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Efficacy and safety of sonic hedgehog pathway inhibitors in cancer

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Abstract

The hedgehog pathway, for which sonic hedgehog (Shh) is the most prominent ligand, is highly conserved and is tightly associated with embryonic development in a number of species. This pathway is also tightly associated with development of several types of cancer, including basal cell carcinoma and acute promyelocytic leukemia (APL) among many others. Inactivating mutations in Patched 1 (PTCH1), leading to ligand-independent pathway activation, are frequent in several cancer types but most prominent in basal cell carcinoma. This has led to the development of several compounds targeting this pathway as a cancer therapeutic. These compounds target the inducers of this pathway in Smoothened (SMO) and the GLI transcription factors, although targeting SMO has had the most success. Despite the many attempts at targeting this pathway, there are only three FDA-approved drugs for cancers that affect the Shh pathway. Two of these compounds, vismodegib and sonidegib, target SMO to suppress signaling from either PTCH1 or SMO mutations that lead to upregulation of the pathway. The other approved compound is arsenic trioxide (ATO), which can suppress this pathway at the level of the GLI proteins, although current evidence suggests it also has other targets. This review focuses on the efficacy and safety of these clinically-approved drugs targeting the Shh pathway along with a discussion on other Shh pathway inhibitors being developed.

1. Introduction

The hedgehog pathway is a highly conserved signaling pathway that is linked to many biological processes. This signaling pathway has been linked to development in many species, including humans (1). It has been linked to growth and patterning in many of these multicellular species including the development of the neural system and bone development (2, 3). The hedgehog pathway and its components have also been linked to several diseases, prominently including human cancer (4). Because of the importance of this pathway to human cancer, there have been several attempts to target this pathway for cancer therapies

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with few successes and many failures. In this review, we aim to provide an update on the successful agents targeting the hedgehog pathway that have been FDA approved for treatment in human cancers. We will also briefly discuss agents that are currently being developed to target this pathway for the treatment of cancer.

2. The Hedgehog Pathway in Cancer

Mammalian hedgehog signaling can be initiated by three unique ligands in Sonic Hedgehog (Shh), Indian hedgehog, and Desert hedgehog. However, Shh is the most widely expressed and also the most potent of these ligands (1, 5). The ligand Shh is expressed as an inactive full-length protein that is proteolytically cleaved to two proteins and the N-terminal 19 kDa fragment is the active Shh ligand (6). The receptor for this active Shh ligand is Patched1 (PTCH1), a 12-transmembrane protein that binds Shh ligand. Binding of Shh to PTCH1 relieves repression of Smoothened (SMO) by PTCH1 thereby activating SMO signaling activity (Figure 1). The activation of SMO ultimately decreases the interaction between suppressor of fused homolog (SUFU) and GLI proteins that allows GLI proteins to enter the nucleus and bind transcriptional targets to regulate cellular gene expression. There are three GLI isoforms in mammals in GLI1-3 wherein gene expression can be induced by GLI1 and repressed by GLI3 whereas GLI2 can regulate expression in either direction. The GLI proteins are the terminal effectors of the Shh signaling pathway and regulate genes that control organismal patterning and development. Many of the genes regulated by GLI proteins are co-opted by cancer cells as they regulate several cancer-related processes including proliferation, migration and invasion, as well as neovascularization (4).

There have been numerous reports of genetic alterations in key components of the Shh pathway in different tumor types that leads to constitutive signaling of this pathway and that paracrine signaling of Shh may be an important factor in multiple tumor types (7, 8). While there are reports of the Shh pathway being modified in several tumor types such as breast, pancreatic, colorectal, and rhabdomyosarcoma among several, genetic alterations in this pathway are most consistently seen in basal cell carcinomas (BCCs) and medulloblastomas (9–19). The genetic alterations in this pathway are commonly loss-of-function changes to suppressors of the pathway (e.g. PTCH1, SUFU) or gain-of-function changes to promoters of the pathway (e.g. SMO, GLI). This is very prevalent in BCC as PTCH1 has a gene inactivating alteration in 73% of these tumors while SMO has a genetic activation in 20% (20). Therapies targeted to the Shh pathway primarily inhibit the components that promote signaling flux through the pathway including Shh ligand itself, SMO, and GLI proteins. The most successful strategy has been to target SMO with small molecule compounds and the two FDA-approved drugs targeting this pathway use this strategy. Targeting SMO in BCC, for instance, has the potential to target the large percentage of these tumors that harbor inactivating alterations to PTCH1 or activating mutations to SMO. There are also inactivating alterations to SUFU in 8% of BCCs (20) and GLI1 is amplified in several tumor types (4) but SMO inhibitors are unlikely to show efficacy against these populations. There have been attempts to develop inhibitors to Shh and GLI1 but these have yet to make it past clinical trials.

