“Precision Medicine in Pediatric Brain Tumors: Challenges and Opportunities”

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Precision Medicine in Pediatric Brain Tumors: Challenges and Opportunities

DATA-DRIVEN PRECISION MEDICINE AND TRANSLATIONAL RESEARCH IN THE ERA OF BIG DATA – MAY 1, 2020

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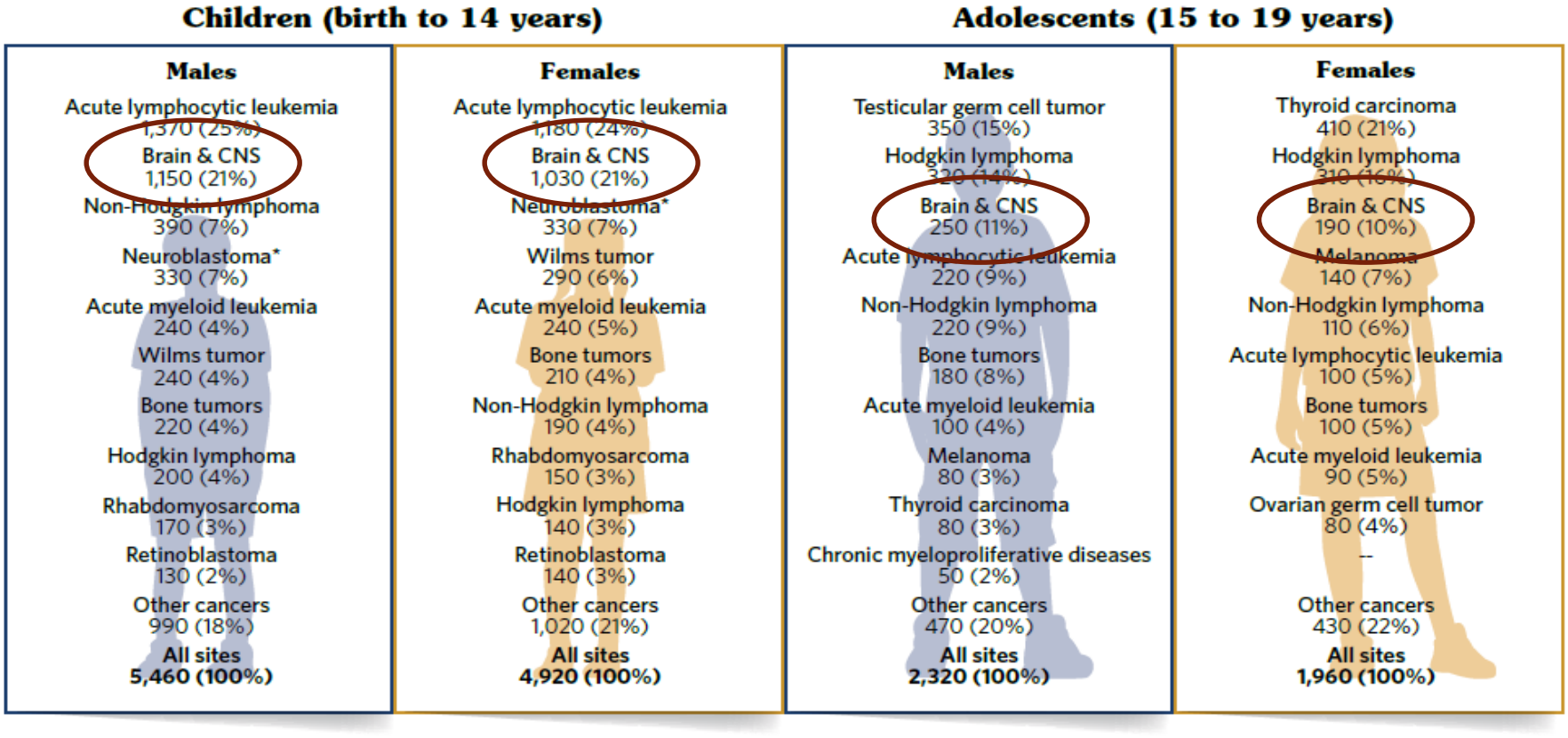
Disclosures

Limited advisory role for Roche and Eli Lilly

Grants and other support (e.g. investigational agent) for PBTC studies from:

- Novartis, Pfizer, Celgene, Apexigen, SecuraBio, Senhwa, Incyte, Novocure

New Case Estimates for Leading Childhood and Adolescent Cancers by Sex, 2016



CNS indicates central nervous system. Estimates are rounded to the nearest 10 and exclude basal cell and squamous cell carcinomas, in situ and borderline brain, and all other in situ carcinomas except urinary bladder. An estimate for the tenth most common cancer in female adolescents is unavailable due to estimate being <50 cases.

*Includes ganglioneuroblastoma.

Figure 2: In 2016 there will be an estimated 14,660 new cases of childhood cancer. The types of cancers that are common in younger children (0-14) differ from those in adolescents (15-19). The specific types of cancers also differ between boys and girls.

Brain cancer now leading childhood cancer killer

By MIKE STOBBE Sep. 16, 2016 8:35 AM EDT

NEW YORK (AP) — Brain cancer is now the deadliest childhood cancer in the U.S., now ahead of leukemia, a result of improved leukemia treatment and a frustrating lack of progress on brain cancer.

Government statisticians reported the change in rankings Friday, drawing from a review of 15 years of death certificates.

"I think most people, when they think of childhood cancer, think of leukemia," said Sally Curtin of the Centers for Disease Control and Prevention. "This is kind of a changing of the guard."

Cancer is the fourth leading cause of death for children overall, accounting for about 1 in 10 childhood deaths in 2014. About a quarter these cancer deaths, or 534, were due to brain cancer. There were 445 leukemia deaths.

Accidental injuries remained the leading cause of death for those under 19, followed by suicide and murder, according to the report.

There are still more new cases of leukemia each year than new cases of brain cancer, but it no longer accounts for the most deaths. That's due to advances in leukemia treatment over the past few decades and because leukemia is easier than brain cancer to treat, experts said.

Special considerations for precision medicine in pediatric cancers

- Childhood cancers are often **biologically different** than similarly named cancers in adults.
- **Treatment side effects may differ** between children and adults
  - Health impacts of pediatric cancer treatment may be more severe since they occur during a vulnerable period of development.
- Children have a **special protective status** in research
  - Research that may be ethical in adults many not be so for children.
- The **rarity of childhood cancers** can make designing and completing clinical trials challenging
  - small number of diagnosed patients or
  - competition between different research studies for the same children.

Childhood Cancer Research Landscape Report, American Cancer Society

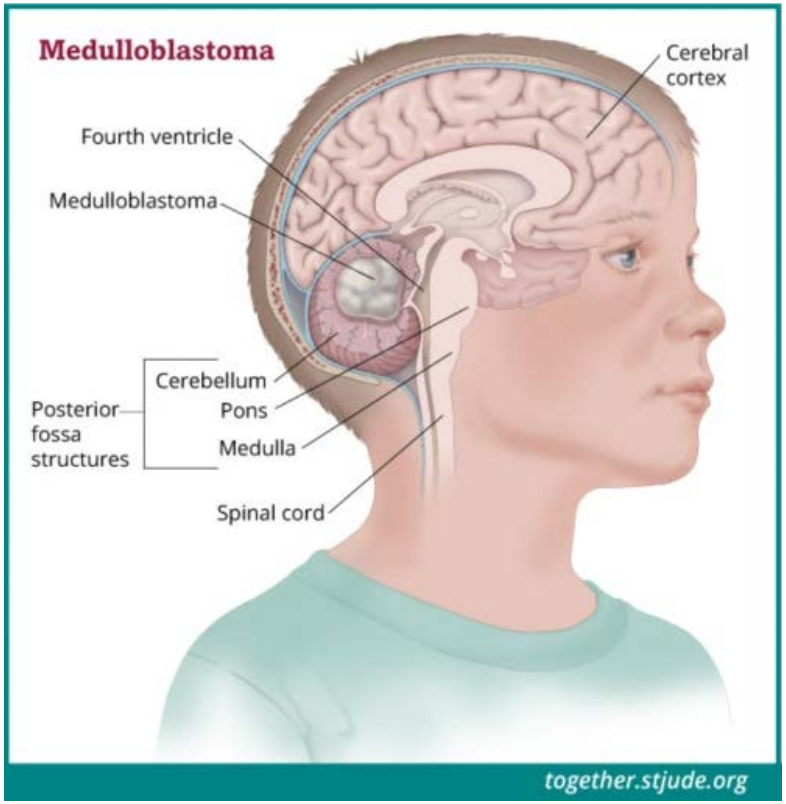
"Sometimes reality is too complex. Stories give it form."

