PO13

Safety outcomes from monarchE: phase 3 study of abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2−, node-positive, high risk, early breast cancer

monarchE

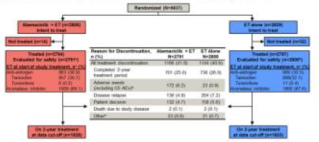
Hope S. Rugo[1], Joyce O'Shaughnessy[2], Chuangui Song[3], Reuben Broom[4], Mahmut Gumus[5], Toshinari Yamashita[6], Belen San Antonio[7], Ashwin Shahir[7], Annamaria Zimmermann[7], Flora Zagouri[8], Mattea Reinisch[9]

[1]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA; [2]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas TX; [3]Fujian Medical University Union Hospital, Fujian, China; [4]Auckland City Hospital, Auckland, New Zealand; [5]Istanbul Medeniyet University, School of Medicine, Istanbul, Turkey; [6]Kanagawa Cancer Center, Yokohama, Japan; [7]Eli Lilly and Company, Indianapolis, IN; [8]General Hospital of Athens 'Alexandra', Athens, Greece; [9]Brustzentrum Kliniken Essen-Mitte, Essen, Germany

OBJECTIVE

- Approximately 20% of patients with HR+, HER2- early breast cancer (EBC) will experience disease recurrence within the first 10 years[1]
- Abemaciclib, an oral, continuously dosed, CDK4 & 6 inhibitor is approved for HR+, HER2− advanced breast cancer in combination with endocrine therapy (ET)[2,3]
- In monarchE, at primary outcome (PO) analysis, abemaciclib in combination with ET as adjuvant treatment for HR+ HER2− high risk, EBC demonstrated a statistically significant improvement in invasive disease-free survival (IDFS) compared to ET alone (data cut-off: 8July 2020)[4]
  - p=0.0009, HR (95% CI): 0.713 (0.583, 0.871)
- The median follow-up time in both arms was 19.1 months
- Here we report the safety analyses from the preplanned PO analysis

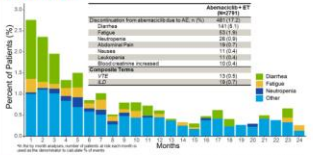
CONSORT DIAGRAM – SAFETY



Exposure/Compliance/Median Duration

- At PO IDFS analysis, median exposure to ET was balanced across both arms (18 mo. in the abemaciclib arm and 19 mo. in the ET alone arm)
- Median duration of abemaciclib was 17 months
- Median compliance for abemaciclib in patients completing 2 years of study treatment was 98.3% (IQR: 91.5-100.1)

ABEMACICLIB DISCONTINUATIONS DUE TO AES: HIGHEST IN EARLY MONTHS[a]



	Abemaciclib + ET (N=2791)
Discontinuation from abemaciclib due to AE, n (%)	481 (17.2)
Diarrhea	141 (5.1)
Fatigue	53 (1.9)
Neutropenia	26 (0.9)
Abdominal Pain	19 (0.7)
Nausea	11 (0.4)
Leukopenia	11 (0.4)
Blood creatinine increased	10 (0.4)
Composite Terms	
VTE	13 (0.5)
ILD	19 (0.7)

- Abemaciclib discontinuation rate due to AEs was highest during the 1[st] month: 77 (2.8%) patients
- 321 of the 481 (66.7%) abemaciclib discontinuations were due to low grade (G1/2) AEs, mostly not protocol mandated
- 324 of 481 (67.4%) pts who discontinued abemaciclib due to AEs remained on ET after stopping abemaciclib. 172 patients (6.2%) discontinued both abemaciclib and ET (157 at the same time) because of AEs. However, those patients could continue to receive ET in long-term follow-up after discontinuing from the on-study treatment period
- For reference comparison, 23 (0.8%) patients in the ET alone arm discontinued the study treatment due to an AE

Methods

- Study enrollment, design and key eligibility criteria were previously reported[5]
- Patients who received at least one dose of study treatment were evaluated for safety
- Abemaciclib dose modifications (holds and reductions) were mandated to manage related and clinically significant adverse events (AEs). A maximum of 2 dose reductions were allowed
- Compliance for abemaciclib is derived based on actual tablet count (dispensed vs returned)
- Incidence of AEs, including most clinically relevant AEs, management and outcomes are summarized
  - VTE is a composite term that includes catheter site thrombosis, cerebral venous thrombosis, deep vein thrombosis, device related thrombosis, embolism, hepatic vein thrombosis, jugular vein occlusion, jugular vein thrombosis, ovarian vein thrombosis, portal vein thrombosis, pulmonary embolism, subclavian vein thrombosis, venous thrombosis limb
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Overview of Serious AEs

	Abemaciclib + ET N=2791	ET Alone N=2800
Patients with ≥1 SAE, n (%)	372 (13.3)	219 (7.8)
VTE[a]	33 (1.2)	8 (0.3)
Pneumonia	25 (0.9)	14 (0.5)
Diarrhea	15 (0.5)	0
ILD[a]	14 (0.5)	1 (<0.1)
Cellulitis	13 (0.5)	9 (0.3)
Urinary tract infection	12 (0.4)	4 (0.1)
Cholecystitis	10 (0.4)	3 (0.1)
Patients who died due to an AE on study treatment	10 (0.4)[b]	7 (0.3)
Patients who died due to an AE ≤30 days from discontinuation of study treatment	1 (0.0)	2 (0.1)

