

Solid and CNS Tumors at Relapse: Creativity and Challenges for the APN

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Disclosure

- We have nothing to disclose.
- We will be talking about off-label use of medications.

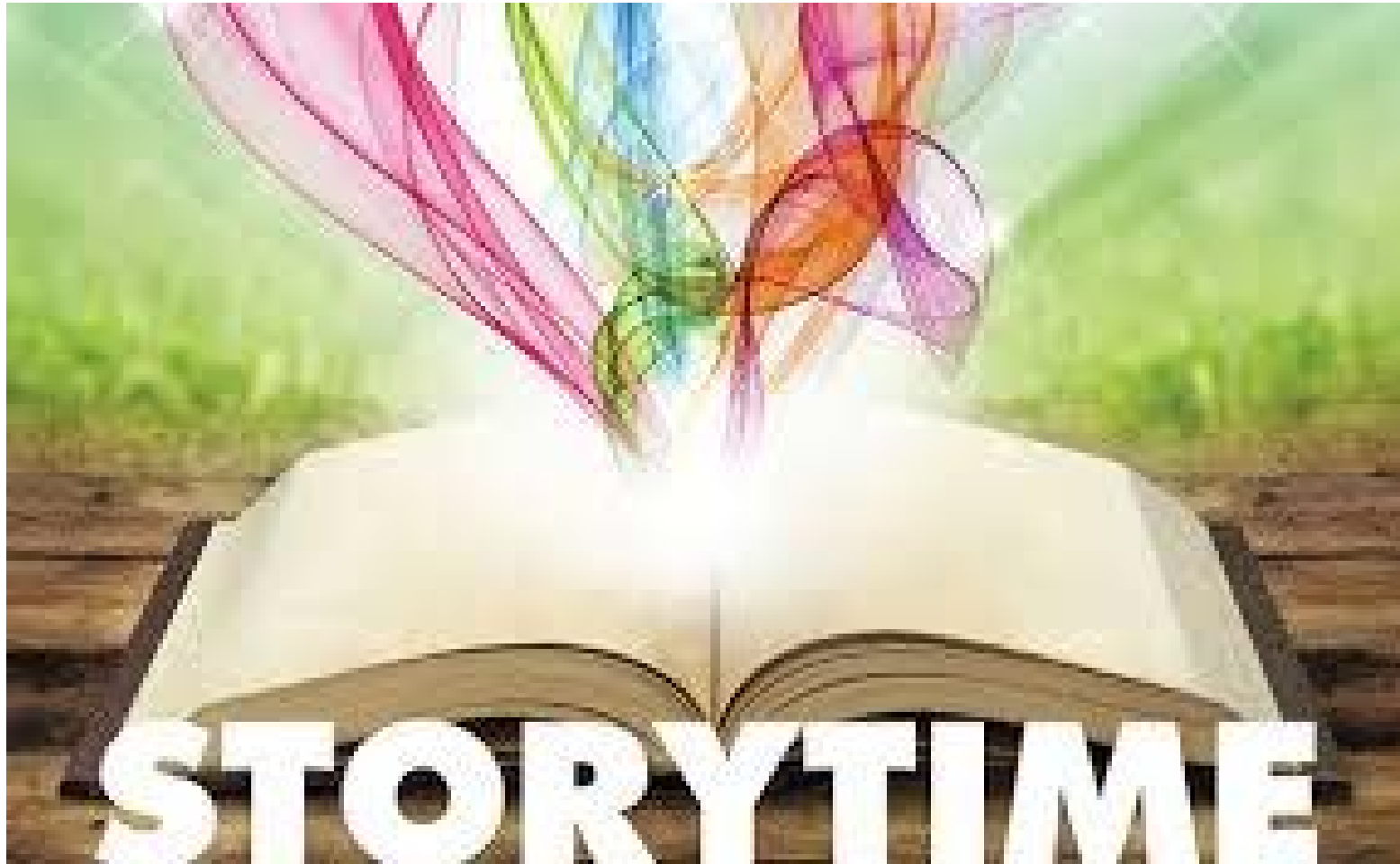
Objectives

- Increase knowledge of relapsed therapies for solid and CNS tumors.
- Discuss the challenges providers and patients/families face determining treatment at relapse.
- Identify the various testing done to help guide the best course of action for relapsed solid and CNS tumors.
- Adopt new pathways for decision making and carrying out of new treatment protocols.

Introduction

- Relapsed tumors (or progression on therapy) challenge providers to provide and deliver new and innovative therapies
- There are few well-proven, successful treatments at the time of relapse
- Without a proven therapy or applicable early phase clinical trial, physicians often develop new creative therapies that can target identified mutations, combine with known cytotoxic agents with or without autologous stem cell transplantation, and give new and novel therapies based on recent research findings
- Unfortunately, there is not usually a consensus or standard of care
- APNs need to be able to assist in delivery of the therapy including roadmap development, prescribing, insurance authorization, determining monitoring guidelines, evaluating for drug-drug interactions and side effects, and delivery of the therapy to the individual
- There is significant movement toward targeted therapies to directly impact known genetic mutations present in the tumor

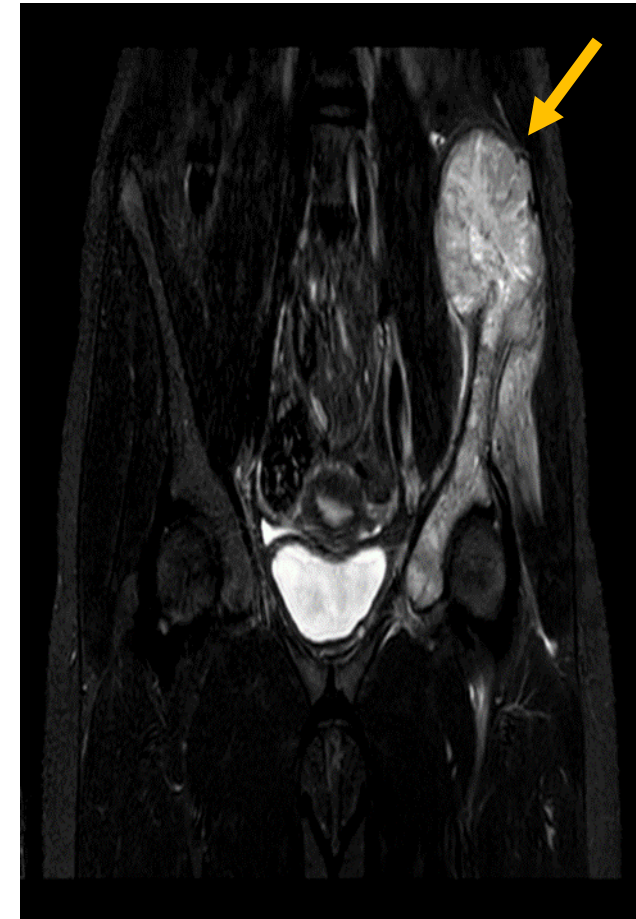
It's Story Time...





Marcia

14 y/o female with Ewing sarcoma of the pelvis with metastatic disease in contralateral pelvis and sacrum

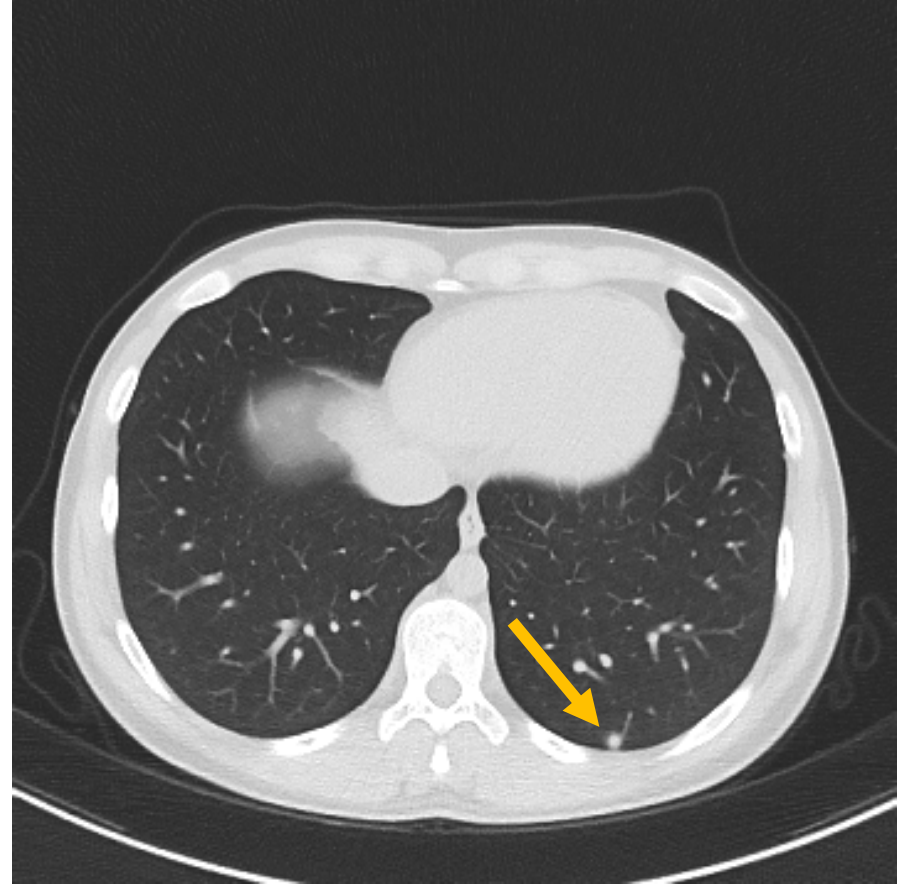
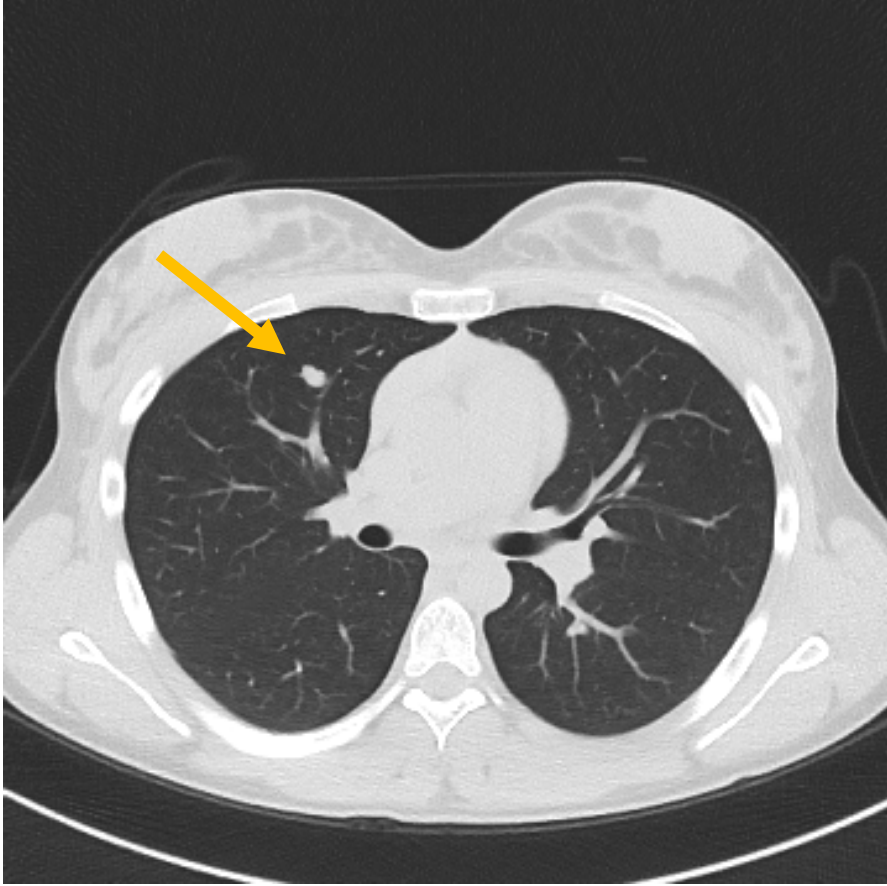


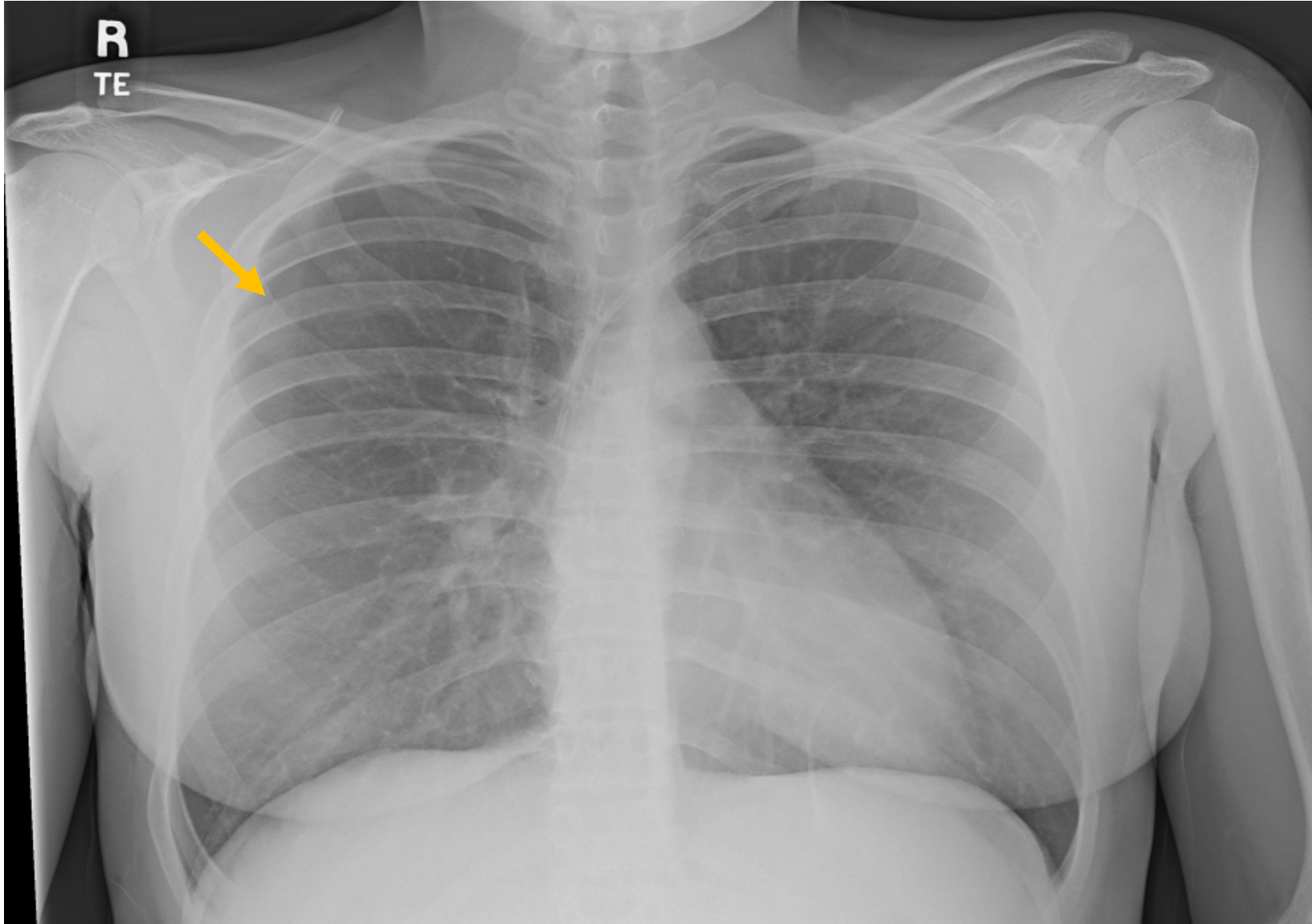
Treatment

- AEWS1221, arm A (NCT02306161)
 - vincristine/doxorubicin/cyclophosphamide/ifosfamide/etoposide
 - Local control: radiation (55.8Gy) to primary and metastatic sites

