European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

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High-grade glioma with EZHIP overexpression

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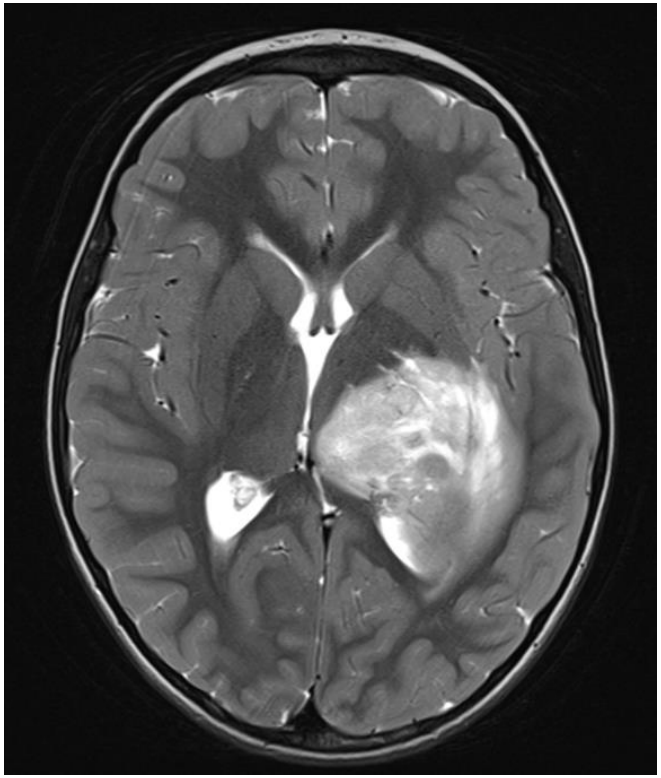
COI declaration

