

Pediatric Subcommittee of ODAC

Vismodegib Hedgehog Pathway Inhibitor

Jennifer Low, MD, PhD

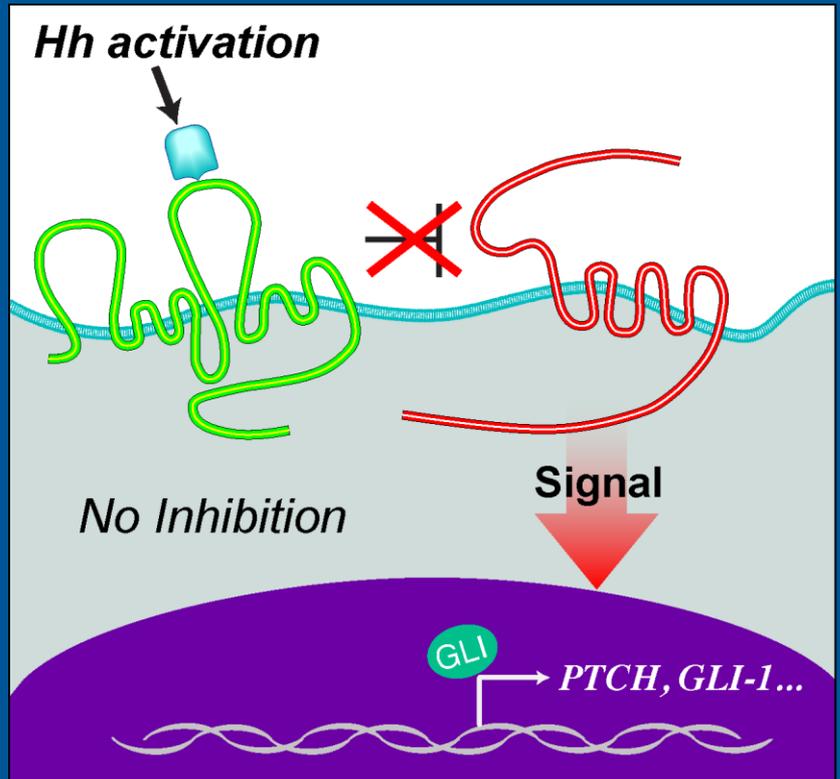
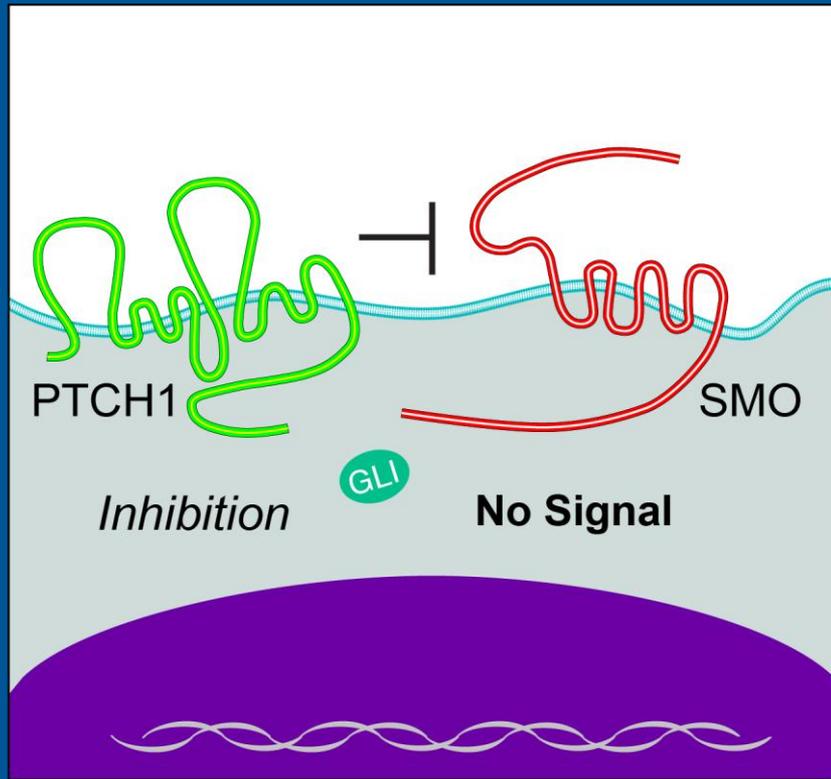
**Global Development Leader, Vismodegib
Genentech, a Member of the Roche Group**

November 1, 2011

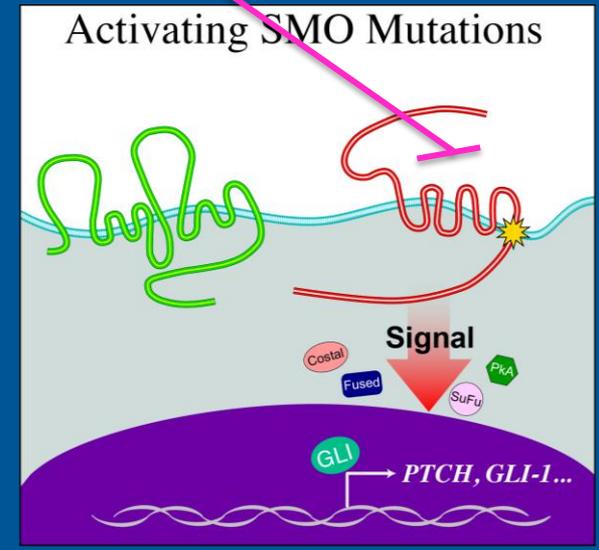
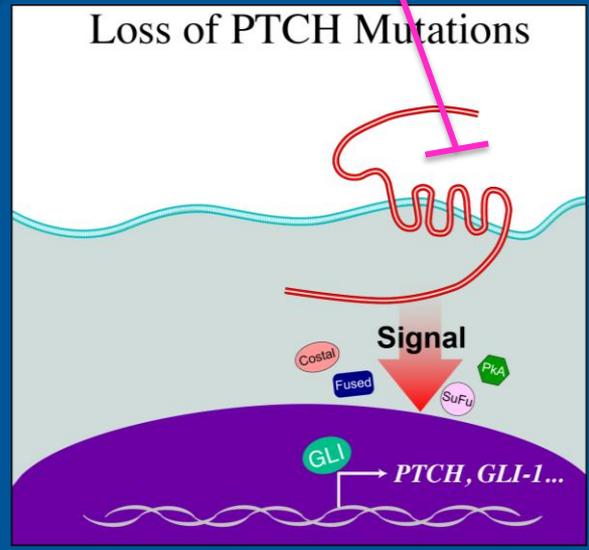
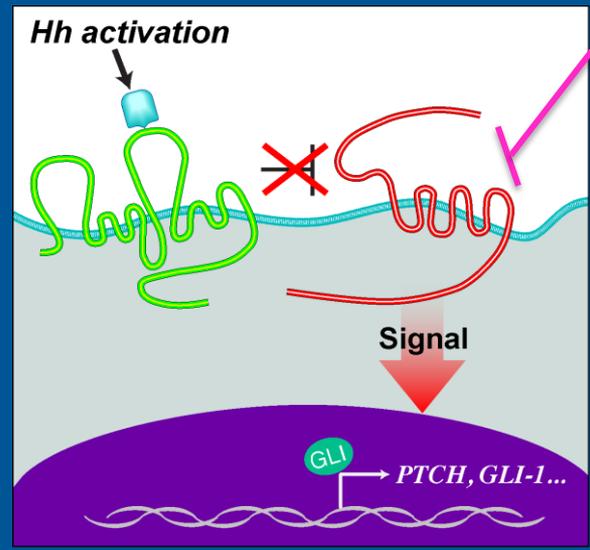
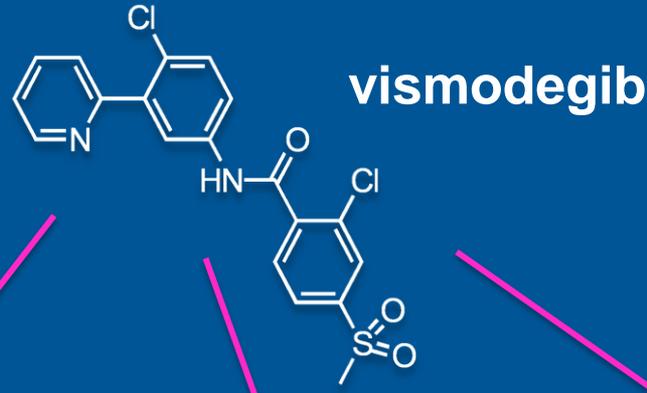
Presentation Outline

