

Sotorasib and other drugs comparison in treating non-small cell lung cancer

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Abstract. KRAS G12C is associated with poor diagnosis in non-small cell lung cancer (NSCLC), and this mutation accounts for 14% of total lung adenocarcinomas. Sotorasib is a KRAS G12C inhibitor drug that selectively treats NSCLC with KRAS G12C mutation. Other target therapies are available to treat NSCLC, and how Sotorasib differs in drug performance compared to other targeted therapies are not fully understood. This literature review compared Sotorasib with other NSCLC targeted therapy drugs to discuss the efficacy, side effect, and resistance between Sotorasib and other drugs that target NSCLC. Overall, Sotorasib did not show a pharmaceutical development innovation as it does not show an advantage in efficacy, side effects, and resistance compared to other drugs. Through reviews, Sotorasib could involve in group treatment with ErbB inhibition drug to better enhance the resistance outcome of the drug. As the side effect of both drugs is all severe, the safety of the combination needs further experiments.

Keywords: Sotorasib, non-small cell lung cancer (NSCLC), KRAS, Clinical trial.

1. Introduction

NSCLC accounts for 85% of lung cancer [1]. For subtypes of lung cancer there is adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, which respectively account for 38.5%, 20%, and 3% of total lung cancer in 2018 (1). For NSCLC cancer, there are multiple therapy types available, including surgery, radiation, chemotherapy, immunotherapy, radiofrequency ablation palliative procedures, and targeted therapy.

FDA approved Sotorasib as a targeted therapy drug that targets NSCLC in May 2021 [2]. Sotorasib inhibits KRAS (Kirsten rat sarcoma viral oncogene homolog), specifically in cancer cells with G12C mutation [2]. KRAS is a small GTPase associated with cell proliferation through PI3K and RAF pathways [3]. KRAS G12C mutation makes a KRAS an extra active form. KRAS G12C mutation is observed in approximately 14% of lung adenocarcinomas, associated with poor prognosis and therapy resistance [3]. In lung cancers, KRAS G12C mutation is also observed in approximately 5% of colorectal adenocarcinomas [3]. In NSCLC, KRAS G12C was observed approximately of 7.97% prevalence [4]. Therefore, Sotorasib has a tremendous therapeutic market. Sotorasib also has a high selectivity toward KRAS G12C mutation. It irreversibly binds to the mutated cysteine residue and locks the KRAS into an inactive state, thus efficiently inhibiting the downstream proliferation signal [3]. As KRAS protein has a very low turnover rate (half-life 22h), KRAS inhibition could bind to all the KRAS protein with a limiting amount, and the effect can last very long [5]. In the Sotorasib phase II trial, 960mg orally per day was given, and the objective response reached 37.1% with a 3.2% complete response; a significant tumor control effect was observed in 82.3% of the total participants, and the median of the overall survival is 12.5 month [6]. The progression-free survival has a median of 6.8 months, and using Kaplan–Meier estimate, there is 52.2% at six months and 37.5% at nine months of progression-free survival [6]. Sotorasib has a high percentage of adverse events, 99.2%, during phase II clinical trials [6]. The drug-related adverse event, from mild to severe, involves symptoms like nausea, fatigue, hypokalaemia, dyspnea, and pneumonitis [6]. Sotorasib is also subject to drug resistance. The downstream PI3K pathway can be activated by multiple proteins but not just KRAS; after KRAS inhibition, the cell with KRAS mutation may develop other pathways for proliferation and thus create resistance to Sotorasib [7]. There is also been shown that the amplification of YAP1

could regulate epithelial-mesenchymal transition (EMT), thus bypassing the suppressive effect KRAS inhibitor has [8].

Towards NSCLC, multiple targeted therapies are available for treatment with different therapeutic benefits and side effects. Therefore, the study aimed to discuss the difference between the efficacy, side effects and resistance caused by various targeted treatments to their target mutation compared to Sotorasib in treating NSCLC.

2. Different targets than Sotorasib

Sotorasib targets NSCLC with KRAS G12C mutation specifically. However, NSCLC cancer cells could have other mutations, which could be targeted for NSCLC treatment. For example, Erlotinib, Afatinib, and Osimertinib are Epidermal Growth Factor Receptor (EGFR) inhibitors. Crizotinib, Alectinib, and Brigatinib are Anaplastic Lymphoma Kinase (ALK) inhibitors. Larotrectinib is a Neurotrophic tyrosine receptor kinase (NTRK) inhibitor. Dabrafenib and Trametinib are BRAF inhibitor. Tepotinib is a MET inhibitor. Palestine, and Scleractinia are RET inhibitors.

