

A BALANCING ACT: TREATING DISEASE AND SIDE EFFECTS 2023 PATIENT FAMILY GATHERING

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A Balancing Act: Treating Disease and Side Effects

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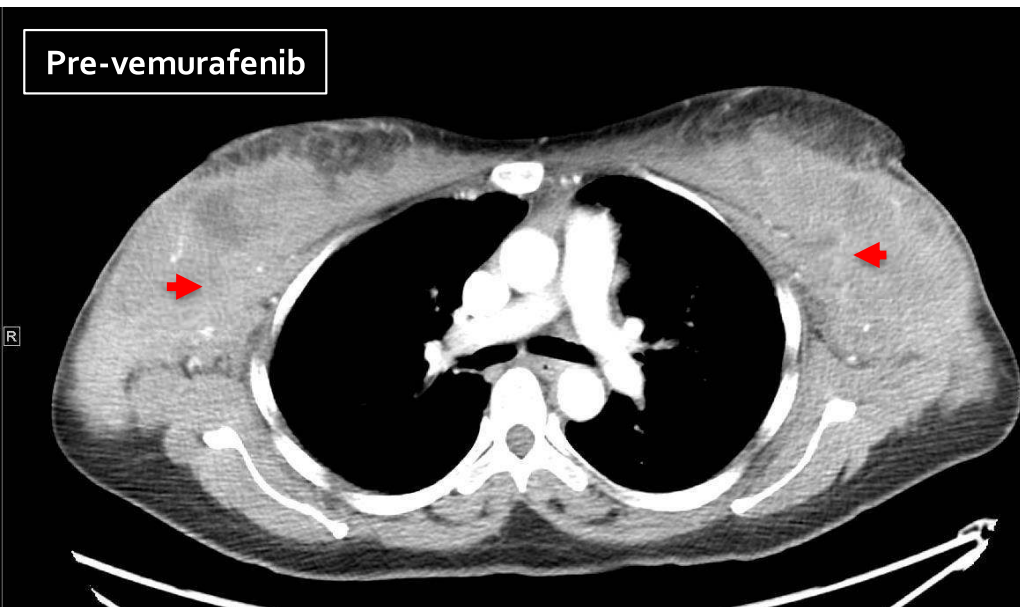
Overview

- Where we stand with targeted therapies, why the balancing act
- BRAF inhibitor specifics
- MEK inhibitor specifics
- General philosophy towards ECD treatment

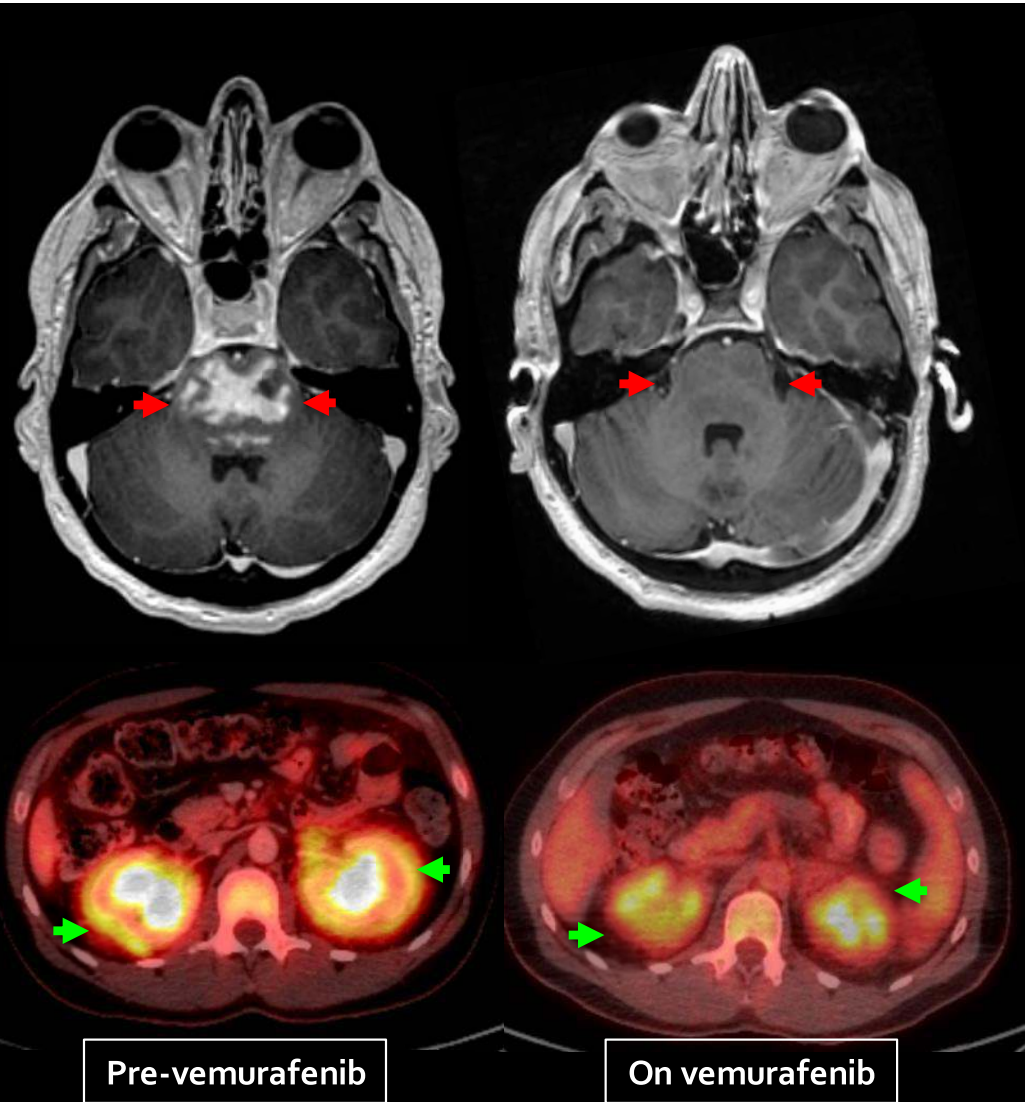
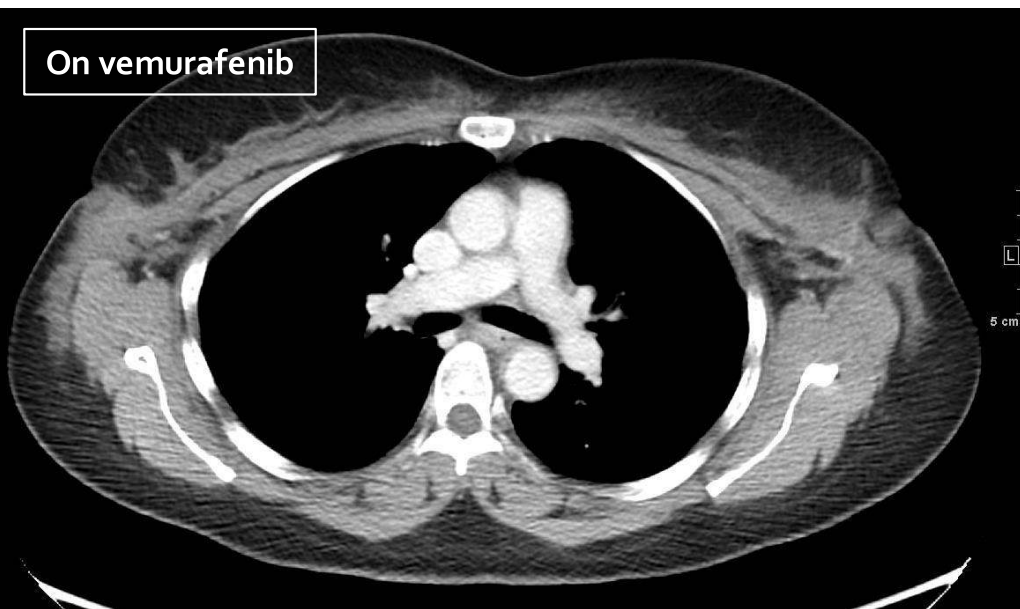


