NCCN 2023 BREAST CANCER CONGRESS
with Updates from the 2022 San Antonio Breast Cancer Symposium

Friday, February 3, 2023
1:00 PM – 2:00 PM [CST]

Multigene and Biomarker Testing in Breast Cancer: What is the Role?

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Early Stage Breast Cancer

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Learning Objectives

- Identify the biomarker tests that are recommended for early stage breast cancer and their roles.
- Compare and contrast the various techniques/assays available for biomarker testing.
- Incorporate biomarker testing and test results into clinical practice for the management of patients with breast cancer.

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Prognostic Biomarkers

Multiplex panels:

- 21-gene RS, 70-gene MammaPrint, BCI, 50 gene Prosigna, 12-gene Endopredict
- All identify breast cancers that have low recurrence risk in absence of chemotherapy
- Recurrence risk for low scores:

OncotypeDx:	~10% at 10 years for N0
	~10% for N1-3
MammaPrint:	~11% at 8 years
Prosigna:	~3.5% at 10 years for N0/N1-3
EndoPredict:	~4-5.6% at 10y for N0/N1-3
BCI	

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NCCN: 21-gene recurrence score (OncotypeDx)

Menopausal status	Node Status	RS	Treatment Implications
Post	0-3 LN	<26	• ET only, no benefit from chemotherapy[1,2] • T1b-2 N0 with RS 0-10 have DDFS >96%[1]
		≥26	• Chemo plus ET recommended[1,2]
Pre	pN0	≤15	• ET only, no benefit from chemotherapy[1]
		16-25	• Small benefit to addition of chemotherapy[1] • Ovarian function suppression could be considered in lieu of chemo
		≥26	• Chemo plus ET recommended[1]
	1-3 LN	<26	• Chemo plus ET recommended[2] • Ovarian function suppression could be considered in lieu of chemo
		≥26	• Chemo plus ET recommended[2]

- 21-gene RS: NCCN Breast Panel considers the assay both predictive and prognostic regarding benefit of chemotherapy and is preferred for early stage ER+/Her2- BC
- Evidence is Category 1, except for the opinion that OFS could be considered in lieu of chemo (NCCN Category 2A)
- Only ~10% in RxPONDER had G3 or 3 LN+

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1Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. NEJM 2018; 379: 111-121.
2Kalinsky K, Barlow WE, Gralow JR, et al. 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. NEJM 2021; 285: 2336-2347.

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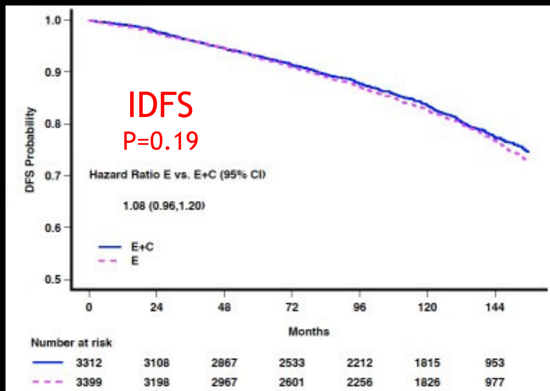
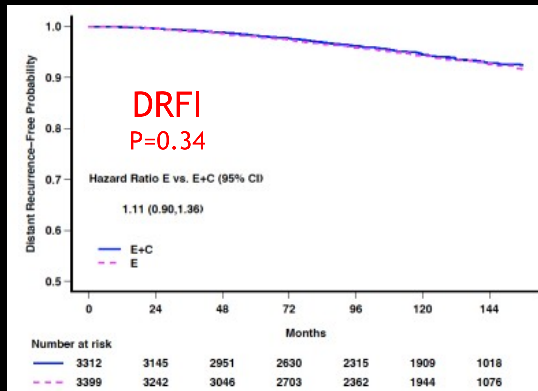
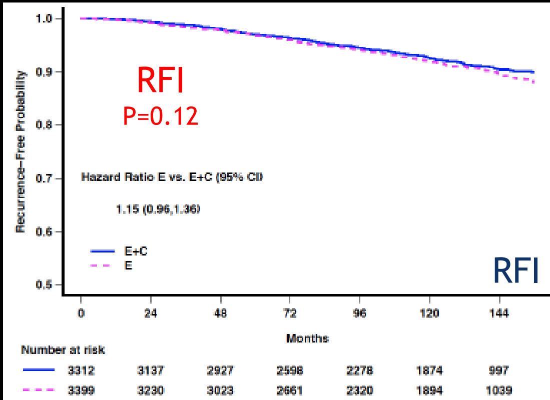
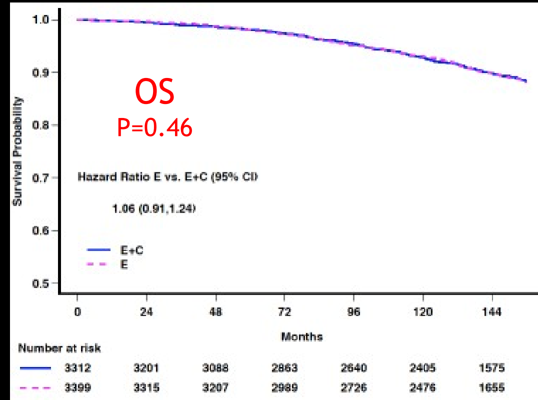
San Antonio Breast Cancer Symposium – December 6-10, 2022

TAILORx: Updated Analysis - Kaplan-Meier Curves in RS 11-25 Arms (ITT population)









Primary trial conclusions unchanged: ET non-inferior to CET (N=6711)

Event	Hazard Ratio: Arm B vs. C (95% CI)
IDFS	Primary analysis: 1.08 (0.94, 1.24, p=0.26)
	Updated analysis: 1.08 (0.96, 1.20)
DRFI	Primary analysis: 1.10 (0.85,1.41, p=0.48)
	Updated analysis: 1.11 (0.90, 1.36)
RFI	Primary analysis: 1.11 (0.90, 1.37, p=0.33)
	Updated analysis: 1.15 (0.96, 1.36)
OS	Primary analysis: 0.99 (0.79, 1.22, p=0.89)
	Updated analysis: 1.06 (0.91, 1.24)

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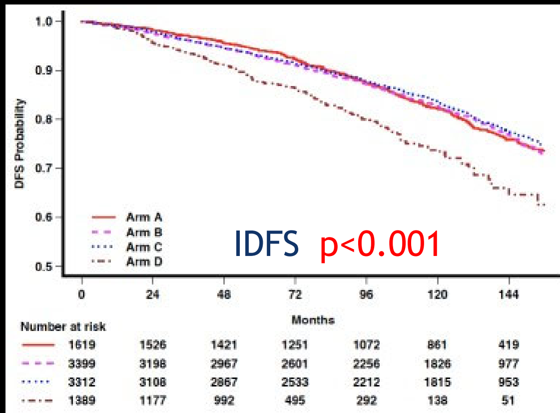
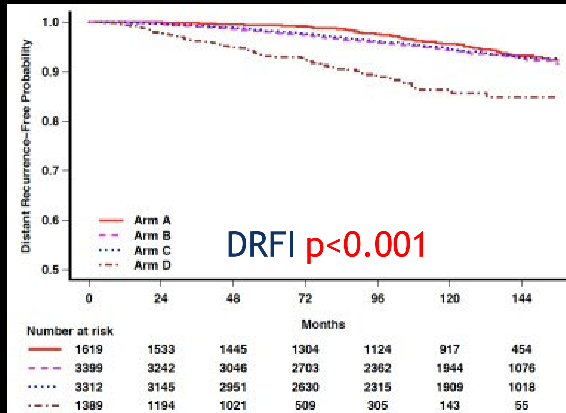
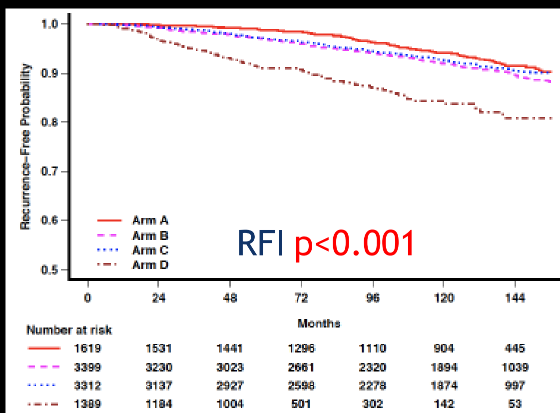
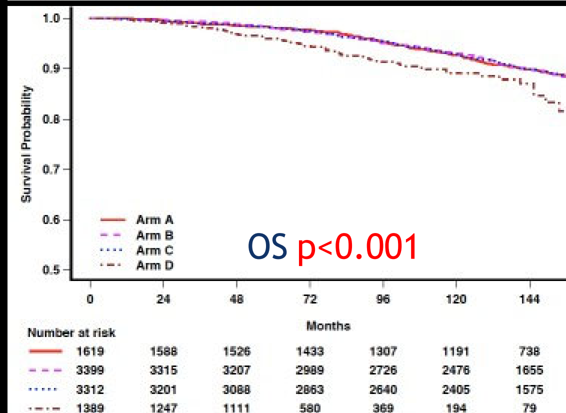
San Antonio Breast Cancer Symposium – December 6-10, 2022

TAILORx: Updated Analysis- Kaplan-Meier Curves in All Arms (ITT population)









12-Year Event Rates (N=9719)

- **RS prognostic for all endpoints**
- **RS 0-10 (Arm A) – ET Alone**
  - DFRI rate: 93.2% (SE 0.8)
  - RFI rate: 91.4% (SE 0.9)
- **RS 11-25 (Arms B & C) – ET vs. CET**
  - < 1 % difference for all endpoints
    - IDFS: 76.8 vs. 77.4%
    - DRFI: 92.6 vs. 92.8%
    - RFI: 89.6 vs. 90.4%
    - OS: 89.8 vs. 89.8%
- **RS 26-100 (Arm D) – CET**
  - DFRI rate: 84.8% (SE 1.8)
  - RFI rate: 80.9 (SE 2.2)

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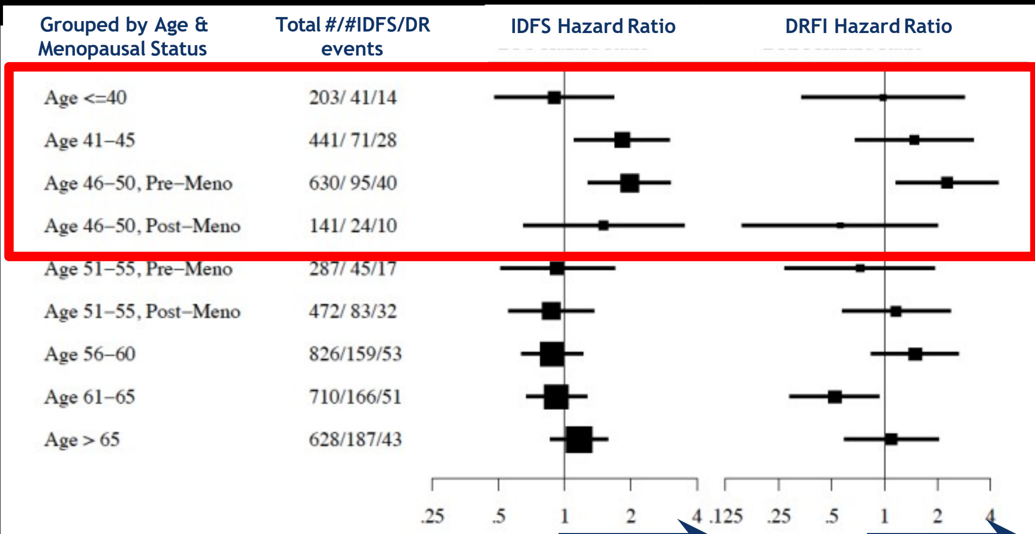
TAILORx: Updated Analysis - Effect of Age, RS, and Clinical Risk on Chemotherapy Benefit (ITT Population)



Chemo better

Chemo better

3-way treatment interaction test

- IDFS
  - Chemo-Age-RS (p=0.007)
  - Chemo-Menopause-RS (p=0.06)
- DRFI
  - Chemo-Age-RS (p=0.43)
  - Chemo-Menopause-RS (p=0.26)

12-Year DRFI Rates in Age ≤ 50 Years & RS 16-25

	Estimated Absolute Chemo Benefit Not Stratified by Clinical Risk	Clinical Risk	No.	Estimated Absolute Chemo Benefit Stratified by Clinical Risk
RS 16-20 (N=886)	Δ +0.4% (±SE 2.1%)	Low	671 (76%)	Δ -0.5% (±SE 2.2%)
		High	215 (24%)	Δ +3.1% (±SE 5.4%)
RS 21-25 (N=476)	Δ +7.8% (+SE 3.4%)	Low	319 (67%)	Δ +5.9% (±SE 3.4%)
		High	157 (33%)	Δ +11.7% (±SE 7.2%)

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NCCN: 70-gene assay (MammaPrint): MINDACT

Pt pop	Clinical/Genomic Risk	CT (% 8y DDFS)	No CT (% 8y DDFS)	Therapeutic Implications
All (1497) (139 ER-)	High/Low	92.0	89.4	HR 0.66 (0.48-0.92) CT still has impact
HR+ <50y (464)	High/Low	93.6	88.6	
HR+ >50 y (894)	High/Low	90.2	90.0	
HR+ N0 (699)	High/Low	91.7	89.2	
HR+ 1-3 LN (658)	High/Low	91.2	89.9	

- 70-gene RS: NCCN Breast Panel considers the assay prognostic
- Evidence is Category 1, however genomic low risk/clinical high risk still benefitted from chemotherapy; 8y DDFS <90%
- Genomic high risk/clinical low risk had no benefit from chemotherapy – i.e., assay not predictive
- Retrospective analysis revealed an "ultra-low risk" group in both the Stockholm Tamoxifen trial (20 year BC specific survival of 97%), and the MINDACT trial (8y BCSS >99%)

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1Cardoso R, van't Veer LJ, Bogaerts J, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. NEJM 2016; 375: 717-729.
2Piccart M, van't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer. Updated results of the phase 3 randomized MINDACT trial with an exploratory analysis by age. Lancet Oncol 2021; 22: 476-488.
3Lopes Cardozo JMN, Drukker CA, Rutgers EJT, et al. Outcome of patients with an ultralow-risk 70-gene signature in the MINDACT trial. J Clin Oncol 2022; 40: 1335-1345.

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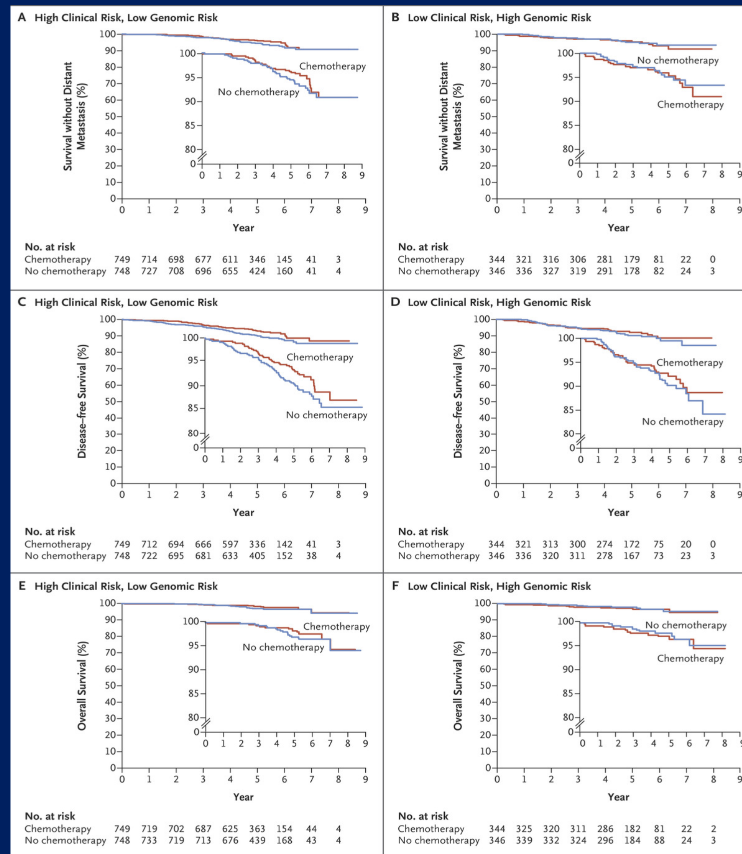
Survival without Distant Metastasis, Disease-free Survival, and Overall Survival in the Two Discordant-Risk Groups, According to Randomized Treatment

High Clinical/Low Genomic



Low Clinical/High Genomic

Cardoso F et al. N Engl J Med 2016;375:717-729.

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NCCN: 50-gene assay (Prosigna)(PAM50)

Pt pop	Score	ET only	Therapeutic Implications
T1-2 N0 ER+/Her2-	0-40 (Low ROR)	96.5% 10y DFS	Danish Cohort[1]
T1-2 N0 ER+/Her2-	60-100 (High ROR)	77.9% 10y DFS	
1-3 LN+ ER+/Her2-	0-40 (Low ROR)	96.5% 10y DFS	TransATAC trial[2]
1-3 LN+ ER+/Her2-	40-100 (High ROR)	77.9% 10y DFS	

- 50-gene RS: NCCN Breast Panel considers the assay prognostic
- NCCN Category 2A
- Unproven uses:
  - ER 1-9% (differentiate between luminal and basal tumors)
  - Her2+/- (differentiate between Her2-enriched and luminal) (EGF30008 letrozole +/- lapatinib)
  - Caveat: intrinsic subtype may change across therapy

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1Laerkholm AV, Jensen MB, Eriksen JO, et al. PAM50 risk of recurrence score predicts 10-year distant recurrence in a comprehensive Danish cohort of postmenopausal women allocated to 5 years of endocrine therapy for hormone receptor-positive early breast cancer. J Clin Oncol 2018; 36: 735-740.
2Sestak I, Buus R, Cuzick J, et al. Comparison of the performance of 6 prognostic signatures for ER+ BC: a secondary analysis of a randomized clinical trial. JAMA Oncol 2018; 4: 545-553.

