MONOGRAPH

SONIDEGIB PHOSPHATE

Smoothened (SMO) receptor antagonist
Oncolytic

Rec INNM; USAN

M. Salati and A. Stathis

Phase I Unit, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

CONTENTS

LDE-225
NVP-LDE-225

N-[6-(*cis*-2,6-Dimethylmorpholin-4-yl)pyridin-3-yl]-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide diphosphate

InChI = 1S/C26H26F3N3O3.2H3O4P/c1-16-14-32(15-17(2)34-16)24-12-9-20(13-30-24)31-25(33)23-6-4-5-22(18(23)3)19-7-10-21(11-8-19)35-26(27,28)29;2*1-5(2,3)4/h4-13,16-17H,14-15H2,1-3H3,(H,31,33);2*(H3,1,2,3,4)/t16-,17+

$C_{26}H_{26}F_3N_3O_3.2H_3O_4P$; Mol wt: 681.4885
CAS RN®: 1218778-77-8
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SUMMARY

Sonidegib phosphate (LDE-225) is a potent, orally bioavailable, selective inhibitor of smoothened protein, a key downstream transducer of the hedgehog signaling pathway. This pathway has been recently associated with cancer development and progression in several tumor types, and components of this pathway have been regarded as targets for the development of new anticancer agents. In preclinical studies, sonidegib bound to smoothened protein with high affinity, leading to dose-related inhibition of hedgehog signaling, ultimately resulting in tumor growth arrest and regression. In early clinical studies, sonidegib showed a favorable safety profile and demonstrated promising antitumor activity, mainly in basal cell carcinoma and medulloblastoma. Ongoing trials are evaluating sonidegib either alone in selected cancer types or in combination with conventional cytotoxic drugs against a broad range of solid tumors.

