AVANCEES THERAPEUTIQUES DANS LE CANCER DU SEIN TRIPLE NEGATIF ET HER2 POSITIF

CHU de Liège

J Collignon, Medical Oncologist
GI and BREAST CANCER
BOARD MEMBER of Belgian Society of Senology

DISCLOSURES

ADVISORY BOARD,LECTURES,MEETING SPONSORING:
AMGEN,SERVIER,BAYER,MERCK,ROCHE,LILLY,SANOFY,SIRTEX,CELGENE,PFISER,SIRTEX,IPSEN,NOVARTIS,NOVARTIS,BMS,MSD

TRAVEL AND ACCOMODATION or VIRTUEL CONGRES INSCRIPTION:
ROCHE,AMGEN,PFIZER,MSD,BAYER,LILLY,GILEAD,SERVIER

AVANCEES THERAPEUTIQUES
DANS LE CANCER DU SEIN
TRIPLE NEGATIF ET HER2 POSITIF

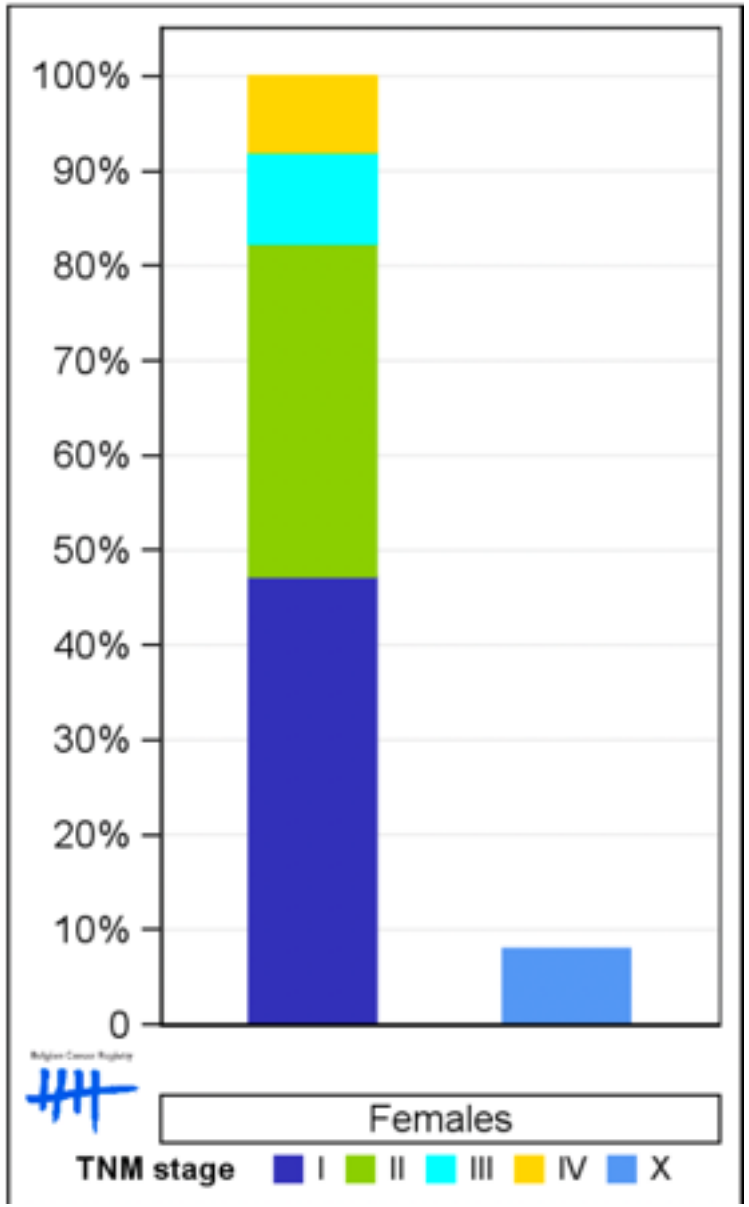
OUTLINE:

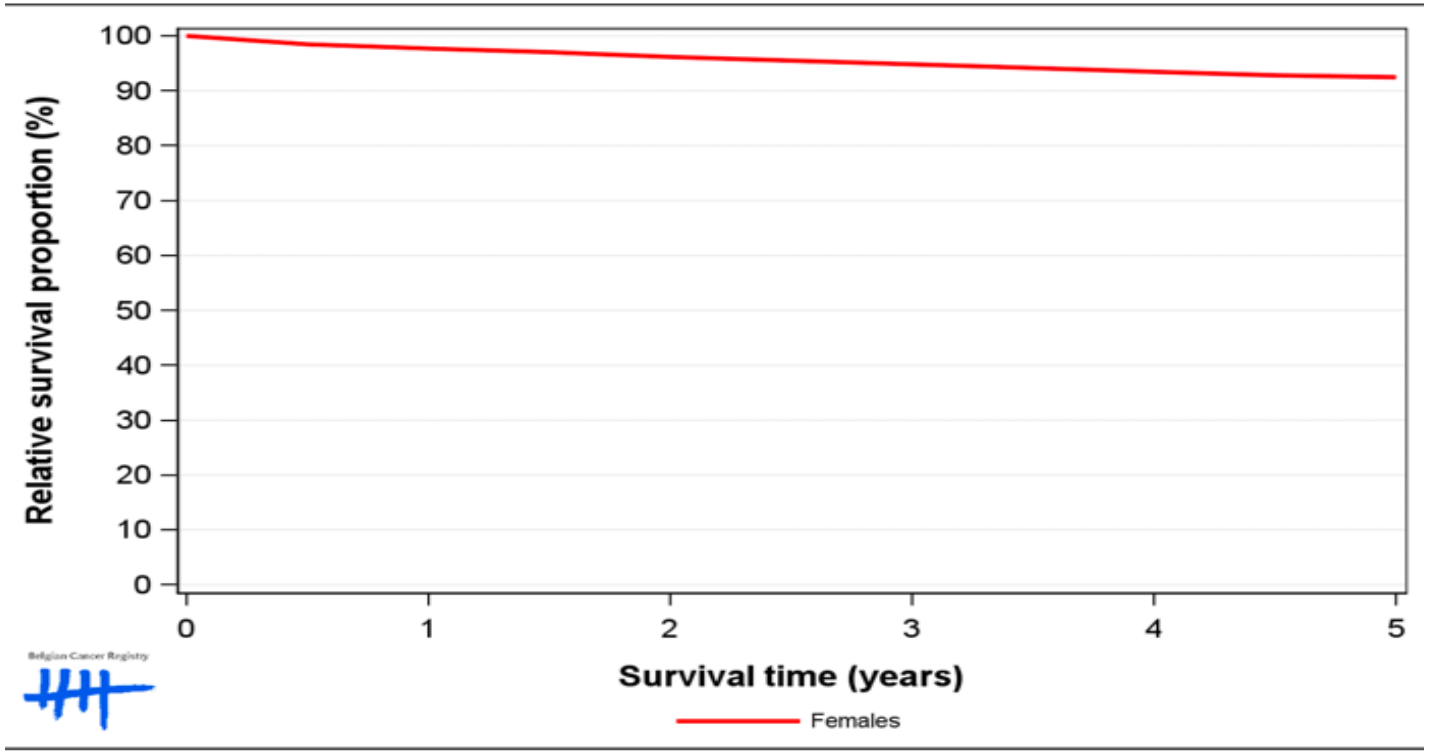
- **Introduction**
- **Immunothérapie et cancer du sein triple negative**
- **PARP inhibiteurs et TNBC**
- **Nouveaux anticorps monoclonaux conjugués et cancer du sein**
    - **HER2 positif**
    - **Triple négatif**

INTRODUCTION

GOOD NEWS IN BREAST CANCER

Cancer Fact sheet:Breast Cancer
BELGIUM 2020





	5-year relative survival 2016-2020 (%)		
	Females		
	N at risk	estimate	95% CI
Overall	53,721	92.4	[92.0, 92.9]
Age group			
15-49 years	10,063	94.7	[94.1, 95.3]
50-69 years	25,363	94.3	[93.8, 94.8]
70+ years	18,295	88.1	[86.8, 89.4]
Region			
Brussels-Capital Region	4,632	93.3	[91.7, 94.9]
Flemish Region	31,698	92.3	[91.7, 92.9]
Walloon Region	17,391	92.5	[91.6, 93.3]

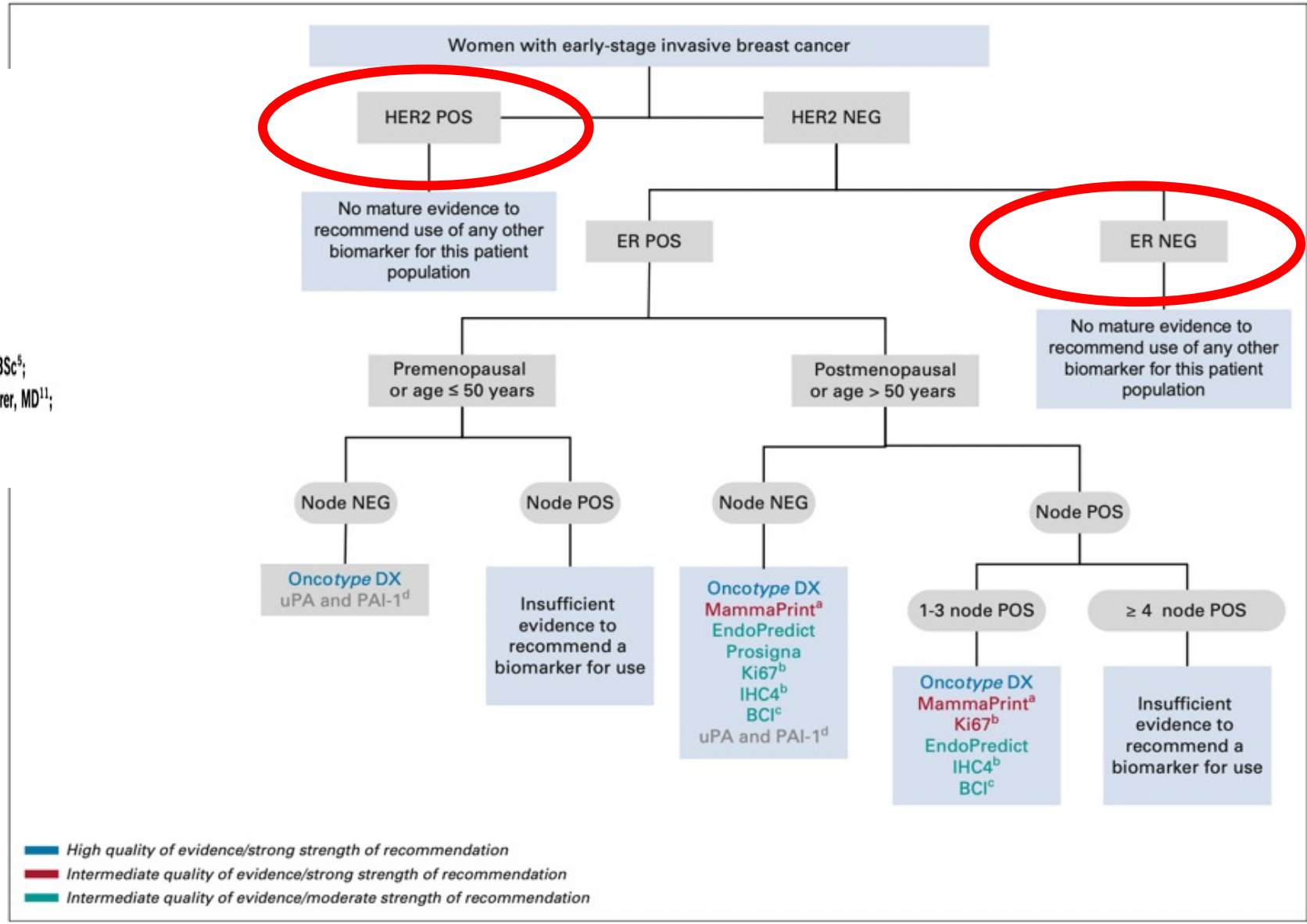
ER,PGR ET HER2

Systématiquement évalués pour chaque cancer du sein précoce et si possible à la rechute

Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update

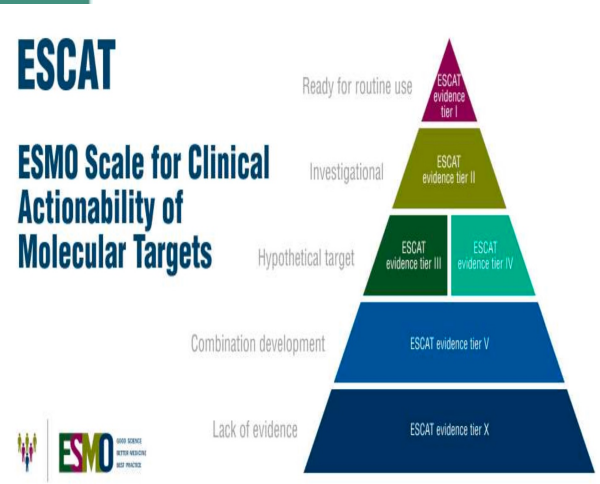
Fabrice Andre, MD[1]; Nofisat Ismaila, MD, MSc[2]; Kimberly H. Allison, PhD[3]; William E. Barlow, PhD[4]; Deborah E. Collyar, BSc[5]; Senthil Damodaran, MD, PhD[6]; N. Lynn Henry, MD, PhD[7]; Komal Jhaveri, MD[8,9]; Kevin Kalinsky, MD, MS[10]; Nicole M. Kuderer, MD[11]; Anya Litvak, MD[12]; Erica L. Mayer, MD, MPH[13]; Lajos Pusztai, MD[14]; Rachel Raab, MD[15]; Antonio C. Wolff, MD[16]; and Vered Stearns, MD[16]

- KI 67 (ER+ HR ABEMA en adjuvant)
- Signature moléculaire
- BRCA1/2 (post NAD si résidu pour TNBC et si résidu et score CPS-EG ≥ 3



ER,PGR ,HER2 et…..

Gene or protein	Alteration	Prevalence	ESCAT score
ER	**Protein expression ≥ 1% by IHC** **ESR1 mutation**	**75%** **40%**	**NA** **II-A**
ERBB2	Amplifications or 3+ (IHC) HER2-low (IHC (1+, 2+ NA)	15%-20% 40%-50%	I-A II-B
	Hotspot mutations	4%	II-B
BRCA1/2	**Germline mutations**	**4%**	**I-A**
	Somatic mutations	3%	II-A
PALB2	Germline mutations	1%	II-A
PD-L1 (TNBC)	Expression by IHC on ICs and tumor cells (CPS)	40%	I-A
PIK3CA (ER+, HER2-)	**Hotspot mutations**	**30%-40%**	**I-A**
MSI	MSI-H	1%-2%	I-C
NTRK	Fusions	<0.1%	I-C
ESR1 (ER+, HER2-)	**Mutations (mechanism of resistance)**	**30%**	**II-A**
AR (TNBC)	AR expression (not validated)	?	II-B
AKT1^{E17K}	Mutations	5%	II-B



ESMO MBC Guidelines, Ann Oncol 2021

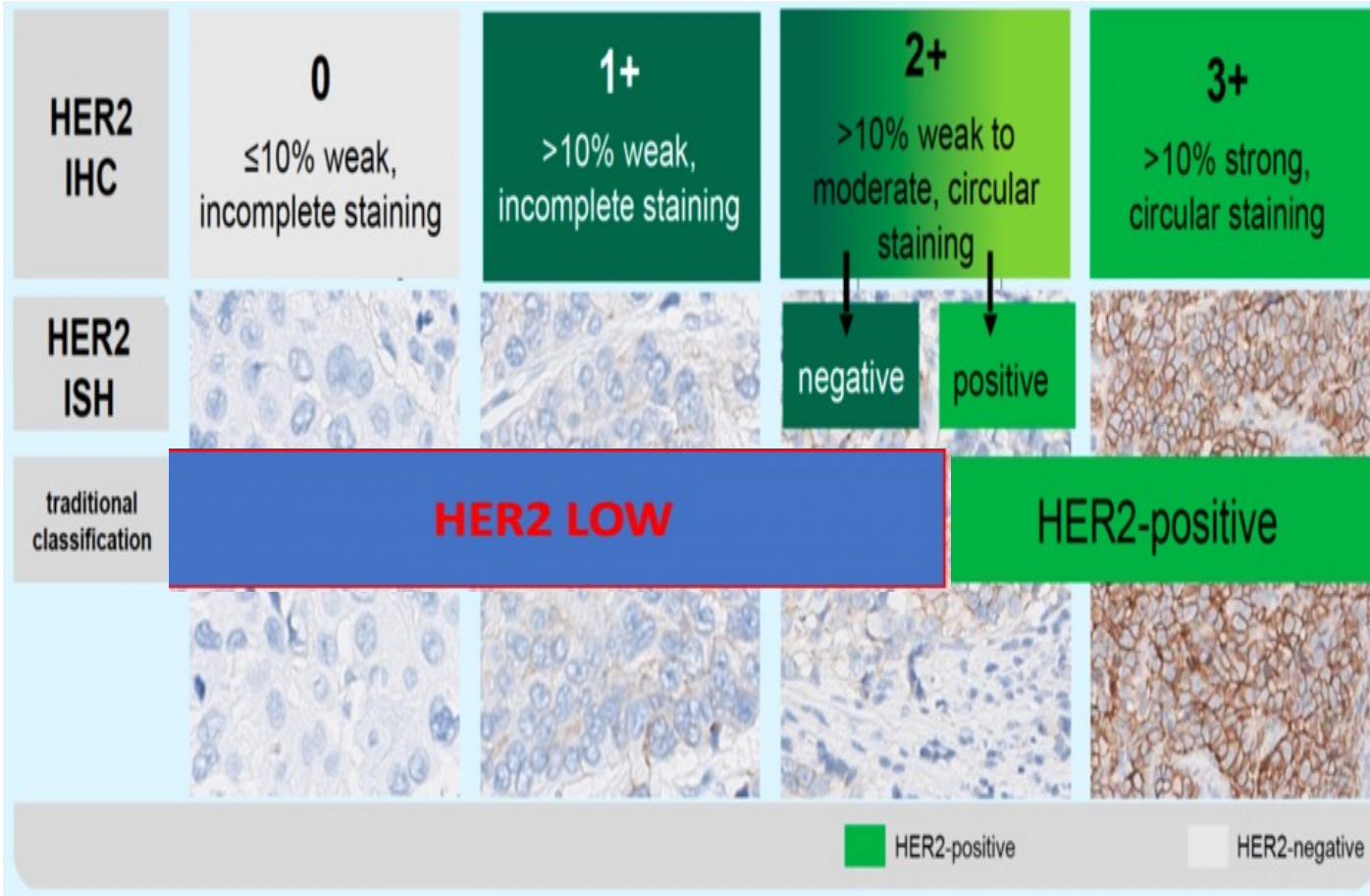
ER,PGR ET HER2

Systématiquement évalués pour chaque cancer du sein précoce et si possible à la rechute

Results (following ER testing by validated IHC assay)		Interpretation/ Report As:
0% – <1% of nuclei stain		ER-negative
1%–100% of nuclei stain	1%–10% of nuclei stain	ER-low–positive (with recommended comment)
	>10% of nuclei stain	ER-positive

Correlation of ER and Histology: Highly Unusual Results

Highly Unusual ER-Negative Results	Highly Unusual ER-Positive Results
Low-grade invasive carcinomas of no special type (also known as invasive ductal carcinoma)	Metaplastic carcinomas of all subtypes
Lobular carcinomas (classic type)	Adenoid cystic carcinomas and other salivary gland-like carcinomas of the breast
Pure tubular, cribriform, or mucinous carcinomas	Secretory carcinoma
Encapsulated papillary and solid papillary carcinomas	Carcinomas with apocrine differentiation



Denkert, Pathologie 2022 · 43:457–466

CANCER TRIPLE NEGATIF
Maladie localisée

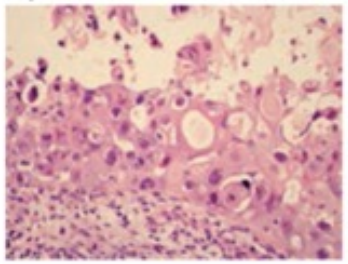
- **Place de l'immunothérapie (NAD)**
- **Traitements ciblés: inhibiteurs PARP (AD/mTNBC)**

TNBC are highly heterogeneous

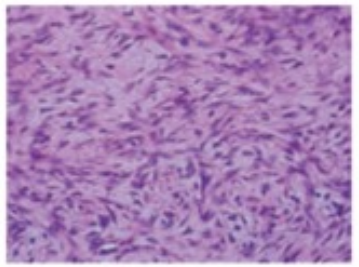
a Histological subtypes

- Invasive ductal carcinoma (95%)
- Invasive lobular carcinoma (1–2%)
- Metaplastic carcinoma with squamous differentiation (<1%)
- Spindle-cell metaplastic carcinoma (<1%)
- Adenoid cystic carcinoma (<1%)
- Secretory carcinoma (<1%)
- Typical medullary carcinoma (<1%)
- Atypical medullary carcinoma (<1%)
- Apocrine carcinoma (<1%)

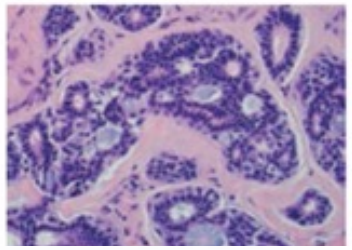
Metaplastic carcinoma with squamous differentiation



