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

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High grade glioma with ALK fusion

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COI declaration

- No conflict of interest

Case Presentation

- Girl, 13 years old
- June 2024
- History: 10 days of recurrent frontal headache and vomiting
- Family history:
  - Parents: both healthy (Spanish origin)
  - 1 younger sister, 6 years old. Healthy
  - No family history of cancer
  - No consanguinity

Case Presentation

- Emergency Department:
  - Right-sided facial palsy
  - No cutaneous stigmata
  - No other relevant findings in clinical examination
  - Brain-CT: large right intraventricular mass and acute bleeding signs

Case Presentation

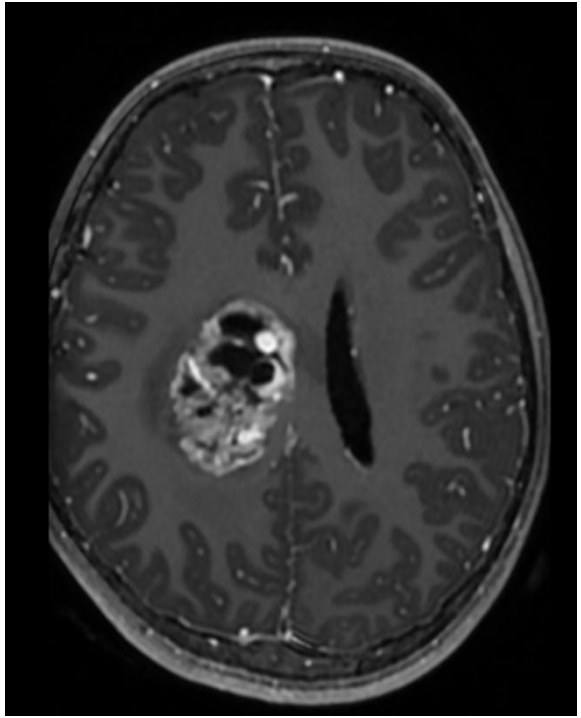
- Admitted to the ward:
  - **Craniospinal MRI**

Case Presentation

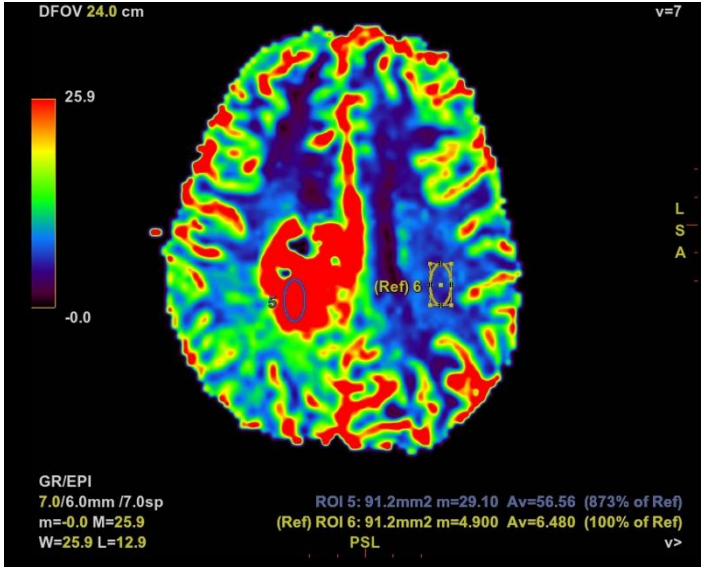
A large periventricular tumor with intraventricular invasion

Heterogeneous appearance with necrotic and cystic areas, and signs of hemorrhage.

