VISMODEGIB BRIEFING PACKAGE

Pediatric ODAC Subcommittee Meeting

Vismodegib

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1. EXECUTIVE SUMMARY

1.1 INTRODUCTION

Vismodegib (previously known as GDC-0449) is an investigational, oral, targeted medicine designed to selectively inhibit signaling in the Hedgehog (Hh) pathway. The Hh signaling pathway plays an important role in regulating proper growth and development in the early stages of life and becomes less active in adults. However, abnormal signaling in the pathway is implicated in a number of cancers. In particular, mutations leading to abnormal Hh signaling are implicated in 90% of cases of basal cell carcinoma (BCC) and also in certain cases of medulloblastoma.

While BCC is the most common skin cancer in adults, it is extremely rare in children. Medulloblastoma, however, is the most common malignant brain tumor in children and accounts for approximately 20% of newly diagnosed brain tumors in the pediatric age group. Currently, therapy for pediatric medulloblastoma consists of surgery, radiation therapy, and, for early-stage disease, chemotherapy. Approximately 60-80% of children with this type of brain cancer can be cured (Gajjar et al. 2010; Gajjar et al. 2006) although younger children who survive often have significant neurocognitive impairment that prevents them from completing their education and seeking gainful employment (Mulhern et al. 2005). Children with recurrent or refractory medulloblastoma have an extremely poor prognosis, with long-term survival unlikely.

To date, Genentech's clinical development program for vismodegib has focused on adult cancers. The company recently submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration for vismodegib for the treatment of adults with advanced BCC for whom surgery is inappropriate.

Given the potential role of the Hh pathway in medulloblastoma, there is strong clinical rationale in evaluating vismodegib in children with this devastating disease. However, a number of challenges exist. As previously noted, the Hh pathway plays an important role in normal early development. It is known that vismodegib has the potential to cause developmental defects in unborn children and, importantly, data is limited regarding the adverse effects it may cause in young children, raising concern about the benefit/risk assessment of evaluating this investigational medicine in children.

Additionally, abnormal signaling in the Hh pathway is only thought to be implicated in approximately 15-30% of medulloblastoma cases (compared to 90% of BCC cases), and there is currently no validated diagnostic to identify the group of patients with this subtype of medulloblastoma.

The Pediatric Brain Tumor Consortium (PBTC) in collaboration with the National Cancer Institute's Cancer Therapy Evaluation Program (NCI CTEP) sponsorship is currently evaluating the safety and effectiveness of vismodegib in pediatric patients with relapsed and refractory medulloblastoma in Phase I and Phase II studies.

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Genentech is seeking input from the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) regarding the potential for future development of vismodegib in pediatric medulloblastoma where there is a significant unmet need for new therapies.

The following briefing document serves as general background for discussions with the Pediatric Oncology Subcommittee of the ODAC on this topic. The document describes the mechanism of action, toxicology, clinical pharmacology and clinical safety and efficacy of vismodegib in adult patients with advanced BCC, and also provides an overview of available data in pediatric patients (i.e., patients ≤ 21 years of age).

1.2 REGULATORY HISTORY OF VISMODEGIB

- On 29 September 2006, Genentech filed an investigational new drug (IND) application.
- On 11 May 2011, a pre-submission meeting was held between representatives of the Food and Drug Administration (FDA) and Genentech to reach agreement on the content and format of a NDA for registration of vismodegib in advanced BCC.
- On 8 September 2011, a NDA was submitted to the FDA for vismodegib for use in adults with advanced BCC for whom surgery is inappropriate based on results of the pivotal ERIVANCE BCC study.
- Ongoing and past pediatric Phase I and II studies of vismodegib have been conducted under Genentech and collaborator INDs. A waiver request was included in the NDA submitted to FDA, as BCC is one of the adult-related conditions that could qualify for a disease-specific waiver because of the studies being impossible or highly impractical based on the number of pediatric patients (DHHS/FDA 2005).
- No pediatric studies have been initiated to date within the European Union territories. BCC currently is categorized under the class waiver for pediatric development, as published by the PDCO in 2007 (Article 12 of Regulation [EC] No. 1901/2006). Roche was granted a class waiver for vismodegib under the advanced BCC indication.

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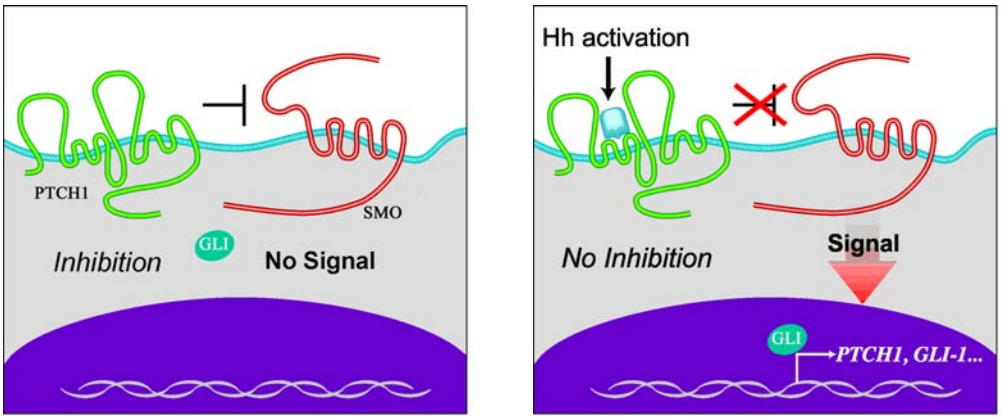
2. MECHANISM OF ACTION: HEDGEHOG SIGNALING IN CANCER

The Hh signaling pathway presents a novel and potentially beneficial target for cancer therapy. Hh signaling regulates epithelial and mesenchymal interactions in a variety of tissues during mammalian embryogenesis (Ingham and McMahon 2001). The Hh ligand in the extracellular space binds to Patched 1 (PTCH1), a receptor on the surface of cells. Hh binding relieves the inhibitory effect of PTCH1 on the transmembrane protein Smoothened (SMO). Signal transduction by SMO then leads to the activation and nuclear localization of GLI transcription factors and the transcriptional activation of Hh target-genes many of which are involved in proliferation, survival, and differentiation (see Figure 1).

Figure 1 Diagram of the Hh Pathway



PTCH1, the transmembrane receptor for Hh, normally inhibits the signaling function of another transmembrane protein, SMO, thereby blocking the expression of target genes, including *PTCH1* and *GLI1*. Sonic Hh binding to the PTCH1 receptor relieves the inhibition of SMO, leading to the activation of GLI transcription factors and transcriptional activation of target genes such as *PTCH1, GLI1,* and other genes involved in proliferation, survival and differentiation.

The role for aberrant Hh signaling in cancer was discovered initially in patients with Gorlin syndrome (or basal cell nevus syndrome), a rare autosomal dominant disease (Shih et al. 2008). Gorlin syndrome is characterized by larger body size, developmental and skeletal anomalies, fibromas of soft tissues, radiation sensitivity, and predisposition to BCCs and medulloblastoma (Levanat et al. 1996). In these patients, mutations in the *PTCH1* gene lead to a dysfunctional PTCH1 receptor which in turn leads to ligand-independent activation of SMO and constitutive activity of the Hh pathway (Epstein 2008).

