U.S. FOOD & DRUG ADMINISTRATION

AACR American Association for Cancer Research

Liquid Biopsies in Oncology Drug and Device Development Workshop Part 2

October 10, 2017

Renaissance Downtown Hotel

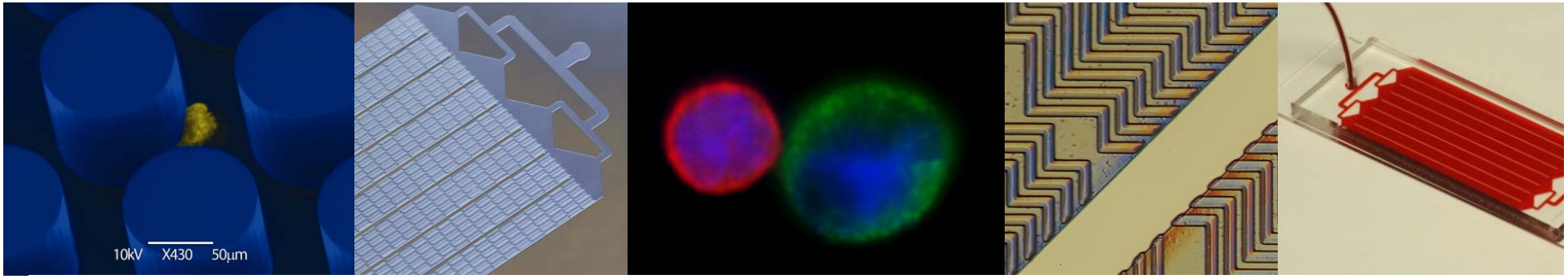
Washington, DC

@FDAOncology @AACR #FDAAACRLiqBiop

Welcome and Workshop Objectives

Workshop Cochairs:

Julia A. Beaver, MD
Gideon M. Blumenthal, MD
Reena Philip, PhD
Carlos L. Arteaga, MD
Pasi Jänne, MD, PhD



Molecular scoring of circulating tumor cells

Daniel Haber MD PhD
Massachusetts General Hospital Cancer Center
Harvard Medical School
Howard Hughes Medical Institute

Disclosures

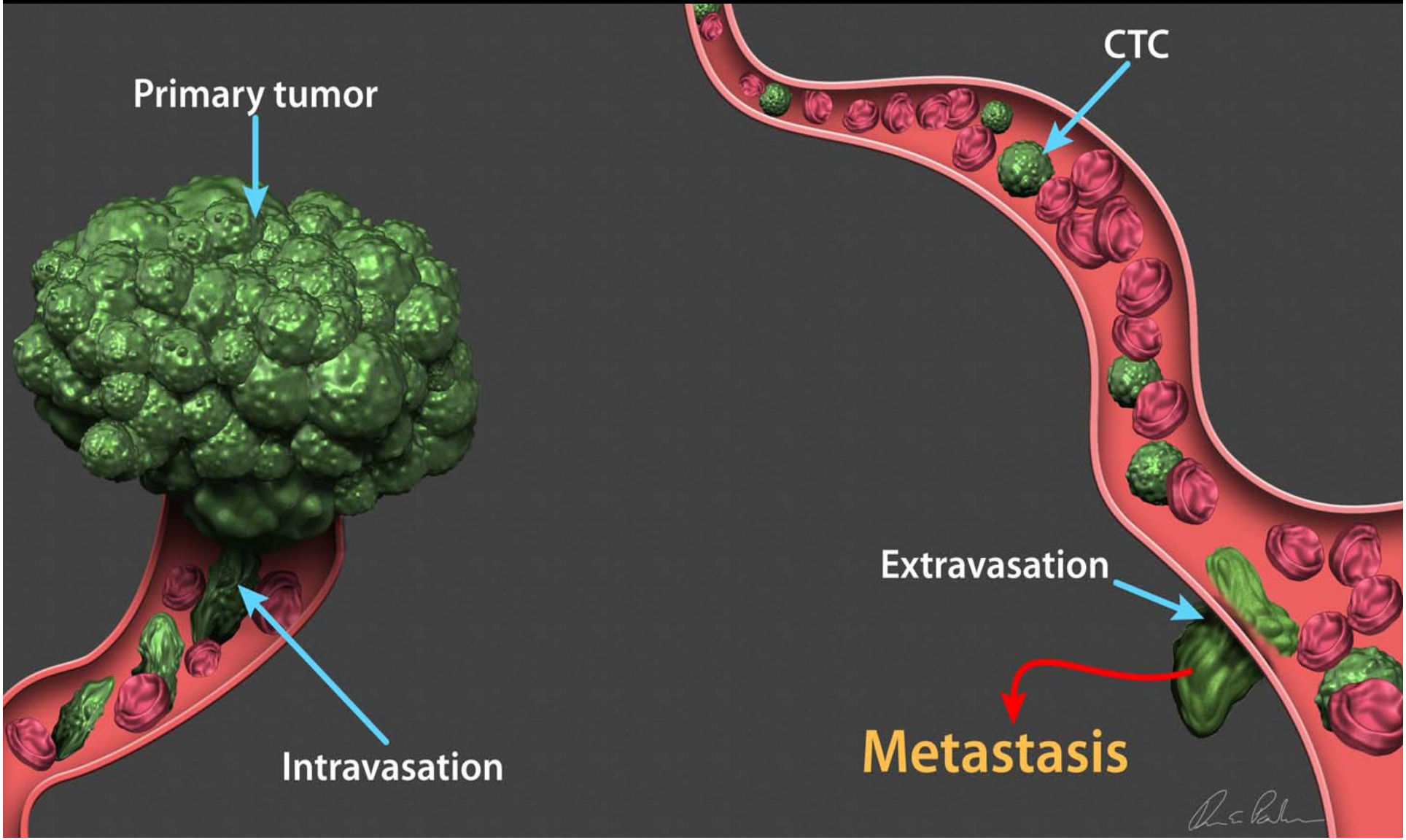
Scientific Advisory Boards

Janssen
Genomicare

Co-Founder

Torpedo Diagnostics

1. ***Understanding*** blood-borne metastasis
2. Noninvasively ***monitoring*** of therapy
3. ***Early detection*** of localized invasive cancer



