Targeting the Hedgehog pathway in solid tumors

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Consorzio Interuniversitario Nazionale per la Bio-Oncologia

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is pleased to present

ADVANCES IN TARGETING CANCER PATHWAYS

by Cinbo delegates

April 8, 2016

Rome, Italy
Domus Sessoriana
P.zza Santa Croce in Gerusalemme n. 10

Director
Clara Natoli

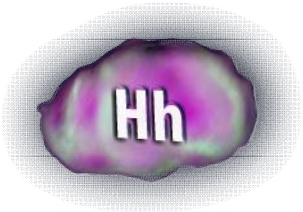
The Hedgehog signalling pathway plays a fundamental role in normal embryonic development

- The Hedgehog pathway was discovered in fruit fly (Drosophila) and is conserved in vertebrates (including humans)[1,2]
- The Hedgehog pathway is involved in cell growth and differentiation to control organ formation during embryonic development
  - Hedgehog signalling regulates embryonic development, ensuring that tissues reach their correct size and location, maintaining tissue polarity and cellular content[2]
  - In the skin, the Hedgehog pathway is critical for regulating hair follicle and sebaceous gland development[3]
  - Germline mutations in components of the Hedgehog signalling pathway results in a number of developmental abnormalities[4,5]
- Hedgehog signalling normally remains inactive in most adult tissues[2]

1. Nüsslein-Volhard C, Wieschaus E. Nature 1980;287:795–801
2. Scales SJ, de Sauvage FJ. Trends Pharmacol Sci 2009;30:303–12
3. Chiang C, et al. Dev Biol 1999;205:1–9
4. Wilkie AO et al. Nat Rev Genet 2001;2:458–68
5. McMahon AP et al. Curr Top Dev Biol 2003;53:1–114

Key components involved in Hedgehog signalling

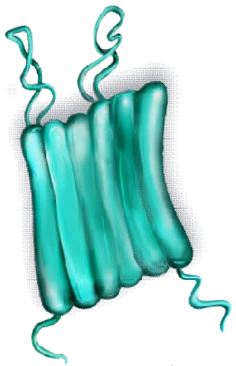
The Hedgehog ligand, Hedgehog (Hh)



- Sonic
- Desert
- Indian

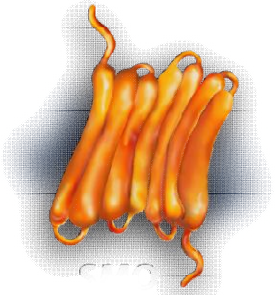
Initiates signal transduction of the Hedgehog pathway

The Hedgehog ligand receptor, Patched (PTCH)



Normally suppresses the activity of SMO

The cell surface signal transducer, Smoothened (SMO)



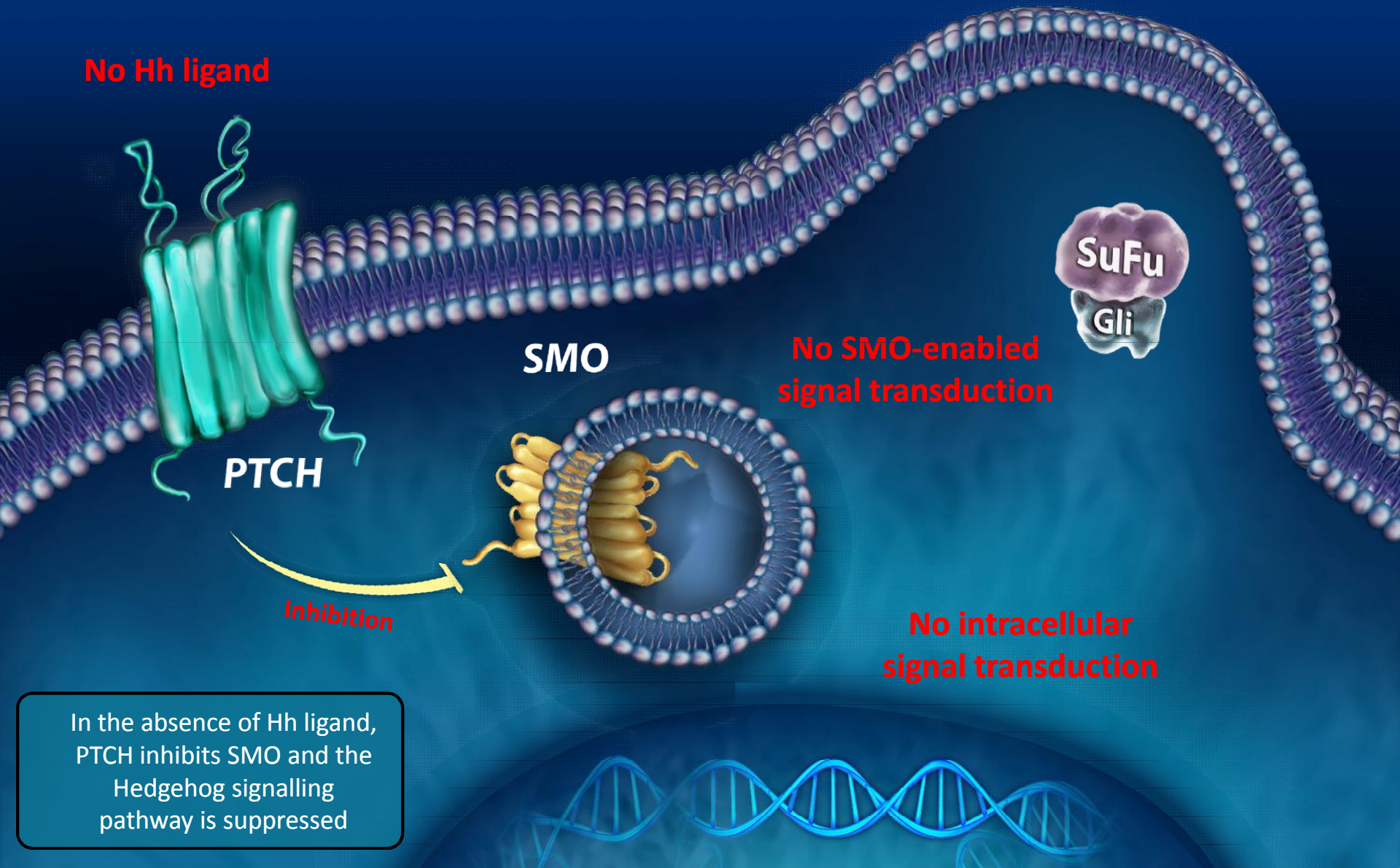
Normally suppressed by PTCH, preventing its activation of the Hedgehog signalling cascade

The downstream effectors, the Gli transcription factors

Cytosolic complex of proteins including Suppressor of Fused (SuFu) and the Gli family of transcription factors. Activation leads to expression of specific genes that promote cell proliferation and differentiation

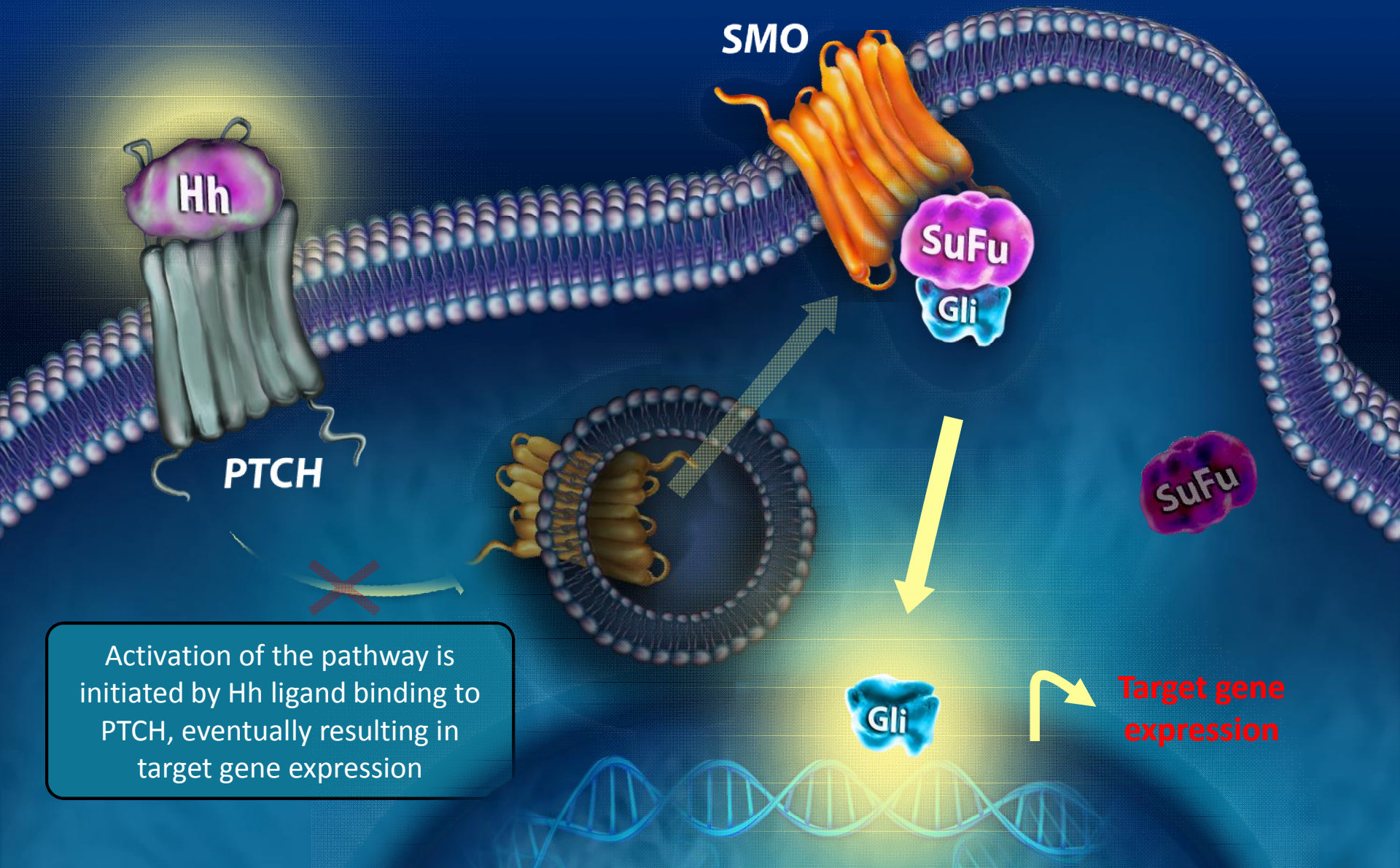
Scales SJ, de Sauvage FJ. Trends Pharmacol Sci 2009;30:303–12

When the Hedgehog pathway is inactive
Patched inhibits Smoothened activity



In the absence of Hh ligand, PTCH inhibits SMO and the Hedgehog signalling pathway is suppressed

When Hedgehog ligand activates the Hedgehog pathway the cell responds by activating expression of target genes



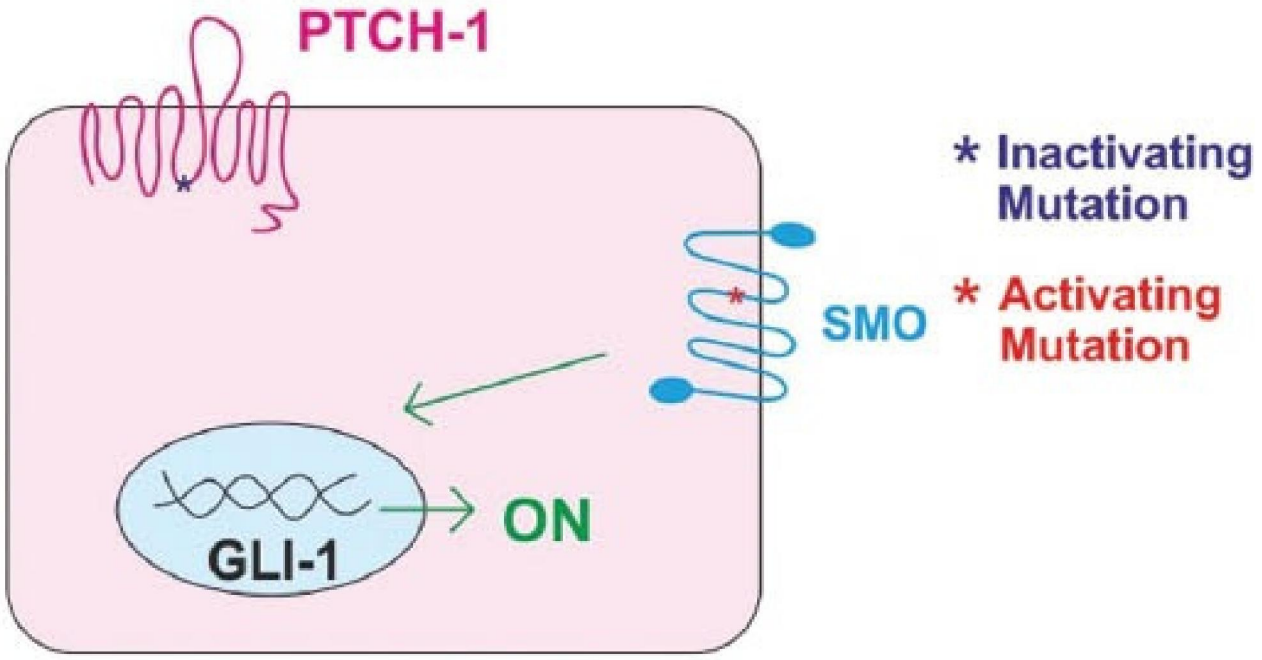
Activation of the pathway is initiated by Hh ligand binding to PTCH, eventually resulting in target gene expression

Abnormal Hedgehog pathway signalling plays an important role in the pathogenesis of certain types of cancer

