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UNC CANCER CARE

Breast Cancer Management: Updates for 2021

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In the United States, breast cancer is the **most commonly diagnosed female cancer**, and the **second most common** cause of cancer death in women.

Estimated new cases

Females

Breast	281,550	30%
Lung & bronchus	116,660	13%
Colon & rectum	69,980	8%
Uterine corpus	66,570	7%
Melanoma of the skin	43,850	5%
Non-Hodgkin lymphoma	35,930	4%
Thyroid	32,130	3%
Pancreas	28,480	3%
Kidney & renal pelvis	27,300	3%
Leukemia	25,560	3%
All Sites	**927,910**	**100%**

Estimated deaths

Females

Lung & bronchus	62,470	22%
Breast	43,600	15%
Colon & rectum	24,460	8%
Pancreas	22,950	8%
Ovary	22,950	5%
Uterine corpus	12,940	4%
Liver & intrahepatic bile duct	9,930	3%
Leukemia	9,760	3%
Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	8,100	3%
All Sites	**289,150**	**100%**

Cancer Statistics, 2021. *CA Cancer J Clin.* 2021: 71: 7- 33.

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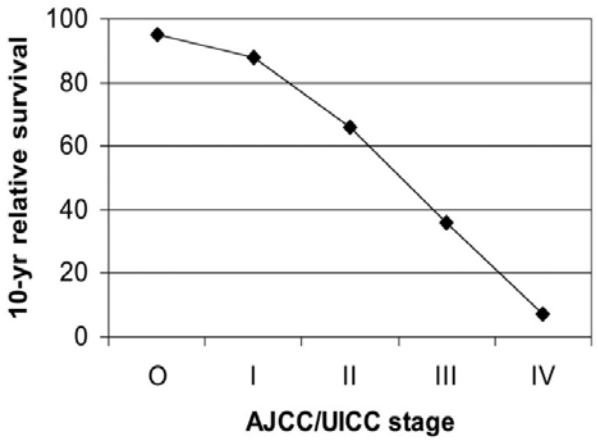

Singletary CA cancer J clin 2006

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5-yr BCSS According to Subtype

	HR+/HER2-	HR+/HER2+	HER2+/HR-	TNBC
Stage T2N0	96%	94%	92%	88%

	HR+/HER2-	HR+/HER2+	HER2+/HR-	TNBC
Stage IV	47%	39%	24%	17%

Chavez-MacGregor, et al. *Oncologist* 2017;22:1292-1300

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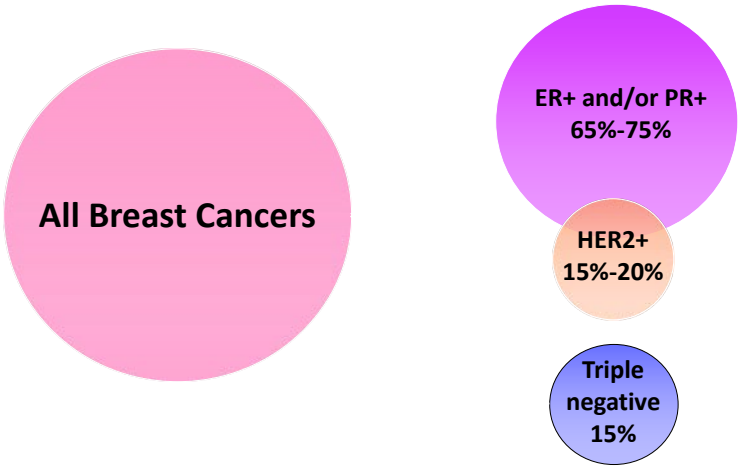
Clinical Breast Cancer Subsets



Burstein, Goldhirsch. St Gallen 2007.

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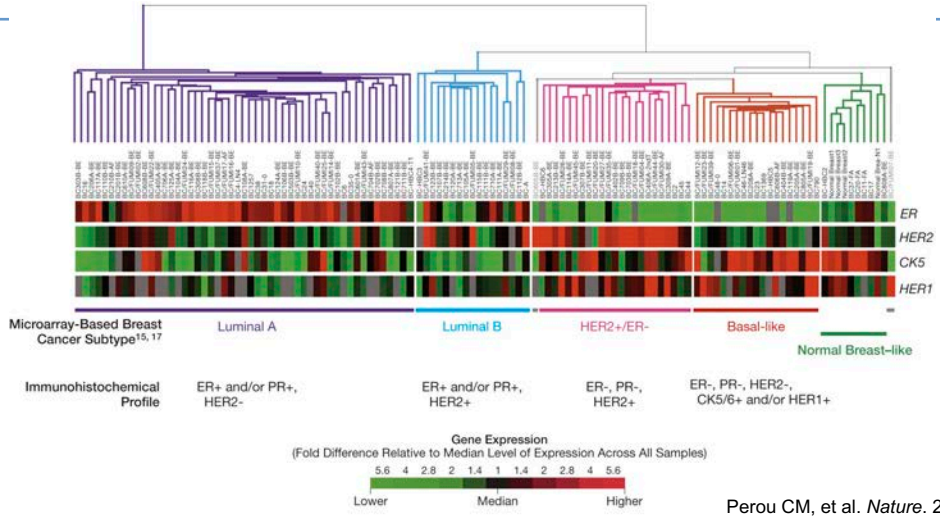
Breast Cancer is Not just one disease



Perou CM, et al. *Nature*. 2000 Aug 17;406(6797):747-52.
Carey LA, et al. *JAMA*. 2006 Jun 7;295(21):2492-502.

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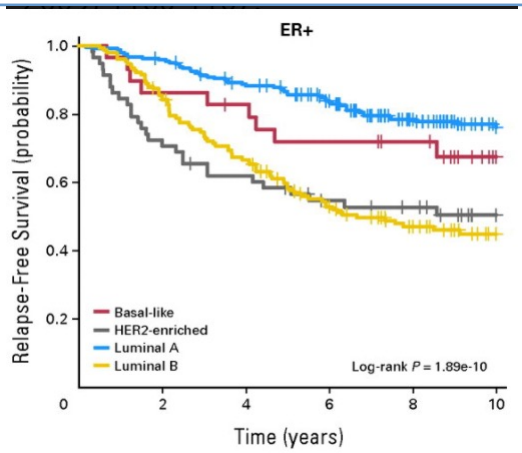
Outcomes vary by tumor subtype



Parker et al, JCO 2009

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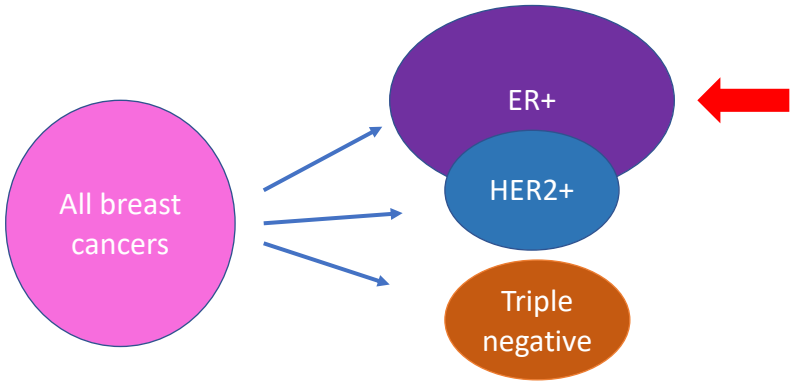
Breast Cancer Clinical Subsets



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Historical Approach
2000 NIH Consensus Conference

- "Because adjuvant polychemotherapy **improves survival**, it should be recommended to the **majority of women** with localized breast cancer **regardless of nodal, menopausal, or hormone receptor status**."
- Bottom line: Tumor >1 cm, give chemo

Adjuvant Therapy for Breast Cancer. NIH Consensus Statement 2000 November 1-3; 17(4): 1-23.

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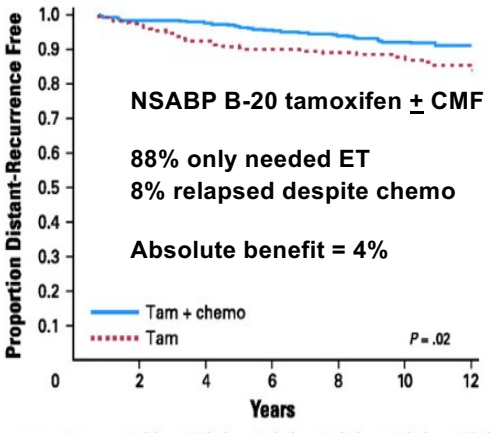
Overtreatment of ER+, node-negative disease



Early 2000s:

Most ER+ node-negative breast cancer patients received chemo

Most did not benefit—but which ones did?

Paik et al. J Clin Oncol 2006

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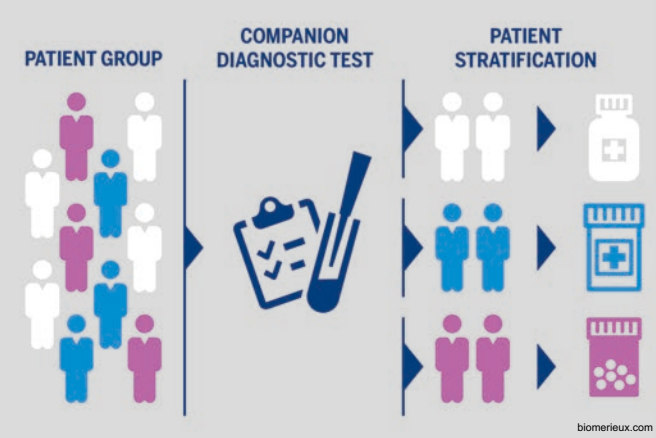
Current Era

Moving away from an era of overtreatment towards a more personalized approach



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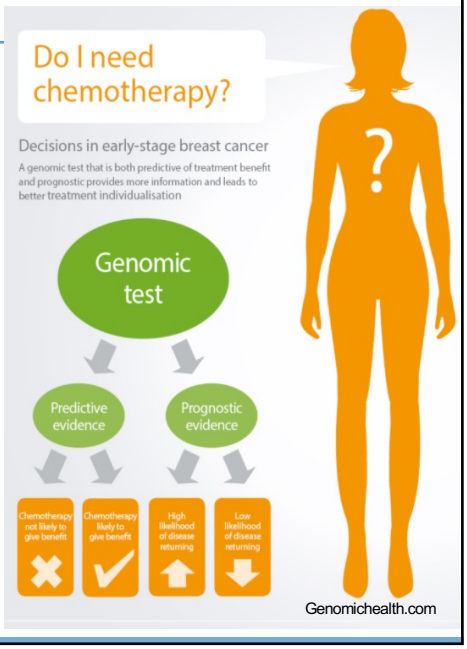
Which patients with ER+ breast cancer should receive chemotherapy?

- **Tumor is sensitive to chemotherapy, and**
- **There is no competing co-morbidity, and**
- **The realistic benefits outweigh the risks of chemotherapy.**

Who exactly are these patients?



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Predictive / Prognostic Genomic Assays

Assay	RNA-based assays
Oncotype Dx® Recurrence Score	From 250 known genes modeled for relapse in mixed pop'n (esp NSABP B-20 HR+ N0 Rx tamoxifen) to derive 16 most relevant genes
Prosigna® ROR-PT	50 intrinsic subtype genes + proliferation genes + tumor size modeled for relapse in N0 untreated population
Mammaprint®	Select 70 genes from case/control study of relapse within 5y (all N0, mostly HR+)
EndoPredict®	Select 8 genes + T + N modeled for distant mets in HR+ HER2- Rx tamoxifen.
BCI®	Select 2-gene ratio (HOXB13:IL17BR), tailored to include Molecular Grade Index for distant mets

Paik S, NEJM 2004; Parker JS, JCO 2007; Van't Veer, Nature 2000; Filipits M, CCR 2011; Ma XJ, Cancer Cell 2004

★Covered by Medicare/commercial insurance

★ER+/HER-2 neg tumors >0.5cm, node negative or 1-3 nodes

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TAILORx

ORIGINAL ARTICLE

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

- **The 21-gene recurrence score predicts chemotherapy benefit if it is high and a low risk of recurrence in the absence of chemotherapy if it is low**
- **But what about patients who have a midrange score?**

Sparano JA, NEJM 2018

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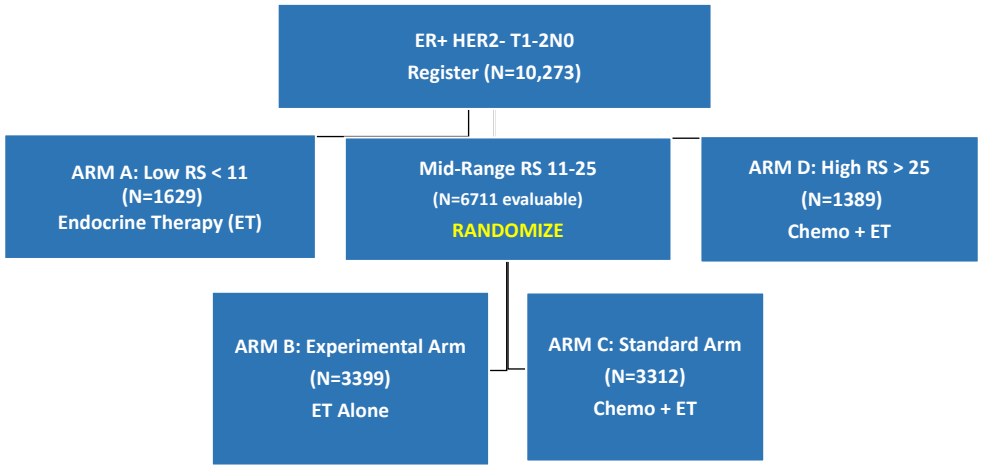

Sparano JA, NEJM 2018

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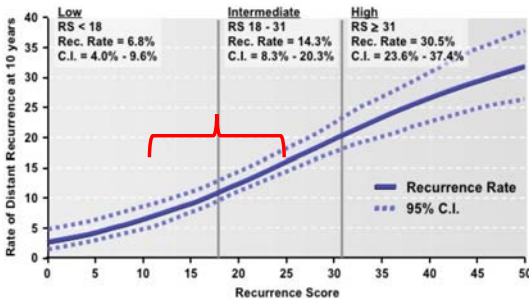
TAILORx

TailoRx randomized population



Non-inferiority, 5-yr IDFS threshold HR 1.32

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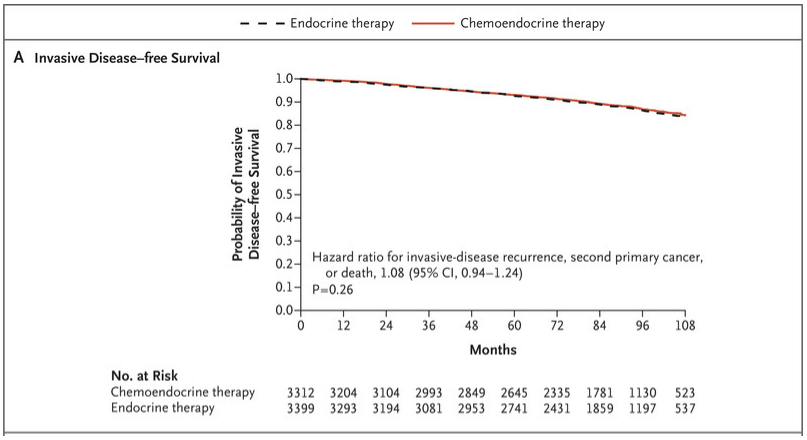

Can spare many patients the toxicities of chemotherapy

HR for IDFS 1.08 (95% CI 0.94 – 1.24)

Endocrine therapy is non-inferior to chemotherapy in patients with ER+, node-negative breast cancer with **21-gene recurrence score of 11-25**

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TAILORx – Women age ≤50

In women 50 years of age or younger, chemotherapy was associated with a lower rate of distant recurrence than endocrine therapy if the recurrence score was:

- 16 to 20 (1.6% difference at 9 years)
- 21 to 25 (6.5% difference at 9 years)

Still consider chemotherapy for these patients

Rates of overall survival were similar (at 9 years of follow up).

See Table 3 in manuscript for Estimated Survival Rates According to Recurrence Score and Assigned Treatment

Sparano JA, NEJM 2018

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TAILORx

Supplementary Table 1. Characteristics of patients by assigned treatment in intention-to-treat population

Tumor size (cm)				
Median (interquartile	1.5 (1.2, 2.0)	1.5 (1.2, 2.0)	1.5 (1.2, 2.0)	1.7 (1.3, 2.3)
Mean – cm (+/- SD)	1.74 (+/-0.76)	1.71 (+/-0.81)	1.71 (+/-0.77)	1.88 (+/-0.99)
Distribution –no./total				
</= 1.0	202 (12%)	446 (13%)	423 (13%)	188 (14%)
1.1 - 2.0	1018 (63%)	2150 (63%)	2103 (64%)	741 (53%)
2.1 – 3.0	297 (18%)	640 (19%)	625 (19%)	348 (25%)
3.1 – 4.0	83 (5%)	122 (4%)	119 (4%)	91 (7%)
>/= 4.1	19 (1%)	41 (1%)	40 (1%)	20 (1%)
Unknown	0	0	2	1

We really don't know how the 21-gene recurrence score performs for larger tumors.

Sparano JA, NEJM 2018

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Practical Applications

	Premenopausal				Postmenopausal	
Node negative	Genomic assay to guide adjuvant therapy				Genomic assay to guide adjuvant therapy	
	RS 0-16 ET alone	RS 16-20 ET +/- chemo	RS 21-25 Chemo + ET	RS ≥26 Chemo + ET	RS 0-25 ET alone	RS ≥26 Chemo + ET

*Patient comorbidities, preferences, and tumor clinicopathologic features must be considered

Sparano JA, NEJM 2018
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Take-Homes from TAILORx

The **RSClin tool** provides individualized prognosis estimates and chemotherapy benefit based on entry of patient information for the RS result, age, tumor size, and tumor grade.

