PRESCRIPTIONS FOR A RARE DISEASE. IS THERE A CURE? 2023 PATIENT FAMILY GATHERING

JITHMA ABEYKOON, MD
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ERDHEIM-CHESTER DISEASE GLOBAL ALLIANCE

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ERDHEIM CHESTER DISEASE TREATMENTS:

PRESCRIPTIONS FOR A RARE DISEASE. IS THERE A CURE?

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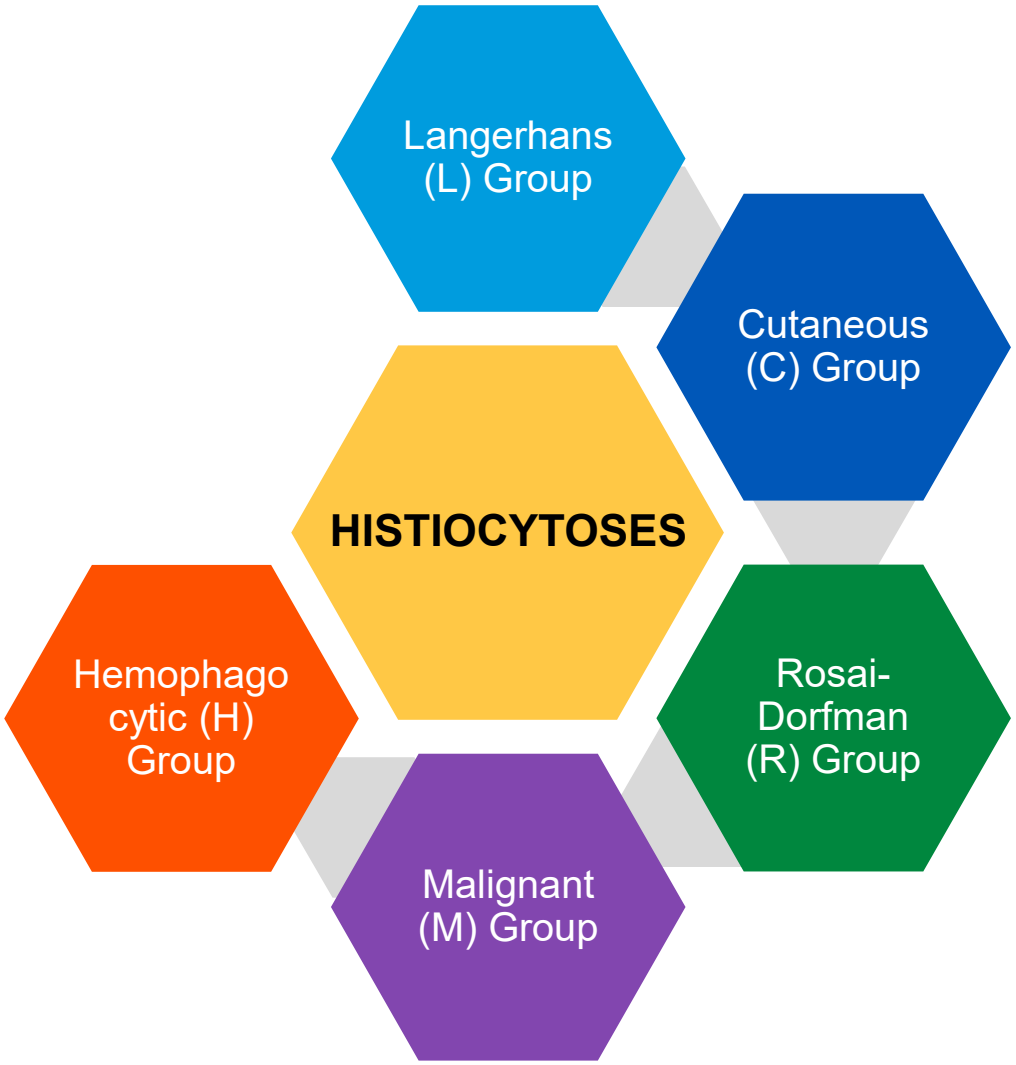
OUTLINE

- Introduction
- Walk with a case
- Treatment options
- Definition of cure
- Is there a cure?
- Future directions



