

Supplementary Information - Impact of dose reductions on adjuvant abemaciclib efficacy for patients with high-risk early breast cancer: analyses from the monarchE study

Supplementary Table 1. Yearly invasive disease-free survival rates by abemaciclib relative dose intensity subgroup

Analysis		IDFS rates, % (95% CI)^b		
Population	RDI group^a	2 years	3 years	4 years
Intent-to-treat	≤66%	94.1 (92.3, 95.5)	91.2 (89.1, 92.9)	87.1 (84.0, 89.7)
	66%-93%	92.5 (90.6, 94.1)	89.5 (87.2, 91.3)	86.4 (83.6, 88.7)
	≥93%	91.5 (89.4, 93.1)	86.8 (84.4, 88.9)	83.7 (80.7, 86.3)
Cohort 1 ^c	≤66%	94.1 (92.3, 95.6)	91.0 (88.8, 92.8)	87.2 (84.0, 89.8)
	66%-93%	92.2 (90.2, 93.9)	89.0 (86.6, 90.9)	86.1 (83.3, 88.5)
	≥93%	91.4 (89.2, 93.1)	86.3 (83.7, 88.5)	83.1 (79.9, 85.8)

Data cutoff date: July 01, 2022.

^aRDI was defined as the average daily dose of abemaciclib received by each patient over the treatment duration, relative to the full dose (150 mg twice per day). For efficacy analyses, patients were divided into three equal-sized subgroups according to their abemaciclib RDI.

^bEstimated by the Kaplan-Meier method.

^cCohort 1 included patients with ≥4 positive pathologic ALNs or 1-3 positive ALNs plus tumor size ≥5 cm and/or tumor grade 3.

ALN, axillary lymph nodes; CI, confidence interval; IDFS, invasive disease-free survival; RDI, relative dose intensity.

Supplementary Table 2. Discontinuation rates in the abemaciclib arm of monarchE by baseline patient characteristics

Factors		N	Rates of Discontinuation, % (95% CI)^a		
			6 months	12 months	24 months
Geographic region	North America/Europe	1458	16.5 (14.7, 18.5)	23.5 (21.3, 25.7)	32.2 (29.8, 34.7)
	Asia	573	10.3 (8.0, 13.0)	13.9 (11.2, 16.9)	18.5 (15.4, 21.8)
	Other	760	12.1 (9.8, 14.5)	15.8 (13.3, 18.5)	21.2 (18.2, 24.4)
Menopausal status	Premenopausal	1217	9.3 (7.8, 11.0)	12.8 (10.9, 14.7)	18.2 (16.0, 20.5)
	Postmenopausal	1574	17.7 (15.8, 19.6)	24.6 (22.5, 26.8)	32.9 (30.4, 35.3)
Age group	<65 years	2361	11.6 (10.3, 12.9)	16.3 (14.9, 17.9)	22.7 (21.0, 24.5)
	≥65 years	430	27.6 (23.4, 31.9)	36.4 (31.8, 41.0)	46.6 (41.5, 51.6)
Baseline ECOG PS	0	2392	13.7 (12.4, 15.2)	18.7 (17.1, 20.3)	25.2 (23.4, 27.0)
	1	399	15.8 (12.4, 19.6)	24.0 (19.9, 28.3)	33.9 (29.2, 38.7)
Number of positive nodes	1–3	1115	16.1 (14.0, 18.3)	22.3 (19.8, 24.8)	30.5 (27.8, 33.3)

	4–9	1096	13.2 (11.3, 15.3)	17.9 (15.7, 20.3)	24.5 (21.9, 27.2)
	≥10	573	11.6 (9.1, 14.4)	16.8 (13.8, 20.0)	22.1 (18.5, 25.9)
Number of unique pre-existing comorbidities	0	460	9.4 (6.9, 12.3)	11.8 (9.1, 15.0)	16.2 (13.0, 19.8)
	1–3	1373	12.9 (11.2, 14.7)	17.7 (15.7, 19.8)	23.7 (21.5, 26.1)
	≥4	958	17.9 (15.6, 20.4)	25.5 (22.8, 28.3)	35.1 (32.0, 38.3)

Data cutoff date: July 01, 2022.

