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2020 Year in Review: Breast Cancer

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HER2-Positive Disease

Courtesy of Lisa Carey, MD

ExteNET

Background: Final efficacy analysis of a trial that was the basis for approval of neratinib for extended adjuvant therapy in HER2-positive BrCa.

Methods: Placebo-controlled phase III trial of neratinib for 1 year in stage I-IIIC HER2+ BrCa after completion of 1 year of trastuzumab-based therapy.

Primary endpoint: iDFS

Findings, including exploratory:

	5y iDFS*	5y iDFS HR+*	5y DDFS	5y CNS relapse	8y OS
Neratinib	95.3%	90.8%	92.4%	0.7%	91.5%
Placebo	90.8%	85.7%	87.7%	2.1%	89.4%
Absolute Δ	4.5%	5.1%	4.7%	1.4%	2.1%

* starting within 1y of trastuzumab completion

Courtesy of Lisa Carey, MD

Chan A et al, Clin Breast Cancer, in press

Chan A. Final efficacy results of neratinib in HER2-positive hormone receptor-positive early stage breast cancer from the Phase III ExteNET trial. Clin Breast Cancer (in press)

Impact on patient care and treatment algorithms

- Confirmed impact on adjuvant outcomes, especially high risk ER+ HER2+ breast cancer.

Implications for future research

- Exploratory analysis supportive of CNS protective effect. Some similarities to tucatinib that was more directly tested in active CNS metastases.

NALA

Background: Neratinib, an irreversible pan-HER small molecule inhibitor, delayed CNS progression when added to a taxane in 1st-line HER2+ MBC (NeferTT), and is active as single agent in CNS mets (TBCRC 022) and as extended adjuvant therapy (ExteNET).

Capecitabine plus lapatinib is an older approved regimen in pretreated HER2+ MBC with some evidence of activity in CNS-involved HER2+ MBC (EGF100151).

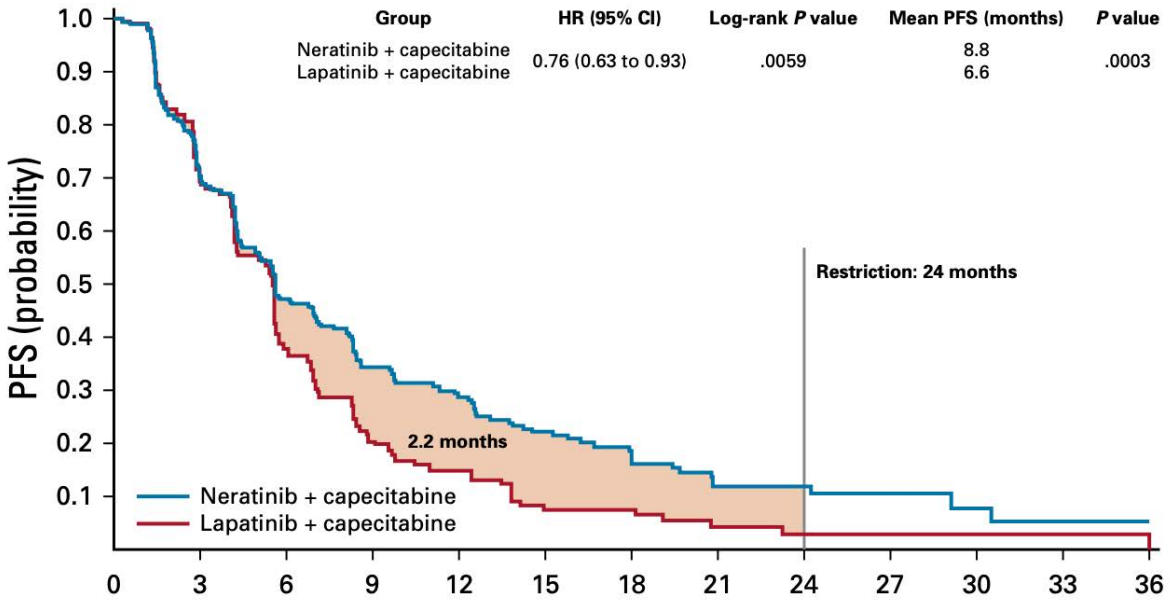
Objective: Compare neratinib to lapatinib when added to capecitabine in third-line+ setting.

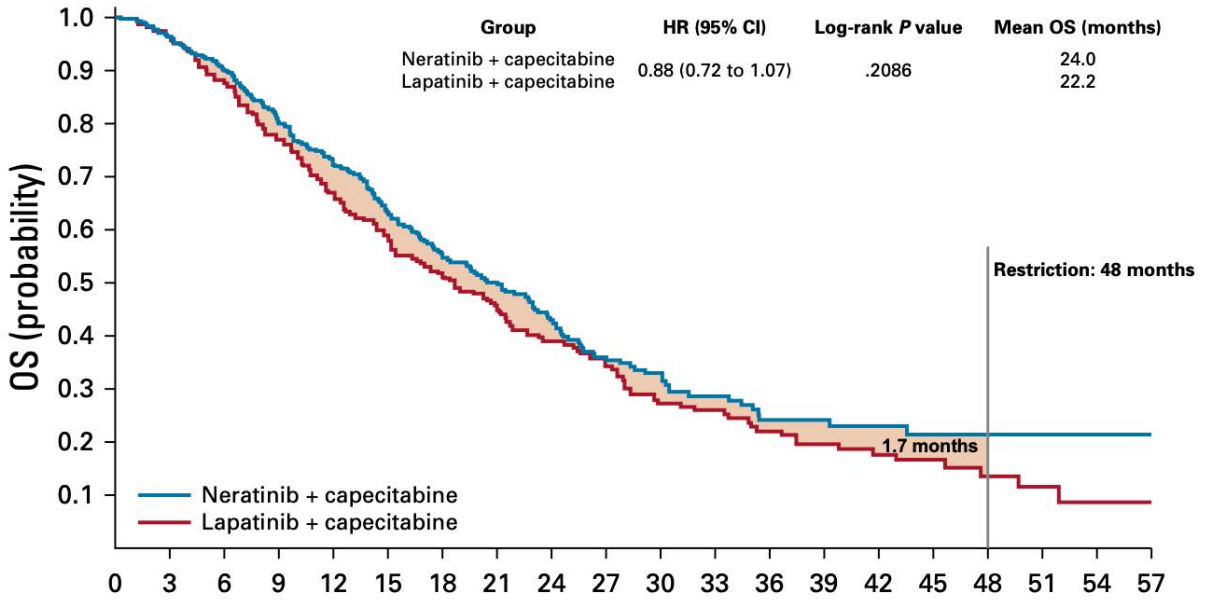
Methods: Randomized Phase III trial of neratinib versus lapatinib added to capecitabine in HER2+ MBC patients previously treated with ≥ 2 prior anti-HER2 regimens (one-third prior trastuzumab, pertuzumab, T-DM1). Stable brain mets allowed.

Co-primary endpoints: PFS and OS. CNS intervention prespecified endpoint.

NALA: Results

N=621 @ 30m. Met PFS endpoint (HR 0.76), but not OS endpoint (0.88)





- **HR- benefited more than HR+ (opposite of ExteNET); N. America, Europe little benefit.**
- **CNS intervention incidence: 23% neratinib + cape, 29% lapatinib + cape**
- **Toxicity: gr3+ diarrhea 25% despite prophylaxis. Only 3% discontinuation rate.**

Courtesy of Lisa Carey, MD

Saura C et al, J Clin Oncol 2020

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Saura C et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with > 2 HER2-directed regimens: Phase III NALA Trial. J Clin Oncol 2020;38:3138-3149

Impact on patient care and treatment algorithms

- Neratinib modestly outperformed lapatinib when combined with capecitabine in pretreated MBC. FDA-approved 2/2020 for HER2+ MBC with ≥ 2 prior regimens.
- Tucatinib, a less toxic HER2 small molecule inhibitor, added to capecitabine + trastuzumab has become favored 3rd line small molecule due to toxicity and documented CNS efficacy, and T-DXd is also in this space; placement of neratinib in pretreated HER2+ MBC is challenging.