Effectiveness of BRAF inhibitors

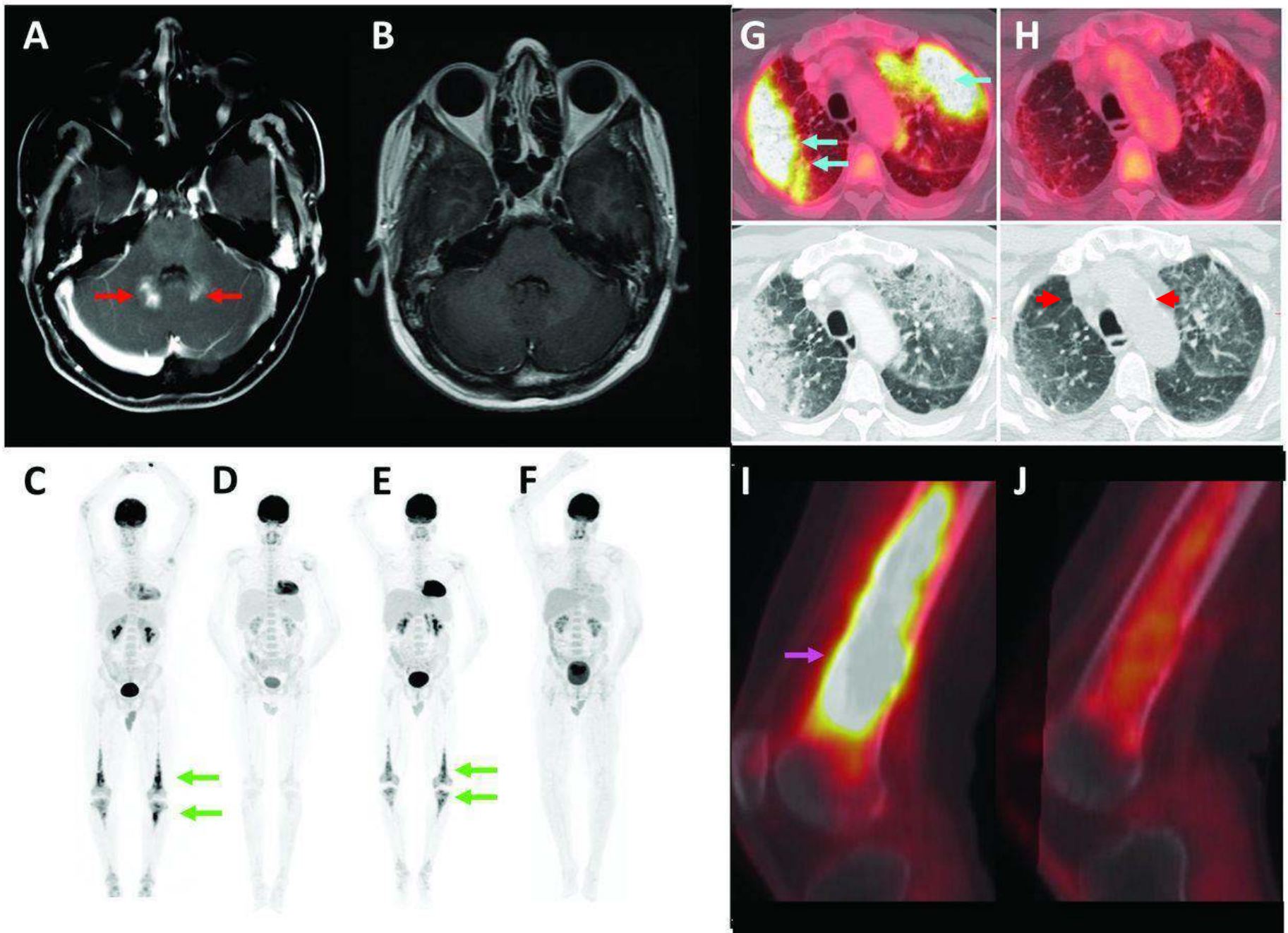
Pre-vemurafenib



On vemurafenib



Similar results with dabrafenib



Treatment limited by side effects

BRAF inhibitors

- Fatigue, arthralgias
- Skin toxicities
 - Rash
 - Skin cancers
 - Painful welts
- Tendon injuries
- Hand deformities
- kidney and liver impairment
- **1/3 stopped for intolerance in vemurafenib trial**