Recurrence

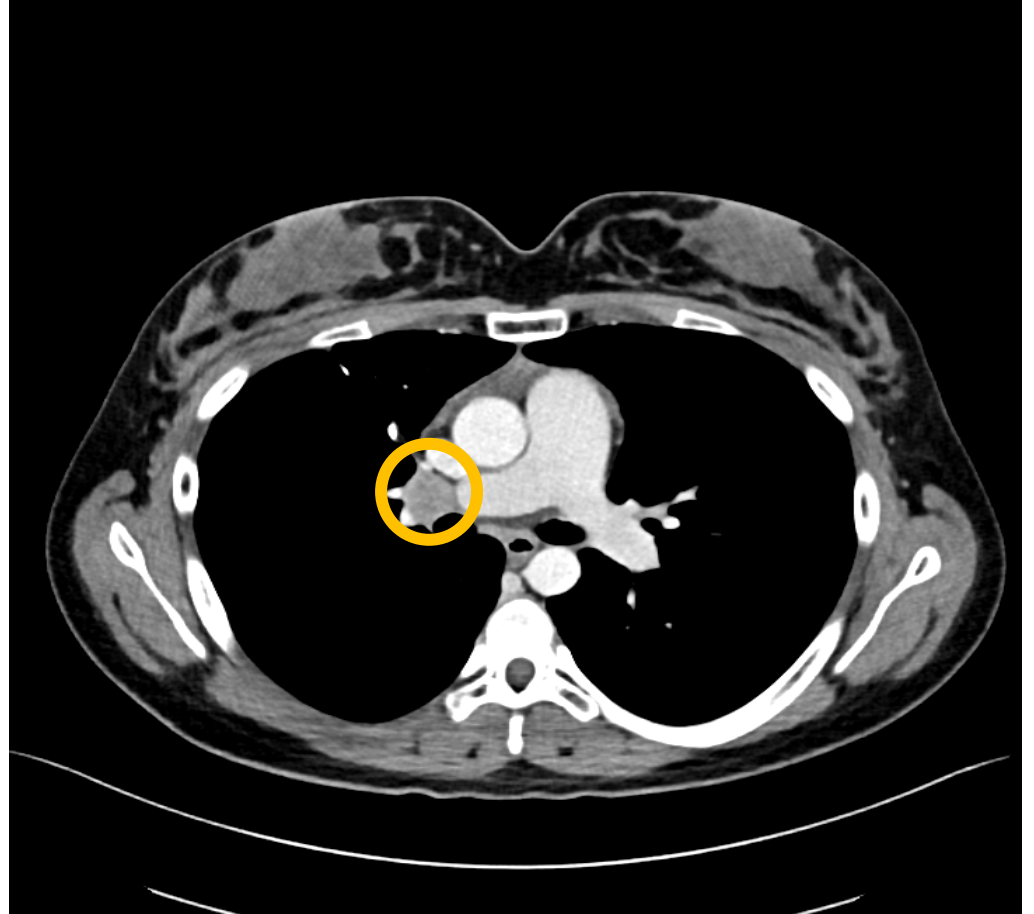
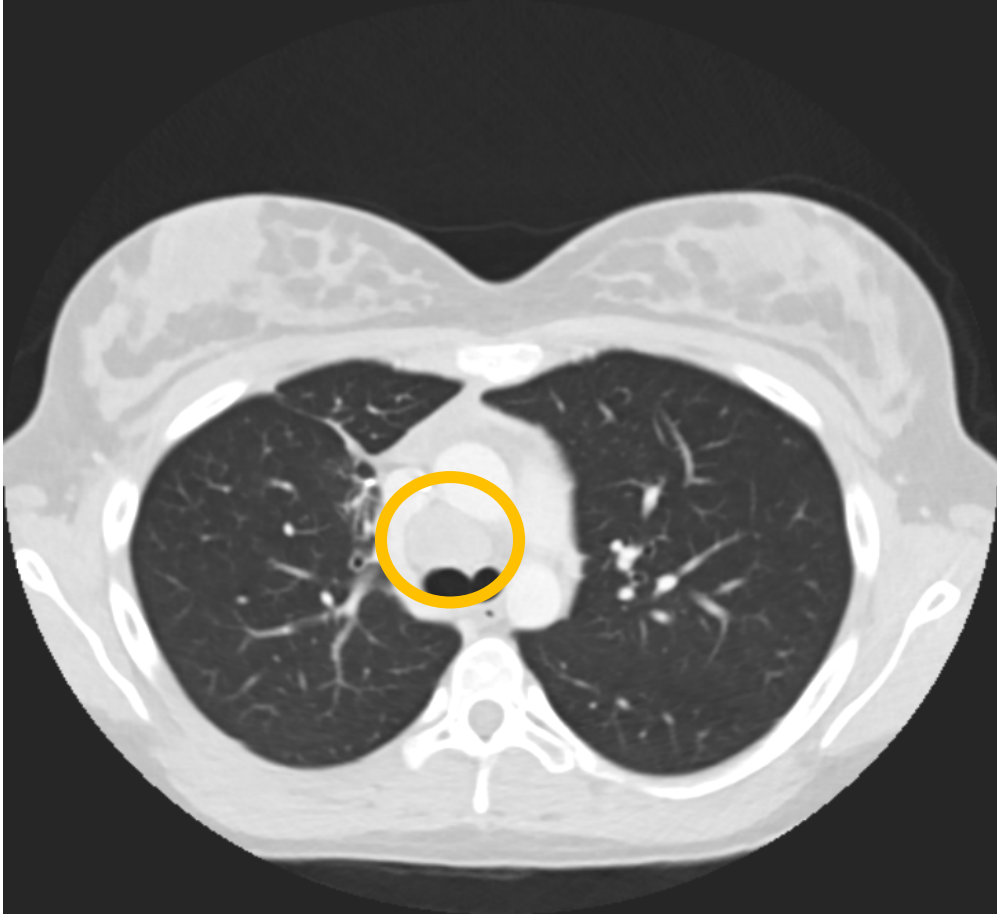
- 1st: New LLL and RUL nodules (biopsy proven)-17 months off therapy
 - GAIN sent (NCT02520713)
 - cyclophosphamide/topotecan
 - vincristine/oral irinotecan/temozolomide (VOIT)
 - olaparib (PARP inhibitor) + irinotecan/temozolomide (another state)
 - Surgery-RUL resection
- 2nd: Above resection positive for Ewing sarcoma-8 months later
 - Whole lung irradiation (15 Gy) and focal boost to resection bed (36 Gy)
 - pazopanib

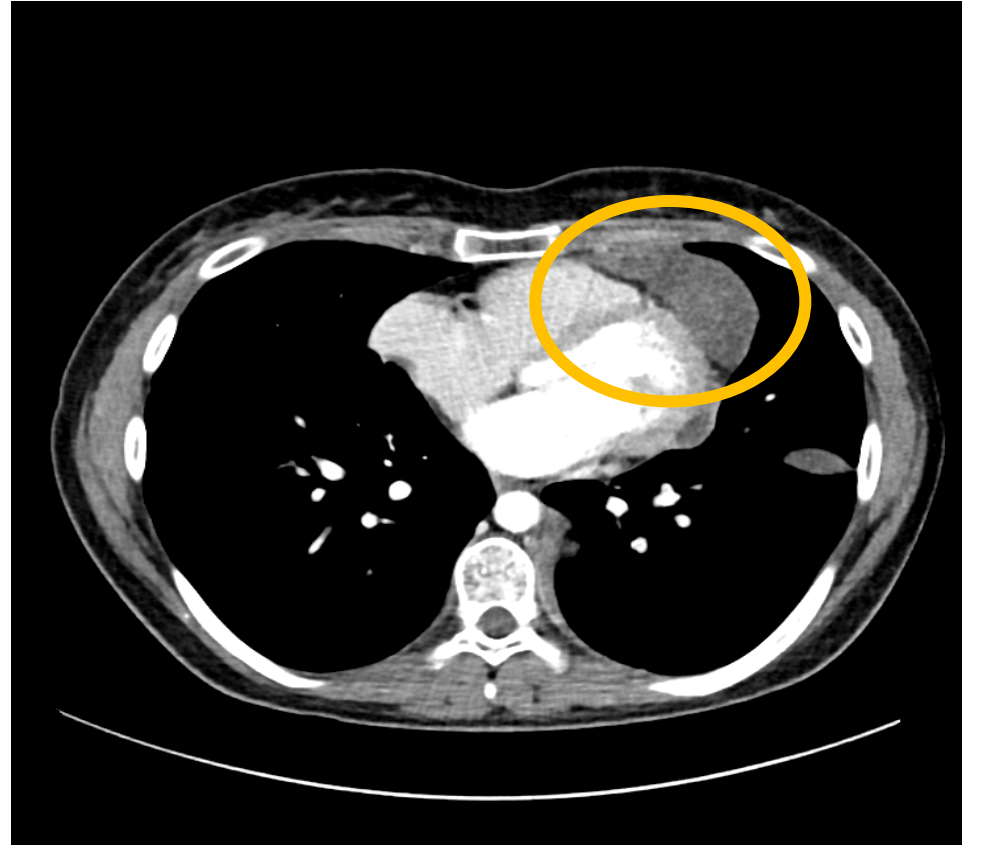
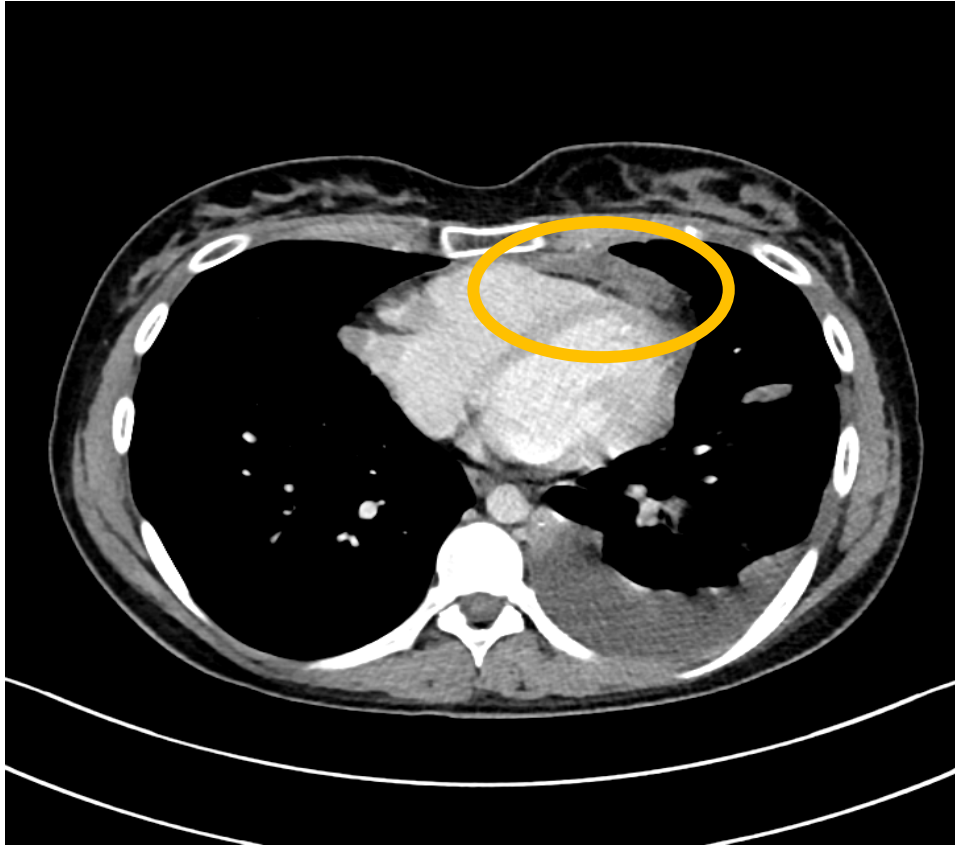




Recurrence

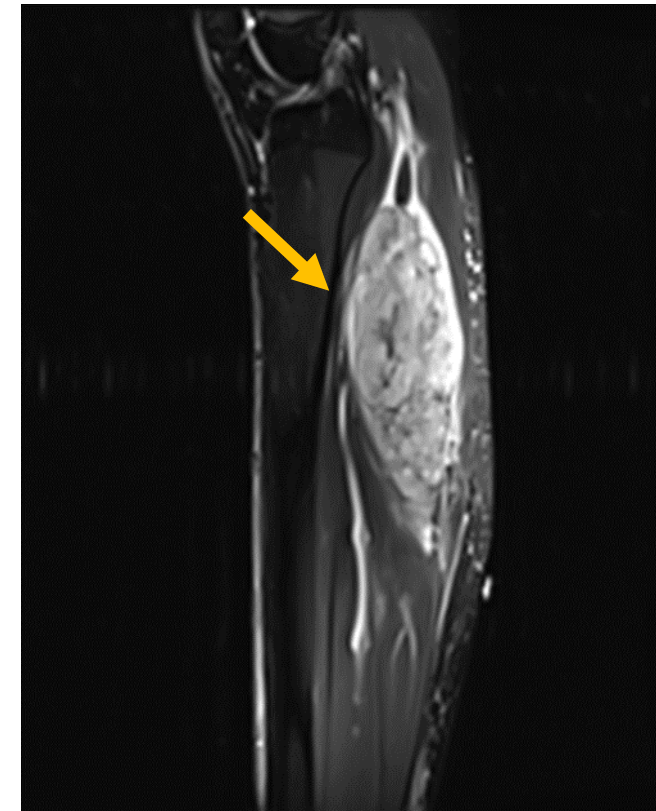
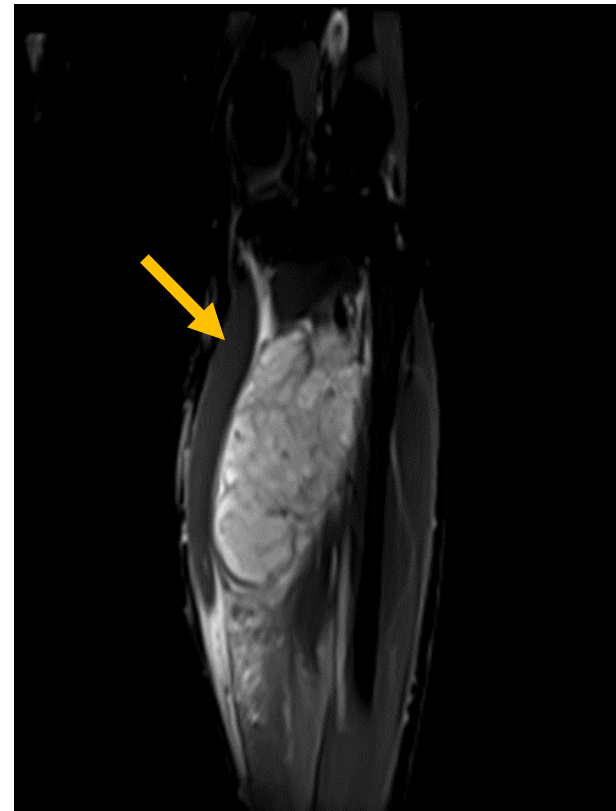
- 3rd: Mediastinal nodal disease-3 weeks after stopping pazopanib
 - Palbociclib/irinotecan/temozolomide
- 4th: Progression at 2 months
 - 14 day continuous ifosfamide/mesna infusion x 6 cycles
 - Foundation One sent: no actionable targets
- 5th: Recurrence in left lung pleura and parenchyma- 5 months later
 - Phase 1 trial with TK216
- 6th: Progression at 1 month-biopsy proven
 - Carboplatin/etoposide
- 7th: Progression to LLL and pleural based masses-6 weeks later