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status;

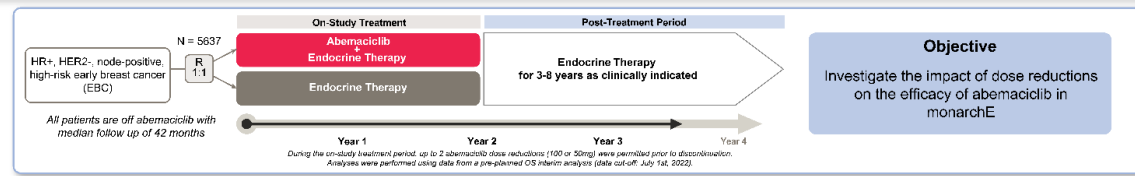
^aDiscontinuation rates (95% CI) during the on-study treatment period were estimated using the Kaplan-Meier method.

Supplementary Table 3. Recommendation for management of adverse events.

Adverse Events		CTCAE Grade	Dose Modifications
Hematologic Toxicities ^a	Monitor complete blood counts prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	Grade 1 or 2	No dose modification is required.
		Grade 3	Suspend dose until toxicity resolves to ≤Grade 2. Dose reduction is not required.
		Grade 3 recurrent, or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2. Resume at next lower dose.
Diarrhoea	At the first sign of loose stools, start treatment with antidiarrheal agents and increase intake of oral fluids	Grade 1	No dose modification is required.
		Grade 2	If toxicity does not resolve within 24 hours to ≤Grade 1, suspend dose until resolution. No dose reduction is required.
		Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to ≤Grade 1. Resume at next lower dose
		Grade 3 or 4 or requires hospitalization	Suspend dose until toxicity resolves to ≤Grade 1. Resume at next lower dose.
Hepatotoxicity	Monitor ALT, AST, and serum bilirubin prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	Grade 1 (>ULN-3.0 x ULN)	No dose modification is required.
		Grade 2 (>3.0-5.0 x ULN), WITHOUT increase in total bilirubin above 2 x ULN	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
		Persistent or Recurrent Grade 2, or Grade 3 (>5.0- 20.0 x ULN), WITHOUT increase in total bilirubin above 2 x ULN	Discontinue Abemaciclib
		Elevation in AST and/or ALT >3 x ULN WITH total bilirubin >2 x ULN, in the absence of cholestasis	Discontinue Abemaciclib
Interstitial Lung Disease/Pneumonitis		Grade 4 (>20.0 x ULN)	Discontinue Abemaciclib
		Grade 1 or 2	No dose modification is required
		Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or ≤Grade 1. Resume at next lower dose
Other Toxicities ^b		Grade 3 or 4	Discontinue Abemaciclib
		Grade 1 or 2	No dose modification is required.
		Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or ≤Grade 1. Resume at next lower dose
		Grade 3 or 4	Suspend dose until toxicity resolves to baseline or ≤Grade 1. Resume at next lower dose.

A dose reduction corresponds to a reduction of 50 mg of abemaciclib at a time. Discontinue abemaciclib for patients unable to tolerate 50 mg twice daily. ^aIf blood cell growth factors are required, suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume at next lower dose unless already performed for the toxicity that led to the use of the growth factor. Growth factor use as per current treatment guidelines. ^bExcluding diarrhea, hematologic toxicity, hepatotoxicity,ILD/pneumonitis, and VTEs. Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ILD, interstitial lung disease; ULN, upper limit of normal. Reproduced from Rugo, H. S. et al. *Oncologist* **26**, e53–e65 (2021) and Abemaciclib package insert

Dose Reductions in monarchE Do Not Compromise Efficacy of Adjuvant Abemaciclib and were Commonly Used to Manage Side Effects and Retain Patients on Treatment