--Jean Luc Godard, film writer, film critic, film director

VIGNETTE 1: SHH MEDULLOBLASTOMA

Medulloblastoma

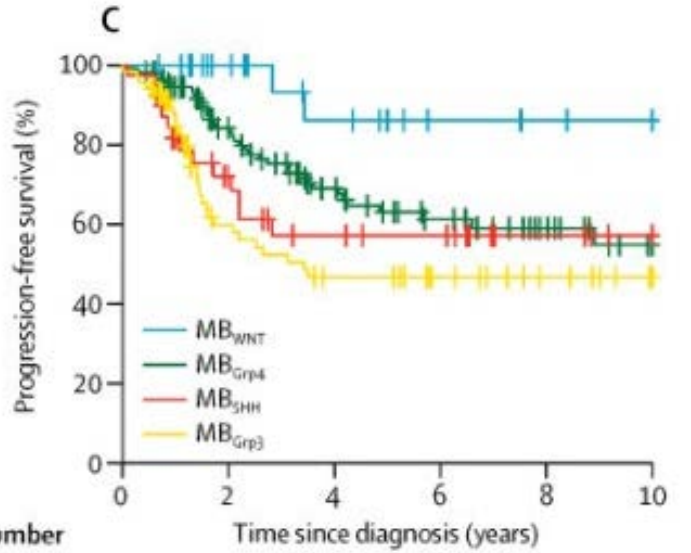
- The most common malignant brain tumor in children
  - ~400-500 new cases/yr in the US
- One of the better understood pediatric brain tumors
- A relative success story with a 5-year PFS of ~70-75%
  - Prognosis depends on degree of surgical resection and whether tumor is localized or has spread
  - Molecular subgroup
- St Jude investigators have made significant contributions to the understanding of medulloblastoma.
  - A large number of basic and translational science papers (674 papers since 1990)
  - Landmark treatment trials: SJMB96, SJMB03, SJYC07, SJMB12



Significant Molecular Heterogeneity

	Subgroup	WNT	SHH	Group 3	Group 4
Clinical Characteristics	% of Cases	10	30	25	35
	Age at Diagnosis				
	Gender Ratio (M:F)	1:1	1:1	2:1	3:1
	Anatomic Location				
	Histology	Classic, Rarely LCA	Desmoplastic, Classic, LCA	Classic, LCA	Classic, LCA
	Metastasis at Diagnosis (%)	5-10	15-20	40-45	35-40
	Recurrence Pattern	Rare; Local or metastatic	Local	Metastatic	Metastatic
	Prognosis	Very good	Infants good, others intermediate	Poor	Intermediate
Molecular Characteristics	Proposed Cell of Origin	Progenitor cells in the lower rhombic lip	Granule precursors of the external granule layer	Neural stem cells	Unipolar brush cells
	Recurrent Gene Amplifications	-	*MYCN* *GLI1* or *GLI2*	*MYC* *MYCN* *OTX2*	*SNCAIP* *MYCN* *OTX2* *CDK6*
	Recurrent SNVs	*CTNNB1* *DDX3X* *SMARCA4* *TP53*	*PTCH1* *TERT* *SUFU* *SMO* *TP53*	*SMARCA4* *KBTBD4* *CTDNEP1* *KMT2D*	*KDM6A* *ZMYM3* *KTM2C* *KBTBD4*
	Cytogenetic Events ■ Gain ■ Loss	6	3q, 9p 9q, 10q, 17p	1q, 7, 18 8, 10q, 11, 16q i17q	7, 18q 8, 11p, X i17q
	Other Recurrent Genetic Events	-	-	*GFI1* and *GFI1B* enhancer hijacking	*PRDM6*, *GFI1*, and *GFI1B* enhancer hijacking

Age: Infant Child Adult



Number at risk (censored)						
MB$_{WNT}$	26 (0)	18 (8)	12 (12)	6 (18)	4 (20)	3 (21)
MB$_{Grp4}$	115 (0)	76 (23)	50 (36)	32 (49)	19 (61)	10 (69)
MB$_{SHH}$	40 (0)	20 (10)	13 (13)	11 (15)	5 (21)	2 (24)
MB$_{Grp3}$	69 (0)	32 (13)	23 (15)	17 (21)	11 (27)	6 (32)

MB$_{Grp3}$ vs MB$_{Grp4}$: HR 1·99 (95% CI 1·22–3·25), p=0·015

Juraschka and Taylor, J Neurosurg Pediatr 24:353–363, 2019
Schwalbe et al. Lancet Oncology 18: 958-971, 2017

SHH Medulloblastoma

- ~ 30% of medulloblastomas are classified as SHH tumors
- Most common in infants and adults, accounting for 60-70% of medulloblastoma cases in these age groups.
- Prognosis varies according to clinical and molecular characteristics.
  - Usually good outcomes in infants with localized tumors
  - If tumors recur post initial treatment (especially after radiation treatment), prognosis is very poor
- The majority contain germline or somatic mutations or copy number alterations in the SHH signaling pathway, leading to constitutively activated SHH signaling, driving tumor development and progression

Juraschka and Taylor, J Neurosurg Pediatr 24:353–363, 2019

Targeted Therapy in SHH Medulloblastoma

- Inhibition of SHH signaling has long been recognized as a potential targeted therapy for medulloblastoma harboring genetic alterations in SHH pathway genes.
  - Smoothened (SMO) functions as a key component of the SHH pathway by regulating suppressor of fused (SUFU).
  - SMO inhibitors block SUFU activation, thereby preventing translocation of GLI proteins into the nucleus.
  - SMO inhibitors have shown efficacy in the treatment and prevention of basal cell carcinoma and responses have been reported in recurrent MB.

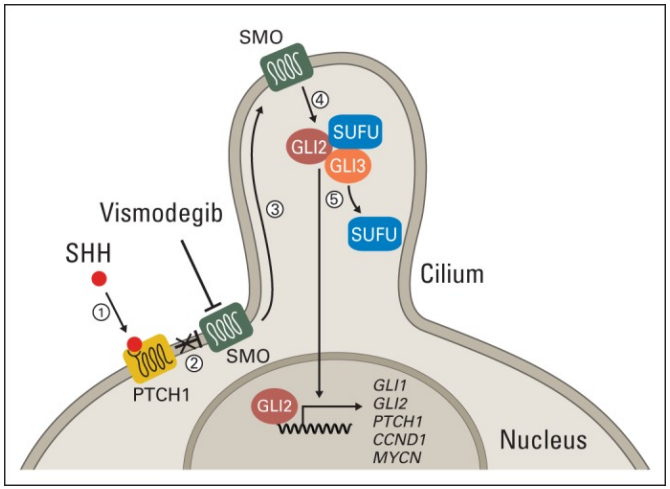
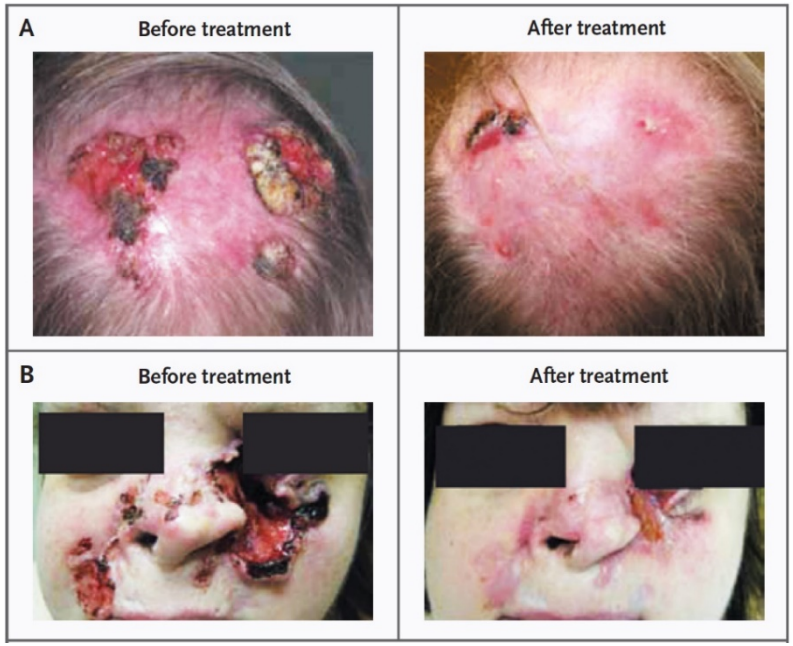


Illustration of sonic hedgehog (SHH) signaling pathway. In SHH-subgroup medulloblastoma, disruptions to SHH pathway occur through mutation of PTCH1, SMO, or SUFU and/or amplification of GLI2 or MYCN. Vismodegib inhibits SMO.

Robinson et al. JCO 2015 Aug 20; 33(24): 2646–2654.

