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Targeted Therapy in Lung Cancer

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INTRODUCTION TO TARGETED THERAPY IN LUNG CANCER

Advances in understanding the molecular mechanisms of lung cancer oncogenesis and progression have shifted the treatment paradigm for this deadly disease. Targeting the "driver" genomic alterations including Epidermal Growth Factor Receptor **(EGFR)** mutations, Anaplastic Lymphoma Kinase **(ALK)** rearrangements, and ROS1 translocations has led to improved clinical outcomes in subgroups of patients with lung adenocarcinoma.

Decoding of the human cancer genome and identification of oncogenic driver mutations have been important milestones for the treatment of Non-Small Cell Lung Cancer **(NSCLC).** The Cancer Genome Atlas **(TCGA)** Research Network has successfully profiled lung adenocarcinoma and squamous cell lung cancers in an effort to characterize driver mutations [1,2]. Most oncogenic driver mutations are found in adenocarcinoma, where over 50% of tumors harbor genomic aberrations [1,3,5]. Characterization of genomic alterations in squamous cell lung carcinoma has also shed light on "personalized therapy" although targetable drivers have are less frequently observed [2,3].

In this chapter, we will review the biology, highlight existing therapy, and discuss emerging treatment strategies for distinct molecular subtypes of NSCLC.

EGFR-TARGETED THERAPY

The EGFR gene encodes for a transmembrane tyrosine kinase receptor. Mutations can lead to aberrant EGFR signaling, tumor growth and cellular proliferation [6]. The majority of patients (85-90%) with EGFR mutations harbor in-frame deletions in exon 19 or L858R in exon 18. Activating EGFR mutations such as deletion 19, exon 21 (L858R, L861Q), exon 18 (G719X), and exon 20 (S768I) are associated with sensitivity to EGFR Tyrosine Kinase Inhibitors **(TKIs)** [6-11], while exon 20 insertion mutations confer resistance. EGFR mutations are more common in women, Asians, and those with no or light history of smoking [9,12]. There are four FDA approved, orally bioavailable, EGFR TKIs in the United States: the first generations of erlotinib (Tarceva, OSI Pharmaceuticals) and gefitinib (Iressa, Astra-Zeneca), the second generation of afatinib (Gilotrif, BoehringerIngelheim), and the third generation of osimertinib (Tagrisso, Astra-Zeneca) [13].

First Generation EGFR TKI: Erlotinib and Gefitinib

The BR.21 trial evaluated erlotinib versus placebo in the second or third line setting and demonstrated a benefit in Overall Survival **(OS)** in patients with stage IIIB or IV NSCLC (6.7 versus 4.7 months, HR 0.70, p<0.001) [14], leading to the approval of erlotinib for advanced NSCLC.

Later studies indicated that the presence of EGFR mutations is predictive of response to targeted therapy with EGFR TKIs, such as erlotinib [12]. First line TKI monotherapy in EGFR mutant lung cancer demonstrated improved Progression Free Survival **(PFS)** compared to chemotherapy [15-18]. The Iressa Pan-Asia Study **(IPASS)** phase III trial compared untreated patients in East Asia treated with gefinitib or carboplatin plus paclitaxel. Gefitinib was associated with superior 12 month PFS: 24.9% versus 6.7% (HR 0.74; 95% CI: 0.65-0.85; P<0.001). Furthermore, subgroup analysis predicted better outcomes in patients with EGFR mutations [15]. The phase III WJTOG3405 trial compared chemotherapy naïve Japanese patients with advanced EGFR mutant NSCLC treated with gefitinib versus cisplatin plus docetaxel. Gefitinib prolonged PFS to 9.2 months (95% CI: 8.0-13.9) compared to 6.3 months (95% CI: 5.8-7.8) [16]. The OPTIMAL trial evaluated first line platinum doublet therapy compared to erlotinib in EGFR mutant patients with advanced NSCLC. Erlotinib was associated with median PFS of 13.1 months versus 4.6 months with chemotherapy, while activating EGFR mutations were the most important factor predicting treatment efficacy [18]. The EURTAC trial was the first randomized trial targeting a non-Asian population in EGFR positive NSCLC patients. It compared erlotinib to standard platinum doublet as first line therapy; median PFS was 9.7 months (95% CI: 8.4-12.3) in the erlotinib group, versus 5.2 months (95% CI: 4.5-5.8) with chemotherapy (HR 0.37, 95% CI: 0.25-0.54; p<0.0001) [19].

