



Commentary

Evaluation of Biomarkers for HER3-targeted Therapies in Cancer

Niki Karachaliou ^{a,*}, Rafael Rosell ^{a,b,c}^a Translational Research Unit, Dr Rosell Oncology Institute, Quirón Dexeus University Hospital, 08028 Barcelona, Spain^b Cancer Biology and Precision Medicine Program, Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Ctra Canyet s/n, 08916 Badalona, Barcelona, Spain^c Fundación Molecular Oncology Research (MORe), Sabino Arana 5-19, 08028 Barcelona, Spain

Integration of biomarkers into the majority of drug development programs has led to a need for robust measurements and assay validation techniques for analyses of biological samples. The importance of solid methodologies for biomarker assessment is heightened by the fact that new drugs frequently only offer modest benefit and that many potential biomarkers are continuous variables, the application of which relies on data interpretation, with the risk of subjectivity bias, to establish thresholds. Patritumab is a fully human anti-human epidermal growth factor receptor 3 (HER3) antibody that inhibits HER3 from binding to HRG (Mendell et al., 2015). In the HERALD phase II trial, before data unblinding but after subject enrollment, heregulin (HRG) was prospectively declared to be the predictive biomarker for patritumab efficacy. Advanced non-small cell lung cancer (NSCLC) patients previously treated with at least one chemotherapy regimen were randomized to erlotinib plus patritumab (high- or low-dose) or erlotinib plus placebo (Mendell et al., 2015). Testing a single primary predictive biomarker hypothesis to identify those patients most likely to benefit from patritumab was a secondary objective of the trial and HRG was identified as a continuous biomarker to predict outcome.

Members of the HER family of receptor tyrosine kinases (RTK) and their respective ligands constitute a robust biologic system that plays a key role in the regulation of cell-proliferative growth, survival, and differentiation (Ma et al., 2014). HER3 transactivation via dimerization with other RTKs is frequently observed in various malignancies, including NSCLC. Binding of the alpha and beta forms of neuregulin 1, collectively known as HRG, exposes a dimerization arm in the extracellular domain of HER3 and promotes receptor–receptor interactions (Ma et al., 2014; Carraway et al., 1994). HER3 contains six phosphotyrosine binding sites for the p85 subunit of PI3K, the greatest number of all HER family members, and is a major cause of treatment failure in cancer therapy (Ma et al., 2014; Fedi et al., 1994). Recently, the role of HER3 in primary and acquired resistance to EGFR-targeted or other targeted therapies in NSCLC patients has attracted considerable attention (Ma et al., 2014; Torika et al., 2014). Since HER3 lacks or has weak intrinsic kinase activity, targeting it with blocking antibodies that inhibit HRG binding is one strategy currently being investigated in order to overcome therapeutic resistance (Ma et al., 2014).

In the study by Mendell et al., although no progression-free survival (PFS) benefit was observed overall with the addition of patritumab to

erlotinib, when patients were stratified according to HRG mRNA levels HRG-high patients treated with patritumab and erlotinib had significantly improved PFS compared with patients treated with erlotinib alone in both the high- and low-dose arms (Hazard Ratio (HR), 0.37 [95%CI, 0.16–0.85] and 0.29 [95%CI, 0.13–0.66]) (Mendell et al., 2015). No PFS benefit was observed in HRG-low patients. An exploratory analysis suggested that high HRG expression might also be a negative prognostic factor in patients treated with single-agent erlotinib (Mendell et al., 2015).

The role of HRG expression as a marker of HER3 activity has been previously reported. Constitutive activation of HER3 signaling can occur in the absence of direct genetic activation of HER3 or HRG while HER3 activation does not occur as a result of mutation or amplification of the HER3 co-receptors EGFR or HER2. Chronic HER3 signaling is driven by high level and potentially autocrine expression of HRG (Holmes et al., 1992). When HRG and HER3 expressions were profiled in more than 750 patients with head and neck squamous cell carcinoma, high-level expression of HRG was associated with constitutive activation of HER3, defining an actionable biomarker for interventions targeting HER3 (Shames et al., 2013).

