Management of Metastatic Breast Cancer

Joanne Mortimer MD, FACP, FASCO

Professor and Vice Chair, Department of Medical Oncology and Therapeutics
Director, Women's Cancers Program
Associate Director for Education and Training
Baum Family Professor of Women's Cancers
City of Hope

Faculty Disclosure

Commercial Interest	Nature of Relevant Financial Relationship	
	What was received	**For what role**
PUMA	Consultant Fees	DSMB
Incyte	Consultant Fees	ODAC preparation
Lily	Consultant Fees	ODAC prep
Astra Zeneca	Consultant and Research	Advisory Board
Novartis	Consultant Fees	Advisory Board

Metastatic Breast Cancer

- Biopsy confirmation of recurrence and markers
- Germline testing
- NGS

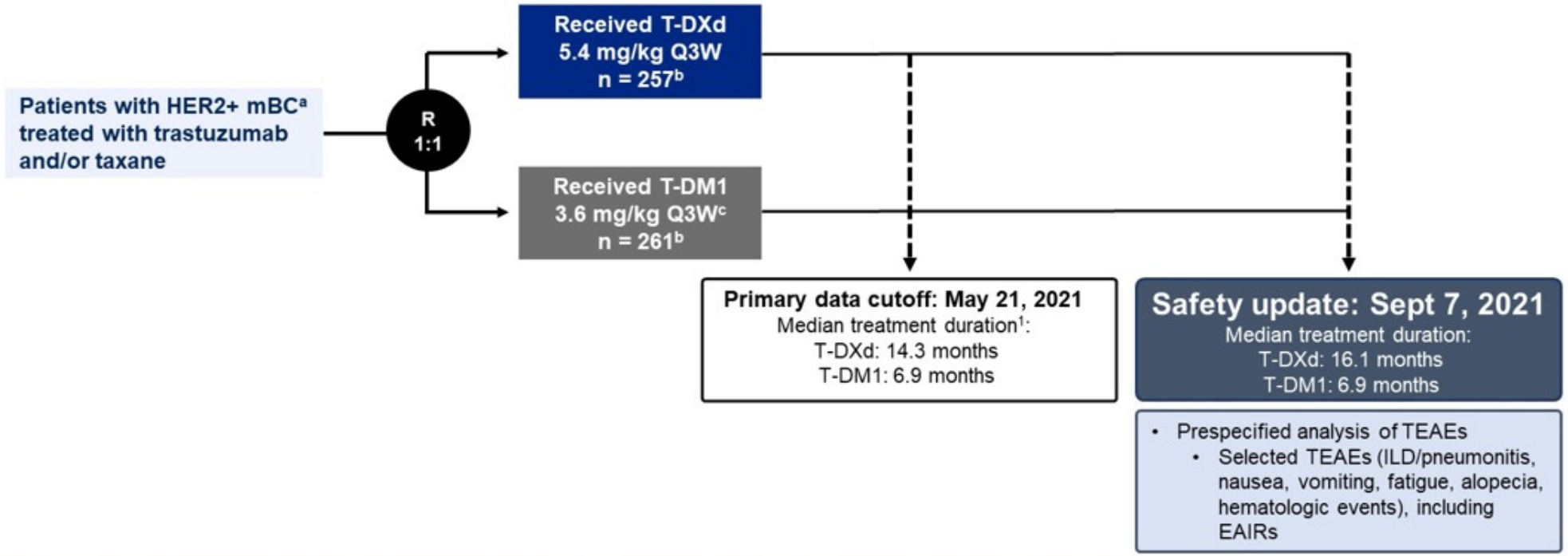
