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

Friday, February 3, 2023
9:55 AM – 10:55 AM [CST]

Neoadjuvant/Adjuvant Treatment for Breast Cancer with SABCS Updates

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NCCN 2023 BREAST CANCER CONGRESS
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Neoadjuvant/Adjuvant Treatment for Breast Cancer with SABCS Updates

HER2-Negative Breast Cancer

Rachel C. Jankowitz, MD

Abramson Cancer Center at the University of Pennsylvania

Outline

- **Neoadjuvant Therapy (NAT) for breast cancer**
  - Evolution, guiding principles
- **Systemic Therapy for TNBC**
  - NAT: current standard, role of platinum and immunotherapy
  - Adjuvant therapy
- **Systemic Therapy for HR+, HER2-negative breast cancer**
  - NAT: traditional indications, future directions
  - Adjuvant therapy update
- **Conclusions**

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Neoadjuvant Therapy (NAT) for Breast Cancer

- NAT: preferred for high risk TNBC & HER2+ & indicated for some HR+, HER2-negative
- RCTs: Similar outcomes when same treatment given pre-op vs. post-op
- Older studies: suggest increased risk of LRR following NAT, but included now non-standard chemotherapy, did not include targeted therapies, & did not use modern imaging techniques/ local regional management.
- Correlation between increased pCR & long-term outcome =strongest for TNBC, somewhat less for HER2+, and least for ER+
- Improves operability: (facilitate breast conservation, decrease ALND)
- Prognostic information based on response:
  - Inform adjuvant therapy
  - Platform for drug-development: (novel agents, predictive biomarkers)
  - Adaptive designs can facilitate earlier assessment of response

Spring, L. J Natl Compr Canc Netw 2022;20(6):723–734
BINV-M. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer (Version 1.2023).
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Systemic Therapy for TNBC:

- Up-front surgery only for small, node-negative tumors
- Neoadjuvant (NAT) Therapy for most
  - NCCN: NAT therapy preferred for ≥cT2 or ≥ cN1 TNBC; can be considered for cT1cN0
  - ASCO 2021: NAT therapy with anthracycline and taxane- for node-positive and/or at least T1c TNBC (any stage other than cT1a/bN0)

Spring, L. J Natl Compr Canc Netw 2022;20(6):723–734; Tamirisa, N. Ann Surg Oncol (2022) 29:1489–1492
BINV-M. NCCN Guidelines® for Breast Cancer (Version 1.2023).

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Neoadjuvant Platinum for TNBC:

- Cytotoxic polychemotherapy (Anthracyclines, taxanes) has been the mainstay of NAT for TNBC, but what is the current evidence for adding platinum?

- 2018 meta-analysis of adding platinum to NACT for TNBC: reported significant increases in pCR rates [absolute gain 15% (37% → 52%) OR 1.96 95% CI 1.46-2.62 p<0.001], but no significant EFS benefit[1]
  - -meta-analysis included 2109 patients from 9 RCTs
  - -only 2 trials reporting on survival outcomes

1. Poggio F. Ann Oncol 2018;29:1497–1508.

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BrighTNess Trial

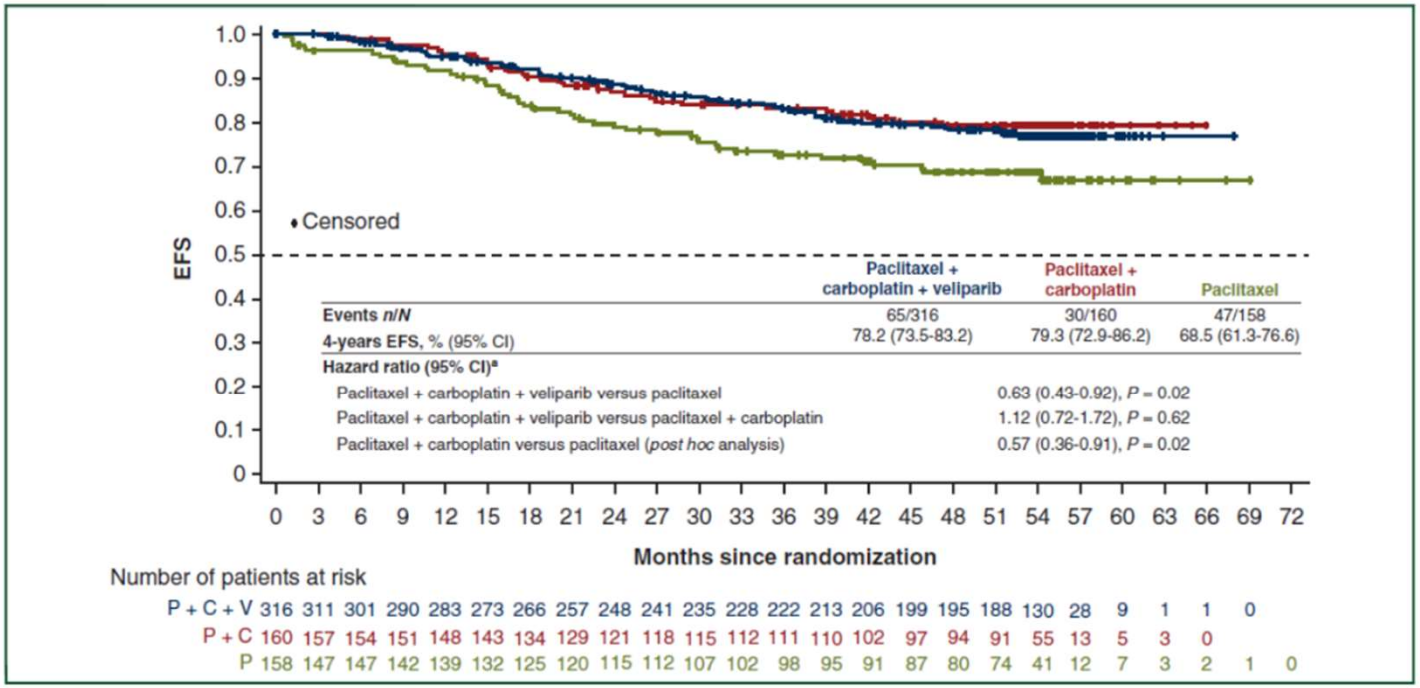

Figure 2. EFS with a median of ≥4.5 years of follow-up.
Final analysis of EFS carried out ≥4 years after surgery.
C, carboplatin; CI, confidence interval; EFS, event-free survival; g*BRCA*, germline *BRCA*; P, paclitaxel; V, veliparib.
[a]Stratified by g*BRCA* status, lymph node status, and planned doxorubicin/cyclophosphamide dose intensity.

Geyer CE. Ann Oncol 2022; 33:384–394

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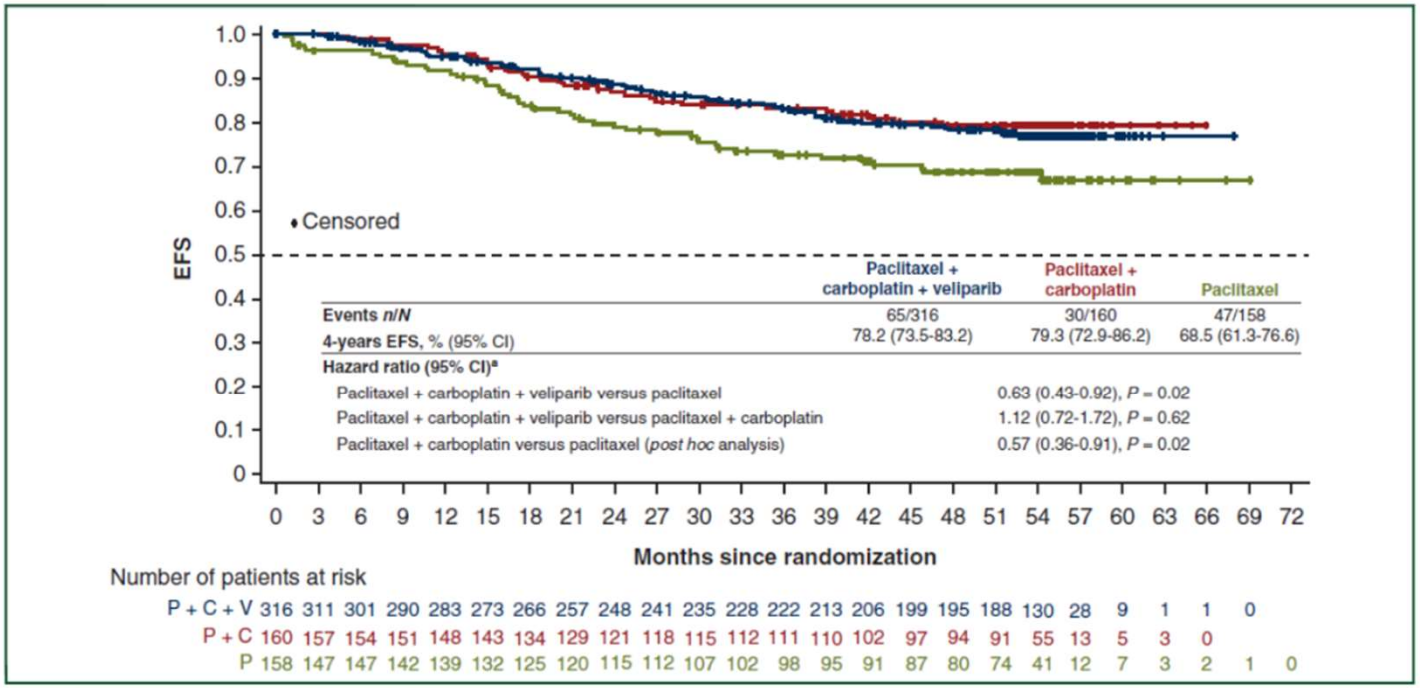
BrighTNess Trial



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- 4.5 Year f/u: significant EFS (~10%) benefit with carboplatin added to NACT (HR 0.57; p=0.18)

Geyer CE. Ann Oncol 2022; 33:384–394

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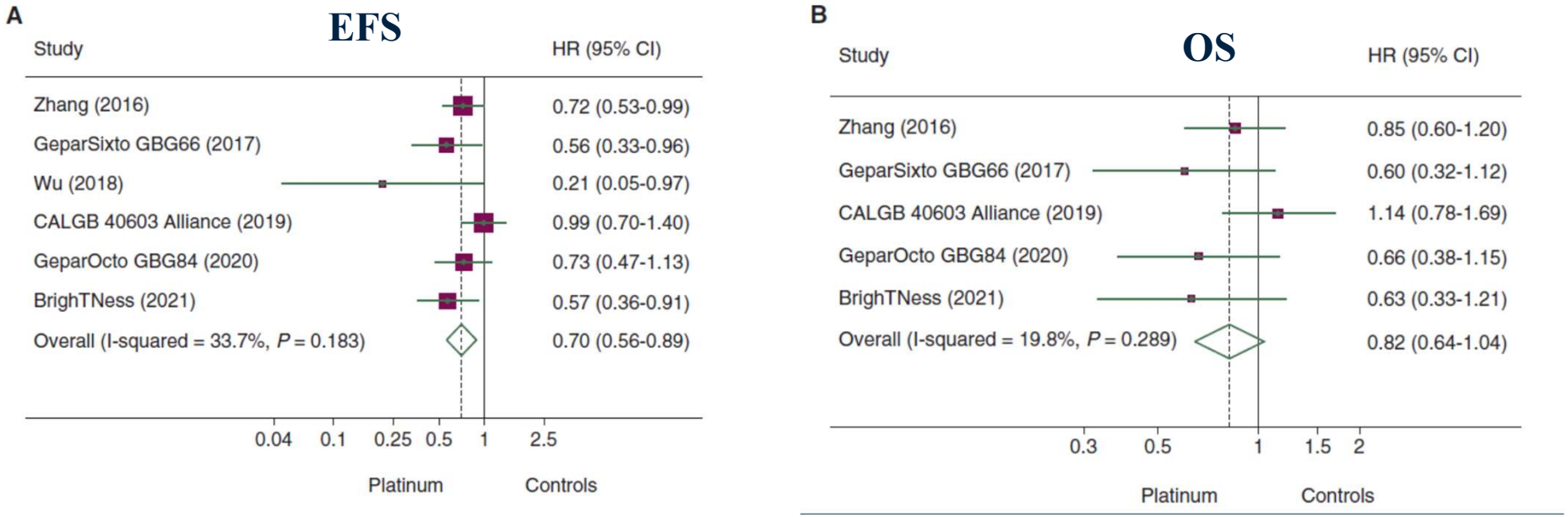
Role of Platinum in TNBC: "The End of the Debate," or More Fodder?

- Updated meta-analysis[3]: significantly increased EFS (HR 0.70) & nonsignificant 18% reduction in the risk of death (HR, 0.82) with platinum-based NACT



Poggio F. Ann Oncol 2022;33:347–349

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Addition of platinum to sequential taxane-anthracycline neoadjuvant chemotherapy in patients with triple-negative breast cancer: A phase III randomized controlled trial

Sudeep Gupta, M.D., D.M.; on behalf of

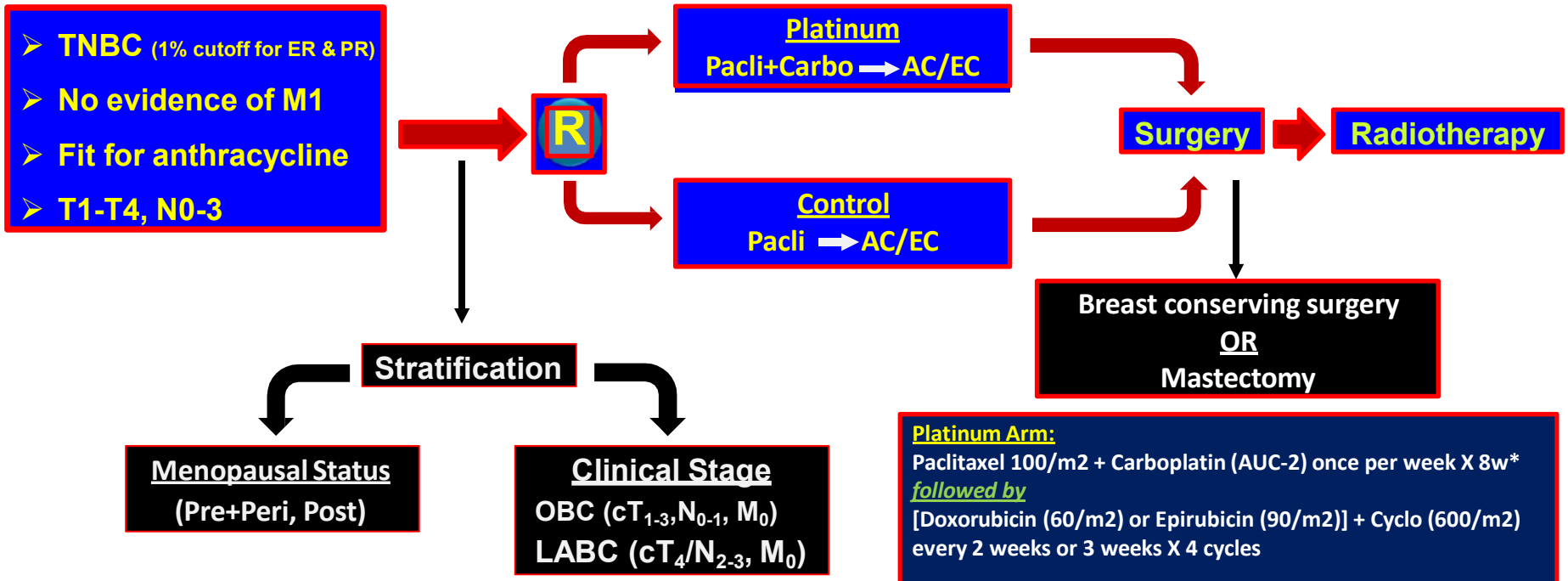
Nita S Nair, Rohini W Hawaldar, Vaibhav Vanmali, Vani Parmar, Seema Gulia, Jaya Ghosh, Shalaka Joshi, Rajiv Sarin, Tabassum Wadasadawala, Tejal Panhale, Sangeeta Desai, Tanuja Shet, Asawari Patil, Garvit Chitkara, Sushmita Rath, Jyoti Bajpai, Meenakshi Thakur, and Rajendra A Badwe.

Breast Cancer Working Group, Tata Memorial Centre, Mumbai

Funded by Tata Memorial Centre, Mumbai

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

TMC Neoadjuvant Platinum TNBC Study



Platinum Arm:
Paclitaxel 100/m2 + Carboplatin (AUC-2) once per week X 8w*
followed by
[Doxorubicin (60/m2) or Epirubicin (90/m2)] + Cyclo (600/m2) every 2 weeks or 3 weeks X 4 cycles

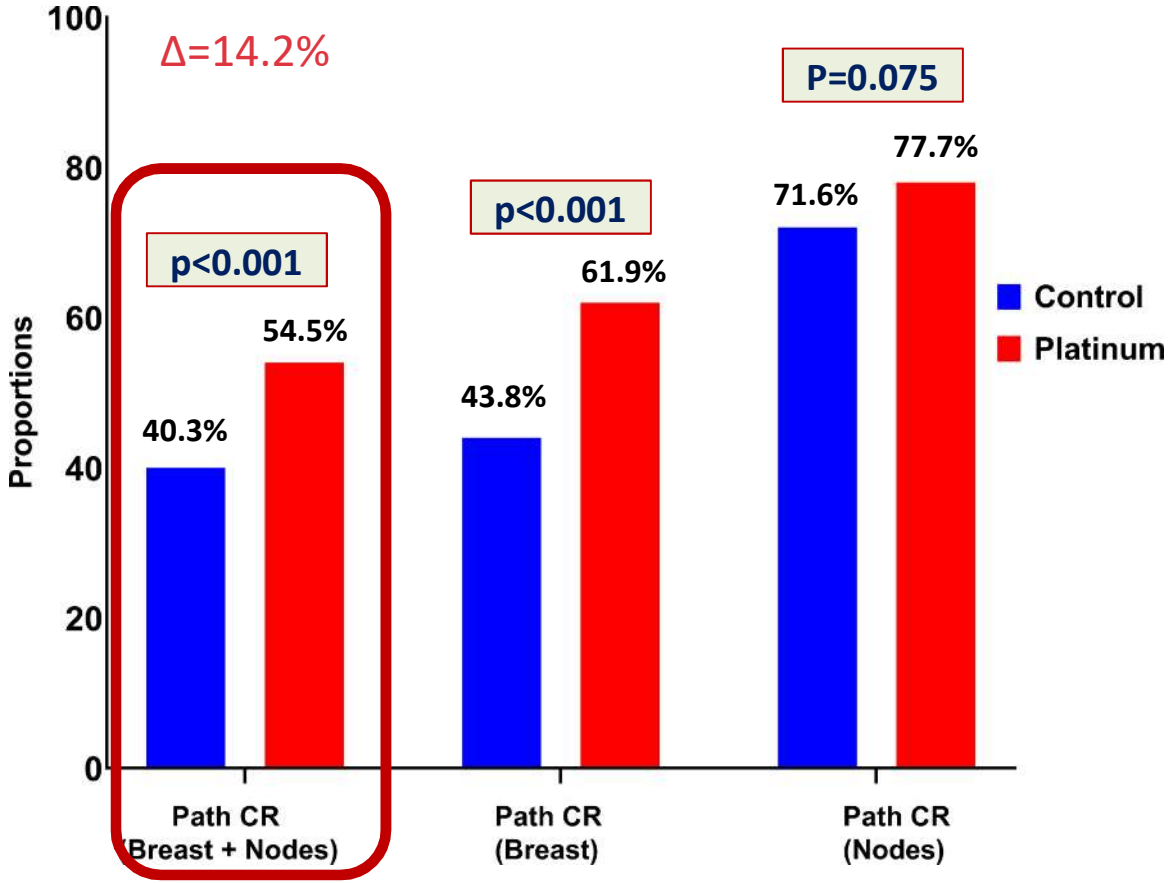
Control Arm: Same as above, without carboplatin

*Gupta S, et al. Single agent weekly paclitaxel as neoadjuvant chemotherapy in locally advanced breast cancer: a feasibility study. Clin Oncol (R Coll Radiol). 2012 Nov;24(9):604-9

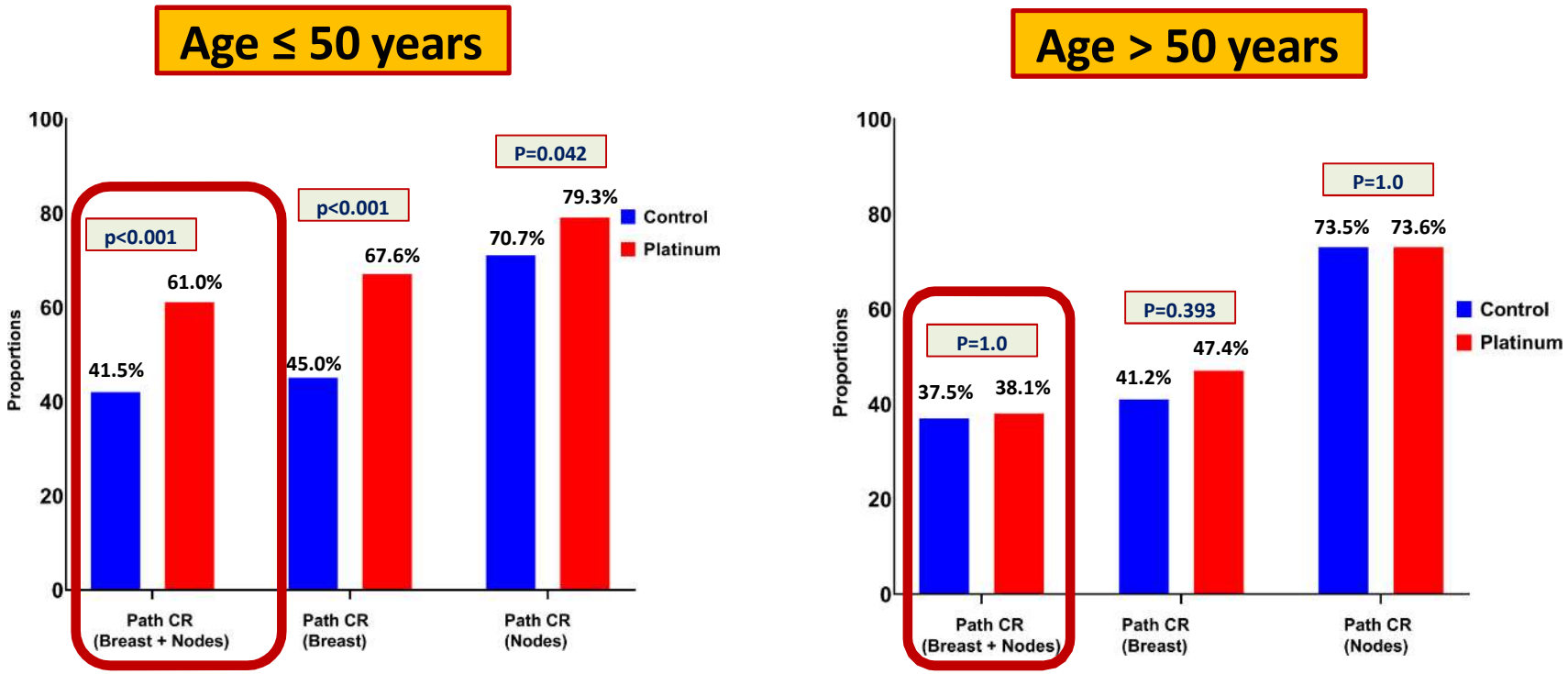
	Control Arm (N=356)	Platinum Arm (N=361)	Total (N=717)
Age (years)			
Median (Range)	46 (26-69)	46 (25-67)	46 (25-69)
≤ 50 years	245 (68.8%)	255 (70.6%)	500 (69.7%)
> 50 years	111 (31.2%)	106 (29.4%)	217 (30.3%)
Menopausal Status			
Pre- or Peri-menopausal	209 (58.7%)	209 (57.9%)	418 (58.3%)
Post-menopausal	147 (41.3%)	152 (42.1%)	299 (41.7%)
Family History of Any Cancer			
Yes	72 (20.2%)	62 (17.2%)	134 (18.7%)
No	284 (79.8%)	299 (82.8%)	583 (81.3%)

	Control Arm (N=356)	Platinum Arm (N=361)	Total (N=717)
Clinical Stage (pre-NACT)			
Operable (cT1-3, N0-1)	142 (39.9%)	143 (39.6%)	285 (39.7%)
Locally Advanced (cT4 / N2-3)	214 (60.1%)	218 (60.4%)	432 (60.3%)
Clinical Node Status (pre-NACT)			
Negative	39 (11.0%)	41 (11.4%)	80 (11.2%)
Positive	317 (89.0%)	320 (88.6%)	637 (88.8%)
Clinical T-size (pre-NACT) (cm)			
Median (Range)	6.0 (1.2-20.0)	6.0 (1.5-20.0)	6.0 (1.2-20.0)
≤ 5 cm	79 (22.2%)	81 (22.4%)	160 (22.3%)
> 5 cm	277 (77.8%)	280 (77.6%)	557 (77.7%)

ITT: Pathological Response to NACT by Rx-Arm



Pathological Response to NACT by Age & Rx-Arm



Multivariable (binary logistic) analysis for factors affecting pCR: Rx-Arm X Age interaction significant in a model including Rx-Arm, Age, cT size, cN status, Family History