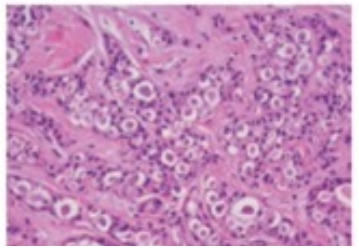
Spindle-cell metaplastic carcinoma



Adenoid cystic carcinoma

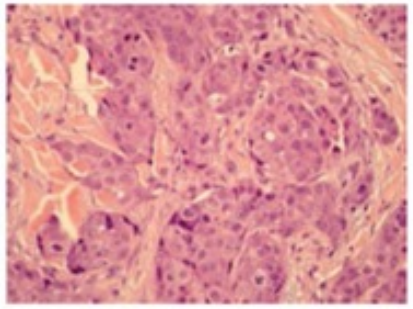


Secretory carcinoma

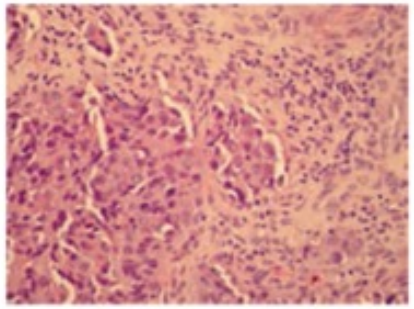


e Heterogeneity of tumour-infiltrating lymphocytes

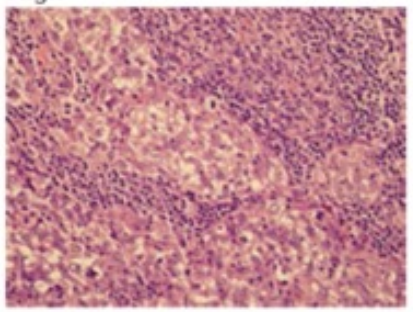
Low



Intermediate



High

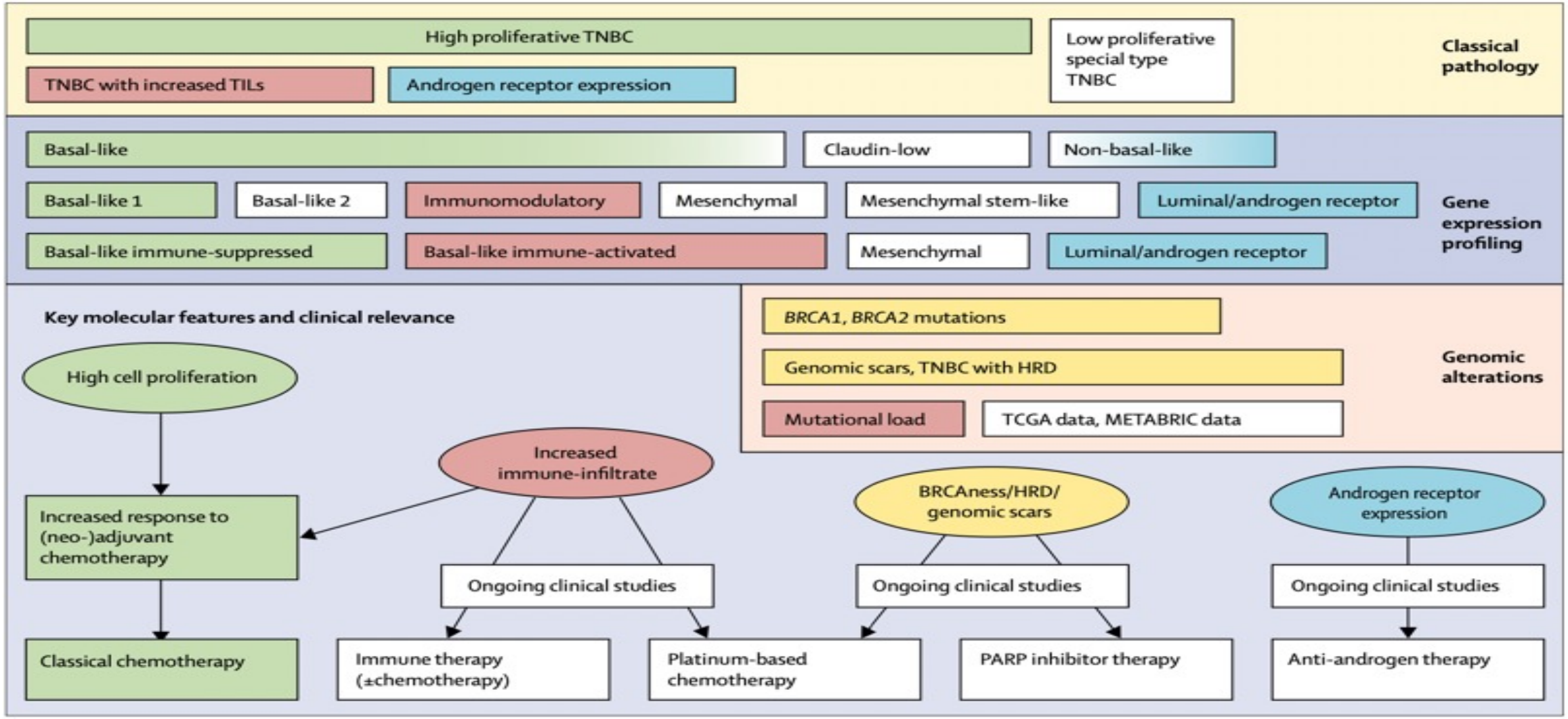


DEFINITION

ER < 1%, PR < 1%, HER2-negative (ASCO/CAP)
More proliferative, grade 2/3 and moderate high Ki67
Mostly ductal, but some special histologies warrant special attention

Bianchini G et al, Nat Rev Clin Oncol 2016

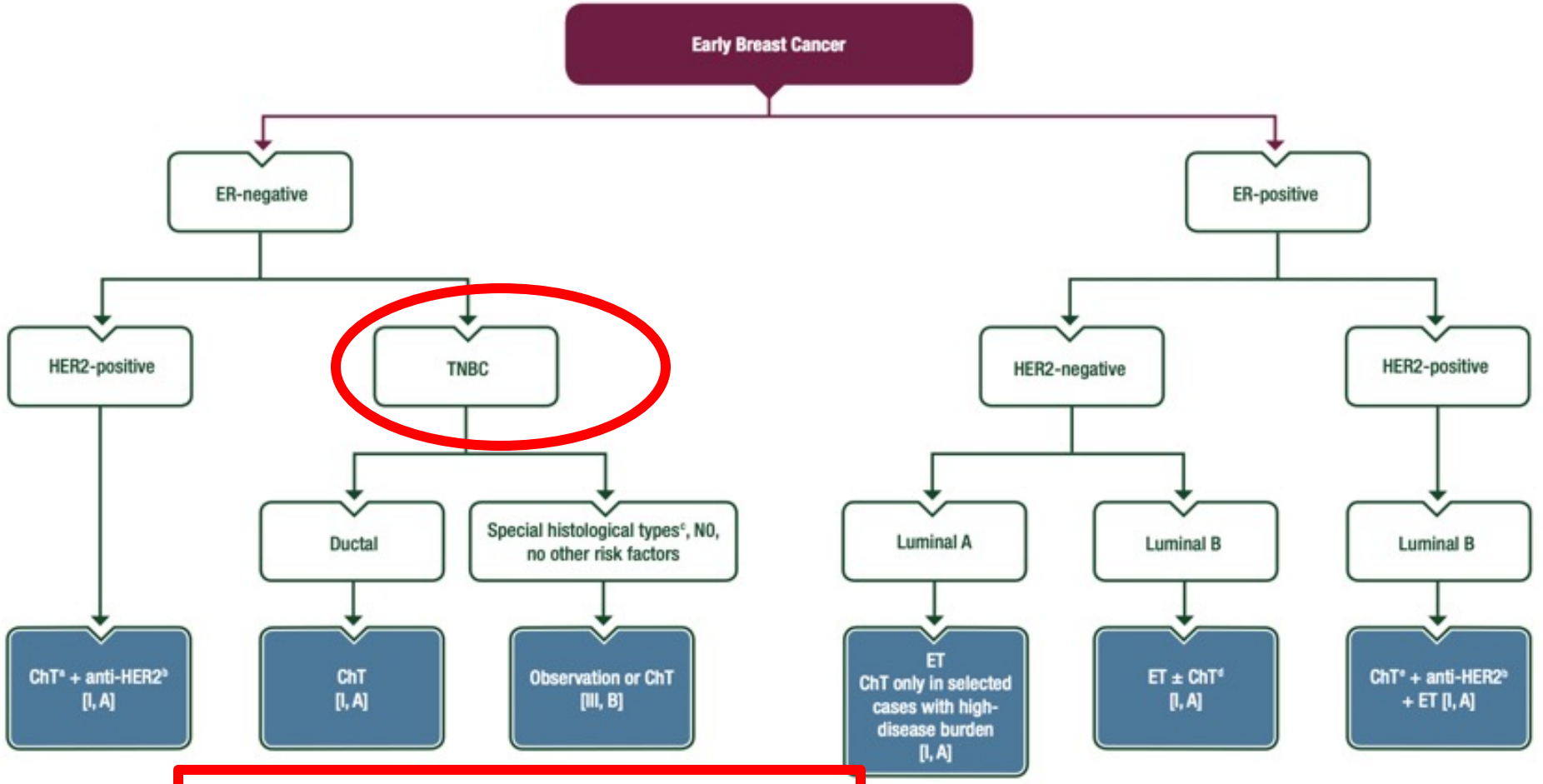
TNBC are highly heterogeneous on molecular level



Overview of relevant molecular alterations in triple-negative breast cancer

Lancet 2017; 389: 2430–42

EARLY BC TREATMENT



NEWS:
IMMUNOTHERAPY
BRCA GERMLINE MUT: OLAPARIB

Annals of Oncology 30: 1194–1220, 2019

Belgique 2022: cancer du sein
Sous type Triple Negative (TNBC)

KEYNOTE 522
Design

NEO-ADJUVANT
Treatment
Stage II and III
(T1cN1-2 or T2-4N0)

WHEN T IS...	AND N IS...	AND M IS...	THEN THE STAGE GROUP IS...[b]
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

- PDL1+ (22C3 CPS1) 82%
- N+ 52%, T3/4 26%
- Carbo QW 41%

XELODA not allowed

Co-primary endpoints:
- pCR (ypT0/Tis ypN0)
- Event-free Survival

Pembrolizumab: 200 mg given IV q3w
Paclitaxel: 80 mg/m² given IV qw for 12 weeks;Carboplatin: AUC5 q3w x 4 or AUC1.5 qw x 12
Doxorubicin: 60 mg/m² given IV q2w/Cyclophosphamide: 600 mg/m² given IV q2w

Schmid,NEJM 2022

KEYNOTE 522 results

Table 2. Pathological Complete Response, According to Pathological Stage.*

Variable	Pembrolizumab–Chemotherapy (N=401)	Placebo–Chemotherapy (N=201)	Estimated Treatment Difference†	P Value
			percentage points (95% CI)	
Pathological stage ypT0/Tis ypN0				
No. of patients	260	103		
Percentage of patients with response (95% CI)	64.8 (59.9–69.5)	51.2 (44.1–58.3)	13.6 (5.4–21.8)	P<0.001
Pathological st				
No. of pa				
Percenta resp				
Pathological				
No. of pa				
Percentag response (95% CI)				

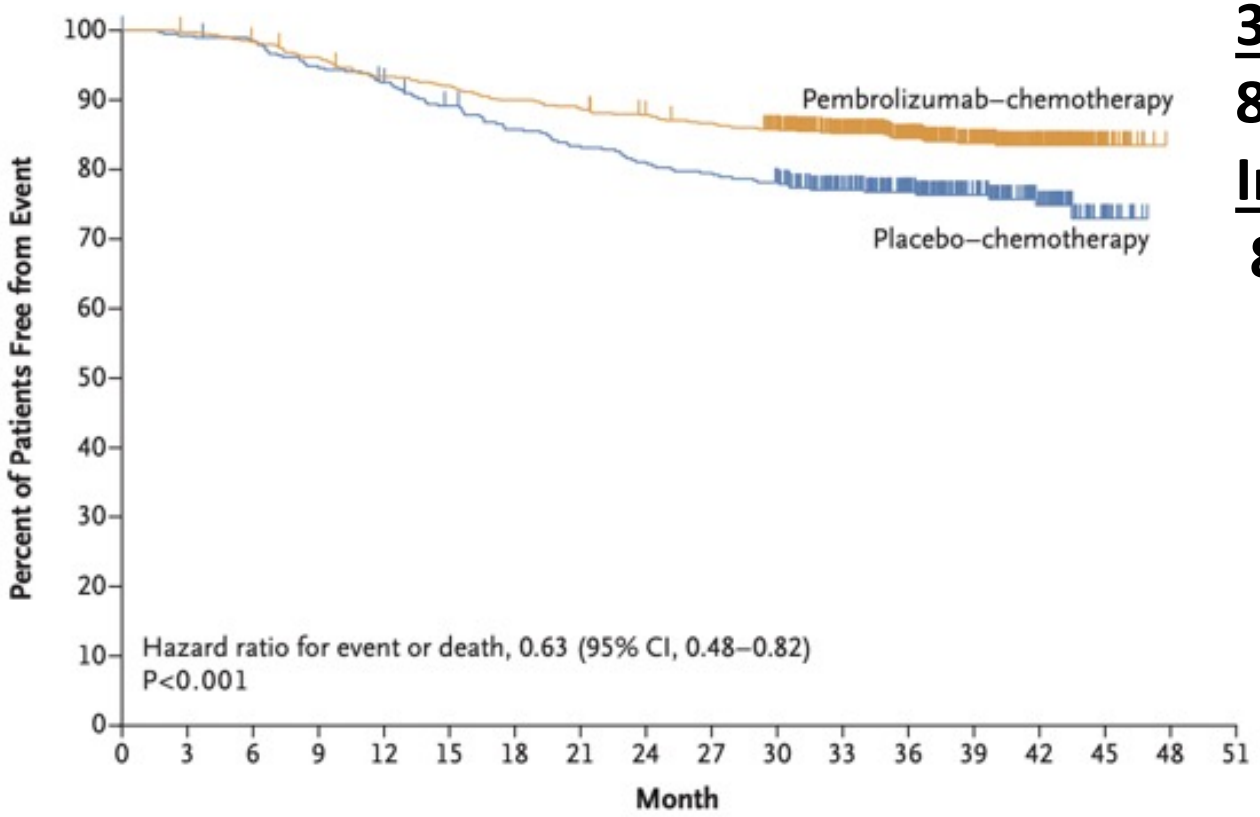
pCR rate : 64,8 % vs 51,2 %

Schmid,NEJM 2022

KEYNOTE 522 results

PRIMARY EFS ANALYSIS

NEO-ADJUVANT treatment



No. at Risk																		
Pembrolizumab–chemotherapy	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo–chemotherapy	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

3 Y EFS at 39,1 Mo FU

84,5 % vs 76,8 % HR 0,63

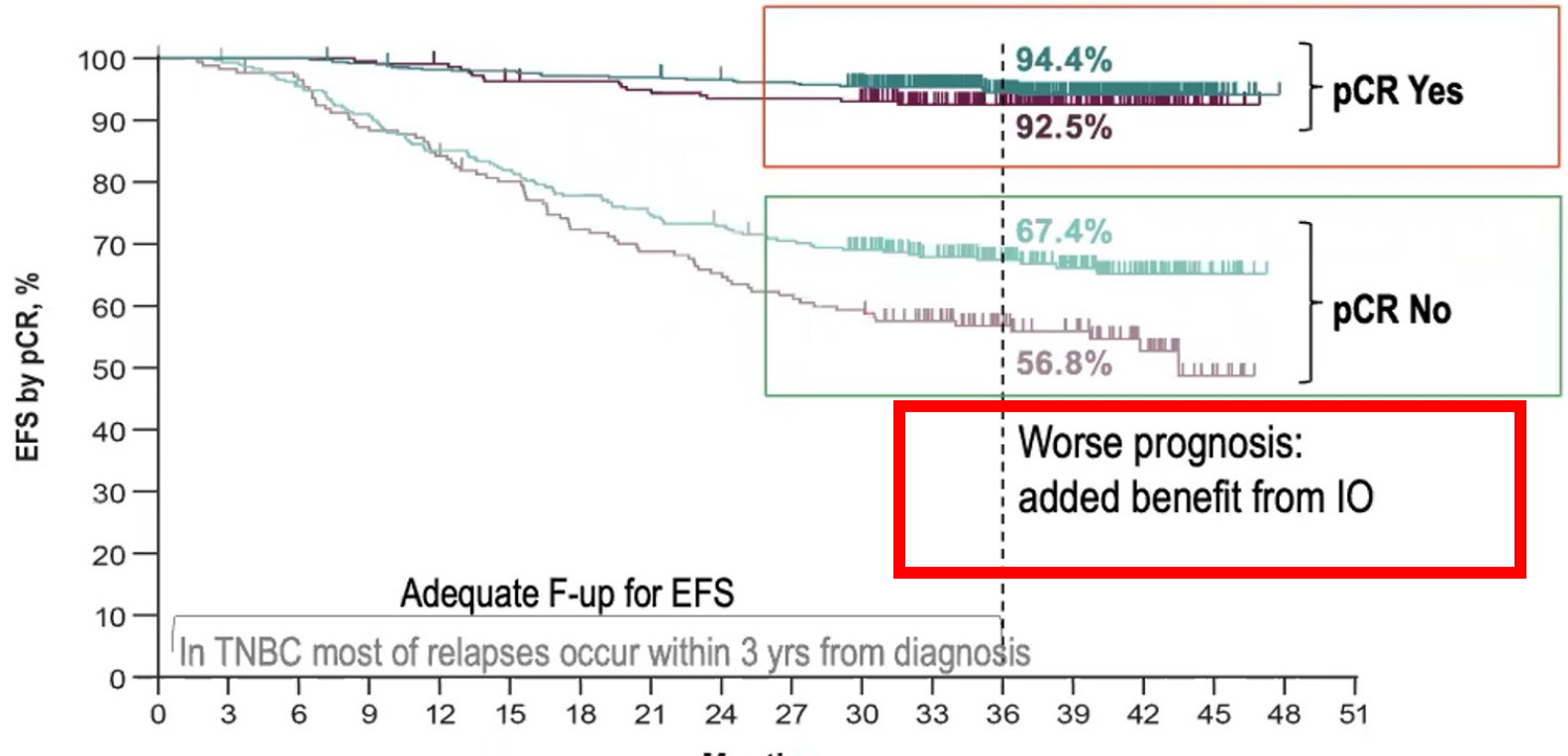
Immature OS at 36 Mo

89,7 % vs 86,9 %

Schmid,NEJM 2022

KEYNOTE 522 results

EFS ANALYSIS BY pCR)



No. at Risk																		
Pembro + Chemo/Pembro Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Pbo + Chemo/Pbo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembro + Chemo/Pembro Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Pbo + Chemo/Pbo Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

Schmid,NEJM 2022

KEYNOTE 522 TOXICITY

Adverse events occurred predominantly during the neoadjuvant phase and were consistent with the established safety profiles of pembrolizumab and chemotherapy

Event	Pembrolizumab–Chemotherapy (N=781)		Placebo–Chemotherapy (N=389)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	777 (99.5)	633 (81.0)	389 (100.0)	295 (75.8)
Treatment-related adverse event†	773 (99.0)	600 (76.8)	388 (99.7)	281 (72.2)
Nausea	490 (62.7)	26 (3.3)	246 (63.2)	5 (1.3)
Alopecia	471 (60.3)	14 (1.8)	220 (56.6)	8 (2.1)
Anemia	430 (55.1)	142 (18.2)	215 (55.3)	58 (14.9)
Neutropenia	365 (46.7)	270 (34.6)	183 (47.0)	129 (33.2)
Fatigue	321 (41.1)	27 (3.5)	147 (37.8)	6 (1.5)
Diarrhea	230 (29.4)	17 (2.2)	92 (23.7)	5 (1.3)
Elevated alanine aminotransferase level	199 (25.5)	41 (5.2)	96 (24.7)	9 (2.3)
Vomiting	199 (25.5)	18 (2.3)	85 (21.9)	6 (1.5)
Asthenia	191 (24.5)	25 (3.2)	99 (25.4)	9 (2.3)
Constipation	185 (23.7)	0	82 (21.1)	0
Decreased neutrophil count	185 (23.7)	146 (18.7)	112 (28.8)	90 (23.1)
Rash	170 (21.8)	7 (0.9)	59 (15.2)	1 (0.3)
Peripheral neuropathy	154 (19.7)	15 (1.9)	82 (21.1)	4 (1.0)
Immune-mediated adverse event‡	262 (33.5)	101 (12.9)	44 (11.3)	4 (1.0)
Hypothyroidism	118 (15.1)	4 (0.5)	22 (5.7)	0
Severe skin reaction	45 (5.7)	37 (4.7)	4 (1.0)	1 (0.3)
Hyperthyroidism	41 (5.2)	2 (0.3)	7 (1.8)	0
Adrenal insufficiency	20 (2.6)	8 (1.0)	0	0
Pneumonitis	17 (2.2)	7 (0.9)	6 (1.5)	2 (0.5)
Thyroiditis	16 (2.0)	2 (0.3)	5 (1.3)	0
Hypophysitis	15 (1.9)	10 (1.3)	1 (0.3)	0

Schmid,NEJM 2022

Use of Immune Checkpoint Inhibitor Pembrolizumab in the Treatment of High-Risk, Early-Stage Triple-Negative Breast Cancer: ASCO Guideline Rapid Recommendation Update

Larissa A. Korde, MD[1]; Mark R. Somerfield, PhD[2]; and Dawn L. Hershman, MD[3]; for the Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer Guideline Expert Panel

2022 update recommendation

For patients with T1cN1-2 or T2-4N0 (stage II or III), early- stage TNBC, the Panel recommends use of pembrolizumab (200 mg once every 3 weeks or 400 mg once every 6 weeks) in combination with neoadjuvant chemotherapy, followed by adjuvant pembrolizumab after surgery.

Adjuvant pembrolizumab may be given either concurrent with or after completion of radiation therapy.

There are no data to support the use of pembrolizumab in combination with either capecitabine or olaparib (tolerable but unknown efficacy and high financial toxicity).

Question of which treatment if no pCR ????

