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Paediatric Cancer  
(ERN PaedCan)



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# ALK-POSITIVE HISTIOCYTOSIS, A RECENTLY DESCRIBED RARE SUBTYPE OF HISTIOCYTOSIS

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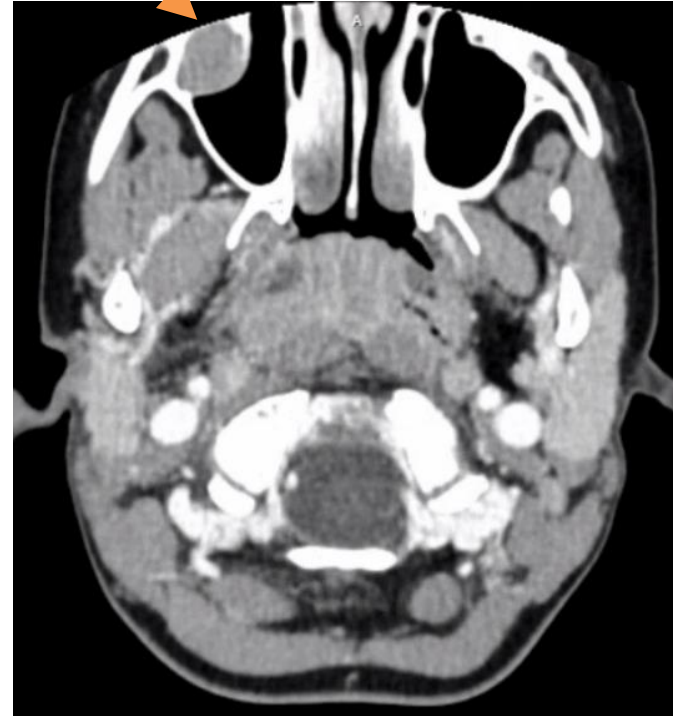


# COI declaration

- No conflicts of interest to declare

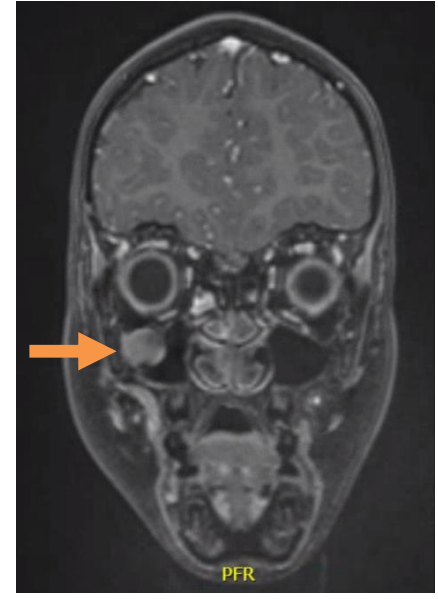
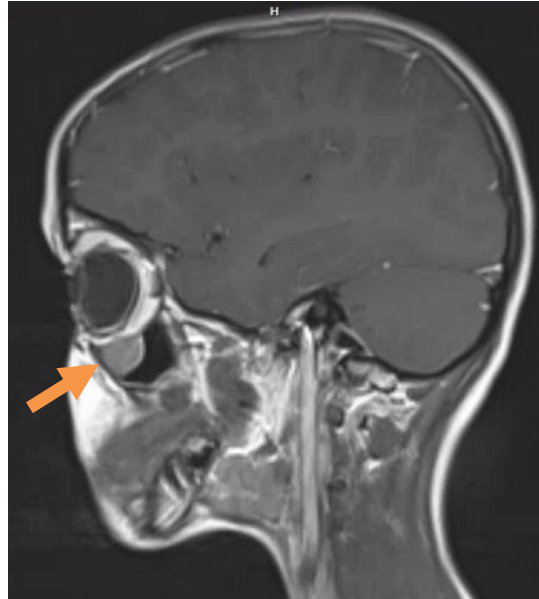
# Case: girl, 8y

- Uneventful medical history
- The last 6 months: recurrent pharyngitis/tonsillitis with flares of psoriasis guttata
- 02/2023: incidental finding on a CT scan performed to excluded a peritonsillar abscess



# Case: girl, 8y

- MRI : tumoral mass at the base of the right orbit, protruding into the cavity of the maxillary sinus



# Question 1

Which of the following diagnoses do you think is more likely?

