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Editorial

Targeting IGF-1R: throwing out the baby with the bathwater?

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There are intense commercial pressures in industry to develop drugs for large unselected populations, although this remains a risky and expensive strategy. Several examples now exist where targeted treatments are utilised in molecularly defined cancer patient populations. The EGFR tyrosine kinase inhibitor (TKI) gefitinib is a case in point, failing to show a clear benefit in non-small-cell lung cancer (NSCLC) patients when given with first-line chemotherapy. Gefitinib has nevertheless re-emerged as an important therapeutic following the confirmation that mutations in the TK domain of EGFR confer sensitivity to it (Mok *et al*, 2009), with evidence that this population is enriched within Asian, female and never-smoker patients with adenocarcinoma (Lynch *et al*, 2004; Paez *et al*, 2004). More recently, two large-phase III trials, investigating the addition of the fully human monoclonal antibody (mAb) to the insulin-like growth factor 1 receptor (IGF-1R) figitumumab (CP-751,871, Pfizer) to carboplatin/paclitaxel (ADVIGO 1016) and to the EGFR TKI erlotinib (ADVIGO 1018), in advanced NSCLC patients have been suspended after planned interim analyses indicated futility (Jassem *et al*, 2010). These data raise several important questions: Was there sufficient evidence to support these phase III trials? Could we have learnt more from early-phase data to identify the patients who are most likely to benefit? Is IGF-1R a key target in NSCLC? How should we design our trials to identify predictive biomarkers that decrease the risk of such late and costly failures?

Gualberto and colleagues now publish valuable data in this edition of *The British Journal of Cancer* (Gualberto *et al*, 2010b) evaluating putative predictive circulating biomarkers of sensitivity to figitumumab. Their study highlights the complexities of predictive biomarker clinical qualification. They conclude that, independent of tumour characteristics, pre-treatment free IGF-1 (fIGF-1) concentration is a predictive biomarker of clinical benefit from figitumumab at 20 mg kg^{-1} but not at 10 mg kg^{-1} in NSCLC. Their results are consistent with observations that low IGF-1 levels are associated with prolonged survival in NSCLC (Han *et al*, 2006). Nevertheless, their finding that higher baseline fIGF-1 is present in females and patients with adenocarcinoma is at odds with reported data indicating that patients with squamous cell carcinoma derive more benefit from figitumumab and calls into question whether this is simply a prognostic biomarker (Karp *et al*, 2009a). Importantly, however, in this manuscript under discussion, pre-treatment fIGF-1 was not predictive of PFS in patients receiving chemotherapy alone, suggesting that this may not be simply a prognostic biomarker. Recent reports profiling molecular determinants of sensitivity to figitumumab also identified increased IGF-1R expression within squamous cell tumours, which were more likely to respond, but could not definitively establish whether this was a prognostic or predictive factor (Gualberto *et al*, 2010a).

Overall, analysis of these data is complicated by the small sample size and the biological heterogeneity of patients on trial, which are common issues in such clinical research. Their use of one-sided tests limits the statistical power and calls into question whether this study is adequately powered. Moreover, the addition of chemotherapy renders the determination of biomarkers that are truly figitumumab-specific more complex. Other factors that cannot be underestimated are measures of the analytical validity of the assay. Overall, evaluation of the reproducibility and variability of the assay by using two baseline readings should be recommended for such studies. Indeed, concerns remain that current assay methodologies to measure IGF-1 bioactivity are controversial and imperfect (Frystyk, 2007).

