The discovery and treatment of Sotorasib in cancer immune

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Abstract. Sotorasib is a targeted drug that cures Non-small lung cancer (NSCLC), approved by the FDA recently. It is the only drug from now that can inhibit the KRAS G12C mutation invented by Amgen. Compared to the standard treatment for lung cancer, Sotorasib is a more effective and safer drug for patients to use. According to the clinical trials data published online, we found that the patients were getting other previous treatments like chemotherapy to deal with their cancer. This is a mandatory requirement for patients to get Sotorasib. By collecting and analyzing the data from clinical research, we found out that patients who take Sotorasib rather than the standard treatment live longer. The cancer cells reduce their size significantly and stop growing for several months, which is a great success for science. Also, most of the patient who takes this drug does not show a very high and serious degree of adverse effects, proving that this drug is safe for the human body. But for, patients who continue taking this drug should regularly see a professional doctor check their liver's function since this drug can cause serious cirrhosis. However, we also find out some of the significant disadvantages of this drug. For example, the unbearable financial budget the patient might have suffered by taking this expansive drug, the availability to take this drug in various countries, and its limitation to cure cancer. This article will briefly introduce the reader and comprehensively the development, structure and primary function, mechanism, preferred doses, and further latest repurposing marketing research about Sotorasib.

Keywords: Sotorasib, Clinical, Cancer, Treatment.

1. INTRODUCTION

Cancer is a hazardous disease caused by the uncontrolled growth of cells that spread throughout the body. Cancer can start anywhere and is made up of trillions of different cells. Normally, cells grow and multiply themselves to keep the body functioning all the time. They die as the cells grow old or are lost and replaced by new cells. Although this process is orderly, factors beyond our bodies' control can also happen sometimes, leading to our normal body cells uncontrollably multiplying and reproducing themselves all the time, which leads to them becoming cancer cells. Then the tumors form, and these tumors are tissue masses. Tumors can be malignant or benign [1]. NSCLC is different from small cell lung cancer (SCLC) for it occurs on epithelial surface of the lung. Because NSCLC is generally less sensitive to chemotherapy and radiotherapy and radiotherapy is not effective enough to cure the disease, the combination of radiotherapy and chemotherapy can achieve long-term survival for locally advanced unresectable diseases [2].

KRAS G12C is one of the most common driving mutations in NSCLC, with approximately 13% of non-squamous NSCLC patients in the United States having KRAS G12C mutations. Since KRAS was first reported to be associated with cancer, evidence for its carcinogenic effect has been accumulating. Activation of KRAS mutations is common in human cancers. Amgen's Sotorasib is based on a single-arm, open-label, Phase I/II trial that enrolled patients carrying KRASG12C mutations. Among 124 patients with disease progression, the median duration of response was ten months. Continued acceptance of this indication may depend on the validation and description of clinical benefits in confirmatory trials. The FDA approved Sotorasib after receiving the largest clinical trial results of CodeBreaK with about 100 patients. CodeBreaK 100 is also the most extensive clinical trial study conducted in patients with the genetic abnormality -- KRAS G12C mutation. In

this clinical trial, patients showed exciting medical outcomes, and all of them were followed by immunotherapy or chemotherapy. In all trials, the objective response rate achieved by Sotorasib 960 mg was 36 percent, with 81 percent of patients achieving the desired disease control: complete response, partial response, and remission of disease stability for more than three months. The mean duration of remission from the first assessment of CR or PR to the initial evaluation of PD and death from any cause was ten months. It is worth noting that 9 percent of patients with excessive adverse reactions have permanently discontinued Sotorasib [3]. Two hundred four once-daily Sotorasib doses of 960 mg were recorded in CodeBreak 100 patients with KRAS G12C mutated NSCLC, all of which showed well-controlled tolerability. The incidence of the most common adverse events (AE) was more significant than or equal to 20% in patients treated with Sotorasib, among which the most representative adverse events (AE) of hepatotoxicity and their probability were diarrhea (42%), cough (20%), etc. The most common grade 3 or 4 AE involving laboratory abnormalities is greater than or equal to 5 percent, typically hepatotoxicity (12 %), diarrhea (5 %), etc [4]. In another experiment, 50% of patients treated with Sotorasib have Severe AE. More precisely, 8% of those patients get pneumonia, 3% of them have hepatotoxicity, and 2% of them have diarrhea. Due to AE,5% of patients were required to reduce their Sotorasib dosage, and 34% of them were required not to take up this drug. Most patients reported that they can take the side effects of the GP5 program of Sotorasib 's Assessment of Cancer Therapeutic Function - General Questionnaire [5]. However, in some extreme cases, Sotorasib can cause some serious side effects to humans. According to the prescribing information in the US, Sotorasib may cause hepatotoxicity and potentially fatal interstitial lung disease (ILD)/pneumonia [6].