Deaths due to AE on study treatment or ≤30 days of discontinuation

- 11 (0.4%) in abemaciclib + ET: cardiac arrest (1), cardiac failure (2), cerebral hemorrhage (1), cerebrovascular accident (1), diarrhea (1), general physical health deterioration (1), hypoxia (1), myocardial infarction (1), pneumonitis (1), ventricular fibrillation (1)
- 9 (0.3%) in ET alone: death (1), gastrointestinal adenocarcinoma (1), influenza (1), pleural effusion (1), pneumonia (1), pulmonary embolism (1), septic shock (1), sudden death (1), urosepsis (1)

AEs by Age

- The observed safety profile of abemaciclib across the age subgroups analyzed was generally consistent with the overall safety profile

References: [1]Early Breast Cancer Trialists' Collaborative G. Lancet 2015;386:1341-1352; [2]Sledge GW, Jr., et al. J Clin Oncol 2017;35:2875-84; [3]Goetz et al. J Clin Oncol 2017;35:3638-46; [4]Rastogi P. et al. SABCS 2020, presentation number GS1-01; [5]Johnston SRD, et al. J Clin Oncol 38:3987-3998, 2020

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Disclosures: **Dr. Rugo** reports institutional research support: Pfizer, Merck, Novartis, Lilly, Genentech, Odonate, Daiichi, Seattle Genetics, Eisai, Macrogenics, Sermonix, Boehringer Ingelheim, Polyphor, AZ, Immunomedics; travel support: Daiichi, Mylan, Pfizer, Merck, AZ, Novartis, and Puma; honoraria: Puma, Mylan, Samsung. **Dr. O'Shaughnessy** reports honorarium: Abbvie, Agendia, Amgen, AZ, BMS, Celegene, Eisai, Genentech, Genomic Health, GRAIL, Immunomedics, Heron, Ipsen, Jounce, Lilly, Merck, Myriad, Novartis, Ondonate, Pfizer, Puma, Prime Oncology, Roche, Seattle Genetics, Syndax, Takeda. **Dr. Song and Broom** have no conflicts to disclose. **Dr. Gumus** reports consulting: Bayer, Roche, Novartis, Astellas; speaker's bureaus: Gen Ilac, Janssen, Roche, MSD. **Dr. Yamashita** reports honorarium: Lilly, Chugai, Eisai, Novartis, Taiho, Nippon Kayaku, AZ, Kyowa Kirin, Pfizer Japan, Daiichi-Sankyo; research grant: Chugai, Nippon Kayaku, Kyowa Kirin, Taiho. **Dr. San Antonio, Shahir and Zimmermann** report employee/shareholder of Lilly. **Dr. Zagouri** reports receiving honoraria for lectures and advisory role: AZ, Daiichi, Lilly, Merck, Novartis, Pfizer, Roche. **Dr. Reinisch** reports consulting: Lilly, MSD, AZ, Roche, Novartis, Soulatex; travel fees: Novartis, Pfizer.

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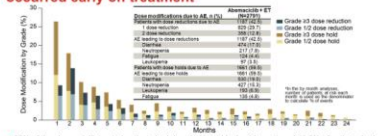
Most abemaciclib dose modifications due to AEs occurred early on treatment[a]



Dose modifications due to AE, n (%)	Abemaciclib + ET (N=2791)
Patients with dose reductions due to AE	1187 (42.5)
1 dose reduction	829 (29.7)
2 dose reductions	358 (12.8)
AE leading to dose reductions	1187 (42.5)
Diarrhea	474 (17.0)
Neutropenia	217 (7.8)
Fatigue	124 (4.4)
Leukopenia	97 (3.5)
Patients with dose holds due to AE	1661 (59.5)
AE leading to dose holds	1661 (59.5)
Diarrhea	530 (19.0)
Neutropenia	427 (15.3)
Leukopenia	190 (6.8)
Fatigue	135 (4.8)

- 26% of the abemaciclib treated patients had dose holds within the 1[st] month and 13.9% of patients had dose reductions within the 2[nd] month
- Approximately half of the dose holds and reductions were for G≥3 events, per protocol requirement
- 123 (4.4%) and 105 (3.8%) patients discontinued abemaciclib or all study treatment, respectively, due to AEs after 1 or 2 abemaciclib dose reductions
- More than half (253 patients, 53%) of total discontinuations and 88% of discontinuations during the 1[st] month occurred without an attempt to address the AE via a dose modification

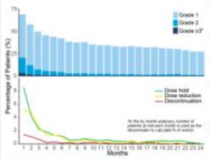
Clinically relevant AEs observed in ≥10% patients in abemaciclib + ET arm

