NCCN 2021 Virtual Congress: Breast Cancer
with Updates from the 2020 San Antonio Breast Cancer Symposium

Friday, February 12, 2021
3:05 PM – 3:50 PM EST

Updates to the Systemic Treatment of Metastatic Breast Cancer, Including SABCS Updates

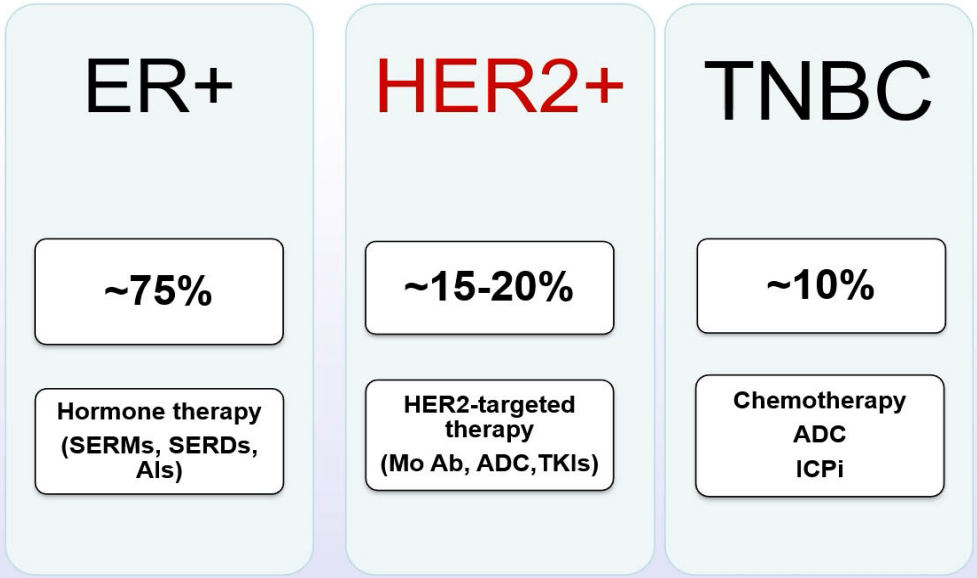
William J. Gradishar, MD

Robert H. Lurie Comprehensive Cancer Center of Northwestern University

National Comprehensive Cancer Network®

NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients

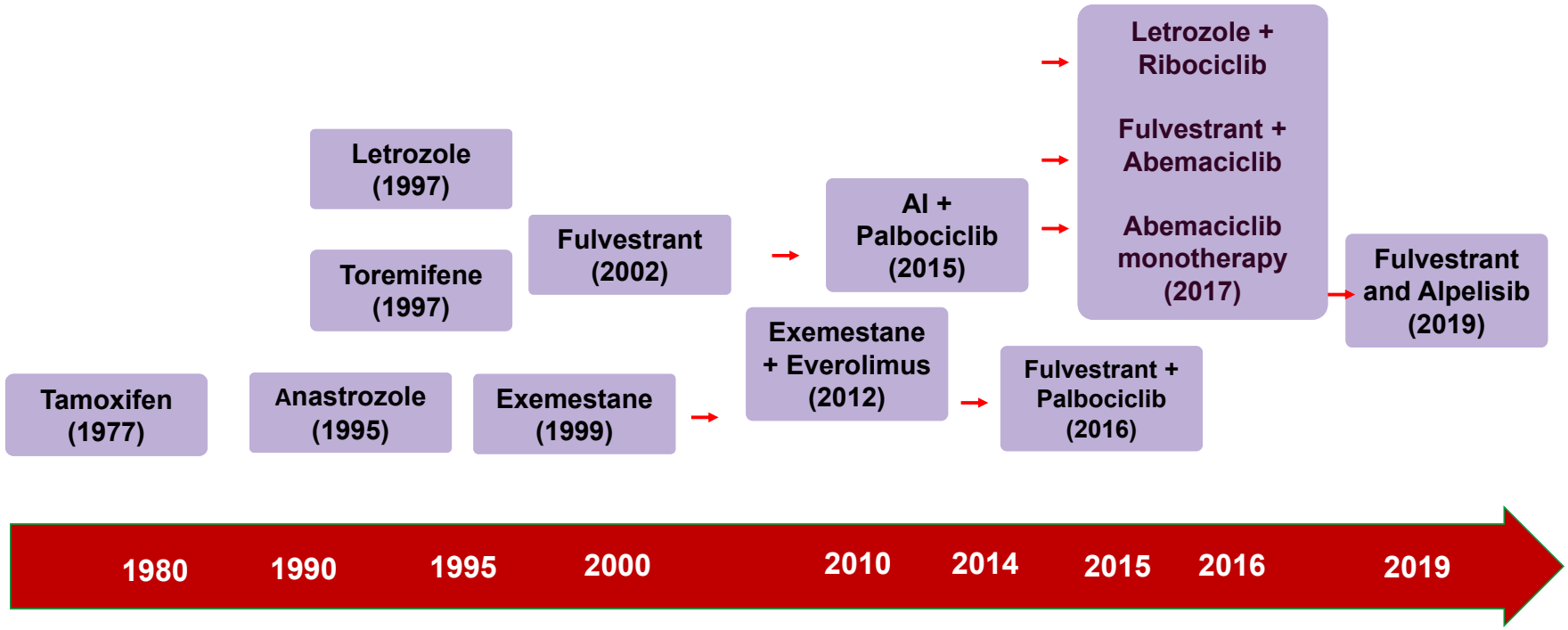
Clinical subtypes of breast cancer



ER= Estrogen receptor , HER2=Human epidermal growth factor receptor,
TNBC= Triple negative (ER,PR,HER2 -ve) Breast cancer

Northwestern Medicine®

Examples of Hormonal Therapies for ER+ Breast Cancer: *Evidence of Recent Acceleration*



Northwestern Medicine®

U.S. Food and Drug Administration. http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Invasive Breast Cancer

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT OR STAGE IV (M1) DISEASE[a]

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Preferred Regimens
First-Line Therapy

- Aromatase inhibitor + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)
- Selective ER down-regulator (fulvestrant, category 1)[b] ± non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[b]
- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Selective estrogen receptors modulator (tamoxifen or toremifene)
- Steroidal aromatase inactivator (exemestane)

Preferred Regimens
Second- and Subsequent-Line Therapy

- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[c]
- For *PIK3CA*-mutated tumors, see additional targeted therapy options (see BINV-R)[c,d]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[c,f]
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator (exemestane)
- Selective ER down-regulator (fulvestrant)
- Selective estrogen receptors modulator (tamoxifen or toremifene)

Useful in Certain Circumstances[d]

- Megestrol acetate
- Estradiol
- Abemaciclib[c,e]

HER2-Positive and Postmenopausal[g,h,i] or Premenopausal Receiving Ovarian Ablation or Suppression

- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

BINV-P

ER +/HER2-

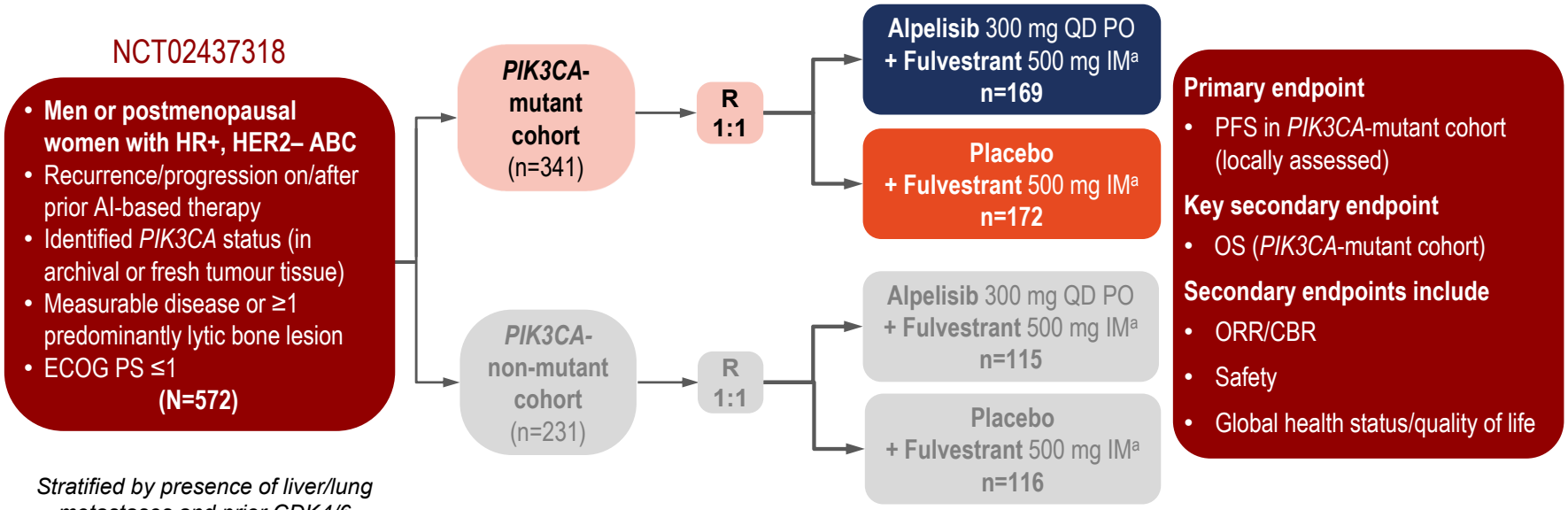
- What is the role of Alpelisib in Advanced ER + in patients with PIK3CA mutations?
  - Overall Survival data; SOLAR1 (ESMO 2020)
- Is there a role for AKT inhibition in Advanced ER + Breast CA?
  - Progression-Free Survival data; IPATunity130 (ESMO 2020)
- HDAC inhibition in ER + MBC?
  - Survival data; E2112 trial of etinostat (SABCS 2020)
- Oral taxanes?
  - Progression-Free Survival data; CONTESSA, tesetaxel + capecitabine (SABCS 2020)

Northwestern Medicine®

San Antonio Breast Cancer Symposium®, December 8–11, 2020

SOLAR-1: OS is a Key Secondary Endpoint

Prospective evaluation of an α-selective PI3K inhibitor in HR+, HER2– ABC

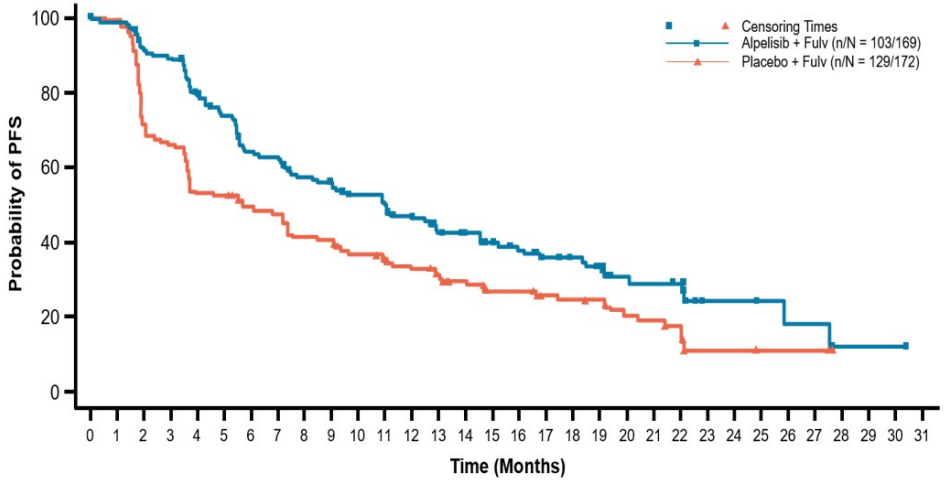


Stratified by presence of liver/lung metastases and prior CDK4/6 inhibitor treatment

Northwestern Medicine®

André F ESMO 2020; Annal Oncol 2020

Primary endpoint: Locally assessed PFS in the PIK3CA-mutant cohort



Data cut-off: Jun 12, 2018	Alpelisib + fulvestrant (N=169)	Placebo + fulvestrant (N=172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5–14.5)	5.7 (3.7–7.4)
HR (95% CI)	0.65 (0.50–0.85)	
p-value	0.00065	

~ 5.5 months benefit in PFS

Only ~ 7% pretreated with CDK 4/6i

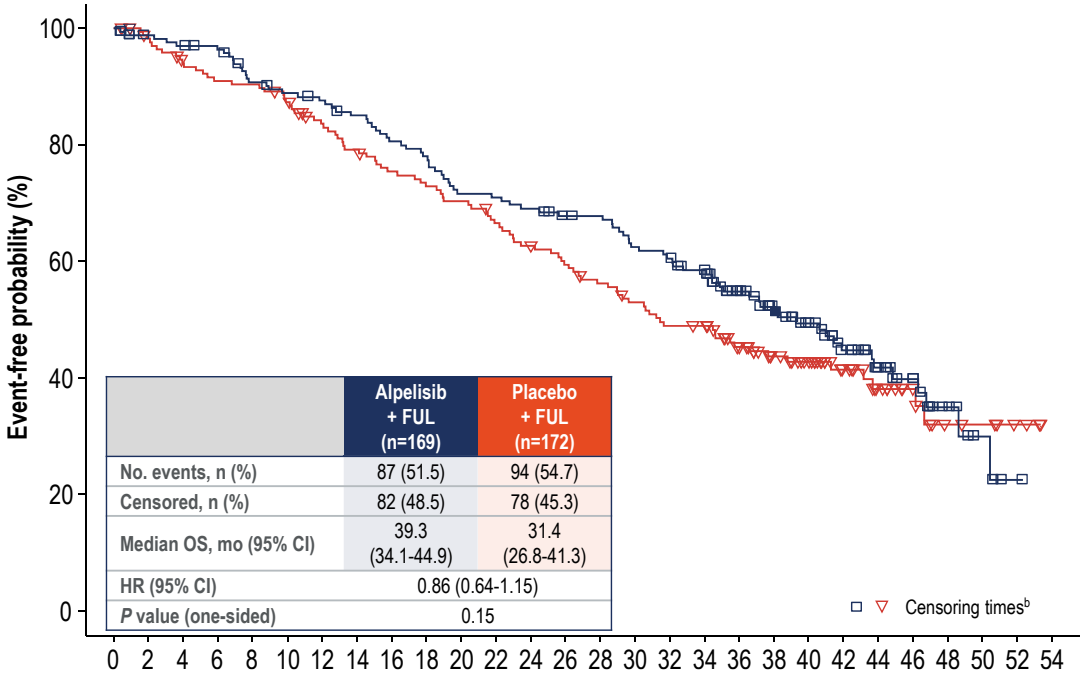
See Rugo H et al. SABCS 2020 – Alpelisib in prior CDKi treated patients

Northwestern Medicine®

André F ESMO 2020; Annal Oncol 2020

OS in Patients in PIK3CA-mutant Cohort

- **mOS was prolonged by 7.9 mo** for patients in the alpelisib + fulvestrant arm
- Final OS analysis in the *PIK3CA*-mutant cohort numerically improved OS but **did not cross the prespecified O'Brien-Fleming efficacy boundary** (1-sided $P \leq 0.0161$)



	Alpelisib + FUL (n=169)	Placebo + FUL (n=172)
No. events, n (%)	87 (51.5)	94 (54.7)
Censored, n (%)	82 (48.5)	78 (45.3)
Median OS, mo (95% CI)	39.3 (34.1-44.9)	31.4 (26.8-41.3)
HR (95% CI)	0.86 (0.64-1.15)	
P value (one-sided)	0.15	

Northwestern Medicine®

André F ESMO 2020; Annal Oncol 2020

San Antonio Breast Cancer Symposium®, December 8–11, 2020

SOLAR-1: Updated Adverse Events

- After a median follow-up of 42.4 months, safety profile remains consistent[1]

AEs ≥20% in Either Arm, %	Alpelisib + FUL (n=284)			Placebo + FUL (n=287)		
	All-Grade	Grade 3	Grade 4	All-Grade	Grade 3	Grade 4
Any AE	282 (99.3)	187 (65.8)	35 (12.3)	267 (93.0)	90 (31.4)	17 (5.9)
Hyperglycaemia	184 (64.8)	94 (33.1)	11 (3.9)	27 (9.4)	2 (0.7)	1 (0.3)
Diarrhoea	169 (59.5)	20 (7.0)	0	47 (16.4)	2 (0.7)	0
Nausea	133 (46.8)	8 (2.8)	0	65 (22.6)	1 (0.3)	0
Decreased appetite	103 (36.3)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash	103 (36.3)	28 (9.9)	0	20 (7.0)	1 (0.3)	0
Vomiting	81 (28.5)	2 (0.7)	0	29 (10.1)	1 (0.3)	0
Weight decreased	79 (27.8)	15 (5.3)	0	7 (2.4)	0	0
Fatigue	72 (25.4)	10 (3.5)	0	51 (17.8)	3 (1.0)	0
Stomatitis	71 (25.0)	7 (2.5)	0	20 (7.0)	0	0
Asthenia	64 (22.5)	7 (2.5)	0	39 (13.6)	0	0
Alopecia	58 (20.4)	0	0	7 (2.4)	0	0

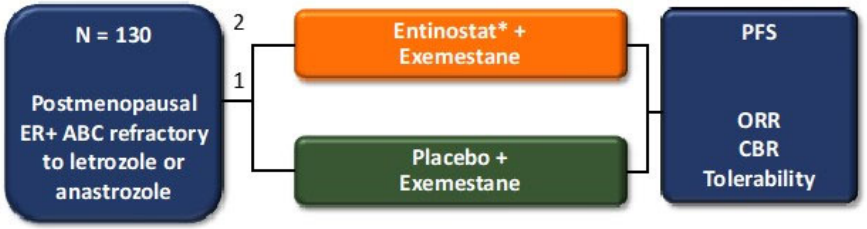
Safety Set

- AESI of rash[a] was observed in 153 (53.9%) and 27 (9.4%) of patients in the alpelisib + fulvestrant vs placebo + fulvestrant arms, respectively; the majority of these events were grade 1 or grade 2

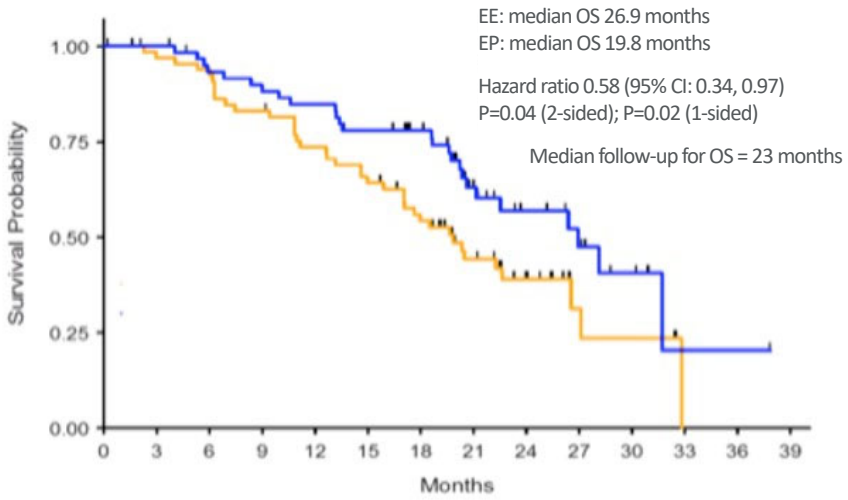
Northwestern Medicine®

San Antonio Breast Cancer Symposium®, December 8–11, 2020

Epigenetic Regulation - The ENCORE 301 Study



Median PFS: 4.3 vs 2.3 months; HR = 0.73, *P* = .055 (one-sided)



Yardley J Clin Oncol 2013

HDAC inhibition in ER + MBC?

