CEFPAS

AIRTUM

Corso di Aggiornamento per Operatori dei Registri Tumori

CEFPAS Caltanissetta - 4, 5 e 6 Ottobre 2023

Aggiornamento sui Tumori Mammari
Il punto di vista dell'oncologo

Vincenzo Adamo

Coordinatore Rete Oncologica Siciliana

DECLARATION OF INTERESTS

During the past three years prof. Vincenzo Adamo received honoraria for consultant, advisory roles, and speaker bureau by:

Astra Zeneca
Daichii-Sankyo
Gilead
GSK
Lilly
MSD
Novartis
Pfizer
Seagean
Servier
Veracyte

Figura D.1 u – Incidenza proporzionale prime 10 cause tumorali (Sicilia; tutte le età; uomini)

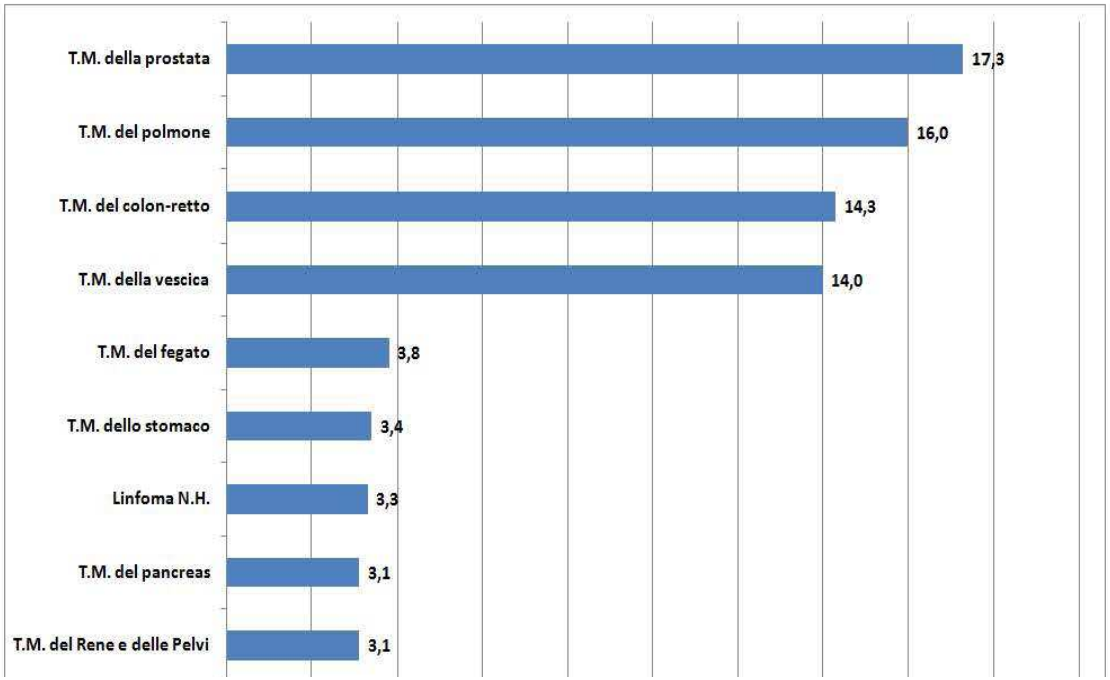


Figura F.1 u. – Mortalità proporzionale per tumori (Sicilia; tutte le età; uomini)

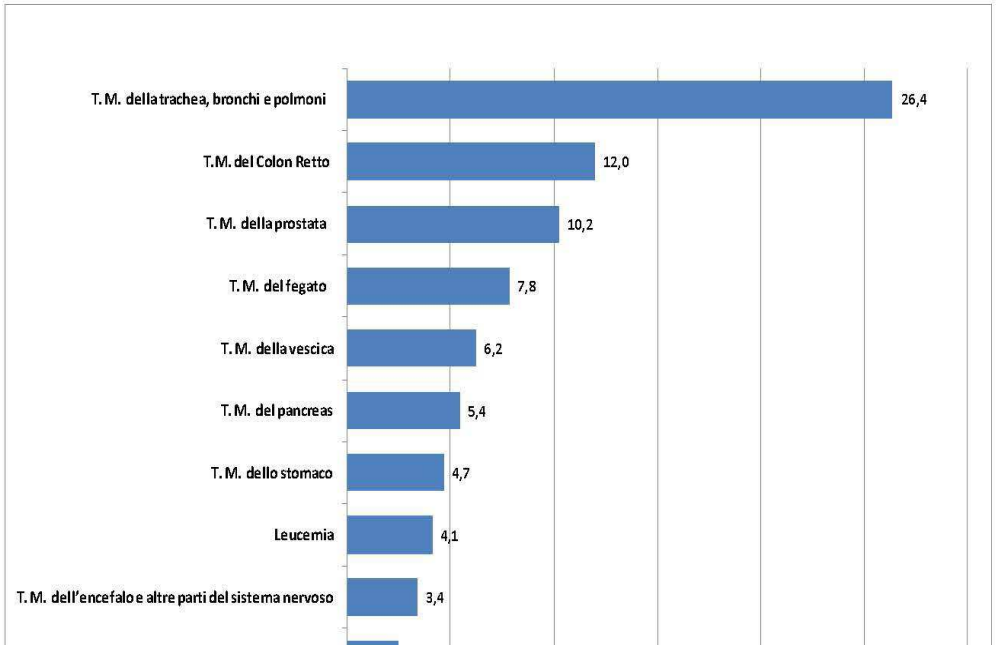


Tabella B. Rapporto U/D

Incidenza			
	Uomini	Donne	U/D
cinomi della cute)	391.0	312.9	1.
	9.5	3.8	2.
	2.1	0.4	5.
	12.9	7.0	1.
	53.7	37.1	1.
	14.5	5.6	2.
	5.4	4.5	1.
	11.6	9.2	1.
	8.6	0.9	9.

Tabella D. Trend di incidenza per le principali sedi anni 2003-2014

Incidenza		
ede	Uomini	Donne
utte (escluso carcinomi della cute)	↓	↑
ADS	↓	=
sofago	=	=
tomaco	↓	↓
olon-Retto	=	=
egato	↓	↓
ie biliari	=	↓
ancreas	=	↑
olmone	↓	↑
elanoma	↑	↑
esotelioma	=	=
ammella		↑
tero collo		=
tero corpo		=

Incidenza

Incidenza

Sede	Uomini		Donne	
	Sicilia	Italia	Sicilia	Italia
Tutte (escluso carcinomi della cute)	↓	↓	↑	↓
VADS	↓	↓	=	=
Stomaco	↓	↓	↓	↓
Colon-Retto	=	↓	=	↓
Fegato	↓	↓	↓	↓
Pancreas	=	↑	↑	=
Polmone	↓	↓	↑	↑
Melanoma	↑	↑	↑	↑
Mammella			↑	↑
Prostata	=	↓		
Rene	=	=	=	=
Vescica	↓	↓	↑	=
Tiroide	↑	↑	=	↑
Linfoma Hodgkin	=	=	=	↓

Sede	Sicilia	Italia	Sicilia	Italia

Mortalità

Sede	Uomini		Donne	
	Sicilia	Italia	Sicilia	Italia
Tutte (escluso carcinomi della cute)	↓	↓	=	↓
VADS	=	↓	↑	=
Stomaco	↓	↓	=	=
Colon-Retto	=	↓	=	↓
Fegato	↓	↓	↓	↓
Pancreas	=	=	=	=
Polmone	↓	↓	↑	↑
Melanoma	↑	=	=	=
Mammella			=	↓
Prostata	↓	↓		
Rene	↑	=	=	=
Vescica	=	=	=	=
Tiroide	=	=	↓	↓
Linfoma Hodgkin	=	↓	=	↓

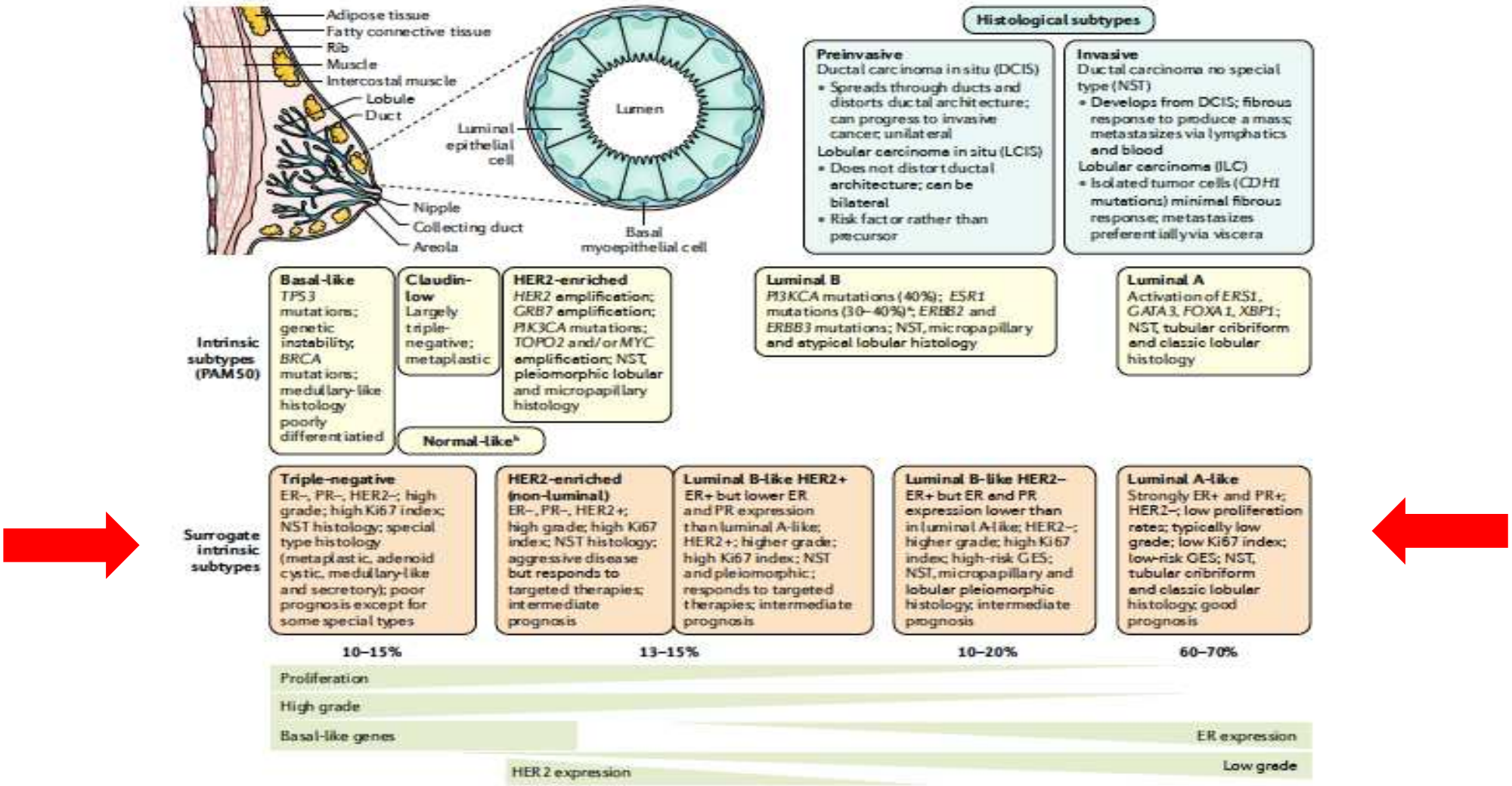
Sopravvivenza

Tutti, donne	57	60	60	63
Mammella	81	85	85	87
Prostata	78	88	88	91
Colon-retto	56	59	60	65
Polmone	12	14	14	16

OUTLINE

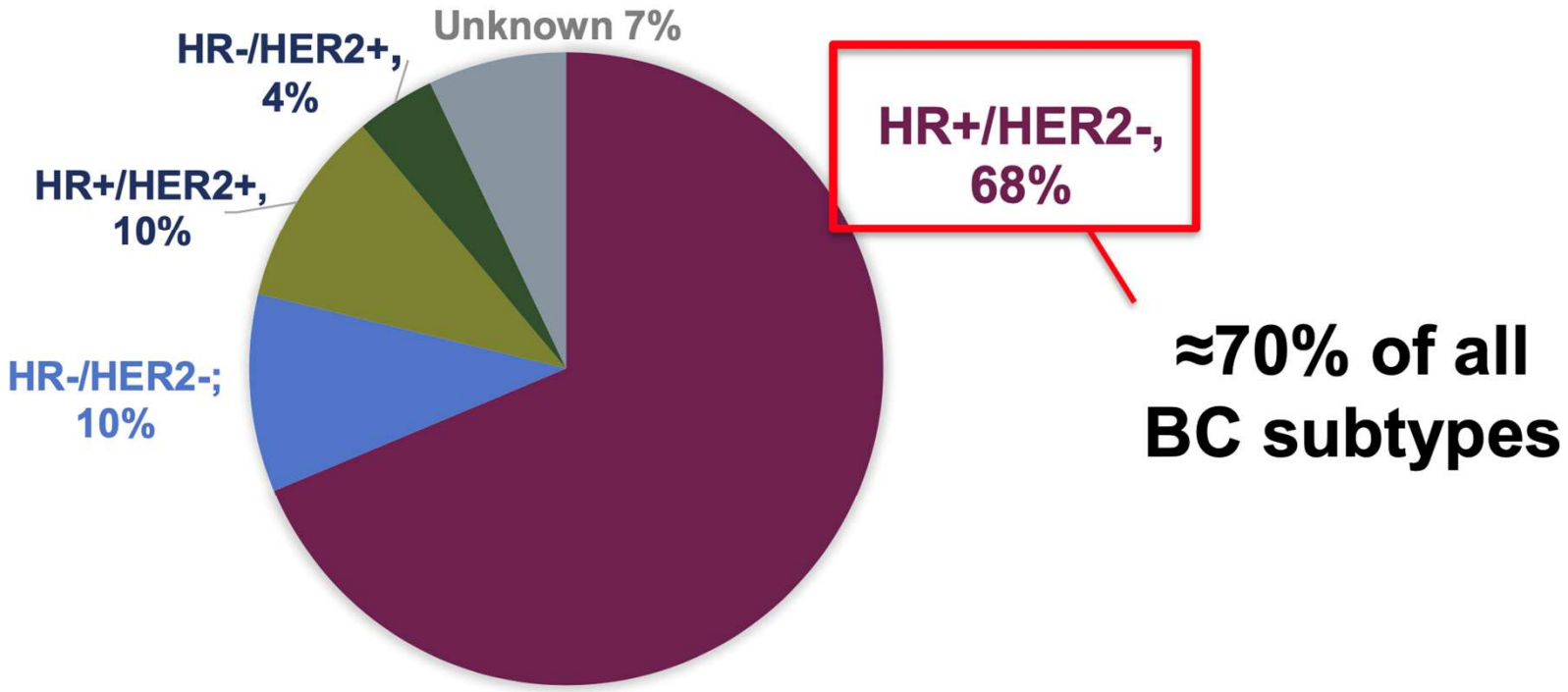
- **The actually therapeutic landscape in HR+HER2- Early BC**
- **How can we decrease the relapse risk during the first 5 years and beyond ?**
- **The new therapeutic paradigm in the adjuvant setting in High risk**
- **The actually and the future therapeutic landscape in Early TNBC**
- **The BRCA1-2 mutant in HR+HER2- & TN EBC**
- **The actually and the future therapeutic landscape in HER2+ Early BC**

Breast Cancer: histological and molecular characteristics



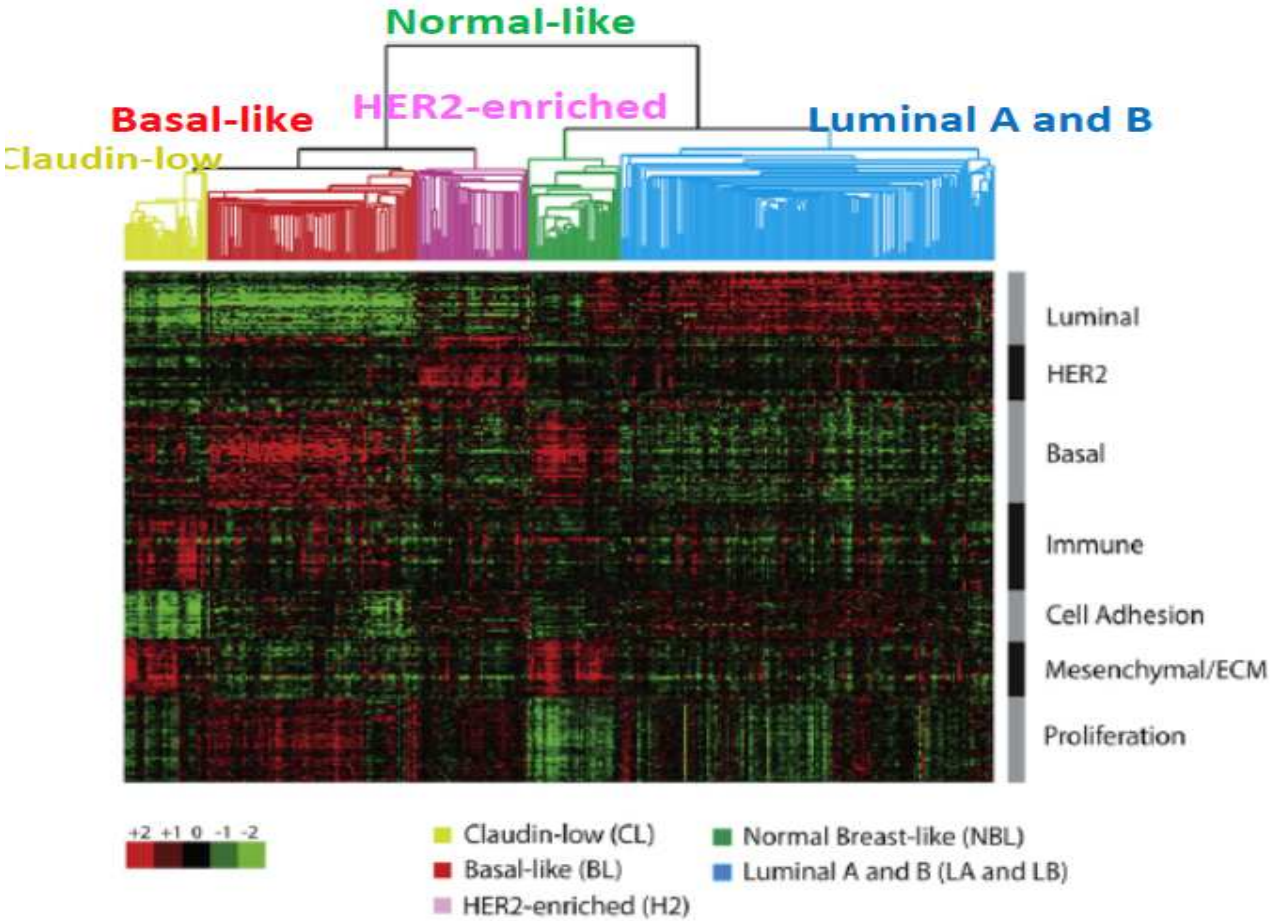
Harbeck N et al. NatRevDisPrimers. 2019 Sep23;5(1):66.

