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7TH ANNUAL PUERTO RICO
WINTER CANCER SYMPOSIUM 2018
"Beating Cancer by Applying Individualized Therapy"

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7TH PUERTO RICO WINTER CANCER SYMPOSIUM

LIQUID BIOPSY IN THE MANAGEMENT OF LUNG CANCER

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March 24, 2018

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Edgardo S. Santos, M.D., FACP

EGFR and ALK in NSCLC

&

Liquid Biopsy in the Management of Lung Cancer

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

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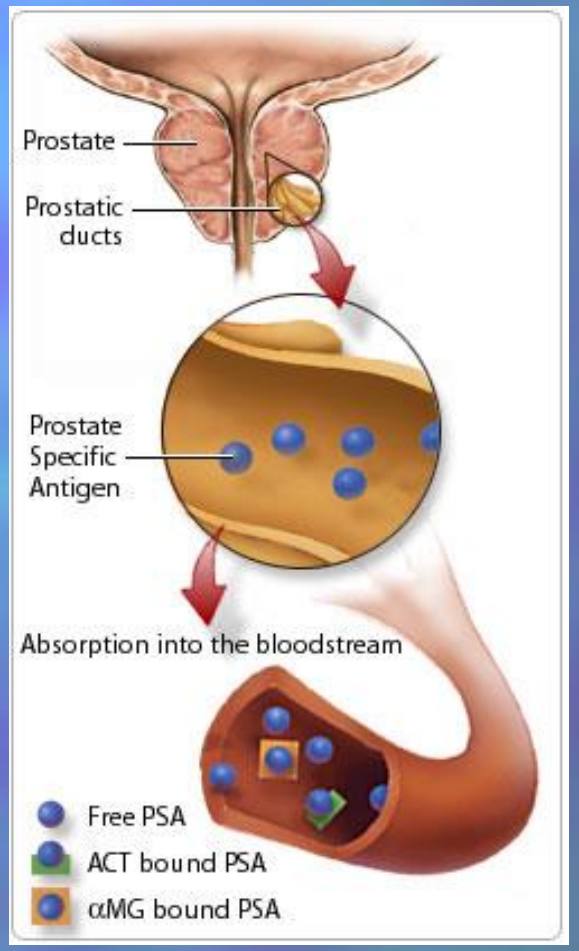
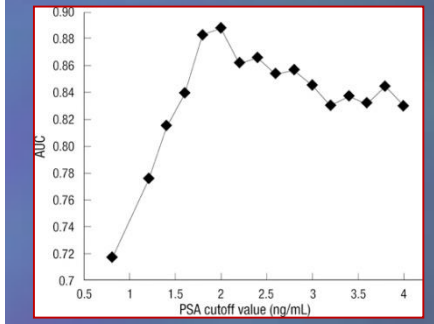
The Medical Educator Consortium

7th Annual Puerto Rico Winter Cancer Symposium

The concept of Non Invasive Test....



Is a Reality



What can it offer?

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FACTS IN LIQUID AND TUMOR BIOPSIES

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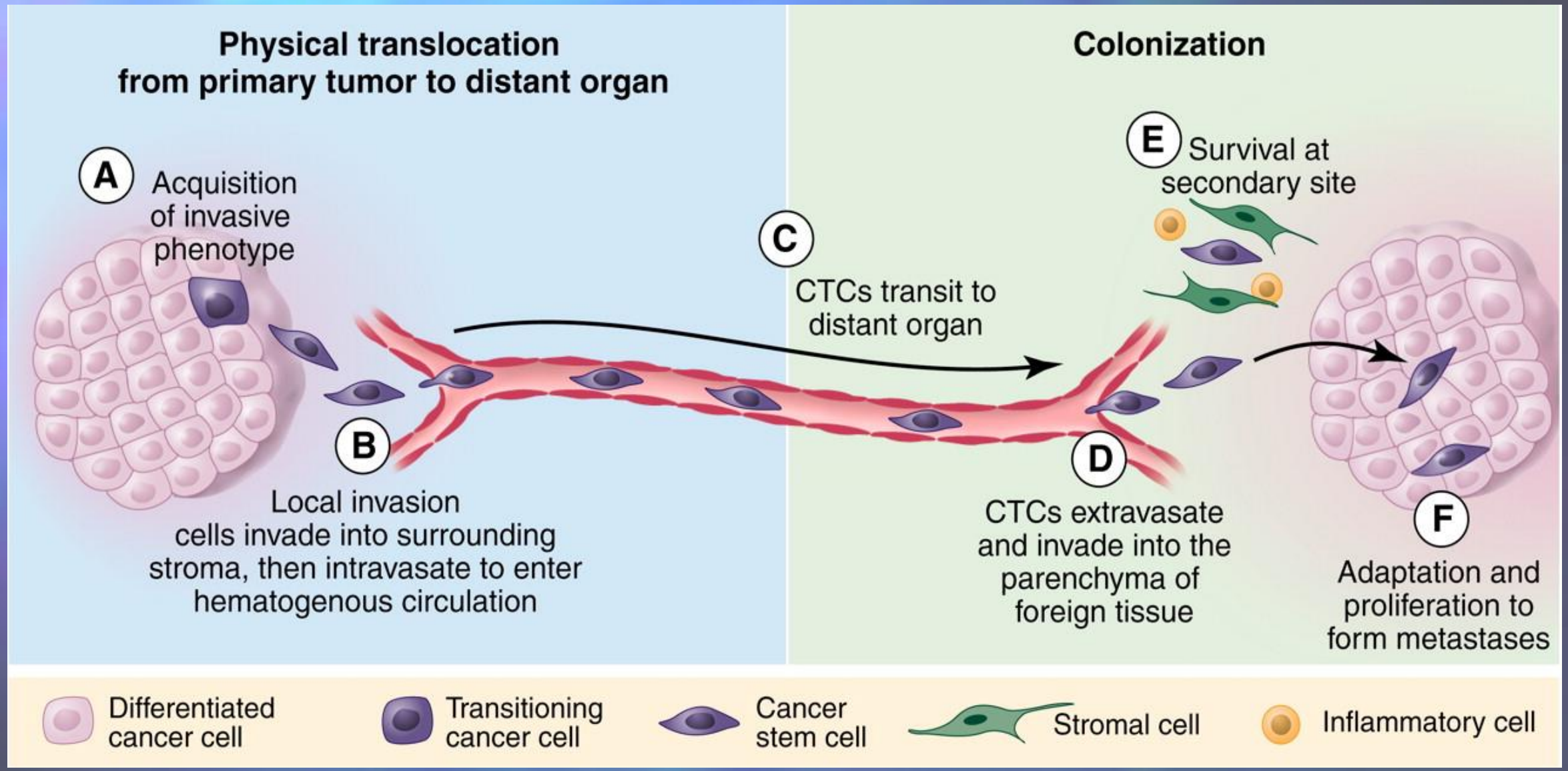
Beginning of Concept of Liquid Biopsy

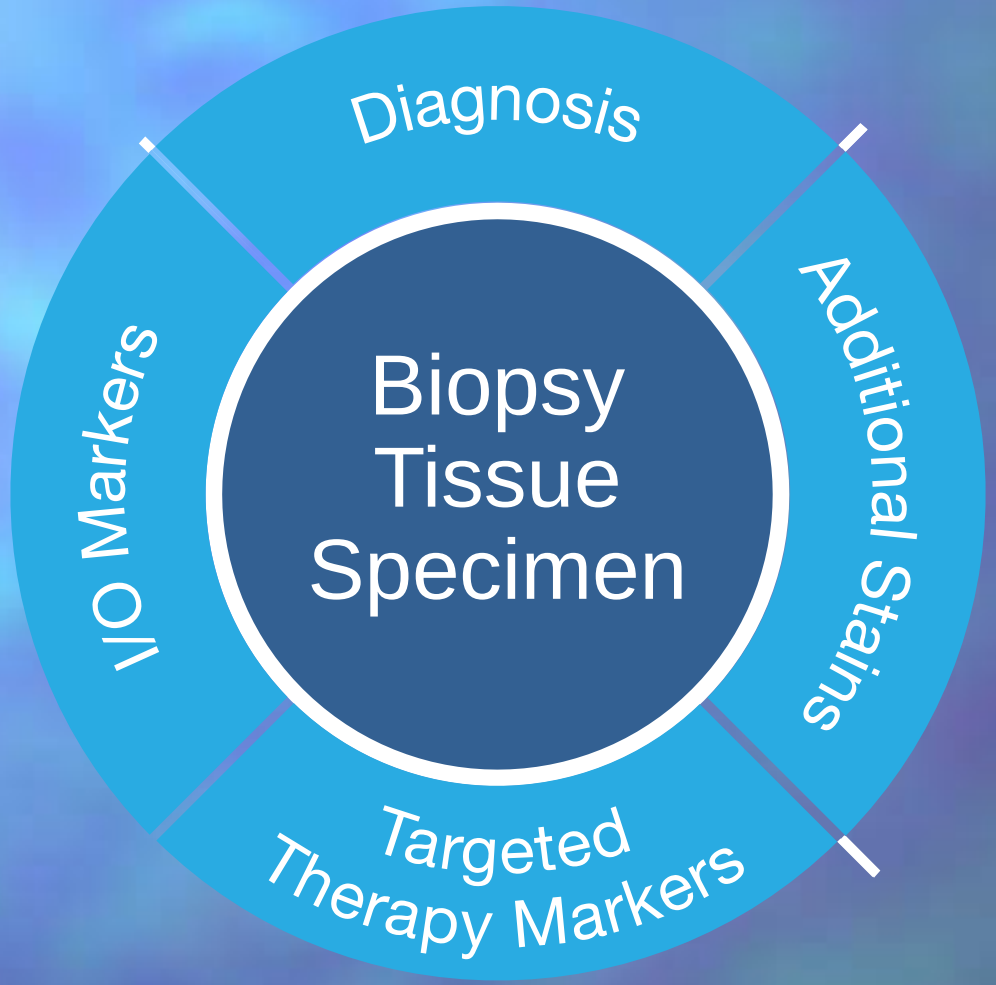


Why the need for Liquid Biopsy?

- **Tumor biopsies** of both primary and metastases is ***often difficult*** **for practical reason (a lot of tumor volume is needed)**
- **Tissue** biopsy is **not always representative** for the all tumor (especially for fine-needle biopsy) → ***Tumor Heterogeneity***
- **Lack of sensitive and specific biomarker** for tumor ***early detection and monitoring*** (treatment response, relapse, etc…)
- The concept of ***tempo-spatial heterogeneity***

Increasing Demands on the Tissue Specimen

How often do you get all the information you need?



How often do you have to prioritize one over another?