	Abemaciclib + ET (N=2791)				ET Alone (N=2800)			
	Any Grade	G1	G2	G≥3	Any Grade	G1	G2	G≥3
Patients with ≥1 AE[a], n (%)	2733 (97.9)	189 (6.8)	1221 (43.7)	1323 (47.4)	2441 (87.2)	693 (24.8)	1351 (48.3)	397 (14.2)
Diarrhea	2304 (82.6)	1249 (44.8)	840 (30.1)	215 (7.7)[b]	218 (7.8)	168 (6.0)	45 (1.6)	5 (0.2)
Infections[c]	1330 (47.7)	235 (8.4)	963 (34.5)	132 (4.7)	1020 (36.4)	223 (8.0)	725 (25.9)	72 (2.6)[d]
Neutropenia	1262 (45.2)	177 (6.3)	552 (19.8)	533 (19.1)	145 (5.2)	61 (2.2)	64 (2.3)	20 (0.7)
Fatigue	1094 (39.2)	623 (22.3)	393 (14.1)	78 (2.8)	464 (16.6)	357 (12.8)	103 (3.7)	4 (0.1)
Nausea	796 (28.5)	598 (21.4)	184 (6.6)	13 (0.5)	232 (8.3)	182 (6.5)	49 (1.8)	1 (0.1)
Anemia	656 (23.5)	380 (13.6)	225 (8.1)	51 (1.8)	94 (3.4)	69 (2.5)	15 (0.5)	10 (0.4)
Headache	500 (17.9)	381 (13.7)	113 (4.0)	6 (0.2)	387 (13.8)	298 (10.6)	85 (3.0)	4 (0.1)
Vomiting	466 (16.7)	356 (12.8)	97 (3.5)	13 (0.5)	122 (4.4)	92 (3.3)	28 (1.0)	2 (0.1)
Stomatitis[e]	365 (13.1)	296 (10.6)	65 (2.3)	4 (0.1)	140 (5.0)	126 (4.5)	14 (0.5)	0
Thrombocytopenia	353 (12.6)	264 (9.5)	56 (2.0)	33 (1.2)	45 (1.6)	36 (1.3)	6 (0.2)	3 (0.1)
Decreased appetite	320 (11.5)	239 (8.6)	65 (2.3)	16 (0.6)	61 (2.2)	50 (1.8)	9 (0.3)	2 (0.1)
Alanine aminotransferase increase (ALT)	291 (10.4)	160 (5.7)	63 (2.3)	68 (2.4)	136 (4.9)	99 (3.5)	21 (0.8)	16 (0.6)
Rash	287 (10.3)	225 (8.1)	51 (1.8)	11 (0.4)	113 (4.0)	93 (3.3)	20 (0.7)	0
Aspartate aminotransferase increase (AST)	281 (10.1)	189 (6.8)	43 (1.5)	49 (1.8)	120 (4.3)	91 (3.3)	15 (0.5)	14 (0.5)

ALT/AST and neutropenia were well managed in abemaciclib treated patients

- Incidence of G≥3 ALT and AST was <2.5% and median time to onset of ~3 months, with median time to resolution to G<3 of 13 and 11 days, respectively
  - All G≥3 ALT central laboratory elevations were reversible with dose modifications or abemaciclib discontinuation
  - Discontinuation of abemaciclib or all treatment due to any grade ALT and AST was 0.6% and 0.1%
- 9 patients had AST and/or ALT >3X ULN with TBILI >2X ULN per central laboratory and 3 patients had AEs of drug induced liver injury
  - None of those cases met the criteria for drug induced liver injury (CIOMS 2020)
- Neutropenia was the most frequently reported grade ≥3 AE, with a median time to onset of 30 days, a median duration of 16 days, and was rare after the first 6 months
- G≥3 neutropenia was well managed with dose modifications, resulting in a low discontinuation rate (0.9%)

Diarrhea was well managed in monarchE[a]



- Median time to onset of any grade diarrhea was 8 days and incidence decreased over time
  - G2/3 events occurred primarily in the first 3 months and were short lived (≤6 days)
- 78.0% of patients who experienced diarrhea, received anti-diarrheal medication (71.2% for G1, 85.5% for G2, 87.9% for G3)
- Among 2304 patients who experienced diarrhea, 472 (20.5%) had ≥1 dose reduction and 528 (22.9%) held administration
- Discontinuation rate was low (5%), most due to low grade events and within first 2 months of treatment
  - 59% of total discontinuations due to diarrhea and ~90% of events during the 1st month occurred without a prior dose reduction
- ~30% of abemaciclib treated patients had G1 diarrhea after 1 year of treatment, but ≤0.3% pts held administration and ≤0.2% had a dose reduction

Venous thromboembolic events (VTE)

Event term, n (%)	Abemaciclib + ET (N=2791) Any Grade	G1	G2	G≥3	ET Alone (N=2800) Any Grade	G1	G2	G≥3
VTE	67 (2.4)	3 (0.1)	27 (1.0)	37 (1.3)	16 (0.6)	0	9 (0.3)	7 (0.3)[b]
PE[a]	26 (0.9)	0	0	26 (0.9)	4 (0.1)	0	0	4 (0.1)[b]
Serious *VTE*	33 (1.2)				8 (0.3)			
VTE by First ET	Abemaciclib + ET				ET Alone			
Tamoxifen (N=867 [abemaciclib + ET], 888 [ET alone])	35 (4.1)	2 (0.2)	14 (1.6)	19 (2.2)	6 (0.7)	0	2 (0.2)	4 (0.4)
Aromatase Inhibitors (N=1929 [abemaciclib + ET], 1892 [ET alone])	32 (1.7)	1 (0.1)	13 (0.7)	18 (0.9)	10 (0.5)	0	7 (0.4)	3 (0.2)
Time to onset of first *VTE* event (days); median (range)	182.0 (8.0 – 714.0)				187.5 (9.0 – 716.0)			
Discontinuation due to *VTE*	13 (0.5)				2 (0.1)			

- In abemaciclib-treated patients, most *VTEs* were G≥3 and were primarily pulmonary embolism events, including 6 (0.2%) G4 *VTEs* (3 PE)
  - 17 PEs had a serious outcome (e.g. hospitalization), the remaining 9 PEs did not qualify as SAEs
- The observed rate of *VTEs* was higher when tamoxifen, rather than AI, was administered as initial ET
- Risk factors for *VTE* were generally well-balanced across arms
- ~94% patients who experienced *VTEs* received anti-coagulation treatment

Interstitial lung disease (ILD)