TNBC: BRCA 1/2 MUT
OLYMPIA TRIAL

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

≥ 6 cycles Neoadjuvant Chemotherapy → **Surgery** → **+/- Radiotherapy**

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes

Surgery → **≥ 6 cycles Adjuvant Chemotherapy** → **+/- Radiotherapy**

1:1 Randomization N=1836

Olaparib 300 mg twice daily for 1 year

Placebo twice daily for 1 year

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

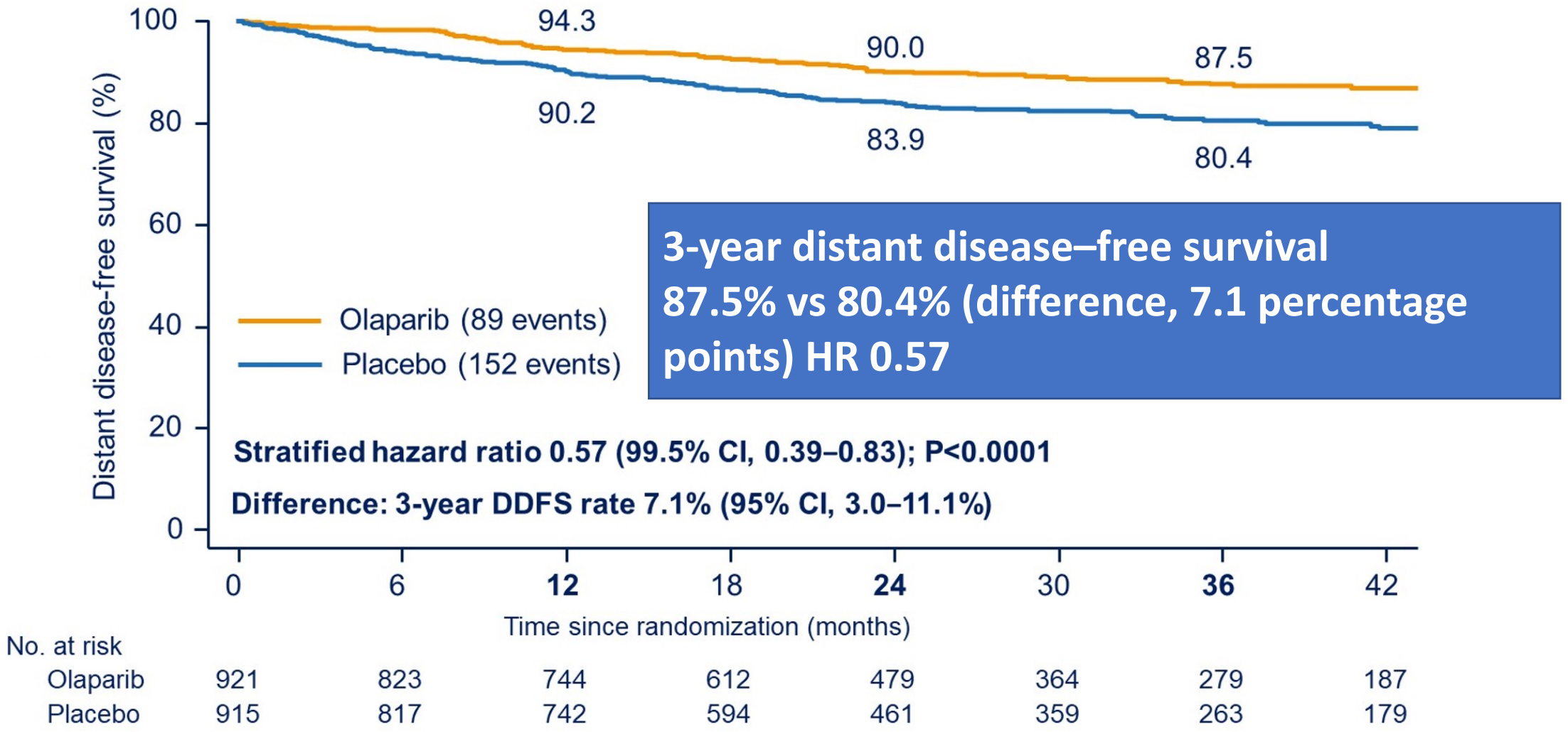
Stratification Factors
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

The CPS+EG scoring system estimates relapse probability on the basis of clinical and pathological stage (CPS) and estrogen-receptor status and histologic grade (EG); scores range from 0 to 6, with higher scores indicating worse prognosis
http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=bcnt

Tutt, ASCO 2021 and N Engl J Med 2021;384:2394-405

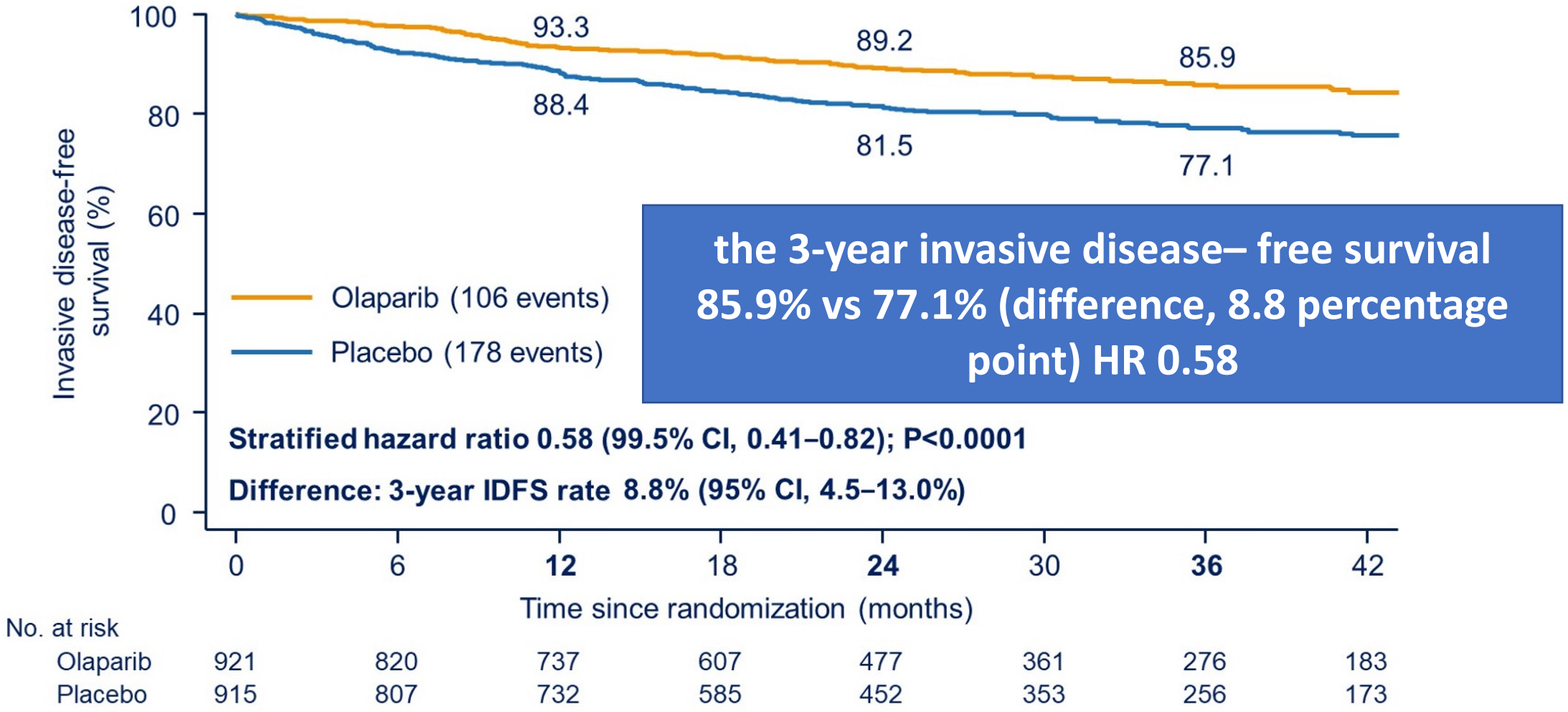
OLYMPIA TRIAL: DDFS



3-year distant disease–free survival 87.5% vs 80.4% (difference, 7.1 percentage points) HR 0.57

Tutt, ASCO 2021 and N Engl J Med 2021;384:2394-405

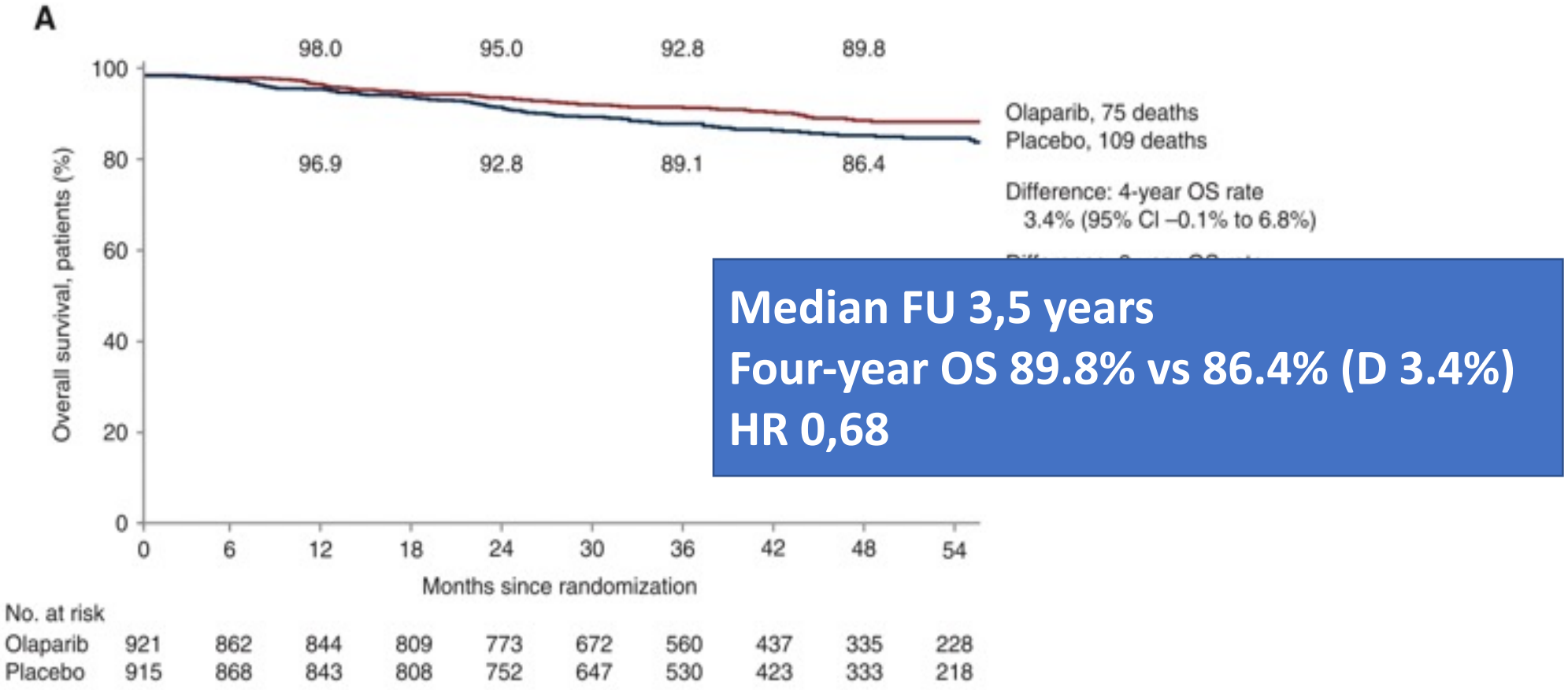
OLYMPIA TRIAL: IDFS



the 3-year invasive disease– free survival 85.9% vs 77.1% (difference, 8.8 percentage point) HR 0.58

Tutt, ASCO 2021 and N Engl J Med 2021;384:2394-405

OLYMPIA TRIAL: OS



Median FU 3,5 years
Four-year OS 89.8% vs 86.4% (D 3.4%)
HR 0,68

Geyer,Annals of Oncology,2022

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 2.2023 — February 7, 2023

REMBOURSEMENT 1/7/2023
EN BELGIQUE

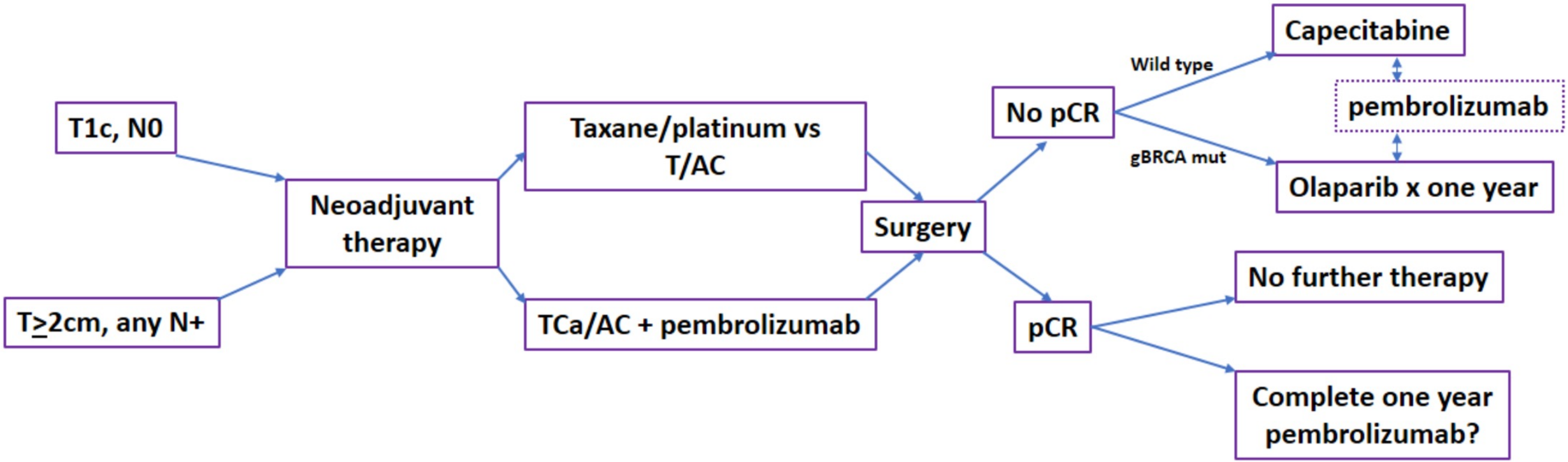
Consider addition of adjuvant olaparib for 1 y for those with germline *BRCA1/2* mutations and:

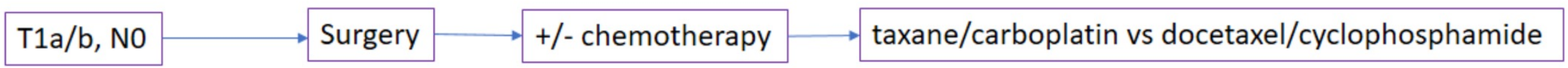
- **<u>TNBC</u>, if**
  - **1) ≥pT2 or ≥pN1 disease after adjuvant chemotherapy, or**
  - **2) residual disease after preoperative chemotherapy**

- **<u>HR-positive, HER2-negative tumors,</u> if**
  - **1) ≥4 positive lymph nodes after adjuvant chemotherapy (category 2A),**
  - **2) residual disease after preoperative therapy and a clinical stage, pathologic stage, ER status, and tumor grade (CPS+EG) score ≥3 (category 2A).**

Olaparib should be given after completion of RT.
Adjuvant olaparib can be used concurrently with endocrine therapy

Roadmap for Early TNBC





Ongoing Trials: Tailoring neoadjuvant therapy to response; optimizing post-neoadjuvant therapy – ADCs, checkpoint inhibitor?

AC: anthracycline/cyclophosphamide; Ca: carboplatin

gBRCA mutation: neoadjuvant PARP inhibitors?

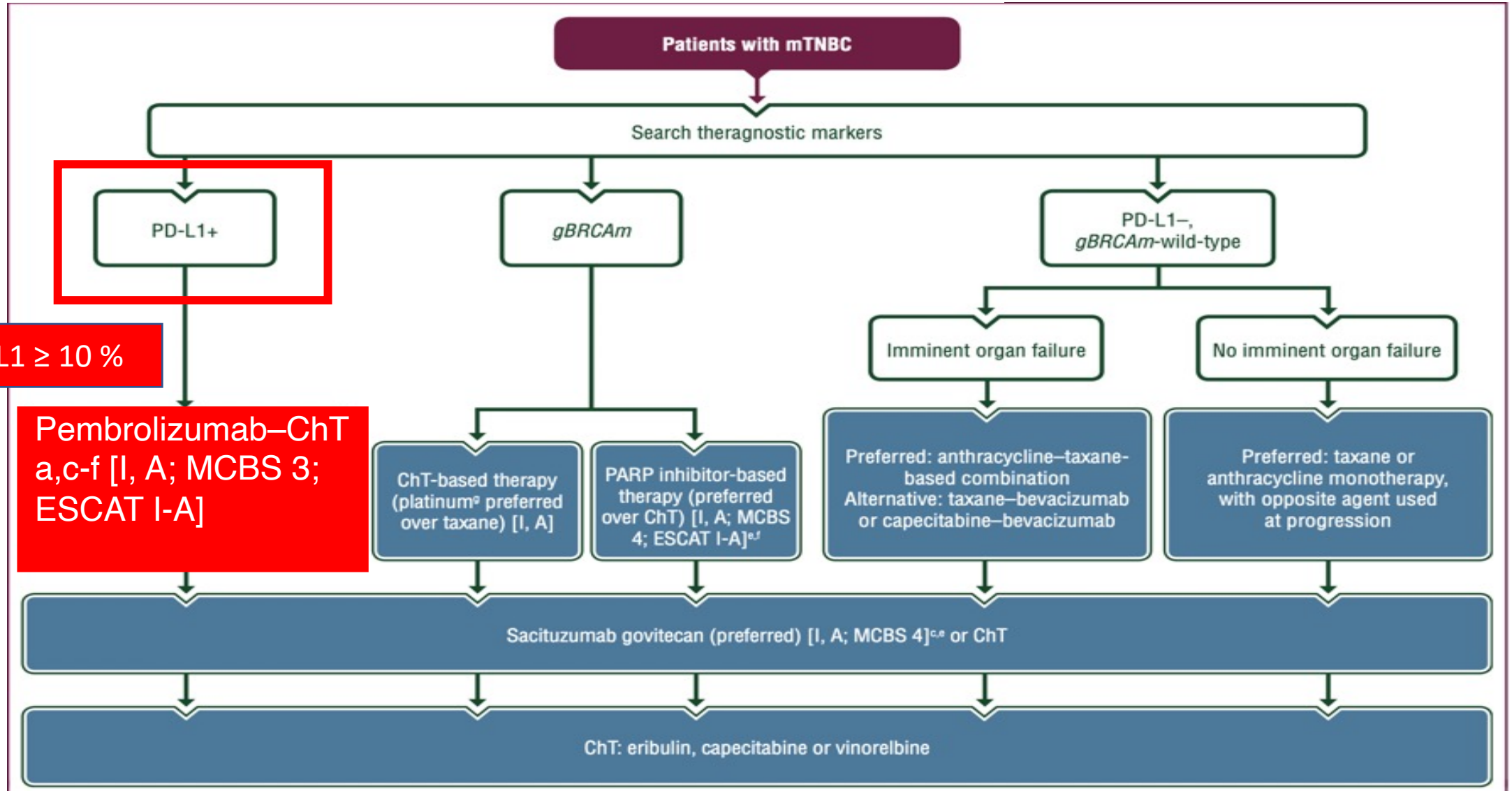
Rugo,SABCC 2021

CANCER TRIPLE NEGATIF
Maladie métastatique

- **TROIS CIBLES:**

PD-L1
BRCA1/2
TROP2

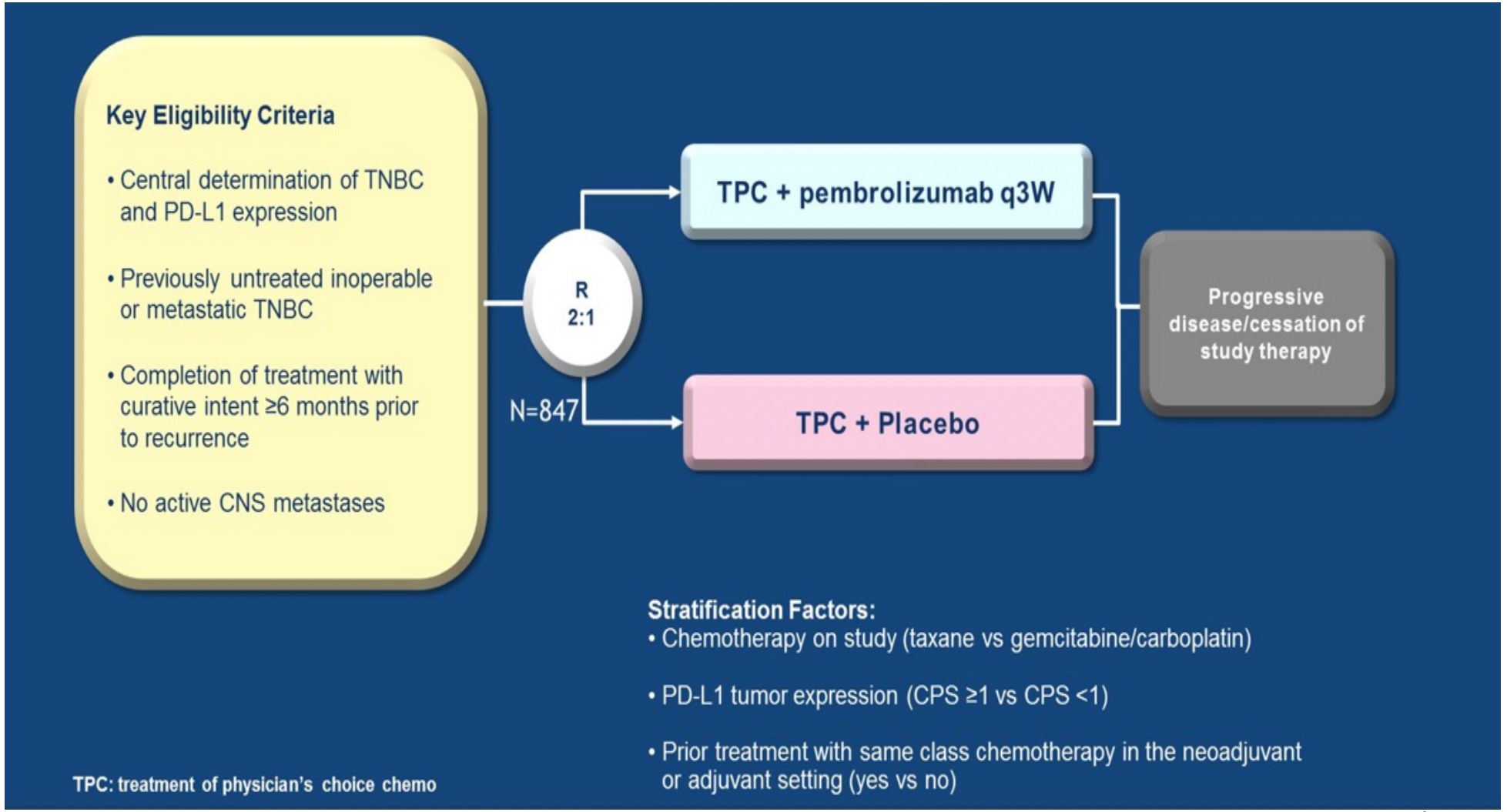
ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer☆



KEYNOTE 355 design

Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial

*Javier Cortes, David W Cescon, Hope S Rugo, Zbigniew Nowecki, Seock-Ah Im, Mastura Md Yusof, Carlos Gallardo, Oleg Lipatov, Carlos H Barrios, Esther Holgado, Hiroji Iwata, Norikazu Masuda, Marco Torregroza Otero, Erhan Gokmen, Sherene Loi, Zifang Guo, Jing Zhao, Gursel Aktan, Vassiliki Karantza, Peter Schmid, for the KEYNOTE-355 Investigators**



Dual primary efficacy endpoints

PFS

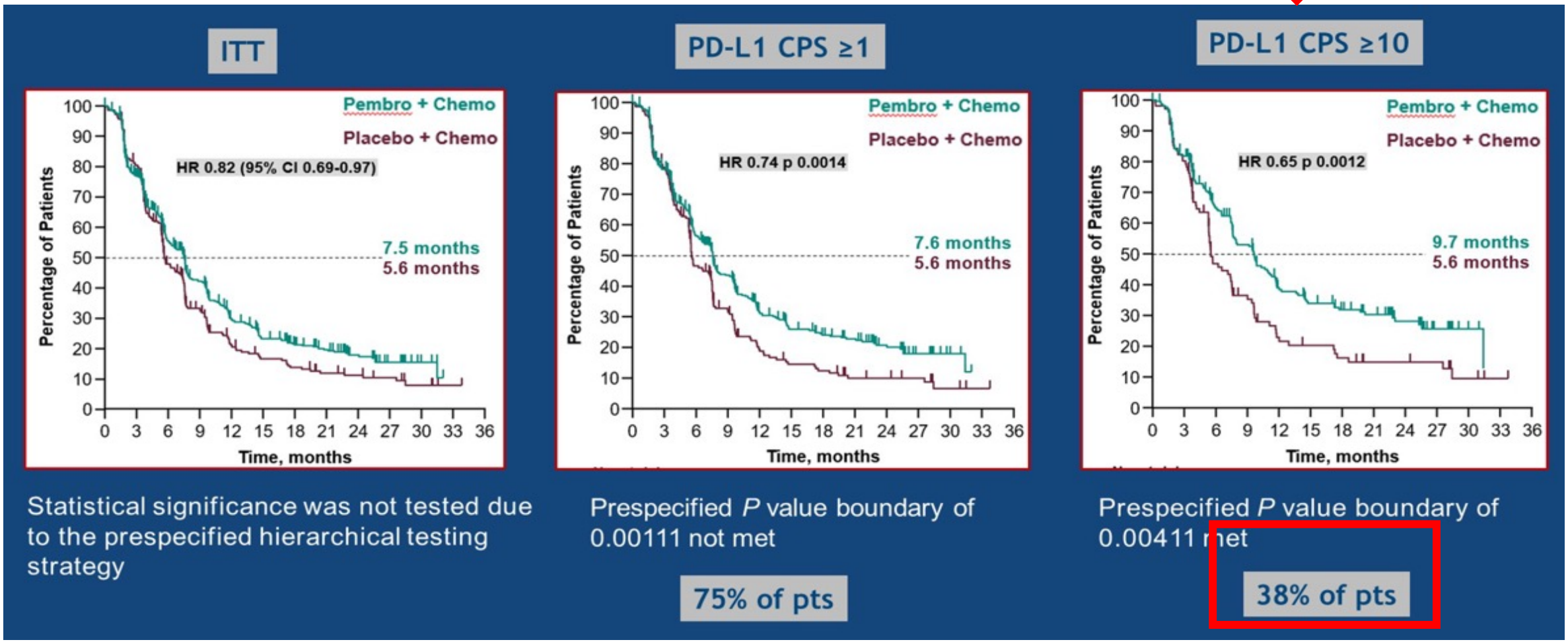
OS assessed:

