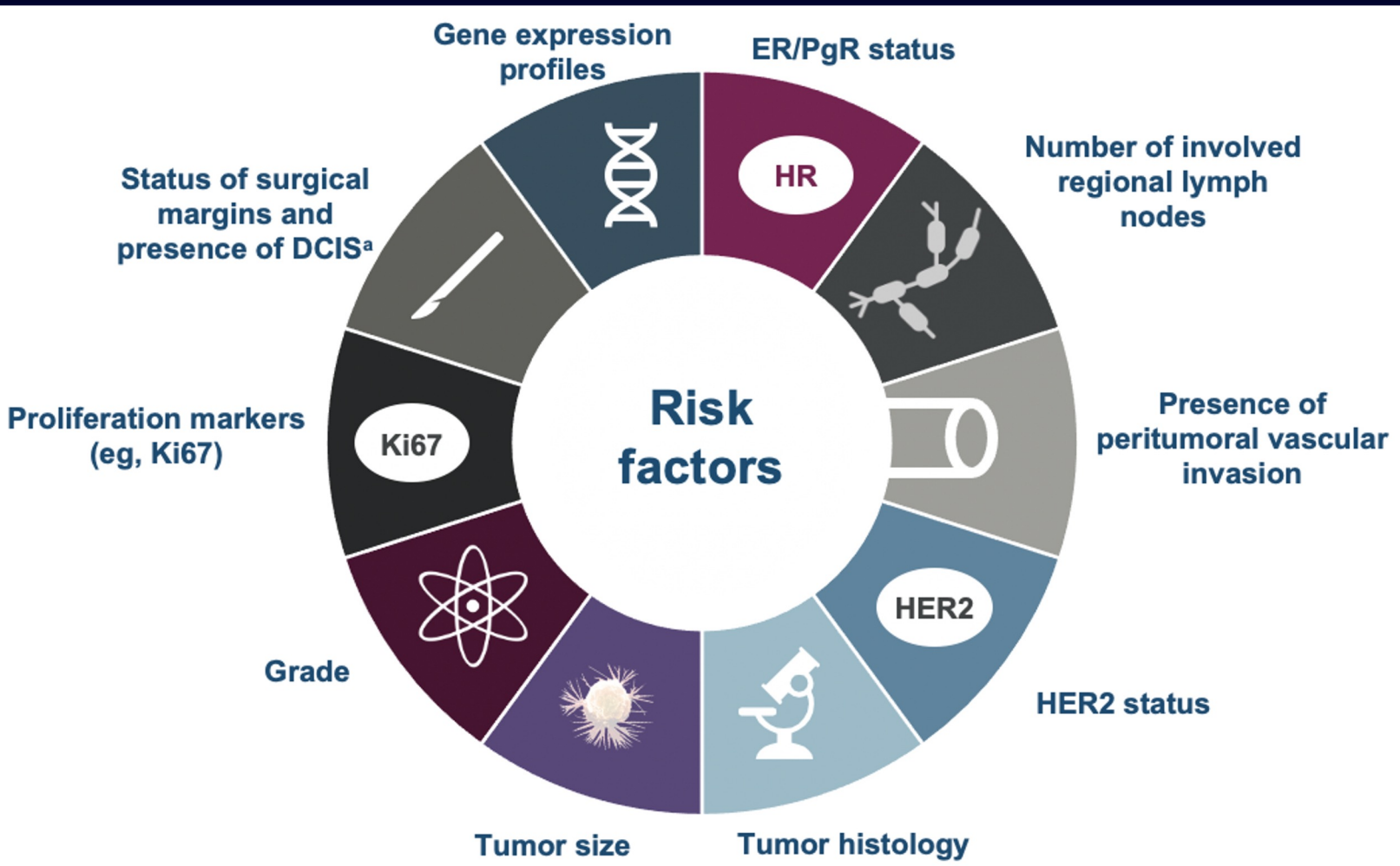
Endocrine Therapy for Early-Stage Breast Cancer: Who Needs More?

Mohammad Jahanzeb, MD, FACP, FASCO
Florida Atlantic University, Boca Raton

Introduction

- The role of endocrine therapy in early-stage HR+ Breast Cancer is well established
- While this treatment has largely consisted of tamoxifen and/or an aromatase inhibitor, residual recurrence risk remains for a sizeable proportion of patients
- Longer duration (10 vs. 5 years) for some, or OFS for high-risk premenopausal women has been recommended
- There is a need to identify these high-risk patients where additional therapy may be warranted
- We have now entered the era of adding concurrentnon-endocrine interventions to endocrine therapy in selected subgroups

High Risk Features



Clinica/Pathological Staging, Estrogen Receptor Status & Grade

Stage/Feature		Points
Clinical stage (pre-treatment)	I/IIA	0
	IIB/IIIA	1
	IIIB/IIIC	2
Pathologic stage (post-treatment)	0/1	0
	IIA/IIB/IIIA/IIIB	1
	IIIC	2
Receptor status	ER positive	0
	ER negative	1
Nuclear grade	Nuclear grade 1-2	0
	Nuclear grade 3	1

:3 required for patients with HR-positive breast cancer.

(Residual disease post NAC and an aggregate score of ≥ 3 required for entry to OlympiA)

Mittendorf et. al. J Clin Oncol 2011;29: 1956-62.

rapid communications

Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2−, Node-Positive, High-Risk, Early Breast Cancer (monarchE)

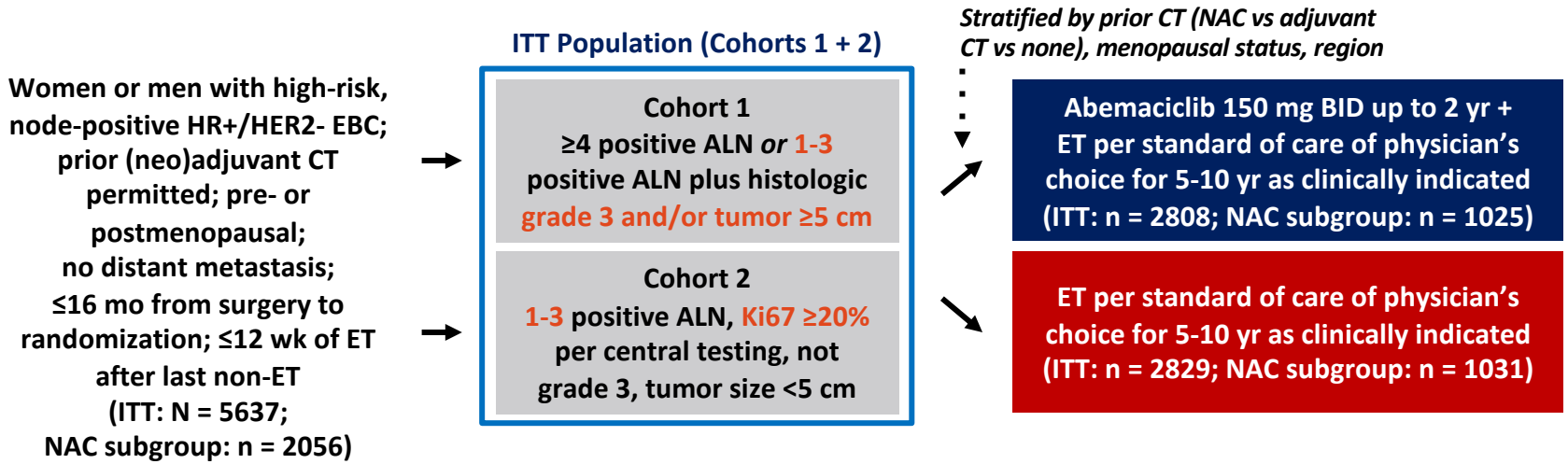
Stephen R. D. Johnston, MD, PhD[1]; Nadia Harbeck, MD, PhD[2]; Roberto Hegg, MD, PhD[3]; Masakazu Toi, MD, PhD[4]; Miguel Martin, MD, PhD[5]; Zhi Min Shao, MD[6]; Qing Yuan Zhang, MD, PhD[7]; Jorge Luis Martinez Rodriguez, MD[8]; Mario Campone, MD, PhD[9]; Erika Hamilton, MD[10]; Joohyuk Sohn, MD, PhD[11]; Valentina Guarneri, MD, PhD[12]; Morihito Okada, MD, PhD[13]; Frances Boyle, MD, MBBS, PhD[14]; Patrick Neven, MD, PhD[15]; Javier Cortés, MD, PhD[16]; Jens Huober, MD[17]; Andrew Wardley, MD, MBChB[18]; Sara M. Tolaney, MD, MPH[19]; Irfan Cicin, MD[20]; Ian C. Smith, MD[21,22]; Martin Frenzel, PhD[22]; Desirée Headley, MSc[22]; Ran Wei, PhD[22]; Belen San Antonio, PhD[22]; Maarten Hulstijn, PhD[22]; Joanne Cox, MD[22]; Joyce O'Shaughnessy, MD[23]; and Priya Rastogi, MD[24]; on behalf of the monarchE Committee Members and Investigators

