



Istituto Giannina Gaslini
Ospedale Pediatrico IRCCS

LABORATORIO NEUROGENETICA E NEUROSCIENZE

U.O.S.D. NEURO-ONCOLOGIA

Alessandro Raso, Samantha Mascelli



Voghera, 21/04/2018

Laboratorio ricerca tumori cerebrali

**DIPARTIMENTO TESTA-COLLO E
NEUROSCIENZE**

U.O.C. NEUROCHIRURGIA

U.O.S.D. NEURO-ONCOLOGIA



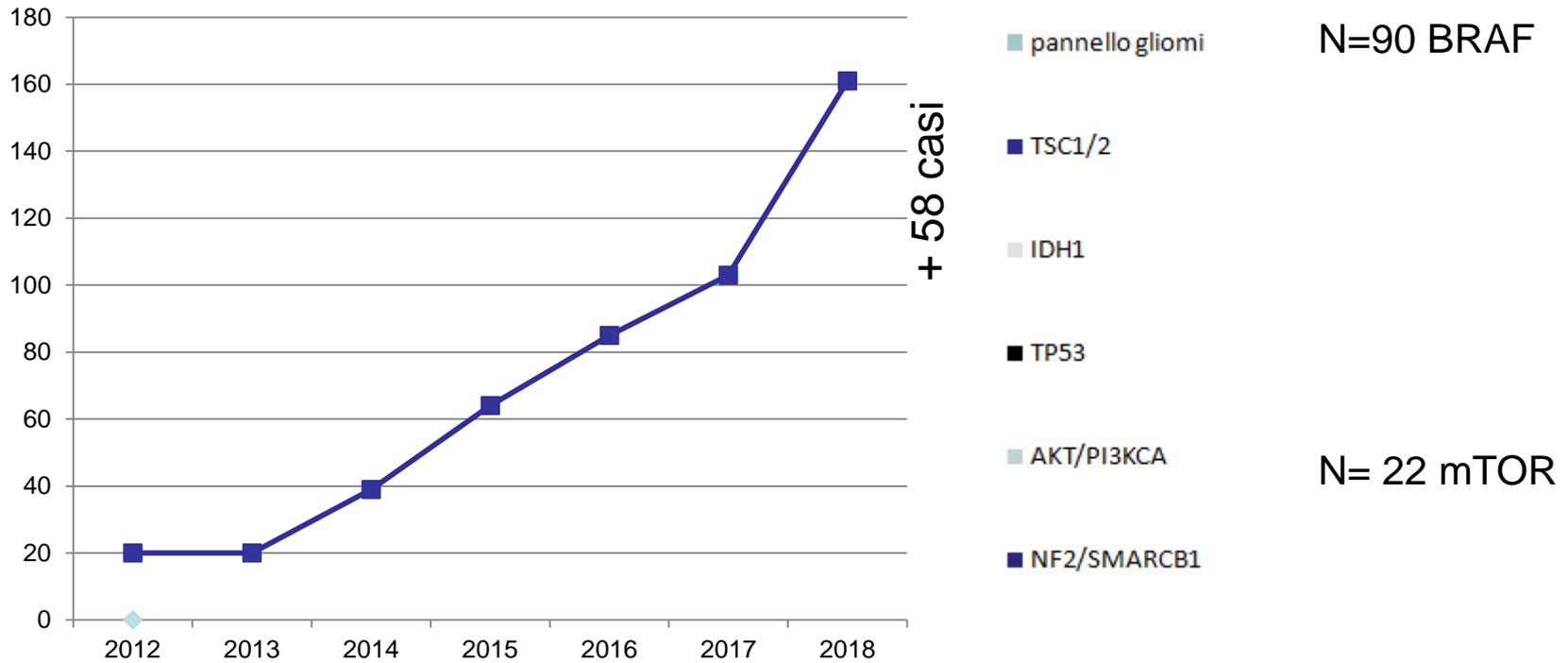
Area Aggregazione – Laboratori di Ricerca