- **Mechanism of Action**
- **Key clinical findings**
- **Pediatric Development in Medulloblastoma**
- **Opportunities and Challenges**

Hedgehog Signaling is Critical for Embryonic Development

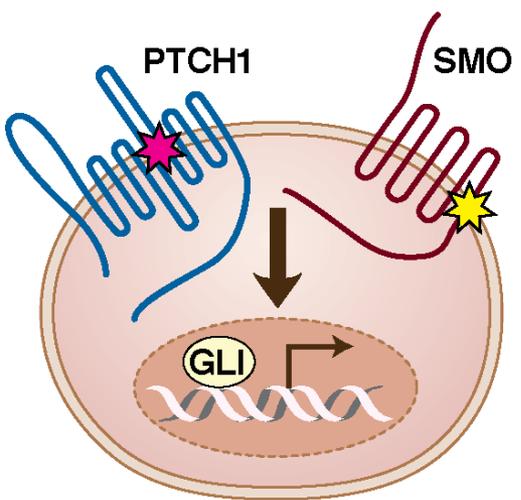


Activation of Smoothened or Functional Loss of Patched Leads to Hedgehog Pathway Activation



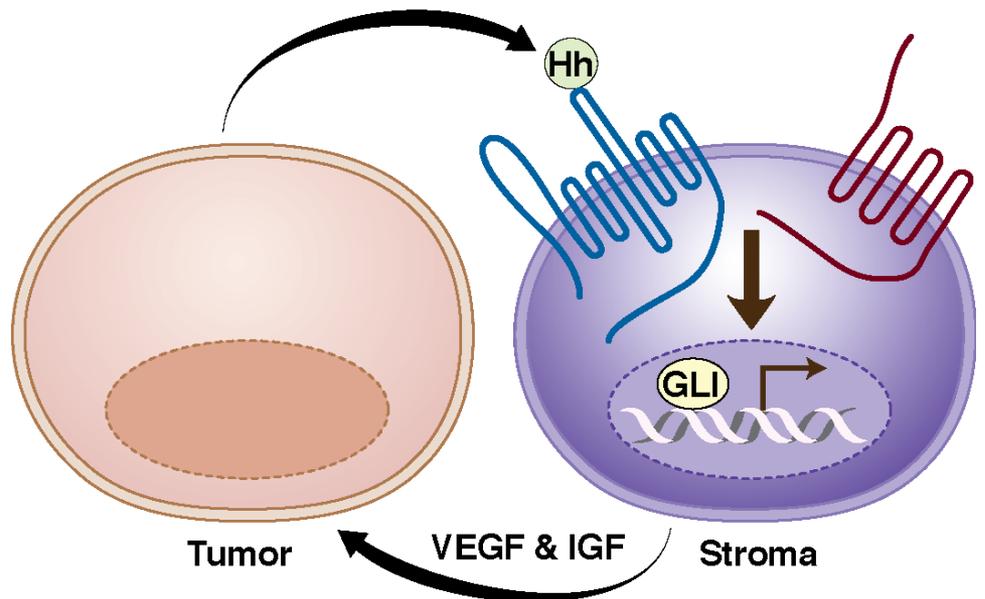
Role of Hh Pathway Activation in Mutation-Associated and Paracrine-Driven Cancer

