Metastatic Inflammatory Myofibroblastic Tumor

September 14, 2021

Katie Janeway, MD, MMSc
Associate Professor, Pediatrics, Harvard Medical School
Director, Clinical Genomics, Dana-Farber Cancer Institute

Alanna Church, MD
Assistant Professor, Pathology, Harvard Medical School
Associate Director LaMPP, Boston Children's Hospital

Dana-Farber Cancer Institute | Boston Children's

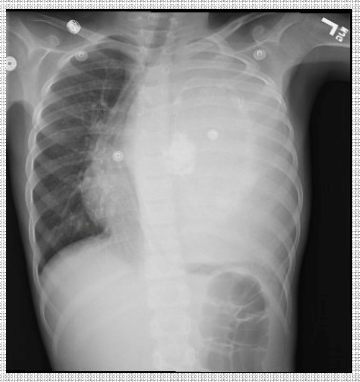
Dana-Farber/Boston Children's Cancer and Blood Disorders Center

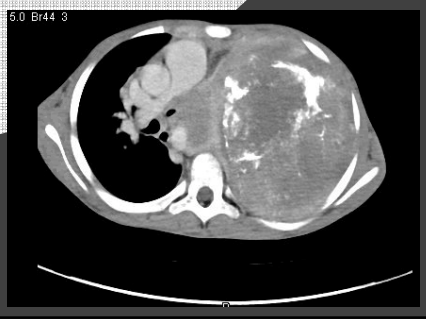
Disclosures

- Dr. Janeway
  - Consulting Ipsen, Bayer
  - Honoraria Foundation Medicine, Takeda
  - I am a pediatrician so I will discuss off-label use
- Dr. Church
  - Consulting, Bayer

Metastatic Inflammatory Myofibroblastic Tumor (IMT)

- Presentation
- Pathology and Molecular Diagnostics
- Overview molecular features of IMT
- Treatment
  - Molecularly targeted therapy
    - Key considerations in pediatric patients
    - Duration of therapy
    - Selection when multiple agents exist
    - Side effects
    - Resistance
  - Integration of other treatment approaches
- Germline cancer risk in young patients





Presentation: Syncopal event due to large chest mass

9y previously healthy male

Chest X-Ray thought to show large pleural effusion. Attempt at chest tube placement at OSH.

Able to be stabilized and transferred

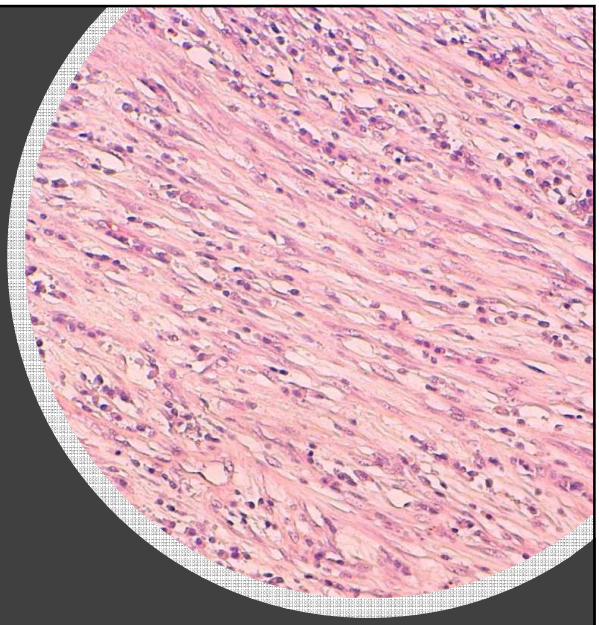
Exam: Absent breath sounds L chest, palpable peri-rectal mass

ESR 120, CRP 6.88mg/dL

IR biopsy left chest mass

Pathology: Inflammatory Myofibroblastic Tumor

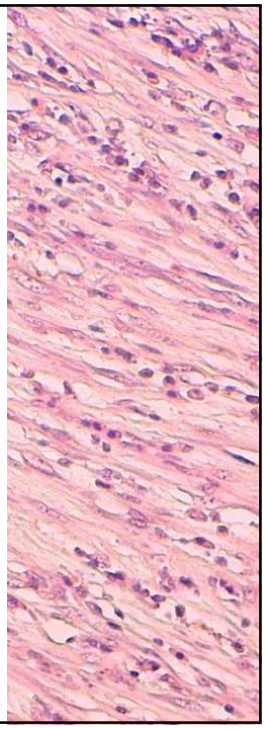
- Fibroblast-myofibroblast-like cells in a myxoid matrix with inflammatory cells (plasma cells and occasional eosinophils). Nuclear atypia. Psammomatous calcifications.
- Positive for SMA (patchy), desmin (patchy), ROS, glut-1 (sparse), and CD163
- Negative for ALK1, EMA, S100, CD34, SOX10, and MNF116.