Cindy

- 16 y/o female with CIC-DUX 4 sarcoma of the left lower leg (calf) with pulmonary metastatic disease



Treatment

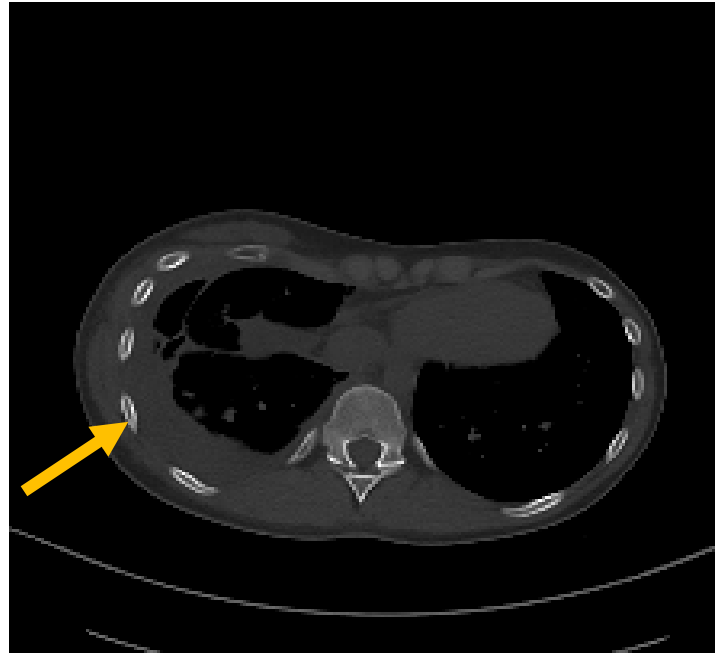
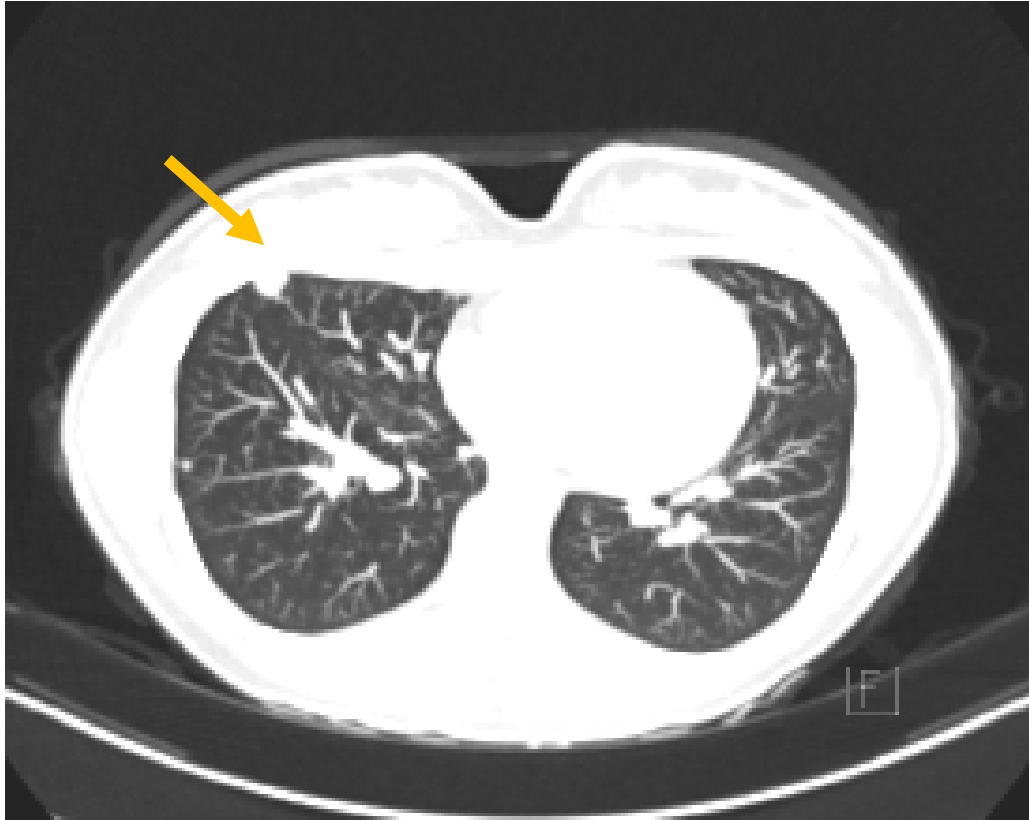
- AEW50031 (NCT00006734)
 - vincristine/doxorubicin/cyclophosphamide/ifosfamide/etoposide
- Local control:
 - Radiation to left calf mass (55.8 Gy)
 - Resection of residual left calf mass (no viable tumor)
 - whole lung radiation after chemotherapy completed (15Gy)
- GAIN (NCT02520713)

Recurrence

- 1st: Pulmonary relapse 6 months off therapy
 - Doxorubicin/ifosfamide with olaratumab
 - Pulmonary nodule resection, 60% necrosis
 - Autologous stem cell transplant with busulfan/mephalan
- 2nd: Recurrence to right pleura 8 months after autologous stem cell transplant. Biopsy proven
 - Irinotecan/temozolomide x 3 cycles with resection of nodule (positive margins)
- 3rd: New pleural lesion to RLL-9 weeks later
 - focal RT and cyclophosphamide/topotecan

Recurrence

- 4th: Improvement in pleural disease, but new soft tissue mass to medial right lung-6 weeks later
 - SBRT in 10fx to lesion adjacent to R atrium and continuous ifosfamide
- Blood counts with low platelets, concern for MDS. Marrow reassuring. Stem cell boost
 - Continued continuous ifosfamide
- 5th?: Current disease with thickening to pleural, awaiting biopsy results

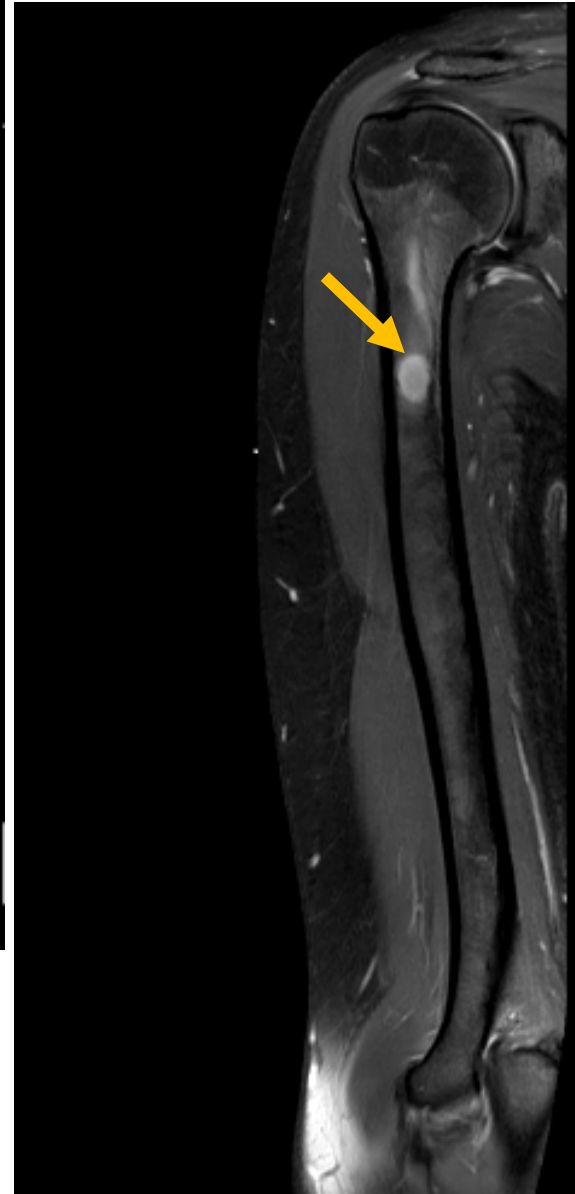
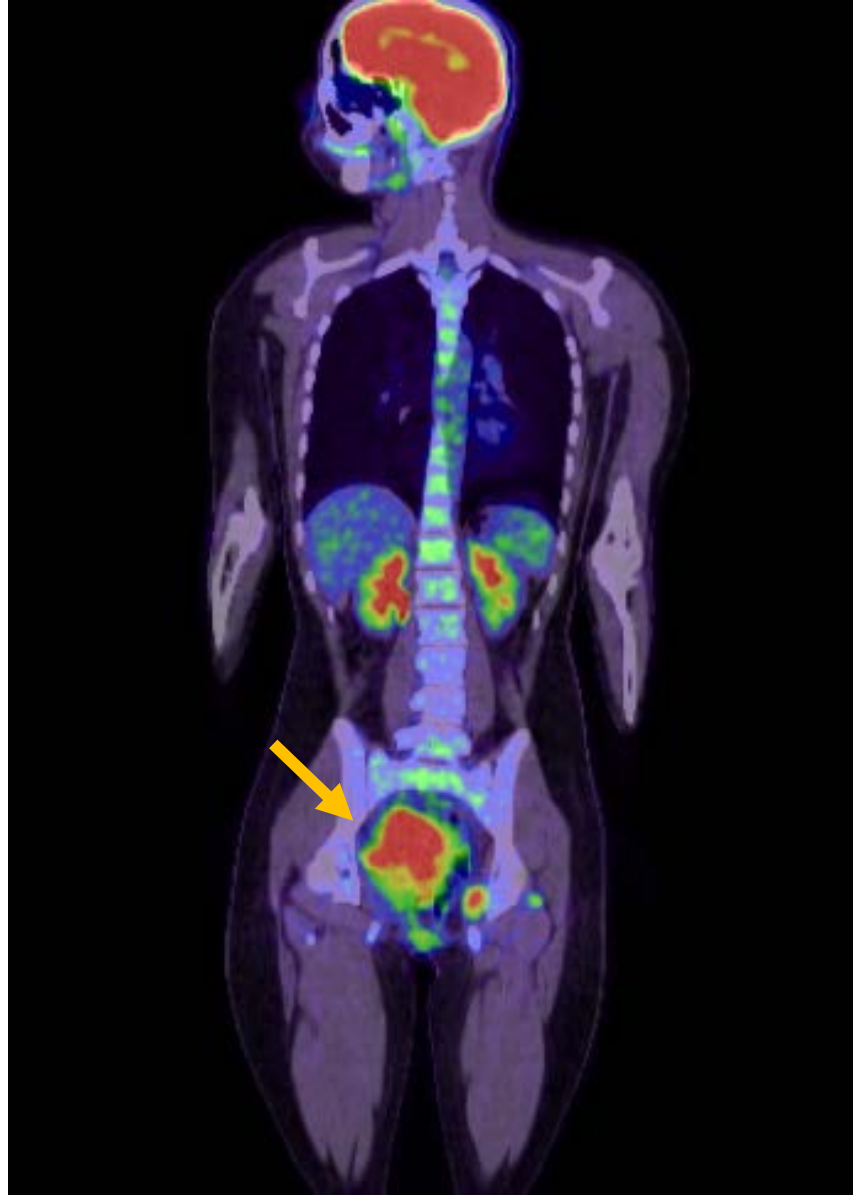
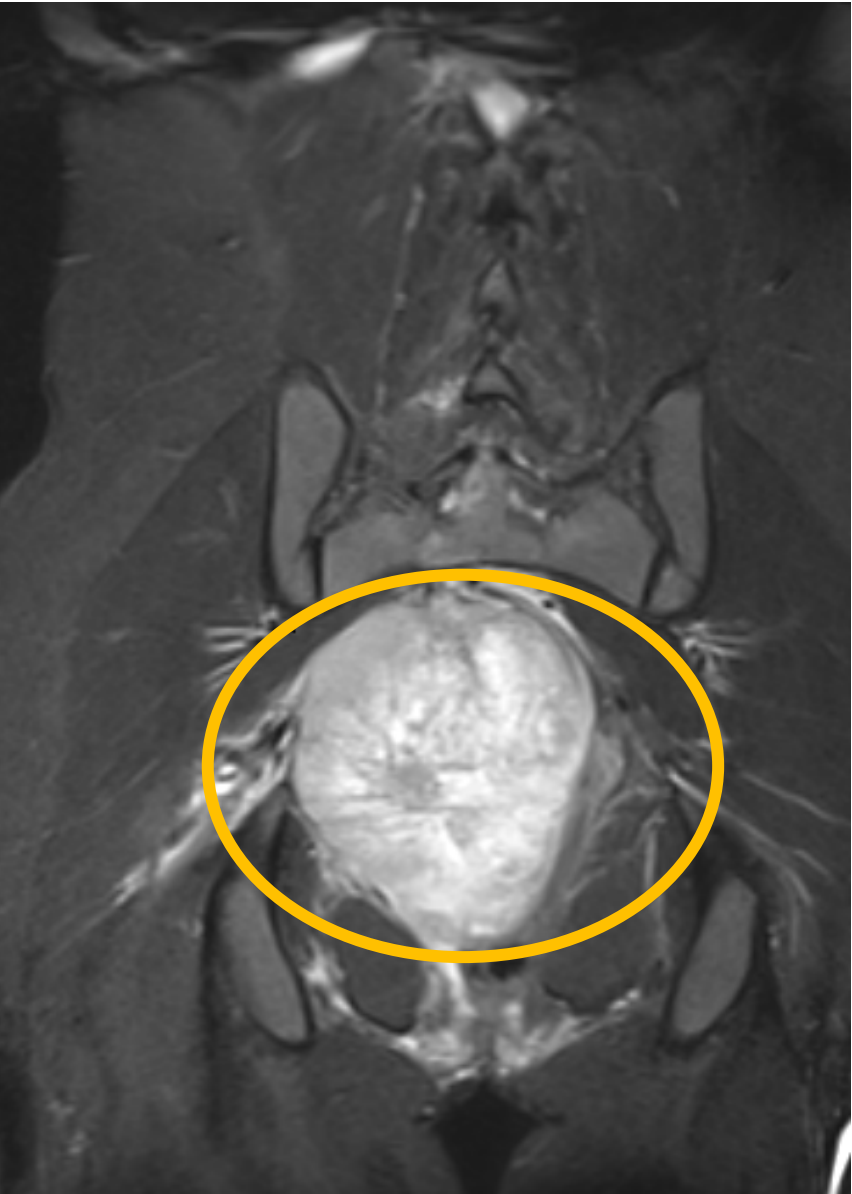


Clinical Pearls (Marcia and Cindy)

- Quality of life
 - Oral vs IV chemotherapy vs autoHSCT
 - Travel for open trials
 - Toxicity
- Palliative care consult timing
- Multiple recurrences
- Complications with initial therapy

