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277MO SAR439859, an oral selective estrogen receptor (ER) degrader (SERD), in ER+ HER2- metastatic breast cancer (mBC): Biomarker analyses from a phase I/II study

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Background: SAR439859 has antitumor activity in patients (pts) with wild type (WT) and mutated *ESR1* mBC. Here we describe tumor molecular features and evidence of on target activity in SAR439859-treated pts.

Methods: Plasma circulating cell-free DNA (cfDNA) and paired biopsies were collected at baseline (BL), on treatment (OT) and end of treatment (EOT: cfDNA only) from heavily pretreated postmenopausal pts with ER+/HER2- mBC who received SAR439859 monotherapy (Part A: dose range 20–600 mg QD; Part B: 400 mg QD) in a phase I/II study (NCT03284957). In cfDNA at BL and EOT, mutation (mut) analysis was performed on a next generation sequencing panel of 77 genes. *ESR1* muts in cfDNA at BL and OT were assessed by droplet digital polymerase chain reaction (ddPCR). In tumor tissue, ER and progesterone receptor (PgR), Ki67 and Bcl-2 expression over time were assessed by immunohistochemistry; changes in ER signaling pathway activation were assessed by gene set variation analysis (RNA sequencing). Response was assessed in pts who received SAR439859 ≥ 150 mg QD.

Results: At BL, in cfDNA from 63 pts, 95% had ≥ 1 mut, 52% had ≥ 1 *ESR1* mut, 92% had ≥ 1 non-*ESR1* mut and 49% had concurrent *ESR1* and other muts. Most prevalent BL non-*ESR1* muts were in *PIK3CA* (44% of pts), *EGFR* (33%), *TP53* (30%) and *MET* (25%). *ESR1* muts most commonly detected at BL and EOT were D538G, Y537S and Y537N. *ESR1* muts tended to decrease OT; of 14 pts with *ESR1* muts at BL, 2 had WT *ESR1* OT. In 8 paired biopsies (7 were highly proliferative luminal B tumors), ER, PgR and Ki67 decreased (median relative change from BL: -58%, -88% and -33%), while

Bcl-2 increased (24%). ER activation score decreased in 3/5 paired biopsies tested (median change from BL -0.38). SAR439859 showed clinical benefit (complete response + partial response [PR] + stable disease ≥ 24 weeks) in 40% (12/30) of WT *ESR1* pts and 32% (9/28) of mutated *ESR1* pts, per ddPCR. Of the 5 pts with PRs, 4 had WT *ESR1* and 1 had 2 *ESR1* muts, at BL.

Conclusions: Common genomic alterations, including in *ESR1* and *PIK3CA*, were detected in most mBC pts. SAR439859 showed clinical benefit irrespective of *ESR1* mut status and resulted in ER degradation and pathway inhibition in heavily pretreated pts.

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278MO cfDNA analysis from phase I/II study of lerociclib (G1T38), a continuously dosed oral CDK4/6 inhibitor, with fulvestrant in HR+/HER2- advanced breast cancer patients

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Background: Despite significant improvements in progression-free survival for patients (pts) with HR+/HER2- advanced breast cancer (ABC) treated with approved CDK4/6 inhibitors combined with fulvestrant, treatment is limited by neutropenia and gastrointestinal (GI) side effects. Lerociclib, dosed twice daily (BID) with no drug holiday in combination with fulvestrant, has a favorable safety profile with low rates of GI adverse events and Grade 3/4 neutropenia, as well as encouraging antitumor activity in pts with HR+/HER2- ABC (NCT02983071). Cell-free DNA (cfDNA) analysis in peripheral blood was conducted to characterize mechanisms of response and resistance in pts that received lerociclib and fulvestrant.

Methods: Pts with pretreated ABC were enrolled across doses of lerociclib 200–650 mg once daily and 100–250 mg BID in combination with fulvestrant 500 mg. Peripheral blood samples were drawn and cfDNA was isolated at baseline, cycle 1 day 15, each time point when tumor assessments were performed during the treatment

period, and at the end of treatment. Samples were analyzed using the Guardant360 platform.