Implications for future research

- Active drug that is being studied in activating HER2 somatic mutations and non-breast HER2+ cancer trials.
- CNS is major challenge in HER2+ MBC, anti-HER2 small molecules appear active (esp tucatinib, neratinib); optimizing and sequencing unknown.

Courtesy of Lisa Carey, MD

CONTROL Trial

Background: Neratinib is approved for extended adjuvant therapy in HER2-positive BrCa

However, it is poorly tolerated – in ExteNET 17% discontinued, 40% had grade 3 diarrhea

Objective: Improve GI tolerability of neratinib

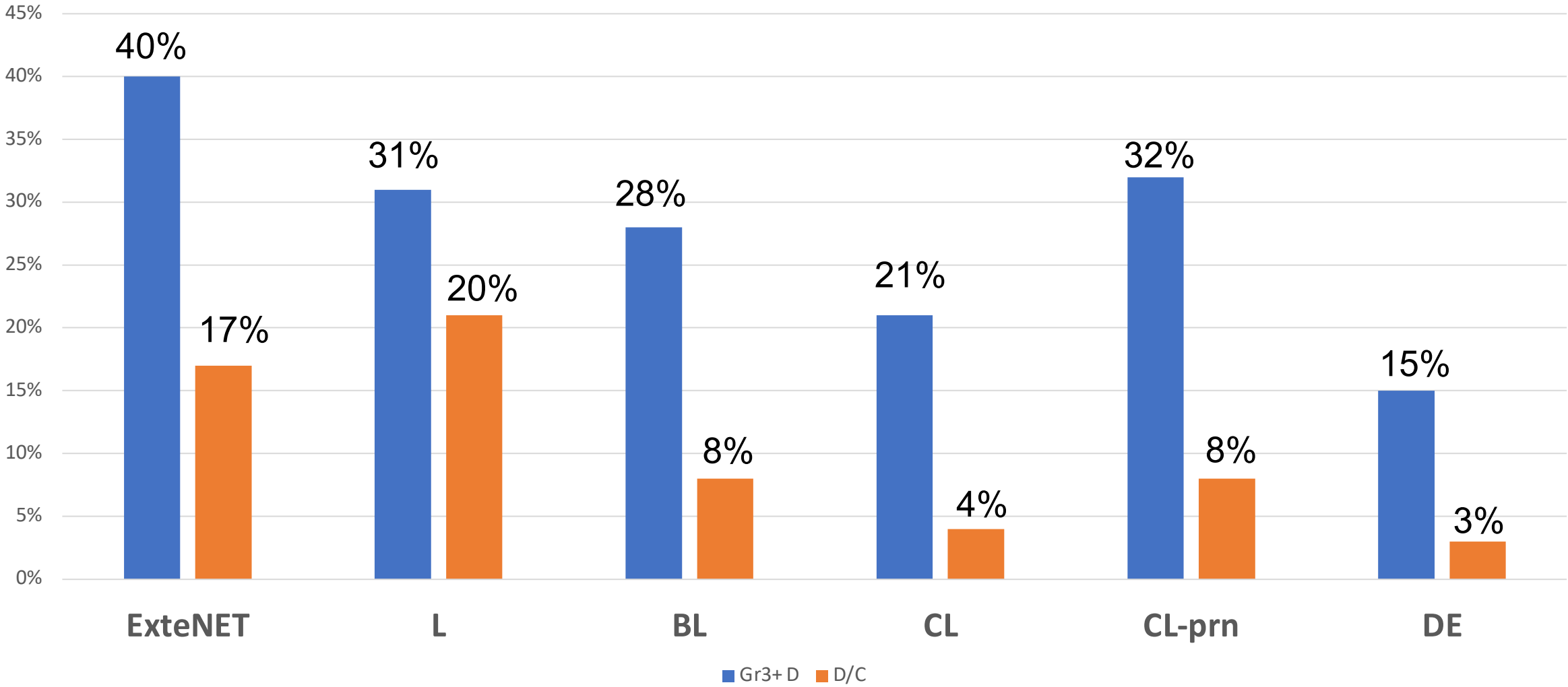
Methods: Sequential single arm interventions in adjuvantly treated patients

- Cohort 1 (n=137): Loperamide x 1-2m
- Cohort 2 (n=64): Budesonide + loperamide x 1m
- Cohort 3 (n=136 + 104): Colestipol + loperamide or prn loperamide x 1m
- Cohort 4 (n=60, ongoing): Dose escalation (120 mg/d x 1w, 160 mg/d x 1w)

Courtesy of Lisa Carey, MD

Barcenas CH et al, Ann Oncol 2020

CONTROL: Results



Courtesy of Lisa Carey, MD

Barcenas CH et al, Ann Oncol 2020

Barcenas CH et al. Improved tolerability of neratinib in patients with HER2-positive early stage breast cancer: The CONTROL trial. Ann Oncol 2020;31(9):1223-1230

Impact on patient care and treatment algorithms

- Adherence and quality of life matter!
- Neratinib remains a drug used for high risk adjuvant and metastatic HER2-positive breast cancer, being able to give it better is crucial.

Implications for future research

- Inform and improve interpretability of trials examining neratinib in novel approaches: somatic HER2 mutations, non-breast HER2-positive cancers, and in more fragile patients e.g. elderly.

HER2CLIMB

Background: Tucatinib, an irreversible small molecule HER2 inhibitor, showed promise in small trials of heavily pretreated HER2+ BrCa, including those with CNS metastases.

While we have many anti-HER2 agents, in the third-line+ setting patients have poor prognosis with a high degree of CNS involvement (~ 25% in NALA).

Objective: Test tucatinib in a population of pretreated metastatic HER2+ BrCa patients with preplanned cohort with CNS involvement.

Methods: Randomized (2:1) placebo-controlled phase II trial of tucatinib added to capecitabine + trastuzumab in heavily pretreated* patients with metastatic HER2+ BrCa with preplanned analysis of patients with brain metastases.

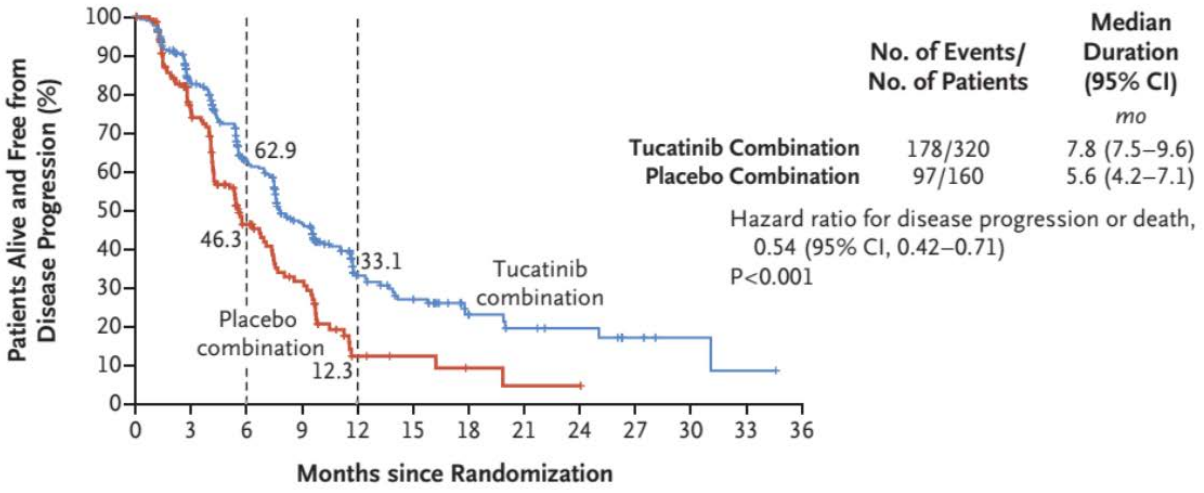
** Prior trastuzumab, pertuzumab, T-DM1 required. Median # prior lines for MBC = 3*

