Sponsor: Sanofi **Drug substance(s):** amcenestrant	**Study Identifiers:** U1111-1233-0486; NCT04478266; EudraCT Number: 2020-001824-33 **Study code:** EFC15935

Title of the study:

A randomized, multicenter, double-blind Phase 3 study of amcenestrant (SAR439859) plus palbociclib versus letrozole plus palbociclib for the treatment of patients with ER (+), HER2 (-) breast cancer who have not received prior systemic anti-cancer treatment for advanced disease

Study center(s):

This study was conducted at 251 centers that enrolled participants in 30 countries.

Study period:

Study initiation date: 14 October 2020

Last participant last visit date: 26 May 2023

Early study termination date: 17 August 2022

Study Status: Terminated. (The study was terminated based on the review by an independent data monitoring committee of the prespecified interim analysis of the Phase 3 AMEERA-5 efficacy data. No new safety signals were observed.)

Phase of development: Phase 3

Objectives:

Primary:

To determine whether amcenestrant in combination with palbociclib improves progression free survival (PFS) when compared with letrozole in combination with palbociclib in participants with ER+, HER2- advanced breast cancer who have not received prior systemic anticancer therapies for advanced disease

Secondary:

•To compare the overall survival (OS) in both treatment arms

•To evaluate the objective response rate (ORR) in both treatment arms

•To evaluate the duration of response (DOR) in both treatment arms

•To evaluate the clinical benefit rate (CBR) in both treatment arms

•To evaluate progression-free survival on next line of therapy (PFS2)

•To evaluate the pharmacokinetics (PK) of amcenestrant, and Palbociclib

•To evaluate health-related quality of life (HRQL) in both treatment arms

•To evaluate the time to first chemotherapy in both treatment arms

•To evaluate safety in both treatment arms

Methodology:

This is a prospective, multicenter, international, randomized, double-blind, double-dummy, Phase 3 trial comparing the efficacy and safety of amcenestrant in combination with palbociclib versus letrozole in combination with palbociclib in men, pre/peri-menopausal women (with goserelin) and postmenopausal women with ER(+)/HER2(-) breast cancer who have not received prior systemic treatment for advanced disease.

Eligible participants should have histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of either loco-regional recurrent or metastatic disease not amenable to radiation therapy or surgery with curative intention, and for whom chemotherapy was not indicated.

The study had 3 main periods: screening, active treatment, and follow up. After being screened, participants meeting the eligibility criteria were randomly assigned using an IRT to either amcenestrant plus palbociclib (experimental) arm or letrozole plus palbociclib (control) arm in a 1:1 ratio.

- Arm A: Amcenestrant 200 mg + letrozole-matching placebo + palbociclib 125 mg
- Arm B: Amcenestrant-matching placebo + letrozole 2.5 mg + palbociclib 125 mg

The study population was stratified by:

- De-novo metastatic disease (Yes or No)
- Postmenopausal women (Yes or No)
- Visceral metastasis defined by at least 1 liver, lung, brain metastasis, pleural, or peritoneal involvement (Yes or No).

An abnormal laboratory test result is considered an adverse event if it meets at least one of the following criteria:

- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion, and/or
- Defined as an AESI

Number of participants:

Per protocol, approximately 1333 participants were planned to be screened in the study, and 1066 participants were planned to be randomly assigned to study intervention with a balanced randomization ratio (533 participants randomized per treatment arm).

The intent-to-treat (ITT) population was 1068 (534 in each arm) with 2 participants who were randomized but not exposed to study treatment (1 was randomized in Arm A and 1 was in Arm B). The safety population was 1066 participants with 533 participants in Arm A and 533 participants in Arm B.

Diagnosis and criteria for inclusion:

This study included participants with estrogen receptor positive (ER[+]), human epidermal growth factor receptor 2 negative (HER2 [-]) advanced or metastatic breast cancer who have not received prior systemic anti-cancer treatment for advanced disease. Exclusion criteria included an Eastern Cooperative Oncology group (ECOG) performance status >2 and participants with a diagnosis of any other malignancy within 3 years prior to randomization. However, participants with adequately treated basal cell or squamous cell skin cancer or in-situ cervical cancer are allowed.

Study products

Investigational medicinal product(s):

Amcenestrant (SAR439859) and Amcenestrant (SAR439859) -matching placebo

- Dosage form and strength: 200 mg tablets
- Routes of administration: oral route
- Dose regimen: the recommended dose is 200 mg once daily, continuously, to be taken approximately at the same time each day, with food.
- Amcenestrant (SAR439859)-matching placebo was supplied as tablets identical to amcenestrant (SAR439859) 200 mg tablets in appearance.

Letrozole and letrozole-matching placebo

- Dosage form and strength: 2.5 mg tablets over-encapsulated
- Routes of administration: oral route
- Dose regimen: 1 capsule once daily, continuously, taken approximately at the same time each day, with food.
- Letrozole-matching placebo was supplied as capsules identical to letrozole 2.5 mg capsules in appearance.

Palbociclib (Ibrance®)

- Dosage forms and strengths: 125 mg, 100 mg, 75 mg capsules or tablets.
- *Study initiated with the capsules and switched to tablets as commercially available.*
- Routes of administration: oral route
- Dose regimen: the recommended dose was 125 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. This was taken at approximately the same time each day.
- Taken with food, regardless of the administered formulation.

