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

"Therapeutic strategies on BRAFV600E mutated patients and prognostic implications."

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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.

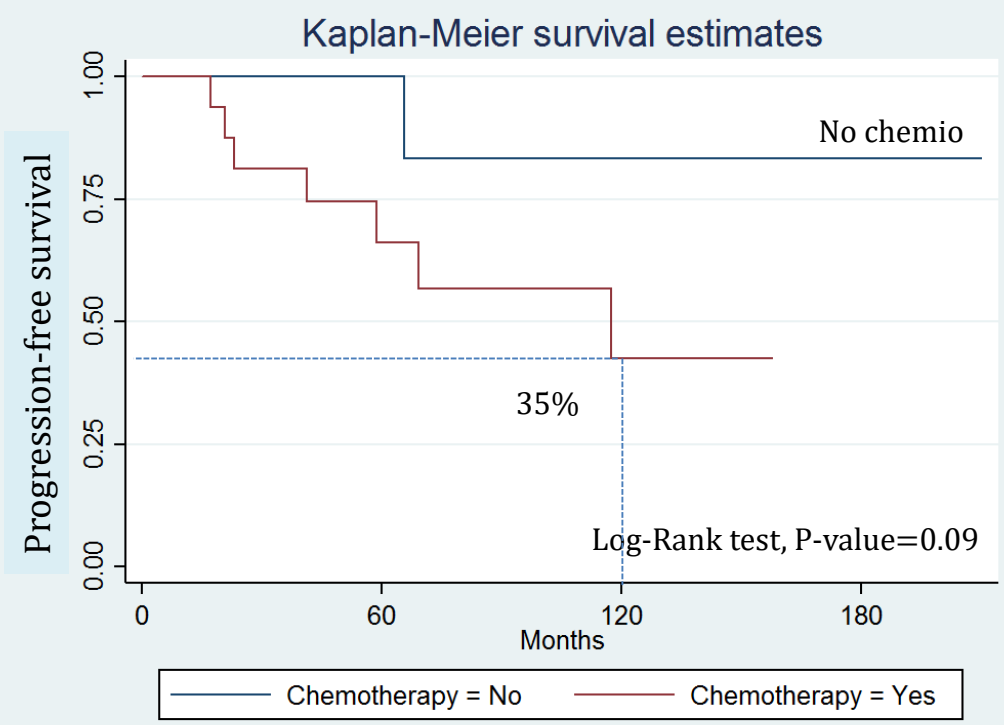
4. To correlate genetic data with clinical outcomes using long-term follow-up data.

IGG PLGG cohort (N. 62) from 2000 to 2016

- 25 Pilocytic Astrocytoma (PA)
- 13 Ganglioglioma (GG)
- 9 Desmoplastic Infantile Ganglioglioma (DIG)
- 7 Astrocitoma Low-grade *
- 6 Diffuse Astrocytoma (DA)
- 1 Pilomixoid Astrocytoma (PMA)
- 1 SubEpendymal Giant cells Astrocytoma (SEGA)