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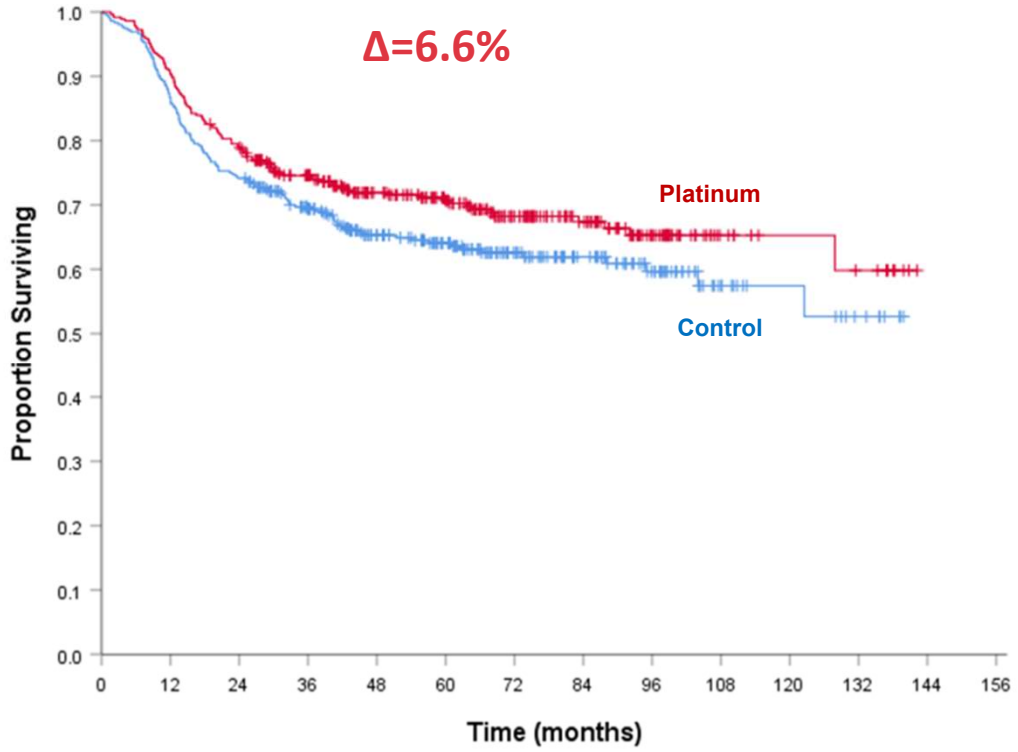
Event-free Survival in ITT (N=717)



5 Year EFS (95% CI):
70.7% platinum vs.
64.1% control

HR 0.798 (0.62-1.028) p =0.081

Control	**356**	**308**	**264**	**218**	**169**	**141**	**101**	**70**	**45**	**19**	**12**	**7**
Platinum	**361**	**326**	**284**	**239**	**190**	**159**	**112**	**79**	**47**	**17**	**12**	**10**

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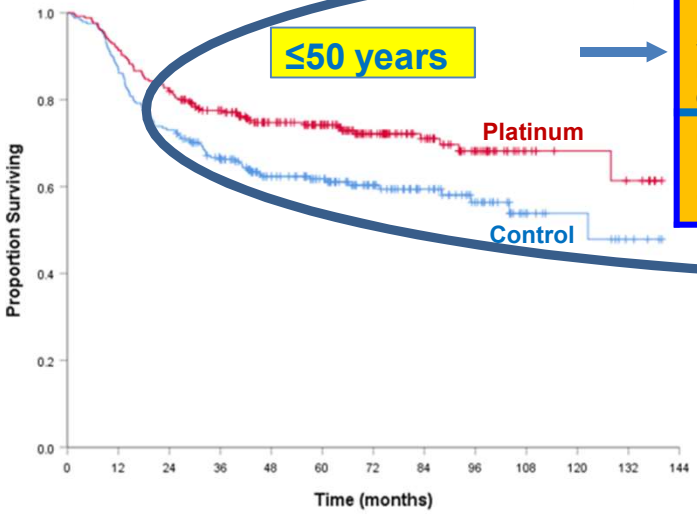
Event-free Survival in Younger and Older Patients

≤50 years

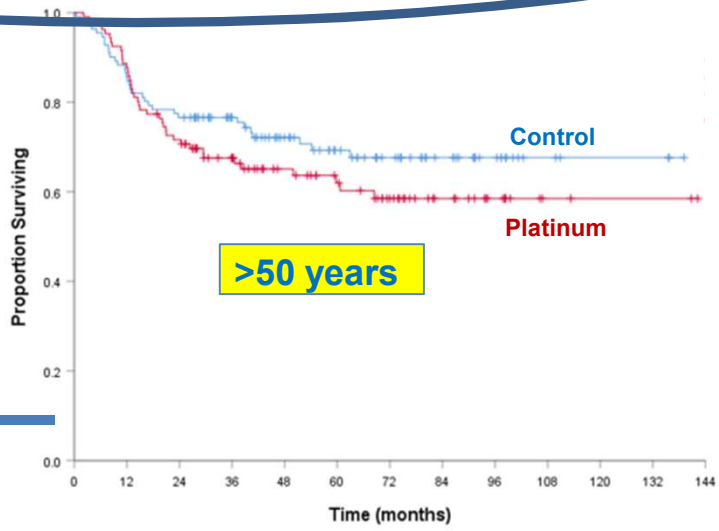


Control	245	213	179	149	115	98	69	49	32	14	9	4
Platinum	255	233	209	180	145	122	85	62	37	14	10	8

	Platinum	Control
5-year EFS (95% CI)	74.2% (68.71 - 79.69%)	61.7% (55.43 - 67.97%)
HR (95% CI)	0.642 (0.473 - 0.871)	
'p'	0.004	

Δ=12.5%

>50 years



Control	111	95	85	69	54	43	32	21	13	5	3	3
Platinum	106	93	75	59	45	37	27	17	10	3	2	2

	Platinum	Control
5-year EFS (95% CI)	62.0% (52.2 - 71.8%)	69.3% (60.28 - 78.32%)
HR (95% CI)	1.309 (0.825-2.076)	
'p'	0.253	

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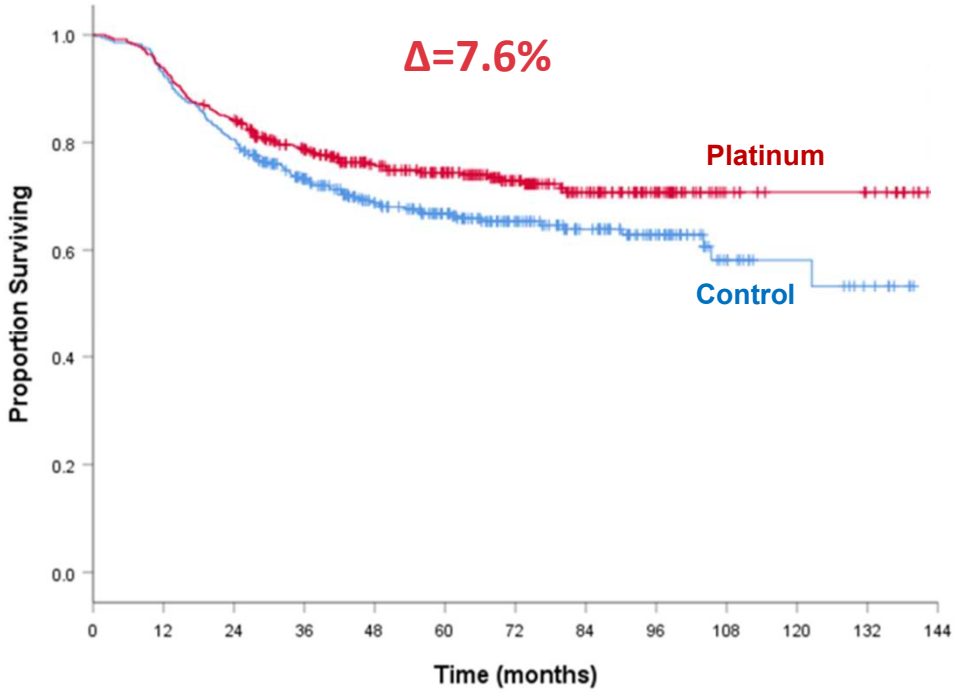
Overall Survival in ITT (N=717)



Control	356	330	287	229	179	147	106	74	48	20	12	7
Platinum	361	339	303	252	201	168	122	83	51	19	14	12

5 Year OS (95% CI):
74.4% platinum vs.
66.8% control

HR 0.74 (0.565-0.969) p =0.029

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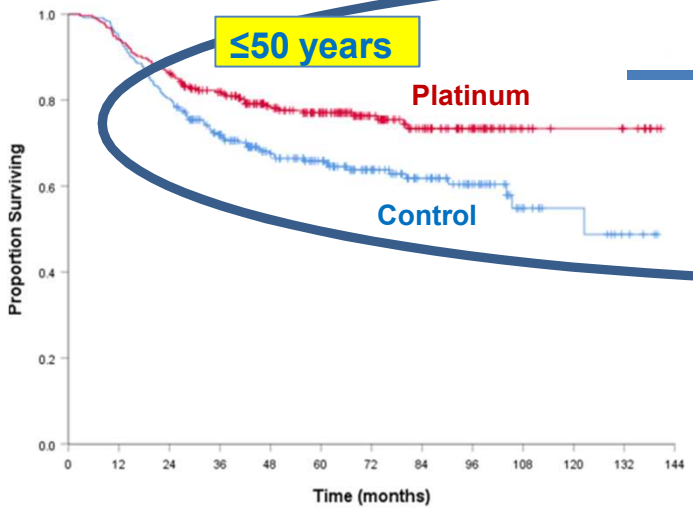
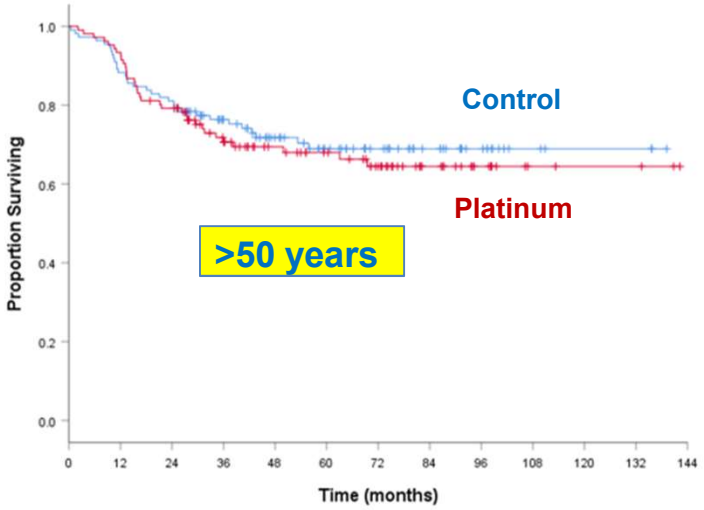
Overall Survival in Younger and Older Patients



	Platinum	Control
5-year OS (95% CI)	77.1% (71.81 - 82.39%)	65.9% (59.82 - 71.98%)
HR (95% CI)	0.611 (0.440 - 0.848)	
'p'	0.003	

Δ=11.2%

Control	245	232	197	160	125	104	74	53	35	15	9	4
Platinum	255	240	220	190	153	127	91	64	40	15	11	9



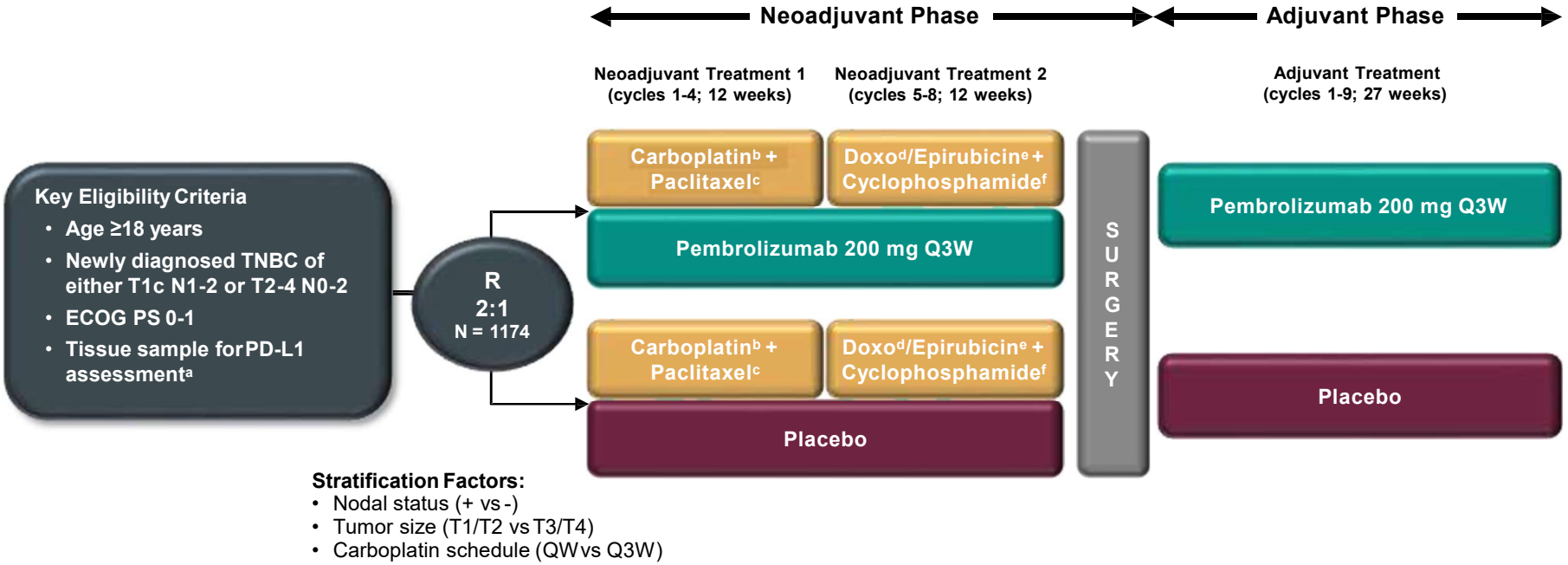
	Platinum	Control
5-year OS (95% CI)	68.0% (58.79 - 77.21%)	68.9% (59.69 - 78.11%)
HR (95% CI)	1.132 (0.698 - 1.835)	
'p'	0.615	

Control	111	98	90	69	54	43	32	21	13	5	3	3
Platinum	106	99	83	62	48	41	31	19	11	4	3	3

CONCLUSIONS

- Addition of carboplatin to sequential taxane-anthracycline neoadjuvant chemotherapy significantly improves overall survival and tends to improve event-free survival among patients with operable and locally-advanced TNBC.
  - The benefit seems confined to younger or premenopausal patients in whom there is substantial and significant improvement in EFS and OS.
- Increased pCR with carboplatin is predictive of EFS and OS benefit in younger patients ***AND*** lack of improvement in pCR is predictive of lack of EFS and OS benefit in older patients.

KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m^2 QW.
[d]Doxorubicin dose was 60 mg/m^2 Q3W.
[e]Epirubicin dose was 90 mg/m^2 Q3W.
[f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

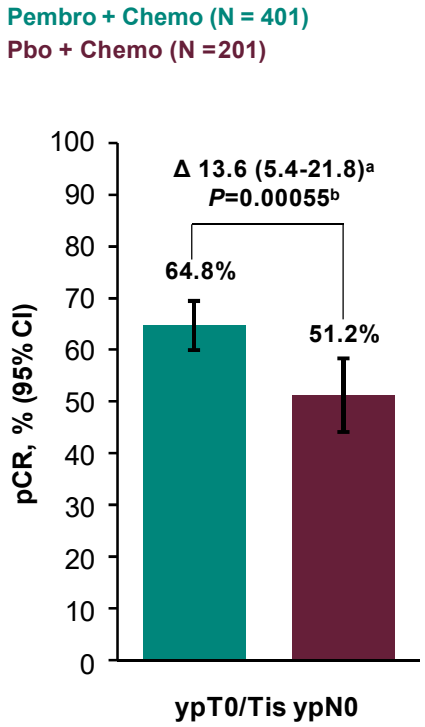
Neoadjuvant Immune Checkpoint Inhibitors (ICIs) for TNBC:

Trial		Primary Endpoint	Improved pcR?	Improved EFS?	Improved DFS/OS
Keynote-522 (Phase III)	PTX+Cb+Plac→ AC/EC+Plac PTX+Cb+Pembro→ AC/EC+Pembro * Adjuvant Pembro/Pla	pCR &EFS	**Yes-** 55.6 vs.63	**Yes-** 3-y EFS, 76.8% vs 84.5% HR, 0.63 (95% CI, 0.48–0.82)	
IMpassion 031 (Phase III)	nab-PTX+Plac→ AC+Plac nab-PTX+Atezo→ AC+Atezo * Adjuvant Atezo/Plac	pCR in ITT & pCR in PD-L1+	**Yes-** 41 vs 58 P= .004	Not powered - **Nonsig EFS**, HR, 0.76 (95% CI, 0.4–1.44)	
Gepar-Nuevo (Phase II)	nab-PTX + Plac →AC+Plac nab-PTX+Durva→ AC+Durva *No adjuvant durva	pCR	**No-** 44.2 vs 53.4 P= .29		**Yes-** 3-y **IDFS**, 76.9 vs 84.9 HR, 0.48 (p =.036) Improved **DDFS** & **OS**: HR, 0.24 (p = .006)

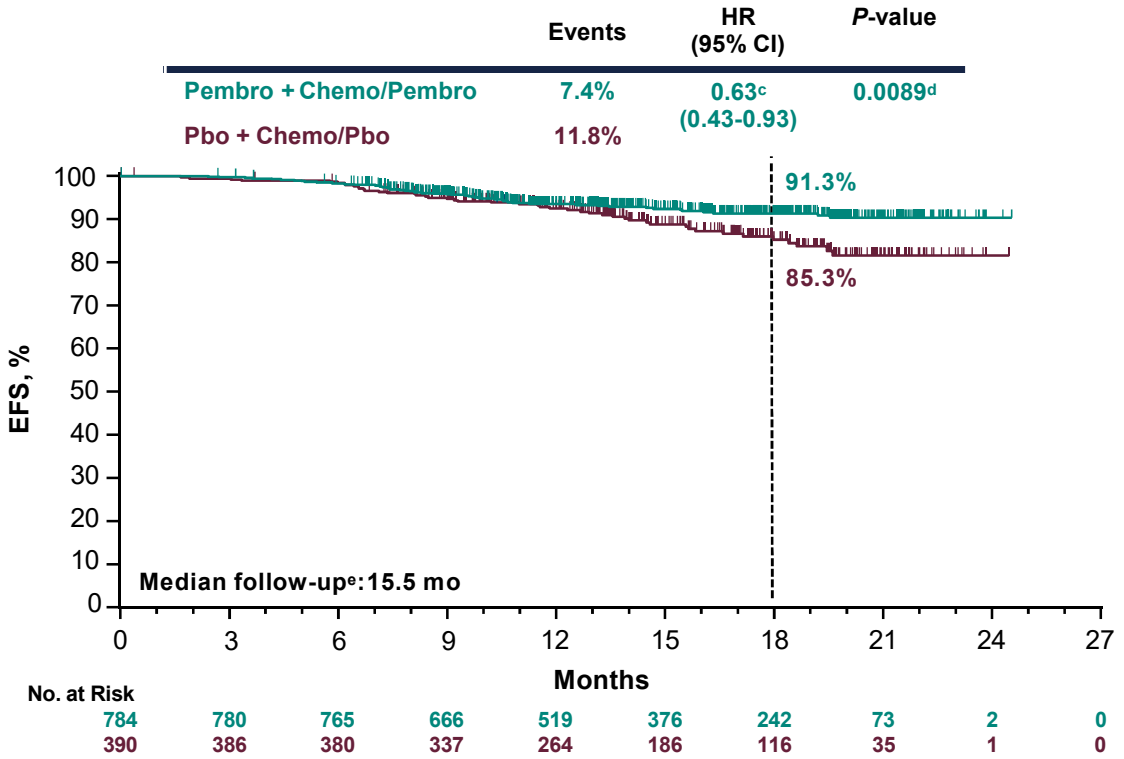
Adapted from: Spring, L. J Natl Compr Canc Netw 2022;20(6):723–734

Prior Analyses of KEYNOTE-522

Primary pCR Endpoint at IA1[1]

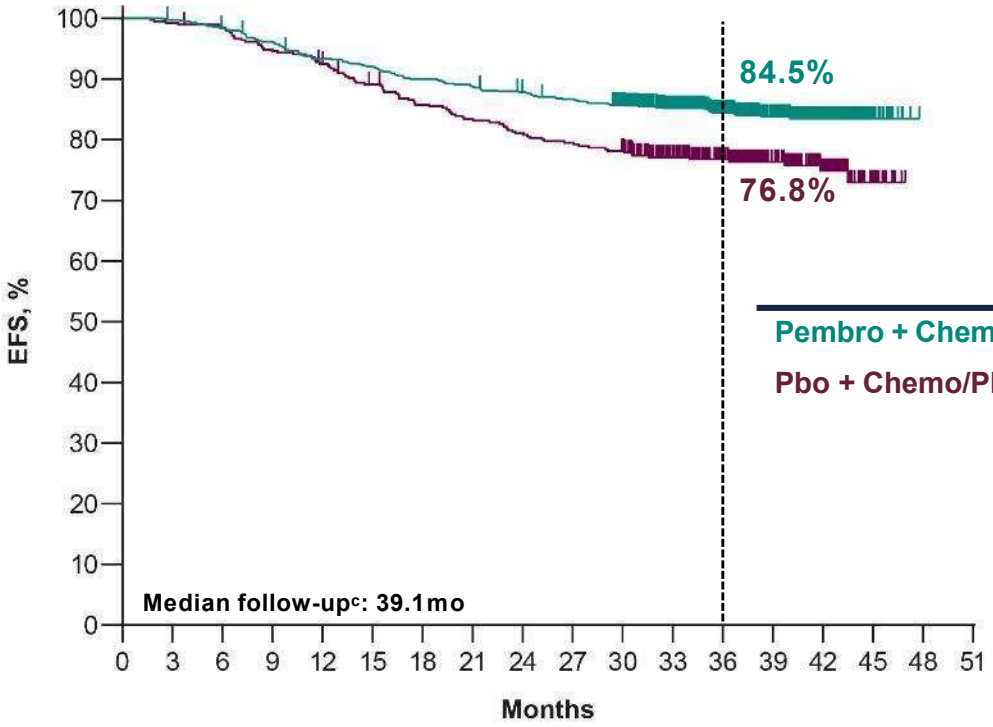


First EFS Analysis at IA2[1]



[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]Prespecified *P*-value boundary for significance of 0.003 was crossed; data cutoff date: September 24, 2018.
[c]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [d]Prespecified *P*-value boundary for significance of 0.000051 not reached at this analysis.
[e]Defined as the time from randomization to the date of death or data cutoff date of April 24, 2019, if the patient was alive. 1. Schmid P, et al. *N Engl J Med* 2020;382:810-21.

Statistically Significant and Clinically Meaningful EFS at IA4



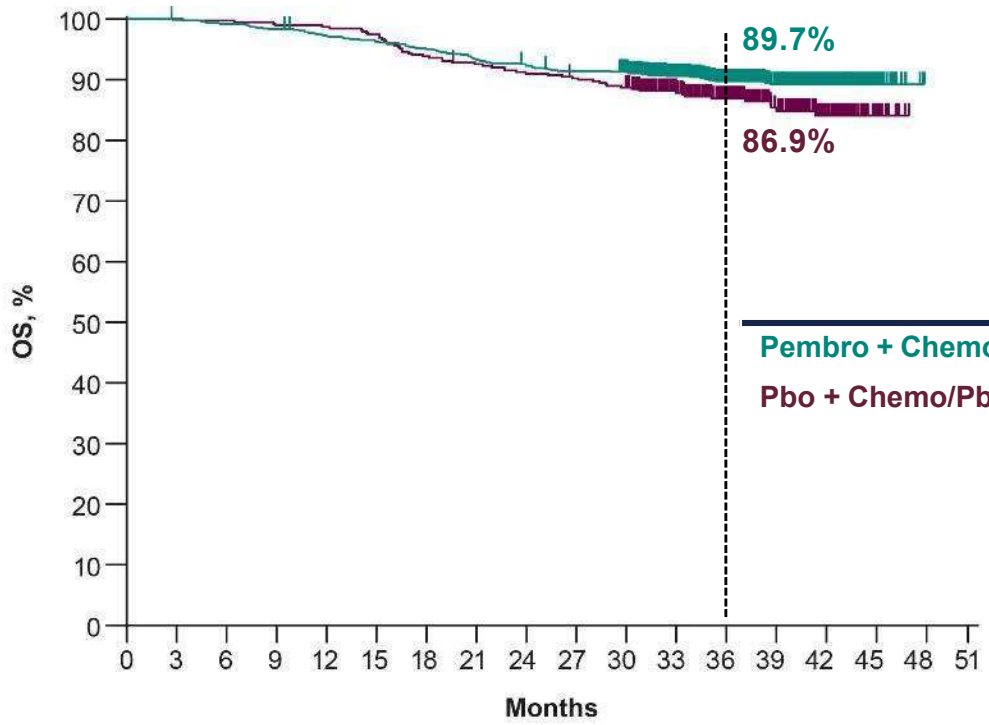
	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

No. at Risk

Pembro + Chemo/Pembro	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Pbo + Chemo/Pbo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00517 reached at this analysis.
[c]Defined as the time from randomization to the data cutoff date of March 23, 2021.

