Review Article

Immuno-targeted combinations in oncogene-addicted non-small cell lung cancer

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Abstract: The identification of tumor "oncogenic drivers" and the subsequent development of targeted therapy represented a milestone in the treatment of lung cancer over the last years. Tumor genotyping has been incorporated into therapeutic decision making of advanced non-small cell lung cancer (NSCLC) since has become clear that individuals with actionable molecular alterations receiving a matched targeted agent certainly live longer and better. The recent understanding of biological mechanisms underlying cancer immune evasion has allowed the development of a new class of immunomodulatory agents which are able to reactivate host immune-response, offering the potential for long-term disease control and survival in a significant subgroup of lung cancer patients. The complementary therapeutic effects of these two different approaches suggested intriguing potential for therapeutic synergy with combination strategies. Indeed, immunotherapy could consolidate the dramatic but transient tumor responses achieved with targeted therapy into long-term survival benefit, due to the induction of specific anti-tumor memory. However, the great emphasis and expectations linked to immune-targeted combinations have been mostly disappointed by the initial controversial results of early-phase trials, raising relevant concerns about the use of these combinations for lung cancer treatment. This review briefly summarizes the basis of immunogenicity and immune escape in oncogene addicted NSCLC, providing an updated overview of clinical trials, with the final aim of defining the current unmet needs of immuno-targeted combinations in clinical practice.

Keywords: Targeted therapy; immunotherapy; combinations; oncogene drivers; non-small cell lung cancer (NSCLC)

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Introduction

The identification of molecular networks underlying tumor cell growth and proliferation marked a new era in the treatment of lung cancer. Tumor genotyping has been incorporated into therapeutic decision making of advanced non-small cell lung cancer (NSCLC) (1), since has become clear that individuals with actionable molecular alterations receiving a matched targeted agent certainly live longer and better (2,3). The impressive tumor response and clinical benefit observed with tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor *(EGFR)* (4-6) and anaplastic lymphoma kinase *(ALK)* (7-9) generated growing emphasis on personalized treatment leading to increasing inclusion of molecular biomarkers in clinical trials. Beyond *EGFR* and *ALK*, new tailored drugs effectively targeting both *ROS-1* rearrangements and *BRAF* mutations have been recently approved for clinical use, with

several other molecules under different stages of clinical development. The College of American Pathologists (CAP) and the International Association for the Study of Lung Cancer (IASLC) updated recommendations in 2018 include upfront testing for *EGFR*, *ALK*, and *ROS-1* mutations in all patients with advanced non-squamous NSCLC (10). Routine testing for *BRAF*, *RET*, *HER2*, *KRAS*, and *MET* genes by using multiplex gene panels is recommended as part of a broader testing panel or if *EGFR*, *ALK*, and *ROS-1* testing are negative (11), with the final goal of identifying rare molecular drivers for which effective drugs may be available in the context of clinical trials. The application of precision medicine is leading to a significant improvement of life expectancy in a subset of patients with advanced NSCLC. However intra-tumor heterogeneity and acquired resistance are well-known biological phenomena which might significantly impact sensitivity to specific molecular targeted agents. A deeper understanding of the immune landscape of tumors and immune-evasion process has recently led to breakthrough therapeutic advances for patients with advanced NSCLC. Although the great benefit observed with PD-1/PD-L1 inhibitors regardless of tumor subtype and PD-L1 expression status (12-15), randomized studies suggested lack of efficacy for single agent checkpoint inhibitors in patients with oncogene-addiction (16), thus creating a platform for alternative approaches including combination strategies. The addition of pembrolizumab to standard first-line platinum-chemotherapy resulted in a significant survival benefit for patients with EGFR/ALK wild-type NSCLC (17), while patients with high tumor mutation burden (TMB) seem to derive most benefit from PD-1 plus CTLA-4 checkpoint inhibitors combinations (18). The analysis of available evidence suggested that targeted therapy and immunotherapy have different therapeutic effects with potential complementary and synergistic role in cancer treatment. It's known that targeted therapy is able to induce dramatic tumor response, thus favouring the release of large amounts of antigens upon tumor cell death. Furthermore it may directly enhance the immune response by modulating activation, effector function, and differentiation of specific subsets of immune cells (19,20). As result of this complex and multifactorial interactions, immunotherapy could consolidate the transient tumor responses achieved with targeted therapy into long-term survival benefit, due to the generation of potent anti-tumor memory. This review briefly summarizes the basis of immunogenicity and immune escape in oncogene addicted NSCLC, providing an updated overview of clinical trials, with the final aim of defining the current unmet needs of immuno-targeted combinations in clinical practice.