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12-gene assay (EndoPredict)

Pt pop	Score	ET only	Therapeutic Implications
T1-2 N0 ER+/Her2-	Low (≤3.3)	>95%	ABCSG 6/8
T1-2 N0 ER+/Her2-	High (>3.3)		
1-3 LN+ ER+/Her2-	Low (≤3.3)	94.4% 10y DFS	TransATAC trial[2]
1-3 LN+ ER+/Her2-	High (>3.3)		

- 12-gene ROR: NCCN Breast Panel considers the assay prognostic
- NCCN Category 2A

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1Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, Her2-negative breast cancer adds independent information to conventional clinical risk factors. Clin Cancer Res 2011; 17: 6012-6020.
2Sestak I, Martin M, Dubsky P, et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. Breast Cancer Res Treat 2019; 176: 377-386.

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NCCN: Breast Cancer Index (BCI)

BCI (H/I) Low:
- T1-2 N0 ER+ have similar prognosis to T1a/T1b treated with endocrine therapy alone
- These patients have low late recurrence, and do not appear to benefit from extended endocrine therapy

BCI (H/I) High:
- T1 N0 ER+ have higher rates of late distant recurrence (years 5-10)
- T1-T3 ER+ appear to benefit from extended ET (MA.17, Trans-aTTom, IDEAL)

- NCCN Category 2A

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1Noordhoek I, Treuner K, Putter H, et al. Breast cancer index predicts extended endocrine benefit to individualize selection of patients with HR(+) early-stage breast cancer for 10 years of endocrine therapy. Clin Cancer Re 2021; 27: 311-319.
2Sgroi DC, Carney E, Zamella E, et al. Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17FR biomarker. JNCI 2013; 105;: 1036-1042.

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Biomarkers for Extended Endocrine Therapy

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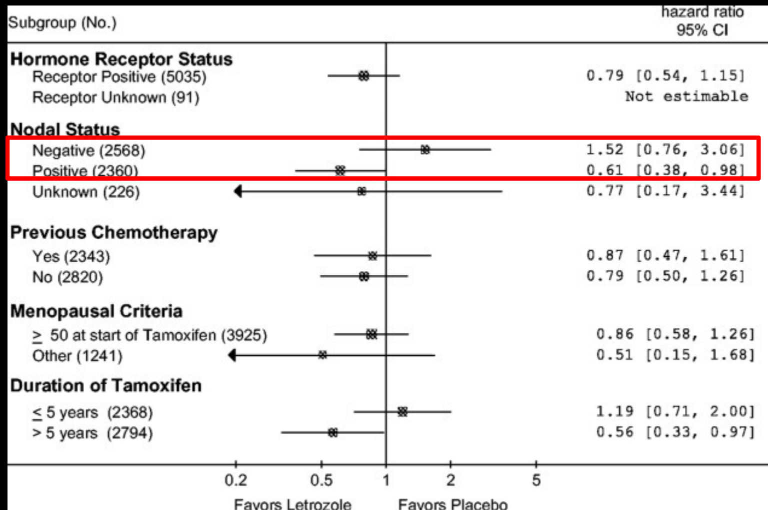
Post-tamoxifen AI: Who is at risk?

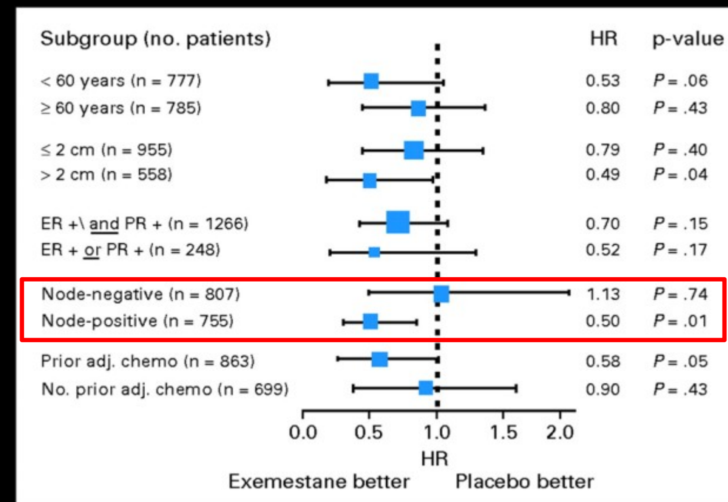
MA.17
OS (n = 5137)

4y BCFI 94.4% (letrozole); 89.8% (placebo)
LN+: OS better with letrozole (HR 0.61; p 0.04
Goss et al. JNCI 2005



NSABP-B33
DFS (n = 1598)

- Unblinded early with crossover
- 4y DFS: 91% (exemestane); 89% (placebo), HR 0.68, p = 0.07
- 4y BCFI: 96% (exe); 94% (plac), HR 0.44, p = 0.004
- Mamounas et al. JCO 2008



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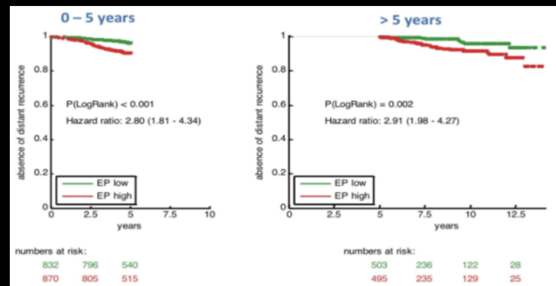
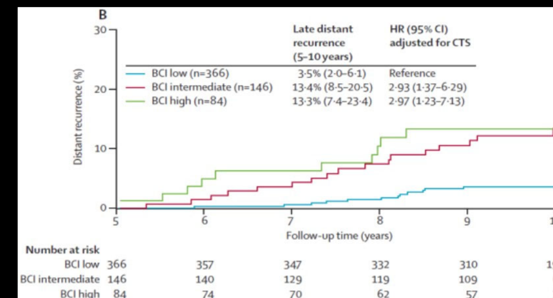
Gene Expression Profiles Predict Risk of Late Recurrence in ER+/HER2- Breast Cancer

8-Gene Assay (EP)



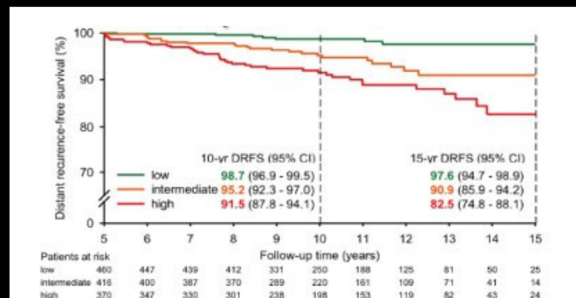
Dubsky et al. Br J Cancer 2013

Breast Cancer Index



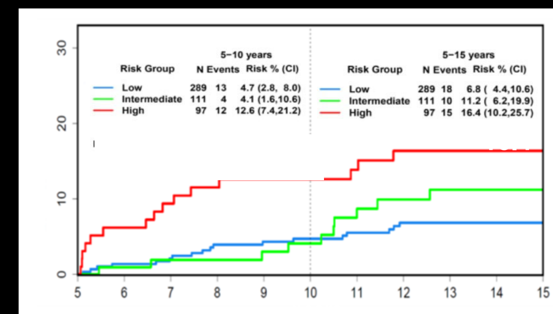
Sgroi D, et al: Lancet Oncol, 2013

PAM-50 ROR



Filipits M, et al. *Clin Cancer Res.* 2014

21-Gene RS



Wolmark N, et al: J Clin Oncol, 2016

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NSABP B-42: Significant extended ET benefit in patients with MammaPrint Low (non-UltraLow) Risk tumors

NSABP B42: 5-year endocrine therapy followed by randomization 5-year Letrozole versus placebo
10 years endocrine versus 5 years

Endpoint	MP Risk Group	Letrozole: 10-yr event rate (%)	Placebo: 10-yr event rate (%)	Abs. benefit (%)	HR (95%CI)	p	P interaction
DR (R to distant recurrence)	UltraLow	2.9	5.8	3.0	0.53 (0.13,2.15)	0.37	0.69
	Low (non-UL)	3.6	7.6	4.0	0.42 (0.23,0.76)	0.003	
	High	4.9	7.3	2.4	0.65 (0.34,1.24)	0.19	
BCFI (R to BC recurrence or CBC)	UltraLow	7.3	11.4	4.1	0.67 (0.28,1.65)	0.38	0.02
	Low (non-UL)	8.7	16.6	7.9	0.48 (0.32,0.73)	<0.001	
	High	14.6	11.6	-3.0	1.15 (0.74,1.79)	0.53	
DFS	Low (non-UL)	21.1	30.6	9.5	0.64 (0.49,0.83)	<0.001	0.042

Evaluated in a translational cohort (N=1866): UltraLow (N=252), Low (non-UL; N=908), and High Risk (N=706); DFS UltraLow and High not shown

Rastogi et al; ASCO 2021 Abstract #502

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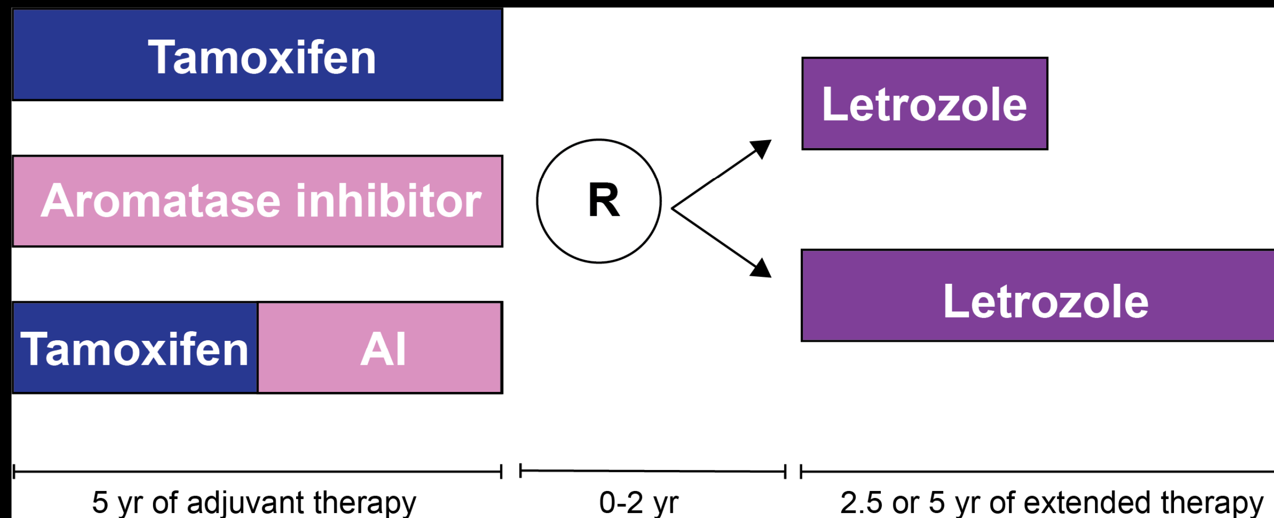
IDEAL Trial

Liefers et al: GS5-10



- Prospective, randomized, open-label phase-III trial
- Postmenopausal patients with HR+, early-stage (I-IIIa) breast cancer
- Initial 5 years of adjuvant ET completed within 2 years before randomization
- Tested: Extended Endocrine Therapy 5 years versus 2.5 years

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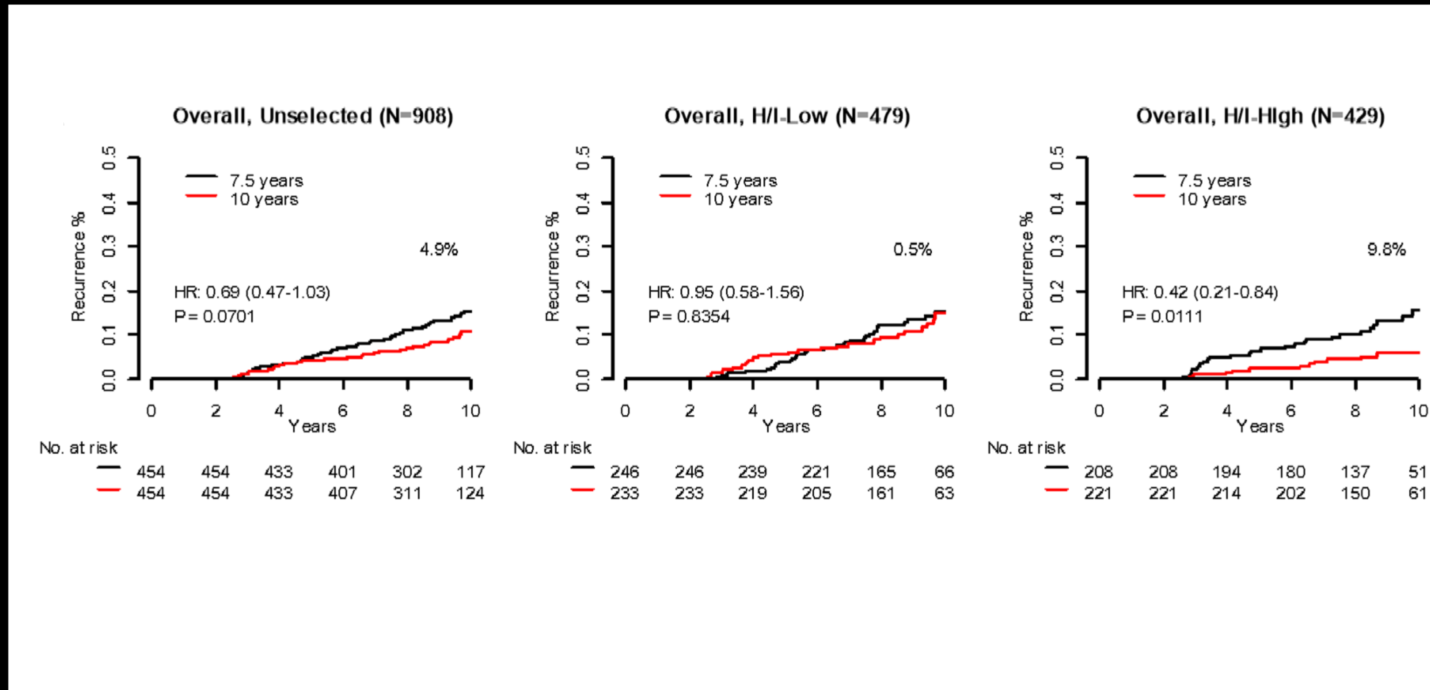
IDEAL Trial: Benefit of Extended AI Therapy by BCI (H/I) (n=908)



Noordhoek I, et al Clin Cancer Res 2021

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IDEAL: MammaPrint Low Risk (non-UltraLow) tumors derive the most EET benefit for all endpoints

MammaPrint Result	EndPoint	10-yr Outcome 2.5 y EET (%)	10-yr Outcome 5y EET (%)	Absolute Benefit (%)	HR (95% CI)	p	p interaction	Relative Benefit (%)
High Risk (n=259)	DR	90.0	90.9	Δ 0.9	0.88 (0.40-1.99)	0.758	Ref	none
	RFI	90.1	86.5	Δ -3.6	1.28 (0.62-2.67)	0.505	Ref	none
	BCFI	87.0	84.8	Δ -2.2	1.10 (0.57-2.14)	0.777	Ref	none
Low Risk (non-UltraLow; n=223)	DR	85.2	→ 95.3	Δ 10.1	0.32 (0.12-0.87)	0.025	0.120	68
	RFI	81.5	→ 93.2	Δ 11.7	0.35 (0.15-0.82)	0.016	0.024	63
	BCFI	80.6	→ 90.3	Δ 9.7	0.48 (0.225-1.02)	0.055	0.103	52
Ultralow (n=23)	n/a							

(p interaction Low Risk (non-UltraLow) & High Risk)

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What Are the Current Guidelines? ASCO

Patient Population	Recommendation
N0, NED After 5 Years of ET	Insufficient Evidence to Use OncotypeDX, EndoPredict, Prosigna, ki67 or IHC4 scores to guide decision about EET
N0 or N1 (1-3+) NED After 5 Years of ET	The clinician may offer BCI test to guide decisions about EET
≥ 4 + nodes, NED After 5 Years of ET	Insufficient evidence to use BCI test to guide decisions about EET
Postmenopausal, NED After 5 Years of ET	The clinical treatment score post 5 years (CTS5) can be used to estimate risk of Late Recurrence, which could assist with decisions on EET

Andre F et al; J Clin Oncol 2022

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What Are the Current Guidelines? NCCN

Patient Population	Recommendation
HR+, T1–T2, pN0	BCI (H/I) Low (0-5) places the patient in the same low risk category for late recurrence as T1a,bN0M0 and no benefit in DFS or OS has been shown with EET in BCI (H/I) low patients
HR+, T1–T3, pN0 or pN1	BCI (H/I) High (5.1-10) confers higher risk for late recurrence and benefit from EET in MA.17, Trans-aTTom and IDEAL Trials

Accessed on 12/3/22

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My take:

Benefit of extended ET is largely confined to those patients with high enough residual risk at 5 years who have endocrine-driven tumors

BCI or MammaPrint may provide additional information for patients/physicians struggling with this decision

Additional questions:

1. Would some patients benefit from >10 years of ET, e.g., EBCCTG data?
2. Do women who remain premenopausal at 5 years benefit from OFS during extended endocrine therapy?
3. Will patients who receive adjuvant cdk4/6 inhibitors benefit from extended endocrine therapy?
4. Will ctDNA monitoring be useful?