•*1 case NF1 associated

•33 supratentorial and 29 infratentorial



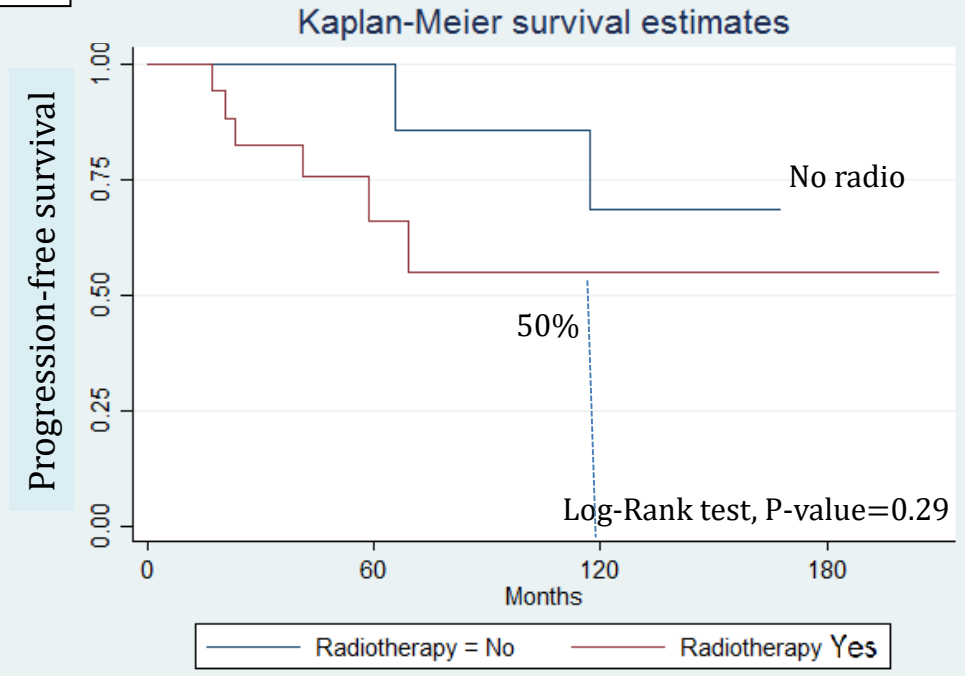
N. 27/62 tumors underwent to subtotal resection (STR) and adjuvant conventional therapies

