ADVANCES IN THE TREATMENT OF EARLY STAGE HORMONE RECEPTOR POSITIVE BREAST CANCER

Yael Zack, MD
White Plains Hospital
Center for Cancer Care

EMPIRE STATE HEMATOLOGY & ONCOLOGY SOCIETY

Disclosure of Conflicts of Interest

Yael Zack, MD, has no relevant financial relationships to disclose.

AC – 44yo Woman, BRCA2 Mutation +, left breast lump.

- MAMMOGRAM/SONOGRAM:

Suspicious palpable mass within the left 4:00 axis - Corresponding to the palpable nodule, is an irregular, hypoechoic, slightly vascular mass, measuring 1.1 x 1.2 x 1.1 cm

- MRI:

Biopsy-proven malignancy in the left breast at 4:00, measuring up to 1.6 cm.

Small enhancing masses noted inferior to the index malignancy, highly suspicious for satellite lesions.

No adenopathy noted.

- LEFT LUMPECTOMY + SLNB:

INVASIVE DUCTAL CARCINOMA, POORLY DIFFERENTIATED 3.5CM

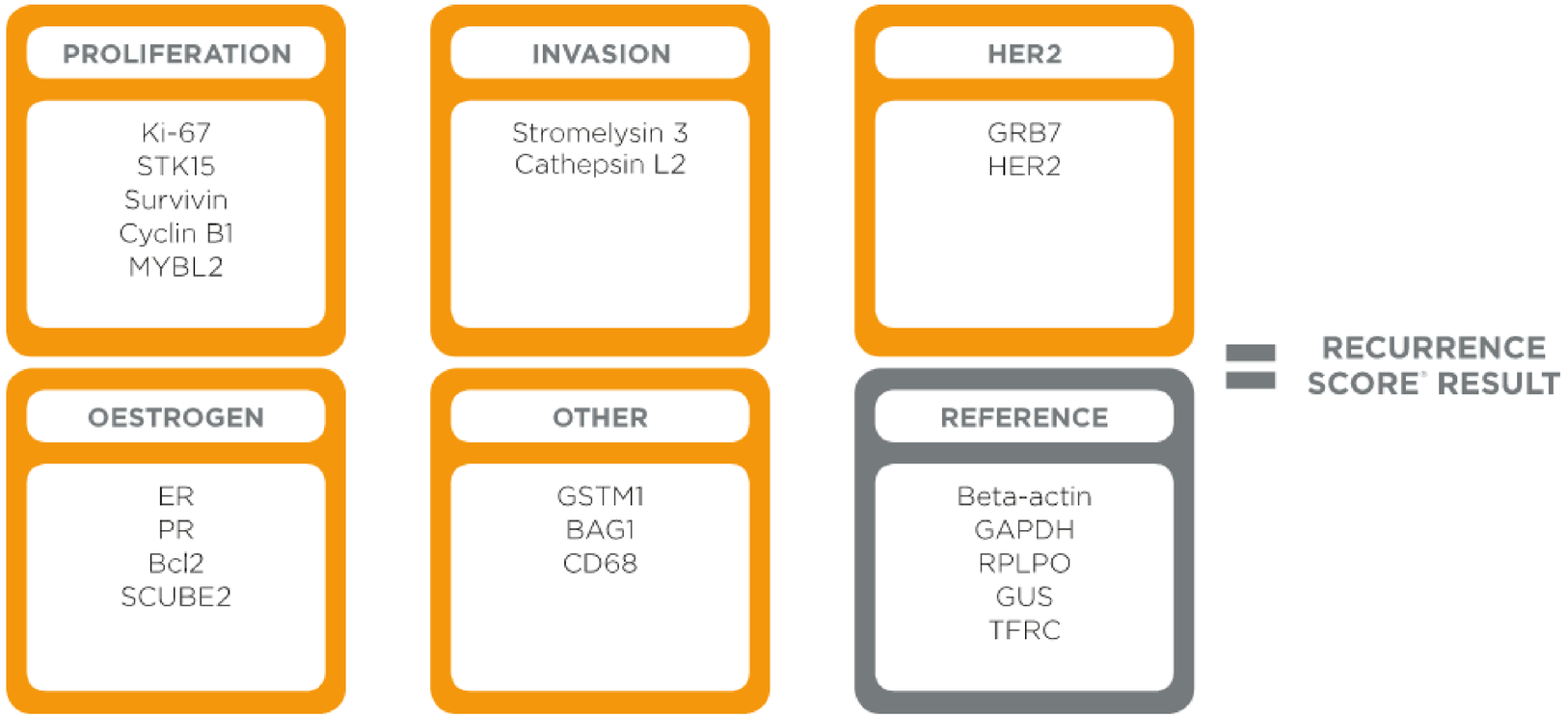
ER and PR - 91-100%/Strong/Positive; Her2 - 0/Negative; Ki67 - 40%.

1/2 LN POSITIVE FOR MACROMET

Does everyone need chemo?

oncotype DX®
Breast Recurrence Score

The Oncotype DX test reveals individual tumour biology based on measuring the expression of 21 genes[9]



