Association of Cancer Physicians

Representing and supporting medical oncologists in the UK

- Promote the views and interests of medical oncologists to the DoH and RCP
- Influence policy on consultant expansion
- Assist in the development of training curricula and the specialty examination
- Participate in NICE appraisals and guideline development
- Encourage the development of best practice to benefit patients

Fellowship of Association of Cancer Physicians FACP(UK).

Contact me ACPUKChair@outlook.com or Dan Hughes

Breast cancer update

Professor Andrew M. Wardley

In the UK [average per annum, based on 2017-2019 data]

- Breast cancer is the 4th most common cause of cancer death and the 2nd most common cause of any death in women

- Around 11,400 women and 85 men die from breast cancer every year. This is equivalent to 32 deaths every day

- 48% of deaths from breast cancer are in those aged 75 and over

- Since the mid-1980s, breast cancer mortality rates have decreased by 45%

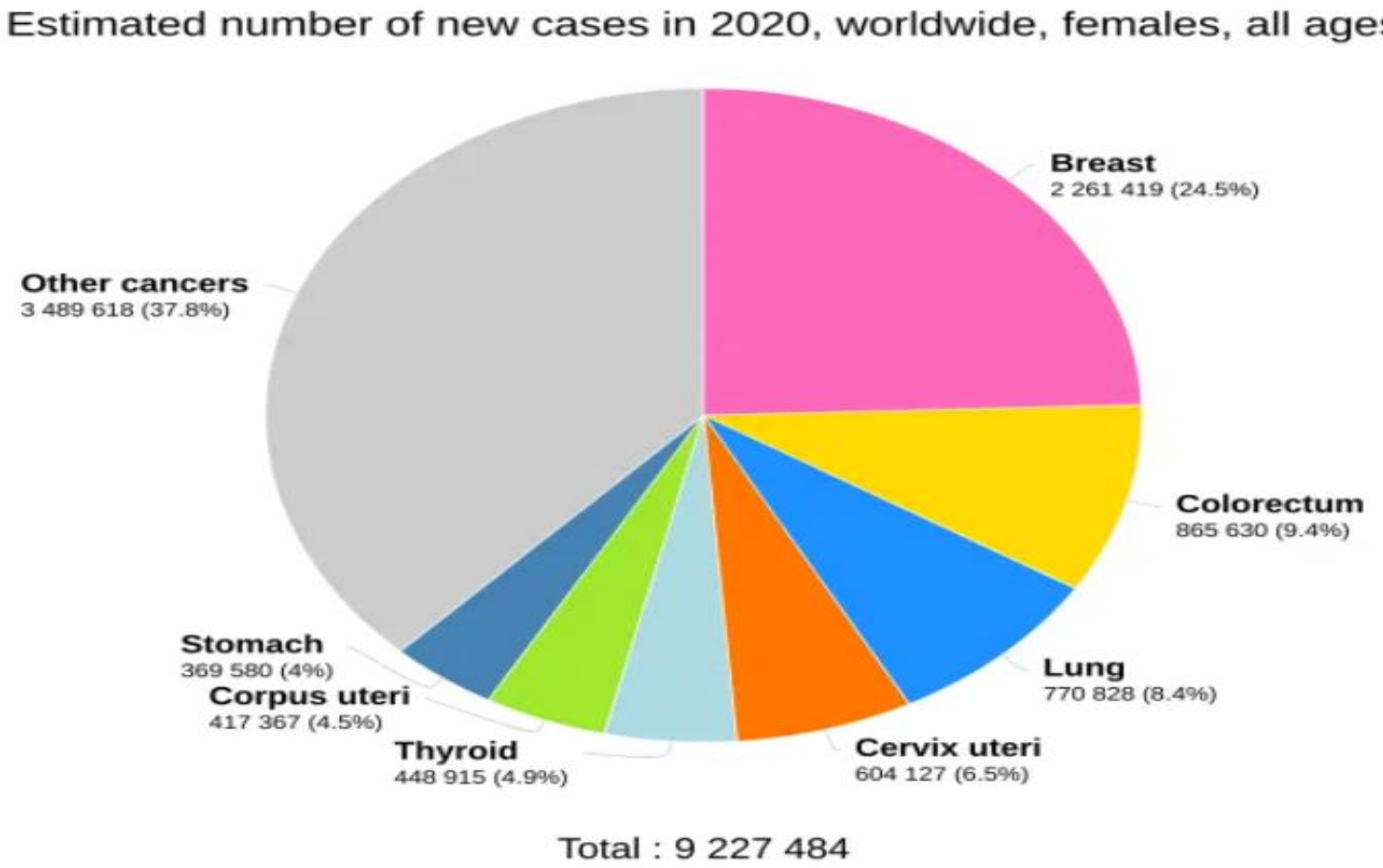
- Breast cancer is the most common cause of death for women between 35-49 years of age

- Breast cancer mortality rates have been declining and are projected to fall by 26% between 2014 and 2035

- The UK has had a consistently higher breast cancer mortality rate compared to most other **OECD** countries

https://www.breastcanceruk.org.uk/about-breast-cancer/facts-figures-and-qas/facts-and-figures/ Accessed 9 November 2023

UICC data



Age-standardized breast cancer mortality in high-income countries dropped by 40% between the 1980s and 2020 **Breast cancer (who.int) accessed 11 Nov 2023**

Evolution of patients' characteristics at MBC diagnosis – HER2+ subtype

	2008 (N=378)	2009 (N=408)	2010 (N=407)	2011 (N=451)	2012 (N=461)	2013 (N=490)	2014 (N=451)	2015 (N=429)	2016 (N=444)	2017 (N=285)	Total (N=4204)
N	378	408	407	451	461	490	451	429	444	285	4204
Med age	57	56	57	57	58	57	58	58	55	55	57
Systematic diagnosis	186 (50.3%)	213 (53.9%)	231 (58.5%)	274 (63.3%)	265 (61.1%)	289 (59.3%)	254 (56.4%)	268 (62.8%)	287 (64.9%)	166 (60.1%)	2433 (59.2%)
Visceral mets	238 (63.0%)	261 (64.0%)	270 (66.3%)	322 (71.4%)	294 (63.8%)	315 (64.3%)	299 (66.3%)	267 (62.2%)	283 (63.7%)	167 (58.6%)	2716 (64.6%)
De novo MBC	125 (33.1%)	125 (30.6%)	159 (39.1%)	163 (36.1%)	175 (38.0%)	206 (42.0%)	193 (42.8%)	215 (50.1%)	235 (52.9%)	147 (51.6%)	1743 (41.5%)
Met-free interval* (med-Q1Q3)	43.40 (25.56, 95.66)	40.34 (24.75, 83.08)	46.89 (26.98, 92.53)	45.25 (26.72, 88.53)	48.28 (27.02, 88.72)	45.20 (24.63, 80.21)	46.75 (23.79, 95.59)	47.24 (25.02, 97.36)	51.97 (26.97, 107.79)	53.42 (31.07, 116.43)	46.16 (25.76, 92.31)
≥ 3 met sites	72 (19.0%)	73 (17.9%)	97 (23.8%)	106 (23.5%)	93 (20.2%)	102 (20.8%)	92 (20.4%)	97 (22.6%)	104 (23.4%)	66 (23.2%)	902 (21.5%)

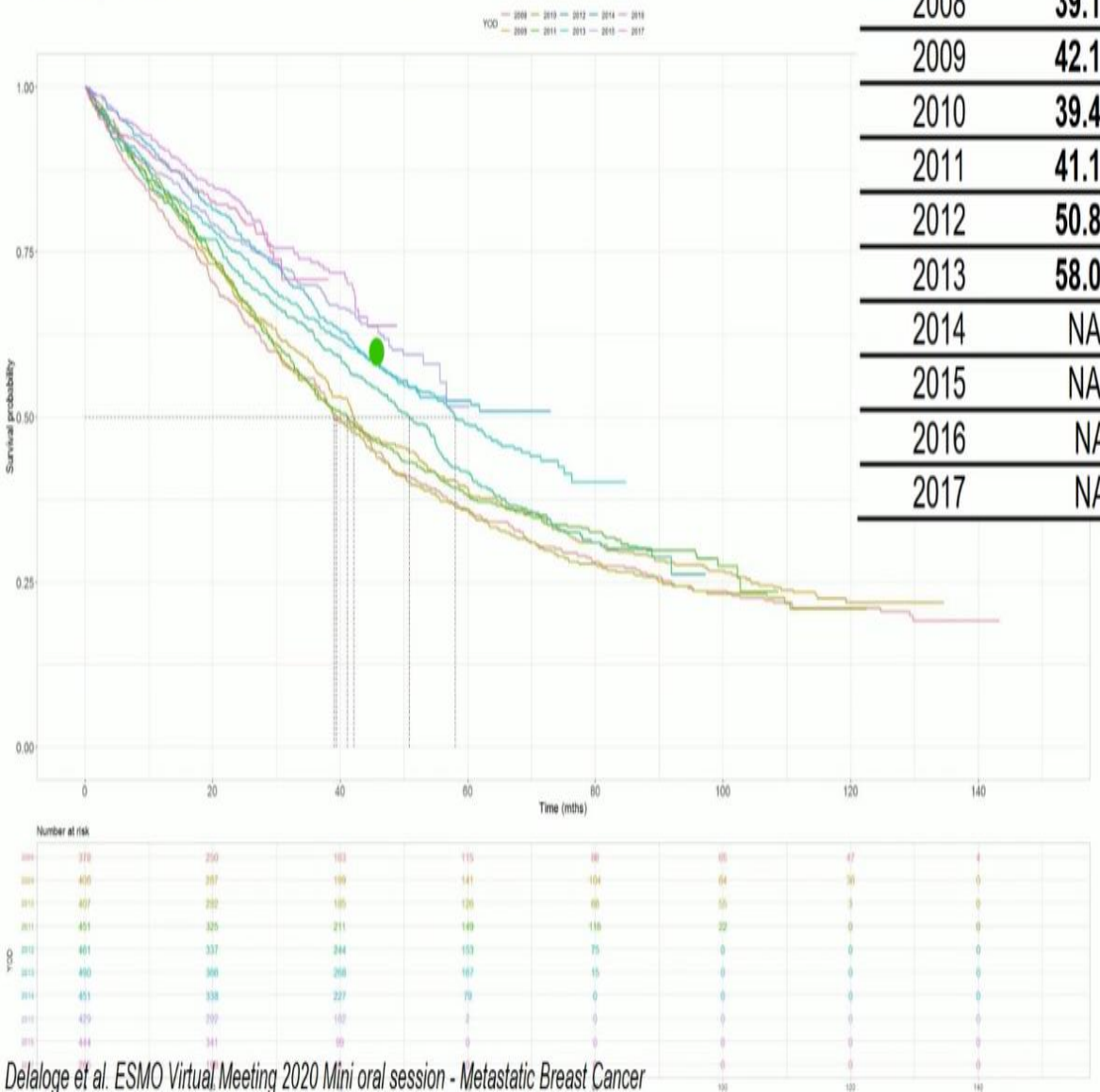
The proportion of de novo HER2+ MBC has increased, as well as diagnosis on screening exams (versus symptoms).
Among relapsed cases, the metastases-free interval increased.

* For relapsed cases

Evolution of OS over time HER2+ subtype

Overall survival according to the YOD in the HER2+ subcohort

Based on Kaplan-Meier estimates



	Med OS (95% CI) (months)
2008	**39.1** (36.2, 46.5)
2009	**42.1** (38.2, 50.8)
2010	**39.4** (35.9, 45.4)
2011	**41.1** (35.5, 48.3)
2012	**50.8** (45.0, 55.5)
2013	**58.0** (52.0, 68.4)
2014	NA (50.6, NA)
2015	NA (55.7, NA)
2016	NA (NA, NA)
2017	NA (NA, NA)

Delaloge et al. ESMO Virtual Meeting 2020 Mini oral session - Metastatic Breast Cancer

Evolution of patients' characteristics at MBC diagnosis – HR+/HER2- subtype

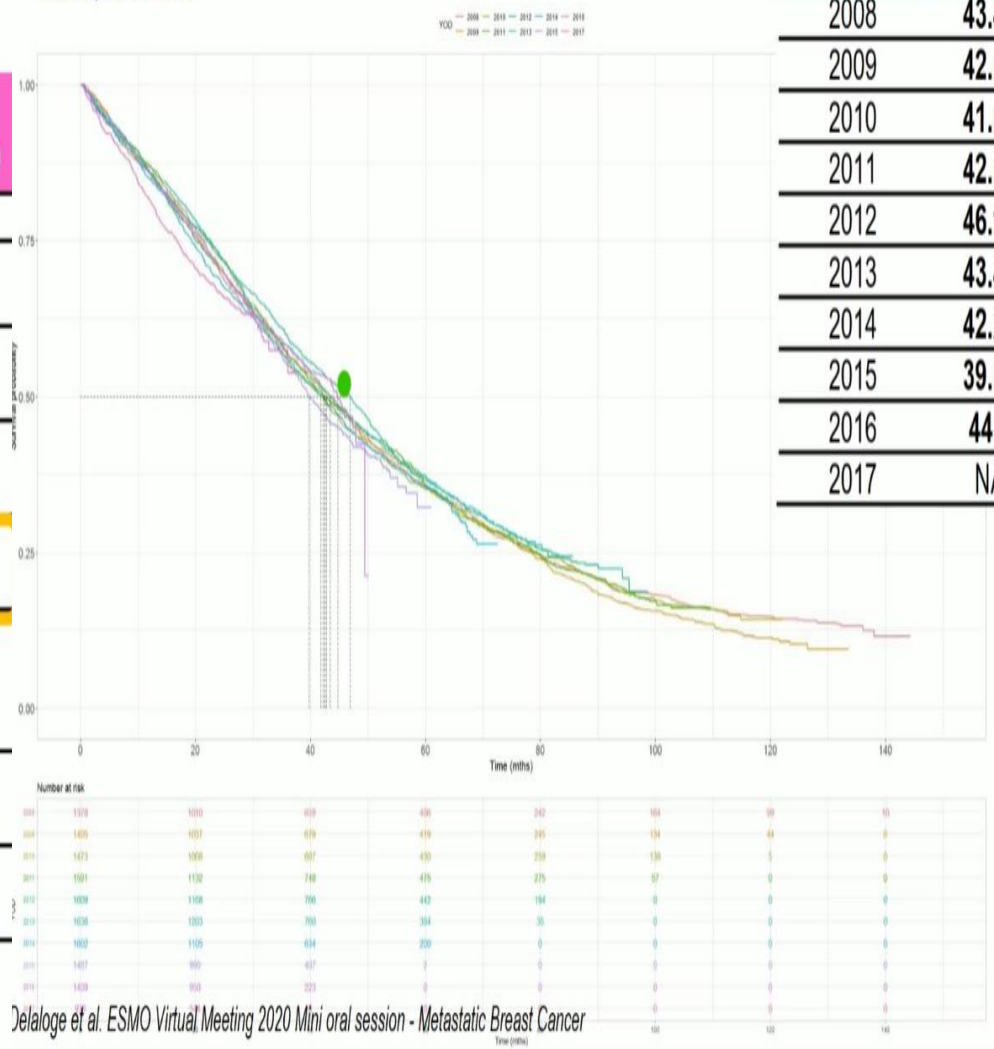
	2008 (N=1378)	2009 (N=1405)	2010 (N=1473)	2011 (N=1591)	2012 (N=1609)	2013 (N=1636)	2014 (N=1602)	2015 (N=1487)	2016 (N=1409)	2017 (N=936)	Total (N=14526)
N	1378	1405	1473	1591	1609	1636	1602	1487	1409	936	14526
Med age	61	61	62	62	63	62	62	63	63	63	62
Systematic diagnosis	690 (52.0%)	721 (53.8%)	769 (54.5%)	777 (51.9%)	802 (53.2%)	863 (53.1%)	820 (51.6%)	758 (51.6%)	857 (61.7%)	477 (51.8%)	7534 (53.5%)
Visceral mets	721 (52.3%)	748 (53.2%)	785 (53.3%)	845 (53.1%)	859 (53.4%)	878 (53.7%)	843 (52.6%)	832 (56.0%)	716 (50.8%)	492 (52.6%)	7719 (53.1%)
De novo MBC	358 (26.0%)	350 (24.9%)	406 (27.6%)	474 (29.8%)	467 (29.0%)	489 (29.9%)	469 (29.3%)	479 (32.2%)	478 (33.9%)	307 (32.8%)	4277 (29.4%)
Met-free interval* (med-Q1Q3)	78.76 (39.45, 135.05)	82.75 (42.12, 135.77)	83.44 (42.35, 143.63)	81.37 (39.03, 141.72)	82.39 (37.72, 147.19)	76.05 (38.63, 138.23)	79.86 (38.57, 141.46)	84.92 (41.88, 151.72)	83.54 (42.71, 145.70)	75.62 (36.10, 141.89)	80.98 (39.78, 142.18)
≥ 3 met sites	236 (17.1%)	241 (17.2%)	269 (18.3%)	287 (18.0%)	341 (21.2%)	337 (20.6%)	333 (20.8%)	346 (23.3%)	315 (22.4%)	199 (21.3%)	2904 (20.0%)
Received adj CT*	649 (63.6%)	704 (66.7%)	685 (64.2%)	751 (67.2%)	744 (65.1%)	770 (67.1%)	768 (67.8%)	690 (68.5%)	644 (69.2%)	423 (67.2%)	6828 (66.6%)