2.1. Target Epidermal Growth Factor Receptor (EGFR) compared to Sotorasib

EGFR is a tyrosine kinase belonging to the ErbB family. Its inhibitor is a group of drugs that inhibit EGFR to inhibit downstream signal PI3K and RAS pathway, thus inhibiting cell proliferation [9]. Compared to Sotorasib, KRAS inhibitors, although they target different proteins, target the same downstream signal, PI3K and RAS pathway [9]. ErbB family includes, ErbB-1 (EGFR), ErbB-2 (HER2/neu), ErbB-3 (HER3), and ErbB-4 (HER4), in which some drugs can inhibit more than one ErbB dimer type to induce multiple cellular apoptoses, anti-migration, and anti-proliferation process [9]. EGFR exon 19 deletion and L858R mutation are often found in NSCLC patients with 10–26% [10]. The mechanism and the generation of EGFR inhibitors are listed in Figure 1.

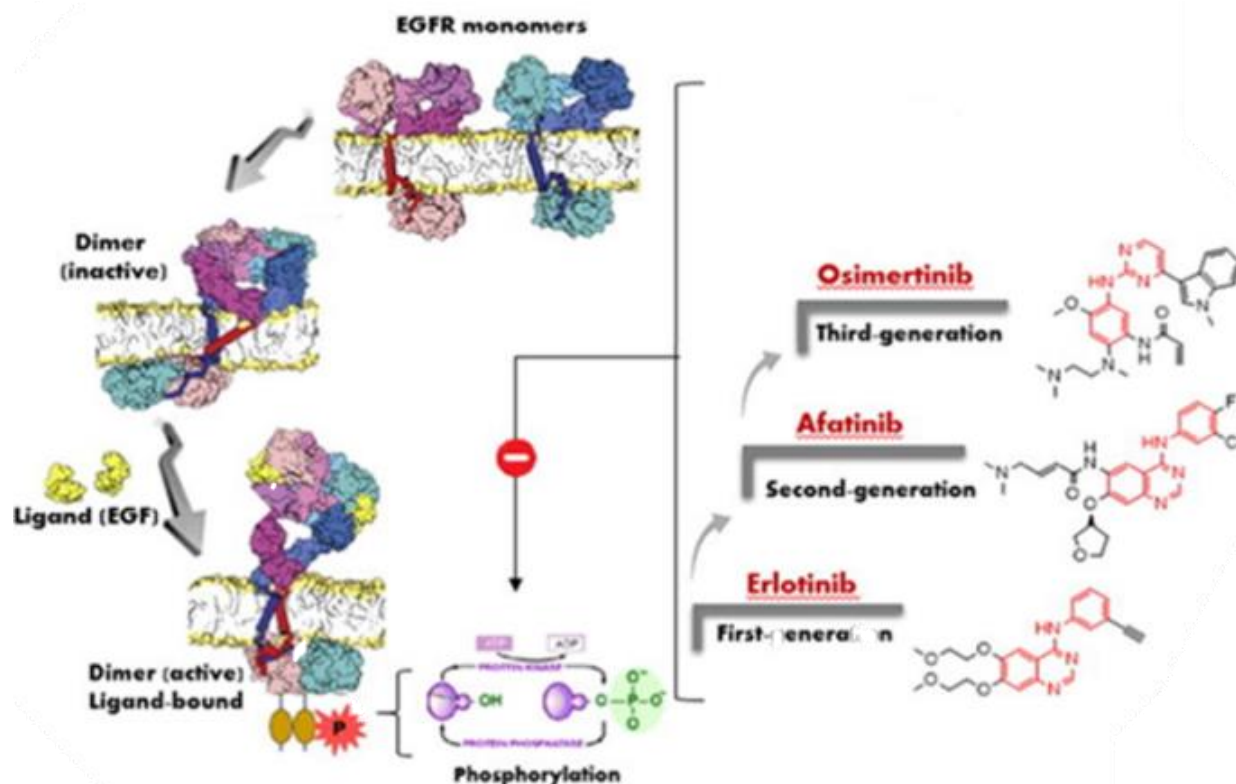


Figure 1. Mechanism of EGFR inhibitor drugs and the generation of Erlotinib, Afatinib and Osimertinib [11].

