Review Article

Molecular landscape of non-squamous, non-small cell carcinoma of the lung

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Abstract: The treatment of advanced or metastatic non-small cell lung cancer (NSCLC) has undergone a major change over the past decade, from a single option of platinum-based systemic chemotherapy to an increasingly personalized approach to treatment based on specific molecular alterations within tumors. The scope of this paper is to review the literature on the treatment of non-squamous NSCLC and give a broad understanding of the current molecular targets for which therapies currently exist, as well as other targets for which therapies may soon be developed. Additionally, issues of resistance with targeted therapies will be discussed. This manuscript only summarizes the work done to date, and in no way is meant to be comprehensive.

Keywords: Non-small cell lung cancer (NSCLC); molecular; adenocarcinoma; lung; cancer

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Introduction

Lung cancer is the leading cause of cancer related mortality in the United States, with an estimated 200,000 new cases and 160,000 deaths annually (1). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers (2) and is further subtyped into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Over the past decade it has become clear that subsets of NSCLC can be further subdivided based on the driver mutations occurring in multiple oncogenes including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), kirsten rat sarcoma viral oncogene homolog (KRAS), ros oncogene 1 (ROS1), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), human epidermal growth factor receptor 2 (HER2)/NEU, Ret proto-oncogene (RET), MAPK/Erk kinase (MEK), and C-mesenchymal-epidermal transition (C-MET)/recepteur d'origine nantais (RON). Targeting therapy toward these specific genetic alterations is becoming the standard for NSCLC treatment.

This review aims to provide an overview on the genetic alternations most often seen in non-squamous NSCLC and treatments aimed at targeting these alterations. We also examine some of the mechanisms of resistance to these therapies and ways of overcoming resistance to further improve overall survival rates in these patients.

Epidermal growth factor receptor (EGFR)

EGFR is a receptor tyrosine kinase involved in cellular differentiation, proliferation, angiogenesis and apoptosis. It is estimated that 10% of NSCLC patients in the United States with NSCLC and 35% in East Asia have tumors with EGFR mutations (3,4), making this receptor an important molecular target for disease treatment. The classic activating mutations including exon 19 deletions and exon 21 L858R substitution account for approximately 45% and 40% of all EGFR mutations respectively (5). Many large studies have emerged in the last few years validating the clinical use of EGFR tyrosine kinase inhibitors (TKIs) over chemotherapy as first line treatment for NSCLC patients harboring EGFR mutations (3,4,6). These therapies initially included first line EGFR TKIs gefitinib and erlotinib, both of which work by reversibly binding and blocking the ATP binding site of EGFR's tyrosine kinase domain preventing

homodimer formation and subsequent activation of the signaling cascade (4,6-8).

The combination of first generation TKIs and standard chemotherapy regimens have historically not shown to have any significant benefit in patients not selected for EGFR mutations (9-12). The FASTACT 2 study, which used an intercalated approach combining intermittent dosing of chemotherapy with EGFR tyrosine kinase inhibition demonstrated encouraging progression free survival and overall survival specifically when selected for EGFR mutated NSCLC (13). This trial however, did not compare results with single agent EGFR TKI's which are now standard of care for EGFR mutation positive tumors and are less toxic to the patient than combination therapy (14).

Initial responses to EGFR-TKIs are favorable, however, most patients will go on to become resistant to these treatments within 1-2 years. There are many mechanisms of resistance, the most common of which is the acquired mutation T790M, which occurs in approximately 50% of patients (15,16). The T790M mechanism of resistance prevents drug binding to the domain through steric hindrance. Other resistance mechanisms to TKIs include transformation to small cell carcinoma, emergence of HER2 amplification, and MET overexpression (17).

Afatanib is a second generation TKI that acts as an irreversible EGFR inhibitor. Phase III trials including the Lux-3 and Lux-6 studies showed a progression free survival benefit when compared with standard chemotherapy in patients with EGFR mutated tumors (18,19). A joint analysis of both trials showed that the median overall survival was not significantly increased for patients given afatanib as compared with chemotherapy. However, when the combined trial data were analyzed based upon the specific mutation present, a statistically significant benefit was observed in both overall and progression-free survival in patients with exon 19 deletions. In patients with the L858R mutation there was a significant benefit in progression-free, but not overall survival (20). The currently ongoing Lux-7 trial is a phase IIb trial comparing afatinib to gefitinib as first line treatment in patients with documented EGFR mutations (NCT01466660).