Mutation-associated



Basal Cell Carcinoma (BCC)
Medulloblastoma

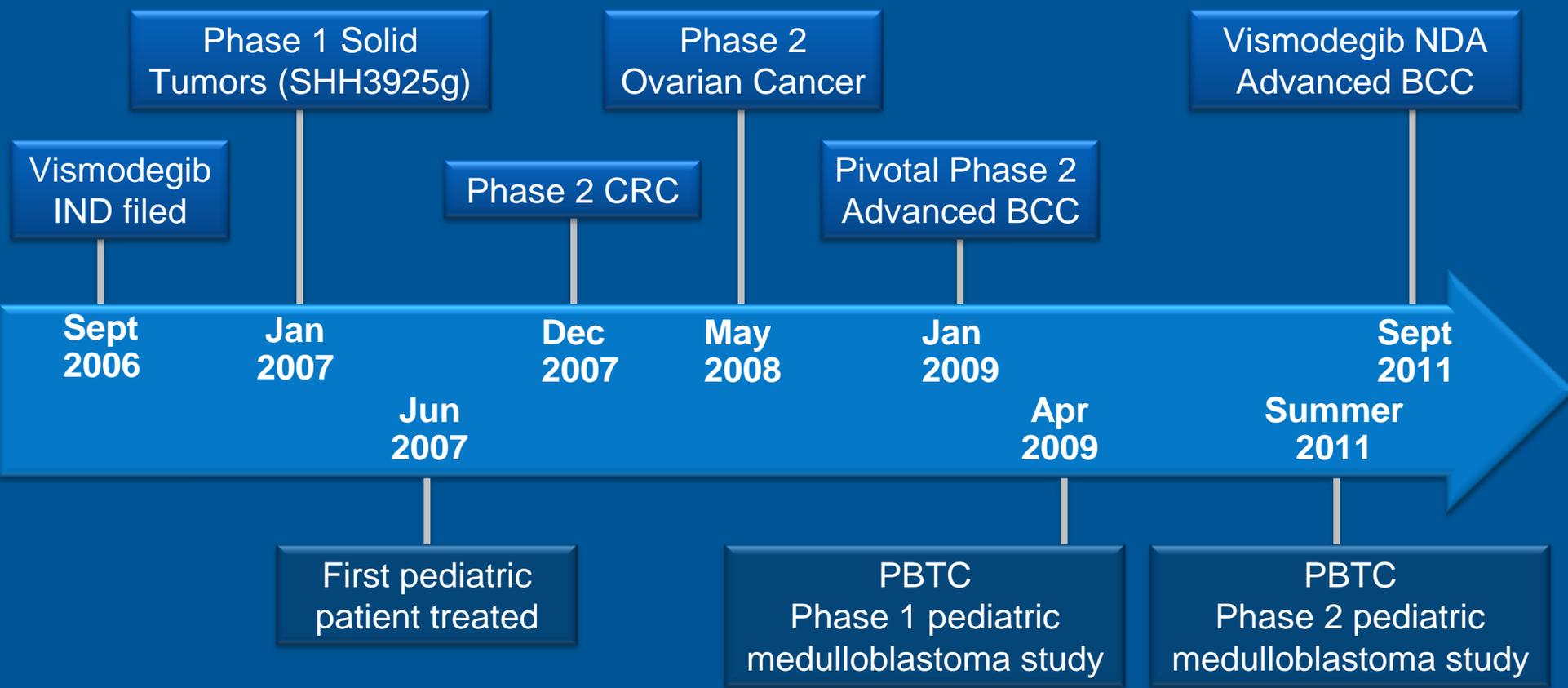
Paracrine



Colorectal, Ovarian Cancer
Pancreatic, Gastric, Others

Key Clinical Findings

Vismodegib Development Milestones



Waiver request (included in NDA) given absence of known aBCC cases in children

CRC= Colorectal cancer; BCC= Basal cell carcinoma; PBTC= Pediatric Brain Tumor Consortium; NDA= New drug application

Phase 1: Vismodegib Activity in Locally Advanced and Metastatic BCC

	Advanced BCC (combined mBCC + laBCC)
Overall Response Rate by investigator	58%
Median duration of response (range)	12.8 m (3.7 –26.4+ months)

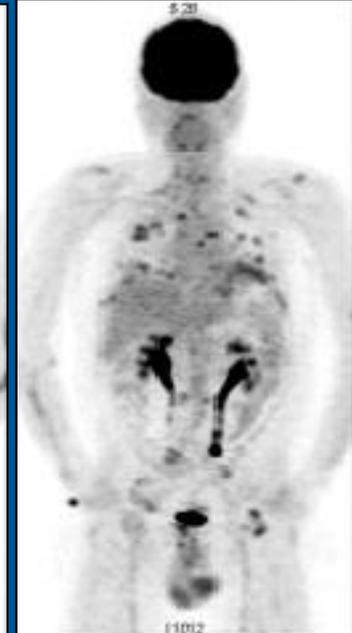
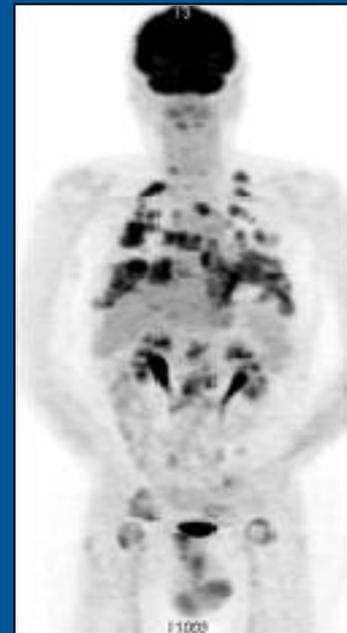
Before treatment

After 5 months treatment



Before treatment

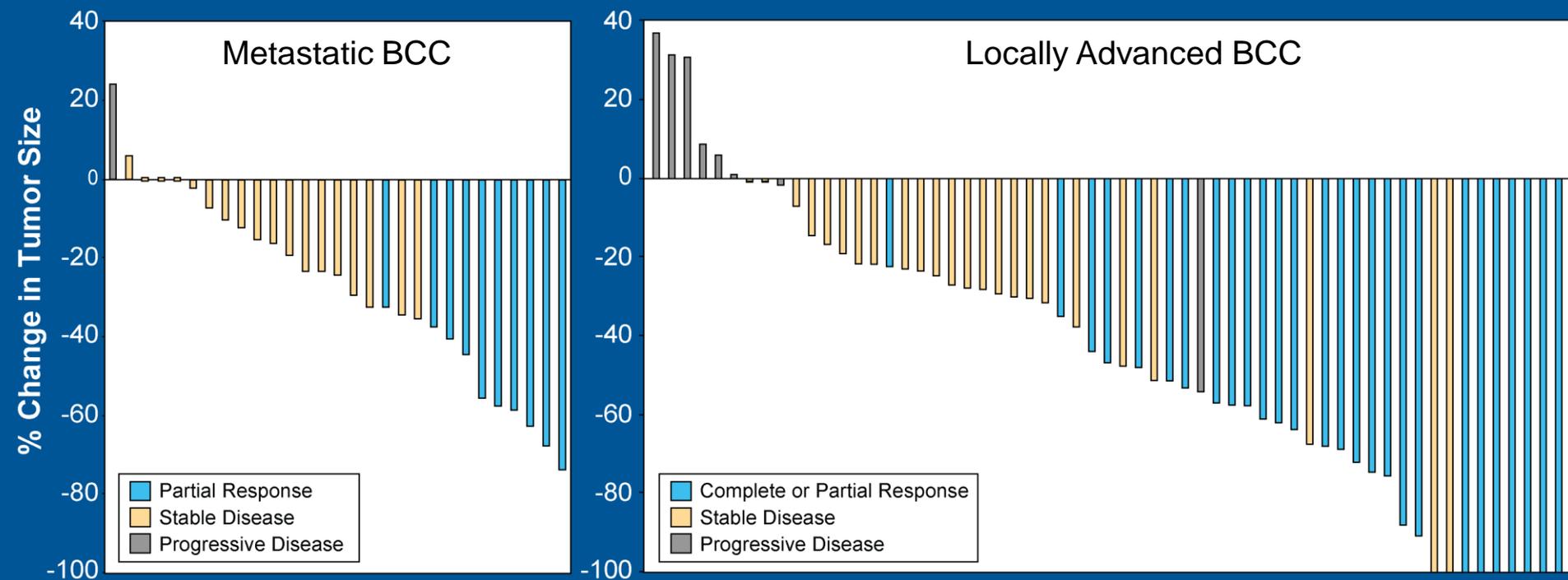
After 8 months



Von Hoff DD et al., NEJM (2009)