Erlotinib is a first-generation EGFR-only reversible inhibitor that works through the ATP competition pocket in the intracellular domain [12]. In phase III clinical trial, 150 mg orally per day

of Erlotinib, progression-free survival median is 9.4 months, 40% of individuals achieve 1-year progression-free survival, and 11% of individuals achieve two years progression-free survival [10]. Overall, it is better than sotorasib performance. The total adverse reaction incidence is the similar between the two drugs (Table 1). For Erlotinib, about 98% of participants experience various kinds of side effects, for example, fatigue, rash, diarrhea, anemia, neuropathy, alopecia, arthralgia, and aminotransferase rise [10]. As EGFR inhibition drugs bind to the ATP pocket on EGFR, the cancer cells will develop resistance through ATP binding pocket mutation, thus affecting binding or increasing ATP binding affinity [13]. For example, T790M secondary mutation changes ATP pocket shape to an increase ATP affinity [13]. Erlotinib tolerance mechanism can also be achieved through the mutation or extra activation of other pathways, for example, ERBB2 amplification that increases HER2 expression and amplification of MET, thus activating downstream PI3K and RAS [13]. As Sotorasib could target KRAS mutation G12C, patients with the KRAS G12C resistance created from EGFR inhibitor could be treated with Sorotasib to enhance a better result by acquired T790M, ERBB2 amplification, and MET amplification.

Afatinib is a second-generation tyrosine kinase inhibitor that inhibits ErbB as an intracellular ATP-competitor [14]. Afatinib inhibits and binds irreversibly to all ErbB family dimers [13] with a different target than Sotorasib. In phase III clinical trial of Afatinib, NSCLC patients with a genetic test with a mutation with extra active EGFR are given 40mg drug orally once daily. Patients have 11.1 months of progression-free survival [15], higher than Sotorasib, 6.8 months. Nearly all participants experience some degree of adverse events, which is similar to Sotorasib. However, Afatinib has fewer side effects incidences above and is equal to grade 3 than Sotorasib (Table 1). Other common adverse event includes skin irritation, stomatitis, fatigue, rash, paronychia, and decreased appetite [15]. The rare adverse event includes leukopenia and neutropenia [15]. In addition, Afatinib resistance can be achieved through acquired T790M, ERBB2 amplification, and MET amplification similar to Erlotinib.

Osimertinib is a third-generation EGFR irreversible inhibitor that targets Cys-797 on the intracellular ATP binding site [16]. Unlike the first and second generation of EGFR inhibitors, where the resistance could accumulate at the ATP binding site, Osimertinib could bind with cells with EGFR T790M mutation and inhibit EGFR function. In the phase II clinical trial, 80mg drug was administered daily through an oral route. The progression-free survival has a median of 8.3 months, better than Sotorasib. Side effects involved in gastrointestinal discomfort and skin manifestations were shown in 89.5% of participants, similar to Sotorasib. A severe pneumonitis adverse event was observed in 1 of 19 patients [17], which is not seen in Sotorasib. EGFR-dependent resistance was observed after Osimertinib treatment, including acquired C797S, loss of T790M, and ex19de. Independent EGFR resistants were also raised, including KRAS mutations, MET amplification, and gene fusion that could bypass EGFR-mediated cell growth [18].