Effectiveness of MEK Inhibition

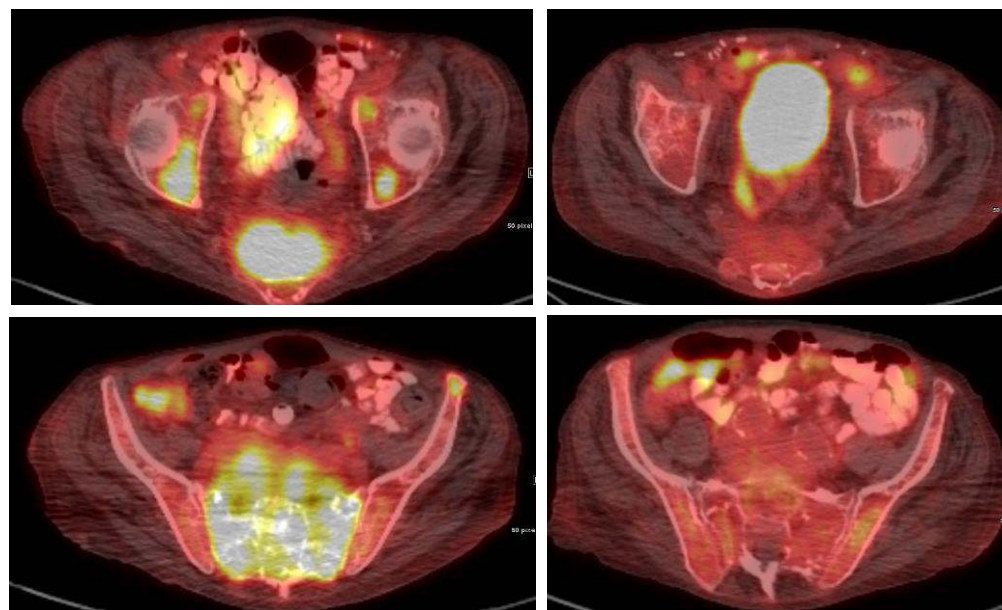
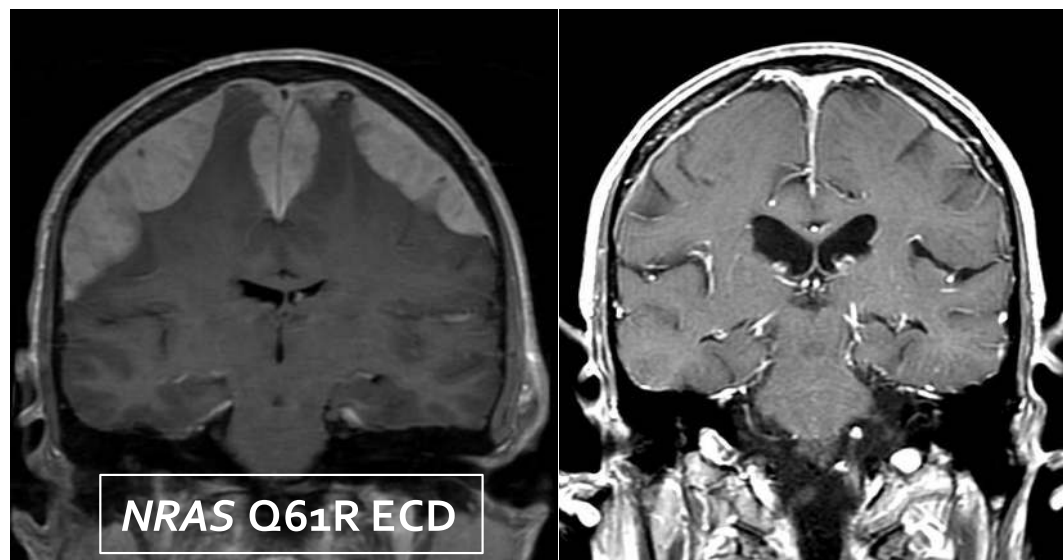
- Very dramatic responses noted starting in 2016
- Many patients treated in France, US
- Clinical trial of Cobimetinib
- Off-trial use of Trametinib

Pre-Trametinib

Trametinib

Pre-Trametinib

Trametinib



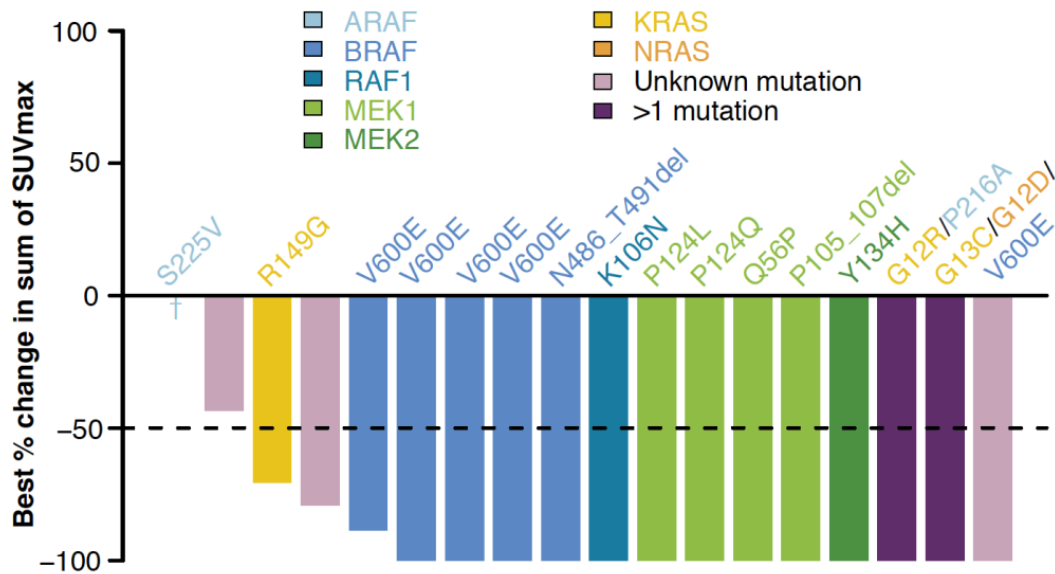
High prevalence of myeloid neoplasms in adults with non-Langerhans cell histiocytosis