- **in the PD-L1 CPS of 10 or more,**
- **CPS of 1 or more,**
- **intention-to-treat populations.**

J Cortes ASCO 2020/Lancet 2020; 396: 1817–28

KEYNOTE 355 results:
PFS

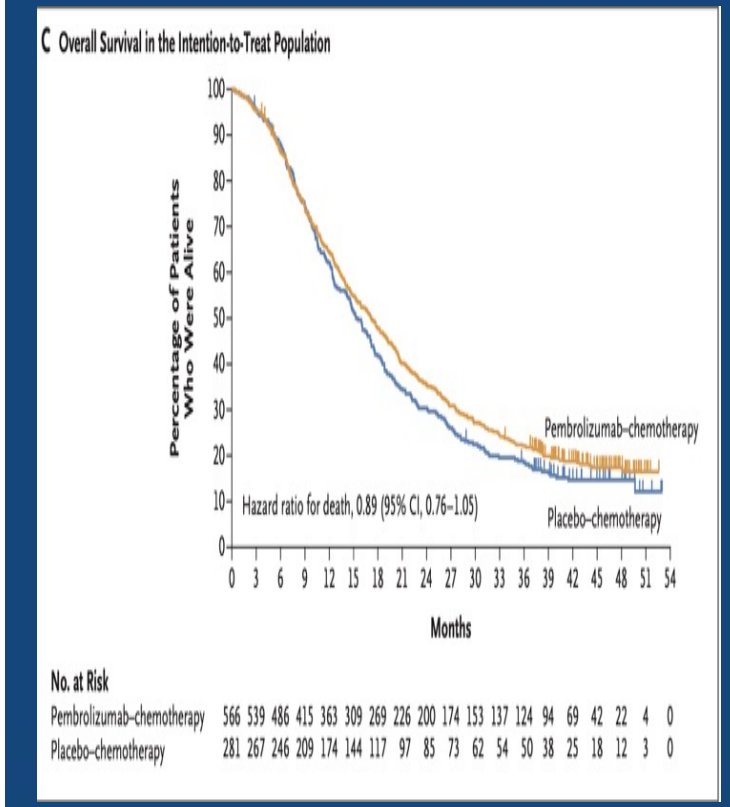
9,7 vs 5,6 Mo
HR 0,65

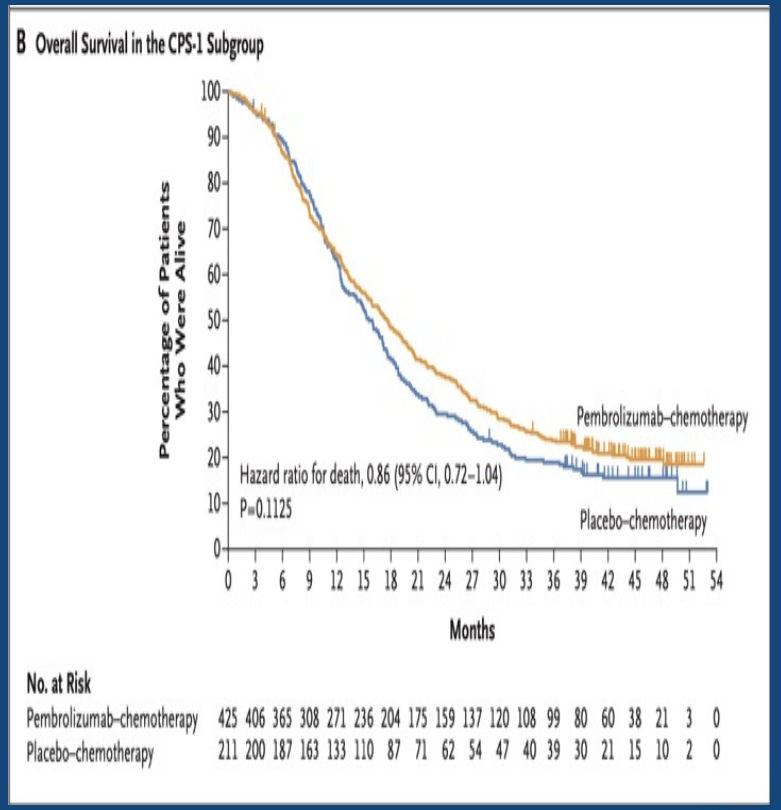


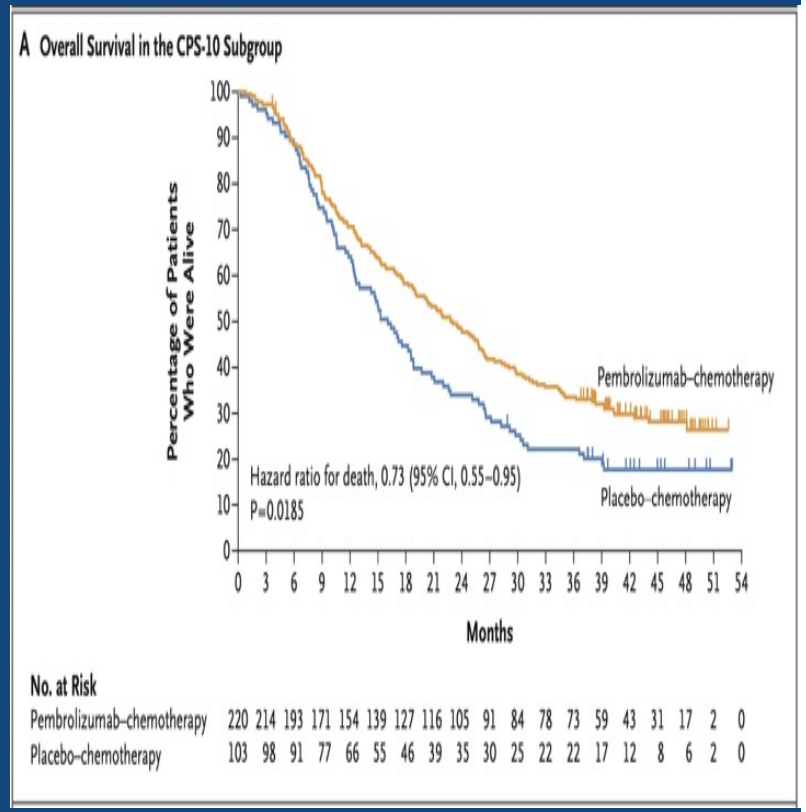
Objectif principal (SURVIE SANS PROGRESSION)atteint dans les PD-L1 CPS>10 (pas dans les CPS> 1; non testé dans la population globale)
Tendance à l'augmentation du bénéfice avec enrichissement score PD-L1

KEYNOTE 355 results:
recent update
OS

23 vs 16,1Mo
HR 0,73





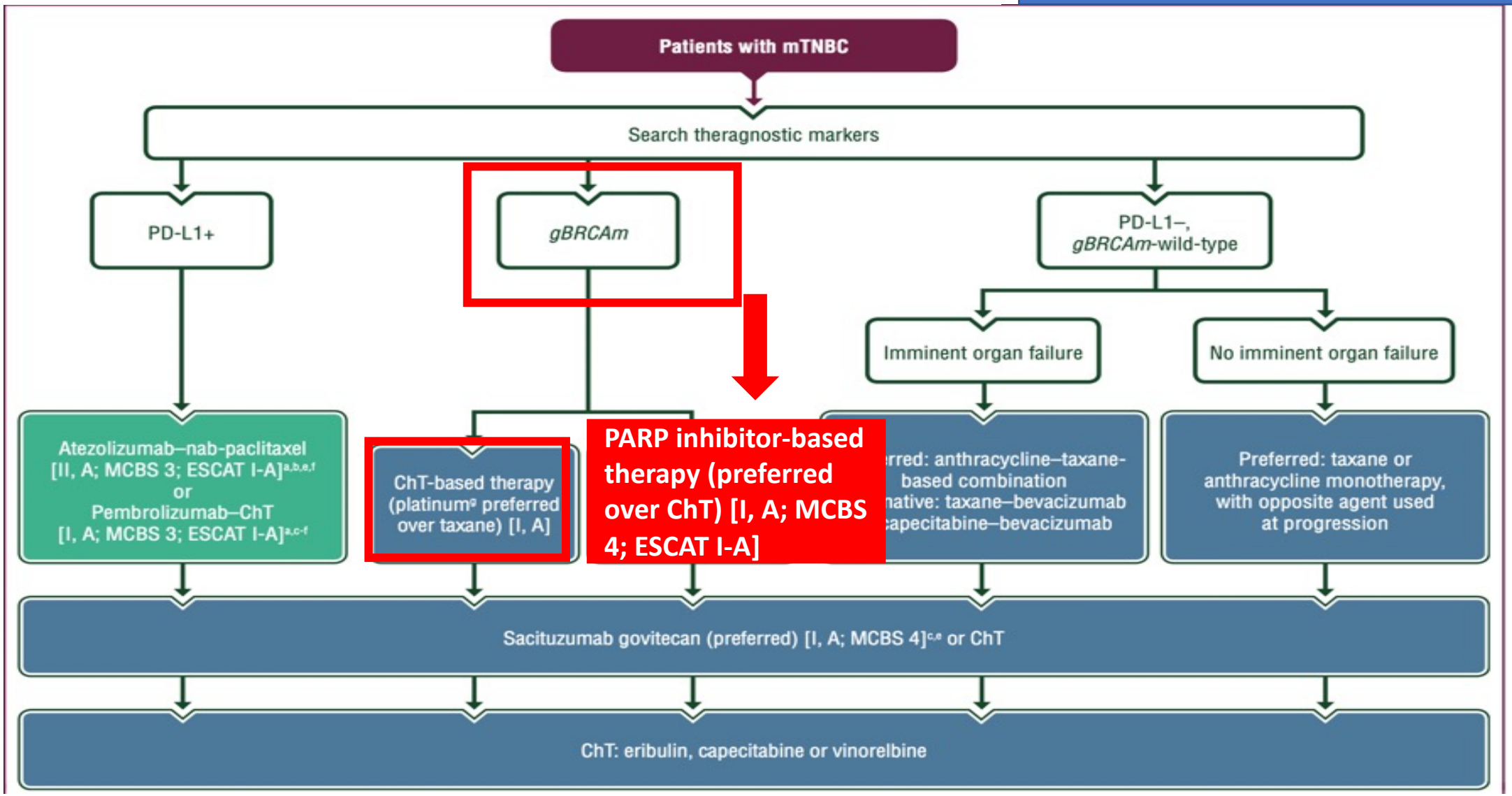


Objectif principal (SURVIE GLOBALE)atteint dans les PD-L1 CPS>10 (pas dans les CPS> 1; non testé dans la population globale)

Cortes,NEJM, 2022

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

OLAPARIB (LYNPARZA)
TALAZOPARIB (TALZENNA)

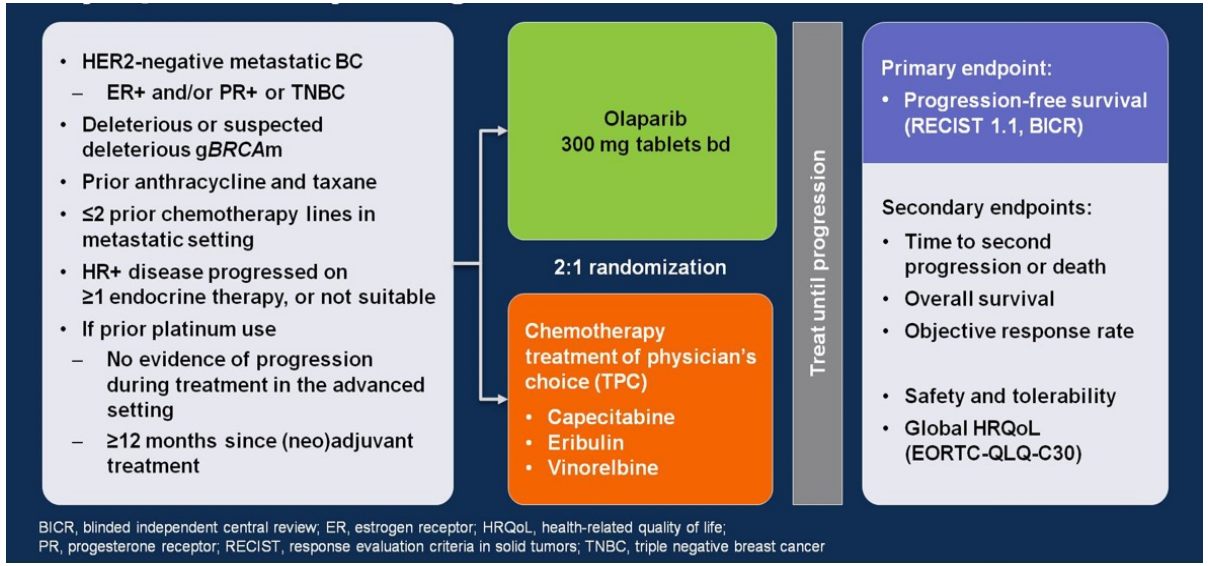


ORIGINAL ARTICLE

Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation

Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D.,

OLYMPIAD trial



N Engl J Med 2017;377:523-33

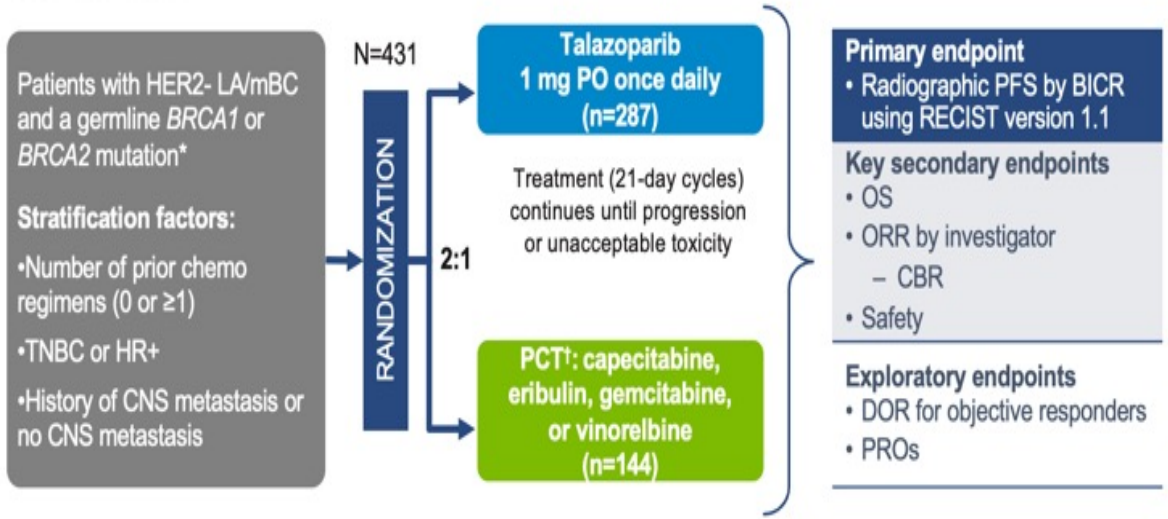
ORIGINAL ARTICLE

Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation

Jennifer K. Litton, M.D., Hope S. Rugo, M.D., Johannes Ettl, M.D.,

EMBRACA trial

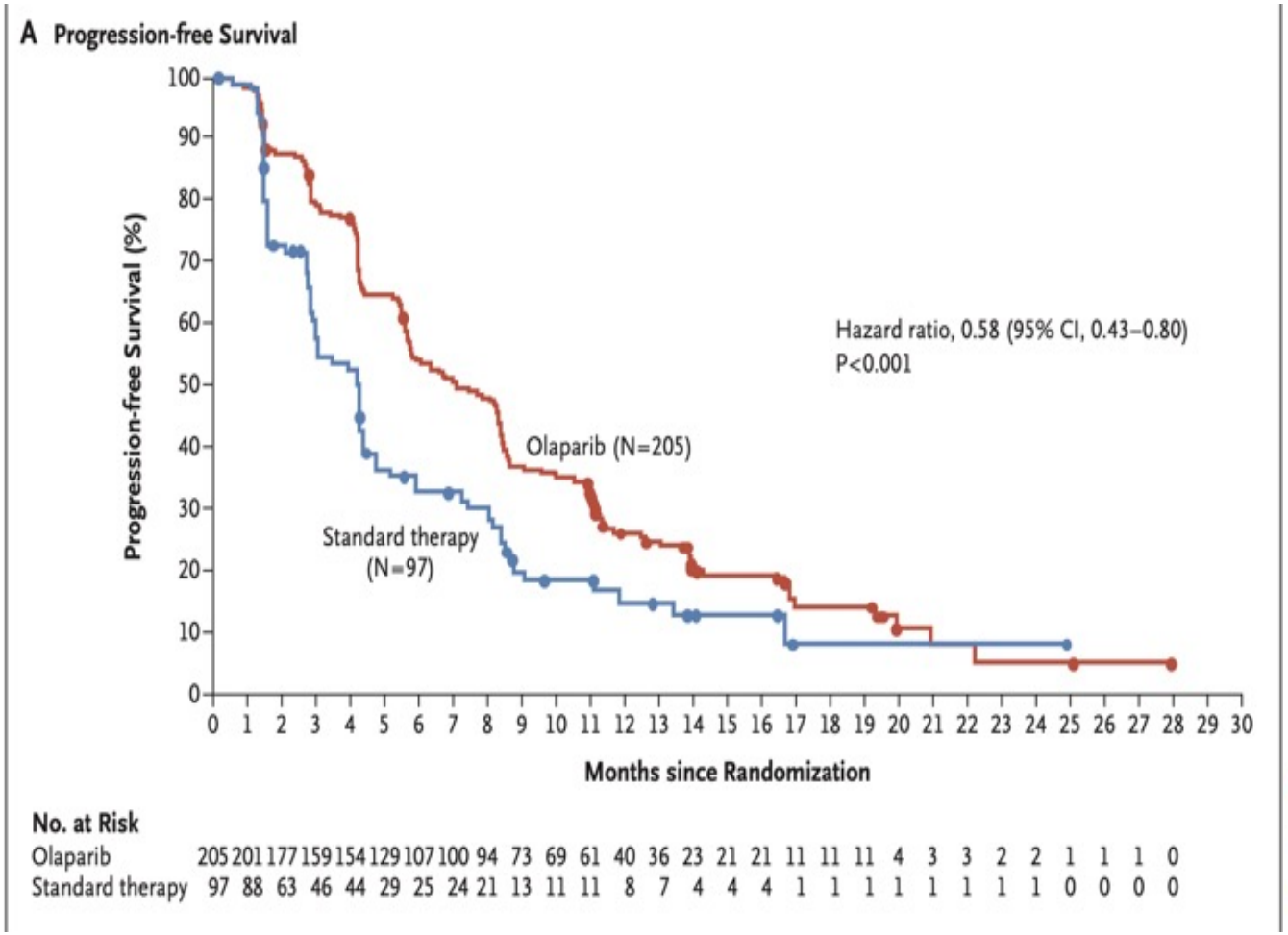
Phase 3, international, open-label study, randomized 431 patients in 16 countries and 145 sites



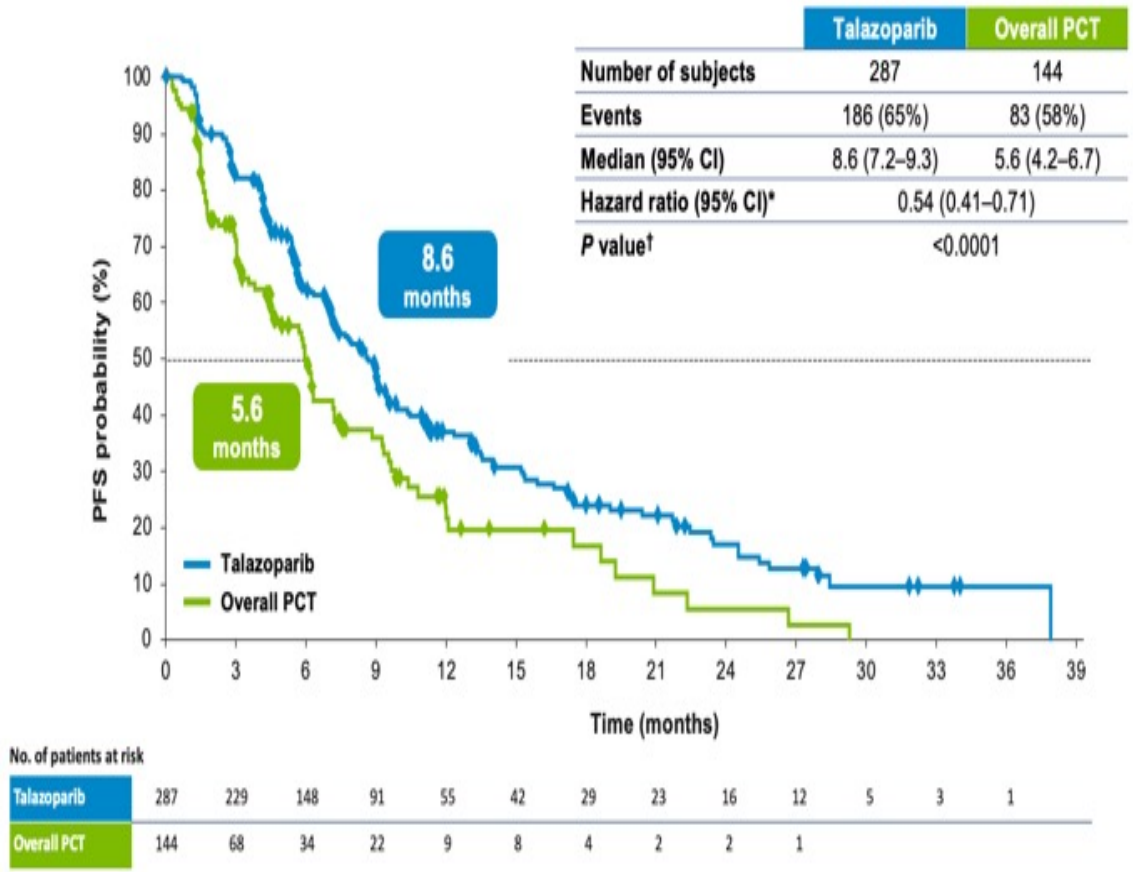
- The EMBRACA trial was designed with adequate power to detect certain effect sizes for both PFS and OS

N Engl J Med, 379 (8) (2018), pp. 753-763

OLYMPIAD trial
RESULTS:PFS



EMBRACA trial
RESULTS:PFS



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 2.2023 — February 7, 2023

- **Patients with HER2-negative MBC and germline pathogenic or likely pathogenic variants in BRCA1 or BRCA2 should be offered treatment with a PARP inhibitor (olaparib or talazoparib), independent of HR status, as an alternative to ChT [I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A].**
- **Prior treatment with anthracyclines et taxanes should not be required before offering patients with MBC and gBRCAm treatment with a PARP inhibitor; nor should HR-positive patients be required to demonstrate complete endocrine resistance [I, D].**
- **There is insufficient evidence to determine the optimal sequencing of PARP inhibitors with other active treatments such as ChT combinations in mTNBC or ET and targeted therapy combinations in HR-positive disease [I, A].**
- **Patients who may be considered for treatment with a PARP inhibitor should be offered genetic testing for pathogenic variants in BRCA1 and BRCA2 regardless of age, family history or BC subtype.**