On the other hand, the phase III TRIBUTE study compared untreated NSCLC patients treated with carboplatin and paclitaxel combined with either erlotinib or placebo. No improvement in OS was gained by adding erlotinib to chemotherapy, but subgroup analysis of those patients with EGFR mutant or KRAS wild type tumors found both were associated with erlotinib response [20,21].

Finally, the SATURN trial demonstrated that erlotinib maintenance led to both prolonged PFS and OS in patients who had stable disease after traditional chemotherapy (HR 0.72; p=0.0019). Interestingly, the erlotinib-related OS benefit was significant in all subgroups irrespective of EGFR mutation status [22].

Second Generation EGFR TKI: Afatinib

Afatinib binds irreversibly to wild-type and aberrant EGFR. It also inhibits ErbB2, ErbB4, ErbB family dimers and the transphosphorlylation of ErbB3 [23].

LUX-Lung 3, a randomized phase III study of treatment naïve patients with stage IIIB/IV adenocarcinoma, compared afatinib to cisplatin/pemetrexed **(CP).** Median PFS was 11.1 months with afatinib compared with 6.9 months for patients treated with CP (HR 0.58; 95% CI: 0.43-0.78; p=0.001). In patients with exon 19 deletions and L858R EGFR mutations, PFS benefit was even larger (13.6 months versus 6.9 months). This trial is also notable for enrolling a large non-Asian population [24,25]. The LUX-Lung 6 trial compared afatinib to gemcitabine/cisplatin in first line treatment of an Asian population with EGFR mutant advanced NSCLC. PFS was significantly extended in the afatinib group (11.0 months) compared to the gemcitabine/cisplatin group (5.6 months) [26].

Both LUX-Lung 3 and 6 identified improved PFS with afatinib based on EGFR mutation type; PFS was most improved in those individuals with exon 19 deletion [24,26]. Neither trial identified improved OS but preplanned subgroup analysis demonstrated those patients with EGFR mutations had improved OS with afatinib. In LUX-Lung 3, OS was 33.3 months in the afatinib group compared to 21.1 months with chemotherapy (HR 0.54, 95% CI: 0.36-0.79, p=0.0015); in LUX-Lung 6, OS was 31.4 months versus 18.4 months (HR 0.64, 95% CI: 0.44-0.94, p=0.023) [27].

The phase IIb LUX-Lung 7 trial compared afatinib to gefitinib as first line therapy in EGFR-mutant NSCLC. At median follow up of 27.3 months, PFS was 11.0 months with afatinib compared to 10.9 months with gefitinib (HR 0.73, 95% CI: 0.57-0.95, p=0.017). OS data was not mature at the time of publication. Despite preclinical data that afatinib could overcome T790M-mediated resistance, this has not been observed in patients likely due to failure to reach preclinical concentrations *in vivo* as a result of dose-limiting toxicity [28].

Third Generation EGFR TKI: Osimertinib and Rociletinib

The initial response to EGFR TKIs and prolongation of PFS is often impressive, but the majority of patients will progress after 1 year [15,19,24,29]. Approximately 60% of acquired EGFR resistance results from exon 20 T790M mutations [30-32]. Alternative bypass pathways also contribute, including PI3K/AKT, MAP kinase, JAK/STAT, BRAF mutation, and ERBB2/MET amplification [4,32-34]. Histological transformation is the third mechanism of acquired EGFR resistance, via conversion to small cell histology [35] or epithelial to mesenchymal transition [36]. Due to the variability and frequency of secondary mutations after initial therapy, repeat biopsy after progression on first line EGFR TKI is becoming the standard of care [4].

