PRIMARY OUTCOME ANALYSIS OF INVASIVE DISEASE-FREE SURVIVAL FOR monarchE: ABEMACICLIB PLUS ADJUVANT ENDOCRINE THERAPY FOR HIGH-RISK EARLY BREAST CANCER

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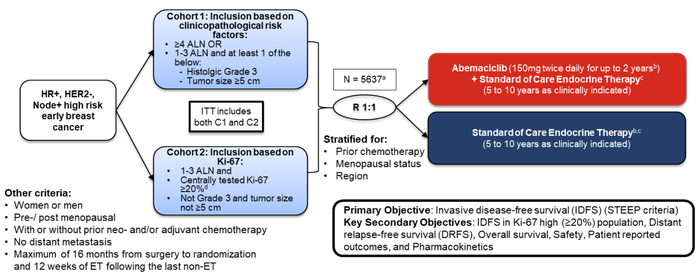
INTRODUCTION

- Approximately 20% of patients with HR+, HER2- early breast cancer (EBC) will experience disease recurrence within the first 10 years[1]
  - Certain clinical and/or pathological features including high expression of Ki-67 have been shown to be associated with a higher recurrence rate[2,3]
- Abemaciclib, an oral, continuously dosed, CDK4 & 6 inhibitor is approved for HR+, HER2- advanced breast cancer in combination with ET[4,5]
- At the second preplanned interim analysis (IA2) with 323 invasive disease-free survival (IDFS) events, monarchE achieved its primary endpoint by demonstrating superior IDFS when abemaciclib was combined with ET compared to ET alone in patients with HR+, HER2-, node-positive, high risk, EBC[6]
  - p=0.0096, HR (95% CI): 0.747 (0.598, 0.932)
- Here we report results from the primary outcome (PO) IDFS analysis which was planned to occur at approximately 390 IDFS events

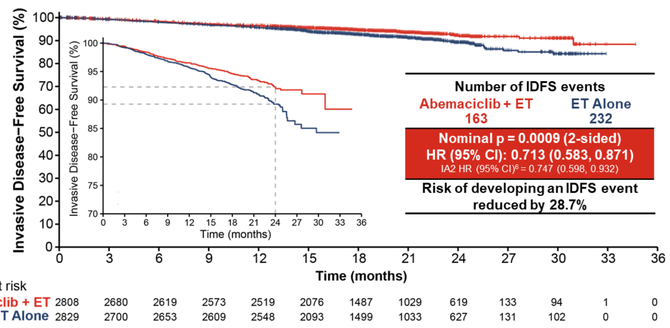
monarchE STUDY DESIGN



[a]Recruitment from July 2017 to August 2019; [b]Treatment period = first 2 years on study treatment after randomization; [c]Endocrine therapy of physician's choice [e.g. aromatase inhibitors, tamoxifen, LHRH agonist]; [d]Ki-67 expression assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochemistry Assay by Dako/Agilent; Abbreviations: ALN, positive axillary lymph nodes; R, randomized

RESULTS

Invasive Disease-Free Survival (ITT) at PO Analysis

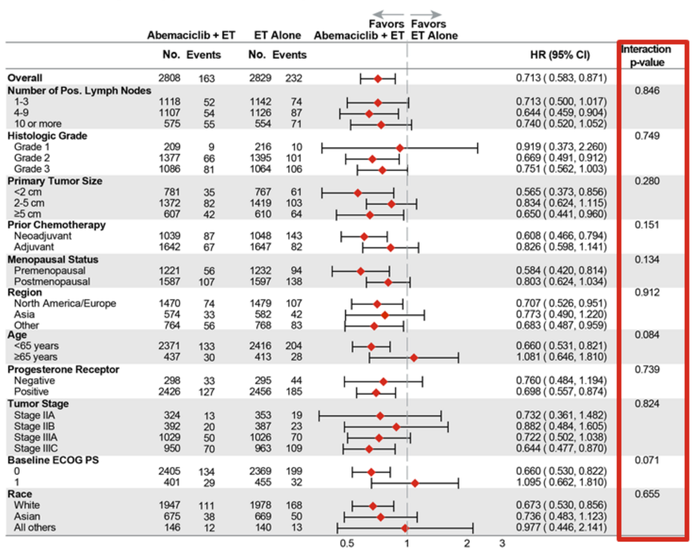


Number at risk

Abemaciclib + ET	2808	2680	2619	2573	2519	2076	1487	1029	619	133	94	1	0
ET Alone	2829	2700	2653	2609	2548	2093	1499	1033	627	131	102	0	0

