AMEERA-1: Subgroup analyses of Phase 1/2 study of amcenestrant (SAR439859), an oral selective estrogen receptor (ER) degrader (SERD), with palbociclib in postmenopausal women with ER+/human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (aBC)

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AMEERA-1

BACKGROUND

- AMEERA-1 (NCT03284957) is an ongoing Phase 1/2 study investigating amcenestrant, an optimized, oral SERD, as monotherapy (Arm 1) and in combination with targeted therapies (Arms 2–5) among postmenopausal women with ER+/HER2– aBC
- Acquired mechanisms of resistance to endocrine therapies (ETs) in breast tumors dependent on ER signaling include mutations in the *ESR1* gene as well as genomic aberrations in non-ER-dependent genes[1,2]
- In AMEERA-1 Arm 1, results with amcenestrant monotherapy in heavily-pretreated patients have demonstrated:
  - Antitumor activity in response-evaluable patients (N = 59) with endocrine-resistant, ER+/HER2– advanced/metastatic breast cancer (objective response rate [ORR] of 8.5% and clinical benefit rate [CBR] of 33.9%)[3]
  - Clinical benefit irrespective of baseline *ESR1* mutation status, including with resilient Y537S and D538G mutations, in patients assessed for baseline *ESR1* mutational analysis in circulating free DNA (N = 30)[3]
  - On-treatment reduction in *ESR1* mutation allele frequency in 93% of patients with available data at baseline and Day 28 (N = 31)[3]
  - Favorable overall safety profile in the safety population (N = 62), with limited treatment-related adverse events (TRAEs) occurring in 39/62 patients (62.9%; all were Grade 1–2) and no clinically significant cardiac or ocular safety findings[3]
- In AMEERA-1 Arm 2, results with amcenestrant in combination with the cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) palbociclib have demonstrated:
  - Antitumor activity in response-evaluable patients (N = 35) with endocrine-resistant, ER+/HER2– advanced/metastatic breast cancer (ORR of 34.3% and CBR of 74.3%)[4]
  - Favorable overall safety profile in the safety population (N = 39) with similar amcenestrant TRAEs with the combination therapy (28/39 patients [71.8%]; all grade events) as observed with monotherapy; palbociclib TRAEs (35/39 patients [89.7%]; all grade events) were as expected with ET in combination with palbociclib[4]
- Here we report updated AMEERA-1 Arm 2 data, including antitumor activity by subgroups and genomic profiling

METHODS

- Arm 2 of this open-label, Phase 1/2 study assessed the standard dose of palbociclib (125 mg; 21 days on/7 days off) in combination with amcenestrant (once daily in 28-day cycles) in dose escalation (N = 15; Part C) at 200 mg (n = 9) and 400 mg (n = 6), and in dose expansion (Part D; N = 30) at the 200 mg recommended Phase 2 dose (RP2D) established in Part C
- Key eligibility criteria:
  - Postmenopausal women with ER+/HER2– locally advanced or metastatic BC
  - Measurable disease and ≥ 6 months of prior ET in the advanced setting or adjuvant ET resistance (i.e., relapse on adjuvant ET started ≥ 24 months ago or < 12 months after completing adjuvant ET)[5]
  - ≤ 1 prior line of chemotherapy for advanced disease
  - ≤ 2 prior lines of advanced ET in Part D
  - ≤ 1 prior advanced CDK4/6i-based therapy in Part C; no prior CDK4/6i, phosphoinositide 3 kinase inhibitor (PI3Ki), mammalian target of rapamycin inhibitor (mTORi), or protein kinase B inhibitor (AKTi) in Part D
  - Eastern Cooperative Oncology Group performance status < 2
- Antitumor activity was evaluated by the ORR (confirmed complete response [CR] and confirmed partial response [PR]) and the CBR (CR, PR, or stable disease [SD] ≥ 24 weeks) per Response Evaluation Criteria in Solid Tumors v1.1, as assessed by investigators/local radiologists, in response-evaluable patients without prior CDK4/6i or mTORi receiving amcenestrant at the RP2D (N = 34; n = 5 from Part C and n = 29 from Part D)
  - Subgroup analyses of antitumor activity by prior treatment regimen and baseline *ESR1* mutation status (wild-type or mutated) were conducted.
  - *ESR1* mutation status at baseline was analyzed by multiplex digital droplet polymerase chain reaction (ddPCR) from plasma circulating free DNA (cfDNA)
- Molecular profiling in cfDNA at baseline was conducted using next-generation sequencing (NGS) Roche AVENIO extended panel (77-gene) (Ambry Genetics; Aliso Viejo, CA, USA). Pathogenicity data were generated by ClinVar (version Aug 05 2021)