16 Cancer Genes and **5 Reference Genes**

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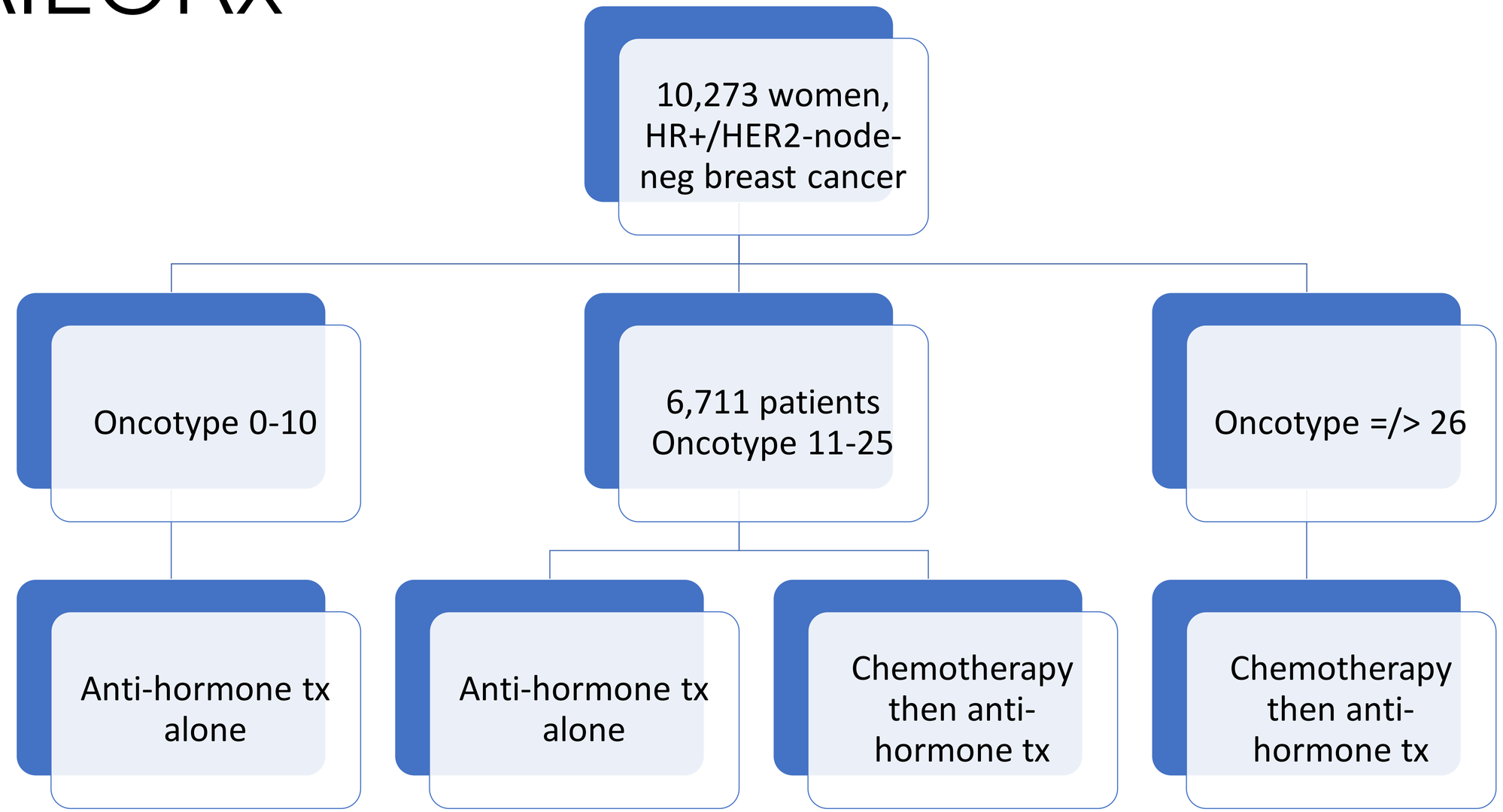
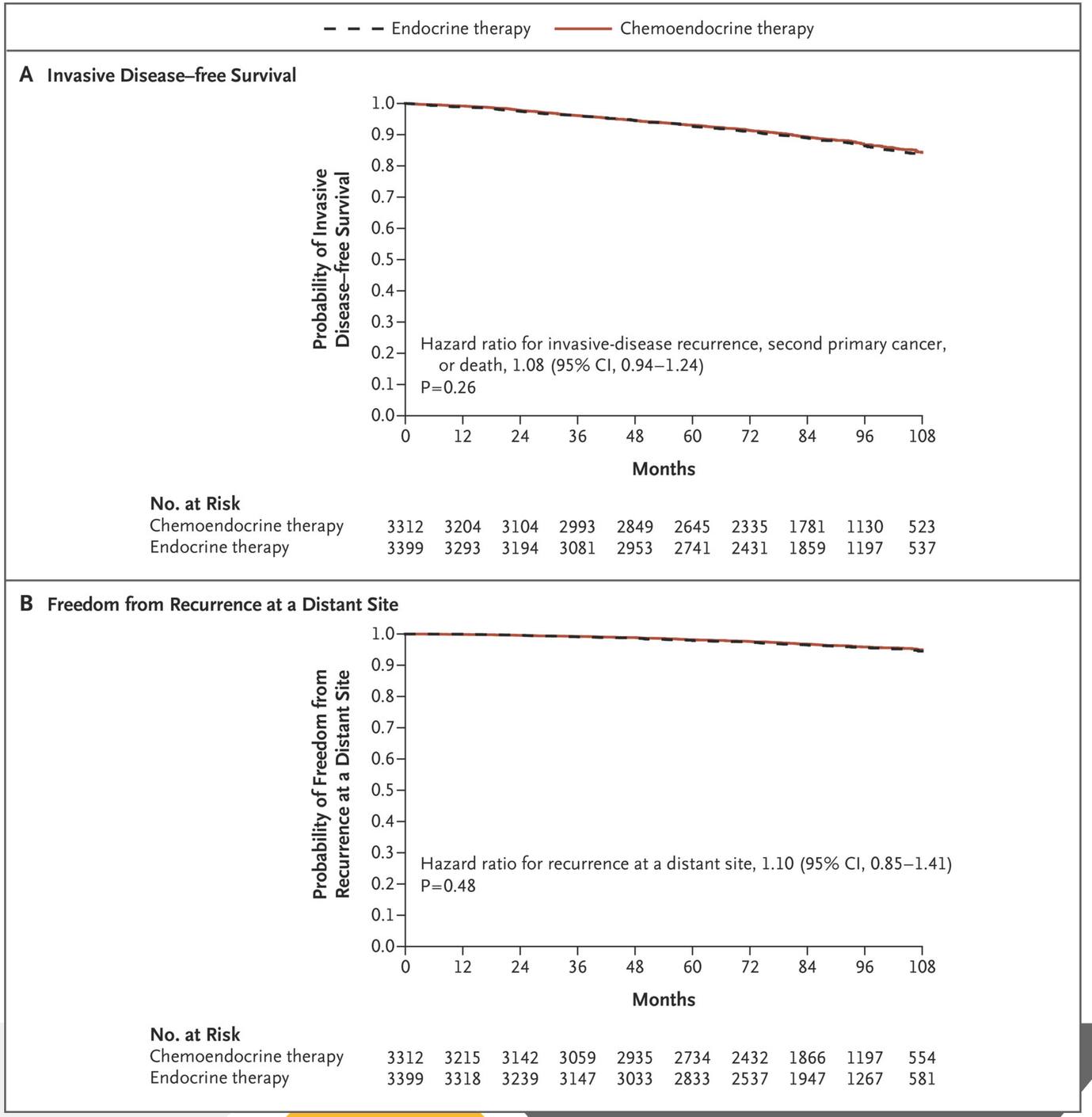
TAILORx


10,273 women, HR+/HER2-node-neg breast cancer
Oncotype 0-10
6,711 patients Oncotype 11-25
Oncotype =/> 26
Anti-hormone tx alone
Anti-hormone tx alone
Chemotherapy then anti-hormone tx
Chemotherapy then anti-hormone tx

TAILORx



Sparano, et al. NEJM, 2018.

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TAILORx – women under 50yo do benefit from chemo.

Table 3. Estimated Survival Rates According to Recurrence Score and Assigned Treatment among Women 50 Years of Age or Younger in the Intention-to-Treat Population.*

End Point and Treatment Group	Rate at 5 Yr	Rate at 9 Yr
	percent	
Invasive disease–free survival†		
Score of ≤10, endocrine therapy	95.1±1.1	87.4±2.0
Score of 11–15, endocrine therapy	95.1±1.1	85.7±2.2
Score of 11–15, chemoendocrine therapy	94.3±1.3	89.2±1.9
Score of 16–20, endocrine therapy	92.0±1.3	80.6±2.5
Score of 16–20, chemoendocrine therapy	94.7±1.1	89.6±1.7
Score of 21–25, endocrine therapy	86.3±2.3	79.2±3.3
Score of 21–25, chemoendocrine therapy	92.1±1.8	85.5±3.0
Score of ≥26, chemoendocrine therapy	86.4±1.9	80.3±2.9

Sparano, et al. NEJM, 2018.

