Controversy in Breast Cancer Topic

Should be pCR Be an Acceptable Endpoint for Approval of New Therapies for Early-Stage Breast Cancer: NO

Cesar A. Santa-Maria, MD MSCI

Associate Professor of Oncology

Breast and Gynecological Malignancies Group

Sidney Kimmel Comprehensive Cancer Center

Johns Hopkins Medicine

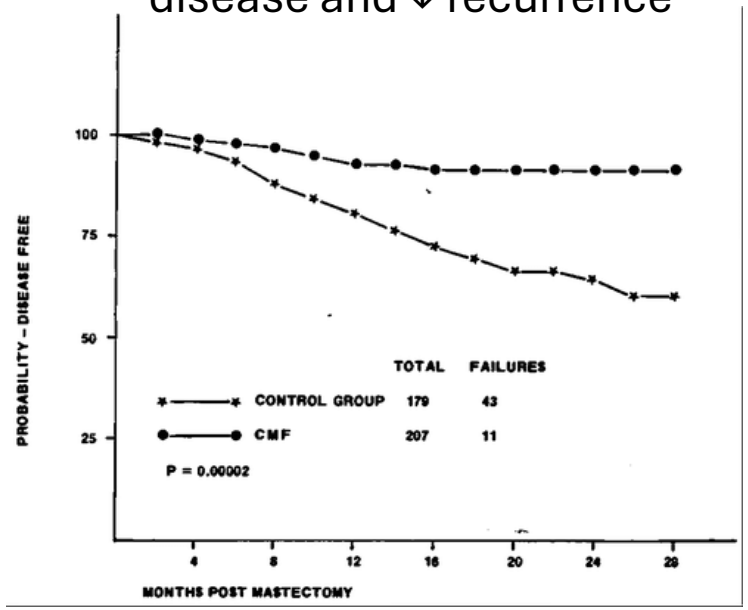
Overview

- Neoadjuvant therapy in breast cancer
- Accelerated approval and pCR
- Relationship between pCR and survival endpoints
  - Unique considerations with immunotherapy

Neoadjuvant therapy in breast cancer

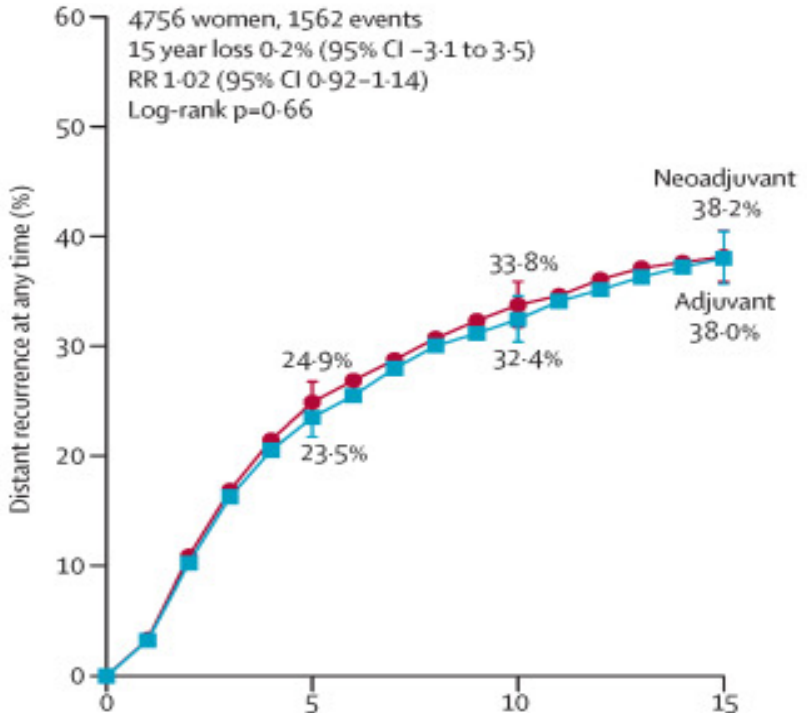
Adjuvant versus neoadjuvant chemotherapy: a historical perspective

Adjuvant chemotherapy can eliminate micrometastatic disease and ↓ recurrence



Bonadonna NEJM 1976

Does giving neoadjuvant chemotherapy improve outcomes since immediately eliminating micrometastatic disease early? Not historically (for chemo)



EBCTCG Lancet Oncol 2018

Historical indications for neoadjuvant therapy were surgical

Table. Indications, Considerations, and Relative Contraindications for Neoadjuvant Therapy

Indications
- Inoperable disease
- Inflammatory breast cancer
- Patient desires, but is not a candidate for, breast-conserving surgery at presentation
- Patient is medically unfit for surgery

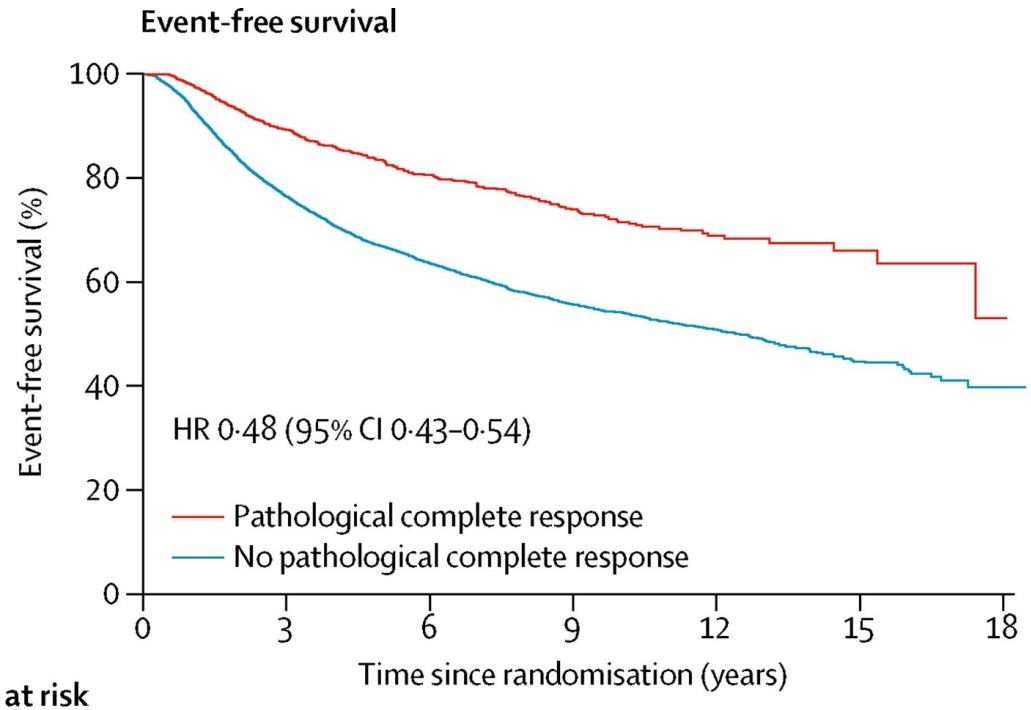
Considerations
- Research
- Stage II and III chemoresponsive subtypes (HER2-positive, TNBC)
- Node-positive disease

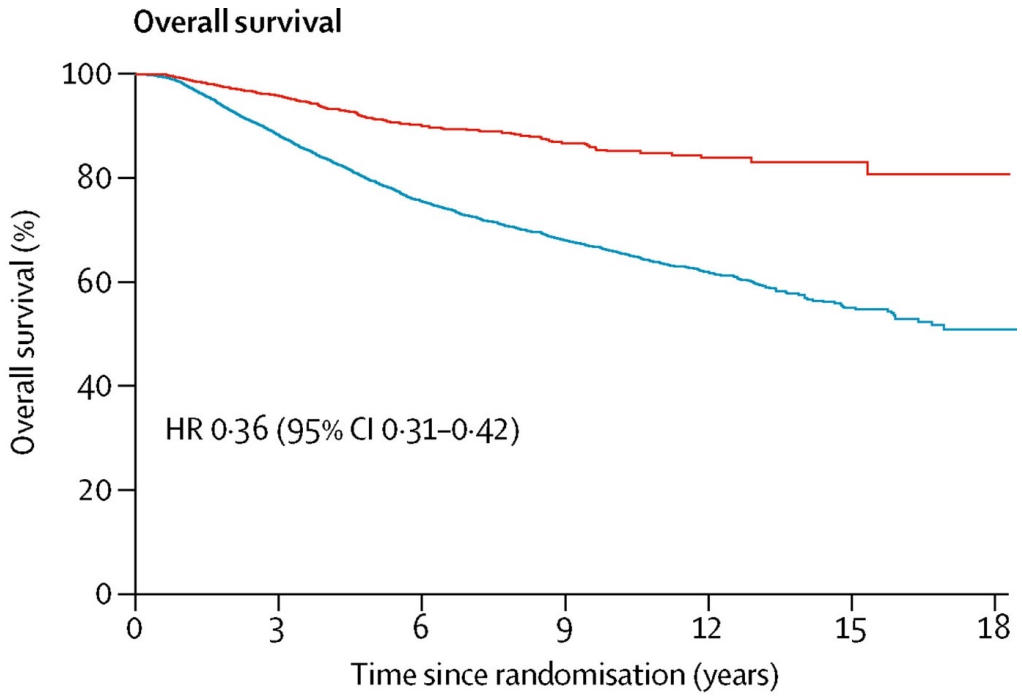
Relative contraindications
- Chemo-insensitive subtypes (classic lobular, luminal A)
- Stage I breast cancer

HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer.