Presentation Outline

1. ***Negative depletion*** microfluidic technologies for viable CTC enrichment

2. Functional studies using ***cultured CTCs***

3. ***RNA-based digital scoring*** of CTC for clinical applications

10 mL Whole Blood

50 billion RBCs

50 million WBCs

0-100 CTCs

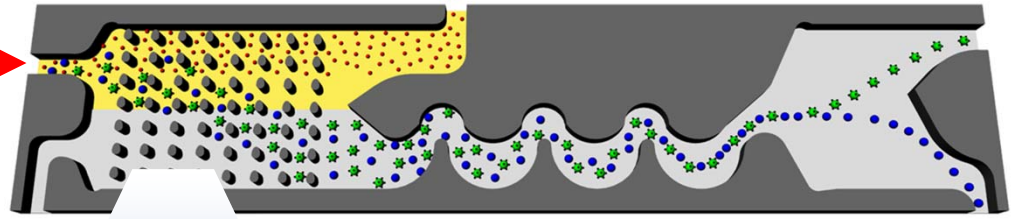
3rd Generation: CTC-iChip

Microfluidic depletion of hematopoietic cells ⟶ untagged CTCs

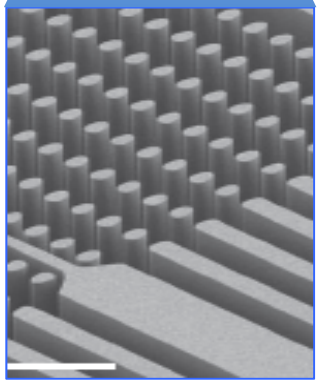
Anti-WBC magnetic beads

RBCs, platelets

Whole blood



Hydro-dynamic Cell Sorting



Mehmet Toner

Ozkumur, Shah et al., Sci Transl Med, 2013

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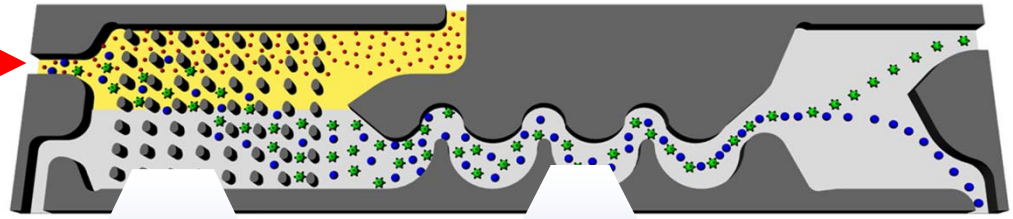

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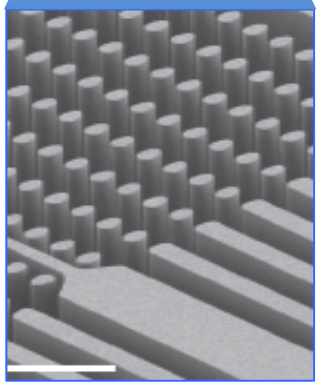
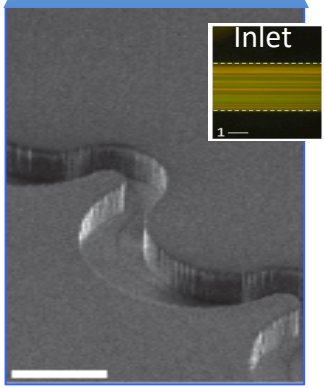


Inertial Focusing



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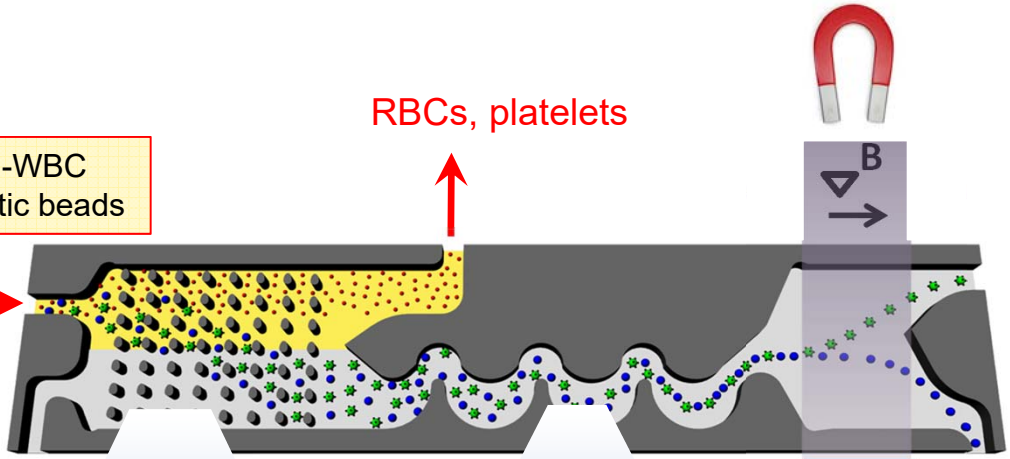
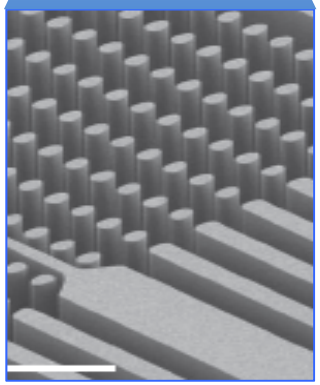
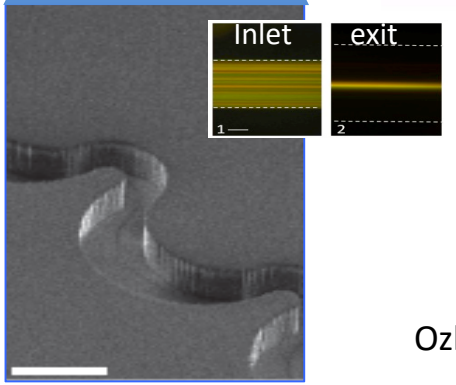


Hydro-dynamic Cell Sorting

Inertial Focusing

Magneto-phoresis





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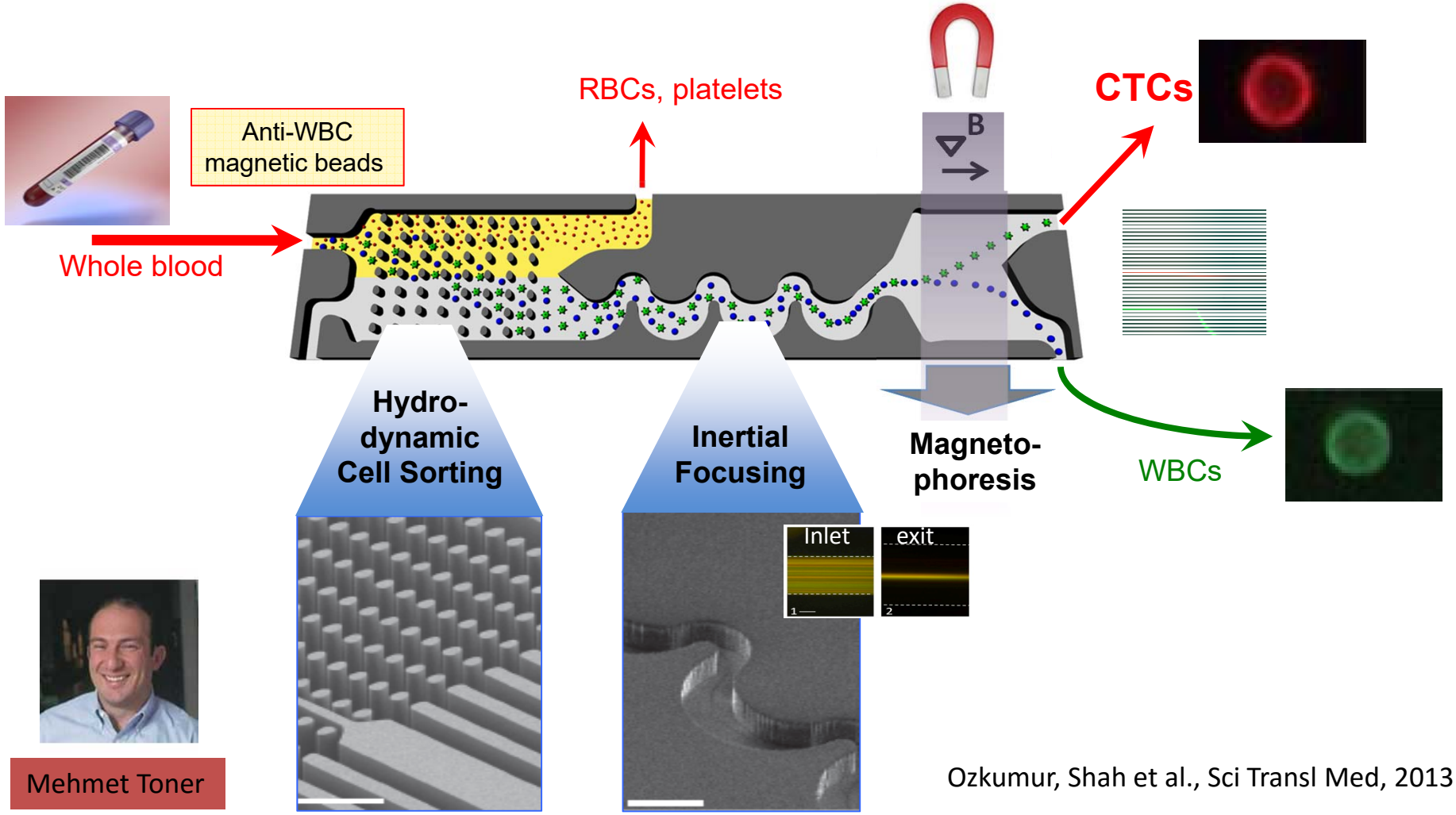