Overall Survival

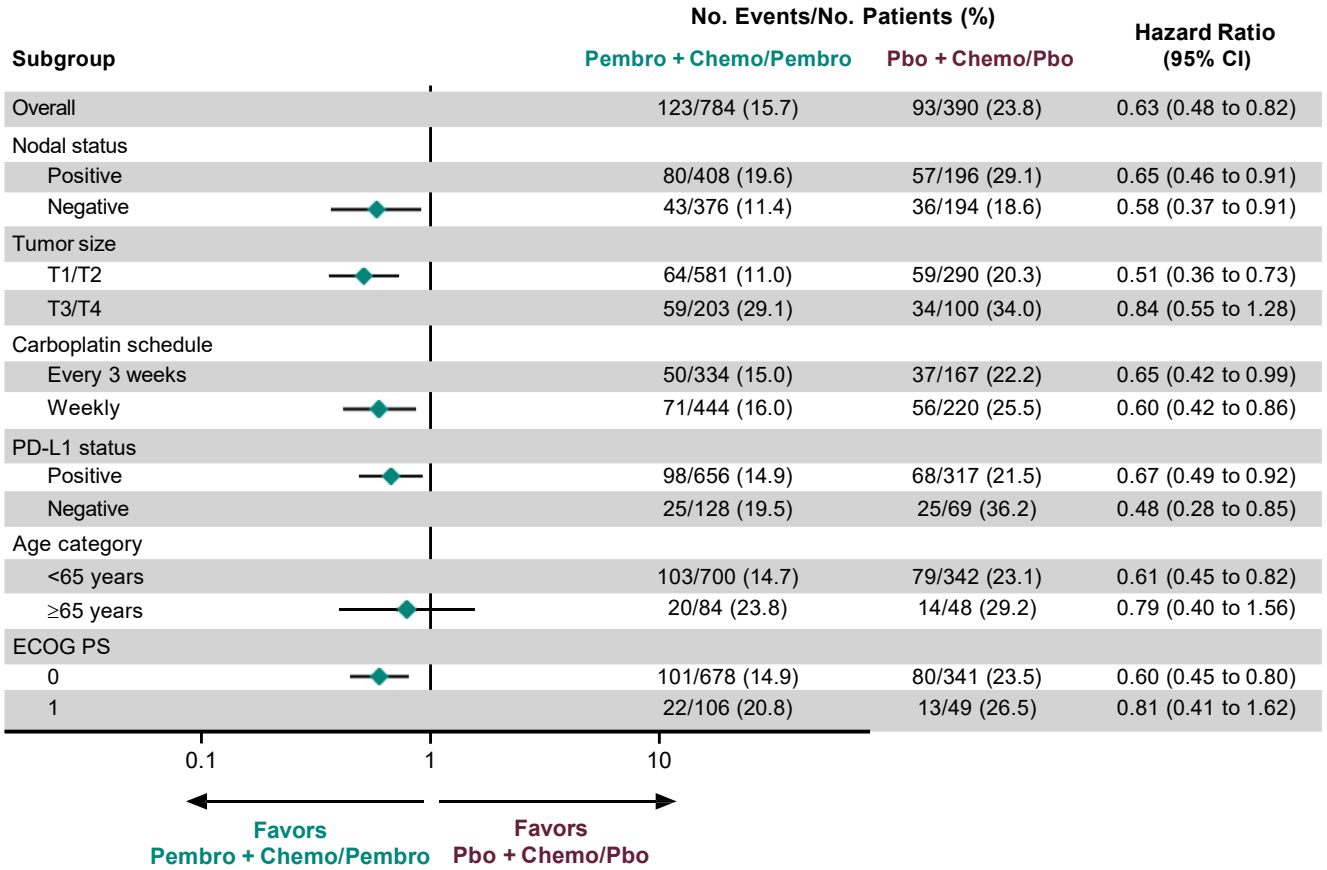


	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	10.2%	0.72[a] (0.51-1.02)	0.03214[b]
Pbo + Chemo/Pbo	14.1%		

No. at Risk																		
Pembro + Chemo/Pembro	784	782	777	770	759	752	742	729	720	712	701	586	461	323	178	30	0	0
Pbo + Chemo/Pbo	390	390	389	386	385	380	366	360	354	350	343	286	223	157	89	17	0	0

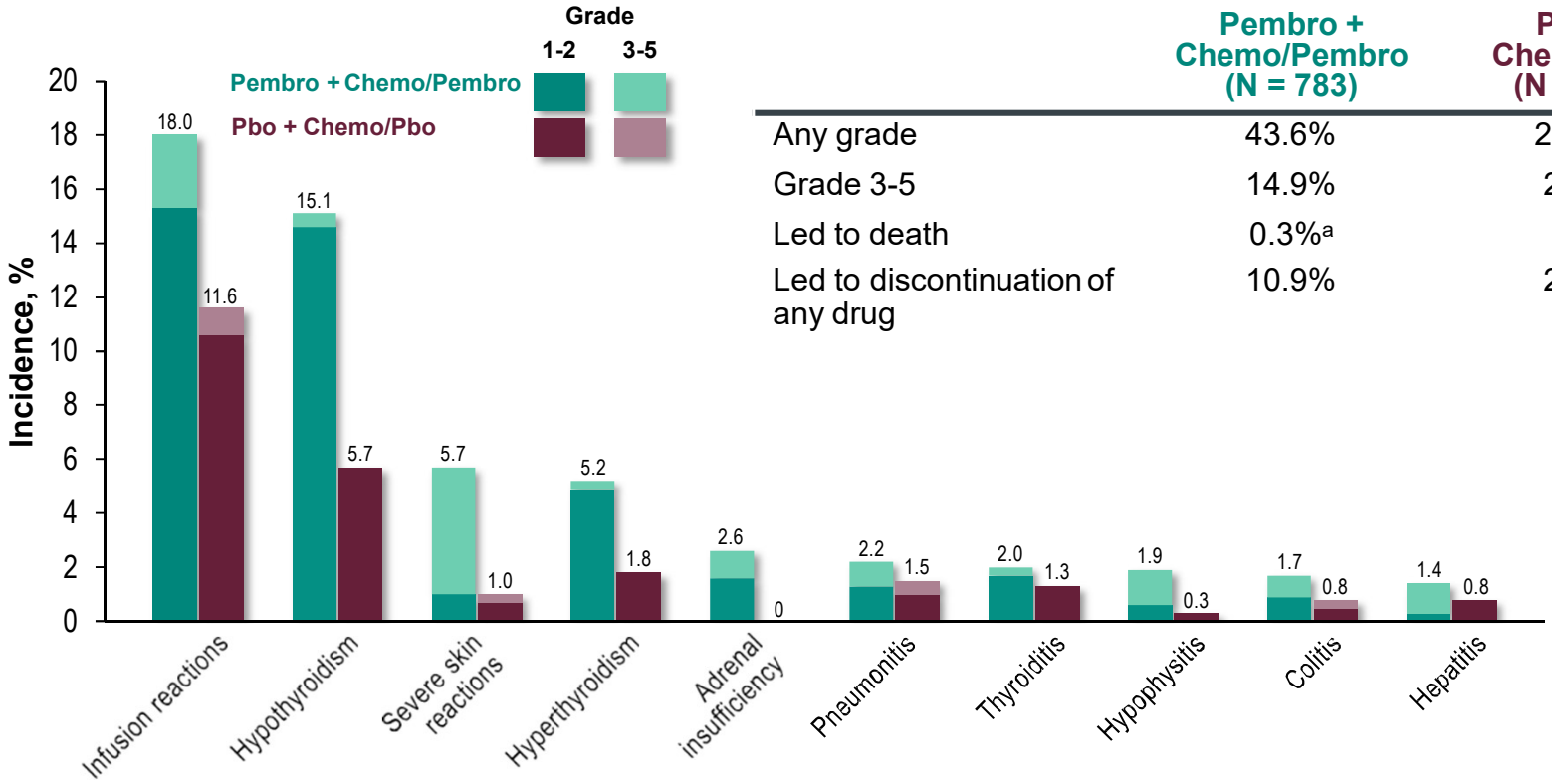
[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00086 not reached at this analysis.
Data cutoff date: March 23, 2021.

EFS in Patient Subgroups



For overall population and PD-L1 subgroups, analyses based on Cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4), and frequency of carboplatin (once weekly vs once every 3 weeks); for other subgroups, analysis based on unstratified Cox model. Data cutoff date: March 23, 2021.

Immune-Mediated AEs and Infusion Reactions in Combined Phases

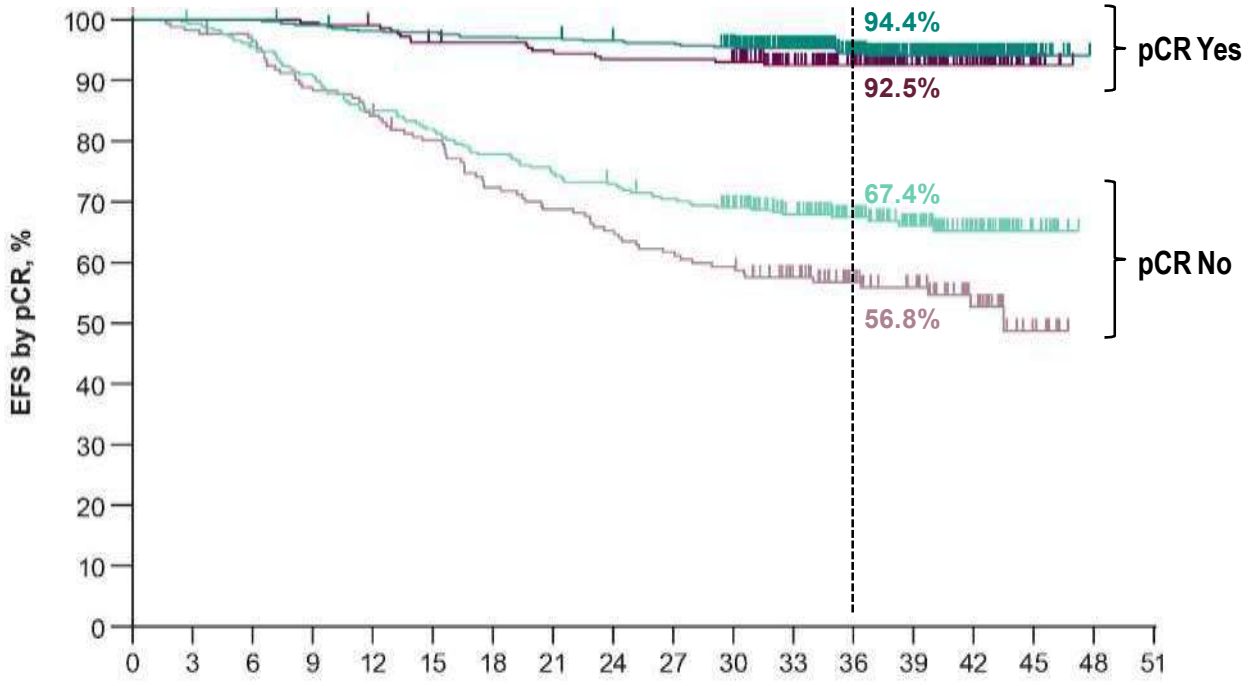


	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%

Immune-Mediated AEs and Infusion Reactions with Incidence ≥10 Patients

[a]1 patient from pneumonitis and 1 patient from autoimmune encephalitis. Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: March 23, 2021.

EFS by pCR (ypT0/Tis ypN0)



No. at Risk																		
Pembro + Chemo/Pembro Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Pbo + Chemo/Pbo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembro + Chemo/Pembro Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Pbo + Chemo/Pbo Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

Data cutoff date: March 23, 2021.

Systemic Therapy for TNBC: Adjuvant Therapy after NAC

- ypT0N0 or pCR:

  For high risk (stage II or III): adjuvant pembrolizumab
  (if pembro-containing regimen was given preop.)
  *adjuvant pembrolizumab (cat 2A) may be individualized

- ypT1-4, N0 or ypN≥1:

  -adjuvant pembrolizumab*
  (if pembro-containing regimen was given preop.)
  or
  -Adjuvant capecitabine* (6-8 cycles) (CREATE-X)
  or
  -Adjuvant olaparib* for 1 year if germline BRCA mutation

*there are no data on sequencing/combining these 3; sequential or combined use may be considered in certain patients at high risk of recurrence

BINV-16. NCCN Guidelines® for Breast Cancer (Version 1.2023).

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Adjuvant Capecitabine in TNBC- CREATE-X Trial

- (CREATE-X) trial, which was a multi-center, open-label, randomized, phase 3 trial that was designed to evaluate the efficacy and safety of adjuvant capecitabine monotherapy in patients with HER2-negative primary breast cancer who had **residual invasive disease after the receipt of standard neoadjuvant chemotherapy containing anthracycline, taxane, or both**
- After surgery, patients randomized to oral capecitabine (at a dose of 1250 mg per square meter of body-surface area, twice per day, on days 1 to 14) every 3 weeks for six or eight cycles or control (standard therapy)
- Median age 48
- 40% Stage IIIA or IIIB
- 32.2% TNBC
- 95.3% had received anthracycline and taxane as neoadjuvant therapy

Masuda N Eng J Emd 376; 22. Jun 2017

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Adjuvant Capecitabine in TNBC- CREATE-X Trial

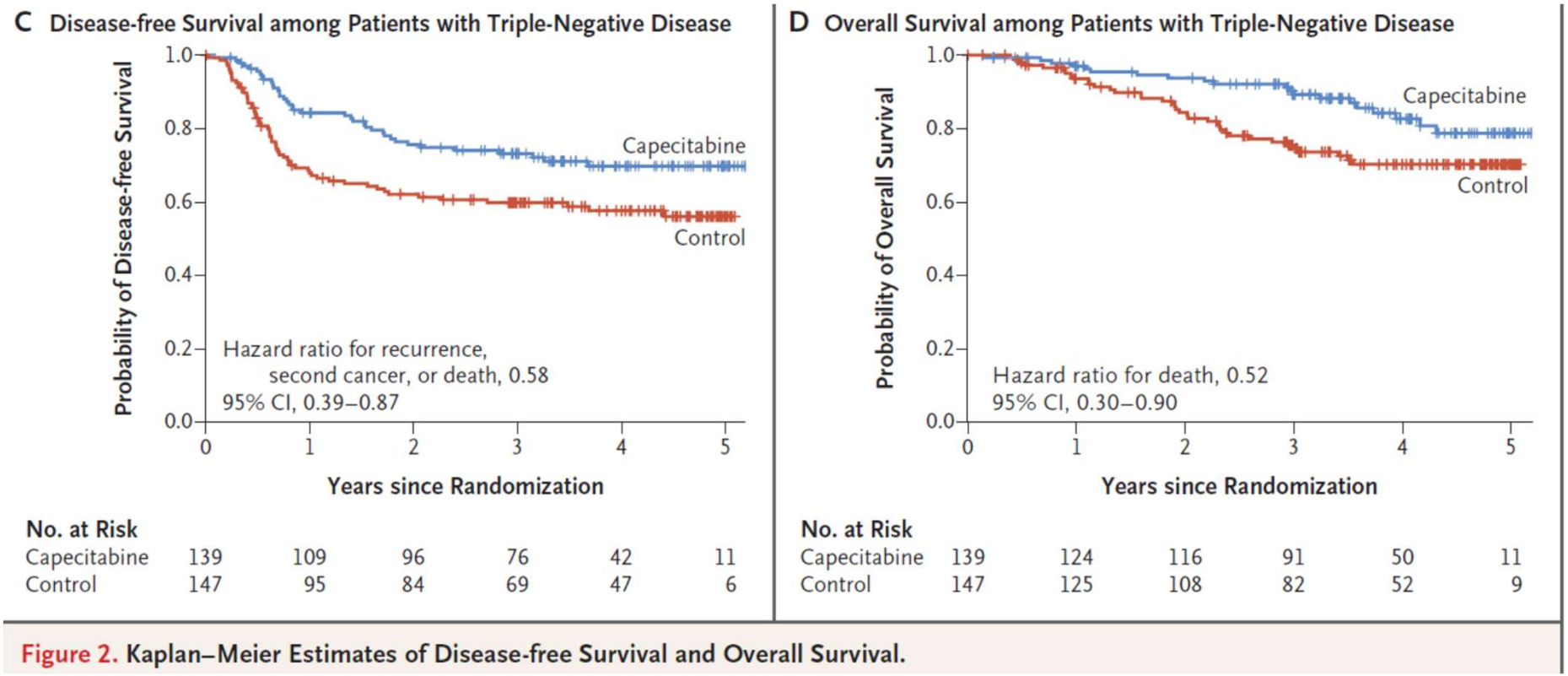

Figure 2. Kaplan–Meier Estimates of Disease-free Survival and Overall Survival.

Masuda N Eng J Emd 376; 22. Jun 2017

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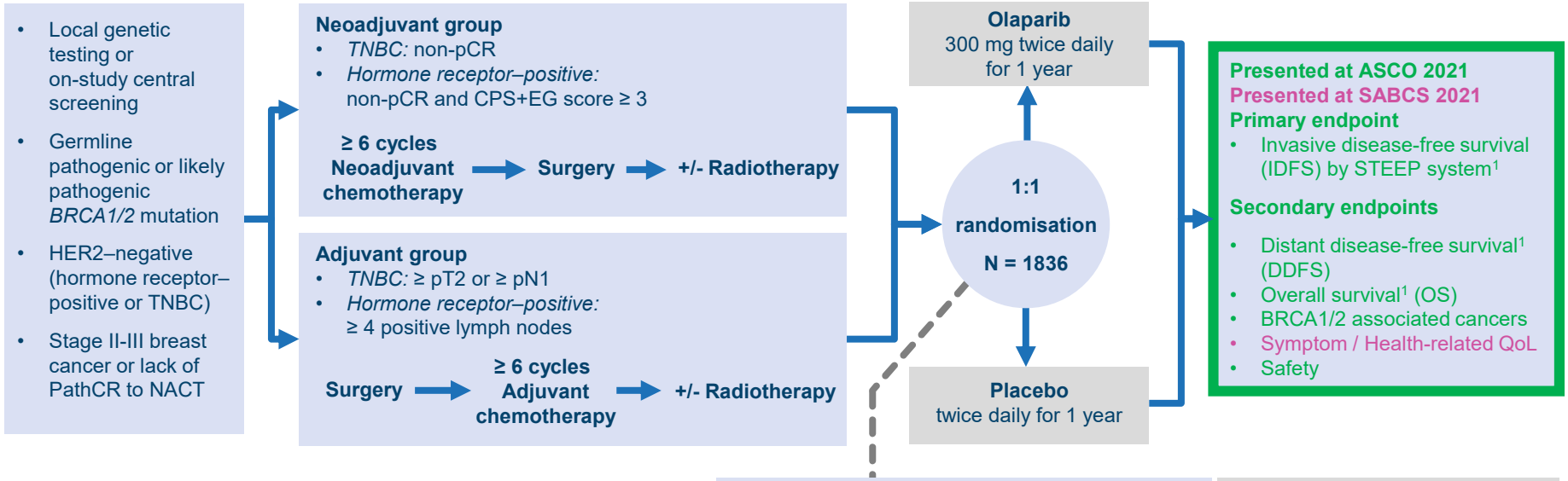
OLYMPIA: TRIAL SCHEMA



Hormone receptor-positive defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

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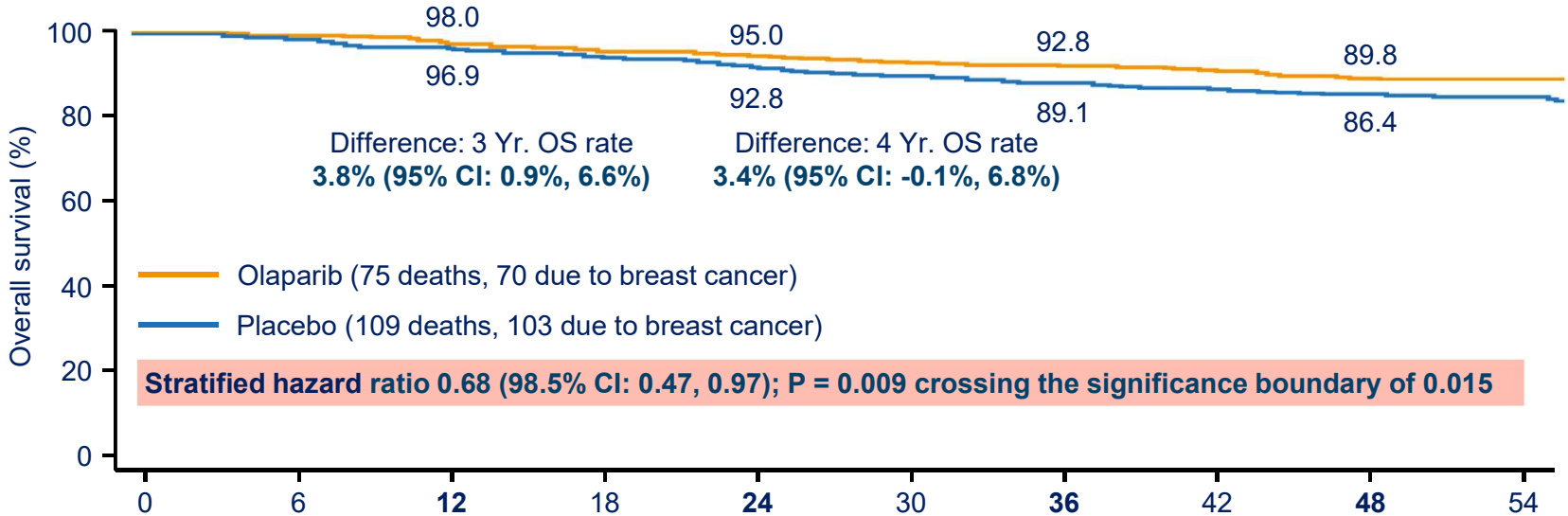
SECOND OVERALL SURVIVAL INTERIM ANALYSIS - OS IA 2 (ITT)



No. at risk	0	6	12	18	24	30	36	42	48	54
Olaparib	921	862	844	809	773	672	560	437	335	228
Placebo	915	868	843	808	752	647	530	423	333	218

Time since randomisation (months)

98.5% confidence intervals are shown for the hazard ratio because P < 0.015 is required for statistical significance

Andrew Nicholas James Tutt MB ChB PhD FMedSci

Conclusions-TNBC

- NAC (anthracyclines, taxanes) for majority with TNBC unless small & LN-negative
- Addition of **platinum** to NAC improves EFS, but not consistently OS
  - Benefit may be more pronounced in **younger** patients
- **KEYNOTE 522** regimen improves pCR and EFS:
  - Indicated for high risk early- stage TNBC (Stage II and III)
  - ASCO 2022 guidelines recommend pembrolizumab be added to NAT for **stage II and III TNBC**
  - Urgent need for predictive biomarkers to neoadjuvant immunotherapy given toxicity risk:
    - NCCN Guidelines: Supportive Care for Management of Immunotherapy-Related Toxicities
- Patients with residual disease after NAC have high risk of recurrence:
  - Adjuvant pembrolizumab, or adjuvant capecitabine, or adjuvant olaparib (if gBRCA+): no data on sequencing/combining but can be considered if high risk

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Future Directions, TNBC

- Reduce neoadjuvant anthracycline use in TNBC?
  - Phase II NeoStop: impressive responses for carboplatin and docetaxel vs. standard anthracycline/taxane- regimen in patients with early TNBC
  - Phase II NeoPACT trial: NCT 03639948 : evaluating combination of pembrolizumab with anthracycline-free NACT
- Neoadjuvant PARP inhibitors: single-arm phase II NeoTALA trial:
  - Talazoparib in patients with BRCA-mutated TNBC: ->49.2% pCR rate
- Neoadjuvant Sacituzumab: NeoSTAR, NCT04230109
- Postneoadjuvant Sacituzumab: SASCIA, NCT04595565; ASPRIA, NCT04434040
- I-SPY 2.2

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Neoadjuvant Therapy for HR+, HER2-Negative Breast Cancer:

- **Neoadjuvant Therapy (NAT)- Where are we now?**
- Traditional Indications[1]:
  - Inflammatory breast cancer
  - Bulky or matted cN2 axillary nodes
  - cN3 nodal disease
  - T4 tumors
  - large primary tumor relative to breast size in a patient who desires conservation
  - cN+ disease likely to become cN0 with preoperative therapy
  - Patients in whom definitive surgery may be delayed

- **Neoadjuvant Therapy- Where are we headed?**
  - pCR rates to NAC not as high
  - Correlation between pCR & long term outcome not as strong
  - Need better approaches?
  - Future strategies/new studies:
    - ?ADCs: TDX-d for HER2 low (SABCS)
    - I Spy 2 Trial: (SABCS)

