SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
IRCCS Istituto di ricovero e cura a carattere scientifico

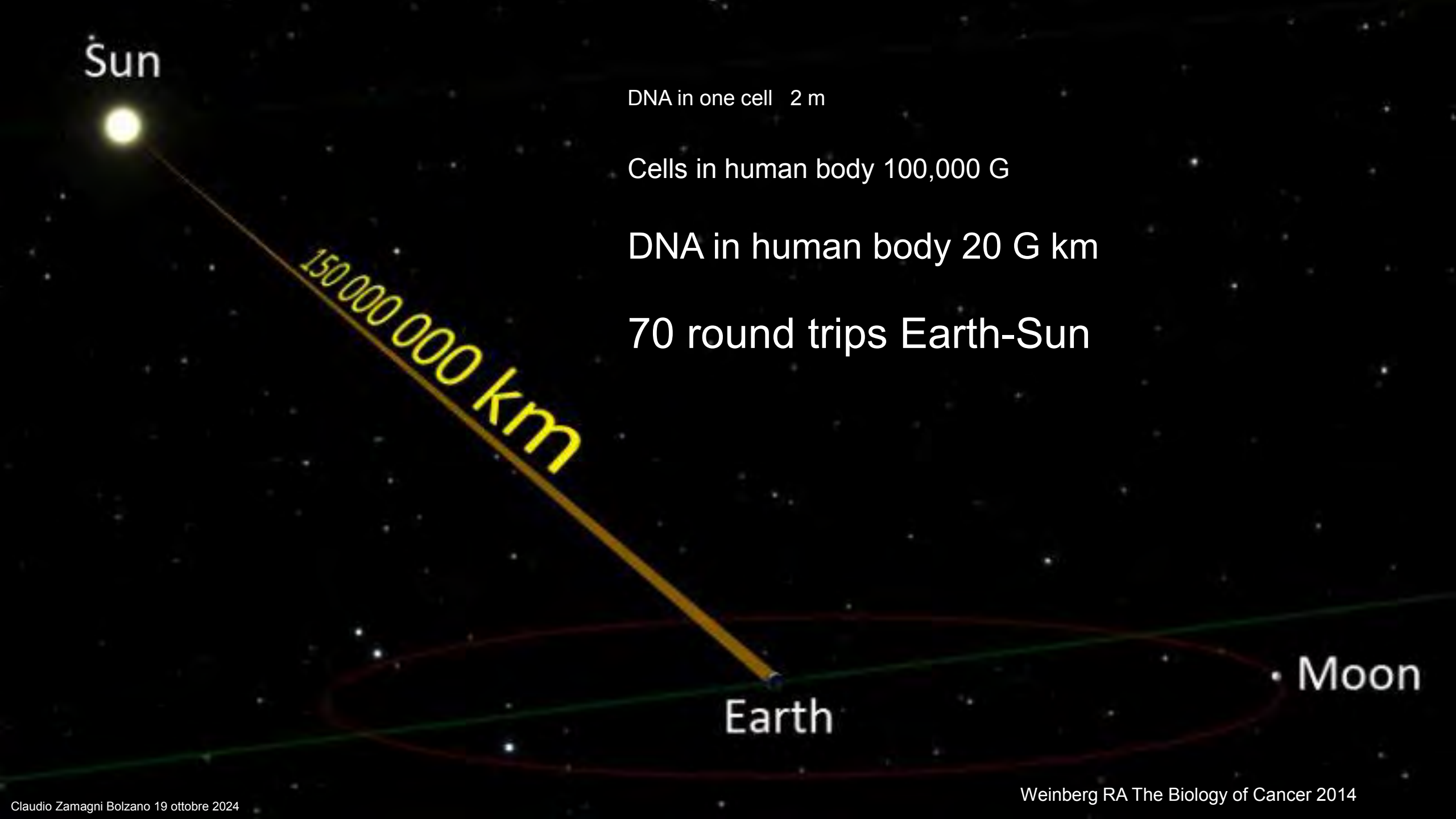
POLICLINICO DI SANT'ORSOLA

mamazones
PROJEKT DIPLOMPATIENTIN

17ª Conferenza sul tumore al seno DIPLOMPATIENTIN®
„Paziente diplomata" - un seminario per donne con e senza tumore al seno

Il ruolo degli inibitori CDK 4/6 nella terapia del tumore al seno in fase precoce e metastatica

Claudio Zamagni
Direttore Oncologia Medica senologica e ginecologica & Breast Unit
IRCCS Azienda Ospedaliero-universitaria di Bologna
Ospedale di Sant'Orsola



DNA in one cell 2 m

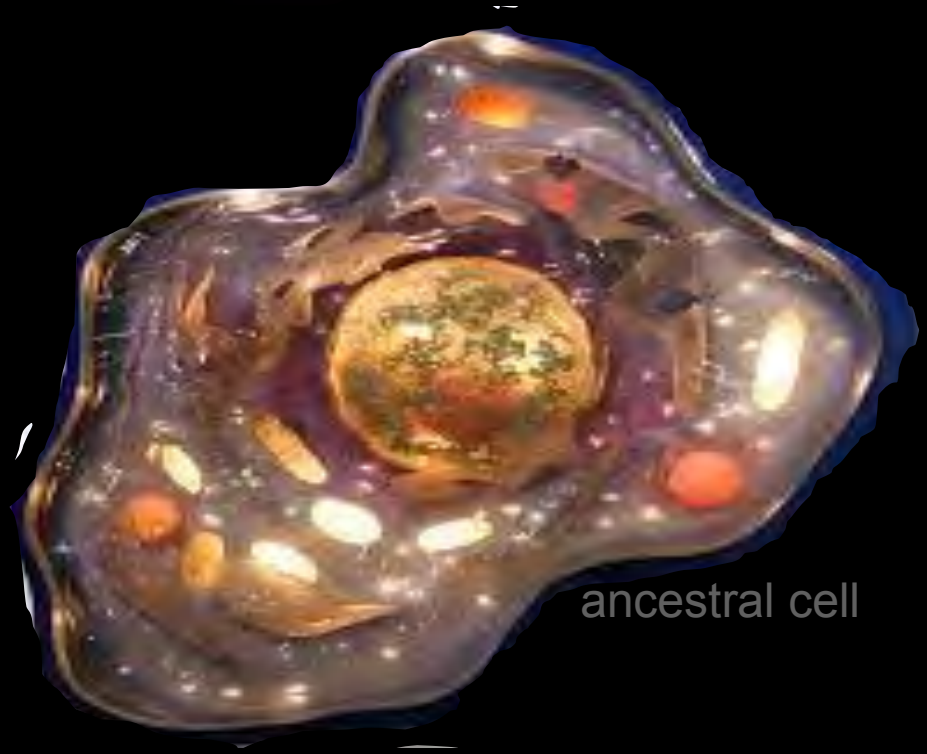
Cells in human body 100,000 G

DNA in human body 20 G km

70 round trips Earth-Sun

Weinberg RA The Biology of Cancer 2014

3 billion years ago



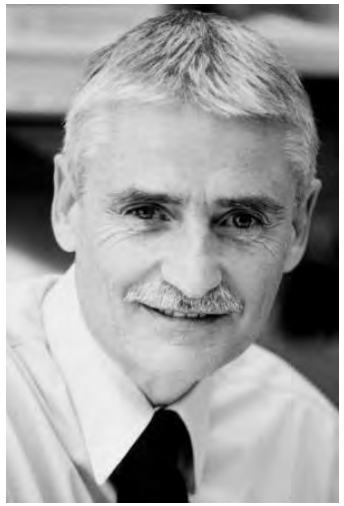
ancestral cell

unbroken series of cell divisions since then.

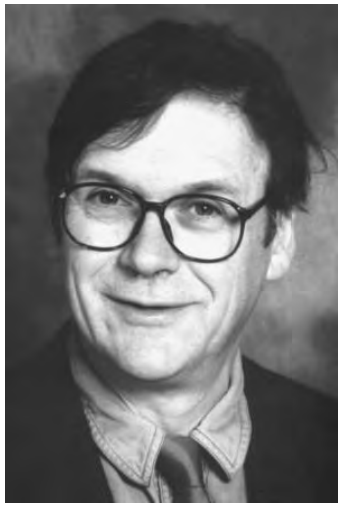
Every second millions of cells divide in our body

Zetterberg A. Presentation Speech for the 2001 Nobel Prize

The Nobel Prize in Physiology or Medicine 2001



Leland Hartwell



Tim Hunt

Paul Nurse

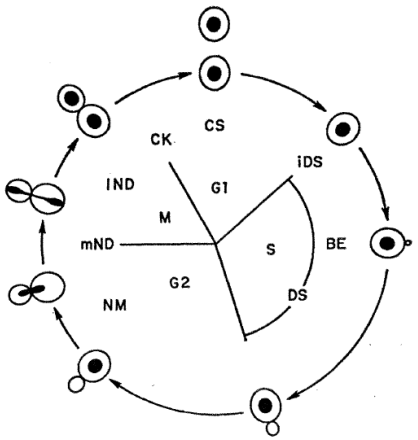
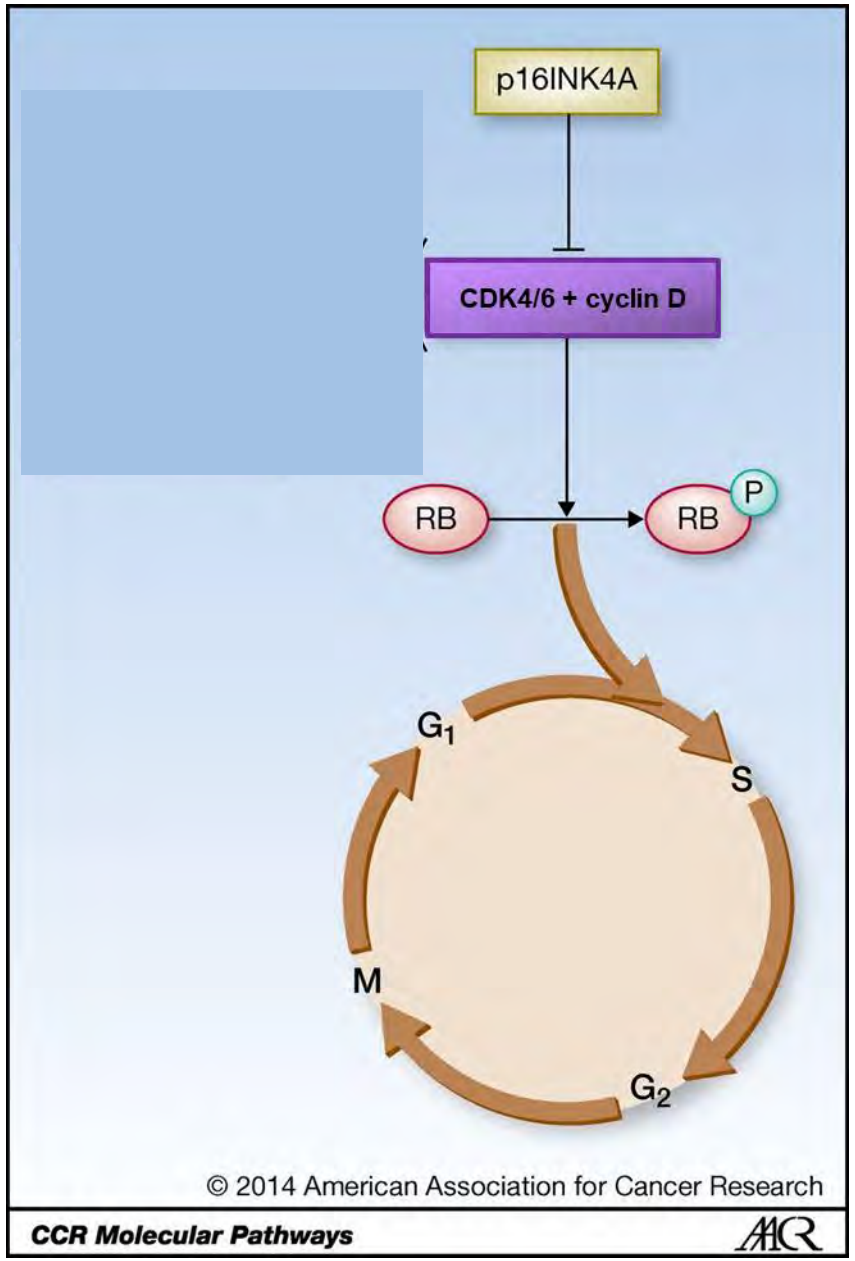
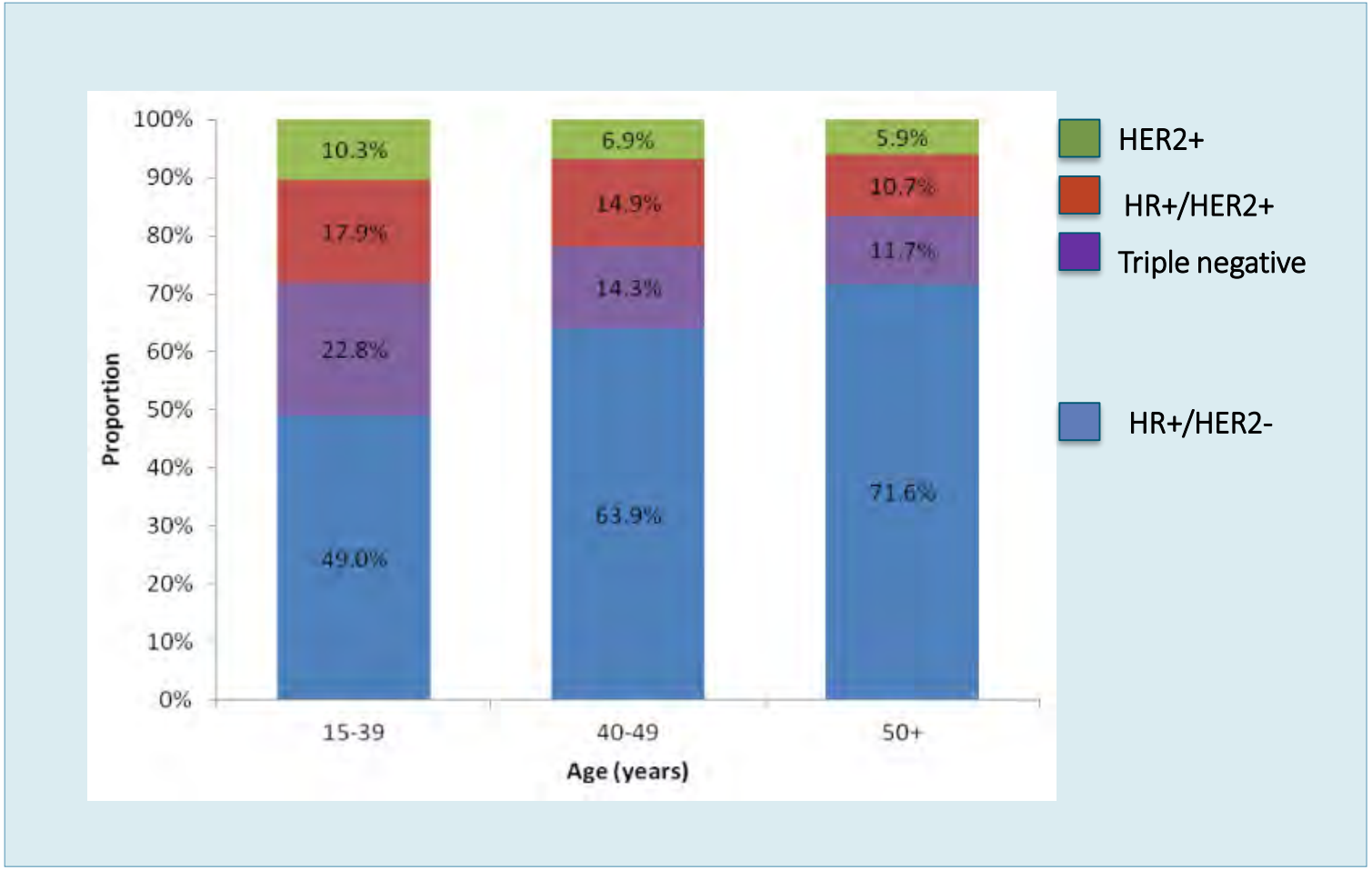


Fig. 1. The sequence of events in the cell division cycle of yeast: *iDS*, initiation of DNA synthesis; *BE*, bud emergence; *DS*, DNA synthesis; *NM*, nuclear migration; *mND*, medical nuclear division; *lND*, late nuclear division; *CK*, cytokinesis; *CS*, cell separation. Other abbreviations: *G1*, time interval between previous cytokinesis and initiation of DNA synthesis; *S*, period of DNA synthesis; *G2*, time between DNA synthesis and onset of mitosis; and *M*, the period of mitosis.

