Terapia sistemica della fase precoce e della fase metastatica

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Early Breast Cancer

LOCAL TREATMENT

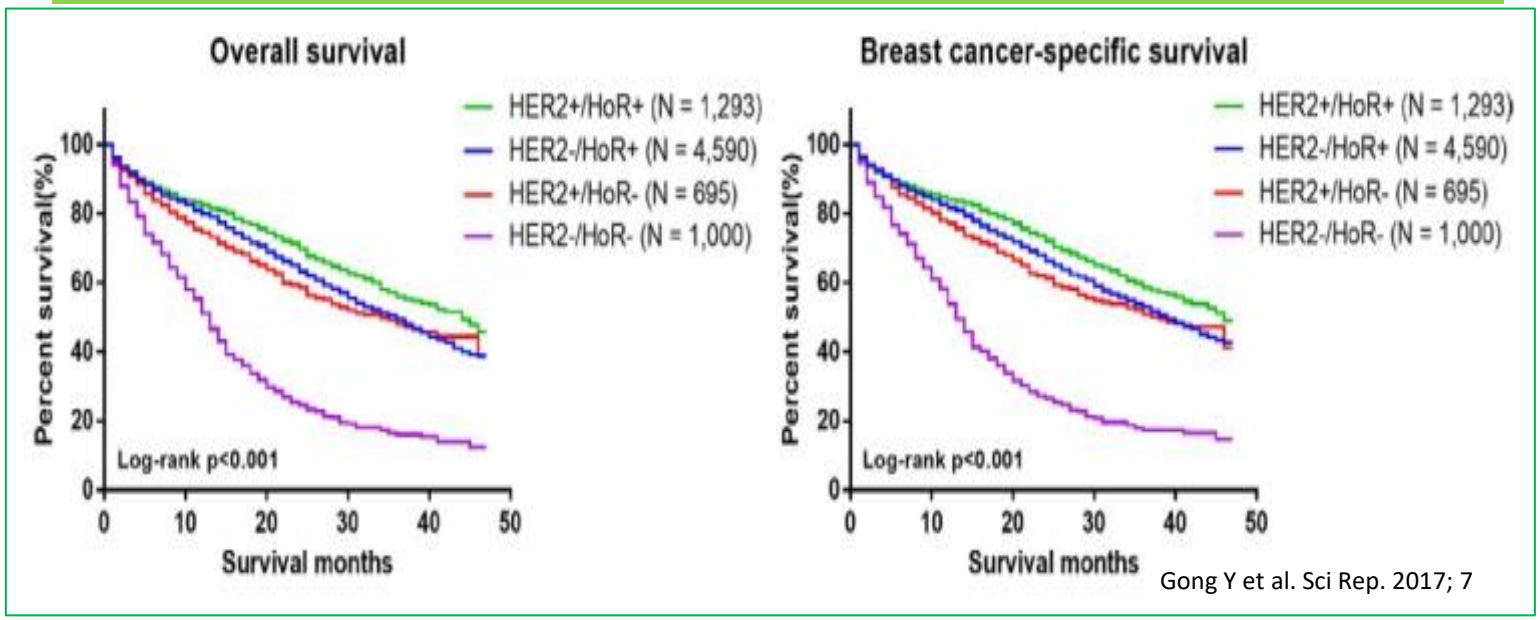
- Surgery
- Radiation

Tumor size
Grade
Age
Ki67
ER expression
PgR expression
HER2 expression

SYSTEMIC TREATMENT

Endocrine therapy
Chemotherapy
HER2- target therapy

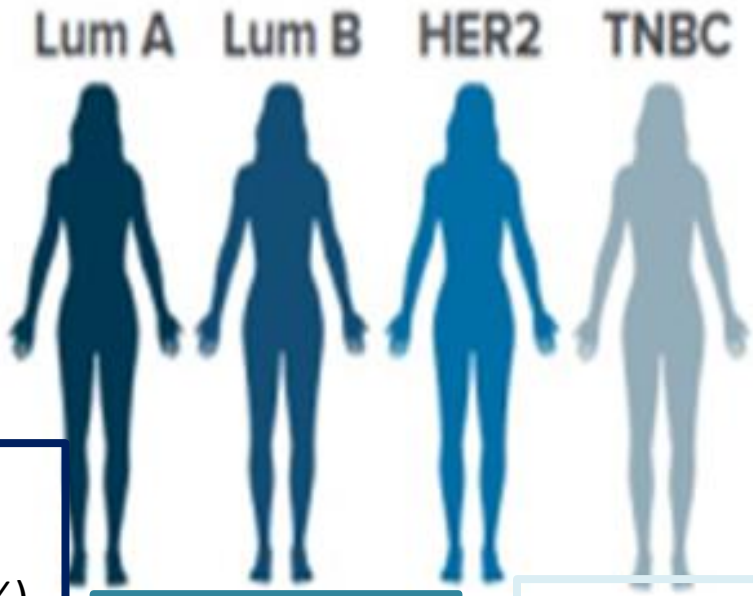
Survival by breast cancer subgroups



Gong Y et al. Sci Rep. 2017; 7

Intertumor heterogeneity

Differences among different patients affected by breast cancer, including different cancer subtypes



ER positive
HER2 **POSITIVE**
Any Ki67
Any PgR

HER2 positive
ER and PgR absent

ER positive
HER2 negative
Ki67 low (≤ 10%)
PgR high

ER positive
HER2 **NEGATIVE**
And either
Ki67 high or
PgR low

«basal-like»/triple negative
ER and PgR absent
HER2 negative

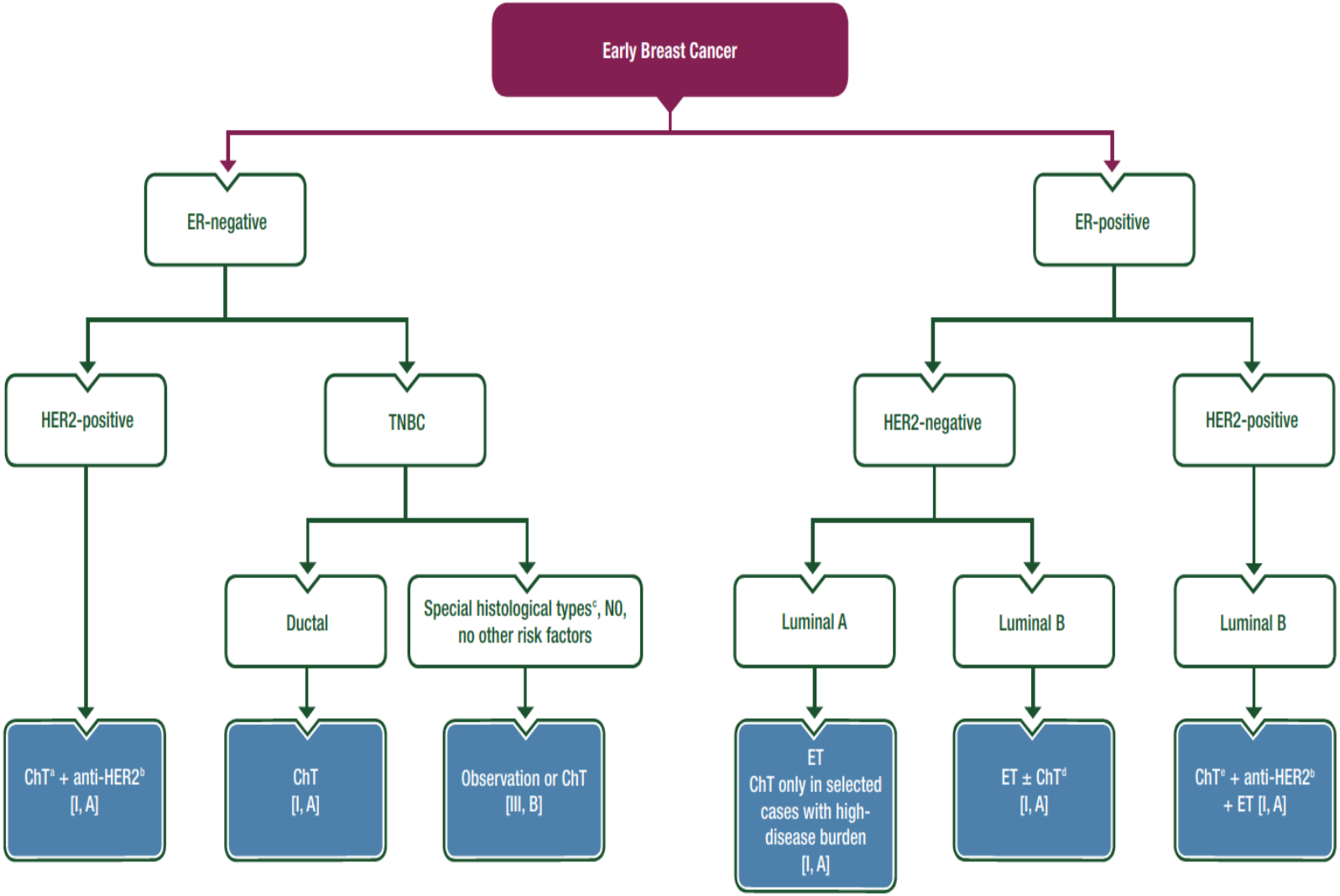
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 1194–1220, 2019
doi:10.1093/annonc/mdz173
Published online 4 June 2019

SPECIAL ARTICLE

Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Cardoso[1], S. Kyriakides[2], S. Ohno[3], F. Penault-Llorca[4,5], P. Poortmans[6,7], I. T. Rubio[8], S. Zackrisson[9] &



TEST GENOMICO
valuta gruppi di geni espressi nel tessuto neoplastico: può aiutare a caratterizzare meglio il rischio di ricaduta e la risposta alle terapie

I test genomici sono indicati:

-casi incerti per valutare l'effettiva utilità della chemioterapia adiuvante post-operatoria, in aggiunta alla ormonoterapia, per le pazienti affetti da **carcinoma mammario in fase iniziale** (stadio I-IIIA) con **recettori ormonali positivi** (ER+) e con **recettore HER2-negativo**

I test genomici non sono indicati:

-paziente, informata, nega il consenso alla eventuale chemioterapia adiuvante né quando, a giudizio clinico dell'oncologo, le caratteristiche e le condizioni cliniche della paziente facciano escludere la possibilità della chemioterapia.

-nel carcinoma in fase iniziale ER+ HER- identificati dopo stratificazione clinico-patologica come a basso rischio di ricorrenza o ad alto rischio di ricorrenza

- Oncotype DX® (21-gene panel)
- MammaPrint® (70-gene panel; "Amsterdam signature")
- EndoPredict® (EP and EPclin scores)
- Prosigna® PAM50-ROR® (Breast Cancer Intrinsic Classifier)

REGIONE DEL VENETO

ALLEGATO A DGR n. 1279 del 21 settembre 2021 pag. 1 di 3

Indicazione, prescrizione, esecuzione, utilizzo e monitoraggio dei test genomici nell'ambito del percorso di cura con garanzia di presa in carico multidisciplinare e di appropriatezza d'uso

The Oncotype DX® Assay

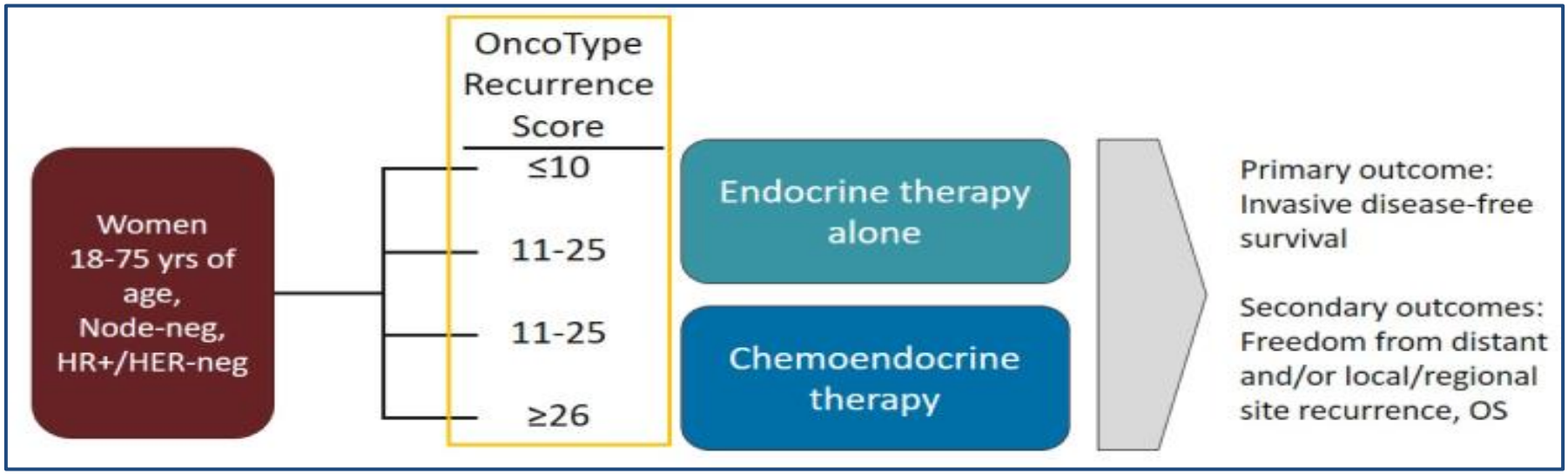
- 16 breast cancer-related genes

Estrogen	Proliferation	HER2	Invasion	Others
ER PR BCL2 SCUBE2	Ki67 STK15 Survivin Cyclin B1 MYBL2	GRB7 HER2	Stromelysin 3 Cathepsin L2	CD68 GSTM1 BAG1