Case Presentation

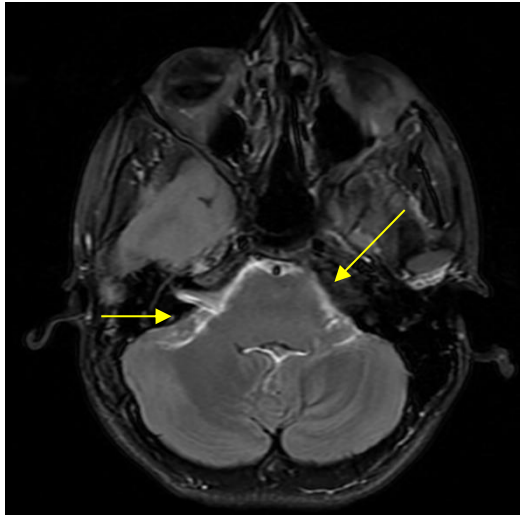


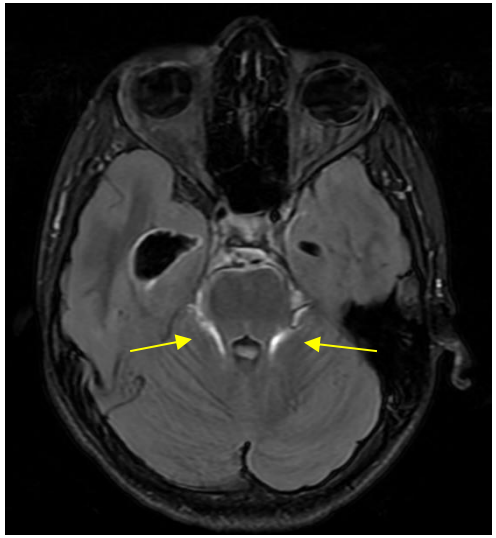
Intense and heterogeneous contrast enhancement.



Perfusion study shows markedly increased relative cerebral blood volume compared to normal white matter

Case Presentation





Leptomeningeal dissemination involving the brainstem, perimedullary and cerebellar regions, as well as the cranial nerves.

Question 1

- What is your differential diagnostic suspicion?

a. Choroid plexus carcinoma

b. High grade Glioma

c. Ependymoma

d. Metastasis

e. All correct

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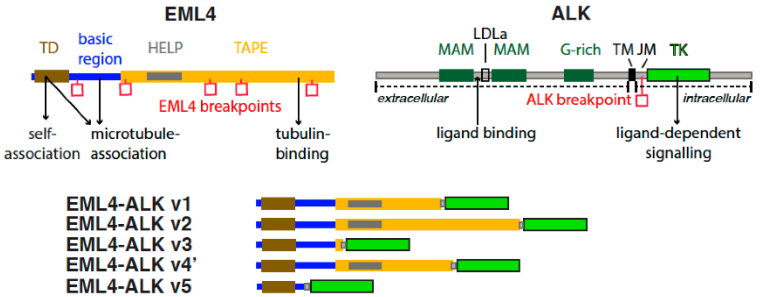
Case Presentation

- Surgery: June 28th, 2024 → Gross total resection achieved (primary tumor)
- Post-surgical sequelae: left hemiparesis.
- Pathology: **High-grade glioma**, H3 G34-mutant, WHO 2021 grade 4, *TP53* and *ATRX* mutant , with methylation of the MGMT promoter.
- EML4(2)-ALK(20) fusion (v5) (confirmed by IC)
- Tumor predisposition NGS panel negative (including *TP53*).

Case Presentation

- EML4(2)-ALK(20) fusion
  - Represents a variant 5 of a such rearrangement
  - Mostly described in non-small cell lung cancer, but in very low number of cases.
  - No previously reported in CNS tumors
  - Due to its molecular structure, similar to variant 3, it is predicted to show a resistance profile to some ALK-inhibitors



Question 2

- Would you ideally routinely perform comprehensive molecular profiling (including ALK, NTRK, ROS1, etc.) in pediatric gliomas?
  a. Yes, in all cases
  b. Only in high-grade tumors
  c. Only if progression occurs
  d. No, limited by resources