HER2 Positive Disease

	Treatment
1st Line	Trastuzumab, Pertuzumab, + Taxane
2nd Line	

HER2 Positive Disease

	Treatment
1st Line	Trastuzumab, Pertuzumab, + Taxane
2nd Line	

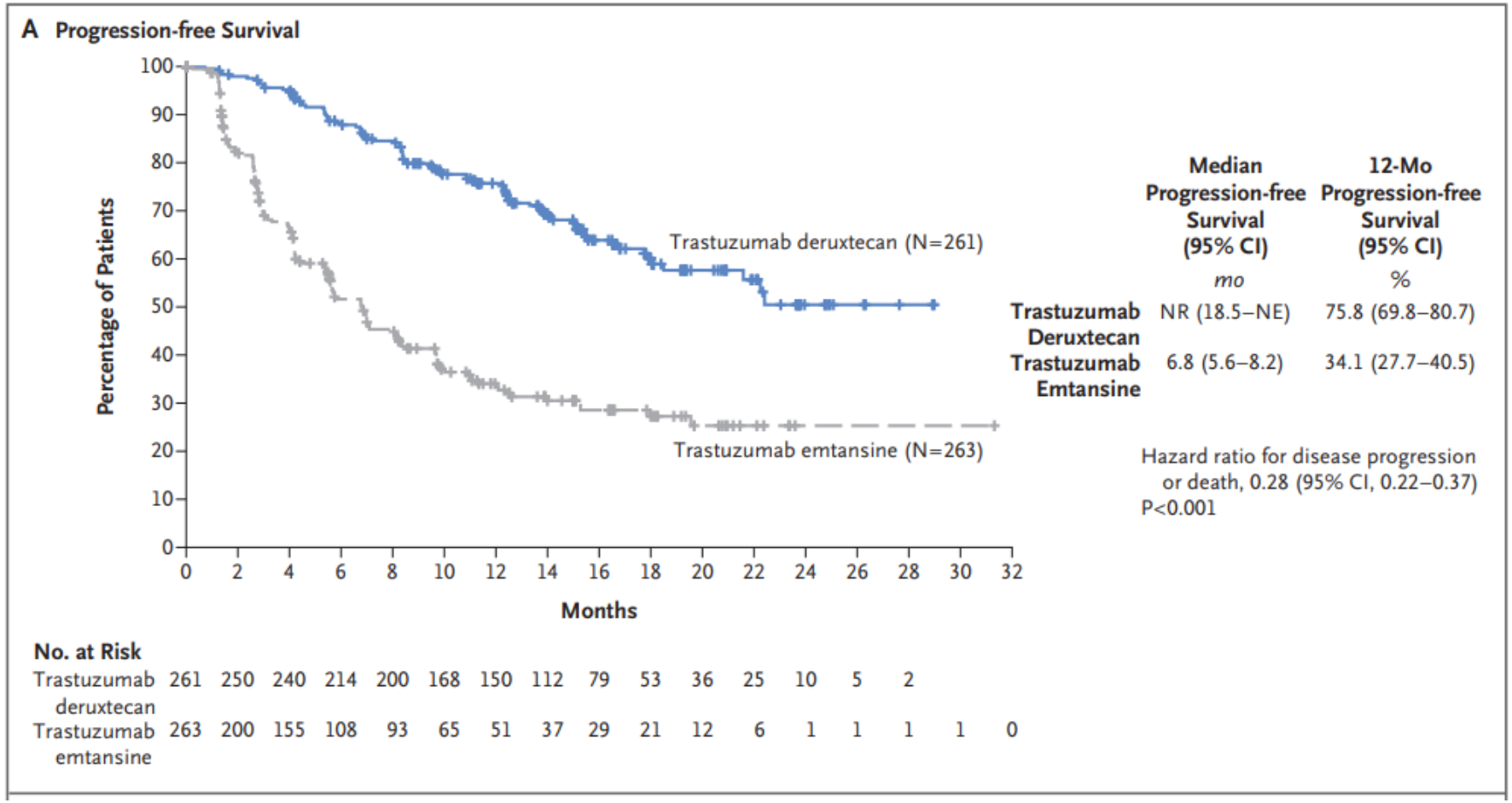
DESTINY 03 – Study Design



Objective of the study was to provide updated safety data with additional analyses in patients with HER2+ mBC treated with T-DXd or T-DM1 in DESTINY-Breast03

Cortes, New Engl J of Med 2022;386:1143-54

DESTINY03 Progression Free Survival

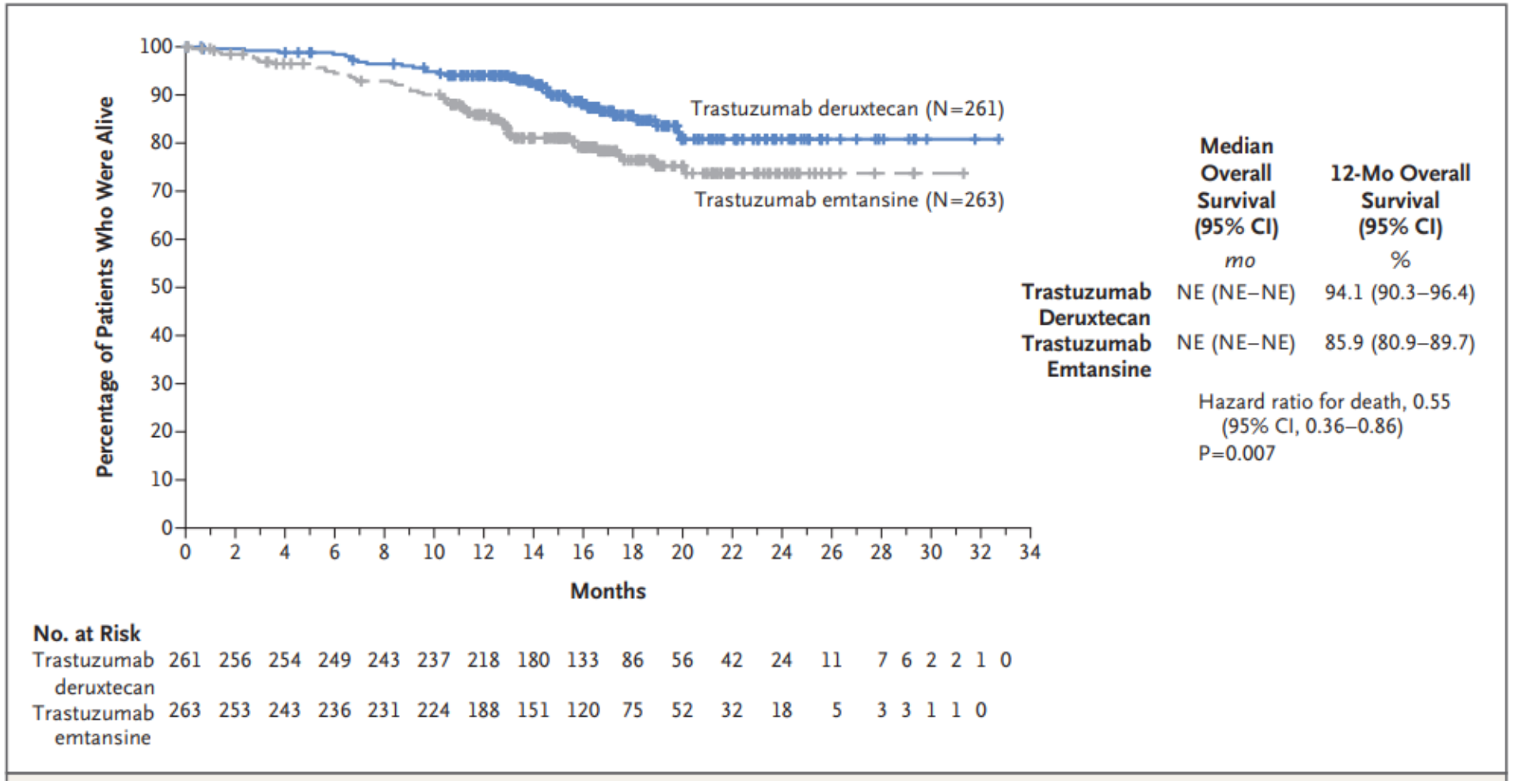


	Median Progression-free Survival (95% CI)	12-Mo Progression-free Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NR (18.5–NE)	75.8 (69.8–80.7)
Trastuzumab Emtansine	6.8 (5.6–8.2)	34.1 (27.7–40.5)

Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

Cortes, New Engl J of Med 2022;386:1143-54

Overall Survival 12 months in the IIT population



	Median Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NE (NE–NE)	94.1 (90.3–96.4)
Trastuzumab Emtansine	NE (NE–NE)	85.9 (80.9–89.7)

Hazard ratio for death, 0.55 (95% CI, 0.36–0.86)
P=0.007

Cortes, New Engl J of Med 2022;386:1143-54

Treatment of metastatic HER2+ breast cancer

	Treatment
1st Line	Trastuzumab, Pertuzumab, + Taxane
2nd Line	Trastuzumab-Deruxtecan
3rd Line	Trastuzumab, Tucatinib, Capecitabine
Additional Therapies	TDM1
	Neratinib + Capecitabine
	Trastuzumab + Lapatinib
	Margituximab + Chemotherapy
	Trastuzumab + Chemotherapy

With 8 year follow-up on CLEOPATRA, 37% of patients are alive.

Brain metastases
Options for therapy in HER2 positive disease

Trial	Agent tested
LANDSCAPE	Lapatinib
NALA	Neratinib
PATRICIA	HD trastuzumab and pertuzumab
HER2CLIMB	Tucatinib
DESTINY Breast01	Trastuzumab-deruxtecan

Triple Negative Breast Cancer

- Check PDL1 status
- NGS
- Germline testing

	Therapy
1st Line	Taxane + Pembrolizumab if PDL1+ or high TMB
2nd Line	Sacituzumab
3+	Other chemotherapy, Investigational agents

Hormone Receptor Positive Breast Cancer

CDK4/6 inhibitor treatment for patients with hormone receptor-positive, HER2-negative, advanced or metastatic breast cancer: a US Food and Drug Administration pooled analysis

Jennifer J Gao, Joyce Cheng*, Erik Bloomquist, Jacquelyn Sanchez, Suparna B Wedam, Harpreet Singh, Laleh Amiri-Kordestani, Amna Ibrahim, Rajeshwari Sridhara, Kirsten B Goldberg, Marc R Theoret, Paul G Kluetz, Gideon M Blumenthal, Richard Pazdur, Julia A Beaver†, Tatiana M Prowell†*