Hammas, N., Chbani, L., Rami, M. *et al.* A rare tumor of the lung: inflammatory myofibroblastic tumor.*Diagn Pathol* **7**, 83 (2012). https://doi.org/10.1186/1746-1596-7-83

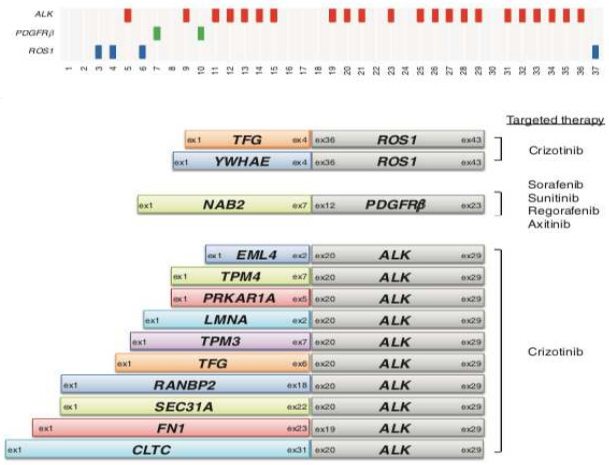
Inflammatory Myofibroblastic Tumor -- Overview

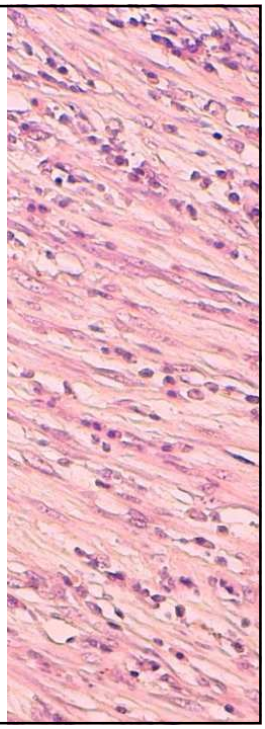
- IMT is a rare mesenchymal tumor that can occur at any age, but has a predilection for children, adolescents.
- 150 to 200 new cases are diagnosed annually in the United States.
- Location: at any side but often located in abdomen, lung and retroperitoneum.
- Prior to molecular era
  - Standard therapy has been resection.
  - Known to harbor ALK fusions



Lovly CM, Gupta A, Lipson D, et al. Inflammatory Myofibroblastic Tumors Harbor Multiple Potentially Actionable Kinase Fusions. *Cancer Discovery*. 2014;4(8):889-895. doi:10.1158/2159-8290.CD-14-0377.

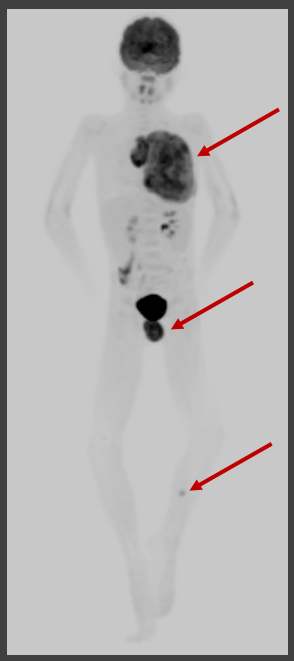
IMTs Harbor Multiple Potentially Actionable Kinase Fusions





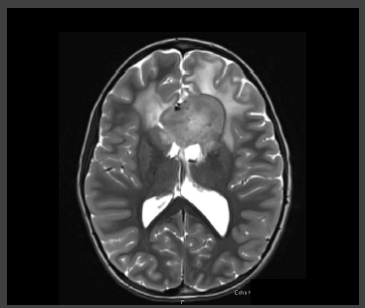
Lovly CM, Gupta A, Lipson D, et al. Inflammatory Myofibroblastic Tumors Harbor Multiple Potentially Actionable Kinase Fusions. *Cancer Discovery*. 2014;4(8):889-895. doi:10.1158/2159-8290.CD-14-0377.