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

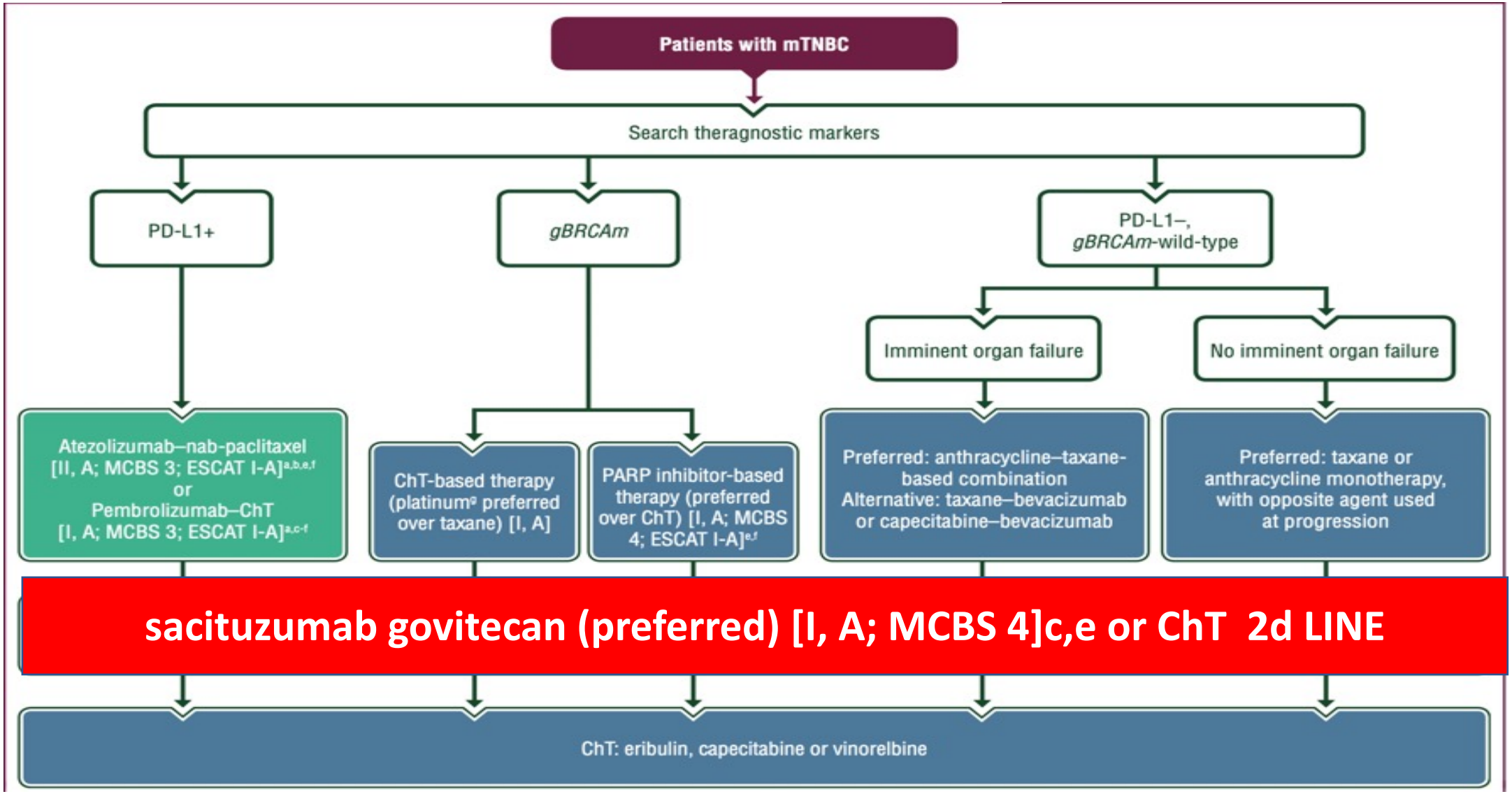
Breast Cancer

Version 2.2023 — February 7, 2023

- **Patients with HER2-negative MBC and germline pathogenic or likely pathogenic variants in BRCA1 or BRCA2 should be offered treatment with a PARP inhibitor (olaparib or talazop**[illegible]**MCBS v1.1 score: 4; I**[illegible]
- **Prior tre**[illegible]**ffering patients v**[illegible]**-positive patients I**[illegible]
- **There is**[illegible]**nibitors with other active treatments such as CHT combinations in mTNBC or ET and targeted therapy combinations in HR-positive disease [I, A].**
- **Patients who may be considered for treatment with a PARP inhibitor should be offered genetic testing for pathogenic variants in BRCA1 and BRCA2 regardless of age, family history or BC subtype.**

Si BRCA ½ mutation germinale, PARPi est une alternative à la chimiothérapie en première ligne métastatique (I, A; ESMO-MCBS v1.1 score: 4; ESCAT score: I-A])

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

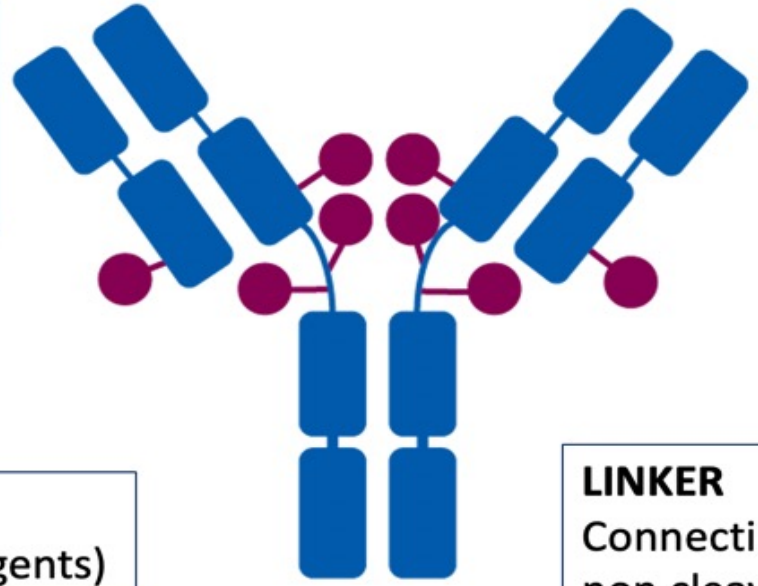


NEW CLASS OF TREATMENT: ANTICORPS MONOCLONAUX CONJUGUES

Antibody Drug Conjugates (ADCs) Mechanism: 3 components

Drug specific delivery to antigen-expressing tumour cells.
Designed to improve the therapeutic index of antineoplastic agents.

MONOCLONAL ANTIBODY BACKBONE
Humanized
Targets an Ag expressed or overexpressed on cancer cells



PAYLOAD
Cytotoxic (microtubule, DNA-damaging agents)

LINKER
Connecting payload to antibody
non cleavable vs cleavable

NEW CLASS OF TREATMENT: ANTICORPS MONOCLONAUX CONJUGUES

SACITUZUMAB GOVITECAN(SG) OU TRODELVY

First in class Trop-2 directed ADC

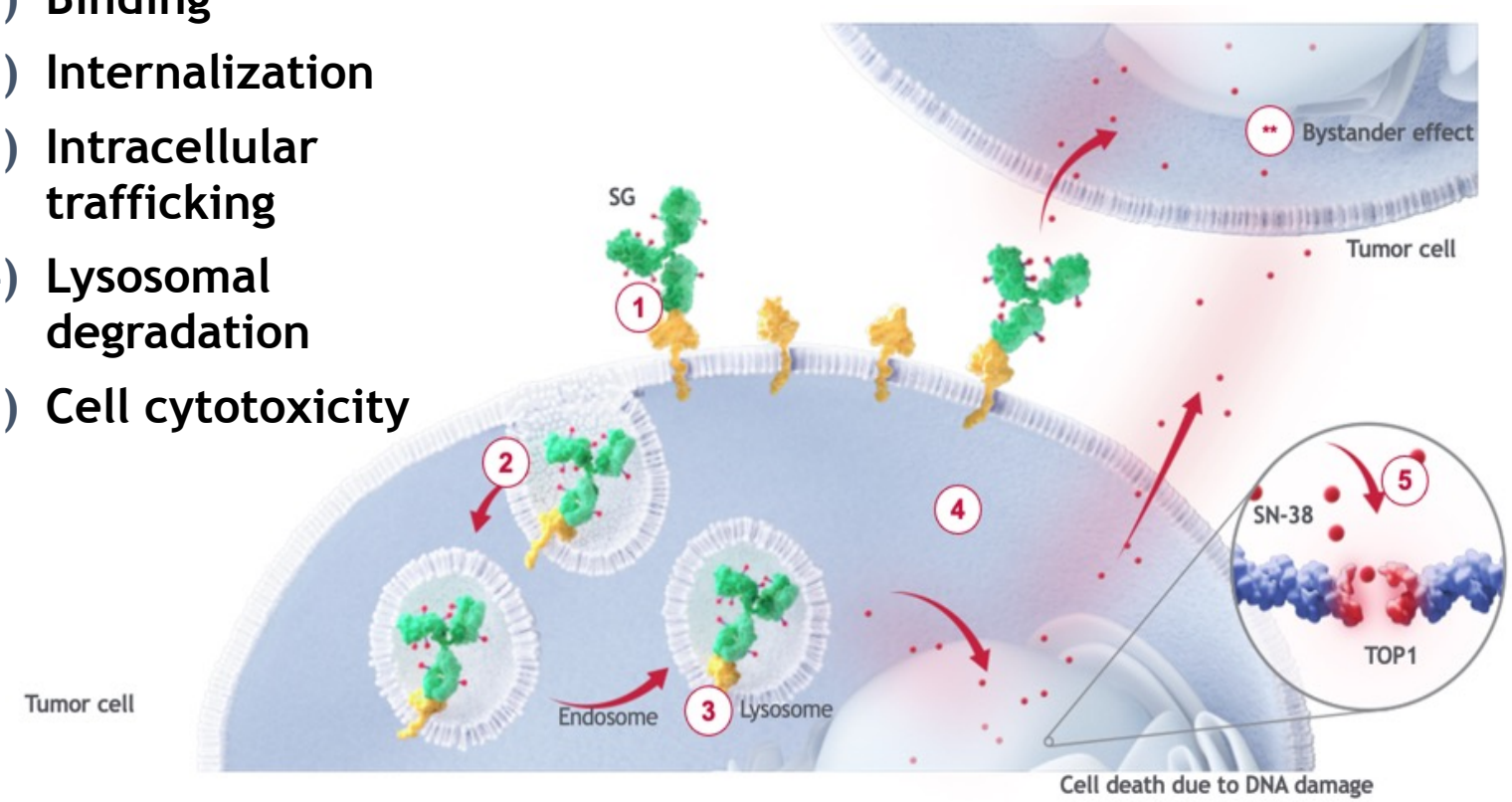
SG is distinct from other ADCs

- **Antibody highly specific for trop-2**
- **High drug to antibody ratio 7.6:1**
- **Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody**

Trop-2 Overexpression		
Solid Tumors		Hematologic Malignancies
• Breast	• Pulmonary adenocarcinoma	• Extranodal NK/T-cell lymphomas
• Bladder carcinoma	• Oral squamous cell carcinoma	• Non-Hodgkin lymphomas
• Cervical carcinoma	• Ovarian cancer	
• Colon cancer	• Pancreatic cancer	
• Colorectal cancer	• Prostate cancer	
• Endometrial cancer	• Thyroid cancer	
• Esophageal cancer		
• Gastric cancer		
• Gliomas		
• Hilar cholangio-carcinoma		
• Large intestine cancer		

96% of triple-negative breast cancer (TNBC) tumors and many solid tumors
overexpress Trop-2, making it an attractive target for new therapies

1) Binding
2) Internalization
3) Intracellular trafficking
4) Lysosomal degradation
5) Cell cytotoxicity

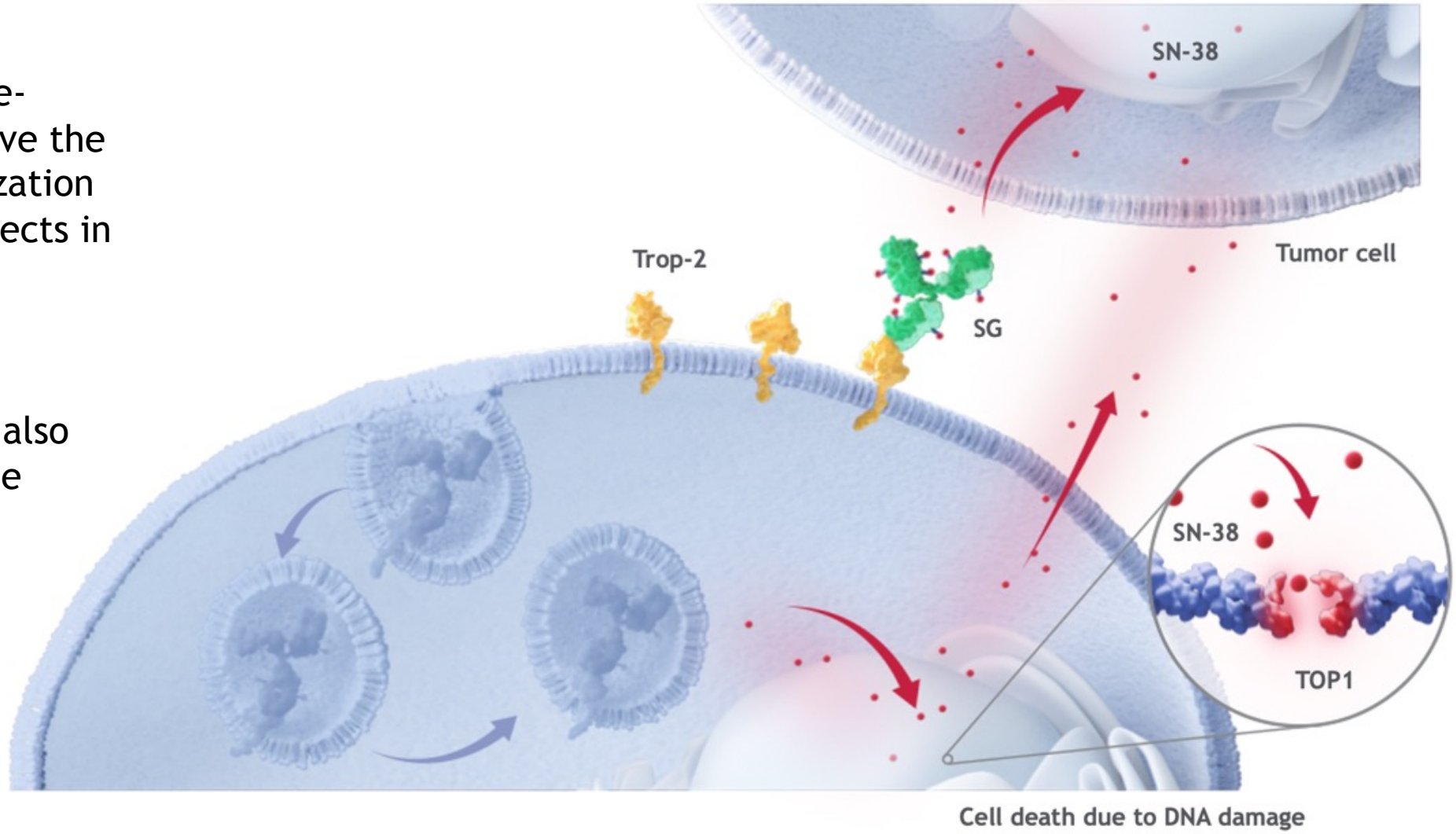


NEW CLASS OF TREATMENT: ANTICORPS MONOCLONAUX CONJUGUES

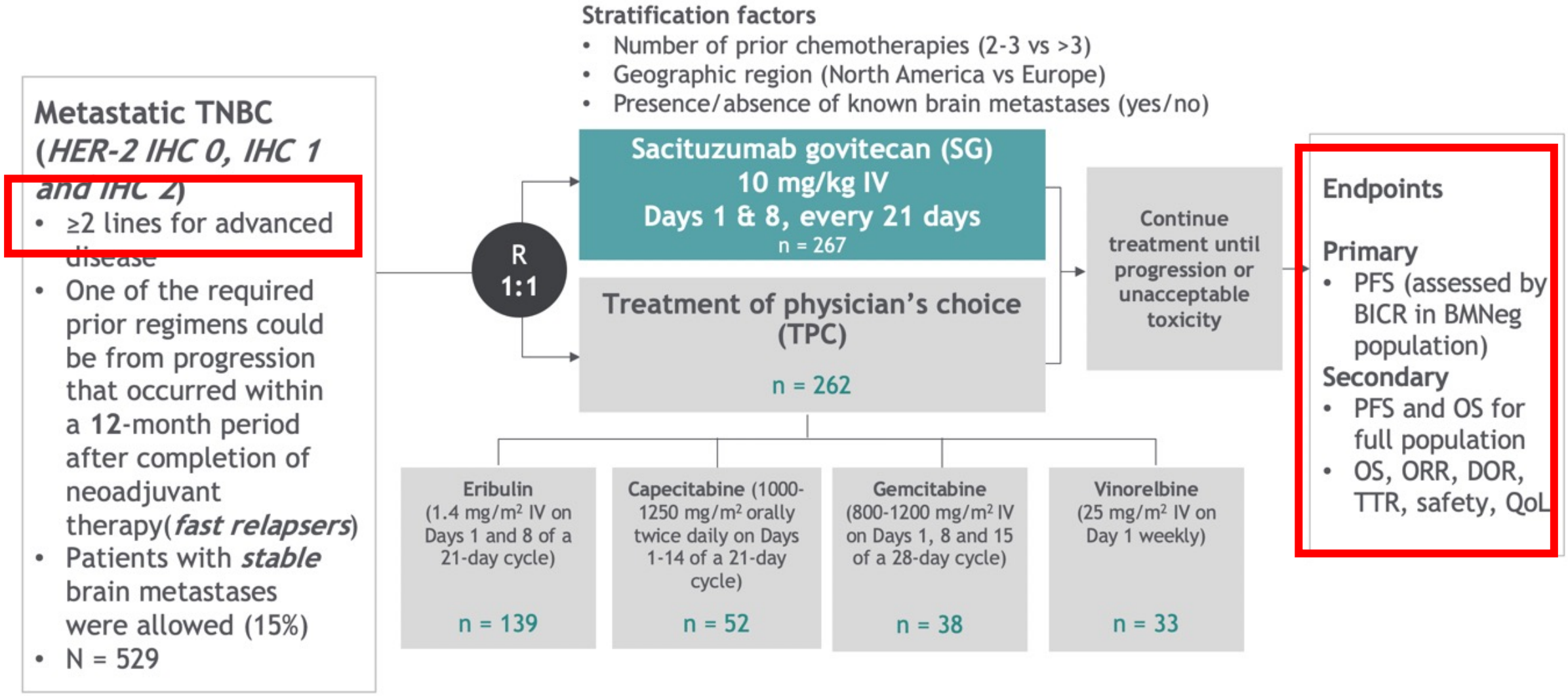
SACITUZUMAB GOVITECAN(SG)

BYSTANDER EFFECT

- Free SN-38 is membrane-permeable and may leave the cell after ADC internalization and elicit antitumor effects in adjacent tumor cells
- Extracellularly released SN-38 in the tumor microenvironment may also permeate and act on the targeted tumor cell



ACCENT trial design



.Bardia A, et al. *N Engl J Med*. 2021;384(16):1529-1541

ACCENT trial results

The NEW ENGLAND JOURNAL of MEDICINE

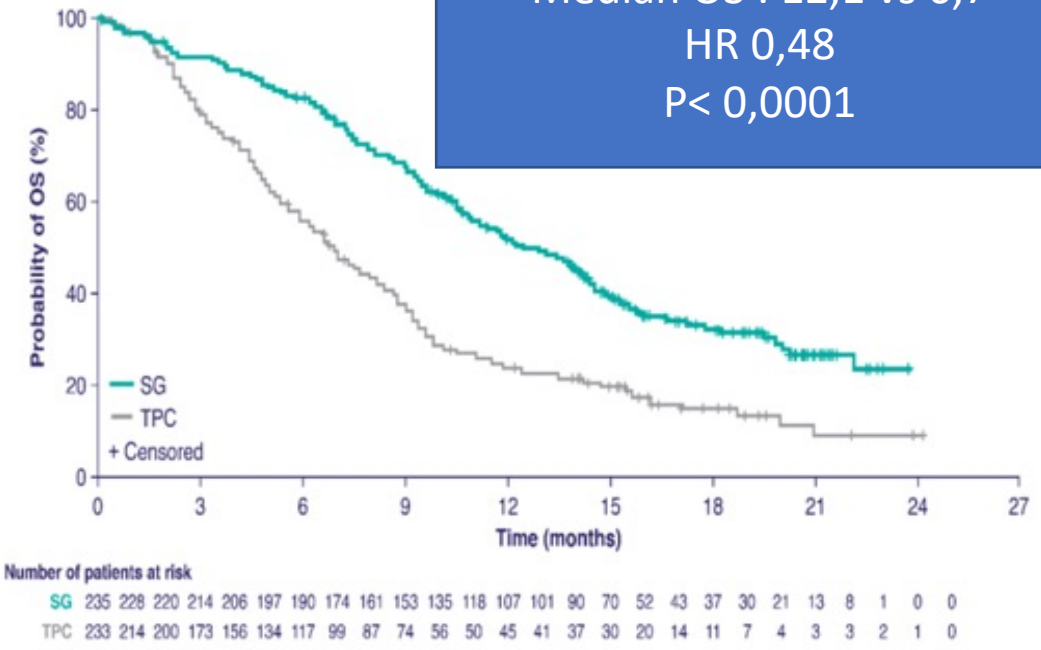
ORIGINAL ARTICLE

Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

A. Bardia, S.A. Hurvitz, S.M. Tolaney, D. Loirat, K. Punie, M. Oliveira, A. Brufsky, S.D. Sardesai, K. Kalinsky, A.B. Zelnak, R. Weaver, T. Traina, F. Dalenc, P. Aftimos, F. Lynce, S. Diab, J. Cortés, J. O'Shaughnessy, V. Diéras, C. Ferrario, P. Schmid,

ASCENT: Sacituzumab Associated With 52% Increase in OS!