Key words: Smoothened protein – Hedgehog signaling pathway – Solid tumors – Basal cell carcinoma – Medulloblastoma – Sonidegib phosphate – LDE-225
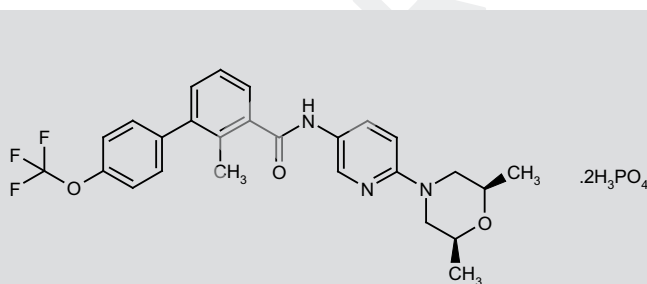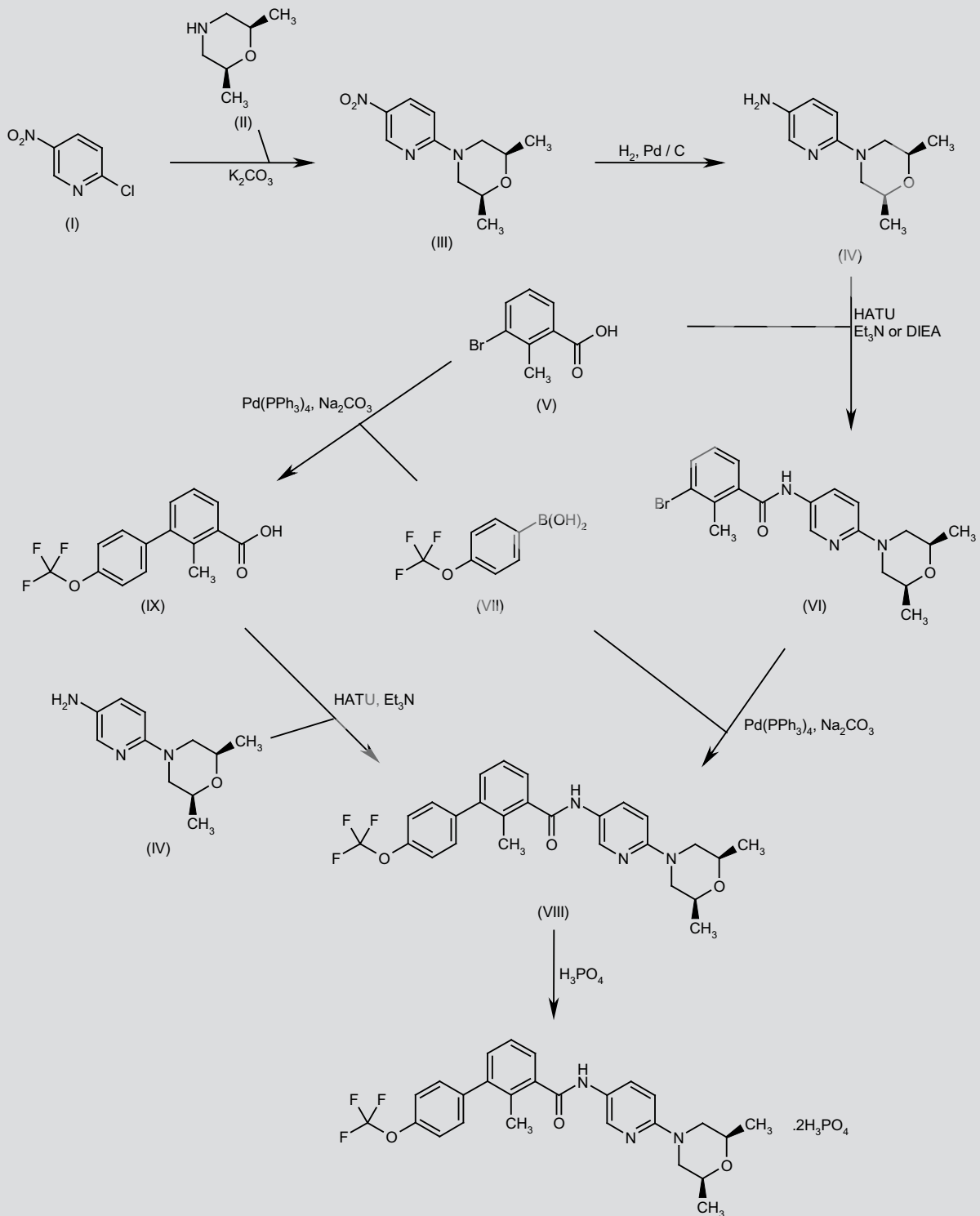
SYNTHESIS*

Sonidegib can be prepared by two related routes.

Condensation of 2-chloro-5-nitropyridine (I) with *cis*-2,6-dimethyl-morpholine (II) by means of K_2CO_3 in DMF at 50 °C gives intermediate (III), which is hydrogenated with H_2 over Pd/C in MeOH to yield amine (IV) (1-3). Coupling of amine (IV) with 3-bromo-4-methylbenzoic acid (V) using HATU and Et_3N (1, 2, 4) or DIEA (3) in DMF affords the corresponding amide (VI), which is finally submitted to Suzuki coupling with 4-(trifluoromethoxy)phenyl boronic acid (VII) in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 in toluene/EtOH/H_2O (1, 2), DME (3) or DME/H_2O (4) at 135 °C. Scheme 1.

Alternatively, Suzuki coupling of 3-bromo-4-methylbenzoic acid (V) with 4-(trifluoromethoxy)phenylboronic acid (VII) in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 in DME/H_2O gives intermediate (IX), which is finally coupled with amine (IV) using HATU and Et_3N in DMF (4). Scheme 1.

The phosphate salt is obtained by treatment of sonidegib with H_3PO_4 in acetonitrile (5).

Correspondence: A. Stathis, Phase I Unit, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland. E-mail: Anastasios.Stathis@ccoc.ch.

