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Sponsor / Company: Sanofi	Study Identifiers: NCT00644124, EudraCT 2007-003737-16
Drug substance(s): AVE0005 (aflibercept)	Study code: TCD10173
Title of the study: A Phase I open-label dose-escalation study of intravenous aflibercept (AVE0005, VEGF Trap) in combination with RCHOP administered every 2 weeks or every 3 weeks in patients with non Hodgkin's B-cell lymphoma	
Study center(s): Four (4) centers in France	
Study period: Date first patient enrolled: 21/May/2008 Date study report cutoff: 06/Nov/2009 Date study completion: 20/Oct/2011	
Phase of development: Phase 1, dose escalation	
Objectives: Primary objective To determine the selected dose (SD) of aflibercept (AVE0005, vascular endothelial growth factor [VEGF] Trap) when administered in combination with RCHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone +/- intrathecal methotrexate) every 2 weeks (RCHOP14) or every 3 weeks (RCHOP21). Secondary objectives <ul style="list-style-type: none"> • To assess the safety profile of intravenous (IV) aflibercept when administered in combination with RCHOP every 2 or 3 weeks. • To explore preliminary efficacy (preliminary assessment of antitumor effects of the combination). • To determine the immunogenicity of IV aflibercept. • To explore the biomarkers in both cohorts (exploratory analyses). • To assess the progression free survival (PFS). 	
Methodology: Open label, multicenter, dose escalation study of aflibercept in combination with fixed dose of rituximab (R), cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) administered every 2 weeks (RCHOP14) or every 3 weeks (RCHOP21).	
Number of patients (RCHOP14):	Planned: 25 Treated: 3
Evaluated:	Efficacy/antitumoral activity: 3 Safety: 3
Number of patients (RCHOP21):	Planned: 25 Treated: 25

Evaluated:

Efficacy/antitumoral activity: 25

Safety: 25

Diagnosis and criteria for inclusion: Patients with non-Hodgkin's B-cell lymphoma CD20+ with no previous treatment and:

- Age ≥ 18 years old.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 .
- Adequate biological function: absolute neutrophil count $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, hemoglobin ≥ 9.0 g/dL, creatinine ≤ 1.5 x upper limit of normal (ULN) (if creatinine 1.0-1.5 x ULN, then calculated creatinine clearance ≥ 60 mL/min according to the Cockcroft-Gault formula, and either urine protein creatinine ratio (UPCR) ≤ 1 or proteinuria ≤ 500 mg/24h. In case of bone marrow involvement no hematological criteria were required.
- Negative human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) tests within 4 weeks before study treatment.
- RCHOP14 cohort: Diffuse large B-cell lymphoma (DLBCL), ≤ 60 years old, and with at least 2 age-adjusted International Prognostic Index (IPI) factors (poor prognosis).
- RCHOP21 cohort: All non Hodgkin's B-cell lymphoma eligible to RCHOP21 and aged ≤ 80 years old.

Study treatments
Investigational medicinal product: Aflibercept at a concentration of 25 mg/mL

Dose and escalation (planned): RCHOP14

Dose level	Aflibercept dose	Nb of patients
1	2.0 mg/kg	3-6
2	4.0 mg/kg	3-6
Expansion group	SD	Up to 15 evaluable patients

RCHOP21

Dose level	Aflibercept dose	Nb of patients
-1 (*)	2.0 mg/kg	0
1	3.0 mg/kg	3-6
2	6.0 mg/kg	3-6
Expansion group	SD	Up to 15 evaluable patients

(*) If dose limiting toxicity (DLT) observed at dose level 1 proceed to dose level -1

The selected dose (SD) was the dose level just below the maximum administered dose (MAD). Initially, the design of this study was a classical Phase I design with dose escalation permitted until MAD was reached. Then based on aflibercept Phase 1 studies results (TCD6117, TCD6118, TCD6119), the SD of aflibercept was expected to be 6 mg/kg for RCHOP21 schedule and 4 mg/kg for RCHOP14 schedule. The selected dose level was to be completed up to a total of 15 evaluable patients, and even if stopping dose escalation criteria were not met at dose level 2 for each of the RCHOP regimen, further aflibercept dose escalation was not permitted. This was a major change to the protocol introduced by Amendment No. 2.

