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

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YES

Two types of US-FDA approvals

Enables patients to receive a potentially life saving therapy earlier that required for traditional approval

Accelerated Approval

- Allows earlier approval of drugs that treat serious conditions **based on a surrogate endpoint**.
- A surrogate endpoint is a marker that **predicts clinical benefit** but is not itself a measure of clinical benefit.
- Drug companies are **required to conduct studies to confirm clinical benefit.**

Traditional Approval

- Applicants must demonstrate direct evidence of clinical benefit

https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program

Does the FDA consider pCR a valid surrogate for improved disease-free survival (DFS)* or event-free survival (EFS)* in breast cancer?

If YES, accelerated approval is justified based on improved pCR rate

* DFS and EFS are the traditional FDA registration endpoints in adjuvant breast cancer trials

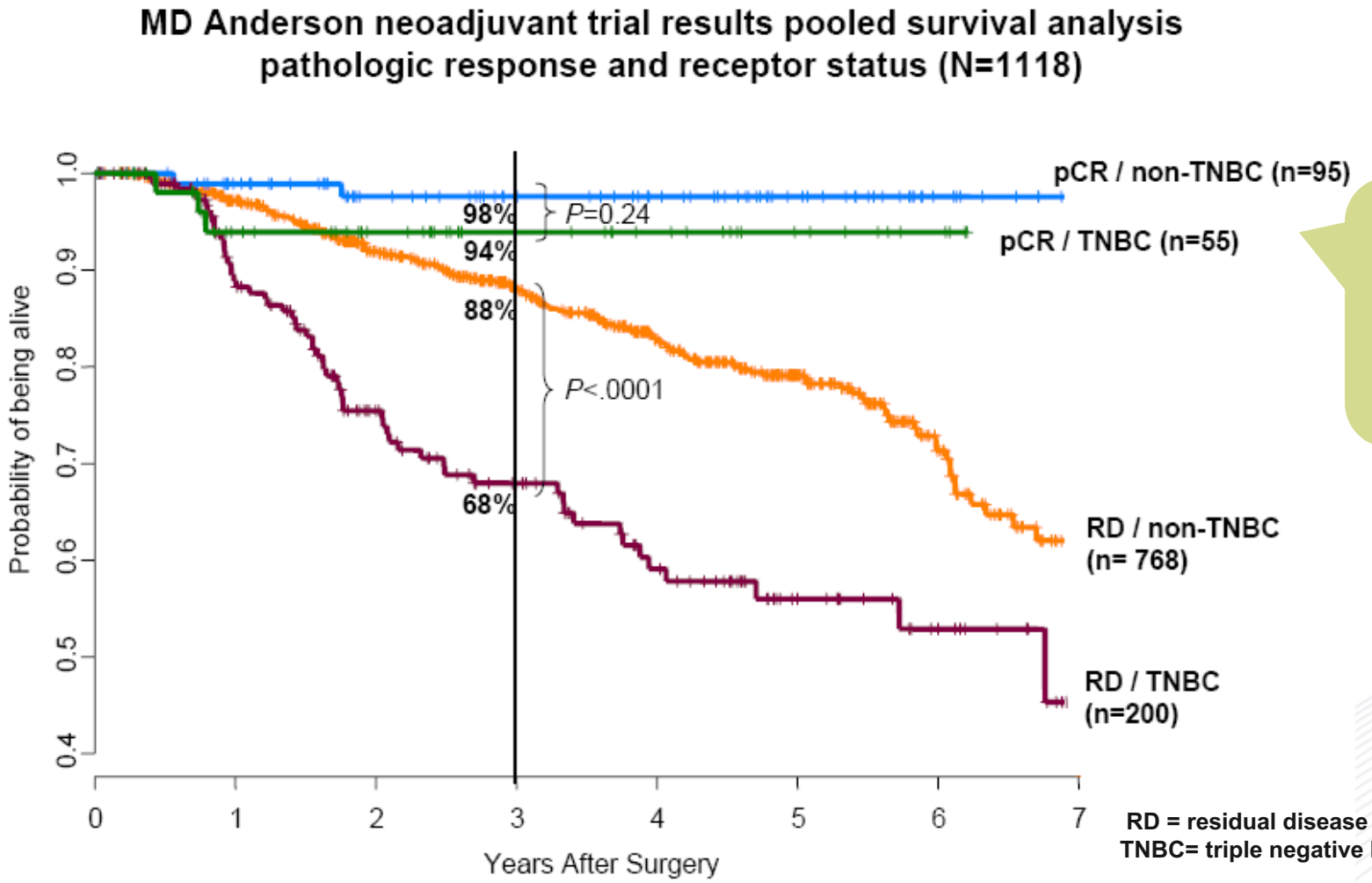
FDA Adult Surrogate Endpoint Table

Disease or Use	Patient Population	Surrogate endpoint	Type of approval appropriate for	Drug mechanism of action
Cancer: solid tumors	Patients with breast cancer	Pathological complete response	Accelerated	Mechanism agnostic
Cancer: solid tumors	Patients with nonmetastatic castrate-resistant prostate cancer	Metastasis-free survival	Accelerated/Traditional	Mechanism agnostic
Cancer: solid tumors	Patients with advanced prostate cancer	Plasma testosterone levels	Traditional	Gonadotropin-releasing hormone antagonist
Cancer: solid tumors	Patients with breast cancer; ovarian cancer; renal cell carcinoma; pancreatic neuroendocrine cancer; colorectal cancer; head and neck cancer; non-small cell lung cancer; melanoma; tuberous sclerosis complex-associated SEGA and renal angiomyolipoma; merkel cell carcinoma; unresectable or metastatic cutaneous basal cell carcinoma; urothelial carcinoma; cervical cancer; endometrial cancer; hepatocellular carcinoma; fallopian tube cancer; microsatellite