PragueONCO 2020

January 29, 2020

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

Circulating Biomarkers in Precision Oncology and Immunoncology

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Associate Professor

Investigational Cancer Therapeutics (Phase I Clinical Trials Program)

Center Medical Director

Clinical & Translational Research Center

Bench to Bedside & Back

Disclosures

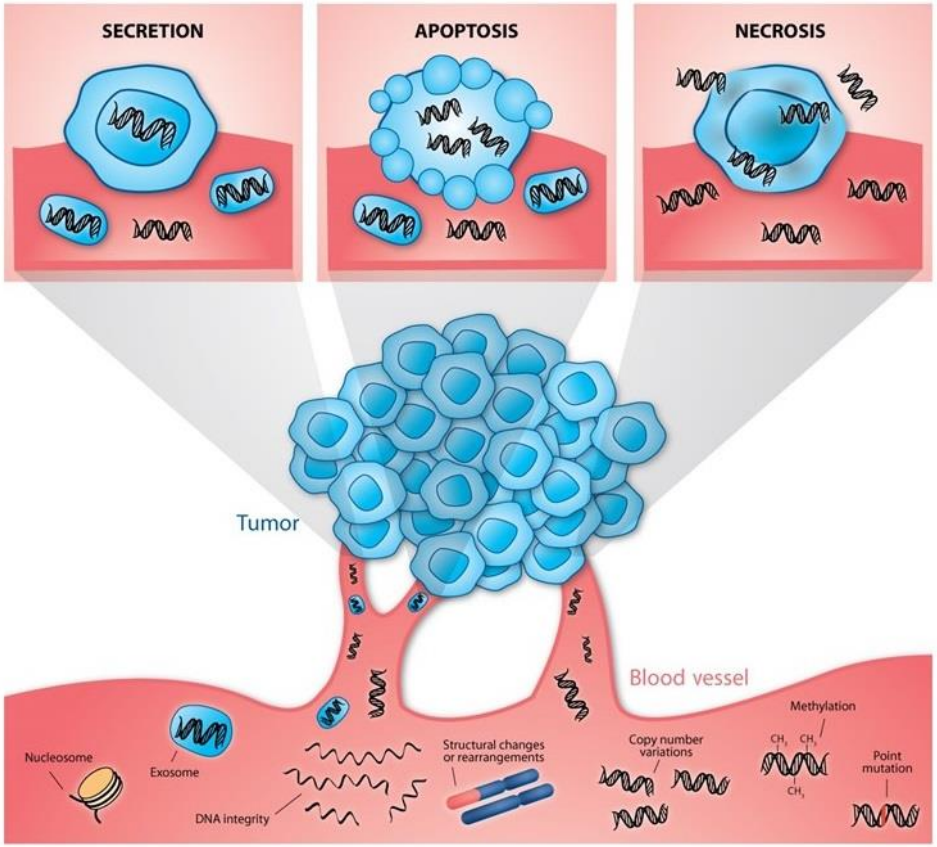
- **Research Funding (through institution):** Agios, Asana, Astellas, Astex, Bayer, BioMed Valley Discoveries, Bristol-Myers Squibb, Cotinga, Ideaya, Deciphera, FujiFilm Pharma, Genentech, Novartis, Piqur, Plexxikon, Proximagen, Symphogen, Sotio, Sanofi, SynthoRx, SpringBank Pharma, Synlogic

- **Consulting:** Baush, Bicara, Deciphera, Guardant Health, Grail, Ideaya, IFM Therapeutics, Immunomet, Illumina, Jazz Pharmaceuticals, Novartis, Primmune Therapeutics, PureTech Health, Sotio, Synlogic, SpringBank Pharma, Tessa Therapeutics, Trovagene

- **Ownership Interests:** Trovagene

- **Other:** Bio-Rad, Biocartis

Concept of “liquid” biopsy



Polivka, Janku. Expert Rev Mol Diagn 2015

Liquid Biopsies in the Clinic

1. Treatment indication

2. Efficacy monitoring

3. Molecular profiling in the real-time

4. Indirect assessment of target engagement and inhibition

5. Early detection

Concordance Between Discordantly Collected Liquid (plasma cell-free DNA) and Tissue Biopsies

PCR and digital PCR

- Idylla QAS PCR: 88%-90%
- BEAMING: 83%-99%
- ddPCR 85%-95%

Janku F. Mol Cancer Ther 2016
Janku F. Oncotarget 2015
Janku F. Ann Oncol 2017

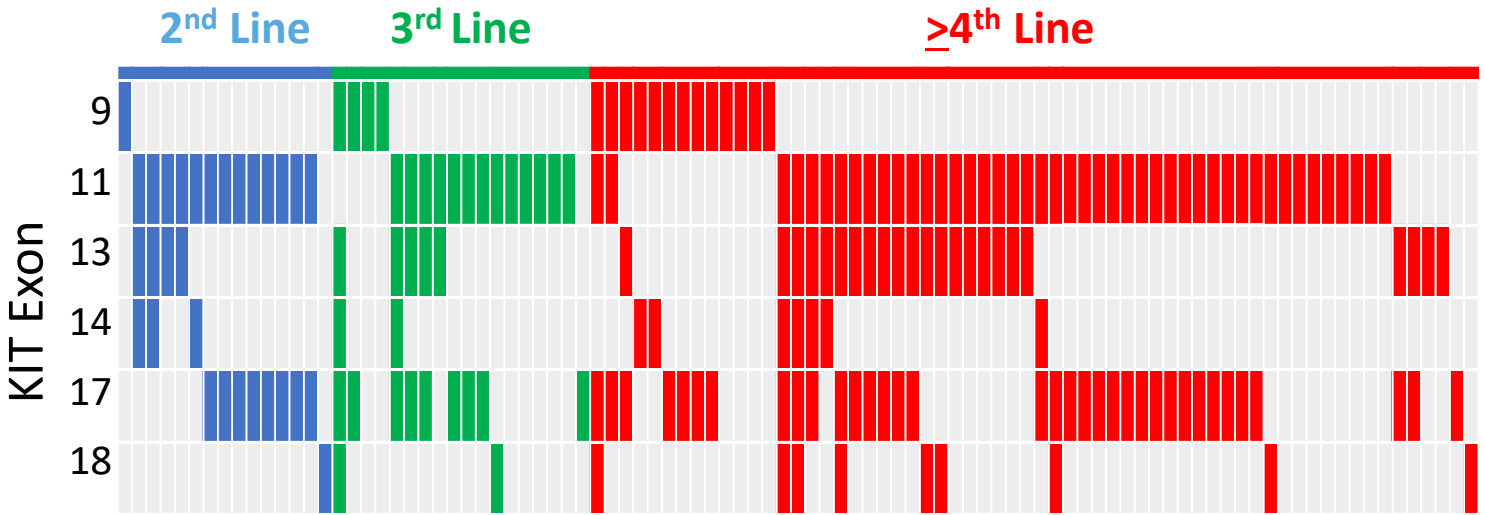
NGS

Concordance between ultra-deep NGS of plasma cfDNA and clinical molecular testing of archival tumor tissue for the 55 patients with advanced cancers

Type of agreement between plasma cfDNA and tumor tissue	Number of patients (%)
Complete detection	45 (82%)
Partial detection	3 (5%)
Aggregate complete and partial detection	48 (87%)
Complete disagreement	7 (13%)

Janku F. Clin Cancer Res 2017

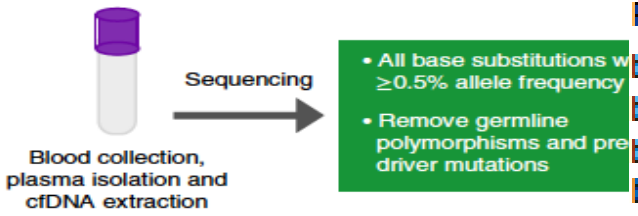
Liquid Biopsies (NGS) Detect Broad Spectrum of KIT Mutations in Previously Treated GIST

