Memorial Sloan Kettering Cancer Center

Mirdametinib for Tumorous and Neurodegenerative Histiocytosis

Eli L. Diamond, MD, MPhil
Associate Attending
Department of Neurology
Memorial Sloan Kettering Cancer Center
New York, NY

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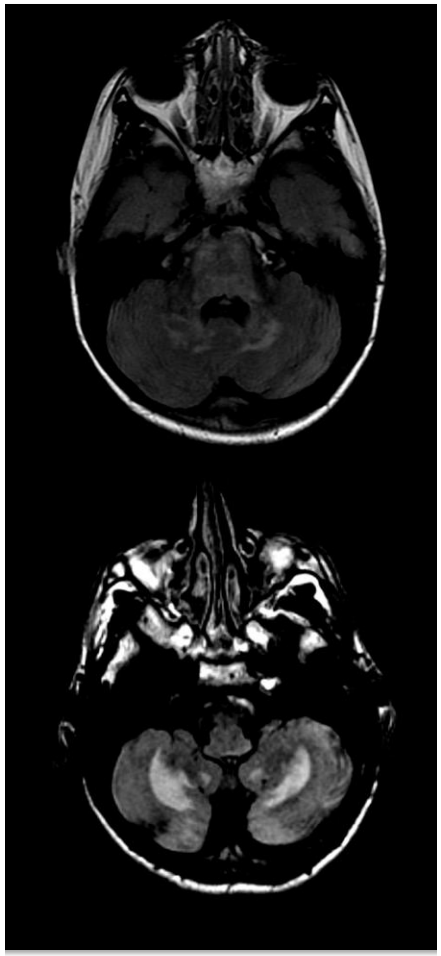
Background

- Neurologic histiocytosis (tumorous and ND) are associated with morbidity and mortality
- Limited efficacy of commercially available BRAK and MEK inhibitors
- Smoldering or progressive symptomatology in many patients
- Agents with greater brain penetration are emerging into phase 1 and 2 trials
- No experience to date with histiocytic neoplasms



Study

- Mirdametinib is brain penetrant oral MEK1/2 inhibitor
- Favorable results in NF1 associated plexiform neurofibromas
- Uniform IRB-approved single-patient protocols
- Treatment with 2mg → 4mg BID
- CTCAE 5.0 safety assessment every two cycles
- Radiologic and/or functional assessment every ~4 cycles
- Functional assessments: ataxia rating scale, dysarthria scale, visual acuity, speech discrimination

Results: Patients (N=9)

Characteristic	N (%)	Median	Range
Age at diagnosis (years)	9 (100%)	37.3	(2.5-60.1)
Dx to Mirdametinib (years)		7.0	(3.3-23.4)
Sex			
Male	5 (55%)		
Female	4 (44%)		
Race			
White	9 (100%)		
Diagnosis			
Tumorous LCH	1 (11%)		
Neurodegenerative LCH	3 (33%)		
Tumorous ECD	1 (11%)		
Neurodegenerative ECD	2 (22%)		
Tumorous+ND ECD	1 (11%)		
Rosai-Dorfman Disease	1 (11%)		
Sites of systemic disease			
Cardiovascular	3		
Pulmonary	0		
Retroperitoneum	2 (22%)		
Abdomen	2 (22%)		
Bone	6		
Skin or subcutaneous	5		
Lymph nodes	1 (11%)		
Other (reproductive)	1 (11%)		
Histiocytosis mutation			
BRAFV600E	6		
BRAF fusion	1 (11%)		
No mutation identified	2 (22%)		

Characteristic	N (%)	Median	Range
Prior lines of therapy			
0	0		
1-2	4 (44%)		
3 or more	5 (55%)		
Prior chemotherapy	6 (66%)		
Prior targeted therapy	7 (77%)		
Functionally evaluable	7 (77%)		
Radiologically evaluable	7 (77%)		

Neurologic sites (N=9)	N (%)
Brainstem/cerebellum (tumorous)	2
Brainstem/cerebellum (ND)	6
Optic/auditory nerves	1
Hypothalamus/pituitary stalk	2
Pachymeninges	1
Base of skull	1

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Results: Treatment Response

- Final dose: 2mg BID (3) 4mg BID (2), 2mg/4mg (3), 2mg/3mg (1)
- Median duration of treatment: 13.5 cycles (range 2.5-39)