EGFR-mutations

The biological background supporting the use of checkpoint inhibitors in *EGFR*-mutant NSCLC come from pre-clinical studies showing that EGFR oncogenic signaling could directly induce PD-L1 expression in lung cancer cell lines, thus enhancing sensitivity to PD-1 blockade in pre-clinical models (21,22). However the very low rate of tumor infiltrating lymphocytes (TILs) along with the low TMB and consequent reduced number of "neo-antigens" featuring *EGFR*-mutated tumors , makes the chances that immunotherapy could trigger an effective immune response rather negligible (23,24). In addition to that, *EGFR*-mutant NSCLC displayed significant myeloid cell recruitment, while failed to activate a CD8+ immune response (25). Gainor *et al.* showed that high tumor PD-L1 expression and TILs rate were simultaneously detected only in 1/57 TKI-naïve and 5/57 TKI-resistant *EGFR*-mutated NSCLC patients with objective response rate (ORR) around 3% (26), suggesting that very few, highly selected patients could gain benefit from immunotherapy. In line with these evidences subgroup analysis of randomized studies included in a recent meta-analysis (16), showed no survival benefit with checkpoint inhibitors in EGFR mutated subset. These data were confirmed in the real-word setting of the Italian expanded access program (EAP), showing ORR of 9% and median OS of 8.3 months in about 150 pre-treated patients with advanced NSCLC harboring EGFR-activating mutations (27). ATLANTIC represented the first prospective trial investigating activity and safety of the PD-L1 inhibitor durvalumab in a cohort of oncogene addicted, pre-treated NSCLC patients. Consistently with previous results the activity of durvalumab was modest in the overall population, with 4% and 12% ORR observed in patients with low and high tumor PD-L1 expression, respectively (28). Considering that EGFR-TKI downregulate PD-L1 expression in a lab setting, clinical studies explored immunotherapy activity also in TKI-naïve, PD-L1 positive, *EGFR*-mutant NSCLC patients. Modest but encouraging activity was initially observed with atezolizumab in the phase II BIRCH study (29), while pembrolizumab has recently shown lack of efficacy in this setting (30), regardless of tumor PD-L1 expression levels, suggesting that single agent PD-1/PD-L1 inhibitor should not be considered as an appropriate treatment. Since the

majority of patients with *EGFR*-mutant NSCLC do not respond to PD-1 blockade, the development of immune-based combinations remains a crucial unmet need. Pre-clinical studies showed that combination of EGFR-TKIs and PD-1 inhibitors did not induce synergistic tumor cell killing effects in co-culture systems, suggesting that targeting both molecular pathways may have similar but not additional effects on PD-1 mediated antitumor immune response (22). Despite this evidence early clinical trials investigated activity and safety of checkpoint inhibitors and EGFR-TKIs combinations in *EGFR*-mutant NSCLC and for some of them preliminary results have been recently reported. Nivolumab was combined with erlotinib in a cohort of 20 patients with chemotherapy-naïve, TKI-resistant, *EGFR*-mutant advanced NSCLC included in the multi-arm phase I CheckMate 012 study, showing ORR: 15%, 2-year PFS rate: 48%, grade 3 adverse events (AEs): 25%, with no grade 4 toxicities. The combination of erlotinib and atezolizumab reached 75% ORR, with 9.7 months of response duration and about 40% grade 3–4 AEs, in a phase Ib study including 20 TKI-naïve *EGFR*-mutant NSCLC patients (31). Similar activity and safety profiles were observed in 10 TKI-naïve *EGFR*-mutant NSCLC patients included in a phase I trial of durvalumab plus gefitinib, showing ORR: 78% and any grade AEs: 80%, with no reported grade 3–4 AEs leading to treatment discontinuation (32). Finally the phase Ib multi-arm TATTON trial investigated durvalumab and osimertinib combination in both TKI naïve and pre-treated NSCLC patients. Despite encouraging activity with combination reaching an ORR nearly to 70%, recruitment was early stopped because of high incidence of grade 3–4 AEs and pulmonary toxicity, with interstitial lung disease occurring in 26% of EGFR TKI-pretreated and 64% of EGFR TKI-naïve patients (33). These studies overall suggested that the addition of checkpoint inhibitors to EGFR-TKI do not significantly enhance clinical activity observed with TKI alone, confirming data emerging from pre-clinical models. Furthermore, the high incidence of severe AEs and pulmonary toxicities raise relevant concerns about the use of this kind of combinations in clinical practice.

