIVE/ HER2-NEGATIVE METASTATIC BREAST CANCER







Chemotherapy only for Visceral Crisis

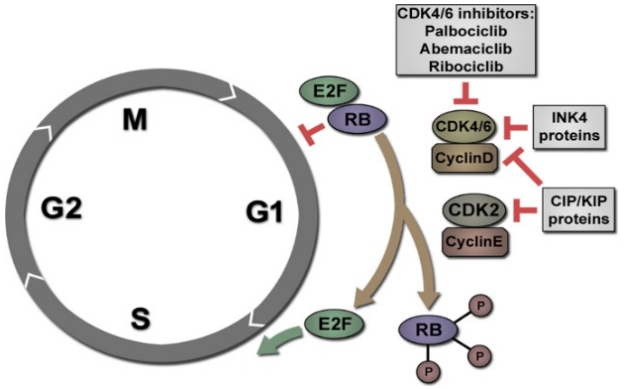
Endocrine therapy for Oligometastatic Luminal Breast Cancer

HORMONE RECEPTOR POSITIVE/ HER2-NEGATIVE METASTATIC BREAST CANCER

Cyclin-dependent kinase (CDK) 4/6 inhibitors revolutioned the treatment of HR-positive/HER2-negative metastatic breast cancer patients

Mechanism of action
- Suppression of phosphorylation of the retinoblastoma tumor suppressor protein, which serves to prevent cancer cell proliferation

In combination with
- Endocrine therapy (aromatase inhibitors, fulvestrant)



Less toxic than chemotherapy…

…**More Effective than Endocrine therapy alone** (PFS and OS benefit)

RIBOCICLIB

ABEMACICLIB

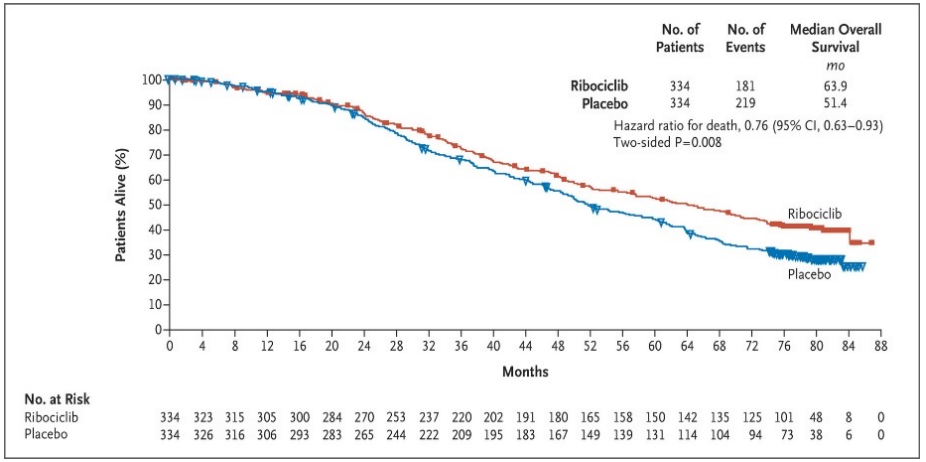
PALBOCICLIB

Wagner et al,, Oncogene, 2020

HORMONE RECEPTOR POSITIVE/ HER2-NEGATIVE METASTATIC BREAST CANCER

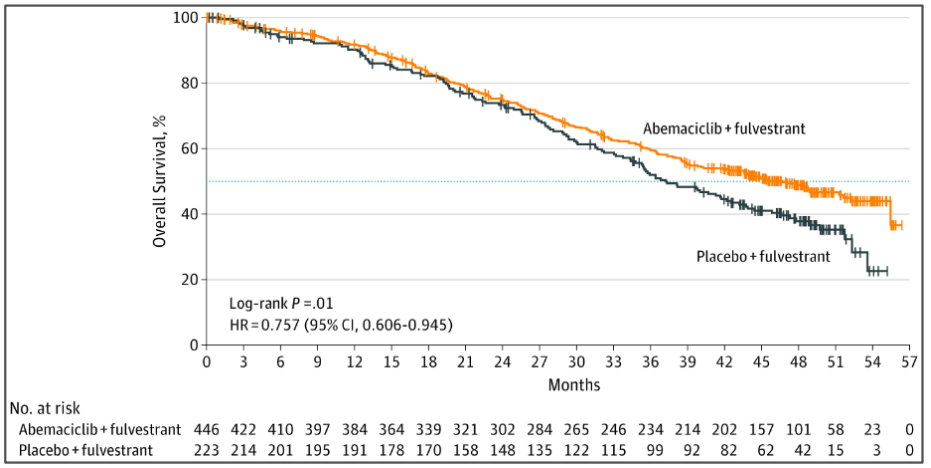
MONALEESA-2: **Ribociclib** + Letrozolo VS Placebo +Letrozolo