Dose Reductions, an Effective Measure to Proactively Manage AEs in monarchE

In patients treated with adjuvant abemaciclib¹

- 43% had dose reductions due to AEs, majority occurring within the first 6 months
- ~50% who discontinued early due to an AE did not have a prior dose reduction
- Only 8.9% discontinued abemaciclib after a dose reduction

Patients ≥65 Years Old or ≥4 Co-Morbidities Are More Likely to have Reductions

Dose Reductions by Age

Age Group	No Dose Reduction	One Dose Reduction	Two Dose Reductions
<65 years old	~80	~15	~5
≥65 years old	~60	~25	~15

Dose Reductions by Number of Pre-existing Co-morbidities

Co-morbidities	No Dose Reduction	One Dose Reduction	Two Dose Reductions
None - 1-3 co-morbidities	~70	~20	~10
≥4 co-morbidities	~40	~30	~30

Abemaciclib Benefit is Maintained when Dose Modifications are Undertaken to Manage AEs

Time-dependent Cox model in patients treated with abemaciclib

Efficacy Endpoint	HR (95% CI) Staying at full dose vs Being reduced to lower doses
ITT	0.906 (0.727, 1.125)
IDFS	0.942 (0.742, 1.195)
DRFS	
Cohort 1	
IDFS	0.899 (0.718, 1.125)
DRFS	0.958 (0.750, 1.223)

When considering timing of dose reductions, abemaciclib benefit was similar when staying at the 150 mg dose vs. being reduced to 100 or 50 mg.

IDFS according to RDI in patients treated with abemaciclib

4-year IDFS rates were generally consistent (87.1% vs 86.4% vs 83.7% from the lowest RDI group to the highest). Similar findings observed in Cohort 1.

Relative Dose Intensity (all ages included)

- 0 - 66%
- 66 - 93%
- 93% and above

Time (months)	0	6	12	18	24	30	36	42	48	54	60
Number at risk	928	879	856	835	809	759	731	388	158	24	0
Number at risk	928	894	898	841	817	801	769	428	181	21	0
Number at risk	927	843	820	798	777	751	710	411	182	34	0

Dose Reductions were Associated with Improved Patient Retention

	No Dose Reduction N = 1570	1 Dose Reduction N = 632	2 Dose Reductions N = 358
Treatment Duration, months			
Median (Q1 - Q3)	23.7 (14.9 - 23.8)	23.7 (20.6 - 23.8)	23.7 (13.2 - 23.8)
ITT			
> 3 months, %	86	95	94
> 6 months, %	81	90	86
Cumulative dose, mg			
Median (Q1 - Q3)	192450 (112800 - 210900)	137475 (98825 - 151950)	77200 (50100 - 96500)
Relative Dose Intensity (RDI), %			
Median (Q1 - Q3)	84.6 (63.4 - 99.0)	66.5 (59.5 - 74.4)	40.2 (34.5 - 50.7)