- A. Rhabdomyosarcoma
- B. Langerhans cell histiocytosis
- C. Epidermoid cyst
- D. Lymphoma

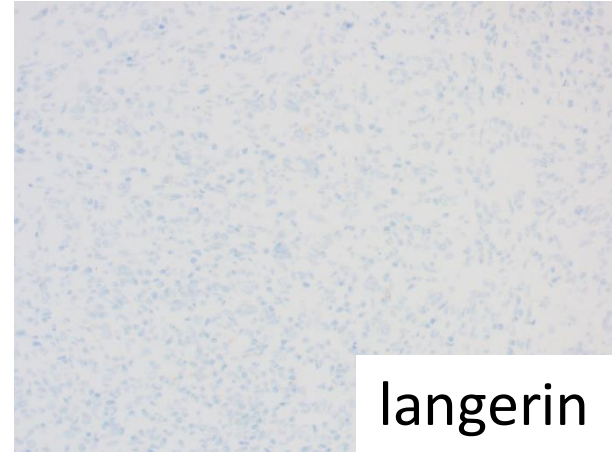
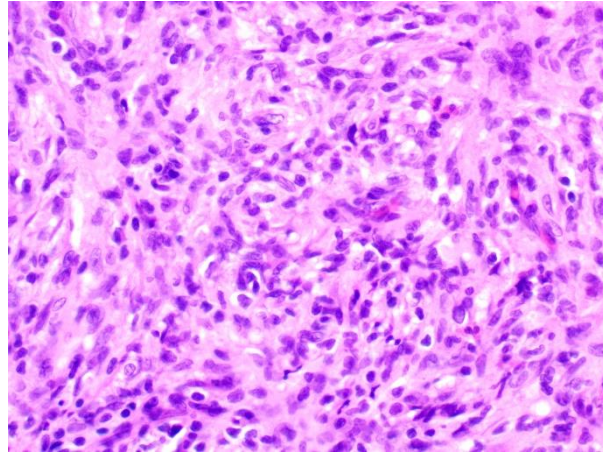
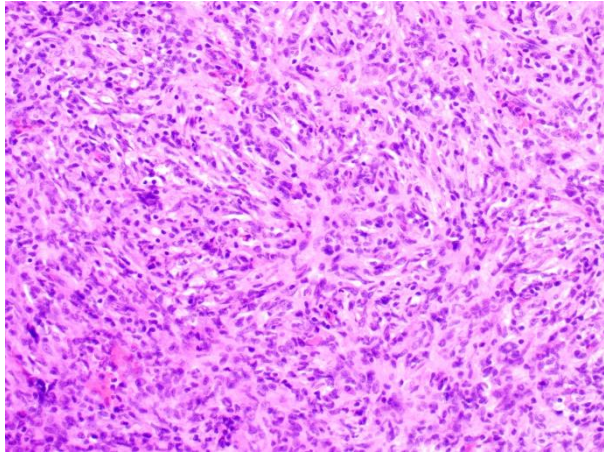
# Question 2

Which of the following investigations would you NOT do as initial work-up?