SCIENCE, VOL. 183, 1974

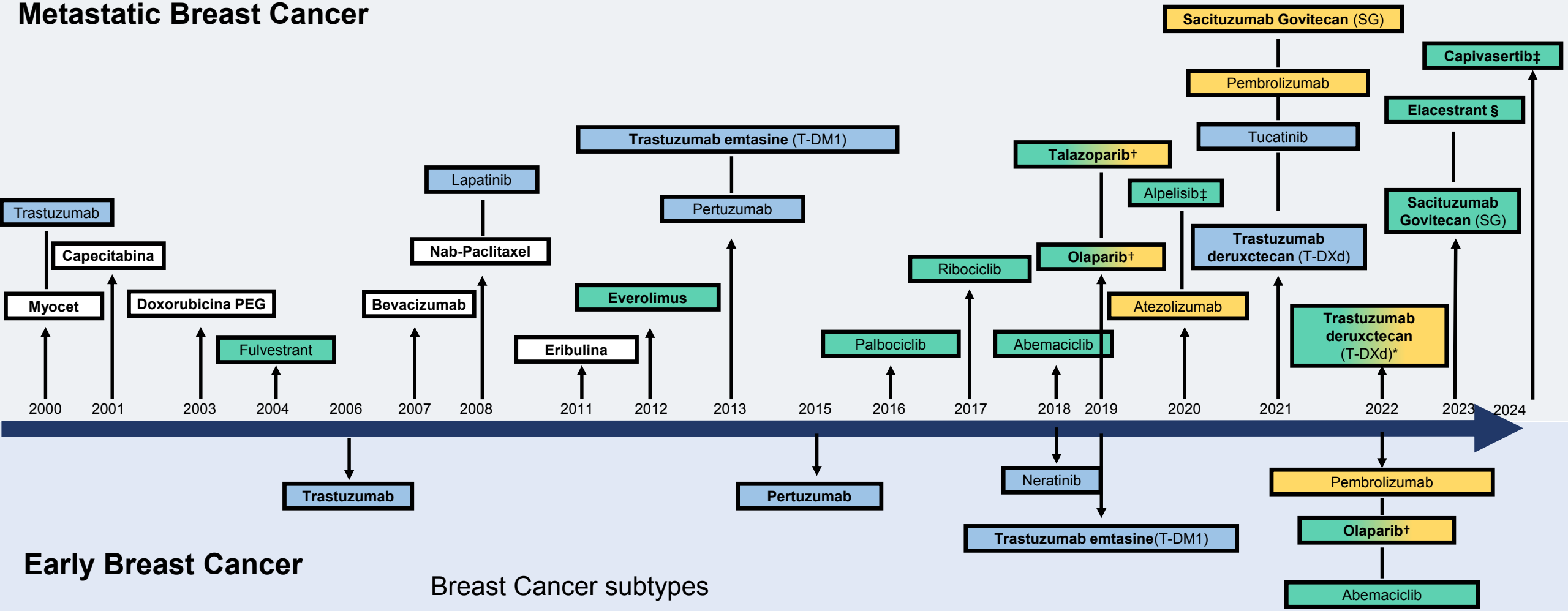


Hormone receptor positive is the most common BC subtype



Keegan et al, BCR, 2012

Metastatic Breast Cancer



Early Breast Cancer

Breast Cancer subtypes

- All BC
- HR+/HER2-
- HER2+
- **TNBC**

† gBRCA1/2 mut

§ ESR1mut

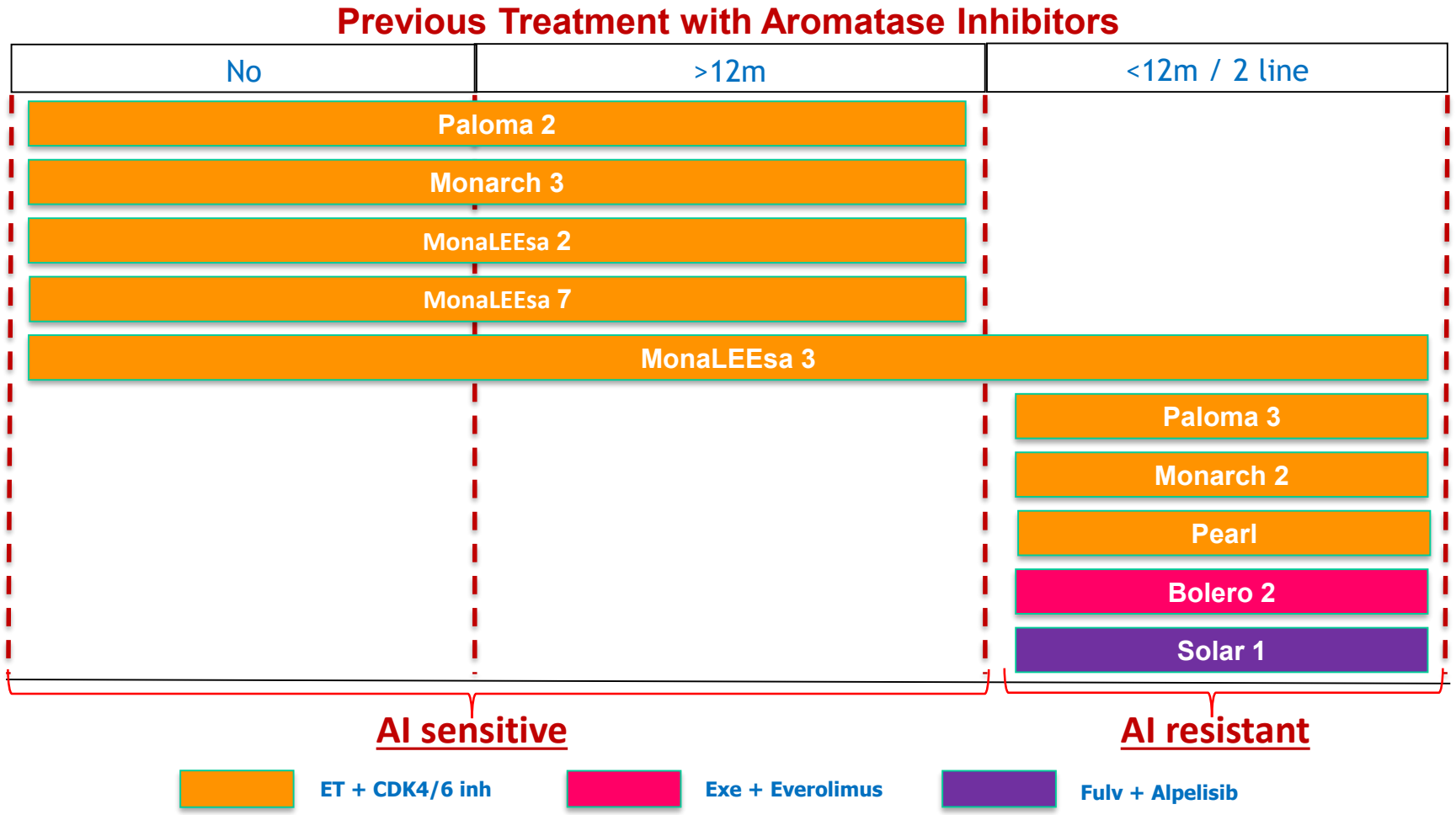
* HER-2 low

‡ PIK3CA/PTEN/AKT1 alterations

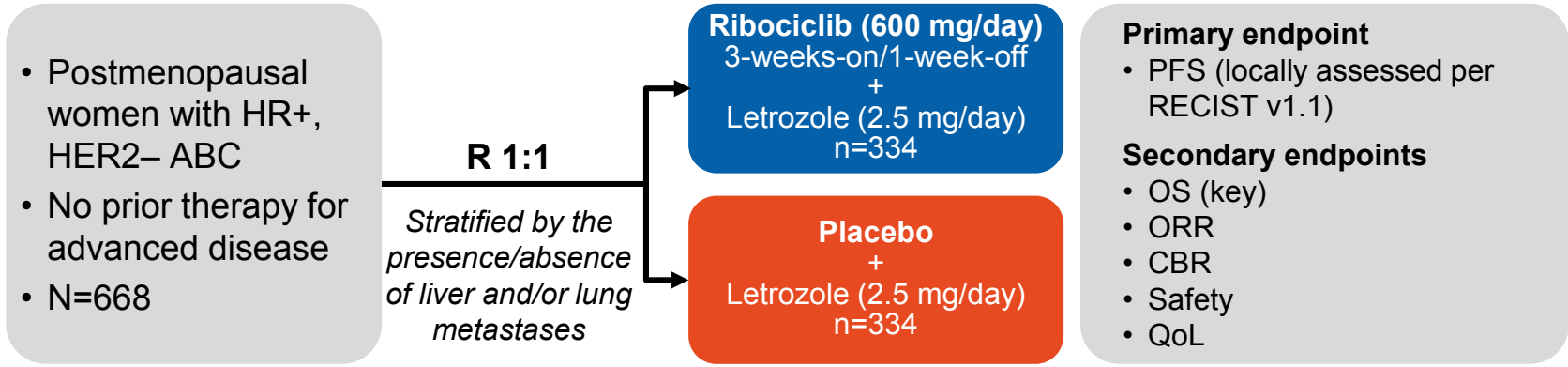
EMA APPROVED

Courtesy G. Bianchini

Overview of Modern RCT for Luminal MBC



MONALEESA-2: Phase III ribociclib + letrozole in HR+, HER2– ABC[1,2]

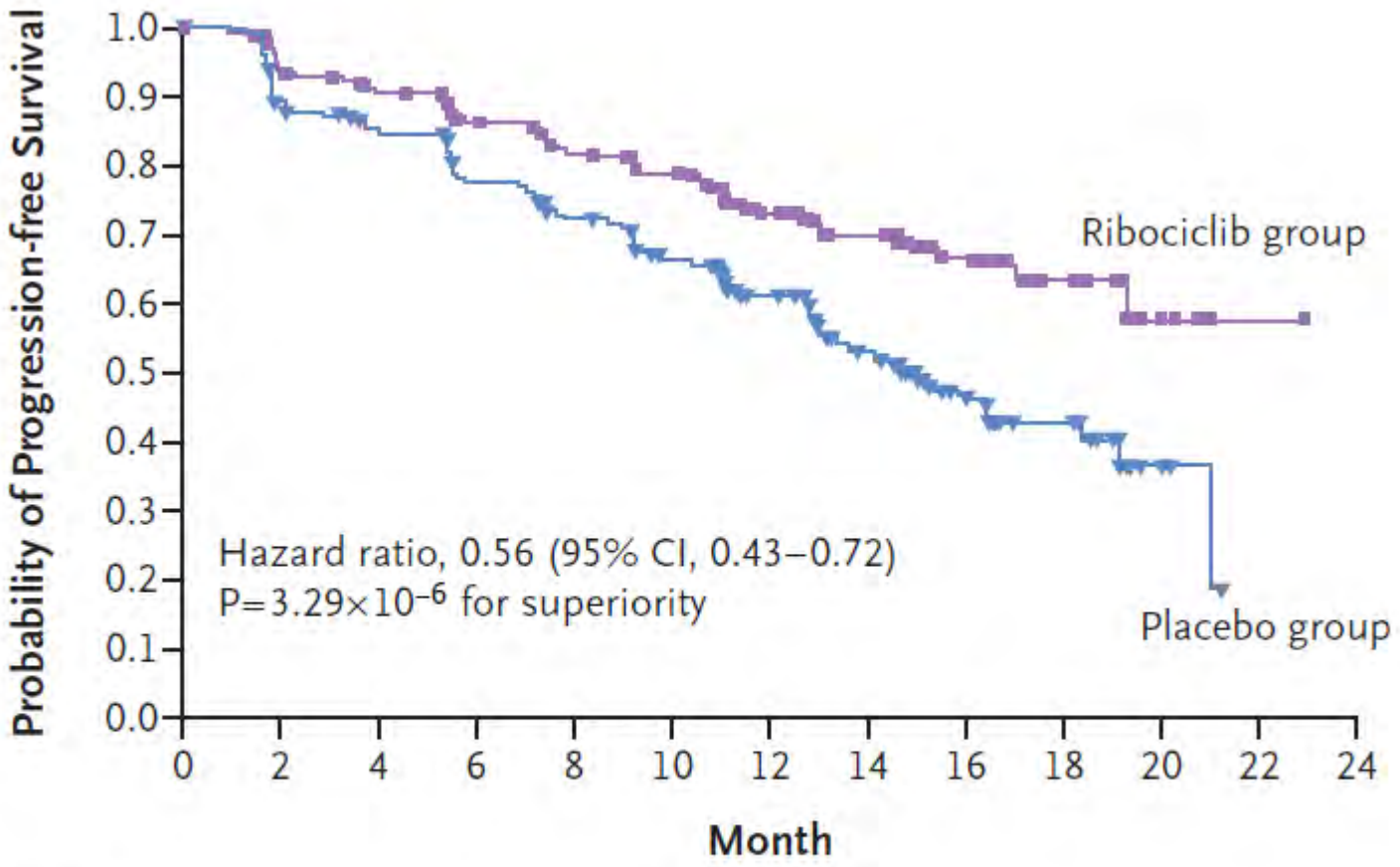


- Tumor assessments were performed every 8 weeks for the first 18 months, then every 12 weeks thereafter
- Final analysis planned after 302 PFS events
  - 93.5% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%
- Interim analysis planned after ~70% PFS events
  - Two-look Haybittle–Peto stopping criteria: hazard ratio ≤0.56 and p<0.0000129
- At the interim analysis data cut-off date (Jan 29, 2016), 243 PFS events had occurred (80% information fraction)

ABC, advanced breast cancer; CBR, clinical benefit rate; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumors.

1. Hortobagyi GN *et al. N Engl J Med* 2016;375:1738–1748;
2. Hortobagyi GN *et al. Ann Oncol* 2016;27(Suppl 6): abstr LBA 3552 (oral).

MONALEESA-2 Primary Endpoint Progression-free Survival



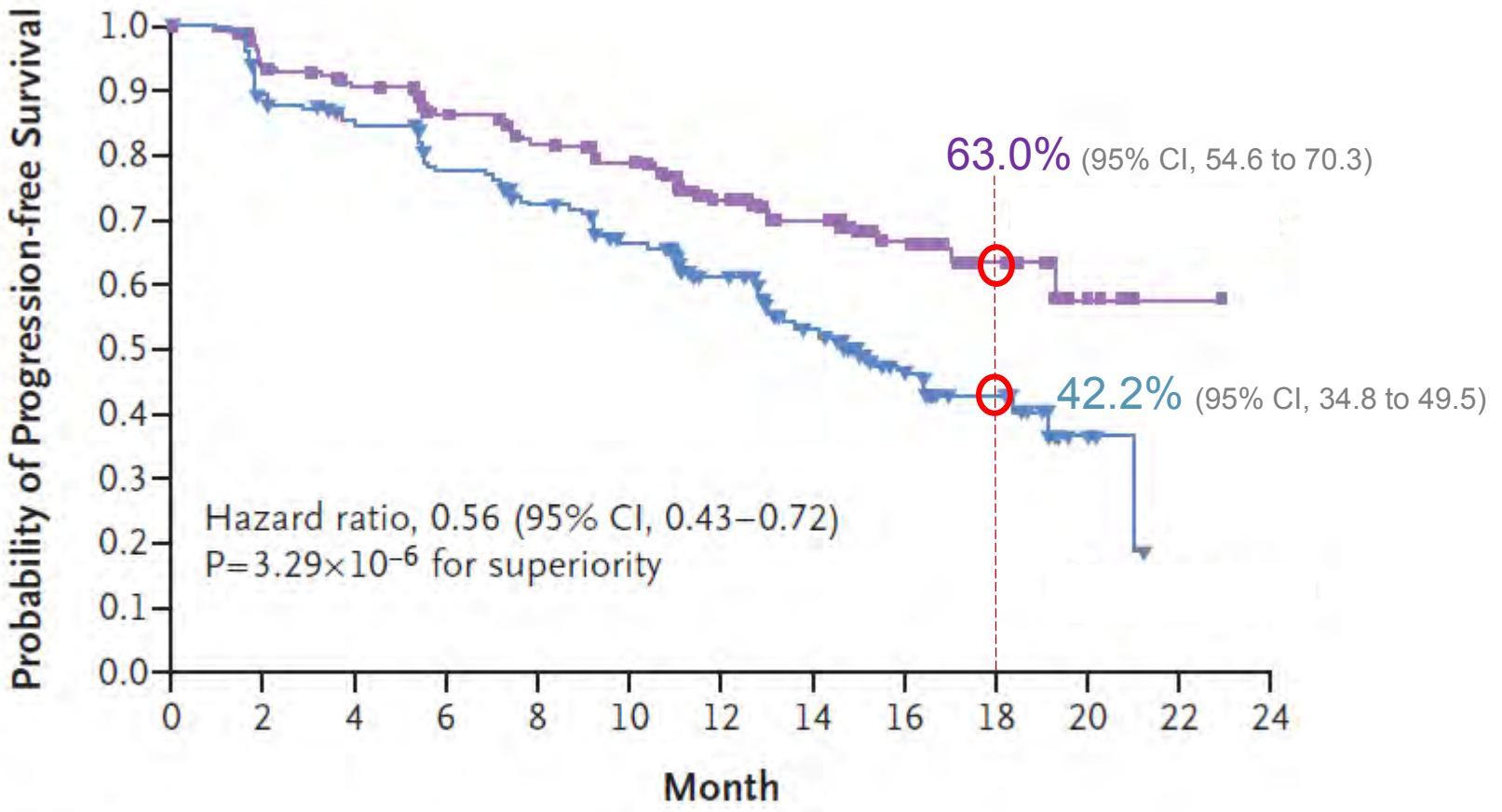
No. at Risk

Ribociclib	334	294	277	257	240	226	164	119	68	20	6	1	0
Placebo	334	279	264	237	217	192	143	88	44	23	5	0	0

The median duration of progression-free survival was not reached in the ribociclib group and was 14.7 months in the placebo group