Table 1. Comparison between Sotorasib and EGFR Inhibitors

Drug	Target	Efficacy	Side effect	Resistance
Sotorasib	irreversible KRAS G12C inhibitor	Objective response 37.1%. Tumor shrinkage 82.3%. Progression-free survival median 6.8 months. Median of the overall survival is 12.5 months	Total (all level: (99.2%), level \geq Grade 3: (61.2%)). diarrhea (50.8%), nausea (31.0%), fatigue (25.4%), hypokalemia (4%), dyspnea (1.6%), pneumonitis (1.6%)	other PI3K activation, YAP1 amplification
Erlotinib	reversible EGFR inhibitor	Progression-free survival 9.4 months.	Total (all level: (98%), level \geq Grade 3: (45%)), fatigue (57%), rash (80%), diarrhea (57%), anemia (12%), neuropathy (9%), alopecia (14%), arthralgia (11%) and aminotransferase rise (6%)	T790M, ERBB2 amplification, and MET amplification
Afatinib	irreversible inhibition to all ErbB family dimer	Objective response rate 70%. Progression-free survival 11.1 months. Overall survival 25.8 months	Total (all level: (95.2%), level \geq Grade 3: (14.4%)) diarrhea (95.2%), rash (89.1%), stomatitis (72.1%), fatigue (17.5%), paronychia (56.8%), decreased appetite (20.5%), leukopenia (1.7%), neutropenia (0.9%)	T790M, ERBB2 amplification, and MET amplification
Osimertinib	EGFR with/without T790M mutation	Objective response rate 66.7%. Progression-free survival 8.3 months.	Total (all level: (89.5%), level \geq Grade 3: (31.6%)), gastritis (21%), paronchia (21%) rash (15.8%), pneumonitis (5.3%)	acquired C797S, loss T790M, and ex19de, KRAS mutations, MET amplification

2.2. Target Anaplastic Lymphoma Kinase (ALK) compare to Sotorasib

ALK is a tyrosine kinase in the insulin receptor family mainly expressed during embryonic development. ALK mutation accounts for 5-6% of total NSCLC. In NSCLC cancer cells, ALK arrangement (ALK-R), like fusion with EML4, amplification (ALK-A), and point mutation like C1156Y and L1196M, can increase ALK activation, thus increasing cell proliferation and migration through Ras, JAK, PI3K and PLC- γ pathways [19].

Crizotinib is a first-generation tyrosine inhibitor that can inhibit ALK, ROS1, and MET receptors [20]. The progression-free survival is 10.4 months which is better than Sotorasib. The side effect between Crizotinib and Sotorasib are similar. Almost all participants have adverse events, including nausea, fatigue, hypokalemia, dyspnea, and pneumonitis [21].

Alectinib is the second generation of ALK, which has better efficacy and a lower high level of side than Crizotinib. The progression-free survival is 25.7 months which is also better than Sotorasib. Side effects were similar to Sotorasib and various adverse events were shown in all participants, such as nausea, diarrhea, vomiting, peripheral edema, anemia, and alopecia [21].

Brigatinib is the third generation of ALK. It has better efficacy and similar side effect. The progression-free survival is 16.8 months which is better than Sotorasib. Almost every participant has shown various types of adverse reactions which is also similar to Sotorasib. One of the adverse reactions, blood creatine phosphokinase increases in 50% of participants, is not observed in the clinical trial of Sotorasib [22].

Table 2. Comparison between Sotorasib and ALK Inhibitors

Drug	Target	Efficacy	Side effect	Resistance
Sotorasib	irreversible KRAS G12C inhibitor	Objective response 37.1%. Tumor shrinkage 82.3%. Progression-free survival median 6.8 months. Median of the overall survival is 12.5 months	Total (all level: (99.2%), level \geq Grade 3: (61.2%)). diarrhea (50.8%), nausea (31.0%), fatigue (25.4%), hypokalemia (4%), dyspnea (1.6%), pneumonitis (1.6%)	other PI3K activation, YAP1 amplification
Crizotinib	ALK, ROS1, and MET tyrosine kinase competitive inhibitor	Objective response rate 75.5%. Progression-free survival 10.4 months.	Total (all level: (97%), level \geq Grade 3: (50%)) nausea (48%), diarrhea (45%), vomiting (38%), peripheral edema (28%), anemia (5%), alopecia (7%)	extra activation of EGFR, KIT, IGF-1R, SRC, and MEK/ERK pathway. For acquired mutation, G1202R and E1210K
Alectinib	ALK selective competitive inhibitor	Objective response rate 82.9% Progression-free survival 25.7 months.	Total (all level: (97%), level \geq Grade 3: (41%)) nausea (14%), diarrhea (12%), vomiting (7%), ALT increase (15%), anemia (20%), myalgia (16%), peripheral edema (17%)	extra activation of EGFR, KIT, IGF-1R, SRC, and MEK/ERK pathway. For acquired mutation, G1202R and E1210K
Brigatinib	ALK and crizotinib-resistant ALK mutants' competitive inhibitor	Objective response rate 57%. Progression-free survival 16.8 months.	Total (all level: (100%), level \geq Grade 3: (78%)) diarrhea (58%), nausea (33%), dyspnea (24%), fatigue (21%), blood creatine phosphokinase increase (50%), hypertension (32%), pneumonia (10%)	extra activation of EGFR, KIT, IGF-1R, SRC, and MEK/ERK pathway. For acquired mutation, G1202R and E1211K