Sparano JA. *Journal of Clinical Oncology* 2021.

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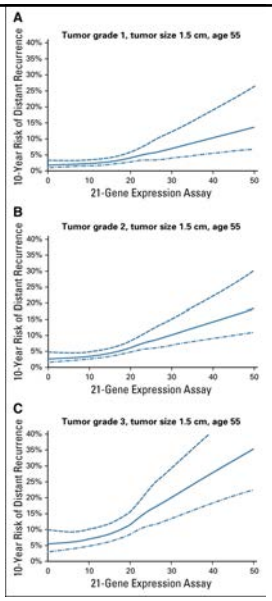
Example estimates provided by the RSClin tool for 10-year distant recurrence risk for ET alone, varying by tumor grade

55 yo woman with 1.5 cm tumor



Sparano JA. *Journal of Clinical Oncology* 2021.

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RxPONDER

RxPONDER: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer

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RxPONDER

Key Entry Criteria

- Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- breast cancer with 1*-3 LN+ without distant metastasis
- Able to receive adjuvant taxane and/or anthracycline-based chemotherapy**
- Axillary staging by SLNB or ALND

REGISTRATION

Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by
Endocrine Therapy Recommended

RANDOMIZATION

Arm 1: Chemotherapy Followed by Endocrine Therapy

Arm 2: Endocrine Therapy Alone

N = 5,000 pts

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RxPONDER

- **Primary Objective**
  - Determine the effect of chemotherapy on invasive disease-free survival (IDFS) in pts with 1-3 LN+ breast cancer and a RS ≤ 25 and assess whether the effect depends on the RS
- **Primary Hypothesis**
  - Chemotherapy benefit will increase as the RS increases from 0 to 25 in an Intent-to-Treat (ITT) analysis

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RxPONDER

Baseline variable	Endocrine Therapy (n=2,506)	Chemotherapy (n=2,509)	Overall (n=5,015)
Race			
White	64.9%	66.4%	65.7%
Black	4.8%	5.1%	5.0%
Asian	6.8%	6.1%	6.5%
Other/Unknown	23.5%	22.3%	22.9%
Hispanic			
Yes	13.0%	11.9%	12.4%
No	67.6%	68.9%	68.3%
Unknown	19.4%	19.3%	19.3%
Menopausal status			
Premenopausal	33.2%	33.2%	33.2%
Postmenopausal	66.8%	66.8%	66.8%
Recurrence Score			
RS 0-13	42.7%	42.9%	42.8%
RS 14-25	57.3%	57.1%	57.2%
Nodal Dissection			
Full ALND	62.7%	62.5%	62.6%
Sentinel nodes only	37.4%	37.5%	37.4%

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RxPONDER

Baseline variable	Endocrine Therapy (n=2,506)	Chemotherapy (n=2,509)	Overall (n=5,015)
Positive Nodes			
1 node	65.9%	65.0%	65.5%
2 nodes	24.9%	25.7%	25.3%
3 nodes	9.2%	9.2%	9.2%
Grade			
Low	24.6%	24.7%	24.7%
Intermediate	64.1%	66.1%	65.1%
High	11.3%	9.2%	10.3%
Tumor size			
T1	58.5%	57.7%	58.1%
T2/T3	41.5%	42.3%	41.9%

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Primary Analysis with Interaction Term

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	0.56	0.07	0.30 – 1.05
RS (per unit change)	1.05	<0.001	1.02 – 1.07
Menopausal status	1.00	0.97	0.82-1.24
Chemo x RS Interaction	1.02	0.30	0.98-1.06

Amongst pts with RS 0-25, RS does not predict the relative benefit of chemotherapy for IDFS

Relative benefit of chemo is not smaller with a lower RS and not greater with a higher RS

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Primary Analysis without Interaction Term:

Chemotherapy use and RS are independently prognostic for IDFS

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	0.81	0.026	0.67 – 0.96
RS (per unit change)	1.06	<0.001	1.04 – 1.07
Menopausal status	1.03	0.77	0.82-1.26

Pts who received chemotherapy less likely to have an IDFS event
Pts with a higher RS more likely to have an IDFS event

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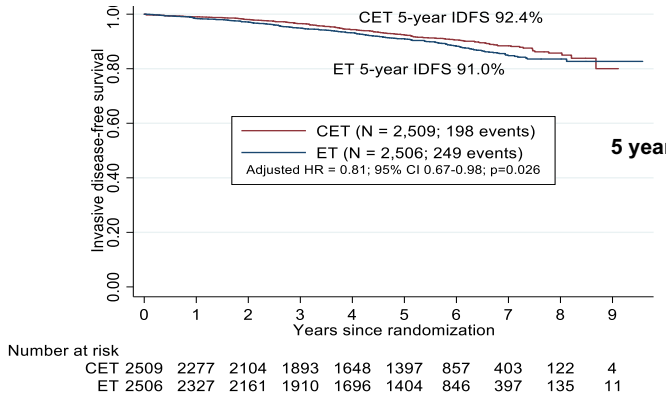
RxPONDER



5 year IDFS Absolute Difference: 1.4%

CET = Chemotherapy + Endocrine Therapy; ET = Endocrine Therapy Alone

447 observed IDFS events (54% of expected at final analysis) at a median follow-up of 5.1 years

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RxPONDER

Pre-specified Analysis by Menopausal Status

Chemotherapy benefit for IDFS is different depending on menopausal status

Term	Hazard ratio	2-sided p-value	95% CI
Chemotherapy	0.53	<0.001	0.37 – 0.76
RS (per unit change)	1.06	<0.001	1.04 – 1.08
Menopausal status	0.79	0.08	0.60-1.03
Chemo x Menopause Interaction	1.79	0.008	1.17-2.74

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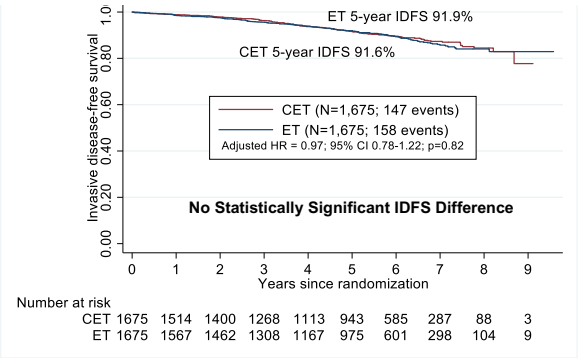
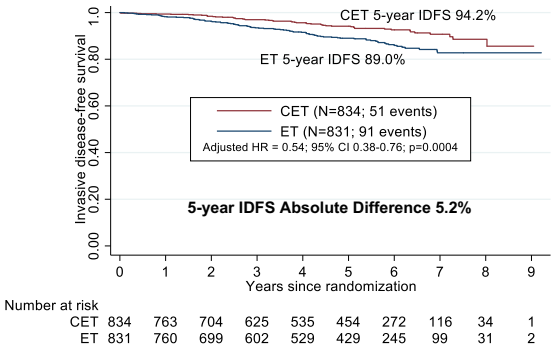
IDFS Stratified by Menopausal Status

Postmenopausal



Premenopausal



Absolute Difference in Distant Recurrence as 1st site: 0.3% (2.3% CET vs. 2.6% ET)

Absolute Difference in Distant Recurrence as 1st site: 2.9% (3.1% CET vs. 6.0% ET)

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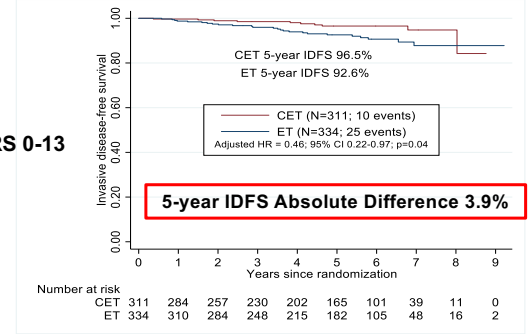
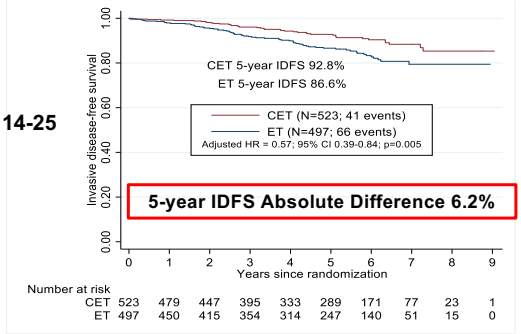
IDFS Stratified by Recurrence Score and Menopausal Status

Premenopausal

RS 0-13



RS 14-25



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RxPONDER

- At this interim analysis with 54% of anticipated IDFS events in the overall population, the 21-gene RS 0-25 was prognostic but did not show a treatment interaction with chemotherapy
  - Relative benefit of chemotherapy was similar across RS 0-25
- Postmenopausal women with RS 0-25 did not benefit from adjuvant chemotherapy in any subgroup
- Premenopausal women with RS 0-25 had benefit from the addition of chemotherapy to endocrine therapy
  - 46% decrease in IDFS events; benefit was observed across premenopausal subgroups
  - 53% decrease in deaths, leading to a 5-year OS absolute improvement of 1.3%

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Practical Applications

	Premenopausal				Postmenopausal	
Node negative	Genomic assay to guide adjuvant therapy				Genomic assay to guide adjuvant therapy	
	RS 0-16 ET alone	RS 16-20 ET +/- chemo	RS 21-25 Chemo + ET	RS ≥26 Chemo + ET	RS 0-25 ET alone	RS ≥26 Chemo + ET
Node positive (1-3 LN)	No role for genomic assays Chemo + ET (see RxPONDER for estimates of absolute benefit according to number of nodes, risk score)				Genomic assay to guide adjuvant therapy RS 0-25 ET alone	 RS ≥26 Chemo + ET
Node positive (4+ nodes)	No role for genomic assays Chemo + ET					

*Patient comorbidities, preferences, and tumor clinicopathologic features must be considered

Sparano JA, NEJM 2018
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HR+ HER2- *metastatic* breast cancer

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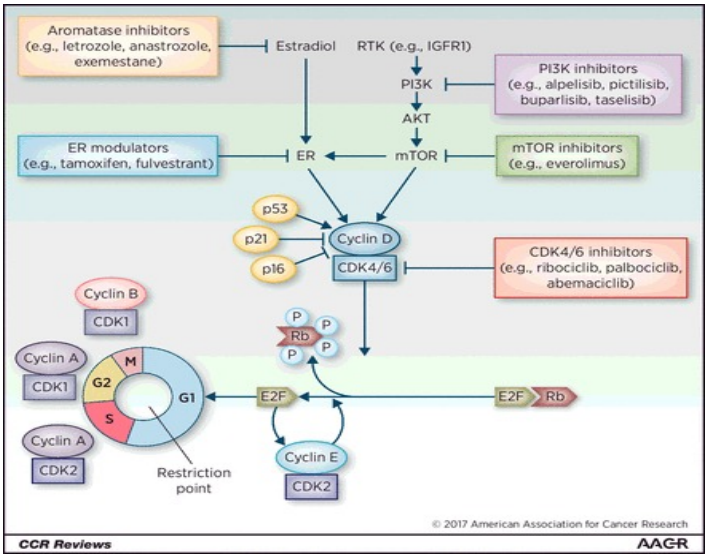
Endocrine targeted therapy



Tripathy et al, CCR 2017

CDK 4/6 inhibitors in 1st and 2nd line

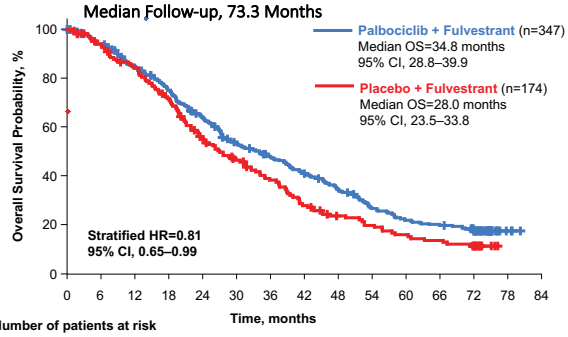
	1st LINE TREATMENT					≥ 2nd LINE TREATMENT		1st AND 2nd LINE TREATMENT
	PALOMA-2	MONALEESA-2	MONARCH-3	MONALEESA-7	PARSIFAL	PALOMA-3	MONARCH-2	MONALEESA-3
Design	Phase III placebo control	Phase III placebo control	Phase III placebo control	Phase III placebo control (pre-menopausal patients only)	Phase II open label	Phase III placebo control	Phase III placebo control	Phase III placebo control
Endocrine partner	Letrozole	Letrozole	Letrozole	Letrozole (or Tamoxifen) + LHRH agonist	Letrozole or Fulvestrant	Fulvestrant	Fulvestrant	Fulvestrant
CDK4/6 Inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Palbociclib (control arm)	Palbociclib	Abemaciclib	Ribociclib
Patients on study, n	666	668	493	672	486	521	669	726
Primary Endpoint = PFS (CDK4/6 inhibitor + ET vs. ET)								
HR	0.58	0.56	0.54	0.55	1.13	0.46	0.55	0.59
Median PFS, months	24.8 vs 14.5 (10.3 mo)	25.3 vs 16 (9.3 mo)	28 vs 14.7 (13.3 mo)	23.8 vs 13 (10.8 mo)	27.9 vs 32.8 (5 mo)	9.5 vs 4.6 (4.9 mo)	16.4 vs 9.3 (7.1 mo)	20.5 vs 12.8 (7.7 mo)

Ingrid Mayer, SABCS 2020

Consistent OS advantage for CDK 4/6i

PALOMA-3

Median Follow-up, 73.3 Months

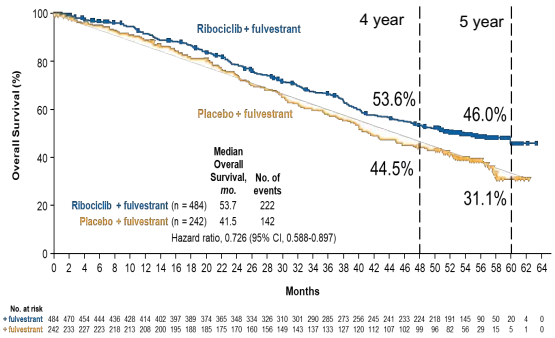


Number of patients at risk

PAL+FUL	347	322	288	250	211	167	149	128	109	84	68	60	54	4
PBO+FUL	174	156	138	117	89	71	58	43	33	27	22	19	17	0

MONALEESA-3

Median Follow-up, 56.3 Months



Christofanilli et al, ASCO 2021; Slamon et al, ASCO 2021

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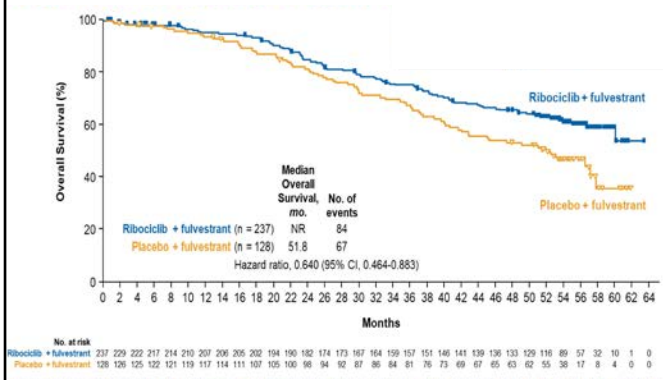
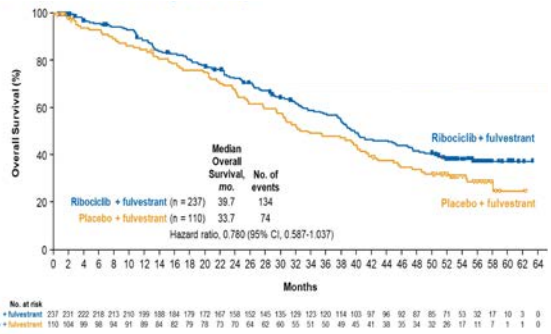
MONALEESA 3: OS benefit independent of therapy line

First line



Early relapse + 2nd line



Slamon et al., ASCO 2021

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MONALEESA 3: OS benefit across subgroups

Subgroup	Ribociclib + Fulvestrant No. of deaths/total no. (%)	Placebo + Fulvestrant No. of deaths/total no. (%)	Hazard Ratio (95% CI)
All patients	222/484 (45.9)	142/242 (58.7)	0.73 (0.59-0.90)
Treatment line of ET for advanced disease			
First line	84/237 (35.4)	67/128 (52.3)	0.64 (0.46-0.88)
Early relapse or second line	134/237 (56.5)	74/110 (67.3)	0.78 (0.59-1.04)
Liver or lung involvement			
Yes	118/242 (48.8)	77/122 (63.1)	0.73 (0.55-0.98)
No	104/242 (43.0)	65/119 (54.6)	0.74 (0.54-1.01)
Bone lesion only			
Yes	45/102 (44.1)	29/51 (56.9)	0.67 (0.42-1.08)
No	177/382 (46.3)	113/190 (59.5)	0.74 (0.58-0.93)
No.of metastasis sites			
< 3	132/308 (42.9)	84/147 (57.1)	0.73 (0.55-0.96)
≥ 3	90/176 (51.1)	58/94 (61.7)	0.74 (0.53-1.04)
Most recent therapy			
(Neo)adjuvant	130/264 (49.2)	94/152 (61.8)	0.78 (0.60-1.01)
Metastatic	57/112 (50.9)	25/41 (61.0)	0.67 (0.42-1.09)
Age			
< 65 Years	116/258 (45.0)	75/129 (58.1)	0.73 (0.54-0.97)
≥ 65 Years	106/226 (46.9)	67/113 (59.3)	0.72 (0.53-0.99)
Prior endocrine therapy			
Endocrine naive	48/139 (34.5)	39/74 (52.7)	0.62 (0.41-0.95)
Endocrine resistance	34/53 (64.2)	18/25 (72.0)	0.82 (0.45-1.47)
Endocrine sensitive	139/289 (48.1)	85/140 60.7)	0.73 (0.56-0.96)