RESULTS

Table 1. Baseline demographics and disease characteristics

	Response-evaluable Population (Parts C + D; N = 34)
Age, years, median (range)	61 (33–86)
ECOG performance score of 0	27 (79.4)
Visceral metastases[a], n (%)	31 (91.2)
Endocrine resistance status, n (%)	
Primary resistance[b]	3 (8.8)
Secondary resistance[c]	31 (91.2)
Sensitive[d]	0
Immediate prior therapy, n (%)	
Neoadjuvant or adjuvant	15 (44.1)
Advanced	19 (55.9)
Prior lines of therapy in the advanced setting, n (%)	
0	15 (44.1)
1 line	14 (41.2)
2 lines	5 (14.7)
≥ 3 lines	0
Prior lines of ET in the advanced setting, n (%)	
0	16 (47.1)
1 line	15 (44.1)
2 lines	3 (8.8)
≥ 3 lines	0
Prior types of anti-cancer treatment in the advanced setting, n (%)	
Prior chemotherapy	6 (17.6)
Prior ET	18 (52.9)
AI	14 (41.2)
SERM	5 (14.7)
SERD (fulvestrant)	1 (2.9)
Prior targeted therapy	2 (5.9)

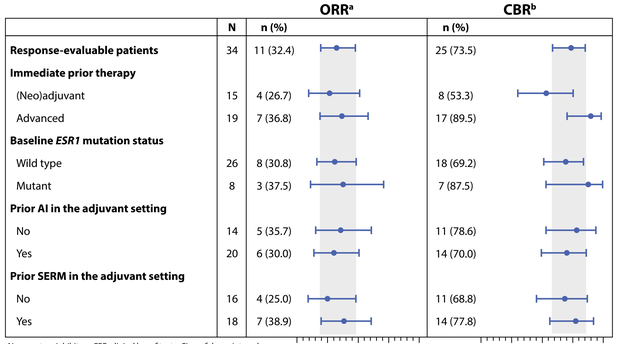
aBC, advanced breast cancer; AI, aromatase inhibitors; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; PD, progressive disease; SERM, selective estrogen receptor modulator; SERD, selective estrogen receptor degrader.
[a]Defined by metastasis in any organ except bone and lymph nodes; [b]Relapse while on the first 2 years of adjuvant ET, or PD within the first 6 months of first-line ET for aBC, while on ET; [c]Relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or PD ≥ 6 months after initiating ET for aBC, while on ET; [d]Relapse ≥ 12 months after the end of adjuvant
ET and treatment-naive in advanced therapy.

- As of May 30, 2021, 19/34 (55.9%) patients remain on study treatment (Part C: n = 1; Part D: n = 18)

Antitumor Activity

- In response-evaluable patients with available data for baseline *ESR1* mutational analyses in cfDNA by ddPCR (N = 34):
  - Objective response (OR) was observed in 3/8 (37.5%) patients with *ESR1* mutations (2 patients had E380Q and 1 patient had D538G) and in 8/26 (30.8%) patients with wild-type *ESR1* (**Table 2**)
  - Clinical benefit (CB) was observed in 7/8 (87.5%) patients with D538G, E380Q, Y537N, or Y537S baseline *ESR1* mutations, and in 18/26 (69.2%) patients with wild-type *ESR1* (**Table 3**)
- In response-evaluable patients with baseline NGS data (N = 33):
  - 23 patients had wild-type *ESR1* and other genomic aberrations, with OR in 5/23 (21.7%) and CB in 16/23 (69.6%) (**Table 4; Table 5**)
  - Of 10/33 patients with OR (**Table 4**), 7 patients had wild-type *ESR1*, comprising 5 patients with other genomic aberrations and 2 patients without genomic aberrations
  - Of 5/33 patients with mutated *ESR1* and concurrent aberrations, 2/5 had OR (**Table 4**) and 4/5 had CB (**Table 5**)
  - Of 9/33 patients with no CB (**Table 5**), genomic aberrations included *PIK3CA* and *TP53*

Figure 1. Antitumor activity by subgroup in the response-evaluable population receiving amcenestrant 200 mg in combination with palbociclib



AI, aromatase inhibitors; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.
[a]Confirmed CR or PR; [b]CR, PR, or SD ≥ 24 weeks.
Gray shading represents the 90% CI of the response-evaluable population.

Table 2. Objective response in response-evaluable patients with available data for baseline *ESR1* mutational analyses in cfDNA by ddPCR (N = 34)

ESR1 Mutations	Nonresponders (N = 23)	Responders (N = 11)
Patients with wild-type *ESR1*, n	18	8
Patients with mutated *ESR1*, n	5	3
D538G, n (%)	1 (20.0)	1 (33.3)
E380Q, n (%)	1 (20.0)	2 (66.7)
Y537N, n (%)	1 (20.0)	0 (0)
Y537S, n (%)	2 (40.0)	0 (0)

cfDNA, circulating free DNA; ddPCR, digital droplet polymerase chain reaction.