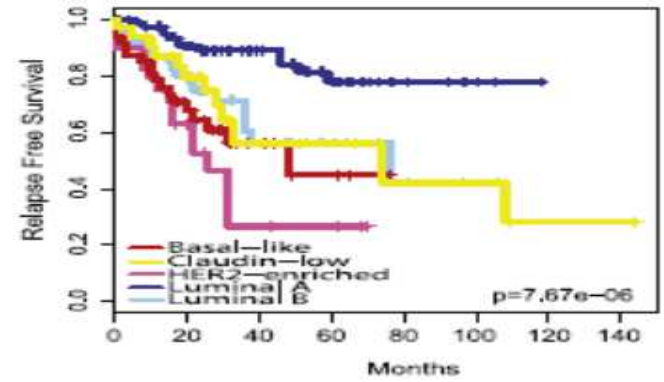
Luminal Breast Cancer is the most represented breast cancer subtype

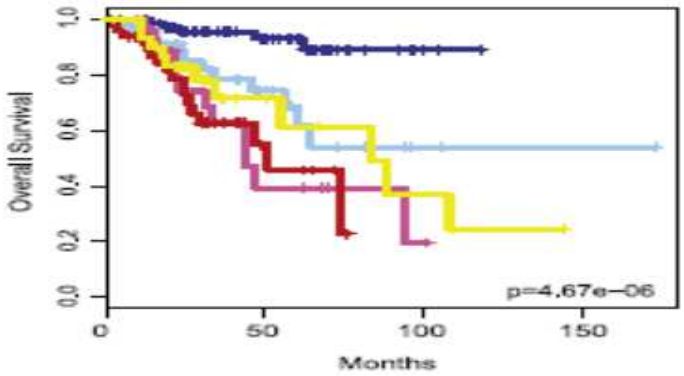


Surveillance, Epidemiology and End Results Program (SEER) 22, 2015-2019

Breast Cancer Intrinsec Molecular Subtypes







Prat A, et al. Mol. Oncol. 2011

Guideline-Recommended Biomarker Testing for Breast Cancer

HER2 per ASCO/CAP guidelines[1,2]

IHC ± dual-probe ISH assay

ER and PR[2,3]

IHC assay

Gene expression assays

To guide adjuvant chemotherapy

BRCA[4]

For:

- *TNBC (at any age)*
- *Male patients*
- *Meet criteria for personal or family history*
- *When considering olaparib as adjuvant therapy*

1. Wolff. JCO. 2018;36:2105. 2. NCCN. Clinical practice guidelines in oncology: breast cancer. v.4.2023. nccn.org.
3. Allison. JCO. 2020;38:1346. 4. NCCN. Clinical practice guidelines in oncology: genetic/familial high-risk assessment: breast, ovarian, and pancreatic. v.3.2023. nccn.org.

Treatment Individualization

100 BC patients
20% HER2+ BC
15% TN BC

65 HR+/HER2- BC patients
5% ≥4 Node positive
2-3% too frail for CT

50 HR+/HER2- BC PATIENTS POTENTIALLY CANDIDATE TO ADJUVANT CHEMOTHERAPY
BENEFIT/NO TOXICITY
BENEFIT/TOXICITY
NO BENEFIT/NO TOXICITY
NO BENEFIT/TOXICITY

SERIE GENERALE

Spediz. abb. post. - art. 1, comma 1
Legge 27-02-2004, n. 46 - Filiale di Roma

Anno 162° - Numero 161

GAZZETTA UFFICIALE

DELLA REPUBBLICA ITALIANA

PARTE PRIMA **Roma - Mercoledì, 7 luglio 2021** SI PUBBLICA TUTTI I GIORNI NON FESTIVI

MODALITÀ E REQUISITI PER L'ACCESSO AI *TEST* GENOMICI PER IL CARCINOMA MAMMARIO ORMONORESPONSIVO IN STADIO PRECOCE

BASSO RISCHIO	ALTO RISCHIO
Le seguenti 5 caratteristiche	Almeno 4 delle seguenti caratteristiche
G1 T1 (a-b)* Ki 67 <20% ER>80% N Negativo	G3 T3 T4 Ki 67>30% ER<30% N Positivo (>3 linfonodi non indicazione al *test*)
*In caso di T1a non è indicato l'accesso al *test* in presenza di almeno altri 2 parametri favorevoli	

Most Common Commercially Available Prognostic Gene Signatures for Breast Cancer

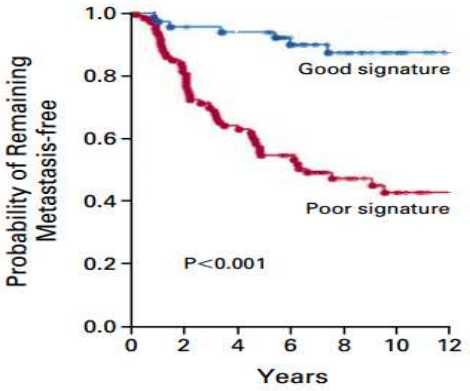
	Mammaprint	OncotypeDx	PAM50 ROR	EndoPredict	Breast Cancer Index
Method	Microarrays qRT-PCR	qRT-PCR	NannoString	qRT-PCR	qRT-PCR
Material	Frozen FFPE	FFPE	FFPE	FFPE	FFPE
Assessment	Central lab	Central lab	Local lab	Local lab	Central Lab
Population	pT1-T2, pN0, age <61	ER+	All	ER+/ HER2-	ER+
Early risk	Yes	Yes	Yes	Yes	Yes
Late risk		Moderate	Good	Good	Good
Level I evidence	Yes	Yes	Yes	Yes	Yes

Kwa M, Nat Rev Clin Oncol 2017

Predicting Baseline Prognosis

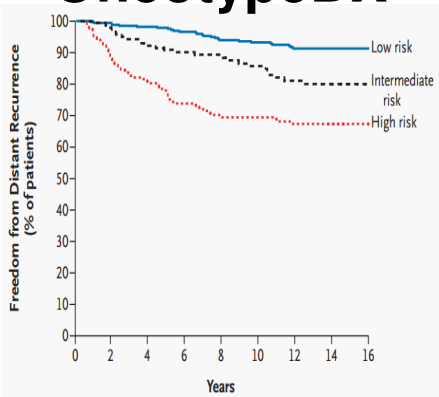
All tests have at least level IB evidence for HR+/HER2-, T1-2 and N0-1 early BC

Mammaprint



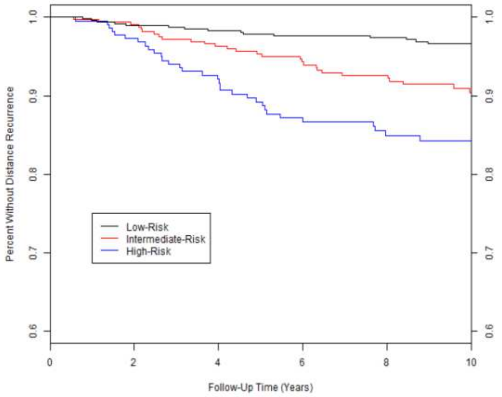
Vijver NEJM 2002

OncotypeDX



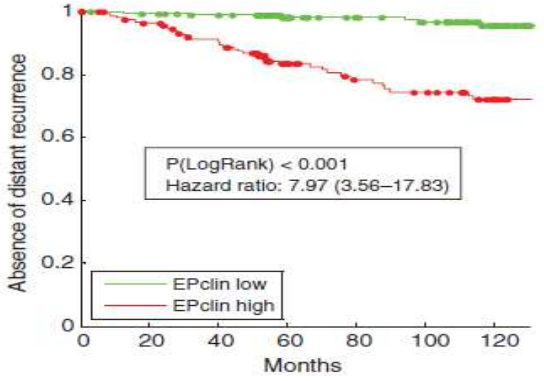
Paik NEJM 2006

PAM50 ROR



Dowsett JCO 2013

EndoPredict



Filipits CCR 2011

(include tumor size+nodal status)

Analytical Validation of Decentralized Gene Expression-based tests (only EndoPredict and PROSIGNA)

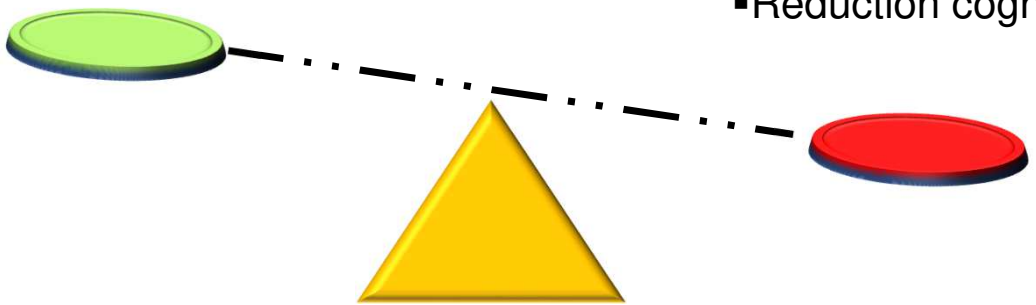
DATA FROM PROSPECTIVE RANDOMIZED TRIALS

* *FDA Approval: Mammaprint & PAM50 ROR*

Adjuvant Chemotherapy in Early Breast Cancer: Benefit/Risk Balance

Benefit
Increase Survival
(2 to12%)

Long-Term Risks
- Secondary Cancer
- Cardiac toxicity
- Early Menopause
- Reduction cognitive function



… and Socio-Economic Burden

Adpted by M. Piccart AACR 2016

Treatment of Early-Stage, HR+/HER2- Breast Cancer

Endocrine Therapy

- Tamoxifen
- Aromatase inhibitors
- Ovarian suppression (LHRH analogues) in high-risk premenopausal women
- Extended adjuvant therapy (10 yr vs 5 yr)

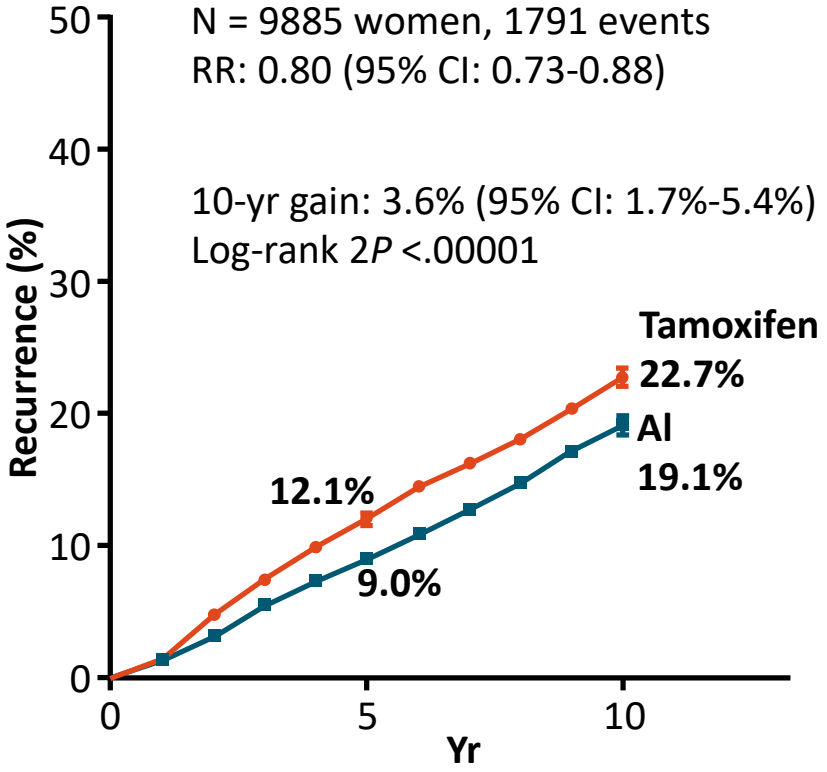
Chemotherapy

- Benefit depends on risk for recurrence and biology of the disease

Unmet Need

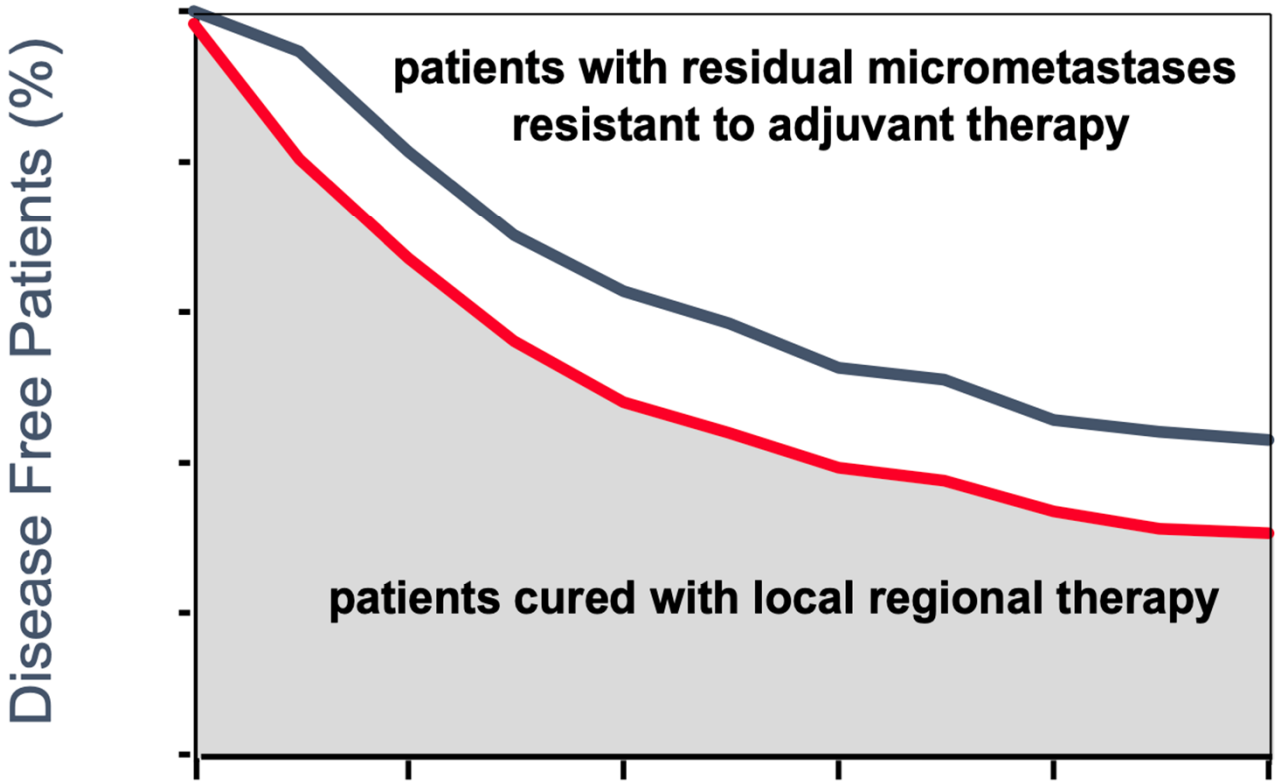
- Identifying patients with HR+ breast cancer who have primary endocrine resistance and preventing or delaying recurrence with additional therapy