OS



MedianOS 63.9 vs 51.4 months
(improved by 12.5 months)

MONARCH-2: **Abemaciclib** + Fulvestrant VS Placebo + Fulvestrant

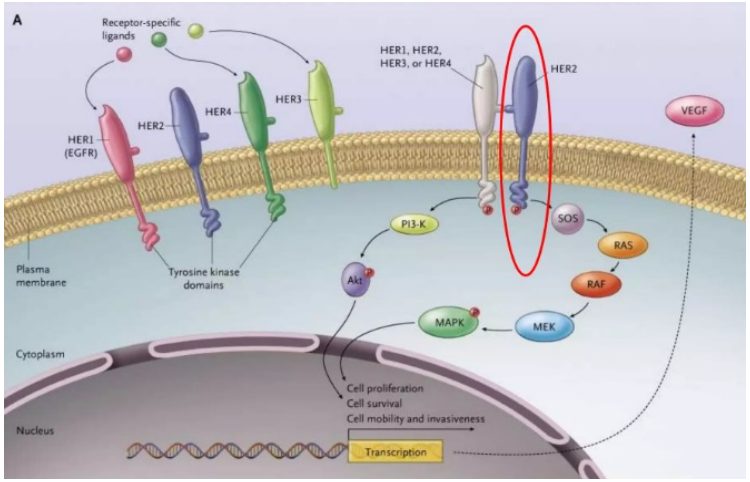


MedianOS 46.7 months vs 37.3 months
(improved by 9.4 months)

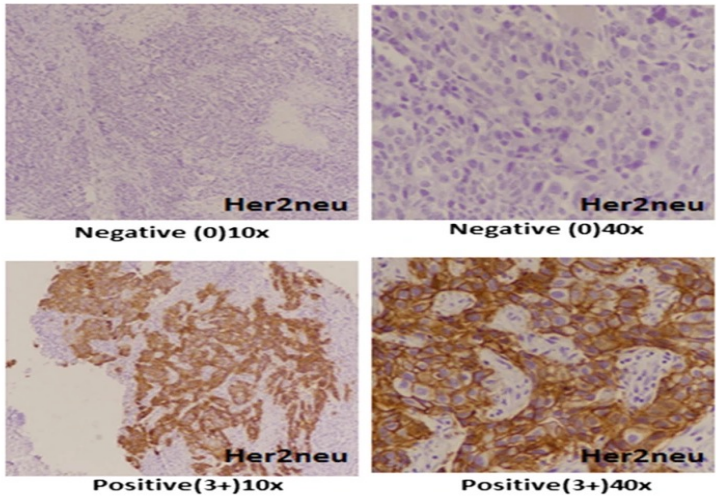
Hortobagyi et al, N Eng J Med, 2022
Sledge et al, JAMA, 2019

HER2-POSITIVE METASTATIC BREAST CANCER

HER2 proteins are receptors that control how the cells grow and divide



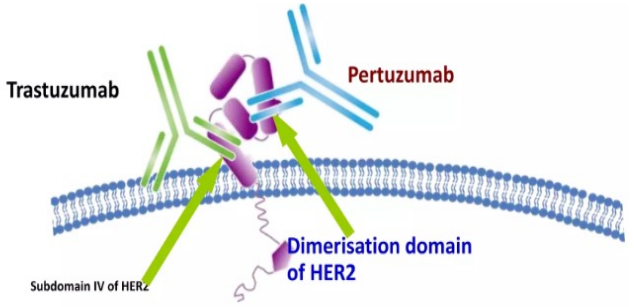
Tests that examine HER2 include: Immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH)