Santa-Maria Oncology 2015

Patients achieving pCR have a better prognosis than those who do not: but not a perfect relationship



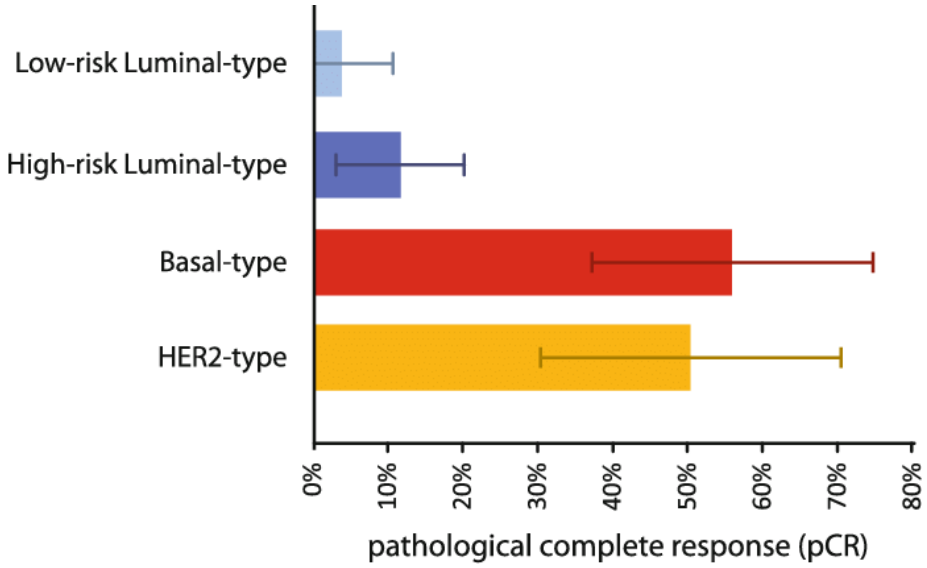


Number at risk							
Pathological complete response	2131	1513	583	337	124	35	2
No pathological complete response	9824	6169	2674	1523	525	165	1

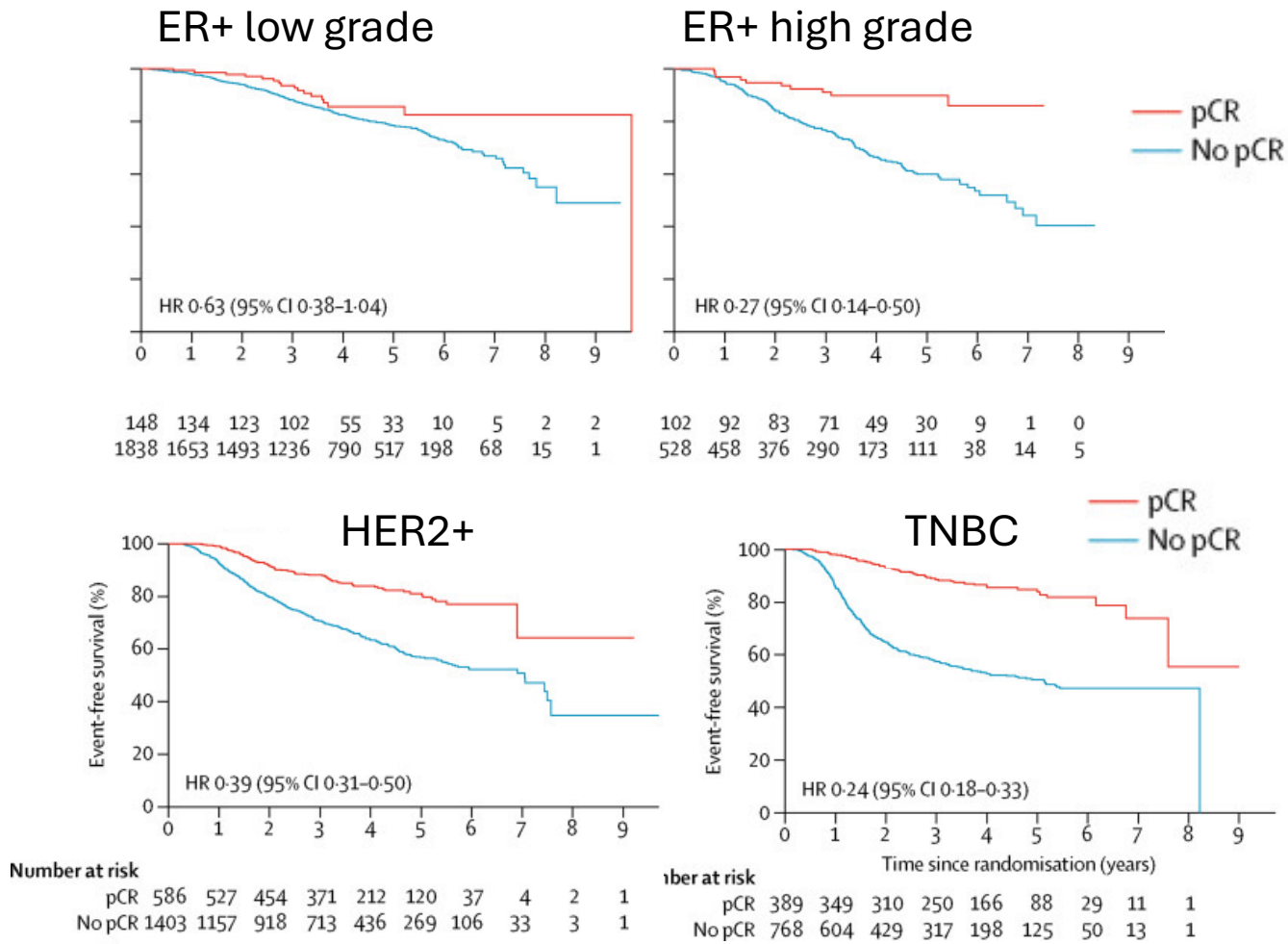
2131	1618	640	383	145	43	3
9824	7119	3173	1859	659	209	3

Cortazar et al Lancet 2014

pCR rate to chemotherapy varies by subtype, pCR relationship with survival does as well