Osimertinib (AZD9291, AstraZeneca) is a third generation EGFR TKI approved for patients with EGFR T790M after progression on prior EGFR TKI treatment [37]. Osimertinib has nearly 200 times higher potency to EGFR harboring L828R/T790M mutations compared to wild-type [38]. The phase I/II AURA trial evaluated patients treated with osimertinib who had progressed after prior EGFR TKI treatment: Overall Response Rate **(ORR)** was 61% (95% CI: 52-70) with EGFR T790M compared to 21% (95% CI: 12-34) in those without T790M [39]. PFS in EGFR T790M-positive patients was 9.6 months (95% CI: 8.3 - not reached) compared to 2.8 months (95% CI: 2.1-4.3). Adverse events included diarrhea, rash, nausea, and decreased appetite. Osimertinib has also induced central nervous system responses, an observation not made with earlier generations of EGFR TKIs [39]. In the BLOOM phase I study, preliminary data from 21 patients with leptomeningeal disease showed intracranial radiological and neurologic responses in seven and five patients, respectively [40].

Rociletinib (CO-1686) is another oral, irreversible, potent inhibitor of activating EGFR mutations as well as the T790M mutation [41]. Rociletinib was evaluated in the TIGER-X phase I/II trial in patients with T790M-positive tumors. Similar adverse events were noted to osimertinib, but additional toxicities including QTc interval prolongation (20.6%), hyperglycemia (46.9%), and cataracts (53%) were observed [42-44]. Initial data was promising [42,43] but updated results presented at ASCO 2016 noted more modest ORR (21.8%) and duration of response (12.2 months) [45].

Novel EGFR TKIs continue to emerge. For instance, AZD3759 was also evaluated in the BLOOM trial, where encouraging intracranial anti-tumor activity was observed and toxicities were limited to diarrhea and skin rash [46]. Expansion cohorts are ongoing (NCT02228369).

Future Directions– Plasma Based Mutation Testing

The cobas EGFR Mutation Test v2 (Roche) is the first peripheral blood-based liquid biopsy test approved by the FDA. It was designed for evaluation of EGFR mutations. Detection of circulating free tumor DNA (ctDNA) or circulating tumor cells is an emerging strategy for tumor genotyping due to the importance of tumor genetics in treatment selection. The development of non-invasive genotyping allows for rapid detection of EGFR mutations and continual monitoring for additional resistance mechanisms, specifically T790M [47]. Existing techniques for tumor biopsy include fine needle aspirations and image-guided or endoscopic biopsies that place a burden on patients at the time of progression and carry additional risk. Plasma-based assays provide for rapid and non-invasive monitoring in what is now established as a molecularly dynamic disease. Next generation sequencing and digital PCR have allowed for detection of ctDNA at levels as low as 0.1% of total blood DNA [48]. Positive predictive value appears to approach that of tissue-based testing, while the presence of the T790M EGFR mutation has 81% positive concordance with tissue testing [49]. Limitations exist because not all tumors “shed” ctDNA, and the complexity of tumor heterogeneity cannot yet be replicated by plasma testing. Therefore, the two techniques currently appear best suited for a complimentary approach.

Uncommon EGFR Mutations

Approximately 10% of EGFR mutations consist of so called “uncommon” mutations, including G719X, L861Q, S768I, G719X + L861Q, and G719X + S768I. Patients with these mutations display inferior response rates (41.6% versus 66.5%; p<0.001), PFS (7.7 versus 11.4 months; p<0.001) and OS (24.0 versus 29.7 months; p = 0.005) compared to individuals with common EGFR mutations [50]. Moreover, the exon 20ins mutation is associated with particularly poor outcomes (ORR 8.3%) [51]. Additional studies to evaluate the efficacy of second and third generation EGFR TKIs in this EGFR subgroup are ongoing.