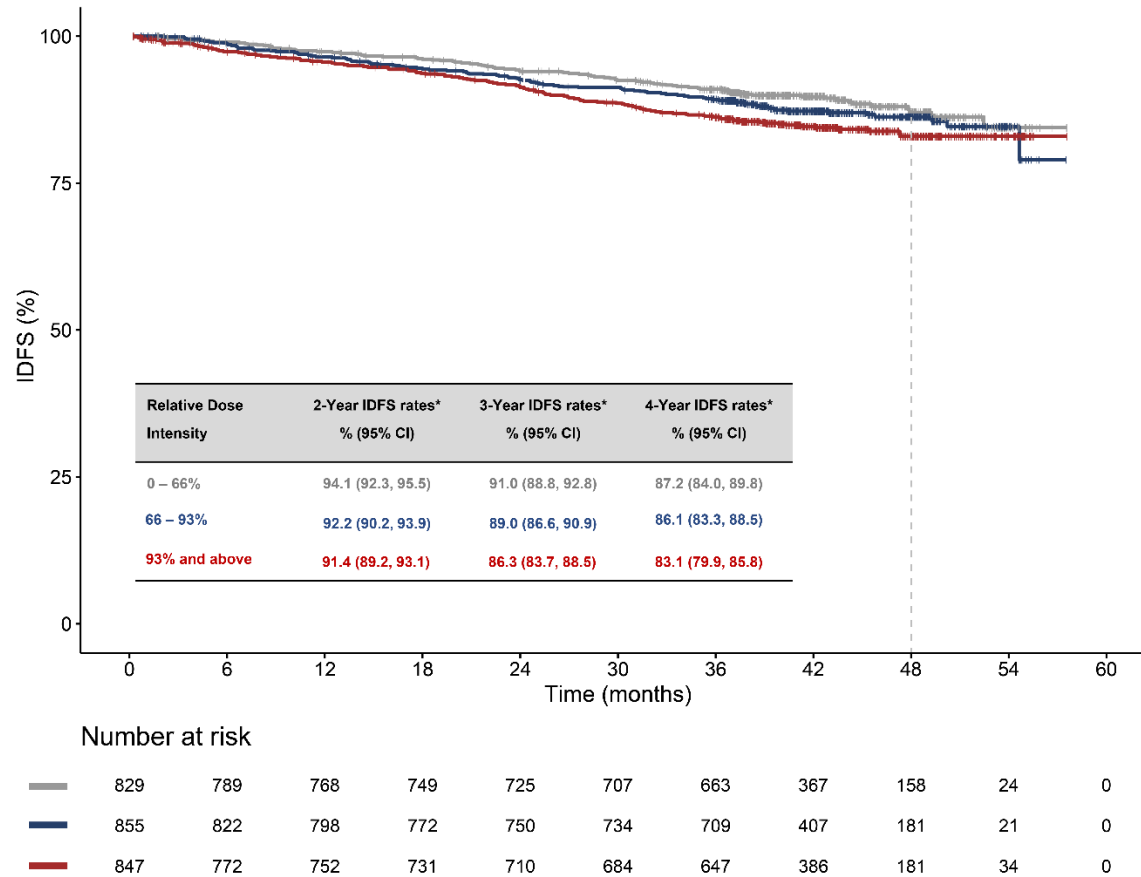
Patients with dose reductions had a lower cumulative dose and RDI but were more likely to remain on abemaciclib treatment.

These data support the use of dose reductions as needed with adjuvant abemaciclib, with the goal of maximizing adherence to maintain benefit for high-risk HR+ HER2- EBC patients

References: Rugo HS, OShaughnessy J, Doyle F, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: safety and patient-reported outcomes from the monarchE study. *Ann Oncol* 2022; 33: 616-627.