Matthias Papo,^{1,*} Eli L. Diamond,^{2,*} Fleur Cohen-Aubart,^{1,*} Jean-François Emile,^{3,4} Damien Roos-Weil,⁵ Nishant Gupta,⁶ Benjamin H. Durham,⁷ Neval Ozkaya,⁷ Ahmet Dogan,⁷ Gary A. Ulaner,⁸ Raajit Rampal,⁹ Jean-Emmanuel Kahn,¹⁰ Thomas Sené,¹¹ Frédéric Charlotte,¹² Baptiste Hervier,¹³ Caroline Besnard,¹ Olivier A. Bernard,⁵ Catherine Settegrana,¹⁴ Nathalie Droin,¹⁵ Zofia Hélias-Rodzewicz,^{3,4} Zahir Amoura,¹ Omar Abdel-Wahab,^{9,16,*} and Julien Haroche^{1,*}



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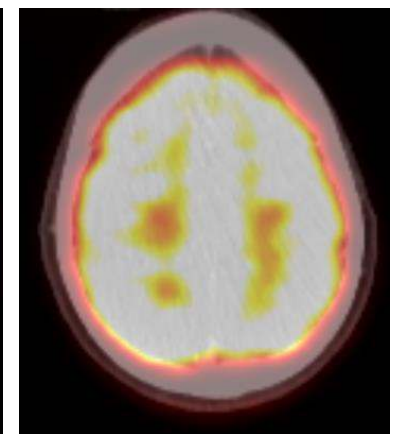
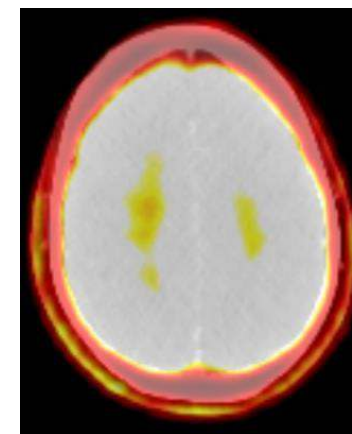
FDA Approval of Cobimetinib 2022



Baseline



Cobimetinib



Response	PET Response (N=18)	RECIST Response (N=14)
Overall response rate, % (90% one-sided Confidence Interval)	89 (73-100)	64 (44-100)
Best Response, N (%)		
Complete	13 (72)	2 (14)
Partial	3 (17)	7 (50)
Stable	1 (6)	4 (29)
Progressive	0 (0)	0 (0)
Not Evaluable	1 (6)	1 (7)

Efficacy of MEK inhibition in patients with histiocytic neoplasms

Eli L. Diamond^{1,2,12}, Benjamin H. Durham^{3,4,12}, Gary A. Ulaner^{2,5}, Esther Drill⁶, Justin Buthorn¹, Michelle Ki⁴, Lillian Bitner⁴, Hana Cho⁴, Robert J. Young^{2,5}, Jasmine H. Francis⁷, Raajit Rampal^{2,8}, Mario Lacouture^{2,9}, Lynn A. Brody², Neval Ozkaya^{3,10}, Ahmet Dogan⁴, Neal Rosen^{2,8,11}, Alexia Iasonos^{2,8}, Omar Abdel-Wahab^{2,4,8*} & David M. Hyman^{2,8*}

Diamond et al, *Nature*, 2019



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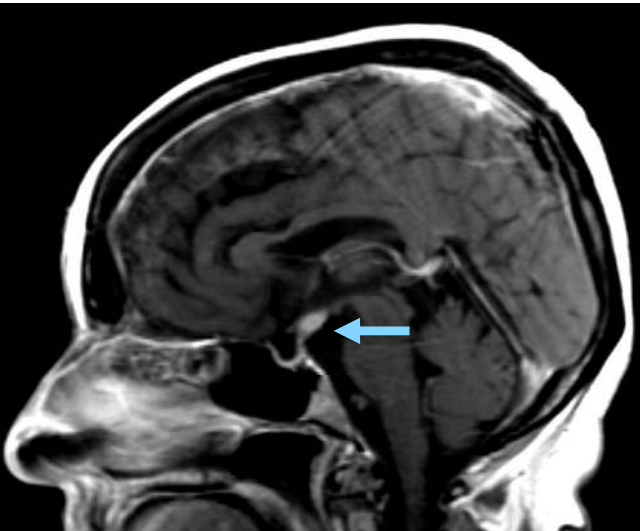
Treatment limited by side effects

MEK inhibitors

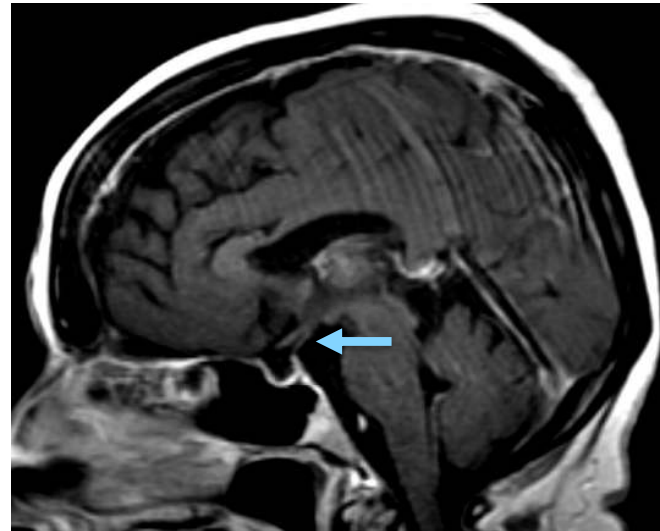
- Fatigue
- Skin toxicities
 - Acne rash
 - Itching
 - Hives
- Nausea, diarrhea, bloating
- Eye problems
- Heart problems
- Muscle problems
- **2/36 stopped in Cobimetinib trial (different approach to dosing)**



