MAYO CLINIC

EFFICACY OF MEK INHIBITORS IN ERDHEIM-CHESTER DISEASE

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ON BEHALF OF THE MAYO CLINIC – UAB HISTIOCYTOSIS WORKING GROUP

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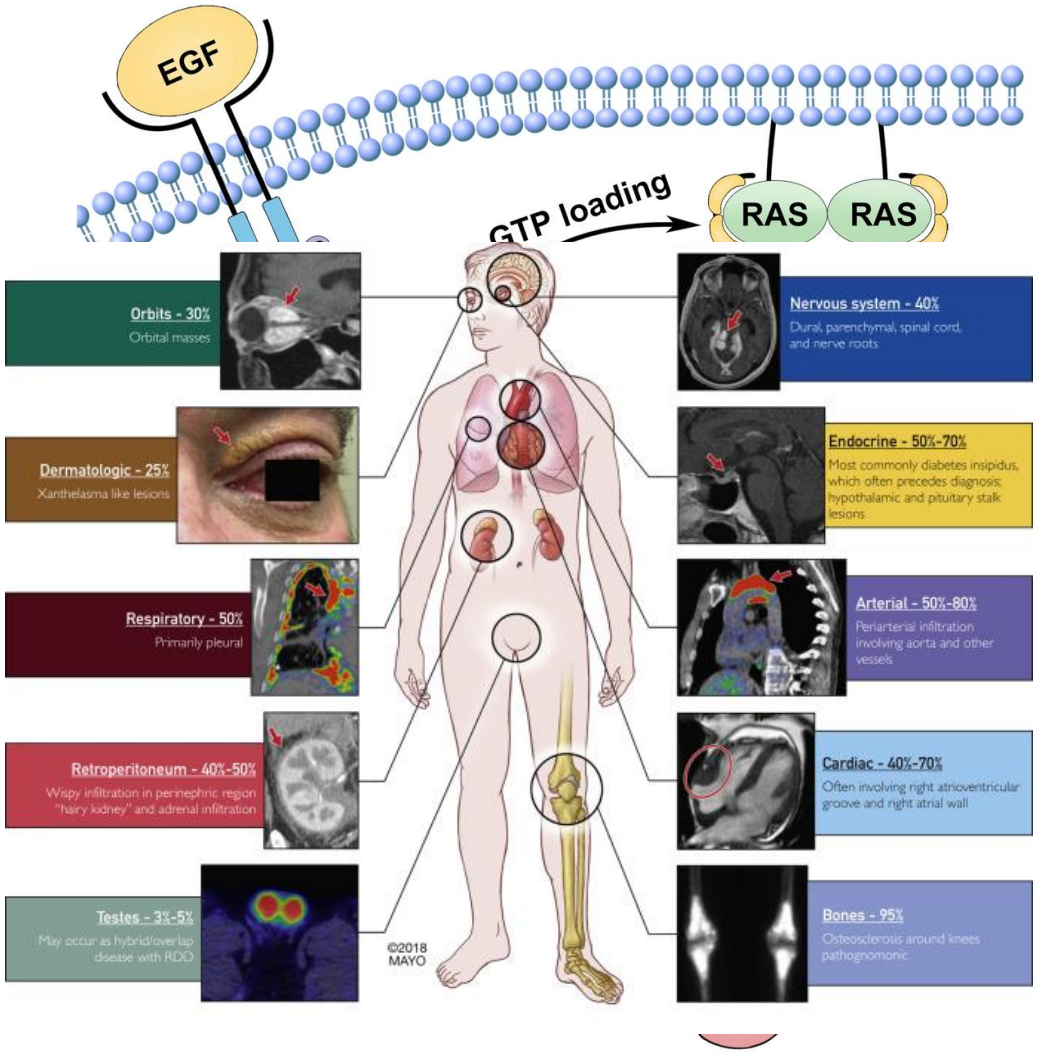
BACKGROUND

- Erdheim-Chester disease is a rare and heterogeneous disorder known to be driven by mutations in the MAPKinase pathway[1]
- *BRAF* inhibitors were the first targeted therapy used given the presence of *BRAF*^{V600E} in 50-60%, response is not universal[2,3]
- Further understanding led to use of MEK inhibitors in *BRAF*^{V600E}-negative histiocytic neoplasms



1. Goyal G, et al. *Mayo Clin Proc.* 2019 Oct;94(10):2054-2071.
2. Diamond E, et al. *Nature.* 2019 Mar;567(7749):521-524.
3. Goyal G, et al. *Blood.* 2020 May 28;135(22):1929-1945.