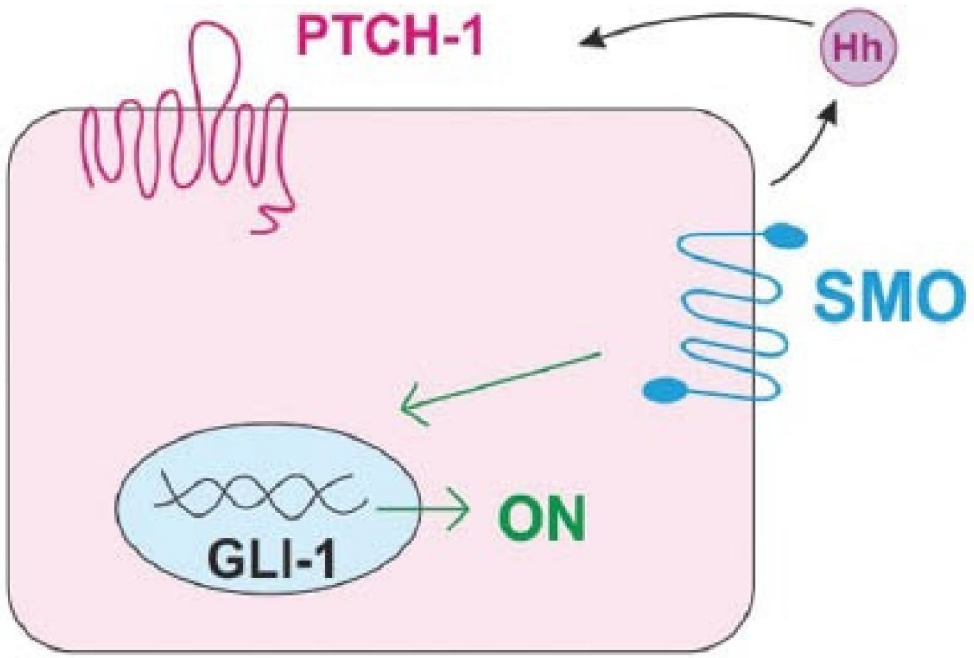
- Inappropriate reactivation of the Hedgehog pathway has been linked to several human cancers[1]
- Two different mechanisms drive abnormal Hedgehog pathway signalling in different types of cancer:[2]
  1. Ligand-independent signalling driven by mutations (e.g. BCC and medulloblastoma)
     Mutations in key pathway regulators (e.g. PTCH or SMO) cause SMO to be in a constitutively active state
  2. Ligand-dependent signalling driven by overexpression of Hh ligand by tumour cells (e.g. ovarian cancer, colorectal cancer, pancreatic cancer)

1. Scales SJ, de Sauvage FJ. Trends Pharmacol Sci 2009;30:303–12
2. Low JA, de Sauvage FJ. J Clin Oncol 2010;28:5321–6
3. Rudin CM. Cancer Prev Res 2010;3:1–3

Type I- Ligand-Independent Signaling

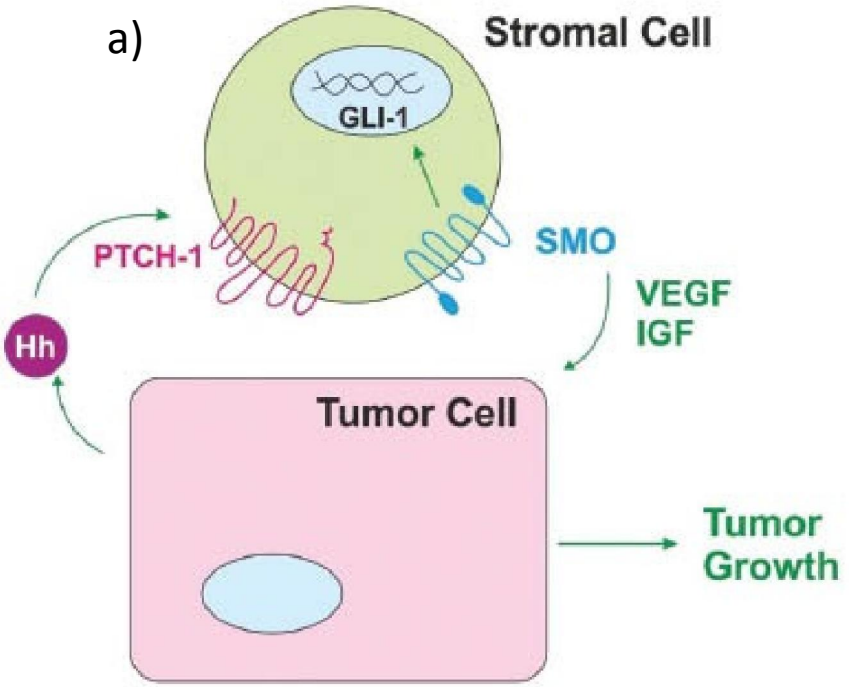


Type II- Ligand-Dependent Signaling (autocrine or juxtacrine manner)

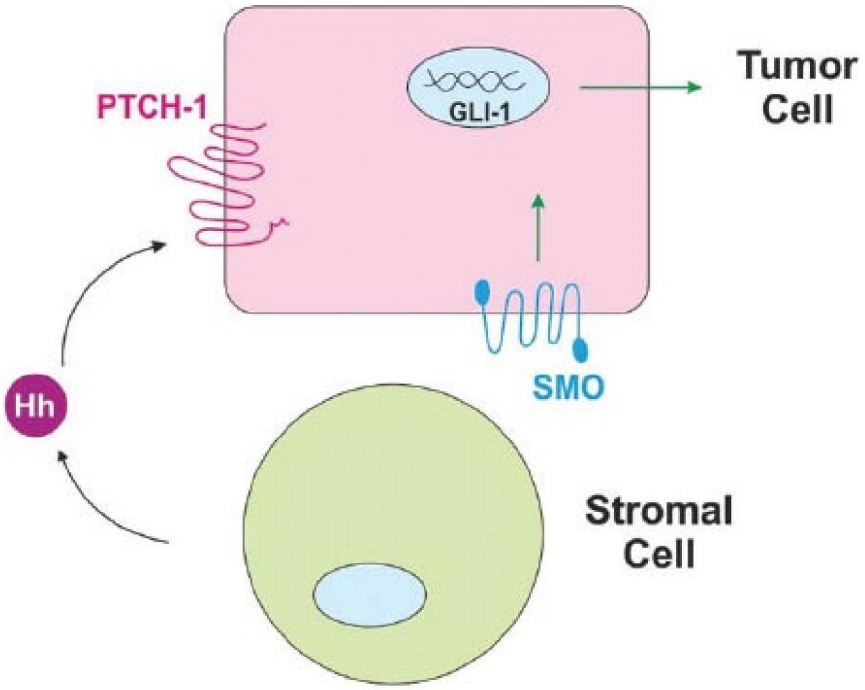


Type II- Ligand-Dependent Signaling (paracrine manner)

a)



b) Reverse

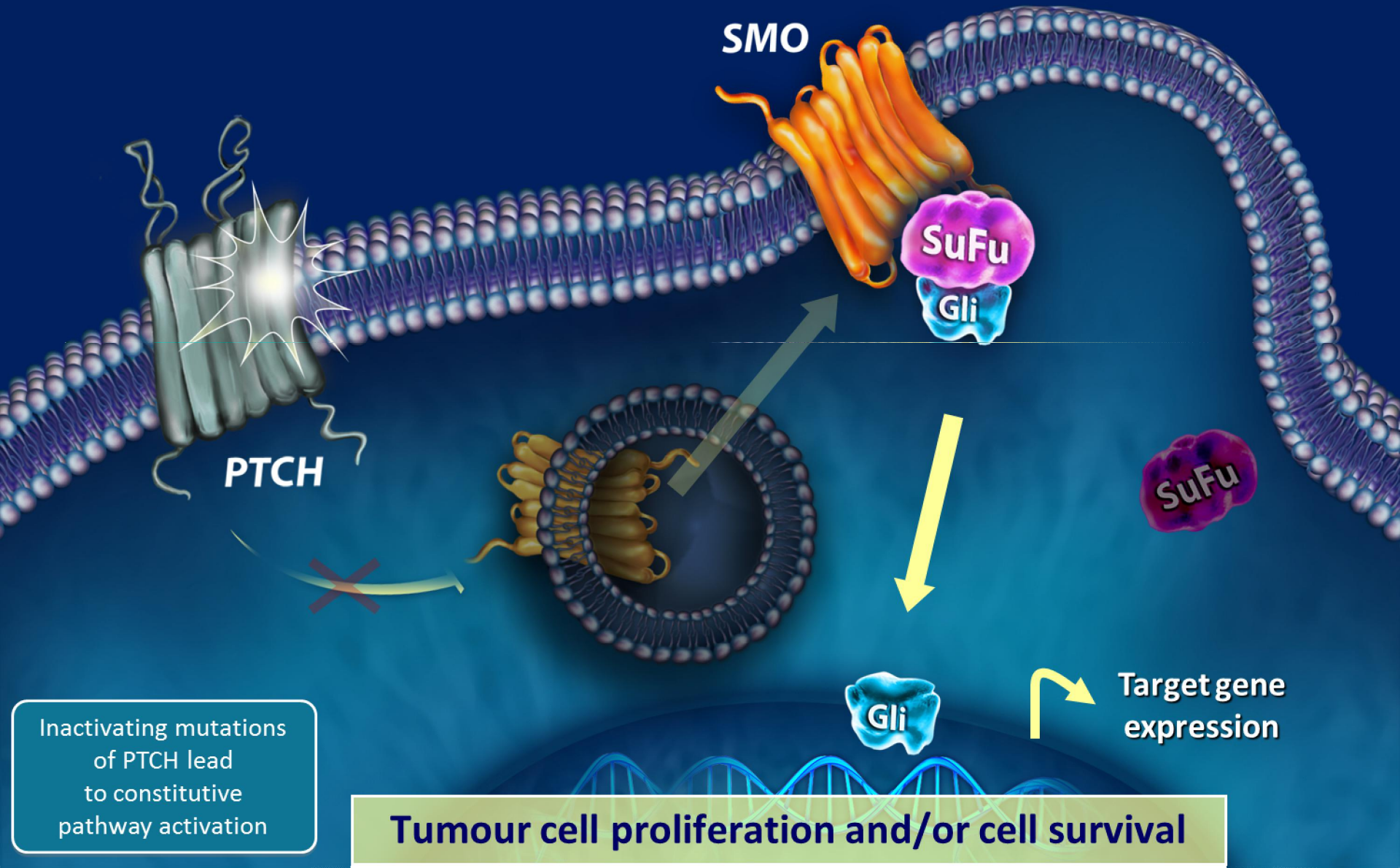


BCC and the Hedgehog signalling pathway

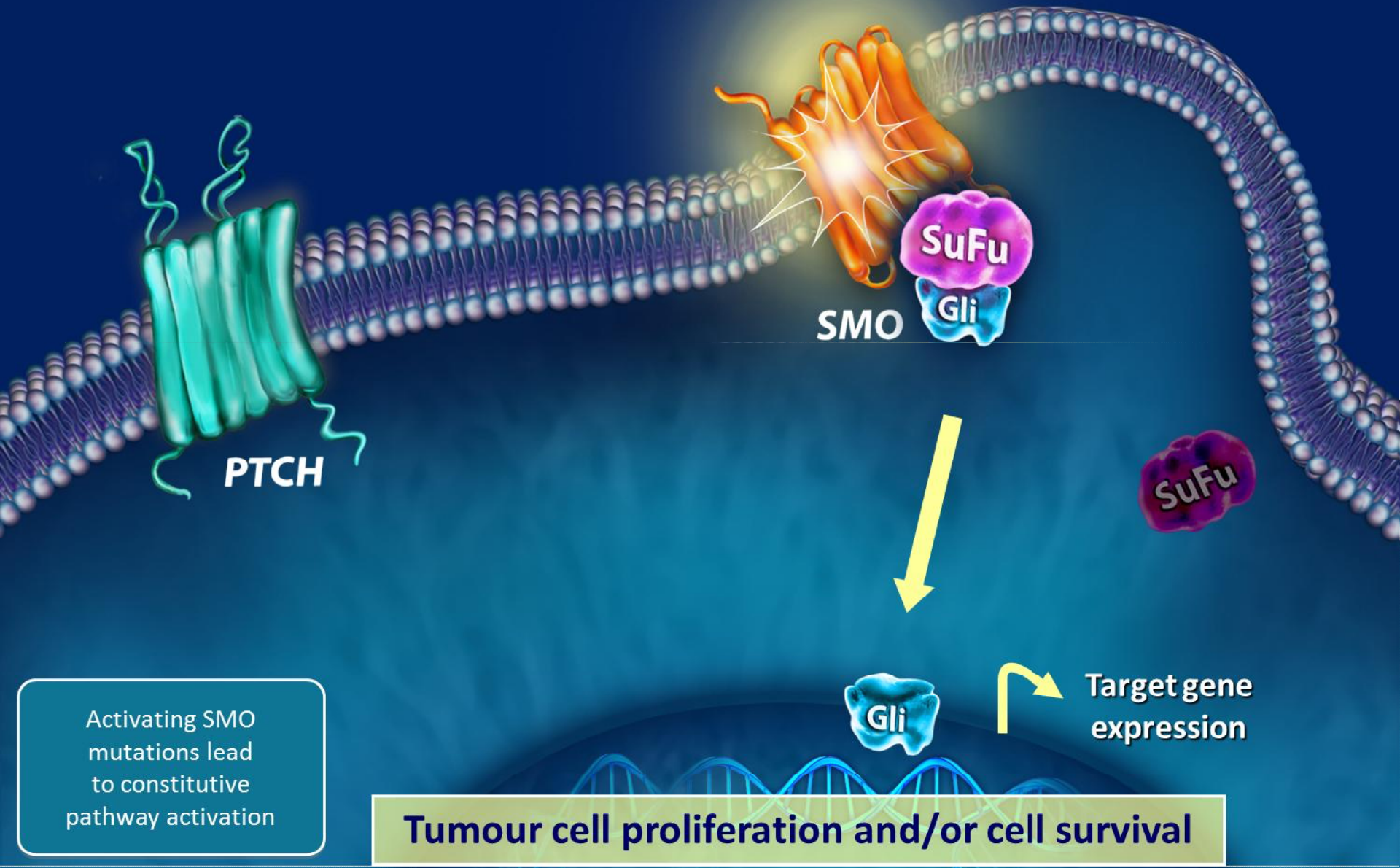
- Abnormal activation of the Hedgehog signalling pathway is thought to play a critical role in the pathogenesis and progression of BCC, either by:[1]
  - Inactivating PTCH mutations, or;
  - Activating SMO mutations
- Hedgehog pathway inhibitors may provide a new treatment option for patients with advanced BCC[1]

1. Epstein EH. Nat Rev Cancer 2008;8:743–54

Mutation-driven Hedgehog signalling is involved in BCC: Inactivating PTCH mutations



Mutation-driven Hedgehog signalling is involved in BCC: Activating SMO mutations



Abnormal Hedgehog pathway signalling is synonymous with BCC

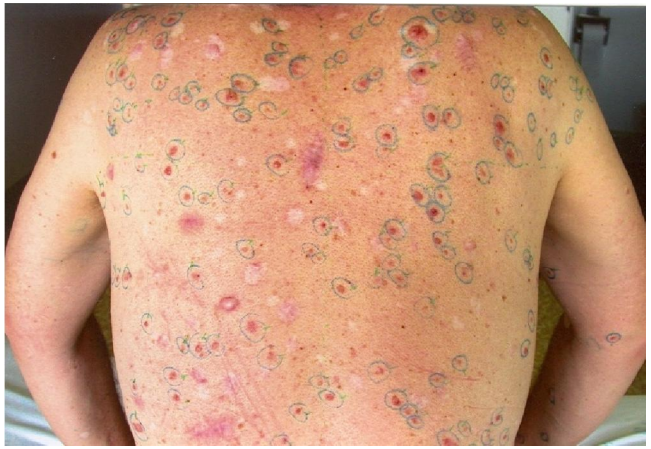
- In BCC, abnormal Hedgehog pathway signalling is the key molecular driver of the disease[1-3]
- More than 90% of BCCs have abnormal activation of Hedgehog pathway signalling[4-6]
- Most BCC tumours have either inactivating mutations in PTCH or, less commonly, activating mutations in SMO[3,7–9]
  - As a result of inactivating PTCH mutations[3,7,9] or activating SMO mutations,[3,7,9] SMO moves to the cell surface leading to activation of the GLI family of transcription factors[9]
  - Activated GLI then moves to the nucleus and initiates the transcription of target genes[9]