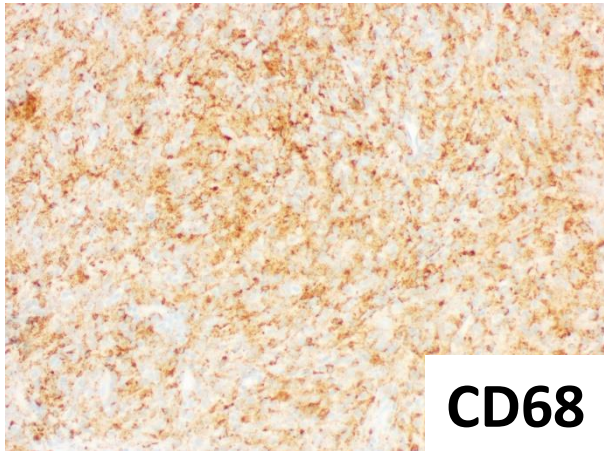
- A. Skeletal X-ray
- B. Abdominal ultrasound
- C. Complete blood count
- D. Lumbar puncture
- E. Lung X-ray

# Case: girl, 8y

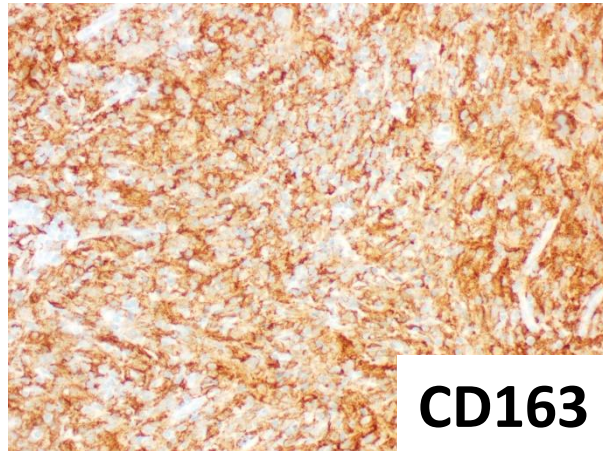
- In the next 2 weeks: pain in tumor region and visual complaints (diplopia)
- Biopsy pathology:
  - Initial report: morphological and immunohistochemical picture of non-LCH
    - CD163 ++ / CD68 ++ / S100 - / CD1a - / langerine - / BRAF -
    - Suggestive for non-lipidized variant (early phase) of juvenile xanthogranuloma
  - Additional stainings: strong and diffuse cytoplasmatic ALK expression
    - RNA sequencing: KIF5B::ALK fusion
- Final diagnosis: **ALK-positive histiocytosis**



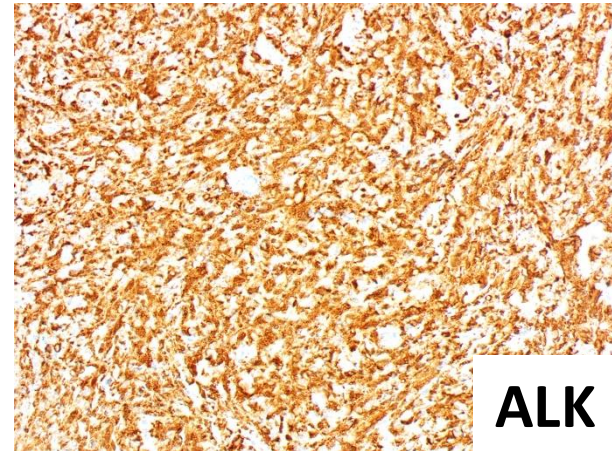
langerin



**CD68**



**CD163**



**ALK**



# Question 3

Have you ever seen a patient with ALK-positive histiocytosis?