- 5 reference genes

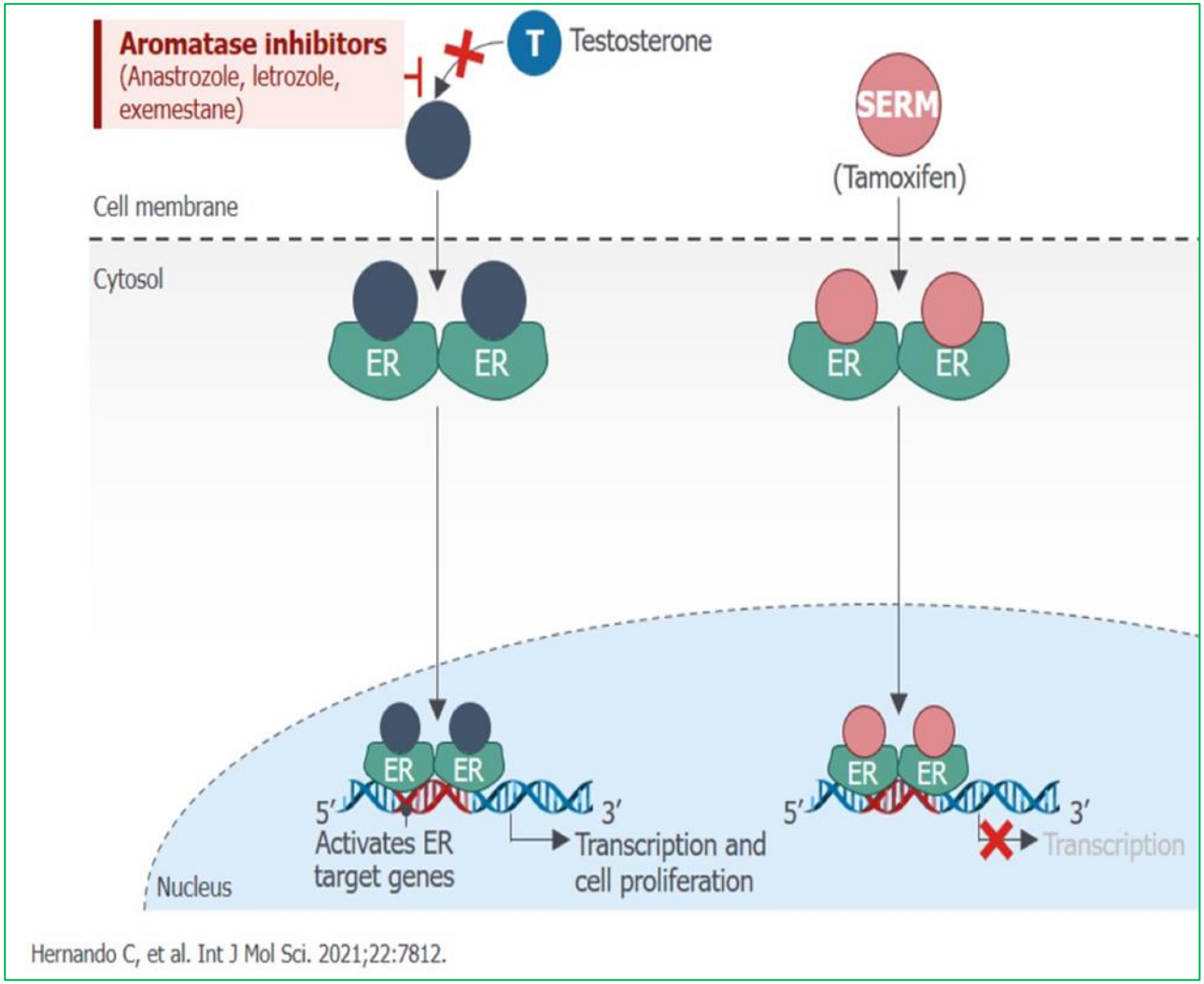
Beta-actin	GAPDH	RPLPO	GUS	TFRC

Paik S, et al. *J Clin Oncol*. 2006;24:3726-3734.



Sparano JA, et al. N Engl J Med. 2018 Jul 12;379(2):111-121.

ENDOCRINE ADJUVANT THERAPY in early Breast Cancer: MECHANISM OF ACTION



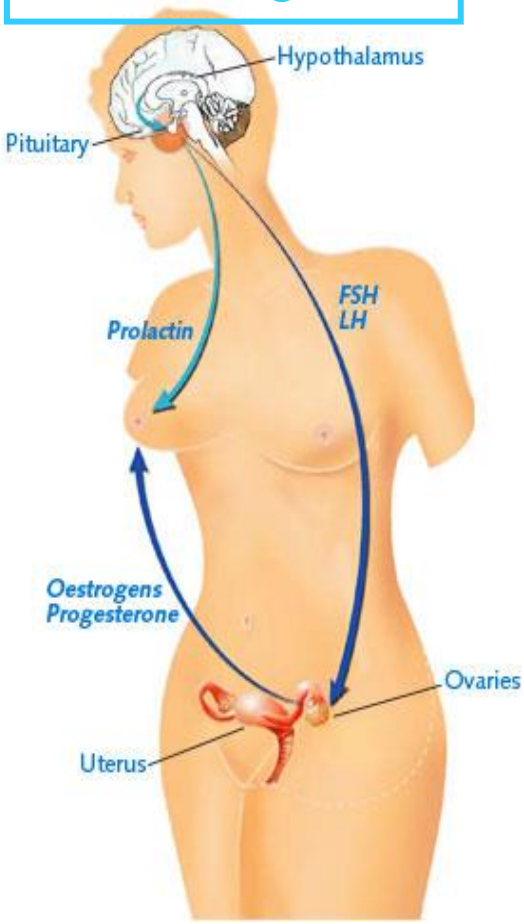
Hernando C, et al. Int J Mol Sci. 2021;22:7812.

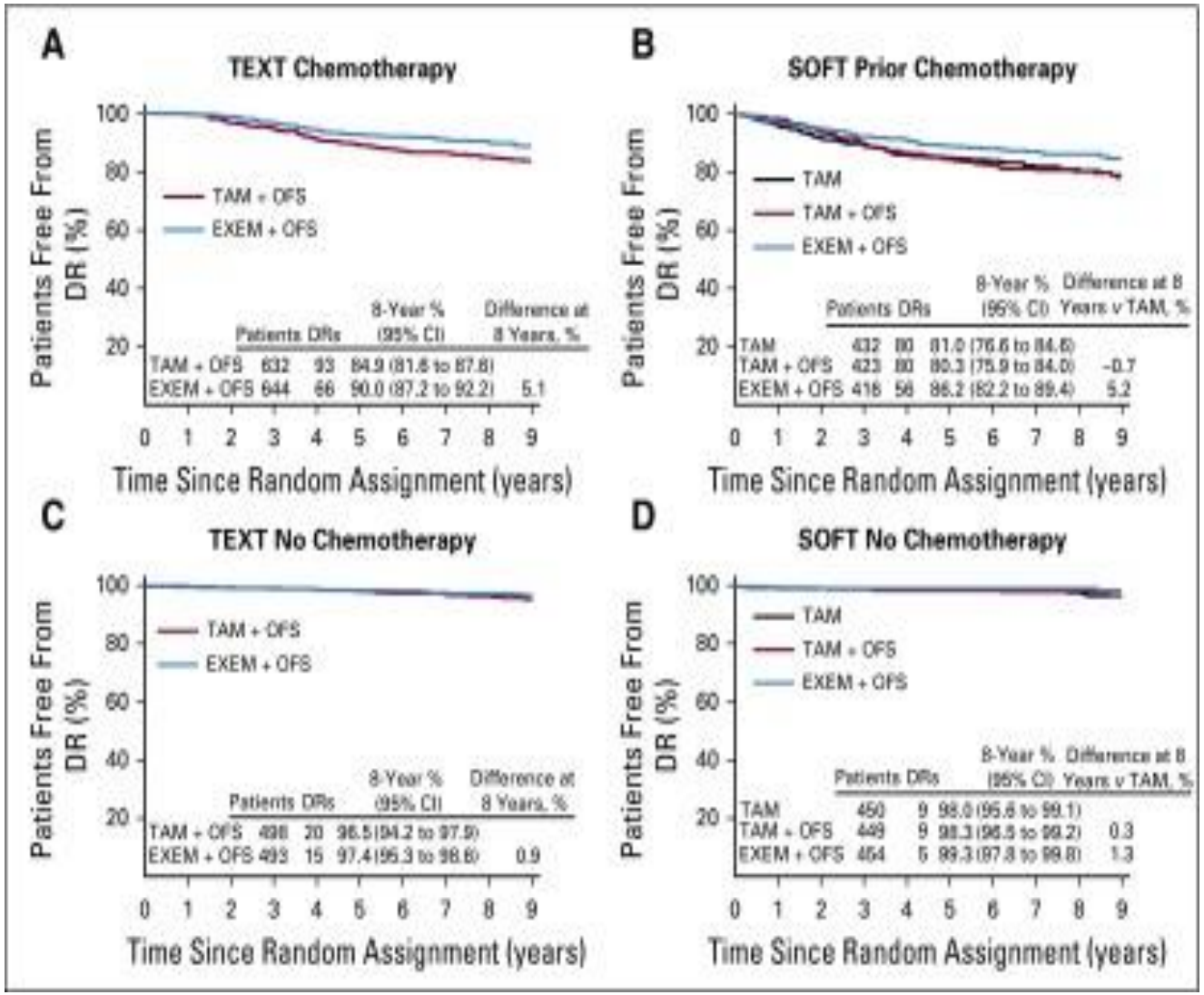
Menopausal status

Pre-menopausal status

Adjuvant ET for **young** HR+/HER2- breast cancer premenopausal women: ovarian suppression with **LHRHa**

