SABCS 2022: Precision Medicine and Genomics Update

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NCCN National Comprehensive Cancer Network®

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

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UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Disclosures

- None

Agenda

1. Genomic predictors for adjuvant therapy selection in localized ER+ breast cancer:
    - Long term outcomes from the TAILORx trial
    - Does Breast Cancer Index predict benefit of ovarian function suppression in pre-menopausal women in the SOFT trial?

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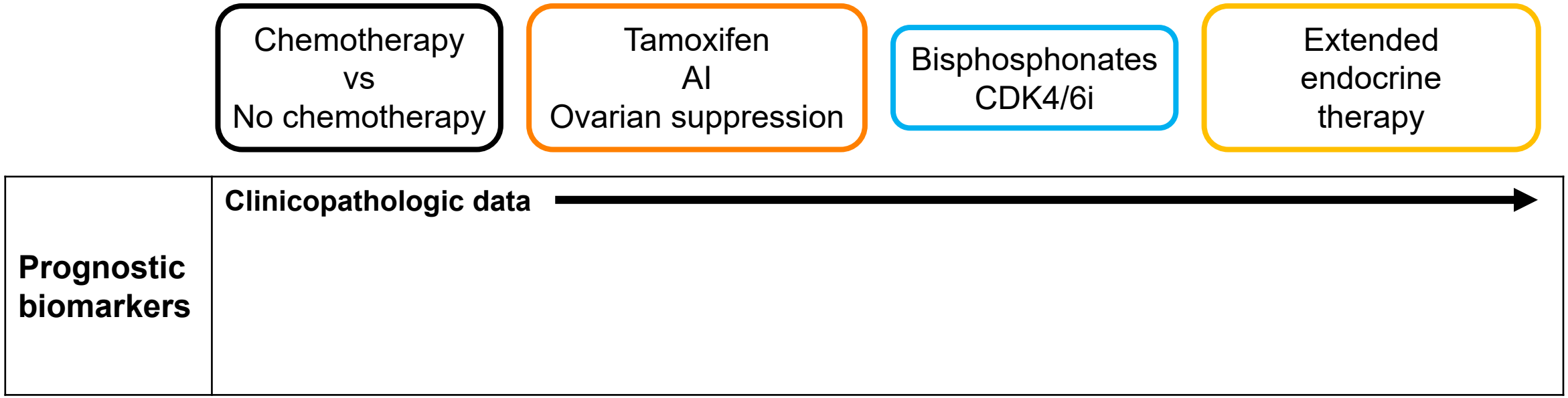
    - Long term outcomes from the TAILORx trial
    - Does Breast Cancer Index predict benefit of ovarian function suppression in pre-menopausal women in the SOFT trial?
2. Liquid biopsies for evaluation of endocrine therapy resistance in localized and advanced ER+ breast cancer
    - ctDNA monitoring in a phase II study of adjuvant endocrine therapy with ribociclib for localized ER+ breast cancer
    - ctDNA molecular response and clinical outcomes in advanced ER+ breast cancer on first line AI

Agenda

1. Genomic predictors for adjuvant therapy selection in localized ER+ breast cancer

Precision medicine and adjuvant therapy for ER+ breast cancer



Precision medicine and adjuvant therapy for ER+ breast cancer

	Chemotherapy vs No chemotherapy	Tamoxifen AI Ovarian suppression	Bisphosphonates CDK4/6i	Extended endocrine therapy
Prognostic biomarkers	**Clinicopathologic data** →			
	Oncotype DX RS			
	MammaPrint			
	Prosigna			
	EndoPredict			
	Breast Cancer Index			

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Predictive biomarkers	Oncotype DX RS			Breast Cancer Index

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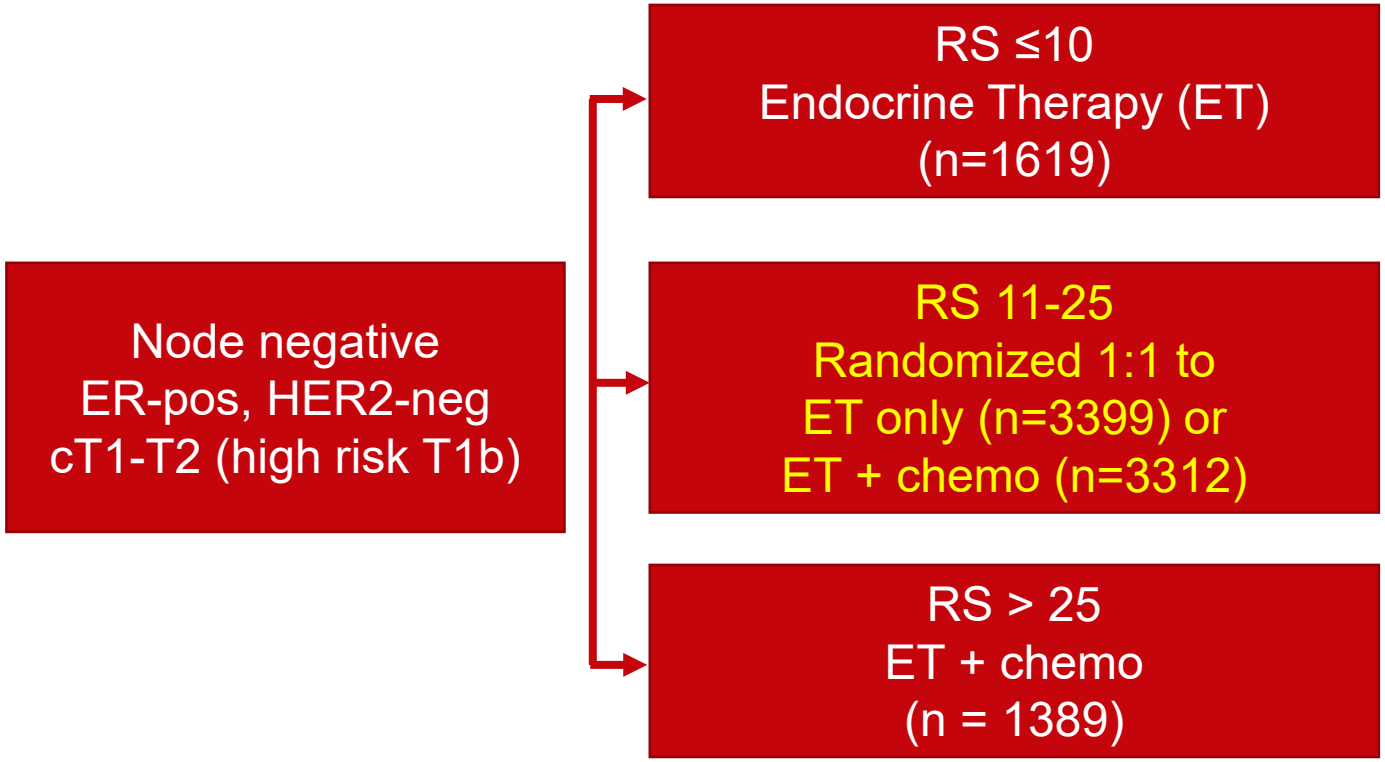
Predictive biomarkers	Oncotype DX RS			Breast Cancer Index

- **Long term outcomes from the TAILORx trial (GS01-05, Sparano et al)**

12 year update of the TAILORx trial

- Oncotype DX RS: 21-gene expression signature of genes involved in proliferation and estrogen receptor signaling

TAILORx design



Sparano et al. NEJM 2018 (PMID: 31157962), Sparano et al. JCO 2021 (PMID: 33306425), Albain et al. JNCI 2021 (PMID: 32986828)

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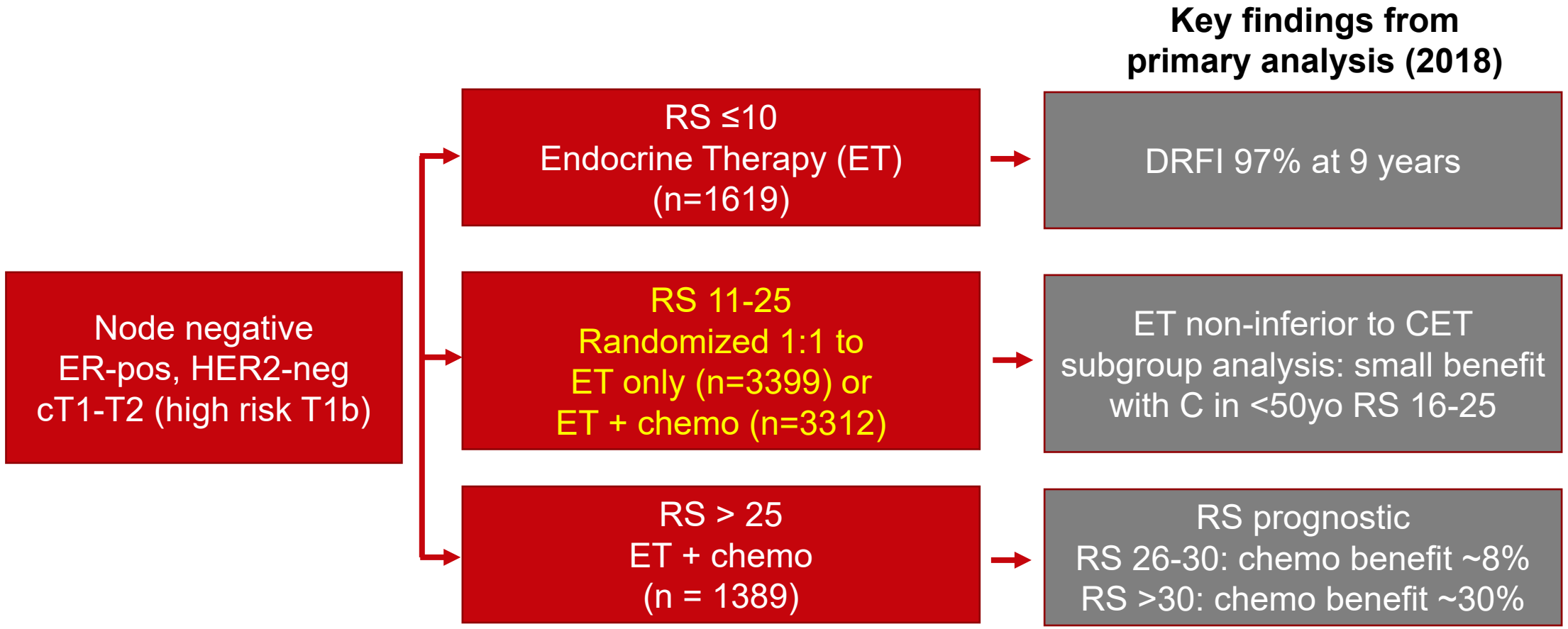

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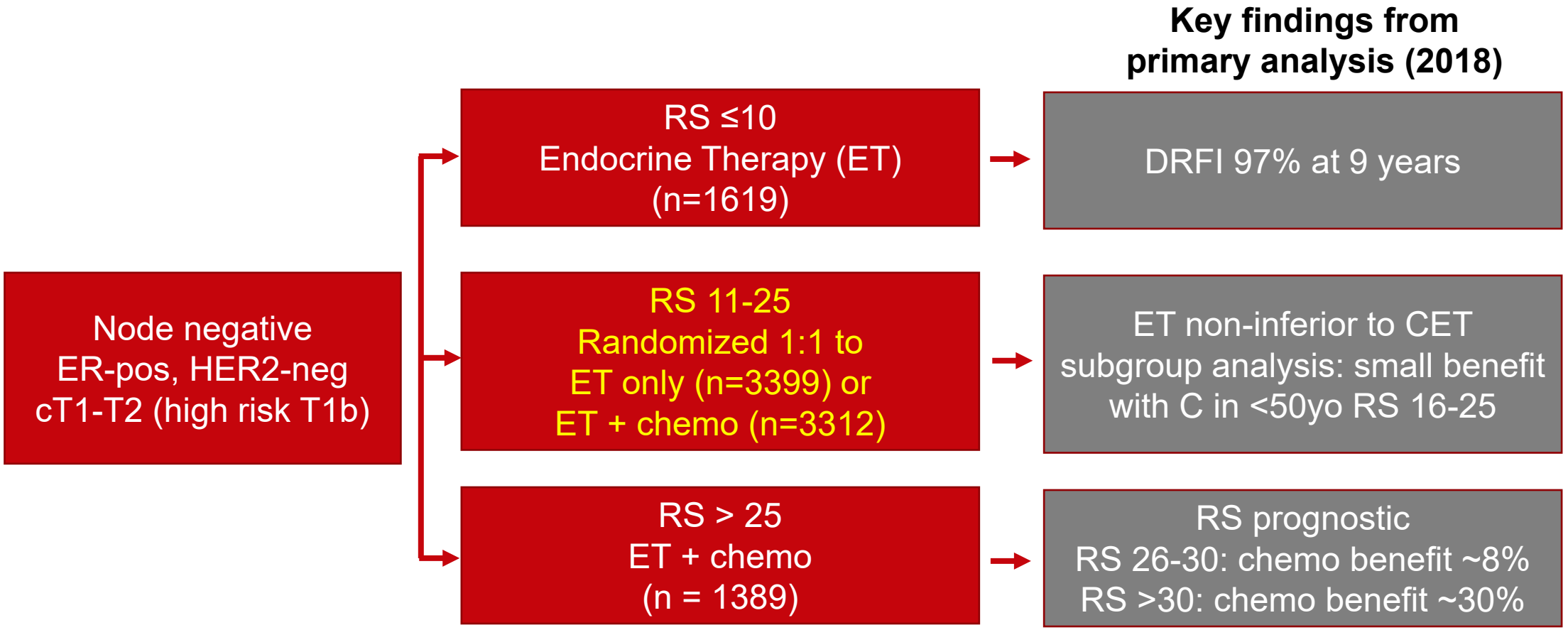

Subsequent key findings:

- Integration of RS with clinicopathologic factors gives additional prognostic information (RSClin)
- Black race associated with worse outcomes but still prognostic and predictive

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TAILORx update

- Over half of ER+ breast cancer recurrences occur after 5 years, and trial design pre-specified follow up to 20 years