- A. Yes
- B. No

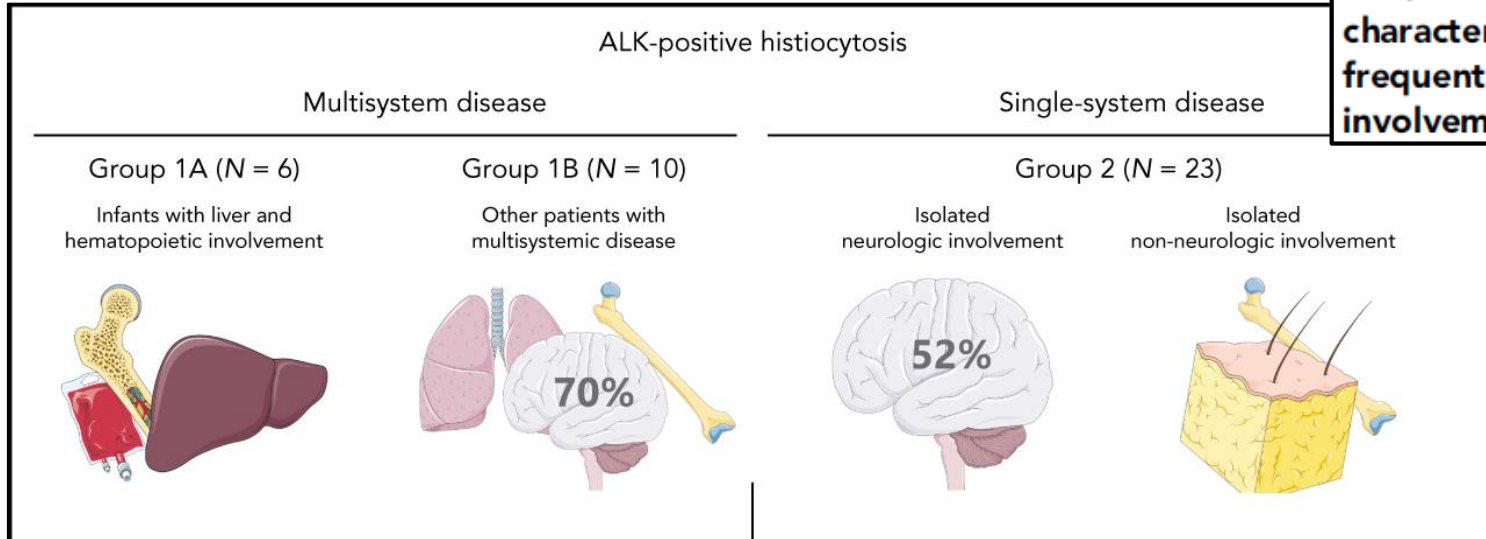
# ALK-positive histiocytosis

- Recently described entity of non-LCH with ALK overexpression and underlying ALK fusion
- Rare subtype of histiocytosis first reported by Chan et al. (Blood, 2008)
- Initial clinical phenotype (3 cases):
  - Early infancy
  - Multisystem disease
  - Massive hepatosplenomegaly
  - Hematopoietic involvement with marked cytopenias

# ALK-positive histiocytosis

- Largest case series: Kemps et al (Blood, 2022)
  - Expanding the clinical spectrum

**ALK-positive histiocytosis is a distinct entity associated with *KIF5B-ALK* fusions and characterized by frequent neurologic involvement.**