Hh pathway activation has been implicated in several types of cancer, principally by two mechanisms: mutation-associated pathway activation within the tumor itself and paracrine-driven pathway activation in stromal tissue (see Figure 2). Mutations or other genetic alterations in *PTCH1* or *SMO*, the genes encoding for Hh receptor components, result in constitutive pathway activation and have been

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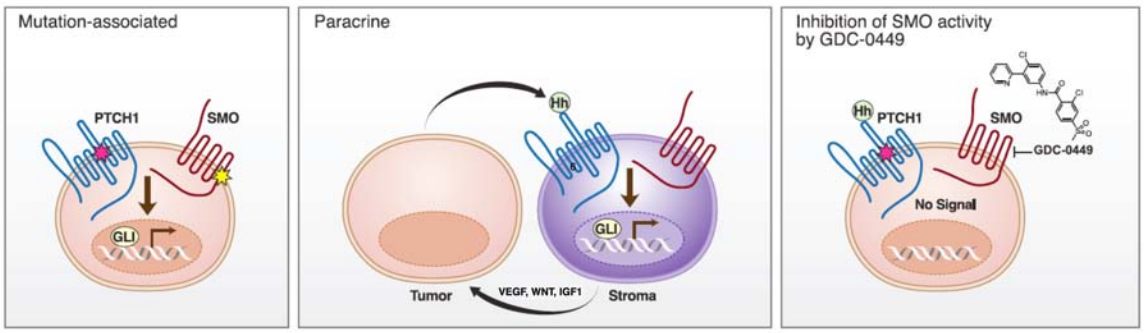
identified thus far only in BCC and medulloblastoma (Pasca di Magliano and Hebrok 2003; Romer and Curran 2005). It has also been observed that aberrant Hh ligand production by some types of tumor cells can promote the growth of the tumor through activation of the pathway in the tumor stroma via a paracrine mechanism (Yauch et al. 2008). Ligand overexpression has been detected in colon, ovarian, and pancreatic tumor cells, and is postulated to be the primary mechanism of activity in non-mutation-driven tumor types. Aside from medulloblastoma, other pediatric tumors hypothesized to be hedgehog-pathway driven are probably through paracrine-mediated activity of the hedgehog pathway.

Figure 2 Role of Hh Pathway Activation in Mutation-Associated and Paracrine-Driven Cancer



The Hh pathway has been implicated in two categories of cancers. The first category includes those such as BCC and medulloblastoma, which can be driven by genetic or epigenetic inactivation of the PTCH1 receptor or activating mutations in the SMO receptor. The second category includes those such as colorectal cancer and pancreatic cancer where aberrant expression of Hh ligands leads to paracrine signaling between the tumor and surrounding stroma which supports tumor growth. Vismodegib (GDC-0449) binds directly to and inhibits the action of SMO, a 7-pass transmembrane protein.

As shown in Figure 2, vismodegib binds directly to and inhibits the action of SMO thereby inhibiting downstream Hh pathway activation. Because vismodegib inhibits the pathway at the SMO receptor, it can both inhibit mutation-associated Hh pathway activation by binding SMO that is activated by a loss-of-function alteration in the PTCH1 receptor, as well as inhibit SMO in stromal cells activated by increased Hh-ligand-driven activation of the Hh pathway.

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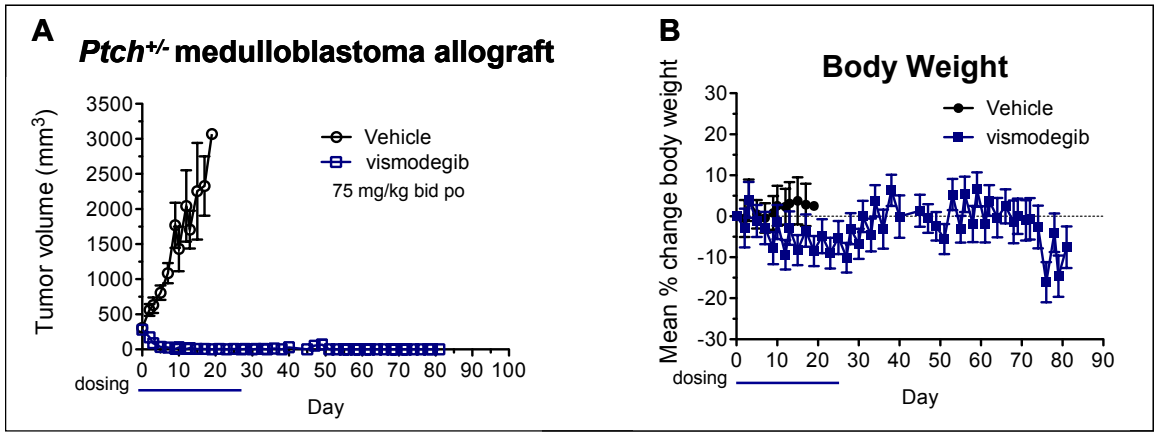
3. NONCLINICAL PROGRAM

Vismodegib shows anti-tumor activity in nonclinical tumor models of both mutated and ligand-driven tumors, including nonclinical models of medulloblastoma (Romer et al. 2004; Sasai et al. 2007), as well as other malignant tumors (Yauch et al. 2008). For medulloblastoma, mouse models of medulloblastoma have demonstrated shrinkage and disappearance of tumor (see Figure 3) when treated with HhAntag, a Hh pathway inhibitor molecule highly related to vismodegib. In contrast, the antitumor activity seen in ligand-driven paracrine models such as in colorectal and pancreatic cancer xenografts (Yauch et al. 2008) shows tumor growth delay, without actual tumor shrinkage. However, in both murine models, the anti-tumor effect of vismodegib correlates with blockade of the Hh pathway measured by reduction in the expression of *Gli1* mRNA, a transcriptional target of Hh signaling, in target cells.

Figure 3 Hedgehog Pathway Inhibition of Medulloblastoma in Murine Allograft



A) Treatment of murine Ptch1(+/-) allograft medulloblastoma with hedgehog pathway inhibitor vismodegib at clinically relevant dosing leads to durable response. B) Concurrent measurement of mouse body weight demonstrates no significant changes to contribute to bias of tumor growth.

Nonclinical pharmacokinetic (PK) studies have shown that vismodegib is orally bioavailable, and no human-specific metabolites are observed in vitro. In addition, vismodegib is highly protein bound in plasma of all species; ex vivo plasma protein binding is > 99% in patient samples. Based on in vitro data generated from human biomaterials (e.g., liver microsomes, hepatocytes, and recombinant enzymes), vismodegib is unlikely to cause clinically relevant drug-drug interactions.

The highest doses administered in Good Laboratory Practice (GLP) repeat-dose toxicity studies approached or exceeded the maximum tolerated dose in each species and resulted in systemic exposures that were comparable to those typically observed at steady-state in patients. Some toxicities observed in animals, including alopecia in rats and dogs, decreased number of taste buds in

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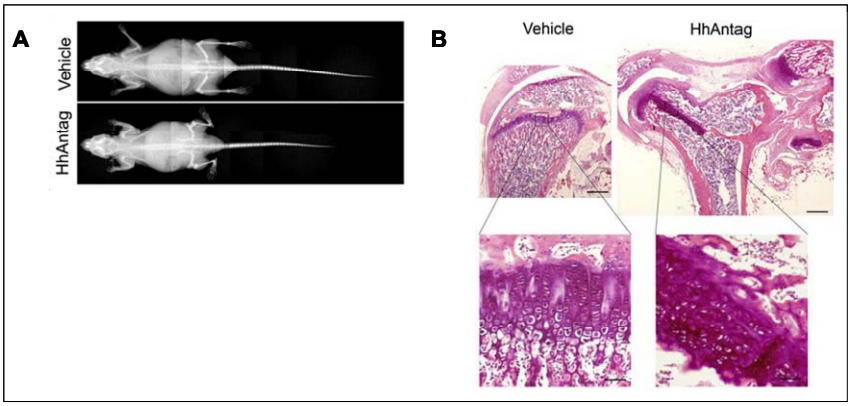
rats, and follicular cysts and pilomatricoma in rats, were attributable to the pharmacologic mechanism of action. Irreversible effects on growing teeth and bones observed in rats were also consistent with the pharmacologic mechanism of action, although no juvenile toxicity studies have been conducted.
Other findings included tremors and other involuntary movements and decreased corpora lutea in rats, hypercholesterolemia in rats and dogs, and decreased platelet counts, hemorrhage, and decreased hematocrit observed sporadically in dogs. Vismodegib was determined to be nongenotoxic. Vismodegib was confirmed to be teratogenic at clinically relevant exposures in an embryo-fetal development study.

Alterations in Hh pathway signaling have been associated with irreversible post-natal developmental defects, including irreversible effects on growing teeth and bones (Dassule et al. 2000; Cobourne et al. 2009). There are sufficient nonclinical experimental data to indicate that vismodegib poses a substantial risk of developmental defects beginning in early embryonic development and continuing into the postnatal period. In addition, adverse effects on growing teeth and partial to complete closure of the epiphyseal plate have been observed in rat toxicity studies with vismodegib. The Hh signaling pathway has been implicated in bone and teeth development in animal studies (Dassule et al. 2000).
While adverse events associated with bone or teeth development are not an expected concern in adult patients, vismodegib may adversely affect the development and maintenance of teeth, bones, or growth plates in a pediatric patient population (Kimura et al. 2008).