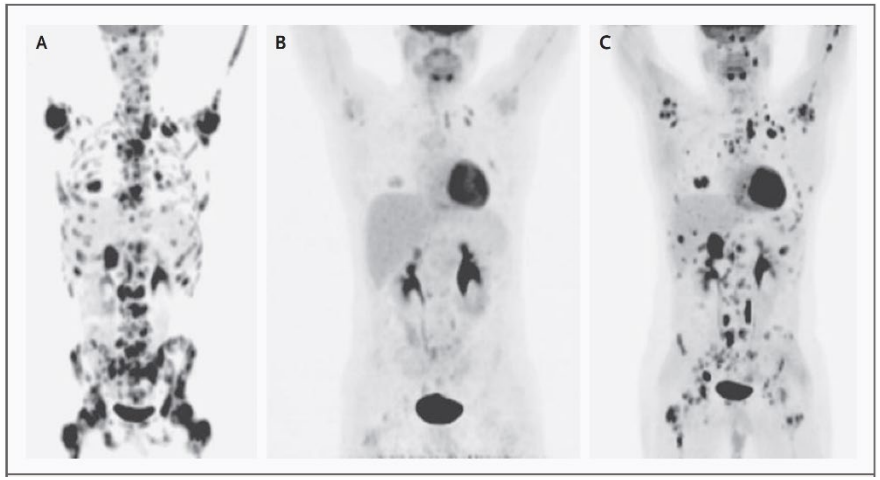
Impressive Responses with SMO Inhibitors

BASAL CELL CANCER



Von Hoff et al. NEJM. 2009;361(12):1164-72

MEDULLOBLASTOMA

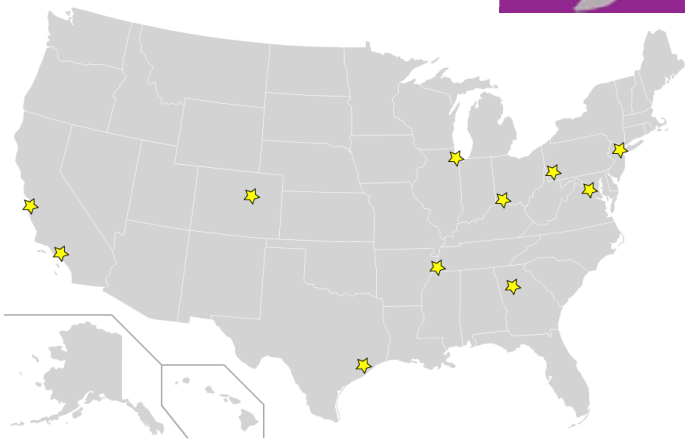


Tumor Response on FDG PET Panel A shows the pretreatment scan; Panel B, the repeat scan after 2 months of therapy with the hedgehog pathway inhibitor GDC-0449; and Panel C, the repeat scan after 3 months of therapy.

Rudin et al. NEJM. 2009;361(12):1173-6

PBTC-025, -025B & -032 Clinical Trials

- **The Pediatric Brain Tumor Consortium (PBTC)**
  - was formed by the NCI in 1999 to improve the treatment of brain tumors in children.
  - aims to conduct novel phase I and II studies of new therapeutic agents in children with primary CNS tumors.
  - the Operations Biostatistics and Data Management Core of the Consortium is based within the Dept of Biostatistics at St Jude



During 2009-2013, PBTC conducted 3 clinical trials with Vismodegib (Erivedge, Genentech) in Medulloblastoma led by Dr. Gajjar at St Jude

- PBTC-025 determined the pediatric safe dose
- PBTC-025B and -032 were single arm Phase II studies in adult and pediatric medulloblastoma (stratified by SHH vs. non-SHH subjects)

Outcome on PBTC-025, -025B and -032 Studies

VOLUME 33 · NUMBER 24 · AUGUST 20 2015

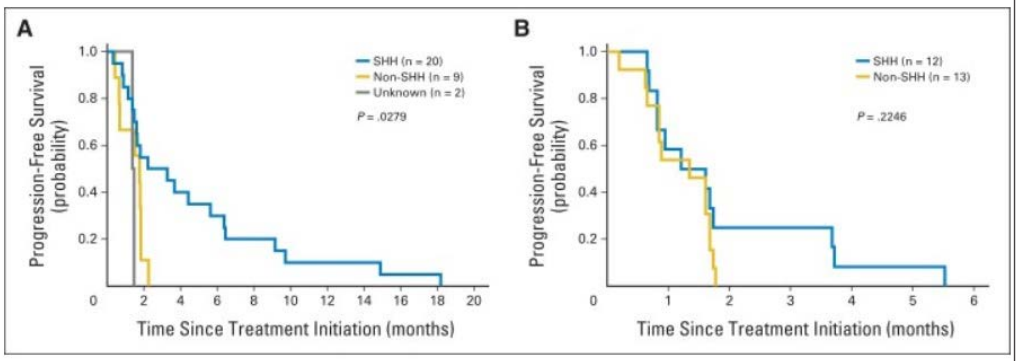
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

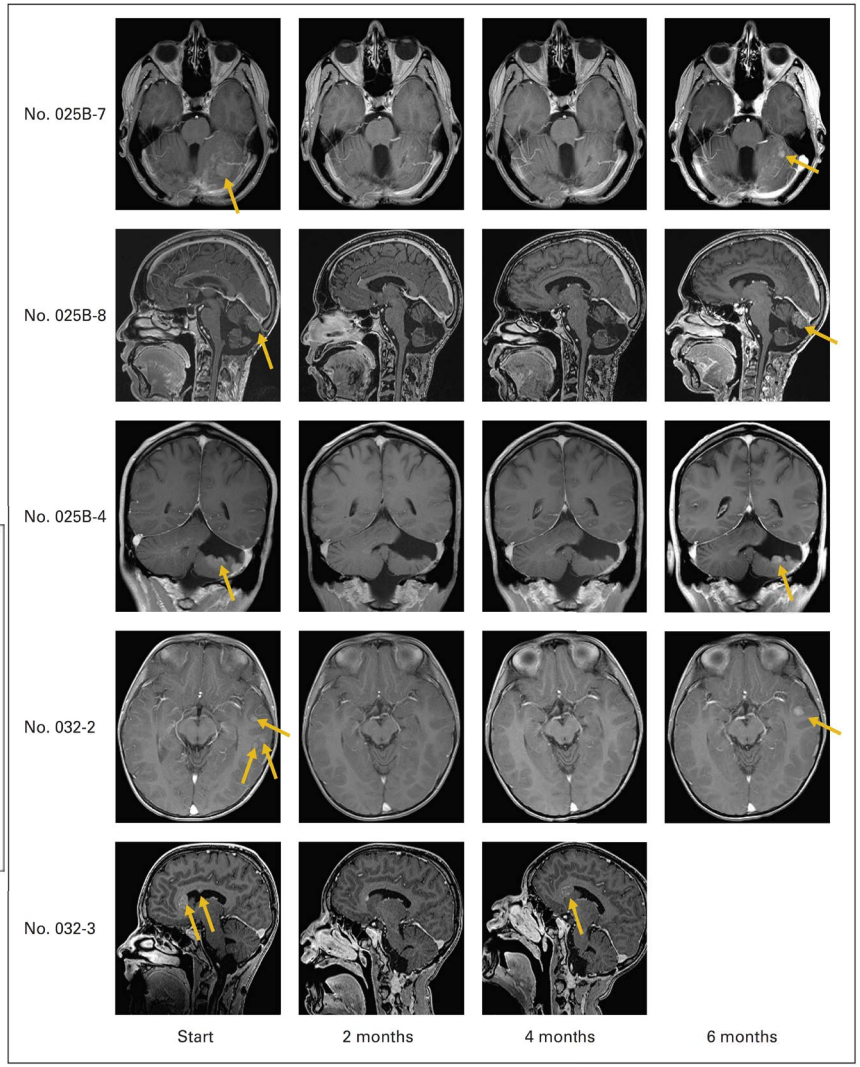
Vismodegib Exerts Targeted Efficacy Against Recurrent Sonic Hedgehog–Subgroup Medulloblastoma: Results From Phase II Pediatric Brain Tumor Consortium Studies PBTC-025B and PBTC-032

Giles W. Robinson, Brent A. Orr, Gang Wu, Sridharan Gururangan, Tong Lin, Ibrahim Qaddoumi, Roger J. Packer, Stewart Goldman, Michael D. Prados, Annick Desjardins, Murali Chintagumpala, Naoko Takebe, Sue C. Kaste, Michael Rusch, Sariah J. Allen, Arzu Onar-Thomas, Clinton F. Stewart, Maryam Fouladi, James M. Boyett, Richard J. Gilbertson, Tom Curran, David W. Ellison, and Amar Gajjar