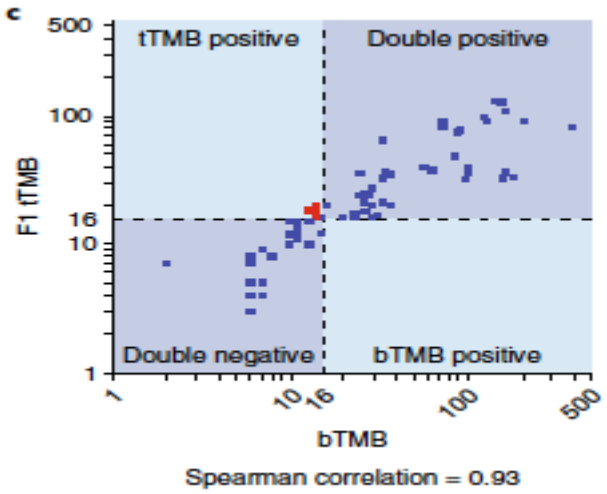


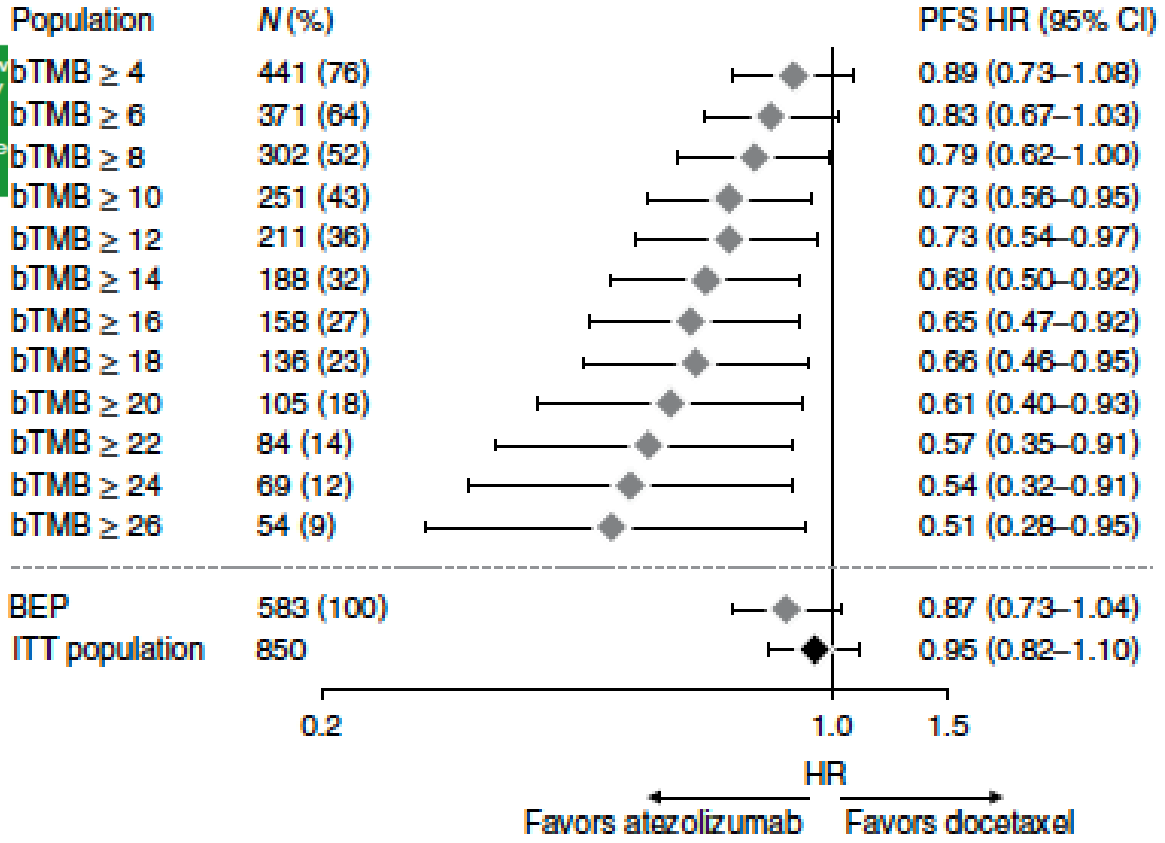
- Each column represents an individual patient
- In pts where a KIT mutation was detected in baseline ctDNA, secondary KIT mutations in exon 13, 14 17 and 18 were found across 2nd to ≥4thline pts.

George , Janku. ASCO 2018

Blood (cfDNA) TMB and Response to Immune Checkpoint Inhibitors

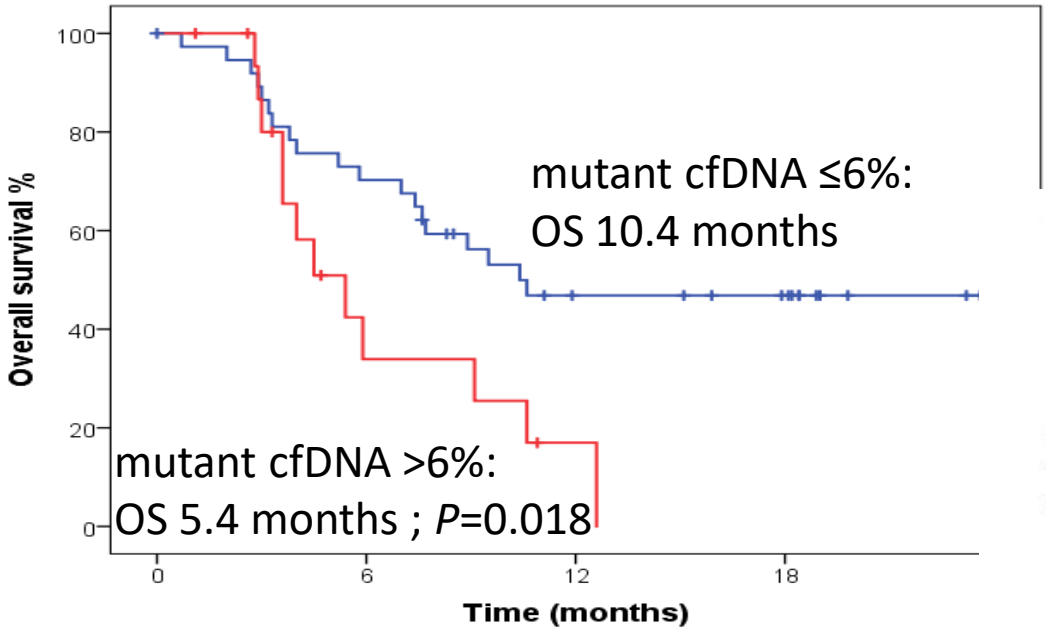




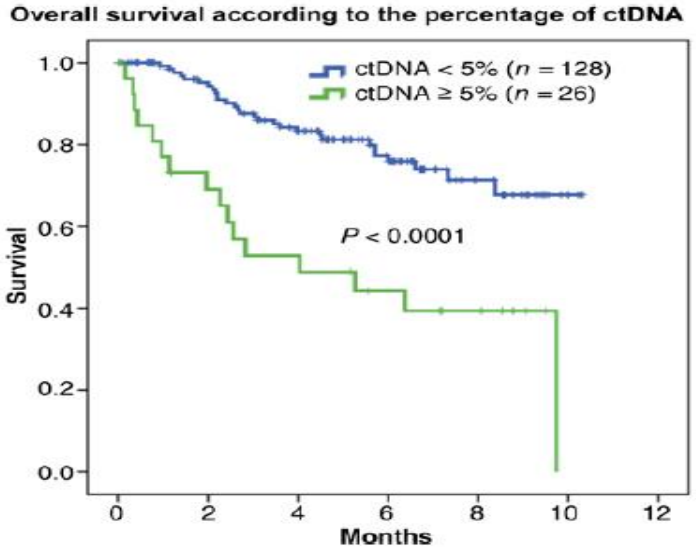


Gandhara et al. Nat Med 2018

The median OS duration in with advanced cancers per variant allele frequency of mutant cfDNA

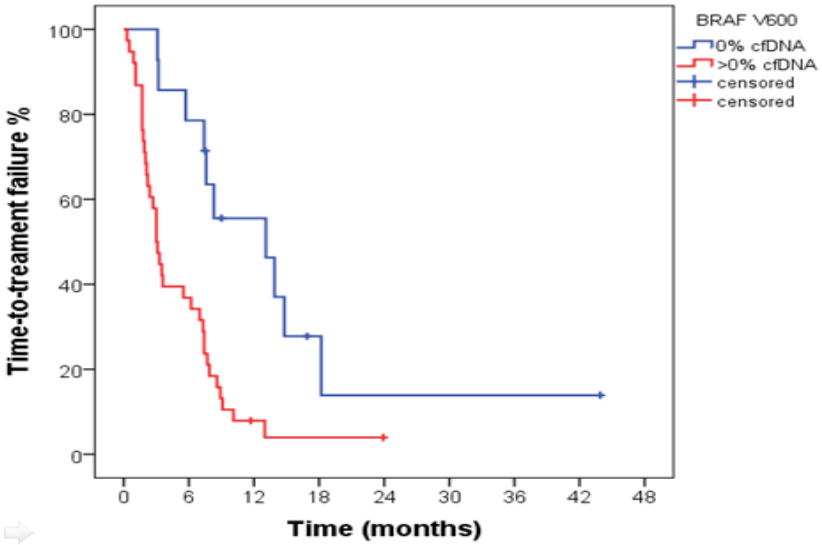


Janku, Salathia. Clin Cancer Res 2017



Schwaederle M, Clin Cancer Res 2016

Detection of *BRAF* V600 mutant plasma cfDNA is associated with shorter time-to-treatment failure on systemic therapy



Janku F et al., Mol Cancer Ther 2016

Median TTF in 51 patients per plasma BRAF

Tumor *BRAF*+/Plasma *BRAF*- **13.1** months,
13 patients 95% CI 5.0-21.2

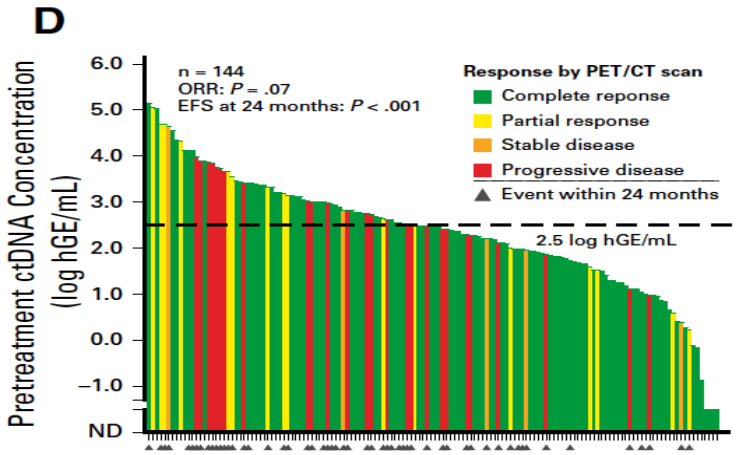
Tumor *BRAF*+/Plasma *BRAF*+ **3.0** months
38 patients 95% CI 2.3-3.7

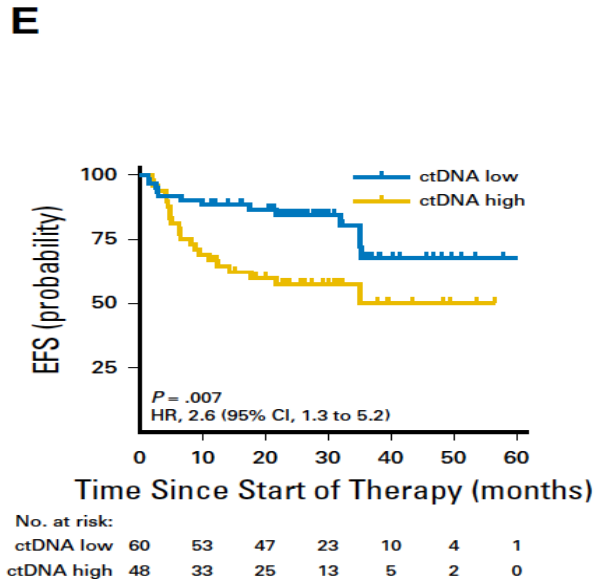
***P*=0.001**

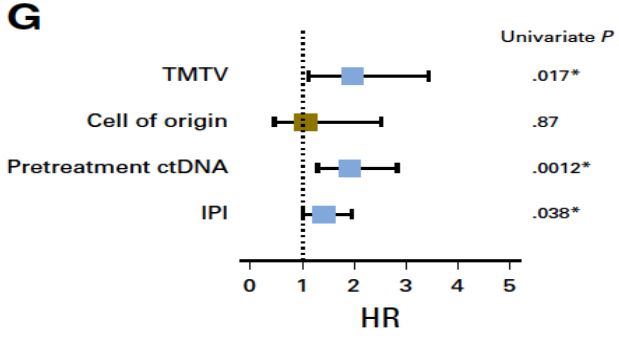
Preliminary data suggest that amount of circulating tumor DNA does correlate with the total tumor volume and liver tumor volume