Only follow up = 5

Only chemiotherapy = 4

Only radiotherapy = 5

Chemio + radio post = 13

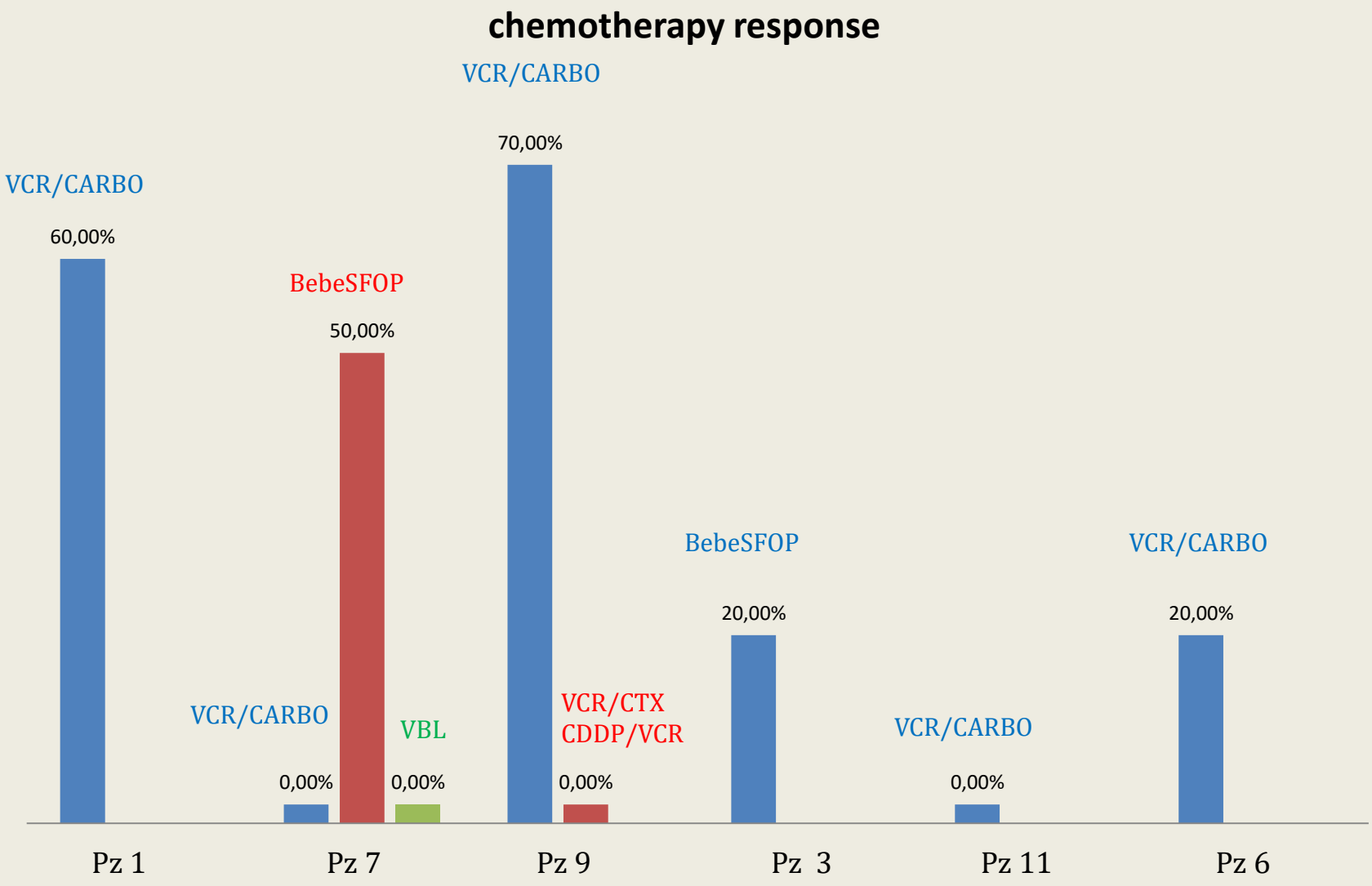


BRAFV600E mutated tumors (N.12/62, 19.3%)

patient ID	Age at diagnosis (years)	gender	pathology	site of lesion	BRAFV600E method	type of surgery	additional treatment	progression	outcome	Arg72Pro, TP53
pz 1	14	M	PA	spinal cord	pyrosequencing on FFPE mat	STR	chemio	20 months	pseudo progression	Arg/Arg
pz 2 *	3	M	PA	FCP	pyrosequencing on frozen tissue	GTR	0	0	ANED	Arg/Arg
pz 3	1,5	M	PA	cerebellar pedunculum	pyrosequencing on frozen tissue	STR	chemio, radio post	0	SWD	Arg/Arg
pz 4	2,8	F	PA	FCP	pyrosequencing on frozen mat	GTR	0	0	ANED	Arg/Pro
pz 5	11	F	PA	FCP	pyrosequencing on frozen mat	GTR	0	0	ANED	Arg/Pro
pz 6	12	F	PA	brainstem	sequencing on frozen mat	STR	chemio, surgery, radio	6 months under chemio	SWD	Arg/Arg
pz 7	0,5	F	DIG	hipothalam chiasmatic	pyrosequencing on FFPE mat	biopsy	chemio	4,5 years	SWD	Arg/Arg
pz 8	0,5	F	DIG	cerebral hemisphere	pyrosequencing on frozen mat	GTR	0	0	ANED	Pro/Pro
pz 9	1,1	F	mixed glioneural	OPG	pyrosequencing on FFPE mat	biopsy	chemio	1 year	SWD	Arg/Arg
pz 10	12,5	F	GG	cerebral hemisphere	pyrosequencing on frozen mat	GTR	0	0	ANED	Arg/Arg
pz 11	12,6	M	GG + metastasis	cerebral hemisphere	pyrosequencing on frozen mat	STR	chemio, radio post	3 years, 6 years + metastasis	SWD	Arg/Pro
pz 12	0,5	F	AstroLGG	cerebral hemisphere	pyrosequencing on frozen mat	near GTR	0	0	ANED	Pro/Pro

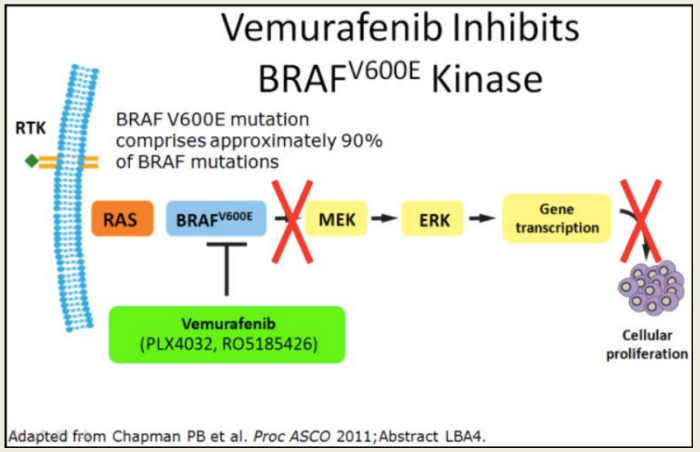
- * KIAA16-BRAF9 gene fusion
- H3.3A, H3.1B, H3.1C and TP53 wild-type in all BRAFV600E mutated cases

Additional conventional chemotherapy



Desmoplastic Infantile Gangliogliomas successfully treated with BRAF inhibitor.

