SYNOPSIS

Title of the study:	Uncontrolled, multicenter, dose finding, safety and pharmacokinetic study of AVE1642, an anti-Insulin-like Growth Factor-1 Receptor (IGF-1R/ CD221) monoclonal antibody, administered as single agent and in combination with anticancer therapies in patients with advanced solid tumors
Investigator:	Not disclosed.
Study centers:	There were 6 centers in 4 countries (France, Switzerland, US, and UK)
Publications:	A phase I study of AVE1642, a humanized monoclonal antibody IGF-1R (insulin like growth factor 1 receptor) antagonist, in patients with advanced solid tumor. A.W. Tolcher et al. Abstract N°. ID3582; ASCO, 2008.
Study period:	
Date first patient enrolled:	18 June 2007 (date of first informed consent signed)
Date last patient completed:	15 October 2010
Phase of development:	Phase 1

Primary objective:

- To select the dose of AVE1642 to be administered in patients with advanced solid tumors.

Secondary objectives:

- To confirm the selected dose when AVE1642 is given in combination with other anti-cancer agents.
- To assess the safety profile of AVE1642 as single agent and in combination with other anti-cancer agents.
- To define the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of AVE1642 when given as single agent and in combination in patients with advanced solid tumors.
- To detect any PK interaction between AVE1642 and the combined therapies.
- To assess the preliminary clinical activity of AVE1642 when added to other anticancer therapies in terms of response rate, stable disease rate, duration of response and duration of stabilization.
- To assess any potential immunogenicity by detection of anti-AVE1642 antibodies (human antihumanized antibodies [HAHA]).
- To assess the biological activity of AVE1642 on circulating tumoral cells and on tumor tissues when feasible.

Methodology: This was a Phase 1, multicenter, 2-part study, uncontrolled, with repeated doses of AVE1642 administered intravenously every 3 weeks, as single agent and in combination with docetaxel (dose escalation, Part 1) or in combination with other treatments (docetaxel, gemcitabine + erlotinib, and doxorubicin, Part 2) to patients with advanced solid tumors.

In the context of its Research & Development portfolio review, sanofi-aventis research decided to discontinue the development of AVE1642. This decision was not due to any safety or efficacy concerns or results. All patients who had not completed the study were informed of the company decision to stop AVE1642 development program. At that time, the study TED6421 Part 2 was discontinued, with 58 patients finally enrolled instead of up to 90 patients initially planned per protocol.

A study cut-off date, for the main analysis of the study, was defined as 60 days after completion of the first cycle of the last patient enrolled in study Part 2 (ie, 20 August 2009).

Number of patients:

Study Part 1:

Planned: 3 to 6 patients at each dose level (up to 30 patients).

Evaluated:

	AVE1642 planned dose level					
	3 mg/kg (N=4)	**6 mg/kg (N=7)**	**12 mg/kg (N=6)**	**18 mg/kg (N=8)**	**24 mg/kg (N=2)**	**All (N=27)**
Number of patients						
- All treated population	4 (100%)	7 (100%)	6 (100%)	8 (100%)	2 (100%)	27 (100%)
- Evaluable for DLT at cycle 1	4 (100%)	7 (100%)	6 (100%)	8 (100%)	2 (100%)	27 (100%)
- Evaluable for DLT at cycle 1 and cycle 2	3 (75.0%)	7 (100%)	5 (83.3%)	7 (87.5%)	2 (100%)	24 (88.9%)
- PK/PD population	3 (75.0%)	7 (100%)	5 (83.3%)	7 (87.5%)	2 (100%)	24 (88.9%)
- PK population	3 (75.0%)	7 (100%)	5 (83.3%)	7 (87.5%)	2 (100%)	24 (88.9%)
- PD population	3 (75.0%)	7 (100%)	5 (83.3%)	7 (87.5%)	2 (100%)	24 (88.9%)

Note: 7 patients were enrolled in the study but not treated .

Study Part 2:

Planned: up to 90 patients.

Evaluated:

	Cohort A (N=20)	Cohort B (N=20)	Cohort C1 (N=4)	Cohort C2 (N=6)	Cohort D1 (N=4)	Cohort D2 (N=4)
Number of patients						
All treated population	20 (100%)	20 (100%)	4 (100%)	6 (100%)	4 (100%)	4 (100%)
Evaluable for DLT at cycle 1	20 (100%)	20 (100%)	4 (100%)	6 (100%)	4 (100%)	4 (100%)
PK/PD population	20 (100%)	20 (100%)	4 (100%)	6 (100%)	4 (100%)	4 (100%)
PK population	20 (100%)	20 (100%)	4 (100%)	6 (100%)	4 (100%)	4 (100%)
PD population	20 (100%)	20 (100%)	4 (100%)	6 (100%)	4 (100%)	4 (100%)

Diagnosis and criteria for inclusion:

Study Part 1:

- Pathologically confirmed advanced-stage solid tumors;
- Patients for whom docetaxel 75 mg/m² is indicated or is a reasonable option (as per tumor characteristics and previous treatment) and for whom this treatment can be postponed by 3 weeks (during AVE1642 single treatment cycle).