Third generation TKIs like AZD9291 and rociletinib (CO1686) have emerged as potential therapeutics in tumors harboring acquired T790M resistance mutations (21). A recently published phase I/II clinical trial evaluating patients with acquired resistance to EGFR TKI's showed favorable results with AZD9291 (22). Multiple ongoing phase III trials are examining AZD9291 compared to standard chemotherapy regimens (NCT02296125, NCT02474355). Further clinical trials under investigation are examining AZD929 in combination with novel immunotherapeutic agents such as MED 4736, a PD-L1 antibody (NCT02143466, NCT02454933). In a recently published phase I/II clinical trial Rociletinib showed favorable results in patients who progressed on previous TKI therapy (23). More data on the use of rociletinib will be examined in the ongoing phase 3 TIGER-3 study, which aims to examine Rociletinib versus single agent chemo in patients who have failed at least one previous TKI and platinum doublet chemotherapy (NCT02322281).

The N-methyl-N'-nitrosoguanidine human osteosarcoma transforming gene (*MET*) receptor kinase is involved in tumor-cell proliferation, mobilization and angiogenesis. Overexpression, amplification or aberrant signaling of the *MET* receptor tyrosine kinase has been implicated as a mechanism of erlotinib resistance in tumors with EGFR- activating mutations (24-26). MET activation increases the expression of some EGFR ligands and coactivation of EGFR and MET has been described to result in resistance (27). Small molecule inhibitors of MET have not yet demonstrated much therapeutic success. ARQ197 (Tivantinib) is a selective small molecule that inhibits MET receptor tyrosine kinase causing inhibition of cell proliferation and induction of cellular apoptosis, and has been studied in combination with EGFR TKIs. The recent phase III MARQUEE trial comparing erlotinib with or without tivatinib showed increased progression free survival but did not improve overall survival in nonsquamous NSCLC patients treated with the combination (28). The similar phase III ATTENTION trial was terminated early due to increased incidence of interstitial lung disease in the ARQ197 group (29). There is encouraging data for the role of MET inhibition using monoclonal antibodies against MET. Onartuzumab, a monoclonal antibody against the MET receptor has been shown in a recent phase II trial to increase progression free survival and overall survival in MET+ patients when combined with EGFR TKIs (30). This is being further investigated in an ongoing phase phase III trial evaluating onartuzumab in combination with erlotinib in patients With MET-Positive, EGFR mutant NSCLC (NCT01887886).

Improving progression free survival in EGFR mutated NSCLC tumors by employing synergy with other small molecules (such as VEGF inhibitors) is another goal of many ongoing trials. Although a recent phase III clinical trial showed no benefit of bevacizumab plus erlotinib

versus erlotinib alone after failure of standard first-line chemotherapy in an unselected group of non-squamous NSCLC patients (31), further data suggests that there may be a survival benefit in patients with tumors specifically known to harbor EGFR driver mutations (32). Further clinical trials evaluating small molecules such as VEGF inhibitors or immune therapy with EGFR inhibitors are ongoing [NCT01532089 (VEGF), NCT01998126 (CTLA-4), and NCT02013219 (PDL1)].

Anaplastic lymphoma kinase (ALK)

It is estimated that 3-5% of patients with NSCLC harbor a fusion mutation involving ALK. The most common variant contains an inversion in chromosome 2 that juxtaposes the 5' end of the echinoderm microtubule-associated protein-like 4 (*EML4*) gene with the 3' end of the anaplastic lymphoma kinase (*ALK*) gene, resulting in the novel fusion oncogene *EML4-ALK* (33). Patients with ALK-rearrangements tend to be young, never or former light smokers, and most likely to have tumors of the adenocarcinoma histologic subtype (34).

Crizotinib is an orally available ALK/MET/ROS1 TKI. The phase III PROFILE 1007 study compared crizotinib with chemotherapy as second-line therapy in ALK^+ patients. Findings demonstrated an increase in progression free survival in the experimental arm but no significant increase in overall survival (35). Similar results were seen in the phase III PROFILE 1014 study comparing crizotinib with chemotherapy in patients with ALK-arranged NSCLC who had not received prior systemic treatment. Progression free survival was prolonged in the experimental group but no significant difference was seen in overall survival in the interim analysis. Interpretation of overall survival is complicated by exposure of the patients assigned to the control arm to crizotinib during follow-up (36). To investigate this treatment option further, an ongoing study is evaluating pemetrexed with or without crizotinib for patients with advanced ALK-rearranged NSCLC that has progressed after treatment with crizotinib alone (NCT02134912).