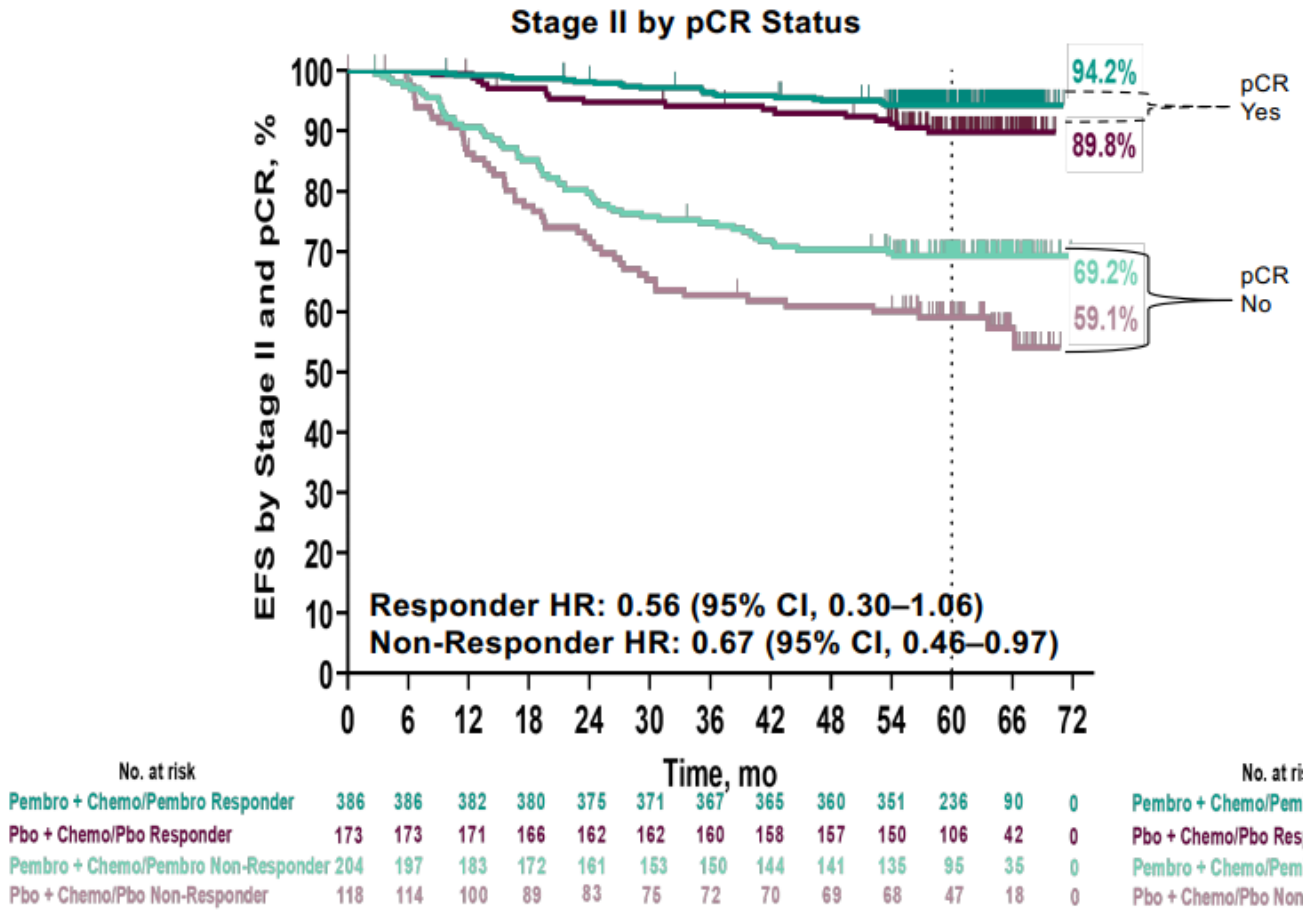


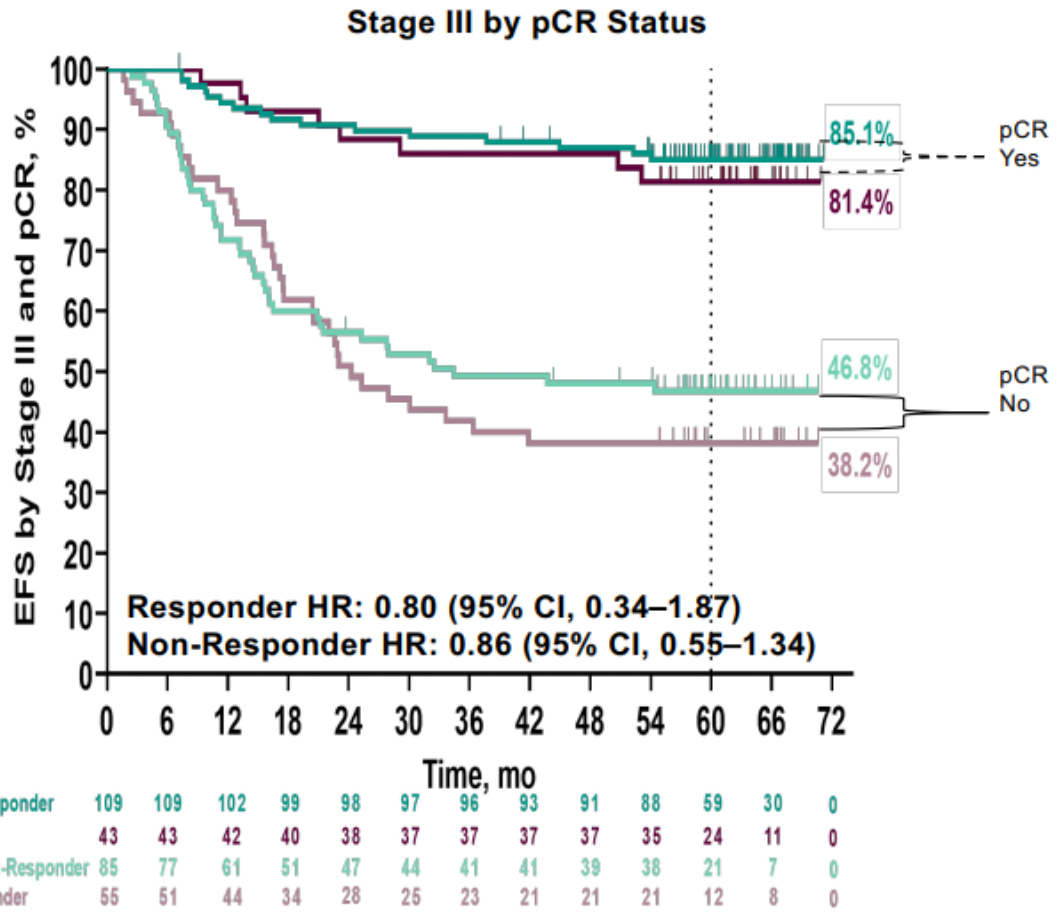
Krijgsman et al BCRT 2012



Cortazar et al Lancet 2014

Baseline clinical stage still matters, irrespective of pCR…

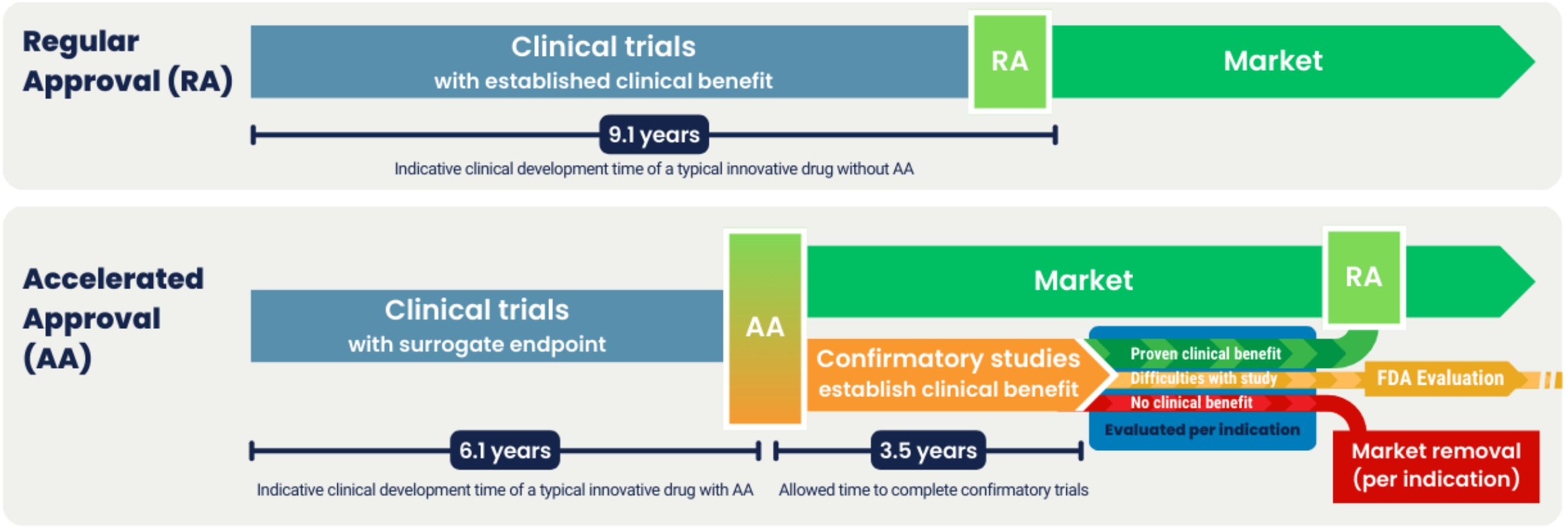




Schmid et al SABCS 2023

FDA approval process: accelerated approval and pCR

Accelerated vs Regular Approval



- Shorter time to market (~3yrs historically) → **Early access for patients**
- Reduced costs for clinical development (maybe)

- Confirmatory studies may not pan out
- **Clinical/financial toxicity of an unproven** drug
- Other fast track programs to consider (Breakthrough Therapy Designation, Fast Track Designation, Priority Review Designation)

Figure: tracercro.com

Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2020
Clinical/Medical
Revision 1

History of FDA accelerated approvals based on neoadjuvant studies in breast cancer