* For relapsed cases

Evolution of OS over time HR+/HER2- subtype

Overall survival according to the YOD in the HR+/HER2- subcohort

Based on Kaplan-Meier estimates



	Med OS (95% CI) (months)
2008	**43.4** (40.9, 46.5)
2009	**42.8** (40.5, 45.7)
2010	**41.8** (38.9, 44.1)
2011	**42.5** (40.0, 45.9)
2012	**46.9** (43.4, 49.3)
2013	**43.4** (41.4, 46.4)
2014	**42.2** (39.3, 44.5)
2015	**39.8** (38.0, 42.6)
2016	**44.8** (42.5, NA)
2017	NA (36.1, NA)

Delaloge et al. ESMO Virtual Meeting 2020 Mini oral session - Metastatic Breast Cancer

ESME-Evolution of OVERALL SURVIVAL across MBC subtypes

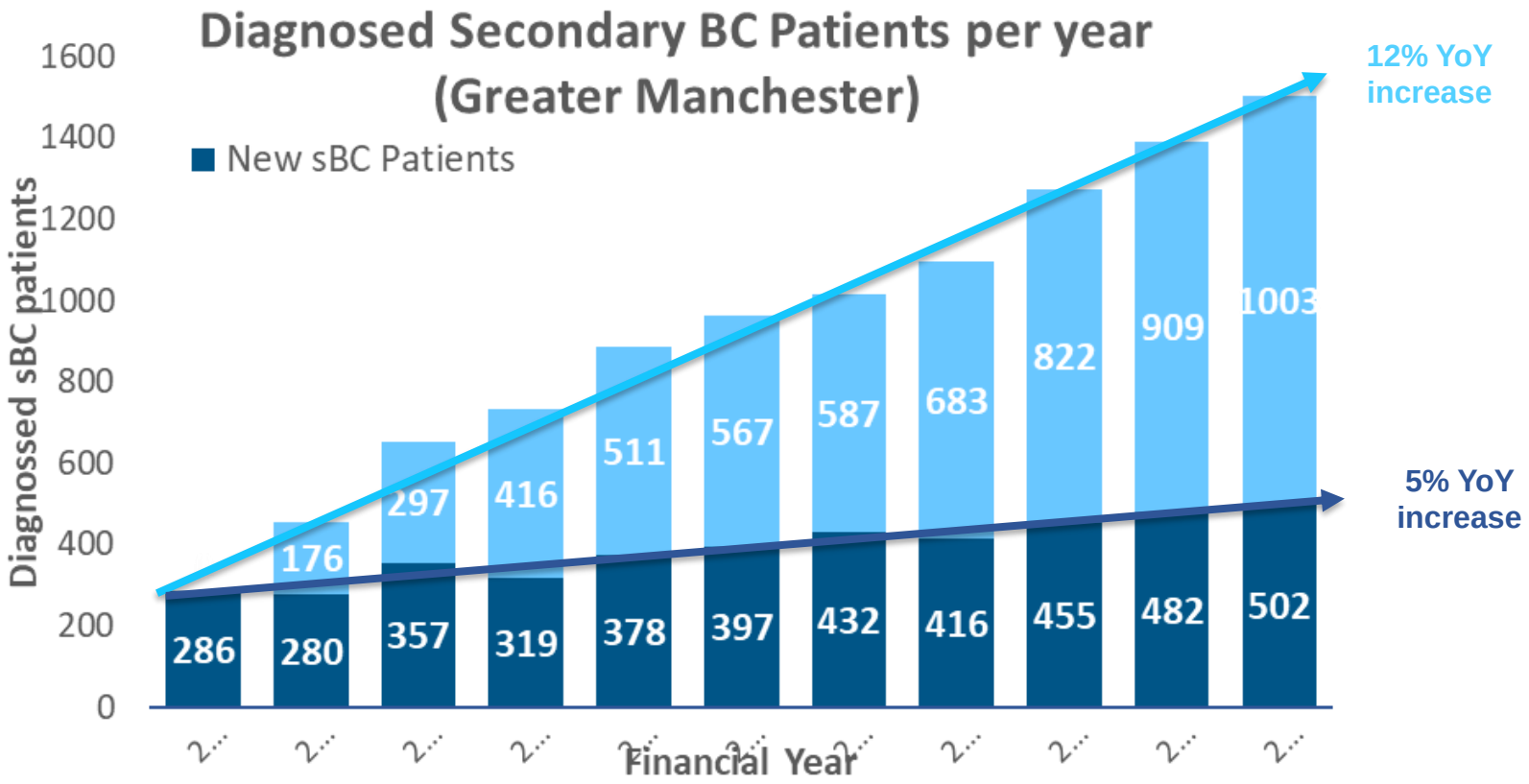
Multivariable predictors of OS – HER2+ subtype

		HR	95% CI	p-value
Year of MBC diagnosis	Ref 2008			
	2009	0.91	0.77, 1.07	0.24
	2010	0.92	0.78, 1.08	0.31
	2011	0.83	0.71, 0.98	0.032
	2012	0.84	0.71, 0.99	0.039
	2013	0.72	0.60, 0.85	<0.001
	2014	0.63	0.52, 0.76	<0.001
	2015	0.62	0.50, 0.76	<0.001
	2016	0.52	0.42, 0.66	<0.001
	2017	0.59	0.45, 0.78	<0.001
Age at MBC diagnosis (per additional year)		**1.02**	**1.01, 1.02**	**<0.001**
No. of metastatic sites at MBC diagn.	Ref <3			
	>=3	**1.73**	**1.56, 1.92**	**<0.001**
Presence of visceral metastases	Ref: no			
	Yes	**1.56**	**1.41, 1.73**	**<0.001**
Metastasis free interval (mths)	Ref < 6 months			
	[6-24] months	**2.69**	**2.38, 3.04**	**<0.001**
	>24 months	**1.35**	**1.23, 1.49**	**<0.001**

Multivariable predictors of OS – HR+/HER2- subtyp

		HR	95% CI	p-value
Year of MBC diagnosis	Ref 2008			
	2009	1.04	0.95, 1.13	0.41
	2010	1.02	0.94, 1.11	0.61
	2011	1.01	0.93, 1.10	0.79
	2012	0.94	0.86, 1.03	0.17
	2013	0.97	0.89, 1.05	0.44
	2014	1.04	0.95, 1.14	0.42
	2015	1.03	0.94, 1.14	0.52
	2016	1.02	0.91, 1.13	0.77
	2017	1.14	1.00, 1.29	**0.050**
Age at MBC diagnosis (per additional year)		**1.01**	**1.01, 1.01**	**<0.001**
No. of metastatic sites at MBC diagn.	Ref <3			
	>=3	**1.39**	**1.32, 1.47**	**<0.001**
Presence of visceral metastases	Ref: no			
	Yes	**1.49**	**1.42, 1.56**	**<0.001**
Metastasis free interval (mths)	Ref < 6 months			
	[6-24] months	**2.41**	**2.24, 2.60**	**<0.001**
	>24 months	**1.16**	**1.10, 1.22**	**<0.001**

EXISTING SECONDARY BREAST CANCER PATIENTS



As treatment gets better, more patients stay in the system for longer

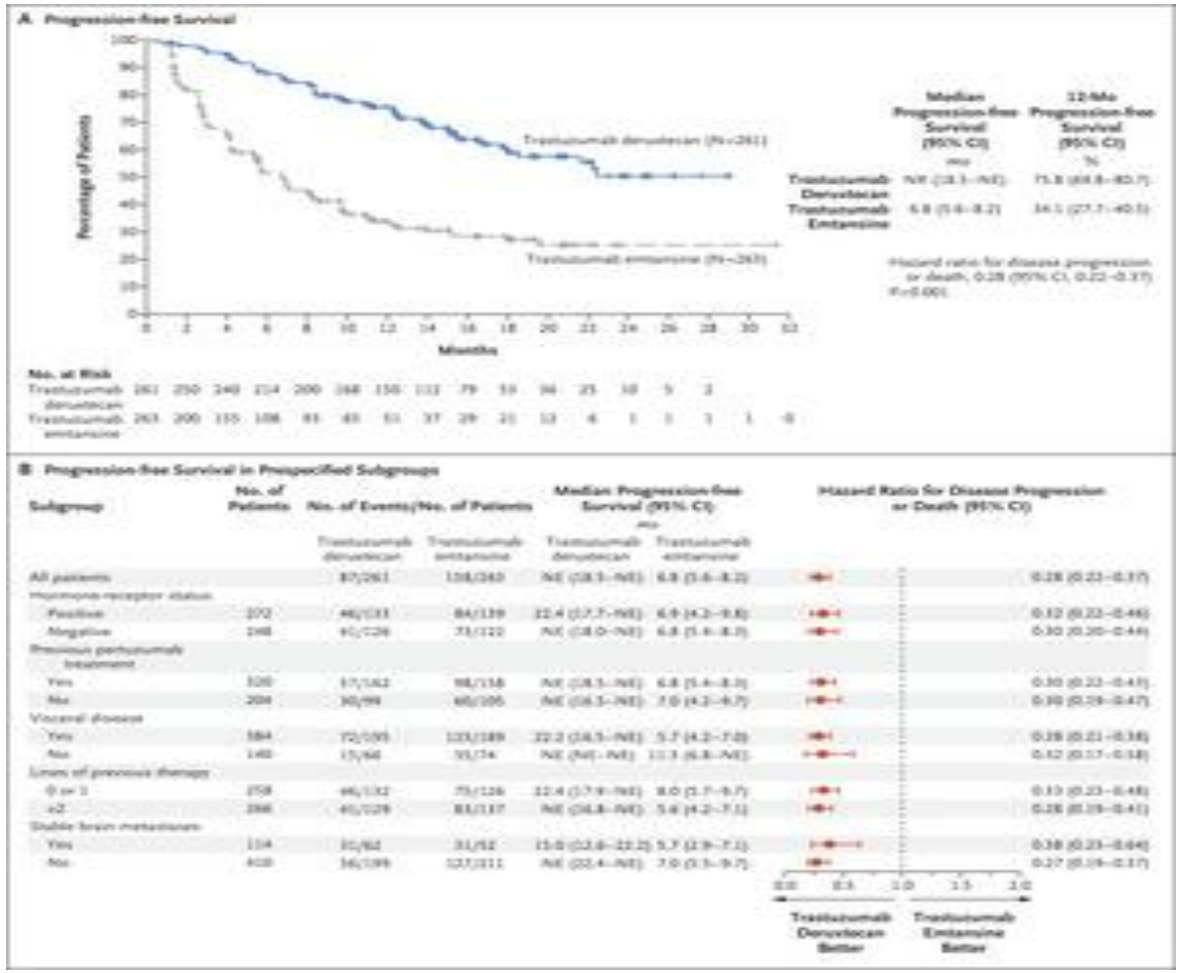
Current trends are of a 12% increase in patients in the system every year

Wardley, HSJ Conference 2019

Metastatic breast cancer

A new sub-class = HER-2 low

Trastuzumab-deruxtecan vs trastuzumab-emtansine HER2+ mBC



hazard ratio DFS **0.28** (95% CI, 0.22 to 0.37; P<0.001)

Median PFS NR (95% CI, 18.5 to NE) TDxd
6.8 (95% CI, 5.6 to 8.2) in the TDM1

12 months alive without PD

75.8% (95% CI, 69.8 to 80.7) with trastuzumab deruxtecan
34.1% (95% CI, 27.7 to 40.5) with trastuzumab emtansine;

J.Cortes, et al,
N Engl J Med 2022; 386:1143-1154 DOI: 10.1056/NEJMoa2115022

Background

- ~60% of mBC cases traditionally categorized as HER2-negative actually express low levels of HER2, designated as **HER2-low** (IHC 1+ or IHC 2+/ISH−)[1,2]
- T-DXd is a HER2-directed antibody drug conjugate that targets tumor cells with HER2 expression as well as neighboring cells through a bystander effect[3,4]
- The **DESTINY-Breast04** trial demonstrated superior PFS and OS in patients with HER2-low mBC treated with T-DXd vs TPC at the primary analysis[5]
  - DESTINY-Breast04 established HER2-low mBC as a new targetable patient population, with T-DXd as a new standard of care[6,7]
  - At the primary analysis (data cutoff, January 11, 2022), median follow-up was 18.4 months

The objective of this analysis is to report updated efficacy and safety results from an extended follow-up (data cutoff, March 1, 2023)

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physicians' choice.