Resistance to Crizotinib inevitably occurs within the first few years of treatment. Resistance mechanisms identified include an acquired secondary mutation within the ALK tyrosine kinase domain, most common being the gatekeeper L1196M mutation, followed by the G1269A mutation (37,38). Other resistance mechanisms include amplification of the ALK fusion gene, which is observed in about 9% of crizotinib-resistant cases (39), and a number of so-called "bypass signaling pathways" involving abnormal functioning of epidermal growth factor receptor (EGFR), KIT, and insulin-like growth factor-1 receptor (IGF1R) pathways (40-42).

Patients with ALK translocated tumors often relapse in the CNS, which is a challenge for patients who progress while receiving crizotinib (43). Relapse is common in the CNS as it acts as a sanctuary site for metastasis given the inability of most chemotherapeutic agents to cross the blood brain barrier. Ceritinib (a second generation ALK inhibitor discussed below), has blood-brain barrier penetration in preclinical studies and showed intracranial activity in the ASCEND-1 trial (44).

Certinib is a second generation ALK inhibitor that was recently approved based on a single-arm clinical trial which demonstrated durable improvement in overall response rates in patients who have failed crizotinib. It is currently undergoing phase III trials to explore the antitumor activity of this novel agent compared to reference chemotherapy in previously untreated ALK-positive, stage IIIB or IV, nonsquamous NSCLC (NCT01828099). A second study will evaluate the antitumor activity of certinib compared to chemotherapy in patients previously treated with chemotherapy (platinum doublet) and crizotinib (NCT01828112). Other second-generation ALK inhibitors in development include Alectinib, which has demonstrated an increased survival benefit in phase II studies. This drug is currently undergoing phase III trials evaluating alectinib vs. crizotinib in treatment-naive ALK-positive advanced NSCLC (NCT02075840), as well as alectinib alone in patients after disease progression on or intolerance to prior ALK TKI therapy (NCT02271139). Additionally, phase II studies are currently underway for 2^{nd} generation TKI inhibitors brigatinib (AP26113) (NCT02094573), and PF-06463922 (NCT01970865). X-396 is a potent ALK inhibitor with a similar chemical structure to that of crizotinib, but with a 10-fold higher potency and is currently being studied in a phase I trial (NCT01625234).

Potential Therapeutic Strategies to overcome ALK TKI Resistance include the addition of heat shock protein 90 (HSP90) inhibitors. ALK fusion proteins bind to HSP90 and are thought to depend on HSP90 as a chaperone protein to form tertiary structure and stabilize the protein. A number of ongoing trials are currently testing safety and efficacy of HSP90 inhibitors in addition to ALK inhibitors. (NCT01752400, NCT01712217).

Early data suggest checkpoint inhibitor immunotherapy

with EGFR inhibitors may improve response and survival by matching the cancer's ability to mutate and evolve, thus increasing the potential for durable response (17). These data appears to be similar with ALK translocated tumors hence there is current interest in adding checkpoint inhibitors in ALK-rearranged NSCLC patients. A current phase I study using nivolumab [an antibody which functions as a programmed cell death receptor/ligand programmed death receptor (PD1)/programmed cell death ligand (PDL1) checkpoint inhibitor] in addition to ceritinib is currently ongoing (NCT02393625). Alectinib is being evaluated with PDL-1 inhibitors in patients with tumors that are ALK translocated and treatment naïve [NCT02013219].

Kirsten rat sarcoma viral oncogene homolog (KRAS)

KRAS mutations are found predominately in the adenocarcinoma histologic subtype of NSCLC (30%) and less frequently in the squamous cell carcinoma subtype (approximately 5%) (45). Most often, these mutations are found in patients with a smoking history (46,47). Mutations in KRAS are typically mutually exclusive with aberrations of other oncogenic drivers including EGFR, BRAF, HER2 mutations and ALK and ROS1 rearrangements (15). KRAS mutations in NSCLC predominantly occur in codons 12 or 13 and with a lower frequency in codon 6 (48). Mutant Ras proteins are insensitive to GTPase activating protein (GAP), rendering the proteins constitutively GTP bound and activated, leading to stimulus-independent, persistent activation of RAS downstream effectors, in particular, the Raf (Rapidly Accelerated Fibrosarcoma)-MAPK (Mitogen-activated Protein Kinase)-ERK (Extracellular signal regulated kinases) cascade (49).