Lancet Oncol 2020;21:250-60

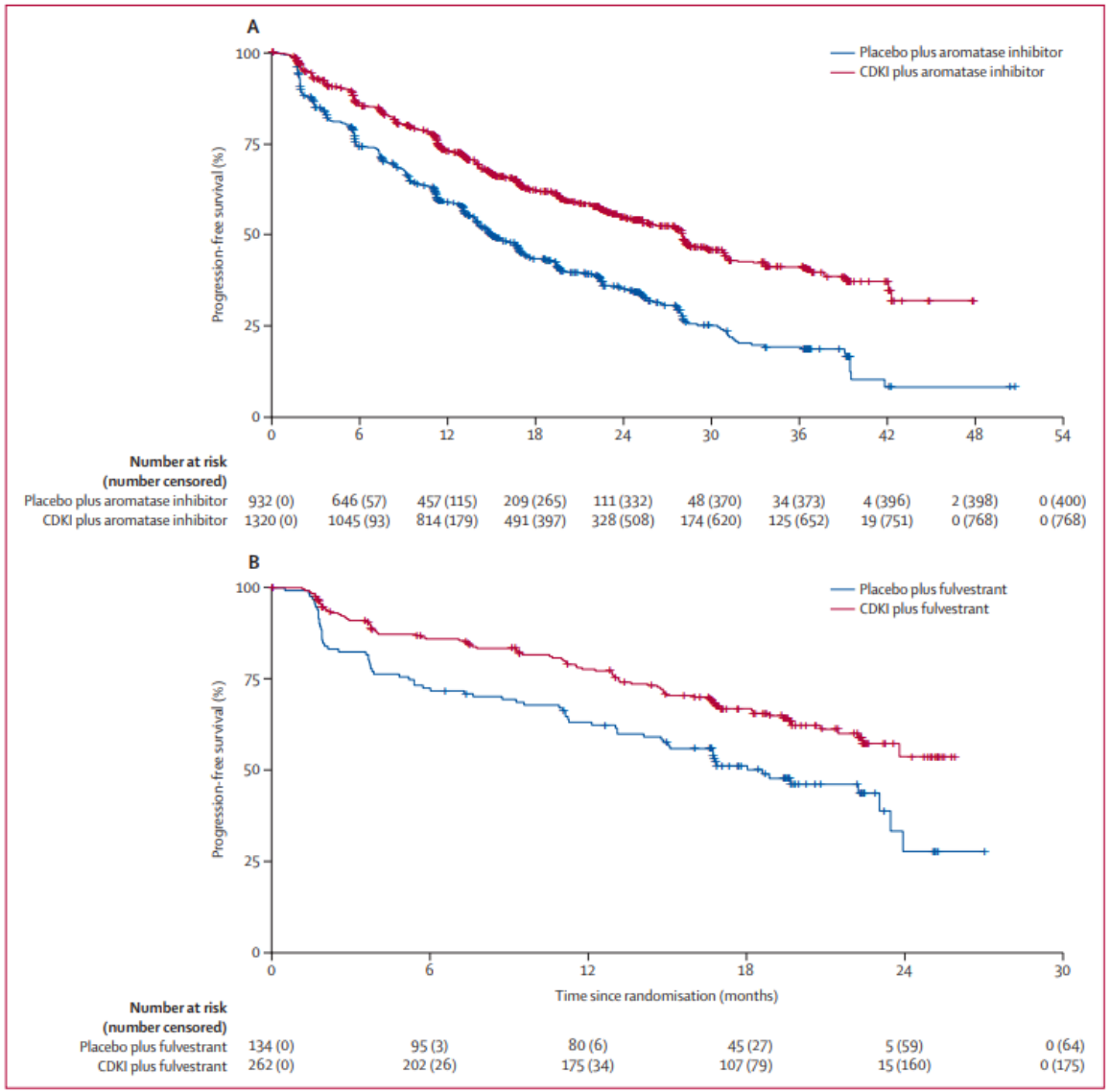
FDA pooled analysis of CDK4/6i

	CDKI agent	Hormonal therapy	Randomly assigned patients, n	Patient population in the locally advanced or metastatic setting	Primary endpoint	Secondary endpoints
MONARCH 2[6]	Abemaciclib	Fulvestrant	713	First-line, second-line, or later, postmenopausal women	Local investigator-assessed progression-free survival	Overall survival; objective response
MONARCH 3[7]	Abemaciclib	Letrozole or anastrozole	493	First-line, postmenopausal women	Local investigator-assessed progression-free survival	Overall survival; objective response
PALOMA 2[3]	Palbociclib	Letrozole	666	First-line, postmenopausal women	Local investigator-assessed progression-free survival	Overall survival; objective response
PALOMA 3[4]	Palbociclib	Fulvestrant	521	Second-line or later, postmenopausal women*	Local investigator-assessed progression-free survival	Overall survival; objective response
MONALEESA 2[8]	Ribociclib	Letrozole	668	First-line, postmenopausal women	Local investigator-assessed progression-free survival	Overall survival; objective response
MONALEESA 3[10]	Ribociclib	Fulvestrant	726	First-line, men and postmenopausal women	Local investigator-assessed progression-free survival	Overall survival; objective response
MONALEESA 7[9]†	Ribociclib	Letrozole or anastrozole†	672 (495 in aromatase inhibitor subgroup)‡	First-line or second-line, premenopausal and perimenopausal women	Local investigator-assessed progression-free survival	Overall survival; objective response

CDKI=cyclin-dependent kinase 4/6 inhibitor. *Premenopausal and perimenopausal women were eligible if they also received goserelin. †All patients on MONALEESA 7 received goserelin. ‡In this trial, 177 patients received tamoxifen as their endocrine therapy; ribociclib is not indicated in combination with tamoxifen.

Lancet Oncol 2020;21:250-60

FDA Kaplan Meier pooled analysis of PFS with CDK4/6i



Aromatase Inhibitors

Median PFS 28.0 mos
vs 14.9 mos

Fulvestrant

Median PFS 18.6 mos
vs Not Estimable

Lancet Oncol 2020;21:250-60

FDA pooled analysis of CDK4/6i
What about OS?

	CDKI agent	Hormonal therapy	Randomly assigned patients, n	Patient population in the locally advanced or metastatic setting	Primary endpoint	Secondary endpoints
MONARCH 2[6]	Abemaciclib	Fulvestrant	713	First-line, second-line, or later, postmenopausal women	Local investigator-assessed progression-free survival	Overall survival; objective response
MONARCH 3[7]	Abemaciclib	Letrozole or anastrozole	493	First-line, postmenopausal women	Local investigator-assessed progression-free survival	Overall survival; objective response
PALOMA 2[3]	Palbociclib	Letrozole	666	First-line, postmenopausal women	Local investigator-assessed progression-free survival	Overall survival; objective response
PALOMA 3[4]	Palbociclib	Fulvestrant	521	Second-line or later, postmenopausal women*	Local investigator-assessed progression-free survival	Overall survival; objective response
MONALEESA 2[8]	Ribociclib	Letrozole	668	First-line, postmenopausal women	Local investigator-assessed progression-free survival	Overall survival; objective response
MONALEESA 3[10]	Ribociclib	Fulvestrant	726	First-line, men and postmenopausal women	Local investigator-assessed progression-free survival	Overall survival; objective response
MONALEESA 7[9]†	Ribociclib	Letrozole or anastrozole†	672 (495 in aromatase inhibitor subgroup)‡	First-line or second-line, premenopausal and perimenopausal women	Local investigator-assessed progression-free survival	Overall survival; objective response

CDKI=cyclin-dependent kinase 4/6 inhibitor. *Premenopausal and perimenopausal women were eligible if they also received goserelin. †All patients on MONALEESA 7 received goserelin. ‡In this trial, 177 patients received tamoxifen as their endocrine therapy; ribociclib is not indicated in combination with tamoxifen.

Median 47.7 mos OS 46.7 vs 37.3 mos[1]

Median 39 mos PFS advantage [2]

?