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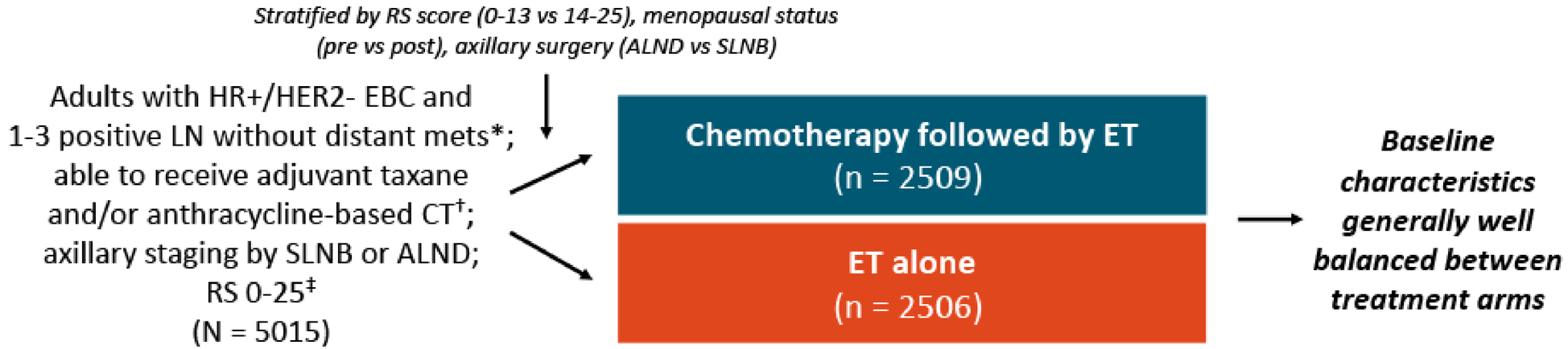
What about node-positive disease?

RxPONDER: Adjuvant ET ± Chemotherapy in HR+/HER2- EBC With 1-3 Positive Lymph Nodes and RS ≤ 25

- Randomized phase III trial



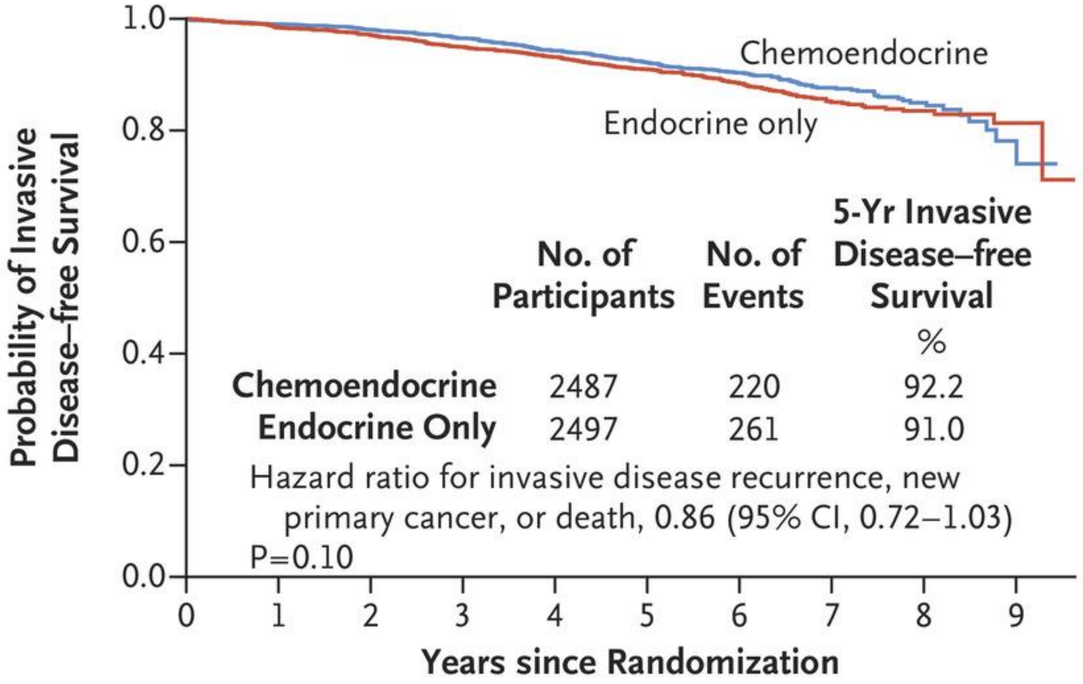
*Protocol amended to exclude patients with pN1mic as only nodal disease after 2493 patients randomized. †Approved CT regimens: TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T); AC alone or CMF not allowed. ‡Patients with RS > 25 recommended to be treated with CT followed ET off study.

- Primary endpoint: iDFS
- Key secondary endpoints: OS, distant DFS, local DFI, toxicity, QoL

Kalinsky. SABCS 2020. Abstr GS3-00.

Slide credit: clinicaloptions.com

A Invasive Disease–free Survival, All Participants



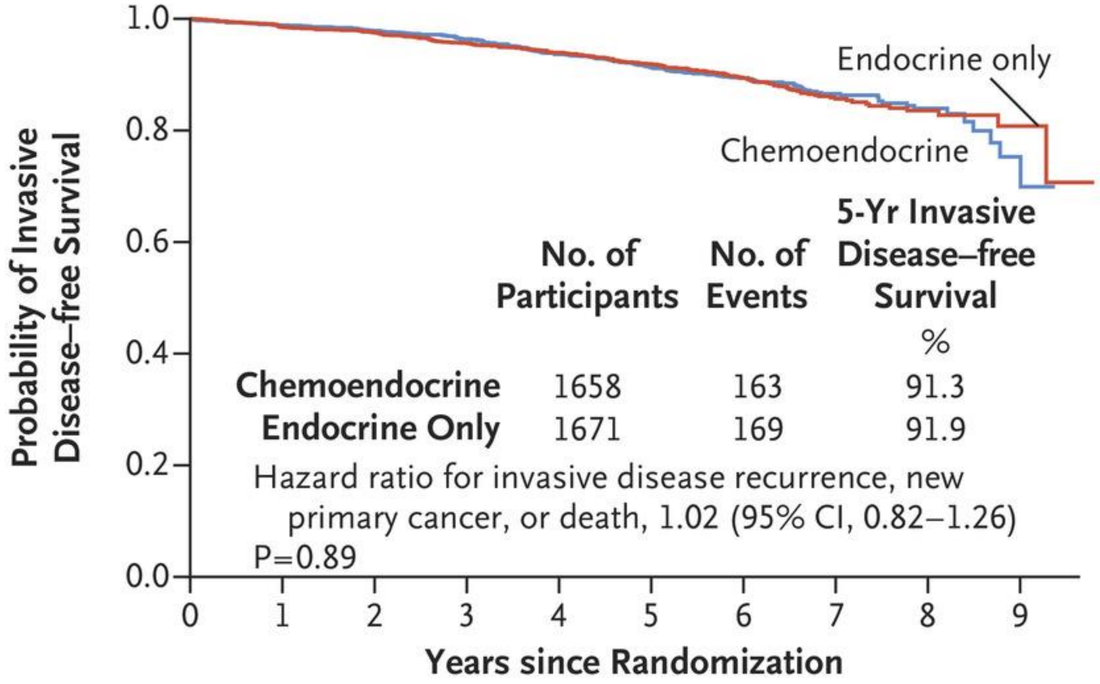
	No. of Participants	No. of Events	5-Yr Invasive Disease–free Survival %
Chemoendocrine	2487	220	92.2
Endocrine Only	2497	261	91.0