REVISED CLASSIFICATION OF HISTIOCYTOSES AND NEOPLASMS OF THE MACROPHAGE-DENDRITIC CELL LINEAGES

Redrawn from: Emile JF, et al. Blood 2016;127:2672-2681
Slides from Dr. Go

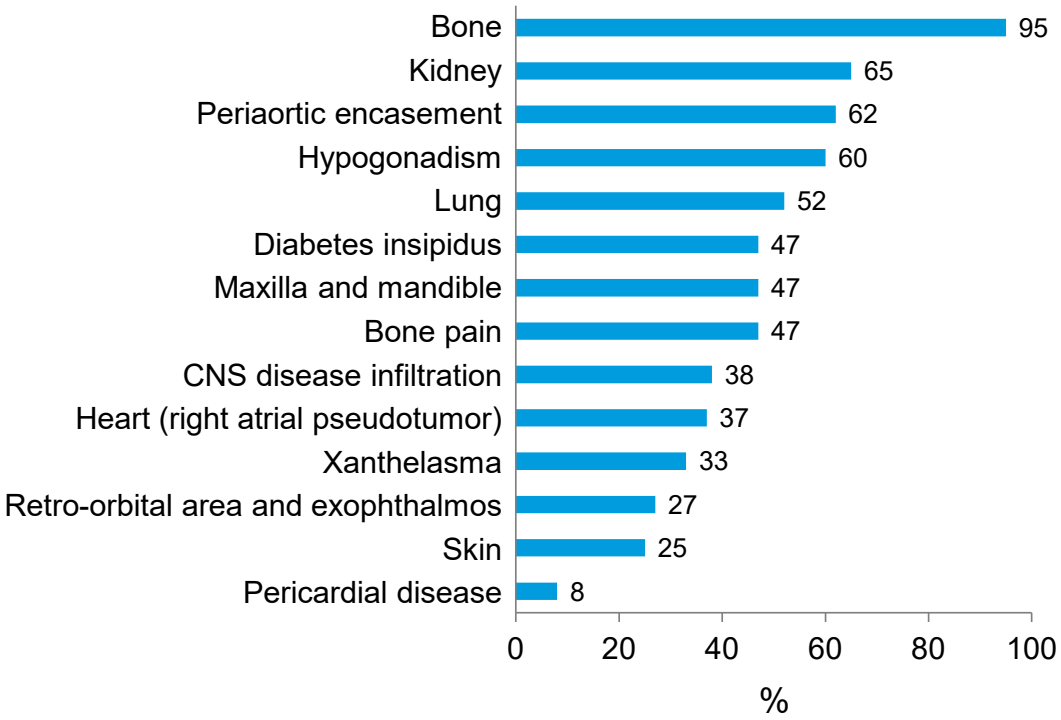
HISTIOCYTIC DISEASES

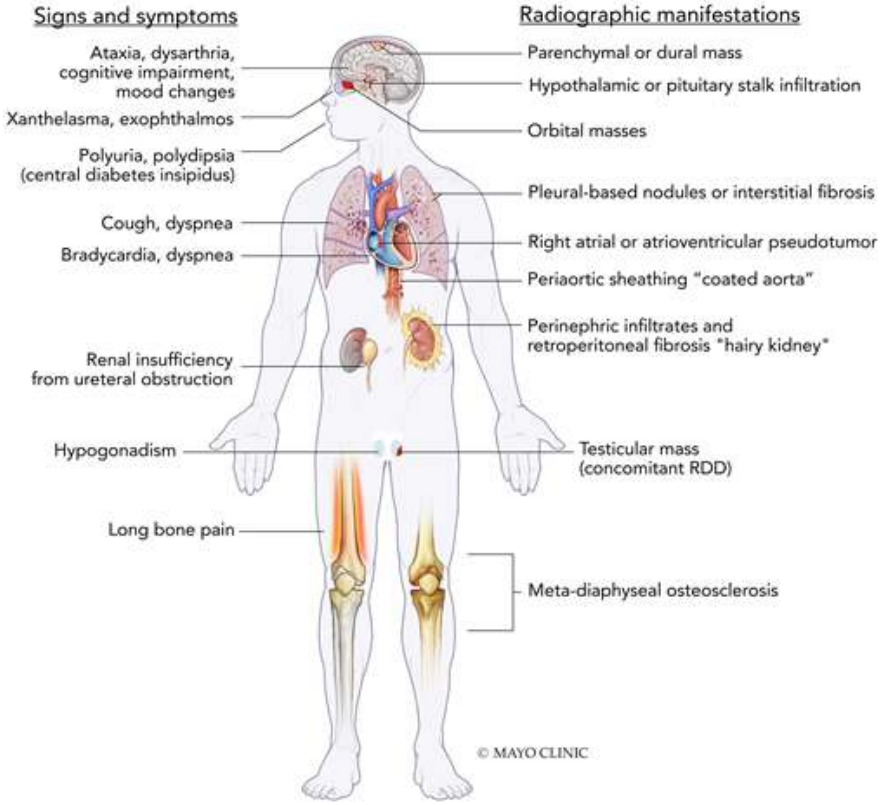
L Group	C Group	R Group	M Group	H Group

• **Langerhans cell histiocytosis**
  • Single system no lung
  • SS lung
  • Multisystem w/o risk organ
  • Multisystem w/ risk organ
  • W/ MPN/MDS
• **Erdheim-Chester disease**
  • Classical
  • Non-classical
  • W/ MPN/MDS
  • Extracutaneous JXG
• **Mixed LCH/ECD**
	• **Xanthogranuloma family**
	  • Juvenile XG
	  • Adult XG
	  • Solitary reticulohistiocytoma
	  • Benign cephalic histiocytosis
	  • Generalized eruptive histiocytosis
	  • Progressive nodular histiocytosis
	• **Non-XG family**
	  • Cutaneous RDD
	  • Necrobiotic xanthogranuloma
		• **Familial RDD**
		  • Faisalabad syndrome
		  • FAS deficiency
		• **Classical RDD**
		  • W/ IgG4
		  • W/o IgG4
		• **Extranodal RDD**
		  • Bone RDD
		  • CNS RDD
		  • Other single-organ RDD
		  • Disseminated RDD
		• **Neoplasia-associated RDD**
		• **Immune disease-associated RDD**
		  • SLE/HIV/AIHA/JA
			• **Histiocytic sarcoma**
			• **Interdigitating dendritic cell sarcoma**
			• **Langerhans cell sarcoma**
			• **Indeterminate cell sarcoma**
			• **Primary**
			• **Secondary**
			  • ALL
			  • CLL
			  • Follicular lymphoma
			  • Hairy cell leukemia
			  • Other histiocytoses
				• **Primary hemophagocytic lymphohistiocytosis**
				  • W/ lymphocyte cytotoxic defects
				  • W/ inflammasome activation
				  • W/Mendelian disorders affecting inflammation
				• **Secondary HLH**
				  • Infection-associated
				  • Malignancy-triggered
				  • Rheumatologic
				  • Transplant-related
				  • Iatrogenic immune activation/suppression

Redrawn from: Emile JF, et al. Blood 2016;127:2672-2681
Slides from Dr. Go

Organ Involvement

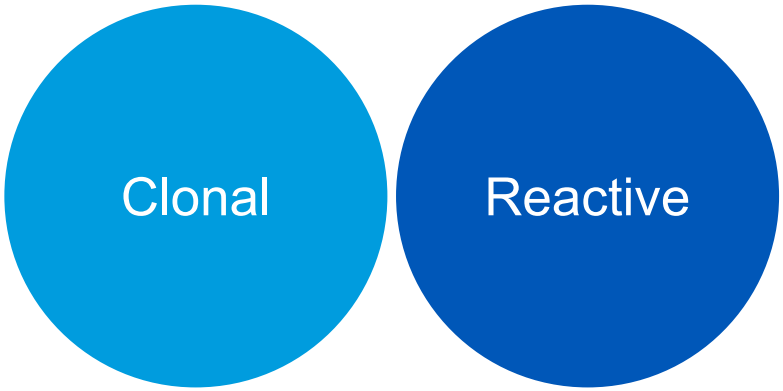




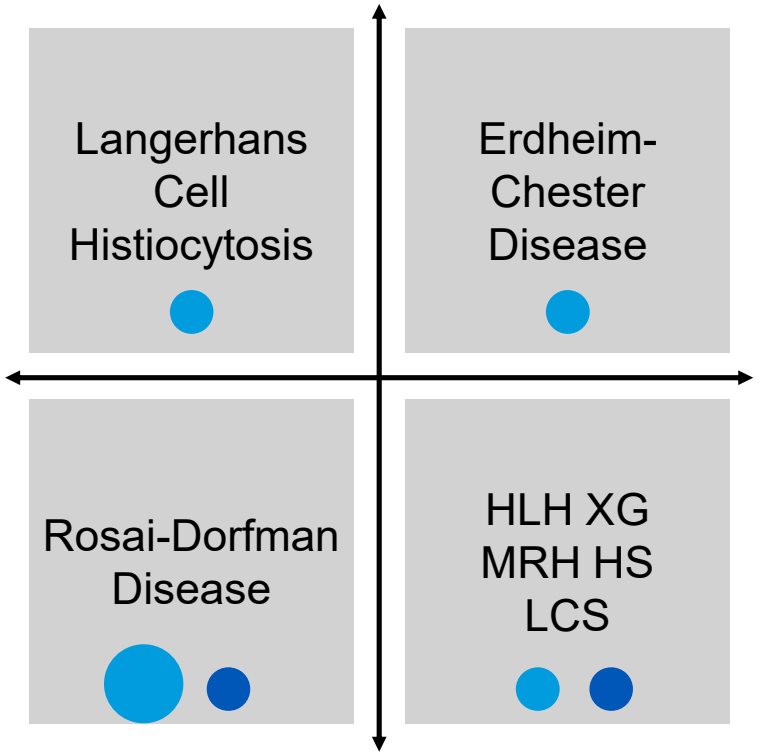
Redrawn from: Goyal et al, Blood, 2020

HISTIOCYTIC DISEASES

Nature

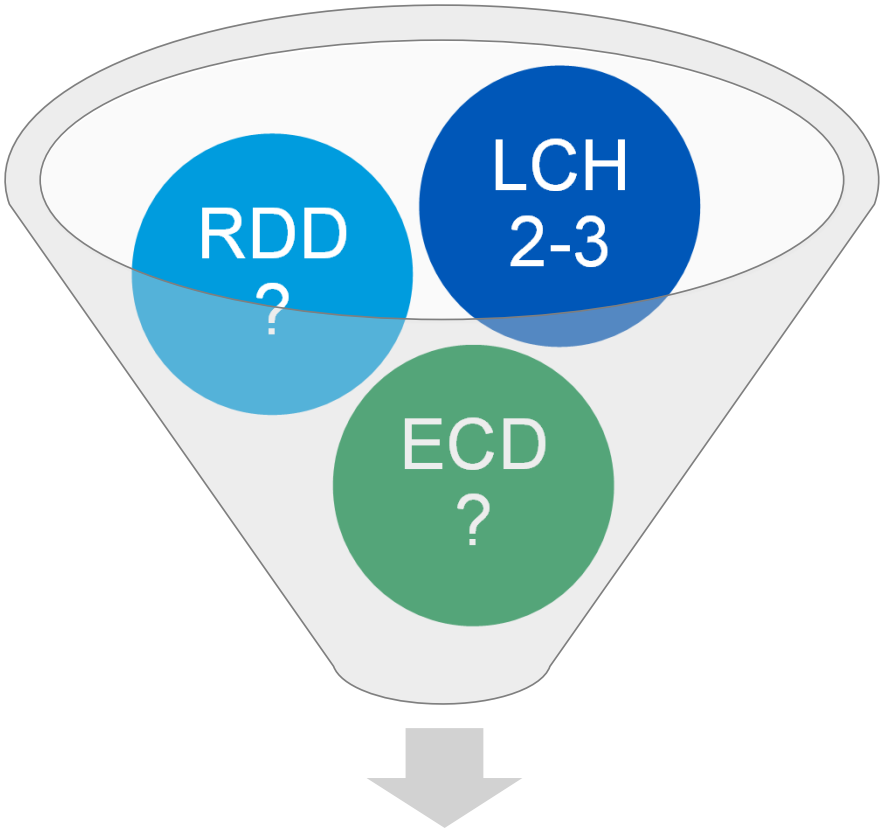


Subtypes



Slides from Dr. Go

ANNUAL INCIDENCE/ 1,000,000 POPULATION



~1,000 per year in US

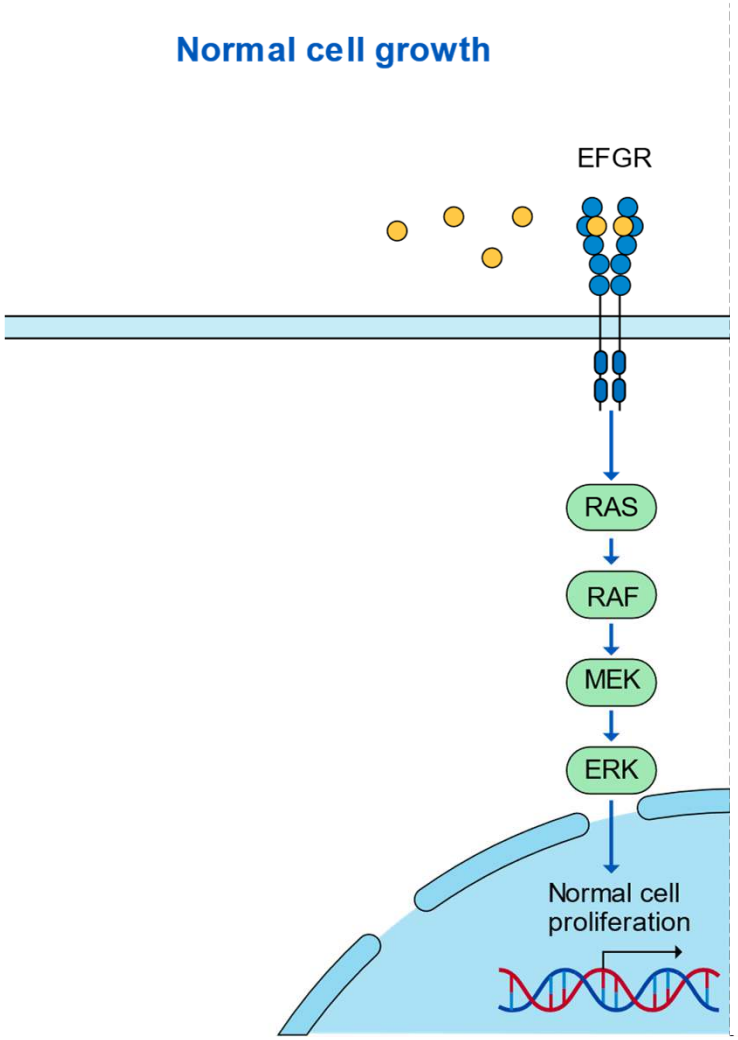
Stalemark H, et al. Pediatr Blood Cancer 2008;51;76-81
Goyal G, et al. Br J Haematol 2018;182:579-581
Makras P, et al. Pediatr Blood Cancer 2020;67:e28422
Slides from Dr. Go