1. NCCN.org

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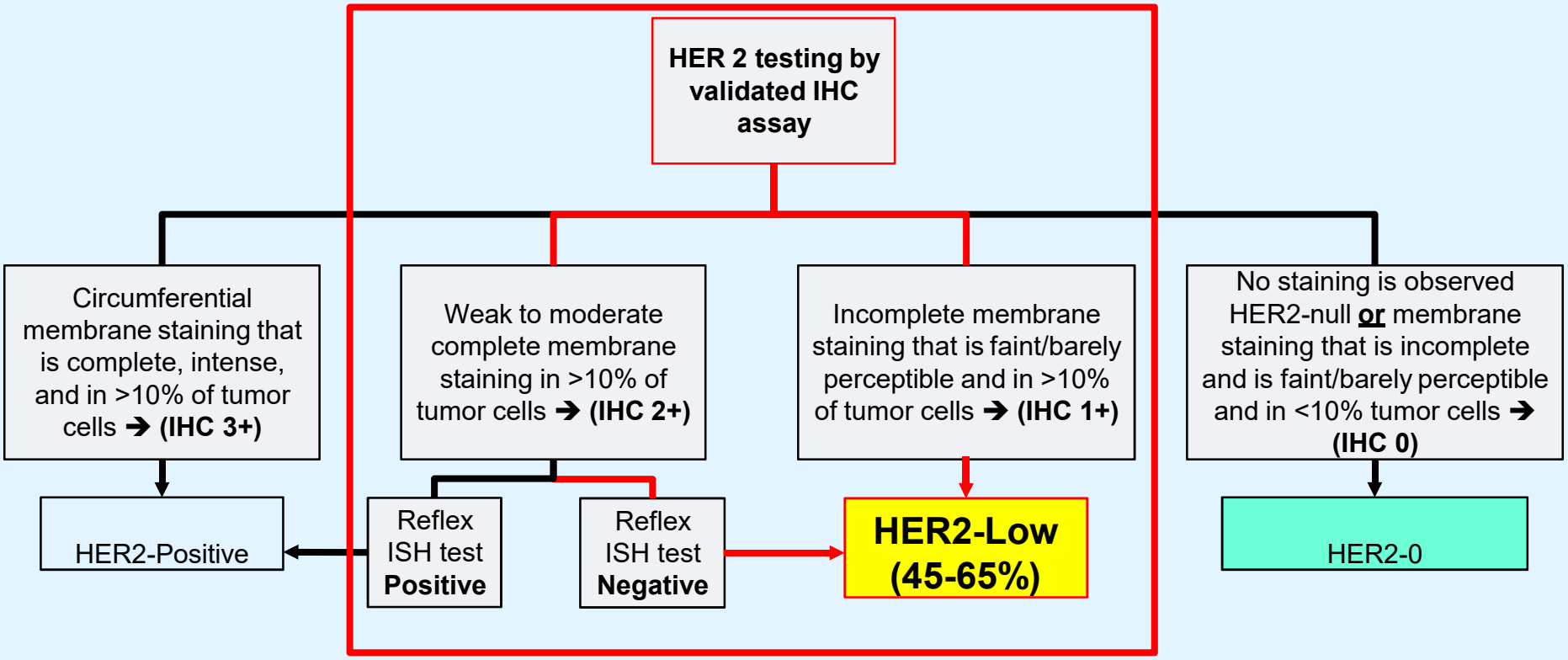
San Antonio Breast Cancer Symposium 2022

TRIO-US B-12 TALENT: Neoadjuvant trastuzumab deruxtecan (T-DXd) with or without anastrozole for HER2-low, HR+ early-stage breast cancer

Sara A. Hurvitz,[1] Lisa S. Wang,[2] Nicholas P. McAndrew, [1] Vu Phan,[3] David Chan,[4] Deborah Villa,[1] Merry L. Tetef,[1] Erin Chamberlain,[1] Nihal Abdulla[4], Thomas Lomis,[5] Laura M. Spring,[6] Steven Applebaum,[1] Shaker Dakhil,[7] Brian DiCarlo,[1] David D. Kim,[1] Evangelia Kirimis,[1] William E. Lawler,[8] Aashini K. Master,[1] Kelly McCann,[1] Edwin Hayashi,[9] Christine Kivork,[1] James Chauv,[1] Michael F. Press, [10] Aditya Bardia[6]

[1]University of California Los Angeles, Jonsson Comprehensive Cancer Center; [2]PIH Health; [3]Cancer Blood and Specialty Clinic; [4]Torrance Memorial Physician Network (TMPN)/Cancer Care; [5]Valley Breast Care and Women's Health Center; [6]Massachussetts General Hospital, Harvard Medical School; [7]Cancer Center of Kansas; [8]St Jude Crosson Cancer Institute/Providence Medical Foundation, [9]Associated Surgeons of San Luis Obispo; [10]USC Norris Comprehensive Cancer Center Department of Pathology

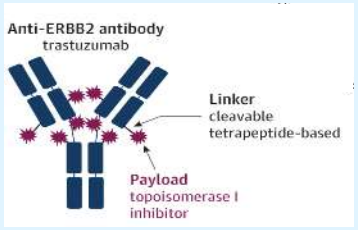
HER2-Low Breast Cancer: Current Definition (operational)

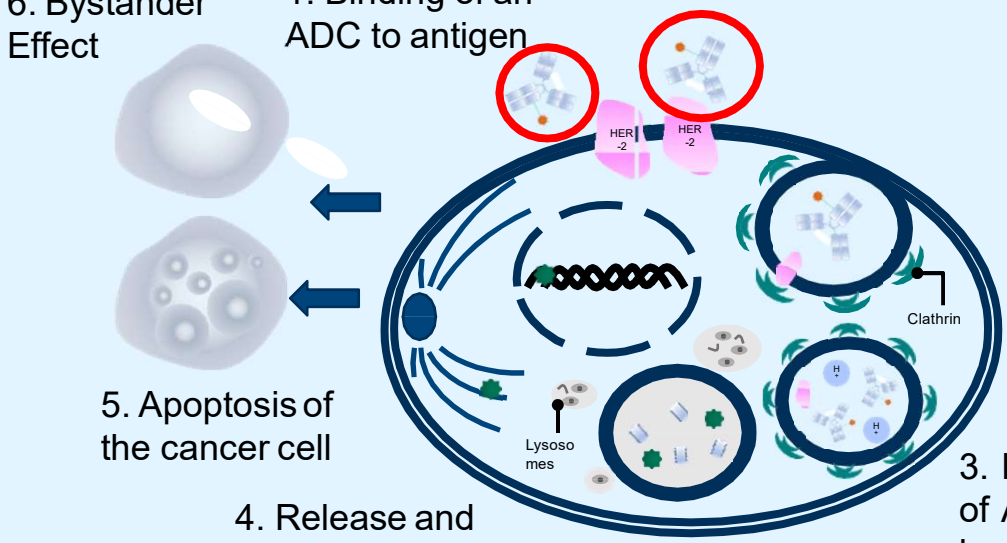


Adapted from: Prat A et al. JAMA Oncol. 2022

Antibody-Drug Conjugates (ADCs): Selective Delivery of Toxic Payload

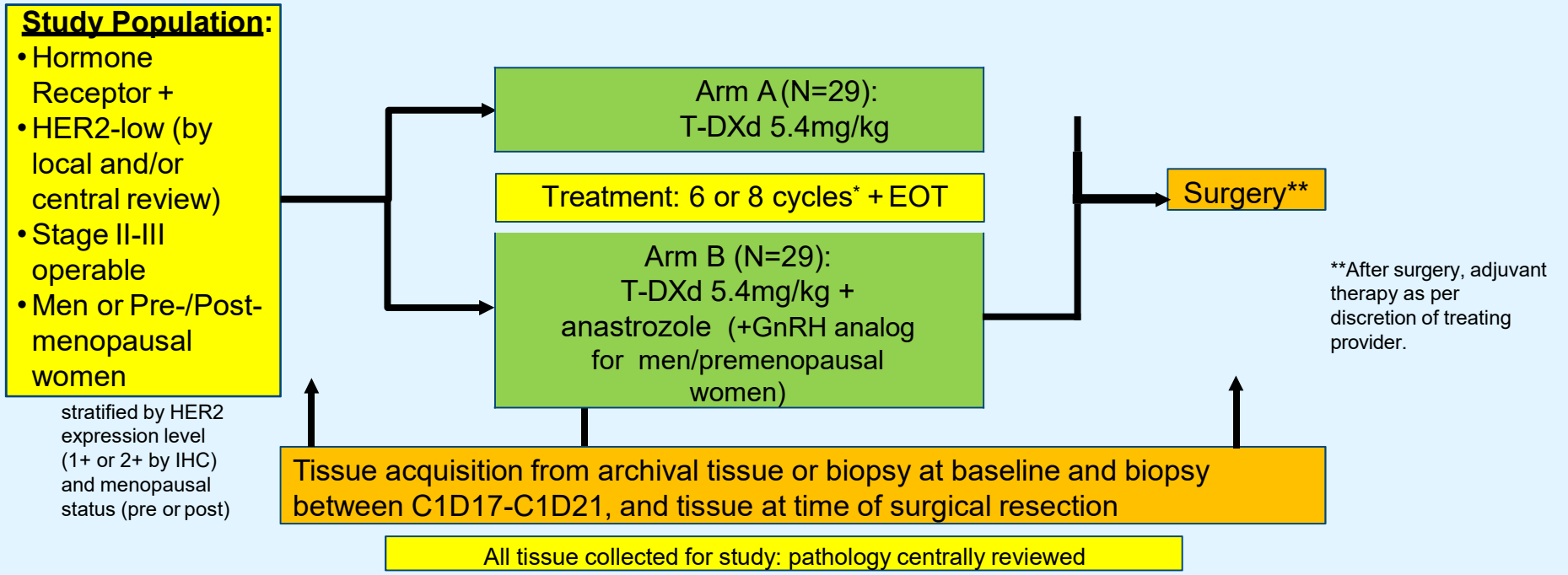
Trastuzumab Deruxtecan (T-DXd)





Adapted from: Prat A et al. JAMA Oncol. 2022;
Nagayama, A, Ellisen L, Chabner B, Bardia A. Target Oncol. 2017

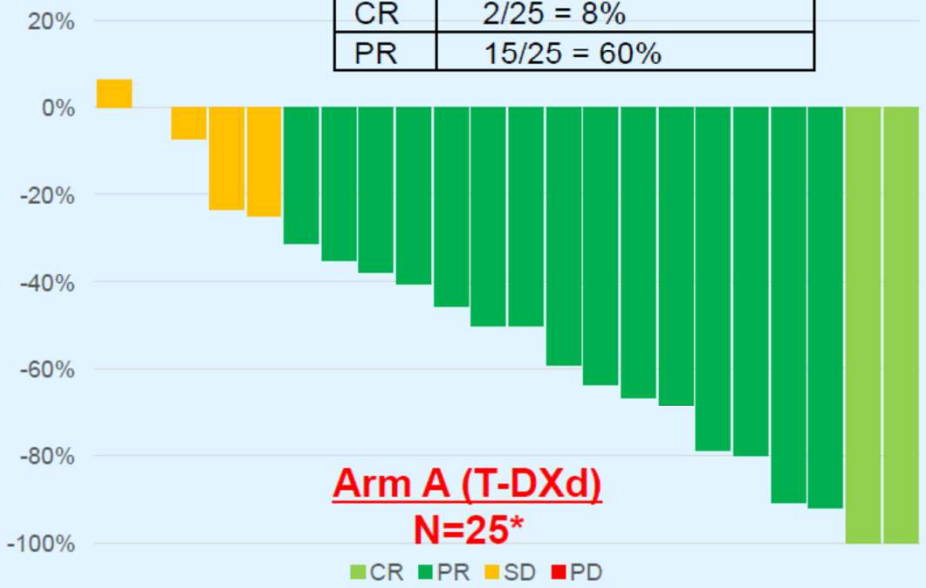
TRIO-US B-12 (TALENT): Study Design



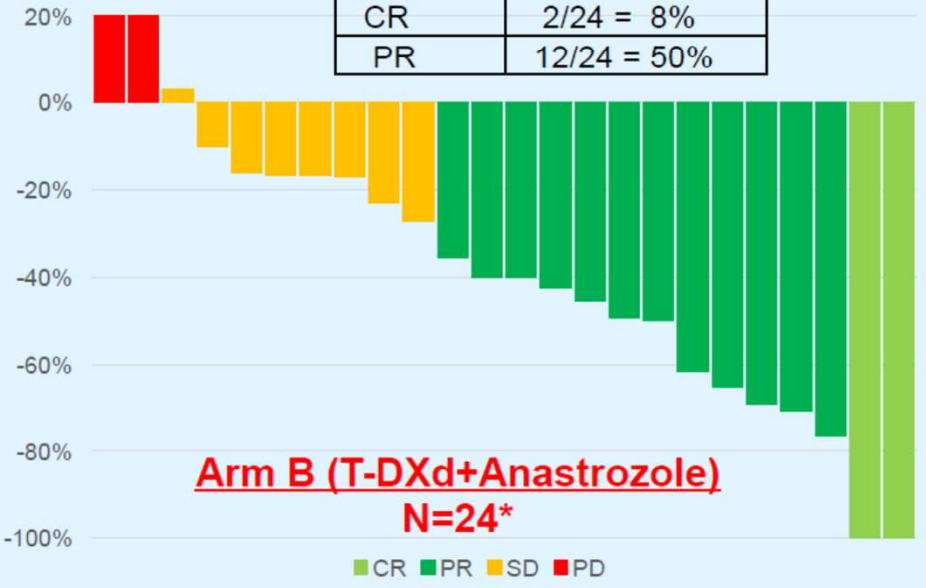
* Originally, 6 cycles of treatment were given but in 02/2022, an amendment increased the number of treatment cycles from 6 to 8 cycles

Objective Response Rate with T-DXd (based on imaging)

Arm A	
ORR	17/25 = 68%
CR	2/25 = 8%
PR	15/25 = 60%



Arm B	
ORR	14/24 = 58%
CR	2/24 = 8%
PR	12/24 = 50%

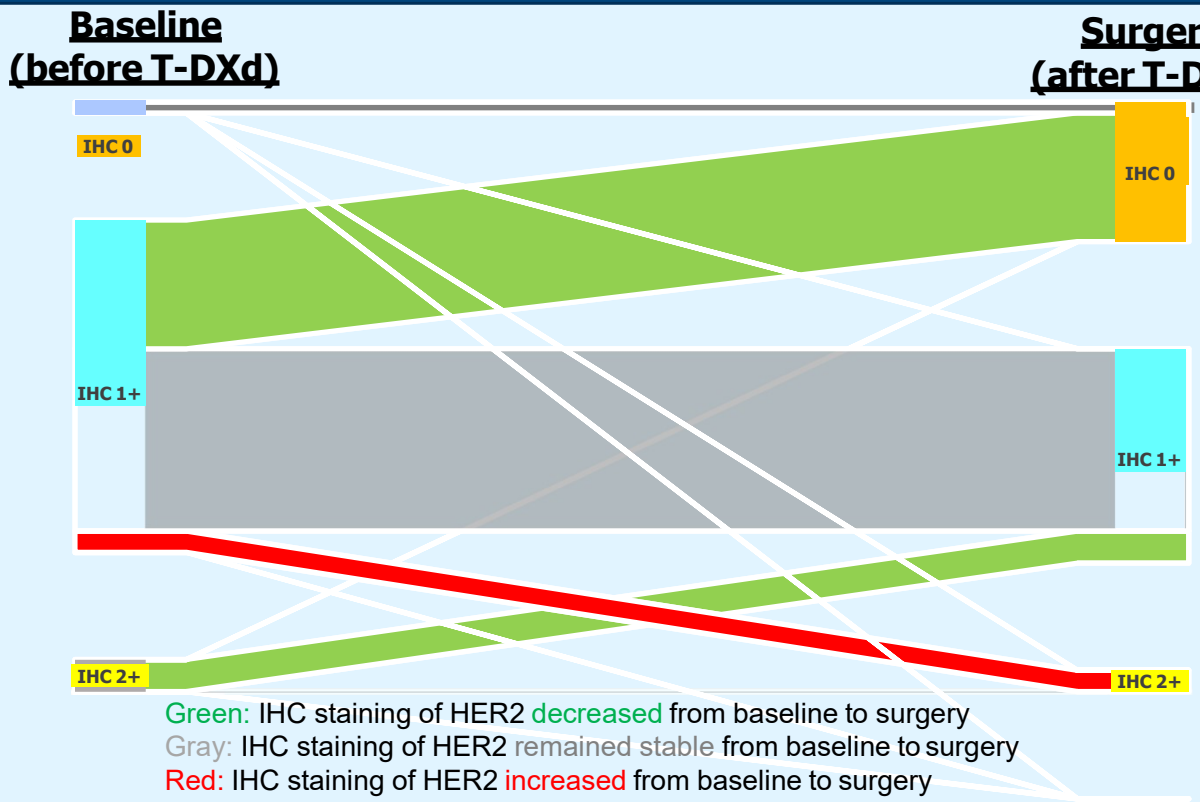


Waterfall plot with bars representing change in tumor size after treatment with T-DXd, compared to baseline, as per RECIST v1.1. Intention to treat population for ORR includes all who received at least 1 cycle of protocol therapy, data cutoff 11/25/2022.

- 4 patients still on treatment; 3 patients did have imaging (treatment discontinued prematurely), but included in intention to treat (ITT) denominator for ORR analysis per protocol

* 5 patients still on treatment

HER2 IHC Change from Baseline to Surgery with T-DXd (central review)



49% (17/35) had change in HER2 IHC after T-DXd treatment

Of those who had change, majority (88%) had decrease in HER2 IHC expression

Green: IHC staining of HER2 decreased from baseline to surgery
Gray: IHC staining of HER2 remained stable from baseline to surgery
Red: IHC staining of HER2 increased from baseline to surgery

Note: The observed change in IHC immunostaining may not accurately reflect changes in HER2 protein expression in carcinoma cells

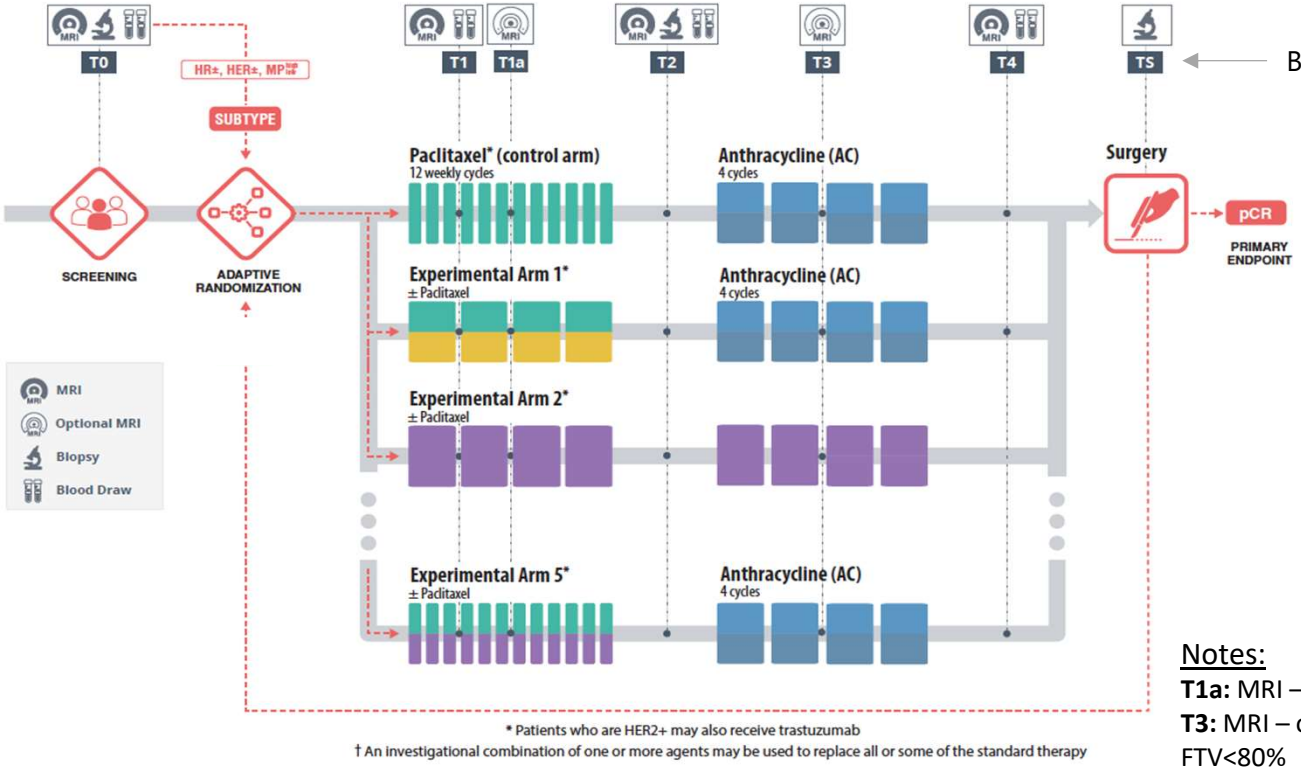
Residual Cancer Burden after T-DXd (by arm, cycles and stage)

Cycles	Stage at Baseline	Arm A (T-DXd) N=22*				Arm B (T-DXd+Anastrozole) N=20**			
		RCB-0	RCB-I	RCB-II	RCB-III	RCB-0	RCB-I	RCB-II	RCB-III
6 Cycles	Stage IIA	0	1 (5%)	2 (9%)	0	0	1 (5%)	6 (30%)	0
	Stage IIB	0	1 (5%)	4 (18%)	2 (9%)	0	0	3 (15%)	1 (5%)
	Stage IIIA	0	0	1 (5%)	2 (9%)	0	0	1 (5%)	1 (5%)
	Stage IIIB	0	0	1 (5%)	0	0	0	0	0
8 Cycles	Stage IIA	0	0	2 (9%)	0	0	1 (5%)	1 (5%)	0
	Stage IIB	0	0	1 (5%)	1 (5%)	0	0	2 (10%)	0
	Stage IIIA	1 (5%)	0	0	0	0	1 (5%)	0	0
	Stage IIIB	0	0	0	0	0	0	0	0

As of data cutoff 11/25/2022: surgical outcomes pending for 24% (7/29) patients being treated in Arm A and 31% (9/29) in Arm B.