1. Schettini F et al. *NPJ Breast Cancer*. 2021;7:1. 2. Tarantino P et al. *J Clin Oncol*. 2020;38:1951-1962. 3. Nakada et al. *Chem Pharm Bull*. 2019;67:173-185. 4. Ogitani et al. *Cancer Sci*. 2016;107:1039-1046.
5. Modi S et al. *N Engl J Med*. 2022;387:9-20. 6. Enhertu (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use. Prescribing information (Daiichi Sankyo, Inc., Basking Ridge, NJ, 2022).
7. Enhertu. Summary of product characteristics. Pfaffenhofen, Germany: Daiichi Sankyo Europe GmbH; 2023).

DESTINY-Breast04 Study Design:

An open-label, multicenter study (NCT03734029)[1-3]

Patients[a]
- HER2-low (IHC 1+ or IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Stratification factors
- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6i) vs HR−

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[d]
- PFS by BICR (all patients)
- **OS (HR+ and all patients)**

Secondary endpoints[d]
- **PFS by investigator**
- ORR by BICR and investigator
- DOR by BICR
- **Safety**
- Patient-reported outcomes (HR+)[e]

At the updated data cutoff (March 1, 2023), median follow-up was 32.0 months (95% CI, 31.0-32.8 months)

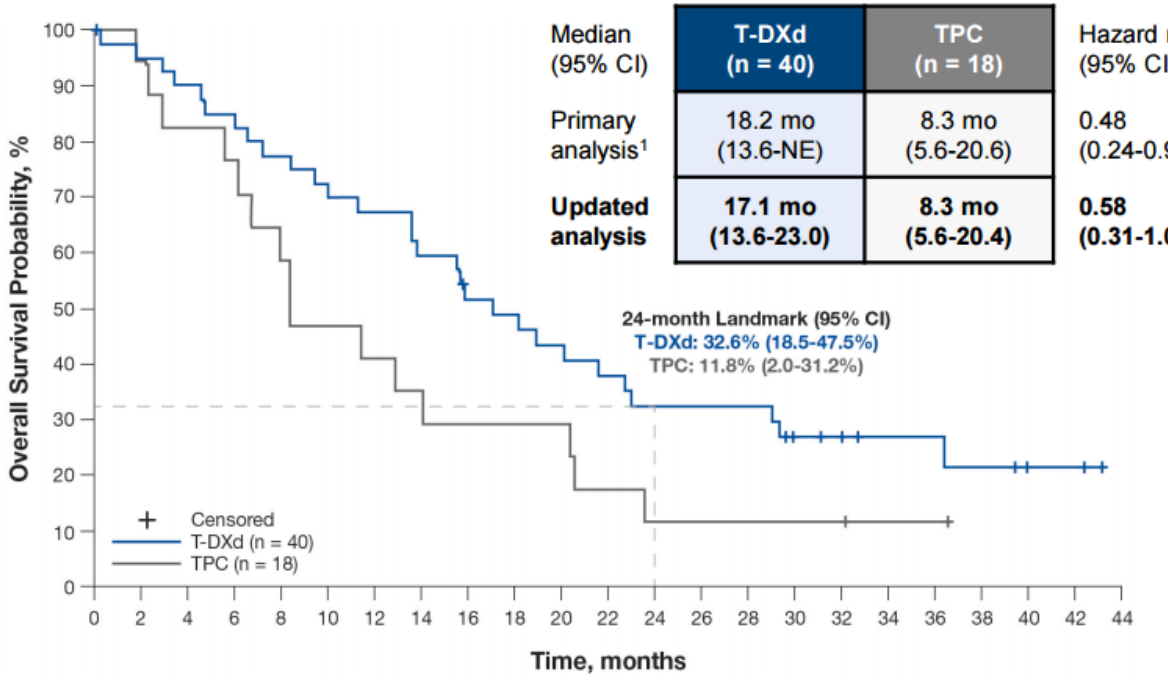
ASCO, American Society of Clinical Oncology; BICR, blinded independent central review; CAP, College of American Pathologists; CDKi, cyclin-dependent kinase 4/6 inhibitors; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational-use-only [IUO] assay system, at the time of study. [c]TPC was administered according to the label. [d]Efficacy in the HR− cohort was an exploratory endpoint. [e]The patient-reported outcomes analysis was conducted in the HR+ cohort (per the statistical analysis plan) since the primary efficacy endpoint was evaluated in the HR+ cohort.

1. Modi S et al. *N Engl J Med*. 2022;387:9-20. 2. Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0. 3. Prat A et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

Efficacy in the HR− Cohort (Exploratory Analyses)

Overall Survival

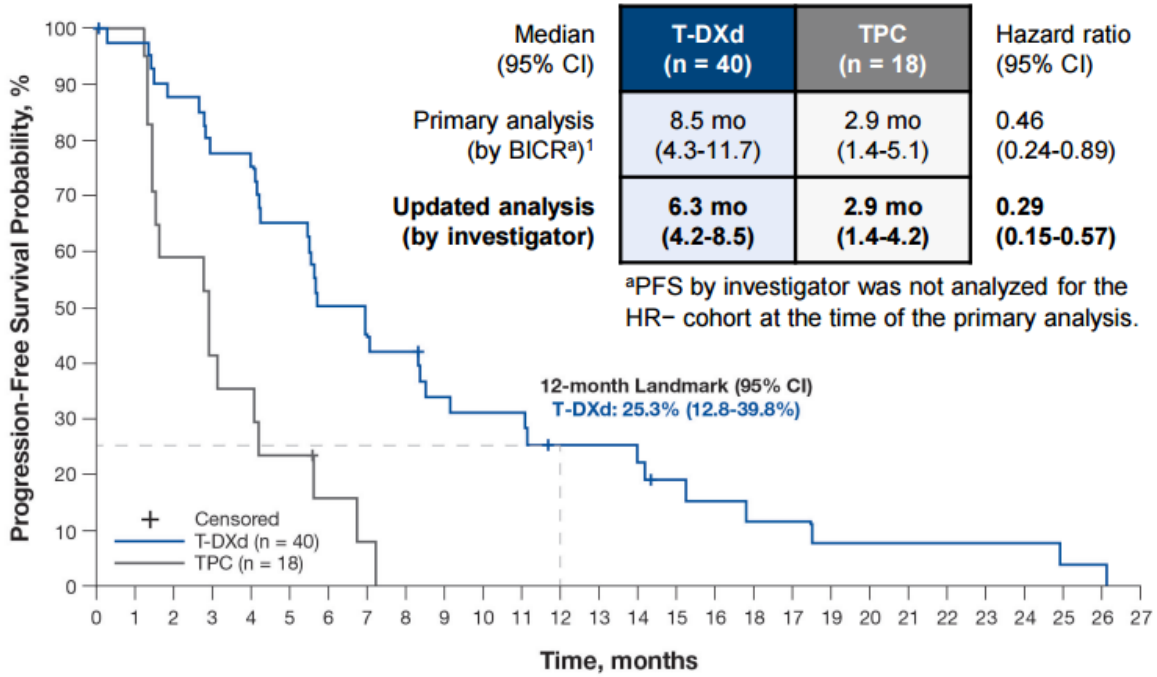


Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**

Patients still at risk:

T-DXd (n = 40)	40	38	36	34	31	28	26	23	19	18	16	14	12	12	12	8	7	5	5	4	2	2	0
TPC (n = 18)	18	16	14	13	10	8	7	6	5	5	5	3	2	2	2	2	2	1	1	0	0	0	0

Progression-Free Survival (by Investigator)



Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.

Patients still at risk:

T-DXd (n = 40)	40	39	35	31	30	26	19	17	16	12	11	11	8	8	7	5	4	3	3	2	2	2	2	2	2	1	1	0
TPC (n = 18)	18	17	10	7	6	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- There was a 42% reduction in risk of death and 71% reduction in risk of disease progression or death for HR− patients receiving T-DXd compared with TPC

BICR, blinded independent central review; HR, hormone receptor; mo, month; NE, not evaluable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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

Overall Safety Summary

- Median treatment duration was 8.2 months (range, 0.2-39.1 months) for T-DXd and 3.5 months (range, 0.3-19.7 months) for TPC
  - 16.4% of patients underwent treatment for ≥18 months in the T-DXd arm compared with 1.2% of patients in the TPC arm
- The most common TEAEs associated with treatment discontinuation for patients receiving T-DXd and TPC were investigator-assessed ILD/pneumonitis (10.2%) and peripheral sensory neuropathy (2.3%), respectively
- The most common TEAEs associated with dose reduction were nausea (4.6%) and decreased platelet count (3.0%) among patients receiving T-DXd vs decreased neutrophil count (10.5%) and palmar-plantar erythrodysesthesia syndrome (5.2%) among patients receiving TPC
- Exposure-adjusted incidence rates for any-grade TEAEs were 1.2 and 2.6 per patient-year for the T-DXd and TPC arms, respectively
  - This supports that longer T-DXd exposure does not increase toxicity
- Overall, the safety profile is consistent with results from the primary analysis (data cutoff, January 11, 2022)[1]

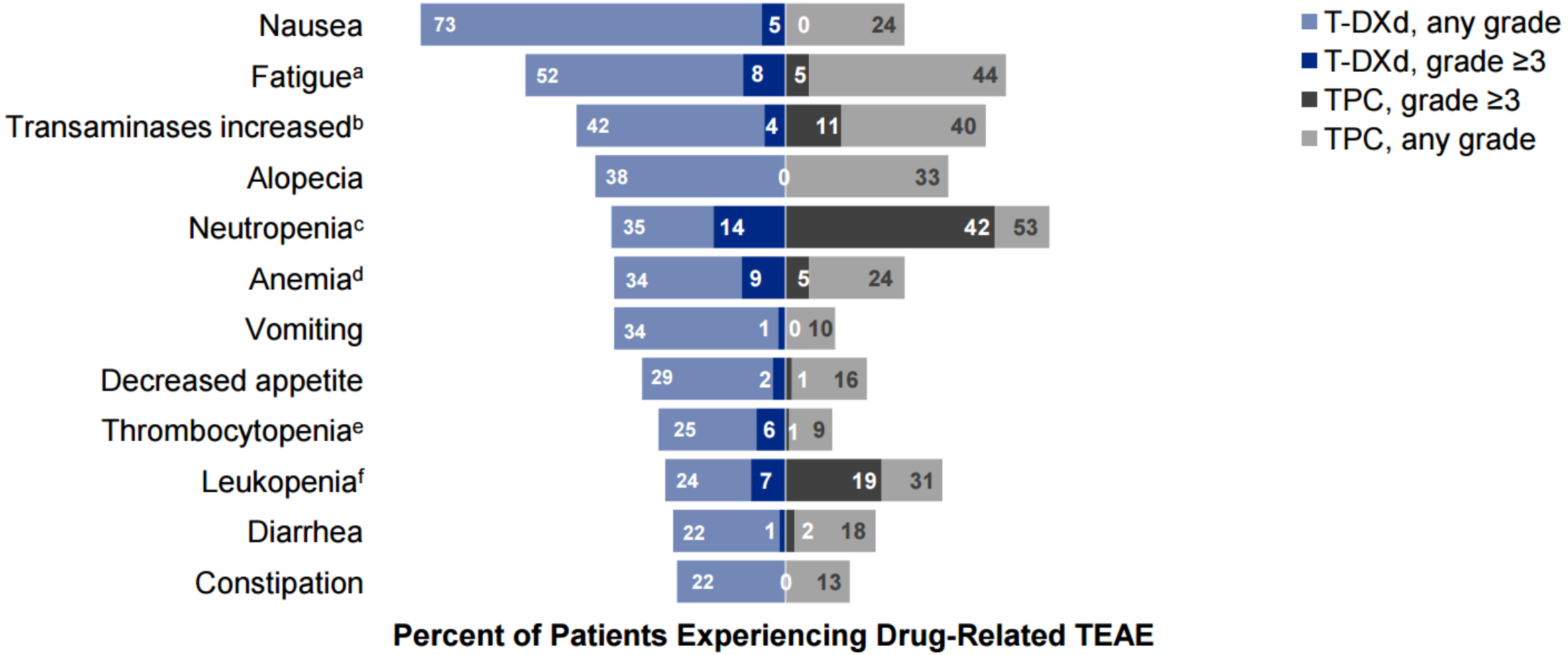
Safety analysis set[a]

n (%)	T-DXd (n = 371)	TPC (n = 172)
TEAEs	369 (99.5)	169 (98.3)
Grade ≥3	202 (54.4)	116 (67.4)
Serious TEAEs	108 (29.1)	44 (25.6)
TEAEs associated with dose discontinuation	62 (16.7)	14 (8.1)
TEAEs associated with dose interruptions	155 (41.8)	73 (42.4)
TEAEs associated with dose reductions	89 (24.0)	65 (37.8)
TEAEs associated with deaths	15 (4.0)	5 (2.9)
Total on-treatment deaths[b]	14 (3.8)	8 (4.7)

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b]On-treatment death is defined as death that occurred any time from date of first dose through 47 days after the last dose of the study treatment.

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

Drug-Related TEAEs in ≥20% of Patients



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, and hepatic function abnormal. [c]This category includes the preferred terms neutrophil count decreased and neutropenia. [d]This category includes the preferred terms hemoglobin decreased, red cell count decreased, anemia, and hematocrit decreased. [e]This category includes the preferred terms platelet count decreased and thrombocytopenia. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

Adverse Events of Special Interest

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
ILD/pneumonitis (adjudicated, drug-related), n (%)						
T-DXd (n = 371)	13 (3.5)	24 (6.5)	4 (1.1)[a]	0	4 (1.1)[a]	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)
Left ventricular dysfunction						
Ejection fraction decreased, n (%)						
T-DXd (n = 371)	2 (0.5)	15 (4.0)	1 (0.3)	0	0	18 (4.9)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure, n (%)						
T-DXd (n = 371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
TPC (n = 172)	0	0	0	0	0	0

- There were no new cases of ILD/pneumonitis since the primary analysis (data cutoff, January 11, 2022)[1]

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]At the primary analysis (data cutoff, January 11, 2022), grade 3 adjudicated drug-related ILD was reported in 5 patients (1.3%). At the current data cutoff, grade 3 adjudicated drug-related ILD is reported in 4 patients (1.1%) as 1 grade 3 ILD case worsened to grade 5 ILD. Consequently, there is an increase in the rate of grade 5 ILD (from 0.8% to 1.1%) without impact on the overall rate of adjudicated drug-related ILD. No ILD cases were pending adjudication at the updated data cutoff.