E2112 Study Design

Eligible:

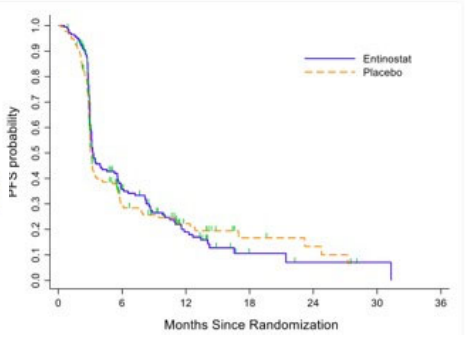
- Advanced breast cancer
- HR+, HER2-
- Pre/peri/post-menopausal women and men
- Progression on prior non-steroidal AI
- ≤ 1 prior chemo for metastatic disease

N=600
NCT02115282

RANDOMIZE

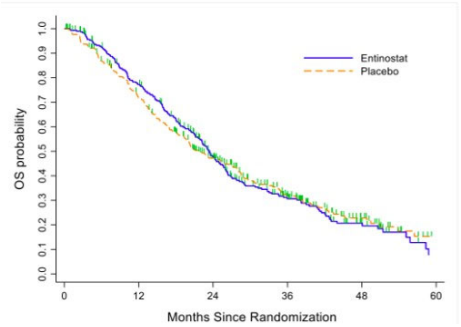
- Exemestane 25mg po daily plus ENTINOSTAT 5mg po weekly*
- Exemestane 25mg po daily plus PLACEBO 5mg po weekly*

Primary Endpoint: PFS



	Entinostat (n=180)	Placebo (n=180)
Median PFS (Months)	3.3	3.1
HR (95% CI)	0.87 (0.67-1.13)	
Stratified log-rank test P value	0.30	
Overall Response Rate	4.6%	4.3%

Primary Endpoint: OS



	Entinostat (n=305)	Placebo (n= 303)
Median OS (Months)	23.4	21.7
HR (95% CI)	0.99 (0.82-1.21)	
Stratified log-rank test P value	0.94	

Northwestern Medicine

Connolly RM et al. SABCS 2020

IPATunity130 Cohort B (NCT03337724): Double-blinded placebo-controlled randomised trial[a]

- HR+ (≥1%) HER2-negative measurable aBC
- *PIK3CA/AKT1/PTEN* alteration[b]
- Not considered appropriate for endocrine-based therapy
- No prior chemotherapy for aBC
- Prior CDK4/6 inhibitor and/or mTOR inhibitor permitted
- Candidate for taxane therapy
- ECOG performance status 0/1

222 patients enrolled between 6 Jan 2018 and 29 Mar 2019 (50% Europe, 26% Asia-Pacific)

R 2:1

- PAC 80 mg/m² days 1, 8 & 15 + IPAT 400 mg od days 1–21 q28d
- PAC 80 mg/m² days 1, 8 & 15 + PBO days 1–21 q28d

Treatment until disease progression, intolerable toxicity[c] or elective withdrawal

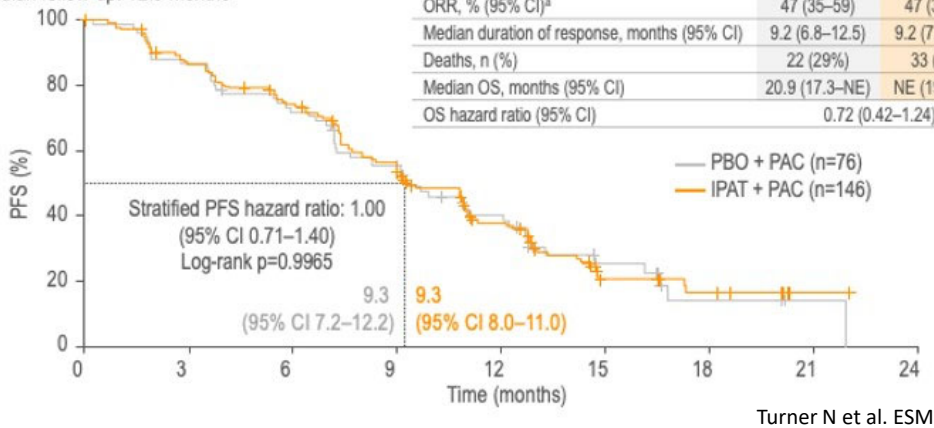
Crossover from PBO to IPAT is not permitted

Analysis of primary endpoint (investigator-assessed PFS) planned after ~150 PFS events
- 80% power to detect an increase in median PFS from 8.5 → 13.8 months with the addition of IPAT to PAC
- Target hazard ratio = 0.62 at 2-sided 5% significance level

Summary of efficacy

-AKT inhibition in ER + MBC? Not in combination with chemo
-May be a role with endocrine therapy – FAKTION trial

Primary endpoint: investigator-assessed PFS
Median follow-up: 12.9 months



Secondary endpoints	PBO + PAC (n=76)	IPAT + PAC (n=146)
ORR, % (95% CI)[a]	47 (35–59)	47 (38–55)
Median duration of response, months (95% CI)	9.2 (6.8–12.5)	9.2 (7.2–11.3)
Deaths, n (%)	22 (29%)	33 (23%)
Median OS, months (95% CI)	20.9 (17.3–NE)	NE (19.2–NE)
OS hazard ratio (95% CI)	0.72 (0.42–1.24)	

Northwestern Medicine®

Turner N et al. ESMO 2020

Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial

Robert H Jones, Angela Casbard*, Margherita Carucci, Catrin Cox, Rachel Butler, Fouad Alchami, Tracie-Ann Madden, Catherine Bale, Pavel Bezecny, Johnathan Joffe, Sarah Moon, Chris Twelves, Ramachandran Venkitaraman, Simon Waters, Andrew Foxley, Sacha J Howell*

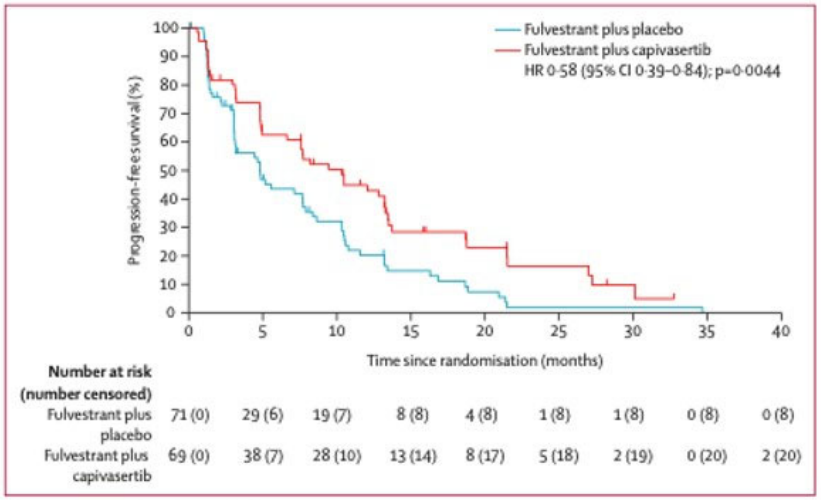


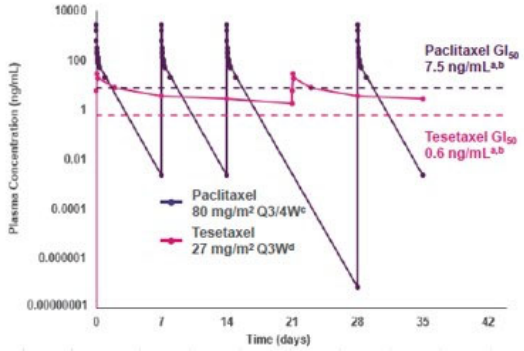
Figure 2: **Progression-free survival**
HR=hazard ratio.

Northwestern Medicine®

Jones RH Lancet Oncology 2020

Results from CONTESSA: A Phase 3 study of tesetaxel plus a reduced dose of capecitabine versus capecitabine alone in patients with HER2-, hormone receptor + (HR+) metastatic breast cancer (MBC) who have previously received a taxane

Tesetaxel Dosing and Administration



	Paclitaxel[e]	Tesetaxel
Route	Intravenous	Oral
Frequency	Once every 7 days	Once every 21 days
Dose	80 mg/m²	27 mg/m² (2-5 capsules)
Anti-allergy Premedication	Yes[f]	No

GI_{50}=concentration of drug required to inhibit growth by 50%; Q3/4W=once per week for 3 of 4 weeks; Q3W=once every 3 weeks

Northwestern Medicine®

O'Shaughnessy J SABCS 2020

CONTESSA

Study Design

Key Eligibility Criteria

- HR positive, HER2 negative MBC
- 0-1 prior chemotherapy regimens for MBC
- Prior taxane in the neoadjuvant or adjuvant setting required
  - No restriction on disease-free interval (DFI)
- Any number of prior endocrine therapies
- Any number of prior approved targeted therapies (*e.g.*, CDK 4/6 inhibitors, everolimus)
- Measurable disease per RECIST 1.1 or bone-only disease with lytic component

PO=oral dosing; BID=twice per day

Multinational, Multicenter, Randomized

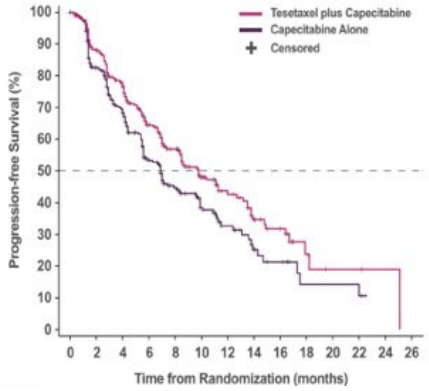
1:1 Randomization

Tesetaxel 27 mg/m² PO (Day 1 of a 21-day cycle) + **Capecitabine** 1,650 mg/m² PO (825 mg/m² BID) (Evening Day 1 to Morning Day 15 of a 21-day cycle)

Treat until progressive disease or unacceptable toxicity

Capecitabine 2,500 mg/m² PO (1,250 mg/m² BID) (Evening Day 1 to Morning Day 15 of a 21-day cycle)

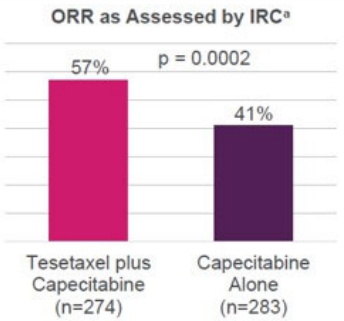
PFS as Assessed by IRC

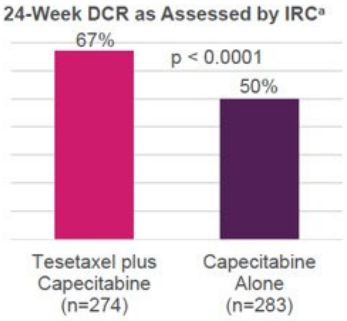


	Tesetaxel plus Capecitabine (N=343)	Capecitabine Alone (N=342)
Events	155	169
Median Months (95% CI)	9.8 (8.4 – 12.0)	6.9 (5.6 – 8.3)
	2.9-Month Improvement	
Hazard Ratio (95% CI)	0.716 (0.573 – 0.895)	
P-value	0.003	

CI=confidence interval

Secondary Endpoints





Northwestern Medicine®

O'Shaughnessy J SABCS 2020

All Grade Treatment-Emergent Adverse Events (TEAEs) That Occurred in ≥20% of Patients in Either Arm

System Organ Class	TEAE	Tesetaxel plus Capecitabine (N=337) (%)	Capecitabine Alone (N=337) (%)
Hematologic	Neutropenia	76.9	22.6
	Anemia	29.7	19.0
	Thrombocytopenia	20.5	6.2
Gastrointestinal	Nausea	62.6	42.7
	Diarrhea	61.1	46.9
	Constipation	33.2	15.1
	Vomiting	30.6	19.9
	Abdominal pain	21.7	17.2
	Stomatitis	20.5	29.1
Other	Hand-foot syndrome	50.7	66.2
	Neuropathy	48.1	13.6
	Fatigue	47.8	34.4
	Decreased appetite	28.8	19.3
	Alopecia*	28.2	2.4
	Hypokalemia	20.5	6.8

*Grade 2 alopecia (tesetaxel plus capecitabine vs. capecitabine alone): 8.0% vs. 0.3%

Northwestern Medicine

San Antonio Breast Cancer Symposium®, December 8–11, 2020

Grade ≥3 TEAEs That Occurred in ≥5% of Patients in Either Arm

System Organ Class	TEAE	Tesetaxel plus Capecitabine (N=337) (%)		Capecitabine Alone (N=337) (%)	
		Grade 3	Grade 4	Grade 3	Grade 4
Hematologic	Neutropenia	32.6	38.3	7.4	0.9
	Febrile neutropenia	10.4	2.7	0.3	0.9
	Anemia	8.0	0.0	2.4	0.0
	Leukopenia	6.8	3.0	0.6	0.3
Gastrointestinal	Diarrhea	12.5	0.6	8.9	0.0
	Nausea	6.2	0.0	2.1	0.0
Other	Fatigue	8.6	0.0	4.5	0.0
	Hypokalemia	8.0	0.6	2.7	0.0
	Hand-foot syndrome	6.8	0.0	12.2	0.0
	Neuropathy[a]	5.3	0.6	0.9	0.0

No treatment-related hypersensitivity reactions

Doublet not surprisingly shows more toxicity and superior to cape alone

Future registration plans?