Hortobagyi G et al N Engl J Med 2016

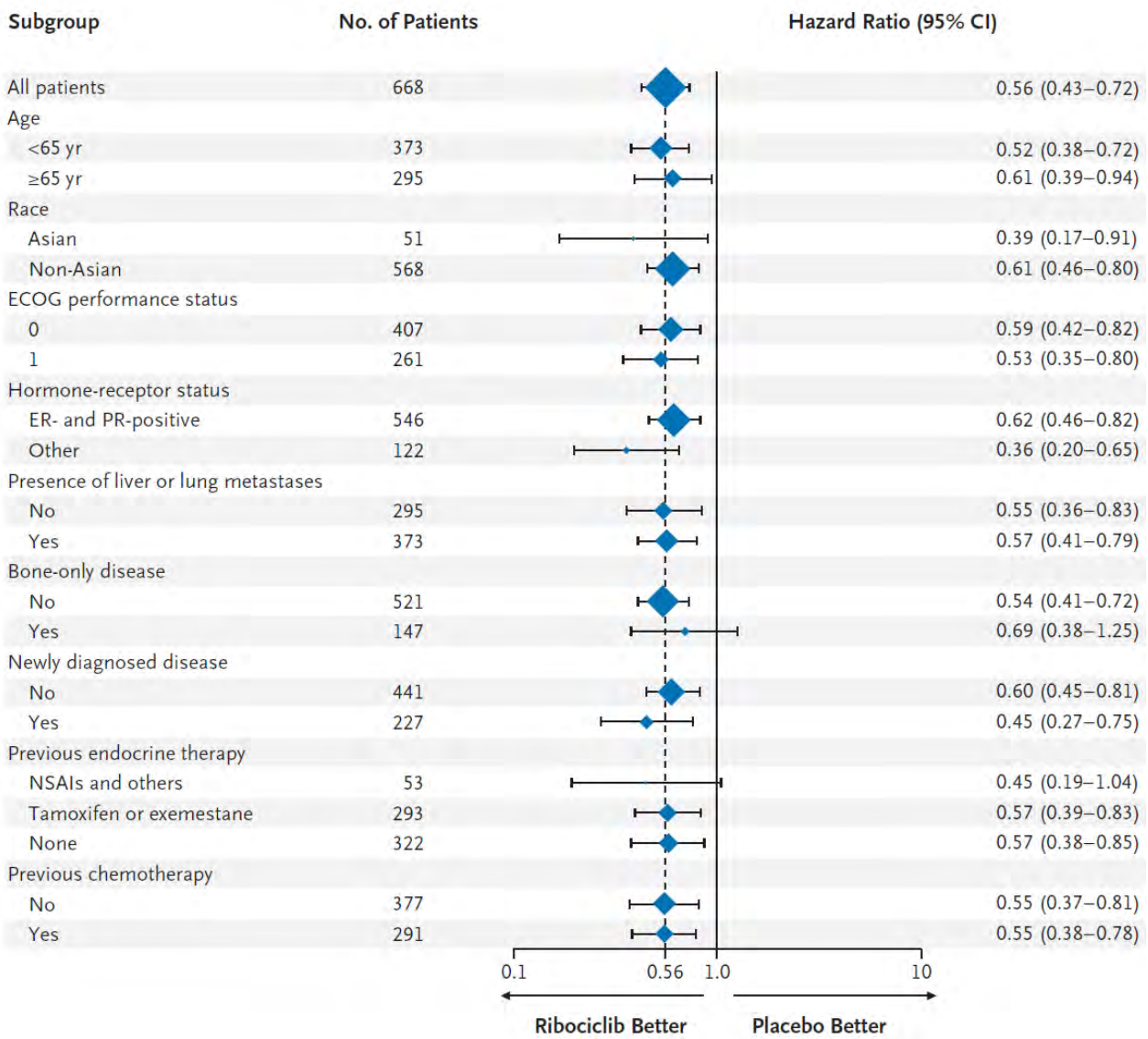
MONALEESA-2 Progression-free Survival



The median duration of progression-free survival was not reached in the ribociclib group and was 14.7 months in the placebo group

Hortobagyi G et al N Engl J Med 2016

MONALEESA-2 Progression-free Survival by Subgroups



Hortobagyi G et al N Engl J Med 2016

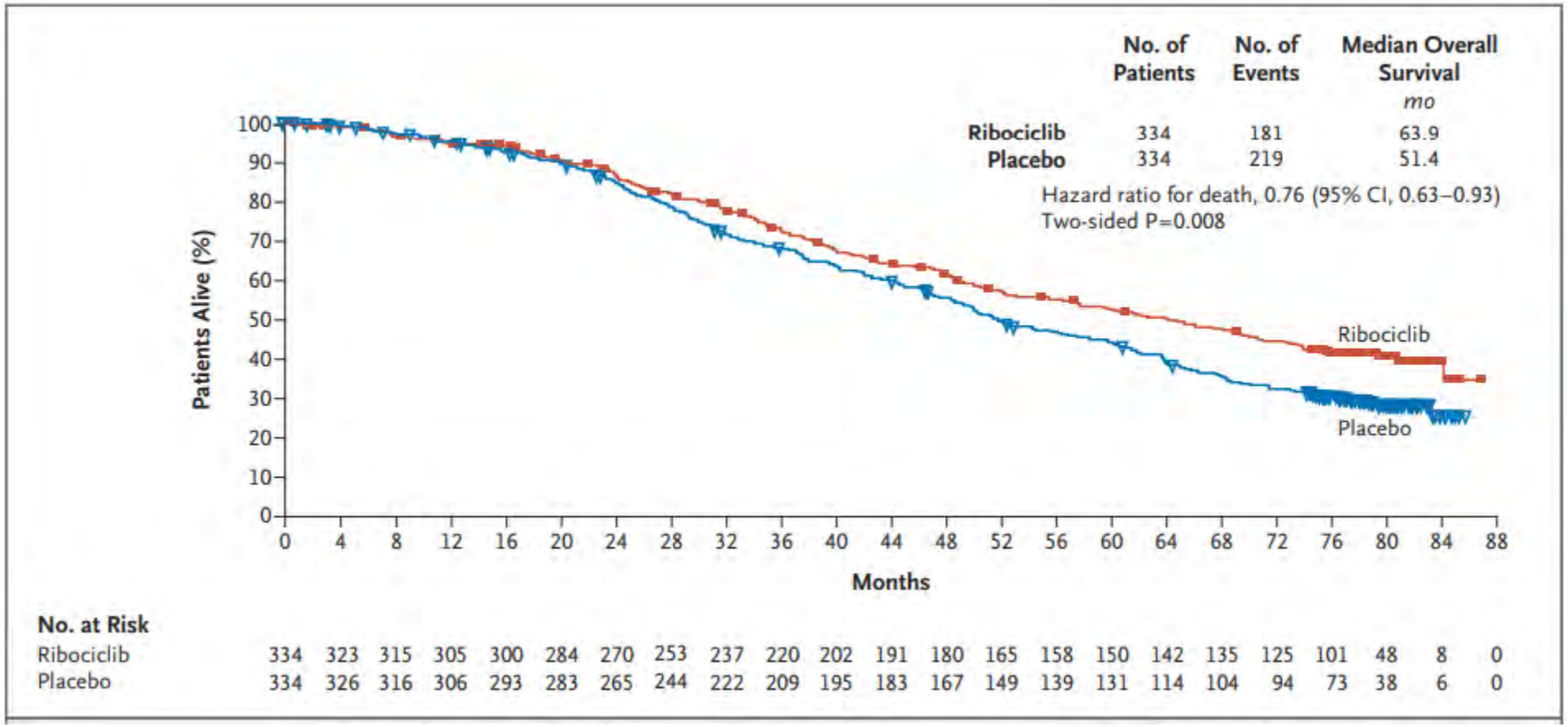
Robustness and Consistency of Randomised Phase 3 Clinical Trials Evaluating CDK4/& Inhibitors in HR+/HER2- mBC

	PALOMA-2[1-3] (N = 666)	PALOMA-3[4,5] (N = 521)	MONALEESA-2[6-8] (N = 668)	MONALEESA-3[9,10] (N = 726)	MONALEESA-7[11-13] (N = 672)	MONARCH-2[14,15] (N = 669)	MONARCH-3[16,17] (N = 493)
Treatment arms	Letrozole ± **palbociclib**	Fulvestrant ± **palbociclib**	Letrozole ± **ribociclib**	Fulvestrant ± **ribociclib**	Tamoxifen, anastrozole, or letrozole ± **ribociclib**	Fulvestrant ± **abemaciclib**	Anastrozole or letrozole ± **abemaciclib**
Patient population	Postmenopausal adv BC; no previous systemic tx	Any menopausal status; prior ET; MBC	Postmenopausal adv BC with recurrent or MBC; no previous systemic tx	Postmenopausal adv BC; ≤1 prior ET for adv BC; no previous systemic tx	Premenopausal/ perimenopausal adv BC; no previous ET for adv BC	Any menopausal status; prior ET; advanced or MBC	Locally advanced or MBC; postmenopausal; no previous systemic tx
Median PFS, CDK4/6i + ET vs ET, mo	**27.6 vs 14.5*** **(HR: 0.56)[2]**		**25.3 vs 16.0*** **(HR: 0.57)[7]**		**23.8 vs 13.0*** **(HR: 0.55)[11]**		**29.0 vs 14.8*** **(HR: 0.54)[16]**

*Statistically significant.

1. Finn. NEJM. 2016;375:1925. 2. Rugo. Breast Cancer Res Treat. 2019;174:719. 3. Slamon. JCO. 2024;42:994. 4. Cristofanilli. Lancet Oncol. 2016;17:425. 5. Cristofanilli. Clin Cancer Res. 2022;28:3433. 6. Hortobagyi. NEJM. 2016;375:1738. 7. Hortobagyi. Ann Oncol. 2018;29:1541. 8. Hortobagyi. NEJM. 2022;386:942. 9. Slamon. JCO.2018;36:2465. 8. Neven. Breast Can Res. 2023;25:103. 10. Tripathy. Lancet Oncol. 2018;19:904. 11. Im. NEJM. 2019;381:307. 12. Lu. Clin Cancer Res. 2022;28:851. 13. Goetz. JCO. 2017;35:3638. 14. Sledge Jr. J Clin Oncol. 2017;35:2875-2884. 15. Neven. Breast Cancer Res. 2021;23:87. 16. Johnston. NPJ Breast Cancer. 2019;5:5. 17. Goetz. Ann Oncol. 2024;[Epub].

MONALEESA-2 Overall Survival



Hortobagyi G et al N Engl J Med 2022

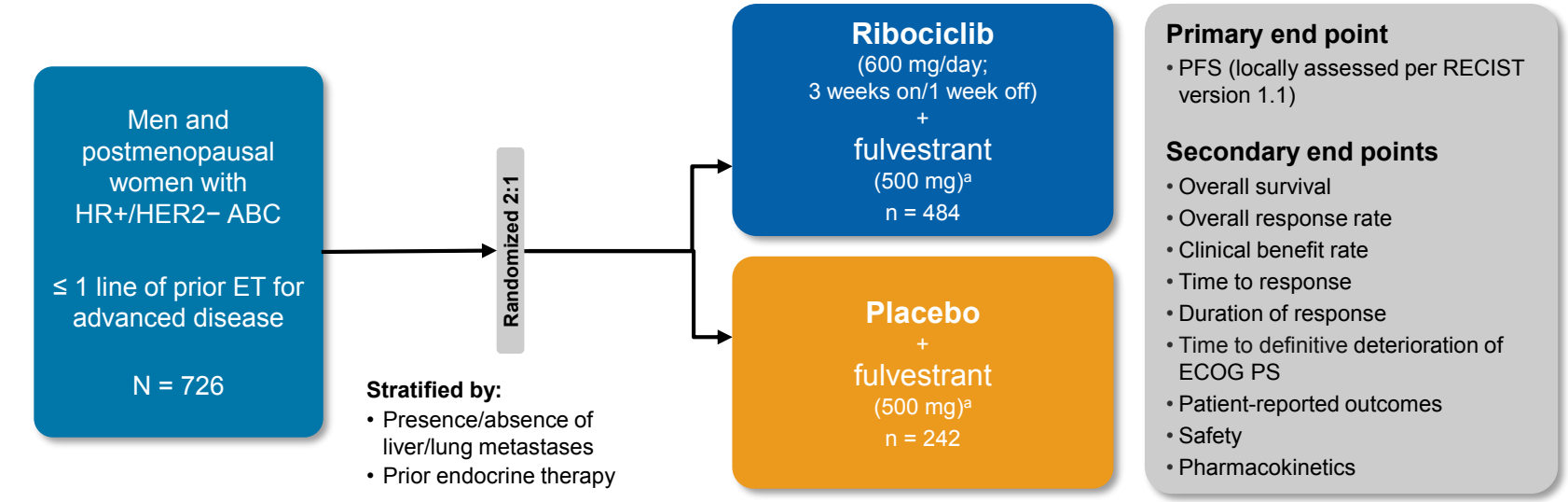
Robustness and Consistency of Randomised Phase 3 Clinical Trials Evaluating CDK4/& Inhibitors in HR+/HER2- mBC

	PALOMA-2[1-3] (N = 666)	PALOMA-3[4,5] (N = 521)	MONALEESA-2[6-8] (N = 668)	MONALEESA-3[9,10] (N = 726)	MONALEESA-7[11-13] (N = 672)	MONARCH-2[14,15] (N = 669)	MONARCH-3[16,17] (N = 493)
Treatment arms	Letrozole ± **palbociclib**	Fulvestrant ± **palbociclib**	Letrozole ± **ribociclib**	Fulvestrant ± **ribociclib**	Tamoxifen, anastrozole, or letrozole ± **ribociclib**	Fulvestrant ± **abemaciclib**	Anastrozole or letrozole ± **abemaciclib**
Patient population	Postmenopausal adv BC; no previous systemic tx	Any menopausal status; prior ET; MBC	Postmenopausal adv BC with recurrent or MBC; no previous systemic tx	Postmenopausal adv BC; ≤1 prior ET for adv BC; no previous systemic tx	Premenopausal, perimenopausal adv BC; no previous ET for adv BC	Any menopausal status; prior ET; advanced or MBC	Locally advanced or MBC; postmenopausal; no previous systemic tx
Median PFS, CDK4/6i + ET vs ET, mo	27.6 vs 14.5 (HR: 0.56)[2]	9.5 vs 4.6 (HR: 0.46)[4]	25.3 vs 16.0 (HR: 0.57)[7]	20.5 vs 12.8 (HR: 0.59)[9]	23.8 vs 13.0 (HR: 0.55)[11]	16.4 vs 9.3 (HR: 0.55)[14]	29.0 vs 14.8 (HR: 0.54)[16]
Median OS, CDK4/6i + ET vs ET, mo	**53.8 vs 49.8 (HR: 0.92)[3]**		**63.9 vs 51.4 (HR: 0.76)[8]***		**58.7 vs 48.0 (HR: 0.76)[13]***		**66.8 vs 53.7 (HR: 0.80)[16]**

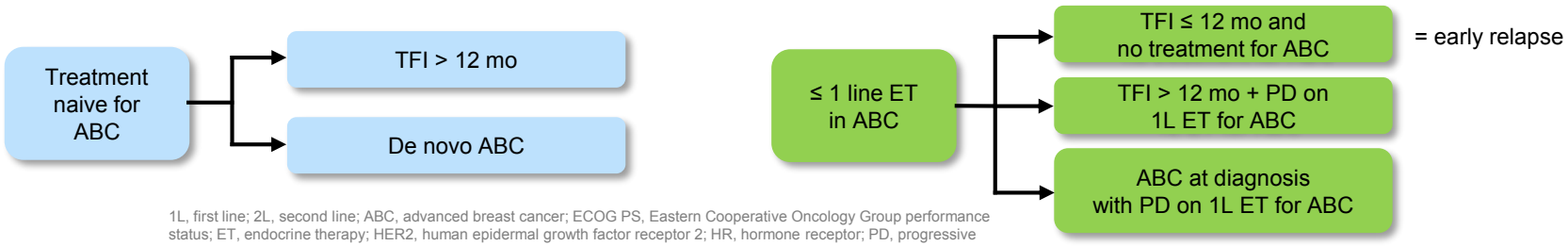
*Statistically significant.

1. Finn. NEJM. 2016;375:1925. 2. Rugo. Breast Cancer Res Treat. 2019;174:719. 3. Slamon. JCO. 2024;42:994. 4. Cristofanilli. Lancet Oncol. 2016;17:425. 5. Cristofanilli. Clin Cancer Res. 2022;28:3433. 6. Hortobagyi. NEJM. 2016;375:1738. 7. Hortobagyi. Ann Oncol. 2018;29:1541. 8. Hortobagyi. NEJM. 2022;386:942. 9. Slamon. JCO.2018;36:2465. 8. Neven. Breast Can Res. 2023;25:103. 10. Tripathy. Lancet Oncol. 2018;19:904. 11. Im. NEJM. 2019;381:307. 12. Lu. Clin Cancer Res. 2022;28:851. 13. Goetz. JCO. 2017;35:3638. 14. Sledge Jr. J Clin Oncol. 2017;35:2875-2884. 15. Neven. Breast Cancer Res. 2021;23:87. 16. Johnston. NPJ Breast Cancer. 2019;5:5. 17. Goetz. Ann Oncol. 2024;[Epub].