Radiologic best response	Tumorous	ND
CR	1/5	
PR	3/5	
SD	1/5	3/3
PD		
NE		
Radiologic progression		
Yes		
No		

Functional best response	Speech	Balance	Vision	Hearing
CR	1/7			
PR	3/7	6/7	1/1	1/1
SD	2/7			
PD	0			
Not yet evaluated	1/7	1		
Functional recurrence				
Yes	3/6*	3/6*	0	0
No	3/6	3/6	1/1	1/1

*after stopping mirdametinib

- 6 remain on treatment
- 1 withdrew for lack of benefit, 1 for functional progression, 1 paused
- 1 died following termination of treatment

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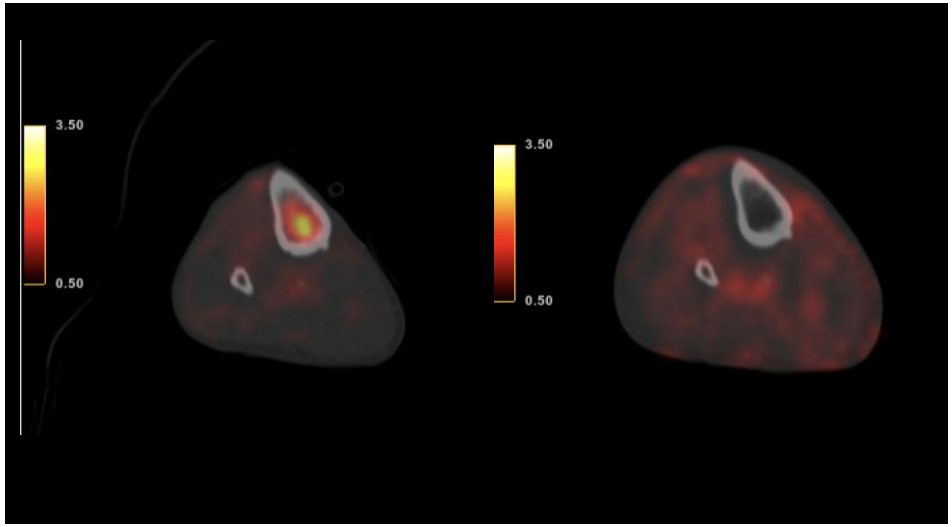
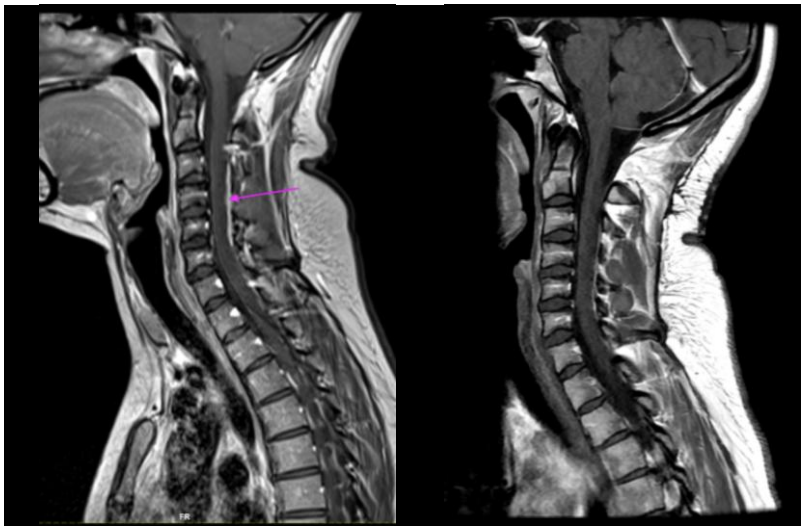
Results: Radiologic Responses