Potential Quality of Life Benefits of PO taxane over IV taxanes
-once every 3-week dosing
-no premedication
-less alopecia
-less neuropathy

AEs Resulting in Treatment Discontinuation in ≥1% of Patients in Either Arm

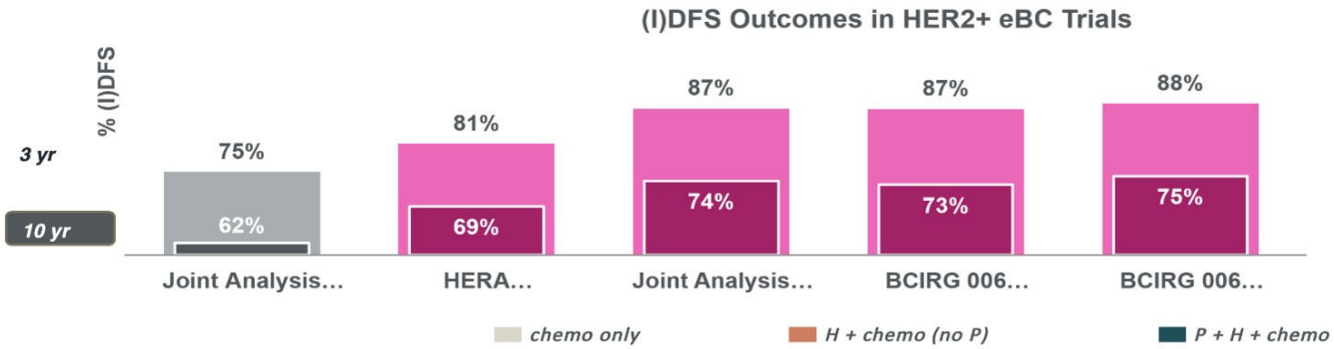
	Tesetaxel plus Capecitabine (N=337) (%)	Capecitabine Alone (N=337) (%)
Neutropenia or febrile neutropenia	4.2	1.5
Neuropathy	3.6	0.3
Sepsis or septic shock	1.8	0.6
Diarrhea	0.9	1.5
Hand-foot syndrome	0.6	2.1
Patients discontinuing treatment due to any AE[a]	23.1	11.9

Northwestern Medicine®

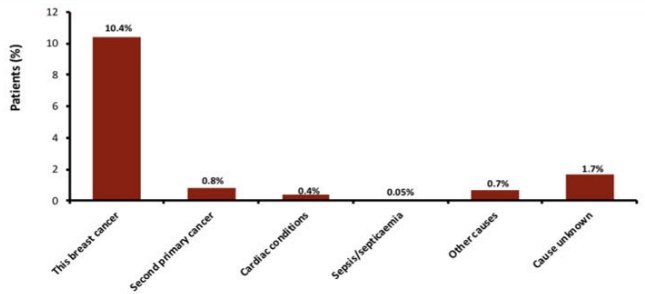
A Very Productive Year in HER2-Positive MBC

Northwestern Medicine®

HER2+ Breast Cancer – Remains a High Unmet Need

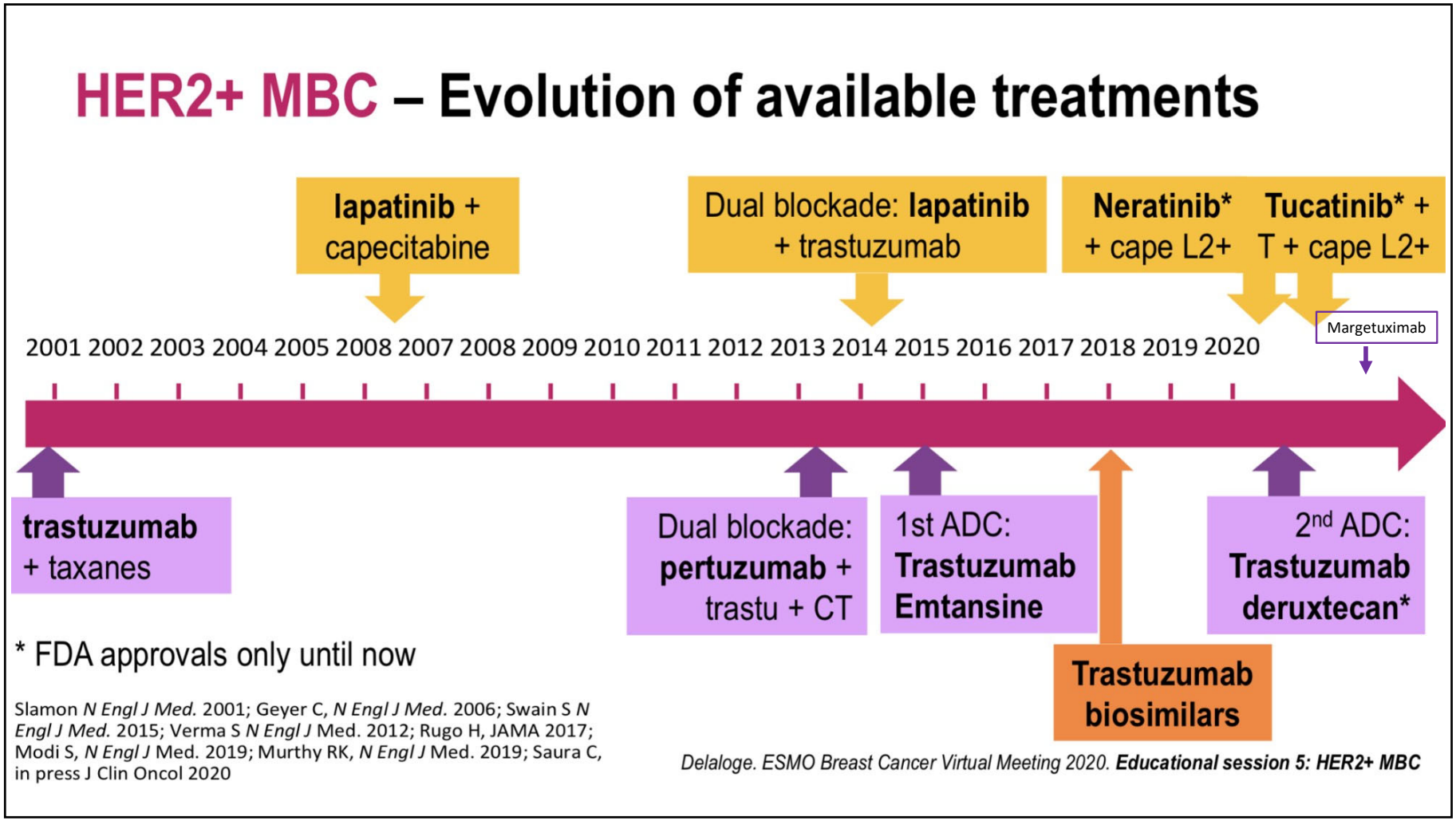


B-31/N9831: 10-year overall survival events and causes of death in patients treated with trastuzumab



BC was the cause of death for the majority of the ~14% of patients who died

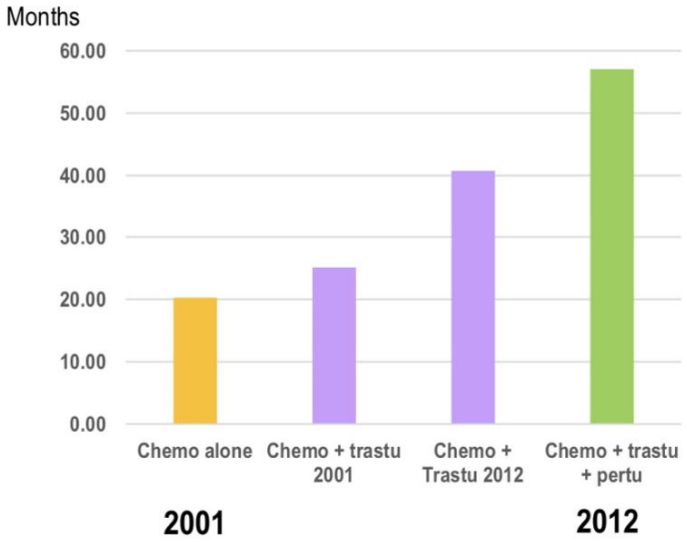
Perez EA, *et al. J Clin Oncol* 2014; 32:3744–3752



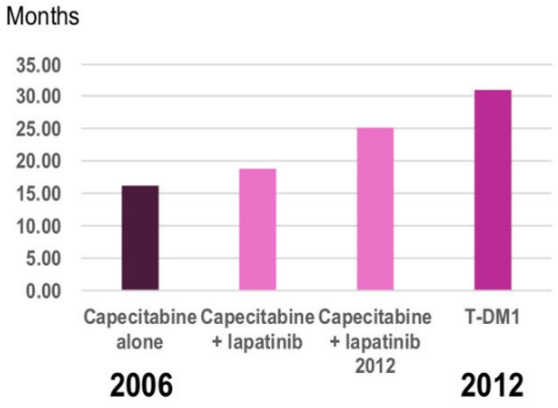
HER2+ MBC – Evolution of predicted outcomes

Data from clinical trials

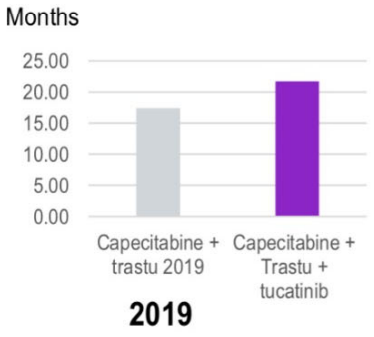
Overall survival – 1st line



Overall survival – 2nd line



3rd+line



Slamon *N Engl J Med.* 2001; Geyer C, *N Engl J Med.* 2006; Swain S *Lancet Oncol 2020*; Verma S *N Engl J* Med. 2012; Rugo H, JAMA 2017; Modi S, *N Engl J* Med. 2019; Murthy RK, *N Engl J* Med. 2019; Saura C, in press J Clin Oncol 2020

Delaloge. ESMO Breast Cancer Virtual Meeting 2020. ***Educational session 5: HER2+ MBC***

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Invasive Breast Cancer

SYSTEMIC THERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE[a,b,c]

HER2-Positive[l,j,k]	
Preferred Regimens	**Other Recommended Regimens**
• Pertuzumab + trastuzumab + docetaxel (category 1)[l] • Pertuzumab + trastuzumab + paclitaxel	• Tucatinib + trastuzumab + capecitabine (category 1)[m] • Ado-trastuzumab emtansine (T-DM1) (category 1) • Fam-trastuzumab deruxtecan-nxki[n] • Trastuzumab + paclitaxel ± carboplatin • Trastuzumab + docetaxel[l] • Trastuzumab + vinorelbine[l] • Trastuzumab + capecitabine • Lapatinib + capecitabine • Trastuzumab + lapatinib (without cytotoxic therapy) • Trastuzumab + other agents[l,o,p] • Neratinib + capecitabine • See additional targeted therapy options (BINV-R)[e]

[a] Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m^2.

[b] Consider scalp cooling to reduce incidence of chemotherapy-induced alopecia for patients receiving chemotherapy. Results may be less effective with anthracycline-containing regimens.

[c] For treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.

[e] See Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-R).

[i] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

[j] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki.

[k] Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use may be substituted anywhere that the combination of intravenous pertuzumab and intravenous trastuzumab are given as part of systemic therapy. Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use has different dosing and administration instructions compared to the intravenous products.

[l] Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

[m] For adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more lines of prior HER2-targeted therapy in the metastatic setting.

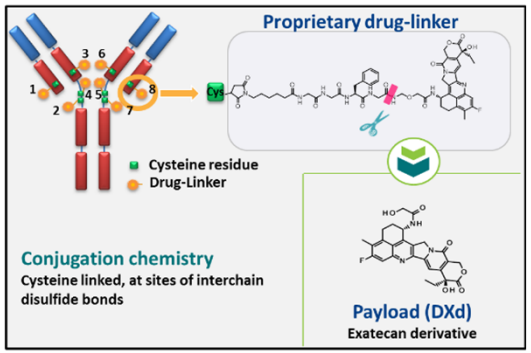
[n] Fam-trastuzumab deruxtecan-nxki is indicated following two or more lines of prior HER2-targeted therapy in the metastatic setting. This agent is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).

[o] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

[p] Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents listed on BINV-Q (1 of 7) for recurrent or metastatic breast cancer.

Trastuzumab Deruxtecan (DS-8201a): Novel, uniquely designed ADC for optimal anti-tumor effect

- Three components
  - Humanized anti-HER2 IgG1 mAb with same amino acid sequence as trastuzumab
  - Topoisomerase I inhibitor payload (Dxd), exatecan derivative
  - Tetrapeptide-based, tumor selective cleavable linker
- Key features of novel payload - high potency, short systemic half-life, membrane-permeable, stable linker, tumor selective

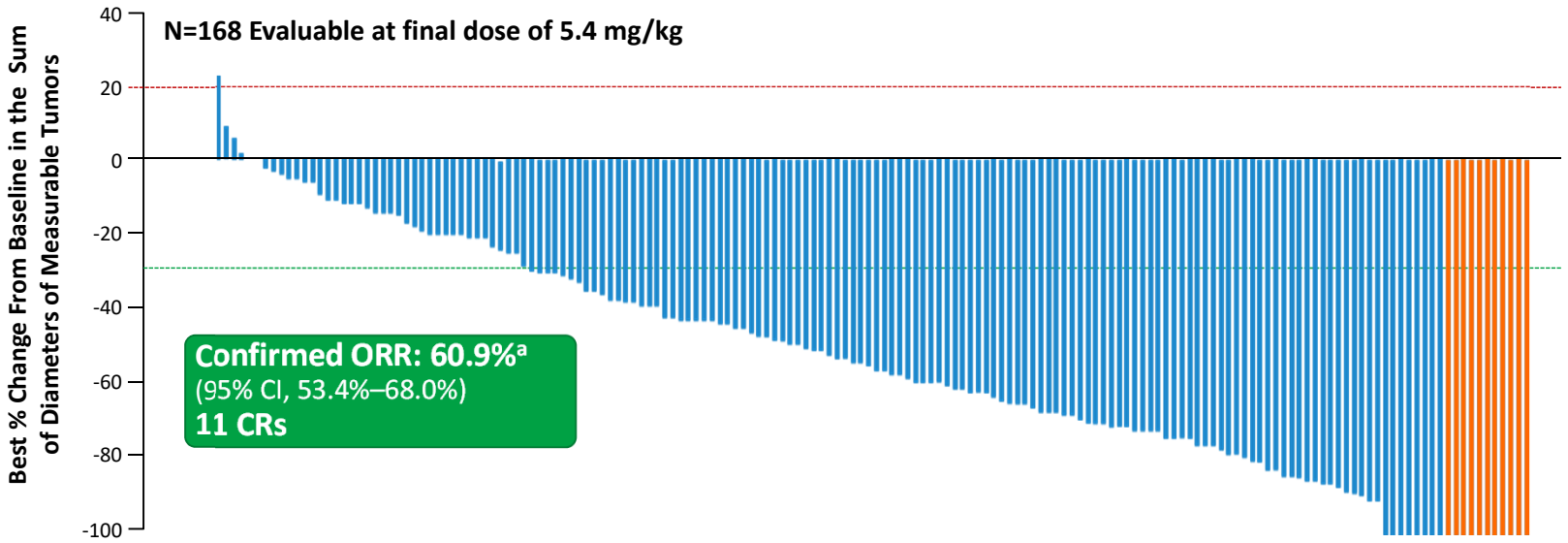


	DS-8201a	T-DM1
Antibody	Anti-HER2 Ab	Trastuzumab
MOA	Topoisomerase I Bystander effect*	Tubulin
Drug-to-antibody ratio	7-8	3.5**

Northwestern Medicine

Takegawa N et al. Int J Cancer 2017; Nakada T et al. Chem Pharm Bull 2019; Ogitani Y et al. Clin Cancer Res 2016; Trail PA et al. Pharmacol Ther 2018; Ogitani Y et al. Cancer Sci 2016.

DESTINY-Breast01 Trial: Phase 2 Study of Trastuzumab Deruxtecan



Median lines of therapy = 6 (range 2-17)	Patients, % T-DXd 5.4 mg/kg (N=184)
Trastuzumab	100
T-DM1	100
Pertuzumab	65.8
Other anti-HER2 therapies	54.3
Hormone therapy	48.9
Other systemic therapy	99.5

11/168 CRs

Northwestern Medicine®

Modis S et al, NEJM 2019

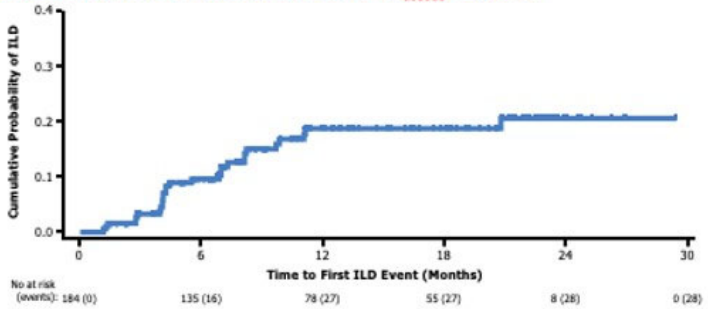
Updated Results From DESTINY-Breast01

Median follow up now 20.5 months
ORR = 61.4%
Duration of Response = 20.8 months
Median PFS =19.4 mo
Median OS = 24.6 mo

Table 4. Drug-related ILD/Pneumonitis[a]

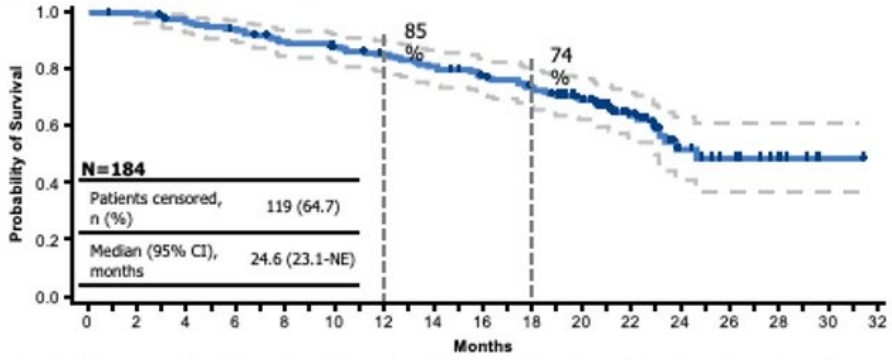
Interstitial lung disease, n (%)	T-DXd 5.4 mg/kg (N=184)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade/ Total
Aug 2019 data cutoff	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**
June 2020 data cutoff	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	**28 (15.2)**

Figure 6. Cumulative Probability of Adjudicated Drug-related Any-grade ILD in Patients With HER2-Positive Breast Cancer (T-DXd 5.4 mg/kg)



Not cumulative

Figure 5. Kaplan-Meier Analysis of Overall Survival



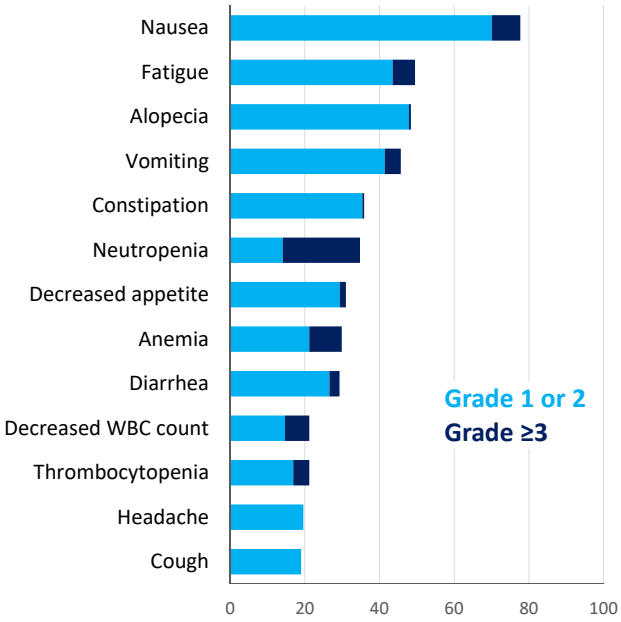
Other DESTINY Breast trials ongoing in earlier settings and HER2 low

Northwestern Medicine

Modi S SABS 2020

San Antonio Breast Cancer Symposium®, December 8–11, 2020

DESTINY Breast01: TEAEs in >15% of Patients



ILD requires awareness via monitoring, dose interruptions and modification, and adherence to management guidelines

Interstitial lung disease , n (%)	T-DXd 5.4 mg/kg (N=184)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade/ Total
Aug 2019 data cutoff	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**
June 2020 data cutoff	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	**28 (15.2)**

[a] As determined by an independent ILD adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication.