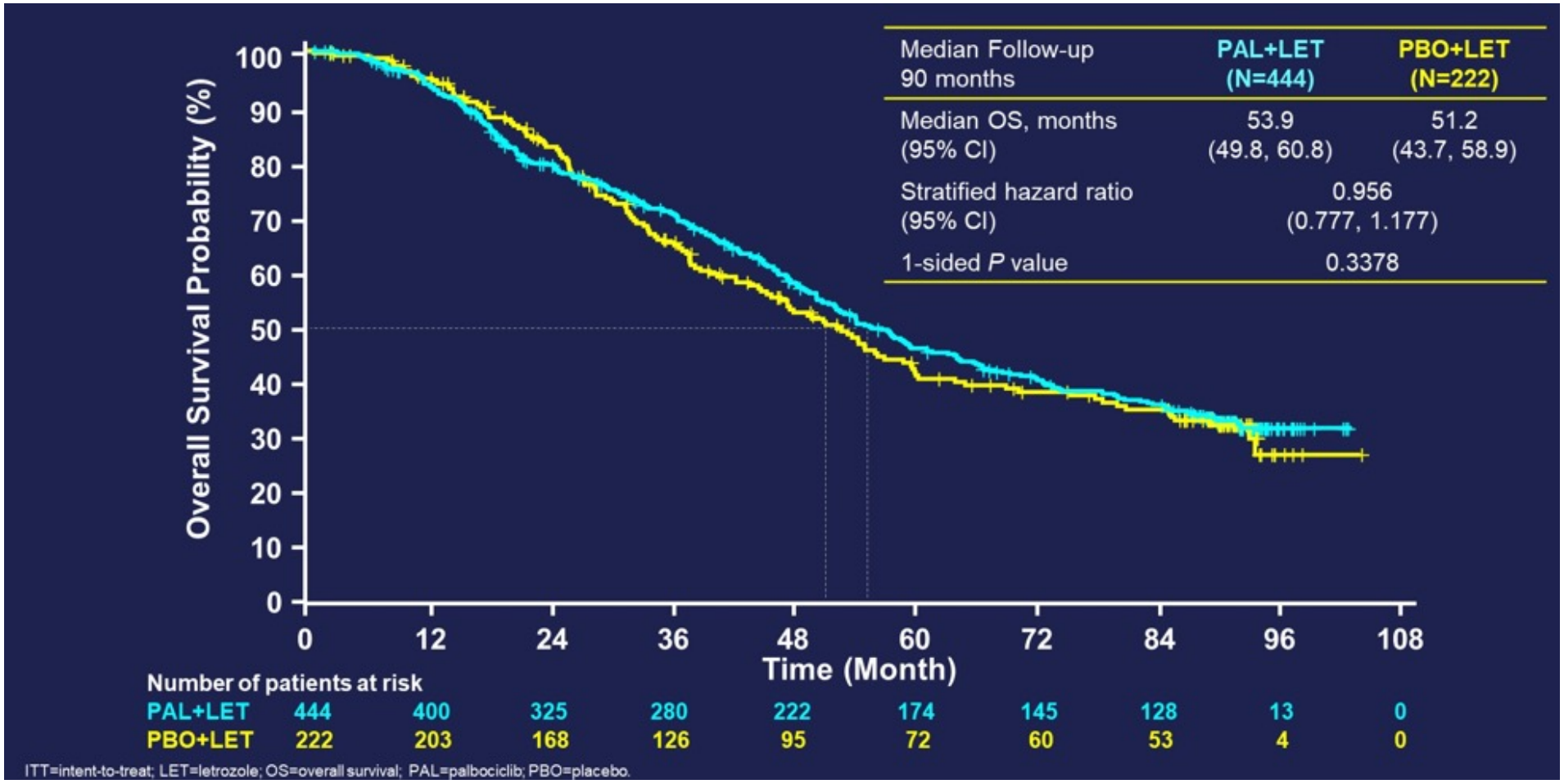
Median 80 mos OS 63.9 vs 51.4 mos[3]

Median 56.3 mos OS 53.7 vs 41.4 mos[4]

Median 53.4 mos OS 58.7 vs 48 mos[5]

[1]Sledge JAMA Oncol 2020;6:116-124
[2]Johnston, NPJ Breast Cancer 7 no1(20221) 1-5 [3]Hortobayhi, ESMO 2021
[4]Slamon, Ann Oncol 2021;32:1015-1024
[5]Lu CI Cancer Res OF1-9

PALOMA 2 OS – ITT



Finn, ASCO 2022

Hormone Receptor Positive Metastatic Disease

	Postmenopausal	Premenopausal
1st Line therapy	AI or Fulvestrant + CDK4/6i[b]	LHRH agonist + Tamoxifen or AI + CDK4/6i[b]
2nd Line therapy	Fulvestrant[d] + CDK 4/6i OR Alpelisib + Endocrine therapy OR Everolimus + Endocrine therapy	LHRH agonist + Fulvestrant[d] or AI + CDK4/6i Alpelisib + Endocrine therapy OR Everolimus + Endocrine therapy
Other options	Megestrol acetate, Estradiol, Abemaciclib	

[b] In phase 3 randomized controlled trials, ribociclib + endocrine therapy has shown overall survival benefit in the first-line setting