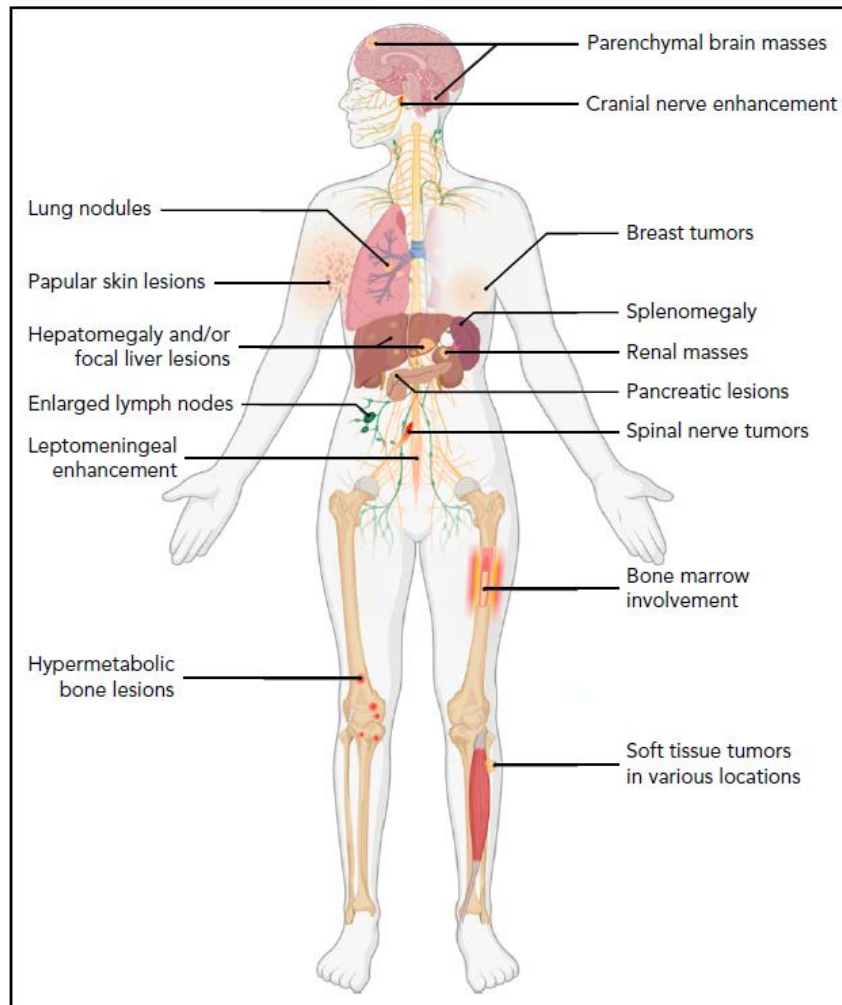
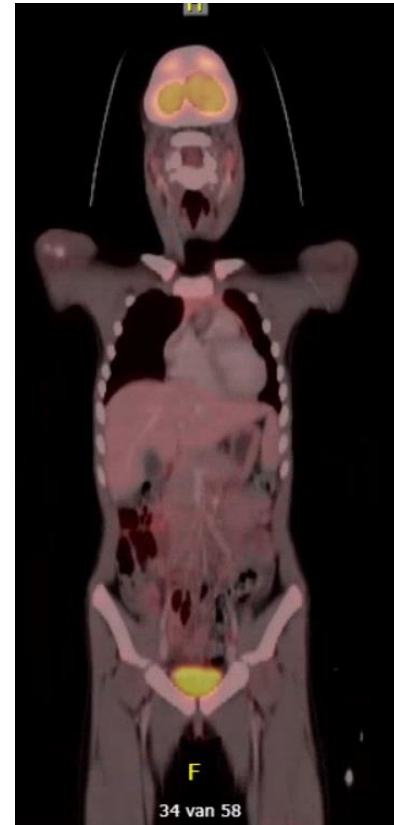