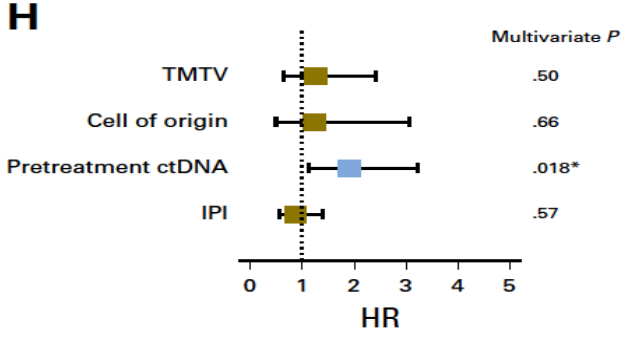
Ahmed, Colen, Janku. EORTC-NCI-AACR 2018

Circulating Tumor DNA as Early Outcome Predictor in DLBCL









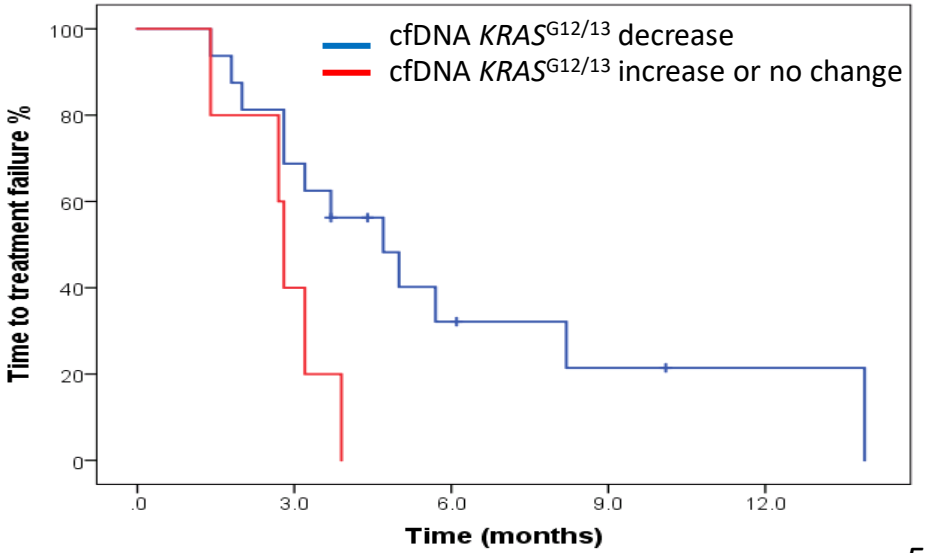
Kurtz et al. J Clin Oncol 2018

Mutation-Enrichment NGS: Association between changes in cfDNA *KRAS*$^{G12/13}$ copies in URINE and PLASMA and time to treatment failure (TTF)

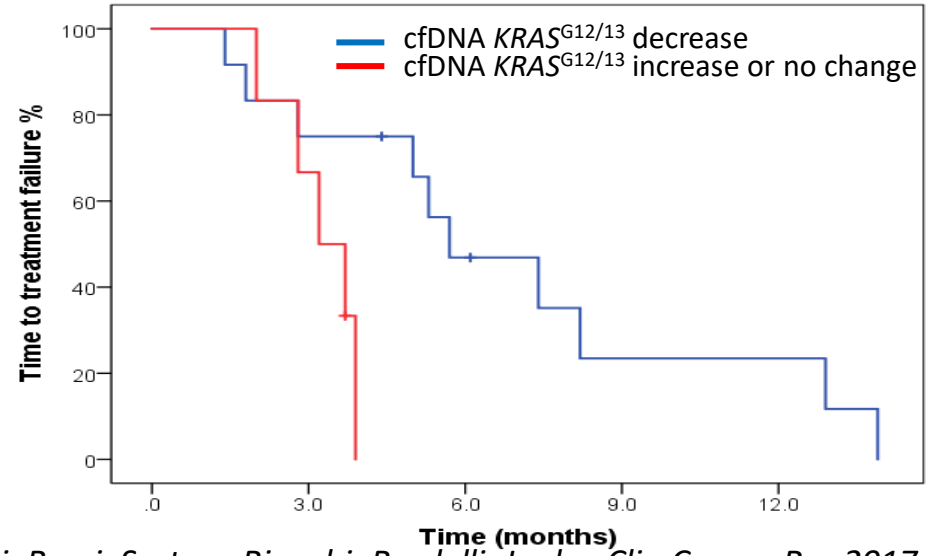
TTF and *KRAS*$^{G12/G13}$ copy numbers in urine:
Decrease (4.7 months; blue)
vs.
No change/increase (2.8 months; red; *P* = 0.03)

TTF and *KRAS*$^{G12/G13}$ copy numbers in plasma:
Decrease (5.7 months; blue)
vs.
No change/increase (3.2 months; red; *P* = 0.04)

A. **URINE**



B. **PLASMA**



Fujii, Barzi, Sartore-Bianchi, Bardelli, Janku Clin Cancer Res 2017

50yo F with metaplastic breast cancer *PIK3CA E542K, KRAS G12S*
Everolimus-Bevacizumab-Doxorubicin Liposome

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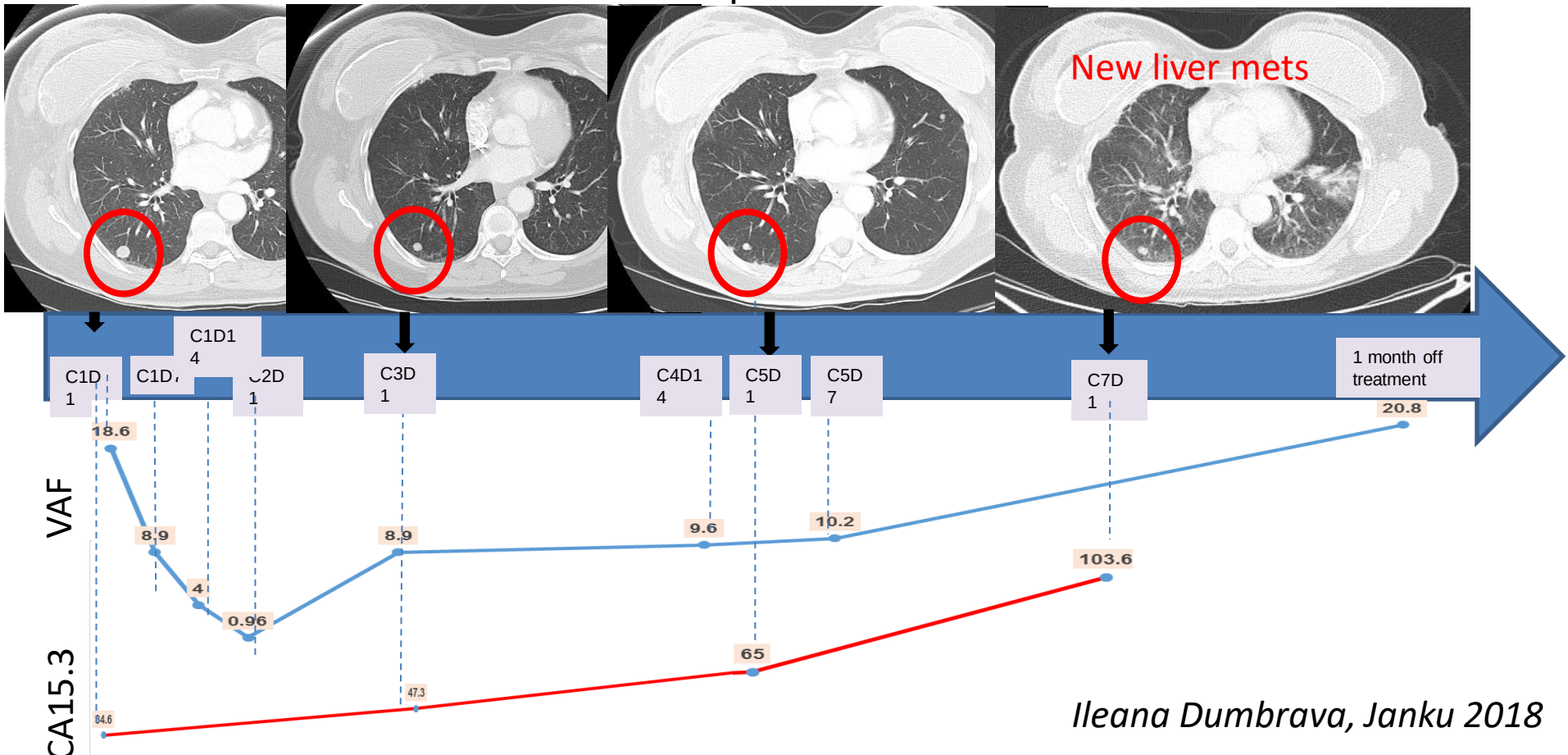
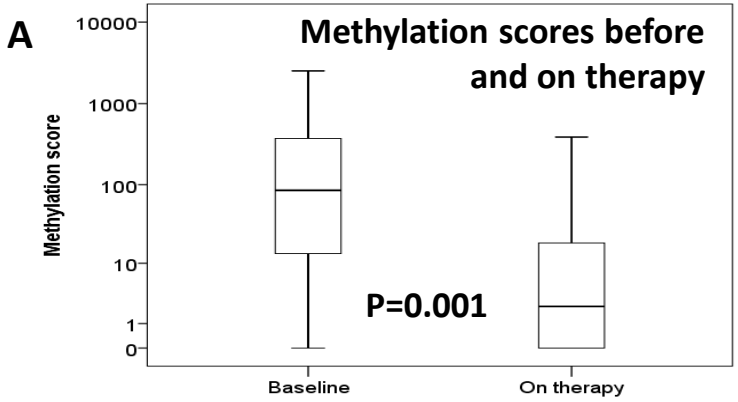
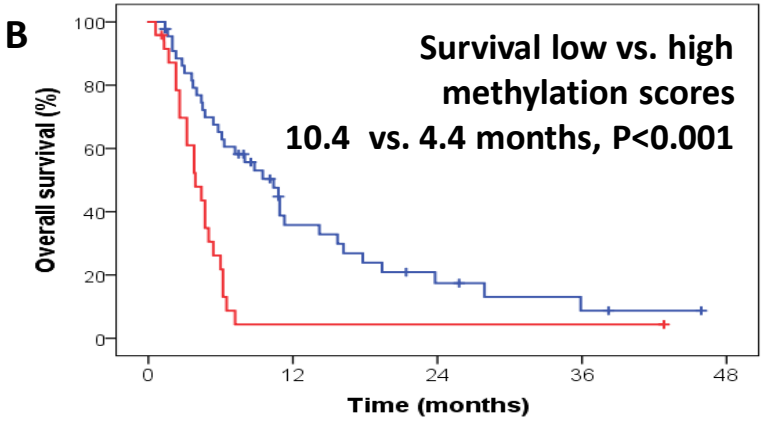
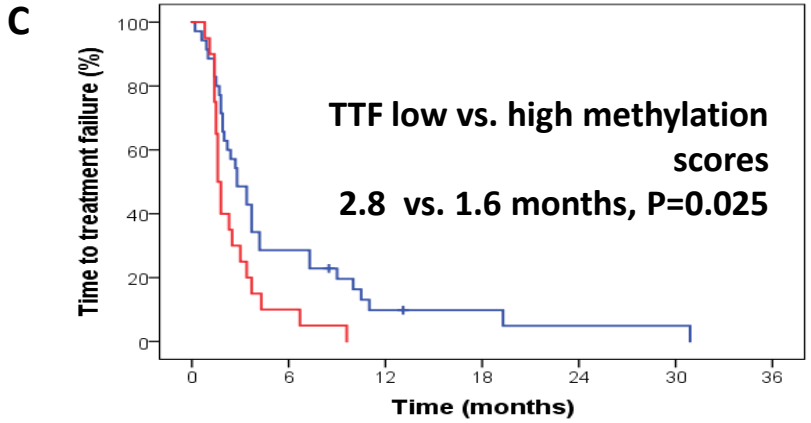