Modified

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Other Molecular Markers

Germline BRCA 1/2: If the patient is a candidate for Olaparib in the adjuvant setting

- Adjuvant chemotherapy:
  - TNBC T2N0 or N1 or greater
  - ER+ 4+ nodes
- Neoadjuvant chemotherapy:
  - TNBC any residual disease
  - ER+ residual invasive disease and CPS&EG score $\geq$3 (grade, AJCC stage both pre-treatment clinical stage and stage after neoadjuvant chemotherapy)

Germline BRCA1/2: if the patient is a candidate for genetic screening

PD-L1 (CPS): not needed for KN522 candidates, although might be useful in T2N0 (borderline candidates) as pathologic response is enhanced in that group; may be needed in the ER+ space

PIK3CA mutations: most of these are in the primary cancer; but are not needed for therapeutic decisions.

ESR1, HER2 and other mutations are typically acquired, and not detected in primary disease

Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for patients with BRCA1- or BRCA2- mutated breast cancer. NEJM 2021; 384: 2394-2405.
Geyer CE, Garber JE, Gelber RD, et al. Overall survival in the OlympiA phase III trial of adjuvant Olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. Ann Oncol 2022; 33: 1250-1268.

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ctDNA to assess risk of recurrence

At diagnosis (prognostic)

After surgery (prognostic)

After neoadjuvant therapy (prognostic)

- Merely lead time bias? Picks up disease recurrence ~9-11m prior to clinical relapse
- Does finding early MRD result in effective treatment?
  - *Change tamoxifen to letrozole (MA17)*
  - *ESR1m post AI exposure (oral SERDs as a potential treatment)*
  - *Her2m acquired in both Her2+ and Her2- metastatic disease*
  - *AKT1 and PIK3CA mutations might be actionable if acquired and detectable*

Risks

- Potential CHIP related mutations, unless specific to the tumor tissue
- Cost
- Very high screening ratios

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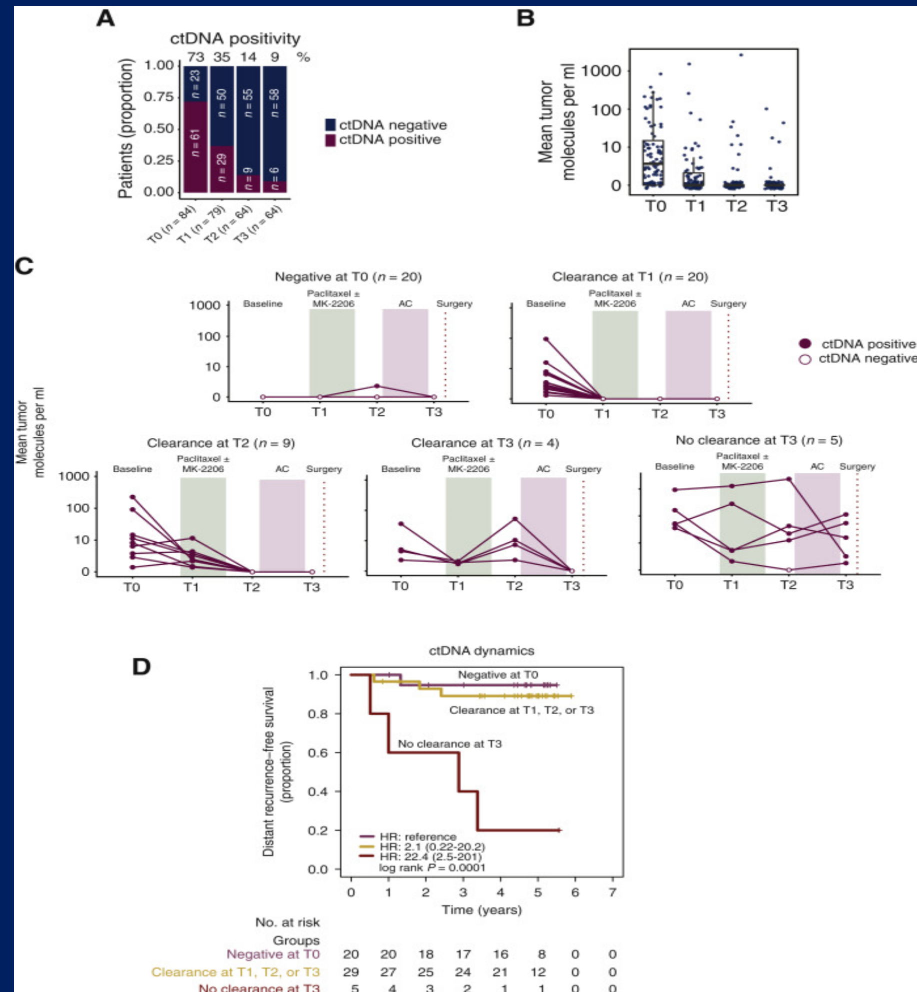
Should we accept "tumor-informed" ctDNA to monitor preoperative therapy?

I-SPY2 standard NAC +/- MK-2206

- Failure to clear preop ctDNA associated with high RCB and increased relapse (HR 10.4)
- Clearance associated with excellent DFS, even if not pCR
- Magbanua MJM, et al. Ann Oncol 2021; 32: 229-239

Papakonstantinou A, et al. Prognostic value of ctDNA detection in patients with early BC undergoing NACT: A systematic review and meta-analysis. Cancer Treat Rev 2022; 104: 102352.



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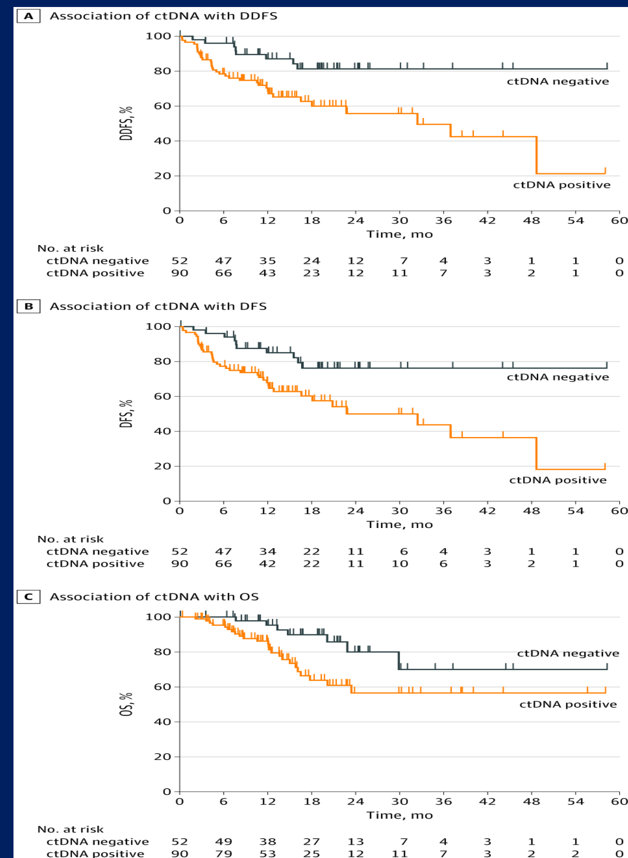
Association of Circulating Tumor DNA and Circulating Tumor Cells After Neoadjuvant Chemotherapy With Disease Recurrence in Patients With Triple-Negative Breast Cancer: Preplanned Secondary Analysis of the BRE12-158 Randomized Clinical Trial

JAMA Oncol. 2020;6(9):1410-1415. doi:10.1001/jamaoncol.2020.2295

A: median DDFS (32.5 months vs not reached; hazard ratio [HR], 2.99; 95% CI, 1.38-6.48; P = .006).

B: median DFS: (22.8 months vs not reached; HR, 2.67; 95% CI, 1.28-5.57; P = .009).

C: median OS (not reached vs not reached; HR, 4.16; 95% CI, 1.66-10.42; P = .002).



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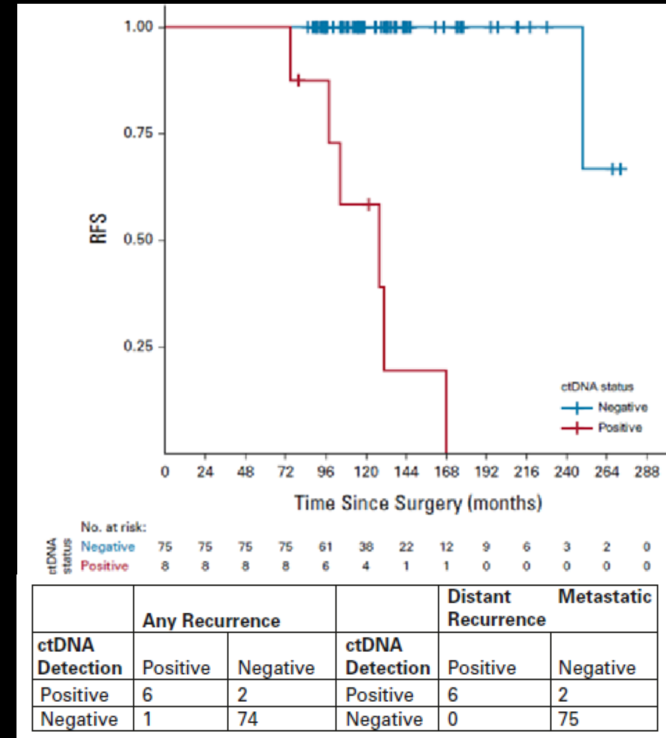
San Antonio Breast Cancer Symposium – December 6-10, 2022

ctDNA For Prediction of Late Recurrence

- **103 pts with high-risk stage II-III HR+ BC NED >5 years**
- Whole-exome sequencing (WES) on primary tumor
- Plasma at consent and every 6-12 months
- 83 of 103 patients had successful WES
- Median F/U 10.4y from diagnosis and 2.0y from first sample
- **10%** of patients had **positive MRD testing** at any time
- **Six patients (7.2%) developed distant mets**
  - **all were MRD-positive before overt clinical recurrence**
  - **median ctDNA lead time of 12.4 months**
- MRD not identified in one patient (1.2%) with local recurrence



	Any Recurrence	
ctDNA Detection	Positive	Negative
Positive	6	2
Negative	1	74

	Distant Recurrence	Metastatic
ctDNA Detection	Positive	Negative
Positive	6	2
Negative	0	75

Lipsyc-Sharf M, et al: J Clin Oncol, 2022

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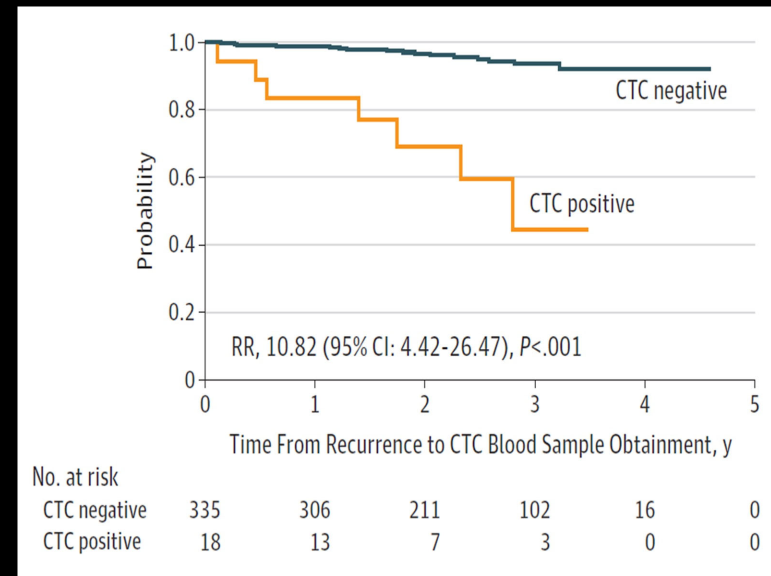
Circulating Tumor Cells (CTCs) and Late Recurrence

- ECOG 5103 (Adjuvant Chemo +/- Bevacizumab)
- CTCs obtained ~5 years after diagnosis
- 547 women included in this analysis
- CTC assay was positive in 5.1% of pts with ER+ disease
- 6.5% of pts had clinical recurrence
- Positive CTC assay associated with a 13.1-fold higher risk of recurrence (95% CI, 4.7-36.3)
- 30.4% of pts with recurrence had a positive CTC assay at a median of 2.8 years (range, 0.1-2.8 years) before clinical recurrence



Sparano J, et al: JAMA Ondol 2018

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Biomarkers in Early Stage BC: Summary

Prognosis vs Prediction in Adjuvant Therapy:

- 21-gene RS: Identifies value of chemotherapy for patients with ER+ BC N0/LN+ 1-3
- 70-gene assay does not: benefit from chemo related to clinical risk score rather than genomic risk score in MINDACT trial
- Multiple assays identify low risk populations who may not require chemotherapy

Extended endocrine therapy:

- BCI (H/I) High: higher late recurrences; potential benefit from extended ET
- 70-gene assay Low (not UL): sufficient relapses; potential benefit from extended ET
- However, most benefit of extended ET is in N+ BC

Germline BRCA mutations: Adjuvant PARP inhibitor (Olaparib)

Other mutations not actionable

ctDNA not quite ready for implementation, but has enormous potential

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Who We Are

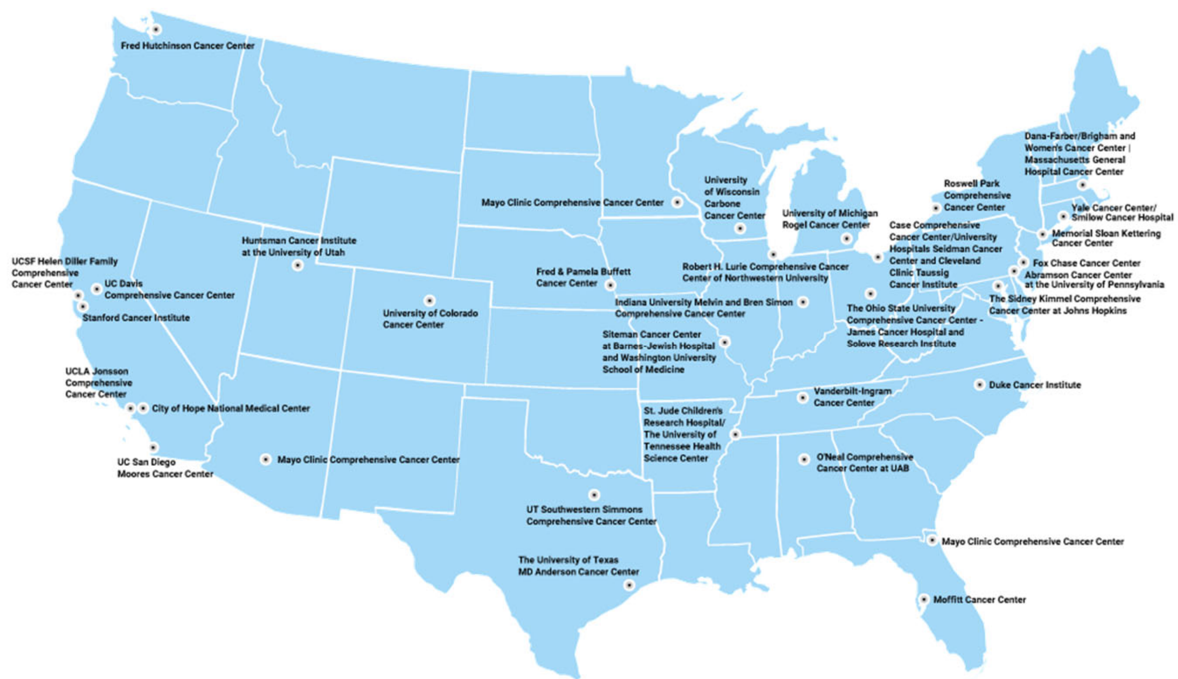
An alliance of leading cancer centers devoted to patient care, research, and education

Our Mission

To improve and facilitate quality, effective, equitable, and accessible cancer care so all patients can live better lives

Our Vision

To define and advance high-quality, high-value, patient-centered cancer care globally



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Multigene and Biomarker Testing in Breast Cancer: What is the Role?

Metastatic Breast Cancer

Harold J. Burstein, MD, PhD
Dana-Farber/Brigham and Women's Cancer Center | Massachusetts General Hospital Cancer Center

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Two related but slightly different dialogues:

- Should we get genomic sequencing on all cancers to characterize the tumor and chart evolution?
- Which biomarkers have therapeutic significance in advanced breast cancer?

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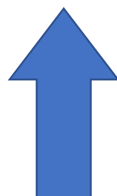
Convergence:

- Should we get genomic sequencing on all cancers to characterize the tumor and chart evolution? MORE RATIONALE FOR HERE



GROWING NUMBER HERE

- Which biomarkers have therapeutic significance in advanced breast cancer?