Median OS : 12,1 vs 6,7
HR 0,48
P< 0,0001



Treatment-related discontinuation rates: Sacituzumab 4.7%, TPC 5.4%

TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

		SG (n=258)			TPC (n=224)		
	TRAE*	All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	Neutropenia†	63	46	17	43	27	13
	Anemia‡	34	8	0	24	5	0
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	Diarrhea	59	10	0	12	<1	0
	Nausea	57	2	<1	26	<1	0
	Vomiting	29	1	<1	10	<1	0
Other	Fatigue	45	3	0	30	5	0
	Alopecia	46	0	0	16	0	0

Toxicity: neutropenia and diarrhea

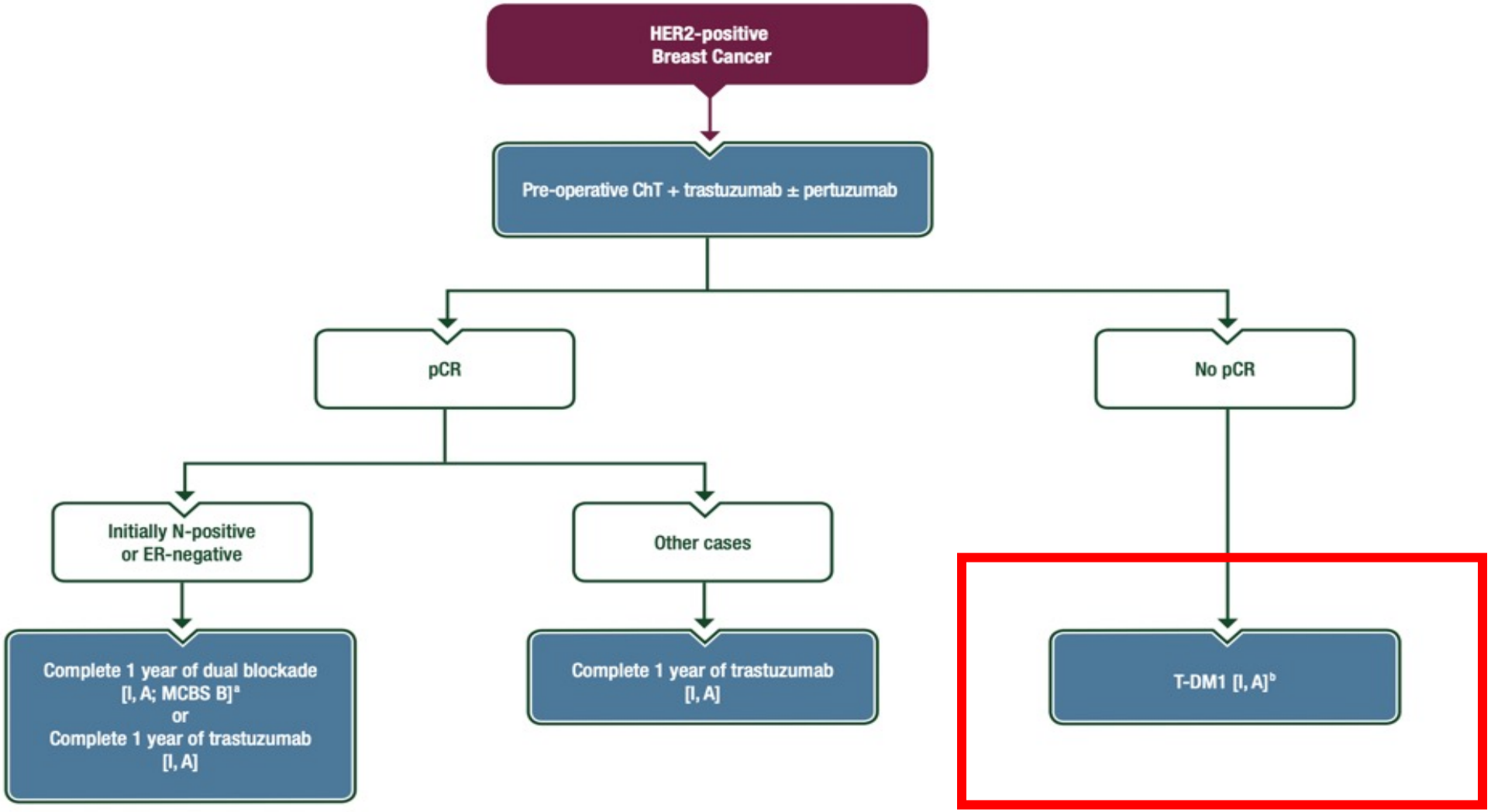
Sacituzumab approved for metastatic TNBC with at least one line of prior Tx

.Bardia A, et al. *N Engl J Med*. 2021;384(16):1529-1541

CANCER HER2 POSITIF

PLACE DES ADCs anti HER2

HER2 BC maladie localisée



Annals of Oncology 30: 1194–1220, 2019

NEW CLASS OF TREATMENT: ANTICORPS MONOCLONAUX CONJUGUES

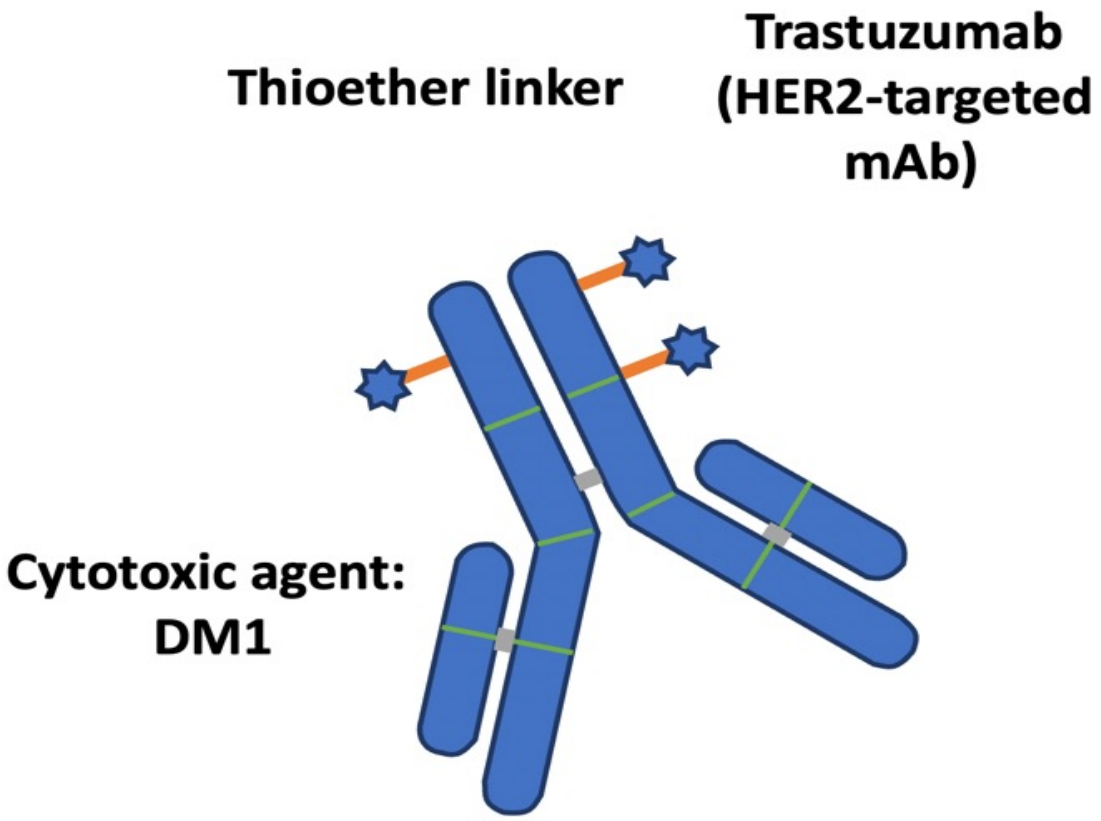
ado-Trastuzumab-Emtansine (T-DM1)

Tumor antigen: HER2

Antibody: monoclonal antibody trastuzumab

Linker: systemically stable thioether, no cleavable

Cytotoxic drug payload: DM1, a highly potent tubulin destabilizer (up to 400 times more potent than paclitaxel)



Lewis Phillips et al. Cancer Res. 2008.

KATHERINE: T-DM1 superior to Trastuzumab for HER2+ Residual Disease

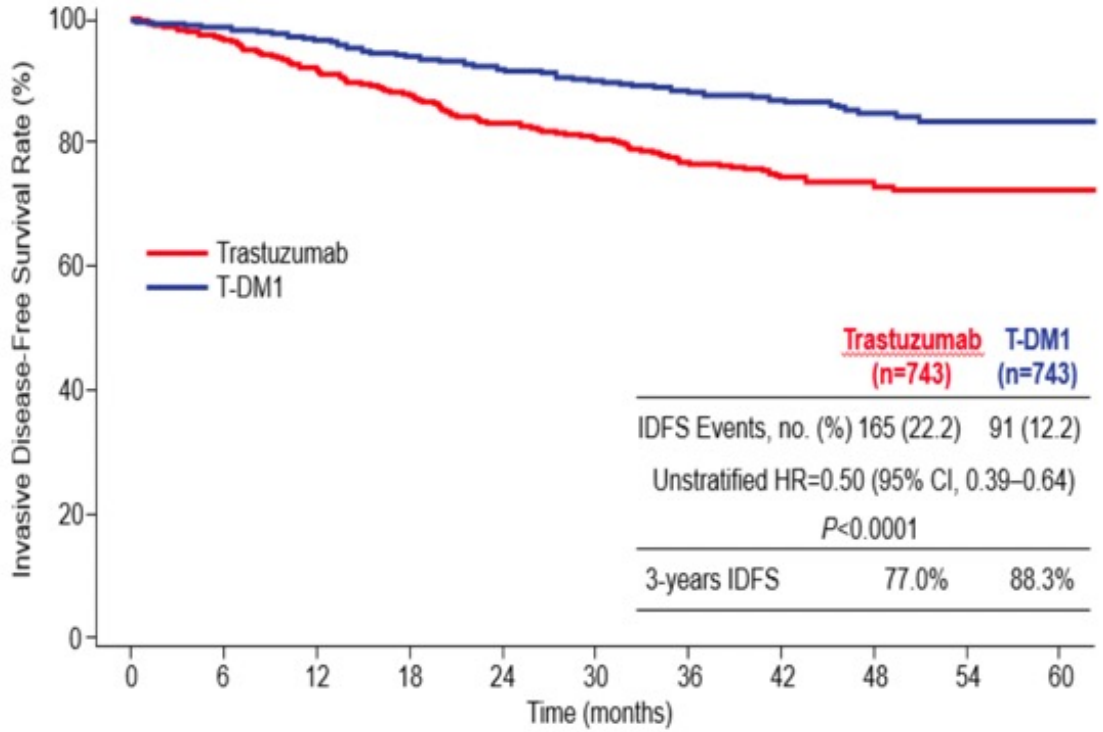
- Centrally confirmed HER2-positive breast cancer
- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Received neoadjuvant therapy consisting of
  - Minimum of 6 cycles of chemotherapy
  - Minimum of 9 weeks of taxane+ trastuzumab
- Pathologic residual invasive tumor in breast or axilla

R 1:1

N=1486

T-DM1
3.6 mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles



Primary endpoint:
Invasive DFS
Secondary endpoints:
DFS,OS,distance Recurrence free,safety

T-DM1: Standard of Care for HER+ EBC with residual disease post NAT

Von Minckwitz G, et al. N Engl J Med 2019;380:617-628.

NEW CLASS OF TREATMENT: ANTICORPS MONOCLONAUX CONJUGUES

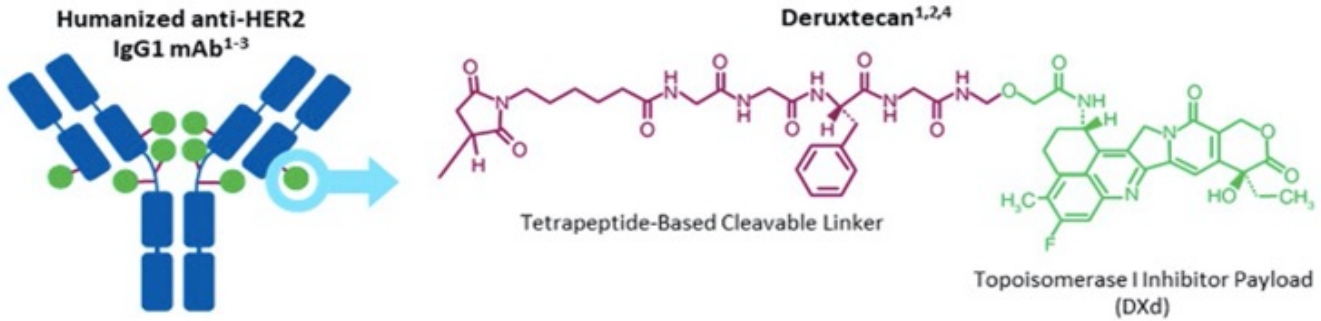
TRASTUZUMAB DERUXTECAN

NOUVEAU LINKER!!!!!!

T-DXd is a Novel ADC Designed to Deliver an Antitumor Effect

T-DXd is an ADC with 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



- T-DXd is being clinically evaluated across a number of HER2-expressing or mutated cancers, including breast cancer, CRC, non-small cell lung cancer, and others

BYSTANDER KILLING EFFECT

Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate.

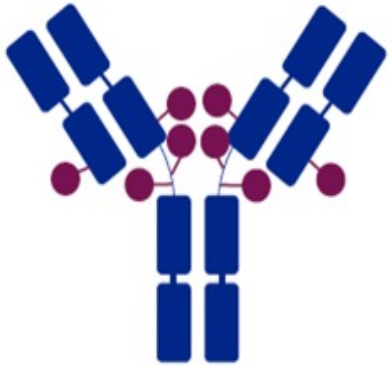
1. Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142. 4. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

PRESENTED BY: Prof Salvatore Siena; Università degli Studi di Milano, Milan, Italy; salvatore.siena@unimi.it

HER2 BC maladie métastatique

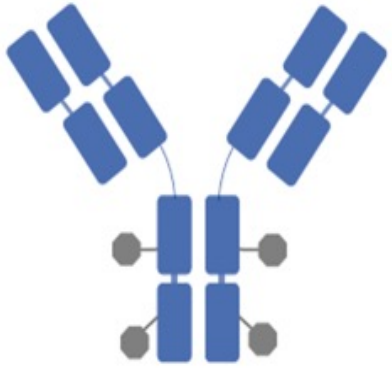
HER2 Targeting ADCs with similar mAB Backbone

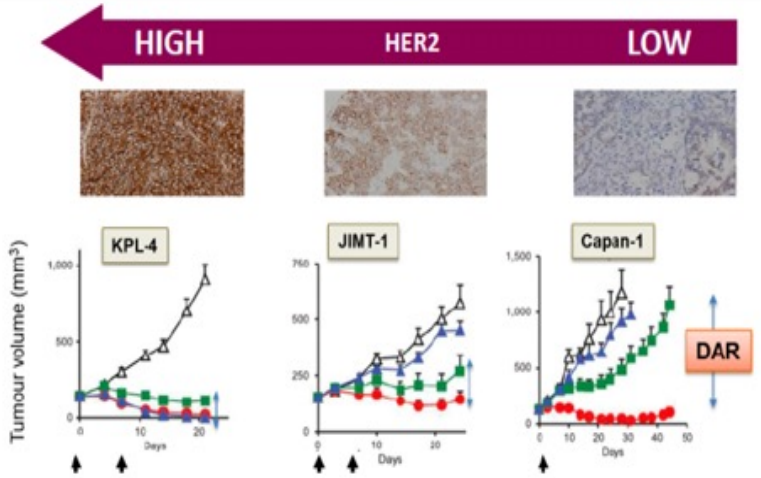
Trastuzumab deruxtecan (T-DXd)



T-DXd	ADC Attributes	T-DM1
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)

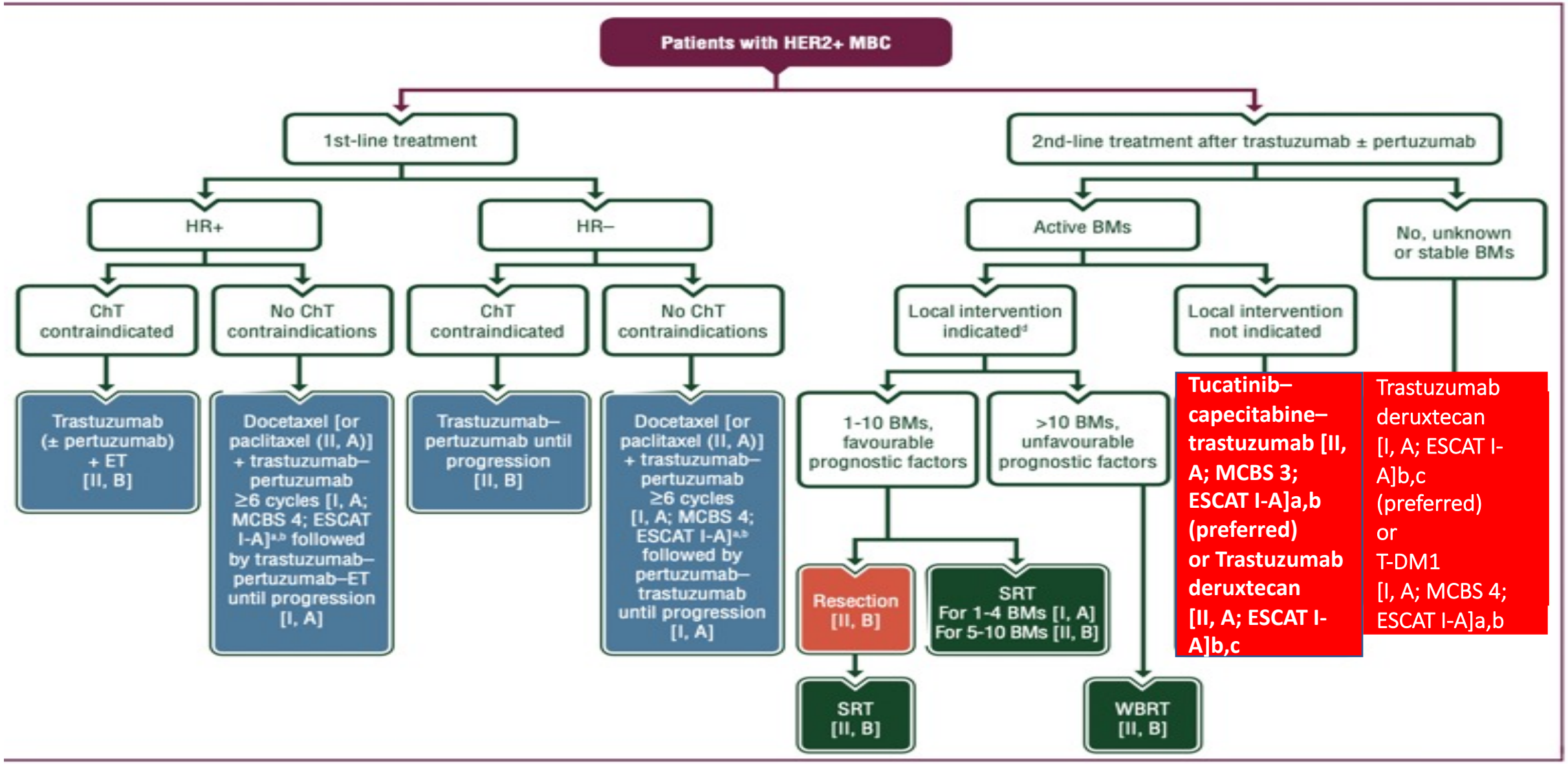




High membrane permeability
T-DXd is active in a wide range of models

Cortès J. ESMO 2021

HER2 BC maladie métastatique

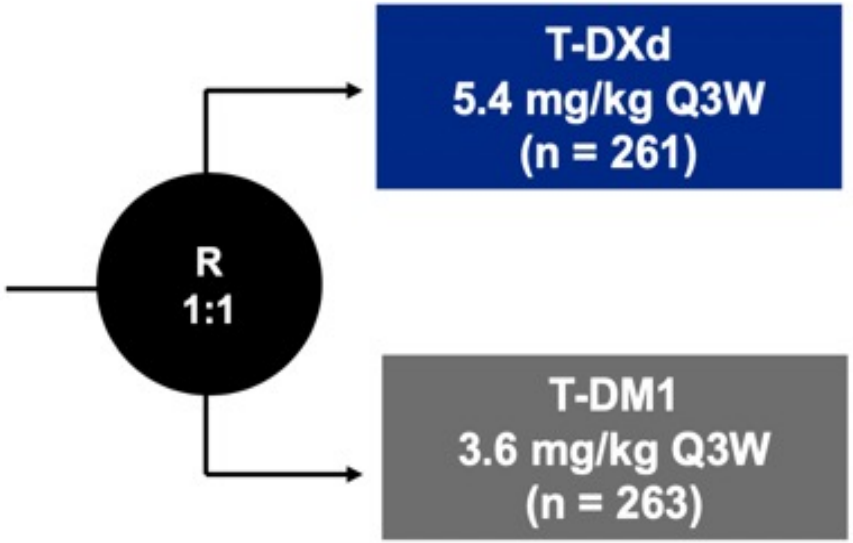


Annals of Oncology 30: 1194–1220, 2019

HER2 BC maladie métastatique

DESTINY BREAST-03 trial design

Patients
- Unresectable or metastatic HER2-positive breast cancer
- **Previously treated with trastuzumab and taxane in advanced/metastatic setting**
- Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

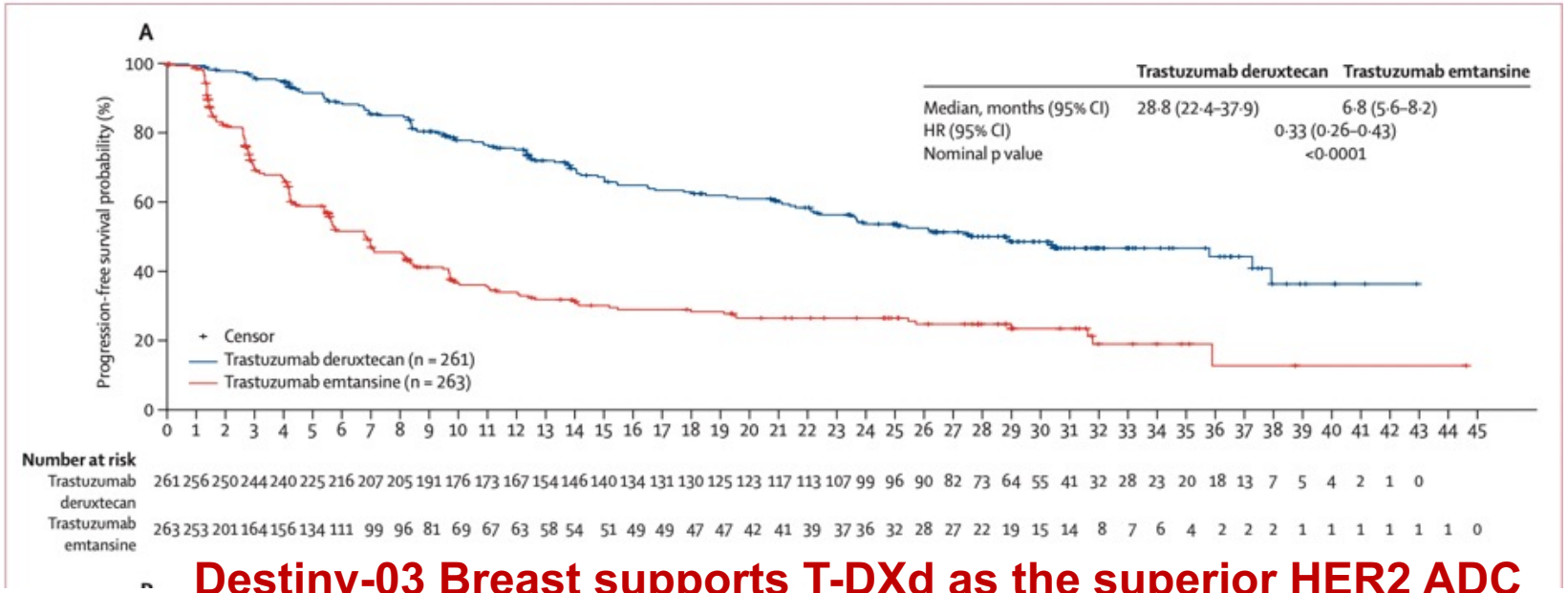
Median study follow-up
- **T-DXd arm: 28.4 months (range, 0.0-46.9 months)**
- **T-DM1 arm: 26.5 months (range, 0.0-45.0 months)**