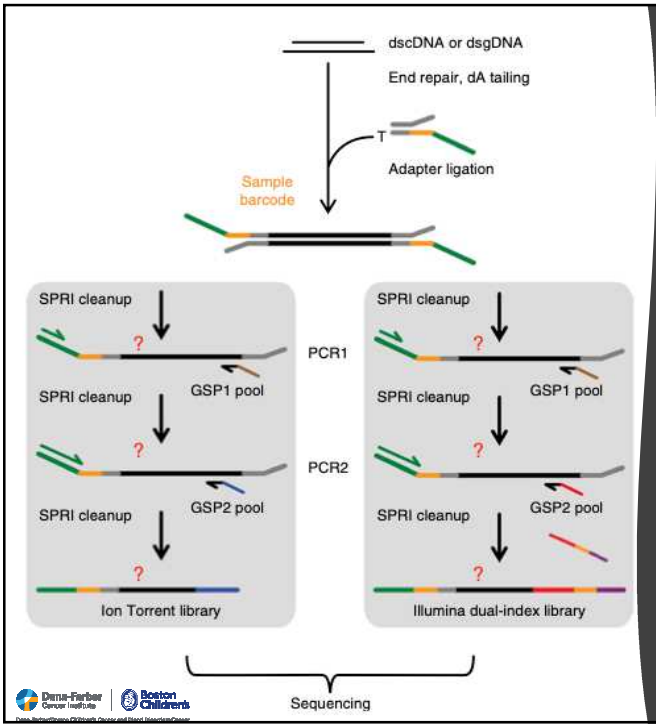
Staging



PET-CT

- Known chest mass
- Peri-rectal mass
- Mass in left calf
- Photopenic area → Mass left frontal/caudate region and hydrocephalus;

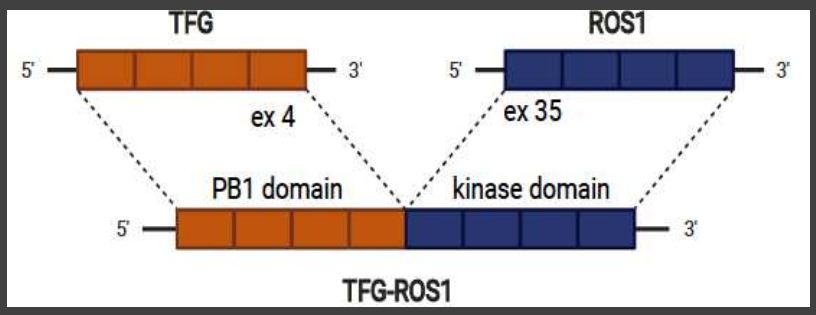




Boston Children's Hospital LaMPP Solid & Brain Tumor Fusion Panel

Targeted genes: *ALK, BCOR, BRAF, BRD3, BRD4, C11orf95, CAMTA1, CCNB3, CIC, CDH11, DNAJB1, EGFR, EPC1, ERG, ETV1, ETV4, ETV5, ETV6, EWSR1, FGFR1, FGFR3, FOSB, FOXO1, FOXO4, FUS, GLI1, HMGA2, MAML2, MEAF6, MET, MKL2, MYB, MYBL1, NCOA1, NCOA2, NTRK1, NTRK2, NTRK3, NUTM1, PDGFB, PHF1, PLAG1, PPARG, PRKACA, PRKCA, PRKCB, PRKCD, QKI, RAF1, RELA, RET, ROS1, SMARCB1, SS18, SS18L1, STAT6, TAF15, TCF12, TFE3, TFEB, TFG, USP6, VGLL2, YAP1, YWHAE.*

Solid and Brain Tumor Fusion Panel: *TFG-ROS1* gene fusion IMT



- The predicted *TFG-ROS1* fusion joins the 5' portion of TFG to the 3' portion of ROS1, likely connecting the coiled-coil domain of TFG to the intracellular kinase domain of ROS1.
- This fusion pairing has been observed in multiple tumor types, including IMT. These breakpoints have been recurrently reported
- Lung cancers with activating *ROS1*-rearrangements are known to respond to targeted inhibition
- Two case reports have been published of children with IMT harboring a *TFG-ROS1* fusion which responded to treatment with targeted inhibitors

OncoPanel, Center for Advanced Molecular Diagnostics, Brigham and Women's

- DNA NGS test targeting 447 genes (coding) with 60 genes targeted more fully to enable detection of structural variants
- TruSeq LT library preparation kit (Illumina, San Diego, California)
- Custom RNA bait set (Agilent SureSelect)
- Illumina HiSeq2500.
- Analysis of sequence variants, copy number alterations, structural variants, TMB, MSI and mutational signatures
- Validated for FFPE and frozen tumor

Oncopanel (initial biopsy)

9717500 aligned, mean of 193 reads across all targeted exons and 97% of all exons having more than 30 reads.