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

Conclusions

- Results from the 32-month median follow-up for DESTINY-Breast04 confirm the sustained clinically meaningful improvement for T-DXd vs TPC previously demonstrated in HER2-low (IHC 1+, IHC 2+/ISH−) mBC,[1] regardless of HR status
- With longer treatment duration, the overall safety profile of T-DXd was acceptable and generally manageable, and was consistent with the primary analysis[1]
  - Rates of ILD/pneumonitis remained unchanged with longer follow-up, and rates of left ventricular dysfunction were consistent with previously observed rates

Outcomes from the longer follow-up of DESTINY-Breast04 continue to support the use of T-DXd as the new standard of care after 1L+ chemotherapy in patients with HER2-low mBC

1L, first-line; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; TPC, treatment of physicians' choice.

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

MADRID 2023 ESMO congress

Adjuvant abemaciclib plus endocrine therapy for HR+, HER2-, high-risk early breast cancer: results from a preplanned monarchE overall survival interim analysis, including 5-year efficacy outcomes

Nadia Harbeck, Priya Rastogi, Joyce O'Shaughnessy, Frances Boyle, Javier Cortes, Hope S. Rugo, Matthew P. Goetz, Erika Hamilton, Chiun-Sheng Huang, Elzbieta Senkus, Alexey Tryakin, Patrick Neven, Jens Huober, Ran Wei, Valérie André, Maria Munoz, Belen San Antonio, Ashwin Shahir, Miguel Martin, Stephen Johnston

Nadia Harbeck, MD
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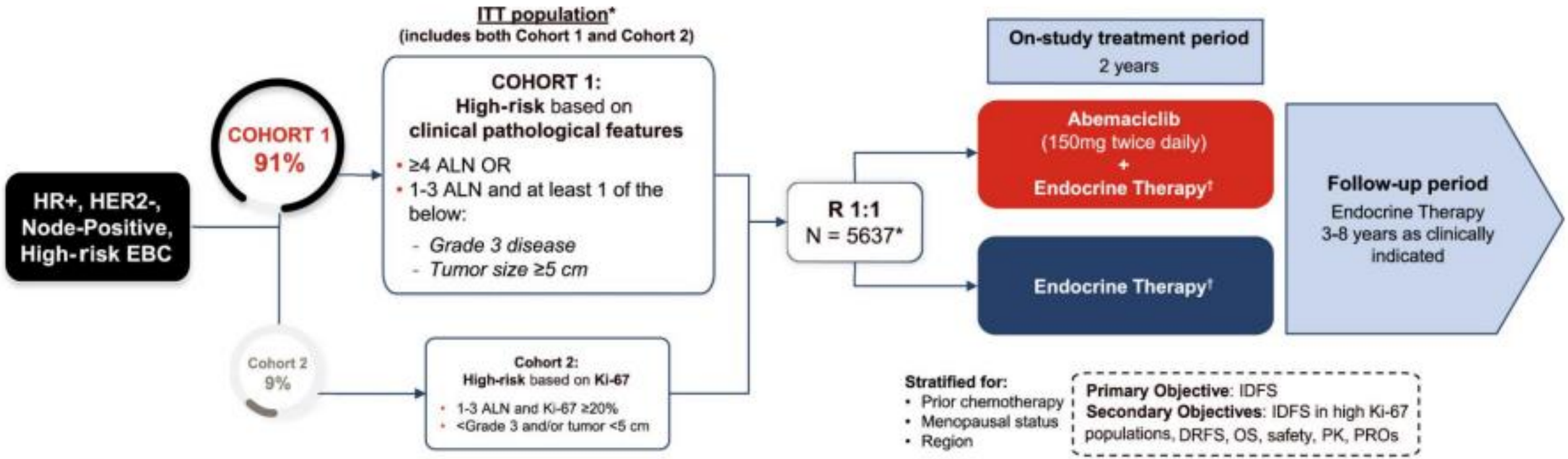
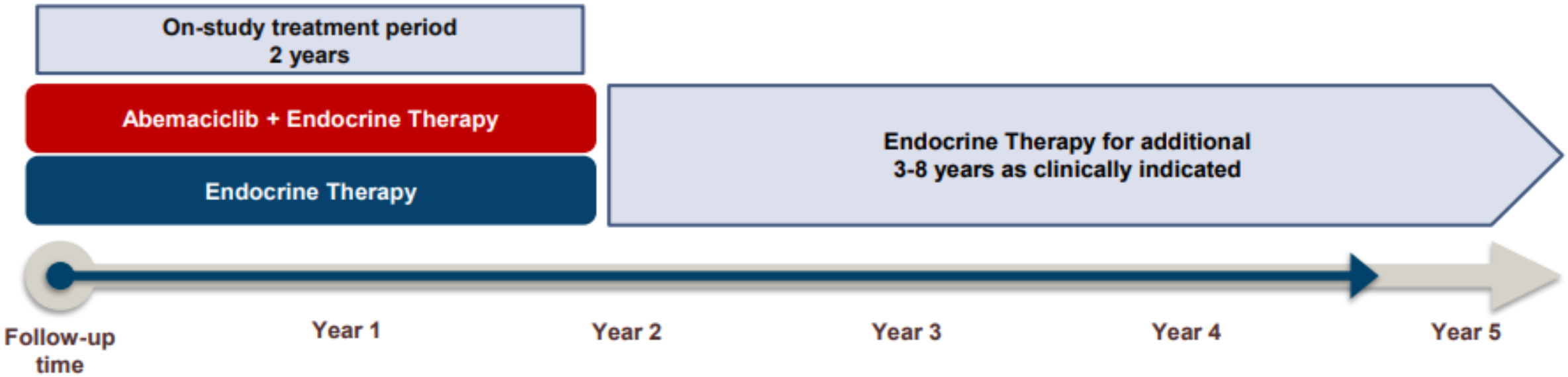
Madrid, Spain. 20 October 2023

monarchE Study Design (NCT03155997)



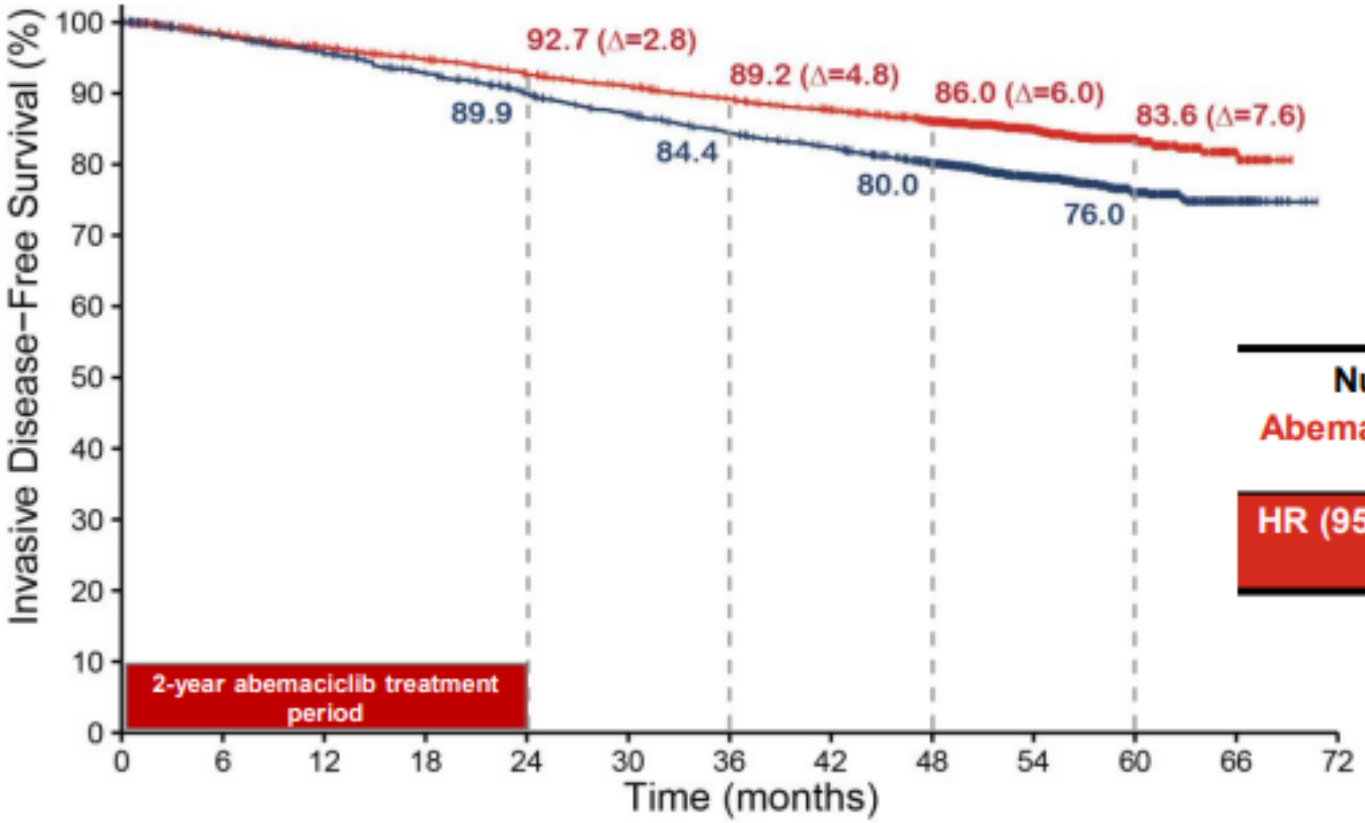
*Recruitment from July 2017 to August 2019.
†Endocrine therapy of physician's choice [e.g., aromatase inhibitors, tamoxifen, GnRH agonist].

Overall Survival Interim Analysis 3 (OS IA3)



- Here, we report 5-year efficacy results from a prespecified monarchE analysis
  - Data cutoff July 3rd, 2023
- Extent of follow-up at OS IA3 allows for robust estimation of IDFS and DRFS at the critical 5-year landmark
- Median follow-up time is 4.5 years (54 months)
- All patients are off abemaciclib
  - More than 80% of patients have been followed for at least 2 years since completing abemaciclib

Sustained IDFS Benefit in ITT



Number of IDFS events

Abemaciclib + ET	ET Alone
407	585

HR (95% CI): 0.680 (0.599, 0.772)
Nominal p <0.001

Number at risk

Abemaciclib + ET	2808	2621	2549	2479	2408	2347	2284	2220	2095	1175	490	74	0
ET alone	2829	2653	2573	2474	2374	2281	2195	2125	1974	1124	473	67	0

32% reduction in the risk of developing an IDFS event.
The KM curves continue to separate and the absolute difference in IDFS rates between arms was 7.6% at 5 years

Efficacy Outcomes by Ki-67 Index in Cohort 1

	Cohort 1 Ki-67 High		Cohort 1 Ki-67 Low	
	Abemaciclib + ET	ET	Abemaciclib + ET	ET
	n=1017	n= 986	n=946	n=968
IDFS				
Number of events, n	176	251	116	171
HR (95% CI)	**0.643 (0.530, 0.781)**		**0.662 (0.522, 0.839)**	
Nominal p-value	p<0.001		p<0.001	
5-year IDFS rate, % (95% CI)	81.0 (78.1, 83.4)	72.0 (68.7, 75.0)	86.3 (83.6, 88.6)	80.2 (77.2, 82.9)
DRFS				
Number of events, n	152	221	96	143
HR (95% CI)	**0.634 (0.515, 0.781)**		**0.664 (0.512, 0.861)**	
Nominal p-value	p<0.001		p=0.002	
5-year DRFS rate, % (95% CI)	83.4 (80.7, 85.8)	75.2 (72.1, 78.0)	88.6 (86.1, 90.7)	83.5 (80.7, 86.0)
OS (immature)				
Number of events, n	92	121	56	62
HR (95% CI)	**0.717 (0.546, 0.941)**		**0.911 (0.633, 1.309)**	
Nominal p-value	p=0.016		p=0.613	

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

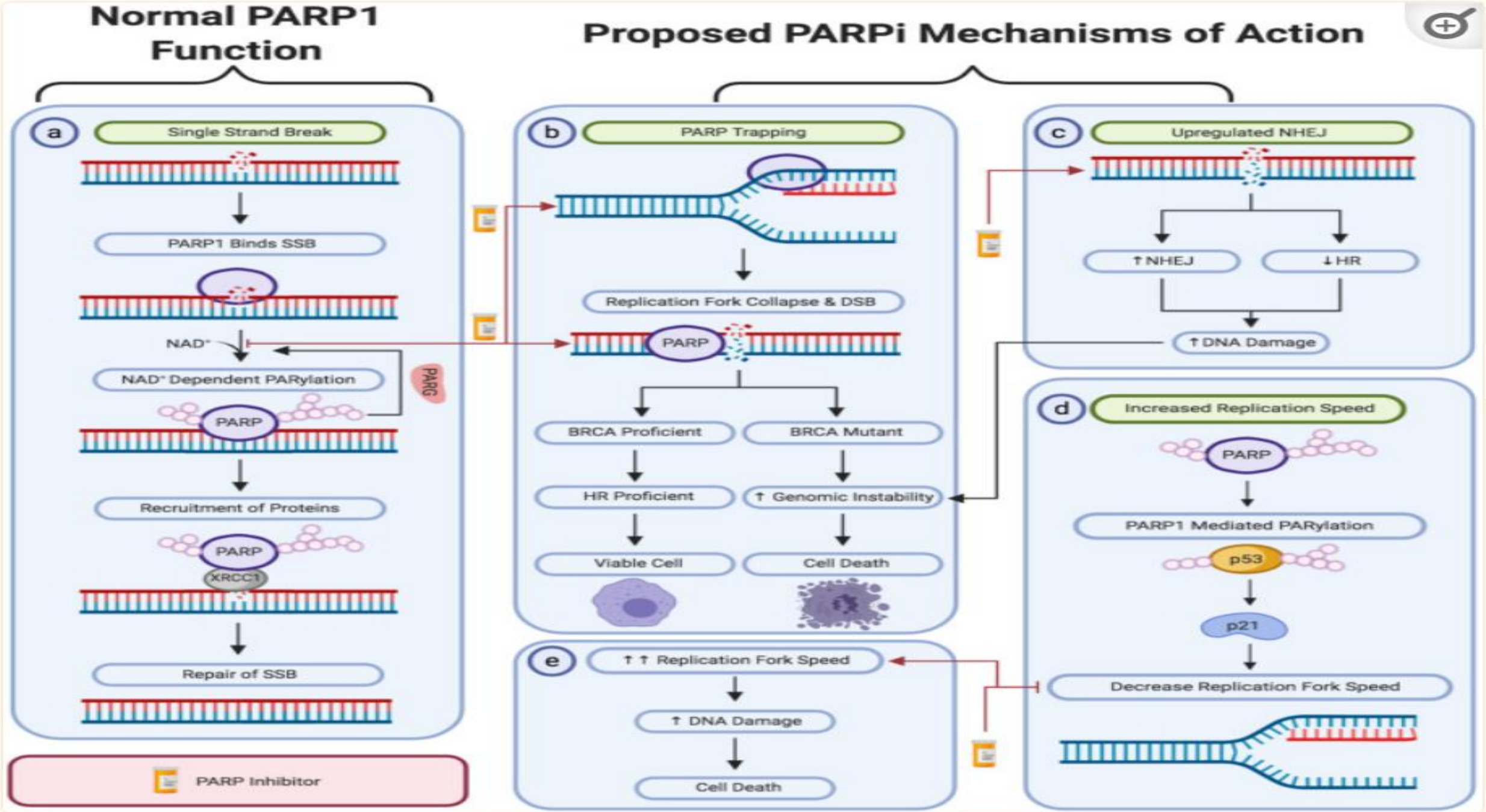
Genetics and family history

•Around 15-20% of men and women with breast cancer will have a family history of the disease