1. Bale AE, Yu KP Hum Mol Genet 2001;10:757–62
2. Hutchin ME, et al. Genes Dev 2005; 19:214–23
3. Epstein EH. Nat Rev Cancer 2008;8:743–54
4. Teh MT, et al. Cancer Res 2005;65:8597–603
5. Kallassy M, et al. Cancer Res 1997;57:4731–5
6. Unden AB, et al. Cancer Res 1997;57:2336–40
7. Caro I, Low JA. Clin Cancer Res 2010;16:3335–9
8. Rudin CM. Cancer Prev Res 2010;3:1–3
9. Scales SJ. Trends Pharmacol Sci 2009;30:303–12

Hereditary defects in PTCH predispose to BCC: Gorlin syndrome

- Also known as basal cell nevus syndrome (BCNS)
- Rare hereditary condition that predisposes the individual to develop multiple BCCs[1]
  - The severity of the disease is wide-ranging and it affects about 1 in 57,000 people (0.0018%)[2]
- Gorlin syndrome occurs in individuals who inherit one defective copy of the PTCH gene
- Leads to an array of congenital defects[3]
  - Preaxial polydactyly, immobile thumbs, short metacarpals, broad faces, rib defects, dental abnormalities, and high predisposition to certain malignancies such as medulloblastoma

Patient with Gorlin syndrome and multiple lesions[4]



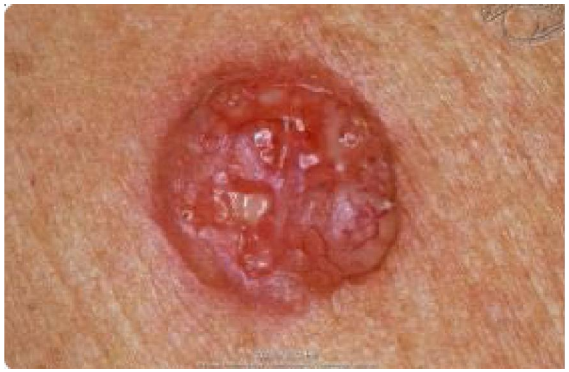
Active BCC tumours are circled in green

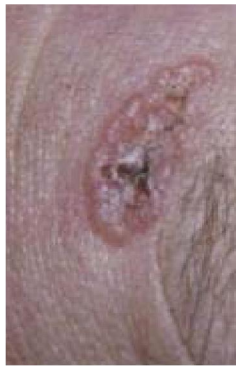
1. Roewert-Huber J et al. Br J Dermatol 2007;157:47–51
2. Farndon PA et al. Lancet 1992;339:581–2
3. McMahon AP et al. Curr Top Dev Biol 2003;53:1–114
4. Tang JY et al. Cancer Prev Res 2010;3:25–34

Basal cell carcinoma (BCC)

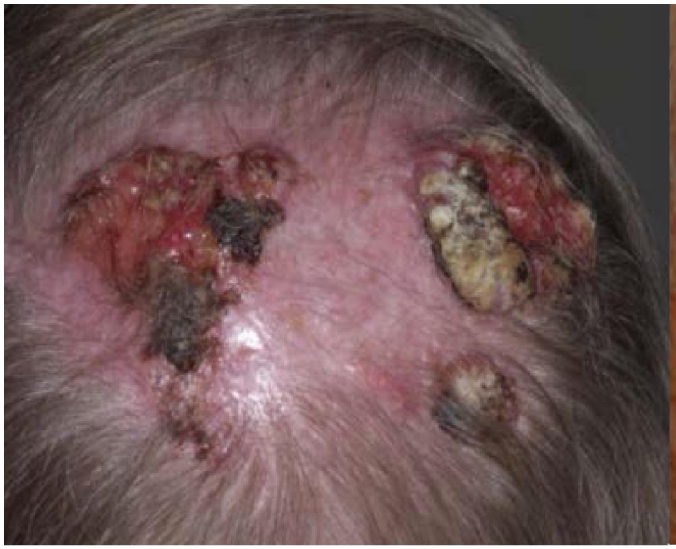
BCC is the most commonly diagnosed human cancer

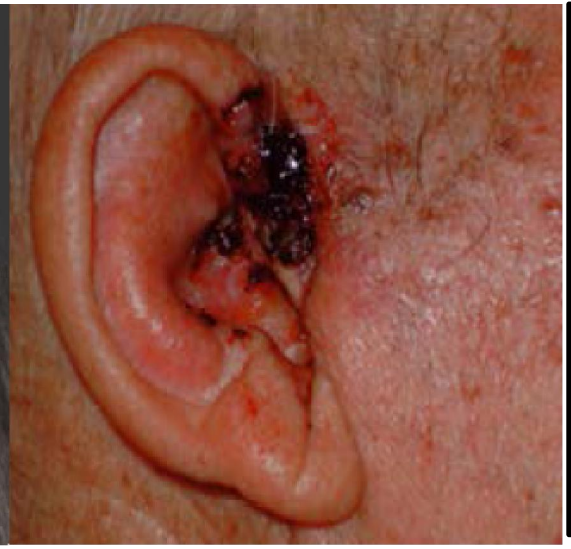
2 million cases per year in the USA, most curable by surgery

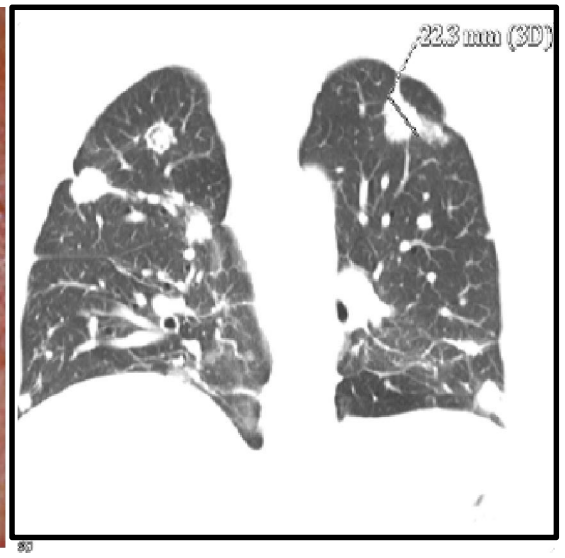




Some progress to locally advanced (laBCC) or metastatic disease (mBCC). Therapeutic options are limited.





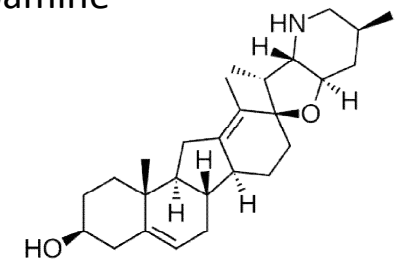


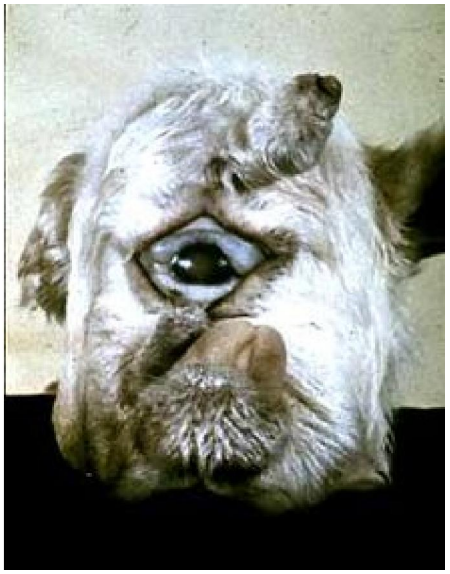
Development of Smoothened Inhibitors

•Endemic cyclopia in lambs born in western USA

•Pregnant ewes ingesting corn lily at specific time of year. No effect in adult sheep

•Chemical identified: cyclopamine





•Cyclopamine directly binds to Smoothened and inhibits the hedgehog pathway[1]

•

•Cyclopamine blocks cancer growth in tissue culture[2]

•Development of synthetic smoothened inhibitors as drugs

1. Chen JK et al: Gen Dev 16:2743, 2002
2. Taipale et al: Nature 406:1005, 2000

HH pathway antagonists for the treatment of BCC

Inhibitor	Target	Stage of development	Reference
Vismodegib	SMO	In clinical use	Sekulic et al. 2012
PF-04449913	SMO	Phase I	Munchhof et al. 2012
Erismodegib	SMO	Phase II	Skvara et al. 2011
LEQ506	SMO	Phase I	Lappano and Maggiolini 2011
BMS-833923	SMO	Phase I	Bristol-Myers Squibb 2013
Saridegib	SMO	Phase II	Tremblay et al. 2009
Itraconazole	SMO	Phase I	Kim et al. 2013
CUR61414	SMO	Preclinical	Tang et al. 2011
ALLO-1 and 2	SMO	Preclinical	Tao et al. 2011
Robotnikinin	SHH	Preclinical	Hassounah et al. 2012
5E1	SHH	Preclinical	Maun et al. 2010
ATO	GLI	Phase I	Kim et al. 2013
GANT-61	GLI?	Preclinical	Lauth et al. 2007
GANT-58	GLI?	Preclinical	Lauth et al. 2007
HPI-1 through -4	GLI?	Preclinical	Hyman et al. 2009
Sirolimus	mTOR	Phase I	Campbell et al. 2012
PF-4708671	S6K1	Preclinical	Pearce et al. 2010
PSI	aPKC	Preclinical	Atwood et al. 2013

SMO, Smoothened; SHH, Sonic Hedgehog; ATO, arsenic trioxide; mTOR, mammalian target of rapamycin; S6K1, S6 kinase 1; aPKC, atypical protein kinase C ι/λ.

Phase I: Vismodegib demonstrated activity in patients with mBCC and laBCC

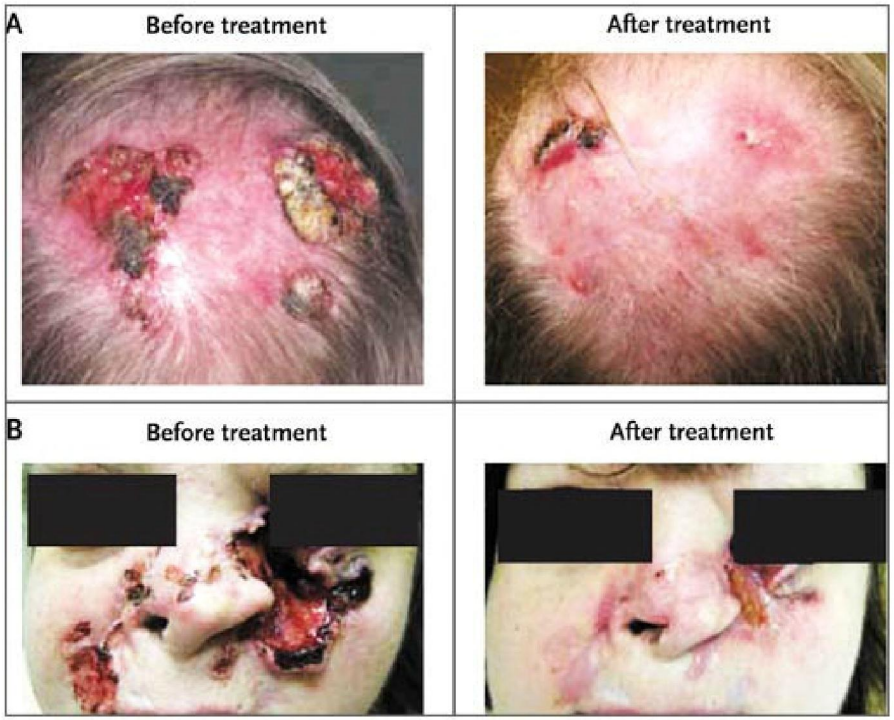
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inhibition of the Hedgehog Pathway in Advanced Basal-Cell Carcinoma

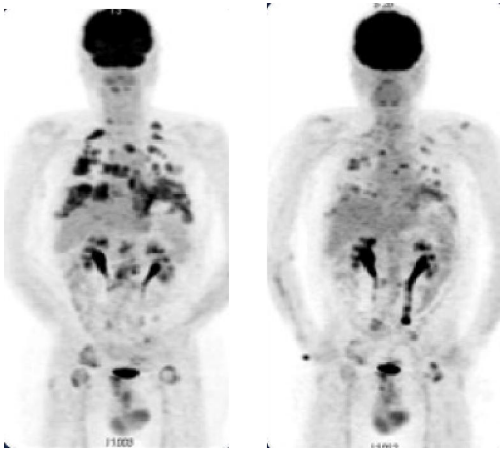
Daniel D. Von Hoff, M.D., Patricia M. LoRusso, D.O., Charles M. Rudin, M.D., Ph.D., Josina C. Reddy, M.D., Ph.D., Robert L. Yauch, Ph.D., Raoul Tibes, M.D., Glen J. Weiss, M.D., Mitesh J. Borad, M.D., Christine L. Hann, M.D., Ph.D., Julie R. Brahmer, M.D., Howard M. Mackey, Ph.D., Bertram L. Lum, Pharm.D., Walter C. Darbonne, M.S., James C. Marsters, Jr., Ph.D., Frederic J. de Sauvage, Ph.D., and Jennifer A. Low, M.D., Ph.D.

