High-Risk Orbital and Maxillary Rhabdomyosarcoma with CSF Involvement: A Case Report

14-year-old female, FOXO1-positive alveolar subtype

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Multidisciplinary Tumor Board

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Case Introduction

Patient Demographics & Presentation

- **Demographics:** 14-year-old female
- **Chief Complaint:** Progressive right eye proptosis for 6 weeks
- **Associated symptoms:** Decreased visual acuity, diplopia, facial pain
- **PMH/FH:** Unremarkable, no family history of cancer
- **Physical Exam:** 3mm proptosis, limited extraocular movement, palpable right maxillary mass
- **Initial Impression:** Suspected orbital malignancy

Clinical Timeline

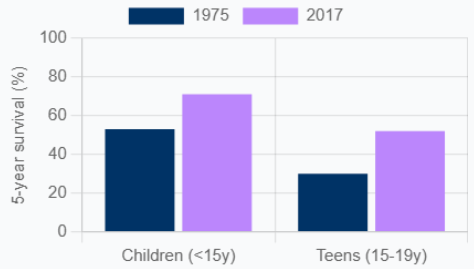
1. **Week 0: Symptom Onset**
   Initial eye discomfort and mild proptosis
2. **Week 4: First Medical Visit**
   Ophthalmology referral for worsening symptoms
   MRI ordered for visible proptosis
3. **Week 6: Diagnosis**
   Biopsy confirms alveolar rhabdomyosarcoma
   Staging workup initiated

Rhabdomyosarcoma Overview

Incidence & Epidemiology

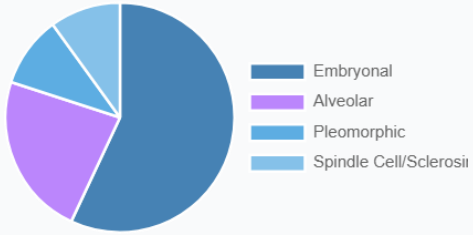
- Most common soft tissue sarcoma in children
- ~350 new cases annually in US
- Head & neck region: 40% of cases

5-year Survival Improvement (1975-2017)



Data source: NCI SEER 1975-2017

Subtype Distribution



Key Prognostic Factors

FOXO1 status
Fusion positive: worse

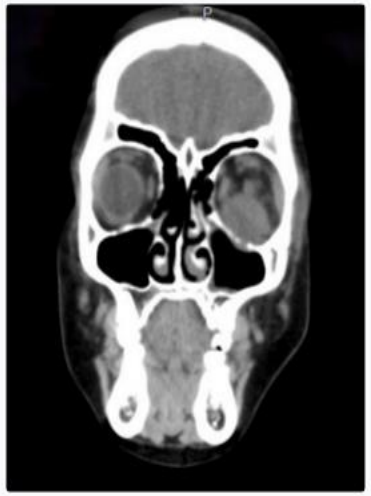
Primary site
Parameningeal: worse

Age
Teen: worse

CNS invasion
CSF+: significantly worse

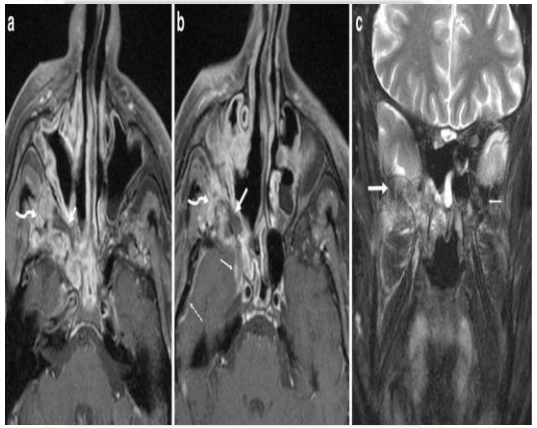
Diagnostic Imaging

MRI: Axial T1 with Contrast



Findings: Right orbital enhancing mass (3.2 × 2.8 cm) with medial and inferior orbital wall invasion
Features: Heterogeneous enhancement, extra-ocular muscle infiltration, optic nerve displacement