ALK-rearrangements

Patients with ALK-rearranged NSCLC have higher frequency of tumor PD-L1 overexpression as compared to EGFR or *KRAS*-mutant disease (25,34). *ALK* rearrangements upregulated PD-L1 expression by activating PI3K-AKT and MEK-ERK signaling pathways in NSCLC cell lines (35). However, the very low rate of associated TILs along with the lack of an inflammatory microenvironment limited the efficacy of immunotherapy in this tumor subset. Gainor *et al.* showed that tumor PD-L1 overexpression and high TILs rate were simultaneously detected in none of *ALK*-rearranged NSCLC patients, with objective response to PD-1 inhibitors of 3.6% as compared to 23.3% reported in those with wild type/unknown EGFR/ALK status (26). In line with these retrospective evidences the preliminary results of the phase II prospective ATLANTIC trial showed no clinical responses to durvalumab in a small cohort of 15 patients with pre-treated *ALK*-rearranged NSCLC (28). Pre-clinical studies showed that ALK targeted inhibition promoted T-cells interactions with monocytes and tumor cells, enhanced T-cell proliferation as well as cytokine production, and increased T-cell tumor infiltration (36,37), providing biological rationale for combination strategies. The CheckMate 370 phase 1/2 study investigated activity and tolerability of crizotinib plus nivolumab in patients with previously untreated, *ALK*-rearranged advanced NSCLC. Similarly to TATTON trial, recruitment was early stopped due to the occurrence of severe hepatic toxicities leading to treatment discontinuation in 5/13 (38%) of patients (38). Likewise, combination of ceritinib and nivolumab was associated with high rate of AEs (83%), in a cohort of ALK-positive NSCLC patients, leading to protocol amendment to address observed toxicities (39). The JAVELIN Lung 101 is a phase 1b/2 dose finding trial evaluating two different combinations: crizotinib plus avelumab in 12 pre-treated patients with ALK-negative advanced NSCLC, and lorlatinib plus avelumab in 28 patients with *ALK*-rearranged NSCLC (40). The preliminary results of this trial revealed that crizotinib plus avelumab was not well tolerated due to the high incidence of dose limiting toxicities (DLT), leading to discontinuation of this combination regimen. Conversely lorlatinib plus avelumab showed manageable safety profile (no DLT observed) along with great antitumor activity (ORR: 46.4%), in a heavily pre-treated population with *ALK*-rearranged NSCLC, ensuring further development in clinical trials. Similarly alectinib plus atezolizumab also showed an acceptable tolerability profile with no DLT and grade 4–5 AEs in TKI-naïve patients with ALK-positive disease. Early efficacy data were also very promising with ORR of 85% and median duration of response of 20.3 months (41). However additional follow-up is needed to confirm the potential survival benefit of these combinations including checkpoint inhibitors and second/

third generation ALK-TKIs in these molecular selected NSCLC patients.

KRAS mutations

KRAS represents the most common oncogene driver detected in about 30% of non-squamous NSCLC (42) with no effective targeted therapy available yet for clinical use. Pre-clinical and clinical evidences suggested that *KRAS*-mutant tumors are characterized by high PD-L1 expression and the presence of CD8+ TILs (43). Beyond PD-L1, the cross-talk between cancer cells intrinsic RAS signaling and tumor microenvironment has different other potential immune-modulating effects, including regulation of immune T-cells and myeloid cells density, cancer associated fibroblasts and endothelial cells properties, and extra-cellular matrix (ECM) composition, with significant impact on tumor immune-escape, growth and metastatic process (44). Clinical trials and recent meta-analysis showed a greater benefit of PD-1 inhibitors in *KRAS*-mutant subgroups, however lack of significant difference precluded any definitive conclusion (45). More recently has become clear that *KRAS*-mutant NSCLC is a heterogeneous disease, with patients harboring simultaneous *KRAS/P53* mutations deriving the greatest and durable benefit from PD-1 blockade, because of the high PD-L1 expression, CD8+ T-cells and TMB associated with this molecular subtype (46). Conversely co-occurring inactivation of *LKB1* was associated with lack of tumor response and survival benefit in patients with *KRAS*-mutant lung adenocarcinoma, likely due to the low PD-L1 expression and paucity of infiltrating CD8+ TILs, suggesting *LKB1*-loss as a genomic biomarker of innate resistance to PD-1 blockade (47). The molecular subtyping of *KRAS*-mutant NSCLC supports the development of immuno-targeted combinations strategies which require further investigation in prospective clinical trials including larger cohorts of patients.