The prognostic and predictive role of KRAS mutations remains controversial. These mutations have not shown to be predictive for the use of adjuvant chemotherapy (50). In metastatic NSCLC KRAS mutations did not predict response to standard chemotherapy (51,52). KRAS mutations also seem to negatively predict response to EGFR TKIs (53-55).

At present there is no established therapy for patients with KRAS mutations. No direct inhibitor of KRAS exists, but targets downstream of KRAS, such as the MEK pathway have shown some encouraging results (56). The MEK1/2 inhibitor selumetinib has shown some promising activity in a recent phase II clinical trial comparing selumetinib versus standard chemotherapy in previously treated KRAS mutant NSCLC patients (57). Currently, a phase III trial with selumetinib is ongoing (SELECT-1, NCT01933932).

Trametinib is another inhibitor of MEK, which has not shown to improve survival outcomes of KRAS mutant patients in a phase II trial when compared to standard chemotherapy as a second line therapy (58). Positive response rates have been noted in clinical trials evaluating at Trametinib plus docetaxel or pemtrexed (59,60), but further investigation is required. Inhibition of other downstream signaling pathways such as PI3K and focal adhesion kinase (FAK), have shown benefit in KRAS positive tumors (61,62) and multiple clinical trials with FAK inhibitors (defactinib/VS-6063) and PI3K inihibitors (BKM120) are ongoing.

Ros oncogene-1 (ROS-1) translocation

The C-ros oncogene 1 (ROS1) is a receptor tyrosine kinase of the insulin receptor family that that acts as a driver oncogene via a genetic translocation between ROS1 and a number of other genes, most commonly CD74 (63). This translocation is seen in only 1 to 2 percent of NSCLC typically in younger non-smoking patients (63-65). Crizotinib, a potent inhibitor of ALK and MET has also shown activity against ROS1-rearranged NSCLC likely due to a high degree of homology between the ALK and ROS tyrosine kinase domains (66). The PROFILE 1001 phase I trial showed favorable response rates in patients with ROS1 tumors treated with crizotinib (67). Phase II trials evaluating crizotinib in pre-treated patients with ROS1 mutations is ongoing NCT02499614. Other agents are currently being investigated for ROS1-positive lung cancer patients including foretinib, ceritinib, AP26113, PF-06463922 as well as HSP90 inhibitors (68).

Resistance to crizotinib in ROS1 mutated tumors is known to occur. It has been shown that in patients harboring CD74-ROS1 fusions, resistance to crizotinib was partly mediated by the ROS1 G2032R mutation (69). Other possible mechanisms of resistance include EGFR pathway activation, epithelial-to-mesenchymal transition, and various ROS1 tyrosine kinase mutations (65,70). A number of novel TKIs with activity against ROS1 are being investigated including AP26113, Foretinib, and PF-06463922 (71-73), (NCT01970865).

BRAF

BRAF (v-Raf murine sarcoma viral oncogene homolog B) is a downstream signaling mediator of KRAS, which

activates the MAP kinase pathway. BRAF mutations have been observed in 1 to 3 percent of NSCLC. Of NSCLC patients harboring BRAF mutations ~50% contain the classical V600E mutation (74), seen commonly in metastatic melanoma. BRAF V600E mutations are associated with light/never smoker status, micropapillary histology and occur more frequently in female patients (68). In contrast, non-V600E mutations (for example mutations within exons 5 or 11) are seen in former or current smokers and are associated with poorer outcomes (75,76).

BRAF targeting TKIs including dabrafenib and vemurafenib are being studied in the treatment of BRAF mutated NSCLC. Preliminary results from a recent phase II trial with dabrafenib in patients harboring V600E mutant NSCLC have shown positive partial response rates (77). Several case reports show responses in NSCLC patients with vemurafenib (78-80). Studies with metastatic melanoma suggest synergy with the combination of BRAF- and MEK-inhibition (81), and are now being studied in combination in a phase II clinical trial in BRAF mutant NSCLC (NCT01336634).