Meta-analysis of 5 Yr of AI vs 5 Yr of Tamoxifen



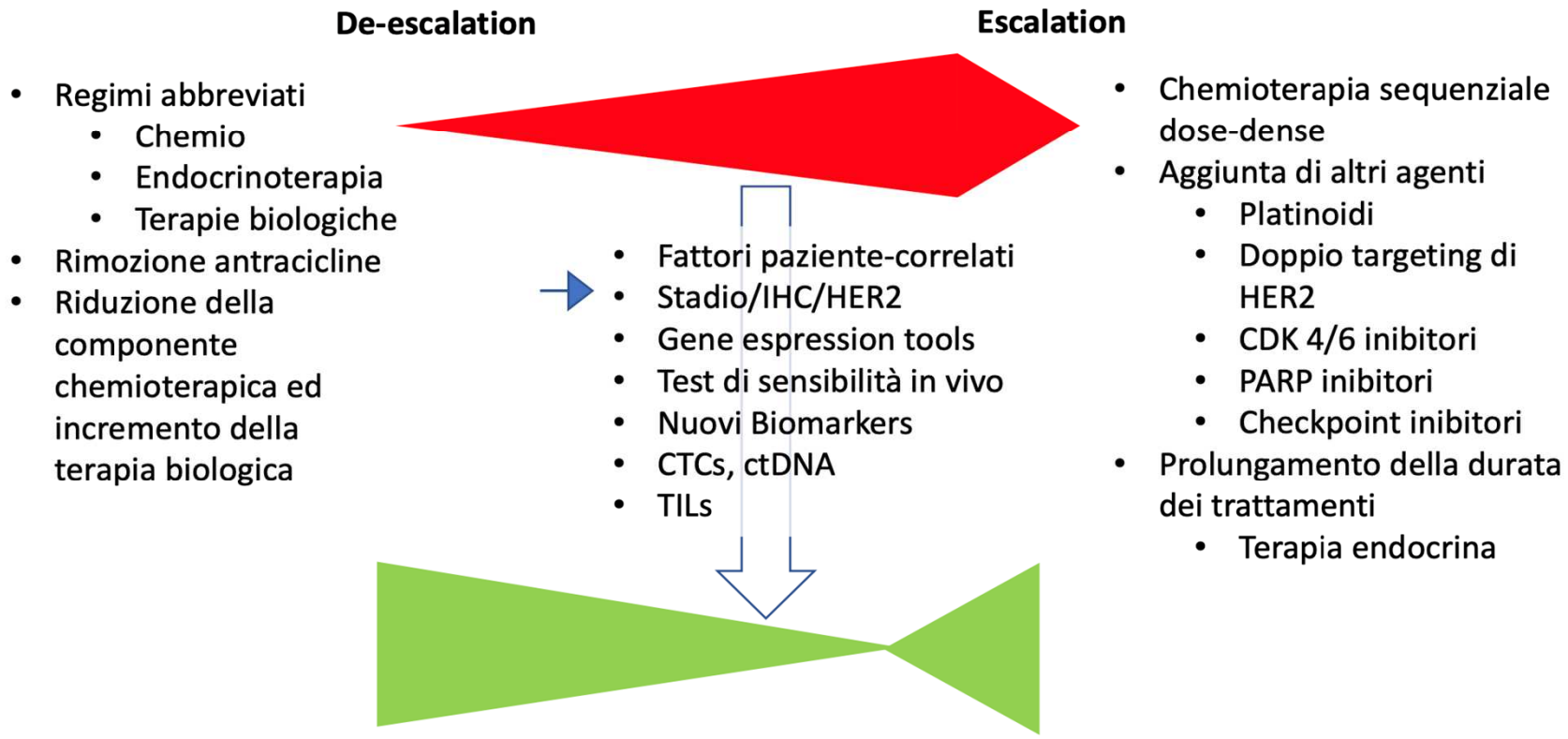
Early Breast Cancer Trialists Collaborative Group. Lancet. 2015;386:1341. Cardoso. Ann Oncol. 2019;30:1194

EBC


Disease Free Patients (%)
patients with residual micrometastases resistant to adjuvant therapy
patients cured with local regional therapy
patients with residual micrometastases sensitive to adjuvant therapy
Patients sensitive to stronger treatments
Patients sensitive to "smarter treatments"

EBC

Strategia per migliorare l'indice terapeutico dei trattamenti adiuvanti



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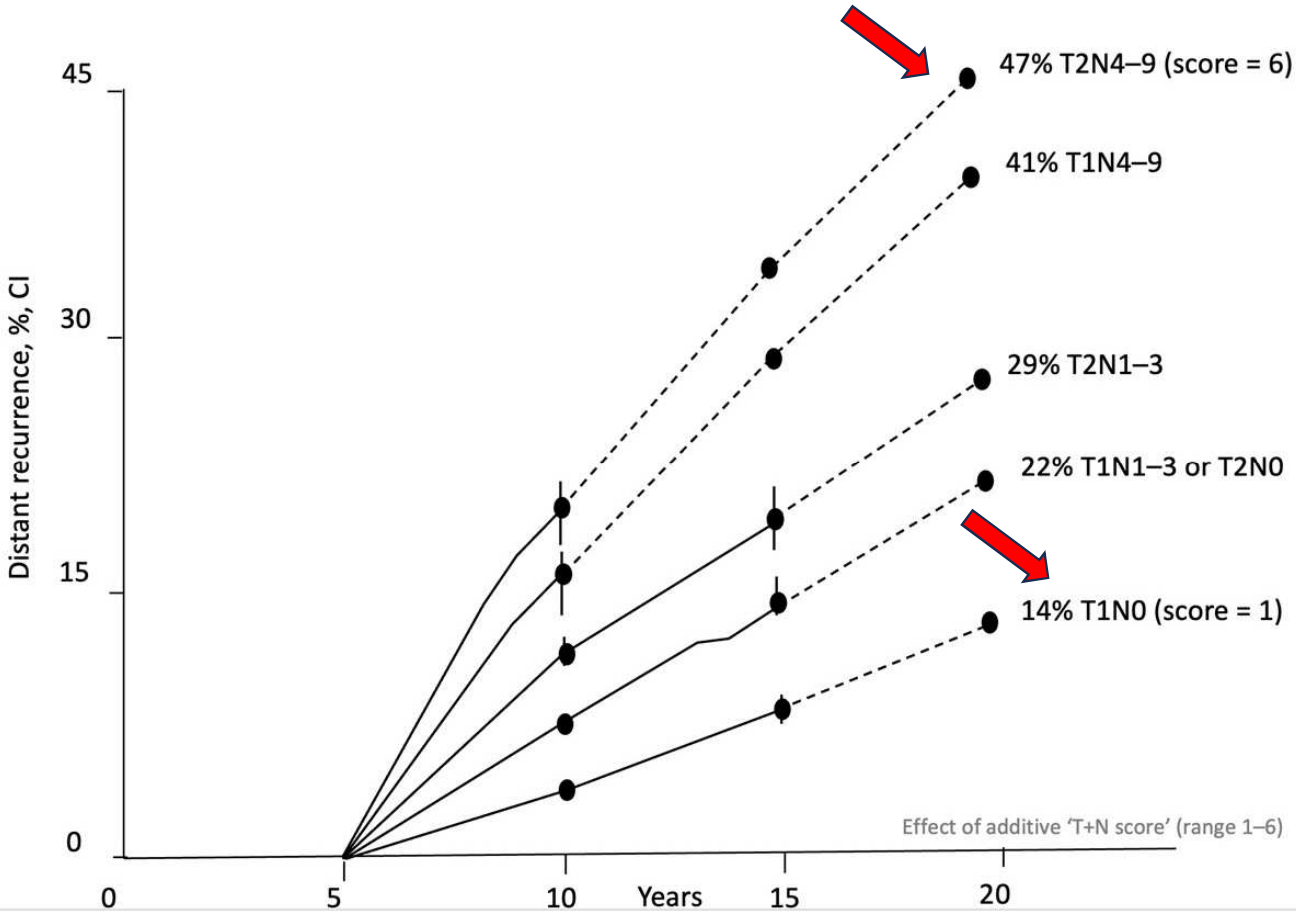
EBCTCG main findings: Long-Term Risk

After 5 years' endocrine therapy, recurrences continue steadily to at least year 20

Absolute recurrence risk in years 5–20 is appreciable even for T1N0 disease



Pan H et al, N Engl J Med 2017; 377: 1836-46

Efficacy on extended adjuvant endocrine therapy

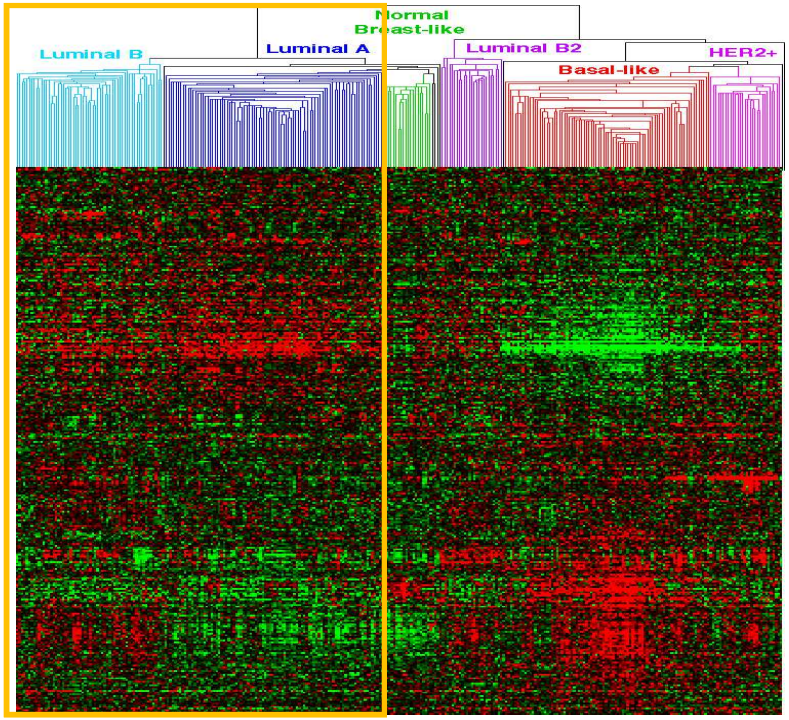
Trial	Sample size	Median FU (yrs)	Treatment arm	Yrs 1	2	3	4	5	6	7	8	13	14	15	DFS HR (95%CI)	OS HR (95%CI)
MA.17[34]	5187	5.3	I												0.68 (0.56-0.83)	0.99 (0.79-1.24)
			C													
NSABP B-33[33]	1598	2.5	I												0.68 (0.45-1.03)	NR
			C													
ABCSG 6a[32]	856	5.2	I												0.62 (0.40-0.96)*	0.89 (0.53-1.34)
			C													
ATLAS[26]	6846	7.6	I												0.84 (0.76-.93)*	0.87 (0.78-0.97)
			C													
aTTom[28,27]	6953	~9.0	I												0.86 (0.77-0.96)*	0.94 (0.86-1.03)
			C													
MA.17R[6]	1918	6.3	I												0.80 (0.63-1.01)	0.97 (0.73-1.28)
			C													
DATA[3]	1660	4.4	I												0.79 (0.62-1.02)	0.91 (0.65-1.29)
			C													
IDEAL[4]	1824	6.6	I												0.92 (0.74-1.16)	1.04 (0.78-1.38)
			C													
NSABP B-42[5]	3966	6.9	I												0.85 (0.73-0.99)	1.15 (0.92-1.44)
SOLE[36]	4884	5.0							Intermittent 9 months per year						1.08 (0.93-1.26)	0.85 (0.68-1.06)
									Continuous							

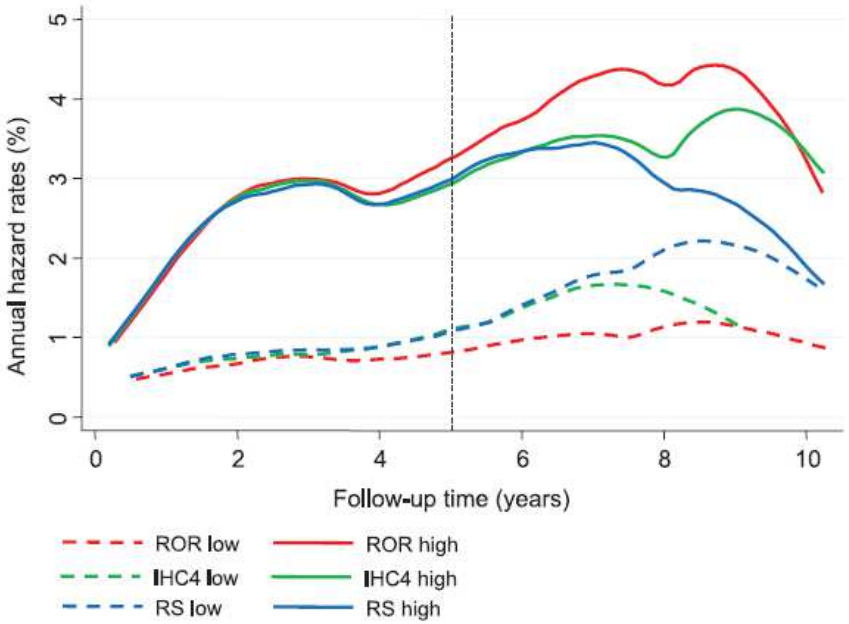
Red: tamoxifen. Gray: aro… …agonal lines: either tamoxifen or an aromatase inhibitor.

Extended Adjuvant ET with AIs did reduce the occurrence of secondary breast tumors, but had no or only a small impact on distant metastases free survival

Van Hellemon IEG, et al. Curr Treat Options Oncol 2018

Predicting Late Recurrence





"…ROR was the strongest molecular prognostic factor in predicting late recurrence and discriminating patients into low and high risk for late distant recurrence"

1. Prat A Ann Oncol 2012; 2. Sestak I J Natl Cancer Inst 2013 ; 3. Curigliano G. Ann of Oncol 2017

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Adjuvant CDK4/6i trials: Study Design

	PENELOPE-B	PALLAS	NATALEE	MONARCH-E
Agent	Palbociclib	Palbociclib	Ribociclib	Abemaciclib
Sample Size	1250	5600	5000	4580
Dose Schedule	125 mg qD 3 wk on /1 wk off	125 mg qD 3 wk on /1 wk off	400 mg qD 3 wk on /1 wk off	150 mg BID, continuous
Duration	1 year	2 years	3 years	2 years
Eligibility **Lower risk group**	Residual dx post-NACT CPS-EG≥2 with ypN+	Stage IIA (capped at 1000)	Stage IIA: N1 or N0 with G2/Ki-67>20% G2/High risk G3	1-3 + LN *w/1:* T size ≥5 cm Grade 3 Ki-67 ≥20%
Higher risk group	CPS-EG≥3	Stage IIB/III	Stage IIB/III	≥4 + LN

monarchE

HR+, HER2-, node positive high-risk EBC

- Women or men
- Pre-/postmenopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No metastatic disease
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Cohort 1: High risk based on **clinical pathological features**

- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on **Ki-67**

- 1-3 ALN and
- Ki-67 ≥20% and
- Grade 1-2 and tumor size <5 cm

Stratified for:

- Prior chemotherapy
- Menopausal status
- Region

R 1:1
N = 5637

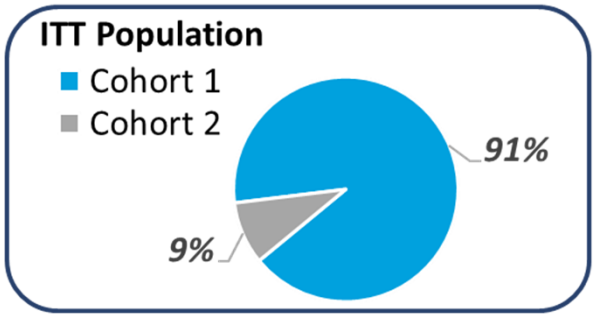
On-study treatment period
2 years

Abemaciclib
(150mg twice daily)
+
Endocrine Therapy: AI or tamoxifen

Endocrine Therapy: AI or tamoxifen

Follow-up period
Endocrine Therapy
3-8 years as clinically indicated

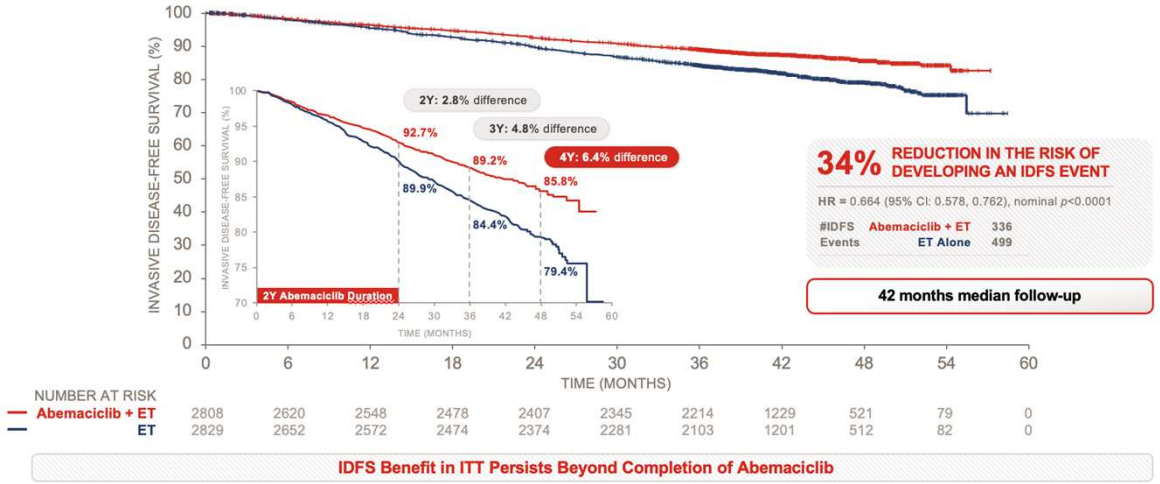
Primary Objective: IDFS
Secondary Objectives: IDFS in high Ki-67 populations, DRFS, OS, Safety, PK, PRO



