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Randomized, phase III trial of figitumumab in combination with erlotinib versus erlotinib alone in patients with non-adenocarcinoma non-small cell lung cancer.

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UNIVERSITÀ DEGLI STUDI DI TORINO

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Randomized, phase III trial of figitumumab in combination with erlotinib versus erlotinib alone in patients with nonadenocarcinoma nonsmall-cell lung cancer.

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Randomized, phase III trial of figitumumab in combination with erlotinib versus erlotinib alone in patients with nonadenocarcinoma nonsmall-cell lung cancer

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Abstract

Background Figitumumab (CP-751,871) is a fully human IgG2 monoclonal antibody that inhibits the insulin-like growth factor 1 receptor. This multicenter, randomized, phase III study investigated the efficacy of figitumumab plus erlotinib compared with erlotinib alone in patients with pretreated, nonsmall-cell lung cancer (NSCLC).

Patients and methods Patients (stage IIIB/IV or recurrent disease with nonadenocarcinoma histology) who had previously received at least one platinum-based regimen were randomized to receive open-label figitumumab (20 mg/kg) plus erlotinib 150 mg/day or erlotinib alone every 3 weeks. The primary end point was overall survival (OS).

Results Of 583 patients randomized, 579 received treatment. The study was closed early by an independent data safety monitoring committee due to results crossing the prespecified futility boundary. At the final analysis, median OS was 5.7 months for figitumumab plus erlotinib and 6.2 months for erlotinib alone [hazard ratio (HR) 1.09; 95% confidence interval (CI) 0.91–1.31; $P = 0.35$]. Median progression-free survival was 2.1 months for figitumumab plus erlotinib and 2.6 months for erlotinib alone (HR 1.08; 95% CI 0.90–1.29; $P = 0.43$). Treatment-related nonfatal serious adverse events occurred in 18% and 5% of patients in the figitumumab arm or erlotinib alone arm, respectively. There were nine treatment-related deaths (three related to both drugs, four related to erlotinib alone and two related to figitumumab).

Conclusions The addition of figitumumab to erlotinib did not improve OS in patients with advanced, pretreated, nonadenocarcinoma NSCLC. Clinical development of figitumumab has been discontinued.

Clinical Trial ID NCT00673049.

Key words

figitumumab, erlotinib, non-small-cell lung cancer

Introduction

Most patients with advanced non-small-cell lung cancer (NSCLC) and activating mutations in the epidermal growth factor receptor (EGFR) gene respond initially to EGFR tyrosine kinase inhibitors (TKIs), but invariably become resistant over time. Sensitivity loss may involve signaling between EGFR and the insulin-like growth factor 1 receptor (IGF-1R) [1, 2]. Targeting both EGFR and IGF-1R delays or prevents resistance to EGFR TKIs in various cancer cells [2, 3], enhances antiproliferative activity against breast cancer and malignant glioma cells [4, 5] and inhibits tumor growth in NSCLC xenograft models [6]. In EGFR-overexpressing NSCLC cells, IGF-1R inhibition abolishes erlotinib resistance, reduces proliferation and promotes apoptosis [7]. These data provide a strong rationale for combining agents that target EGFR and IGF-1R against NSCLC.

Figitumumab (CP-751,871) is a fully human IgG2 monoclonal antibody inhibiting IGF-1R. In phase I studies, it was well tolerated alone or with chemotherapy [8, 9]. A phase II study suggested activity in combination with paclitaxel and carboplatin against NSCLC, particularly in squamous cell histology [10]. However, corrected data (published 2012) showed it was less effective than previously reported [11].

This prospective, randomized, phase III study was initiated in 2008 to compare overall survival (OS) with figitumumab plus erlotinib to erlotinib alone in pretreated patients with advanced NSCLC. Based on the original analysis of the phase II study [10], the population was limited to nonadenocarcinoma NSCLC.

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Methods

patients

Eligible patients were ≥ 18 years old, had histologically or cytologically confirmed advanced NSCLC and stage IIIB, stage IV or recurrent disease. Patients had primary histology of predominantly squamous cell, large cell or adenosquamous carcinoma and had previously received ≥ 1 platinum-based regimen. Patients aged ≥ 70 years were eligible if they had received ≥ 1 single-agent therapy. At least 1 and 2 weeks, respectively, must have elapsed since the last radiotherapy or systemic therapy, with all acute toxicities resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v3.0) grade ≤ 1 . Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, measurable disease using Response Evaluation Criteria in Solid Tumors (RECIST v1.0) [12], and adequate organ function. Exclusion criteria included uncontrolled hypertension or diabetes [defined as glycosylated hemoglobin (HbA1c) level $> 8\%$], symptomatic brain metastases, other active malignancies, pregnancy or breast-feeding. A protocol amendment limited enrollment to patients with HbA1c $< 5.7\%$ to reduce the risk of hyperglycemia, but was not implemented fully before study termination. Anticancer therapies for the primary diagnosis other than study treatment were not allowed.