LoRusso PM et al., Clin Cancer Res (2011)

Pivotal Phase 2 Study of Metastatic and Locally Advanced BCC Patients



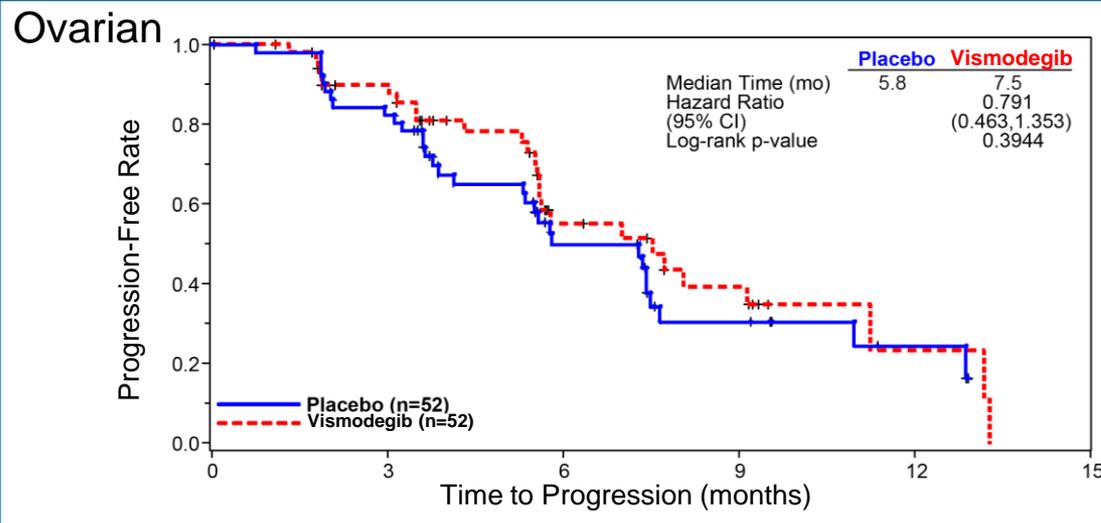
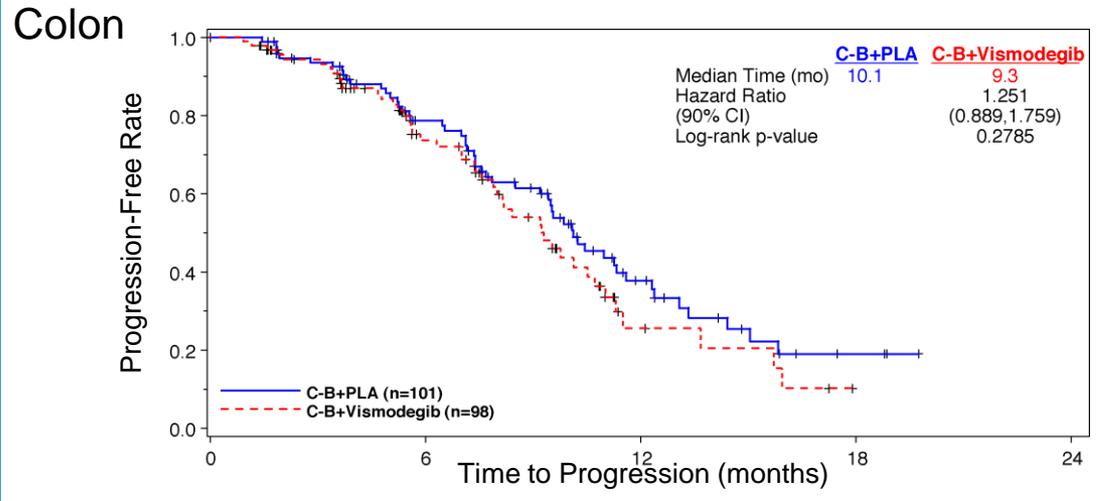
	mBCC (n=33)	laBCC (n=63)
ORR by Independent Review	30.3%	42.3%
PFS by Independent Review	9.5 m	9.5 m

Adverse Events Reported in $\geq 20\%$ of Patients in the Pivotal Phase II Study (n=104)

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	-
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

Efficacy in Phase 2 Clinical Trials in Hedgehog Paracrine-driven Tumors

Reported Phase 2 Studies



Ongoing Phase 2 Studies in Other Indications:

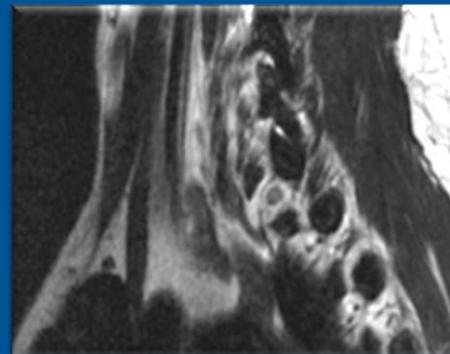
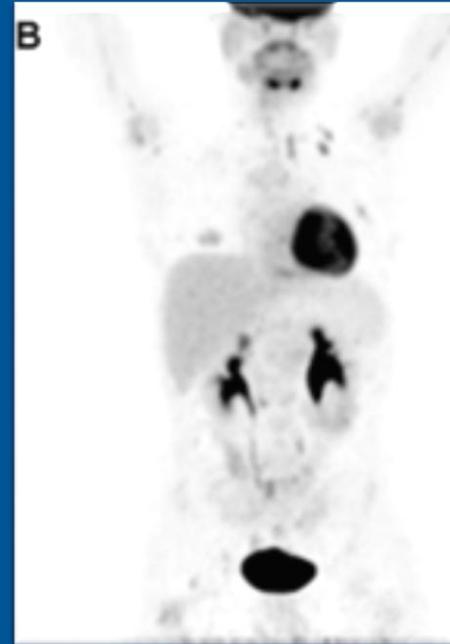
- Breast cancer
- Chondrosarcoma
- Gastric cancer
- Glioblastoma
- Multiple myeloma
- Pancreatic cancer
- Prostate cancer
- Small cell lung cancer