MONALEESA-3 Phase III ribociclib + fulvestrant in HR+, HER2– ABC



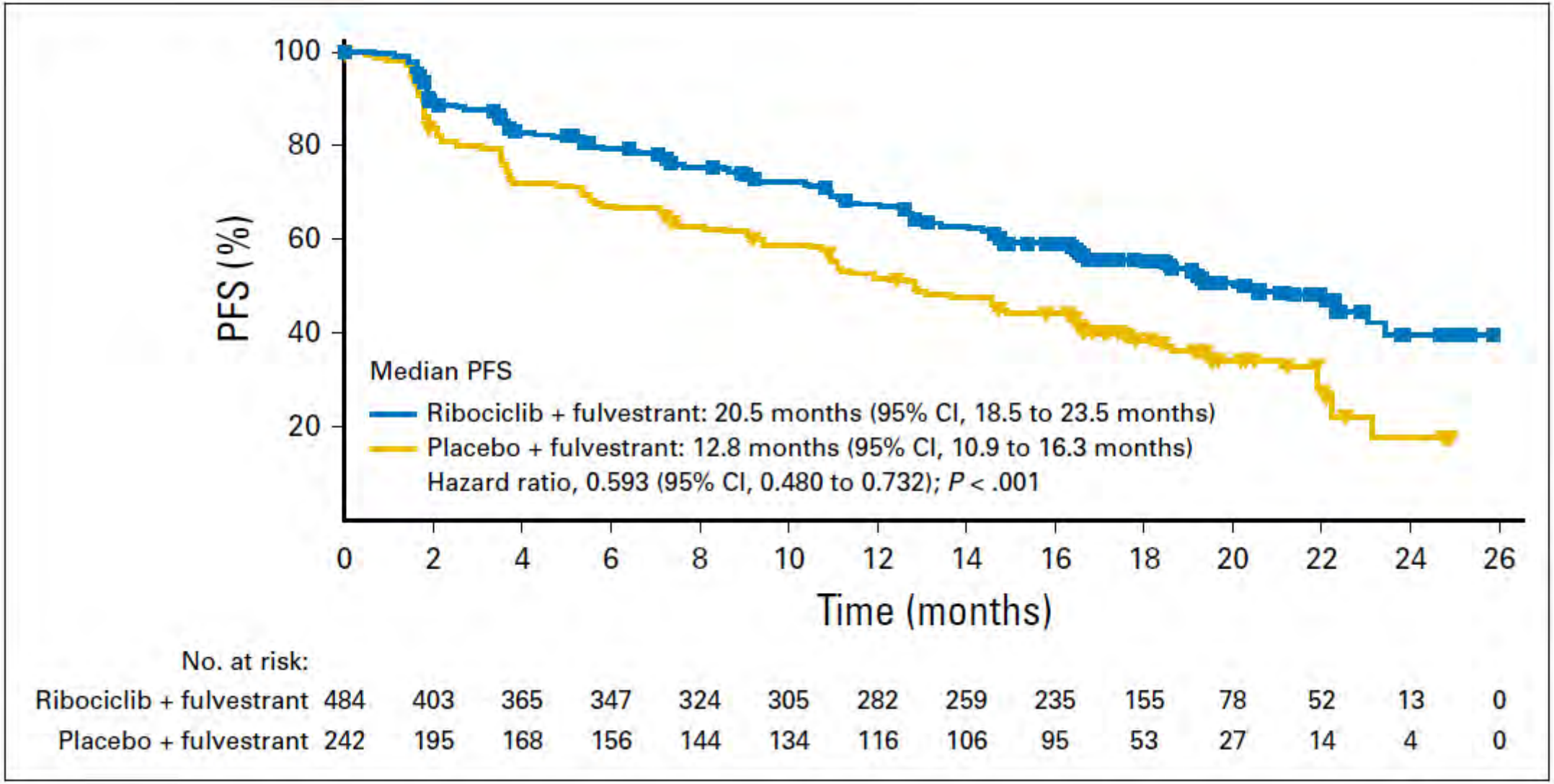
Patient population definitions



1L, first line; 2L, second line; ABC, advanced breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TFI, treatment-free interval.
[a] Fulvestrant 500 mg intramuscularly every 28 days plus an additional dose on Cycle 1, Day 15.
Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-247.

Slamon D et al ESMO 2019

MONALEESA-3 Progression-free Survival



Slamon DJ et al J Clin Oncol 2018

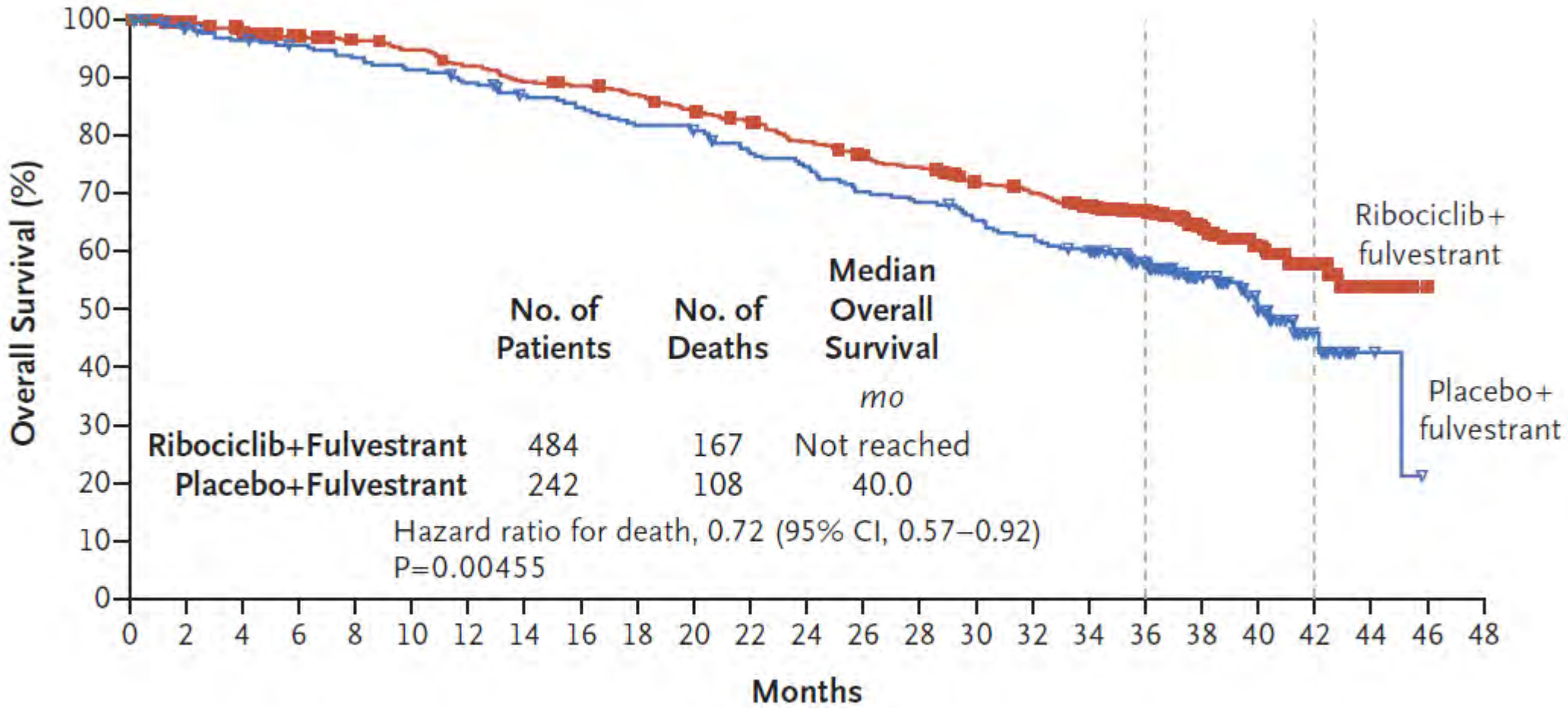
Robustness and Consistency of Randomised Phase 3 Clinical Trials Evaluating CDK4/& Inhibitors in HR+/HER2- mBC

	PALOMA-2[1-3] (N = 666)	PALOMA-3[4,5] (N = 521)	MONALEESA-2[6-8] (N = 668)	MONALEESA-3[9,10] (N = 726)	MONALEESA-7[11-13] (N = 672)	MONARCH-2[14,15] (N = 669)	MONARCH-3[16,17] (N = 493)
Treatment arms	Letrozole ± **palbociclib**	Fulvestrant ± **palbociclib**	Letrozole ± **ribociclib**	Fulvestrant ± **ribociclib**	Tamoxifen, anastrozole, or letrozole ± **ribociclib**	Fulvestrant ± **abemaciclib**	Anastrozole or letrozole ± **abemaciclib**
Patient population	Postmenopausal adv BC; no previous systemic tx	Any menopausal status; prior ET; MBC	Postmenopausal adv BC with recurrent or MBC; no previous systemic tx	Postmenopausal adv BC; ≤1 prior ET for adv BC; no previous systemic tx	Premenopausal/ perimenopausal adv BC; no previous ET for adv BC	Any menopausal status; prior ET; advanced or MBC	Locally advanced or MBC; postmenopausal; no previous systemic tx
Median PFS, CDK4/6i + ET vs ET, mo	27.6 vs 14.5 (HR: 0.56)[2]	**9.5 vs 4.6* (HR: 0.46)[4]**	25.3 vs 16.0 (HR: 0.57)[7]	**20.5 vs 12.8* (HR: 0.59)[9]**	23.8 vs 13.0 (HR: 0.55)[11]	**16.4 vs 9.3* (HR: 0.55)[14]**	29.0 vs 14.8 (HR: 0.54)[16]

*Statistically significant.

1. Finn. NEJM. 2016;375:1925. 2. Rugo. Breast Cancer Res Treat. 2019;174:719. 3. Slamon. JCO. 2024;42:994. 4. Cristofanilli. Lancet Oncol. 2016;17:425. 5. Cristofanilli. Clin Cancer Res. 2022;28:3433. 6. Hortobagyi. NEJM. 2016;375:1738. 7. Hortobagyi. Ann Oncol. 2018;29:1541. 8. Hortobagyi. NEJM. 2022;386:942. 9. Slamon. JCO.2018;36:2465. 8. Neven. Breast Can Res. 2023;25:103. 10. Tripathy. Lancet Oncol. 2018;19:904. 11. Im. NEJM. 2019;381:307. 12. Lu. Clin Cancer Res. 2022;28:851. 13. Goetz. JCO. 2017;35:3638. 14. Sledge Jr. J Clin Oncol. 2017;35:2875-2884. 15. Neven. Breast Cancer Res. 2021;23:87. 16. Johnston. NPJ Breast Cancer. 2019;5:5. 17. Goetz. Ann Oncol. 2024;[Epub].

MONALEESA-3 Overall Survival



No. at Risk

Ribociclib+fulvestrant	484	470	454	444	436	428	414	402	397	389	374	365	348	334	326	309	300	287	237	159	92	41	14	2	0
Placebo+fulvestrant	242	233	227	223	218	213	207	199	194	187	184	174	169	159	155	147	141	134	107	64	37	14	3	0	0

Slamon DJ NEJM 2020

Robustness and Consistency of Randomised Phase 3 Clinical Trials Evaluating CDK4/& Inhibitors in HR+/HER2- mBC

	PALOMA-2[1-3] (N = 666)	PALOMA-3[4,5] (N = 521)	MONALEESA-2[6-8] (N = 668)	MONALEESA-3[9,10] (N = 726)	MONALEESA-7[11-13] (N = 672)	MONARCH-2[14,15] (N = 669)	MONARCH-3[16,17] (N = 493)
Treatment arms	Letrozole ± **palbociclib**	Fulvestrant ± **palbociclib**	Letrozole ± **ribociclib**	Fulvestrant ± **ribociclib**	Tamoxifen, anastrozole, or letrozole ± **ribociclib**	Fulvestrant ± **abemaciclib**	Anastrozole or letrozole ± **abemaciclib**
Patient population	Postmenopausal adv BC; no previous systemic tx	Any menopausal status; prior ET; MBC	Postmenopausal adv BC with recurrent or MBC; no previous systemic tx	Postmenopausal adv BC; ≤1 prior ET for adv BC; no previous systemic tx	Premenopausal/ perimenopausal adv BC; no previous ET for adv BC	Any menopausal status; prior ET; advanced or MBC	Locally advanced or MBC; postmenopausal; no previous systemic tx
Median PFS, CDK4/6i + ET vs ET, mo	27.6 vs 14.5 (HR: 0.56)[2]	9.5 vs 4.6 (HR: 0.46)[4]	25.3 vs 16.0 (HR: 0.57)[7]	20.5 vs 12.8 (HR: 0.59)[9]	23.8 vs 13.0 (HR: 0.55)[11]	16.4 vs 9.3 (HR: 0.55)[14]	29.0 vs 14.8 (HR: 0.54)[16]
Median OS, CDK4/6i + ET vs ET, mo	53.8 vs 49.8 (HR: 0.92)[3]	**34.8 vs 28.0 (HR: 0.81)[5]**	63.9 vs 51.4 (HR: 0.76)[8]*	**67.6 vs 51.8 (HR: 0.67)[10]***	58.7 vs 48.0 (HR: 0.76)[13]*	**46.7 vs 37.3 (HR: 0.757)[15]**	66.8 vs 53.7 (HR: 0.80)[16]

*Statistically significant.

1. Finn. NEJM. 2016;375:1925. 2. Rugo. Breast Cancer Res Treat. 2019;174:719. 3. Slamon. JCO. 2024;42:994. 4. Cristofanilli. Lancet Oncol. 2016;17:425. 5. Cristofanilli. Clin Cancer Res. 2022;28:3433. 6. Hortobagyi. NEJM. 2016;375:1738. 7. Hortobagyi. Ann Oncol. 2018;29:1541. 8. Hortobagyi. NEJM. 2022;386:942. 9. Slamon. JCO.2018;36:2465. 8. Neven. Breast Can Res. 2023;25:103. 10. Tripathy. Lancet Oncol. 2018;19:904. 11. Im. NEJM. 2019;381:307. 12. Lu. Clin Cancer Res. 2022;28:851. 13. Goetz. JCO. 2017;35:3638. 14. Sledge Jr. J Clin Oncol. 2017;35:2875-2884. 15. Neven. Breast Cancer Res. 2021;23:87. 16. Johnston. NPJ Breast Cancer. 2019;5:5. 17. Goetz. Ann Oncol. 2024;[Epub].

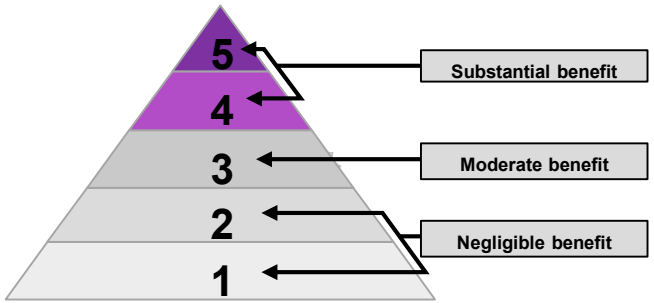
RCTs with CDK 4/6i : Safety Data

	Paloma 2		MONALEESA 2*		Monarch 3	
Item (% any grade/% G3-4)	Palbociclib	Placebo	Ribociclib	Placebo	Abemaciclib	Placebo
Any	99/76	96/24	98/81	97/33	98/55	90/22
Neutropenia	80/66	6/1	74/59	5/1	41/21	2/1
Febrile Neutropenia	1.8	0	1.5	0	-	-
Anemia	24/5	11/1	19/1	4/1	28/6	5/1
Diarrhea	26/1	19/1	35/1	22/1	81/37	30/1
Nausea	35/0	26/2	52/3	28/1	38/12	20/2
Vomiting	16/1	17/1	29/4	16/1	28/9	12/4
Alopecia	33/0	16/0	33/0	16/0	27/0	11/0
Need for dose interruption	67%	41%	77%	41%	43%	6%
Need for dose adjustment	36	1	54	7	43	6
Discontinuation for adv. ev.	10	6	8	2	20	2

*Clinically silent Qtc prolongation in 3.3% of the patients require initial and repeat ECG

ESMO Magnitude of Clinical Benefit Scale in HR+ MBC

The ESMO Magnitude of Clinical Benefit Scale (MCBS) uses a rational, structured, and consistent approach to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from anticancer treatments



ESMO MCBS Scores[1]

Agent	Endocrine Partner	Line of Prior ET for MBC	Treatment Setting	MCBS Agent Score
Ribociclib[2-4]	NSAI or tamoxifen	0	Premenopausal	5
Ribociclib[5]	Letrozole	0	Postmenopausal	4
Ribociclib[6,7]	Fulvestrant	≤ 1	Postmenopausal	4
Palbociclib[8-10]	Fulvestrant	1	MBC	4
Palbociclib[11]	Letrozole	0	MBC	3
Abemaciclib[12,13]	Fulvestrant	1	Postmenopausal MBC	4
Abemaciclib[14]	AI	0	Postmenopausal MBC	3
Alpelisib[15]	Fulvestrant	1	Postmenopausal *PIK3CA*-mutated HR+/HER2–	3
Everolimus[16]	Exemestane	1	MBC	2

AI, aromatase inhibitor; ESMO, European Society for Medical Oncology; MBC, metastatic breast cancer; NSAI, nonsteroidal aromatase inhibitor.

1. Cardoso F, et al. *Ann Oncol*. 2018;29:1634-1657. 2. Tripathy D, et al. *Lancet Oncol*. 2018;7:904-915. 3. Im SA, et al. *N Engl J Med*. 2019;381:307-316. 4.Harbeck N, et al. *Ther Adv Med Oncol*. 2020;12:1-8. 5.Hortobagyi GN, et al. *Ann Oncol*. 2018;29:1541-1547. 6. Slamon DJ, et al. J Clin Oncol. 2018;24: 2465-2472. 7. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524. 8. Cristofanilli M, et al. *Lancet Oncol*. 2016;17:425-439. 9. Turner NC, et al. *N Engl J Med*. 2018;379:1926-1936. 10. Harbeck N, et al. *Ann Oncol*. 2016;27:1047-54. 11. Finn RS, et al. *N Engl J Med*. 2016;375:1925-1936. 12. Sledge GW, et al. *J Clin Oncol*. 2017;35:2875-2884 13. Sledge GW, et al. *JAMA Oncol*. 2019;6:116-124. 14. Goetz M, et al. *J Clin Oncol*. 2017;35:3628-3646. 15. André F, et al. *N Engl J Med*. 2019;380:1929-1940. 16. Baselga J, et al. *N Engl J Med*. 2012;366:520-529.

Choosing the Most Appropriate CDK4/6 Inhibitor

- All agents improve PFS compared to ET alone
- Ribociclib highest level of evidence
- Abemaciclib and palbociclib have clear clinical benefit
- All 3 agents delay time to chemotherapy
- No randomized head-to-head trials comparing these agents
  - The nonrandomized, population based, comparative trials are inconclusive
  - Real-world data must be interpreted with caution
- Consider dosing, side effects, patient factors, and comorbidities

Vernieri. ASCO 2024. Abstr LBA1014. Jhaveri. Cancer Treat Rev. 2023;123:102670. NCCN. Clinical practice guidelines in oncology: breast cancer. v4.2024. nccn.org. society.asco.org/practice-patients/guidelines/breast-cancer#/9676.