Human epidermal growth factor receptor 2 (HER2)/NUE

HER2 is a member of the ERBB receptor tyrosine kinase family and mutations have been detected in approximately 1 to 2 percent of NSCLC tumors (68). These mutations are more prevalent among never-smokers and women (82,83). Unlike HER2 overexpression in patients with breast cancer and GI malignancies, NSCLC tumors have mutations that have not been shown to respond to anti-HER2 therapies (84-86). Further studies have showed favorable response when combining HER2 inhibitors with chemotherapy (83,87), and with the EGFR inhibitor, afatanib (88). A recent phase I trial with neratinib (an irreversible pan HER inhibitor) combined with the mTOR inhibitor temsirolimus has also showed promising clinical activity (89) and is currently undergoing phase II trials (NCT01827267).

Currently, several clinical trials are investigating the role of HER2-directed antibodies such as trastuzumab, pertuzumab, as well as the HER2-targeting TKIs (afatinib, dacomitinib and neratinib) NCT00004883 NCT02289833, NCT00063154, NCT00818441.

RET

RET (rearranged during transfection) encodes a surface receptor tyrosine kinase found to be mutated in about 1.5% of NSCLC patients who are generally younger, light or never smokers with adenocarcinoma histology and poorly differentiated tumors (90). The most common RET translocation is the KIF5B-RET fusion variant on chromosome 10. Additional gene fusion partners including CCD6, NCOA4 and TRIM33 have also been described (68).

RET TKIs such as vandetanib, sorafenib and sunitinib, have overall not shown significant survival benefit in unselected NSCLC patients. Case reports have shown positive response rates in patients with RET translocations who were treated with vandetanib (91,92) and another inhibitor cabozantinib (93). A preliminary report from a phase II clinical trial NCT01639508 investigating cabozantinib in RET fusion positive NSCLC tumors with 16 evaluable patients showed that 7 had partial responses (38 percent) and 9 had stable disease (72 percent) (93). With a median follow-up of two years, the median progression-free survival was seven months and the median overall survival was 10 months (94). Clinical trials are ongoing going looking at different multi-kinase TKIs, which include RET as a target, including Ponatinib (NCT01813734), vandetanib (NCT01823068), and Lenvatinib (NCT01877083).

MAPK/Erk kinase1 (MEK1)

MEK1 also named MAP2K1, is a serine-threonine kinase with mutations occurring in approximately 1% of NSCLC (mostly adenocarcinoma) (95). MEK itself is not an oncogene product, but it is the focus of many of the signal transduction pathways activated by known oncogenes (including BRAF and KRAS mutations) and tyrosine kinase receptors (95). Therefore, inhibition of MEK has the potential to prevent the subsequent downstream phosphorylation and activation of MAP kinase (to pMAPK/pERK) to potentially induce tumor regression and/or stasis (96,97). A phase two study looking at PD-0325901 a small-molecule inhibitor of both MEK isoforms, MEK1 and MEK2 did not show significant survival benefit in non-selected NSCLC patients (98).

C-mesenchymal-epidermal transition (C-MET)/ recepteur d'origine nantais (RON)

Mesenchymal-epidermal transition (MET) is a receptor tyrosine kinase, which undergoes homodimerization by binding its ligand; hepatocyte growth factor (HGF) causing autophosphorylation of MET and ultimately leads to the activation of various intracellular signaling pathways

including RAS-RAF-MAPK and PI3K-AKT-mTOR (99). MET abnormalities are most often overexpression due to gene amplification and exon 14 skip splice mutations (100). Studies have suggested that approximately 40% of lung cancer tissue overexpresses MET (101).

In general, studies of multiple MET inhibitors have not shown significant improvement in survival data. In the last two years, three landmark phase III trials investigating Met targeted agents (including HGF monoclonal antibody ornatuzumab and small molecule met inhibitor tivantinib) in combination with erlotinib (an EGFR inhibitor) in pre-treated lung cancer were suspended following interim analyses that indicated no improvement in survival and/or safety concerns (30,102-104).

Further studies with MET inhibition are ongoing, including a study of Crizotinib which is being evaluated in patients with NSCLC who have intermediate or high *MET* gene amplification (NCT00585195).

RON is a MET-related receptor tyrosine kinase. It's natural ligand is macrophage stimulating protein, but beta-1-integrins can also activate RON via c-Src-dependant signaling pathways (105). RON signaling has roles in the regulation of inflammation and the motility and activation of macrophages, and therefore contributes to tumor growth and metastasis. RON signaling activity is synergistic or additive with MET leading to transformation, cell spreading, motility and cell survival (106,107). At present no specific c-met/RON inhibitors exist. An early clinical trial for MGCD265 (a multikinase inhibitor directed against c-MET, VEGR1, 2, 3, RON, and Tie-2) has not yet reported results (NCT00975767).