Question 2

- Would you ideally routinely perform comprehensive molecular profiling (including ALK, NTRK, ROS1, etc.) in pediatric gliomas?
  a. **Yes, in all cases**
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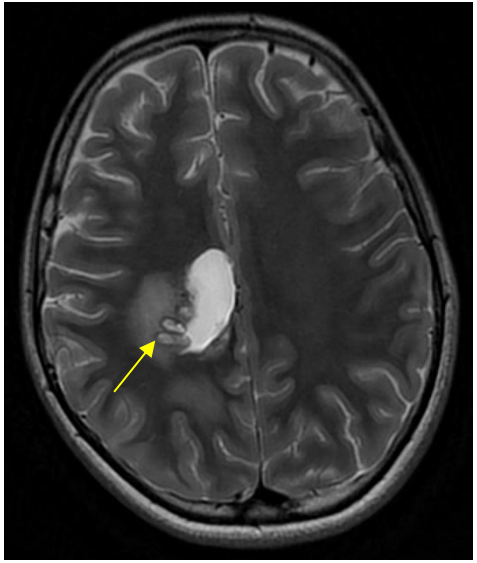
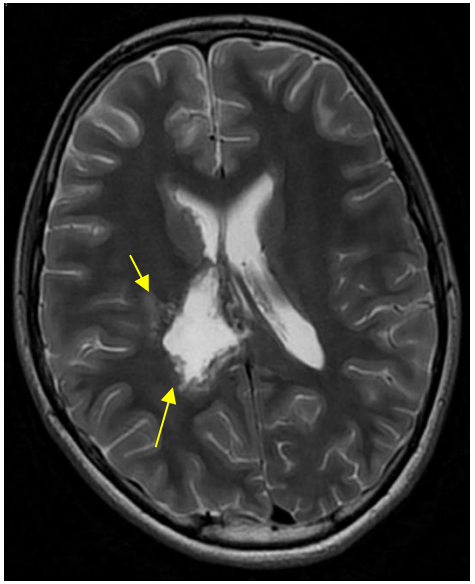
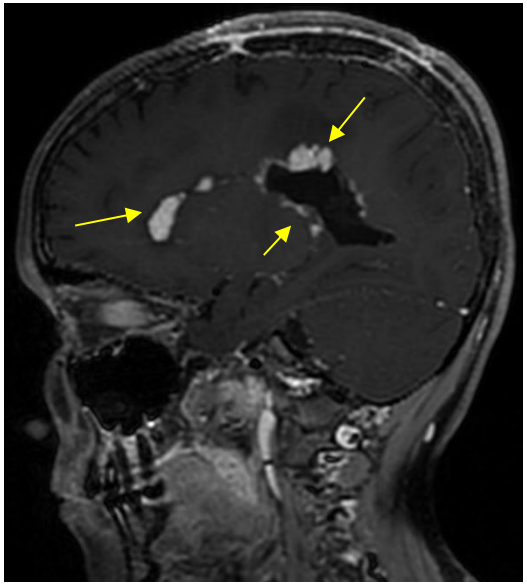
Case Presentation

- Early Progression → local recurrence + leptomeningeal spread 3w after surgery







Case Presentation

- Acute Complications:
  - Obstructive hydrocephalus due to cystic lesion in right lateral ventricle →External ventricular drain placement.
  - Right intraventricular hemorrhage

Question 3

- What would ideally be your first-line systemic approach after surgery in an ALK-rearranged glioma?

a. Conventional radiochemotherapy

b. Only chemotherapy (Temozolamide, Lomustine…)

c. Targeted therapy alone (ALK inhibitor)

d. Combination of radiotherapy + chemotherapy + targeted therapy

Question 3

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Case Presentation

- Treatment Strategy:
  - Craniospinal irradiation (36Gy + 18Gy tumor bed boost) + Temozolomide
  - MRI evaluation after completing chemoradiotherapy → stable disease.

Question 4

- Which ALK inhibitor would you prioritize in this case?

a. Crizotinib (1st generation)

b. Alectinib / Brigatinib (2nd generation)

c. Lorlatinib (3rd generation)

d. Depends on CNS involvement

Question 4

- Which ALK inhibitor would you prioritize in this case?

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c. Lorlatinib (3rd generation)