CDK4/6 Inhibitors Dosing/AE/Monitoring Considerations

	Abemaciclib	Palbociclib	Ribociclib
Pill burden	With ET: 150 mg (1 tablet) Monotherapy: 200 mg (1 tablet)	125 mg (1 tablet or capsule)	600 mg **(3 tablets)**
Dosing schedule	**Twice daily** x 28 d; 28-d cycle	Once daily **x 21 d**; 28-d cycle	Once daily **x 21 d**; 28-d cycle
Food considerations	With or without food	**Capsule: with food** Tablet: with or without food	With or without food
Common AEs	Neutropenia Fatigue **Diarrhea** **Nausea**	Neutropenia Fatigue	Neutropenia Fatigue
Monitoring	CBC LFTs	CBC	**CBC** **LFTs** **ECG** **Electrolytes**
Special Considerations	VTE Hepatobiliary toxicity		QTC prolongation Hepatobiliary toxicity

Use of first line HT & multiple lines of HT was low before CDK4/6i

Analysis	Nº ER+/ HER2-	First line treatment for HR+ ABC		Number of ET lines before 1st CT		
		CT	ET	1 line	2 lines	≥ 3 lines
US[1]	19,120	**40%**	**60%**	**74%**	**19%**	**7%**
Europe[2]	399	**31%**	**69%**	**62%**	**7%**	-
Europe & Canada[3]	901	**35%**	**65%**	**26%**	**45%**	-

[1]Swallow E, et al. *Curr Med Res Opin*. 2014; [2]Andre F, et al. *Curr Med Res Opin*. 2014; [3]*Kurosky* S et al *Clin Breast Cancer* 2017.

Patient Factors When Considering CDK4/6i for HR+/HER2- MBC

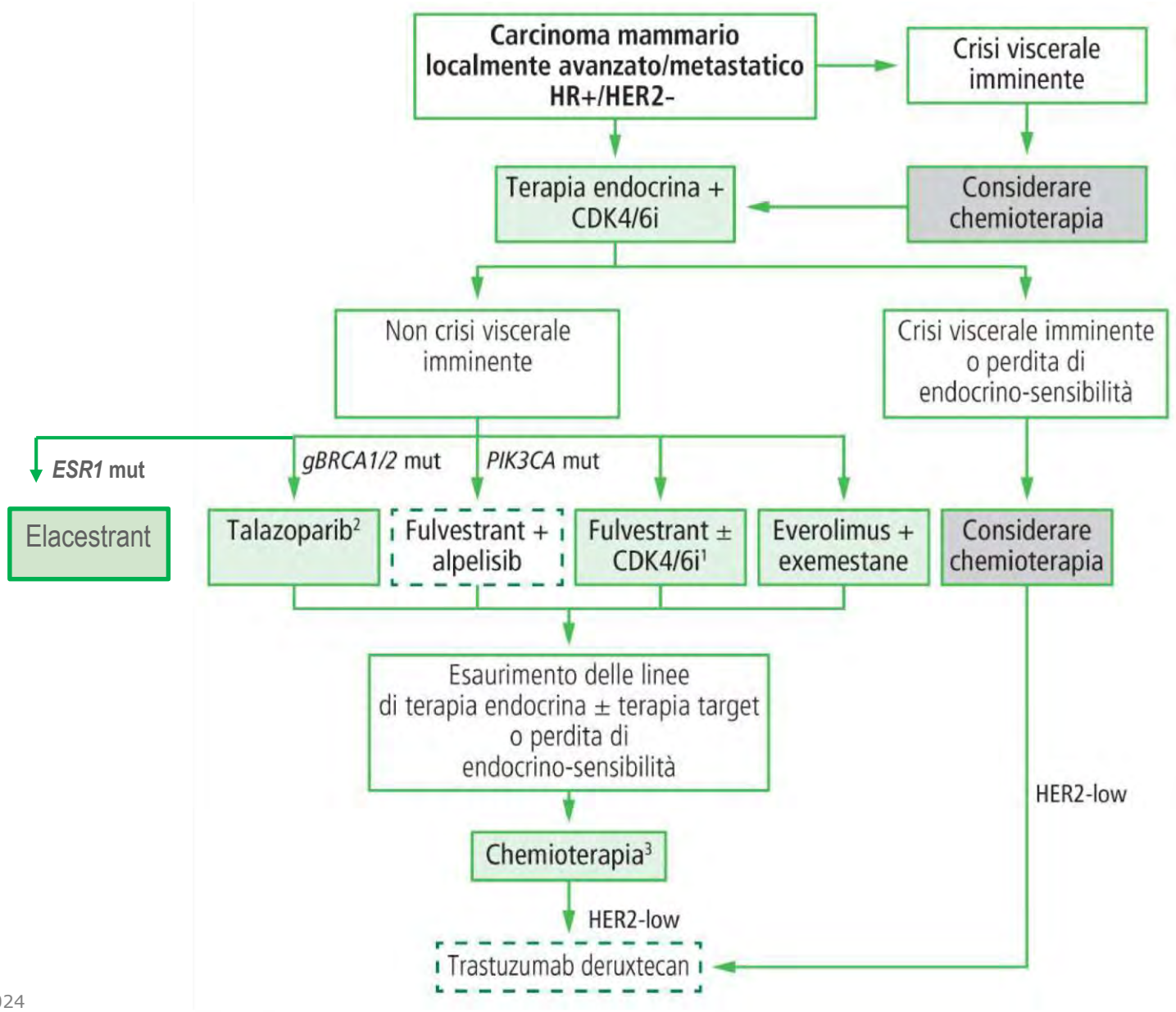
- Endocrine sensitive vs resistant disease
- Menopausal status
  - **Monaleesa 7:** only trial with exclusively premenopausal population
  - **NCCN:** premenopausal women should have adequate ovarian suppression/ablation (put into medically or surgically induced menopause) and be treated as postmenopausal patients
- Visceral crisis
  - **Right Choice Trial** included preMP in visceral crisis randomized to physician's choice (doublet chemo) vs ribociclib/ET
  - CDK4/6 arm showed median PFS 24 vs 12 mo with chemo and fewer adverse events, dose reductions or dose discontinuation
- Performance status
- Comorbidities (eg underlying cardiac disease, GI issues/liver function)

Im. NEJM. 2019;381:307. Lu. JCO. 2024;42:23. NCCN. Clinical practice guidelines in oncology: breast cancer. v4.2024. nccn.org. onclive.com/view/factors-in-selecting-1l-therapy-for-patients-with-hr-positive-metastatic-breast-cancer.

Endocrine Therapy for HR$^+$ ABC: consolidated paradigms

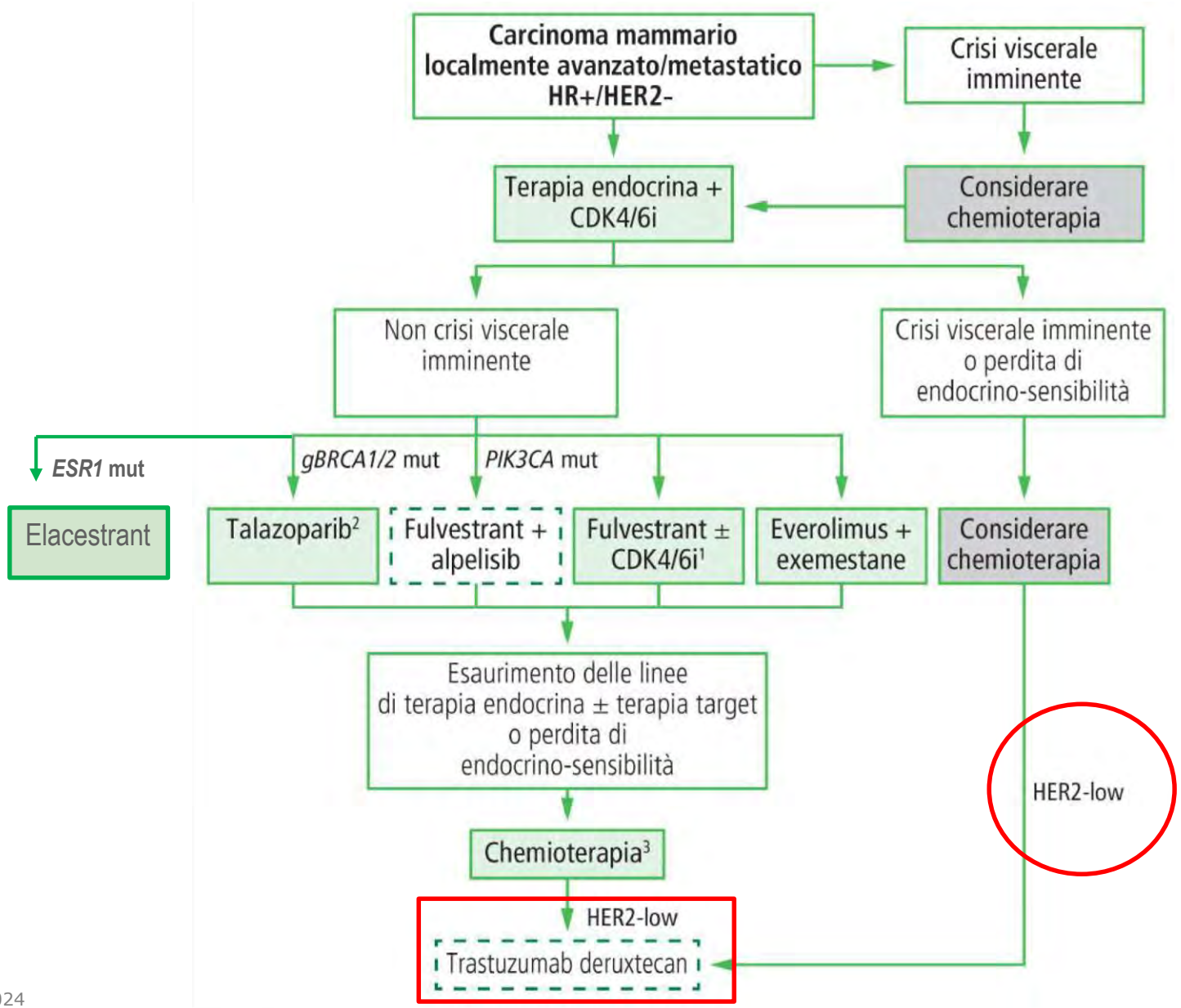
- **Endocrine therapy is the preferred option for most of the patients**
- **In case of prior response, multiple lines of endocrine therapy can be effective**
- **Visceral metastases are not a contraindication to endocrine therapy. Patients at risk of visceral crisis because of severe organ dysfunction should be treated upfront with chemotherapy**

Dunque cosa facciamo oggi?



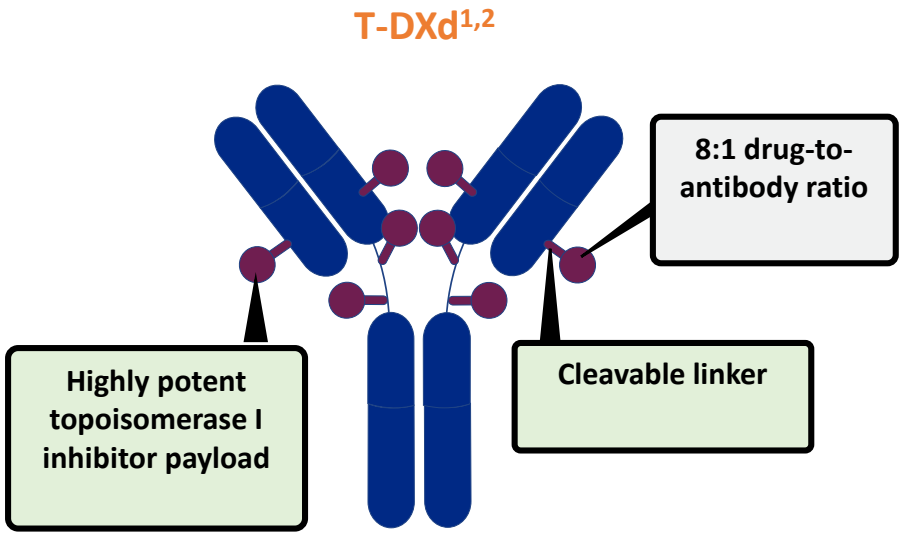
Linee Guida AIOM 2023 (modificato)

L’efficacia delle terapie dopo CDK4/6i è relativamente modesta, ma…

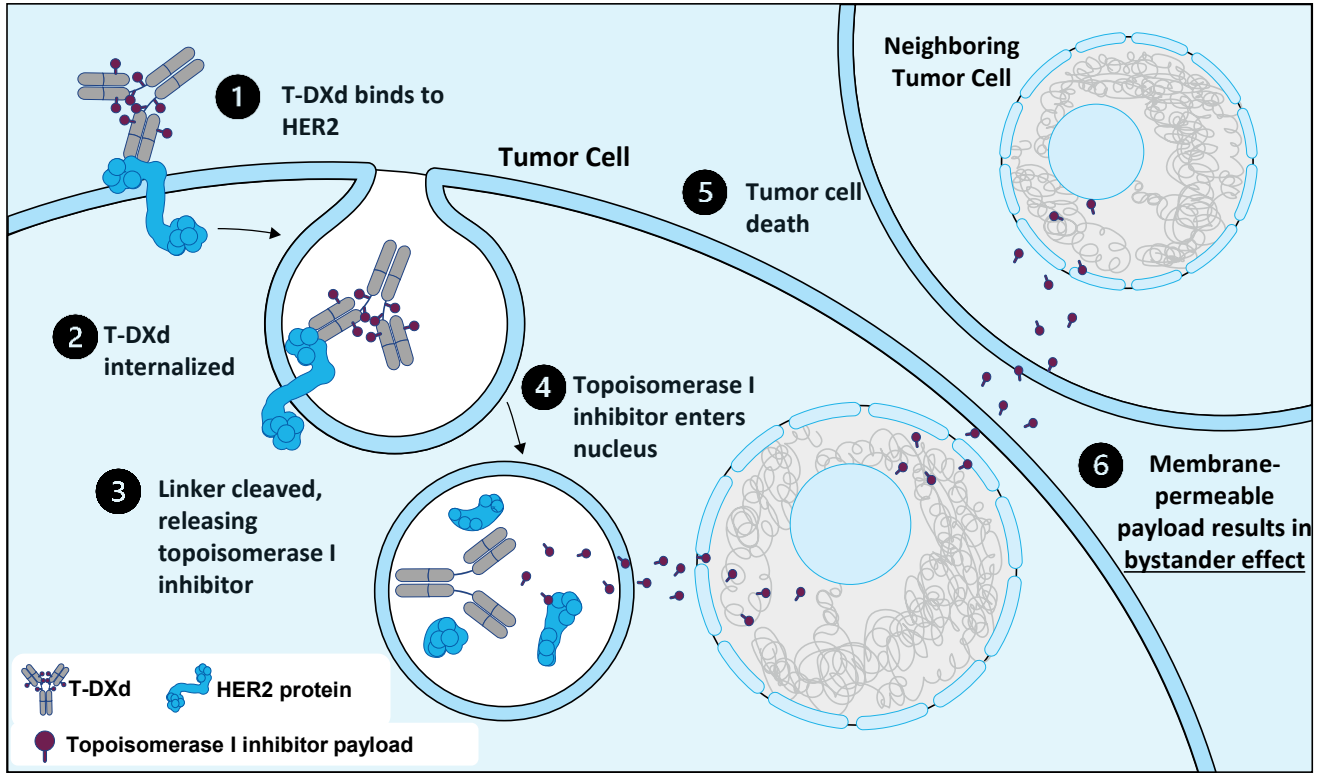


Linee Guida AIOM 2023 (modificato)

T-DXd MOA, bystander antitumor effect, and rationale for targeting HER2-low mBC



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]

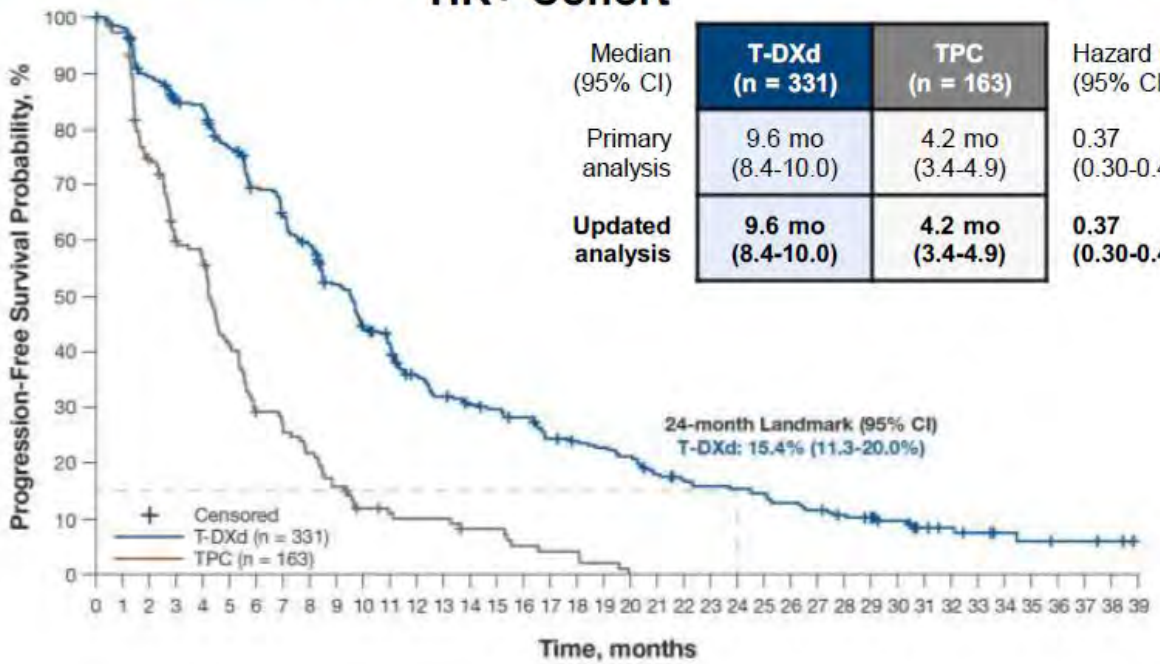


1. Nakada T et al. *Chem Pharm Bull*. 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Modi S et al. *J Clin Oncol* 2020;38:1887-96.