Courtesy of Lisa Carey, MD

Murthy R et al, NEJM 2020

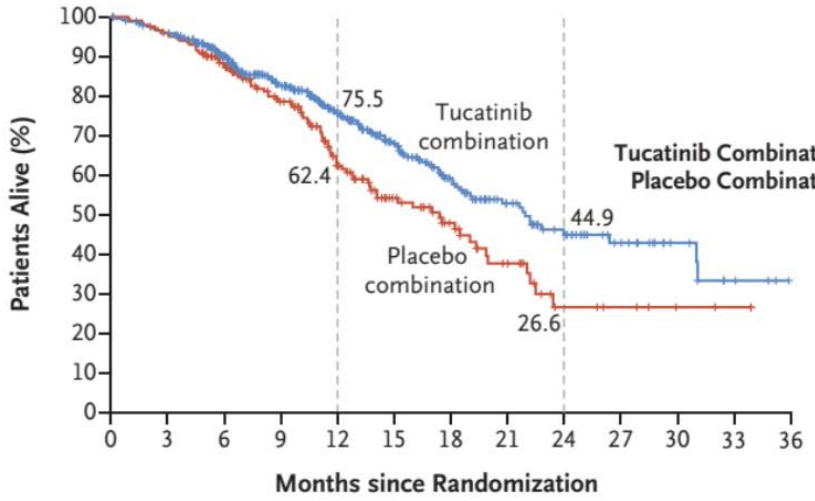
HER2CLIMB: Results

N=612 (48% with CNS mets). Event-driven reporting of primary endpoint (PFS) at 14m.



	No. of Events/ No. of Patients	Median Duration (95% CI) mo
Tucatinib Combination	178/320	7.8 (7.5–9.6)
Placebo Combination	97/160	5.6 (4.2–7.1)

Hazard ratio for disease progression or death, 0.54 (95% CI, 0.42–0.71)
P<0.001



	No. of Deaths/ No. of Patients	Median Duration (95% CI) mo
Tucatinib Combination	130/410	21.9 (18.3–31.0)
Placebo Combination	85/202	17.4 (13.6–19.9)

Hazard ratio for death, 0.66 (95% CI, 0.50–0.88)
P=0.005

- **All subgroups benefited essentially equally**.
- **Toxicity gr3+:** Diarrhea (13% vs 9%), PPE (13% vs 9%), LFT ↑ (~ 5% vs <1%). 6% discontinued drug.
- **Triggered *a priori* CNS cohort analysis**:

CNS cohort (n=291)	1y PFS	mPFS
Tucatinib	25%	7.6m
Placebo	0%	5.4m

Courtesy of Lisa Carey, MD

Murthy R et al, NEJM 2020

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Murthy R et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. NEJM 2020;382(7):597-609

Impact on patient care and treatment algorithms

- Tucatinib (Tuc) is well-tolerated and highly active when added to capecitabine (X) plus trastuzumab (H) in heavily pretreated patients, including those with active brain mets. FDA approved 4/2020 for HER2+ MBC with at least one prior Rx in the metastatic setting.
- TucXH has become a preferred third-line option, supplanting others such as capecitabine plus neratinib although these have not been tested head-to-head. Main question is sequence vs T-DXd

Implications for future research

- Tucatinib's effectiveness particularly in the CNS compartment, a significant problem in HER2-positive disease, has made it a very hot drug in combination therapy, including T-DM1 in the adjuvant (COMPASS-RD) and metastatic (HER2CLIMB-02) settings, with T-DXd (HER2CLIMB-04).
- Trials in non-breast HER2-positive cancers are ongoing.

Courtesy of Lisa Carey, MD

HER2CLIMB: CNS Cohort

- **HER2CLIMB allowed patients with CNS metastases, even active / progressing.**

- **291 / 612 (48%) in CNS cohort (198 tucatinib-treated, 93 placebo). Most had extracranial disease also.**
  - Stable BM after CNS Rx n=117
  - Progressive after CNS Rx n=108
  - New / untreated brain mets n=66

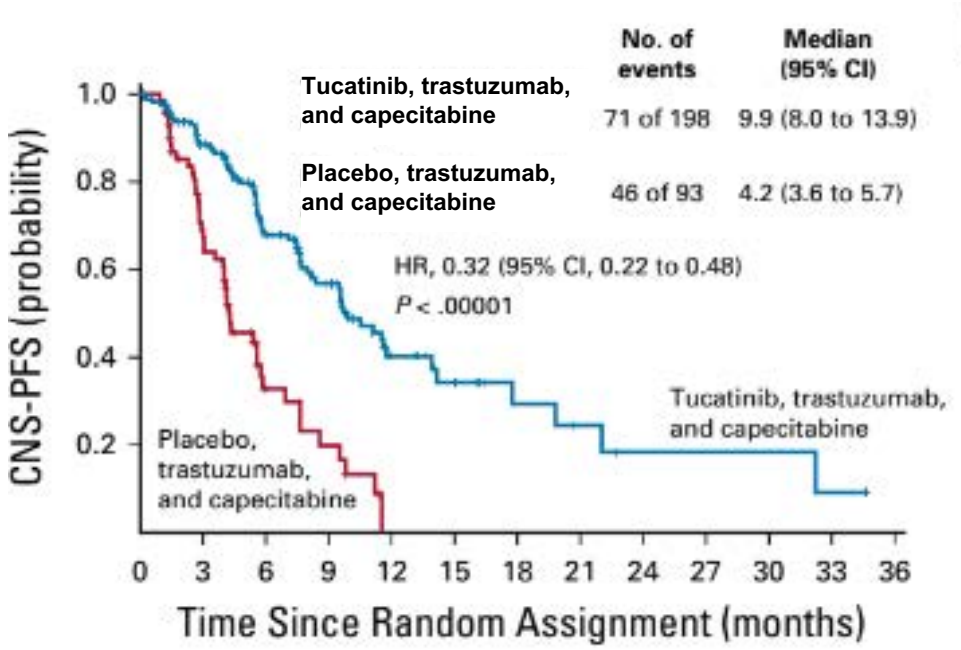
  } **"Active" BM**

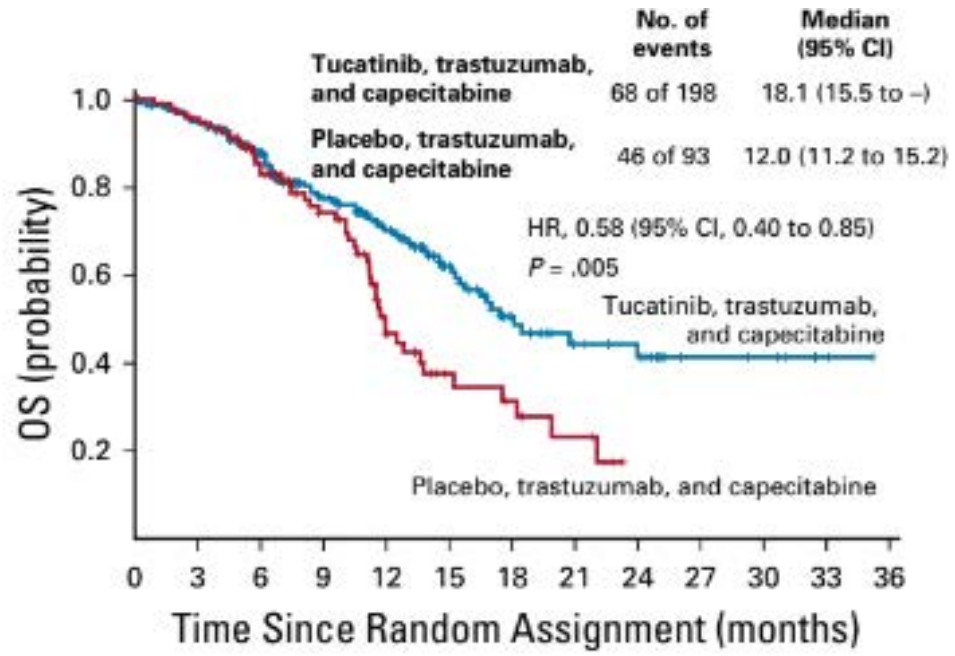
- **CNS-PFS secondary endpoint of parent trial**

Courtesy of Lisa Carey, MD

Lin N et al, JCO 2020

HER2CLIMB: CNS Cohort Results





	1y CNS-PFS	1y CNS-PFS Active BM	1y OS Active BM	ORR-CNS (n=75)
Tucatinib (+XH)	40%	35%	72%	47%
Placebo (+XH)	0%	0%	41%	20%

Courtesy of Lisa Carey, MD

Lin N et al, JCO 2020

Lin N et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. J Clin Oncol 2020;38:2610-2619

Impact on patient care and treatment algorithms

- Clear evidence of at least equal effect in the intracranial space as extracranial.
- Other anti-HER2 drugs typically have only been studied in stable disease; near-doubling of OS in those with active CNS mets is unique.