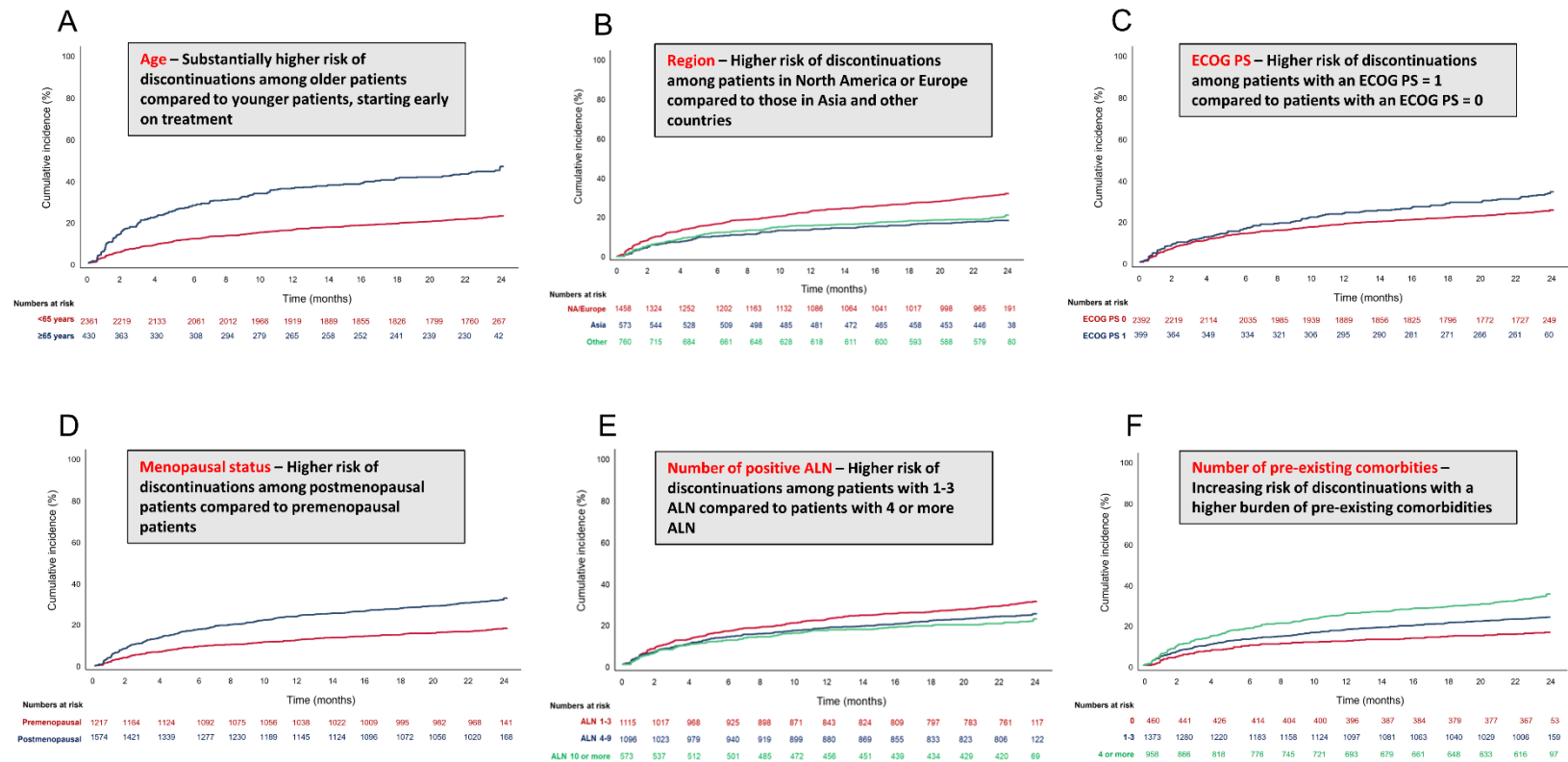
Abbreviations: AE, adverse event; CI, confidence interval; DRFS, distant relapse-free survival; EBC, early breast cancer; ET, endocrine therapy; HER2-, human estrogen receptor 2-negative; HR, hormone receptor; HR+, hormone receptor positive; IDFS, invasive disease-free survival; ITT, intent-to-treat; OS, overall survival; R, randomized; RDI, relative dose intensity.

Supplementary Figure 1. Summary



Supplementary Figure 2. Invasive disease-free survival by relative dose intensity subgroup in patients treated with abemaciclib (Patients in Cohort 1) RDI was defined as the average daily dose of abemaciclib received by each patient over the treatment duration, relative to the full dose (150 mg twice per day). *Estimated by the Kaplan-Meier method. For efficacy analyses, patients were divided into three equal-sized subgroups according to their abemaciclib RDI. Data cutoff date: July 01, 2022.

CI, confidence interval; IDFS, invasive disease-free survival; RDI, relative dose intensity



Supplementary Figure 3. Discontinuations in the abemaciclib arm of the monarchE trial. Discontinuations during the on-study treatment period for subgroups categorized by baseline factors, including A) age; B) geographic region; C) ECOG PS; D) menopausal status; E) number of positive ALN; and F) number of pre-existing comorbidities.

ALN, axillary lymph nodes; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, North America