•Inherited mutations in BRCA1 and BRCA2 genes account for about 4-6% of all breast cancer cases in women and around 11-12% of cases in men

•In the general population, around 1 in 300-400 people carry a BRCA1 or BRCA2 mutation. People of Ashkenazi Jewish descent have a 1 in 40 chance of carrying a BRCA mutation.

https://www.breastcanceruk.org.uk/about-breast-cancer/facts-figures-and-qas/facts-and-figures/ Accessed 9 November 2023



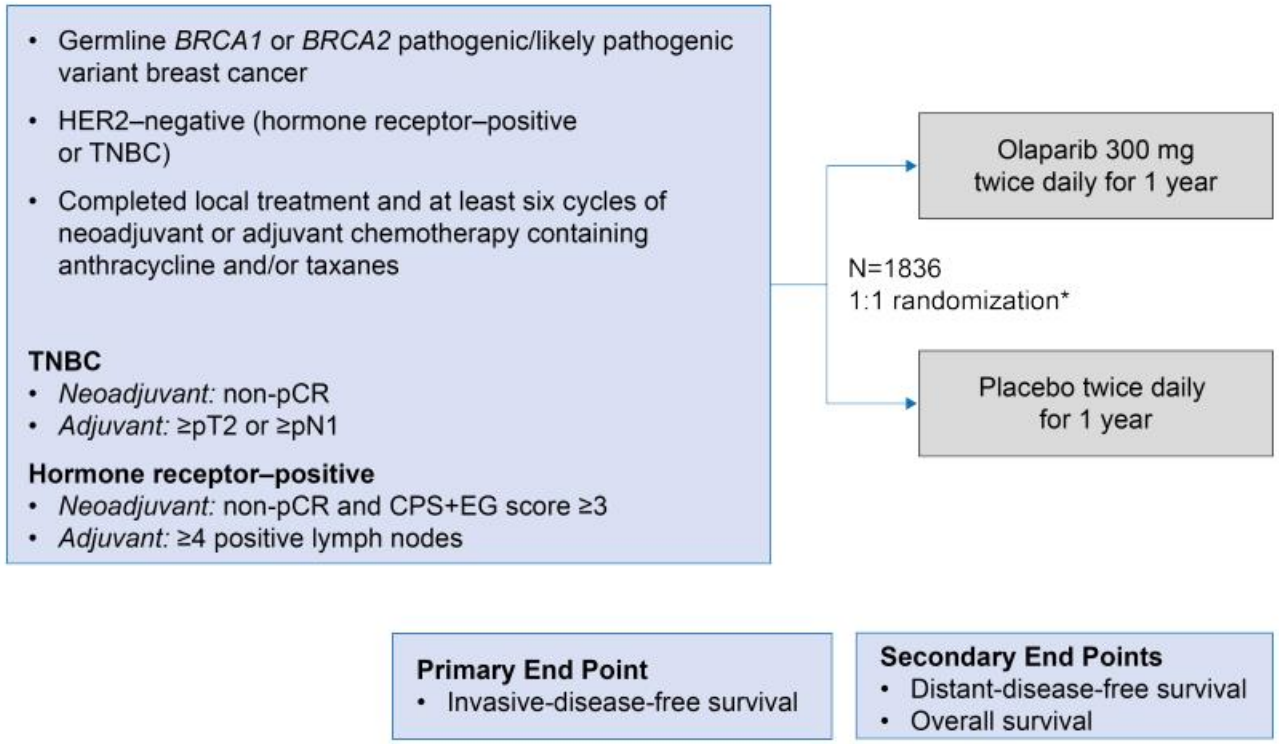
Rose M, et al, Front Cell Dev Biol. 2020 Sep 9;8:564601. doi: 10.3389/fcell.2020.564601.

ORIGINAL ARTICLE

Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer

Andrew N.J. Tutt, M.B., Ch.B., Ph.D., Judy E. Garber, M.D., M.P.H., Bella Kaufman, M.D., Giuseppe Viale, M.D., Debora Fumagalli, M.D., Ph.D., Priya Rastogi, M.D., Richard D. Gelber, Ph.D., Evandro de Azambuja, M.D., Ph.D., Anitra Fielding, M.B., Ch.B., Judith Balmaña, M.D., Ph.D., Susan M. Domchek, M.D., Karen A. Gelmon, M.D., et al., for the OlympiA Clinical Trial Steering Committee and Investigators*

FIGURE S1: OLYMPIA TRIAL SCHEMA



surgery and adjuvant chemotherapy - TNBC (≥pN1, any pT) or (pN0, pT2+)

ER and/or PgR positive/HER-2 -ve ≥4 pathologically confirmed positive lymph nodes

PMT

- TNBC non-pCR

- ER and/or PgR positive/HER-2 -ve non-pCR AND a CPS&EG score ≥3. Instructions how to calculate CPS&EG score

Tutt A, et al,

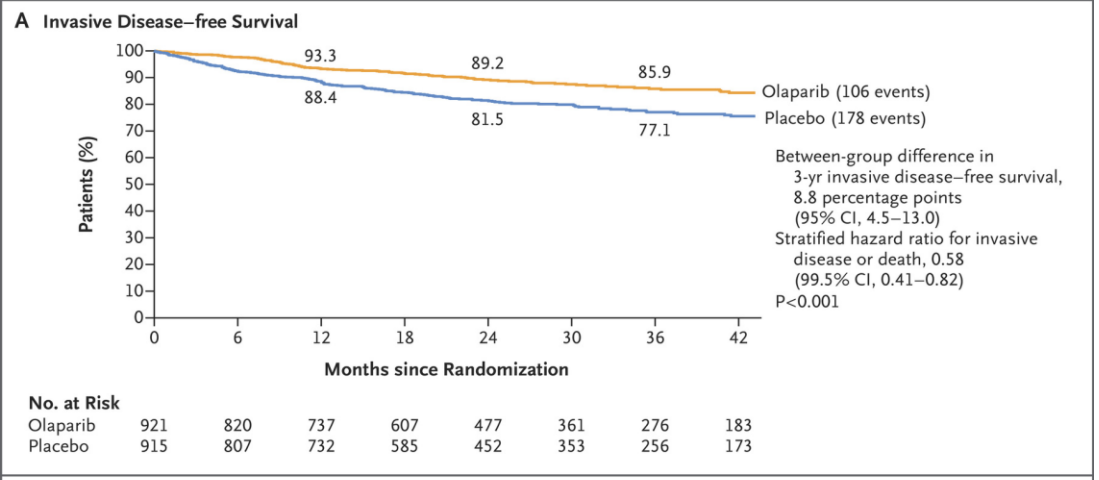
N Engl J Med 2021; 384:2394-2405 DOI: 10.1056/NEJMoa2105215

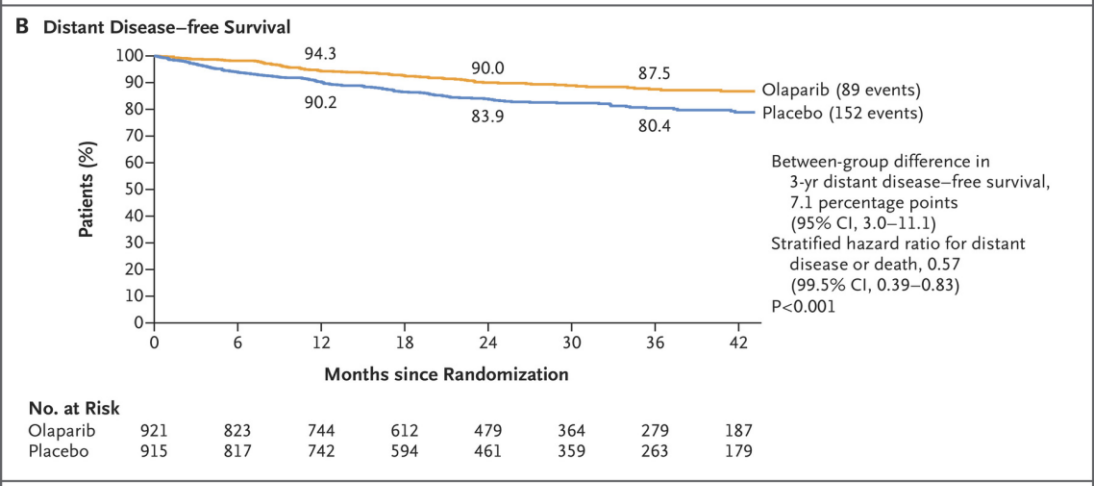
Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

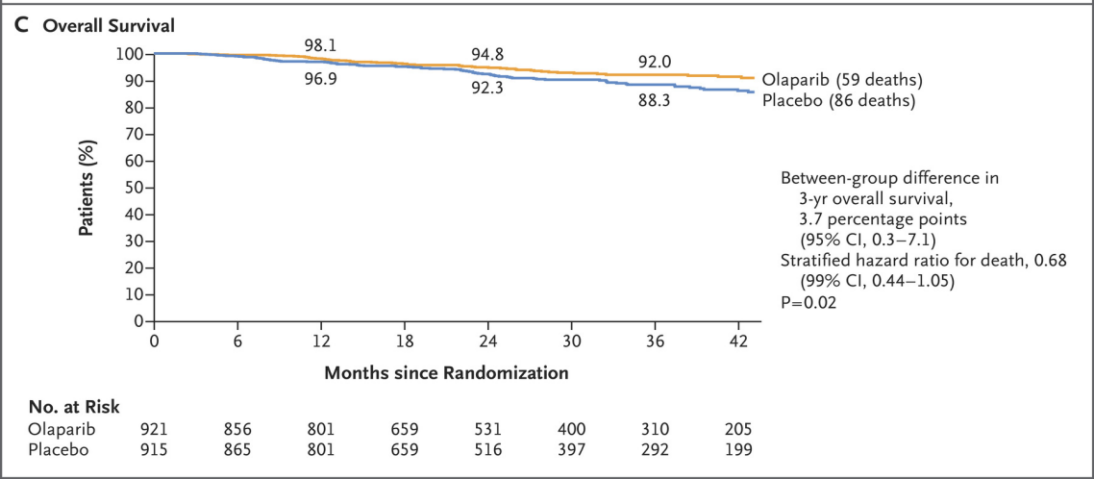
Characteristic	Olaparib (N=921)	Placebo (N=915)
Median age (interquartile range) — yr	42 (36–49)	43 (36–50)
Germline *BRCA* mutation — no. (%)†		
BRCA1	657 (71.3)	670 (73.2)
BRCA2	261 (28.3)	239 (26.1)
BRCA1 and *BRCA2*	2 (0.2)	5 (0.5)
Missing data	1 (0.1)	1 (0.1)
Previous adjuvant or neoadjuvant chemotherapy — no. (%)		
Adjuvant	461 (50.1)	455 (49.7)
Neoadjuvant	460 (49.9)	460 (50.3)
Regimen with both anthracycline and taxane	871 (94.6)	849 (92.8)
Anthracycline regimen, without taxane	7 (0.8)	13 (1.4)
Taxane regimen, without anthracycline	43 (4.7)	52 (5.7)
Regimen not reported	0	1 (0.1)
<6 Cycles of neoadjuvant or adjuvant chemotherapy	7 (0.8)	15 (1.6)
Platinum-based neoadjuvant or adjuvant therapy		
No	674 (73.2)	676 (73.9)

Tutt A, et al,

N Engl J Med 2021; 384:2394-2405 DOI: 10.1056/NEJMoa2105215







IDFS: (hazard ratio, 0.58; 99.5% CI, 0.41 to 0.82; P<0.001)

3 years 85.9% in the olaparib group vs. 77.1%

DDFS

hazard ratio, 0.57; 99.5% CI, 0.39 to 0.83; P<0.001)

3 years 87.5% in the olaparib group vs. 80.4%

OS hazard ratio of 0.68 (99% CI, 0.44 to 1.05; P=0.02)

Tutt A, et al,

N Engl J Med 2021; 384:2394-2405 DOI 10.1056/NEJMoa2105215

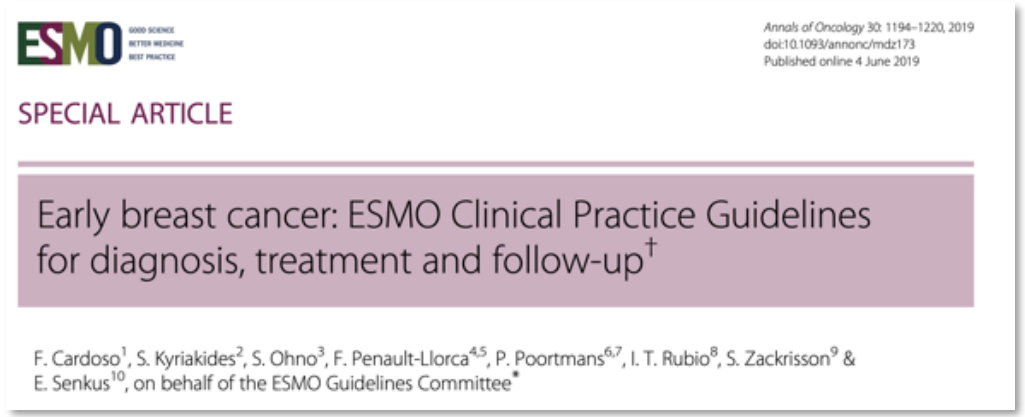
Table 3. Summary of Adverse Events in the Safety Analysis Set.*

Adverse Event	Olaparib (N=911)	Placebo (N=904)
	no. of patients (%)	
Any adverse event	835 (91.7)	753 (83.3)
Serious adverse event	79 (8.7)	76 (8.4)
Adverse event of special interest†	30 (3.3)	46 (5.1)
MDS or AML	2 (0.2)	3 (0.3)
Pneumonitis‡	9 (1.0)	11 (1.2)
New primary cancer§	19 (2.1)	32 (3.5)
Grade ≥3 adverse event	221 (24.3)	102 (11.3)
Grade 4 adverse event¶	17 (1.9)	4 (0.4)
Adverse event leading to permanent discontinuation of olaparib or placebo‖	90 (9.9)	38 (4.2)
Adverse event leading to death**	1 (0.1)	2 (0.2)