instability-high cancer; gastric cancer; gastroesophageal junction cancer; thyroid cancer; astrocytoma; Kaposi's sarcoma; unresectable or metastatic cutaneous squamous cell carcinoma; neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation; prostate cancer; esophageal cancer; tumor mutational burden high solid tumors; cholangiocarcinoma; bladder cancer; neuroblastoma; mismatch repair deficient solid tumors	Durable objective overall response rate	Accelerated/Traditional	Mechanism agnostic
Cancer: solid tumors	Patients with breast cancer; renal cell carcinoma; pancreatic neuroendocrine tumor; soft tissue sarcoma; ovarian, fallopian tube, or primary peritoneal cancer; prostate cancer; thyroid cancer; colorectal cancer; non-small cell lung cancer; head and neck cancer; tuberous sclerosis complex; merkel cell carcinoma; basal cell carcinoma; urothelial carcinoma; cervical cancer; endometrial cancer; hepatocellular carcinoma; fallopian tube cancer; melanoma; astrocytoma; gastrointestinal stromal tumors	Progression-free survival	Accelerated/Traditional	Mechanism agnostic
Cancer: solid tumors	Patients receiving adjuvant therapy following complete surgical resection of colon cancer; colorectal cancer; melanoma; renal cell cancer; gastrointestinal stromal tumor; breast cancer and adjuvant therapy for stage III non-small cell lung cancer	Disease-free survival	Accelerated/Traditional	Mechanism agnostic

Accessed on July 9, 2024: The SE table is updated by CBER and CDER every 6 months to reflect current thinking as mandated by section 507 of the FD&C Act.

Let’s review the evidence

Pathologic complete response (pCR = no invasive cancer in the breast and lymph nodes, ypT0 ypN0) is a powerful predictor of long-term survival in both ER+ and ER- cancers



These observations were confirmed and replicated by EVERY STUDY that examined pCR and survival

RD = residual disease
TNBC= triple negative breast cancer

C Liedtke et al, J Clin Oncol, 26, 2008

All agents that increased pCR rate eventually improved EFS in properly powered randomized adjuvant trials

