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Review

Immune checkpoint inhibitors in epidermal growth factor receptor mutant non-small cell lung cancer: Current controversies and future directions

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ABSTRACT

Major advances with the development of epidermal growth factor receptor tyrosine kinase inhibitors and immune check-point inhibitors have ushered in a new era in lung cancer therapy. Whilst pre-clinical studies suggest EGFR-driven NSCLC inhibit antitumor immunity through the activation of the PD-1/PD-L1 pathway, epidemiology studies suggest *EGFR* mutant NSCLC are more likely to have decreased PD-L1 expression. The superiority of single agent PD-1/PD-L1 inhibitors over docetaxel in pre-treated *EGFR* mutant NSCLC appears to be moderated. Several mechanisms for a poor response to immune checkpoint have been proposed including a lower tumor mutation burden, and an uninflamed and immunosuppressive tumor microenvironment. Predictive biomarkers to PD-1/PD-L1 inhibitors sensitivity in patients with *EGFR* mutations are required. The role of EGFR TKI in combination with an immune checkpoint inhibitor is currently being investigated intensively in multiple clinical trials and outcomes from these trials are immature and the optimal sequence, schedule and dosing remains to be determined. A careful evaluation will be required in view of the increased toxicities reported in some of the early studies of combination therapy.

1. Introduction

Over the past decade, multiple significant oncogenic molecular alterations have been identified in lung adenocarcinoma that not only contribute to their tumorigenic potential but also serve as potential targets for therapy. Sensitising somatic mutations of the epidermal growth factor receptor (*EGFR*) gene are seen in about 10% and 50% of Caucasian and East Asian patients with lung adenocarcinoma, respectively [1,2] and lead to constitutive signalling via the PI3 K/AKT and RAS/RAF pathways. The management of patients with advanced *EGFR* mutant non-small cell lung cancer (NSCLC) with EGFR tyrosine kinase inhibitors (TKIs) directed at this oncogenic mutation represents one of the most significant advances in lung cancer management in decades. Multiple phase III studies in patients with advanced NSCLC harbouring *EGFR* mutations have shown significant improvement in objective response rates (ORR) and progression-free survival (PFS) of EGFR TKIs when compared to platinum based chemotherapy [3–9]. However, progression inevitably occurs and novel therapeutic strategies are required.

Intense research is under way to identify approaches to improve the outcomes of patients treated with EGFR TKIs. This has led to the use of combining EGFR TKI with other treatment modalities. An example of this is approach is the combination of EGFR TKI with an anti-angiogenic agent. When erlotinib and bevacizumab are combined together in the first line treatment of *EGFR* mutant NSCLC, PFS is prolonged, but patients experience disease progression by 13.2 [10] to 16 months [11], yet again underlining the necessity to improve the durability of survival from therapy.

Another area of achievement in the treatment of advanced NSCLC has been the use of immune checkpoint inhibitors targeting programmed death receptor-1 (PD-1) and programmed death receptor ligand-1 (PD-L1) [12], with multiple randomised studies showing superior overall survival with immune checkpoint inhibitors compared to second- or third-line docetaxel. More recently, single agent pembrolizumab, a PD-1 inhibitor, was demonstrated to be superior to platinum doublet chemotherapy in the first-line setting in patients with

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tumor PD-L1 overexpression of at least 50% [13]. Separately, trends seen in randomised trials of immune checkpoint inhibitors suggest an association between PD-L1 expression and clinical efficacy. The predictive nature of tumor PD-L1 expression is supported by subgroup findings from the KEYNOTE-010 and CheckMate 057 trials [14,15], and has also been observed in the recent POPLAR and OAK studies, in which patients with higher tumor and immune cell PD-L1 staining appeared to derive greater overall survival benefit from atezolizumab [16,17].

In contrast to the data indicating that sensitising *EGFR* mutations and PD-L1 expression are predictive biomarkers of response to EGFR TKIs and PD-1/PD-L1 blockade respectively, it is intriguing that no consensus has been established regarding the optimal treatment approach for *EGFR* mutant/PD-L1 positive NSCLC patients. Part of the current controversy surrounding the deployment of immune checkpoint inhibitors in *EGFR* mutant NSCLC relates to the circumstantial nature of evidence. Interest in this approach was originally stimulated by a series of preclinical and retrospective studies which suggested an association between activating *EGFR* mutations and PD-L1 upregulation in NSCLC [18–21], thus opening up the possibility that *EGFR*-mutant patients could have heightened sensitivity to anti-PD-1 therapy. Additionally, reports that PD-1 inhibition leads to improved survival in mouse models with *EGFR*-driven adenocarcinomas by enhancing effector T cell function, and reduces the viability of *EGFR* positive NSCLC cells co-cultured with human peripheral blood mononuclear cells [18,19] lent further credibility to this notion.

Here we retrace the roots of these opposing viewpoints and highlight outstanding research questions which are central to the gaps in our knowledge. Furthermore, we consider the opportunities afforded by recent insights into the immunopathology of *EGFR*-mutant NSCLC, focusing in particular on the prospects of immune checkpoint inhibitors in EGFR TKI pre-treated patients and combination strategies.