Hazard ratio for invasive disease recurrence, new primary cancer, or death, 0.86 (95% CI, 0.72–1.03)
P=0.10

No. at Risk

Chemoendocrine group	2487	2279	2123	1940	1691	1477	971	511	175	19
Endocrine-only group	2497	2328	2177	1965	1738	1493	969	502	181	23

B Invasive Disease–free Survival, Postmenopausal Participants



	No. of Participants	No. of Events	5-Yr Invasive Disease–free Survival %
Chemoendocrine	1658	163	91.3
Endocrine Only	1671	169	91.9

Hazard ratio for invasive disease recurrence, new primary cancer, or death, 1.02 (95% CI, 0.82–1.26)
P=0.89

No. at Risk

Chemoendocrine group	1658	1515	1413	1298	1145	993	659	358	129	14
Endocrine-only group	1671	1568	1474	1343	1196	1030	679	364	137	21

Kalinsky, et al. *NEJM* Dec 2021.

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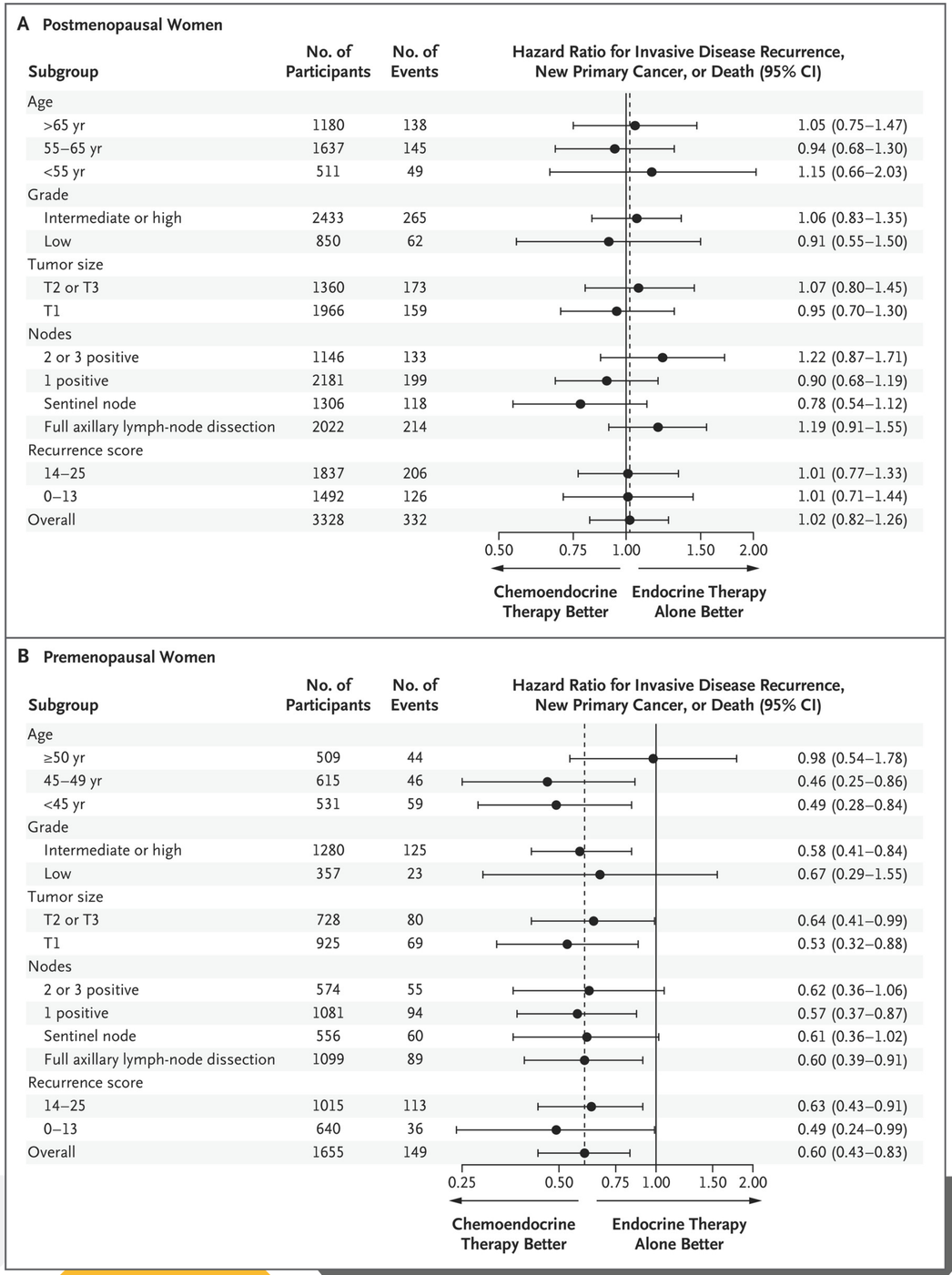
Women < 50yo BENEFIT from Chemo.



Post menopausal

Pre menopausal

Kalinsky, et al. *NEJM* Dec 2021.

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Our Pt AC, 44yo woman, pT2N1, left breast cancer.