- *4 pts discontinued early Arm A **3 pts discontinued early (included in denominator for intention to treat analysis) Arm B
- RCBi = Residual cancer burden index; RCB 0 = pCR; Histology or IHC Status did not appear to be associated with RCB response

I-SPY 2 TRIAL Study Schema



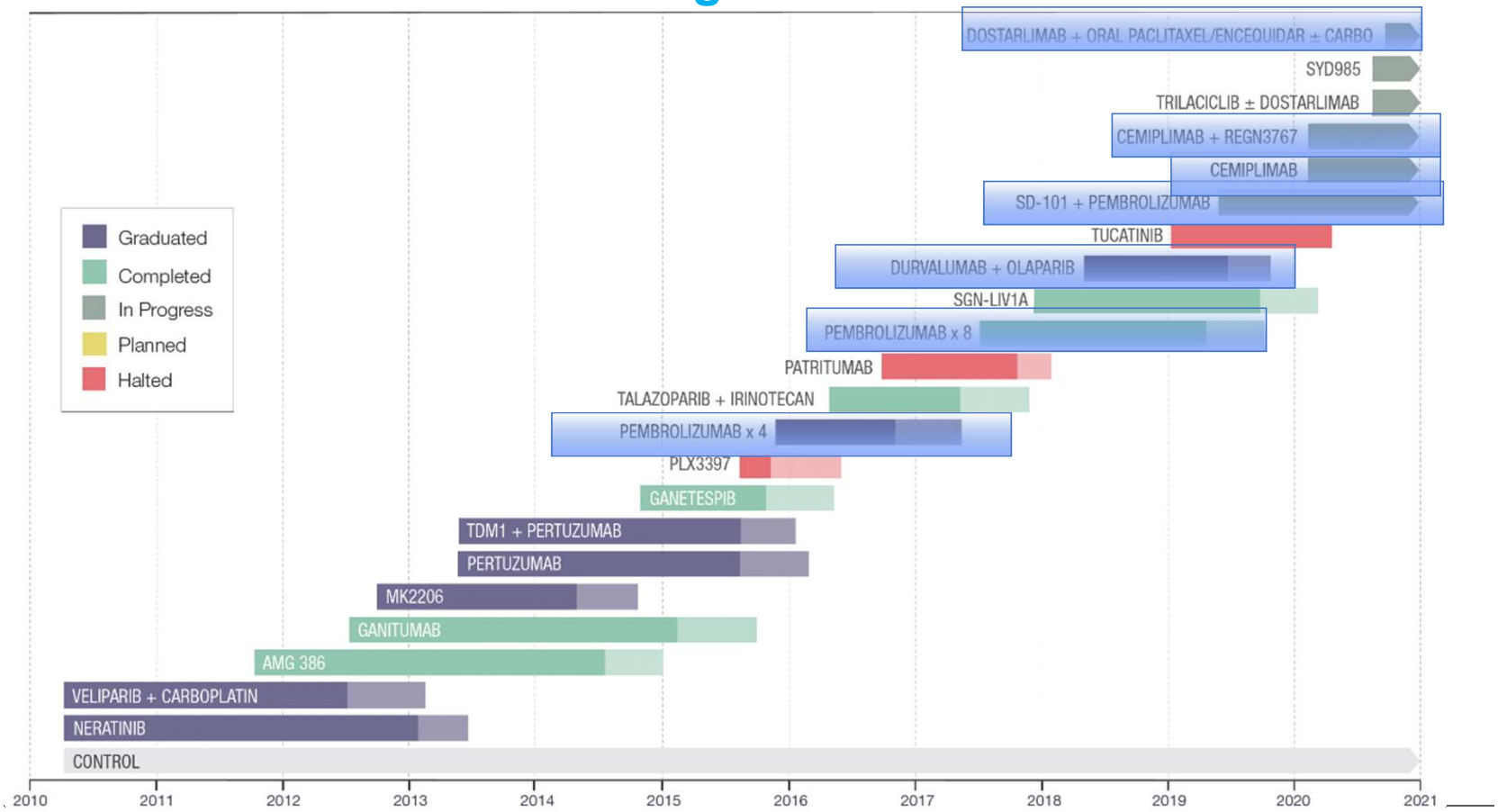
Biomarker-rich protocol

Notes:

T1a: MRI – optional, physician discretion

T3: MRI – only for patients with FTV<80%

I-SPY 2 Agent Timeline



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

Evaluation of anti-PD-1 Cemiplimab plus anti-LAG-3 REGN3767 in Combination with Paclitaxel in Early-Stage, High-Risk HER2-negative Breast Cancer: Results from the Neoadjuvant I-SPY 2 TRIAL

Claudine Isaacs, Rita Nanda, Christina Yau, Jo Chien, Megna Trivedi, Erica Stringer-Reasor, Christos Vaklavas, Judy Boughey, Amy Sanford, Anne Wallace, Amy Clark, Alexandra Thomas, Kathy Albain, Laura Kennedy, Tara Sanft, Kevin Kalinsky, Heather Han, Williams N, Mili Arora, Anthony Elias, Carla Falkson, Smita Asare, Ruixiao Lu, Maria Pitsiouni, Amy Wilson, Jane Perlmutter, Hope S Rugo, Richard Schwab, Frasier Symmans, Nola Hylton, Laura Van 't Veer, Douglas Yee, Angela DeMichele, Don Berry, Laura Esserman

on behalf of the I-SPY 2 TRIAL Consortium

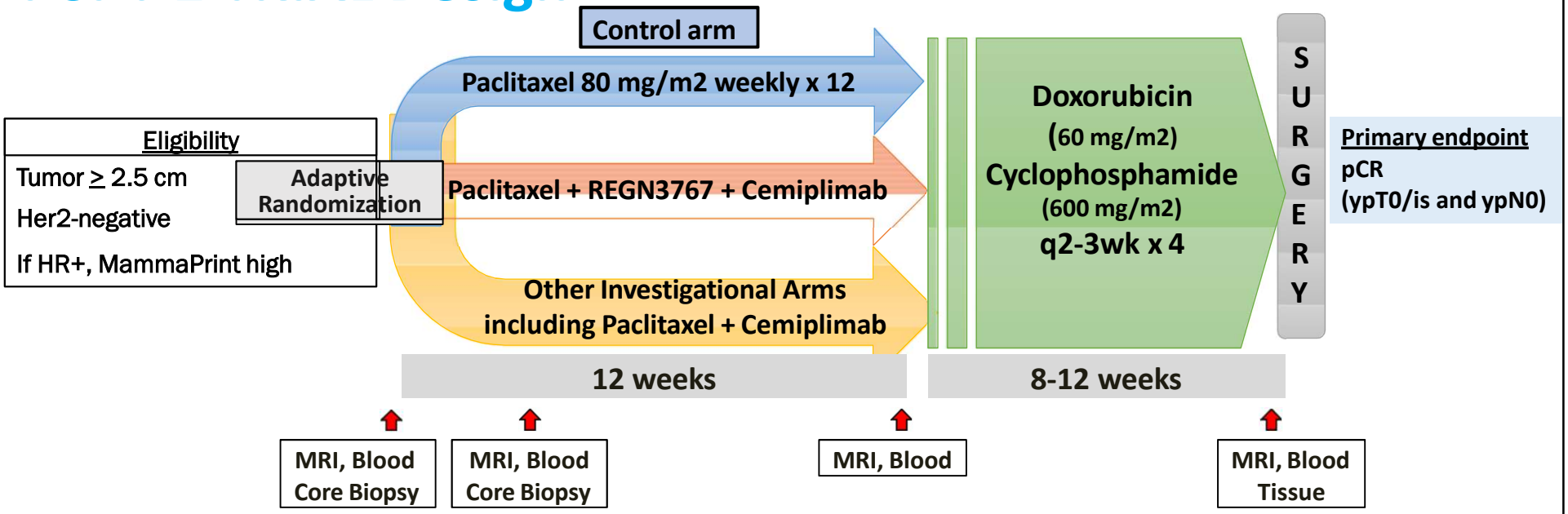
Rationale for REGN3767 + Cemiplimab Combination

- The addition of pembrolizumab, an anti-PD-1, to standard neoadjuvant chemotherapy improves outcomes
  - Phase 2 I-SPY2 trial: near tripling of estimated pathologic complete response (pCR) rate in TN and high-risk HR+ signatures[1]
  - Phase 3 Keynote 522: improved pCR and EFS in TNBC[2]
- Preclinical data suggest a synergistic interaction between anti-LAG3 and anti-PD-1 therapy
- In previously untreated melanoma:
  - Phase 1 expansion cohort (n=80) of cemiplimab + REGN3767 in anti-PD-1/PDL-1- naïve advanced melanoma[3]: ORR 64%
  - RELATIVITY-047 phase 2/3 RCT[4]: median PFS 10.1 months with nivolumab + relatlimab (anti-LAG-3) vs 4.6 months with nivolumab + placebo (p = 0.006)

[1]Nanda et al, JAMA Oncology 2020; [2]Schmid et al, NEJM 2020; [3]Hamid et al. ESMO 2022; Tawbi et al. NEJM 2022

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

I-SPY 2 TRIAL Design



- REGN3767 + Cemiplimab was studied in **3 HER2-negative** biomarker signatures: **all HER2-; TNBC; HR+/HER2**
- Agent Graduation:
  - ≥85% predicted probability of success in a 300-patient phase 3 neoadjuvant trial
- Graduation is assessed for each pre-specified biomarker signature

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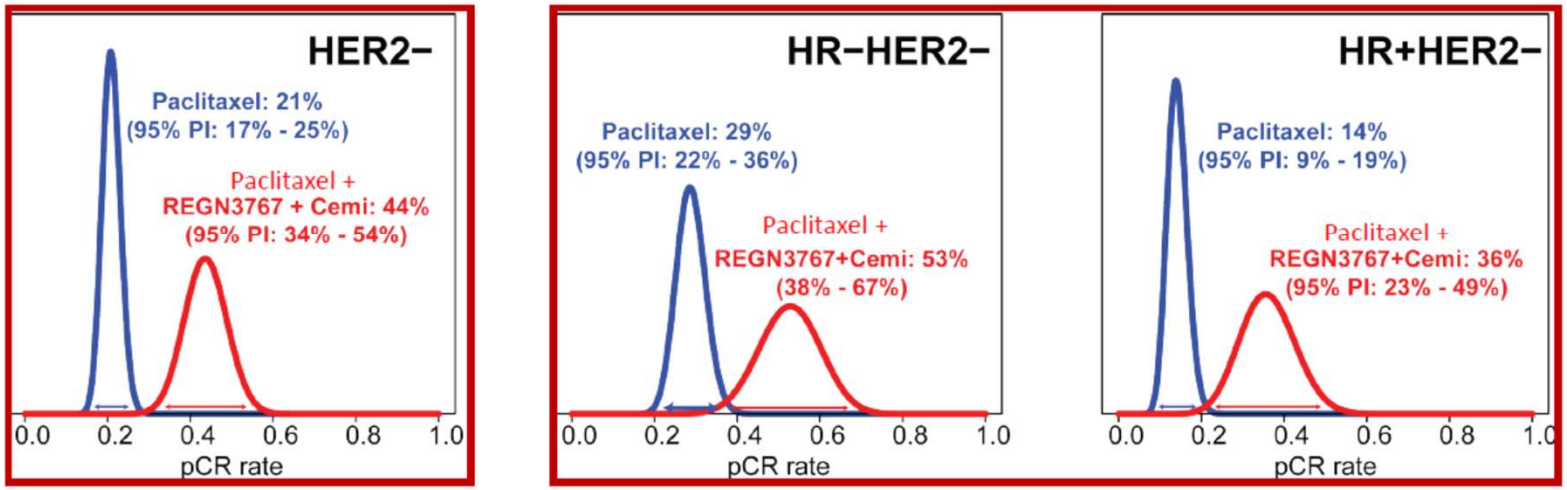
Efficacy Analysis

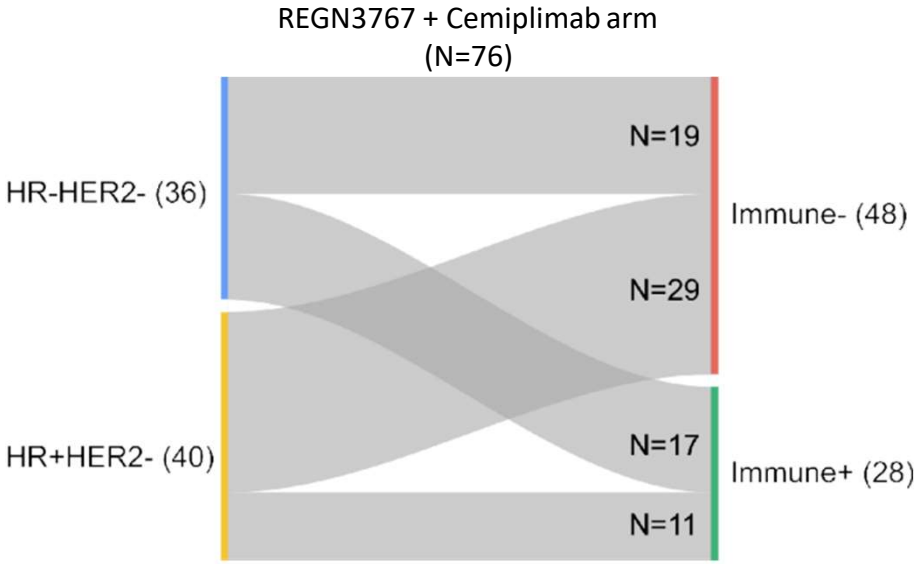


Signature	Estimated pCR Rate (95% Probability Interval)		Probability Pac + REGN3767 + Cemi Superior to Control	Predictive Probability of Success in Phase 3 (relative to Control)
	Pac + REGN3767 + Cemi (n=76)	Control (n=350)		
HER2-	44% (34% - 54%)	21% (17% - 25%)	>0.999	0.955
HR-HER2-	53% (38% - 67%)	29% (22% - 36%)	0.999	0.915
HR+HER2-	36% (23% - 49%)	14% (9% - 19%)	>0.999	0.940

Pac + REGN3767 + Cemiplimab graduated in all 3 eligible biomarker signatures by demonstrating increased pCR

ImPrint: 53-gene Signature of Neoadjuvant Immunotherapy Response

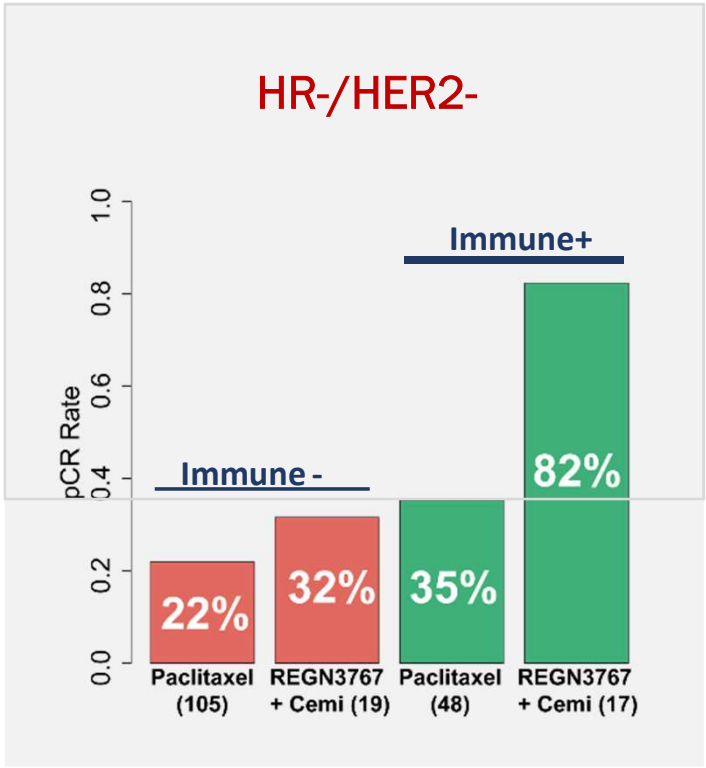
- Developed to predict response to neoadjuvant immunotherapy in pts with HR-HER2- and HR+HER2- BC[1]
- Derived from patients treated on the I-SPY 2 pembrolizumab arm and independently validated in durvalumab/olaparib arm
- In partnership with industry partner developed a diagnostic, ImPrint[2]
- IDE filed and approved on March 2022
- Further refined by introducing subtype-specific templates to improve performance in triple negative patients

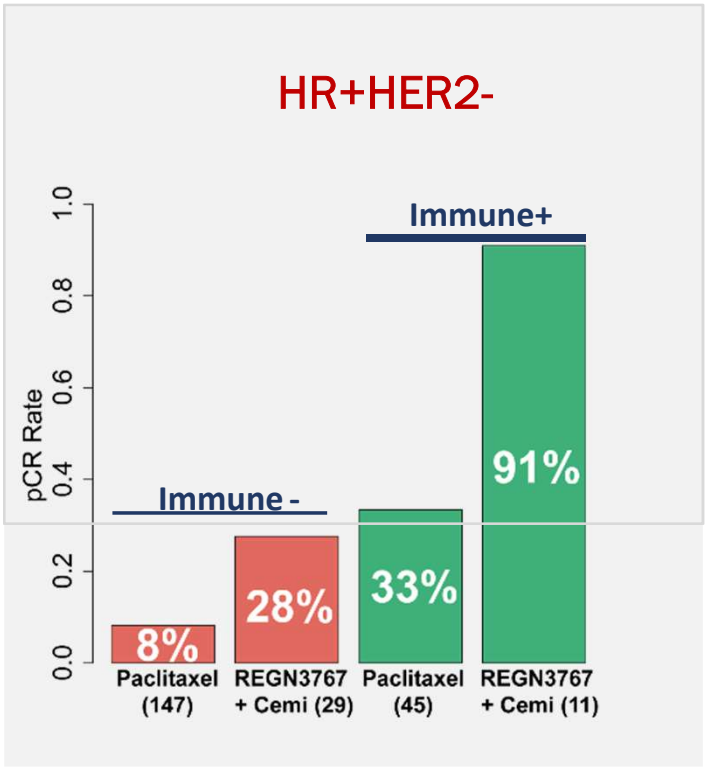


37% Immune+ overall
- **47% of TNBC Immune+**
- **28% of HR+/HER2- Immune+**

[1]*Wolff et al. Cancer Cell 2022;* [2] *Journal of Clinical Oncology* 40, no. 16_suppl (June 01, 2022)514-514

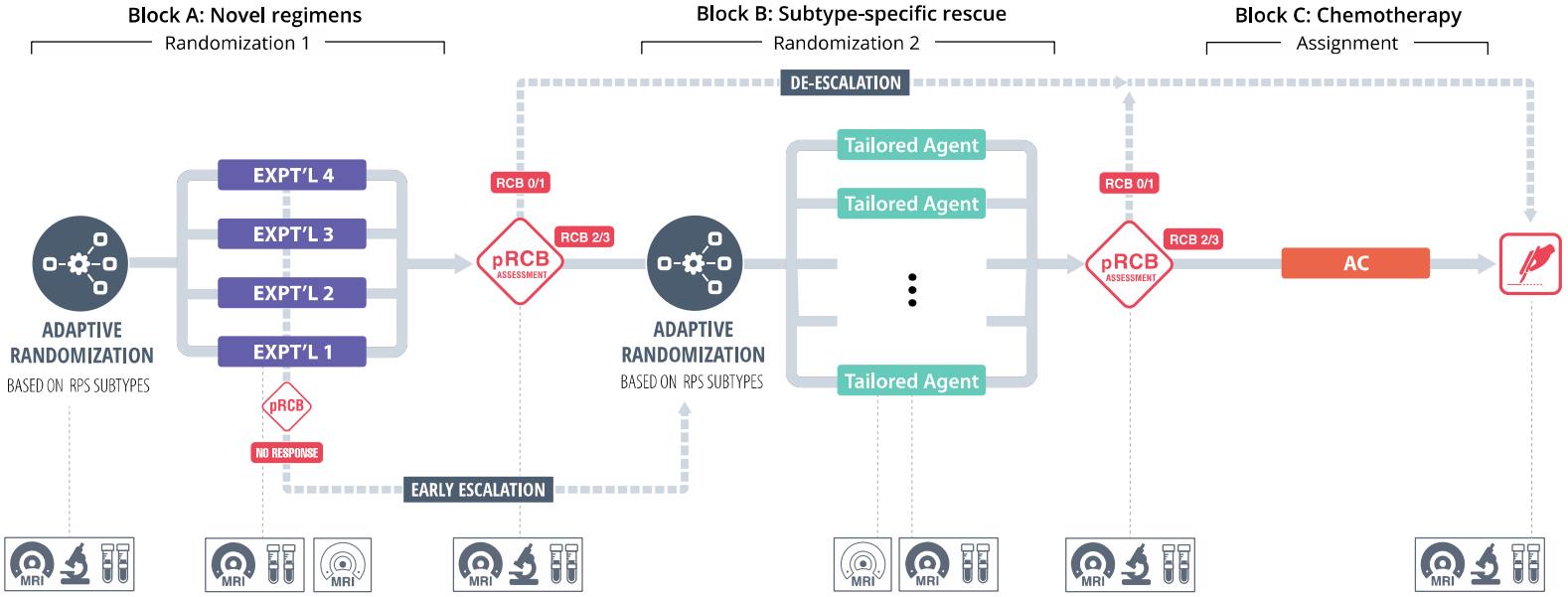
pCR by HR Status and Immune Subtype





Observed (not modeled) pCR rates are shown
345 control and 76 cemi+REGN3767 of primary efficacy analysis population have ImPrint data

I SPY 2.2: Sequential Blocks of treatment *with built in opportunities for escalation and de-escalation*



- Optimize pCR for each patient
- Tailor regimens to response
  - Stop at pCR, continue if not
- Goal: Accelerated approval for agents that generate optimal pCR rates
- Confirm DRFS at 3 years ≥92%
- Test Agents for effectiveness alone (in Block A) as well as in sequence (A, B, C)

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

Abemaciclib plus endocrine therapy for HR+, HER2-, node-positive, high-risk early breast cancer: results from a pre-planned monarchE overall survival interim analysis, including 4-year efficacy outcomes

Stephen R.D. Johnston[1], Masakazu Toi, Joyce O'Shaughnessy, Priya Rastogi, Mario Campone, Patrick Neven, Chiun-Sheng Huang, Jens Huober, Georgina Garnica Jaliffe, Irfan Cicin, Sara M. Tolaney, Matthew P. Goetz, Hope S. Rugo, Elzbieta Senkus, Laura Testa, Lucia Del Mastro, Chikako Shimizu, Ran Wei, Ashwin Shahir, Maria Munoz, Belen San Antonio, Valérie André, Nadia Harbeck, Miguel Martin

[1]Royal Marsden NHS Foundation Trust, London, United Kingdom

monarchE: Adjuvant Abemaciclib in Early Breast Cancer

- Adjuvant abemaciclib combined with ET previously demonstrated significant improvement in IDFS and DRFS in high-risk, HR+/HER2-, node-positive EBC[1, 2]
  - When statistical significance was first met, follow-up was limited (median 15.5 months)[1]
  - A subsequent analysis confirmed abemaciclib treatment benefit persisted beyond the 2-year treatment period[2]
- Data presented today are from a pre-planned OS interim analysis defined to occur 2 years following the primary outcome analysis
  - All patients are now off abemaciclib
  - Median follow-up is 42 months
  - Includes a 4-year landmark analyses

[1]Johnston SRD, et al. J Clin Oncol. 2020;38(34):3987-3998
[2]Harbeck* N, Rastogi* P, et al. Ann Oncol. 2021;32(12):1571-1581
***co-first authors**

monarchE Study Design (NCT03155997)

HR+, HER2-, node positive high-risk EBC
- Women or men
- Pre-/postmenopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No metastatic disease
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Cohort 1: High risk based on **clinical pathological features**
- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Grade 3 disease
  - Tumor size ≥5 cm

Cohort 2: High risk based on **Ki-67**
- 1-3 ALN and
- Ki-67 ≥20% and
- Grade 1-2 and tumor size <5 cm

Stratified for:
- Prior chemotherapy
- Menopausal status
- Region

R 1:1
N = 5637

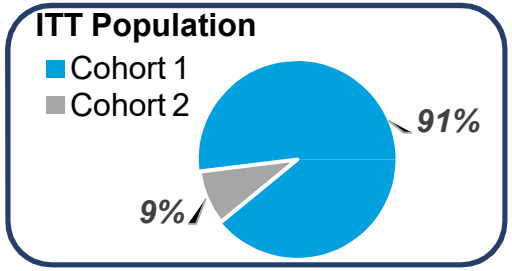
Abemaciclib
(150mg twice daily)
+
Endocrine Therapy: AI or tamoxifen

Endocrine Therapy: AI or tamoxifen

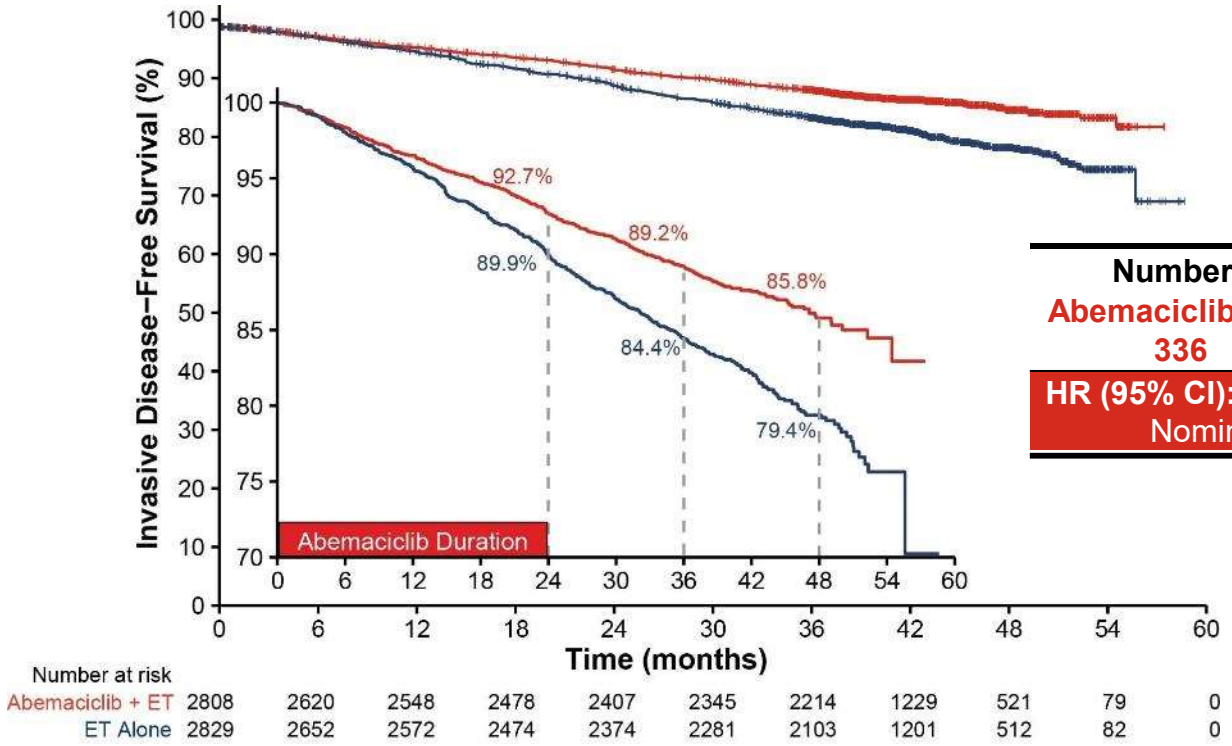
On-study treatment period
2 years

Follow-up period
Endocrine Therapy
3-8 years as clinically indicated

Primary Objective: IDFS
Secondary Objectives: IDFS in high Ki-67 populations, DRFS, OS, Safety, PK, PRO



