ECD International Medical Symposium
Paris, France
September 15, 2016

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Clinical molecular profiling to detect targetable alterations in archival tumor tissue and cell-free DNA from patients with Erdheim-Chester disease

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Bench to Bedside & Back

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Rationale

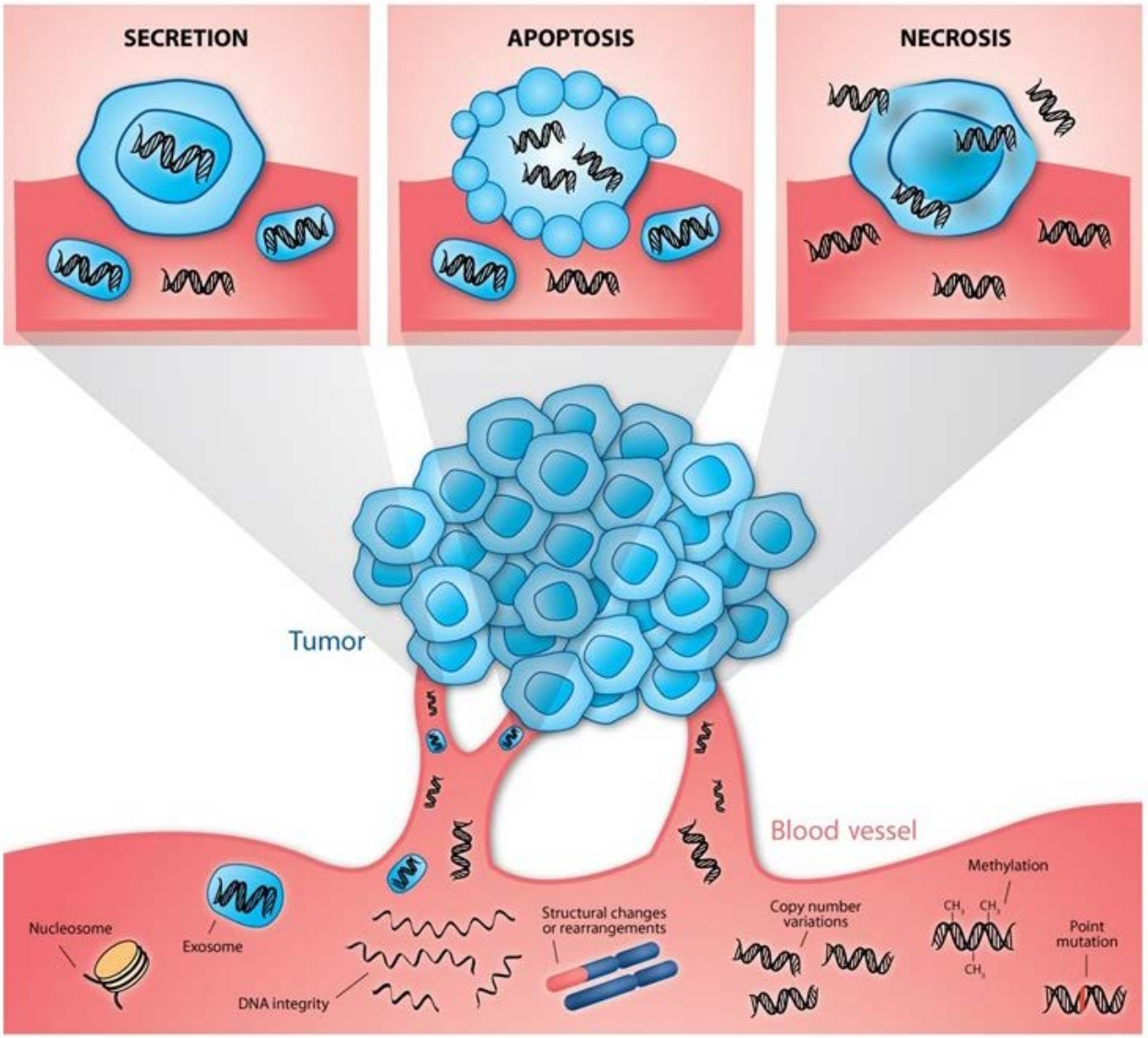
- *BRAF* V600E mutations and other druggable molecular alterations can be detected in majority of patients with Erdheim-Chester disease (ECD)

- ECD patients with *BRAF* V600E mutations and other druggable molecular alterations can respond to appropriately selected targeted therapies (e.g. BRAF and MEK inhibitors)

- Molecular testing of tumor tissue is often problematic in patients with ECD especially in patients with bone disease

Haroche J. Blood 2012
Diamonnd EL. Cancer Discov 2016

Concept of “liquid” biopsy



Polivka, Janku. Expert Rev Mol Diagn 2015

BRAF mutations in Erdheim-Chester disease (non-Langerhans cell histiocytosis) with droplet digital PCR