Implications for future research

- COMPASS-RD is testing tucatinib added to T-DM1 in the residual disease adjuvant setting, based on little evidence of T-DM1 impact on CNS relapse in the KATHERINE trial.
- Future trials of anti-HER2 drugs should include active CNS mets in order to address this unmet need.

Courtesy of Lisa Carey, MD

DESTINY-Breast01

Background: Trastuzumab deruxtecan (DS-8201a, T-DXd) is an antibody-drug conjugate (ADC) of an anti-HER2 antibody, cleavable linker, and topoisomerase I inhibitor payload.

It was designed to have a) a much higher drug-to-antibody ratio than T-DM1 (8 vs <4), b) permeable payload that crosses the cell membrane so can kill bystander cells, and c) short half-life to minimize toxicity.

In early studies it was very active in heavily pretreated patients with HER2-positive MBC.

Objective: Examine safety and ORR of T-DXd in third-line+ setting.

Methods: Single arm two-part Phase II trial of T-DXd in HER2+ MBC patients previously treated with T-DM1 (was a heavily pretreated population, median # prior treatments = 6).

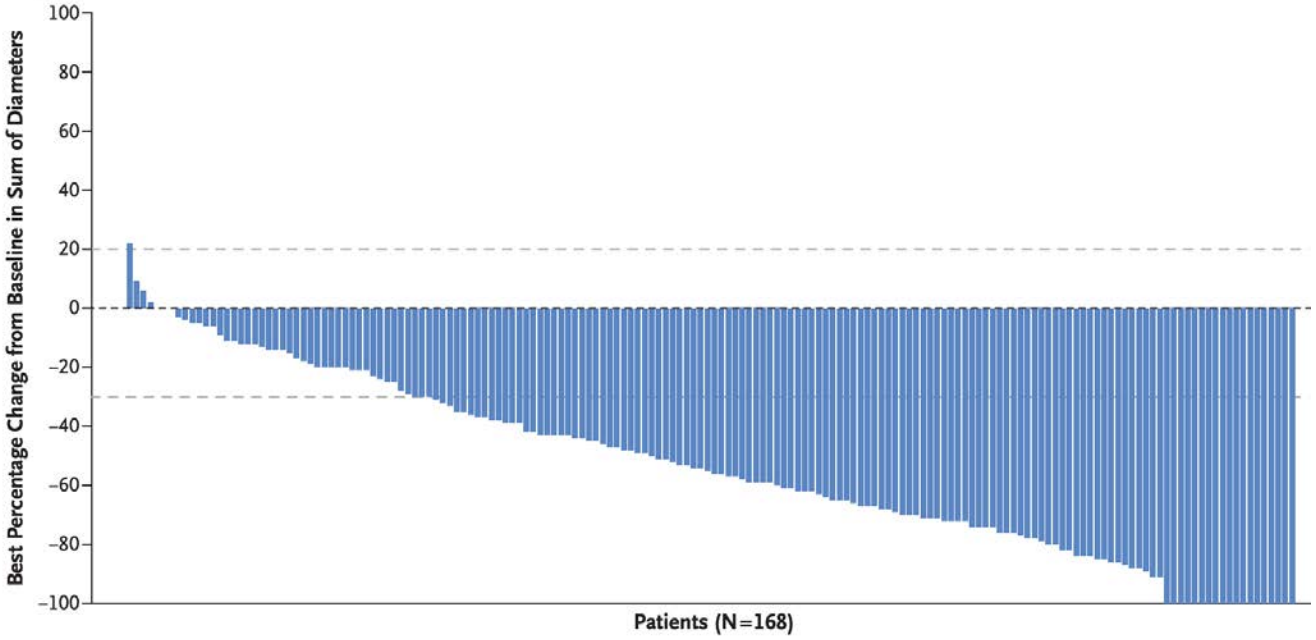
DESTINY-Breast01: Results

N=253 in Parts 1 (dose-finding, PK analysis) and 2 (efficacy by ORR, n=184 Rx@ 5.4 mg/kg) @ 11m

ORR 62% (same across subsets)
PFS 16m
1y OS 86%

Toxicity:

- Grade 3+: ANC (21%), anemia (9%), nausea (8%)
- Discontinuation: 15%
- ILD: 14%, mostly grade 1/2
  - 4 (2.2%) deaths
  - Median onset 193d
  - Reversible in ~ 50% (?)



24 had stable CNS metastases; ORR 58%
CNS site of progression in overall trial 8%

Modi S et al, NEJM 2020; Jerusalem G et al, ESMO 2020

Courtesy of Lisa Carey, MD

Modi S et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. NEJM 2020;382(7):610-621

Impact on patient care and treatment algorithms

- T-DXd is very active in pretreated HER2+ MBC. FDA-approved 12/2019 for 3rd+ line HER2+ MBC.
- Both T-DXd and tucatinib + XH are commonly used after T-DM1; preferred sequence unclear.
- Main concerning toxicity is ILD, which can be fatal; particularly an issue in early setting.

Implications for future research

- Multiple DESTINY breast trials ongoing: with tucatinib (HER2CLIMB04), versus T-DM1 in residual disease (DESTINY-Breast05) and metastatic (DESTINY-Breast03). Also multiple trials in HER2-low BrCa and non-breast HER2+ cancers.
- Activity appears similar in stable CNS metastases. Active BM not yet studied but DEBBRAH phase II trial includes untreated asymptomatic, progressive, and leptomeningeal disease.

Courtesy of Lisa Carey, MD

SOPHIA

Background: Margetuximab is a novel Fc-engineered anti-HER2 antibody with enhanced affinity for activating Fc gamma receptor (FcR) CD16A and decreased affinity for inhibitory FcR CD32B. This may increase activation of innate and adaptive anti-HER2 immune responses. Promising activity as monotherapy in pretreated HER2+ MBC phase I trial.

85% of people carry lower-affinity CD16A FV and FF genotypes, 15% have high-affinity VV.

Objective: Compare margetuximab (M) to trastuzumab (H) when added to chemotherapy in third-line+ setting.

Methods: Randomized open-label Phase III trial of M vs H added to chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) in HER2+ MBC patients previously treated with ≥ 2 prior anti-HER2 regimens. > 90% had received prior T-DM1, most were 3rd line.

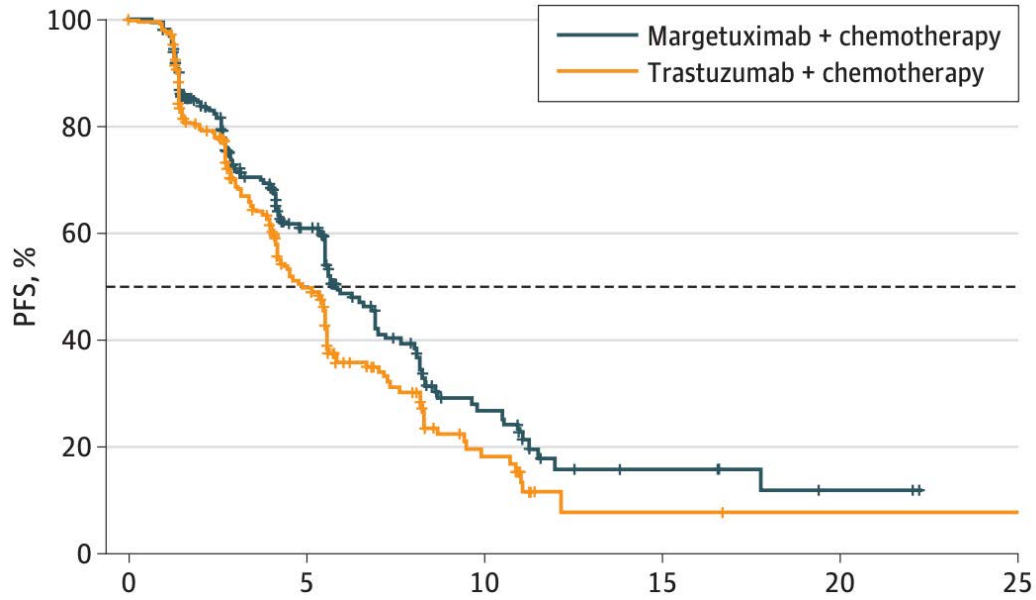
Sequential primary endpoints: centrally assessed PFS and OS