Adult Subjects

Pediatric Subjects



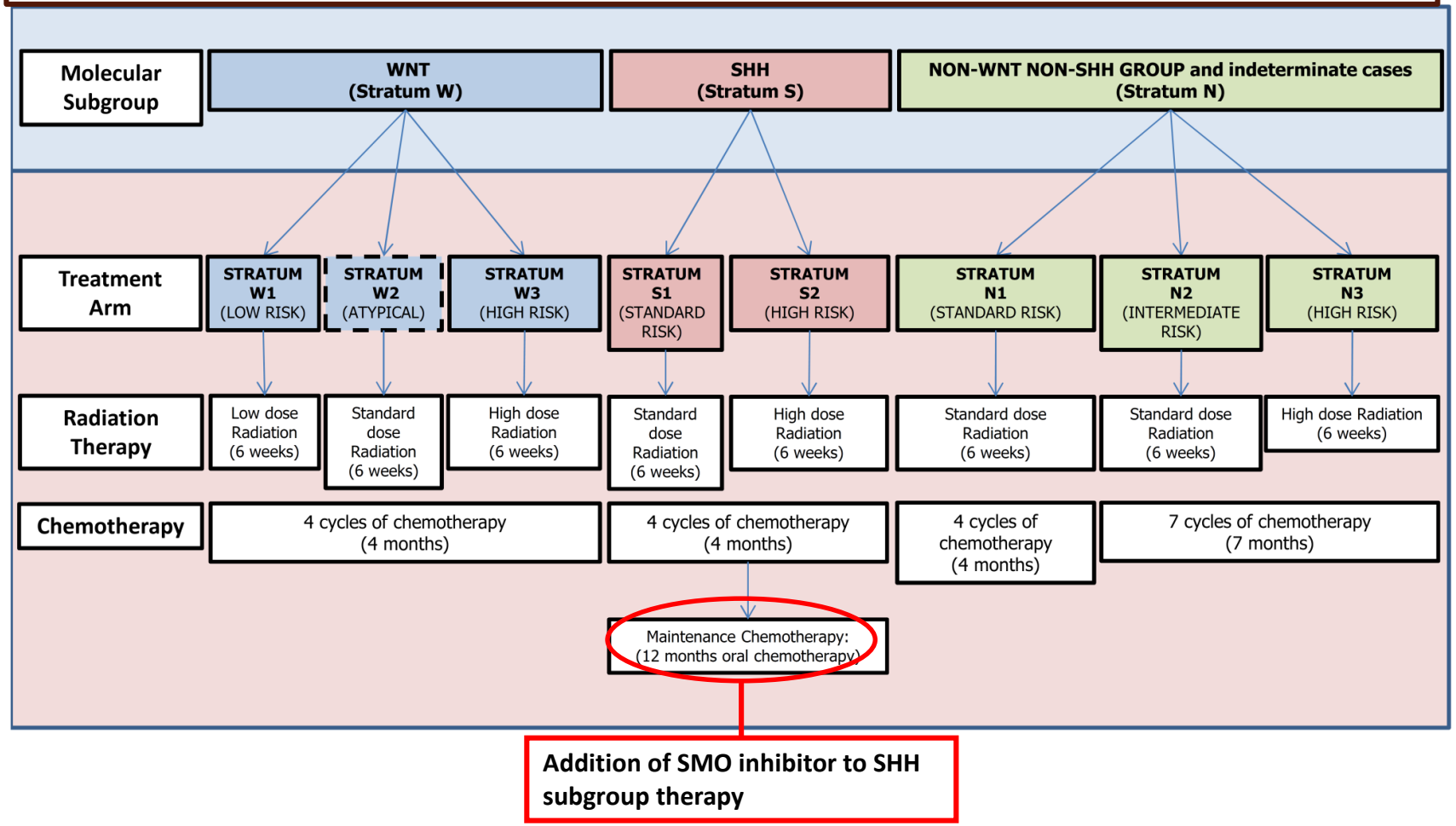


Encouraging results were observed in SHH medulloblastoma though resistance to the treatment ultimately developed

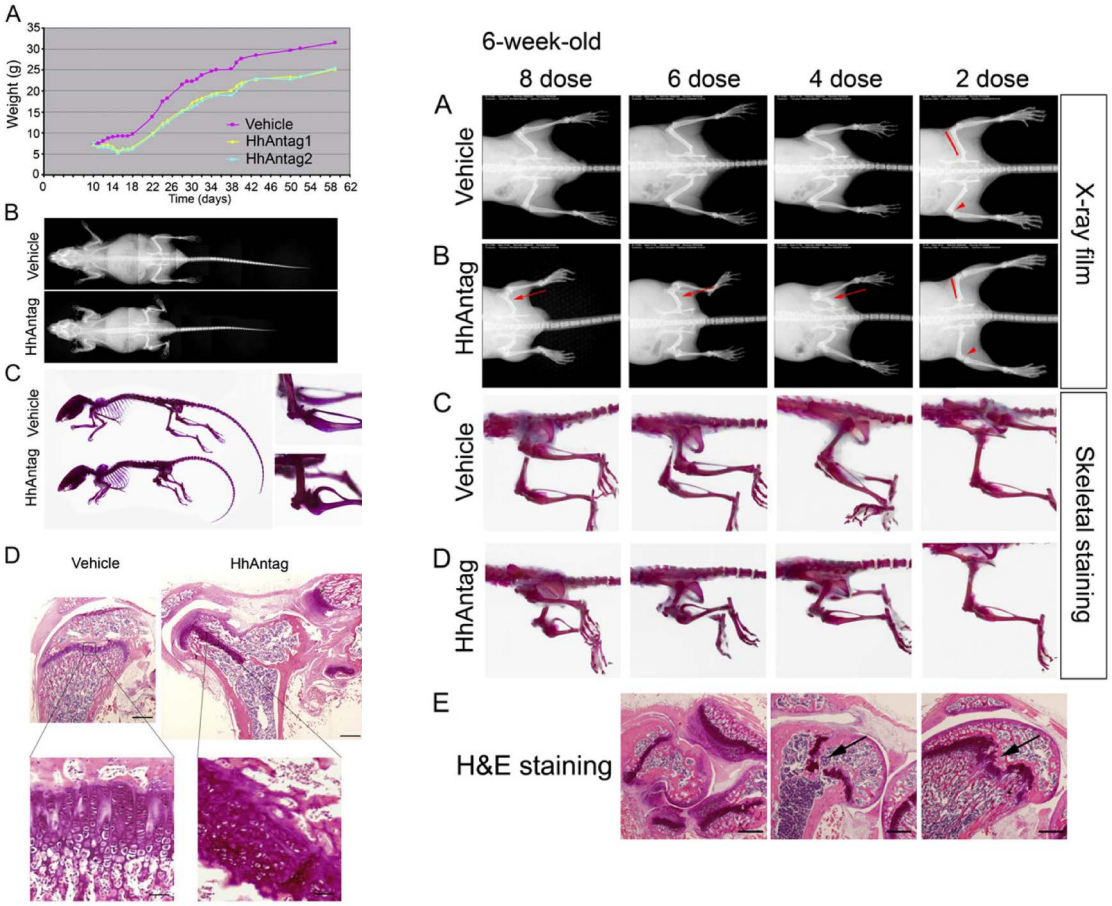
SJMB-12 (First molecularly stratified medulloblastoma trial)

SMO inhibitor was added to ***front-line*** therapy for SHH subgroup

SJMB12: A Clinical and Molecular Risk-Directed Therapy for Newly Diagnosed Medulloblastoma
Clinical Trial for Newly Diagnosed Medulloblastoma
United States, Canada, Australia, *and* ***New Zealand***



But what effect does this drug have on developing children?

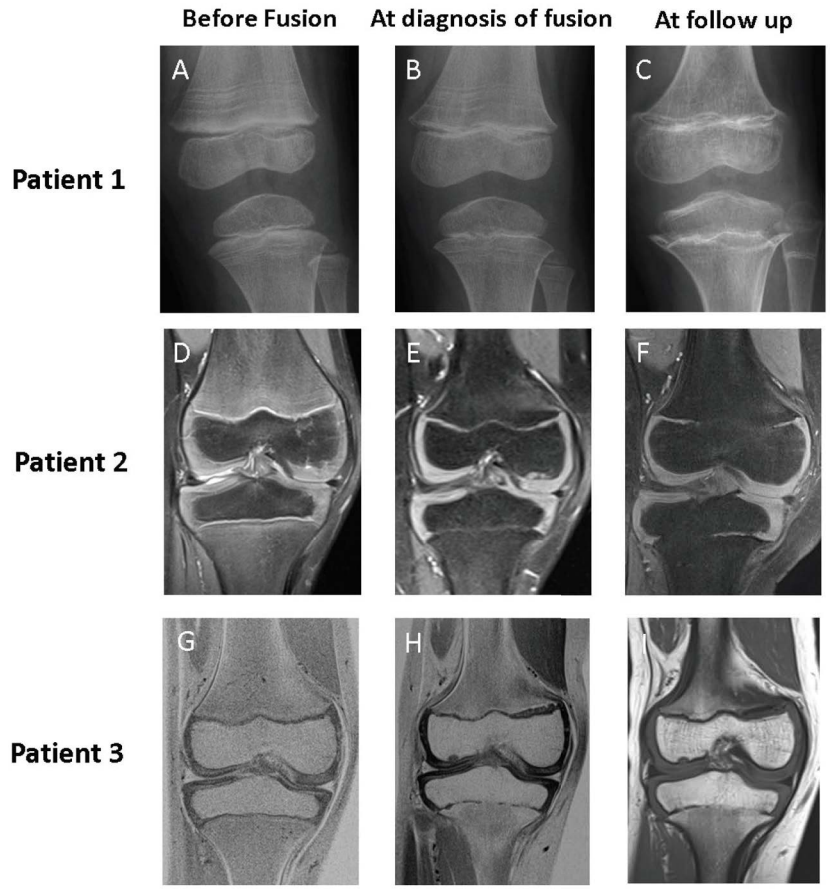


Hh pathway inhibition using SMO-inhibitors in young mice resulted in severe and permanent defects in bony growth plates (…*but not in 31 skeletally-immature children on PBTC studies*)

Inhibitor blocked proliferation of chondrocytes but promoted early differentiation and mineralization of growth plate once agent was withdrawn

Kimura et al. Cancer Cell. 2008;13:249-260

Then 3 patients present with growth plate fusions…



Characteristic	Patient 1	Patient 2	Patient 3
Gender	F	F	M
Reason for vismodegib	Relapse	SJMB12	SJMB12
At diagnosis			
Age - y	2.3	4.9	6.7
Height - SD (percentile)	-0.1(45%)	1.0(84%)	0.5(71%)
1 yr post dx			
Age - y	3.3	5.8	7.5
Height SD (percentile)	-0.4(35%)	0.2(58%)	0(48%)
At fusion			
Time on vismodegib – mo (cycles)	5 (5)	11(12)	11(12)
Age – y	3.5	6.6	8.2
Height SD (percentile)	-0.6(28%)	-0.2(40%)	-0.6(29%)
At 1st endocrine follow up			
Time off vismodegib – mo	19	10	0
Age – y	5.1	7.3	8.2
Height SD (percentile)	-1.8(3%)	-0.7(23%)	-0.6(29%)
At most recent endocrine follow up			
Time off vismodegib – mo	28	28	19
Age – y	5.8	8.8	9.8
Height SD (percentile)	-2.7(0%)	-1.4(7%)	-1.3(8%)

Robinson et al. Oncotarget. 2017 Sep 19; 8(41): 69295–69302

Why were bony defects not seen previously?