TNBC trials pCR rates and EFS

BrighTNess[17]	III	PTX → AC PTX+Cb → AC PTX+Cb+Vel → AC	pCR	31 vs 58 vs 53 *P*=.0001 (PTX+Cb +Vel vs PTX)	4-y EFS, 68.5% vs 79.3% vs 78.2% HR, 0.63 (PTX+Cb+Vel vs PTX) HR, 1.12 (PTX+Cb+Vel vs PTX+Cb HR, 0.57 (PTX+Cb vs PTX)	Showed the translation of platinum-related pCR Improvement into long-term clinically meaningful benefit
CALGB 40603[11]	II	PTX → AC PTX+Bev → AC+Bev PTX+Cb → AC PTX+Cb+Bev → AC+Bev	pCR	39 vs 43 vs 49 vs 60 *P*=.0029 (with Cb vs without Cb) *P*=.057 (with Bev vs without Bev)	5-y EFS: HR, 0.99 (95% CI, 0.70–1.40) (with Cb vs without Cb) HR, 0.91 (95% CI, 0.64–1.29) (with Bev vs without Bev)	Showed platinum agents improve pCR rate, did not demonstrate improvement in EFS with platinum
GeparSixto[13,100]	II	PTX+npLD+Bev → EC PTX+npLD+Bev+Cb → EC	pCR	36.9 vs 53.2 *P*=.005	3-y DFS, 76.8% vs 86.1% HR, 0.56 (95% CI, 0.34–0.93)	Showed platinum agents improve pCR rate and demonstrated improvement in EFS with platinum
NeoSTOP[40]	II	PTX+Cb → AC DXP+Cb	pCR	54 vs 54		Showed clinically meaningful pCR results with anthracycline-free regimen for TN patients
KEYNOTE-522[19,30]	III	PTX+Cb+Pla → AC/EC+Pla PTX+Cb+Pembro → AC/EC+Pembro * Adjuvant Pembro/Pla	pCR and EFS	55.6 vs 63	3-y EFS, 76.8% vs 84.5% HR, 0.63 (95% CI, 0.48–0.82)	Established the role of immunotherapy in the neoadjuvant/adjuvant treatment paradigm of TN patients Innovative coprimary endpoints design
IMpassion031[27]	III	nab-PTX +Pla → AC+Pla nab-PTX+Atezo → AC+Aetzo * Adjuvant Atezo/Pla	pCR in ITT and pCR in PD-L1+	41 vs 58 *P*=.004	EFS, HR, 0.76 (95% CI, 0.4–1.44)	Demonstrated pCR improvement with the addition of immunotherapy to NACT
GeparNuevo[28,31]	II	nab-PTX+Pla → AC+Pla nab-PTX+Durva → AC+Durva	pCR	44.2 vs 53.4 *P*=.29	3-y IDFS, 76.9% vs 84.9% HR, 0.48 (95% CI, 0.24–0.97)	Evaluated the role of immune-system priming with a 'window' phase Demonstrated long-term benefit from neoadjuvant ICI without the administration of postsurgery immunotherapy
FAIRLANE[101]	II	PTX+Ipata PTX+Pla * Adjuvant Ctx	pCR in ITT and pCR in PTEN-low	13.3 vs 17.1		Explored a biomarker-driven design and analysis
GeparOLA[102]	II	PTX+Cb → EC PTX+Ola → EC (HRD)	pCR	48.6 vs 55.1 *P*=.99		Evaluated the role of PARPi in the neoadjuvant setting of HRD (*BRCA* and non-*BRCA*) patients
NeoTALA[47]	IIs	Tala * Adjuvant Ctx(*BRCA*-mutated)	pCR	49.2 (in ITT)		Promising pCR results with PARPi monotherapy for *BRCA*-mutated patients

Paclitaxel + anthracycline (qwT +ddAC)
pCR ~ 30-40%

Paclitaxel/Carboplatin + ddAC
pCR ~ 50-55%

Paclitaxel/Carboplatin + AC + Pembrolizumab
pCR ~ 63%

In HER2 positive disease the pCR improvements with trastuzumab and trastuzumab/pertuzumab and subsequent EFS improvements are well known (and was the first FDA approval based on pCR rate improvement).

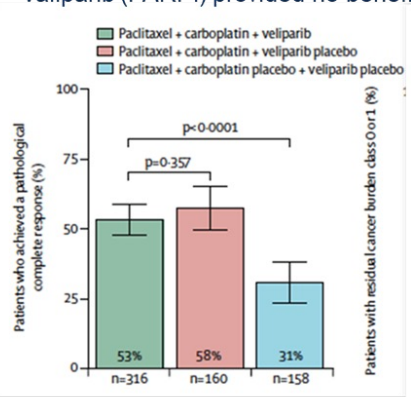
Spring LM, et al. J Natl Comp Cancer Network. 20:723-34, 2022.