Despite these criticisms, these attempts to detect circulating predictive biomarkers are to be commended. We are convinced that circulating predictive biomarkers are critically important in cancer research; these are repeatable, less invasive and more easily implemented in large randomized trials. Nonetheless, the relationship between circulating biomarkers and tumour characteristics must be analysed to evaluate whether these reflect tumour biology. Moreover, pre-treatment biomarkers provide a 'snapshot' suggesting which patients may benefit from treatment, but repeated analyses are required to establish a picture of adaptive changes through acquired resistance mechanisms. Indeed, earlier phase I trials evaluating figitumumab reported that treatment was associated with increased circulating IGF-1 levels and decreased soluble IGF-1R from baseline (Lacy *et al*, 2008; Molife *et al*, 2010). This supports repeated analyses of such biomarkers, which is best done through circulating biomarkers. Importantly, the feedback increase in IGF-1 post treatment with figitumumab may explain why the higher dose of 20 mg kg^{-1} is more active than the 10 mg kg^{-1} dose.

Figitumumab phase I trial data suggested that bioactive IGF-1 levels may influence treatment sensitivity following the observation of responses in patients treated with figitumumab at doses above 10 mg kg^{-1} who had a high baseline free fIGF-1 to IGF-binding protein-3 (IGF-BP3) ratio (Karp *et al*, 2009b). In a phase II, randomised NSCLC trial of first-line paclitaxel/carboplatin (PC) alone or in combination with figitumumab (PCF), the combination resulted in an impressive overall response rate (ORR) of 54% (Karp *et al*, 2009a). Intriguingly, there was an apparent

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dose response to figitumumab in both ORR and 12-week PFS in patients with adenocarcinoma and squamous cell carcinoma histology, with the greatest benefit seen with the higher antibody dose of 20 mg kg^{-1} (78% ORR and 89% 12-week PFS). Moreover, anti-tumour activity was observed in two patients with squamous histology receiving figitumumab monotherapy after PC discontinuation for progression. Despite this, no patient stratification or population enrichment based on histological subtype, IGF-1R tumour expression or circulating fIGF1 levels was pursued in Phase III trials (Jassem *et al*, 2010).

Several questions remain; deregulation of the IGF signalling axis in NSCLC is supported by findings that increased IGF-1 and low levels of its binding protein IGF-BP3 are associated with an increased risk of lung cancer (Yu *et al*, 1999; Han *et al*, 2006). Furthermore, IGF-1R is frequently over-expressed in NSCLC, mediating signalling that results in tumour growth and drug resistance (Morgillo *et al*, 2007). However, IGF-1-overexpressing transgenic mice with functionally upregulated IGF-1R are predisposed towards increased formation of adenomata but not malignant tumours, whereas preclinical work indicates that IGF-II may instead be the critically important autocrine/paracrine ligand in NSCLC by also signalling via the insulin receptor (IR) (Quinn *et al*, 1996; Ulanet *et al*, 2010). It remains to be seen whether treatments targeting both IGF-1R and IR, or both IGF-1 and IGF-II, in NSCLC will yield different results (Olmos *et al*, 2010a). Nonetheless, we have observed impressive anti-tumour activity of figitumumab in metastatic Ewing's sarcoma as a single agent, with some patients experiencing durable responses up to 3 years, suggesting that targeting IGF-1R alone deserves further evaluation (Olmos *et al*, 2010b).

Finally, several different strategies can be pursued to gain most information from early-phase studies. These include phase I trial expansions, phase II Bayesian adaptive designs where all-comers are initially treated, but patients are then enriched for 'responding phenotypes' as in the Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) clinical trial programme, and randomised phase II trials with either *a priori* selection of patients with or without the presence of the biomarker or, as in this case, a retrospective analysis of putative biomarkers against outcome from treatment. Overall, however, we urgently need to develop smarter trial designs that can accelerate the clinical qualification of putative predictive biomarkers in concert with targeted drug trials to expedite the successful delivery of less costly drug approval and patient benefit. Although the initial and NSCLC trials of figitumumab have been negative, the evaluation of drugs targeting the IGF pathway should continue. We should not throw out the baby with the bathwater.

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Conflict of interest

Johann de Bono has served as a paid consultant for Pfizer, Genentech, Novartis, Astellas, Boehringer Ingelheim, Merck, and AstraZeneca.

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