Median to onset of ILD was 27.6 weeks (range, 6-76 weeks)

3 additional cases of T-DXd related ILD

Rate of discontinuation or ILD did not increase

Northwestern Medicine®

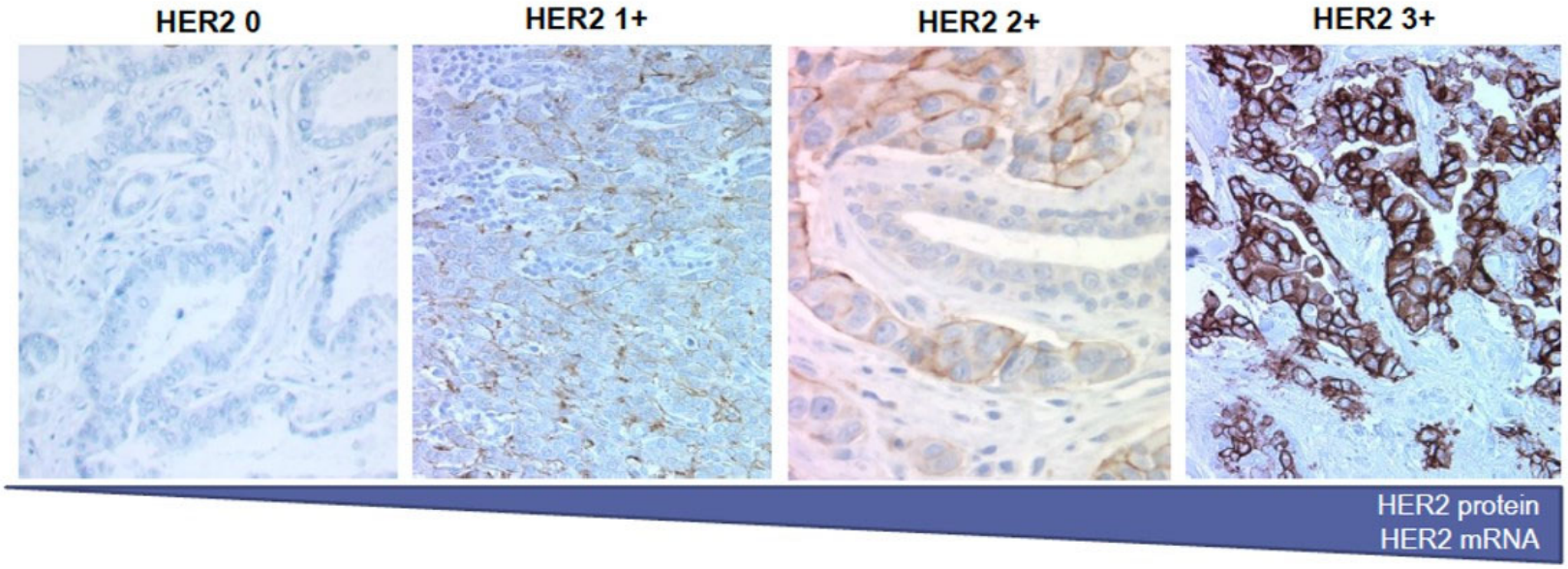
Modi et al, NEJM 2019; SABCS 2020

Recommended Guidelines for the Management of Trastuzumab Deruxtecan-Induced Interstitial Lung Disease

Grade 1	Grade 2	Grade 3/4

• Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry
• Consider follow-up imaging in 1-2 weeks (or as clinically indicated)
• Consider starting systemic steroids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks
• If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines[a]
	• Promptly start systemic steroids (eg, at least 1 mg/kg/day prednisone or equivalent) until clinical improvement, followed by gradual taper over at least 4 weeks
	• Monitor symptoms closely
	• Re-image as clinically indicated
	• If worsening or no improvement in clinical or diagnostic observations in 5 days,
	  • Consider increasing dose of steroids (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to IV (eg, methylprednisolone)
	  • Re-consider additional work-up for alternative etiologies as described above
	  • Escalate care as clinically indicated
		• Hospitalization required.
		• Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1000 mg/day for 3 days), followed by at least 1 mg/kg/day of prednisone (or equivalent) until clinical improvement, followed by gradual taper over at least 4 weeks
		• Re-image as clinically indicated
		• If still no improvement within 3 to 5 days,
		  • Re-consider additional work-up for alternative etiologies as described above
		  • Consider other immunosuppressants and/or treat per local practice

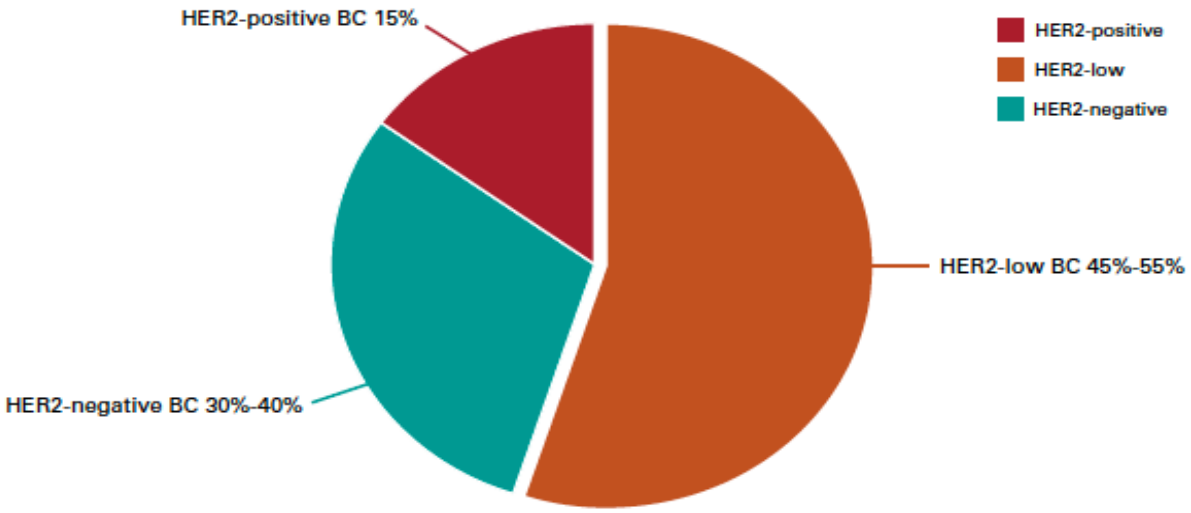
Expression of HER2 is Continuous



Northwestern Medicine

Courtesy of Frederique Penault-Llorca

Prevalence of HER2-Low Breast Cancer



Northwestern Medicine®

Tarantino P et al, JCO 2020

Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients With HER2-Low–Expressing Advanced Breast Cancer: Results From a Phase Ib Study

mPFS-11 ms

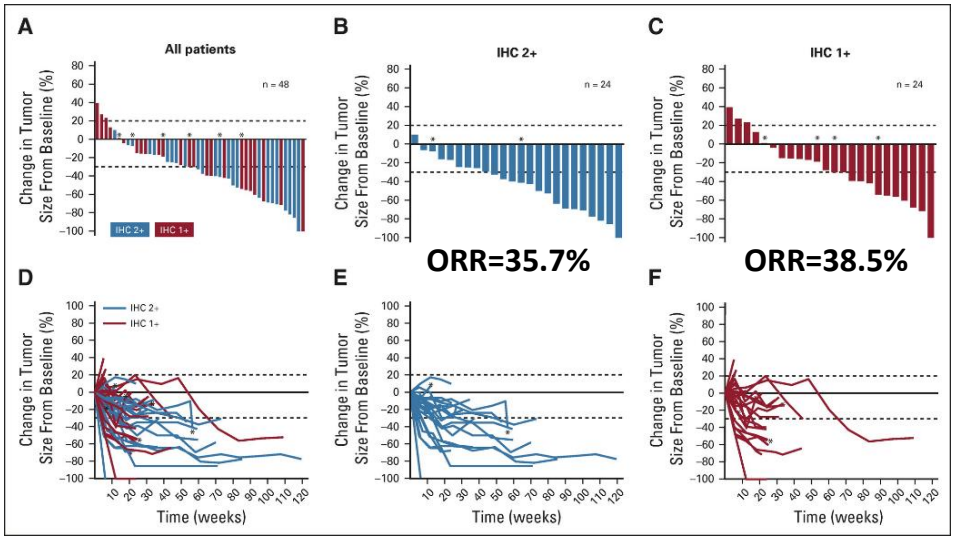
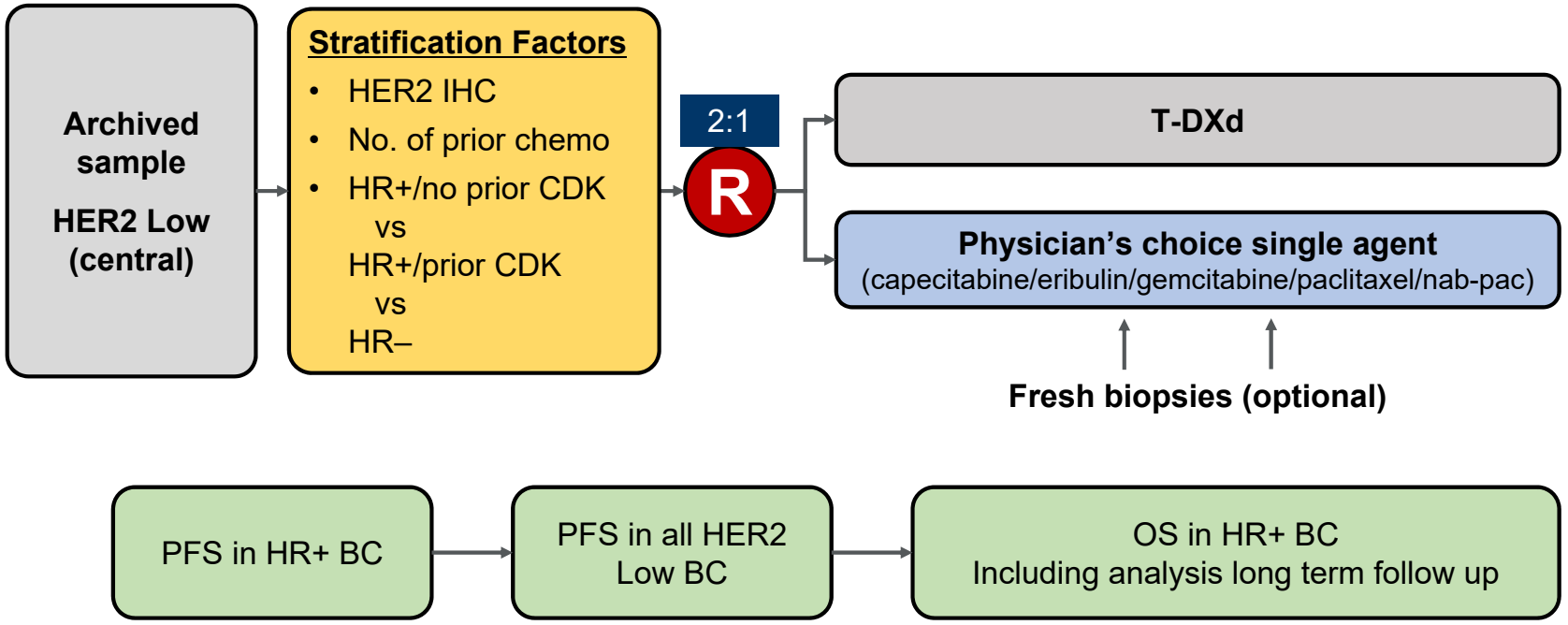


FIG 1. Best percent change in tumor size and percent change in tumor size, respectively, over time for individual patients in (A, D) the entire human epidermal growth factor receptor 2 (HER2)-low population, (B, E) the HER2 immunihistochemistry (IHC) 2+ group, and (C, F) the HER2 IHC 1+ group. Data cutoff was February 1, 2019. Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for partial response and progressive disease, respectively. Tumor responses shown are per independent central review. The IHC status subgroups represent the IHC status as determined by local assessment. (*) HR negative. HR, hormone receptor.

Shanu Modi; Haeseong Park; Rashmi K. Murthy; Hiroji Iwata; Kenji Tamura; Junji Tsurutani; Alvaro Moreno-Aspitia; Toshihiko Doi; Yasuaki Sagara; Charles Redfern; Ian E. Krop; Caleb Lee; Yoshihiko Fujisaki; Masahiro Sugihara; Lin Zhang; Javad Shahidi; Shunji Takahashi;
***Journal of Clinical Oncology* 2020 381887-1896.**

Northwestern Medicine®

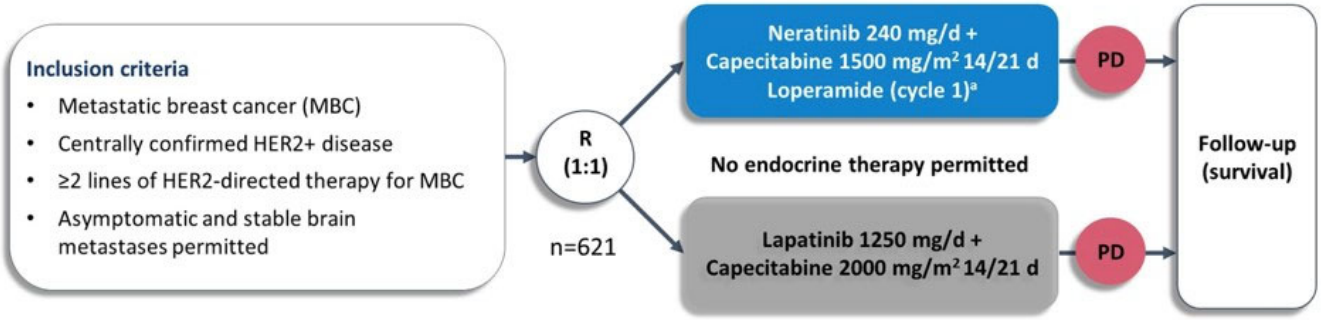
DESTINY-Breast04: Study design for HER2 LOW MBC



Northwestern Medicine

Modi S, et al., Presented During SABCS 2019. San Antonio, TX. Abstract OT1-07-02; ClinicalTrials.gov Identifier: NCT03734029.

NALA: Phase 3 Trial of Neratinib for HER2+ MBC



Stratification variables

- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

Endpoints

- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

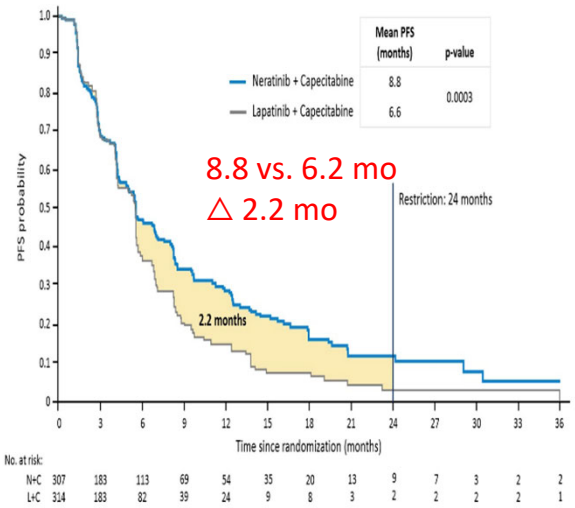
Anti-diarrheal prophylaxis was mandated on the Neratinib arm: Loperamide 4mg with first dose of neratinib, followed by 2mg every 4h for first 3d, then loperamide 2mg every 6-8h until end of cycle 1. Thereafter as needed.