N Engl J Med 2009; 361:1164-1172September 17, 2009



Before treatment

After 8 months



Response rate: 58%
Median duration of response: 12.8+ months

LoRusso PM ,et al. Clin Cancer Res 2011; 17:2502–2511

ERIVANCE BCC: Pivotal Phase 2 multicenter study in advanced BCC

Australia, Belgium, France, Germany, UK, US

Metastatic BCC

Locally advanced BCC

Registration

150 mg vismodegib p.o. daily until:
- **Progression**
- **Intolerable toxicity**
- **Withdrawal from study**

Primary endpoint: Objective response rate (ORR) per IRF
- mBCC: RECIST
- laBCC: novel composite endpoint

Secondary endpoints:
- ORR per investigator
- Duration of response
- Progression-free survival
- Absence of residual BCC on biopsy (laBCC only)

N Engl J Med 2012; 366:2171-2179, June 7, 2012

Tumor response criteria

Tumor response:

mBCC: ≥30% size reduction (RECIST)

laBCC: novel composite endpoint

- ≥30% size reduction (physical exam and/or CT) and/or
- Complete resolution of ulceration

Progression:

≥20% size increase

New lesions or new ulcerations

Stable disease: does not meet criteria for response or progression

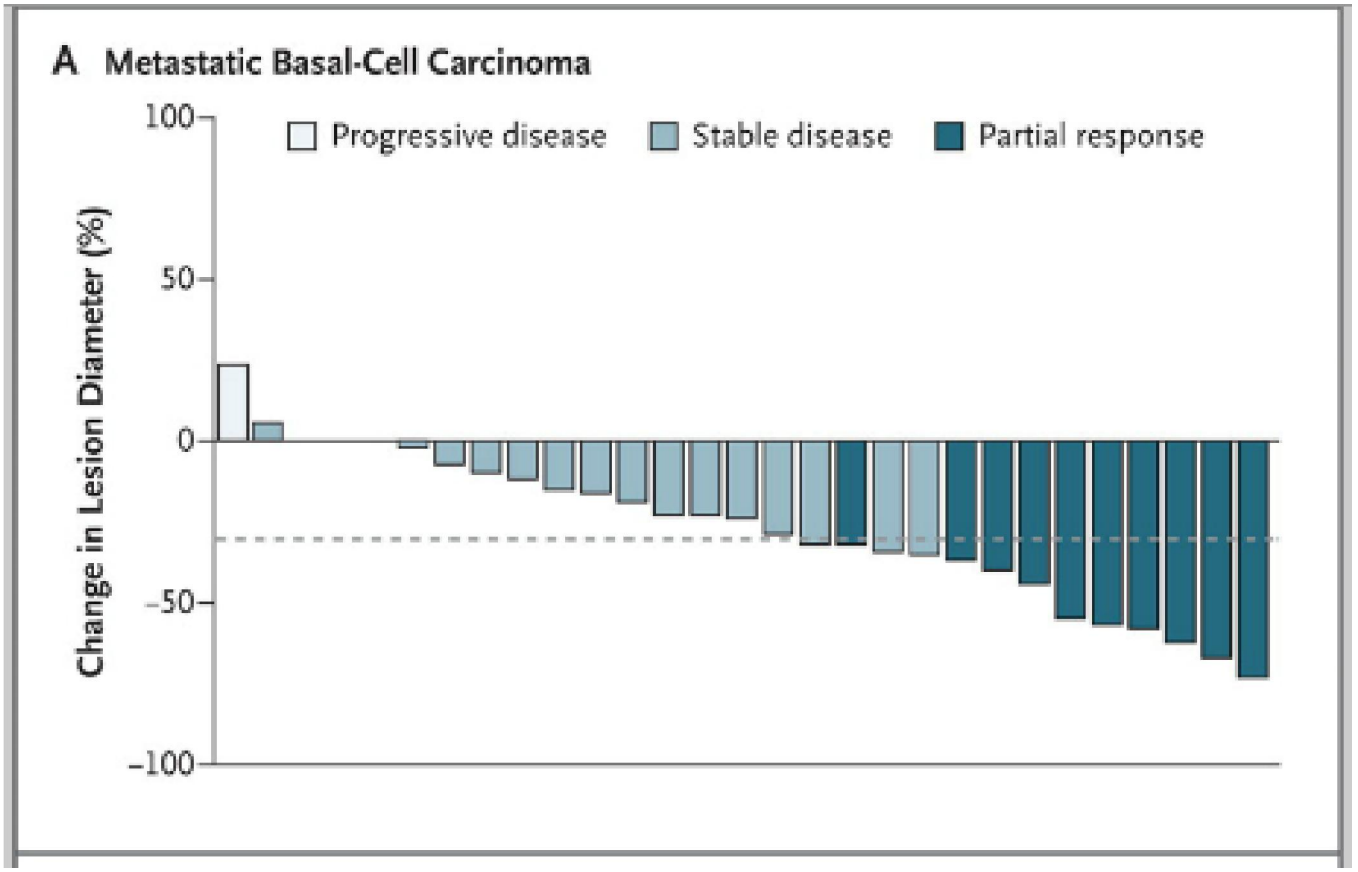
Vismodegib demonstrates a significant objective response rate in mBCC

	mBCC (n = 33)	
	IRF (1°)	INV (2°)
Responders, n (%)	10 (30.3)	15 (45.5)
Stable disease, n (%)	21 (63.6)	15 (45.5)
Progressive disease, n (%)	1 (3.0)	2 (6.1)
Unevaluable/missing, n (%)	1 (3.0)	1 (3.0)
95% CI for objective response	(15.6 – 48.2)	(28.1 – 62.2)
p-value	0.0011	
Median duration of response, months	7.6	12.9

CI, confidence interval; IRF, independent review; INV, investigator review

ERIVANCE BCC Study: Maximum decrease in tumor size by IRF

Metastatic cohort



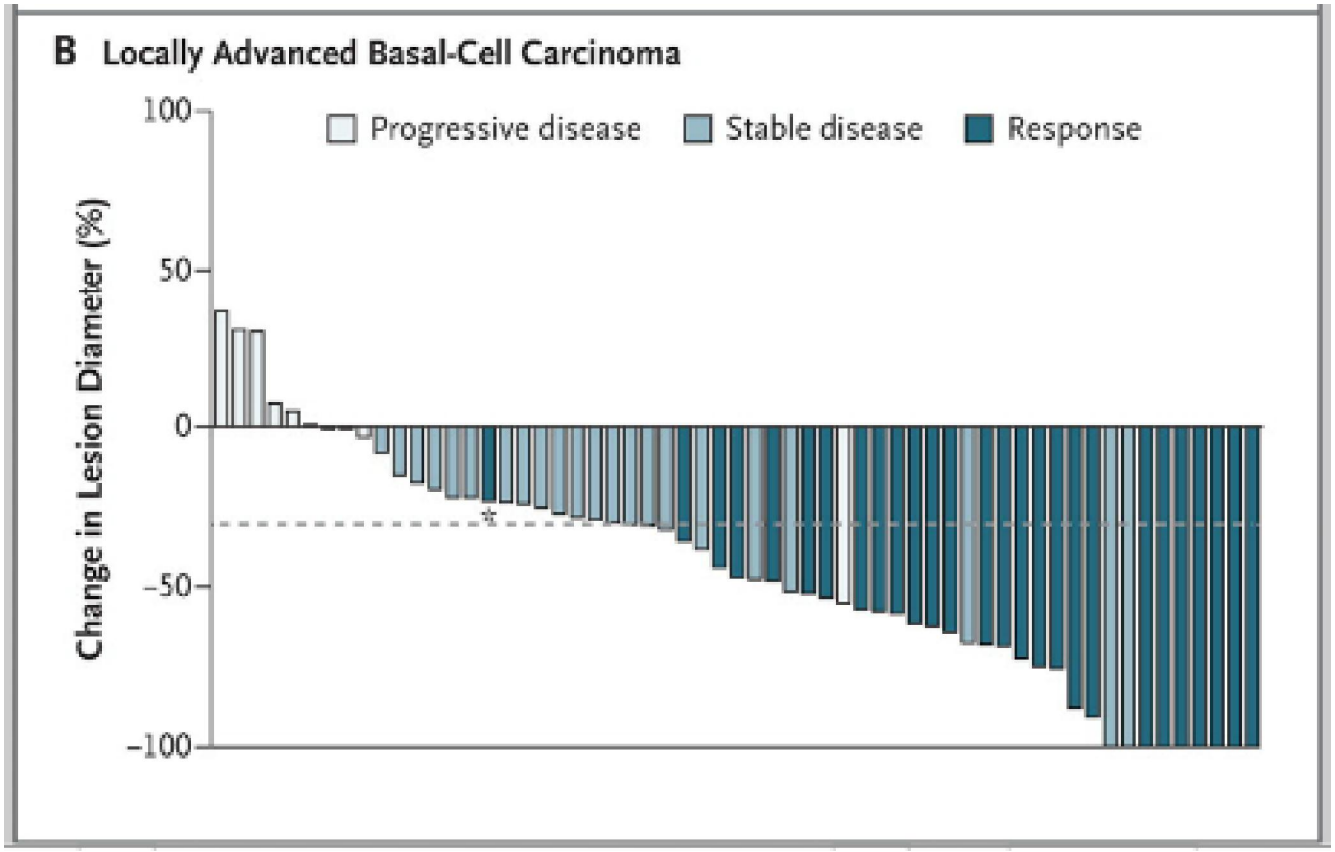
Maximum decrease in size prior to IRF-determined disease progression

Vismodegib demonstrates a significant objective response rate in laBCC

	laBCC (n = 63)	
	IRF (1°)	INV (2°)
Responders, n (%)	27 (42.9)	38 (60.3)
Stable disease, n (%)	24 (38.1)	15 (23.8)
Progressive disease, n (%)	8 (12.7)	6 (9.5)
Unevaluable/missing, n (%)	4 (6.3)	4 (6.3)
95% CI for objective response	(30.5 – 56.0)	(47.2 – 71.7)
p-value	<0.0001	
Median duration of response, months	7.6	7.6

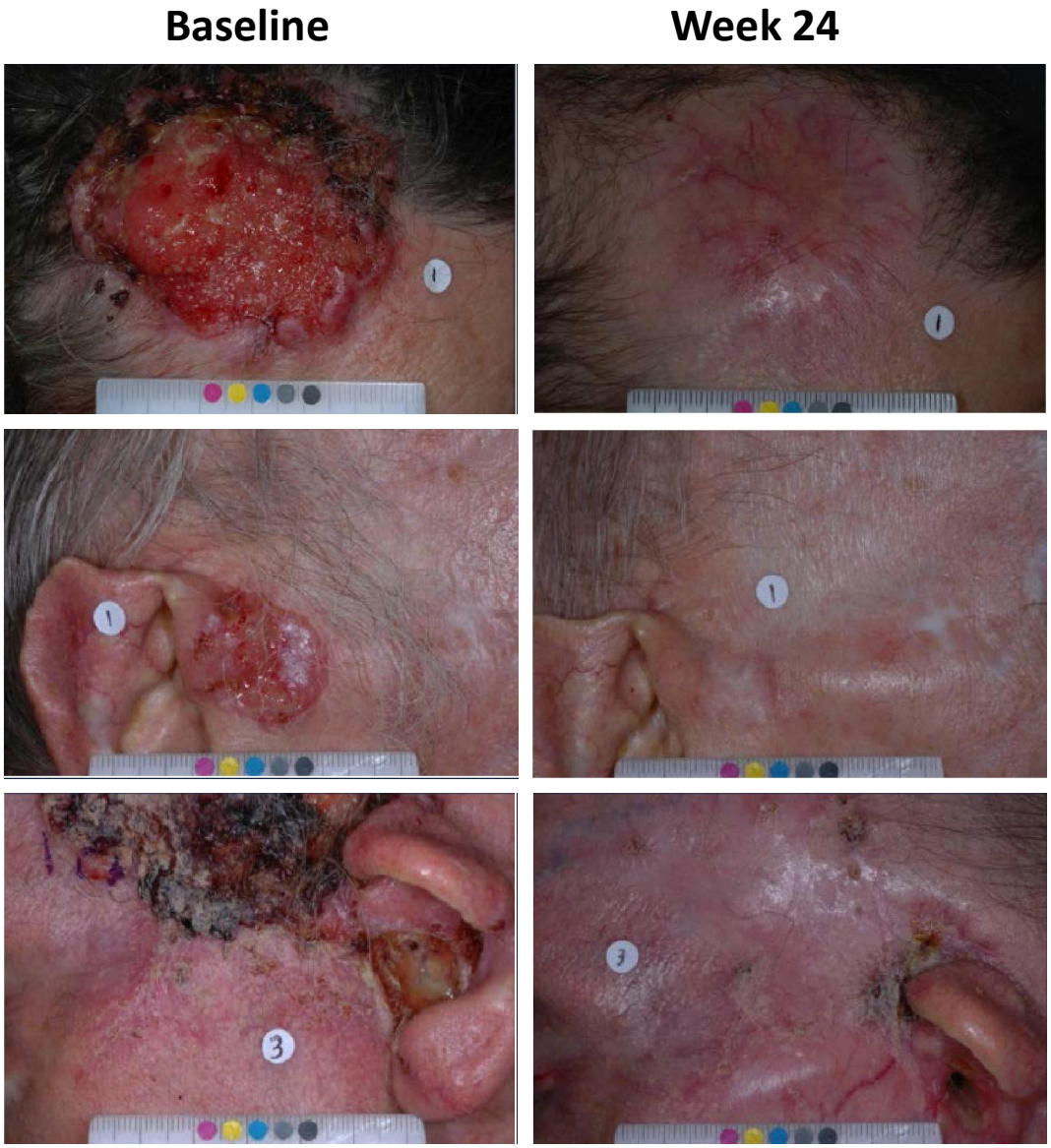
ERIVANCE BCC Study: Maximum decrease in tumor size by IRF

Locally Advanced cohort



Maximum decrease in size prior to IRF-determined disease progression

Vismodegib in locally advanced BCC



Week 24:
residual BCC on biopsy

Vismodegib demonstrates durable clinical benefit in mBCC and laBCC

	mBCC (n=33)	laBCC (n=63)
Median progression-free survival by IRF, in months	9.5	9.5
Clinical benefit rate*, n (%)	25 (76)	47 (75)

*Clinical benefit rate = response at any time (prior to or post-PD) + stable disease lasting 24 or more weeks, as assessed by IRF

Vismodegib treatment duration

All treated patients (n=104)

	mBCC (n=33)	laBCC (n = 71)
Median duration of treatment, months (Range)	10.0 (0.7 – 16.4)	9.7 (1.1 – 18.7)
Patients remaining on treatment*, n (%)	19 (57.6)	32 (45.1)

*As of data cutoff: 26 November 2010, nine months after last patient enrolled

Most common adverse events

All treated patients (n=104)

MedDRA preferred term	All 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

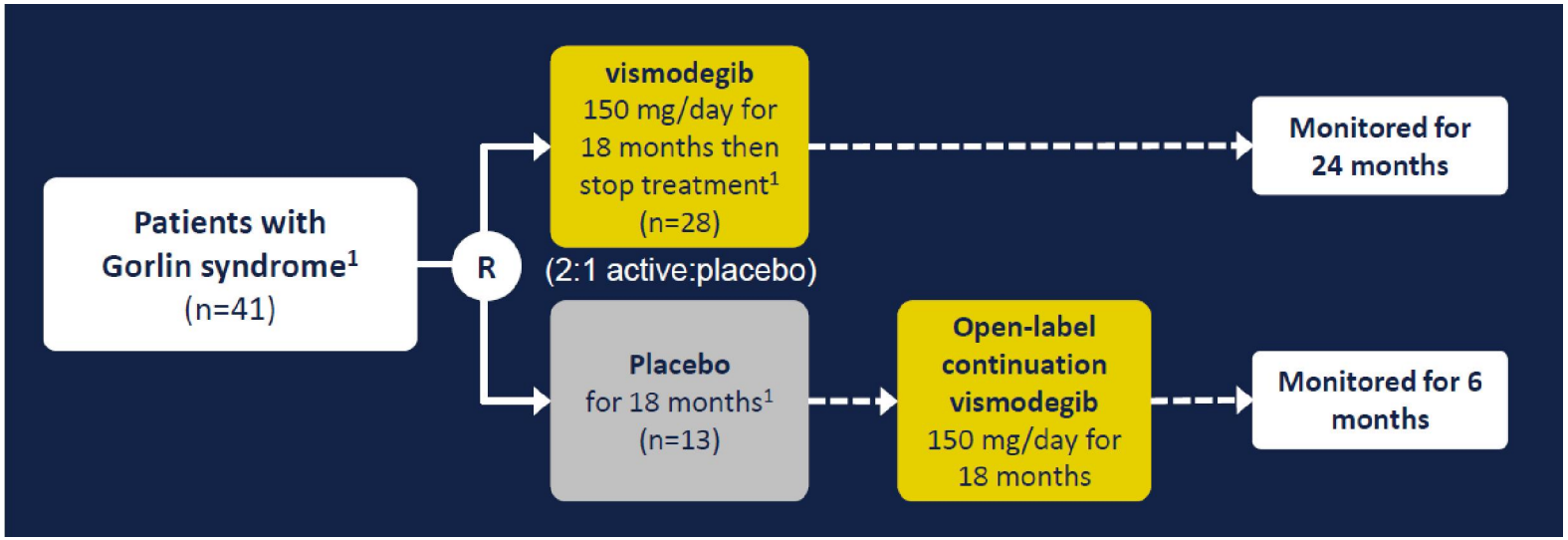
MedDRA, Medical Dictionary for Regulatory Activities

Serious adverse events

	All	Possibly related to vismodegib
Serious events, n (%)	26 (25)	4 (4)*
Fatal events, n (%)	7 (7)^	0

*One patient each with cholestasis; pulmonary embolism; syncope and dehydration; cardiac failure and pneumonia.