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RECURRENT/STAGE IV (M1) DISEASE

CLINICAL STAGE

Stage IV (M1) or Recurrent →

WORKUP[a]

- History and physical exam
- Discuss goals of therapy, adopt shared decision-making, and document course of care
- CBC
- Comprehensive metabolic panel, including liver function tests and alkaline phosphatase
- Imaging for systemic staging:
  - Chest diagnostic CT ± contrast
  - Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast
  - Brain MRI with contrast if suspicious CNS symptoms
  - Spine MRI with contrast if back pain or symptoms of cord compression
  - Bone scan or sodium fluoride PET/CT (category 2B)
  - Useful in certain circumstances:
    - ◊ FDG PET/CT (consider FES PET/CT for ER-positive disease)
  - X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan
- Biomarker testing:
  - Biopsy of at least first recurrence of disease (consider re-biopsy if progression)
  - Evaluation of ER/PR and HER2 status[d,fff,ggg]
  - Comprehensive germline and somatic profiling to identify candidates for additional targeted therapies,[iii] see Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-Q 6)
- Genetic counseling if patient is at risk[e] for hereditary breast cancer
- Assess for distress[g]

→ See Treatment of Local and Regional Recurrence (BINV-19) and Supportive care[hhh]

→ See Systemic Treatment of Recurrent Unresectable (local or regional) or Stage IV (M1) (BINV-20)[iii] and Supportive care[jjj]

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Histopathology

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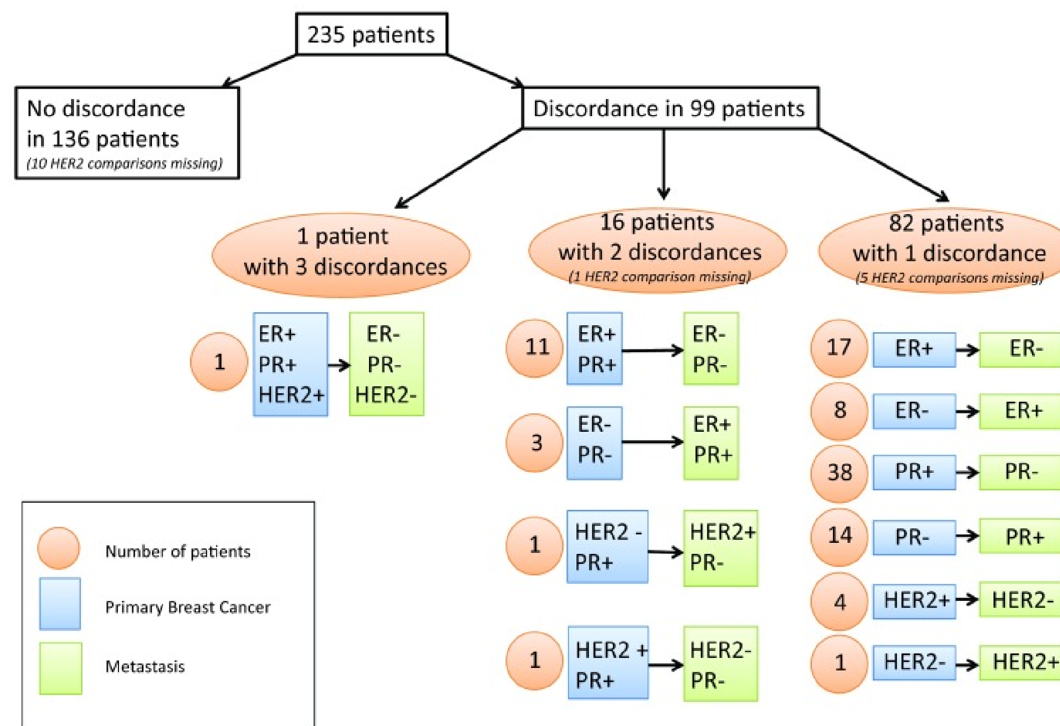
Importance of Testing Metastatic Lesions for ER/PR/HER2



Curtit E, et al. Oncologist 2013.

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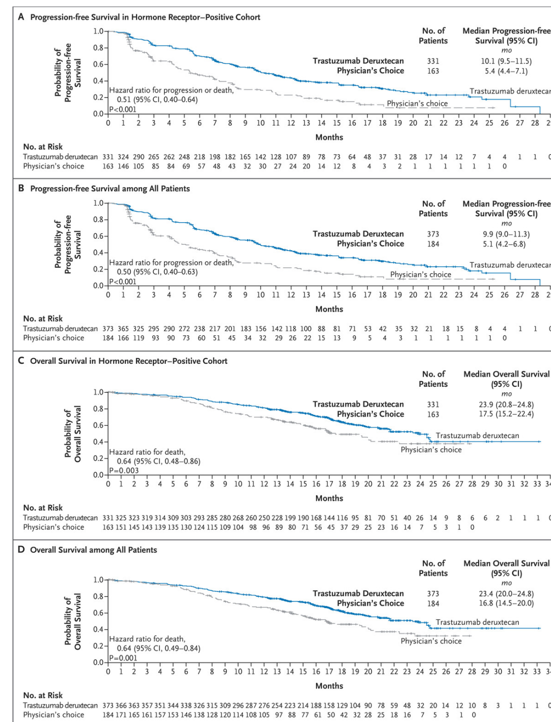
Destiny Breast-04: Trastuzumab deruxtecan vs chemotherapy in HER2 low MBC



S Modi et al. N Engl J Med 2022;387:9-20.

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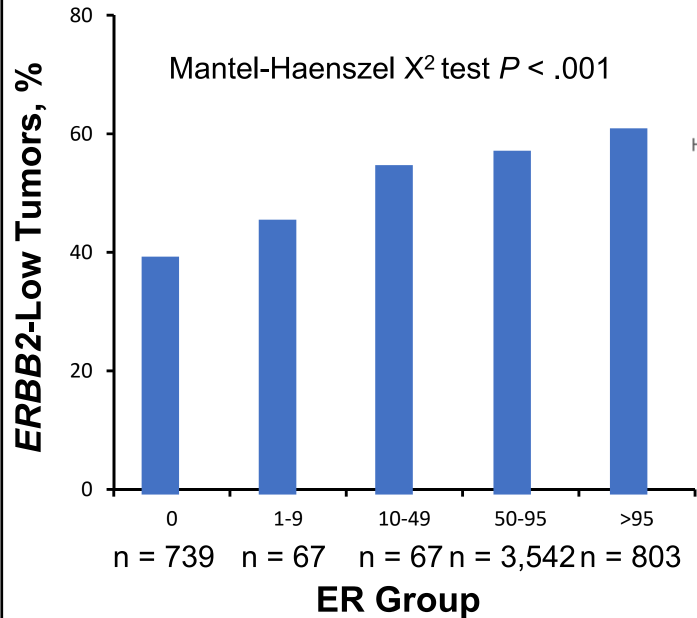
San Antonio Breast Cancer Symposium®, December 6-10, 2022

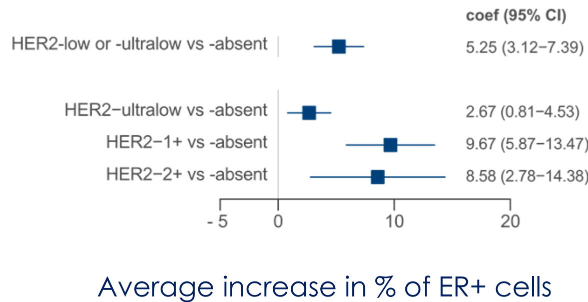
HER2-low disease increases as ER increases

Dana-Farber Cancer Institute Series



Tarantino P et al. JAMA Oncol. 2022;8:1177-1183.

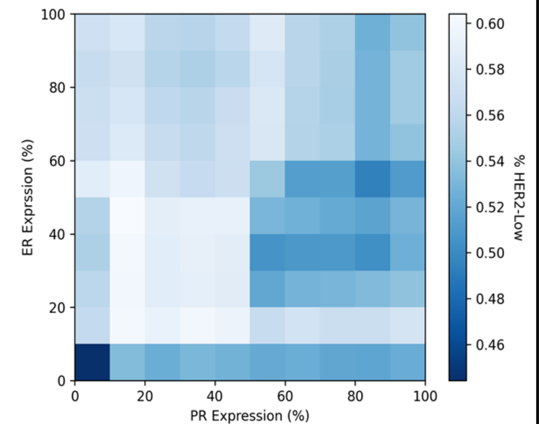
University Hospitals Leuven



Average increase in % of ER+ cells

Geukens T et al, SABCS 2022

National Cancer Data Base



Peiffer D et al, SABCS 2022

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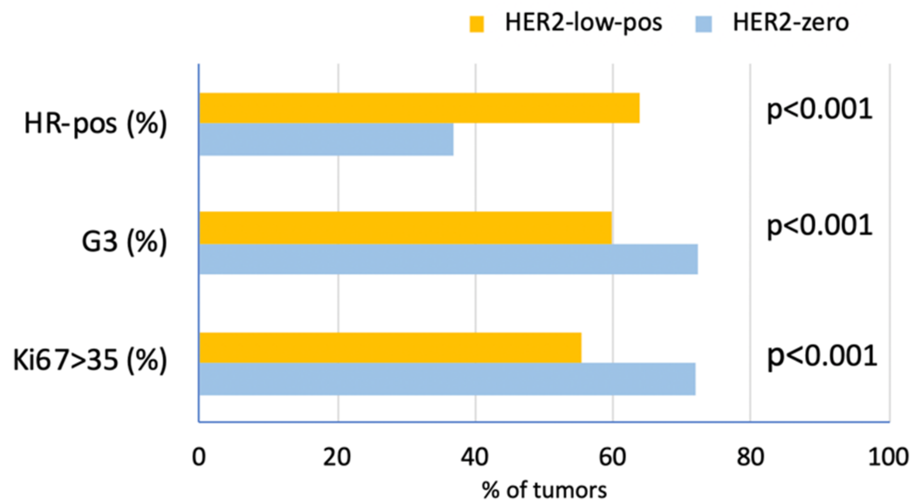
Clinical and Pathologic Differences of HER2-low tumors

Pooled Analysis of 4 GBG Trials



Denkert C et al, Lancet Oncology 2021

National Cancer Data Base

		HER2-0	HER2-Low
n		**392,246**	**743,770**
Age (%)	< 40	4.5	3.9
	40 - 59	36.7	36.3
	60 - 79	49.2	49.8
	≥ 80	9.6	10
Grade (%)	1 - 2	69	75.7
	3	31	24.3
Histology (%)	Ductal	75.5	78.9
	Lobular	12.4	11.3
	Other	12.1	9.8
Stage (%)	I - II	86.3	87.3
	III - IV	13.7	12.8
% ER Expression (mean)		70.8	82.5
% PR Expression (mean)		49.8	56.4
Ki-67 (mean)		27.6	22.8

Peiffer D et al, SABCS 202

HER2-low-positive: more HR+, fewer grade 3 tumors, lower proliferation

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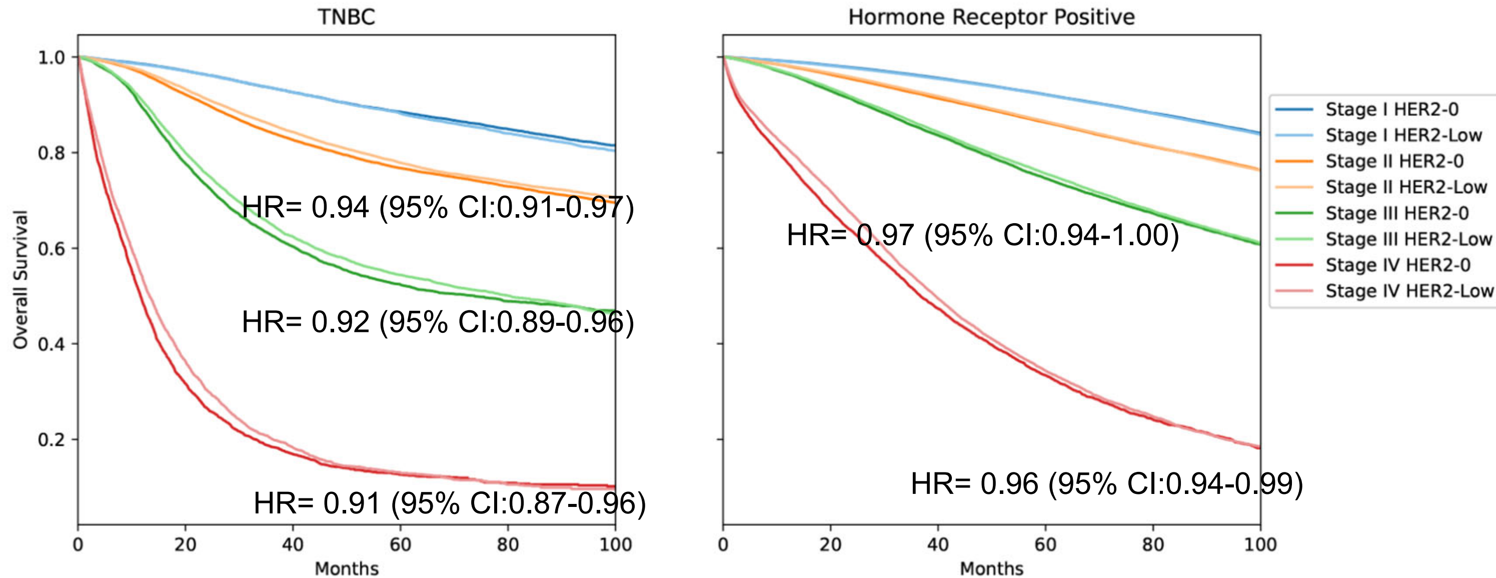
San Antonio Breast Cancer Symposium®, December 6-10, 2022

Overall Survival Outcomes: HER2-low vs HER2 0

Retrospective Cohort Study: National Cancer Data Base (2010-2019) N=1,136,016



Large Cohort With Only Potential Marginal Differences in Survival

Peiffer D et al, SABCS 2022

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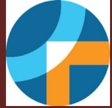
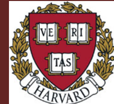


Comprehensive genomic characterization of HER2-low breast cancer

Paolo Tarantino, Hersh Gupta, Melissa E. Hughes, Janet Files, Sarah Strauss, Gregory Kirkner, Anne-Marie Feeney, Yvonne Li, Ana Garrido-Castro, Romualdo Barroso-Sousa, Brittany Bychkovsky, Laura MacConaill, Neil Lindeman, Bruce Johnson, Matthew Meyerson, Rinath Jeselsohn, Xintao Qiu, Rong Li, Henry Long, Eric Winer, Deborah Dillon, Giuseppe Curigliano, Andrew Cherniack, Sara M. Tolaney*, and Nancy U. Lin*.

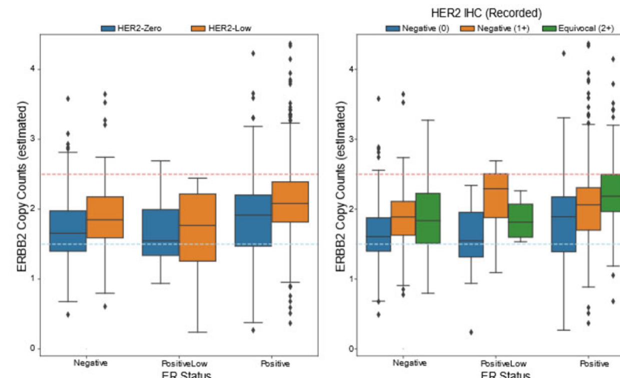
*Affiliations: Dana-Farber Cancer Institute, Boston, USA; Harvard Medical School, Boston, USA; Brigham and Women's Hospital, Boston, USA; European Institute of Oncology IRCCS, Milan, Italy; University of Milan, Italy. *contributed equally*

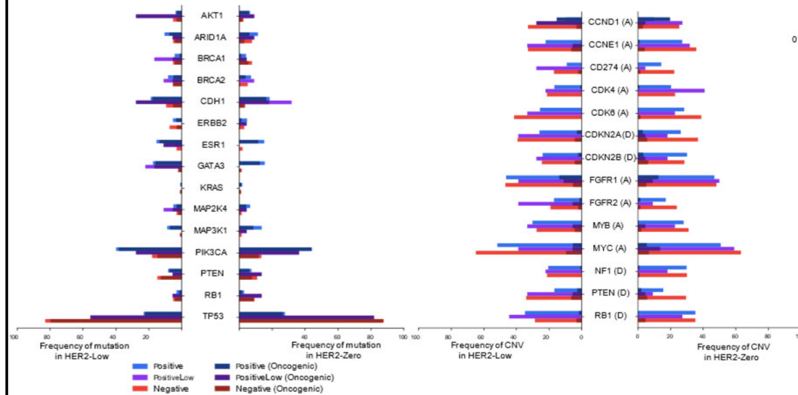


Methods: analysis of NGS (Oncopanel) findings among **1039 patients with HER2-negative MBC** seen at DFCI between 2013-2020, divided between **HER2-low** (n=487) and **HER2-0** (n=552) depending on the HER2 status on the specimen receiving NGS testing.

No significant differences in the incidence of oncogenic mutations or CNVs between HER2-low and HER2-0 tumors, after correcting the analyses for ER expression and multiple hypothesis testing.

No significant differences in TMB after correcting for ER expression. Median TMB was 7.26 (0.76-85.94) for HER2-low and 7.60 (0.00-111.36) for HER2-0, P=0.17





Higher ERBB2 copy counts were found in HER2-low cases, in concordance with measured HER2 IHC.

HER2-low included 15.0% of the samples having a single-copy deletion, 67.4% having no change, and 17.6% having an amplification, versus 30.6%, 60.5%, and 8.9% for HER2-0.