Case Report: 26-Year-old Patient with Disseminated Medulloblastoma

Baseline



After 2 months

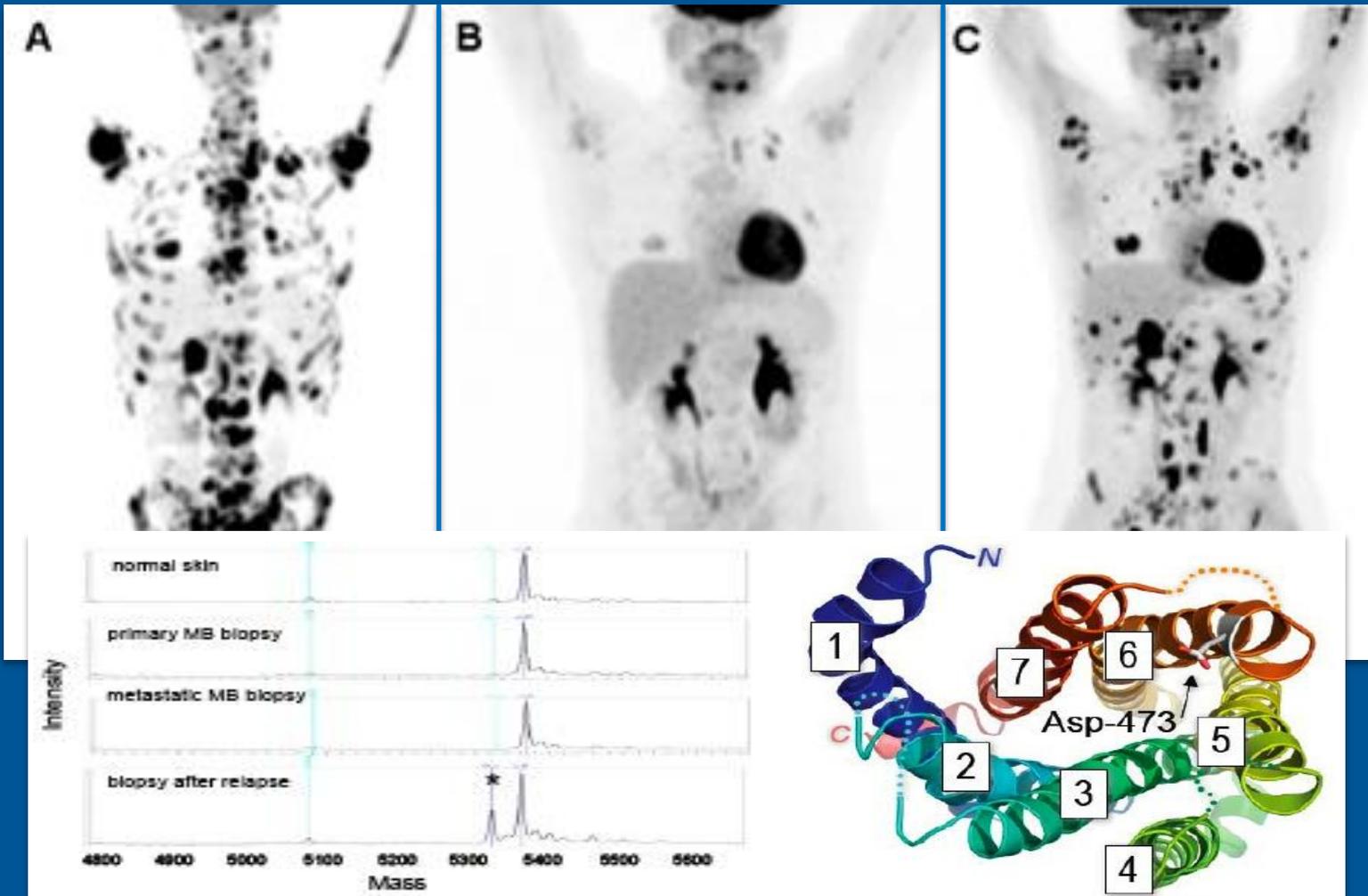


Metastatic Medulloblastoma with Transient Response to Vismodegib

Baseline

After 2 months

After 3 months



Vismodegib Pediatric Development

Medulloblastoma

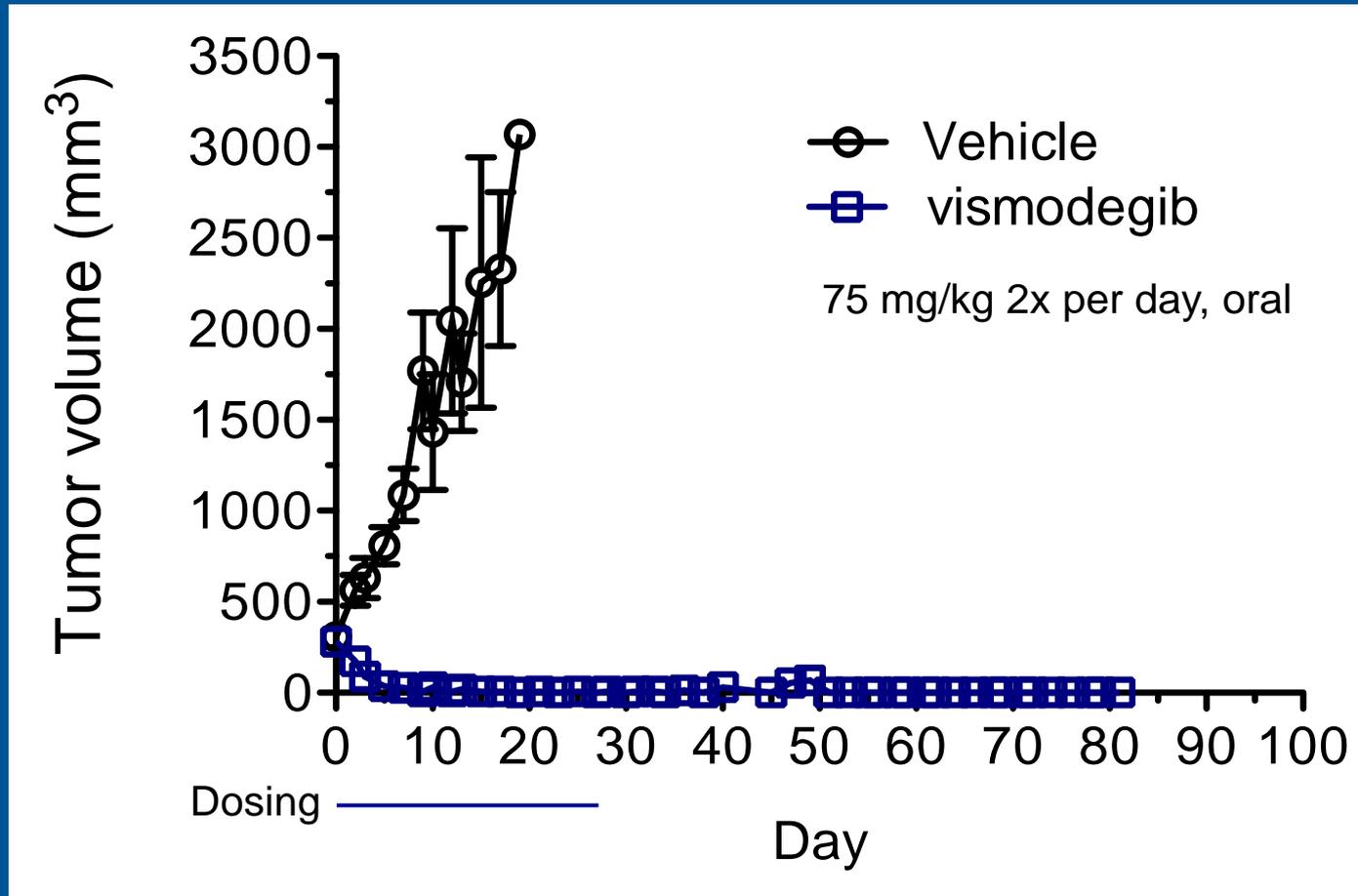
- **Most common CNS tumor in childhood (15-30% of CNS tumors)**
 - ~500 patients/yr diagnosed in the U.S.
- **Front-line treatment: optimal surgical excision *plus* adjuvant radiochemotherapy in children >3 yrs**
 - 60-80% of patients with long-term survival
- **Therapy for relapsed/refractory medulloblastoma is chemotherapy with or without radiation or surgery**
 - Long-term control in less than 30% of patients