Prior therapy for MBC:
100% received prior trastuzumab
~60% received prior pertuzumab
~15% received other HER2 Tx
Median lines of prior tx: 2
One line of Tx: ~40%

Hurvitz S, SABC 2022/***Lancet* 2023; 401: 105–17**

HER2 BC maladie métastatique

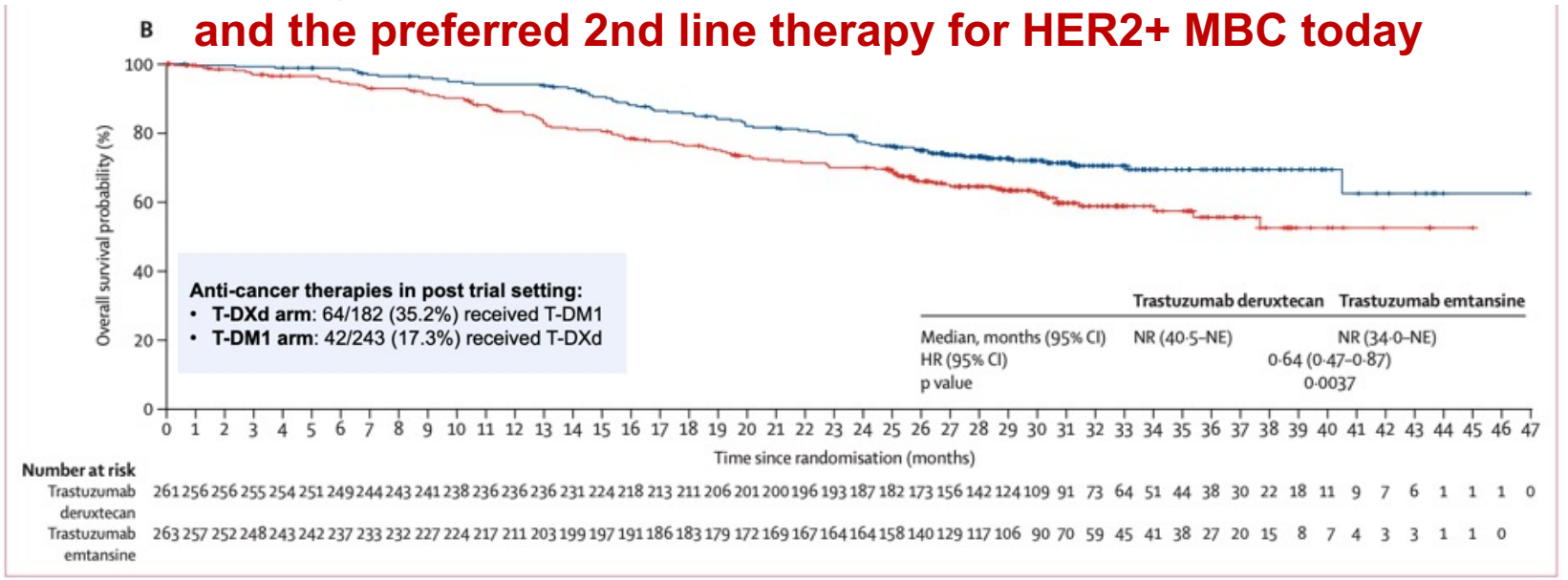
DESTINY BREAST-03 trial Results (recent update)



PFS: 28,8 vs 6,8 HR 0,33
P< 0,0001

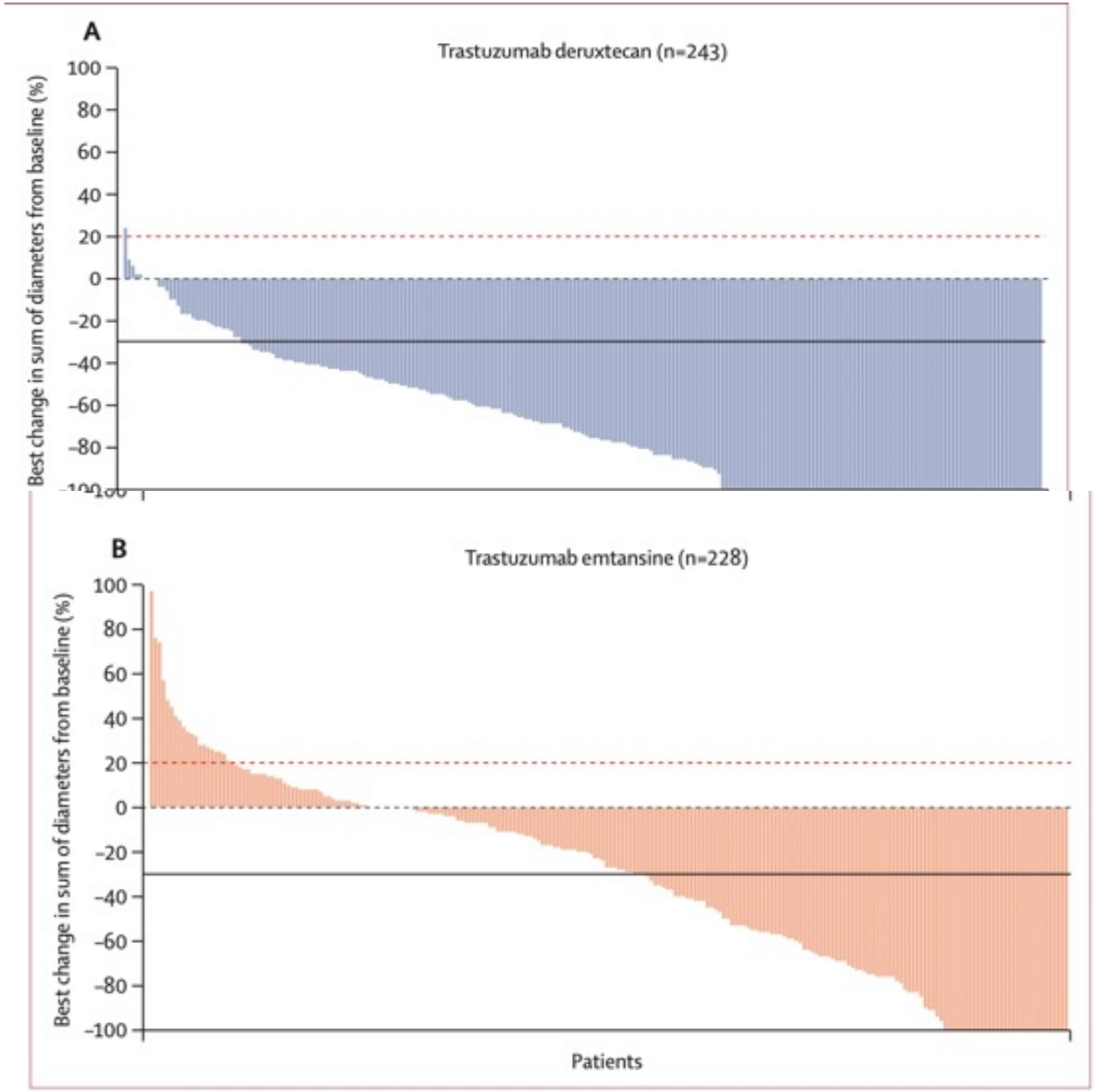
OS: NR
with 28 % of events in T-DXd vs 37 %
HR 0,64
P **0.0037**

Destiny-03 Breast supports T-DXd as the superior HER2 ADC and the preferred 2nd line therapy for HER2+ MBC today



Hurvitz,SABCC 2022
***Lancet* 2023; 401: 105–17**

HER2 BC maladie métastatique



DESTINY BREAST-03 trial Results (recent update)

	T-DXd n = 261[a]	T-DM1 n = 263[a]
Confirmed ORR by BICR		
n (%)	205 (**78.5**)	92 (**35.0**)
[95% CI]	[73.1-83.4]	[29.2-41.1]
Nominal *P* value	< 0.0001	
CR, n (%)	55 (**21.1**)	25 (**9.5**)
PR, n (%)	150 (57.5)	67 (25.5)
SD, n (%)	47 (18.0)	110 (41.8)
PD, n (%)	3 (1.1)	47 (17.9)
NE, n (%)	6 (2.3)	14 (5.3)
CBR, n (%) [95% CI]	233 (89.3) [84.9-92.8]	122 (46.4) [40.2-52.6]
Nominal *P* value	< 0.0001	

Response rates:

CR rates of 21%

ORR 78.5%

***Lancet* 2023; 401: 105–17**

HER2 BC maladie métastatique

DESTINY BREAST-03 trial toxicity

	Trastuzumab deruxtecan group (n=257)		Trastuzumab emtansine group (n=261)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Blood and lymphatic system disorders				
Anaemia	95 (37%)	24 (9%)	51 (20%)	17 (7%)
Platelet count decreased*	64 (25%)	20 (8%)	114 (44%)	52 (20%)
White blood cell count decreased	60 (23%)	16 (6%)	16 (6%)	2 (<1%)
Gastrointestinal disorders				
Nausea	198 (77%)	18 (7%)	79 (30%)	1 (<1%)
Vomiting	133 (52%)	4 (2%)	28 (11%)	2 (<1%)
Constipation	96 (37%)	0	51 (20%)	0
Diarrhoea	83 (32%)	3 (1%)	21 (8%)	2 (<1%)
General disorders				
Fatigue	79 (31%)	15 (6%)	53 (20%)	2 (<1%)
Headache	61 (24%)	1 (<1%)	40 (15%)	0
Investigations				
Neutrophil count decreased†	79 (31%)	41 (16%)	30 (11%)	8 (3%)
Aspartate aminotransferase increased	72 (28%)	2 (<1%)	108 (41%)	14 (5%)
Alanine aminotransferase increased	59 (23%)	4 (2%)	83 (32%)	12 (5%)
Metabolism and nutrition disorders				
Decreased appetite	78 (30%)	4 (2%)	46 (18%)	1 (<1%)
Bodyweight decreased	58 (23%)	6 (2%)	23 (9%)	2 (<1%)
Skin and subcutaneous disorders				
Alopecia	102 (40%)	1 (<1%)‡	9 (3%)	0

Event, n (%)	T-DXd n = 257	T-DM1 n = 261
Grade 1	11 (4)	4 (2)
Grade 2	26 (10)	3 (1)
Grade 3	2 (<1)	1 (<1)
Grade 4	0	0
Grade 5	0	0
Overall	39 (15)	8 (3)

ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

drug-related ILD/pneumonitis

15 % vs 3 %

But lower grade 3 than other trials

Better knowledge and early treatment

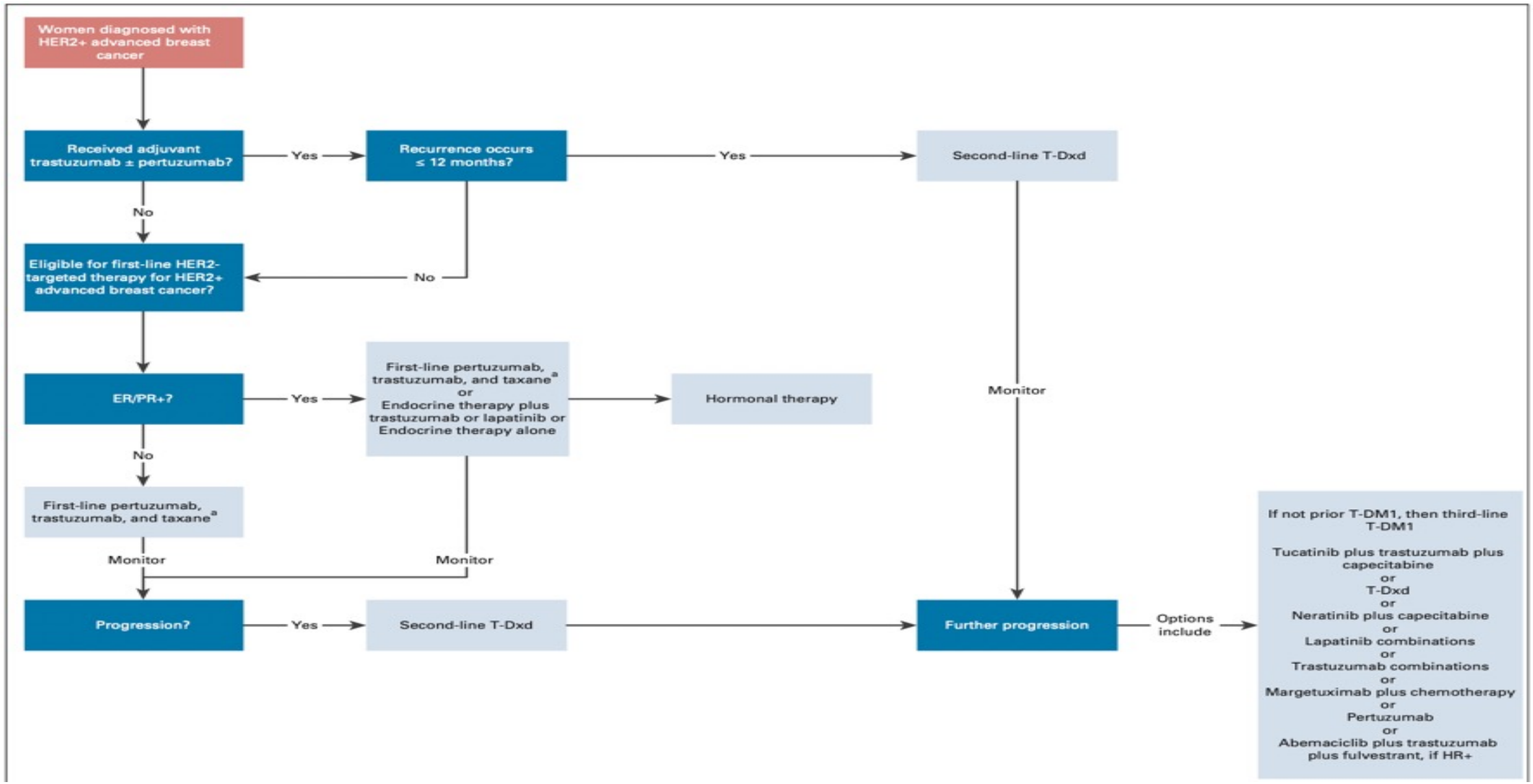
Standard 2nd line

BUT IN BELGIUM reimbursement pending

MNP 3rd line and beyond

***Lancet* 2023; 401: 105–17**

HER2 positive mBC: ASCO GUIDELINES UPDATE 2022



CONCLUSIONS
ET
PERSPECTIVES

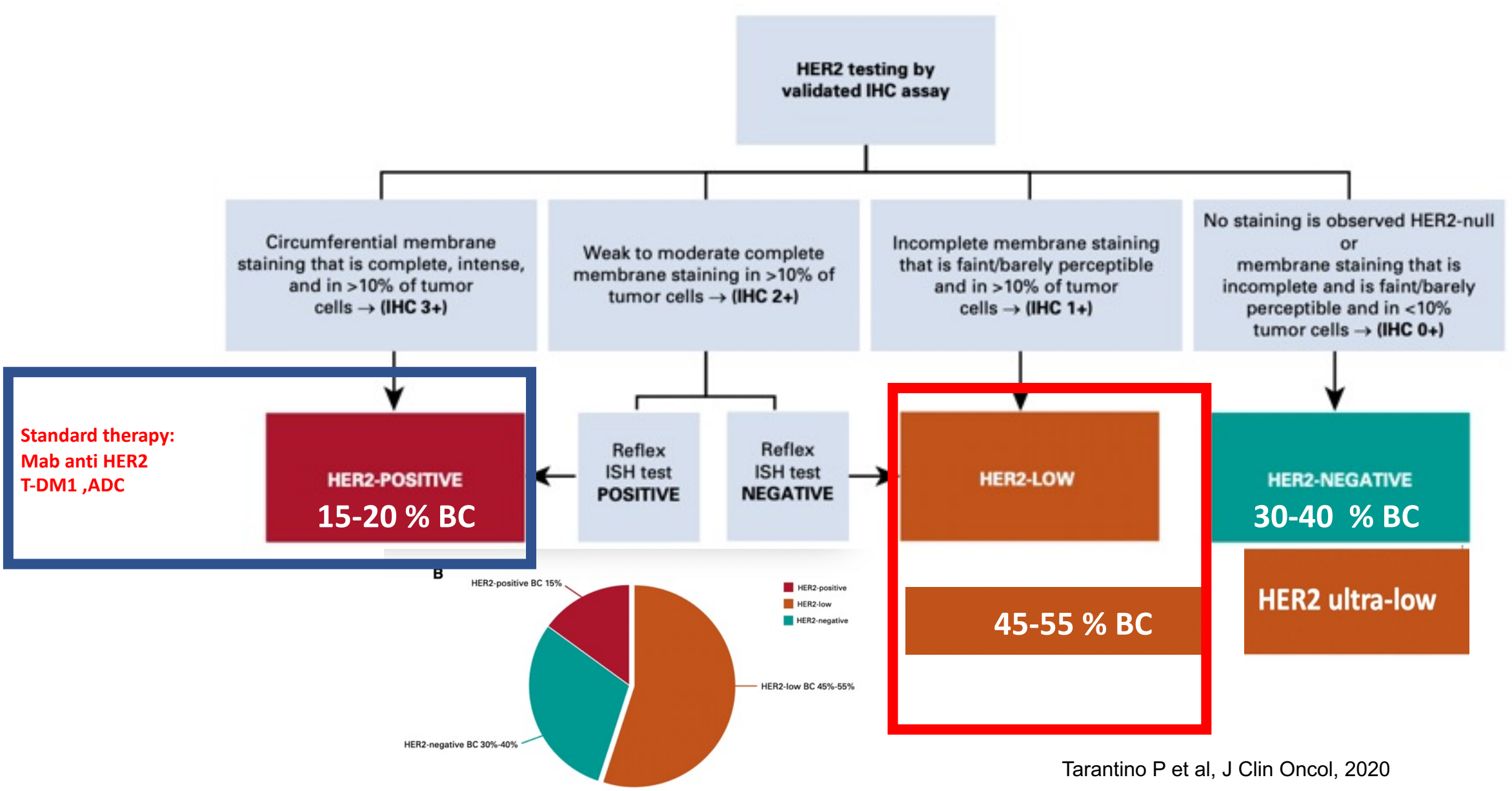
L'immunothérapie fait sa place dans le cancer du sein triple négatif à la fois en maladie localement avancée mais aussi métastatique

MAIS l'avancée la plus importante, après les inhibiteurs de cycline kinase (HR +) est l'arrivée des nouveaux ANTICORPS MONOCLONAUX CONJUGUES avec linker clivable et effet sur les cellules du micro-environnement tumoral

TOUS les sous types peuvent en bénéficier y compris HR +

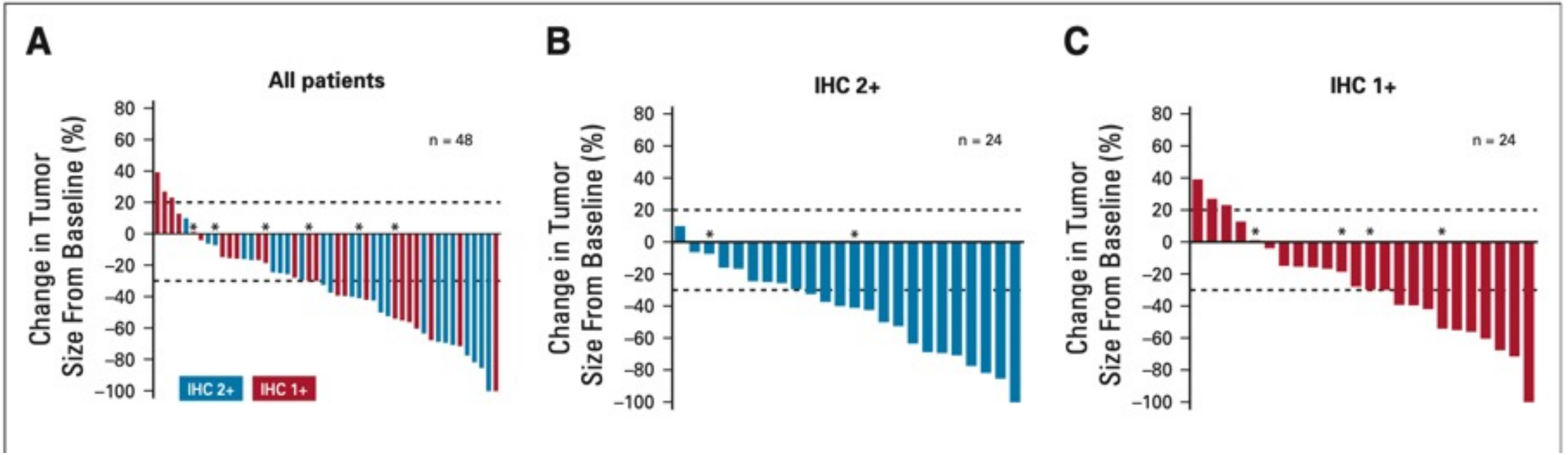
- **HER2 ++ SISH+/HER2+++:trastuzumab deruxtecan**
- **HER2 low…probablement ultra-low :trastuzumab deruxtecan**
- **TROP2 comme cible: cancer du sein et autre cancer**
    - **Sacituzumab govitecan, Datopotamab Deruxtecan …**

Evolving concepts in HER2 evaluation in breast cancer: Heterogeneity, HER2-low carcinomas and beyond



Tarantino P et al, J Clin Oncol, 2020

NEW ADC AND TUMOR HETEROGENEITY: HER2 TARGET EFFICACY EVEN IN LOW HER2 BC AND GC



HEAVILY PRE TREATED PATIENT

ORR(overall response rate) =44 %
Median duration of response= 11 months

Modi,JCO,2020

DESTINY-Breast04: First randomized ph 3 of T-DXd in the HER2-Low mBC

An open-label, multicenter study (NCT03734029)

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[d]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

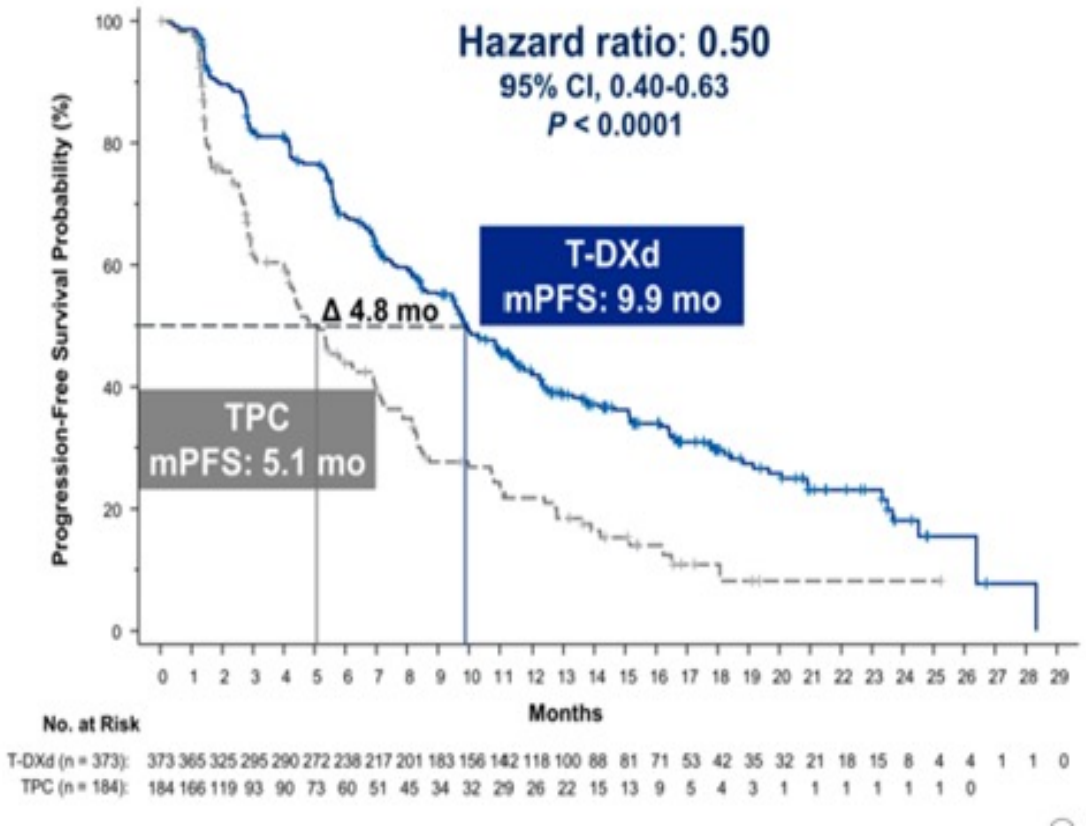
Stratification factors
- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) vs HR−