Study Part 2:

- Pathologically confirmed advanced-stage solid tumor;
- Patients for whom the following selected combined therapy was indicated or was a reasonable option (as per tumor characteristics and previous treatment), at the discretion of the Investigators, and provided no grade ≥3 toxicities had been observed during previous treatment with compounds in the same class:
  - docetaxel 100 mg/m²,
  - docetaxel 75 mg/m² or,
  - gemcitabine (1250 mg/m² or 1000 mg/m²) + erlotinib (100 mg/day or 75 mg/day), except in patients between 15-18 years of age,
  - doxorubicin 60 mg/m² or 50 mg/m².

DLTs occurred in Study Part 2 (Cohort C, and D). An amendment (number 5) was performed, and led to add 2 new cohorts: one Cohort (C2) with a lower dose of gemcitabin/erlotinib combined with AVE1642, and one Cohort (D2) with a lower dose of doxorubicin combined with AVE1642.

Investigational product: AVE1642 was provided at a concentration of 2 mg/mL, in single-use 30 mL vials containing 26 mL of AVE1642 sterile solution for intravenous (IV) infusion.

***Dose*:** AVE1642 was administered on Day 1 of each cycle, every 3 weeks

- Study Part 1: Dose escalation, starting at 3 mg/kg/infusion.
- Study Part 2: AVE1642 administered at the dose of 6 mg/kg/infusion, in combination with the selected anticancer therapy of the corresponding cohort

Administration: For Study Part 1 and Part 2, slow IV infusion at a rate of 1 mL/mn for 30 minutes, and then increased to a maximal rate of 5 mL/mn. The duration of the infusion was depending on the dose and on the tolerance during infusion.

Batch number(s): Not disclosed.

Duration of treatment: In study Part 1, the patients were treated for at least 2 cycles of treatment (1 cycle of AVE1642 alone, and at least 1 cycle of AVE1642 in combination with docetaxel); in study Part 2, they were to receive at least 1 cycle of the combination treatments. They were treated until disease progression, intolerable drug-related toxicity, Investigator's decision or withdrawal of consent. Patients still on treatment after the cut-off date (20 August 2009) were to receive up to 12 months of study treatment, at a maximum.

Duration of observation: Patients were followed for a minimum of 30 days after the last study treatment administration, and when possible approximately 60-day after the last study treatment administration, for potential immunogenicity detection (HAHA determination), PK, PD, and safety evaluation. In case of positivity for HAHA, additional HAHA assessments were performed at 6 months and 1 year after the last administration of AVE1642.

Combination products:

Study Part 1 (docetaxel)**:**

Dose: From the second cycle of treatment, docetaxel 75 mg/m²;

Administration: 1-hour IV infusion, 30 minutes after the end of the infusion of AVE1642.

Batch numbers: Not disclosed.

Study Part 2:

Cohort A and Cohort B (docetaxel)

Dose: From the first cycle of treatment, docetaxel 75mg/m² (Cohort A) or 100mg/m² (Cohort B) every 3 weeks;

Administration: 1-hour IV infusion, 30 minutes after the end of the infusion of AVE1642 6 mg/kg.

Batch numbers: Not disclosed.

Cohort C1 and Cohort C2 (gemcitabine and erlotinib)

Dose: From the first cycle of treatment, gemcitabine 1250 mg/m² (Cohort C1) or 1000 mg/m² (Cohort C2) at Day 1 and Day 8 of each cycle (every 3 weeks), and erlotinib 100 mg/day (Cohort C1) or 75 mg/day (Cohort C2);

Administration: For gemcitabine, 30 minutes IV infusion, 30 minutes after the end of the infusion of AVE1642 6 mg/kg. For erlotinib, orally once daily on continuous schedule.

Batch numbers:

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Not disclosed.

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Cohort D1 and Cohort D2 (doxorubicin)

Dose: From the first cycle of treatment, 60 mg/m² (Cohort D1) or 50 mg/m² (Cohort D2) every 3 weeks.

Administration: IV injection (1 to 2 minutes), 30 minutes after the end of the infusion of AVE1642 6 mg/kg.

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 listings of best overall response in both study parts, are available in appendices.

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

Efficacy: Tumor assessments were performed via computed tomography-scan (CT-scan) or magnetic resonance imaging (at baseline, at the end of every other treatment cycle [Cycle 2, Cycle 4, Cycle 6, Cycle 8…], whenever disease progression was suspected, and at the end of treatment/withdrawal visit). Blood collection for circulating tumoral cells quantification, and Insulin Like Growth factor 1 Receptor (IGF-1R) analysis were performed at baseline and at the end of each cycle, except for sarcomas, melanomas and neuroendocrine tumors.

