Lung Cancer: Targets and Therapy

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REVIEW

Emerging Targets in Non-Small Cell Lung Cancer

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Abstract: The identification of molecular driver mutations in non-small cell lung cancer (NSCLC) has changed the therapeutic landscape for this disease. Over the last 20 years, a growing number of driver mutations have been identified in addition to new targeted therapies that have resulted in significant improvement in survival for a subset of patients. There is ongoing research to identify additional molecular targets and therapeutic strategies to improve outcomes in a greater percentage of patients with lung cancer. This review aims to highlight new therapeutic strategies targeting known driver mutations and data regarding emerging molecular targets for the treatment of NSCLC.

Keywords: non-small cell lung cancer, molecular alterations, targeted therapy, driver mutations

Introduction

Non-small cell lung cancer (NSCLC) represents approximately 85% of all lung cancer cases and is a leading cause of cancer-related death globally.[1,2] Although the prognosis of metastatic NSCLC is generally poor, with a 5-year overall survival rate of approximately 5%, the development of targeted therapies has resulted in significant improvements in the survival of a subset of patients with NSCLC.[3,4] The increased utilization of next-generation sequencing (NGS) and molecular characterization of NSCLC has led to the identification of a growing number of oncogenic driver mutations that propagate cellular proliferation and metastases and are targets for drug development.[5] Over the past two decades, tyrosine kinase inhibitors (TKIs) have become the standard treatment for many patients in whom oncogenic driver mutations have been identified, resulting in significant improvements in overall survival (OS) and progression-free survival (PFS) compared to treatment with chemotherapy for these subgroups.[6,7] There are ongoing efforts to identify new therapeutic options for known driver mutations and to identify additional molecular targets for therapeutic intervention. This review aims to highlight new therapeutic strategies targeting known driver mutations and data regarding emerging molecular targets for the treatment of NSCLC.

KRAS

Kirsten rat sarcoma viral oncogene homologue (KRAS) is a member of the oncogene family (RAS), which encodes intracellular guanine nucleotide-binding proteins belonging to the GTPase family.[6] KRAS proteins function as regulated molecular switches that control multiple signaling cascades by cycling between activated (GTP-bound) and inactivated (GDP-bound) conformations. Activated KRAS protein can activate multiple signaling pathways, including RAF/MEK/ERK, PI3K/AKT/mTOR, RalA/B, and TIAM1/RAC1, which regulate cell proliferation, differentiation, and apoptosis, revealing a wide range of KRAS communications with multiple signaling pathways involving the regulation of cell proliferation, differentiation and apoptosis.[6] Molecular mutations that result in alterations in KRAS proteins impede the interaction of KRAS with GTPase-activating proteins (GAPs) and the hydrolysis of GTP bound to KRAS, leaving KRAS in a constitutively active state (GTP-bound).[7] The most frequent mutations are the nucleotide substitutions in 12 codons of KRAS exon 2p. G12C, p.G12D, and p. G12V.[8,9] Therapeutic targeting of KRAS mutations has posed a significant challenge due to the lack of a deep binding pocket suitable for small-molecule inhibitors.[6] In 2021, the accelerated approval of sotorasib by the FDA marked a turning point, as it became the first drug approved for the treatment of locally

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advanced or metastatic KRAS G12C-mutant NSCLC in patients who had previously undergone treatment with at least one prior line of systemic therapy based on the CodeBreak 200 study that showed an ORR of 37%, improved PFS, and favorable safety profile compared to docetaxel.[10–12] Similar results were reported with adagrasib from the KRYSTAL-1 study, in which adagrasib demonstrated an ORR of 42.9% and a PFS of 6.5 months, resulting in accelerated FDA approval as a second-line therapy for locally advanced or metastatic KRAS G12C-mutant NSCLC.[13,14]

In addition to sotorasib and adagrasib, multiple novel agents and drug combinations targeting KRAS G12C have been evaluated in early phase clinical trials.[15–17] Olomorasib (LY3537982) is a highly selective and potent inhibitor of the GDP-bound KRAS-G12C protein and has demonstrated efficacy in treating solid tumors harboring KRAS G12C mutations.[18] Recently, olomorasib was studied in combination with pembrolizumab for first-line treatment of patients with solid tumors harboring KRAS G12C mutations and demonstrated a favorable safety profile with ORR of 77% (NCT04956640).[19,20] Results of an ongoing randomized Phase III study of chemoimmunotherapy plus olomorasib versus placebo have the potential to be practice changing with regards to first-line treatment of KRAS G12C mutated NSCLC.[21]