A consistent OS benefit was observed across most subgroups, including harder-to-treat patients, eg, patients with liver/lung metastases, ≥ 3 metastatic sites, and endocrine resistance

Slamon et al., ASCO 2021

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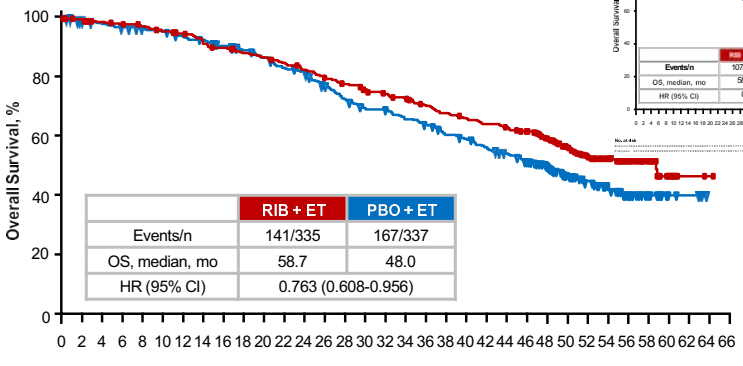
Ribociclib in premenopausal women (MONALEESA-7)

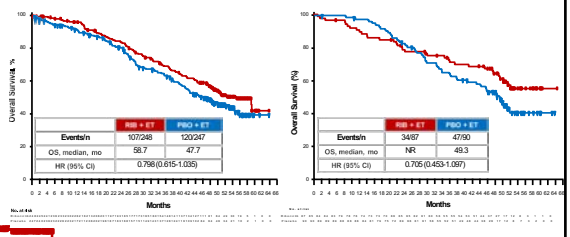
- **Median survival with CDK 4/6i almost 5 years in young women**

Figure 2. OS in the Intent-to-Treat Population



	RIB + ET	PBO + ET
Events/n	141/335	167/337
OS, median, mo	58.7	48.0
HR (95% CI)	0.763 (0.608-0.956)	

Figure 3. OS Subgroup Analyses by Endocrine Partner



[1]Tripathy et al, SABCS 2020

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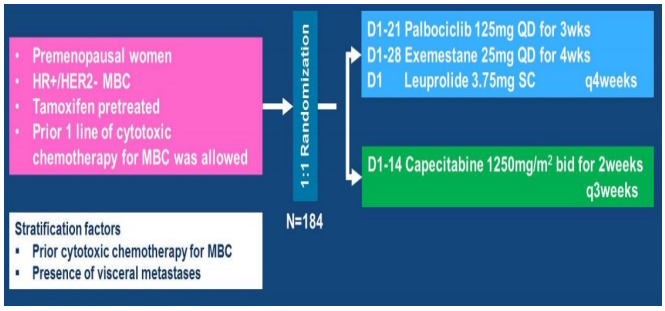
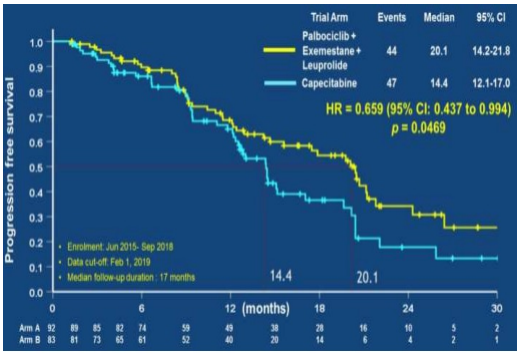
Young- Pearl: Comparing CDK4/6i to chemo in premenopausal women





Park et al ASCO 2019

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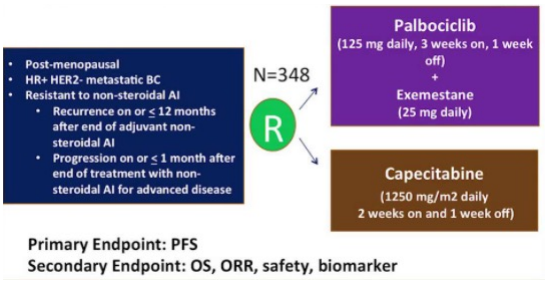
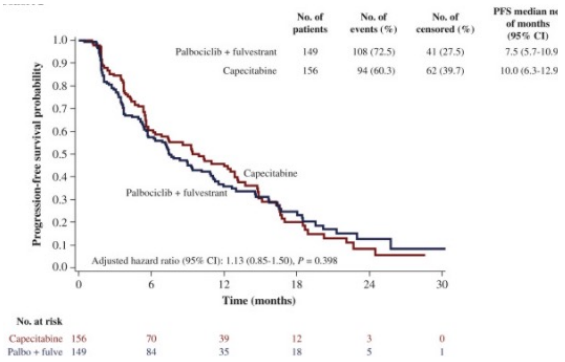
Pearl: Comparing CDK4/6i to chemo in premenopausal women





Martin et al, Annals of Oncology 2020

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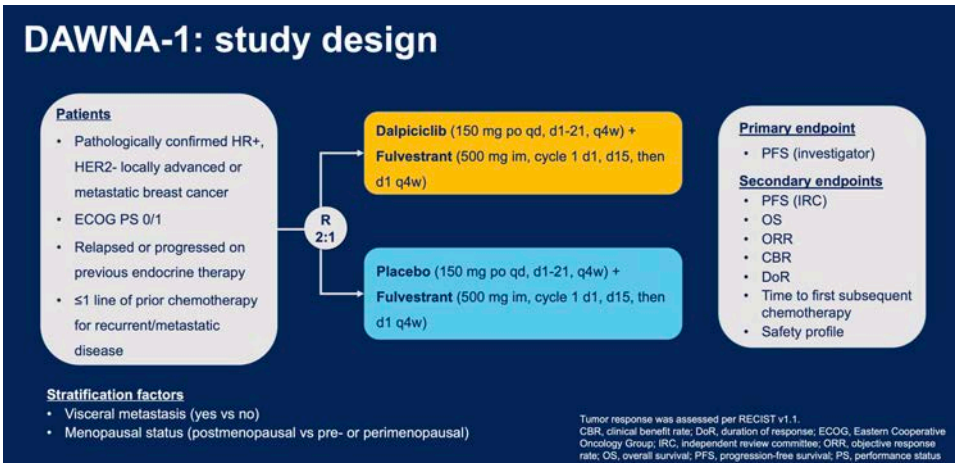

Binghe Xu, ASCO 2021

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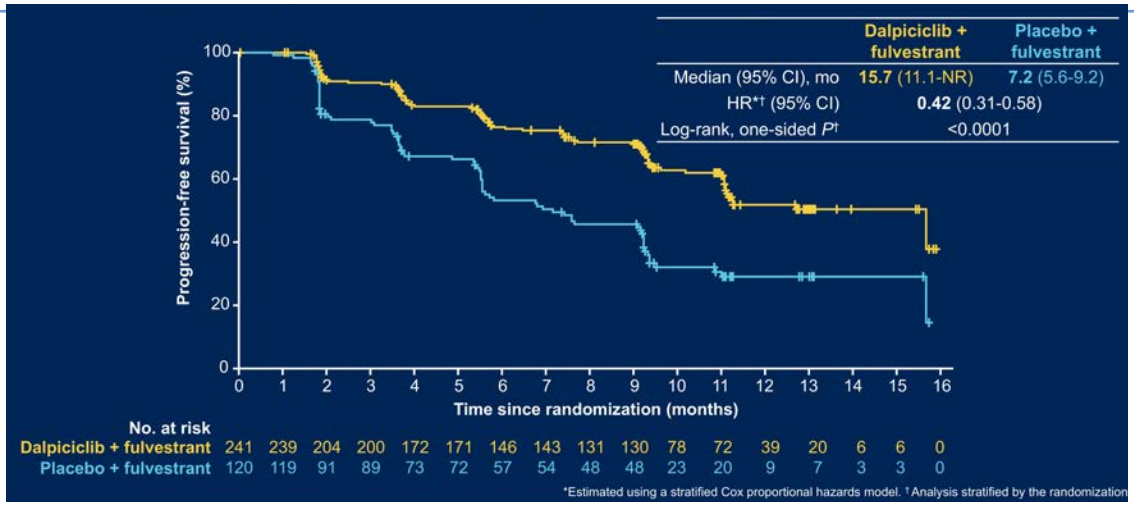

Binghe Xu, ASCO 2021

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Conclusions

- The phase 3 DAWNA-1 met its primary endpoint at the interim analysis, with PFS significantly improved with dalpiciclib + fulvestrant vs placebo + fulvestrant
  - PFS: HR 0.42 (95% CI: 0.31-0.58)
- Benefit of dalpiciclib vs placebo extended beyond initial study treatment
  - Time to first subsequent chemotherapy: HR 0.47 (95% CI: 0.32-0.69)
- Dalpiciclib + fulvestrant demonstrated a tolerable safety profile

These findings support dalpiciclib + fulvestrant as a new treatment option in patients with HR+/HER2- advanced breast cancer who relapsed or progressed on prior endocrine therapy

Binghe Xu, ASCO 2021

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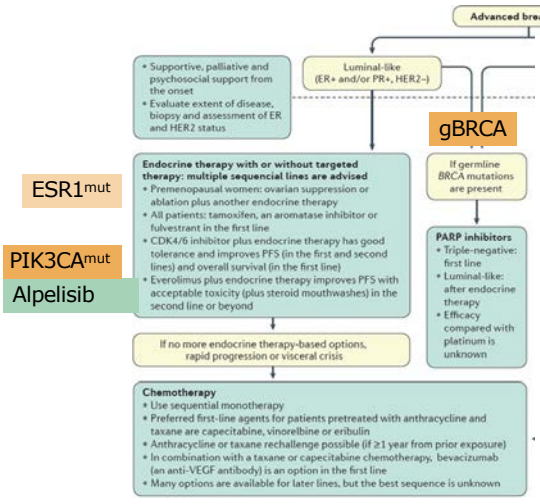
HR+ HER2- *metastatic* breast cancer
Therapeutic algorithm[1]

ER, PR IHC
HER2 IHC, ggf. ISH



[1]Harbeck N, ... Cardoso F, NATURE Reviews 2019

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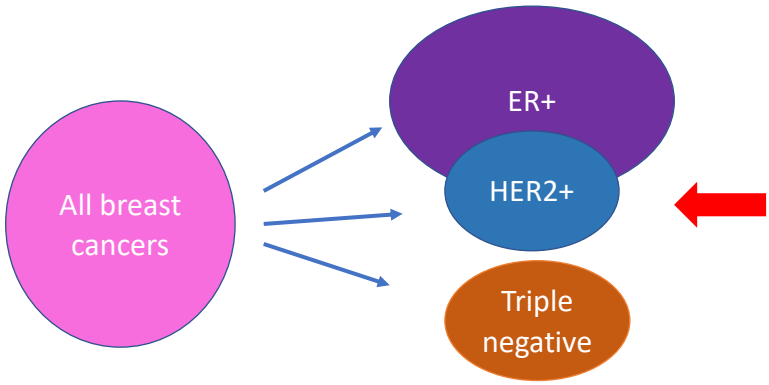
Choosing Wisely in HER2+ Breast Cancer



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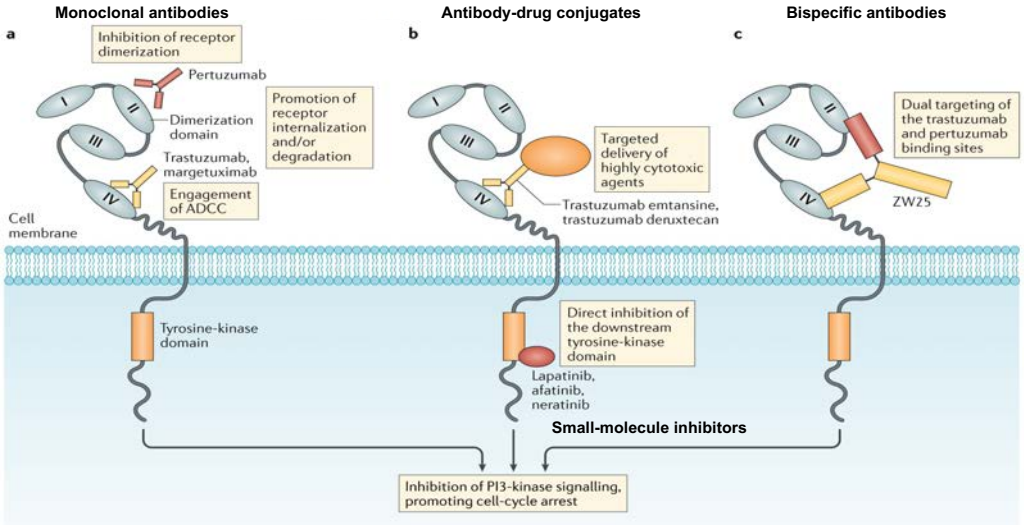
Targeting HER2:



Do-Youn et alNature Reviews Clinical Oncology 2020

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Building on Trastuzumab in adjuvant setting

Trastuzumab (H)	Pertuzumab (added to H)	Neratinib (after H)	TDM1 (in RD)	TH/TDM1 in stage 1	Tailoring to risk…
2005	2013-18	2018	2019	2017-19	2020+

- Therapeutic regimens with augmented effectiveness
- Role and benefits of the neoadjuvant approach
- Personalized approaches, including de-escalation

Slide courtesy of L. Carey (modified)

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Stage I HER2+: How low should we go?

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APT TRIAL: STUDY DESIGN

HER2+
ER+ or ER-
Node Negative
≤ 3 cm

Enroll

P T P T P T P T P T P T P T P T P T P T P T P T

PACLITAXEL 80 mg/m² + TRASTUZUMAB 2 mg/kg x 12

T T T T T T T T T T T T T

FOLLOWED BY 13 EVERY 3 WEEK DOSES
OF TRASTUZUMAB (6 mg/kg)*

Tolaney SM et al, NEJM 2015
Tolaney SM et al, JCO 2019

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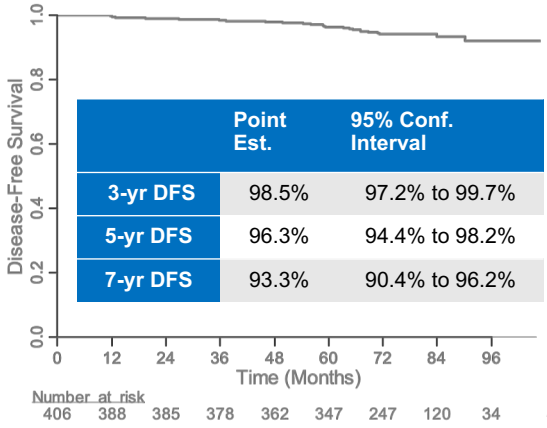
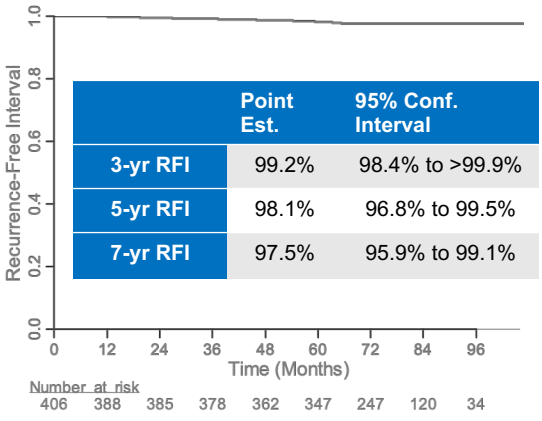
APT: OUTCOMES AT 7 YRS

DISEASE-FREE SURVIVAL



	Point Est.	95% Conf. Interval
3-yr DFS	98.5%	97.2% to 99.7%
5-yr DFS	96.3%	94.4% to 98.2%
7-yr DFS	93.3%	90.4% to 96.2%

RECURRENCE FREE INTERVAL



	Point Est.	95% Conf. Interval
3-yr RFI	99.2%	98.4% to >99.9%
5-yr RFI	98.1%	96.8% to 99.5%
7-yr RFI	97.5%	95.9% to 99.1%

Tolaney SM et al, JCO 2019

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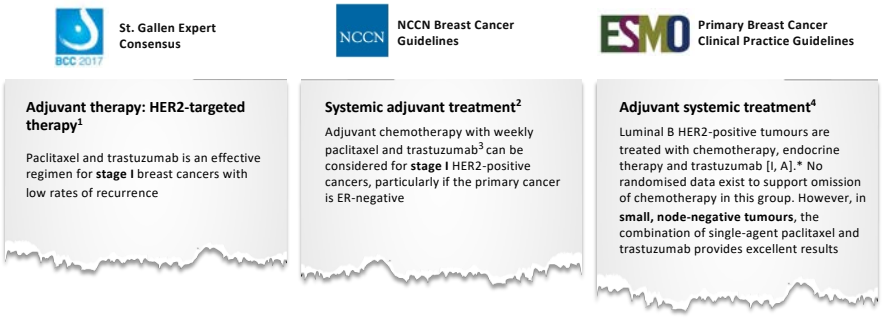
International guidelines recommend the APT treatment regimen in patients with small, node-negative tumors



1. Curigliano G, *et al. Ann Oncol* 2017; **28**:1700–1712; 2. NCCN Breast Cancer Guidelines. Version 3, 2017; 3. Tolaney SM, *et al. N Engl J Med* 2015; **372**:134–141; 4. Senkus E, *et al. Ann Oncol* 2015; **26(Suppl. 5)**:v8–30.