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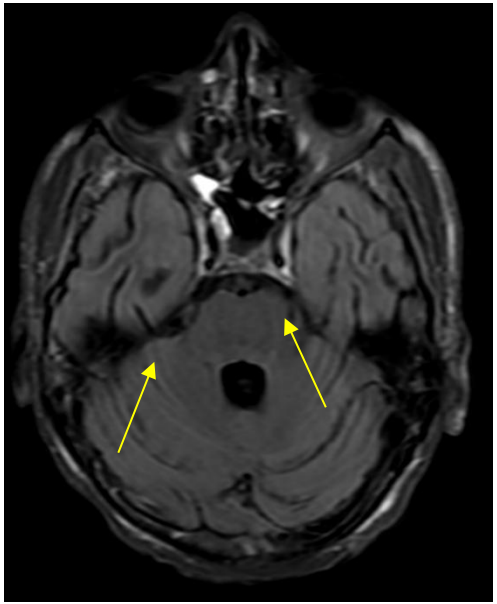
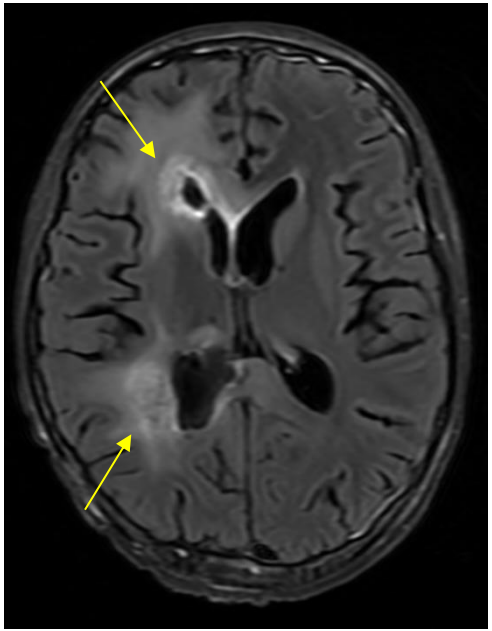
Case Presentation

- Treatment Strategy after RT:
  - Initiated concomitant temozolomide + lorlatinib.
    - Rationale:
      - Lorlatinib (3rd gen): superior CNS penetration than others ALK inh
        - » Goldsmith KC, et al. Lorlatinib with or without chemotherapy in ALK-driven refractory/relapsed neuroblastoma: phase 1 trial results. Nat Med. 2023 (NCT03107988)
      - Temozolomide: standard alkylating backbone.

Case Presentation

- Early response (after 2 cycles TMZ-Lorlatinib):





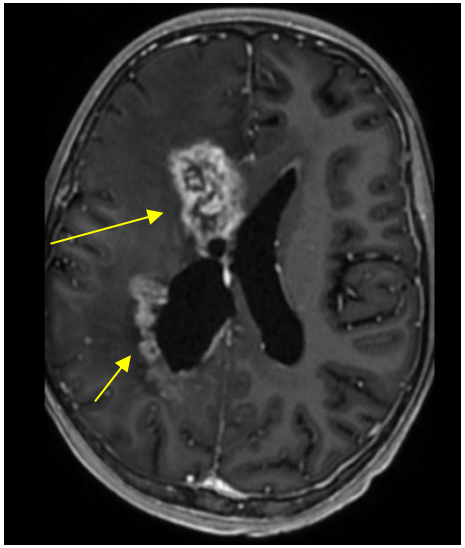
Case Presentation

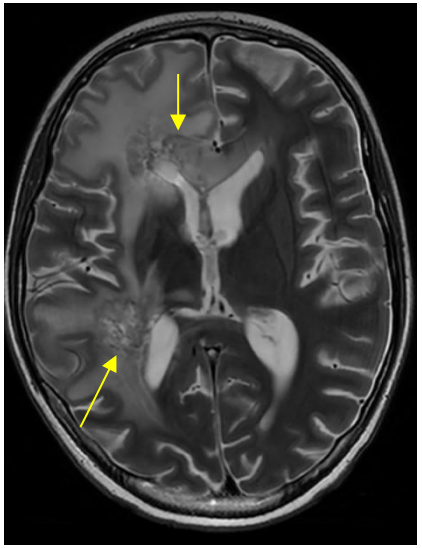
- Early response (after 2 cycles TMZ-Lorlatinib):
  - Periventricular progression.
  - Post-radiotherapy changes
  - Resolution of leptomeningeal lesions (brainstem, cranial nerves).

- Decision: continue same regimen due to partial response + stability.

Case Presentation

- After 4 cycles TMZ - Lorlatinib → periventricular progression + new brainstem involvement.