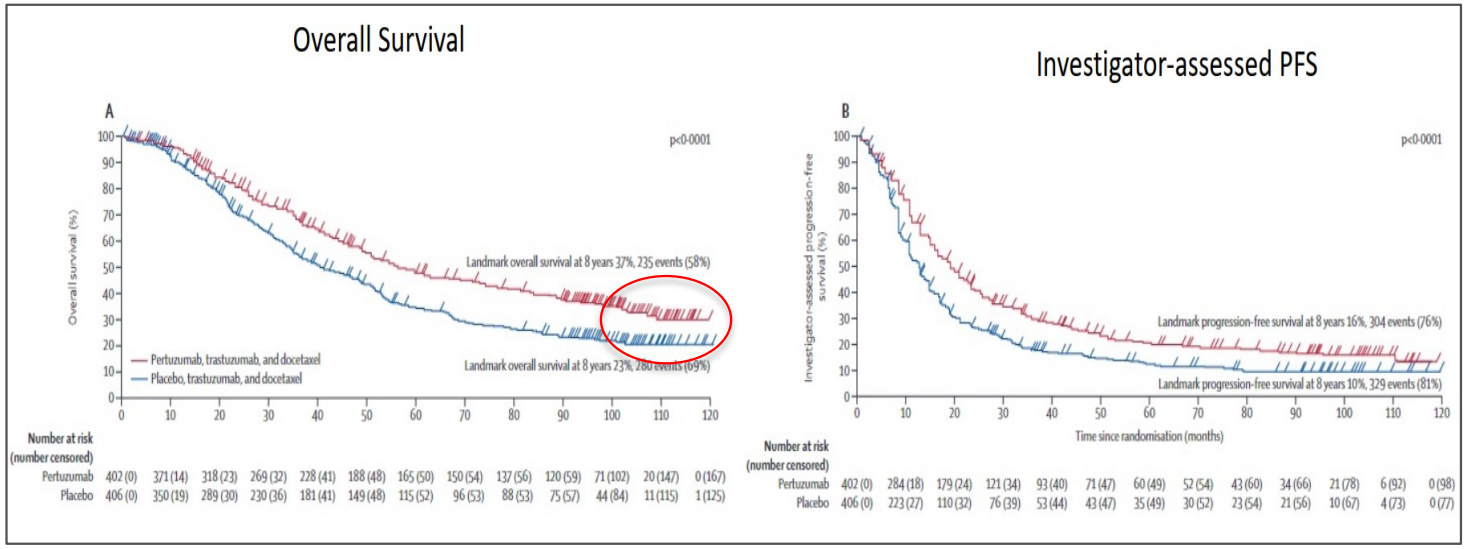
.Breast cancer identified as HER2-positive are **MORE AGGRESSIVE BUT**…

Houdis C et al, N Eng J Med, 2007

… Now we have **MONOCLONAL ANTIBODIES** that **target** different extracellular regions of the **HER-2 tyrosine kinase receptor** preventing the activation of HER signaling pathways



CLEOPATRA Study: Docetaxel+**Trastuzumab + Pertuzumab** VS Docetaxel + Trastuzumab + Placebo



8-year landmark OS rate was **37%** for **docetaxel + trastuzumab + pertuzumab**

Can we **improve** this **OS** rate in Oligometastatic HER-2 positive patients by **adding metastases-directed therapy**?

Swain et al, Lancet, 2020

TRIPLE-NEGATIVE METASTATIC BREAST CANCER

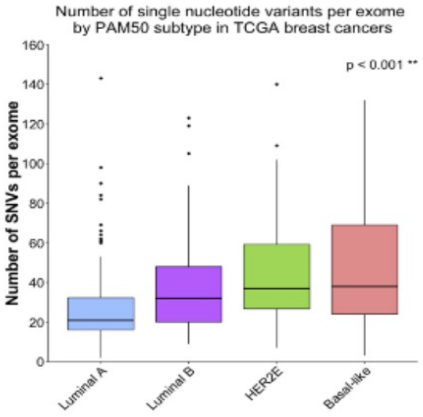
Does not have any of the receptors that are commonly found in breast cancer

Lack of targets

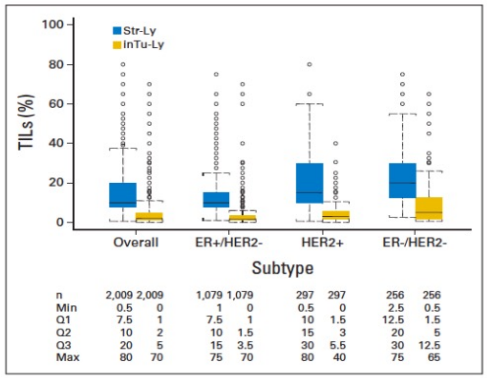
Historically treated with chemoterapy

...BUT...