Scheme 1. Synthesis of Sonidegib Phosphate

BACKGROUND

The hedgehog signaling pathway regulates multiple fundamental processes both in normal and malignant cells. Under normal conditions, this pathway plays a central role in developmental growth, morphogenesis and pattern formation during embryonic development, but it is also active in adult tissues during stem cell renewal, tissue repair and regeneration (6-8). There are three mammalian hedgehog proteins —Sonic, Indian and Desert— which act as ligands and activate the pathway. They bind to the 12-pass transmembrane protein patched homolog 1 (PTCH1) on the primary cilium of target cells and initiate the hedgehog signaling cascade. In the resting state, when the hedgehog ligand is absent, PTCH1 inhibits the activity of smoothened (SMO), a G protein-coupled receptor-like molecule acting as a key downstream component of the hedgehog signaling pathway. Upon binding of the hedgehog ligand to PTCH1, its inhibition is released and SMO subsequently activates downstream GLI transcription factors. There are three distinct GLI zinc-finger proteins —GLI1 and GLI3— which function as transcriptional activators and repressors, respectively, and GLI2, which can either activate or repress downstream genes (7, 9).

Known target genes regulated by the hedgehog-GLI signal transduction axis include *cyclin D1*, *MYC*, *BCL2*, *BMI1*, *SNAI1* and *VEGF*, which are involved in the regulation of cell cycle progression, proliferation, survival, self-renewal, epithelial-mesenchymal transition (EMT) and angiogenesis (10, 11). Total GLI function relies on the presence of specific levels of hedgehog ligands. The modulation of GLI activity can occur at several levels, particularly on the balance between positive (activator) and negative (repressive) activities. In the absence of hedgehog ligands, GLI2/3 proteins are processed to generate truncated transcriptional repressors lacking the *C*-terminal transactivation domain, which ultimately silences hedgehog target genes. Protein kinase A (PKA), glycogen synthase kinase-3 beta (GSK-3 beta) and casein kinase I isoform alpha (CK1) are intracellular molecules engaged in GLI processing (12). Suppressor of fused homolog (SUFUH) represents another negative regulator of this pathway able to either prevent nuclear translocation of GLI molecules or inhibit GLI1-mediated transcriptional activity (13). Contrariwise, hedgehog pathway activity abrogates GLI processing, thereby promoting target gene expression by full-length and active GLI. Additionally, multiple components and target genes of this pathway form regulatory loops that are involved in modulating the hedgehog-GLI signaling cascade. For instance, protein patched homolog 1 (PTC1) and hedgehog interacting protein provide negative feedback regulation, whereas GLI1 expression positively boosts GLI1 transcription. Interestingly, recent data also suggested the role for non-canonical SMO-independent regulation of GLI activity by several other signaling pathways, including the PI3K/AKT and RAS/RAF/MEK/ERK axes (14).

Abnormal hedgehog signaling pathway activation has been associated with the development of cancer, including cancer of the skin, brain, colon, lung, prostate, pancreas and hematological malignancies (15-19). The involvement of this pathway in cancer initiation, progression and invasiveness, as well as acquired drug resistance, has been recently studied in in vitro and in vivo models. In vivo models of basal cell carcinoma (BCC), medulloblastoma, rhabdomyosarcoma and gastrointestinal stromal tumor (GIST) have served to elucidate its role in cancer initiation (20-22), whereas in small cell lung cancer

(SCLC), this pathway is mainly involved in cancer promotion rather than cancer initiation (23). In fact, treatment with cyclopamine, a naturally occurring steroidal alkaloid SMO inhibitor, decreased proliferation and increased apoptosis of SCLC cell lines and mouse models, whereas the constitutively mutant allele of SMO (SmoM2) alone is insufficient to initiate tumors in lung epithelium.

