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MEK inhibition with trametinib in patients with non-Langerhans cell histiocytosis irrespective of *BRAF* mutation status

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- **Ownership Interests:** Trovagene
- **Other:** Bio-Rad, Biocartis

Brief report

High prevalence of *BRAF V600E* mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses

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Bapt… le Canioni,[8]
Loui… ner,[12]
Mari… dieu,[14] and
Jean…

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Diverse and Targetable Kinase Alterations Drive Histiocytic Neoplasms AC

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Molecular Profiling of Tumor Tissue and Plasma Cell-Free DNA from Patients with Non-Langerhans Cell Histiocytosis

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Mol Cancer Ther; 18(6) June 2019

Rationale

- Activation of the MAPK pathway through *BRAF* mutations or other molecular alterations is a hallmark of non-LCH
- Molecular testing of tumor tissue fails to identify targetable molecular alterations in about one third of ECD patients
- Targeting the MAPK kinase pathway with MEK inhibitors can be effective in patients with *BRAF* or other MAPK molecular alterations

Haroche, Emil Blood 2012
Diamond, Durham, Abdel-Wahab Cancer Discov 2016
Janku, Diamond, Kurzrock Mol Cancer Ther 2019
Diamond Nature 2019

Methods

- **Eligible patients:** Individuals with non-LCH with unknown or pending molecular testing test (tumor tissue targeted NGS, plasma cfDNA targeted NGS) or any molecular profile
- **Treatment:** Inhibitor of MEK1/2 kinase trametinib administered orally 1-2mg daily
- **Regulatory:** Data collection and analyses were performed in accordance with participating institutions protocol and respective IRBs' guidelines

Patients (N=16)

- **Type of histiocytosis**
  - ECD: 12
  - RDD: 3
  - ECD/LCH: 1
- **Prior therapies**
  - No prior therapy: 9
  - 1 prior therapy: 1
  - 2 prior therapies: 2

Molecular Profile

- ***BRAF*^{V600E}: 3 patients**
- **MAPK other than *BRAF*^{V600E}: 7 patients***
  - *CAPZA2-BRAF* fusion: 1
  - *RAF1* amplification: 1
  - *GNAS* mutation: 3
  - *HMGA2* rearrangement: 1
  - *NF1* mutation: 1
  - *KRAS* mutation: 1
  - *MAP2K1* mutation: 1