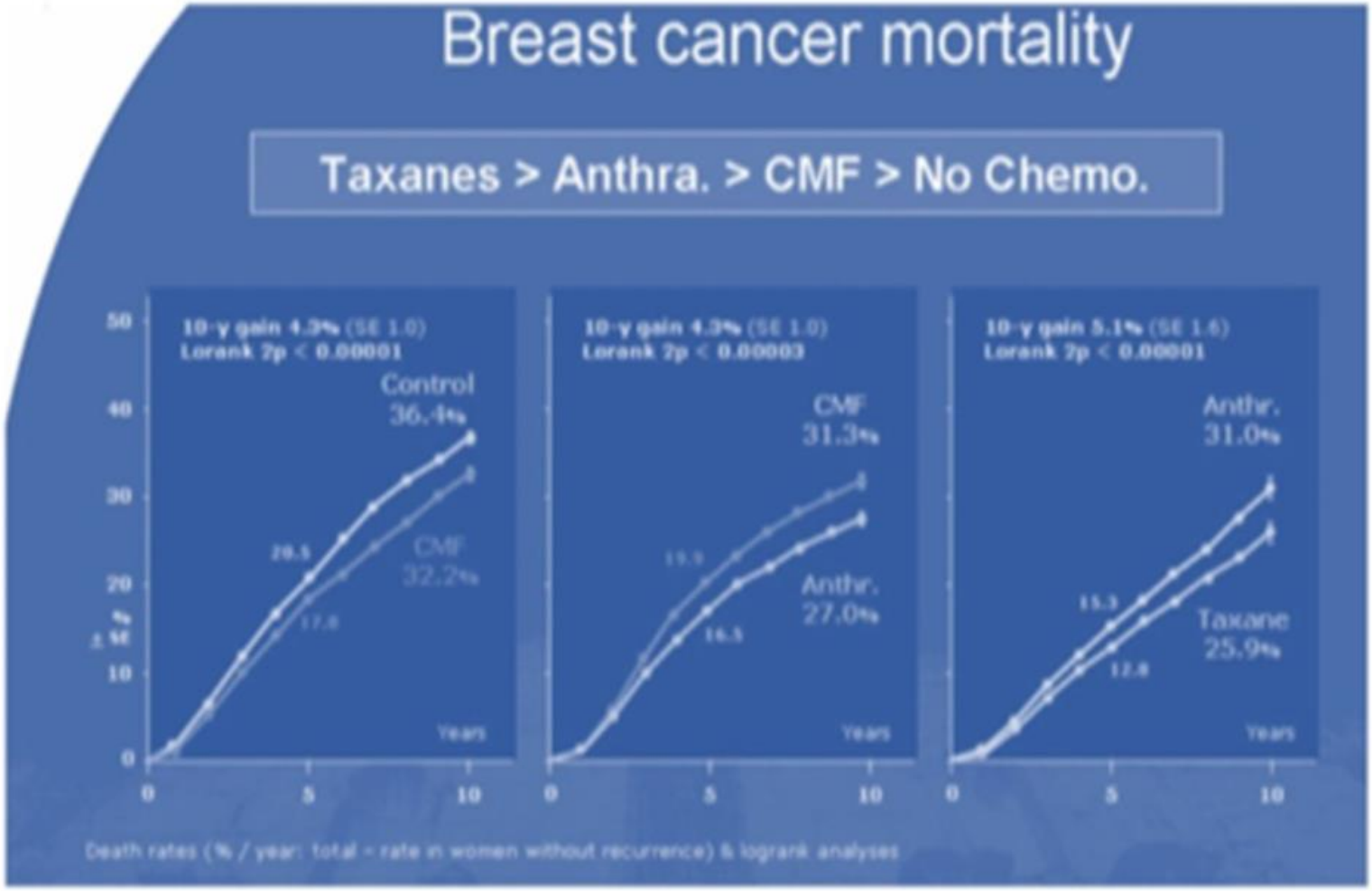
LHRH antagonisti



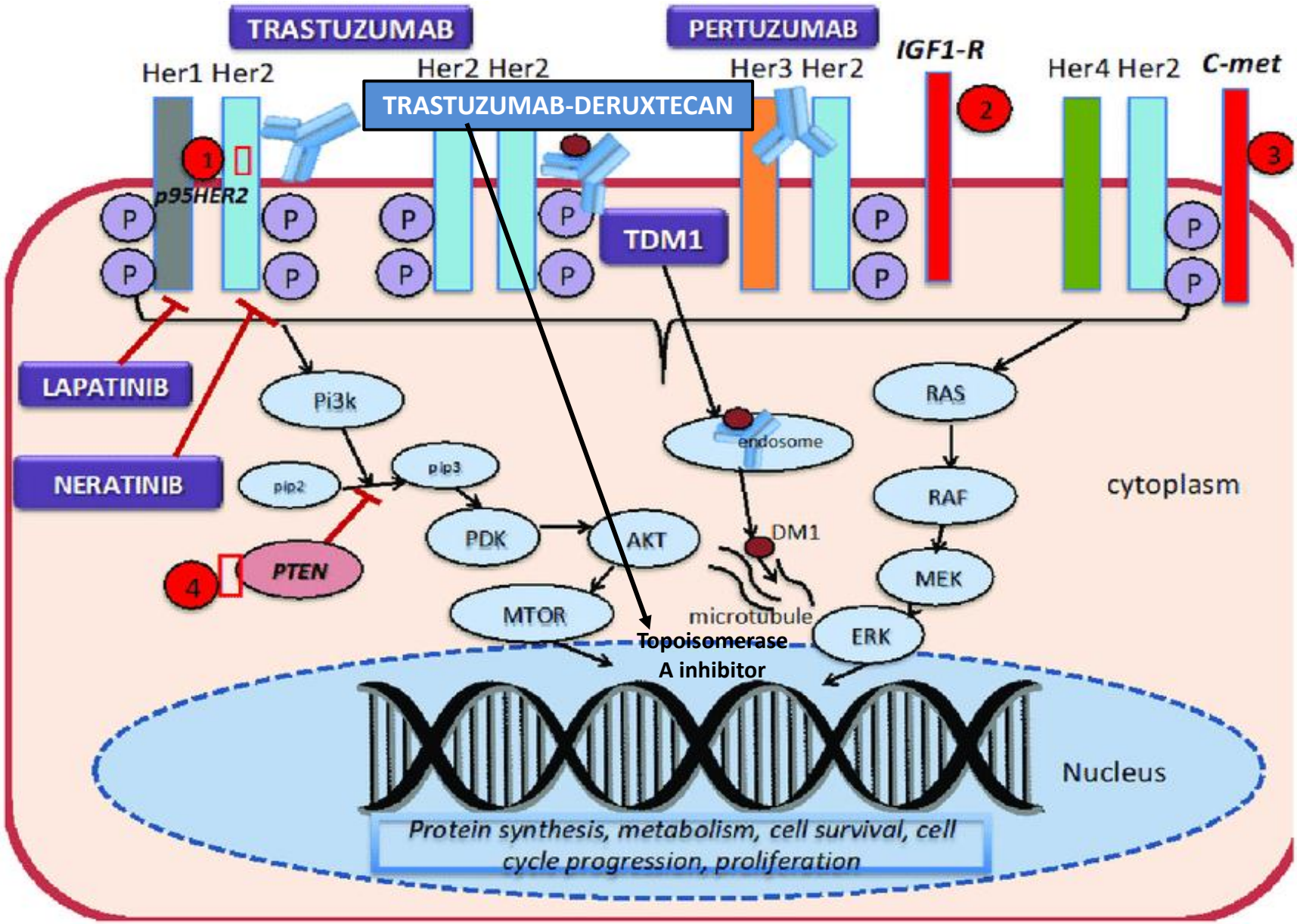


Pagani et al, J Clin Oncol. 2020; 38

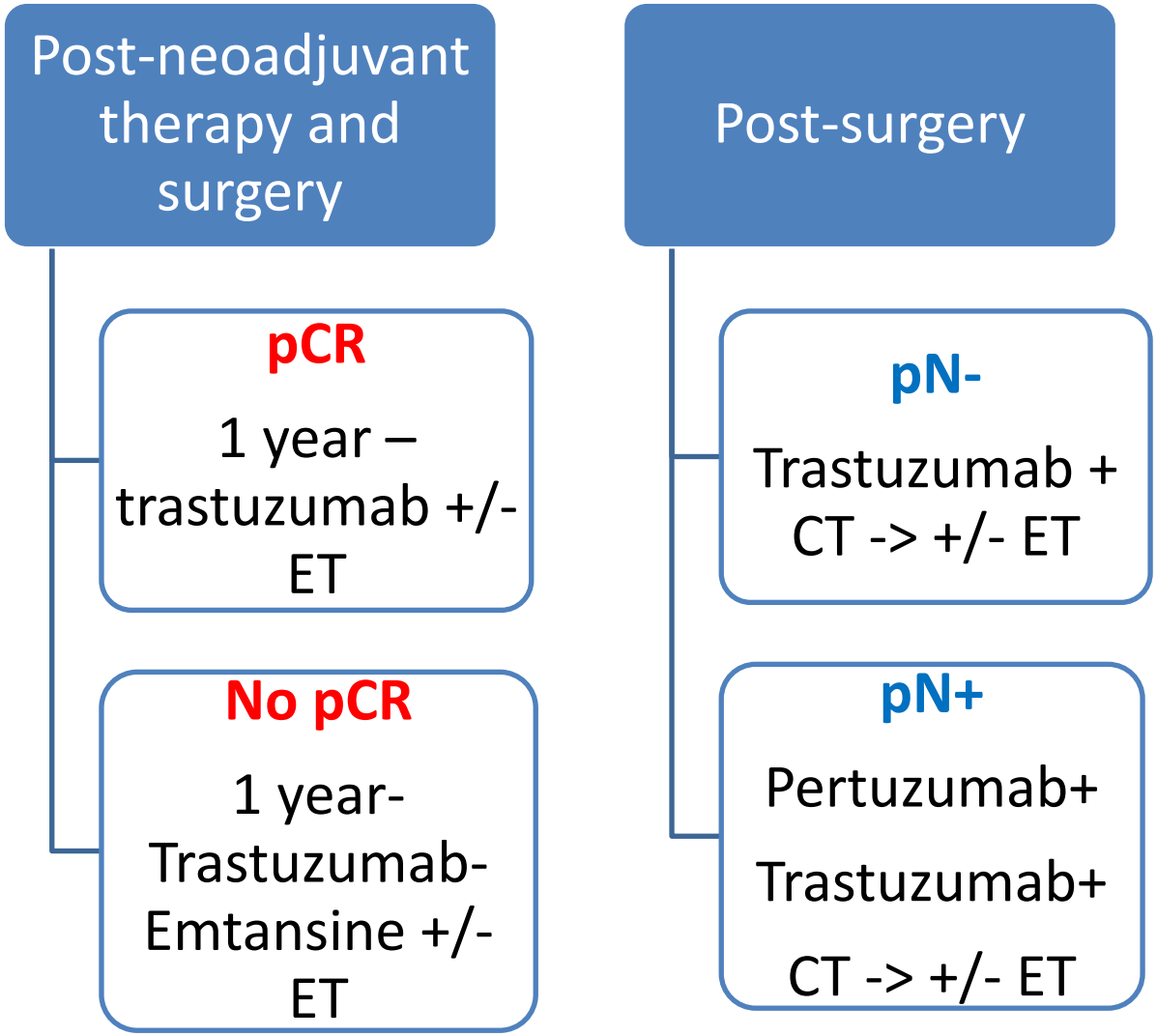
Adjuvant CT for Node-POSITIVE BC: EBCTCG Meta-Analysis 2005-2006



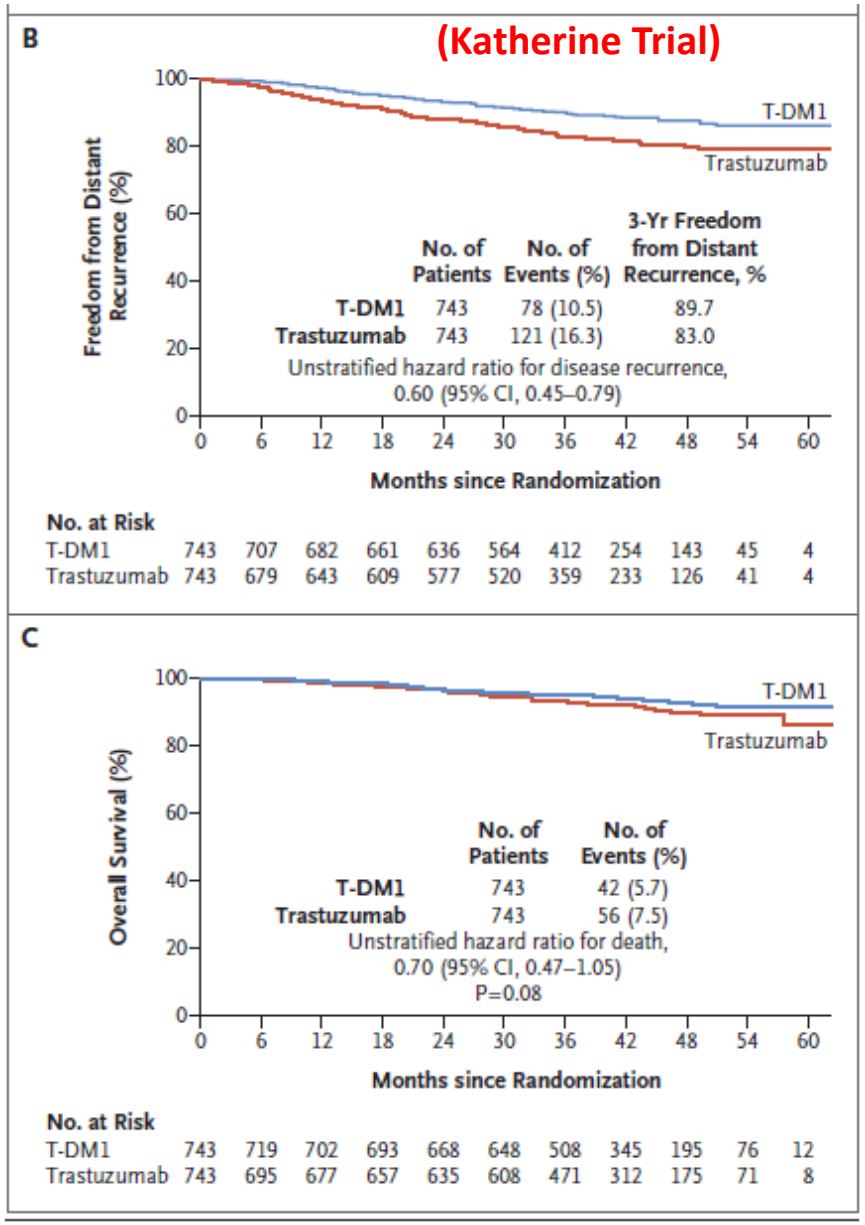
Verrill M. Br J Cancer. 2009;101(suppl 1):S2-S5.