CT: Coronal View with Contrast



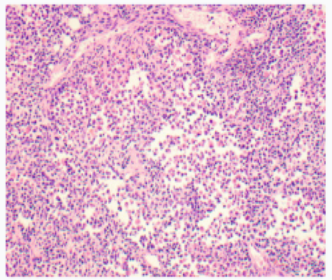
Findings: Right maxillary sinus involvement with bone erosion
Features: Extension to pterygopalatine fossa, classified as parameningeal site

Initial Radiologic Impression

- ✓ Aggressive orbital mass with maxillary extension
- ✓ Parameningeal involvement (critical prognostic factor)
- ✓ No initial evidence of intracranial extension or distant metastasis

Pathology and Molecular Studies

Histopathology



Alveolar Rhabdomyosarcoma (H&E stain, 400×)

- → Malignant small round blue cells
- → Characteristic fibrous septa
- → Alveolar pattern architecture

Diagnostic Approach

Core needle biopsy performed via transconjunctival approach with rapid diagnosis in frozen section followed by definitive histopathology and molecular testing

Immunohistochemistry & Molecular Profile

Marker	Result	Significance
Desmin	Positive	Muscle differentiation
Myogenin	Positive (diffuse)	Skeletal muscle lineage
MyoD1	Positive	Skeletal muscle lineage
Ki-67	60%	High proliferation index

Molecular Testing Results

FOXO1 Fusion Status: **POSITIVE**

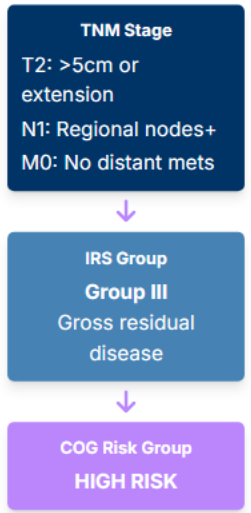
PAX3-FOXO1 fusion detected by RT-PCR

⚠ Clinical Significance:

- Associated with alveolar histology
- Poorer prognosis than fusion-negative cases
- Higher risk of metastasis and recurrence

Disease Staging & Risk Stratification

Risk Classification Pathway



High-Risk Determinants

- **Histology:** Alveolar subtype
- **Molecular:** FOXO1 fusion positive
- **Site:** Parameningeal (orbit with maxillary sinus extension)
- **Size:** >5cm with invasive features
- **Age:** 14 years (adolescent)

Initial CNS Evaluation

MRI Brain with Contrast

- No evidence of brain parenchymal involvement
- No leptomeningeal enhancement

Cerebrospinal Fluid Analysis

- Initial CSF: Negative for malignant cells
- Cytology: No tumor cells detected
- Flow cytometry: Negative

> Despite initial CNS-negative status, close monitoring required due to parameningeal location and high-risk features

Initial Treatment Plan

High-Risk Chemotherapy Protocol

Agent	Dose	Schedule
Vincristine (V)	1.5 mg/m²	Weeks 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34
Dactinomycin (A)	1.5 mg/m²	Weeks 1, 13, 25
Cyclophosphamide (C)	2.2 g/m²	Weeks 1, 13, 25
Irinotecan (I)	50 mg/m²/day × 5	Weeks 4, 7, 10, 16, 19, 22, 28, 31, 34
Vincristine (V)	1.5 mg/m²	Weeks 4, 7, 10, 16, 19, 22, 28, 31, 34

VAC/VI Regimen Details

- Duration: 42 weeks total
- G-CSF support with each cycle
- Response assessment after weeks 12, 24

Planned Radiotherapy

Modality: Proton Therapy
To minimize dose to developing brain

Dose: 50.4 Gy in 28 fractions
1.8 Gy per fraction

Target: Orbit and maxillary sinus
CTV = GTV + 1.5cm anatomically constrained

Timing: After week 12 of chemo
Concurrent with continued chemotherapy

Multidisciplinary Input

> *"Given the parameningeal site and high-risk features, we recommend comprehensive therapy with VAC/VI plus radiation, though initial CSF studies are negative."*
>
> — Tumor Board Consensus

Plan included regular CSF monitoring during treatment due to high risk of CNS involvement

Critical Treatment Pivot

Detection of CNS involvement after initial negative findings

Day 0

Initial Diagnosis

- Brain MRI negative
- CSF cytology negative
- Treatment initiated

Week 6

Routine Monitoring

- VAC/VI cycle 2
- CSF monitoring
- Still negative

Week 12

CSF Positive

- Malignant cells in CSF
- MRI: leptomeningeal enhancement
- Treatment pivot required