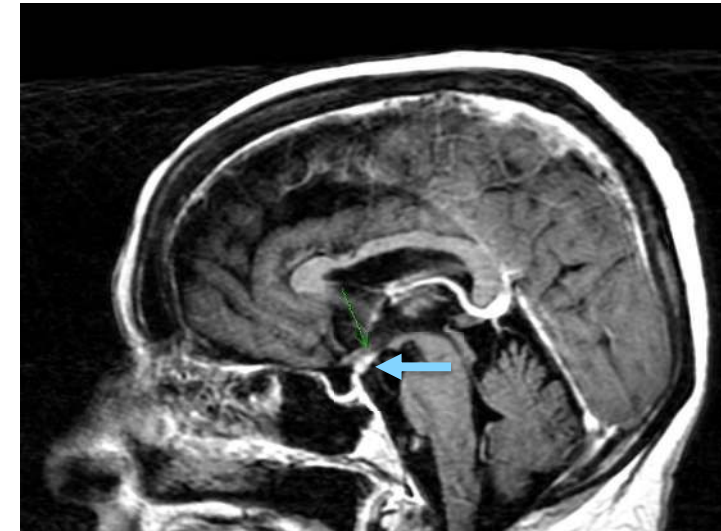
Limited brain penetration of BRAF/MEK



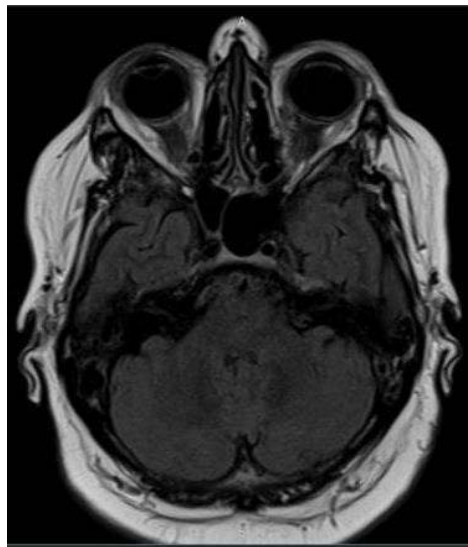
Pre-vemurafenib



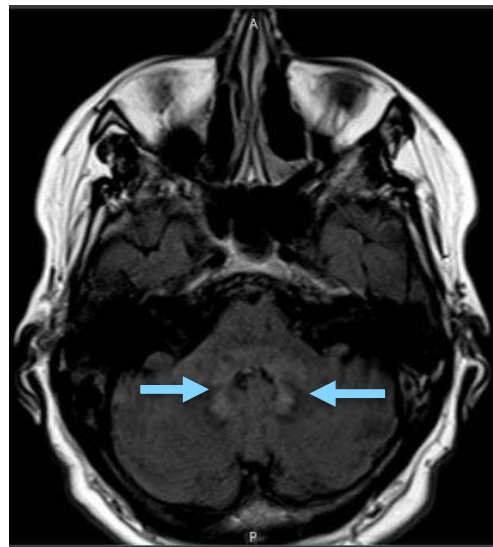
Vemurafenib



Chronic low-dose vemurafenib



Pre-vemurafenib



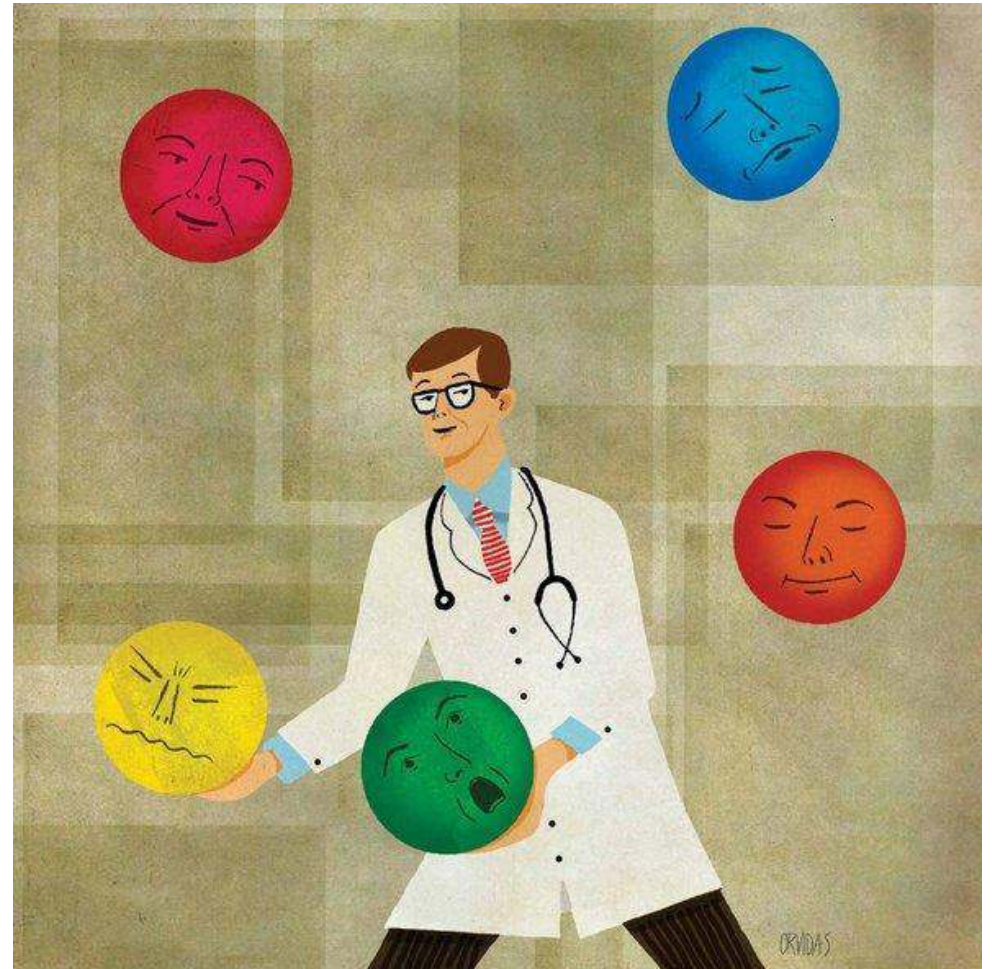
Chronic low-dose vemurafenib

- ECD progression despite BRAF inhibitors
- Progressive symptoms even if scans “stable”
- **Limitation of chronic low dosing in some patients**



Balancing Competing Priorities

- Disease control
 - PET
 - Organ function
 - Disease symptoms
- Side effects
- Neurologic health



Overall philosophy

- Side effects are generally related to drug dose
- Some resolve with dose adjustment, some improve but do not resolve, some resolve over time
- Reduced dosing for some patients
- Intermittent dosing for some patients
- Currently voodoo but needs to be studied formally
- **Treat the patient and not the scan**