All three generations of ALK inhibitors have resistance mechanisms, and they are generally not subject to KRAS-involved caused resistance mechanisms. Bypass ALK signaling resistance is present in all ALK inhibition drugs which includes the extra activation of EGFR, KIT, IGF-1R, SRC, and MEK/ERK pathways. For acquired mutation, although the further generation of ALK inhibitor could target possible mutation, they are subject to acquired mutations like G1202R and E1210K [23]

2.3. Target Neurotrophic tyrosine receptor kinase (NTRK) compare to Sotorasib

NTRK is the oncogene that encodes for receptor tyrosine kinases (TRK), which involves neural and embryonic development. NTRK fusion protein is a common type of mutation observed in cancer cells that can create TRK protein to activate without ligand stimulation. In addition, overexpression of TRK can result in over proliferation through downstream PI3K and MAPK pathways [24].

Table 3. Comparison between Sotorasib and NTRK Inhibitors

Drug	Target	Efficacy	Side effect	Resistance
Sotorasib	irreversible KRAS G12C inhibitor	Objective response 37.1%. Tumor shrinkage 82.3%. Progression-free survival median 6.8 months. Median of the overall survival is 12.5 months	Total (all level: (99.2%), level \geq Grade 3: (61.2%)). diarrhea (50.8%), nausea (31.0%), fatigue (25.4%), hypokalemia (4%), dyspnea (1.6%), pneumonitis (1.6%)	other PI3K activation, YAP1 amplification
Larotrectinib	tyrosine kinase type A, B and C competitive inhibitor	Objective response rate 75%. Progression-free survival median is 28.3 months. Overall survival median 44.4 months.	Total (mainly in grade1 and grade 2, level \geq Grade 3: (14%)) fatigue (30%), cough (27%), elevation of alanine/aspartate aminotransferase (28%)	TRKA G595R and G667C, TRKC G623R, and ALK and ROS1 extra-activation

Larotrectinib is selective for tyrosine kinase type A, B, and C. Larotrectinib is very effective in NSCLC. For patients with NSCLC, the progression-free survival median is 28.3 months higher than Sotorasib. Common side effect includes fatigue and cough, which is similar to Sotorasib. However, Larotrectinib has fewer adverse events in grade 3 and above than Sotorasib [25]. For resistance, although Larotrectinib has a better affinity toward both wild-type and mutated NTRK, resulting in less acquired resistance through structure mutation than Sotorasib, its kinase domain could still have resistance from mutations that increases ATP affinity toward NTRK [24]. For example, resistance can also be produced from Larotrectinib through mutation, such as TRKA G595R and G667C, and TRKC G623R. In addition, the resistance also can be caused by the amplification through other proliferation pathways like ALK and ROS1 extra-activation [26].

2.4. Target B-Raf Proto-Oncogene, Serine/Threonine Kinase (BRAF) compare to Sorotasib

In the MAPK pathway, BRAF V600E is the mutation that accounts for 1-5% of total NSCLC. Dabrafenib and Trametinib often are prescribed together to treat cancer cells with BFAR V600E mutation. Dabrafenib is a competitive inhibitor selective to BRAF V600E mutation, often prescribed 150mg twice daily orally. Trametinib is a MEK inhibitor and is prescribed with 2mg once daily orally. BRAF and MEK belong to the MAPK pathway, and the dual inhibition has clinical efficacy with a 10.8 progression-free survival median in patients without previous systemic treatment. The side effect includes pyrexia, nausea, vomiting, diarrhea, peripheral edema, cough, hypertension, and increased alanine aminotransferase [27]. Overall, this combination treatment has shown to have higher efficacy and a worse level of side effects compared to Sotorasib.

The dual drug combination is also subject to drug resistance, although the resistance is lower than Sotorasib. The combination of Dabrafenib and Trametinib lowers the resistance by avoiding other MAPK pathway protein resistance mutations. For example, only Dabrafenib could result in resistance like MET, CRAF, and COT up-regulation. In addition, only Trametinib could result in resistance, like increased BRAF expression. The acquired mutation decreases as two targets in the MAPK pathway are targeted [28]. However, the mutation caused by bypassing the MAPK pathway still exists, such as genomic mutations like PTEN and AKT mutations [29].