Tissue Can Be Insufficient for Biomarker Profiling

25-60%
of lung biopsy specimens

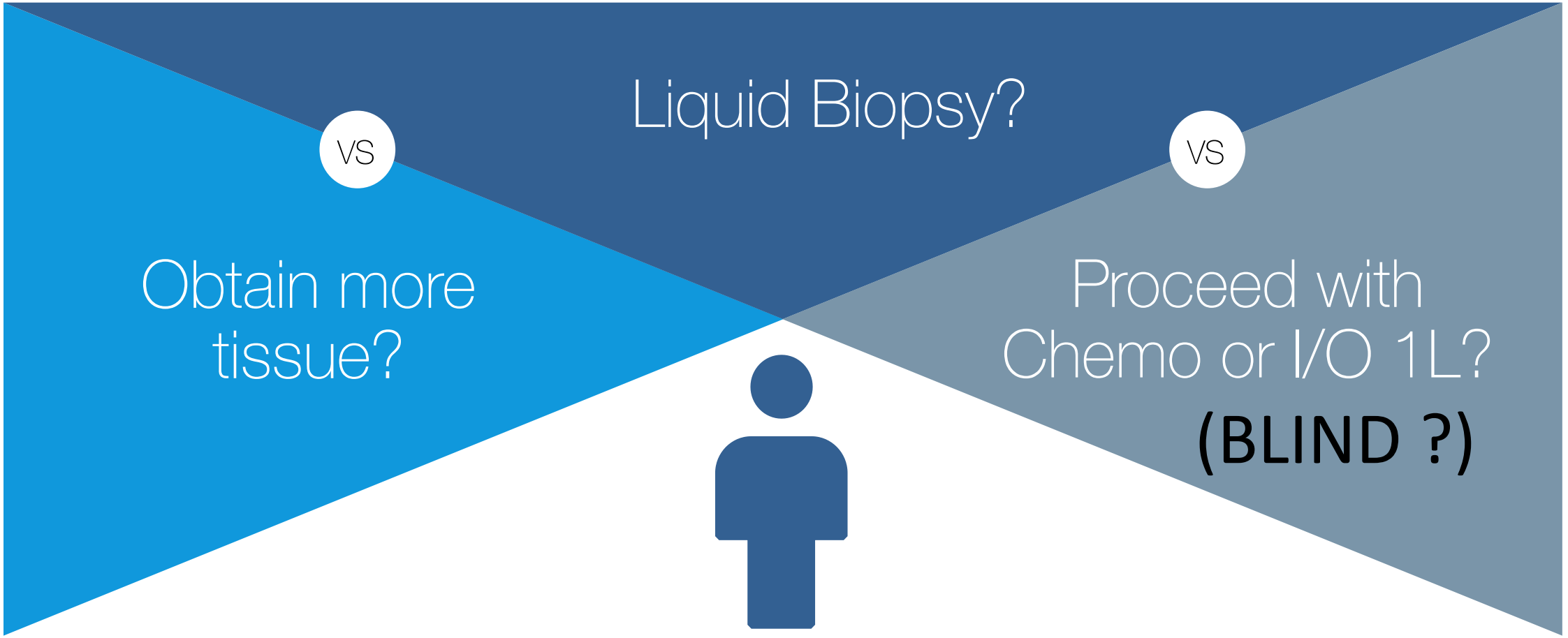
23%
pan-cancer clinical cohort

30-50%
of bone biopsy specimens

Your experience?

Kris et al 2014 JAMA; Hagemann et al. 2015 Cancer; Villaflor et al. 2016 Oncotarget; Thompson et al. 2016 Clin Canc Res; Meric Bernstam et al. 2015 JCO; Hilton et al 2011 BCRT; Zheng et al. 2016 Cancer Cytopathology

The Challenge When Tissue is Insufficient



Guidelines & Recommendations by ASCO-NCCN-AMP/CAP/IASLC Include Liquid Biopsy

"If repeat biopsy is not feasible, plasma biopsy should be considered"

"Testing should be conducted as part of broad molecular profiling"

NCCN 2017 NSCLC Practice Guidelines[1]

"In clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA (cfDNA)"

AMP/CAP/IASLC 2016 Draft Molecular Testing Guidelines for Lung Cancer[2]

"Even for patients who are able to undergo a traditional tissue biopsy, a liquid biopsy may be safer, quicker, and more convenient—and perhaps even more informative"

2017 **ASCO** Clinical Cancer Advances[3]

[1]NCCN Guidelines v. 5.2017 [2]AMP/CAP/IASLC Draft Molecular Testing Guidelines [3]Burstein et al. Journal of Clinical Oncology 2017

Multiple Tests Require Large Tissue Volume

Tumor Biopsy

Finite tissue

Histology

Cancer

≥2 slides

Anatomy

Adeno-carcinoma

≥1 slide

cMET

EGFR

5 µm tissue

BRAF

PI3K

FGFR

≥5 slides

IHC (ALK+)