In pancreatic cancer, abnormal hedgehog pathway activation is associated with induction and maintenance of the proliferative activity, local invasiveness and the development of metastases (24). Inhibition of the hedgehog pathway with cyclopamine, together with gemcitabine, significantly decreased lung and liver metastases as compared with cyclopamine or gemcitabine alone in a mouse pancreatic cancer model (25). Another example of hedgehog signaling involvement in tumor invasiveness and distant spread is represented by prostate cancer, where an abnormal activity of the pathway results in upregulation of the transcription factor SNAIL and downregulation of E-cadherin, two key elements involved in the epithelial-mesenchymal transition (18). Additionally, there is evidence to support a regulatory role of this pathway in cancer stem cells (CSCs) in both solid and hematological malignancies, including breast cancer, glioma, acute leukemia, multiple myeloma (MM) and chronic myelogenous leukemia (CML) (26-29). In in vitro studies, treatment of malignant human mammary cell lines with cyclopamine or siRNA against GLI1 or GLI2 led to depletion of CSCs and loss of tumorigenic potential (30). Interestingly, very recent data showed for the first time that hedgehog signaling transcriptionally upregulates human telomerase reverse transcriptase (hTERT), a telomerase catalytic subunit involved in the maintenance of telomere length, which is aberrantly restored in cancer cells (31).

Two different mechanisms, ligand-independent (type I) and ligand-dependent (further subdivided into type II, type IIIa and type IIIb) of hedgehog hyperactivation have been studied in cancer development (11). Loss of function mutations in onco-suppressor genes, or gain of function mutations in proto-oncogenes, leading to inappropriate activation of hedgehog signal transduction, regardless of its ligand levels, are at the basis of type I ligand-independent cancers. Basal cell carcinomas (BCCs) and medulloblastomas (MBs) represent prototypes of this mechanism: roughly 90% of BCCs associated with nevoid basal cell carcinoma syndrome (NBCCS), 85% of sporadic BCCs and one-third of MBs harbor inactivating mutations of PTCH1. Furthermore, activating mutations in SMO have been reported in approximately 10% of sporadic BCCs (32).

While the above reported mutations can explain an abnormal hedgehog pathway activation in BCCs and MBs, no specific hedgehog component mutations have been described thus far in other tumors, and mechanisms based on excessive/inappropriate expression of hedgehog ligands have been described. Lung, gastric, pancreatic, prostate and esophageal cancer are some examples where the pathway is hyperactivated through ligand-dependent autocrine activation (type II), in the absence of specific mutations (33, 34). In type IIIa ligand-dependent paracrine activation of the pathway, cancer cells secrete hedgehog ligands which then activate it in surrounding stromal cells, resulting in the production and release of several soluble factors (e.g., IGF, Wnt, VEGF) or the expression of extracellular matrix components, which support tumor growth and survival. An elevated expression of stromal PTCH1 and GLI in response to hedgehog production from

human tumor xenografts was first described in a prostatic cancer model (17).

More recently, a reverse paracrine signaling (type IIIb) mechanism has been described. In B-cell hematological malignancies, namely non-Hodgkin's lymphoma, MM and leukemia, hedgehog ligands are secreted from the stroma and may lead to increased Bcl-2 antiapoptotic activity and prolonged survival of malignant cells (35, 36). Overall, it is likely that the exact role and the specific activation mode is dependent on specific cancer types, as well as distinct clinical and biological features, such as disease stage and genetic lesions; nevertheless, overlapping patterns of hedgehog pathway activation could not be excluded even within the same cancer type. Advances in understanding the role of the hedgehog pathway in cancer, along with improvements in medicinal chemistry technologies, have allowed the development of new classes of drugs that are able to target different components of this pathway. Major targeting sites for hedgehog signaling inhibitors are represented by SMO, hedgehog proteins and GLI transcription factors. In Table I the most promising hedgehog inhibitors that are currently in clinical development have been summarized.