Table 4. Comparison between Sotorasib and BRAF Inhibitors

Drug	Target	Efficacy	Side effect	Resistance
Sotorasib	irreversible KRAS G12C inhibitor	Objective response 37.1%. Tumor shrinkage 82.3%. Progression-free survival median 6.8 months. Median of the overall survival is 12.5 months	Total (all level: (99.2%), level \geq Grade 3: (61.2%)). diarrhea (50.8%), nausea (31.0%), fatigue (25.4%), hypokalemia (4%), dyspnea (1.6%), pneumonitis (1.6%)	other PI3K activation, YAP1 amplification
Dabrafenib	BRAF competitive inhibitor	Objective response rate 63.9% progression-free survival median is 10.8 months. Overall survival median 17.3 months	Total (all level: (99%), level \geq Grade 3: (74%)) pyrexia (56%), nausea (51%), vomiting (41%), dry skin (39%), peripheral edema (38%), diarrhea (37%), decreased appetite (33%), and cough (31%).	Only dabrafenib, MET, CRAF, COT up regulation. Only trametinib, increase BRAF expression.

2.5. Target MET Proto-Oncogene, Receptor Tyrosine Kinase (MET) compare to Sorotasib

MET is a tyrosine kinase that can activate downstream Akt, JNK, and Ras/Raf/MAPK pathways [30]. Tepotinib is a type 1b MET inhibitor that inhibits kinase function through ATP competition. MET alternation was seen in 3-4% NSCLC which MET exon 14 is often seen in patients 70+. 150mg orally once daily was administered, and progression-free survival of patients with brain metastasis has a median of 10.9 months which is better than Sotorasib. Almost all participants experienced different adverse events, like edema and gastrointestinal side effects [31]. The number of participants who experience adverse events greater than level three is lower than Sotorasib, and the common adverse events are similar.

The acquired resistance can be caused by increased kinase activate sites like D1228X, L1195X, and Y1230X, or through MET expression amplification. The resistance also can be caused by bypassing MET signalling through EGFR, HER2, HER3, and MAPK pathway amplification. Dual drug combinations are sometimes used in clinical to overcome the resistance caused by single inhibition [32]. Sotorasib could be used in this combination to decrease drug resistance.

Table 5. Comparison between Sotorasib and MET Inhibitors

Drug	Target	Efficacy	Side effect	Resistance
Sotorasib	irreversible KRAS G12C inhibitor	Objective response 37.1%. Tumor shrinkage 82.3%. Progression-free survival median 6.8 months. Median of the overall survival is 12.5 months	Total (all level: (99.2%), level \geq Grade 3: (61.2%)). diarrhea (50.8%), nausea (31.0%), fatigue (25.4%), hypokalemia (4%), dyspnea (1.6%), pneumonitis (1.6%)	other PI3K activation, YAP1 amplification
Tepotinib	MET competitive inhibitor	Objective response rate 46%. Progression-free survival median is 10.9 months. Overall survival median 17.1 months	Total (all level: (89%), level \geq Grade 3: (27%)) peripheral edema (63%), nausea (26%), diarrhea (22%), aspartate/alanine aminotransferase increased (14%), amylase increase (11%)	D1228X, L1195X, and Y1230X, MET expression amplification, bypass MET signaling (amplification of EGFR, HER2, HER3, and MAPK)

2.6. Target RET Proto-Oncogene, Receptor Tyrosine Kinase (RET) compare to Sorotasib

RET-fusion accounts for 1-2% of the total NSCLC. Common RET fusion partners, including KIF5B and CCDC6, induce an active conformation of RET when ligands are not present. The extra active RET drives cell proliferation [33].

Pralsetinib has a progression-free survival is 9.14 months which is better than Sotorasib. However, Pralsetinib has adverse effects on neutropenia (45%) and decreases white blood cell count (27%), not seen in Sotorasib. Overall, the percentage of patients who experience grades bigger than grade 3 is lower than Sotorasib [34].

Selpercatinib has a progression-free survival is 18.4 months which is better than Sotorasib. For both Selpercatinib and Sotorasib participants, nearly everyone experiences any adverse event, like diarrhea and fatigue. However, Selpercatinib shows adverse effects of prolonged QT and thrombocytopenia, not seen in Sotorasib. [35].

