ALK mutations in infant type hemispheric glioma: targeting the future

Ana Carolina Izurieta
Pediatric Cancer Center Barcelona

Veronica Biassoni
Istituto Tumori di Milano

ERN PaedCan – Young SIOPE webinar series

"Most challenging cases in paediatric oncology"

Funded by the European Union's EU4Health Programme

COI declaration

- No conflicts of interest

Clinical case

July/18

2 month-old
Seizures

Baby POG protocol

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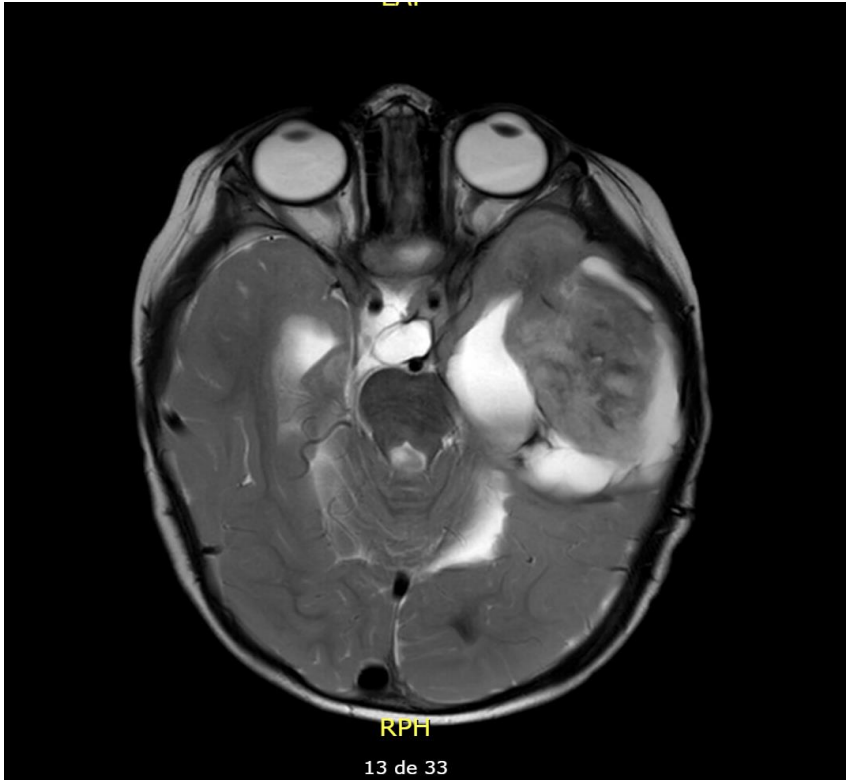
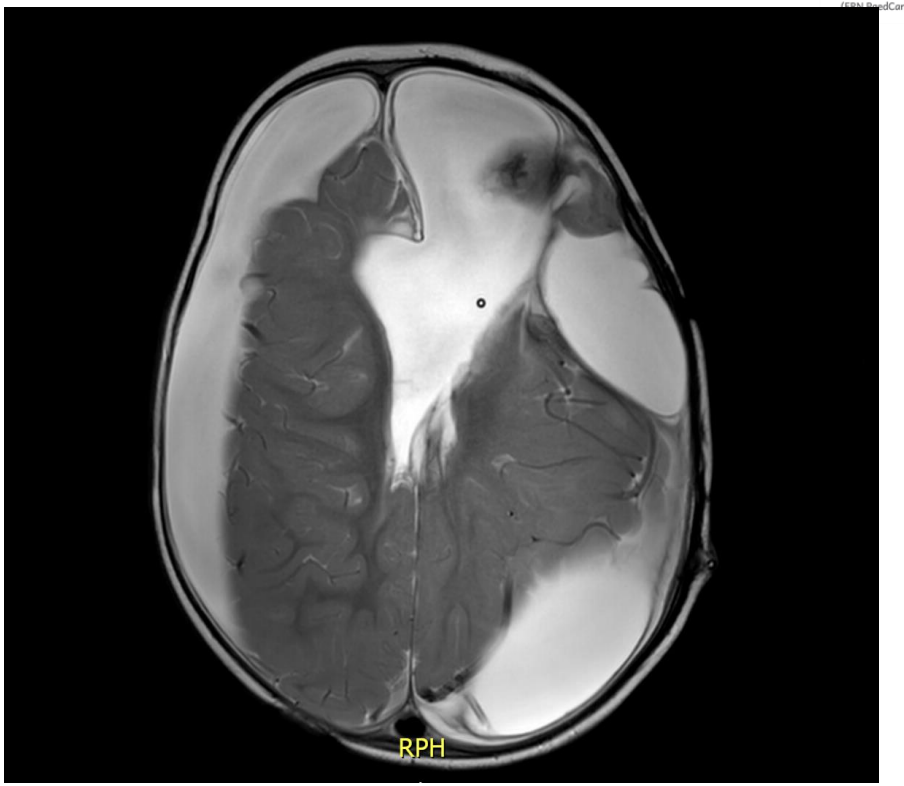
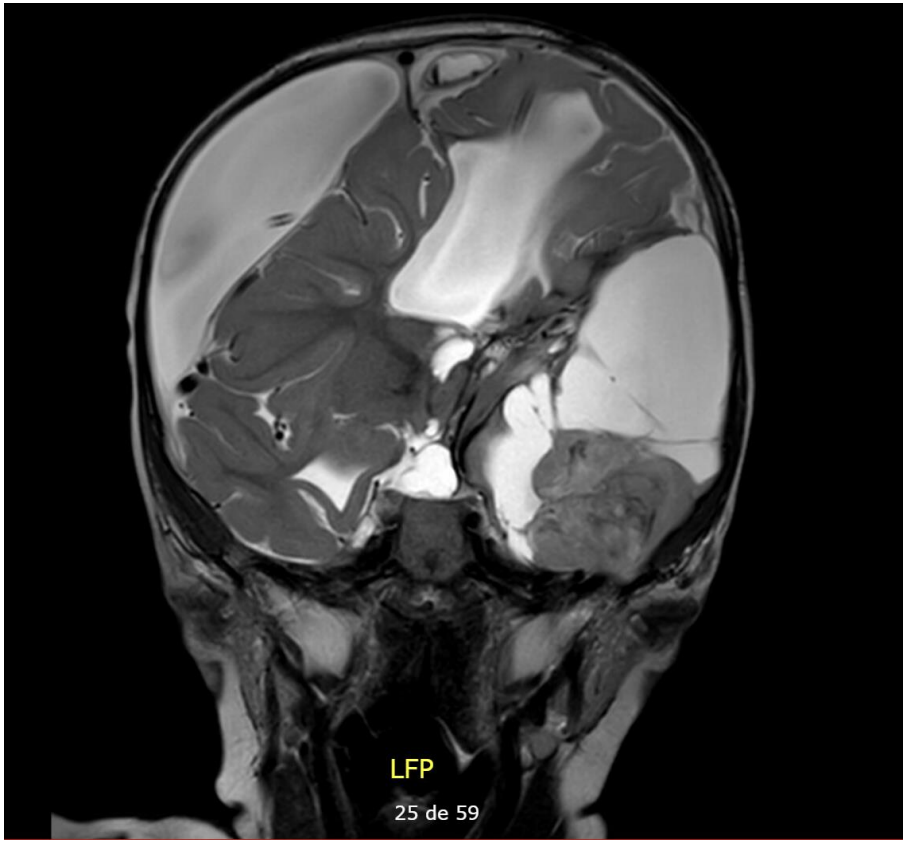
March/20