When given the same day, amcenestrant (SAR439859) plus letrozole matching placebo plus palbociclib or letrozole plus amcenestrant (SAR439859) matching placebo plus palbociclib was taken at the same time.

Non investigational medicinal product(s):

Goserelin

- Additional treatment with goserelin was required for men and pre/perimenopausal participants.
- Dosage form and strength: 3.6 mg injection
- Routes of administration: subcutaneous

Dose regimen: administered once every 28 days into the anterior abdominal wall below the navel line using an aseptic technique prior to study IMPs.

Duration of study intervention:

The duration of the study for each participant included a screening period of up to 28 days and active treatment period, for which the duration varies based on the progression date, followed by a follow-up period. The cycle duration for both arms was 28 days.

The total estimated duration of enrollment was approximately 18 months.

Criteria for evaluation:

Primary

Progression-free survival is defined as the time interval from the date of randomization to the date of first documented tumor progression as per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) assessed by local radiologist/investigator or death (due to any cause), whichever comes first.

Secondary:

- Overall survival is defined as the time interval from the date of randomization to the date of documented death (due to any cause).
- ORR is defined as the proportion of participants who have a complete response (CR) or partial response (PR), as best overall response determined as per RECIST 1.1, from the date of randomization until disease progression, death, cutoff date, initiation of post-treatment anti-cancer therapy, whichever occurs first.
- DOR is defined as the time from first documented evidence of CR or PR until progressive disease (PD) as determined as per RECIST 1.1 or death from any cause, whichever occurs first.
- CBR is defined as the proportion of participants who have a confirmed CR, PR, or stable disease (SD) for at least 24 weeks determined as per RECIST 1.1, from the date of randomization until disease progression, death, cutoff date, initiation of post treatment anti-cancer therapy, whichever occurs first.
- The PFS2 is defined as the time from the date of randomization to the date of first documentation of PD on the next systemic anti-cancer therapy according to Investigator or death due to any cause in the absence of documented PD on the next systemic anti-cancer therapy, whichever occurs first.
- Plasma concentrations of amcenestrant, Palbociclib
- Symptoms and function related to HRQL as measured by EORTC QLQ-C30, breast cancer specific module (QLQ-BR23/BR45) and EQ-5D-5L. Disease-specific and generic HRQL, disease and treatment-related symptoms, the impact of symptoms and treatment, health state utility, and health status will be evaluated using the European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30), the EORTC-QLQ breast cancer specific module (QLQ-BR23/BR45) and the EuroQoL questionnaire with 5 dimensions and 5 levels per dimension (EQ-5D-5L), from Cycle 1 Day 1 until 90 days after last dose of study treatment
- Time to chemotherapy is defined as the time interval from the date of randomization to the start date of the first chemotherapy after study treatment discontinuation
- Treatment emergent adverse events (TEAEs)/serious adverse events (SAEs) and laboratory abnormalities

Statistical methods:

Continuous data was summarized using the number of available data (N), mean, standard deviation (SD), median, minimum and maximum for each treatment group (for closed report) and overall (for both open and closed reports). Categorical and ordinal data was summarized using the number and percentage of participants. The baseline value was defined as the last available value or measurement prior to randomization.

Primary efficacy analysis will consist of PFS according to local radiologist's/investigator's assessment comparison between the amcenestrant + palbociclib arm and the letrozole + palbociclib arm through a logrank test procedure stratified by the stratification factors as entered in the IRT (ie, de-novo metastatic disease, postmenopausal women and visceral metastasis defined by at least 1 liver, lung, brain metastasis, pleural, or peritoneal involvement). A one-sided Type I error rate of 2.5% was used for statistical testing.

Two interim analyses were planned based on the primary PFS endpoint. The first one was to be conducted at 40% of the planned total number of events expected (non-binding futility only). The stopping boundary for futility was based on the observed HR based on stratified Cox proportional hazard model, ie, a HR>1.1. The observed HR based on Cox proportional hazard model stratified by the stratification factors as entered in the IRT system was compared with the futility boundary. The second interim analysis was to be conducted at 70% of the planned total number of events expected (efficacy only). The stopping boundary for efficacy was derived based on the O'Brien and Fleming α-spending function and depend on the actual number of PFS events observed at the time of the interim analysis

ITT population

All participants from the enrolled population and for whom there was a confirmation of successful allocation of a randomization number by IRT. Participants were analyzed according to the treatment arm assigned at randomization.

Safety population

All participants randomly assigned to study intervention and who took at least 1 dose of study intervention. Participants were analyzed according to the treatment arm they actually received on C1D1.

In addition:

- Pharmacokinetic-evaluable population:
    - All participants from the safety population who receive at least 1 dose of amcenestrant or palbociclib and with at least one evaluable corresponding plasma concentration post-treatment.

Summary Results:

Demographic and other baseline characteristics:

No imbalance between the amcenestrant + palbociclib treatment arm and letrozole + palbociclib treatment arms has been identified in either demographic or disease characteristics at study entry.

Demographic:

Letrozole + palbociclib treatment arm

The median age for participants was 57 years (ranging from 26 – 87 years). Of the 533 participants, 529 (99.2%) were female and 4 (0.8%) were male. In this Arm, 179 (33.6%) participants were Asian. Most participants had an ECOG performance status (PS) of 0 (326 [61.6%]). The remaining participants had an ECOG PS of 1 (187 [35.3%]) or 2 (16 [3.0%]). Most participants were postmenopausal (384 [72.6%]) with 145 (27.4%) as premenopausal (Table 1).