Johnston et. al. J Clin Oncol 38:3987-3998, 2020

monarchE : Study Design

International, randomized, open-label phase III trial

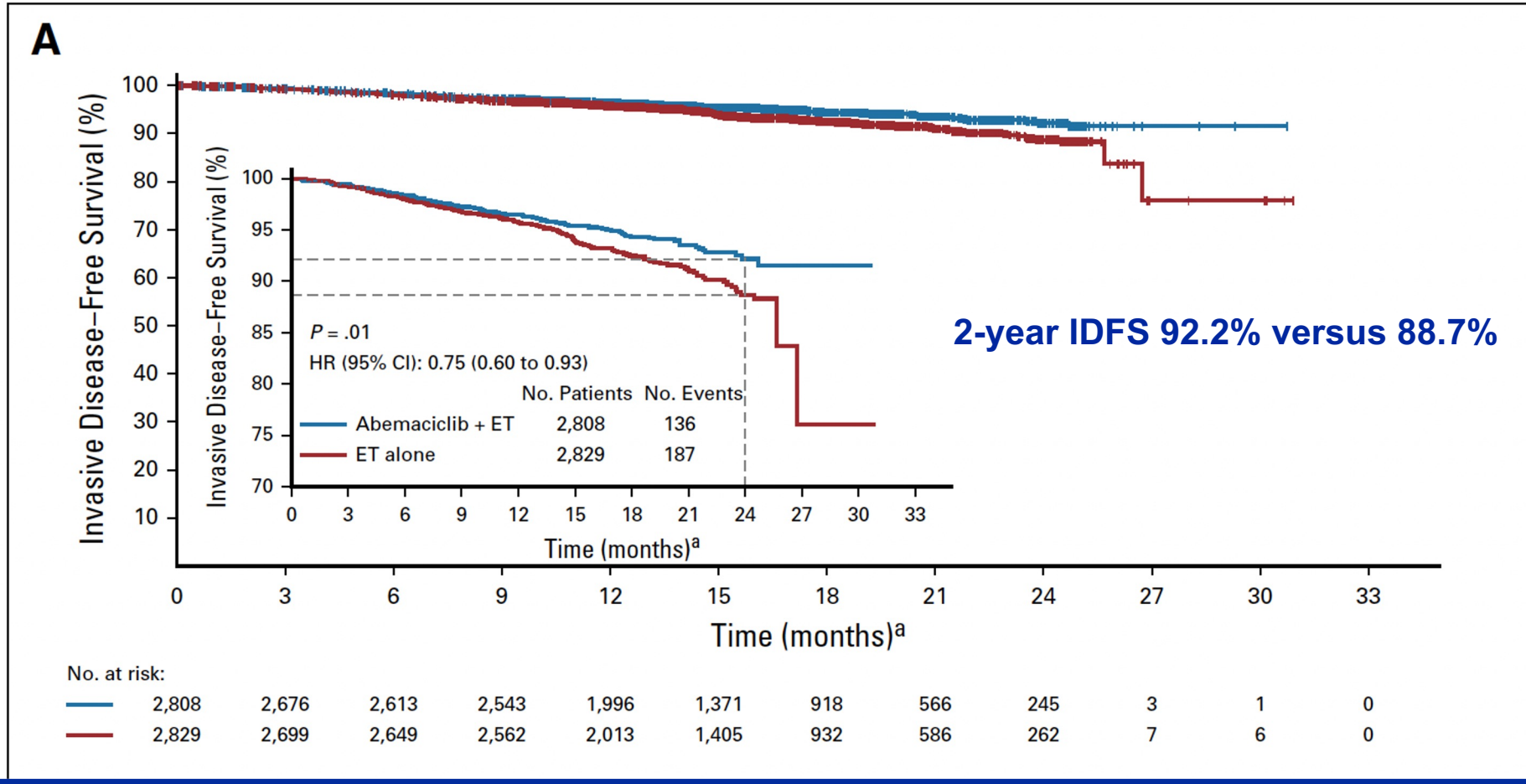
– Prespecified subgroup analysis in those with prior NAC (NAC subgroup) performed at primary outcome analysis



- Primary endpoint: iDFS (primary outcome analysis occurred after 395 iDFS events in ITT population)
- Key secondary endpoints: distant RFS, iDFS in Ki67-high (≥20%) population, OS, safety, PROs, PK

Martin. ASCO 2021. Abstr 517. Johnston. JCO. 2020;38:3987. Rastogi. SABCS 2020. Abstr GS1-01.

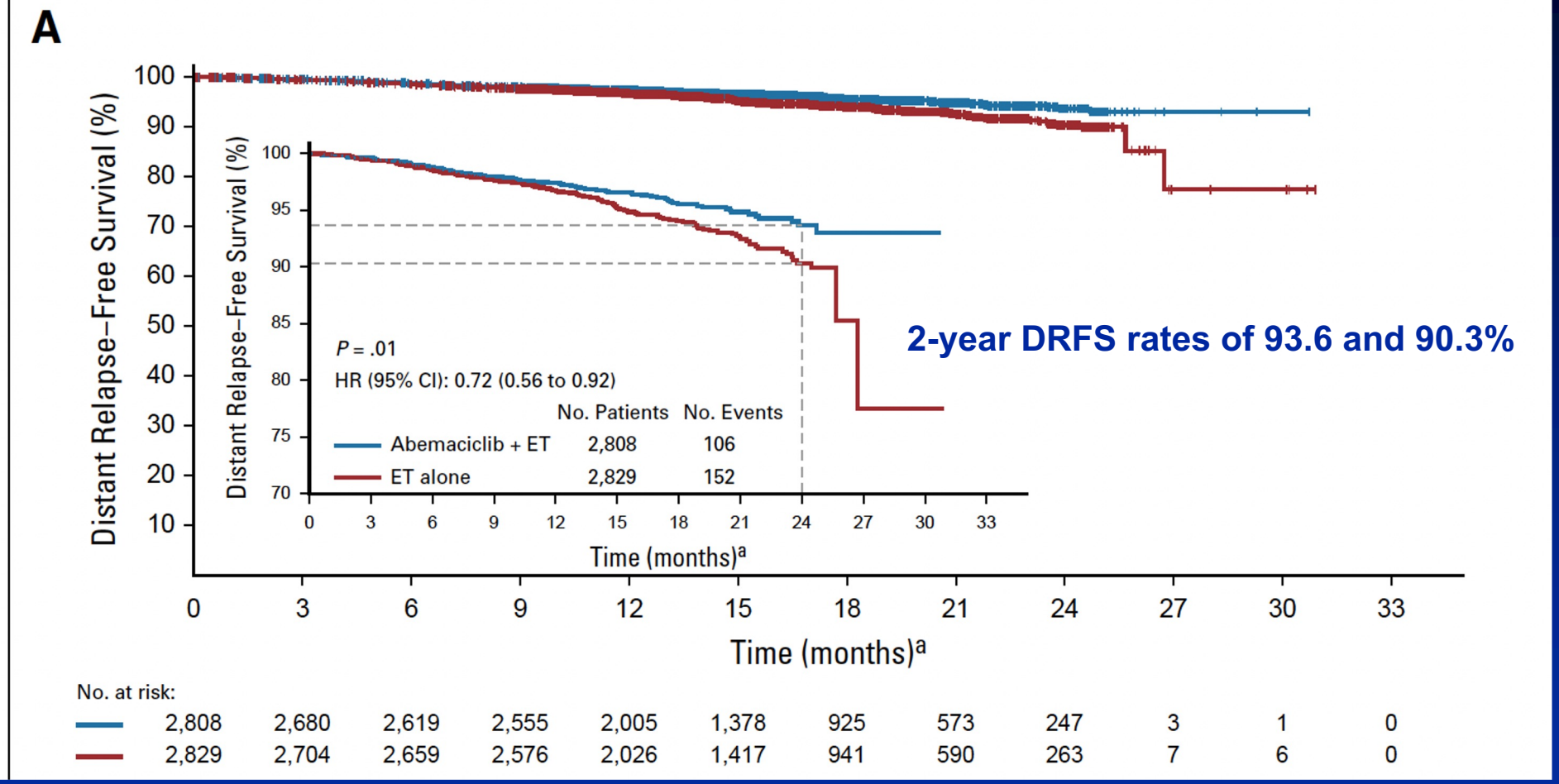
Abemaciclib in Node-Positive, High-Risk Early Breast Cancer



2-year IDFS 92.2% versus 88.7%

Johnston et. al. J Clin Oncol 38:3987-3998, 2020

Abemaciclib in Node-Positive, High-Risk Early Breast Cancer



Johnston et. al. J Clin Oncol 38:3987-3998, 2020

FDA approves abemaciclib with endocrine therapy for early breast cancer

Resources for Information | Approved Drugs

Oncology (Cancer) / Hematologic Malignancies Approval Notifications

Ongoing | Cancer Accelerated Approvals

Verified Clinical Benefit |

On October 12,2021, the Food and Drug Administration approved abemaciclib with endocrine therapy (tamoxifen or an aromatase inhibitor) for adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20%, as determined by an FDA approved test. This is the first CDK 4/6 inhibitor approved for adjuvant treatment of breast cancer.

FDA also approved the Ki-67 IHC MIB-1 pharmDx as a companion diagnostic for selecting patients for this indication.

Content current as of:
10/13/2021

Regulated Product(s)
Drugs
Prescription Drugs

JAMA Oncology | Brief Report

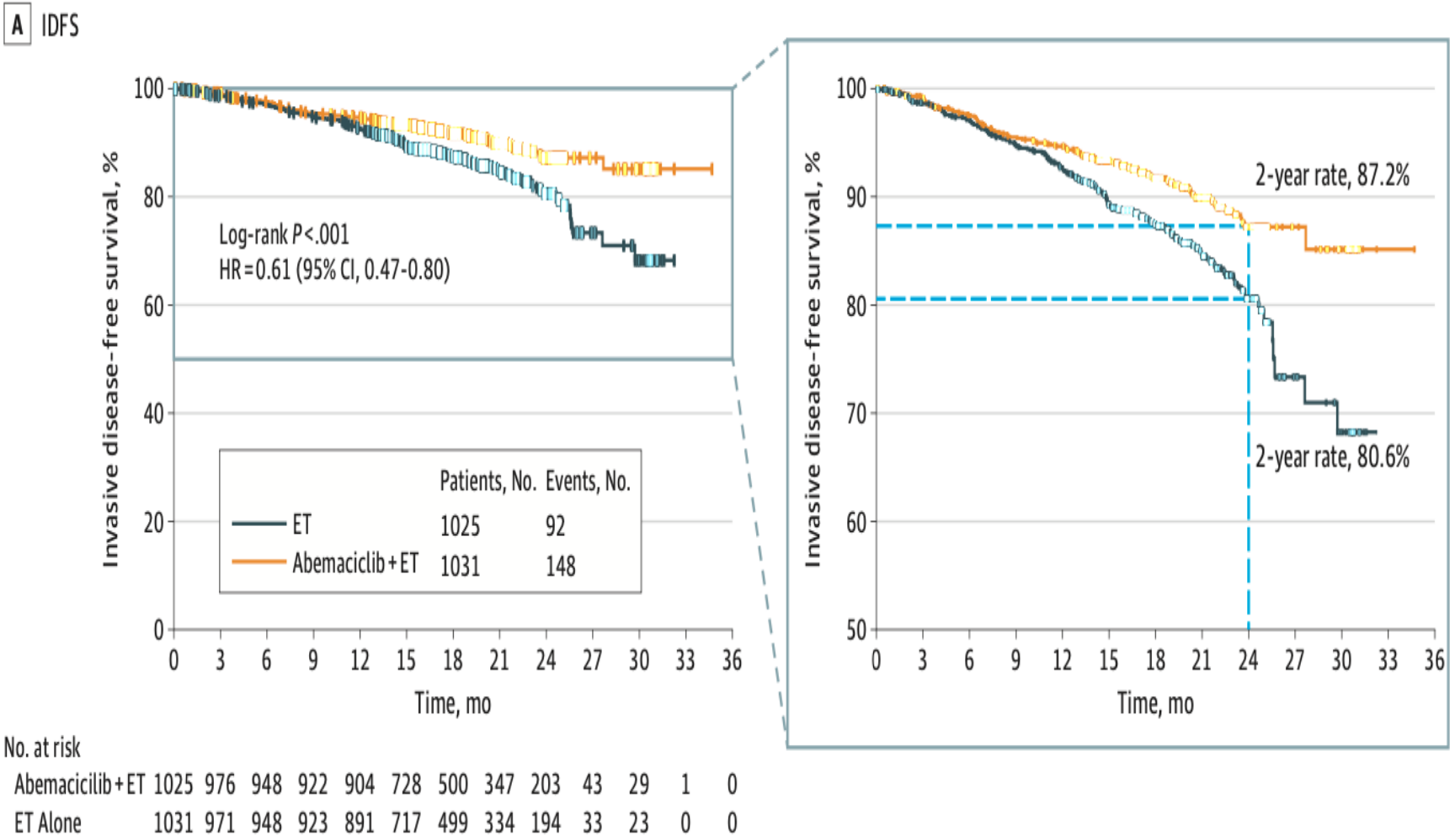
Treatment With Adjuvant Abemaciclib Plus Endocrine Therapy in Patients With High-risk Early Breast Cancer Who Received Neoadjuvant Chemotherapy