Dose and escalation (actual): The dose of 2.0 mg/kg was administered in the RCHOP14 regimen in parallel to 3.0 mg/kg in the RCHOP21 regimen as Dose Level 1 for each cohort, respectively. The next dose level tested during the study was 6 mg/kg as Dose Level 2 escalation for the RCHOP21 cohort.

For the RCHOP21 regimen, since no dose limiting toxicity (DLT) was observed at Dose Level 1 (3.0 mg/kg), Dose Level -1 was not used. Finally, 2 dose levels were administered for RCHOP21; 3 mg/kg and 6 mg/kg.

For the RCHOP14 regimen, even though 4 mg/kg was planned to be tested as Dose Level 2, due to the lack of recruitment, the cohort was stopped. Finally, only 1 dose level (2.0 mg/kg) was tested.

Administration: Aflibercept by IV infusion over a period of 1 hour on Day 1 and before RCHOP. A minimum of 2 hours interval was considered between the end of aflibercept infusion and the start of RCHOP.

Duration of treatment: Dose escalation was performed as long as safety profile of the combination chemotherapy permitted (ie, no DLTs related to aflibercept). Patients were treated until completion of treatment (8 cycles) except if disease progression, absence of at least a partial response (PR) at Cycle 4 evaluation, unacceptable toxicity, patient refusal of further study treatment or consent withdrawn during the treatment have occurred earlier. In addition, in RCHOP14 cohort, patients without a complete response (CR) on positron emission tomography (PET) scan at Cycle 2 were discontinued from the study treatment after Cycle 4 as defined in the protocol.

Duration of observation: The duration of the recruitment phase was approximately 12 months.

For the primary objective, a main cutoff was to be established 3 months after the last patient last treatment of each cohort.

For the secondary objectives, a second cutoff was to occur 2 years after the last patient last treatment of each cohort.

Combined therapy: Marketed formulation of rituximab (R), doxorubicin, cyclophosphamide, vincristine, methotrexate and prednisone (CHOP).

Dose: Doses were the same for RCHOP14 and RCHOP21 cohorts and were to be administered as provided below.

Chemotherapy agents	Dose	Day 1	Day 2	Day 3	Day 4	Day 5
Prednisone (p.o.)	40 mg/m ²	X	X	X	X	X
Rituximab (i.v.)	375 mg/m ²	X				
Doxorubicin (i.v.)	50 mg/m ²	X				
Cyclophosphamide (i.v.)	750 mg/m ²	X				
Vincristine (i.v.)	1.4 mg/m ² (max 2 mg)	X				
Methotrexate* (I.T.)	15 mg	X				

p.o. = per os; IV = intravenous; IT = intrathecal, * for DLBCL with IPI > 0, from cycle 1 to cycle 4

Administration: Routes of administration (IV, p.o., I.T.) are described per treatment in the table above. Rituximab was given before doxorubicin, cyclophosphamide and vincristine, and after prednisone. Methotrexate was given only for DLBCL with age adjusted IPI >0, from Cycle 1 to Cycle 4 only.

For logistical constraints (length of perfusion) the chemotherapy of the RCHOP regimen could be administered on Day1-Day 2. Prophylactic medications usually used by the center for RCHOP treatment were to be used, ie, prevention of lysis syndrome by alkalinisation or anti-hyperuricemic treatment when necessary, antiemetic therapy with anti 5HT3.

The use of granulocyte colony stimulating factor (G-CSF) was left to the Investigator's discretion, but routine prophylactic hematopoietic growth factors was recommended in subsequent cycles for patients experiencing Grade 4 neutropenia of any duration.