OBJECTIVE

We aimed to describe characteristics and outcomes of the largest cohort of ECD patients treated with MEKi outside of a clinical trial.

METHODS

- Patients with ECD treated with MEKi (cobimetinib, trametinib, or binimetinib) at Mayo Clinic between 2019-2021.
- Tumor MAPK pathway mutation status determined via NGS or, if unavailable, IHC or allele-specific PCR was used to determine *BRAF* mutation status.
- Response assessment based on established positron emission radiography (PET)-response criteria used for clinical trials of targeted therapies in histiocytosis

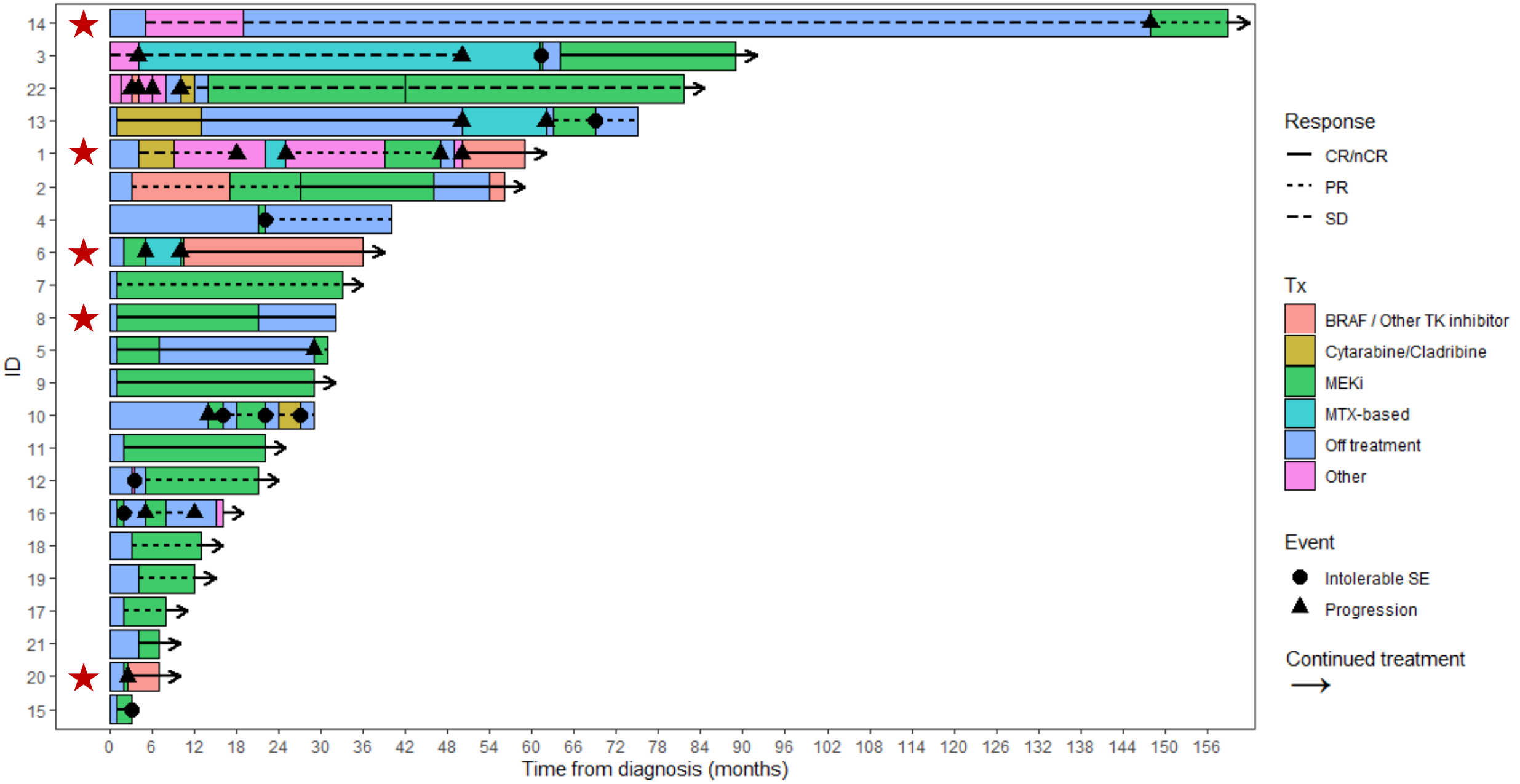
General characteristics	*N*= 22
Age at diagnosis [years], *median* (IQR)	52 (35.8 – 70.8)
Sex, *n* (%)	
Female	12 (55)
Male	10 (45)
***MAPK* variant assessment, *n* (%)**	
Next-generation sequencing	18 (81.8)
Allele-specific PCR	4 (18.2)
Immunohistochemistry	21 (95.5)
Pathogenic variants identified, *n* (%)	
BRAF^{V600E}	1 (4.5)
Other *BRAF* variants	6 (27.3)
Other *MAPK* pathway variants	10 (45.5)
No variants identified*	5 (22.7)
MEKi exposure, *n* (%)	
Cobimetinib	15 (68.2)
Sequential exposure to MEKi	
Cobimetinib / Trametinib	3 (13.6)
Cobimetinib / Binimetinib	2 (9.1)
Trametinib / Binimetinib	1 (4.5)
Cobimetinib rechallenge	1 (4.5)