BRAF mutations

Recent evidences revealed that v-Raf murine sarcoma viral oncogene homolog B (BRAF)-mutant NSCLC is characterized by high tumor PD-L1 expression, low TMB and microsatellite-stable status (48), thus questioning the efficacy of immunotherapy in this subgroup of patients. Since none of randomized trials with checkpoint inhibitors reported survival outcomes in this specific subset, preliminary data emerging from retrospective series revealed that immunotherapy has a favorable clinical activity with ORR of 28% and median PFS of 3.9 months, which is comparable to that observed in the unselected population (48). These data have been recently confirmed by a retrospective multicenter study including patients with advanced NSCLC harboring different genomic alterations, showing ORR of 24%, PFS: 2.9 months, and OS: 17.2 months for *BRAF*-mutant subgroup (49). Immunotherapy activity observed in BRAF-mutant NSCLC was somewhat higher than that observed in other specific molecular subtypes, with no significant association to the tumor PD-L1 expression status. An extensive immunogenomic analysis of more than 9,000 tumors showed that *BRAF* mutations are correlated with high leucocyte levels across 33 different cancer types analyzed by The Cancer Genome Atlas (TCGA) (50). Furthermore, both *RAS* and *BRAF* V600 mutations are among the most frequently predicted neoantigens in cancer and could thus be directly steering immune response (51). The PanCancer Atlas analysis has recently revealed the complex relationship between molecular signaling and immune-cell composition of tumor microenvironment. These data revealed that BRAF-driven cancers are associated with an inflammatory immune subtype and are characterized by higher CD8+ TILs than NRAS-driven tumors, identifying a signaling loop where simultaneous targeting of BRAF and PD-L1 might have synergistic effects (50). Taken together these evidences support the design of prospective clinical trials of immuno-targeted combinations in *BRAF*-mutant advanced NSCLC.

MET alterations

MET-driven NSCLC include both high-level MET amplification and *MET* exon 14 skipping mutations (METex14), overall accounting for 3–7% of this molecular subtype (3). Pre-clinical studies showed that MET-positive lung cancer cell lines were characterized by high PD-L1-expression levels regardless from the IFNγ-mediated pathway. However the oncogenic activation of MET signaling induced an immunosuppressive tumor microenvironment through the transcriptional control of immunosuppressive molecules (i.e., *PDCD1LG2*, *SOCS1*) and pro-angiogenic factors *(VEGFA* and *NRP1*) (52). Although PD-L1 expression ≥50% has been detected in about half of patients with advanced NSCLC harboring *MET* exon 14 skipping mutations, clinical responses to immunotherapy were generally poor, with ORR of 13% in the overall population and 30% in selected patients with

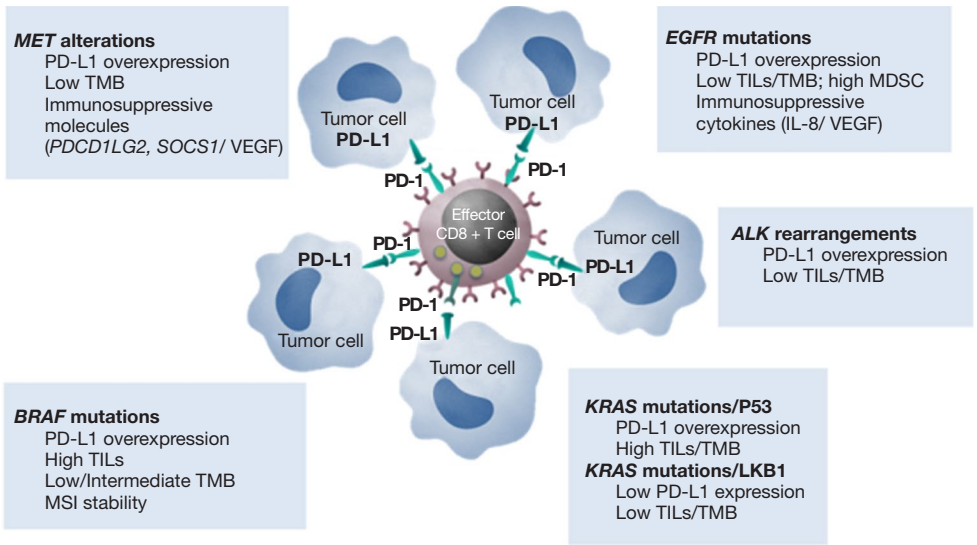

Figure 1 The biological background underlying immuno-targeted combinations in oncogene addicted non-small cell lung cancer.

high PD-L1 levels (53). The lack of efficacy observed in this subset of patients could be partially ascribed to the low TMB found in the majority of METex14-positive tumor samples analyzed within large retrospective series. Interestingly the average TMB observed in patients with METex14-driven NSCLC was 6.9 mutations per MB, thus significantly lower than 10.7 mutations per MB reported for all lung cancer cases (54) but somewhat higher than the average of 4.5 and 2.8 mutations per MB, respectively observed with *EGFR*-mutated and *ALK*-rearranged NSCLC patients (23). Conversely high MET expression, defined as MET IHC 3+ or MET H-Score in the upper quartile, was associated with favorable survival outcomes in patients with advanced NSCLC receiving checkpoint-inhibitors, regardless of smoking history, PD-L1 expression or *KRAS* mutations (55). Overall these data suggest that MET-driven NSCLC is a heterogeneous disease with different tumor biology, supporting the development of biomarker driven combination strategies.