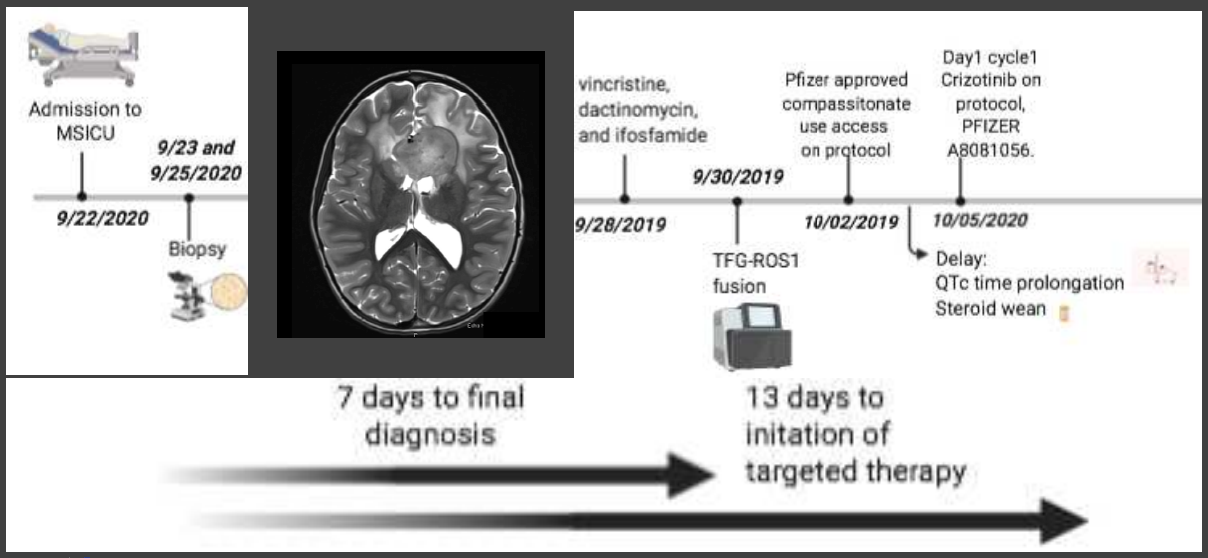
Tumor Mutational Burden/Megabase: 0.76.
Mismatch Repair Status: Proficient (MMR-P / MSS)

Mutations:
Tier 2 variants: NBN c.2140C>T (p.R714*), exon 14 - in 45% of 231 reads#

Structural Variants:
Tier 1 variants: Rearrangement - ROS1 intron 34 (chr6:117644651) :: TFG intron 4 (chr3:100449604)