LFP
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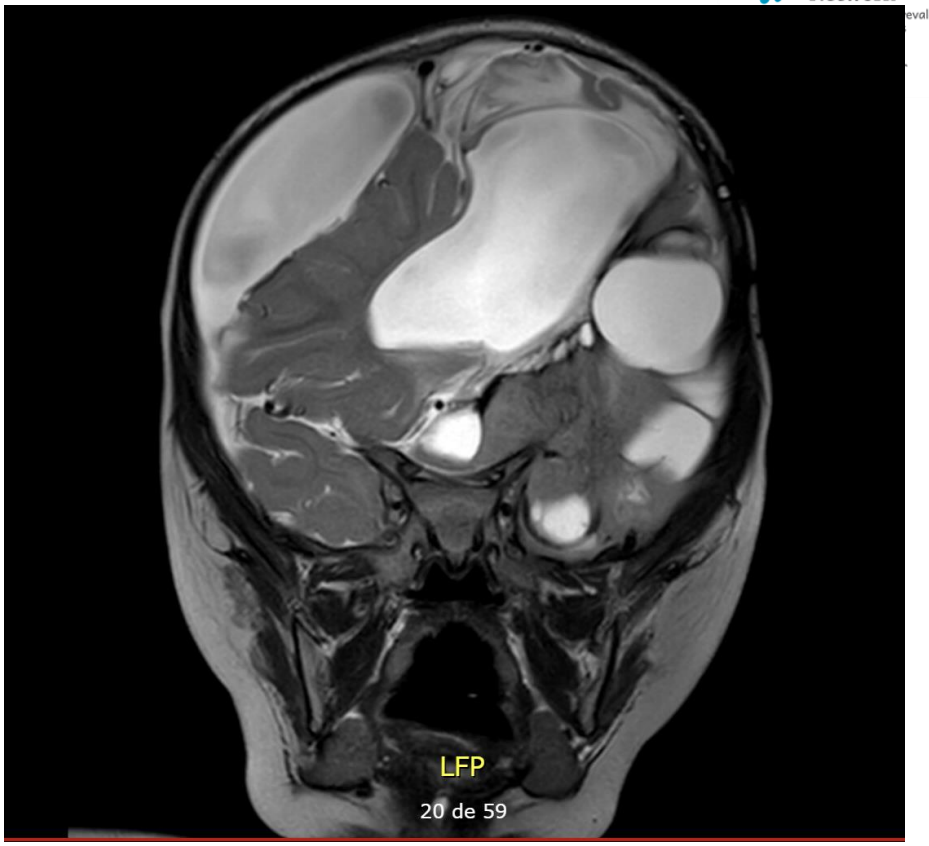
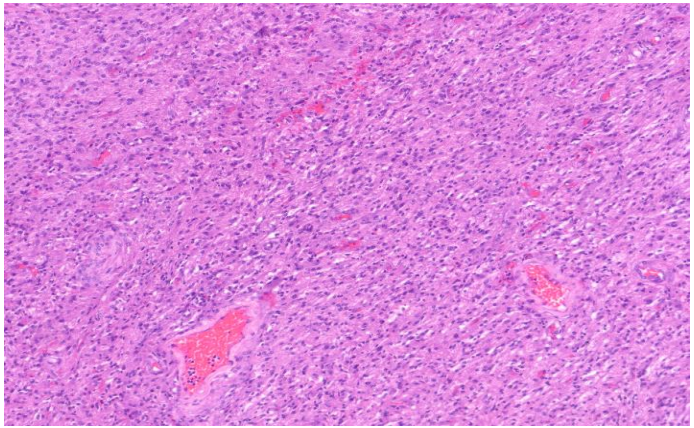
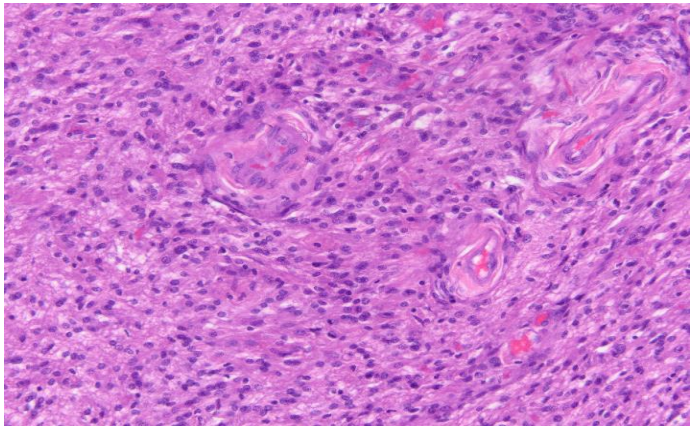
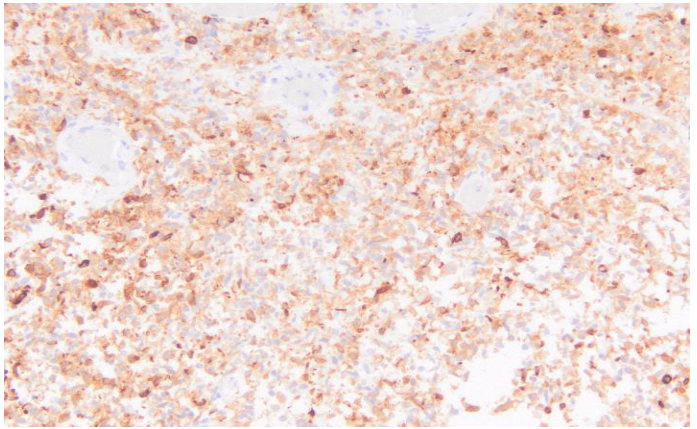