U.O.S.D. di Neurogenetica e Neuroscienze

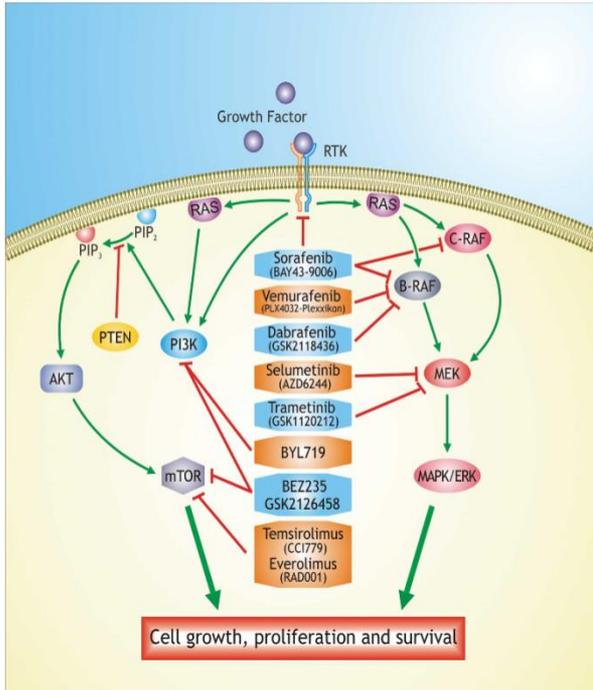
U.O.S.D. NEURO-ONCOLOGIA

U.O.C. NEUROCHIRURGIA

Diagnostica molecolare neuro-oncologica dal 2012-2018



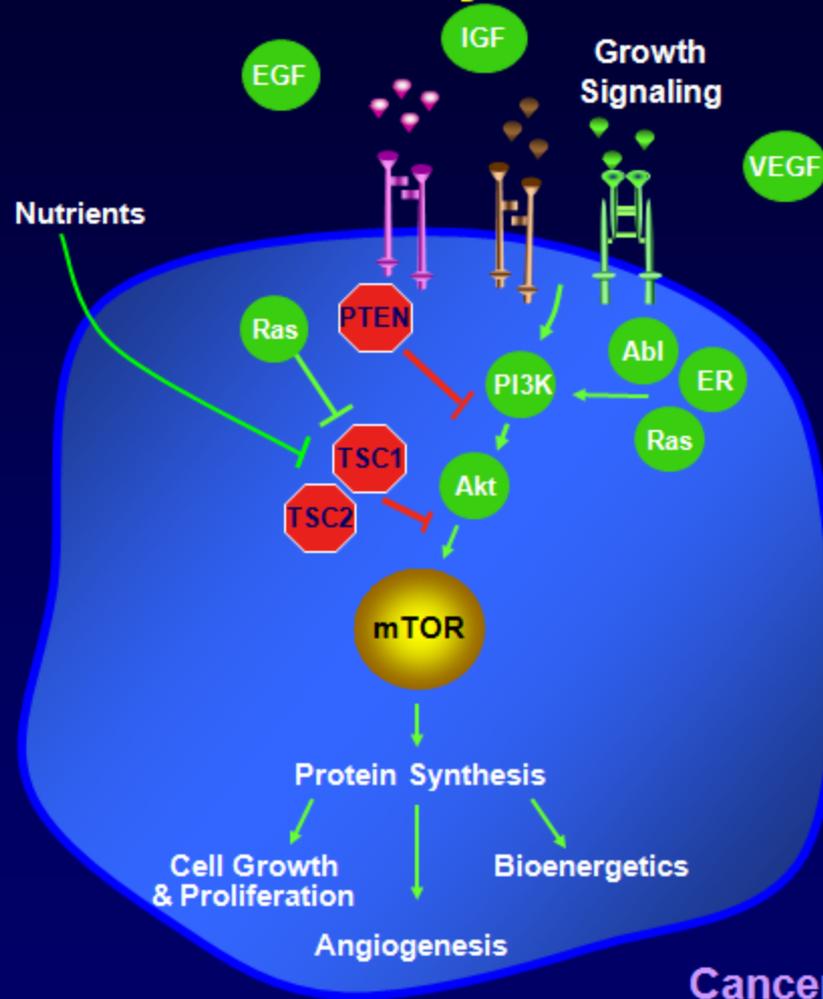
TEST Farmacogenomica



MAPK/AKT inhibitors and their targets.

Drug	Target	Pathway
Sorafenib (BAY43-9006)	B-RAF, C-RAF, VEGF-R, PDGF-R	Ras/Raf/MEK/ERK
Vemurafenib (PLX-4032)	B-RAF(v600E, v600K)	
Dabrafenib (GSK 2118436)	B-RAF(v600E, v600K)	
Trametinib (GSK1120212)	MEK1/2	
Selumetinib (AZD6244)	MEK1/2	
BEZ235	PI3K-mTOR	PI3K/AKT/mTOR
GSK2126458	PI3K-mTOR	
BYL719	PI3K	
CCI-779 (Temoirrolimus)	mTORC1	
RAD001 (Everolimus)	mTORC1	
Ipilimumab	Anti-CTLA-4	CTLA-4 receptor

mTOR Pathway is Deregulated by Mutations in Cancer



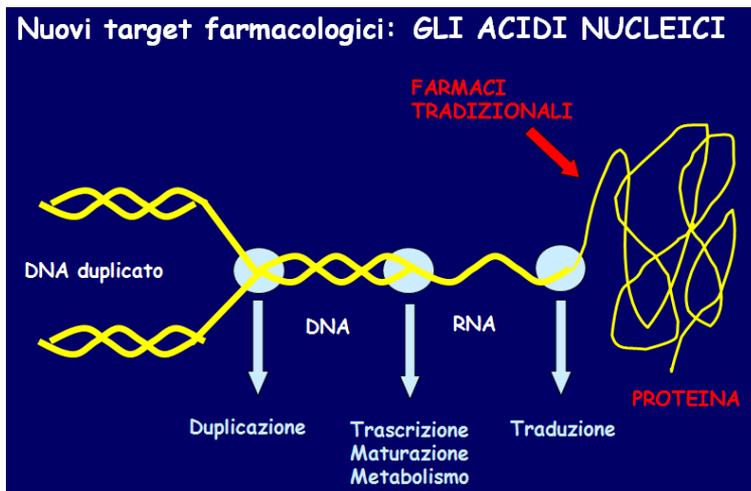
- Normal cell growth, proliferation, and metabolism are maintained by a number of mTOR regulators^{1,2}
- Regulators of mTOR activity
 - mTOR activating
 - mTOR deactivating
- Deregulation of mTOR can result in loss of growth control and metabolism^{1,3}
- Mutations in the mTOR pathway have been linked to specific cancers⁴

Cancer Cell

MODULAZIONE DELL'ESPRESSIONE GENICA MEDIANTE RNA NON CODIFICANTI: STRATEGIA MOLECOLARE INNOVATIVA PER IL TRATTAMENTO DELLA SCLEROSI TUBEROSA

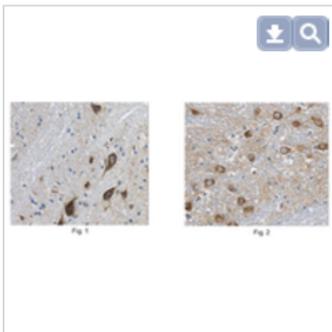
La sclerosi tuberosa (TSC) è una malattia genetica multi-sistemica caratterizzata da lesioni benigne circoscritte che possono colpire diversi organi ed in particolare l'encefalo. Inoltre, circa la metà dei casi manifesta un'epilessia difficile da controllare e una importante disabilità intellettiva. La patologia a trasmissione autosomica dominante è causata, nel 75-90% dei pazienti, da mutazioni a carico dei geni onco-soppressori *TSC1* e *TSC2*, codificanti un complesso, detto “amartina-tuberina”, ad azione inibitoria sulla via di segnale del complesso 1 di mTOR (TORC1) [1]. L'attività di questo complesso cellulare è fondamentale per la regolare crescita e l'omeostasi cellulare ed è implicato in numerose condizioni patologiche [2].

Il progetto prevede di sviluppare molecole di RNA non codificante dette SINEUP in grado di incrementare selettivamente l'attività residuale degli alleli *wild-type* (wt) di *TSC1* e *TSC2* per sopperire alla perdita di funzione dovuta all'allele mutante. Questo recupero di funzione delle proteine TSC1 e TSC2 è attesa riportare a livelli fisiologici di attivazione il complesso di mTORC1.



“SNAT1 is involved in (18) F-DOPA uptake in malignant gliomas.”

MABN502 | Anti-SNAT1 Antibody, clone N104/37



Detect Sodium-coupled neutral amino acid transporter 1 using this mouse monoclonal antibody, Anti-SNAT1 Antibody, clone N104/37 validated for use in western blotting & IHC.