SMO inhibitors represent a new family of promising small-molecule inhibitors of the hedgehog pathway. In January 2012, the FDA (followed by the EMA in July 2013) approved vismodegib (Erivedge®), a first-in-class SMO inhibitor for the treatment of patients with symptomatic metastatic BCC or locally advanced BCC inappropriate for surgery or radiotherapy (37).

Herein we review the preclinical and the ongoing clinical development of the novel selective SMO inhibitor, sonidegib (LDE-225), focusing on the pharmacokinetics, safety and preliminary efficacy of this compound.

PRECLINICAL PHARMACOLOGY

Structure-activity relationship studies (SARs) applied to the biphenyl-3-carboxamides with properties of inhibiting hedgehog pathway signaling led to the discovery of a potent and selective SMO antagonist, sonidegib. This molecule displaces the binding of the synthetic SMO

antagonist BODIPY-cyclopamine, with an IC_{50} value of 1.3 nM in mice and 2.5 nM in humans, respectively (4).

Sonidegib displayed a favorable pharmacokinetic (PK) profile across preclinical species, with oral bioavailability ranging from 69 to 102%, high to moderate binding to plasma proteins, mean residence time ranging from 3.04 to 6.81 hours and moderate to high volume of distribution, as well as brain exposure upon oral administration. Sonidegib resulted negative in tests for genotoxicity (Ames and micronucleus tests) and had low potential for drug–drug interactions, showing an IC_{50} value greater than 10 μM for the major human CYP450 drug metabolizing enzymes (4).

A low potential for off-target effects was also suggested by a substantial absence of activity (i.e., $IC_{50} < 10$ μM) against a large panel of receptors, ion channels, transporters, kinases and proteases. When evaluating the antitumor activity in both s.c. and orthotopic $PTCH^+$/p53/MB allograft models, sonidegib demonstrated dose-related antitumor activity after 10 days of oral administration of a suspension of the diphosphate salt: at a dose of 10 and 20 mg/kg/day once daily, sonidegib yielded 51% and 83% regression, respectively. Additionally, a dose- and time-dependent suppression of GLI1 mRNA levels was observed in the $PTCH^+$/p53/MB models, thus providing evidence for inhibition of the hedgehog signaling pathway. Sonidegib also efficiently penetrated the blood–brain barrier, leading to tumor growth inhibition in orthotopic $PTCH^+$/p53/Mb allograft models (4).

In more recent years, sonidegib showed remarkable antitumor activity in several in vitro and in vivo models, including osteosarcoma, islet cell neoplasms, glioblastoma and melanoma (38-41). Sonidegib also demonstrated potent blockade of basaloid tumor nest formation and regression of preformed basaloid tumors in skin cultures derived from PATCH1 heterozygous knockout mice. The activity of sonidegib resulted in an IC_{50} of < 150 nM compared to 10 μM for cyclopamine (42).

PHARMACOKINETICS AND METABOLISM

Major PK features (absorption, distribution, metabolism and excretion) of sonidegib were investigated using the radioisotope

Table I. *Hedgehog pathway inhibitors currently in clinical trials for cancer (as listed on http://clinicaltrials.gov on July 13, 2014).*

Drug	Target	Phase	Tumor types in clinical investigation	FDA status
GDC-0449	SMO	0, I, II	BCC, MB, solid tumors, colorectal, ovarian, pancreatic, GBM, glioma, MM, SCLC prostate, esophageal, gastric, sarcoma, CLL breast, chondrosarcoma, lymphoma, AML	Approved*
LDE-225	SMO	0, I, II	BCC, MB, solid tumors, pancreatic, breast, prostate, esophageal, SCLC, HCC, CML, MM, myeloid cancer, acute leukemia	
IPI-926	SMO	I, II	BCC, solid tumors, chondrosarcoma, pancreatic, head and neck	
LEQ-506	SMO	I	Solid tumors	
BMS-833923	SMO	I, II	Solid tumors, BCC, SCLC, CML, gastric, esophageal, MM, CML	
PF-04449913	SMO	I, II	Solid tumors, hematologic malignancies	
TAK-441	SMO	I	Solid tumors	
LY-2940680	SMO	I, II	Solid tumors, SCLC, MB, RMS	
Itraconazole	SMO	0, I, II	BCC, NSCLC, prostate	