Mut load across BC subtypes



TILs across BC subtypes



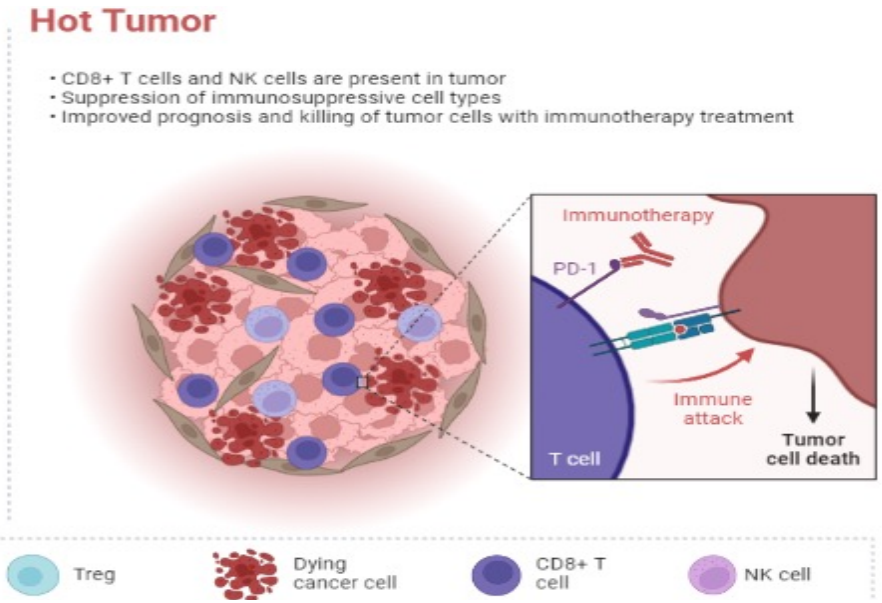
- **Higher mutational burden** → "neoantigens" → stronger antitumor immune response
- Increased levels of tumor infiltrating lymphocytes (**TILs**) in the tumor microenvironment
- Elevated levels of **PD-L1 expression**

The most immunogenic breast cancer subtype

IMMUNE CHECKPOINT INHIBITORS

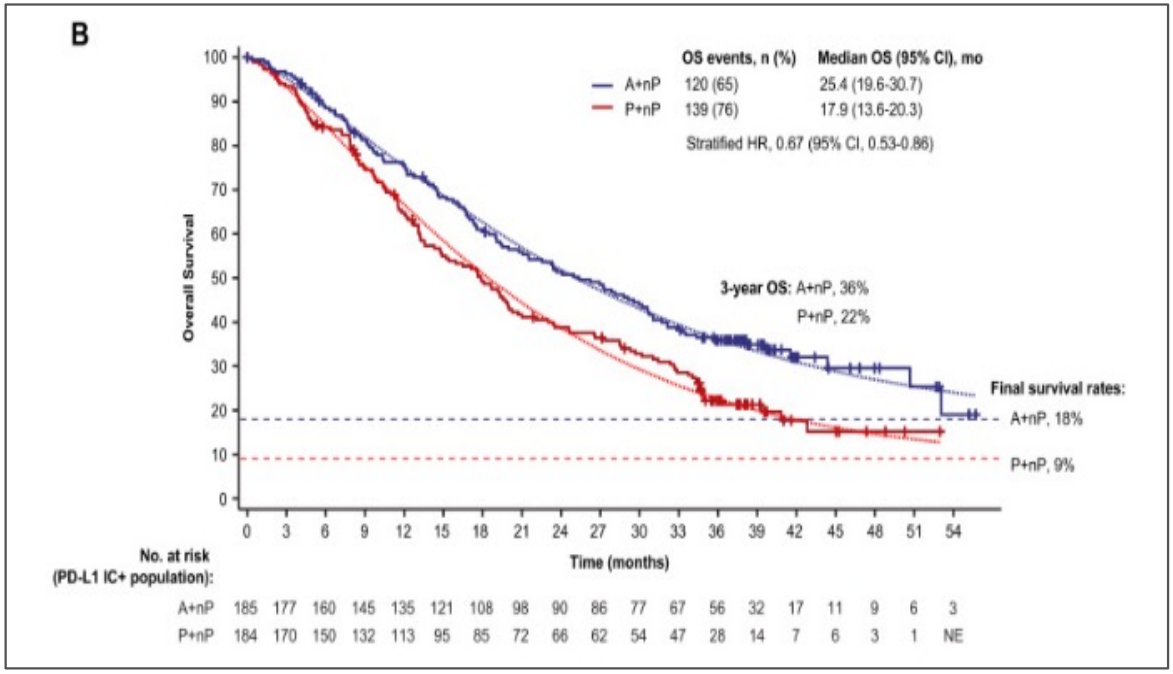
The role of Immune checkpoints is to prevent an immune response from being so strong that it destroys healthy cells in the body but it can also prevent the immune system from destroying cancer.