CASES	PATHOLOGY	BRAFV600E	KIAA1549-BRAF gene fusion	H3.3A	H3.1B	H3.1C	TP53
Pz 7	DIG	V600E	WT	WT	WT	WT	WT
Pz 9	MIXED GLIONEURAL	WT	-	WT	WT	WT	WT
progression Pz 9		V600E	WT	WT	WT	WT	WT



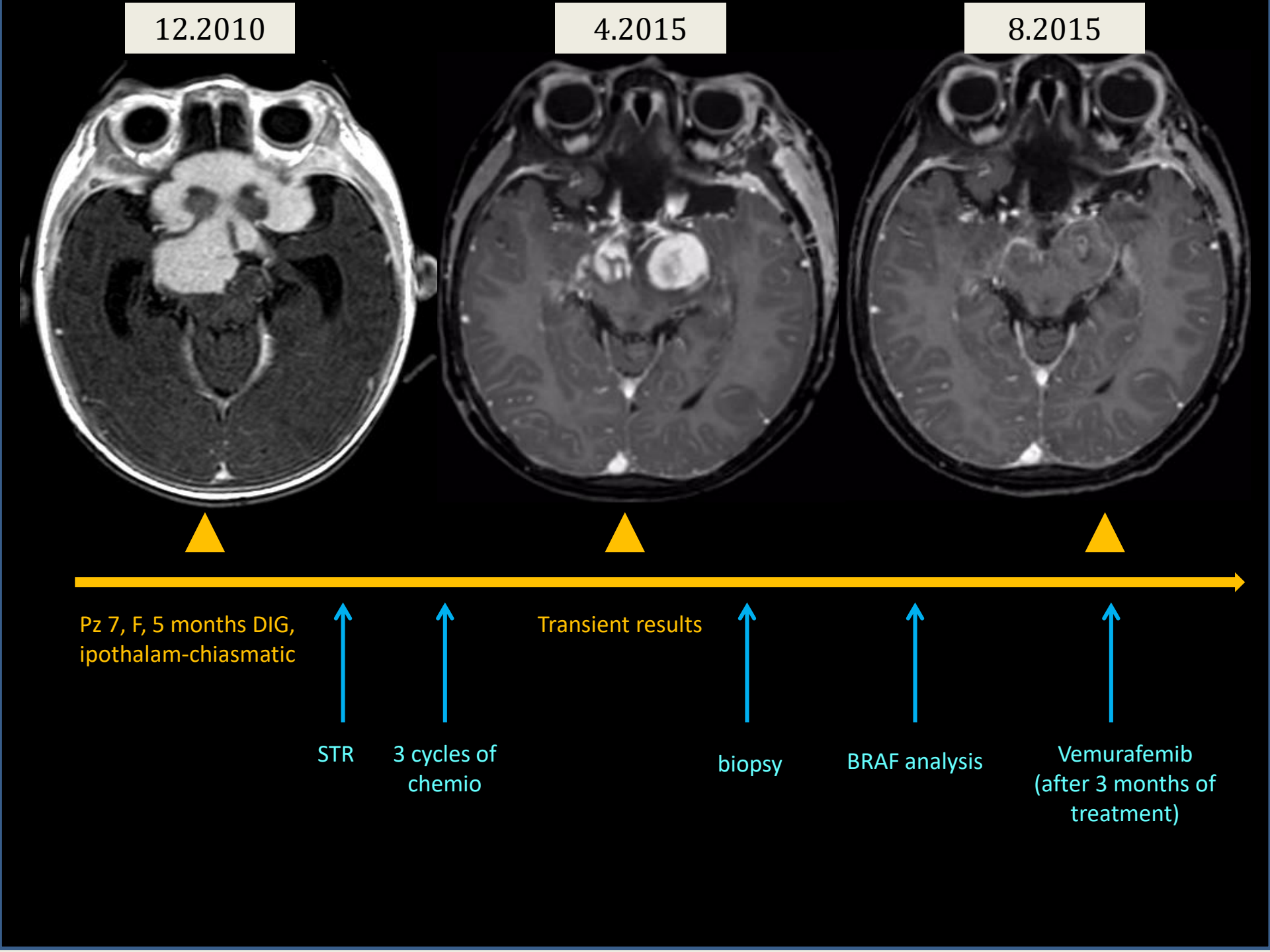
Pz 7 is affected by DIG with poor response or resistance to conventional chemotherapy

Pz 9 is affected by a biphasic neoplasia;
Front component: PA with good response to conventional chemotherapy
Lateral component: DIG resistant to therapies.