Sara Tolaney, ESMO breast 2021

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Could there be even lower toxicity approaches for stage I disease?

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Does T-DM1 have a role for Stage I HER2+ Disease?

ATEMPT Trial

Key Eligibility Criteria
- Stage 1 HER2+ breast cancer
  - HER2 centrally tested (ASCO CAP 2013 guidelines)
- N0 or N1mic
- Left Ventricular EF ≥ 50%
- No prior invasive breast cancer
- ≤90 days from last surgery

N = 497

R 3:1

3

1

N = 383

T-DM1
3.6 mg/kg IV q3 wks x 17

N = 114

TH
Paclitaxel 80 mg/m² IV + Trastuzumab 2 mg/kg IV wkly x12 → Trastuzumab 6 mg/kg every 3 wks x13

Stratification factors:
- Age (<55, ≥55)
- Planned radiation (Yes/No)
- Planned hormonal therapy (Yes/No)

Tolaney S et al. SABCS 2019

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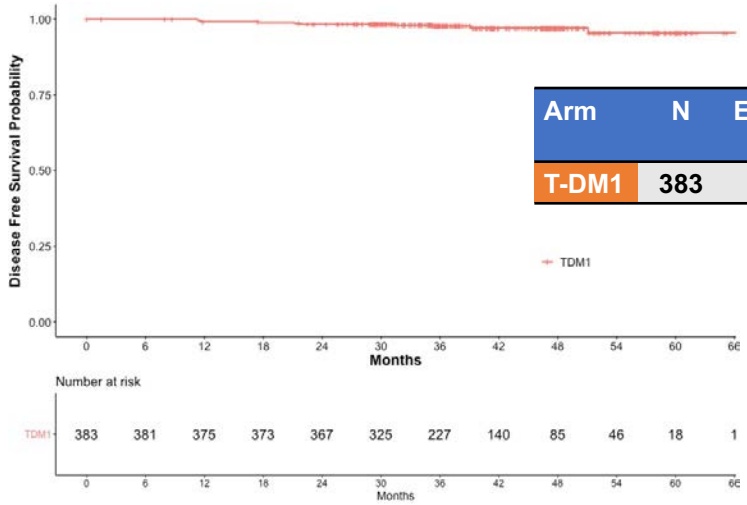
ATEMPT: DISEASE-FREE SURVIVAL



Arm	N	Events	3-yr DFS	95% CI
T-DM1	383	10	97.7%	96.2-99.3%

Tolaney S et al. SABCS 2019

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ATEMPT: CLINICALLY RELEVANT TOXICITY

Clinically Relevant Toxicity	T-DM1 (n = 383) N (%)	TH (n = 114) N (%)
Grade ≥3 non-hematologic toxicity	37 (10%)	13 (11%)
Grade ≥ 2 neurotoxicity	42 (11%)	26 (23%)
Grade ≥4 hemat		0%)
Febrile neutrope		2%)
Any toxicity requ		26%)
Any toxicity requiring early discontinuation	67 (17%)	7 (6%)
Total	176 (46%)	53 (46%)

T-DM1 may be an alternative to TH in select patients

Tolaney S et al. SABCS 2019

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Outcomes without systemic chemotherapy or trastuzumab

HR+/HER2+ (5-year estimates)	T1aN0 (n=102)	T1bN0 (n=89)
iDFS	86% (95% CI: 76-92)	86% (95% CI 76-92)
DRFS	96% (89-98%)	94% (95% CI:86-98%)
HR-/HER2+	**T1aN0 (n=49)**	**T1bN0 (n=17)**
iDFS	84% (95% CI: 69-92)	68% (95% CI 40-86)
DRFS	93% (95% CI 80-98)	94% (95% 63-99)

Vaz-Luis, I et al. JCO 2014

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Which stage I HER2+ breast cancer patients should get systemic therapy

Hormone Receptor Status	<0.5 cm	0.5-1.0cm	>1.0-2.0cm
HR+	NO	YES	YES
HR-	Sometimes*	YES	YES

*if high risk features (high grade with LVI), and relatively larger size

courtesy of Sara Tolaney

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Can we do better in Stage 2-3 HER2 + BC?

- Pertuzumab
- Trastuzumab-DM1 (T-DM1)
- Neratinib

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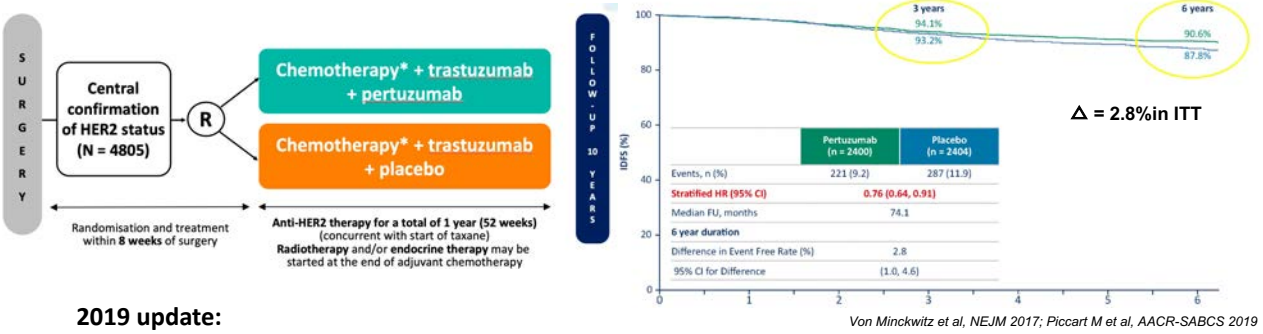
Can we do better in Stage 2-3 HER2 + BC?

- Pertuzumab
- Trastuzumab-DM1 (T-DM1)
- Neratinib

APHINITY - Dual Anti-HER2 Therapy



Von Minckwitz et al, NEJM 2017; Piccart M et al, AACR-SABCS 2019

2019 update:

- Little effect in N-, 4.5% Δ in N+
- Benefit in ER+ and ER-
- No cardiac safety signals

Add pertuzumab in N+ regardless of ER

Can we do better in Stage 2-3 HER2 + BC?

- **Pertuzumab**
- **Trastuzumab-DM1 (T-DM1)**
- **Neratinib**

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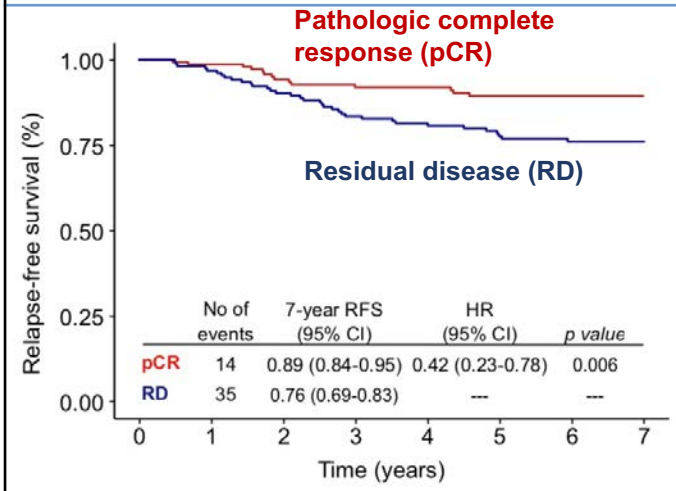
Neoadjuvant Therapy Optimizes Rx and Risk Stratifies



#1 Response allows surgical minimization - >50% of N+ converted to N-

= facilitates omission of ALND

#2 Strong consistent relationship between pCR and relapse/survival in multiple trials

= risk stratification for systemic Rx

Fernandez Martinez et al, JCO 2020

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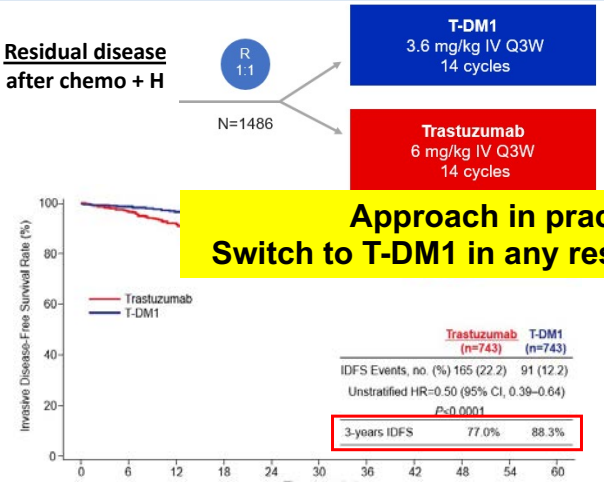
KATHERINE: Tailoring treatment according to pCR



Approach in practice:
Switch to T-DM1 in any residual disease

First IDFS Event, %	T-DM1	T
Any	12.2	22.2
Distant recurrence	10.5*	15.9†
Locoregional recurrence	1.1	4.6
[illegible]eral	0.4	1.3
Death without prior event	0.3	0.4

CNS events: *5.9% vs †4.3%.

- **T-DM1 toxicity:**
  - **gr 3+ 26% (vs 15%), 18% discontinued early**
  - **LFT, neuropathy, thrombocytopenia dominant**

Von Minkwitz et al, NEJM 2018

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Can we do better in Stage 2-3 HER2 + BC?

- **Pertuzumab**
- **Trastuzumab-DM1 (T-DM1)**
- **Neratinib**

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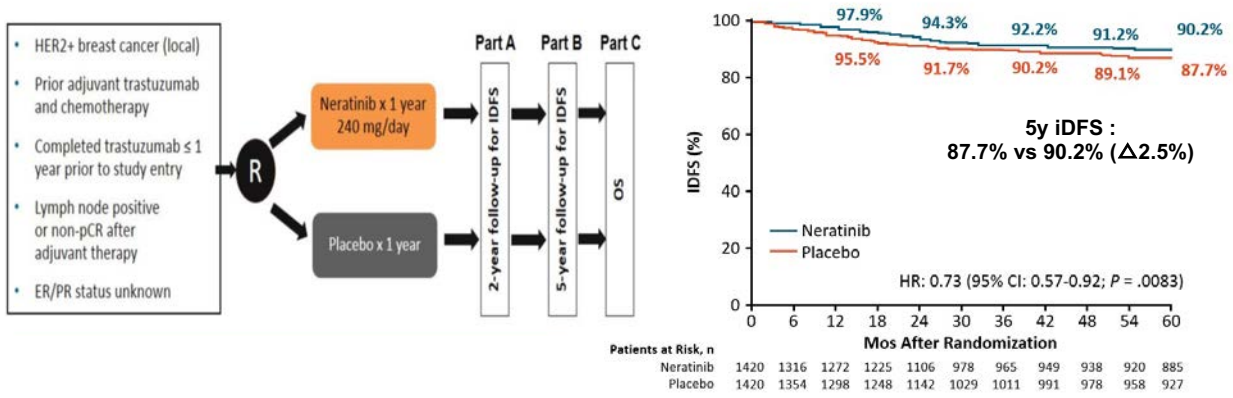
ExteNET: Extended Adjuvant Therapy



Martin M et al, Lancet Oncol 2017; Barcenas CH et al, Ann Oncol 2020

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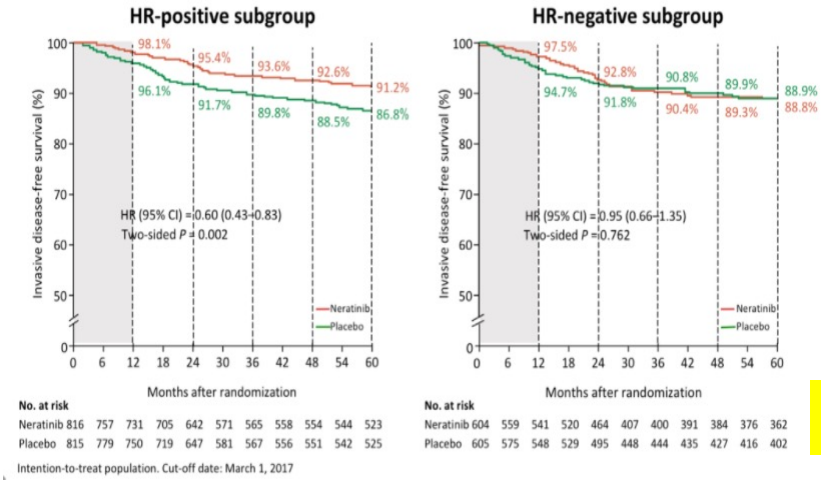
ExteNET: iDFS by hormone receptor status



Intention-to-treat population. Cut-off date: March 1, 2017

- **Benefit seen in HR (Δ4.4%)**
- **Value post-TDM-1? Post-Pertuzumab?**
- **Grade 3 diarrhea seen in 40%**

Benefit in select group of patients?

Martin M et al, Lancet Oncol 2017; Barcenas CH et al, Ann Oncol 2020

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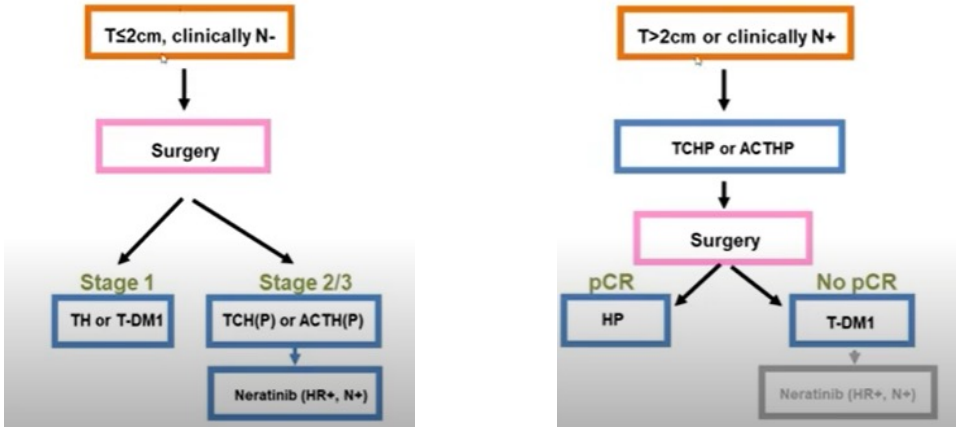
Treatment Algorithm in Early stage HER-2 positive BC



Adapted from Sara Tolaney – ESMO breast 2020

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- **Less is More: De-escalating therapy in early stage HER2+ BC**

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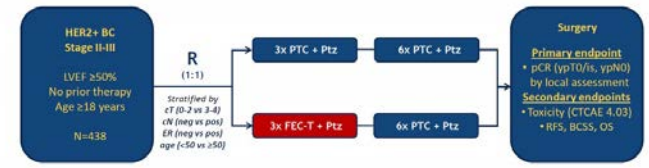
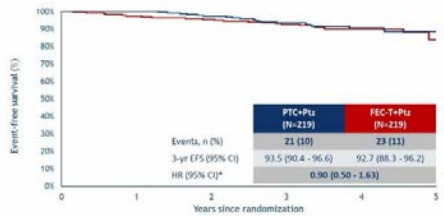
TRAIN -2: Do we need Anthracyclines in HER2+ BC?