3. Currently Approved Shh Pathway Inhibitors

The first FDA-approved drug for cancer that targeted the Shh pathway was arsenic trioxide (ATO) in 2000, which was approved for treatment of acute promyelocytic leukemia (APL) (21). While it has been proven to have significant effects suppressing the Shh pathway, it likely also targets other mechanisms promoting APL development and progression. Despite, ATO being the first FDA-approved drug that does have effects on the Shh pathway, the first FDA-approved agent that was specifically designed to target the Shh pathway was vismodegib (GDC-449), which was originally discovered in 2009 and later approved for treatment of basal cell carcinoma in 2012 (22, 23). A year later in 2010, sonidegib (LDE225) was discovered and was later also approved for treatment of basal cell carcinoma in 2015 (24, 25). These are currently the only approved agents targeting the Shh pathway with indications for cancer (Table 1).

3.1. Arsenic Trioxide (ATO)

Arsenic formulations have been used for their beneficial therapeutic effects as far back as the 17th century (21). However, chronic exposure to arsenic is also labeled as a carcinogen and has been shown to promote solid tumors (26, 27). As an anti-cancer therapeutic, ATO has been shown to suppress growth in preclinical models in many tumor types including breast cancer, pancreatic cancer, colon cancer, acute promyelocytic leukemia (APL), melanomas, glioblastoma, and medulloblastoma among others (28–32).

Arsenic trioxide (ATO) was initially approved as a therapy for patients with acute promyelocytic leukemia (APL) who are refractory or have relapsed on retinoid and anthracycline chemotherapy (21). This approval came after two landmark trials wherein APL patients had become resistant to standard therapies of chemotherapy or all-trans retinoic acid (ATRA) (33, 34). ATO treatment increased the complete response rate from <40% to >90% and extended the time of this complete response (33, 34). ATO has since been approved for patients with low- and intermediate-risk APL by the EU and approved by the US FDA in combination with ATRA for newly-diagnosed low-risk APL with the t(15; 17) translocation of PML-RARA. ATO has been investigated in several other tumor types, including those with increased Shh dependence, but APL is currently the only indication approved for ATO.

3.1.1. Mechanism of action: APL develops in 95% of cases due to fusion of the promyelocytic gene (PML) on chromosome 15 with the retinoic acid receptor alpha gene (RARA) on chromosome 17 resulting in the PML-RARA t(15; 17) fusion protein (35). The PML-RARA fusion protein acts a transcriptional repressor to block myeloid differentiation. Early studies indicated ATO was effective against PML as exposure to ATO led to decreased levels of PML-RARA protein, as well as other cell survival proteins, and differentiation (29, 36–38). These results led to studies that found significant clinical benefit for APL patients receiving ATO and eventual FDA approval (37, 39). Despite this obvious link of ATO affecting the precise mechanism leading to APL, recent studies have also indicated that ATO has an effect in suppressing the Shh pathway. One of these early findings indicated that ATO suppressed GLI transcriptional activity that was not linked to cell viability, suggesting ATO

was specifically targeting the Shh pathway (40). Further confirmation was found when ATO suppressed GLI activity in the presence of SMO agonists or SMO activating mutants (40). These studies also indicated ATO suppressed GLI2 trafficking and other studies with similar results indicated ATO directly bound to GLI1, suggesting ATO has inhibitory effects on several aspects of the Shh pathway (28, 40, 41). These studies, and others showing similar suppression of the Shh pathway by ATO, have been shown in several tumor types (28, 40–51). Studies have also shown that ATO suppresses the Shh pathway in APL including clinical studies that showed ATO treatment led to clinical response and significant suppression of the Shh pathway (50). Thus, it appears that ATO has pleiotropic effects in the suppression of APL that likely include both suppression of PML-RARA and the Shh pathway, among several other possible mechanisms (52).

3.1.2. Metabolic profile: ATO hydrolyzes to arsenious acid (As^{III}) in solution. After administration of the instructed dose at 0.15mg/kg daily for 5 days a week, As^{III} reaches peak concentrations in the plasma in approximately 2 hours. As^{III} has a half-life of 10-14 hours (52). As^{III} metabolizes to two main products, monomethylarsonic acid (MMA^{V}) and dimethylarsinic acid (DMA^{V}). It can also oxidize to arsenic acid, although at low levels. The half-lives of MMA^{V} and DMA^{V} are 32 and 72 hours, respectively. Arsenious acid has a high volume of distribution, although not as high as sonidegib, and is present in tissues. As^{III} metabolism to MMA and DMA occurs in the liver but oxidation to arsenic acid occurs in various tissues utilizing various processes. About 15% of As^{III} is excreted through the urine without being metabolized (52). The total and renal clearance of As^{III} is 49L/h and 9L/h, respectively. The metabolic breakdown of ATO, the pharmacodynamics, and the pharmacokinetics has led to approval for treatment of ATO using a dose of approximately 0.15 mg/kg via intravenous administration with tretinoin and the half-life of 10-14 hours has led to daily administration according to these recommendations.