HISTOPATHOLOGIC FEATURES

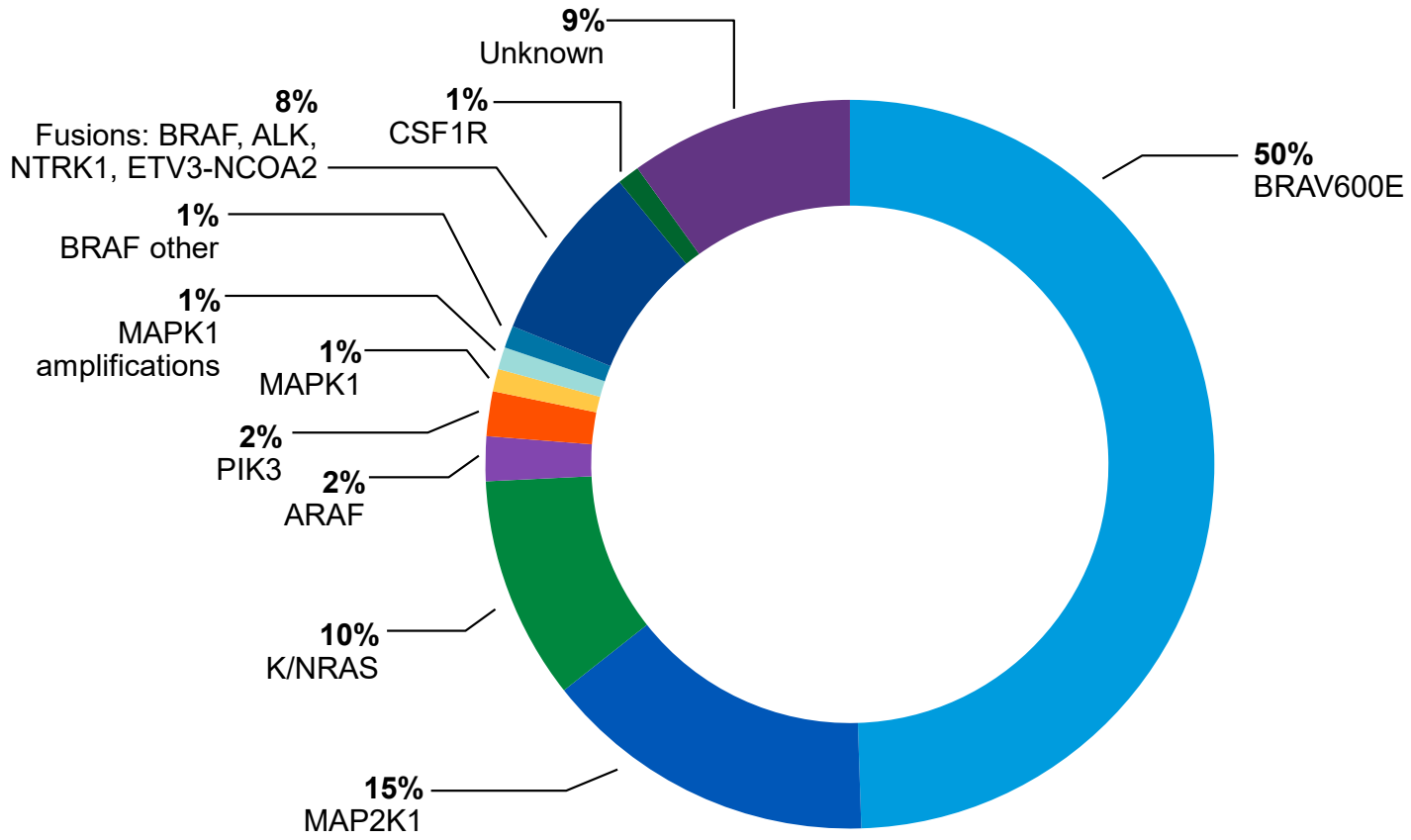
Tests		ECD	LCH	RDD
CD68	Monocyte/macrophage protein Binds to tissue lectin/selectin	**+**	+	+
CD163	Monocyte/macrophage protein Receptor for hgb-haptoglobin complex	**+**	+	+
CD1a	Related to MHC proteins Binds to b2-microglobulin	**-**	+	-
CD207	Langerin; C-type lectin Localized in Birbeck granules	**-**	+	-
S100	Homodimeric polypeptides Cell marker: neural crest, melanocyte	**+/-**	+	+
Factor XIIIa	Monocyte/macrophage protein AKA fibrin-stabilizing factor	**+**	-	-
Touton giant cells	Macrophage-derived multinucleated giant cells with high lipid content	**+**	-	-
Emperipolesis	Intact inflammatory cells within cytoplasm of histiocytes	**-**	-	+
BRAFV600E	Proto-oncogene; cell division	**50%**	60%	0%
MAPK/ERK	Cell growth and proliferation	**40%**	30%	40%

Diamond EL, et al. Blood 2014;124:483-492; Durham BH. Semin Cell Dev Biol 2019;86:62-76.

RAS/RAF PATHWAY ALTERATIONS



MOLECULAR ALTERATIONS IN HISTIOCYTOSIS



Redrawn from: Durham BH. Semin Cell Dev Biol 2019;86:62-76

MEET ANYA

Permission obtained from the patient

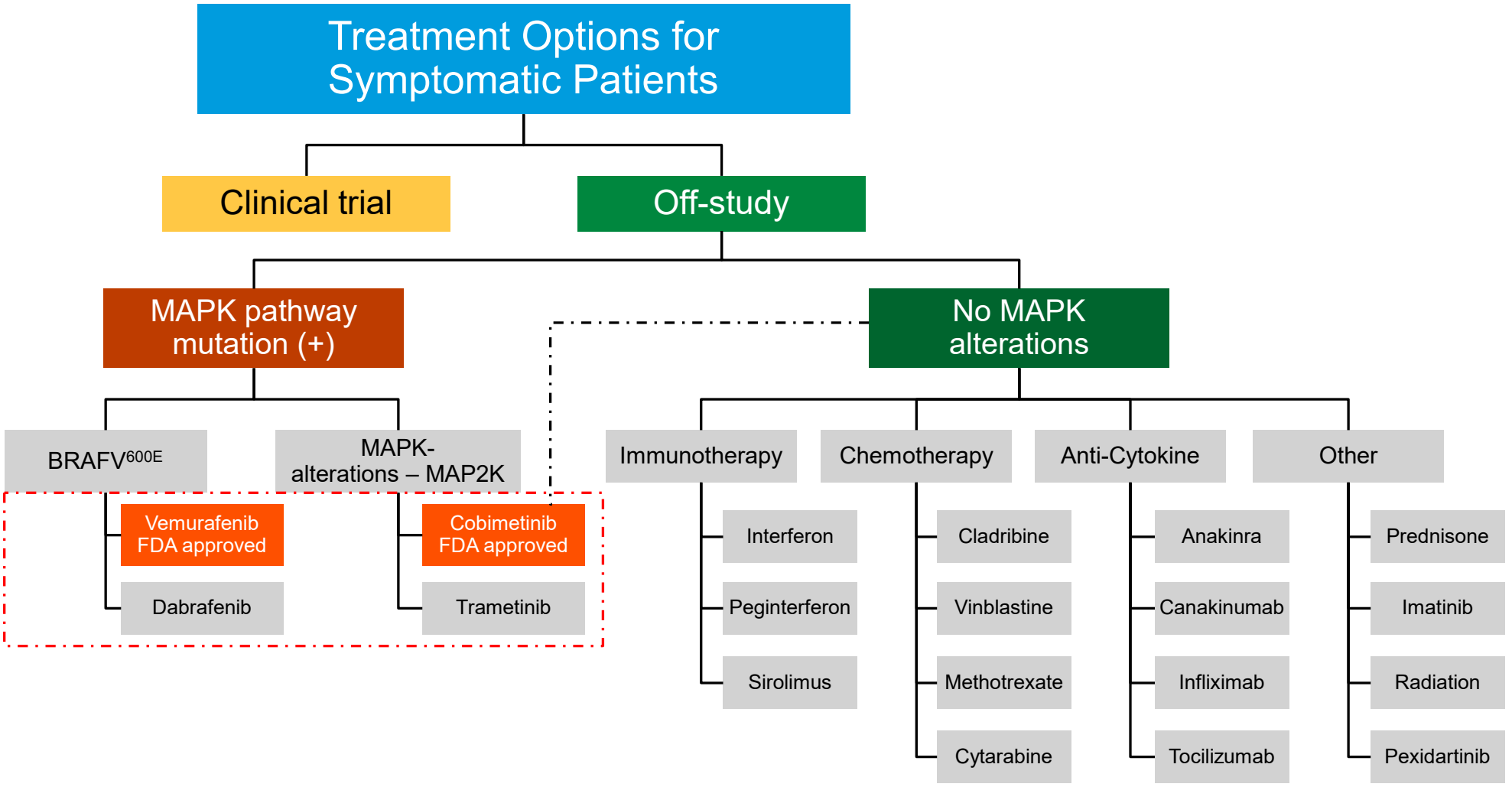
22-YEAR-OLD FEMALE WITH CNS INVOLVED ECD