- No conflicts of interest

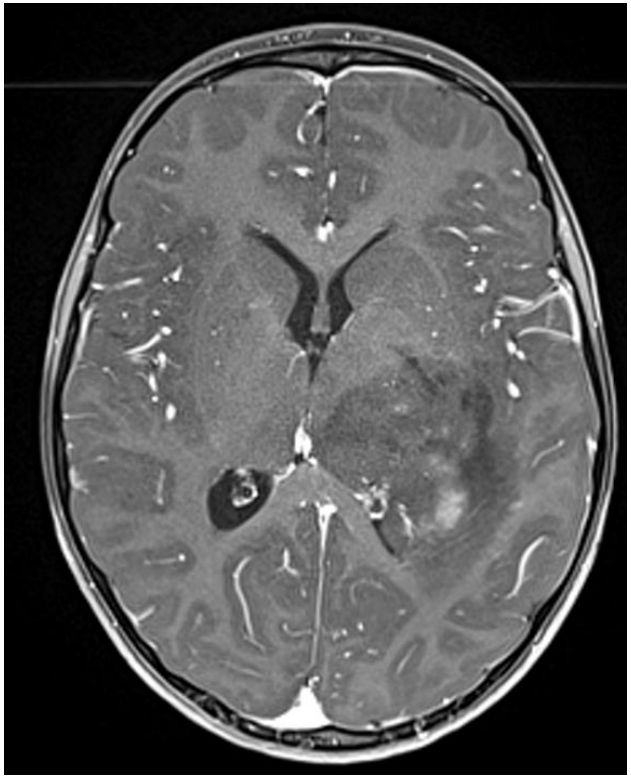
Clinical Case

- 6 year-old girl
- cefalea, vomiting, dysartria
- 1/2021 diagnostic MRI

Diagnostic MRI



T2 weighted 1/2021

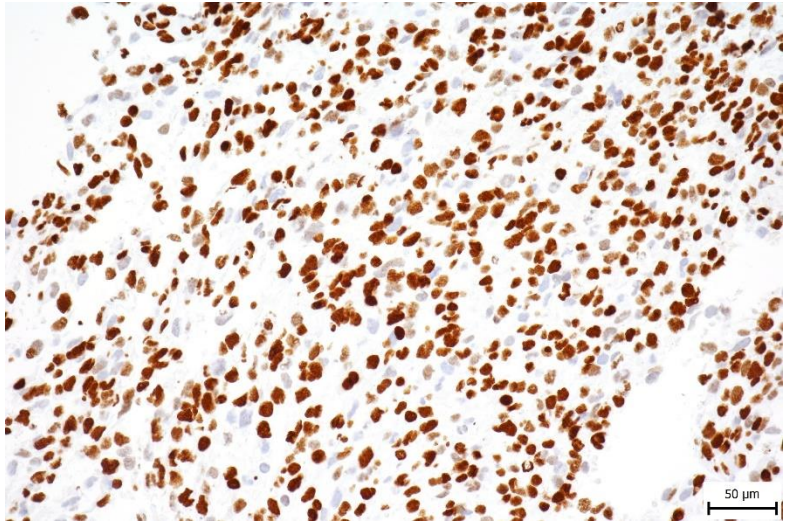


T1 GAD 1/2021

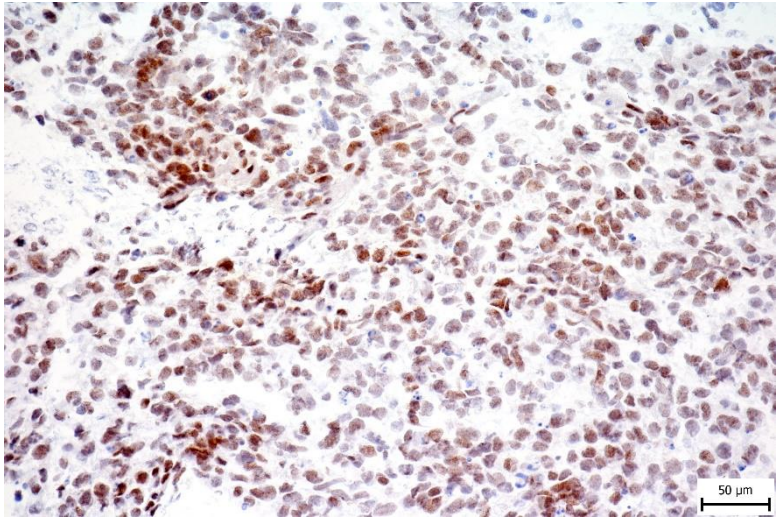
Clinical Case

- Partial resection
- Histopathology:
  - High grade astrocytoma, CNS WHO grade 3 with transformation to grade 4
- Immunohistochemistry:
  - Ki-67 80% positive cells
  - IDH1(R132H) neg., p53 expression wt
  - H3K27me3 – partial loss
  - EZHIP – overexpression
- Direct sequencing:
  - *histon H3* wildtype
  - *BRAF, IDH1,2* wildtype

Immunohistochemistry



H3K27me3 loss (50%)



EZHIP overexpression (50-70%)

Clinical Case

- Treatment
  - RT concomitant with TMZ

Question 1

- Mutation in the *Histone H3.3 or H3.1* genes is a prognostically favorable marker in pediatric high-grade gliomas.

a. True

b. False

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a. True

b. False

Question2

- Which statement is correct?

a. EZHIP overexpression causes the H3K27me3 loss
b. H3K27me3 loss causes the EZHIP overexpression

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Clinical Case

RT concomitant with TMZ

Hydrocephalus

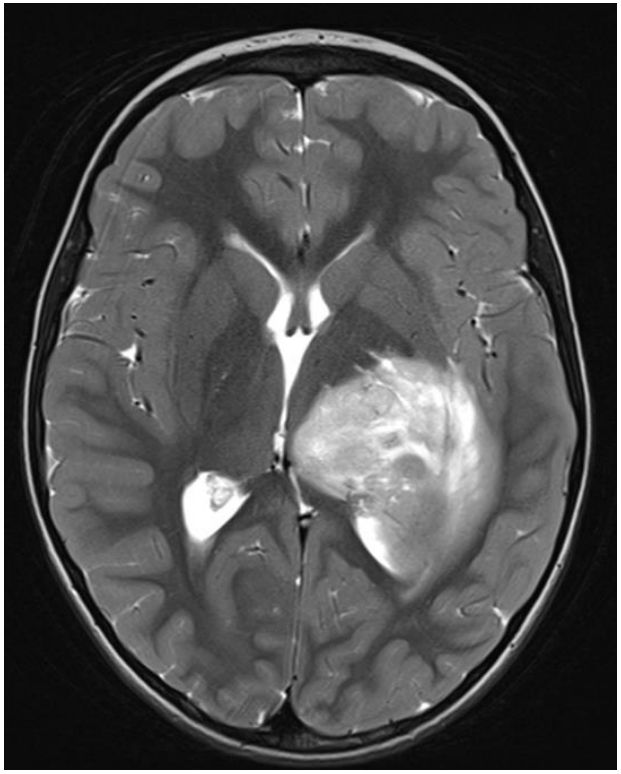
EVD, recurrent infections

methylation array:

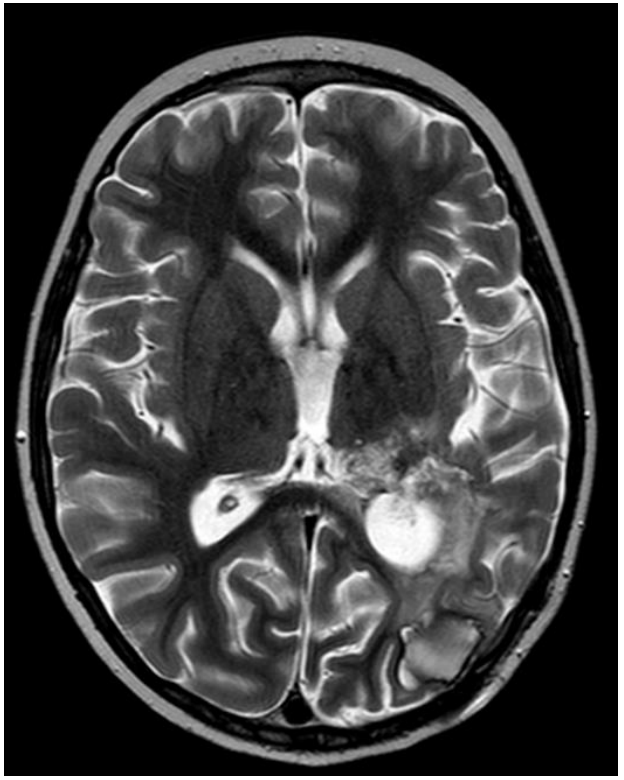
- 11b4 version: Glioblastoma, IDH wild type, subclass midline (0.56)
- 12.5 version: family: Paediatric-type diffuse high-grade gliomas (0.99)
  subclass: Diffuse paediatric-type HGG, RTK1 subtype, subclass C (novel) (0.72)

RNA-Seq (Archer) panel: no fusion

MRI after RT+TMZ



RT+TMZ



T2 weighted 1/2021

T2 weighted 5/2021

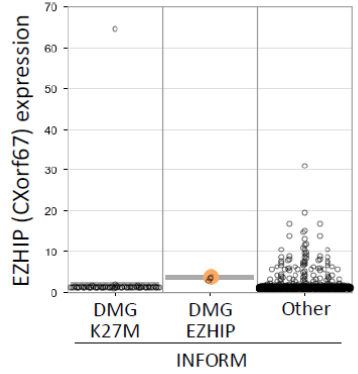
Clinical Case

6weeks — rapid metastatic progression

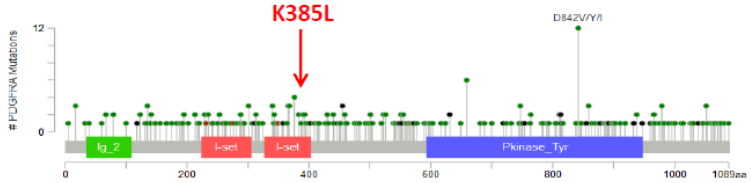
Trametinib — symptomatic home palliative care

INFORM

- EZHIP overexpression

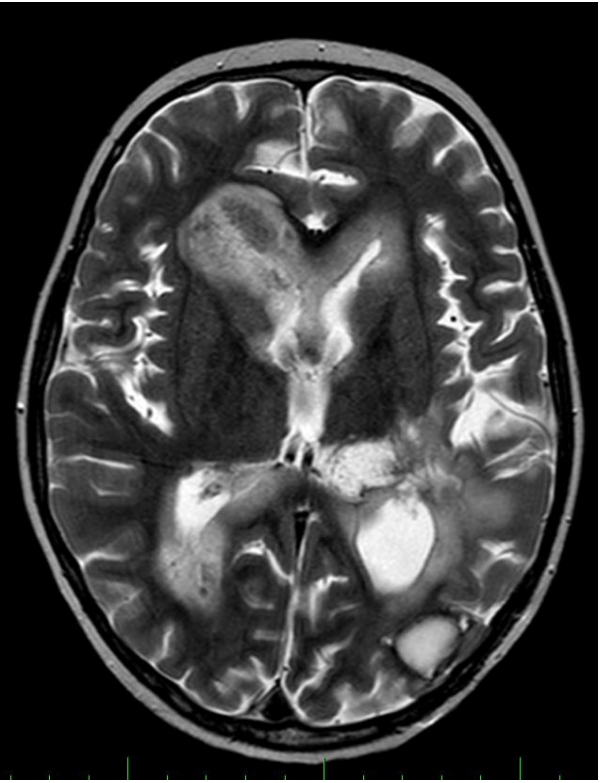


- mutation in the extracellular PDGFRα domain (K385L)