Vismodegib Gorlin trial



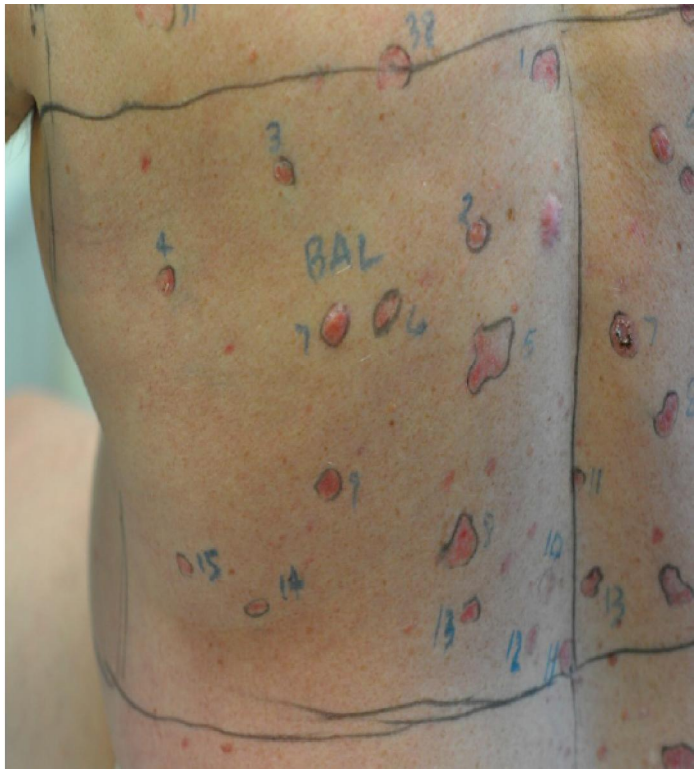
Primary endpoints:

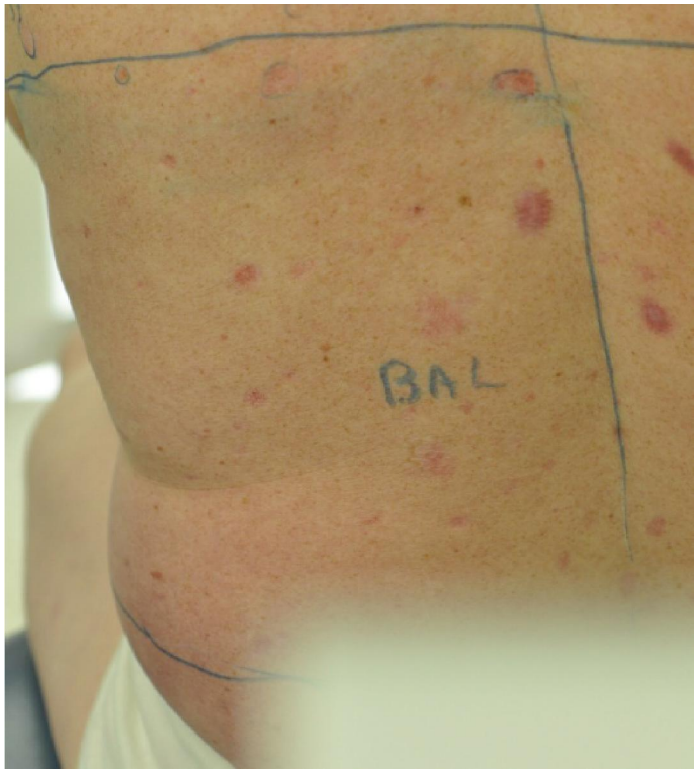
- Efficacy in reducing new surgically eligible BCCs
- Safety

Secondary endpoints:

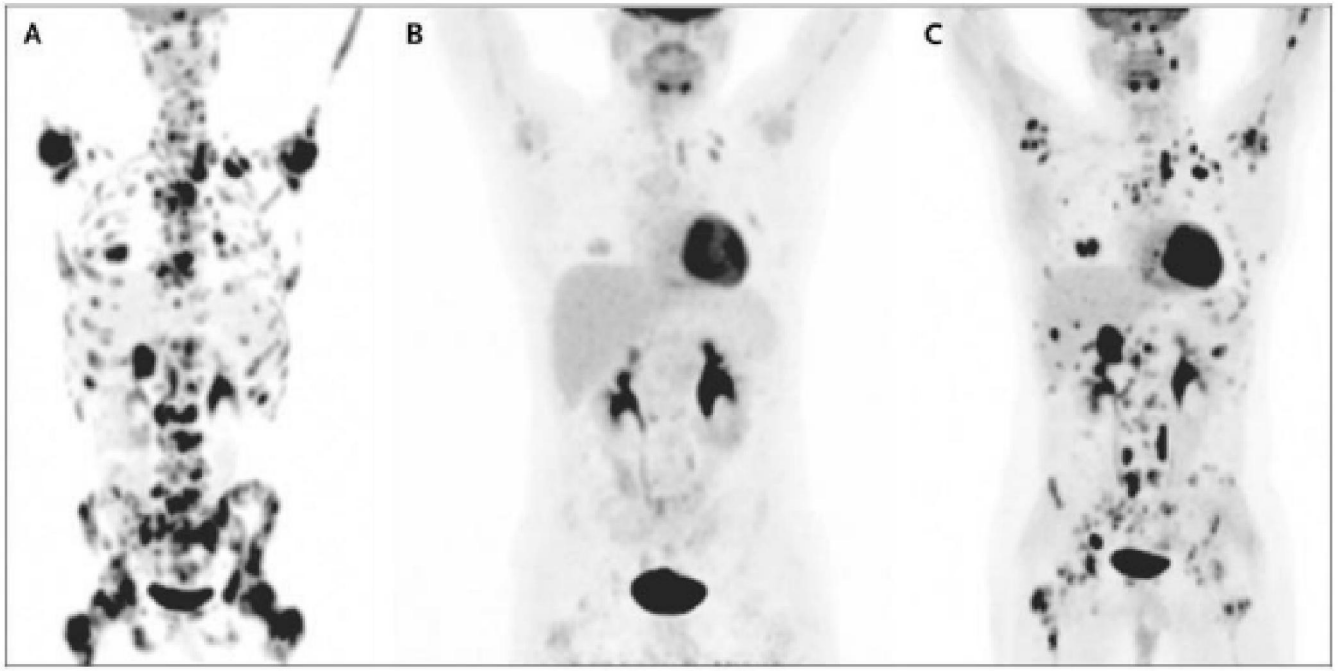
- Efficacy in reducing the number of BCCs (diameter ≥5 mm) on the upper back
- Duration of any anti-BCC effect after administration of the drug is stopped

Gorlin: multiple SEBs





Treatment of Medulloblastoma with vismodegib



Basal | After 2 months | After 3 months

N Engl J Med 2009; 361:1173-1178September 17, 2009

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

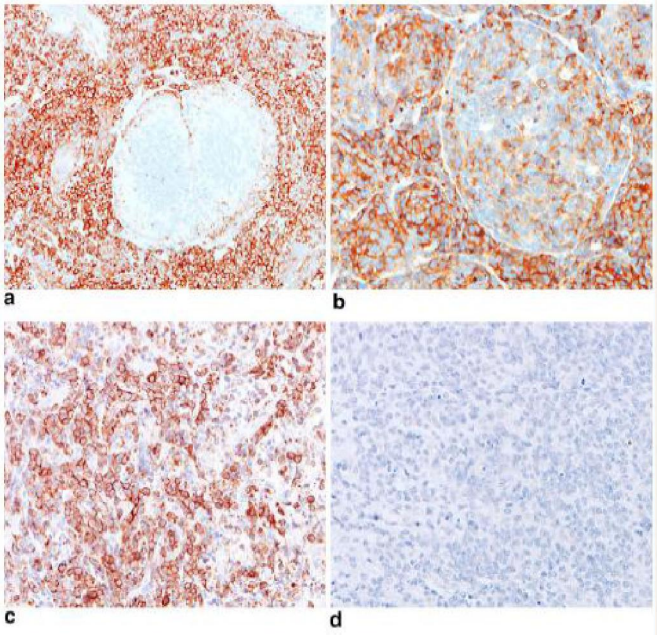
	Molecular Group		
	Hh	Wnt	Non-Wnt/Hh
Proportion of medulloblastoma	15-30%	~15%	~60%
Age at presentation	Mainly infancy & adulthood; Uncommon in 5-15 yrs old	Childhood-pre-teen yrs; mean age ~10 yrs	Mainly childhood; mean age ~8 yrs
Pathological variant	Desmoplastic/Nodular tumors and MBENs ~50% of Large 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

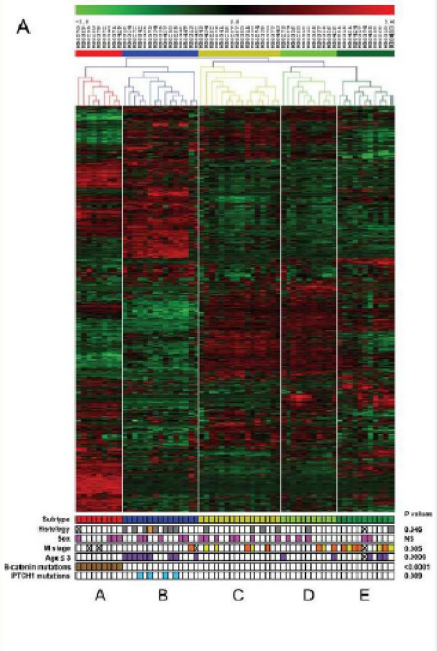
MBEN= medulloblastomawith extensive nodularity.

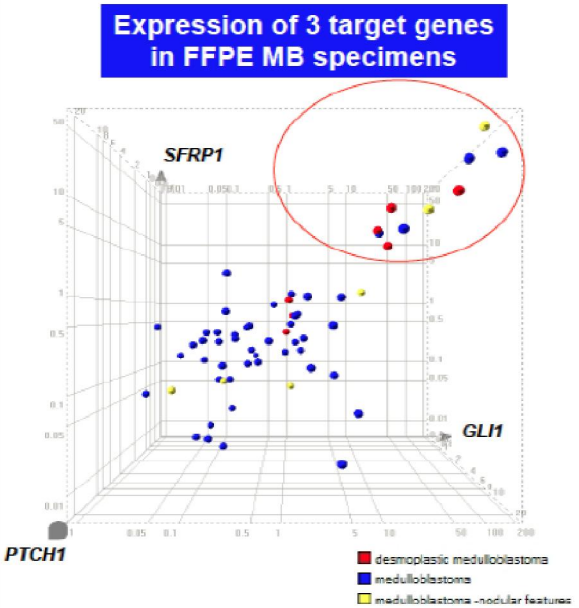
Molecular Classification of Medulloblastoma

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)