This review focuses on Sotorasib, a non-small cell lung cancer drug. Sotorasib is a cancer drug developed by Amgen. Amgen's phase I clinical trial of the drug was completed in 2020. In December 2019, a Phase II clinical trial was approved to begin. Because KRAS G12C mutations are common in cancer types, including more than 10 percent of non-small cell lung cancer patients and 5 percent of colorectal cancer patients, Sotorasib is the first drug to target this mutation. Expectations are high. Sotorasib has been granted fast track designation in the United States for the treatment of metastatic non-small cell lung cancer with KRAS G12C mutations [7].

2. The development of Sotorasib

In September 2020, Trial results showed that Sotorasib (AMG510) obtained an excellent antitumor activity in treating NSCLC carrying KRAS G12C mutations. In the multicentre, non-blind, phase I CodeBreaK100 trial, 34 patients with severe pre-treated KRAS G12C-positive NSCLC received a 960mg dose of Sotorasib, and a good safety profile [7]. FDA granted Breakthrough Therapy designation to Sotorasib to treat locally advanced or metastatic KRAS G12C mutant non-small cell lung cancer. This designation was obtained based on the Phase II CodeBreaK 100 trial results in patients with advanced NSCLC who developed disease progression following chemotherapy and/or immunotherapy. Sotorasib demonstrated persistent antitumor activity and a good safety profile [8].

Amgen submitted a New Drug Application (NDA) for Sotorasib to the FDA and a marketing authorization application (MAA) for Sotorasib to the European Medicines Agency (EMA) for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS G12C mutation [8]. In CodeBreaK 100's Phase II trial results, Sotorasib was reported in 126 patients with KRAS G12C mutation in advanced non-small-cell lung cancer. It demonstrated a determined objective response rate of 37.1%, a disease control rate of 80.6%, and a median duration of response of 10 months. Then China granted Breakthrough therapy designation to Sotorasib for Amgen. It is the first time and the first such certification after strategic cooperation with Baekgenshenzhou. FDA recommends conducting a multicentre randomized clinical trial comparing a once-daily dose of LUMAKRAS (Sotorasib) at 960mg to a lower daily dose as part of an ongoing development program. Based on preclinical, pharmacokinetic, and clinical data, Amgen plans to compare 960mg once daily with 240mg once daily [9].

3. The structure and mechanism of Sotorasib

The *KRAS* gene is an oncogene, which belongs to the RAS family. RAS family as a group of common oncogenes accounts for not only NSCLC but also colorectal cancer (CRC)and pancreatic duct adenocarcinoma (PDAC) according to the National Cancer Institute database. When KRAS mutated, it will turn normal cells into cancer cells.

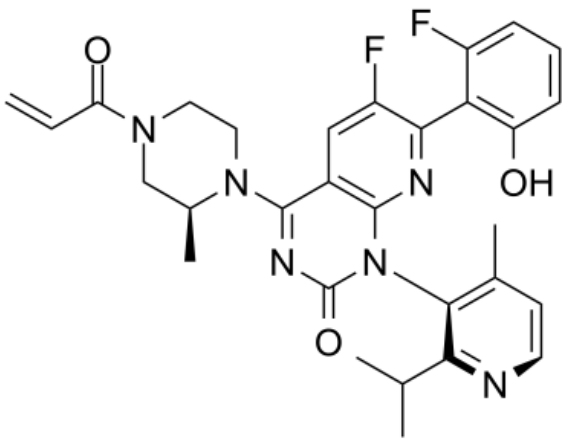

Figure 1. The structure of Sotorasib.