Sparano et al. SABCS 2022 GS01-05

TAILORx update

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- Median follow up now 10.4 up from 7.5 years → captures more late recurrences/deaths
  - Median ET duration 5.1 years

Sparano et al. SABCS 2022 GS01-05

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Endpoint	Definition	Original RS 11-25	Current RS 11-25	Original All Arms	Current All Arms
IDFS	Any recurrence + second primary + death	836	1295	1210	1819
DRFI	Distant recurrence	250	375	384	561
RFI	Distant + locoregional recurrence	367	528	543	764
OS	Death	343	660	499	910

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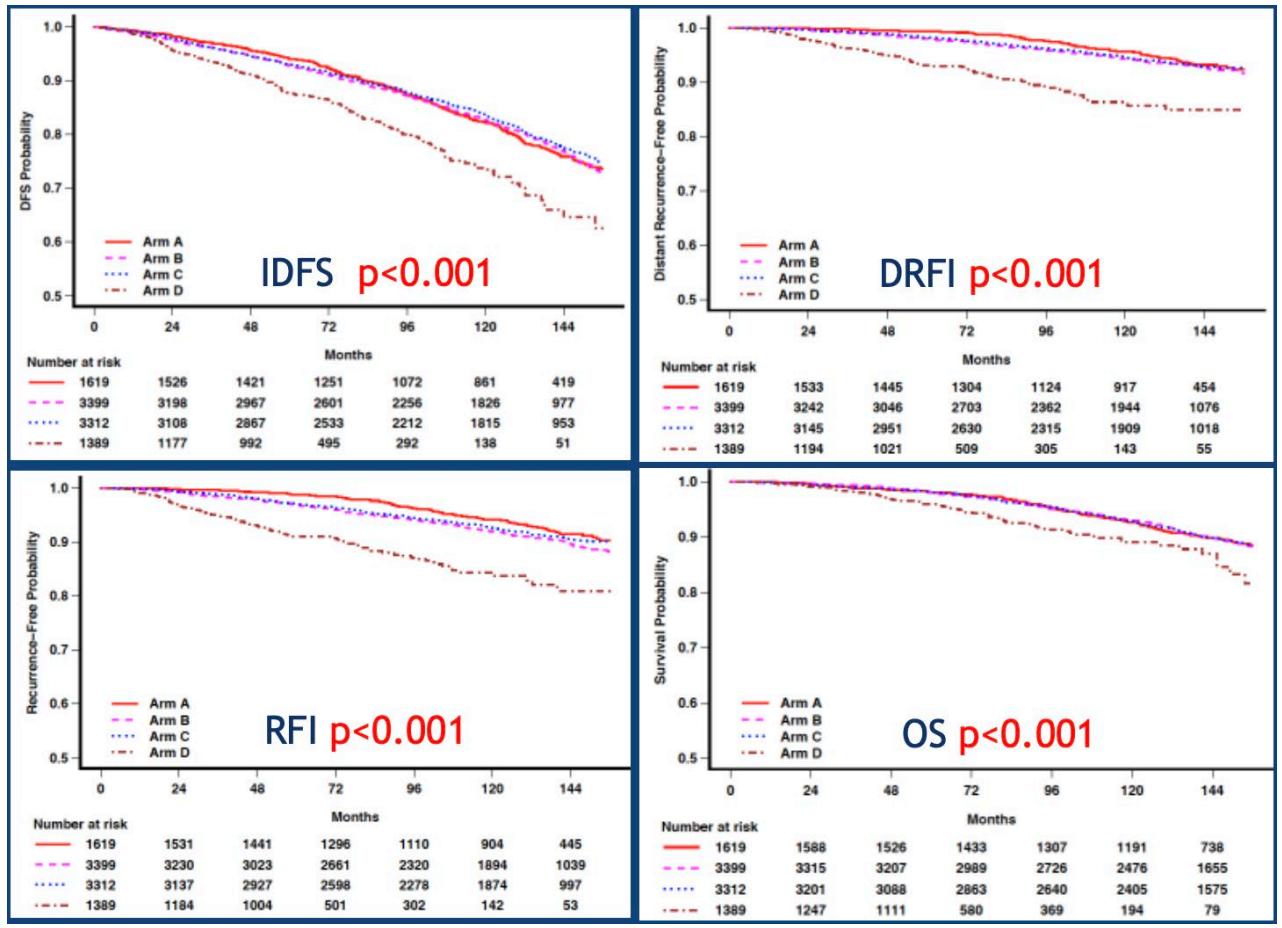
RS score and prognosis



Endpoint	RS <11	RS 11-25	RS > 26
RFI	91.4%	89.6%	80.9%
DRFI	93.2%	92.8%	84.8%

Sparano et al. SABCS 2022 GS01-05

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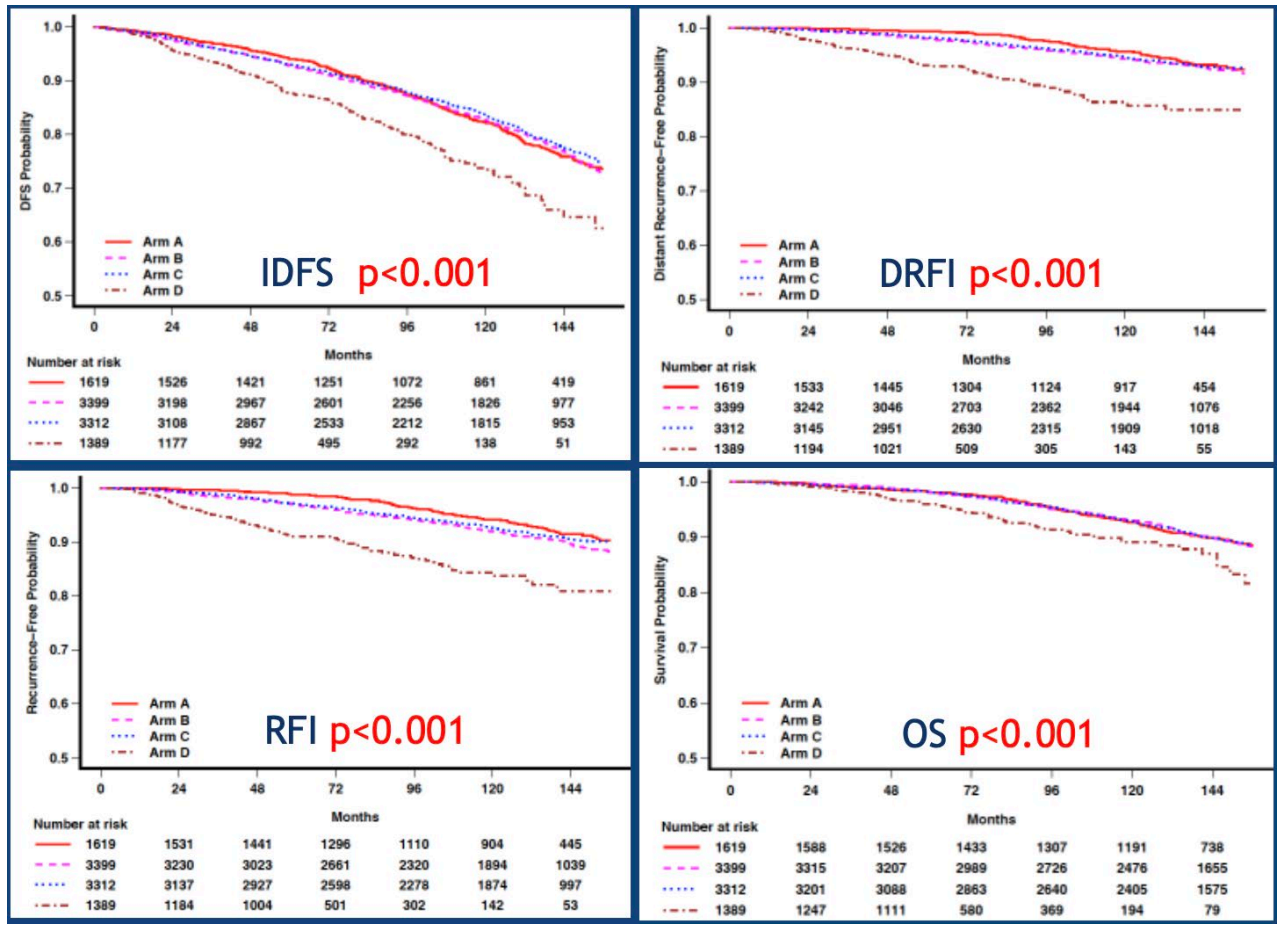

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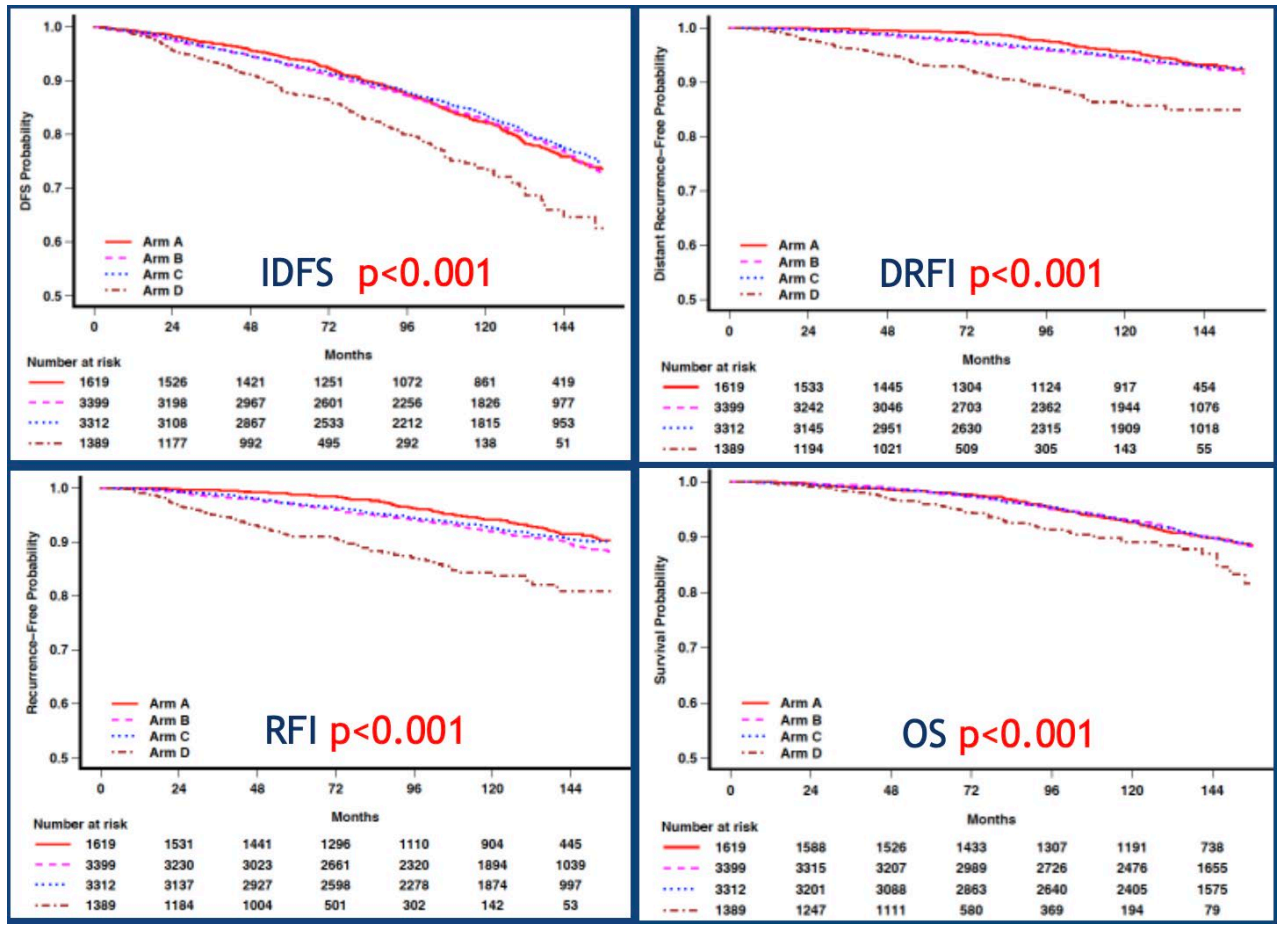