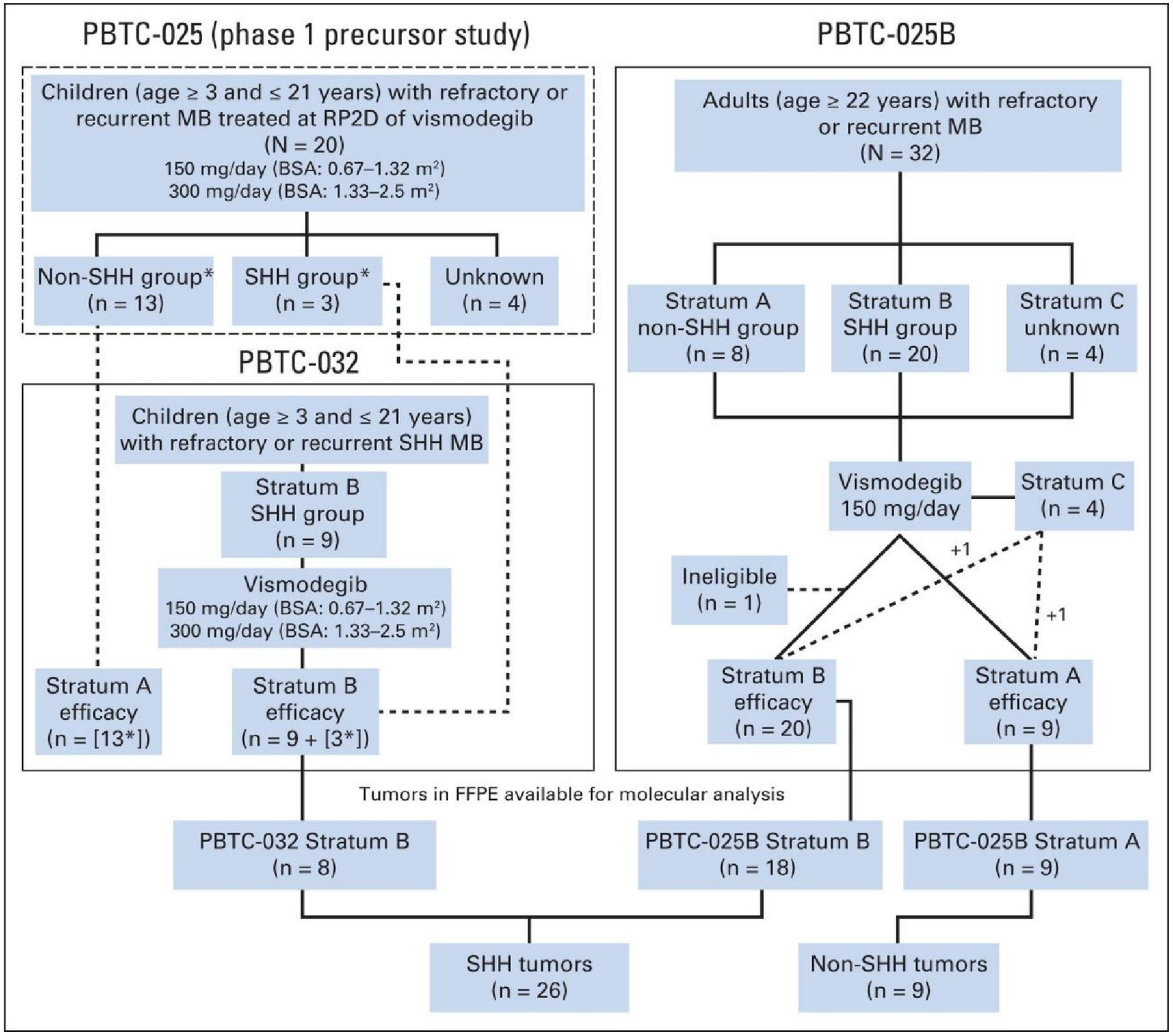






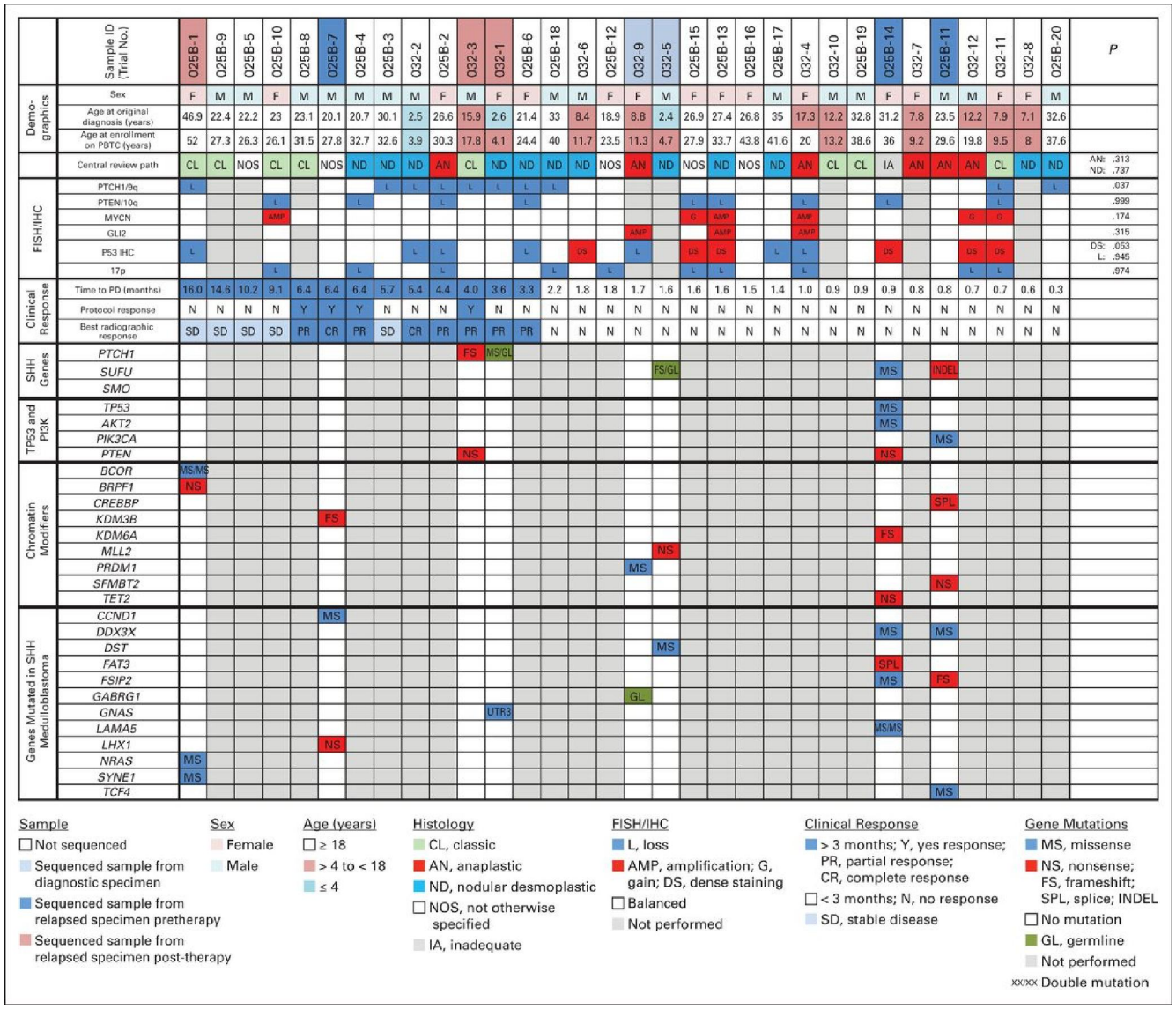
Ellison, DW et al, ActaNeuropathol(2011)
Koolet al,PLoS(2008)

Trial schematics and distribution of patients from PBTC-025 (phase I precursor study), PBTC-032 (children), and PBTC-025B (adults).



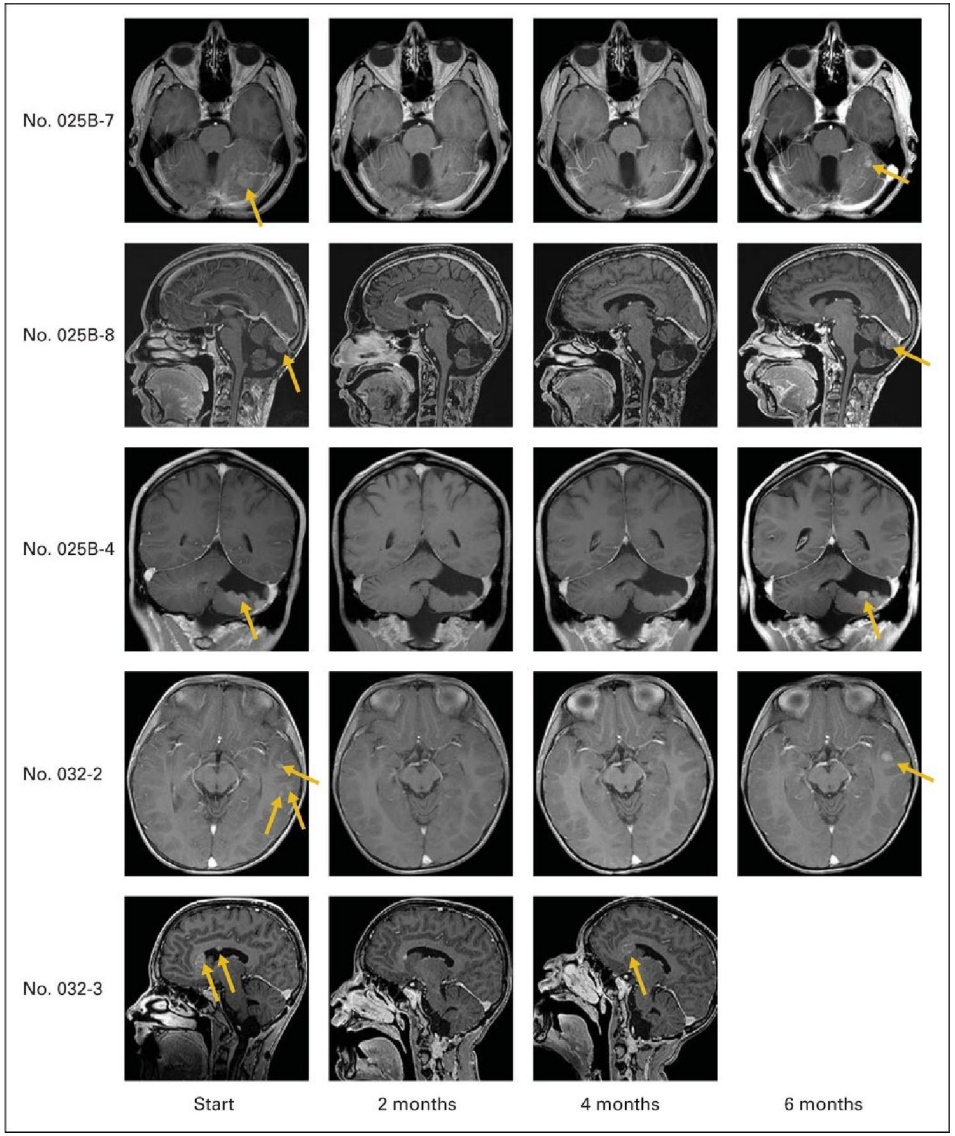
Giles W. Robinson et al. JCO 2015;33:2646-2654

Clinical and molecular characteristics of patients with sonic hedgehog (SHH) – subgroup medulloblastoma (SHH-MB) enrolled onto PBTC-025B or PBTC-032.



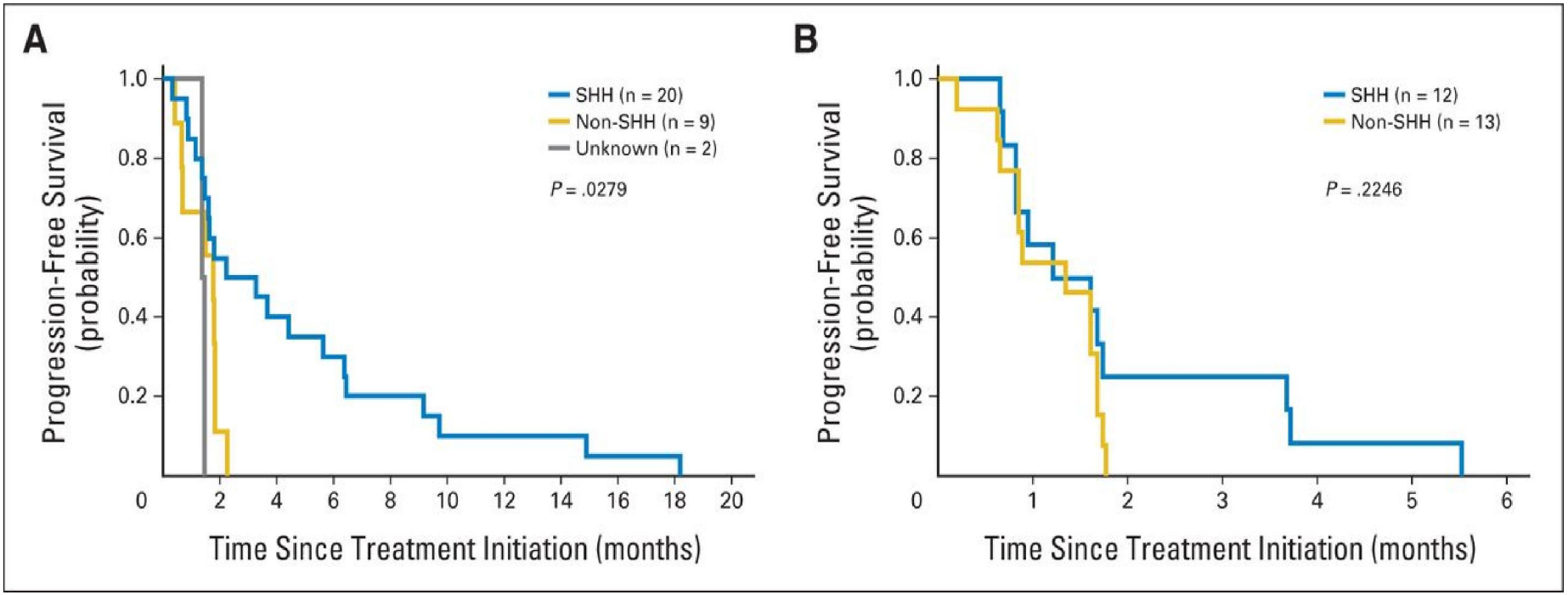
Giles W. Robinson et al. JCO 2015;33:2646-2654

Magnetic resonance images showing responses in five patients with recurrent sonic hedgehog–subgroup medulloblastoma (MB) treated with vismodegib.



Giles W. Robinson et al. JCO 2015;33:2646-2654

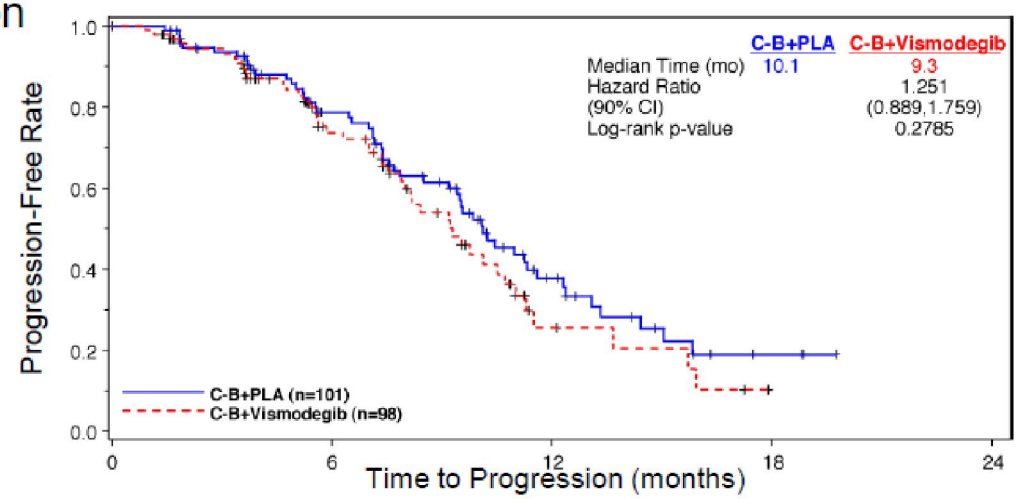
Progression-free survival (PFS) of patients enrolled onto (A) PBTC-025B or (B) PBTC-032 and PBTC-025.