Amcenestrant + palbociclib treatment arm
Similarly, the median age was 58 years (ranging from 26 – 87 years). Of the 533 participants, 524 (98.3%) were female and 9 (1.7%) were male. In this Arm, 175 (32.8%) participants were Asian. Most participants had an ECOG performance status (PS) of 0 (329 [61.8%]). The remaining participants had an ECOG PS of 1 (192 [36.1%]) or 2 (11 [2.1%]). Most participants were postmenopausal (384 [73.3%]) with 140 (26.7%) as premenopausal (Table 1).

Disease characteristics at study entry:

Letrozole + palbociclib treatment arm
The median time from initial diagnosis to randomization was 0.32 years (range 0 – 29.5) (Table 2). Most participants had Stage IV disease at initial diagnosis (276 [51.8%]). The majority of participants had ductal adenocarcinoma (376 [70.5%]). The histopathology type was most frequently moderately differentiated (265 [49.7%]). At study entry, 287 (53.8%) participants had de-novo metastatic disease and 292 (54.8%) participants had visceral metastasis (Table 2). Tumor sites involved besides the breast were bone (356 [66.8%]), lymph node (329 [61.7%]) and lung (170 [31.9%]). All participants were ER(+) and HER2(-), and the majority (433 [81.5%]) had a positive PgR status.

Amcenestrant + palbociclib treatment arm
The median time from initial diagnosis to randomization was 0.36 years (range 0 - 30.0) (Table 2). Most participants had Stage IV disease at initial diagnosis (275 [51.7%]). The majority of participants had ductal adenocarcinoma (378 [70.9%]). The histopathology type was most frequently moderately differentiated (256 [48.0%]). At study entry, 282 (52.9%) participants had de-novo metastatic disease and 301 (56.5%) participants had visceral metastasis (Table 3). Tumor sites involved besides the breast were bone (359 [67.4%]), lymph node (321 [60.2%]) and lung (195 [36.6%]). All participants were ER(+) and HER2(-), and the majority (455 [86.0%]) had a positive PgR status.

Table 1 - Summary of demographic and other baseline characteristics – Safety population

	Letrozole + Palbociclib (N=533)	SAR439859 + Palbociclib (N=533)	All (N=1066)
Age (years)			
Number	533	533	1066
Mean (SD)	57.3 (12.3)	57.8 (12.1)	57.6 (12.2)
Median	57.0	58.0	58.0
Min ; Max	26 ; 87	26 ; 87	26 ; 87
Age group (years) [n(%)]			
Number	533	533	1066
From 18 - 64 years	371 (69.6)	359 (67.4)	730 (68.5)
From 65 - 84 years	161 (30.2)	172 (32.3)	333 (31.2)
85 years and over	1 (0.2)	2 (0.4)	3 (0.3)
Sex [n(%)]			
Number	533	533	1066
Male	4 (0.8)	9 (1.7)	13 (1.2)
Female	529 (99.2)	524 (98.3)	1053 (98.8)
Race [n(%)]			
Number	533	533	1066

American Indian or Alaska Native	0	1 (0.2)	1 (<0.1)
Asian	179 (33.6)	175 (32.8)	354 (33.2)
Black or African American	10 (1.9)	10 (1.9)	20 (1.9)
Native Hawaiian or other Pacific Islander	1 (0.2)	1 (0.2)	2 (0.2)
White	306 (57.4)	304 (57.0)	610 (57.2)
Multiple	1 (0.2)	1 (0.2)	2 (0.2)
Not reported	21 (3.9)	23 (4.3)	44 (4.1)
Unknown	15 (2.8)	18 (3.4)	33 (3.1)
Ethnicity [n(%)]			
Number	533	533	1066
Hispanic or Latino	95 (17.8)	95 (17.8)	190 (17.8)
Not Hispanic or Latino	391 (73.4)	397 (74.5)	788 (73.9)
Not reported	22 (4.1)	21 (3.9)	43 (4.0)
Unknown	25 (4.7)	20 (3.8)	45 (4.2)
ECOG performance status [n(%)]			
Number	529	532	1061
0	326 (61.6)	329 (61.8)	655 (61.7)
1	187 (35.3)	192 (36.1)	379 (35.7)
2	16 (3.0)	11 (2.1)	27 (2.5)
3	0	0	0
4	0	0	0
Baseline Weight (kg)			
Number	529	533	1062
Mean (SD)	68.50 (16.40)	68.43 (16.07)	68.46 (16.23)
Median	65.80	66.00	66.00
Min ; Max	38.0 ; 160.0	27.1 ; 141.4	27.1 ; 160.0
Geographical region[a] [n(%)]			
Number	533	533	1066
Europe	153 (28.7)	172 (32.3)	325 (30.5)
Americas	157 (29.5)	150 (28.1)	307 (28.8)
Asia	209 (39.2)	204 (38.3)	413 (38.7)
Other regions	14 (2.6)	7 (1.3)	21 (2.0)
Menopausal status[b] [n(%)]			
Number	529	524	1053
Premenopausal	145 (27.4)	140 (26.7)	285 (27.1)
Postmenopausal	384 (72.6)	384 (73.3)	768 (72.9)

a Based on ISO-3166. Other regions category includes Oceania and Africa

b female only

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Table 2 - Summary of disease characteristics at initial diagnosis – Safety population