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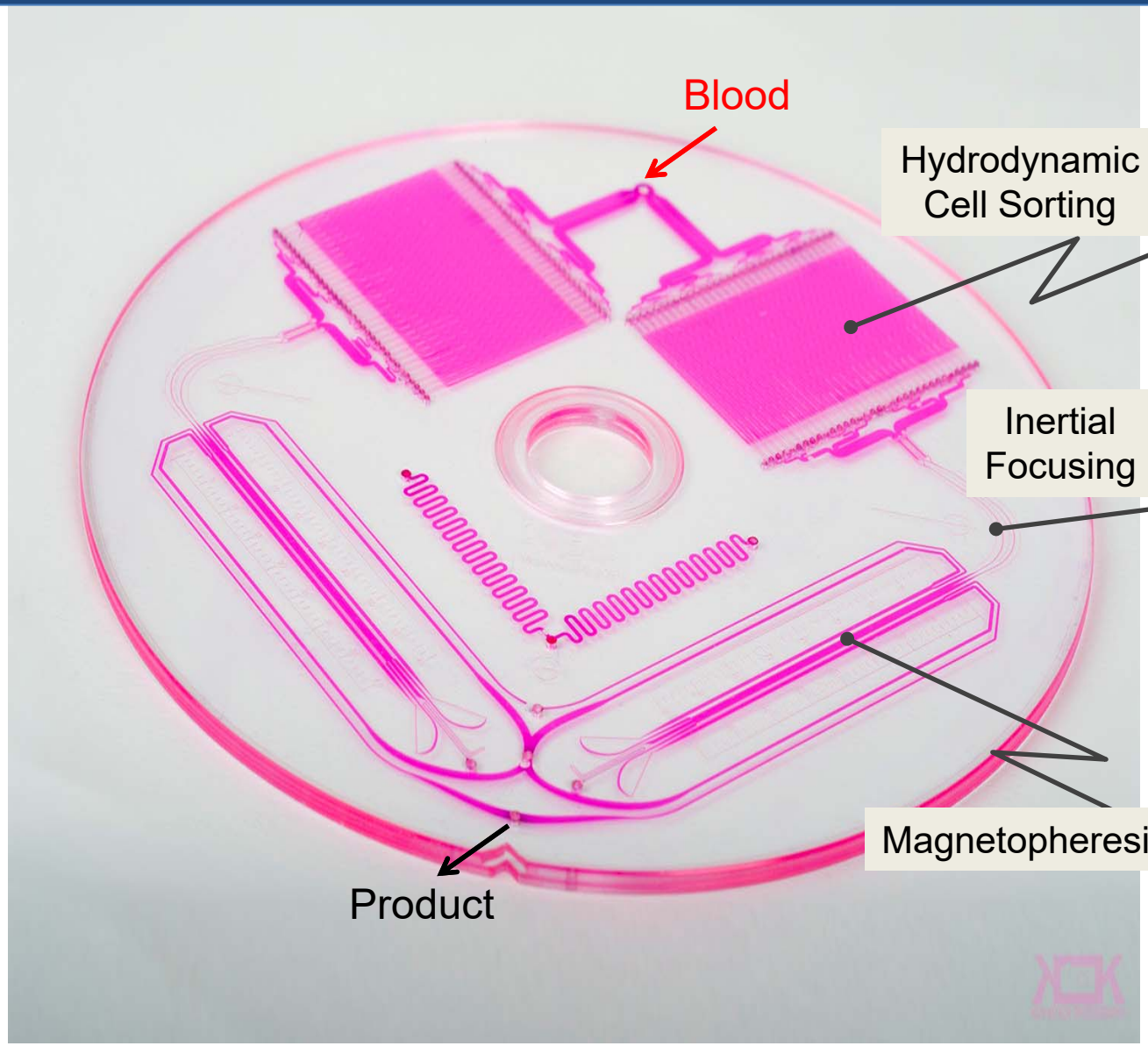
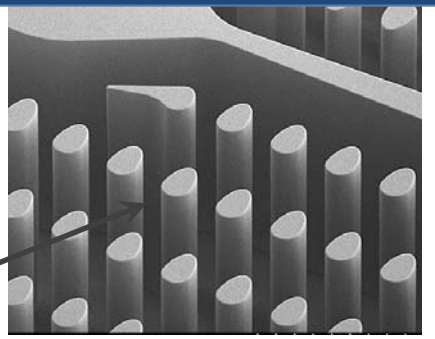
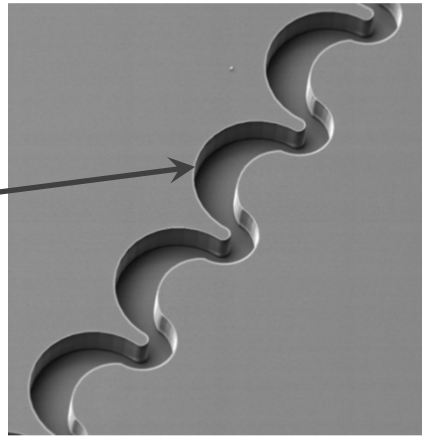
CTC-iChip