Event term, n (%)	Abemaciclib + ET (N=2791) Any Grade	G1	G2	G≥3	ET Alone (N=2800) Any Grade	G1	G2	G≥3
ILD	82 (2.9)	39 (1.4)	32 (1.1)	11 (0.4)[a]	34 (1.2)	23 (0.8)	10 (0.4)	1 (0.1)
Pneumonitis	43 (1.5)	17 (0.6)	19 (0.7)	7 (0.3)[a]	10 (0.4)	7 (0.3)	3 (0.1)	0
Radiation pneumonitis	25 (0.9)	13 (0.5)	10 (0.4)	2 (0.1)	14 (0.5)	8 (0.3)	5 (0.2)	1 (0.1)
ILD	5 (0.2)	2 (0.1)	2 (0.1)	1 (0.1)	1 (0.1)	0	1 (0.1)	0
Serious *ILD* Events	14 (0.5)				1 (0.1)			
Time to onset of first *ILD* event (days); median (range)	190.0 (23.0 – 817.0)				158.0 (29.0-539.0)			
Discontinuation due to *ILD*	19 (0.7)				0			

[a] grade 5 event

- In abemaciclib-treated patients, most *ILD* events were G1 and primarily pneumonitis, 10 pts (0.4%) experienced G3 events and 1 fatal event
  - The majority of the G≥3 *ILDs* (82%) had a serious outcome (e.g. hospitalization)
- 95.4% patients had prior adjuvant radiotherapy, a known risk factor for *ILD*; which was balanced across both arms
- In the abemaciclib arm, the incidence of any grade *ILD* was higher in patients from Asia (5.9%), compared to the overall population (2.9%); however, the overall incidence of G≥3 or SAE was <1.0% and similar across regions
- Approximately half of the patients who experienced an *ILD* in the abemaciclib arm, received concomitant medications, including steroids and antibiotics, consistent with the treatment requirement of symptomatic (G≥2) events per CTCAE definition.

CONCLUSIONS

- The overall safety profile of abemaciclib in monarchE is generally consistent with the established safety profile of abemaciclib, with no new safety concerns
- Most common AEs, including AESI, started early in treatment and were manageable with dose adjustments and comedication, which allowed most patients to remain on treatment
  - Tamoxifen is associated with a numerically higher incidence of VTE compared to AIs
- The small percentage of patients discontinuing abemaciclib after a dose reduction supports its tolerability in combination with ET in the EBC population
  - More than half of abemaciclib discontinuations due to an AE occurred without a prior attempt to address the AE with a dose reduction
- Safety data collection continues since >50% of patients are still on treatment

St Gallen Breast Cancer Conference
March 17 – 21, 2021

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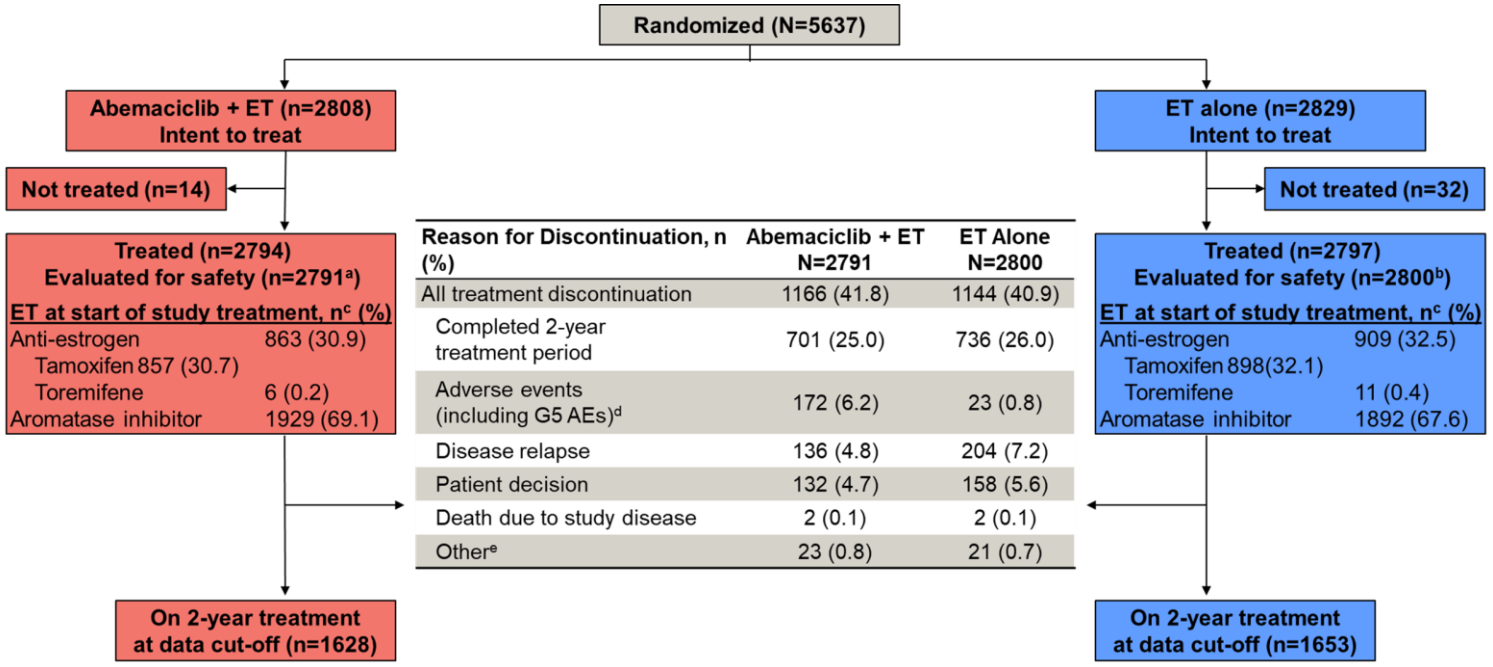
Consort Diagram - safety