Including carboplatin with paclitaxel improves pCR rate and event-free survival

BrighTNess trial results

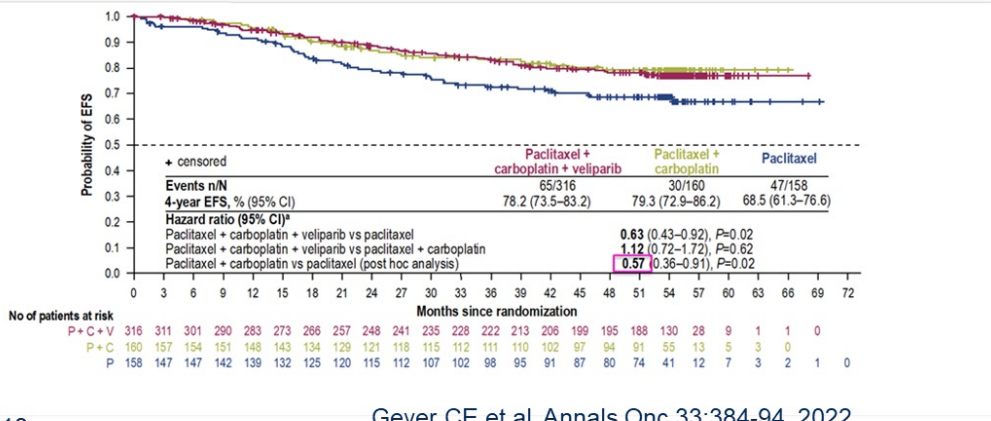
pCR rate 53-58%

Valiparib (PARPi) provided no benefit



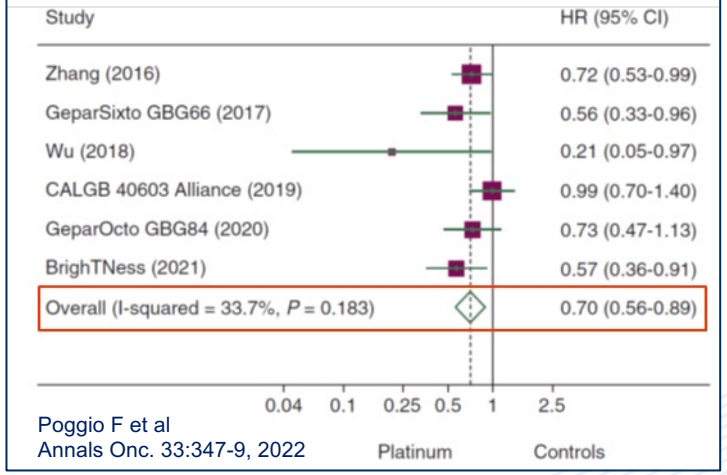
Loibl S et al. Lancet Oncol 19:497-509, 2018

4.5-year Event Free Survival



Geyer CE et al. Annals Onc 33:384-94, 2022

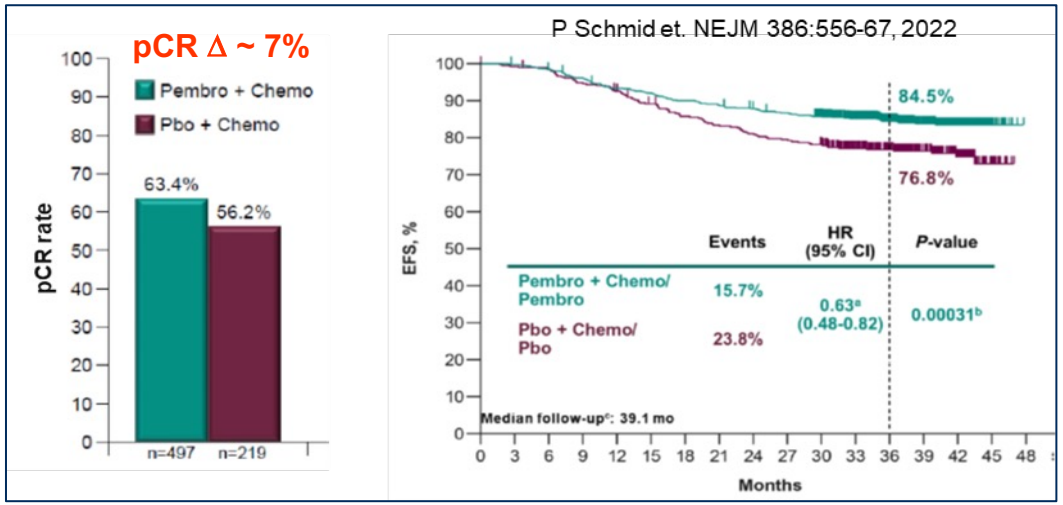
Meta-analysis of EFS in 6 randomized trials