Courtesy of Lisa Carey, MD

Rugo H et al, JAMA Oncol 2021

SOPHIA: Results

N=536 @ 16m. Met primary endpoint for PFS (HR 0.76), OS immature (HR 0.89)



	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	130	135
Median PFS (95% CI)	5.8 mo (5.52-6.97)	4.9 mo (4.17-5.59)
3-mo PFS rate	72% (65%-77%)	70% (63%-76%)
6-mo PFS rate	48% (41%-56%)	36% (28%-44%)
9-mo PFS rate	30% (22%-38%)	22% (15%-30%)

HR by stratified Cox model, 0.76 (95% CI, 0.59-0.98)

- **Well-tolerated, same discontinuation rate as trastuzumab.**
- **Exploratory analysis by CD16A genotype:**

M vs H	PFS
FV or FF (lower-affinity, 86%)	6.9 vs 5.1m
VV (higher-affinity, 14%)	4.8 vs 5.6m

Courtesy of Lisa Carey, MD

Rugo H et al, JAMA Oncol 2021

Rugo H et al. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: a phase 3 randomized clinical trial. JAMA Oncol 2021; Jan 22 online ahead of print

Impact on patient care and treatment algorithms

- Margetuximab + chemotherapy was FDA-approved 12/2020 for HER2+ MBC with ≥ 2 prior Rx, ≥ 1 for MBC. No genotypic restriction. Without OS data and with an apparent interaction with CD16A genotype, this may have relatively low uptake for now.
- If confirmed to be superior, would have implications for the trastuzumab-based regimens in early and metastatic disease.

Implications for future research

- TBCRC 052, MARGOT, is comparing M vs H added to paclitaxel + pertuzumab in the neoadjuvant setting in lower-affinity FcR patients only.
- Potential interaction with FcR CD16A genotype must be addressed; if confirmed this may ultimately either require genotyping or make it less appealing to use this drug.

Triple-Negative Disease

Courtesy of Lisa Carey, MD

IMpassion130

Background: This is the pivotal trial responsible for anti-PDL1 immune checkpoint inhibitor (ICI) atezolizumab added to chemotherapy in PDL1+ metastatic TNBC (mTNBC). The OS endpoint was updated in 2020.

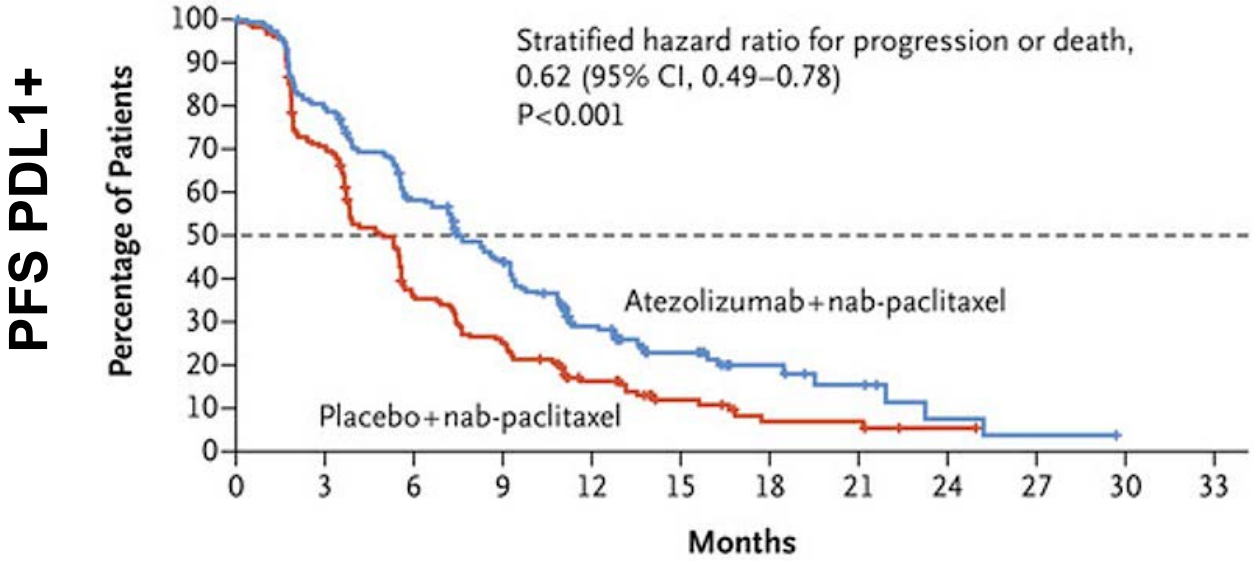
Objective: Update the PFS and survival benefit of atezo added to nab paclitaxel in first-line setting.

Methods: Randomized placebo-controlled Phase III trial of atezo added to nab paclitaxel in mTNBC who have not been treated for metastatic disease. Half had previously received taxane for early disease; 12m PFI was required.

Co-primary endpoints: PFS and OS, hierarchically tested in ITT and PDL1+ (41%) populations.

IMpassion130: Results

	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	138/185	7.5 (6.7–9.2)	29.1 (22.2–36.1)
Placebo+Nab-Paclitaxel	157/184	5.0 (3.8–5.6)	16.4 (10.8–22.0)



Nab paclitaxel + atezolizumab in PDL1+:

- **PFS advantage = 2.5m**
- **OS advantage @ 20m f/u = 7.5m**
- **No impact in PDL1-**

Courtesy of Lisa Carey, MD

Schmid P et al, Lancet Oncol 2020

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Schmid P et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:44-59

Impact on patient care and treatment algorithms

- Confirmed benefit of atezolizumab added to nab paclitaxel in PDL1+ mTNBC in first-line setting. This regimen was FDA-approved and broadly used beginning in March 2019. This update did not provide a reason to alter this approach.
- With pembrolizumab approval, using a different IHC assay, the optimal predictive biomarker is unknown.

Implications for future research

- If ICI become standard for early TNBC, whether this approach will remain valuable is unknown.
- This trial opened the door for multiple efforts to leverage ICI effects in PDL1-negative or more conventionally immune “cold” BrCa such as ER+.

Courtesy of Lisa Carey, MD

KEYNOTE-355

Background: The anti-PD1 ICI pembrolizumab significantly augmented pCR in I-SPY2 added to neoadjuvant therapy, but has modest activity as a single agent in mTNBC especially in pretreated patients. This is the pivotal trial of pembro added to chemotherapy in mTNBC.

Objective: Examine the PFS and OS impact of pembrolizumab added to chemotherapy in first-line mTNBC

Methods: Randomized placebo-controlled Phase III trial of pembro added to chemotherapy (”taxane” = nab paclitaxel or paclitaxel, or gemcitabine + carboplatin) in mTNBC who have not been treated for metastatic disease. 22% had received “same class” chemo in the early setting; only 6m PFI was required.