Results: Currently, 58 pts have been evaluated at baseline, with 44 pts (75.9%) harboring at least one somatic single nucleotide variant (mutation) in the genes evaluated. Seventeen pts (29.3%) harbored mutations in PIK3CA, with H1047R being the most common (8/17, 47.1%). Seven pts (12.1%) harbored mutations in ESR1, with D583G being the most common (4/7, 57.1%). No pts had mutations in both ESR1 and PIK3CA at baseline. Additionally, 3 pts (5.2%), 2 pts (3.4%), and 1 pt (1.7%) had mutations in genes at baseline associated with CDK4/6 resistance (RB1, CCND1, and CCNE1, respectively). Additional analyses of cfDNA (cycle 1 day 15 and end of treatment) along with correlation of cfDNA dynamics with clinical response are ongoing and will be presented.

Conclusions: The most common baseline mutations detected were PIK3CA and ESR1. Additional analyses, including cycle 1 day 15 change from baseline and correlation with clinical response, are anticipated to help elucidate predictors of response and/or resistance to the combination of lerociclib and fulvestrant in patients with HR+ ABC.

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279MO Divergent evolution of overall survival across metastatic breast cancer (MBC) subtypes in the nationwide ESME real life cohort 2008-2016

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Background: Treatment (trt) strategies for HER2+ and HER2-/hormone receptor-positive (HR+) MBC have made great strides over the past 10 years (yrs). Real world data evaluate the final impact of care strategies.

Methods: ESME gathers full clinical data of all pts who initiated MBC trt in 18 French Cancer Centers between 01/2008-12/2016 (N=22109). Primary objective: prognostic effect of yr of diagnosis (YOD) on overall survival (OS) among pts with the 3 main subtypes: HR+/HER2- (n = 13656), HER2+ (n = 4017), triple-negative (TNBC) (n = 2963). We used multivariate adjusted Cox regression analyses including classical prognostic factors (R software).

Results: Median follow-up was 51.8 months (mo) (95%CI 51-52.7). YOD had no effect on the OS of TNBC pts. However, YOD >2013 appeared as an independent predictor of better OS in pts with HER2+ MBC, while it had an opposite effect in HR+/HER2-cases (Table). In the latter, median OS was 36.7 mo (95% CI: 35-38.7) YOD 2015 versus 44.5 mo (42.1-47.7) YOD 2008. Several sensitivity analyses showed similar trends. We will present explanatory analyses. Unlike baseline characteristics and adjuvant trts, MBC trts progressively changed during this pre-CDK period (including less CT).

Table: 279MO

	HER2+		HR+/HER2-	
	HR (95% CI)	p	HR (95% CI)	p
YOD (Ref 2008)				
2009-2011	NS	NS	NS	NS
2012	0.84 (0.71-0.99)	.04	0.99 (0.91-1.09)	.90
2013	0.75 (0.63-0.90)	.002	1.02 (0.93-1.12)	.67
2014	0.72 (0.59-0.88)	.001	1.17 (1.06-1.30)	.002
2015	0.69 (0.55-0.86)	.001	1.17 (1.05-1.31)	.005
2016	0.59 (0.45-0.78)	<.001	1.20 (1.06-1.37)	.005
Age at MBC (per yr)	1.02 (1.01-1.02)	<.001	1.01 (1.01-1.02)	<.001
Cancer-free interval 6-24 mo (Ref <6)	2.67 (2.34-3.04)	<.001	2.50 (2.30-2.72)	<.001
>24 mo	1.34 (1.21-1.48)	<.001	1.15 (1.09-1.21)	<.001
Visceral disease	1.48 (1.33-1.65)	<.001	1.56 (1.47-1.63)	<.001
Number of MBC sites ≥ 3	1.85 (1.66-2.06)	<.001	1.39 (1.31-1.47)	<.001

Conclusions: OS of pts with HER2+ MBC has dramatically improved over the past decade. However, it unexpectedly worsened among those with luminal cancers. These data prompt careful surveillance of real life outcomes as indicators of the final impact of global trt strategies.

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