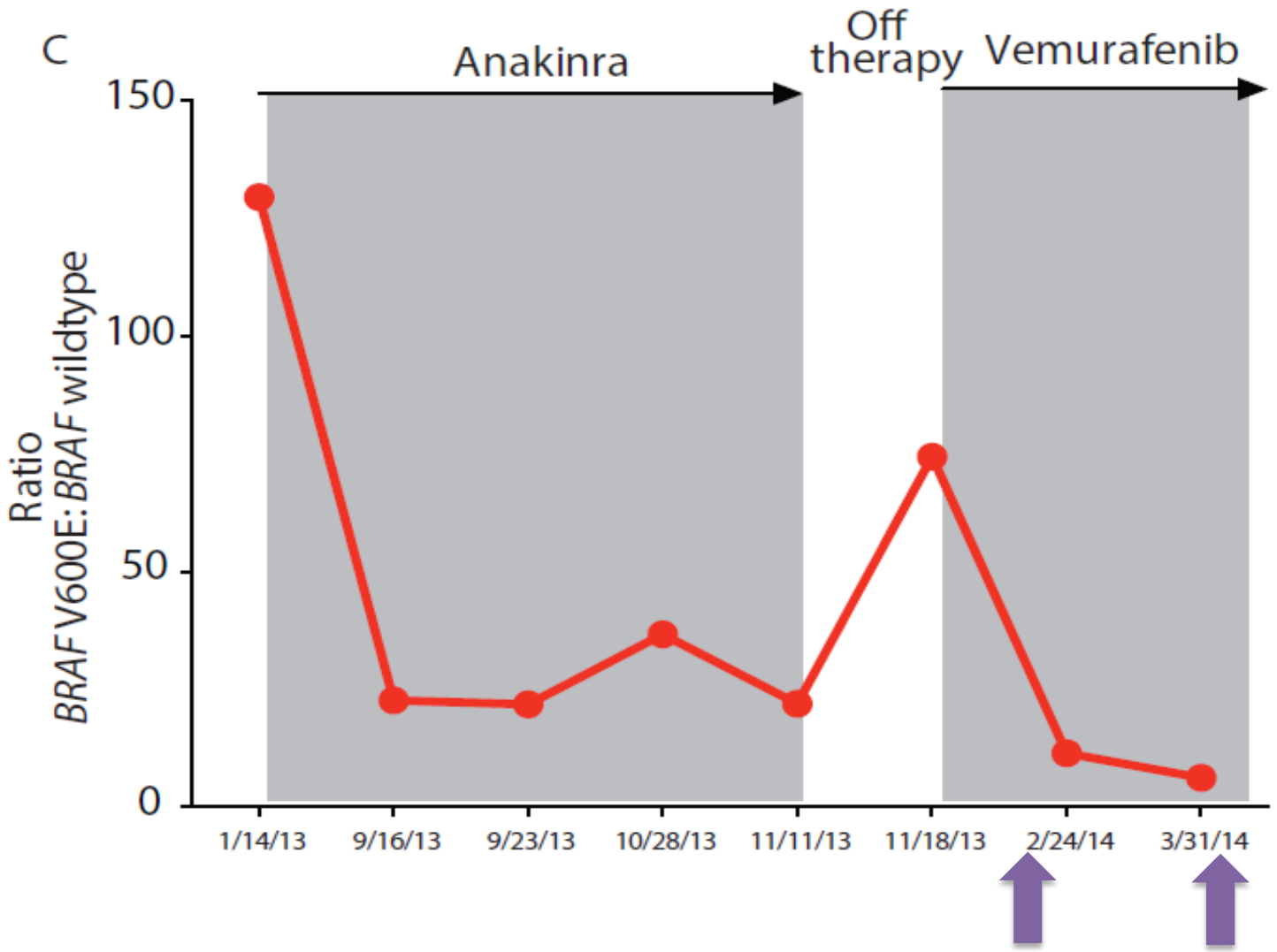
Patient #	Urine *BRAF* V600E/WT	Plasma *BRAF* V600E/WT	Patient Tissue *BRAF* status
1	V600E (22.59%)	V600E (8.598%)	V600E
2*	V600E (0.311%)	V600E (1.522%)	V600E
3	Wild-type (0.010%)	Wild-type (0.063%)	Wild-type
4	V600E (0.159%)	Wild-type (0.047%)	Unknown**
5	V600E (4.940%)	V600E (0.261%)	Unknown**
6	Wild-type indeterminate (0.079%)	Wild-type (0.048%)	Unknown**

*Urine and plasma collected on different dates

** Insufficient tissue for molecular analysis

Janku et al. Oncotarget 2014

63-yo patient with Erdheim-Chester histiocytosis treated with BRAF inhibitor vemurafenib (ddPCR of urine cfDNA)