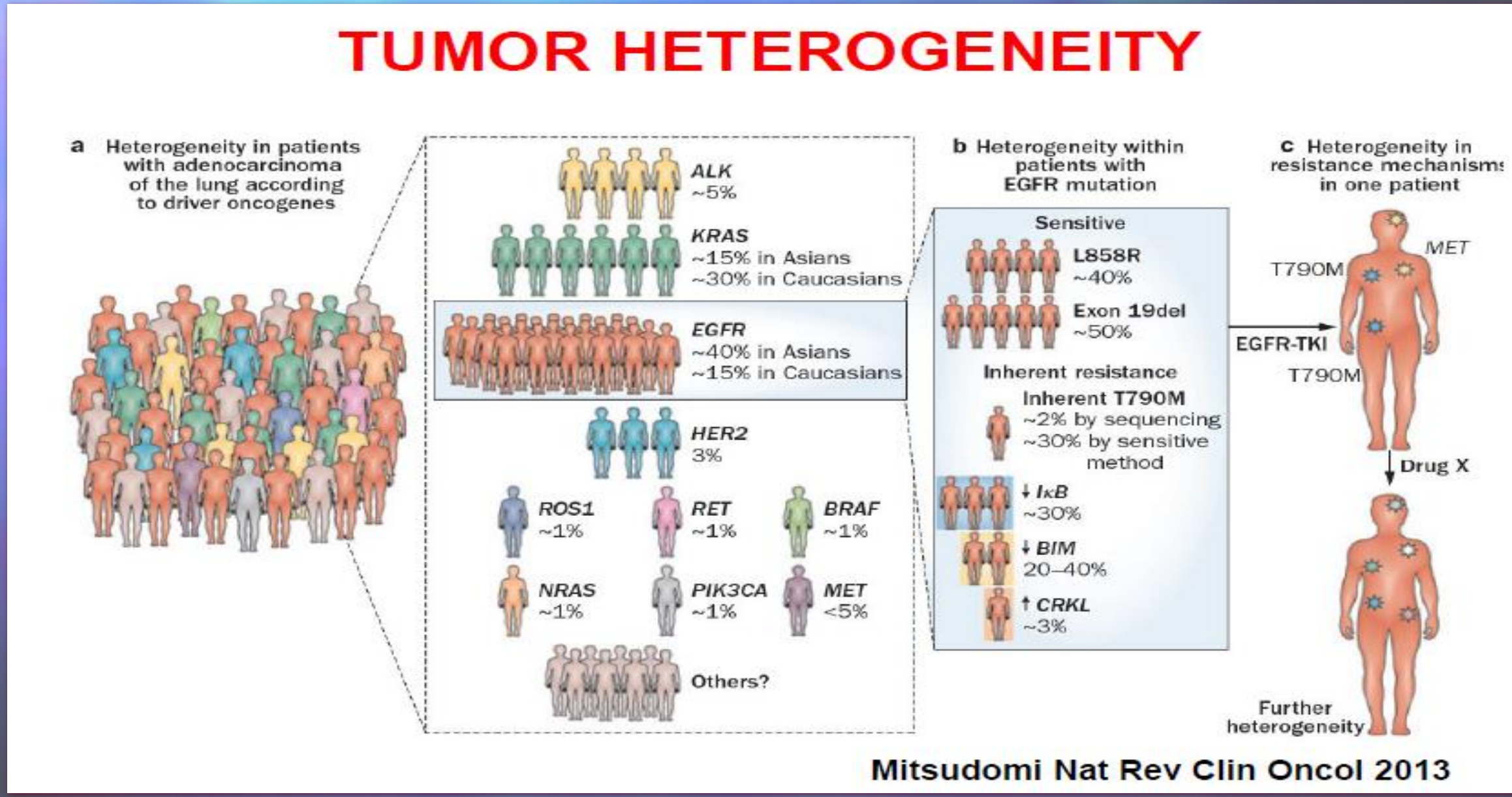
≥2 slides but no tissue

Confirmatory FISH

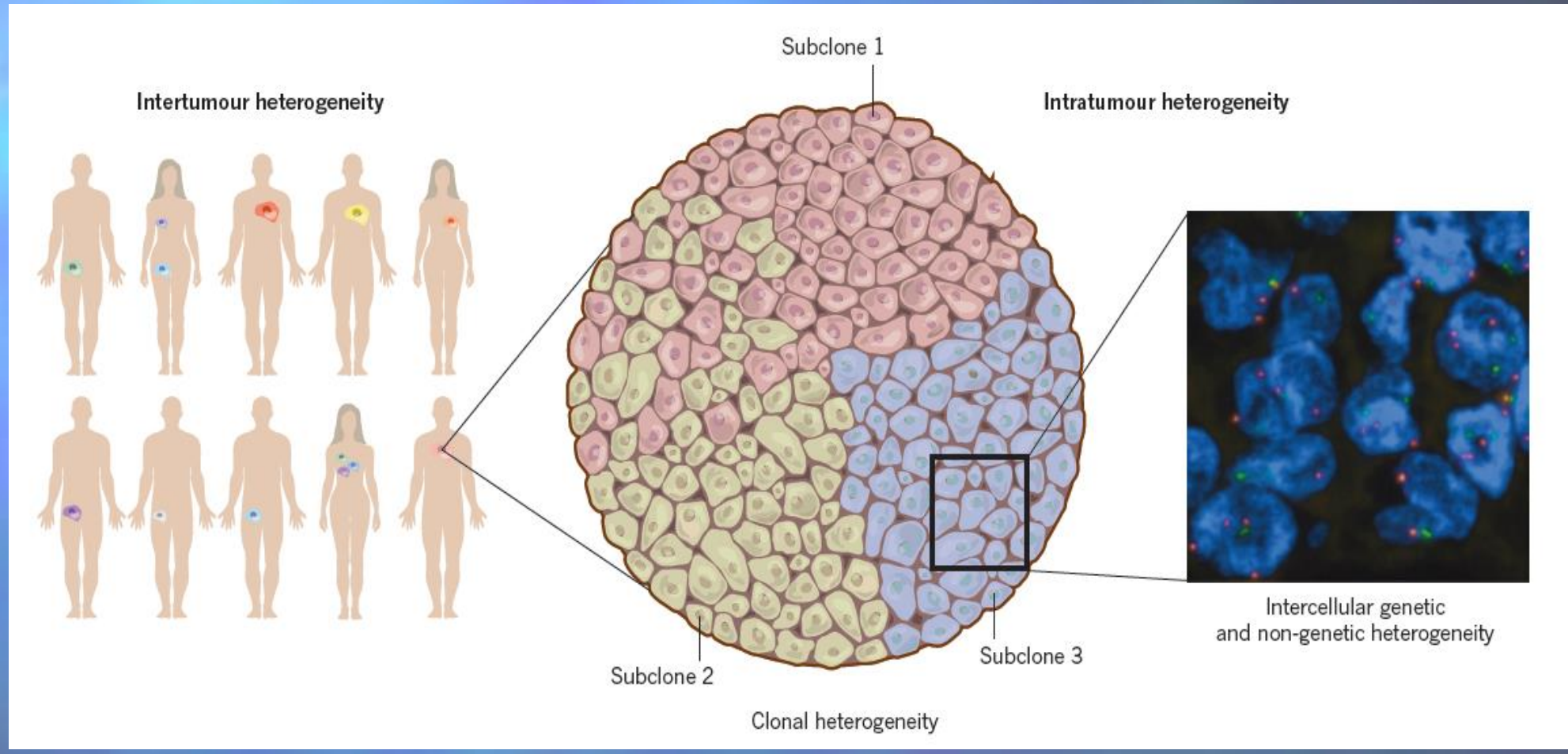
≥2 slides

RELAPSE

The efficacy of target therapy is affected by…

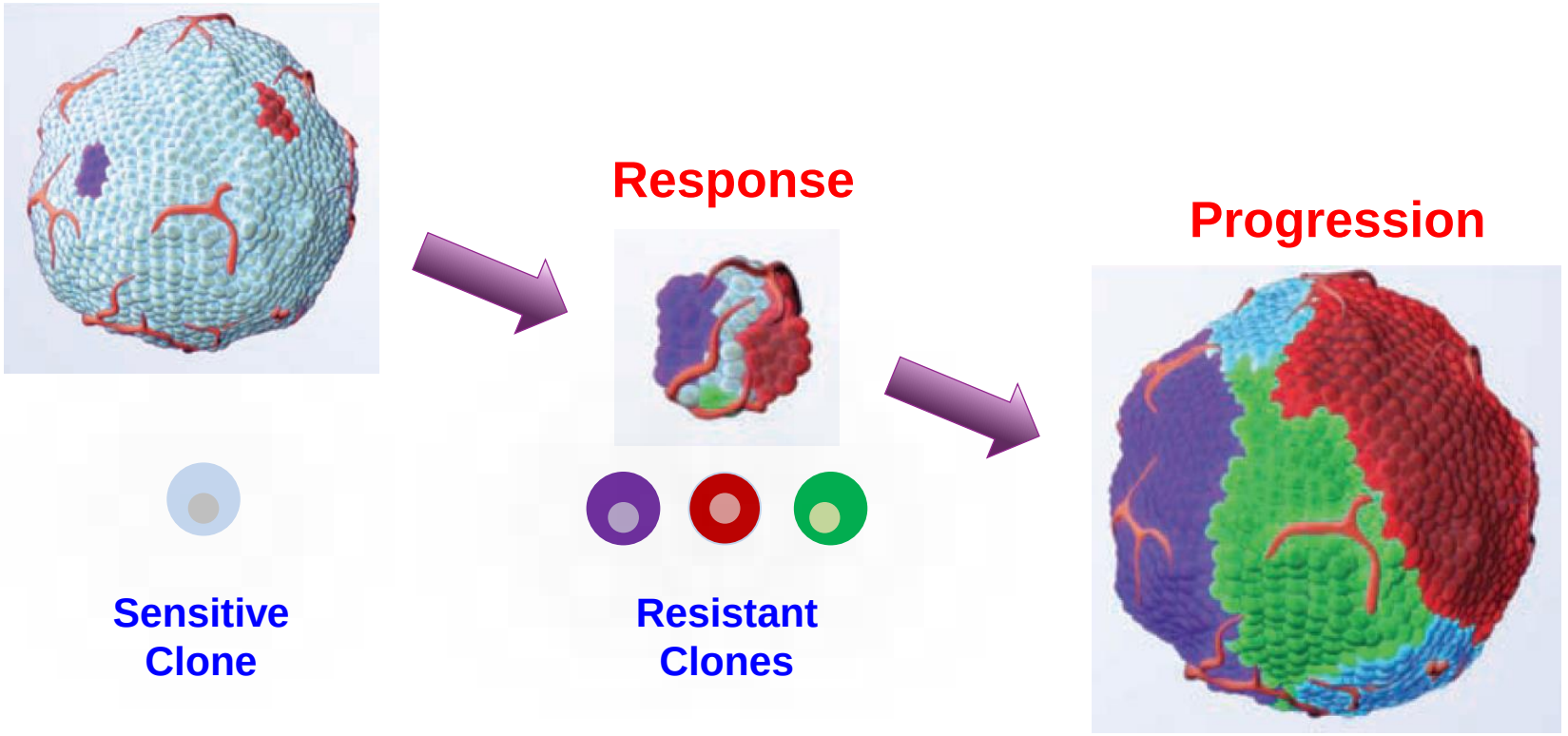


Inter-tumor and Intratumor heterogeneity



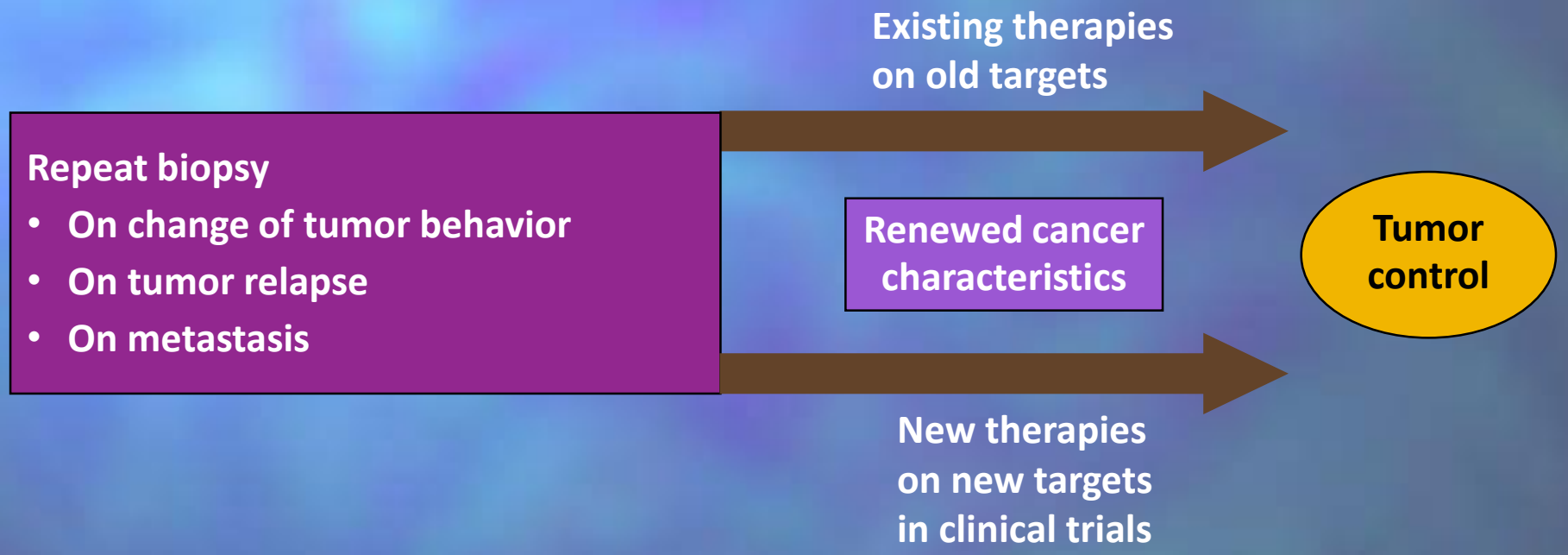
Identify biomarkers to define phenotypic similarity, yet genetically diverse, to guide treatment – Still A Challenge

Temporal Heterogeneity: Tumors Evolve Over Time to Develop Treatment Resistance



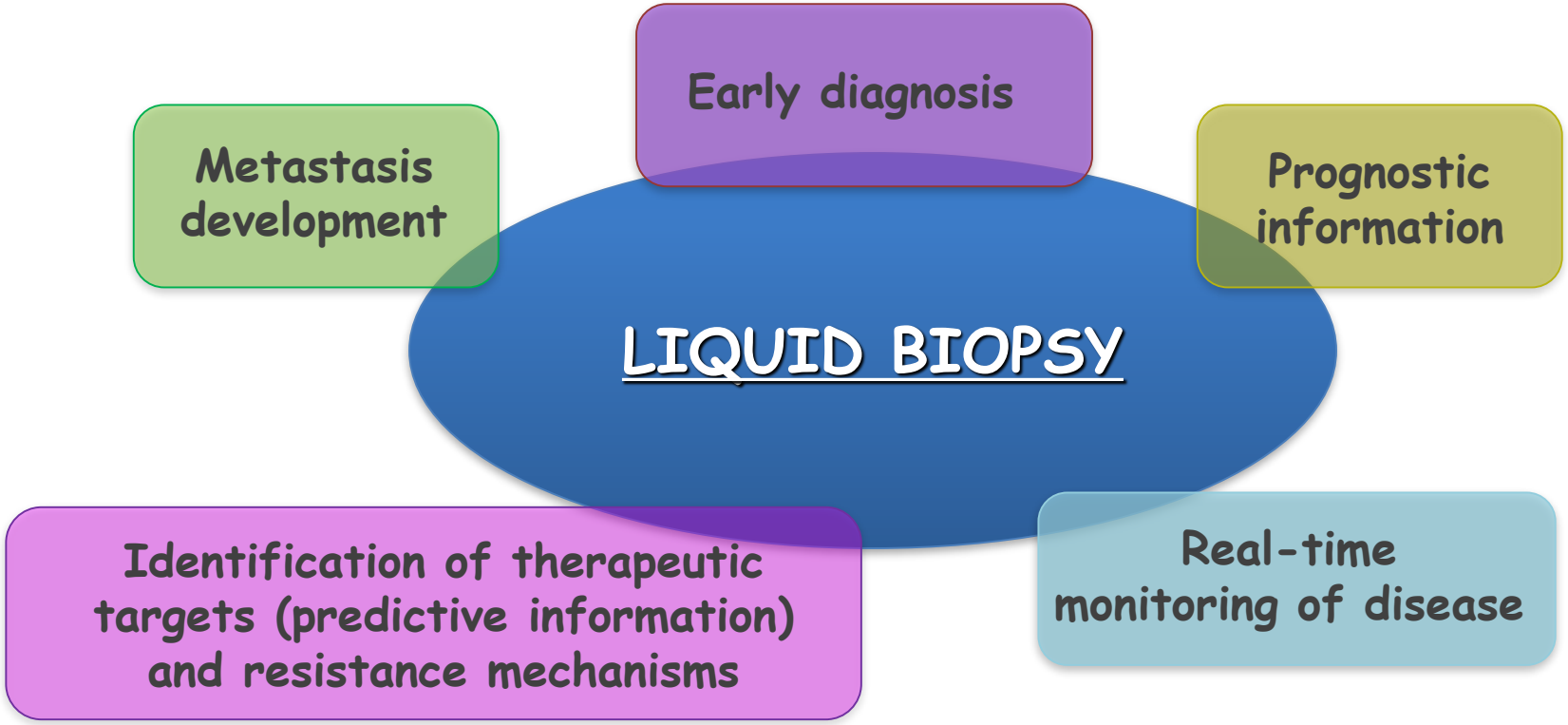
Re-Biopsy May Give Insight into Resistance Mechanisms

- Repeat biopsies can drive our understanding and could lead to future treatment
- They have the potential to predict future therapy response



Jekunen AP. J Oncol. 2015;2015:809835.