TRAIN-2: study design



Event-free survival



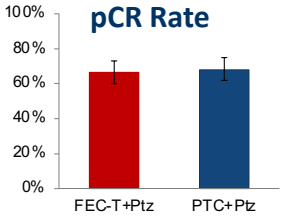
Safety: cardiotoxicity

	PTC+Ptz (n=218) n (%)	FEC-T+Ptz (n=220*) n (%)	p-value
LVEF decrease ≥10% or LVEF <50%	49[2] (22%)	80 (36%)	0.0016
LVEF decrease ≥10% and LVEF <50%	7 (3%)	17 (8%)	0.044

Safety: new malignancies

	PTC+Ptz (n=218*) n (%)	FEC-T+Ptz (n=220*) n (%)
Acute leukemia[3]	0	2 (1%)
Female genital cancer	0	2 (1%)
Lung carcinoma	1 (<1%)	0
Melanoma	1 (<1%)	0
Papillary thyroid carcinoma	0	2 (1%)
Tongue carcinoma	1 (<1%)	0
Non-melanoma skin cancer	2 (1%)	5 (2%)
Total	5 (2%)	11 (5%)

pCR Rate



Anna van der Voort at ASCO 2020

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DE-ESCALATION ALERT

Conclusions

- Three-year follow-up of the TRAIN-2 study shows no EFS and OS benefit for an anthracycline-containing regimen in stage II and III HER2-positive breast cancer
- There is no evidence that higher risk HER2-positive breast cancer patients require anthracyclines
- The addition of anthracyclines increases the risk of febrile neutropenia and cardiac toxicity
- Next step: further de-escalate chemotherapy

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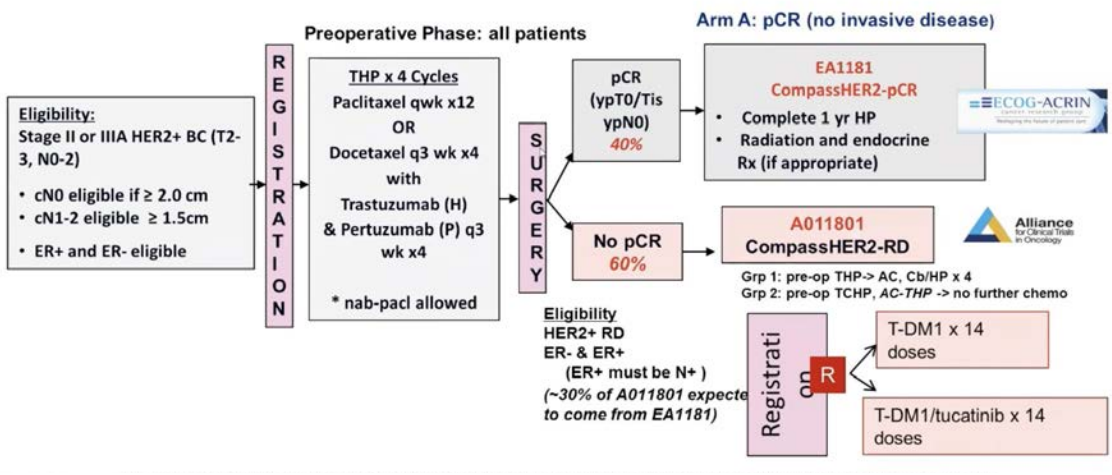
COMPASSHER2 TRIALS



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- Adapting adjuvant therapy based on response to preoperative therapy is a paradigm shift for HER2+ breast cancer
- Most patients with HER2+ T>2 cm or cN+ should receive preop TH-based CT
- All patients who fail to achieve a pCR should receive adjuvant T-DM1
- Extending adjuvant therapy with 1 yr of neratinib can benefit some patients
- Most patients with stage I HER2+ breast cancer should receive adjuvant TH
  - The value of neoadjuvant TH in stage I should be explored
- Future studies are looking at both escalation and de-escalation strategies
  - New predictive/prognostic tools are needed for this purpose

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- **Metastatic HER-2 positive BC**

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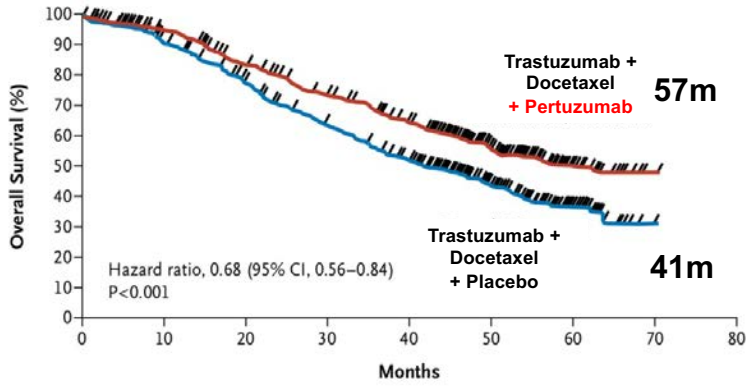
CLEOPATRA: Adding Pertuzumab in First-Line Therapy



Δ OS16m

ER or PgR status			0.47
Positive	388		0.71 (0.53–0.96)
Negative	408		0.61 (0.47–0.81)

Swain et al, ASCO 2019

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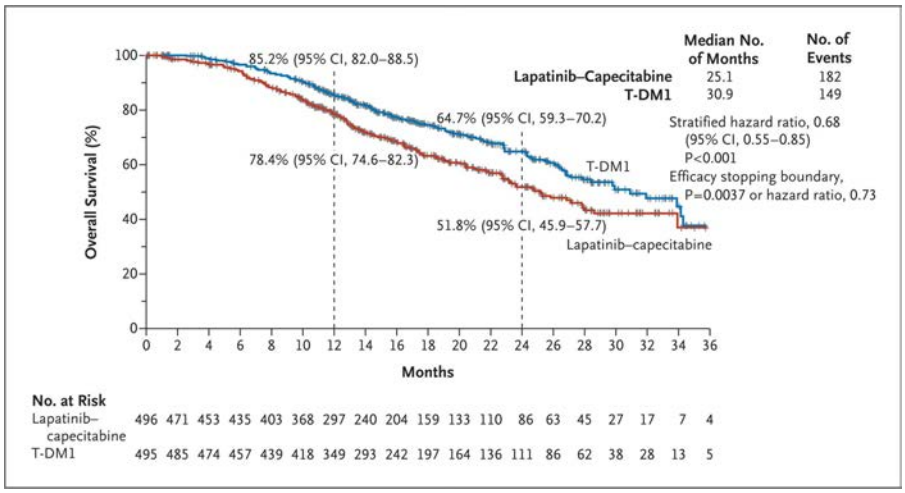
EMILIA: TDM-1 in second line HER2+ MBC

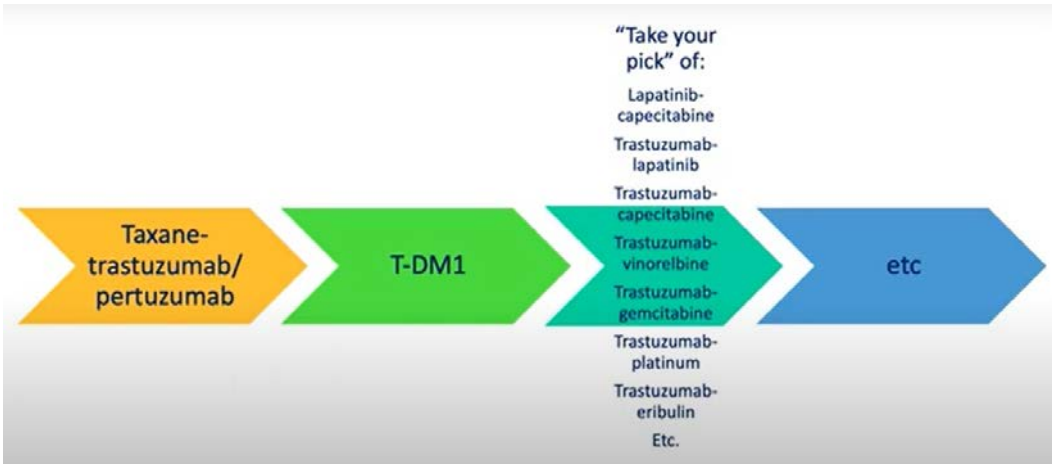


Median OS: 25.1 vs 30.9m

Verna et a, NEJM 2012 (Landmark study)

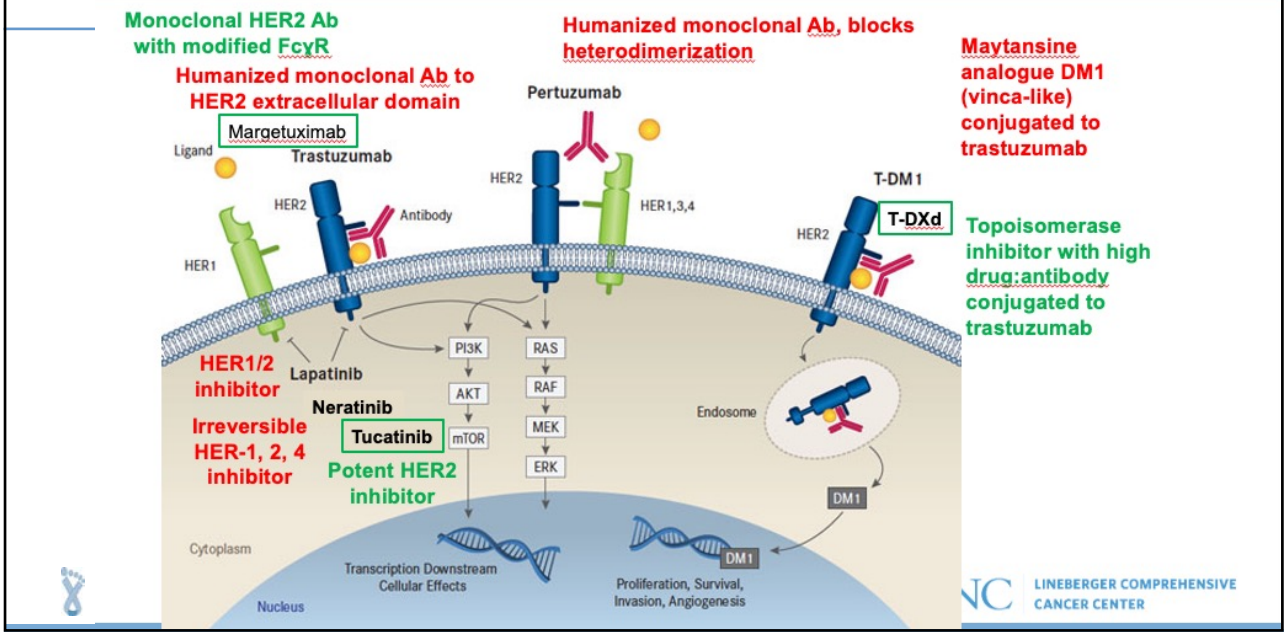
79

Management of HER2+ MBC in 2018:



80

Metastatic HER2+ Breast Cancer: Advances since 2018!



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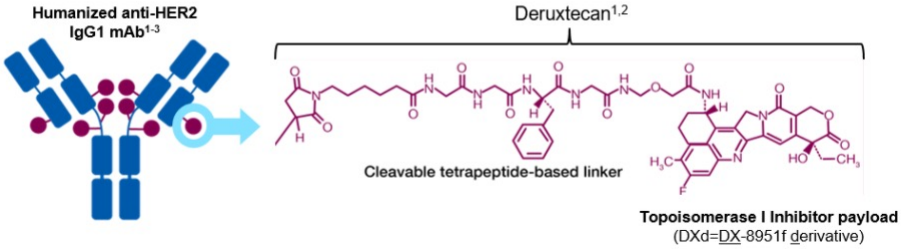
Trastuzumab Deruxtecan (T-DXd):

A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab, covalently linked to a **topoisomerase I** inhibitor payload, an exatecan derivative, via a **tetrapeptide-based** cleavable linker



Ogitani Y, et al. Cancer Sci. 2016

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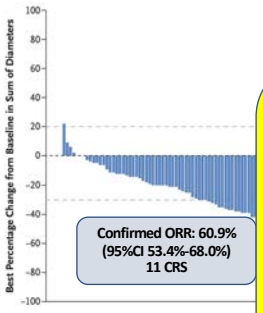
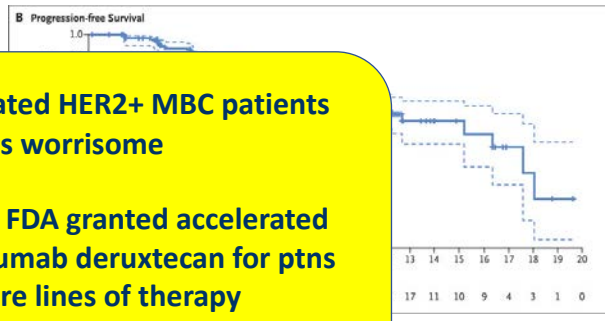
DESTINY-Breast01: Trastuzumab Deruxtecan for 3L+ HER2+ MBC



Median of 6 (2-27) prior lines of therapy

Confirmed ORR: 60.9%
(95%CI 53.4%-68.0%)
11 CRS



- **Very active in pretreated HER2+ MBC patients**
- **ILD risk is worrisome**

On December 20, 2019, FDA granted accelerated approval to fam-trastuzumab deruxtecan for ptns who had 2 or more lines of therapy

Toxicity:

- **Gr3+: Neutropenia**
- **Discontinuation: 15%**
- **ILD: 14%, mostly grade 1/2**
  - **4 (2.2%) deaths**
  - **Median onset 193d**
  - **Reversible in ~ 50% (?)- treat with dose reduction and steroids**

Modi S et al, NEJM 2020

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Tucatinib : Oral, HER2 selective TKI

HER2CLIMB: Tucatinib added to Capecitabine + Trastuzumab

Key Eligibility Criteria

- HER2+ MBC
- Prior trastuzumab, pertuzumab, and T-DM1
- Brain MRI: no mets or mets not needing immediate local Rx

R* (2:1)

N=410 → **Tucatinib + Trastuzumab + Capecitabine**

N=202 → **Placebo + Trastuzumab + Capecitabine**

N=612, 48% with brain metastasis

Murthy R et al, NEJM 2020

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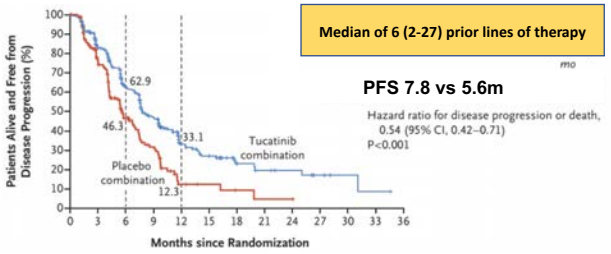
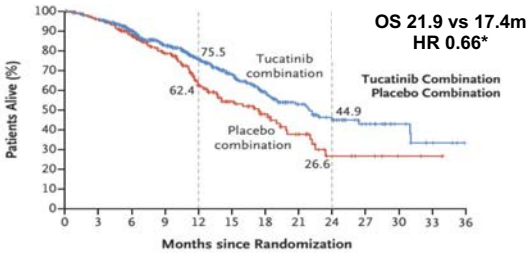
HER2CLIMB: Results @ 14m (Event-Driven)





- **All subgroups benefited essentially equally**.

FDA approves tucatinib for patients with HER2-positive metastatic breast cancer

Murthy R et al, NEJM 2020

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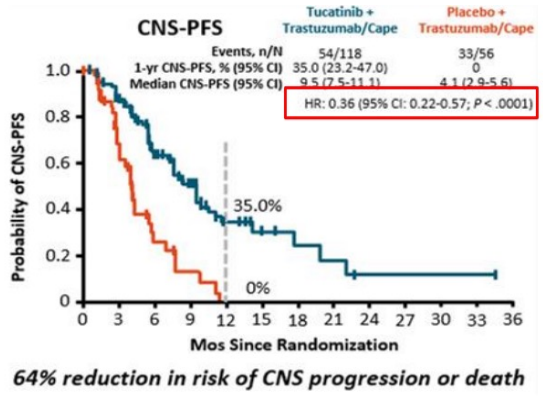
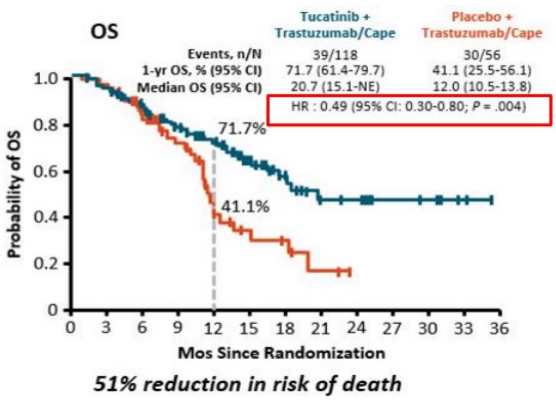
HER2CLIMB Intracranial Activity: CNS-PFS and OS in Patients With Active Brain Metastases





First RCT to report a TKI leading to prolonged OS in patients with HER2+ MBC and brain mets

Nancy Lin al, ASCO 2020

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SOPHIA: Margetuximab vs Trastuzumab in HER2+ MBC post 2nd line

- Randomized, open-label phase III trial (data cutoff: September 30, 2019)

Stratified by CT, no. of prior lines of tx (> 2 vs ≤ 2), no. of metastatic sites (> 2 vs ≤ 2)

Patients with HER2+ advanced BC with ≥ 2 previous anti-HER2 therapies, including pertuzumab; 1-3 prior lines of tx for metastatic disease; prior brain metastasis allowed if treated/stable (N = 536)

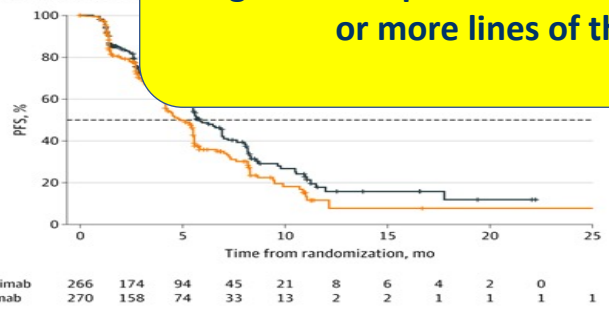
Margetuximab 15 mg/kg Q3W + CT* in 3 wk cycles

Exploratory analysis by CD16A genotype:

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

On December 16, 2020, FDA approved Margetuximab plus chemo for ptns who had 2 or more lines of therapy

A PFS by CBA, October 2018



No. at risk

Margetuximab	266	174	94	45	21	8	6	4	2	0
Trastuzumab	270	158	74	33	13	2	2	1	1	1

vs 4.9 m

- Enhanced benefit for lower affinity FV and FF genotypes?

Rugo et al, JAMA 2021

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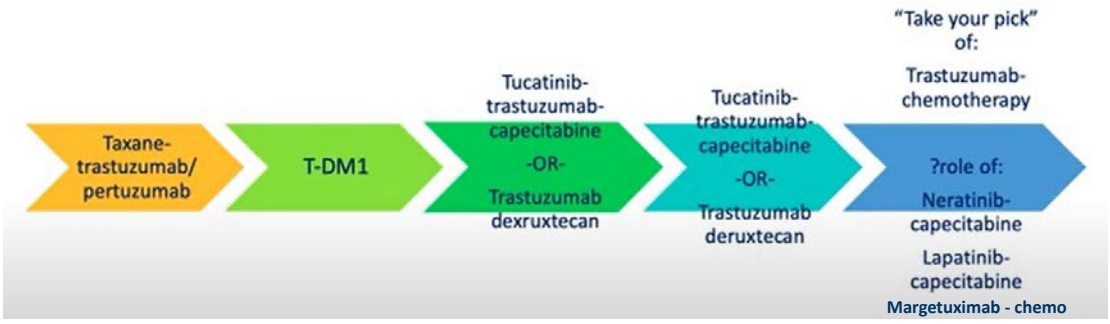
Current Management Algorithm: 2021



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Several New Agents in Development

- Trastuzumab duocarmazine (SYD 985)
- Zanidatamab (ZW25)
- ZW49
- ZN-A-1041
- Pyrotinib
- Combinations with CDK 4/6 inhibitors
- Combinations with immunotherapy

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CARISMA CT-0508 STUDY 101

- CT-0508 is a cell product comprised of autologous, peripheral blood monocyte-derived, pro-inflammatory macrophages, transduced with adenoviral vector containing an anti-HER2 chimeric antigen receptor (CAR)
- CAR-T cell therapies have shown success in numerous hematologic malignancies, solid tumors remain a major challenge in the field.
- A Phase 1, First in Human Study of Adenovirally Transduced Macrophages Engineered to Contain an Anti-HER2 CAR in HER2 Overexpressing Solid Tumors.
- These engineered myeloid cells traffic to tumors, reduce tumor burden, reprogram the TME, and induce a broad anti-tumor adaptive immune response in pre-clinical models of HER2 overexpressing solid tumors.

