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EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: updated results by duration of prior CDK4/6i in metastatic setting

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Disclosures

- Presenter: Virginia Kaklamani
- Speaker: Pfizer, Gilead, Genentech, Exact Sciences, Novartis, AstraZeneca, Daiichi Sankyo, Seagen
- Consultant: Puma, AstraZeneca, Daiichi Sankyo, Menarini, Gilead
- Research: Eisai

Introduction

- **Endocrine therapy plus CDK4/6i is the mainstay** for the management of ER+/HER2- mBC as 1st-line therapy.[1]
- However, **tumors eventually develop hormonal resistance**, mainly through the development of *ESR1* mutations.
- In current practice, sequential endocrine monotherapy or combination therapies are used in the 2nd/3rd line.
- **Sequential endocrine monotherapy is associated with low PFS after CDK4/6i** (1.94 months).[2] In addition, fulvestrant has low bioavailability and an IM injection burden.
- Main **combinations such as everolimus + exemestane and alpelisib + fulvestrant can be associated with significant toxicity** with discontinuation rates around 25%.[3,4]
- In this context, there is **a significant need for potent oral SERDS for monotherapy use** and for enabling oral-oral combinations.
- Elacestrant is a next-generation oral SERD, which has demonstrated a statistically significant improvement in PFS compared with single-agent endocrine therapy in the EMERALD trial, including in patients with *ESR1* mutated tumors. Emerald is the only pivotal oral SERD trial where prior CDK 4/6i usage was mandated.[5]
- Here we examine the impact of the duration of prior CDK4/6i on PFS and share updated safety results.

1. Moy B, et al. *J Clin Oncol.* 2021:JCO2101374; 2. Lindeman GJ et al. J Clin Oncol 2021,39(suppl 15):1004-1004; 3. Everolimus US Prescribing Information; 4. Alpelisib US Prescribing Information
5. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256.

Oral SERD Trial Landscape in Pretreated mBC

	EMERALD[1]	SERENA-2[2]	EMBER-3[3]	AMEERA-3[4-6]	acelERA[6-9]
Treatment	**Elacestrant**	**Camizestrant**	**Imlunestrant** +/- abemaciclib	**Amcenestrant**	**Giredestrant**
Control Arm	fulvestrant / AIs	fulvestrant	fulvestrant / exemestane	fulvestrant / AIs / tamoxifen	fulvestrant / AIs
Phase (n)	Phase 3 (478)	Phase 2 (240)	Phase 3 (800)	Phase 2 (367)	Phase 2 (303)
Patients	Men or postmenopausal women	Postmenopausal women	Men or postmenopausal women	Men or women (any menopausal status)	Men or women (any menopausal status)
Prior CDK4/6i	**Required (100%)**	Permitted	Permitted	Permitted (79.7%)	Permitted (42%)
Allowed Prior Fulvestrant	**YES**	NO	NO	YES	YES
Allowed Prior Chemotherapy in mBC	**YES**	YES	NO	YES	YES
Data readout	**Positive (Registrational)**	Positive (Non-Registrational)	Ongoing	Negative	Negative

1. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256. 2. SERENA2. ClinicalTrials.gov identifier: NCT04214288. Accessed November 18, 2022, https://clinicaltrials.gov/ct2/show/NCT04214288; 3. EMBER-3. Clinical Trials.gov identifier: NCT04975308. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04975308; 4. AMEERA3. ClinicalTrials.gov identifier: NCT04059484. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04059484; 5. Tolaney SM, et al. *Ann Oncol.* 2022; 33(7):S88-S121 (Abstr 212MO); 6. Evaluate Vantage. https://www.evaluate.com/vantage/articles/news/trial-results/roche-has-rare-breast-cancer-setback. Accessed July 20, 2022; 7. acelERA ClinicalTrials.gov identifier: NCT04576455. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04576455; 8. Martin M, et al. *J Clin Oncol.* 2021;39(15):abstr TPS1100; 9. Martin Jimenez M, et al. *Ann Oncol.* 2022;33(7):S88-S121 (abstr 211MO).