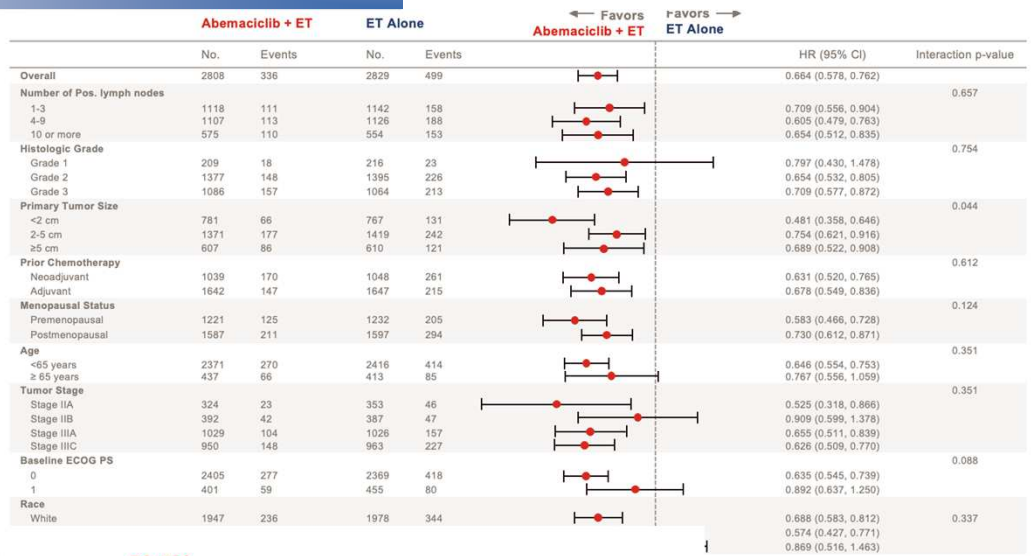
Johnston S.R.D. presented @SABCS 2022

monarchE: Efficacy

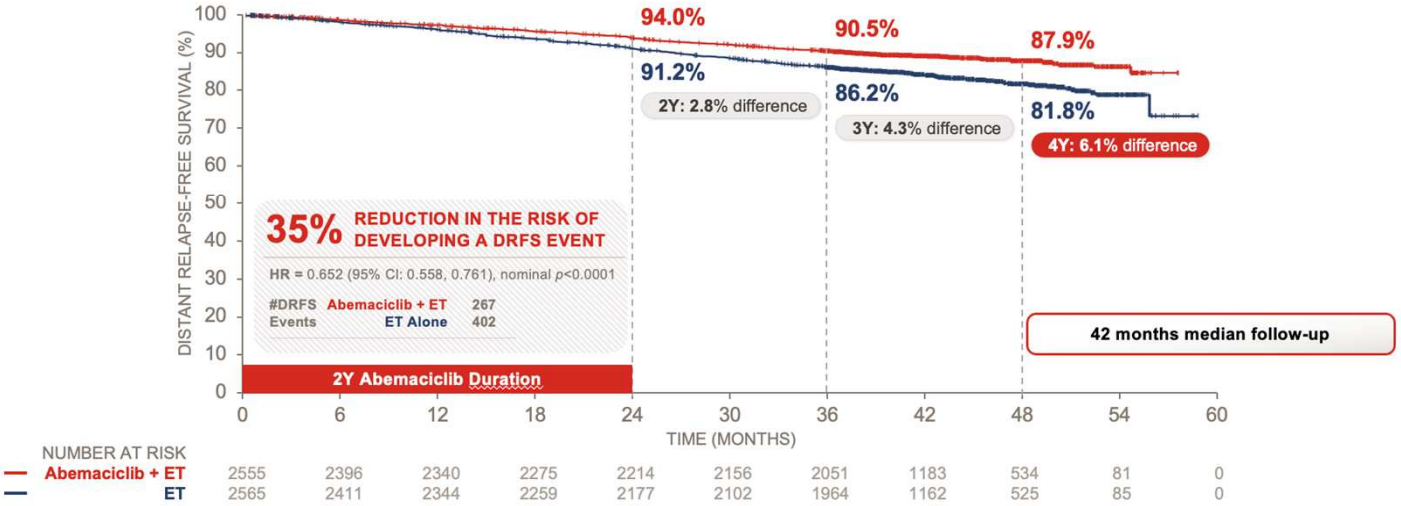
IDFS



IDFS Benefit in ITT Persists Beyond Completion of Abemaciclib



DRFS

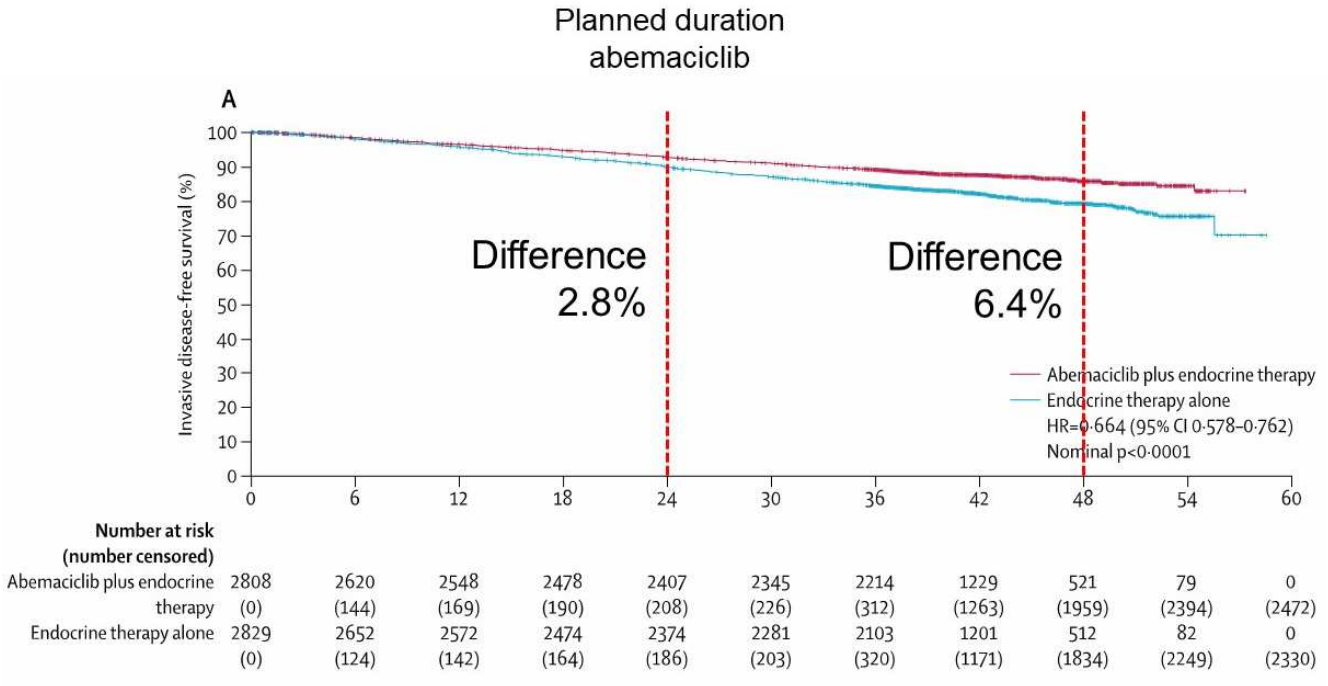


DRFS Benefit in Cohort 1 Persists Beyond Completion of Abemaciclib

1. Johnston et al SABCS 2022. Oral Presentation GS1-09; ***2.*** *Johnston et al. Lancet Oncol.2023*

monarchE: Efficacy

Increasing benefit with longer follow-up – “carryover effect”



Relative benefit potentially increases with time

Piecewise HR by year

Year	HH	
0-1	HR 0.78	On abema
1-2	HR 0.67	
2-3	HR 0.62	Off abema
3-4	HR 0.60	

Follow-up currently too short to assess overall survival

Johnston *et al* Lancet Oncol 2023

NATALEE study design[1,2]

2023 ASCO ANNUAL MEETING

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%
      - Oncotype DX Breast Recurrence Score ≥ 26 *or*
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

R 1:1[c]

Ribociclib
400 mg/day
3 weeks on/1 week off
for 3 y

NSAI
Letrozole or anastrozole[d] for ≥ 5 y
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[d] for ≥ 5 y
+ goserelin in men and premenopausal women

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

Primary End Point
- iDFS using STEEP criteria

Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

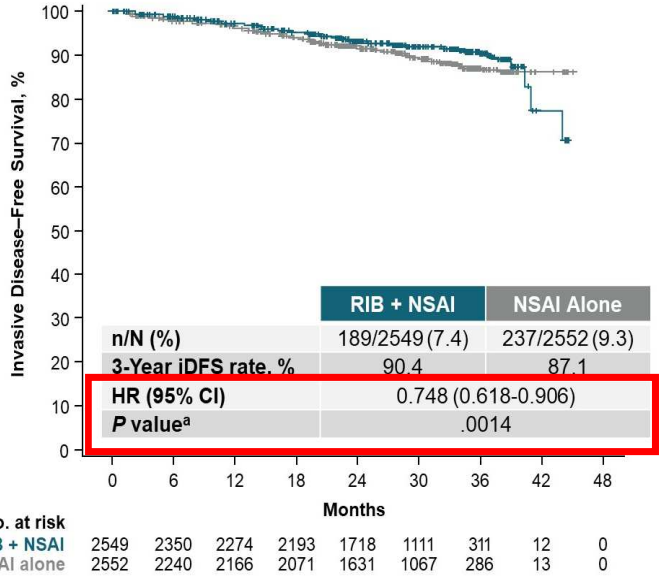
Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.
CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl) [abstract TPS597].

NATALEE TRIAL: RESULTS (1)

2023 ASCO ANNUAL MEETING

Ribociclib achieved highly significant iDFS benefit



	RIB + NSAI	NSAI Alone
n/N (%)	189/2549 (7.4)	237/2552 (9.3)
3-Year iDFS rate, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906)	
P value[a]	.0014	

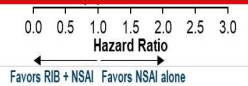
No. at risk									
RIB + NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0

iDFS, invasive disease–free survival; IDMC, Independent Data Monitoring Committee; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] One-sided *P* value.

- Median follow-up for iDFS was 27.7 months
- Based on the *P* value of 0.0014, the IDMC concluded that the results met the criteria to demonstrate statistically significant and clinically superior efficacy
- Absolute iDFS benefit with RIB + NSAI at 3 years was 3.3%
- Risk of invasive disease was reduced by 25.2% with RIB + NSAI vs NSAI alone
- Ongoing patients will remain on treatment a follow-up will continue as prespecified

iDFS benefit was consistent across prespecified key subgroups

Subgroup	RIB + NSAI n = 2549	NSAI Alone n = 2552	HR	(95% CI)
Menopausal status				
Men and premenopausal women	71/1126	93/1132	0.722	(0.530-0.983)
Postmenopausal women	118/1423	144/1420	0.781	(0.613-0.997)
AJCC stage				
Stage II	49/1011	65/1034	0.761	(0.525-1.103)
Stage III	140/1528	172/1512	0.740	(0.592-0.925)
Prior CT				
Neoadjuvant	111/1085	132/1095	0.785	(0.610-1.011)
Adjuvant	63/1223	89/1220	0.671	(0.486-0.927)
Prior ET				
Yes	127/1824	157/1801	0.756	(0.598-0.955)
No	62/725	80/751	0.774	(0.556-1.079)
Region				
North America/Western Europe/Oceania	111/1563	139/1565	0.759	(0.591-0.974)
Rest of world	78/986	98/987	0.757	(0.562-1.019)
Histological grade at time of surgery				
Grade 1	9/213	12/217	0.778	(0.328-1.846)
Grade 2	102/1460	125/1432	0.749	(0.577-0.973)
Grade 3	61/684	78/702	0.776	(0.555-1.085)
Ki-67 status[a]				
Ki-67 ≤ 20%	76/1199	95/1236	0.801	(0.593-1.083)
Ki-67 > 20%	82/920	105/938	0.746	(0.559-0.996)
Nodal status[b,c]				
N0	16/285	28/328	0.630	(0.341-1.165)
N1-N3	173/2261	208/2219	0.771	(0.630-0.944)

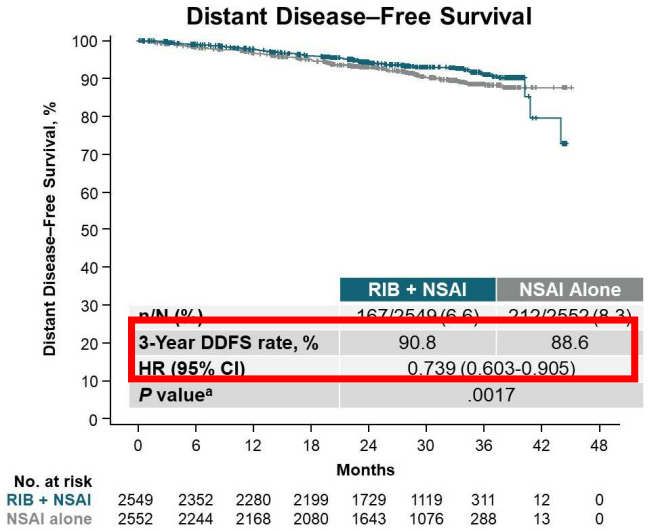


AJCC, American Joint Committee on Cancer; CT, chemotherapy; ET, endocrine therapy; iDFS, invasive disease–free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] From archival tumor tissue. [b] Nodal status classification according to AJCC staging. [c] Nodal status is from the worse stage derived per surgical specimen or at diagnosis.