November 2017
New onset of headaches with increased intracranial pressure; placed VP shunt

May 2, 2019
MRI brain with leptomeningeal enhancement and enhancing nodularity along the entire spinal cord involving cord and nerve roots

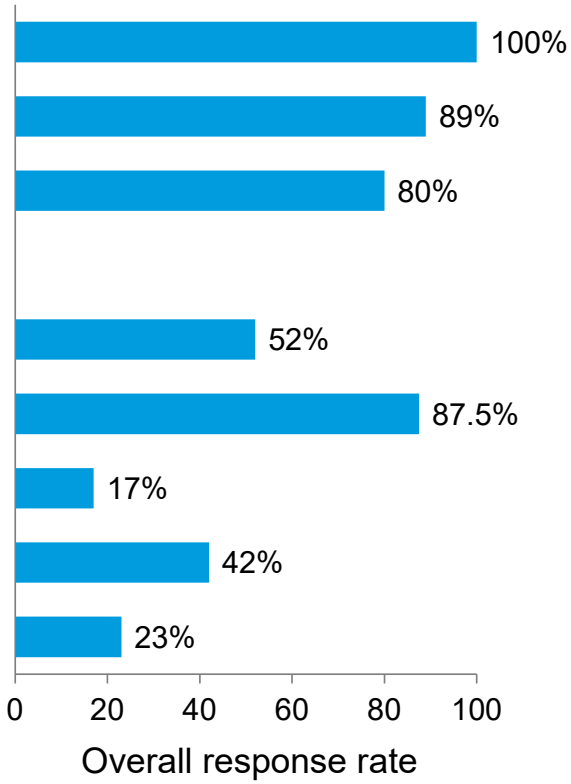
May 14, 2019
L2-L3 laminectomy, durotomy and bx

- Pathology: atypical histiocytic infiltrate which was positive for **cyclin D1, factor XIIIa**, and **negative for CD1a and BRAF-V600E** on IHC.
- Final diagnosis was **Erdheim-Chester disease**



TREATMENT

Regimen	Study	No.	Response	Comments
★ Vemurafenib[1]	Phase II	22	100% by mod PERCIST	Newly diagnosed BRAFV600 mutant; 80% CR; no relapse at 29 month-FU; recommend starting at half-dose 480 mg PO BID; most relapsed w/ vemurafenib discontinuation[2]
★ Cobimetinib[2,3]	Phase 2	18	89% by PRC	Newly diagnosis and previously treated. 72% CR, 17% PR and 6% SD. All responses were durable during 1 year of follow-up
Sirolimus + prednisone[4]	Open label	10	80%	1 CR; Highest responses in retroperitoneal and cardiovascular areas
Interferon a[5]	Prospective cohort	46	Not reported	All w/ CNS involvement; interferon-treated group better than no interferon (HR: 0.32)
Cladribine[6]	Retrospective cohort	21	52%	1 CR; Median of 2.5 cycles; median duration of response: 9 months; all sites responded including CNS
Cytarabine[7]	Retrospective cohort	9	87.5% by PERCIST	1 CR; CNS response 91%; 2-year PFS and OS was 75% and 93.5%
Anakinra[8]	Retrospective cohort	12	17% by PERCIST	1 CR; median duration of rx: 22 months; 50% symptom improvement; 22% stable disease
Infliximab[9]	Retrospective cohort	12	42% by PERCIST	No CR; 25% stable disease; median duration of rx: 14 months; cardiac and CNS responses noted
Methotrexate[10]	Retrospective cohort	13	23%	No CR; 54% stable disease; median duration of rx: 4 months (FU incomplete); ophthalmologic responses noted



[1]Diamond EL, et al. JAMA Oncol 2018;4:384-388
[2]Diamond et al, Nature, 2019; 567(7749): 521–524
[3]Aubart FC, et al. Blood 2017;130:1377-1380.
[4]Gianfreda D, et al. Blood 2015;126:1163-1171
[5]Arnaud L, et al. Blood 2011;117:2778-2782
[6]Goyal G, et al. JAMA Oncol 2017;3:1253-1256
[7]Liu et al, Orphanet J Rare Dis. 2022; 17: 39
[8]Cohen-Aubart F, et al. Blood 2016;127:1509-1512.
[9]Cohen-Aubart F, et al. Ann Rheum Dis 2018;epub ahead
[10]Goyal G, et al. Blood Cancer J 2017;7:647

TARGETED THERAPY AND ASSOCIATED ADVERSE EFFECTS (AES)

- In the phase II trial of vemurafenib, all patients required dose reductions below the 960mg twice daily dose due to intolerable AEs
- 29% discontinued the medication due to intolerable AEs
- 56% had dose reduction with cobimetinib due to AEs

AEs

- Rash
- Diarrhea
- Electrolyte imbalance
- Cardiac dysfunction
- Abnormalities in red blood cells, white blood cells and platelets

1. Diamond E, Subbiah V, Lockhart A, et al. Vemurafenib for BRAF V600-Mutant Erdheim-Chester Disease and Langerhans Cell Histiocytosis: Analysis of Data From the Histology-Independent, Phase 2, Open-label VE-BASKET Study. JAMA Oncol, 2018, 4 (3): 384-388.
2. Gordon JR, Antonious H, Low-dose vemurafenib monotherapy in BRAFV600Emutated Erdheim-Chester disease. Leuk Lymphoma, 2020, 61(11):2733-2737.
3. Diamond et al, Nature, 2019; 567(7749): 521–524.

ADVERSE EFFECTS

Continuous therapy (% total, % grade >3) (vemurafenib/cobimetinib)	Fixed duration therapy (% total, % grade >3) (cladribine/cytarabine)
Joint pain (82, 14)	Infection (20)
Rash (50-80, 10-18)	Hematologic (40-100, 100)
Fatigue (20-55, 5)	Nausea (20)
Hair loss (55)	Fatigue (80)
Diarrhea (50-60)	Diarrhea (50%)
Neuropathy (41)	Hair loss
Nausea and vomiting (20—30)	Itching (50)
Edema (22)	
Decrease white blood cell count (17)	

CLINICAL TRIALS

Phase	Treatment	Institutions	Comments	Status
I	Anakinra or denosumab + everolimus (mTOR inhibitor)	MD Anderson (Houston)	NCT01624766; previously treated	completed
I	DCC-2618 (c-Kit inhibitor)	Multiple	NCT02571036 previously treated	completed
I	Ulixertinib or BVD-523 (ERK inhibitor)	Multiple	NCT01781429; newly diagnosed or previously treated	completed
I	Selinexor + choline salicylate	Mayo Clinic, MN	NCT04640779; previously treated	recruiting
I	Virotherapy	Mayo Clinic, MN	NCT03017820; previously treated	recruiting
I/II	PLX8394 (BRAF inhibitor)	Multiple (11 sites)	NCT02428712; previously treated BRAF mutated	active, not recruiting
I/II	HH2710 (ERK1/2 inhibitor)	Multiple	NCT04198818; previously treated MAPK mutated	terminated
II	Lenalidomide (immunomodulatory agent)	Dana Farber (Boston)	NCT02523040; newly diagnosed or previously treated	active, not recruiting
II	HLX208 (BRAF inhibitor)	China	NCT05092815; BRAF mutated; Newly diagnosed or previously treated	recruiting
II	Cobimetinib	NACHO (Baltimore, Dallas, DC, Houston, Madison, Memphis, Orange)	NCT04079179; previously treated patients	recruiting
II	Dabrafenib (BRAF inhibitor) or trametinib (MEK inhibitor)	National Institute of Health (Bethesda)	NCT02281760; BRAF mutated; Newly diagnosed or previously treated; study suspended	completed
II	Nivolumab (PD1 antibody)	Multiple (52 sites)	NCT02832167; previously treated	completed
II	LY3023414, selumetinib, ensartinib, olaparib, palbociclib, ulixertinib, selpercatinib	Children's Oncology Group: Pediatric MATCH trial; multiple US sites	NCT03155620; previously treated	recruiting
II/III	Vemurafenib and cobimetinib	Multiple (UK)	NCT05768178; BRAF mutated; Newly diagnose	recruiting

Updated April 2023

BACK TO OUR PATIENT

NGS TESTING ON 05/2019

GENOMIC VARIANTS

Somatic - Potentially Actionable / Biologically Relevant

No reportable pathogenic variants were found.