Liquid Biopsy: Multiple Potential Uses In Clinic

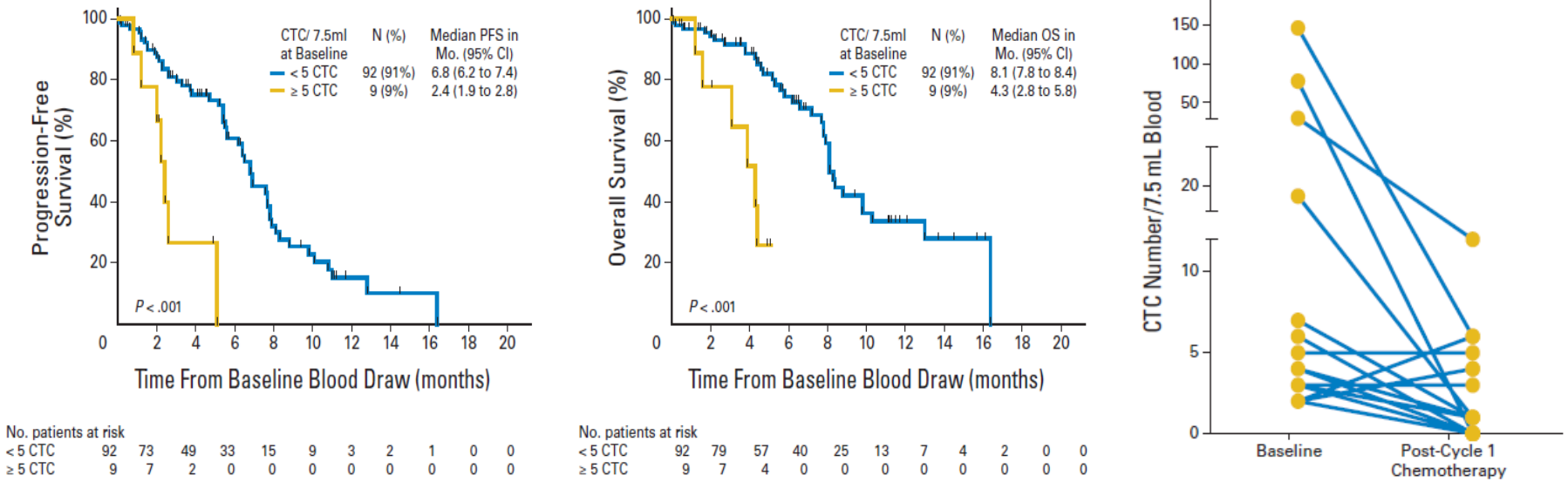


Prognostic Information

CTC clinical application:

Evaluation and Prognostic Significance of Circulating Tumor Cells in Patients With Non-Small-Cell Lung Cancer

- Single-center prospective study
- Blood samples for CTCs analysis from 101 NSCLC patients (untreated, stage III or IV) collected before and after one cycle of standard chemotherapy



Kaplan-Meier curves for PFS and OS of patients with < 5 and >5 CTC in 7.5ml at baseline

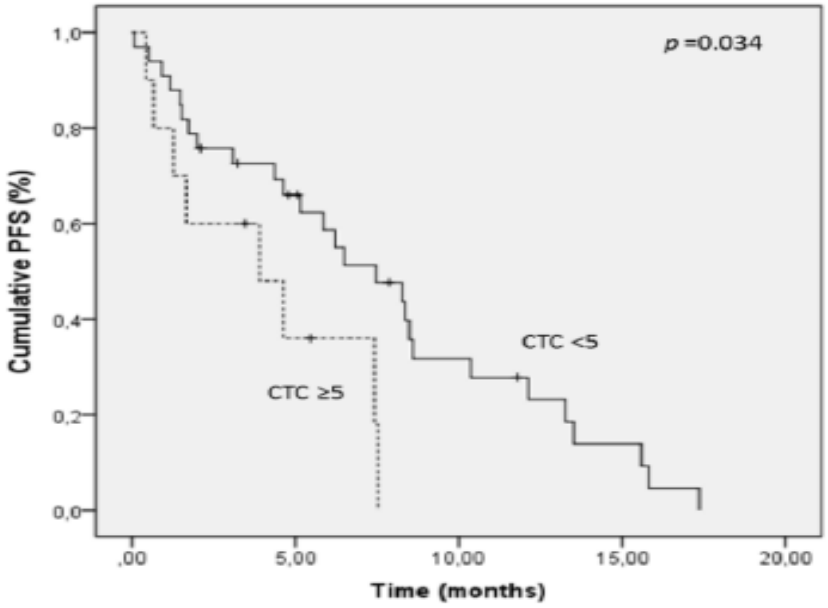
Krebs et al. JCO 2011

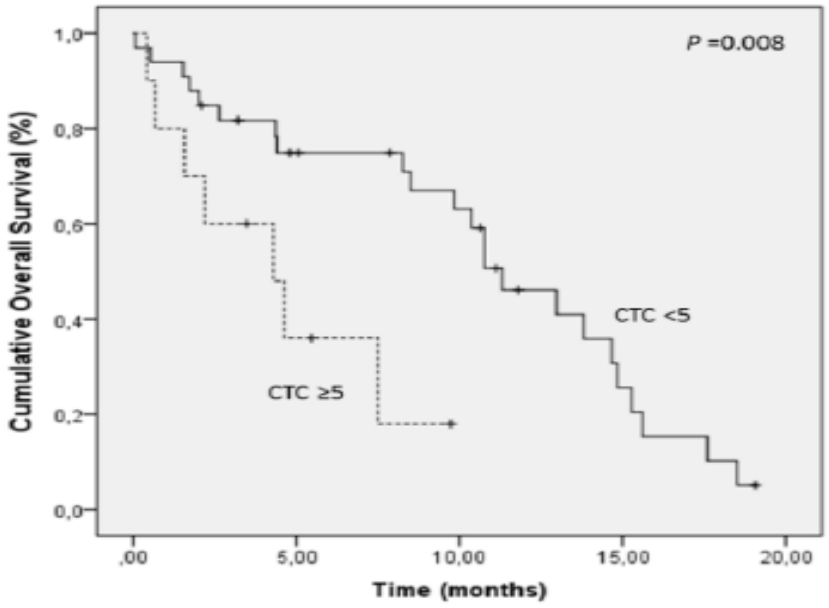
Prognostic Information

CTC clinical application:

Evaluation of Circulating Tumor Cells and Related Events as Prognostic Factors and Surrogate Biomarkers in Advanced NSCLC Patients Receiving First-Line Systemic Treatment

"The clinical value of CTC as a surrogate biomarker relies on how consistently and accurately CTC can reflect tumor burden, prognosis and response to therapy. The possibility that CTC enumeration could stratify patients into prognostic subgroups with differential outcomes, and modify treatment plans to alter the course of NSCLC, would have an impact on patient management."

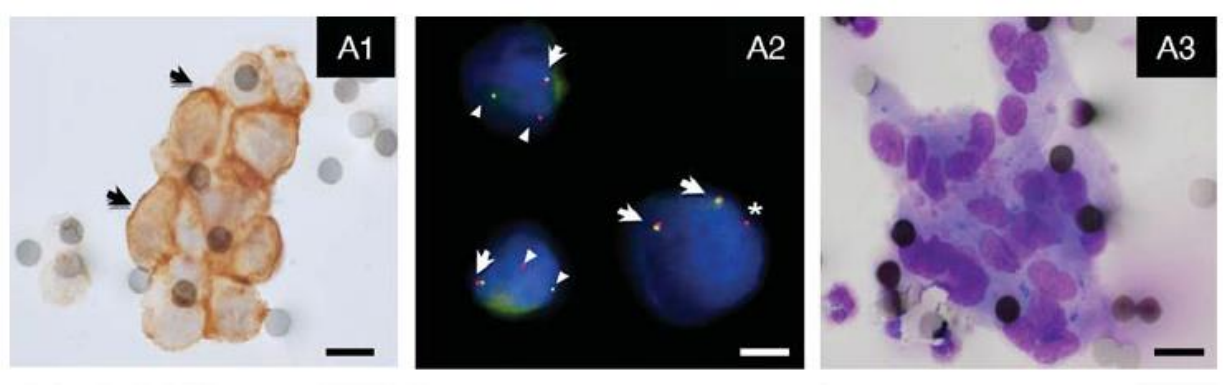




Muinelo-Romay L. et al., Cancers 2014

CTCs: FISH and IHC testing:

ALK-gene rearrangement: a comparative analysis on circulating tumors cells and tumors tissue from patients with lung adenocarcinoma.



- Circulating tumor cells showing an intense and cytoplasmic staining with some membrane reinforcements for ALK
- Circulating cell nuclei hybridized with a dual-color 2p23 LSI ALK locus-specific split probe. The two probes show a distinct separation of the red and green signals indicating a rearrangement in the 2p23 ALK-gene locus.

Ilie M; at al, Ann Oncol 2012

Cell Free DNA and Circulating Tumor DNA:

Pantel K, Diaz LA Jr, Polyak K. Tracking tumor resistance using 'liquid biopsies'. Nat Med. 2013