- [MSDS](#)
- [Cert. d'Analisi](#)

UniProt Number: [Q9JM15](#) Gene Symbol: [Slc38a1](#), [Ata1](#), [GlnT](#), [Sa2](#), [Sat1](#), [Snat1](#) Research Sub-Category: [Developmental Signaling](#)
Research Category: [Neuroscience](#)



MABN502

100 µg

EUR 316.00

[La preghiamo di effettuare il log-in per visualizzare le condizioni economiche a Lei riservate.](#)

Disponibilità limitata 🚫

[Offerte speciali](#)

Quantità:

[Aggiungi al carrello](#)

[Aggiungi ai preferiti](#)

Publicazioni del 2017

Catanzaro G, Besharat ZM, Miele E, Chiacchiarini M, Po A, Carai A, Marras CE, Antonelli M, Badiali M, **Raso A, Mascelli S**, Schrimpf D, Stichel D, Tartaglia M, Capper D, von Deimling A, Giangaspero F, Mastronuzzi A, Locatelli F, Ferretti E. "[The miR-139-5p regulates proliferation of supratentorial paediatric low-grade gliomas by targeting the PI3K/AKT/mTORC1 signalling](#)". Neuropathol Appl Neurobiol. 2018 Feb 25. doi: 10.1111/nan.12479. [Epub ahead of print]

Morana G, Alves CA, Tortora D, Severino M, Nozza P, Cama A, Ravegnani M, D'Apolito G, **Raso A**, Milanaccio C, da Costa Leite C, Garrè ML, Rossi A "[Added value of diffusion weighted imaging in pediatric central nervous system embryonal tumors surveillance](#)". Oncotarget. 2017 Jul 25;8(36):60401-60413. doi: 10.18632/oncotarget.19553. eCollection 2017 Sep 1.

Morana G, Tortora D, Staglianò S, Nozza P, **Mascelli S**, Severino M, Piatelli G, Consales A, Lequin M, Garrè ML, Rossi A. "[Pediatric astrocytic tumor grading: comparison between arterial spin labeling and dynamic susceptibility contrast MRI perfusion](#)". Neuroradiology. 2018 Apr;60(4):437-446. doi: 10.1007/s00234-018-1992-6. Epub 2018 Feb 16.

Morana G, Piccardo A, Tortora D, Puntoni M, Severino M, Nozza P, Ravegnani M, Consales A, **Mascelli S, Raso A**, Cabria M, Verrico A, Milanaccio C, Rossi A. "[Grading and outcome prediction of pediatric diffuse astrocytic tumors with diffusion and arterial spin labeling perfusion MRI in comparison with 18F-DOPA PET](#)". Eur J Nucl Med Mol Imaging. 2017 Nov;44(12):2084-2093. doi: 10.1007/s00259-017-3777-2. Epub 2017 Jul 27.

Lassaletta A, Zapotocky M, Mistry M, Ramaswamy V, Honnorat M, Krishnatry R, Guerreiro Stucklin A, Zhukova N, Arnoldo A, Ryall S, Ling C, McKeown T, Loukides J, Cruz O, de Torres C, Ho CY, Packer RJ, Tatevossian R, Qaddoumi I, Harreld JH, Dalton JD, Mulcahy-Levy J, Foreman N, Karajannis MA, Wang S, Snuderl M, Nageswara Rao A, Giannini C, Kieran M, Ligon KL, Garre ML, Nozza P, **Mascelli S, Raso A**, Mueller S, Nicolaidis T, Silva K, Perbet R, Vasiljevic A, Faure Conter C, Frappaz D, Leary S, Crane C, Chan A, Ng HK, Shi ZF, Mao Y, Finch E, Eisenstat D, Wilson B, Carret AS, Hauser P, Sumerauer D, Krskova L, Larouche V, Fleming A, Zelcer S, Jabado N, Rutka JT, Dirks P, Taylor MD, Chen S, Bartels U, Huang A, Ellison DW, Bouffet E, Hawkins C, Tabori U. "[Therapeutic and Prognostic Implications of BRAF V600E in Pediatric Low-Grade Gliomas](#)". J Clin Oncol. 2017 Sep 1;35(25):2934-2941. doi: 10.1200/JCO.2016.71.8726. Epub 2017 Jul 20.

Therapeutic and Prognostic Implications of BRAF V600E in Pediatric Low-Grade Gliomas

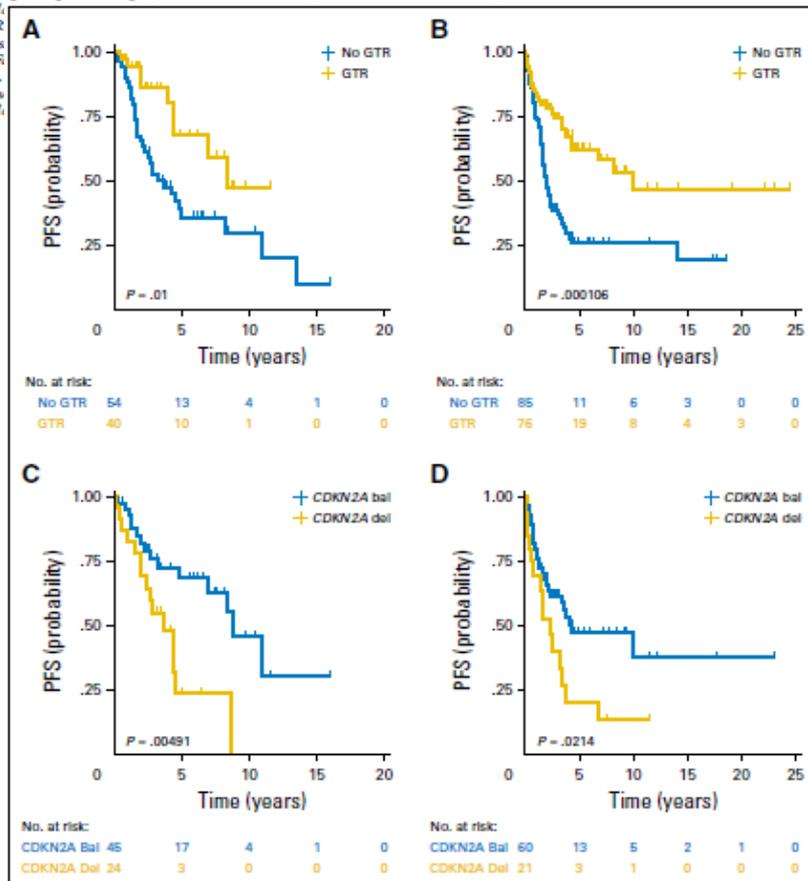
Alvaro Lassaletta, Michal Zapotocky, Matthew Mistry, Vijay Ramaswamy, Marion Honnorat, Rahul Krishnatry, Ana Guerreiro Stucklin, Nataliya Zhukova, Anthony Arnoldo, Scott Ryall, Catriona Ling, Tara McKown, Jim Loukides, Ofelia Cruz, Carmen de Torres, Cheng-Ying Ho, Roger J. Packer, Ruth Tatevosian, Ibrahim Qaddoumi,