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 yrs old	Childhood-pre-teen yrs; mean age ~10 yrs	Mainly childhood; mean age ~8 yrs
Pathological variant	Desmoplastic/Nodular tumors and MBENs ~50% of Large Cell/Anaplastic tumors	Nearly all classic tumors; No Desmoplastic/Nodular tumors	Mainly classic tumors ~50% of Large Cell/Anaplastic tumors
Outcome with first-line therapies	Good/Average	Very good	Poor

Hh= Hedgehog; MBEN= medulloblastoma with extensive nodularity.

Durable Response by Vismodegib in Medulloblastoma Mouse Model



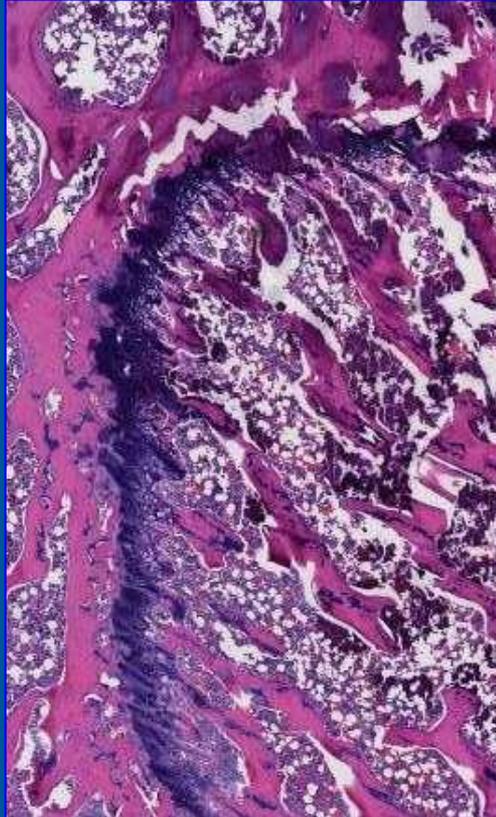
Ptch^{+/-} medulloblastoma allograft

Non-clinical Safety Profile

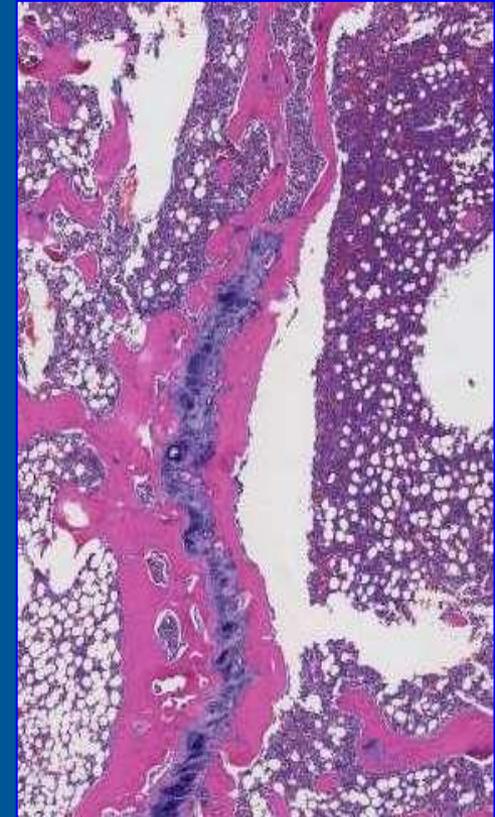
Vehicle HhAntag



Vehicle



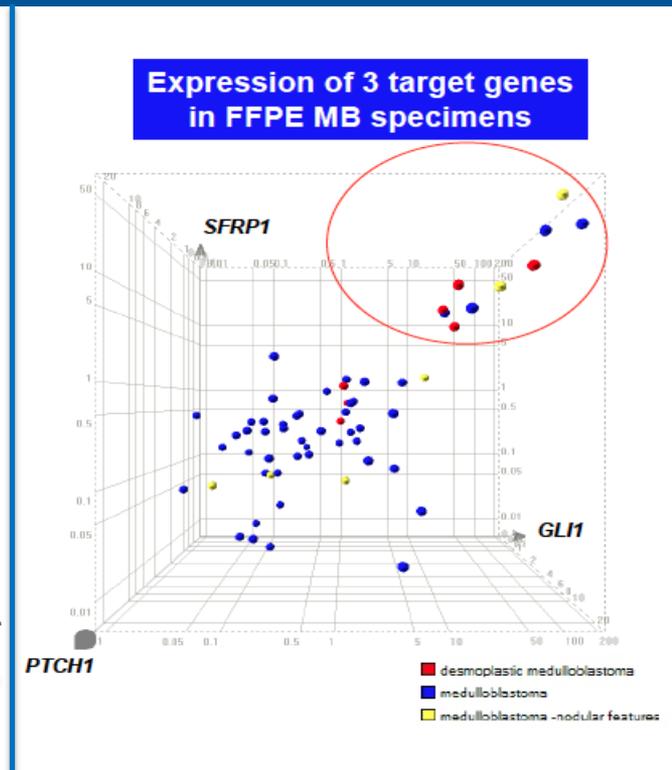