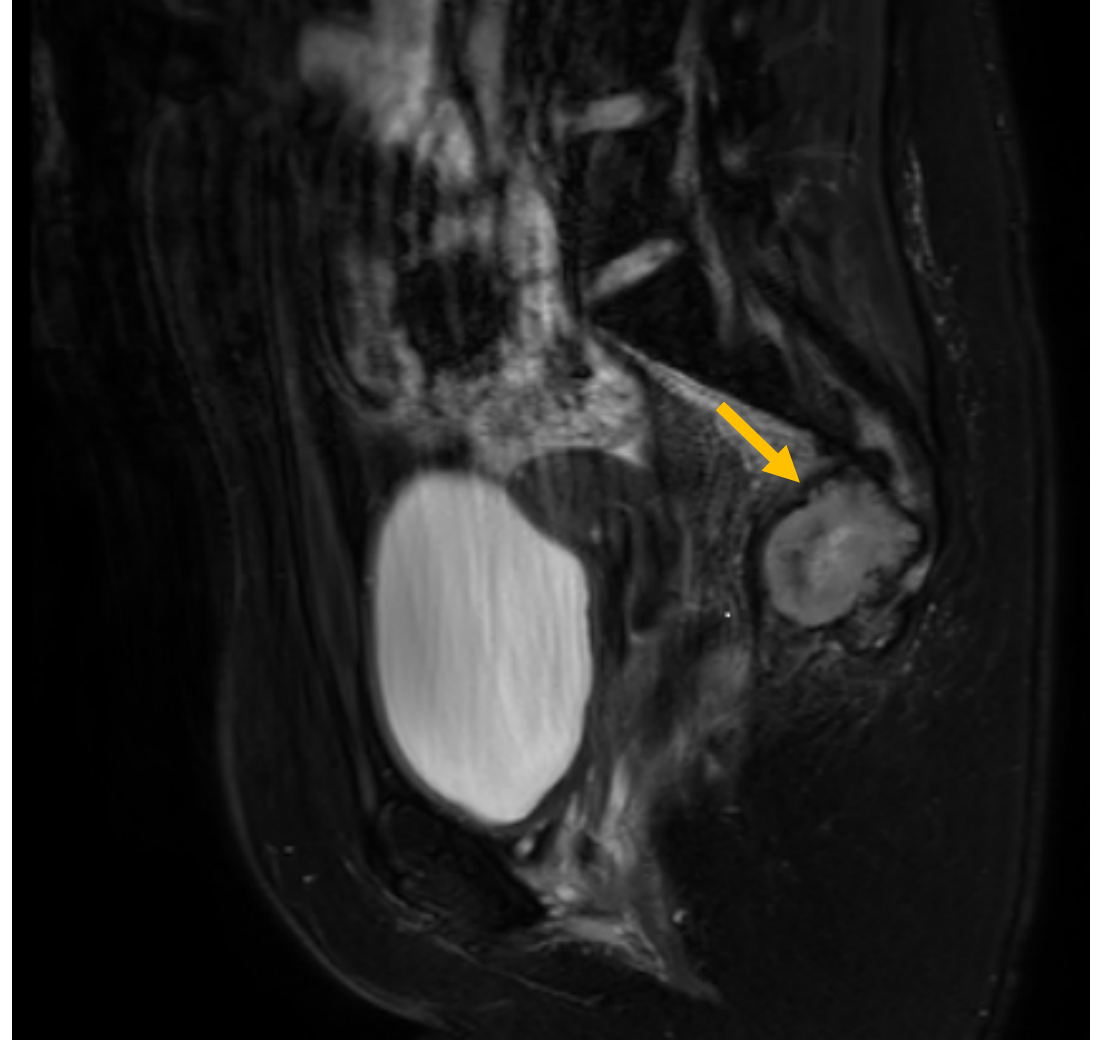
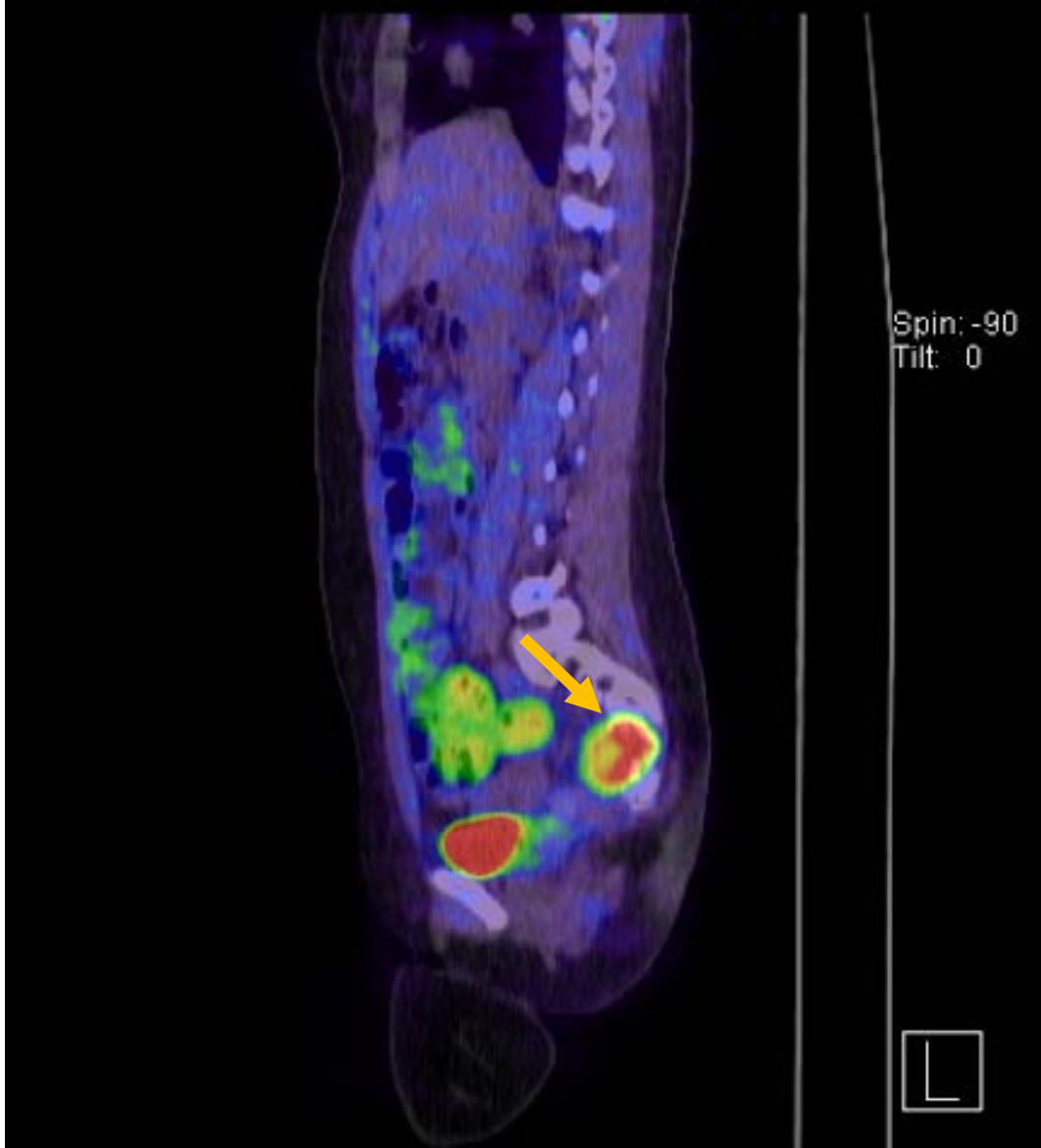
Alice

- 17 y/o female
- Diagnosed with Ewing Sarcoma of the sacrum with proximal right humerus metastasis 9/2018
 - Cytogenetics notable for EWSR1 rearrangement with EWSR1/FLI1 fusion protein
- Enrolled on AEWS1221 (on study) and randomized to Regimen A (nonexperimental arm, received VDC/IE)
 - Received radiation to the primary tumor as well as to the right humerus met per protocol
- Completed treatment 5/2019



Recurrence

- Came to clinic 1/2020 for routine surveillance scans
- MRI and PET showed right sacral mass, concerning for disease recurrence
 - Also had a new left sacral osseous lesion concerning for metastatic disease
- Biopsied showed recurrent Ewing Sarcoma
- Discussed with Alice that she had a <10% chance of cure
- Discussed Alice at our weekly tumor conference and determined:



Recurrence

- Presented three options in terms of treatment moving forward:
 - 1) “standard care” with chemotherapy + localized radiation to the tumor
 - 2) experimental treatment options + localized radiation to the tumor
 - 3) palliative chemotherapy and/or radiation
 - **Did not offer the option of bone marrow transplant
 - **Also discussed no therapy as a viable option
- Alice and her mother met with our Experimental Therapeutics Team

Recurrence

- Alice stated it was important for her to be in school and with her friends
- She did not want to be in the hospital
- She wanted to travel back to Mexico to see family
- She wanted to start making a bucket list

Recurrence

- Enrolled on Hospice
- Alice enrolled in the TK216 clinical trial
 - Also consented to the GAIN study
- Interval scans 2/2020: Progression
- Discussed various options, including VOIT, Pazopanib, and no further cancer directed therapy
- Alice again voiced goals of being in school and home with family
 - She didn't mind getting chemotherapy and having side effects (hair loss) but did not want to be "sick"

Recurrence

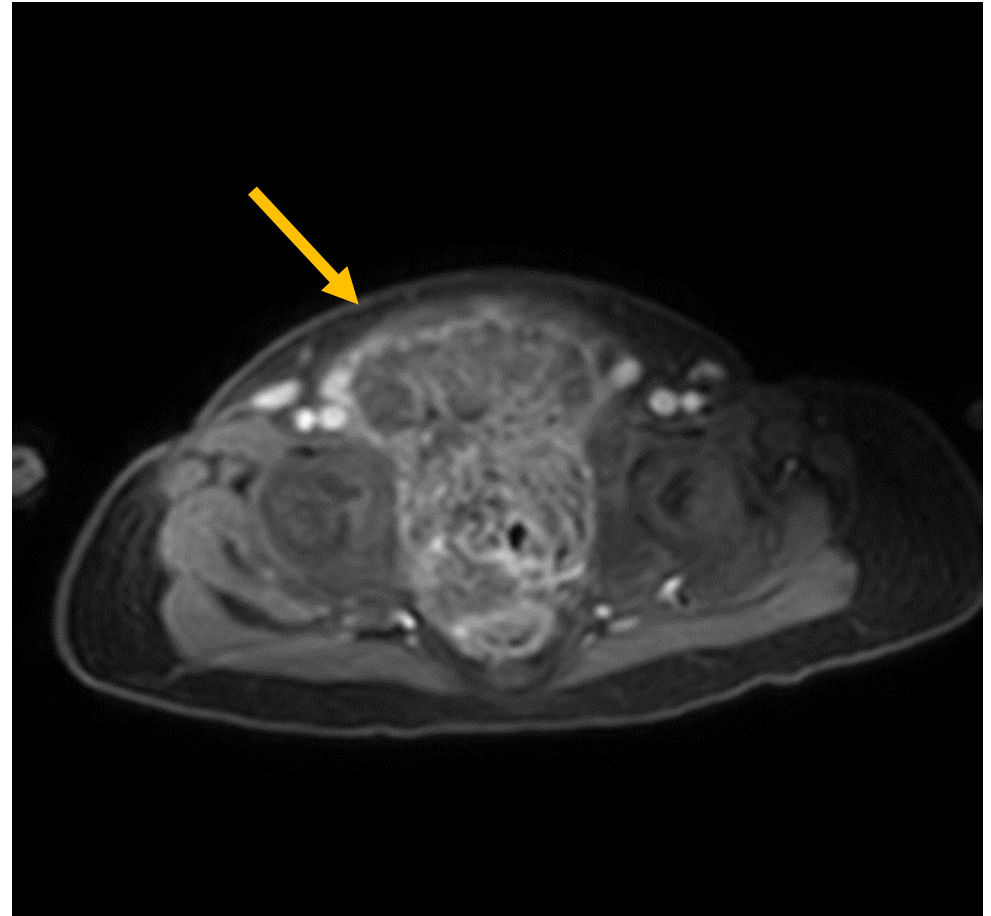
- Started on VOIT
- Scans after 2 cycles show some response to therapy, particularly with decreased FDG-avidity on the PET scan
- Despite PET results, Alice discontinued VIT/VOIT due to unacceptable side effects (epigastric pain/nausea)
- Started Cyclophosphamide/Topotecan as another palliative alternative
 - Has currently received one cycle

Clinical Pearls (Alice)

- Goals of care often change at recurrence
- Not always a good standard of care
- Risk/Benefit
- Concurrent enrollment in hospice and continuing to receive treatment

Peter

2 y/o male with fusion positive alveolar rhabdomyosarcoma of the bladder/prostate with tiny pulmonary nodules concerning for metastatic disease

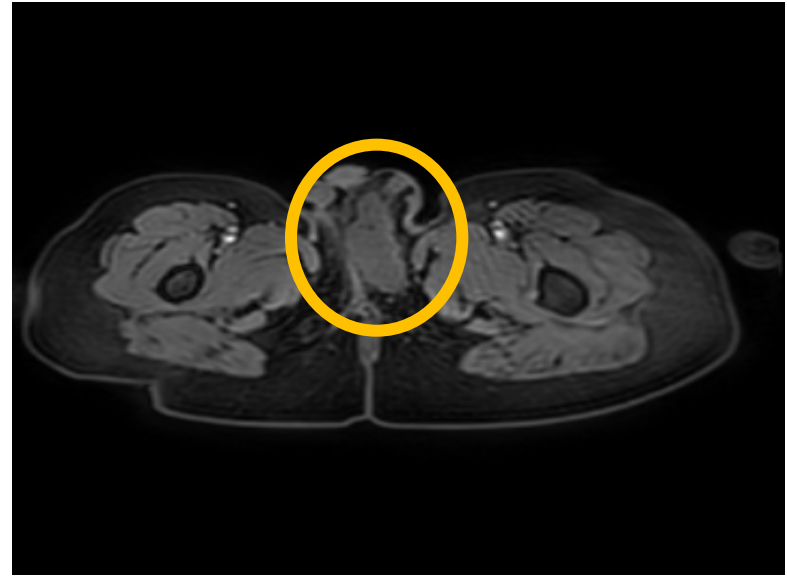
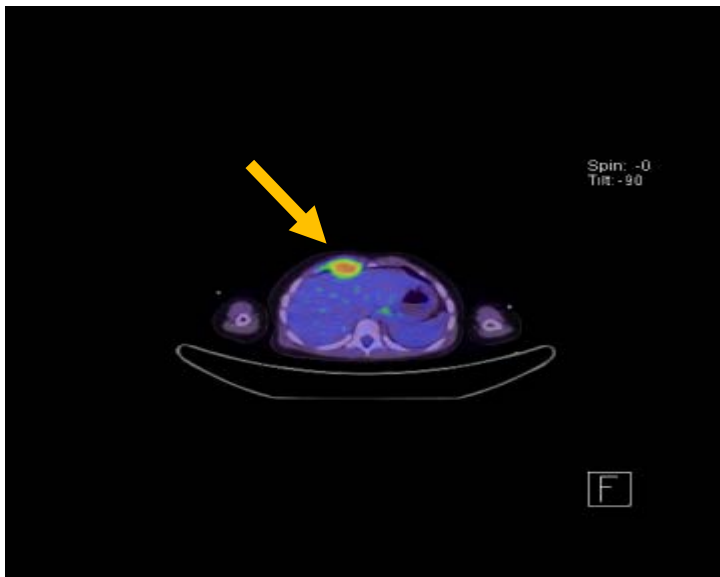
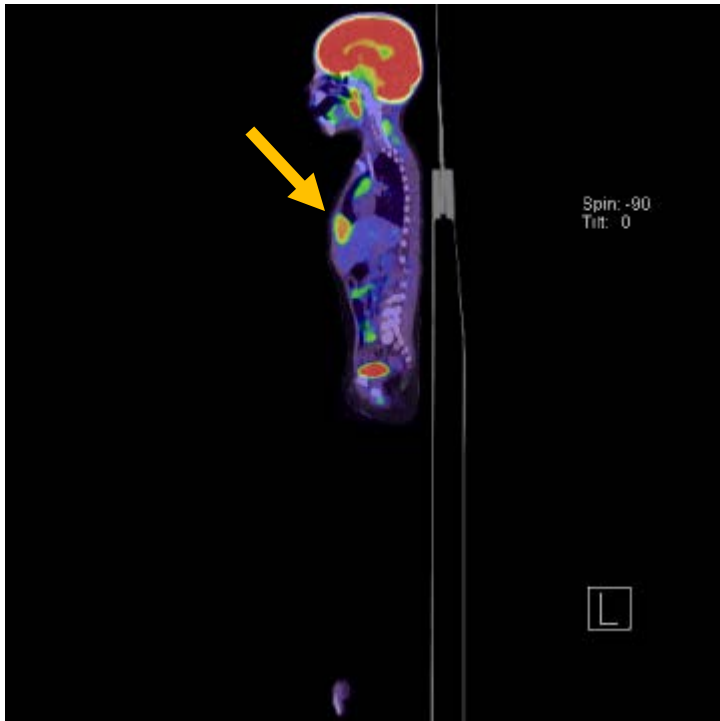