Medications for best supportive care and other concomitant systemic therapies were permitted, including insulin and other antidiabetic agents.

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the declaration of Helsinki, and applicable local requirements/laws. Approval from the institutional review board or independent ethics committee was obtained for each center. All patients provided written informed consent.

study design and treatment

Patients were randomized 1 : 1 to receive open-label figitumumab plus erlotinib (investigational arm) or erlotinib alone (control arm). Randomization was stratified by gender, ECOG performance status (0/1 versus 2) and region (United States/Canada versus Europe versus rest of the world).

The primary end point was OS (the time from randomization to death from any cause). Secondary end points included progression-free survival (PFS), tumor response (RECIST v1.0; complete plus partial responses) and safety.

All patients received erlotinib 150 mg/day \geq 1 h before or 2 h after food. In the investigational arm, patients received figitumumab 20 mg/kg i.v. on day 1 of each 3-week cycle with an additional dose on day 2 of cycle 1 to expedite steady-state drug levels. Treatment continued until disease progression, unmanageable toxicity or 17 cycles (longer if the investigator and sponsor considered that it was providing clinical benefit). Patients in the control arm who discontinued erlotinib because of disease progression could receive figitumumab alone (labelled as ‘crossover’), as phase I studies in other malignancies suggested possible benefits of monotherapy with acceptable toxicity [9, 13]. Patients in the investigational arm who discontinued erlotinib could continue on single-agent figitumumab and vice versa until progression.

study procedures

Tumors were assessed at 6, 9, 12, 15 and 18 weeks after randomization and every 6 weeks thereafter, with objective responses confirmed \geq 4 weeks after initial observation. Off-treatment tumor assessments were to be carried out at least once every 8 weeks until objective disease progression. After progression, patients were to be followed for survival monthly by telephone until death or \sim 14 months after accrual completion. Adverse events (AEs) were graded using NCI CTCAE v3.0 and collected until 150 days after the last dose of study drugs, withdrawal of consent or initiation of subsequent anticancer therapy. Clinical and laboratory assessments occurred at baseline, day 1 of each cycle and end of treatment.

statistical analysis

The primary OS analysis was a 0.024-level stratified log-rank test, with one interim analysis. The primary PFS analysis was a 0.001-level stratified log-rank test with no interim. Statistical analyses were undertaken by Pfizer, the study sponsor. The [supplementary Material, available at *Annals of Oncology* online](#), provides additional detail.

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results

patients and treatment exposure

Between 5 June 2008 and 2 March 2010, 583 patients were randomized and 579 received treatment (figitumumab plus erlotinib: $n = 289$; erlotinib alone: $n = 290$; Figure 1). Baseline characteristics generally were well balanced between treatments (Table 1). Fewer than 10% of patients in each arm received ≥ 3 prior treatment regimens.

Table 1.

Patient characteristics at baseline (all randomized, as randomized)

The diagram is a flowchart titled 'Patient characteristics at baseline (all randomized, as randomized)'. It branches into several categories, each with a table of counts for the Figitumumab + Erlotinib (n=289) and Erlotinib alone (n=290) groups. The categories include:

- Demographics:** Age (Median, Range), Sex (Male/Female), Race (White/Black/Asian/Hispanic/Latino/Other), and Performance Status (ECOG 0-4).
- Medical History:** Prior treatment regimens (0, 1, 2, 3+), History of prior metastatic disease (Yes/No), and History of prior brain metastases (Yes/No).
- Baseline Laboratory Values:** Hemoglobin, Hematocrit, Platelets, Creatinine, Bilirubin, and Hemoglobin A1c.
- ECOG Performance Status:** 0, 1, 2, 3, 4.
- ECOG Performance Status by Age:** Stratified by age groups (18-64, 65-74, 75-84, 85+).
- ECOG Performance Status by Sex:** Stratified by gender.
- ECOG Performance Status by Race:** Stratified by race.
- ECOG Performance Status by History of prior metastatic disease:** Stratified by presence of metastatic disease.
- ECOG Performance Status by History of prior brain metastases:** Stratified by presence of brain metastases.