Figure 4 Bone Growth Changes with Treatment with Hedgehog Pathway Inhibitor



(A) X-ray images of 12-week-old mice after eight doses of HhAntag (upper, Vehicle; lower, HhAntag). (B) H&E staining of longitudinal cross-sections of femurs in 12-week-old mice after eight doses of Vehicle or HhAntag. Magnified regions show details of the growth plate. (Adapted from Reference: Kimura et al. 2008)

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4. CLINICAL PROGRAM IN ADULT PATIENTS WITH BASAL CELL CARCINOMA

4.1 CLINICAL STUDIES

Vismodegib has been investigated in >450 adult patients with various refractory malignancies in Genentech-sponsored clinical trials and is currently being tested in clinical trials in patients with various tumor types. Genentech-sponsored clinical trials have been conducted in patients with:

- Advanced (metastatic or locally advanced) basal cell carcinoma
- Metastatic colorectal cancer, previously untreated for metastatic disease
- Recurrent ovarian cancer in second or third complete remission

In addition, several NCI and investigator-sponsored trials (ISTs) are ongoing. The clinical studies discussed in this briefing package are presented in Appendix Table A1.

Vismodegib activity has been established in the pivotal study in patients with advanced BCC. A single patient case report in an adult patient with disseminated medulloblastoma has also been published. Although there are multiple ongoing studies in other cancer types with vismodegib through collaborators, in the two studies (colorectal and ovarian cancer) conducted in colorectal and ovarian cancers, there was insufficient clinical activity in these study settings to warrant further clinical trials by Genentech in these cancer types.

Thus, Genentech has observed clinical activity in tumor types that have a mutation-driven phenotype (BCC and medulloblastoma), and not in paracrine/ligand-dependent tumor types (CRC and ovarian cancer).

4.1.1 PHASE I DOSE-ESCALATION STUDY IN ADULTS WITH SOLID TUMORS AND ADVANCED BASAL CELL CARCINOMA

Study SHH3925g was the first clinical trial conducted to evaluate the safety and tolerability of oral vismodegib, given at escalating doses to patients with advanced solid malignancies. Encouraging tumor response rates were noted early in the study in patients with locally advanced or metastatic BCC, and an additional expansion cohort of patients with advanced BCC was included in order to more accurately estimate the efficacy of vismodegib in a Phase II-like setting.

The recommended Phase II dose was established at 150 mg/day because PK analyses indicated that higher doses did not result in higher steady-state plasma concentrations of vismodegib and that no dose-limiting toxic effects were observed.

Of the 33 patients enrolled with advanced BCC, 58% had a confirmed response as assessed by investigators (Von Hoff et al. 2009; LoRusso et al. 2011).

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In addition, one adult patient with multiple recurrences of widely disseminated medulloblastoma had an unconfirmed, short-lived partial response to vismodegib (see Section 5.3.2.2).

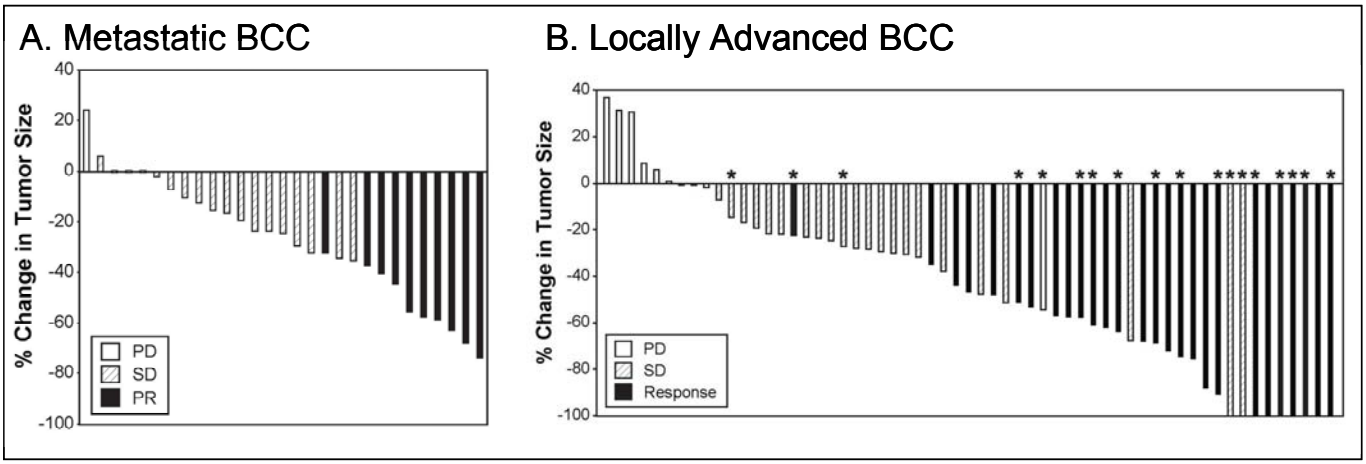
4.1.2 PIVOTAL STUDY IN ADVANCED BASAL CELL CARCINOMA

The pivotal study, SHH4476g, was a single-arm, two-cohort, multicenter clinical study to evaluate the efficacy and safety of vismodegib in patients with metastatic and locally advanced BCC. All patients received oral vismodegib at 150 mg daily until disease progression.

The primary efficacy endpoint was independent review facility (IRF)-determined objective response rate (ORR). For the locally advanced BCC patients, the IRF ORR was 43% (95% CI: 31, 56), and for metastatic patients, the IRF ORR was 30% (95% CI: 16, 48) (Sekulic et al. 2011).

The waterfall plots below demonstrate the tumor shrinkage seen as determined by IRF. Metastatic BCC (see Figure 5A) patients are represented by percentage change of sum of longest diameters as assessed by RECIST v. 1.0 and locally advanced patients (see Figure 5B) were assessed by photographs with tumor or areas involving residual scar measured in the longest dimension, and/or by RECIST v. 1.0 if measurable radiographically. Patients denoted as stable disease with more than 30% reduction were generally unconfirmed responses. Asterisks by each patient bar indicate that tumor ulceration on the skin that was present at baseline had completely resolved in all target lesions.

Figure 5 Waterfall Plots of Patients with Metastatic and Locally Advanced BCC



Alterations in the Hh signaling pathway have been reported in the majority (>90%) of BCC patients and, thus, the development of a predictive diagnostic for patients with advanced BCC was not considered necessary. This was confirmed by the high rate of clinical benefit reflected in the waterfall plots.

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Overall, vismodegib was generally well-tolerated. Adverse events occurring in ≥ 30% of patients included muscle spasms, alopecia, dysgeusia, weight loss, and fatigue (Table 1). Serious adverse events were reported in 26 patients (25%) of which the majority occurred in 1 patient with the exception of death of unknown cause in 3 patients, and cardiac failure, pneumonia, pulmonary embolism, and deep vein thrombosis in 2 patients each. Fatal adverse events were reported in 7 patients (7%) and none were considered related to vismodegib.

These data have been submitted in an NDA to the FDA.

Table 1 Adverse Events Reported in ≥ 20% of Patients in the Phase II Pivotal Study

MedDRA Preferred Term	Any Adverse Events (%)	Grade 1 Mild (%)	Grade 2 Moderate (%)	Grade 3–4 Severe (%)
Muscle spasms	68	48	16	4
Alopecia	64	49	14	0
Dysgeusia	51	28	23	0
Weight decreased	46	27	14	5
Fatigue	36	27	5	4
Nausea	29	21	7	1
Decreased appetite	23	14	6	3
Diarrhea	22	16	5	1

MedDRA = Medical Dictionary for Regulatory Activities

4.1.3 PHASE II CONTROLLED STUDIES IN LIGAND-DRIVEN TUMORS

4.1.3.1 Phase II Ovarian Cancer in Second or Third Complete Remission

Study SHH4489g was a Phase II, randomized, double-blind, placebo-controlled, multicenter clinical trial of single-agent vismodegib in patients with ovarian cancer in a second or third complete remission. The primary objective of this Phase II study was to estimate the clinical benefit of vismodegib as maintenance therapy for patients with ovarian cancer in a second or third complete remission, as measured by progression-free survival (PFS). Of 104 women patients enrolled, 57 PFS events were included in the analysis, with a median follow-up time of 5.7 months (Kaye et al. 2011). The median PFS was 5.8 versus 7.5 months for the placebo- and vismodegib-treated arms, respectively. The hazard ratio (HR) for PFS was 0.79 (95% CI: 0.46, 1.35; p=0.39). The HR for second complete remission patients was 0.66 (95% CI, 0.36, 1.20) and for third complete remission patients, the HR was 1.79 (95% CI, 0.50, 6.48).