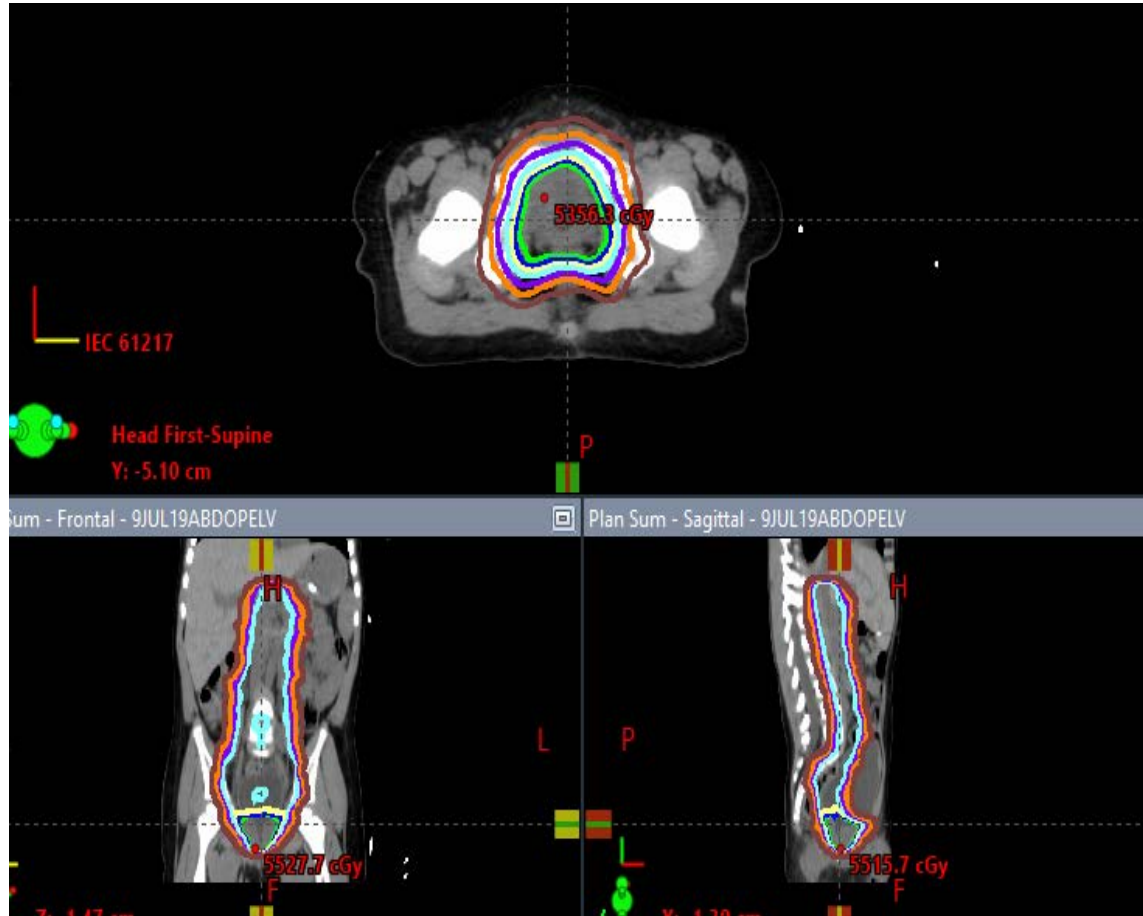
Treatment

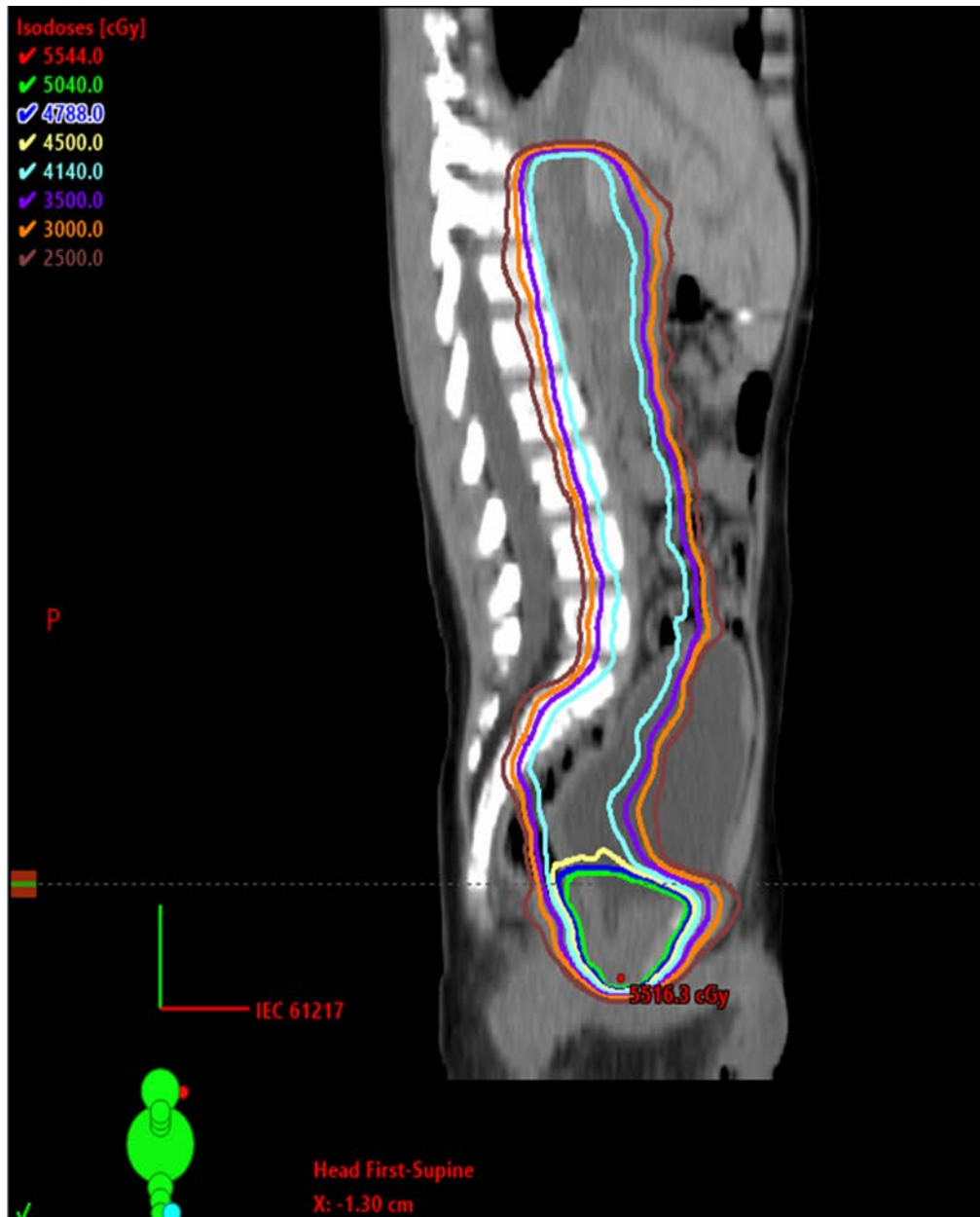
- D9803 (NCT00003958)
- Local control (week 13):
 - Radiation: 41.4Gy to bladder/pelvis; 9Gy boost to prostate. Total dose 50.4Gy

Recurrence

- Parents called with redness/swelling to testicle
- Imaging (3 months off therapy) with mass to testicle/scrotum and right chest wall
- No biopsy done. Foundation One medicine sent on initial tumor
 - No actionable targets
- Local hospice involved
- New chemotherapy ARST0921 (NCT01222715) (vinorelbine/temsirolimus/cyclophosphamide)
 - continues on this chemotherapy







Clinical Pearls (Peter)

- Family opinions
- Re-biopsy/chemotherapy choice
- Second opinions
- Length of treatment/having a plan

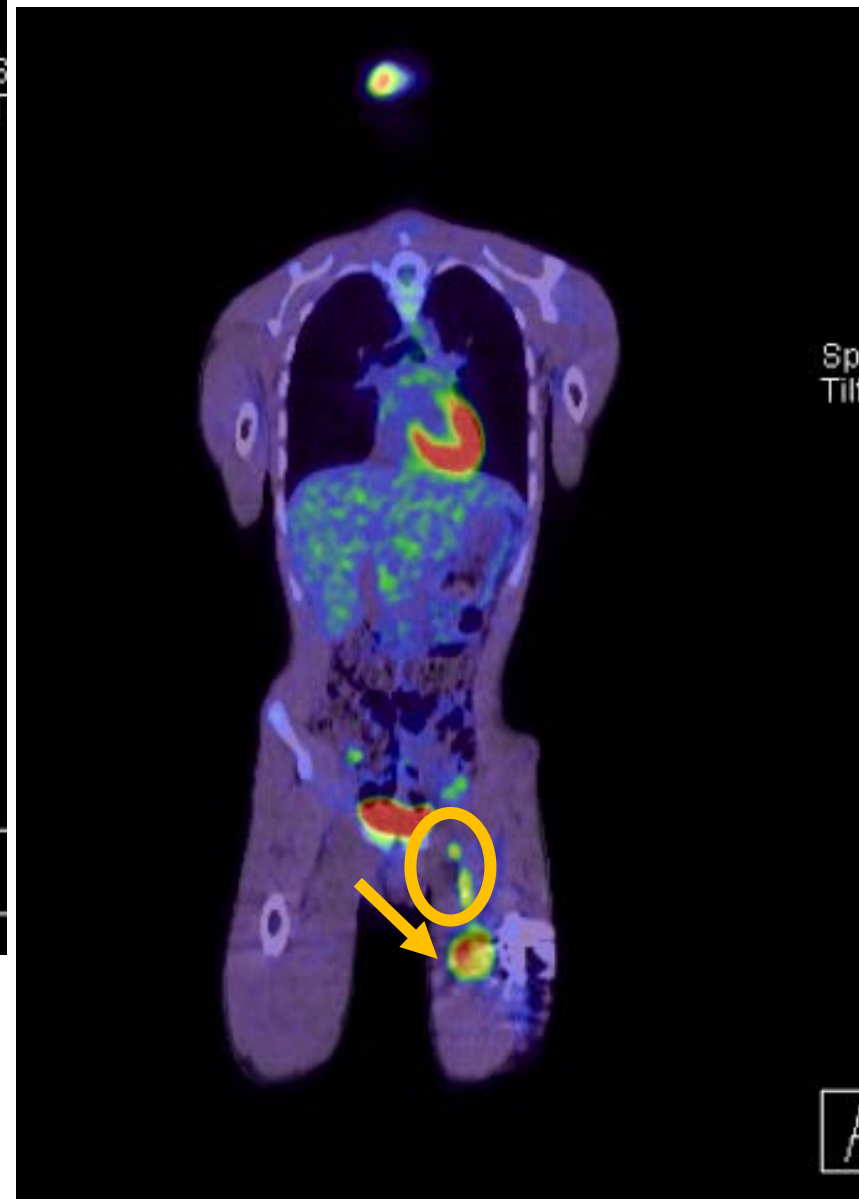
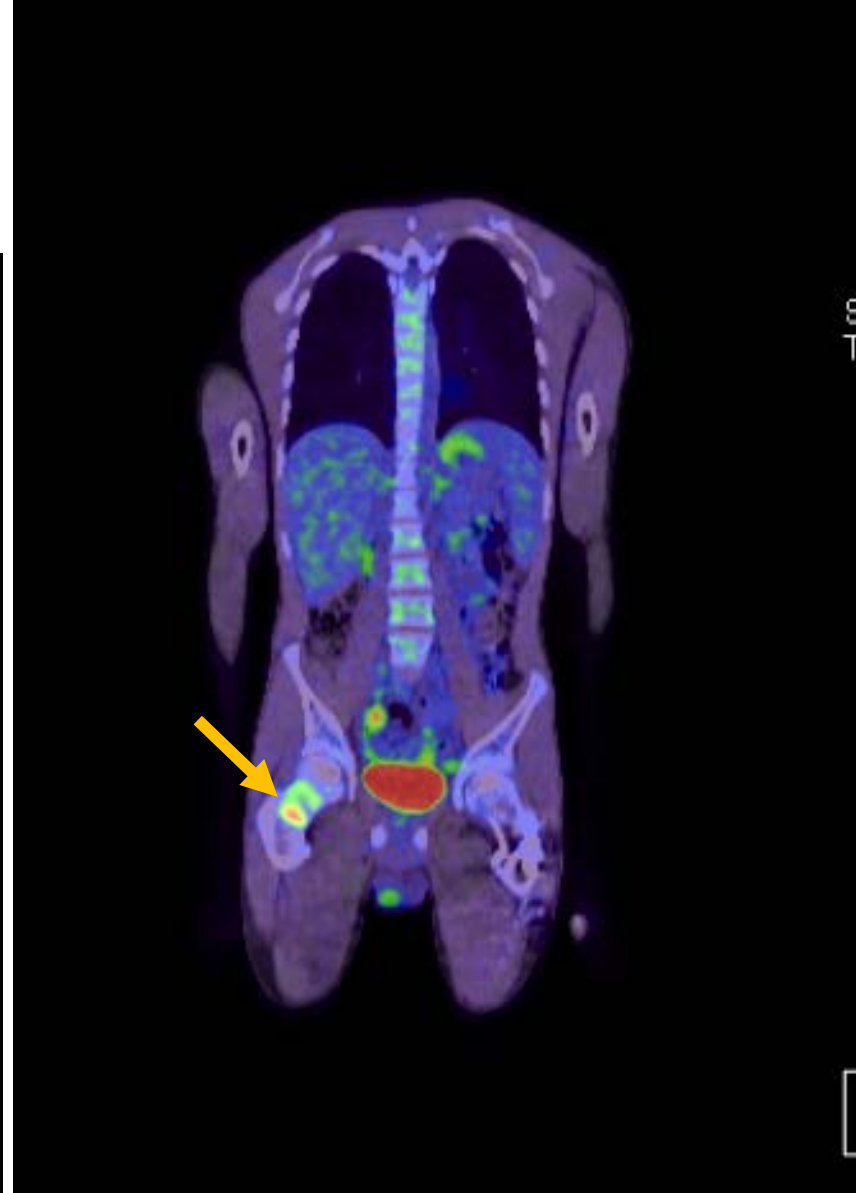
Greg