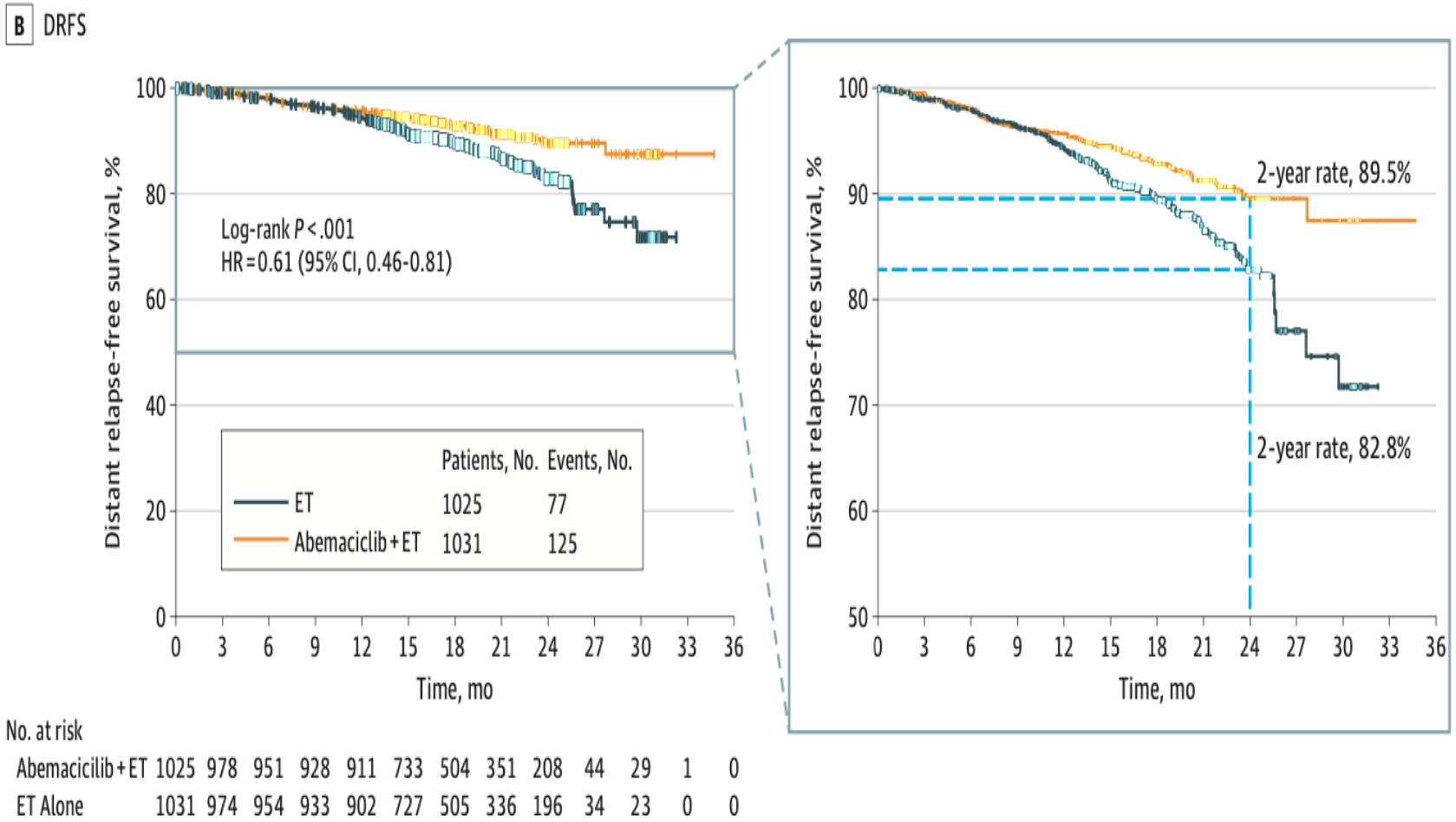
A Prespecified Analysis of the monarchE Randomized Clinical Trial

Miguel Martin, MD, PhD; Roberto Hegg, MD; Sung-Bae Kim, MD, PhD; Michael Schenker, MD, PhD; Daniela Grecea, MD, PhD; Jose Angel Garcia-Saenz, MD, PhD; Konstantinos Papazisis, MD, PhD; QuChang Ouyang, MD; Aleksandra Lacko, MD, PhD; Berna Oksuzoglu, MD; James Reeves, MD; Meena Okera, MD; Laura Testa, MD; Chikako Shimizu, MD, PhD; Neelima Denduluri, MD; Hryhoriy Adamchuk, MD; Shaker Dakhil, MD; Ran Wei, PhD; Tammy Forrester; Maria Munoz Fernandez, PhD; Annamaria Zimmermann; Desiree Headley; Stephen R. D. Johnston, MD, PhD

Martin et. al. JAMA Oncol. Published online June 2, 2022.

Figure. Kaplan-Meier Curves of Invasive Disease-Free Survival (IDFS)/Distant Relapse-Free Survival (DRFS) in Patients Who Received Neoadjuvant Chemotherapy (NAC)





No. at risk

Abemaciclib + ET	1025	978	951	928	911	733	504	351	208	44	29	1	0
ET Alone	1031	974	954	933	902	727	505	336	196	34	23	0	0

Kaplan-Meier curves of IDFS (A), DRFS (B), and IDFS/DRFS (inset) to better visualize separation of the curves in patients who received NAC. The inset tables present the number of events per arm, unstratified hazard ratio (HR) in the NAC subgroup, and the 2-year rates in each arm (blue dotted lines). ET indicates endocrine therapy.

Martin et. al. JAMA Oncol. Published online June 2, 2022.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

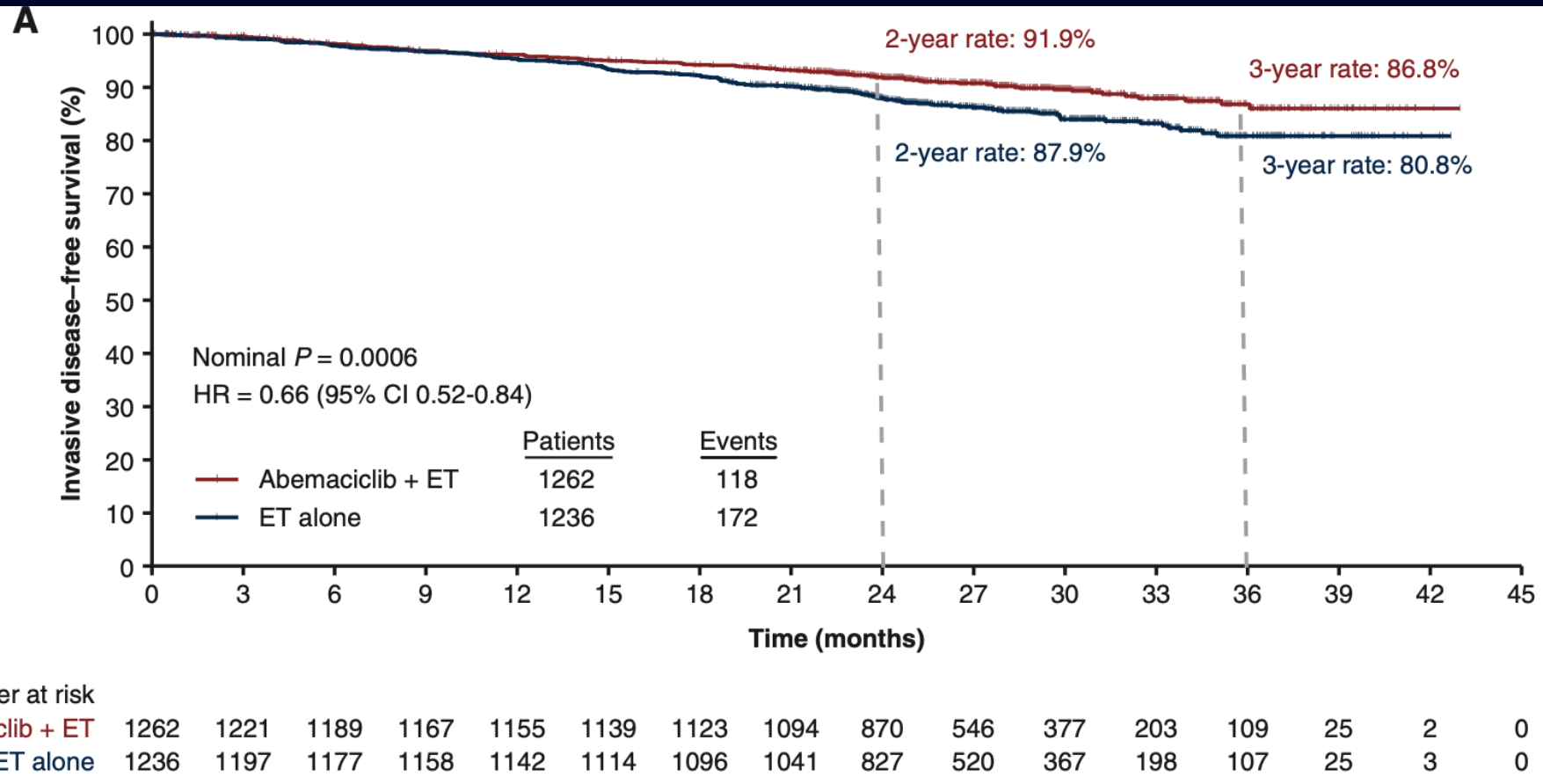
ORIGINAL ARTICLE

Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study

N. Harbeck[1*†], P. Rastogi[2†], M. Martin[3], S. M. Tolaney[4], Z. M. Shao[5], P. A. Fasching[6], C. S. Huang[7], G. G. Jaliffe[8], A. Tryakin[9], M. P. Goetz[10], H. S. Rugo[11], E. Senkus[12], L. Testa[13], M. Andersson[14], K. Tamura[15], L. Del Mastro[16,17], G. G. Steger[18], H. Kreipe[19], R. Hegg[20], J. Sohn[21], V. Guarneri[22,23], J. Cortés[24,25], E. Hamilton[26], V. André[27], R. Wei[27], S. Barriga[27], S. Sherwood[27], T. Forrester[27], M. Munoz[27], A. Shahir[27], B. San Antonio[27], S. C. Nabinger[27], M. Toi[28], S. R. D. Johnston[29‡] & J. O'Shaughnessy[30‡], On behalf of the monarchE Committee Members