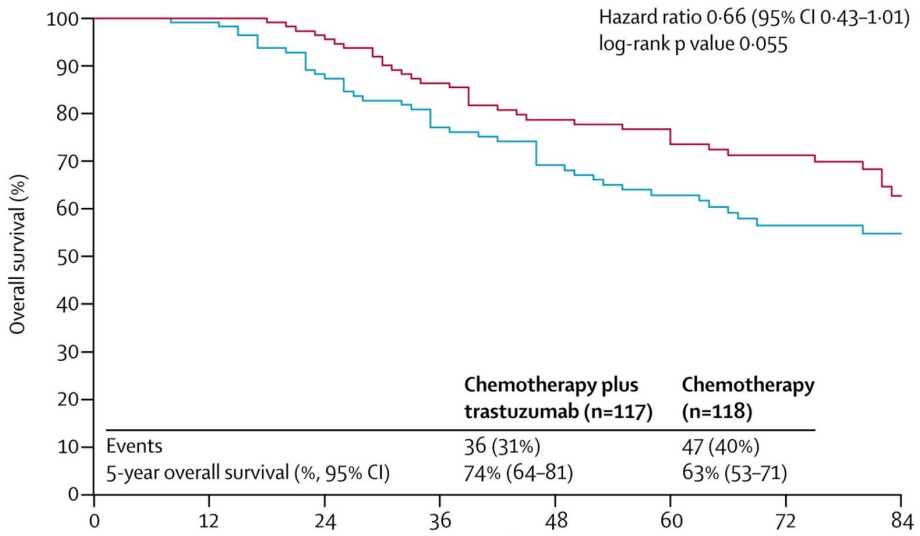
- **Pertuzumab:** FDA *granted* accelerated approval 9/2013, regular approval 12/2017 (APHINITY showing iDFS benefit)
- **Pembrolizumab:** FDA *declined* accelerated approval with IA 1, 2, and 3 → regular approval 7/2021 with IA4 (KEYNOTE-522 showing EFS benefit)

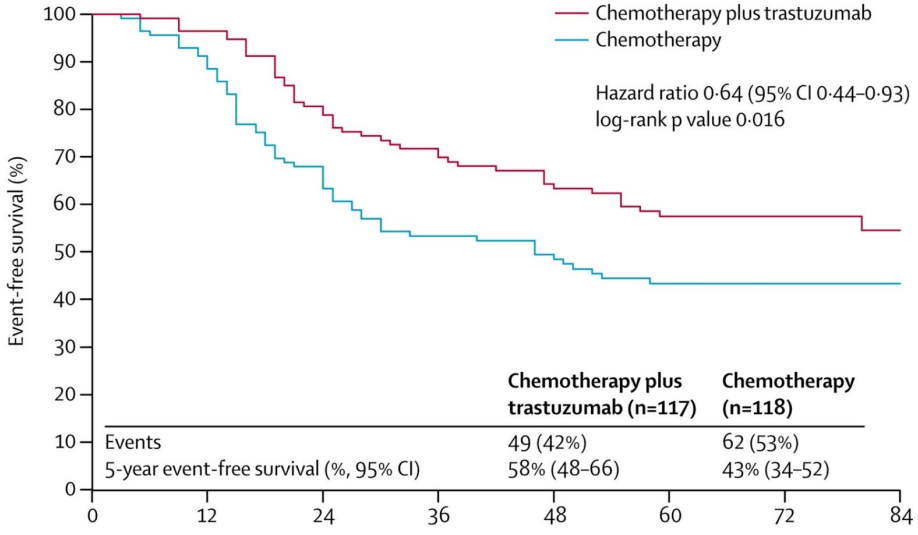
What is the relationship between a drug effects on pCR rate with survival?

Examples when ↑ in pCR leads to ↑ in survival

Trastuzumab: ↑pCR = ↑EFS/OS

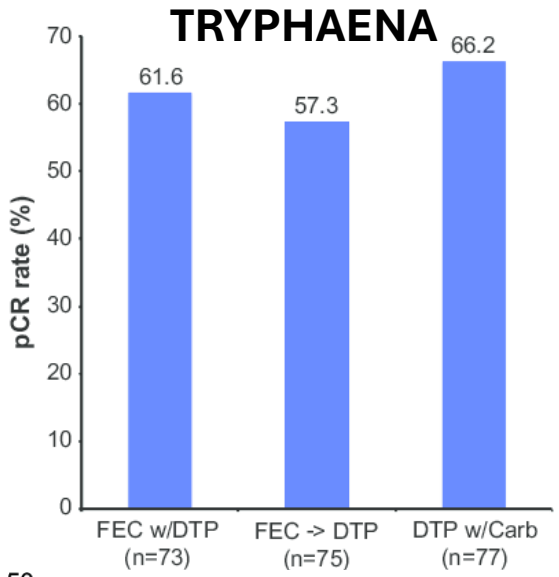
	HER2-positive disease		p value*
	With trastuzumab (n=117)	Without trastuzumab (n=118)	
bpCR	50 (43%)	26 (22%)	0·0007
tpCR	45 (38%)	23 (19%)	0·001
OR‡	102 (87%)	87 (74%)	0·009

