

Pathway Targeted Immunotherapy: Rationale and Evidence of Durable Clinical Responses with a Novel, EGF-directed Agent for Advanced Non-small Cell Lung Cancer

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Short-Communication

Immunization that targets the EGF pathway can produce durable responses and long-term patient survival in late-stage non-small cell lung cancer (NSCLC), according to a review of this immunotherapeutic approach published by an international group of investigators [1]. This novel approach is within the heart of IO but different from the better known checkpoint inhibitors as EGF-PTI is activating patients' immune B-cells to produce neutralizing antibodies to a growth factor whereas Checkpoint inhibitors are re-activating patient tumour suppressed T-cells. This latter has been demonstrated to be effective but holds a certain risk of immune-related adverse events (irAE's) as reported in clinical trials, [2-4], a phenomenon not observed with EGF PTI [5].

Rodriguez and co-authors describe a successful randomized, controlled trial conducted in Cuba [5] that met its primary endpoint of achieving a three months' overall survival (OS) benefit in late stage NSCLC patients. Patients who had received EGF pathway targeted immunotherapy survived for a median of 12.4 months, compared with 9.4 months among controls when maintenance therapy with EGF-PTI started after completing First line doublet chemotherapy.

This initial study did not attempt to enrich the patient study population. However, a retrospective analysis showed that the OS benefit from active treatment reached 6.2 months (compared with 3 months overall) when only patients with significantly increased EGF concentration were enrolled. In the multinational open-label phase III now in progress in Asia and Europe and soon in US, an EGF threshold has been introduced as biomarker for enrollment in the trial.

This biomarker is a commercially available biomarker directly associated with the mechanism of action. In this regard, it seems that B-cell targeted IO is more specific when compared to Checkpoint Inhibitors for which there is still today an active debate on the most appropriate and prognostic biomarker [6]. The current pivotal trial, which is being sponsored by Bioven (the company that in-licensed the EGF agent from the Cuban researchers who developed it) is also more focused in a number of other ways.

First, it excludes patients with the EGFR mutations that make patients eligible for treatment with Tyrosine Kinase Inhibitors (TKI). This is partly an ethical consideration, since the TKIs probably offer the best outcome to such patients. But it also reflects preclinical work suggesting the anti-EGF approach is more effective in EGFR mutated lung cancer cells [7].

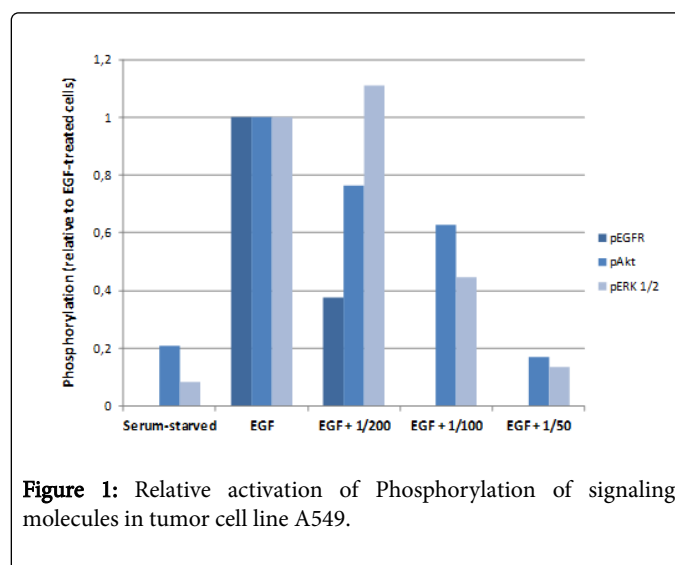


Figure 1: Relative activation of Phosphorylation of signaling molecules in tumor cell line A549.

In contrast to EGFR wild type cell lines, where anti-EGF conjugate antibodies completely inhibited phosphorylation of Signaling molecules such as EGFR, AKT and ERK1/2, the anti-EGF antibodies did not have the same significant inhibitory effect in cells with EGFR mutation. Hence the strategy of combining a biomarker and a genetic marker to select those patients who will benefit most from the specific treatment. It is our understanding that this combination of biomarker and genetic markers is unique in phase III trials.

Also interesting is the fact that data show that antibodies against the EGF- conjugate molecule totally inhibit all signaling molecules present in a tumor cell line with ALK rearrangement as well as in KRAS mutated cell line indicating that this B-cell targeting IO treatment has broader effect when compared to personalized medicine based on specific gene mutations. In (Figure 1) hereunder the stimulatory effect of EGF is demonstrated as well as, the dose related inhibitory effect of antibodies against the EGF-PTI biological molecule on all intracellular signaling molecules;

This effect on KRAS mutated cell line was unexpected as KRAS mutation seems to be "un-druggable" still [8]. Secondly, the population now being studied is less likely to contain patients with an adverse prognosis. It is noteworthy that, as reported 8% of the study population died even before the initial immunization schedule was completed when immunization was initiated after completing Chemotherapy [5]. To address the fact that active immunization takes some time before sufficient antibody titres are reached, in Bioven's international Pivotal