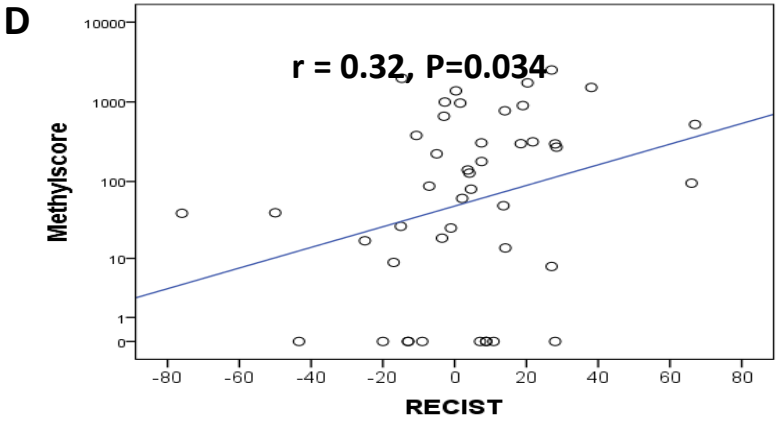
Ileana Dumbrava, Janku 2018

MUTATION AGNOSTIC APPROACH: Methylation (>9,000 CpG sites) in cfDNA and outcomes in advanced cancers (breast, CRC, NSCLC, melanoma)