BRAF/MEK inhibitors: fatigue

- Invariably present as disease symptom and side effect
- Modestly better with lower doses of treatment
- Evaluate addressable causes
 - Endocrine
 - Sleep apnea
 - Testosterone
- Stimulants?
- Exercise



BRAF inhibitors: joint/tendon pains

- Common and underappreciated
- Hips, shoulders, knees
- Can be immediate side effect when starting
- Can start months after starting (often one shoulder)
- anti-inflammatories, steroids
- Dose reduction
- Can be reason to change treatment entirely



BRAF inhibitors: skin

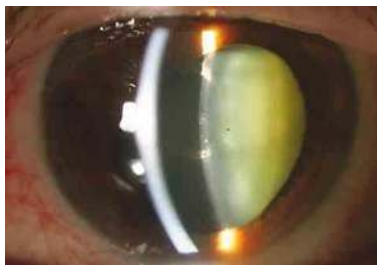
- Extremely common!
- Hand-foot syndrome
- Dramatic callouses
- Itching/burning without much rash
- Welts (that move around!)
- Acanthomas, basal cell, squamous CA

- Absolutely need dermatologist
- Various topical / oral treatments
- Dose reduction helps
- Can consider adding MEK inhibitor

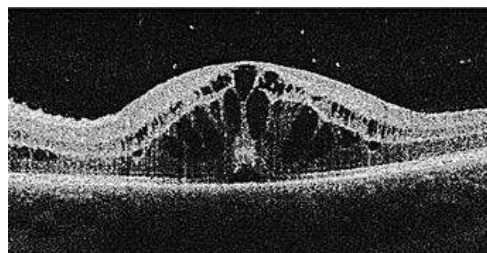
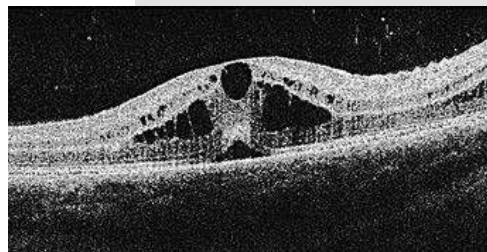


BRAF inhibitors: eyes

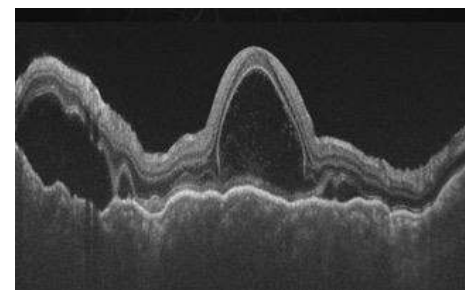
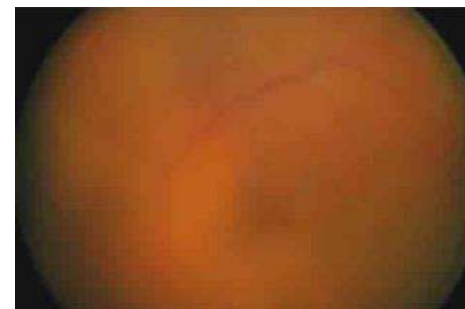
Uveitis 4.5%
*Bilateral, nongran,
anterior*



Cystoid Macula Edema
<1%



Panuveitis <<1%
w/ serous RD



Prognosis Can respond to steroids (+/- drug cessation)



How I give BRAF inhibitors

- Full dose: NOT tolerable
- One dose reduction: not tolerable chronically (few exceptions)
- Two dose reductions: tolerable chronically for most patients
- Intermittent dosing: tolerable to nearly everyone

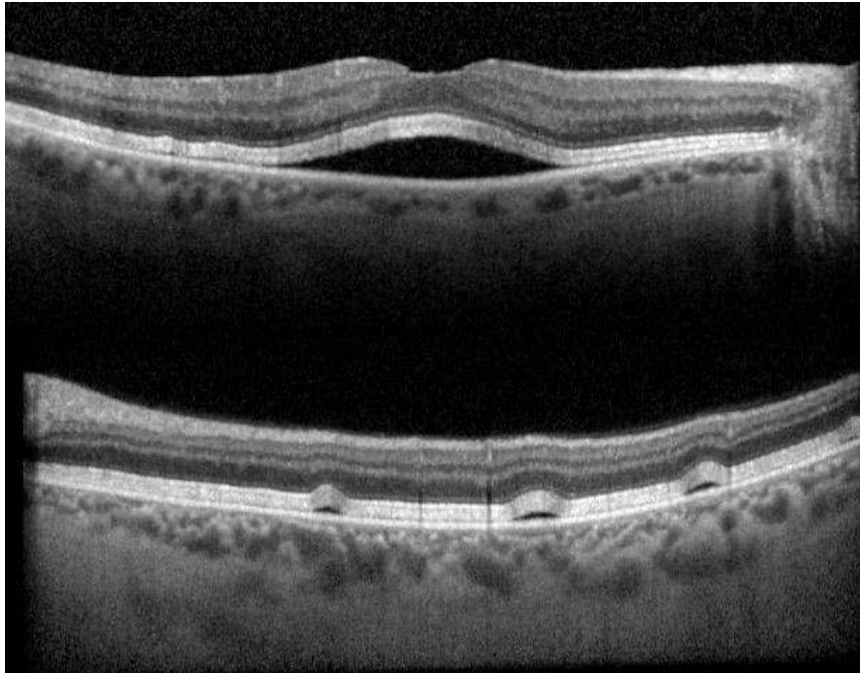
- NO brain ECD: low-mid dosing to best response and then as low/continuous or intermittent dosing to maintain
- YES brain ECD: mid-high dosing to remission and then intermittent mid-high dosing