- Underwent chemo with dose dense AC-T

- Underwent bilateral mastectomies

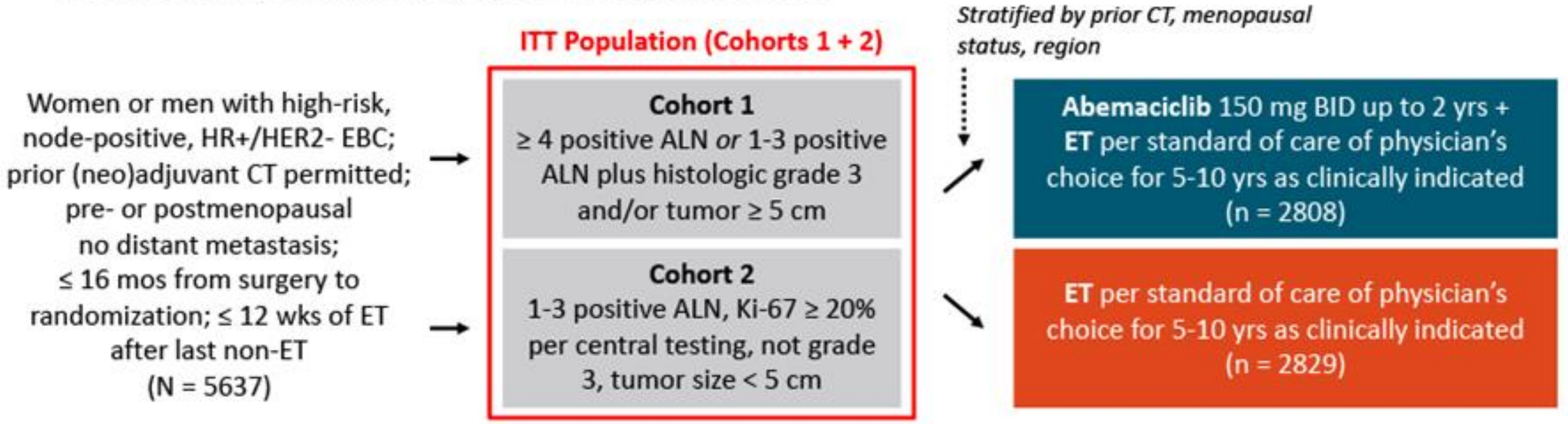
LEFT MASTECTOMY - RESIDUAL INVASIVE DUCTAL CARCINOMA, POORLY DIFFERENTIATED, WITH THERAPEUTIC CHANGES, MEASURING 3MM IN GREATEST DIMENSION.

- Underwent prophylactic BSO

Can we further improve her outcomes??

monarchE: Adjuvant Abemaciclib + ET in High-Risk, Node-Positive, HR+/HER2- EBC

- International, randomized, open-label phase III trial

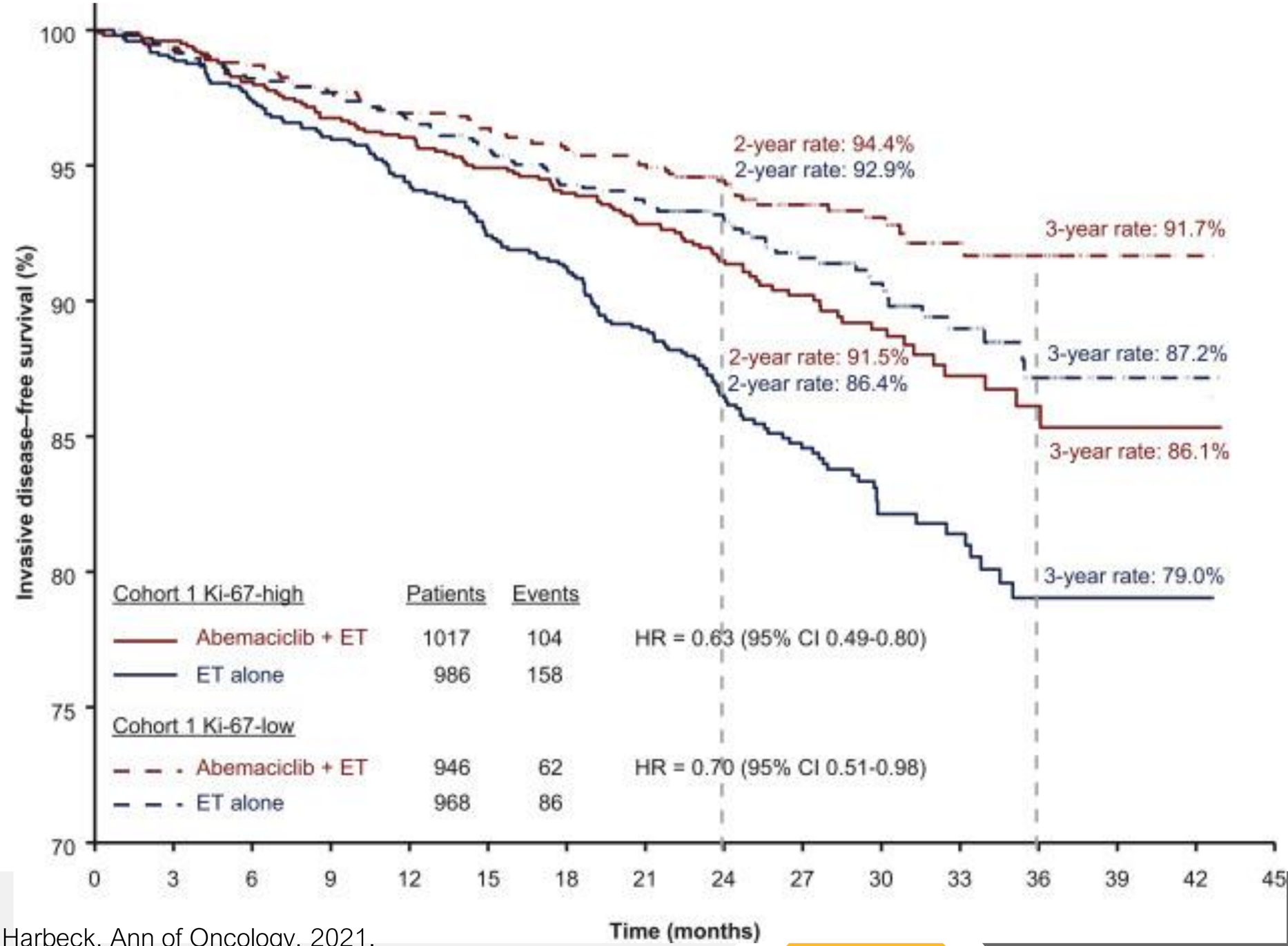


- Primary endpoint: iDFS
  - Planned for after ~ 390 iDFS events (~ 85% power, assumed iDFS HR of 0.73, cumulative 2-sided $\alpha = 0.05$)
  - Current primary outcome efficacy analysis occurred after 395 iDFS events in ITT population
- Key secondary endpoints: iDFS in Ki-67 high (≥ 20%) population, distant RFS, OS, safety, PRO, PK

Johnston. JCO. 2020;38:3987. Rastogi. SABCS 2020. Abstr GS1-01.

Slide credit: clinicaloptions.com

MONARCH-E



DFS At 3 yrs:

86 vs 79% in Ki67 high

91.7 vs 87.2% in Ki67 low

Harbeck, Ann of Oncology, 2021.