	Letrozole + Palbociclib (N=533)	SAR439859 + Palbociclib (N=533)	All (N=1066)
Time from initial diagnosis to randomization (years)			
Number	518	510	1028
Mean (SD)	4.18 (6.21)	4.19 (5.82)	4.19 (6.02)
Median	0.32	0.36	0.35
Min ; Max	0.0 ; 29.5	0.0 ; 30.0	0.0 ; 30.0
Histology [n(%)]			
Number	533	533	1066
Diffuse adenocarcinoma	24 (4.5)	25 (4.7)	49 (4.6)
Mixed adenocarcinoma	10 (1.9)	19 (3.6)	29 (2.7)
Ductal adenocarcinoma	376 (70.5)	378 (70.9)	754 (70.7)
Lobular carcinoma	66 (12.4)	58 (10.9)	124 (11.6)
Other carcinoma[a]	41 (7.7)	38 (7.1)	79 (7.4)
Unknown	10 (1.9)	10 (1.9)	20 (1.9)
Other	6 (1.1)	5 (0.9)	11 (1.0)
Location [n(%)]			
Number	533	533	1066
Right breast	254 (47.7)	269 (50.5)	523 (49.1)
Left breast	268 (50.3)	240 (45.0)	508 (47.7)
Bilateral breast	9 (1.7)	23 (4.3)	32 (3.0)
Other	2 (0.4)	1 (0.2)	3 (0.3)
Histopathology type at initial diagnosis [n(%)]			
Number	533	533	1066
Cannot be assessed	3 (0.6)	13 (2.4)	16 (1.5)
Well differentiated	43 (8.1)	45 (8.4)	88 (8.3)
Moderately differentiated	265 (49.7)	256 (48.0)	521 (48.9)
Poorly differentiated	111 (20.8)	104 (19.5)	215 (20.2)
Not done	18 (3.4)	16 (3.0)	34 (3.2)
Unknown	93 (17.4)	99 (18.6)	192 (18.0)

Staging at initial diagnosis [n(%)]			
Number	533	532	1065
Stage 0	0	0	0
Stage IA	39 (7.3)	40 (7.5)	79 (7.4)
Stage IB	6 (1.1)	7 (1.3)	13 (1.2)
Stage IIA	51 (9.6)	44 (8.3)	95 (8.9)
Stage IIB	44 (8.3)	40 (7.5)	84 (7.9)
Stage IIIA	36 (6.8)	37 (7.0)	73 (6.9)
Stage IIIB	11 (2.1)	8 (1.5)	19 (1.8)
Stage IIIC	14 (2.6)	11 (2.1)	25 (2.3)
Stage IV	276 (51.8)	275 (51.7)	551 (51.7)
Unknown	56 (10.5)	70 (13.2)	126 (11.8)

a Other carcinoma: includes other histological subtypes of carcinoma and carcinoma without specification.

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Table 3 - Summary of disease status at study entry – Safety population

	Letrozole + Palbociclib (N=533)	SAR439859 + Palbociclib (N=533)	All (N=1066)
Extent of the disease [n(%)]			
Number	533	533	1066
De-novo Metastatic	287 (53.8)	282 (52.9)	569 (53.4)
Loco Regional Recurrence	21 (3.9)	19 (3.6)	40 (3.8)
Distal Recurrence	225 (42.2)	232 (43.5)	457 (42.9)
Disease status [n(%)]			
Number	533	533	1066
Measurable disease	478 (89.7)	479 (89.9)	957 (89.8)
Non-measurable bone-only disease	44 (8.3)	40 (7.5)	84 (7.9)
Non-measurable excluding bone-only disease	11 (2.1)	14 (2.6)	25 (2.3)
Number of organ(s) involved			
Number	533	533	1066
1	95 (17.8)	99 (18.6)	194 (18.2)
2	139 (26.1)	138 (25.9)	277 (26.0)
3	177 (33.2)	161 (30.2)	338 (31.7)
4	75 (14.1)	90 (16.9)	165 (15.5)
>=5	47 (8.8)	45 (8.4)	92 (8.6)
Visceral metastasis[a] [n(%)]			
Number	533	533	1066
Yes	292 (54.8)	301 (56.5)	593 (55.6)
No	241 (45.2)	232 (43.5)	473 (44.4)
Type of organ(s) involved[b]			
Adrenal gland	10 (1.9)	7 (1.3)	17 (1.6)
Bladder	0	1 (0.2)	1 (<0.1)
Bone	356 (66.8)	359 (67.4)	715 (67.1)
Brain	4 (0.8)	0	4 (0.4)
Breast	262 (49.2)	262 (49.2)	524 (49.2)
Colon	0	1 (0.2)	1 (<0.1)
Colon, sigmoid	1 (0.2)	0	1 (<0.1)
Eye	1 (0.2)	0	1 (<0.1)
Heart	1 (0.2)	1 (0.2)	2 (0.2)
Kidney	2 (0.4)	7 (1.3)	9 (0.8)
Liver	117 (22.0)	97 (18.2)	214 (20.1)