Jean Mul-
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l D, Taty-
Tabori

Table 1. Patient and Tumor Characteristics in the SickKids Cohort (patients from 2000 to 2015)

Characteristic	All Patients (N = 405)	WT (n = 336; 83%)	V600E Mutant (n = 69; 17%)
Sex, %			
Male/female	50.6/49.4	51.2/48.8	47.8/52.2
Age, years			
Median	8.52	8.08	11.1
Range	0-18.28	0.52-18.28	0-17.46
25th/75th quartile	4.34/12.55	4.05/12.02	6.5/14.32
Location, No. (%)			
Hemispheric	157 (100)	114 (72.6)	43 (27.4)
Diencephalic	74 (100)	61 (82.4)	13 (17.6)
Brainstem	39 (100)	33 (84.6)	6 (15.4)
Cerebellum	112 (100)	108 (96.4)	4 (3.6)
Spine	15 (100)	12 (80)	3 (20)
Disseminated	8 (100)	8 (100)	0 (0)
Pathology, No. (%)			
Pilocytic astrocytoma	167 (100)	162 (97)	5 (3)
Piloxyoid astrocytoma	15 (100)	13 (86.7)	2 (13.3)
Ganglioglioma	51 (100)	26 (51)	25 (49)
PXA	9 (100)	2 (22.2)	7 (77.8)
Diffuse astrocytoma	23 (100)	13 (56.5)	10 (43.5)
LGG NOS	70 (100)	56 (80)	14 (20)
Others	70 (100)	64 (91.4)	6 (8.6)

Abbreviations: LGG NOS, low-grade glioma not otherwise specified; PXA, pleomorphic xanthoastrocytoma, WT, wild type.



I gliomi pediatrici low-grade con mutazione in *BRAFV600E* e *CDKN2A* costituiscono un'entità peculiare a prognosi più sfavorevole quando trattati con chemioterapia convenzionale.

Added value of diffusion weighted imaging in pediatric central nervous system embryonal tumors surveillance

Giovanni Morana^{1,*}, Cesar Augusto Alves^{1,2,*}, Domenico Tortora¹, Mariasavina Severino¹, Paolo Nozza³, Armando Cama⁴, Marcello Ravegnani⁴, Gabriella D'Apollito⁵, Alessandro Raso⁴, Claudia Milanaccio⁶, Claudia da Costa Leite², Maria Luisa Garrè⁶ and Andrea Rossi¹

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-017-3777-2



ORIGINAL ARTICLE

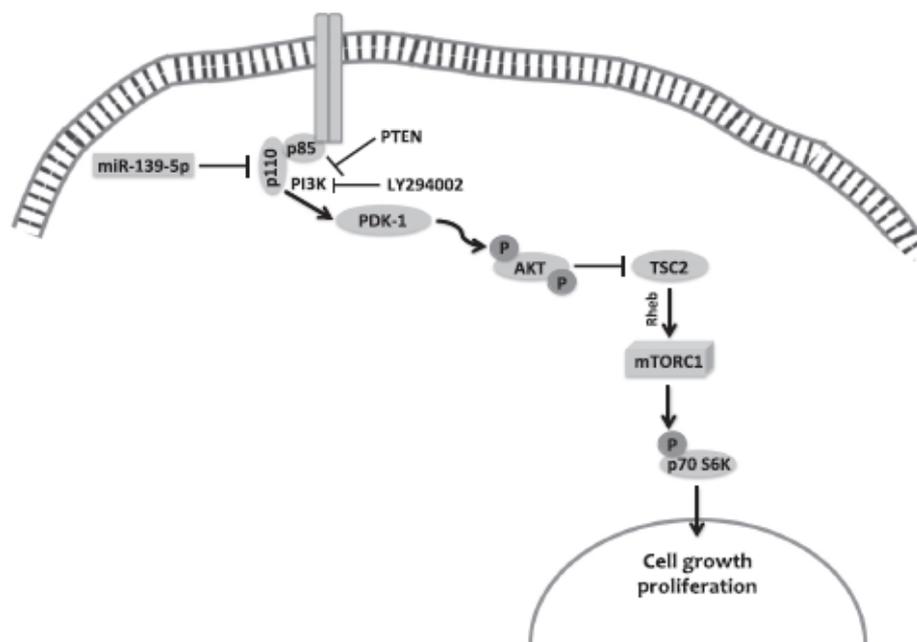
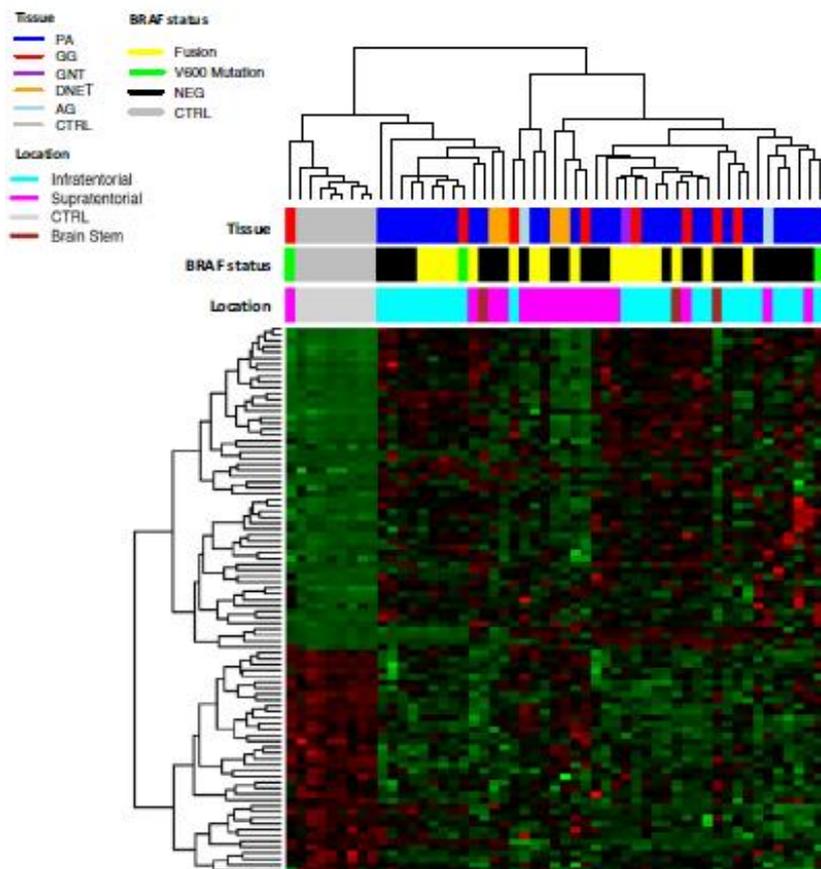
Grading and outcome prediction of pediatric diffuse astrocytic tumors with diffusion and arterial spin labeling perfusion MRI in comparison with 18F-DOPA PET