CSF Findings

- **Cytology:** Malignant small round blue cells consistent with rhabdomyosarcoma
- **Flow cytometry:** Positive for tumor cells (CD56+, desmin+)
- **Molecular:** PAX3-FOXO1 fusion detected in CSF sample

MRI Findings

- **New finding:** Subtle leptomeningeal enhancement along basilar cisterns
- **Primary tumor:** Partial response (30% reduction in orbit/maxilla)
- **Interpretation:** CNS metastasis despite ongoing chemotherapy

Adapted Treatment Strategy

Systemic Therapy

Modified high-risk regimen with intensification

Agent	Do
Topotecan	0.7 mg × 5
Cyclophosphamide	25(mg × 5

Alternating with VAC/V

- 42-week total duration maintained
- G-CSF support intensified

CNS-Directed Therapy

Intrathecal chemotherapy added

Agent	Dosing
Methotrexate (IT)	Age-based: 12 mg

Schedule: Weekly × 6, then monthly × 6

- CSF monitoring with each IT administration
- Continue until CSF negative × 3

Radiation Therapy

Expanded to include craniospinal irradiation

Target	Dose
Craniospinal axis	36 Gy/20 fractions
Primary site boost	50.4 Gy total (14.4 Gy boost)

- Literature supports 36 Gy CSI dose for CNS+ RMS (Int J Radiat Oncol Biol Phys 2017; 99(2): S047)

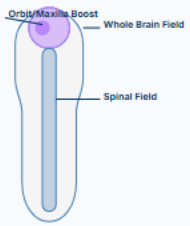
Multidisciplinary Decision

"The detection of CSF involvement necessitates an immediate and comprehensive adaptation of our treatment approach. We recommend intensification of systemic therapy with topotecan/cyclophosphamide, addition of intrathecal methotrexate, and expansion of radiation to include craniospinal irradiation."

— Consensus statement, Pediatric Neuro-Oncology Tumor Board

Radiotherapy Details

Craniospinal Irradiation Fields



CSI: Whole brain + full spine to S2/S3

Treatment Planning Considerations

- Special attention to lens, cochlea, pituitary doses
- Adolescent growth considerations
- Cardiac sparing techniques employed
- Ovarian shielding to preserve fertility

Technical Specifications

Radiation Treatment Parameters

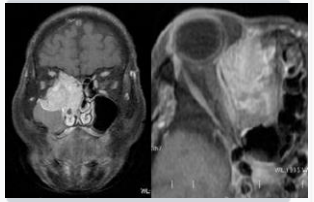
Modality	IMPT (Intensity Modulated Proton Therapy)
CSI Dose	36 Gy in 20 fractions (1.8 Gy/fraction)
Boost Dose	14.4 Gy in 8 fractions to orbit/maxilla
Total Dose	50.4 Gy to primary site
Treatment Duration	5.5 weeks (5 fractions/week)
Timing	Initiated within 7 days of CSF+ finding

Dose Constraints for Organs at Risk

Structure	Constraint	Achieved
Lens	Mean < 7 Gy	5.8 Gy
Optic nerves	Max < 54 Gy	52.1 Gy
Cochlea	Mean < 35 Gy	32.6 Gy
Pituitary	Mean < 40 Gy	38.2 Gy
Heart	Mean < 15 Gy	12.3 Gy

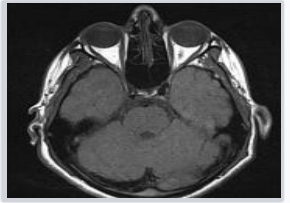
Treatment Response

Pre-Treatment (Week 0)



Tumor size: 3.2 × 2.8 cm
Extensive orbital and maxillary involvement

Post-Treatment (Week 42)



No measurable disease
Residual post-treatment changes only

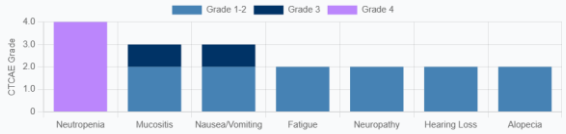
RECIST Response

Timepoint	Response	% Change
Week 12	Partial Response	-30%
Week 24	Partial Response	-80%
Week 42 (End of Tx)	Complete Response	-100%