Tier 4 variants:
POT1 c.133T>C (p.S45P), exon 7 - in 52% of 112 reads

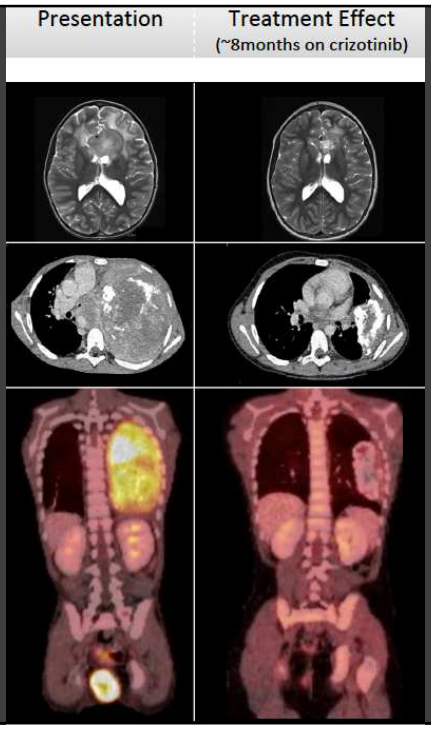
Treatment considerations



Matched targeted therapy in pediatric patients: Considerations

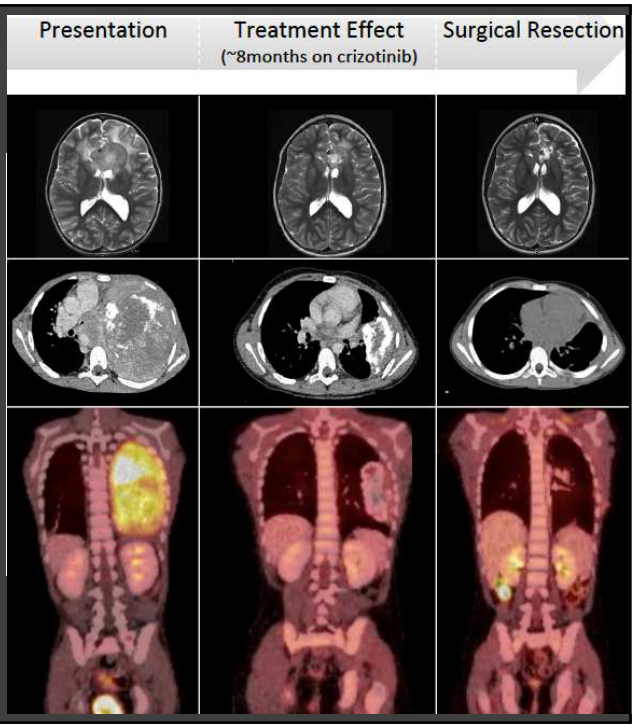
- Evidence for activity, similar / same molecular event in same cancer or different cancer
  - 1 prior reports response to crizotinib in ROS1 fusion IMT
  - ROS1 fusion NSCLC response to crizotinib
    - Objective response rates 60-80%
    - Progression free survival 10-19 months
- If child < 12 years old, dosing in pediatrics has been studied
  - Crizotinib phase 1 / 2 clinical trial completed
- If child unable to swallow pills, liquid formulation available OR some understanding of solubility of tablets (often case report)
- Clinical trial availability

Response to Crizotinib



Integration of other treatment modalities

- In spite of dramatic response, cure with crizotinib monotherapy unlikely
- Risk of resistance developing over time
- Traditionally IMT cured with surgery



Oncopanel s/p resection

Tier 2 variants:
NBN c.2140C>T (p.R714), exon 14* - in 47% of 412 reads #

Structural Variants:

Tier 1 variants:
Rearrangement - ROS1 intron 34 (chr6:117644651) :: TFG intron 4 (chr3:100449604)
Tier 2 variants:
None identified.

Tier 2 variants:
NBN c.2140C>T (p.R714), exon 14* - in 49% of 313 reads #

Structural Variants:

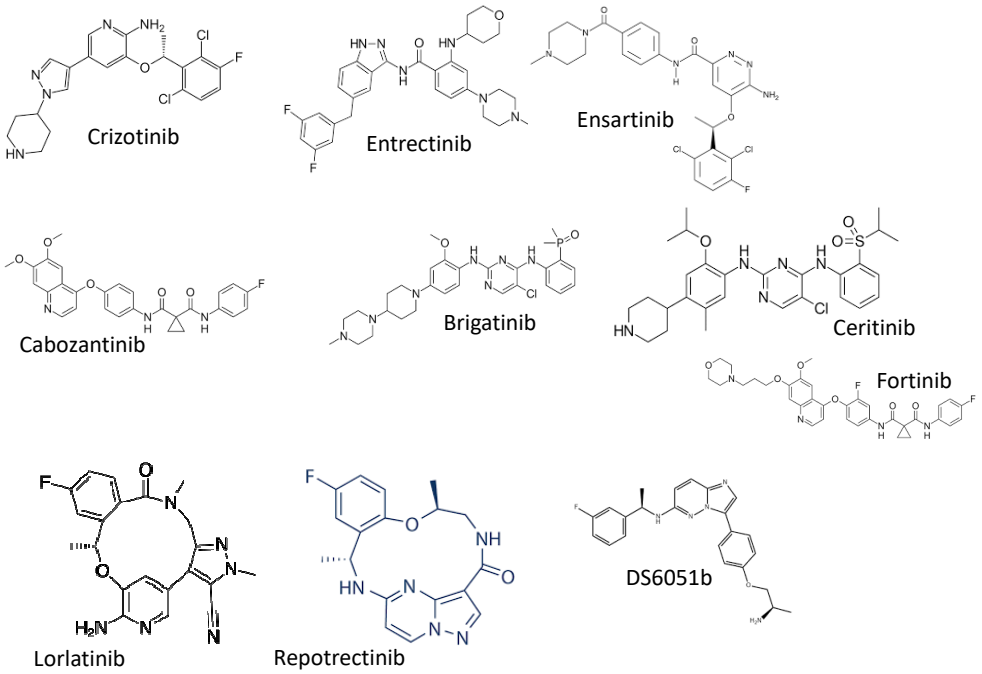
Tier 1 variants:
None identified.

Tier 2 variants:
None identified.