Table 3. Clinical benefit in response-evaluable patients with available data for baseline *ESR1* mutational analyses in cfDNA by ddPCR (N = 34)

ESR1 Mutations	No CB (N = 9)	CB (N = 25)
Patients with wild-type *ESR1*, n	8	18
Patients with mutated *ESR1*, n	1	7
D538G, n (%)	0 (0)	2 (28.6)
E380Q, n (%)	1 (100)	2 (28.6)
Y537N, n (%)	0 (0)	1 (14.3)
Y537S, n (%)	0 (0)	2 (28.6)

CB, clinical benefit (CR + PR + SD ≥ 24 weeks); cfDNA, circulating free DNA; ddPCR, digital droplet polymerase chain reaction.

Table 4. Objective response among response-evaluable patients with baseline NGS data (N = 33)

Number of patients	Nonresponders (N = 23)	Responders (N = 10)
Wild-type *ESR1* without other genomic aberrations , n (%)	1 (4.3)	2 (20.0)
At least one genomic aberration, n (%)	22 (95.7)	8 (80.0)
mutated *ESR1*, n (%)	4 (17.4)	3 (30.0)
other genomic aberrations than *ESR1*, n (%)	21 (91.3)	7 (70.0)
mutated *ESR1* with other genomic aberrations, n (%)	3 (13.0)	2 (20.0)
mutated *ESR1* without other genomic aberrations, n (%)	1 (4.3)	1 (10.0)
wild-type *ESR1* with other genomic aberrations, n (%)	18 (78.3)	5 (50.0)

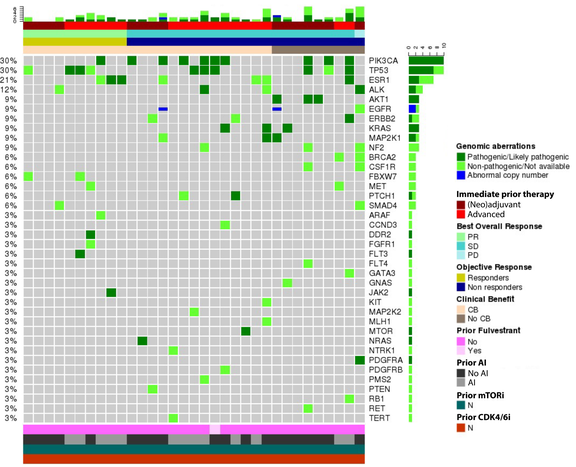
NGS, next-generation sequencing.

Table 5. Clinical benefit among response-evaluable patients with baseline NGS data (N = 33)

Number of patients	No CB (N = 9)	CB (N = 24)
Wild-type *ESR1* without other genomic aberrations , n (%)	1 (11.1)	2 (8.3)
At least one genomic aberration, n (%)	8 (88.9)	22 (91.7)
mutated *ESR1*, n (%)	1 (11.1)	6 (25.0)
other genomic aberrations, n (%)	8 (88.9)	20 (83.3)
mutated *ESR1* with other genomic aberrations, n (%)	1 (11.1)	4 (16.7)
mutated *ESR1* without other genomic aberrations, n (%)	0 (0)	2 (8.3)
wild-type *ESR1* with other genomic aberrations, n (%)	7 (77.8)	16 (66.7)

CB, clinical benefit (CR + PR + SD ≥ 24 weeks); NGS, next-generation sequencing.

Figure 2. Baseline OncoPrint diagram in response-evaluable patients with NGS data (N = 33) showing baseline genomic aberrations



Pathogenicity data by ClinVar (version Aug 05 2021).
AI, aromatase inhibitor; CB, clinical benefit (CR + PR + SD ≥ 24 weeks); CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; mTORi, mammalian target of rapamycin inhibitor; NGS, next-generation sequencing; PD, progressive disease; PR, partial response; SD, stable disease.