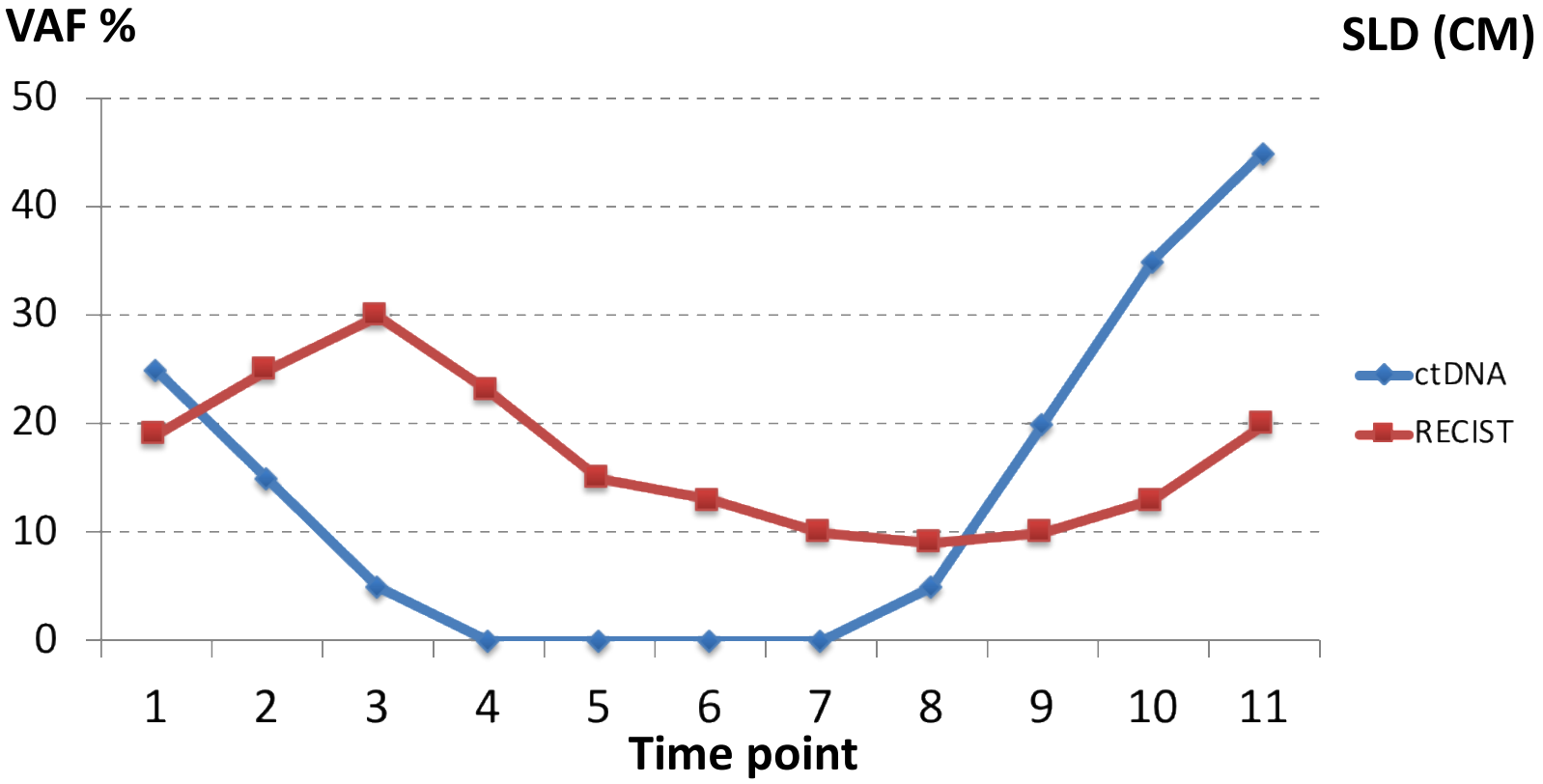




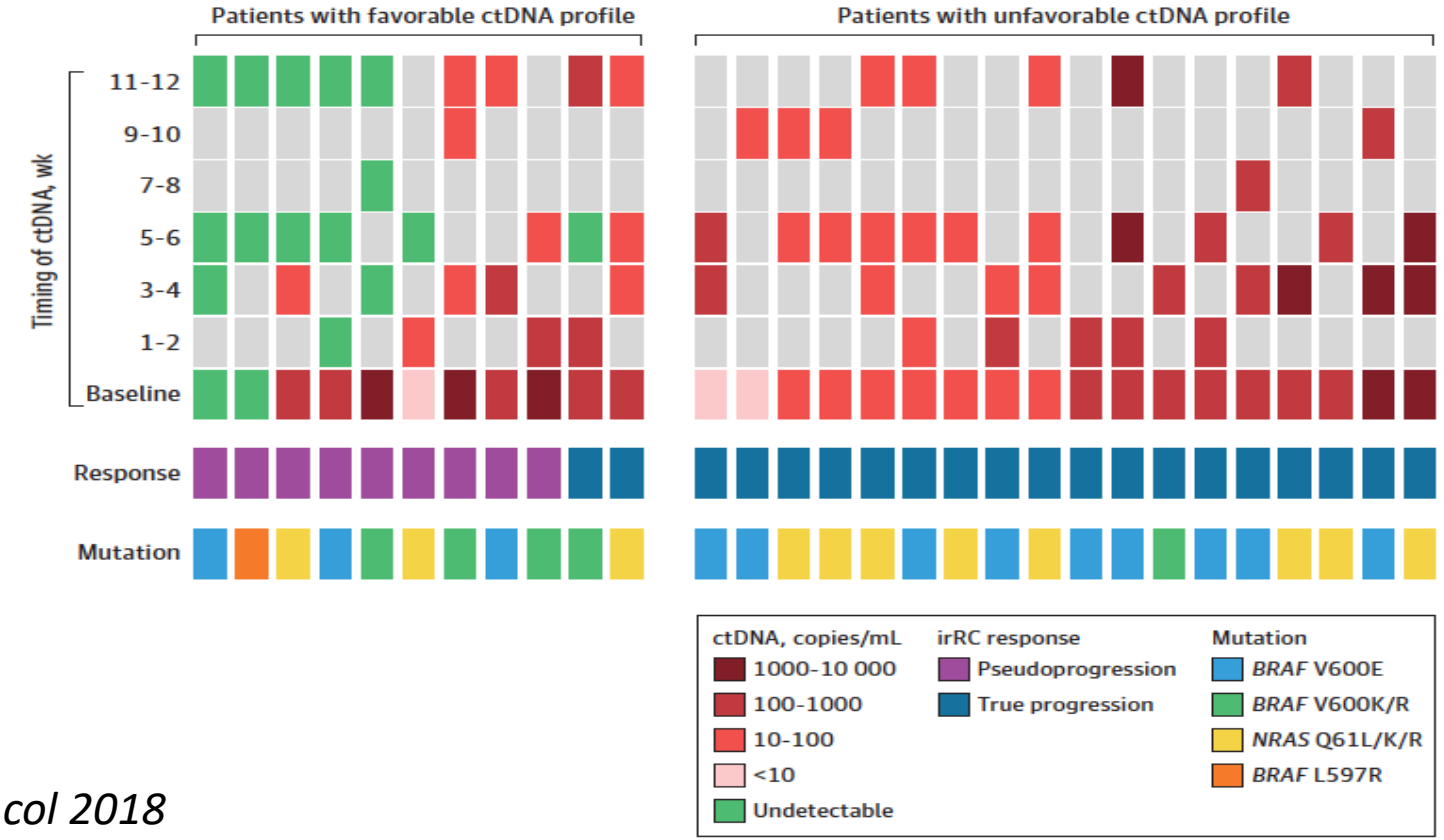


Liu, Toung, Jassowicz, Janku. Ann Oncol 2018

Concept of Dynamic Tracking of Circulating Tumor DNA to Detect Pseudoprogression

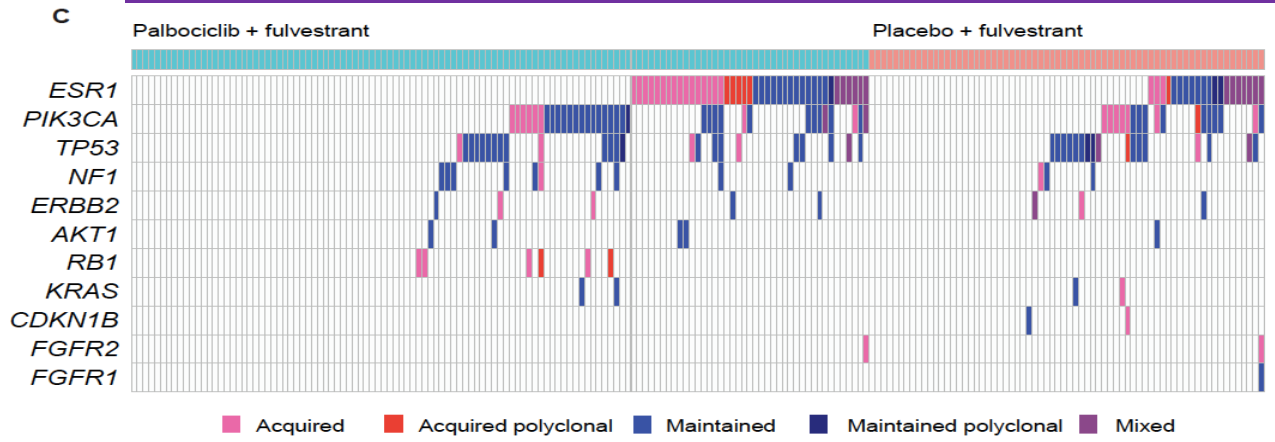


Association Between Changes in Plasma-Derived Mutated Cell-Free DNA and Pseudoprogression to PD1 Antibodies in Melanoma

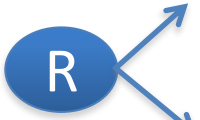


Lee JH. JAMA Oncol 2018

Clonal Evolution in ctDNA and Therapeutic Resistance in HR+ Breast Cancer



Phase III Study



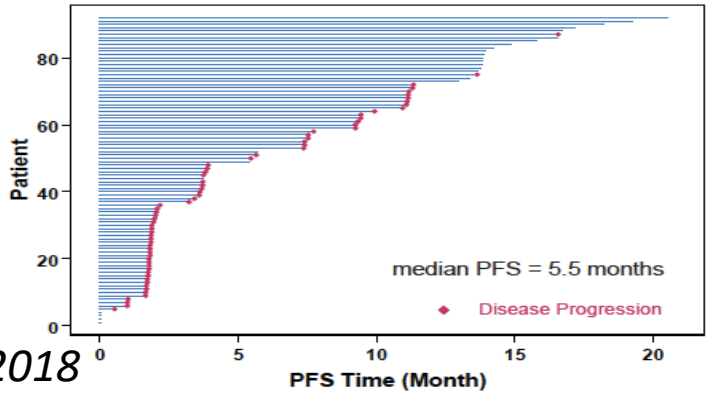
Fulvestrant
Palbociclib

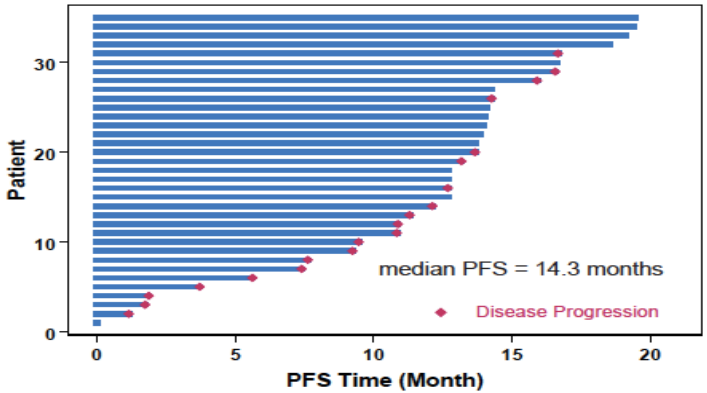
Fulvestrant
Placebo

No acquired mutation

p = 0.0018

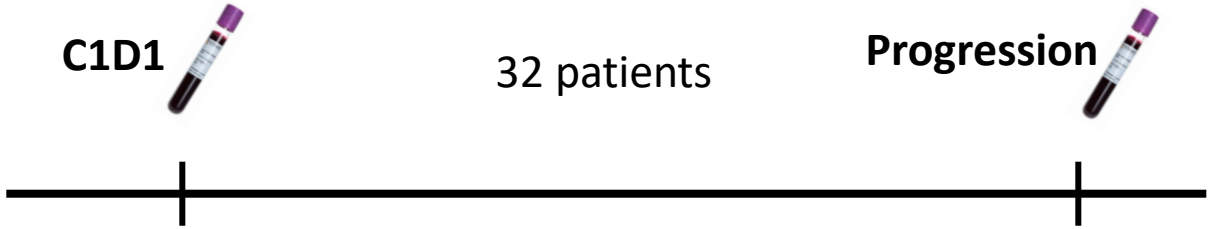
Acquired mutation





O'Leary Cancer Discov 2018

Monitoring of dynamic changes and clonal evolution in circulating tumor DNA from patients with *IDH*-mutated cholangiocarcinoma treated with IDH inhibitors



Agreement plasma vs. tissue *IDH* mutations

-**Droplet digital PCR**: 84%

-**NGS**: 83%

Agreement plasma vs. tissue other mutations

- **Droplet digital PCR:** 60%

- **NGS**: 100%

Time-to –treatment failure: NGS

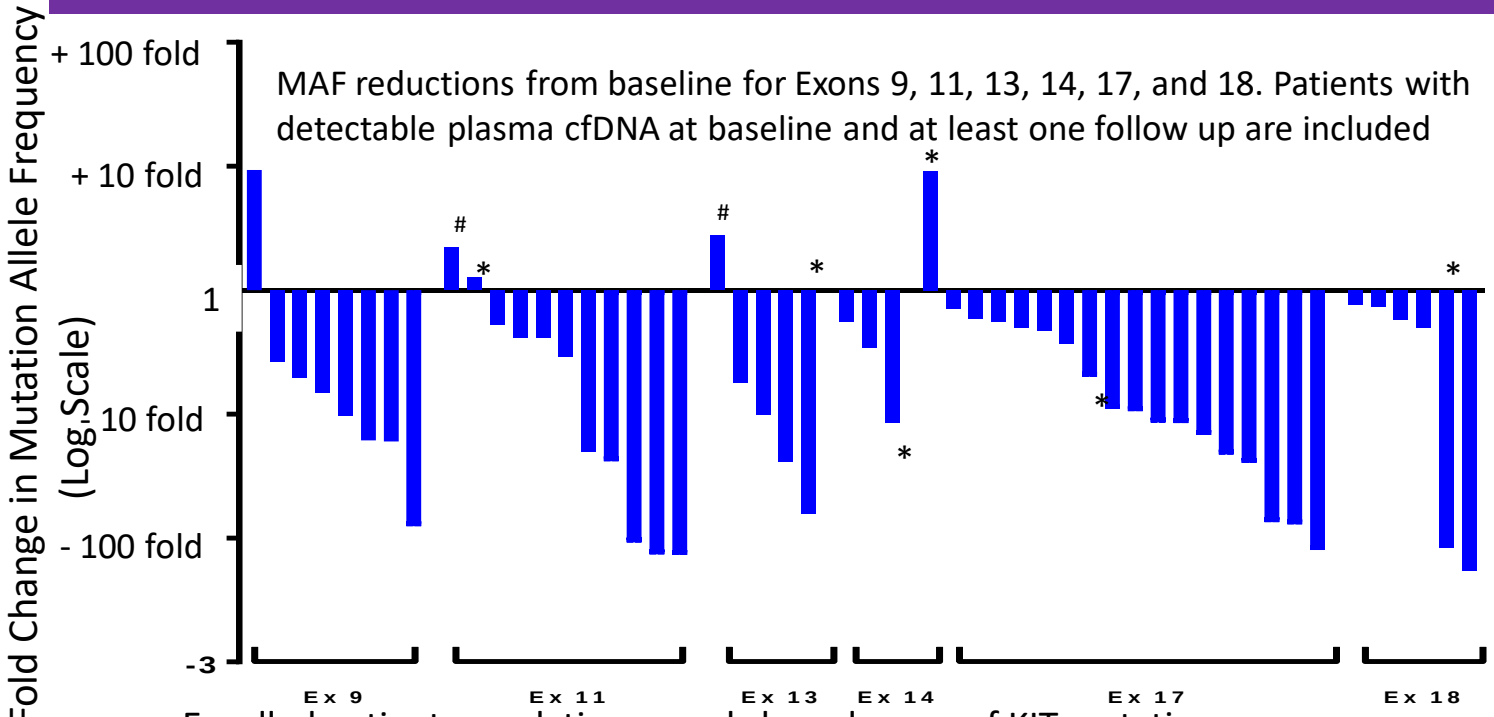
ctDNA low - 3.6 months

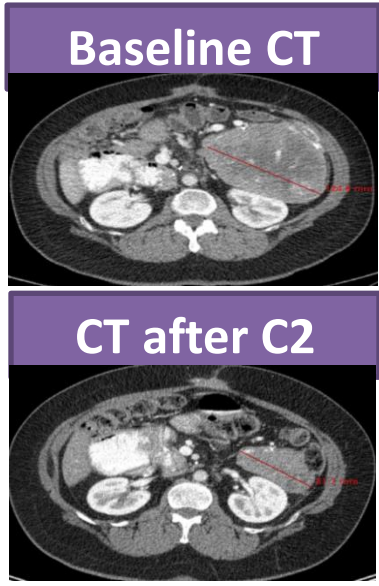
ctDNA high - 1.8 months (p=0.01)