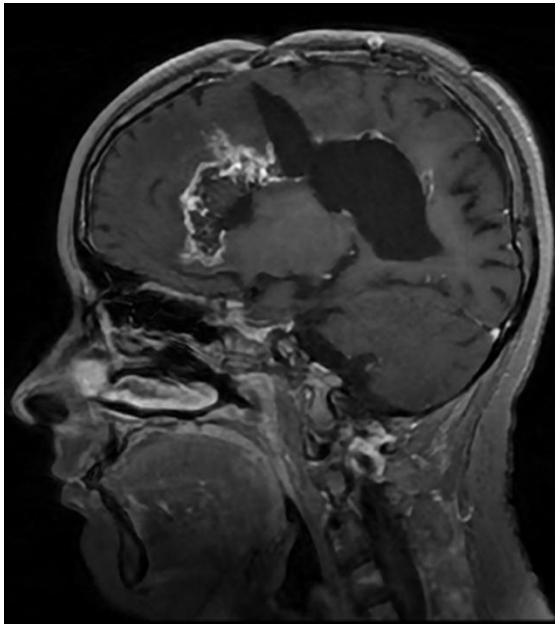


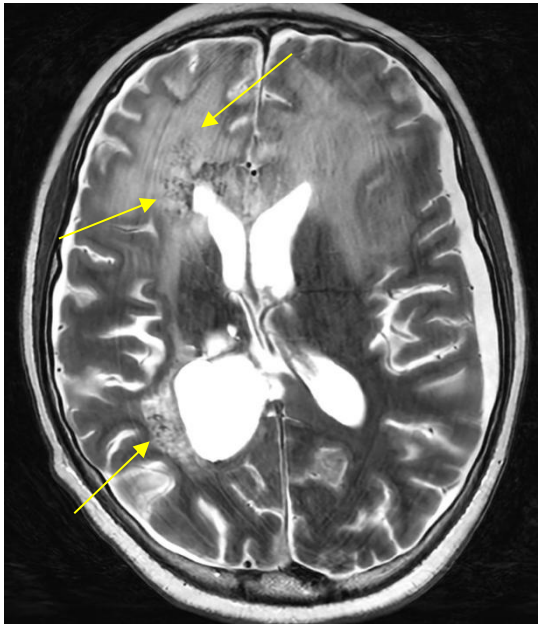
Case Presentation

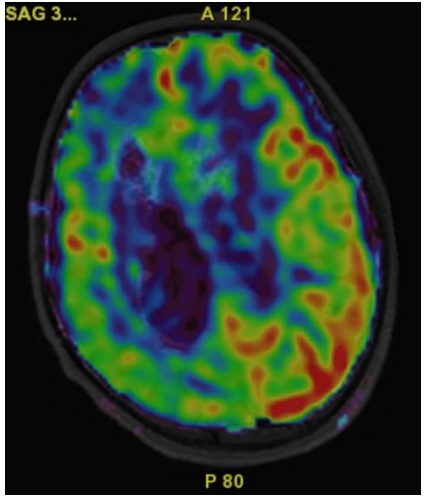
- After 4 cycles → periventricular progression + new brainstem involvement.
- Clinical status: stable.
- Decision: add lomustine (CCNU) to regimen (6 cycles planned). Continue Lorlatinib.

Case Presentation

- After 3 cycles (TMZ-Lomustine- Lorlatinib):







Perfusion imaging: predominant hypoperfusion in regions of radionecrosis, with reduced cerebral blood flow.