Criteria for evaluation:

Efficacy/antitumoral activity: The measurement of efficacy was a secondary endpoint of this study. The overall response rate (ORR) and the response rate (RR) at Cycle 4 defined by Cheson were to be assessed in both cohorts, and the percentage of complete response (CR) observed on PET scan at Cycle 2 was to be assessed in RCHOP14 cohort.

The PFS was defined as the time interval from first treatment until lymphoma progression or death as a result of any cause, whichever came first. Progression Free Survival efficacy criteria will be analyzed at the final cutoff, ie, 2 years after the last patient last treatment of each cohort, and is therefore not presented in this 3-month follow-up report.

Tumor burden was assessed by abdominal and chest PET and/or CT scan at baseline, Cycle 4 and Cycle 8. In addition, PET scan was to be performed for DLBCL after Cycle 2. Tumor assessment was to be confirmed by a central radiological review performed at baseline, at cycles 2, 4 and at the end of treatment. Bone marrow biopsy was to also be performed at Cycle 4 (\pm Cycle 8) in case of bone marrow involvement at baseline.

Safety - selected dose as primary endpoint: The primary safety endpoint was the determination of the selected dose (the dose level just below the maximum administered dose or MAD) of aflibercept administered in combination with RCHOP14 and with RCHOP21 based on the observed DLTs (hematological and non-hematological toxicities) as defined in the study protocol. Dose-limiting toxicities were to be analyzed for dose escalation at Cycle 1 and Cycle 2 in RCHOP14 cohort, at Cycle 1 in RCHOP21 cohort.

Overall safety and tolerability profile: The safety and tolerability of IV aflibercept in both cohorts were assessed via clinical examinations (including vital signs, physical examination, ECOG performance status), previous cardiac history (at baseline only) and laboratory safety tests (including complete blood counts, serum chemistries) prior to drug administration at every visit before treatment and up to 30 days after the last study treatment administration. Clinical examination was to be performed every week during the first 4 cycles and once on Day 1 of further cycles thereafter. Complete blood cell counts were to be performed every week during all cycles. Adverse events (AEs)/treatment-emergent AEs (TEAEs) type, severity (according to NCI-CTCAE v.3.0), cycle, seriousness and relationship to study treatment were assessed.

Laboratory, vital signs, or electrocardiogram (ECG) abnormalities were to be recorded as AEs/TEAEs only when they were medically relevant, ie, only if symptomatic or leading to permanent investigational product discontinuation, to investigational product dose modification (cycle delay or dose reduction or dose omission), fulfill a seriousness criterion.

Immunogenicity/anti-aflibercept antibody in both cohorts: Blood sample was to be collected before aflibercept administration at Cycle 1, and at 30 and 90 days after the last aflibercept administration to detect anti-aflibercept antibody. Anti-aflibercept antibody sample was also to be taken if hypersensitivity reaction was observed during the course of treatment.

Pathology and biomarkers exploration: Pathology study and biomarkers evaluations using blood and tissue samples were intended to be performed in all patients enrolled in the study (see study protocol Section 9.3.4) and consisted of:

- Central anatomopathological review to confirm the B-cell lymphoma diagnosis and obtain a homogeneous characterization
- Tumoral microvessel density assessment CD31, CD34, and factor VIII
- VEGF, VEGF-R1, and VEGF-R2 tumoral expression, circulating and blood marrow EPC
- One blood sample for endogen VEGF before Cycle 1

To note that results for these analyses will be provided at the final database lock.

Statistical methods: The number of dose levels examined and the emerging aflibercept related toxicities were to determine the final sample size. It was anticipated that up to approximately 50 patients (25 in each cohort) were required to establish the selected dose of aflibercept when administered in combination with RCHOP every 2 or every 3 weeks.

Safety evaluations were performed on the safety evaluable population, defined as all patients exposed to at least one dose of or infusion of any component of study treatment. These data were descriptively summarized for each cohort at each dose level.