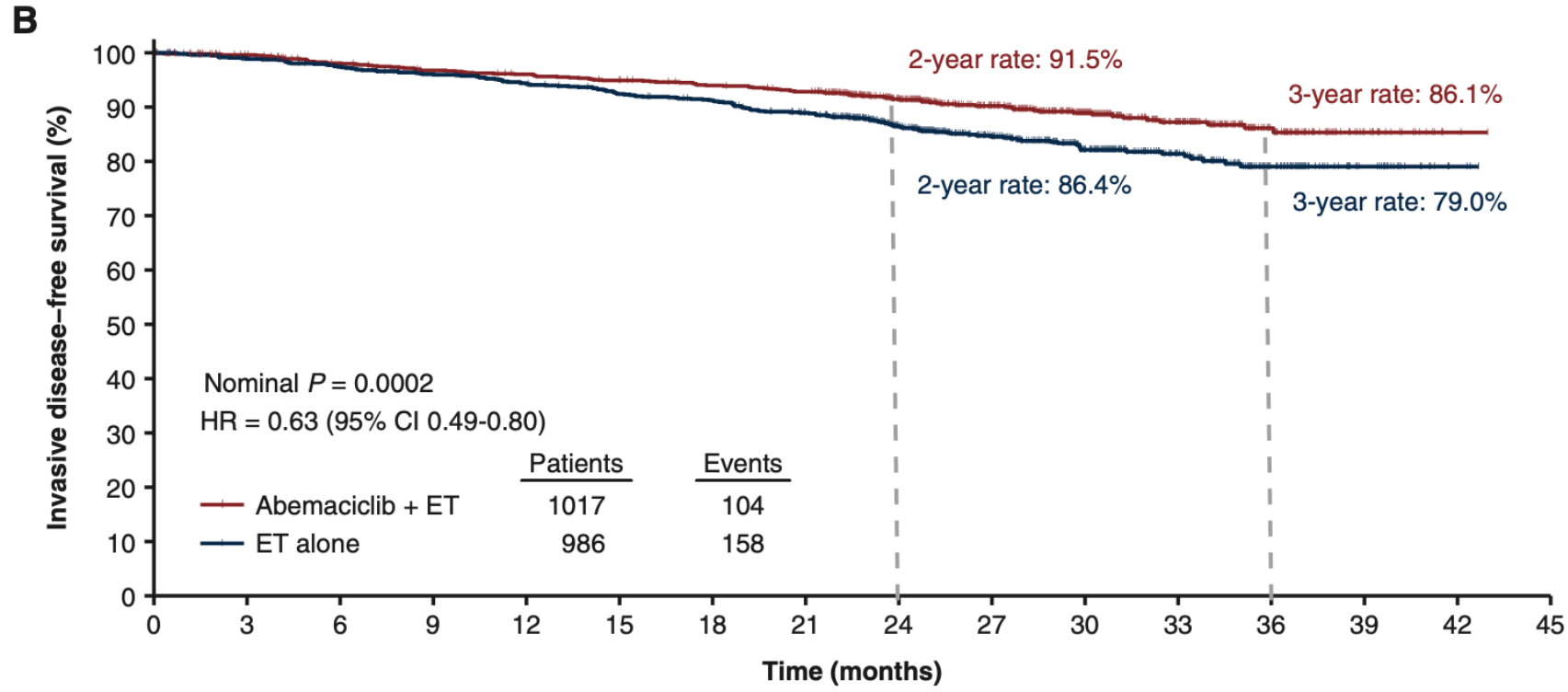
Harbeck et. al published online https://doi.org/10.1016/j.annonc.2021.09.015

monarchE Invasive Disease-Free Survival: ITT Ki-67 high: Additional Follow UP 27mo



Harbeck et. al published online https://doi.org/10.1016/j.annonc.2021.09.015

monarchE Invasive Disease-Free Survival: Cohort 1 Ki-67 high: Additional Follow UP 27mo



Number at risk																
Abemaciclib + ET	1017	989	963	946	936	922	908	894	733	484	348	203	109	25	2	0
ET alone	986	955	938	922	906	883	868	835	687	457	333	197	107	25	3	0

Harbeck et. al published online https://doi.org/10.1016/j.annonc.2021.09.015

monarchE Invasive Disease-Free Survival in Cohort 1 Ki-67 High vs. Low at Additional Follow Up 27 mo

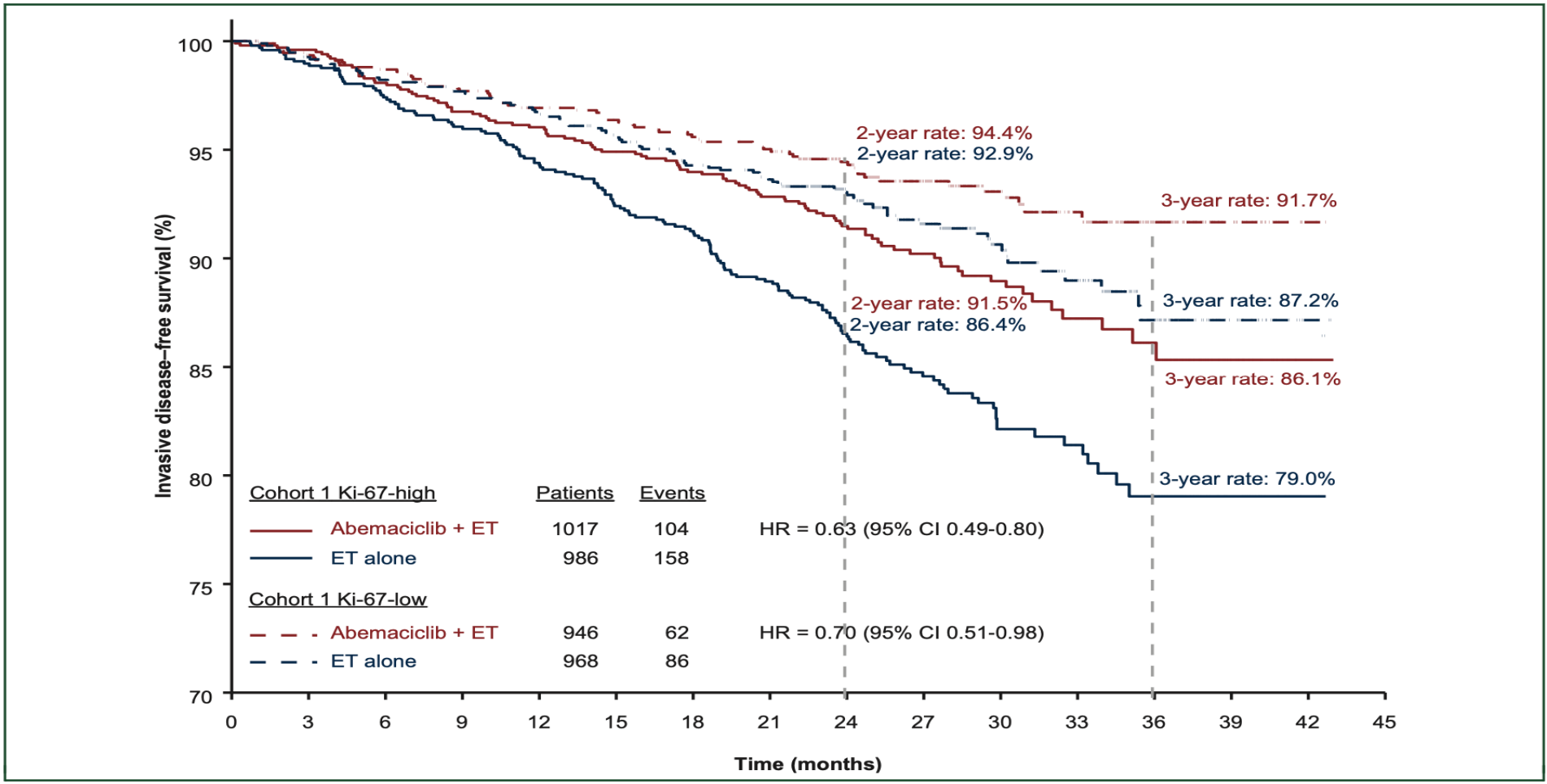


Figure 3. **Kaplan-Meier curves of invasive disease-free survival in Cohort 1 Ki-67 high versus Ki-67 low at additional follow-up 1 (AFU1).**
CI, confidence interval; ET, endocrine therapy; HR, hazard ratio.

Harbeck et. al published online https://doi.org/10.1016/j.annonc.2021.09.015

Adjuvant Olaparib

Majority of gBRCAm Patients are ER+

In 2021, an estimated 282,000 new cases of breast cancer were diagnosed in the United States[1]

TNBC (HR−/HER2−)
≈34,000 patients[1,2]

14% g*BRCA*m[3] | ≈4,800 patients[1-3,a]

HR+/HER2−
≈205,000 patients[1,2]

5% g*BRCA*m[3] | ≈10,000 patients[1-3,a]

Statistics shown on slide are for female breast cancer.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