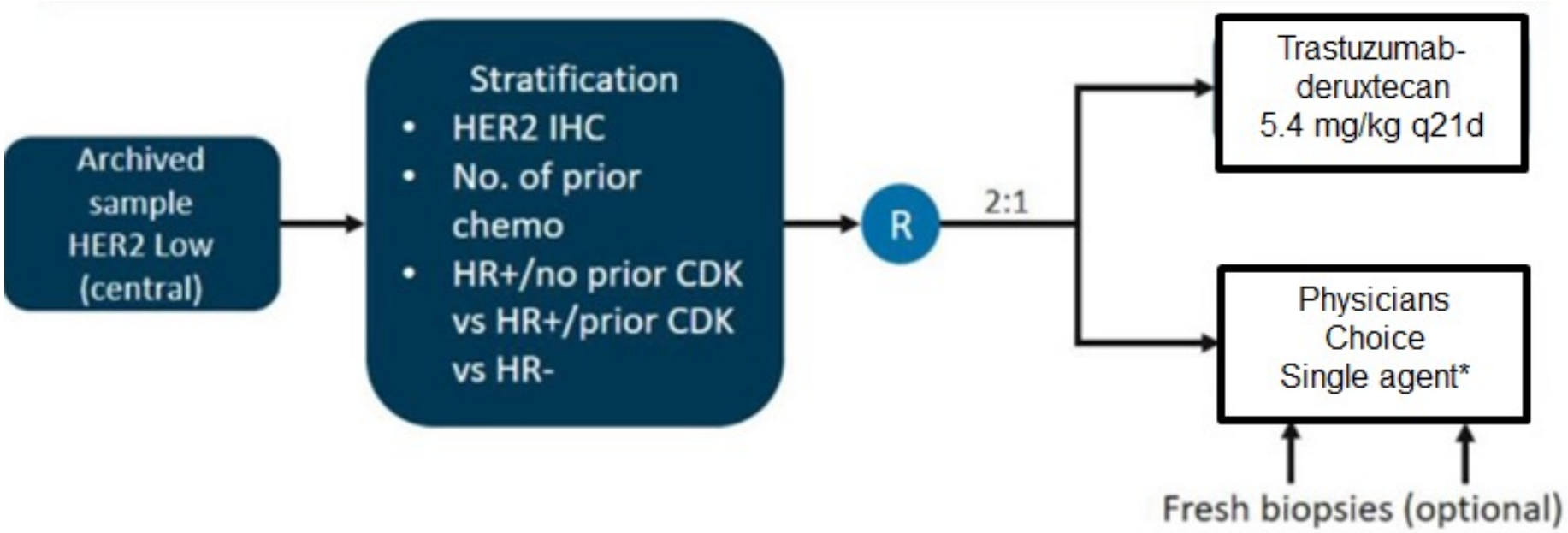
[d] In phase 3 randomized controlled trials, fulvestrant in combination with a CDK4/6 inhibitor (abemaciclib, palbociclib, and ribociclib) has shown overall survival benefit in the second-line setting

NCCN Guidelines 6.2022

With development of Endocrine Resistance →Chemotherapy

- Anthracyclines
  - Doxorubicin
  - Liposomal Doxorubicin
- Taxanes
  - Paclitaxel
- Antimetabolites
  - Capecitabine
  - Gemcitabine
- Microtubule Inhibitors
  - Vinorelbine
  - Eribulin
- PARP inhibitors
  - Olaparib
  - Talazoparib

DESTINY 04 - Study Design

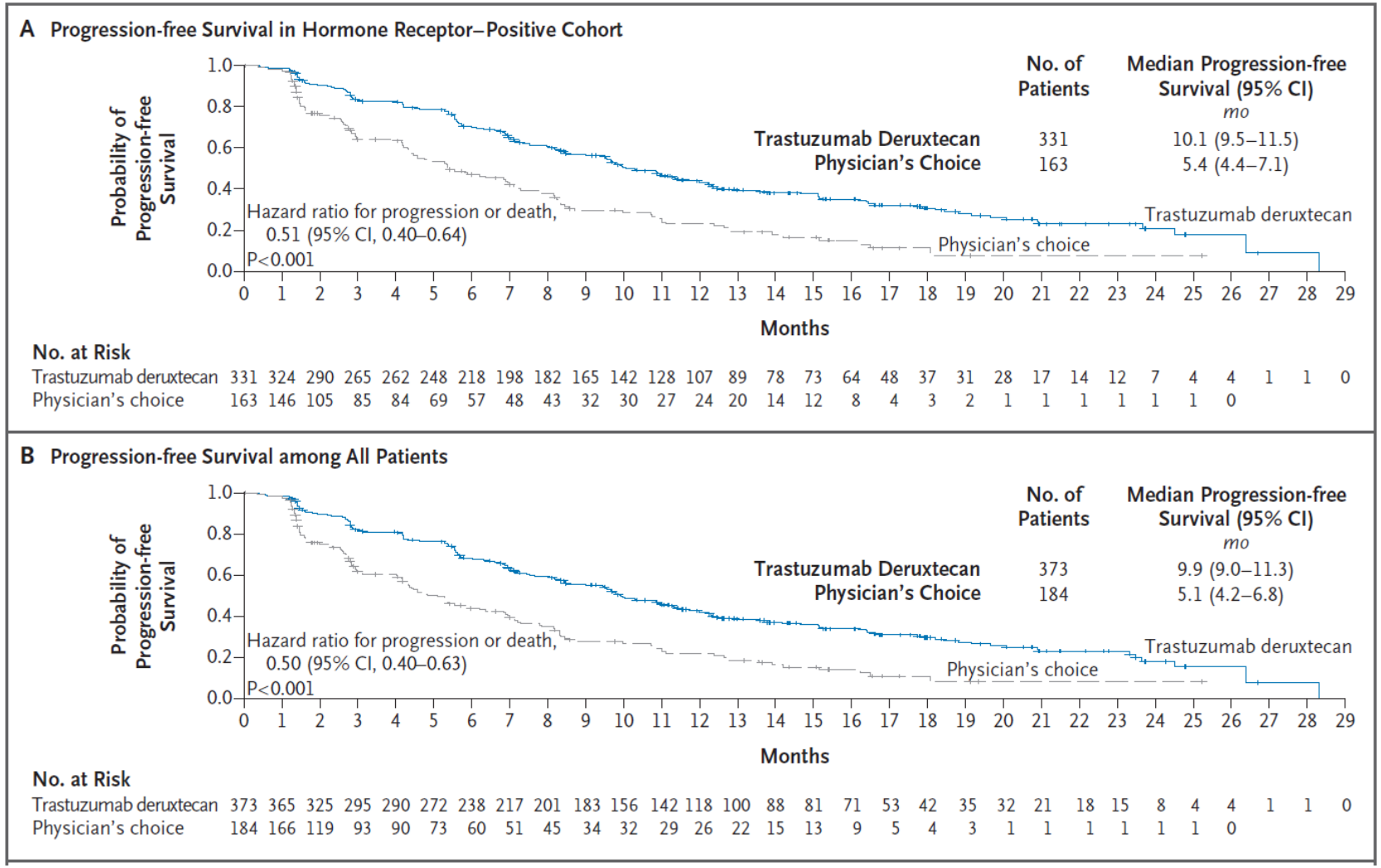


* Physicians Choice: Capecitabine, Eribulin, Gemcitabine, Paclitaxel, nab-Paclitaxel