Germline - Pathogenic / Likely Pathogenic

No pathogenic variants were found in the limited set of genes on which we report.

IMMUNOTHERAPY MARKERS

Tumor Mutational Burden

0.8 m/MB 16th percentile

TREATMENT IMPLICATIONS

No reportable treatment options found.

CLINICAL TRIALS

Single-agent Cobimetinib for Adults With Histiocytic Disorders (NCT02649972)	**Phase II** New York, NY - 970 mi

VARIANTS OF UNKNOWN SIGNIFICANCE

Anya Magnuson | TL-19-B24BFC

Somatic	Mutation effect	Variant allele fraction
UGT1A8	c.1366G>A p.V456M Missense variant NM_019076	17.0%
NDUFC2-KCTD14	c.136_138delinsGTG p.L46V Missense variant NM_001203260	11.0%

Germline	Mutation effect	Condition
APC	c.5335A>G p.I1779V Missense variant chr5:112176626 NM_000038	Familial adenomatous polyposis

LOW COVERAGE REGIONS

GFRA2	GSTT1	HDAC4	NOTCH1	PDPK1	SEMA3C
ZNRF3					

TREATMENT

Jul–Sep 2019

Cobimetinib; cycle 1 complicated by diarrhea and dose was decreased to 40 mg from 60 mg

Response: progressive disease in the lumbar spine and nerve roots

Oct 2019

1 dose of interferon with poor tolerance; intractable headaches requiring hospital admission

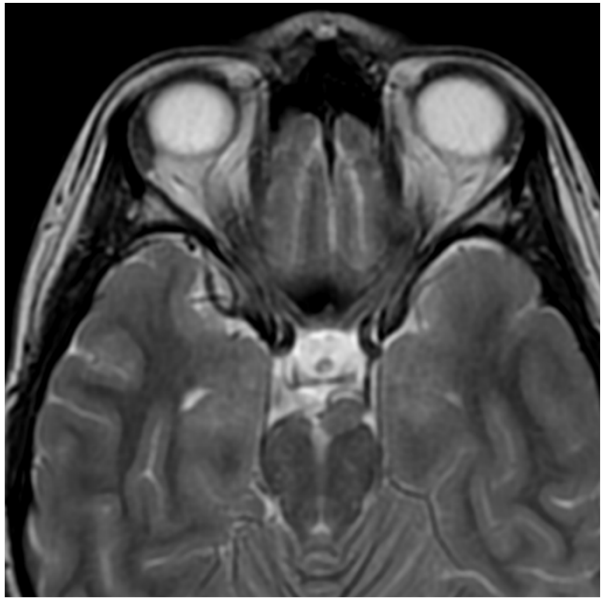
Nov 2019 – Feb 2020

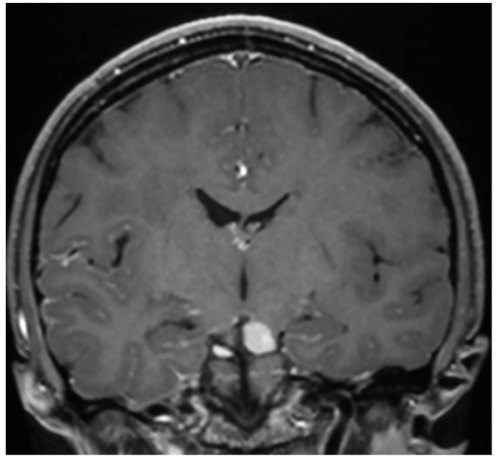
6 cycles of high-dose methotrexate

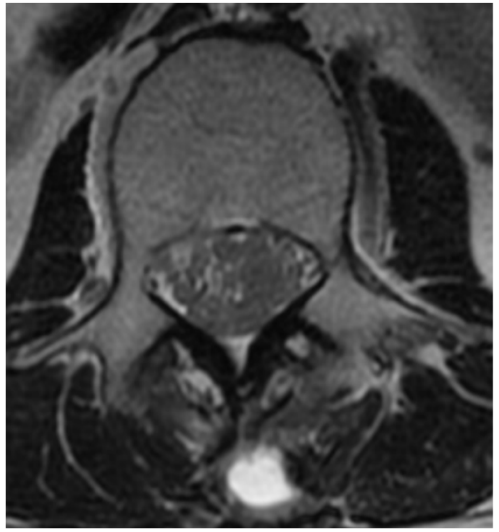
Response: clinical response with improvement of lower extremity numbness, tingling and motor strength as well as headaches

Mar 2020

Radiographic and clinical progression as well as clinical progression







GENOMIC VARIANTS

Somatic - Potentially Actionable / Biologically Relevant

No reportable pathogenic variants were found.

IMMUNOTHERAPY MARKERS

Tumor Mutational Burden

3.7 m/MB 60th percentile

TREATMENT IMPLICATIONS

No reportable treatment options found.

CLINICAL TRIALS

Single-agent Cobimetinib for Adults With Histiocytic Disorders (NCT02649972)	**Phase II** New York, NY - 969 mi

VARIANTS OF UNKNOWN SIGNIFICANCE

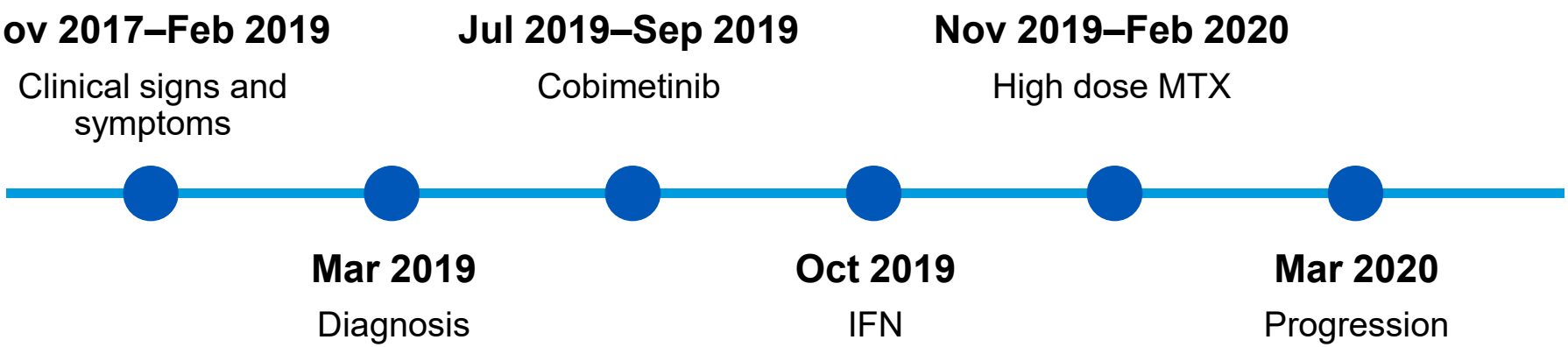
Anya Magnuson | TL-20-8B2AB9

Somatic	Mutation effect	Variant allele fraction
APC	c.5335A>G p.I1779V Missense variant NM_000038	66.5%
ERBB3	c.316C>T p.R106* Stop gain NM_001982	44.4%
EGLN1	c.320C>G p.A107G Missense variant NM_022051	36.9%
LRP1B	c.11833G>A p.G3945R Missense variant NM_018557	34.7%
RANBP2	c.3278T>C p.I1093T Missense variant NM_006267	31.2%
CSF1R	c.1646_1660del p.R549_E554delinsQ Inframe deletion NM_005211	27.4%
UGT1A8	c.1366G>A p.V456M Missense variant NM_019076	20.0%
MAGI2	c.501G>T p.E167D Missense variant NM_012301	6.5%