IDFS Benefit in ITT Persists Beyond Completion of Abemaciclib



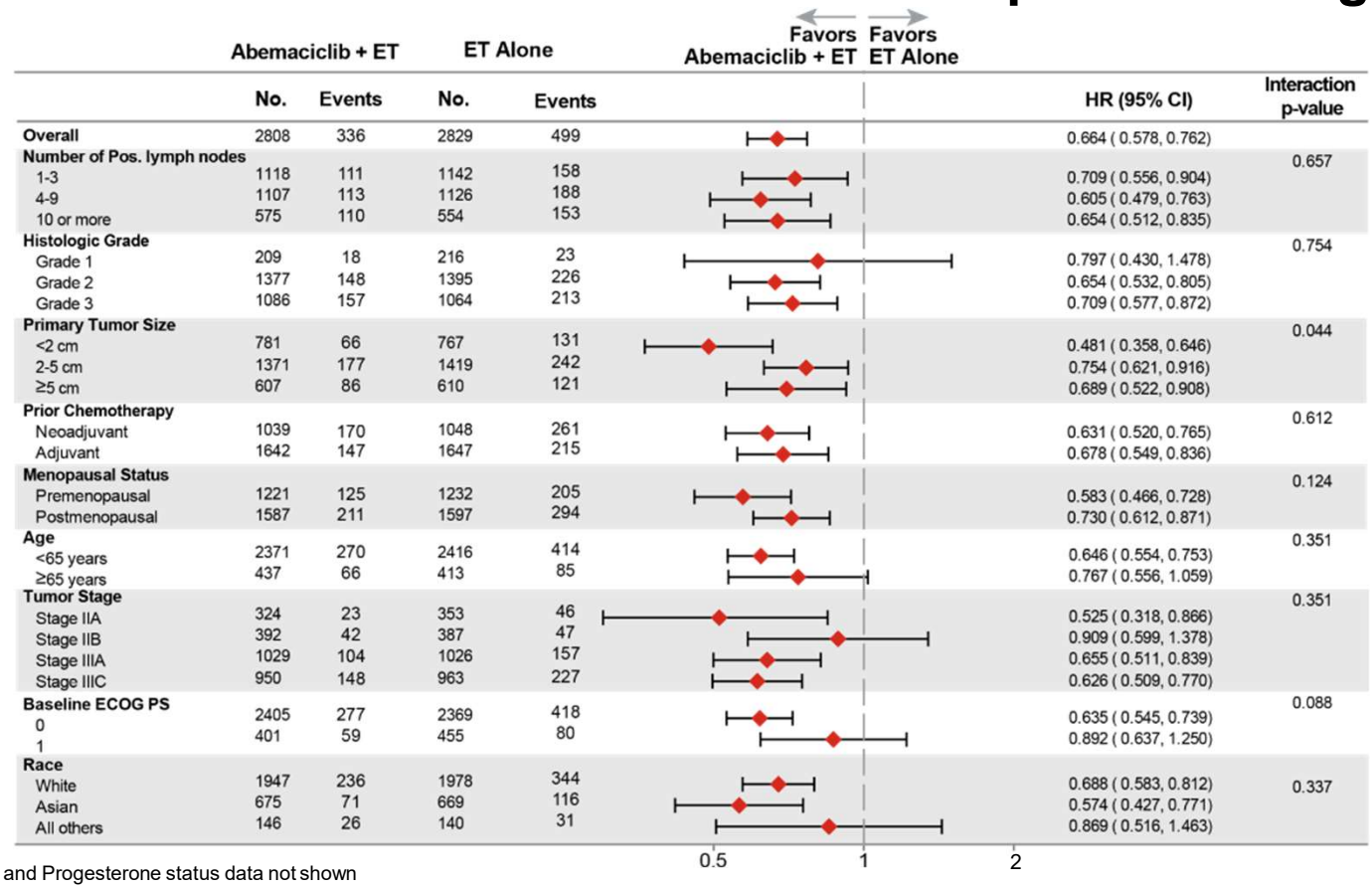
Number of IDFS events

Abemaciclib + ET	ET Alone
336	499

HR (95% CI): 0.664 (0.578, 0.762)
Nominal p < 0.0001

33.6% reduction in the risk of developing an IDFS event with an increase in absolute benefit in IDFS 4-year rates (6.4%) compared to 2-and 3-year IDFS rates (2.8% and 4.8% respectively)

Consistent IDFS Benefit Observed in all Prespecified Subgroups*



	Abemaciclib + ET No.	Abemaciclib + ET Events	ET Alone No.	ET Alone Events	HR (95% CI)	Interaction p-value
Overall	2808	336	2829	499	0.664 (0.578, 0.762)	
Number of Pos. lymph nodes						0.657
1-3	1118	111	1142	158	0.709 (0.556, 0.904)	
4-9	1107	113	1126	188	0.605 (0.479, 0.763)	
10 or more	575	110	554	153	0.654 (0.512, 0.835)	
Histologic Grade						0.754
Grade 1	209	18	216	23	0.797 (0.430, 1.478)	
Grade 2	1377	148	1395	226	0.654 (0.532, 0.805)	
Grade 3	1086	157	1064	213	0.709 (0.577, 0.872)	
Primary Tumor Size						0.044
<2 cm	781	66	767	131	0.481 (0.358, 0.646)	
2-5 cm	1371	177	1419	242	0.754 (0.621, 0.916)	
≥5 cm	607	86	610	121	0.689 (0.522, 0.908)	
Prior Chemotherapy						0.612
Neoadjuvant	1039	170	1048	261	0.631 (0.520, 0.765)	
Adjuvant	1642	147	1647	215	0.678 (0.549, 0.836)	
Menopausal Status						0.124
Premenopausal	1221	125	1232	205	0.583 (0.466, 0.728)	
Postmenopausal	1587	211	1597	294	0.730 (0.612, 0.871)	
Age						0.351
<65 years	2371	270	2416	414	0.646 (0.554, 0.753)	
≥65 years	437	66	413	85	0.767 (0.556, 1.059)	
Tumor Stage						0.351
Stage IIA	324	23	353	46	0.525 (0.318, 0.866)	
Stage IIB	392	42	387	47	0.909 (0.599, 1.378)	
Stage IIIA	1029	104	1026	157	0.655 (0.511, 0.839)	
Stage IIIC	950	148	963	227	0.626 (0.509, 0.770)	
Baseline ECOG PS						0.088
0	2405	277	2369	418	0.635 (0.545, 0.739)	
1	401	59	455	80	0.892 (0.637, 1.250)	
Race						0.337
White	1947	236	1978	344	0.688 (0.583, 0.812)	
Asian	675	71	669	116	0.574 (0.427, 0.771)	
All others	146	26	140	31	0.869 (0.516, 1.463)	

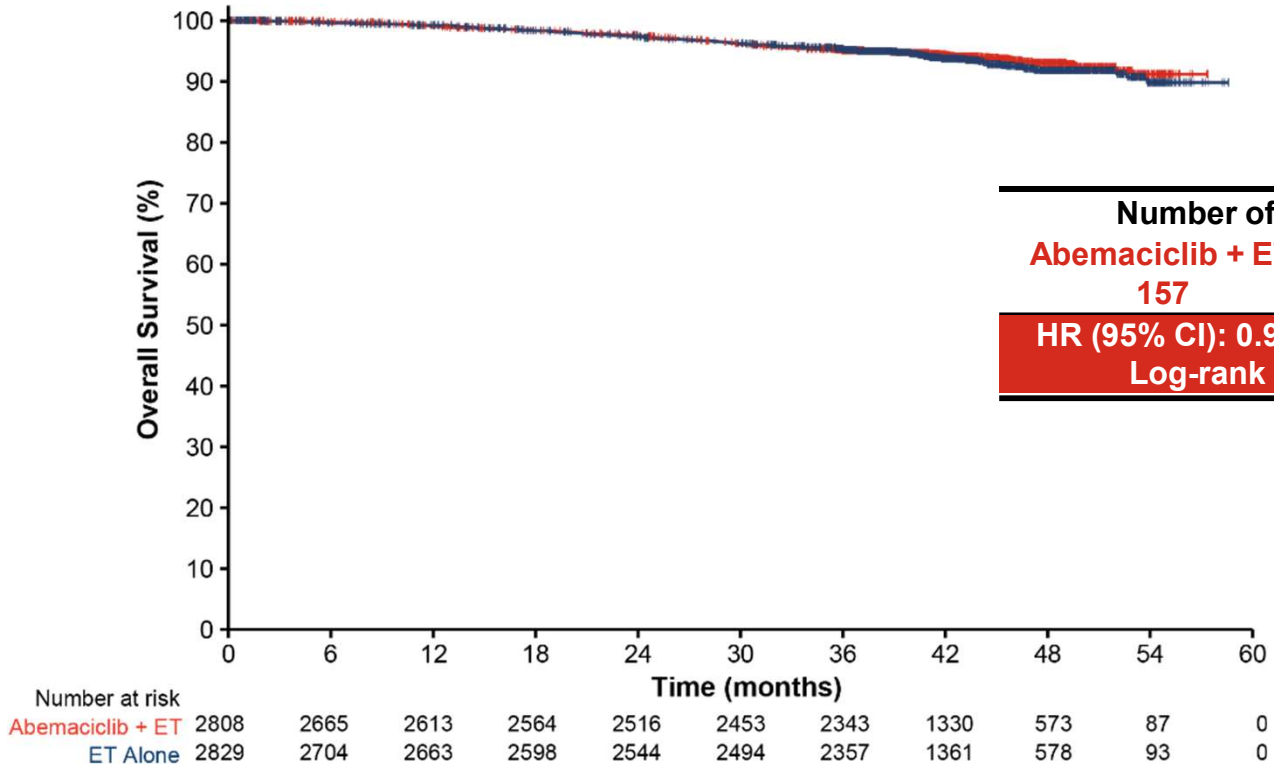
*Region of enrollment and Progesterone status data not shown

Abemaciclib Treatment Benefit Deepened Over Time

	Analysis landmark	IDFS	DRFS
		Piecewise HR[a] (95% CI[b])	Piecewise HR[a] (95% CI[b])
Study Treatment Period	Year 0-1	0.782 (0.583, 1.018)	0.725 (0.519, 0.983)
	Year 1-2	0.674 (0.521, 0.858)	0.691 (0.521, 0.887)
	Year 2-3	0.618 (0.477, 0.788)	0.651 (0.497, 0.851)
	Year 3+	0.602 (0.428, 0.803)	0.581 (0.391, 0.818)

[a]Piecewise hazard ratio as a post-hoc analysis was estimated using piecewise exponential model to assess the yearly treatment effect size;
[b]95% credible intervals were calculated by equal tails in the posterior samples of Bayesian exponential models

OS Data Remain Immature in ITT



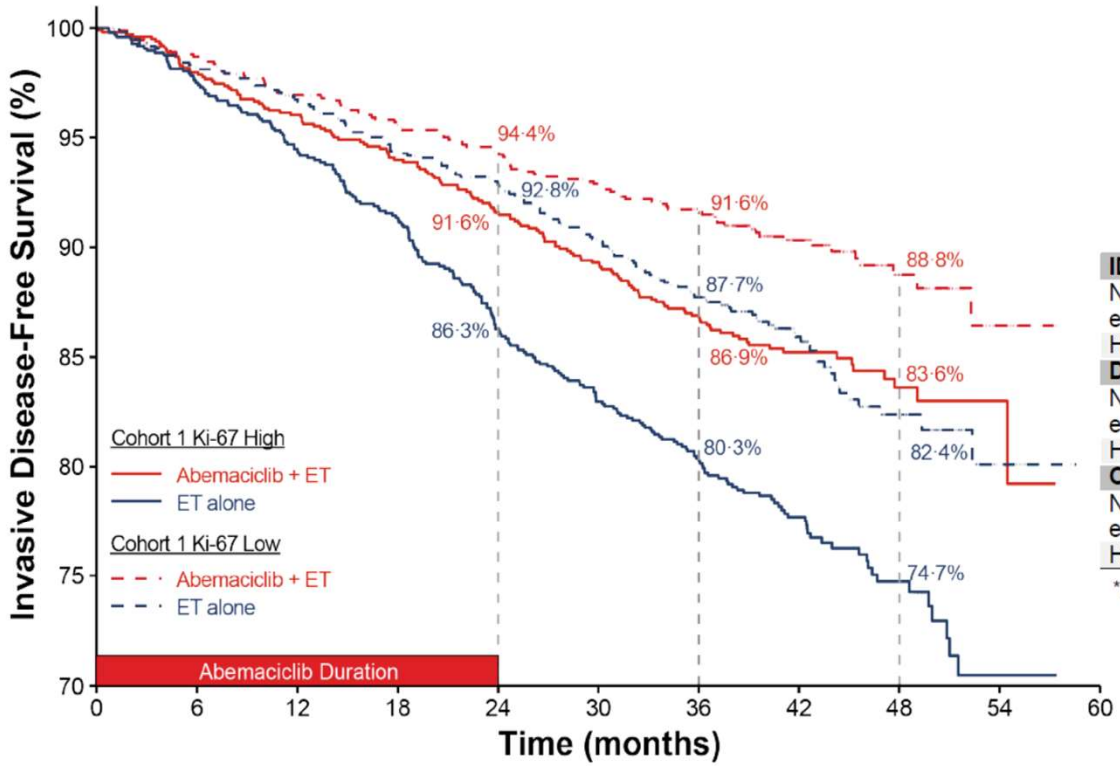
Number of OS events	
Abemaciclib + ET	ET Alone
157	173

HR (95% CI): 0.929 (0.748, 1.153)
Log-rank P = 0.5027

Fewer deaths (157 vs 173) were observed in the abemaciclib plus ET group versus the ET group

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

Ki-67 is Prognostic, but Not Predictive of Abemaciclib Benefit

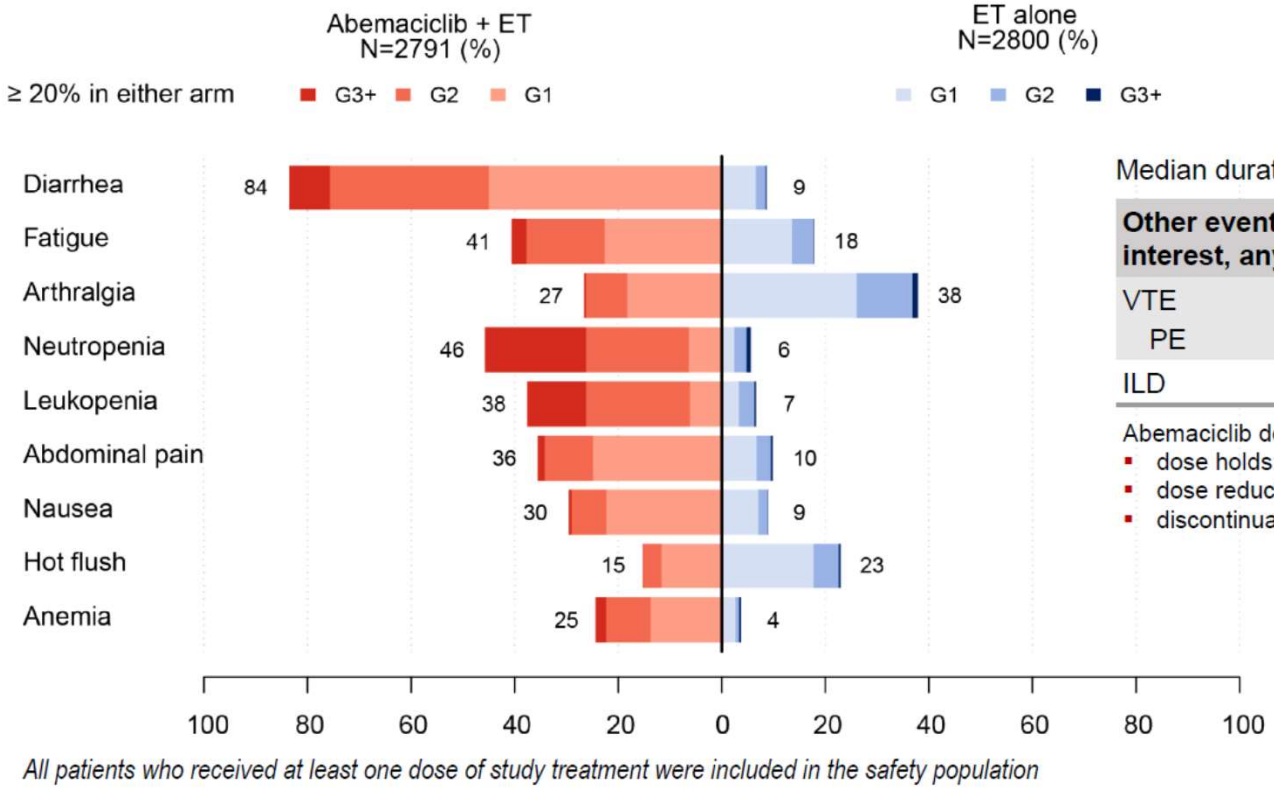


	Cohort 1*			
	C1 Ki-67 High		C1 Ki-67 Low	
	Abemaciclib + ET N=1017	ET alone N=986	Abemaciclib + ET N=946	ET alone N=968
IDFS				
Number of events, n	147	224	91	141
HR (95% CI)	**0.618** (0.501, 0.762)		**0.624** (0.478, 0.814)	
DRFS				
Number of events, n	126	193	74	119
HR (95% CI)	**0.612** (0.488, 0.767)		**0.613** (0.458, 0.821)	
OS (Immature)				
Number of events, n	68	88	39	50
HR (95% CI)	**0.733** (0.533, 1.007)		**0.772** (0.506, 1.175)	

*Ki-67 value was missing in 1203 (23.5%) patients

Within Cohort 1, similar abemaciclib treatment effects were observed regardless of Ki-67 index

Safety Findings Consistent with Previous Analyses



Median duration of abemaciclib: 23.7 months.

Other events of interest, any grade	Abemaciclib + ET N = 2791, %	ET Alone N = 2800, %
VTE	2.5	0.7
PE	1.0	0.1
ILD	3.3	1.3

Abemaciclib dose adjustments due to AEs

- dose holds: 61.7%
- dose reductions: 43.6%
- discontinuations 18.5% [8.9% after dose reduction]

All patients who received at least one dose of study treatment were included in the safety population

The safety profile of abemaciclib is considered manageable and acceptable for this high-risk population

Conclusions: HR+, HER2-Negative Breast Cancer

- Patient selection for NAT is evolving over time via novel NAC trials

- Adjuvant abemaciclib added to ET in patients with high risk HR+HER2-neg, node positive early BC:

  -yields increases in absolute IDFS and DRFS benefit at 4 years as compared to 2- and 3 years across all pre-specified subgroups for IDFS and DRFS

  -Abemaciclib benefit is similar regardless of Ki-67 index

  -toxicity is manageable with supportive care and dose reductions

Penn Medicine

Conclusions: Neoadjuvant and Adjuvant Therapy for HER2-Negative Breast Cancer

- Incremental survival gains have been seen with recent treatment changes for early-stage, HER2-negative breast cancer
- Innovative clinical trial design in the preoperative setting: drive biomarker development, inform patient selection for novel therapies, including immunotherapy
- Adjuvant therapy is an important consideration for patients with high-risk, HER2 negative breast cancer
- Awareness of toxicity risk and supportive care are important for patients with early-stage breast cancer undergoing curative intent treatment

Penn Medicine

National Comprehensive Cancer Network®

NCCN Member Institutions

Who We Are

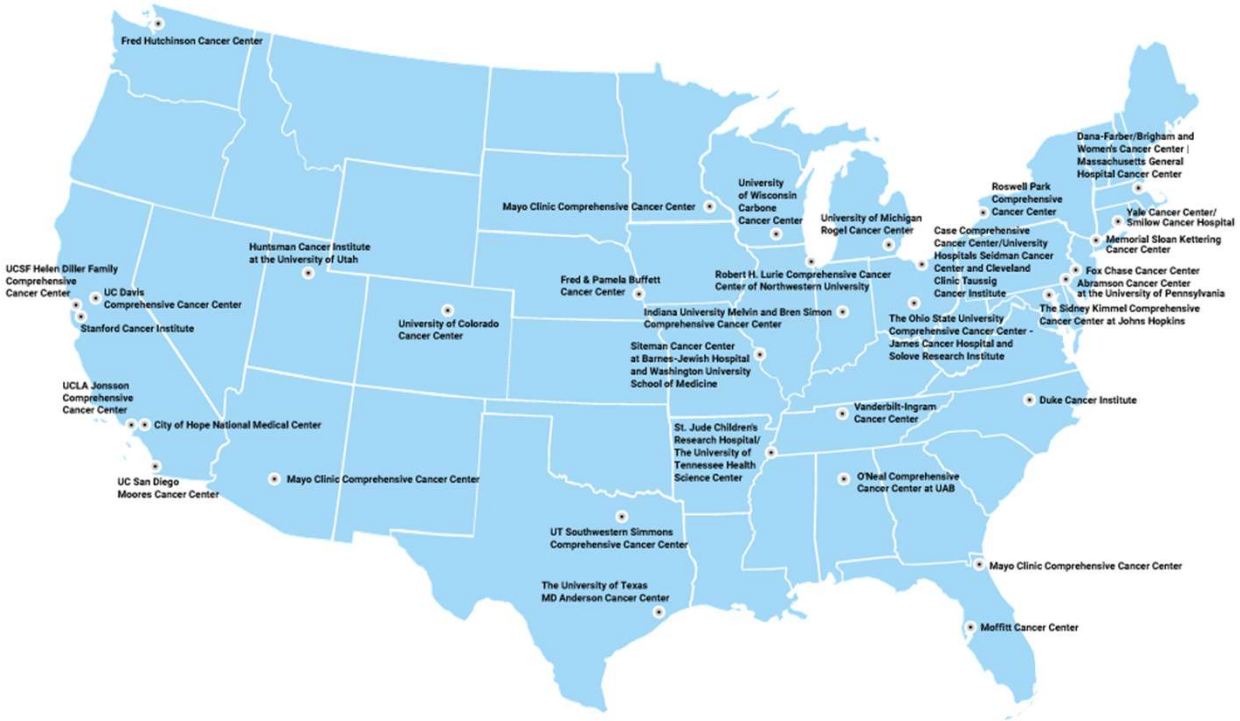
An alliance of leading cancer centers devoted to patient care, research, and education

Our Mission

To improve and facilitate quality, effective, 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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NCCN 2023 BREAST CANCER CONGRESS
with Updates from the 2022 San Antonio Breast Cancer Symposium

Neoadjuvant/Adjuvant Treatment for Breast Cancer with SABCS Updates

HER2-Positive Breast Cancer

Ami Shah, MD

Robert H. Lurie Comprehensive Cancer Center of Northwestern University

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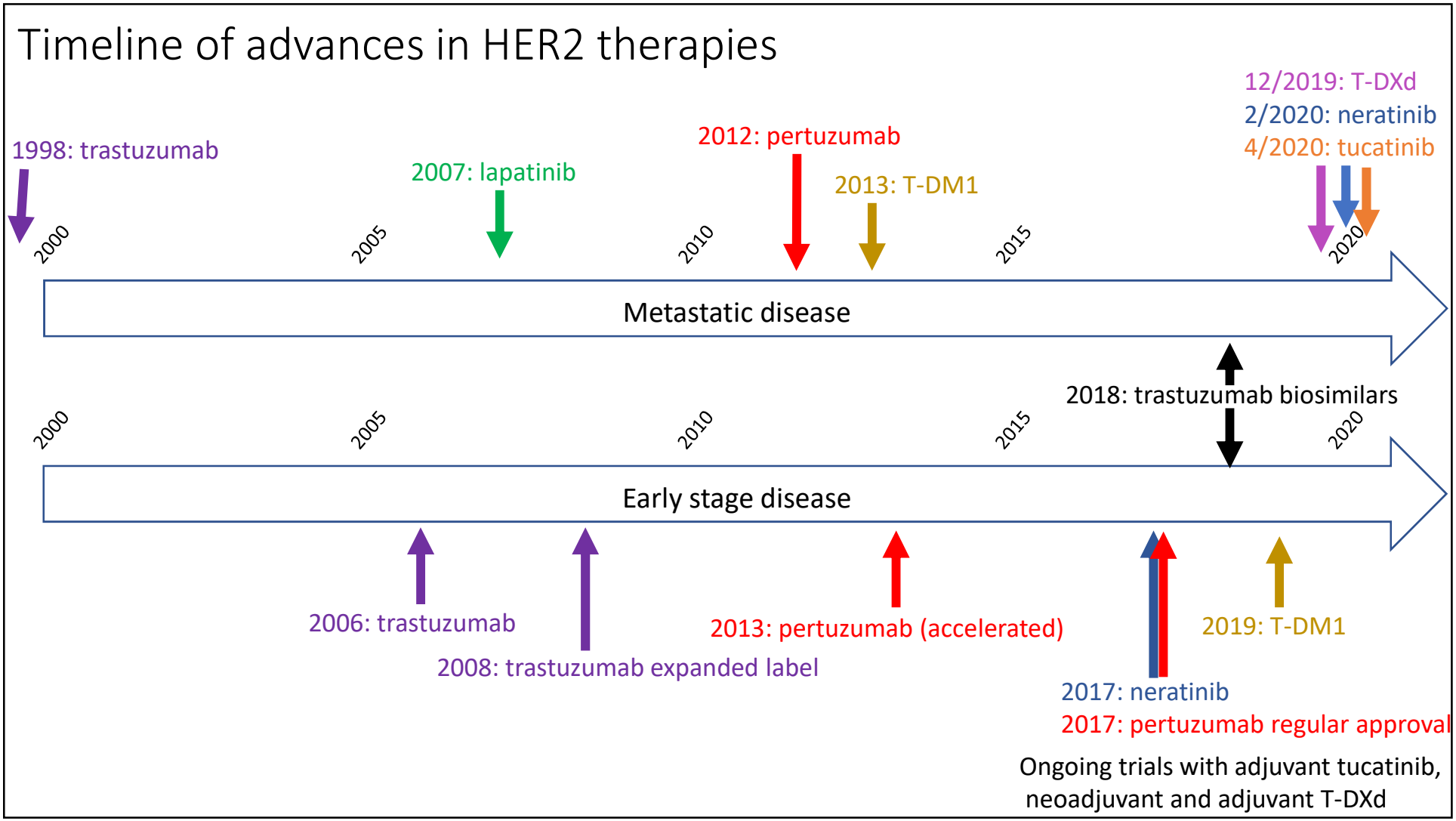
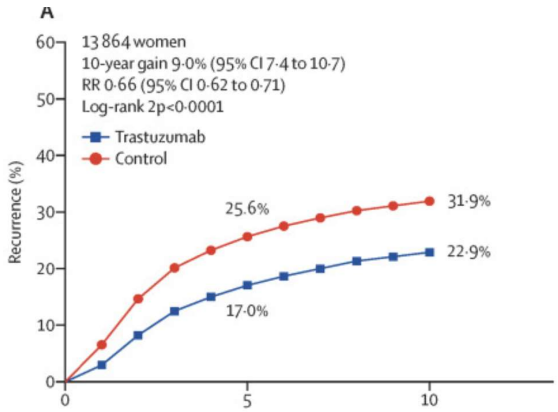