There are several pathways inside the cells to ensure they can work properly. Two of the millions of the cell reaction pathways are RAF/MEK/ERK pathway and the P13K/AKT/mTOR pathway. But both pathways do not depend on KRAS gene regulation, so it might raise a high probability to increase the KRAS inhibitors resistance in the human body [10]. To improve the performance of target drugs, scientists added SHP2 inhibitor with KRAS inhibitor together to treat patients, and they found that by using this method, 71% of NSCLC patients with KRAS G12C mutation shows some degree of disease control. KRAS G12C/SHP2 co-inhibitor conferred extended survival in all models with no evidence of toxicity and, with the preference of SHP2 inhibitor, KRAS G12C inhibitor's performance is well enhanced. Because this particular co-inhibition creates a more favourable micro immune environment and sensitized tumours to PD-1 inhibition. Co-inhibition methods can also work well with RTKs. Although co-inhibition has some fascinating benefits to overcome the KRAS G12C mutation resistance, it does have some major downfalls. For example, the efficacy of the drug could be different when scientists let the drug goes in different stream or pathways. If the drug chose to go into the upstream co-inhibition, it will have a higher efficacy to target cancer than downstream co-inhibition [10].

RAS proteins are regulated by different effectors to control signal transduction for a variety of cellular functions (RAS is upstream of these targets), such as survival, proliferation, and differentiation. The dysfunction of these cells constitutes many of the hallmarks of cancer. RAF is the first kinase (MAPK) pathway in mitogen-activated protein kinases that phosphorylates MEK, which in turn activates extracellular signal-regulated kinase (ERK). ERK activates cytoplasmic substrates and is transferred to the nucleus to stimulate participation in cell proliferation, survival, differentiation, and cell cycle regulation. MAPK signaling has been widely documented in ras-mediated tumorigenesis. Phosphatidylinositol-4, 5-diphosphate 3-kinase (PI3K) plays a key role in RAS-mediated tumgenesis. AKT activates phosphorylated substrates leading to several of its physiological functions, such as mammalian target of rapamycin (mTOR), stimulating cell cycle progression, survival, metabolism, migration, and resistance to apoptosis.

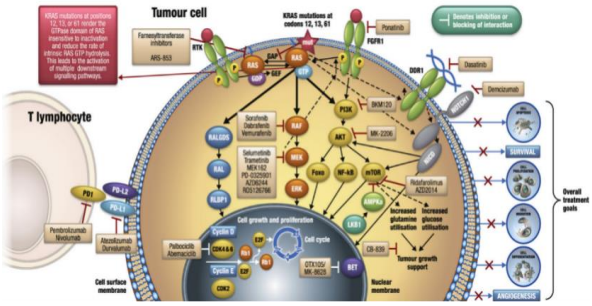

Figure 2. RAF/MEK/ERK pathway and the P13K/AKT/mTOR pathway.

4. The application of Sotorasib in NSCLC

Sotorasib has shown a positive benefit-risk profile in patients with locally advanced and metastatic NSCLC with rapid, profound, and long-lasting anticancer activity and is taken orally once daily. The KRAS G12C inhibitor Sotorasib has long-lasting clinical benefits and mild side effects — including diarrhea (30%), fatigue (23%), and nausea (21%). Although some of the patients showed stubborn cancer resistance, the response rate (32%) and the majority achieved disease control (88%) of patients with NSCLC is good. Their median progression-free survival was 6.3 months [11]. The City of Hope Gastrointestinal Cancer Program director stated that combining Sotorasib with other therapies that block epidermal growth factor receptor (EGFR) seems more promising than only use KRAS G12C inhibition.