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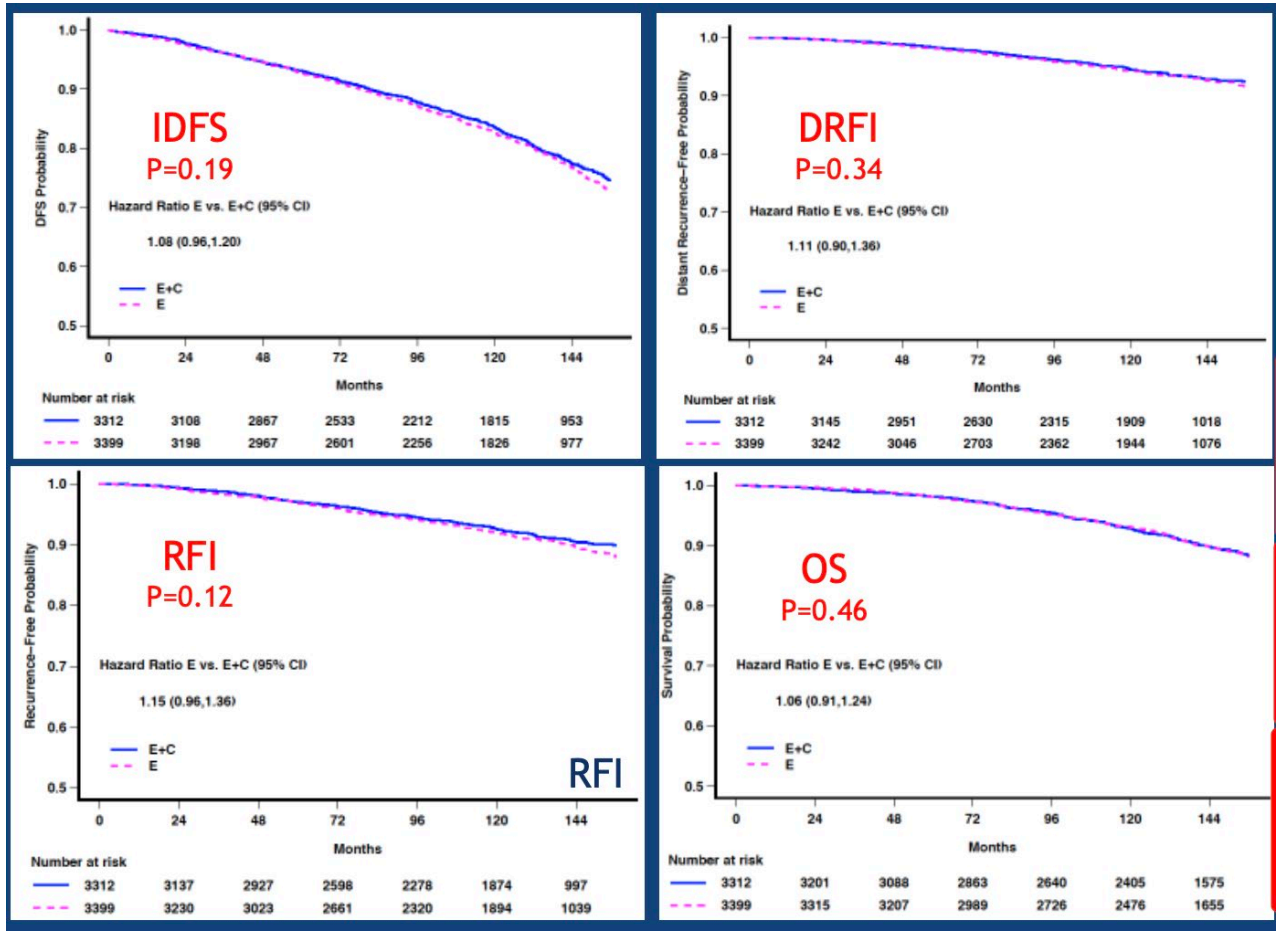
ET vs Chemo/ET in RS 11-25 ITT population



Endpoint	Cut-point	ET only	C/ET
IDFS	5 years	92.8%	93.1%
	12 years	76.8%	77.4%
DRFI	5 years	98.0%	98.2%
	12 years	92.6%	92.8%
RFI	5 years	96.9%	97.0%
	12 years	89.6%	90.5%
OS	5 years	98.0%	98.1%
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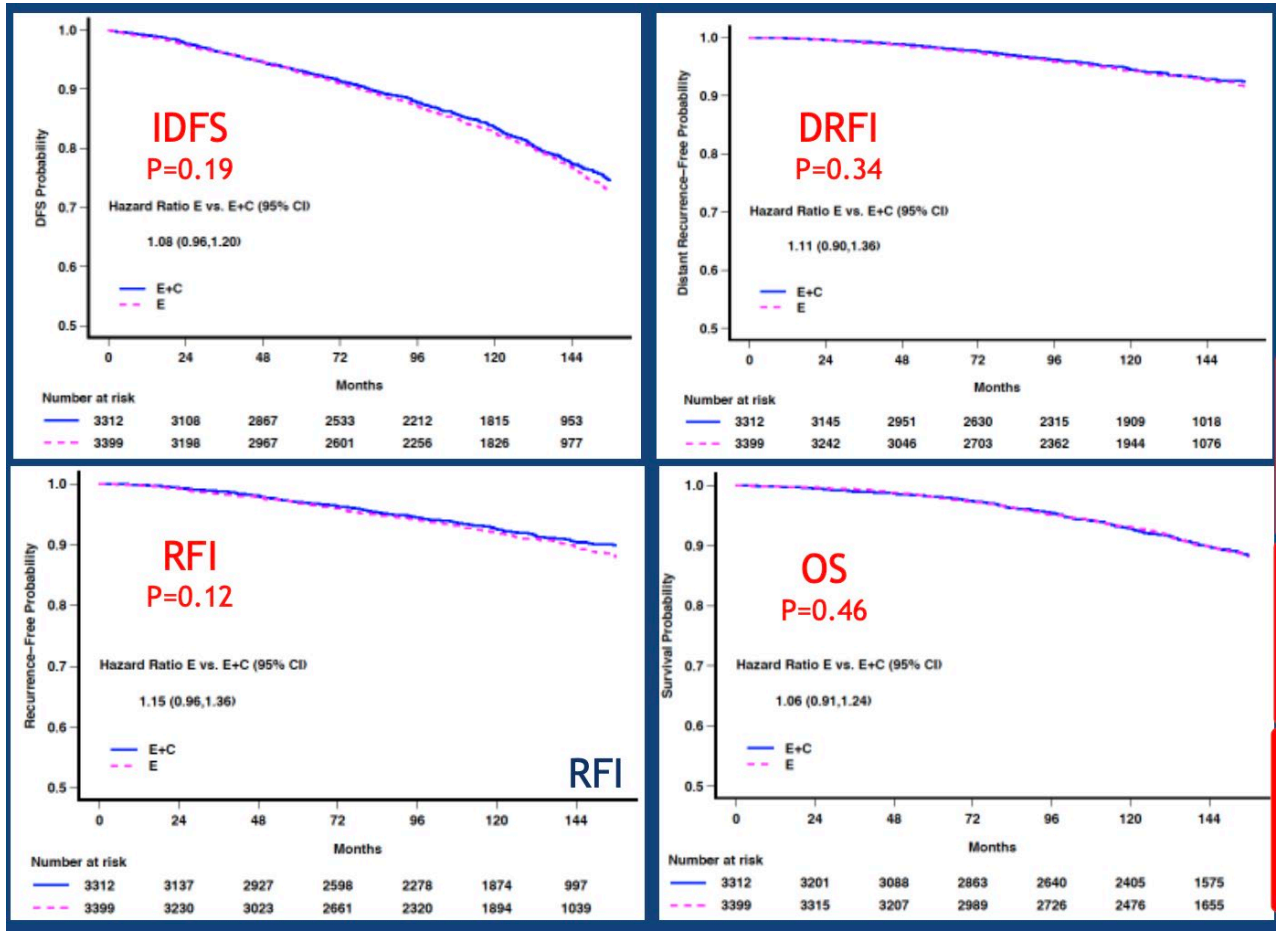

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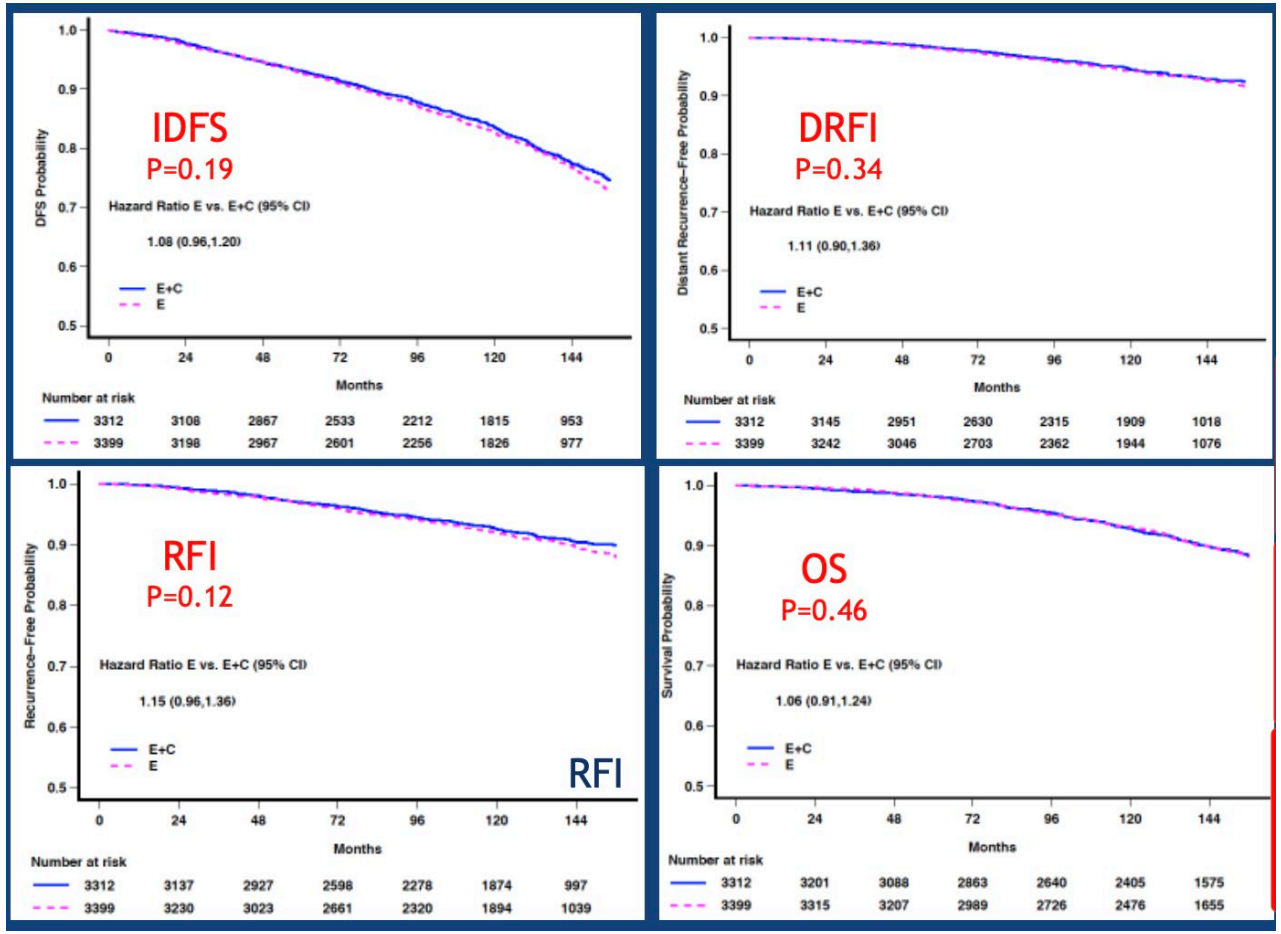

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- No change in primary conclusions
- More recurrences > 5 years as expected
- Distant recurrence ~7% at 12 years

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ET vs Chemo/ET in RS 11-25 women < 50

Endpoint	Cut-point	ET only	CET	Δ
IDFS	11-15	82.3%	83.9%	NS
DRFI	11-15	96.5%	95.2%	NS
IDFS	16-20	77.2%	84.8%	7.6%
DRFI	16-20	92.3%	92.9%	NS
IDFS	21-25	75.0%	82.4%	7.4%
DRFI	21-25	85.5%	93.3%	7.8%

- **No benefit in RS 11-15**

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Clinical Risk	No.	Abs chemo benefit
Low	671 (76%)	-0.5% (SE 2.2%)
High	215 (24%)	+3.1% (SE 5.4%)
Low	319 (67%)	+5.9% (SE 3.4%)
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Sparano et al. SABCS 2022 GS01-05

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- Significant DRFI benefit in RS 21-25 **especially** in clinical high risk

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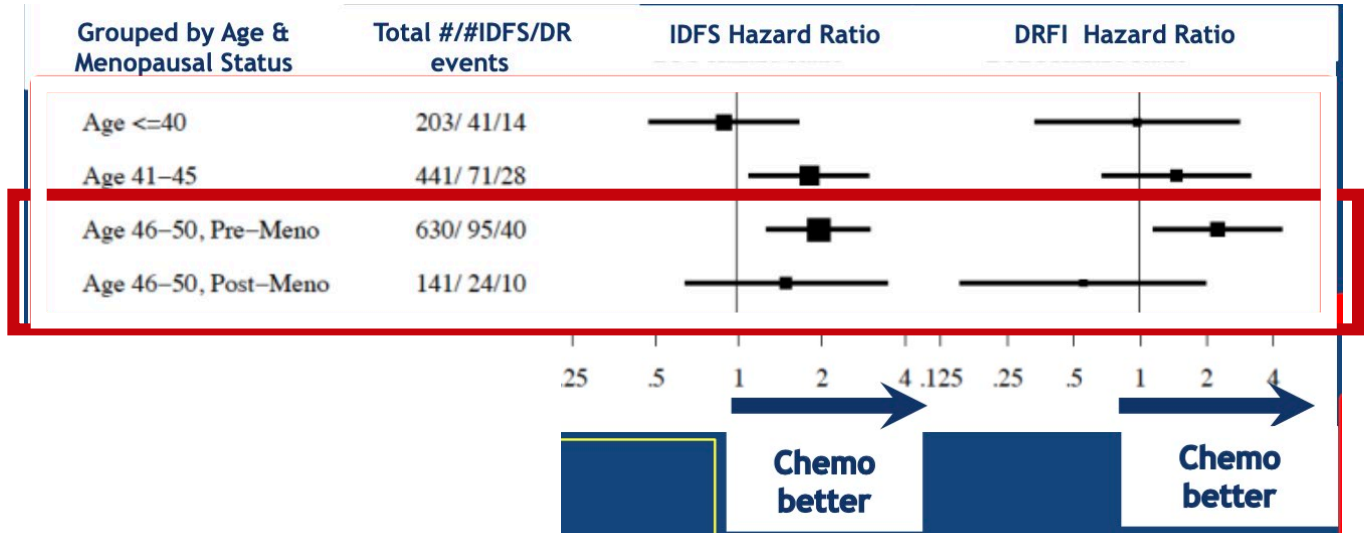

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Sparano et al. SABCS 2022 GS01-05

TAILORx update - summary

Conclusions:

- Excellent long-term outcomes for RS <11 with ET alone
- Lack of chemotherapy benefit in post-menopausal women with RS <26 confirmed in longer term follow up
- In pre-menopausal women <50, chemotherapy benefit for RS 21-25, and high clinical risk RS 16-20, but not low clinical risk RS 16-20
- RS >26 DRFI 15% at 12 years

TAILORx update - summary

Caveats:

- The subgroup analysis of women <50 is an exploratory endpoint
- details of ET duration not reported (median 5.1y) and may have varied by clinicopathologic recurrence risk.