- 16 y/o male
- Presented with a painful left femur thigh lesion
- Diagnosed with Osteosarcoma of the left distal femur 10/2017
- Received MAP therapy according to AOST0331
 - Had a radical resection with an allograft reconstruction of the left femur for local control with 75% tumor necrosis
- Finished treatment 7/2018



Recurrence

- In April 2019 presented with a hard-palpable nodule at the medial left thigh
 - Recurrent metastatic Osteosarcoma to the left femur, left inguinal lymph nodes, right proximal femoral head and neck
- Discussed poor prognosis with family (~10-20%)
- Family met with REACH team to discuss goals of care
- Greg and his parents expressed the need to do everything possible for cure



Recurrence

- Presented three options in terms of treatment moving forward:
 - 1) “Standard of care” with Ifosfamide/Etoposide
 - 2) Potential experimental therapeutic options
 - 3) No therapy as a viable option
- Family consented to GAIN study
- Family expressed concern and need to get second opinions
 - MD Anderson
 - Boston Children's
 - St Jude

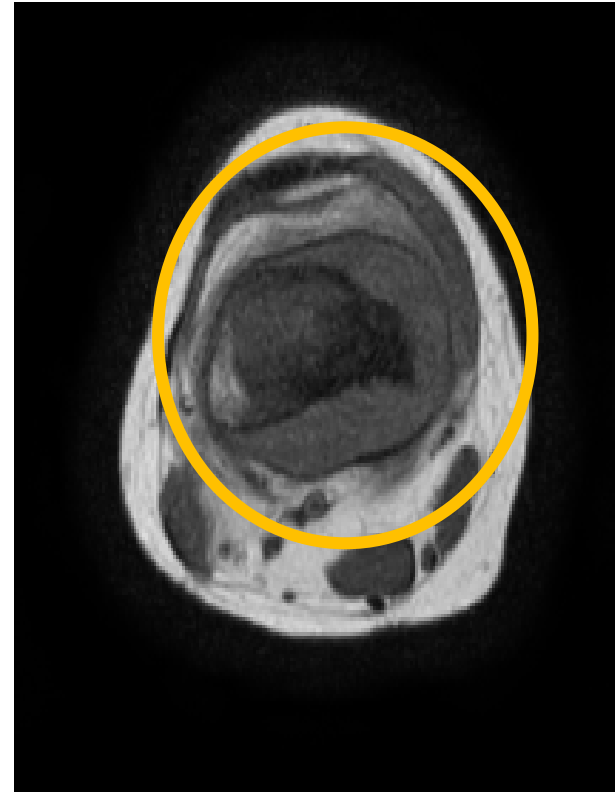
Recurrence

- Started chemotherapy with Ifosfamide/Etoposide on 4/10/2019
 - Recommended 12 cycles
- Responded well to chemotherapy
- Surgery for local control
 - Amputation vs limb sparing
- Completed 10 cycles 12/2019
- Off-therapy and doing great!



Jan

- 11 y/o female with right distal femur osteosarcoma. Non-metastatic.

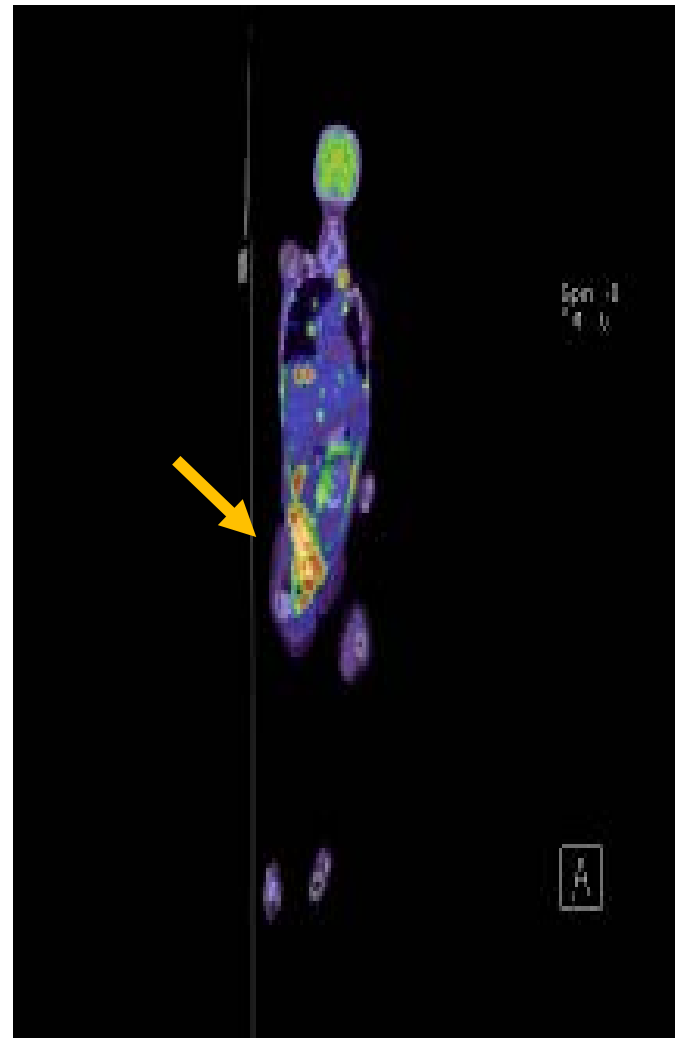
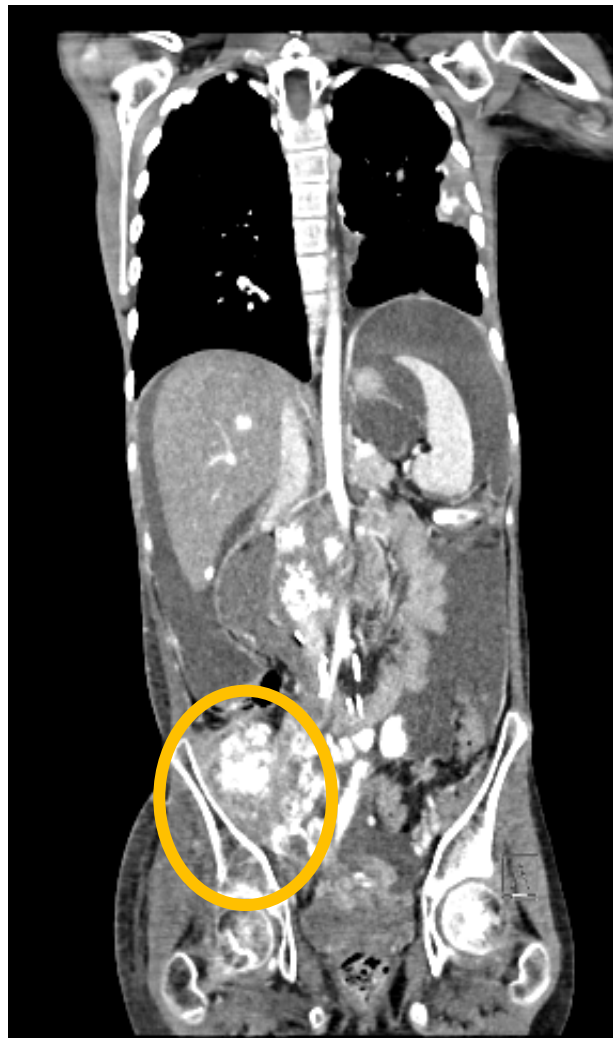
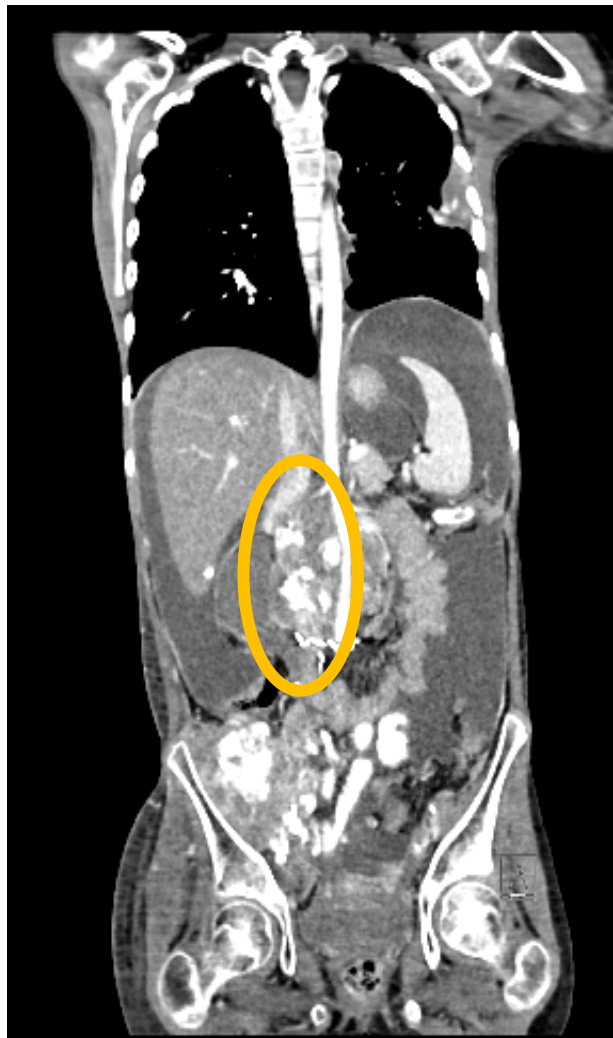


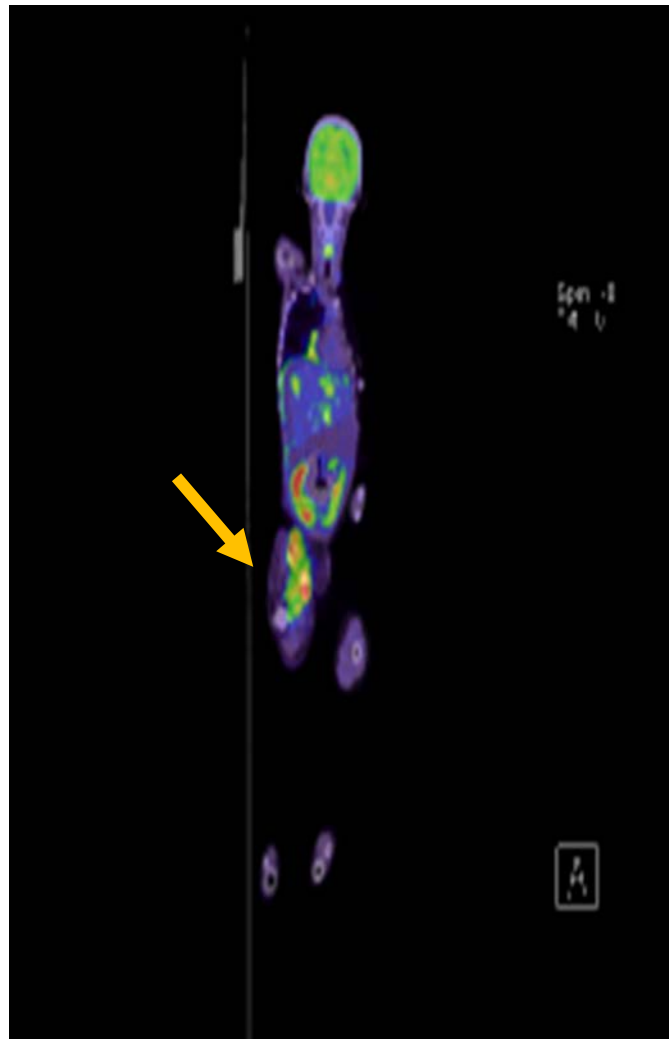
Treatment

- AOST0331 (NCT00134030)
- Surgery-50% tumor necrosis
- GAIN

Recurrence

- 1st: Off therapy imaging with new calcified pelvic node and new pulmonary nodule
 - No biopsy
 - Chemotherapy with HD ifosfamide/etoposide
- F&N admit, PNA. Bloody sputum, CT chest with PE vs angioinvasive fungal infection
 - Pulmonary mucomycosis, thoracotomy
 - GAIN-repeated
- 2nd: Progression to right iliac/retroperitoneal nodal disease 5 months later
 - RPLND
- 3rd: Progression again pelvic and retroperitoneal nodes, bones, liver, lungs, and supraclavicular node 2 months later
 - Pazopanib





Recurrence

- 4th: Progression again 6 weeks later
 - Phase 1 trial-but ineligible
 - Palliative care, passed away

Clinical Pearls (Greg and Jan)

- Not always an early phase clinical trial available
- Overwhelming surgical treatment decisions
 - Quality of life vs cure
- Second opinions
 - May get several recommendations
 - Difficulty choosing “best option”
 - Decision fatigue
 - Knowing where to get a second opinion
 - Guidance from the team
 - May need to travel
 - Could delay treatment

Sam: presented June 2018

- 12 yo with history of occipital headache for the last 6 months, initially thought to be migraines but worsened over the 4 weeks prior to diagnosis
- MOC reported slower speech and “not walking as before”
- MRI showed a large solid and cystic mass with surrounding edema in the left parietal region, evidence of increased ICP
- Subtotal resection completed
- Initial pathology was an atypical meningioma, WHO Grade II
- Rule out NF2

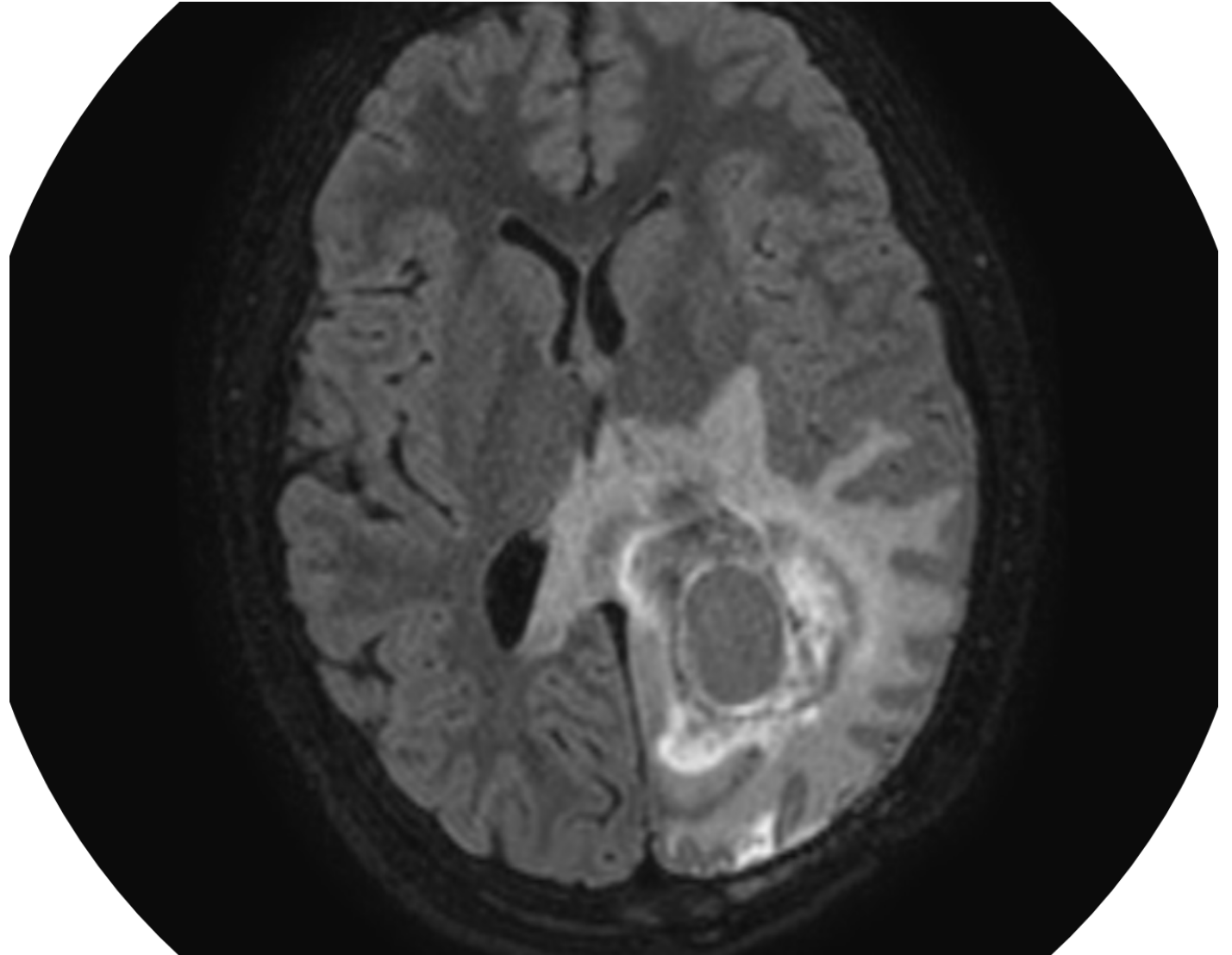


Sam

- Molecular testing on the tumor confirmed an EWSR1-ATF1 fusion consistent with angiomatoid fibrous histiocyoma
- PET/CT was completed to rule out metastatic disease
- Completed 6 weeks of radiation therapy