3.1.3. Serious and life-threatening adverse reactions: Perhaps the most serious life-threatening adverse reaction to ATO is QT interval disruption. For example, 38 out of 99 patients treated with ATO for cancers developed prolonged QTc intervals (53). Further, several studies have also observed, although rare, development of torsade de pointes after treatment with ATO (54–56). The ongoing management of these complications is accomplished by regular EKG monitoring, discontinuation of other QT interval prolonging drugs, and ensuring sufficiently high levels of serum magnesium and potassium (57).

In addition to QT elongation, ATO can also cause differentiation syndrome which can be fatal. When used in combination with tretinoin, ATO can lead to elevated levels of hepatic transaminase which can be toxic to the liver. In addition, ATO is a carcinogen, teratogen, and toxic to fetuses and embryos (27).

3.1.4. Most frequent other adverse reactions: In addition to QT interval elongation and tachycardia, ATO has numerous adverse effects on the circulatory system. Many of these involve levels of cells or substances in the blood including leukocytosis, neutropenia, thrombocytopenia, hyperglycemia, hypokalemia, and hypomagnesemia. ATO also affects the GI system and has caused vomiting, diarrhea, and abdominal pain. Reactions affecting the respiratory system include dyspnea, cough, and sore throat. Other general adverse reactions

such as nausea, fever, rigor, fatigue, insomnia, edema, rash or itching, arthralgia, headaches, paresthesia and dizziness can also occur (Table 2).

There are various treatments available to manage these adverse events. Leukocytosis, neutropenia, and thrombocytopenia can be managed with specific medications for these conditions as well as transfusions. Hyperglycemia can be managed with insulin injection and nutrition counseling. Potassium and magnesium supplements have been used for hypokalemia and hypomagnesemia, respectively. Dyspnea can be treated using opioids with morphine a common treatment for dyspnea in cancer patients (58).

3.1.5. Drug interactions: ATO should not be taken with drugs that prolong the QT interval, alter electrolyte levels, or are hepatotoxic. The adverse reactions to ATO, especially QT prolongation, dictate avoiding these interactions for the safety of the patients.

3.1.6. Post-marketing spontaneous reports of adverse reactions: Many additional adverse reactions to ATO have been reported post-marketing. These include various cardiac disorders, nerve damage, seizure, confusion, deficiency of white and red blood cells and platelets, herpes zoster infection, muscle and bone pain, rhabdomyolysis, deafness, and toxic epidermal necrolysis. Development of other cancers, melanoma, pancreatic cancer, and squamous cell carcinomas have also been reported.

3.2. Vismodegib (GDC-0449)

Vismodegib was discovered in 2009 from a compound screen with GLI-responsive luciferase cells and was observed to have suppression of medulloblastoma allografts (23). There was clear evidence that supported vismodegib inhibiting SMO leading to tumor suppression in Shh-dependent preclinical models including medulloblastoma, pancreatic cancer, colorectal cancer, lung cancer, prostate cancer, leukemia, and cholangiosarcoma among others (23, 59–73). Clinical trials have been undertaken in many of these tumor types, as well as other diseases with relevance to Shh signaling, but currently it has only been FDA-approved for basal cell carcinoma.

Despite the potential efficacy in a myriad of tumor types, BCC was the obvious setting for the greatest clinical utility as BCC has constitutive activation of the Shh pathway in >85% of cases (74). This overwhelming majority of cases involving the Shh pathway is primarily due to mutations in PTCH1 that leads to ligand-independent activation of SMO (11, 20). The first phase I clinical trial for vismodegib in BCC resulted in 18 out of 33 patients having an objective response (75, 76). The primary clinical evidence of efficacy for vismodegib in BCC was from a multicenter, two-cohort, non-randomized clinical trial (22, 77). In this trial, metastatic BCC patients showed a 33% objective response rate whereas locally advanced BCC had an objective response rate of 43% (77). Furthermore, stable disease was observed in 64% of metastatic BCC patients and 38% of locally advanced BCC patients (77). These outcomes resulted in a median response duration of >7 months and progression-free survival of >9 months (77). Additionally, there has been an overall survival increase from 24 months to 33.4 months for BCC patients since vismodegib became available (78, 79). To further this point, the historical median survival of BCC prior to 1990 was approximately 8 months but is now approximately 7 years due to the introduction of agents targeting the sonic hedgehog

pathway such as vismodegib and sonidegib (80–83). The summation of these encouraging clinical results led to FDA approval of vismodegib for metastatic or locally advanced BCC in 2012.

3.2.1. Mechanism of action.—Vismodegib was discovered from a screening of cyclopamine derivatives on a GLI luciferase reporter cell line and it was found to inhibit SMO (23). Further studies confirmed that vismodegib directly bound to SMO via competitive binding assays and molecular docking prediction studies (59, 63, 65, 69, 70, 72). In confirming that vismodegib binds to SMO, it was also observed that vismodegib exposure could induce a mutations in SMO that ablated the interaction of the drug with SMO (72, 84). This mutation was observed in patient samples and animal models that led to vismodegib adaptive resistance (72).

