The insulin-like growth factor-I receptor inhibitor figitumab (CP-751,871) in combination with docetaxel in patients with advanced solid tumours: results of a phase Ia dose-escalation, open-label study

**Keywords:** figitumab (CP-751,871); insulin-like growth factor type 1 receptor (IGF-IR); chemosensitisation; monoclonal antibody; docetaxel

Alterations in the expression of components of the insulin-like growth factor (IGF) signalling pathway have been shown to have a critical role in the development of a variety of human malignancies, including lung, breast, prostate, thyroid, colorectal cancers, and sarcomas (Hankinson et al, 1998; Chang et al, 2002; Cardillo et al, 2003; Durai et al, 2005; Pollak, 2008). The IGF type 1 receptor (IGF-IR) pathway, initiated by the ligands IGF-1 and IGF-2, is associated with cellular mitogenesis, angiogenesis, tumour cell survival, and tumourigenesis in various tumour cell lines (Kalli et al, 2002; Kurmasheva and Houghton, 2006; Samani et al, 2007). Inhibition of IGF-IR in a range of tumour types has antiproliferative effects and synergises with other anticancer therapies, including cytotoxic chemotherapies (Benini et al, 2001; Cohen et al, 2005; Yin et al, 2005; Abe et al, 2006). Preclinical models have shown evidence of chemosensitisation of androgen-independent human prostate cancer cells when IGF-IR blockade was combined with either cisplatin, mitoxantrone, or paclitaxel (Hellawell et al, 2003). Inhibition of IGF-IR also enhanced docetaxel antitumour activity in animal models of castration-resistant prostate cancer (CRPC) (Cardillo et al, 2003), and synergised with trastuzumab in HER2+ breast cancer cells (Esparís-Ogado et al, 2008).

Figitumab (CP-751,871) is a fully human IgG2 monoclonal antibody (mAb) highly specific for IGF-IR. Figitumab blocks the binding of IGF-1 to IGF-IR, inhibits the downstream signalling activated by both IGF-1 and IGF-2, and induces prolonged receptor internalisation and degradation (Cohen et al, 2005). It inhibits the growth of tumour xenografts derived from colon (Colo-205), breast (MCF7), and lung (H460) cancer cell lines (Cohen et al, 2005). Additive tumour growth inhibition was observed when figitumab was combined with adriamycin, 5-fluorouracil, or tamoxifen (Cohen et al, 2005), when compared with either of these cytotoxic therapies alone.

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Figitumumab has been reported to be well tolerated in patients with solid tumours (Haluska et al, 2007) and myeloma (Lacy et al, 2008). The majority of adverse events were of grade 1 and 2, and included elevated transaminases, hyperglycaemia, anorexia and fatigue. Grade 3 hyperglycaemia was observed in one patient in the study of Lacy et al (2008), alongside grade 3 elevated aspartate aminotransferase (AST), whereas there was one episode each of grade 3 elevated γ-glutamyl transferase (GGT), arthralgia and fatigue in the study of Haluska et al (2007). No dose-limiting toxicities (DLTs) were observed in these phase I studies, in which the maximum tolerated dose (MTD) was not reached, and the maximal feasible dose and recommended phase II dose (RP2D) was 20 mg kg⁻¹ every 3 or 4 weeks (Haluska et al, 2007; Lacy et al, 2008). On the basis of its ability to block IGF-IR and modulate chemosensitivity, the addition of figitumumab to docetaxel may improve the antitumour activity of single-agent docetaxel. This phase I dose-escalation trial was designed to determine the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) effects of figitumumab given in combination with docetaxel in subjects with advanced solid tumours.

