Memorial Sloan Kettering Cancer Center

Single-agent dabrafenib for $BRAF^{V600E}$-mutated histiocytosis

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Introduction

- ECD and LCH are clonal disorders of the monocyte/macrophage and dendritic cell lineages
- Infiltration of multiple organ systems is common with a wide range of clinical phenotypes
- Both harbor BRAF V600E mutations in ~50% of cases

Badalian-Very et al. 2010, Haroche et al. 2012.

Vemurafenib / Dabrafenib

- Several retrospective and one prospective clinical trial demonstrated robust and durable response to vemurafenib
- Dabrafenib is another oral BRAF V600E inhibitor
- There is modest evidence of a lower incidence of adverse reactions in melanoma with dabrafenib
- Only single cases of dabrafenib for ECD
- No studies have explored the use of dabrafenib in vemurafenib intolerance

Haroche et al. 2013, 2015.; Hyman et al. 2015, Welsh et al. 2015.

Objective

- Retrospective review of 10 patients with ECD or ECD/LCH treated with single agent dabrafenib as

  1) Initial histiocytosis therapy

  2) Following failure of conventional therapy

  3) Following discontinuation of vemurafenib therapy for toxicity or intolerance

Methods

- Patients were treated at MSKCC, Shaare Zedek Medical Center, and University of Florida
- All patients met previously published criteria for the diagnosis of ECD and underwent genomic analysis for BRAF V600E mutational status
- Doses ranged from 50mg BID to 150mg BID
- Best overall response by FDG PET/CT was used as a primary response assessment and MRI brain when appropriate

Diamond et al., 2014. Haroche et al 2014.

Results: Partial response with dabrafenib as initial ECD/LCH therapy

Patient	Age/ Sex	Clinical symptoms	Organs involved **(LCH in bold)**	Prior therapies	Toxicities (**reason for dose reduction in bold**)	Final dose	Response	Duration of therapy (**ongoing)**
1	66F	Ear pain, hearing loss, bone pain	**Skullbase**, bones	Skullbase radiation	Panniculitis (Grade 1)	50mg BID	PMR	**11 months**
2	31M	Dizziness, hearing loss, diabetes insipidus	**Skullbase,** cerebellum bones, retroperitoneum	Cytarabine	None	150mg BID	PMR	**13 months**
3	70M	Skin and oral lesions, dyspnea	**Skin**, **oral mucosa,** lungs, bones	Prednisone	**Fever (Grade 3)**, Periorbital swelling (Grade 1)	50mg BID	PMR	5 months
4	59M	Jaw pain, skin lesions	**Skin**, bones, dura	None	None	50mg BID	PMR	**3 months**

Pre-dabrafenib

Post-dabrafenib

Maintenance of response to prior treatment

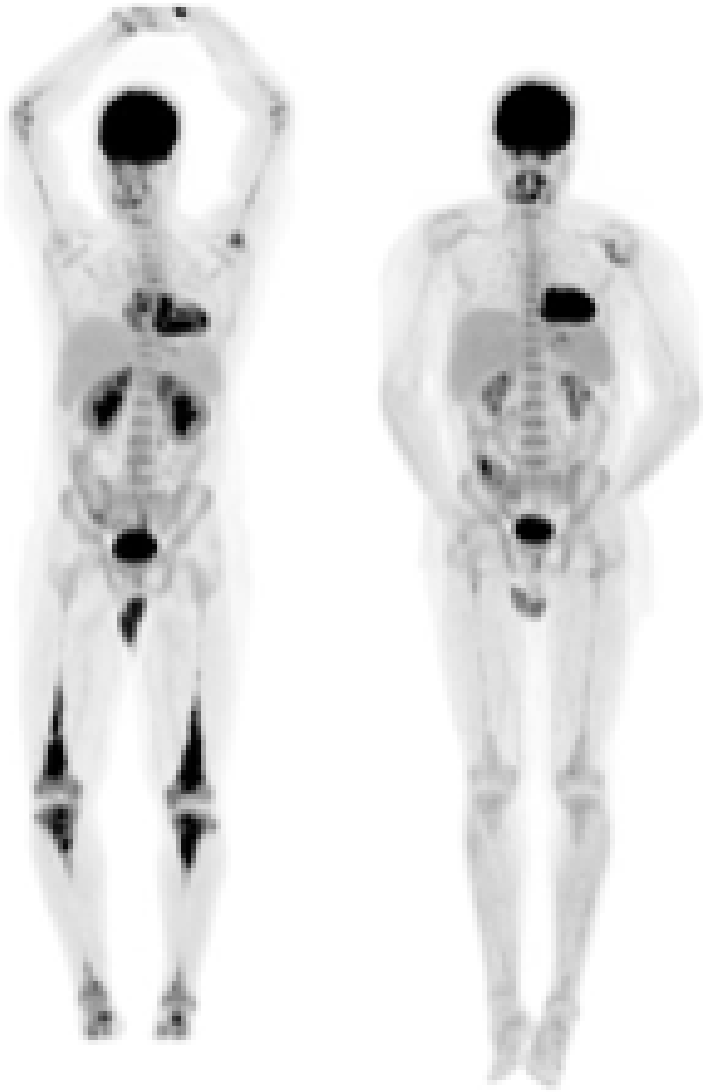
Patient	Age/ Sex	Clinical symptoms	Organs involved	Prior therapies	Toxicities (**reason for dose reduction in bold**)	Final dose	Response	Duration of therapy (**ongoing in bold)**
4	49M	Bone pain	Retroperitoneum, bones, right atrium, peri-aortic tissues	Vinblastine/ prednisone, Vemurafenib, IFN-α	keratoacanthoma (Grade 1)	75mg BID	Maintained PMR from vemurafenib and interferon	**19 months**
6	58F	Bone pain, skin lesions, dysarthria, ataxia	Skin, bones, brain, peri-aortic tissues	Vemurafenib	Fever (Grade 1), arthralgia (Grade 1)	100mg BID	Maintained PMR from vemurafenib	**11 months**
7	75F	Bone pain, skin lesions, exopthalmos ataxia	Bones, orbits, dura, retroperitoneum skin (xanthelesma), right atrium	Vemurafenib	**Fatigue (Grade 2)**, arthralgia (Grade 2)	50mg BID	Maintained PMR from vemurafenib	4 months
9	77M	Proptosis, bone pain	Bones, orbit, craniofacial bones	Anakinra, Vemurafenib	Fatigue (Grade 2)	50mg BID	Maintained PMR from vemurafenib	9 months