3.2.2. Metabolic profile.—Vismodegib has a bioavailability of 31.8% upon oral administration (85). At steady-state levels, which is achieved unusually fast in 7-14 days, more than 99% of the drug binds to proteins in the plasma, including AAG and human serum albumin and is unaffected by concentration until 100 uM (85). It is metabolized primarily by CYP enzymes with CYP3A4, CYP3A5, and CYP2C9 producing most of the metabolites (86). Vismodegib has an unusually long half-life of about 12 days after a single dose of 150 mg (87). However, its half-life with continuous administration on a daily basis is about 4 days (22).

3.2.3. Serious and life-threatening adverse reactions.—Vismodegib, similar to other drugs targeting the hedgehog pathway, is a teratogen. The hedgehog pathway is an important element in the development of various organs and organ systems (88). A drug that disrupts this pathway is therefore expected to be, and is, detrimental to the development of embryos and fetuses. The FDA recommends verifying pregnancy status within 7 days of the start of treatment with vismodegib and use of contraception during treatment and for 24 months after the end of treatment. It is worth noting that vismodegib not only targets the Shh pathway more specifically than ATO, but also does not have the side effect of QT interval prolongation that comes with ATO (89).

3.2.4. Most frequent other adverse reactions.—Several of the most common adverse reactions involve the GI system and include vomiting, diarrhea, constipation, and dysgeusia (disorder of taste). The drug also affects the musculoskeletal system and can cause muscle spasms and joint pain (arthralgias). Another common adverse reaction is alopecia. Other general adverse effects include weight loss, fatigue, nausea, and decreased appetite (75) (Table 2).

These adverse events do have sufficient approaches to management. Strategies for managing dysgeusia, decreased appetite, and weight loss include nutritional consultation and changes in preparation of foods (90, 91). Furthermore, there are medicinal options as well that range from fish oil supplementation to corticosteroids (92). Attention to other factors that may affect taste, such as oral hygiene, infection, acid reflux, and postnasal drip have also been reported to improve symptoms (93). Proper hydration, stretching and other light physical activity may help in the prevention of muscle spasms and joint pain. Calcium blockers, nerve

pain medication, and sports drinks are also recommended. For higher than grade 3 muscle spasms, stopping treatment for 2-4 weeks may help as well as addition of other medications such as gabapentin among other options (90, 92). For management of alopecia, 2-5% minoxidil is the most commonly suggested treatment. Strategies for concealing hair loss can also be considered (90, 92, 93). Serotonin inhibitors taken before and during treatment can be used to prevent nausea (90).

3.2.5. Drug interactions.—When administered with fluconazole, a moderate inhibitor of CYP2C9 and CYP3A4, vismodegib was found to have an increase in steady-state concentrations while itraconazole, a strong inhibitor of CYP3A4, and rabeprazole, a proton pump inhibitor was found to have no effect (94). Vismodegib may inhibit CYP2C8, CYP2C9, CYP2C19 and BCRP transporter (86). These drug interactions are important for the safety of vismodegib administration and minimizing the likelihood of occurrence and severity of the adverse events described above.

3.2.6. Post-marketing spontaneous reports of adverse reactions.—Vismodegib has been associated with hepatotoxicity post-marketing. As of January 2013, 23% of adverse event reports on the FDA Adverse Events Reporting system have included liver toxicity (95). Increase in blood phosphocreatine kinase was also reported post-marketing (96).

3.3. Sonidegib (LDE-225)

Sonidegib (LDE-225) was discovered in 2010 using a GLI-responsive luciferase reporter cell line and had efficacy in a medulloblastoma allograft model (25). This study, and others, confirmed sonidegib interacted with and inhibited SMO (25, 59, 63, 69, 70). Sonidegib has shown efficacy in multiple tumor types in preclinical models including medulloblastoma, ovarian cancer, glioblastoma, melanoma, renal cell carcinoma, leukemia, and breast cancer among several others (97–111). As mentioned above, there has been a very large increase in the median survival since these Shh pathway inhibitors were introduced from approximately 8 months to approximately 7 years (80–83). Clinical trials have been undertaken for sonidegib in many of these tumors types but BCC remains the only FDA-approved indication.

Due to the prevalence for the Shh pathway to be activated in BCC, sonidegib was an obvious compound for treatment of BCC. A very early treatment with sonidegib as a topical treatment suggested it may have efficacy in nevoid BCC (112). An initial phase I trial in patients with advanced solid tumors and 37.5% of BCC patients and 33% of medulloblastoma patients showed objective tumor responses (113). This trial established sonidegib as safe with possible efficacy leading to further trials. A phase II multicenter, randomized, double-blind trial was later completed in locally advanced or metastatic BCC with patients receiving either a low (200 mg) or high (800 mg) dose of sonidegib (114). The patients receiving the low dose showed a 36% objective response rate with the high dose group achieving a 43% objective response rate (114). A later update after 12-months of follow-up with these patients indicated a sustained response as the low dose group had a 57.6% objective response rate in locally advanced BCC whereas the high dose group maintained a 43.8% response rate in locally advanced BCC (115). Results of this trial led to

FDA approval in 2015 for adult patients with locally advanced BCC that has recurred following surgery or radiation therapy or those who are not candidates for surgery or radiation therapy.