BCC, basal cell carcinoma; MB, medulloblastoma; GMB, glioblastoma multiforme; MM, multiple myeloma, SCLC, small cell lung cancer; AML, acute myeloid leukemia; HCC, hepatocellular carcinoma; CML, chronic myeloid leukemia; RMS, rhabdomyosarcoma; NSCLC, non-small cell lung cancer. *GDC-0449 has been approved by the FDA for the treatment of locally advanced and metastatic basal cell carcinoma inappropriate for surgery or radiotherapy.

[14]C-sonidegib given once daily at a dose of 800 mg in 6 healthy male subjects. Sonidegib exhibited low absorption, with median t_{max} values of unchanged sonidegib and total radioactivity in plasma of 2 and 3 hours, respectively, as well as long half-lives of 319 and 331 hours, respectively. The mean estimated absorption of sonidegib was 6-7% and it was extensively distributed into the tissues, with an approximate terminal volume of distribution (Vd) of 2,500 L. The compound was slowly metabolized through oxidation and amide hydrolysis, and both sonidegib and metabolites were excreted primarily via the feces (43).

In a recently published first-in-human, multicenter, open-label, dose-escalation phase I study, Rodon et al. assessed the safety, tolerability, PK and pharmacodynamics of sonidegib given orally on a continuous daily dosing schedule in advanced solid tumors. In this study, a total of 103 patients with advanced solid tumors, including MB and BCC, received oral sonidegib continuously according to two different schedules of administration at doses ranging from 100 to 3,000 mg once daily and 250 to 750 mg twice daily (44).

After a single oral dose of sonidegib, the median t_{max} occurred at 2 hours (range 1 to 48 hours) across the dose range (100-3,000 mg). Sonidegib plasma exposure, defined by C_{max} and AUC after a single dose, increased dose-proportionally up to 400 mg daily and displayed non-linear PKs at higher doses. Parallel decline of the plasma concentration profile across the dose range suggested a dose-independent elimination. Accurate estimation of the terminal half-life was not possible because of the shorter 7-day PKs run-in phase, even if, based on the accumulation ratio, the estimated median effective elimination $t_{1/2}$ of sonidegib was roughly 11 days.

Sonidegib showed a favorable safety profile, with mostly grade 1/2 treatment-related adverse events (AEs). The most common AEs (≥ 5% incidence) of all grades included nausea (25.2%), dysgeusia (29.1%), anorexia (29.1%), vomiting (12.6%), muscle spasms (32%), myalgia (16.5%), increased serum creatine kinase (CK) (32%), asthenia (27.2%) and alopecia (12.6%). The most frequent (≥ 5% of patients) grade 3/4 AEs were CK increases, asthenia, increased transaminases, anorexia and myalgia. The maximum tolerated dose (MTD) of sonidegib was 800 and 250 mg for the once daily and twice daily schedule, respectively. The most common dose-limiting toxicity (DLT) was a reversible grade 3/4 increase in serum CK, occurring 3 to 6 weeks after treatment initiation in an exposure-dependent manner in 19 patients (18%) at doses ≥ the MTD. Among all DLTs, three cases of rhabdomyolysis were described on the basis of elevated blood CK with or without myoglobin levels and without evidence of renal dysfunction. CK elevation was generally associated with myalgia and resolved within 4 to 8 weeks of drug discontinuation. Neither clinically significant changes in creatine kinase myocardial B isoenzyme nor deaths due to drug-related toxicities were reported. Interestingly, major AEs related to sonidegib were superimposable to those of other SMO inhibitors, i.e., muscle spasms, dysgeusia, fatigue and alopecia, suggesting a class-specific toxicity profile. The recommended phase II dose of sonidegib in adults was identified at 800 mg once daily since no clinically significant benefits were observed with the b.i.d. dose over the once daily schedule (44).