Another drug, glecirasib (JAB-21822), is a new covalent oral KRAS-G12C inhibitor that was evaluated as a single agent in a phase IIb study of heavily pre-treated patients with solid tumors that harbor KRAS-G12C mutations (NCT05009329) and demonstrated ORR of 47.9% with median OS of 13.2 months.[22] Glecirasib was also studied in combination with JAB-3312, a SHP2 inhibitor. SHP2 has a role in activation of the RAS/MAPK pathway, and suppression of this pathway and may result in immune cell modulation in the tumor microenvironment and may reduce adaptive resistance to KRAS-directed therapies.[23] This phase I/IIa study (NCT05288205) demonstrated that glecirasib and JAB-3312 have a response rate of 77.8% and 12-month PFS of 54% with acceptable safety profile.[24] It is anticipated that this combination will be studied further in phase III study.

Similar to other targeted therapies, acquired resistance to KRAS inhibitors limits the duration of efficacy of KRAS inhibitors, and there are ongoing efforts to understand and overcome mechanisms of resistance.[25–27] It is anticipated that that additional clinical trial trials utilizing novel combinations are anticipated to overcome resistance and improve response rates and survival for this subset of patients.

KRAS G12D

Although there has been success in targeting KRAS G12C, targeting other KRAS mutations, particularly KRAS G12D, remains a challenge, as inhibition of KRAS G12C is dependent on the covalent inhibition of cysteine, which is not present in other KRAS-mutant types. MRTX1133 is a potent selective, non-covalent inhibitor of KRAS G12D that has demonstrated potent in vitro and in vivo anti-tumor efficacy in preclinical studies.[28] When combined with immune checkpoint inhibitors, MRTX1133 resulted in enhanced tumor regression in murine models of KRAS G12D mutated lung cancer and is currently being studied in a Phase I study of patients with solid tumors harboring KRAS G12D mutations (NCT05737706).[29,30] Another agent, HRS-4642, is a highly selective KRAS inhibitor that has also demonstrated significant anti-tumor activity against KRAS G12D mutant tumors in preclinical studies with potential synergy when combined with proteasome inhibitor Carfilzomib.[31] A first-in-human phase I study (NCT05533463) investigated HRS-4642 in patients with advanced solid tumors harboring KRAS G12D mutations, including 10 patients with NSCLC, and reported a disease control rate of 94.4%.[32] There are several other early phase trials clinical trials that are currently enrolling to evaluate agents targeting KRAS G12D or pan-KRAS inhibitors. Although no targeted therapies are currently approved, KRAS G12D is an emerging molecular target for the treatment of solid tumors, including NSCLC.

MAPK

Dysregulation of signaling within the mitogen-activated protein kinase (MAPK) pathway is common in lung cancer and is characterized by increased activity of RAS, RAF, MEK, and ERK.[33] Inhibition of this pathway as a means of targeting driver mutations in KRAS and BRAF has shown varying success rates. Within the MAPK pathway, the binding of RAS to GTP activates RAF kinases, which form dimers at the cell membrane. These dimers phosphorylate and activate MEK, which, in turn, activates ERK. Phosphorylated ERK triggers the transcription factors that promote cell growth, proliferation, differentiation, and survival. In approximately 2% of patients with NSCLC, BRAF V600E mutation is identified and causes constitutive activation of the downstream MEK/ERK signaling pathway, which promotes cancer

cell proliferation.[34] BRAF inhibitors have demonstrated efficacy as monotherapy and in combination with MEK inhibitors in targeting BRAF V600E mutations.[35–38] While BRAF V600E is an established molecular target with efficacious targeted therapy options, additional research is needed to understand the significance of co-mutations as well as establish strategies to target non-V600E BRAF mutations.

The use of RAF/MEK clamps, small molecule inhibitors that target both RAF and MEK in the MAPK pathway, has demonstrated therapeutic potential. Avutometinib (VS-6766) is a RAF/MEK clamp that has shown anti-tumor effects in preclinical studies as well as in a Phase II trial (NCT04620330) in which pretreated patients with metastatic KRAS-mutated NSCLC were randomized to avutometinib with our without defactinib, a small molecule FAK inhibitor.[39] Of the 35 enrolled patients with KRAS G12V mutated metastatic NSCLC, 11% had a partial response in the combination treatment arm, with no responses seen in the monotherapy arm.[40] There are ongoing studies currently evaluating the combination of avutometinib and defactinib. Avutometinib has been studied in combination with sotorasib (NCT05074810), adagrasib (NCT05375994) and everolimus (NCT02407509). When used in combination with sotorasib in the phase I/II RAMP 203 trial (NCT05074810), an ORR of 25% resulted in a combination of fast-track designations by the FDA for the treatment of patients with KRAS G12C mutant NSCLC.[40–42] Further trials are needed to evaluate the efficacy of avutometinib in combination with other agents and to determine which patient population may benefit from the use of FAF/MEK clamps.