Northwestern Medicine®

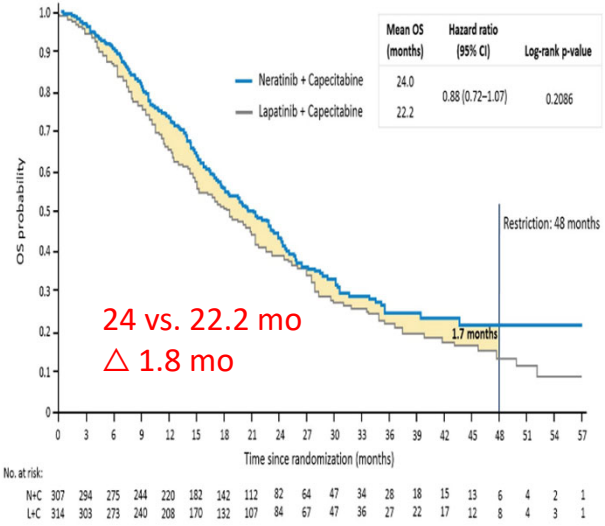
Saura C, et al. ASCO 2019

NALA: Co-Primary endpoint of PFS and OS

Centrally Confirmed PFS



Overall Survival



1 year PFS: 29% vs. 15%
ORR: 33% vs. 27% (p = .1201)
CBR: 45% vs. 36% (p= 0.0328)
Median DOR: 8.5mo vs. 5.6mo (HR 0.50, 95% CI 0.33-0.74, p=.0004)

Northwestern Medicine

Saura C, et al. ASCO 2019

Incidence and Duration of Diarrhea

	ExteNET[1] (n = 1408)	Loperamide[2*] (n = 137)	Budesonide + L[2*] (n = 64)	Colestipol + L[2*] (n = 136)	C + L-PRN[2*] (n = 104)	Dose Escalation 1[2*] (n = 60)
Treatment-emergent diarrhea incidence, n (%)						
Grade 1	323 (23)	33 (24)	16 (25)	38 (28)	34 (33)	25 (42)
Grade 2	458 (33)	34 (25)	21 (33)	47 (35)	32 (31)	25 (42)
Grade 3	**561 (40)**	**42 (31)**	**18 (28)**	**28 (21)**	**33 (32)**	**9 (15)**
Grade 4	1 (0.1)	0	0	0	0	0
Median time to first onset of diarrhea, days						
Grade ≥3	8	7	19	41	15	66
Median cumulative duration per patient, days						
Grade ≥3	5	3	3	4	2	2
Treatment discontinuation due to diarrhea	**17%**	**20%**	**8%**	**4%**	**8%**	**3%**
Hospitalization due to diarrhea	**1%**	**1%**	**0**	**0**	**0**	**0**

Northwestern Medicine®

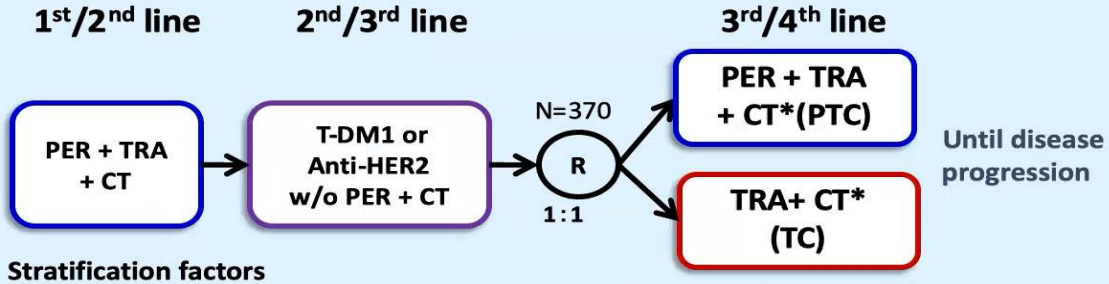
San Antonio Breast Cancer Symposium®, December 8-11, 2020

PRECIOUS: trial design

Objective: To evaluate the efficacy and safety of P, H and CT compared to T and CT in LA/MBC patients who had previously been treated with P

Key Inclusion Criteria

- ECOG Performance status: 0 - 2
- HER2+, confirmed at each institute
- History of PER + TRA + CT for LA/MBC as 1st and/or 2nd line CT
- Latest regimen before enrollment not include PER
- No. of previous CT for LA/MBC regimens < 4
- LVEF ≥ 50% at baseline
- Written informed consent (IC)



Stratification factors

- ✓ER (positive/negative)
- ✓Duration of previous PER
  - (1st line, < 180 days/ ≥ 180 days
  - 2nd line, < 120 days/ ≥ 120 days)
- ✓Previous no. of regimens (2/3) for LA/MBC
- ✓Visceral metastases (+/-)

- Docetaxel
- Paclitaxel
- *nab*-paclitaxel
- Vinorelbine
- Eribulin
- Capecitabine
- Gemcitabine

*CT agents must be chosen by investigators before randomization

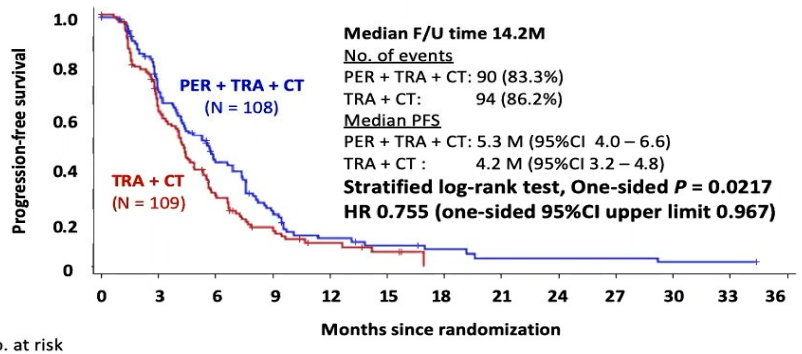
From 10/2015 to 12/2018 at 93 sites in Japan

Yamamoto Y, et al. SABCS 2020 (PD3-11; abstract 288)

San Antonio Breast Cancer Symposium®, December 8-11, 2020

PRECIOUS: PFS

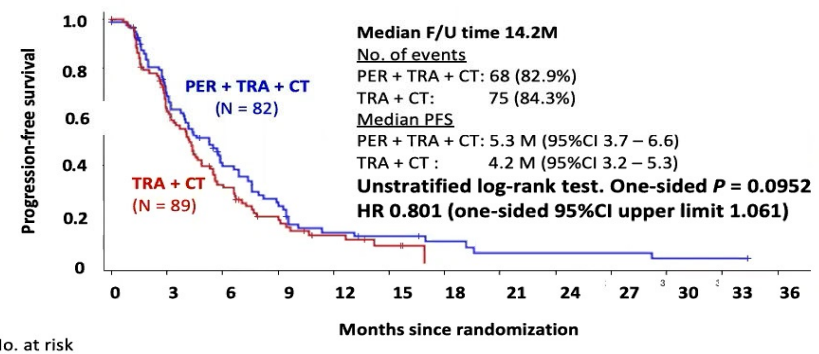
PFS assessed by investigators



No. at risk

PTC	108	68	37	19	9	6	4	2	2	2	1	1	0
TC	109	63	28	17	6	3	0	0	0	0	0	0	0

PFS in patients treated with T-DM1 as the latest regimen

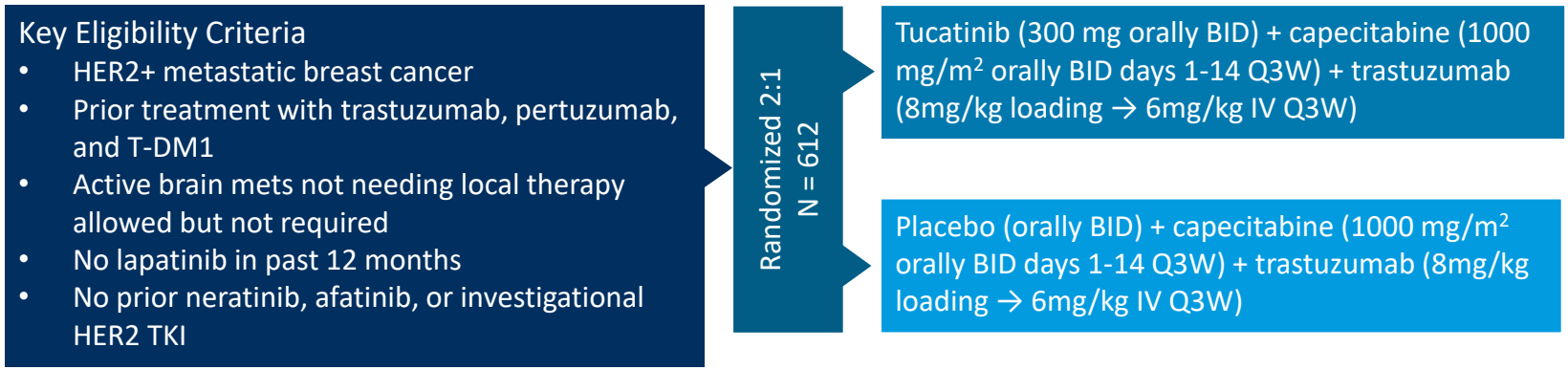


No. at risk

PTC	82	51	27	17	8	6	4	2	2	2	1	1	0
TC	89	52	26	13	6	3	0	0	0	0	0	0	0

Yamamoto Y, et al. SABCS 2020 (PD3-11; abstract 288)

Phase II HER2 CLIMB Trial of Tucatinib: Design

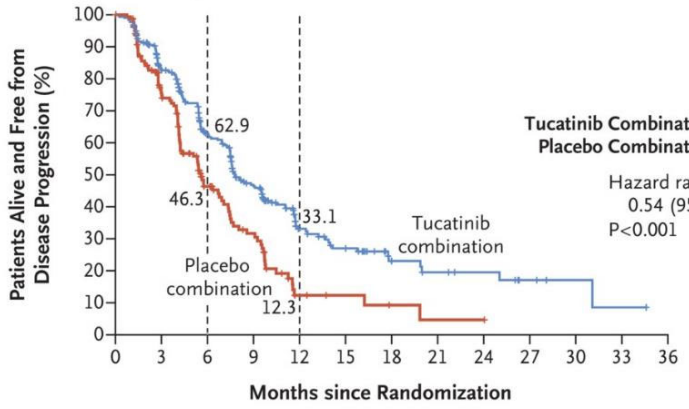


Primary Endpoint	• PFS per RECIST 1.1 by blinded independent central review (BICR)
Secondary Endpoints	• PFS per RECIST 1.1 by BICR in patients with baseline brain metastases • OS • PFS per RECIST 1.1 (investigator assessed) • Objective response rate (ORR); duration of response (DOR); clinical benefit rate (CBR); incidence of AEs

Northwestern Medicine®

HER2CLIMB: PFS and ORR

A Kaplan–Meier Estimates of Progression-free Survival



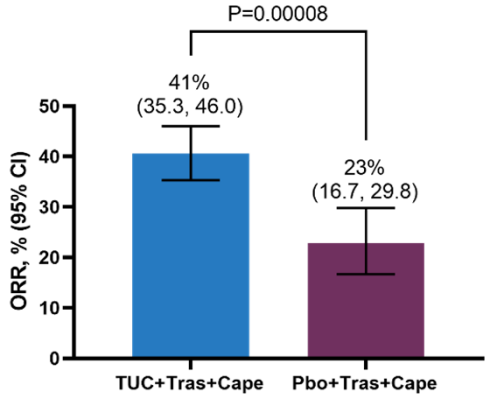
	No. of Events/ No. of Patients	Median Duration (95% CI) mo
Tucatinib Combination	178/320	7.8 (7.5–9.6)
Placebo Combination	97/160	5.6 (4.2–7.1)

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

No. at Risk

Tucatinib combination	320	235	152	98	40	29	15	10	8	4	2	1	0
Placebo combination	160	94	45	27	6	4	2	1	1	0	0	0	0

Confirmed Objective Response Rate (RECIST 1.1, BICR)



	Blinded Independent Central Review		Investigator Assessment	
	Tucatinib Arm (N=340)	Control Arm (N=171)	Tucatinib Arm (N=357)	Control Arm (N=173)
Objective Response, n (%)	138 (40.6)	39 (22.8)	146 (40.9)	37 (21.4)
95% CI[c]	35.3, 46.0	16.7, 29.8	35.8, 46.2	15.5, 28.3
Stratified CMH p-value[d]	0.00008		–	

Northwestern Medicine®

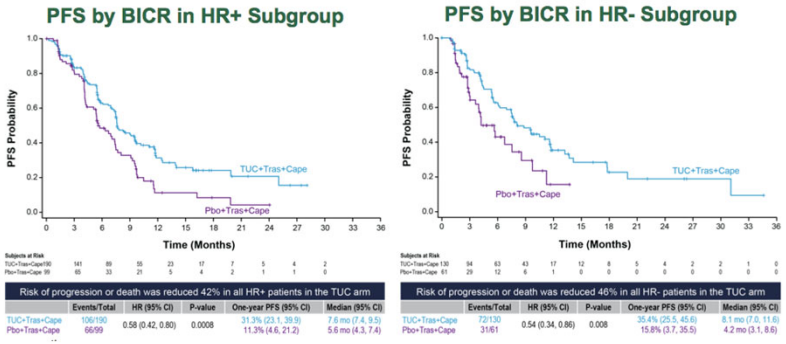
Murthy R, et al. *N Engl J Med* 2020; 382:597-609

San Antonio Breast Cancer Symposium®, December 8–11, 2020

PD3-08 (Abstr #117): HER2CLIMB by HR Status

PFS

PFS benefit was observed in patients in the tucatinib arm of the primary endpoint population regardless of hormone receptor status.

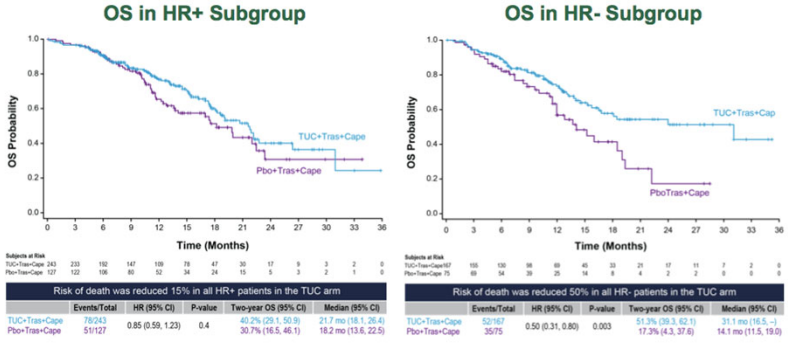


HR+
7.6 vs. 5.6 mo
HR 0.58; p=0.0008

HR-
8.1 vs. 4.2 mo
HR 0.54; p=0.008

OS

Clinically meaningful improvement of OS was observed in patients on the tucatinib arm regardless of hormone receptor status.