***Pharmacokinetics and pharmacodynamics*:** In study Part 1, the relationship between AVE1642 dose, AVE1642 exposure, IGF1, IGF2 and IGFBP3 was investigated. Time -dependency and drug interactions with docetaxel were explored by comparing the data obtained on Cycle 1 versus Cycle 2. In study Part 2, PK and PD interactions with docetaxel, gemcitabine, erlotinib and doxorubicin were assessed mainly on Cycle 1. Pharmacokinetic parameters of combination drugs were compared to published data.

Pharmacokinetic/pharmacodynamic sampling times and bioanalytical methods:

Study Part 1

- **AVE1642**: on Cycle 1, blood samples were collected at pre-dose, 30 min after start of infusion, 5 min. before end of infusion, 3 h and 24 h after the end of infusion, then on Day 3, Day 8, Day 15 and Day 22. On Cycle 2, blood samples were collected at pre-dose, 30 min after start of infusion, 5 min before end of AVE1642 infusion, then 45 min, 1 h 15, 1 h 45, 3 h and 6 h after the start of docetaxel infusion, then 24 h after end of AVE1642 infusion, then on Day 3, Day 8, Day 15 and Day 22 at the same morning time of the AVE1642 infusion. For subsequent cycles: samples were collected at Day 22 before the next infusion.
- **Docetaxel**: Blood samples were collected at pre-dose, then 45 min, 1 h 15, 1 h 45, 3 h and 6 h after the start of docetaxel infusion

- **IGF1, IGF2, IGFBP3**: On Cycles 1 and 2, blood samples were collected at predose then on Day 2, Day 3, Day 8, Day 15 and Day 22 at the same morning time of the AVE1642 infusion. For subsequent cycles, samples were collected at Day 22 just before the administration of AVE1642, then between Day 50-Day 60 after the last study drug administration
- **Immunogenicity**: HAHA samples were collected at predose and Day 22 of Cycle 1. For subsequent cycles, samples were collected at Day 22 just before next infusion, then between Day 50-Day 60 after the last study drug administration.

Study Part 2

Docetaxel cohorts (A and B)

- **AVE1642**: Blood samples were collected at Cycle 1: predose, 30 min after start of infusion, 5 min before end of infusion, 45 min and 24 h after the end of infusion, then on Day 3, Day 8, Day 15 and Day 22. For subsequent cycles, samples were collected at Day 22 before the next infusion, then between Day 22 – Day 30 and Day 50 – Day 70 at end of study treatment
- **Docetaxel**: Blood samples were collected at Cycle 1 at 45 minutes, 1 h 15, 1 h 45, 3 h and 6 h after the start of docetaxel infusion and at Cycle 2 at end of docetaxel infusion, 45 min and 6 h after docetaxel infusion

Doxorubicin cohorts (D1 and D2)

- **AVE1642**: Blood samples were collected in Cycle 1: predose, 30 min after start of infusion, 5 min before end of infusion, 5 h and 24 h after the start of infusion, then on Day 3, Day 8, Day 15 and d22. For subsequent cycles, samples were collected at Day 22 before the next infusion, then between Day 22 – Day 30 and Day 50- Day 70 at end of study treatment
- **Doxorubicin**: Blood samples were collected at Cycle 1 at predose, end of infusion then 3 h, 7 h, 24 h and 48 h after end of infusion

Gemcitabine+erlotininb cohorts (C1 and C2)

- **AVE1642**: Blood samples were collected at Cycle 1: predose, 30 min after start of infusion, 5 min before end of infusion, 4.5 h, 10 h and 24 h after the start of infusion, then on Day 3, Day 8, Day 15 and Day 22. For subsequent cycles, samples were collected at Day 22 before the next infusion, then between Day 22 – Day 30 and Day 50 - Day 70 at the end of the study treatment
- **Gemcitabine**: Blood samples were collected at Cycle 1: predose, end of infusion then 10 min, 20 min, 30 min and 1 h, 2 h, 4.5 h after end of infusion
- **Erlotinib**: Blood samples were collected at Cycle 1 at predose, 1 h, 2.5 h, 5 h, 10 h and 24 h after administration

All cohorts

- **IGF1, IGF2, IGFBP3**: At Cycles 1, blood samples were collected at predose, then, on Day 2, Day 3, Day 8, Day 15, and Day 22 at the same morning time of the AVE1642 infusion. For subsequent cycles, samples were collected at Day 22 just before the administration of AVE1642, then between Day 22 – Day 30 and Day 50 – Day 60 after the last study drug administration.
- **Immunogenicity**: HAHA samples were collected at predose, and Day 22 of Cycle 1. For subsequent cycles, samples were collected at Day 22 just before next infusion, then between Day 22 – Day 30 and Day 50 – Day 60 after the last study drug administration.

AVE1642, docetaxel, doxorubicin, erlotinib, gemcitabine, IGF1, IGF2, IGFBP3, and AVE1642 HAHA were determined in serum or plasma using validated bioanalytical methods.