*some patients had more than one molecular alteration

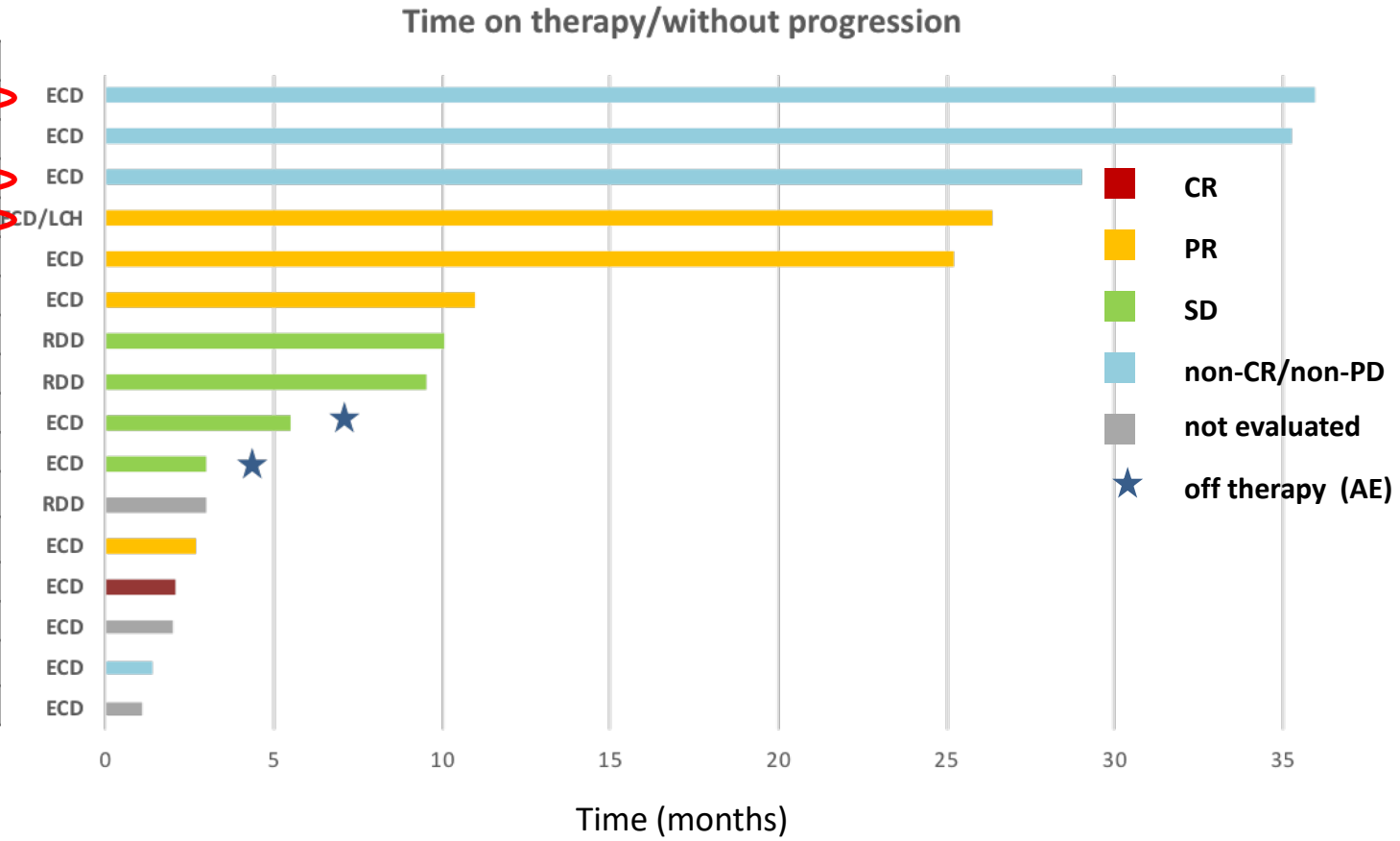
Results: Response (RECIST 1.1)

Type of Response	Number (%)
Complete response	1 (6)
Partial response	4 (25)
CR + PR	5 (31)
Stable disease	4 (25)
Non-CR/non-PD	4 (25)
Not evaluated	3 (19)

Time on therapy

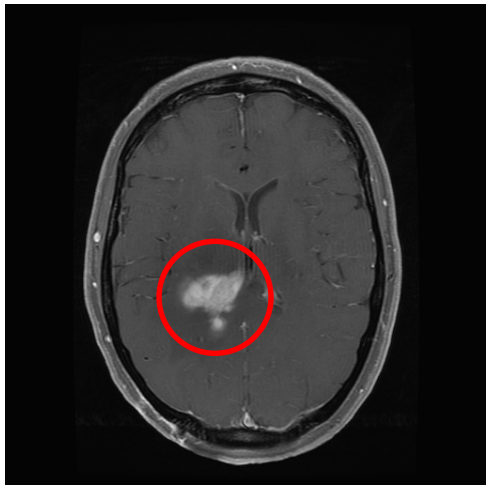
Molecular Profile

Tissue	Plasma
Failed	none
ASXL1	BRAF, ERBB2
Failed	none
Failed	none
BRAF, ASXL1	BRAF, CCNE
CBLC	GNAS, CCNE
CAPZA2-BRAF	RAF1
Failed	GNAS
CD36	NF1
BRAF, ASXL1	BRAF
not done	APC
KRAS	GNAS, RB1
not done	MAP2K1
HMGA2, ZNF703	none
none	TP53
none	STK11

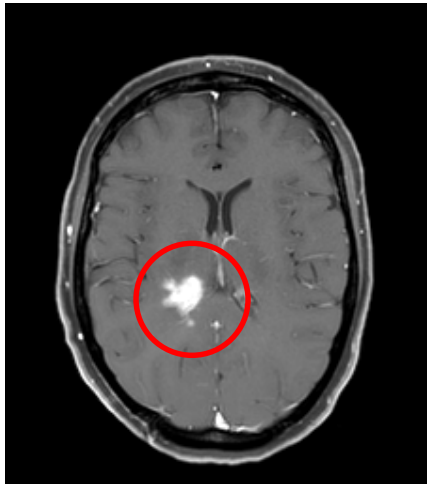


40-yo female with ECD/LCH (no molecular alteration) involving brain and bones and no prior therapy treated with trametinib 1mg