CNS Response

Timepoint	CSF Cytology	MRI Findings
Week 12	Positive	Leptomeningeal enhancement
Week 18	Suspicious	Decreased enhancement
Week 24+	Negative × 3	No enhancement

Treatment-Related Toxicities (CTCAE v5.0)



- **Most severe:** Grade 4 neutropenia requiring hospitalization × 2
- **Persistent:** Grade 2 fatigue, neuropathy, hearing loss

Follow-up & Surveillance

Surveillance Protocol

Current Patient Status

Complete Remission at 18 Months

- **Local response:** No evidence of disease at primary site
- **CNS response:** No evidence of leptomeningeal disease
- **Functional status:** ECOG 1, returned to school
- **Quality of life:** Good, minor persistent visual deficit

Late Effects Monitoring

Ophthalmologic
q6-month visual assessment

Neurocognitive
Annual assessment

Audiologic
Annual audiometry

Cardiac
Annual ECHO

Endocrine
Growth, thyroid, puberty

Fertility
Pubertal development

Patient enrolled in COG ALTE07C1 late effects study for comprehensive long-term follow-up

Survivorship Care Approach

"Our goal is not only to achieve disease control but to optimize quality of life. This patient's care has transitioned from acute treatment to a comprehensive survivorship model, with multidisciplinary monitoring for both disease recurrence and treatment-related late effects."

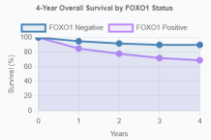
— Pediatric Oncology Survivorship Team

Literature Review

Similar Case Reports & Series

Author	Year	Site	Subtype	CSF+	Treatment	C
Burke et al.	2017	Parameningeal	Alveolar	Yes	VAC + CSI 36 Gy	(3 [
Raney et al.	2011	Head/Neck	Mixed	Yes (n=8)	Chemo + CSI	5
Casey et al.	2019	Orbital	Alveolar	Initial+	VAC/VI + CSI 36 Gy	F a
Zhang et al.	2020	Parameningeal	Alveolar	Delayed+	Intensified + CSI	(2 [

FOXO1 Status Impact



Key finding: Chen et al., Cancer 2021 FOXO1+ RMS 4-year OS 69% vs 90% for FOXO1- High-risk features: adolescent age, alveolar histology, FOXO1+

CNS-Directed Therapy Evidence

Approach	Evidence	Outcome Impact
CSI Dose	36 Gy median	Improved OS/PFS
IT Chemotherapy	Adjunct to CSI	Modest benefit
Systemic Intensification	Topotecan/Cyclo	Improved CNS control

> "For CNS-positive RMS, craniospinal irradiation to a dose of at least 36 Gy with systemic intensification represents the current standard of care, with improved outcomes compared to historical controls."
>
> — Int J Radiat Oncol Biol Phys 2017; 99(2): S047

Evidence-Based Treatment Rationale

- Early CSF monitoring essential for parameningeal cases (COG recommendation)
- Intensified systemic therapy plus CNS-directed therapy improved outcomes (Raney et al.)
- CSI dose of 36 Gy associated with improved CNS control (Burke et al.)
- Early treatment adaptation critical for newly detected CNS disease (Zhang et al.)

Key Learning Points

Molecular Profiling Critical

FOXO1 fusion status is essential for risk stratification and treatment planning in rhabdomyosarcoma, with fusion-positive cases requiring more intensive therapy

Adaptive Treatment Approach

Promptly pivoting treatment strategy when new findings emerge is critical for optimal outcomes; flexibility in protocol adaptation improves survival

Vigilant CNS Monitoring

Regular CSF assessment is mandatory for parameningeal RMS even when initially negative, as delayed CNS involvement can occur despite systemic therapy

Multidisciplinary Coordination

Comprehensive care involving pediatric oncology, radiation oncology, neurosurgery, and rehabilitation medicine is essential for complex cases

CSI Standard for CNS+ Disease

For CSF-positive disease, craniospinal irradiation to 36 Gy with primary site boost represents standard of care based on best available evidence

Long-term Survivorship Planning

Early implementation of survivorship care plan addresses both oncologic surveillance and therapy-related late effects monitoring