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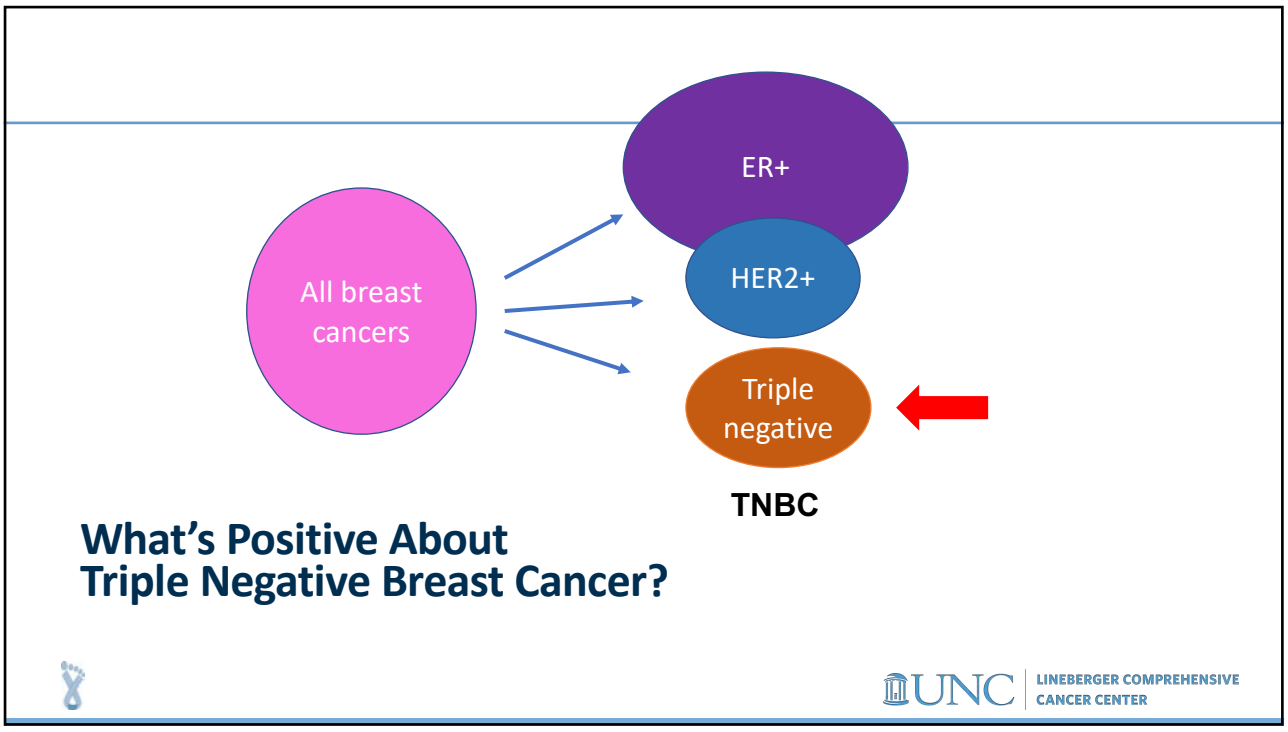
All breast cancers
ER+
HER2+
Triple negative
TNBC
What's Positive About Triple Negative Breast Cancer?
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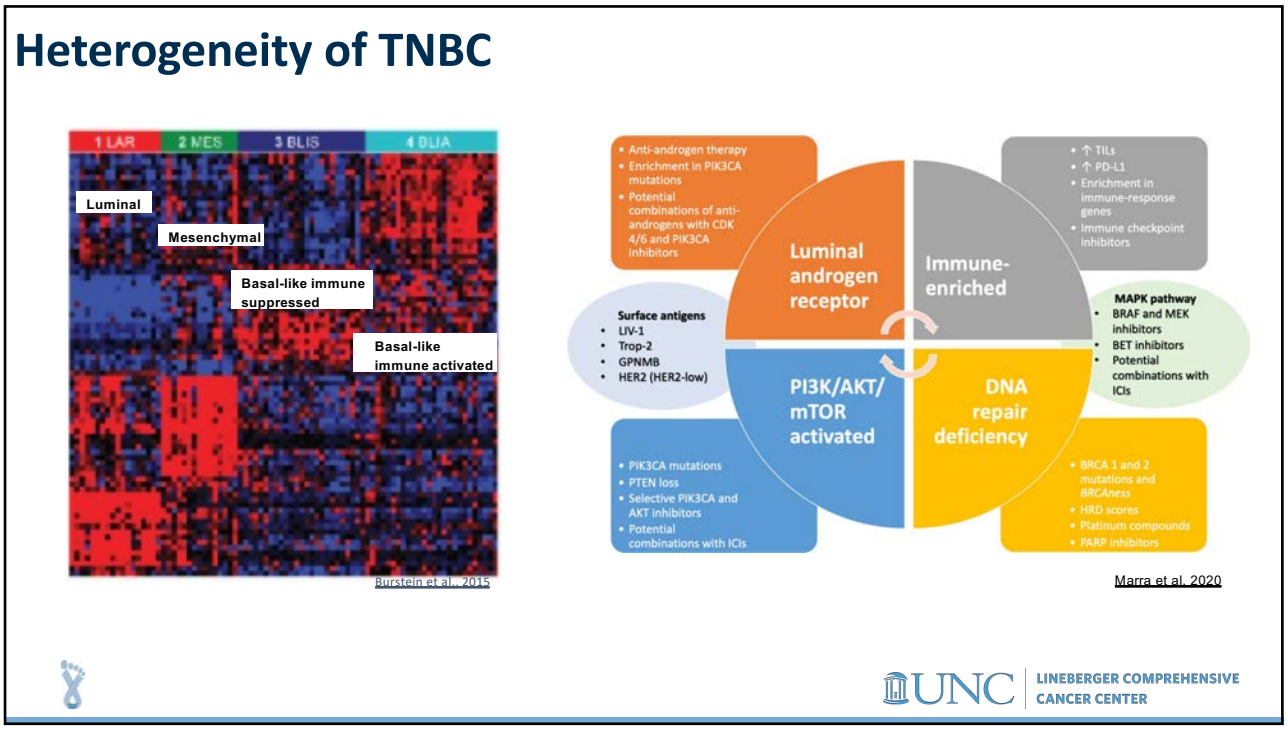
Heterogeneity of TNBC
1 LAR
2 MES
3 BLIS
4 BLIA
Luminal
Mesenchymal
Basal-like immune suppressed
Basal-like immune activated
Burstein et al., 2015
Luminal androgen receptor
• Anti-androgen therapy
• Enrichment in PIK3CA mutations
• Potential combinations of anti-androgens with CDK 4/6 and PIK3CA inhibitors
Immune-enriched
• ↑ TILs
• ↑ PD-L1
• Enrichment in immune-response genes
• Immune checkpoint inhibitors
Surface antigens
• LIV-1
• Trop-2
• GPNMB
• HER2 (HER2-low)
MAPK pathway
• BRAF and MEK inhibitors
• BET inhibitors
• Potential combinations with ICIs
PI3K/AKT/ mTOR activated
• PIK3CA mutations
• PTEN loss
• Selective PIK3CA and AKT inhibitors
• Potential combinations with ICIs
DNA repair deficiency
• BRCA 1 and 2 mutations and BRCAness
• HRD scores
• Platinum compounds
• PARP inhibitors
Marra et al. 2020
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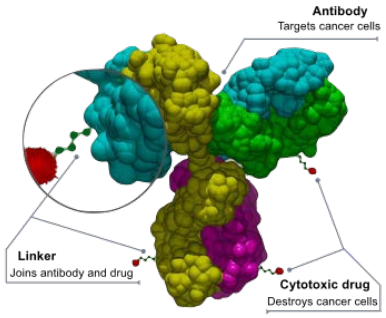
WHAT IS THE ROLE OF ANTIBODY DRUG CONJUGATES IN TNBC?



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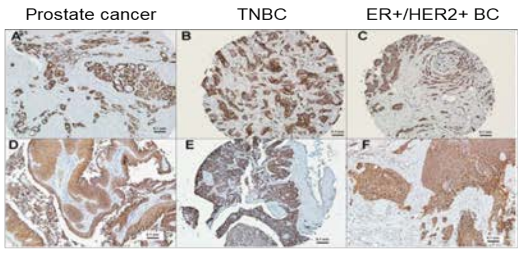
TROP2 as a Therapeutic Target for Breast Cancer

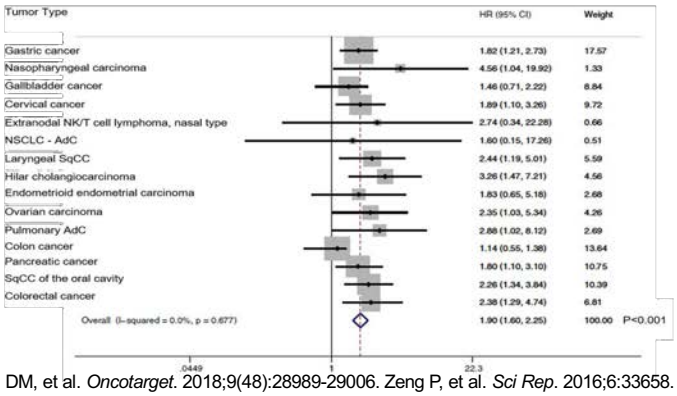
TROP2 is upregulated in many solid tumors

TROP2 staining of solid tumors by IHC



In a meta-analysis, TROP2 overexpression was significantly associated with poor overall and disease-free survival across multiple tumor types

Correlation between TROP2 expression and OS



Goldenberg DM, et al. *Oncotarget*. 2018;9(48):28989-29006. Zeng P, et al. *Sci Rep*. 2016;6:33658.

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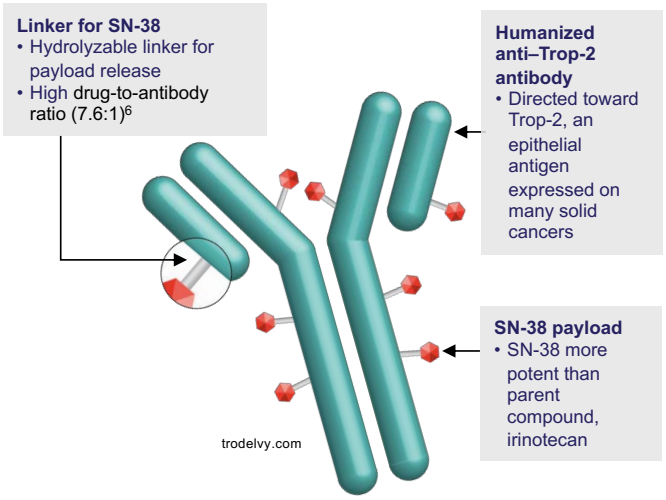
Sacituzumab Govitecan (SG): Trop-2–Directed ADC

- SG is an antibody–drug conjugate that combines a humanized monoclonal antibody, which targets Trop-2, with SN-38, which is conjugated to the antibody by a cleavable linker.
- SG enables delivery of high concentrations of SN-38 to tumors.



Nagayama A et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980.
Cardillo TM et al. *Bioconjugate Chem*. 2015;26:919-931.

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ASCENT: A Phase 3 Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC

Metastatic TNBC (per ASCO/CAP)
≥2 chemotherapies for advanced disease
[no upper limit; 1 of the required prior regimens could be from progression that occurred within a 12-month period after completion of (neo)adjuvant therapy)]
N=529

NCT02574455

R 1:1

Sacituzumab Govitecan (SG)
10 mg/kg IV
days 1 & 8, every 21-day cycle
(n=267)

Treatment of Physician's Choice (TPC)*
(n=262)

Continue treatment until progression or unacceptable toxicity

Endpoints

Primary
- PFS†

Secondary
- PFS for the full population‡
- OS, ORR, DOR, TTR, safety

Data cutoff: March 11, 2020

Stratification factors
- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

Bardia A et al, ESMO 2020

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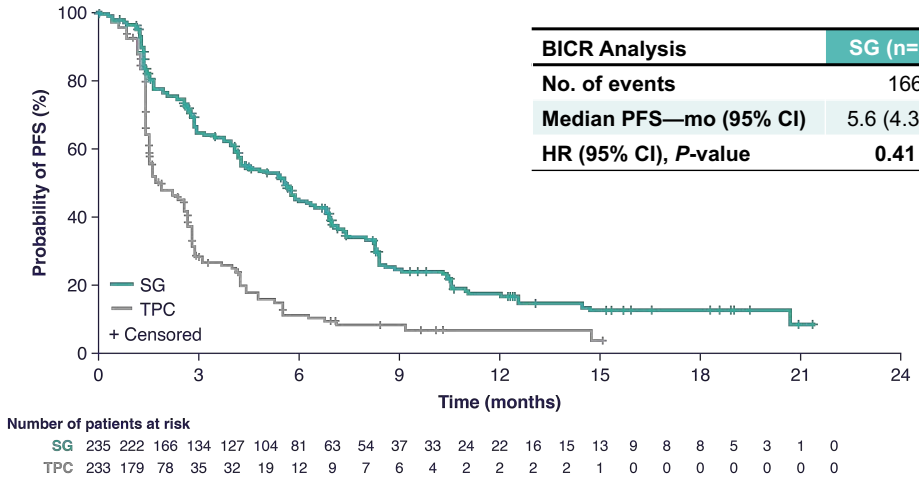
Progression-Free Survival (BICR Analysis)



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**	

Bardia A et al, ESMO 2020

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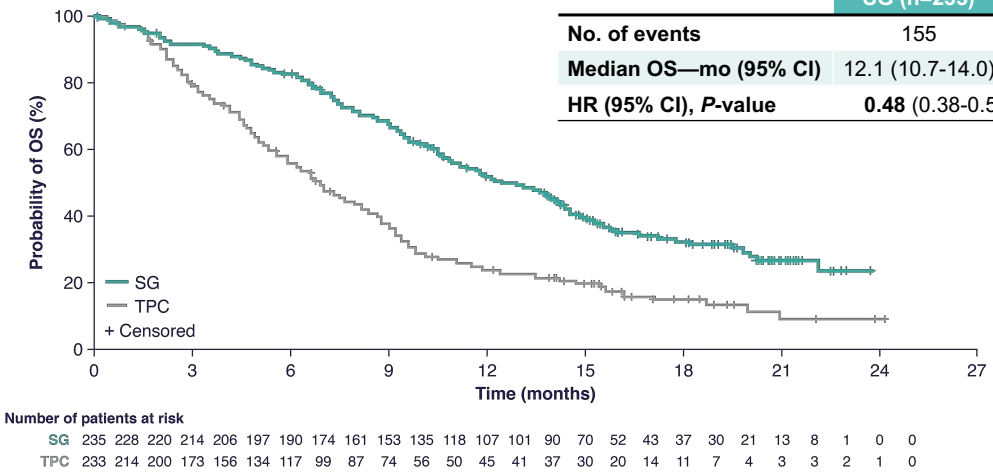
Overall Survival



	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**	

Bardia A et al, ESMO 2020

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TRAEs

	TRAE*	SG (n=258) All grade %	SG (n=258) Grade 3, %	SG (n=258) Grade 4, %	TPC (n=224) All grade, %	TPC (n=224) Grade 3, %	TPC (n=224) 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%)
- 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) Bardia A et al, ESMO 2020

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On April 7, 2021, the FDA granted approval to sacituzumab govitecan for patients with unresectable locally advanced or metastatic TNBC who have received two or more prior systemic therapies, at least one of them for metastatic disease.

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GILEAD
Creating Possible

ASCENT
Clinical Trial

Assessment of Sacituzumab Govitecan in Patients With Prior Neoadjuvant/Adjuvant Chemotherapy in the Phase 3 ASCENT Study in Metastatic Triple-Negative Breast Cancer: 2nd-Line Subgroup Analysis

Lisa A. Carey,[1] Delphine Loirat,[2] Kevin Punie,[3] Aditya Bardia,[4] Véronique Diéras,[5] Florence Dalenc,[6] Jennifer R. Diamond,[7] Christel Fontaine,[8] Grace Wang,[9] Hope S. Rugo,[10] Sara A. Hurvitz,[11] Kevin Kalinsky,[12] Joyce O'Shaughnessy,[13] Sibylle Loibl,[14] Luca Gianni,[15] Martine Piccart,[16] Quan Hong,[17] Martin S. Olivo,[17] Loretta M. Itri,[17] Javier Cortés[18]

[1]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA; [2]Medical Oncology Department and D3I, Institut Curie, Paris, France; [3]Department of General Medical Oncology and Multidisciplinary Breast Centre, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium; [4]Department of Hematology/Oncology, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA; [5]Department of Medical Oncology, Centre Eugène Marquis, Rennes, France; [6]Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France; [7]Division of Medical Oncology, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [8]Medical Oncology Department, Oncologisch Centrum, UZ Brussel, Brussels, Belgium; [9]Miami Cancer Institute, Miami, FL, USA; [10]Department of Medicine, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [11]Department of Medicine, Division of Hematology/Oncology, David Geffen School of Medicine, University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [12]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [13]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA; [14]Department of Medicine and Research, Hämatologisch-Onkologische Gemeinschaftspraxis am Bethanien Krankenhaus, Frankfurt, Germany; [15]Medical Oncology, Gianni Bonadonna Foundation, Milano, Italy; [16]Medical Oncology Department, Institut Jules Bordet and Université Libre de Bruxelles, Brussels, Belgium; [17]Gilead Sciences Inc., Morris Plains, NJ, USA; [18]International Breast Cancer Center, Quiron Group, Barcelona, Spain.