CONCLUSION

The genomic landscape of HER2-low and HER2-0 tumors did not differ significantly after correcting for ER expression, apart from a higher number of ERBB2 alleles among HER2-low tumors.

This study supports the notion that HER2-low, as currently defined, cannot be considered a distinct molecular subtype of breast cancer.

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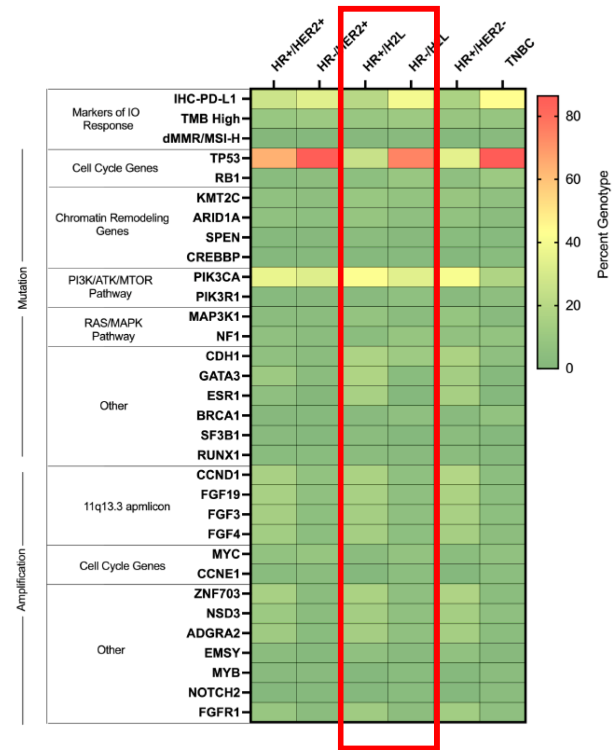
No differences in genomic characterization of HER2-low tumors

Genomics of HER2-low similar to classic subtype of HR+ or TNBC



Bansal R et al, SABCS 2022

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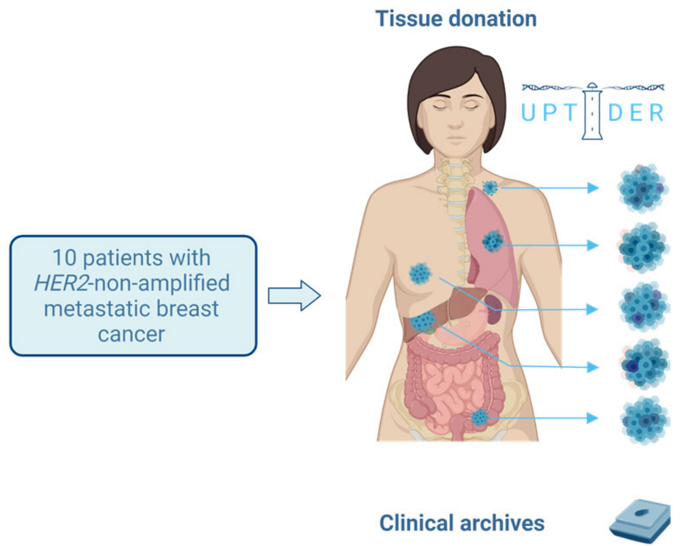
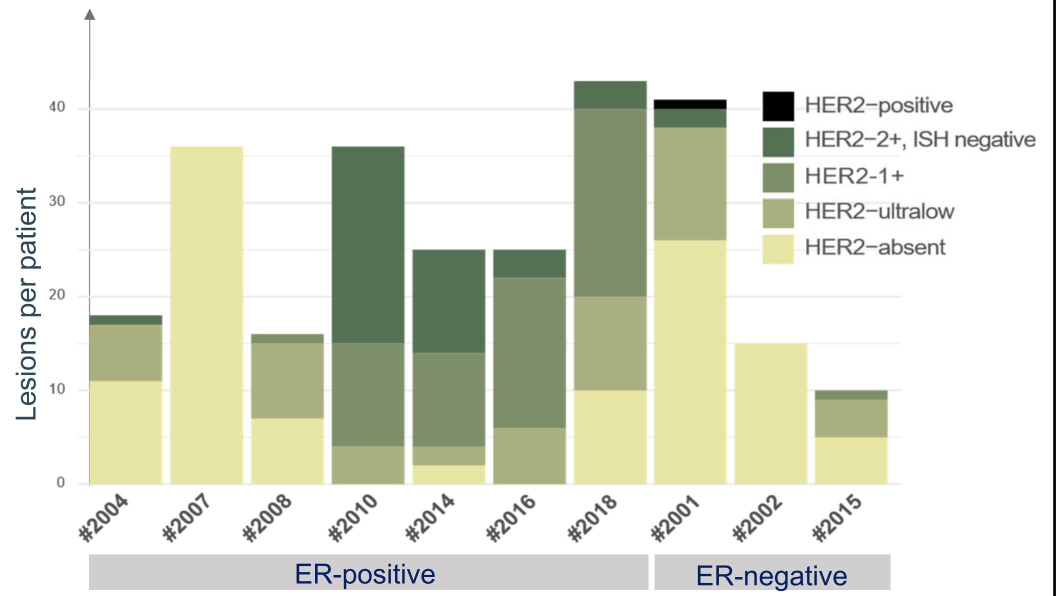
Discordance seen within a patient with tissue from different locations at the same timepoint





HER2-status of different metastases was highly variable within one patient, with HER2-low and zero lesions in 8/10 patients

Geukens T et al, SABCS 2022

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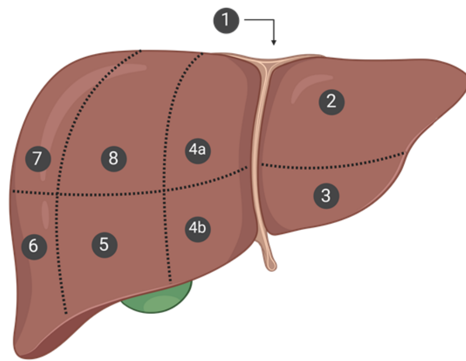
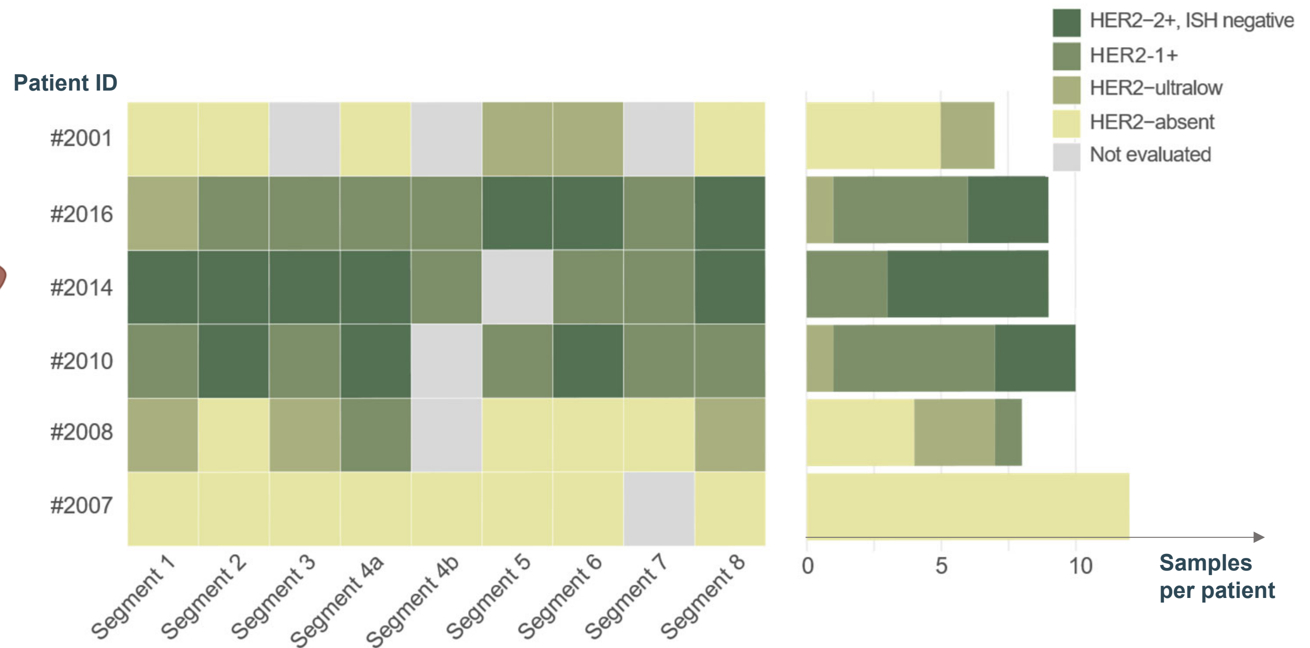
Discordance even within one organ within a patient





5 of 6 patients with heterogeneity in HER2 status from different segments of the liver

Geukens T et al, SABCS 2022

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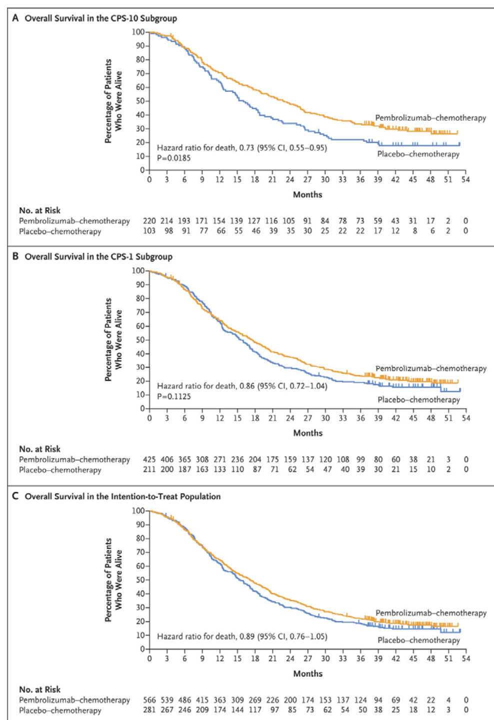
KN355: Chemotherapy +/- pembrolizumab in 1st line TNBC



Subgroup	No. of Patients	Median Overall Survival: Pembrolizumab–chemotherapy (mo)	Median Overall Survival: Placebo–chemotherapy (mo)	Hazard Ratio for Death (95% CI)
Overall	847	17.2	15.5	0.89 (0.76–1.05)
PD-L1 CPS cutoff of 1				
CPS ≥1	636	17.6	16.0	0.86 (0.72–1.04)
CPS <1	211	16.2	14.7	0.97 (0.72–1.32)
PD-L1 CPS cutoff of 10				
CPS ≥10	323	23.0	16.1	0.71 (0.54–0.93)
CPS <10	524	14.7	15.2	1.04 (0.85–1.26)
PD-L1 CPS cutoff of 20				
CPS ≥20	204	24.0	15.6	0.72 (0.51–1.01)
CPS <20	643	15.9	15.5	0.96 (0.80–1.14)

0.25 0.50 1.00 2.00 4.00

← Pembrolizumab–Chemotherapy Better | Placebo–Chemotherapy Better →

J Cortes et al. N Engl J Med 2022;387:217-226.

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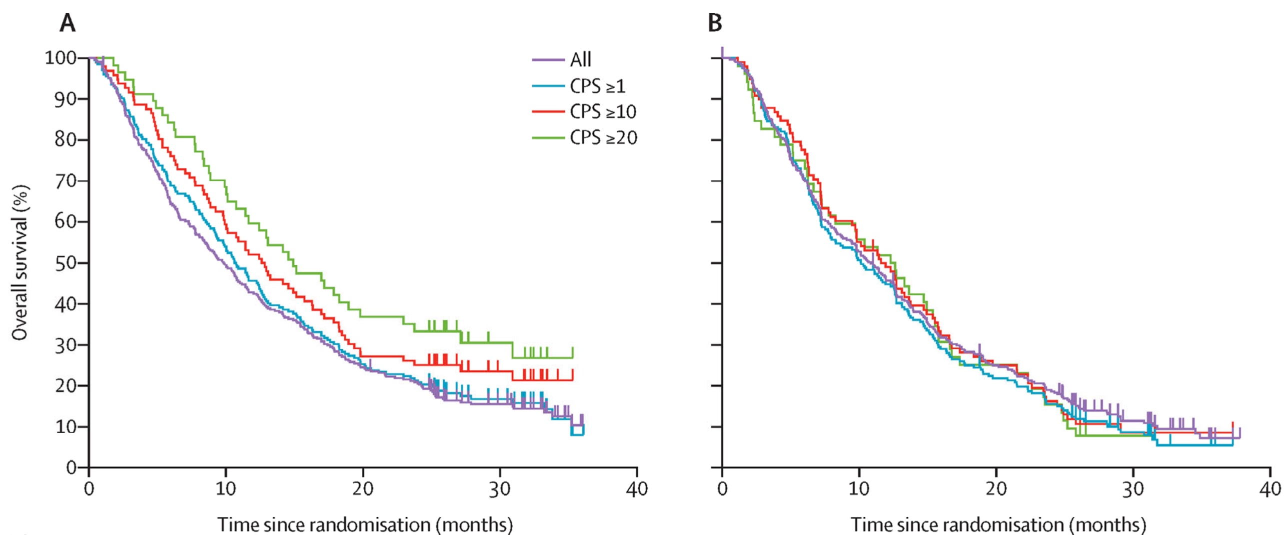
Keynote 119: Chemotherapy vs Pembrolizumab for mTNBC



Number at risk (number censored)	A: 0	A: 10	A: 20	A: 30	A: 40	B: 0	B: 10	B: 20	B: 30	B: 40
All	312 (1)	154 (1)	76 (3)	31 (41)	0 (46)	310 (1)	163 (3)	75 (7)	21 (31)	0 (37)
CPS ≥1	203 (1)	109 (1)	51 (2)	20 (30)	0 (32)	202 (1)	102 (3)	42 (4)	12 (16)	0 (19)
CPS ≥10	96 (0)	57 (0)	26 (1)	11 (21)	0 (22)	98 (0)	54 (1)	23 (2)	4 (10)	0 (11)
CPS ≥20	57 (0)	39 (0)	21 (1)	8 (16)	0 (17)	52 (0)	29 (0)	13 (0)	2 (4)	0 (4)

Winer EP, et al. Lancet Oncol 2021

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Genetic testing

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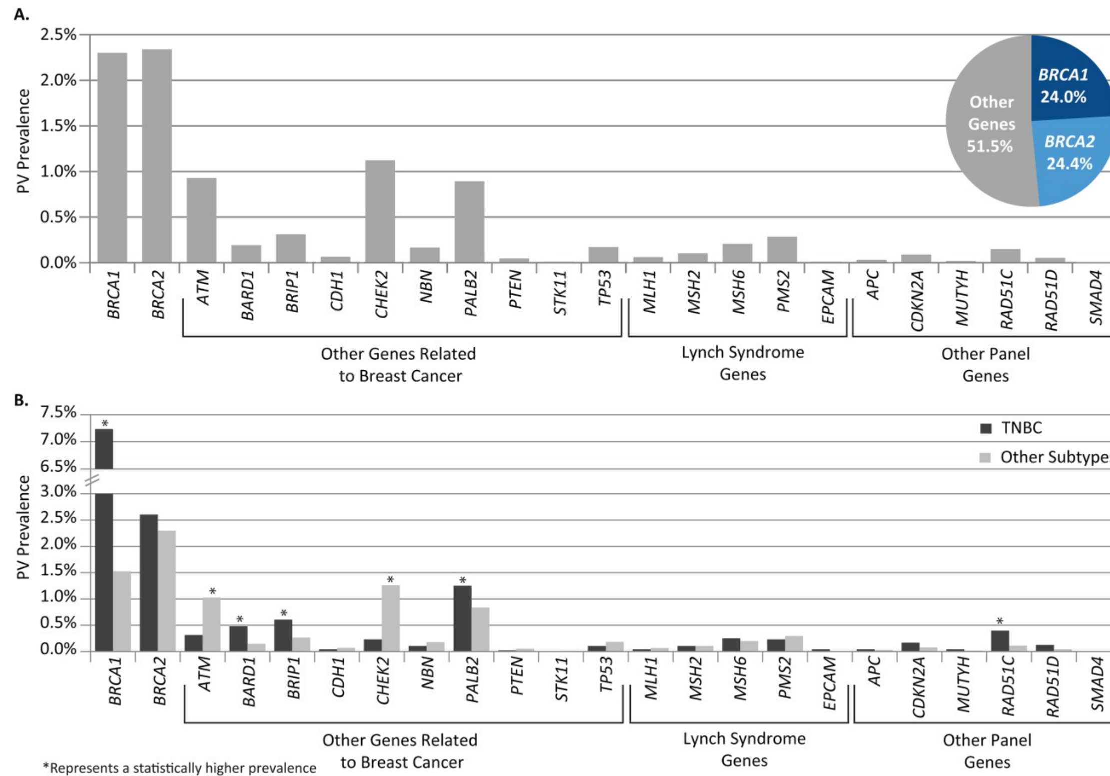
A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes



Buys, et al. Cancer, Volume: 123, Issue: 10, Pages: 1721-1730, First published: 13 January 2017, DOI: (10.1002/cncr.30498)

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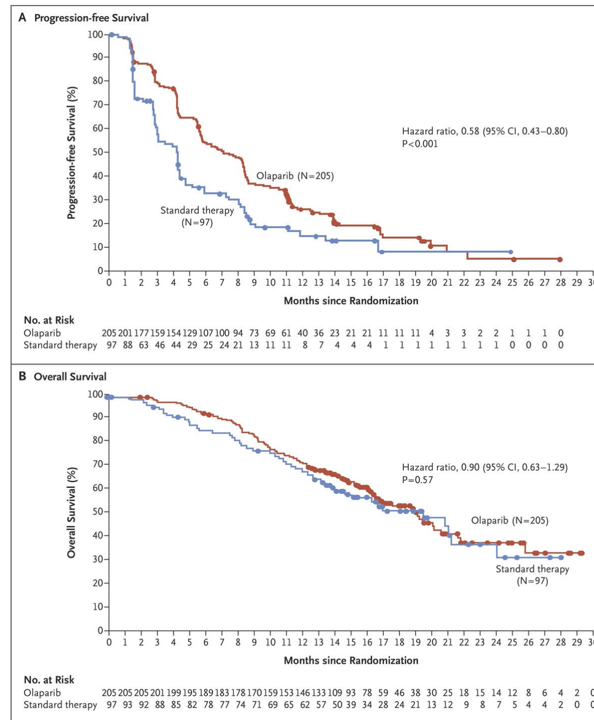
Olaparib vs Std Chemotherapy for BRCA-associated Breast Cancer



Response Rates

Olaparib 60%

Chemo 29%

Robson M et al. N Engl J Med 2017;377:523-533.