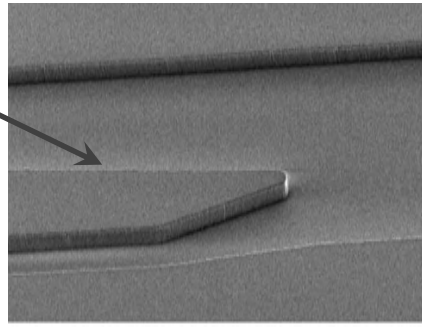
Hydrodynamic Cell Sorting



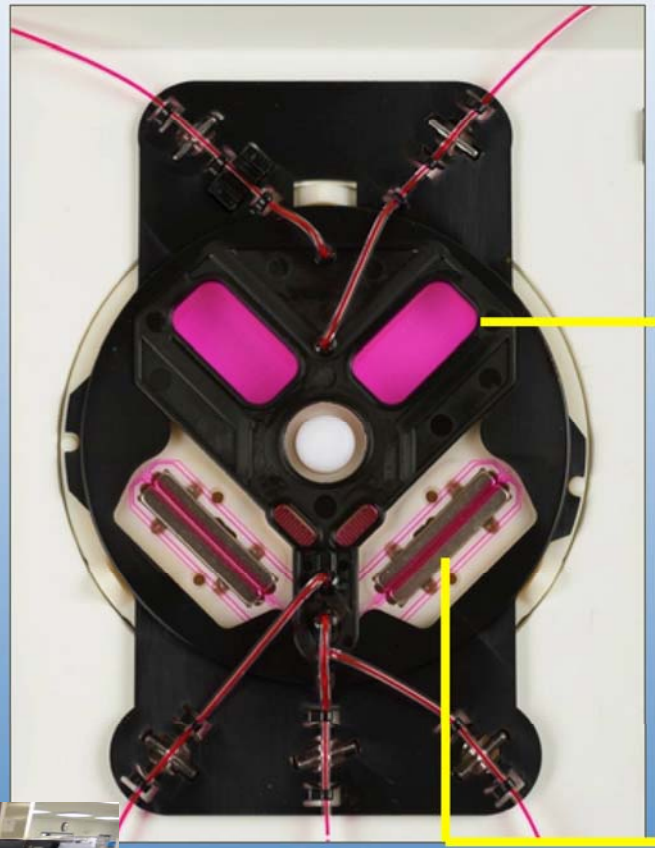
Inertial Focusing

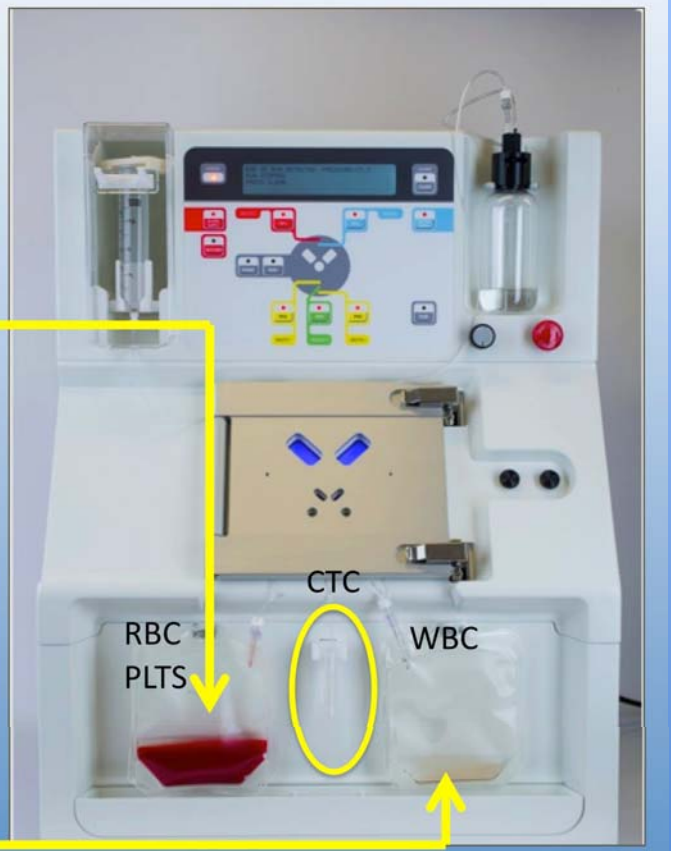


Magnetopheresis



The prototype CTC isolation instrument

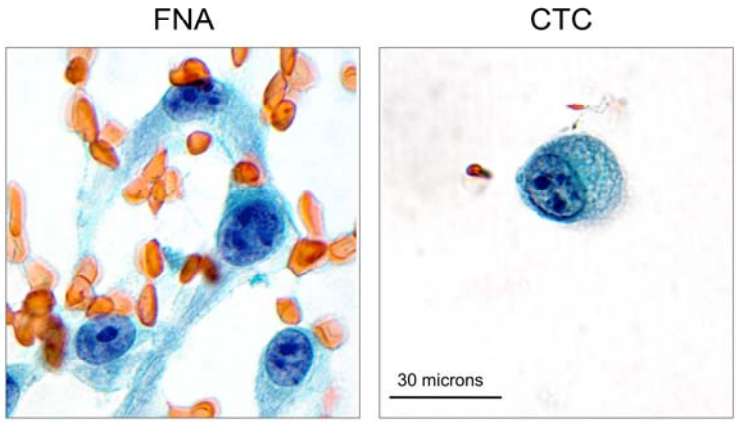




Automated sample processing
Rate: 10ml blood/hr
Volume: up to 30 ml

Negative Depletion:

"Removing the hay to uncover the needle"



1. ***Unbiased*** *enrichment of CTCs from all tumor types*
2. ***Automated*** *microfluidic platform & processing*
3. ***Viable*** *"untouched" CTCs with intact RNA*

Presentation Outline

1. ***Negative depletion*** microfluidic technologies for viable CTC enrichment

2. Functional studies using ***cultured CTCs***

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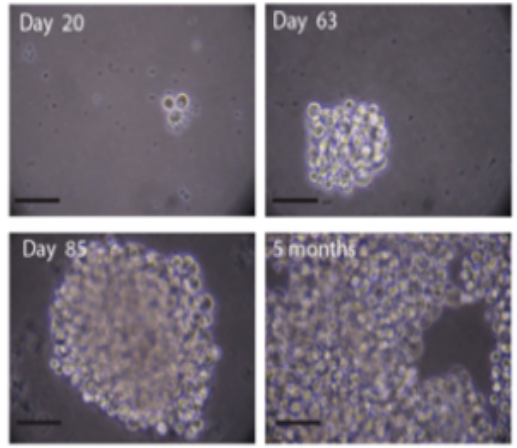
Ex vivo culture of ER+ breast CTCs

In vitro culture of breast CTCs under hypoxic, anchorage independent conditions.

Orthotopic tumors in NSG mice.




Yu, Bardia et al., *Science* 2013

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Orthotopic tumors in NSG mice.

Multiple ***somatically acquired mutations*** during course of treatment:

- *Estrogen Receptor Mutations (ESR1)*
- *Activating FGFR, PIK3CA mutations*

New mutations acquired during treatment

Case	Gene	DNA	Protein	Allele Frequency	In pretreatment Tumor[b]	In Multiple CTC Lines	Known Mutation[c]
BRx33[d]	ESR1	A1613G	D538G	0.24	-	-	Br[f], En
	NUMA1	C5501T	S1834L	0.30	-	-	Br
BRx07[d]	TP53	G853A	E285K	0.99	No	-	Bl, Br, Co, HN, Lu
	PIK3CA	A3140T	H1047L	1	No	-	Br, Co, GBM, HN, Ki, Lu, Me, Mel, Ov, En
	FGFR2	T1651A	N549K	0.46	No	-	Br, En
	CDH1	C790T	Q264*	1	Yes	-	Br
	APC	G7325A	G2409R	0.47	Yes	-	Mel
	DGKQ	G2530A	D844N	0.55	-	-	Lu
	MAML2	A2569G	M857V	0.52	-	-	Lu
BRx68	TP53	C1009T	R337C	0.99	No	Yes	Br, Co, HN, Hem, Ov
	ESR1	A1610C	Y537S	0.47	No	Yes	Br[f], En
	PIK3CA	A3140G	H1047R	0.7	Yes	Yes	Br, Co, GBM, HN, Ki, Lu, Me, Mel, Ov, En
	MSN	G1154A	E385K	0.25	-	-	En
BRx50[d]	ESR1	T1607C	L536P	0.06	-	-	Br[f]
	IKZF1	G1444T	G482C	0.09	-	-	Hem
	BRCA2[e]	6262del	L2039fs	-	-	-	Br (germ line)
BRx42	PIK3CA	G3145C	G1049R	0.60	Yes	Yes	Br, En, Ki
	PIK3CA	C1097G	P366R	0.54	-	-	Br
	KRAS	35T	G12V	0.99	No	Yes	Br, Co, Hem, Es, GBM, Lu, Ov, En
	IGF1R	G3613A	A1205T	0.06	-	-	Hem
BRx61	TP53	G610T	E204*	0.98	No	Yes	Bl, Br, Ki, Lu, Ov

Yu, Bardia et al., *Science* 2013

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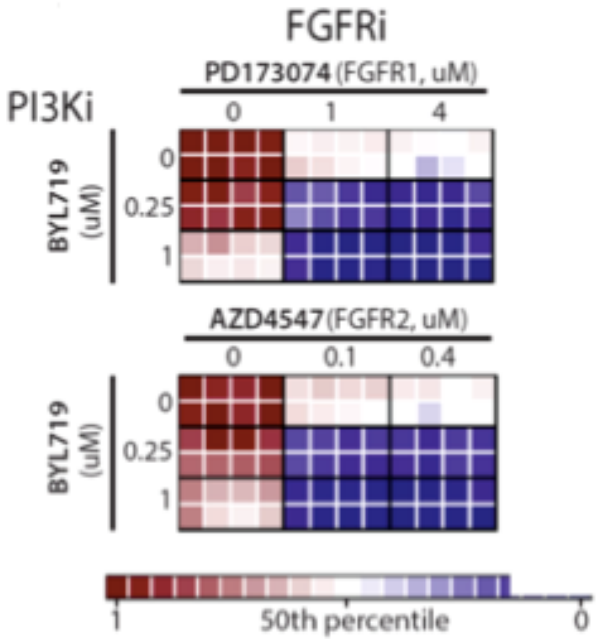
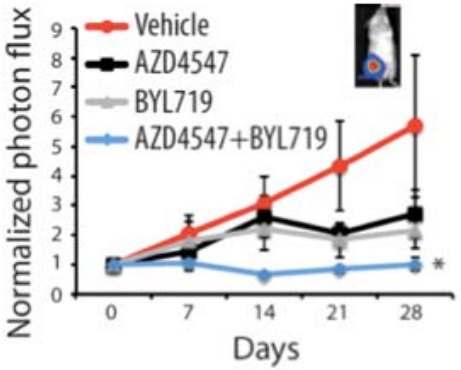
Heterozygous FGFR and PIK3CA mutations direct ***cooperative drug sensitivity*** *in vitro* and *in vivo*





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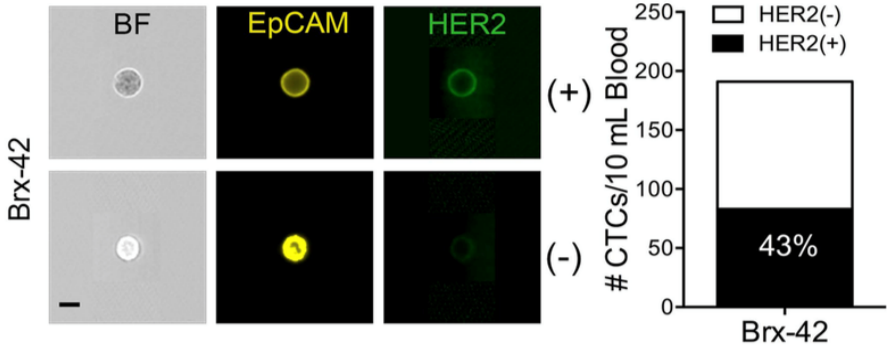
Plasticity in advanced breast cancer

Primary CTCs in metastatic ER+ breast cancer have **acquired expression of HER2** (~45% of cells)



Jordan et al., Nature 2016

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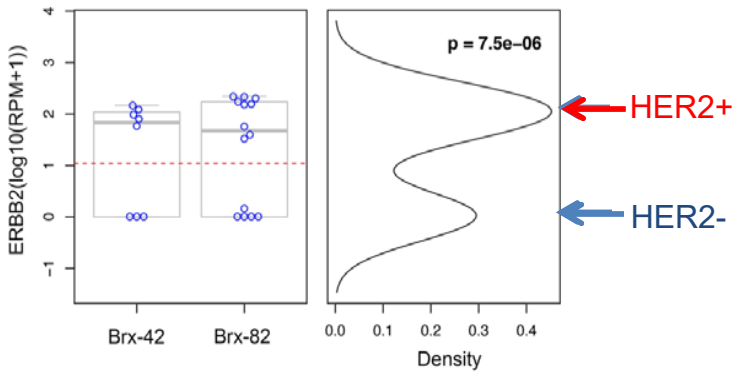
Single cell RNA-Seq shows two discrete populations of CTCs: **HER2+ and HER2-**



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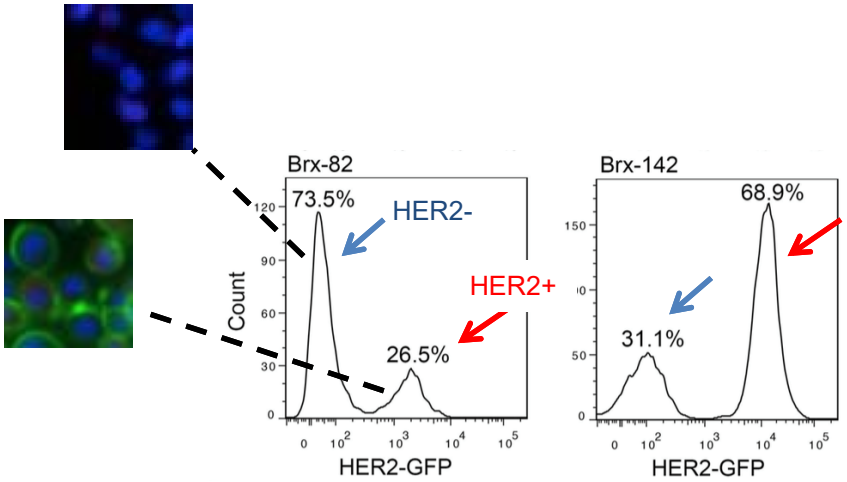
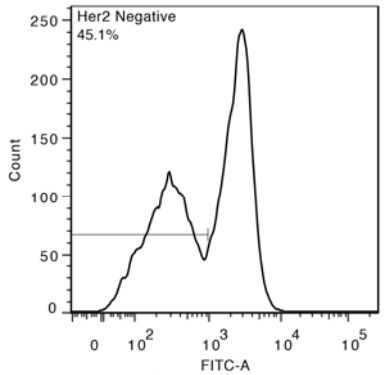
Cultured breast CTCs recapitulate discrete HER2+ vs HER2- populations