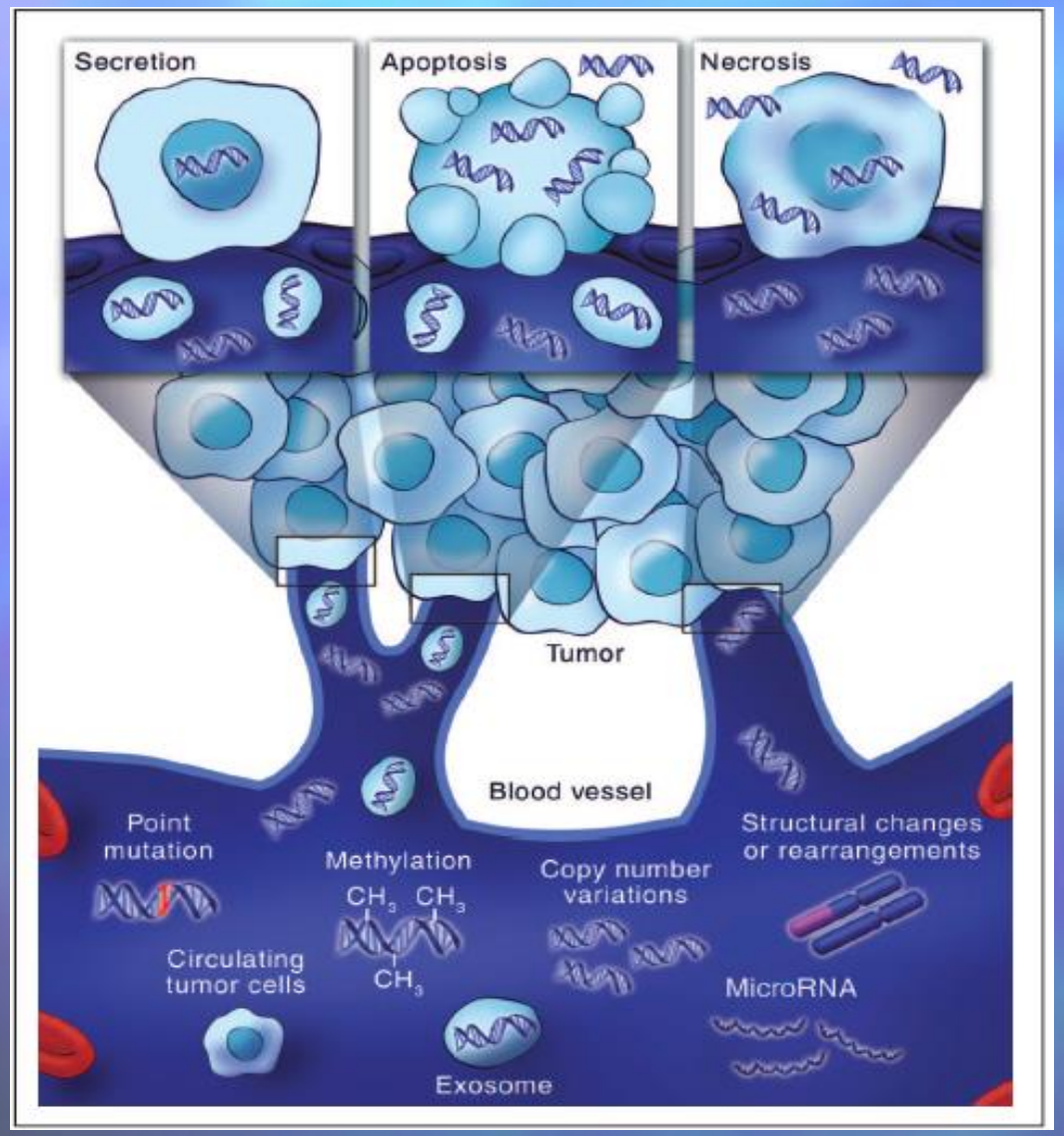
- Cell-free DNA (cfDNA) → DNA released in the bloodstream from apoptotic and necrotic cell
- Circulating-tumor DNA (ctDNA)→ proportion of the cfDNA released from tumor cells
- ctDNA can be used and as a tool to evaluate in real time the "molecular condition" of the disease

PRO & CON

1. Minimal invasive marker
2. Early detection of drug resistance development
3. Driver mutation detection from blood samples
4. Solving the issue regarding "insufficient material for analysis"

1. Lack of standardized and widely approved methods for analysis
2. Contamination with cfDNA from healthy cells

Liquid Biopsies: Circulating Tumor DNA

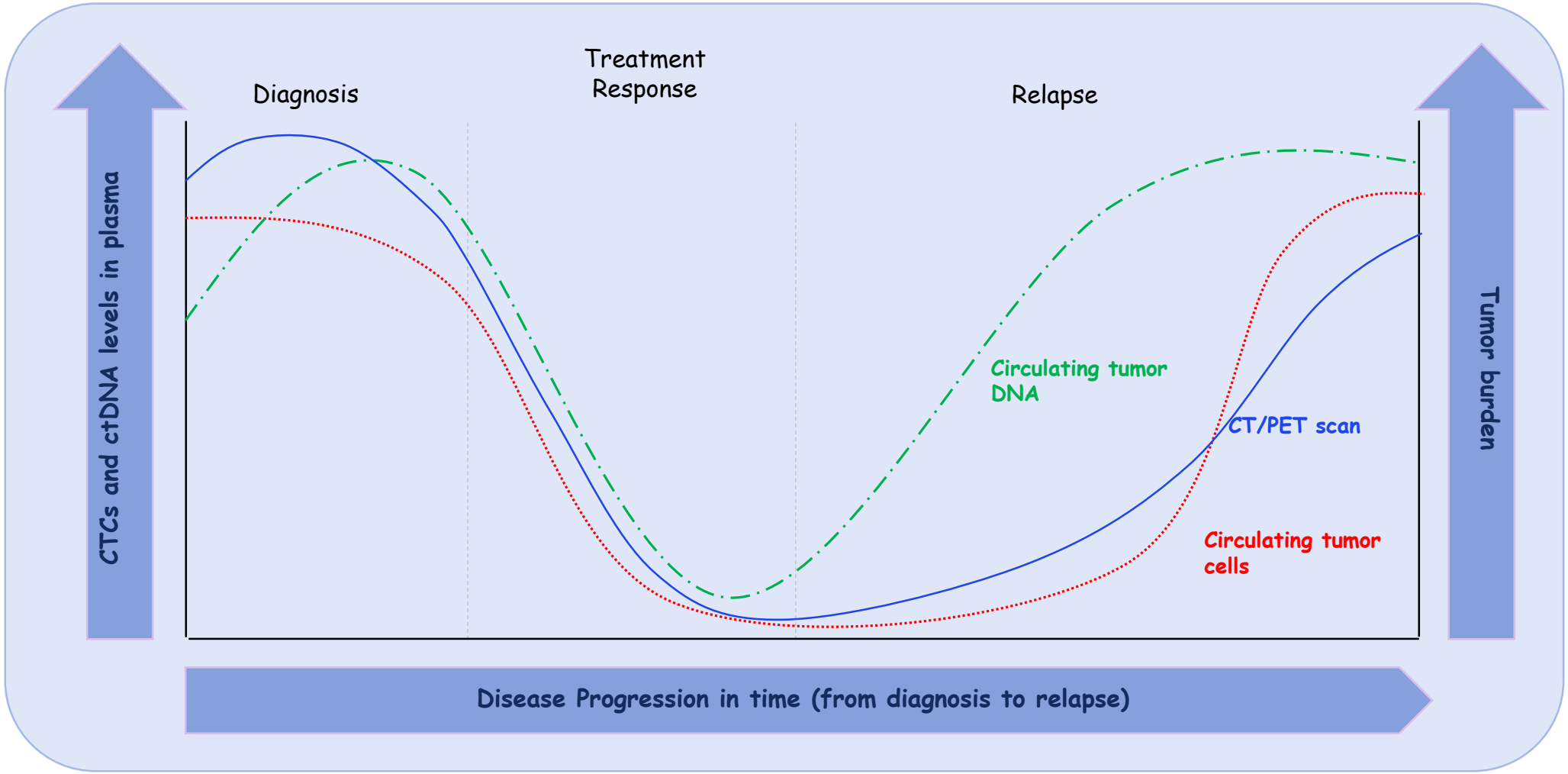


Technique	Sensitivity	Optimal Application
Sanger sequencing	> 10%	Tumor tissue
Pyrosequencing	10%	Tumor tissue
Next-generation seqeuncing	2%	Tumor tissue
Quantative PCR	1%	Tumor tissue
ARMS	0.10%	Tumor tissue
BEAMing, PAP, Digital PCR, TAM-Seq	0.01% or lower	ctDNA, rare variants in tumor tissue

Diaz L. and Bardelli A. JCO , 2014

Modifications of CTCs and ctDNA during Three Phases of Cancer Disease:

Real-time Monitoring of Disease

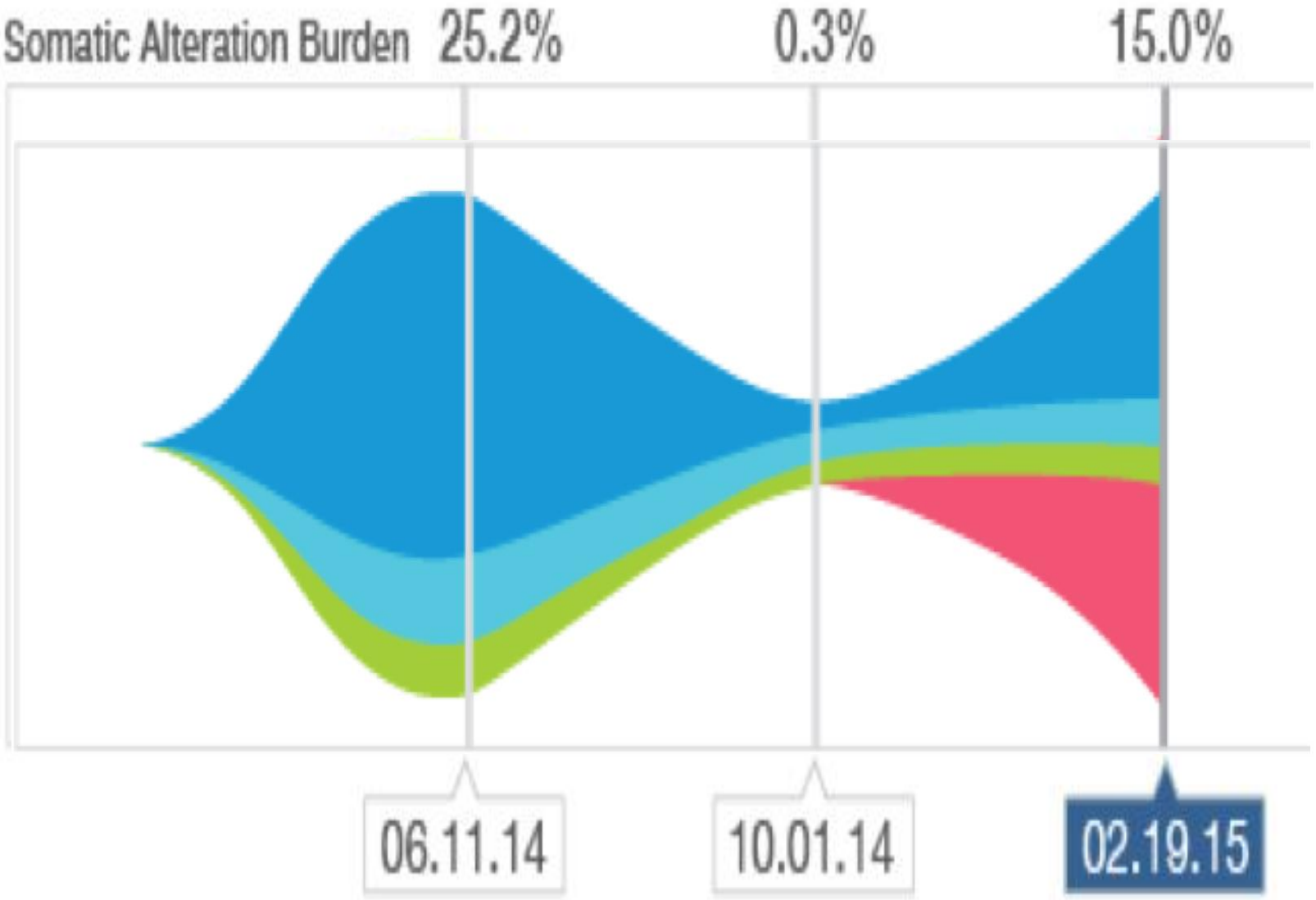


Rolfo, Castiglia, Russo et al. Biochim Biophys Acta. 2014 Dec;1846(2):539-46

Liquid Biopsy in clinical practice:

Real-time Monitoring of Disease

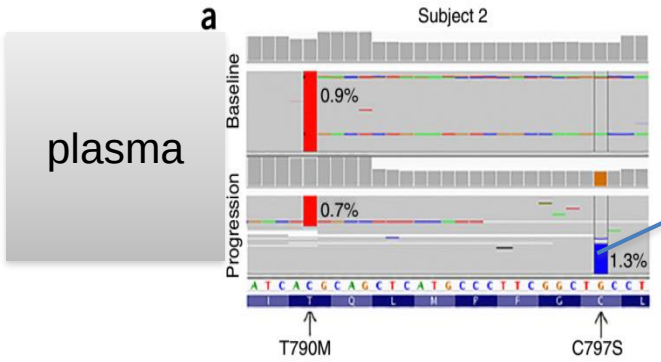
Identification of resistance mechanisms



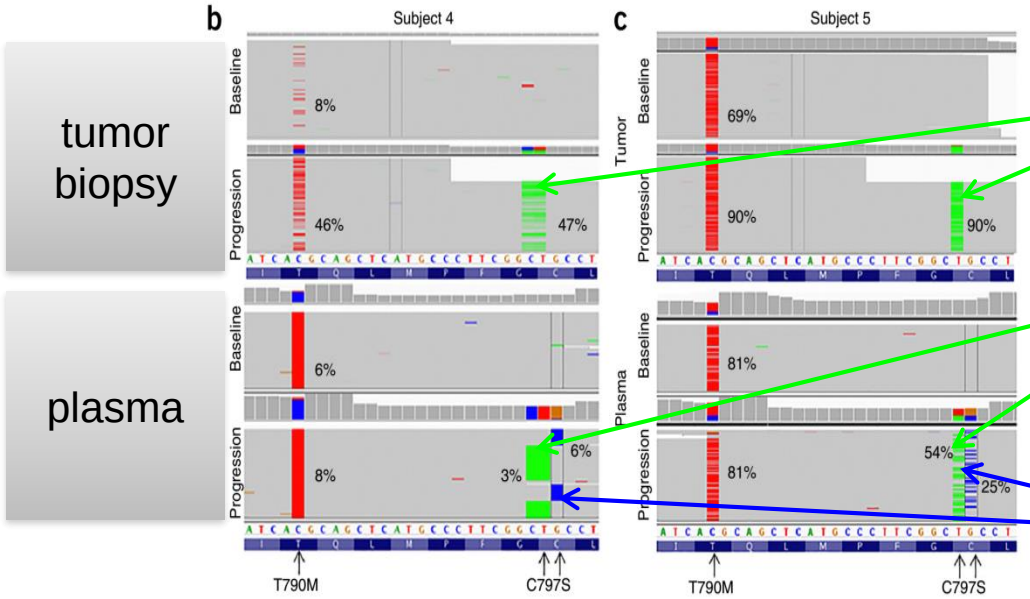
- ***EGFR* exon 19 del**
- ***TP53* Y220C**
- ***NOTCH1* VUS**
- ***EGFR* T790M**

Exploring new mechanism of resistance— Story of c797s:

Identification of resistance mechanisms



Acquired C797S G→C mutation on a different allele detected of cf DNA by NGS



Tumor biopsies (top panels) confirmed the acquired C797S mutation detected with plasma NGS

Plasma NGS detects the same T→A C797S mutation

Plasma NGS additionally detects a second G→C mutation encoding for C797S

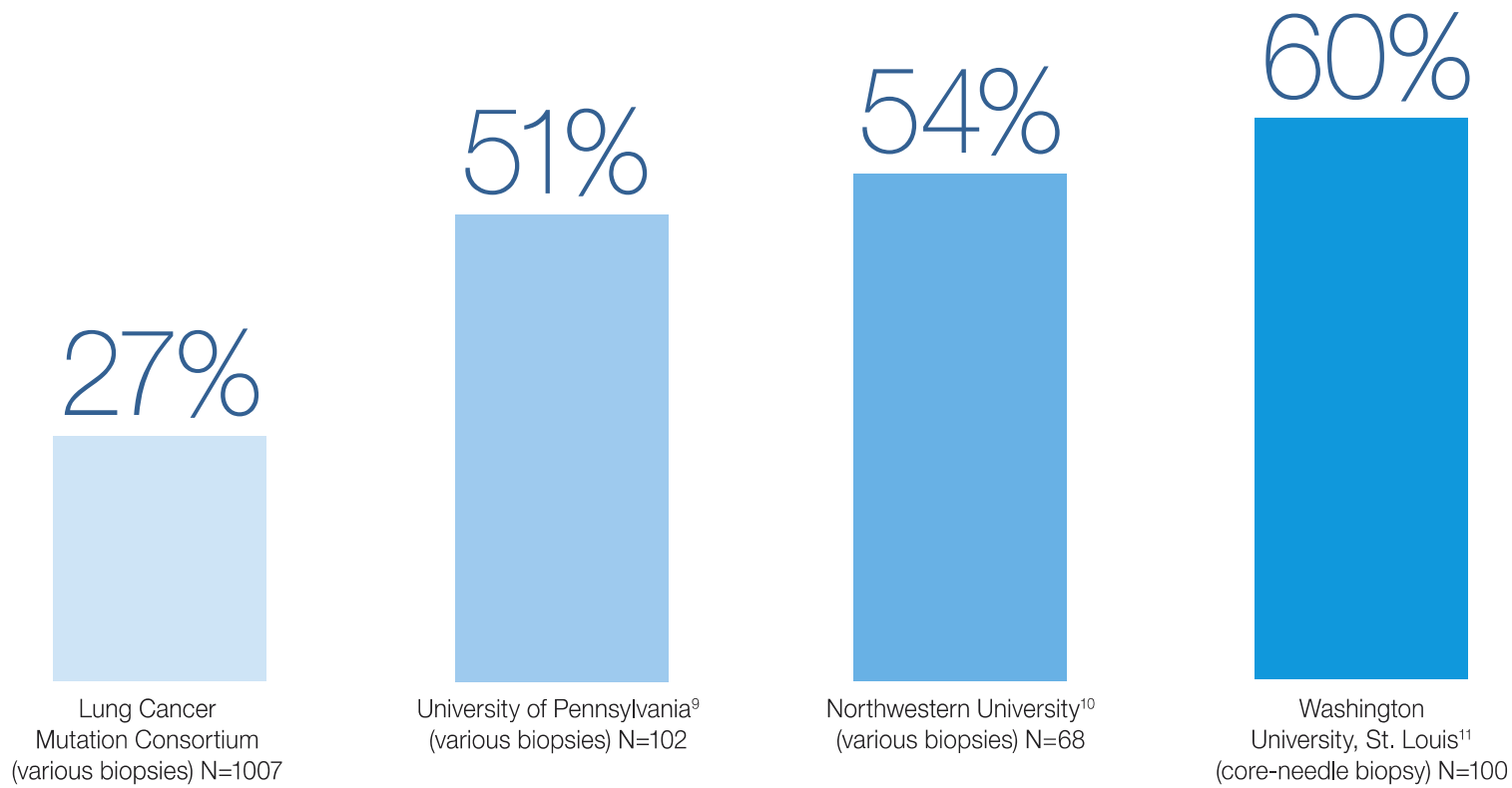
Thress KS, et al, Nat Med.2015 Jun;21(6):560-2

NCCN Somatic Genomic Targets in Solid Cancers

Cancer Type	Targetable Genomic Alterations						
NSCLC	*EGFR*	*ALK* fusion	*ROS1* fusion	*BRAF*	*RET* fusion	*ERBB2*	*MET* amp & exon 14 skipping
Colorectal	*KRAS*	*NRAS*	*BRAF*				
Breast	*ERBB2* (HER2) amp						
Gastric & Gastroesophageal	*ERBB2* (HER2) amp						
Melanoma	*BRAF*	*KIT*					
GIST	*KIT*	*PDGFRA*	*BRAF*				
Ovarian	*BRCA1/2* somatic (and germline)						

Ettinger et al. 2015 JNCCN, Benson et aı. 2014 JNCCN, Gradishar et al. 2015 JNCCN, Ajani et al. 2013 JNCCN, Ajani et al. 2015 JNCCN, Coit et al. 2016 JNCCN, von Mehren et al. 2014 JNCCN

Genomic Profiling of Lung Biopsy Tissue Can Fail



Rates of unsuccessful tissue-based comprehensive genomic profiling in NSCLC

[1]Hagemann (Govindan) et al. 2015 Cancer; [2]Villaflor (Salgia) et al. 2016 Oncotarget; [3]Thompson (Carpenter) et al. 2016 Clin Canc Res.

Guardant360 Test "Rescues" a Tissue T790M-negative

Initial Presentatio

1st Tissue Biopsy–Lung
EGFR L858R

Progressed on Erlotinib after 5 Months

2nd Invasive Biopsy–Lung
EGFR L858R
No resistance alterations found using NGS

Continued Progression

Whole brain radiation and six cycles of carboplatin, pemetrexed, bevacizumab, and erlotinib, then nivolumab