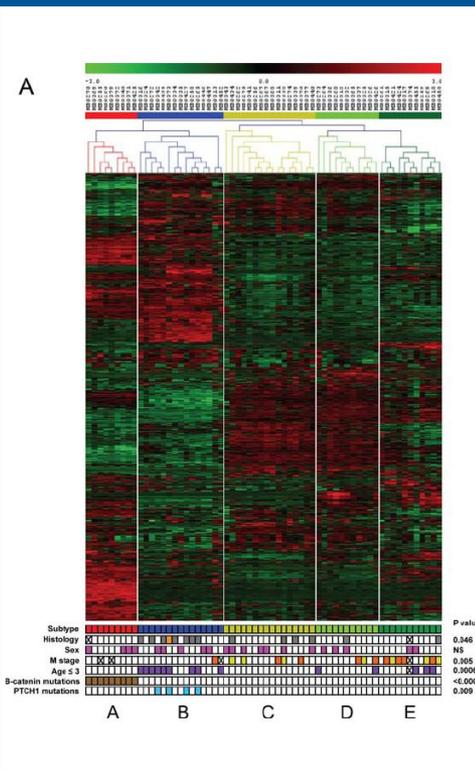
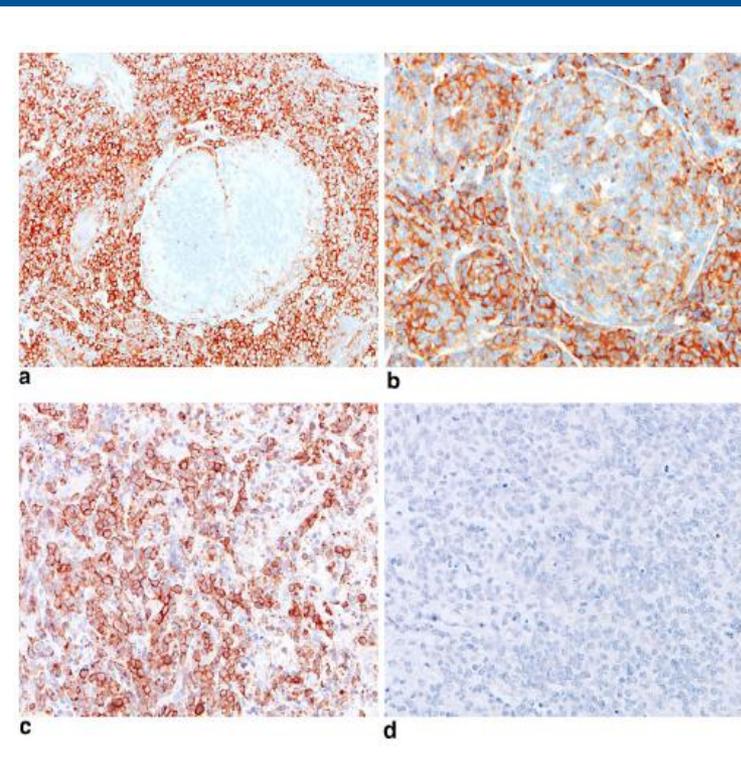
Vismodegib



- Irreversible post-natal developmental defects: growing bones and teeth
- Teratogenic at clinically relevant exposures

Molecular Classification of Medulloblastoma

- Mutation-based test NOT feasible to identify Hedgehog-driven medulloblastoma
 - Multiple genes involved (e.g. PTCH, SMO, SUFU), no hotspots
 - Non-mutation changes possible (e.g. epigenetic silencing, gene inversion)



PBTC Studies of Vismodegib in Relapsed/Refractory Medulloblastoma

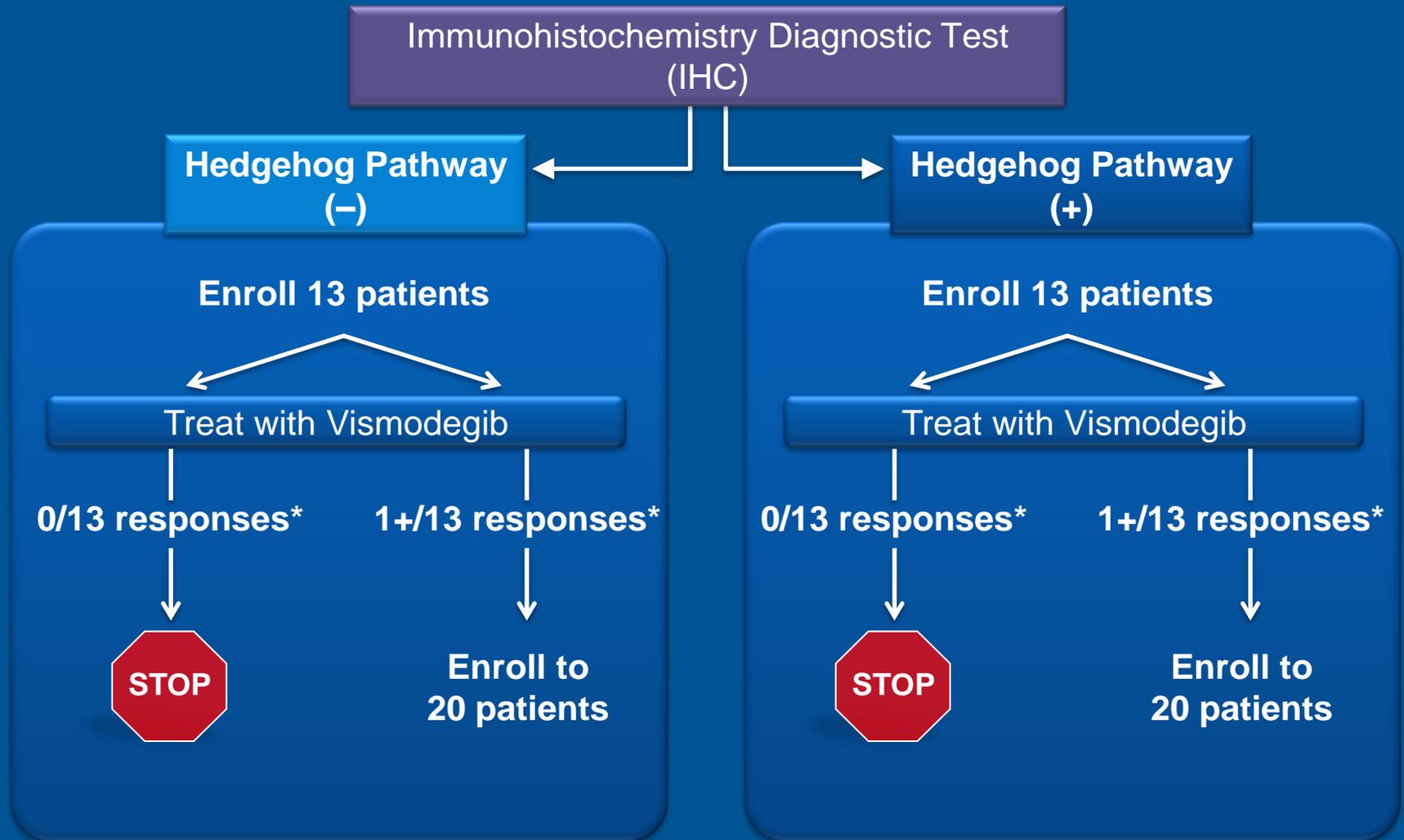
	Age	Primary Endpoint	Doses Tested
PBTC-025 Phase 1	3-21 years	Safety, PK	85/170 mg/m ² and 150/300 mg/d
PBTC-032 Phase 2	3-21 years	Efficacy	150/300 mg/d
PBTC-025B Phase 2	22+ years	Efficacy	150 mg/d