Reason for Discontinuation, n (%)	Abemaciclib + ET N=2791	ET Alone N=2800
All treatment discontinuation	1166 (41.8)	1144 (40.9)
Completed 2-year treatment period	701 (25.0)	736 (26.0)
Adverse events (including G5 AEs)[d]	172 (6.2)	23 (0.8)
Disease relapse	136 (4.8)	204 (7.2)
Patient decision	132 (4.7)	158 (5.6)
Death due to study disease	2 (0.1)	2 (0.1)
Other[e]	23 (0.8)	21 (0.7)

[a]Four patients randomly assigned to the abemaciclib arm only received ET and were evaluated for safety in the control arm; [b]One patient randomly assigned to the control arm received abemaciclib and was evaluated for safety in the abemaciclib arm; [c]A total of 1 patient in each arm double counted as having received both tamoxifen and aromatase inhibitor as first ET due to data entry error; [d]10 patients in the Abemaciclib arm and 7 in ET arm died due to AEs while on treatment; [e]Other includes lost to follow-up (0.3, 0.4), non-compliance (0.3, 0), physician decision (0.2, 0.1), protocol deviation (0, 0.2), and study terminated (0, 0.1) in the abemaciclib + ET alone and ET alone arm, respectively

Exposure/Compliance/Median Duration

- At PO IDFS analysis, median exposure of ET was balanced across both arms (18 mo. in the abemaciclib arm and 19 mo. in the ET alone arm)
- Median duration of abemaciclib was 17 months
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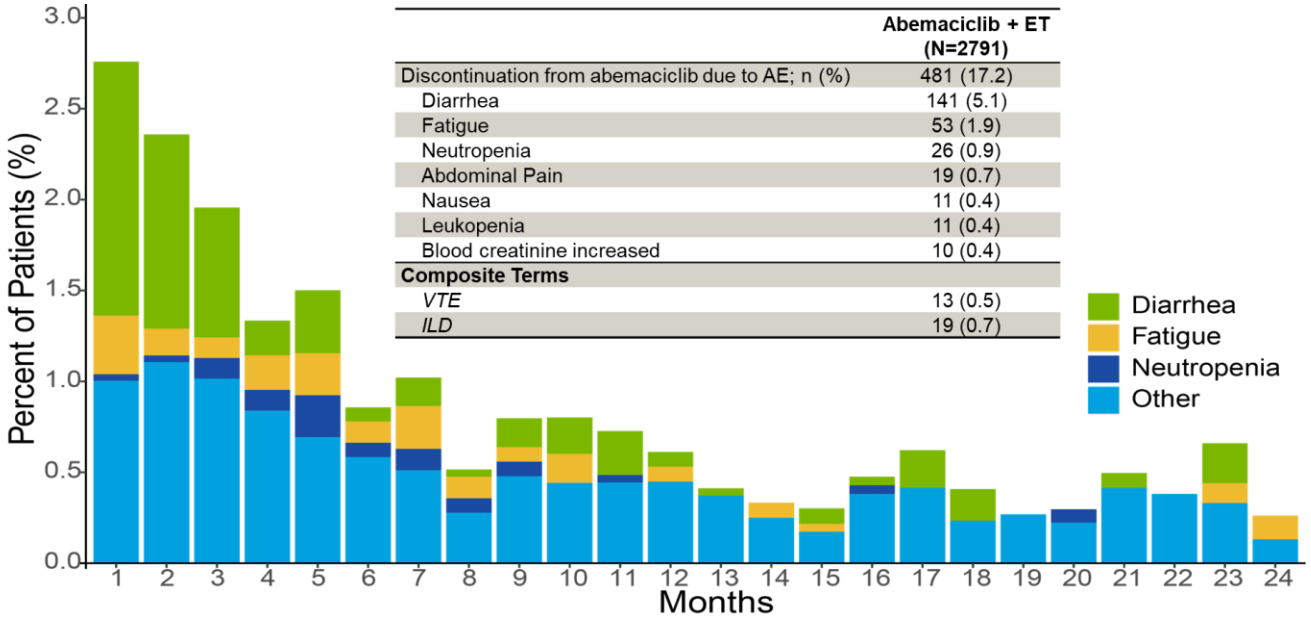
Abemaciclib Discontinuations Due to AE: Highest in Early Months[a]



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Leukopenia	11 (0.4)
Blood creatinine increased	10 (0.4)
Composite Terms	
VTE	13 (0.5)
ILD	19 (0.7)

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

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- 321 of the 481 (66.7%) abemaciclib discontinuations were due to low grade (G1/2) AEs, mostly not protocol mandated
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Cholecystitis	10 (0.4)	3 (0.1)
Patients who died due to an AE on study treatment	10 (0.4)[b]	7 (0.3)
Patients who died due to an AE ≤30 days from discontinuation of study treatment	1 (0.0)	2 (0.1)

[a]VTE and ILD are composite terms; [b] 2 SAEs were assessed by the investigators as possibly related to abemaciclib (pneumonitis and diarrhea)