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Future directions:

- Outcomes in RS >26 patients suggest opportunities for treatment escalation

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Future directions:

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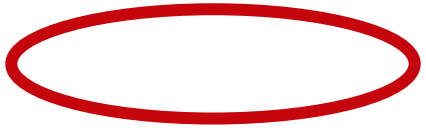
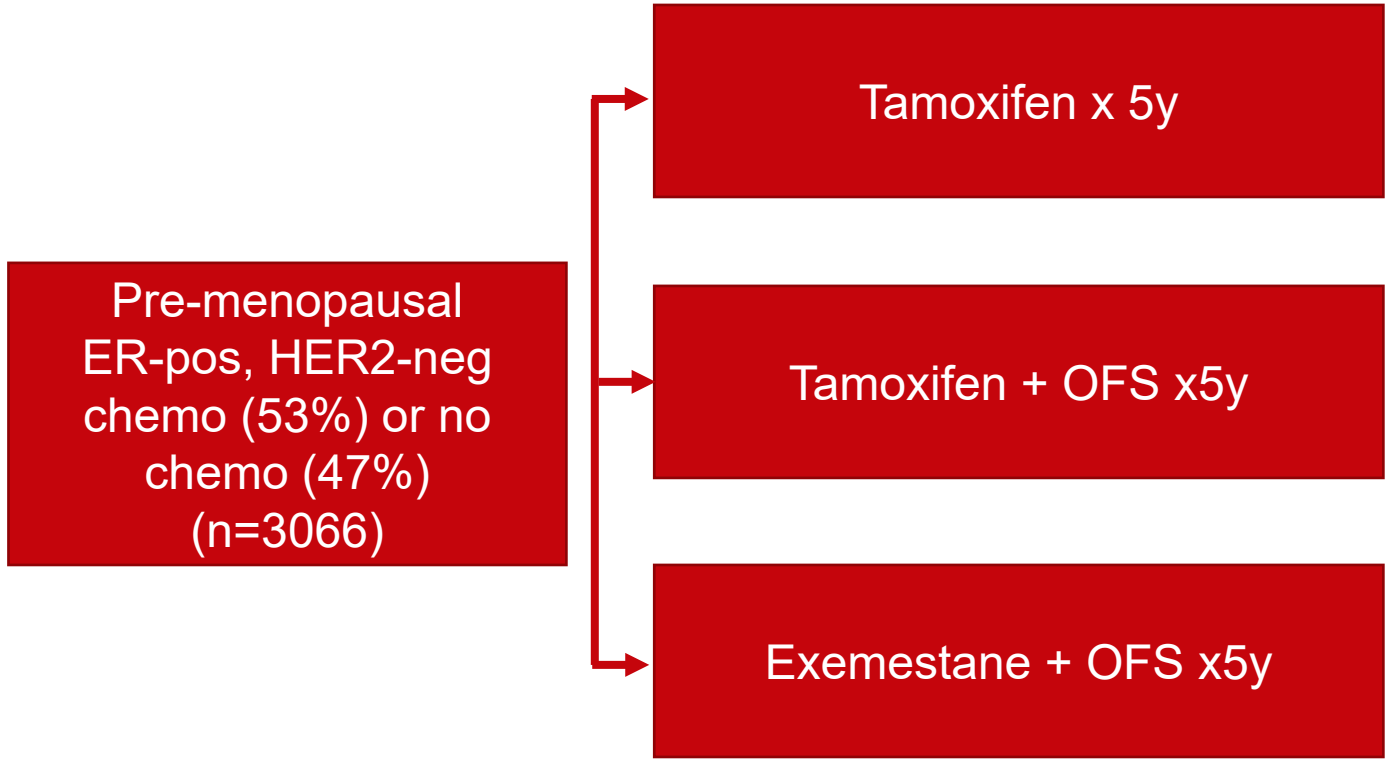
Take home: long term outcomes support the use of Oncotype DX RS in prediction of chemotherapy benefit in pre- and post-menopausal ER+ node negative breast cancer, particularly in combination with clinicopathologic risk features (RS Clin)

Precision medicine and adjuvant therapy for ER+ breast cancer

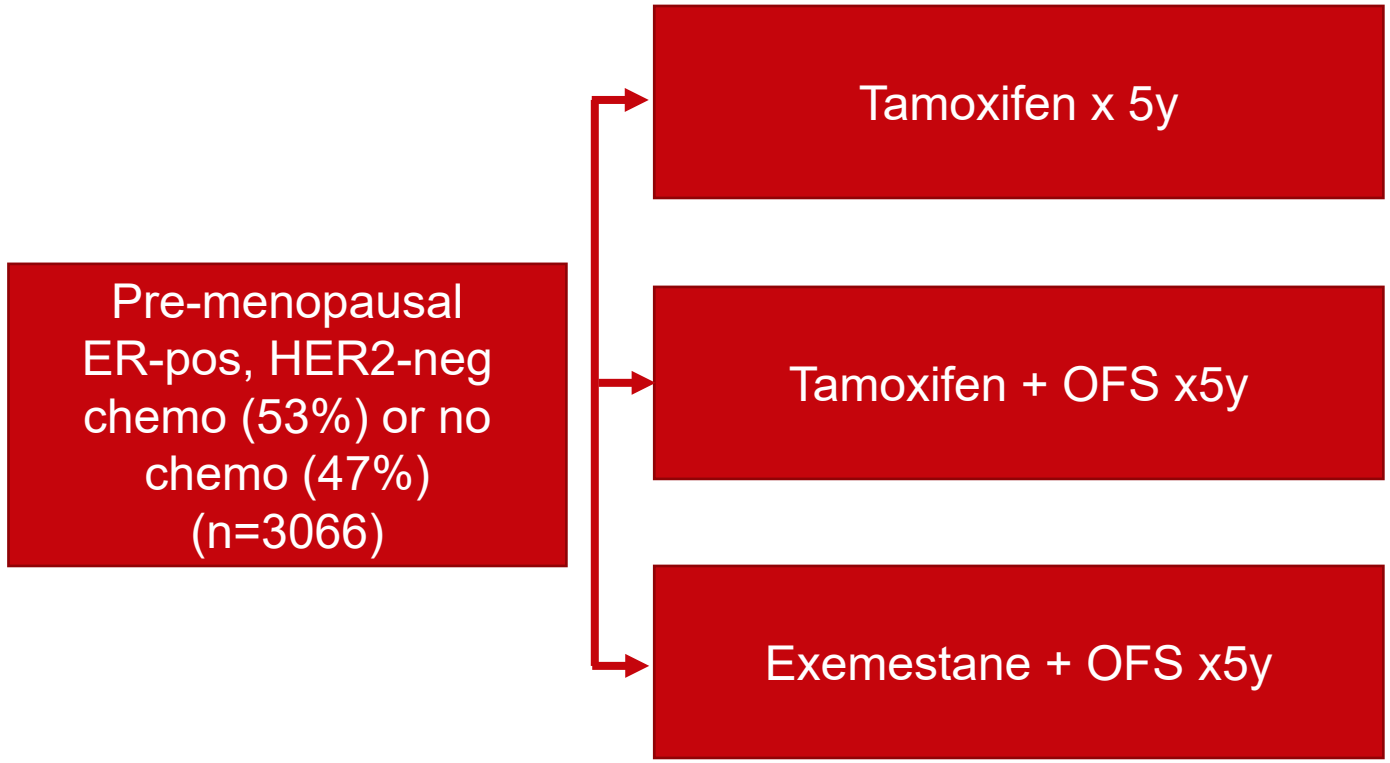
	Chemotherapy vs No chemotherapy	Tamoxifen AI Ovarian suppression	Bisphosphonates CDK4/6i	Extended endocrine therapy
Prognostic biomarkers	**Clinicopathologic data** → Oncotype DX RS, MammaPrint, Prosigna, EndoPredict, Breast Cancer Index			
Predictive biomarkers	Oncotype DX RS			Breast Cancer Index

- **Breast Cancer Index and OFS benefit in the SOFT trial (GS01-06, O'Regan et al)**

SOFT trial


Pre-menopausal ER-pos, HER2-neg chemo (53%) or no chemo (47%) (n=3066)
Tamoxifen x 5y
Tamoxifen + OFS x5y
Exemestane + OFS x5y

SOFT trial



Key findings:

- significant 3% improvement in 12 DRFI for EXE + OFS vs Tam alone
- 1.4% improvement in 12 year DRFI for Tam + OFS vs Tam alone

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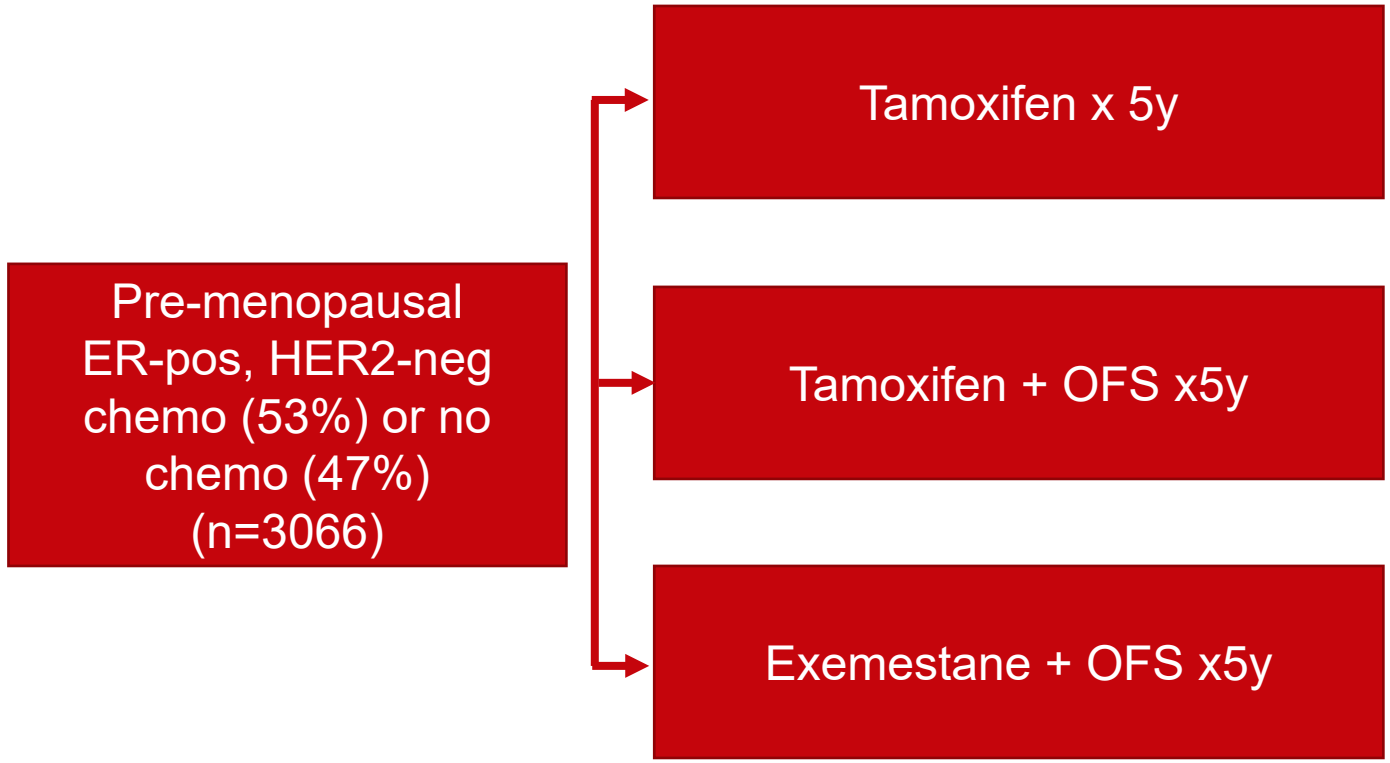

Key findings:

- significant 3% improvement in 12 DRFI for EXE + OFS vs Tam alone
- 1.4% improvement in 12 year DRFI for Tam + OFS vs Tam alone

- Given increased toxicity of OFS + AI approach, biomarkers to select patients who will benefit from this approach are needed
- Currently clinicopathologic risk factors are used
- No genomic biomarkers have been identified to predict benefit

Breast Cancer Index

- BCI consists of two gene expression components:
  - Molecular Grade Index - 5 genes related to tumor proliferation
  - H/I – 2 gene ratio related to estrogen signaling
  - BCIN+ adds tumor size and grade for node positive patients
- BCI prognostic for late (>5 year) recurrence
- High H/I ratio predictive of extended endocrine therapy benefit

Zhang et al. CCR 2013 (PMID: 23757354), Zhang et al. CCR 2017 (PMID: 28939745), Sgroi et al. Lancet Oncology 2013 (PMID: 24035531), Sgroi et al. JNCI 2013 (PMID: 23812955), Bartlett et al. CCR 2022 (PMID: 35144966), Noordhoek et al. CCR 2021 (PMID: 33109739)

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Translational analysis of the SOFT trial to test the following hypotheses:

1. BCI will be prognostic for recurrence in premenopausal women
2. High H/I ratio will predict benefit of OFS

Zhang et al. CCR 2013 (PMID: 23757354), Zhang et al. CCR 2017 (PMID: 28939745), Sgroi et al. Lancet Oncology 2013 (PMID: 24035531), Sgroi et al. JNCI 2013 (PMID: 23812955), Bartlett et al. CCR 2022 (PMID: 35144966), Noordhoek et al. CCR 2021 (PMID: 33109739)