Dose-limiting toxicities was to be assessed and analyzed on all treated patients at the first cycle for aflibercept/RCHOP21 cohort and at the 2 first cycles for aflibercept/RCHOP14 cohort. Patients in the dose escalation part of the RCHOP14 cohort were evaluable for DLT only after 2 cycles of treatment except if they had discontinued the study treatment during Cycle 1 for a DLT.

Type, frequency, seriousness and relatedness of TEAEs were classified by system organ class (SOC)/preferred term (PT) according to MedDRA (Medical Dictionary for Regulatory Affairs latest version). The NCI CTCAE, Version 3.0 was used to grade AEs and for analysis of laboratory abnormalities.

Preliminary efficacy was descriptively presented for patients treated (as specified above) and evaluable for response (patient with at least 1 tumor assessment after baseline and who received at least 2 cycles except in case of early progression) in each cohort.

Summary: To calculate the selected dose, which was the primary objective of this study the main cutoff for data in the 3-month follow-up report was established as 06 November 2009, ie, 3 months after the last patient of each cohort was treated (had 8 cycles). Patient 1 was the last patient treated in cohort RCHOP21 (06 August 2009) and Patient 2 was the only patient to complete 8 cycles in cohort RCHOP14 (15 July 2008). In this final report, efficacy/antitumoral activity for PFS (secondary objectives) and biomarkers data are provided in completion of the initial Clinical Study Report (CSR) at 2 years after the last patient treated in the RCHOP21 cohort. The last patient last visit (LPLV) was on 20 October 2011 and final database lock (DBL) was on 05 December 2011. The listing of adverse events for data after the primary cutoff was also provided for both cohorts.

Between 21 March 2008 and 24 January 2009, only 3 patients received RCHOP14/aflibercept regimen: 2 in center 001 and one in center 004. One of the 3 patients (center 001) received 8 cycles and the 2 others received 4. Following the lack of recruitment, the Sponsor and Investigator agreed to close the RCHOP14 cohort and to inform Health Authorities about the change.

In parallel, between 21 March 2008 and 29 January 2009, 25 patients received RCHOP21 /aflibercept regimen: 8 in center 001, 9 in center 002, 4 in center 003 and 4 in center 004, respectively. Overall, for both cohorts, between 21 March 2008 and 29 January 2009, a total of 28 patients were enrolled in the study: 10 in center 001, 9 in center 002, 4 in center 003 and 5 in center 004.

Eighteen (18)/25 patients (72%) in the RCHOP21 regimen completed the study treatment period, all 3/3 at the 3 mg/kg aflibercept dose and 15/22 at 6 mg/kg. The reason for not completing study treatment period at the 6 mg/kg dose was:

- Adverse event in 4 patients which included weight decreased non serious Grade 2 (Cycle 7), left ventricular dysfunction non serious Grade 1 (Cycle 5), cough Grade 3 serious (Cycle 7), and headache Grade 3 non serious. All were study drug related and ongoing at the time of cutoff.
- “other reason” for 3 patients as follows: 2 patients discontinued because maximal treatment benefit was achieved after 6 cycles and one discontinued because presented with localized disease Stage I with no risks factors and RCHOP x 6 is considered as standard treatment.

Finally, of the 28 patients enrolled in both cohorts, 9 did not complete the study treatment (8 cycles). Two (2) patients in the RCHOP14 regimen did not complete treatment for reason of non achievement of CR at Cycle 2. Consequently, as per protocol, these 2 patients were dropped out after Cycle 4 and an intensification treatment was proposed to them. Seven (7) patients in the RCHOP21 regimen did not complete treatment for reasons as exposed above.

There was one screen failure due to a Grade 4 pulmonary embolism (SAE) occurring at pre-treatment, lasting a week and from which the patient had recovered. This patient did not enroll the study and was not treated to any of the study drug.