EGFR

EGFR is a transmembrane receptor protein that plays an essential role in regulating cell growth, proliferation, and survival. EGFR is the most commonly mutated of the HER/erbB family of growth factor receptors, which also includes HER2, HER3, and HER4, with exon 19 deletion and L858R point mutation in exon 21 being the most commonly identified targetable mutations.[43] These cell surface proteins are composed of an extracellular domain for ligand binding, a transmembrane segment, and an intracellular tyrosine kinase domain. When a ligand binds to a receptor, it triggers receptor dimerization and autophosphorylation of the tyrosine kinase domain, initiating a series of intracellular events that promote cell proliferation, angiogenesis, metastasis, and reduced apoptosis.[43] Since its FDA approval in 2018, osimertinib has been the standard first-line therapy for NSCLC in patients with EGFR exon 19 and 21 L858R mutations.[44] Recent studies have evaluated combination strategies to improve outcomes compared to single-agent osimertinib. The FLAURA 2 Phase 3 trial found that adding platinum and pemetrexed to osimertinib significantly improved PFS (HR 0.62; $p < 0.001$) with manageable side effects.[45] This combination showed an ORR of 83%, compared to 76% with osimertinib alone, and median DORs of 24 versus 15.3 months with more recent analysis showing trend towards OS survival benefit.[46] AmivantamabMET has also shown efficacy for treatment of EGFR mutations. The combination of amivantamab and lazertinib was recently FDA-approved for first-line treatment of EGFR-mutated advanced NSCLC based on the results of the MARIPOSA trial.[47] This phase III trial showed that amivantamab plus lazertinib significantly prolonged PFS (23.7 vs 16.6 months) and had a higher ORR (86% vs 85%) and longer duration of response (25.8 vs 16.8 months) than osimertinib in treatment-naive EGFR-mutated advanced NSCLC. However, it was associated with more treatment-related adverse events, specifically rashes, infusion reactions, and VTEs.[48]

Amivantamab has also demonstrated efficacy in patients who progressed to first-line osimertinib. Amivantimab plus chemotherapy, with or without lazertinib, significantly improved PFS (8.3 and 6.3 months, HR 0.44 and 0.48, $p < 0.001$) compared to chemotherapy alone in the MARIPOSA-2 phase 3 study for patients who progressed on Osimertinib.[48] Again, amivantamab-containing groups had more AEs, with higher rates of grade 3 AEs, including neutropenia, thrombocytopenia, rash, and VTEs.[48] The PALOMA-3 phase 3 trial showed that subcutaneous amivantamab-lazertinib was noninferior to the intravenous formulation, with fewer IRRs, increased convenience, and prolonged survival in patients with EGFR-mutated NSCLC who had progressed on osimertinib and platinum-based chemotherapy.[49] While combination therapy for the first-line treatment of EGFR-mutated NSCLC appears to result in a survival benefit compared to single-agent osimertinib, careful consideration is needed regarding which patients are most likely to benefit, with consideration of toxicity and quality of life.

EGFR Exon 20 Insertion Mutations

EGFR exon 20 insertion mutations are less common than exon 19 deletion and exon 21 L858R mutations and are often resistant to approved EGFR-directed TKIs.[50] Platinum-doublet chemotherapy had been the primary treatment for tumors with exon 20 insertions, but amivantamab with chemotherapy has been shown to improve PFS compared to chemotherapy alone for first-line treatment.[51] There are also newer drugs being evaluated for targeting this driver mutation. Sunvozertinib (DZD9008) is an oral, irreversible EGFR TKI with high specificity for EGFR mutations, including exon 20 insertions, was granted FDA breakthrough therapy designation for treatment of EGFR exon 20 insertion-mutated metastatic NSCLC based on the WU-KONG1 trial (NCT03974022).[52] This trial showed a 54% ORR and 91% disease control rate in heavily pretreated patients with a manageable safety profile.[53] A randomized phase II trial (NCT05668988) is currently ongoing.[54] Furmonertinib is a third-generation, highly CNS-penetrant EGFR TKI that was first approved in China for the treatment of patients with locally advanced or metastatic NSCLC carrying EGFR T790M mutation. A phase I study of EGFR exon 20 in advanced NSCLC demonstrated an ORR of 69% and a median PFS of 10 months for treatment-naïve patients treated with furmonertinib.[55] A global phase III study (FURVENT/FURMO-004; NCT05607550) is currently ongoing to evaluate furmonertinib as a first-line treatment for EGFR exon 20 in NSCLC patients.[56]