3.3.1. Mechanism of action: Sonidegib was discovered via a screen in a GLI luciferase reporter cell line and binding to SMO was confirmed via a GLI1 IC50 shift assay (25). Molecular prediction docking studies further predict sonidegib binds to SMO in the “drug binding pocket” (59, 63, 69, 70). The same mutations in the drug binding pocket that led to vismodegib resistance were also observed to cause sonidegib resistance (116), suggesting these drugs share a similar mechanism of action.

3.3.2. Metabolic profile: Sonidegib has an absorption rate of less than 10% upon oral administration. When taken with a meal high in fat, however, absorption increases 7.4- to 7.8-fold (117). Sonidegib reaches steady state levels after approximately 4 months. It has a very high volume of distribution of 9,166 L suggesting high accumulation in tissues (118). More than 97% of the sonidegib in plasma remains bound to proteins and is unaffected by concentration. Sonidegib has an estimated half-life of 28 days. It is metabolized primarily by CYP3A enzymes in the liver (119). These factors have led to a dosing schedule of 200 mg given once daily via oral administration on an empty stomach.

3.3.3. Serious and life-threatening adverse reactions: As sonidegib is an inhibitor of the sonic hedgehog pathway, like vismodegib, it also is toxic to fetuses and embryos and is a teratogen. Sonidegib has been shown to elevate creatine kinase levels in several patients and was often accompanied by musculoskeletal complications (113). Thus CK level should be monitored before and periodically throughout the duration of treatment with this drug. Similar to vismodegib, sonidegib is more specific than ATO and does not result in QT interval prolongation (120).

3.3.4. Most frequent other adverse reactions: Sonidegib affects the musculoskeletal system in various ways with symptoms including muscle spasms, musculoskeletal pain, and myalgia. It can also cause gastrointestinal disturbances including diarrhea, abdominal pain, vomiting, and dysgeusia. Sonidegib can lead to alopecia and pruritus (severe itching of skin). Other common adverse reactions are nausea, decreased weight, decreased appetite, headache and pain (113) (Table 2). The management of these adverse reactions are similar to those listed for vismodegib. An additional factor worth mentioning is that pruritus can be treated with emollients, antipruritic creams, and antihistamines (93).

3.3.5. Drug interactions: Sonidegib users should avoid concurrently using any strong or moderate CYP3A inhibitors or inducers. Moderate inhibitors may be used if necessary but only for less than 14 days and with close monitoring. Some strong CYP3A inhibitors include saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole and nefazodone. Moderate inhibitors include atazanavir, diltiazem, and fluconazole. Inducers of CYP3A include carbamazepine, efavirenz, modafinil, phenobarbital, phenytoin, rifabutin, rifampin and St. John’s Wort. These drug interaction are of direct importance to the safety of

this drug in patients and minimizing as much as possible the likelihood and severity of the adverse reactions described above.

4. Shh Pathway Agents Under Development

As described above, the primary drug targets for the Shh pathway are molecules that promote active signaling. The primary targets that have been attempted to be therapeutically targeted are Shh itself, SMO, and GLI proteins with GLI1 being the primary target (Table 3).

4.1. Agents Targeting Shh

5E1 is a monoclonal antibody that binds the Shh ligand preventing its interaction with PTCH1 (121, 122). This antibody has been to suppress growth of esophageal PDX models in combination with radiation (111). 5E1 was also shown to enhance the effect of platinum-based chemotherapy delivered concurrently with radiation RTCT on cervical cancer xenografts but there was no effect of 5E1 as a single agent (98). 5E1 also enhanced the effect of platinum-based therapy in models of gastric cancer (123). 5E1 has been shown in a mouse model of breast cancer to decrease tumor size as well as liver and pancreatic metastases (124). 5E1 was effective as a monotherapy in a mouse model of medulloblastoma in suppressing tumor growth and extending survival time (125). 5E1 also reduced primary tumor growth and metastasis in an orthotopic mouse pancreatic cancer model as a single agent (7).

Robotnikinin is a 12-membered macrocycle discovered screening molecules that suppress the Shh pathway (126). This compound was found to directly bind Shh and prevent its interaction with PTCH1 leading to suppression of GLI1 activity (126). This compound has yet to show any antitumor effects in preclinical models.