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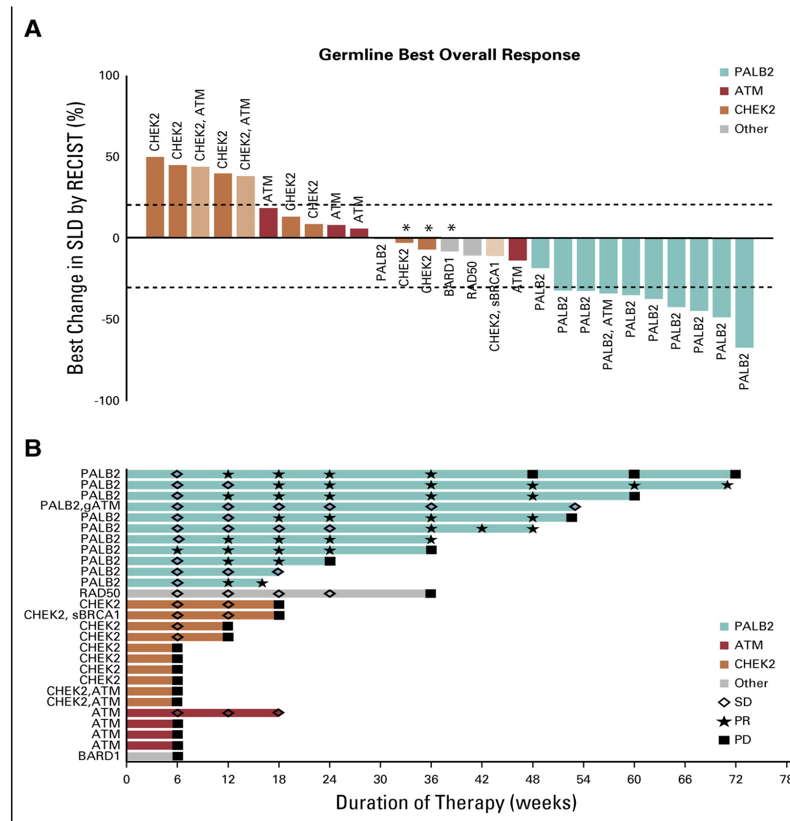

: Nadine M. Tung; Mark E. Robson; Steffen Ventz; Cesar A. Santa-Maria; Rita Nanda; Paul K. Marcom; Payal D. Shah; Tarah J. Ballinger; Eddy S. Yang; Shaveta Vinayak; Michelle Melisko; Adam Brufsky; Michelle DeMeo; Colby Jenkins; Susan Domchek; Alan D'Andrea; Nancy U. Lin; Melissa E. Hughes; Lisa A. Carey; Nick Wagle; Gerburg M. Wulf; Ian E. Krop; Antonio C. Wolff; Eric P. Winer; Judy E. Garber; *Journal of Clinical Oncology* 2020 384274-4282.

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Genomic Mutations

The list keeps growing

ESR1, PIK3CA, HER2 mutated, TMB …

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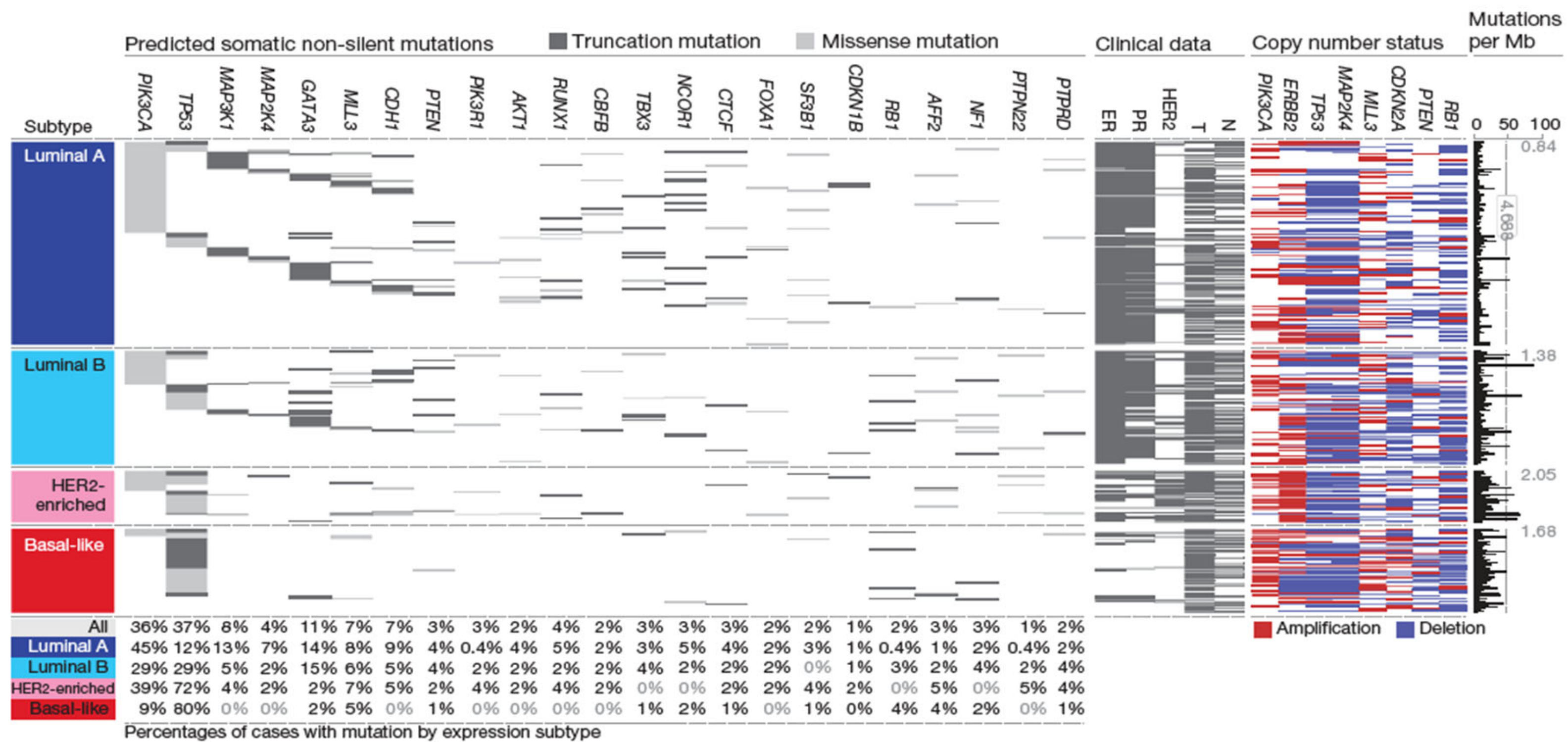
Diverse mutations of primary breast cancer subtypes



	PIK3CA	TP53	MAP3K1	MAP2K4	GATA3	MLL3	CDH1	PTEN	PIK3R1	AKT1	RUNX1	CBFB	TBX3	NCOR1	CTCF	FOXA1	SF3B1	CDKN1B	RB1	AFF2	NF1	PTPN22	PTPRD
All	36%	37%	8%	4%	11%	7%	7%	3%	3%	2%	4%	2%	3%	3%	3%	2%	2%	1%	2%	3%	3%	1%	2%
Luminal A	45%	12%	13%	7%	14%	8%	9%	4%	0.4%	4%	5%	2%	3%	5%	4%	2%	3%	1%	0.4%	1%	2%	0.4%	2%
Luminal B	29%	29%	5%	2%	15%	6%	5%	4%	2%	2%	2%	2%	4%	2%	2%	2%	0%	1%	3%	2%	4%	2%	4%
HER2-enriched	39%	72%	4%	2%	2%	7%	5%	2%	4%	2%	4%	2%	0%	0%	2%	2%	4%	2%	0%	5%	0%	5%	4%
Basal-like	9%	80%	0%	0%	2%	5%	0%	1%	0%	0%	0%	0%	1%	2%	1%	0%	1%	0%	4%	4%	2%	0%	1%

Percentages of cases with mutation by expression subtype

TCGA Nature 2012

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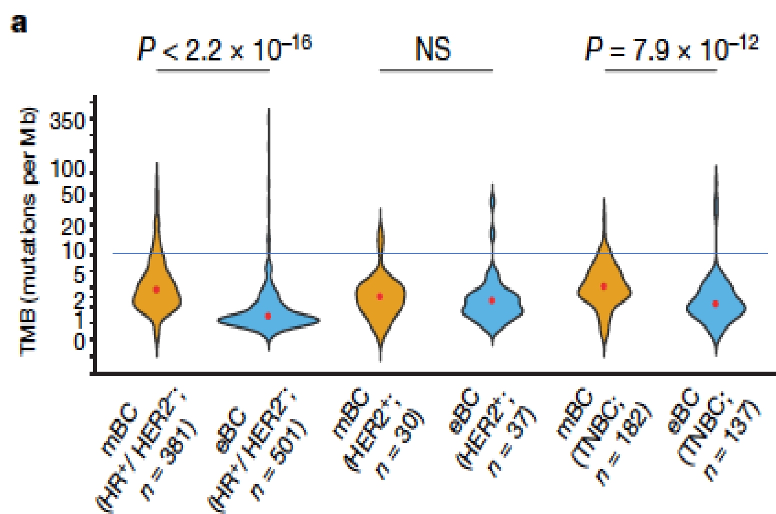
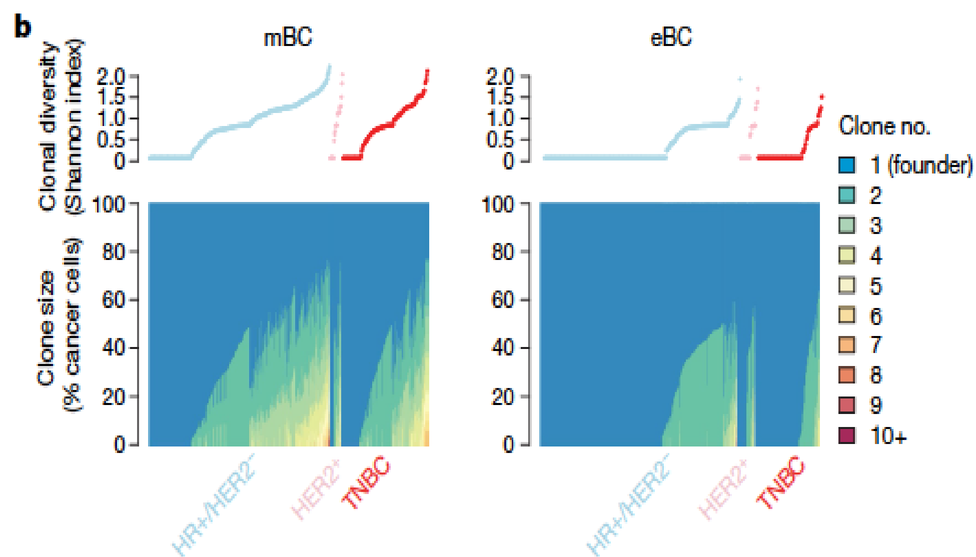
Heterogeneity of metastatic breast cancer

Increased number of mutations



Increased clonal complexity



Bertucci *et al* Nature 2019

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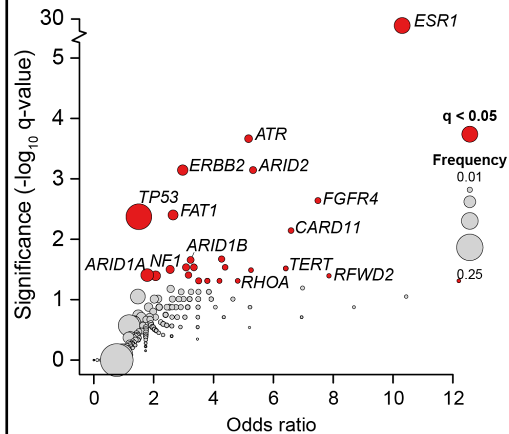
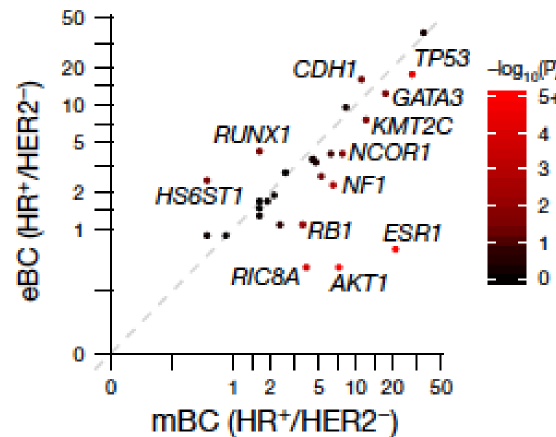
Mutations at higher frequency in advanced ER+ve BC

ER positive

IMPACT Panel N=1501



Exome n=381

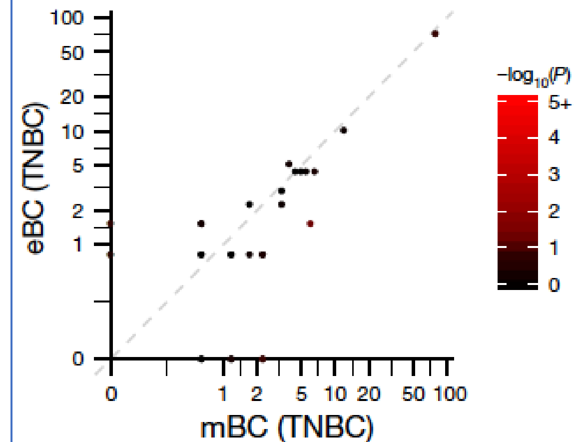


Genes Higher

TP53
ESR1
GATA3
KMT2C
NCOR1
AKT1
NF1
RIC8A
RB1

TNBC

Exome n=182



Two factors drive higher frequency – enrichment and acquisition

Razavi *et al* Cancer Cell 2018
Bertucci *et al* Nature 2019

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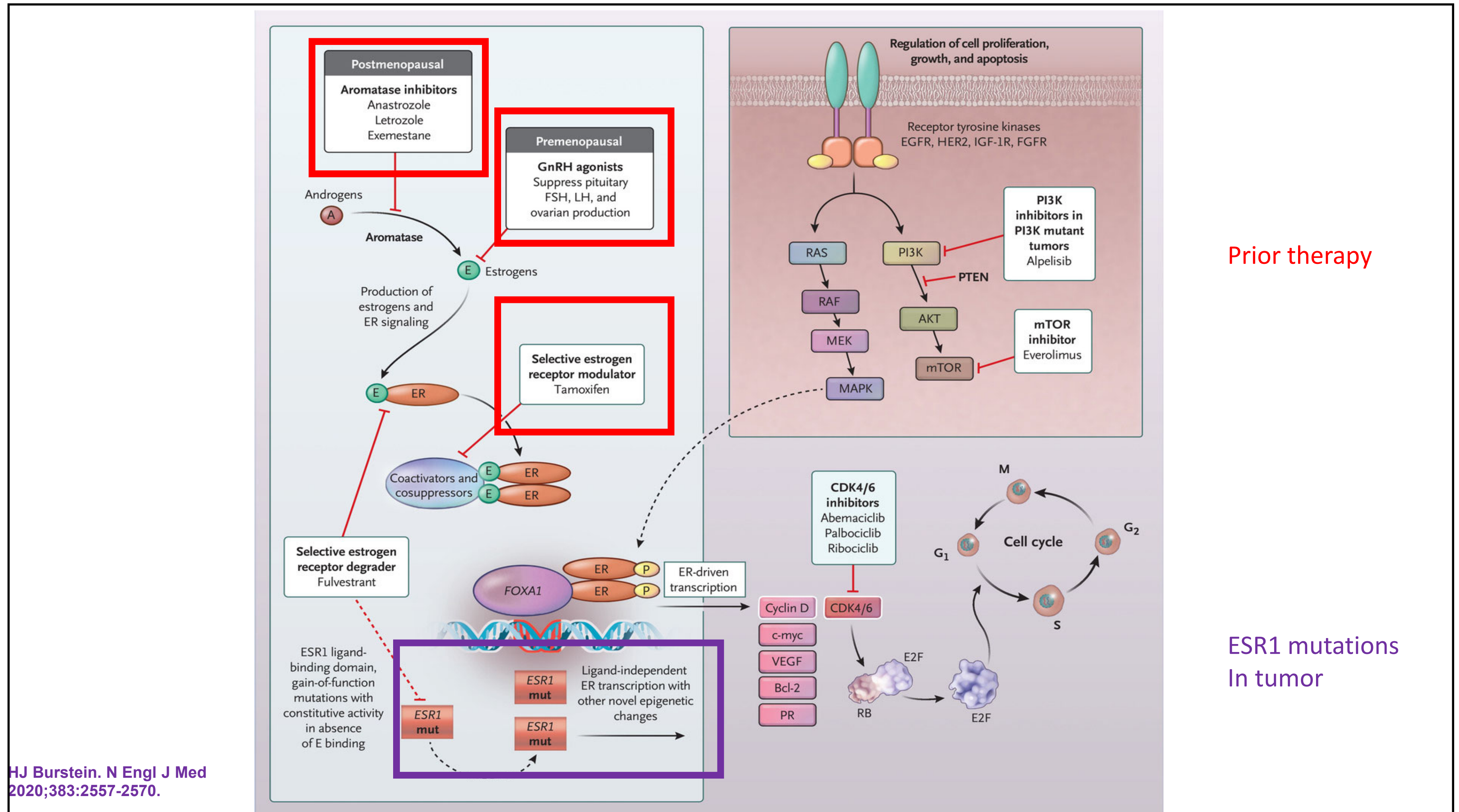