Slamon D, ASCO 2023

NATALEE TRIAL: RESULTS (2)

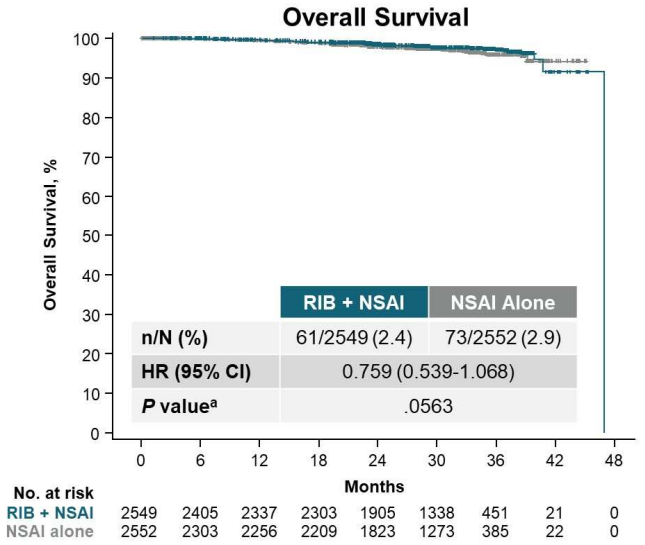
Consistent improvement in DDFS with ribociclib



	RIB + NSAI	NSAI Alone
n/N (%)	167/2549 (6.6)	212/2552 (8.3)
3-Year DDFS rate, %	90.8	88.6
HR (95% CI)	0.739 (0.603-0.905)	
P value[a]	.0017	

- Distant disease–free survival is defined as the time from date of randomization to date of first event of distant recurrence, death (any cause), or second primary non-breast invasive cancer[b]
- The one-sided nominal *P* value was .0017
- Absolute distant disease–free survival benefit with RIB + NSAI at 3 years was 2.2%
- Risk of distant disease was reduced by 26.1% with RIB + NSAI vs NSAI alone

Ribociclib showed a trend for improved OS

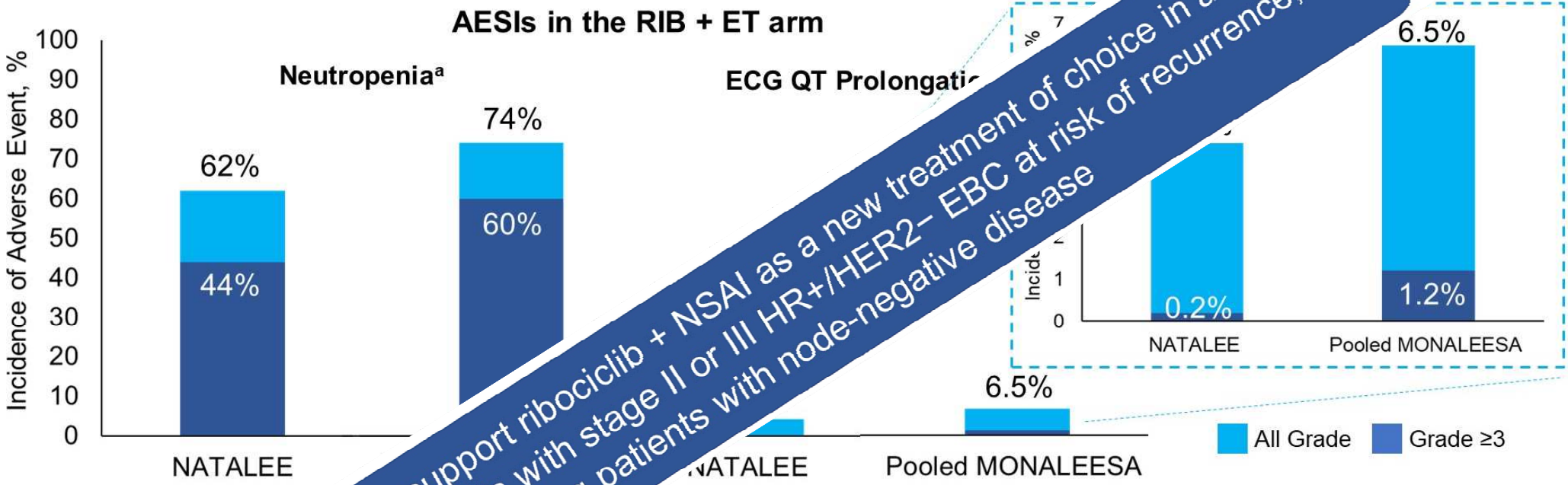


	RIB + NSAI	NSAI Alone
n/N (%)	61/2549 (2.4)	73/2552 (2.9)
HR (95% CI)	0.759 (0.539-1.068)	
P value[a]	.0563	

- Results for secondary end points consistently favored ribociclib + NSAI over NSAI alone

Slamon D, ASCO 2023

Favorable safety profile with ribociclib 400 m… …g



NATALEE results support ribociclib + NSAI as a new treatment of choice in a broad population of patients with stage II or III HR+/HER2− EBC at risk of recurrence, including patients with node-negative disease

- Compared wit… …00 mg, the standard of care in the ABC setting, RIB at a 400-mg starting dose in th… …rates of dose-dependent toxicities (neutropenia and QTc prolongation)[1]
- A ne… …was infrequent in both the RIB + NSAI and NSAI alone arms (0.1% vs < 0.1%), as w… …e of > 60 ms (0.8% vs 0.1%, respectively)[c]

…, electrocardiogram; ET, endocrine therapy; NSAI, nonsteroidal aromatase inhibitor; QTcF, QT interval corrected by Fridericia; RIB, ribociclib.
…eutrophil count decreased. [b] This is a preferred term. [c] The QTcF values reported in NATALEE are based on ECG abnormalities.
…:679-686.

PRESENTED BY: Dennis Slamon MD, PhD

Ormonoterapia adiuvante associata ad inibitori di cicline (CDK4/6i) nelle donne ad alto rischio di recidiva

Aiom
Associazione Italiana di Oncologia Medica

ADDENDUM
Linee guida
CARCINOMA MAMMARIO
IN STADIO PRECOCE

Addendum edizione 2022
Aggiornata a 23.02.2023

In collaborazione con:

Associazione Italiana Radioterapia e Oncologia clinica
A.N.I.S.C.
SIAPEC-IAP
SICO
SIMG
Società Italiana di Radiologia Medica e Interventistica

Bilancio beneficio/danno: In considerazione del vantaggio osservato in termini di IDFS e DRFS, pur in assenza di un vantaggio in OS (dati immaturi), a fronte del profilo di tossicità nel complesso maneggevole e considerati i limiti sopra-descritti, il bilancio beneficio-danno appare probabilmente a favore dell'aggiunta di abemaciclib al trattamento endocrino standard in pazienti con carcinoma mammario a recettori ormonali positivi/HER2-negativo ad alto rischio.

Qualità globale delle evidenze	Raccomandazione clinica	Forza della raccomandazione
MODERATA	*In pazienti con carcinoma mammario HR+/HER2- N+ ad alto rischio* un trattamento adiuvante con abemaciclib + terapia endocrina può essere considerato rispetto a terapia endocrina*	Condizionale a favore
COI: nessuno		

* Alto rischio: positività ≥ 4 linfonodi ascellari o da 1 a 3 linfonodi ascellari con almeno una delle seguenti condizioni: dimensioni della neoplasia ≥ 5 cm e/o grado istologico 3 (coorte 1 dello studio MonarchE).

OUTLINE

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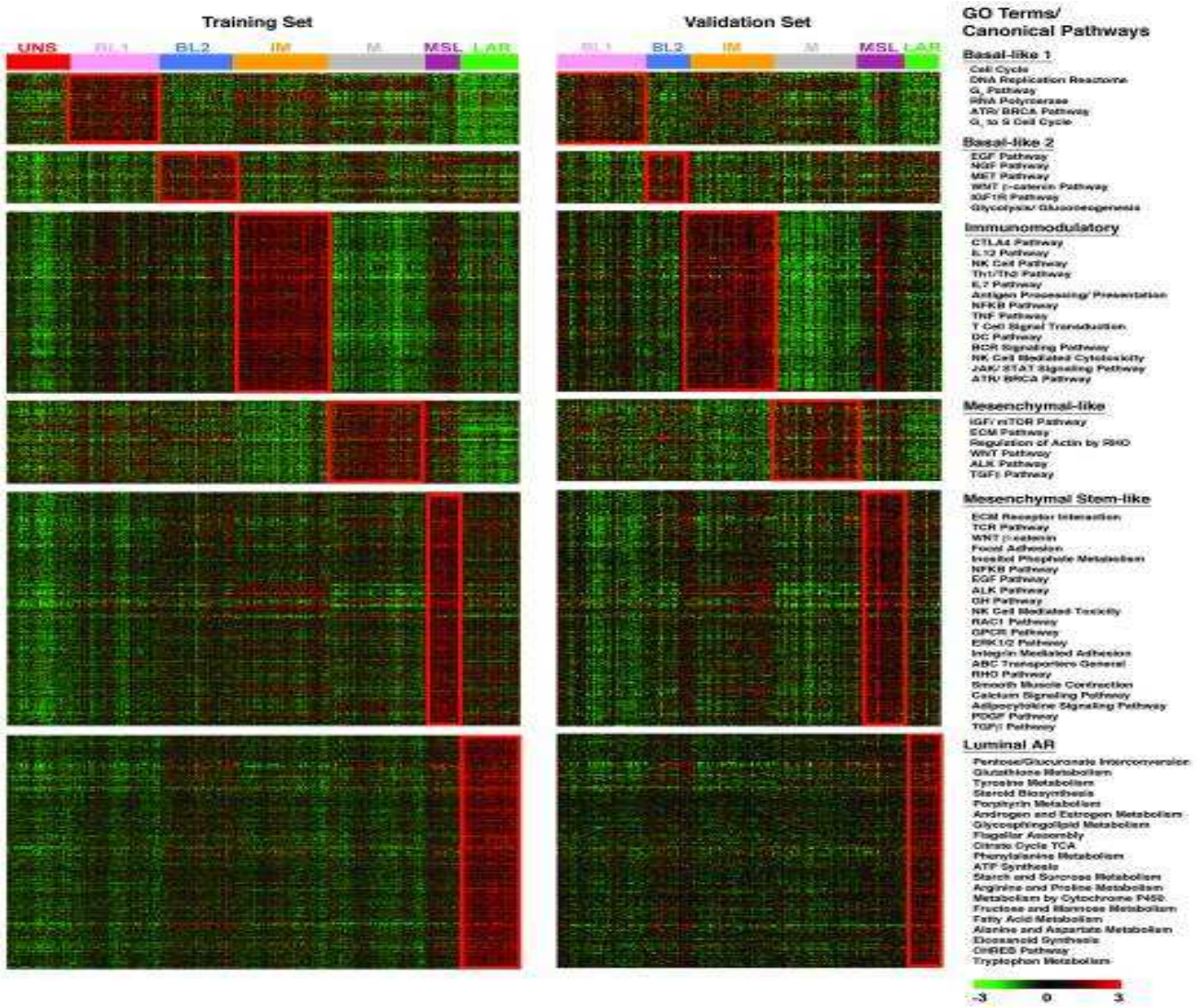
TNBC

- TNBC lacks expression of ER (<1%), PgR (<1%) and HER2
- TNBC comprises approximately 15% of all breast
- BRCA mutations in nearly 20% of TNBC patients (vs 5% non-TNBC): 16% BRCA1 and 4% BRCA2
- Triple negative Paradox→ aggressive clinical course but high sensitivity to cytotoxic treatment
- Patients with metastatic TNBC experience poor outcomes relative to patients with other breast cancer subtypes, with a median of 18 months or less

1.Lin NU. Cancer. 2008; 2. Dent R. Clin Cancer Res. 2007; 3. Liedtke C. J Clin Oncol. 2008

New Classification of TNBC



Basal-like 1: cell cycle, DNA repair and proliferation genes

Basal-like 2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)

IM: immune cell processes (medullary breast cancer)

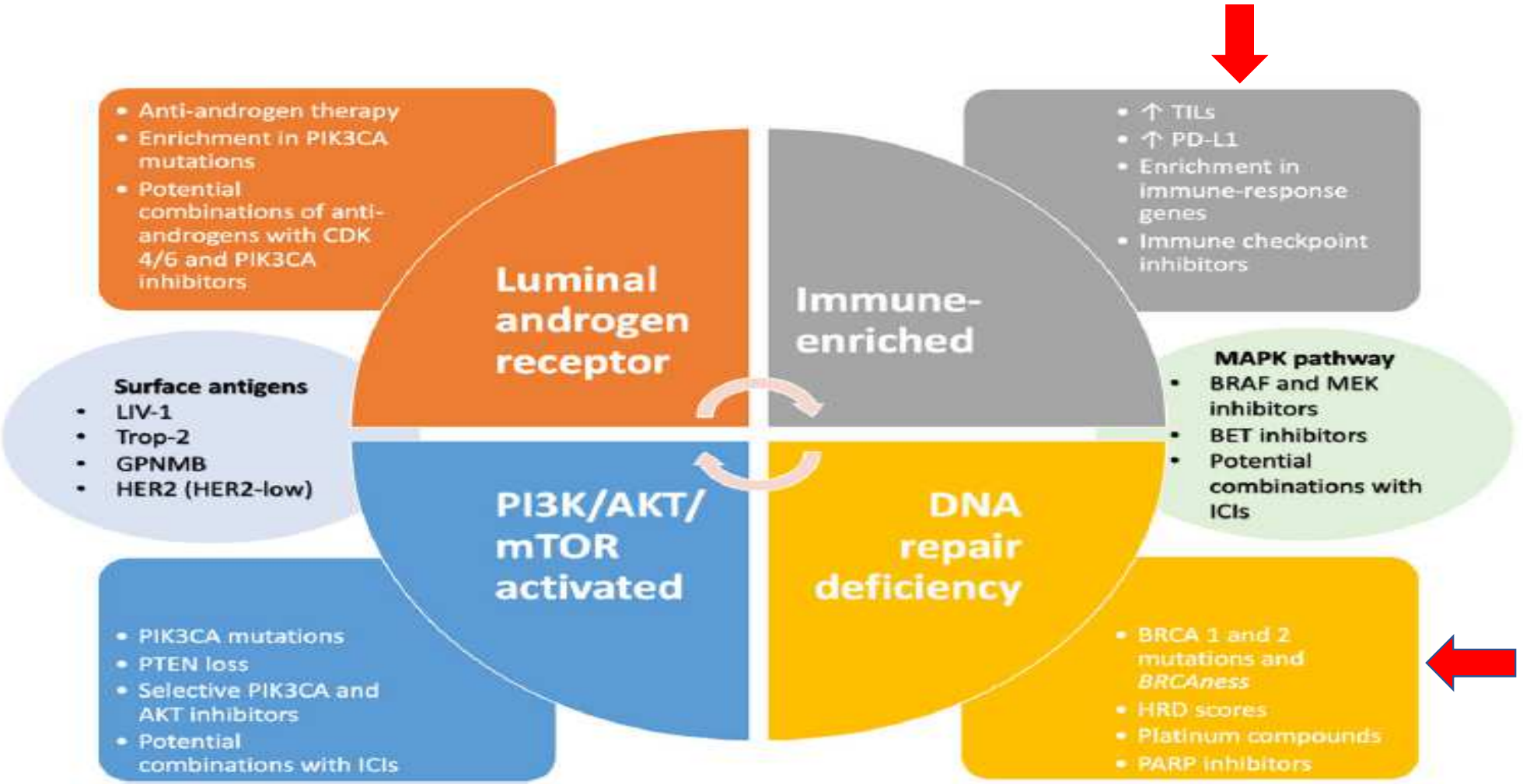
M: Cell motility and differentiation, EMT processes

MSL: similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

LAR: Androgen receptor and downstream genes, luminal features

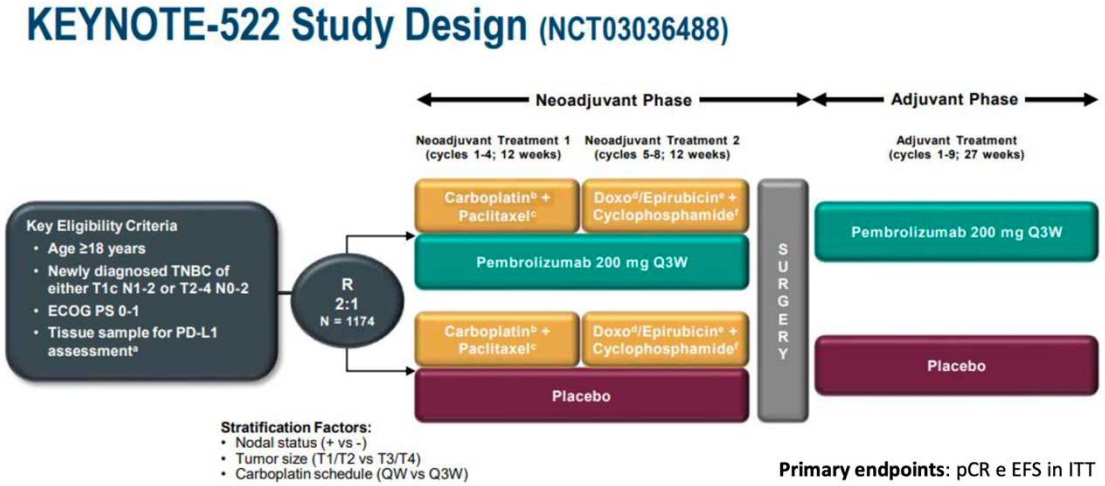
Lehmann BD et al JCI 2011

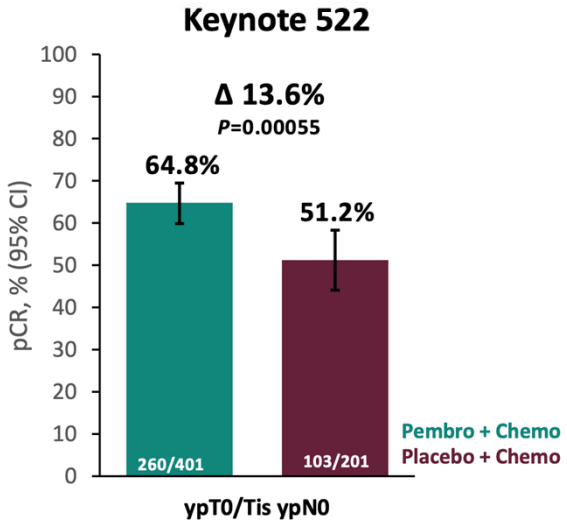
Biomarkers Driven Different Approaches in TNBC