Giovanni Morana¹  · Arnoldo Piccardo² · Domenico Tortora¹ · Matteo Puntoni³ · Mariasavina Severino¹ · Paolo Nozza⁴ · Marcello Ravegnani⁵ · Alessandro Consales⁵ · Samantha Mascelli⁵ · Alessandro Raso⁵ · Manlio Cabria² · Antonio Verrico⁶ · Claudia Milanaccio⁶ · Andrea Rossi¹

Le tecniche MRI combinate di DWI e PET forniscono un maggior potere predittivo nell'evidenziare la progressione tumorale suggerendo un ruolo sinergico di queste metodiche

The miR-139-5p regulates proliferation of supratentorial paediatric low-grade gliomas by targeting the PI3K/AKT/mTORC1 signalling

G. Catanzaro*, Z. M. Besharatt, E. Miele‡, M. Chiacchiarini†, A. Pot, A. Carai§, C. E. Marras§, M. Antonelli¶, M. Badiali**, A. Rasotti, S. Mascelli††, D. Schimpf††,§§, D. Stichel§§, M. Tartaglia¶¶, D. Capper††,§§,***, A. von Deimling††,§§, F. Giangaspero¶,†††, A. Mastronuzzi†††, F. Locatelli†††,§§§ and E. Ferretti*,††† 



La regolazione del miR-139-5p nei LGG sopratentoriali guida la proliferazione cellulare attraverso il controllo del segnale di PI3K/AKT

ANALISI DI BRAFV600E

La mutazione di BRAFV600E che è stata osservata in un'ampia varietà di neoplasie dell'adulto e del bambino, è presente solamente in una piccola percentuale del LGGs pediatrici.

Essa altera il *pathway* della MAPK e costituisce un target terapeutico (**Vemurafenib**)

83 casi di LGG analizzati a livello diagnostico dal 2012, di cui l' 10% ha riportato la mutazione V600E.

3 casi mutati trattati con Vemurafenib

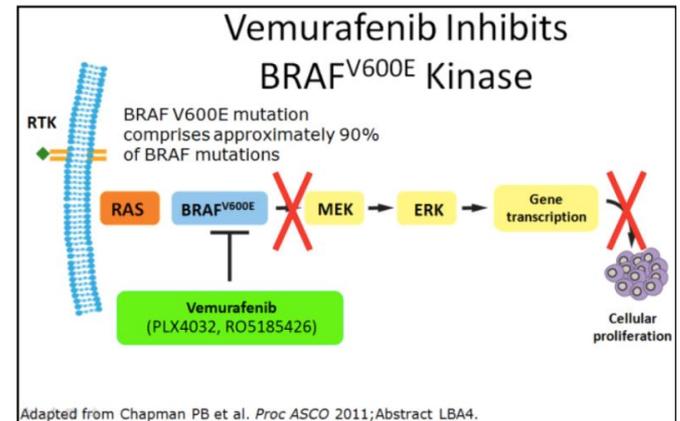
VOLUME 35 • NUMBER 25 • SEPTEMBER 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Therapeutic and Prognostic Implications of BRAF V600E in Pediatric Low-Grade Gliomas