LOW COVERAGE REGIONS

KDM5D

TIMELINE



NEXT-LINE OF THERAPY AND RECOMMENDATIONS

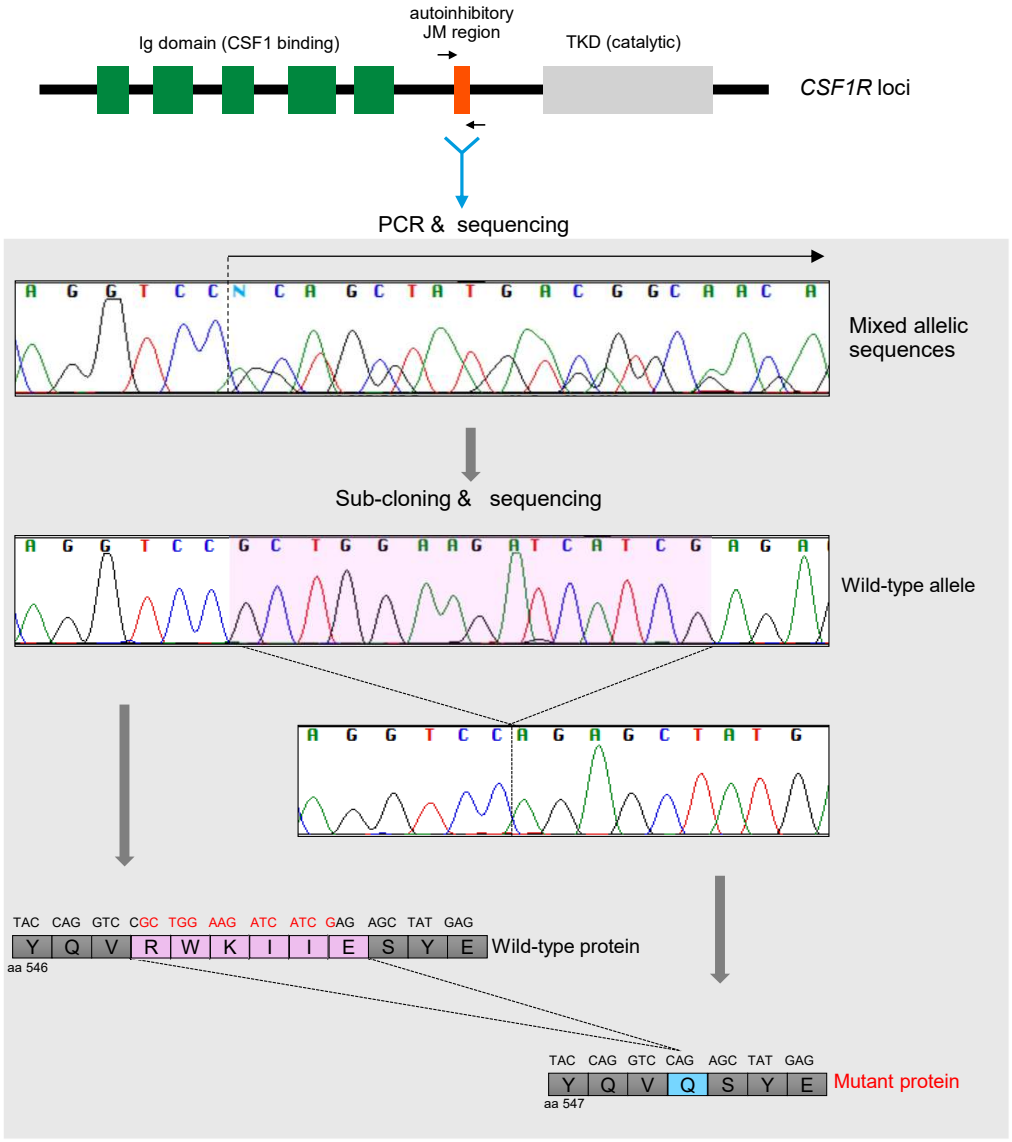
- Cladribine, or
- Cytarabine, or
- Pembrolizumab, or
- Autologous SCT, or…
- Pexidartinib, or palliative/hospice

DECIDED TO ASSESS THE RELEVANCE OF CSF1R VUS

- Colony Stimulating Factor 1 Receptor
- Expressed in macrophages and monocytes
- Ligand: IL34, CSF1 (MCSF1), and upon binding, cause homodimerization and subsequent activation of downstream pathways
- Overexpression, rearrangement and mutations are associated with pathology: tenosynovial giant cell tumor - a destructive synovial tumor associated with *CSF1-COL6A3* translocation leading to overexpression of CSF1

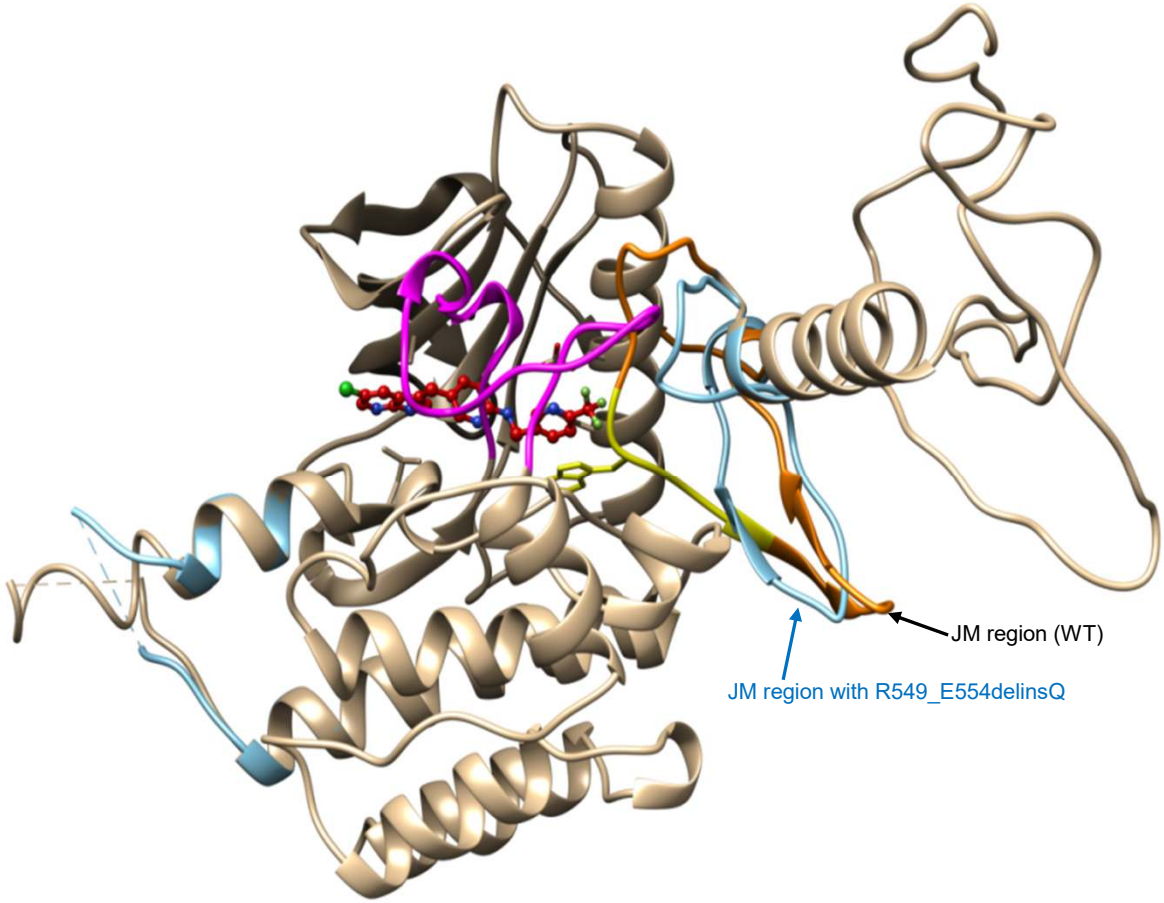
Cancer Immunol Res. 2020 Jun;8(6):829-841