Patients who met the following criteria were included in the RCHOP14 cohort: diffuse large B-cell lymphoma (DLBCL), ≤60 years old and with at least 2 age-adjusted international prognostic index (aIPI) factors (poor prognosis). Two of the 3 patients in this cohort were Caucasian males and one was a black female. Age was 34 in 1 male, 57 in the other male and 59 in the female. For all 3, ECOG PS was 0.

For the RCHOP21 cohort, all eligible patients had non Hodgkin's B-cell lymphoma and were aged ≤80 years old. Median age was 62 years (range: 37 to 78 years), ECOG PS was 0 or 1 for 24 (96.0%) patients and 2 for 1 patient. Almost all patients were Caucasians except 1 Black. Fifteen (60.0%) patients were males and 10 (40.0%) were females.

Overall, half of the patients (14 out of 28) enrolled in the study in both cohorts (RCHOP21: 13 patients; RCHOP14: 1 patient) had a history of hypertension. In the RCHOP21 cohort, 2 hypertension (Grade 1) were at 3 mg/kg dose and 11 (mostly Grade 2 or 3) at 6 mg/kg dose. For both cohorts, hypertension was ongoing at the time of inclusion in the study. The patient with hypertension in the RCHOP14 cohort also presented ongoing hypercholesterolemia at study entry. And amongst those with hypertension in the RCHOP21 cohort, hypercholesterolemia was present for the 2 patients with hypertension at 3 mg/kg and for 6 out of the 11 patients with hypertension at 6 mg/kg group. In addition, in the 6 mg/kg group at inclusion, one patient had diabetes; one was a smoker (tobacco user) with a history of myocardial infarction.

For the 3 patients included in the RCHOP14, time from initial diagnosis to first dose was 5 to 15 days and in the RCHOP21 cohort, the median time was 32 days with a range of 8 to 738 days. Primary tumor location in both cohorts was external lymph nodes in the majority of patients (16 patients: 2 RCHOP14, 14 RCHOP21) with tumor histology in most cases as diffuse large B cell or follicular Grade I, II or III.

One patient on RCHOP14 and 15 patients on RCHOP21 were taking antihypertensive medications prior to study entry; the main drugs received by these patients were angiotensin II antagonist, beta blockers or calcium channel blockers followed by angiotensin-converting-enzyme (ACE) inhibitors and diuretics.

Efficacy/antitumoral activity/biomarkers results:

All patients were evaluable for response, and anti-tumor activity was seen across both dose levels (3 mg/kg and 6 mg/kg). Overall, response rate at the end of the treatment defined by Cheson and based on PET criteria was: 80% complete responses and 20% partial responses. In the RCHOP21 cohort the Kaplan-Meier median PFS estimate was 36.01 months in the 3 mg/kg treatment group and was not reached in the 6mg/kg group (7 events out of 22 patients). There were no deaths in these 2 dose groups. Among the patients who relapsed the mean time from first treatment administration to disease relapse was 22.7 months (min: 9 months; max: 36 months) in the 3 mg/kg treatment group and 14.1 months (min: 6 months; max: 27 months) in the 6 mg/kg treatment group.

As planned, biomarkers were explored in each cohort at 2 years after the last patient treated by evaluating the presence of endothelial precursors cells (EPC) in peripheral blood, in bone marrow and in the tumor. However, updated survival data was only available for RCHOP21 patients, therefore analyses were performed only for these patients (n=25). The list of the results per patient is provided in the supportive section of this report.

Safety results:

Of the 3 patients in the RCHOP14 cohort, one received 8 treatment cycles and completed the study treatment period. The other 2 received 4 cycles each and discontinued the study medication due to treatment failure (partial response) as documented by PET scan at Cycle 4. The median RDI was higher for prednisone compare with the other drugs in the RCHOP14 regimen. For aflibercept, RDI was higher for the 2 patients who discontinued the study for treatment failure at Cycle 4. There was no dose modification or premature discontinuation of any treatment during the RCHOP14 regimen.