Progression-Free Survival (by Investigator[a])

HR+ Cohort

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**



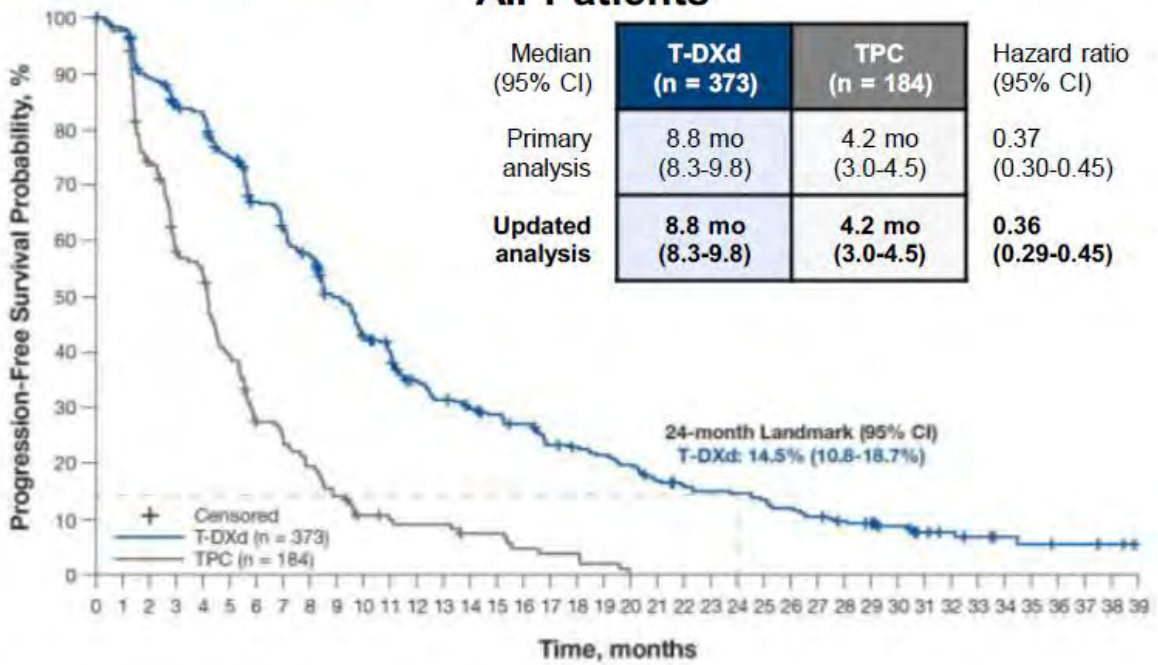
Patients still at risk:

T-DXd (n = 331)

TPC (n = 163)

All Patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	**8.8 mo (8.3-9.8)**	**4.2 mo (3.0-4.5)**	**0.36 (0.29-0.45)**



Patients still at risk:

T-DXd (n = 373)

TPC (n = 184)

- Median PFS was consistent with results from the primary analysis,[1] showing a reduction in risk of disease progression or death of 63% and 64% in the HR+ cohort and all patients, respectively, for the T-DXd arm compared with the TPC arm

BICR, blinded independent central review; HR, hormone receptor; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

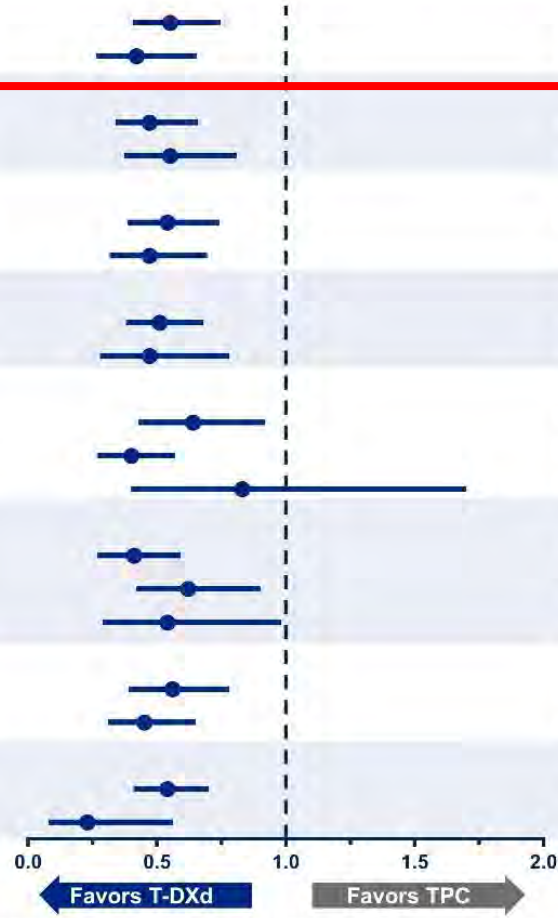
[a]PFS by BICR was stopped after the primary analysis as final PFS by BICR was achieved. At primary analysis, PFS by BICR for HR+ cohort was 10.1 mo and 5.4 mo for T-DXd and TPC, respectively (hazard ratio, 0.51). For all patients, the PFS by BICR was 9.9 mo and 5.1 mo for T-DXd and TPC, respectively (hazard ratio, 0.50). The updated analysis is based on PFS by investigator.

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

Modi S et al ESMO 2023

Subgroup Analysis: PFS in HR+

	No. of Events/No. of Patients		PFS, median (95% CI), mo		Hazard Ratio for Disease Progression or Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.73)
No	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
IHC status					
IHC 1+	119/192	66/96	10.3 (8.6-12.3)	5.3 (4.1-7.8)	0.48 (0.35-0.65)
IHC 2+/ISH−	92/139	44/67	10.1 (8.2-12.2)	5.9 (4.3-7.9)	0.55 (0.38-0.80)
Prior lines of chemotherapy					
1	129/203	63/93	10.9 (8.5-12.3)	6.8 (4.5-8.2)	0.54 (0.40-0.73)
≥2	81/127	47/69	9.9 (8.3-11.7)	4.6 (2.8-6.2)	0.47 (0.33-0.68)
Age					
<65 years	170/260	79/120	9.8 (8.4-11.3)	5.4 (4.1-7.8)	0.51 (0.39-0.67)
≥65 years	41/71	31/43	12.0 (9.5-14.7)	5.6 (4.3-10.8)	0.47 (0.29-0.77)
Race					
White	100/156	43/78	10.0 (8.5-12.2)	7.1 (4.0-10.0)	0.64 (0.44-0.91)
Asian	83/131	54/66	11.0 (8.4-13.8)	4.8 (4.2-6.4)	0.40 (0.28-0.56)
Other	25/37	11/16	6.0 (5.4-10.5)	7.0 (1.4-11.0)	0.83 (0.41-1.69)
Region					
Asia	81/128	48/60	10.9 (8.4-14.7)	5.3 (4.2-6.8)	0.41 (0.28-0.58)
Europe and Israel	90/149	44/73	10.8 (8.5-13.0)	7.1 (3.0-10.7)	0.62 (0.43-0.89)
North America	40/54	18/30	8.5 (6.3-11.3)	4.5 (2.9-8.2)	0.54 (0.30-0.97)
ECOG performance status					
0	116/187	55/95	10.9 (9.5-13.0)	7.0 (4.2-8.5)	0.56 (0.40-0.77)
1	95/144	55/68	9.7 (7.3-11.5)	4.6 (2.9-6.2)	0.45 (0.32-0.64)
Visceral disease at baseline					
Yes	196/298	100/146	9.8 (8.5-11.1)	5.8 (4.4-7.1)	0.54 (0.42-0.69)
No	15/33	10/17	17.9 (10.9-26.4)	4.5 (1.6-12.4)	0.23 (0.09-0.55)



PFS by blinded independent central review. Based on derived data, which include protocol deviations.

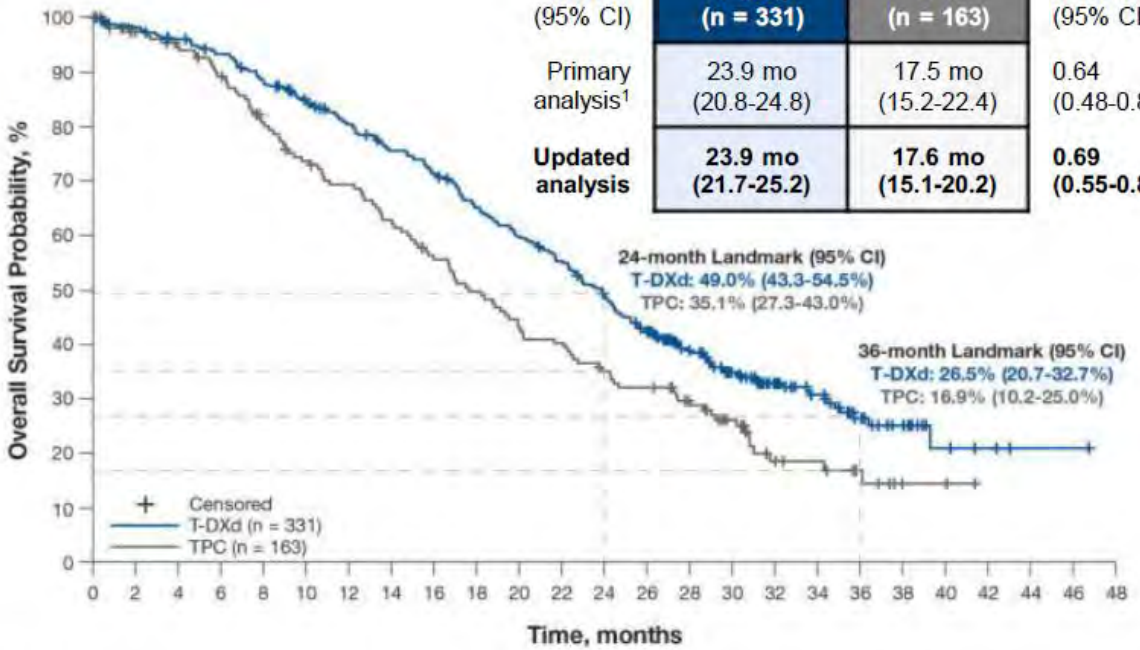
CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PRESENTED BY:
Shanu Modi, MD

Overall Survival

HR+ Cohort

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[1]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1-20.2)**	**0.69 (0.55-0.87)**



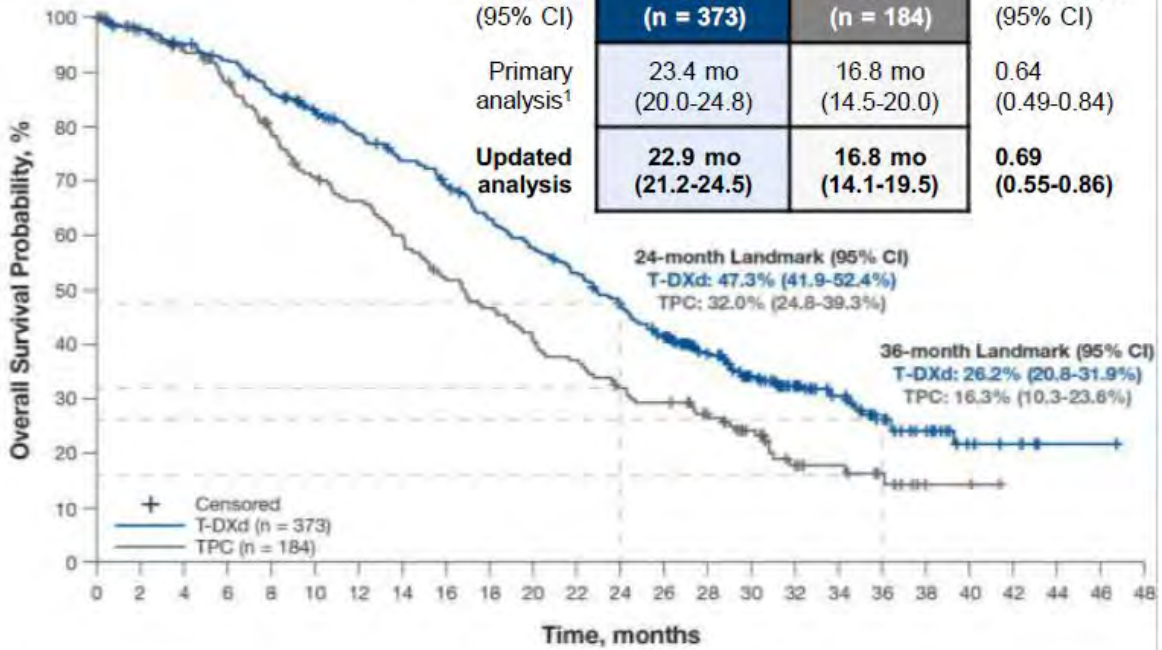
Patients still at risk:

T-DXd (n = 331) 331 325 323 317 311 307 302 292 284 279 267 258 250 243 233 230 220 212 199 188 180 170 158 155 147 135 124 109 94 81 72 66 54 46 42 34 23 17 14 7 6 4 3 2 1 1 1 0

TPC (n = 163) 163 150 144 142 136 134 129 123 114 106 103 97 86 82 67 62 56 51 50 47 43 42 42 35 31 25 16 13 11 11 9 7 5 2 2 2 1 0

All Patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**



Patients still at risk:

T-DXd (n = 373) 373 366 360 355 350 342 337 325 314 308 299 289 278 269 257 254 240 231 217 208 196 191 182 168 160 149 137 122 107 94 89 76 62 52 49 39 29 21 16 11 7 6 5 3 1 1 1 0

TPC (n = 184) 184 170 165 160 156 152 149 137 127 119 113 107 105 100 95 86 81 76 73 69 64 59 58 52 49 45 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

- In the HR+ cohort and all patients, median OS was consistent with results from the primary analysis,[1] showing a 31% reduction in risk of death for patients receiving T-DXd compared with those receiving TPC

HR, hormone receptor; mo, month; 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.

Modi S et al ESMO 2023

Nel cancro metastatico della mammella…..

Guarire

Prolungare
la sopravvivenza

Controllare i sintomi

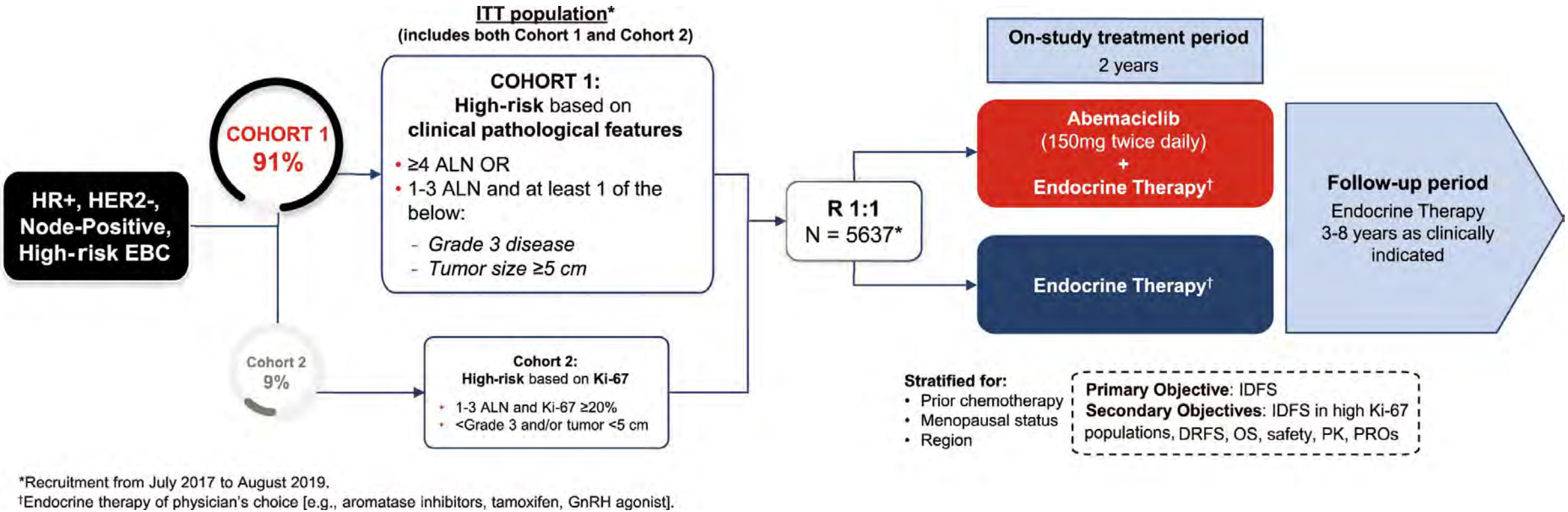
Buona/accettabile QoL
(anche nel fine vita)

Nel cancro della mammella in fase precoce…..

