SYNOPSIS

Title of the study: Multicenter, randomized, open label study evaluating an anti Insulin-like Growth Factor-1 Receptor (IGF-1R/CD221) monoclonal antibody, AVE1642, administered every 4 weeks in combination with fulvestrant (Faslodex®) in postmenopausal patients with advanced hormonodependent breast cancer

Investigator(s): Not disclosed.

Study center(s): There were 11 active centers in 3 countries (France, Italy, and Spain)

Publications (reference): None

Study period:

Date first patient enrolled: 13 October 2008

Date last patient completed: 10 November 2010

Phase of development: Phase 2

Objectives:

Primary objective:

- To evaluate the clinical efficacy of AVE1642 in combination with fulvestrant and of fulvestrant alone in terms of clinical benefit rate, defined as the rate of complete response (CR) + partial response (PR) + stable disease (SDi) lasting at least 24 weeks;

Secondary objectives:

- To assess the safety profile of the combination and of fulvestrant alone;
- To assess the potential immunogenicity of AVE1642 by detection of AVE1642 human anti humanized antibodies (HAHA);
- To assess the Progression Free Survival Rates at 6 months of the combination and of fulvestrant alone;
- To assess the Progression Free Survival;
- To detect any pharmacokinetic (PK)/pharmacodynamic (PD) interactions between AVE1642 and fulvestrant;
- To assess biological characteristics of the tumor and the activity of treatment on tumor biopsies, when possible.

Methodology: This is a Phase 2, multicenter, randomized, open label study of AVE1642 in combination with fulvestrant (arm A) or fulvestrant alone (arm B) administered to patients with advanced hormone-dependent breast cancer.

In the context of its Research and Development portfolio review, sanofi-aventis decided to discontinue AVE1642 development. This decision was not due to neither safety nor efficacy concerns, nor results. As a consequence, this study was discontinued after enrollment of 18 patients in the study: 9 patients both in the arm A and arm B.

The cut-off date (27 December 2009) for the main analysis of the study corresponded to the time the study was considered completed for the primary endpoint: at the latest 28 weeks after the first administration of AVE1642 to the last patient enrolled in the study.

The follow-up period lasted 60 days after the end of study treatment, and was included in the 28-week period.

Number of patients:

Planned: 100 patients in total

Evaluated:

	AVE1642 + Fulvestrant (N=9)	Fulvestrant alone (N=9)	All (N=18)
Number of patients			
- Randomized	9 (100%)	9 (100%)	18 (100%)
- ITT population[a]	9 (100%)	9 (100%)	18 (100%)
- All treated population	8 (88.9%)	9 (100%)	17 (94.4%)
- Evaluable for efficacy population	8 (88.9%)	9 (100%)	17 (94.4%)

[a] : Intent-To-Treated (ITT) population is the all randomized patients. Percentages are calculated among the randomized population

Diagnosis and criteria for inclusion:

- Post-menopausal women (age ≥60 years or history of bilateral oophorectomy or chemical castration or patients ≥50 years old with amenorrhea for >12 months and FSH >50 IU/L) who failed to no more than 2 prior antihormone-therapies (tamoxifen and/or aromatase inhibitors), and for whom chemotherapy was not formally indicated;
- Histologically-proven invasive breast adenocarcinoma with positive hormone receptor (defined as ≥10% tumor staining by immunohistochemistry method);
- Aromatase inhibitor as the last hormonal treatment;
- Histologically-proven metastasis in case of a unique site;
- Measurable disease as per RECIST definition (longest diameter ≥20 mm using conventional technique or ≥10 mm with spiral CT scan);
- Written informed consent.

Investigational product:

AVE1642 was either provided at a concentration of 2 mg/mL, in single-use 30 mL vial containing 26 mL of AVE1642 sterile solution for intravenous (IV) infusion or was provided at a concentration of 5 mg/mL, in single-use 50 mL vials containing 42 mL of AVE1642 sterile solution for IV infusion.

Dose: AVE1642 was administered on Day 1 of each cycle, every 4 weeks. AVE1642 was administered at the dose of 8 mg/kg.

Administration: Slow IV infusion at a rate of 1 mL/mn for 30 minutes, and then increased to a maximum of 5 mL/mn in case of formulation with 2 mg/mL, and to a maximal rate of 3 mL/mn in case of formulation at 5 mg/mL.

Batch number(s): Not disclosed.