LFP
20 de 59

Histopathology







Tumor cells express GFAP, Olig2 and enolase.

ALK +

Negative for synaptophysin, IDH1 and H3K27M.

P53 is expressed in 20% of the cells.

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High grade glioma

NGS: ALK fusion *PPP1CB-ALK*

DNA methylation: Infantile hemispheric glioma

Gliomas quiz

Gliomas are the most common primary CNS neoplasm. Infant LGG have a higher mortality rate, while HGG have a better outcome.

a. True

b. False

Gliomas quiz

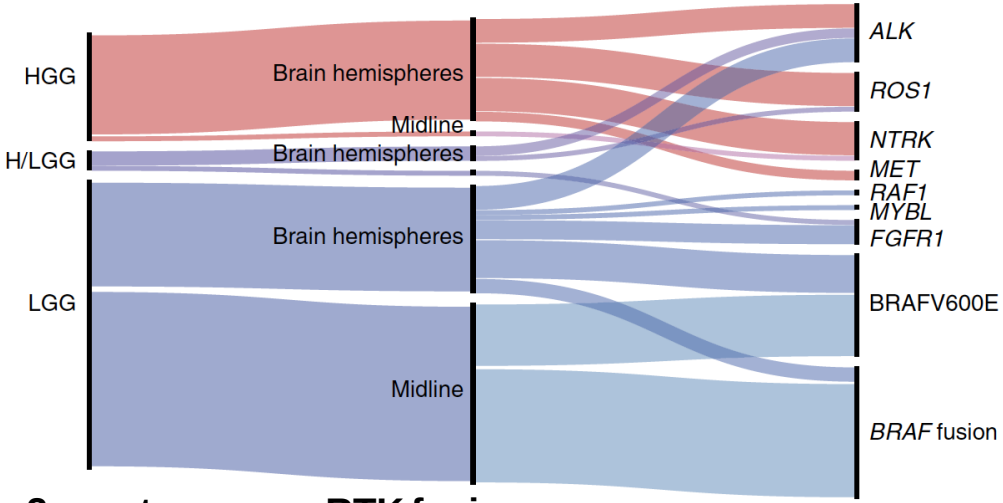
Gliomas are the most common primary CNS neoplasm. Infant LGG have a higher mortality rate, while HGG have a better outcome.

a. True

b. False

Infantile gliomas

Distribution of molecular drivers according to tumor location and histology



2 most common RTK fusions:

PPP1CB-ALK

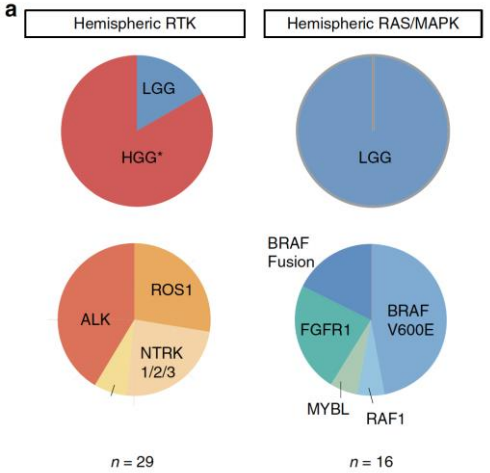
CCDC88A-ALK

n=171 samples

Both in LGG ad HGG

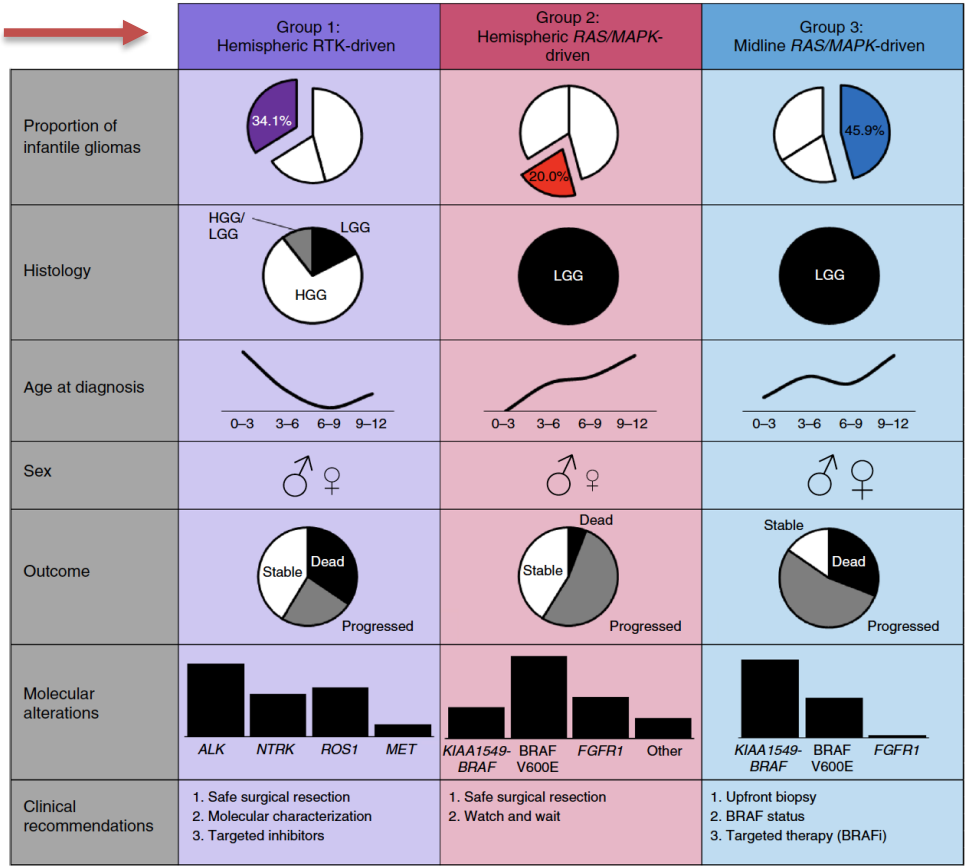
1st: *RAS/MAPK* activating alterations

2nd: alterations in the receptor tirosin kinases oncogenes *ALK, ROS1, NTRK or MET*



Alterations in ALK/ROS1/NTRK/MET drive a group of infantile hemispheric gliomas. Ana S. Guerreiro Stucklin et al. Nature communications, 2019

Infant gliomas subgroups



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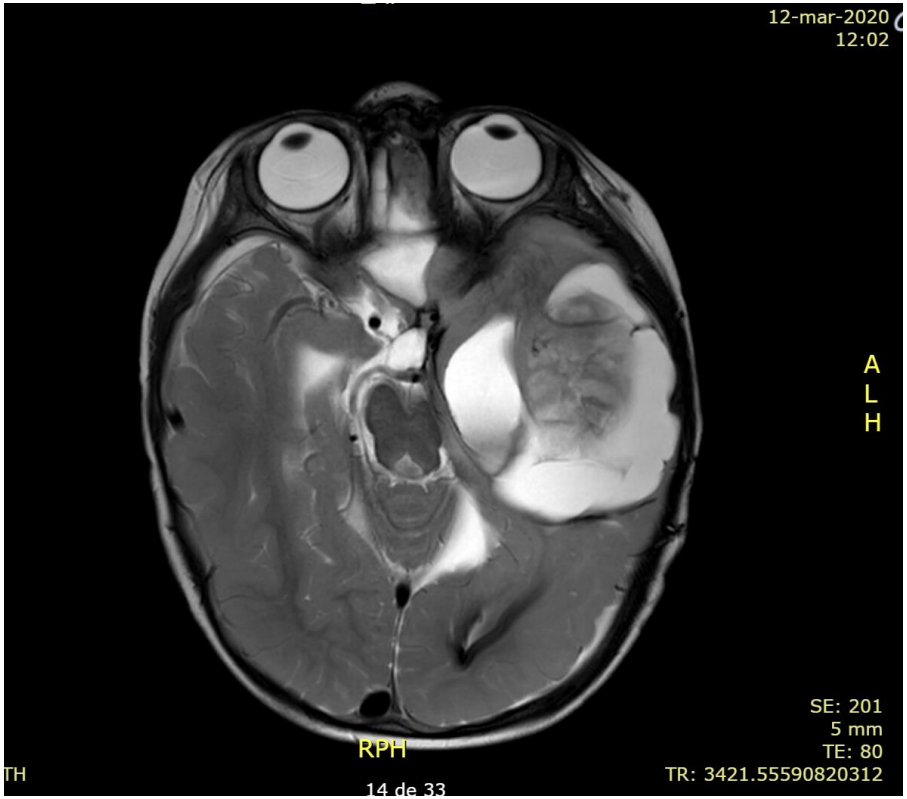
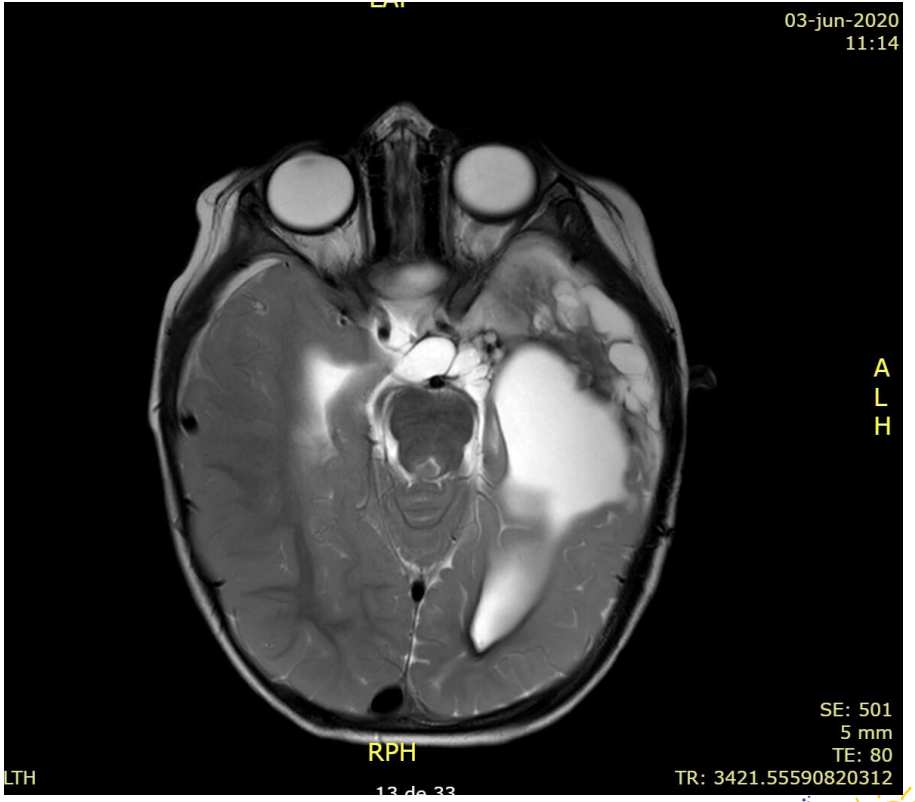
Alectinib CU
150mg BID
No adverse events