TRASTUZUMAB
PERTUZUMAB
TRASTUZUMAB-DERUXTECAN
Her1 Her2
Her2 Her2
Her3 Her2
IGF1-R
Her4 Her2
C-met
1
2
3
4
p95HER2
P
TDM1
LAPATINIB
NERATINIB
Pi3k
pip2
pip3
PDK
AKT
MTOR
PTEN
endosome
DM1
microtubule
RAS
RAF
MEK
ERK
cytoplasm
Topoisomerase
A inhibitor
Nucleus
Protein synthesis, metabolism, cell survival, cell
cycle progression, proliferation

HER2-positive Breast Cancer therapy in **ADJUVANT** SETTING

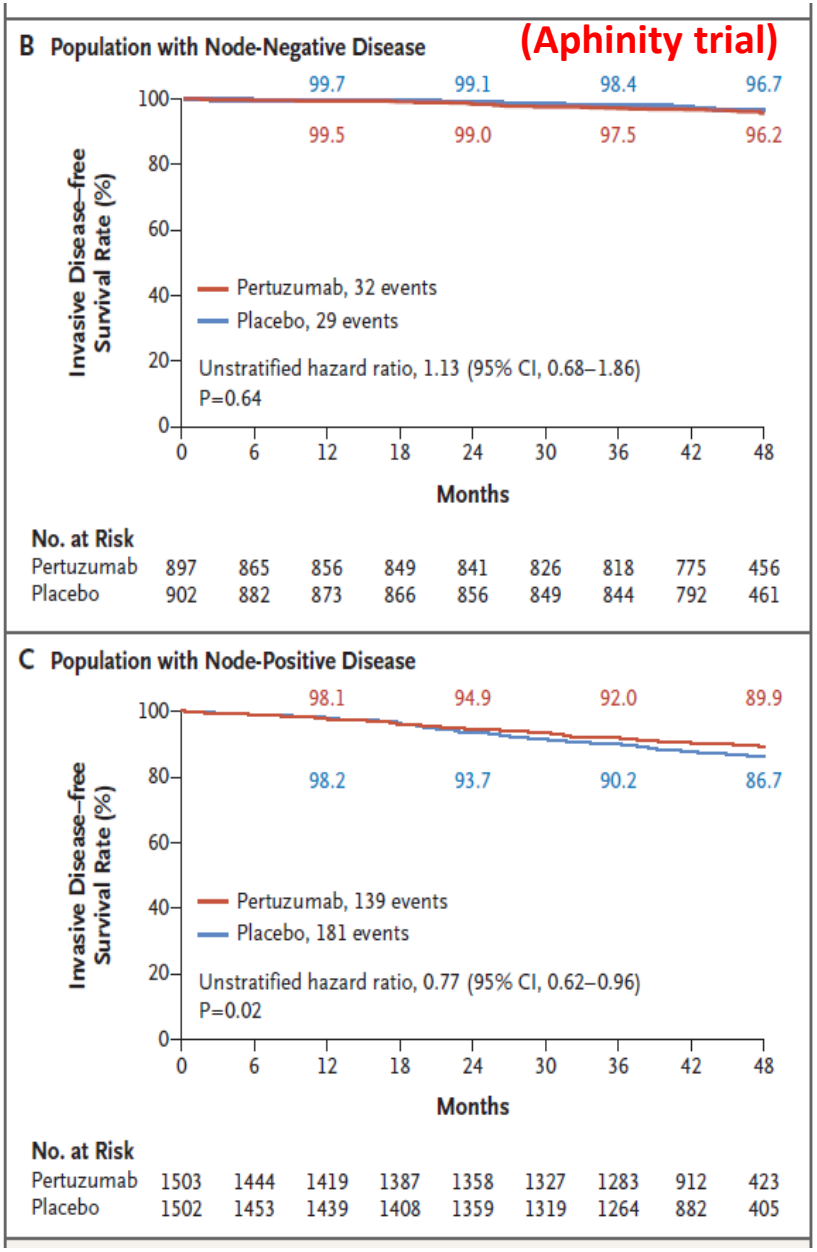


Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer



G.von Mickwitz et al. NEJM 380;7, 2019

Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer



G.Von Mickwitz et al. NEJM 377;2 , 2017

ADJUVANT THERAPY **AFTER NEOADJUVANT**

TNBC

pCR

Follow up

No pCR

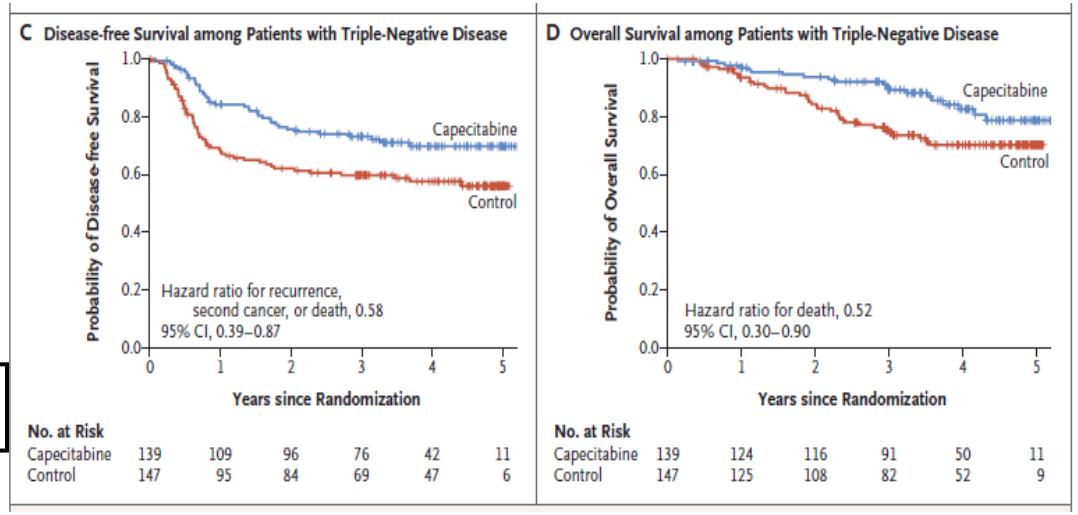
6 months of capecitabine

HR+ AND HER2-

ENDOCRINE THERAPY

Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy

N.Masuda et al. NEJM, 376; 22, 2017



GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

ANNALS OF ONCOLOGY
driving innovation in oncology

SPECIAL ARTICLE

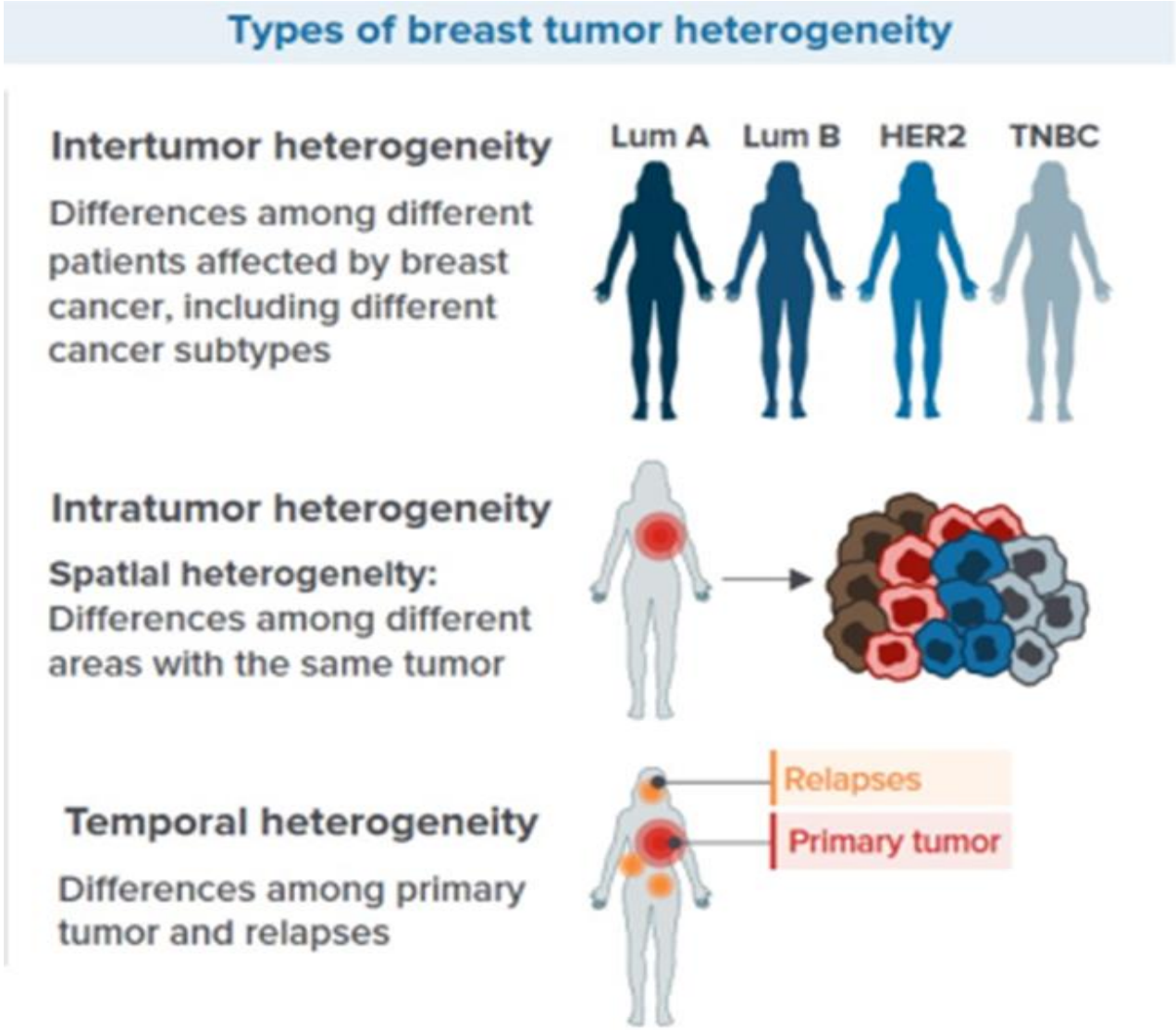
ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer☆

A. Gennari[1], F. André[2], C. H. Barrios[3], J. Cortés[4,5,6,7], E. de Azambuja[8], A. DeMichele[9], R. Dent[10], D. Fenlon[11], J. Gligorov[12], S. A. Hurvitz[13,14], S.-A. Im[15], D. Krug[16], W. G. Kunz[17], S. Loi[18], F. Penault-Llorca[19], J. Ricke[2,17], M. Robson[20], H. S. Rugo[21], C. Saura[22], P. Schmid[23], C. F. Singer[24], T. Spanic[25], S. M. Tolaney[26], N. C. Turner[27], G. Curigliano[28], S. Loibl[29], S. Paluch-Shimon[30] & N. Harbeck[31], on behalf of the ESMO Guidelines Committee*

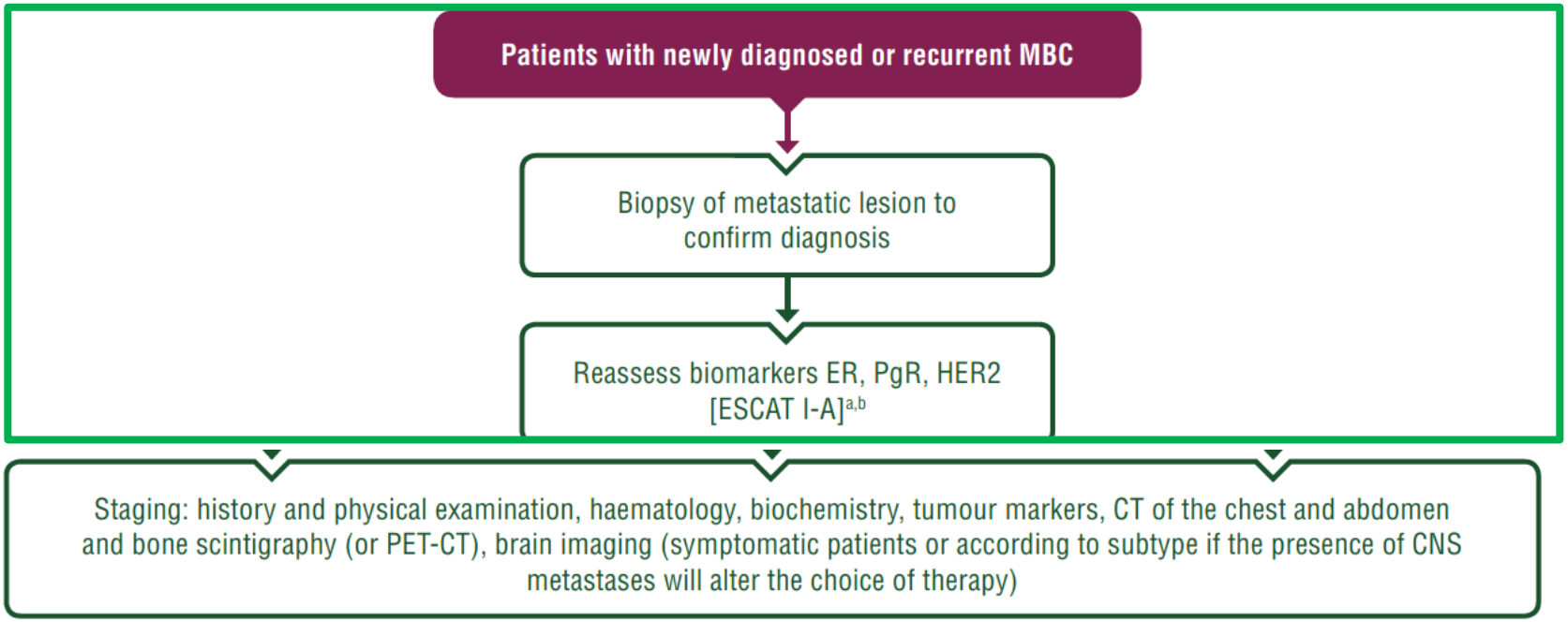
Ann Oncol, 30; 2021

BREAST TUMOR HETEROGENEITY

Therapy pressure
And/or
Microenvironment



a. Fumagalli C, Barberis M. Diagnostics (Basel). 2021;11:1555.