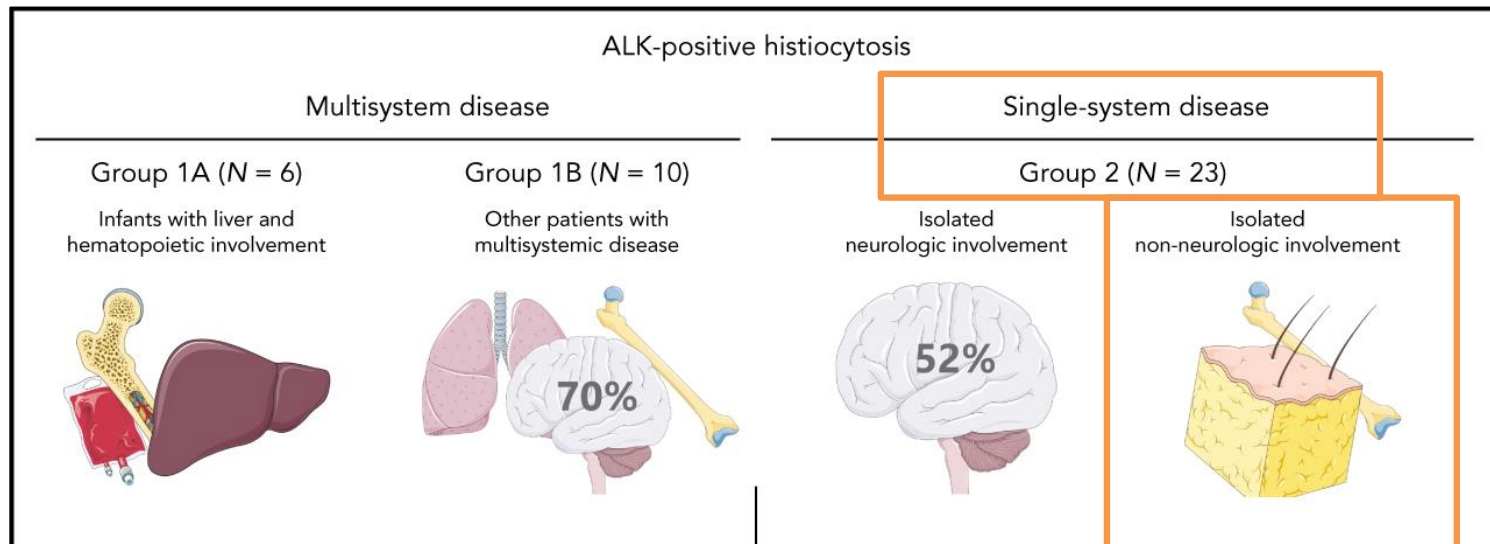
Figure 6. Body diagram showing recurrent anatomic sites of involvement of ALK-positive histiocytosis.

# Case: staging

- Staging methods
  - Whole body MRI
  - PET-CT
- PET-CT : no other lesions
  - Localized disease

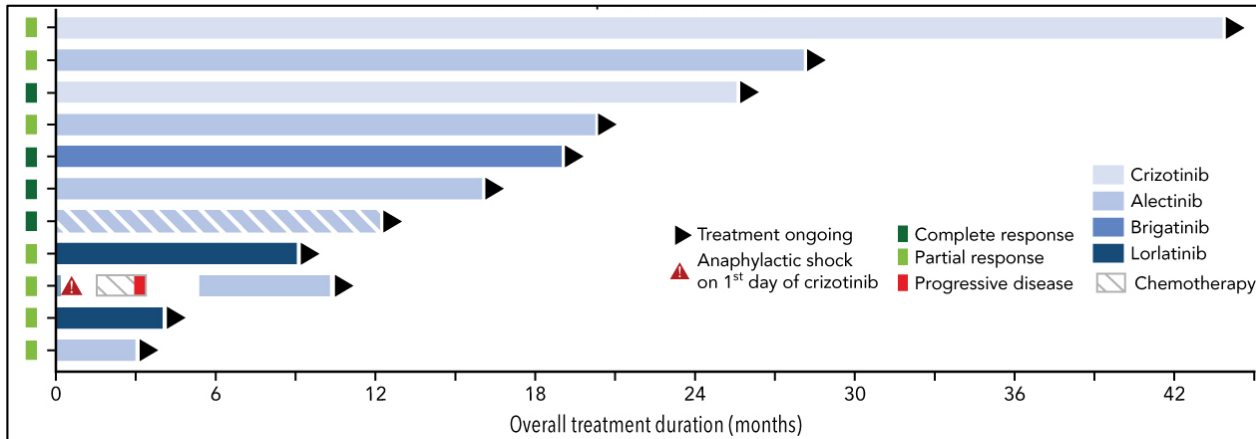


# Case: girl, 8y



# Treatment options

- Watch & wait
- Surgical resection
- Conventional systemic therapy (LCH-like therapy)
- ALK inhibitor
- Conventional systemic therapy + ALK inhibitor
- Radiotherapy



Robust and durable responses in 11/11 patients treated with ALK inhibition, of which 10 with neurologic involvement.