Immune checkpoint inhibitors block checkpoint proteins (es. PD-1 and PD-L1) preventing the "off" signal and allowing the T cells to kill cancer cells.



Atezolizumab: a humanized monoclonal anti-PD-L1 antibody

IMPASSION130 Trial: Nab-paclitaxel + **Atezolizumab** vs Nab.paclitaxel + placebo



Median OS 25.4 vs 17.9 months

in **PD-L1 positive** triple negative metastatic breast cancer patients

Emens et al, Ann Oncol, 2021

IMMUNE CHECKPOINT INHIBITORS COMBINATION WITH RADIOTHERAPY

Pre-clinical and clinical evidence supporting the concept that **radiotherapy can have immunological effects**:

- Abscopal effect
- DNA damage
- Up-regulation of PD-L1

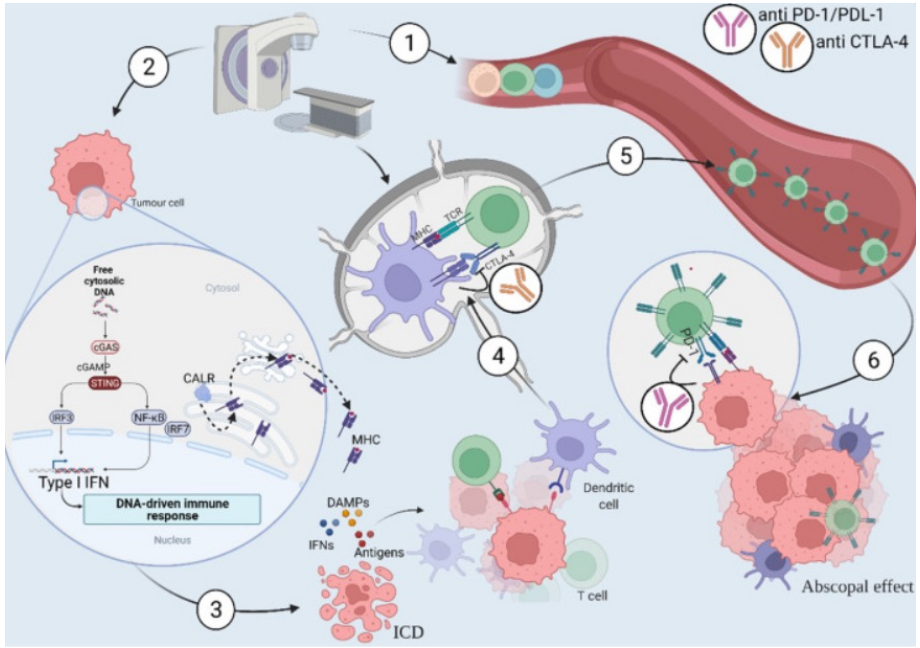
⇩

Immune checkpoint inhibitors against PD-1 or PD-L1 can synergise with radiotherapy

⇩

Is SABR more immunogenic than conventional radiotherapy?

Successful combination for oligometastatic patients?