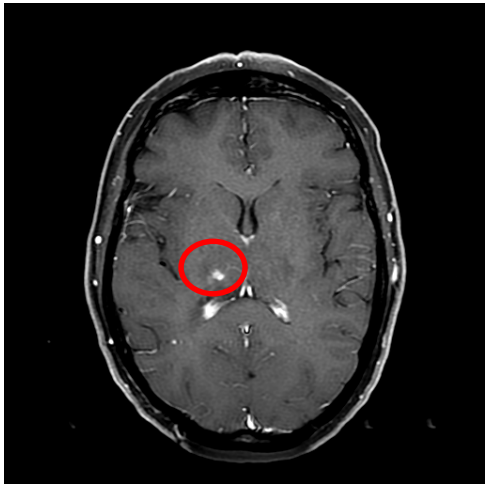
BASELINE



2 MONTHS ON TX

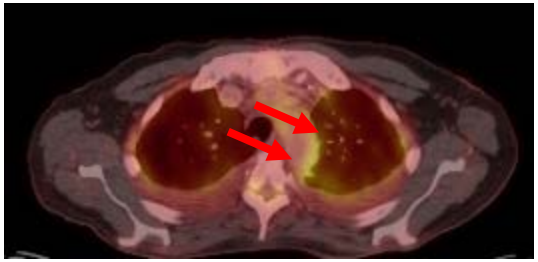


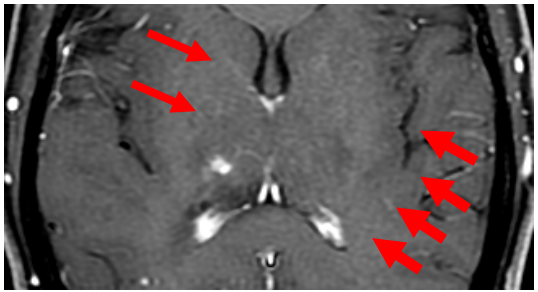
2 YEARS ON TX



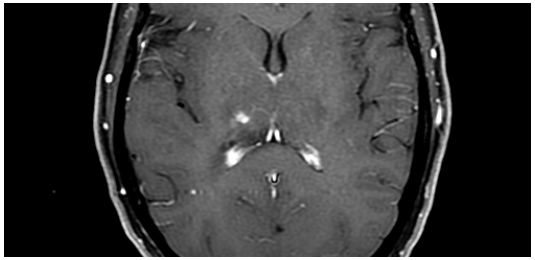
60-yo male with ECD (*BRAF*^{V600E}) involving pericardial, perirenal, retroperitoneal areas and bones and no prior therapy treated with trametinib 1mg

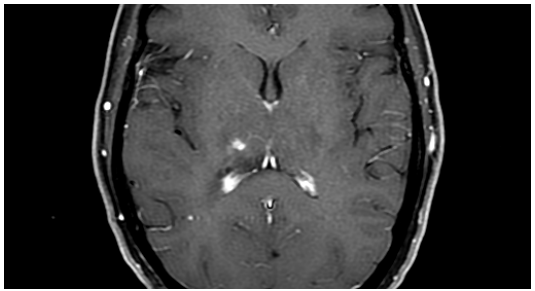
BASELINE





4 MONTHS ON TX





Adverse events: summary

- Most patients started on oral trametinib 1 mg daily, which is lower than FDA approved dose of 2 mg
- Starting on lower dose with possible (de-) escalation is in general well tolerated
- Grade 1 rash was the most frequent AE
- Only 2 patients discontinued therapy because of AE
  - rash and dizziness
  - uveitis

Adverse events: ≥ grade 2

- *Mucositis* (n=2)
- ***Rash*** (n=2)
- **Dizziness** (n=1)
- **Uveitis** (n=1)
- *Decrease in ejection fraction* (n=1)

CONCLUSIONS

- ❑ Oral MEK inhibitor trametinib has encouraging activity in non-LCH patients irrespective of underlying molecular profile

- ❑ Clinical activity has been observed even with 1 mg daily, which is 50% of FDA approved dose for melanoma

- ❑ Our data confirms recently published results with another MEK inhibitor cobimetinib (Diamond Nature 2019)