EMERALD Phase 3 Study Design

Inclusion Criteria

- Men and postmenopausal women with advanced/metastatic breast cancer
- ER-positive,[a] HER2-negative
- Progressed or relapsed on or after 1 or 2 lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6i
- ≤1 line of chemotherapy for advanced disease
- ECOG PS 0 or 1

Stratification Factors:

- *ESR1*-mutation status[f]
- Prior treatment with fulvestrant
- Presence of visceral metastases

R

1:1[b]

Elacestrant 400 mg daily[c]

Investigator's choice (SOC):
Fulvestrant
Anastrozole
Letrozole
Exemestane

PD or withdrawal criterion[d]

Follow Up

Two Primary Endpoints:[e]

- PFS in all pts
- PFS in *ESR1*-mut

[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Restaging CT scans every 8 weeks; [e]Blinded Independent Central Review; [f]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant Health, Redwood City, CA).

PFS, progression-free survival; Pts, patients; R, randomized; SOC, standard of care.

Baseline Characteristics

Parameter	Elacestrant		SOC	
	All (N=239)	*ESR1*-mut (N=115)	All (N=239)	*ESR1*-mut (N=113)
Median age, years (range)	63.0 (24-89)	64.0 (28-89)	63.0 (32-83)	63.0 (32-83)
Gender, n (%) Female Male	233 (97.5) 6 (2.5)	115 (100) 0	238 (99.6) 1 (0.4)	113 (100) 0
ECOG PS, n (%) 0 1 >1	143 (59.8) 96 (40.2) 0	67 (58.3) 48 (41.7) 0	135 (56.5) 103 (43.1) 1 (0.4)	62 (54.9) 51 (45.1) 0
Visceral metastasis*, n (%)	163 (68.2)	81 (70.4)	170 (71.1)	84 (74.3)
Prior CDK4/6i, n (%)	239 (100)	115 (100)	239 (100)	113 (100)
Number of prior lines of endocrine therapy,** n (%) 1 2	129 (54.0) 110 (46.0)	73 (63.5) 42 (36.5)	142 (59.4) 97 (40.6)	69 (61.1) 44 (38.9)
Type of prior endocrine therapy,** n (%) Fulvestrant AI Tamoxifen	70 (29.3) 193 (80.8) 19 (7.9)	27 (23.5) 101 (87.8) 9 (7.8)	75 (31.4) 194 (81.2) 15 (6.3)	28 (24.8) 96 (85.0) 9 (8.0)
Number of prior lines of chemotherapy,** n (%) 0 1	191 (79.9) 48 (20.1)	89 (77.4) 26 (22.6)	180 (75.3) 59 (24.7)	81 (71.7) 32 (28.3)

*Includes lung, liver, brain, pleural, and peritoneal involvement
**In the advanced/metastatic setting

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Type of prior endocrine therapy, n (%)**				
Fulvestrant	**70 (29.3)**	**27 (23.5)**	**75 (31.4)**	**28 (24.8)**
AI	193 (80.8)	101 (87.8)	194 (81.2)	96 (85.0)
Tamoxifen	19 (7.9)	9 (7.8)	15 (6.3)	9 (8.0)
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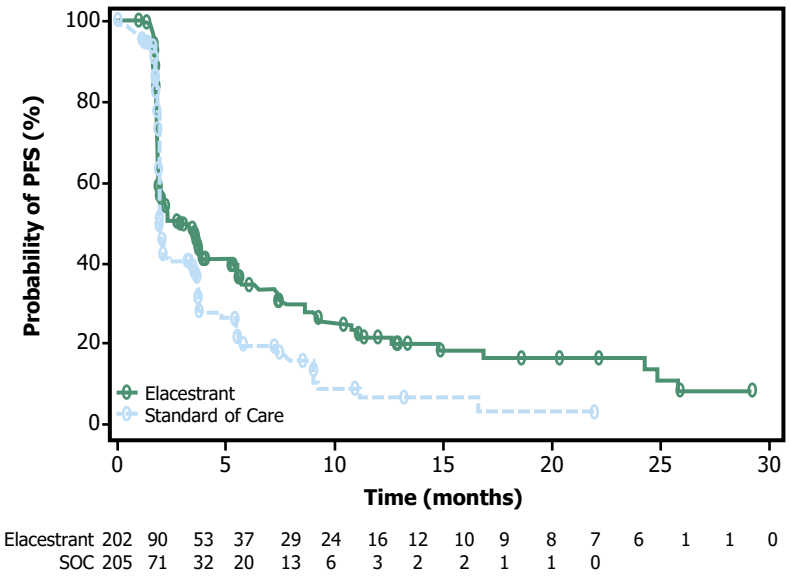
**In the advanced/metastatic setting