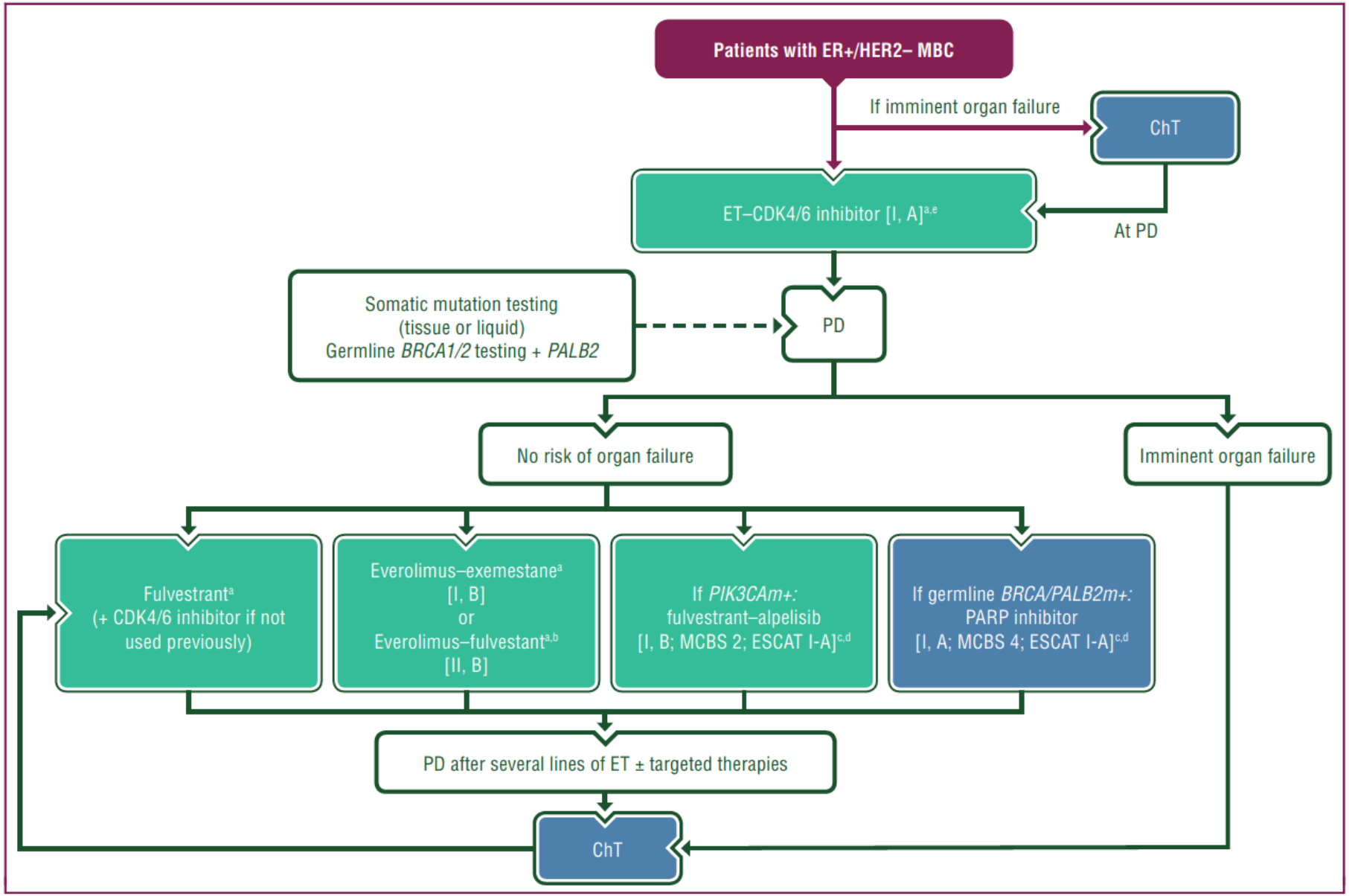
Treatment choice should take into account at least these factors:

- HR and HER2 status
- Previous therapies and their toxicities
- Disease-free interval
- Tumor burden (defined as number and site of metastases)
- Biological age, PS, comorbidities (including organ dysfunction)
- Menopausal status (for ET)
- Need for rapid disease/symptom control
- Socio-economic and psychological factors
- Available therapies in the patient's country
- Patient preference

TAILORED THERAPY

Main Goals in the Treatment of MBC

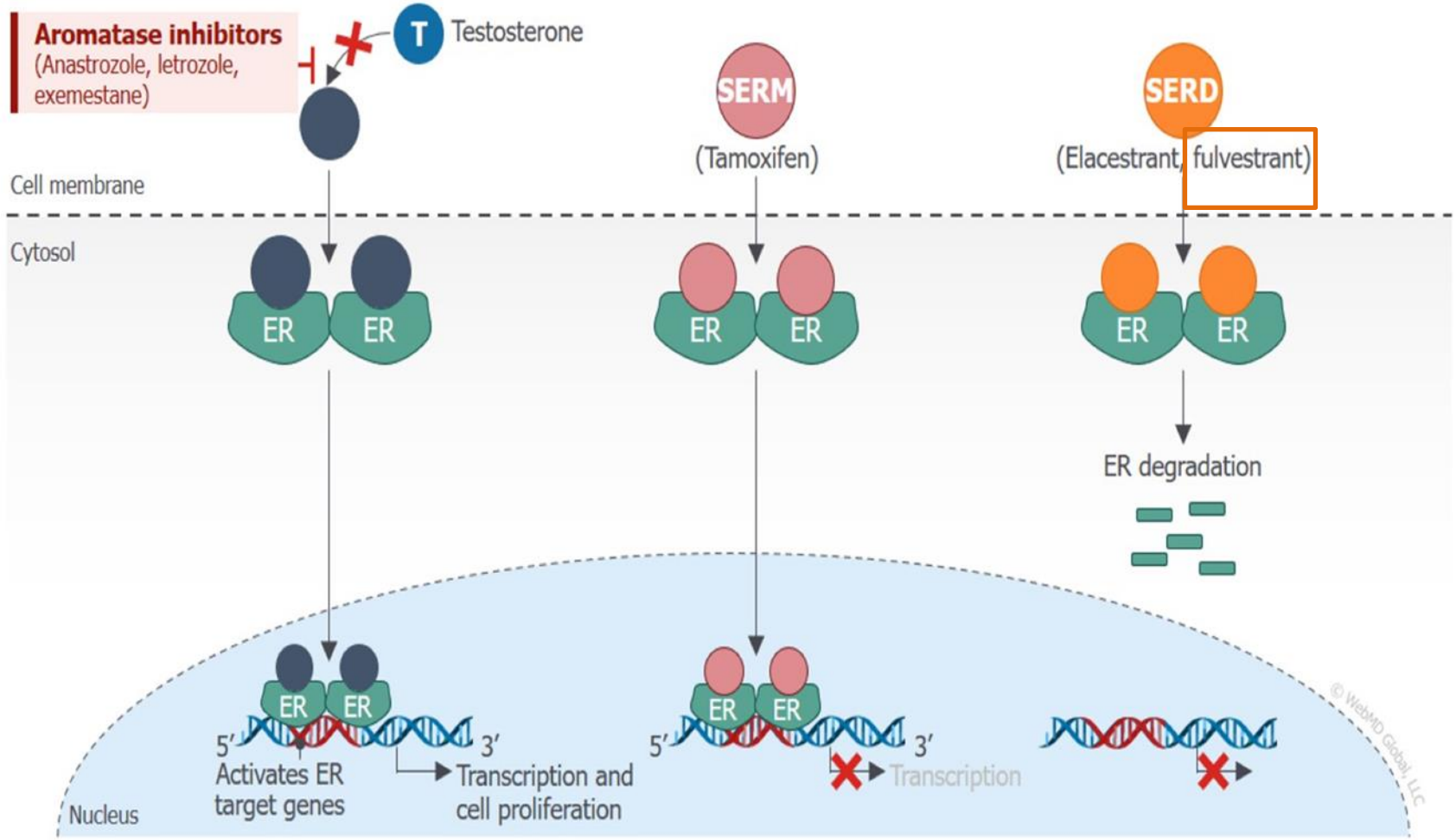
- Balancing treatment efficacy and toxicity is the main objective
- Goals of treatment:
  - Improve survival
  - Delay disease progression
  - Prolong duration of response
  - Palliate symptoms
  - Improve or maintain quality of life



CDK4/6, cyclin-dependent kinase 4/6; ChT, chemotherapy; ESMO, European Society of Molecular Oncology; ET, endocrine therapy; MBC, metastatic breast cancer; PD, progressive disease.

Ann Oncol, 30; 2021

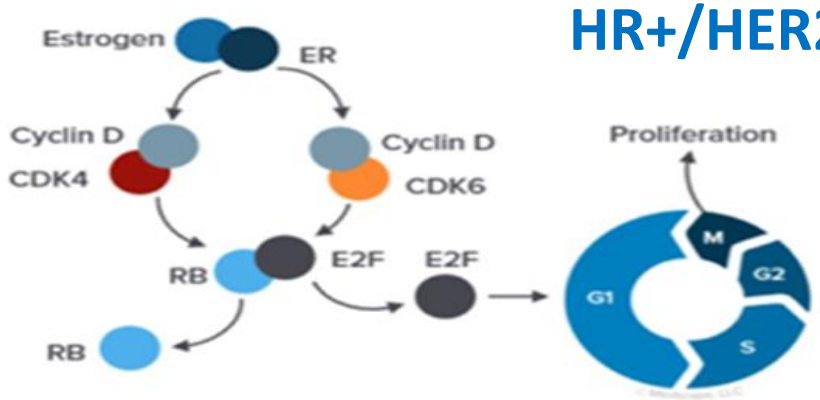
ENDOCRINE THERAPY in metastatic breast cancer: MECHANISM OF ACTION



Hernando C, et al. Int J Mol Sci. 2021;22:7812.

Post- menopausal | **Pre-menopausal** | **Post-menopausal**

INHIBITORS of CD4/CD6 for HR+/HER2- BREAST CANCER

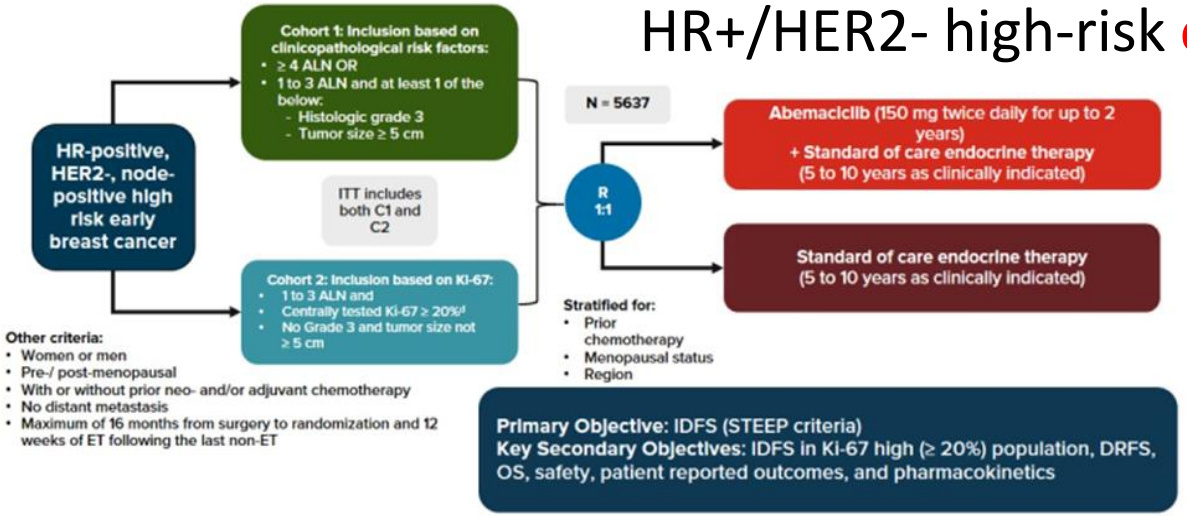


CDK 4/6 Inhibitor Phase 3 Registration Studies
Similar Global Efficacy Results

Agent	Trial	Line	PFS HR	*P* Value	CBR, %	ORR, %
Palbociclib[a]	PALOMA-2	1	0.58	< .0001	85	55
	PALOMA-3	2	0.46	< .0001	68	25
Ribociclib[b]	MONALEESA-2	1	0.57	< .0001	80	53
	MONALEESA-3	1-2	0.59	< .001	70	41
	MONALEESA-7	1	0.55	< .0001	79	51
Abemaciclib[c]	MONARCH-3	1	0.54	< .0001	78	59
	MONARCH-2	2	0.54	< .0001	NK	48

Cross-trial comparisons not intended.
CBR, clinical benefit rate; NK, not known; ORR, overall response rate; PFS, progression-free survival.
a. Palbociclib [PI]. EMA. Published November 25, 2016. Updated July 21, 2021; b. Ribociclib [PI]. EMA. Published August 31, 2017. Updated November 18, 2021; c. Abemaciclib [PI]. EMA. Published October 29, 2018. Updated April 21, 2022.