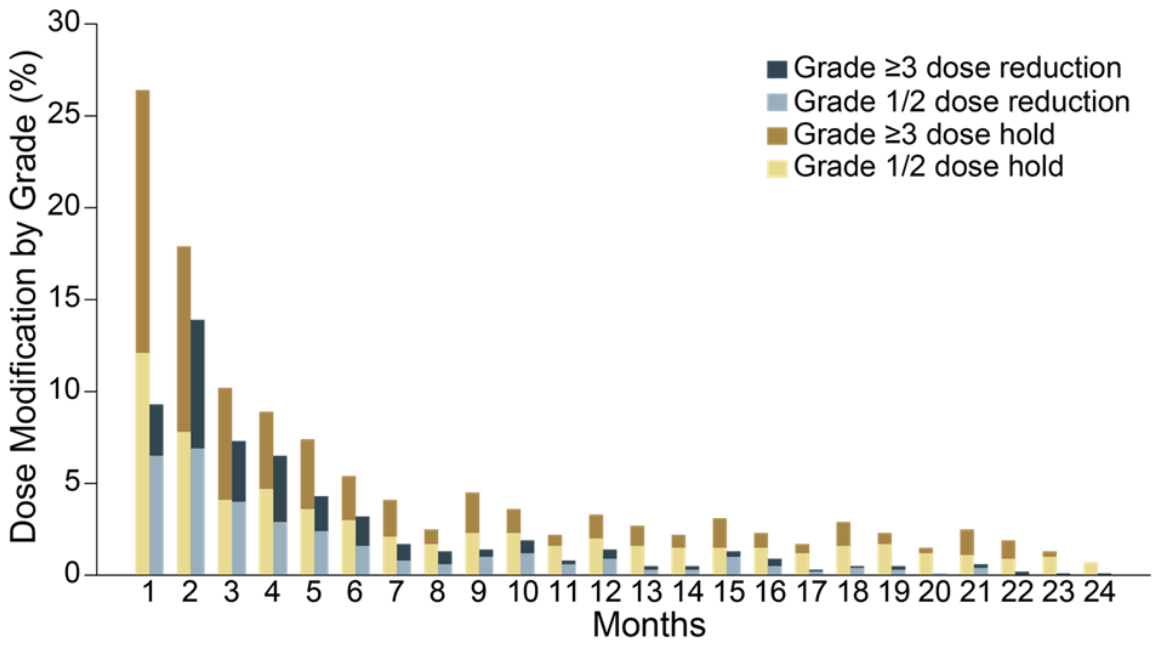
Deaths due to AE on study treatment or ≤30 days of discontinuation

- 11 (0.4%) in abemaciclib + ET: cardiac arrest (1), cardiac failure (2), cerebral hemorrhage (1), cerebrovascular accident (1), diarrhea (1), general physical health deterioration (1), hypoxia (1), myocardial infarction (1), pneumonitis (1), ventricular fibrillation (1)
- 9 (0.3%) in ET alone: death (1), gastrointestinal adenocarcinoma (1), influenza (1), pleural effusion (1), pneumonia (1), pulmonary embolism (1), septic shock (1), sudden death (1), urosepsis (1)

AEs by Age

- The observed safety profile of abemaciclib across the age subgroups analyzed was generally consistent with the overall safety profile

Most abemaciclib dose modifications due to AEs occurred early on treatment[a]



Dose modifications due to AE, n (%)	Abemaciclib + ET (N=2791)
Patients with dose reductions due to AE	1187 (42.5)
1 dose reduction	829 (29.7)
2 dose reductions	358 (12.8)
AE leading to dose reductions	1187 (42.5)
Diarrhea	474 (17.0)
Neutropenia	217 (7.8)
Fatigue	124 (4.4)
Leukopenia	97 (3.5)
Patients with dose holds due to AE	1661 (59.5)
AE leading to dose holds	1661 (59.5)
Diarrhea	530 (19.0)
Neutropenia	427 (15.3)
Leukopenia	193 (6.9)
Fatigue	135 (4.8)

- 26% of the abemaciclib treated patients had dose holds within the 1st month and 13.9% of patients had dose reductions within the 2nd month
- Approximately half of the dose holds and reductions were for G≥3 events, per protocol requirement
- 123 (4.4%) and 105 (3.8%) patients discontinued abemaciclib or all study treatment, respectively, due to AEs after 1 or 2 abemaciclib dose reductions
- More than half (253 patients, 53%) of total discontinuations and 88% of discontinuations during the 1st month occurred without an attempt to address the AE via a dose modification