# Question 4

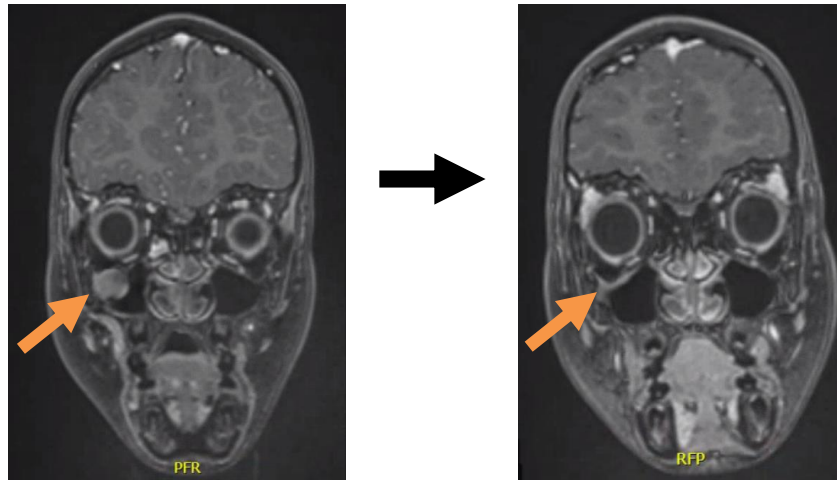
What treatment would you choose in this case?

- A. Watch & wait
- B. Surgical resection
- C. Conventional systemic therapy (LCH-like therapy)
- D. ALK inhibitor
- E. Conventional systemic therapy + ALK inhibitor
- F. Radiotherapy



# Case: treatment

- R0 resection not feasible (*necessary?*)
- ALK-inhibitor: crizotinib 2dd 200mg for 3 months (03-06/2023)
  - Very good tumor response, minimal residual lesion

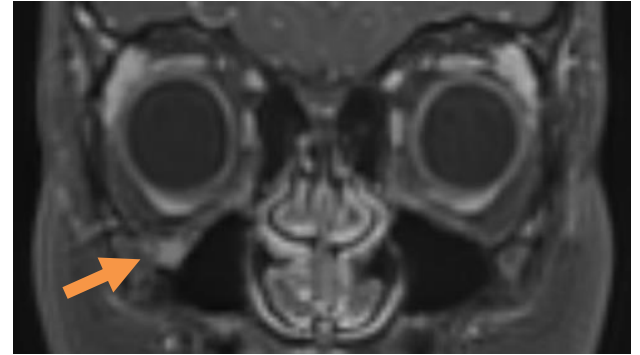


# Crizotinib

- ALK, MET and ROS1 inhibitor
  - Competitive binding within ATP-binding pocket of target RTKs
- Common side effect: ocular toxicity (incl. visual loss)
- Available in capsules and liquid formulation
- EU approved for ALK-positive ...
  - Non-small cell lung cancer in adults
  - Anaplastic large cell lymphoma (recurrent/refractory)
  - Inflammatory myofibroblastic tumor (unresectable, recur/refract)

# Case: follow-up

- MRI 6 months after stopping crizotinib:
  - Recurrence of small nodule 4x5 mm
  - Patient asymptomatic
- Treatment plan
  - R0 resection still not feasible
  - Wait & scan, re-initiate crizotinib in case of progression



# DISCUSSION

# Take home messages

- Non-LCH: screen for ALK overexpression/fusions
- ALK-positive histiocytosis: a new rare subtype of histiocytosis
  - Good tumor response to ALK inhibitors (when to stop?)
- New subtypes of non-LCH histiocytosis
  - Need to develop optimal staging and treatment guidelines