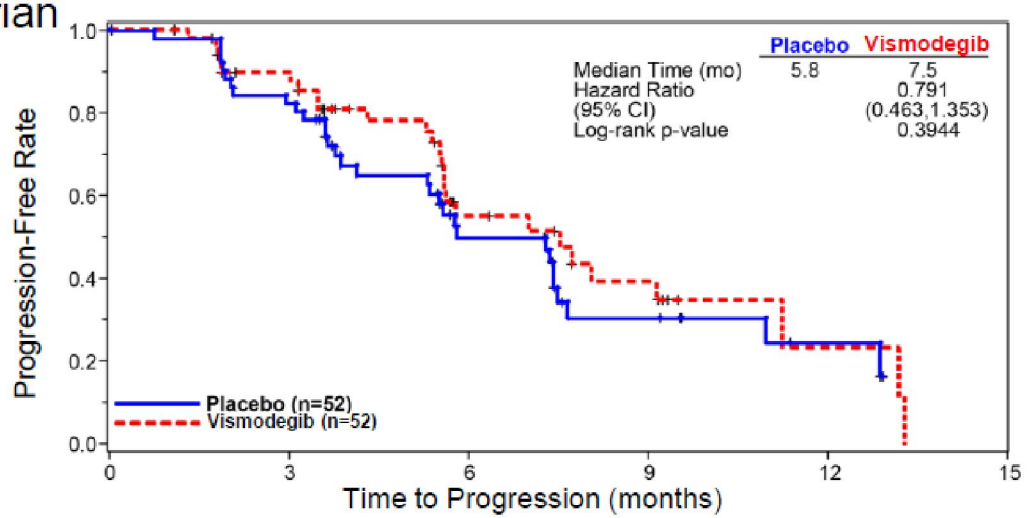
Giles W. Robinson et al. JCO 2015;33:2646-2654

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

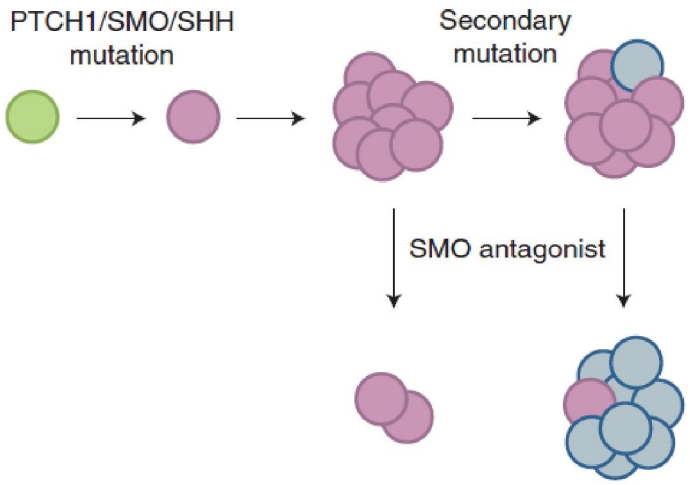
Colon

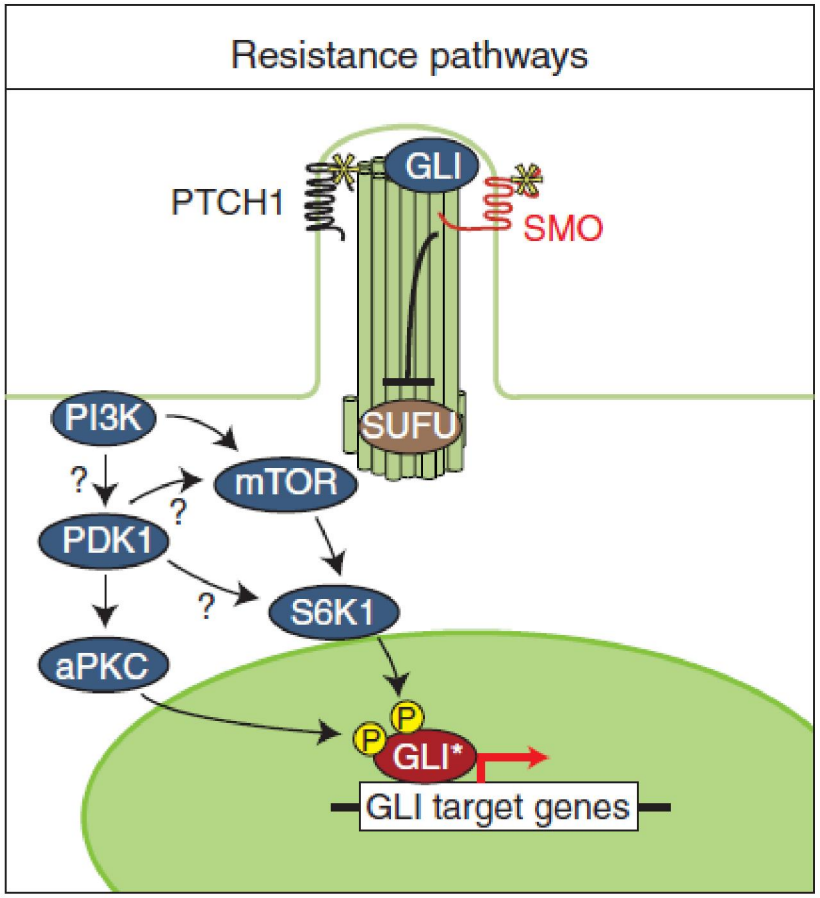


Ovarian

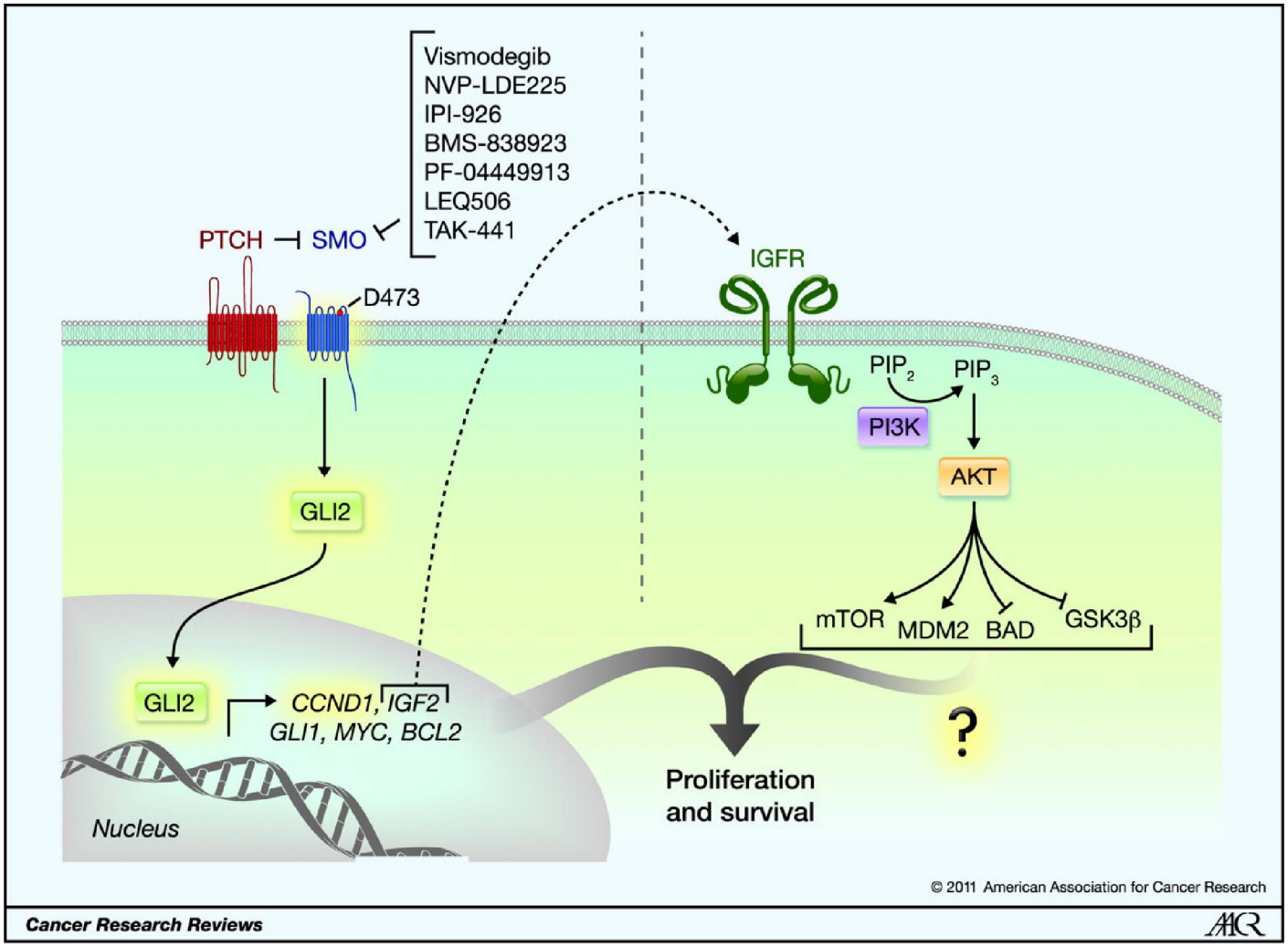


Resistance to SMO inhibition



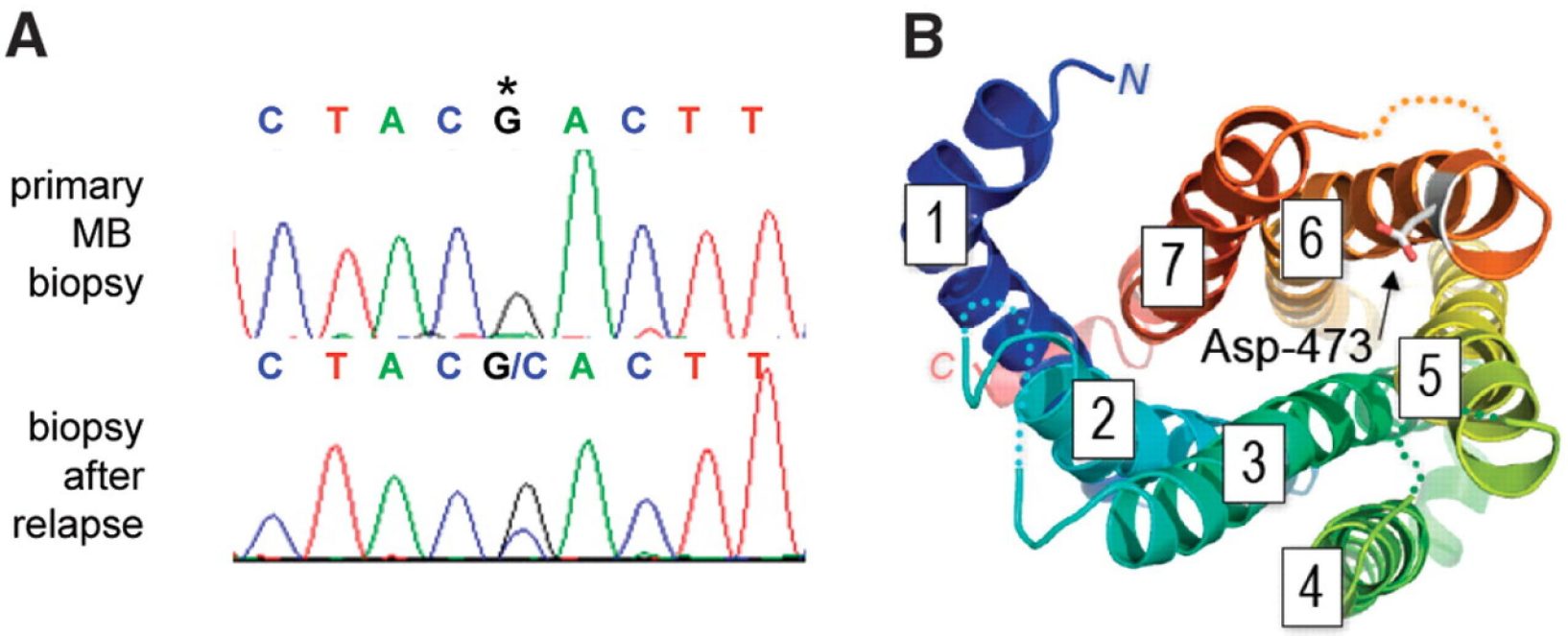


Multiple elements contribute to acquired resistance against SMO antagonists.



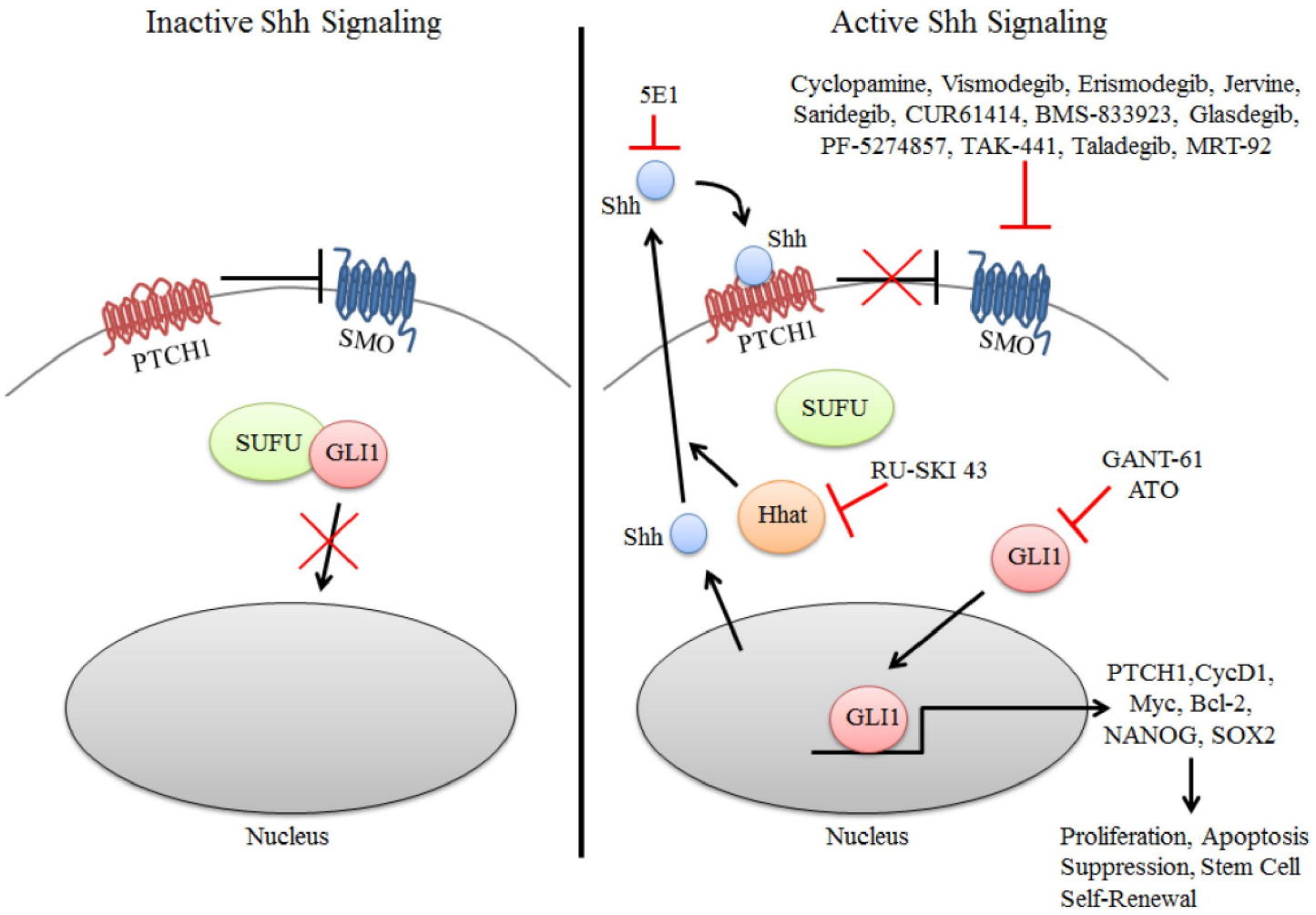
Ciara Metcalfe, and Frederic J. de Sauvage Cancer Res 2011;71:5057-5061

Identification of a SMO mutation in tumor samples from a medulloblastoma patient who relapsed after an initial response to GDC-0449.