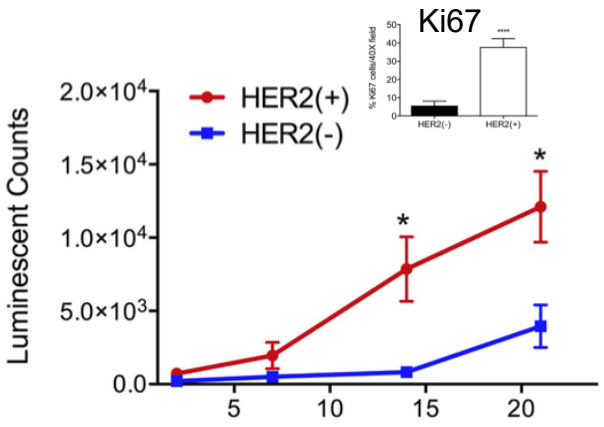


Jordan et al., Nature 2016

Functional properties:
Cultured HER2+ vs HER2- CTCs



FACS



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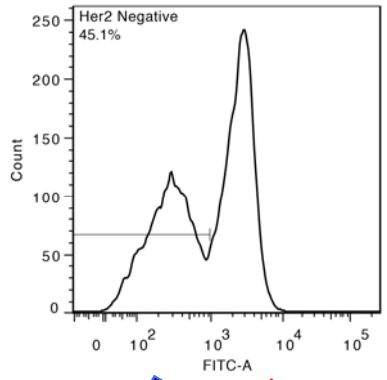

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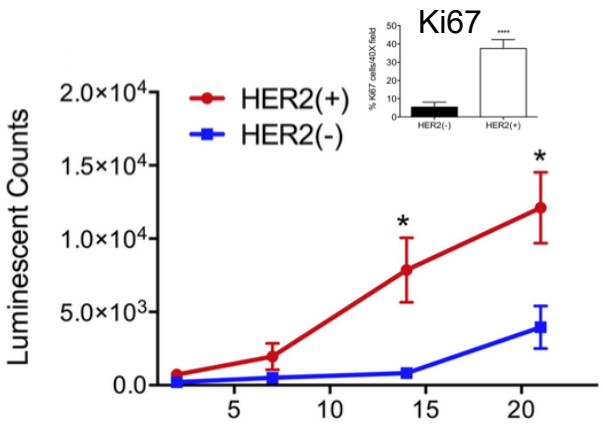
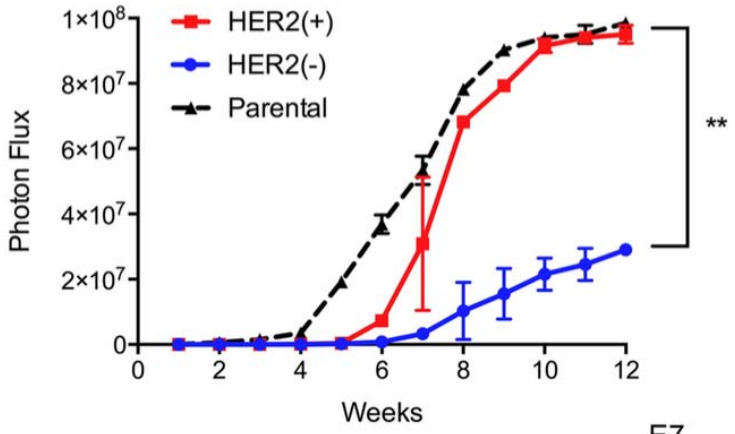
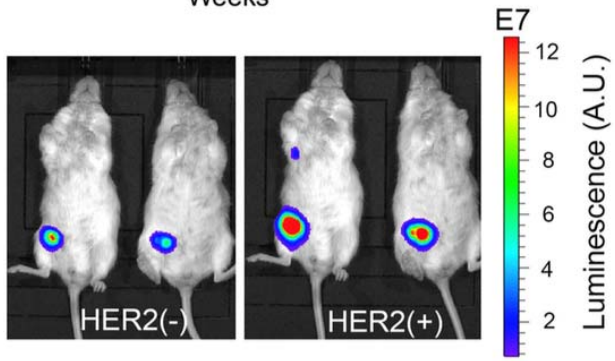






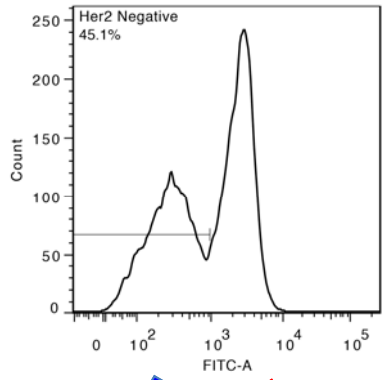
Tumor Initiation from 200 Cells

CTC Cell Line	HER2(+)	HER2(-)
Brx-82	8/8	8/8
Brx-142	4/8	3/8

Jordan et al, Nature 2016

Functional properties:

Cultured HER2+ vs HER2- CTCs



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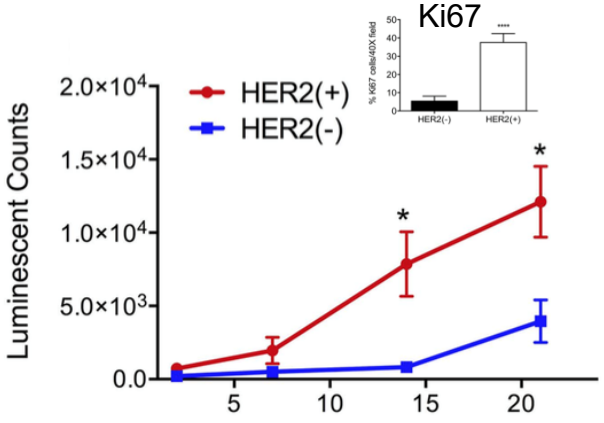

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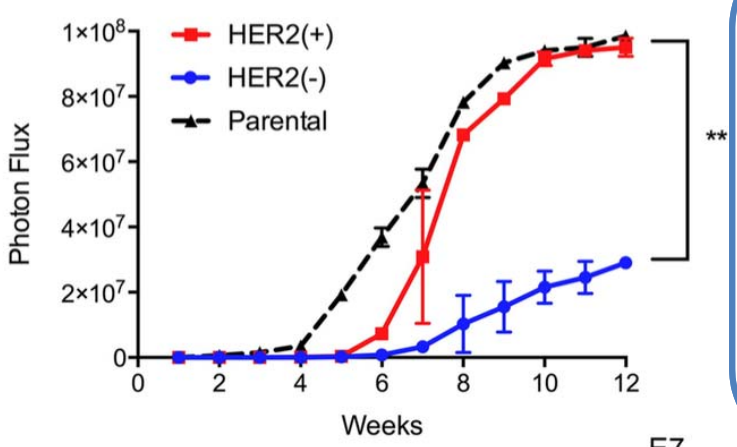
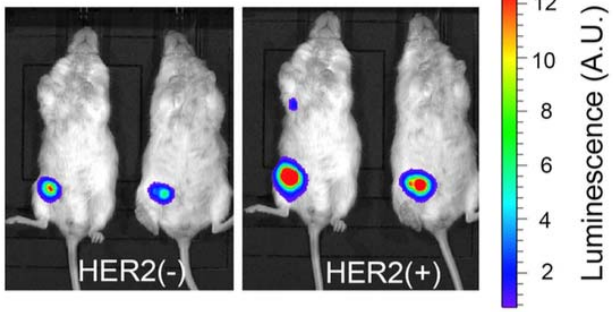
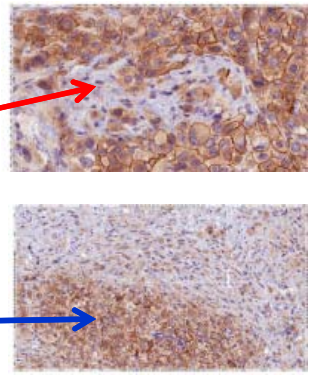