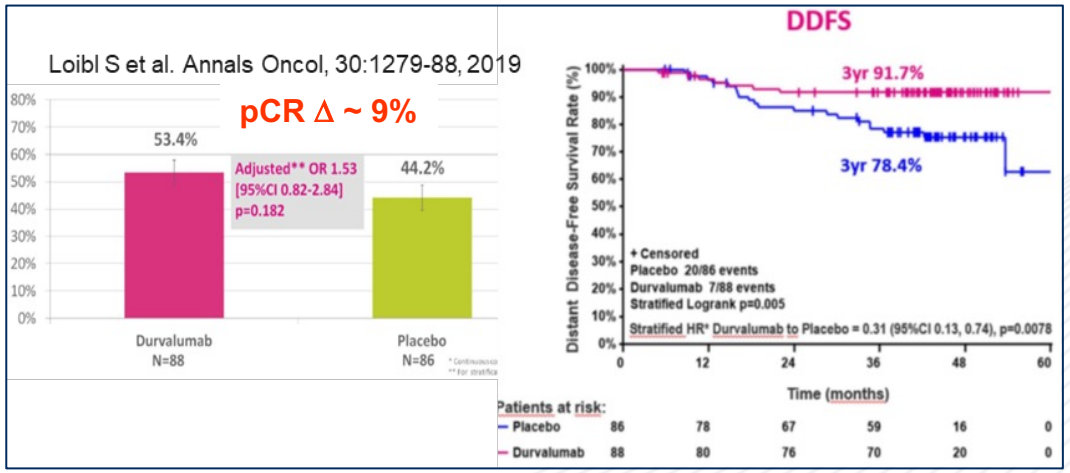
Poggio F et al
Annals Onc. 33:347-9, 2022

Even modest improvements in pCR rates in the KEYNOTE-522 and GeparNuevo trials translated into significant EFS benefit

KEYNOTE-522 pCR rates and EFS



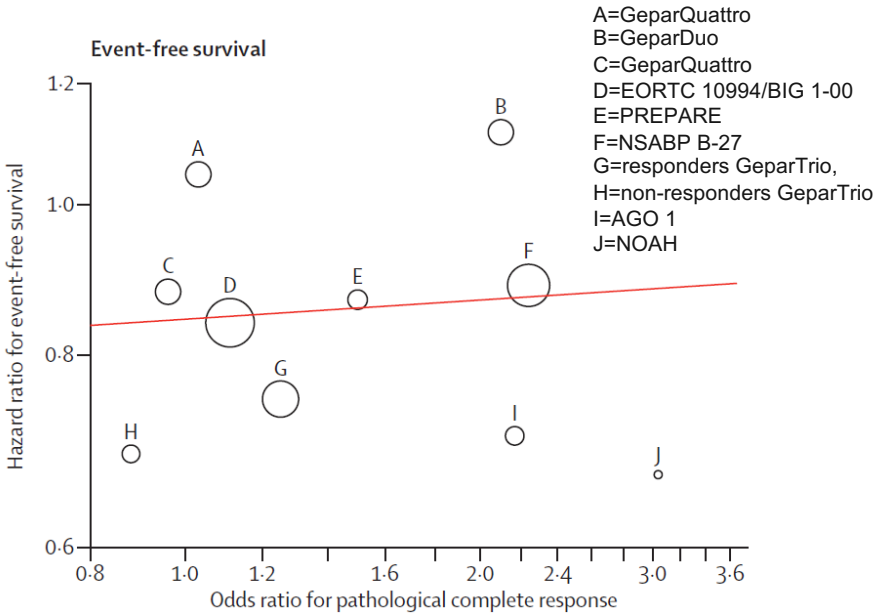
GeparNuevo pCR rates and EFS



So, why the controversy?