- **AVE1642**: EIA (enzyme immuno-assay); low limit of quantification (LLOQ): 2 µg/mL;
- **Docetaxel:** Liquid chromatography/mass spectrometry (LC/MS-MS); LLOQ: 1 ng/mL;
- **Doxorubicin**: LC/MS-MS; LLOQ: 0.1 ng/mL;
- **Erlotinib**: LC/MS-MS; LLOQ: 2 ng/mL;
- **Gemcitabine**: LC/MS-MS; LLOQ: 50 ng/mL;
- **IGF1**: radioimmunoassay; LLOQ: 16.7 ng/mL;
- **IGF2**: radioimmunoassay; LLOQ: 99.9 ng/mL
- **IGFBP3**: EIA; LLOQ: 77.4 ng/mL;
- **HAHA**: Enzyme-linked immunosorbent assay

Statistical methods: The 2 parts of the study were analyzed separately. In the study Part 1, data were analyzed by dose level of AVE1642; in the study Part 2, data were analyzed by cohort. Nine patients were still under study treatment after the study cut-off date (20 August 2009).

Safety:

The primary safety analysis was defined as the frequency of dose-limiting toxicities (DLTs) at Cycles 1 and Cycle 2 for Part 1 of the study, and at Cycle 1 for Part 2. The National Cancer Institute common terminology criteria for AEs (NCI CTCAE), Version 3.0, was used to assess the DLTs. Listings of DLTs were provided (see appendices).

The proportion of patients with AEs (serious and non serious) and laboratory abnormalities were presented descriptively. The NCI CTCAE, Version 3.0, was used to grade AEs and laboratory abnormalities.

Pharmacokinetics and pharmacodynamics: No statistical analyses of the PK and PD results were performed. Descriptive statistics on plasma concentrations for IGF1, IGF2, IGFBP3, and PK parameters ($t_{1/2}$, t_{max}, C_{max}, t_{last}, C_{last}, AUC_{all}, AUC, Clearance [Cl], V_{ss}) for AVE1642 and combination products were provided.

Efficacy: The anti-tumor activity of the study drug regimen was assessed through tumor response and evaluated according to the response evaluation criteria in solid tumors (RECIST).

Summary:

As of 20 August 2009, 85 patients were enrolled and treated in the TED6421 study: 27 patients were treated in the study Part 1, and 58 patients were treated in the study Part 2.

Patient disposition

Study Part 1

Irrespective of the AVE1642 dose level, the main reason for discontinuing the study treatment was disease progression.

	AVE1642 planned dose level					
	3 mg/kg (N=4)	6 mg/kg (N=7)	12 mg/kg (N=6)	18 mg/kg (N=8)	24 mg/kg (N=2)	All (N=27)
Number of patients						
Still on treatment	0	0	0	0	0	0
With treatment discontinuation	4 (100%)	7 (100%)	6 (100%)	8 (100%)	2 (100%)	27 (100%)
End of treatment reason						
Adverse event	0	0	0	1 (12.5%)	0	1 (3.7%)
Disease progression	4 (100%)	6 (85.7%)	5 (83.3%)	6 (75.0%)	2 (100%)	23 (85.2%)
Other reason	0	1 (14.3%)	1 (16.7%)	1 (12.5%)	0	3 (11.1%)

Study Part 2:

Of the 58 patients treated in the study Part 2, 9 patients were still on treatment at time of the cut-off date.
The main reason for discontinuing the study treatment was disease progression in Cohort A, Cohort B, Cohort C1, Cohort D1 and Cohort D2 (15/20 [75%] patients, 10/16 [62.5%], 3/4 [75%] patients, 3/4 [75%] patients, and 2/3 [66.7%] patients, respectively), and other reason for Cohort C2 (3/5 [60%] patients).

	(AVE1642 planned dose level 6 mg/kg)					
	Cohort A (N=20)	**Cohort B (N=20)**	**Cohort C1 (N=4)**	**Cohort C2 (N=6)**	**Cohort D1 (N=4)**	**Cohort D2 (N=4)**
Number of patients						
Still on treatment	1 (5.0%)	5 (25.0%)	0	2 (33.3%)	0	1 (25.0%)
With treatment discontinuation	19 (95%)	15 (75.0%)	4 (100%)	4 (66.7%)	4 (100%)	3 (75.0%)
End of treatment reason						
Adverse event	2 (10.0%)	2 (12.5%)	0	0	1 (25.0%)	0
Disease progression	15 (75.0%)	10 (62.5%)	3 (75.0%)	2 (40.0%)	3 (75.0%)	2 (66.7%)
Other reason	3 (15.0%)	4 (25.0%)	1 (25.0%)	3 (60.0%)	0	1 (33.3%)

Patient demographic and baseline characteristics

Study Part 1

In the overall population, patients were between 18 and 78 years of age (mean age ± standard deviation [SD] = 9.7 ± 19.4 years); 70.4% of the patients were males and 29.6% of the patients were females. The majority of patients (24/27 [88,9%]) were Caucasian.

Study Part 2

In the 6 cohorts, the mean age ranged from 42.8 to 59.0 years old; females were more represented than males in each cohort (proportions of females ranging from 60 to 100%). All patients were Caucasian, except 1 patient in the Cohort C2, who was black.