TARGETING CSF1R



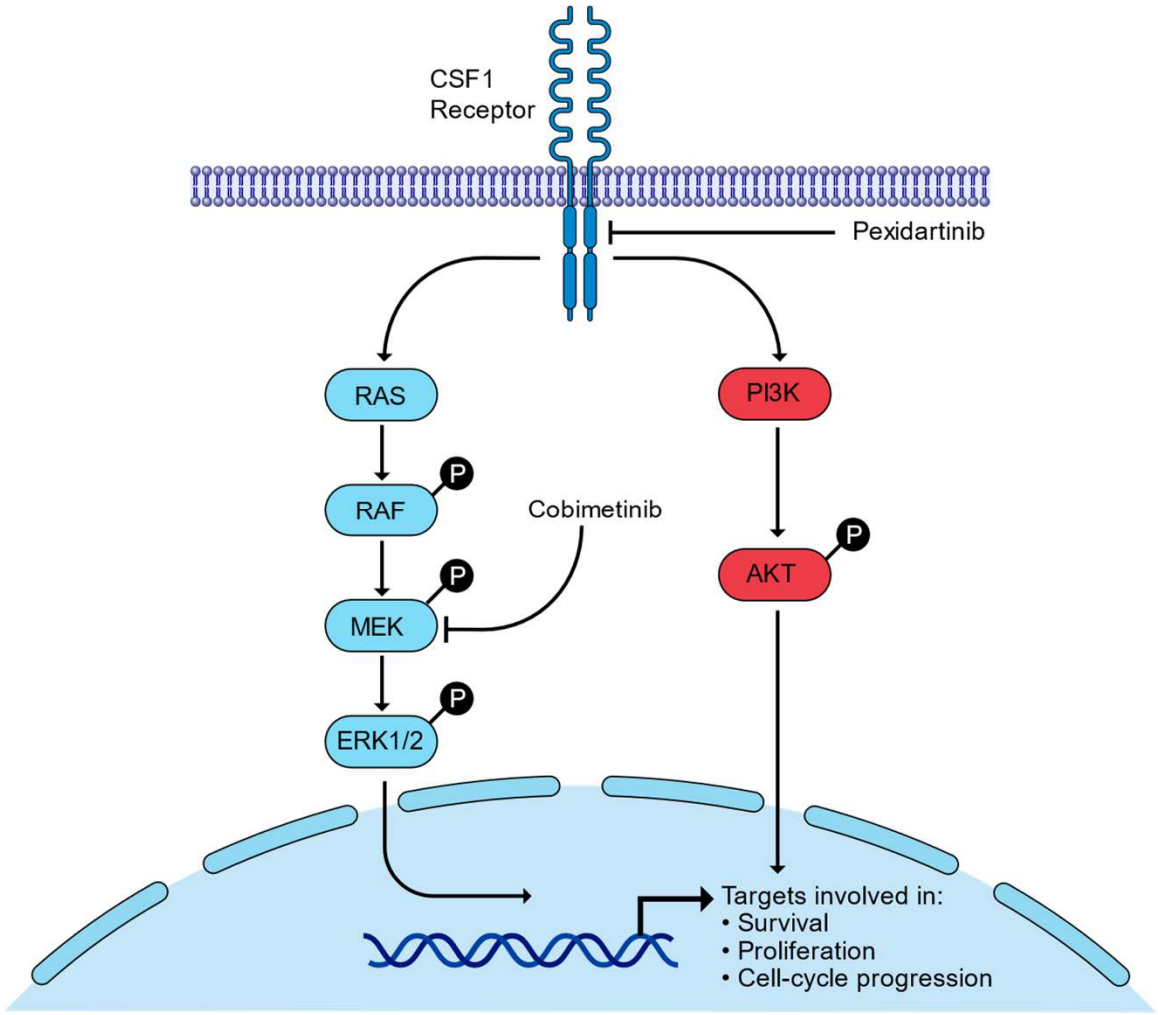
Abeykoon et al, AJH, 2022

IS THIS MUTATION FUNCTIONAL (ACTIVATING) OR NOT?



Abeykoon et al, AJH, 2022

CSF1R SIGNALING PATHWAY

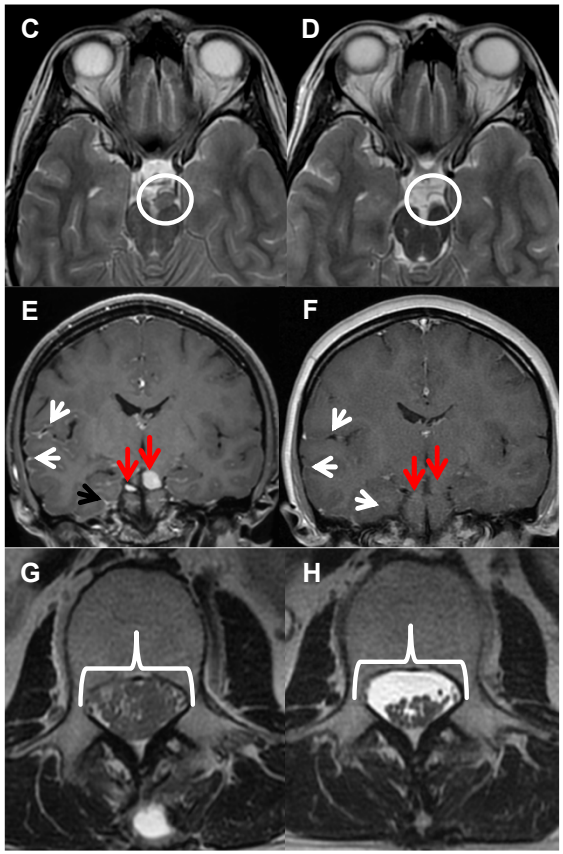


Redrawn from: Abeykoon et al, AJH, 2022

03/2020

- Patient was paraplegic, cachectic and dehydrated due to nausea and vomiting requiring frequent hospitalizations and emergency department visits
- We identified that this VUS in CSF1R (never reported) which could be possibly functional
- Commenced on pexidartinib

- Patient regained the lower extremity strength completely
- Tolerating oral diet well without nausea or vomiting
- All her brown hair turned white



Abeykoon et al, AJH, 2022

Patient's consent was obtained

IS THERE A CURE?

DEFINITION OF A CURE

- That there are no traces of your cancer after treatment and the cancer will never come back
- Cancer has gone away with treatment, no more treatment is needed, and the cancer is not expected to come back

NIH NATIONAL CANCER INSTITUTE

American Cancer Society®

IS THERE A CURE?

- Discontinuation of vemurafenib caused disease relapse in 75% of patients within 6 months

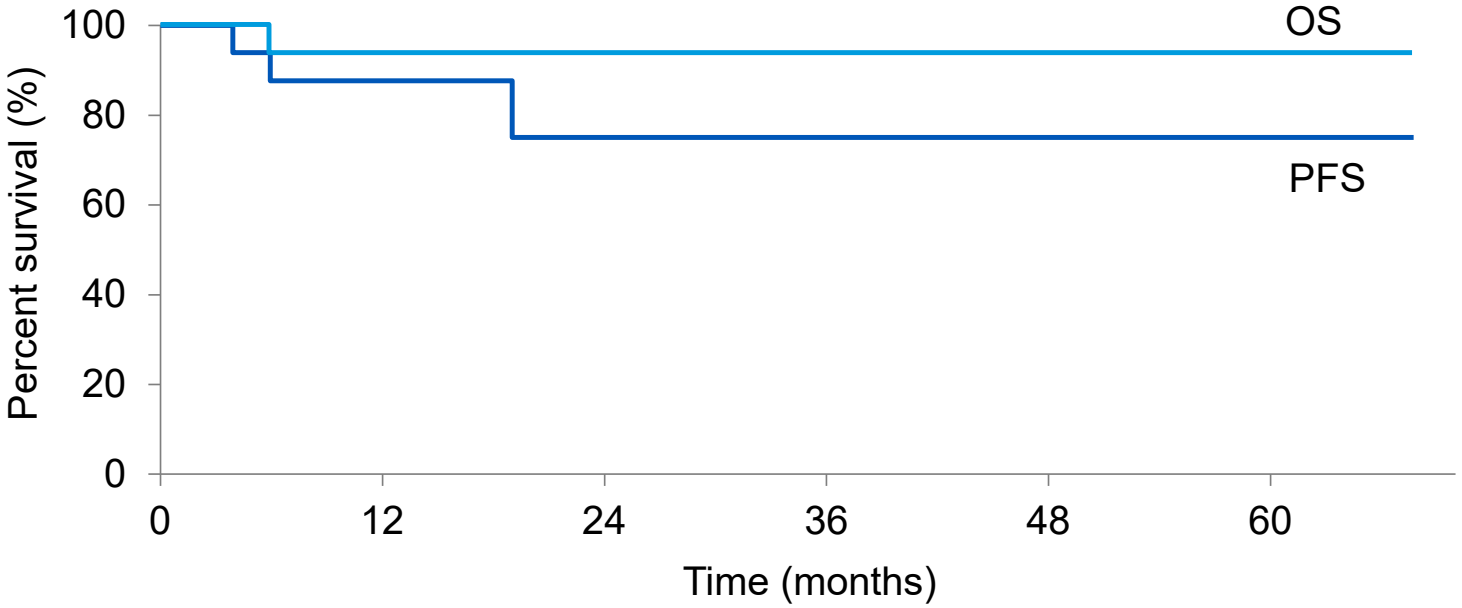
- Fixed duration treatment could have prolonged disease remission with cladribine – cure?

    - Two of the 17 responded patients maintained a response after 6 months of followup

Cohen, Blood, 2017
Goyal, JAMA Onc, 2017

IS THERE A CURE?