Hyman, Diamond, Janku, Abdel-Wahab. Cancer Discov 2014

Methods: all CLIA compliant

- Isolation of tumor DNA, plasma and urine cell-free (cf) DNA
- Molecular testing of tumor tissue
  - PCR
  - Targeted NGS (Ion Torrent, Foundation One)
- Molecular testing of plasma cfDNA
  - Targeted NGS (Guardant 360)
- Molecular testing of urine cfDNA
  - PCR (Trovagene)

Results: at least one valid result was obtained in 19 of 25 (76%) patients

- **Tumor tissue PCR**: 14 patients
  - Molecular testing successful in 9/14 (64%)
- **Tumor tissue targeted NGS**: 16 patients
  - Molecular testing successful in 10/16 (63%)
- **Plasma cfDNA targeted NGS**: 11 patients (+2 pending)
  - Molecular testing successful in 11/11 (100%)
- **Urine cfDNA PCR**: 3 patients
  - Molecular testing successful in 3/3 (100%)

Patient No.	Tissue PCR	Tissue targeted NGS	Plasma targeted NGS	Urine PCR	Genotype driven therapy
MDA2	Not done	**MAP2K1^{Q56P}**	Not done	Not done	MEKi
MDA4	**BRAF^{V600E}**	Failed	Not done	Not done	BRAFi
MDA5	**None**	Not done	Not done	Not done	
MDA6	Failed	Not done	Not done	Not done	
MDA11	Failed	Not done	Not done	Not done	
MDA12	Not done	**BRAF^{V600E}**	Not done	Not done	BRAFi
MDA13	Failed	Not done	Not done	Not done	
MDA14	Failed	Not done	Not done	Not done	
MDA15	Not done	**BRAF^{V600E}**	**BRAF^{V600E}, KRAS^{G12R}**	**BRAF^{V600E}**	
MDA16	Not done	**NTRK1 fusion**	Not done	Not done	
MDA17	Not done	**BRAF^{V600E}**	Not done	*	BRAFi
MDA18	**None**	Failed	Pending	*	
MDA19	Failed	Not done	Not done	Not done	
MDA20	**None**	Failed	**None**	Not done	
MDA21	**BRAF^{V600E}**	Not done	Not done	**None**	
MDA22	**None**	Failed	**None**	**None**	
MDA23	Not done	**BRAF^{V600E}, ASXL1^{E635fs*15}**	**BRAF^{V600E}, CCNE1^{P396L}**	Not done	MEKi
MDA24	Not done	**BRAF^{V600E}**	**BRAF^{V600E}**	Not done	BRAFi/MEKi
MDA25	**BRAF^{V600E}**	Pending	**BRAF^{V600E}, BRAF^{L485W}, ERBB2 CNV**	Not done	MEKi
MDA26	Not done	Not done	Pending	Not done	
UCSD1	**BRAF^{V600E}**	Not done	**NF1^{H1494Y} (on BRAFi)**	Not done	BRAFi
UCSD2	**BRAF^{V600E}**	**None**	**None (on BRAFi)**	Not done	BRAFi
UCSD3	Not done	Failed	**FGFR2^{V274I}**	Not done	
UCSD4	Not done	**BRAF^{V600E}**	**None**	Not done	
UCSD5	Not done	**BRAF^{V600E}, ASXL1^{R693}, U2AFI^{Q157P}**	**JAK2^{V617F}, NF1^{S1407R}, NRAS^{G60R} (on BRAFi)**	Not done	BRAFi, MEKi

Results: concordance tissue and cfDNA

- 11 patients had valid results from both tumor tissue DNA and cfDNA
- Alterations detected in tissue were detected in 6 of 8 samples of cfDNA obtained before therapy
- All 3 cfDNA samples obtained after therapy failed to identify alterations detected in the tissue

Results: turnarounds time

The median turnaround times

- Tumor tissue PCR: 8 (5-41) days
- Tumor tissue targeted NGS: 37 (19-116) days
- Plasma cfDNA NGS: 15 (13-18) days
- Urine cfDNA: 12 (7-25) days

Results: therapeutic implications

- 19 patients had at least one or more successful molecular testing
- 15 (79%) had targetable molecular alterations
- 11 (58%) received appropriate targeted therapy
- 3 patients with *BRAF* mutations from tumor tissue had plasma cfDNA targeted NGS after exposure to BRAF inhibitors and *BRAF* mutations could no longer be detected

CONCLUSIONS

- Clinical molecular testing in patients with ECD identifies targetable molecular alterations in the majority of patients.

- Liquid biopsy approaches appear to have higher success rates, short turnaround times and excellent concordance with the results of conventional tumor tissue testing.