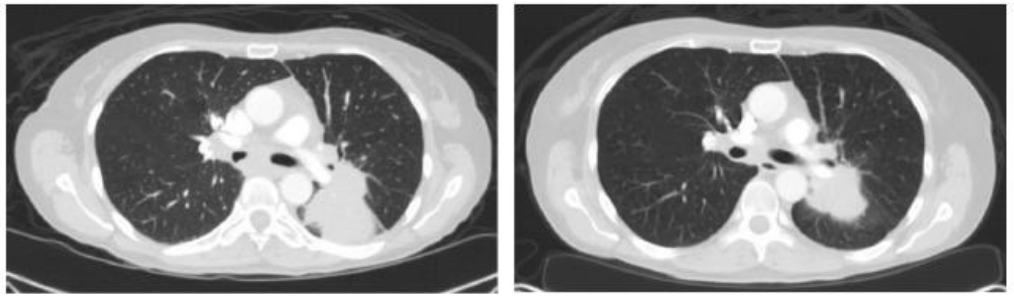
Guardant360

EGFR L858R
EGFR T790M

Response

Clinical and Radiographic Response to 3rd Generation TKI

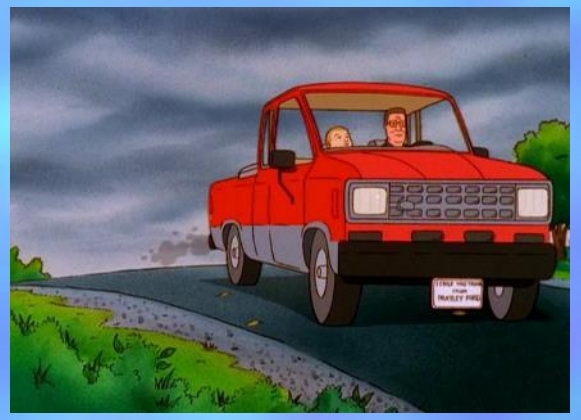
Baseline
Pre-Osimertinib



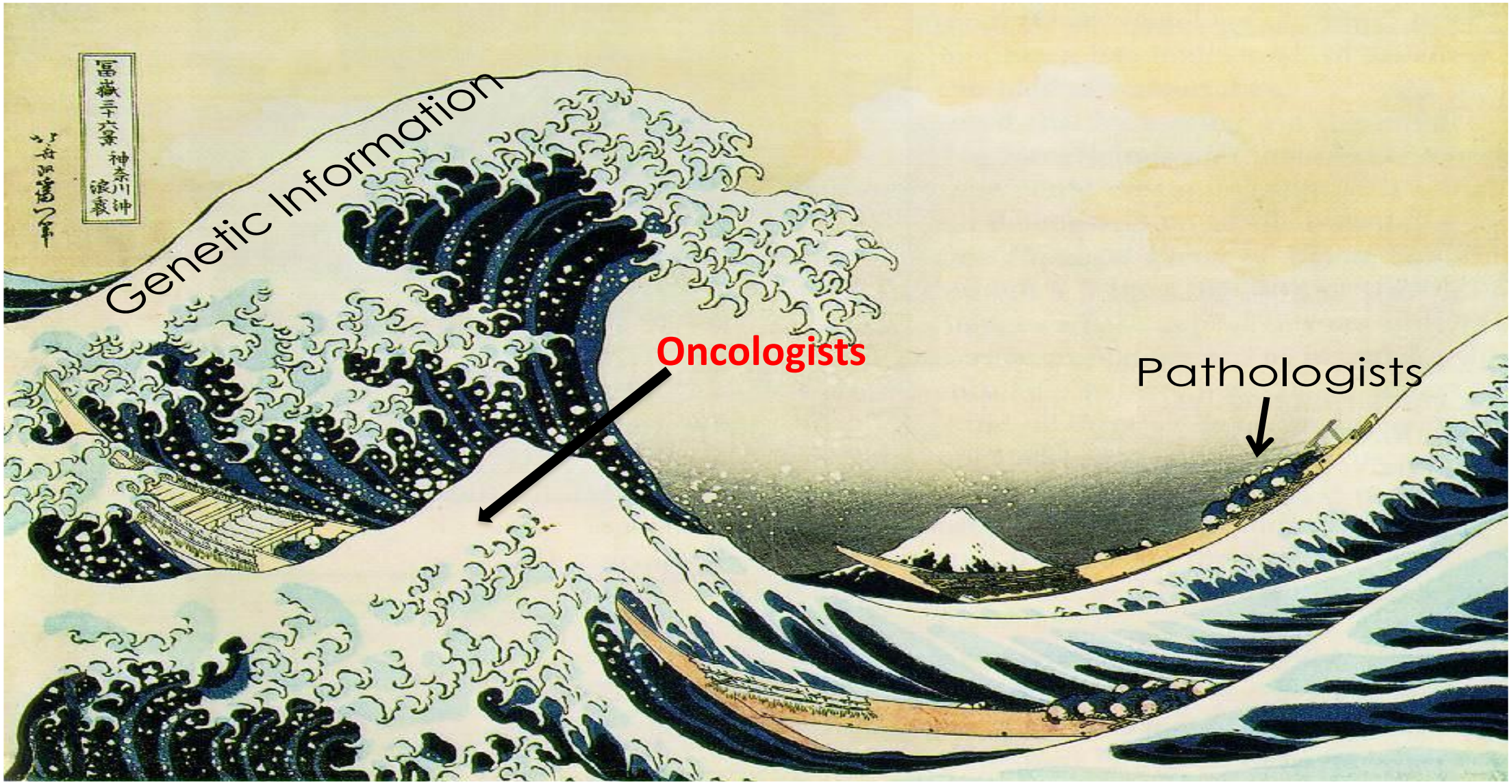
After 4 weeks on Osimertinib

Piotrowska (Sequist) et al. 2016 Journal of Thoracic Oncology

Discriminating a Driver and a Passenger Mutation in Early Phases Can Be Difficult

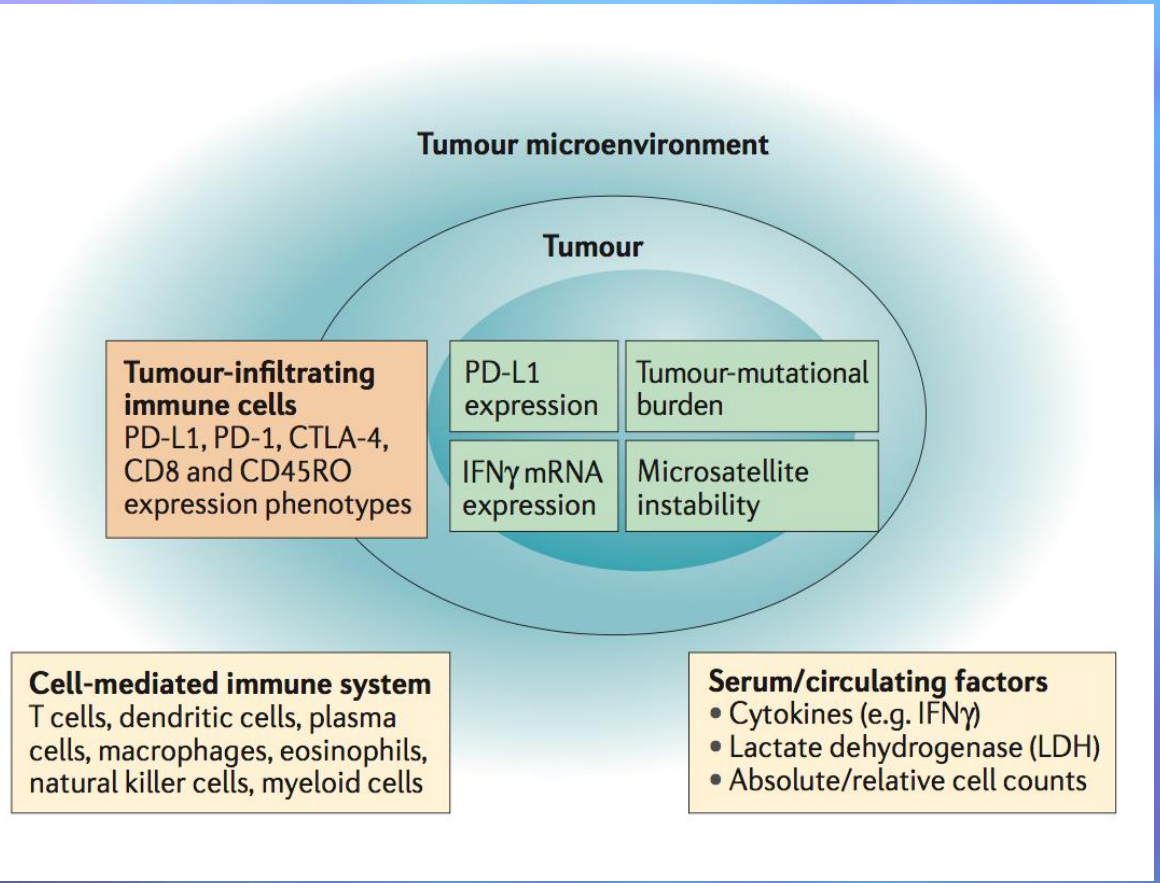


The Tsunami of Molecular Medicine…



To Make the Things Worse… it's not only Targeted Therapy….. Immunotherapy is another wave!!!

Liquid Biopsy in Immunotherapy



Unmet Medical Need:

Validated Biomarkers in Blood!

Potential Utility of Liquid Biopsy in Immunotherapy

- **Diagnostic**
- **Prognostic**
- **Predictive of Response**
- **Monitoring**
- **Mechanisms if Resistance**

Current tools:

- Calculation of circulating TMB
- Detection of PDL1
- Allelic Fraction Variation Dynamic

Image from Nishino et al, Nature Reviews Clinical Oncology, June 2017

Mutational Tumor Burden

Tumor mutational burden in blood (bTMB) and improved atezolizumab (atezo) efficacy in NSCLC

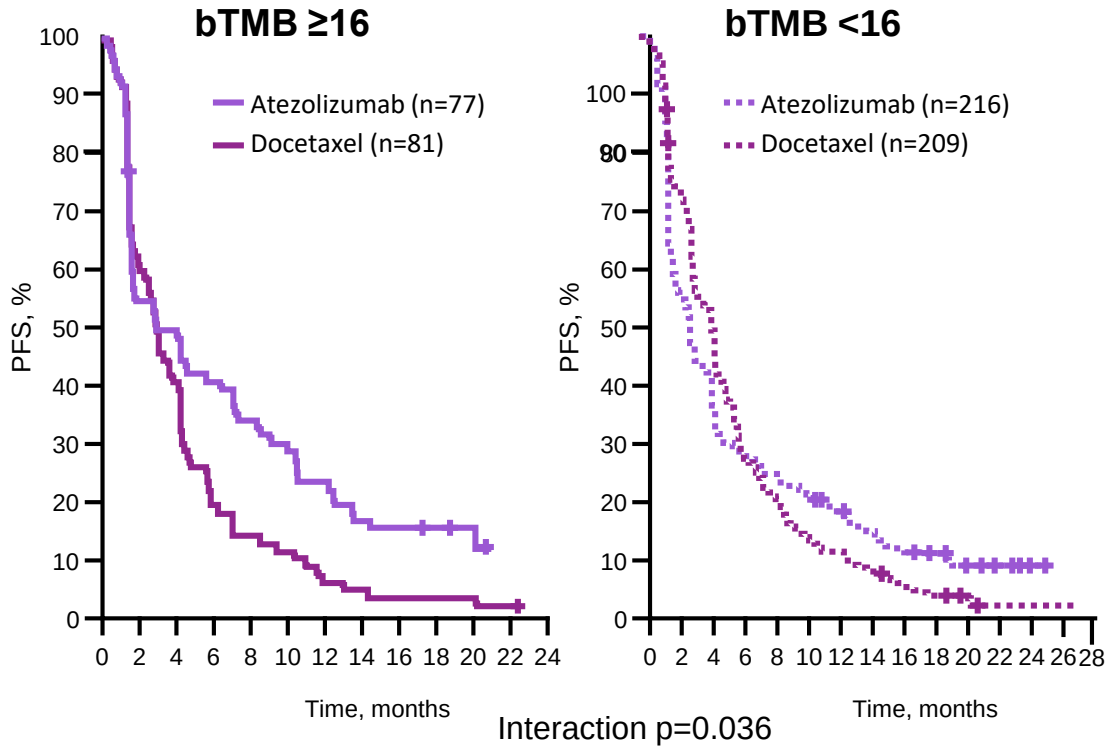
Blood-efficacy in 2L+ NSCLC (POPLAR and OAK)

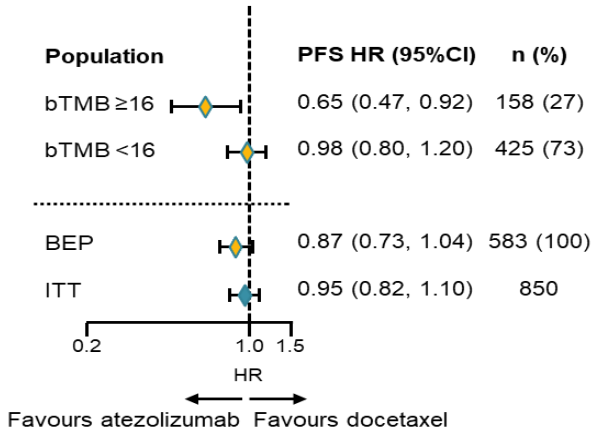
Aim: to evaluate a method for the investigation of tumor mutational burden from peripheral blood and its predictive value on Atezolizumab therapy outcome