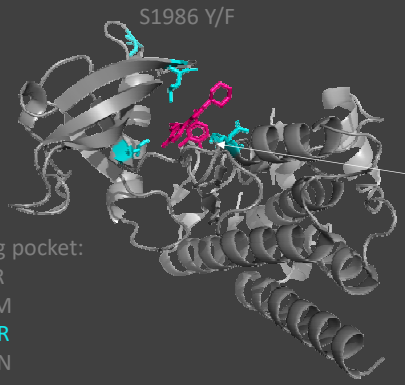
Tier 4 variants:
POT1 c.133T>C (p.S45P), exon 7 - in 52% of 194 reads ###

Brain Metastasis
Metastatic inflammatory myofibroblastic tumor
Estimated percentage of neoplastic cells in submitted specimen - 30%
Tumor Mutational Burden/Megabase: 0.76

Perianal Metastasis
Metastatic inflammatory myofibroblastic tumor
Estimated percentage of neoplastic cells in submitted specimen - 20%
Tumor Mutational Burden/Megabase: 0.76



Crizotinib - Concerns:
1)Poor CNS penetrance
2)Resistance Development



- NSLC: Mutations within the ROS1 kinase domain occur in approximately 50% to 60% of crizotinib-resistant tumors
- The most frequently observed resistant mutation has been the ROS1 G2032R mutation
- G2032R causes steric hindrance to the drug binding and does not alter the oncogenic kinase activity

McTigue, M., Deng, Y., Liu, W., Brooun, A., Stewart, A. Structure of Human ROS1 Kinase Domain in Complex with Crizotinib (2013) N Engl J Med 368: 2395.
Lin JJ, Shaw AT. Recent Advances in Targeting ROS1 in Lung Cancer. J Thorac Oncol. 2017 Nov;12(11):1611-1625. doi: 10.1016/j.jtho.2017.08.002. Epub 2017 Aug 14.

Table 1 Summary of clinical trials of targeted therapies in *ROS1*-rearranged lung cancer and summary of crizotinib resistance mutations

Drug name	Study	Phase	Population	Comparator	ORR, median [95% CI] (%)	PFS, median [95% CI] (months)	OS, median [95% CI] (months)	CNS control	Most common toxicities (>20%)
Crizotinib	Expansion phase of PROFILE 1001, NCT00585195 (8)	I/II	ROS1+ advanced disease, 86% >1 prior regimen (N=50)	None	72 [58–84]	19.2 [14.4–not reached]	16.4 [13.8–19.8	–	Visual impairment (82%), diarrhea (44%), nausea (40%), peripheral edema (40%), constipation (34%), vomiting (34%), fatigue (20%), elevated transaminases (14–22%)
	EUROS1, retrospective multicenter study (9)		ROS1+, stage IV disease. 96% >1 prior regimen (N=31)	None	80 [NR]	9.2 [NR]	–	–	Not reported due to retrospective nature
	ACSé phase II trial, NCT02034981 (10)	II	ROS+, progressing after at least 1 treatment (N=29)	None	63 [41–81]	–	–	–	Visual disorders (62%), peripheral edema (55%), diarrhea (51%), nausea (41%), and elevated transaminases (51%)
	East Asian phase II study, NCT01964157 (11)	II	East Asian, ROS1+, advanced NSCLC (N=127)	None	72 [63–79]	15.9 [12.9–24]	32.5 [32.5–NR]	–	Elevated transaminases (55%), vision disorders (48%), nausea (41%) diarrhea (39%) vomiting (32%), constipation (30%), neutropenia (29%), leukopenia (23%), edema (23%)
Ceritinib	NCT01964157 (12)	II	Advanced ROS1+, NSCLC, heavily pretreated, including 2 with crizotinib prior (N=32), 8 patients with intracranial disease	None	62 [45–77]	9.3 [0–22]	24 [5–43]	Intracranial ORR was 25%, 2/8 evaluable patients	Diarrhea (78%), nausea (59%), vomiting (53%), cough (47%), abdominal pain (41%), musculoskeletal pain (41%), fatigue (22%) and dyspnea (22%), elevated creatinine (41%), elevated LFTs (25–31%)