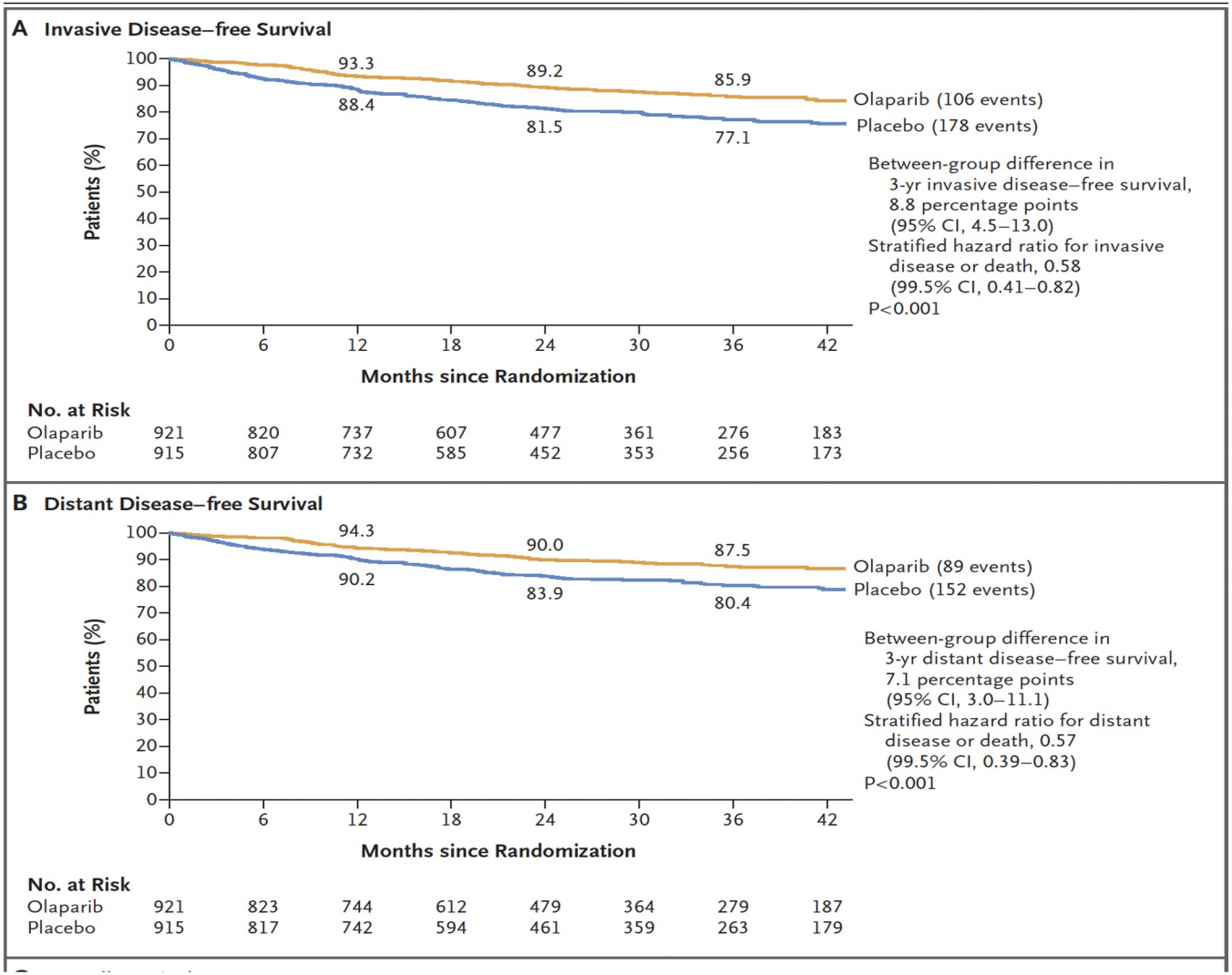
A.N.J. Tutt, J.E. Garber, B. Kaufman, G. Viale, D. Fumagalli, P. Rastogi, R.D. Gelber, E. de Azambuja, A. Fielding, J. Balmaña, S.M. Domchek, K.A. Gelmon, S.J. Hollingsworth, L.A. Korde, B. Linderholm, H. Bandos, E. Senkus, J.M. Suga, Z. Shao, A.W. Pippas, Z. Nowecki, T. Huzarski, P.A. Ganz, P.C. Lucas, N. Baker, S. Loibl, R. McConnell, M. Piccart, R. Schmutzler, G.G. Steger, J.P. Costantino, A. Arahmani, N. Wolmark, E. McFadden, V. Karantza, S.R. Lakhani, G. Yothers, C. Campbell, and C.E. Geyer, Jr., for the OlympiA Clinical Trial Steering Committee and Investigators*

N Engl J Med 2021;384:2394-405.

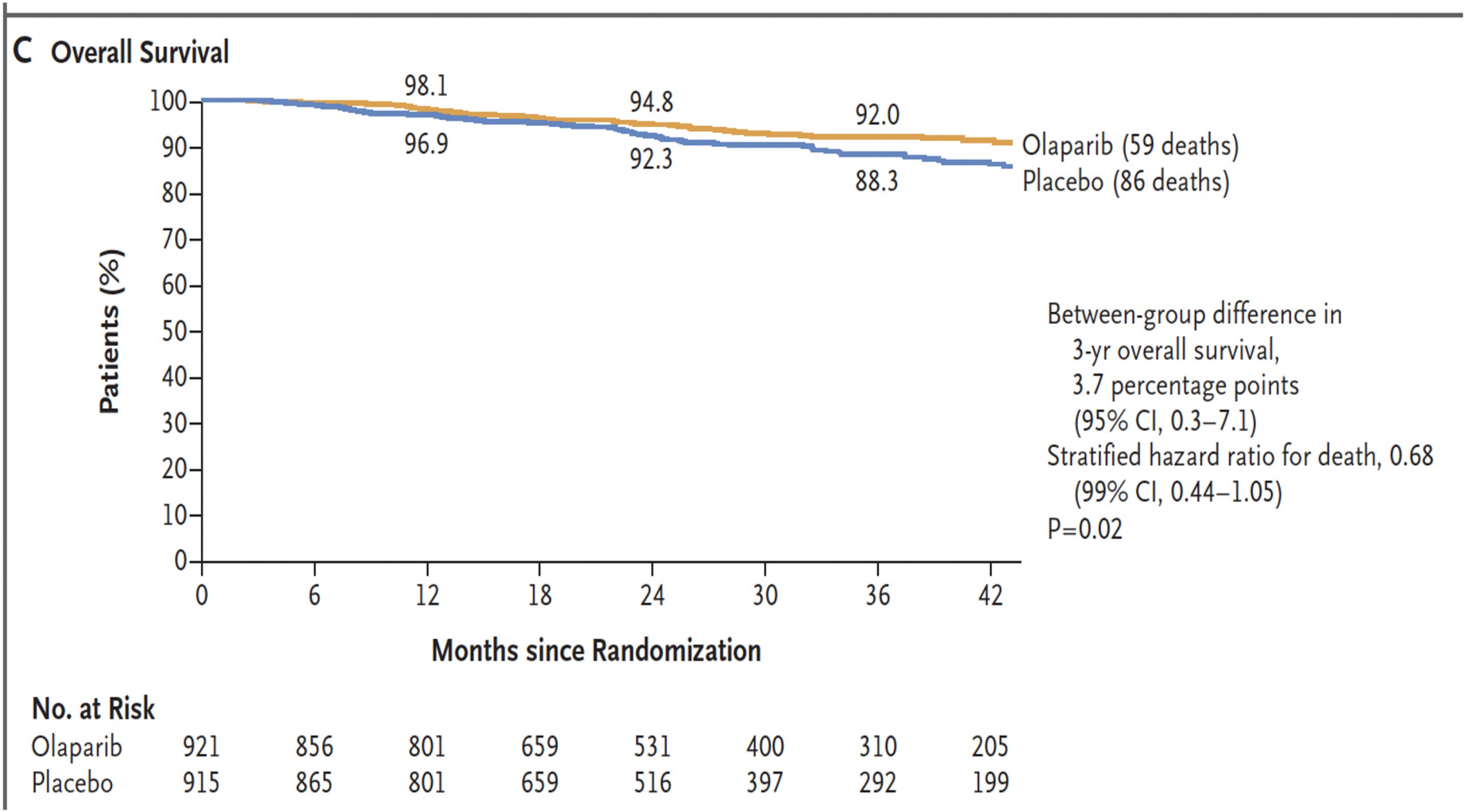
Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

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)
Yes	247 (26.8)	239 (26.1)
Concurrent hormone therapy (hormone-receptor–positive patients only) — no./total no. (%)	146/168 (86.9)	142/157 (90.4)
Hormone-receptor status — no. (%)‡		
Hormone-receptor positive and HER2 negative§	168 (18.2)	157 (17.2)
Triple-negative breast cancer¶	751 (81.5)	758 (82.8)
Menopausal status (women only) — no./total no. (%)		
Premenopausal	572/919 (62.2)	553/911 (60.7)
Postmenopausal	347/919 (37.8)	358/911 (39.3)
Surgery for primary breast cancer — no. (%)		
Mastectomy	698 (75.8)	673 (73.6)
Conservative surgery only	223 (24.2)	240 (26.2)
Missing data	0	2 (0.2)

Tutt et. al. N Engl J Med 2021;384:2394-405.



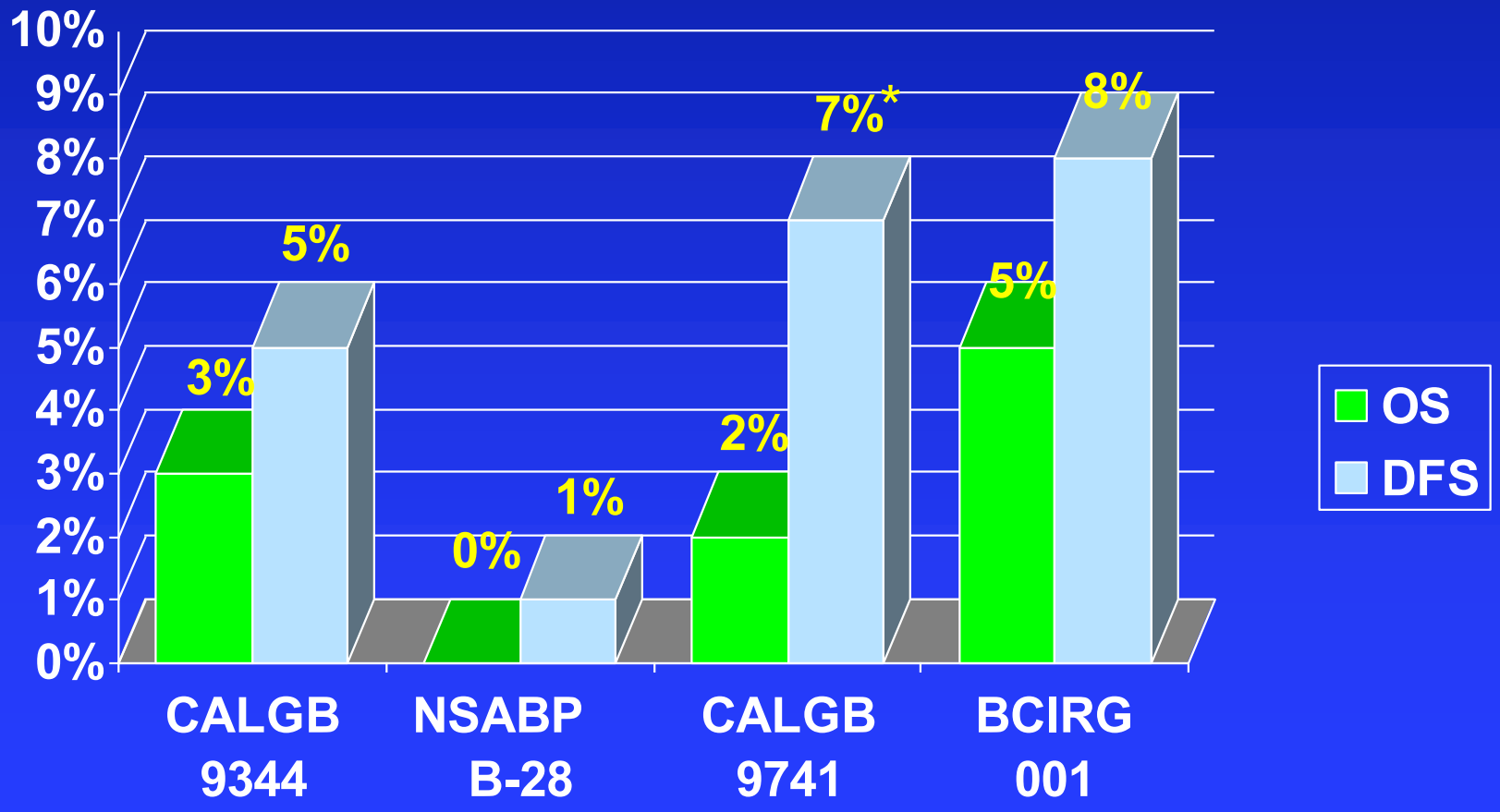
Tutt et. al. N Engl J Med 2021;384:2394-405