ANAPLASTIC LYMPHOMA KINASE (ALK)

The ALK gene encodes a receptor tyrosine kinase not expressed in normal lung tissue [52]. ALK is more typically expressed during embryogenesis and neuron development [53,54]. In lung cancer, oncogenic fusion genes comprising the echinoderm microtubule-associated protein-like 4 **(EML4)** and ALK genes have been observed in 2 to 7% of NSCLC [55-57]. Examples of more rare alternative fusion partners with ALK have also been identified [58,59]. EML4-ALK fusion produces a gain of function mutation that results in constitutive activation [55,58,60,61]. ALK fusions are mutually exclusive of KRAS and EGFR mutations, but occur in patients with similar characteristics (ie. adenocarcinoma, light/never smokers, and young patients) [56,58,62-65].

First Generation ALK TKI: Crizotinib

Crizotinib (Xalkori, Pfizer) is an oral ATP-competitive selective inhibitor of ALK, ROS-1, and MET tyrosine kinases [66-68] and is FDA approved for treatment of ALK-positive NSCLC. PROFILE 1007 was the first phase III trial comparing crizotinib to chemotherapy in patients with locally advanced or metastatic ALK-positive lung cancer as second line therapy [69]. PFS was 7.7 months in the crizotinib group compared to 3.0 months with pemetrexed or docetaxel (HR 0.49; 95% CI: 0.37-0.64). There was no significant improvement in OS. The main adverse effects of crizotinib included visual disorders, gastrointestinal side effects and elevated liver transaminases. PROFILE 1014 evaluated crizotinib versus chemotherapy as first line treatment for advanced ALK translocation-positive NSCLC. Crizotinib significantly improved PFS (10.9 versus 7.0 months; HR 0.45, 95% CI: 0.35-0.60) and ORR (74% versus 45%, p<0.001) [70].

Second Generation ALK TKI: Ceritinib and Alectinib

Unfortunately, acquired resistance to crizotinib generally occurs within one year. In 30% of patients resistance is due to secondary ALK mutations including L1196M, F1174L, S1206Y, G1269A, and G1202R [71,72]. ALK resistance can also be due to ALK amplification (6-16%), increased EGFR signaling (30-35%), and change in driver mutation (10-15%) [73,74]. A common site of progression is to the CNS: by 2 years, 45.5% of patients will have brain metastatic disease [75] due to low CNS penetration by crizotinib [76,77].

Ceritinib (LDK378; Zydakia; Novartis) is a second generation ALK TKI with greater potency compared to crizotinib that inhibits some of the secondary ALK mutations that cause crizotinib resistance [71,78-80]. Ceritinib also inhibits IGF-1 and ROS1, but not MET. Ceritinib was granted accelerated approval in 2014 based on the ASCEND-1 trial, an open-label, phase 1 trial evaluating ceritinib in patients with ALK-rearranged locally advanced or metastatic cancer that had progressed despite prior ALK inhibitor treatment. ORR was 44% (95% CI: 36-52) combined with a manageable side effect profile (diarrhea, nausea, vomiting and increased transaminases) [81,82]. Ceritinib has increased bioavailability in the CNS, as evidenced by observed responses in CNS disease [83].

Alectinib (AF-001JP; Alecensa; Chugai Pharmaceuticals) is a highly selective ALK inhibitor with activity against wild-type ALK and mutated ALK, including the L1196M gatekeeper mutation. It also has activity against RET and IGF-1 [84,85]. It was granted accelerated approval for treatment of crizotinib resistant, ALK positive, metastatic NSCLC. A Japanese phase I/II trial evaluated 46 ALK-inhibitor naïve patients treated with alectinib: ORR was 93.5% with mean follow up of 14.8 months. The most common adverse events were dysgeusia, elevated liver function tests and creatinine, constipation and rash [86]. Phase I data from a North American trial evaluating alectinib after progression on crizotinib confirmed tolerability with the most common adverse events being fatigue, myalgias and edema [87]. Phase II data published in 2016 found 33 of 69 patients had a response to alectinib (ORR 48%, 95% CI: 36-60) [88]. Of this group, 52 patients had CNS disease at baseline; median duration of response to alectinib was 11.1 months. 46 (89%) patients achieved disease control (95% CI: 77-96), including 13 (25%) with a complete response [88]. A second, global, phase II study evaluating alectinib in previously treated patients with advanced ALK positive NSCLC reported similar results including ORR of 50% with PFS of 8.9 months. CNS response was also noted: in 84 patients with CNS metastases, 23 (27%) had observed CNS CR, and overall disease control rate was 83% (95% CI: 74-91) [89]. J-ALEX is a Japanese phase III trial comparing first line alectinib to crizotinib in ALK positive advanced NSCLC that included patients with measurable brain metastases. First interim analysis data found median PFS in the crizotinib group was 10.2 months (95% CI: 8.2-12), and not reached with alectinib (95% CI: 20.3-NR) (HR 0.34, 95% CI: 0.17-0.71, $p<0.0001$). Subgroup analysis of PFS in patients with brain metastases found statistically superior outcomes for patients treated with alectinib [90]. ALEX is the North American counterpart to this trial and has completed recruitment (NCT02075840).