HER3

Human epidermal growth factor receptor 3 (HER3), also known as ERBB3, is a member of the human epidermal receptor (HER) family, which also includes EGFR (ERBB1), HER2 (ERBB2), and HER4 (ERBB4).[57] HER3 interact with receptor tyrosine kinases such as EGFR and HER2 to activate the PI3K/AKT, MEK/MAPK, JAK/STAT pathways, and Src kinase signaling.[57] Upregulation of HER3 is observed in approximately 40% of EGFR-mutant NSCLC tumors treated after prior treatment with EGFR TKIs. A recent anti-HER3 drug conjugate (ADC)m patritumab deruxtecan, the first fully humanized anti-HER3 monoclonal antibody covalently bonded to an exatecan-derived topoisomerase I inhibitor, has demonstrated promising results in early-phase clinical trials.[58,59] In the phase II HERTHENA-Lung-1 study (NCT04619004), there was an ORR of 29.8%, mDOR of 6.4 months, mPFS of 6.5 months and mOS of 6.4 months, and a CNS ORR of 33.3% with a manageable safety profile. The most frequent grade ≥ 3 TRAEs were thrombocytopenia (20.9%) and neutropenia (19.1%).[58] There are two ongoing trials evaluating patritumab deruxtecan in EGFR-mutated NSCLC. One was a phase III trial comparing patritumab deruxtecan with platinum-based chemotherapy in patients who have progressed on third-generation EGFR-TKI therapy (HERTHENA-Lung02; NCT05338970).[60] The second was a phase I trial investigating the combination of patritumab deruxtecan with osimertinib in patients who have progressed on first-line osimertinib or previously untreated patients (NCT04676477).[61]

Izalotamab (SI-B001) is a bi-specific HER3/EGFR monoclonal antibody that binds both EGFR and HER3. In a phase II study of unselected patients with advanced EGFR-wild-type NSCLC, izalotamab was administered as a second-line treatment in combination with docetaxel and demonstrated an ORR of 31.3% and DCR of 77.1% with a tolerable side effect profile.[62] Further data are needed regarding the efficacy of these drugs; however, there is promise for targeting HER3.

VEGF

Vascular endothelial-derived growth factor (VEGF) is an angiogenic growth factor, which regulates angiogenesis and plays an important role in cell proliferation and metastasis with overexpression of VEGF associated with poorer prognosis in NSCLC.[63] Bevacizumab and ramucirumab have been FDA-approved for treatment of NSCLC in combination with chemotherapy.[64,65] While these drugs primarily inhibit angiogenesis, VEGF inhibition also has a role in modulation of immune response in the tumor microenvironment, prompting interest in combining VEGF inhibitors with immune checkpoint inhibitors.[66] Lung-MAP (S1800A) is a phase II randomized trial that compared ramucirumab plus pembrolizumab with standard of care (SOC) as determined by investigator (docetaxel/ramucirumab, docetaxel, gemcitabine, and pemetrexed) in patients with NSCLC previously treated with and platinum doublet chemotherapy and immune checkpoint inhibitor. Treatment with ramucirumab and pembrolizumab resulted in significantly improved

median OS of 14.5 months compared to 11.6 months in the SOC arm, respectively (HR 0.69; 80% CI 0.51–0.92), suggesting further investigation of this combination is warranted.[67]

Ongoing clinical trials are evaluating anti-VEGF agents and immune checkpoint inhibitors for the treatment of NSCLC. A phase II single-arm trial evaluated the safety and preliminary efficacy of docetaxel, ramucirumab, and pembrolizumab as second-line treatments for patients with metastatic NSCLC (NCT04340882), and another phase II study evaluated nivolumab and ramucirumab in previously treated patients with advanced, recurrent, and metastatic NSCLC (NCT03527108). One early phase clinical trial evaluated the feasibility and safety of the combination of nintedanib and nivolumab in pretreated patients with advanced NSCLC adenocarcinoma. (NCT02856425). As more combination strategies utilizing VEGF inhibitors have been explored, VEGF remains an important molecular target for NSCLC treatment.