BASELINE CHARACTERISTICS

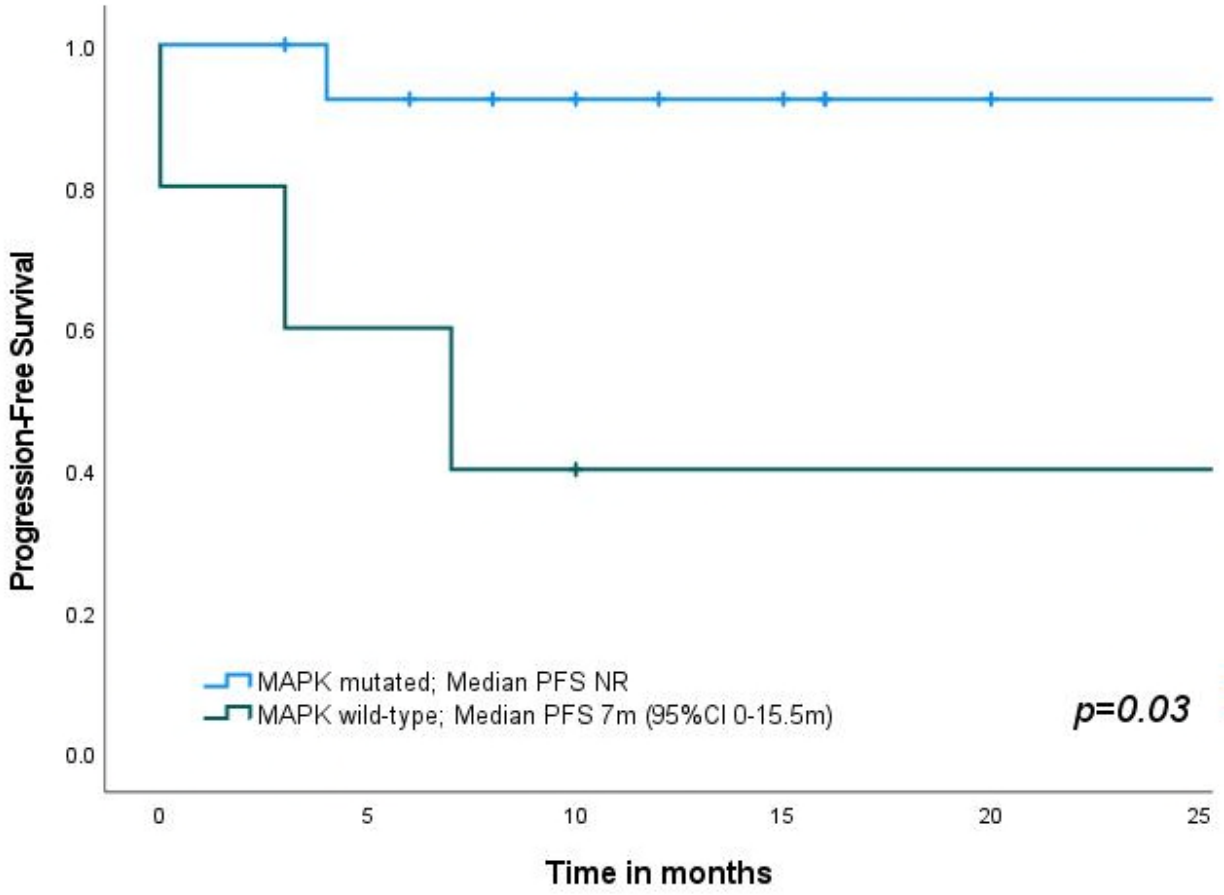
- MEKi as 1st line therapy in 68.2% (n=15)
- Median time on a MEKi
  - 7.1 months (IQR 3 – 18.9 months)