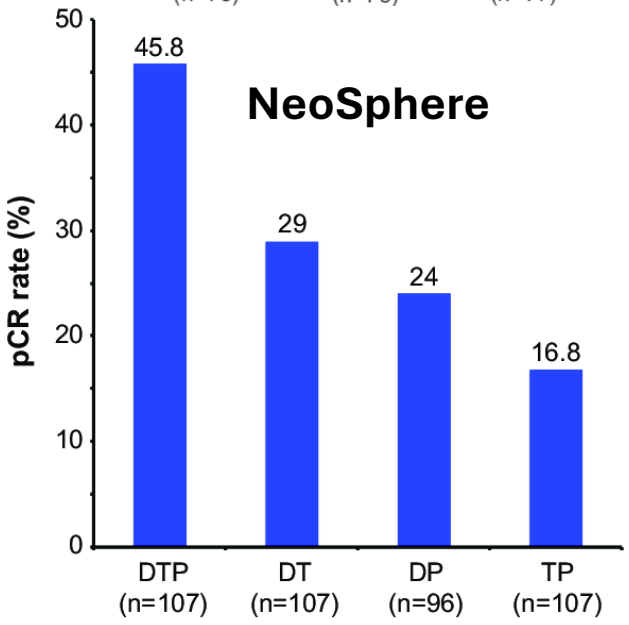




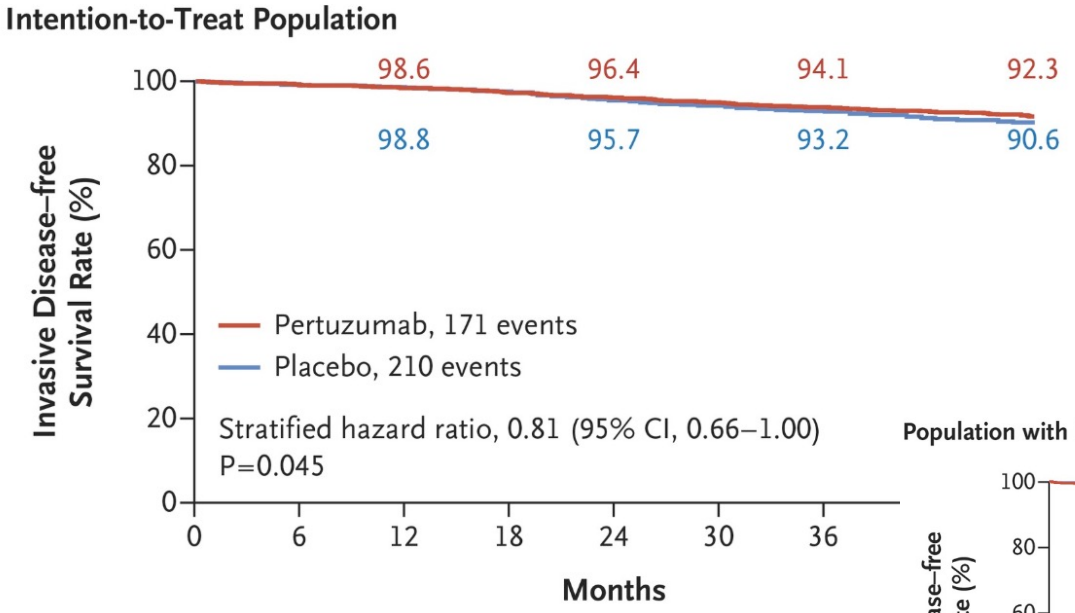
Gianni et al Lancet Oncol 2014

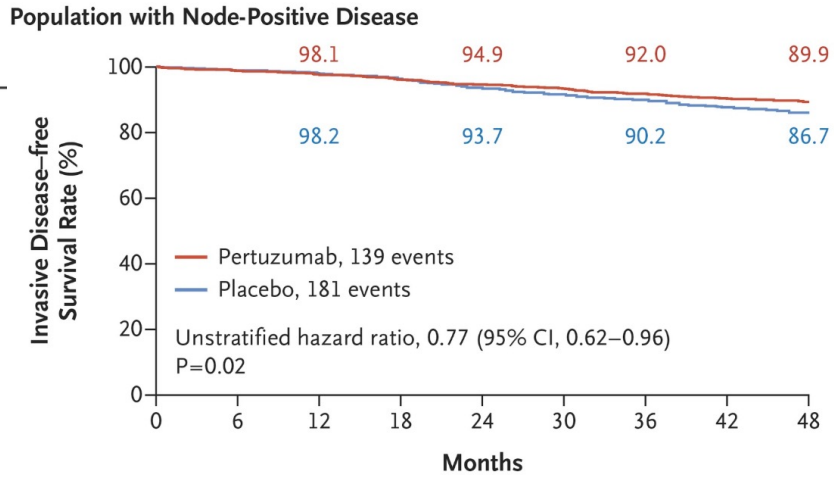
Pertuzumab: ↑pCR = modest ↑EFS





APHNITY: confirmatory adjuvant trial

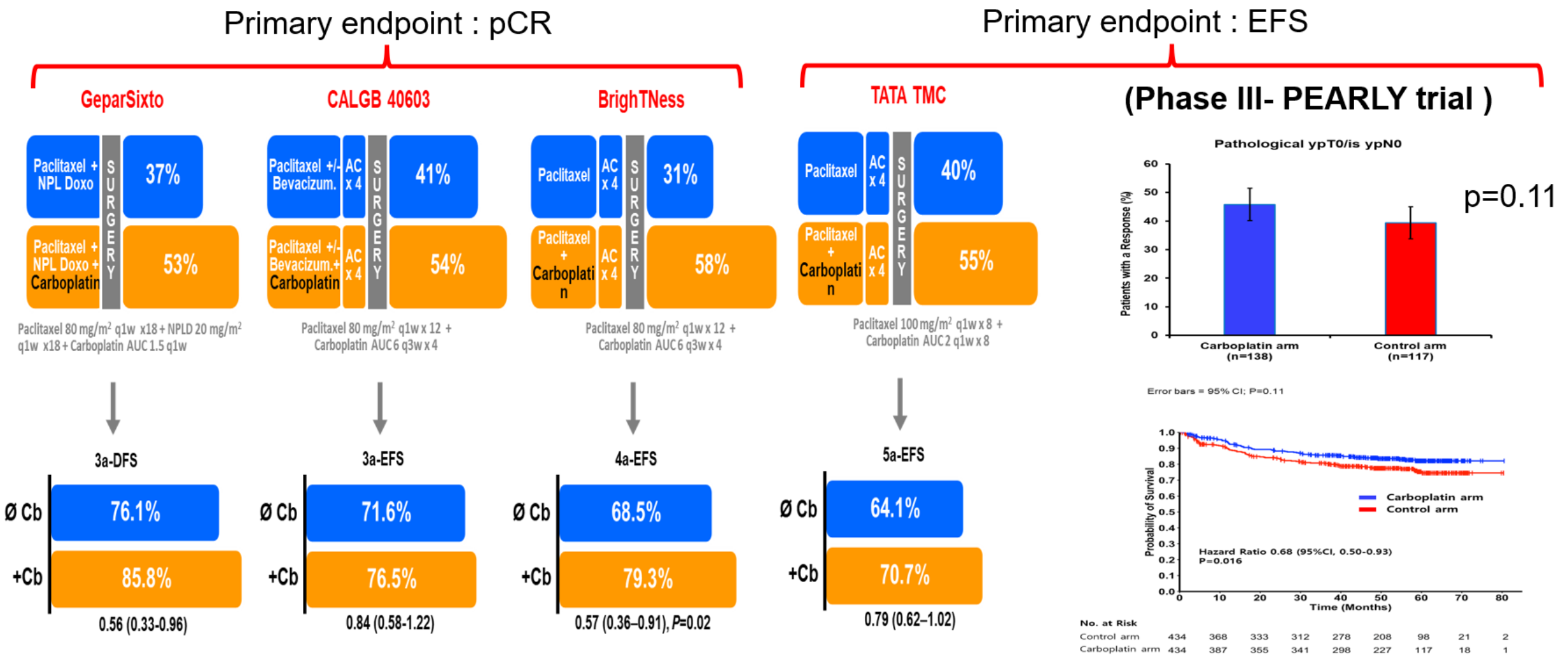




Schneeweiss et al Ann Oncol 2013
Giani et al Lancet Oncol 2012

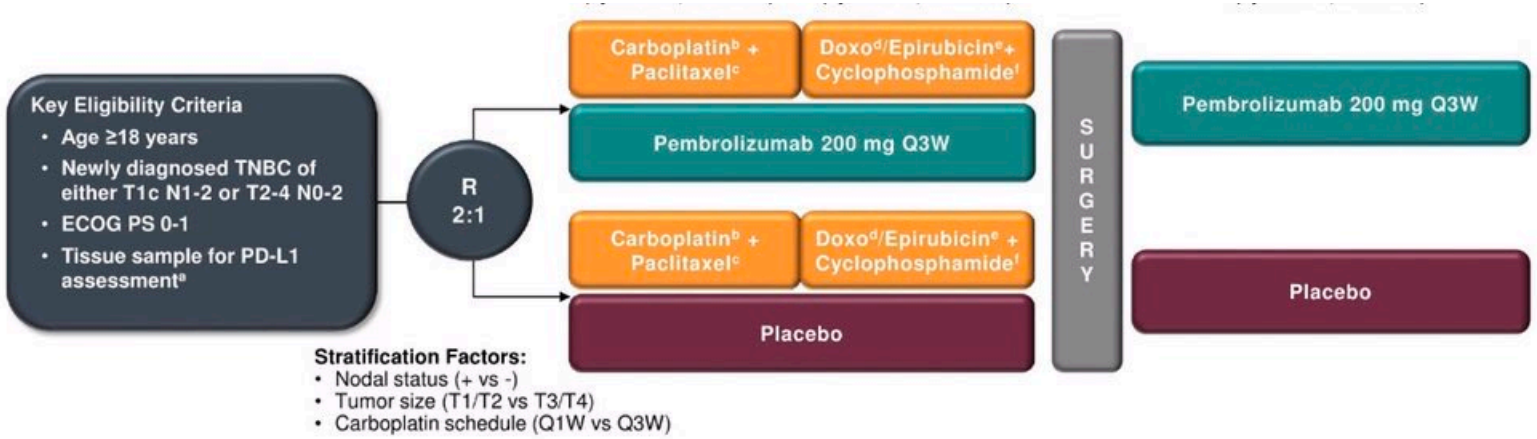
von Minckwitz et al NEJM 2017

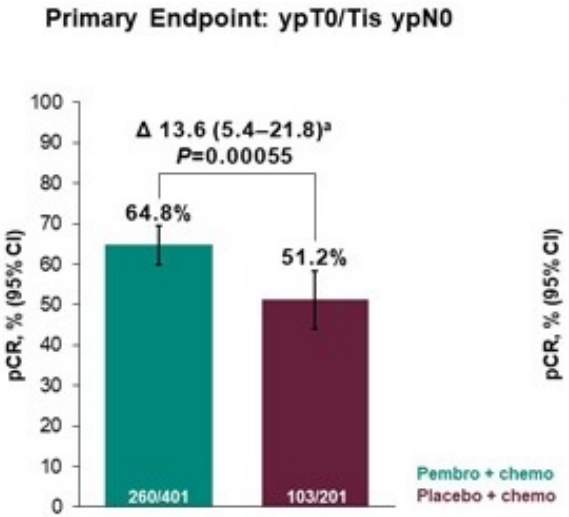
Carboplatin: ↑pCR (for the most part) = ↑DFS



von Minckwitz et al SABCS 2015, von Minckwitz et al *Lancet Oncol* 2014, Sikov et al SABCS/*JCO* 2015, Loibl et al *Lancet Oncol* 2018, Gupta et al SABCS 2022, Sohn et al ASCO 2024, Cortes ASCO 2024