Most frequent **emergent** aberrations detected at **progression** were ***ARID1A*** mutations (25%) and ***TP53*** mutations (25%)

Lapin, Huang, Raymond, Janku

Changes in *KIT*-mutated Plasma cfDNA as a PD Marker in Heavily Pretreated GIST Treated with Allosteric KIT inhibitor DCC-2618



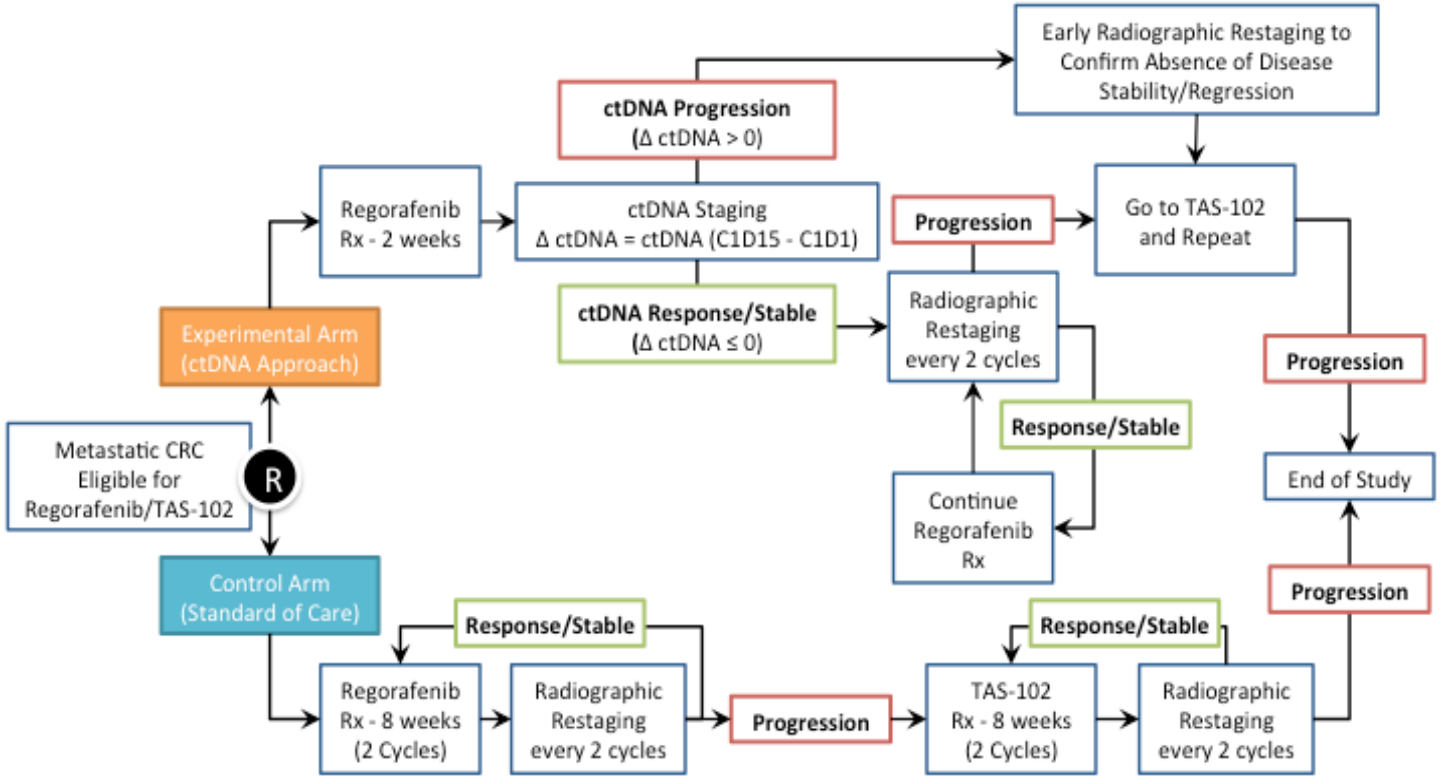


- Enrolled patient population reveals broad range of KIT mutations
- DCC-2618 leads to reductions in MAF in cfDNA across all exons associated with resistance
- Treatment decisions were made based on disease control and not on changes in MAF

Janku et al. ENA 2016, ASCO 2017, ESMO 2017

#Patient in first dose cohort, *Patient represented with mixed histology

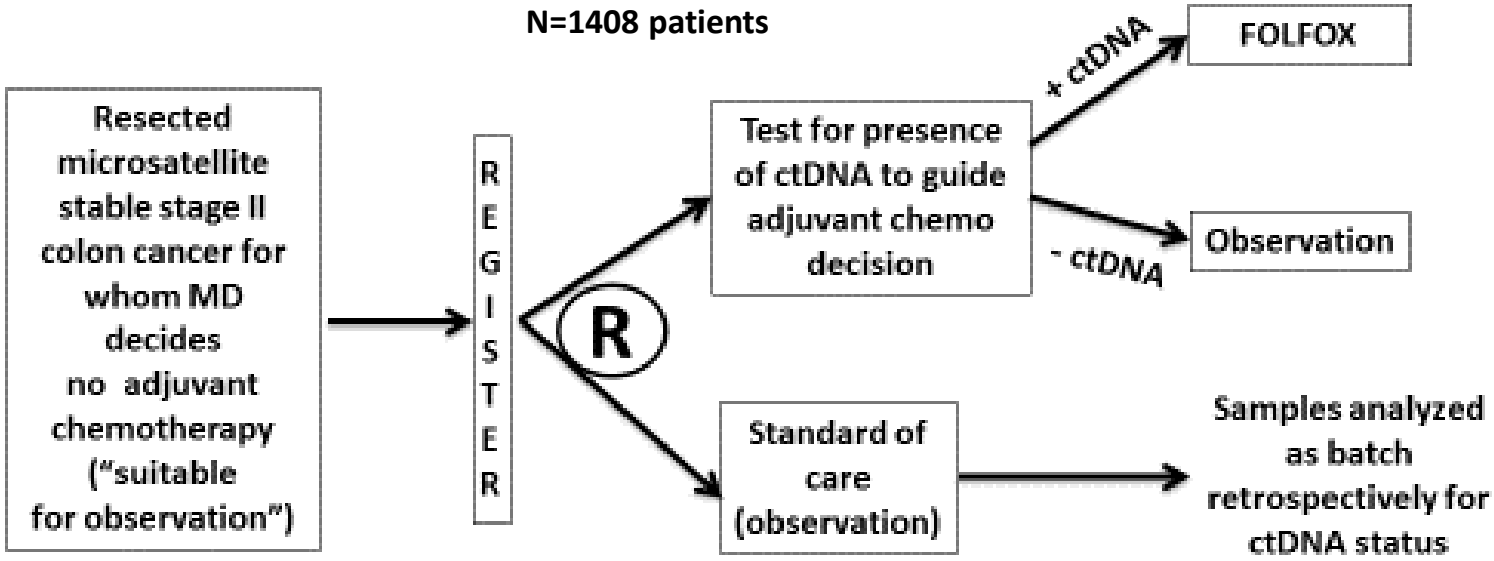
TACT-D schema



Currently enrolling at MD Anderson as a single-site study

Patients can have treatment at home with ctDNA kits mailed to GuardantHealth

NRG GI-005 schema

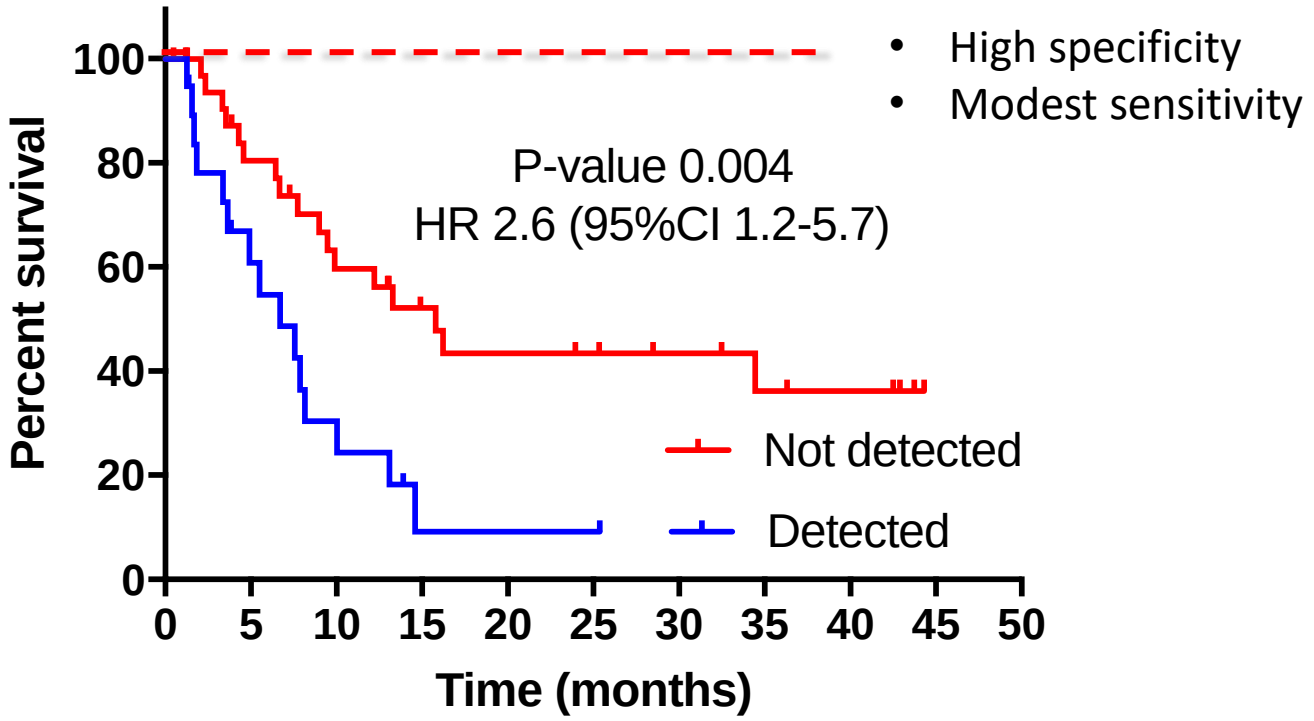


Protocol approved by CTEP/CIRB, with expected activation by 5/2019 across all US and Canadian cooperative groups.