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No new safety signals were observed, with the most common adverse events reported as Grade 1-2 muscle spasms, dysgeusia, and alopecia (all reported higher in the vismodegib-treated arm). Grade 3–4 adverse events were reported in 12 patients (23.1%) in the vismodegib arm and 6 patients (11.5%) in the placebo arm. Based on these data, no further clinical development with vismodegib has been initiated in ovarian cancer.

4.1.3.2 Phase II Metastatic Colorectal Cancer

Study SHH4429g was a Phase II, randomized, double-blind, placebo-controlled multicenter clinical trial of vismodegib with concurrent chemotherapy and bevacizumab as first-line therapy for patients with metastatic colorectal cancer. The primary objective of this study was to make an assessment of whether adding vismodegib to the standard of care (leucovorin, 5-fluorouracil, oxaliplatin [FOLFOX] + bevacizumab or leucovorin, 5-fluorouracil, irinotecan [FOLFIRI] + bevacizumab) increases anti-tumor efficacy as measured by PFS when compared with the standard of care alone in patients with previously untreated metastatic CRC. Of 199 patients (101 placebo and 98 vismodegib), PFS was not significantly improved for those patients in the vismodegib-treated arm compared with those in the placebo-treated arm (Berlin et al. 2010). The HR stratified by chemotherapy regimen was 1.24 (95% CI: 0.83, 1.87; p=0.30). Adverse events occurring more frequently in the vismodegib arm compared with the placebo arm included anorexia, weight loss, dysgeusia, and muscle spasms. Assessments of the pharmacokinetics for each regimen component (including vismodegib) did not reveal significant drug-drug interactions. Based on the results of this study, no further clinical development with vismodegib has been initiated in colorectal cancer.

4.1.4 RELEVANT ADDITIONAL STUDIES

4.1.4.1 Phase I Study Assessing Alternate Schedules

Study SHH4610g was a multicenter, two-stage, open-label Phase Ib study designed to describe the pharmacokinetics of daily (QD), three times weekly (TIW), and once weekly (QW) dosing of 150 mg vismodegib in 63 safety-evaluable patients with advanced solid tumors that were refractory to treatment or for whom no standard therapy existed. Both total and unbound plasma concentrations of vismodegib were sustained through 72 hours after a single dose of vismodegib, and steady-state was achieved within 11 days of continuous once-daily dosing. Total vismodegib plasma concentrations declined in a dosing frequency-related fashion, with the greatest decline observed in the QW group. A similar pattern was observed for unbound vismodegib compared with total vismodegib plasma concentrations, although the magnitude of the decrease in the TIW and QW groups was more pronounced for unbound than for total drug concentrations. The results of this study provided important insights on the nonlinear pharmacokinetics of vismodegib and supported the use of a 150 mg once-daily regimen for future clinical trials (LoRusso et al. 2011).

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4.1.4.2 Dedicated QTc Study

Study SHH4871g was a Phase I, single-center, three-arm, randomized, double-blind, active- and placebo-controlled study investigating the effect of vismodegib on the QT/QTc interval in healthy female subjects of non–childbearing potential. Results of this study suggest that when vismodegib is dosed to steady-state, there is no meaningful change in corrected QT interval compared with baseline. Analyses and review of ECG safety data collected during the study support the observation that vismodegib is associated with relatively low risk for delayed ventricular repolarization, prolongation of the QTc interval, and unstable arrhythmias.

4.2 CLINICAL PHARMACOKINETICS

The clinical pharmacokinetics of vismodegib has been thoroughly characterized in multiple clinical studies in patients with advanced solid tumors, in patients with advanced BCC, and in healthy volunteers. In most clinical studies, vismodegib was given as a capsule, which is the dosage form developed for the treatment of patients with advanced BCC.

After a single oral dose, vismodegib demonstrates a unique PK profile, with sustained plasma levels and an estimated terminal half-life of 12 days. Parallel concentration–time profiles are observed in the terminal elimination phase following oral and intravenous (IV) dosing, indicative of elimination rate-limited pharmacokinetics.

After continuous once-daily dosing, the pharmacokinetics of vismodegib appear to be nonlinear. Considering the single dose half-life, steady-state plasma concentrations in patients are achieved faster than expected (typically within approximately 7 days of continuous daily dosing), with lower than expected accumulation. Increasing the daily dose from 150 mg to 270 or 540 mg does not result in higher steady-state plasma concentrations, suggestive of saturable absorption. The apparent half-life of vismodegib at steady-state is estimated to be 4 days with continuous daily dosing. Vismodegib plasma PK parameters following oral dosing exhibited a moderate degree of inter-subject variability, with %CV for exposure parameters (AUC, C_{ss}) ranging from 32% to 48% in cancer patient studies.

Vismodegib binds to both human serum albumin and alpha-1-acid glycoprotein (AAG). In vitro binding to AAG is high affinity and is saturable within the clinically and physiologically relevant concentration range for vismodegib and AAG, respectively. Ex vivo plasma protein binding in humans is >99%. Vismodegib plasma concentrations are strongly correlated with AAG levels, showing parallel fluctuations of AAG and total drug concentrations over time with consistently low unbound drug levels. Population PK analysis suggests that vismodegib pharmacokinetics is highly dependent on AAG concentration whereas no other intrinsic factors were shown to significantly impact vismodegib exposure.

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An optimal adult dose of vismodegib (150 mg) was identified based on multiple factors, including saturable absorption at daily doses >150 mg and nonlinear protein binding with dosing schedules alternative to QD.

Based on a combination of results from in vitro and in vivo studies, there is a very low potential for drug-drug interactions when vismodegib is administered with other medications. In addition, under clinically relevant conditions (steady-state), the pharmacokinetics of vismodegib is not affected by food.

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5. VISMODEGIB FOR PEDIATRIC PATIENTS

Hh pathway activation has been implicated in a wide variety of adult and pediatric cancers. Activation of the Hh pathway in cancer is believed to occur mainly through a paracrine mechanism or mutations in the pathway. Nonclinical and clinical data suggest that colorectal, ovarian, and pancreatic cancers activate the Hh pathway through a paracrine mechanism (Yauch et al. 2008). Mutation-driven activation of the Hh pathway has only been demonstrated in a significant proportion of BCC and medulloblastoma tumors.

Hh pathway activation may also occur through undiscovered means as well. For example, an initial observation of a Gorlin syndrome patient with rhabdomyosarcoma (Gorlin 2004) suggested a mutation-driven component (summarized in Teglund 2010), but broader examination of the mutations in the rhabdomyosarcoma tumors was not as conclusive and suggested that a SMO antagonist such as vismodegib may not have anti-tumor activity in this cancer type (Tostar et al. 2010). The Hh pathway has also been hypothesized to play a role in maintenance of "cancer stem cells." This role for Hh signaling is plausible with paracrine-mediated pathway activation, yet a clinical mechanism demonstrating anti-stem cell and anti-tumor efficacy remains elusive.

To date, vismodegib has not shown significant anti-tumor activity in paracrine-mediated tumors (i.e., colorectal and ovarian cancer) and proof-of-concept for this mechanism of action has not yet been demonstrated in clinical trials. Genentech is awaiting results of other ongoing studies before initiating additional clinical research in Hh pathway paracrine-activated tumors. For these reasons, the remainder of this briefing book is focused on the most promising clinical data related to a pediatric indication—medulloblastoma.

5.1 MEDULLOBLASTOMA DISEASE BACKGROUND

Pediatric malignancies are relatively rare, accounting for approximately 1% of all cancers diagnosed in the United States annually (Linet et al. 1999; Smith et al. 1998). Medulloblastoma is the most common malignant brain tumor in children and accounts for approximately 20% of newly diagnosed brain tumors in the pediatric age group (Pui et al. 2011). Approximately 500 new patients are diagnosed in the United States annually (McNeil et al. 2002), and the estimated worldwide incidence is 1.5–2 cases per 100,000 population.