Safety results

Study Part 1

Overall, 27 patients received 137 cycles of AVE1642 at doses ranging from 3 mg/kg to 24 mg/kg. A maximum of 10 cycles was administered at dose level 6 mg/kg, 18 mg/kg, and 24 mg/kg. The median duration of exposure during the entire study, ranged from 4 cycles in the 3mg/kg dose level, to 7 cycles in the 24 mg/kg dose level. Dose delays and dose reductions were reported respectively in 8/27 patients, and 3/27 patients.

Two DLTs (both considered by the investigators as not possibly related to the study treatment) were reported at Cycle 1 of the dose level of 18 mg/kg: 1 Grade 3 cytolytic hepatitis, and 1 Grade 4 acute myocardial infarction; the acute myocardial infarction led to treatment discontinuation. As per protocol, the dose escalation was stopped, though, by that time, 2 patients had started receiving treatment at the dose level of 24 mg/kg. No DLTs were reported at Cycle 1 in the 2 patients treated at the dose level of 24 mg/kg. No severe hypersensitivity reaction was reported.

Two patients, 1 on AVE1642 3 mg/kg, and 1 on AVE1642 18 mg/kg, experienced a TEAE leading to death (namely, disease progression in 1 patient , and respiratory failure in 1 patient). Seven additional patients died, all from disease progression.

Over the course of study Part 1, 22 serious TEAEs were observed in 11 of the 27 patients, with no dose-related pattern identified. Two of these events were judged by the Investigator to be possibly related to the study drug, namely, pneumonia, and febrile neutropenia on AVE1642 12 mg/kg.

All 27 patients had at least 1 TEAE. Grade 3-4 TEAEs were observed in 15/27 patients, and were most frequently reported as asthenia (3/27 patients), diarrhoea (2/27 patients), and myalgia (2/27 patients). Across all doses, the most commonly reported TEAEs regardless of relationship to the study drug were diarrhoea (16/27 patients), stomatitis (13/27 patients), asthenia (13/27 patients), alopecia (12/27 patients), nausea (12/27 patients) and dry skin (11/27 patients).

No major safety issues were observed in this study. AVE1642 was well tolerated as single agent and in combination with docetaxel 75mg/m², without increased incidence or severity of expected toxicities due to docetaxel. As per protocol definition, the maximal tolerated dose of AVE1642 was 12 mg/kg. Based on PK/PD data, the dose selected for further combinations was 6 mg/kg.

Grade 3-4 for thrombocytopenia, and anemia were not reported. Grades 3-4 neutropenia were reported as follows:

- AVE1642 (3 mg/kg): Cycle 2 and further [1/4 patient];
- AVE1642 (6 mg/kg): Cycle 2 and further [3/7 patients];
- AVE1642 (12 mg/kg): Cycle 2 and further [4/6 patients];
- AVE1642 (18 mg/kg): Cycle 2 and further [5/8 patients];
- AVE1642 (24 mg/kg): Cycle 2 and further [1/2 patient].

The liver function was well preserved (1 Grade 3 SGOT [AVE1642 18 mg/kg], and 1 Grade 3 SGPT [AVE1642 18 mg/kg] were reported), as was the renal function (no grades 3-4 were reported). Two (2/8) patients on AVE1642 18 mg/kg had Grade 3 hyperglycemia (at Cycle 2 and further).

Assessment was negative for AVE1642 HAHA in all of the 27 treated patients.

Study Part 2

Overall, 58 patients received 255 cycles of AVE1642 at the fixed dose of 6 mg/kg in combination with docetaxel (75 mg/m² [n=20] or 100 mg/m² [n=20]), or in combination with gemcitabine and erlotinib (1250 mg/m^2 gemcitabine + 100 mg/day erlonitib [n=4] or 1000 mg/m^2 gemcitabine + 75 mg/day erlonitib [n=6]), or in combination with doxorubicin (60 mg/m² [n=4] or 50 mg/m² [n=4]). The median duration of exposure during the entire study is reported in the following Table :

	Cohort A	Cohort B	Cohort C1	Cohort C2	Cohort D1	Cohort D2
Sum	95.0	100.0	25.0	18.0	9.0	8.0
Median	4.0	4.0	6.5	2.0	2.0	2.0
Min : Max	1 : 9	2 : 13	1 : 11	2 : 6	2 : 3	1 : 3

Doses delayed were reported in Cohort A (8/20 patients), Cohort B (9/20 patients), Cohort C1 (2/4 patients), Cohort C2 (1/6 patients), and Cohort D1 (3/4 patients); a re-escalated dose (1/58 patient) was reported on AVE1642, in Cohort D2.

Thirteen patients (Cohort A [n=4], Cohort B [n=1], Cohort C1 [n=3], Cohort C2 [n=1], Cohort D1 [n=3], Cohort D2 [n=1]) experienced a DLT at Cycle 1.

Three patients (one in the Cohort A, one in the Cohort C2, and one in the Cohort D1) experienced a TEAE leading to death (namely, disease progression for the 3 patients [1 patient in Cohort A, 1 patient in Cohort C2, and 1 patient in Cohort D1]) (see Narratives in Section 2). Fourteen additional patients died, all from disease progression.