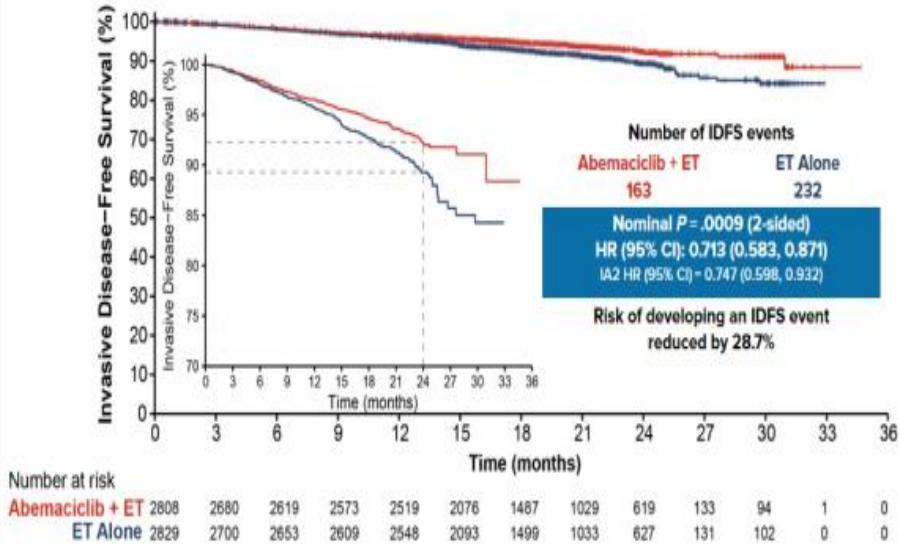
HR+/HER2- high-risk **early** BREAST CANCER



O'Shaughnessy J, et al. SABCS 2020. Abstract GS1-01.

monarchE study design

- Statistically significant + clinically relevant improvement in IDFS; greater treatment benefit at PO analysis



O'Shaughnessy J, et al. SABCS 2020. Abstract GS1-01.

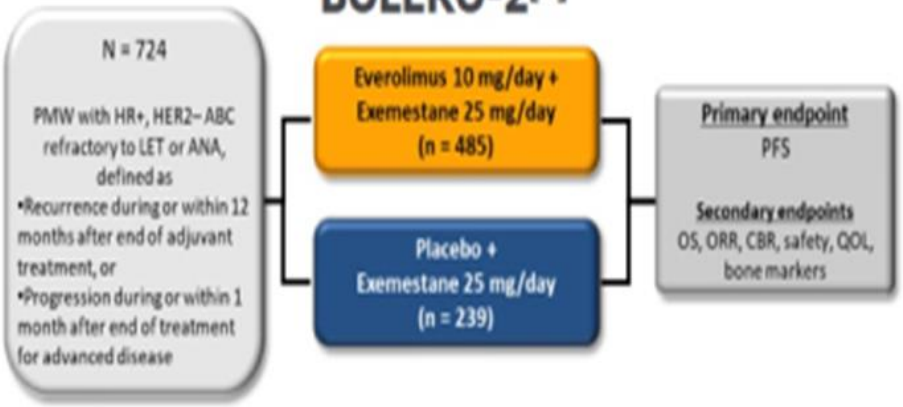
CDK4/6 and AI in **ADJUVANT** setting:

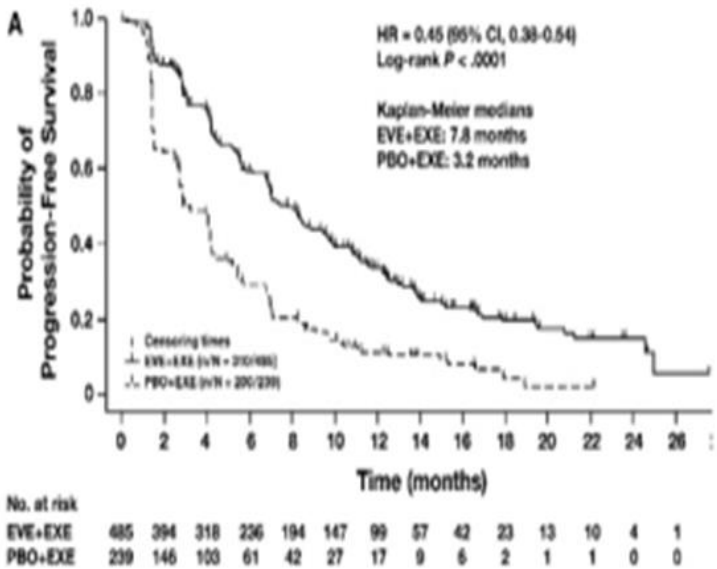
- pN1-3 and G3 and/or pT≥5cm
- pN≥4

EVEROLIMUS: mTOR cascade inhibitor

ALPELISIB: in PK3CA mutation

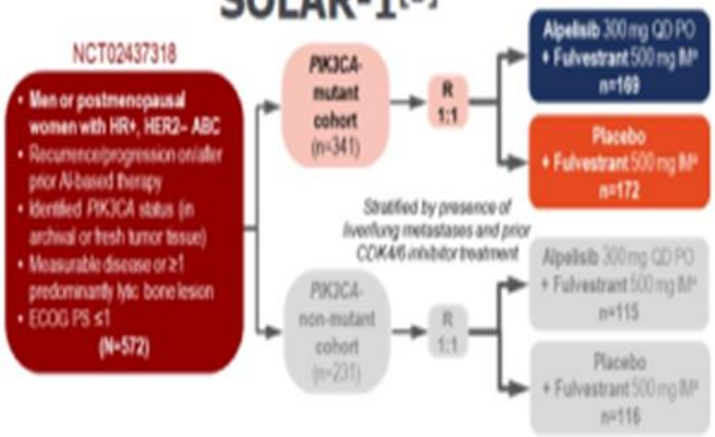
BOLERO-2[a]

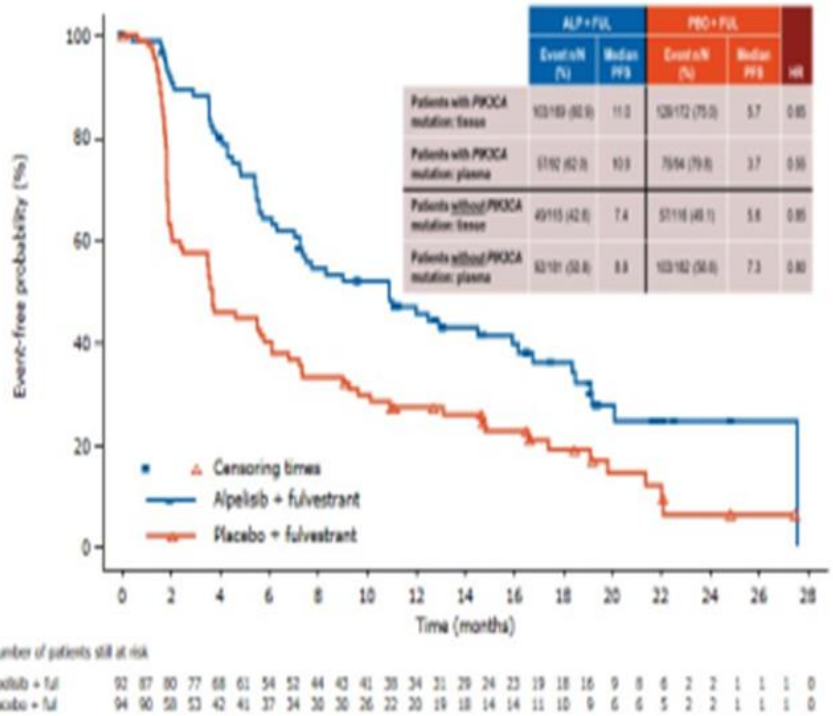




Cross-trial comparisons not intended.
AI, aromatase inhibitor; ALP, alpelisib; ANA, anastrozole; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; IM, intramuscular; PMW, postmenopausal women; PO, by mouth; PS, performance status.
a. Baselga J, et al. N Engl J Med. 2012;366:520-529; b. André F, et al. N Engl J Med. 2019;380:1929-1940.

SOLAR-1[b]





The Role of Chemotherapy in MBC

- Despite the availability of targeted therapies, chemotherapy is still a crucial part of treatment in the metastatic setting
- This includes triple-negative disease and both HER2-positive and HER2-negative disease
- Most patients with HER2-negative disease will relapse after endocrine therapy and then require chemotherapy

Monotherapy vs Combination Chemotherapy

- Both chemotherapy and sequential single-agent CT are reasonable options
- Sequential monotherapy is the preferred choice for MBC
- Combination CT is recommended for patients with:
  - Rapid clinical progression
  - Life-threatening visceral metastases
  - Need for rapid symptom and/or disease control

Duration of Chemotherapy

- Duration of each regimen and number of regimens should be tailored to each individual patient
- Usually each regimen should be given until:
  - Progression of disease

    or
  - Unacceptable toxicity ("unacceptable" should be defined together with the patient)

Preferred Systemic Therapy Regimens for Recurrent or Stage IV HER2-Negative Disease

- Anthracyclines
  - Doxorubicin
  - Liposomal doxorubicin
- Taxanes
  - Paclitaxel ± bevacizumab*
  - Nab-paclitaxel
- Anti-metabolites
  - Capecitabine
  - Gemcitabine
- Microtubule inhibitors
  - Vinorelbine
  - Eribulin
- For germline *BRCA1/2* mutations:
  - Olaparib
  - Talazoparib
- Platinum (for patients with triple-negative tumors and *gBRCA1/2* mutation)
  - Carboplatin
  - Cisplatin
- For PD-L1 positive tNBC:
  - Atezolizumab + *nab*-paclitaxel

*Where approved
Adapted from NCCN Guidelines. Breast Cancer. V2.2020.