David et al, Biomedicines, 2022

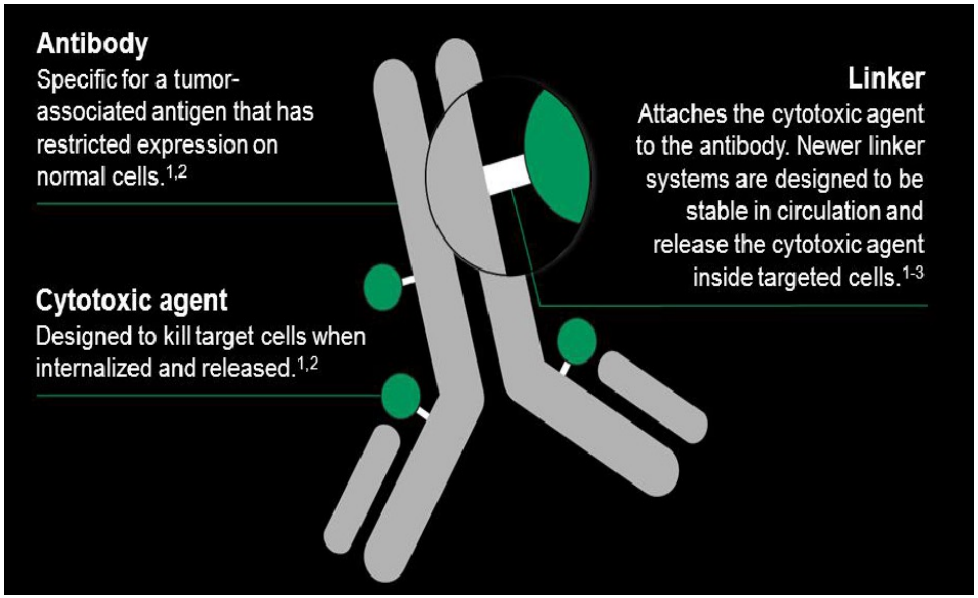
ANTIBODY-DRUG CONJUGATES (ADCs) REVOLUTION

ADCs are composed of an antibody linked to a biologically active cytotoxic payload

- The **antibody** must be highly selective for a tumor-associated antigen
- The **payload** must be a cytotoxic agent able to induce cell death
- The **linker** must be stable in circulation and must release the cytotoxic agents in target cells.

Selective binding of the antibody to tumor → internalization → release of the cytotoxic payload in the target cell → diffusion into the neighboring antigen-negative cells.

BYSTANDER EFFECT



Increase the cell-killing potential

Reduce systemic toxicity

A new opportunity for oligometastatic BC patients ?

TRASTUZUMAB-DERUXTECAN

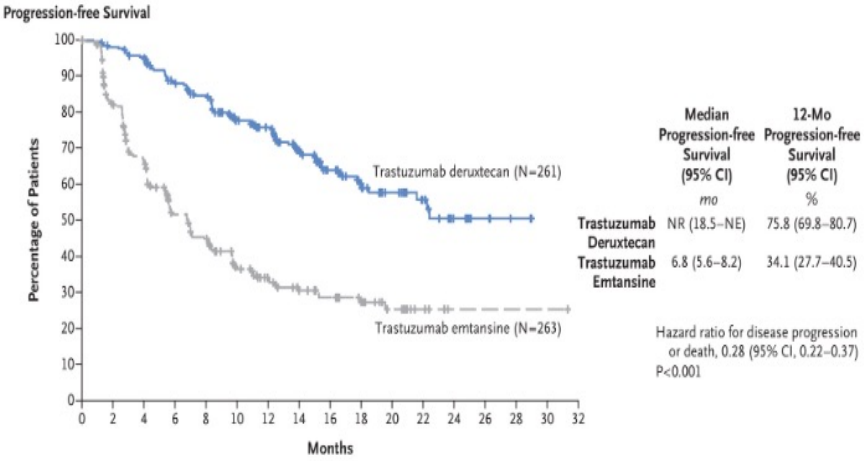
An antibody-drug conjugate composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor.