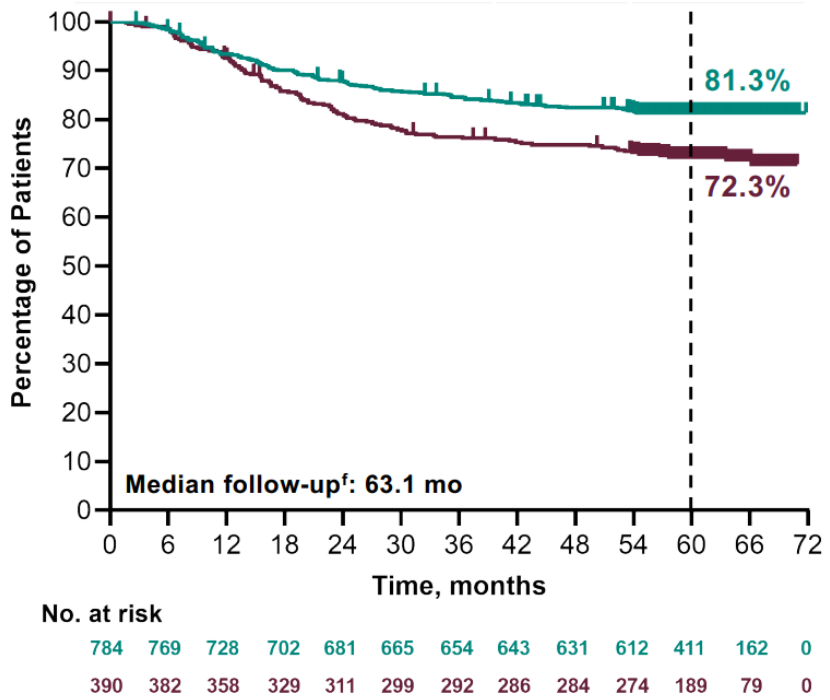
Pembrolizumab: modest/moderate ↑pCR = ↑EFS





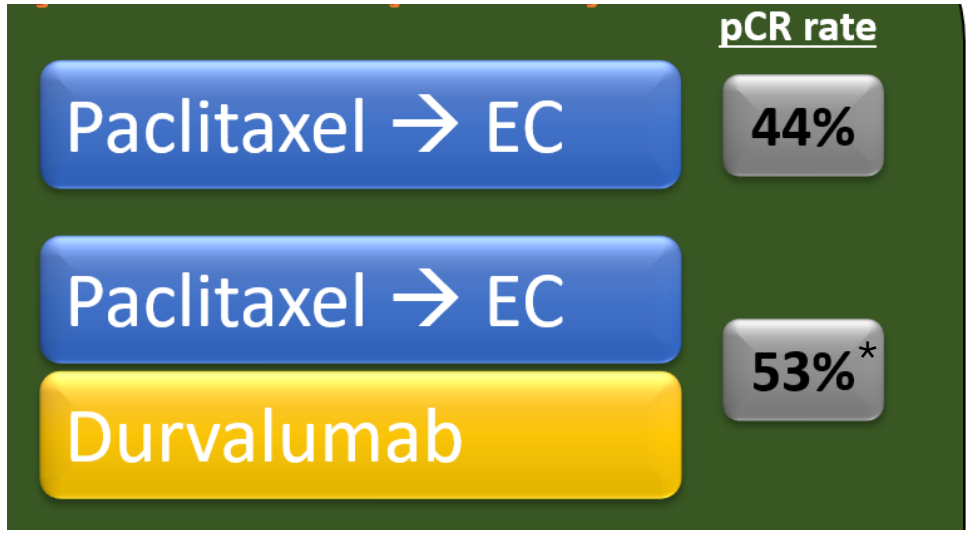
63%	55.6%

IA3 pCR analysis

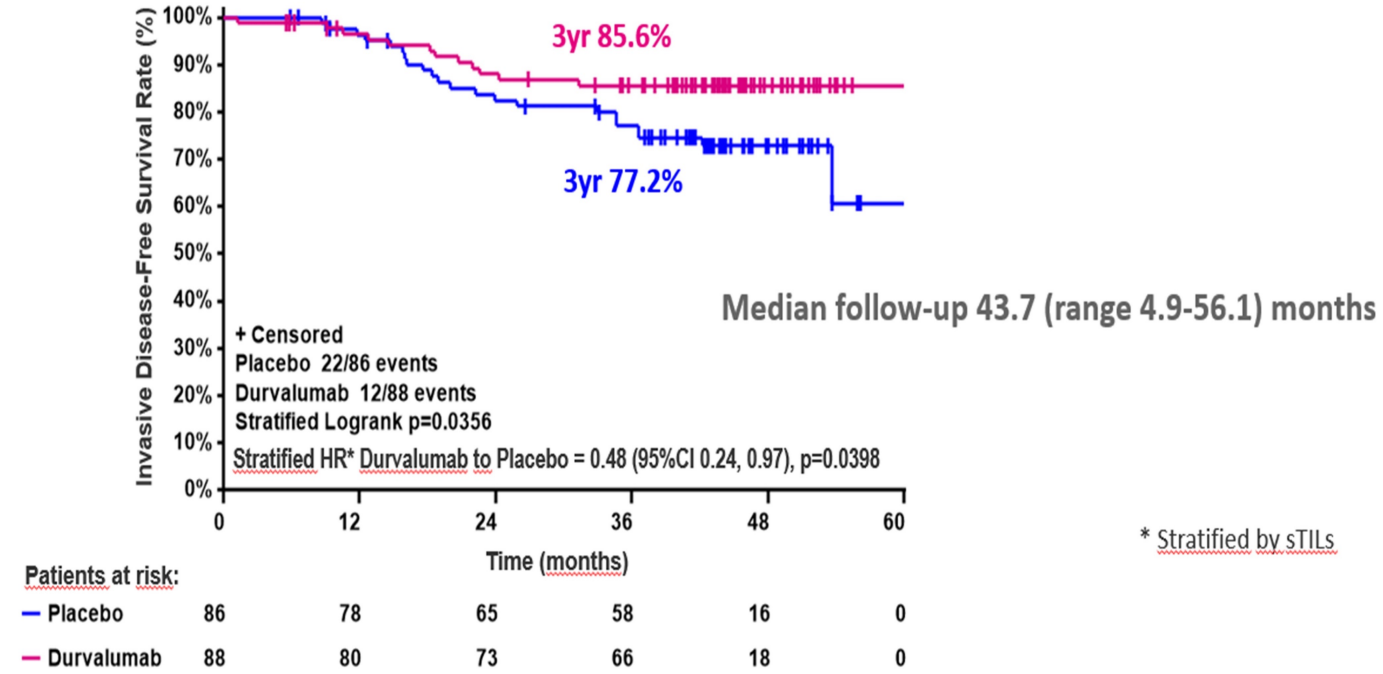


Shah et al CCR 2022
Schmid et al SABCS 2023

Durvalumab: no/?modest ↑pCR = ↑iDFS



*Not statistically significant



Loibl et al ASCO 2018, 2021

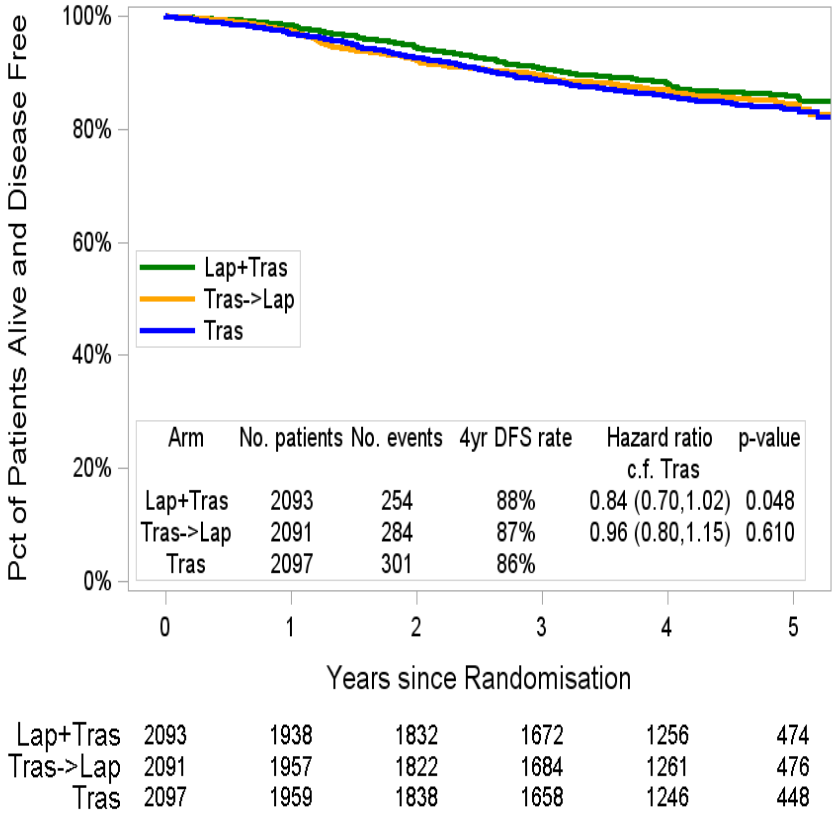
Examples when ↑ in pCR leads to no ↑ in survival