HR+
21.7 vs. 18.2 mo
HR 0.85; p=0.4

HR-
31.1 vs. 14.1 mo
HR 0.50; p=0.003

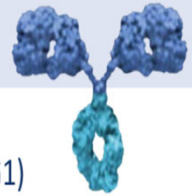
Northwestern Medicine®

Hamilton et al, Abstract #117 SABCS 2020

Margetuximab: Fc-engineered to Alter Fc Receptor Affinities

Trastuzumab

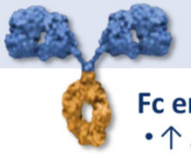
Fab:
- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival



Fc:
- Wild-type immunoglobulin G1 (IgG1) immune effector domains
- Binds and activates immune cells

Margetuximab[1,2]

Fab:
- Same specificity and affinity
- Similarly disrupts signaling



Fc engineering:
- ↑ Affinity for activating FcγRIIIA (**CD16A**)
- ↓ Affinity for inhibitory FcγRIIB (**CD32B**)

Margetuximab Binding to FcγR Variants:

Receptor Type	Receptor	Allelic Variant	Relative Fc Binding	Affinity Fold-Change
Activating	CD16A	158F	Lower	6.6x ↑
		158V	Higher	4.7x ↑
	CD32A	131R	Lower	6.1x ↓
		131H	Higher	↔
Inhibitory	CD32B	232I/T	Equivalent	8.4x ↓

CD16A Genotypes may predict Anti-HER2 antibody benefit

FF in 40% (low binding)

FV in 40-45% (low binding)

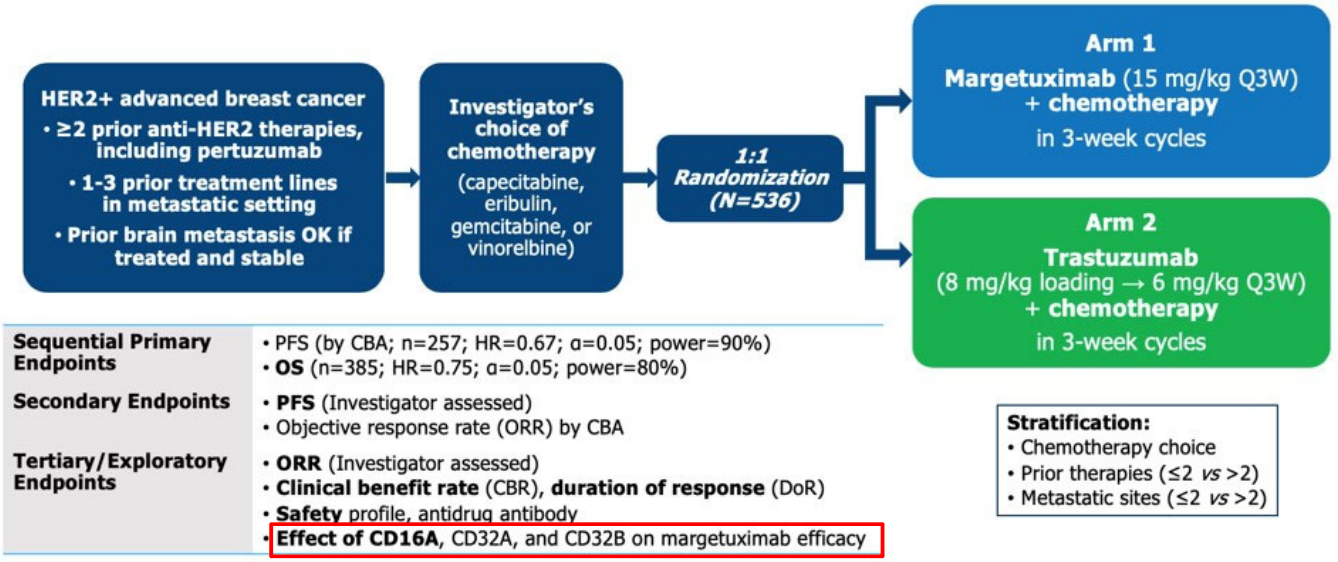
VV in 15% (high binding)

Hypothesis:
Greater M benefit in lower binding CD16A -158F carriers

Northwestern Medicine®

Nordstrom JL, et al. Breast Cancer Res. 2011; Stavenhagen JB, et al. Cancer Res 2007; Musolino A, et al. JCO 2008; Gavin PG, et al. JAMA Oncol 2017; Hurvitz SA, et al. Clin Cancer Res 2012; Norton N, et al. Cancer Immunol Res 2014

SOPHIA: Phase 3 Design



Sequential Primary Endpoints	• PFS (by CBA; n=257; HR=0.67; α=0.05; power=90%) • **OS** (n=385; HR=0.75; α=0.05; power=80%)
Secondary Endpoints	• **PFS** (Investigator assessed) • Objective response rate (ORR) by CBA
Tertiary/Exploratory Endpoints	• **ORR** (Investigator assessed) • **Clinical benefit rate** (CBR), **duration of response** (DoR) • **Safety** profile, antidrug antibody • **Effect of CD16A**, CD32A, and CD32B on margetuximab efficacy

Stratification:
- Chemotherapy choice
- Prior therapies (≤2 *vs* >2)
- Metastatic sites (≤2 *vs* >2)

Prior Therapy
66-67% < 2 lines
100% Trastuzumab
100% Pertuzumab
91-92% TDM1

Northwestern Medicine

Rugo H, et al. ASCO 2019; Rugo H, et al. SABCS 2019

SOPHIA Trial: Updated Results

Sequential Primary Endpoints	• **PFS** (by CBA; n=257; HR=0.67; α=0.05; power=90%) • **OS** (n=385; HR=0.75; α=0.05; power=80%)
Secondary Endpoints	• PFS (Investigator assessed) • Objective response rate (by CBA)
Tertiary/Exploratory Endpoints	• Clinical benefit rate (CBR), duration of response (DoR) • Safety profile, antidrug antibody • Effect of CD16A, CD32A, and CD32B on margetuximab efficacy

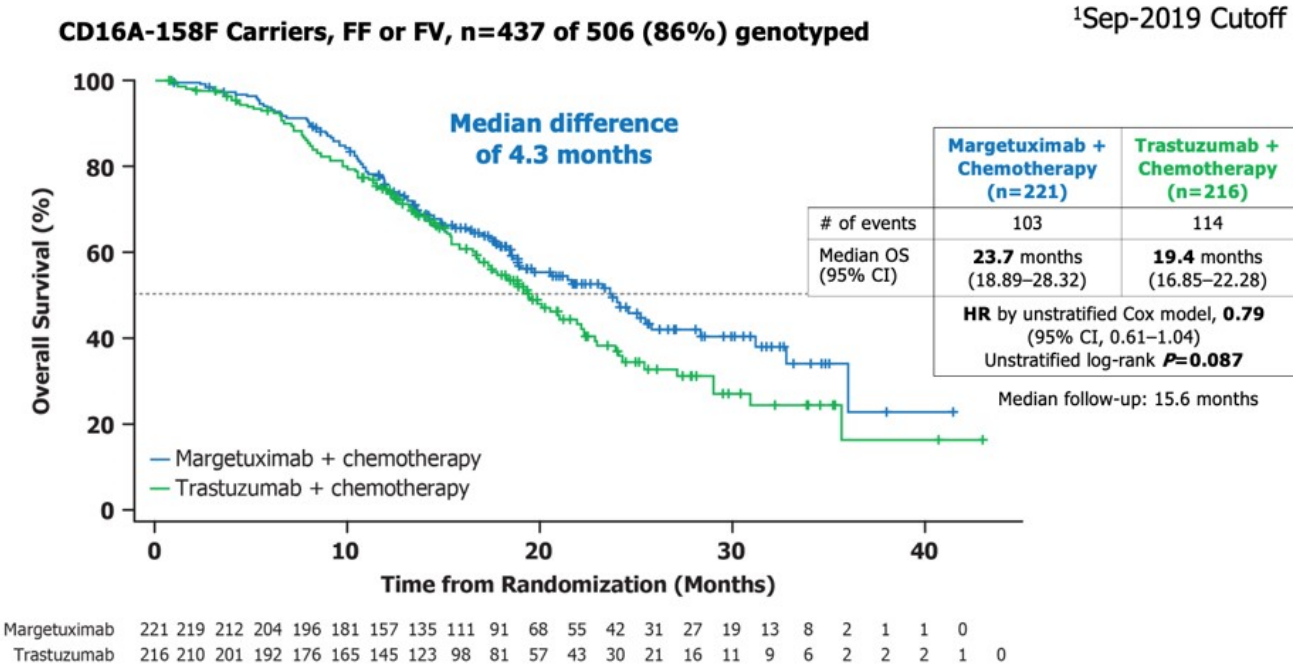
Prior Therapy
66-67% ≤ 2 lines
100% Trastuzumab
100% Pertuzumab
91-92% TDM1

	Margetuximab + Chemotherapy	Trastuzumab + Chemotherapy	
Primary mPFS Central Blinded	5.8 mo	4.9 mo	HR 0.76 (CI 0.59-0.98; p = 0.033)
ORR	25%	14%	p = 0.0006
1st Interim mOS	18.9 mo	17.2 mo	HR 0.95 (CI 0.69-1.31; p=0.75)
2nd Interim mOS	21.6 mo	19.8 mo	HR 0.89 (CI 0.69-1.13; p=0.33)
mOS in CD16A F allele carriers	23.7 mo	19.4 mo	HR 0.79 (CI 0.61-1.04; p=0.087)

Northwestern Medicine

Rugo HR, et al, SABCS 2019

SOPHIA: Pre-Specified Exploratory OS in CD16A-185 F Carriers



Northwestern Medicine®

Rugo H, et al. ASCO 2019; Rugo H, et al. SABCS 2019

Trastuzumab Biosimilars

- **Trastuzumab-dkst***
- **Trastuzumab-anns***
- **Trastuzumab-dttb***
- **Trastuzumab-pkrb***
- **Trastuzumab-qyyp***
- BCD-022
- DMB-3111

*FDA/EC approval

Northwestern Medicine®

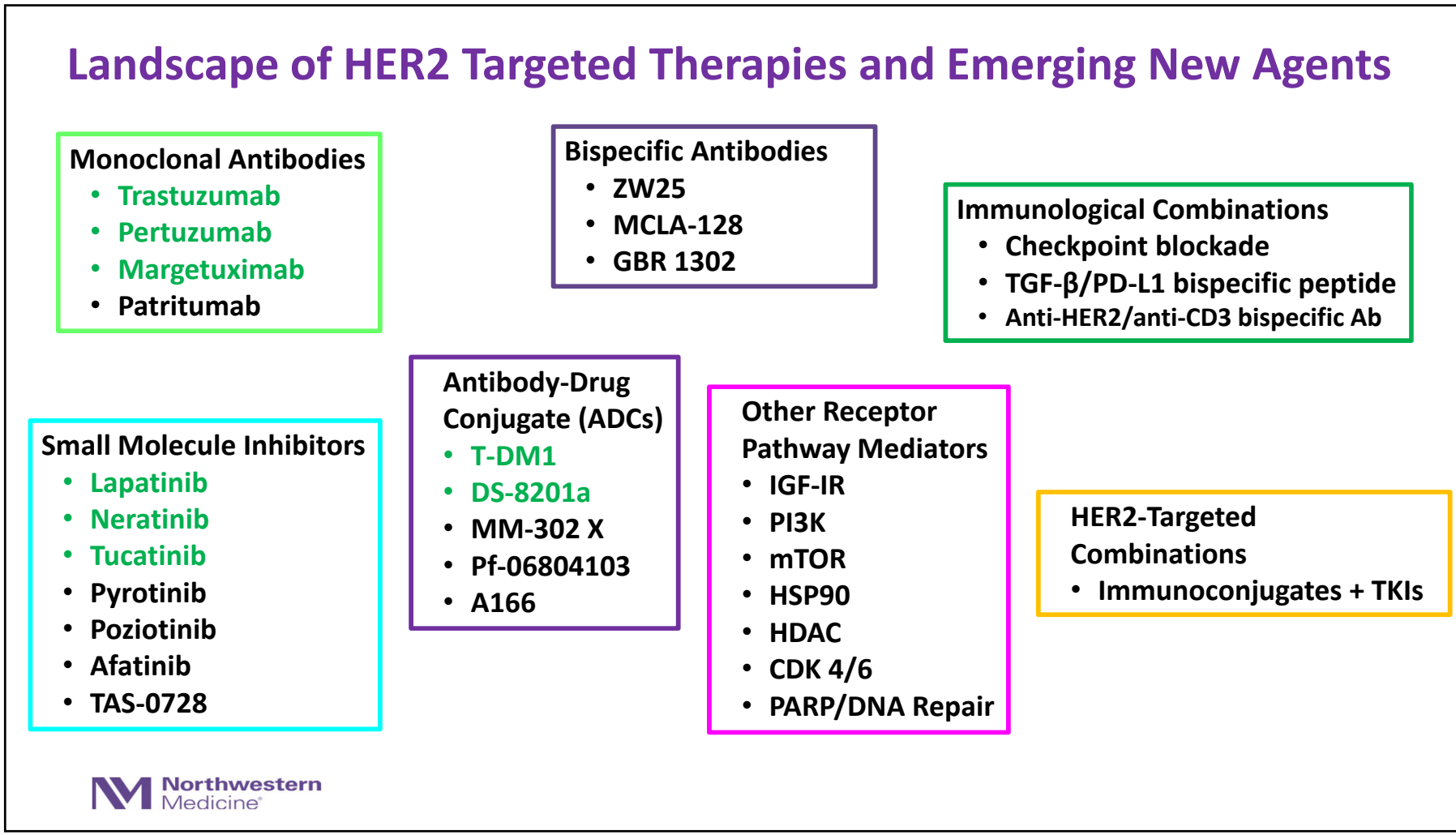
Barbier L, et al. Br J Cancer 2019; 121: 199-210.

pertuzumab, trastuzumab, and hyaluronidase-zzxf

- Pertuzumab and Trastuzumab Subcutaneous Fixed Dose Combination in HER2+BC
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) state that pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use (PHESGO) may be substituted anywhere that IV pertuzumab + trastuzumab are given as part of systemic therapy for HER2+ breast cancer.
- Clinical trials established similar pCR in neoadjuvant setting, shorter infusion times and greater patient preference

Northwestern Medicine®

Landscape of HER2 Targeted Therapies and Emerging New Agents



mTNBC

- **What is the current role for I/Oin mTNBC?**
  - Atezolizumab + Nab-paclitaxel; IMpassion130 (ESMO 2020)
  - Atezolizumab + paclitaxel; IMpassion131 (ES MO 2020)
  - Pembrolizumab + chemotherapy; KEYNOTE-355 (ASCO 2020 and SABCS 2020)

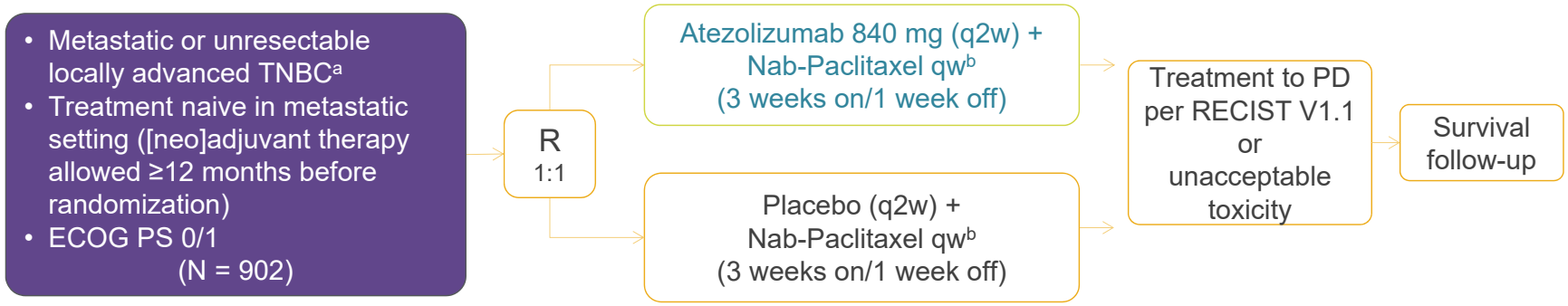
- **Role of the antibody drug conjugates (ADC) in later line mTNBC**
  - Sacituzmab Govitecan; ASCENT (ESMO 2020 and SABCS 2020)

- **Is there a role for AKT inhibition in mTNBC?**
  - Capivasertib; PAKT Phase II (SABCS 2020)
  - Ipatasertib: LOTUS Phase II (ESMO Breast 2020)
  - Ipatasertib; IPATunity 130 Cohort A Phase III (SABCS 2020)

Northwestern Medicine®

IMpassion130 (WO29522): Phase III Atezolizumab + Nab-Pac vs Placebo + Nab-Pac for 1L Metastatic TNBC

Study Design



Co-primary endpoints: PFS per investigator assessment (RECIST v1.1) and OS in ITT and PD-L1 populations

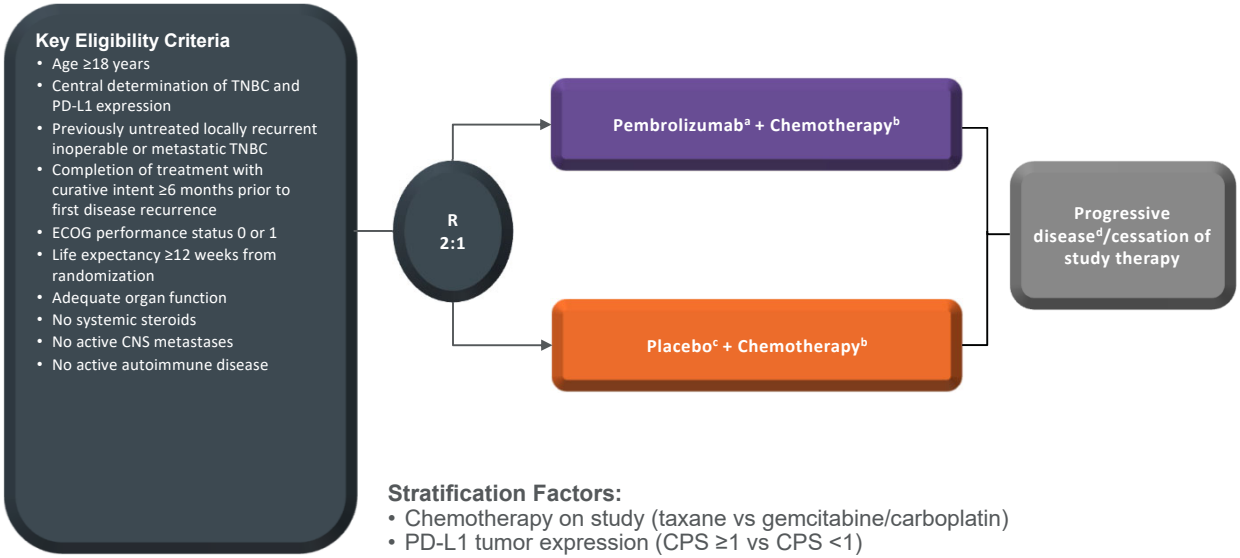
Secondary endpoints: ORR[c] per investigator assessment, DOR[c], and HRQOL in ITT and PD-L1 populations; PK, safety

Stratification factors: presence of liver metastases, prior taxane treatment, tumor PD-L1 status on IC (IC1/2/3, PD-L1 positive [≥ 1%]) vs negative (IC0 negative [< 1%])

HRQOL, health-related quality of life; IC, immune cells; imRECIST, immune Response Evaluation Criteria in Solid Tumors; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer. [a] Locally evaluated and documented per ASCO-CAP. [b] ≥ 6 cycles. [c] Unconfirmed response in patients with measurable disease at baseline. Emens LA, et al. ASCO 2016. (abstr TPS1104); Schmid P, et al. *N Eng J Med* 2018.