3 months after alectinib:





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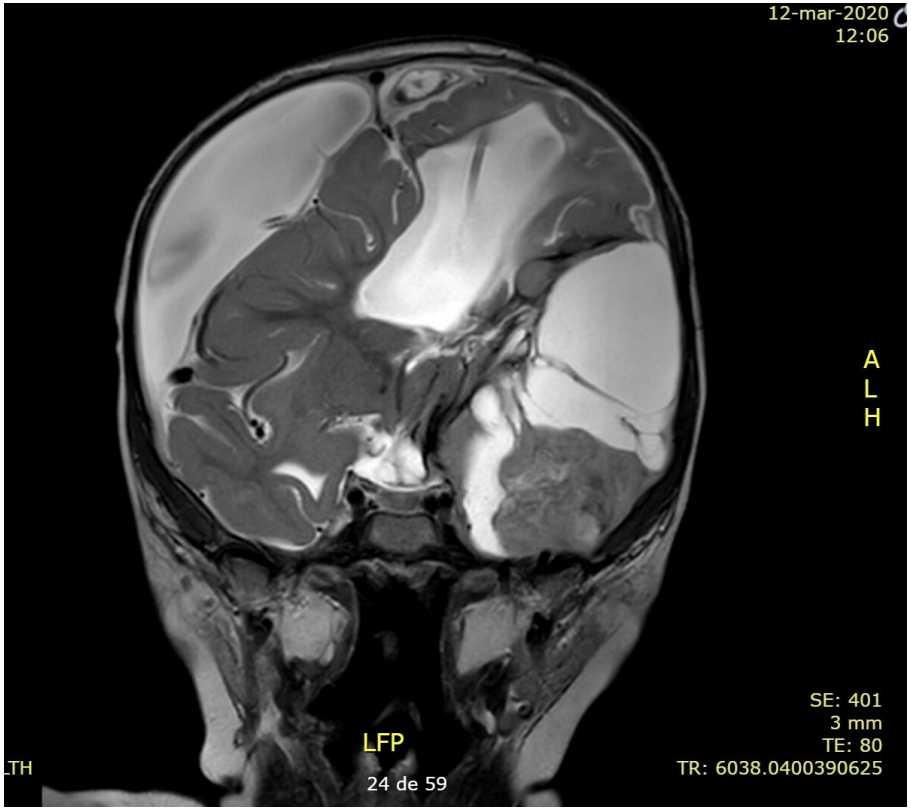