All Patients: PFS by Duration of CDK4/6i

	Duration on CDK4/6i in the metastatic setting					
	At Least 6 Months (87.5%)		At Least 12 Months (66.7%)		At Least 18 Months (46.7%)	
	Elacestrant (n=202)	SOC Hormonal Therapy (n=205)	Elacestrant (n=150)	SOC Hormonal Therapy (n=160)	Elacestrant (n=98)	SOC Hormonal Therapy (n=119)
Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 6 months, % (95% CI)	34.40 (26.70 - 42.10)	19.88 (12.99 - 26.76)	41.56 (32.30 - 50.81)	21.72 (13.65 - 29.79)	44.72 (33.24 - 56.20)	25.12 (15.13 - 35.10)
PFS rate at 12 months, % (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
PFS rate at 18 months, % (95% CI)	16.24 (8.75 - 23.74)	3.21 (0.00 - 8.48)	19.34 (9.98 - 28.70)	3.69 (0.00 - 9.77)	21.03 (9.82 - 32.23)	4.11 (0.00 - 11.33)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)		**0.613** (0.453 - 0.828)		**0.703** (0.482 - 1.019)	

All Patients: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
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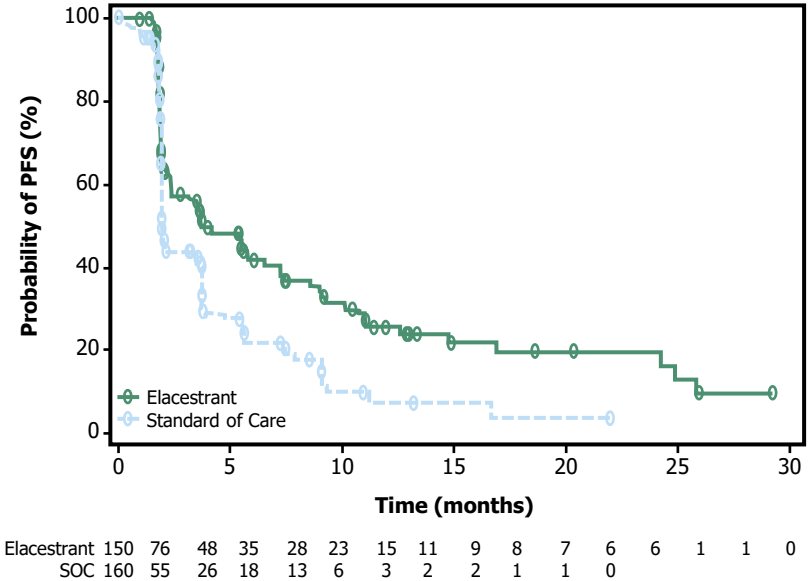
At least 12 mo CDK4/6i