Presented at the Virtual American Society of Clinical Oncology Annual Meeting, June 4-8, 2021

In this sub analysis from the ASCENT study, Lisa Carey and colleagues assessed safety and efficacy outcomes in patients who had **disease recurrence within 12 months of completing (neo)adjuvant chemotherapy and received only 1 regimen in the metastatic setting**, prior to study enrollment.

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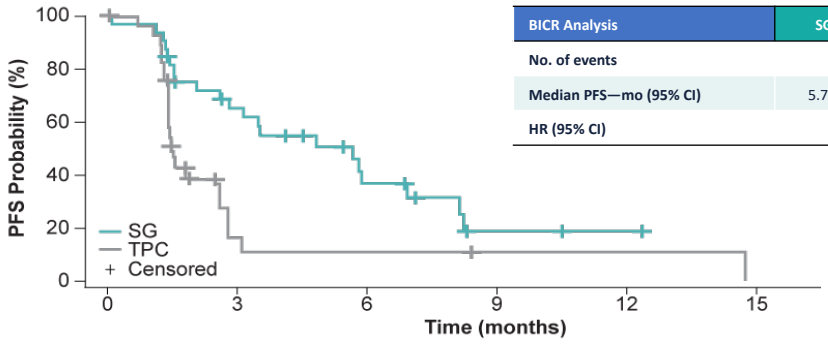
Progression-Free Survival



BICR Analysis	SG (n=33)	TPC (n=32)
No. of events	21	23
Median PFS—mo (95% CI)	5.7 (2.6-8.1)	1.5 (1.4-2.6)
HR (95% CI)	**0.41** (0.22-0.76)	

No. of Patients Still at Risk

SG	33	32	23	19	16	12	8	6	5	2	2	1	1	0	0	0
TPC	32	28	8	3	2	2	2	2	2	1	1	1	1	1	1	0

Carey et al, ASCO 2021

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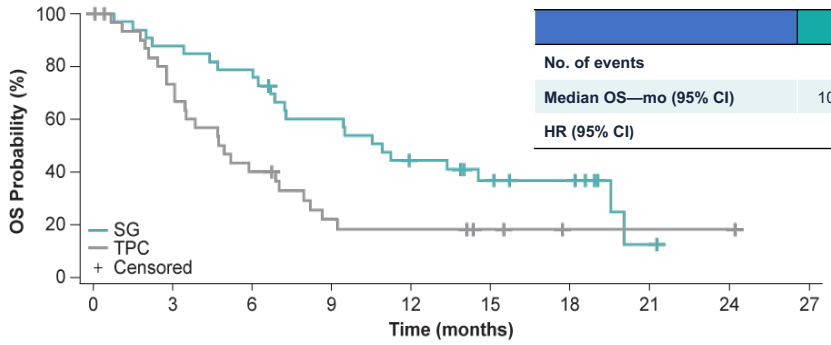
Overall Survival



	SG (n=33)	TPC (n=32)
No. of events	22	24
Median OS—mo (95% CI)	10.9 (6.9-19.5)	4.9 (3.1-7.1)
HR (95% CI)	**0.51** (0.28-0.91)	

No. of Patients Still at Risk

SG	33	32	31	29	28	26	26	21	19	19	17	15	13	13	11	9	7	7	7	4	2	1	0	0	0	0
TPC	32	29	27	22	17	14	12	10	8	6	5	5	5	5	5	3	2	2	1	1	1	1	1	1	1	0

Carey et al, ASCO 2021

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Conclusions

The efficacy benefit and safety profile in this exploratory sub-analysis are consistent with that of the overall ASCENT study population across all key endpoints, suggesting that SG is efficacious in a population of patients with early relapse who may be resistant to chemotherapy

These data support SG as a second-line treatment option for patients with mTNBC who have received only 1 prior systemic therapy for metastatic disease

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Ongoing Studies With Sacituzumab Govitecan in Breast Cancer

Study	Ph	Patients	N	Arms	1º EP	Est Study Completion
NCT04230109 (NeoSTAR)[1]	2	Pts with localized TNBC	~50	Safety and efficacy of sacituzumab govitecan in localized TNBC	DFS, OS	August 31, 2023
NCT03992131 (SEASTAR)[2]	1b/2	Pts with TNBC and other cancers	329	Safety, tolerability, PK, and preliminary efficacy of sacituzumab govitecan + rucaparib in patients an advanced/metastatic solid malignancy	Safety, ORR	March 2024
NCT04039230[3]	1/2	Pts with mTNBC	65	Effects of sacituzumab govitecan + talazoparib	Safety	August 31, 2024

DFS, disease-free survival.
1. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT04230109. Accessed November 7, 2020. Last updated: July 16, 2020; 2. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://clinicaltrials.gov/ct2/show/NCT03992131. Accessed November 7, 2020. Last updated: August 26, 2019; 3. U.S. National Library of Medicine Clinicaltrials.gov. URL: https://www.clinicaltrials.gov/ct2/show/NCT04039230. Accessed November 7, 2020. Last updated: May 5, 2020

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Datopotamab Deruxtecan: New TROP2 ADC on the block

TROPION-PanTumor01 (NCT03401385) – TNBC Cohort

Phase 1, First-in-human, Dose Escalation and Expansion Study

- Advanced/metastatic HR-/HER2- negative breast cancer (TNBC)[a]
- Relapsed/progressed on standard treatment
- Unselected for TROP2 expression[b]
- Measurable disease (per RECIST version 1.1)

→ Dato-DXd 6mg/kg IV Q3W N≈40

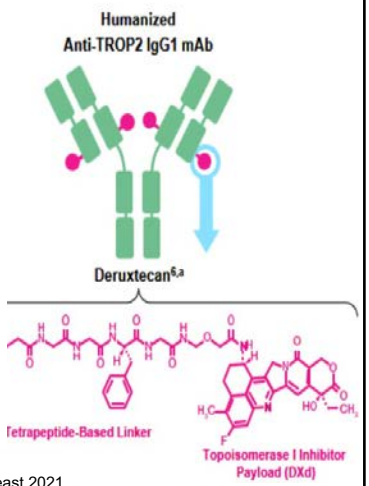
2 patients received 8 mg/kg prior to selection of the 6-mg/kg dose for dose expansion

→ **Primary objectives include:**
- Safety, Tolerability

Secondary objectives include:
- Efficacy, Pharmacokinetics

Data cutoff January 8, 2021

- Current analysis includes 24 patients treated at the 6-mg/kg dose (n=22) and 8-mg/kg dose (n=2)[c] into other advanced tumor types



Bardia A et al, ESMO breast 2021

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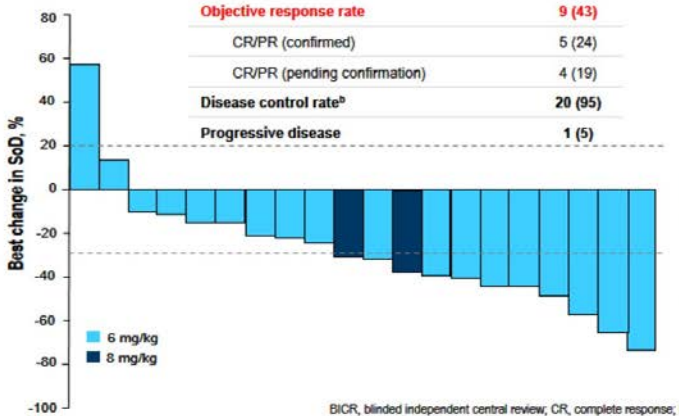
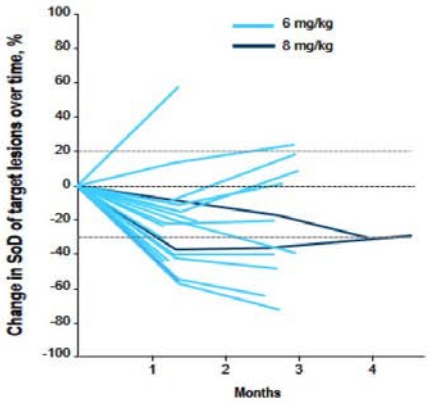
TROPION-PanTumor01: Dato-DXd TNBC Cohort

Antitumor Activity (by BICR)

Patients, n (%)[a]	N=21
Objective response rate	9 (43)
CR/PR (confirmed)	5 (24)
CR/PR (pending confirmation)	4 (19)
Disease control rate[b]	20 (95)
Progressive disease	1 (5)





BICR, blinded independent central review; CR, complete response; PD, progressive disease; PR, partial response; SoD, sum of diameters.

Bardia A et al, ESMO 2021

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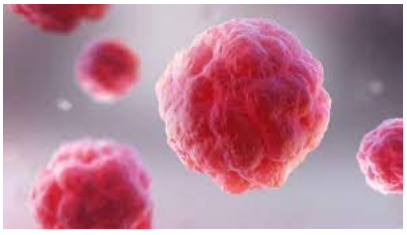
WHAT IS THE ROLE OF IMMUNOTHERAPY IN TNBC?



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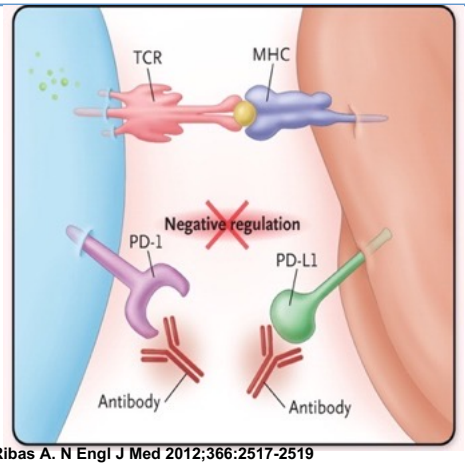
Targeting the PD-1/PDL-1 Pathway in Breast Cancer



In breast cancer, TNBC is the best candidate for cancer immunotherapy:

- Higher rate of mutational complexity
- Presence of TILs
- Higher rates of PD-L1^{+} expression by tumor cells and immune cells

Ribas A. N Engl J Med 2012;366:2517-2519
Cimino-Mathews/Taube/Emens et al Human; Pathol 2016; 47: 52-83; Cimino-Mathews/Foote/; Emens Oncology 2015; 29: 375-385.

Slide courtesy of Sara Tolaney

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IMpassion130

Key eligibility criteria

- Histologically documented metastatic or inoperable, locally advanced TNBC
- No prior therapy for advanced TNBC[a]
  - Prior chemotherapy including taxanes allowed in curative setting if treatment-free interval ≥ 12 mo
- ECOG PS 0-1
- Eligible for taxane monotherapy
- Tumour tissue for PD-L1 testing

(N = 902)

R 1:1

Atezolizumab[b] + *nab*-paclitaxel[c]

Double-blind

Placebo + *nab*-paclitaxel[c]

Treatment until progression or unacceptable toxicity

Stratification factors

- Liver metastases (yes vs no)
- Prior taxanes (yes vs no)
- PD-L1 status (positive vs negative)[a]

Co-primary endpoints:

- PFS[d] and OS (hierarchically tested in ITT and PD-L1 IC+ populations)

Emens LA. ESMO 2020.

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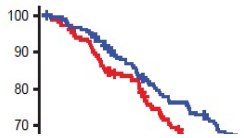
Final OS in the PD-L1 IC+ population



	PD-L1 IC+ population	
	A + nP (n = 185)	P + nP (n = 184)
OS events, n (%)	120 (65)	139 (76)
Stratified HR	0.67 (0.53, 0.86)[a]	

FDA approves atezolizumab for PD-L1 positive unresectable locally advanced or metastatic triple-negative breast cancer

Patients at risk (PD-L1 IC+ population):	Time (months)																
A + nP	185	177	160	145	135	121	108	98	90	86	77	67	56	32	17	11	9	6	3
P + nP	184	170	150	132	113	95	85	72	66	62	54	47	28	14	7	6	3	1	NE

Emens LA. ESMO 2020.

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KEYNOTE-355 Study Design

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease

R 2:1

- Pembrolizumab[a] + Chemotherapy[b]
- Placebo[c] + Chemotherapy[b]

→ Progressive disease[d]/cessation of study therapy

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)

Cortes J et al, ASCO 2020

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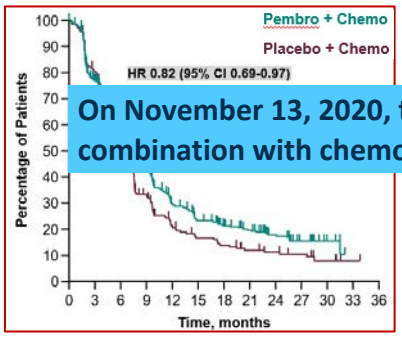
KEYNOTE 355: Progression-free survival

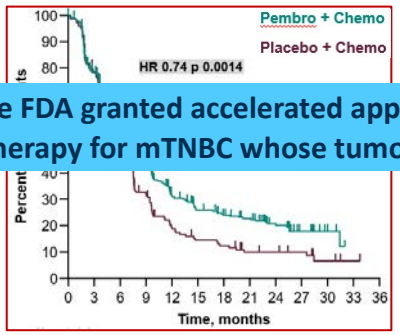
On November 13, 2020, the FDA granted accelerated approval to pembrolizumab in combination with chemotherapy for mTNBC whose tumors express PD-L1 (CPS ≥10).

ITT



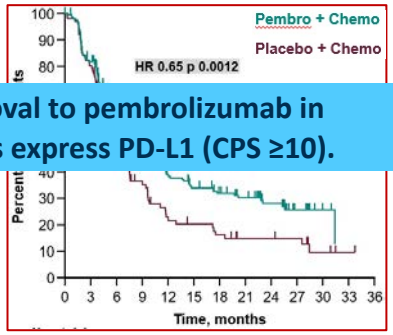
Statistical significance was not tested due to the prespecified hierarchical testing strategy

PD-L1 CPS ≥1



Prespecified *P* value boundary of 0.00111 not met

PD-L1 CPS ≥10



Prespecified *P* value boundary of 0.00411 met

Cortes J et al, ASCO 2020
Slide courtesy of Sara Tolaney

OS follow up ongoing

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IMpassion131 trial design

VIRTUAL 2020 ESMO congress

- Metastatic or unresectable locally advanced TNBC
- No prior chemotherapy or targeted therapy for advanced TNBC
- Previous eBC treatment completed ≥12 months before randomisation
- Taxane eligible
- Measurable disease
- ECOG PS 0/1

R
2:1

Atezolizumab 840 mg d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

8–10 mg dexamethasone or equivalent for at least the first 2 infusions, cycles repeated q28d

Placebo d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

Primary endpoint: PFS (investigator assessed)
Secondary endpoints include:
- OS, ORR, PFS (IRC assessed)
- PROs
- Safety
- Translational research

Miles D et al, ESMO 2020

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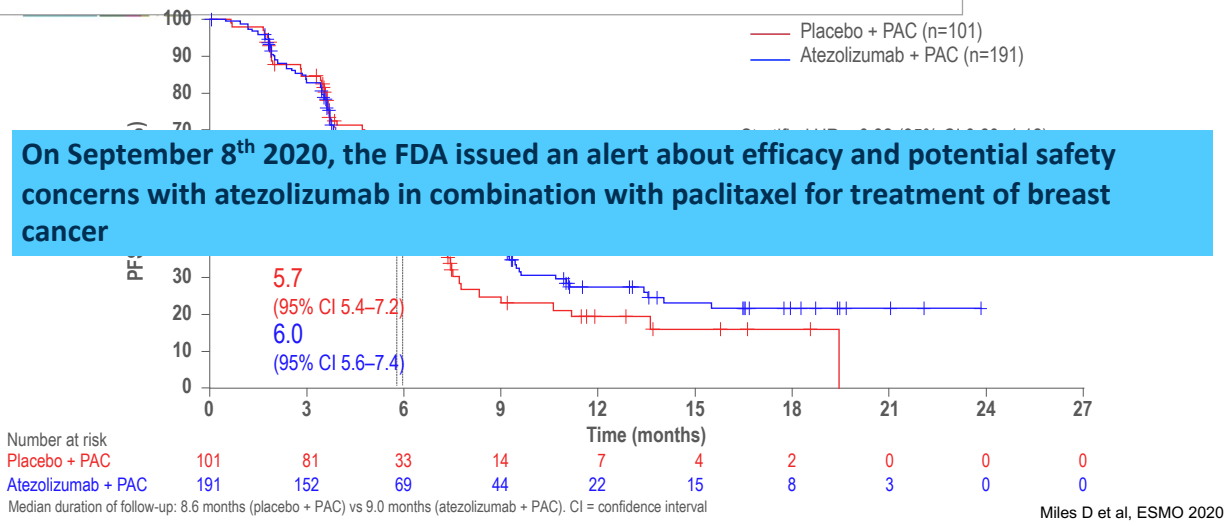
Primary analysis: PFS in the PD-L1+ population



On September 8th 2020, the FDA issued an alert about efficacy and potential safety concerns with atezolizumab in combination with paclitaxel for treatment of breast cancer

Number at risk										
Placebo + PAC	101	81	33	14	7	4	2	0	0	0
Atezolizumab + PAC	191	152	69	44	22	15	8	3	0	0

Median duration of follow-up: 8.6 months (placebo + PAC) vs 9.0 months (atezolizumab + PAC). CI = confidence interval

Miles D et al, ESMO 2020

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What about immunotherapy in early TNBC?