Methods: an NGS panel of 394 genes was used to measure the mutational burden from circulating tumoral DNA in peripheral blood

D. R. Gandara et al., ESMO 2017 abstract 1295O

MTB

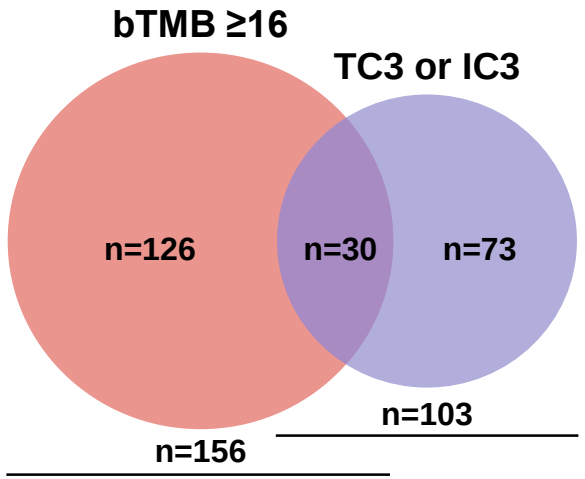




D. R. Gandara et al., ESMO 2017 abstract 1295O

MTB

Limited overlap between bTMB ≥16 and PD-L1 expression: OAK



	PFS HR (95%CI)	OS HR (95%CI)
bTMB ≥16	0.64 (0.46, 0.91)	0.64 (0.44, 0.93)
TC3 or IC3	0.62 (0.41, 0.93)	0.44 (0.27, 0.71)
bTMB ≥16 and TC3 or IC3	0.38 (0.17, 0.85)	0.23 (0.09, 0.58)

Biomarker evaluable population (n=229)

D. R. Gandara et al., ESMO 2017 abstract 1295O

MTB

Conclusions

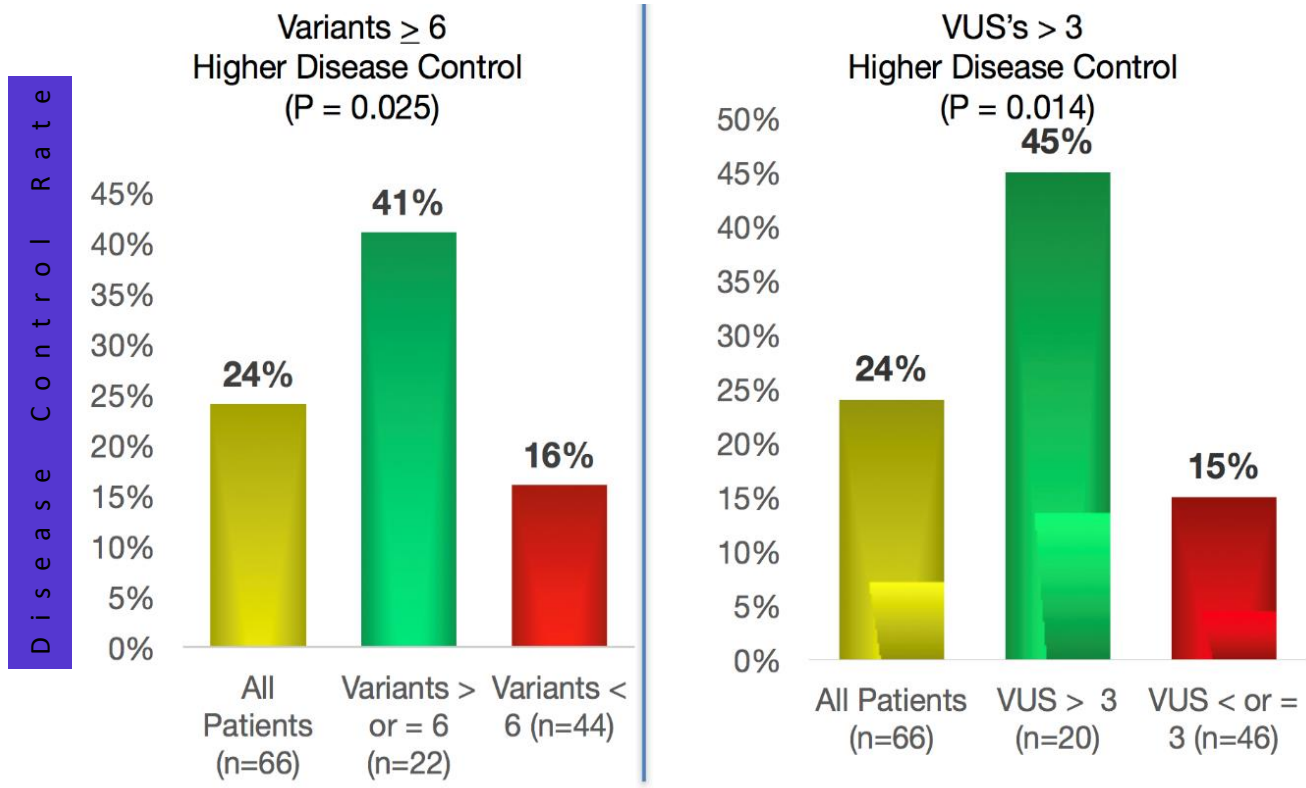
- This exploratory analysis demonstrated that TMB can be measured in blood
- The cut-point of bTMB ≥16 was identified in POPLAR, and independently validated to predict PFS benefit in OAK
- bTMB identified a unique patient population which was not significantly associated with PD-L1 status

Comments

- Great News
- The cut-point of bTMB ≥16 was is a real cut-off?
- Great News: to be validated
- No widely applicable in clinical practice

Hypermutated Circulating Tumor DNA

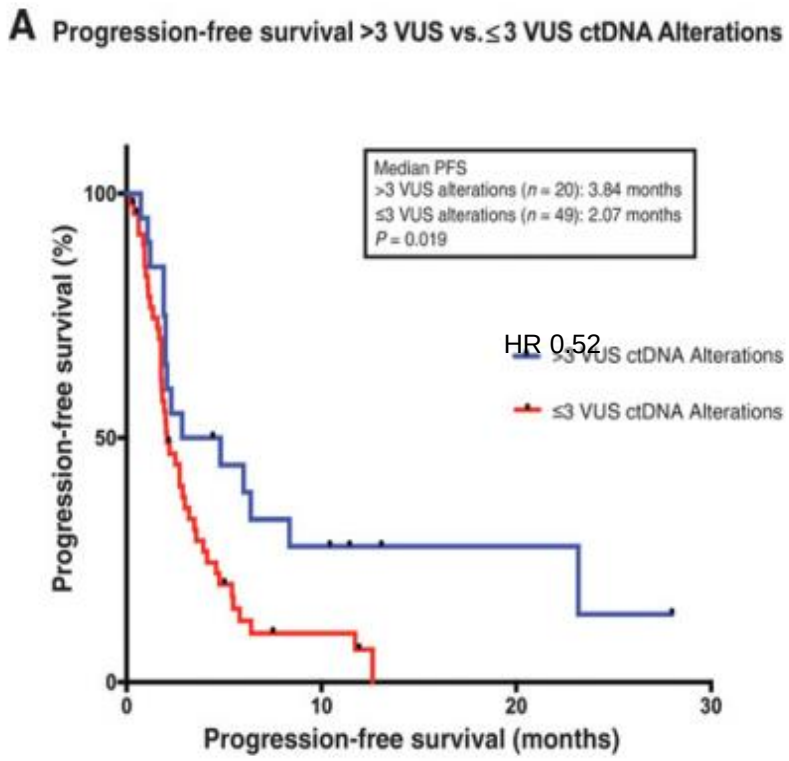
Hypermutated Circulating Tumor DNA: Correlation with Response to Checkpoint Inhibitor–Based Immunotherapy

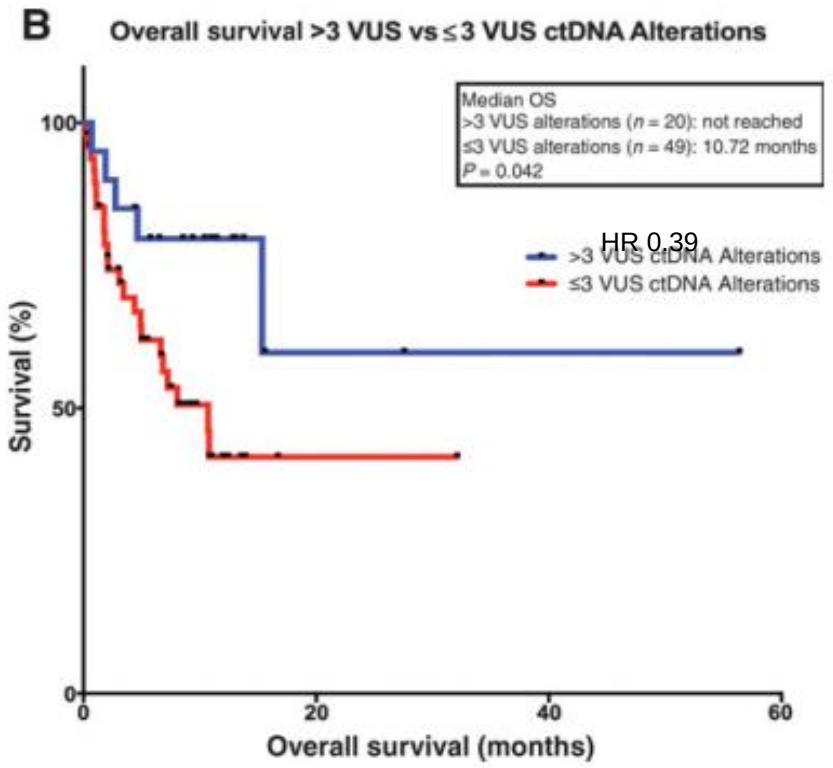


Disease Control Rate: CR+ PR + SD

Khagi (Kurzrock) et al. Oct 2017 Clinical Cancer Research

Hypermutated Circulating Tumor DNA





In patients undergoing therapy with IO a higher amount of mutations was associated with a better PFS and OS

Khagi (Kurzrock) et al. 2017 Clinical Cancer Research

Take home message….

- Liquid biopsy has entered into our oncology clinical practice.
- Important tool in NSCLC, as a non invasive method.
- ctDNA nowdays have a high concordance with tissue and is more easy to obtain.
- Analysis of TMB is feasible in blood, and it could be predictive biomarker for IO response.
- Liquid Biopsy has several potential clinical uses: early detection/screening; monitor response to therapy; prognostic biomarker; predictive biomaker; identification of mechanism of resistance.

MIAMI CANCER MEETING

15th ANNUAL MIAMI CANCER MEETING (MCM)

New Frontiers for the Treatment of Solid and Liquid Tumors: Delivering Precision Medicine

April 27-29, 2018

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Miami, Florida

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"Immunotherapy - Targeted Therapy & Chemotherapy: Breaking the Enigma of Solid & Liquid Cancers"

July 20-22, 2018

The Roosevelt Hotel New Orleans
New Orleans, LA

13th ANNUAL NEW ORLEANS SUMMER CANCER MEETING

"Immunotherapy - Targeted Therapy & Chemotherapy: Breaking the Enigma of Solid & Liquid Cancers"

July 20-22, 2018

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