Case Presentation

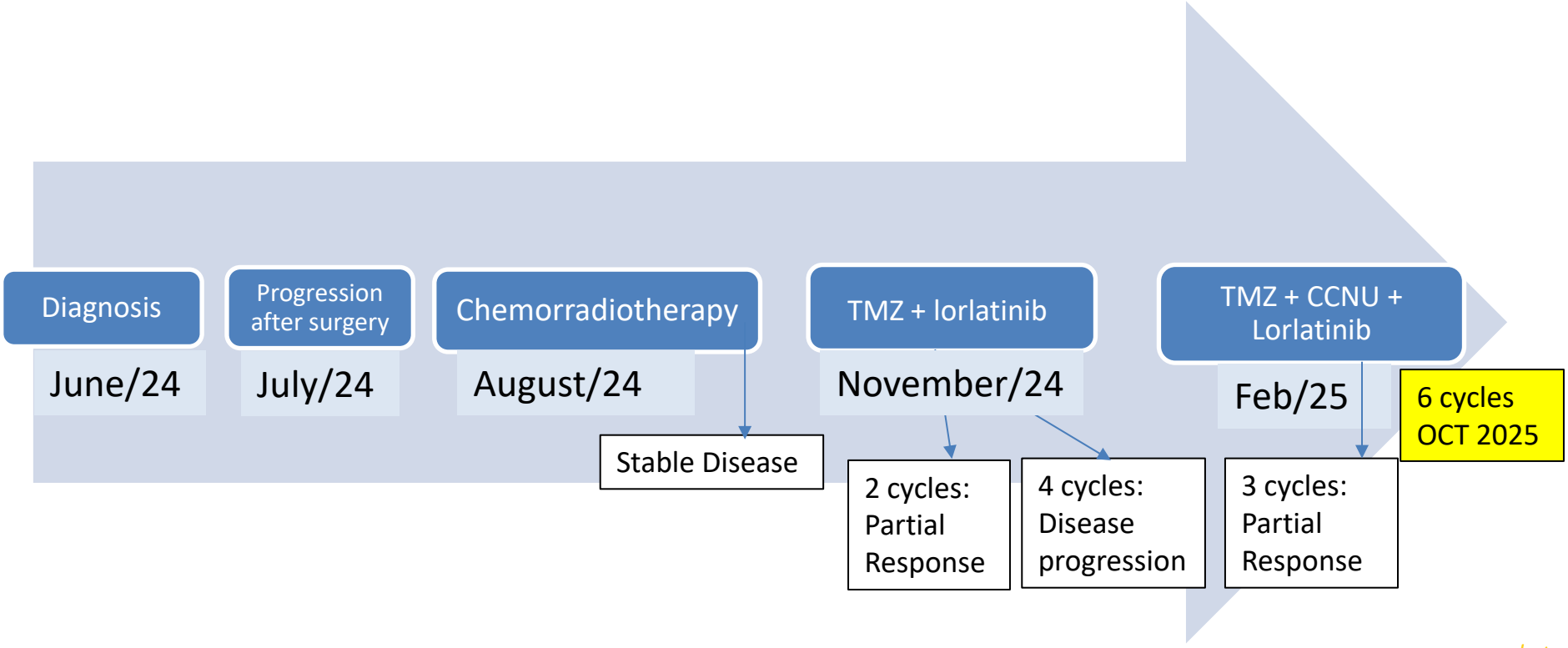
- After 3 cycles:
  - Bilateral frontal periventricular + right periatrial radionecrosis. Important edema.
  - **Reduction** of nodular component.
  - No new lesions.

PARTIAL RESPONSE

Case Presentation

- Treatment-Related Toxicities:
  - Cytopenias → delayed 4th cycle, dose reduction.
  - Weight gain + grade 2 hypertriglyceridemia (lorlatinib-related).
  - Supportive care provided.

Case Overview



Case Presentation

- Currently → Alive, 16 months after diagnosis
- Partial disease response in the last MRI
- Clinically stable → started 6th cycle (Oct 28, 2025). Awaiting re-evaluation after 6 cycles of TMZ + CCNU

Question 5

- How would you continue treatment in this patient?

a. Continue the same chemotherapy regimen and ALK inhibitor.
b. Continue Lorlatinib and Temozolomide and discontinue Lomustine.
c. Continue Lorlatinib only.
d. Discontinue all treatment and close surveillance.

Question 5

- How would you continue treatment in this patient?

a. Continue the same chemotherapy regimen and ALK inhibitor.

b. Continue Lorlatinib and Temozolomide and discontinue Lomustine.

c. Continue Lorlatinib only.

d. Discontinue all treatment and close surveillance.

e. Depending on MRI findings!

Question 6

- Which of the following adverse effects can be caused by Lomustine?
  a. Irreversible bone marrow aplasia
  b. Secondary neoplasms
  c. Pulmonary fibrosis
  d. All are correct

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DISCUSSION

Funded by the European Union's Health Programme

Take home messages

- Pediatric HGG management remains challenging.
- ALK-rearranged gliomas are rare but biologically targetable.
- Lorlatinib shows promising CNS activity.
- Combination regimens may enhance control but increase toxicity.
- Early molecular profiling and clinical trials participation are key