Lung	170 (31.9)	195 (36.6)	365 (34.2)
Lymph node	329 (61.7)	321 (60.2)	650 (61.0)
Muscle / soft tissue	58 (10.9)	53 (9.9)	111 (10.4)
Nasal cavity	0	1 (0.2)	1 (<0.1)
Ovary	3 (0.6)	2 (0.4)	5 (0.5)
Pericardial cavity	2 (0.4)	6 (1.1)	8 (0.8)
Pericardium	2 (0.4)	2 (0.4)	4 (0.4)
Peritoneal cavity	9 (1.7)	8 (1.5)	17 (1.6)
Peritoneum	14 (2.6)	13 (2.4)	27 (2.5)
Pleura	76 (14.3)	89 (16.7)	165 (15.5)
Skin	24 (4.5)	17 (3.2)	41 (3.8)
Spleen	1 (0.2)	0	1 (<0.1)
Stomach	2 (0.4)	1 (0.2)	3 (0.3)
Thyroid gland	1 (0.2)	0	1 (<0.1)
Trachea	0	2 (0.4)	2 (0.2)
Ureter	1 (0.2)	1 (0.2)	2 (0.2)
Uterus	1 (0.2)	2 (0.4)	3 (0.3)
Other	9 (1.7)	8 (1.5)	17 (1.6)
Missing	3 (0.6)	1 (0.2)	4 (0.4)
HER2 Status[C] [n(%)]			
Number	533	531	1064
Positive	0	0	0
Negative	533 (100)	531 (100)	1064 (100)
Equivocal	0	0	0
Unknown	0	0	0
Indeterminate	0	0	0
ER Status[C] [n(%)]			
Number	533	532	1065
Positive	533 (100)	532 (100)	1065 (100)
Low-positive	25 (4.7)	19 (3.6)	44 (4.1)
Negative	0	0	0
Equivocal	0	0	0
Unknown	0	0	0
Indeterminate	0	0	0
PgR Status[C] [n(%)]			
Number	531	529	1060
Positive	433 (81.5)	455 (86.0)	888 (83.8)
Negative	97 (18.3)	74 (14.0)	171 (16.1)
Equivocal	1 (0.2)	0	1 (<0.1)

Unknown	0	0	0
Indeterminate	0	0	0

a At least 1 liver, lung, brain metastasis, pleural, or peritoneal involvement

b A participant can be counted in several categories

c as per eCRF

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Exposure:

Overall, the median duration of IMP exposure was 57 weeks (ranging from 1-112). Cumulative duration of IMP exposure at less than 4 weeks had 5 participants (0.5%). Participants that had completed at least 12 weeks and at least 24 weeks were 1018 (95.5%) and 932 (87.4%) respectively. Overall, the median relative dose intensity of exposure to palbociclib and to letrozole/amcenestrant was 94% and 100% respectively.

Efficacy results:

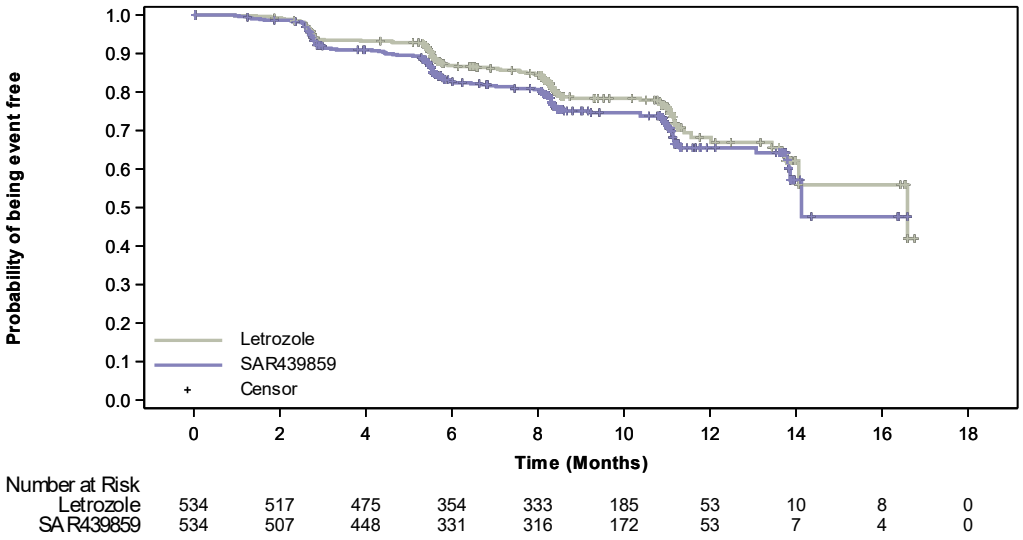
A pre-specified interim analysis for futility was planned when approximately 40% of the PFS events occurred. At the time of the interim analysis, the median follow-up was 8.4 months and 243 PFS events (47% of targeted events) occurred. The observed HR based on the stratified Cox model exceeded the futility boundary of a HR of 1.1.

HR was 1.209 (95% CI [0.939 to 1.557]) and favored letrozole + palbociclib compared to amcenestrant + palbociclib (Figure 1), corresponding to a 20% increase in the risk of disease progression or death (due to any cause) with amcenestrant + palbociclib compared to letrozole + palbociclib was observed.