Duration of treatment:

Both in Arm A and in Arm B, study treatment was continued until disease progression or unacceptable drug-related toxicity, or patient willingness to discontinue.

In arm A, in case of discontinuation of one of the study drugs due to related toxicity, the other combined study drug could be continued as single agent.

Duration of observation: Patients were followed 60 days after the end of study treatment for PK/PD and HAHA evaluation, or until recovery or stabilization of any related adverse event (AE).

Combination product:

Fulvestrant (arm A: in combination with AVE1642; arm B: alone): Faslodex®.

Dose (both arm A and arm B): 250 mg at Day 1 and Day 15 of Cycle 1 and then 250 mg every 4 weeks from Day 29 (Day 29=Day 1 of the next cycle).

Administration: slow intramuscular (IM) injection (in combination with AVE1642, fulvestrant was administered just before the start of AVE1642 IV infusion).

Batch numbers: Not disclosed.

Criteria for evaluation: The current report is a synopsis-report, and as such, presents the main safety and PK/PD analyses (per the cut-off date), while efficacy data are briefly summarized; other relevant safety and PK/PD data, and the patient listing of best overall response, are available in appendices. Additional analyses, which included the data collected after the cut-off date, did not lead to any changes in the conclusions, and are provided as supportive information in the Section "Addendum data"of this report.

Safety: The safety was assessed through the collection of AEs, vital signs, laboratory tests, physical examination and anti-AVE1642 antibodies (HAHA) tests.

Efficacy: The primary endpoint was meant to be the clinical benefit rate on the efficacy evaluable population. Due to the premature discontinuation of the study, only preliminary and descriptive data were provided.

***Pharmacokinetics*:** Serum concentrations of AVE1642 and plasma concentrations of fulvestrant were measured. The following PK parameters were determined from serum concentrations of AVE1642, using standard non-compartmental analysis: C_{max}, t_{max}, AUC, $t_{1/2z}$, AUC_{last}, CL, V_{ss}.

In addition, AVE1642 C_{trough} were obtained from Cycle 1 to Cycle 15.

Pharmacodynamics: Serum concentrations of IGF1, IGF2 and IGFBP3 were measured, and used to determine the following PD parameters: Eo and Emax.

Pharmacokinetic/pharmacodynamic sampling times and bioanalytical methods:

In Arm A (AVE1642 in combination with fulvestrant):

* AVE1642: On Cycle 1 and Cycle 2, blood samples were collected at pre-dose, 30 min after the start of infusion, at the end of infusion, 3h after the end of infusion, then on Day 2, Day 3, Day 8, Day 15, Day 22 and Day 28.

* IGF1, IGF2 and IGFBP3: On Cycle 1, blood samples were collected at pre-dose, then on Day 2, Day 3, Day 8, Day 15, Day 22 and Day 28 at the same morning time than the AVE1642 infusion.

For subsequent cycles, blood samples were collected on Day 28 just before the administration of AVE1642.

In arm A, and in arm B (fulvestrant alone):

Blood samples for PK assessment of fulvestrant were collected at pre-dose, then on Day 3, Day 8, Day 15, Day 22 and Day 28 of Cycle 1, and on Day 28 of subsequent cycles. PK analysis of fulvestrant is not presented in this report. Fulvestrant concentrations are available in Appendices.

AVE1642, IGF1, IGF2, IGFBP3, and fulvestrant were determined in serum or plasma using validated bioanalytical methods.

Statistical methods:

***Safety*:** The proportion of patients with AEs (serious and nonserious) and laboratory abnormalities were presented descriptively. The National Cancer Institute common terminology criteria for AEs (NCI CTCAE), Version 3.0, was used to grade AEs and laboratory abnormalities.

***Pharmacokinetic and pharmacodynamic*:** Descriptive statistics on serum concentrations and PK parameters of AVE1642 were provided. Descriptive statistics on serum concentrations and PD parameters of IGF1, IGF2 and IGFBP3 were provided.