GuardantHealth LUNAR assay – assessing combination of somatic mutations and CRC-specific methylation profiles- will be utilized for study conduct.

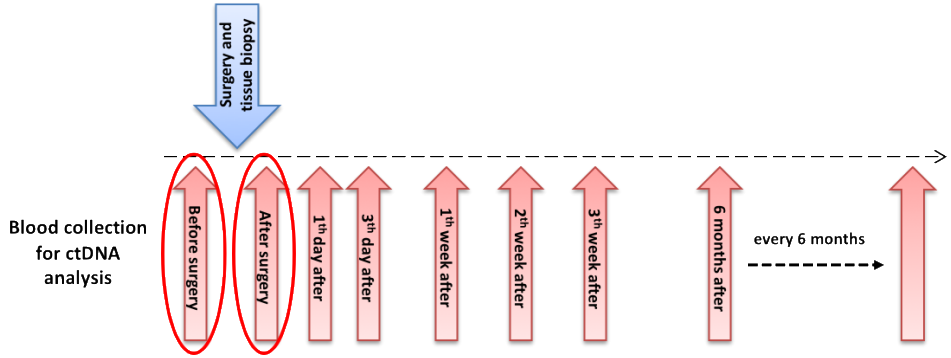
PI: V Morris (MD Anderson)

NGS in Post-Operative Recurrence Detection in Stage IV Colorectal Cancer



Overman ASCO 2018

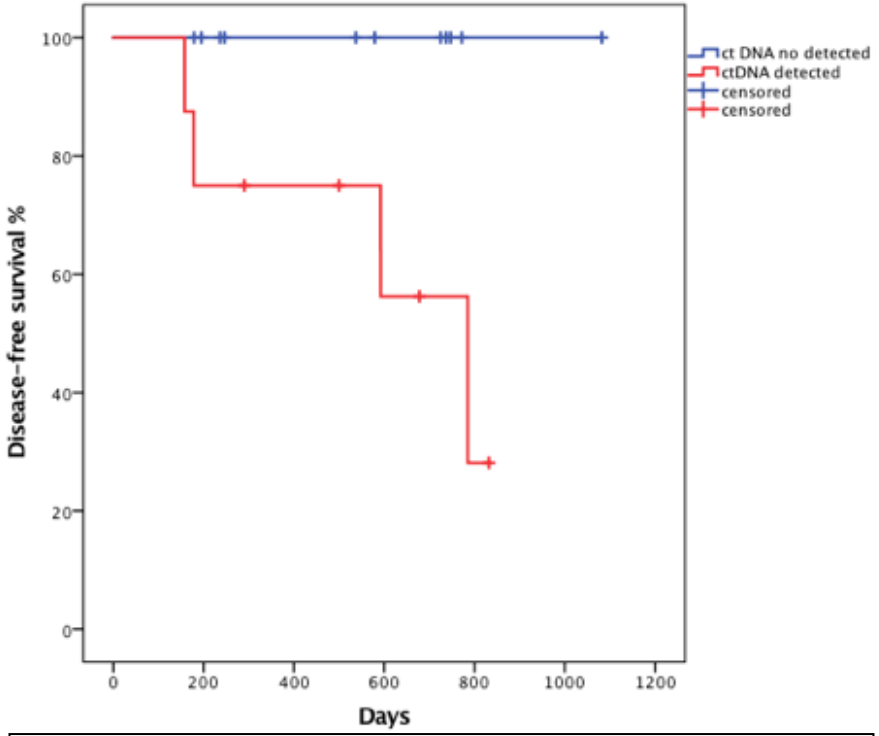
Ultrasensitive Detection of Circulating Tumor DNA Identifies Patients in High Risk of Recurrence in Early Stages Melanoma (N=23)



***BRAF*^{V600E} mutations in ctDNA and melanoma recurrence in 19 patients with available data**

Category	Number	Disease Recurrence (%)	P value
***BRAF*^{V600E} in tissue**	23	4 (17)	-
***BRAF*^{V600E} in ctDNA before surgery**	11	2 (18)	NS
No ***BRAF*^{V600E} in ctDNA before surgery**	8	2 (25)	
***BRAF*^{V600E} in ctDNA after surgery**	8	4 (50)	**0.02**
No ***BRAF*^{V600E} in ctDNA after surgery**	11	0 (0)	

Polivka, Huang, Janku. ESMO 2019



Patients with ctDNA in samples collected after surgery had shorter Disease-free survival than patients without ctDNA (P=0.03)

Methods of ctDNA detection

Somatic alteration sequencing

1. Most studied

2. Can detect targets for cancer therapy

3. Lower sensitivity in the absence of recurrent alterations

4. Lower sensitivity in early stages

Detection methylation changes

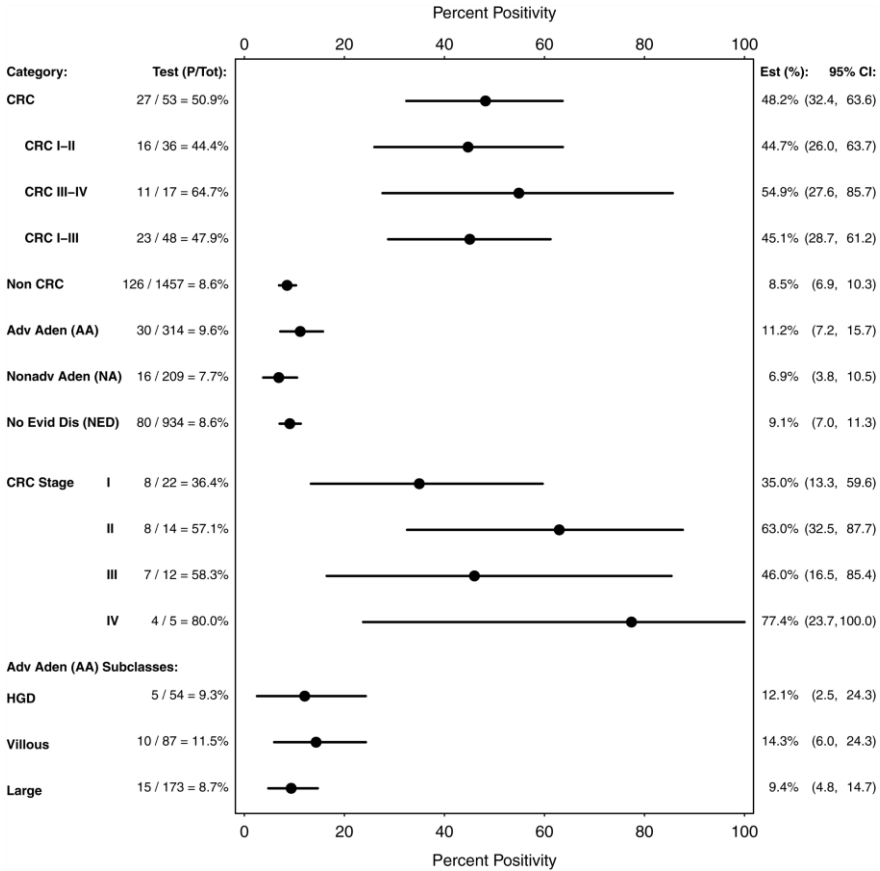
1. Tissue and cancer type specific

2. Independent on somatic alterations

3. High DNA degradation during bisulfite conversion

Testing for mSEPT9 in plasma cfDNA in subjects in colorectal cancer screening

7,941 subjects undergoing screening colonoscopy



		Epi proColon		
		Negative	Positive	Total
Colonoscopy	CRC	14	30	44
	Non-CRC	1182	318	1500
	Total	1196	348	1544

Sensitivity = 68.2% (95% CI, 53.4–80.0)
Specificity = 78.8% (95% CI, 76.7–80.8)

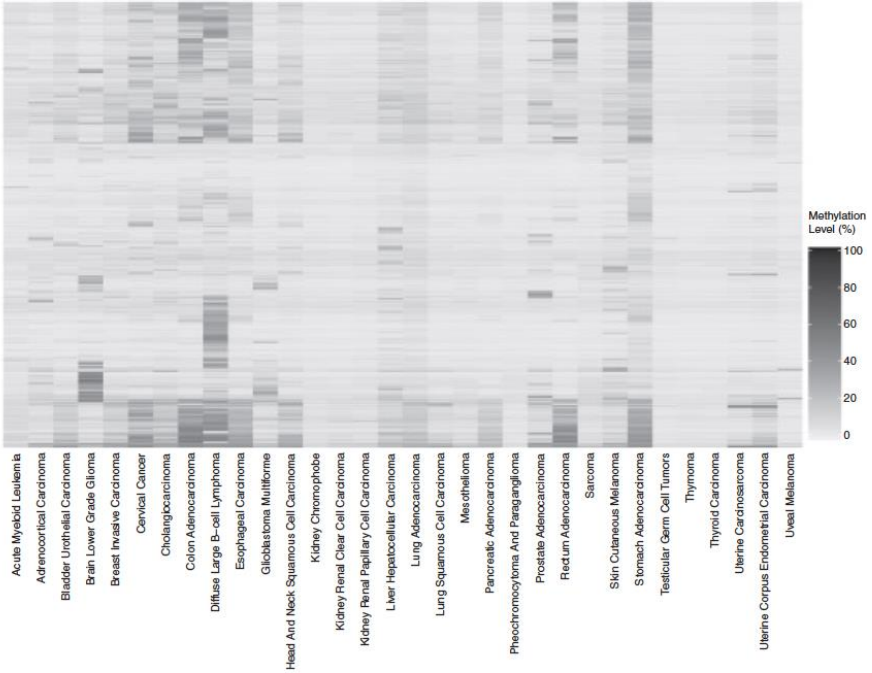
Negative Predictive Value (NPV) = 99.7% (CI, 99.6–99.8)
Positive Predictive Value (PPV) = 2.4% (CI, 2.0–3.0)