Tutt et. al. N Engl J Med 2021;384:2394-405

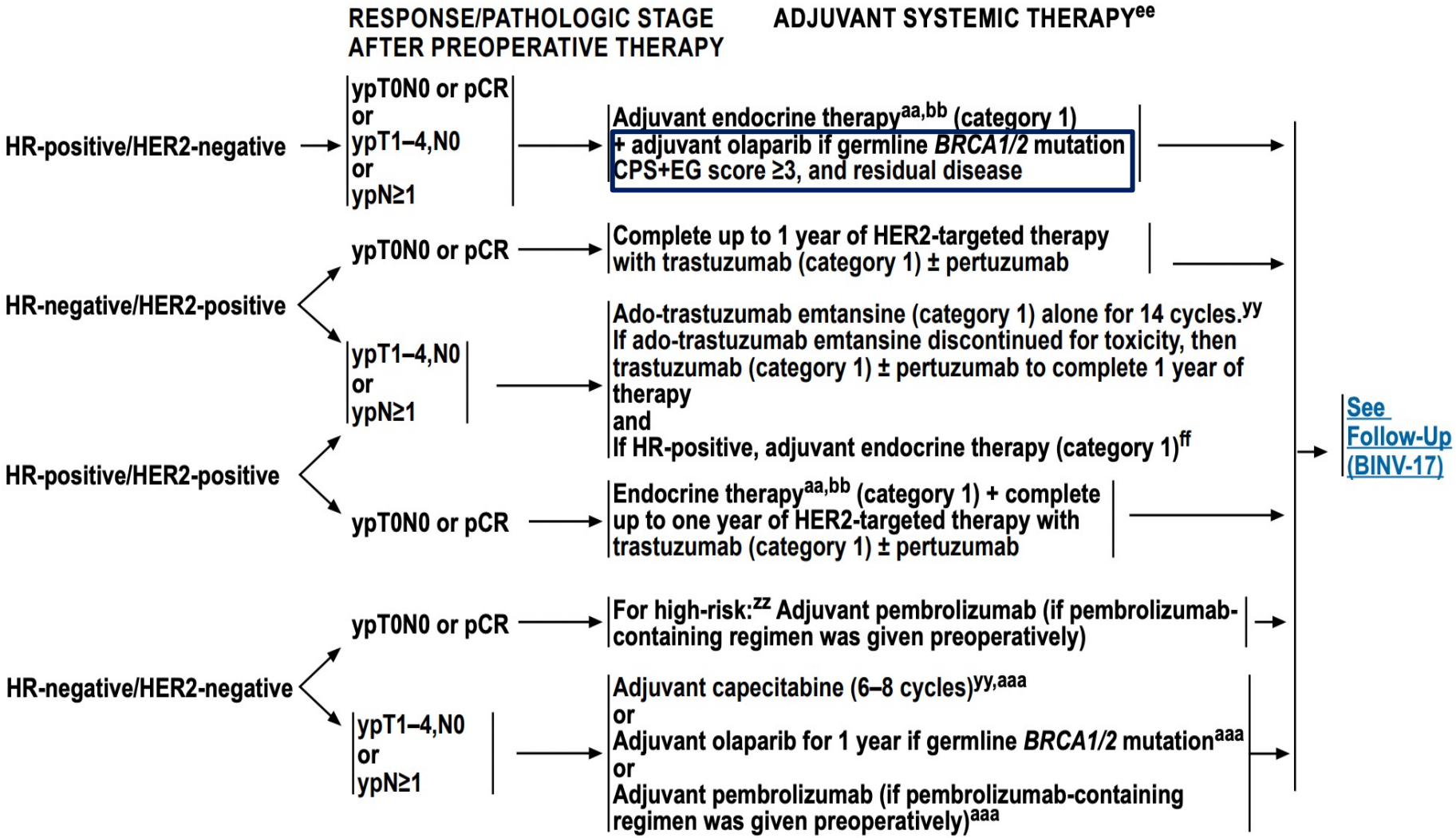
Absolute Differences at 3 Years in Disease-Free & Overall Survival

(all patients)

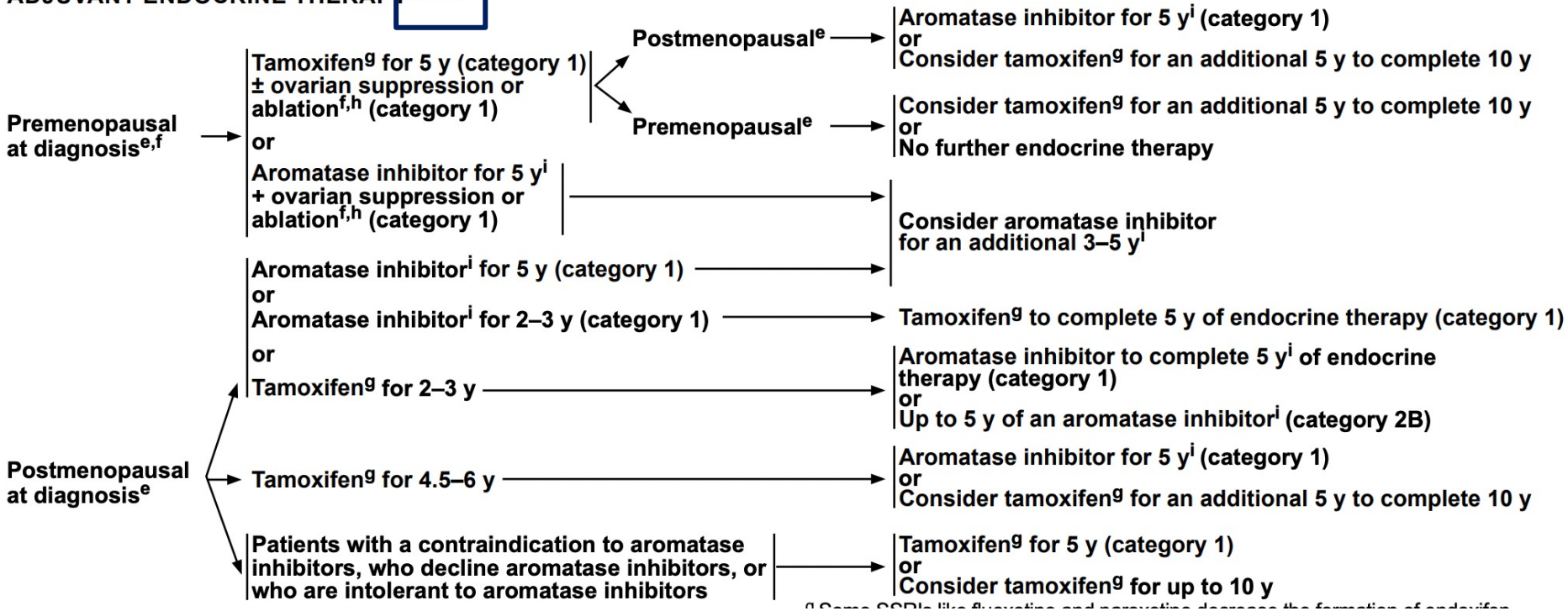


*only 4 year DFS reported

ADJUVANT SYSTEMIC THERAPY AFTER PREOPERATIVE SYSTEMIC THERAPY[ee]



ADJUVANT ENDOCRINE THERAPY[a,b,c,d]



[d] In patients with HR-positive/HER2-negative, high-risk breast cancer (ie, those with ≥4 positive lymph nodes, or 1–3 positive lymph nodes with one or more of the following: Grade 3 disease, tumor size ≥5 cm, or a Ki-67 score of ≥20%) 2 years of adjuvant abemaciclib can be considered in combination with endocrine therapy.

Case Study

44 year old Ashkenazi Jewish woman, gBRCA1 mutation+, presents after bilateral mastectomy and left ALND for left breast invasive ductal carcinoma, high grade, that is pT2pN2MX, ER+/PR+, HER2-, seeking advice regarding systemic therapy

What do you propose she do after completing adjuvant chemotherapy with ACT?

Olaparib? Abemaciclib? Both??!!