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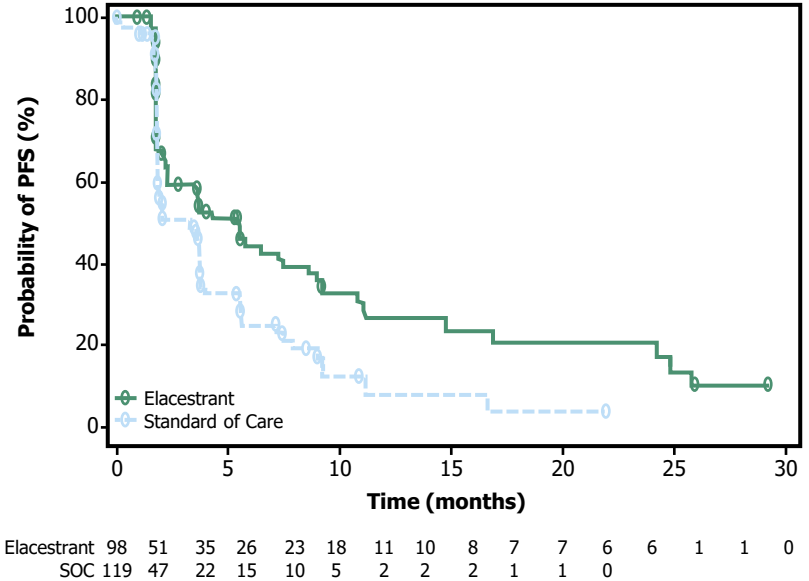
PFS rate at 12 months, % (95% CI)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)
Hazard ratio (95% CI)	**0.613** (0.453 - 0.828)	

At least 18 mo CDK4/6i



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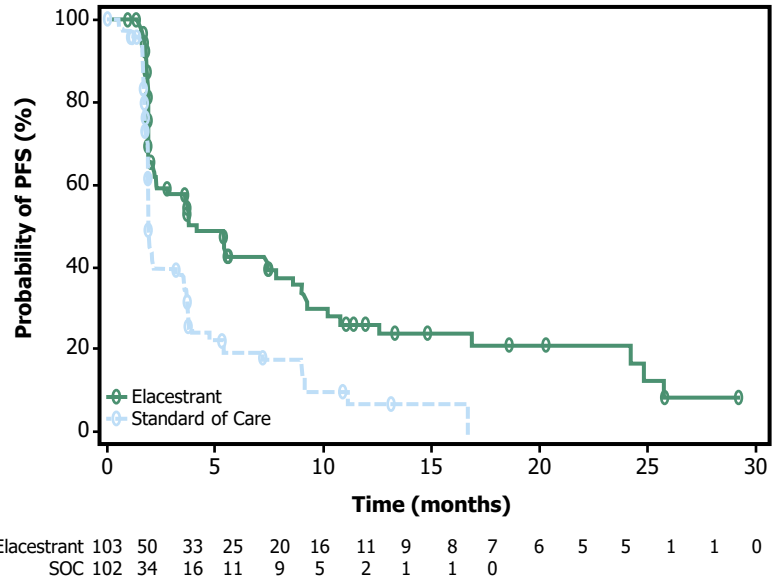
Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

Duration on CDK4/6i in the metastatic setting

	At Least 6 Months (92.3%)		At Least 12 Months (71.6%)		At Least 18 Months (50.0%)	
	Elacestrant (n=103)	SOC Hormonal Therapy (n=102)	Elacestrant (n=78)	SOC Hormonal Therapy (n=81)	Elacestrant (n=55)	SOC Hormonal Therapy (n=56)
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 6 months, % (95% CI)	42.43 (31.15 - 53.71)	19.15 (9.95 - 28.35)	55.81 (42.69 - 68.94)	22.66 (11.63 - 33.69)	58.57 (43.02 - 74.12)	27.06 (13.05 - 41.07)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
PFS rate at 18 months, % (95% CI)	20.70 (9.77 - 31.63)	0.00 (. - .)	28.49 (14.08 - 42.89)	0.00 (. - .)	30.68 (13.94 - 47.42)	0.00 (. - .)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		**0.410** (0.262 - 0.634)		**0.466** (0.270 - 0.791)	

Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



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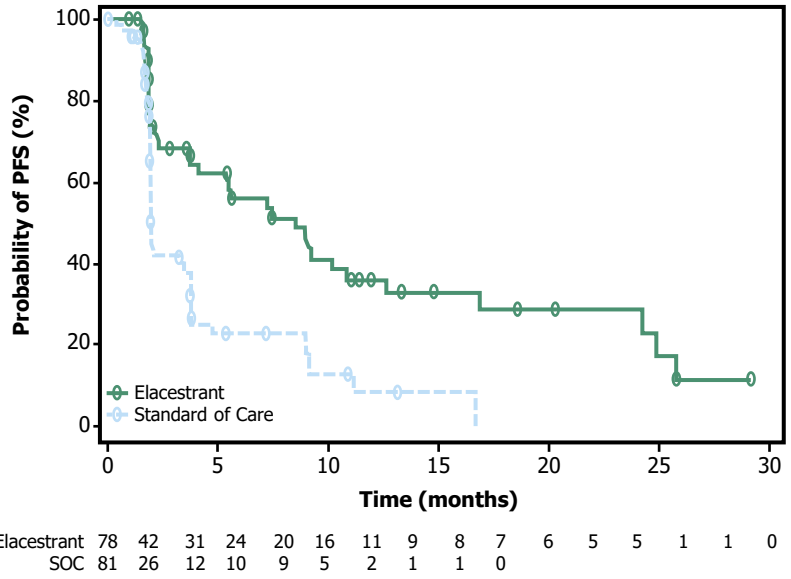
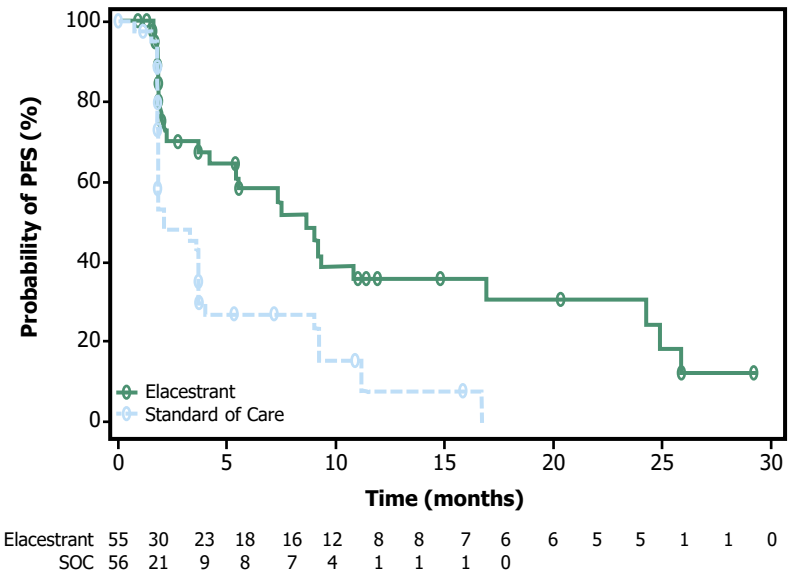