MATERIALS AND METHODS

Eligibility

Patients with histologic or cytologic confirmation of advanced solid tumours refractory to standard therapy were eligible. Other inclusion criteria included: age ≥18 years; Eastern Cooperative Oncology Group performance status of 0 or 1; adequate bone marrow, renal, and hepatic function (absolute neutrophil count ≥1500 μl⁻¹, haemoglobin ≥10 g per 100 ml, platelets ≥100 000 μl⁻¹, creatinine clearance ≥30 ml min⁻¹, and total bilirubin equal to or less than the institution upper limit of normal (ULN), AST, and alanine aminotransferase (ALT) ≤1.5 × ULN); and use of adequate contraception in patients with reproductive potential. Exclusion criteria included: anticancer therapy or surgery within 4 weeks, excluding luteinising hormone-releasing hormone (LHRH) analogues in prostate cancer patients; severe hypersensitivity reaction to docetaxel or drugs formulated releasing hormone (LHRH) analogues in prostate cancer patients; and use of colony-stimulating factors (G-CSF and GM-CSF) was a contraindication. Exclusion criteria included: age <18 years; Eastern Cooperative Oncology Group performance status of 2 or 3; patients with descemet’s mitral thickening (>5 mm) with mitral regurgitation greater than mild or valve gradient >5 mm Hg on echocardiogram, as minor granulocytic and lymphocytic infiltration, oedema, and deposition of myxomatous material was observed in the mitral valve and subvalvular endocardium in preclinical testing; and (6) grade 4 thrombocytopenia (platelets <50 000 cells mm⁻³). The relative sensitivity of the assay was approximately 1 ng ml⁻¹.

Toxicities were characterised according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0. Radiologic (using Response Evaluation Criteria in Solid Tumours-1 (RECIST) guidelines) and biochemical evaluation of disease response was conducted every 6 weeks. A DLT was defined as any one of the following adverse events occurring during cycle 1 if considered related to study treatment: (1) grade ≥3 gastrointestinal toxicity despite the use of adequate medical intervention and/or prophylaxis; (2) any other grade ≥3 toxicity not classified under CTCAE blood/bone marrow (except for grade 3 alopecia and grade 3 γ-glutamyl transpeptidase); (3) grade 4 γ-glutamyl transpeptidase; (4) grade 4 neutropenia (absolute neutrophil count <500 cells mm⁻³) persisting for ≥7 consecutive days or complicated by fever (body temperature >38.0 °C or 100 °F) and requiring hospitalisation; (5) asymptomatic mitral thickening (>5 mm) with mitral regurgitation greater than mild or valve gradient >5 mm Hg on echocardiogram, as minor granulocytic and lymphocytic infiltration, oedema, and deposition of myxomatous material was observed in the mitral valve and subvalvular endocardium in preclinical testing; and (6) grade 4 thrombocytopenia (platelets <25 000 cells mm⁻³). The use of colony-stimulating factors (G-CSF and GM-CSF) was permitted for the management of recurrent febrile neutropaenia.

Evaluation of figitumumab and docetaxel PKs

For patients in the dose-escalation and expansion cohorts, blood samples for the evaluation of figitumumab PKs were collected before dose, at 1 h and 5, 8, 12, and 24 h after the end of docetaxel infusion. In addition, blood samples for determination of figitumumab concentrations dose-doubling cohorts of three to six patients. Dose reduction of docetaxel to 60 mg m⁻² was permitted. In an expansion cohort to evaluate PK drug–drug interaction (DDI), in cycle 1 docetaxel was administered on day 1 followed by figitumumab on day 2; for subsequent cycles, both agents were administered on day 1. Patients were pre-medicated with oral dexamethasone 8 mg twice daily for 3 days starting at day –1. Patients continued treatment with the combination or single-agent figitumumab if docetaxel was discontinued, until disease progression or unacceptable toxicity was observed.