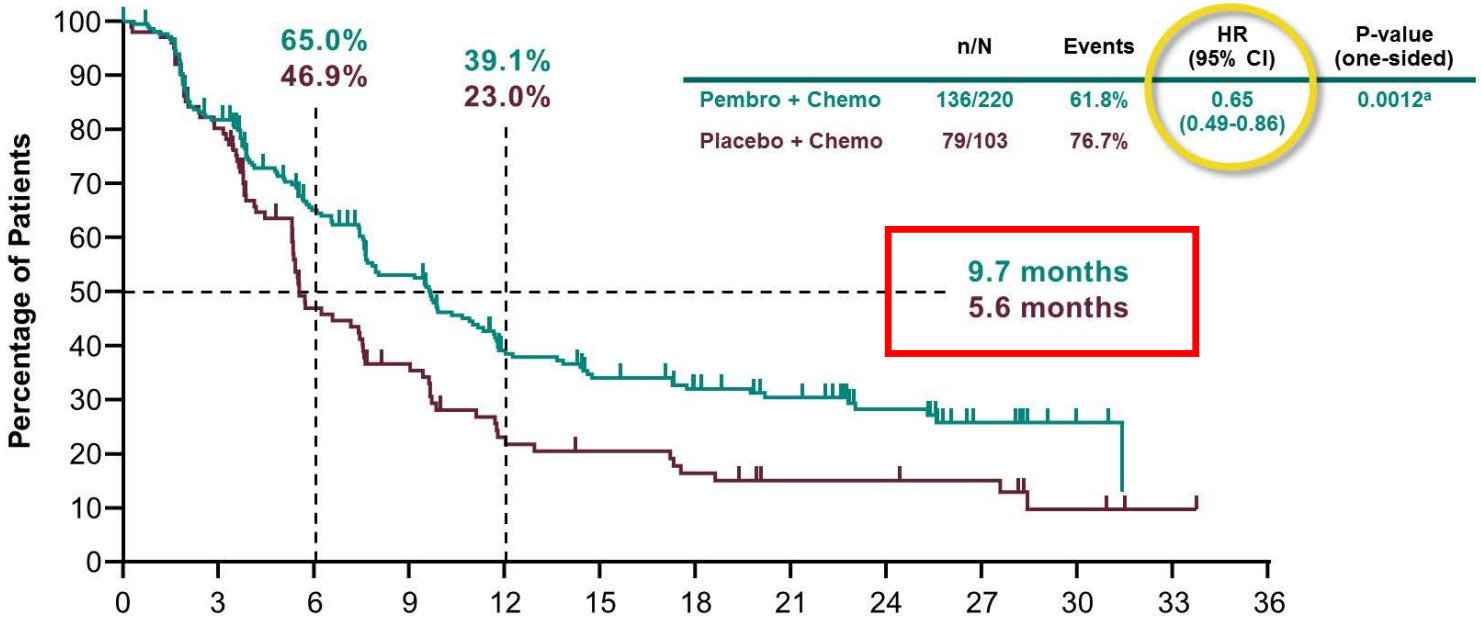
Co-primary endpoints: PFS and OS, hierarchically tested in strongly PDL1+ (38%+ CPS $\geq$10 in 22C3 IHC) and less strongly PDL1+ populations.

Courtesy of Lisa Carey, MD

Cortes J et al, Lancet 2020

KEYNOTE-355: Results

N=847 @ 26m
PDL1+ (CPS ≥ 10):



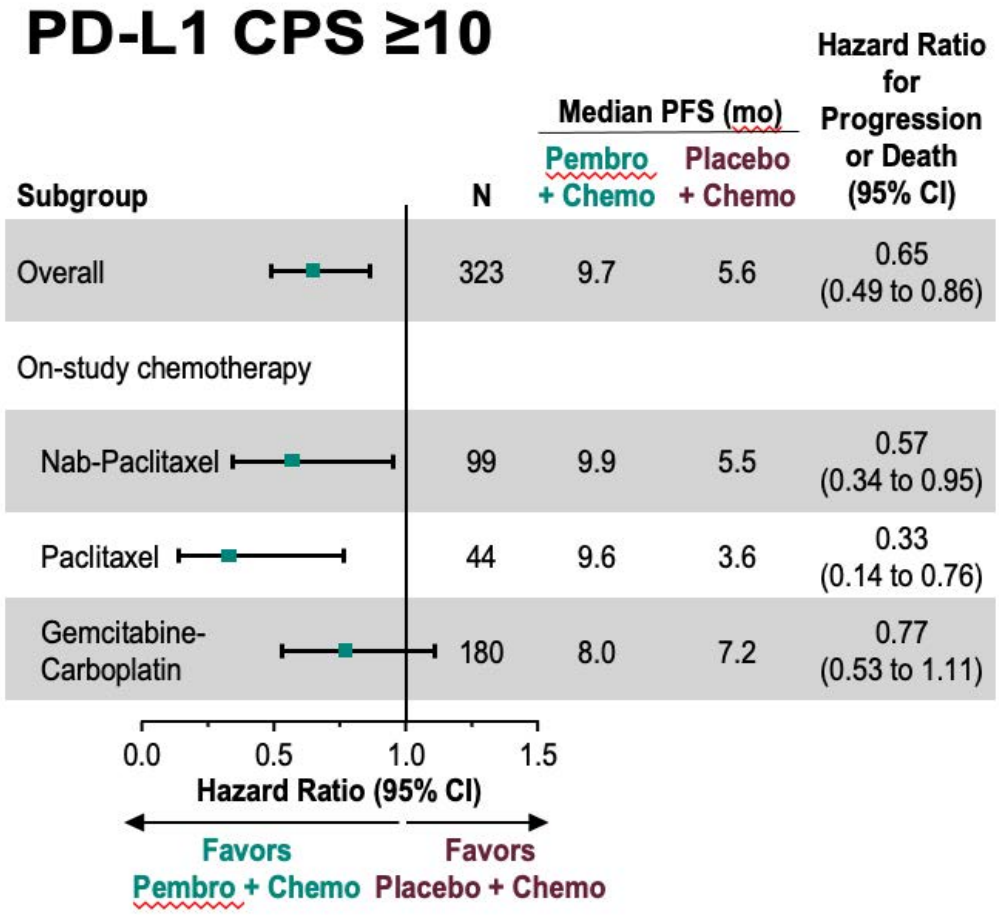
- **CPS ≥ 1: PFS 7.6 vs 5.6m, ns. ITT also ns.**
- **IRAE: 26% (5% gr 3+) vs 6% (0 gr 3+). Mostly skin.**

Similar HR as IMpassion130 PDL1+

PFS subgroups:

- **Chemotherapy backbone:**
  - **Taxane (n=143): HR 0.51 (0.33-0.78)**
    - **Nab pac (n=99): HR 0.57 (0.34-0.95)**
    - **Paclitaxel (n=44): HR 0.33 (0.14-0.76)**
  - **Gem/carbo (n=180): HR 0.77 (0.53-1.11)**
- **DFI:**
  - **De novo (n=103): HR 0.48 (0.29-0.79)**
  - **< 12m DFI (n=66): HR 1.00 (0.51-1.95)**
  - **> 12m DFI (n=153): HR 0.64 (0.43-0.95)**

KEYNOTE-355: Additional Efficacy Endpoints



Chemotherapy backbone: taxane appears to > doublet. *NB: paclitaxel does not appear to underperform.*

Other secondary endpoints of ORR, DCR, and DOR also favored pembrolizumab arm.

Rugo H et al. SABCS 2020; Cortes J et al, Lancet 2020

Courtesy of Lisa Carey, MD

Cortes J et al. Pembrolizumab plus chemotherapy vs placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomized, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 2020;396:1817-1828.

Impact on patient care and treatment algorithms

- Pembrolizumab has generally same impact on PFS as atezolizumab, but more evidence for freedom with chemotherapy backbone. Paclitaxel and nab paclitaxel appear most effective.
- OS not yet available so atezo + nab pac remains preferred first-line option for mTNBC.

Implications for future research

- Opens the door for pembrolizumab combinations.
- KEYNOTE 522 demonstrated effectiveness of pembrolizumab in early TNBC; if that becomes the norm what happens in this setting? Does ICI work across lines of therapy and goals of care?

Courtesy of Lisa Carey, MD

IMpassion131

Background: Building on the success of IMpassion130, this trial used the same approach in the same setting but with a different chemotherapy backbone, the more conventional paclitaxel.

Objective: Examine the impact of atezolizumab added to paclitaxel in first-line mTNBC

Methods: Randomized placebo-controlled Phase III trial of atezo added to paclitaxel in mTNBC who have not been treated for metastatic disease. As in IMpassion130, half had previously received taxane for early disease; 12m PFI was required.