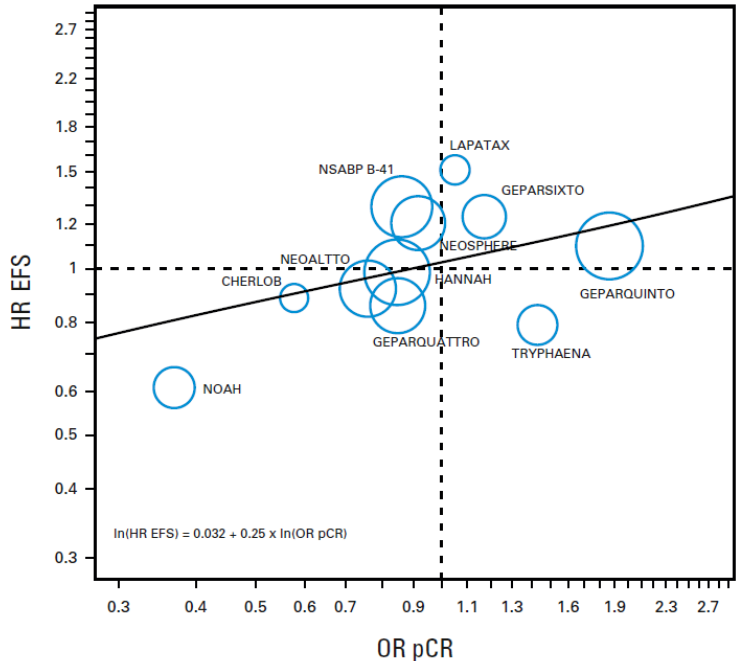
Trial level meta-analysis of small underpowered studies show weak correlation between two statistical metrics, Odds Ratio for pCR and Hazard rate for EFS

CTNeoBC pooled analysis



Cortazar P, et al. The Lancet, 384:164-172, 2014

Pooled analysis of HER2+ trials



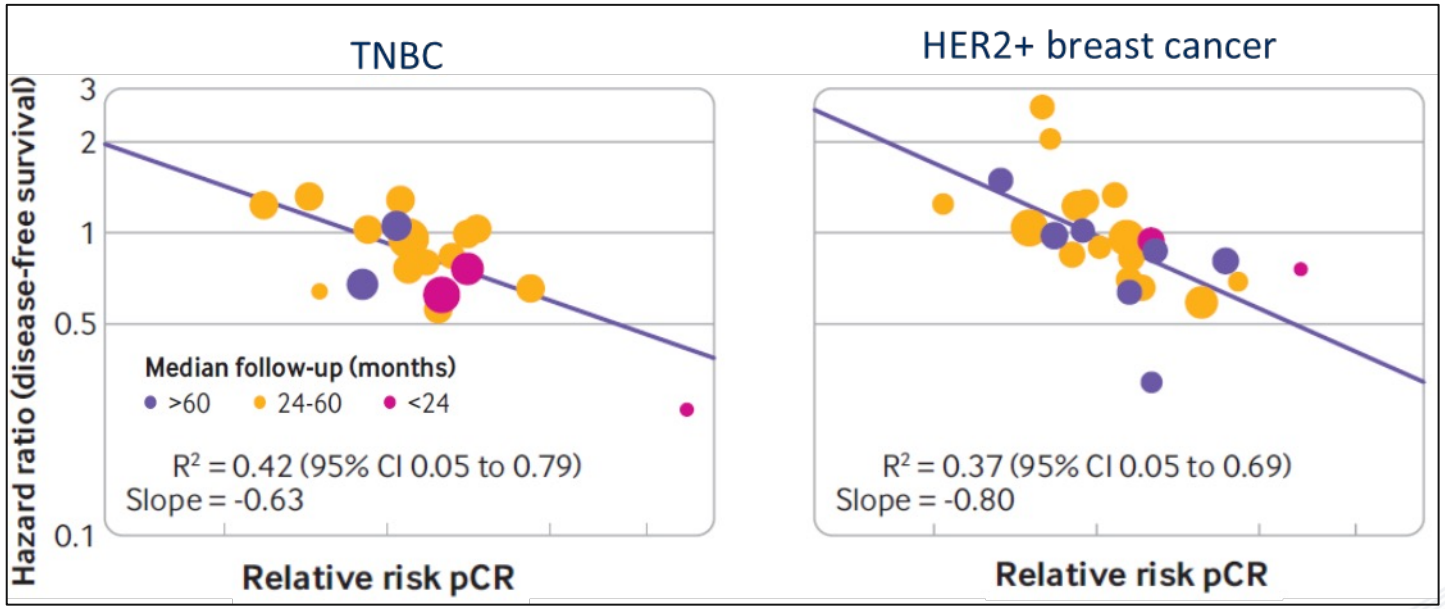
Squifflet P, et al. J Clin Oncol, 41:2988-1997, 2023