Since the arrival of erlotinib and gefitinib, metastatic EGFR positive lung cancer patients can be offered therapeutic alternatives with proven superiority over standard platinum-based chemotherapy (Rosell et al., 2013). Testing for EGFR mutations to guide patient selection for EGFR inhibitors, in all patients with advanced-stage adenocarcinoma, regardless of sex, race, smoking history, or other clinical risk factors, is highly recommended (Lindeman et al., 2013). As commented by Mendell et al., the use of a prospective–retrospective approach applied to a single predictive biomarker hypothesis has the advantage of avoiding a high false-positive rate due to multiple comparisons when multiple biomarker hypotheses are evaluated on an equal footing in an exploratory fashion (Mendell et al., 2015). But are statistical simulations able to dismiss the confounding interactions that EGFR-sensitizing mutations could have on the HRs observed in the study? Some readers may also wonder why, in a study of primarily erlotinib treatment where samples were obtained from most patients, EGFR mutations were not assessed? Clinical trials with EGFR inhibitors designed without using EGFR mutation status, as an enrolment criterion should not be an acceptable practice anymore. Finally, having lost >50% of samples for analyzing HRG mRNA, can we safely conclude that high HRG mRNA and not HER3 expression levels are correlated with patritumab efficacy?

Although technological improvements in terms of specimen acquisition and processing have been made, much work remains to be done to

DOI of original article: <http://dx.doi.org/10.1016/j.ebiom.2015.02.005>.

* Corresponding author.

E-mail address: nkarachaliou@oncorosell.com (N. Karachaliou).

ensure the quality of biospecimens and harmonization of tissue collection, processing and storage procedures, attributable largely to the long-standing success of formalin-fixed paraffin-embedded tissue analysis as the standard in diagnostic pathology. There is an ongoing trend to improve standardization of procedures for biomarker development in oncology that involves academia, professional organizations, and industry. Identification and widespread use of biomarkers will ensure that patients receive the best possible therapeutic strategies, thereby avoiding unnecessary treatments and associated toxicities, and reducing total health costs. Increased awareness of HER3 function in cancer progression and tumor recurrence following drug resistance has several implications for future lines of investigation. High expression of HRG seems to accurately define a population of tumors that may have an oncogenic dependency on ligand-activated signaling via HER3 (Mendell et al., 2015). Based on the results of the Mendell et al. study, a two-part phase III study (NCT02134015) has been initiated to examine patritumab plus erlotinib treatment in EGFR wild-type patients with advanced NSCLC. Part A will enroll subjects with any HRG value to further refine the HRG cutoff level while evaluating the efficacy of patritumab plus erlotinib versus erlotinib in the HRG-high group. Part B will enroll only HRG-high (as per revised criteria) patients to evaluate efficacy and safety of patritumab plus erlotinib versus erlotinib.

Conflict of Interest

The authors declare no conflicts of interest.

References

- Carraway III, K.L., Sliwkowski, M.X., Akita, R., et al., 1994. The erbB3 gene product is a receptor for heregulin. *J. Biol. Chem.* 269 (19), 14303–14306.
- Fedi, P., Pierce, J.H., di Fiore, P.P., et al., 1994. Efficient coupling with phosphatidylinositol 3-kinase, but not phospholipase C gamma or GTPase-activating protein, distinguishes ErbB-3 signaling from that of other ErbB/EGFR family members. *Mol. Cell. Biol.* 14 (1), 492–500.
- Holmes, W.E., Sliwkowski, M.X., Akita, R.W., et al., 1992. Identification of heregulin, a specific activator of p185erbB2. *Science* 256 (5060), 1205–1210.
- Lindeman, N.I., Cagle, P.T., Beasley, M.B., et al., 2013. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J. Thorac. Oncol.* 8 (7), 823–859.
- Ma, J., Lyu, H., Huang, J., et al., 2014. Targeting of erbB3 receptor to overcome resistance in cancer treatment. *Mol. Cancer* 13, 105.
- Mendell, J.F.D., Feng, W., et al., 2015. Clinical translation and validation of a predictive biomarker for patritumab, an anti-human epidermal growth factor receptor 3 (HER3) monoclonal antibody, in patients with advanced non-small cell lung cancer. *EBioMedicine* 8 (3), 265–272.
- Rosell, R., Bivona, T.G., Karachaliou, N., 2013. Genetics and biomarkers in personalisation of lung cancer treatment. *Lancet* 382 (9893), 720–731.
- Shames, D.S., Carbon, J., Walter, K., et al., 2013. High heregulin expression is associated with activated HER3 and may define an actionable biomarker in patients with squamous cell carcinomas of the head and neck. *PLoS One* 8 (2), e56765.
- Torka, R., Penzes, K., Gusenbauer, S., et al., 2014. Activation of HER3 interferes with anti-tumor effects of Axl receptor tyrosine kinase inhibitors: suggestion of combination therapy. *Neoplasia* 16 (4), 301–318.