Third Generation ALK TKI: Lorlatinib and Brigatinib

Lorlatinib (PF-06463922, Pfizer) is a reversible, third generation, ALK inhibitor with improved brain bioavailability and broad-spectrum potency against ALK-resistant mutations [91]. In a phase I clinical trial evaluating its use in patients resistant to both crizotinib and ceritinib, patients with history of one or more prior ALK TKI therapies had an ORR of 46% (95% CI: 31-63%) and PFS of 11.4 months (95% CI: 3.4-16.6 months) [92]. The most common toxicities noted were hypercholesterolemia, peripheral neuropathy and edema [93].

Lorlatinib treatment may result in acquisition of the L1198F mutation, which paradoxically restores crizotinib sensitivity [94]. Lorlatinib is the first ALK TKI with identified activity against the G1202R mutation [91].

Brigatinib (AP26113) is a next generation ALK inhibitor with high selectivity towards clinically relevant ALK mutations, including L1196M, and activating EGFR mutations, including T790M [95,96]. Breakthrough therapy designation was granted in 2014. Phase I/II data has been reported by Rosell et al. (2016); 79 patients with ALK positive NSCLC (70 with prior treatment with crizotinib) treated with brigatinib had an ORR of 71% and median PFS of 13.4 months. 53% (8/15) of patients with measurable CNS disease had an intracranial objective response, and median duration of response in these patients was 18.9 months. The most common adverse effects were nausea, fatigue, diarrhea, hypertension and cough [97,98]. ALTA, a phase II trial of brigatinib in patients with ALK positive NSCLC who progressed on crizotinib, has completed recruitment of patients (NCT02094573). Preliminary data included 67% with CNS disease and 74% with prior treatment who were treated at 180mg daily. Reported PFS 12.9 months (95% CI: 11.1-NR), ORR 54% (97.5% CI: 43-65) and CNS response 67% compare favorably with previously reported outcomes with ceritinib and alectinib [81,89].

ROS1-TARGETED THERAPY

ROS1 is related to ALK and is normally expressed in tissues during development with little to no expression in normal adult tissues [99,100]. ROS1 fusion results in oncogenic activation. Rearrangements occur in only 1-2% of patients with NSCLC [101]. Those patients identified with ROS1 rearrangements share similar characteristics to those with EGFR mutations, including younger age, never-smokers, and Asian ethnicity [102]. ROS1 mutations are mutually exclusive to both EGFR and ALK [56,101-103].

In an expanded phase I study evaluating crizotinib in patients with NSCLC who had tested positive for ROS1, ORR was 72% (95% CI: 58-84), median duration of response was 17.6 months (95% CI: 14.5 to not reached) and PFS was 19.2 months (95% CI: 14.4 to not reached) [104]. Toxicities in patients with ROS1 were similar to that in patients treated with ALK mutations [104]. Despite dramatic improvements in PFS compared to historical means, eventual resistance to ROS1 inhibition usually develops [105].