Over the course of study Part 2, 40 serious TEAEs were observed in 19 of the 58 patients. Thirteen of these events were judged by the Investigator to be possibly related to AVE1642 treatment.

Six patients (4 patients in Cohort A, 1 patient in Cohort B, and 1 patient in Cohort D1) had a TEAE leading to treatment discontinuation. The reasons for the treatment discontinuation were: asthenia, paraesthesia, general physical health deterioration, deep vein thrombosis, hypocalcaemia, and neutropenia.

All 58 patients had at least 1 TEAE. Grade 3-4 TEAEs were observed in 36/58 patients and were most frequently reported as neutropenia (Cohort A: 6/20 patients; Cohort B: 2/20 patients; Cohort C1: 2/4 patients). Across all cohorts, the most commonly reported TEAEs regardless of relationship to the study drug were diarrhoea (37/58 patients), asthenia (34/58 patients), nausea (30/58 patients), and stomatitis (21/58 patients).

Grades 3-4 for thrombocytopenia, neutropenia, and anemia were reported as follows:

- Cohort A: thrombocytopenia (Cycle 2 and further [1/20 patient]), neutropenia (Cycle 1 [15/20 patients], Cycle 2 and further [11/20 patients]);
- Cohort B: neutropenia (Cycle 1 [4/20 patients], Cycle 2 and further [4/20 patients]);
- Cohort C1: neutropenia (Cycle 1 [1/4 patient], Cycle 2 and further [1/4 patient]), and anemia (Cycle 1 [1/4 patient]);
- Cohort C2: thrombocytopenia (Cycle 2 and further [2/6 patients]);
- Cohort D1: neutropenia (Cycle 1 [3/4 patients], Cycle 2 and further [2/4 patients]), and anemia (Cycle 2 and further [2/4 patients]);
- Cohort D2: thrombocytopenia (Cycle 1 [1/4 patient]), neutropenia (Cycle 1 [1/4 patient]).

In the 5 cohorts (Cohort A, B, C1, C2, D1, and D2), renal function was well preserved (no grades 3-4 were reported). Liver function was less preserved, with the following Grades 3-4 reported:

- Cohort B: total bilirubin increased (Cycle 2 and further [1/20 patient]);
- Cohort C1: SGOT (Cycle 1 [1/4 patient]), alkaline phosphatase increased (Cycle 1 [1/4 patient], total bilirubin increased (Cycle 1 [1/4 patient], and Cycle 2 and further [1/4 patient]).

Grades 3-4 hyperglycemia were observed:

- Cohort A (Cycle 1 [1/20 patient]; Cycle 2 and further [1/20 patient]);
- Cohort B (Cycle 1 [1/20 patient], Cycle 2 and further [2/20 patients]).

Grades 3-4 hypoglycemia was detected:

- Cohort C2 (Cycle 2 and further [1/6 patient]).

Assessment of AVE1642 HAHA was positive in one patient, at a single time point, at the end of treatment.

Pharmacokinetics results:

Study Part 1

A summary of AVE1642 PK parameters (Cycles 1 and 2 combined) in study Part 1 is provided in the next Table. AVE1642 exposure was approximately dose-proportional between 3 and 24 mg/kg. Clearance was similar at all dose levels, suggesting that a plateau of Cl was reached from the lowest dose of 3 mg/kg. The volume of distribution was comparable to blood volume, as frequently observed for IgG1 monoclonal antibody.

	3 mg/kg	6 mg/kg	12 mg/kg	18 mg/kg	24 mg/kg
$t_{½}$ (day)	9.49 ± 1.63 (17.1) [9.38]	9.02 ± 1.89 (21.0) [8.78]	11.7 ± 3.63 (31.0) [11.2]	10.7 ± 3.82 (35.6) [10.1]	11.4± 2.80 (24.6) [11.2]
t_{max} (day)	0.159 (0.0333 – 0.310)	0.121 (0.0403 – 0.230)	0.0722 (0.0625 – 0.222)	0.147 (0.0938 – 0.271)	0.610 (0.104 – 1.12)
C_{max} (µg/mL)	76.4 ± 9.68 (12.7) [75.9]	148 ± 41.2 (27.8) [143]	258 ± 73.1 (28.3) [250]	397 ± 95.2 (23.9) [387]	337 ± 57.3 (17.0) [334]
t_{last} (day)	20.9 (21 – 21.9)	20.9 (6.9 – 28.1)	21.5 (21 – 28.7)	20.9 (13 – 25.9)	20.9 (21.0 – 21.0)
C_{last} (µg/mL)	7.12 ± 2.72 (38.2) [6.74]	18.0 ± 8.94 (49.7) [16.3]	32.2 ± 13.3 (41.4) [29.4]	52.5 ± 22.8 (43.5) [48.4]	61.3 ± 25.4 (41.4) [58.6]
AUC_{all} (day*µg/mL)	401 ± 80.2 (20) [395]	1030 ± 348 (33.7) [978]	1760 ± 481 (27.3) [1700]	2660 ± 763 (28.7) [2560]	2530 ± 224 (8.9) [2520]
AUC (day*µg/mL)	500 ± 113 (22.7) [490]	1200 ± 387 (32.2) [1140]	2170 ± 781 (36.0) [2060]	3010 ± 850 (28.3) [2900]	2960 ± NC (NC) [2960]
Cl [a] (mL/day)	417 ± 98.8 (23.7) [407]	464 ± 144 (31.0) [440]	363 ± 109 (30.1) [348]	477 ± 116 (24.4) [465]	439 ± NC (NC) [439]
V_{ss} (mL)	4860 ±1400 (28.8) [4670]	5200 ± 1340 (25.8) [5030]	4620 ± 999 (21.6) [4530]	5540 ± 1600 (29.0) [5310]	5450 ± NC (NC) [5450]