	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

At least 18 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

PFS Analysis by CDK4/6i Duration

Duration on CDK4/6i in the Metastatic Setting	< 6 Months		6- 12 Months		12 - 18 Months		≥ 18 Months	
All Patients	**Elacestrant (n=29)**	**SOC Hormonal Therapy (n=29)**	**Elacestrant (n=52)**	**SOC Hormonal Therapy (n=46)**	**Elacestrant (n=52)**	**SOC Hormonal Therapy (n=40)**	**Elacestrant (n=98)**	**SOC Hormonal Therapy (n=119)**
Median PFS, months (95% CI)	**3.55 (1.87 - 9.43)**	**1.87 (1.74 - 2.20)**	**1.91 (1.84 - 1.94)**	**1.87 (1.81 - 2.14)**	**3.52 (1.87 - 7.29)**	**1.84 (1.84 - 1.87)**	**5.45 (2.33 - 8.61)**	**3.29 (1.87 - 3.71)**
PFS rate at 6 months, % (95% CI)	34.54 (9.75 - 59.33)	19.52 (4.21 -34.83)	14.91 (3.12 - 26.70)	12.79 (0.46 - 25.11)	35.40 (19.80 - 51.00)	12.83 (0.09 - 25.56)	44.72 (33.24 - 56.20)	25.12 (15.13 -35.10)
PFS rate at 12 months, % (95% CI)	23.03 (0.00 - 47.78)	11.71 (0.00-24.15)	7.46 (0.00 - 19.35)	NA	24.78 (8.07 - 41.49)	4.28 (0.00 - 12.33)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
PFS rate at 18 months, % (95% CI)	11.51 (0.00 - 31.71)	11.7 (0.00 -24.15)	7.46 (0.00 - 19.35)	NA	18.59 (2.22 - 34.95)	NA	21.03 (9.82 - 32.23)	4.11 (0.00 - 11.33)
Hazard ratio (95% CI)	0.709 (0.347 - 1.405)		1.070 (0.638 - 1.814)		0.367 (0.204 - 0.654)		0.703 (0.482 - 1.019)	
***ESR1*-mut**	**Elacestrant (n=9)**	**SOC Hormonal Therapy (n=8)**	**Elacestrant (n=25)**	**SOC Hormonal Therapy (n=21)**	**Elacestrant (n=23)**	**SOC Hormonal Therapy (n=25)**	**Elacestrant (n=55)**	**SOC Hormonal Therapy (n=56)**
Median PFS, months (95% CI)	**1.87 (1.64 - .)**	**1.87 (1.68 - 5.55)**	**1.91 (1.87 - 2.79)**	**1.84 (1.68 - 3.45)**	**5.49 (1.94 - .)**	**1.84 (1.84 - 1.94)**	**8.61 (5.45 - 16.89)**	**2.10 (1.87 - 3.75)**
PFS rate at 6 months, % (95% CI)	NA	14.29 (0.00 -40.21)	5.46 (0.00 - 15.78)	7.22 (0.00 - 20.35)	49.32 (25.11 - 73.53)	13.65 (0.00 - 30.31)	58.57 (43.02 - 74.12)	27.06 (13.05 - 41.07)
PFS rate at 12 months, % (95% CI)	NA	0	0	0	36.99 (9.28 - 64.70)	6.82 (0.00 - 19.43)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
PFS rate at 18 months, % (95% CI)	NA	0	0	0	24.66 (0.00 - 51.69)	NA	30.68 (13.94 - 47.42)	0
Hazard ratio (95% CI)	1.565 (0.424 - 5.769)		1.122 (0.547 - 2.347)		0.302 (0.126 - 0.677)		0.466 (0.270 - 0.791)	

Safety Summary

Updated safety data were consistent with previously reported results:

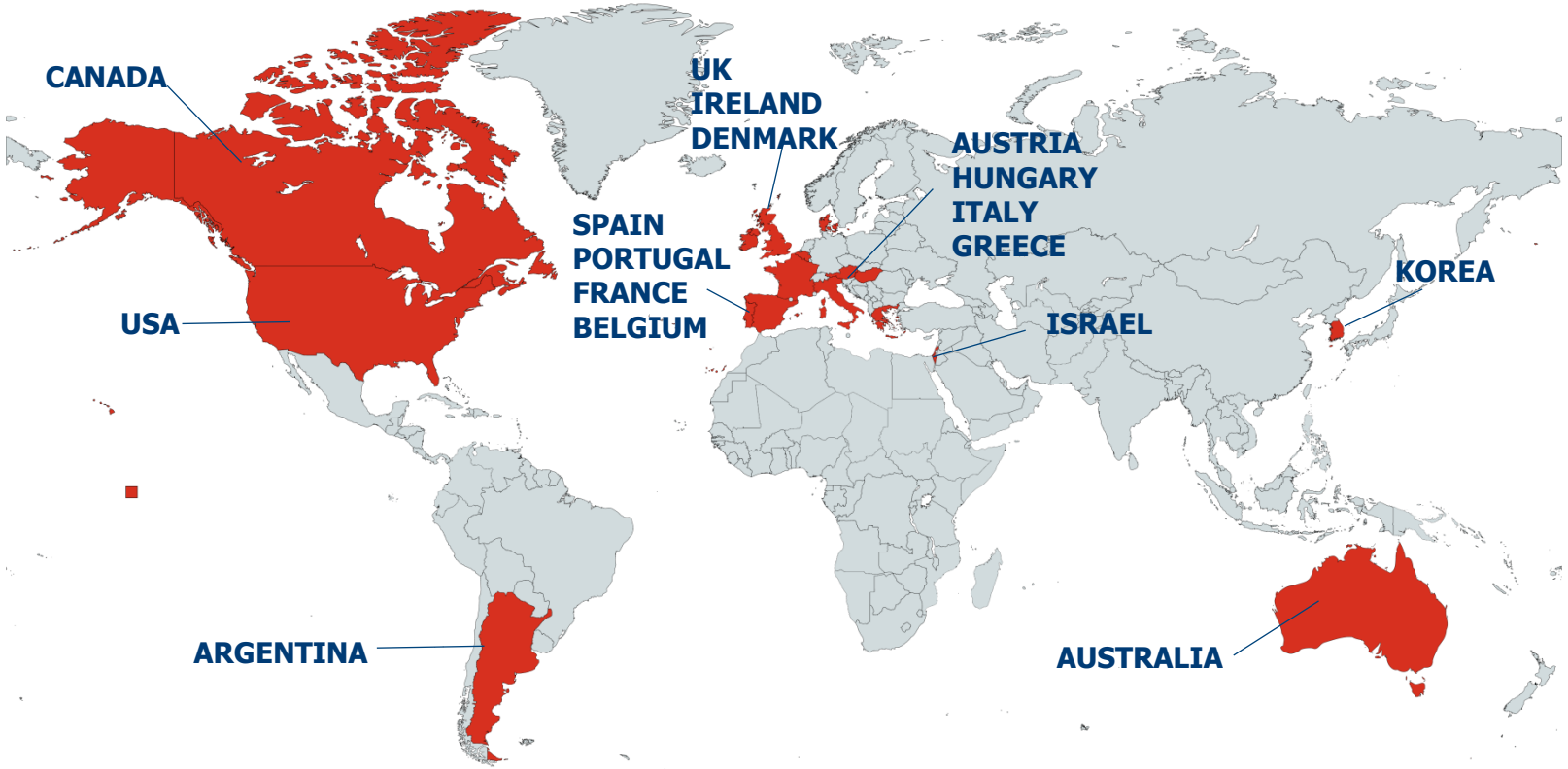
- Most adverse events (AEs), including nausea, were grade 1 and 2, and no grade 4 treatment-related AEs (TRAEs) were reported.
- Only 3.4% of patients receiving elacestrant and 0.9% receiving SOC discontinued therapy due to any TRAE.
- No deaths assessed as treatment-related were reported in either arm.
- No hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia.

Nausea Summary	Elacestrant (n=237)	SOC (n=230)
Grade 3 nausea, n (%)	6 (2.5%)	2 (0.9%)
Dose-reduction rate due to nausea, n (%)	3 (1.3%)	Not applicable
Discontinuation rate due to nausea, n (%)	3 (1.3%)	0 (0%)
Antiemetic use	8%	10.3% (AI) 1.3% (Ful)

Conclusions

- EMERALD is the only pivotal trial in 2nd/3rd-line mBC with 100% prior CDK4/6i usage.
- Duration of CDK4/6i was associated with PFS in the EMERALD trial. The longer the duration of prior CDK4/6i, the longer PFS on elacestrant as compared with SOC.
- This was even more pronounced in patients with *ESR1*-mut tumors, where patients who had at least 12 months of prior CDK4/6i duration achieved a mPFS of 8.6 months with elacestrant vs 2 months mPFS with SOC.
- No new safety signals were identified. Low-grade nausea was common in both treatment arms, but antiemetic usage was low with both drugs: 8% on elacestrant and 10.3% on AIs. There was no incidence of bradycardia.
- These results showed that elacestrant significantly prolongs PFS vs SOC with a low rate of adverse events.
- Elacestrant can become an important oral endocrine monotherapy agent in 2nd/3rd line as an alternative to combination therapies that are associated with challenging safety profiles.

Acknowledgements



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