Translational analysis cohort

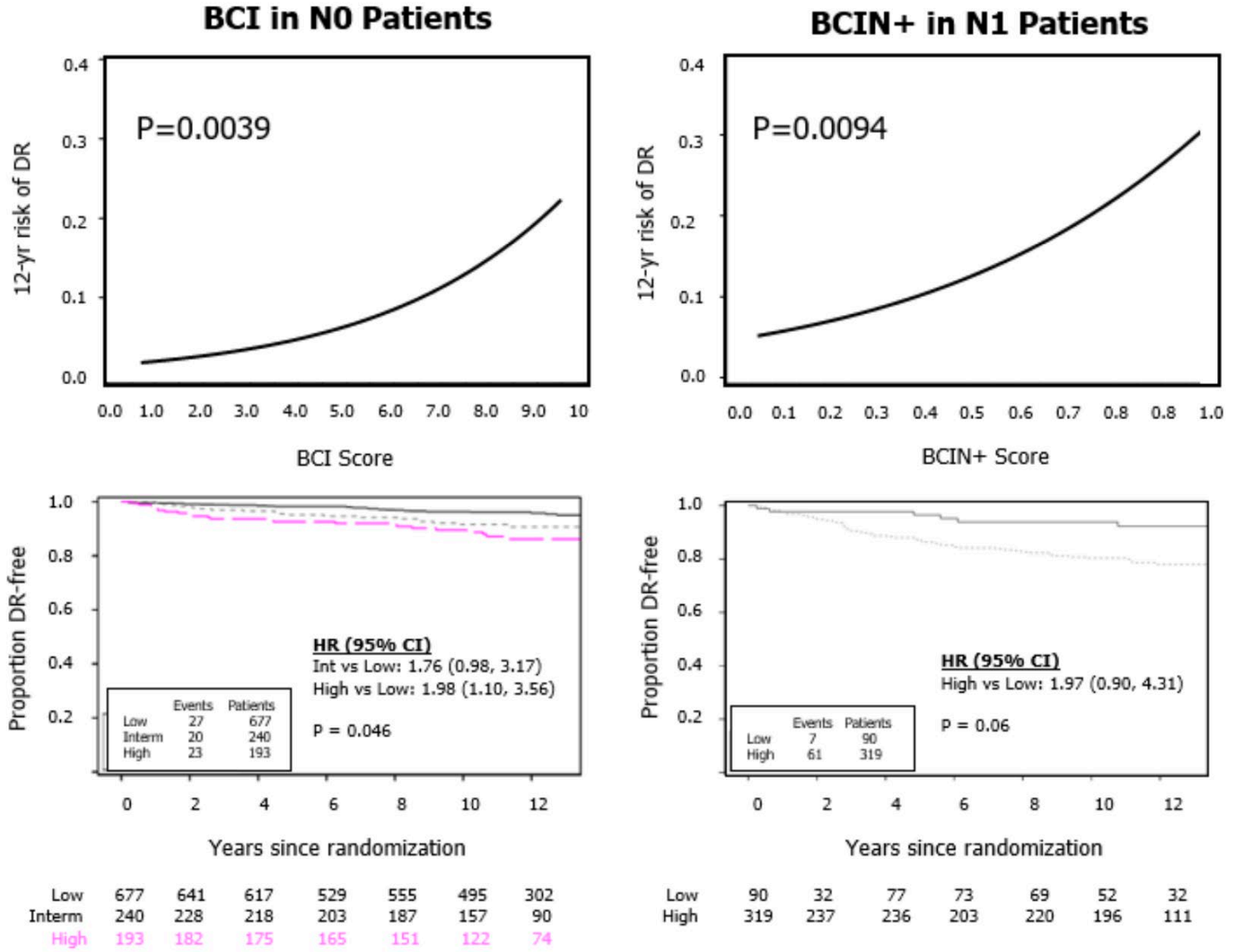
	SOFT ITT Cohort		BCI Analysis Cohort	
	N	%	N	%
N patients randomized	3047	100	1687	100
Chemotherapy				
No	1419	46.6	878	46.7
Yes	1628	53.4	900	53.3
Nodal Status				
pN0	1995	65.5	1110	65.8
pN+ 1-3	754	24.7	426	25.3
pN+ 4+	298	9.8	151	9.0
Age at randomization				
<35	350	11.5	190	11.3
35-39	583	19.1	322	19.1
40-44	907	29.8	498	29.5
45-49	910	29.9	499	29.6
50+	297	9.7	178	10.6
Tumor size				
≤ 2cm	2013	66.1	1082	64.1
> 2cm	964	31.6	580	34.4
Unknown	70	2.3	25	1.5
Tumor grade				
1	789	25.9	428	25.4
2	1555	51.0	846	50.1
3	642	21.1	387	22.9
Unknown	61	2.0	26	1.5

Treatment in the BCI analysis cohort:

Tam n = 573
Tam + OFS n = 551
Exe + OFS n = 563

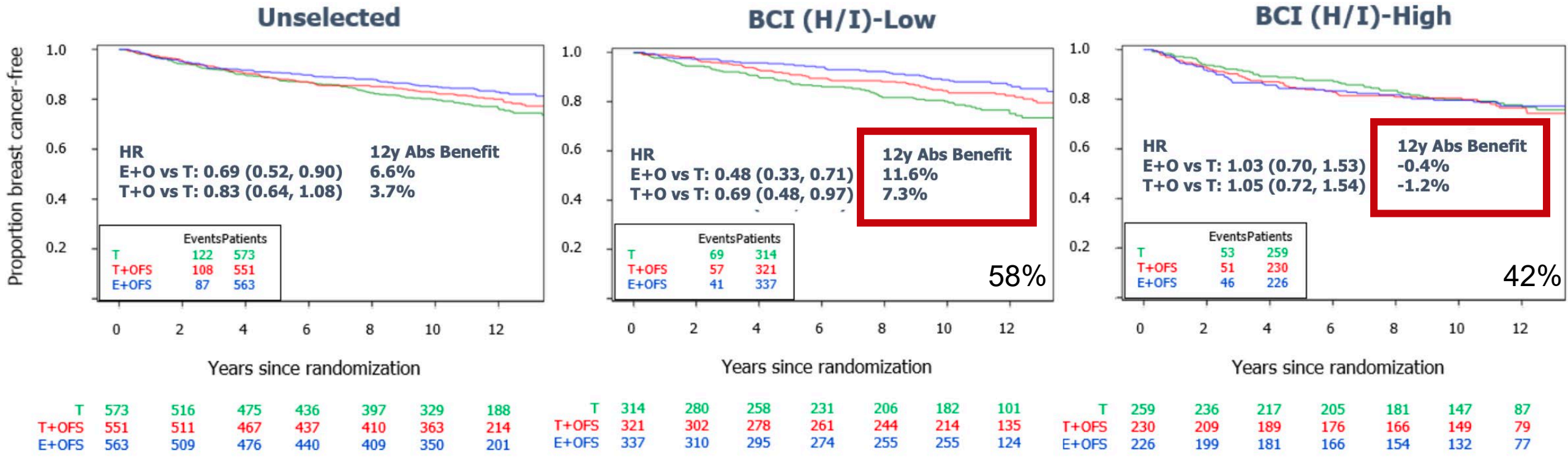
O'Regan et al. SABCS 2022 GS01-06

BCI is prognostic in pre-menopausal women



O'Regan et al. SABCS 2022 GS01-06

Low H/I ratio predicts OFS benefit vs Tam



T	573	516	475	436	397	329	188
T+OFS	551	511	467	437	410	363	214
E+OFS	563	509	476	440	409	350	201

T	314	280	258	231	206	182	101
T+OFS	321	302	278	261	244	214	135
E+OFS	337	310	295	274	255	255	124

T	259	236	217	205	181	147	87
T+OFS	230	209	189	176	166	149	79
E+OFS	226	199	181	166	154	132	77

O'Regan et al. SABCS 2022 GS01-06

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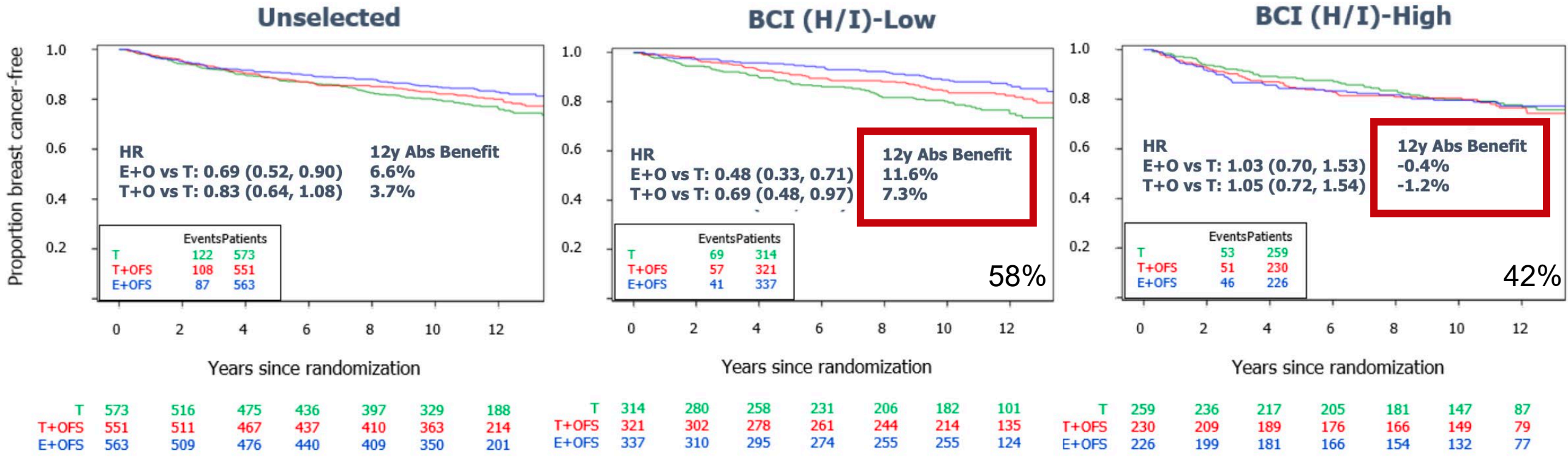
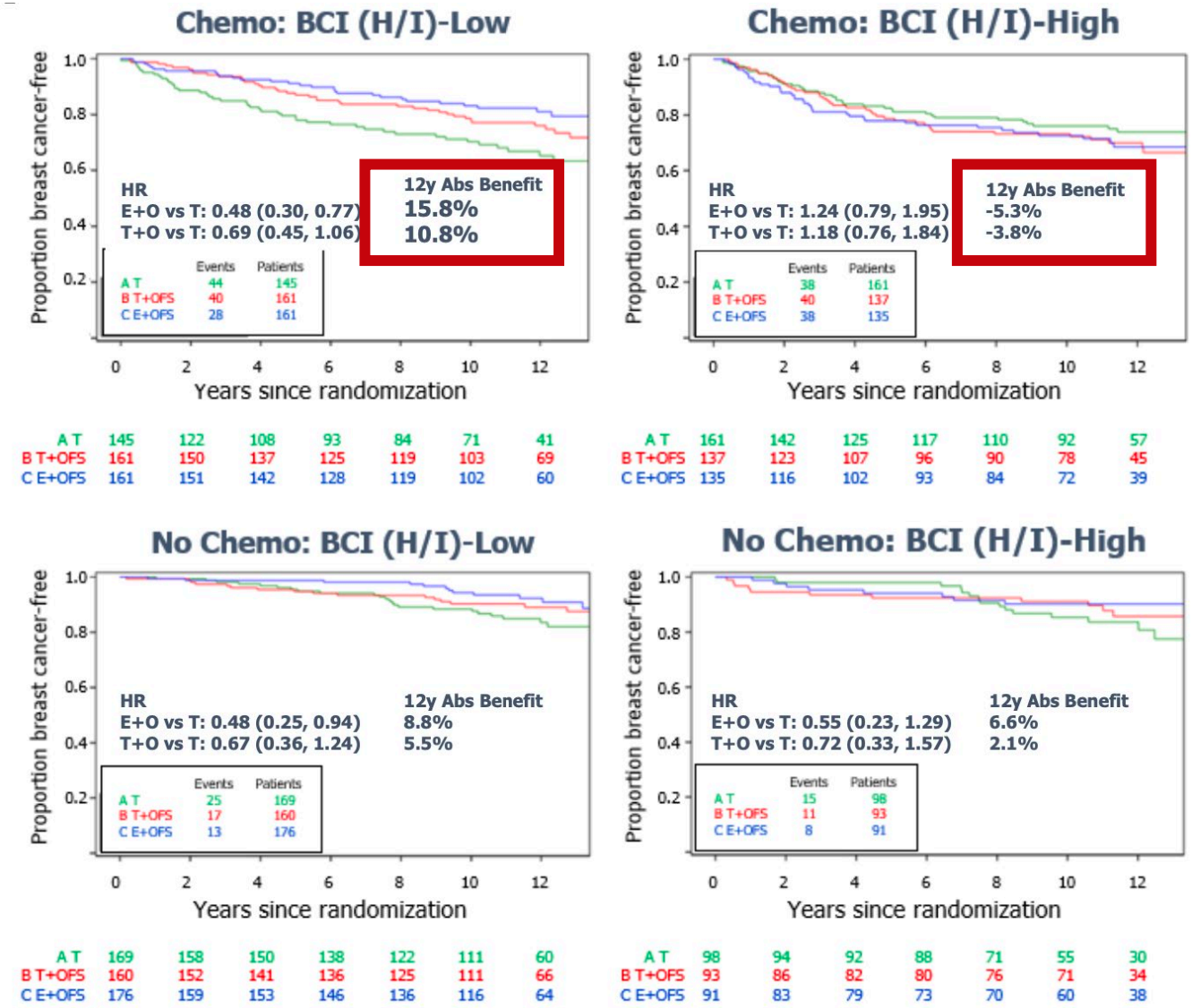


- Unexpectedly, H/I **low** was predictive of OFS benefit with significant treatment by biomarker interaction for Exe + OFS vs Tam