For resistance, Pralsetinib and Selpercatinib competitively inhibit RET through ATP binding site. The resistance could be acquired through the structure change of non-gatekeeper mutation, for example, V738A, Y806C, and G810C [36]. In addition, resistance can bypass RET signaling to mediate cell proliferation, for example, through amplification of EGFR and ALK-driven signaling [37]. Therefore, RET inhibitors are also subject to structure and systemic mutation like Sotorasib.

Table 6. Comparison between Sotorasib and RET Inhibitors

Drug	Target	Efficacy	Side effect	Resistance
Sotorasib	irreversible KRAS G12C inhibitor	Objective response 37.1%. Tumor shrinkage 82.3%. Progression-free survival median 6.8 months. Median of the overall survival is 12.5 months	Total (all level: (99.2%), level \geq Grade 3: (61.2%)). diarrhea (50.8%), nausea (31.0%), fatigue (25.4%), hypokalemia (4%), dyspnea (1.6%), pneumonitis (1.6%)	other PI3K activation, YAP1 amplification
Pralsetinib	RET competitive inhibitor	Progression-free survival, median 9.14 months.	Total (all level: (93%), level \geq Grade 3: (48%)) neutropenia (45%), decrease white blood cell count (27%), hypertension (21%), anemia (31%), and pneumonia (6%)	non-gatekeeper mutation V738A, Y806C, and G810C. EGFR and ALK amplification
Selpercatinib	RET competitive inhibitor	Objective response 64%. Progression-free survival, median 16.5 months.	Total (all level: (100%), level \geq Grade 3: (58%)) diarrhea (48%), dry mouth (41%), hypertension (31%), fatigue (29%), aspartate aminotransferase level increase (30%), constipation (26%), Prolonged QT (16%), thrombocytopenia (15%)	

3. Future Perspectives

Sotorasib is a new targeted drug for NSCLC that FDA has newly passed. For efficacy, Sotorasib showed a lower progression-free survival with 6.8 months, lower than most target therapy drugs, but higher than chemotherapy. However, Sotorasib gives patients who have a KRAS G12C a better choice of drug as Sotorasib dose show selectivity toward that mutation. In addition, it is the only type

of drug that targets KRAS in NSCLC treatment. Therefore, for patient KRAS G12C mutation, Sotorasib shows acceptable clinical efficacy.

Although Sotorasib shows acceptable clinical efficacy, the resistance and side effects are still the main issue during treatment. When comparing Sotorasib with other NSCLC targeted therapy drug, Sotorasib show a better percentage of severity above and equal grade 3. Both structure and systemic mutation for resistance are shown after long-term drug use, just like other target therapy drugs approved before. Therefore, Sotorasib did not show a progression in drug discovery of side effects and anti-resistant treatment in NSCLC. In the example of the MAPK pathway, drugs dabrafenib and trametinib are often used together to target two proteins within the MAPK pathway, thus decreasing drug resistance.

As RAS is involved in multiple signalling pathways, Sotorasib could be administered currently with another targeted therapy drug to minimize the possibility of drug resistance, thus increasing the progression-free survival period of NSCLC patients. Cancer cells could acquire Sotorasib resistance through PI3K amplification, bypassing KRAS, for example, ErbB [38]. Cancer treated with ErbB inhibitors could also acquire KRAS mutation to acquire resistance. Therefore, ErbB inhibitors could group with Sotorasib for better resistance and clinical outcome. KRAS is also involved in the MET inhibitor-resistant mechanism. Therefore, Sotorasib could decrease MET inhibitor resistance when administered along with MET inhibitor. However, both drugs have profound side effects. So, the safety of the combination and dosage should be better tested before experimenting.

4. Conclusion

Sotorasib is a newly admitted KRAS-targeted drug that is used to treat NSCLC. Sotorasib is the first approved KRAS inhibition cancer treatment drug that passed FDA approval. Although Sotorasib has a better selectivity to KRAS mutation than other targeted drugs, Sotorasib shows lower efficacy, a higher possibility of experiencing profound side effects, and is prone to resistance. Therefore, Sotorasib did not present better pharmaceutical development. For resistance, ErbB inhibitors and RAS inhibitors could be combination drugs that treat concurrent with Sotorasib to lower its resistance. However, as the side effect of the targeted therapy drug is severe, the combination's safety still needs further testing.

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