International Journal of
Molecular Sciences

MDPI

Article

A Novel CDK4/6 and PARP Dual Inhibitor ZC-22 Effectively Suppresses Tumor Growth and Improves the Response to Cisplatin Treatment in Breast and Ovarian Cancer

Chenchen Tian [1,†], Yufan Wei [1,†], Jianjun Li [1], Zhi Huang [1], Qiong Wang [1], Yingxue Lin [1], Xingping Lv [1], Yanan Chen [1], Yan Fan [1], Peiqing Sun [2], Rong Xiang [1], Antao Chang [3,*] and Shuang Yang [1,*]

Int. J. Mol. Sci. **2022**, *23*, 2892. https://doi.org/10.3390/ijms23052892 https://www.mdpi.com/journal/ijms

Summary

- Adjuvant treatment beyond chemotherapy for high-risk HR+ patients has evolved
- Abemaciclib and Olaparib are now approved for use in the adjuvant setting setting for those who meet the criteria
- We are in a data-free zone for those who meet criteria for both

Appendix

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

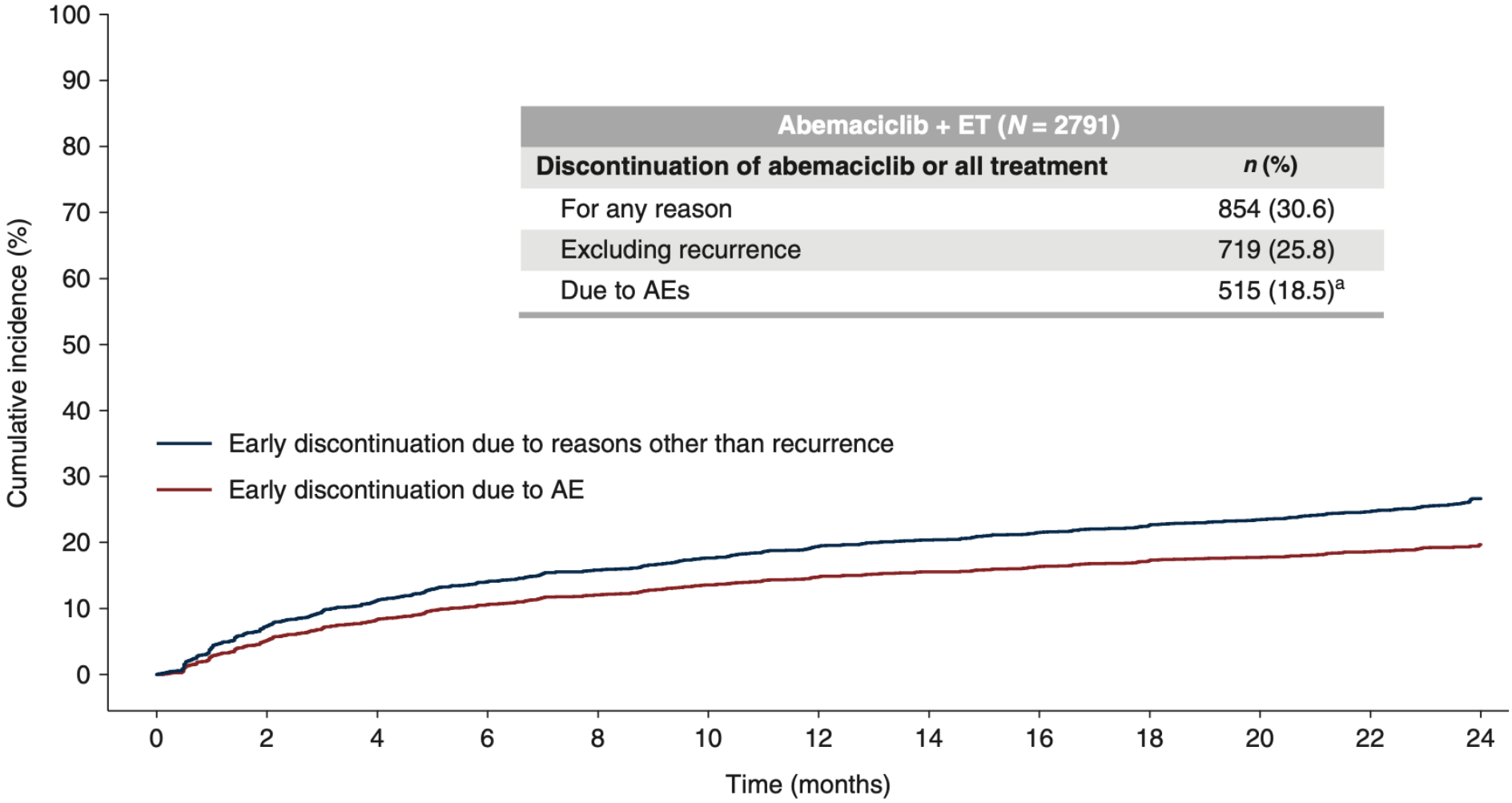
ORIGINAL ARTICLE

Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: safety and patient-reported outcomes from the monarchE study

H. S. Rugo[1*], J. O'Shaughnessy[2], F. Boyle[3,4], M. Toi[5], R. Broom[6], I. Blancas[7,8], M. Gumus[9], T. Yamashita[10], Y.-H. Im[11], P. Rastogi[12], F. Zagouri[13], C. Song[14], M. Campone[15], B. San Antonio[16], A. Shahir[16], M. Hulstijn[16], J. Brown[16], A. Zimmermann[16], R. Wei[16], S. R. D. Johnston[17], M. Reinisch[18] & S. M. Tolaney[19], on behalf of the monarchE Committee Members[†]

Volume 33 - Issue 6 - 2022 Published Online March 22 https://doi.org/10.1016/j.annonc.2022.03.006

A

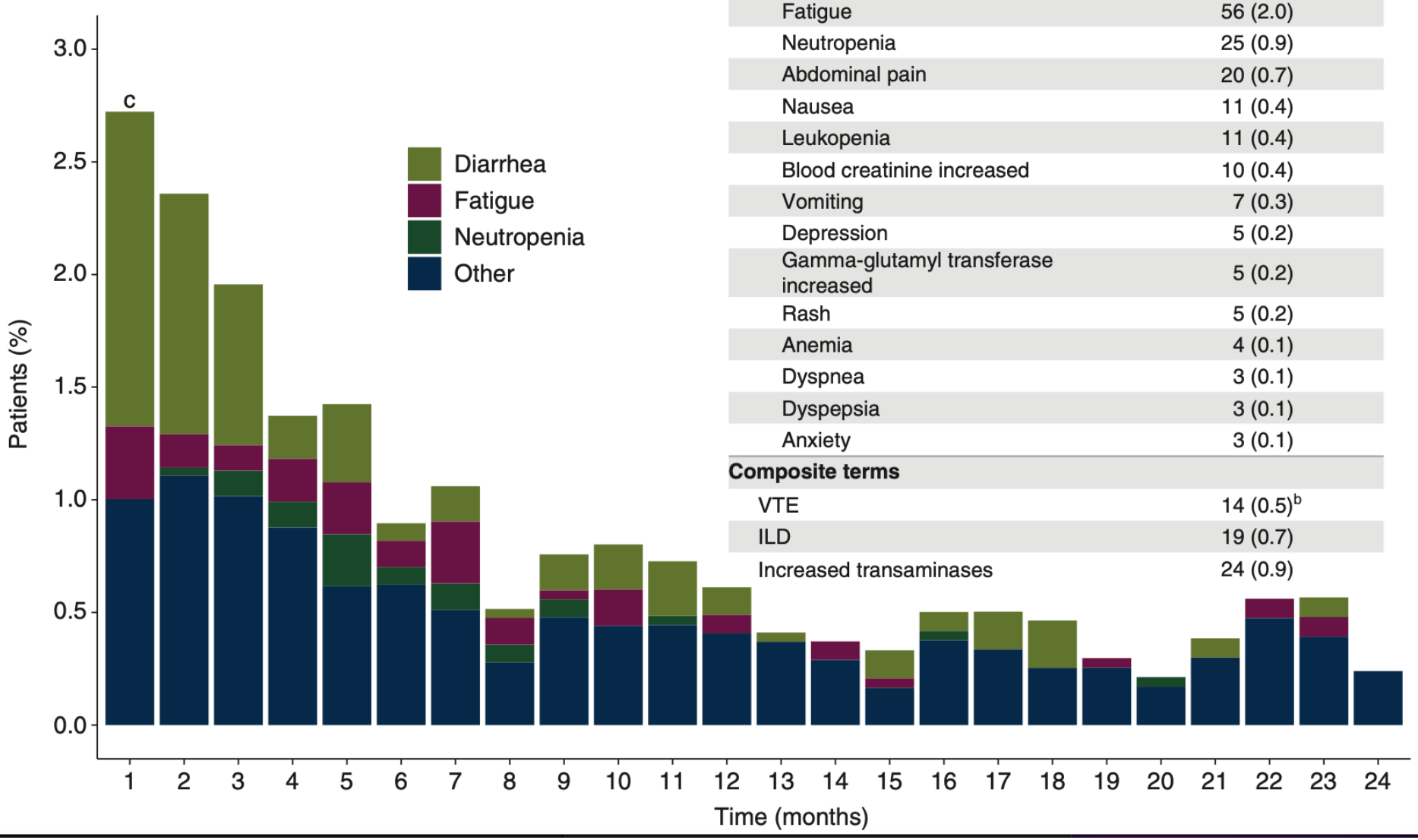


Abemaciclib + ET (*N* = 2791)	
Discontinuation of abemaciclib or all treatment	***n* (%)**
For any reason	854 (30.6)
Excluding recurrence	719 (25.8)
Due to AEs	515 (18.5)[a]

Rugo et. al. Published Online March 22 https://doi.org/10.1016/j.annonc.2022.03.006

B

Abemaciclib + ET (*N* = 2791)	
AEs leading to discontinuation	***n*** **(%)**
Diarrhea	147 (5.3)
Fatigue	56 (2.0)
Neutropenia	25 (0.9)
Abdominal pain	20 (0.7)
Nausea	11 (0.4)
Leukopenia	11 (0.4)
Blood creatinine increased	10 (0.4)
Vomiting	7 (0.3)
Depression	5 (0.2)
Gamma-glutamyl transferase increased	5 (0.2)
Rash	5 (0.2)
Anemia	4 (0.1)
Dyspnea	3 (0.1)
Dyspepsia	3 (0.1)
Anxiety	3 (0.1)
Composite terms	
VTE	14 (0.5)[b]
ILD	19 (0.7)
Increased transaminases	24 (0.9)



Rugo et. al. Published Online March 22 https://doi.org/10.1016/j.annonc.2022.03.006