Lapatinib in HER2+ BC: ↑pCR = no ↑DFS/OS

Several studies demonstrated increase in pCR by adding lapatinib

Study	Preoperative chemo regimen	+ trastuzumab	+ lapatinib	+ trastuzumab & lapatinib
EORTC 10054	Doc → FEC	52%	36%	56%
NSABP B-41	AC → Pac	53%	53%	62%
CALGB 40601	Pac	43%	29%	52%
neoALTTO	Pac	30%	25%	51%

ALLTO: confirmatory adjuvant trial



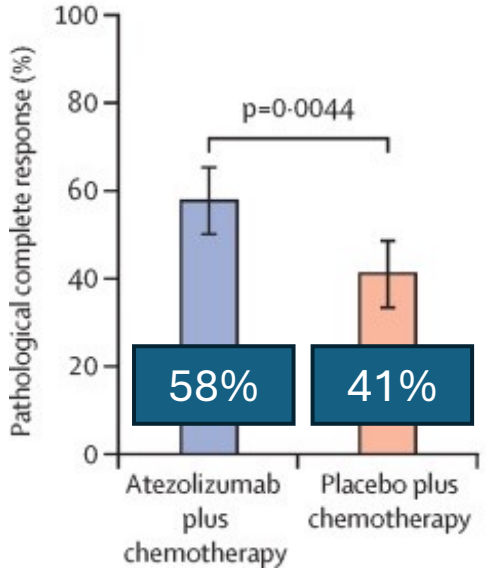
Piccart-Gebhart ASCO 2015

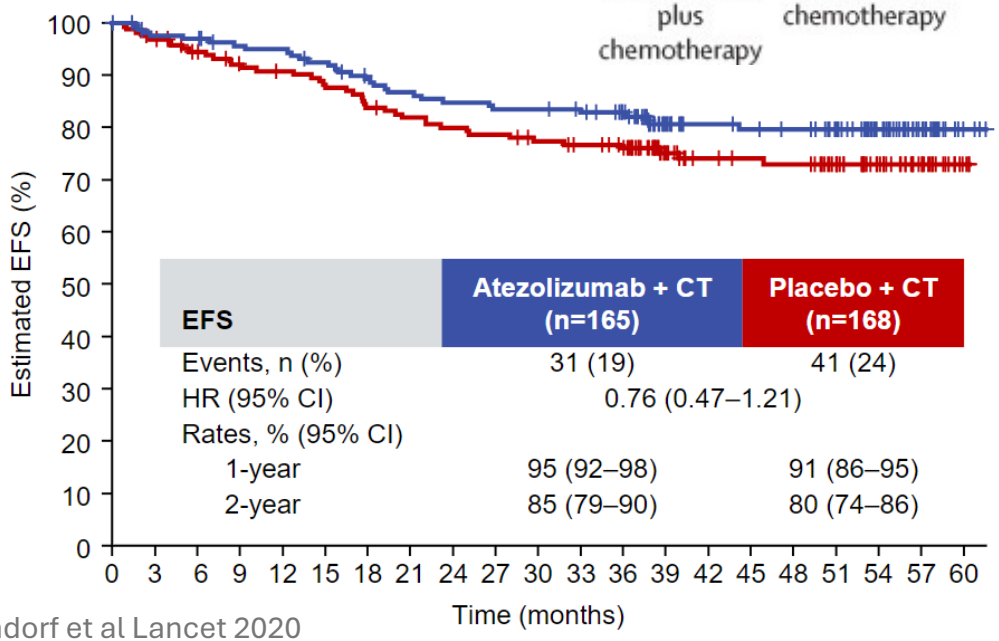
Bevacizumab: ↑pCR = no ↑DFS/OS

	Trial	Subtype	pCR improved	DFS improved	OS improved
Neoadjuvant	GBG 44	HER2-	yes (ER-)	no	no
	NSABP B-40	HER2-	yes (ER+)	no	-
	ARTEMIS	HER2-	yes (ER-)	-	-
	CALGB 40603	TNBC	yes	-	-
	ABCSG-32	HER2-	yes (esp ER-)	-	-
	SWOG 0800	HER2-	yes (ER-)	-	-
Adjuvant	ECOG 5103	HER2-	-	no	no
	BEATRICE	TNBC	-	no	no
	BETH	HER2+	-	no	no

Atezolizumab: ↑pCR = ?modest/no ↑EFS

IMpassion031: neoadjuvant atezolizumab ↑pCR but ?modest ↑EFS (not powered for EFS)





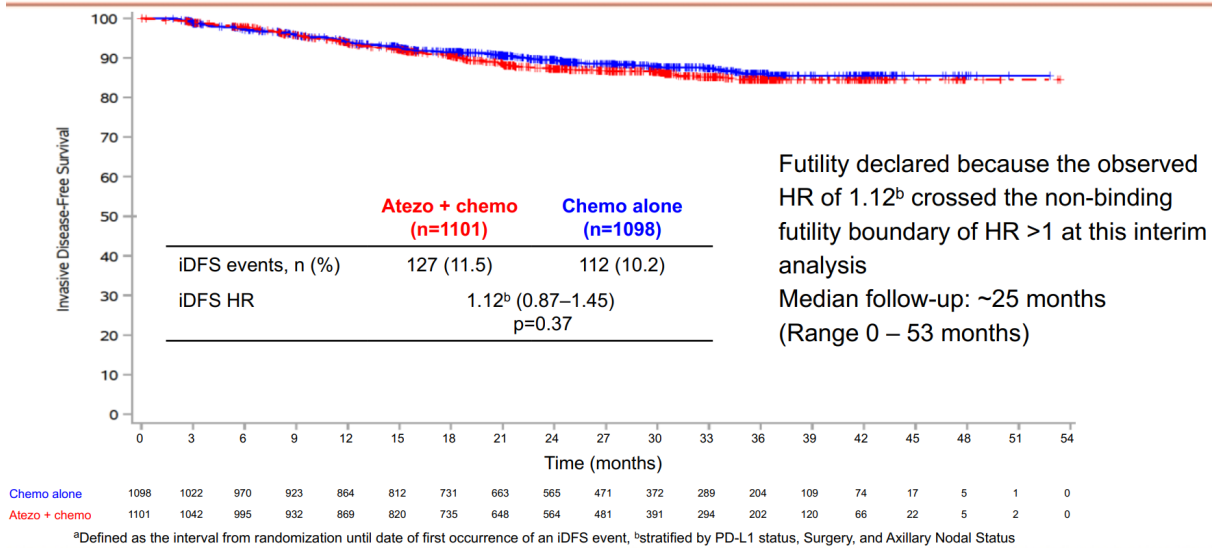
EFS	Atezolizumab + CT (n=165)	Placebo + CT (n=168)
Events, n (%)	31 (19)	41 (24)
HR (95% CI)	0.76 (0.47–1.21)	
Rates, % (95% CI)		
1-year	95 (92–98)	91 (86–95)
2-year	85 (79–90)	80 (74–86)

Mittendorf et al Lancet 2020
Barrios et al ESMO 2023

IMpassion030: adjuvant atezolizumab does not improve iDFS

Primary efficacy endpoint: iDFS[a] (ITT population)

San Antonio Breast Cancer Symposium®
December 5-9, 2023 | San Antonio, TX
@SABCSSanAntonio



