Editorial

FGFR1 as a novel prognostic and predictive biomarker in squamous cell cancers of the lung and the head and neck area

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Abstract: FGFR1 amplification is a genomic aberration recently identified in various types of cancer. Especially squamous cell carcinomas of the lung and the head and neck show this genetic alteration in high frequencies. In these cancers FGFR1 is not only a therapeutic target but does also serve as a biomarker that correlates with parameters of worse outcome. However, since FGFR1 amplification does not always correlate with high protein expression defining the best predictive biomarker for a FGFR1 targeted therapy is of great importance.

Key Words: FGFR1; lung cancer; head and neck cancer; therapeutic target; biomarker

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Lung cancer is the most common type of cancer in the world with over 1.5 million new cases per year. Within this devastating disease, squamous cell carcinomas account for approximately 25% in the group of non-small-cell lung cancers (NSCLC). Smoking is the main cause for lung cancer as 85% of patients were exposed to this risk factor (1).

In the last decades the research focus regarding classification of cancers developed from pure histomorphological features to the inclusion of molecular subtyping of genetic aberrations. This led to new treatment strategies using small molecule inhibitors or specific antibodies in cancers of different organ sites with major advances in tumors of the lung. For example epidermal growth factor receptor (EGFR) inhibitors such as gefitinib and erlotinib (2) and an anaplastic lymphoma kinase (ALK) inhibitor (crizotinib) (3) are already being used for specific lung cancer therapies. However, new treatment options are desperately needed to improve overall survival and life quality of patients.

In 2010 Weiss *et al*. were the first to describe frequent fibroblast growth factor receptor 1 (FGFR1) amplification in squamous cell cancer (SCC) of the lung. The FGFR1 amplification was detected in an unbiased approach using SNP (Single Nucleotide Polymorphisms) arrays on a large cohort of patients with SCC of the lung (n=155) and was validated in an independent cohort (n=153) by fluorescence in-situ hybridization (FISH) with a frequency of 22%. Weiss *et al*. were also able to show growth inhibition of FGFR1 amplified cell lines *in vitro* and *in vivo* using the FGFR inhibitor PD173074 (4). The FGFR1 amplification rate described by Weiss *et al*. for SCC of the lung was confirmed by Dutt *et al*. shortly afterwards (5). In a follow-up study, we detected the occurrence of FGFR1 amplification not only at a similar frequency in primary SCCs of the lung but also in the corresponding regional lymph node metastases of FGFR1 amplified primary tumors, suggesting a clonal event in tumor progression. Our findings provide a rationale for treating patients with advanced disease with FGFR small molecule inhibitors and suggest that biopsy of the metastases would be adequate for determining the FGFR1 status of the primary tumor and vice versa (6). Of interest, Weiss *et al*. and we observed an association between inhalative tobacco consumption and FGFR1 amplification status (4,6).

These studies led to clinical trails using two pan FGFR small molecule inhibitors. BGJ398 is being tested in a phase 1 dose escalation study in patients with advanced solid malignancies harboring either FGFR1 or 2 amplification or FGFR3 mutations (NCT01004224). In contrast, AZD4547 is investigated in a phase 2 clinical trial, assessing the efficacy, safety and tolerability of this inhibitor compared with paclitaxel in patients with advanced gastric or lower-oesophageal cancer, showing a FGFR2 copy number gain (NCT01457846).

In a very recent publication by Kim *et al*., the authors reported on the evaluation of FGFR1 amplification status in a large cohort consisting of 262 clinically annotated East Asian patients, all suffering from squamous cell carcinomas (SCC) of the lung (7). Using FISH, they observed a FGFR1 amplification frequency of 13%, slightly below the frequency described in the aforementioned publications. In contrast to some genetic aberrations that are enriched in distinct ethnical populations, the frequency of FGFR1 amplification seems to be comparable between Western and East Asian Countries. Furthermore, they discovered a significantly shorter disease-free survival and greater risk for relapse in patients with FGFR1 amplified SCC of the lung as compared to non-amplified tumors. Therefore, they claim FGFR1 to be an independent prognostic biomarker in patients with SCC of the lung. In addition, they could confirm the already described association between FGFR1 amplification and smoking status. Interestingly, they showed that non-smokers never displayed a FGFR1 copy number gain whereas the incidence of FGFR1 amplification increased in a smoking dosage dependent manner. In addition, Kim *et al*. found evidence that patients with FGFR1 amplification had a better response to an adjuvant chemotherapy than patients with non-FGFR1 amplified cancer (7).

SCC of the lung and SCC of the head and neck region share risk factors, morphologic features as well as mechanisms of tumorigenesis. Therefore, we analyzed FGFR1 amplification in a well defined cohort of 555 patients with primary and progressed SCC of the head and neck region including all relevant localizations of this region (larynx, hypopharynx, oropharynx, oral cavity) via FISH. We measured an overall amplification frequency of 15%, although this number differed between the respective localizations. In this study, FGFR1 amplification was also strongly associated with inhalative tabacco smoking and parameters of worse outcome (8). Therefore we hypothesize FGFR1 to be a prognostic biomarker not only in SCC of the lung as described by Kim *et al*., but also in SCC of the head and neck region. In a current study, we set out to further elucidate the importance of FGFR1 not only as a prognostic biomarker but also as a target for therapy in patients with SCC of the head and neck region. We characterized SCC cell lines of the head and neck region according to their FGFR1 copy number, mRNA and protein expression status and subsequently tested their sensitivity towards the small molecule FGFR inhibitor BGJ398. We found FGFR1 gene amplification neither correlating with mRNA nor with protein expression. Interestingly, sensitivity to BGJ398 was only observed in those cell lines harboring high protein and mRNA levels (manuscript under review).

In another publication, Freier *et al*. described a FGFR1 amplification frequency of 17.4% in oral SCC (n=92), but could not find an association between FGFR1 copy number and protein overexpression (9). In lung cancer, Pros *et al*. also specified the association between FGFR1 amplification and overexpression as inconclusive (10). In contrast, Kim *et al*. observed a high correlation between FGFR1 amplification by FISH and FGFR1 mRNA levels as well as protein expression by immunohistochemistry in SCC of the lung (7). Thus, we suppose that there is still a need to define the best predictive biomarker to select patients who will profit most from a FGFR1 targeted therapy. As emphasized, this could be gene copy number, mRNA expression as well as protein expression or mutational status of cancers.

Beyond serving as a targetable prognostic biomarker, Kim *et al*. noted FGFR1 amplification in SCC of the lung to be a predictor of sensitivity towards chemotherapy (7). This indicates that certain patients might also benefit from a combined treatment with conventional chemotherapy.

Taken together, the study by Kim *et al*. confirmed and extended the FGFR1 amplification frequency in SCC of the lung to East Asian patients. Furthermore, they demonstrated an association of FGFR1 amplification with smoking habits and provided evidence that this particular genomic aberration is not only a prognostic biomarker but does also have predictive implications on the success of a chemotherapy in lung cancer patients (7).

The success story of the discovery of FGFR1 amplification as a targetable genomic alteration in SCC of the lung and head and neck region and the quick entrance of small molecule FGFR inhibitors into first clinical trials highlights genomic profiling as a promising approach to detect so far unknown aberrations in the genomes of cancer cells. These might not only serve as a predictive

or prognostic marker, but could also be a target in tumor therapy.

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