Figure 1.

Patient disposition. AE, adverse event.

Enrollment was closed permanently in March 2010 by Data Safety Monitoring Committee (DSMC) recommendation because the results of the interim analysis crossed the prespecified futility boundary, indicating that the addition of figitumumab to erlotinib did not improve OS. Patients could continue study treatment if considered in their best interest, and if the local authorities permitted, but figitumumab was no longer offered to patients who progressed on single-agent erlotinib. Follow-up for survival continued until 31 March 2011. Three patients continued on treatment after this date (two in the figitumumab arm and one in the control arm) and are shown here as ongoing; additionally six patients were ongoing in safety or long-term follow-up.

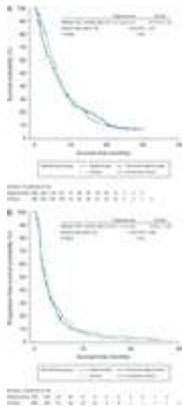
Patients in the figitumumab arm received a median of three cycles of figitumumab and two cycles of erlotinib (range 1–37 for both), and patients in the control arm received a median of four cycles of erlotinib (range 1–26). In the figitumumab arm, figitumumab doses were delayed in 12% of patients and reduced in 5%; erlotinib doses were reduced in 21%. In the control arm, 14% of patients had dose reductions; 29% crossed over to figitumumab after progression and completed a median of two cycles; 2% of these patients had dose reductions.

efficacy

At the final analysis, 483 patients had died (241 figitumumab and 242 control). Median OS was 5.7 versus 6.2 months [HR 1.09; 95% confidence interval (CI) 0.91–1.31; $P = 0.35$; Figure 2A]. No benefit of figitumumab on OS was demonstrated by gender, ECOG performance status, histology, smoking status, HbA1c and regional subset (supplementary Figure S1, available at *Annals of Oncology* online). Median OS in patients with baseline HbA1c $< 5.7\%$ was 6.9 months with figitumumab and 6.5 months with erlotinib alone; for patients with HbA1c $\geq 5.7\%$, median OS was 4.6 and 6.1 months, respectively. Median PFS was 2.1 months with figitumumab and 2.6 months with erlotinib alone (HR 1.08; 95% CI 0.90–1.29; $P = 0.43$; Figure 2B). Objective response rate was 5.5% versus 3.8% ($P = 0.34$; Table 2).

Table 2.

Efficacy results (all randomized, as randomized)



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Figure 2.

Kaplan–Meier plot for (A) overall survival; (B) progression-free survival (as-randomized population). CI, confidence interval; OS, overall survival; PFS, progression-free survival.

safety

The most common all-causality AEs in both study arms were rash, diarrhea and decreased appetite (Table 3). Grade 3/4 AEs that differed most between study arms included fatigue, asthenia, decreased appetite and dehydration. Any-grade rash occurred in a similar number of patients in each arm and was rarely severe. Hyperglycemia occurred more frequently with figitumumab but was mostly mild in severity. Antidiabetic agent use increased in figitumumab-treated patients from 8% before enrollment to 19% on-study (versus 10% at baseline and 11% on control treatment). The incidence of most AEs was similar in patients with baseline HbA1c <5.7% and \geq 5.7% (supplementary Tables S2 and 3, available at *Annals of Oncology* online), except hyperglycemia, which was more common in the latter. Five patients discontinued figitumumab due to hyperglycemia and three of them also discontinued erlotinib.

Table 3.

Most common treatment-emergent (all-causality) adverse events (\geq 10% of patients for any grade or >5% of patients for grade 3 and 4)

Among crossover patients, all-causality AEs were generally similar to those in the figitumumab plus erlotinib arm, with the exception of gastrointestinal events, which were somewhat less frequent with single-agent figitumumab (Table 3). The most frequent treatment-related AEs with single-agent figitumumab were rash (40%), decreased appetite (18%), asthenia (14%) and hyperglycemia (13%). One crossover patient discontinued figitumumab due to hyperglycemia.

The most common (all-causality) serious AEs (SAEs) in the figitumumab and erlotinib arms, respectively, were: dehydration (5% versus 2%), diarrhea (4% versus 1%), dyspnea (4% versus 1%) and pneumonia (3% versus 4%). Nonfatal treatment-related SAEs occurred in 18% versus 5%, respectively.