During the synthesis of Shh, the enzyme SHHhat catalyzes the final steps to attach a palmitate to the Shh protein (127, 128). The compound RU-SKI 43 was a compound found from screening for inhibitors of SHHhat that suppressed Shh production and signaling (129). This compound was observed to reduce proliferation and anchorage-independent growth of breast cancer cells (130) as well as pancreatic tumor growth (131).

4.2. Agents Targeting SMO

Cyclopamine is an alkaloid from *V. californicum* that is one of the early discovered compounds to have significant inhibitory action toward SMO and suppressing signaling through the Shh pathway (132, 133). Cyclopamine was shown to have several antitumor effects in many tumor types (134–137). However, this compound had many adverse effects preventing its widespread clinical use and led to the development of second generation derivatives of cyclopamine such as vismodegib described above.

Another derivative of cyclopamine is Saridegib (IPI-926), which has shown antitumor activity in models of medulloblastoma, ovarian cancer, chondrosarcoma, and osteosarcoma (138–142). There have been early stage clinical trials with Saridegib that have shown favorable pharmacodynamics and pharmacokinetics while having some antitumor activity toward solid tumors (143–146). However, Saridegib was not recommended for further

developing in patients with myelofibrosis or pancreatic cancer (145, 147). Clinical trials with Saridegib for other tumor types, such as head and neck cancer (NCT01255800) and chondrosarcoma (NCT01310816), have been completed but not all results have been made public as of the time of this review. No new clinical trials for Saridegib have been initiated.

Another cyclopamine derivative in BMS-833923 (XL139) had shown effectiveness in suppressing SMO (59, 148, 149). Preclinical studies indicate efficacy of BMS-833923 in esophageal, prostate, cholangiosarcoma, and lung cancers (148–151). A number of early phase clinical trials were initiated with BMS-833923 in the early part of this decade but little success has led to Bristol-Myers Squibb, the BMS-833923, to discontinue their research in the area of SMO inhibitors (see NCT01218477).

Another compound, Glasdegib (PF-04449913), was described in 2011 has since made significant progress in preclinical and clinical settings (152). Glasdegib was described to interact with and suppress SMO activity, which was effective in targeting myeloid leukemias in preclinical models (59, 152–155). Several phase I clinical trials with Glasdegib have reported favorable drug profiles with some instances of efficacy suggesting further development (156–163). A phase II trial with Glasdegib plus cytarabine/daunorubicin was well tolerated and showed clinical activity in patients with untreated acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS) (164). There are a number of phase I and II trials ongoing with Glasdegib in both hematological and solid tumors as well as one phase III trial in AML (NCT03416179). These clinical successes have led to the FDA recently granting Priority Review for Glasdegib in untreated AML.

The compound TAK-441 is another SMO inhibitor discovered in the last decade with some clinical relevance (165). It has a potent ability to inhibit SMO and the Shh pathway and has shown the ability to suppress growth of multiple solid tumor types in preclinical studies (59, 165–169). One unfortunate side effect of SMO inhibition can be adaptive mutations in the SMO gene making them resistant to vismodegib or cyclopamine (170). An encouraging finding is that TAK-441 has been shown in preclinical studies to maintain activity in cells expressing these SMO adaptive mutants, suggesting it may be highly relevant to resistant patients (171, 172). To date, there has only been clinical trial with TAK-441, a phase I trial that found it was well tolerated and showed preliminary antitumor activity in advanced solid tumors (173). There are no further trials registered for TAK-441 so the current status and future plans for development are unknown.

Taladegib (LY2940680) is another inhibitor developed in recent years with potent SMO binding and inhibitory action, including inhibition of the adaptive SMO mutant (70, 174–176). Two separate phase I trials indicated a favorable safety profile for Taladegib in patients with solid tumors, including patients resistant to previous Shh therapies (177, 178). There are several phase I and II trials ongoing with Taladegib in multiple solid tumor types.

The compound LEQ506 was also developed in recent years and has ability to bind and inhibit SMO leading to suppression of Shh pathway signaling (179, 180). This binding to SMO including binding to the adaptive mutant SMO following vismodegib administration

(179). This compound was subjected to a phase I trial in patients with advanced solid tumors but results have yet to be posted.

Lastly, Itraconazole is a known anti-fungal drug but has shown the ability to inhibit SMO in basal cell carcinoma (181–183). Itraconazole has seen efficacy in combination with other chemotherapies in phase II trials for castration-resistance prostate cancer, non-small cell lung cancer, and basal cell carcinoma (184–186). There are many ongoing trials that include Itraconazole with the purpose of treating several different solid tumor types, although these are all phase I and II trials. There are higher level phase trials including Itraconazole but these are all for its antifungal properties.