Sam: January 2019

- Presented to the ED with worsening morning headaches, RLE weakness, and report of feeling weakness and numbness in the RLE which progressed to a focal to generalized tonic clonic seizure
- MRI showed increased cystic portion of the tumor with increased surrounding edema

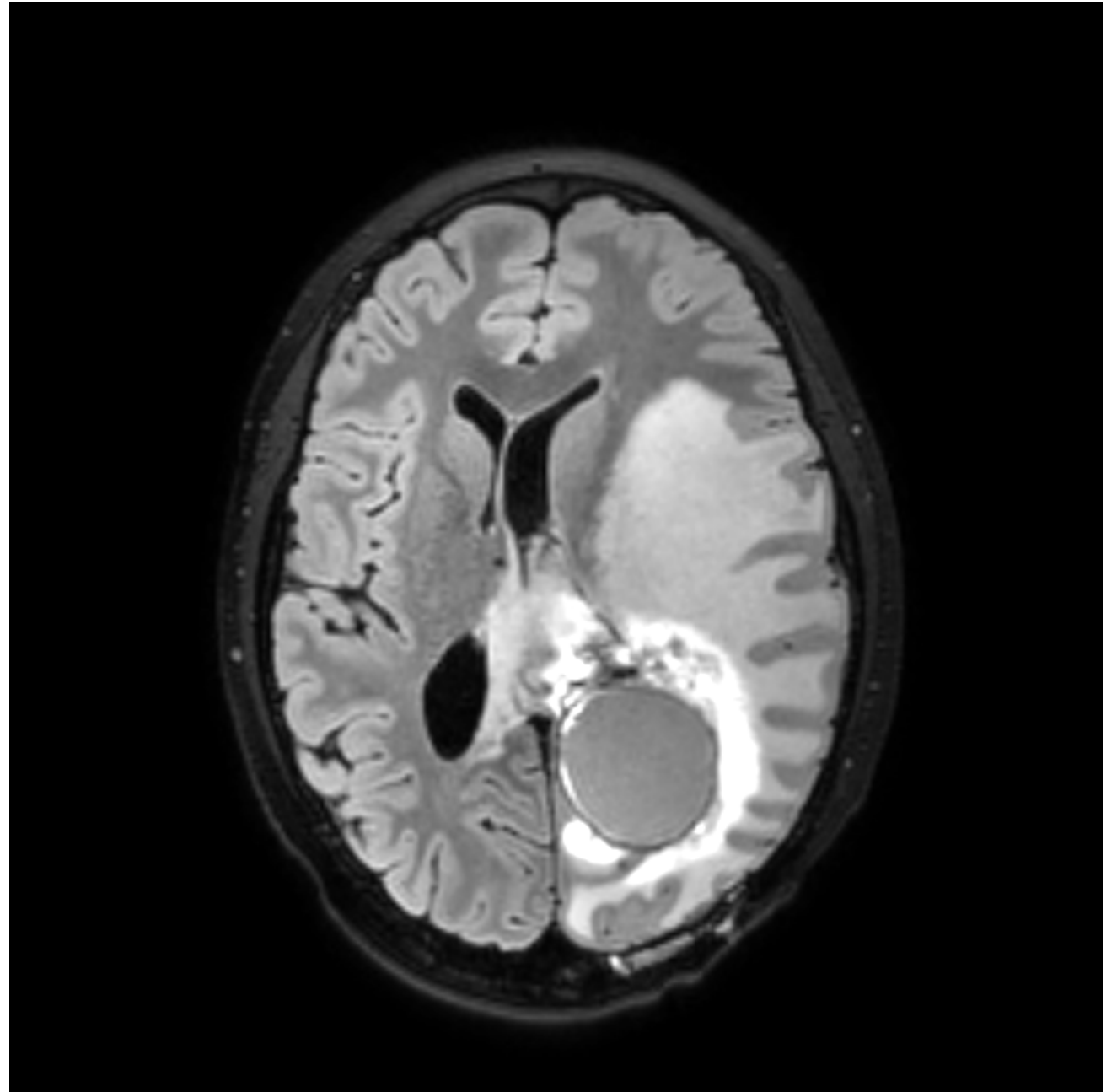


Sam

- Went back to surgery for a resection and pathology again showed an angiomatoid fibrous histiocytoma
- Completed full workup with whole body PET, chest CT, MRI spine, and bilateral BM aspirate and biopsy
- With the known EWS fusion, will start treatment with compressed Ewing's therapy (AEWS0331)

Sam: May 2019

- Completed 12 weeks of chemo with VCR, Doxo, CTX, Ifos, Etoposide
- On therapy MRI showed:
 - Significantly increased enhancement around the resection cavity, increased diffuse white matter edema and swelling, and shift causing obstruction of the 3rd ventricle, concern for tumor recurrence



Sam

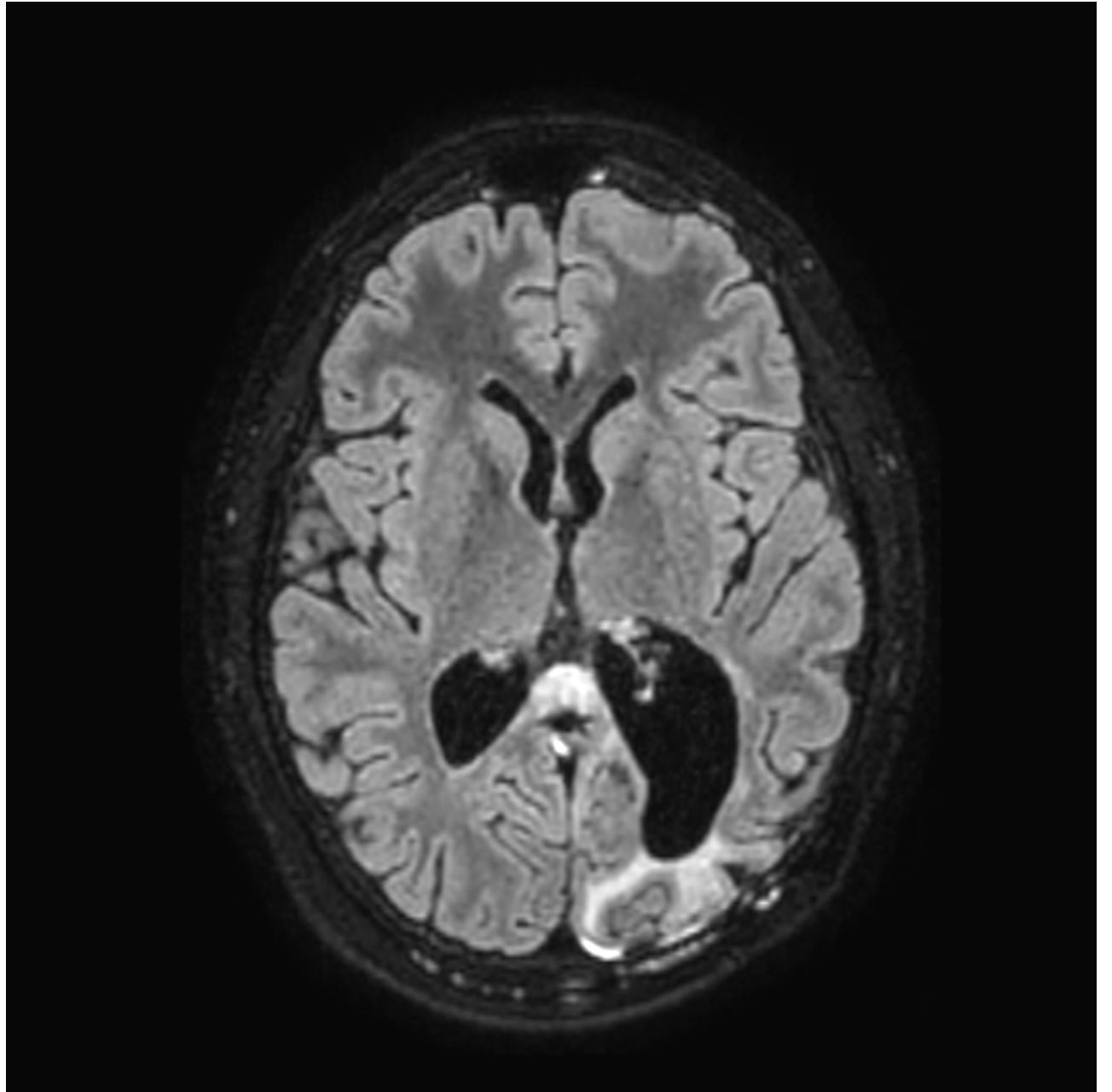
- What is next?
- Sent Foundation One
- Sent 2nd opinion request to St. Jude. They wanted to independently review the pathology (took 2-3 weeks), but in the meantime they agreed with the plan to start TMZ/irinotecan/Avastin
- Neurosurgery consult to discuss further surgery which unfortunately would be extensive and likely leave Brayan with permanent neurologic deficits.
- Palliative Care consult completed
- If additional targetable mutations are discovered, will consider altering therapy.

Sam

- Foundation One (comprehensive genomic profiling test designed to identify genomic alterations within hundreds of cancer-related genes in hematologic malignancies and sarcomas)
- EWSR1-ATF1 fusion: no direct targeted therapies but discussion that IGF1 inhibitors are being investigated
- GRIN2A C1236: no targeted therapies available
- Fun Fact: Foundation One also will include a list of “variants of unknown significance” that are detected in case they become relevant in the future

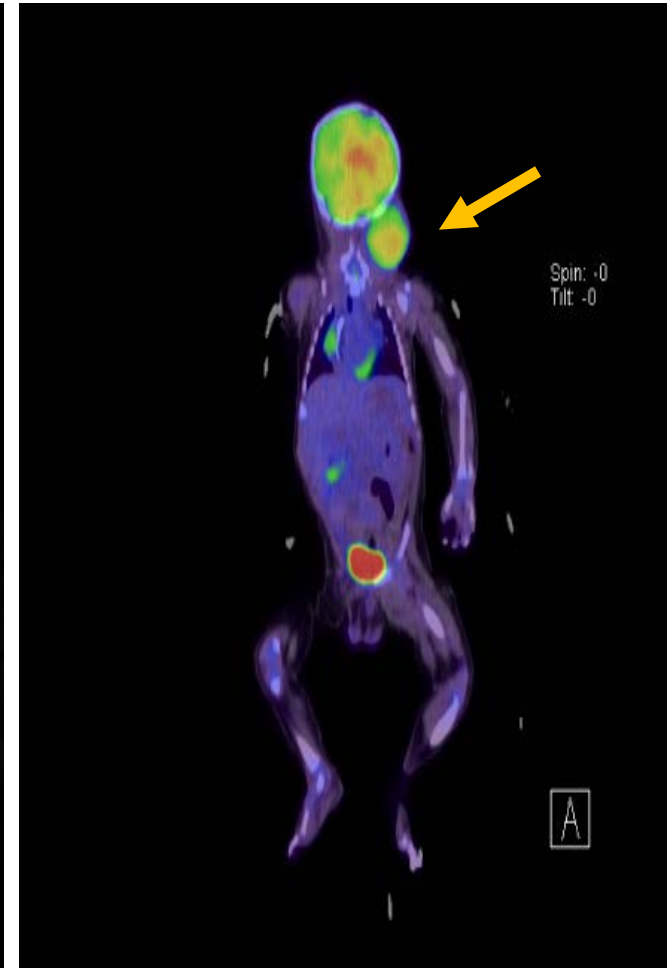
Sam: May 2019

Started therapy with Ativan, irinotecan, and TMZ (relapsed/refractory Ewing's therapy) and completed 13 months of therapy with stable disease



Bobby

- 70 day old male with stage 3, group 3 spindle cell rhabdomyosarcoma of the left posterior neck with intracranial extension

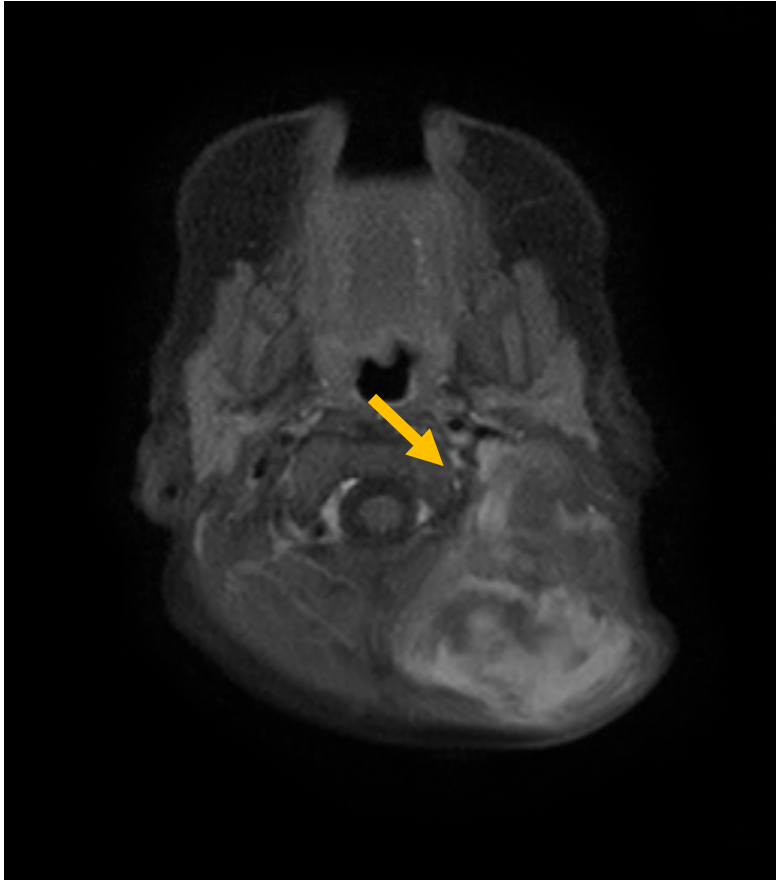
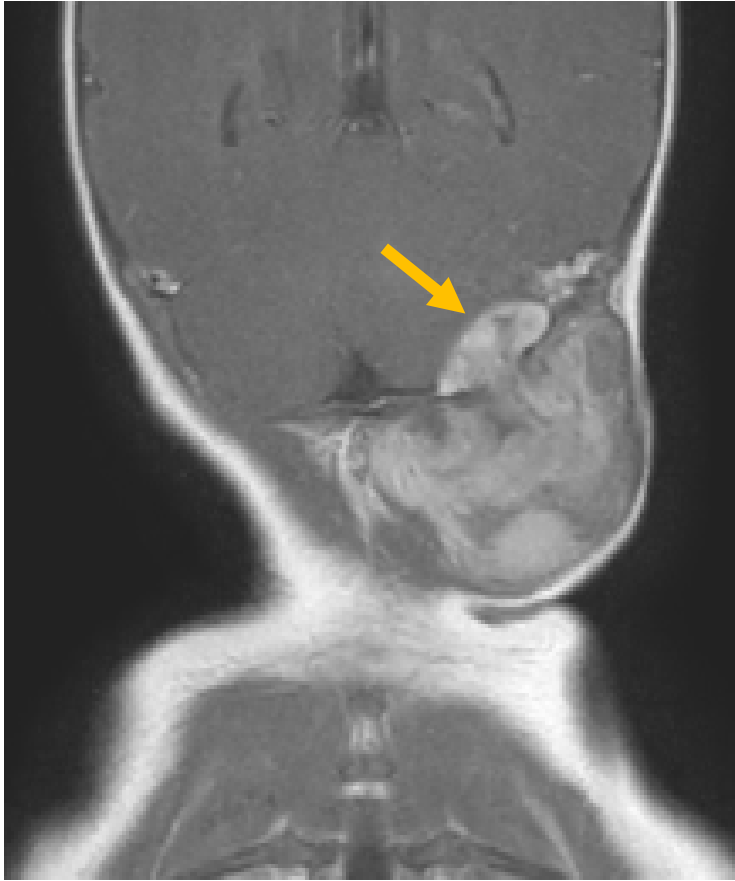