Safety evaluation

Clinical and laboratory assessments for safety (physical examination, blood chemistry and haematology, urinalysis, adverse event, and concomitant medication queries) were performed before enrolment, before the next cycle, and at the end of treatment. Doppler echocardiograms were performed at baseline, end of cycles 1 and 6, end of study, and at follow-up (see below). Serum samples for monitoring ADA were collected from all patients at 30 min before dose in each cycle, at the end of study, and during follow-up visits. When figitumumab plasma concentrations were below the lower limit of quantification (LLOQ) of 120 ng ml⁻¹, the ADA samples were analysed using a validated semiquantitative enzyme-linked immunosorbent assay (ELISA). In brief, the ADA samples were first incubated with figitumumab immobilised on a microtitre plate. After removal of unbound material by washing, anti-figitumumab antibodies were detected using biotinylated figitumumab, followed by addition of streptavidin-horseradish peroxidase conjugate and visualisation with 3,3',5,5'-tetramethylbenzidine (TMB). The relative sensitivity of the assay was approximately 1 ng ml⁻¹. The test for the occurrence of any antidrug antibody (ADA) response to figitumumab, to monitor the efficacy of figitumumab when given in combination with docetaxel, and to characterise the effect of figitumumab on docetaxel PK.
were collected from patients enrolled into the PK DDI cohort before dose in cycles 1–6 and 1 h after dose in cycle 4.

Plasma concentrations of figitumab were analysed by a validated ELISA as previously described (Haluska et al., 2007). In brief, an IGF-1 soluble receptor extracellular domain was used in this assay to capture figitumab. Figitumab bound to the capturing receptor was then detected using horseradish peroxidase-conjugated mouse anti-human IgG2. The LLOQ for the assay was determined to be 120 ng ml\(^{-1}\). Plasma concentrations of docetaxel were determined using a validated high-performance liquid chromatography method coupled with tandem mass spectrometry (HPLC-MS/MS). The LLOQ of the HPLC-MS/MS assay was 10 ng ml\(^{-1}\).

Figitumab and docetaxel plasma concentration–time data were analysed by noncompartmental methods (Gibaldi and Perrier, 1982) using WinNonlin version 3.2 (Pharsight, Mountain View, CA, USA). For treatment cycles with sufficient figitumab PK data, area under the plasma concentration–time curve (AUC) from time 0 to the last sampling time point with quantifiable concentration within a cycle (AUC\(_{\text{last}}\)) and from time 0 to the last day of a cycle (AUC\(_{0–\text{day22}}\)) were determined using the linear/log trapezoidal approximation. The accumulation ratio of figitumab was calculated as the ratio of cycle 4 AUC\(_{0–\text{day22}}\) to cycle 1 AUC\(_{0–\text{day22}}\). For docetaxel PK, the peak plasma concentration (C\(_{\text{max}}\)) was determined by inspection of individual patient plasma concentration–time data. AUC\(_{\text{last}}\) values were determined using the linear/log trapezoidal approximation. For comparison of exposures of cycles 1 and 4, the C\(_{\text{max}}\) and AUC\(_{\text{last}}\) values were normalised to dose level.

PD studies

Blood samples for the measurement of soluble (s)IGF-1R levels and the enumeration of CTCs, including IGF-1R-expressing CTCs, were collected from all patients on days 1 (before dosing of figitumab) and 8 of each treatment cycle, and at the end of treatment. Total and IGF-1R-positive CTCs were isolated and enumerated using the CellTracks system (Immunicon, Huntingdon Valley, PA, USA) as previously described (de Bono et al., 2007). The sIGF-1R levels were determined using an enzyme immunoassay that detects the extracellular domain of the IGF-1R (Pollak et al., 2007; Pollak, 2008). The IGF-1R assay was validated and performed in the laboratory of the co-author Dr Laurence Demers. IGF-1R was determined in serum with a microtitre plate ELISA method (reagents obtained from R&D Systems, Minneapolis, MN, USA). The assay uses recombinant human IGF-1R for the standard, a mouse anti-human IGF-1R capture antibody, and a biotinylated detection antibody raised in goats. The mouse anti-human IGF-1R capture antibody showed <1% crossreactivity with IGF-1, IGF-II, and IGFBP 1-6. Assay sensitivity was 0.1 pg ml\(^{-1}\) and within-run imprecision was 5.3 and 7.1% at IGF-1R concentrations of 8.4 and 0.52 pg ml\(^{-1}\).