MET

The mesenchymal–epithelial transition gene (c-MET) is a proto-oncogene that encodes a receptor tyrosine kinase that regulates cell proliferation, adhesion, and angiogenesis. Genomic alterations in MET occur in about 4% of patients with NSCLC and include exon 14 skipping mutations, MET amplification and MET fusions.[68] Several drugs, including tepotinib and capmatinib, are FDA-approved for treatment of NSCLC with MET exon 14 skipping mutations, and newer drugs are being studied with promising activity in early trials.[69–72]

MET amplification is also recognized as a potential therapeutic target although measuring amplification and determining the patient population most likely to benefit from MET-directed treatment can be challenging.[70] Gene amplification does not always correlate with MET protein expression assessed by IHC and measurement by FISH or NGS is necessary, with FISH being the gold standard. MET amplification is a recognized as mechanism of resistance to TKIs in EGFR-mutated NSCLC and occurs as a co-mutation in about 15% of those with EGFR and KRAS mutations and ALK and RET fusions.[72] Telisotuzumab vedotin is an antibody drug conjugate consisting of a c-Met antibody and a microtubule inhibitor. It achieved an ORR of 28.6%, mDOR of 8.3 months, mOS of 14.5 months and mPFS of 5.7 months in a phase II trial (NCT03539536) including patients with locally advanced/metastatic c-Met protein–over-expressing NSCLC with a manageable safety profile.[73]

REGN5093-M114 is an ADC that combines REGN, a human bispecific antibody that binds to two distinct epitopes of MET, to a microtubule inhibitor.[74] A phase I/II study (NCT04982224) is currently underway to evaluate the potential role of REGN5093-M114 in the treatment of patients with MET-overexpressing advanced NSCLC.[75] MET amplification remains an emerging molecular target for which there is potential for therapeutic intervention.

AXL/STK11

AXL is a receptor tyrosine kinase of the TAM family, which also includes TYRO3 and MERTK, with signaling mediated by the binding of its ligand, growth arrest-specific protein 6 (GAS6), and AXL receptor tyrosine kinase. This interaction triggers autophosphorylation of AXL and activates downstream pathways, such as PI3K-AKT-mTOR, MAPK/ERK, NF-κB, and JAK/STAT, which contribute to oncogenic processes.[76] AXL are overexpressed in several tumors, including NSCLC, and may be a mechanism of therapy resistance.[76,77] Additionally, STK11/LKB1 mutations in NSCLC drive upregulation of AXL and promote innate immune suppression by inhibiting dendritic cell activation and type I interferon signaling.[76,78]

AXL inhibitors have been studied in combination with immune checkpoint inhibitors with some promise. Bemcentinib (BGB324), a selective oral AXL inhibitor, has shown synergistic anti-tumor activity with immune checkpoint inhibitors by overcoming immune suppression conferred by STK11 mutations in a NSCLC a xenograft mouse model.[79] A Phase II trial (NCT03184571) of bemcentinib and pembrolizumab in second-line treatment of advanced/metastatic NSCLC patients showed an overall ORR of 11.1% and 21.9% in AXL>5 (H-score) patients, with a median OS of 13 months overall and 14.8 months in AXL>5 patients.[80] In November 2021, the FDA granted fast track designation to bemcentinib in combination with a PD-L1 agent for patients with STK11-altered advanced/metastatic NSCLC without actionable mutations. An ongoing phase Ib/IIa trial (NCT05469178) is investigating bemcentinib combined with pembrolizumab, carboplatin and pemetrexed as first-line treatment for advanced or metastatic non-

squamous NSCLC with a focus on patients with STK11 mutations.[81] Bemcentinib is also being studied in combination with docetaxel. A Phase I trial (NCT02922777) in previously treated advanced NSCLC patients showed that 6 of 17 patients (35%) had a partial response to bemcentinib plus docetaxel, and 9 (47%) had stable disease.[82] The main treatment-related adverse event was neutropenia, which occurred in 86% of patients despite receiving prophylactic G-CSF support.