Tutt A, et al,

N Engl J Med 2021; 384:2394-2405 DOI 10.1056/NEJMoa2105215

Neoadjuvant approach – now the *treatment of choice* in HER2+ EBC



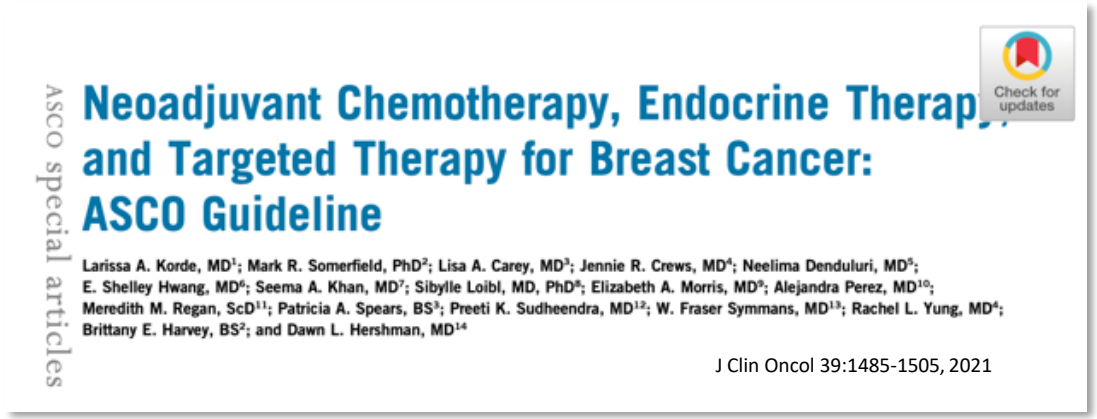
ESMO

SPECIAL ARTICLE

Annals of Oncology 30: 1194–1220, 2019
doi:10.1093/annonc/mdz173
Published online 4 June 2019

Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Cardoso[1], S. Kyriakides[2], S. Ohno[3], F. Penault-Llorca[4,5], P. Poortmans[6,7], I. T. Rubio[8], S. Zackrisson[9] & E. Senkus[10], on behalf of the ESMO Guidelines Committee*



ASCO special articles

Check for updates

Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline

Larissa A. Korde, MD[1]; Mark R. Somerfield, PhD[2]; Lisa A. Carey, MD[3]; Jennie R. Crews, MD[4]; Neelima Denduluri, MD[5]; E. Shelley Hwang, MD[6]; Seema A. Khan, MD[7]; Sibylle Loibl, MD, PhD[8]; Elizabeth A. Morris, MD[9]; Alejandra Perez, MD[10]; Meredith M. Regan, ScD[11]; Patricia A. Spears, BS[3]; Preeti K. Sudheendra, MD[12]; W. Fraser Symmans, MD[13]; Rachel L. Yung, MD[4]; Brittany E. Harvey, BS[2]; and Dawn L. Hershman, MD[14]

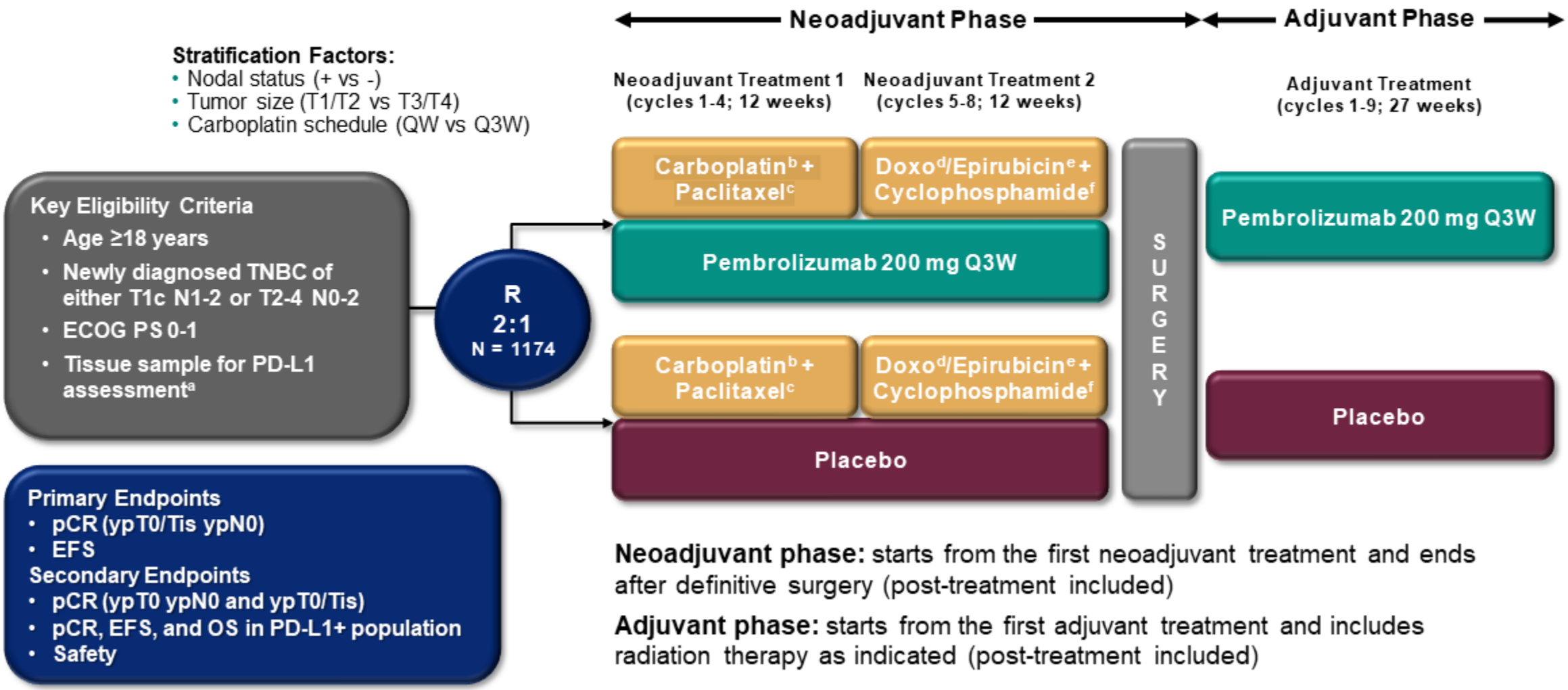
J Clin Oncol 39:1485-1505, 2021

"A neoadjuvant approach should be preferred in subtypes highly sensitive to chemotherapy, such as triple-negative and HER2-positive, in tumours >2 cm and/or a positive axilla."

"neoadjuvant therapy is the treatment of choice in all but small (<1cm), node-negative, TNBC, or HER2-positive tumors."

the presence or absence of residual disease after neoadjuvant therapy may alter treatment recommendations in the adjuvant setting

KEYNOTE-522 Study Design (NCT03036488)



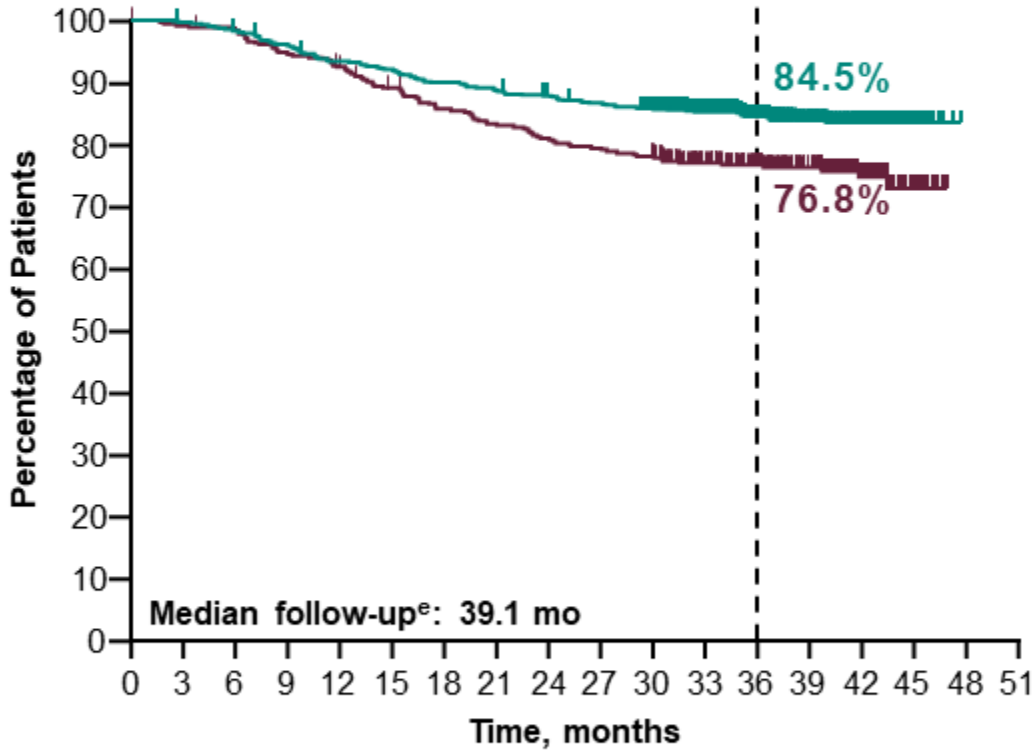
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

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.

EFS

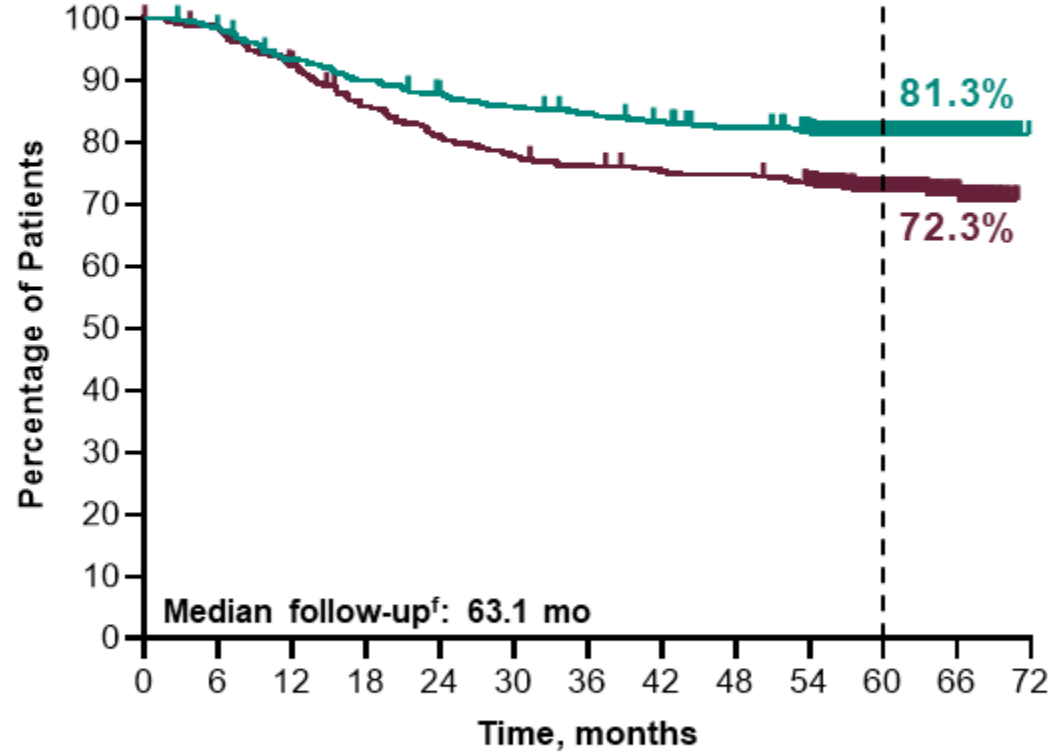
IA4[a]	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[c] (0.48-0.82)	0.00031[d]
Placebo + Chemo/Placebo	23.8%		



No. at risk

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

IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49-0.81)
Placebo + Chemo/Placebo	27.7%	



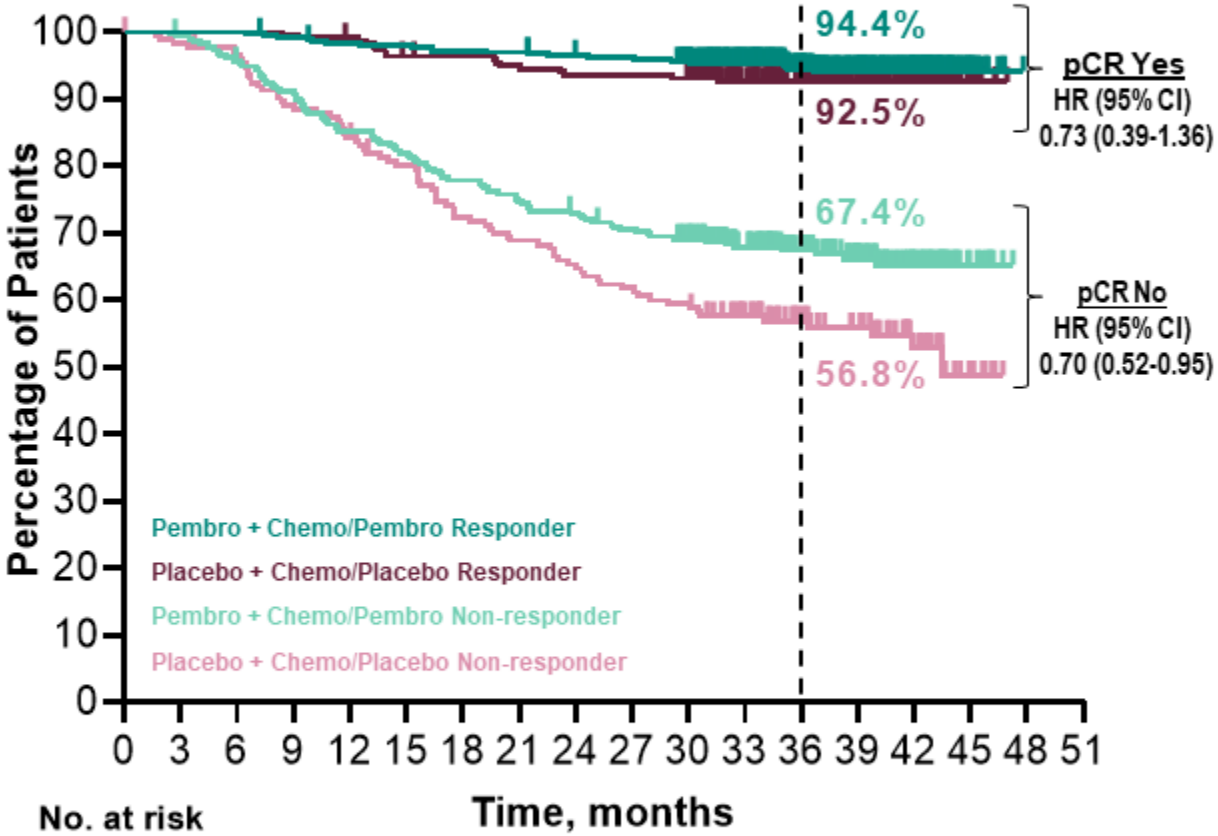
No. at risk

784	769	728	702	681	665	654	643	631	612	411	162	0
390	382	358	329	311	299	292	286	284	274	189	79	0

[a]The 4th prespecified interim analysis of EFS was calendar-driven planned to occur ~48 months after the first participant was randomized. [b]The 6th prespecified interim analysis of EFS was calendar-driven planned to occur ~72 months after the first participant was randomized. [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 of 0.00517 was crossed. [e]Defined as the time from randomization to the data cutoff date of March 23, 2021. [f]Defined as the time from randomization to the data cutoff date of March 23, 2023.