Discussion Questions

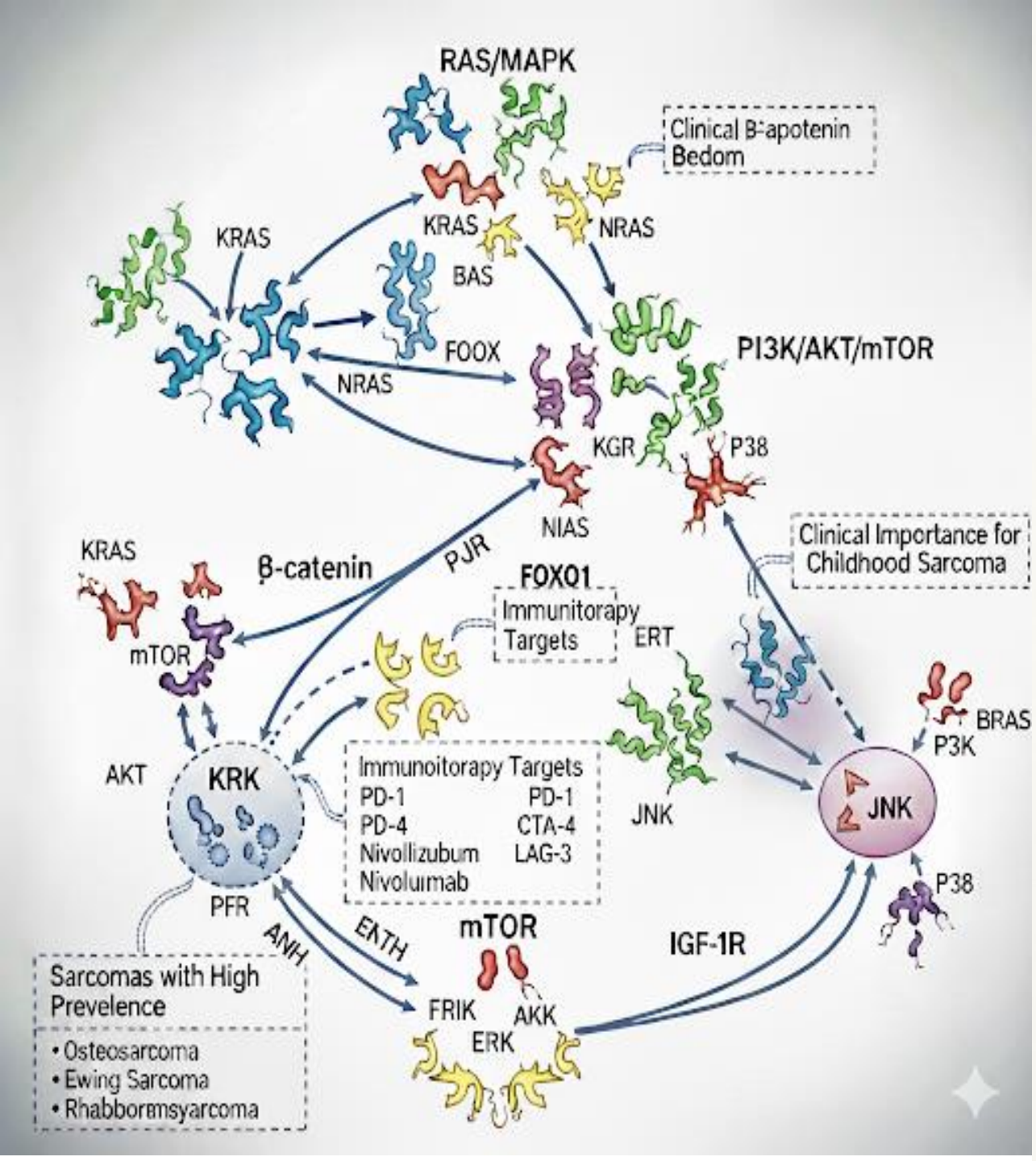
1. How would your approach differ if this patient had presented with initial CSF positivity rather than delayed involvement?

2. What is the optimal frequency of CSF monitoring for parameningeal rhabdomyosarcoma patients who are initially CSF-negative?