- Dermatologist on hand
- Labs every month for first few months, then spaced out

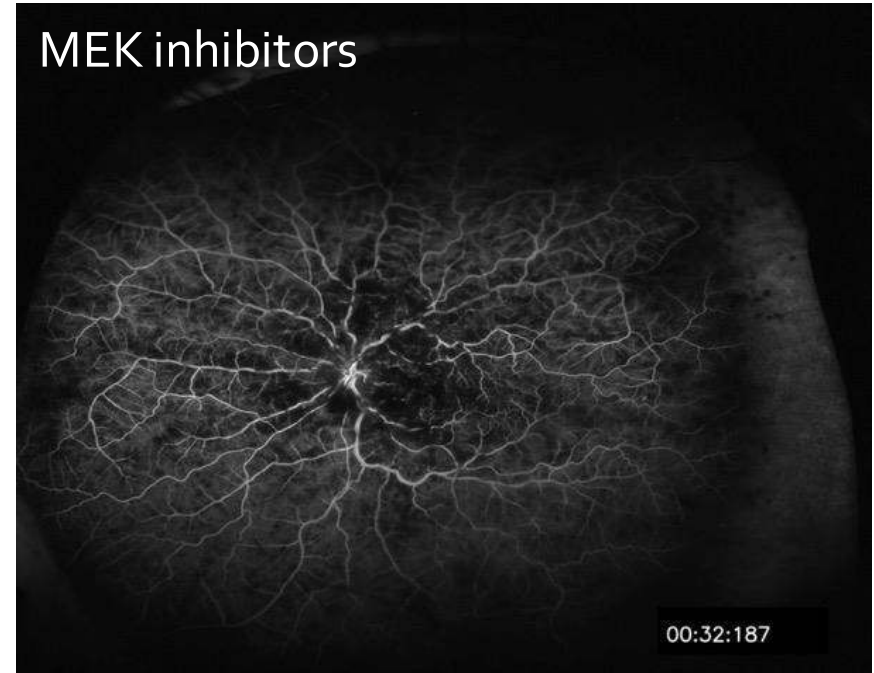


MEK inhibitors: eyes

MAPKinase Retinopathy (15%)



Retinal vein occlusion (0.5%)



- Ophthalmology evaluation prior to treatment
- Some form of eye complication fairly common, most serious is very very rare
- Almost never forces complete discontinuation



MEK inhibitors: muscle and heart

- Cause muscle injury, measured by “CPK” lab
- Can be high without any clinical importance, or can represent serious problem
- High CPK without symptoms generally ok to follow
- Periodic heart ultrasound to look for reduced heart function
- Rare apart from highest doses
- Resolves with holding drug



MEK inhibitors: skin, GI

- Acne-like rash
- Itching, hives, severe sensitivity
- Face and chest most common
- Some providers give preventative medications, others do not
- Dermatologists can really help
- Diarrhea, constipation, bloating all very common
- All of these better with lower doses



How I give MEK inhibitors

- Full dose: RARELY tolerable
- One dose reduction: Typically tolerable
- Two dose reductions: Nearly always tolerable
- Intermittent dosing: tolerable to nearly everyone

- NO brain ECD: low-mid dosing to best response and then low continuous/intermittent dosing to maintain
- CNS-disease: mid-high dosing to best response and then intermittent mid-high dosing to maintain

- Dermatologist and ophthalmologist on hand
- Labs every month for first few months



Other points on targeted treatment

- Breaks are okay!
- Consider adding MEK inhibitor to BRAF inhibitor alone to curb side effects
- BRAF+ patients can take MEK inhibitor alone
- Do not be enslaved to the PET scan
- Getting to the best treatment plan is trial and error
- Consider research participation



Patient-Centered ECD Registry

- ECD Global Alliance issued RFP for collaborative creation of Registry protocol
- Awarded to MSK in 2014
- Designed in partnership with ECD Global Alliance Board
- Survey battery from patient/caregiver focus groups
- **Goal to improve diagnosis, treatment options, symptom recognition and management for ECD patients**

Clinical presentation and course

Diagnosis and sites of disease

Treatment outcomes

Patient-reported outcomes



Study about Fatigue and Pain

- All ECD registry participants complete detailed survey about fatigue and pain every 6-12 months
- Rate 9 items about fatigue, 11 about pain from 1-10
- Severity, interference, total scores
- Clinically relevant fatigue – any score 4 or greater
- Frequency of pain and fatigue
- Examined correlation between pain and fatigue
- Examined clinical factors associated with pain or fatigue
- One on one individual interviews

PRO Item/Construct	Description
BFI Item 1	Fatigue right now
BFI Item 2	Usual fatigue
BFI Item 3	Worst fatigue
BFI Item 4	General activity
BFI Item 5	Mood
BFI Item 6	Walking ability
BFI Item 7	Normal work
BFI Item 8	Relationships
BFI Item 9	Life enjoyment

BPI Item 1	Worst pain
BPI Item 2	Least pain
BPI Item 3	Average pain
BPI Item 4	Right now pain
BPI Item 5	General activity
BPI Item 6	Mood
BPI Item 7	Walking ability
BPI Item 8	Normal work
BPI Item 9	Relations
BPI Item 10	Sleep
BPI Item 11	Life enjoyment



Pain and fatigue: frequency and association

- 74% reported clinically relevant fatigue, 53% pain, 48% both
- 91% of those with pain also had fatigue
- 65% of those with fatigue also had pain
- Fatigue and pain correlated with one another
- 100% of patients who are unemployed reported pain
- Fatigue associated with BRAF-negative status
- Pain associated with 2 or more prior treatments
- No association with disease treatment, PET status, medication dose