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

Clinically relevant AEs observed in ≥10% patients in abemaciclib + ET arm

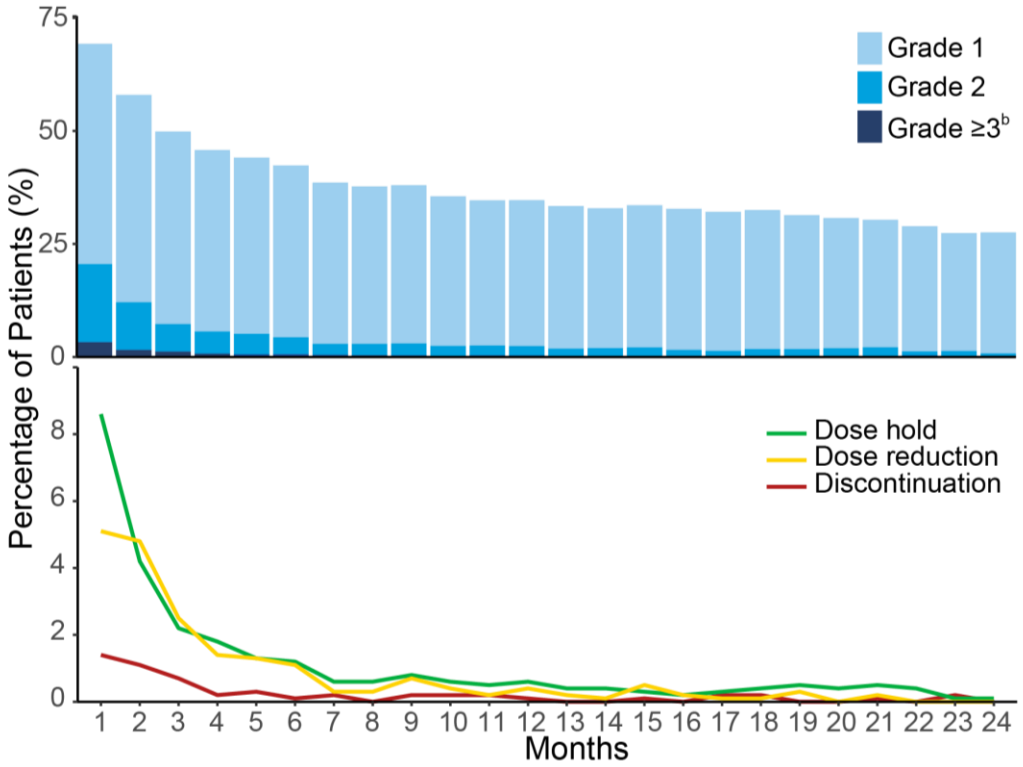
	Abemaciclib + ET (N=2791)				ET Alone (N=2800)			
	Any Grade	G1	G2	G≥3	Any Grade	G1	G2	G≥3
Patients with ≥1 AE[a]; n (%)	2733 (97.9)	189 (6.8)	1221 (43.7)	1323 (47.4)	2441 (87.2)	693 (24.8)	1351 (48.3)	397 (14.2)
Diarrhea	2304 (82.6)	1249 (44.8)	840 (30.1)	215 (7.7)[b]	281 (7.8)	168 (6.0)	45 (1.6)	5 (0.2)
Infections[c]	1330 (47.7)	235 (8.4)	963 (34.5)	132 (4.7)	1020 (36.4)	223 (8.0)	725 (25.9)	72 (2.6)[d]
Neutropenia	1262 (45.2)	177 (6.3)	552 (19.8)	533 (19.1)	145 (5.2)	61 (2.2.)	64 (2.3)	20 (0.7)
Fatigue	1094 (39.2)	623 (22.3)	393 (14.1)	78 (2.8)	464 (16.6)	357 (12.8)	103 (3.7)	4 (0.1)
Nausea	795 (28.5)	598 (21.4)	184 (6.6)	13 (0.5)	232 (8.3)	182 (6.5)	49 (1.8)	1 (0.1)
Anemia	656 (23.5)	380 (13.6)	225 (8.1)	51 (1.8)	94 (3.4)	69 (2.5)	15 (0.5)	10 (0.4)
Headache	500 (17.9)	381 (13.7)	113 (4.0)	6 (0.2)	387 (13.8)	298 (10.6)	85 (3.0)	4 (0.1)
Vomiting	466 (16.7)	356 (12.8)	97 (3.5)	13 (0.5)	122 (4.4)	92 (3.3)	28 (1.0)	2 (0.1)
Stomatitis[e]	365 (13.1)	296 (10.6)	65 (2.3)	4 (0.1)	140 (5.0)	126 (4.5)	14 (0.5)	0
Thrombocytopenia	353 (12.6)	264 (9.5)	56 (2.0)	33 (1.2)	45 (1.6)	36 (1.3)	6 (0.2)	3 (0.1)
Decreased appetite	320 (11.5)	239 (8.6)	65 (2.3)	16 (0.6)	61 (2.2)	50 (1.8)	9 (0.3)	2 (0.1)
Alanine aminotransferase increase (ALT)	291 (10.4)	160 (5.7)	63 (2.3)	68 (2.4)	136 (4.9)	99 (3.5)	21 (0.8)	16 (0.6)
Rash	287 (10.3)	225 (8.1)	51 (1.8)	11 (0.4)	113 (4.0)	93 (3.3)	20 (0.7)	0
Aspartate aminotransferase increase (AST)	281 (10.1)	189 (6.8)	43 (1.5)	49 (1.8)	120 (4.3)	91 (3.3)	15 (0.5)	14 (0.5)

[a]The severity of AEs were recorded by investigators and graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4
[b]1 G5 event
[c]Infection is a composite term that includes all reported preferred terms that are part of the infections and infestations system organ class
[d]4 G5 events
[e]Stomatitis is a consolidated term that includes mouth ulceration, mucosal inflammation, oropharyngeal pain, stomatitis

ALT/AST and neutropenia were well managed in abemaciclib treated patients

- Incidence of G≥3 ALT and AST was <2.5% and median time to onset of ~3 months, with median time to resolution to G<3 of 13 and 11 days, respectively
  - All G≥3 ALT central laboratory elevations were reversible with dose modifications or abemaciclib discontinuation
  - Discontinuation of abemaciclib due to any grade ALT and AST was 0.6% and 0.1%
- 9 patients had AST and/or ALT >3X ULN with TBILI >2X ULN per central laboratory and 3 patients had AEs of drug induced liver injury
  - None of those cases met the criteria for drug induced liver injury (CIOMS 2020)
- Neutropenia was the most frequently reported grade ≥3 AE, with a median time to onset of 30 days, a median duration of 16 days and was rare after first 6 months
  - G≥3 events were not associated with severe complications such as febrile neutropenia or severe infections
- G≥3 neutropenia was well managed with dose modifications, resulting in a low discontinuation rate (0.9%)