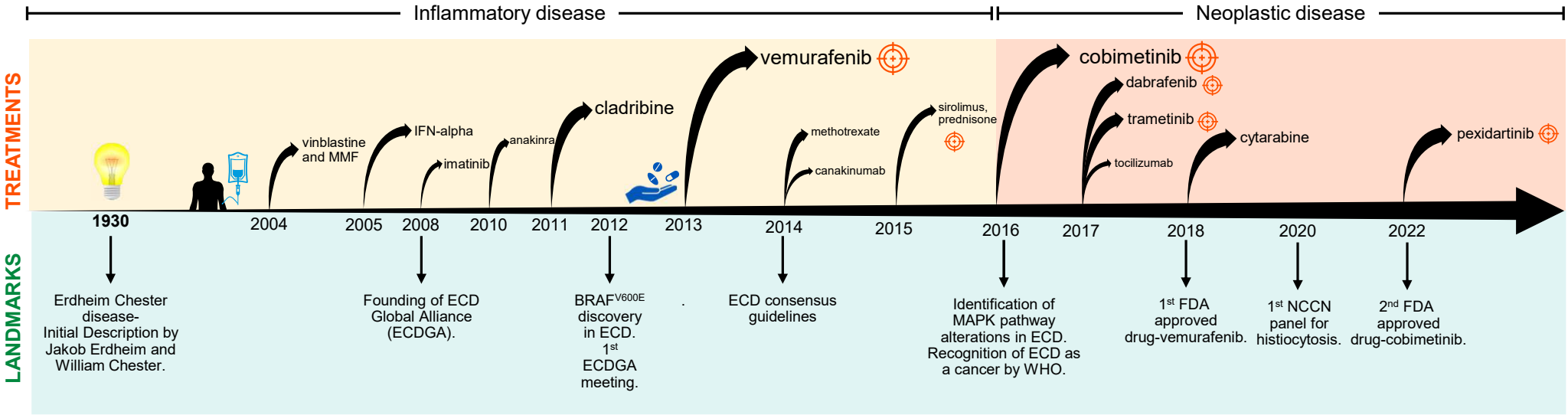
With cytarabine



No. at risk						
OS	16	12	7	6	4	3
PFS	16	11	6	5	4	3

Cytarabine responses; redrawn from: Liu et al, Orphanet J Rare Dis. 2022; 17: 39

EVOLUTION OF ECD



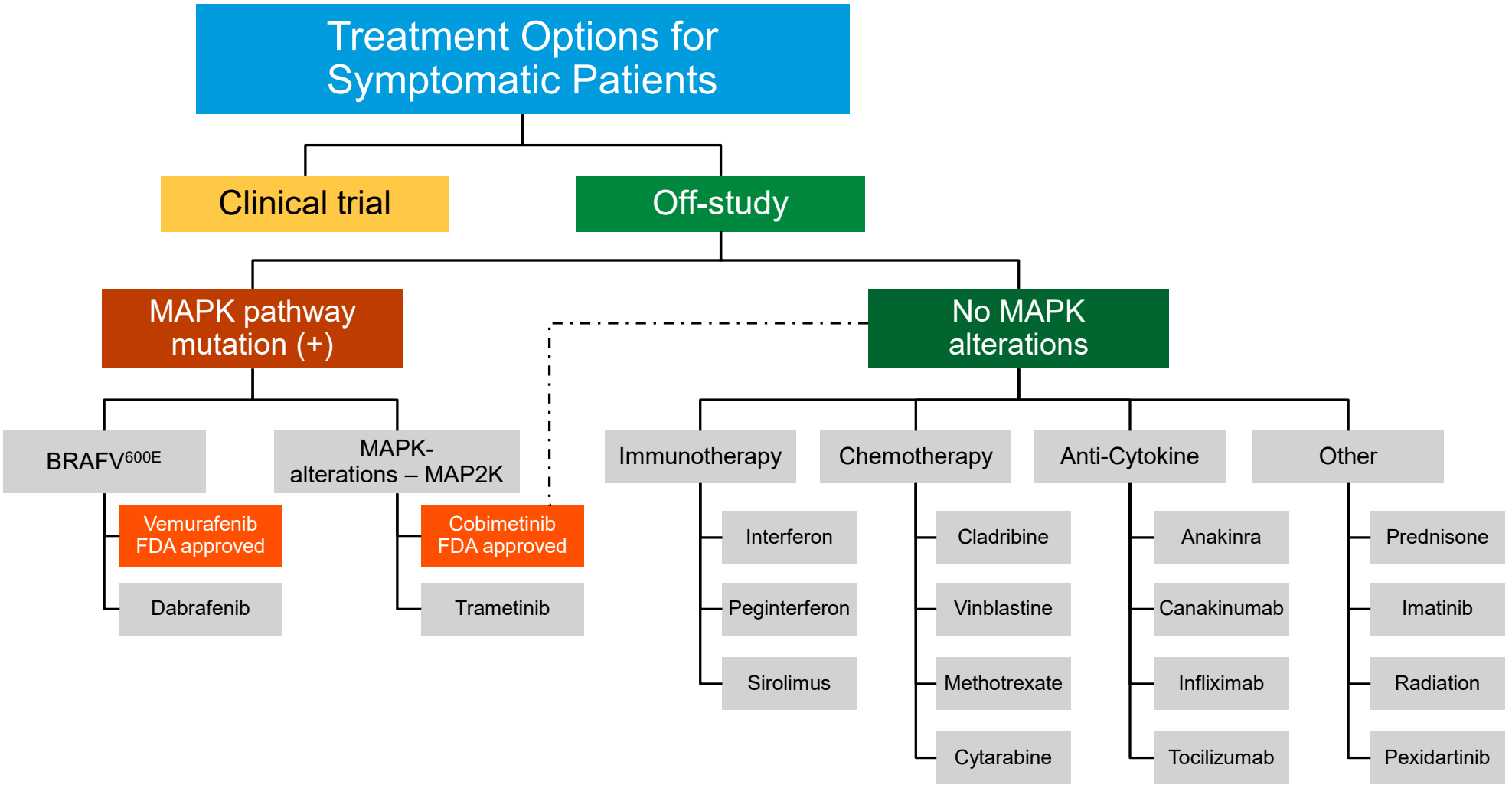
Arrow width and font size depict the impact of the respective regimens in the treatment of Erdeim-Chester disease
Treatment year represents the reported year of the index case(s) or clinical trial(s)

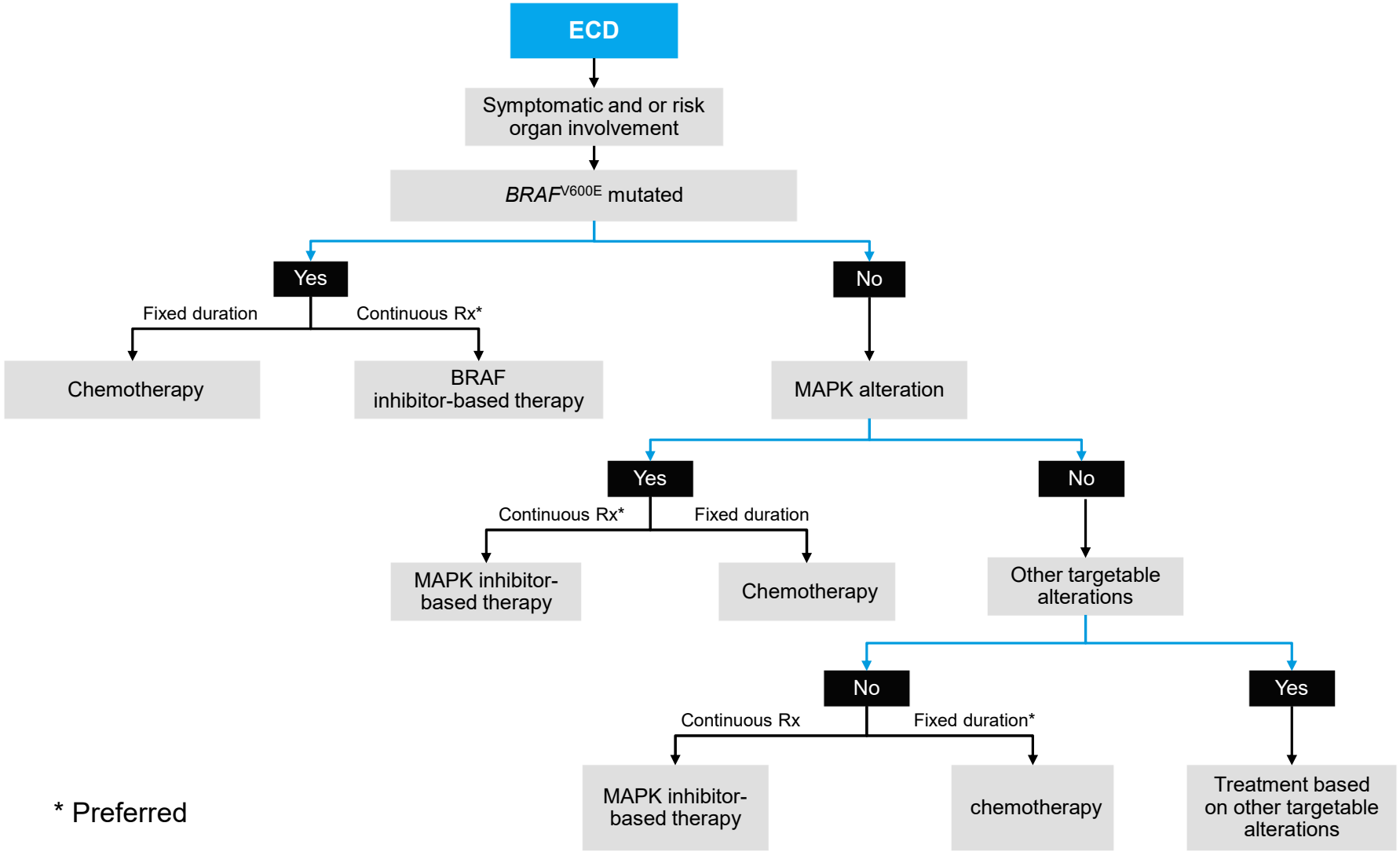
Targeted oncologic therapy

SUMMARY

- ECD is a cancer with driver mutations.
- There could be other epiphenomenal alterations.
- Targeting genetic alterations (BRAF, MAPK, CSF1R) could lead to durable responses but is unlikely to achieve a cure.
- Chemotherapy could sometimes be beneficial and could achieve deep and durable responses – perhaps a cure in some patients.
- There is an unmet need to find new driver alterations in ECD and understand the mechanisms associated with resistance to targeted therapy.
- Practicing team science, and precision medicine is critical.

PERHAPS?





* Preferred

THANK YOU FOR ALL THE PATIENTS AND PROVIDERS!

QUESTIONS & ANSWERS