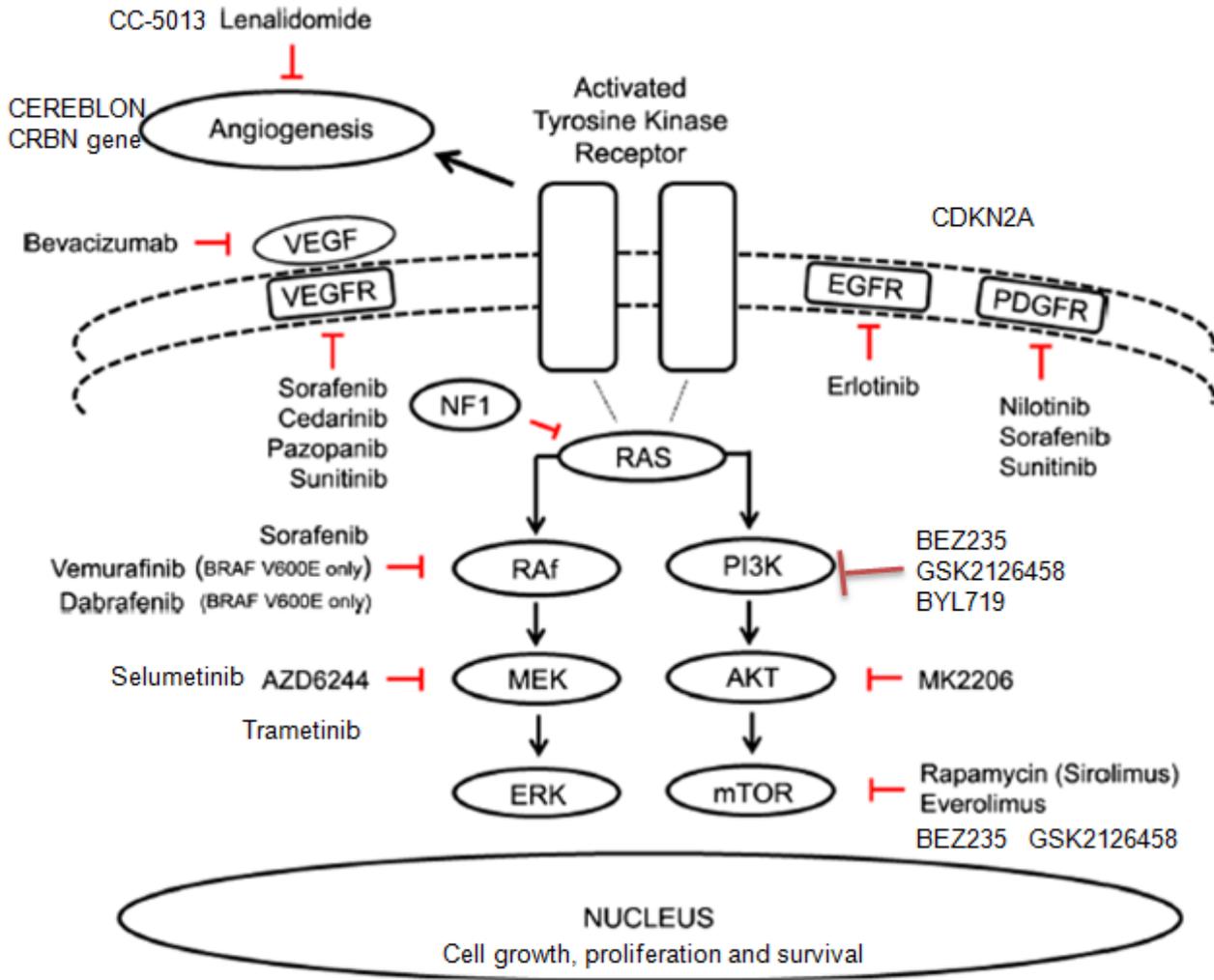
Alvaro Lassaletta, Michal Zapotocky, Matthew Mistry, Vijay Ramaswamy, Marion Honnorat, Rahul Krishnatry, Ana Guerreiro Stacklin, Nataliya Zhukava, Anthony Arnoldo, Scott Ryall, Catriona Ling, Tara McKee, Jim Loukides, Ojelia Cruz, Carmen de Torres, Cheng-Ying Ho, Roger J. Packer, Ruth Tatevosian, Ibrahim Qaddoumi, Julie H. Harrel, James D. Dalton, Jean Mulcahy-Levy, Nicholas Foreman, Matthias A. Karajannis, Shiyang Wang, Matija Smuderl, Amulya Nageswara Rao, Caterina Giannini, Mark Kieran, Keith L. Ligon, Maria Luisa Garre, Paolo Nozza, Samantha Mascelli, Alessandro Raso, Sabine Mueller, Theodore Nicolaides, Karen Silva, Romain Perbet, Alexandre Vasiljev, Cecile Faure Conter, Didier Fraipanz, Sarah Leary, Courtney Crane, Aiden Chan, Ho-Kwang Ng, Zhi-Feng Shi, Ying Mao, Elizabeth Finch, David Eisenstat, Rev Wilson, Anne Sophie Carret, Peter Hauser, David Sumerauer, Lenka Krskova, Valerie Larouche, Adam Fleming, Shayna Zeker, Nada Jabado, James T. Rutka, Peter Dirks, Michael D. Taylor, Shiyi Chen, Ute Bartels, Annie Huang, David W. Ellison, Eric Bouffet, Cynthia Hawkins, and Uri Tabori



In corso una pubblicazione in collaborazione con Sick.Children H (Toronto) sugli effetti a lungo termine degli inibitori di *BRAF* nel controllo della malattia

- Urgente necessità di eseguire studi clinici su ogni nuovo farmaco sperimentale per una conoscenza più dettagliata del meccanismo di azione delle molecole.
- Offrire nuove possibilità terapeutiche personalizzate ai pazienti.
- Ridurre la neurotossicità farmacologica.

New drugs in trial



Geni discriminanti gliomi diffusi da gliomi circoscritti e con farmaci disponibili o in fase di trial:

- CDKN2A
- VGFR1
- VGFR2
- PDGFRA
- EGFR
- MEK1
- MEK2
- ATRX
- KRAS
- TERT

- Pannello BRAF
- Pannello mTOR
- Pannello AKT/PI3K

GENI DI RESISTENZA ALLE TERAPIE:

- MLH1, MSH2, MSH3, MSH6, PMS2
- AKT/MTOR
- TP53, PTEN, EGFR, NF1, RB1, PIK3CA, PIK3R1, IDH1

STUDI DI FASE II

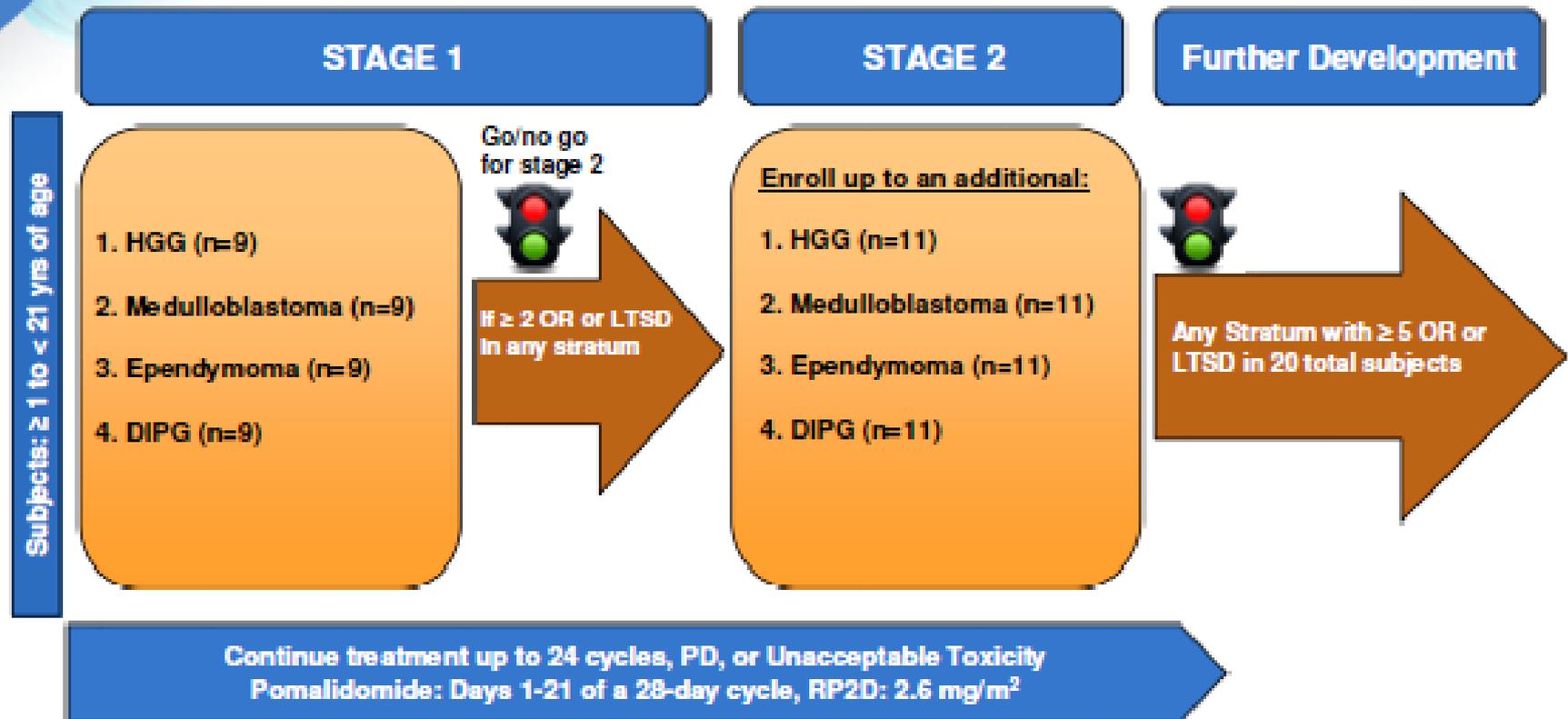
- CC-4047-BRN-001: A PHASE 2 CLINICAL STUDY OF POMALIDOMIDE (CC-4047) MONOTHERAPY FOR CHILDREN AND YOUNG ADULTS WITH RECURRENT OR PROGRESSIVE PRIMARY BRAIN TUMORS

Celgene

Introduction to Celgene and Pomalidomide Overview

Bouchra Benettaib, MD
Executive Medical Director , R&D

Study Design: Simon's Optimal 2-Stage



HGG: High-grade glioma

DIPG: Diffused Intrinsic Pontine Glioma

OR: Objective Response (CR or PR)

LTSD: Long Term Stable Disease (SD ≥ 6 cycles; SD ≥ 3 cycles for DIPG only)

- Up to 80 subjects (Stage 1: 36 subjects, Stage 2: 44 subjects)

CC-4047-BRN-001: Pomalidomide

CC-4047-BRN-001: A PHASE 2 CLINICAL STUDY OF POMALIDOMIDE (CC-4047) MONOTHERAPY FOR CHILDREN AND YOUNG ADULTS WITH RECURRENT OR PROGRESSIVE PRIMARY BRAIN TUMORS

POMALIDOMIDE is an immunomodulatory antineoplastic agent (2.6 mg/m² die)

1. HGG (n=9)
2. Medulloblastoma (n=9)
3. Ependymoma (n=9)
4. DIPG (n=9)

Centro	pazienti screenati	pazienti trattati
Ospedale " Bambino Gesù" Roma	6	6
S.C Pediatria Oncologica Milano	2	2
U.O Emato-Oncologia Pediatrica Genova	7	7



DRB436G2201

STUDIO DI FASE II SULL'EFFETTO COMBINATO DI **VEMURAFENIB**
E **TRAMETENIB** NEI GLIOMI AD ALTO E BASSO GRADO MUTATI
NEL GENE *BRAFV600E*



Istituto Giannina Gaslini

Via Gerolamo Gaslini, 5
16147 Genova - Italia
tel. +3901056361
WWW.GASLINI.ORG

ATTENDEES

Istituto Giannina Gaslini
Sapienza University, Rome
Microcitemico Children's Hospital
Cagliari University
Ospedale Pediatrico Bambino Gesù, Rome
DKFZ Institute, Heidelberg
Aix-Marseille Univ, APHM, Marseille
Sainte-Anne Hospital, Paris
Queen Mary University of London

LOCATION

Sala Nautilus, Padiglione Acquario
Area Porto Antico, Ponte Spinola - 16128 Genova

HOTEL

BEST WESTERN PORTO ANTICO:

<http://www.hotelportoantico.it/>
Via al ponte calvi, 5 16124 Genova
Tel. +39 010 2518249 Fax +39 010 265759
portoantico.ge@bestwestern.it

CONFORT HOTEL EUROPA GENOVA CITY CENTRE

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Tel. +39 010256955 Fax. +39 010261047
info@hoteleuropagenova.it

RESTAURANT

I TRE MERLI RISTORANTE

<http://www.itremerli.it>
vico delle Monachette, 8 16126 Genova
Calata Cattaneo 17 16128 Genova Tel. +39 0102464416

WITH THE CONTRIBUTION OF:

O.N.L.U.S. Associazione per la ricerca sui tumori cerebrali del bambino.
Artuceba.org



SIOP - LGG
Preclinical Working Group

SCIENTIFIC WORKSHOP

14TH, 15TH SEPTEMBER 2017

Genova





SIOP - LGG Preclinical Working Group

THURSDAY, 14 SEPTEMBER 2017

- 14.00 **Arrival of participants and check-in the hotels**
(walking distance from Padiglione Acquario)
- 15.00 **Welcome and introduction:** Maria Luisa Garrè (Genova, Italy) and Mario Gianelli of "ONLUS Associazione per la ricerca sui tumori cerebrali del bambino"
- 15.15 **Summary of objective of the SIOP-LGG preclinical working reoup and trial update:** Olaf Witt and Stefan Pfister (Heidelberg, Germany)
- 15.35 **Material workflow and reference diagnostics" in LOGGIC Europe :**
David Jones (Heidelberg, Germany)
- 16.00 **Development of a novel assay suitable for pre-clinical testing of MAPK inhibitors in low-grade glioma:** Timm Milde (Heidelberg, Germany)
- 16.30 **Characterization of OIS and the role of SASP in PA:**
Juliane Hohloch (Heidelberg, Germany)
- 17.00 *Coffe break at Sala Mostra "Mr. Good Fish"*
- 17.30 **Updates to the classification of LGG:** David Jones (Heidelberg, Germany)
- 18.30-19.30 *Old Genova Panoramic Tour*
- 20.30 *Dinner at "I Tre Merli Restaurant Porto Antico"*