Currently, therapy for pediatric medulloblastoma consists of surgery, radiation therapy, and, for early-stage disease, chemotherapy. Approximately 60-80% of children with this type of brain cancer can be cured (Gajjar et al. 2010; Gajjar et al. 2006). Despite this, children with recurrent or refractory medulloblastoma have extremely poor survival.

Recently, subgroups of medulloblastoma have been described based on the primary signaling pathways involved in the cancer; these include Wnt, Hh and others. Approximately 15-30% of young patients with newly diagnosed sporadic medulloblastoma have shown increased signaling via the Hh pathway

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(see Table 2) and mutations in *PTCH1*, *SMO*, or *SUFU* have been identified in these tumors. Gene-expression profiling studies have suggested that medulloblastoma actually encompasses four or five molecularly distinct diseases with different clinical, pathological and prognostic features (Thompson et al. 2006; Northcott et al. 2011). The subgroup of newly-diagnosed medulloblastoma patients with mutations in the Hh signaling pathway are thought to have an intermediate prognosis with 5-year event-free survival rate of 75–85% when treated with conventional therapy (Remke et al. 2011; Ellison et al. 2011).

Approximately 65% of children ≤ 3 years of age diagnosed with medulloblastoma have tumors with the Hh pathway activated compared with 15% in children 4–15 years of age and 71% in adults ≥16 years of age suggesting a bimodal age distribution (see Table 2; Kool et al. 2008; Korshunov et al. 2010).

Table 2 Clinicopathological and Genetic Associations of Medulloblastoma Molecular Subgroups

	Molecular Group		
	Hh	Wnt	Non-Wnt/Hh
Proportion of medulloblastoma	15-30%	~15%	~60%
Age at presentation	Mainly infancy & adulthood; Uncommon in 5–15 years old	Childhood–pre-teen years; mean age ~10 years	Mainly childhood; mean age ~8 years
Metastatic disease at presentation	Rare	Rare	Most cases of metastatic disease in this group
Pathological variant	D/N tumors and MBENs ~50% of LC/A tumors	Nearly all classic tumors; No D/N tumors	Mainly classic tumors ~50% of LC/A tumors
Outcome with primary therapy	Good	Very good	Poor, if metastatic disease; Poor, if LC/A tumor

Wnt=wingless-int; Hh=hedgehog; D/N=desmoplastic/nodular; LC/A=large cell/anaplastic; MBEN=medulloblastoma with extensive nodularity.

Data in this table have been derived from Northcott et al. 2011; Kool et al. 2008; and Thompson et al. 2006.

Activation of the Hh signaling pathway in cerebellar granule-cell precursors promotes the development of medulloblastoma in nonclinical models. Heterozygous deletion of the murine homologue of *Ptch1* results in medulloblastoma by 25 weeks of age in approximately one third of mice (Goodrich et al. 1997). These tumors are associated with loss of expression or mutation of the remaining wild-type *Ptch1* allele (Oliver et al. 2005). Inhibition of the Hh pathway results in regression of medulloblastoma tumors in *Ptch1*+/ mice (Berman et al. 2002; Romer et al. 2004).

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Constitutive activation of Hh signaling often due to inactivating mutations of *PTCH1* has been shown in approximately 15–20% of medulloblastomas in humans (Lee et al. 2003). Medulloblastoma develops in approximately 1-2% of patients with Gorlin syndrome (Evans et al. 1991).

5.2 PREDICTIVE DIAGNOSTIC TESTING IN MEDULLOBLASTOMA

Medulloblastoma is a heterogeneous disease consisting of molecularly defined tumors with overlapping histological features. Disease variants can be characterized by molecular subgroups (Hh, Wnt, and non-Hh/Wnt tumors) that demonstrate distinct genetic, epigenetic, and clinicopathologic features, and clinical outcomes.

Development of diagnostic tools that could identify these molecular subclasses of pediatric medulloblastoma may help advance treatment approaches. By identifying the key signaling pathway underlying a person's disease, treatment can be individualized with targeted 'pathway-specific' therapies. This offers the potential to reduce the need for cytotoxic chemotherapy and radiation, individualize therapy, and minimize long-term adverse effects for some patients.

The development of a predictive diagnostic assay to select patients who may benefit from a targeted therapy, such as vismodegib, while excluding patients unlikely to benefit has now become an expected aspect of drug development. However, an additional layer of complexity exists for the development of a predictive diagnostic for Hh inhibitors, such as vismodegib, as the Hh pathway is activated through a variety of mechanisms and pathway components. In medulloblastoma, several Hh pathway receptors and signaling molecules, including PTCH, SMO, and SUFU, have been reported to be dysregulated. This occurs through mutations causing loss-of-function, activating mutations, chromosomal or gene rearrangements, or even epigenetic silencing. This heterogeneity of mechanisms for Hh pathway activation precludes the use of a simplified test, such as identification of a genetic hotspot mutation, to determine susceptibility to Hh pathway inhibitors.

Multiple publications in 2011 have identified at least two different diagnostic strategies for subgrouping medulloblastoma, and by extension, potentially identifying a population that may respond to vismodegib. Both strategies suggest classifying medulloblastomas based on the involvement of the Hh pathway versus Wnt or Wnt-/Hh-independent disease subgroups as described by Schwalbe et al. (2011). One method proposes the use of gene expression signatures, while another group has identified immunohistochemical methods that identify Hh, Wnt, and non-Hh/Wnt tumors in patients with medulloblastoma which may be used with formalin-fixed paraffin-embedded (FFPE) tissue in the setting of a diagnostic laboratory (Ellison et al. 2011). In addition to these two published strategies, Genentech is also aware of ongoing efforts in academia to identify other methods of identifying medulloblastoma subgroups.

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To date, none of the emerging tests has been proven to identify patients whose tumors would be susceptible to Hh pathway inhibition. One inherent limitation of currently published strategies is that they are focused on clinical and molecular subgrouping of the disease and do not indicate whether Hh pathway activation occurs proximal or distal to SMO, the target of current clinical Hh pathway inhibitors, including vismodegib. In addition, the different assays used have not yet been compared to each other for reliability, consistency, or superiority in selecting patients with Hh pathway activated tumors. More importantly, none of these tests have published clinical data that supports their use in predicting improved efficacy of Hh pathway inhibitors, although various early stage clinical trials are ongoing.

5.3 TREATMENT OF PEDIATRIC PATIENTS WITH MEDULLOBLASTOMA

5.3.1 CURRENT TREATMENT OPTIONS OF PEDIATRIC MEDULLOBLASTOMA PATIENTS

Multimodality treatment with chemotherapy before or after radiotherapy has greatly improved survival in children with average-risk medulloblastoma (i.e., no evidence of metastasis and residual disease ≤ 1.5 cm^2). It is now possible to achieve cure rates greater than 80% in children ≥ 3 years of age.
The ntroduction of effective chemotherapy has reduced the dose of craniospinal radiotherapy needed to treat average-risk medulloblastoma. However, children with high-risk medulloblastoma (i.e., residual disease > 1.5 cm^2 or metastatic disease) still have extremely poor cure rates and fewer than 55% of children survive longer than 5 years. For these patients, treatments such as myeloablative chemotherapy, have shown limited effectiveness in relapsed medulloblastoma, and are associated with high toxic mortality (Gajjar et al. 2010). Therefore, molecularly targeted therapies with favorable benefit-risk profiles are needed to improve outcomes and potentially reduce the need for cytotoxic chemotherapy.

5.3.2 PEDIATRIC MEDULLOBLASTOMA CLINICAL TRIALS AND EXPERIENCE

5.3.2.1 SHH4318g: Phase I Study in Pediatric Medulloblastoma

Study SHH4318g was an open-label study conducted between June and July of 2007 to evaluate the safety and tolerability of 62 mg/m^2/day (rounded down to 50 mg/day for a BSA of 1.0 m^2) vismodegib administered orally as a single agent on a once-daily schedule in children at least 3 years old with medulloblastoma. After the treatment of the first patient, Genentech made the decision to pursue further studies with a cooperative group partner and to close this study.