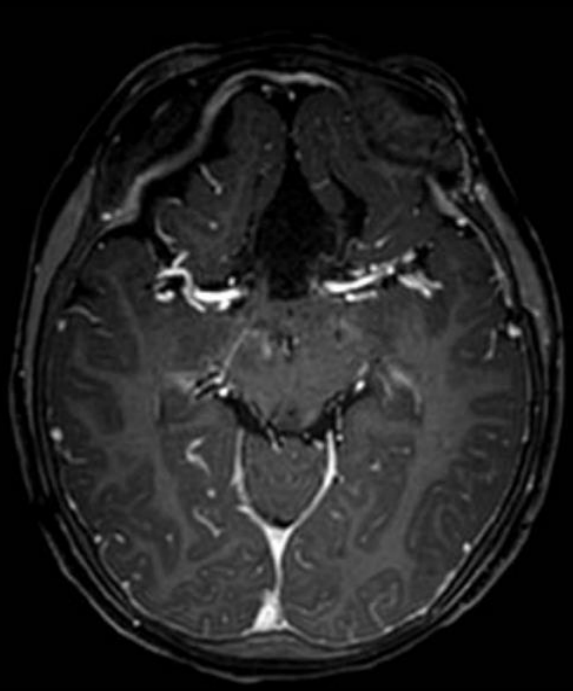
Second hit for BRAFV600E mutation.

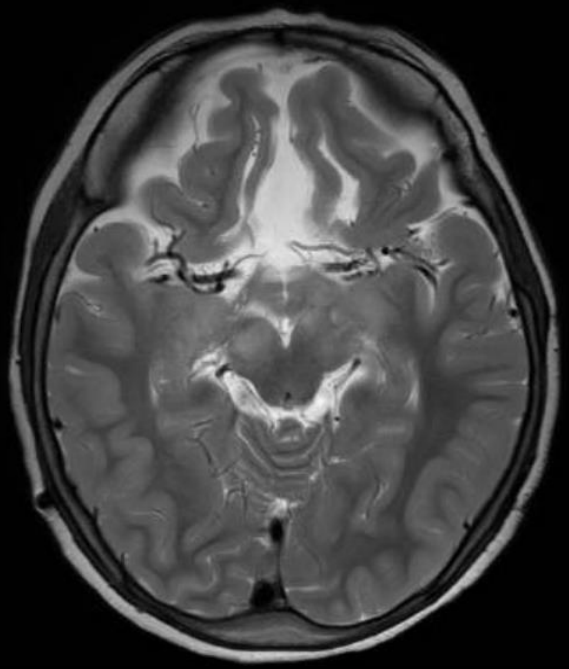
From May 2015 to March 2017, around 1500 VEMURAFENIB CART for Patient 7 were placed.

The Patient 9 has been related to the resident hospital health after training of medical and pharmacy collectors and sharing procedures.


12.2010
4.2015
8.2015
Pz 7, F, 5 months DIG, ipothalam-chiasmatic
STR
3 cycles of chemio
Transient results
biopsy
BRAF analysis
Vemurafemib (after 3 months of treatment)