Time on drug/exposure was inadequate

- Mice are not human
  - Mice developed fusions after very short exposure (2-6 days)
  - Bone growth in mice is complete in 21 days
- # of children who received prolonged exposure on phase I/II was small
  - Median exposure was 56 days on PBTC studies
    - In 2014 (Kool et al. Cancer Cell) demonsrated that only subjects with mutations upstream of SMO would benefit from SMO inhibitors.
      - Estimated 52% of infants, 42% of children and 82% of adults
  - Most of those who had prolonged exposure were already skeletally mature
  - Relapse pool of children contained a high proportion of aggressive SHH that are non responsive to SMO inhibitors (i.e. TP53 mutants.)

- These findings resulted in a “boxed warning” for Vismodegib
- The SJMB12 study has been amended so Vismodegib is given only to skeletally mature subjects
- Efficacy evaluation is ongoing.

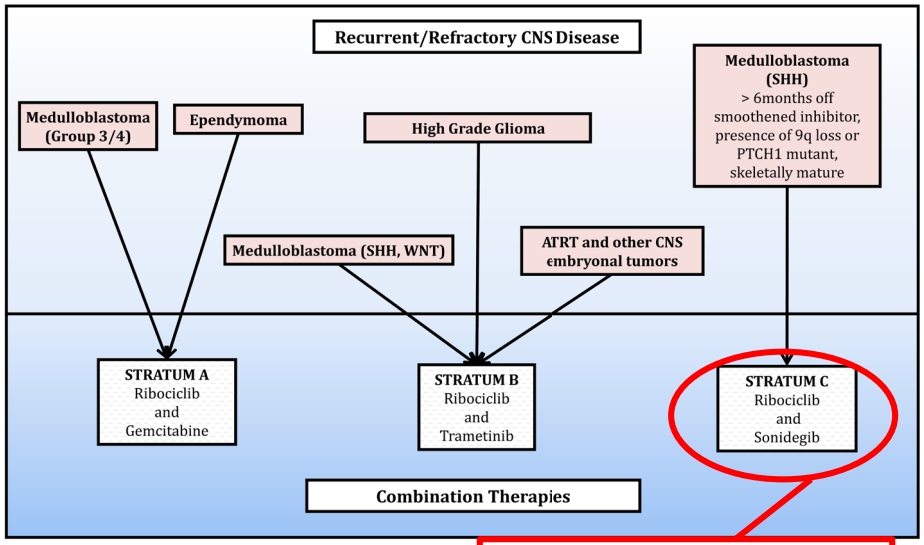
More Recent Clinical Trials in SHH Medulloblastoma…

PBTC-053 Phase I/II and Surgical Study of CX-4945 in Recurrent SHH Medulloblastoma (activated in 2019 and currently open to accrual)

- CK2 is a kinase critical for stabilization and activity of GLI2 and a promising therapeutic target in SHH medulloblastoma
- Preclinically CX-4945 inhibits both wild-type and mutant CK2, and may prevent or delay acquired resistance
- PBTC-053 is *stratified by skeletal maturity* rather than age and employs rigorous monitoring of bone toxicities in skeletally immature cohort

SJDAWN Phase I Basket Trial for Recurrent CNS tumors

- Phase 1: Opened to accrual 3/2018, accrual ongoing.
- Determine the safety, tolerability, dose, and preliminary efficacy of 3 novel combination therapies.
- Extensive molecular analyses are planned.



Pairs cell cycle inhibitor with SHH (SMO) inhibitor in SHH MB predicted to be sensitive to sonidegib.

“If you want a happy ending, that depends, of course, on where you end your story."

--*Orson Welles*

VIGNETTE 2: MEK INHIBITORS IN PEDIATRIC LOW GRADE GLIOMA

Pediatric Low Grade Glioma (pLGG)

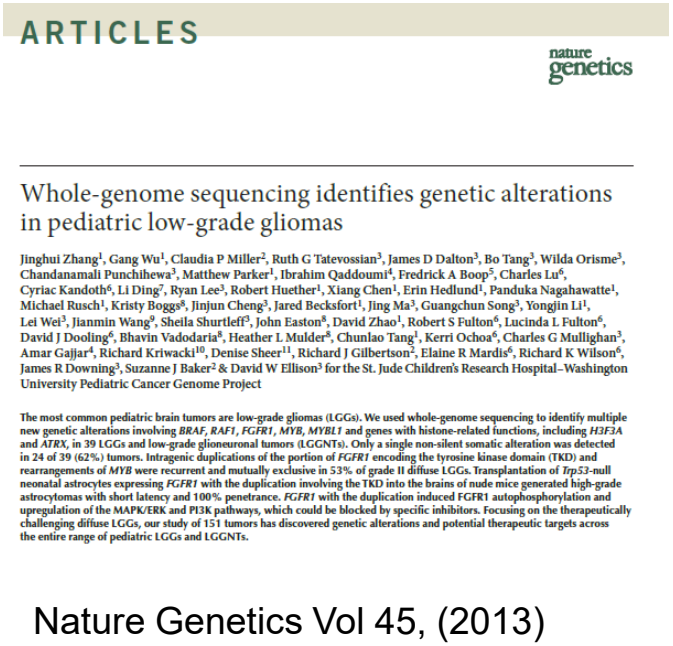
pLGG is the most common CNS tumor of childhood (~800 cases/year in the US).

Although overall survival is good, disease often recurs.

Mainstay of therapy is surgical resection (which can be curative)

For children whose tumors cannot be completely resected or whose tumors return, no universally accepted treatment exists however, standard cytotoxic chemotherapies are generally used. Radiation treatment is often reserved for older children.

The majority of pLGG are driven by a single genetic event resulting in up-regulation of the RAS/MAPK pathway.



ARTICLES

nature genetics

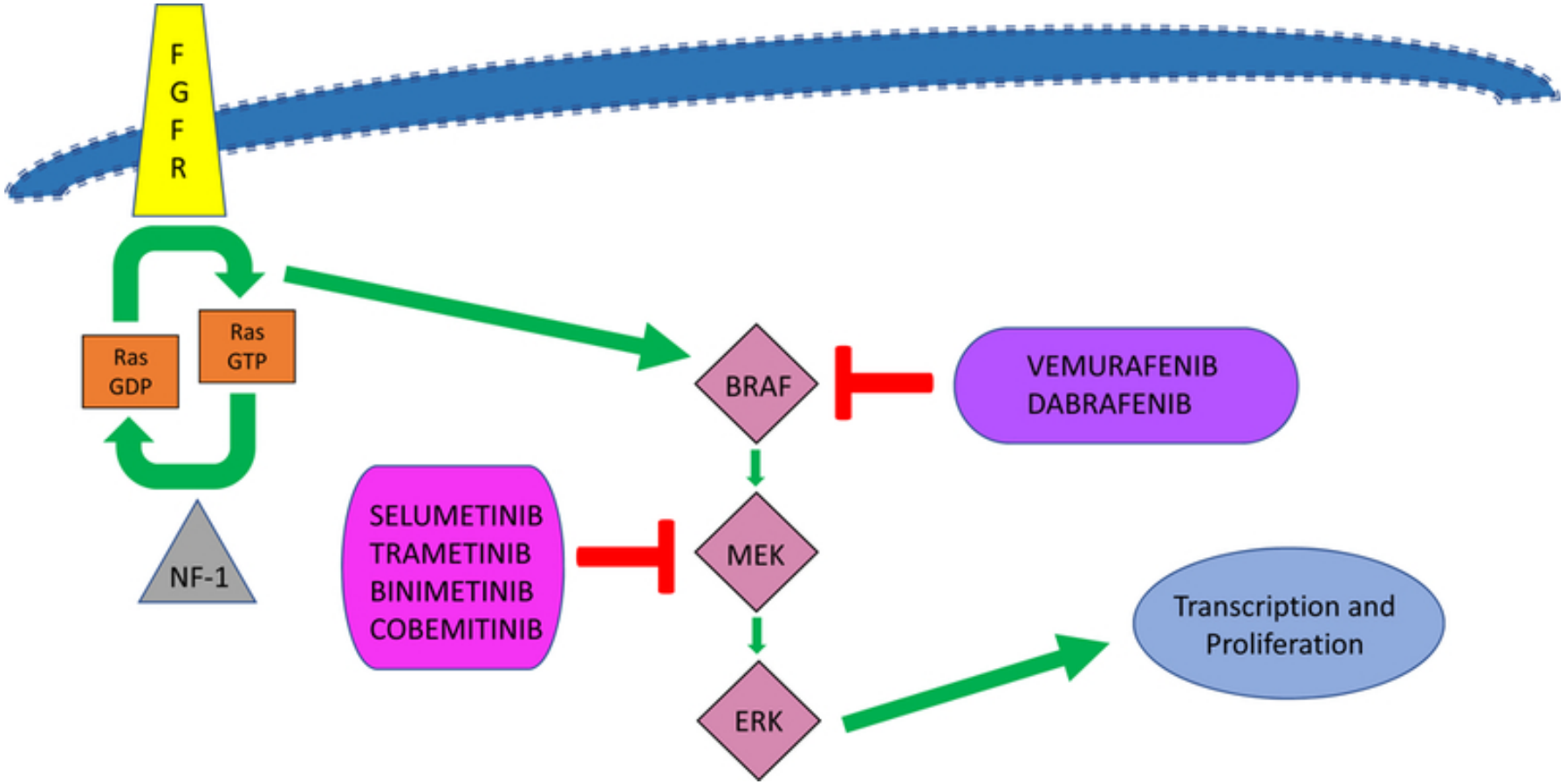
Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas

Jinghui Zhang[1], Gang Wu[1], Claudia P Miller[2], Ruth G Tatevossian[3], James D Dalton[3], Bo Tang[3], Wilda Orisme[3], Chandanamali Punchihewa[3], Matthew Parker[1], Ibrahim Qaddoumi[4], Fredrick A Boop[5], Charles Lu[6], Cyriac Kandoth[6], Li Ding[7], Ryan Lee[3], Robert Huether[1], Xiang Chen[1], Erin Hedlund[1], Panduka Nagahawatte[1], Michael Rusch[1], Kristy Boggs[8], Jinjun Cheng[3], Jared Becksfort[1], Jing Ma[3], Guangchun Song[3], Yongjin Li[1], Lei Wei[3], Jianmin Wang[9], Sheila Shurtleff[3], John Easton[8], David Zhao[1], Robert S Fulton[6], Lucinda L Fulton[6], David J Dooling[6], Bhavin Vadodaria[8], Heather L Mulder[8], Chunlao Tang[1], Kerri Ochoa[6], Charles G Mullighan[3], Amar Gajjar[4], Richard Kriwacki[10], Denise Sheer[11], Richard J Gilbertson[2], Elaine R Mardis[6], Richard K Wilson[6], James R Downing[3], Suzanne J Baker[2] & David W Ellison[3] for the St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project

The most common pediatric brain tumors are low-grade gliomas (LGGs). We used whole-genome sequencing to identify multiple new genetic alterations involving *BRAF*, *RAF1*, *FGFR1*, *MYB*, *MYBL1* and genes with histone-related functions, including *H3F3A* and *ATRX*, in 39 LGGs and low-grade glioneuronal tumors (LGGNTs). Only a single non-silent somatic alteration was detected in 24 of 39 (62%) tumors. Intragenic duplications of the portion of *FGFR1* encoding the tyrosine kinase domain (TKD) and rearrangements of *MYB* were recurrent and mutually exclusive in 53% of grade II diffuse LGGs. Transplantation of *Trp53*-null neonatal astrocytes expressing *FGFR1* with the duplication involving the TKD into the brains of nude mice generated high-grade astrocytomas with short latency and 100% penetrance. *FGFR1* with the duplication induced FGFR1 autophosphorylation and upregulation of the MAPK/ERK and PI3K pathways, which could be blocked by specific inhibitors. Focusing on the therapeutically challenging diffuse LGGs, our study of 151 tumors has discovered genetic alterations and potential therapeutic targets across the entire range of pediatric LGGs and LGGNTs.

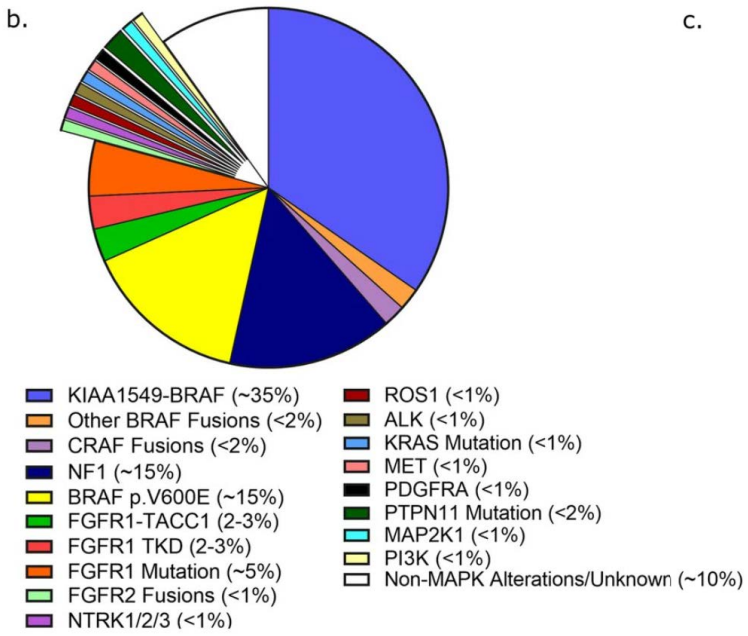
Nature Genetics Vol 45, (2013)

A simplified diagram of the MAP kinase pathway



De Blank et al, Curr Opin Pediatr. 2019 Feb; 31(1): 21–27.

The Molecular Landscape of pLGG



Ryall, Tabori and Hawkins, Acta Neuropathologica Communications vol. 8 (2020)

- BRAF is an oncogene and a part of the Ras/Raf/MAP kinase signaling cascade.
- Constitutive activation of BRAF leads to a increase in MAP kinase signaling which subsequently leads to cellular proliferation and oncogenesis.
- Neurofibromatosis Type I is the most common inheritable tumor predisposition syndrome
- The fact that 10-15% of children with NF1 develop a LGG within the optic pathway, and an additional 3-5% outside of the optic pathway provided the initial clues of RAS/MAPK involvement in pLGG pathogenesis

PBTC-029:

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Neuro Oncol. 2017 Aug; 19(8): 1135–1144.
Published online 2017 Feb 28. doi: 10.1093/neuonc/now282
PMCID: PMC5570236
PMID: 28339824

A phase I trial of the MEK inhibitor selumetinib (AZD6244) in pediatric patients with recurrent or refractory low-grade glioma: a Pediatric Brain Tumor Consortium (PBTC) study

Anuradha Banerjee,[1] Regina I. Jakacki,[1] Arzu Onar-Thomas,[1] Shengjie Wu,[1] Theodore Nicolaides,[1] Tina Young Poussaint,[1] Jason Fangusaro,[1] Joanna Phillips,[1] Arie Perry,[1] David Turner,[1] Michael Prados,[1] Roger J. Packer,[1] Ibrahim Qaddoumi,[1] Sridharan Gururangan,[1] Ian F. Pollack,[1] Stewart Goldman,[1] Lawrence A. Doyle,[1] Clinton F. Stewart,[1] James M. Boyett,[1] Larry E. Kun,[1] and Maryam Fouladi[1]

- PBTC-029: a multi-center Phase I pharmacokinetic trial to estimate MTD of Selumetinib in children with recurrent/progressive LGG.
- Dose escalation started at adult recommended phase II dose (RP2D), 33mg/m^2 BID and was not to exceed the adult MTD, 43mg/m^2.
- During 7/2010 and 3/2013 38 subjects were enrolled
  - Initially eligibility was restricted to >12 years who had already received RT due to concerns about secondary skin cancers observed in adults
    - Only 16 subjects were enrolled in the first 2 years
  - Following an amendment to expand eligibility to subjects ≤12 years and those without prior RT in 9/2012, we enrolled 22 additional patients in 6m.
- Using the CRM, the MTD/RP2D was determined to be 25mg/m^2, 1 dose level below the adult RP2D
  - DLTs were primarily rash, mucositis, headache *all in the >12 yr cohort*
  - No premalignant or malignant skin lesions

PBTC-029: Efficacy

Subjects received a median of 13 cycles (range: 1–26).

14/38 (37%) completed all protocol treatment with at least stable disease.

5/25 (20%) treated at the RP2D had a partial responses.

- 4 had BRAF aberrations, 1 had insufficient tissue

2-year progression-free survival at the RP2D was 69 ± 9.8%.

These data led to development of the Phase II study.