The single patient (14000) enrolled was a 9-year-old White male with recurrent medulloblastoma who received 29 daily doses of 50-mg vismodegib and terminated from the study because of clinical disease progression. The patient did not demonstrate evidence of clinical benefit while in the study.

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Transcriptional profiling of Hh pathway target genes in the archival tissue specimen was consistent with a lack of active Hh signaling in this tumor specimen (see Figure 6).

Total plasma concentrations of vismodegib were observed to increase continually during the 4 weeks of treatment for the patient treated at 50 mg/dose/day, reaching a level of 20 μM at Day 28. Cerebrospinal fluid (CSF) levels in the 1 patient were ≤ 0.32% of total plasma concentrations at all timepoints tested. Unbound vismodegib was not measured in study SHH4318g, however assuming protein binding is similar to adults (>99%), the calculated unbound plasma concentration is similar to the measured CSF concentration.

No safety signals were identified during the course of the study. All reported adverse events were considered related to the disease under study and none were considered related treatment.

5.3.2.2 Adult Medulloblastoma Patient Treated with Vismodegib

One adult patient (12004) with evidence of a loss-of-function mutation in *PTCH1* and multiple recurrences of widely disseminated medulloblastoma had an unconfirmed, short-lived partial response (Rudin et al. 2009) while treated on the Phase I dose-escalation study (SHH3925g). This 26-year-old male patient had metastatic medulloblastoma that was initially diagnosed at age 22 at which time his disease was confined to the cerebellum and he was treated with surgery, radiation and chemotherapy. Two years later, he developed recurrent and metastatic disease which was treated with multiple therapies including additional surgeries and radiotherapy, autologous stem cell transplant, and additional chemotherapy. At the time he was enrolled in the Phase I study of vismodegib, his disease was widely disseminated and he was pancytopenic requiring weekly blood transfusions and twice-weekly platelet transfusions due to bone marrow involvement. Baseline tumor tissue from his primary tumor and a biopsy from a metastatic site of disease showed up-regulation of the Hh pathway responsive genes, GLI1 and PTCH1 (see Figure 6). After initiating treatment with vismodegib, the patient had a significant response by physical exam and as visualized on radiographic imaging at 2 months, and reported a substantial reduction in pain symptoms. Representative images are provided in the Rudin et al paper in Appendix A. However, a confirmatory scan at 3 months demonstrated disease progression and a biopsy obtained at the time of progression indicated that a new mutation in the SMO receptor, not previously seen in submitted archival tissue from primary and pre-treatment metastatic disease, was present in the recurrent disease and conferred resistance to vismodegib (Yauch et al. 2009).
We speculate that combination of the patient's prior tumor burden and prior therapies with DNA-damaging agents may have contributed to the rapid selection of resistant tumor cells leading to the rapid relapse.

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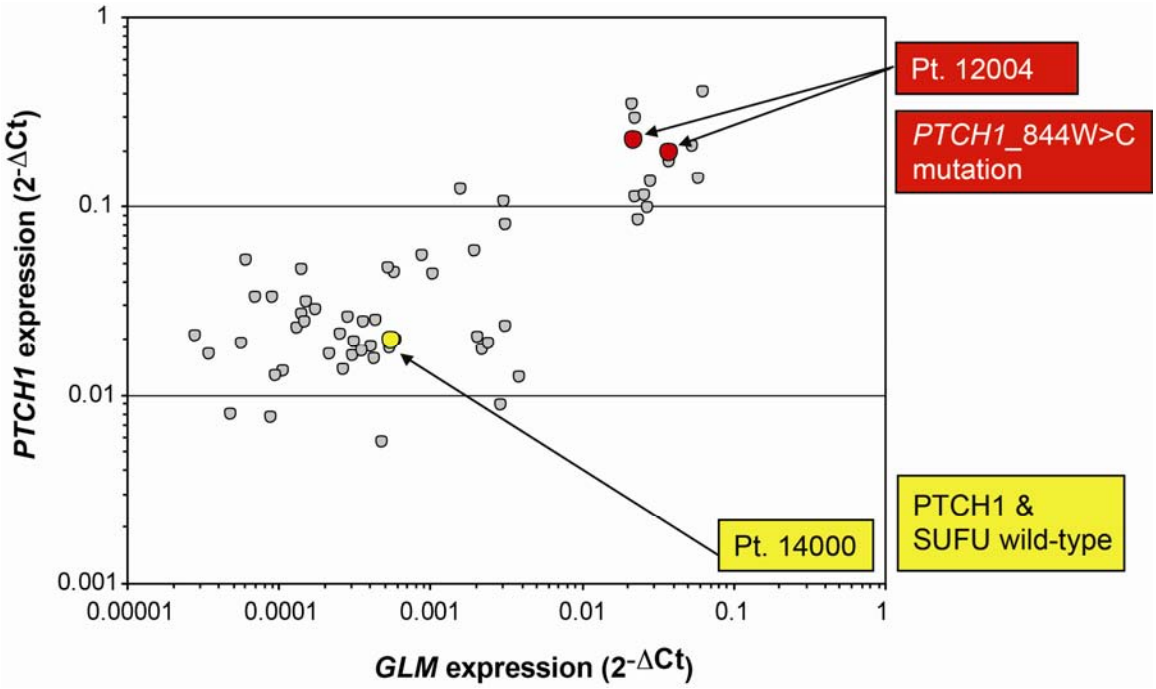
Figure 6 Baseline Expression of Markers of Hh Pathway Activation



Relative expression by RT-PCR of Hh pathway responsive genes, *GLI1* and *PTCH1*. Medulloblastoma tumor samples from tumor banks were profiled for expression of *GLI* and *PTCH1*. Shown in yellow are the samples from Patient 14000 from study SHH4318g, who did not respond to vismodegib and did not have *PTCH1* or *SUFU* mutations, and the tumor samples from Patient 12004 from Study SHH3925g, who did have a transient response to vismodegib and a loss-of-function *PTCH1* mutation.

5.3.2.3 PBTC-025: Phase I Study in Pediatric Medulloblastoma

PBTC-025 (A Phase I Pharmacokinetic and Safety Study in Children with Recurrent or Refractory Medulloblastoma to Identify a Pharmacokinetic-Based Dose for GDC-0449) was a multicenter Phase I pharmacokinetic and safety study in children aged 3–21 years with recurrent or refractory medulloblastoma to select the recommended dosing for a pediatric phase II trial. This study was part of a cooperative research agreement between Genentech and the NCI Division of Cancer Treatment and Diagnosis, sponsored by the NCI, and proposed and conducted by the Pediatric Brain Tumor Consortium (PBTC). Secondary objectives were safety and tolerability, pharmacokinetics, preliminary anti-tumor activity, and identification of CNS tumors with activation of Hh pathway using exploratory immunohistochemistry (IHC) and in situ hybridization (ISH) assays on formalin-fixed paraffin-embedded (PPFE) tissue to determine which tumors belonged to the Hh subtype.

Vismodegib was administered once daily for 28 days at dose levels of (1) 85 mg/m^2/dose and (2) 170 mg/m^2/dose, rounded to the nearest dose by 25 mg capsule increments. A course was defined as 28 days in duration. PK analysis of total/unbound vismodegib and AAG was performed during the first

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course and steady-state concentrations were obtained prior to each subsequent course (Day 21). Samples were also collected during the first course to characterize the PK of vismodegib in CSF (in consenting, applicable patients). MRI scans of the knees were obtained at baseline and 3 months to assess potential abnormalities in long-bone and joint development.

Twelve patients (10 male, 2 female) were enrolled and considered evaluable, with a median age of 11.6 years (range 4.4 to 21 years) and median duration of treatment of 56 days (range 7-500 days). Twenty-five percent (25%) of the first 12 patients had a Hh molecular subtype as evaluated by an immunohistochemistry assay, while the remainder had a non-Wnt, non-Hh subtype. No dose limiting toxicities were seen at the 85 mg/m^2 dose level, and a single patient out of 6 had an isolated elevation of gamma-glutamyl transferase as a dose-limiting toxicity at the 170 mg/m^2 dose level (Gajjar et al. 2010). No MRI abnormalities in the knees were found.

Following a single dose of 85 mg/m^2 or 170 mg/m^2 vismodegib, median (range) maximum total and unbound plasma concentrations were achieved at 60 hours (8–76 hours) and 14 hours (2–72 hours), respectively with a flat profile over the subsequent 3 days. The median maximum total and unbound vismodegib concentrations observed within the first 72 hours increased with dosage.