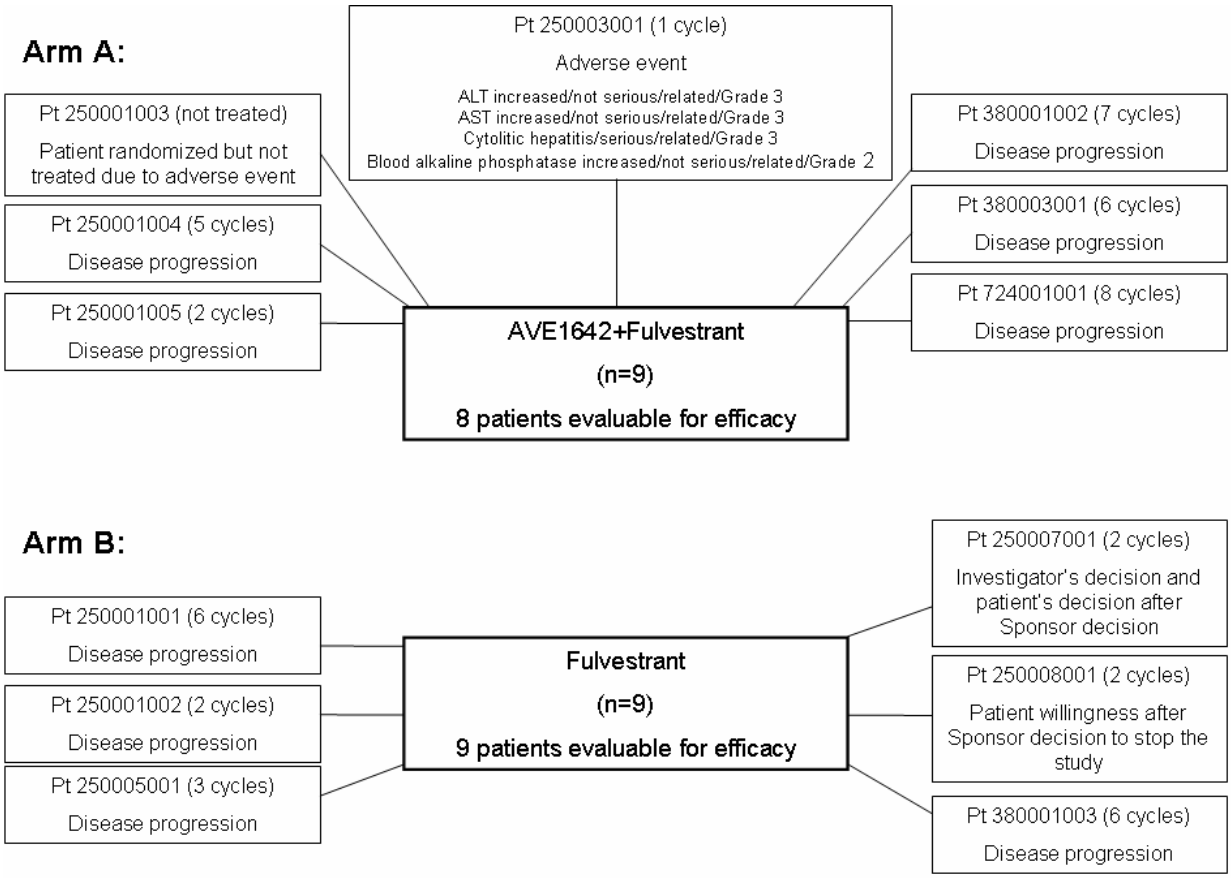
***Efficacy*:** The anti-tumor activity of the drug regimen was assessed through tumor response and evaluated according to RECIST criteria.

Summary:

Patient disposition

Seventeen patients were randomized and treated in the TCD10631 study (8 patients in arm A, and 9 patients in arm B).

At the cut-off date, 5 patients were still on treatment (2 patients in arm A, and 3 patients in arm B). One patient in arm A was randomized, but not treated. The reasons for discontinuing the study treatment (7 patients in arm A, and 6 patients in arm B) are provided in the diagram that follows:



Patient demographic and baseline characteristics

In the overall population, patients were between 53 and 73 years of age (mean age ± SD = 63.8 ± 5.8 years); all were Caucasian females.

Safety results

Extent of exposure

The extent of exposure to AVE1642 (arm A) and to fulvestrant (arm A and arm B) is shown in the following table:

	Arm A		Arm B
	AVE1642 (N=8)	**Fulvestrant (N=8)**	**Fulvestrant (N=9)**
Total number of cycles			
Sum	51.0	51.0	47.0
Median	6.5	6.5	6.0
Min : Max	1 : 14	1 : 14	2 : 9
Cumulative dose [a]			
Number	8	8	9
Mean (SD)	52.06 (32.67)	1812.50 (1058.55)	1555.56 (758.06)
Median	51.89	1875.00	1750.00
Min : Max	8.0 : 112.5	250.0 : 3750.0	750.0 : 2500.0
Dose intensity [b]			
Number	8	8	9
Mean (SD)	2.00 (0.09)	71.50 (9.63)	79.29 (10.97)
Median	1.98	69.60	73.35
Min : Max	1.9 : 2.2	62.5 : 93.8	69.4 : 93.8
Relative dose intensity (%)			
Number	8	8	9
Mean (SD)	1.00 (0.04)	0.92 (0.17)	0.99 (0.02)
Median	0.99	0.98	1.00
Min : Max	0.9 : 1.1	0.5 : 1.0	1.0 : 1.0

Note: Number corresponds to the count of patients with non missing data used for the calculation of the percentage
[a] : Cumulative dose in mg/kg for AVE1642 and in mg for Fulvestrant
[b] : Dose intensity in mg/kg/week for AVE1642 and in mg/week for Fulvestrant

Cycle delay was the only treatment modification for AVE1642, and fulvestrant:

- AVE1642: it occurred in 4/8 (50%) patients on arm A;
- Fulvestrant: it occurred in 4/8 (50%) patients on arm A and 1/9 (11.1%) patient on arm B.

Treatment-emergent adverse events

An overview of patients with at least one treatment-emergent adverse event (TEAE) is presented in the following table:

	AVE1642 + Fulvestrant (N=8)	**Fulvestrant alone (N=9)**
Patients with any TEAE	8 (100%)	7 (77.8%)
Patients with any related TEAE	6 (75.0%)	6 (66.7%)
Patients with any TEAE Gr.3-4	3 (37.5%)	0
Patients with any related TEAE Gr.3-4	2 (25.0%)	0
Patients with any serious TEAE	3 (37.5%)	0
Patients with any related serious TEAE	1 (12.5%)	0
Patients with any TEAE leading to Death	0	0
Patients permanently discontinued treatment due to TEAE	1 (12.5%)	0

TEAE: Treatment Emergent Adverse Events

In arm A, one death was reported in 1 patient. This 60-year-old woman experienced anaemia (reported as worsening of preexisting anemia) on 12 November 2009. The Investigator considered this AE as serious and not possibly related to the study drug. Red blood cells were given as corrective treatment. The patient recovered from anaemia on 14 November 2009. She died on 07 December 2009, ie, 26 days after the occurrence of anaemia, and 52 days after the last intake of AVE1642 and fulvestrant.

Serious TEAEs were only observed in arm A: 6 serious TEAEs were observed in 3 patients (see next Table).

One patient, in arm A, had TEAEs leading to treatment discontinuation. These TEAEs were alanine aminotransferase increased, aspartate aminotransferase increased, cytolitic hepatitis, and blood alkaline phosphatase increased.

All patients (n=8) in arm A, and 7/9 patients in arm B had at least 1 TEAE. Grade 3-4 TEAEs were only observed in arm A (3/8 patients), and were reported as:

- asthenia (2/8 patients);
- cytolitic hepatitis (1/8 patient);
- alanine aminotransferase increased (1/8 patient);
- aspartate aminotransferase increased (1/8 patient);
- hyperglycaemia (1/8 patient);
- convulsion (1/8 patient).

In arm A, the most commonly reported TEAEs regardless of relationship were:

- asthenia (6/8 [75%] patients);
- hyperglycaemia (5/8 [62.5%] patients);
- diarrhoea (3/8 [37.5%] patients);
- muscle spasms (3/8 [37.5%] patients).

The most commonly reported related TEAEs were:

- asthenia (5/6 [83.3%] patients);
- hyperglycaemia (5/6 [83.3%] patients)
- nausea (2/6 [33.3%] patients).

In arm B, the most commonly reported TEAEs regardless of relationship were:

- asthenia (3/7 [42.9%] patients);
- headache, abdominal pain upper, myalgia, and hot flush (2/7 [28.6%] patients for each).

The most commonly reported related TEAEs were:

- asthenia, abdominal pain upper, nausea, (2/6 [33.3%] patients for each).