EFS by pCR (ypT0/Tis ypN0)

IA4

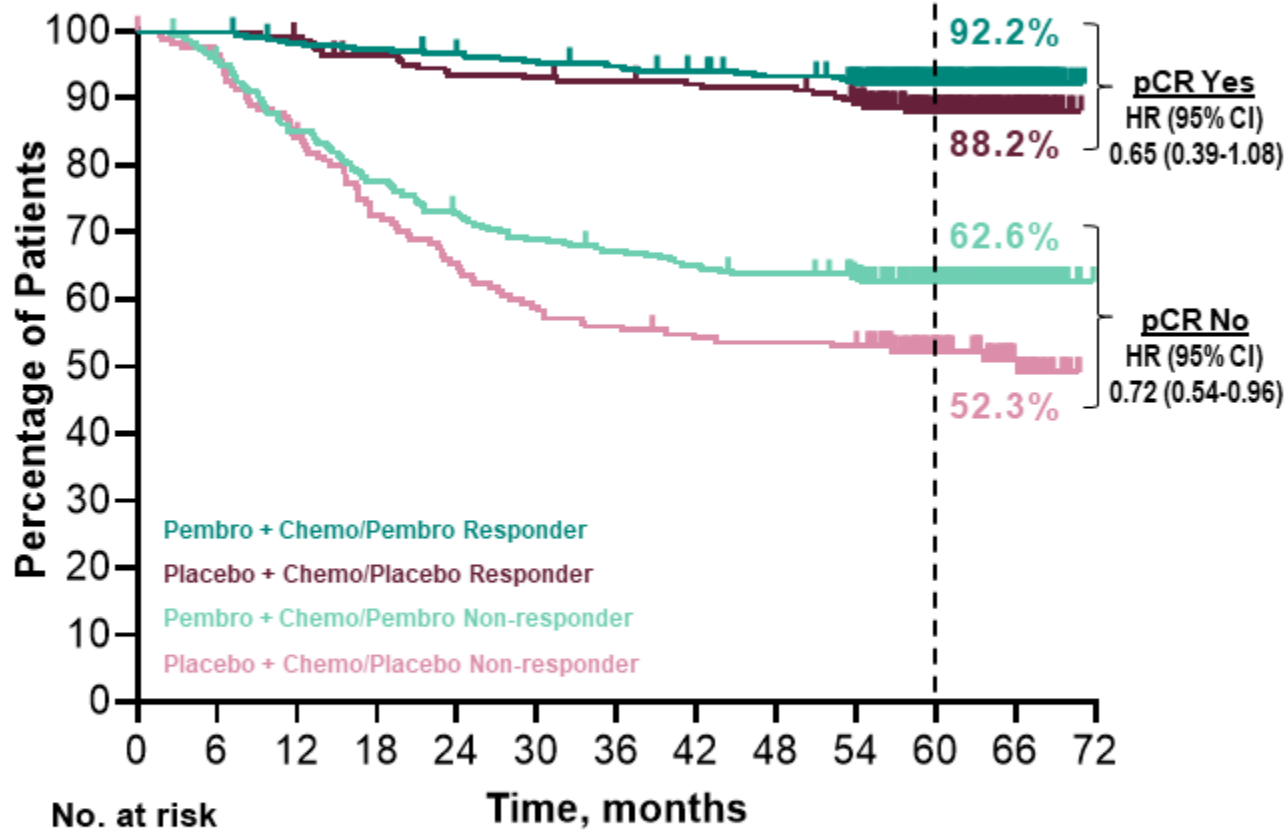


No. at risk

494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

Data cutoff date: March 23, 2021.

IA6



No. at risk

495	495	484	479	473	468	463	458	451	439	295	120	0
217	217	214	206	200	199	197	195	194	185	130	53	0
289	274	244	223	208	197	191	185	180	173	116	42	0
173	165	144	123	111	100	95	91	90	89	59	26	0

Data cutoff date: March 23, 2023.

Summary and Conclusions

- After a median follow-up of >5 years, neoadjuvant pembro + chemo followed by adjuvant pembro continues to show a clinically meaningful improvement in EFS compared with neoadjuvant chemo alone in patients with high-risk, early-stage TNBC
  - The EFS benefit with pembro was generally consistent across prespecified subgroups, including those defined by PD-L1 expression and nodal involvement
  - The reduction in EFS events in the pembro group was observed regardless of pCR outcome; in a prespecified, non-randomized, exploratory analysis, pembro improved EFS by 4.0 percentage points in patients with a pCR and 10.3 percentage points in patients without a pCR compared to placebo
  - There was a higher rate of distant recurrence-free survival with pembro versus placebo
- Follow-up for OS is ongoing
- **These results provide further support for pembro plus platinum-containing neoadjuvant chemo followed by adjuvant pembro after surgery, regardless of the pCR outcome, as a standard-of-care treatment regimen for patients with high-risk, early-stage TNBC**

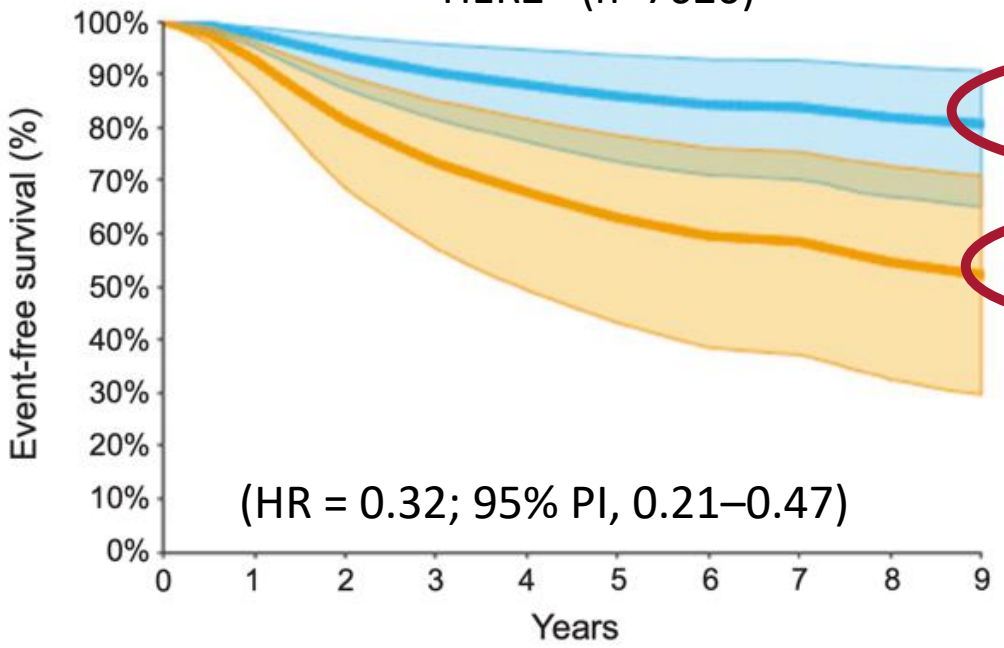
..and actionable

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Pathologic Complete Response after Neoadjuvant Chemotherapy and Impact on Breast Cancer Recurrence and Survival: A Comprehensive Meta-analysis

Laura M. Spring[1,2], Geoffrey Fell[3], Andrea Arfe[4], Chandni Sharma[1], Rachel Greenup[5], Kerry L. Reynolds[1,2], Barbara L. Smith[1,2], Brian Alexander[2,3], Beverly Moy[1,2], Steven J. Isakoff[1,2], Giovanni Parmigiani[3,6], Lorenzo Trippa[3,6], and Aditya Bardia[1,2]

HER2+ (n=7620)



RESPONSE-ADAPTED THERAPY?

pCR → NOT YET

no pCR → YES

Adjuvant T-DM1
KATHERINE (2019)

KATHERINE: design

- cT1c - T4 / N0-3 / M0
- completed neoadjuvant chemotherapy plus HER2-targeted therapy‡
- **residual invasive tumour in breast or axillary nodes**
- (N = 1486)

R
1:1

T-DM1
3.6 mg/kg Q3W
14 cycles

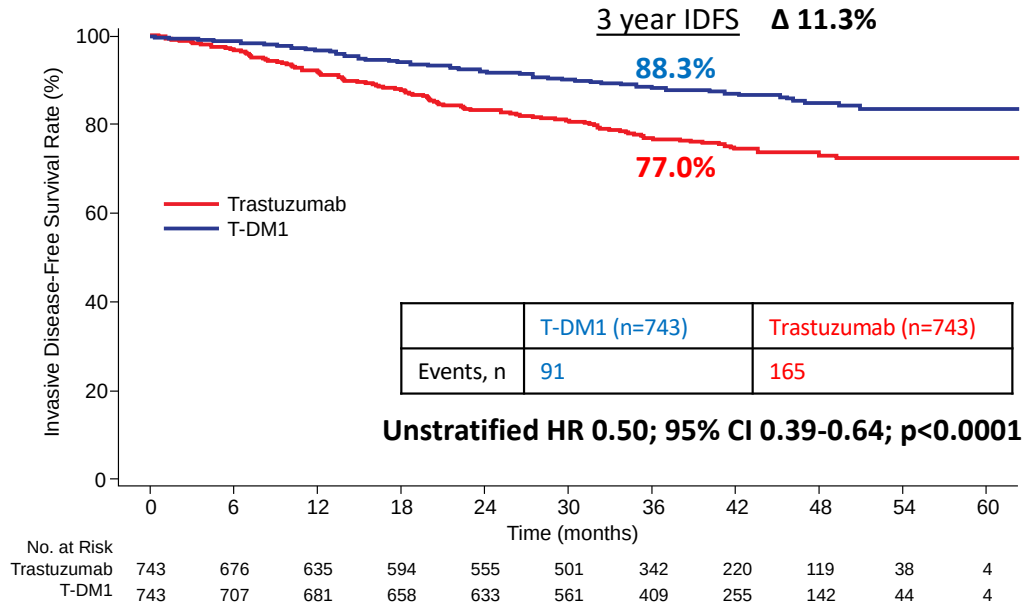
Trastuzumab
6mg/kg IV Q3W
14 cycles

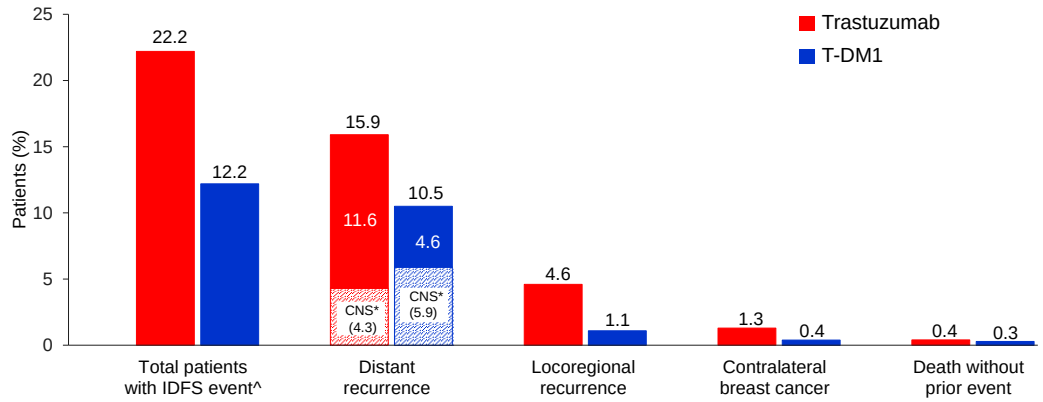
‡Neoadjuvant therapy
- ≥ 6 cycles of chemotherapy with ≥ 9 weeks of taxane
- ≥ 9 weeks trastuzumab

Stratification factors
- Clinical presentation: inoperable vs operable
- ER status
- Pre-operative therapy: trastuzumab versus combination with additional HER2 agent
- ypN status

Statistics
- **1º endpoint: IDFS**
- single interim analysis of IDFS when 67% of events had occurred

KATHERINE: results - IDFS





DR: 15.9% → 10.5%

LRR: 4.6% → 1.1%

But, CNS: 4.3% → 5.9%

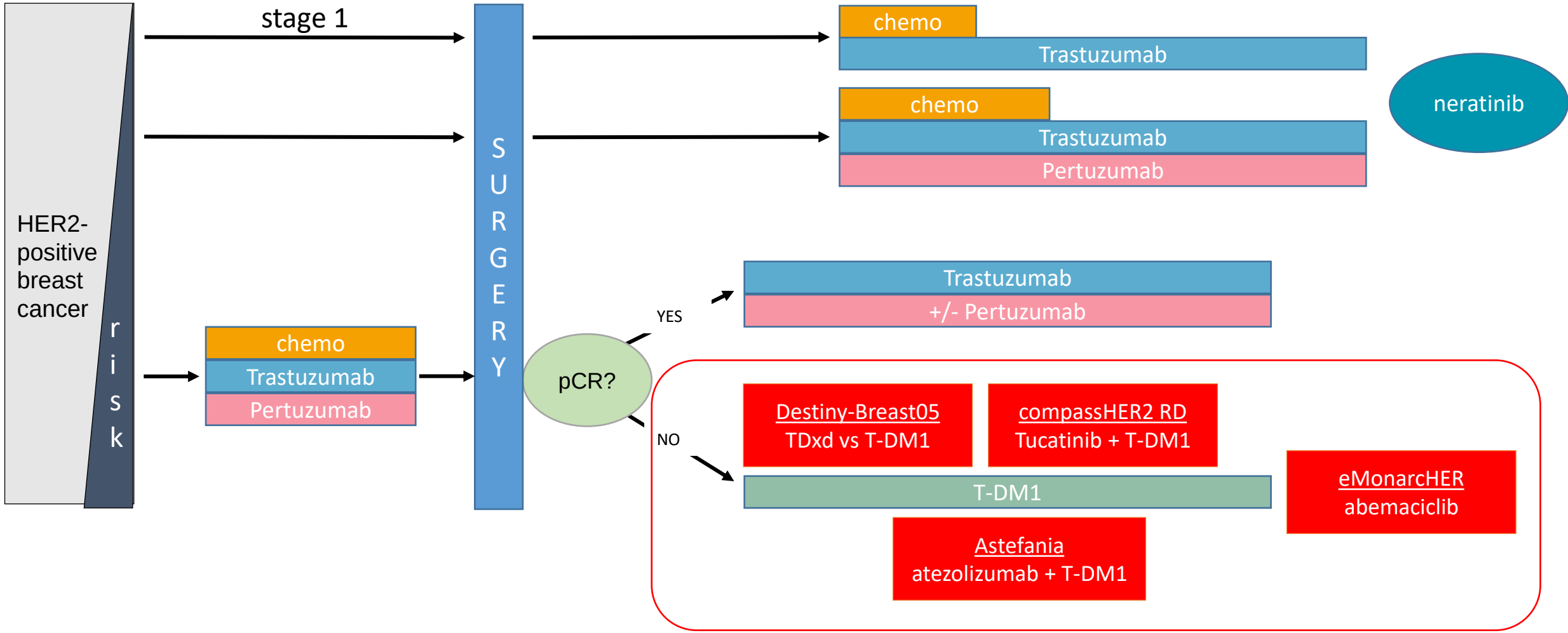

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 14, 2019 VOL. 380 NO. 7

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

G. von Minckwitz, C.-S. Huang, M.S. Mano, S. Loibl, E.P. Mamounas, M. Untch, N. Wolmark, P. Rastogi, A. Schneeweiss, A. Redondo, H.H. Fischer, W. Jacot, A.K. Conlin, C. Arce-Salinas, I.L. Wapnir, C. Jackisch, M.P. DiGiovanna, P.A. Fasching, J.P. Crown, P. Wülfing, Z. Shao, E. Rota Caremoli, H. Wu, L.H. Lam, D. Tesarowski, M. Smitt, H. Douthwaite, S.M. Singel, and C.E. Geyer, Jr., for the KATHERINE Investigators*