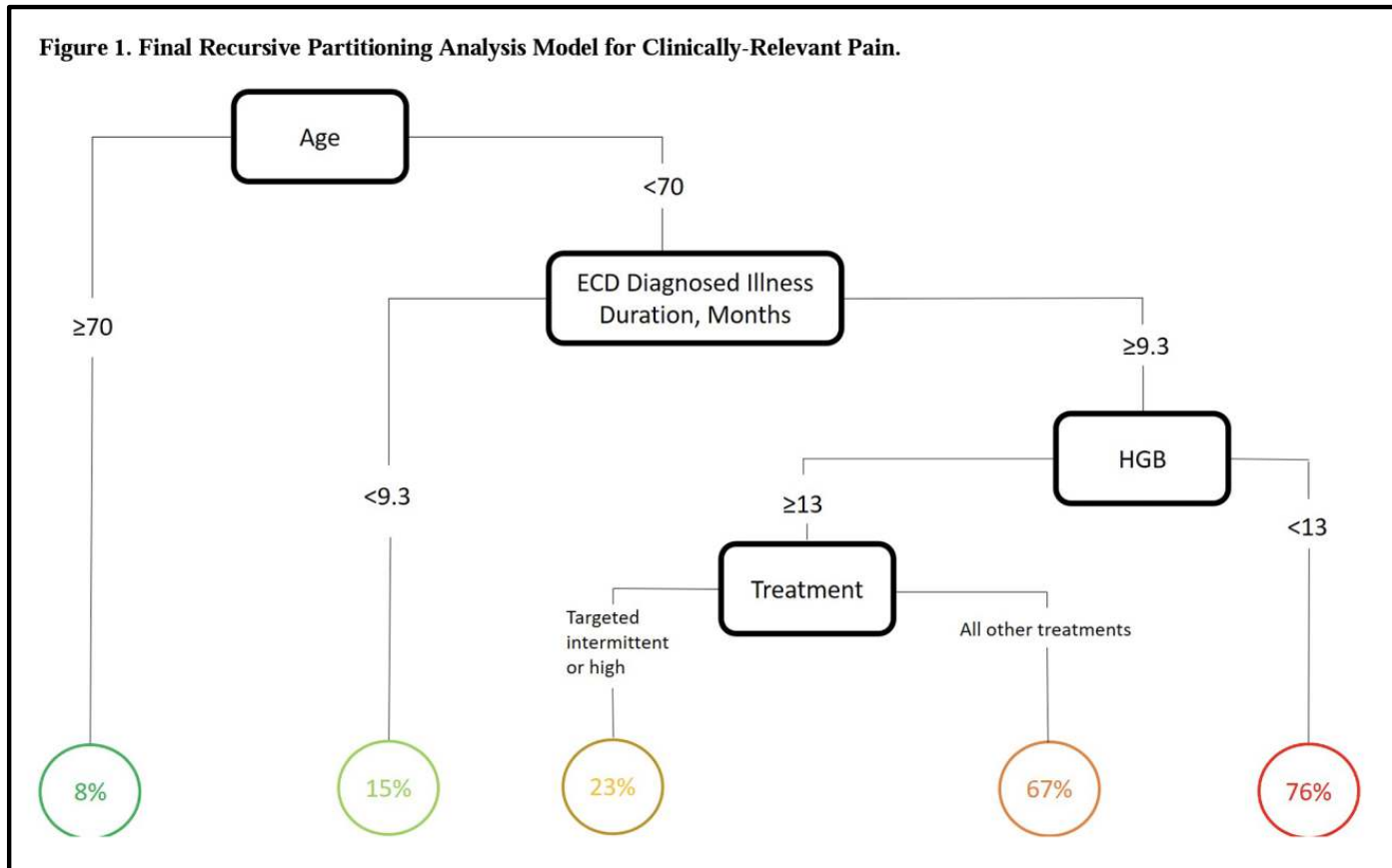
	Clinically-Relevant Pain (Any BPI Item 4+)		
Clinically-Relevant Fatigue (Any BFI Item 4+)	No	Yes	P-value
No	25 (21%)	6 (5%)	<0.0001
Yes	31 (26%)	58 (48%)	



Factors associated with pain

- Age < 70
- ECD diagnosis > 9.3 months
- Anemia

Figure 1. Final Recursive Partitioning Analysis Model for Clinically-Relevant Pain.



Fatigue: Patient Voice

Fatigue

Severity and pervasiveness

“Fatigue is like—I can't even describe it. **It's like, um, the most exhausting thing ever, and you didn't really do anything.**”

Lack of energy. **Just don't want to get out the bed. Want to stay in bed. Everything takes extra effort**, like, uh, everything feels going uphill. Nothing is just smooth. Everything takes an effort to do, to get up. And I'm like, "Oh. Do I really want to get up?"

Variable interference

Uh, I would say that, overall, I'm able to do what I want to do. Uh, my stamina over that period has decreased slightly and continues to decrease slightly, but I'm able to do what I want to do. Maybe not quite as long, but I can do whatever I want to do.

I really have to pace myself with what I do, um, you know, to determine—I-I can't—I just can't do as much. Like, today, I'm doing this and this, and then, I have to wait till tomorrow to do something else because I don't want to overdo it. **Because if I overdo it then, tomorrow is a whole day wasted because I'm having to rest.**



Pain: Patient Voice

<p>Variable pain quality and Fatigue exacerbates pain</p>	<p>Um, so I'm getting, like, this electrical—literally, that's what it feels like. I don't know if you've ever had anything like that before. But in my left arm, I'm getting, like, this electrical, um, like, feeling from my elbow to my hand. Like, I'll hear like a-a shooting electrical pain.</p> <p>It's no sharp pain or anything. It's more so with exertion. When I walk, after a certain period of time, my bottom calves tighten up and it starts aching. That over the timeframe of the disease has probably developed not only in the bottom legs, but now in the top, upper thigh muscles start to ache. Uh, I don't have muscle pain or any discomfort in—above my waist.</p> <p>It's a diffused pain. It's an all-over pain. You know, it is—it comes and goes. And what I mean with that, if I overdo it, <u>I'm really fatigued, the pain is worse</u>. The pain at night, and I wake up in the morning with pain. And I'm taking Neurontin at bedtime and that helps me get through the night. However, it takes me a lot in the morning to get around some mornings... I don't always schedule early morning appointments because I'm just—I'm late. You know? And that's not-that's not like me.</p>
<p>Pain location</p>	<p>I'm having shoulder pain, a lot of joint pain. Joints, my ankles, my shoulders, my elbows [...] My ankle, it feels like this nerve pain, and so does my elbows. It feels like an electric shock, something like that.</p>
<p>Pain is side effect of treatment</p>	<p>Now I know that it has its own set of side effects. Now, it—now, I have the same—not the same but, you know, similar side effects as the other medications where the hair is, you know, thinning and falling out and the fatigue and the pain, those things. Because before, it was just combatting what the other ones had made me go through. So it was a better version, I guess. And it didn't seem like it was as harsh.</p> <p>So, um, but the pain, you know—when I was on the Zelboraf the pain was—it was really bad. And that's why I quit working, I overdo it. It's just too much.</p>

Summary: Pain and fatigue

- Pervasive and severe across ECD patients
- Not improved by treatment or improvement in disease status by PET
- Fatigue in BRAF-negative (?)
- Pain in younger patients, longer duration of disease
- Lots of room for improvement



Conclusions

- Very difficult balancing act
- We need you to figure it out!
- Join Registry and other research studies



THANKS



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