Planned arm	Patient number	Cycle	Preferred term (verbatim)	Status of AE [a]	Onset date / Recovery date	Grade	Causality/ Serious	Action taken [b]	Outcome [c]	Period of onset [d]
AVE1642 + Fulvestrant	250003001	1	Cytolytic hepatitis (hepatic cytolisis and tp alteration)	New	2008-12-18 /	3	Y / Y	Perm. Disc.	Not rec.	E
		1	Gamma-glutamyltransferase increased (GGT increased)	New	2009-01-02 /	3	Y / Y	None	Not rec.	E
		80	Hyperglycaemia (hyperglycemia)	Ong. w/	2008-12-15 /	3	Y / Y	None	Not rec.	P
		81	Hyperglycaemia (hyperglycemia)	Ong. w/	2008-12-15 / 2009-01-26	3	Y / Y	None	Rec.	P
	380003001	6	Convulsion (seizure)	New	2009-09-25 / 2009-10-12	3	N / Y	None	Rec.	E
	724001001	8	Anaemia (worsening of preexisting anemia)	New	2009-11-12 / 2009-11-14	2	N / Y	None	Rec.	E

Note: Adverse events are reported using MedDRA version 12.1 and graded using NCI CTC version 3.0
[a] : Ong. w/=Ongoing with change, Ong. w/out=Ong. without change
[b] : Perm. Disc.=Permanently discontinued, Del=Delayed, Red=Reduced
[c] : Rec.=Recovered, Recg.=Recovering, Not rec.=Not recovered, Rec. w/ seq.=Recovered with sequelae, Unk=Unknown
[d] : Null=Pre-treatment adverse event, E=Treatment emergent adverse event, P=Post treatment adverse event
Dates are blank when not filled in for any reason e.g. missing or ongoing event

Clinical laboratory data

Grade 3-4 for thrombocytopenia, anemia, and neutropenia were not reported.

Grade 3-4 for liver functions and renal functions were observed only in arm A:

- 1/8 patient with Grade 3 alanine aminotransferase increased;
- 1/8 patient with Grade 3 creatinine;
- 4/8 patients with Grade 3 gamma glutamyltransferase.

In arm A, 2/8 (25%) patients with Grade 4 hypoglycemia, and 1/8 (12.5%) patient with Grade 3 hyperglycemia were observed.

Two patients experienced Grade 1-2 tinnitus or vertigo, and 2 patients experienced eye irritation or pain. No cases of dizziness were reported.

Assessment was negative for AVE1642 HAHA in all patients.

Pharmacokinetic results

A summary of AVE1642 PK parameters following single IV infusion of AVE1642 dose of 8 mg/kg in combination with IM fulvestrant dose of 250 mg twice monthly is presented as follows:

AVE1642 serum pharmacokinetics parameters (Cycle 1)

	Mean ± SD (Geometric Mean) [CV%]
	Arm A
N	5
C_{max} (µg/mL)	177 ± 31.8 (174) [18.0]
t_{max}[a] (day)	0.17 (0.04 - 0.21)
AUC (µg•day/mL)	1600 ± 341 (1570) [21.3]
$t_{1/2z}$ (day)	10.9 ± 3.36 (10.5) [30.8]
AUC_{last} (µg•day/mL)	1370 ± 368 (1330) [26.9]
CL (L/day)	0.342 ± 0.0544 (0.338) [15.9]
V_{ss} (L)	4.55 ± 1.61 (4.25) [35.4]

a Median (Min - Max)

Profiles of Subjects 250002001, 250001005 and 250001006 were excluded from PK analysis

Arm A: AVE1642 8 mg/kg q4w + Fulvestrant 250 mg q2w

After single AVE1642 IV infusion in combination with a single IM administration of fulvestrant in 5 female subjects, AVE1642 was eliminated slowly from serum with a low systemic clearance. AVE1642 volume of distribution was low and comparable to blood volume. The total variability of AUC, Cl and V_{ss} as measured by CV% was low to moderate (17 to 35%).

Pharmacodynamic results:

Pharmacodynamic parameters were obtained from serum concentrations and theoretical times.

IGF1, IGF2, IGFBP3 parameters are summarized in the table that follows:

Biomarkers parameters - serum

Mean ± SD [CV%] N	IGF1 8	IGF2 8	IGFBP3 8
E_0 (ng/mL)	166 ± 90.8 [55]	699 ± 200 [29]	2760 ± 842 [31]
E_{max} (ng/mL)	744 ± 179 [24]	920 ± 264 [29]	5910 ± 1900 [32]

Efficacy results:

No PRs or CRs were reported. In each arm, 3 patients experienced SDi lasting at least 24 weeks. The time to progression ranged from 1.6 to 7.3 months in arm A, and from 2 to 5.9 months in arm B.

Conclusion:

Not disclosed.

Date of report: 27-Jan-2011