Endpoints: Primary Efficacy PFS in HR+; Final Efficacy PFS all pts

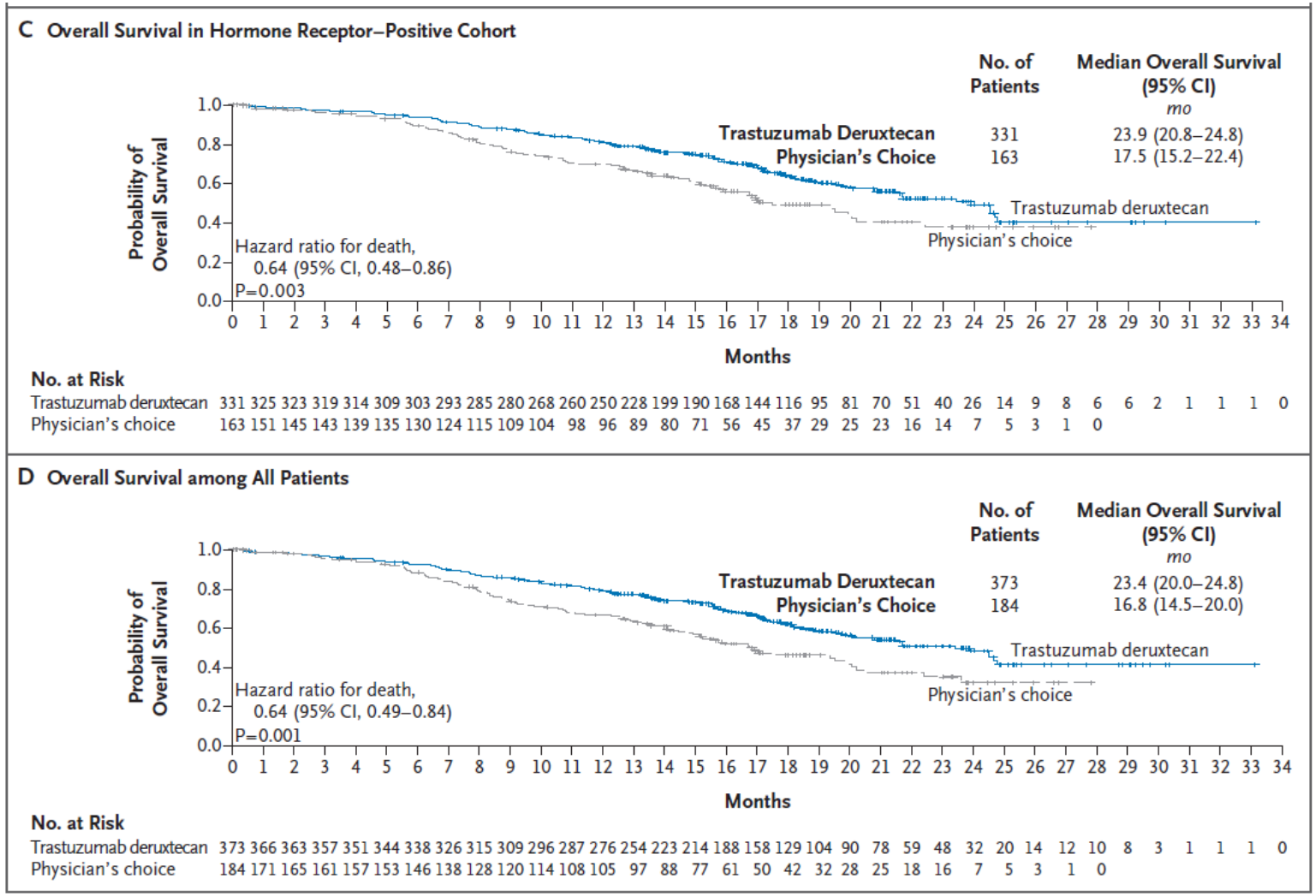
Modi, NEJM 2022; June 5

DESTINY-04 – Progression Free Survival Results



Modi, NEJM 2022; June 5

DESTINY-04 – Overall Survival Results



23.9 vs 17.5 mos

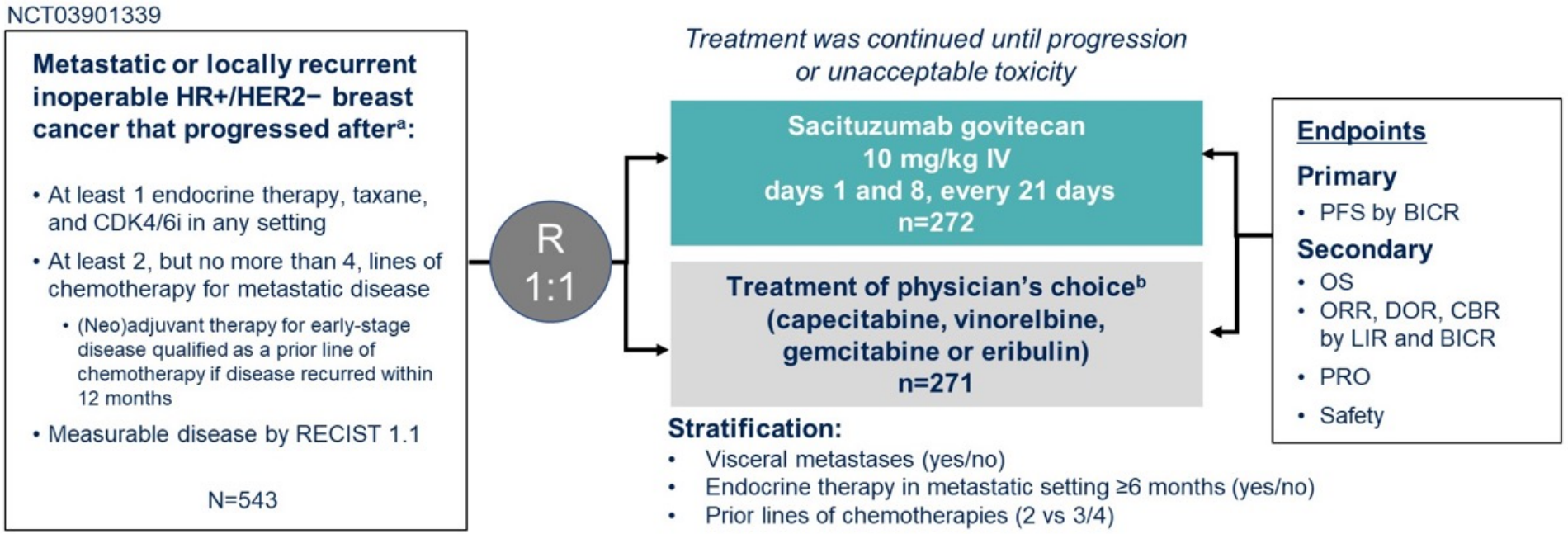
23.4 vs 16.8 mos

Modi, NEJM 2022; June 5

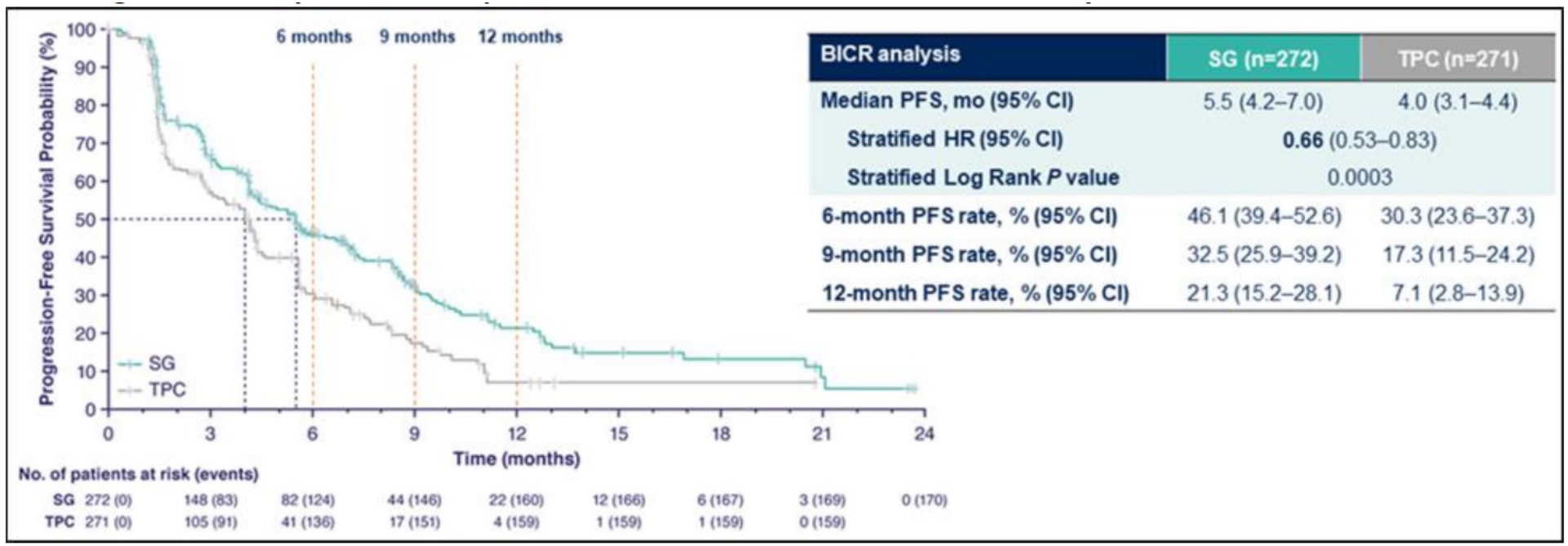
HER2 Definitions

HER2 “positive”	IHC 3+ or FISH Amplified
HER2 “low”	IHC 2+ and FISH Non-amplified
	IHC 1+ and FISH Non-amplified
HER2 negative	IHC 0 and FISH Non-amplified

TROPiCS-02 – Design



TROPiCS-02 – PFS by Independent Review



BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2–28.1)	7.1 (2.8–13.9)

With development of Endocrine Resistance →Chemotherapy

- Anthracyclines
  - Doxorubicin
  - Liposomal Doxorubicin
- Taxanes
  - Paclitaxel
- Antimetabolites
  - Capecitabine
  - Gemcitabine
- Microtubule Inhibitors
  - Vinorelbine
  - Eribulin
- PARP inhibitors
  - Olaparib
  - Talazoparib
- **Antibody Drug Conjugates**
  - **Trastuzumab-deruxtecan (HER2 1+ or 2+)**
  - **Sacituzumab HR+/HER2-**