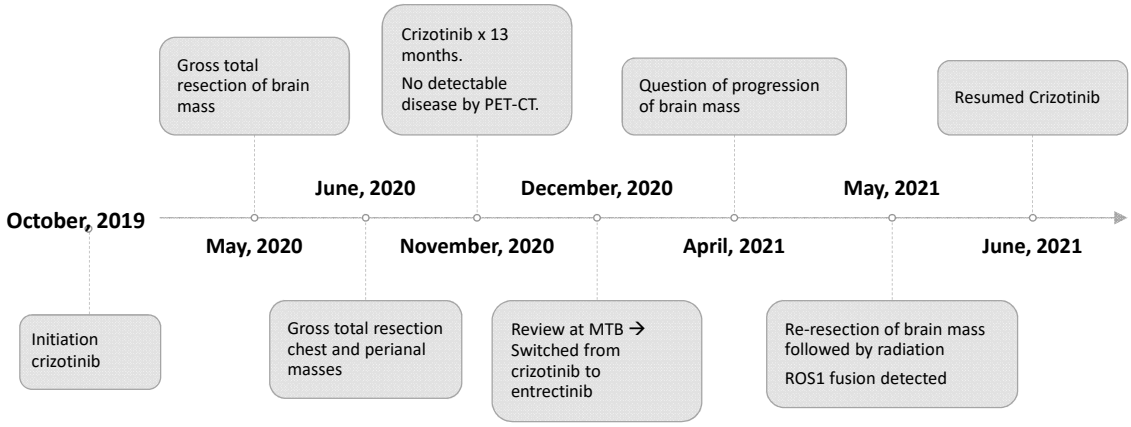
Table 1 Summary of clinical trials of targeted therapies in *ROS1*-rearranged lung cancer and summary of crizotinib resistance mutations

Drug name	Study	Phase	Population	Comparator	ORR, median [95% CI] (%)	PFS, median [95% CI] (months)	OS, median [95% CI] (months)	CNS control	Most common toxicities (>20%)
Entrectinib	ALKA-372-001, EudraCT 2012-000148-88 and STARTRK-1, NCT02097810 (13)	I	Advanced solid tumors (including 60% NSCLC) with *NTRK1/2/3*, *ROS1*, or *ALK* gene fusions (N =119); 14 patients with ROS1+ NSCLC treated with recommended phase II dose	None	86 [60–96]	19.0 [6.5–not reached]	–	63% (5/8 patients with baseline CNS disease, including 2 responders with ROS1+ disease)	Fatigue/asthenia (24%), dysgeusia (47%), paraesthesias (29%), nausea (24%) and myalgias (19%) (reported for all 119 patients)
Lorlatinib	NCT03052608 (14)	I	ALK+ or ROS1+ advanced NSCLC (N=54); 12 patients with ROS1+ NSCLC, of whom 7 had been treated with crizotinib previously and 5 had baseline CNS disease	None	50 [21–79]	7.0 [1.4–13.9]	–	3/5 (60%) had intracranial objective responses	Hypercholesterolemia (59%), hypertriglyceridemia (33%) peripheral edema (39%), peripheral neuropathy (39%) (reported for all 54 patients)
DS-6051b	Japanese study, NCT02675491 (15)	I	ROS1+ NSCLC (N=15), 4 had received crizotinib prior, 5 baseline CNS disease	None	58.3	NR	–	–	Elevated transaminases (80%), diarrhea (53%), nausea (47%), constipation (33%), decreased appetite (20%), dysgeusia (20%), malaise (20%), vomiting (20%)
Brigatinib	NCT01449461 (16)	I/II	Advanced malignancies; all histologies, except leukemia (N=137), 3 patients with ROS1+ NSCLC enrolled in cohort 4	None	33: 1 crizotinib naïve patient had partial response, 2 crizotinib previously treated patient, stable disease	–	–	–	Nausea (53%), fatigue (43%), diarrhea (41%)

ORR, objective response rate; PFS, progression-free survival; OS, overall survival; CNS, central nervous system; NSCLC, non-small cell lung cancer; NR, not reached; LFT, liver function tests.

Sehgal, K., et al. Translational Cancer Research, 2018

Disease course after initiating Crizotinib



Re-resection Pathology and Molecular Findings

- Pathology
  - Brain involved by a myofibroblastic process involving the perivascular spaces, in keeping with the patient's imaging studies and prior diagnosis of residual/recurrent inflammatory myofibroblastic tumor
- Molecular
  - ROS1 IHC negative
  - LAMPP SBT fusion panel

Gene Rearrangement	Clinical Significance
TFG-ROS1	Tier I

  - OncoPanel
    - Previously identified NBN and POT1 mutations but no ROS fusion
    - Tumor cellularity 10%