Gain of HER2-

Gain of HER2+



Tumor IHC: **HER2**

Tumor Initiation from 200 Cells

CTC Cell Line	HER2(+)	HER2(-)
Brx-82	8/8	8/8
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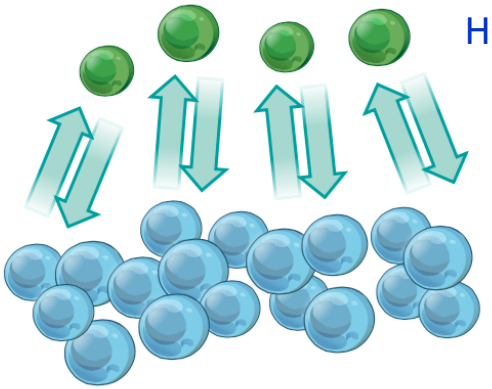
Dynamic equilibrium between HER2+ and HER2- cancer cells promotes tumorigenesis

NOTCH-driven
(Drug resistance)

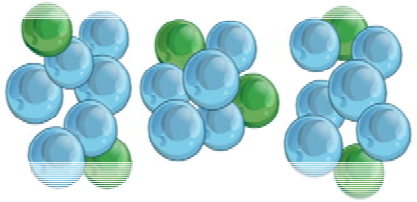
RTK-driven
(Proliferation)



HER2-

HER2+

Response and progression on multiple courses of hormonal/chemotherapy



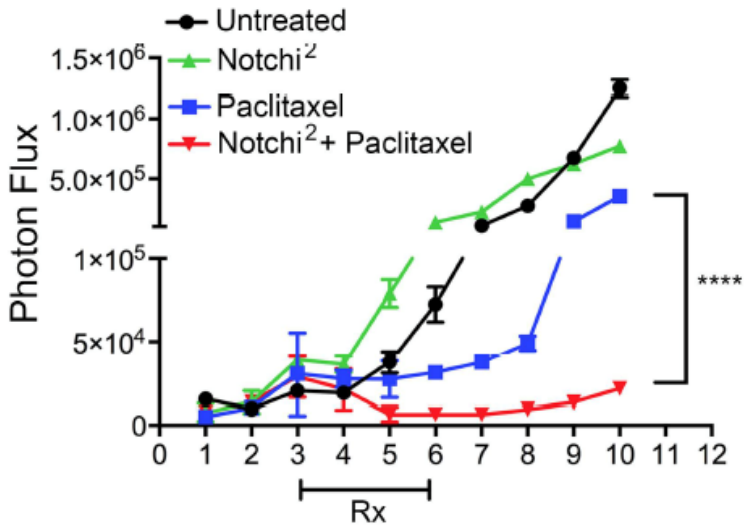
Acquired HER2 Heterogeneity and drug resistance

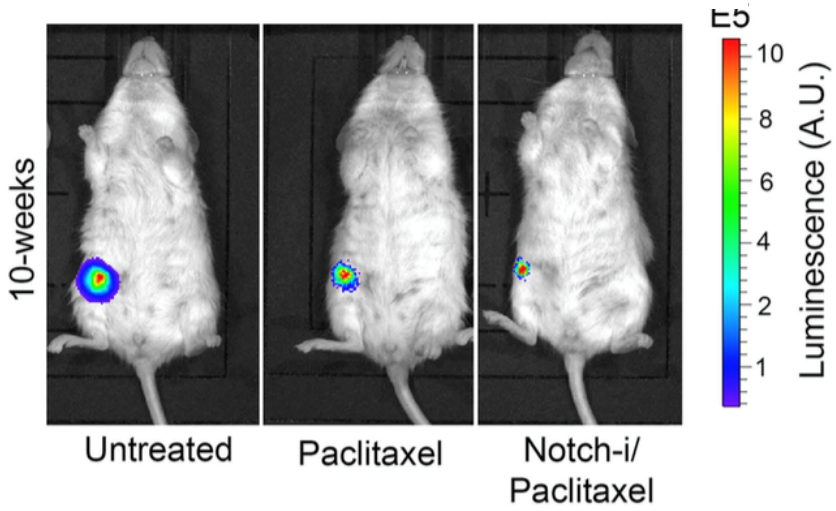
Combination Notch-i + Chemotherapy

Abrogation of mixed HER2+/- tumor

Simultaneous (4 week)
Notch-i + chemotherapy
suppresses tumor recurrence

Parental CTC-derived tumor (HER2+/-)





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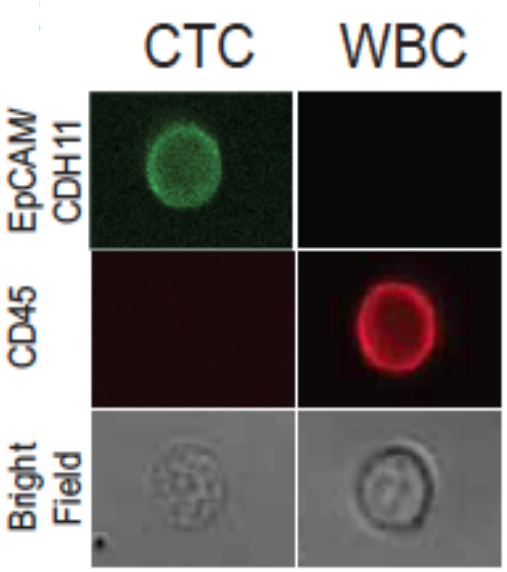
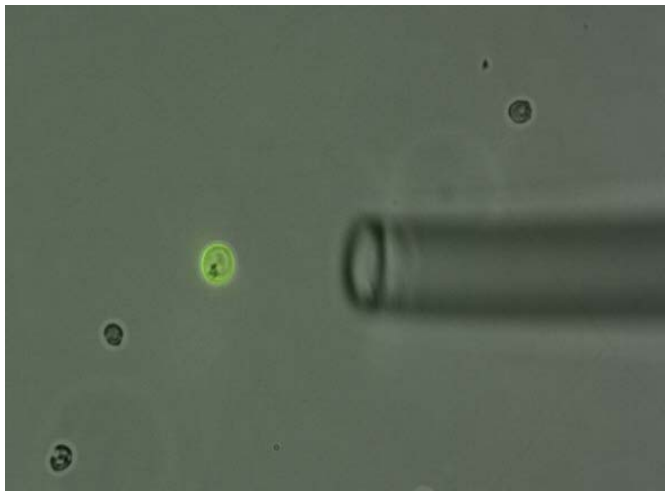
Toward RNA-based CTC diagnostics…