O'Regan et al. SABCS 2022 GS01-06

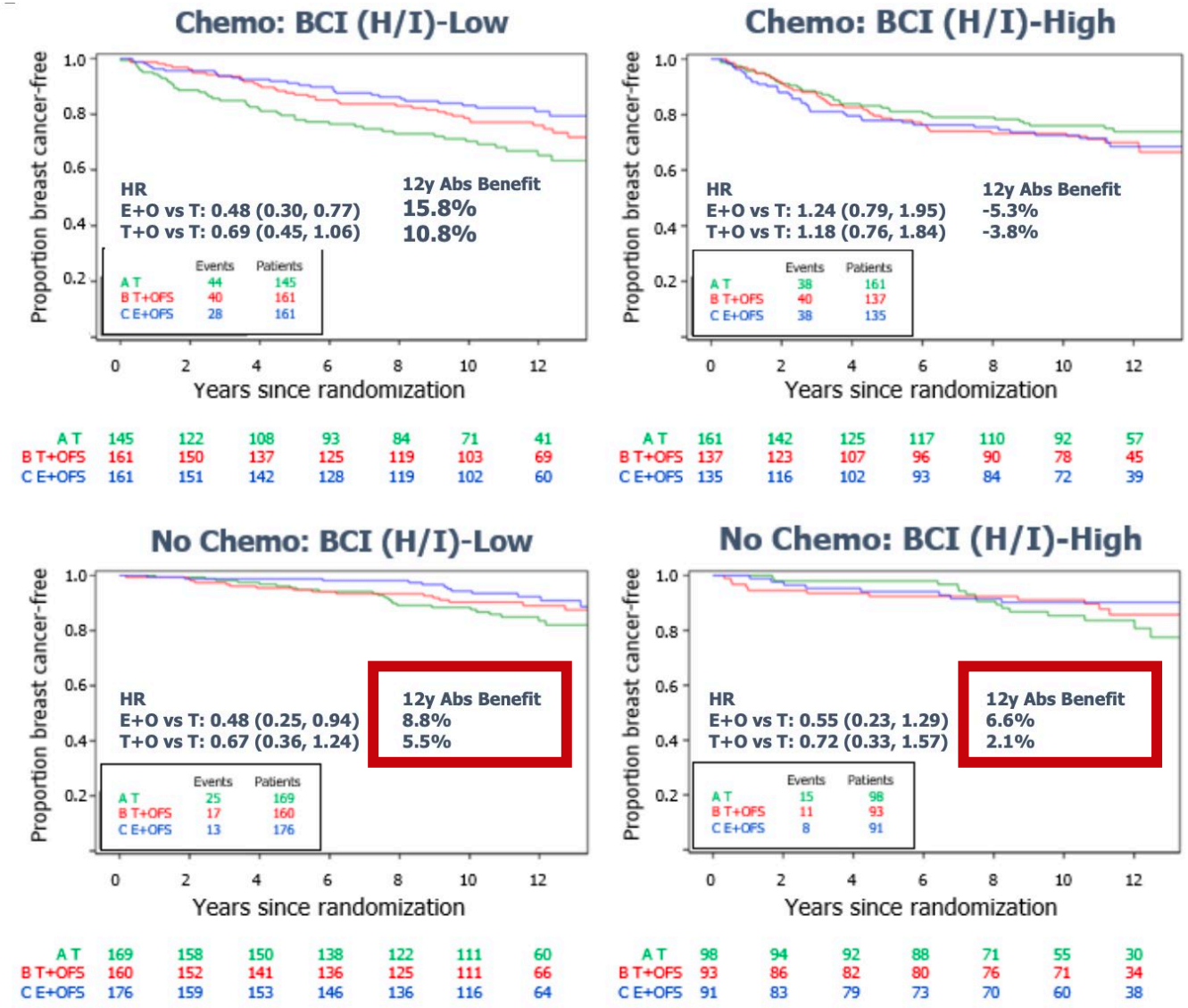
Low H/I ratio predicts OFS benefit vs Tam



- This is true regardless of prior chemotherapy

O'Regan et al. SABCS 2022 GS01-06

Low H/I ratio predicts OFS benefit vs Tam



- This is true regardless of prior chemotherapy

O'Regan et al. SABCS 2022 GS01-06

BCI in the SOFT trial - summary

Conclusions:

- BCI prognostic in pre-menopausal women with early-stage ER+ breast cancer, **concordant** with prior studies
- Unexpectedly, **low** H/I ratio predicted benefit for OFS versus tamoxifen alone, **in contrast** to high ratio previously shown to predict extended endocrine therapy benefit

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- Unexpectedly, **low** H/I ratio predicted benefit for OFS versus tamoxifen alone, **in contrast** to high ratio previously shown to predict extended endocrine therapy benefit
  - Suggests difference in tumor biology in pre-menopausal women or between early and late recurrence

BCI in the SOFT trial - summary

Caveats:

- BCI predictive analyses including this one have been entirely retrospective thus far
- Discordant predictive value of H/I ratio for OFS versus EET may be due to underlying biological differences but this remains unclear

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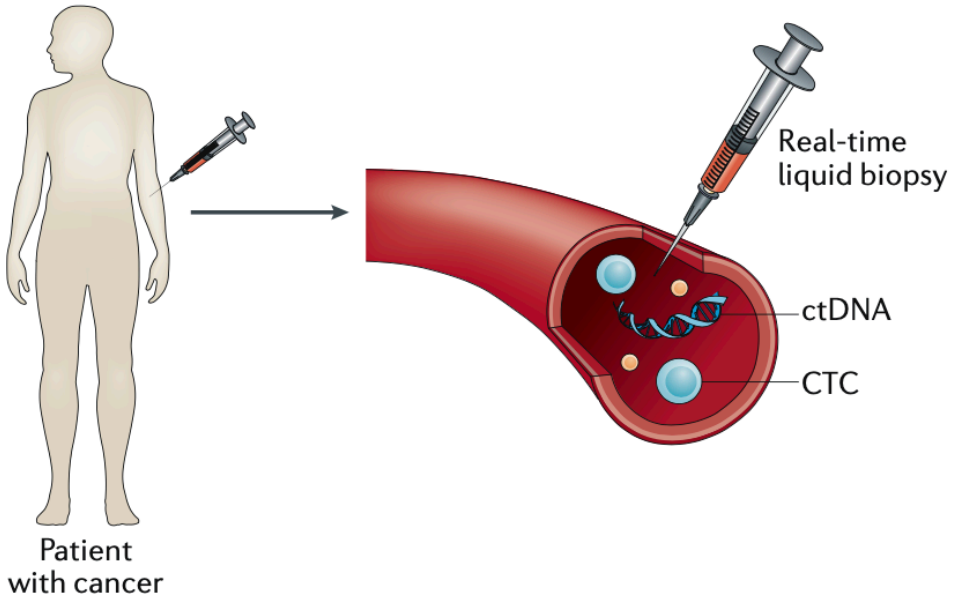
Take home: intriguing data suggesting a possible genomic biomarker to select patients most likely to benefit from OFS, but would benefit from additional validation and translational studies before routine clinical implementation

Agenda

1. Genomic predictors for adjuvant therapy selection in localized ER+ breast cancer:
    - Long term outcomes from the TAILORx trial
    - Does Breast Cancer Index predict benefit of ovarian function suppression in pre-menopausal women in the SOFT trial?
2. Liquid biopsies for evaluation of endocrine therapy resistance in localized and advanced ER+ breast cancer

circulating tumor DNA - detection



Pantel et al. Nature Reviews Clinical Oncology 2019 (PMID: 30796368)

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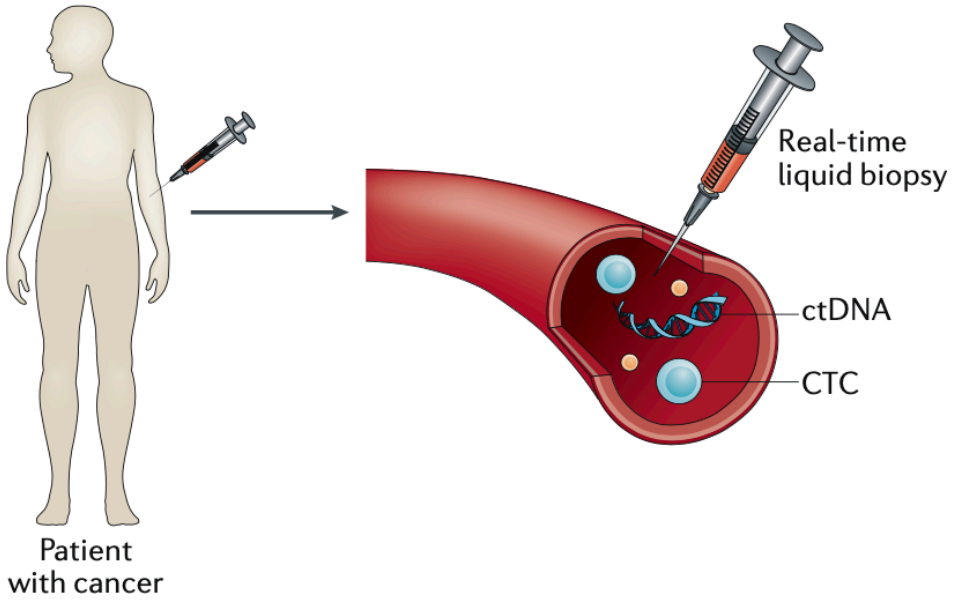

ctDNA detection – many different types of approaches:

- Single genes
- Targeted sequencing
- Whole exome/genome

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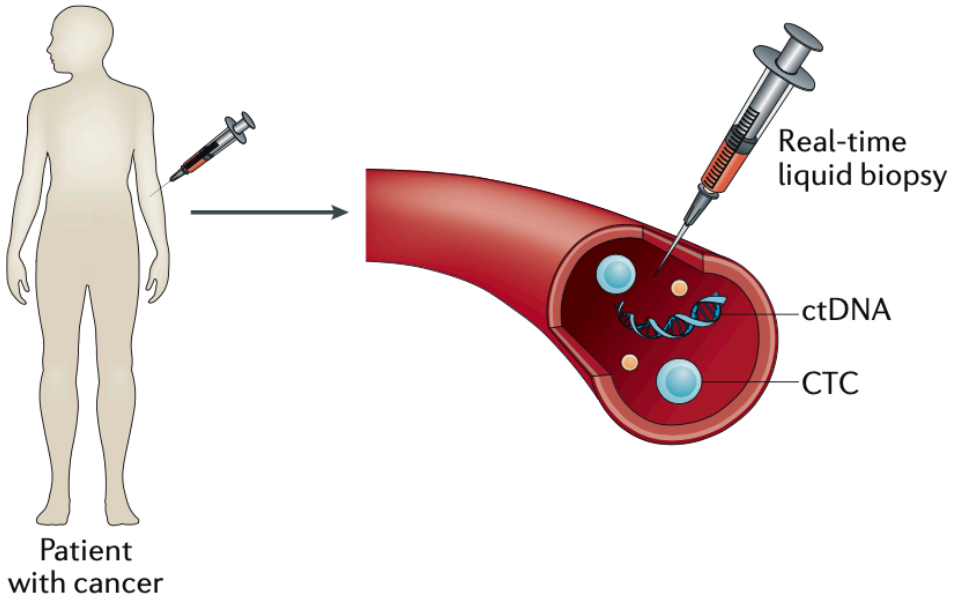

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1. Tumor agnostic = the same set of genes for every patient
    - Lower sensitivity but faster turnaround and less expensive - best for detecting mutations in metastatic disease

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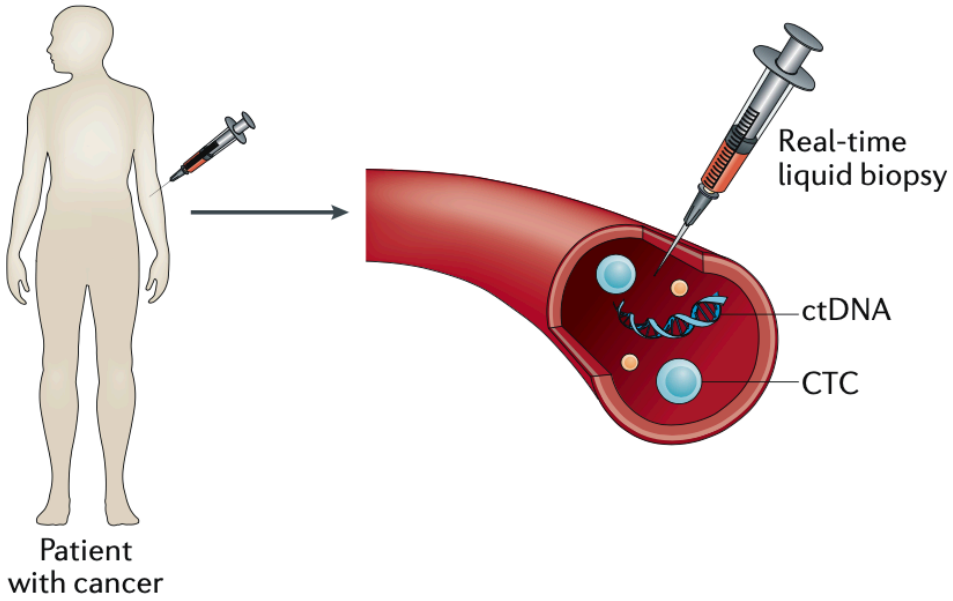

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2. Tumor informed = custom patient-specific mutation panel developed from tissue biopsy
    - Higher sensitivity, typically used for MRD detection