With continuous daily dosing of 85 mg/m^2 or 170 mg/m^2 vismodegib, steady-state was reached by Day 14 (although Day 21 was used as the steady-state value upon which protocol decisions were based). The median Day 21 plasma concentrations of total and unbound vismodegib increased with dosage. There was a strong, linear correlation between concentrations of total vismodegib and AAG, suggesting the steady-state pharmacokinetics of vismodegib is highly influenced by AAG in pediatric patients.

CSF concentrations were 0.13 to 0.35% of total plasma concentrations at steady-state. Assuming protein binding is similar to adults (>99%), the calculated unbound plasma concentration in pediatric patients is similar to the measured CSF concentration.

The recommended Phase II dose based on this portion of the study was daily 170 mg/m^2 vismodegib. The study was amended to enroll additional cohorts of patients with a fixed dosing regimen of either 150 or 300 mg/day, based on BSA less than or greater than 1.33 m^2, respectively. The results of this portion of the study have not been presented, although the fixed dosing regimen is being used in the PBTC-032 study described below.

5.3.2.4 PBTC-032: Phase II Study in Pediatric Medulloblastoma

PBTC-032 (A Phase II Clinical Trial Evaluating the Efficacy and Safety of GDC-0449 in Children with Recurrent or Refractory Medulloblastoma) is a multicenter Phase II trial in collaboration with the Pediatric Brain Tumor Consortium and NCI-CTEP. Patients aged 3 to 21 years diagnosed with recurrent or refractory medulloblastoma tumors receive a fixed dose of oral

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vismodegib (150 or 300 mg) daily depending on body surface area (BSA). Patients receive vismodegib treatment for 28 days and are stratified by IHC evidence of Hh pathway activation.

The primary objectives of Study PBTC-032 are to estimate the efficacy of vismodegib treatment for pediatric patients with recurrent or refractory medulloblastoma, as measured by the sustained objective response rates for at least 8 weeks in patients without versus patients with evidence of activation of Hh signaling pathway in their tumors, as well as characterization of the pharmacokinetics of vismodegib in children/adolescents with refractory medulloblastoma. Correlative studies on FFPE tissue and snap frozen tissue aim to select patients with tumors in whom the Hh signaling pathway is activated.

Patients are stratified to one of three cohorts: Hh pathway activated, Hh pathway inactive, or Hh pathway indeterminant, based on IHC as described by Ellison et al. 2011. The study was designed with a two-stage enrollment, allowing for early closure of stratification arms that did not have evidence of clinical activity. This study began enrolling in 2011, and is currently enrolling only patients with Hh pathway activation.

A Phase II study in adult patients (> 21 years old) with medulloblastoma, PBTC-025B, which is analogous to the pediatric Phase II study PBTC-032, has also been initiated and is currently enrolling patients. The dosing and objectives of these studies are similar.

5.4 CONSIDERATIONS FOR PEDIATRIC PHARMACOKINETICS BASED ON ADULT PHARAMACOKINETICS OF VISMODEGIB

For drugs that exhibit linear pharmacokinetics, the exposure (i.e., AUC) is primarily mediated by the clearance and volume of distribution, which are both a function of body size. Therefore adult drug dosages are often adjusted based on mg/kg body weight or mg/m^2 of body surface area (BSA), in order to achieve similar exposures in children to those observed in adults to be safe and effective. However, based on the current understanding of vismodegib metabolism, protein binding, and pharmacokinetics in adults, it is not expected that the pharmacokinetics of vismodegib would be different in children, even when administered as a fixed dose.

While vismodegib was shown to form metabolites in vitro using recombinant CYP enzymes, metabolic stability data suggest that vismodegib is not metabolized efficiently, with 96% of parent drug remaining after 3-hour incubation with human hepatocytes. The in vitro metabolic stability of vismodegib is in qualitative agreement with the clinical observation that vismodegib exhibits slow clearance following an IV dose and parent compound was the predominant circulating drug species in plasma. The extremely slow rate of clearance in humans is reflective of the in vitro data, which suggest that vismodegib is also a poor CYP substrate in vivo. Therefore, given the inefficient in vitro CYP metabolism and other factors

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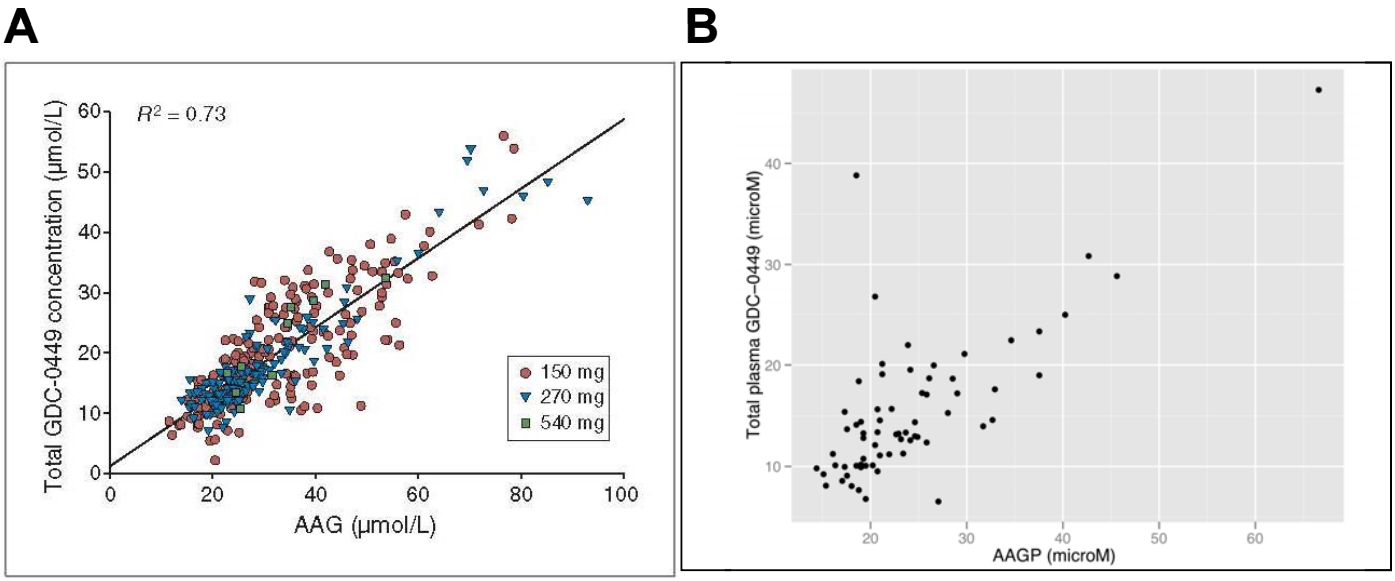
that govern the clinical pharmacokinetics of vismodegib, it is unlikely that differences between adult and pediatric drug metabolizing enzymes would lead to different plasma concentrations of vismodegib.

As shown in Figure 7, vismodegib pharmacokinetics has been shown to strongly correlate with AAG levels in adult and pediatric patients accounting for over 70% of pharmacokinetic variability (Graham et al. 2011; Gajjar et al. 2010). Several studies have shown that the levels of AAG in children ≥ 1 year old (35–90 mg/dL) are similar to levels in adults (55-100 mg/dL; Meistelman et al. 1990; Lerman et al. 1989; Israili and Dayton 2001). Compared with AAG levels in healthy populations, AAG levels in patients with malignant tumors are highly variable and can be elevated up to 5-fold (Duche et al. 2000). Protein binding is expected to be similar in adults and pediatric patients based upon (1) the similar relationship between total vismodegib and AAG plasma concentration, (2) similar levels of AAG, and (3) no expected differences in AAG binding affinity.

Figure 7 Scatter Plots in A) Adults (Graham et al. 2011) and B) Children (Gajjar et al. 2010) Demonstrate that Total Vismodegib and AAG Plasma Concentrations Are Highly Correlated



Based on the current understanding of vismodegib metabolism, protein binding, and pharmacokinetics in adults, it is not expected that the pharmacokinetics of vismodegib would be different in children. Therefore, a fixed dosing regimen of 150 mg QD is expected to be appropriate for pediatric medulloblastoma patients.