Epi proColon test approved by FDA in 2016

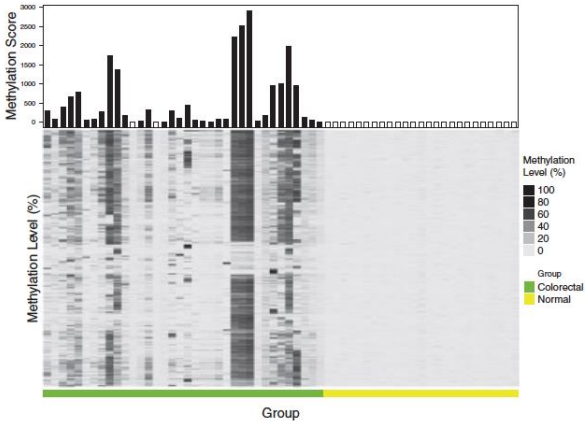
Church Gut 2014

Targeted Methylation Sequencing (9,223 CpG sites) of Plasma cfDNA in Advanced Cancer

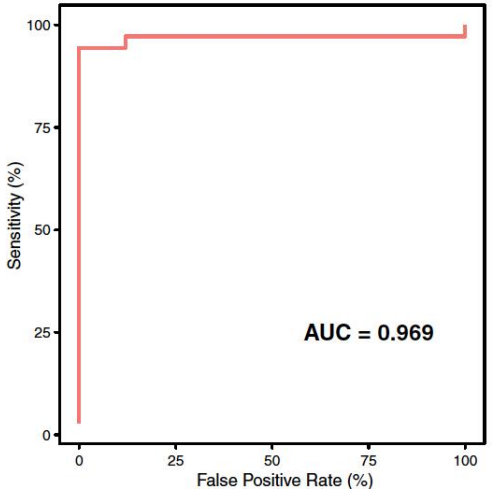
Heat map of methylation profiling in 32 cancers based on TCGA



Assay performance in plasma cfDNA samples from patients with colorectal cancer and healthy controls



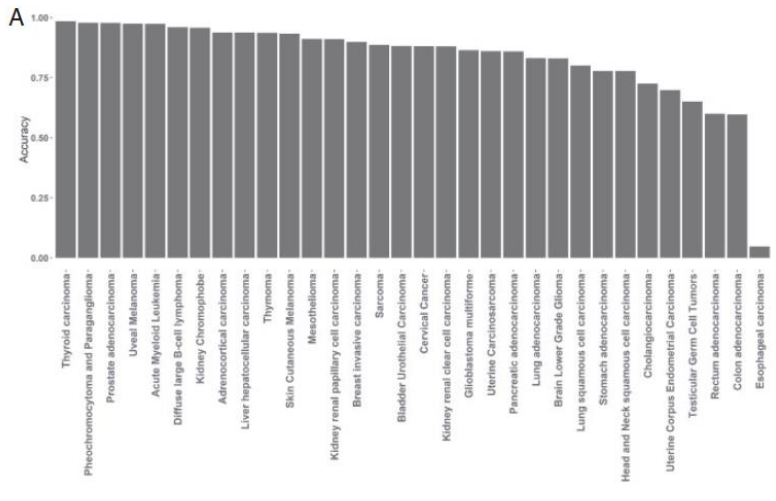
ROC curve for colorectal cancer



Liu, Toung, Jassowicz, Janku. Ann Oncol 2018

Targeted Methylation Sequencing (9,223 CpG sites) of Plasma cfDNA in Advanced Cancer

Predicting tissue of origin in 32 cancer types in TCGA set (overall accuracy 83.5%)



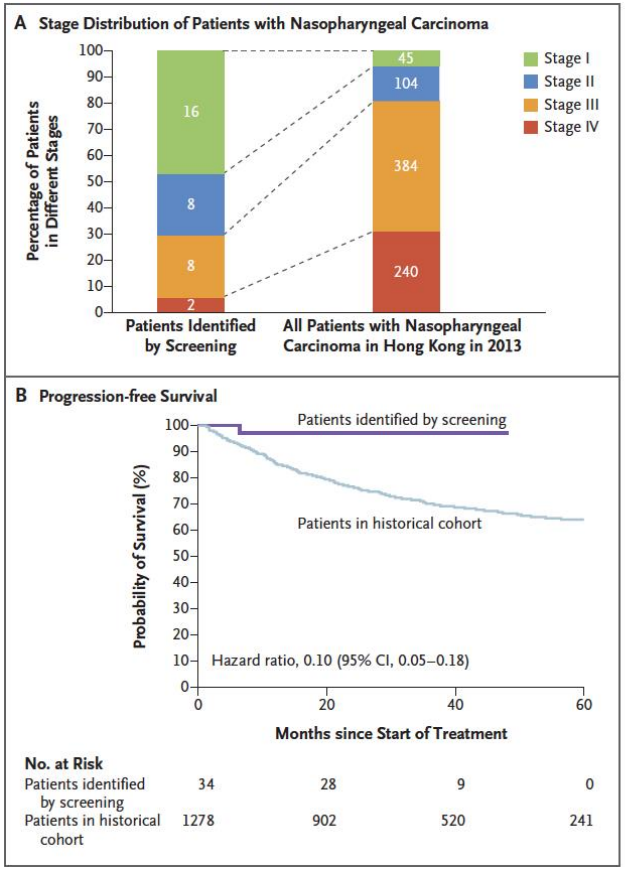
Liu, Toung, Jassowicz, Janku. Ann Oncol 2018

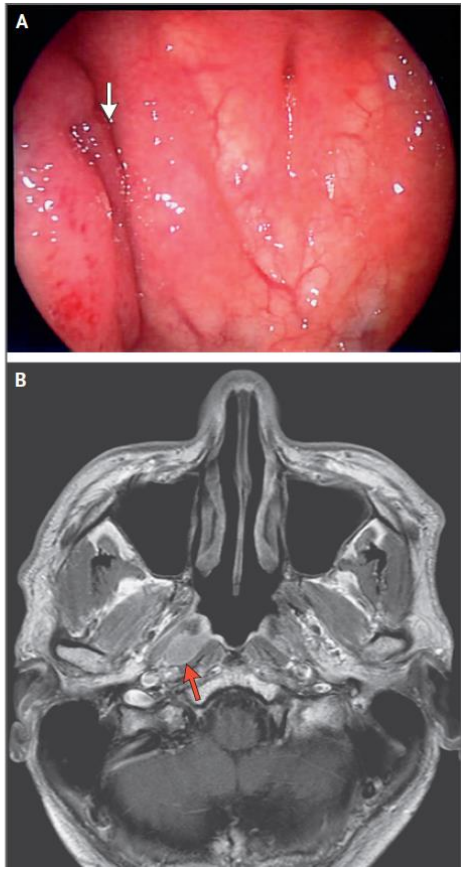
Clinical Validation in Breast Cancer, Colorectal Cancer, Lung Cancer and Melanoma

Plasma samples collected from patients off-therapy					
		Actual class			
		Breast (n=12)	Colorectal cancer (N=27)	NSCLC (N=18)	Melanoma (N=11)
Predicted Class[1]	AML	2	0	0	0
	Breast	8	0	0	0
	Colorectal	1	23	0	0
	Cholangiocarcinoma	0	0	0	1
	Esophageal	0	0	0	1
	Liver	0	1	1	1
	Lung	0	0	9	0
	Lymphoma	0	1	0	0
	Melanoma	0	0	0	5
	Pancreatic	0	1	0	0
	Sarcoma	0	0	1	1
	Stomach	0	0	0	0
	Not cancer	1	1	7	2
Total		12	27	18	11
Accurate classification of cancer irrespective of cancer type		91.7%	96.3%	61.1%	81.8%
		86.8%			
Accurate to classification of cancer type (out of set classified as cancer)		72.7%	88.5%	81.8%	55.6%
		76.3%			

[1] Each sample was evaluated against 24 cancer type signatures. Cancer types to which no samples were as signed are not listed in this table.
[2] Non-small cell lung cancer.

Plasma EBV DNA in Screening of Nasopharyngeal Carcinoma





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CONCLUSIONS

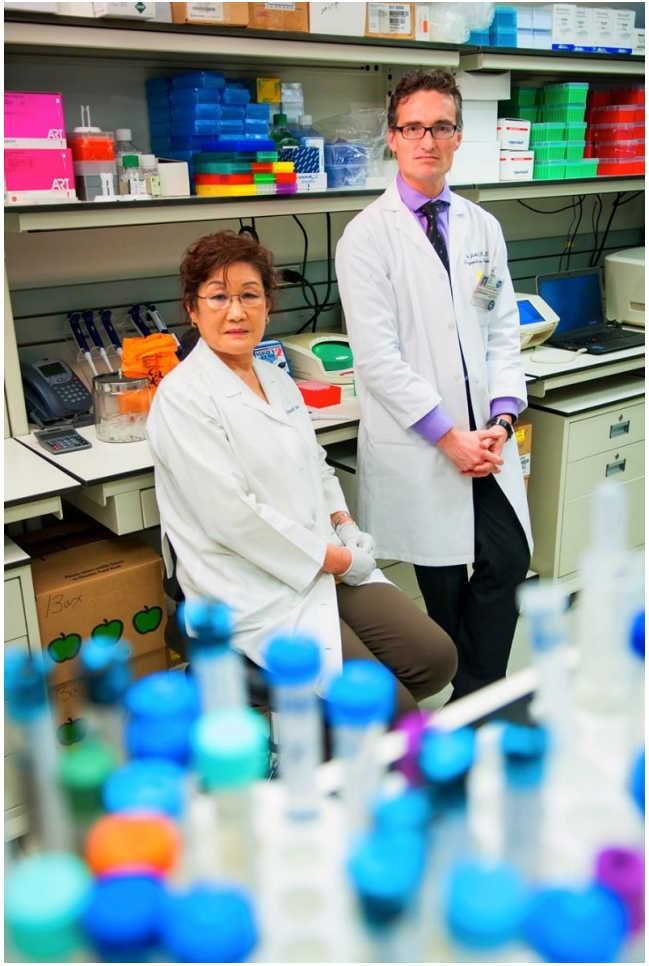
- Liquid biopsies help to further advance personalized targeted therapy and immunotherapy by offering a source of easily obtainable material for mutation analysis.

- Liquid biopsies have a potential to be used in efficacy assessment especially if imaging cannot be used or the interpretation is problematic.

- Liquid biopsies can be used for monitoring of molecular profile and clonal evolution in patients undergoing cancer therapy to detect mechanisms of resistance.

- Liquid biopsies can be used to address pharmacodynamic endpoints in clinical trials.

- Liquid biopsies have potential to determine prognosis, early detection , detect early recurrence and disease progression.



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OUR PATIENTS AND THEIR FAMILIES