Statistically significant and clinically meaningful improvement in IDFS with greater treatment benefit at PO analysis
Two-year IDFS rates were 92.3% in the abemaciclib + ET arm and 89.3% in the ET arm - 3.0% difference

IDFS in Prespecified Subgroups at PO Analysis



	Abemaciclib + ET No.	Abemaciclib + ET Events	ET Alone No.	ET Alone Events	HR (95% CI)	Interaction p-value
Overall	2808	163	2829	232	0.713 (0.583, 0.871)	
Number of Pos. Lymph Nodes						0.846
1-3	1118	52	1142	74	0.713 (0.500, 1.017)	
4-9	1107	54	1126	87	0.644 (0.459, 0.904)	
10 or more	575	55	554	71	0.740 (0.520, 1.052)	
Histologic Grade						0.749
Grade 1	209	9	216	10	0.919 (0.373, 2.260)	
Grade 2	1377	66	1395	101	0.669 (0.491, 0.912)	
Grade 3	1086	81	1064	106	0.751 (0.562, 1.003)	
Primary Tumor Size						0.280
<2 cm	781	35	767	61	0.565 (0.373, 0.856)	
2-5 cm	1372	82	1419	103	0.834 (0.624, 1.115)	
≥5 cm	607	42	610	64	0.650 (0.441, 0.960)	
Prior Chemotherapy						0.151
Neoadjuvant	1039	87	1048	143	0.608 (0.466, 0.794)	
Adjuvant	1642	67	1647	82	0.826 (0.598, 1.141)	
Menopausal Status						0.134
Premenopausal	1221	56	1232	94	0.584 (0.420, 0.814)	
Postmenopausal	1587	107	1597	138	0.803 (0.624, 1.034)	
Region						0.912
North America/Europe	1470	74	1479	107	0.707 (0.526, 0.951)	
Asia	574	33	582	42	0.773 (0.490, 1.220)	
Other	764	56	768	83	0.683 (0.487, 0.959)	
Age						0.084
<65 years	2371	133	2416	204	0.660 (0.531, 0.821)	
≥65 years	437	30	413	28	1.081 (0.646, 1.810)	
Progesterone Receptor						0.739
Negative	298	33	295	44	0.760 (0.484, 1.194)	
Positive	2426	127	2456	185	0.698 (0.557, 0.874)	
Tumor Stage						0.824
Stage IIA	324	13	353	19	0.732 (0.361, 1.482)	
Stage IIB	392	20	387	23	0.882 (0.484, 1.605)	
Stage IIIA	1029	50	1026	70	0.722 (0.502, 1.038)	
Stage IIIC	950	70	963	109	0.644 (0.477, 0.870)	
Baseline ECOG PS						0.071
0	2405	134	2369	199	0.660 (0.530, 0.822)	
1	401	29	455	32	1.095 (0.662, 1.810)	
Race						0.655
White	1947	111	1978	168	0.673 (0.530, 0.856)	
Asian	675	38	669	50	0.736 (0.483, 1.123)	
All others	146	12	140	13	0.977 (0.446, 2.141)	

No statistically significant interactions observed supporting consistent benefit across all subgroups at PO analysis

Statistical Considerations

- Primary outcome efficacy analysis
  - Planned: study required approximately 390 IDFS events, at ~85% power with assumed IDFS hazard ratio (HR) of 0.73 and cumulative 2-sided alpha level of 0.05
  - Observed: 395 IDFS events in the ITT population[a]
- Key efficacy analyses
  - IDFS in ITT: statistical significance was achieved at the second interim analysis
  - IDFS in Ki-67 high (≥20%) in ITT (cohorts 1 and 2): sequentially tested at the primary outcome analysis, with two-sided p-value boundary at 0.0424[b]
  - DRFS in ITT: not alpha controlled

[a]Data cutoff July 8, 2020; [b]Remaining alpha level for this endpoint at the primary outcome analysis, calculated using method of Slud and Wei (1982)

Accrual and Analysis

- Median follow-up: 19.1 months in both arms (15.5 months at IA2[6])
  - 25.5% (n=1437) patients completed the 2-year treatment period (12.5% at IA2[6])
  - 58.2% (n=3281) were still on the 2-year treatment period (72.8% at IA2[6])

- Ki-67 was centrally tested in all available primary untreated tumor samples in the ITT population and the Ki-67 high population includes all patients in cohorts 1 and 2 with Ki-67 ≥20%