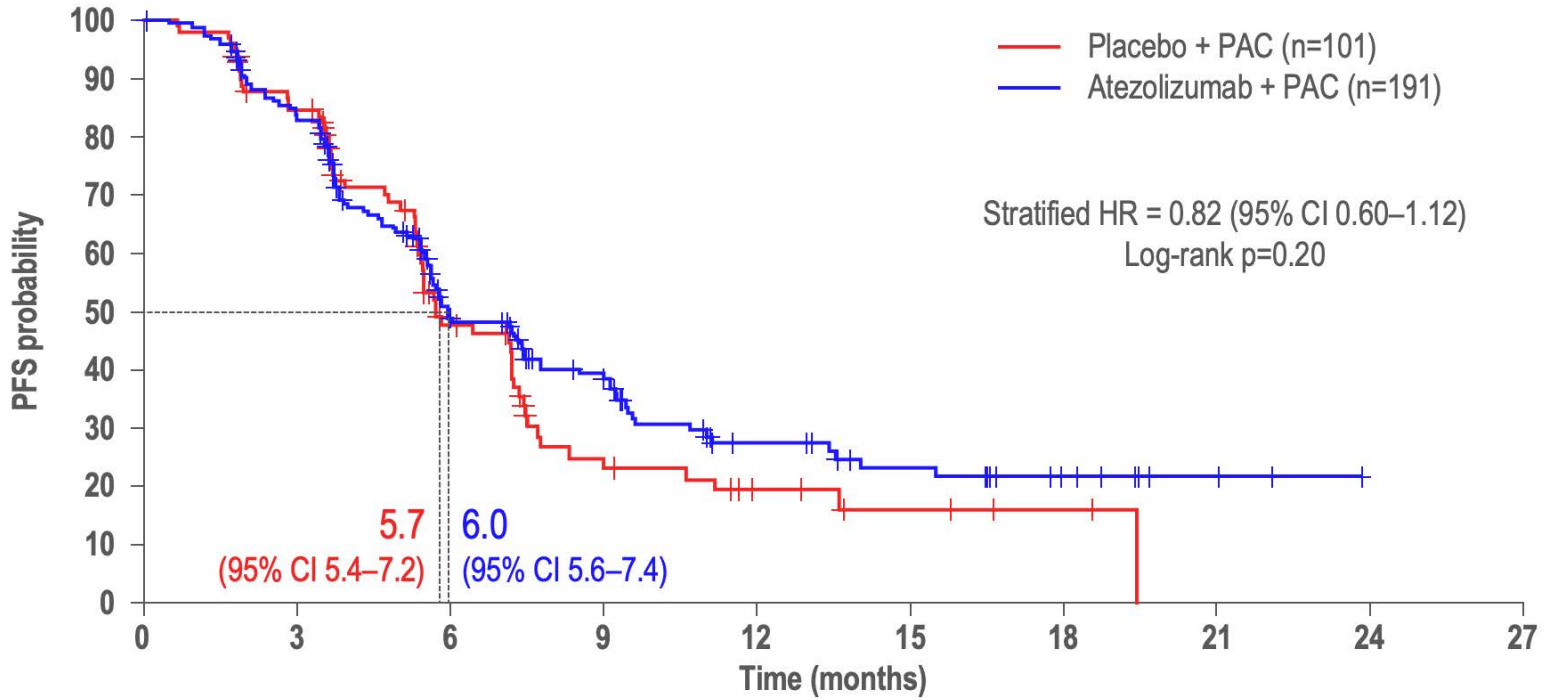
Co-primary endpoints: PFS and OS, hierarchically tested in ITT and PDL1+ (41%) populations.

Courtesy of Lisa Carey, MD

Miles DW et al, ESMO 2020

IMpassion131: Results

N=651, followup 8.6m, met desired # events



PFS
PDL1+ population: 6.0 vs 5.7m
ITT population: 5.6 vs 5.7m

- **ORR PDL1+: 63% vs 55%**
- **Toxicity:** hyper/hypothyroid 13% vs 4%, difficult-to-treat immune AE 8.4% vs 2.8%
- **Discontinuation 20% vs 15%**

Courtesy of Lisa Carey, MD

Miles DW et al, ESMO 2020

Miles DW et al. Primary results from IMpassion131, a double-blind, placebo-controlled randomized phase III trial of first-line paclitaxel ± atezolizumab for unresectable locally-advanced / metastatic triple-negative breast cancer. ESMO 2020.

Impact on patient care and treatment algorithms

- Atezolizumab + nab paclitaxel approved and effective. There is no reason to substitute paclitaxel.

Implications for future research

- Why this backbone differed is unclear; particularly since the neoadjuvant atezolizumab trial in which it was added to an anthracycline + paclitaxel backbone demonstrated improved pCR.
- Trials depending on paclitaxel as the backbone may be reconsidering although this may have been a play of chance. PFS HR 95% CI (0.82, 0.60-1.12) overlapped IMpassion130 and KN-355.

Courtesy of Lisa Carey, MD

KEYNOTE-522

Background: Immune checkpoint inhibitors (ICI) in TNBC were disappointing as single agents but better combined with immunomodulatory chemotherapy as demonstrated by the success of first-line metastatic trials.

Objective: Examine impact on pCR and outcome of adding pembrolizumab (P) to neoadjuvant anthracycline/taxane/platinum-based chemotherapy for TNBC and continuing it into the adjuvant phase for a total of one year.

Methods: Randomized (2:1) placebo-controlled phase III trial of P concurrently with preoperative paclitaxel + carboplatin followed by AC, then up to 9 cycles of adjuvant P.

Mostly clinical stage II patients, ~ 50% N+.

Endpoints: pCR, EFS in ITT comparing P to placebo arms. Only pCR endpoint is currently mature.

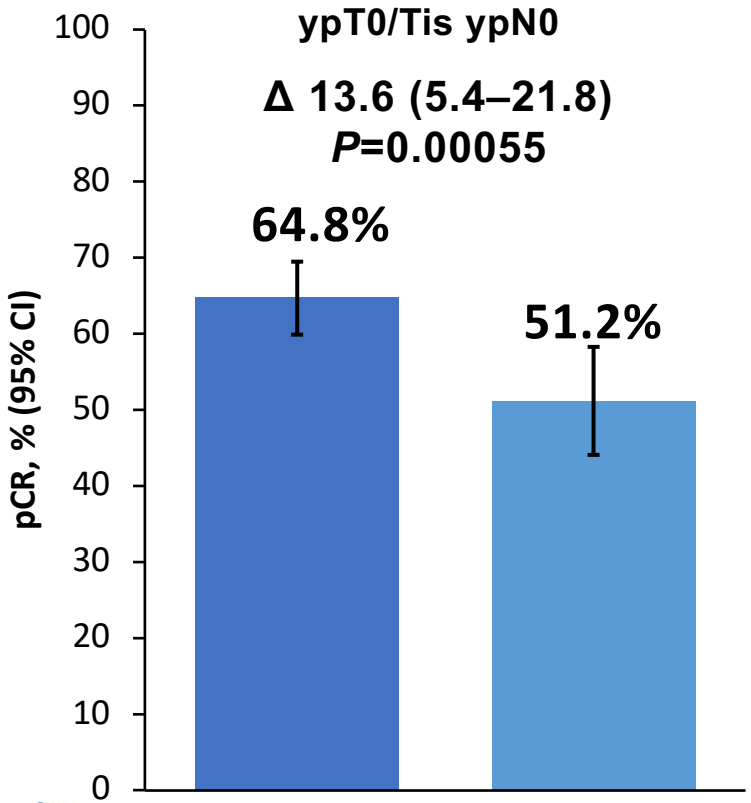
Courtesy of Lisa Carey, MD

Schmid P et al, NEJM 2020

KEYNOTE-522: Results

N= 1174, followup ~18m

Primary Endpoint #1: pCR



Courtesy of Lisa Carey, MD

No apparent relationship to PDL1 status

(higher pCR both arms in PDL1+)

- **Primary endpoint #2 (EFS) immature**

  (HR 0.63 @ 18m, ns)

- **Grade 3+ AE of interest (all the "itis" + immune complications): 13% vs 2%**
  - **Thyroid < 1%**

Schmid P et al, NEJM 2020

Schmid P et al. Pembrolizumab for early triple-negative breast cancer. NEJM 2020;382:810-821

Impact on patient care and treatment algorithms

- Pembrolizumab added to chemotherapy significantly improves pCR rate by approximately 14%, which can be clinically meaningful given the impact on surgical extent and need for axillary dissection. However, high grade immune toxicity was seen in 13%, and impact on EFS as yet unclear.
- Unlike metastatic TNBC, PDL1 status was not a predictive biomarker

Implications for future research

- Predictive biomarkers for ICI are sorely lacking; particularly in this setting, and should be a priority especially if EFS improvement is seen and these become standard therapy.
- Future trial designs should consider: 1) that ICI may have a role in management of early TNBC; 2) what is optimal duration of ICI therapy, 3) whether pCR and RD should be managed differently, 4) optimizing chemotherapy, and 4) implications for treatment in the metastatic setting.