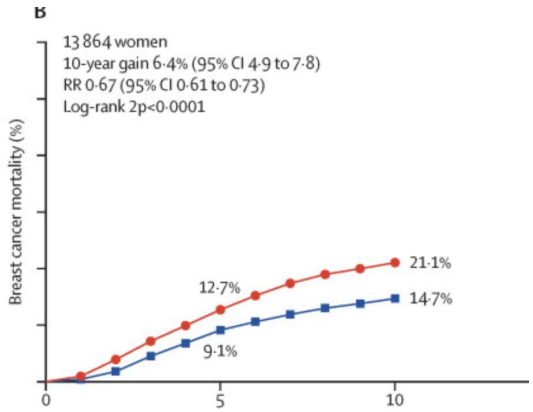
Meta-analysis with individual data from 13,864 patients demonstrating benefit of trastuzumab therapy

- Pooled from 7 RCTs



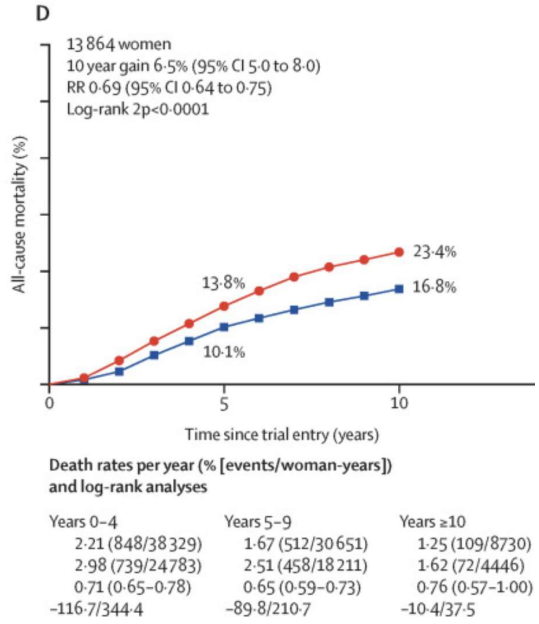
Recurrence rates per year (% [events/woman-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Trastuzumab	4·10 (1469/35 853)	1·53 (422/27 648)	0·95 (75/7858)
Control	6·24 (1385/22 180)	1·87 (291/15 601)	1·12 (43/3835)
Rate ratio (95% CI)	0·62 (0·58–0·66)	0·83 (0·72–0·95)	0·91 (0·63–1·31)
from (O–E)/V	−284·0/591·3	−29·6/154·9	−2·5/25·3



Death rates per year (%; 95% CI) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
	1·99 (1·85–2·13)	1·38 (1·25–1·51)	0·75 (0·57–0·93)
	2·73 (2·53–2·94)	2·18 (1·97–2·40)	1·15 (0·83–1·46)
	0·70 (0·63–0·76)	0·63 (0·56–0·70)	0·64 (0·47–0·88)
	−113·6/312·9	−84·2/179·8	−10·9/24·6



Death rates per year (% [events/woman-years]) and log-rank analyses

Years 0–4	Years 5–9	Years ≥10
2·21 (848/38 329)	1·67 (512/30 651)	1·25 (109/8730)
2·98 (739/24 783)	2·51 (458/18 211)	1·62 (72/4446)
0·71 (0·65–0·78)	0·65 (0·59–0·73)	0·76 (0·57–1·00)
−116·7/344·4	−89·8/210·7	−10·4/37·5

EBCTG. Lancet Oncol, 2021

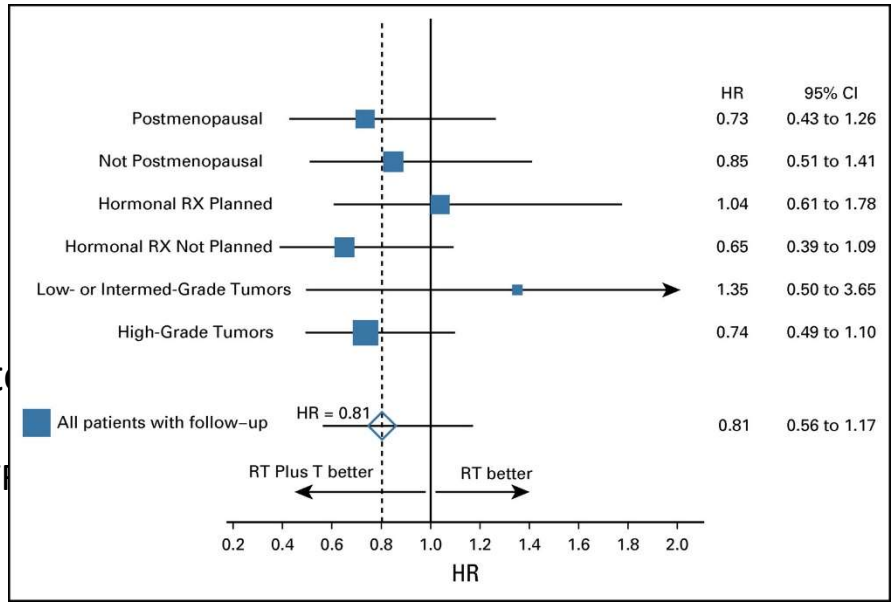
Neoadjuvant and adjuvant treatment of HER2-positive breast cancer

- HER2-positive DCIS
- Stage 1 HER2+ breast cancer
- Stage 2-3 HER2+ breast cancer
- Future directions
  - De-escalation
  - Brain metastases
  - Strategies for high-risk patients

HER2+ DCIS

- High-grade/poorly differentiated DCIS is associat
  - High rate of progression to invasive carcinoma
  - Higher rate of ipsilateral breast tumor recurrence (IBT
  - Frequent overexpression of HER2

- B-43 trial: radiation vs radiation + trastuzumab for HER2-positive DCIS after a lumpectomy
  - Phase III randomized trial
  - Stratified by menopausal status, adjuvant ET plan, and nuclear grade
  - n=2014, median follow up 79.2 mo, primary analysis done after all patients with 5+ years follow up



HR 0.81 (95% CI 0.56-1.17), p=.26

Annual IBTR rate:

- RT: 0.99%/year
- RT + trastuzumab: 0.79%/year

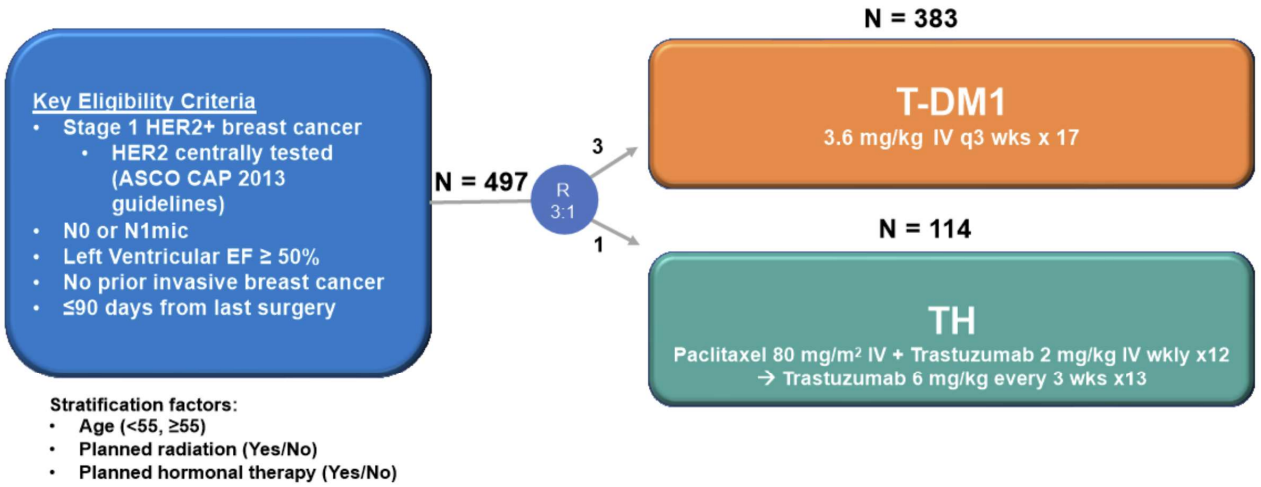
Cobleigh et al. J Clin Oncol 2021

Adjuvant TH – APT trial, 10 year results

- 406 patients, single arm study, tumor ≤3cm, node negative (except 6 N1mic)
- Adjuvant paclitaxel 80mg/m2 + trastuzumab 2mg/kg weekly x 12 weeks → trastuzumab 6mg/kg q3 weeks x 13
- 49% T1a/T1b, 42% T1c, 9% T2; 67% HR+
- 31 events
  - 6 distant recurrences (including occurrence years 5-10)
  - 6 ipsilateral recurrences
  - 9 contralateral new BC (1 HER2+)
  - 10 year relapse free interval 96.3% (95% CI 94.3-98.3%)
  - No different by HR status

Tolaney et al, SABCS 2022

ATEMPT: Stage 1 HER2+ BC: Adjuvant TH vs T-DM1



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

***Radiation and endocrine therapy could be initiated after 12 weeks on study therapy**

Tolaney SM et al, SABCS 2019
Tolaney SM et al, JCO 2021

Tumor size:
-T1a 16%
-T1b 34%
-T1c 50%
Grade:
-G1 3%
-G2 39%
-G3 57%
HR+ 75%

Tolaney et al. J Clin Oncol 2019

ATEMPT trial 5 year results and other updates

- 5.8 years follow up
  - T-DM1: 11 iDFS events; 3 distant recurrences, 3 non-related deaths, 3 contralateral HER2- breast cancers, 2 ipsilateral recurrences (1 HER2+)
    - Outcomes similar across HR and tumor size

	T-DM1 (N=383)	TH (ATEMPT) (N=114)	TH (APT) (N=406)
3-year iDFS	97.8% 10 events	93.4% 8 events	98.5%
5-year iDFS	97.0% 11 events*	91.1% 9 events	96.3%
5-year RFI	98.3% 6 events	93.2% 7 events	98.1% 7 events
5-year OS	97.8% 3 events	97.9%	98.7% 5 events
5-year BCSS	99.4%	Not reported	99.7% 1 event

Table from Hurvitz SABCS 2022
Tarantino et al SABCS 2022
Tolaney et al. J Clin Oncol 2019

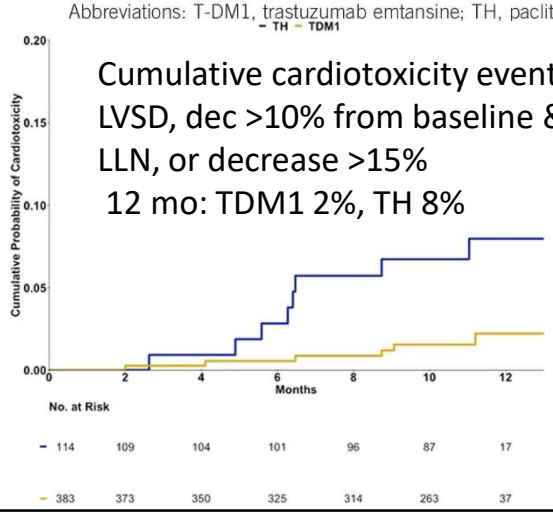
Toxicities

TABLE 2. Clinically Relevant Toxicities

Clinically Significant Toxicity	Arm 1: T-DM1 (n = 383), No. (%, 95% CI)	Arm 2: TH (n = 114), No. (%, 95% CI)	Overall (N = 497), No. (%, 95% CI)
Grade 3 or higher nonhematologic toxicity	36 (9, 7 to 13)	13 (11, 7 to 19)	49 (10, 8 to 13)
Grade 2 or higher neurotoxicity	42 (11, 8 to 14)	26 (23, 16 to 31)	68 (14, 11 to 17)
Grade 4 or higher hematologic toxicity	4 (1, 0 to 3)	0 (0, 0 to 3)	4 (1, 0 to 2)
Febrile neutropenia	0 (0, 0 to 1)	2 (2, 0 to 6)	2 (0, 0 to 1)
Any toxicity requiring dose delay	106 (28, 23 to 32)	30 (26, 19 to 35)	136 (27, 24 to 31)
Any toxicity requiring early discontinuation of protocol therapy	67 (17, 14 to 22)	7 (6, 3 to 12)	74 (15, 12 to 18)
Serious adverse event	11 (3, 2 to 5)	6 (5, 2 to 11)	17 (3, 2 to 5)
Total	177 (46, 41 to 51)	54 (47, 38 to 56)	231 (46, 42 to 51)

Abbreviations: T-DM1, trastuzumab emtansine; TH, paclitaxel plus trastuzumab.

G2+ neurotox 11% vs 23%
G4+ hematology tox 1% vs 0%
Tox requiring early dc 17 vs 6%
SAE 3% vs 5%

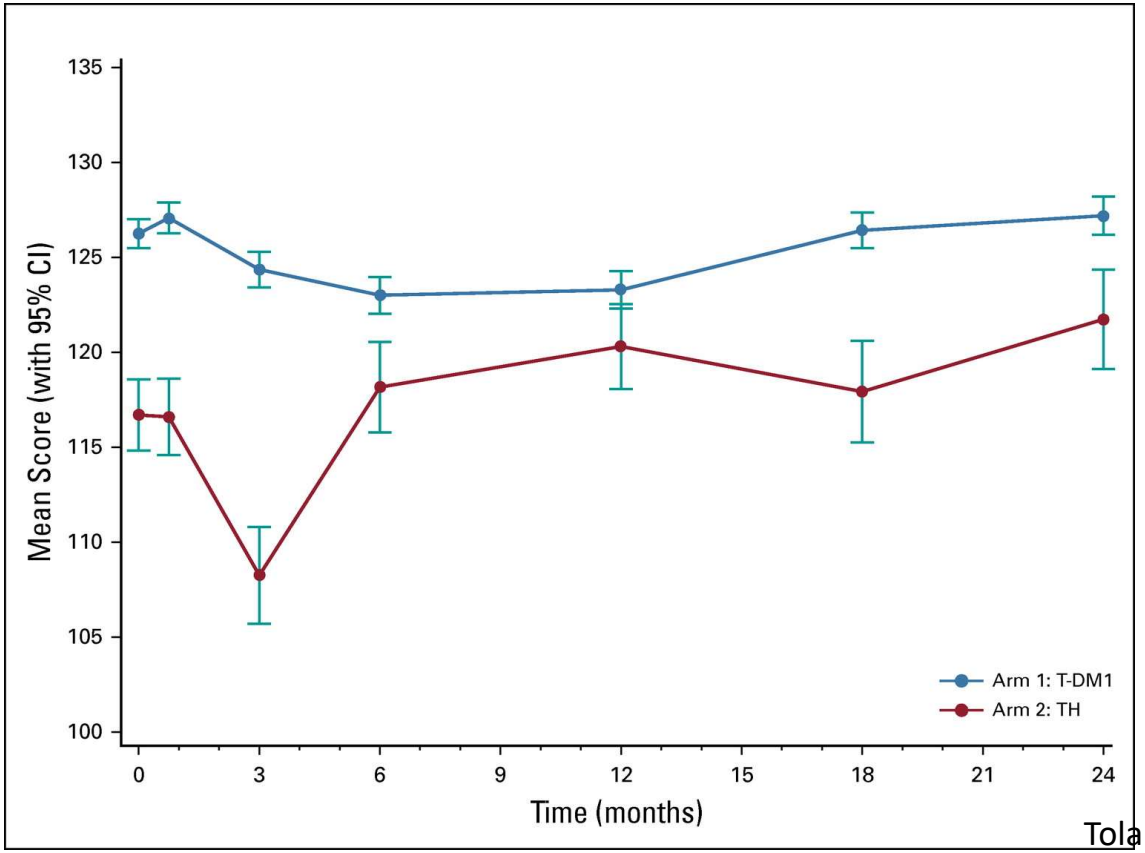


Cumulative cardiotoxicity event (G3-4 LVSD, dec >10% from baseline & below LLN, or decrease >15%
12 mo: TDM1 2%, TH 8%

18-month chemotherapy related amenorrhea rate among a subgroup of 76 premenopausal women without GnRH agonist, oophorectomy, or hysterectomy and with menstrual survey data:
50% after TH, 24% after T-DM1 p=0.045

Tolaney et al. J Clin Oncol 2021
Ruddy et al. BCRT 2021
Barroso-Sousa et al. NPJ 2022

Patient reported outcomes



Tolaney et al J Clin Oncol 2021

Stage 1 HER2+ breast cancer

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Breast Cancer

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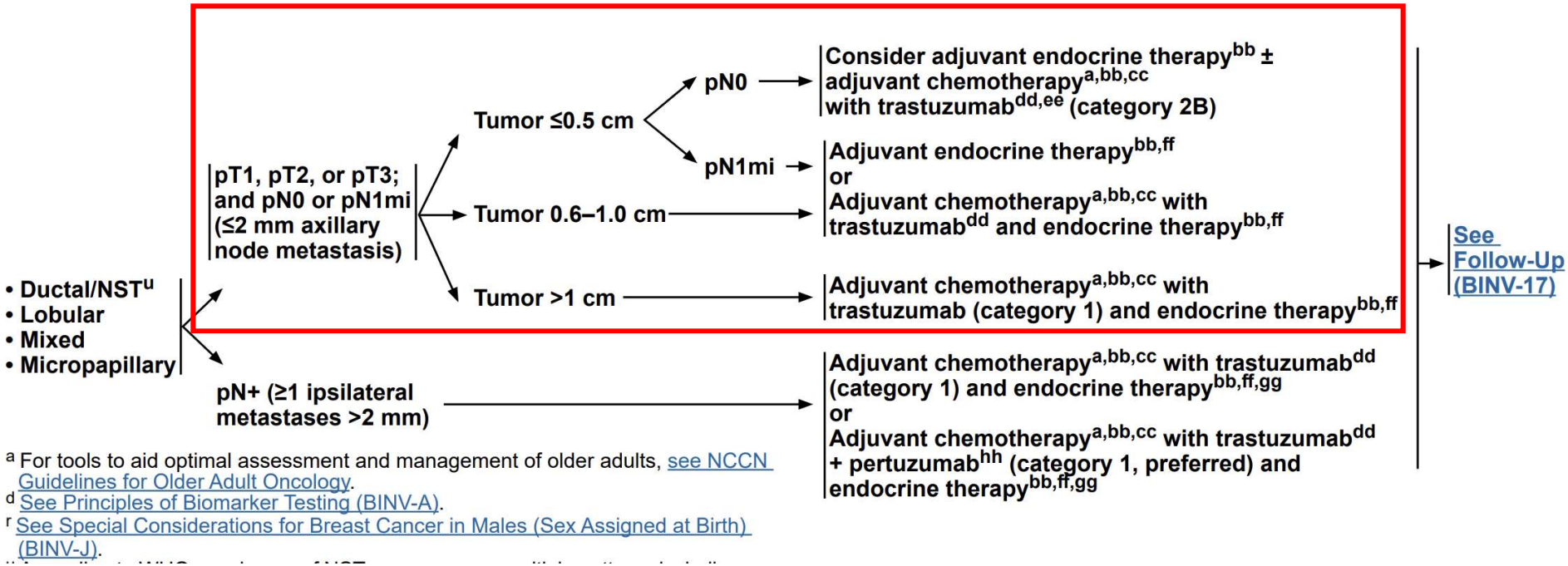
SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-POSITIVE DISEASE[d,r,z]



[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[d] See Principles of Biomarker Testing (BINV-A).
[r] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).

T1aN0 tumors

- NCCN Guidelines:
  - The prognosis of patients with pT1a and pT1b tumors that are pN0 is uncertain even when HER2 is amplified or overexpressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.
  - Adjuvant chemotherapy with weekly paclitaxel and trastuzumab can be considered for pT1,N0,M0, HER2-positive cancers, particularly if the primary cancer is HR-negative. The absolute benefit of HER2-based systemic chemotherapy is likely negligible in patients with HR-positive cancers and tumor size bordering on T1mic (<1 mm), when the estimated recurrence risk is less than 5% and endocrine therapy remains a viable option for systemic treatment.

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PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Positive

Preferred Regimens:

- Paclitaxel + trastuzumab[h]
- TCH (docetaxel/carboplatin/trastuzumab)
- TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab)
- If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[j] (category 1) ± pertuzumab.
- If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.[i,j]

Useful in Certain Circumstances:

- Docetaxel + cyclophosphamide + trastuzumab
- AC followed by T[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)
- AC followed by T[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab, various schedules)
- Neratinib[i] (adjuvant setting only)
- Paclitaxel + trastuzumab + pertuzumab[j]
- Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)

Other Recommended Regimens:

- AC followed by docetaxel[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab)
- AC followed by docetaxel[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab)

See Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3)

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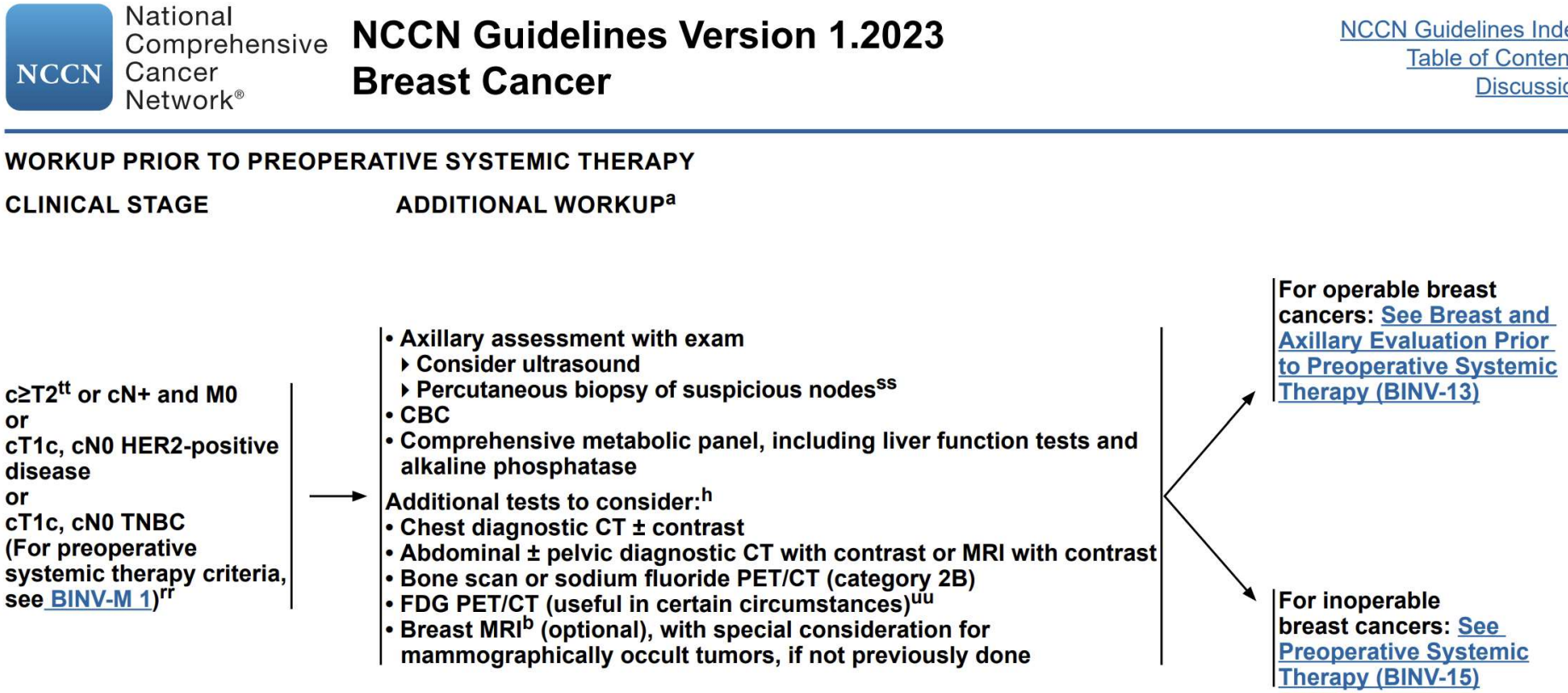
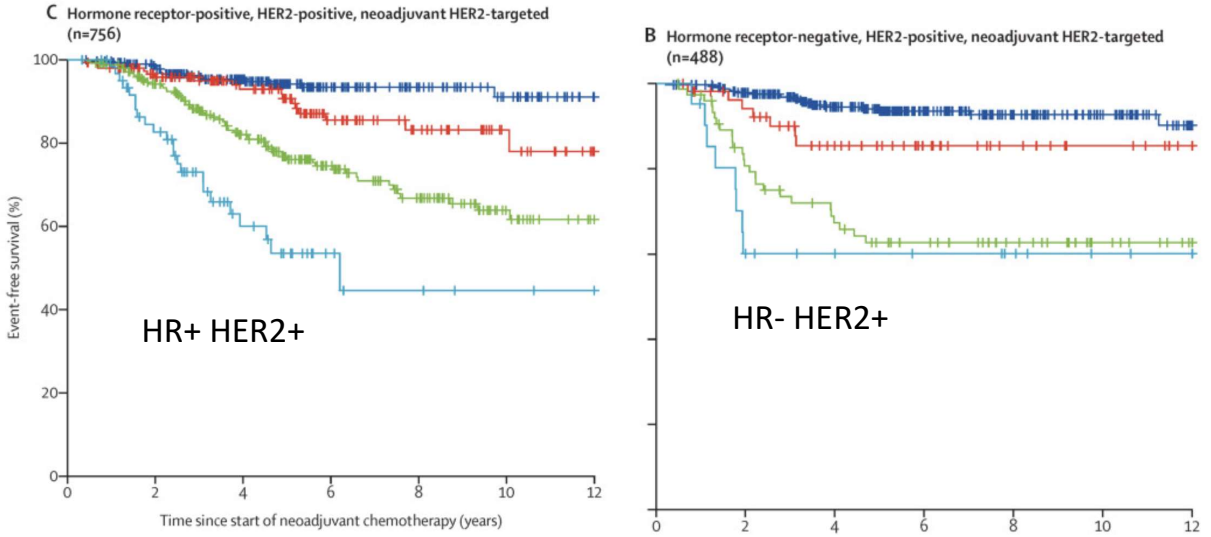
WORKUP PRIOR TO PREOPERATIVE SYSTEMIC THERAPY



Response to neoadjuvant therapy

- Pooled analysis of 5 neoadjuvant RCTs (HannaH, NeoSphere, TRYPHAENA, BERENICE, KRISTINE), >1000 patients
  - HR+ 34.4% pCR
  - HR- 55.4% pCR

Pooled analysis of RCB after neoadjuvant therapy and long term EFS



Yau et al. Lancet Oncol 2021, Swain et al Cancers 2022

Preoperative therapy for HER2+ tumors

- cT2 (>2cm) or cN+ recommended to receive neoadjuvant therapy
- Consider for some cT1c tumors; however, may lead to overtreatment given excellent outcomes from APT and ATEMPT regimens
- TCHP, ~1 year HER2 therapy, remains on current standard
  - When compared to anthracycline based regimen, similar outcomes, fewer cardiac toxicities
    - BCIRG 006, >3000 pts w high risk HER2+ BC, 10 year DFS 74.6% (269 events) AC-TH vs 73.0% (279 events) TCH; G3/4 CHF 21 vs 4, treatment related leukemia 7 vs 0, sustained LVEF loss >10% 200 vs 97.
    - TRAIN-2 – modern regimen, included pertuzumab, neoadjuvantly; similar findings, HR 0.9 (95% CI 0.5-1.63) 3-year EFS 92.7% vs 93.6%, favor non-anthracycline.