- The most prevalent pathogenic mutations across all response-evaluable patients with baseline NGS data (N = 33) were in *PIK3CA*, *TP53*, and *ESR1* genes (**Figure 2**)
- Per OR assessment, nonresponders displayed more genomic aberrations than responders at baseline, although the clinical relevance is unknown (**Figure 2**)
- Pathogenic gene aberrations detected exclusively in nonresponders vs responders included the following genes: *AKT1*, *ERBB2 (HER2)*, *KRAS*, *MAP2K1*, *PTCH1*, *MTOR*, *NRAS*, *and PDGFRA* (**Figure 2**)

CONCLUSIONS

- Among patients with endocrine-resistant ER+/HER2– advanced/metastatic breast cancer, amcenestrant combined with palbociclib demonstrated encouraging ORR and CBR across various subgroups, including in patients previously treated in either the (neo)adjuvant or advanced setting, and in patients with tumors harboring multiple genomic aberrations, including tumors with baseline *ESR1* mutations and other concurrent mutations
- AMEERA-1 is an ongoing Phase 1/2 clinical trial; future arms of this study will investigate amcenestrant in combination with other targeted therapies, including the PI3Ki alpelisib in patients with ER+/HER2–, *PIK3CA*-mutated aBC (ESMO 2021; 333TiP)

DISCLOSURES

SC has served in a consulting or advisory role for Sermonix Pharmaceuticals, Novartis, Lilly, Bristol-Myers Squibb, Paige.ai, Totus Medicines, and Sanofi; reports travel/accommodations/other expenses from Bristol-Myers Squibb; reports their institution has patents for (1) targeting mutant ER with ER PROTACS and (2) detecting genomic and histologic alterations in breast cancer using machine learning algorithms; and reports their institution has received research funding from Novartis, Daiichi Sankyo, Sanofi, Lilly, and Paige.ai. HML has an immediate family member with leadership interests in Evolent; has an immediate family member with stock/other ownership interests in Evolent; has served in a consulting or advisory role for Genomic Health, Context Therapeutics, Syndax, AstraZeneca, and Eisai; has received research funding from Eisai; and reports their institution has received research funding from Sanofi and GTx. PN reports their institution has served in a consulting or advisory role for Lilly, Pfizer, Novartis, Roche, and Radius Health; and reports their institution has received travel/accommodations/other expenses from Lilly, Pfizer, and Novartis. KP has served in a consulting or advisory role for Roche, Bristol-Myers Squibb, Lilly, and Pfizer; and has served in a speakers bureau for Roche, Bristol-Myers Squibb, Lilly, and Pfizer. AB has served in a consulting or advisory role for Novartis, Genentech, Pfizer, Spectrum Pharmaceuticals, Biotheranostics, Merck, Radius Health, Innocrin Pharma, Immunomedics, Sanofi, Puma Biotechnology, and Daiichi Sankyo/AstraZeneca; and reports their institution has received research funding from Novartis, Genentech, Pfizer, Merck, Sanofi, Radius Health, Immunomedics, and AstraZeneca/Daiichi Sankyo. PK has served in a consulting or advisory role for Lilly; and reports their institution has received research funding from Genentech, Lilly, Pfizer, AstraZeneca, Sanofi, and Radius Health. VB reports honoraria from Loxo and IDEAYA Biosciences; has served in a consulting or advisory role for OncoArt and Guidepoint Global; has served in a speakers bureau for Sollt; reports their institution has received research funding from Sanofi, Seattle Genetics, Lowa, Novartis, CytomX Therapeutics, Kura Oncology, Tesaro, Roche/Genentech, Bristol-Myers Squibb, Menarini, Synthon, Janssen, Merck, Lilly, Merus, Pfizer, Incyte, Abbvie, Zenith Epigenetics, Gemnab, AstraZeneca, Adaptimmune, Alkermes, Array BioPharma, BioNTech AG, Boston Biomedical, Boehringer Ingelheim Pharmaceuticals Inc., Amgen, and Bayer HealthCare Pharmaceuticals, Inc.; and reports travel/accommodations/other expenses from START. MC has served in a consulting or advisory role for Menarini, Pfizer, and Daiichi Sankyo Europe GmbH; reports their institution has served in a consulting or advisory role for Novartis, SERVIER, Sanofi, Lilly, AstraZeneca/MedImmune, Abbvie, Pierre Fabre, Accord Healthcare, Sandoz-Novartis, and Seattle Genetics; has served in a speakers bureau for Novartis and Amgen; reports travel/accommodations/other expenses from Novartis, AstraZeneca, and Pfizer; reports other relationships with Roche; reports honoraria from Novartis, Lilly, and GT1; and reports their institution has received research funding from Novartis. VP, NT, JSL, AG, MCe, PC, and GP are employees of Sanofi. SB has no disclosures to report.

Presented at the ESMO 2021 Virtual Scientific Program. September 16–21, 2021.

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ACKNOWLEDGMENTS

- Research and analyses were supported by Sanofi
- Palbociclib kindly provided by Pfizer
- The authors were responsible for all content and editorial decisions
- Editorial support was provided by Rohan Keshwara, PhD, and Julian Martins, MBBS, MA, of inScience Communications (Philadelphia, PA, USA), funded by Sanofi