Modi S ASCO 2022

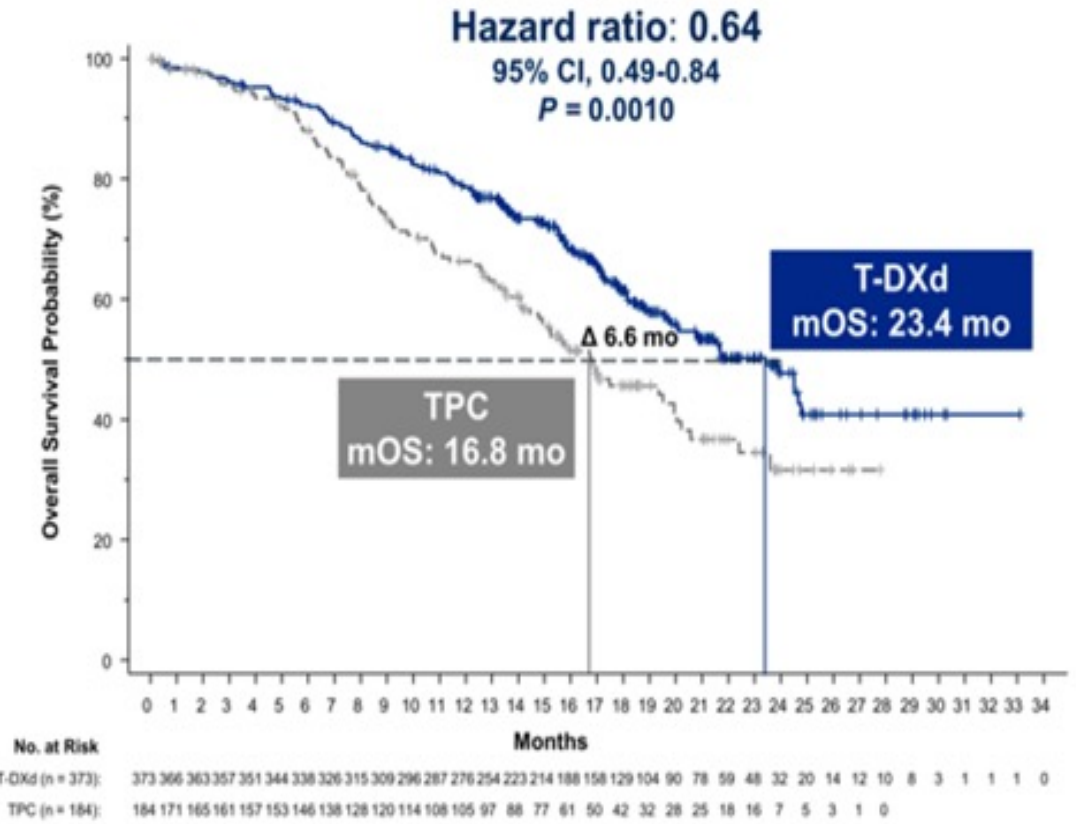
DESTINY-BREAST 04 RESULTS

HER2-LOW

Progression Free Survival



Overall Survival



2022 FDA Approved T-DXd as the new SOC for HER2 (1+ or 2+/ISH-)Low MBC

Mody,ASCO 2022/NEJM,2022

TROP-2

TROPiCS-02: A Phase 3 Study of SG in HR+/HER2- Locally Recurrent Inoperable or Metastatic Breast Cancer

NCT03901339

Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]:

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
  - (Neo)adjuvant therapy for early-stage disease qualified as a prior line of chemotherapy if disease recurred within 12 months
- Measurable disease by RECIST 1.1

N=543

R 1:1

Treatment was continued until progression or unacceptable toxicity

Sacituzumab govitecan
10 mg/kg IV
days 1 and 8, every 21 days
n=272

Treatment of physician's choice[b]
(capecitabine, vinorelbine, gemcitabine or eribulin)
n=271

Stratification:
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)

Endpoints

Primary
- PFS by BICR

Secondary
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

[a]Disease histology based on the ASCO/CAP criteria. [b]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IV, intravenously; LIR, local investigator review; (Neo)adjuvant, neoadjuvant or adjuvant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

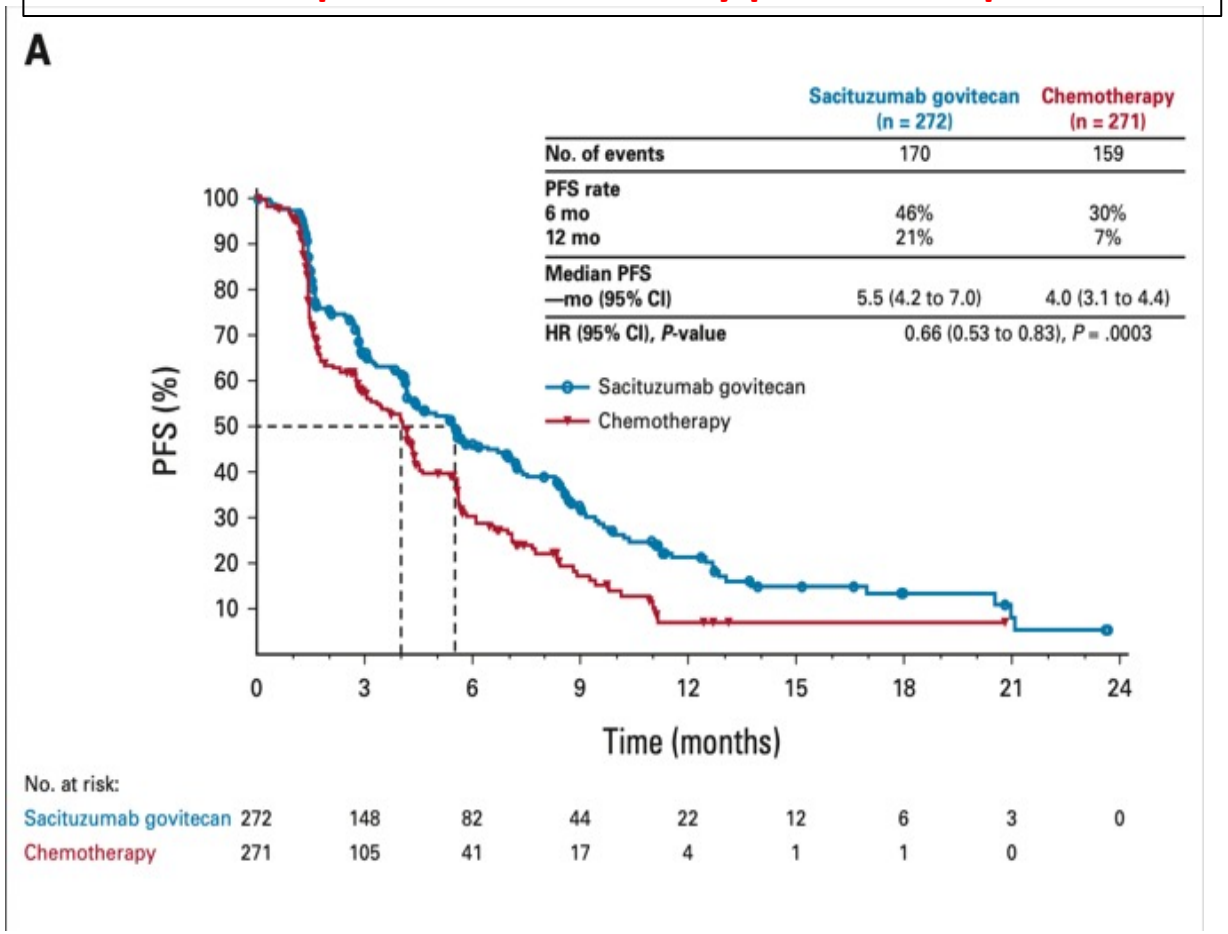
RUGO ASCO 2022

TROPICS-02 RESULTS

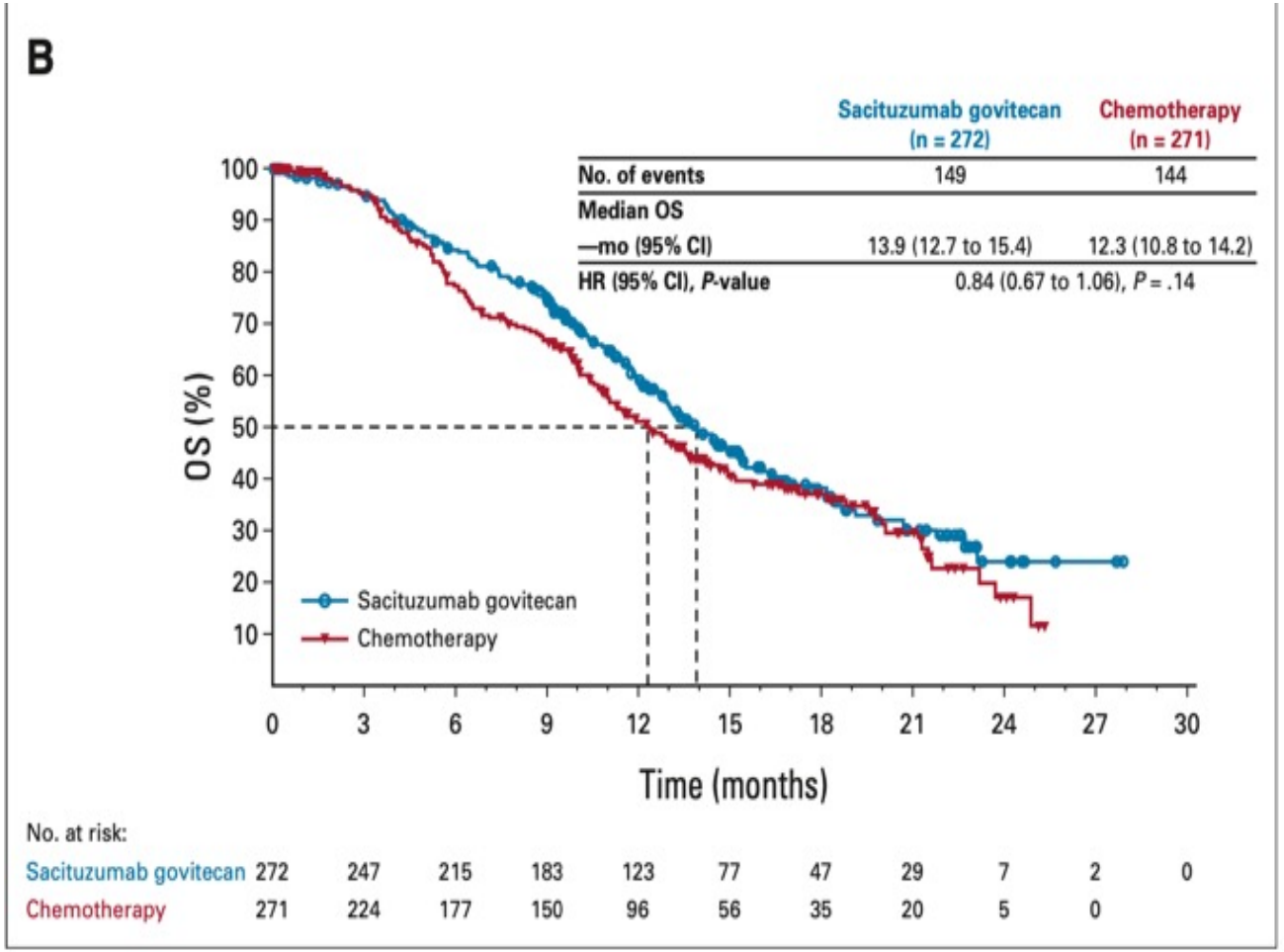
TROP-2

PRIMARY endpoint PFS + in heavily pre treated patient

A

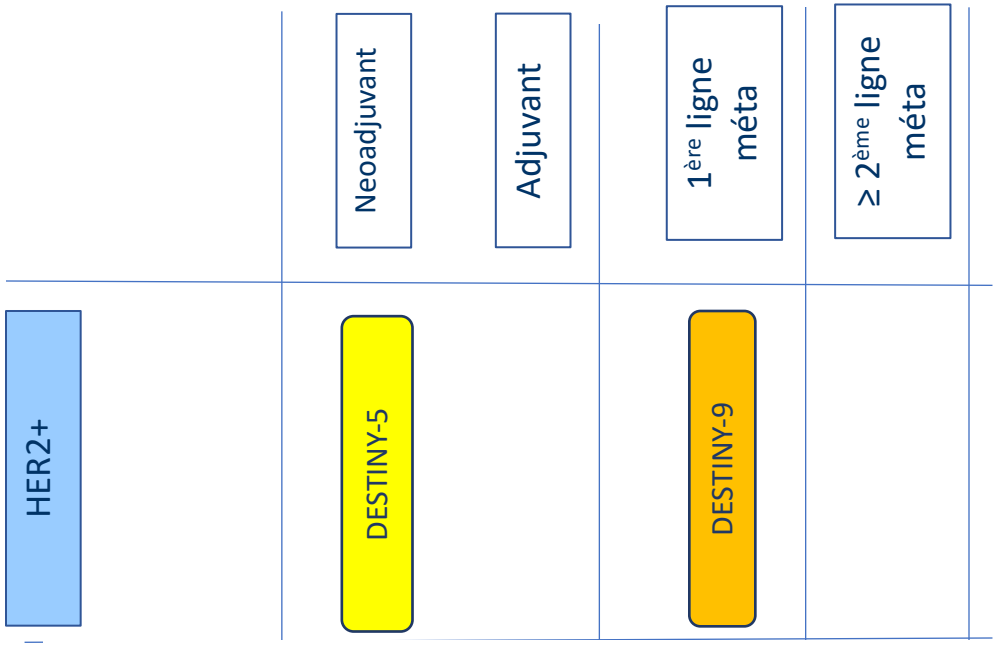


B



Benefit regardless of TROP-2 expression level

Rugo,JCO 2023



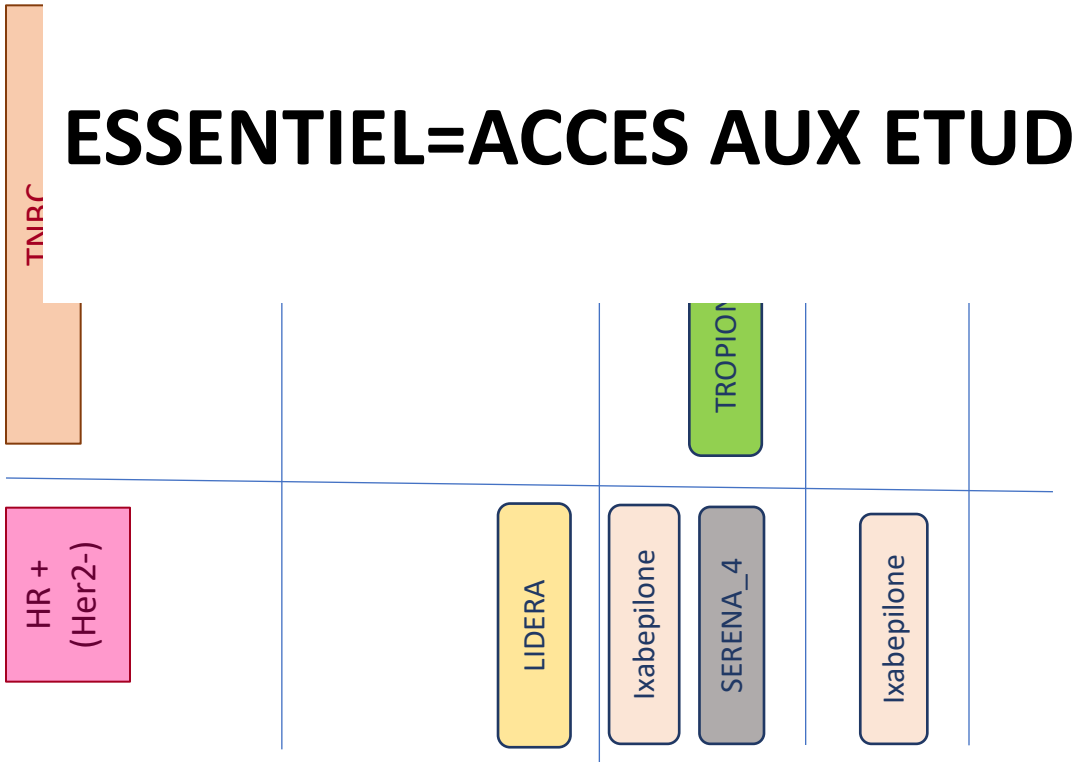
Cancers du sein

Destiny-5
(**Trastu + T-DXd** vs **TDM-1**)
- **Homme/femme**
- Her2 positif **IHC 3+ et/ou FISH +**
- 1-4, N0-3, M0 diagnostique Tumeurs bilatérales OK si les 2 sont Her2 positif et/ou 3+
- **Résidu post chir : sein ou ganglion**

T-DXt

Destiny - 9
(**T-DXd + Pertu** vs **T-DXd + placebo** vs **Taxane - Trastu - Pertu**)
- - Her2 positif **IHC 3+ ou FISH +** et statut récepteur sur méta (Biopsie) (confirmation central HER +)
- rechute > 6mois dernier trastu +/-Pertu

ESSENTIEL=ACCES AUX ETUDES CLINIQUES

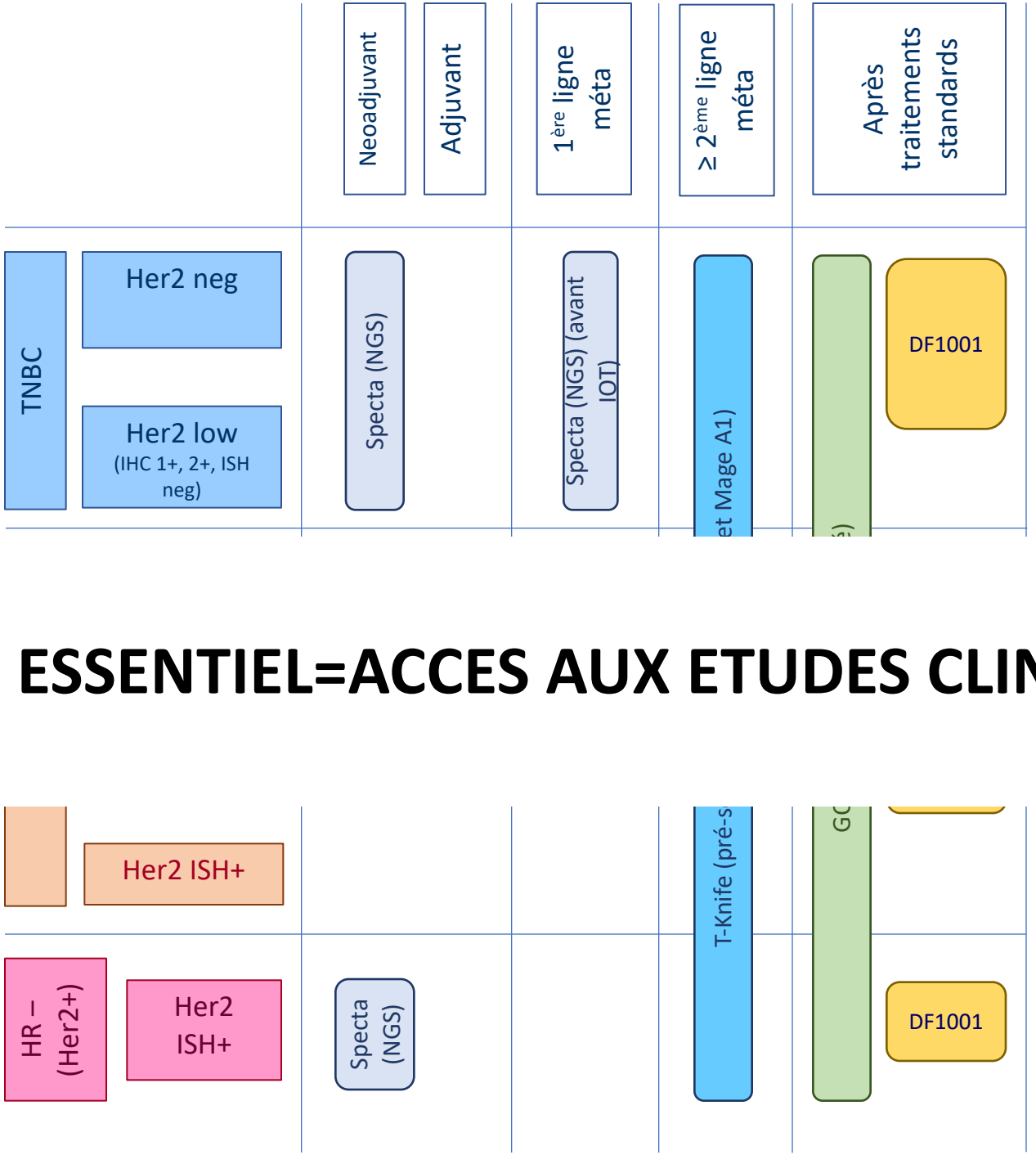


Tropion-2
- **Her2 neg ER/PR < 1% - eligible pour Pacli ou Nab-Pacli**
- **De Novo OK si eligible pour Nab pacli ou Pacli dans bras contrôle**
- RECIST 1.1 mesurable
- DFI > 12 mois
- PDL1 neg ou si PDL + doivent avoir reçu immuno en Neo-Adj/Adj

Anti TROP-2

LIDERA
Giredestrant vs Tamoxifene ou Letrozole)
- Her2 neg/ ER ≥ 1%
- N2-3 ou T4Nx
- HT seule post CT et/ou RT

SERENA-4
Oral serd AZD9833 +PALBO VS Anastrozole+PALBO
- Her2 neg ER + >10%
- RECIST 1 ,1 évaluable (mesurable ou lytrique seul)
- **Pas de *de novo***



Cancers du sein

Specta (NGS)

- Séquençage via FMI sur tissu et blood sample
- TNBC ou Her2 néoadjuvant avant traitement
- TNBC 1ère LM, treatment naive

DF1001

(cible

- GDC-6036 (KRAS inhibiteur) (P.O.)
- KRAS G12C muté

T-knife

- Pré-screen pour HLA-A 02*01
- Pré-screen pour MAGE A1
- CarT cells

ESSENTIEL=ACCES AUX ETUDES CLINIQUES

AVANCEES THERAPEUTIQUES DANS LE CANCER DU SEIN TRIPLE NEGATIF ET HER2 POSITIF

CHU de Liège

J Collignon, Medical Oncologist
GI and BREAST CANCER
BOARD MEMBER of Belgian Society of Senology