Nine deaths were considered treatment-related; five in the figitumumab arm, of which three were related to both drugs (pulmonary hemorrhage, cardiac arrest, acute respiratory distress syndrome) and two to erlotinib only (intestinal ischemia, allergic alveolitis). Four were in the control arm, of

which two were related to erlotinib (respiratory failure, pneumonia aspiration/renal failure/acute cardiac arrest), and two to figitumumab after crossover (pulmonary hemorrhage, cerebral hemorrhage) (supplementary Table S1, available at *Annals of Oncology* online).

In the figitumumab arm, 7% of patients discontinued treatment due to figitumumab-related AEs and 8% due to erlotinib-related AEs. In the control arm, 2% of patients discontinued treatment due to erlotinib-related AEs.

discussion

In this randomized, phase III study, adding figitumumab to erlotinib failed to improve survival over erlotinib alone in pretreated patients with advanced NSCLC, causing the DSMC to close the study early due to a survival HR that crossed the prespecified futility boundary. No significant difference was found between study arms for PFS.

These results are disappointing given preclinical findings that suggested blockade of IGF-1R signaling may sensitize tumors to inhibition of EGFR [4–7]. However, the results are consistent with another study showing that erlotinib combined with an IGF-1R-targeted antibody did not prolong survival and was associated with higher toxicity than erlotinib alone in unselected patients with advanced, pretreated NSCLC [14].

The response rate in our study was low in both arms, possibly reflecting the advanced stage of NSCLC and nonadenocarcinoma histology. We did not assess EGFR status in tumor tissue samples, but our patients were unlikely to harbor *EGFR* mutations based on their nonadenocarcinoma histology. The tumor response rate in the erlotinib arm of our study (3.8%) was similar to that (3%) in the EGFR-negative subgroup of erlotinib recipients in the pivotal registration study [15]. Our protocol included optional collection of tissue samples for exploratory biomarker analysis, but too few samples were collected.

Certain AEs (notably nausea/vomiting, diarrhea, decreased appetite/weight, asthenia, mucosal inflammation, dehydration and hyperglycemia) and SAEs (dehydration, diarrhea and dyspnea) were more common with figitumumab. For patients who crossed over from erlotinib to figitumumab, AEs reported after commencing figitumumab were documented in the figitumumab crossover arm, not the erlotinib control arm. Therefore, AE rates may be underestimated in the control arm. Rash was the most common any-grade AE reported and is a known toxicity of erlotinib.

Hyperglycemia, mostly transient, is a known side-effect of figitumumab [8, 9] and other IGF-1R inhibitors [16, 17]. Here, hyperglycemia (any grade) occurred in 15% (6% grade 3/4) of patients receiving figitumumab versus 4% (<1% grade 3/4) receiving erlotinib alone. In an exploratory analysis, OS in patients with baseline HbA1c $\geq 5.7\%$ was slightly worse with figitumumab than with erlotinib alone, while OS for patients with HbA1c $< 5.7\%$ appeared similar.

A phase III clinical trial of figitumumab plus carboplatin and paclitaxel for advanced nonadenocarcinoma NSCLC was also closed early due to futility [18]. Initially, it was reported that a subset of figitumumab-treated patients with elevated circulating IGF-1 experienced longer PFS than those treated with chemotherapy alone. However, these data were subsequently retracted, and no biomarkers have been clearly associated with anti-IGF-1R activity [19].

When our study was designed, there was a good preclinical rationale for combining figitumumab with erlotinib in NSCLC. However, without phase II combination data, information may have been insufficient to predict success in phase III. Figitumumab development has been discontinued.

funding

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disclosure

Employment or leadership position: RJB (Pfizer); SG (Pfizer); KM (Pfizer); Consultant or advisory role: F. Barlesi (Pfizer); F. Blackhall (Pfizer, Roche); SP (Pfizer, Roche); FAS (Pfizer); Stock ownership: RJB (Pfizer), SG (Pfizer), KM (Pfizer); Honoraria: F. Barlesi (Pfizer); F. Blackhall (Pfizer); SP (Pfizer); GVS (Eli Lilly, AstraZeneca, Roche, Pfizer); FAS (Pfizer); J.-C. S. (Pfizer); Research funding: F. Blackhall (Pfizer, Roche). All remaining authors have declared no conflicts of interest.

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appendix

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