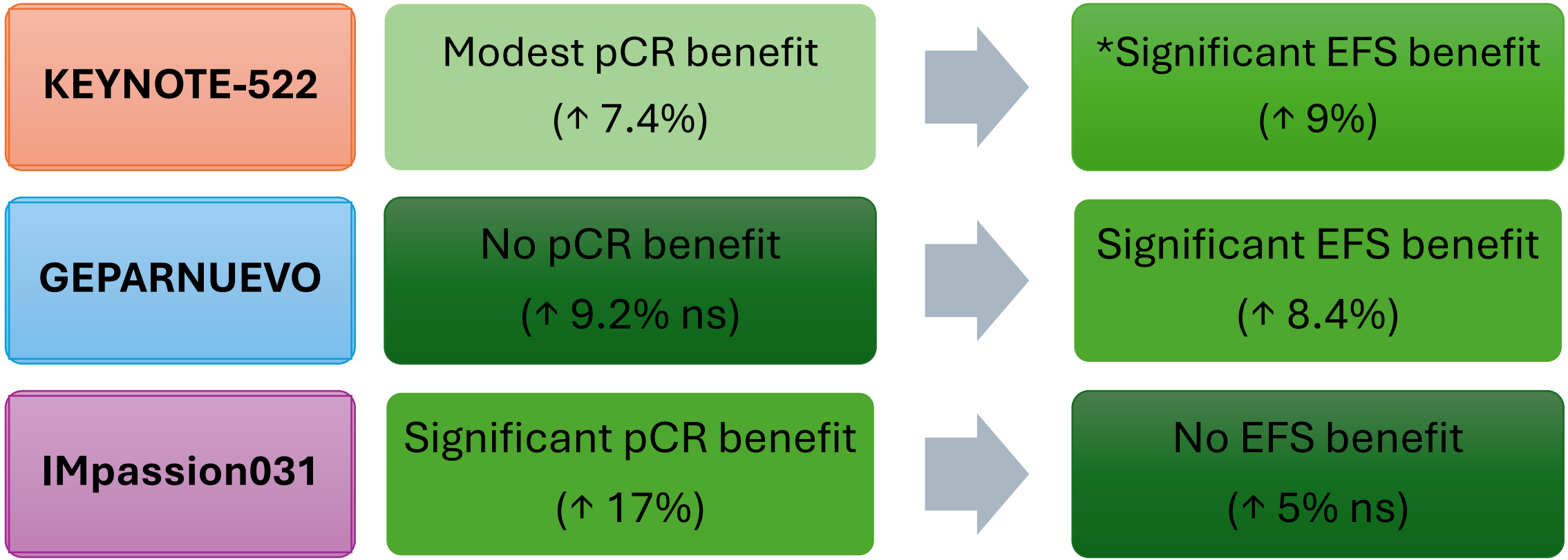
	Atezo + chemo (n=1101)	Chemo alone (n=1098)
iDFS events, n (%)	127 (11.5)	112 (10.2)
iDFS HR	1.12[b] (0.87–1.45) p=0.37	

Futility declared because the observed HR of 1.12[b] crossed the non-binding futility boundary of HR >1 at this interim analysis
Median follow-up: ~25 months (Range 0 – 53 months)

[a]Defined as the interval from randomization until date of first occurrence of an iDFS event, [b]stratified by PD-L1 status, Surgery, and Axillary Nodal Status

Ignatiadis et al SABCS 2023

pCR/EFS relationship in chemo IO



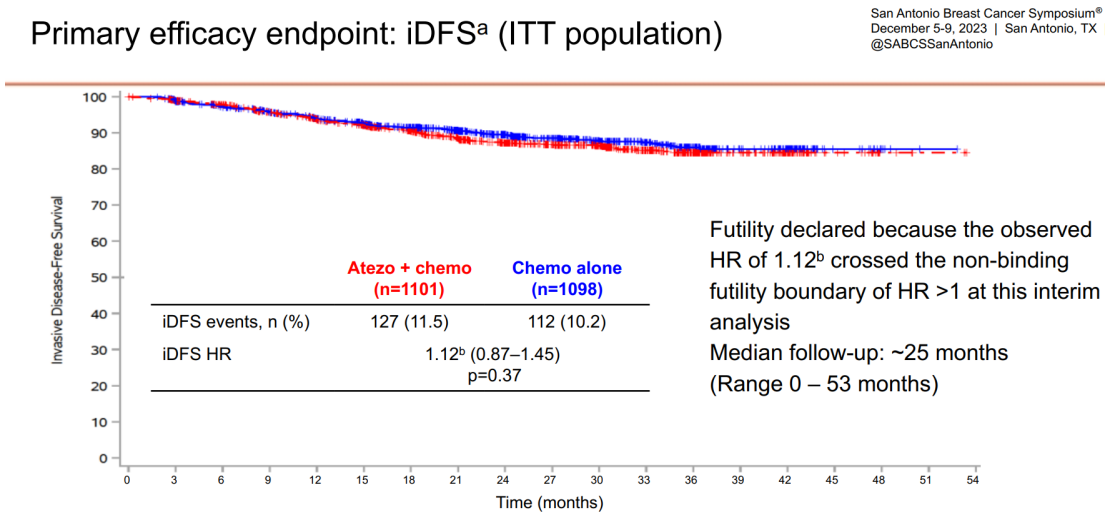
*powered for EFS

Santa-Maria NCCN Congress 2024

Unique considerations with immunotherapy

Does neo vs adj matter?

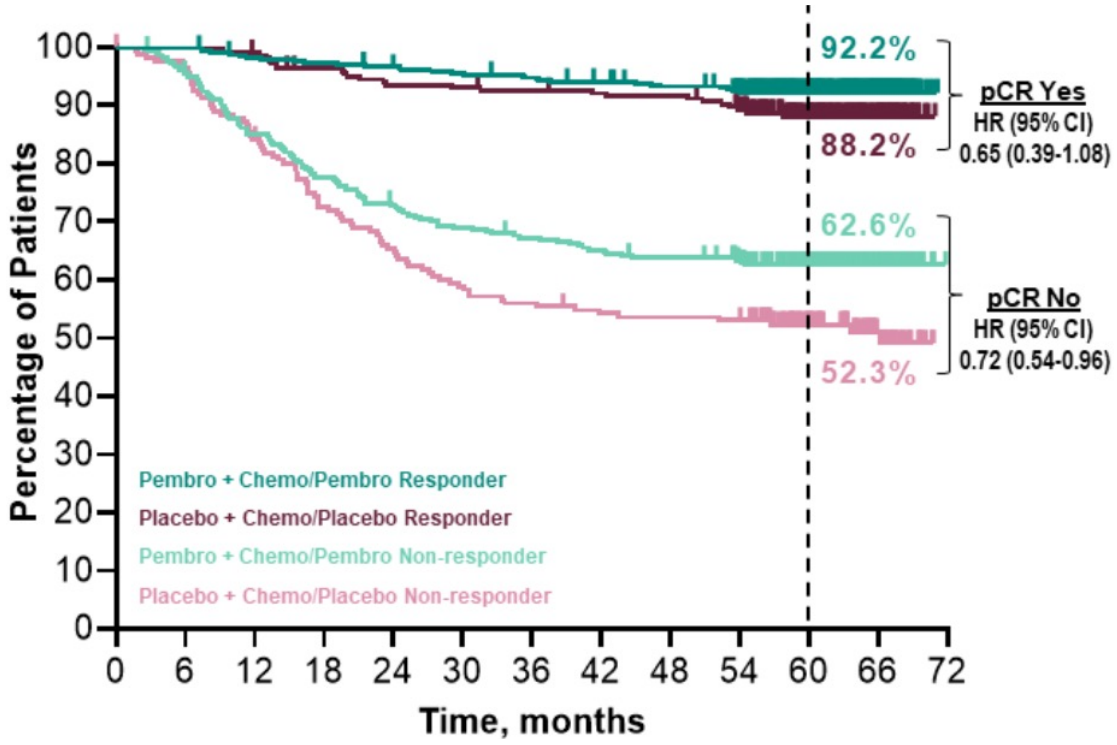
- Data in melanoma suggests it does (SWOG 1801)
- Could this explain diff between IMP031 vs 030?



Ignatiadis et al SABCS 2023

Does road to path to pCR matter?

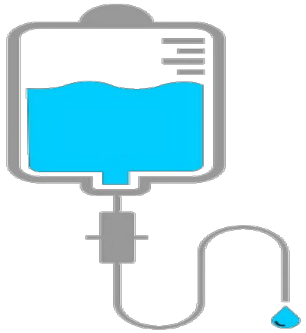
KN522: pts achieving pCR on pembro did better



Schmid et al ESMO 2023

What does pCR mean in breast cancer?

For the individual patient:
pCR = ↓relative risk of recurrence (except for lumA)



For drugs neoadjuvantly:
ΔpCR rate ≠ Δ iDFS

- Neoadjuvant therapy can risk stratify patients and inform adjuvant therapy to optimize outcomes
- Relationship of a drug on pCR rate with iDFS is variable, factors that may influence this:
  - Breast cancer subtype
  - Depth of pCR
  - Biological effects of drug (ie neoadjuvant administration of IO)
  - How EFS validated (ie adjuvant validation of neoadjuvant regimen, IMp030/031)
  - Adjuvant therapies administered (ie in ER+)

Should pCR be an acceptable endpoint for *accelerated* approval of new therapies for early-stage breast cancer?

- Many factors can influence relationship between pCR rate and survival endpoints
- pCR rate is not reliable surrogate for survival endpoints → studies need to be powered for survival
- Need to weigh risk of toxicity with unproven drug *vs* faster access for pts (but how much faster for neoadjuvant?)

Therefore, for most drugs, pCR not sufficient for accelerated approval