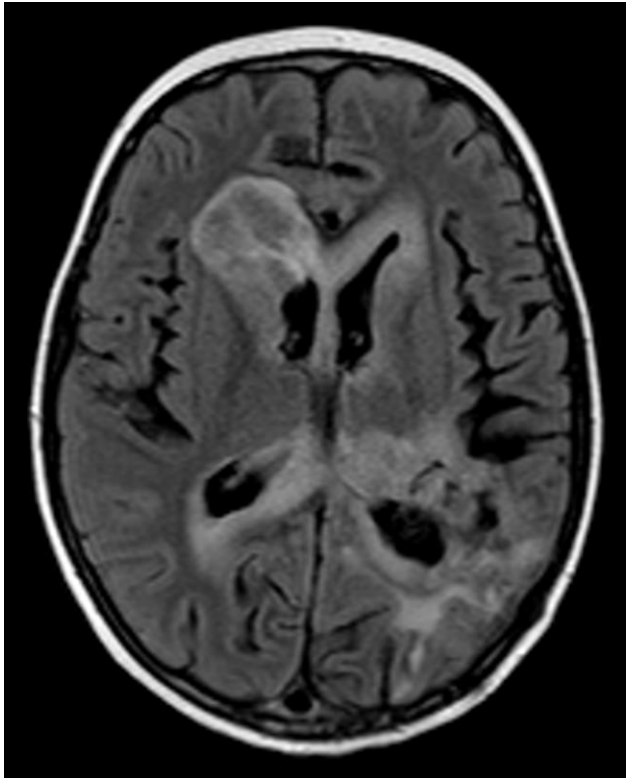


- methylation profile: Diffuse midline glioma, H3 K27 mutant (0,67)

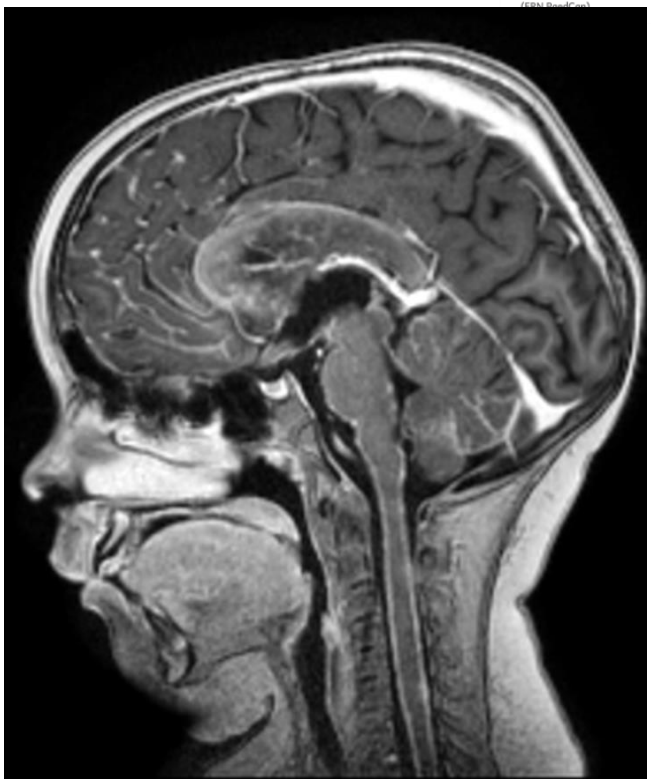
Metastatic progression



T2 weighted 6/2021



T2 FLAIR 6/2021



T1 GAD 6/2021

Question 3

What cellular pathway is blocked by the inhibitor Trametinib?

- JAK-STAT pathway
- MAP-Kinase pathway
- Wnt pathway

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Take home messages

- Group of H3 wild type HGG is very heterogenous
- The classification system is still being finetuned
- Such rare and challenging patients should be referred to the international tumour board
- In the context of pediatric HGG, the loss of trimethylation because of the EZHIP overexpression is a imunohistochemically detectable marker associated with dismal prognosis
- Novel treatment modalities are required in frontline settings as our current approaches are ineffective