Mean ± SD (CV%) [geometric mean] values are presented for all PK parameters except for t_{max} and t_{last}, where median (min, max) values are presented.

[a] Clearance calculated at Cycle 2 assuming negligible drug accumulation

Study Part 2

A summary of AVE1642 PK parameters (Cycle 1) in study Part 2 is provided below. AVE1642 PK parameters were similar between all cohorts.

	A	**B**	**C1**	**C2**	**D1**	**D2**
Cohort	D 75 mg/m²	D 100 mg/m²	G 1250 mg/m² + E 100 mg/day	G 1000 mg/m² + E 75 mg/day	Dox 60 mg/m²	Dox 50 mg/m²
t_{max} (day)	0.138	0.156	0.074	0.0573	0.0646	0.0618
C_{max} (µg/mL)	129 ± 22.0 (17) [127]	129 ± 28.6 (22) [126]	135 ± 23.8 (18) [134]	118 ± 24.8 (21) [116]	118 ± 13.4 (11) [117]	115 ± 29.5 (26) [112]
t_{last} (day)	20.9	20.9	20.9	20.4	27.5	17.9
C_{last} (µg/mL)	11.8 ± 4.87 (41) [10.6]	11.3 ± 4.78 (42) [10.1]	13.2 ± 3.22 (24) [12.9]	11.1 ± 3.03 (27) [10.7]	8.06 ± 4.61 (57) [6.85]	17.6 ± 17.9 (102) [12.2]
AUC_{last} (day*µg/mL)	776 ± 181 (23) [757]	735 ± 166 (23) [716]	776 ± 235 (30) [746]	661 ± 189 (29) [635]	730 ± 176 (24) [711]	617 ± 197 (32) [587]
AUC (day*µg/mL)	899 ± 224 (25) [872]	858 ± 225 (26) [828]	918 ± 341 (37) [873]	819 ± 192 (23) [799]	805 ± 260 (32) [772]	629 ± 386 (61) [567]
t½ (day)	7.97 ± 2.34 (29) [7.59]	9.10 ± 2.73 (30) [8.74]	8.87 ± 2.02 (23) [8.68]	7.51 ± 2.42 (32) [7.18]	10.3 ± 2.66 (26) [10.1]	11.2 ± 8.73 (78) [8.95]
Cl (mL/day)	472 ± 189 (40) [445]	566 ± 206 (36) [536]	476 ± 153 (32) [457]	520 ± 180 (35) [496]	439 ± 207 (47) [410]	876 ± 189 (22) [866]
V_{ss} (mL)	3970 ± 967 (24) [3870]	5190 ± 1330 (26) [5040]	4930 ± 1760 (36) [4730]	3920 ± 341 (9) [3900]	4270 ± 1200 (28) [4160]	5610 ± 2060 (37) [5420]

Mean ± SD (CV%) [geometric mean] values are presented for all PK parameters except for t_{max} and t_{last}, where median values are presented.

D: docetaxel; G: gemcitabine; E: erlotinib; Dox: doxorubicin

A summary of combination products PK parameters is provided in the Table that follows; erlotinib PK parameters could not be determined due to erratic plasma profiles.

After a 1-hour IV infusion of docetaxel at 75 mg/m², the docetaxel Cl (mean ± SD) was 22.9 ± 8.9 L/h/m² (range: 4.1 to 37.9) at Cycle 1 and 26.4 ± 14.6 L/h/m² (range: 10.2 to 53.7) at Cycle 3. The corresponding AUC was 4.59 ± 4.20 µg.h/mL (range: 1.92 to 18.85) at Cycle 1, and 3.67 ± 1.94 µg.h/mL (range: 1.35 to 7.31) at Cycle 3.

After a 1-hour IV infusion of docetaxel at 100 mg/m², the the docetaxel Cl (mean ± SD) was 26.3 ± 7.8 L/h/m² (range: 15.5 to 45.0) at Cycle 1 and 28.9 ± 10.3 L/h/m² (range :12.5 to 46.1) at Cycle 3. The corresponding AUC was 4.00 ± 1.23 µg.h/mL (range: 2.22 to 6.58) at Cycle 1 and 3.87 ± 1.59 µg.h/mL (range: 2.13 to 7.43) at Cycle 3.