PIK3CA

The phosphatidylinositol 3-kinase (PI3K)-AKT-mTOR pathway is one of the most often deregulated signaling cascades in human cancers, including NSCLC, detected in 2% of tumors and is more commonly seen in squamous cell lung cancers (108). PIK3CA encodes the catalytic subunit of PI3K, which is an intracellular central mediator of cell survival signals (109). PIK3CA mutations can occur in combination with other known driver mutations like EGFR or KRAS mutations as well as in the setting of acquired EGFR TKI resistance (109). Pre-clinical models have shown that tumors harboring PIK3CA mutations are highly sensitive to PI3K inhibitors (110), and further clinical evaluation are ongoing with other PI3K inihbitors including BKM120 (NCT01723800), GDC0941 (NCT01493843), and XL-147 (NCT00692640).

Programmed death receptor (PD1) and programmed cell death ligand (PDL1)

PDL1 is a cell surface signaling molecule that binds to PD1 on T-cells, causing anergy and prevention of secretion of pro-inflammatory cytokines in cytotoxic T-cells and transformation of helper T-cells into immune-suppressing T-regulatory cells (111). In a healthy host, this immune checkpoint mechanism prevents over-activity or inappropriate activation of the adaptive immune system. When PDL1 is overexpressed by cancer cells, an appropriate immune response to the tumor is suppressed (111). The rationale behind PD1 and PDL1 as treatment targets is that preventing the interaction of the receptor and ligand will increase anti-tumor immune activity. PDL1 has found to be expressed on the surface of 45-50% of NSCLC cells regardless of subtype (112). PDL1 overexpression is associated with presence of EGFR mutations, solid predominant subtype, and advanced pathologic stage (113-115). The prognostic significance of elevated PDL1 in NSCLC h as been unclear, with two studies focused exclusively on the adenocarcinoma substype reporting an opposite effect on overall survival (115,116), though a recent meta-analysis in NSCLC in general (which included the adenocarcinoma studies) found overall decreased overall survival with increased PDL1 expression (117).

Immune checkpoint inhibition using PD1/PDL1 disruption has been studied in multiple malignancies, now including NSCLC. In 2012, a phase I trial of nivolumab (a monoclonal antibody against PD1) in a variety of solid tumors demonstrated an objective response in 5 of 49 patients with non-small-cell lung cancer with six additional patients with NSCLC who had stable disease lasting at least 24 weeks (118). Some responses were quite durable: in the overall cohort, responses lasted for 1 year or more in 8 of 16 patients with at least 1 year of follow-up (118). Trials of other immune checkpoint inhibitors are ongoing. Early results from a phase I/II clinical trial of MEDI4736, (an antibody against PDL1) have demonstrated a response rate of 10% in adenocarcinoma (119,120). Though overall, the response rates to PD1/PDL1 checkpoint inhibition have not been as robust as in the squamous subtype, there may be subpopulations within adenocarcinoma that may receive additional benefit. Patients with a smoking history (121), and higher levels of PDL1 expression (112,118) have been found to have a more robust response to PD1/PDL1 checkpoint

inhibition. The EGFR positive population, with higher levels of PDL1 expression as above, may represent a subgroup of adenocarcinoma patients with a potential for benefit from PD1 inhibition.

Ongoing studies of PDL1/PD1 inhibition in NSCLC (including adenocarcinoma) include a phase III trial of pembrolizumab (an antibody against PD1) versus placebo with or without standard adjuvant chemotherapy for resected stage IB-IIIA NSCLC (Clinicaltrials.gov identifier: NCT02504372) and two phase I studies of the novel anti-PDL1 antibodies MPDL3280A, a dose-escalation study in a variety of malignancies and a tolerability study in NSCLC patients who have undergone stereotactic ablative radiotherapy (Clinicaltrials.gov identifier NCT01375842 and NCT02400814).

Conclusions

As this review article has attempted to illustrate, there are numerous molecules that have been identified as potential targets for the treatment of non-squamous NSCLC. Although not covered in this review, many novel molecular targets for the treatment of squamous cell NSCLC are on the horizon as well. A great deal of research is currently underway to further our understanding of these molecular targets and ways that they can be translated to ultimately prolong survival and improve quality of life in patients with this disease. The most promising part of this research effort is in its ability to bring us closer to a more personalized approach to patient care, which will hopefully result in overall improvement in patient outcomes.

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