The median PFS in the letrozole + palbociclib and amcenestrant + palbociclib treatment arm were 16.6 months (95% CI [14.1 to NC]) and 14.1 (95% CI [13.9 to NC]) months respectively. The PFS rate at 6 months in the letrozole + palbociclib treatment arm was 86.9 (95% CI [83.5 to 89.6]) and the rate at 9 months was 78.3 (95% CI [74.0 to 82.1]). The PFS rate at 6 months and 9 months in the amcenestrant + palbociclib treatment arm was 82.7 (95% CI [79.0 to 85.8]) and 75.1 (95% CI [70.6 to 79.0]) respectively.

The Data Monitoring Committee recommended to stop the study and switch all patients under amcenestrant + palbociclib to the appropriate standard of care therapy. Consequently, all study participants' study intervention was unblinded.

Figure 1 - Kaplan-Meier estimates of PFS (based on investigator assessment) - Intent-to-treat population



PFS: Progression-Free Survival

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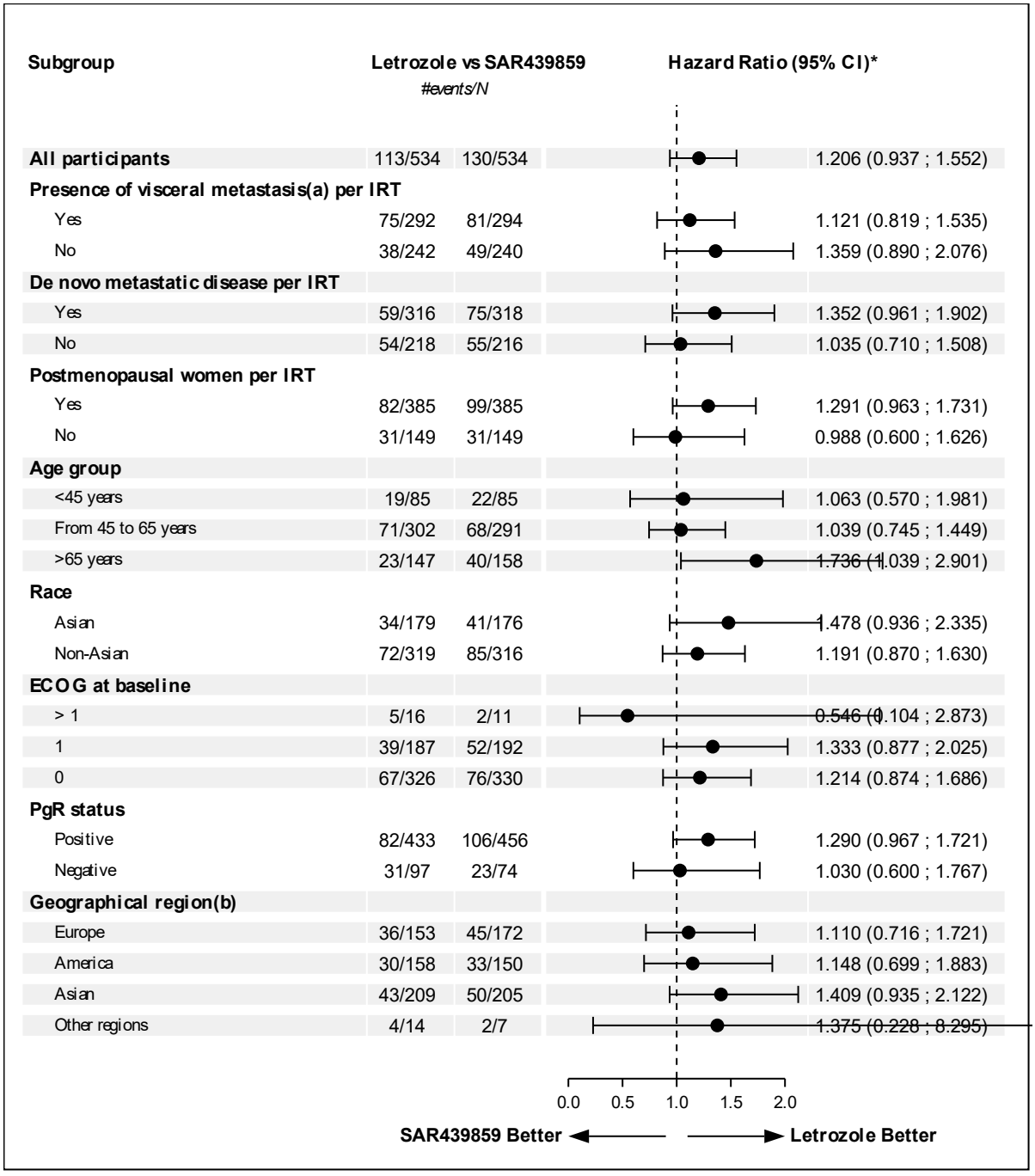
PFS subgroup analyses

Primary analysis results are supported by sensitivity analysis. In the PFS analysis, no subgroup drove the results in the ITT population (Figure 2). Treatment effects based on key subgroup analyses are qualitatively consistent with the ITT population. All HR were above 1 except for the subgroup ECOG PS >1 at baseline probably due to small sample size. Worse treatment effect (amcenestrant + palbociclib compared to letrozole + palbociclib) was observed in de-novo metastatic participants compared to participants with recurrence (HR=1.352 versus HR=1.035), those without visceral metastasis compared to those with visceral metastasis (HR=1.359 versus HR= 1.121), and postmenopausal compared to premenopausal (HR = 1.291 versus HR = 0.988). Worse treatment effect (amcenestrant + palbociclib compared to letrozole) was also observed in participants >65 years old versus those who were between the ages of 45 and 65 years old and versus participants <45 years old (HR=1.736, 1.039, and 1.063 respectively). Worse treatment effect (amcenestrant + palbociclib compared to letrozole + palbociclib) was observed in Asian population compared to non-Asian (HR = 1.478 versus HR = 1.191).