Referral to cancer predisposition clinic

Dana-Farber Cancer Institute

Find a Doctor

Pediatric Cancer Genetic Risk Program

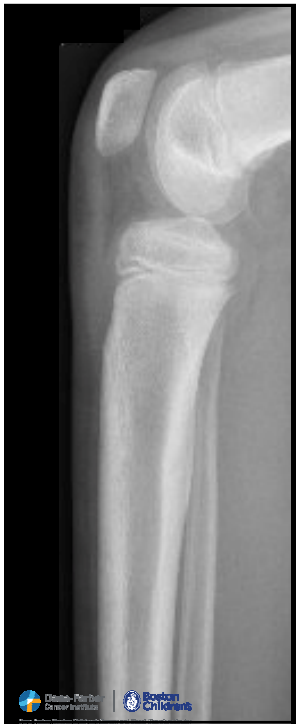
Dana-Farber's Junne Kamihara, MD, PhD; Jaclyn Schienda, CGC, LGC; and Alexander Holtz.

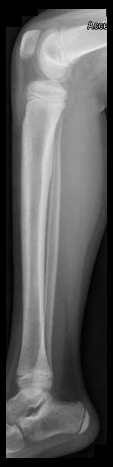
- Family history
  - Maternal grandfather had prostate cancer at age 51
  - Maternal grandmother had thyroid cancer at age 40
- Multi-Cancer panel testing, Invitae laboratory
- NBN c.2140C>T (p.Arg714*) mutation identified
- Patient is a carrier for a recessive Nijmegen Breakage syndrome
- Individuals who carry one NBN mutation may have moderately increased risks of cancer; especially increased breast cancer risks in female carriers
  - Mother tested and she also caries this NBN gene mutation and has a personalized breast cancer screening plan

Germline Cancer Risk in Pediatric Patients

- GAIN/iCat2 study data
  - 160 participants with tumor-only and germline sequencing OncoPanel
  - Germline sequencing identified 38 pathogenic or likely pathogenic (P/LP) variants among 35 (22%) patients
    - Similar to other cohorts
    - All variants were heterozygous,
      - 18 variants in 12 genes known to have an autosomal dominant pattern of inheritance
      - 20 variants identified in 10 genes with an autosomal recessive pattern of inheritance
  - Twenty-five (66%) of these germline variants were present in the tumor sequencing report
    - Most were suspected to be germline in origin

Scheinda J, et al., manuscript under review





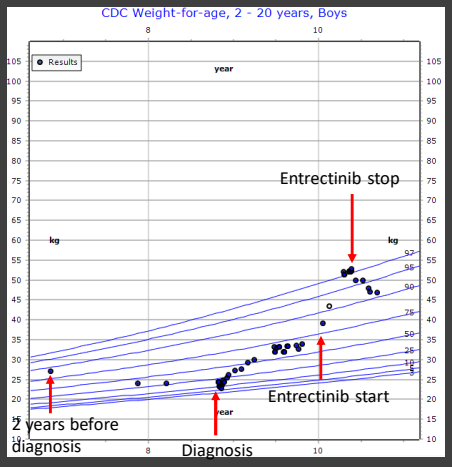
Unique Pediatric Side Effects Molecularly Targeted therapy

- Abnormal imaging of the leg / foot.
- Brief, transient difficulties to walk.

>crizotinib induced osteitis

Guisier F, et al.BMC Cancer. 2020

Unique Pediatric Side Effects Molecularly Targeted therapy



Treatment allowed for catch up growth.

Crizotinib → catch up growth

Entrectinib → weight gain

BCH IMT CASES

AGE AT PRESENTATION	FUSION	LOCATION	METASTATIC	Medical treatment	Surgery / radiation
8y	TFG-ROS1	brain, lung, perianal, leg	yes	crizotinib	resection brain/chest/perianal mass
9y	ETV6-NTRK	lung	?no	loratrectinib	?pending
1m	TPM4-ALK	liver, peritoneal deposits	yes	crizotinib	resection liver mass ((prior to medical treatment)
10y	TFG-ROS1	brain, lung, MSK, abdominal	yes	repotrectinib	Lung mass resection (prior to medical treatment)
11y	EML4-ALK	lung	no	none	Lung mass resection (no medical treatment)
5y	ALK fusion	abdomen	yes	crizotinib (rash) > ceritinib	Abdominal mass resection
12y	EML4-ALK	chest, multiple lesion	yes	doxorubicine / ifosphamide prior to transfer then ceritinib	resection of chest mass (prior to targeted therapy), radiation

Acknowledgements

Pediatric Oncology
- Franziska Wachter

Pediatric Cancer Risk Program
- Jaclyn Schienda
- Junne Kamihara

BCH Pathology
- Alyaa Al-Ibraheemi
- Harrison Tsai
- Marian Harris

BWH Pathology
- Neal Lindeman