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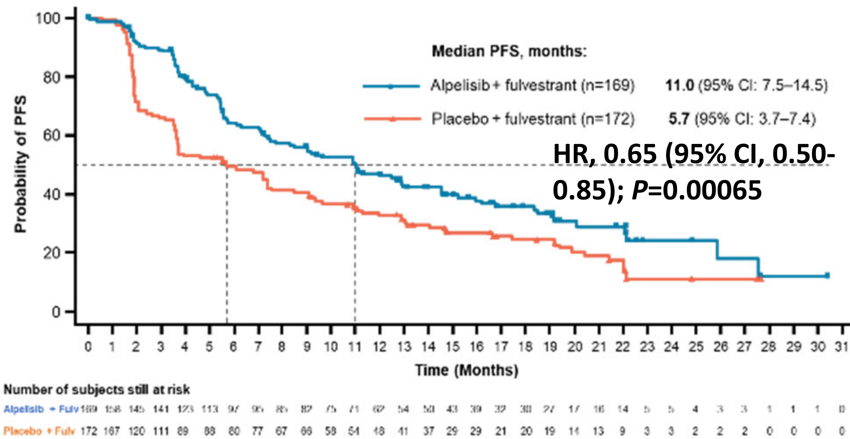
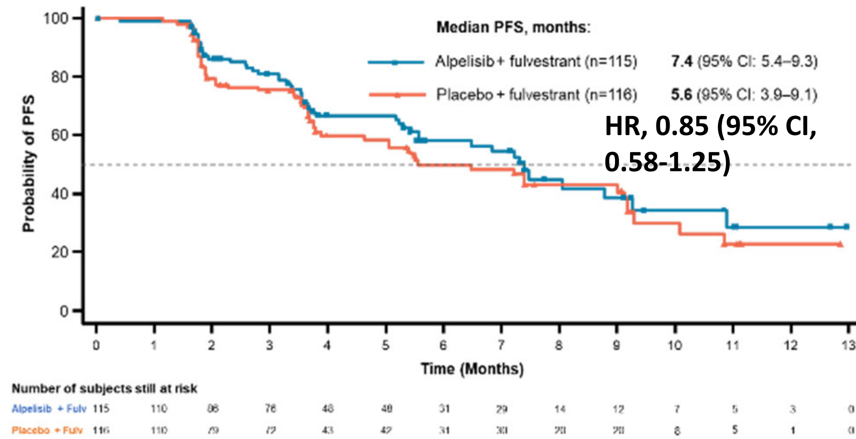
SOLAR-1 – alpelisib and fulvestrant in *PIK3CA* mutant

PIK3CA mutant cohort



PIK3CA non-mutant cohort



Testing for *PIK3CA* mutations now a standard of care

Andre *et al* NEJM 2019

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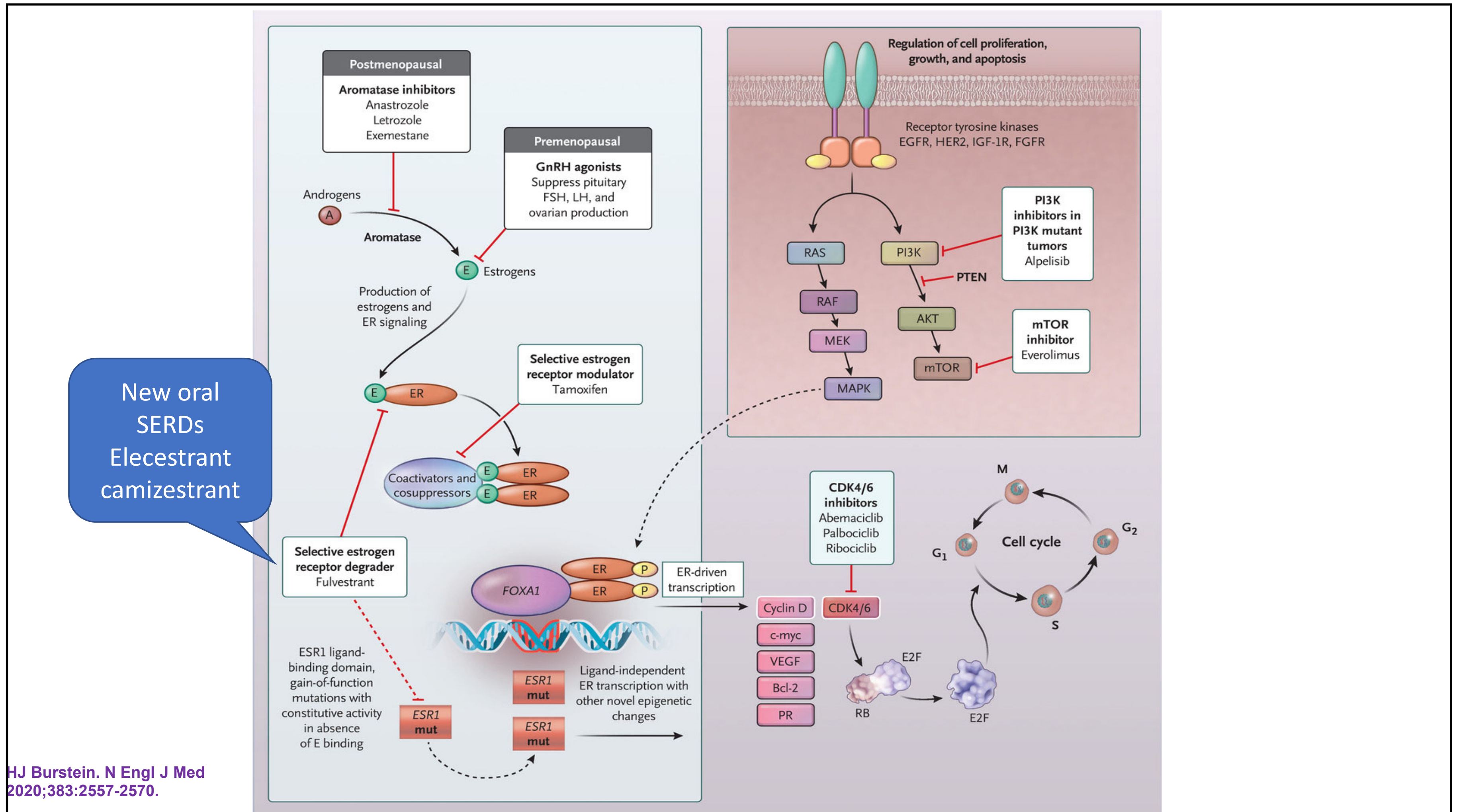

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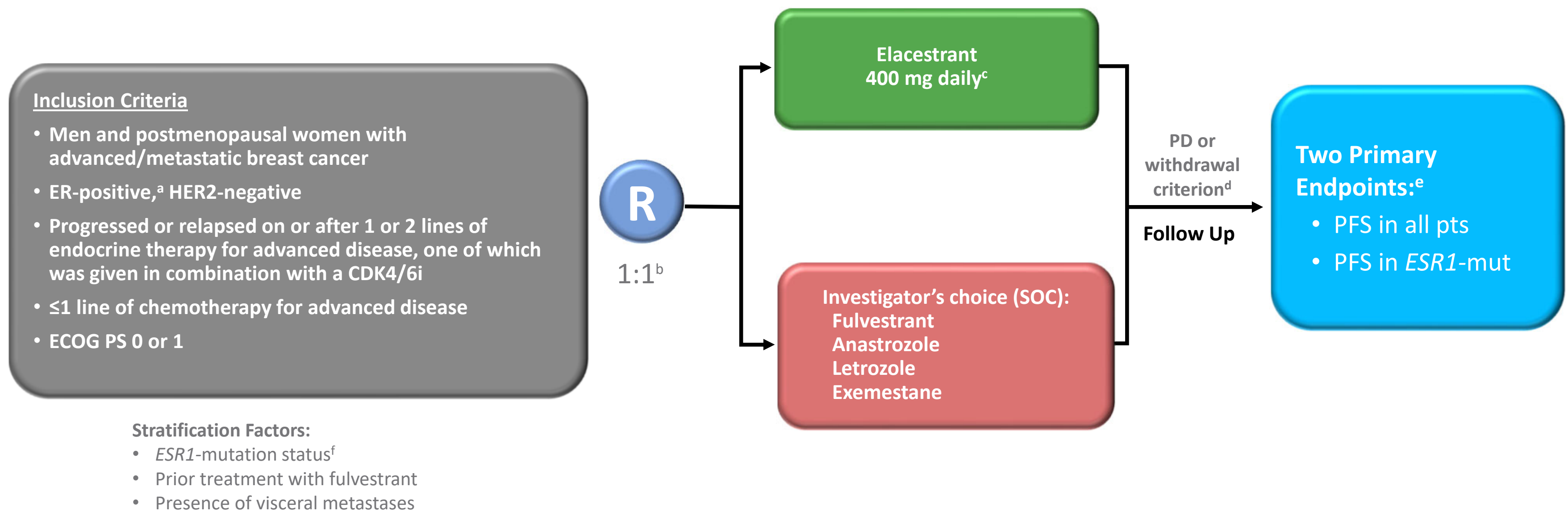

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On January 27, 2023, the Food and Drug Administration (FDA) approved elacestrant for postmenopausal women or adult men with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

FDA also approved a companion diagnostic device to identify patients with breast cancer for treatment with elacestrant.

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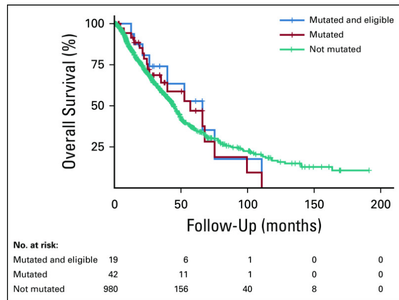
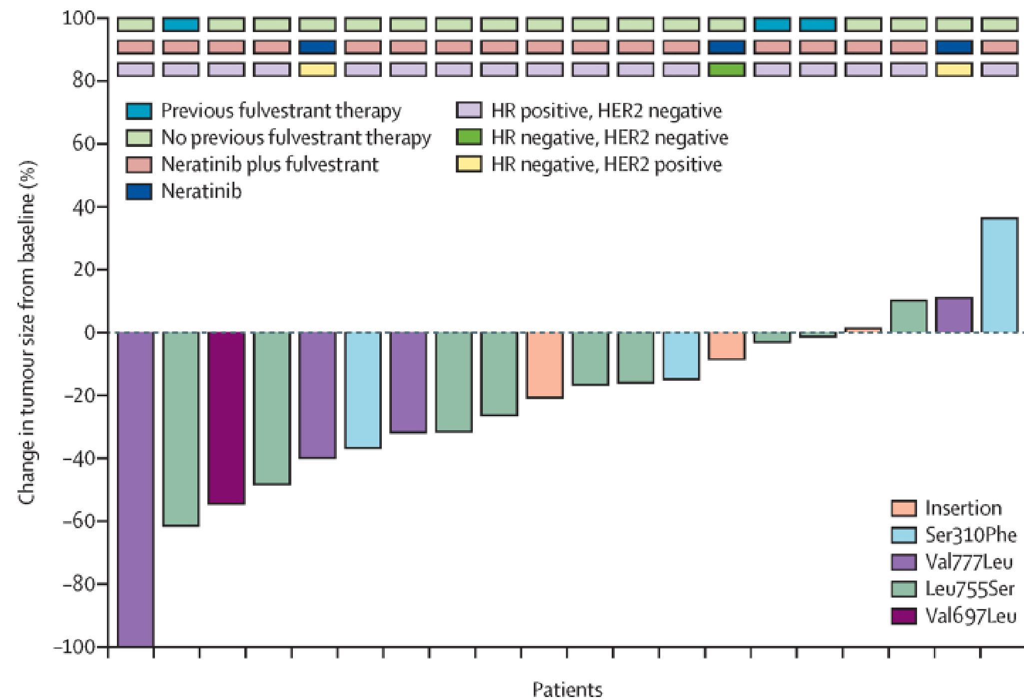
Exman P, et al.
JCO Precision Oncol 2019

HER2 activating mutations in
1.8% of patients with HER2 non-amplified
advanced breast cancer

MutHER trial:
Clinical benefit from neratinib + fulvestrant
Ma C, et al. Clin Canc Res 2022



PlasmaMATCH Platform Study
Turner NC, et al. Lancet Oncol 2020



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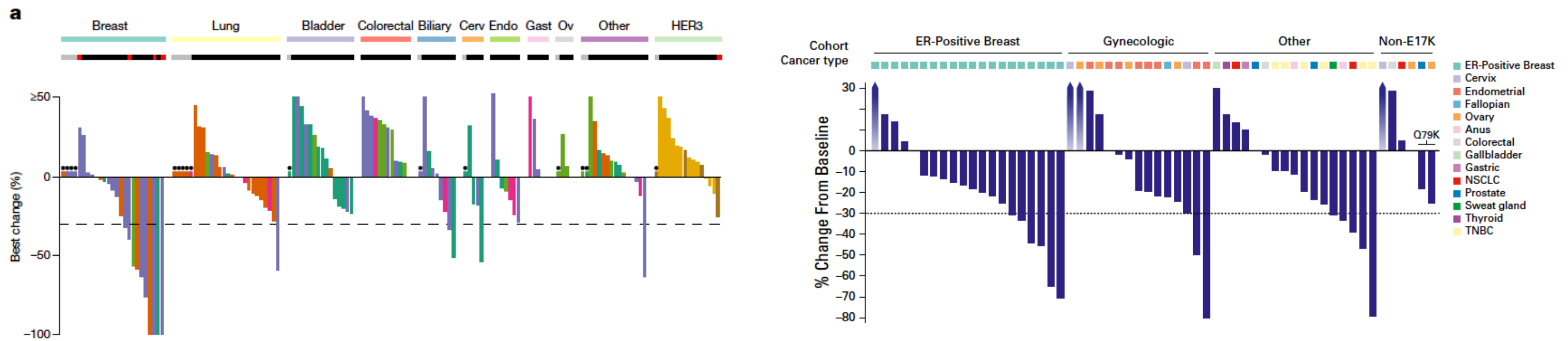
Research use Mutations in ER positive breast cancer

Neratinib for *HER2* mutations

Capivasertib for AKT1 mutations



New oral ER targeting drugs for *ESR1* mutations

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Postmenopausal

Aromatase inhibitors
Anastrozole
Letrozole
Exemestane

Premenopausal

GnRH agonists
Suppress pituitary
FSH, LH, and
ovarian production

Androgens
A
Aromatase
E Estrogens

Production of
estrogens and
ER signaling

E ER

Selective estrogen
receptor modulator
Tamoxifen

Coactivators and
cosuppressors
E ER
E ER

Selective estrogen
receptor degrader
Fulvestrant

FOXA1
ER P
ER P
ER-driven
transcription

ESR1 ligand-
binding domain,
gain-of-function
mutations with
constitutive activity
in absence
of E binding

ESR1 mut
ESR1 mut
ESR1 mut

Ligand-independent
ER transcription with
other novel epigenetic
changes

Regulation of cell proliferation,
growth, and apoptosis

Receptor tyrosine kinases
EGFR, HER2, IGF-1R, FGFR

RAS
RAF
MEK
MAPK

PI3K
PTEN
AKT
mTOR

PI3K
inhibitors in
PI3K mutant
tumors
Alpeli...

AKT inhibitor
capivasertib

mTOR
inhibitor
Everolimus

CDK4/6
inhibitors
Abemaciclib
Palbociclib
Ribociclib

Cyclin D
CDK4/6
c-myc
VEGF
Bcl-2
PR

E2F
RB
E2F

M
G_2
Cell cycle
G_1
S

HJ Burstein. N Engl J Med
2020;383:2557-2570.