References

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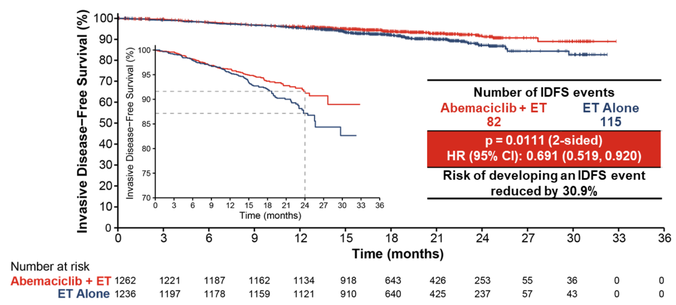
IDFS in Ki-67 High (≥20%) in the ITT Population at PO Analysis



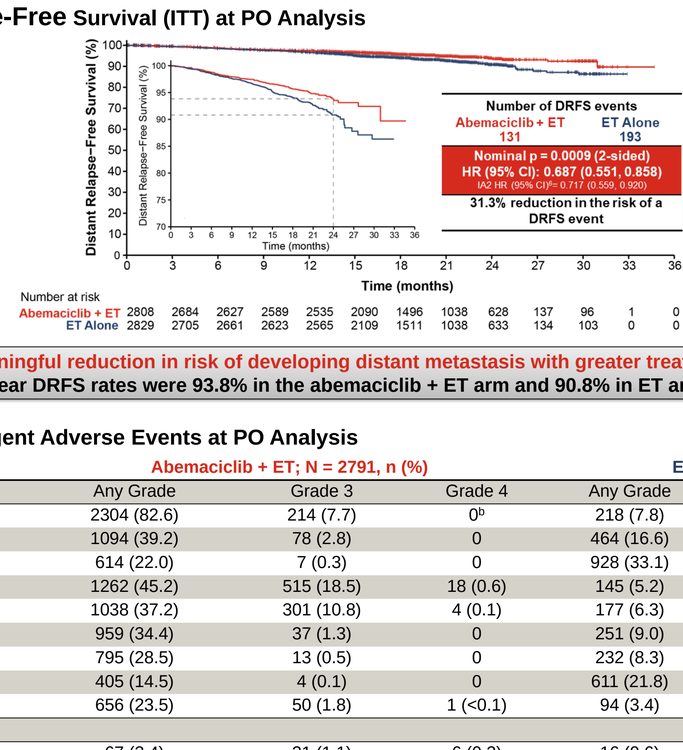
Number at risk

Abemaciclib + ET	1262	1221	1187	1162	1134	918	643	426	253	55	36	0	0
ET Alone	1236	1197	1178	1159	1121	910	640	425	237	57	43	0	0

Ki-67 was tested in all eligible patients in cohorts 1 and 2 with suitable untreated breast tissue

Statistically significant and clinically meaningful improvement in IDFS in patients with high Ki-67 tumors
Two-year IDFS rates were 91.6% in the abemaciclib + ET arm and 87.1% in the ET arm – 4.5% difference

Distant Relapse-Free Survival (ITT) at PO Analysis



Number at risk

Abemaciclib + ET	2808	2684	2627	2589	2535	2090	1496	1038	628	137	96	1	0
ET Alone	2829	2705	2661	2623	2565	2109	1511	1038	633	134	103	0	0

Clinically meaningful reduction in risk of developing distant metastasis with greater treatment benefit at PO analysis
Two-year DRFS rates were 93.8% in the abemaciclib + ET arm and 90.8% in ET arm – 3.0% difference

Treatment-Emergent Adverse Events at PO Analysis

	Abemaciclib + ET; N = 2791, n (%)			ET alone; N = 2800, n (%)		
≥20% in either arm	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Diarrhea	2304 (82.6)	214 (7.7)	0[b]	218 (7.8)	5 (0.2)	0
Fatigue[a]	1094 (39.2)	78 (2.8)	0	464 (16.6)	4 (0.1)	0
Arthralgia[a]	614 (22.0)	7 (0.3)	0	928 (33.1)	20 (0.7)	0
Neutropenia	1262 (45.2)	515 (18.5)	18 (0.6)	145 (5.2)	17 (0.6)	3 (0.1)
Leukopenia	1038 (37.2)	301 (10.8)	4 (0.1)	177 (6.3)	10 (0.4)	0
Abdominal Pain[a]	959 (34.4)	37 (1.3)	0	251 (9.0)	9 (0.3)	0
Nausea[a]	795 (28.5)	13 (0.5)	0	232 (8.3)	1 (<0.1)	0
Hot Flush[a]	405 (14.5)	4 (0.1)	0	611 (21.8)	10 (0.4)	0
Anemia	656 (23.5)	50 (1.8)	1 (<0.1)	94 (3.4)	9 (0.3)	1 (<0.1)
Other AEs of interest						
VTE	67 (2.4)	31 (1.1)	6 (0.2)	16 (0.6)	6 (0.2)	0[b]
PE	26 (0.9)	23 (0.8)	3 (0.1)	4 (0.1)	3 (0.1)	0[b]
ILD	82 (2.9)	10 (0.4)	0[b]	34 (1.2)	1 (<0.1)	0