ORIGINAL ARTICLE

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

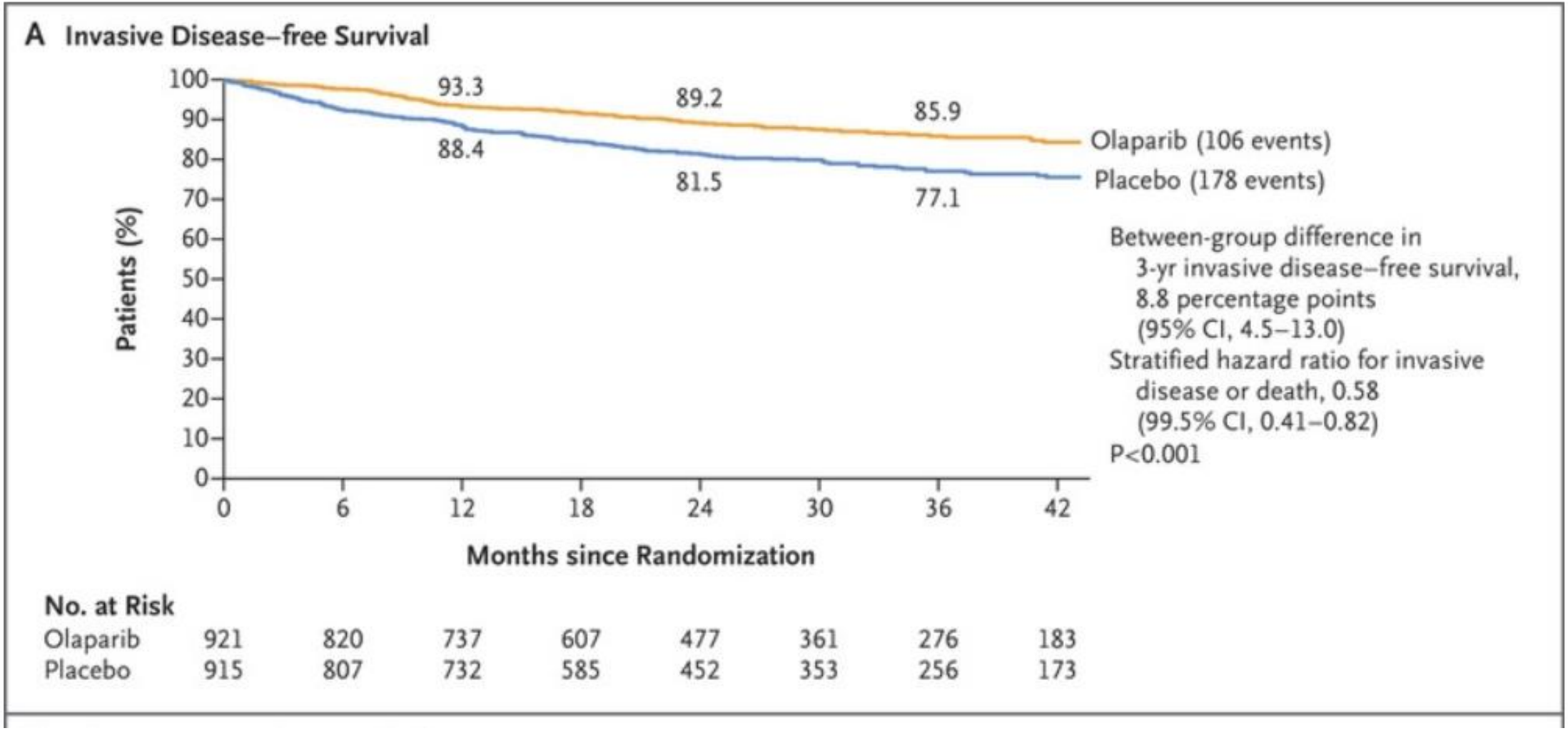
Andrew N.J. Tutt, M.B., Ch.B., Ph.D., Judy E. Garber, M.D., M.P.H., Bella Kaufman, M.D., Giuseppe Viale, M.D., Debora Fumagalli, M.D., Ph.D., Priya Rastogi, M.D., Richard D. Gelber, Ph.D., Evandro de Azambuja, M.D., Ph.D., Anitra Fielding, M.B., Ch.B., Judith Balmaña, M.D., Ph.D., Susan M. Domchek, M.D.,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

June 24, 2021
N Engl J Med 2021; 384:2394-2405

-1832 patients with mutation in BRCA1 or BRCA2 with early HER2- breast cancer
-If triple neg, tumor at least 2cm or LN+ or lack of pathCR after neoadjuvant chemo
-If HR+, at least 4 involved LN or lack of pathCR after neoadjuvant chemo

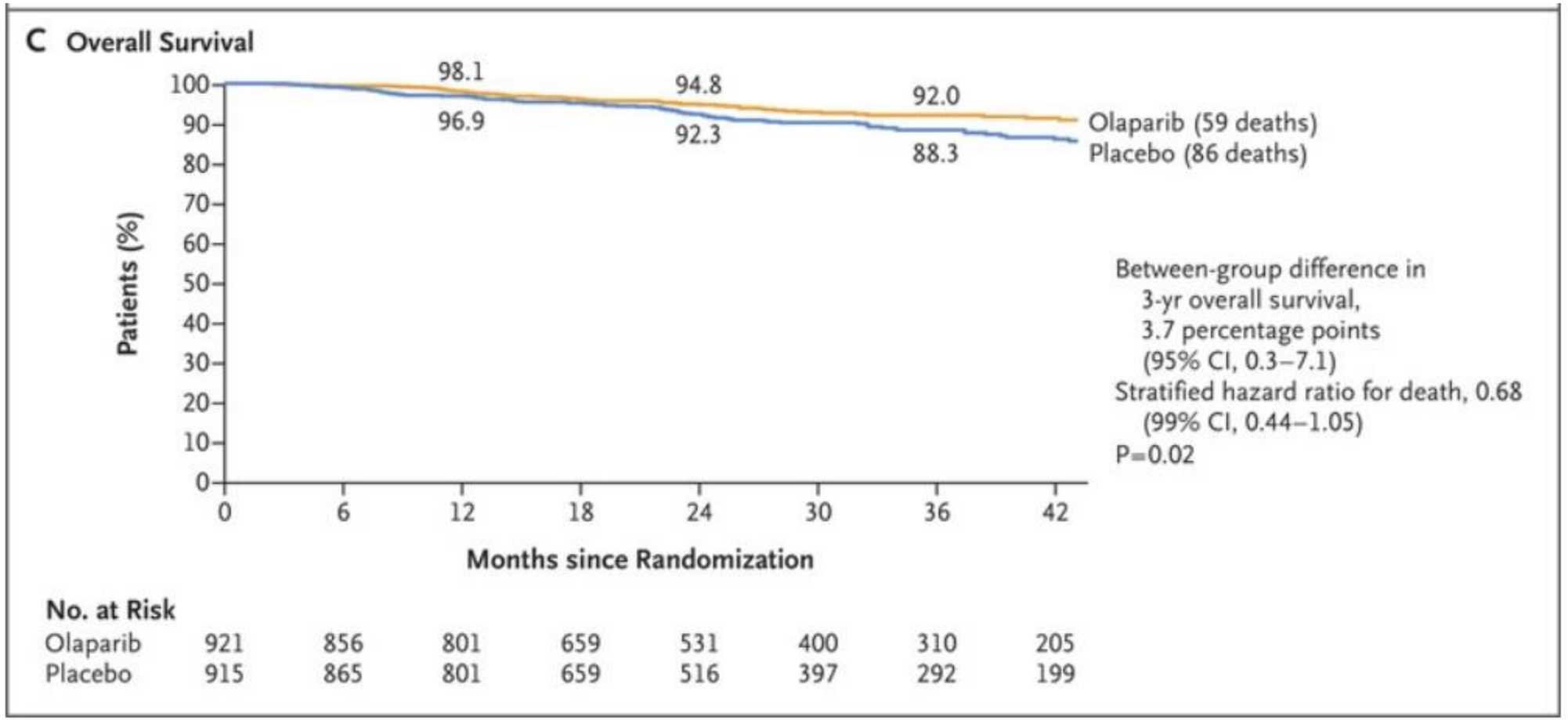
Adjuvant Olaparib significantly improved DFS.