NOTE: Re-publishing results in aggregate of many individually underpowered trials does not increase the level of evidence

The major limitation of trial level meta-analysis of neoadjuvant studies

Neoadjuvant trials were designed to rapidly identify more effective chemotherapy regimens than large adjuvant trials and therefore BY DESIGN ARE UNDERPOWERED FOR SURVIVAL ENDPOINTS

Correlation between pCR and DFS in TNBC and HER2+ breast cancer



If these correlations were calculated only for trials that were powered to compare DFS (and therefore are truly informative!), these figures would be almost empty.

Despite the lack of power at trial level for DFS, these slopes indicate a significant correlation!!!

Conforti F. et al. Br Med J 2021 Dec 21;375

pCR is imperfect, as all surrogate markers are

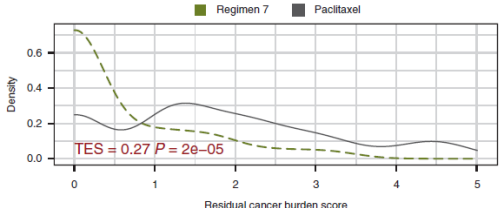
It is not straightforward to translate absolute improvement in pCR to absolute improvement in EFS

(i.) 3-5% of patients with pCR still recur

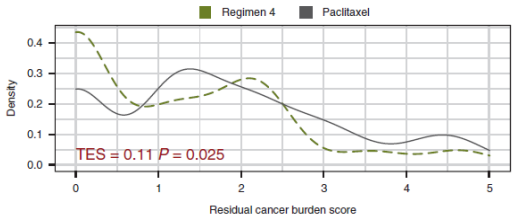
(ii.) Patients with RD can also benefit from neoadjuvant therapy

(iii.) Post operative adjuvant therapies also affect EFS

(iv.) For low-risk patients, cured by surgery, pCR or RD does not matter



Immunotherapy effect on residual cancer burden distribution*



Experimental drug X effect on residual cancer burden distribution*

However, these limitations should not distract

pCR is a clear and direct measure of cytotoxic efficacy, and more effective regimens have always improved EFS when tested in properly powered randomized trials in high-risk populations

* Marczyk M, et al. Annals of Oncol. 33:814-823, 2022

Conclusions

1. **pCR is an FDA endorsed endpoint for accelerated approval of drugs in early-stage breast cancer**

2. **I suggest we should agree with the FDA**

Please remember all agents that increased pCR rate eventually showed improvement in EFS in properly powered randomized adjuvant trials (**paclitaxel**, **trastuzumab**, **carboplatin**, **pembrolizumab**)

3. **There remains uncertainty about what degree of improvement in pCR justifies approval**

Please keep in mind that even small improvements in pCR could translate into meaningful and significant EFS benefit as demonstrated by KN522 and GeparNuevo trials

All accelerated FDA approvals must be followed by larger confirmatory trial with EFS endpoint.

If EFS benefit not confirmed, society incurred costs and some patients experienced added side effects.

If EFS benefit is conformed, you saved lives due to accelerated approval, that would have been lost if waiting many years until data justifies traditional approval.