2. Association between EGFR mutations and PD-l1 expression in NSCLC

In order to better appreciate the current controversies and to envision future directions, it seems apposite to scrutinize the early motivations for targeting the PD-1/PD-L1 axis in *EGFR*-mutated NSCLC. This concept was in part promulgated by retrospective studies which suggested frequent PD-L1 expression in *EGFR*-mutant NSCLC [20–22]. The co-occurrence of PD-L1-positivity and activating *EGFR* mutations in clinical NSCLC specimens was first reported by Azuma and colleagues, who observed an odds ratios (OR) of 25.4 (95% confidence interval (CI): 2.9–47.9) based on a study of 164 surgically resected samples [20]. At least two ensuing publications corroborated this trend, albeit with lower OR estimates of 1.92 (95% CI: 0.95–3.88) [21] and 6.23 (95% CI: 1.90–20.37) [22] and using different PD-L1 IHC assays. For the purpose of this review article, we evaluated the literature (please refer to Supplementary material for the search methodology and Supplementary Fig. 1 on the selection of studies included in the pooled analysis) and conducted a pooled analysis of 3969 patients from 18 studies (Table 1) [20–38]. We found *EGFR* mutant NSCLC was less likely to be PD-L1-positive compared with wildtype *EGFR* mutant tumors with an odds ratio (OR) of 0.59 (95% CI 0.39–0.92, $p < 0.02$) (Fig. 1). It has to be noted one study describing a positive association between *EGFR* mutations and higher PD-L1 expression [20] was excluded from the pooled analysis due to having insufficient data available. It should be highlighted that the PD-L1 assays and antibody clones used in the majority of these studies were different from the companion diagnostics used in phase II–III studies of immune checkpoint inhibitors in advanced NSCLC, thus there are challenges in extrapolating these findings into clinical practice. Two recent pooled analyses have provided further credence of an inverse relationship. In one study, patients harbouring *EGFR* mutations were more likely to have decreased PD-L1 expression (OR 1.79, 95% CI: 1.10–2.93) [39] and in the second, PD-L1 expression was associated with EGFR wild-type status (OR 0.61, 95% CI: 0.42–0.90, P = 0.01) [40].

One reason for these conflicting signals could be the differences in immunohistochemistry (IHC) PD-L1 assays, antibody clones, and interpretive scoring [41] used in the studies. As will be discussed in the succeeding section, cancer cell-intrinsic EGFR signalling can lead to upregulation of PD-L1 expression on tumor cell membranes. Hence, PD-L1 staining that is assessed chiefly on tumor cell expression may appear intensified as compared with IHC platforms which measure PD-L1 staining on both tumor and immune cells. Additionally, results derived from analyses of the TCGA NSCLC cohorts [39,42], wherein PD-L1 expression is quantified in terms of mRNA or protein expression, are unlikely to be compatible with studies which measured PD-L1 expression using IHC methods. Other causes of variability include the assessment of biomarkers from a single lesion site at a single time point which often provides poor insights into spatio-temporal dynamics. For instance, PD-L1 expression has been shown to fluctuate during EGFR blockade and post-progression [18–20,43]. Evidently, these sources of heterogeneity between studies imply that much work remains to validate the associations between *EGFR* mutations and PD-L1 positivity.

3. Biological associations between EGFR signalling and PD-L1 expression

Whilst it is now apparent that the epidemiological relationship between *EGFR* mutations and PD-L1 expression is equivocal or possibly inversely related, other initial impetuses for deploying immune checkpoint blockade in *EGFR* mutant NSCLC relate to the purported biological crosstalk between EGFR signalling and PD-L1 expression (Fig. 2), as well as experimental data indicating that treatment of *EGFR* mutant NSCLC cells (co-cultured with immune cells) or mice with PD-1 inhibitors had significant antiproliferative and antitumor effects [18,19].

There is some evidence to support the notion that PD-L1 is a downstream target of EGFR signalling, and this is interceded via the IL-6/JAK/STAT3 [44], NFκB [45], and *p*-ERK1/2/p-c-Jun [19] pathways (Fig. 2). The biological association is indirectly corroborated by reports of co-occurrence of PD-L1 upregulation in *EGFR*-mutant NSCLC, as was observed in some retrospective cohorts [19–21] but not supported in subsequent pooled analysis discussed earlier (Fig. 1). EGFR TKI has been shown to repress PD-L1 expression [20,45]. In contrast, one study found PD-L1 expression was increased following gefitinib treatment [46].

However, this tumor cell-centric mode of PD-L1 upregulation is contrasted by adaptive immune resistance [47], which is characterized by an increased expression of PD-L1 on neoplastic cells and certain immune cell subsets in response to robust CD8+ T-cell-mediated immunosurveillance. Adaptive PD-L1 upregulation relies on successful immunorecognition, which is enhanced by an increased somatic mutational and neoantigen burden. However, for hitherto unclear reasons, the mutational burden appears to be lower in oncogene- and especially *EGFR*-driven tumors [39,48,49].

From the preceding discussions, one crucial area of enquiry is whether intrinsic PD-L1 overexpression may be a spurious signal generated by oncogenic EGFR signalling, and if adaptive PD-L1 expression may be a better gauge of tumor immunogenicity in *EGFR* mutant NSCLC? If the latter hypothesis is confirmed, then we may surmise that immune cell PD-L1 staining may be a more sensitive biomarker for predicting immunotherapy benefit since EGFR-dependent PD-L1 overexpression may confound assessments based on cancer cell staining alone. Another possible approach for identifying subsets of *EGFR*-mutant tumors that are likely susceptible to immune checkpoint blockade is to assess the density of tumor infiltrating lymphocytes (TILs), because even if a tumor expresses PD-L1, anticancer immunosurveillance is unlikely to be reinstated if a tumor is devoid of cytotoxic T cells [39].