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Phase I dose-escalation study of intravenous aflibercept administered in combination with irinotecan, 5-fluorouracil and leucovorin in patients with advanced solid tumours

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Abstract ***Background:*** To determine dose-limiting toxicities (DLTs), recommended phase II trial dose (RPTD), safety, preliminary antitumour activity and pharmacokinetics of intravenous aflibercept with irinotecan, 5-fluorouracil and leucovorin (LV5FU2).

Patients and methods: In this open-label study, 38 patients with advanced solid tumours received aflibercept 2, 4, 5, or 6 mg/kg on day 1, then irinotecan and LV5FU2 on days 1 and 2 every 2 weeks.

Results: Two grade 3/4 aflibercept-associated DLTs occurred with 4 mg/kg: proteinuria lasting >2 weeks and acute nephrotic syndrome with thrombotic microangiopathy. Two DLTs with 5 mg/kg (grade 3 stomatitis and grade 3 oesophagitis reflux) and three with 6 mg/kg (febrile neutropenia, grade 3 stomatitis and grade 3 abdominal pain) were considered related to concurrent chemotherapy and underlying disease. The most common grade 3/4 adverse events were neutropenia, hypertension and diarrhoea. Nine patients had partial responses, five with 4 mg/kg. Twenty-two patients had stable disease (five with 4 mg/kg), lasting >3 months in 17 patients. No anti-aflibercept antibodies were detected. Free aflibercept was in excess of bound in most patients on 4 mg/kg.

Conclusion: Based on pharmacokinetics, acceptable safety and encouraging antitumour activity, aflibercept 4 mg/kg was selected as the RPTD with irinotecan and LV5FU2 every 2 weeks.

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1. Introduction

Inhibition of vascular endothelial growth factor (VEGF) and its receptors, VEGFR-1 (flt-1) and VEGFR-2 (flk-1/KDR), suppresses angiogenesis and tumour growth in preclinical models.[1,2] VEGF-targeted therapies, including the anti-VEGF monoclonal antibody (bevacizumab) and small-molecule VEGF receptor tyrosine kinase inhibitors (sorafenib, sunitinib and pazopanib) have demonstrated clinical efficacy in patients with advanced cancer.[3–5] In a phase III study in metastatic colorectal cancer (mCRC), the combination of bevacizumab plus irinotecan, bolus 5-fluorouracil and leucovorin (IFL) increased overall survival by 4.7 months compared with IFL alone (20.3 months versus 15.6 months; hazard ratio 0.66, $P < 0.001$).[4] Further evaluation of anti-VEGF therapies with different characteristics, including the aim of bypassing secondary resistance to current VEGF inhibition is warranted.

Aflibercept (VEGF Trap, Regeneron Pharmaceuticals, Tarrytown NY and sanofi-aventis Oncology, Bridgewater, NJ) is a soluble decoy receptor composed of domain 2 of VEGFR-1 and domain 3 of VEGFR-2 fused to the fragment crystallizable (Fc) region of human immunoglobulin G1 (IgG1).[6] Aflibercept binds and neutralises all forms of VEGF-A and VEGF-B and inhibits the activity of proangiogenic placental growth factors (PIGF).[6,7] Aflibercept exhibited antiangiogenic activity and induced inhibition or regression of tumour growth in mouse xenograft models.[6–10] In phase I studies in patients with advanced solid tumours, aflibercept monotherapy was well tolerated and provided evidence of clinical benefit.[11,12]

The present study reports the dose-escalation part of a phase I study of intravenous (IV) aflibercept in combination with irinotecan and 5-fluorouracil and leucovorin (LV5FU2) in patients with advanced solid tumours. The second part of the study describing the expansion of the recommended dose and measurement of anti-vascular effects is reported separately (submitted for concomitant publication).

2. Patients and methods

2.1. Eligibility

Key eligibility criteria included men or non-pregnant women aged $\geqslant 18$ years with histologically or cytologically confirmed solid malignancy with metastatic or unresectable disease for which no standard therapy existed but for which irinotecan and 5-fluorouracil and leucovorin (LV5FU2) was considered appropriate; Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant 2$; adequate haematological, hepatic and renal function; obtention of informed consent. Key exclusion criteria included primary central nervous system tumour or metastases; squamous cell lung carcinoma; radiotherapy, hormonal therapy, minor surgery or chemotherapy during the previous 3 weeks; immunotherapy, cytokine therapy or major surgery within the previous 6 weeks; and uncontrolled hypertension. The study was approved by local ethics committees and conducted according to the Declaration of Helsinki. All patients provided written informed consent.

2.2. Study design

This was an open-label, sequential cohort, dose-escalation study conducted in Belgium and France. Patients received (IV) aflibercept over 1 h on day 1 immediately followed by IV irinotecan 180 mg/m^2 over 1 h, then leucovorin 200 mg/m^2 (or L-leucovorin 100 mg/m^2) over 2 h and 5-fluorouracil (5-FU) 400 mg/m^2 IV bolus then 600 mg/m^2 infusion over 22 h on days 1 and 2 (LV5FU2). The starting dose of aflibercept was 2 mg/kg, with enrolment to higher dose levels (4, 5 and 6 mg/kg) based on safety. Before enrolling patients into a higher dose level, demonstration of acceptable safety at that dose level was required in the ongoing parallel dose-escalation aflibercept monotherapy study.[11] Three to six patients were initially enrolled at each dose level. If patients developed a dose limiting toxicity (DLT) during the first two cycles (minimal exposure to assess DLT and pharmacokinetics), dose-escalation decision rules were applied to determine if dose escalation should be stopped and more patients enrolled at a lower dose. Cycles were repeated every 2 weeks until progression, defined by Response Evaluation Criteria in Solid Tumours (RECIST) or unacceptable toxicity, concomitant treatment with a systemic anticancer agent or withdrawal of patient's consent.

2.3. Study objectives

Primary objectives were to evaluate DLTs during the first two cycles of treatment and to determine the recommended phase II trial dose (RPTD) of aflibercept with irinotecan and LV5FU2. Secondary objectives were to assess pharmacokinetics during cycles-1 and -2, the safety profile of the combination, any aflibercept immunogenicity and preliminary antitumour activity during the study period.

2.4. Safety and antitumour assessments

Safety and tolerability were assessed based on adverse events (AEs), laboratory data, vital signs, electrocardiograms, physical examinations and ECOG performance status. Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Haematological DLTs were febrile neutropenia or neutropenic infection, grade 4 neutropenia for $\geqslant 7$ days, grade 4 thrombocytopenia or grade 3 thrombocytopenia with haemorrhage. Non-haemato-