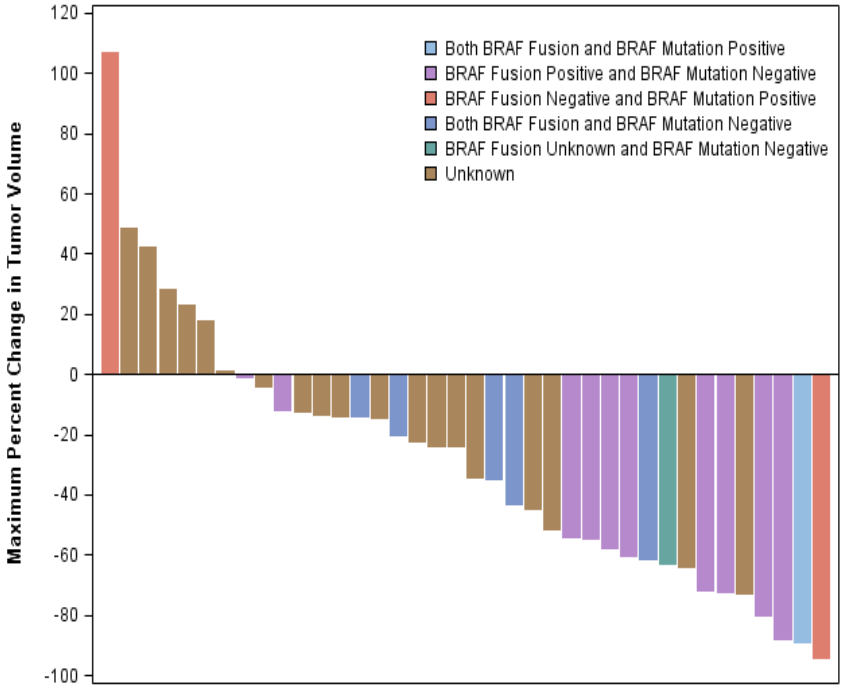


Figure 2a, Banerjee et al. Neurooncology 2017

PBTC-029B: Phase II Trial of Selumetinib in Recurrent pLGG

- Stratification by histology, NF-1 status, tumor location and absence/presence of 2 most common BRAF alterations (BRAF KIAA 1549 fusion and BRAF V600e mutation)
  - Stratum 1: BRAF+ Non-NF1 Pilocytic Astocytoma (PA)
  - Stratum 2: BRAF- Non-NF1 PA
  - Stratum 3: NF-1 Driven pLGG
  - Stratum 4: non-NF1 Optic Pathway Glioma (OPG)
  - Stratum 5: BRAF+ Non-NF1 pLGG except PA or OPG
  - Stratum 6: Subjects who failed molecular classification

- Identical but separate design for each stratum:
  - Objective response (PR or CR) rate observed and sustained for ≥8 weeks
  - Simon's Minimax design with response rates of 10% vs 30%
  - 25 patients/stratum with 10% type 1 error and 90% power.
  - An interim analysis after 16 patients: ≥2 responses to expand accrual
  - The final success threshold: ≥ 5 responses in 25 patients.

- **Current Status:** Total 138 subjects enrolled to date. All strata except 2 and 5 are complete.

Efficacy Results in Strata 1 and 3

Stratum 1: BRAF+ PA

9/25 (36%) with OR,

median time to OR=7.5m

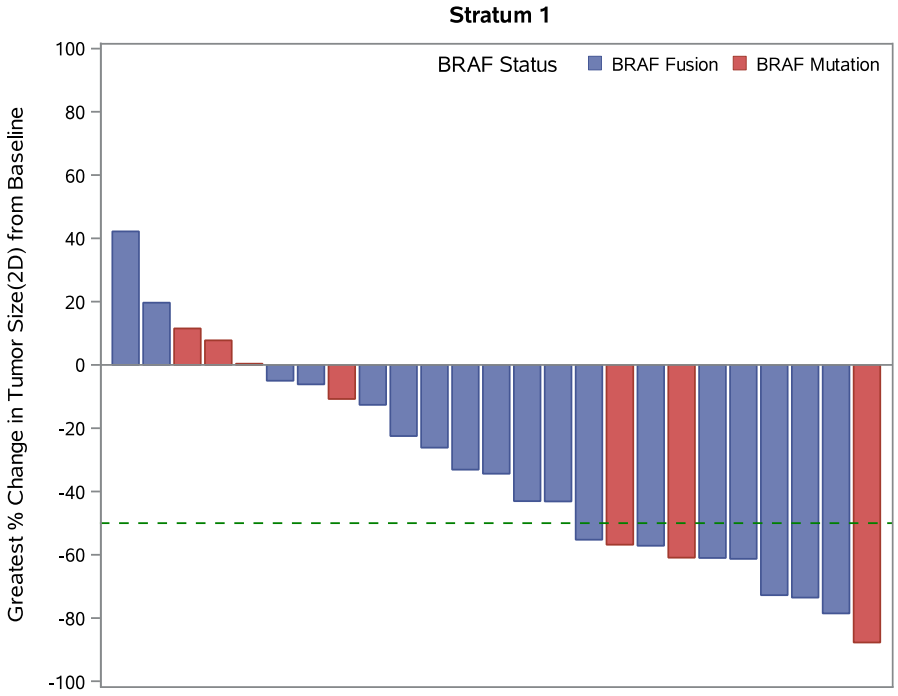
2-year PFS 70% (95% CI 47–85)

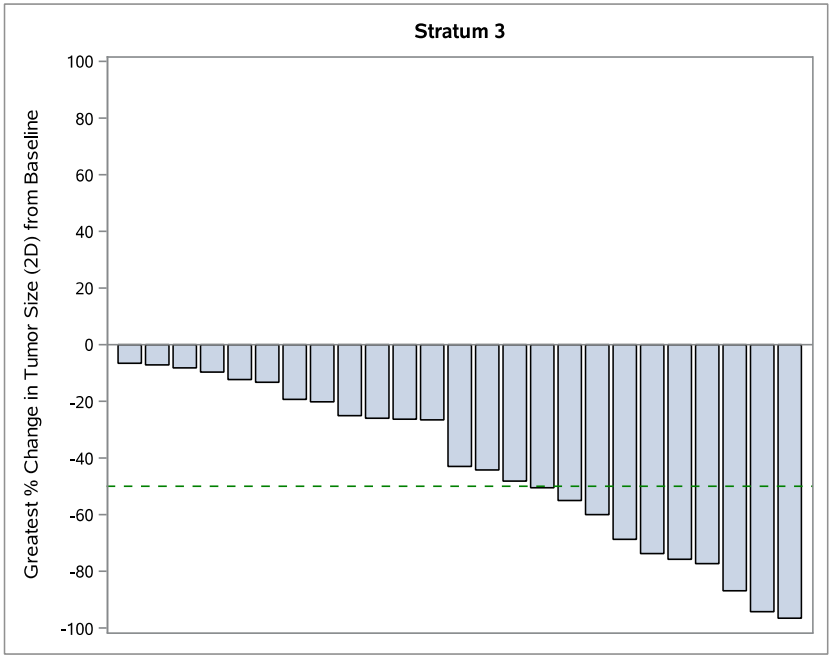
Stratum 3: NF-1 driven pLGG

10/25 (40%) w/ OR

median time to OR=3.5m

2-year PFS 96% (95% CI 74–99)





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Oncology
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Articles

Selumetinib in paediatric patients with *BRAF*-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial

Jason Fangusaro MD [a], Prof Arzu Onar-Thomas PhD [b], Prof Tina Young Poussaint MD [f], Shengjie Wu MS [b], Azra H Ligon PhD [g], Neal Lindeman MD [g], Anuradha Banerjee MD [h], Prof Roger J Packer MD [j], Lindsay B Kilburn MD [k], Prof Stewart Goldman MD [m], Prof Ian F Pollack MD [o], Ibrahim Qaddoumi MD [c], Regina I Jakacki MD [p], Prof Paul G Fisher MD [r], Girish Dhall MD [s], Patricia Baxter MD [u], Prof Susan G Kreissman MD [v], Prof Clinton F Stewart PharmD [d] ... Prof Maryam Fouladi MD [af, †]

asco special articles

Clinical Cancer Advances 2020: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology

Merry Jennifer Markham, MD[1]; Kerri Wachter, BS[2]; Neeraj Agarwal, MD[3]; Monica M. Bertagnolli, MD[4]; Susan Marina Chang, MD[5]; William Dale, MD, PhD[6]; Catherine S. M. Diefenbach, MD[7]; Carlos Rodriguez-Galindo, MD[8]; Daniel J. George, MD[9]; Timothy D. Gilligan, MD[10]; R. Donald Harvey, PharmD[11]; Melissa L. Johnson, MD[12]; Randall J. Kimple, MD, PhD[13]; Miriam A. Knoll, MD, DABR[14]; Noelle LoConte, MD[15]; Robert G. Maki, MD, PhD[16]; Jane Lowe Meisel, MD[11]; Jeffrey A. Meyerhardt, MD, MPH[16]; Nathan A. Pennell, MD, PhD[10]; Gabrielle B. Rocque, MD, MSPH[17]; Michael S. Sabel, MD[18]; Richard L. Schilsky, MD[2]; Bryan James Schneider, MD[18]; William D. Tap, MD[19]; Robert G. Uzzo, MD, MBA[20]; and Shannon Neville Westin, MD[21]

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

ACNS1831 (NF1) and ACNS1833 (non-NF1 LGG)

Two Randomized Phase III Noninferiority Studies to be conducted globally by the Children's Oncology Group

Primary Efficacy Objective:

- Demonstrate that the efficacy selumetinib as measured by PFS is non-inferior to treatment with Carboplatin+Vincristine.
- Carboplatin+Vincristine involves weekly clinic visits due to IV treatments

ACNS1831 additional primary functional outcome objective

- Demonstrate improvement in visual acuity.