Cardoso F et al. Ann Oncol 2016; 28

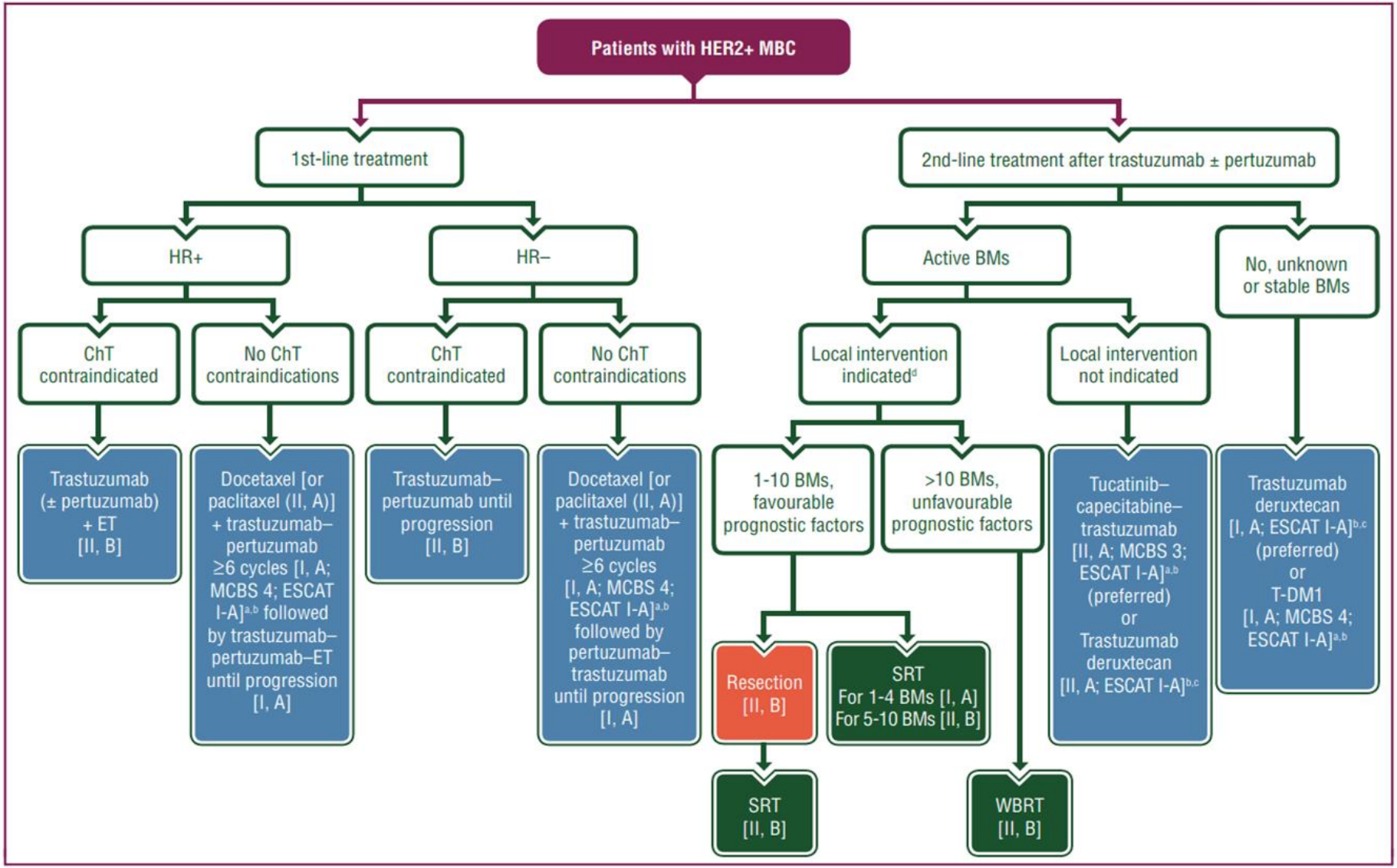
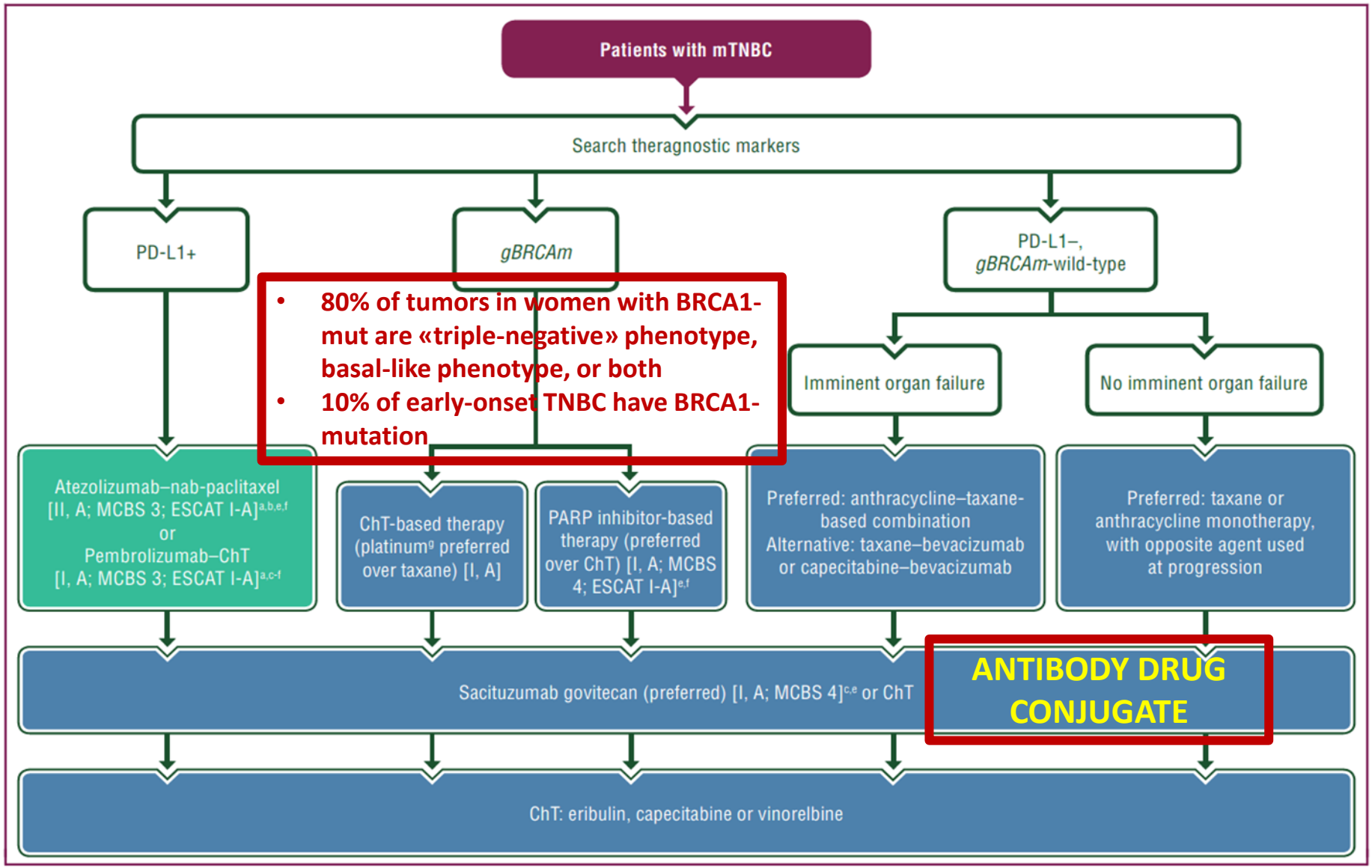


Figure 3. First- and second-line treatment of HER2-positive MBC.

BM, brain metastases; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; MCBS, Magnitude of Clinical Benefit Scale; SRT, stereotactic radiation; T-DM1, trastuzumab emtansine; WBRT, whole-brain radiation therapy.

Ann Oncol, 30; 2021



- **80% of tumors in women with BRCA1-mut are «triple-negative» phenotype, basal-like phenotype, or both**
- **10% of early-onset TNBC have BRCA1-mutation**

Figure 5. Treatment of mTNBC.

Ann Oncol, 30; 2021

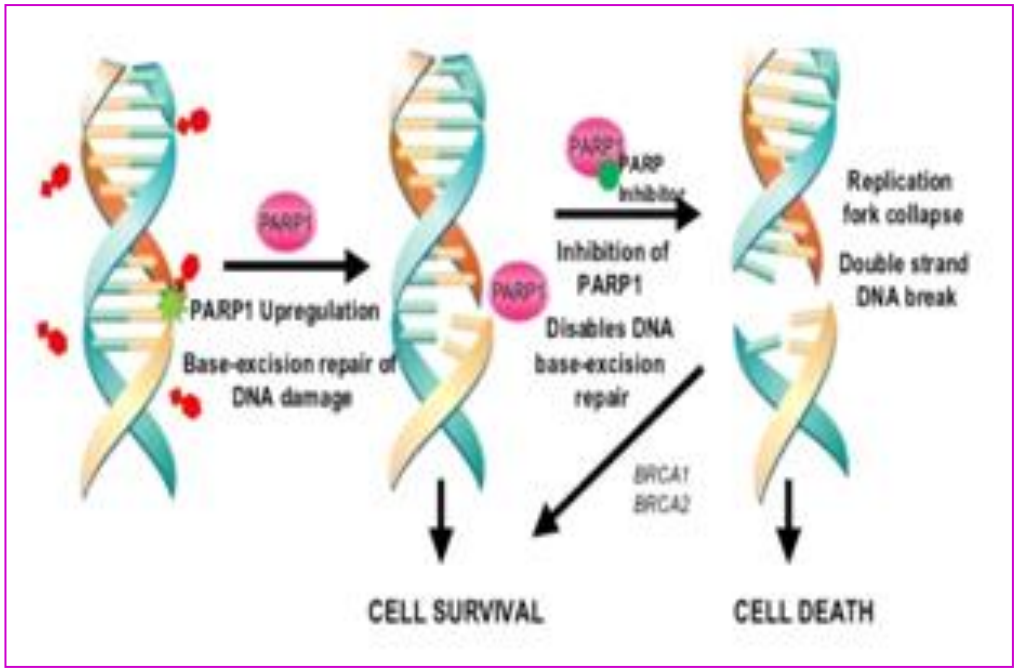
BREAST CANCER gBRCA positive

ESMO clinical practice guidelines for early BC recommend testing if there is

- Strong family history of breast, ovarian, pancreatic, and/or high-grade/metastatic prostate cancer
- Diagnosis of BC before age 50 y
- Diagnosis of TNBC before age 60 y
- Personal history of ovarian cancer
- Second BC or male sex

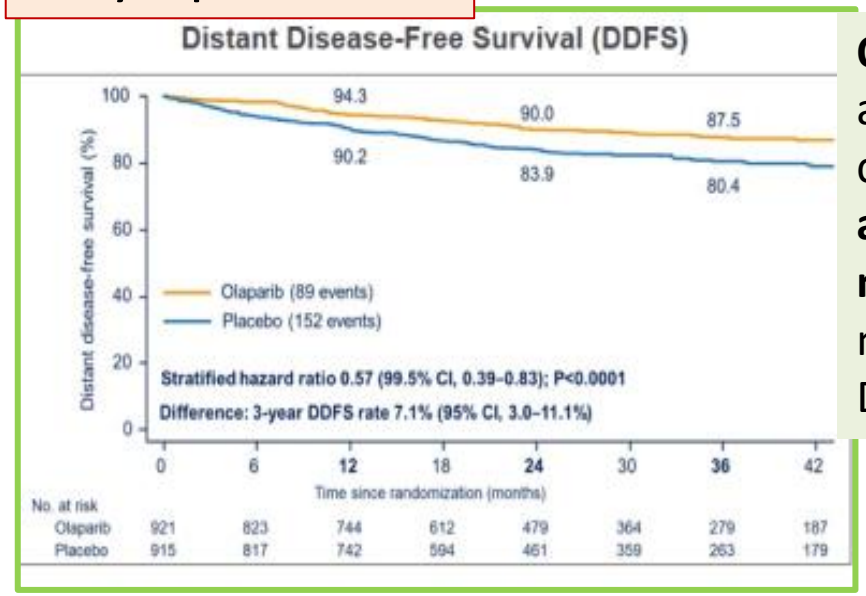
ESMO, Cardoso F. et al. Ann Oncol 2019; 30

- BRCA1 and BRCA2 encode proteins for homologous recombination DNA repair
- BRCA1 and BRCA2 germline alterations show deficiency in homologous recombination repair
- PARP inhibitors are inhibitors of polyadenosine diphosphateribose polymerase, selective killer for tumor cells with deficiency in homologous recombination repair.



Olympia TRIAL

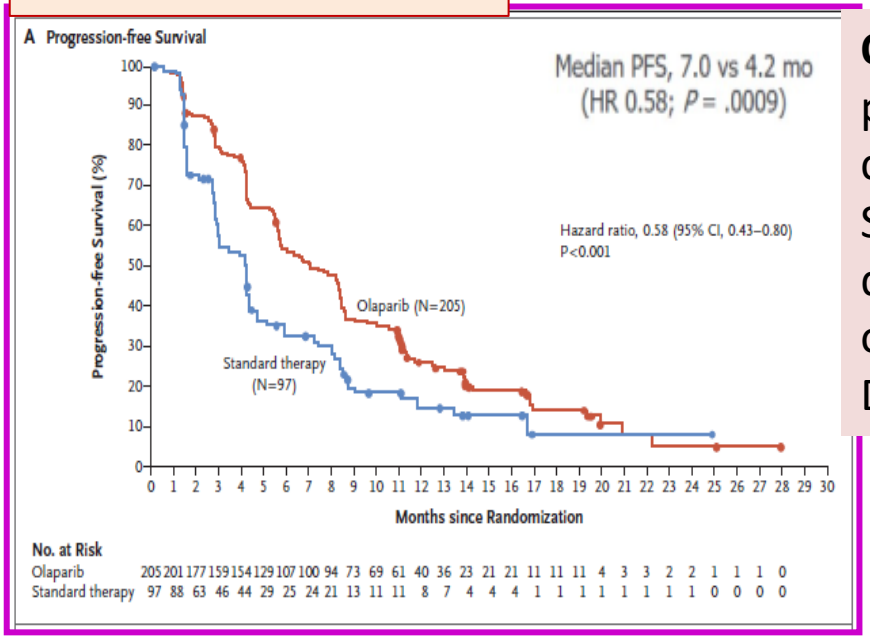
Tutt A et al J Clin Oncol 2021; 39



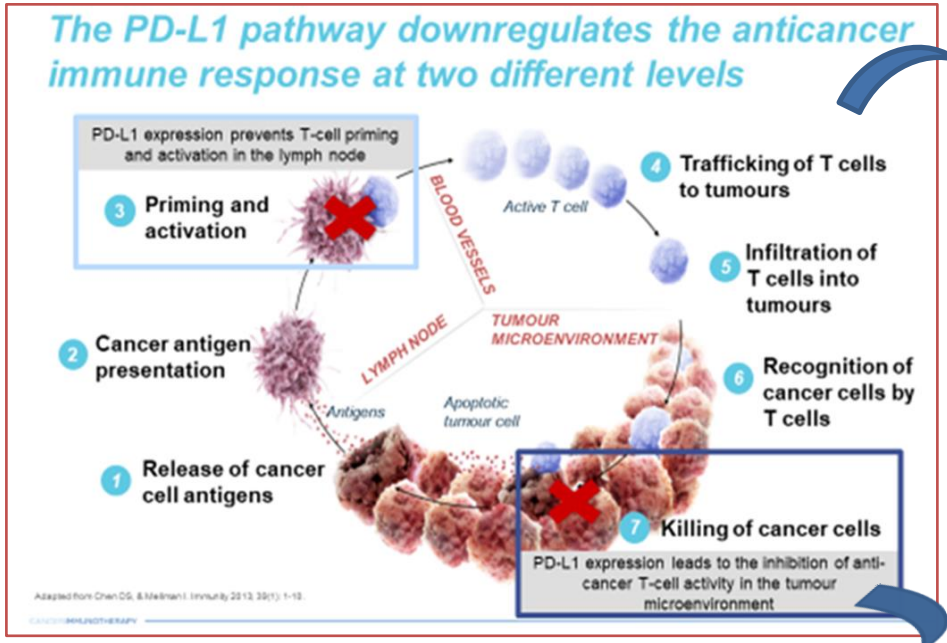
OLAPARIB in fase ADIUVANTE: in monoterapia o in associazione con la terapia endocrina per carcinoma della mammella allo stadio iniziale ad **alto rischio**, **HER2-negativo e con BRCA1/2 mutato**, già trattati con chemioterapia neoadiuvante o adiuvante.
Durata: 1 anno salvo progressione o tossicità (EAP)