Second Generation ROS1 Inhibition

In ROS1 NSCLC, the CNS is a common site of relapse while acquired mutations, including G2032R and D2033N, that confer TKI resistance have been identified [105,106]. Lorlatinib, the CNS penetrant, dual ALK/ROS1 TKI, has demonstrated activity in ROS1 mutant patients with acquired resistance to crizotinib, including those with CNS disease [92,107]. Described toxicities include hyperlipidemia, peripheral edema, and rarely, neurocognitive disturbance. The cMET/RET/VEGFR inhibitor cabozantinib (XL184) has demonstrated activity against crizotinib resistant CD74-ROS1 fusion [108], and in one patient treatment led to rapid clinical and radiographic response [106].

KRAS

KRAS is the most commonly altered gene in NSCLC, comprising 25 to 32% of mutations [1,109,110]. Despite extensive study KRAS remains a poor target for therapy. Downstream effectors of KRAS have been evaluated and show more promise, particularly MEK1/2 and BRAF. However, a growing understanding of KRAS biology and its downstream pathways has led to renewed optimism and new clinical studies evaluating KRAS inhibition [111].

KRAS mutations are strongly associated with smoking [112]. There is also data that KRAS mutations may impart a worse prognosis compared to wild type [113-115]. KRAS mutation may be a negative predictive factor of EGFR TKI response, but no consensus regarding the clinical value of KRAS mutations in NSCLC exists [116,117].

Downstream KRAS Inhibitors: MEK Inhibitors

MEK1 and MEK2 are downstream effectors of KRAS; two MEK1/2 inhibitors, selumetinib and trametinib have been studied in NSCLC [118]. A prospective phase II trial combining docetaxel with and without selumetinib in patients with KRAS mutant NSCLC who progressed after first line chemotherapy did not demonstrate significantly improved OS, but the combination did lead to statistically significant improvements in PFS and patient reported outcomes. The main non-hematologic side effects reported were rash, diarrhea, fatigue and edema [119]. Combining selumetinib with erlotinib did not show improved ORR or PFS compared to erlotinib alone in either KRAS mutant or wild type patients [120].

In phase I evaluation studies, trametinib has exhibited a side effect profile that includes rash, diarrhea, and CNS retinopathy [121]. Synergy with chemotherapy has been evaluated and shows modest promise in early stage trials [118,122,123].

BRAF V600E

BRAF is a serine-threonine kinase that belongs to the RAF kinase family and is downstream of KRAS [124]. Frequency of BRAF mutations in NSCLC is approximately 1-5%, but is more common in those with a history of smoking [1,3]. V600E is the most commonly observed mutation in BRAF NSCLC [125] and is associated with more aggressive disease and worse OS [126]. Initial case reports documented activity of BRAF inhibitors in V600E positive NSCLC [127,128], including one report of CNS response [129]. Later phase II data in dabrafenib treated BRAF V600E mutated NSCLC has shown ORR of 54%. Adverse effects were decreased appetite, fatigue, asthenia, dyspnea, and nausea [130]. BRAF V600 positive NSCLC patients have also been evaluated in a phase II "basket study" with ORR of 43% (95% CI: 18-71) [131]. The MEK inhibitor trametinib has also been combined with dabrafenib, increasing ORR to 63% (95% CI: 40-81.2) [132]. Despite no FDA approval for BRAF inhibitors in NSCLC, current NCCN guidelines support the use of vemurafenib and dabrafenib alone or in conjunction with trametinib in patients with BRAF V600E mutations [37].

RET

RET acts as a proto-oncogene in a small subset of patients with NSCLC, primarily those with adenocarcinoma [1,3,133,134]. RET rearrangements result in gain of function mutations. Four RET fusion partners have been identified in NSCLC, including CCDC6-RET and KIF5B [134-136]. KIF5B-RET can be inhibited via TKIs with anti-RET activity including sunitinib, sorafenib, vandetanib and lenvatinib [137-140]. Clinical trials evaluating the addition of anti-RET therapy to standard chemotherapy in non-RET selected NSCLC have demonstrated limited improvement in ORR [141-143]. However, RET-fusion positive NSCLC appears to respond well to cabozantinib [136]. Vandetanib is also active in RET selected patients [144,145]. Phase II Japanese data evaluating vandetanib in advanced stage RET fusion positive non-squamous NSCLC described ORR of 20% (95% CI: 3-56) in KIF5B-RET and 83% (95% CI: 36-99.6) in those with CCDC6-RET [146]. The most common adverse events were hypertension, diarrhea, and rash. Analysis of a global registry of RET-rearranged NSCLC has identified off-label activity using cabozantinib, vandetanib, sunitinib, sorafenib, alectinib, lenvatinib, nintedanib and ponatinib [146].