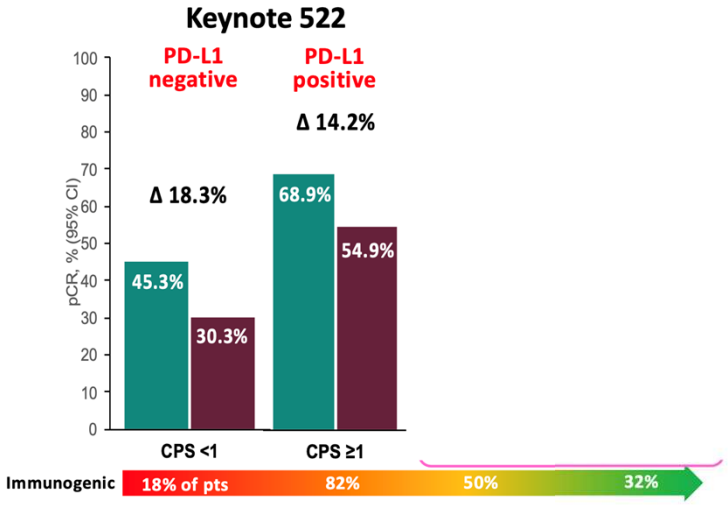


Marra & Curigliano NPJ Breast Cancer 2020

Neoadjuvant Immunotherapy in early TNBC





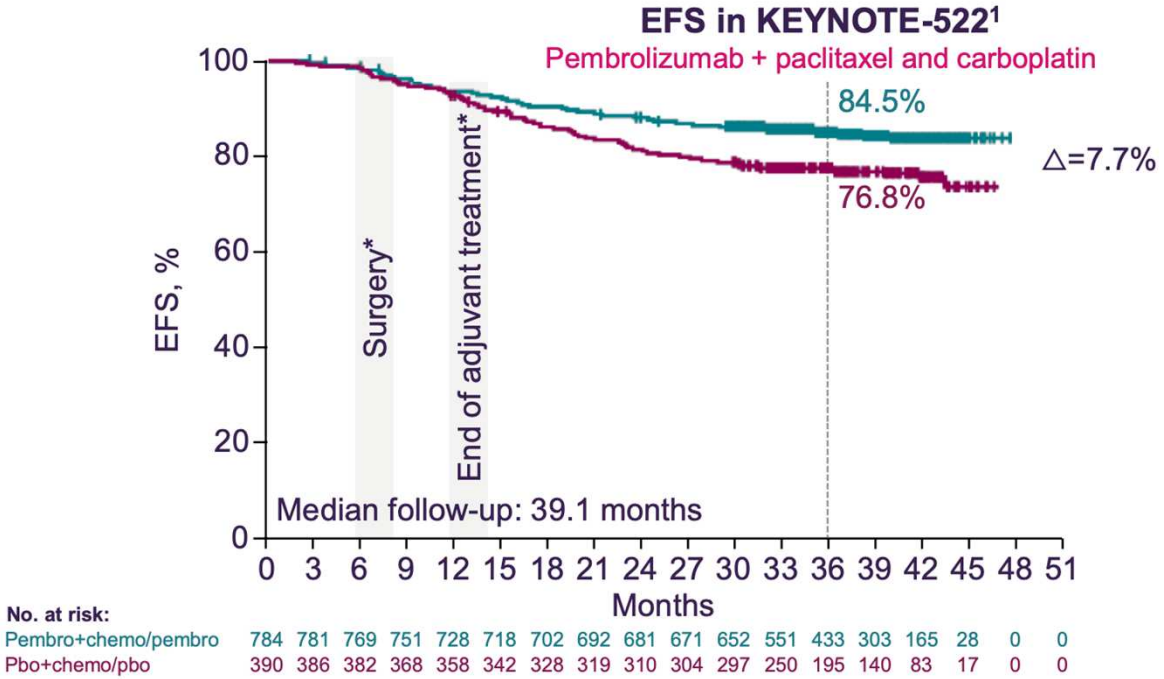


Schmid P, NEJM 2020;

Neoadjuvant Immunotherapy in early TNBC

In KEYNOTE-522, pembrolizumab added to chemotherapy resulted in a significant improvement of EFS vs. placebo in early TNBC[1]

Pembrolizumab received FDA approval for high-risk, early-stage TNBC in combination with NACT, and then continued as a single agent as adjuvant treatment after surgery based on these data[2]



	Pembrolizumab + chemotherapy / pembrolizumab (n=784)	Placebo + chemotherapy / placebo (n=390)
Events	15.7%	23.8%
	Hazard ratio **0.63**† (95% CI 0.48–0.82) p=0.00031‡	

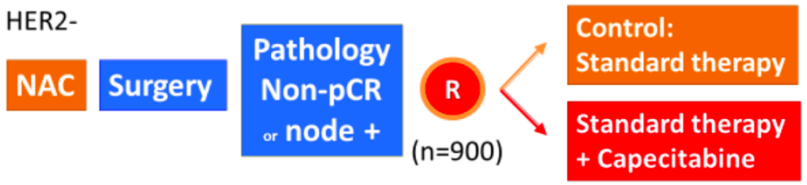
EFS data for IMpassion031 are not yet mature. After a median follow-up of 20.6 months, median EFS was not reached in either treatment arm (HR=0.76, 95% CI 0.40–1.44)[1]

CI=confidence interval; EFS=event-free survival; TNBC=triple-negative breast cancer

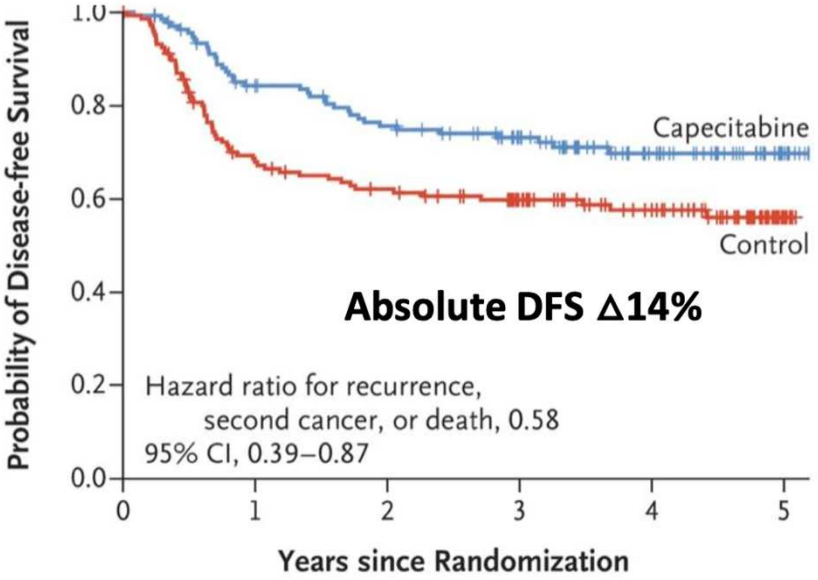
1. Schmid P, et al. Presented at ESMO Virtual Plenary 2021; 15–16 July Schmid P, NEJM 2022

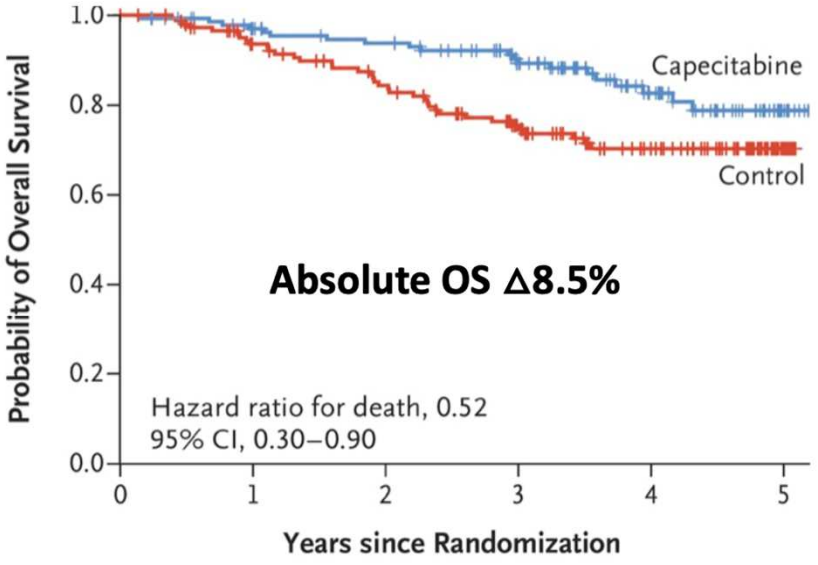
Tailored Chemotherapy Escalation in Residual Disease

CREATE-X: Trial Design



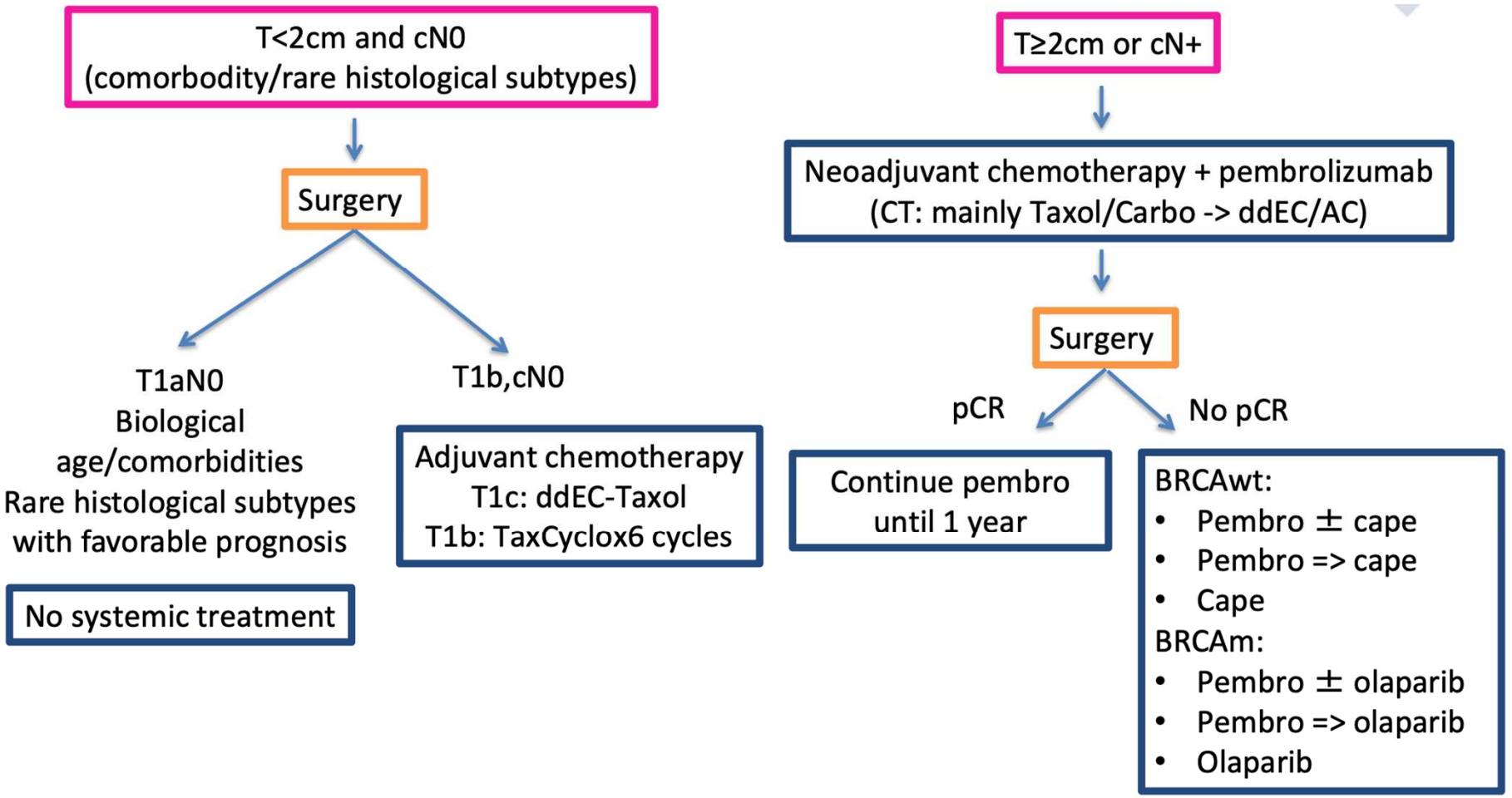
Overall positive trial @ 3.5y
Results driven by TNBC subset





Masuda et al, NEJM 2017

Systemic Treatment Approach STAGE 1-3 TNBC



Strategie di trattamento sistemico neoadiuvante

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Bilancio beneficio/danno: In considerazione del vantaggio osservato in termini di pCR e EFS, pur in assenza di un vantaggio in OS (dati immaturi), a fronte dell'incremento del carico di tossicità, il Panel ha giudicato il bilancio beneficio/danno come probabilmente a favore dell'aggiunta di pembrolizumab al trattamento chemioterapico neoadiuvante standard in pazienti con carcinoma mammario triplo-negativo stadio II-III.

Quesito 22: ***Dovrebbe un trattamento neoadiuvante con pembrolizumab + chemioterapia versus chemioterapia essere utilizzato per pazienti con carcinoma mammario triplo-negativo ad alto rischio?***

La direzione e la forza della raccomandazione verranno definite non appena pembrolizumab sarà autorizzato da parte di AIFA.

I risultati dello studio Keynote522 si basano sulla somministrazione di pembrolizumab anche nel setting adiuvante indipendentemente dalla risposta patologica. È importante sottolineare l'attuale incertezza riguardo al trattamento adiuvante ottimale in pazienti con malattia residua dopo terapia neoadiuvante, considerati i dati indipendenti di beneficio (in assenza di pembrolizumab) conferito da capecitabina in pazienti triplo-negative e da olaparib nel sottogruppo con mutazione germinale di BRCA1/2. Ad oggi non sono disponibili dati che supportino l'uso di pembrolizumab in combinazione a capecitabina o olaparib.

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BRCA1/2 mutant in TN & HR+HER2- Breast Cancer

TNBC patients

~17%

have BRCA mutations

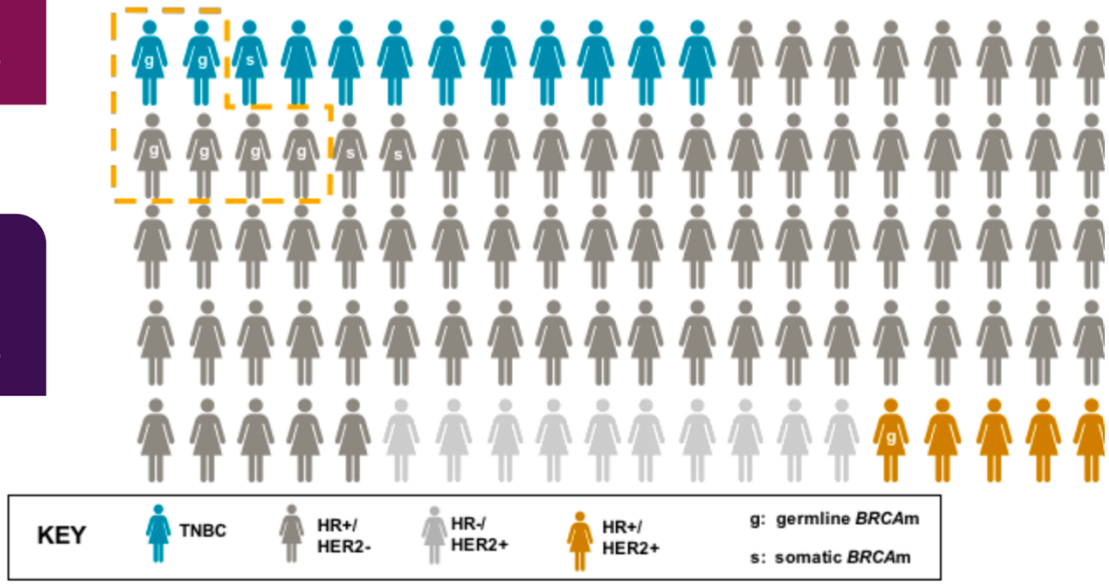
HR+ patients

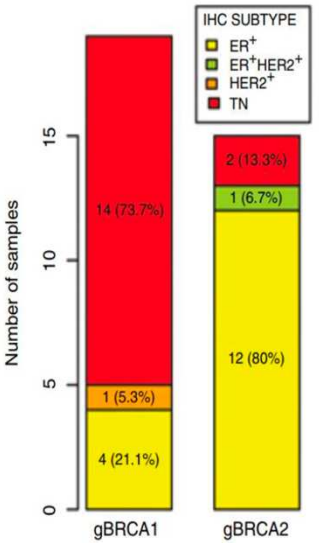
~6%

have BRCA mutations

Estimated prevalence of *BRCA*m within mBC segments

Based on Winter et al, 2016[1]