Figure 1 - PFS subgroup analyses (based on investigator assessment) – Forest plot - Intent-to-treat population



*: Hazard ratio and CIs are computed from an unstratified Cox model. Ties are handled using the exact method. Assuming proportional hazard, an HR < 1 indicates a reduction in hazard rate in favor of SAR439859.

(a): Defined as at least 1 liver, lung, brain metastasis, pleural, or peritoneal involvement (b): Based on ISO-3166. Other regions category includes Oceania and Africa. CI: Confidence interval, PFS: Progression-free survival

PGM=DEVOPS/SAR439859/EFC15935/CSR/REPORT/PGM/eff_subgroup_i_f.sas
OUT=REPORT/OUTPUT/eff_subgroup_pfs_strat_i_f_i.rtf (07NOV2022 10:33)

Safety results:

Out of 1066 participants, 23 (2.2%) died during the treatment emergent (TE) period. Of the 23 who died, 10 were in the letrozole + palbociclib arm and 13 were in amcenestrant + palbociclib arm. A total of 14 (1.3%) participants (7 from each arm) died from progressive disease (PD).

A total of 6 (0.6%) participants died from adverse events (AEs). Of the 6 participants, 3 were from the letrozole + palbociclib arm and died from pneumonia, sepsis, and an unknown cause. The remaining 3 participants were from the amcenestrant + palbociclib arm and died from asthma-COPD overlap syndrome, interstitial lung disease (ILD), and gastrointestinal procedural complication. Three (0.3%) from the amcenestrant + palbociclib arm died from other causes (cardiopulmonary arrest, acute respiratory failure, and an unknown cause). Of those who died from AEs during the TE period, none were related to the IMP.

A total of 1066 (99.8%) participants in the ITT population had permanent full intervention discontinuation with 533 (99.8%) in each arm. Of the 1066 total participants who discontinued, 41 (3.8%) discontinued due to AE (20 in the letrozole + palbociclib arm and 21 in the amcenestrant + palbociclib arm), 314 (29.4%) due to progressive disease (146 in the letrozole + palbociclib arm, and 168 in the amcenestrant + palbociclib arm), 35 (3.3%) due to withdrawal by subject (19 in the letrozole + palbociclib arm and 16 the in amcenestrant + palbociclib arm), and 1 (0.2%) discontinued due to poor compliance to the protocol from the letrozole + palbociclib arm. After the first interim analysis, the DMC recommendation was to discontinue the study, therefore 675 (63.2%) participants discontinued the treatment (347 in the letrozole + palbociclib arm and 328 in the amcenestrant + palbociclib arm).

Treatment emergent adverse events most frequently reported regardless of the relationship to the treatment

The most frequently reported treatment emergent adverse events (TEAEs), regardless of the relationship to the treatment, in ⩾ 5% of participants by PT in the letrozole + palbociclib treatment arm (N=533) were: neutropenia (201 [37.7%]), arthralgia (102 [19.1%]), fatigue (101 [18.9%]), neutrophil count decreased (114 [21.4%]), nausea (93 [17.4%]), hot flush (82 [15.4%]), stomatitis (93 [17.4%]), constipation (68 [12.8%]), diarrhoea (82 [15.4%]), headache (65 [12.2%]), alopecia (72 [13.5%]), COVID-19 (61 [11.4%]), asthenia (46 [8.6%]), vomiting (57 [10.7%]), back pain (51 [9.6%]), decreased appetite (44 [8.3%]), insomnia (39 [7.3%]), dyspnoea (36 [6.8%]), urinary tract infection (39 [7.3%]), and dizziness (34 [6.4%]).

The most frequently reported TEAEs, regardless of the relationship to the treatment, in ⩾5% of participants by PT in the amcenestrant + palbociclib treatment arm (N=533) were: neutropenia (133 [21.2%]), arthralgia (110 [20.6%]), fatigue (94 [17.6%]), neutrophil count decreased (67 [12.6%]), nausea (85 [15.9%]), hot flush (87 [16.3%]), stomatitis (64 [12.0%]), constipation (70 [13.1%]), diarrhoea (62 [11.6%]), headache (56 [10.5%]), alopecia (44 [8.3%]), COVID-19 (64 [12.0%]), asthenia (45 [8.4%]), vomiting (40 [7.5%]), back pain (46 [8.6%]), decreased appetite (40 [7.5%]), insomnia (40 [7.5%]), dyspnoea (34 [6.4%]), urinary tract infection (38 [7.1%]), pain in extremity (45 [8.4%]), and alanine aminotransferase increased (41 [7.7%]).

Treatment emergent serious adverse events (TESAEs) related to letrozole/amcenestrant

Seven (1.3%) participants had Grade ⩾ 3 TESAEs (urinary tract infection, cerebral infarction, syncope, pulmonary embolism, vomiting, and hepatorenal failure and deep vein thrombosis [DVT]) related to letrozole.