Additional agents targeting AXL have been investigated, including Mecbotamab vedotin (CAB-AXL-ADC), an ADC that selectively targets AXL-expressing tumor cells.[83] This was evaluated in a phase II study as monotherapy and in combination with nivolumab in patients with AXL-expressing tumors who had progressed on prior immune checkpoint inhibitors, EGFR, or ALK inhibitors. It was found that patients with KRAS-mutated tumors had one-year OS of 58% versus 23% in the KRAS wild-type group.[84] While additional data are needed, and AXL is a promising molecular target for therapeutic intervention.

TROP2

Trophoblast cell surface antigen (TROP-2) is a transmembrane glycoprotein/intracellular calcium signal transducer that that is overexpressed in many cancers, including NSCLC, and its expression is associated with drug resistance and poor survival rates.[85] TROP2 acts as an intracellular calcium signal transducer, with downstream signaling pathways promoting cell survival, proliferation, and migration in cancer cells. ADCs targeting TROP2 offer a promising therapeutic strategy for treating TROP2-expressing NSCLC.[85] Sacituzumab govitecan (IMMU-132) is an antibody–drug conjugate (ADC) that consists of a humanized anti-TROP2 monoclonal antibody (hRS7) linked via a cleavable linker to SN-38, a cytotoxic payload and active metabolite of irinotecan. After binding to TROP2, hRS7 is internalized, delivering SN-38 into the tumor cell, where it triggers apoptosis.[85] A randomized phase III study evaluated Sacituzumab govitecan (SG) versus docetaxel in patients with advanced NSCLC who had progressed on platinum doublet chemotherapy and immunotherapy.[86] While not reaching statistical significance, there was an improvement in median OS in the SG arm compared to docetaxel arm (11.1 v 9.8 months). SG was also recognized as having a better safety profile than docetaxel.[86] While there may be potential in using a TROP2 inhibitor in the treatment of NSCLC, its efficacy is limited in an unselected population, and a biomarker is needed to direct patient selection for future studies.

Additional studies targeting TROP2 are ongoing. m deruxtecan (DS-1062, Dato-DXd), is a humanized TROP2 directed antibody linked to a topoisomerase 1 inhibitor via a tetrapeptide-based cleavable linker.[87] In a phase I study of previously treated patients (NCT03401385), Dato-DXd demonstrated encouraging antitumor activity in the NSCLC cohort with ORR of 26% and median duration of response of 10.5 months at the 6 mg/kg dose.[88] The phase II TROPION-Lung02 trial (NCT04526691) evaluated Dato-DXd in combination with pembrolizumab with or without chemotherapy in a cohort of patients with primarily treatment-naive NSCLC showed a promising ORR of 62% for patients and a tolerable safety profile.[89] A phase III study (NCT05215340, TROPION-Lung08) is currently ongoing to evaluate the safety and efficacy of first-line Dato-Dxd plus pembrolizumab versus pembrolizumab monotherapy in patients with advanced/metastatic NSCLC without AGAs and with a PD-L1 tumor proportion score ≥50%.[90]

PRMT5

The protein arginine methyltransferase (PRMT) family of enzymes is responsible for the methylation of arginine residues in histone proteins, a process that plays an important role in gene expression, DNA damage repair, and immune response.[91,92] Elevated expression of PRMT5 is associated with poor prognosis in NSCLC. Although several early stage trials targeting PRMT5 have not been successfully completed, a recent first-in-human study on AMG193 has demonstrated promise. AMG193 is an MTA-cooperative PRMT5 inhibitor that preferentially binds to and inhibits MTA-bound PRTM5. MTAP or CDKN2A deletion detected by NGS or MTAP deficiency of protein expression detected by immunohistochemistry were required for study enrollment, as deletion of MTAP results in MTA accumulation. The study found that AMG193 had a manageable safety profile at doses up to 1200 mg daily and an objective response rate of 21.4%.[91] While no therapies are currently FDA-approved to target PRMT5, there are clinical trials that are ongoing or planned, and this remains a potential therapeutic target warranting further study.

Conclusion

Targeted therapies have dramatically reshaped the treatment of NSCLC in a subset of patients; however, the lack of targetable driver mutations and the development of resistance to targeted therapies remain significant limitations for most patients to derive prolonged benefits. To overcome these challenges, ongoing research is focused on exploring novel molecular targets and developing novel combination approaches to enhance efficacy and delay drug resistance. There are currently many early phase clinical trials exploring new therapeutic options, and with continued advancements in the field, there is optimism that individualized, precision-based approaches to treatment will be available for more patients with NSCLC.

Disclosure

The authors report no conflicts of interest in this work.

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