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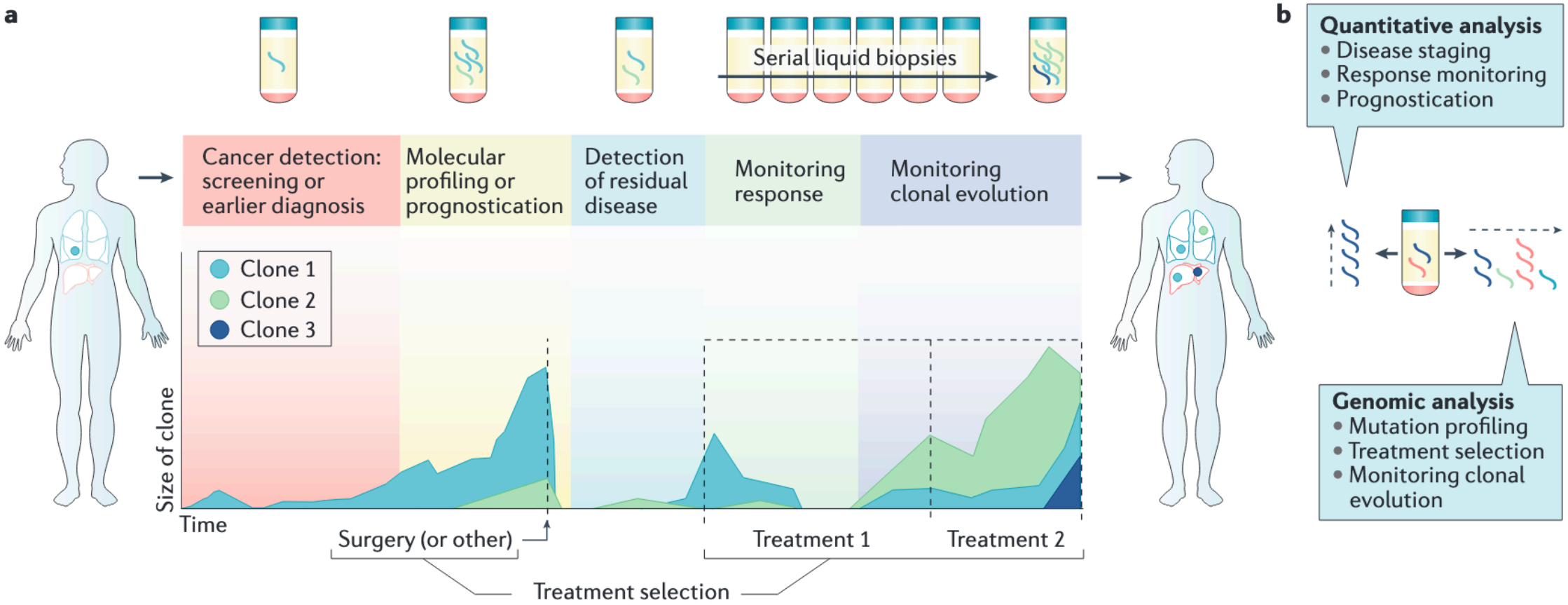
circulating tumor DNA – clinical applications



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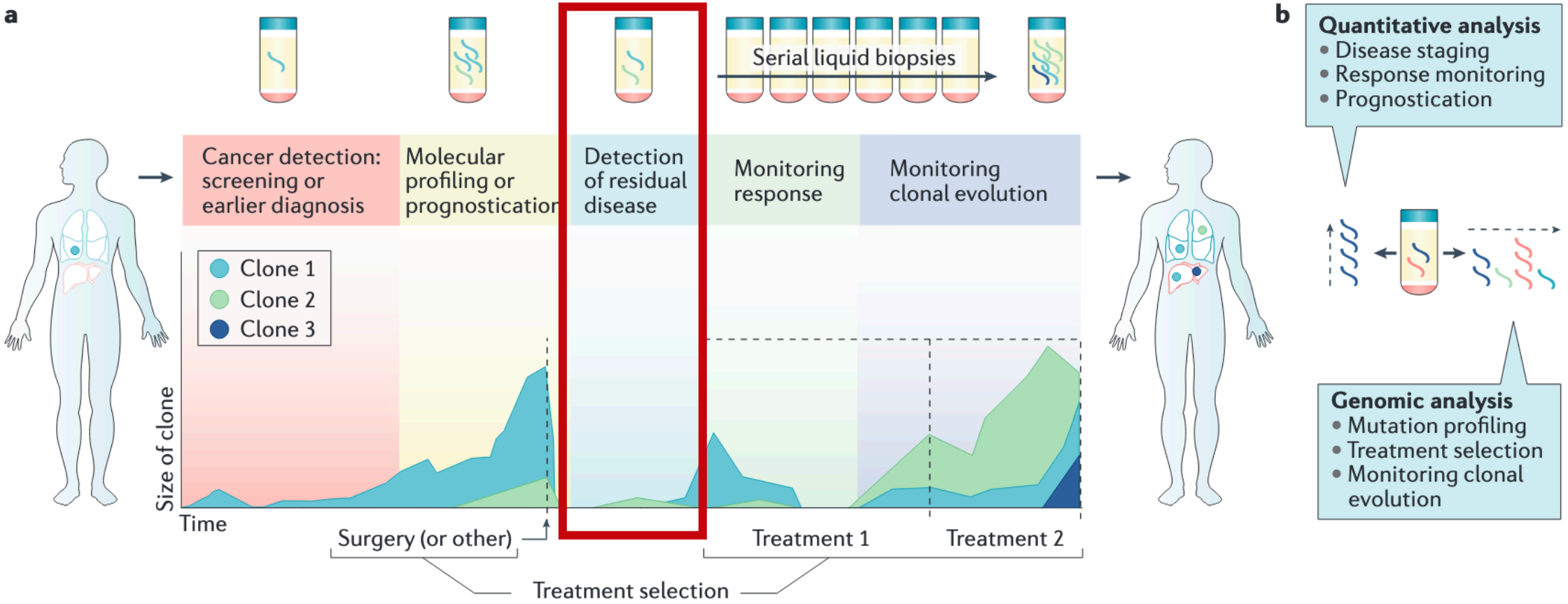

- **ctDNA monitoring in a phase II study of adjuvant endocrine therapy with ribociclib for localized ER+ breast cancer (PD017-03, Medford et al.)**

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The LEADER trial

- Prospective phase II trial evaluating 1 year of ribociclib added to adjuvant endocrine therapy (ET) for patients with at least 1 remaining year of ET
- Part 1 evaluated the safety of two ribociclib schedules when combined with ET
- Plasma samples were collected at baseline and serially on treatment and analyzed via the signatera platform

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- Question: is ctDNA detection on treatment associated with subsequent clinical relapse?

PD017-03: LEADER part 1 ctDNA results

- 42/81 patients had at least 1 ctDNA sample
  - 22 had 3 serial samples
  - 17 had 2 serial samples
  - 3 had 1 sample
- Clinical follow up: 20 months, 2-year RFS 97%

Medford et al, SABCS 2022 PD017-03

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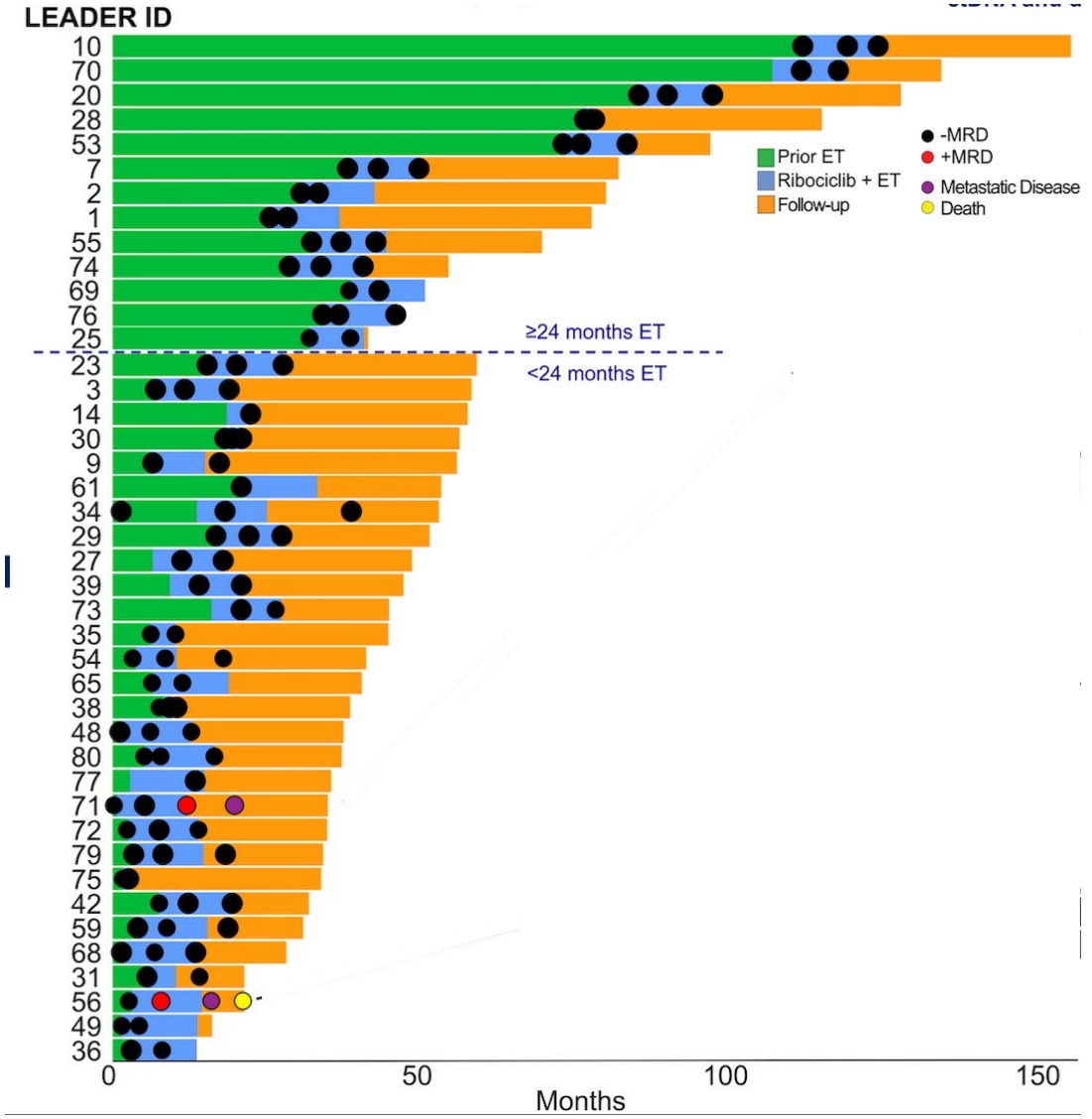
- 42/81 patients had at least 1 ctDNA sample
  - 22 had 3 serial samples
  - 17 had 2 serial samples
  - 3 had 1 sample
- Clinical follow up: 20 months, 2-year RFS 97%
- Only 2/42 patients had detectable ctDNA during follow up
- Both ctDNA+ patients relapsed with 7-8 months between ctDNA positivity and radiographic progression



Medford et al, SABCS 2022 PD017-03

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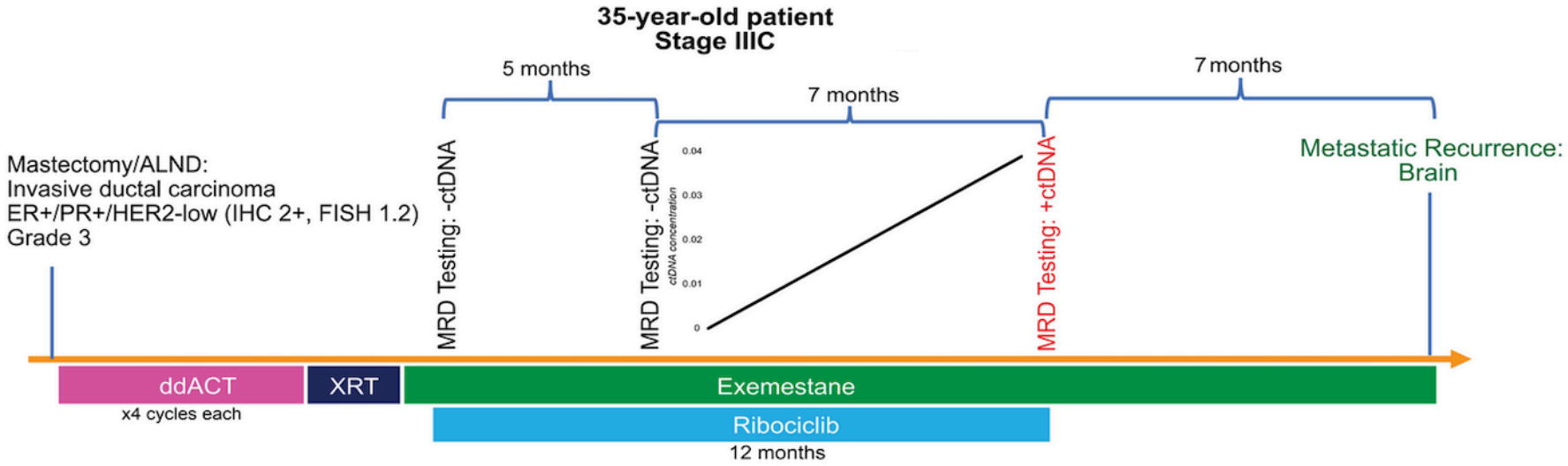