Of the reported Grade ⩾ 3 TESAEs, urinary tract infection, cerebral infarction, syncope, pulmonary embolism, vomiting and hepatorenal failure was described with 1 participant reported in each. In addition, 2 participants reported TESAEs of DVT.

Ten participants (1.9%) had Grade ⩾3 TESAEs related to amcenestrant. The TESAEs were myocardial infarction, vena cava thrombosis, pulmonary embolism, pneumothorax, hepatic function abnormal, pyrexia, alanine aminotransferase increased, and aspartate aminotransferases increased.

Of the reported Grade ⩾ 3 TESAEs myocardial infarction, vena cava thrombosis, pneumothorax, abnormal hepatic function, and pyrexia was described with 1 participant reported in each. In addition, alanine aminotransferase increased, and aspartate aminotransferase increased was reported in 2 participants in each. Pulmonary embolism was reported in 3 participants.

Adverse events of special interest

Adverse events of special interest (AESIs) included pregnancy of a female participant entered in the study as well as pregnancy occurring in a female partner of a male participant entered in the study with IMP/non-investigational medicinal product (NIMP), symptomatic overdose (serious or nonserious) with IMP/NIMP, increase in ALT Grade ⩾3, photosensitivity, and interstitial lung disease (ILD)/pneumonitis, any grade.

In the letrozole + palbociclib treatment arm (N = 533), 18 (3.4%) experienced at least 1 AESI. The reported AESIs were ILD (1 [0.2%]), pneumonitis (2 [0.4%]), hepatic function abnormal (1 [0.2%]), hepatic failure (1 [0.2%]), hepatorenal failure (1 [0.2%]), photosensitivity reaction (1 [0.2%]), dermatitis allergic (1 [0.2%]), alanine aminotransferase increased (11 [2.1%]), and hepatic enzyme increased (1 [0.2%]).

In the amcenestrant + palbociclib treatment arm (N = 533), 40 (7.5%) experienced at least 1 AESI. The reported AESIs were symptomatic overdose with IMP (1[0.2%]), pneumonitis (1 [0.2%]), ILD (2 [0.4%]), hepatic function abnormal (2 [0.4%]), hypertransaminasaemia (3 [0.6%]), hepatic failure (1 [0.2%]), hepatotoxicity (2 [0.4%]), photosensitivity reaction (1 [0.2%]), alanine aminotransferase increased (28 [5.3%]), and aspartate aminotransferase increase (1 [0.2%]).

There were 38 reported AESIs that were related to the IMP. For dermatitis allergic, the AE was initially categorized as photosensitivity. However, it was later found to be dermatitis allergic. For the participant with symptomatic overdose with IMP, it was not flagged as an AESI by the Investigator by mistake.

Lab abnormalities

In the letrozole + palbociclib treatment arm, incidences of Grade 3 and Grade 4 neutrophil count decreased was reported in 273 (51.2%) and 86 (16.1%) participants, respectively. Incidences of Grade 3 and Grade 4 alanine aminotransferase increased was reported in 15 (2.8%) and 1 (0.2%) participant, respectively.

In the amcenestrant + palbociclib treatment arm, incidences of Grade 3 and Grade 4 neutrophil count decreased was reported in 203 (38.2%) participants and 30 (5.6%), respectively. Incidences of Grade 3 and Grade 4 alanine aminotransferase increased was reported in 32 (6.0%) and 3 (0.6%) participants, respectively.

No Hy's law cases were identified in any treatment arm.

Other safety evaluations

The safety profile of TEAE related to palbociclib and tolerability (RDI, dose reduction, dose omission) were better in the amcenestrant arm compared to the letrozole one. Concerning the lab abnormalities, the occurrence of neutropenia Grade ⩾3, a known AE related to palbociclib, was lower in the amcenestrant arm (107 [20.1%]) compared to the letrozole arm (196 [36.8%]). Similarly, the rate of neutrophil count decreased Grade ⩾3 was lower in the amcenestrant arm (66 [12.4%]) compared to the letrozole arm (110 [20.6%]).

Pharmacokinetic results

The amcenestrant and palbociclib plasma concentrations were collected as described in protocol and were determined in plasma by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) using validated method. The lower limit of quantification was 5.00 ng/mL for amcenestrant and 0.250 ng/mL for palbociclib.

The mean ± SD amcenestrant plasma concentrations at 3h post dose at Cycle 2 day 1 was 2730 ±1600 ng/mL (N=441) and the steady state pre-dose concentrations of amcenestrant, defined as the median pre-dose of individual patient across study duration, was 342 ± 397 ng/mL (N=428).

In the amcenestrant + palbociclib treatment arm at Cycle 2 day 1, the mean ± SD palbociclib plasma concentrations was 27.1 ± 24.7 ng/mL (N=385) at 3h post dose and 2.16 ± 7.37 ng/mL (N=227) at pre-dose. These concentrations were comparable to those observed in letrozole + palbociclib for the 3h post dose (30.2 ± 27.0 ng/mL (N=316)) and were consistently lower for the pre-dose time point (3.41 ± 8.50 ng/mL (N=201)). This lower concentration observed at predose were consistent across study duration. This

indicates an effect of amcenestrant on palbociclib exposure as previously reported from AMEERA-1 (TED14856, amcenestrant in combination with palbociclib) parts C and D study.
Issue date: 29-Nov-2023