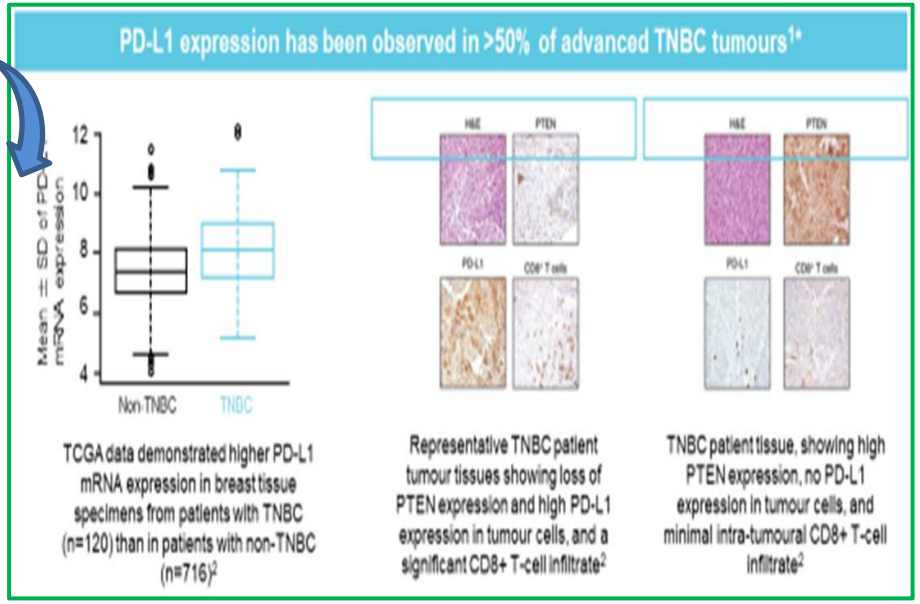
OlympiAD TRIAL

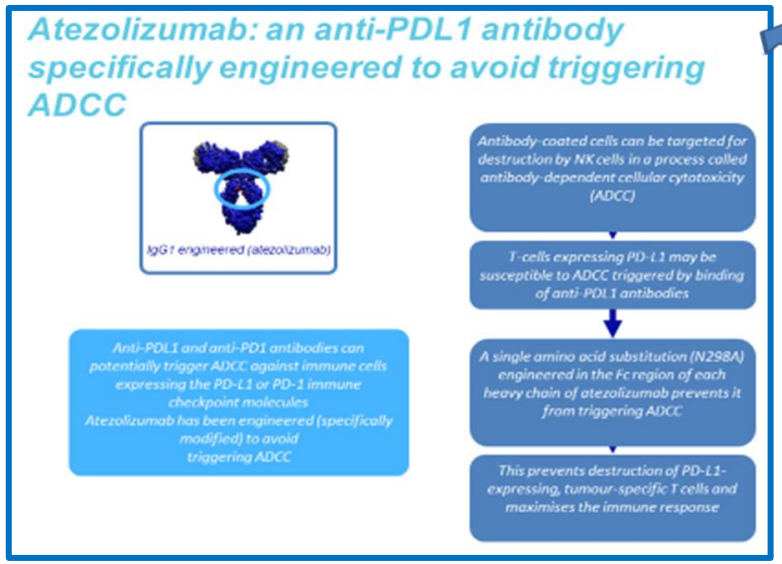
Robson M et al. NEJM 2017; 377



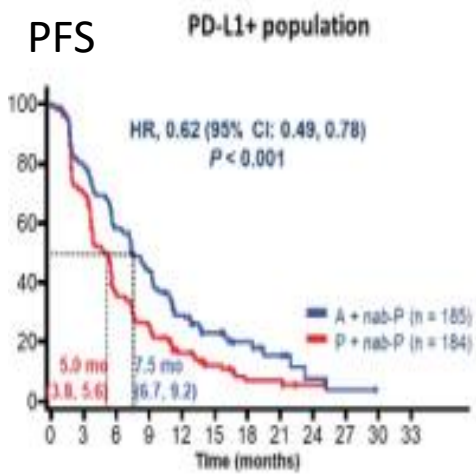
OLAPARIB in fase METASTATICA: in monoterapia per carcinoma della mammella “triple negative” e con BRCA1/2 mutato
Se HER2-negativo e HR-positivo: in progressione durante o dopo una precedente endocrinoterapia o non eleggibili per la terapia endocrina
Durata: fino a progressione o tossicità (AIFA).

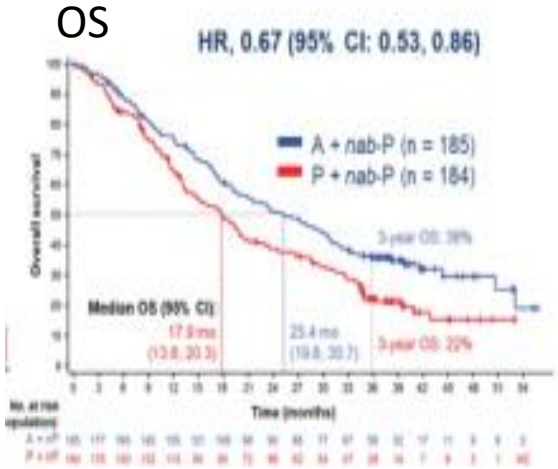






Impassion130 Nab-Paclitaxel+Atezolizumb vs Nab-Paclitaxel+PBO





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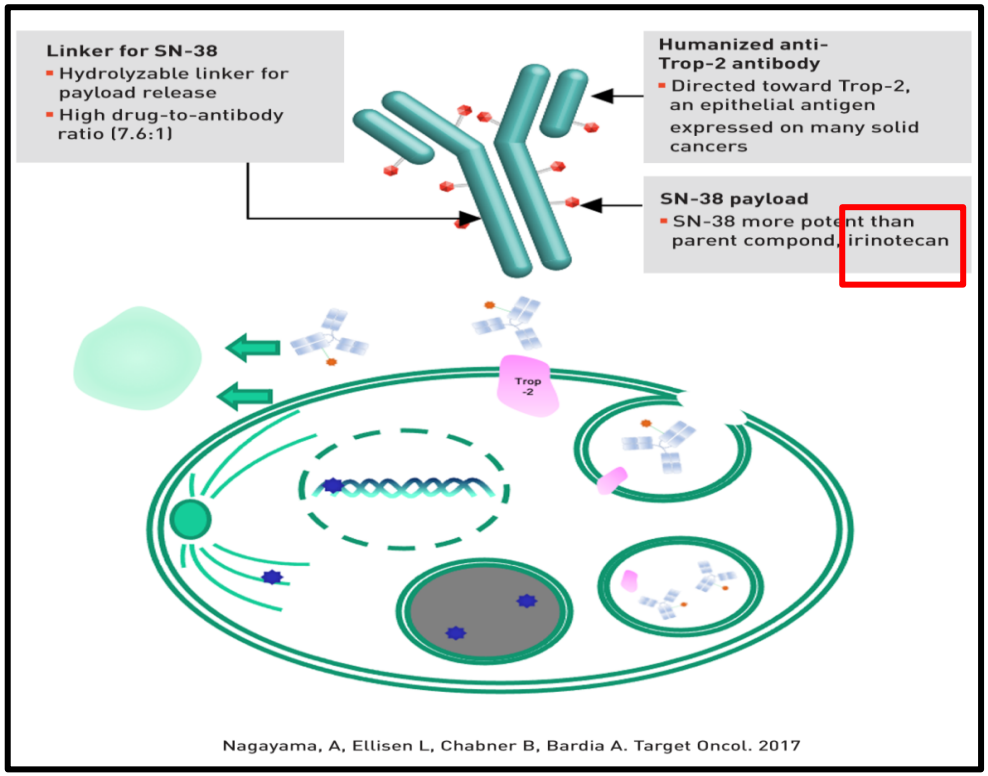
Sacituzumab govitecan antibody in **mTNBC**: “ASCENT” trial



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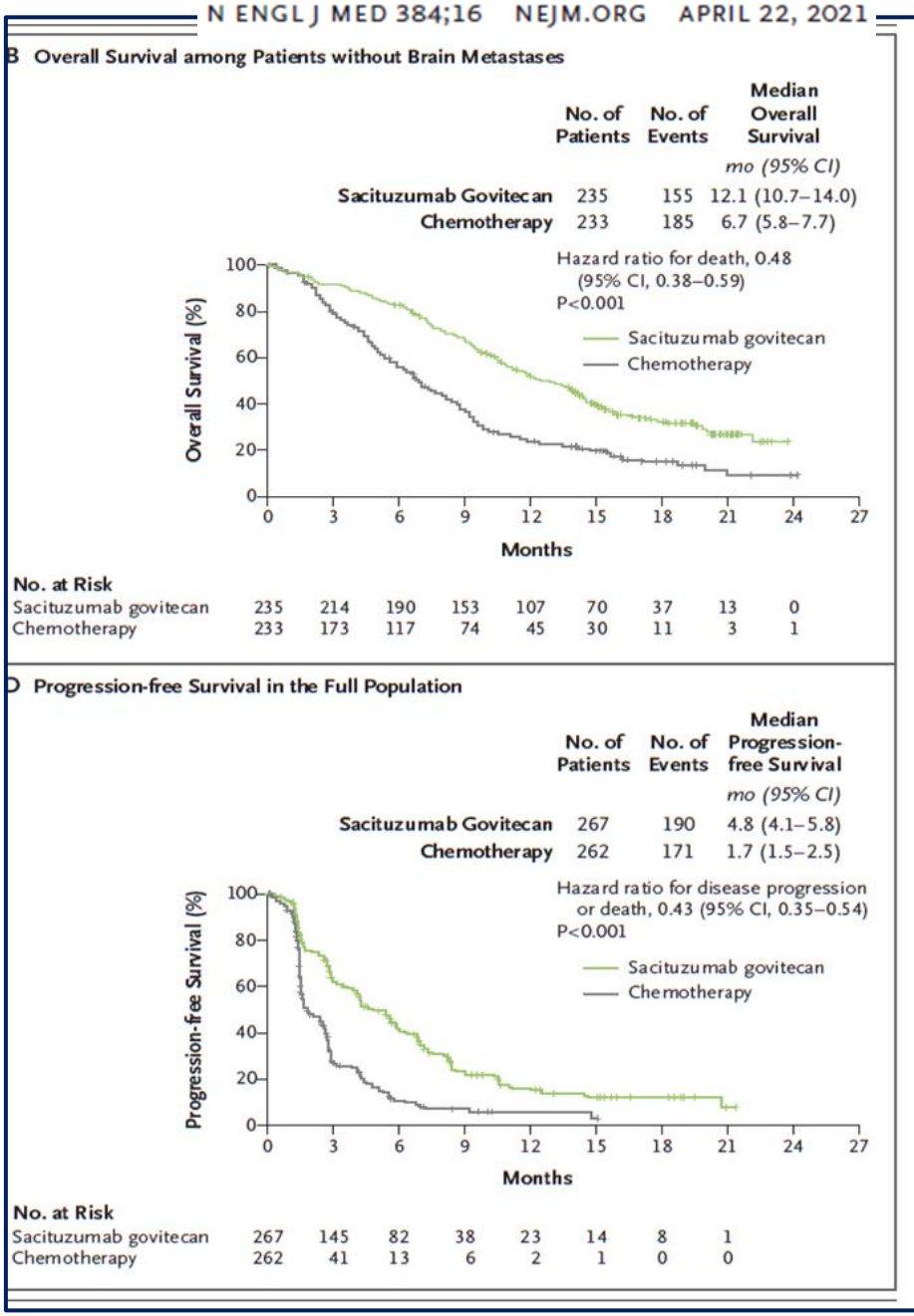

«Trodelvy» in monoterapia è indicato per il trattamento di pazienti adulti con cancro della mammella triplo negativo metastatico o non resecabile (metastatic triple-negative breast cancer, mTNBC) che abbiano ricevuto in precedenza almeno due terapie sistemiche, almeno una delle quali per la malattia avanzata.