Diarrhea was well managed in monarchE[a]



- Median time to onset of any grade diarrhea was 8 days and incidence decreased over time
  - G2/3 events occurred primarily in the first 3 months and were short lived (≤6 days)
- 78.0% of patients who experienced diarrhea, received anti-diarrheal medication (71.2% for G1, 85.5% for G2, 87.9% for G3)
- Among 2304 patients who experienced diarrhea, 472 (20.5%) had ≥1 dose reduction and 528 (22.9%) held administration
- Discontinuation rate was low (5%), most due to low grade events and within first 2 months of treatment
  - 59% of total discontinuations due to diarrhea and ~90% of events during the 1st month occurred without a prior dose reduction
- ~30% of abemaciclib treated patients had G1 diarrhea after 1 year of treatment, but ≤0.3% pts had dose holds or reductions

[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 and 1 G5 events

Venous thromboembolic events (VTE)

Event term, n (%)	Abemaciclib + ET (N=2791) Any Grade	G1	G2	G≥3	ET Alone (N=2800) Any Grade	G1	G2	G≥3
VTE	67 (2.4)	3 (0.1)	27 (1.0)	37 (1.3)	16 (0.6)	0	9 (0.3)	7 (0.3)[b]
PE[a]	26 (0.9)	0	0	26 (0.9)	4 (0.1)	0	0	4 (0.1)[b]
Serious *VTE*	33 (1.2)				8 (0.3)			
VTE by First ET	Abemaciclib + ET				ET Alone			
Tamoxifen (Nx=857 [abemaciclib + ET]; 898 [ET alone])	35 (4.1)	2 (0.2)	14 (1.6)	19 (2.2)	6 (0.7)	0	2 (0.2)	4 (0.4)
Aromatase Inhibitors (Nx=1929 [abemaciclib + ET]; 1892 [ET alone])	32 (1.7)	1 (0.1)	13 (0.7)	18 (0.9)	10 (0.5)	0	7 (0.4)	3 (0.2)
Time to onset of first *VTE* event (days); median (range)	182.0 (8.0 – 714.0)				187.5 (9.0 – 716.0)			
Discontinuation due to *VTE*	13 (0.5)				2 (0.1)			

[a]CTCAE minimum severity for PE is Grade 3 for uncomplicated events; [b]1 grade 5 event

- In abemaciclib-treated patients, most *VTEs* were G≥3 and were primarily pulmonary embolism events, including 6 (0.2%) G4 *VTEs* (3 PE)
  - 17 PEs had a serious outcome (e.g. hospitalization), the remaining 9 PEs did not qualify as SAEs
- The observed rate of *VTEs* was higher when tamoxifen, rather than AI, was administered as the initial ET
- Risk factors for *VTE* were generally well-balanced across arms
- ~94% patients who experienced *VTEs* received anti-coagulation treatment

Interstitial lung disease (ILD)

	Abemaciclib + ET (N=2791)				ET Alone (N=2800)			
Event term, n (%)	**Any Grade**	**G1**	**G2**	**G≥3**	**Any Grade**	**G1**	**G2**	**G≥3**
ILD	82 (2.9)	39 (1.4)	32 (1.1)	11 (0.4)[a]	34 (1.2)	23 (0.8)	10 (0.4)	1 (0.1)
Pneumonitis	43 (1.5)	17 (0.6)	19 (0.7)	7 (0.3)[a]	10 (0.4)	7 (0.3)	3 (0.1)	0
Radiation pneumonitis	25 (0.9)	13 (0.5)	10 (0.4)	2 (0.1)	14 (0.5)	8 (0.3)	5 (0.2)	1 (0.1)
ILD	5 (0.2)	2 (0.1)	2 (0.1)	1 (0.1)	1 (0.1)	0	1 (0.1)	0
Serious *ILD* Events	14 (0.5)				1 (0.1)			
Time to onset of first *ILD* event (days); median (range)	190.0 (23.0 – 517.0)				158.0 (29.0-539.0)			
Discontinuation due to *ILD*	19 (0.7)				0			

[a]1 grade 5 event

- In abemaciclib-treated patients, most *ILD* events were G1 and primarily pneumonitis, 10 pts (0.4%) experienced G3 events and 1 fatal event
  - The majority of the G≥3 *ILDs* (82%) had a serious outcome (e.g. hospitalization)
- 95.4% patients had prior adjuvant radiotherapy, a known risk factor for *ILD*; which was balanced across both arms
- In the abemaciclib arm, the incidence of any grade *ILD* was higher in patients from Asia (5.9%), compared to the overall population (2.9%); however, the overall incidence of G≥3 or SAE was <1.0% and similar across regions
- Approximately half of the patients who experienced an *ILD* in the abemaciclib arm, received concomitant medications, including steroids and antibiotics, consistent with the treatment requirement of symptomatic (G≥2) events per CTCAE definition.

Conclusions

- The overall safety profile of abemaciclib in monarchE is generally consistent with the established safety profile of abemaciclib, with no new safety concerns
- Most common AEs, including AESI, started early in treatment and were manageable with dose adjustments and comedication, which allowed most patients to remain on treatment
  - Tamoxifen is associated with a numerically higher incidence of *VTE* compared to AIs
- The small percentage of patients discontinuing abemaciclib after a dose reduction supports its tolerability in combination with ET in the EBC population
  - More than half of abemaciclib discontinuations due to an AE occurred without a prior attempt to address the AE with a dose reduction
- Safety data collection continues since >50% of patients are still on treatment

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