The evolving HER2 treatment landscape



..and predicts excellent survival outcomes

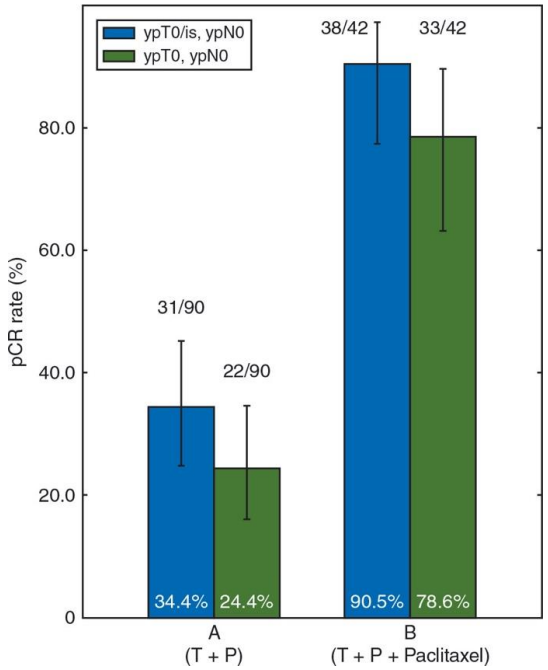
	Neo-sphere[1]	Tryphaena[2]	Tryphaena[2]	KRISTINE[3]	TRAIN-2[4]	TRAIN-2[4]	WSG-ADAPT-HER2+/HR-[5]	WSG-TP-II[6]	DAPHNE[7]
regimen	THPx4 (adjuvant FECx3)	TCHP x 6	FEC x3 → THP x3	TCHP x6	PacCHP x 9	FEC x3 →PacCHP x6	wPacHP x12 wks	wPacHP x12 wks	wPacHP x12wks
N	107	77	75	221	206	212	42	102	97
pCR ER-	63%*	84%	65%	73%	84%	89%	90%	n/a	84%
pCR ER+	26%*	50%	49%	44%	55%	51%	n/a	57%	43%
	5yr PFS 85%			**3yr IDFS 97.5%**			**5yr IDFS 98%**		

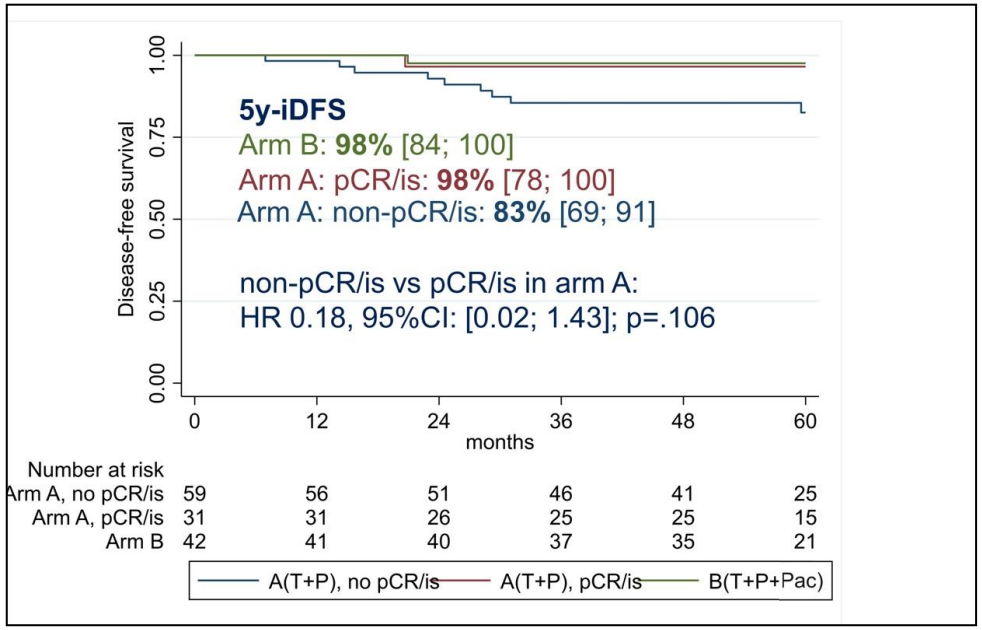
(1) Gianni L, et al. *Lancet Oncol* 2012;13: 25-32; (2) Schneeweiss A, et al. *Ann Oncol* 2013;24: 2278-2284; (3) Hurwitz S, et al. Lancet Oncol 2018; 19: 115-126 (4) van Ramshorst M, et al. *Lancet Oncol* 2018;19:1630-1640; (5) Nitz U, et al. *Ann Oncol* 2017;28: 2768-2772; (6) Gluz O, et al. *J Clin Oncol* 2020;38(15 suppl):515; (7) Waks A, et al. *Cancer Res* 2021;81(4 Suppl): PD3-05.

*breast only

Quality of pCR achieved with reduced versus standard therapy?

WSG-ADAPT HER2+/HR-





no further chemo after pCR:
Arm A - 29%
Arm B - 79%

- 60% cT2-4
- 42% cN+

Nitz, U. et al. *Ann Oncol* 2017; 28:2768-72; Harbeck, N. et al. ASCO 2021

Does more treatment after pCR achieved change outcomes?

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Pathologic Complete Response after Neoadjuvant Chemotherapy and Impact on Breast Cancer Recurrence and Survival: A Comprehensive Meta-analysis

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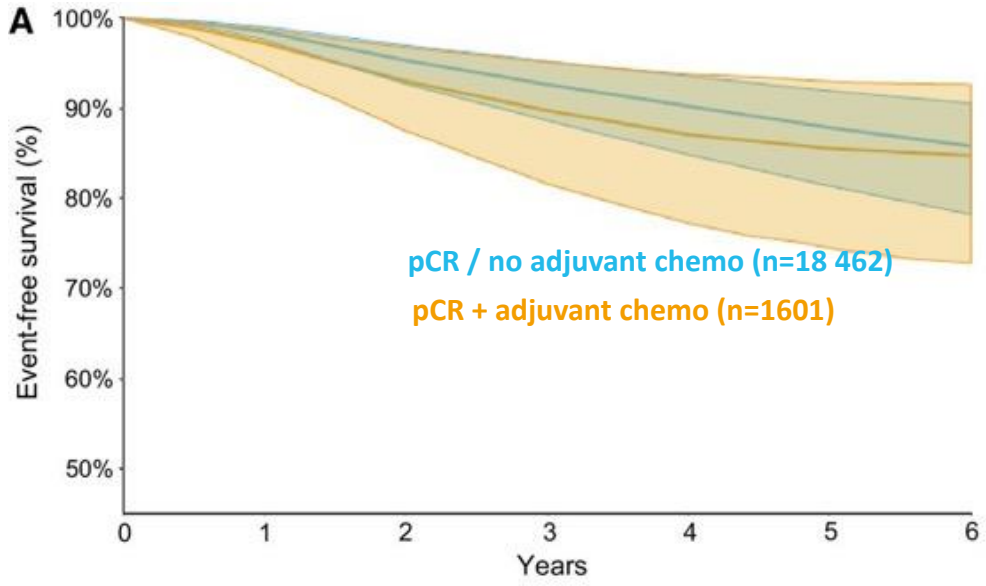
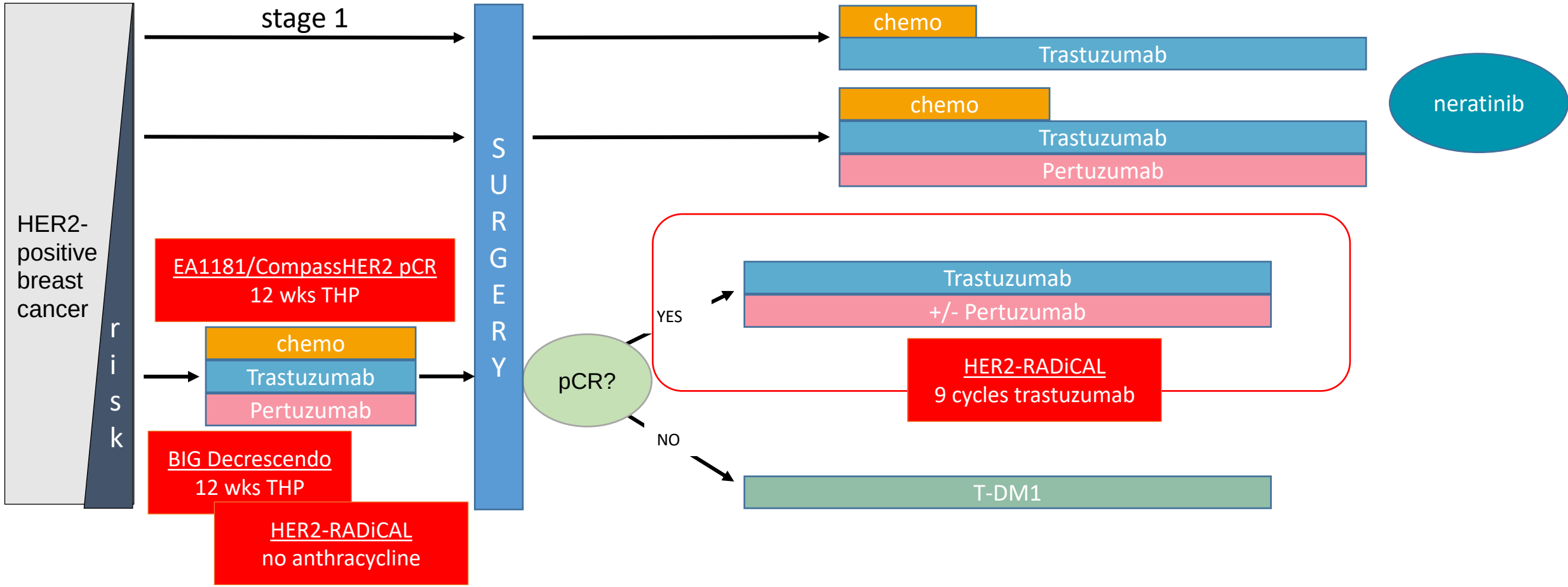


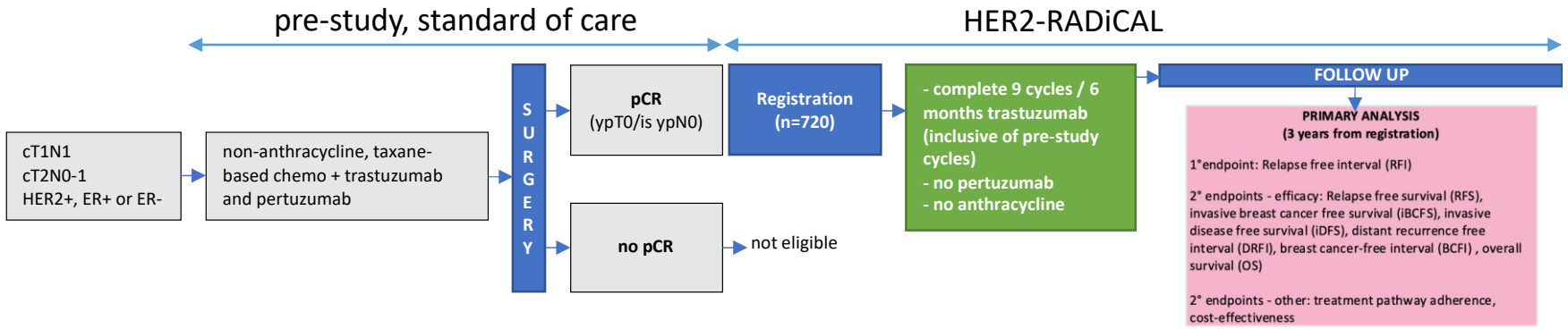
- similar association of pCR with improved EFS:
  - no subsequent adjuvant chemotherapy (HR 0.36, 95% CI: 0.27-0.54)
  - adjuvant chemotherapy (HR 0.36, 95% CI: 0.19-0.67),
  - no significant difference between the groups (p=0.60)

Spring, L. et al. Clin Cancer Res 2020;26:2838–48

The evolving HER2 landscape



HER2-RADiCAL Study (UK)



Participants receive <u>less</u> treatment compared with standard care by:

- A) Receiving a total of 9 cycles of trastuzumab
- B) NOT receiving any further pertuzumab
- C) NOT receiving any further chemotherapy, in particular, not receiving any anthracyclines

1^0 endpoint - 3 year incidence of relapse

- RFI: local or distant relapse or death from breast cancer in the absence of a previously identified relapse (intercurrent deaths censored)
- 90% power to exclude an event rate >6.5% at 3 years

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Breast cancer as a chronic disease

Outcomes for breast cancer patients has improved enormously in 20 years

Treatment options have proliferated

Demands on patients and service increase year on year

Inequity of access to treatment and support is a major concern

Breast cancer as a chronic disease

Is the NHS breast cancer service fit for 2020's

- **Paradigm shift to primary medical therapy**
- **Complexity of adjuvant therapies**
- **Needs of secondary breast cancer patients**
- **Access to research opportunities for patients**

Association of Cancer Physicians

Representing and supporting medical oncologists in the UK

"Before you are a leader, success is all about growing yourself.

When you become a leader, success is all about growing others"

Jack Welch