Guarigione ~ 75-80%

(chirurgia, radioterapia, terapia medica)

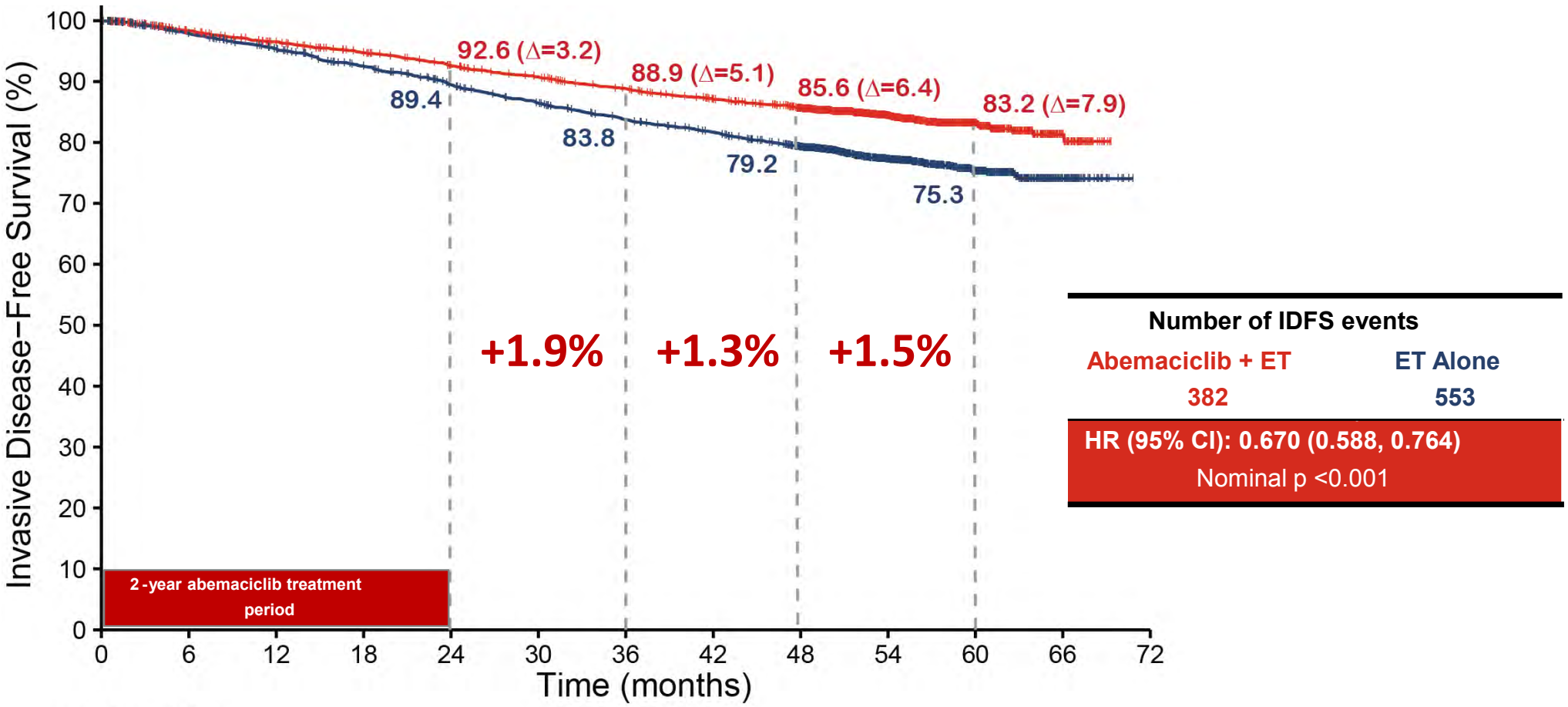
monarchE Study Design (NCT03155997)



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

Nadia Harbeck et al ESMO Congress, October 2023

Continuous increase of IDFS benefit with longer follow up

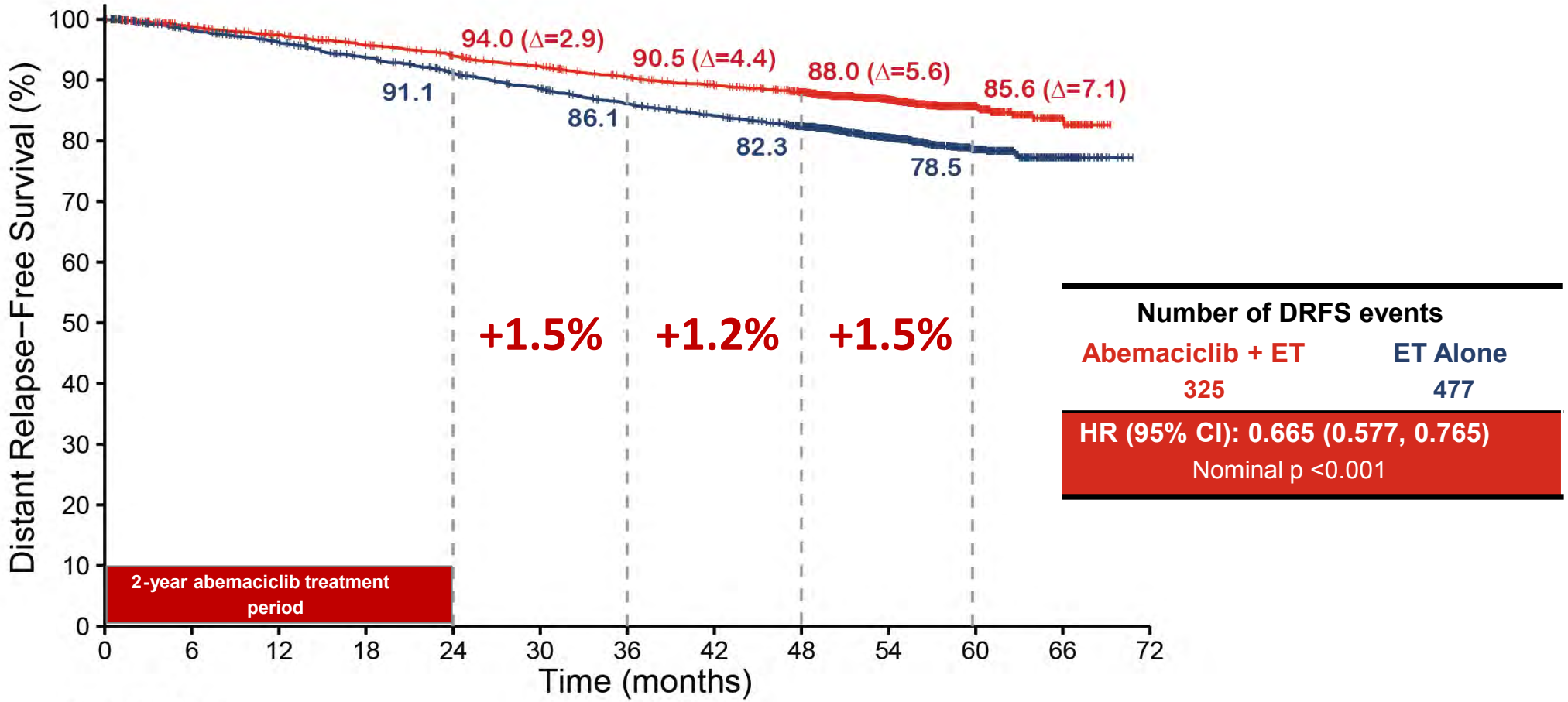


Number at risk

Abemaciclib + ET	2555	2387	2322	2256	2189	2129	2068	2006	1913	1111	490	74	0
ET alone	2565	2405	2328	2236	2143	2059	1979	1915	1795	1056	473	67	0

Harbeck N ESMO 2023

Continuous increase of DDFS benefit with longer follow up



Number of DRFS events

Abemaciclib + ET	ET Alone
325	477

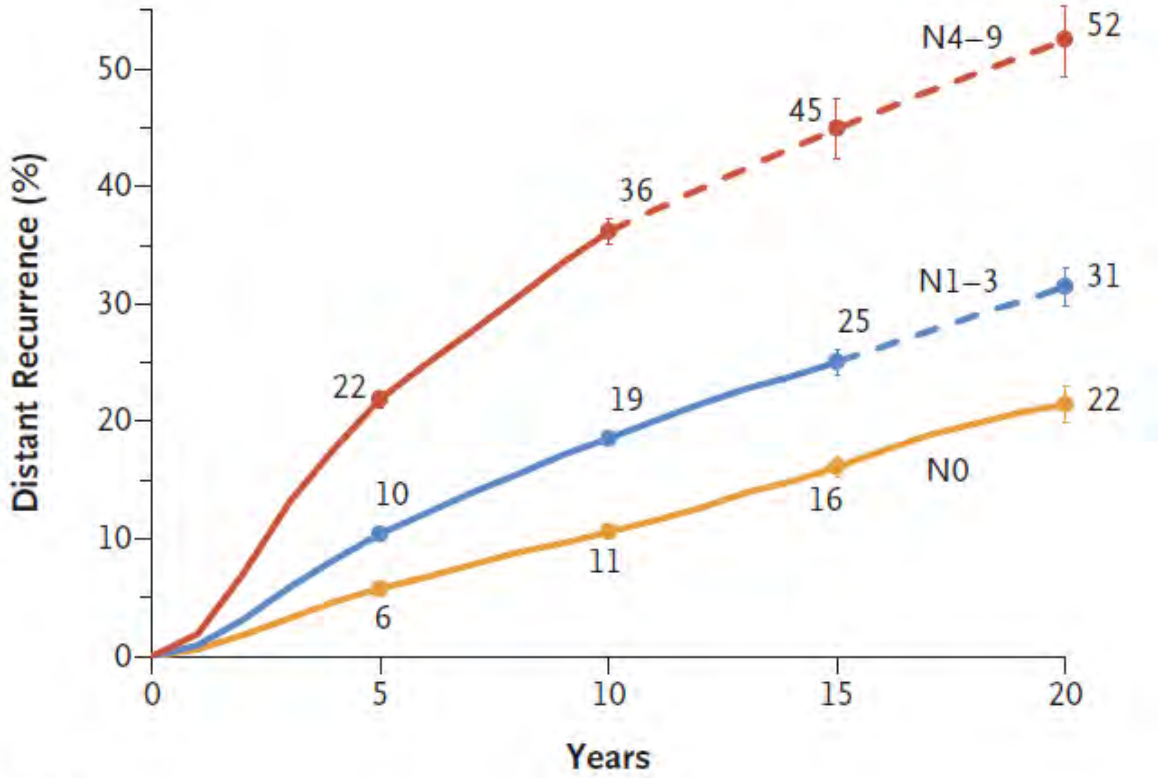
HR (95% CI): 0.665 (0.577, 0.765)
Nominal p <0.001

Number at risk

Abemaciclib + ET	2555	2396	2339	2274	2213	2155	2095	2040	1953	1136	500	75	0
ET alone	2565	2412	2345	2259	2177	2102	2023	1960	1849	1092	488	72	0

Harbeck N ESMO 2023

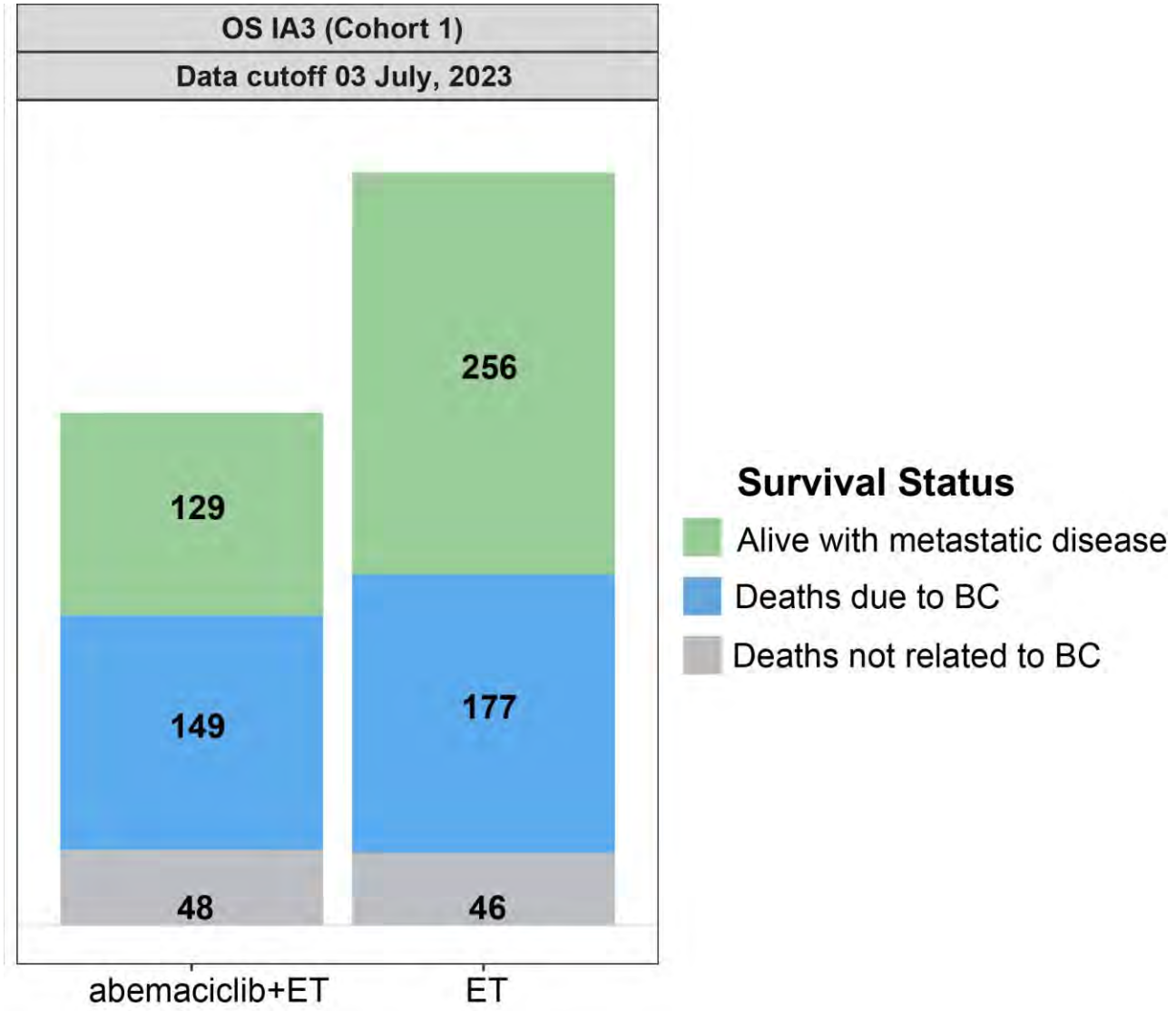
Late breast-cancer recurrences from 5 to 20 years



No. at Risk					
N4–9	12,333	8,116	2165	259	52
N1–3	31,936	23,576	7250	949	183
N0	29,925	24,081	8571	1982	414

Pan H et al NEJM 2017

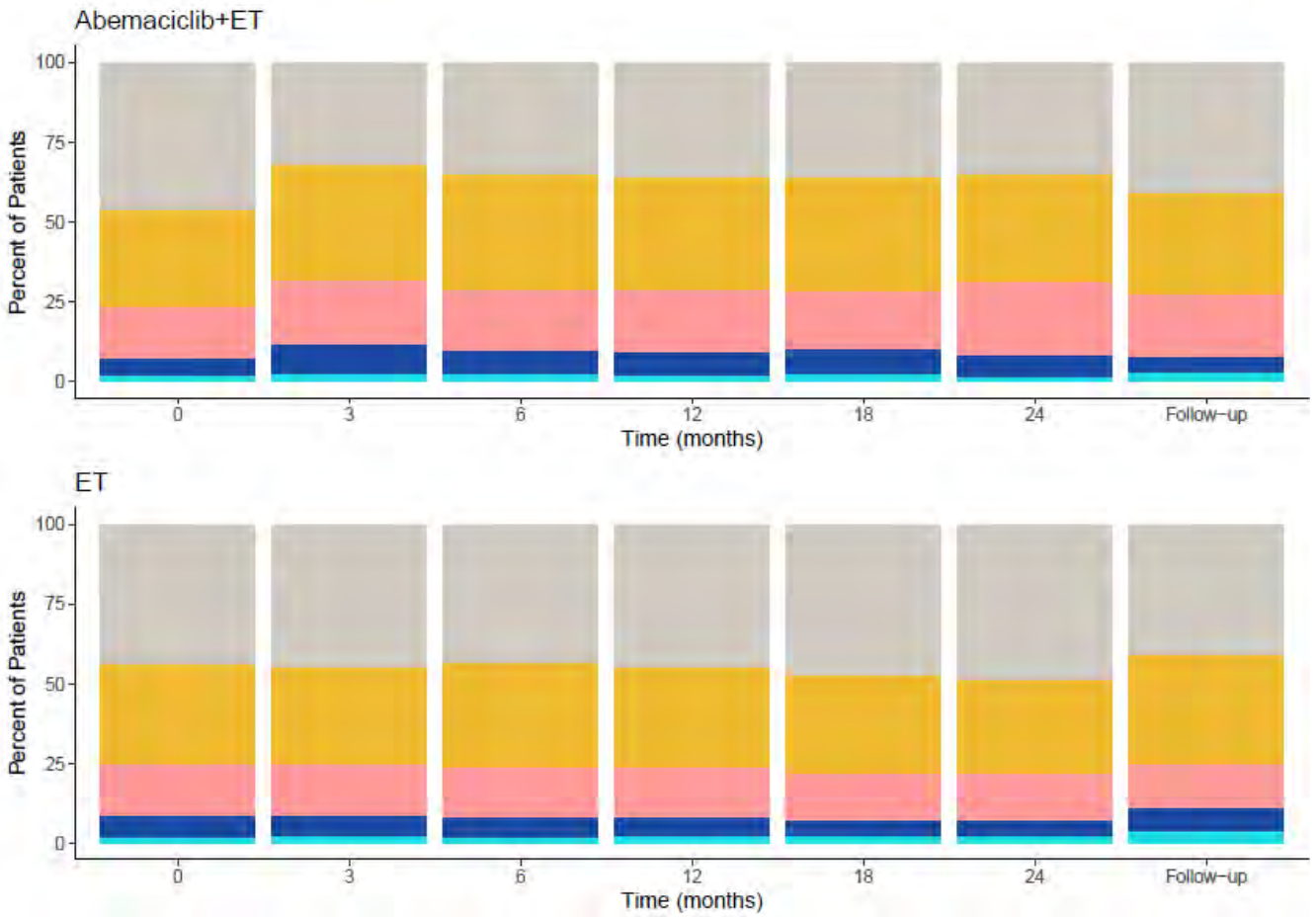
Half patients with metastatic disease



Harbeck N ESMO 2023

FACT-B GP5 “Bothered by Treatment Side Effect”