RESULTS

Patient characteristics

A total of 46 patients with a median age of 59.4 years (range 25–79) were enrolled (Table 1). The most common tumour types treated were CRPC (n = 22, 47.8%) and oesophageal cancer (n = 9, 19.6%). Of the 28 patients who had received previous chemotherapy, 3 had received at least one taxane-based regimen. Patients received a median of 4.5 courses of figitumab (range 1–21) and a median of four courses of docetaxel (range 1–13). In all, 12 patients received ≥10 cycles of figitumab alone or with docetaxel. A dosing summary is provided in Table 2.

| Characteristic | n = 46 |
|---------------|-------|
| Age, years    | 59.4  |
| Range         | 25–79 |
| Sex, n (%)    |       |
| Female        | 6 (13) |
| Male          | 40 (87) |
| ECOG PS, n (%)|       |
| 0             | 9 (19.6) |
| 1             | 37 (80.4) |
| Tumour type, n (%) |     |
| CRPC          | 22 (47.8) |
| Oesophageal   | 9 (19.6) |
| GOJ           | 3 (6.5) |
| Sarcoma*      | 3 (6.5) |
| Gastric       | 2 (4.3) |
| Cervix        | 2 (4.3) |
| NSCLC         | 2 (4.3) |
| Vulva         | 2 (4.3) |
| Ovarian       | 1 (2.2) |
| Previous therapy, n (%) | |
| Surgery       | 31 (67.4) |
| Radiation     | 25 (54.3) |
| Chemotherapy  | 28 (60.9) |
| Hormonal      | 22 (47.8) |
| Other         | 10 (21.7) |

Abbreviations: CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; GOJ = gastro-oesophageal junction; NSCLC = non-small cell lung cancer; PS = performance status. *includes two chondrosarcoma and one peripheral nerve sheath tumour.

Table 2. Treatment summary

| Dose of figitumab (mg kg\(^{-1}\)) | n | Median | Range | Median | Range |
|-----------------------------------|---|--------|-------|--------|-------|
| 0.1                               | 3 | 6      | 3–8   | 10     | 3–13  |
| 0.4                               | 3 | 6      | 5–8   | 10     | 5–10  |
| 0.8                               | 3 | 4      | 3–13  | 10     | 4–14  |
| 1.5                               | 3 | 3      | 2–12  | 3      | 2–17  |
| 5                                 | 3 | 6      | 2–10  | 8      | 2–12  |
| 6                                 | 3 | 7      | 2–8   | 7      | 2–8   |
| 10                                | 9 | 4      | 2–10  | 4      | 2–10  |
| 20                                | 19| 4      | 1–10  | 4      | 1–21  |

Docetaxel was dosed at 75 mg m\(^{-2}\).

Safety

Dose escalation of figitumab proceeded safely from 0.1 to 20 mg kg\(^{-1}\) with no reported DLTs. One episode of grade 4 hyperglycaemia was observed during cycle 1 in a patient with metastatic oesophageal cancer and a history of type II diabetes mellitus treated with figitumab at 20 mg kg\(^{-1}\). Another episode of grade 2 hyperglycaemia was reported. Other figitumab-related toxicities are reported in Table 3 and include elevated ALT (n = 5) and γ-glutamyl transferase (n = 3), fatigue (n = 3), nausea (n = 3), and muscle spasms (n = 3). Grade 3 and 4 toxicities related to docetaxel (Table 3) reflected the expected toxicity profile for this
After repeated administration, there was a moderate accumulation in plasma exposure of figitumumab at dose levels of \( \geq 3 \, \text{mg kg}^{-1} \), with the mean accumulation ratio being approximately two-fold at 10 and 20 mg kg\(^{-1}\) (Table 4).