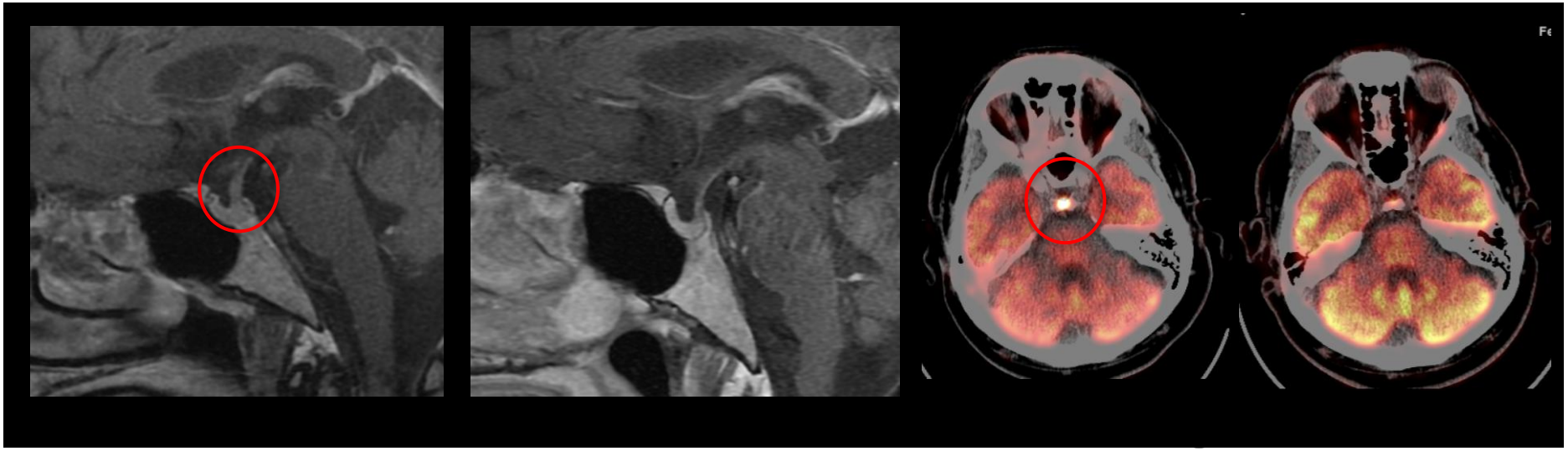
ECD



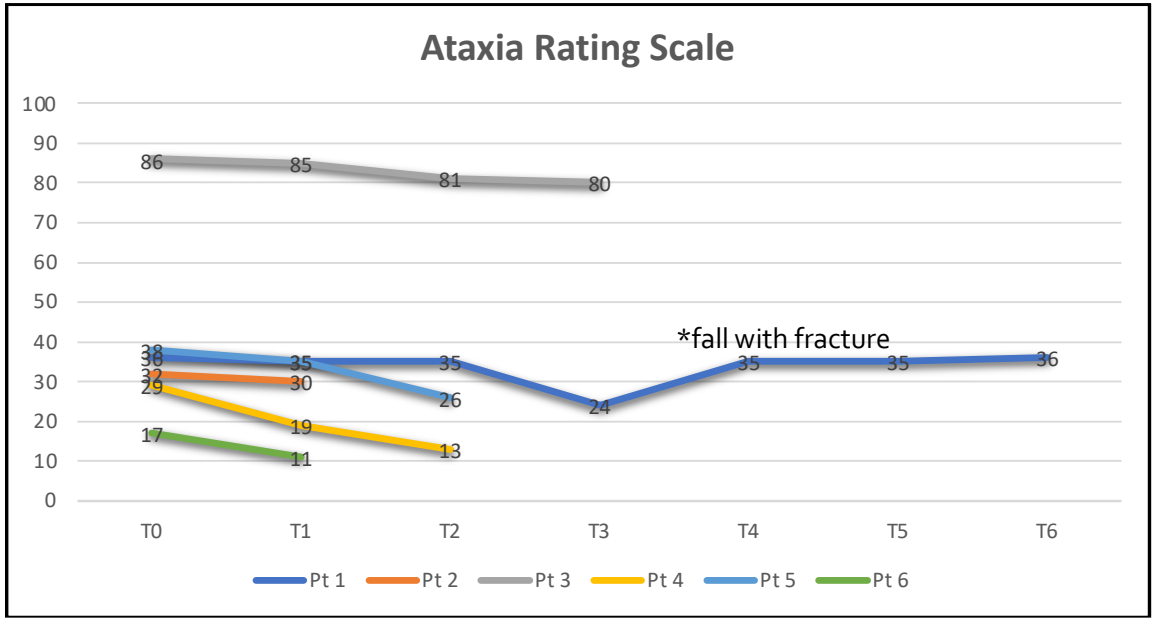
RDD

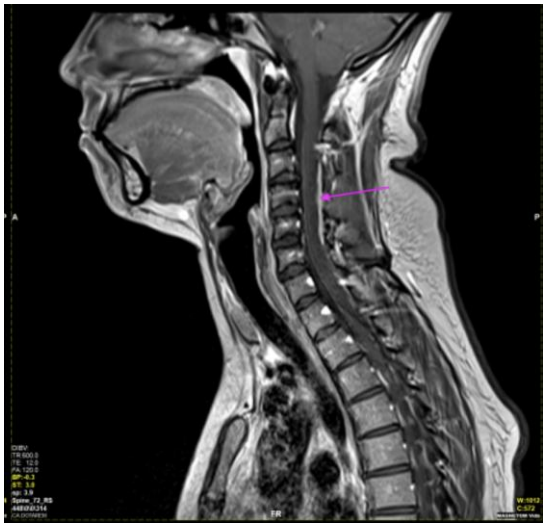


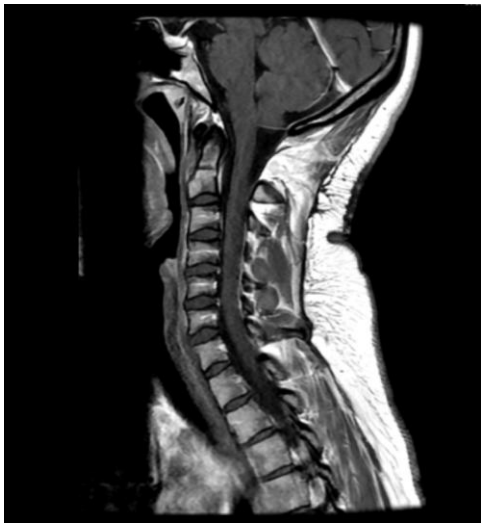
LCH



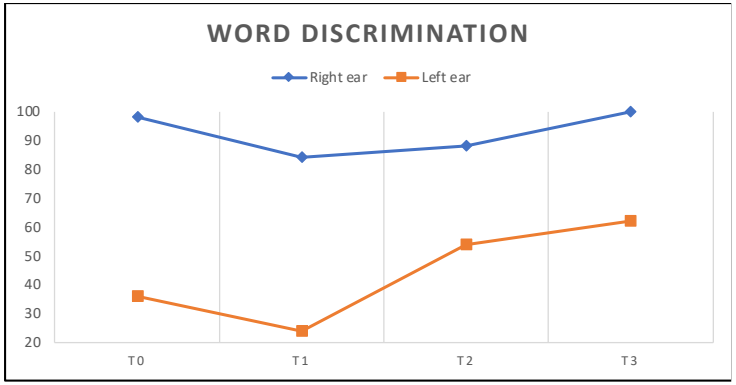
Results: Functional Responses







- Right eye: HM → CF → CF
- **Left eye: CF → 20/400 → 20/100**



Results: Toxicity

Toxicity	Grade	Related	Dose Reduction	Serious Adverse Event
Hyponatremia	4	unlikely	no	**yes**
Cholecystitis	3	unlikely	no	**yes**
Generalized muscle weakness	3	unlikely	no	no
Fracture	3	unlikely	no	**yes**
Urinary tract infection	3	unlikely	no	**yes**
Hyponatremia	3	unlikely	no	**yes**
Glaucoma	2	**possible**	no	no
Fatigue	2	**possible**	no	no
Rash maculo-papular	2	**probable**	no	no
Diarrhea	2	**probable**	no	no
Rash acneiform	2	**probable**	no	no
Ejection fraction decrease	2	**probable**	**yes**	no
Fever	2	unlikely	no	**yes**
Urinary retention	2	unlikely	no	**yes**
Fatigue	1	**possible**	no	no
Alopecia	1	**possible**	no	no
Rash acneiform	1	**possible**	no	no
Fever	1	**possible**	no	no
Dry skin	1	**possible**	no	no
Muscle cramp	1	**possible**	no	no
Rash maculo-papular	1	**probable**	no	no
Diarrhea	1	**probable**	no	no
Flu like symptoms	1	unrelated	no	**yes**

- 8 unrelated serious adverse events
- No grade 3 of higher related events
- One dose reduction owing to AE (reduced EF)

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Conclusions

- Mirdametinib confers responses in both tumorous and neurodegenerative histiocytosis
- Responses surpass those achieved by commercial BRAF/MEK inhibitors
- Speech and balance responses modest, but stabilization was observed in nearly all cases
- Reversal of near-blindness and deafness in one patient
- Modest treatment-related toxicity
- Merits systematic study, earlier in neurologic or ND course

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