Robert L. Yauch et al. Science 2009;326:572-574

New generation HH inhibitors



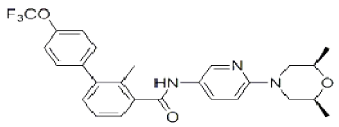
HH inhibitors in clinical development….

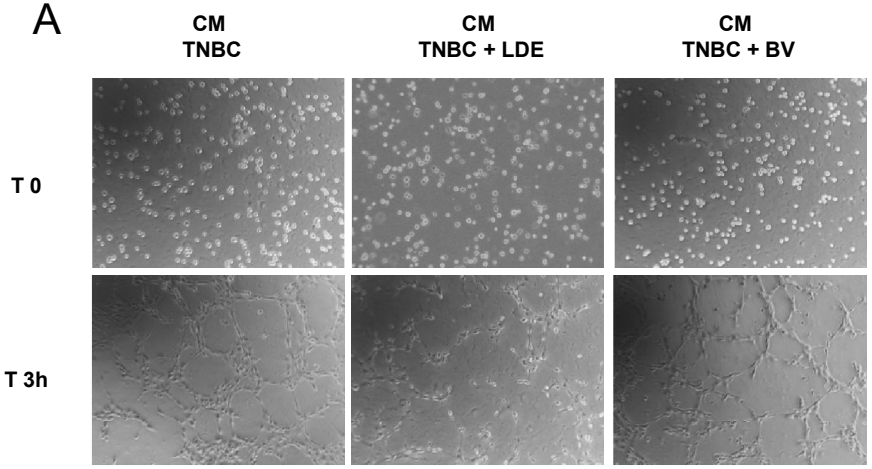
Compound	Organization	Target	Cancer Type	Clinical Trial	NCT Trial
GDC-0449 (Vismodegib/Erivedge)	Roche/Genentech/Curis	SMO	Basal Cell Carcinoma	Phase II	NCT01835626
				Phase I	NCT02639117
				Phase II	NCT02067104
			-	Phase 0	NCT01631331
			-	Phase II	NCT01815840
			-	Phase II	NCT01700049
			-	Phase II	NCT01898598
			-	Phase IV	NCT02436408
			-	Phase II	NCT01367665
			-	-	-
			Advanced/Metastatic Basal Cell Carcinoma	Phase II	NCT01556009
				Phase II	NCT00957229
			Basal Cell Nevus Syndrome	Phase I/II	NCT01601184
			Medulloblastoma	Phase II	NCT01878617
			-	Phase II	NCT01239316
			Recurrent Medulloblastoma	Phase II	NCT00939484
			Metastatic	Phase 0	NCT02115828
			Castration-Resistant Prostate Cancer	-	-
				-	-
			Chondrosarcoma	Phase II	NCT01267955
			Advanced Pancreatic Cancer	Phase II	NCT01195415
			Metastatic Pancreatic Cancer	-	-
			Myelofibrosis	Phase I	NCT00878163
			Metastatic Gastric & Esophageal Cancer	Phase II	NCT01088815
				Phase I	NCT02593760
			Advanced Prostate Adenocarcinoma	Phase II	NCT00982592
				-	-
			Small-Cell Lung Cancer	Phase I/II	NCT01163084
			Keratocystic Odontogenic Tumor	-	-
				Phase II	NCT00887159
			Advanced Solid Tumors	Phase II	NCT02366312
			Acute Myeloid Leukemia	-	-
			Intracranial Meningioma	Phase II	NCT02091141
				Phase II	NCT02073838
				Phase II	NCT02523014
LDE225 (Erismodegib/ Sonidegib/Odomzo®)	Novartis	SMO	Prostate Cancer	Phase I	NCT02111187
				Phase I	NCT02182622
			Castration-Resistant Prostate Cancer	-	-
				Phase I/II	NCT01431794
			Pancreatic Adenocarcinoma	-	-
			Advanced/Metastatic Pancreatic Cancer	Phase I/II	NCT02358161
				-	-
			Refractory Multiple Myeloma	Phase II	NCT02086552
			Recurrent Ovarian Cancer	-	-
			Triple-Negative Breast Cancer	Phase I/II	NCT02195973
			Myeloid Malignancies Basal Cell Carcinoma	Phase I	NCT02027376
				-	-
			Advanced/Metastatic Basal Cell Carcinoma	Phase I	NCT02129101
				Phase II	NCT00961896
			-	Phase II	NCT00961896
			Advanced Solid Tumors	Phase 0	NCT02303041
			-	Phase II	NCT01327053
				Phase I	NCT01769768
				Phase I	NCT01954355

….HH inhibitors in clinical development

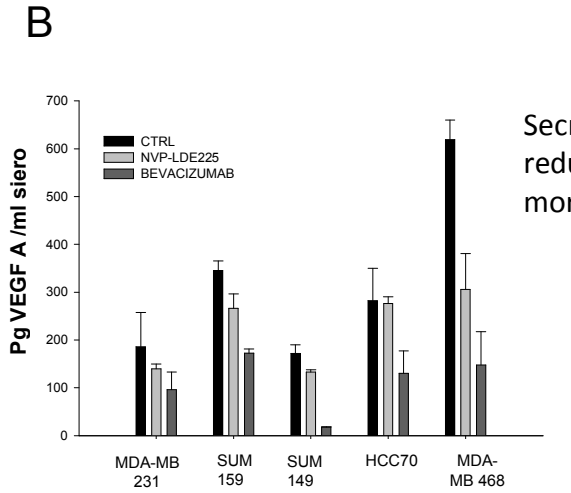
Compound	Organization	Target	Cancer Type	Clinical Trial	NCT Trial
LDE225 (Erismodegib/ Sonidegib/Odomzo®)	Novartis	SMO	Advanced Gastroesophageal Adenocarcinoma	Phase I	NCT02138929
				-	-
				-	-
			Small Cell Lung Cancer	Phase I	NCT01579929
			Myelofibrosis	Phase I/II	NCT01787552
			Advanced/Metastatic Hepatocellular Carcinoma	Phase I	NCT02151864
				-	-
			Relapsed Medulloblastoma	-	-
				Phase II	NCT01708174
				-	-
BMS-833923/XL139	Bristol Myers Squibb/Exelixis	SMO	Basal Cell Nevus Syndrome	Phase I	NCT02100371
				-	-
			Chronic Myeloid Leukemia	Phase II	NCT01357655
				-	-
PF-04449913 (Glasdegib)	Pfizer	SMO	Myelofibrosis	Phase II	NCT02226172
			Chronic Myelomonocytic Leukemia	Phase II	NCT01842646
				-	-
				-	-
			Myelodysplastic Syndrome	Phase II	NCT01842646
				-	-
LY2940680 (Taladegib)	Ignyta	SMO	Esophageal Cancer	Phase I/II	NCT02530437
			Advanced Solid Tumors	Phase I	NCT01919398
				-	-
IPI-926 (Saridegib)	Infinity	SMO	Advanced Pancreatic Adenocarcinoma	Phase I	NCT01383538
				-	-
Arsenic Trioxide (ATO)	-	GLI1		Phase I	NCT02066870
				-	-
				Phase II	NCT01470248
			Non-Small-Cell Lung Cancer	Phase II	NCT01835288
			Small Cell Lung Cancer	-	-
			Acute Myeloid Leukemia	-	-
			Hepatocellular Carcinoma	-	-
			-	Phase II	NCT02018757
			Malignant Glioma	Phase I/II	NCT00275067
			Myelofibrosis	Phase I	NCT01014546
			Acute Promyelocytic Leukemia	Phase III	NCT02339740
				Phase II	NCT01404949
			-	Phase II	NCT01409161
			-	Phase III	NCT00378365
			-	Phase IV	NCT01987297
			-	Phase III	NCT00866918
			-	Phase II	NCT00413166
			-	Phase II	NCT00551460
			-	Phase III	NCT00482833
			-	Phase IV	NCT02200978
			Chronic Myelogenous Leukemia	Phase I	NCT01397734
				-	-
			Acute Myeloid Leukemia	Phase II	NCT02188706
			Myelodysplastic Syndrome	Phase II	NCT02190695
			Chronic Myelomonocytic Leukemia	Phase II	NCT02188706
				Phase II	NCT02190695
				Phase II	NCT02190695
				-	-
				-	-

HH pathway in angiogenesis

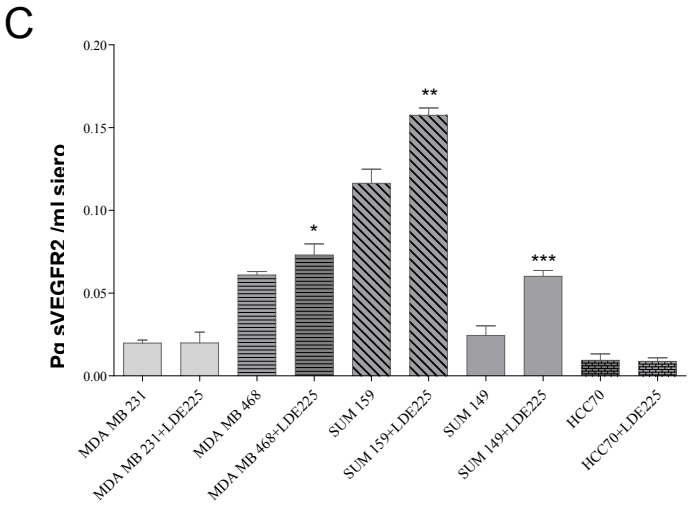




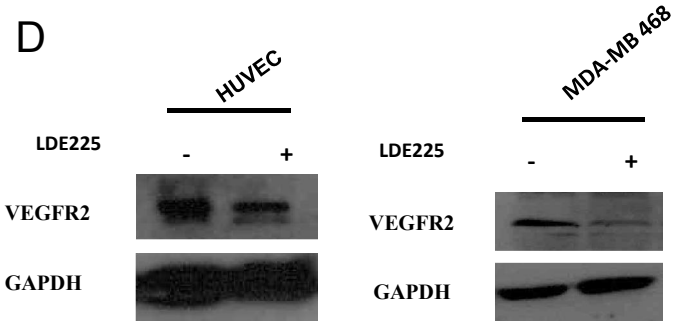
NVPLDE-225 is more efficient than bevacizumab against angiogenesis



Secreted VEFGA is reduced by bevacizumab more than NVPLDE225



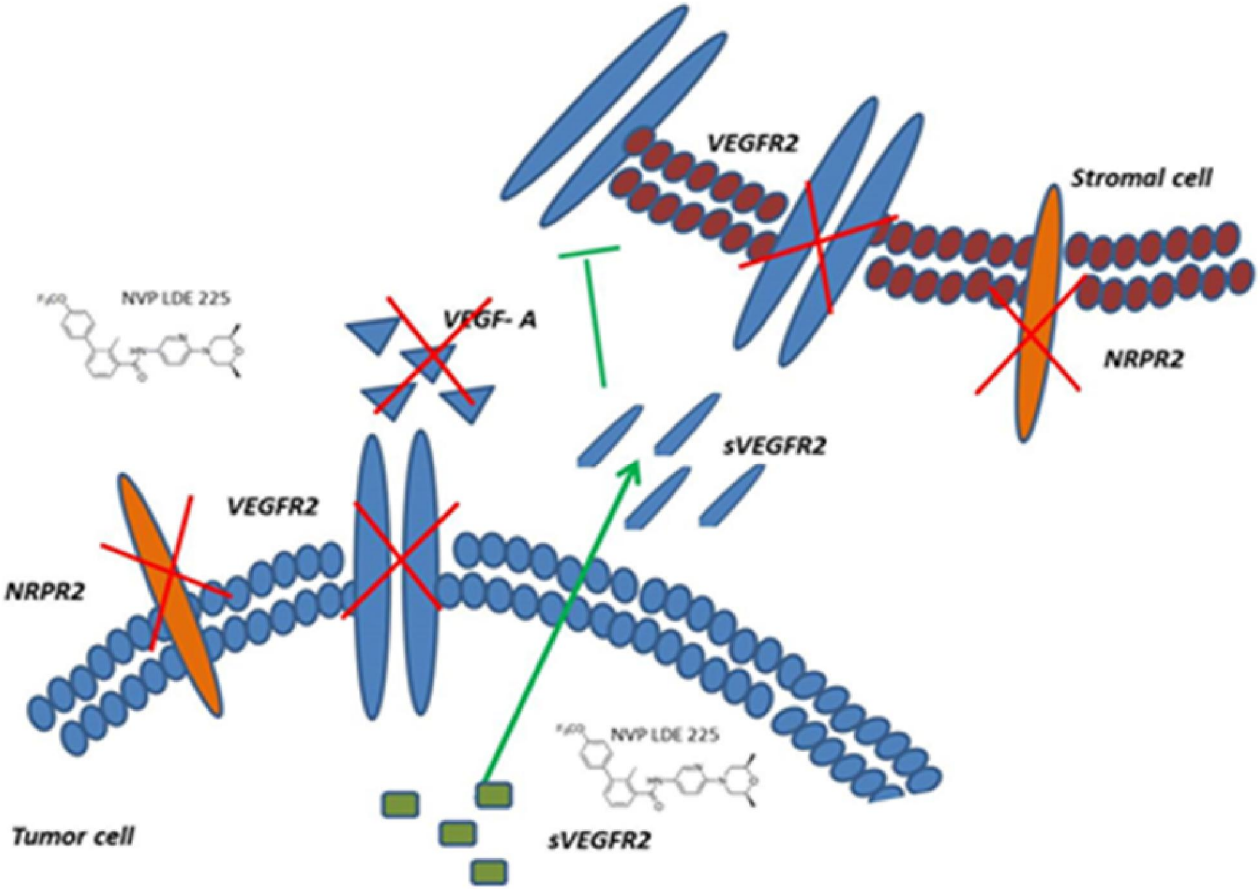
sVEGFR2 increases upon treatment with NVPLDE225.



VEGFR2 is decreased upon treatment with NVPLDE225.

Unpublished data

HH pathway in angiogenesis



Unpublished data