Evaluable docetaxel PK data acquired from the DDI expansion cohort were available from 13 subjects in cycle 1 (without figitumumab) and 5 subjects in cycle 4 (with figitumumab). The dose-normalised docetaxel PK profiles seemed to be similar between cycles 1 and 4. Figure 1B shows that in both cycles, docetaxel concentration increased during the 1-h infusion and decreased rapidly after the end of infusion. The dose-normalised docetaxel PK profiles seemed to be similar between cycles 1 and 4. The mean dose-normalised \( C_{\text{max}} \) (Figure 1C) and \( AUC_{\text{last}} \) (Figure 1D) of docetaxel in both cycles were also comparable. Of the five patients who had both cycles 1 and 4 docetaxel PK data, there was no systematic pattern of change in dose-normalised \( C_{\text{max}} \) and \( AUC_{\text{last}} \) between the two cycles. Overall, in the limited number of patients evaluated, figitumumab did not seem to considerably affect the PK of docetaxel.

**Pharmacodynamics**

All patients had detectable levels of sIGF-IR at study entry. Treatment with figitumumab resulted in a dose-dependent decrease in sIGF-IR, with higher doses translating to increasingly longer periods of serum-marker downregulation. At 1.5 and 3 mg kg\(^{-1}\) of figitumumab, complete sIGF-IR downregulation was achieved for the entire dosing period (Figure 2).

Circulating tumour cells \( \geq 5 \) per 7.5 ml of blood were enumerated in 15 patients, including 10 with CRPC. Of these 10 patients with CRPC, 60% (6 of 10) showed a fall from \( > 5 \) CTCs to \(< 5 \) CTCs, and 80% (8 of 10) showed a \( \geq 30\% \) fall in CTCs.

The maximal CTC fall for each of the 10 patients is shown in Figure 3A. Of the remaining five patients, two had gastric adenocarcinoma, two oesophageal adenocarcinoma, and one ovarian cancer. There was a CTC fall from \( \geq 5 \) per 7.5 ml to \(< 5 \) in one of the two patients with gastric cancers (results not shown); the results of the patient with ovarian cancer were not evaluable. The results of IGF-IR CTCs have been reported elsewhere (de Bono et al, 2007).

**Efficacy**

A total of 39 patients (including 18 CRPC patients) were evaluable for disease response. Four patients showed confirmed partial responses (PR): three with CRPC and one with oesophageal cancer. Figure 3B shows the response in pelvic nodal disease in a patient with metastatic CRPC to the bones and nodes. A fifth patient with CRPC showed an unconfirmed PR. All the radiologic responses were observed at doses of figitumumab \( > 3 \, \text{mg kg}^{-1} \). In all, 12 patients had a best response of stable disease (SD), including eight with CRPC (SD range 6–16 months), one with chondrosarcoma (6 months), one with cervical cancer (7 months), one with gastric cancer (6 months), and one with oesophageal cancer (12 months). The remaining patients showed progressive disease.

Maximal prostate-specific antigen (PSA) declines of \( \geq 30\% \), \( > 50\% \), and \( \geq 90\% \) were observed in 54% (12 of 22), 41% (9 of 22), and 5% (1 of 22) of patients, respectively. The increases or declines in PSA were confirmed with a second reading in a total of 17 patients and these were the patients evaluable for a PSA outcome. The percentage change in PSA from baseline to 12 weeks and maximal PSA decline at any point are depicted for each patient as waterfall plots in Figures 3C and D, respectively.

Of the six patients with CRPC whose CTCs fell from \( \geq 5 \) per 7.5 ml to \(< 5 \) per 7.5 ml, two showed a radiological PR alongside \( \geq 50\% \) and \( \geq 90\% \) PSA decline, respectively. A third patient with nonmeasurable disease showed a \( \geq 50\% \) PSA decline in the presence of a CTC fall. In the remaining three patients, two showed...
Table 4  Pharmacokinetic parameters (mean ± s.d.) of figitumumab given in combination with docetaxel