3. Is there a role for prophylactic CNS-directed therapy in high-risk FOXO1-positive parameningeal rhabdomyosarcoma?

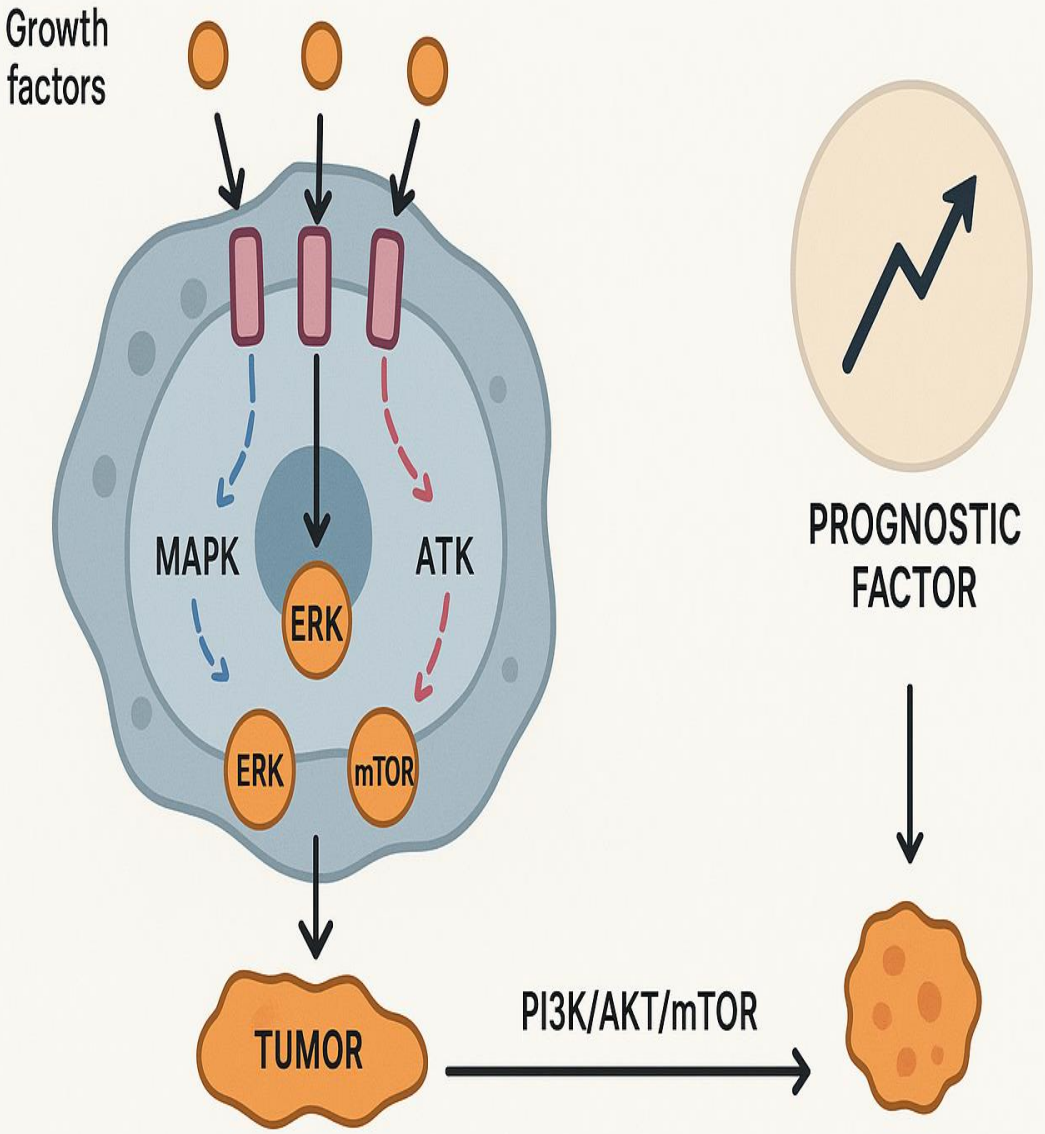
4. How would you modify this patient's long-term follow-up plan given the history of CSF involvement and craniospinal irradiation?

5. What novel therapeutic approaches or clinical trials would you consider for a similar patient who progresses despite initial intensified therapy?



MOLECULAR PATHWAY AND SIGNALING IN SARCOMA

IMPORTANCE OF THAT FOR PROGNOSTIC FACTOR



Thank you for your attention.

Questions about childhood sarcoma?