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6. FORMULATION

To date, a pediatric formulation has not been developed for commercial use. While it is anticipated that a non-capsule formulation would be potentially useful for very young children (for example, children under 5 years old), the current pediatric studies (for children aged ≥ 3 years) have utilized the capsule formulation exclusively.

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7. POTENTIAL CHALLENGES FOR CLINICAL DEVELOPMENT IN PEDIATRIC PATIENTS

7.1 PATIENT POPULATION

Hh signaling is known to play a critical role in normal embryonic and fetal development and it is thought it may continue to play a role in early childhood development. Although the safety profile for vismodegib has been characterized in adult cancer patients, it has not yet been well characterized in children. Given the role the Hh pathway may have in early childhood development, it is possible that Hh pathway inhibitors may have significant toxicities specific to children that have not yet been characterized and may emerge with increased clinical study.

Each year, approximately 500 children are diagnosed with medulloblastoma in the United States. Approximately 60-80% of these patients will be cured with current standard-of-care therapy.

This leaves a very small population with a high unmet need who could benefit from targeted therapies such as Hh pathway inhibitors. It is estimated that 100-200 children have refractory or recurrent medulloblastoma and, of these, 15-30% (30-60 patients/year) are likely to have a tumor that is activated by the Hh pathway.

However, extremely young patients (e.g., ≤ 3 years of age) may be more susceptible to development-related toxicities with Hh pathway inhibitors.
In addition, there is strong biological rationale that pediatric patients, who do not have Hh pathway activated medulloblastomas, are unlikely to derive any benefit from exposure to a targeted Hh pathway inhibitor. These children therefore have an unacceptable benefit-risk profile taking into consideration the increased risk for Hh targeted treatment-related toxicities to the teeth and bones.
Thus, Hh pathway diagnostic-negative pediatric patients should not be enrolled in a confirmatory study to evaluate medulloblastoma efficacy.

The scarcity of patients, lack of a validated diagnostic test to identify patients who may benefit from a Hh pathway inhibitor and those who may not, as well as the potential safety issues, limits what can be reasonably tested within a traditionally designed clinical trial. While randomized comparative trials with an overall survival endpoint are a gold standard for assessing efficacy and safety, the low patient numbers may preclude feasibility of testing new agents such as vismodegib in pediatric patients with medulloblastoma. In addition, the benefit-risk assessment and small numbers makes it challenging to conduct clinical trials of sufficient size and duration to characterize the potential safety issues.

Since medulloblastoma is largely a childhood disease with relatively few young adult patients, even inclusion of adult patients will not significantly improve the numbers or feasibility of conducting these studies. Non-randomized designs, including single arm trials, possible use of external data for a historical control, and surrogate endpoints, will need to be considered in study designs and ODAC feedback is welcomed.

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7.2 DIAGNOSTIC

Current research in medulloblastoma has led to the identification of various subtypes of medulloblastoma with differing prognoses. Ultimately, the goal is for each subtype to have individualized 'pathway-specific' therapies. However, this remains a rapidly evolving field. Currently, there is no validated or accepted standard-of-practice diagnostic test to identify the subset of Hh-activated medulloblastoma patients, nor select those likely to benefit from vismodegib treatment, nor to select those with non-Hh-activated tumors who are likely to derive more toxicity than benefit from vismodegib treatment. Based on the biological rationale, mechanism of action, and relative benefit-risk to the pediatric patient exposed to vismodegib, a predictive biomarker assay will be especially important in this disease setting.

In BCC, mutations in the Hh pathway have been reported in more than 90% of cases, so a predictive diagnostic test is not necessary. However, for medulloblastoma, only 15-30% of tumors are activated by the Hh pathway, and the remaining 70-85% are driven by other cancer signaling pathways.

Sequencing of *PTCH1* and *SMO* is not a viable diagnostic strategy due to the lack of hot-spot mutations and the large variety of genetic alterations (e.g., exon and intron mutations, deletions, loss-of-heterozygosity, and gene methylation) that can lead to pathway activation. In published subtyping assays, biomarkers distal to the point of inhibitor activity (i.e. inhibition of SMO) and in some cases to the well-established components of the Hh signaling pathway have been used. This adds complexity to the process of evaluating the predictive value of a diagnostic assay in a small patient population.

Because there is no broadly used assay to subtype medulloblastoma and this is a rapidly evolving field, current and future research may lead to assay changes upon additional validation, or abandoning a current assay for an improved future assay. These challenges increase the risk of prospectively defining and validating an assay for patient inclusion in a clinical trial, and later changing the assay for clinical practice.

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8. CONCLUSIONS

Vismodegib is a potent and effective inhibitor of the Hh signaling pathway. Vismodegib efficacy has been demonstrated in a pivotal study in adults with advanced BCC and an NDA has been submitted to the FDA for this indication. The biological mechanism of action for Hh pathway inhibition in oncology is most compelling in BCC and in Hh-pathway-driven medulloblastoma. However, BCC is exceptionally rare in children and advanced BCC in children has not been seen. Hh-pathway-driven medulloblastoma is rare occurring in approximately 1 in 5 pediatric patients with medulloblastoma, and although there is no established diagnostic test, there exists a high unmet medical need for treatments of recurrent or relapsed medulloblastoma in pediatrics. Genentech welcomes discussion with the Pediatric Oncology Subcommittee of the ODAC regarding the potential for future development of vismodegib for this indication.

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9. POTENTIAL QUESTIONS FOR THE SUBCOMMITTEE

1. Given the potential for increased development-related toxicity in children and the lack of scientific rationale for testing vismodegib in pediatric patients without activated Hh pathway medulloblastoma, does the committee have concerns if the negative predictive value of the diagnostic assay is not tested in Hh diagnostic-negative patients?

2. If the current Pediatric Brain Tumor Consortium Phase II study evaluating vismodegib treatment shows promising tumor response rates in children with medulloblastoma, does the committee have comments on the most appropriate primary endpoint to establish efficacy in a confirmatory study? Does the committee have comments on the appropriateness of using a historical control or single-arm study?

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11. APPENDIX

The following articles are recommended as supportive background of this briefing book.

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Table A1 Studies Discussed in the Briefing Book

Study Number	Protocol Title	Estimated Number of Patients Enrolled/ Number of Patients Treated
SHH4476g	A Pivotal Phase II, Multicenter, Single-Arm, Two-Cohort Trial Evaluating the Efficacy and Safety of GDC-0449 in Patients with Advanced Basal Cell Carcinoma	100/104
SHH3925g	An Open-Label, Phase I Study of Systemic Hedgehog Pathway Antagonist, GDC-0449, in Patients with Locally Advanced or Metastatic Solid Tumors That Are Refractory to Standard Therapy or for Whom No Standard Therapy Exists	68/68
SHH4429g	A Randomized, Placebo-Controlled Phase II Study of GDC-0449 (Hedgehog Antagonist) with Concurrent Chemotherapy and Bevacizumab as First-line Therapy for Metastatic Colorectal Cancer	198/199
SHH4489g	A Phase II, Multicenter, Randomized, Double-blind, Placebo-controlled Trial Evaluating the Efficacy and Safety of GDC-0449 as Maintenance Therapy in Patients with Ovarian Cancer in a Second or Third Complete Remission	104/104
SHH4610g	A Phase Ib, Open-label, Dose-Scheduling Study of Hedgehog Pathway Inhibitor GDC-0449 in Patients with Locally Advanced or Metastatic Solid Tumors That Are Refractory to Standard Therapy or for Whom No Standard Therapy Exists	67/67
SHH4871g	A Multiple-Dose, Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Parallel Group Study to Investigate the Effect of GDC-0449 on the QT/QTc Interval in Healthy Female Subjects	61/61
PBTC-025	A Phase I Pharmacokinetic and Safety Study in Children with Recurrent or Refractory Medulloblastoma to Identify a Pharmacokinetic-Based Dose for GDC-0449	30/31
PBTC-032	A Phase II Clinical Trial Evaluating the Efficacy and Safety of GDC-0449 in Children with Recurrent or Refractory Medulloblastoma	50/0
PBTC-025B	A Phase II Clinical Trial Evaluating the Efficacy and Safety of GDC-0449 in Adults with Recurrent or Refractory Medulloblastoma	50/17

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