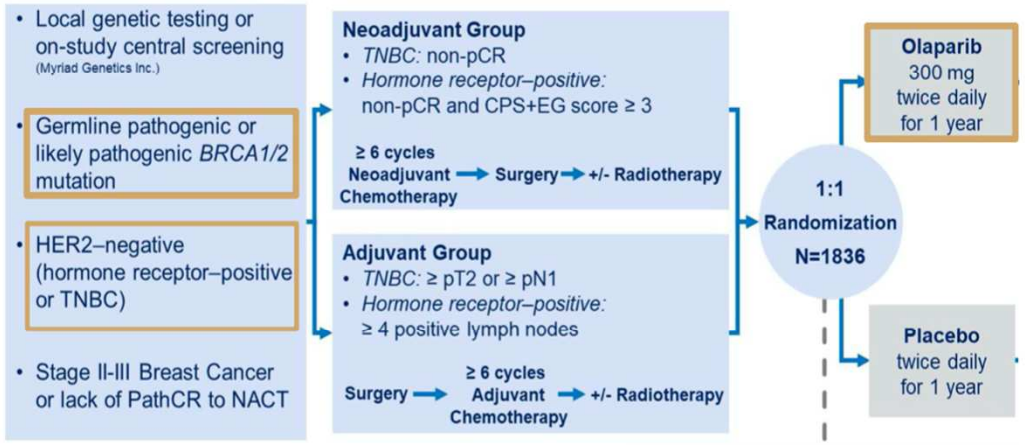


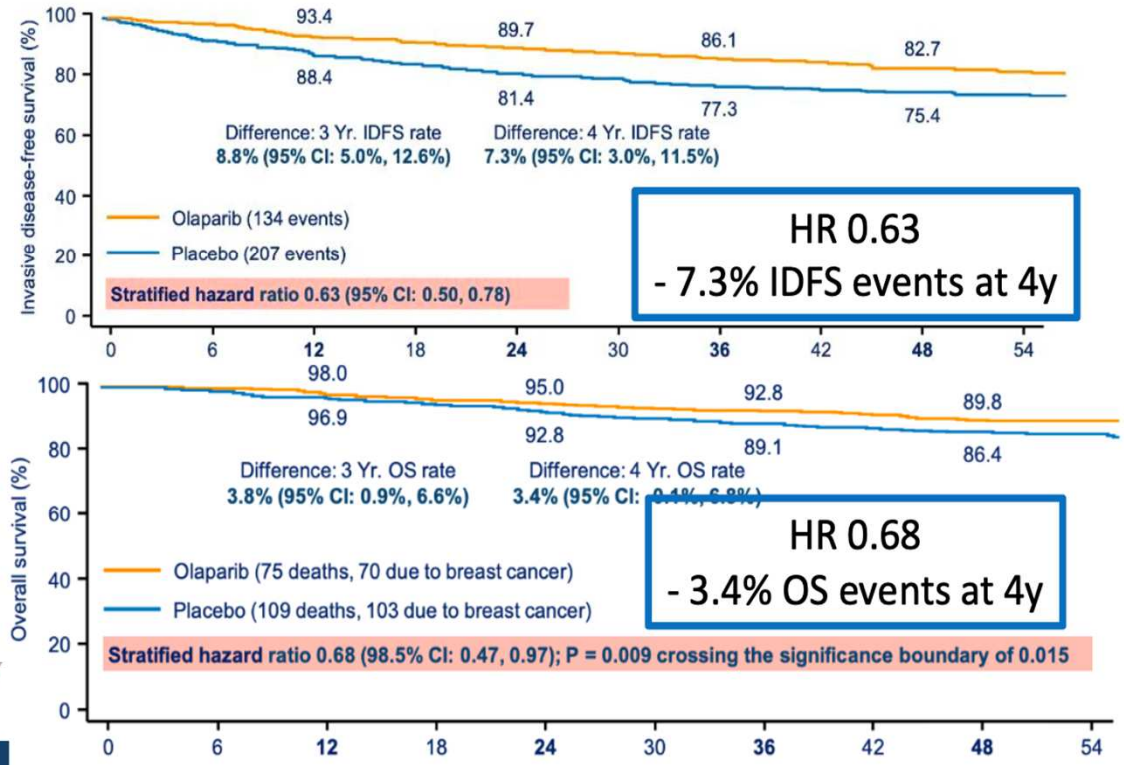


By IHC subtyping **TNBC incidence was higher in the gBRCA1 mut** and ER positive was dominant in the gBRCA2 mut

Park SH, et al. *Mol Cancer Res.* 2020

OLYMPIA TRIAL: OLAPARIB IN EARLY HER2- BRCA mut





OLYMPIA: PATIENT CHARACTERISTICS

	Olaparib (N = 921)	Placebo (N = 915)
Hormone receptor status*		
ER and/or PgR positive ≥ 1% / HER2-negative†	168 (**18.2%**)	157 (**17.2%**)
Triple negative breast cancer‡	751 (**81.5%**)	758 (**82.8%**)

1 year adjuvant olaparib (up to 12 weeks) after completion of local treatment and (neo)adjuvant chemotherapy improves overall survival in patients with high-risk TNBC and (likely) pathogenic variants in *BRCA1/2*

Tutt A, Esmo Virtual Plenary 2022

Terapia sistemica neoplasia mammaria BRCA-correlata

Bilancio beneficio/danno: In considerazione del vantaggio osservato in termini di iDFS, DDFS, OS, secondi tumori, tenuto conto dell'impatto non detrimentale in termini di qualità di vita e dell'impatto in termini di tossicità, il Panel ha giudicato il bilancio beneficio/danno a favore di olaparib in pazienti con mutazione germinale BRCA1/2 affetti da neoplasia mammaria HER2-negativa (a recettori positivi o negativi) ad alto rischio di recidiva.

La direzione e la forza della raccomandazione verranno definite non appena olaparib sarà autorizzato da parte di AIFA.

Si ribadisce che in Italia olaparib è disponibile nell'ambito di un programma ad uso compassionevole *(a partire da Maggio 2022)* per il trattamento adiuvante di pazienti con neoplasia della mammella in stadio precoce, HER2-negativo e con mutazioni germinali nei geni BRCA1/2, che presentino caratteristiche istopatologiche ad alto rischio e che abbiano completato il trattamento loco-regionale e la chemioterapia (neo/adiuvante).

Associazione Italiana di Oncologia Medica

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- SIAPEC-IAP
- SICO Società Italiana di Chirurgia Oncologica
- SIMG Società Italiana di Medicina Generale e delle Cure Primarie
- SIRM Società Italiana di Radiologia Medica e Interventistica

- *La direzione e la forza della raccomandazione verranno definite non appena olaparib sarà autorizzato da parte di AIFA.

ADDENDUM Linee guida CARCINOMA MAMMARIO IN STADIO PRECOCE Addendum edizione 2022 Aggiornata a 23.02.2023

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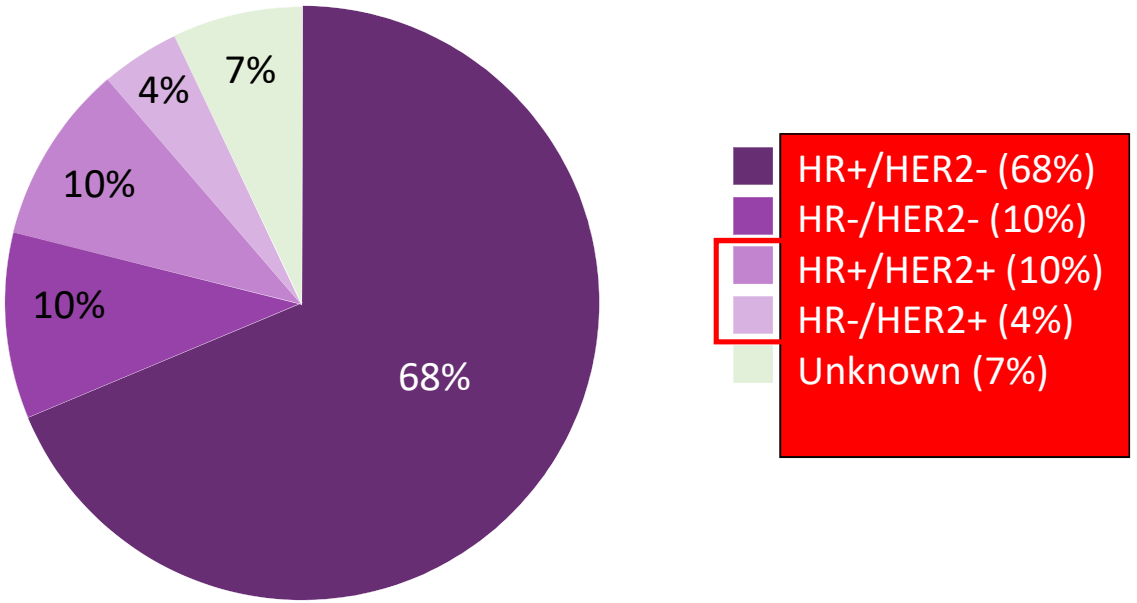
- **The actually and the future therapeutic landscape in HER2+ Early BC**

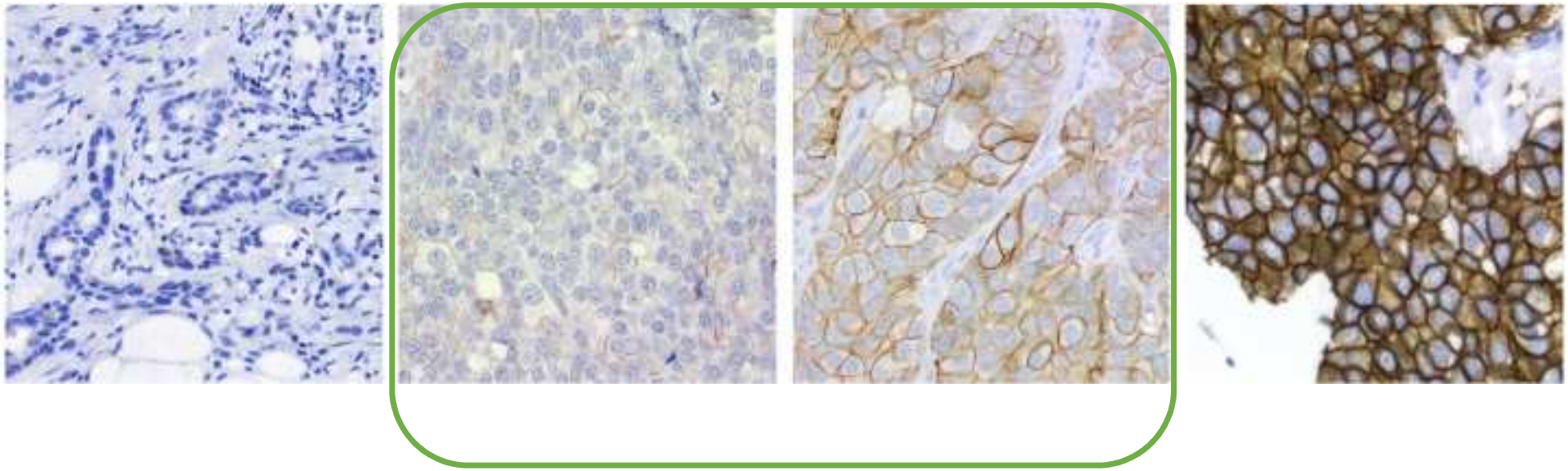
Overview of HER2 in Breast Cancer

- ~15% of breast cancer are considered HER2 “positive”
- HER2 gene amplification and/or HER2 protein overexpression is linked to a more aggressive phenotype
- HER2 is a validated therapeutic target



Slamon. Science. 1987;235:177. Ran. Onco Targets Ther. 2020;13:4385. seer.cancer.gov/statfacts/html/breast-subtypes.html.

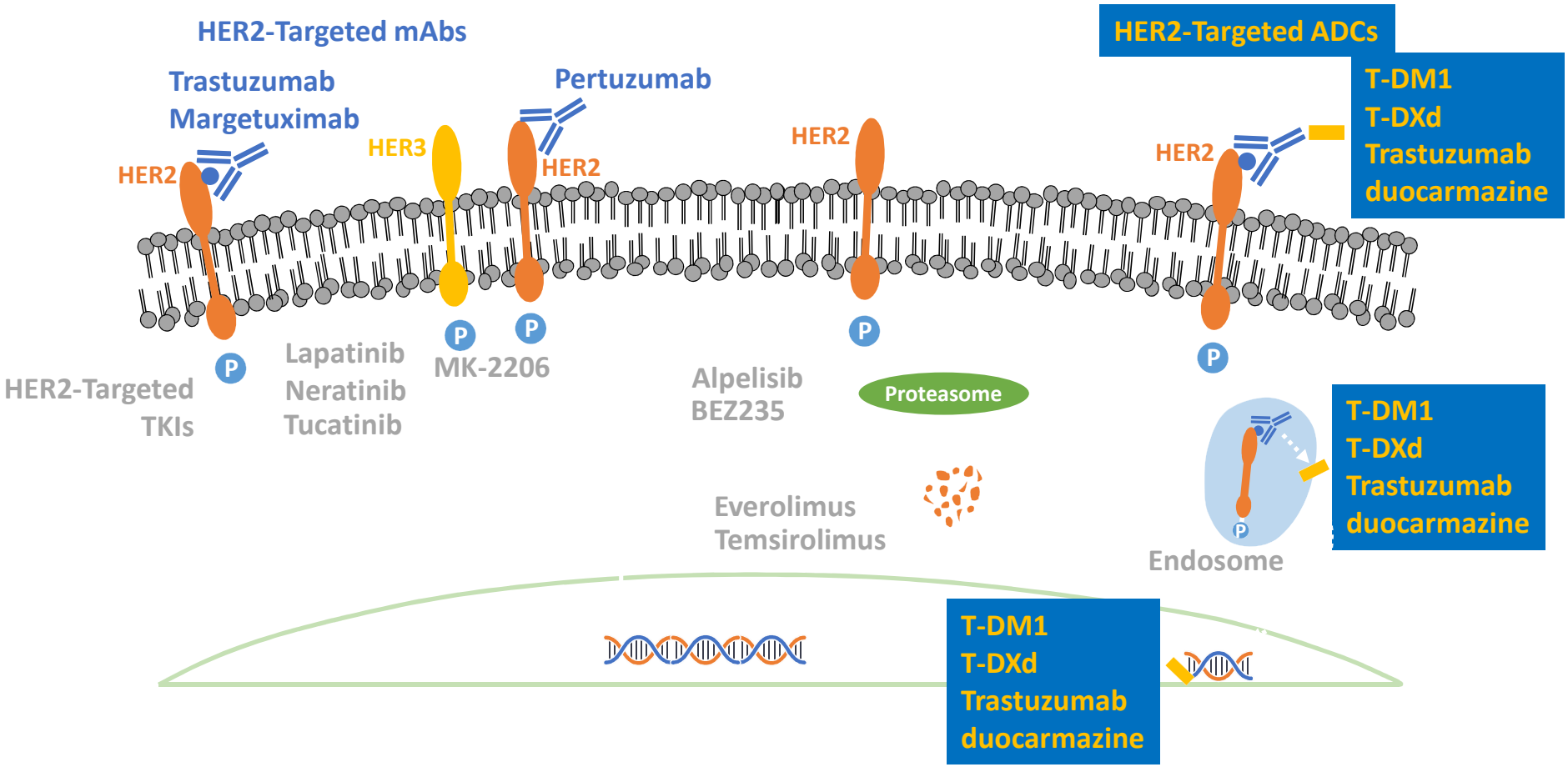
Current Binary Classification of HER2 in Breast Cancer



Adapted from: Marchiò. Semin Cancer Biol. 2021:72:123.

Slide credit: clinicaloptions.com

Targeted Therapies for HER2+ Breast Cancer



Gajria. Expert Rev Anticancer Ther. 2011;11:263. Pernas. Ther Adv Med Oncol. 2019;11:1758835919833519.

APHINITY: Pertuzumab, Trastuzumab, and CT vs Trastuzumab and CT in HER2+ EBC

- International, randomized, double-blind, placebo-controlled phase III trial[1,2]

Wk 52

Surgery

Patients with HER2+ EBC; no prior invasive BC or anticancer tx or RT; N+ any tumor size (no T0) or N0 tumor size >1 cm*; BL LVEF ≥55% (N = 4805)

CT† + Trastuzumab/Pertuzumab (n = 2400)

CT† + Trastuzumab + Placebo (n = 2405)

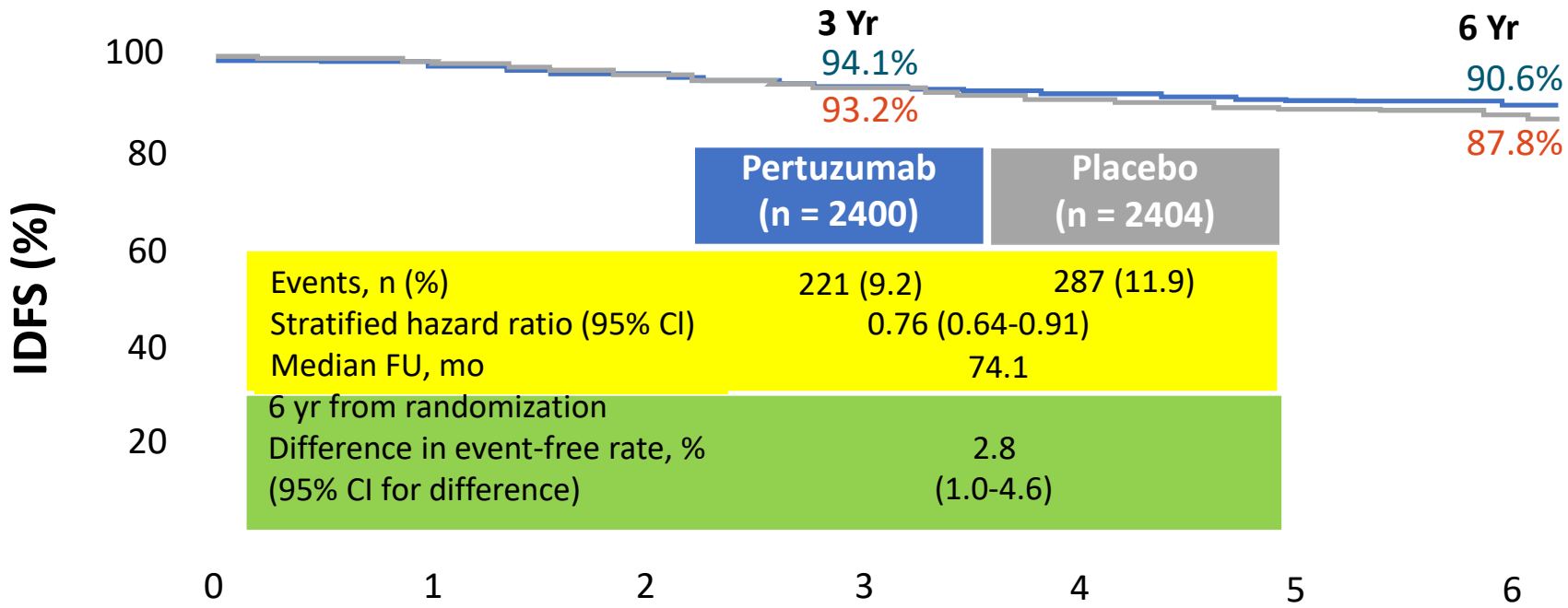
10-yr follow-up

*Or node negative with tumors >0.5 to ≤1 cm + ≥1 of following: histologic/nuclear grade 3; ER- and PR-; aged <35 yr. Node-negative enrollment capped after first 3655 patients randomized.