PBTC-025: Pediatric Phase 1 Findings

- **All dose levels tolerated**
 - 85 mg/m² (n=6): no DLT
 - 170 mg/m² (n=6): 1 DLT (elevated GGT gr 3)
 - 150 mg (n=8) & 300 mg (n=8)
- **No bone toxicities seen**
- **25% of patients with Hedgehog pathway signature**
- **Like adult patients, vismodegib PK levels primarily correlated with AAG, not body surface area**
 - **Similar phase 2 dose recommended:
170 mg/m² ~ 150 mg daily dosing**

PBTC-032 Phase 2 Pediatric Study

Relapsed/Refractory Medulloblastoma



*Simon 2-stage MinMax design

Summary of Pediatric Medulloblastoma Development

- **Case report of efficacy seen in young adult with Hh-pathway-mutated medulloblastoma**
- **Pediatric phase 1 study near completion**
 - **Safety established with recommended phase 2 dose similar to adult dosing**
 - **Significant adverse effects not seen in preliminary reporting**
- **Pediatric phase 2 ongoing**
 - **Patients assigned to cohorts based on a diagnostic assay**
 - **Response rate endpoint will provide estimate of activity in diagnostically-selected population**

Challenges with Pediatric Development in Medulloblastoma

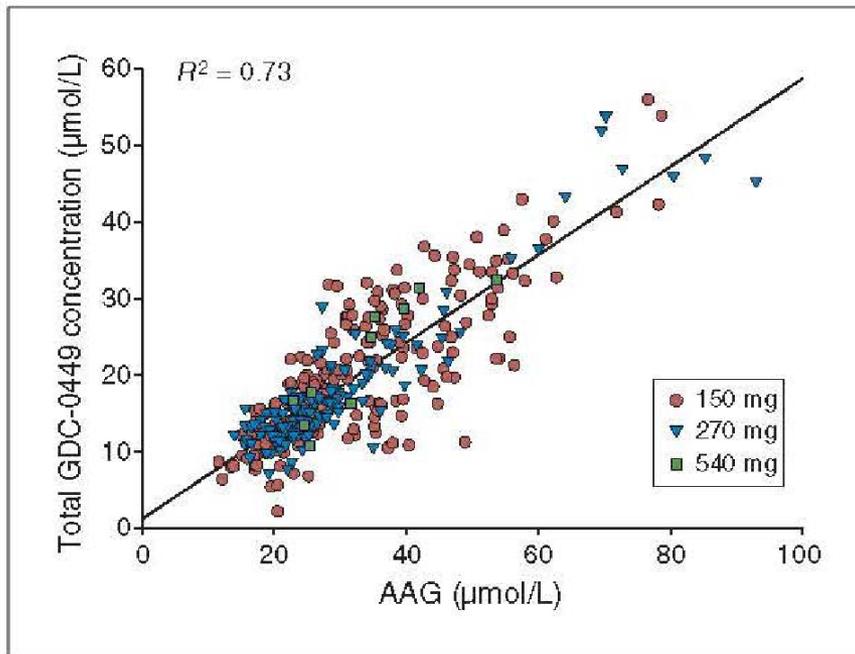
- **Strong rationale for a patient selection assay**
 - Hh pathway dependent tumors constitute ~15-30%, perhaps lower in 3-17 age range
 - Long-term side effects of Hh pathway inhibition unknown in children, especially very young children
 - Disease-specific assays are active area of investigation
- **Continued investigation in a limited, selected population**
 - Small patient numbers in US (30-60 patients/year with relapsed, refractory Hh+ medulloblastoma)

Backup

Total Vismodegib and AAG Plasma Concentrations are Highly Correlated

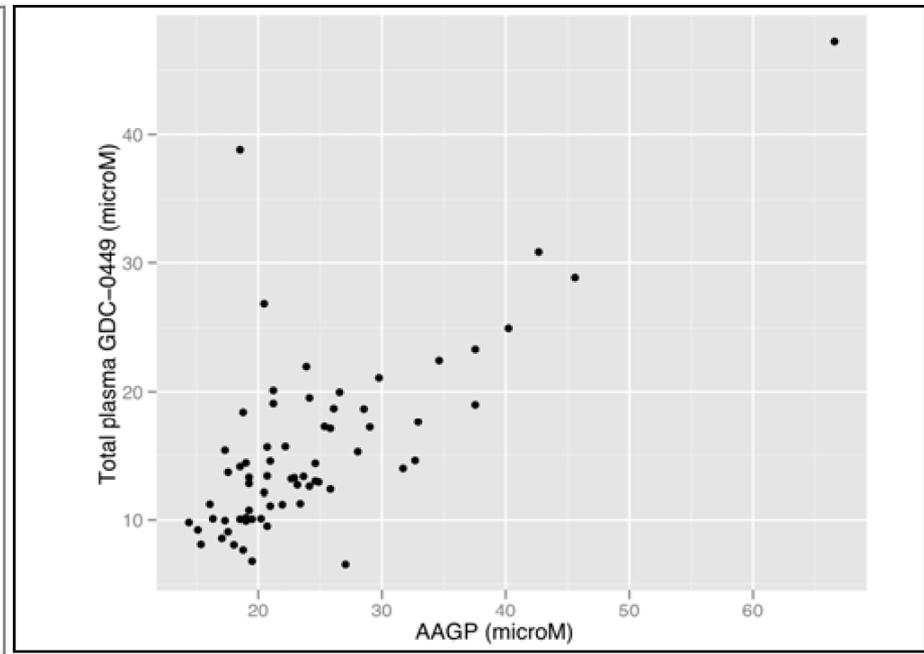
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Adults



Graham et al. 2011

Children



Gajjar et al. 2010

Effect of Age on Plasma Concentrations of α 1-Acid Glycoprotein (AAG)

	Infants (2-12 months)	Children (1-10 yrs)	Adults	Reference
AAG Concentration (mg/dL)	58 \pm 11	70 \pm 19	74 \pm 12	Meistelman et al.
	N/A	35 - 90	55 - 100	Israili and Dayton
	46.4 \pm 18.6	66.3 \pm 27.6	N/A	Lerman et al.

- AAG levels raise rapidly following birth and stabilize by ~12 months.
- AAG concentration is similar in children and adults.
 - Children: 35-90 mg/dL
 - Adults: 55-100 mg/dL
- PK of vismodegib is highly dependent on AAG levels in plasma, therefore PK is not expected to be different in children in adults.

Unbound Steady-state Trough Concentrations for each Dosing Regimen with Predicted Efficacious Levels