Percent stacked bar plot of PRO on FACT-B GP5



- The addition of abemaciclib to ET did not result in a clinically meaningful difference in patients being bothered by treatment side effects
- Most pts in both arms reported being bothered “a little” or “not at all” by side effects of treatment

FACT-B Functional Assessment of Cancer Therapy - Breast; PRO=patient-reported outcomes

Tolaney SM SGBCC 2021; P008
Tolaney SM EJC 2024

NATALEE-Study Design and Methods

- Adult patients with HR+/HER2− EBC
- Prior ET allowed ≤12 mo prior to randomization
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥20%
      - Oncotype DX Breast Recurrence Score ≥26 ***or***
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

R 1:1[c]

RIB
400 mg/day
3 weeks on/1 week off
for 3 years

+

NSAI
Letrozole or anastrozole[d]
for ≥5 years
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[d]
for ≥5 years
+ goserelin in men and premenopausal women

Primary End Point
- iDFS using STEEP criteria

Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- Safety and tolerability
- PROs
- PK

Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Statistical comparisons were performed using a Cox proportional hazards model and the Kaplan-Meier method

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

Data cutoff: 29 April 2024

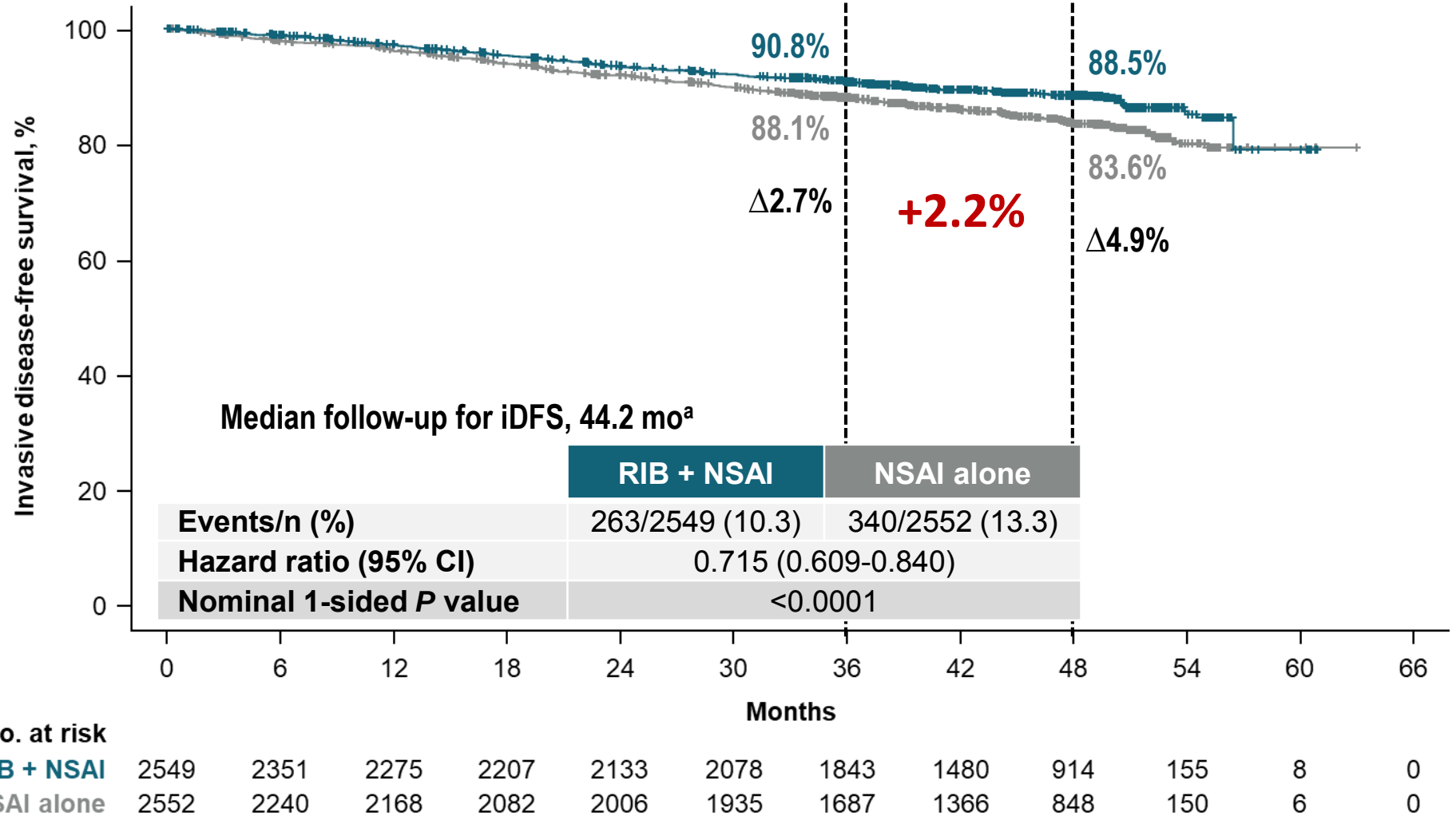
ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; RIB, ribociclib; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.

[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.

1. ClinicalTrials.gov. Accessed March 15, 2024. https://clinicaltrials.gov/ct2/show/NCT03701334. **2.** Slamon DJ, et al. Poster presented at: ASCO 2019. Poster TPS597. **3.** Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:1-16. **4.** Hortobagyi, G, et al. Oral presentation at: SABCS 2023. Oral GS03-03.

NATALEE- iDFS in ITT Population

Significant iDFS benefit with RIB + NSAI after the planned 3-y treatment

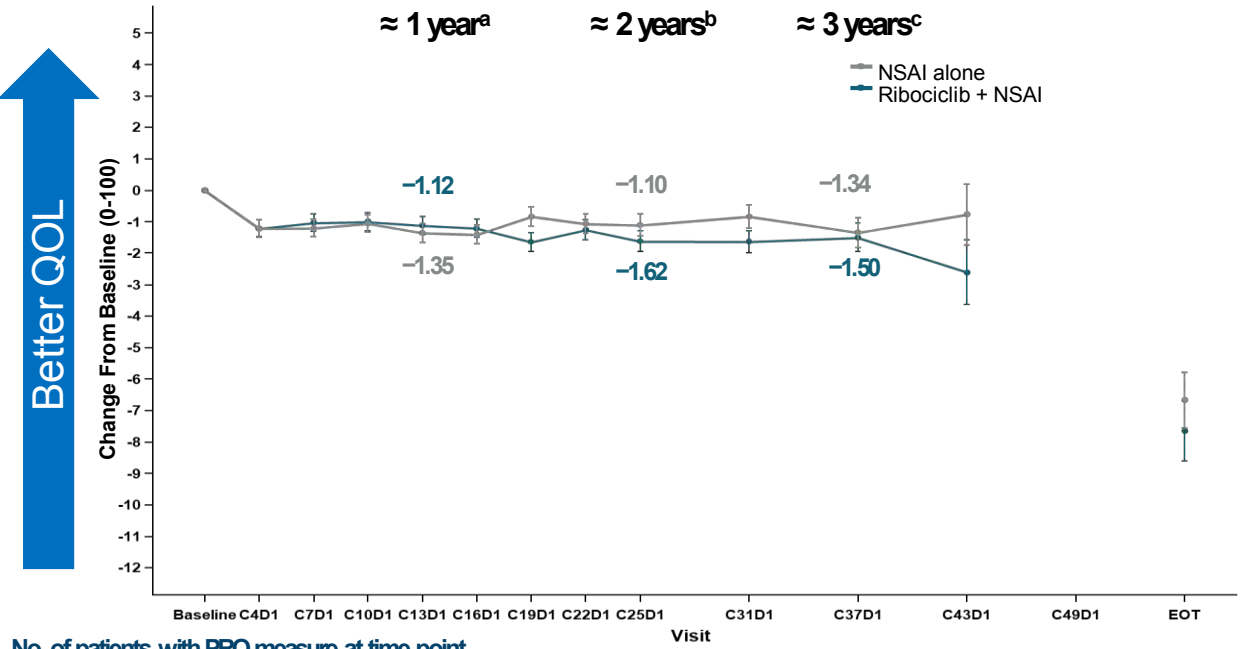


iDFS, invasive disease–free survival; ITT, intent to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] An additional 10.9 months of follow-up compared with the protocol-specified final iDFS analysis.

Peter A. Fasching ESMO 2024

PRIMARY HRQOL OF INTEREST—EORTC QLQ-C30: PHYSICAL FUNCTIONING

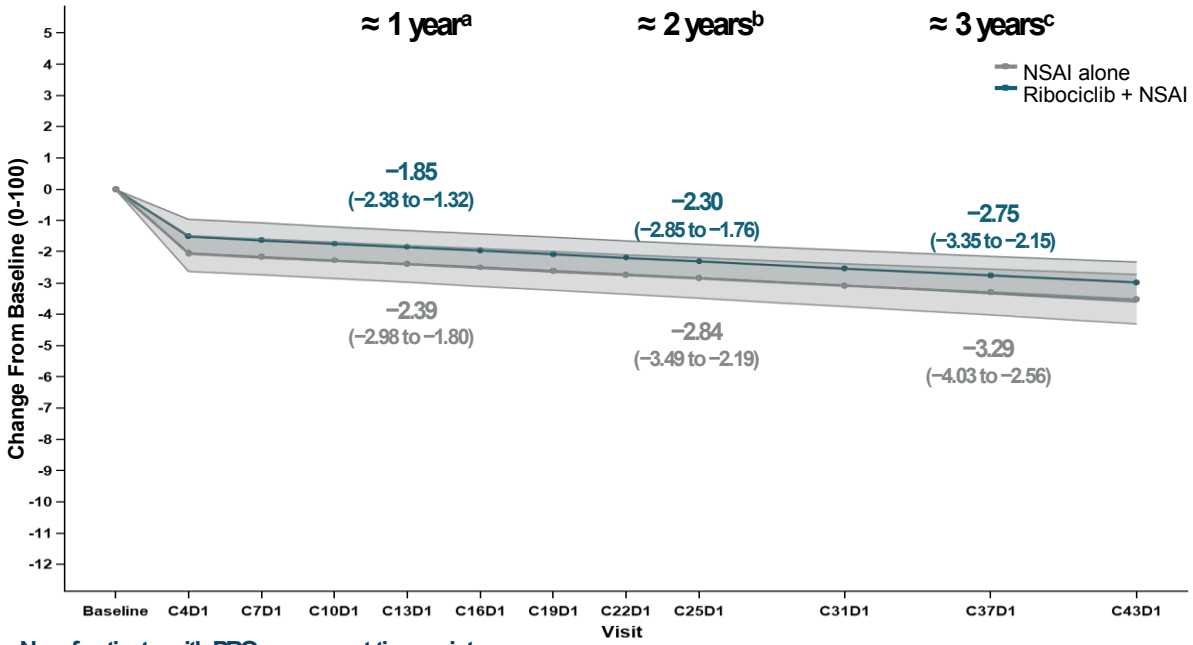
Descriptive Analysis



No. of patients with PRO measure at time point

Ribociclib + NSAI	2162	1939	1051
NSAI alone	2062	1793	989

Model-Based Analyses



No. of patients with PRO measure at time point

Ribociclib + NSAI	2162	1939	1051
NSAI alone	2062	1793	989

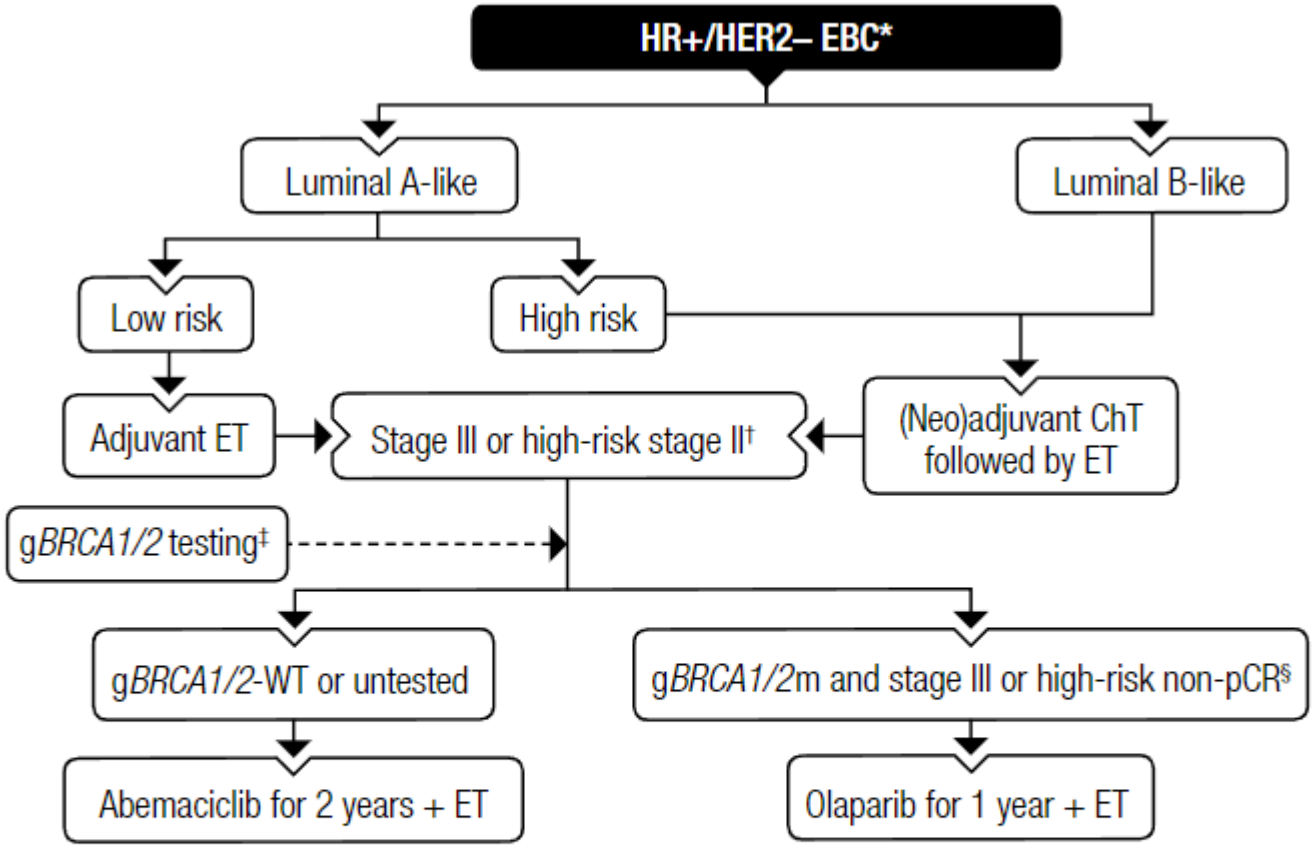
Based on regression analysis, physical functioning scores were higher in premenopausal women and men vs postmenopausal women and those who received prior (neo)adjuvant CT vs no prior (neo)adjuvant CT and were not impacted by the treatment arm

Physical functioning was maintained with the addition of ribociclib to standard-of-care NSAI[1,d,e]

CT, chemotherapy; C, cycle; D, day; EORTC, Organisation for Research and Treatment of Cancer; ET, endocrine therapy; HRQOL, health-related quality of life; NSAI, nonsteroidal aromatase inhibitor;.
[a] Week 49/day 1, C13D1. [b] Week 97/day 1, C25D1. [c] Week 145/day 1, C37D1. [d] No difference from baseline was observed in either arm based on established thresholds for interpreting changes in physical functioning score (−5to 2, no difference)[1] [e] Changes from baseline remained within 0.5 SD of their baseline value: ribociclib + NSAI, 14.87; NSAI alone, 14.87.

1. Cocks K, et al. *Eur J Cancer*. 2012;48(11):1713-1721.

Systemic Treatment for HR+, HER2- early BC



*See figure on page 49 for the role of surgery in HR-positive, HER2-negative EBC

†Stage N1 with primary tumour > 5 cm, and/or grade 3 and/or Ki-67 ≥ 20%

‡If g*BRCA1/2* testing is appropriate and feasible

§Patients with HR-positive tumours and non-pCR after neoadjuvant ChT require a CPS+EG score ≥ 3 to receive olaparib

ChT, chemotherapy; CPS+EG, pre-treatment clinical stage and post-treatment pathological stage, oestrogen receptor and tumour grade; EBC, early breast cancer; ET, endocrine therapy; g*BRCA1/2*; germline *BRCA1/2*; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; m, mutation; N, node; pCR, pathological complete response; WT, wild type

ESMO Guidelines, 2024

Treatment of the Advanced Disease

JOHN HAYWARD,* F.R.C.S.

British Medical Journal, 1970, 2, 469–471

There are now many measures[#] available to treat advanced breast cancer. Nevertheless, only if the right therapies are selected and given in the proper sequence can they be used to the best advantage. At this stage of the disease a cure is impossible at present. Hence the principal aim in the patient's management must be to improve by the simplest means possible the quality of what life remains to her. Such treatment may prolong survival but this is not necessarily the most important aim. In essence, therefore, treatment should be symptomatic, aiming by local or general measures to relieve distressing symptoms and, by sensible anticipation, to postpone the development of further symptoms.

While metastases are still localized, radiotherapy or local surgery may suffice to keep the disease under control. Only when the disease has become more widespread and the use of local treatments has been exhausted should general measures be considered.

#

- Castration
- Androgens and Oestrogens
- Progestogens
- Corticosteroids
- Adrenalectomy and Hypophysectomy
- Cytotoxins (CTX and 5-FU)