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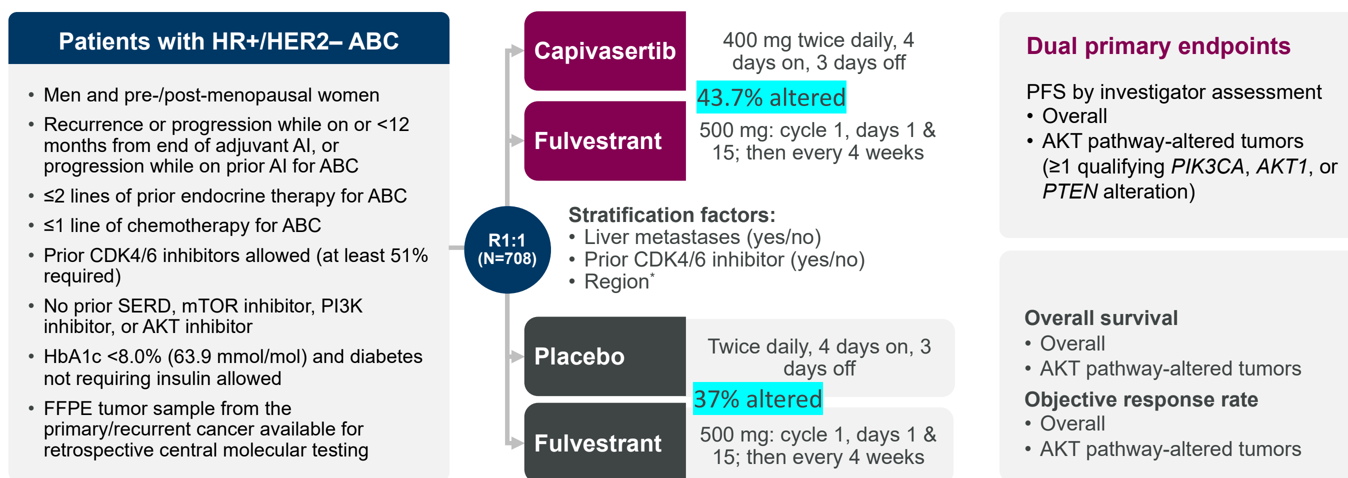
CAPItello-291: Phase III, randomized, double-blind, placebo-controlled study



Summary of Demographics

- Median age ~59
- Asian 26%, Black 1%
- Primary ET resistance ~38%
- Visceral mets ~68%
- One line of prior ET for MBC ~75%
- Prior CDK4/6i for MBC ~70%
- Chemotherapy for ABC ~18%

Turner et al, SABCS 2022

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TMB and TNBC response to pembrolizumab vs chemo in KN119

	TMB ≥10, pembro (n = 14)	TMB ≥10, chemo (n = 12)	TMB < 10, pembro (n = 118)	TMB < 10, chemo (n = 109)
ORR, % (95% CI)	14.3% (4.0-39.9)	8.3% (0.4-35.4)	12.7% (7.9-19.9)	12.8% (7.8-20.4)
PFS, HR (95% CI)	1.14 (0.42-3.07)	–	1.24 (0.92-1.67)	–
OS, HR (95% CI)	0.58 (0.21-1.57)	–	0.81 (0.61-1.07)	–

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San Antonio Breast Cancer Symposium®, December 7-10, 2021

SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS

Dana-Farber Cancer Institute

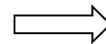
HARVARD MEDICAL SCHOOL

Study Design: NIMBUS trial

Eligibility:

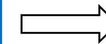
- Metastatic HER2- breast cancer
- 0-3 lines of prior chemotherapy
- TMB ≥ 9 mut/Mb as assessed by a CLIA-approved cancer-gene panel
- Measurable disease by RECIST 1.1
- Mandatory research biopsy if tumor safely accessible
- No prior checkpoint inhibition

REGISTRATION



Nivolumab 3 mg/kg Q2W
+
Ipilimumab 1 mg/kg Q6W

1 cycle = 42 days (6 weeks)



Duration of therapy

Treatment until progression, unacceptable toxicity or up to 24 months

Tumor assessment: Imaging will be performed at baseline and Q6W for 24 weeks, and then Q9W.

Biopsy #1 Stool #1 (Baseline)	Biopsy #2 Stool #2 (Cycle 1 day 29)	Biopsy #3 Stool #3 (End of treatment – optional)

PBMCs collected within 7 days of starting therapy and every 6 weeks for 24 weeks, and then every 9 weeks.

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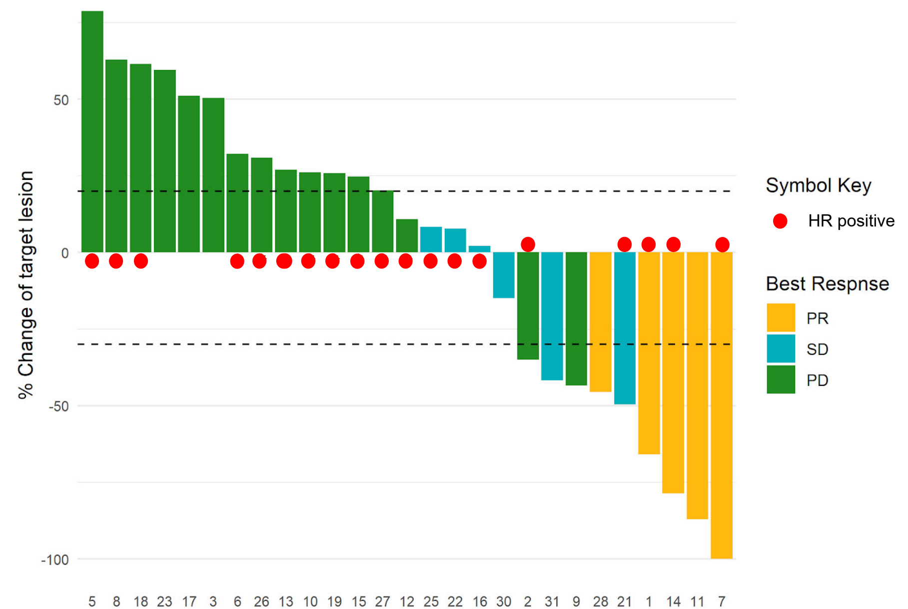
San Antonio Breast Cancer Symposium®, December 7-10, 2021

SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS
Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL

Objective Response Rate (ORR)

Confirmed ORR, n (%)	5 (16.7%)
CR, n (%)	0
PR, n (%)	5 (16.7%)
SD, n (%)	6 (20%)
PD, n (%)	16 (53.3%)
Not evaluable, n (%)	3 (10%)
CBR, n (%)	5 (16.7%)



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HARVARD MEDICAL SCHOOL

Exploratory analysis

	Objective response	No response	Total	P value
Subtype	n = 5	n = 25	n = 30	0.6
TNBC, n (%)	2 (22)	7 (78)	n = 9	
HR+, n (%)	3 (14)	18 (86)	n = 21	
PD-L1 status	n = 4	n = 21	n = 25	1.0
Negative, n (%)	3 (14.3)	18 (85.7)	n = 21	
Positive, n (%)	1 (25)	3 (75)	n = 4	
Stromal TIL	n = 5	n = 23	n = 28	0.3
<10, n (%)	2 (11)	17 (89)	n = 19	
≥ 10, n (%)	3 (33)	6 (67)	n = 9	
TMB (Mut/Mb)	n = 5	n = 25	n = 30	0.02
<14, n (%)	2 (8)	23 (92)	n = 25	
≥14, n (%)	3 (60)	2 (40)	n = 5	

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San Antonio Breast Cancer Symposium®, December 7-10, 2021

SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL

Median PFS and OS according to TMB

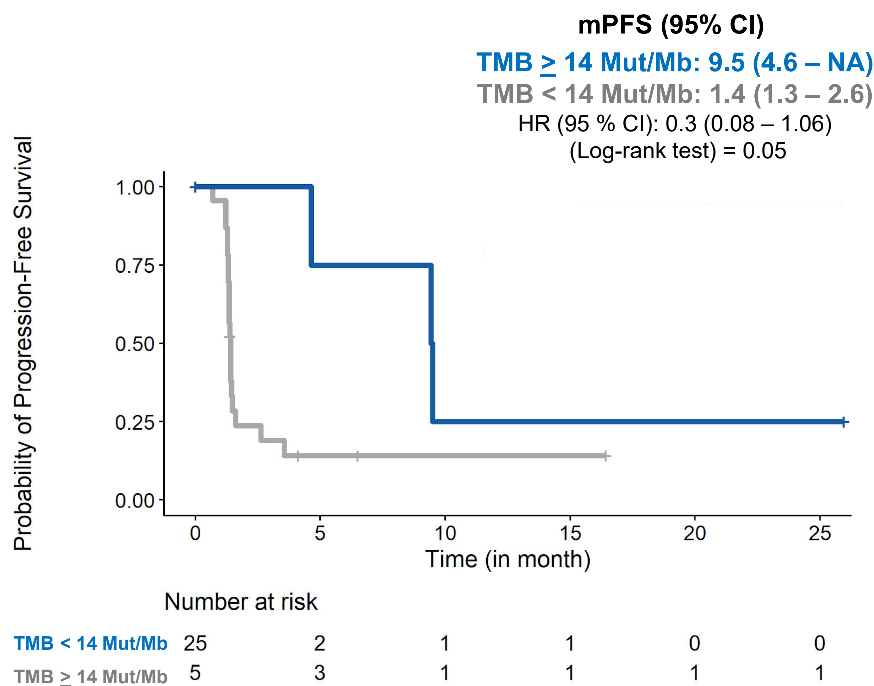
mPFS (95% CI)

TMB ≥ 14 Mut/Mb: 9.5 (4.6 – NA)

TMB < 14 Mut/Mb: 1.4 (1.3 – 2.6)

HR (95 % CI): 0.3 (0.08 – 1.06)

(Log-rank test) = 0.05



Number at risk

	0	5	10	15	20	25
TMB < 14 Mut/Mb	25	2	1	1	0	0
TMB ≥ 14 Mut/Mb	5	3	1	1	1	1

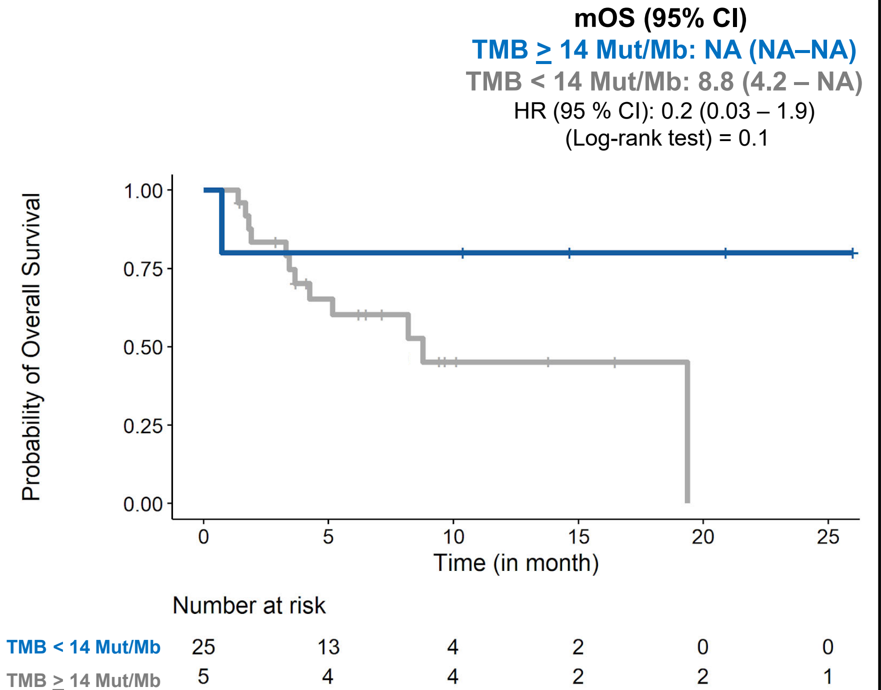
mOS (95% CI)

TMB ≥ 14 Mut/Mb: NA (NA–NA)

TMB < 14 Mut/Mb: 8.8 (4.2 – NA)

HR (95 % CI): 0.2 (0.03 – 1.9)

(Log-rank test) = 0.1



Number at risk

	0	5	10	15	20	25
TMB < 14 Mut/Mb	25	13	4	2	0	0
TMB ≥ 14 Mut/Mb	5	4	4	2	2	1

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Semi-quantitative ctDNA in MBC

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Detection of Progression and Regression of Breast Cancer by circulating Tumor DNA (ctDNA)

Beaumont

Ujjwal Karki[1], Bipin Ghimire[1], Emma Herrman[1], Siddhartha Yadav[3], Mohammad Muhsin Chisti[2]
1- Resident, Internal Medicine, Beaumont Health - Royal Oak, MI;
2- Associate Professor, Hematology and Medical Oncology, Oakland University William Beaumont School - Royal Oak, MI;
3- Assistant Professor of Medicine and Oncology, Mayo Clinic, Rochester, MN

Results

➢ **Correlation of serial ctDNA trends with disease status on imaging**

✓ **Total serial ctDNA pairs: 15**

CtDNA trend	Imaging finding			
	Disease progression	Disease regression	Absence of disease	Total
Up trending	7	0	0	7
Down trending	0	4	0	4
Persistent Negative	0	0	4	4
Total	7	4	4	15

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SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Positive and HER2-Negative with Visceral Crisis or Endocrine Refractory		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib)[c] (Category 1, preferred)
Second Line	HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan- nxki	Sacituzumab govitecan[f] (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
Third Line and beyond	Any	Systemic chemotherapy see BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)

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SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	PD-L1 CPS ≥10 regardless of germline *BRCA* mutation status[g]	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[h] (Category 1, preferred)
	PD-L1 CPS <10* and no germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	PD-L1 CPS <10* and germline *BRCA1/2* mutation[b]	• PARPi (olaparib, talazoparib) (Category 1, preferred) • Platinum (cisplatin or carboplatin) (Category 1, preferred)
Second Line	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib) (Category 1, preferred)
	Any	Sacituzumab govitecan[i] (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
	No germline *BRCA1/2* mutation[b] and HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[j] (Category 1, preferred)
Third Line and beyond	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)
	Any	Systemic chemotherapy see BINV-Q (5)

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Breast Cancer

ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) 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
HR-positive/ HER2-negative[v]	*PIK3CA* activating mutation	PCR (blood or tissue block if blood negative)	Alpelisib + fulvestrant[w]	Category 1	Preferred second- or subsequent-line therapy
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[x] Entrectinib[x]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR (tissue block)	Pembrolizumab[y,z] Dostarlimab-gxly[aa]	Category 2A	
Any	TMB-H (≥10 mut/mb)	NGS	Pembrolizumab[y,z]	Category 2A	
Any	*RET*-fusion	NGS	Selpercatinib[bb]	Category 2A	

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Commentary

- A growing number of biomarkers and genomic readouts are important for treatment of advanced breast cancer
- Genetic testing should be universal
- Histopathology should be universal
- Increasingly hard to escape universal genomic tumor testing
- Serial genomic testing not far off

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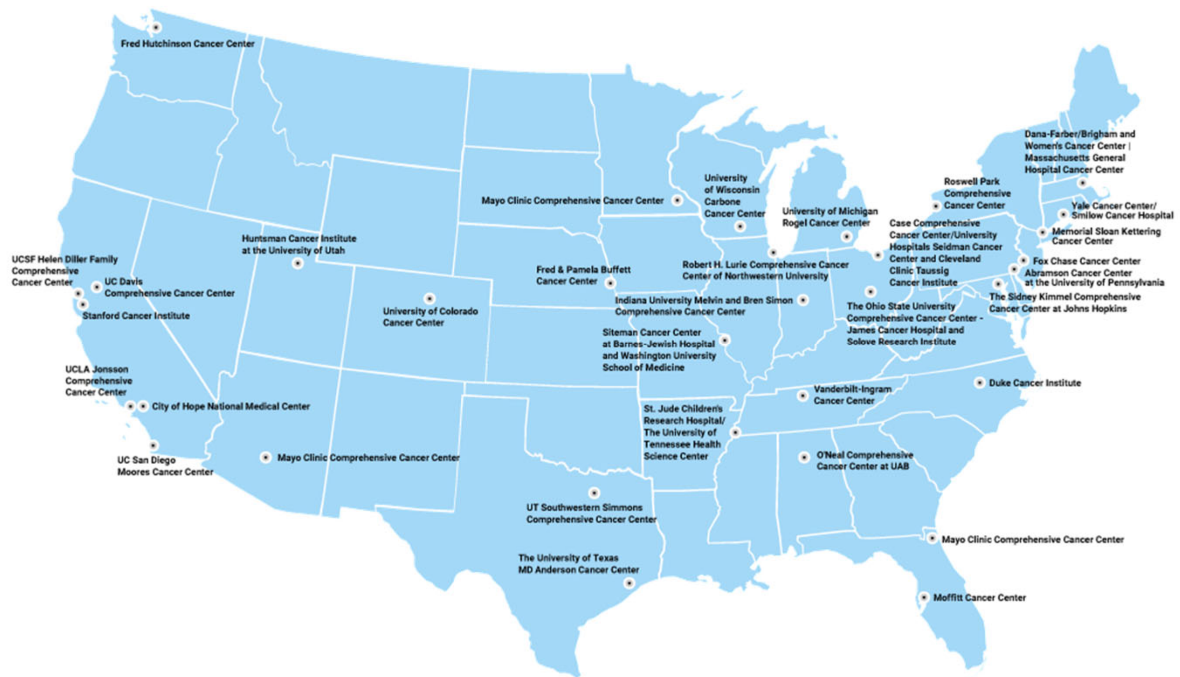
Our Mission

To improve and facilitate quality, effective, equitable, and accessible cancer care so all patients can live better lives

Our Vision

To define and advance high-quality, high-value, patient-centered cancer care globally



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