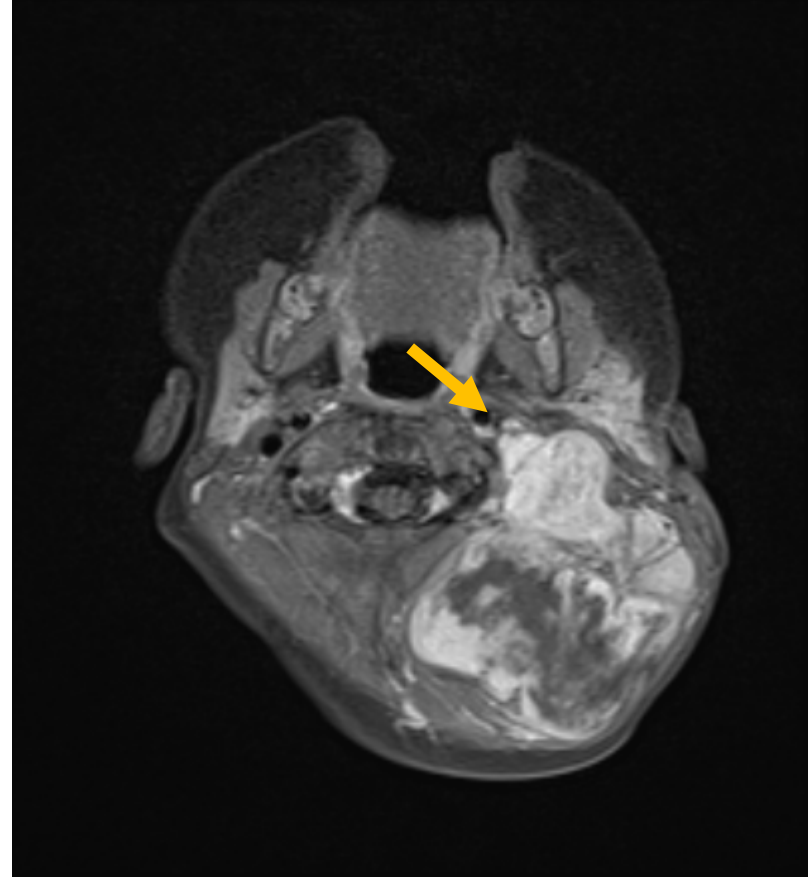
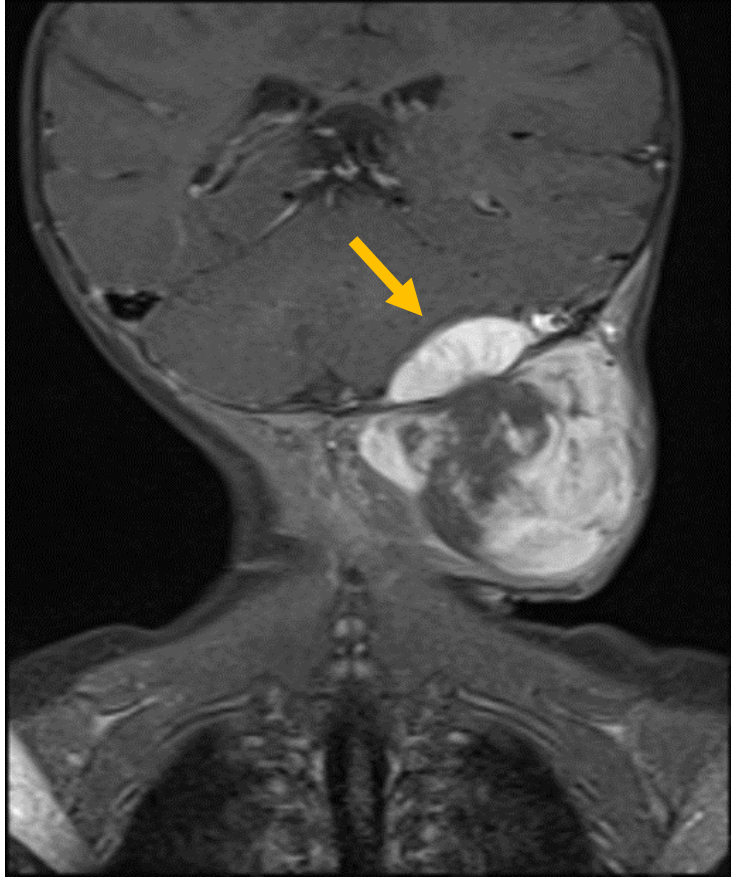
Treatment

- D9803 (NCT00003958)
- Local control (delayed to week 20)

Recurrence

- 1st: Progression at week 16 of therapy
 - Foundation One
 - ARST0431 (NCT00354744) (with VAC cycles removed)
 - RT
- 2nd: Progressed at week 11
 - Options:
 - ARST0921 (NCT01222715) (vinorelbine/temsirolimus/cyclophosphamide)
 - Trametinib
 - Palliative care/hospice
- Concern for airway obstruction ~7 months after stopping therapy, stable MRI/PET





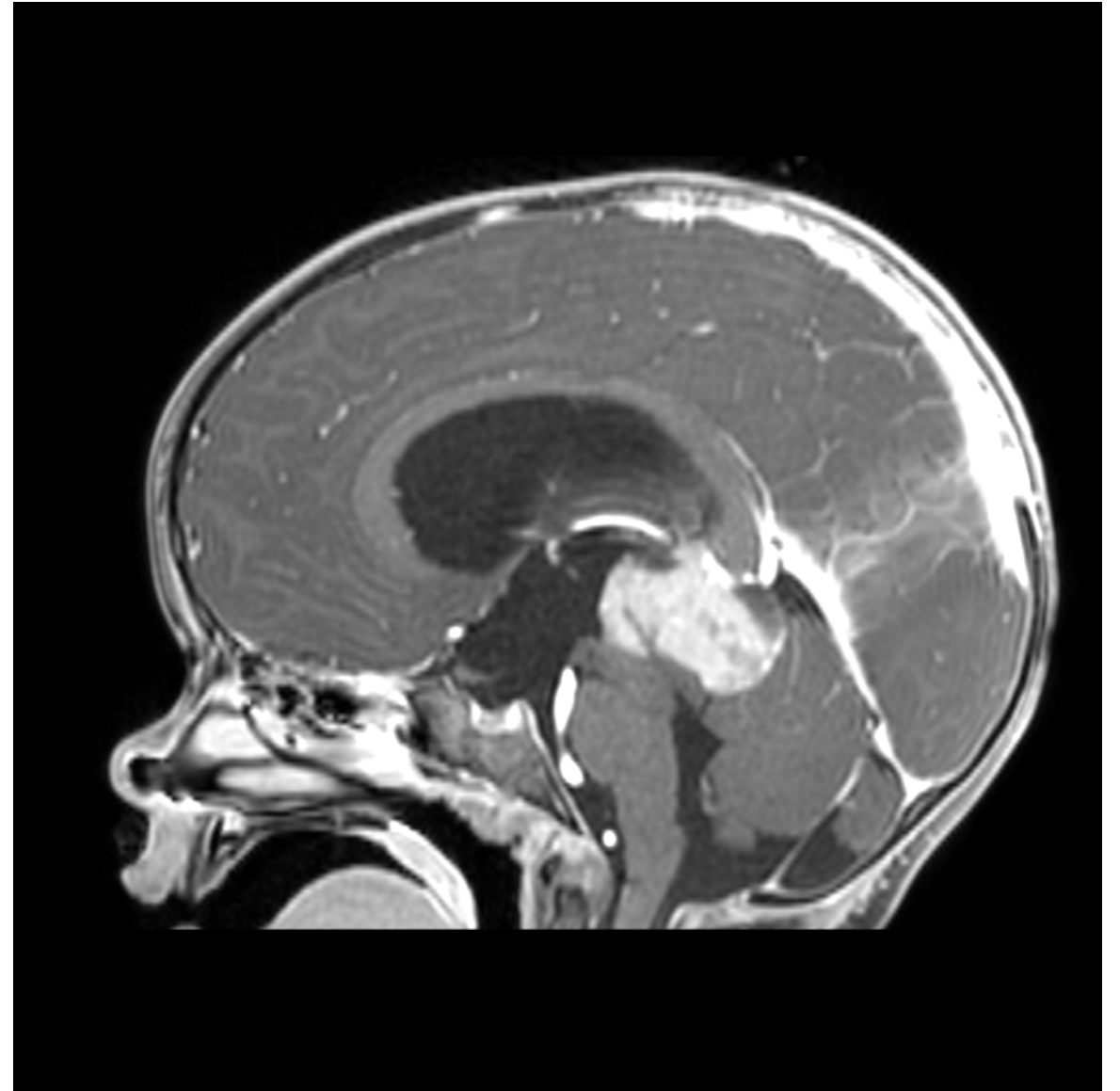
- Transitioned care
- Re-biopsy without malignant elements
- 3rd: PET with avidity
 - Surgery with anaplastic rhabdomyosarcoma
 - Chemotherapy/radiation
- No therapy x 16 months

Clinical Pearls (Bobby and Sam)

- Tumor sequencing
- Information level to parents
- Palliative care
 - Expectation vs reality

Carol

- 2 year old with increasing headaches and sound sensitivity over a couple months
- Few week h/o eye deviation
- Presented to ED
- Papilledema
- MRI showed avidly enhancing pineal region mass causing obstructive hydrocephalus



Carol

- ETV and biopsy
- Pathology showed pineoblastoma
- Treatment with 3 cycles of induction chemo as per ANCS0334 with VCR, etoposide, CPM, cisplatin
- Followed by 2 cycles of high dose chemotherapy with carbo/thiotepa followed by stem cell transplant
- Missed 3rd high dose due to toxicity
- Moved to focal radiation

Carol

- 4 months after radiation she had an asymptomatic metastatic relapse
- Disease progression with new enhancing 1.9 cm mass inferior to the left cerebellum and new punctate enhancing focus along the left lateral aspect of the medulla
- Small 2-3 mm focus in brain stem



Carol

- Discussed several options with the interdisciplinary team and family.
 - craniospinal XRT (unable to do with recent XRT)
 - SRS to posterior fossa lesion
 - no dedicated pineoblastoma trials due to rarity of tumor
 - explored best experimental therapeutics trials

Family decided to do SRS to posterior fossa lesion

Brain stem lesion as left alone due to size and to have measurable untreated disease for ETP study

Carol

- Next routine MRI was 2 months after the last
- MRI results: posterior fossa lesion smaller, brainstem lesion larger, new nodule in the left internal auditory canal
- Enrolled on palbociclib (CDK4/6), TMX, irinotecan study

Carol

- Next MRI after 6 weeks of palbociclib, TMZ, and irinotecan study
- Showed increased size of extra-axial metastatic foci along the lateral medulla, left internal auditory canal, and right trigeminal nerve and additional new tiny extra-axial metastatic foci and new thecal sac tumor
- Off clinical trial due to progressive disease
- Completed SRS to new lesions
- Enrolled on palliative care, discussion of end of life per parent request

Carol

- Following SRS, next MRI 6 weeks after the last showed: New metastatic nodule in the posterior third ventricle and slightly increased size of multiple additional intraventricular and leptomeningeal metastases as described
- Discussions included experimental therapy (no good options), continue cannabis therapy, or start oral etoposide
- Carol's quality of life was excellent with no pain, full function, and happy
- Continue with palliative care support, cannabis, call with any changes, and MRI 8 weeks later

Clinical Pearls (Carol)

- Discuss family priorities
- Quality of life
- When offering options, think of how the therapy could impact quality of life
- Choosing no therapy and close monitoring is an option with recurrent or progressive disease

Questions?

- We appreciate your time to listen and engage.
- Please contact us with further questions at:
 - molly.hemenway@childrenscolorado.org
 - phylise.forsberg@childrenscolorado.org
 - suzanne.smolik@childrenscolorado.org

References

Van Winkle P, Angiolillo A, Krailo M, et al..Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. *Pediatr Blood Cancer*. 2005;44:338-347.

Van Mater D, Wagner L. Management of recurrent Ewing sarcoma: challenges and approaches. *OncoTargets and Therapy*. 2019; 12:2279–2288.

Farhat, R, Raad R, Khoury N, et. al. Cyclophosphamide and Topotecan as First-line Salvage Therapy in Patients With Relapsed Ewing Sarcoma at a Single Institution. *Journal of Pediatric Hematology/Oncology*. 2013; 35: 356-360.

Raciborska, A., Bilska, K., Drabko, K., Chaber, R., Pogorzala, M., Wyrobek, E.....Wozniak, W. Vincristine, Irinotecan and Temozolomide in Patients with Relapsed and Refractory Ewing Sarcoma. *Pediatric Blood Cancer*, 2013;60:1621-1625.

References

Venkatramani, R., Malogolowkin, M. and Mascarenhas, L. Treatment of Multiple Relapsed Wilms Tumor With Vincristine, Irinoteca, Temozolomide and Bevacizumab. *Pediatric Blood Cancer*. 2014;61:756-759.

Kieran MW. Targeted treatment for sonic hedgehog-dependent medulloblastoma
Neuro Oncol. 2014 Aug;16(8):1037-47. doi: 10.1093/neuonc/nou109. Epub 2014 Jun 20. Review.

Robinson GW, Orr BA, Gajjar A. Complete clinical regression of a BRAF V600E -mutant pediatric glioblastoma multiforme after BRAF inhibitor therapy. *BMC Cancer*. 2014 Apr 12;14:258. doi: 10.1186/1471-2407-14-258.