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pCR rates in randomized TNBC neoadjuvant studies

GeparNUEVO	NeoTRIPaPD-L1	KEYNOTE-522	IMpassion 031
Nab-paclitaxel -> EC q2 week +/- Durvalumab (no adj)	Nab-paclitaxel + Carbo weekly 2 on / 1 off x 8 +/- Atezolizumab (no adj)	Paclitaxel + Carbo -> AC/EC q3 week +/- Pembrolizumab 1 year	Nab-paclitaxel -> AC q2 week +/- Atezolizumab 1 year
pCR = 53.4% vs 44.2% △ 9.2% (n=174)	pCR = 43.5% vs 40.8% △ 2.7% (n=280)	pCR = 64.8% vs 51.2% △ 13.6% (n=602) pCR = 63% vs 55.6% △ 7.5% (n=1174)	pCR = 57.8% vs 41.1% △ 16.5% (n=333)

Melinda Telli, ASCO 2021

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Does pCR-benefit with ICIs translate into survival benefit?

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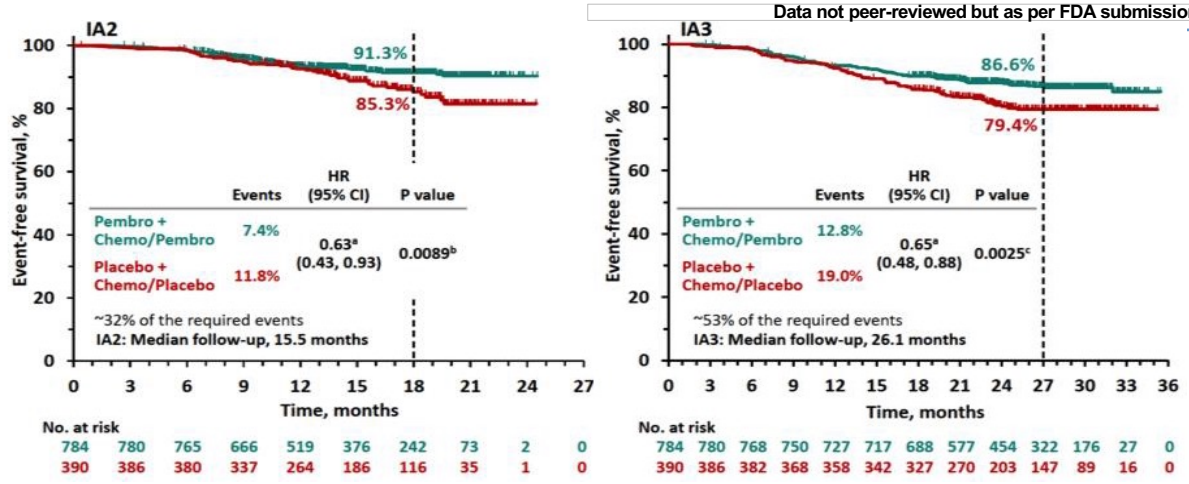
KEYNOTE-522 Study: Event-free Survival (interim analysis)

Data not peer-reviewed but as per FDA submission



ᵇPrespecified *P* value boundary of 0.000051. ᶜ Prespecified *P* value boundary of 0.0021 IA2 Data cutoff April 24, 2019; IA2 Data cutoff March 23, 2020.

Schmid P, et al. ESMO 2019, Schmid P, et al *NEJM* 2020, https://www.fda.gov/media/145654/download

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MERCK

May 13, 2021

Media > News releases > News release

Merck Announces Phase 3 KEYNOTE-522 Trial Met Dual Primary Endpoint of Event-Free Survival (EFS) in Patients With High-Risk Early-Stage Triple-Negative Breast Cancer (TNBC)

Awaiting FDA approval …

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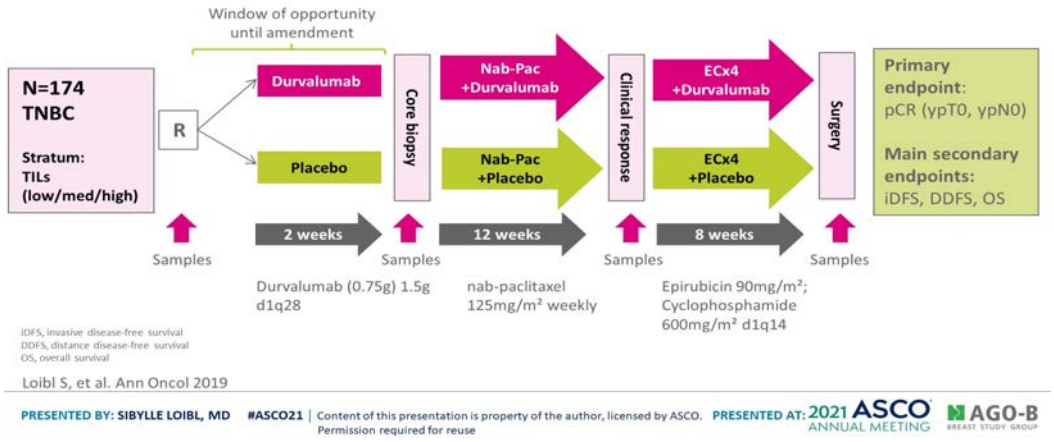
GeparNuevo Study design



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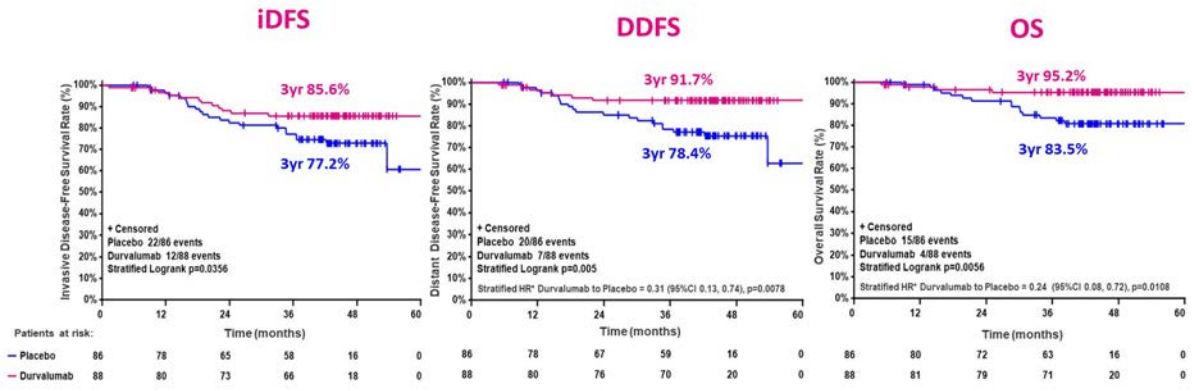
iDFS, DDFS and OS Between Treatment Arms



Sibylle Loibl, ASCO 2021

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Questions remain?

- **Biomarkers to identify optimal responders?**
- **De-escalation strategies in lower risk? Does everyone need that much chemo?**
- **Role of adjuvant ICI? Duration?**
- **Long term benefit and safety data?**

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WHAT IS THE ROLE OF PARP INHIBITORS IN TNBC?

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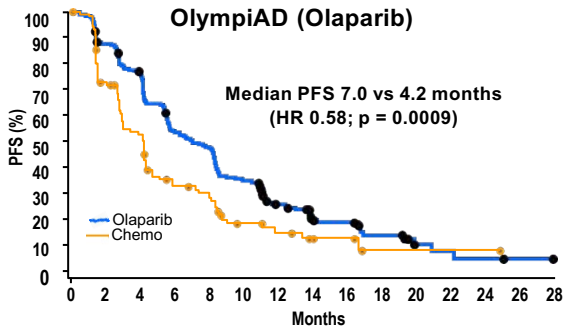
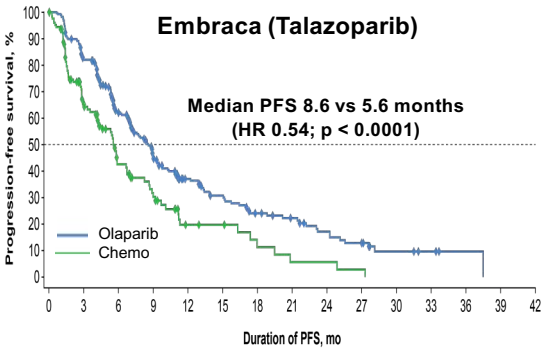
Efficacy of PARP Inhibitors in Patients with gBRCA Mutations





Response rates	Olympia	Embraca
PARPi	60%	62.6%
Chemo	29%	27.2%

Robson M, et al. ASCO 2017, Litton J, et al. SABCS 2017

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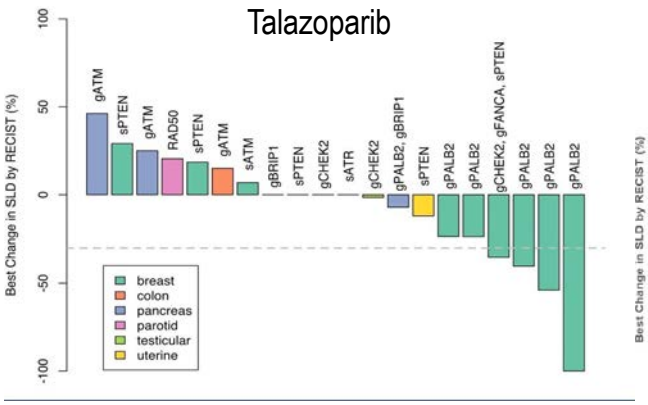
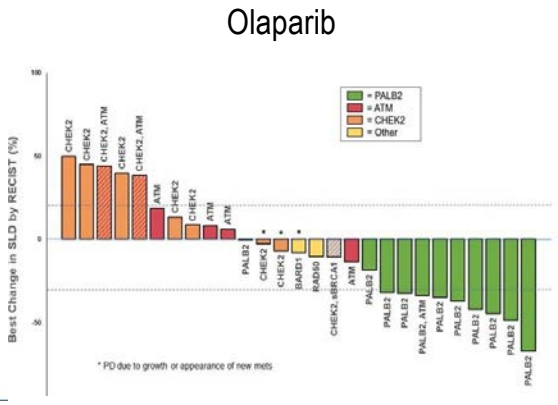
Germline mutations in PALB2





Gruber J, et al ASCO 2019; Tung N, et al. ASCO 2020

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1

OlympiA
OLaparib in Adjuvant BRCAm breast cancer

A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline *BRCA1/2* mutations and high-risk HER2-negative early breast cancer

ASCO 2021 Plenary session

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OlympiA: Trial schema

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

Olaparib 300 mg twice daily for 1 year

Eligibility: n=1836, g*BRCA1/2m* carriers with
- TNBC
  - Adjuvant: pN+ or pT > 2cm or
  - Neoadjuvant: No pCR
- ER or PR+/ HER2-neg
  - Adjuvant: ≥ 4+ nodes or
  - Neoadjuvant: No pCR and CPS & EG score ≥ 3

Intervention
- Adjuvant PARPi vs. placebo x 1 yr after all standard Rx

- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

Tutt et al, ASCO 2021

Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

Hormone receptor +ve defined as ER and/or Pg
Triple Negative defined as ER and PgR negative
[1]Hudis CA, J Clin Oncol 2007

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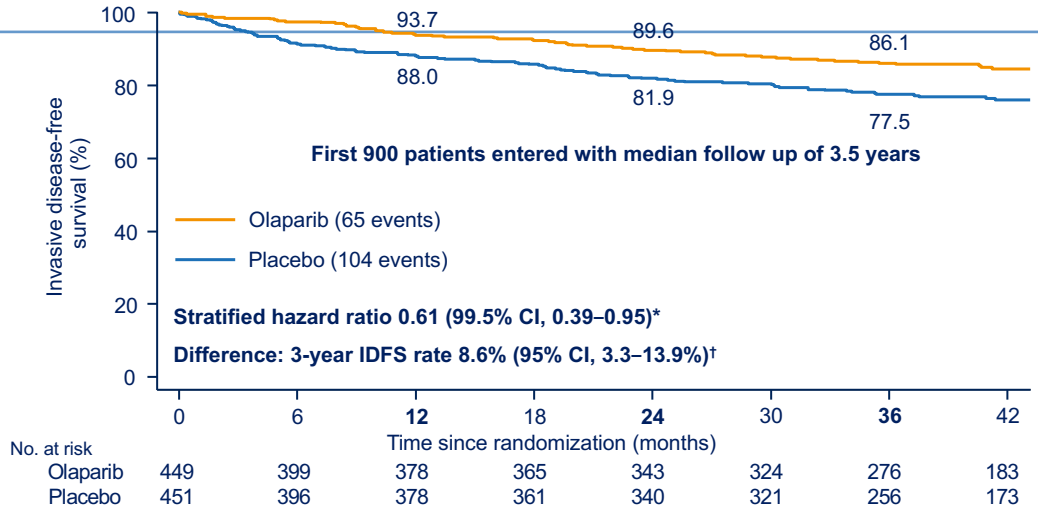
OlympiA: Invasive disease-free survival



Tutt et al, ASCO 2021

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OlympiA: TAKE HOME POINTS

- **Addition of Olaparib to standary therapy significantly improved 3y iDFS and DDFS for gBRCA1/2 carriers with:**
  - **TNBC (>2cm or node +)**
  - **HR+/HER2- (≥ 4+**
- No new safety
- Upfront Genetic testing needed to make treatment decisions

Results are practice changing!!

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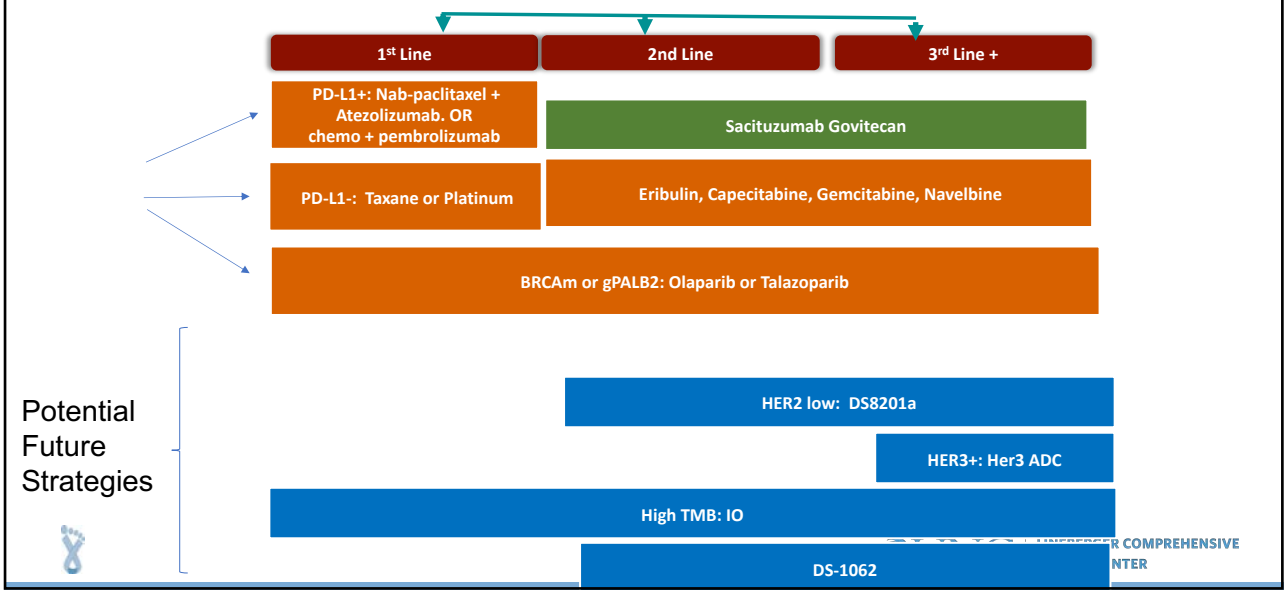
Approach to Therapy for Metastatic TNBC+ disease: Move to Personalization



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Summary

- Immunotherapy is now standard in PD-L1+ mTNBC
  - 2 approved checkpoint inhibitors combined with chemotherapy
  - Only a subset of patients can benefit
- Antibody drug conjugates
  - Sacituzumab is a new treatment option for TNBC
  - Other ADCs in development: LIV1A, TDxd, U3-1402, DS-1062
- PARP inhibitors appear active in patients with gPALB2 and s+gBRCA1/2 mutations
- Novel Immunotherapy combinations are being explored with PARP, anti-angiogenic agents, IL-2 agonists, IL-12, ADCs, and others

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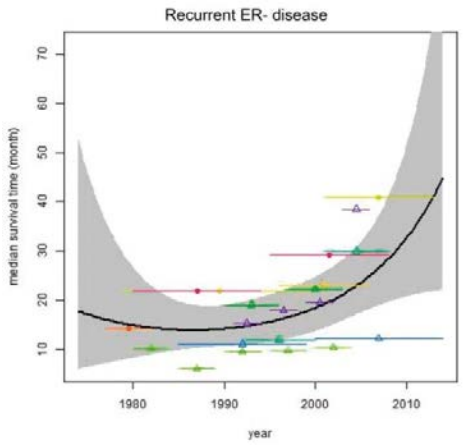
Are We Starting To Make a Difference?



Caswell-Jin et al, JNCI 2018

- **Improved multidisciplinary care** = better surgical and long-term outcomes for early TNBC
- **Improvements in medical management** = beginning to bend the curve in metastatic TNBC
- **Better understanding of TNBC biology** = finding targets for treatment and eliminating the term "triple negative breast cancer"

Slide courtesy of Lisa Carey (modified)

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Acknowledgements:

Lisa Carey
Emily Ray
Sara Tolaney

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Thank you!

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