[a]PT has a maximum CTCAE Grade of 3; [b]1 Grade 5 event occurred; Abbreviations: VTE, venous thromboembolic event; PE, pulmonary embolism; ILD, interstitial lung disease

Safety was consistent with the known profile of abemaciclib and results from the second interim analysis

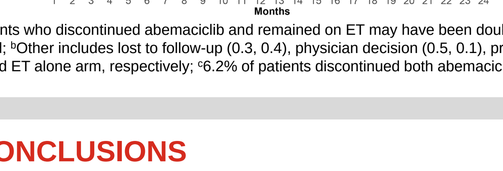
Abemaciclib Dose Holds and Reductions

	Abemaciclib + ET; N=2791 (%)
Patients with ≥1 dose hold and/or reduction	1958 (70.2)
Number (%) of patients with ≥1 dose hold	1844 (66.1)
Reasons leading to dose hold, n (%)[a]	
Adverse events	1661 (59.5)
Diarrhea	530 (19.0)
Neutropenia	427 (15.3)
Leukopenia	193 (6.9)
Pre-planned surgery	340 (12.2)
Scheduling conflict	101 (3.6)
Treatment availability	23 (0.8)
Number (%) of patients with ≥1 dose reduction	1193 (42.7)
Reasons leading to dose reduction, n (%)[a]	
Adverse events	1187 (42.5)
Diarrhea	474 (17.0)
Neutropenia	217 (7.8)
Fatigue	124 (4.4)

[a]Patients may be counted in more than one dose hold or dose reduction sub-category; values not adding up to the total number were due to missing or other reasons

Abemaciclib Discontinuations at PO Analysis

- Over half of the early discontinuations due to AEs occurred within the first 5 months of treatment



Treatment Discontinuation	Abemaciclib + ET N=2791, n (%)	ET alone N=2800, n (%)
For any reason	773 (27.7)[a]	410 (14.6)
Due to AEs, including deaths due to AEs	481 (17.2)[c]	23 (0.8)
Diarrhea	141 (5.1)	0
Fatigue	53 (1.9)	0
Neutropenia	26 (0.9)	0
Withdrawal by subject	156 (5.6)	160 (5.7)
IDFS/DRFS events	136 (4.9)	204 (7.3)
Deaths due to study disease	2 (<0.1)	2 (<0.1)
Noncompliance	8 (0.3)	0
Other[b]	32 (1.1)	21 (0.8)

[a]Some patients who discontinued abemaciclib and remained on ET may have been double counted for an early discontinuation due to a different reason once ET was discontinued; [b]Other includes lost to follow-up (0.3, 0.4), physician decision (0.5, 0.1), protocol deviation (0, 0.3), study terminated (0, 0.1) and other (0.3, 0) in the abemaciclib + ET alone and ET alone arm, respectively; [c]6.2% of patients discontinued both abemaciclib and ET due to AEs

CONCLUSIONS

- At the preplanned PO analysis, with 395 events and an additional 3.6 months median follow-up, abemaciclib combined with standard ET
  - Continued to demonstrate a reduction in the risk of developing IDFS and DRFS events for patients with HR+,HER2-, high risk EBC
  - Resulted in a statistically significant improvement in IDFS in patients with high (≥20%) Ki-67 tumors
- Safety was consistent with IA2 and the known safety profile of abemaciclib
  - Most discontinuations due to AEs occurred within the first 5 months of study treatment
  - Most patients who required a dose hold or reduction were able to remain on study treatment
- Study is ongoing, until the final assessment of overall survival
- Abemaciclib in combination with ET is the first CDK4 & 6 inhibitor to demonstrate efficacy and tolerability for patients with HR+, HER2-, node-positive, high risk, EBC

Acknowledgments

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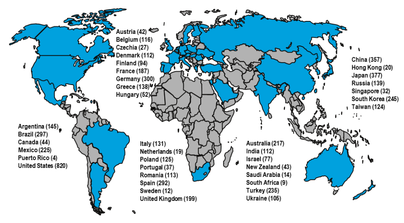
- This study was sponsored by Eli Lilly and Company



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