ERBB2/HER2

Human epidermal growth factor 2 (HER2 or ERBB2) mutations are oncogenic drivers in approximately 2% of NSCLC cases [1,147]. HER2 mutations are most commonly identified in non-smokers, females, and those with adenocarcinoma [148]. The most common mutations are in-frame insertions in exon 20, leading to uncontrolled activation of downstream AKT and MEK [149]. In addition, up to 20% of patients with NSCLC have HER2 amplification or HER2 protein over expression [150-152]. The addition of trastuzumab to standard therapy in HER2-amplified NSCLC has not shown significant benefit [153-155].

Afatinib has activity against EGFR and HER2 [23], and a small phase II trial evaluated afatinib in HER2 mutation positive NSCLC. Partial response or stable disease was noted in 3 of 5 patients, although dose limiting toxicity likely limited benefit as higher doses are required compared to those used in EGFR mutant NSCLC [156]. The pan-HER TKI dacomitinib irreversibly binds to HER2, HER1, and HER4 tyrosine kinases. NSCLC patients with HER2 mutations and amplifications treated with dacomitinib were studied in a phase II trial: 3 of 26 patients with HER2 exon 20 mutation positive tumors had partial responses, while 0 of 4 patients with HER2 amplification had documented response [157].

MET

MET, or Hepatocyte Growth Factor Receptor **(HGFR),** is a receptor tyrosine kinase that activates the PI3K/AKT and MAPK pathways [158]. MET over expression has been identified in approximately 20% of EGFR mutant NSCLC cases with acquired resistance to EGFR TKIs [159,160]. Over expression is associated with a poor prognosis [161]. In comparison, aberrant MET expression acts as a driver mutation in only 2% of lung adenocarcinoma [1,162,163].

Crizotinib has activity against MET and has demonstrated anti-tumor activity in patients with MET amplifications [164,165]. Several anti-MET therapies including tivantinib, crizotinib, and cabozantinib have been tested in advanced NSCLC [166-169]. Rilotumumab, a fully humanized IgG2 monoclonal antibody that blocks HGF, is being tested in combination with erlotinib in patients with recurrent or advanced NSCLC (NCT01233687).

MET exon 14 skipping mutations occur in 3-4% of NSCLC, and are more common in pulmonary sarcomatoid carcinoma [1,160,163,170]. Patients with MET exon 14 splice variants have demonstrated responses to MET-directed therapy, including crizotinib [171].

PTEN/PI3K/AKT/MTOR

The PI3K/AKT/mTOR pathway plays an important role in cell growth and survival and is negatively regulated by PTEN [172]. Ubiquitous activation can lead to inhibition of pro-apoptotic and regulatory functions [173,174]. PTEN inactivating mutations occur in 4-5% of NSCLC and an additional 70% of NSCLC are associated with reductions or loss of PTEN expression. Meanwhile, mutations in PI3K and AKT occur in 2-5% and 1-2%, respectively [175,176]. PI3K mutations commonly coexist with EGFR and KRAS mutations [177]. Increased AKT activity can lead to acquired resistance of EGFR-targeted therapy [178,179]. Mutations in the PI3K/AKT/mTOR pathway appear to be associated with a poor prognosis [175,176].