4.3. Agents Targeting GLI1

Genistein is an isoflavone isolated from *Genista tinctoria* that is widely available in legumes and plant foods. Genistein has been found to suppress GLI1 in recent years leading to an ability to suppress several tumor types and, in particular, the cancer stem cell niche (187–191). Exactly how Genistein suppresses GLI1 remains to be understood but many of its antitumor properties have been attributed to suppression of the Shh pathway despite Genistein also suppressing several other important tumor-related molecules. Phase I trials with Genistein have shown a very favorable safety profile leading to several phase II trials wherein Genistein showed some efficacy in prostate cancers but had mixed results in pancreatic cancers (192–197). Genistein is being evaluated in several ongoing trials, most in phase I or II, and as is often the case with natural compounds, it is frequently being evaluated as a prevention agent.

GANT61 is a compound discovered from a GLI-luciferase drug screen that effectively reduced GLI1/2 DNA-binding (198). GANT61 has shown to have inhibition of GLI activity in multiple preclinical models that also leads to suppression of tumor growth and proliferation (198–212). However, this lone GLI-specific inhibitor does not have any clinical trials registered as the writing of this review.

4.4. Resistance to Shh Pathway-Targeted Therapies

Several agents that target the Shh pathway have been shown to develop resistance, including FDA-approved agents as described above (72, 116, 139). This is highly related to drug safety as patients develop resistance to agents, the dose escalation required to maintain tumor suppression can become toxic or cause the patients to be entirely removed from such therapies. As mentioned above, resistance to vismodegib and sonidegib occurs due to an adaptive mutation in SMO causing ineffectiveness of these compounds to inhibit SMO activity (72, 116). It seems there have been two primary strategies to attempt to overcome the resistance of these FDA-approved therapies in a) developing alternative inhibitors that can inhibit vismodegib-resistant SMO activity or b) combinatorial therapy with other drugs. Many of the therapies under development that are described above have been tested whether they can sufficiently inhibit SMO in the presence of the adaptive mutation caused by long-term vismodegib or sonidegib treatment. Furthermore, the continued development of new inhibitors is due to the resistance these approved therapies eventually succumb. Clinical trials have been, or are continuing, to occur with combinatorial studies with vismodegib and

other agents such as radiation (NCT02956889, NCT01835626), temozolomide (NCT01601184), gemcitabine (NCT01713218, NCT01195415, NCT01064622, NCT00878163, NCT01088815), paclitaxel (NCT02694224), bevacizumab (NCT00636610), oxaliplatin (NCT00982592), and decitabine (NCT02073838). Similarly, sonidegib is also currently in clinical trials in combination with other therapies such as everolimus (NCT02138929), docetaxel/paclitaxel (NCT02027376, NCT01954355, NCT02182622), gemcitabine (NCT01487785, NCT01431794, NCT02358161, NCT03434262), cisplatin (NCT01579929), fluorouracil (NCT01485744). Many of these trials are ongoing and do not have results available, however, the few with obtainable results seem to have mild, if any, enhancement of the efficacy. It is also unclear how these combinatorial studies will affect adverse events as the studies above with available information indicate more events in some cases while others see mild effects. Completion of many of these, and any information on developing resistance, will certainly increase our understanding of how to overcome resistance to these therapies and the correct populations likely to benefit.

In addition to these resistance mechanisms in FDA-approved therapies, there is a small amount of evidence for resistance to agents currently under development. Saridegib, which targets SMO and was shown to inhibit medulloblastoma in a mouse model and increase the lifespan of these animals, but also these animals did develop resistance (139). However, many of these agents have not been tested for long time periods to establish whether they will develop resistance. Aside from the study mentioned above regarding saridegib, there are very few pre-clinical long-term studies that would allow such an observation. Furthermore, while some of these agents have made it to clinical trials, none have currently made it past Phase 2 trials leading to insufficient evidence as to whether any of them will induce an adaptive resistance in patients.

5. Conclusions

There continues to be evidence generated from many laboratories indicating the importance of the Shh pathway in tumor initiation and progression. In particular, this pathway seems highly important to brain tumors, especially medulloblastoma, and skin cancers, especially basal cell carcinoma. The primary target of this pathway that has shown any successful efficacy is SMO. However, targeting this molecule can lead to adaptive mutations that induce resistance. Development of next generation SMO inhibitors should take into account this adaptive mechanism. Due to the lack of an enzymatic domain in the GLI transcription factors, these proteins are likely going to be difficult to directly target with future drug development. Despite this drawback, there continues to be attempts to therapeutically target transcription factors and a breakthrough in this area could lead to new vigor in the attempt to target GLI proteins. Overall, the Shh pathway appears to be important for many types of tumors and at different stages of the disease. Therefore, it is in the interest of future patients to continue basic research on this pathway and continue drug development towards viable targets in the Shh pathway.

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Key Points

- There are three FDA-approved inhibitors to the sonic hedgehog pathway for use in cancers in arsenic trioxide, vismodegib, and sonidegib
- All of these approved inhibitors have common effects on safety of patients but these adverse events are manageable
- Patients often develop resistance to vismodegib and sonidegib leading to a long list of agents under development to target the sonic hedgehog pathway

Figure 1.