GENETIC PROFILE

ID	Evaluation tools	Detected variants
1	IHC, as-PCR & NGS	*FLT3-MEF2C* Fusion
2	IHC	*BRAF* V600E
3	as-PCR	No pathogenic variant identified
4	IHC & as-PCR	No pathogenic variant identified
5	IHC & NGS	*BRAF* N486_P490del
6	IHC & NGS	No pathogenic variant identified **VUS:** *CSF1R*
7	IHC & NGS	*UBTD2-BRAF* chromosomal rearrangement
8	IHC & NGS	No pathogenic variant identified
9	IHC & NGS	*MAP2K1* K57N
10	IHC & NGS	*MAP2K1* Q56P
11	IHC & NGS	*BRAF* T599_V600 DelInsRE
12	IHC & NGS	*NRAS* Q61R *ASXL1* G646fs
13	IHC & NGS	*MAP2K1* E102_103del
14	IHC & NGS	No pathogenic variant identified
15	IHC	Negative for *BRAF* V600E
16	IHC & NGS	*RNF11-BRAF* Fusion
17	IHC & NGS	*UBR2-BRAF* Fusion
18	IHC & NGS	*MAP2K1* Y130C *KRAS* G12D
19	IHC & NGS	*MAP2K1* PE102_I103del
20	IHC & NGS	*POT1 M1?* *PTPN11* E76K **VUS:** *CSF1R*
21	IHC & NGS	*MAP2K1* Q56P
22	IHC, as-PCR & NGS	*BRAF* V471F *NF1* c.1641+1G>A and c.7189+2T>G *MCL1* Amplification



RESPONSE AND ADVERSE EFFECTS



- PFS and ORR (92.9% vs. 40%, *p*=0.013) were significantly greater in MAPK-mutated individuals
- At last follow-up:
  - All patients were alive
  - 10 pts (52.6%) remained on MEKi
- Intolerable AEs with MEKi:
  - G3/4 diarrhea (n=2),
  - G3 lower extremity edema (n=2),
  - G3 acneiform rash (n=1),
  - G2 pericardial effusion (n=1),
  - Dropped-head syndrome (n=1)

LIMITATIONS

Main limitations -> Retrospective nature and sample size

CONCLUSIONS

- MEK inhibitors are a highly efficacious treatment in patients with ECD
- Treatment discontinuation due to toxicities / intolerance was common, but this did not preclude from maintenance of tumor response for extended periods
- Our study suggests that identification of non-MAPK pathogenic variants may predict response to MEK inhibition

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QUESTIONS & ANSWERS