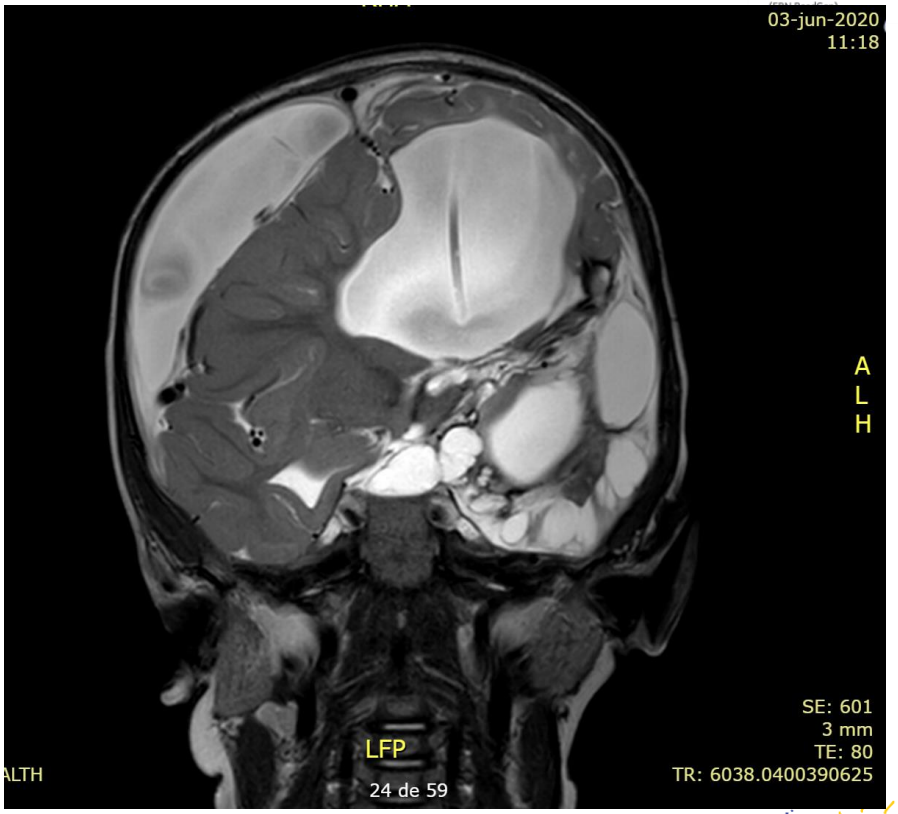

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1g/m²/day

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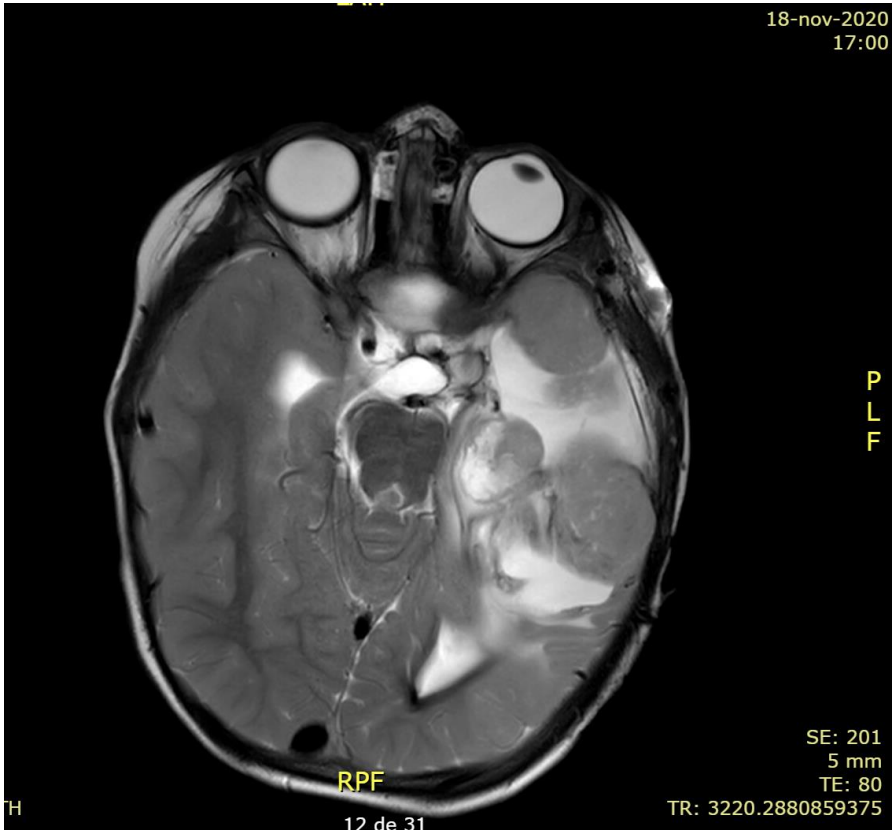
June/20: Major response

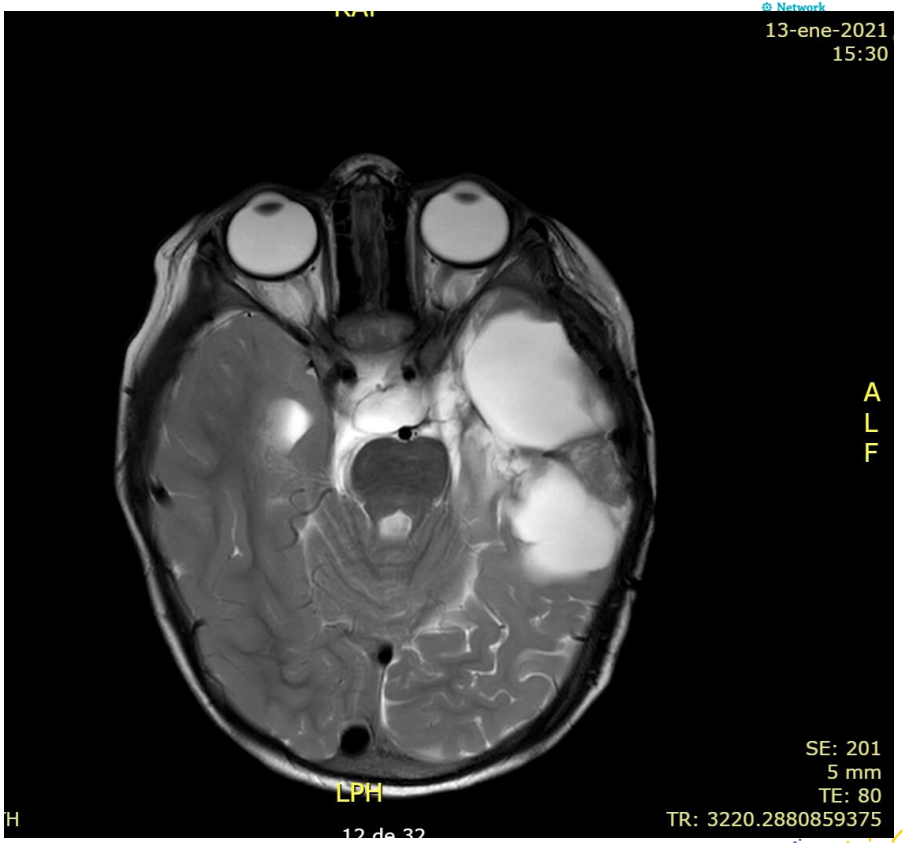
Sept/20 NTR

HGG
Alk mutation
p.G1202R

Nov/20 Lorlatinib CU
45mg/m²/d
No adverse events

2 months after lorlatinib:





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2 month-old Seizures

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August/20
MRI progression

MGMT promoter metilation

NTR

July/21
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3ys-old
PBI
Temozolomide

NO evidence of progression

ALK inhibitors quiz

Which of the following ALK inhibitors has the best CNS penetration?

a. Crizotinib
b. Alectinib
c. Ceritinib
d. Lorlatinib

ALK inhibitors quiz

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Management of CNS disease in anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer: Concentration of tyrosine kinase inhibitors in the cerebrospinal fluid and plasma in published studies.