Impressive results in both **HER2-positive** BC and Luminal or triple negative BC patients with **low HER2 expression**

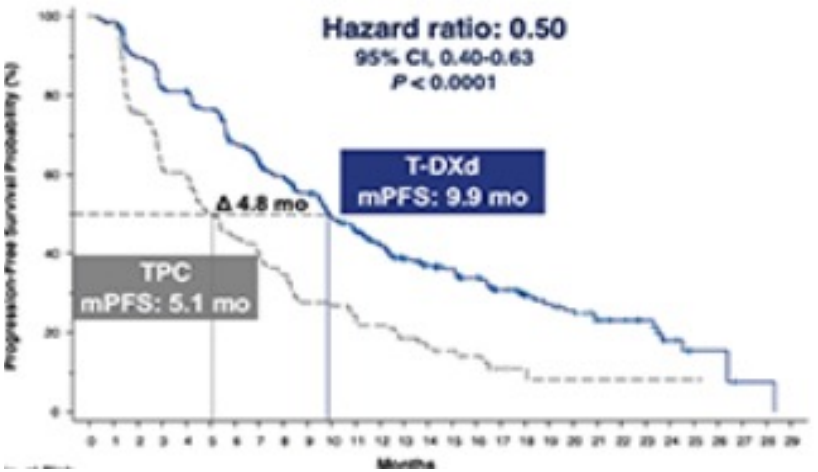
Overcomes the classical breast cancer classification

DESTINY-BREAST03: Trastuzumab-deruxtecan vs TDM-1 in **HER2 positive** metastatic BC

PFS



DESTINY-BREAST04: Trastuzumab-deruxtecan vs chemotherapy **HER2-low** metastatic BC



Cortés et al, N Eng J Med, 2022
Modi et al, N Eng J Med, 2022

SACITUZUMAB GOVITECAN

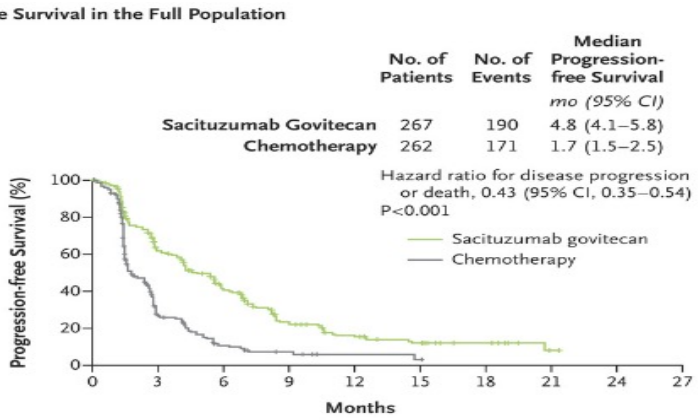
An antibody-drug conjugate composed an antibody targeting Trop-2 (expressed in the majority of breast cancers) and SN-38, a topoisomerase I inhibitor.

Impressive results in both **Triple negative** BC and **Luminal/HER2-negative** BC

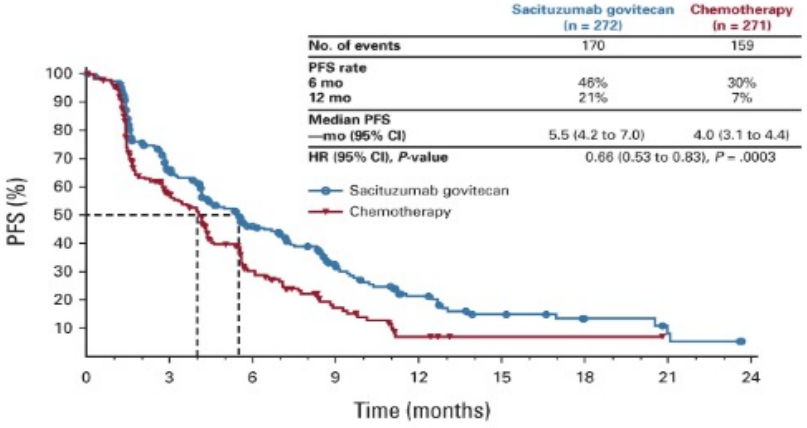
Overcomes the classical breast cancer classification

ASCENT Trial: Sacituzumab govitecan vs chemotherapy in **Triple negative** metastatic BC

PFS



TROPiCS-02: Sacituzumab govitecan vs chemotherapy **Luminal/HER2-negative** metastatic BC



Bardia et al, N Eng J Med, 2021
Rugo et al, J Clin Onc, 2022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Grazie