Both Studies Opened at the end of 2019

Design:

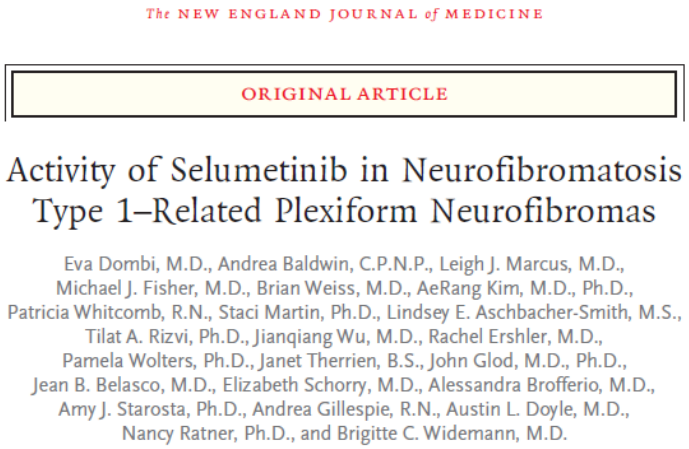
- 2:1 randomization in favor of selumetinib
- ACNS1831: N=240 patients enrolled in 4-5 years and followed for 2 additional years (59 events).
- ACNS1833: N=200 patients enrolled in 4-5 years and followed for 2 additional years (98 events).

NF1–Related Plexiform Neurofibromas

- Plexiform neurofibromas develop in 20 to 50% of people with NF-1
- They can cause substantial complications including pain, functional impairment, disfigurement, and malignant transformation.
- Most are diagnosed in early childhood and grow most rapidly during this period
- Two landmark Phase II single arm trials were conducted by the Pediatric Oncology Branch at the NCI with a primary endpoint of sustained response

Trial 1 (NEJM 2016):

Enrolled 9/11-2/14, N=24


The NEW ENGLAND JOURNAL of MEDICINE

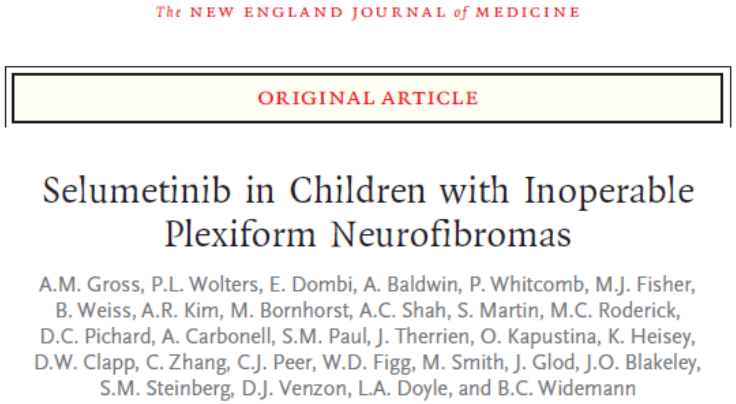
ORIGINAL ARTICLE

Activity of Selumetinib in Neurofibromatosis Type 1–Related Plexiform Neurofibromas

Eva Dombi, M.D., Andrea Baldwin, C.P.N.P., Leigh J. Marcus, M.D., Michael J. Fisher, M.D., Brian Weiss, M.D., AeRang Kim, M.D., Ph.D., Patricia Whitcomb, R.N., Staci Martin, Ph.D., Lindsey E. Aschbacher-Smith, M.S., Tilat A. Rizvi, Ph.D., Jianqiang Wu, M.D., Rachel Ershler, M.D., Pamela Wolters, Ph.D., Janet Therrien, B.S., John Glod, M.D., Ph.D., Jean B. Belasco, M.D., Elizabeth Schorry, M.D., Alessandra Brofferio, M.D., Amy J. Starosta, Ph.D., Andrea Gillespie, R.N., Austin L. Doyle, M.D., Nancy Ratner, Ph.D., and Brigitte C. Widemann, M.D.

Trial 2 (NEJM 2020):

Enrolled 8/15-8/16, N=50; included extensive functional assessments


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Selumetinib in Children with Inoperable Plexiform Neurofibromas

A.M. Gross, P.L. Wolters, E. Dombi, A. Baldwin, P. Whitcomb, M.J. Fisher, B. Weiss, A.R. Kim, M. Bornhorst, A.C. Shah, S. Martin, M.C. Roderick, D.C. Pichard, A. Carbonell, S.M. Paul, J. Therrien, O. Kapustina, K. Heisey, D.W. Clapp, C. Zhang, C.J. Peer, W.D. Figg, M. Smith, J. Glod, J.O. Blakeley, S.M. Steinberg, D.J. Venzon, L.A. Doyle, and B.C. Widemann

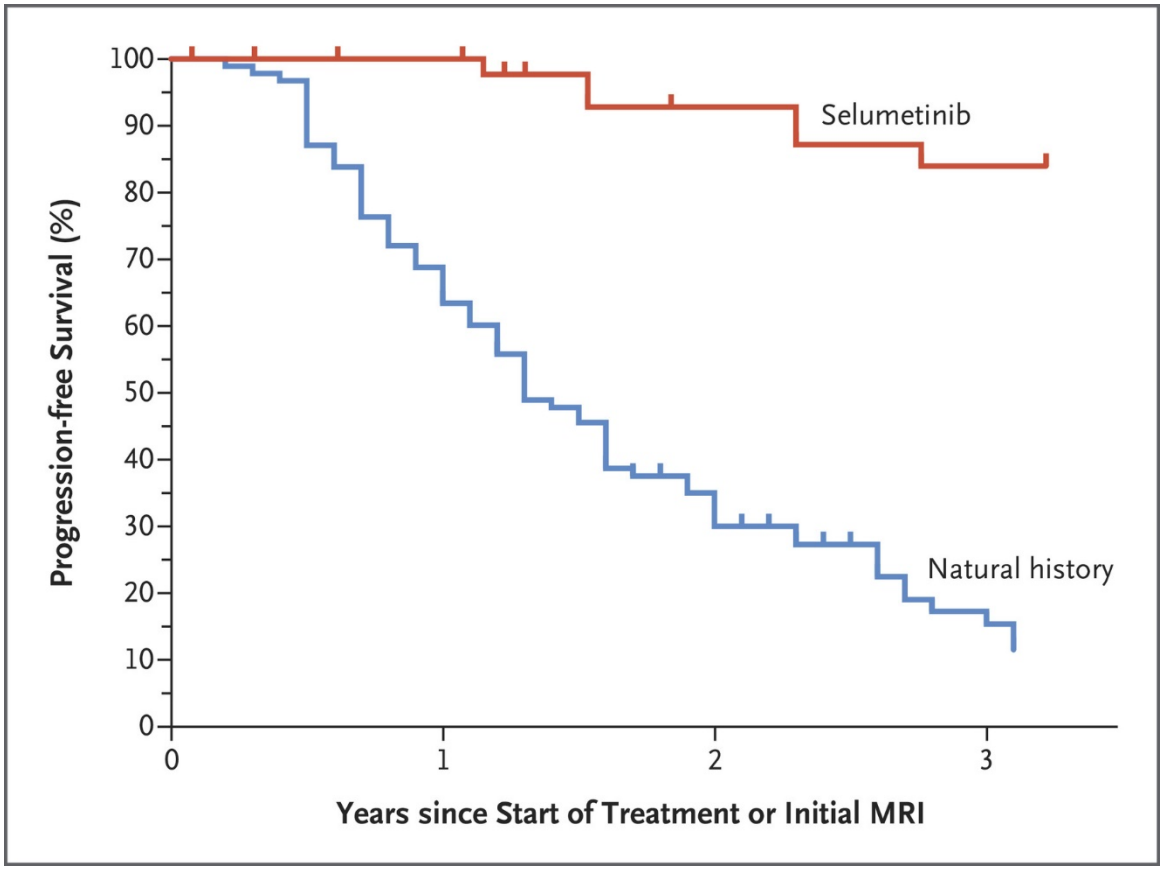


Figure 1. Target Plexiform Neurofibroma Progression–free Survival during Selumetinib Treatment as Compared with Natural History of Neurofibromatosis Type 1.

At 3 years of follow-up, the progression-free survival was 15% in the natural history group and 84% in the selumetinib group.

FDA NEWS RELEASE

FDA Approves First Therapy for Children with Debilitating and Disfiguring Rare Disease

For Immediate Release: April 10, 2020

Today, the U.S. Food and Drug Administration approved Koselugo (selumetinib) for the treatment of pediatric patients, 2 years of age and older, with neurofibromatosis type 1 (NF1), a genetic disorder of the nervous system causing tumors to grow on nerves. Koselugo is the first drug approved by the FDA to treat this debilitating, progressive and often disfiguring rare disease that typically begins early in life.

In the era of precision medicine, we must continue to remember that:

- Kids are not small adults
- Large pediatric efficacy studies in molecularly selected groups will likely require a global effort
- A flexible regulatory environment and continuation of financial incentives for drug companies are needed to ensure that new agents are tested in children
- It takes a (global) village…

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- PBTC Investigators

COG
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- Statistics and Data Center
- CNS Committee

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CHILDREN'S ONCOLOGY GROUP
The world's childhood cancer experts

NIH NATIONAL CANCER INSTITUTE

Patients and Families

Questions…