CLINICAL STUDIES

Based on encouraging results derived from preclinical models, sonidegib was clinically evaluated for the first time in a double-blind, randomized, vehicle-controlled, intraindividual study enrolling patients with nevoid BCC syndrome, a disorder known to be driven by oncogenic activation of the hedgehog pathway. A total of 8 patients with NBCCS presenting 27 BCCs were treated topically twice a day with 0.75% sonidegib cream or vehicle for 4 weeks. The application was well tolerated, without skin irritation. Of 13 BCCs treated with sonidegib, 3 achieved a complete response (CR), 9 a partial response (PR) and 1 had no clinical response. The average volume reduction was 56%. Among 14 vehicle-treated BCCs, only 1 PR was observed (43). This represented proof-of-concept to further test systemic exposure to sonidegib in a clinical trial.

In the previously mentioned first-in-human phase I study, sonidegib exhibited preliminary antitumor activity in advanced BCC and relapsed MB, two tumor types known to harbor activating mutations in the hedgehog pathway. Indeed, sonidegib achieved objective tumor responses (partial or complete response) in 6 of 16 patients with BCC and in 3 of 9 patients with MB. A dose- and exposure-dependent inhibition of the hedgehog pathway was also observed by the reduction in GLI1 mRNA expression within tumor and normal skin biopsies (45).

Positive preliminary results from the pivotal, randomized, double-blind, multicenter phase II BOLT study (Basal cell carcinoma Outcomes in LDE225 Trial; ClinicalTrials.gov Identifier NCT01327053) were presented at the 2014 ASCO meeting. In this trial, sonidegib met its primary endpoint, resulting in an objective response rate (ORR) of 41.8% and 32.5%, respectively, in the 200 and 800 mg treatment arms among patients with locally advanced or metastatic BCC after a median follow-up of 13.9 months, also achieving a disease control rate (CR, PR and stable disease [SD]) up to 92.3% and 78.32% in the 200 and 800 mg arms, respectively. The median progression-free survival (PFS) per central review for patients with metastatic BCC was 13.1 months in the 200 mg arm and 7.6 months in the 800 mg arm (46).

Currently, sonidegib is in clinical evaluation in a variety of cancers, including solid tumors and hematological malignancies (mainly leukemia) (Table II). One of the most intriguing strategies is aimed at exploring the feasibility of combinations of sonidegib with conventional cytotoxic agents in order to develop a useful therapeutic strategy to overcome drug resistance. One such strategy is based on preclinical evidence suggesting that sonidegib may reverse taxane resistance within in vitro and in vivo models of chemoresistant ovarian cancer, probably through the decrease in P-glycoprotein expression (47). Moreover, these findings were also noted in preclinical tumor models, with little constitutive hedgehog activity, thus suggesting that both GLI-dependent and -independent mechanisms contribute to taxane resistance and subsequently expand the potential use of hedgehog inhibitors to all taxane-resistant cancers.

Consistent with this approach, the Swiss Group for Clinical Cancer Research (SAKK) designed the 65/12 trial (ClinicalTrials.gov Identifier NCT01954355), a multicenter phase I dose-escalation study with the aim of determining the MTD and the recommended phase II dose of sonidegib in combination with standard doses of paclitaxel in patients with advanced solid tumors. Secondary endpoints were safety profile and preliminary antitumor activity; in addition, a correlative study to assess the association between the expression of the hedgehog pathway biomarkers on archival tumor specimens with safety and antitumor activity is also planned. Patients with advanced solid tumors can be included in the dose escalation part of the study, and

Table II. *Ongoing clinical trials of sonidegib in cancer (as listed on http://clinicaltrials.gov on July 13, 2014).*