The Sonic Hedgehog Pathway. A) In the absence of Shh ligand, PTCH1 suppresses SMO allowing for SUFU suppression of GLI1. B) In the presence of Shh ligand, PTCH1 repression of SMO is removed allowing for SMO to repress SUFU leading to the release and nuclear translocation of GLI1. GLI1, and the other GLI proteins then promote a gene expression program that promotes multiple cancer phenotypes. The inhibitors to this pathway, the FDA-approved inhibitors highlighted in green, primarily have targeted SMO with some attempts to target Shh itself and the GLI proteins, but with little success.

Table 1.

Approved Shh Pathway Targeting Agents

Drug	Target	FDA Approval Date	EU Approval Date	Disease Indication	Site of Metabolism	Enzymes of Metabolism
ATO	Gli1, PML-RAR α	9/25/2000	3/5/2002	Acute Promyelocytic Leukemia	Primarily liver, oxidation in various tissues	Primarily methyltransferases
Vismodegib	SMO	1/30/2012	7/12/2013	Locally advanced basal cell carcinoma	Primarily liver	CYP enzymes, in particular CYP2C9, CYP3A4, CYP3A5
Sonidegib	SMO	7/24/2015	8/14/2015	Metastatic or locally advanced basal cell carcinoma basal cell carcinoma	Primarily liver	CYP enzymes, in particular CYP3A

Table 2.

Adverse reactions of FDA Approved Shh Targeting Agents

Drug	Adverse Reactions
ATO	Differentiation syndrome, elevated hepatic transaminase, QT interval elongation, tachycardia, leukocytosis, neutropenia, thrombocytopenia, hyperglycemia, hypokalemia, hypomagnesemia, vomiting, diarrhea, abdominal pain, dyspnea, cough, sore throat, nausea, fever, rigor, fatigue, insomnia, edema, rash, itching, arthralgia, headache, paresthesia, dizziness
Vismodegib	Vomiting, diarrhea, constipation, dysgeusia, muscle spasms, arthralgias, alopecia, weight loss, fatigue, nausea, decreased appetite
Sonidegib	Elevated creatine kinase, muscle spasms, musculoskeletal pain, myalgia, diarrhea, abdominal pain, vomiting dysgeusia, alopecia, pruritus, nausea, decreased weight, decreased appetite, headache, pain

Table 3.**Shh Targeting Agents under Development**

Drug	Cancer Types	Target	Clinical Trial Status	Clinical Trial Numbers	Human Efficacy	Reference for efficacy
<u>5E1</u>	Preclinical studies only in various cancer types	Shh	No trials to date	N/A	Unknown	
<u>Robotnikinin</u>	Preclinical studies only in various cancer types	Shh	No trials to date	N/A	Unknown	
<u>RU-SKI3</u>	Preclinical studies only in various cancer types	SMO	No trials to date	N/A	Unknown	
<u>Cyclopamine</u>	Preclinical studies only in various cancer types	SMO	No trials to date	N/A	Unknown	
<u>Saridegib</u>	Chondrosarcoma, head and neck, pancreatic, adenocarcinoma, BCC, myelofibrosis	SMO	Phase 2	NCT01371617, NCT01130142 [*] , NCT00761696, NCT01383538 [*] , NCT01255800 [*] , NCT01310816	Majority result is stable disease	Jimeno 2013, Sasaki 2015
<u>XL139</u>	Leukemia, BCC, BCNS, stomach and esophageal neoplasms, other cancers	SMO	Phase 2	NCT01413906, NCT00670189, NCT01218477 [*] , NCT00927875 [*] , NCT00909402 [*] , NCT01357655 [*] , NCT00884546 [*]	Unknown for XL139 alone, variable with combination therapies	
<u>Glasdegib</u>	AML, other cancers	SMO	Phase 2	NCT03466450 [*] , NCT02226172, NCT03416179 [*] , NCT02367456 [*] , NCT03390296 [*] , NCT02038777 [*] , NCT01546038 [*] , NCT03529448 [*]	Majority result is stable disease	Minami 2017
<u>TAK-441</u>	BCC, advanced nonhematologic malignancies	SMO	Phase 1	NCT01204073	Majority had no response, 25% exhibited stable disease	Goldman 2015
<u>Taladegib</u>	Various carcinomas and sarcomas	SMO	Phase 2	NCT02530437 [*] , NCT01919398, NCT01722292 [*] , NCT01226485, NCT02784795 [*]	Unknown, no results yet	
<u>LEQ506</u>	BCC and Medulloblastoma	SMO	Phase 1	NCT01106508	Unknown	
<u>Itraconazole</u>	Multiple cancer types and other diseases	SMO	Phase 2	>40 Studies	Variable for cancer type and disease type	
<u>Genistein</u>	Multiple cancer types and other diseases	Gli1	Phase 2	30 Studies	Variable for cancer type and disease type	
<u>GANT61</u>	Preclinical studies only in various cancer types	Gli1	No trials to date	N/A	Unknown	

* = Combination studies with other drugs or therapies