A total of 187 cycles were administered to the 25 patients for RCHOP21: 24 cycles in the 3 mg/kg group (3 patients received Cycles 1 to 8) and 163 cycles in the 6 mg/kg group; all 22 patients received cycles 1 to 5, 21 received Cycle 6, 17 received Cycle 7 and 15 received Cycle 8. At the 6 mg/kg dose level, the median number of cycles received was 8. The median relative dose intensity (RDI) was higher for prednisone (1.19 at 3 mg/kg and 1.17 at 6 mg/kg [range from 1.1 to 1.2 at 3 mg/kg and from 0.9 to 1.13 at 6 mg/kg]) compare with the other drugs in the regimen. Median RDI was comparable for aflibercept, cyclophosphamide, rituximab (RDI = 1.13 at both dose levels for each drug [range from 1.0 to 1.1 at 3 mg/kg and from 0.7 to 1.2 at 6 mg/kg] for the 3 drugs), and doxorubicine (RDI= 1.12 at 3 mg/kg and 1.13 at 6 mg/kg [range from 1.0 to 1.1 at 3 mg/kg and from 1.0 to 1.2 at 6 mg/kg]). Median RDI was lower for vincristine (RDI = 0.84 at 3 mg/kg and 0.80 at 6 mg/kg [range 0.7 to 0.9 at 3 mg/kg and 0.6 to 1.2 at 6 mg/kg]) due to the higher incidence of dose reduction for this compound.

Dose reduction and premature treatment discontinuation were more frequently observed for vincristine during the study for the RCHOP21 regimen. No patient prematurely discontinued aflibercept treatment.

Only one DLT (Grade 3 serious polyarthralgia and headache) at 6 mg/kg was observed in the RCHOP21 cohort. No deaths occurred within 30 days from last infusion or 30 days after last infusion in either of the 2 cohorts. None of the 3 patients in the RCHOP14 cohort experienced SAE. For the RCHOP21 cohort, there were 6 related serious Grade 3 or 4 TEAEs, which included 2 cases of febrile neutropenia, one arthralgia, one cough and 2 cases of hypertension. Four (4) patients in the 6 mg/kg dose level were taken off study treatment due to related TEAEs (non serious Grade 2 weight decreased, Grade 1 left ventricular dysfunction, and Grade 3 headache) and one serious Grade 3 cough.

No arterial or venous thromboembolic events were reported. No gastrointestinal (GI) perforation/fistula, osteonecrosis, or reversible posterior leukoencephalopathy syndrome (RPLS) were observed as well. One Grade 3 non serious study related drug hypersensitivity reaction (lasted one day) was observed at 6 mg/kg and recovered after corrective treatment. No Grade 3 or 4 AE was reported at 3 mg/kg.

Grade 2 proteinuria (24h) was observed in 2 patients at the 6 mg/kg dose. In one patient proteinuria was in relation with a non study drug related hemolytic syndrome due to glucose-6-phosphate dehydrogenase (G6PD) deficiency. No patient had UPCR (spot urine ratio) >2.

At both dose level (3 and 6 mg/kg), all patients had abnormal hematologic parameters at Cycle 1, mainly anemia followed by leucopenia, lymphopenia and neutropenia (mostly Grade 1 or 2). Abnormal lymphopenia was more common at baseline, followed by anemia, leucopenia, and neutropenia. By cycle, anemia and lymphopenia were more common (> 60% of patients in each dose group). For all patients, lymphoma cells and schizocytes were absent in the blood at both dose levels at Cycle 1. The hematological profile was as expected with a treatment based on RCHOP combination.

Liver function abnormalities were seen for some patients receiving 6 mg/kg. The occurrence of Grade 3/4 hyperbilirubinemia in one patient receiving 6 mg/kg was in relation with a non study related hemolytic AE due to G6PD deficiency.

All samples were negative for anti-aflibercept antibodies.

The aflibercept 6 mg/kg dose previously selected as the RP2D when combined with background chemotherapy given every 3 weeks was also confirmed in this new RCHOP21 combination in patients with non Hodgkin's B-cell lymphoma.

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