| Dose (mg kg⁻¹) | Cycle 1 | Cycle 4 |
|----------------|---------|---------|
|                | AUC₀–day₂₂ | C₁h | C₁h | AUC₀–day₂₂ | AUC₀–day₂₂ | Accumulation ratio |
| 0.1            | 3        | 1.34 ± 0.36 | —    | 2        | 1.04, 1.54 | —    |
| 0.4            | 3        | 7.42 ± 0.82 | 1010 ± 164 | 3        | 6.9 ± 1.75 | —    |
| 0.8            | 3        | 17.9 ± 6.8 | 2050 ± 649 | 3        | 17.8 ± 2.1 | 0.288* |
| 1.5            | 3        | 32.3 ± 4.2 | 5110 ± 2640 | 1        | 54.6 | —    |
| 3              | 3        | 57.7 ± 22.7 | 10500 ± 3750 | 2        | 75.5, 126 | 31.4, 33.1 |
| 6              | 2        | 120 ± 24 | 26700 ± 2770 | 2        | 203, 172 | 57.1, 37.2 |
| 10             | 9        | 211 ± 33 | 38200 ± 8000 | 7        | 324 ± 48* | 57.6, 101* |
| 20             | 6        | 407 ± 160* | 82100 ± 23500 | 5        | 658 ± 158 | 199 ± 73* |

Abbreviations: AUC₀–day₂₂ = area under the plasma concentration–time curve from time 0 to day 22; C₁h = plasma concentration at 1 h after the end of infusion; Cₐ₀–₂₂ = plasma concentration at day 22 of the cycle. n indicates the number of patients included in the analysis. *n = 1, a = 8, b = 6, c = 2. *n = 5, a = 4.

DISCUSSION

We have previously reported on the safety of single-agent figitumumab, a potent fully human mAb against a key factor in the IGF-1 system, IGF-IR (Haluska et al, 2007; Lacy et al, 2008). We now present our findings from a phase Ib study of patients with solid tumours using this mAb combined with the cytotoxic agent, docetaxel. The combination therapy was well tolerated and the previously reported figitumumab-related adverse events of hyperglycaemia and mild elevations in the liver transaminase enzymes were manageable (Haluska et al, 2007; Lacy et al, 2008). One patient with a past history of diabetes mellitus developed grade 4 hyperglycaemia. Steroid premedication and poor diabetic control were implicated as primary causes of this hyperglycaemic episode.

There was no apparent effect of figitumumab on the frequency or severity of observed neutropaenia. Although haematologic toxicity has been reported with other single-agent IGF-IR monoclonal antibodies such as MK-0646 and AMG-479 (Hidalgo et al, 2008; Tolcher et al, 2009), this toxicity does not seem to be significantly worsened when combined with chemotherapy, as found in our study and those of Sarantopoulos et al (2008) and Tolcher et al (2008). A preliminary report from a study by Tolcher et al (2008), in which AVE1642 (another mAb to IGF-IR) was combined with docetaxel in 14 patients, also reported no apparent exacerbation of docetaxel toxicity.

Increasing doses of figitumumab resulted in increased plasma concentrations of this antibody. The approximately two-fold accumulation in figitumumab plasma levels after dosing at >10 mg kg⁻¹ every 21 days confirmed previous findings that the dosing frequency of every 3 weeks is appropriate at these dose levels (Haluska et al, 2007). The PK exposure parameters (C₁h and
AUC_{0–day22} of figitumumab when combined with docetaxel were similar to those of single-agent figitumumab (Haluska et al., 2007), indicating that this combination does not considerably alter figitumumab PK parameters. Furthermore, in a limited number of patients, figitumumab did not seem to substantially affect the PKs of docetaxel. These results suggest that figitumumab at dose levels up to 20 mg kg\(^{-1}\) can be safely administered with docetaxel, with minimal docetaxel dose modification.

Administration of docetaxel and figitumumab in combination resulted in decreased sIGF-IR levels. At doses \(\geq 3\) mg kg\(^{-1}\), there was a complete downregulation of sIGF-IR levels for the entire dosing cycle (Figure 2). This finding is consistent with the extended PK and PD properties of figitumumab previously reported (Haluska et al., 2007; Lacy et al., 2008).

