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Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer ☆

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Abstract ***Background:*** This phase III study investigated the addition of aflibercept to gemcitabine, in patients with advanced pancreatic cancer.

Patients and methods: Patients with metastatic pancreatic cancer were randomly assigned to receive either intravenous (i.v.) aflibercept, 4 mg/kg every 2 weeks, or matching placebo combined with gemcitabine, 1000 mg/m^2 i.v. weekly for 7 weeks out of 8, then weekly for 3 weeks out of 4 until progressive disease, unacceptable toxicity or withdrawal of consent. The primary objective was to demonstrate an improvement in overall survival (OS) between the treatment arms.

Results: The study was stopped for futility following a planned interim analysis of OS in 427 randomised patients. With a median follow-up of 7.9 months, based on the 546 patients at study termination, median OS was 7.8 months in the gemcitabine plus placebo arm

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($n = 275$) versus 6.5 months in the gemcitabine plus aflibercept arm ($n = 271$), which was not significant (hazard ratio 1.165, 95% confidence interval (CI) 0.921–1.473, $p = 0.2034$). Median progression-free survival was 3.7 months in both arms. Treatment discontinuations due to adverse events were more frequent in the aflibercept than in the placebo-containing arm (23% versus 12%).

Conclusion: Adding aflibercept to gemcitabine did not improve OS in patients with metastatic pancreatic cancer.

1. Introduction

Most pancreatic cancer patients present with unresectable, locally advanced or metastatic disease, and have a poor prognosis, with an age-standardised death rate of 3.7 (per 100,000) equating to 266,000 deaths worldwide in 2008.[1] Single-agent gemcitabine is regarded as a first-line standard of care in this setting.[2] Most chemotherapy regimens have failed to significantly improve survival,[3–8] and recently reported improvements in overall survival (OS) have been associated with significant increases in toxicity.[9]

Targeted biologic agents offer a treatment alternative in this setting. The addition of gemcitabine to the EGFR tyrosine kinase inhibitor (TKI) erlotinib demonstrated an improvement over gemcitabine alone (median OS 6.24 versus 5.91 months; hazard ratio (HR), 0.82, $p = 0.038$).[10] In contrast, gemcitabine combined with the anti-EGFR monoclonal antibody (mAb) cetuximab failed to significantly improve survival.[11] There remains an urgent need for more effective systemic therapy for patients with advanced unresectable pancreatic cancer.

Vascular endothelial growth factor (VEGF) mediates angiogenesis by binding to the VEGFR receptor (VEGFR) and promoting signalling events leading to increased vascular permeability, endothelial cell proliferation and migration.[12] VEGF overexpression is frequent in pancreatic cancer and is associated with tumour progression and poor patient prognosis.[13,14] Blocking angiogenesis pathways through VEGF inhibition reduced pancreatic tumour cell growth, providing a rationale for its use in treating patients with the disease.[15] However, randomised phase III trials with the anti-VEGF mAb bevacizumab plus gemcitabine-based therapy failed to improve survival in patients with advanced disease.[16,17]

Aflibercept (VEGF Trap; Regeneron Pharmaceuticals, Tarrytown, NY, and Sanofi Oncology, Cambridge, MA) is a recombinant fusion protein comprising part of the extracellular portions of VEGFR-1 and VEGFR-2 and the Fc fragment of human immunoglobulin IgG1.[18] Aflibercept binds VEGF which then fails to initiate VEGF-ligand dependent signalling processes. Aflibercept compares favourably with other VEGF inhibitors demonstrating significantly increased binding affinity for VEGF-A than its naive receptor, and the ability to bind to both VEGF-B and to the proangiogenic placental growth factors 1 and 2, in pre-clinical models.[19] Aflibercept suppressed tumour growth in pancreatic cell lines and xenografts,[20] and in phase I studies was well tolerated with demonstrable antitumour activity in advanced solid malignancies, including pancreatic cancers.[21,22]

This phase III study (clinicaltrials.gov NCT00574275) aimed to investigate OS in metastatic pancreatic cancer patients receiving standard gemcitabine and either aflibercept or placebo.

2. Patients and methods

2.1. Main eligibility criteria

Eligibility criteria included: patients $\geqslant$18-year-olds with cytologically or histologically confirmed metastatic adenocarcinoma of the pancreas (measurable disease as per Response Evaluation Criteria In Solid Tumours [RECIST] was not required); Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leqslant 2$ with adequate organ function; no prior systemic treatment or chemotherapy for pancreatic cancer except for 5-fluorouracil, capecitabine or gemcitabine as radiosensitising agents and the time between last dose and randomisation $\geqslant$3 months. Exclusion criteria included: <42 days from prior major surgery (28 days from other surgery) to the time of randomisation; < 28 days from prior radiation therapy; prior treatment with anti-VEGF or VEGFR inhibitors; a history of brain metastases, uncontrolled spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease; a previous history of neoplasm; uncontrolled severe organ or metabolic dysfunction or other severe acute or chronic medical conditions; pregnancy or breast-feeding.

The study was performed in accordance with the declaration of Helsinki (1964). All patients provided signed, written informed consent.

2.2. Study design and treatment

This was a prospective, multicentre, multinational, randomised, double-blind, placebo-controlled, parallel-group study, performed at 116 sites in 23 countries. Randomisation (1:1, permuted-block procedure) was stratified by ECOG PS (0 versus 1 versus 2), prior curative pancreatic cancer surgery (yes versus no) and