Figure 1. Kaplan–Meier Estimates of Survival.



Tutt, et al. *NEJM* Dec 2021.

Adjuvant Olaparib Even Improved OS.



The between-group difference did not cross the prespecified multiple-testing procedure boundary for significance of P<0.01

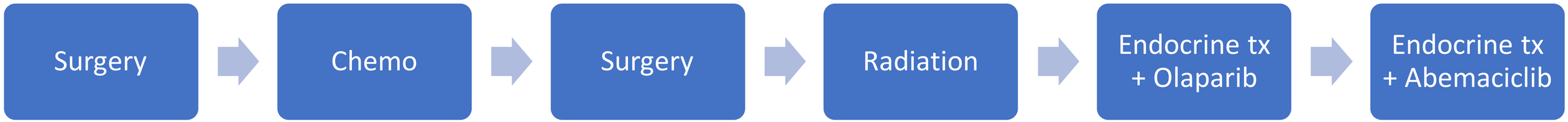
Tutt, et al. *NEJM* Dec 2021.

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, et al. *NEJM* Dec 2021.

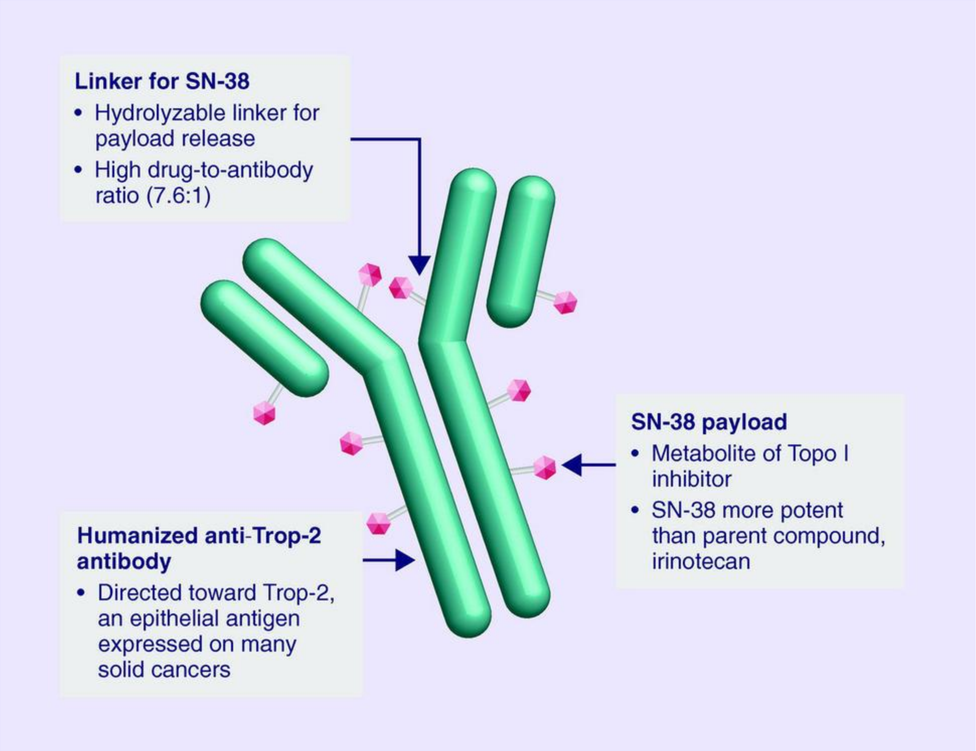
Our pt - AC


Surgery
Chemo
Surgery
Radiation
Endocrine tx + Olaparib
Endocrine tx + Abemaciclib

2 MAJOR PRACTICE CHANGING TRIALS FOR METASTATIC HORMONE-RECEPTOR POSITIVE IN 2022:

- DESTINY-04
- TROPiCS-02

TROPiCS-02: A randomized phase 3 study of Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients with HR+/HER2- advanced breast cancer.



NCI, 2020.

INCLUSION CRITERIA:

-543 patients randomized 1:1

-unresectable locally advanced or metastatic

-2 to 4 prior lines of chemotherapy, or 1 prior therapy if disease progressed </= 12 months after (neo)adjuvant therapy

-must have received taxane, CDK4/6 inhibitor, and endocrine therapy

SG
10mg/kg day
1, 8, q21d

TPC:
Capecitabine, eribulin, vinorelbine, or gemcitabine

TROPiCS-02 RESULTS

Rugo, et al. ASCO 2022.

- Improved median PFS with SG – 5.5 vs 4 months, HR 0.66; 95% CI, 0.53-0.83; p=0.0003

- PFS at 6 months improved with SG: 46% vs 30%
- PFS at 12 months improved with SG: 21% vs 7%

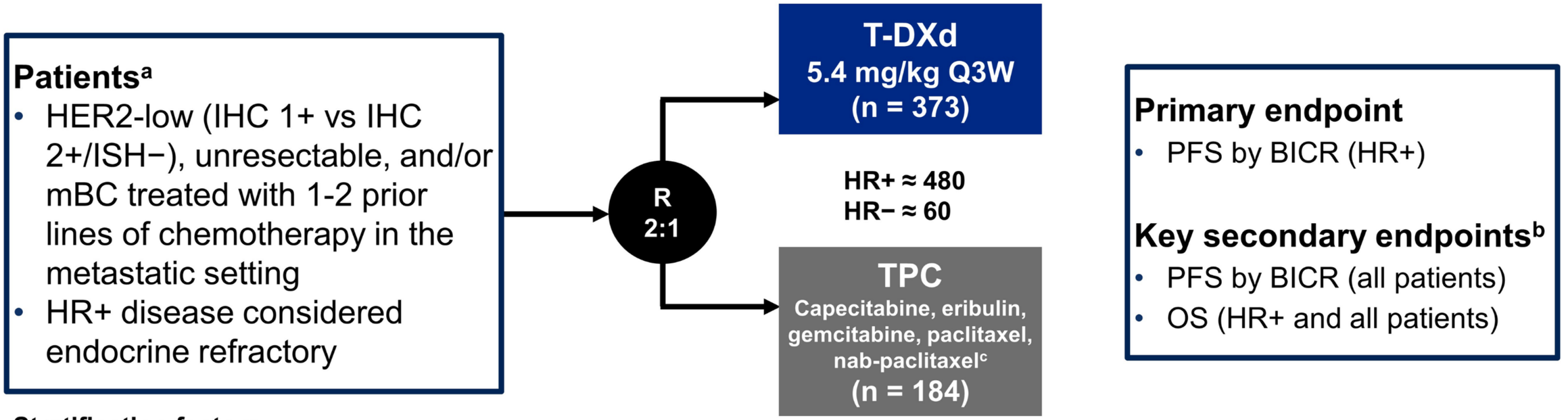
- No statistically significant difference in OS with SG: 13.9 months vs 12.3 months (HR 0.84; p=0.143)

- Improved ORR with SG: 21% vs 14%

- Improved Clinical Benefit rate with SG: 34% vs 22%

DESTINY-04: Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

Modi, et al. *NEJM* July 2022.