- Primary endpoint: IDFS per modified STEEP definition[3] (excludes second primary non-BC as event)
- Secondary endpoints: IDFS per STEEP definition,[3] OS, distant recurrence-free survival, DFS, recurrence-free interval, safety, cardiac safety, health-related QoL

1. von Minckwitz. NJEM. 2017;377:122. 2. Piccart. JCO. 2021;39:1448 3. Hudis. JCO. 2007;25:2127.

APHINITY: 6-Yr Follow-up for IDFS in ITT Population



Patients at Risk, n

Pertuzumab	2400	2277	2198	2122	2055	1978	1482
Placebo	2404	2312	2215	2134	2039	1967	1421

Piccart. JCO. 2021;39:1448.

APHINITY: 6-Yr Follow-up IDFS, OS, Safety

6-yr IDFS rate, %	Pertuzumab	Placebo	Hazard Ratio (95% CI)
ITT	96.0 (n = 2400)	87.8 (n = 2404)	0.76 (0.64-0.91)
▪ HR+	91.2 (n = 1536)	88.2 (n = 1546)	0.73 (0.59-0.92)
▪ HR+	89.5 (n = 864)	87.0 (n = 858)	0.83 (0.63-1.10)
▪ LN+	87.9 (n = 1503)	83.4 (n = 1502)	0.72 (0.59-0.87)
▪ LN-	95.0 (n = 897)	94.9 (n = 902)	1.02 (0.69-1.53)
6-yr OS rate, %	**Pertuzumab**	**Placebo**	**Hazard Ratio (95% CI)**
ITT	94.8 (n = 2400)	93.9 (n = 2404)	0.85 (0.67-1.07)

- No difference in fatal AE (0.9% pertuzumab vs 1.2% placebo)
- More primary cardiac events with the addition of pertuzumab: 0.8% vs 0.3% with placebo

Piccart. JCO. 2021;39:1448.

KATHERINE: Trastuzumab Emtansine vs Trastuzumab as Adjuvant Therapy for HER2+ EBC

- Open-label, phase III trial

Patients with HER2+ EBC (cT1-4/N0-3/M0)
who had residual invasive disease in breast or axillary nodes after neoadjuvant chemotherapy
+ HER2-targeted therapy* at surgery
(N = 1486)

T-DM1† 3.6 mg/kg IV Q3W x 14 cycles
(n = 743)

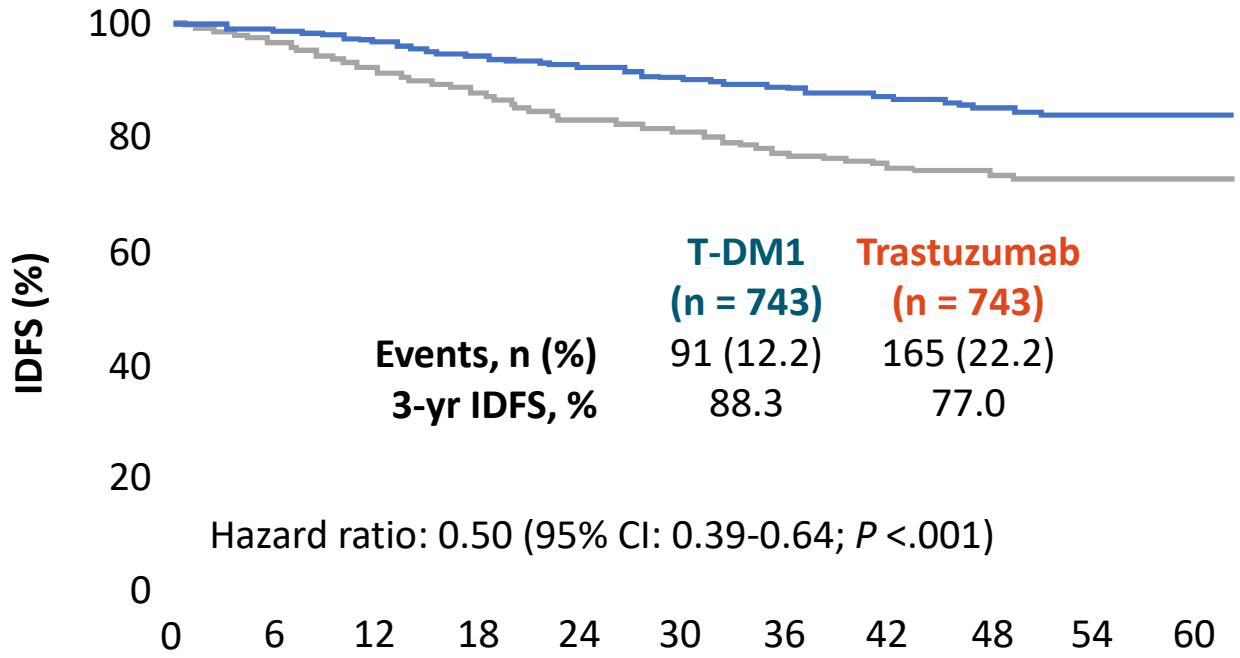
Trastuzumab 6 mg/kg IV Q3W x 14 cycles
(n = 743)

Randomization occurred within 12 wk of surgery; **radiotherapy and/or endocrine therapy given per local standards**.
*Minimum of 9 wk of taxane and trastuzumab. †Patients who d/c T-DM1 for toxicity allowed to switch to trastuzumab to complete 14 cycles.

- Primary endpoint: IDFS
- Secondary endpoints: distant recurrence-free survival, OS, safety

Geyer. SABCS 2018. Abstr GS1-10. von Minckwitz. NEJM. 2019;380:617.

KATHERINE: IDFS



Patients at Risk, n											
T-DM1	743	707	681	658	633	561	409	255	142	44	4
Trastuzumab	743	676	635	594	555	501	342	220	119	38	4

First IDFS Event, %	T-DM1	T
Any	12.2	22.2
Distant recurrence	10.5*	15.9†
Locoregional recurrence	1.1	4.6
Contralateral breast cancer	0.4	1.3
Death without prior event	0.3	0.4

CNS events: *5.9% vs †4.3%.

von Minckwitz. NEJM. 2019;380:617.

ExteNET 5-Yr Update: Neratinib vs Placebo After Adjuvant Trastuzumab in HER2+ EBC

- Multicenter, double-blind, phase III trial

Patients with HER2+ EBC (stage I-III); adjuvant trastuzumab completed ≤2 yr before randomization*; **N+/- disease or residual disease after neoadjuvant therapy** known ER and PR status
(N = 2840)

1 yr

Neratinib 240 mg/day PO
(n = 1420)

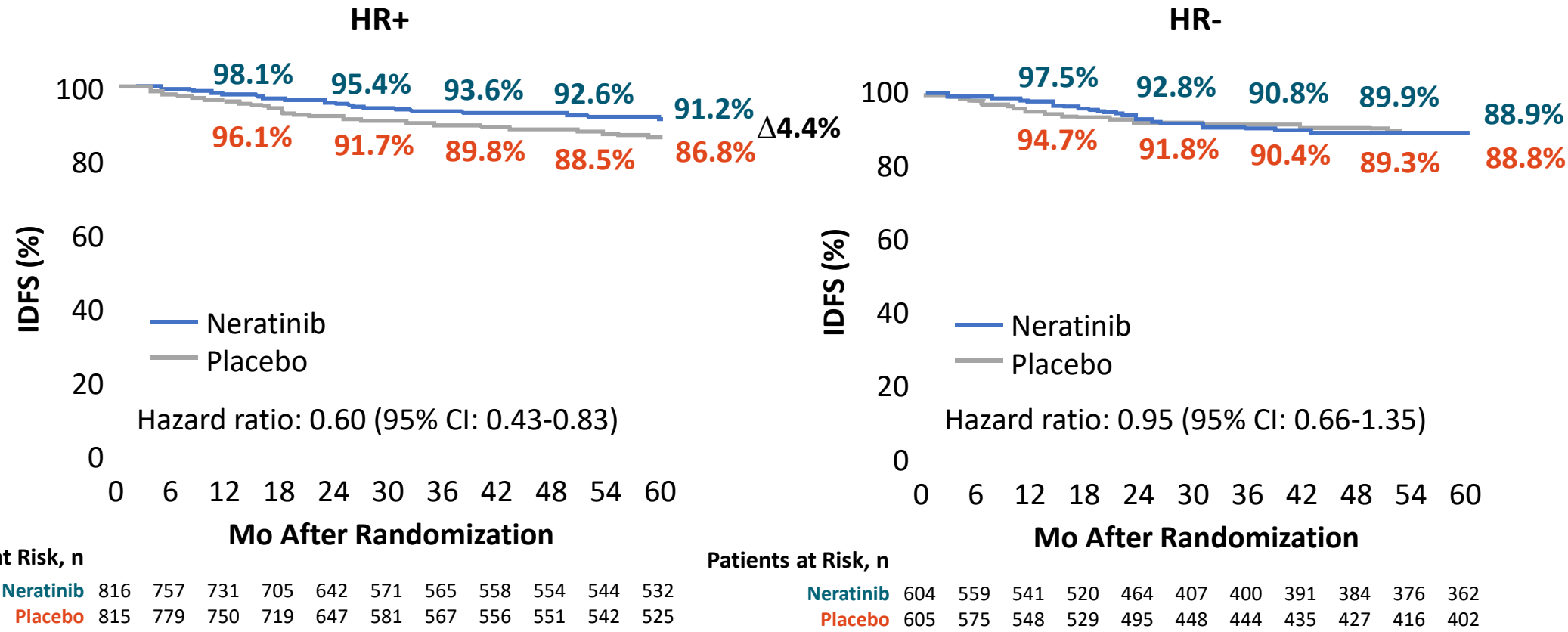
Placebo
(n = 1420)

*Amendment in February 2010 **restricted enrollment to patients with N+ disease** who completed trastuzumab ≤1 yr before randomization.

- Primary endpoint: IDFS at 2 yr
- Primary analysis of 2-yr IDFS rate: neratinib, 93.9%; placebo, 91.6% (hazard ratio: 0.67; 95% CI: 0.50-0.91; *P* = .0091)

Chan. Lancet Oncol. 2016;17:367. Martin. Lancet Oncol. 2017;18:1688. Chan. Clin Breast Cancer. 2021;21:80.

ExteNET: 5-Yr IDFS Analysis by HR Status



Patients at Risk, n

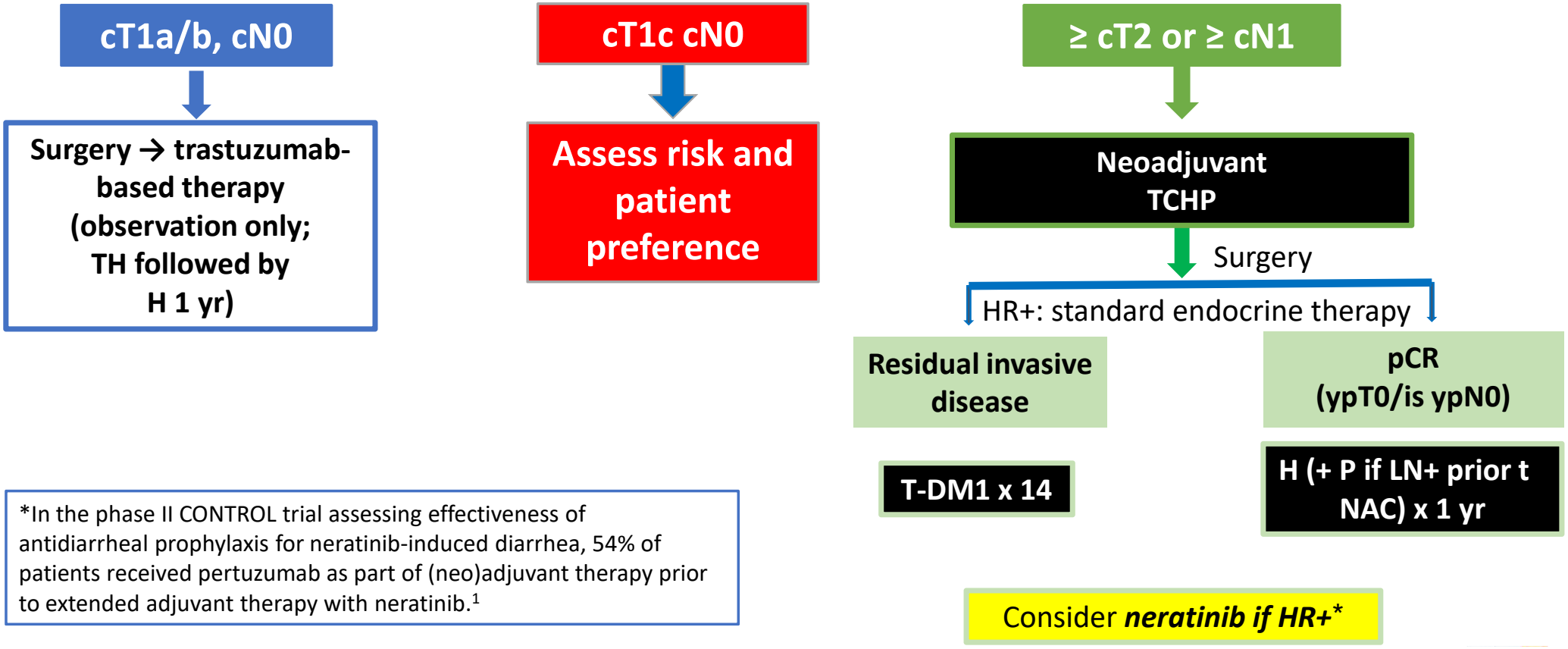
Neratinib	816	757	731	705	642	571	565	558	554	544	532
Placebo	815	779	750	719	647	581	567	556	551	542	525

Patients at Risk, n

Neratinib	604	559	541	520	464	407	400	391	384	376	362
Placebo	605	575	548	529	495	448	444	435	427	416	402

Martin. Lancet Oncol. 2017;18:1688.

Proposed Strategy for Managing Patients With Stage I-III HER2+ EBC



*In the phase II CONTROL trial assessing effectiveness of antidiarrheal prophylaxis for neratinib-induced diarrhea, 54% of patients received pertuzumab as part of (neo)adjuvant therapy prior to extended adjuvant therapy with neratinib.[1]

1. Barcenas. Ann Oncol. 2020;31:1223.

Future Directions: Ongoing Clinical Trials in HER2+ EBC

Trial Name	Phase	Setting	Treatment Arms	Primary Endpoint
IMpassion050[1]	III	Neoadjuvant; T2-4, N1-3, M0 with known HER2, HR, PD-L1 status	AC + atezolizumab → THP + atezolizumab vs AC + Pbo → THP + Pbo	pCR
APTneo[2]	III	Neoadjuvant; early high-risk (T1c-2N1 or T3N0) or LA disease suitable for neoadjuvant tx	TCHP vs TCHP + atezolizumab vs AC + atezolizumab → TCHP + atezolizumab	EFS
DESTINY-11[3]	III	Neoadjuvant; T04, N1-3, M0 or ≥ T3, N0, M0	T-DXd ± THP vs ddAC-THP	pCR
DESTINY-05[4]	III	Adjuvant; patients with residual disease after neoadjuvant therapy	T-DXd vs T-DM1	IDFS
Astefania[5]	III	Adjuvant; patients with residual disease after neoadjuvant therapy	Atezolizumab + T-DM1 vs placebo + T-DM1	IDFS
NCT04886531[6]	II	Neoadjuvant; triple-positive stage I-III	Neratinib plus ET and trastuzumab	pCR

1. NCT03726879. 2. NCT03595592. 3. NCT05113251. 4. NCT04622319. 5. NCT04873362. 6. NCT04886531.

CEFPAS

AIRTUM

Corso di Aggiornamento

per **Operatori dei Registri Tumori**

Aggiornamento sui Tumori Mammari
Il punto di vista dell'oncologo

Vincenzo Adamo

Coordinatore Rete Oncologica Siciliana

Grazie per l'attenzione