

Letter to the Editor

Reply: 'Pre-treatment levels of circulating free IGF-1 identify NSCLC patients who derive clinical benefit from figitumumab'

A Gualberto^{*,1,3}, ML Hixon¹ and M Pollak²

¹Department of Pathology and Laboratory Medicine, Warren Alpert Medical School at Brown University, Providence, RI 02903, USA; ²Department of Medical Oncology, McGill University, Montreal, Quebec H3T 1E2, Canada

British Journal of Cancer (2011) 105, 1467. doi:10.1038/bjc.2011.413 www.bjcancer.com
Published online 11 October 2011
© 2011 Cancer Research UK

Sir,

We read with great interest the Letter to the Editor from Shimokawa *et al* (2011) that reported significant associations between the expressions of the insulin-like growth factor type I receptor (IGF-IR) and those of E-cadherin and γ -catenin in non-small cell lung cancer (NSCLC) biopsies (Shimokawa *et al*, 2011). These data reproduce previous observations from our group. We have also observed a correlation between the expressions of IGF-IR and E-cadherin, particularly in NSCLC tumours with a high degree of differentiation (Gualberto *et al*, 2010). Furthermore, using unsupervised Bayesian clustering of epithelial-to-mesenchymal transition (EMT)- and IGF-IR-related markers, we identified three NSCLC subsets that resembled the steps of the EMT and we named epithelial-like, transitional-like and mesenchymal-like (Gualberto *et al*, 2010). Several markers of the IGF-IR pathway such as nuclear insulin receptor substrate-1 were overexpressed in the transitional subset and a higher objective response rate to the combination of chemotherapy and the anti-IGF-IR antibody figitumumab was observed in patients with transitional tumours (Gualberto *et al*, 2010). Thus, we agree with Shimokawa *et al* (2011) that analysis of tumour EMT status may contribute to a better understanding of the sensitivity to anti-IGF-IR therapy.

REFERENCES

- Goto Y, Sekine I, Tanioka M, Shibata T, Tanai C, Asahina H, Nokihara H, Yamamoto N, Kunitoh H, Ohe Y, Kikkawa H, Ohki E, Tamura T (2011) Figitumumab combined with carboplatin and paclitaxel in treatment-naïve Japanese patients with advanced non-small cell lung cancer. *Invest New Drugs*; e-pub ahead of print 13 July 2011
- Gualberto A, Dolled-Filhart M, Gustavson M, Christiansen J, Wang YF, Hixon ML, Reynolds J, McDonald S, Ang A, Rimm DL, Langer CJ, Blakely J, Garland L, Paz-Ares LG, Karp DD, Lee AV (2010) Molecular analysis of non-small cell lung cancer identifies subsets with different sensitivity to insulin-like growth factor I receptor inhibition. *Clin Cancer Res* 15: 4654–4665
- Gualberto A, Hixon ML, Karp DD, Li D, Green S, Dolled-Filhart M, Paz-Ares LG, Novello S, Blakely J, Langer CJ, Pollak MN (2011)

Shimokawa *et al* (2011) also pointed out that we have reported an inverse correlation in NSCLC patients between serum IGF-1 and tumour E-cadherin levels (Gualberto *et al*, 2011). We speculate that the fact that tumour E-cadherin is directly correlated with tumour IGF-IR and inversely correlated with serum IGF-1 may indicate differential functions for the non-activated (low or no ligand) vs the activated (in the presence of IGFs) IGF-1 receptor. Evidence supports the involvement of the IGF-IR in both differentiation and cellular growth and metastasis, with engagement of the receptor by IGFs-inducing neo-expression of mesenchymal markers, E-cadherin downregulation and cell migration (reviewed in Julien-Grille *et al*, 2005). These observations may have therapeutic implications. Of note, our key finding that high serum (free) IGF-1 levels may identify a subset of NSCLC patients who preferentially benefit from anti-IGF-IR therapy has now been independently corroborated by other groups (Goto *et al*, 2011; Ramalingam *et al*, 2011).

Conflict of interest

M Hixon and M Pollak received research funds from Pfizer Inc. A Gualberto is a former employee of Pfizer Inc.

- Pre-treatment levels of circulating free IGF-1 identify NSCLC patients who derive clinical benefit from figitumumab. *Br J Cancer* 104: 68–74
- Julien-Grille S, Moore R, Denat L, Morali OG, Delmas V, Bellacosa A, Larue L (2005) The role of insulin-like growth factors in the epithelial to mesenchymal transition. In: Savagner P (ed). *Rise and fall of the epithelial phenotype: Concepts of epithelial-mesenchymal transition*. Landes Bioscience: Montpellier, 215–235
- Ramalingam SS, Spigel DR, Steins M, Engelman JA, Schneider C, Novello S, Eberhardt WE, Crino L, Janne PA, Liu L, Brownstein CM, Reck M (2011) Randomized, double-blind, phase II study of erlotinib in combination with placebo or R1507, a monoclonal antibody to insulin-like growth factor receptor-1 (IGF-1R), for advanced-stage non-small cell lung cancer (NSCLC). *J Clin Oncol* 29: 2011 (suppl; abstract 7527)
- Shimokawa H, Uramoto H, Tanaka F (2011) Comment on 'Pre-treatment levels of circulating free IGF-1 identify NSCLC patients who derive clinical benefit from figitumumab'. *Br J Cancer* 105: 1465–1466

*Correspondence: Dr A Gualberto, E-mail: antonio_gualberto@brown.edu

³Current address: Millennium: The Takeda Oncology Company, 35 Landsdowne Street, Cambridge, MA 02139, USA
Published online 11 October 2011