Courtesy of Lisa Carey, MD

IMpassion031

Background: Atezolizumab added to nab paclitaxel in first-line PDL1+ metastatic TNBC was the first ICI approved in breast cancer. Atezo added to paclitaxel in same setting had no impact on outcomes. Early TNBC was unmet need.

Objective: Examine impact on pCR and outcome of adding atezolizumab (Atezo) to neoadjuvant nab paclitaxel followed by anthracycline chemotherapy for TNBC and continuing it into the adjuvant phase for a total of one year.

Methods: Randomized (1:1) placebo-controlled phase III trial of Atezo concurrently with preoperative nab paclitaxel followed by AC; then additional 11 cycles adjuvant Atezo (unblinded).

Mostly (~75%) clinical stage II patients, ~ 40% N+.

Endpoint: pCR comparing Atezo arm to placebo

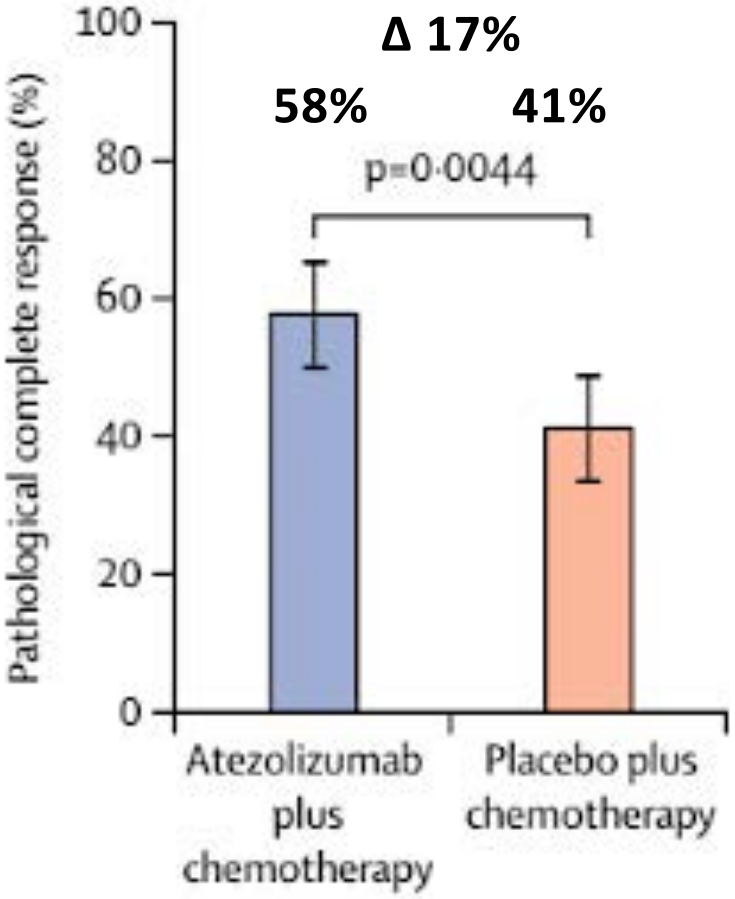
Courtesy of Lisa Carey, MD

Mittendorf E et al, Lancet 2020;396:1090-1100

IMpassion031: Results

N= 333, followup ~20m

pCR breast and axilla



No apparent relationship to PDL1 status

(again higher pCR rate both arms in PDL1+)

- **Secondary endpoint EFS HR 0.76, ns**

Toxicity:

- **Treatment-related serious adverse events: 23% vs 16%**
- **Grade 3+ AE of special interest: 7% vs 5%**

Courtesy of Lisa Carey, MD

Mittendorf E et al, Lancet 2020;396:1090-1100

Mittendorf E et al. IMpassion031: Results from a phase III study of neoadjuvant atezolizumab + chemotherapy in early TNBC. Lancet 2020;396:1090-1100.

Impact on patient care and treatment algorithms

- Similar impact on pCR as KN-522 with different ICI, no platinum. Will not have power for EFS endpoint, trend favorable. High-grade immune-related toxicity numerically lower but still > 5%.
- Whether this regimen will be approved on pCR basis is unknown, but pCR again is unrelated to PDL1 status in early TNBC.

Implications for future research

- Both positive trials for pCR (KN-522 and IMpassion031) had anthracycline/taxane backbones; NeoTRIP did not. Whether anthracyclines are best immunomodulatory chemotherapy agents, as also suggested by the augmented ICI effect with anthracycline in TONIC (Kok, Nat Med 2019) should be considered and studied further.
- Immune activation confers sensitivity to both chemotherapy and immunotherapy; may be opportunity to tailor and optimize in TNBC. Best way to identify immune activation unclear and should be research priority.

Courtesy of Lisa Carey, MD

KEYNOTE-173

Background: I-SPY2 suggested improved pCR with addition of pembrolizumab to chemotherapy. KN-522 later confirmed this, but the optimal anthracycline/taxane-based chemotherapy schedule is uncertain. GeparNuevo suggested that pCR is augmented with a lead-in window of ICI alone.

Objective: Determine optimal schedule and dose of neoadjuvant taxane (with or without carboplatin) followed by AC (all after a lead-in 3-week pembro alone window).

Methods: Six neoadjuvant cohorts, all with 1 cycle pembrolizumab to start, then 4 cycles of taxane + carboplatin (nab paclitaxel, paclitaxel, weekly or q3wk, ± carbo) followed by q3wk AC x 4, then surgery.

Endpoints: Primary — safety, recommended dose/schedule (RPh2D). Secondary — pCR, other clinical, predictive biomarkers

KEYNOTE-173

N=60, followup 20m.

Chemotherapy cohorts:

- Cohort A: nab paclitaxel weekly alone (IMpassion031)
- Cohort E: paclitaxel weekly + carboplatin AUC5 (KN-522, also allowed weekly carbo)
- Rest failed for toxicity, including the NeoTRIP regimen (nab pac + carbo weekly, 25% d/c early)

Toxicity:

- DLT= ANC (not surprisingly)
- Immune-related toxicity in 30%
- Pembro d/c in 13% for hepatitis (3), fatigue (2), SLE, colitis, hyperthyroidism.

- **pCR 60% all cohorts. EFS trend towards association with pCR but # small, short f/u.**
  - Suggestion of higher pCR in PDL1+ but widely overlapping 95% CI (unlike larger trials)
  - Higher sTILs pre- and on-treatment (after window) associated with pCR (but underpowered)

Courtesy of Lisa Carey, MD

Schmid P et al. Pembrolizumab plus chemotherapy as neoadjuvant treatment of high-risk, early-stage, triple-negative breast cancer: results from the phase 1b open-label, multicohort KEYNOTE-173 study. Ann Oncol 2020;31(5):569-581.

Impact on patient care and treatment algorithms

- Primarily to confirm the acceptability of the chemotherapy backbone of KN-522 and IMpassion031. Fairly high IRAE rates confirming importance of tracking long-term effects.
- Other taxane/carboplatin schedules were more toxic; could this have contributed to the high discontinuation rate and negative results of NeoTRIP?

Implications for future research

- Important for future trials incorporating ICI into neoadjuvant polychemotherapy regimens.
- Design similar to GeparNuevo, with similar pCR rate as in the durvalumab lead-in cohort in that study; the sTIL relationship to pCR is modest and a little stronger when measured in on-treatment assay (post ICI induction).

Courtesy of Lisa Carey, MD


Thank You!