GDC 0941, a dual PI3K/mTOR inhibitor, has demonstrated encouraging activity in phase I evaluation when combined with MEK inhibition or carboplatin/paclitaxel [182,183]. The AKT inhibitor MK-2206 is being evaluated in a phase II trial (NCT01294306). XL-765 is an oral dual PI3K/mTOR inhibitor with phase I activity being evaluated in combination with erlotinib in advanced NSCLC (NCT00777699). The mTOR inhibitors everolimus and temsirolimus are FDA approved in several malignancies but there is no current FDA approval for mTOR inhibitors in NSCLC. Temsirolimus has been evaluated in phase II study: adverse events were tolerable but the study did not meet its primary objective [182]. Unselected populations with NSCLC treated with everolimus in combination with erlotinib [183], carboplatin/paclitaxel [184], or docetaxel [185] have reported discouraging results. In unselected populations of NSCLC, dual mTOR1/2 inhibitors have demonstrated limited clinical benefit [186], however, a recently published study detailing RICTOR amplification in NSCLC described a robust response observed with CC-223 and MLN0128, two dual mTORC1/2 inhibitors. RICTOR is a component of mTOR2; amplification occurs in between 8-13% of patients with NSCLC and this finding may suggest a role for genomic stratification specific to RICTOR amplification in the future [187].

EMERGING TARGETED THERAPY IN SQUAMOUS CELL LUNG CANCER

Squamous Cell Lung Cancer **(SQLC)** is strongly associated with tobacco use, and the subsequent genomic alterations observed are complex and highly variable [2]. Unfortunately, recurrent alterations in previously identified kinase genes occur much less frequently as compared to

adenocarcinoma. The most common variants in SQLC are loss of TP53 and CDKN2A, two targets that have historically been poor candidates for targeted therapy [188,189]. Additional alterations or aberrant genetic pathways have been identified in SQLC and include RAS (loss of NF1, RASA1, RAS), PI3K (PIK3A, PTEN, PIK3R1), oxidative stress regulation mutations (ie. NFE2L2/KEAP1/CUL3), differentiation pathways (NOTCH1, TP63 and SOX2 gain), and immune evasion (HLA and B2M) mutations [2,188,189]. RICTOR amplification has been identified in 7.4-15.8% of SQCL patients, and may be an emerging target for novel therapies [186,187].

EGFR over expression and amplification may rarely occur in SQLC. Evaluation of erlotinib in patients with previously treated SQLC found improved survival compared to placebo, resulting in its approval for second line and maintenance therapy [190,191]. Afatinib was evaluated in the second line setting versus erlotinib in the LUX-lung 8 trial. This resulted in a modest improvement of PFS (2.6 versus 1.9 months, HR 0.81, p=0.0103) and OS (7.9 versus 6.8 months, HR 0.81, p=0.0077) [192]. Necitumumab is a fully human IgG1 monoclonal antibody designed to target EGFR, inhibit DNA repair, and induce antibody dependent cell-mediated cytotoxicity [193]. The SQUIRE study compared necitumumab combined with gemcitabine and cisplatin versus chemotherapy alone as first line treatment in advanced NSCLC. Combination therapy attained statistical significance (OS 11.5 versus 9.9 months, HR 0.84; p=0.01) while modest improvement in PFS was also observed (5.7 versus 5.5 months, HR 0.85; p=0.02) [194]. Adverse effects were consistent with previous complications of EGFR inhibition including skin rash, hypomagnesemia, conjunctivitis and diarrhea, as well as increased rates of thromboembolic events [193,194].

CONCLUSION

Molecular targeted therapy plays an important role for many patients in NSCLC. FDA approved treatment in EGFR mutant NSCLC includes, erlotinib, gefitinib, and afatinib, while specific resistance via T790M can be targeted by osimertinib. ALK inhibitors including crizotinib, ceritinib and alectinib are approved, where as third generation inhibitors lorlatinib and brigatinib show promising activity. Crizotinib is approved to target ROS1, while lorlatinib and cabozantinib have shown clinical benefit. Ongoing study in NSCLC subsets including HER2/ERBB2, MET, KRAS, RET, NTRK and PI3K/PTEN/mTOR are underway. Taken together, advances in targeted therapy may further lead to shifting paradigms in the years to come. In addition, as the first plasma based ctDNA test was recently granted FDA approval for EGFR mutations, novel non-invasive biomarker tests also carry great promise.

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