Compound	Plasma concentration	Cerebrospinal fluid concentration	Cerebrospinal fluid penetration rate	Ref
Crizotinib	237 ng/mL	0.616 ng/mL	0.26%	[15]
Alectinib	3.12 nM	2.69 nM	86%	[43]
Ceritinib	Not reported	Not reported	15%	[47]
Lorlatinib	Not reported	Not reported	20–30%	[53]

Management of CNS disease in ALK-positive non-small cell lung cancer: Is whole brain radiotherapy still needed? Wrona A. Cancer Radiother (2019)

ALK inhibitors quiz

Which are the most frequent adverse effects of ALKi?

a. GI toxicities (nausea, vomiting and diarrhea)

b. Visual disorders

c. Respiratory complications (dyspnea, pneumonia, respiratory failure)

d. All of the above

ALK inhibitors quiz

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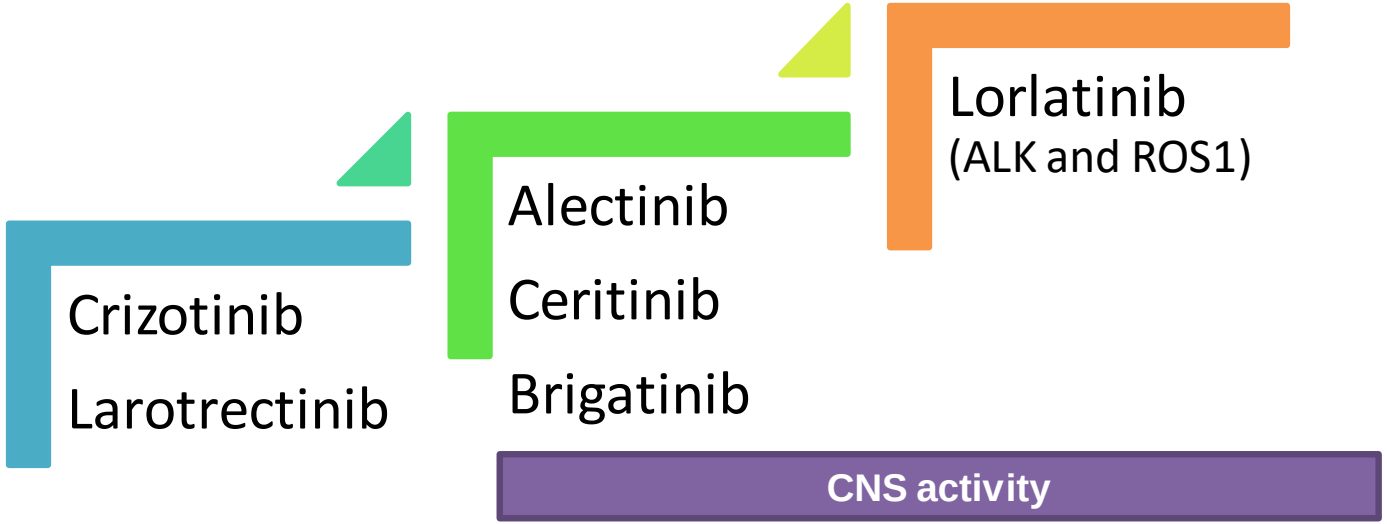
Targeted agents

- The most common somatic alterations in infantile HGG are TRK fusions. Critical role in tumorigenesis.



European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

DISCUSSION

Co-funded by the European Union's Health Programme

Discussion: congenital tumors

- Congenital tumors → definitions?

In the literature the criteria used to classify a CNS tumor as being congenital varies greatly with cutoffs ranging between 4 weeks of life and 1 year at the time of symtoms onset.

Viaene et al,Brain Pathology 2021

Definitely congenital (already symptomatic at birth)
Probably congenital /symptomatic during the first week of life)
Possibly congenital (symptomatic within the first 2-3 months)

Solitare and Krigman 1964, Wakai et al 1984

Congenital: tumours diagnosed within the first 6 weeks of life
Probably congenital: 6 weeks and 6 months
Possibly congenital: 6-12 months

Ellams et al 1986

The incidence of these tumours varies within the literature, ranging between 1.1 and 3.4 per million live births

Viaene et al,Brain Pathology 2021

Discussion: WHO 2021 classification

- **Infant-type hemispheric glioma (WHO 2021):** a cerebral hemispheric, high-grade cellular astrocytoma that arises in early childhood, tipically with receptor tyrosine kinase (RTK) fusions including those in the NTRK family or in ROS1, ALK or MET. *Subtypes: NTRK-altered, ROS1-altered, ALK-altered and MET-altered.*

- Mostly occur in **early childhood**, > in the 1st year of life (in the paper by Guerreiro Stucklin et al Nature Communications 2019, the median age at presentation was 2.8 months –range 0-12 months-) but also under 2 years.

- **Differential diagnosis**: other high-grade gliomas, desmoplastic infantile ganglioglioma/astrocytoma, ganglioglioma and ependymoma.