Phase	Identifier	Indication	Combination	Status
0	NCT01694589	Pancreatic cancer		Ongoing
I	NCT02111187	Prostate cancer		Ongoing
I	NCT01911416	Pancreatic cancer		Ongoing
I	NCT02027376	Breast cancer	Docetaxel	Ongoing
I	NCT01487785	Pancreatic cancer	Gemcitabine	Ongoing
I	NCT01954355	Solid tumors	Paclitaxel	Ongoing
I	NCT02138929	Esophageal cancer	Everolimus	Ongoing
I	NCT01579929	SCLC	Etoposide + Cisplatin	Ongoing
I	NCT01208831	Solid tumors		Ongoing
I	NCT01456676	CML	Nilotinib	Ongoing
I	NCT00880308	Solid tumors		Completed
I	NCT02151864	HCC		Ongoing
I	NCT02182622	Prostate cancer	Prednisone + Docetaxel	Ongoing
I	NCT01576666	Solid tumors	BKM120	Ongoing
I	NCT01485744	Pancreatic cancer	FOLFIRINOX	Unknown
I/Ib	NCT02129101	Myeloid cancers	Azacitidine	Ongoing
I/II	NCT01431794	Pancreatic cancer	Gemcitabine + Nab-Paclitaxel	Ongoing
I/II	NCT01125800	Medulloblastoma		Ongoing
II	NCT02002689	Solid tumors		Ongoing
II	NCT01826214	Acute leukemia		Ongoing
II	NCT01757327	Breast cancer		Ongoing
II	NCT00961896	NBCCS BCC		Completed
II	NCT01529450	BCC		Terminated
II	NCT01033019	BCC		Completed
II	NCT01327053	BCC		Ongoing
II	NCT02086552	Multiple myeloma	Lenalidomide	Ongoing
II	NCT01708174	Medulloblastoma		Ongoing
II	NCT01350115	NBCCS BCC		Completed

SCLC, small cell lung cancer; CML, chronic myeloid leukemia; HCC, hepatocellular carcinoma; NBCCS, nevoid basal cell carcinoma syndrome; BCC, basal cell carcinoma.

upon definition of the recommended phase II dose, an expansion cohort of ovarian cancer patients resistant to chemotherapy will be explored. The study is expected to complete accrual at the end of 2014. Other ongoing clinical trials are evaluating sonidegib either as a single agent or combined with standard chemotherapy in advanced solid tumors. Trials of sonidegib alone are focusing on PTCH1 and SMO mutated tumors (ClinicalTrials.gov Identifier NCT02002689), as well as on cancer types harboring hedgehog pathway activation, such as MB (ClinicalTrials.gov Identifier NCT01708174). Several early-phase combination trials are exploring the association of sonidegib with cytotoxic drugs, including cisplatin and etoposide in SCLC (ClinicalTrials.gov Identifier NCT01579929), FOLFIRINOX in advanced pancreatic cancer (ClinicalTrials.gov Identifier NCT01485744), docetaxel in triple-negative advanced breast cancer (ClinicalTrials.gov Identifier NCT02027376) and docetaxel plus prednisone in metastatic castration-resistant prostate cancer after docetaxel therapy (ClinicalTrials.gov Identifier NCT02182622).

CONCLUSION

Sonidegib is a potent, orally bioavailable, selective inhibitor of SMO protein, a key downstream transducer of the hedgehog signaling pathway. In clinical studies it showed a favorable safety profile, with marked antitumor activity across cancer types driven by mutational activation of the hedgehog pathway, such as BCC and MB. Regarding cancers not strictly dependent on constitutive hedgehog signaling, combinatorial therapies of sonidegib with new targeted agents or conventional cytotoxics represent a promising strategy to successfully improve the efficacy of anticancer treatments. Several clinical trials are currently ongoing with the purpose of investigating the therapeutic potential of sonidegib both in solid and hematological tumors.

ORGANIZATION

Novartis AG (CH).

DISCLOSURES

The authors state no conflicts of interest.

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