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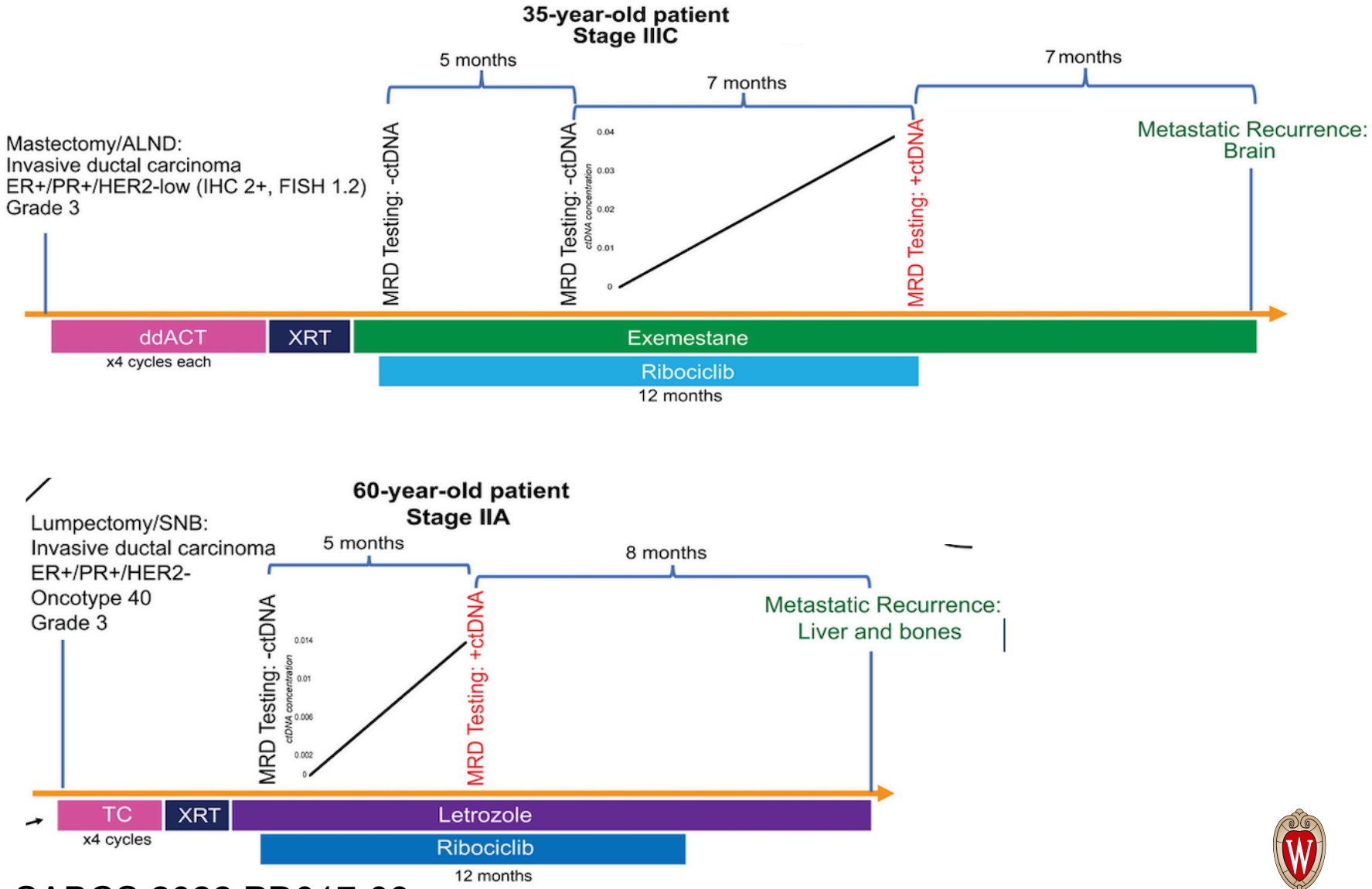

Medford et al, SABCS 2022 PD017-03

PD017-03 and ctDNA MRD monitoring

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  - Ongoing clinical trials across breast cancer subtypes
    - ER+ disease: DARE trial – evaluating switch to fulvestrant/palbociclib if ctDNA positive during adjuvant AI
    - TNBC: PERSEVERE trial – in patients with residual disease after neoadjuvant therapy, evaluating genomically directed therapy for patients who are ctDNA positive

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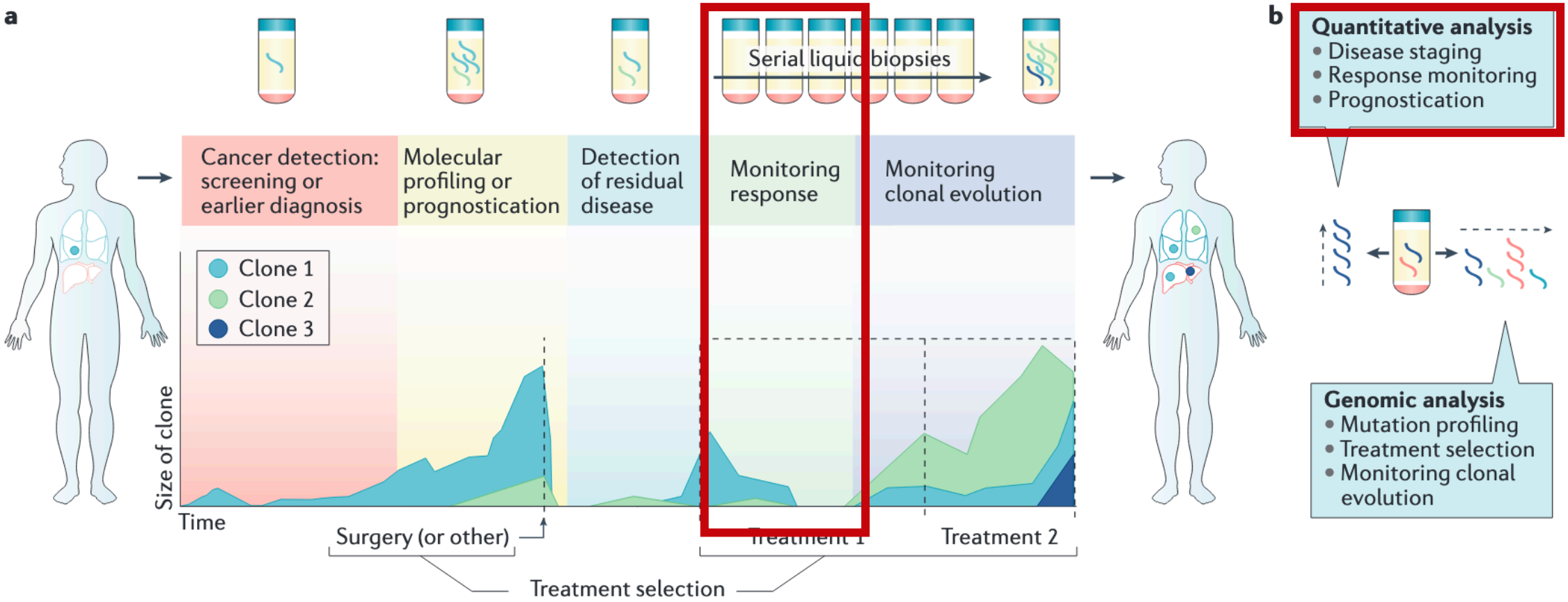
Take home: ctDNA MRD testing shows promise in localized breast cancer, but more research is needed to understand the sensitivity/specificity of these assays in larger populations and identify effective interventions for ctDNA positive patients.

circulating tumor DNA – clinical applications



- **ctDNA molecular response and clinical outcomes in advanced ER+ breast cancer on first line AI (PD017-02, Bailleux et al)**

Wan et al, Nature Reviews Cancer 2017 (PMID: 28233803)

PD017-02: ctDNA molecular response and clinical outcomes in advanced ER+ breast cancer on first line AI

- Evaluated 389 patients starting first line AI for metastatic ER+ breast cancer
- ctDNA collected at baseline and 4 weeks on treatment and targeted NGS (Guardant360 – tumor agnostic) performed

PD017-02: ctDNA molecular response and clinical outcomes in advanced ER+ breast cancer on first line AI

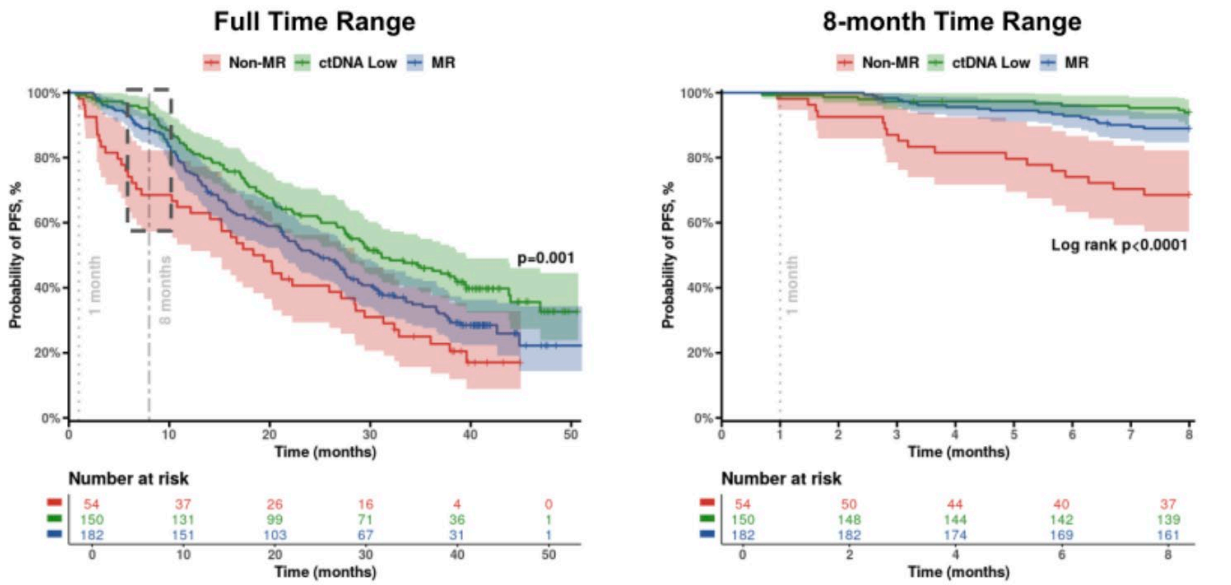
- Evaluated 389 patients starting first line AI for metastatic ER+ breast cancer
- ctDNA collected at baseline and 4 weeks on treatment and targeted NGS (Guardant360 – tumor agnostic) performed
- Question: can ctDNA dynamics early on treatment predict clinical response to AI in metastatic breast cancer?

PD017-02: ctDNA molecular response and clinical outcomes in advanced ER+ breast cancer on first line AI

- 372/389 had evaluable baseline and on-treatment samples
- 238 (64%) had detectable ctDNA at least once
- Molecular response defined as a 50% decrease in ctDNA fraction from baseline to 4-week sample

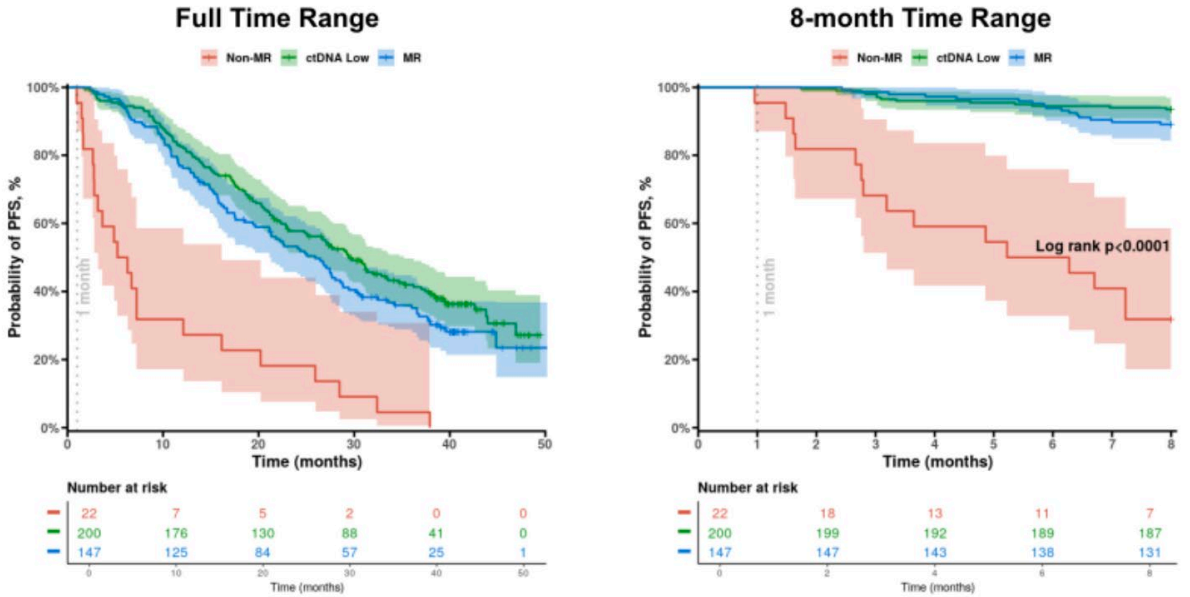
Bailleux et al,
SABCS 2022
PD017-02

PD017-02: ctDNA molecular response and clinical outcomes in advanced ER+ breast cancer on first line AI



	Full time range HR (95% CI); p-value	8-month HR (95% CI); p-value
MR + ctDNA Low vs Non-MR	0.61 (0.44 - 0.85), p<0.01	0.24 (0.13 - 0.43), p=0.0001

All mutations used to calculate MR



	Full time range HR (95% CI); p-value	8-month HR (95% CI); p-value
MR + ctDNA Low vs Non-MR	0.23 (0.14 - 0.35), p < 0.001	0.08 (0.04 - 0.17), p<0.001

Breast cancer specific genes used to calculate MR

- Patients who did not achieve MR had significantly shorter PFS on first line AI than patients with MR or no detectable ctDNA (”ctDNA low”)

Bailleux et al, SABCS 2022 PD017-02

PD017-02: ctDNA response as a pharmacodynamic biomarker in advanced ER+ breast cancer

- Highlights the unique potential of liquid biopsy assays for serial monitoring and the development of pharmacodynamic predictors of response
- While only 64% of patients had at least 1 detectable ctDNA sample, the superior PFS of patients with undetectable ctDNA suggests that a negative result (which may reflect tumor burden) has prognostic value as well.

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Take home: ctDNA dynamics shows early promise as biomarker of treatment response in advanced ER+ breast cancer, and with additional validation, this could be developed into a predictive biomarker to identify early endocrine therapy resistance and target those patients for novel treatment approaches.

Summary

Genomic predictors for adjuvant therapy selection in localized ER+ breast cancer:

- Long term outcomes from the TAILORx trial – *confirmed how we currently use Oncotype DX clinically, and added nuance to our understanding of chemotherapy benefit for premenopausal women with RS 16-25*
- Does Breast Cancer Index predict benefit of ovarian function suppression in pre-menopausal women in the SOFT trial – *BCI is prognostic in pre-menopausal women, and may be predictive of OFS benefit, though with some caveats requiring additional investigation.*

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2. Liquid biopsies for evaluation of endocrine therapy resistance in localized and advanced ER+ breast cancer

- ctDNA monitoring in a phase II study of adjuvant endocrine therapy with ribociclib for localized ER+ breast cancer
- ctDNA molecular response and clinical outcomes in advanced ER+ breast cancer on first line AI
- *Highlighted ways that ctDNA is showing promise as a biomarker of treatment response and resistance in localized and metastatic breast cancer, though further study is required to understand how to implement these types of tests clinically*

Acknowledgements

- Dr. Wisinski, Dr. Kamaraju, and the WAHO team for the opportunity to share these updates!