FRIDAY, 15 SEPTEMBER 2017

- 08.30 **Interest of FISH assays in the diagnosis of pLGG**
Varlet Pascale (Paris, France)
- 09.00 **Update inter-laboratory control:** Felice Giangaspero Manuela Badiali (Rome, Cagliari, Italy) with Dominique Figarella-Branger (Marseille, France)
- 09.30 **Reverse duplications of KIAA1549 and BRAF screening by ddPCR from FFPE DNA is a robust alternative of KIAA1549-BRAF fusions transcripts detection in Pilocytic Astrocytoma:**
Dominique Figarella-Branger (Marseille, France)
- 10.00 **Molecular alteration revision of a PA series:** Felice Giangaspero Patrizia Zavattari (Rome, Italy)
- 10.30 **Update on regulatory networks in pLGG:** Elisabetta Ferretti Giuseppina Catanzaro (Rome, Italy)
- 11.00 *Coffee-break at Sala Mostra "Mr Good Fish"*
- 11.30 **pLGG heterogeneity: our experience:** Maria Vinci Andrea Carai (Rome, Italy)
- 12.00 **The small and mighty miR-21:** Denise Sheer (London, UK)
- 12.30 **Therapeutic strategies on BRAFV600E patients and prognostic implications:** Samantha Mascelli/Alessandro Raso (Genova, Italy)
- 12.50 **Discussion with the whole group and the end of scientific programme:**
Coordinator Stefan Pfister – Olaf Witt
- 13.30 *Lunch at Sala Mostra "Mr Good Fish"*



7th annual Meeting, Genova 14 - 15. 9. 2017

“Therapeutic strategies on BRAFV600E mutated patients and prognostic implications.”

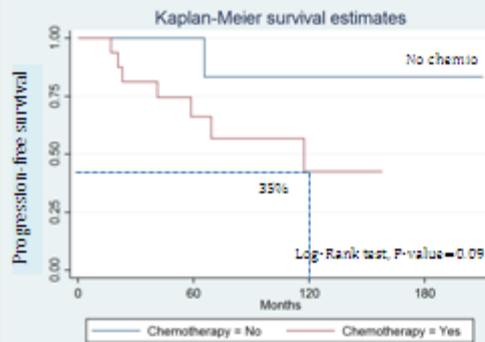
Samantha Mascelli and Alessandro Raso

on behalf of the Neuro-Oncology group,
Dip. Testa Collo Neuroscienze



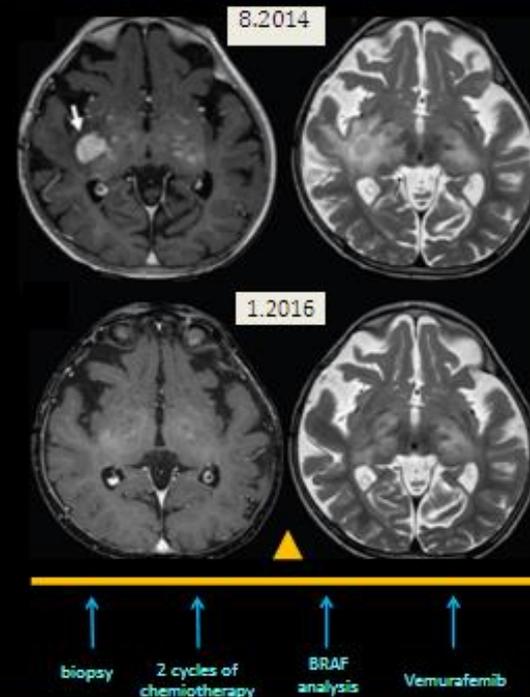
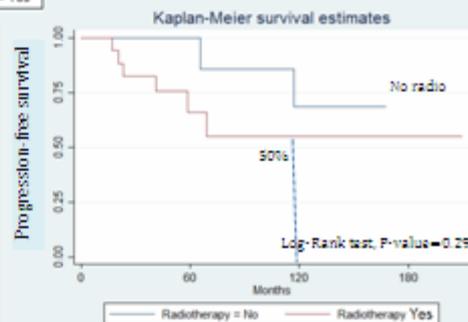
Objectives:

1. To routinely investigate the incidence of BRAFV600E mutation in the patients affected by Pediatric Low Grade Gliomas (PLGG).
2. To study the response to conventional chemotherapy and radiation in PLGG.
3. To assess the response to BRAF-inhibitor treatment (Vemurafenib) in two cases of mixed glioneural tumors.
4. To correlate genetic data with clinical outcomes using long-term follow-up data.



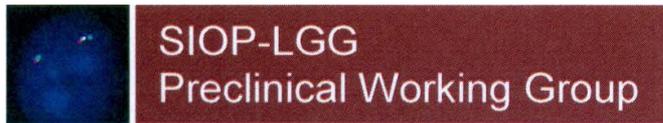
N. 27/62 tumors underwent to subtotal resection (STR) and adjuvant conventional therapies

Only follow up = 5
Only chemotherapy = 4
Only radiotherapy = 5
Chemio + radio post = 13



22 months follow-up

Significant tumor reduction after 3 months of therapy: morphology, dimension, contrast enhancement.



“Analisi della presenza del gene di fusione KIAA1549-BRAF nei gliomi a basso grado e determinazione del valore prognostico al fine di discriminare i gliomi diffusi dai gliomi circoscritti.”

Progetto in collaborazione con il gruppo di ricerca francese di Marsiglia (Dr.ssa Dominique Figarella-Branger)

ISTITUTO GIANNINA GASLINI

Istituto Pediatrico di Ricovero e Cura a carattere Scientifico

gaslinispring.it

gaslini.org

gasliniblog.org

Brain Tumors Group

Neurosurgery

Armando Cama
Marcello Ravegnani
Gianluca Piatelli
Alessandro Consales
Marco Pavanello

Neuro-oncology

Maria Luisa Garrè
Claudia Milanaccio
Antonio Verrico

Neuroradiology

Andrea Rossi
Giovanni Morana
Mariasavina Severino

Neurogenetic and Neuroscience Lab

Federico Zara

Medical Genetist

Valeria Capra

Molecular biologist

Samantha Mascelli
Alessandro Raso

Pharmacist

Paola Barabino
Valentina Iurilli

Psychology

Sonia Di Gallo



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