Northwestern Medicine®

KEYNOTE-355 Study Design (NCT02819518)



Stratification Factors:
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

[a]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days

[c]Normal saline
[d]Treatment may be continued until confirmation of progressive disease

CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed death ligand 1; R=randomized; TNBC=triple-negative breast cancer

Northwestern Medicine®

KEYNOTE355 vs IMPASSION130

KEYNOTE355 chemo options: paclitaxel, nab-paclitaxel, carboplatin/gemcitabine
IMPASSION120 chemo: nab-paclitaxel

		PFS (M)	PFS (M)		
		Chemo + IO	Chemo	HR	P
KEYNOTE 355	ITT	7.5	5.6	0.82	NS
	CPS $\geq$ 10 (38%)	9.7	5.6	0.65	0.0012
	CPS < 10	5.8	5.7	0.94	
IMPASSION 130	ITT	7.2	5.5	0.80	NS
	PDL1+ (41%)	7.5	5.0	0.62	< 0.01

Northwestern Medicine

ASCO 2020 Virtual Meeting. Abstract 1000.

PD-1/PD-L1 Summary

- Atezolizumab or Pembrolizumab with chemotherapy improved PFS in PD-L1+ 1L metastatic TNBC
  - IMpassion131 negative with paclitaxel
  - OS meaningfully improved in exploratory analysis with atezolizumab; not mature for pembrolizumab
  - Potential emergence of a "tail" on survival curve
- Safety consistent with class

PD-L1 Testing		
	Atezolizumab	**Pembrolizumab**
PD-L1 Ab	**SP-142**	**22C3**
Cells tested for protein expression	**Immune Cells**	**Tumor cells, lymphocytes and macrophages**
Positive	**≥1%**	**CPS ≥10**
CPS= combined positive score= PD-L1 staining cells/total number*100		

Northwestern Medicine®

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Invasive Breast Cancer

SYSTEMIC THERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE[a,b,c]

HER2-Negative

Preferred Regimens	Other Recommended Regimens[f]	Useful in Certain Circumstances[f]
• Anthracyclines ▸ Doxorubicin ▸ Liposomal doxorubicin • Taxanes ▸ Paclitaxel • Anti-metabolites ▸ Capecitabine ▸ Gemcitabine • Microtubule inhibitors ▸ Vinorelbine ▸ Eribulin • For germline *BRCA1/2* mutations[d] see additional targeted therapy options (BINV-R)[e] • Platinum (for TNBC and germline *BRCA1/2* mutation)[d] ▸ Carboplatin ▸ Cisplatin • For PD-L1–positive TNBC see additional targeted therapy options (BINV-R)[e]	• Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicin • Ixabepilone • Sacituzumab govitecan-hziy (for TNBC)[g]	• AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/ methotrexate/fluorouracil) • Docetaxel/capecitabine • GT (gemcitabine/paclitaxel) • Gemcitabine/carboplatin • Paclitaxel/bevacizumab[h] • Carboplatin + paclitaxel or albumin-bound paclitaxel

[a] Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m^2.
[b] Consider scalp cooling to reduce incidence of chemotherapy-induced alopecia for patients receiving chemotherapy. Results may be less effective with anthracycline-containing regimens.
[c] For treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.
[d] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy.
[e] See Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-R).
[f] Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis.

HER2-Positive Disease, see BINV-Q (2 of 7)

[g] For adult patients with metastatic TNBC who received at least two prior therapies for metastatic disease.
[h] Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Invasive Breast Cancer

ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
Any[a]	*BRCA1* mutation *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1 Category 1	Preferred
HR-positive/ HER2-negative[b]	*PIK3CA* activating mutation	PCR (blood or tissue block if blood negative), molecular panel testing	Alpelisib + fulvestrant[d]	Category 1	Preferred second-line therapy
HR-negative/ HER2-negative[c]	PD-L1 expression • Threshold for positivity: ≥1% on tumor-infiltrating immune cells	IHC	Atezolizumab + albumin-bound paclitaxel[e]	Category 1	Preferred first-line therapy[h]
	PD-L1 expression • Threshold for positivity combined positive score ≥10		Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[e]	Category 1	
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[f] Entrectinib[f]	Category 2A Category 2A	Useful in certain circumstances[e]
Any	MSI-H/dMMR TMB-H (≥10 muts/mb)	IHC, PCR (tissue block) NGS	Pembrolizumab[e,g]	Category 2A	Useful in certain circumstances[f]

[a] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. While olaparib and talazoparib are FDA indicated in HER2-negative disease, the panel supports use in any breast cancer subtype associated with a germline *BRCA1* or *BRCA2* mutation.

[b] For HR-positive/HER2-negative breast cancer, assess for *PIK3CA* mutations with tumor or liquid biopsy to identify candidates for alpelisib plus fulvestrant. *PIK3CA* mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended.

[c] For TNBC, assess PD-L1 expression biomarker status on tumor-infiltrating immune cells to identify candidates for atezolizumab plus albumin-bound paclitaxel.

[d] The safety of alpelisib in patients with Type 1 or uncontrolled Type 2 diabetes has not been established.

[e] See NCCN Guidelines for Management of Immuotherapy-Related Toxicities.

[f] Larotrectinib and entrectinib are indicated for the treatment of solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation and have no satisfactory alternative treatments or that have progressed following treatment.

[g] Pembrolizumab is indicated for the treatment of patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, or TMB-H tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.

[h] While available data are in the first-line setting, these regimens can be used for second and subsequent lines of therapy if PD-1/PD-L1 inhibitor therapy has not been previously used. If there is disease progression while on a PD-1/PD-L1 inhibitor, there are no data to support an additional line of therapy with another PD-1/PD-L1 inhibitor.

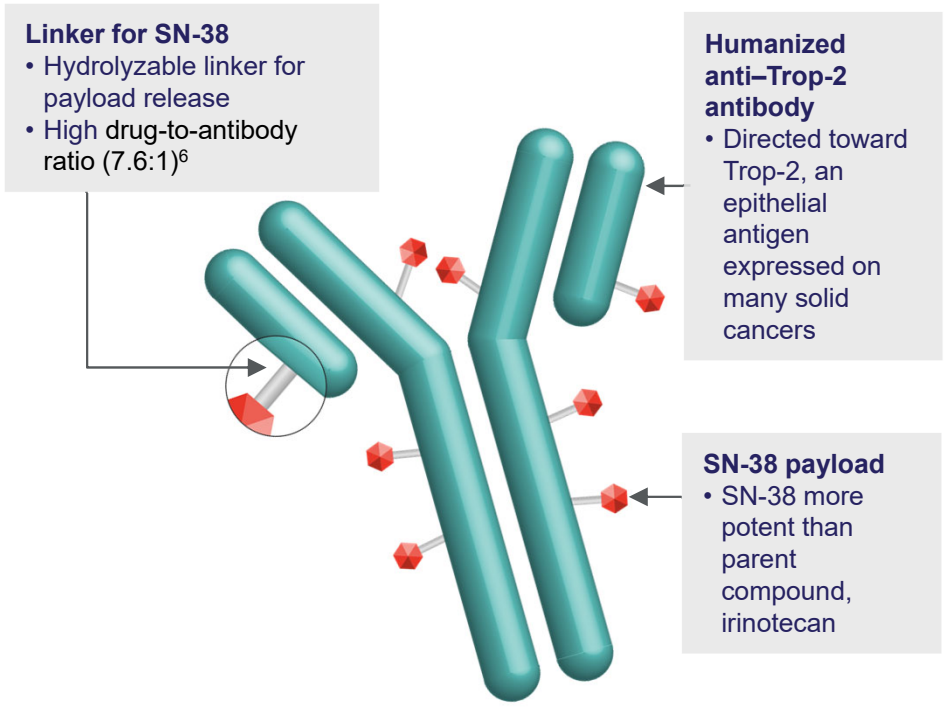
Summary of Immune Checkpoint Inhibition in TNBC circa 2020/2021

- **Two randomized phase III trials confirm benefit of PFS, Atezolizumab and Pembrolizumab approved by FDA**
  - OS data with Atezolizumab shows 7.5mo improvement
  - Await OS data with Pembrolizumab
- **Important to use companion diagnostic relevant to therapeutic agent (i.e. SP-142 – Atezolizumab; 22C3 CPS score ≥ 10 Pembrolizumab)**
  - Cut offs and thresholds still a work in progress
  - Likely better biomarker of benefit than PD-L1 – research in progress
- **Best chemotherapy back bone**
  - If using Atezolizumab, data is only with nab-paclitaxel
  - If using Pembrolizumab, data suggest can use either taxane or carbo/gem
- **Be aware of unique side effects, follow guidelines for IO toxicity**

Northwestern Medicine®

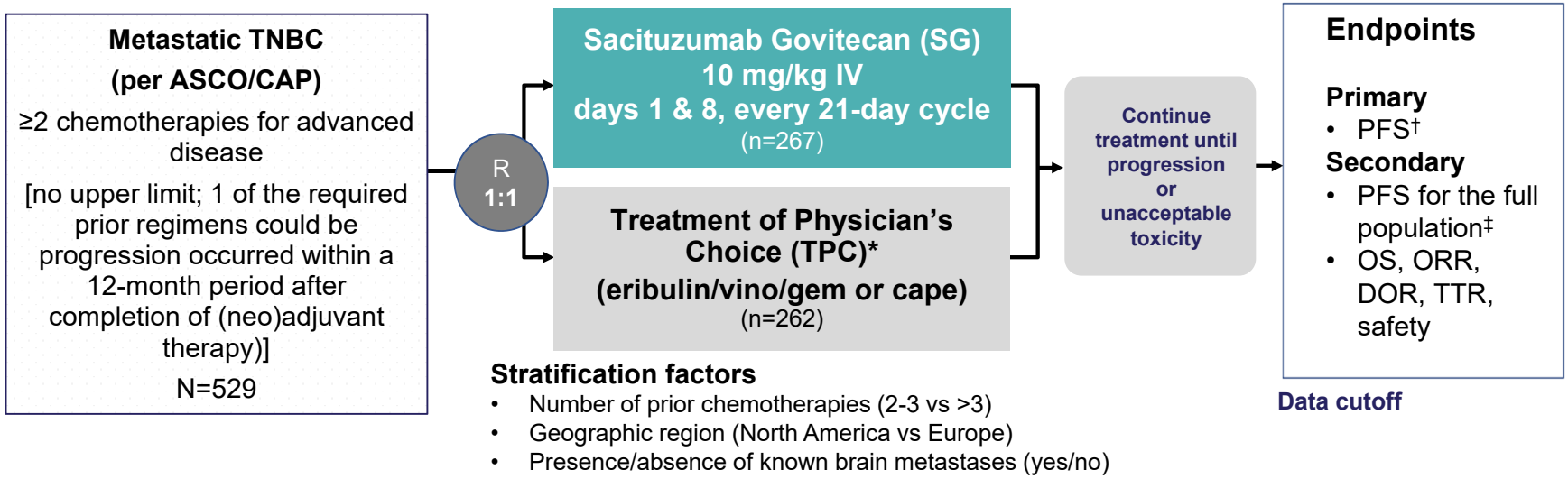
Sacituzumab Govitecan (SG)
First-in-Class Trop-2–Directed ADC

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- SG is distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect



Northwestern Medicine®

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in R/R mTNBC



ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation.

Northwestern Medicine

Bardia A et al. ESMO 2020

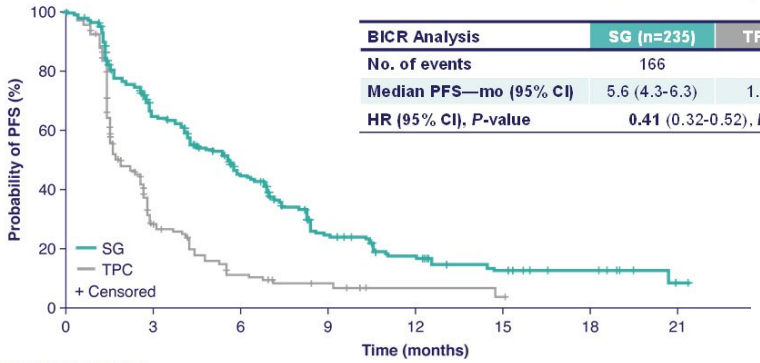
Demographics and Patient Characteristics

	SG (n=235)	TPC (n=233)
Female—no. (%)	233 (99)	233 (100)
Median age—yr (range)	54 (29-82)	53 (27-81)
Race or ethnic group—no. (%)		
White	188 (80)	181 (78)
Black	28 (12)	28 (12)
Asian	9 (4)	9 (4)
Other or not specified	10 (4)	15 (6)
ECOG PS—no. (%)		
0	108 (46)	98 (42)
1	127 (54)	135 (58)
BRCA 1/2 mutational status—no. (%)		
Positive	16 (7)	18 (8)
Negative	133 (57)	125 (54)
Unknown	86 (37)	90 (39)
TNBC at initial diagnosis*		
Yes	165 (70)	157 (67)
No	70 (30)	76 (33)

	SG (n=235)	TPC (n=233)
Previous anticancer regimens† —median no. (range)	4 (2-17)	4 (2-14)
Most common previous chemotherapy—no. (%)		
Taxane‡	235 (100)	233 (100)
Anthracycline§	191 (81)	193 (83)
Cyclophosphamide	192 (82)	192 (82)
Carboplatin	147 (63)	160 (69)
Capecitabine	147 (63)	159 (68)
Previous PARP inhibitor—no. (%)	17 (7)	18 (8)
Previous use of checkpoint inhibitors—no. (%)	67 (29)	60 (26)
Most common sites of disease‖—no. (%)		
Lung only	108 (46)	97 (42)
Liver	98 (42)	101 (43)
Bone	48 (20)	55 (24)

Northwestern Medicine®

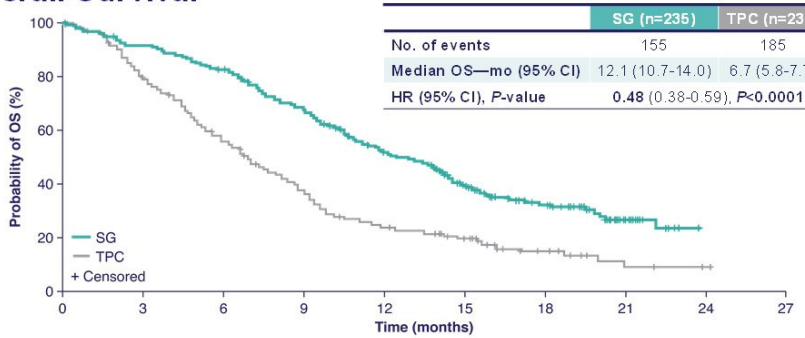
Progression-Free Survival (BICR Analysis)



BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

4 months benefit median PFS

Overall Survival



	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

± 5.5 months benefit median OS

Northwestern Medicine®

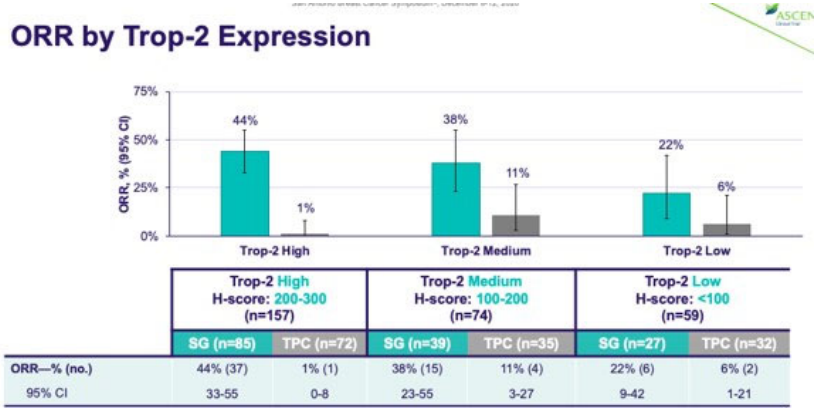
TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

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

- Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%)
  - G-CSF usage was 49% in the SG arm vs 23% in the TPC arm
  - Dose reductions due to TRAEs were similar (22% SG vs 26% TPC)
- No severe cardiovascular toxicity, no grade >2 neuropathy or grade >3 interstitial lung disease with SG
- No treatment-related deaths with SG; 1 treatment-related death (neutropenic sepsis) with TPC
- AEs leading to treatment discontinuation were low for SG and TPC: 4.7% and 5.4%
- Patients received a median of 7 treatment cycles of SG, with a median treatment duration of 4.4 months (range, 0.03-22.9)