It is interesting that sIGF-IR levels in patients receiving figitumumab at doses of 0.1–0.8 mg kg\(^{-1}\) resulted in levels higher than those observed at baseline, suggesting an intracellular feedback mechanism that can overcome the temporal lack of IGF-IR signalling. These preliminary data and those already published on the potential application of CTCs expressing...
IGF-IR (de Bono et al, 2007) support the ongoing analysis of PD end points, with a view to identifying predictive biomarkers of response to this and other agents in this class of drugs (Carden et al, 2009). In this study, IGF-IR + CTCs were detected in all patients with ≥5 CTCs per 7.5 ml at enrolment (de Bono et al, 2007). These patients had higher PSA levels than those patients who were IGF-IR CTC negative and were also more likely to show PSA declines of >50%. From this we suggested a potential for the use of IGF-IR positivity on CTCs as a molecular marker for identifying patients with CRPC who may benefit from anti-IGF-IR therapies (de Bono et al, 2007).

Although the demonstration of objective responses is not a key end point in phase I studies, clinical assessment of response to therapy in this study was of interest. Out of 22 patients with CRPC, 4 showed a confirmed PR, and 54, 41, and 5% of patients showed ≥30, ≥50, and ≥90% falls in PSA, respectively, on therapy. In addition, a ≥30% fall in CTC counts was observed in 80% of patients who had ≥5 CTCs at baseline. Previous studies have shown that patients who convert from a CTC count ≥5 at baseline to <5 after therapy had significantly better overall survival than those who did not (de Bono et al, 2008; Olmos et al, 2009). In addition, CTC counts were found to be an independent predictor of time to disease progression as well as survival. Half of the patients whose CTCs fell from ≥5 to ≤5 cells per 7.5 ml showed a radiological and/or PSA response; the numbers are small but this supports the use of CTCs as a biomarker of response. As a result of the activity observed in patients with CRPC, a randomised phase II study of figitumumab in combination with docetaxel and prednison vs docetaxel and prednison alone in patients with CRPC was initiated and is now close to completion.

A patient with oesophageal cancer completed a total of 18 courses of figitumumab (including an initial 10 courses of the treatment combination), achieving a PR after 4 cycles of the combination that was maintained until disease progression after 18 cycles. A second patient with oesophageal cancer completed 21 cycles of the antibody (including 10 with the combination) with a best response of SD, and complete resolution of tumour-associated dysphagia. This suggests that potentiation of the therapeutic effects of cytotoxic agents through a reversal of chemoresistance can lead to meaningful clinical outcomes. Phase II and III studies are ongoing in subjects with various solid tumours. including non-small cell lung cancer (NSCLC), Ewing’s sarcoma, gastrointestinal cancers, and breast cancer. Interestingly, although no clinical benefit was observed in the two patients with NSCLC in this study, significant clinical activity with the combination of figitumumab with paclitaxel and carboplatin over paclitaxel and carboplatin alone was observed in a randomised phase II study of 156 patients with NSCLC (Karp et al, 2009). In this trial, 54% of patients responded to the combination, compared with 42% of patients on paclitaxel and carboplatin alone. However, a randomised phase III study of this treatment combination was terminated in December 2009 as it was deemed unlikely to meet the primary end point of improved overall survival compared with chemotherapy alone. Further analysis of the data collected from this phase III study will determine whether it is possible to select patients who will likely benefit from this combination.

In conclusion, the combination of figitumumab at a maximum feasible dose of 20 mg kg⁻¹ and docetaxel at 75 mg m⁻² is safe and well tolerated in patients with advanced cancer, with no substantial alteration in the PKs of either agent. Randomised phase II and III studies of this, and other figitumumab treatment combinations, are ongoing in subjects with various solid tumours.

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Conflict of interest

The following authors are full-time employees of Pfizer Oncology: Luisa Paccagnella, Donghua Yin, and Antonio Gualberto. Allan Lipton is in receipt of a research grant from Pfizer, Inc.

Disclaimer

I declare that the content of the manuscript is original and that it has not been published or accepted for publication, either in whole or in part, in any form. No part of the manuscript is currently under consideration for publication elsewhere.

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