- **RTK-fusions** are present in 60-80% of cases: try routine test for such fusions in infants is both diagnostic and therapeutic

- **Better prognosis** than pedHGG maybe with individual drivers events associated with different clinical outcomes: OS ALK-rearranged>ROS1 alterations; NTRK fusion positive tumors intermediate prognosis (Guerreiro Stucklin et al Nature Communications 2019)

Discussion: ALK-inhibitors in CNS

Table 1
Management of CNS disease in anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer: Concentration of tyrosine kinase inhibitors in the cerebrospinal fluid and plasma in published studies.

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Caveats:
- Adult patients/lung cancer
- Brain metastasis
- No brain surgery
- Different BBB status

Discussion: resistance to ALK-inhibitors

- **On-target resistance** = resistance to ALK inhibitors despite continued reliance on ALK fusion signalling

Table 2 II and III generation TKIs in crizotinib pre-treated patients

Drug	Phase	ORR, %	mDOR, mo	mPFS, mo	iORR, %	Ref.
Alectinib	II	51.3	14.9	8.3	64	(31-34)
	III	–	20.1*	7.1	54.2	(35)
Ceritinib	I	56	–	6.9	65	(36)
	II	38.6	9.7	5.7	45	(37)
	III	–	–	5.4	–	(38)
Brigatinib	I/II	83	–	13.2	53†	(39)
	II	54	–	12.9	67	(40)
Lorlatinib	I	57	11.7	9.6	–	(41)
	II	47	NR	NR	87	(42)
Ensartinib	I/II	69	–	9.0	69	(43)

*, weeks; †, in patients with measurable intracranial lesions. TKI, tyrosine kinase inhibitors; ORR, objective response rate; mDOR, median duration of response; mPFS, median progression-free survival; iORR, intracranial objective response rate; mo, months; Ref., reference; NR, not reached.

Delmonte et al,Trasl Lung Cancer Res 2019

- **Off-target resistance** = resistance to tyrosine kinase inhibitor therapy due to genomic alterations involving other receptor tyrosine kinases or downstream pathways mediators.
- Strategies to overcome resistance include also the use of combined therapies that simoultaneously target multiple nodes essential for cells survival: observed synergistic effect of combining ALK inhibitors with mTOR inhibitors (increased inhibition of mTOR effectors and prevention of selection of resistant clones)

Discussion: long-term side effects of ALK-inhibitors in children

«If validated in larger trials, such agents may represent attractive options to spare the long-term sequelae of chemotherapy and radiotherapy, while maintaining the generally good prognosis of these patients»

[Clarke et al, Cancer Discovery 2020]

Discussion: ALK-inhibitors in children

Enrolling in trials and compassionate use

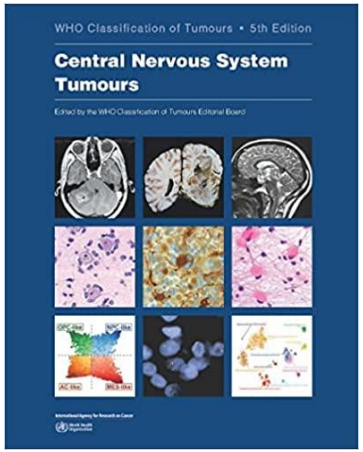
Discussion: «old» therapies still play a role?

RTK-fusions are present in 60-80% of cases (20-40% no «targetable» disease)

- **CCG-945 study**: 8-in-1 regimen (vincristine, carmustine, procarbazine, hydroxyurea, cisplatin, cytosine arabinoside, prednisone, and dimethyl-triazenoimidazole-carboxamide) →3-year PFS and OS of 36% and 51% respectively, markedly better than older children treated with this regimen in combination with RT [Geyer et al, Cancer 1995].
- **Baby POG I (1986-1996):** 24 months using prolonged alternating chemotherapy consisting of two cycles of cyclophosphamide and vincristine followed by a third cycle of cisplatin and etoposide→5-year PFS and OS of 43% and 50% for the 18 HGG patients included [Duffner, P.K., Neuro Oncol, 1999].
- **BBSFOP protocol:** 18-month chemotherapy-only, with a schedule of seven cycles of three drug pairs (carboplatin/procarbazine, cisplatin/etoposide and vincristine/cyclophosphamide) in HGG patients under 5 years of age→ 5-year PFS and OS of 35.3% and 58.8% [Dufour C et al, Eur J Cancer, 2006].
- **UKCCSG/SIOP CNS 9204 trial**: infants with non-brainstem HGG were treated with courses of carboplatin/vincristine, high-dose methotrexate/vincristine, cyclophosphamide monotherapy and cisplatin monotherapy →PFS and OS rates of 13.0% and 30.9% [Grundy, R.G., et al, Eur J Cancer, 2010].

Recommended Papers/Readings

- WHO Classification of Tumours-5° Edition- Central Nervous System Tumours



- Ana S. Guerreiro Stucklin et al, Alterations in ALK/ROS1/NTRK/MET drive a group of infantile hemispheric gliomas, Nature Communications, 2019
- Clarke M. et al, Infant high-grade gliomas comprise multiple subgroups characterized by novel tergetable gene fusions and favorable outcomes, Cancer Discovery 2020 (and related references)
- All the references in the Discussion slides

Take home messages

- Infantile gliomas have a paradoxical clinical behavior.
- Histopathologic grading may not reflect the biology of these tumors.
  - Lower-grade tumors tumors have a high mortality rate while HGG have a more favorable outcome.
- Importance of treatment guided by molecular characterization.
  - RTK – group 1
  - RAS/MAPK – group 2 and 3
- Targeted therapy in group 1 and 3. Best outcomes group 2, surgical resection and wait and see.

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- Submit your case and short CV to edu@siope.eu
- Deadline: **31st October 2022**