Northwestern Medicine®

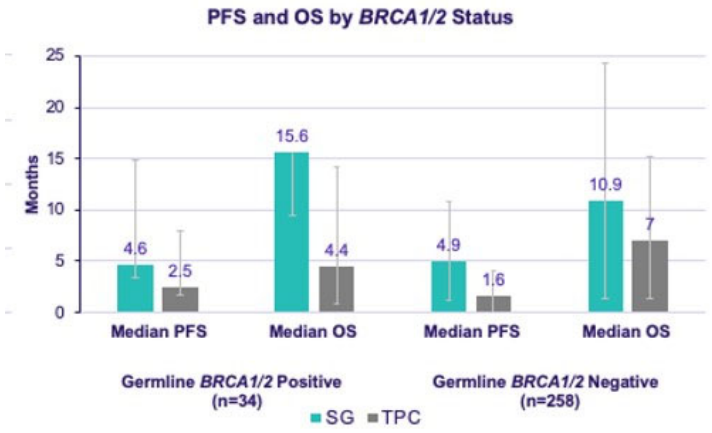
Exploratory Biomarker Analysis



	Trop-2 High H-score: 200-300 (n=157)		Trop-2 Medium H-score: 100-200 (n=74)		Trop-2 Low H-score: <100 (n=59)	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
ORR—% (no.)	44% (37)	1% (1)	38% (15)	11% (4)	22% (6)	6% (2)
95% CI	33-55	0-8	23-55	3-27	9-42	1-21

Higher efficacy outcomes were observed in patients treated with SG who had a medium/high Trop-2 H-score (vs low Trop-2 H-score) versus those treated with TPC

Conclusion:
Benefit *independent* of level of Trop-2 Expression or BRCA status



Northwestern Medicine

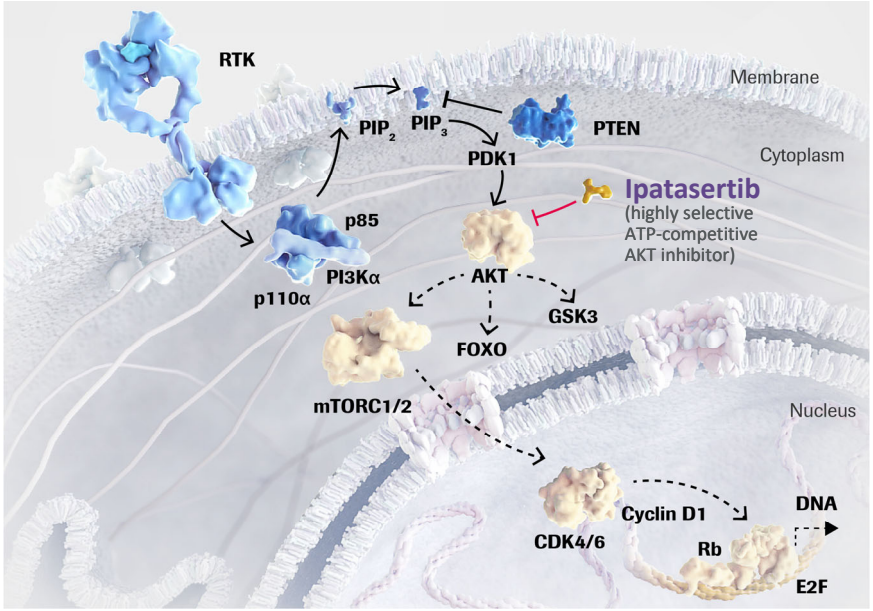
Hurvitz S et al. SABCS 2020

AKT pathway in TNBC

AKT can be activated by:

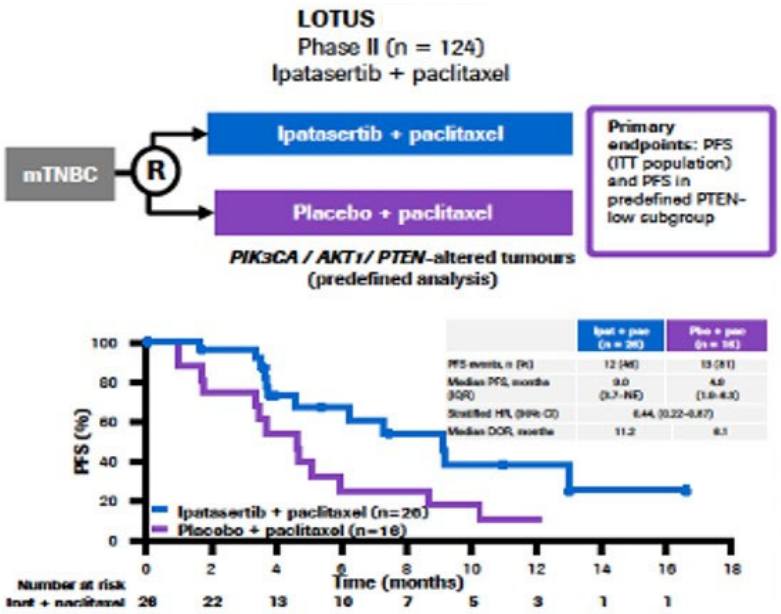
- Loss of function of negative regulators (PTEN, INPP4B, PHLPP, PP2A)
- Gain of function of positive regulators (PI3K, AKT, RTKs [eg HER2])
- Therapy-induced survival response (chemotherapy, endocrine therapy)
- As ~35% of TNBCs harbor *PIK3CA/AKT1/PTEN* alterations, AKT inhibition is an appealing strategy

The AKT pathway

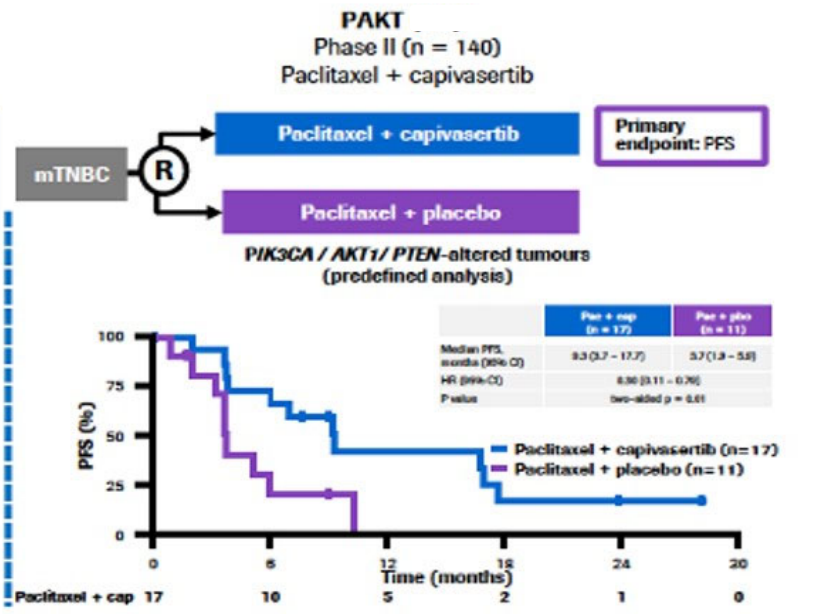


Northwestern Medicine®

AKT inhibitors in *PIK3CA/AKT1/PTEN*-altered TNBC



Kim SB et al. Lancet Oncology 2017

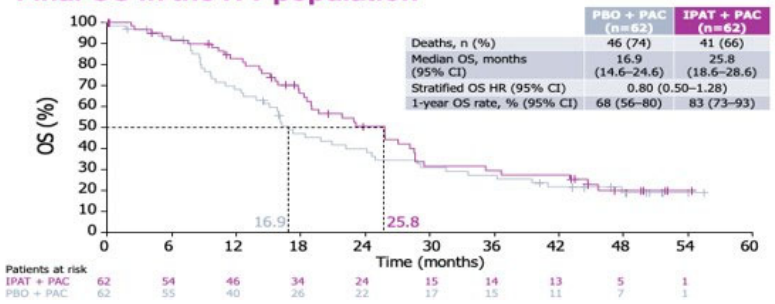


Schmid P et al. JCO 2020

Northwestern Medicine

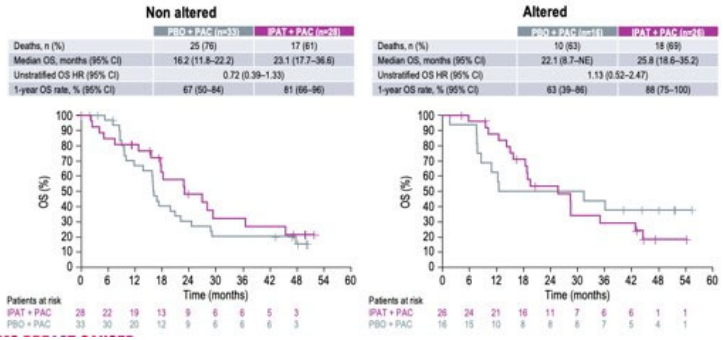
LOTUS ESMO Breast 2020 Dent R et. al

Final OS in the ITT population



	PBO + PAC (n=62)	IPAT + PAC (n=62)
Deaths, n (%)	46 (74)	41 (66)
Median OS, months (95% CI)	16.9 (14.6–24.6)	25.8 (18.6–28.6)
Stratified OS HR (95% CI)	0.80 (0.50–1.28)	
1-year OS rate, % (95% CI)	68 (56–80)	83 (73–93)

OS according to *PIK3CA/AKT1/PTEN* status by NGS



Overview of Overall Survival

With a median follow up of 40.0 months, median OS was longer in the capivasertib arm (19.1 vs 13.5 months, stratified HR 0.70, 95% CI 0.47-1.05, two-sided p=0.085) (Fig. 2).

	Primary Analysis		Updated Analysis	
	PAC + CAPI (N=70)	PAC + PBO (N=70)	PAC + CAPI (N=70)	PAC + PBO (N=70)
Data cut-off	January 2018		July 2020	
Median OS months (95%CI)	19.1 (10.9 – 20.9)	12.6 (10.4 - 16.9)	19.1 (12.6 – 21.4)	13.5 (10.4 – 18.5)
HR (95% CI), *p(2-sided)*	0.61 (0.37 – 0.99), *p=0.04*		0.70 (0.47 – 1.05), *p=0.085*	
Deaths, n (%)	33 (47)	41 (59)	51 (73)	54 (77)

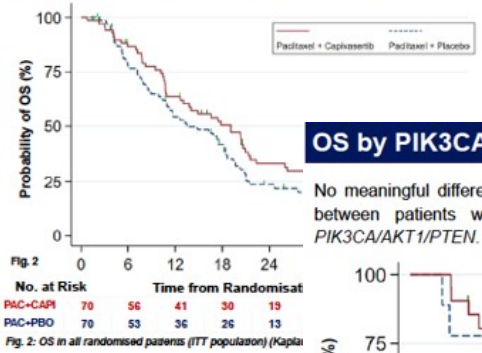
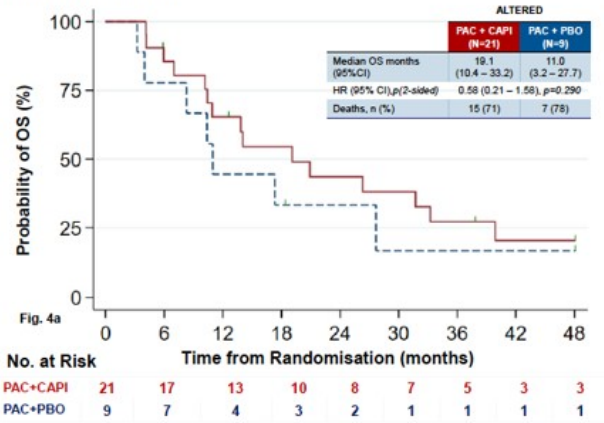


Fig. 2: OS in all randomised patients (ITT population) (Kapla

PAKT SABCS 2020 Schmid P et al.

OS by PIK3CA/AKT1/PTEN status by NGS

No meaningful differences were seen in terms of benefit with capivasertib between patients with (Fig. 4a) or without alterations (Fig. 4b) of *PIK3CA/AKT1/PTEN*.



Northwestern Medicine®

IPATunity130 Cohort A TNBC – Phase III
Double-blind placebo-controlled randomized trial

- Measurable aTNBC
- *PIK3CA/AKT1/PTEN* alteration[a]
- No prior chemotherapy for aTNBC (≥12 months since last [neo]adjuvant chemotherapy)
- Candidate for taxane therapy
- ECOG performance status 0/1

R 2:1

PAC 80 mg/m^2 days 1, 8 & 15 + IPAT 400 mg qd days 1–21 q28d

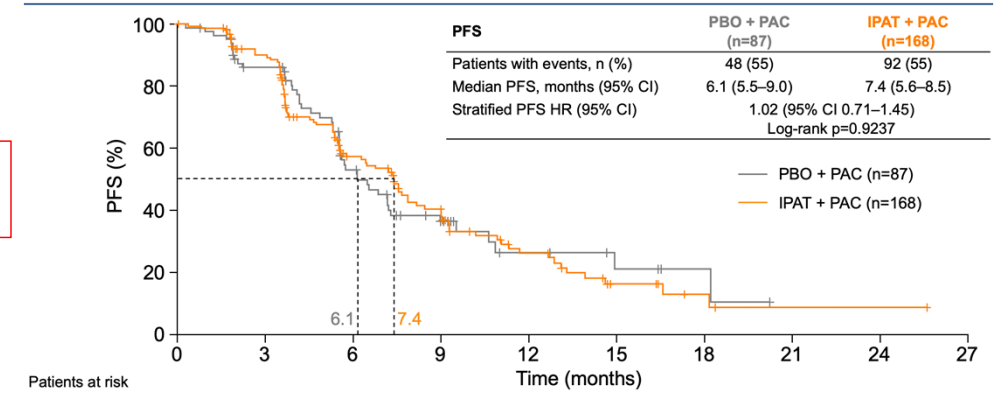
PAC 80 mg/m^2 days 1, 8, & 15 + PBO days 1–21 q28d

Treatment until disease progression, intolerable toxicity,[b] or elective withdrawal

Crossover from PBO to IPAT is not permitted

255 patients enrolled between Feb 6, 2018, and Apr 8, 2020
Primary endpoint: Investigator-assessed PFS
Data cut-off: May 7, 2020 (median follow-up: 8.3 months)

Ideally would have had biomarker negative group



Dent R SABCS 2020

Northwestern Medicine®

Conclusions

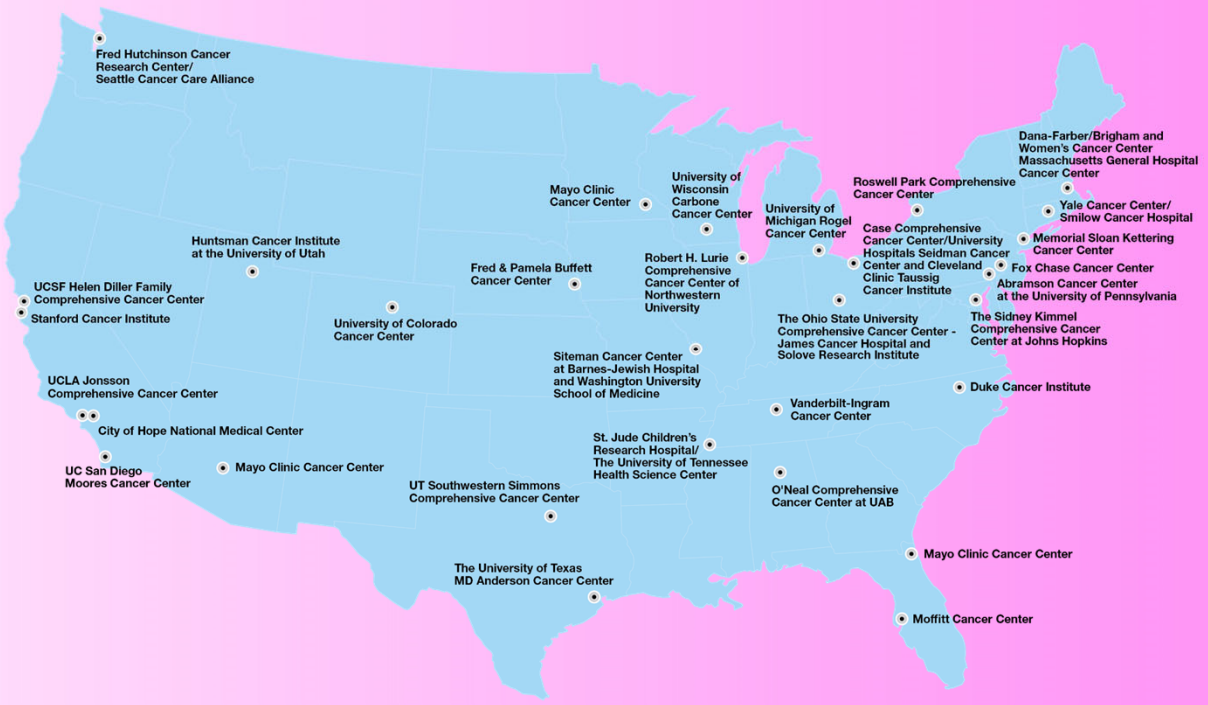
- Much progress in all silos of breast cancer
- Sequencing of available agents will be dependent on pt characteristics, disease manifestations and prior rx
- Ongoing drug development with combinations including targeted agents and I/O

Northwestern Medicine®

National Comprehensive Cancer Network®

NCCN Member Institutions

- **Who We Are**
  An alliance of leading cancer centers devoted to patient care, research, and education
- **Our Mission**
  To improve and facilitate quality, effective, efficient, and accessible cancer care so patients can live better lives
- **Our Vision**
  To define and advance high-quality, high-value, patient-centered cancer care globally



NCCN.org – For Clinicians | **NCCN.org/patients** – For Patients