Phase III trial active immunization is initiated prior to chemotherapy in order to start immunization timely and will benefit from immune competent status prior to chemotherapy [9]. Moreover, the Bioven trial will include only patients with ECOG performance status 0-1, whereas the Cuban trial accepted patients of ECOG PS 2. And, while the Cuban study intentionally enrolled a large proportion of patients aged over 65 years, the age distribution of the current trial will better reflect that of the wider population of NSCLC patients. Since immunological capacity in general wanes with increasing age, the make-up of the new Phase III population should better match the concept of immunotherapy. The prospect of achieving a good immune response is also relevant to the last important difference between the two studies. The Cuban phase III was conducted second-line in patients who had achieved a response or stable disease following platinum doublet chemotherapy. Since chemotherapy damages the immune system, the kinetics of antibody generation are slower in such patients than in those who are fully immune-competent. It is hoped that this combination schedule, involving integration of immunotherapy and chemotherapy, will be optimal for late stage NSCLC patients who need to be protected from rapidly evolving disease. This integrated approach has a further possible advantage. It has been reported that phosphorylation of paxillin confers cisplatin resistance in NSCLC patients via ERK mediated Bcl-2 expression. Since EGF-PTI completely inhibits activation of ERK1/2, we can expect that this mechanism of resistance will be blocked when the mechanism of action of EGF-PTI works in conjunction with Chemotherapy.

Since abnormalities of the EGF/EGFR pathway promote progression in NSCLC and are closely associated with the development of end-stage disease, the rationale for treatment aimed at inhibiting the pathway is clear. The origins and early development of EGF PTI are intriguing. They lie in the Center of Molecular Immunology (CIM) in Havana, which first produced the vaccine consisting of yeast-derived human EGF conjugated with the carrier protein N meningitidis p64K produced in *E. coli*. [11]

The CIM in Havana was also responsible for the early clinical trials, including the “all-comer” phase III study showing the OS benefit of 3 months and durable responses, some of which have lasted longer than five years. It is hoped that the potential shown by these earlier trials will now be more than confirmed, especially since the protocol being followed in the current International pivotal Phase III study is designed to maximize the likelihood of clinical benefit in an enriched patient population. With the current enthusiasm for checkpoint inhibitors, the immunotherapy arena once relatively ignored is now becoming crowded. However, restoration of anti-tumour T-cell activity by checkpoint inhibition and the active induction of B cell responses

by immunization with EGF-PTI are directed at independent and complementary aspects of a cancer patient's immune system. The good tolerability and absence of immunotoxicity with EGF PTI makes it an attractive treatment both as monotherapy and, potentially, also as part of a combination immunotherapy strategy aimed at transforming advanced NSCLC into a more chronic and survivable condition.

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References

1. Rosell R, Neningen E, Nicolson M, Huber RM, Thongprasert S, et al. (2016) Pathway Targeted Immunotherapy: Rationale and Evidence of Durable Clinical Responses with a Novel, EGF-directed Agent for Advanced NSCLC. *J Thorac Oncol* 11: 1954-1961.
2. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, et al. (2015) Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med* 373: 123-135.
3. Robert C, Schachter J, Long GV, Arance A, Grob JJ, et al. (2015) Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med* 372: 2521-2532.
4. Demlova R, ValÁk D, Obermannova R, Zdražilová-dubská L (2016) The safety of therapeutic monoclonal antibodies: implications for cancer therapy including immuno-checkpoint inhibitors. *Physiol Res* 65: S455-455S462.
5. Rodriguez PC, Popa X, Martínez O, Mendoza S, Santiesteban E, et al. (2016) A Phase III Clinical Trial of the Epidermal Growth Factor Vaccine CIMAvax-EGF as Switch Maintenance Therapy in Advanced Non-Small Cell Lung Cancer Patients. *Clin Cancer Res* 22: 3782-3790.
6. Liu X, Cho WC (2017) Precision medicine in immune checkpoint blockade therapy for non-small cell lung cancer. *Clin Transl Med* 6: 7.
7. Codony-Servat J, Molina-Vila MA, Bertram-Alamillo Cancer Res. (2016) Inhibition of epidermal growth factor Receptor pathway by epidermal growth factor antibodies in non-small cell lung cancer 76: 2368
8. Timár J (2014) The clinical relevance of KRAS gene mutation in non-small-cell lung cancer. *Curr Opin Oncol* 26: 138-144.
9. Neningen E, Verdecia BG, Crombet T, Viada C, Pereda S, et al. (2009) Combining an EGF-based cancer vaccine with chemotherapy in advanced nonsmall cell lung cancer. *J Immunother* 32: 92-99.
10. Wu DW, Wu TC, Wu JY, Cheng YW, Chen YC, et al. (2014) Phosphorylation of paxillin confers cisplatin resistance in non-small cell lung cancer via activating ERK-mediated Bcl-2 expression. *Oncogene* 33: 4385-4395.
11. Rodriguez G, Gonzalez G, Crombet T, Lage A (2011) Therapeutic vaccination with an EGF-based vaccine in lung cancer: a step in the transition to a chronic disease. *Expert Rev Respir Med* 5: 337-342.