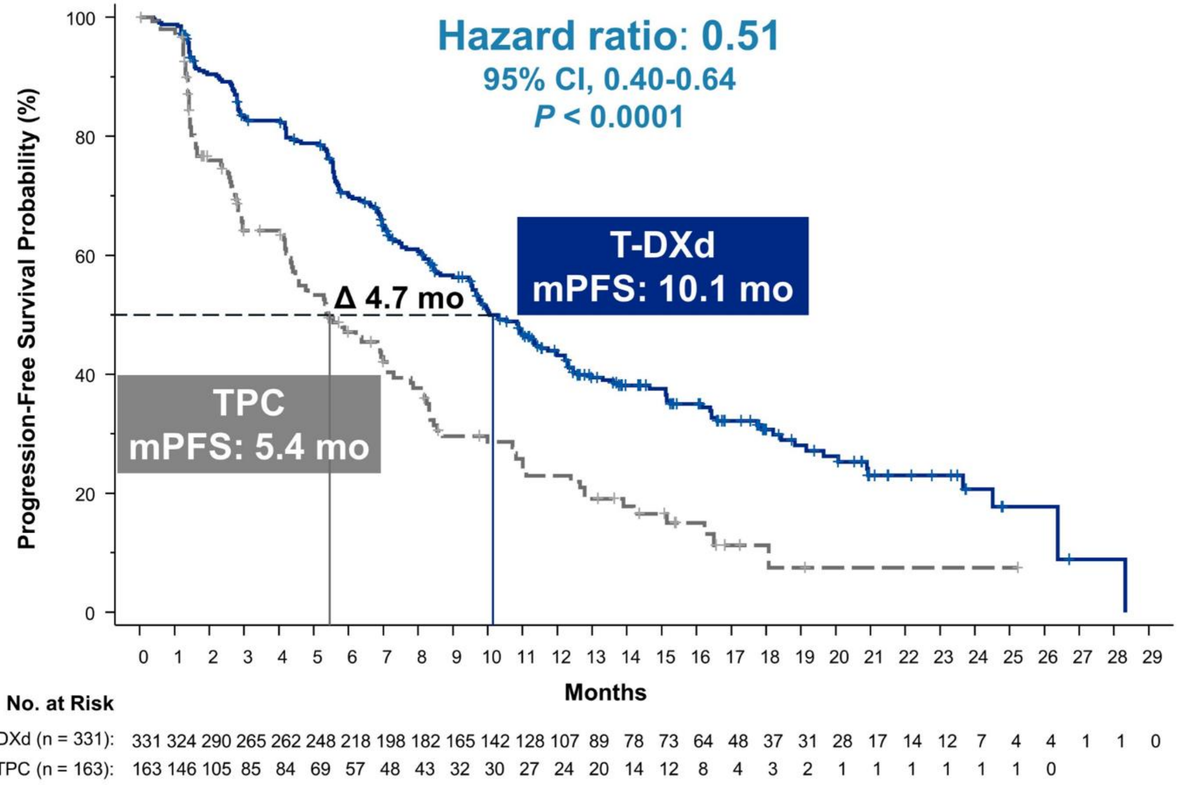


Stratification factors

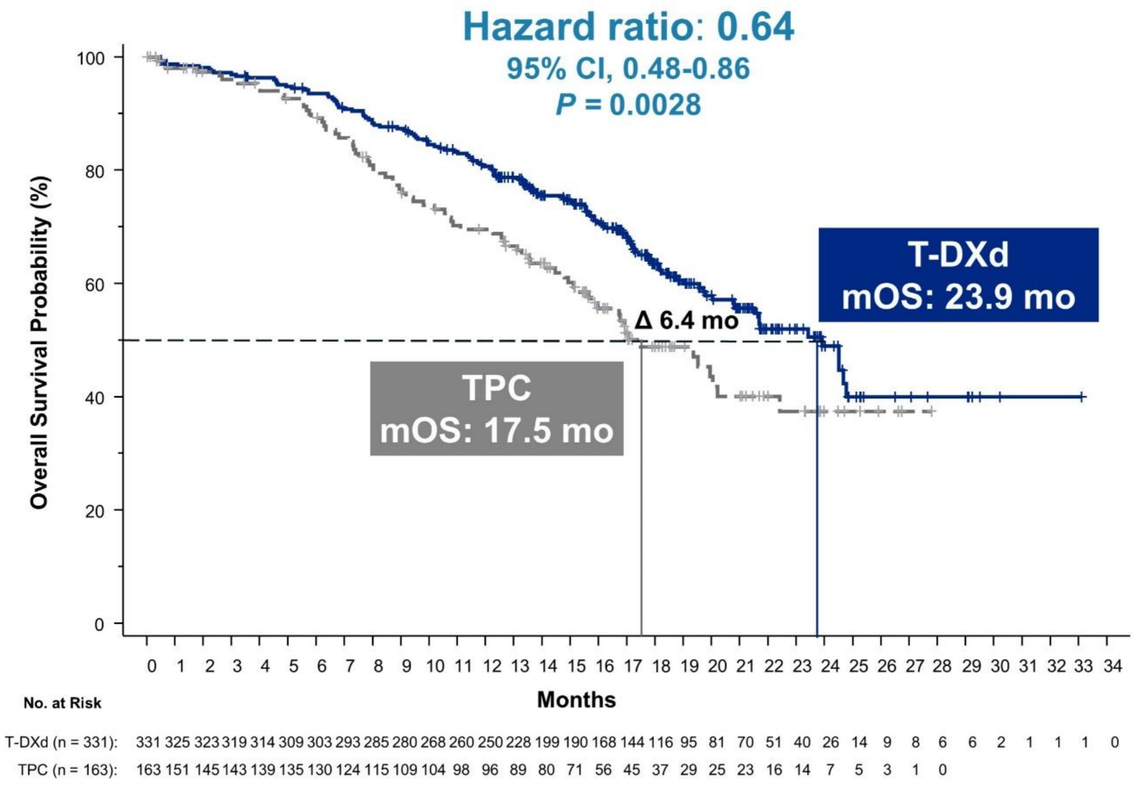
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

DESTINY-Breast04: PFS (BICR) and OS in HR+[33,34]

PFS in HR+
Primary Endpoint



OS in HR+
Secondary Endpoint



Median duration of follow-up: 18.4 months

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Thank you!

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Rugo, et al. Primary results from TROPiCS-02: A randomized phase 3 study of Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (Pts) with hormone rectpro-positive/HER2-negative (HR+/HER2-) advanced breast cancer. *JCO* 2022.

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