Results: Recapturing a response with dabrafenib after stopping vemurafenib

Patient	Age/Sex	Clinical symptoms	Organs involved **(LCH in bold)**	Prior therapies	Toxicities (**reason for dose reduction in bold**)	Final dose	Response (FDG-PET)	Duration of therapy (**ongoing in bold)**
5	55M	Ataxia, spasticity	Brain, bones, retroperitoneum, peri-aortic tissues, brain, spinal cord	Methotrexate, IFN-α, Vemurafenib	**Fever (Grade 2)**, keratosis pilaris (Grade 2), hypophosphatemia (Grade 2)	100mg BID	PMR of relapsed disease after cessation of vemurafenib	**43 months**
8	35M	Proptosis, ataxia, bone pain	Brainstem, skullbase, heart, orbits, retroperitoneum, peri-aortic tissue, bones	Vemurafenib	None	150mg BID	CMR[5] of relapsed disease after cessation of vemurafenib	**16 months**

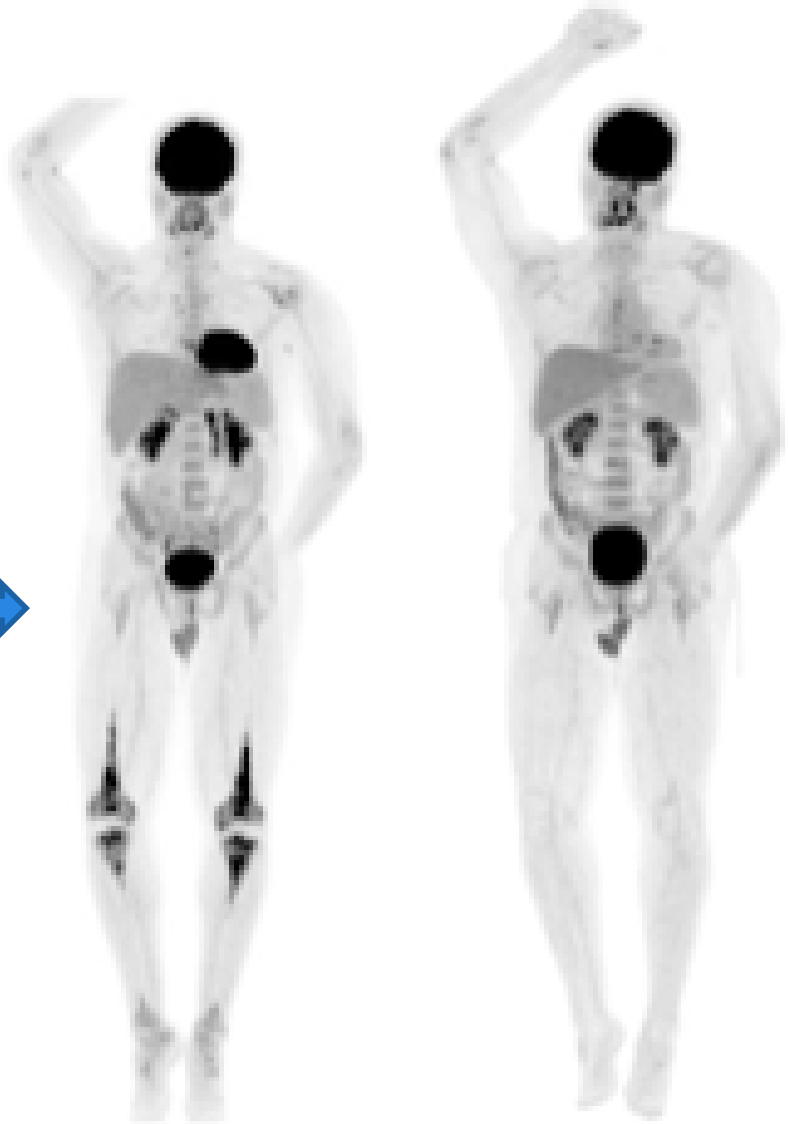
Pre- and post-vemurafenib

Pre- and post-dabrafenib



Relapsed disease

Cessation of vemurafenib



Conclusions

- Treatment with dabrafenib was effective for BRAF V600E-mutant histiocytosis patients
- Including CNS
- Responses seen as initial therapy, maintaining a response to vemurafenib, or by recapturing a response in relapsed disease
- Dabrafenib was tolerated, including patients who could not tolerate vemurafenib
- Doses as low as 50mg BID were therapeutic

Moving forward

- Optimal dosing, duration of treatment with BRAF inhibitors unknown
- LOVE study demonstrated frequent relapse after cessation of vemurafenib
- Combination of BRAF / MEK inhibitors?

Acknowledgements

- Eli L. Diamond
- Gary Ulaner
- Raajit Rampal
- Davidy Hyman
- Omar Abdel-Wahab
- Benjamin Durham
- Ahmet Dogan
- Neval Ozkaya
- Julio Hajdenberg
- Chezi Ganzel
- Lisa DeAngelis