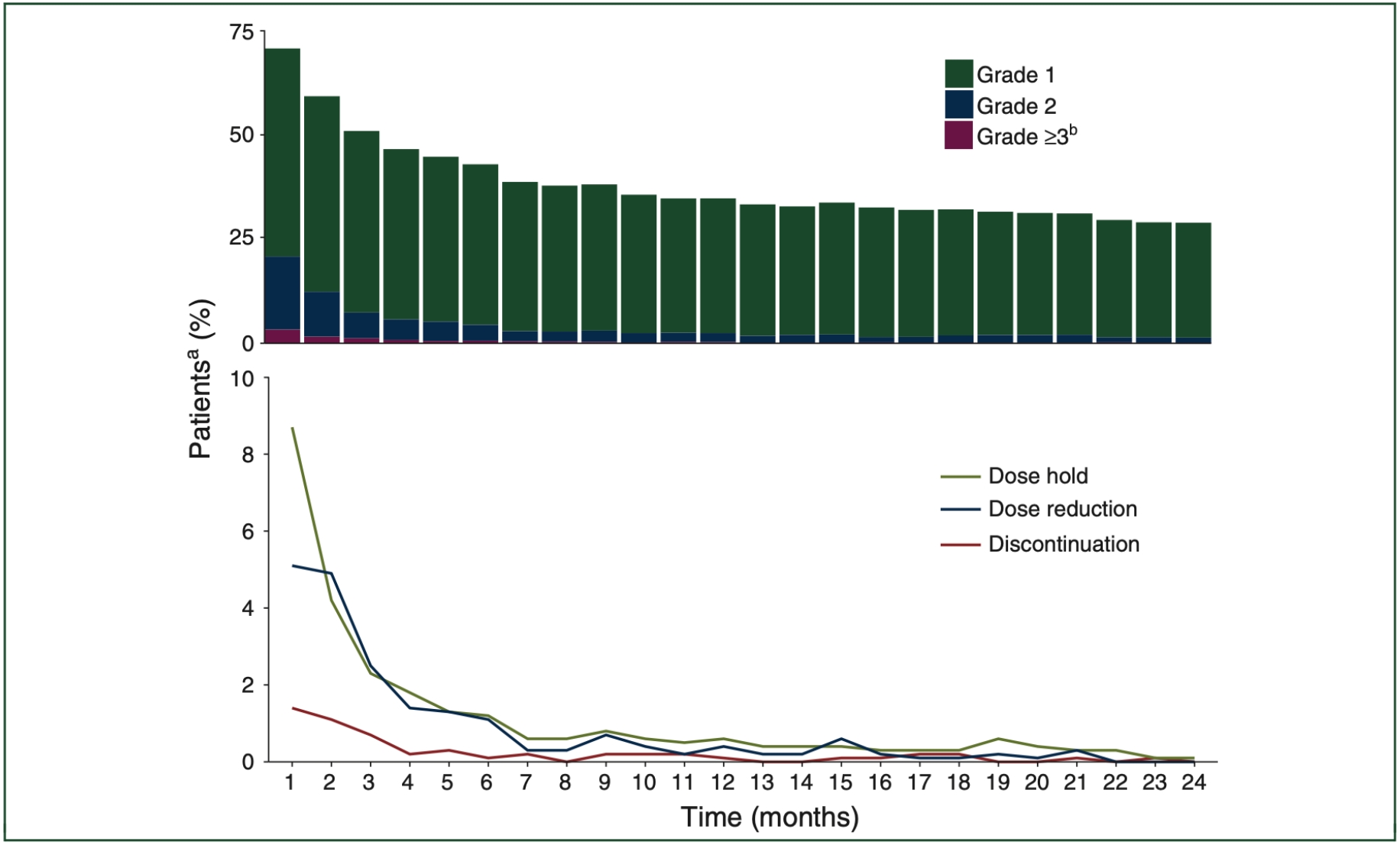


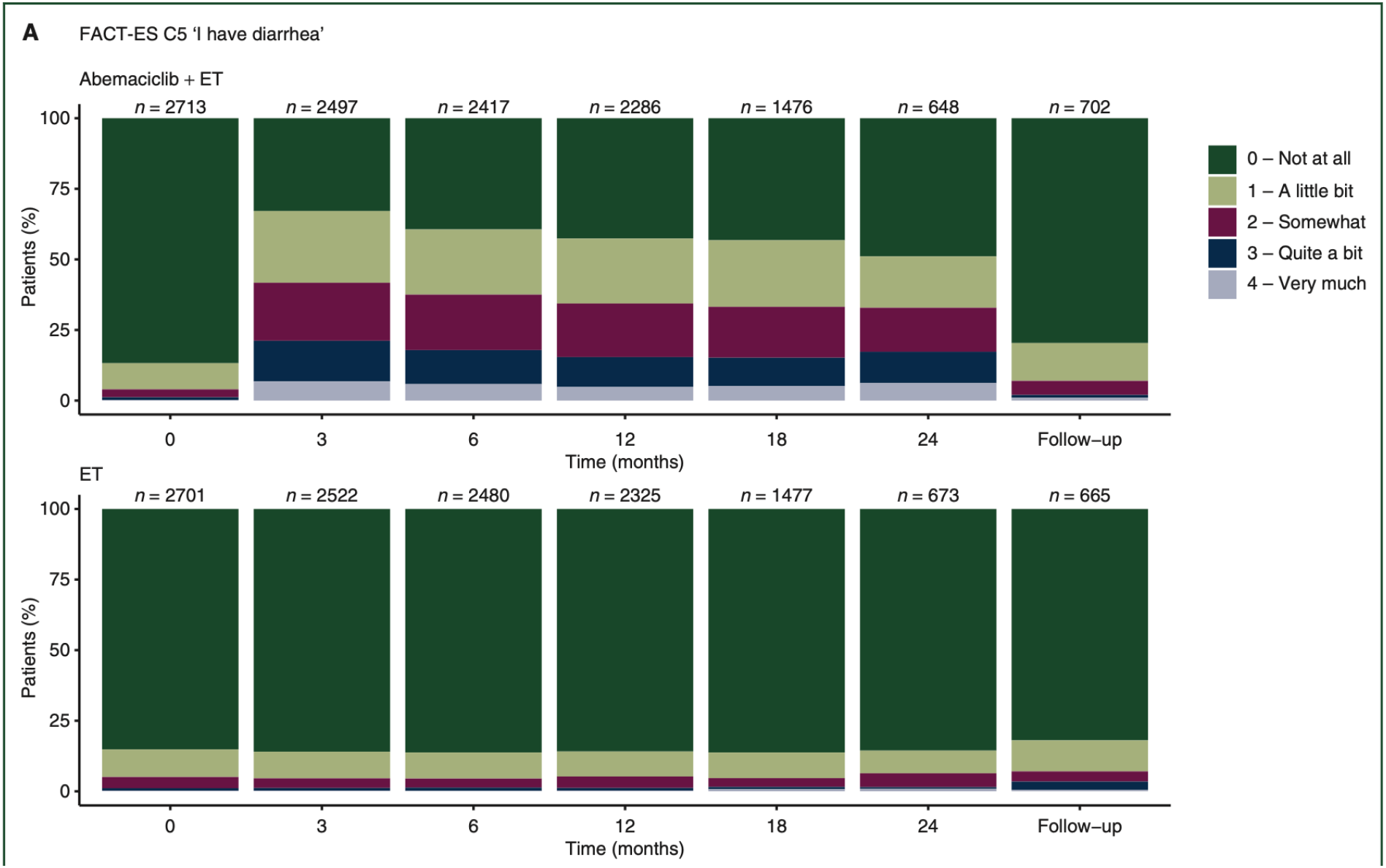
Figure 3. Diarrhea management over time.

G, grade.

[a]In the by-month analyses, number of patients at risk each month is used as the denominator to calculate % of events.

[b]There were no G4 events and one G5 event.

There were no G4 events and one G5 event.



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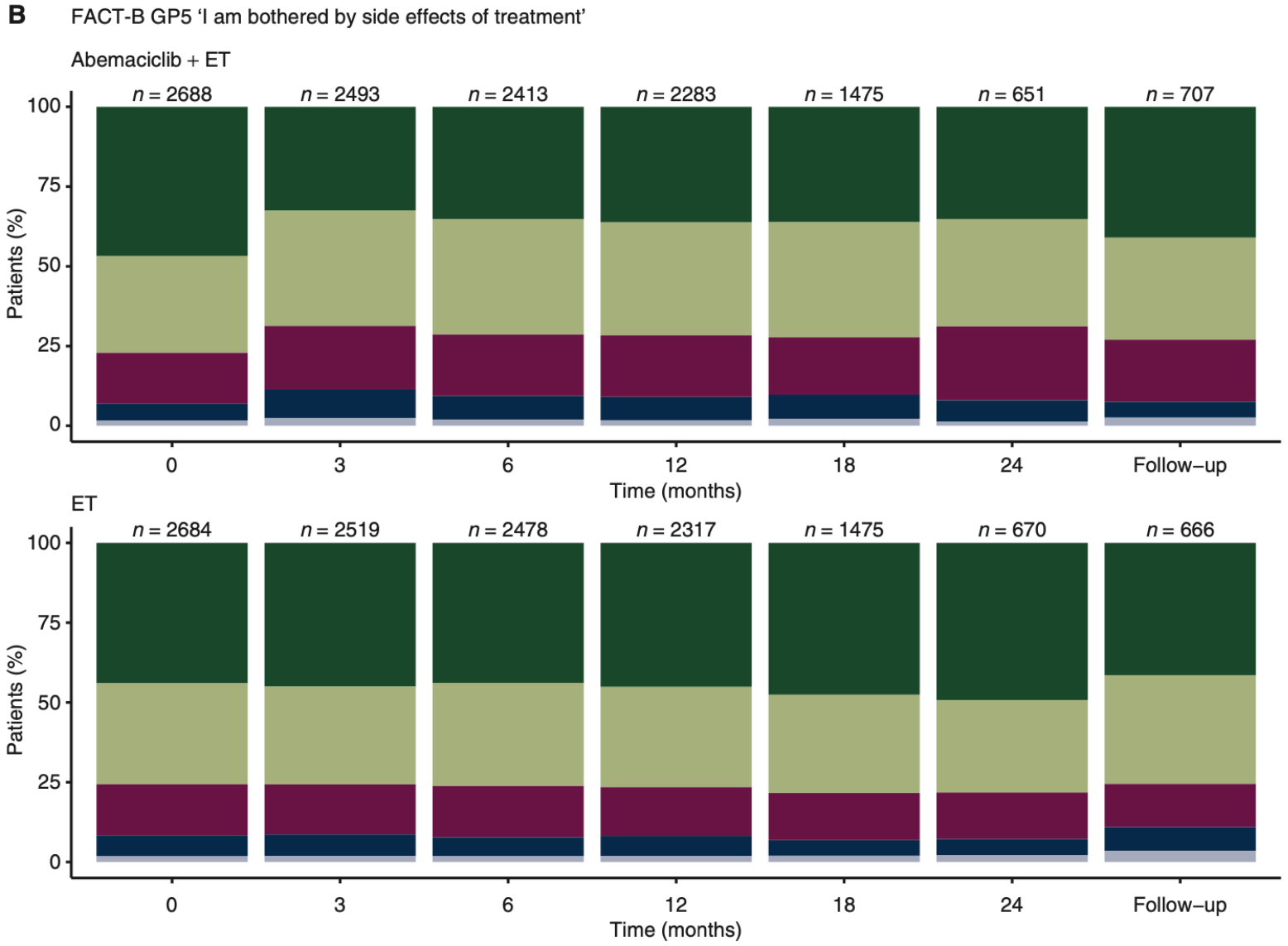

Figure 4. Percent stacked bar plot of patient-reported outcomes (PROs) as per study visit.

(A) PRO on FACT-ES C5 'I have diarrhea' in patients in the abemaciclib arm and (B) PRO on FACT-B GP5 'I am bothered by side-effects of treatment' in patients in the abemaciclib arm and the control arm. The observed differences between the trial arms in patient-reported diarrhea were not, however, reflected in patients' responses to 'I am bothered by side-effects of treatment' (FACT-B GP5).

ET, endocrine therapy; *n*, number of patients having answered the questionnaires at each study visit.

Rugo et. al. Published Online March 22 https://doi.org/10.1016/j.annonc.2022.03.006