These PK parameters were similar to those observed in patients (n=52) with several tumor types, treated with docetaxel monotherapy at a dose of 75 mg/m² with a mean value of 24.3 ± 7.09 L/h/m² and 3.51 ± 1.76 µg.h/mL for Cl and AUC respectively.

	Gemcitabine 1250 mg/m²	Gemcitabine 1000 mg/m²	Erlotinib 100 mg/day	Erlotinib 75 mg/day	Doxorubicin 60 mg/m²	Doxorubicin 50 mg/m²
t_{max} (h)	ND	ND	NC	NC	0.375	0.125
C_{max} (ng/mL)	8950 ± 5360 (60) [7630]	8040 ± 3710 (46) [6970]	NC	NC	1900 ± 529 (28) [1840]	3210 ± 1750 (55) [2830]
t_{last} (h)	1.00	1.12	NC	NC	45.2	44.8
C_{last} (ng/mL)	466 ± 112 (24) [457]	208 ± 115 (56) [169]	NC	NC	12.6 ± 8.57 (68) [10.7]	6.81 ± 1.83 (27) [6.64]
AUC_{last} (h*ng/mL)	2870 ± 1350 (47) [2630]	2500± 1380 (55) [1780]	NC	NC	4800 ± 1330 (28) [4670]	5690 ± 2650 (46) [5220]
AUC (h*ng/mL)	3060 ± 1360 (44) [2830]	3050 ± 851 (28) [2940]	NC	NC	5310 ± 1490 (28) [5150]	5960 ± 2560 (43) [5546]
t½ (h)	0.281± 0.0692 (25) [0.276]	0.242 ± 0.0392 (16) [0.240]	NC	NC	28.0 ± 8.53 (30) [27.0]	27.2 ± 8.85 (33) [26.1]
Cl (L/h/m²)	867 ± 444 (51.2) [792]	634± 230 (36) [602]	NC	NC	11.9± 3.15 (26) [11.6]	9.57± 4.14 (43) [8.87]
V_{ss} (L/m²)	322 ± 236 (73) [271]	185 ± 61.3 (33) [177]	NC	NC	147± 34.0 (23) [144]	83.7±77.1 (92) [50.4]

Mean ± SD (CV%) [geometric mean] values are presented for all PK parameters except for t_{max} and t_{last}, where median values are presented.

ND: not determined ; NC: not possible to calculate

Pharmacodynamics results

A summary of biomarker plasma concentrations following AVE1642 administration as single agent (Study Part 1) or in combination (Study Part 2) is presented in the next Table: IGF1, IGF2 and IGFBP3 plasma concentrations were similar between study Part 1 and Part 2.

		Part 1	Part 2			
	Cycle		A	B	C	D
IGF1 (ng/mL)	1	694 ± 600 (87)	616 ± 281 (46)	632 ± 245 (39)	673 ± 284 (42)	515 ± 332 (64)
	2	475 ± 118 (25)	745 ± 482 (65)	666 ± 297 (45)	674 ± 235 (35)	588 ± 160 (27)
IGF2 (ng/mL)	1	697 ± 150 (22)	725 ± 158 (22)	704 ± 105 (15)	547± 140 (26)	713 ± 158 (22)
	2	648 ± 126 (19)	650 ± 128 (20)	691 ± 101 (15)	614 ± 103 (17)	586 ± 139 (24)
IGFBP3 (ng/mL)	1	3950 ± 1720 (44)	4840 ± 1430 (30)	4910 ± 1750 (36)	4470 ± 1750 (39)	4110 ± 1790 (44)
	2	3500 ± 939 (27)	4880 ± 1530 (31)	4930 ± 1970 (40)	4670 ± 1910 (41)	4910 ± 2260 (46)

Mean ± SD (CV%)

***Efficacy results*:**

Study Part 1:

Across all doses, the best overall response was partial response (PR) in 3 patients (1 patient on AVE1642 6 mg/kg, 1 patient on AVE1642 18 mg/kg, and 1 patient on AVE1642 24 mg/kg). Stable disease (SDi) was reported in 18 patients (3 patients on AVE1642 3 mg/kg, 4 patients on AVE1642 6 mg/kg, 5 patients on AVE1642 12 mg/kg, 5 patients on AVE1642 18 mg/kg, 1 patient on AVE1642 24 mg/kg). In patients (PR + SDi), the time to progression ranged from 76 to 218 days.

Study Part 2:

Partial response was the best overall response, and was reported in 3 patients (Cohort B: 1 patient, Cohort C1: 2 patients). Stable disease was observed in 37 patients (Cohort A: 15 patients, Cohort B: 14 patients, Cohort C1 and C2: 4 patients, Cohort D1 and D2: 4 patients). In patients (PR + SDi), the time to progression ranged from 78 to 268 days in Cohort A, and ranged from 61 to 85 days in Cohort B.

Conclusion :

Not disclosed.

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