Slamon et al. SABCS 2015
Van der Voort, Jama Oncol 2021

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Breast Cancer

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Positive	
Preferred Regimens: • Paclitaxel + trastuzumab[h] • TCH (docetaxel/carboplatin/trastuzumab) • TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab) • If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[j] (category 1) ± pertuzumab. • If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.[i,j]	
Useful in Certain Circumstances: • Docetaxel + cyclophosphamide + trastuzumab • AC followed by T[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules) • AC followed by T[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab, various schedules) • Neratinib[i] (adjuvant setting only) • Paclitaxel + trastuzumab + pertuzumab[j] • Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)	**Other Recommended Regimens:** • AC followed by docetaxel[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab) • AC followed by docetaxel[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab)

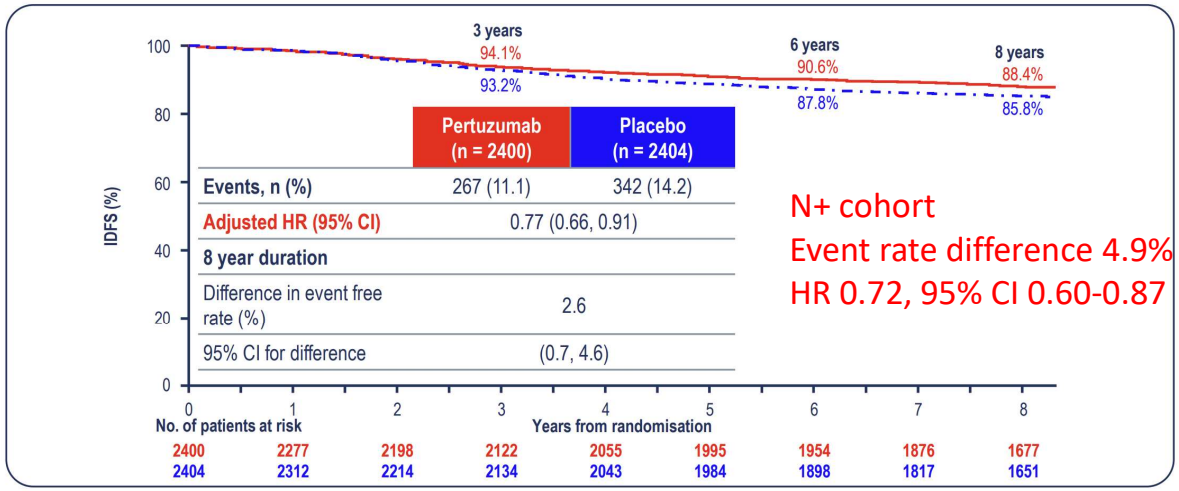
Anthracycline-based regimens are no longer preferred regimens

See Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3)

Approach to high risk HER2+ disease
Adjuvant pertuzumab, APHINITY

- 4805 pts, upfront surgery
  - 40% tumor <2cm
  - Node neg and high risk feature (ER/PR neg, age <35, or G3), 34%
  - N1 37%
  - N2 25%
  - 64% ER+
  - 78% anthracycline based

APHINITY Updated Descriptive IDFS Analysis at 8.4 Years Median FU by Treatment Regimen - ITT population



N+ cohort
Event rate difference 4.9%
HR 0.72, 95% CI 0.60-0.87

ESMO VIRTUAL PLENARY Sibylle Loibl, MD, PhD

Loibl et al. ESMO plenary 2022

APHINITY Updated Descriptive Analysis
8.4 year median FU, Site of First Occurrence of an IDFS Event by Nodal Status

N+
Abs diff 3.6% distant recurrence
Abs diff 1.1% locoregional recurrence
No difference in CNS metastases

	Node-positive Cohort		Node-negative Cohort	
	Pertuzumab N=1503	Placebo N=1502	Pertuzumab N=897	Placebo N=902
Total patients with IDFS event: n (%)	202 (13.4%)	276 (18.4%)	65 (7.2%)	66 (7.3%)
			HR 1.01	
Category of IDFS event: n (%)				
• Distant recurrence	131 (8.7%)	184 (12.3%)	18 (2.0%)	20 (2.2%)
• CNS metastases	43 (2.9%)	48 (2.9%)	8 (0.9%)	5 (0.6%)
• Locoregional BC recurrence	23 (1.5%)	39 (2.6%)	9 (1.0%)	18 (2.0%)
• Contralateral invasive BC recurrence	13 (0.9%)	16 (1.1%)	15 (1.7%)	6 (0.7%)
• Death without prior event	35 (2.3%)	37 (2.5%)	23 (2.6%)	22 (2.4%)

Hierarchy applied if a patient experiences additional IDFS event(s) within 61 days of their 1st IDFS event

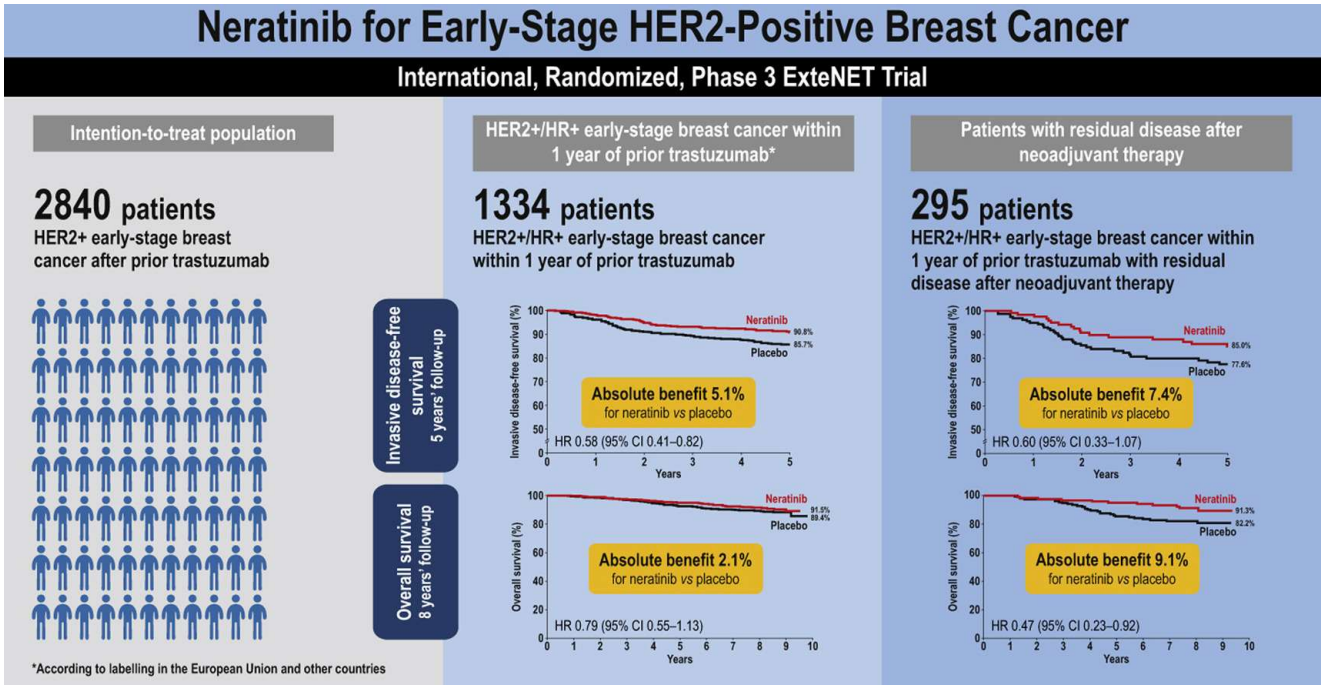
ESMO VIRTUAL PLENARY

Sibylle Loibl, MD, PhD

Loibl et al. ESMO plenary 2022

Approach to high risk HER2+ disease
Adjuvant neratinib, exte-NET

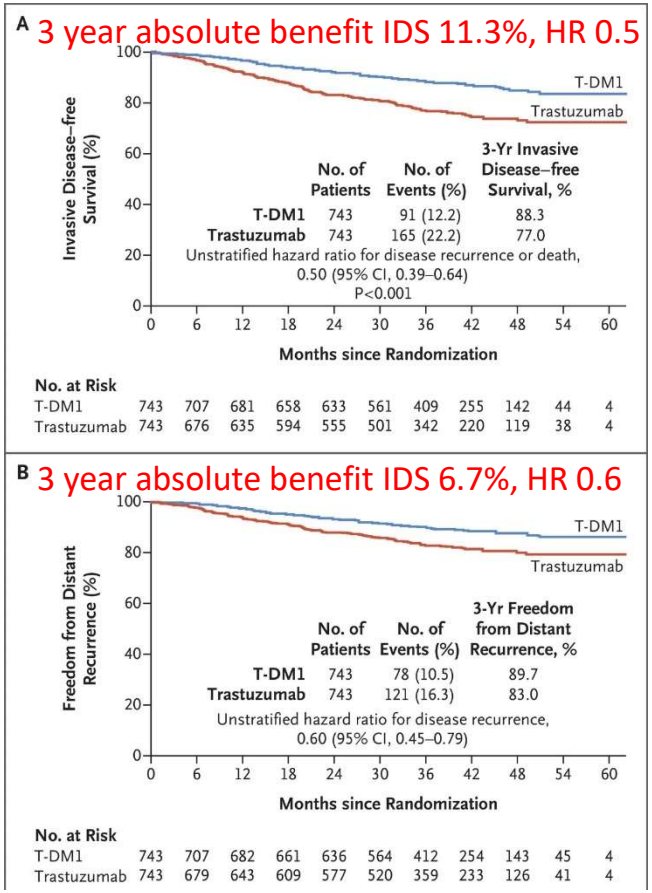
- Stage 1-3 HER2+ BC, adjuvant neratinib x 1 year after completion of chemo-HER2 therapy
- Unclear data with prior pertuzumab or T-DM1
- 5 year follow up
- Among HR+/<1 year of prior trastuzumab, 4 (0.7%) vs 12 (2.1%) CNS recurrences in 5 years
- Improved tolerance with escalation diarrhea management protocol (neratinib 120 mg week 1, 160mg week 2, then 240mg)



Chan et al. Clinical breast cancer 2020

Approach to high risk HER2+ disease
Adjuvant T-DM1, KATHERINE

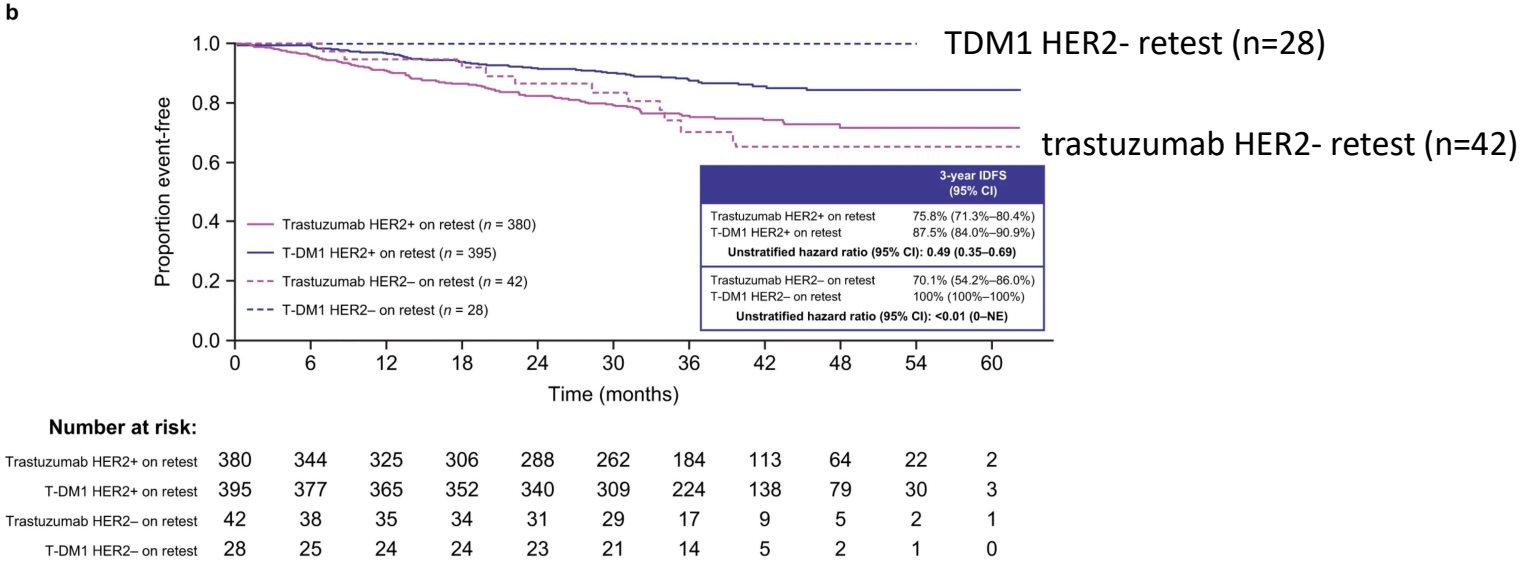
- Residual disease after neoadjuvant chemotherapy
- Adjuvant T-DM1 vs trastuzumab x14 cycles
- 28% HR+, 18% prior pertuzumab, 76% prior anthracycline
- More neuropathy, LFT abnormalities with T-DM1
- Baseline neuropathy associated with longer duration/lower resolution
- Patients with CNS recurrence 6.1% vs 5.4%, as first event 5.9% vs 4.3%



Von Minckwitz et al. NEJM 2019

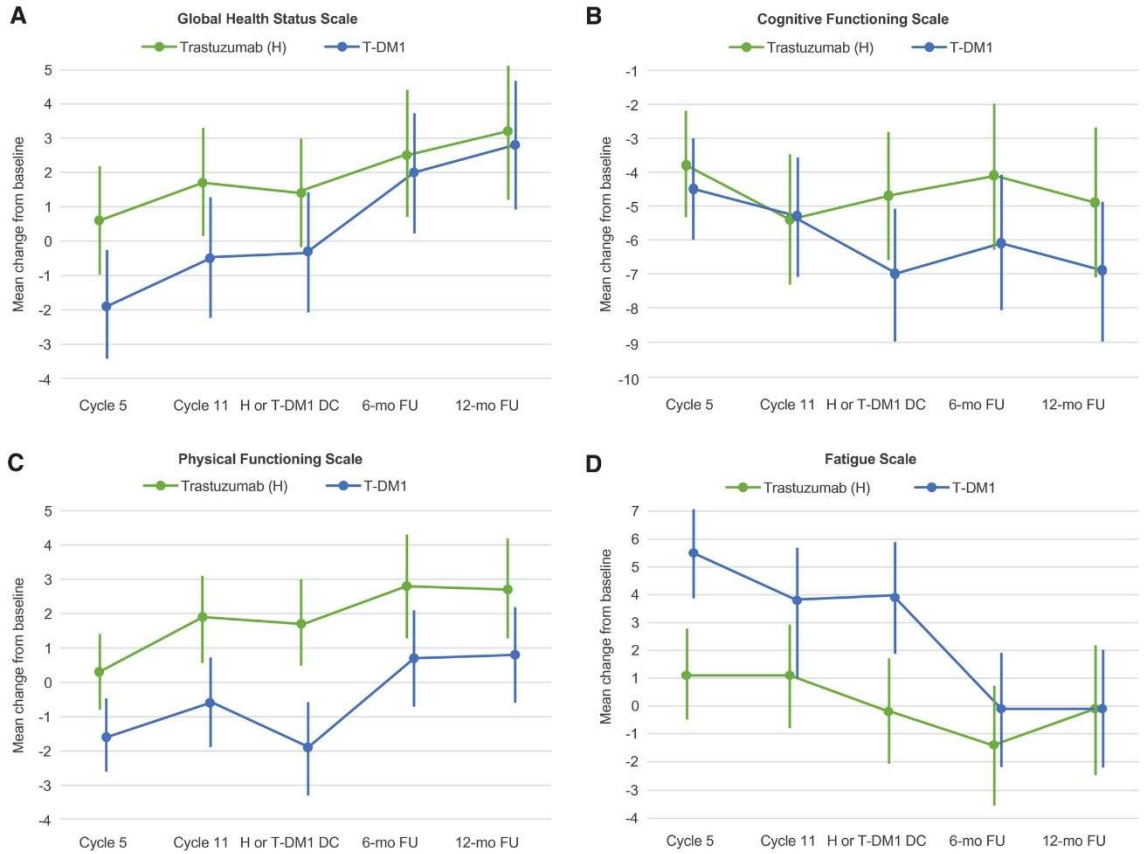
HER2-status of residual disease in KATHERINE study

- 1002 patients with matched pre and post study samples
  - HER2 status of residual disease – positive 775, unknown 175, negative 70
  - Trastuzumab n=42, T-DM1 n=28
  - HER2 negative residual disease still appeared to benefit from T-DM1



Loibl et al NPJ 2022

Patient reported outcomes



Conte et al, Cancer 2020

Important ongoing trials

- Stage 1 BC
  - ATEMPT 2.0 (NCT04893109): Evaluating in stage 1 BC, adjuvant T-DM1 x 6 cycles → trastuzumab q3 weeks to finish 1 year vs TH
- Stage 2 and 3 BC
  - Compass pCR (NCT04266249): neoadjuvant THP x 4 → surgery
    - If pCR, adjuvant HP
    - If residual disease SOC T-DM1 vs CompassHER2-RD (NCT04457596): T-DM1 +/- tucatinib
  - Decrescendo (NCT04675827), same neoadjuvant plan, if residual disease, AC 3-4 cycles → T-DM1
  - Destiny Breast 11 (NCT05113251): Neoadjuvant T-DXd vs T-DXd→THP vs ddAC-THP
  - Destiny Breast 05 (NCT04622319): residual disease at neoadjuvant therapy, T-DXd vs T-DM1

Other important questions/areas of investigation

- Further studies evaluating biomarkers to guide escalation and de-escalation
  - HER2DX – clinical risk and 4 gene signatures (immune, proliferation, luminal differentiation and HER2 amplicon), potentially identify higher risk HER2+ BC
  - ctDNA/MRD assay to guide therapy escalation-de-escalation
  - Imaging (MRI, PET, HER2 PET) to guide duration/choice of neoadjuvant therapy
- Brain metastases
  - Pertuzumab or T-DM1 did not reduce rates of CNS metastases
  - Neratinib demonstrated reduction in risk for CNS metastases
  - COMPASS-RD evaluating if tucatinib can reduce risk
  - T-DXD results to see if in early stage disease can have impact on CNS risk
- Toxicity prediction
  - Neuropathy
  - Risk ILD with potential greater use of ADCs

Summary of standard approaches for early stage HER2+ BC

- HER2+ DCIS – no need to test, no HER2 targeted therapy
- HER2+ Stage 1 – TH. T-DM1 x 1 year is an alternative
- HER2+ Stage 2 and 3 – neoadjuvant TCHP x 6 cycles
  - If residual disease, adjuvant T-DM1 x 14 cycles
  - If pCR adjuvant H(P), in LN negative may not be benefit to continue adjuvant pertuzumab
  - If HR+ HER2+, high-risk (especially residual disease after neoadjuvant therapy), consider adjuvant neratinib

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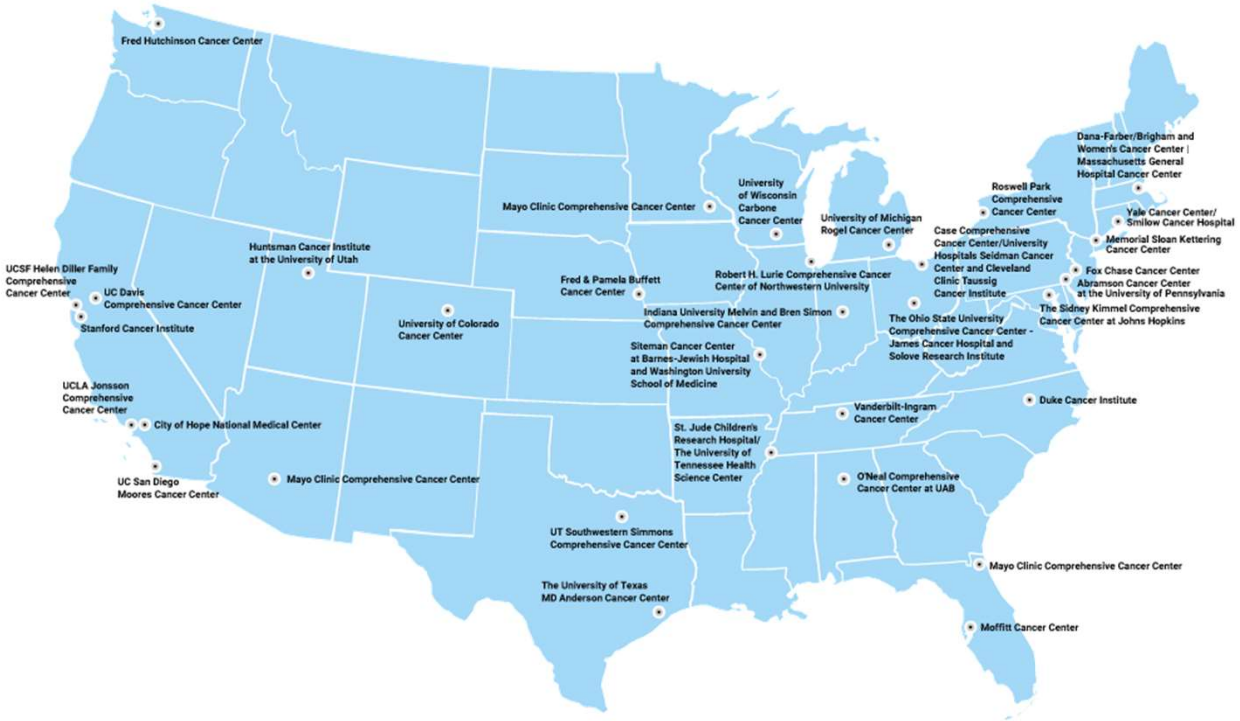

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An alliance of leading cancer centers devoted to patient care, research, and education

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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