5. Sotorasib is also being studied in a variety of other solid tumours

Sotorasib is effective in patients with solid colorectal tumours. In a phase I trial of Sotorasib, patients with pretreated solid tumors performed well in lung and colorectal cancer. Although in multi-site clinical trials, it included 129 pre-treated patients with metastatic cancer who all had KRAS G12C gene mutation increases the individual's chances of being resistant to the treatment. Medical oncologists demonstrated that targeting and inhibition of RAS are possible. These would be the very first steps to effectively treating RAS mutated cancers [12].

KRAS G12C mutations are associated with poorer treatment outcomes for various cancers, including lung and colorectal cancer. In some cases, this proof-of-concept study showed that the median progression-free survival was twice that we encounter in patients today. By blocking specific pockets, Sotorasib deactivates the mutated KRAS protein, so that the tumour will not grow and spread.

The clinical trial was also designed to test the optimal doses of Sotorasib taken orally once a day. And the scientists found out 960mg works the best. In this study, 46% of the patients had refractory metastatic non-small cell lung cancer, and 33% of them had colorectal cancer, and 21% of them had other tumour types. The patients' age average was 62, and they were followed up for a median of 12 months of studies. In all the cell lines, this drug appears to be most effective in non-small cell lung cancer [12].

Patients were also found significantly benefited from this drug. The data shows the overall response rate is approximately 7%, the disease control rate is 74%, the primary tumor-shrinking rate is 7%. Among comparable treatment regiments, remission rates were rare, and the median progression-free survival was about two months which means Sotorasib is very durable. Controlling tumour progression with oral therapy for several months is a significant result [12].

6. Limitation and future development

The latest research shows that some of the human body starts to show the KRAS G12C mutation inhibitors resistance. Scientists try to combine KRAS G12C inhibitors with other inhibitors together to form a co-inhibition strategy to cure the disease. All those other inhibitors are selected from several

main chemical substances shown in KRAS protein regulation pathways inside the cell. Co-inhibition does show a great efficacy and safety in treating cancer in the data that are published in limited pre-clinical trials. It also shows no toxicity to humans.

Price is also a big problem for people to deciding whether they should take Sotorasib. The most effective dose is 960mg orally once a day for several months or years, depending on how serious cancer each patient has, with each 2 mg will cost almost 137 dollars; people who need Sotorasib will have a hefty finical budget to take. More importantly, some countries do not have official access to this drug which is a piece of deadly news to those patients who live in those countries and regions.

Although most of the patients who take this drug do not have serious adverse effects, liver damage and severe cirrhosis do occur in some extreme cases. So every patient needs to do a liver scan each time before you ask the doctor about continuing this drug. Other re-marketing research shows that Sotorasib can cure other types of cancer-related diseases other than lung cancer. We are very looking forward to seeing that Sotorasib can cure more and more people in the great society in the near bright future.

7. Conclusion

Sotorasib is one of the first small molecule inhibitors to target KRAS and enter human clinical development successfully. It can target KRAS protein carrying G12C mutation. In May 2021, Sotorasib was approved as a second-line treatment for advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS G12C mutation. Sotorasib specifically and irreversibly inhibits the proliferative activity of G12C mutant KRAS by locking it in a non-activated GDP-binding state [12]. At present, Amgen is advancing the most extensive global KRASG12C inhibitor development program at an unmatched pace, exploring more than ten drug combinations and clinical trials across five continents. To date, Sotorasib has treated more than 3,000 patients worldwide through clinical development programs and commercial use, with global sales of $90 million in 2021. The approval of Sotorasib breaks the long-standing curse of the KRAS target. The issuance of the first prescription means that the drug has officially moved from being used in clinical studies to being used in real-world clinic patients. Firmly believe that more patients with KRAS G12C mutations will be revitalized by oral Sotorasib in the future, making KRAS G12C no longer a difficult target for a breakthrough.

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