Rare oncogenic drivers

The evidence regarding immunotherapy efficacy in advanced NSCLC patients with rare oncogene drivers, including c-Ros oncogene 1 (ROS1), erythroblastic leukemia viral oncogene homolog 2 (Her2), "rearranged during transfection" proto-oncogene (RET), and neurotrophic tyrosine kinase receptor (NTRK) is very limited. Preliminary results of retrospective studies have recently shown very low activity of single agent PD-1 inhibitors in a limited cohort of pre-treated NSCLC patients harboring Her2 alterations and *RET* rearrangements, with an ORR of 6–7% and a median PFS: 2.1–2.4 months in both oncogene addicted cohorts (49). NSCLC harboring rare oncogenic drivers is usually characterized by never-smoking status and low TMB, however future analysis is needed to further clarify the role of immuno-targeted combinations in these NSCLC subtypes.

Conclusions

The recent sequencing of human genome revealed that lung cancer is the product of dynamic molecular networks, including complex cross-talk between cancer cells intrinsic molecular pathways and tumour microenvironment with significant impact on immunomodulating process. The majority of lung cancer immunotherapies act to re-invigorate pre-existing immunity that has been suppressed in the tumor microenvironment by therapeutic blocking of immune-checkpoints PD-1/PD-L1, providing a relatively anti-tumor-specific immune response. Pre-clinical studies indicated that oncogenic signaling may directly induce PD-L1 expression in lung cancer models providing biological rational to combine different treatment modalities such as targeted therapy and immunotherapy in oncogene addicted NSCLC (*Figure 1*). The complementary therapeutic effects of these two different approaches suggested intriguing potential for therapeutic synergy with combination strategies. However, the great emphasis and expectations

linked to immune-targeted combinations have been mostly disappointed by preliminary results emerging from early-phase trials. The addition of checkpoint inhibitors to both first and third generation EGFR-TKIs showed to not significantly enhance clinical activity observed with EGFR-TKI alone in TKI naïve and pre-treated NSCLC patients, at cost of unexpected high incidence of AEs, resulting in the limitation of further active investigation. In line with pre-clinical evidence these data suggest that targeting both molecular pathways may have similar but not additional/synergistic effects on PD-1 mediated antitumor immune response, raising critical concerns about clinical development of such combination. Similarly phase 1/2 clinical studies in ALK-positive NSCLC showed that combining PD-1/PD-L1 inhibitors with first-generation ALK-TKI was not well tolerated. Conversely the addition of PD-L1 blockers to second-third generation TKIs has recently shown manageable safety profile along with great antitumor activity, ensuring further investigation in larger clinical trials. The clinical evaluation of immunotherapy activity in NSCLC harboring oncogenic drivers other than EGFR and ALK has primarily involved single agent PD-1/PD-L1 inhibitors. The few available evidences emerging from subgroup analysis and retrospective series overall suggested that oncogene addicted NSCLC should be considered a heterogeneous disease with different immunological background and clinical response to immunotherapy according to the specific molecular subtype. Tumors with both *KRAS/P53* and *BRAF* mutations seem to derive major benefit from immunotherapy as compared to LKB1, cMET, HER2 or RET-driven disease. However, these data are still immature and additional long-term follow-up are warranted. Unfortunately, the low prevalence of oncogenic events in advanced NSCLC limits the possibility to address this question in a prospective manner, making the design of clinical trials a real challenge. Other opened questions to be addressed in the near future include timing, dosage, and sequence of combined treatments, in order to optimize the balance between overall anti-tumor effects and toxicity profiles. A deeper understanding of the complex interplay between oncogenic tumor cell signaling, immune cells and tumor microenvironment, identification of reliable predictive biomarkers of response, and characterization of the immune-modulating effects induced by targeted inhibition, will likely help to determine the best ways to combine targeted agents and immunotherapy in the treatment of oncogene addicted NSCLC patients. Technological and computational innovations will be instrumental to overcome existing challenges and to develop a comprehensive model integrating all these parameters to accurately predict patients' response and tolerability to immuno-targeted combinations.

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