Last control 27/7/2017, after 27 months follow up

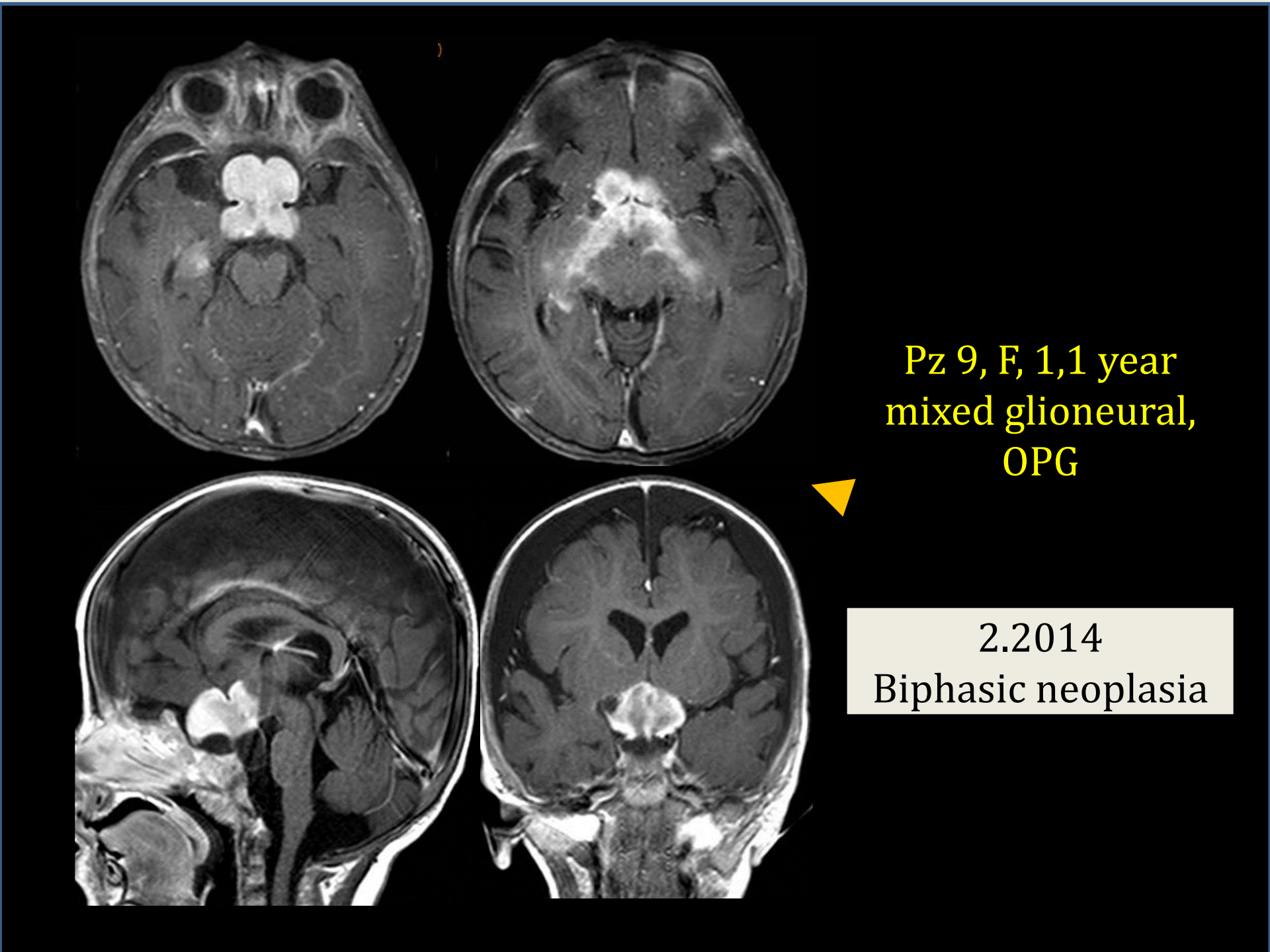




With contrast enhancement

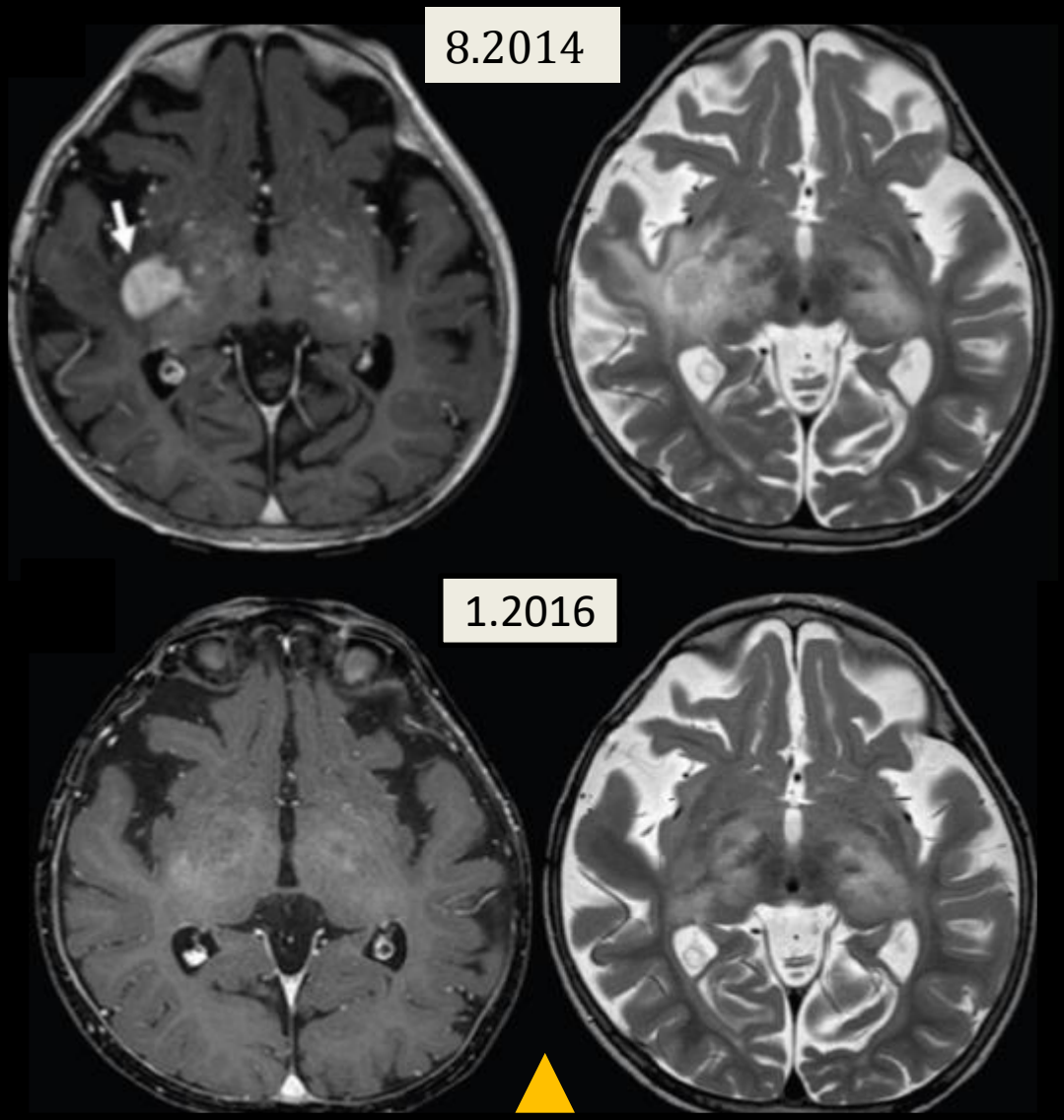
Without contrast enhancement

Significant tumor reduction:
Morphology, Dimension, contrast enhancement



Pz 9, F, 1,1 year
mixed glioneural,
OPG

2.2014
Biphasic neoplasia



22 months follow-up

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

Pz 7

- No cardiac toxicity
- Very mild skin(on the legs) toxicity, only on the begining of treatment.

Pz 9

- Skin toxicity, probably due to difficulties in managing and preparation of the treatment
- Both patients are stable after a median follow-up time of 24 months

Cart preparation of Vemurafenib instead of pill allows pharmacological principle to be better assimilated by pediatric patients, avoiding nausea, vomiting, and growing the beneficial effect.

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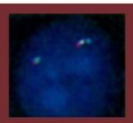
WITH THE CONTRIBUTION OF:

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

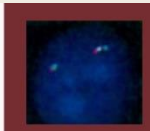


SIOP - LGG
Preclinical Working Group

SCIENTIFIC WORKSHOP

14TH,15TH SEPTEMBER 2017

Genova



SIOP - LGG
Preclinical Working Group

THURSDAY, 14 SEPTEMBER 2017

14.00 **Arrival of partecipants 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 heterogenity: 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"***