CTC purity in enriched product

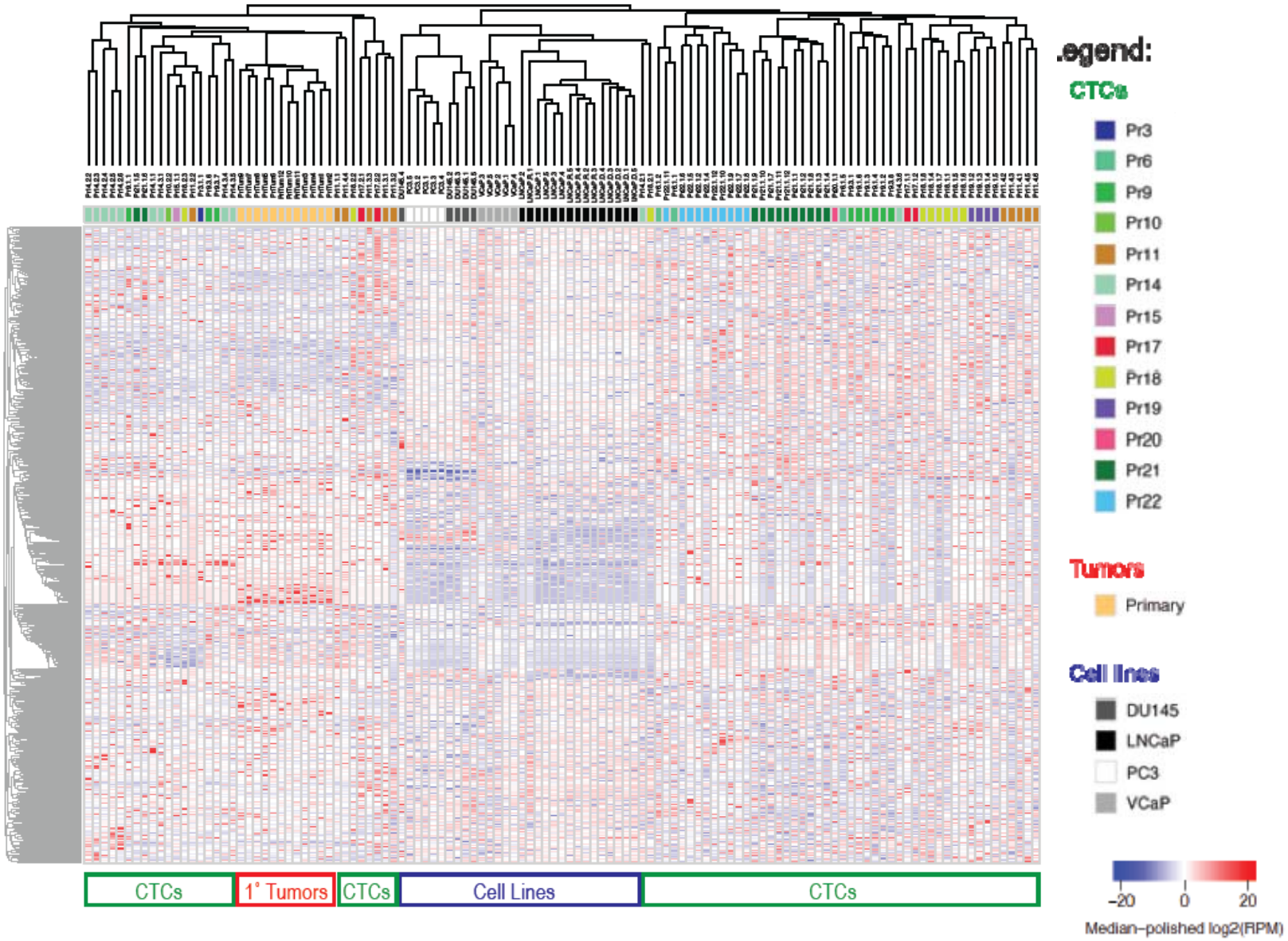
- *10 $^{4\text{-}5}$ enrichment from whole blood*
- *500 WBC in output per 1 ml of input whole blood*
- *0.1-10% purity depending on CTC burden*





Single cell micromanipulation and RNAseq

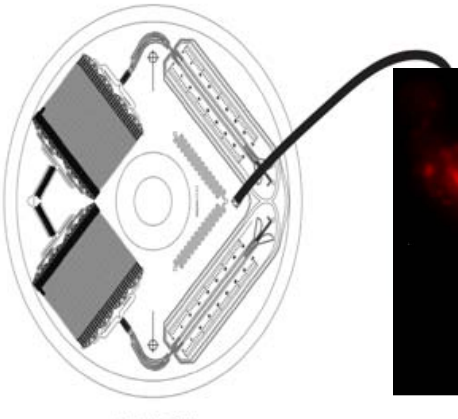
RNA expression heterogeneity of single prostate CTCs



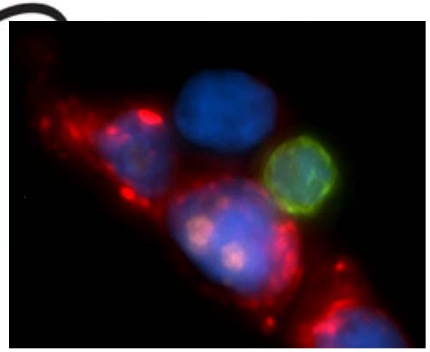
Miyamoto, Zheng et al., Science 2015

Clinical applications of CTC detection

Complex CTC ***scoring methods*** are major hurdles to clinical applications of CTC measurements.



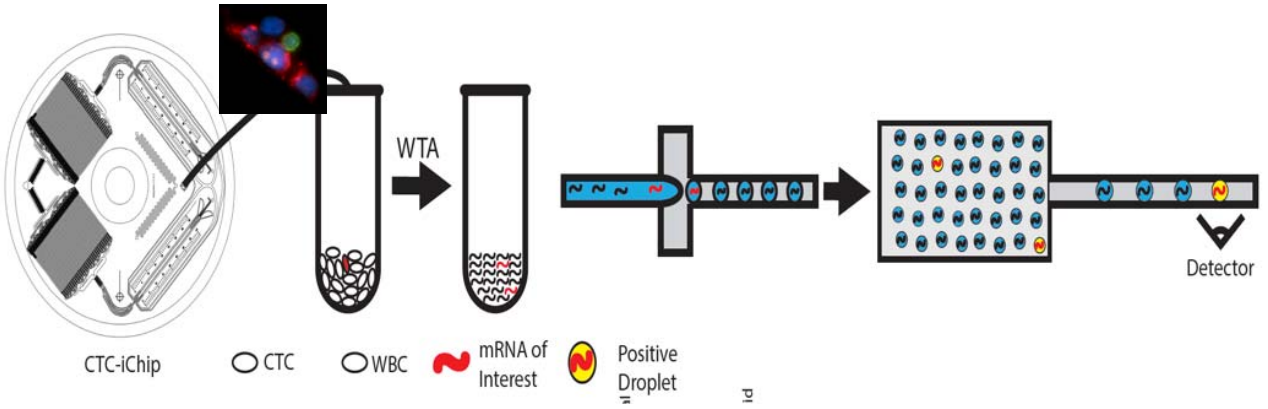
CTC-iChip
(automated)



Fluorescence microscopy
-- antibody-dependent
-- signal thresholding,
-- manual scoring…

Clinical applications of CTC detection

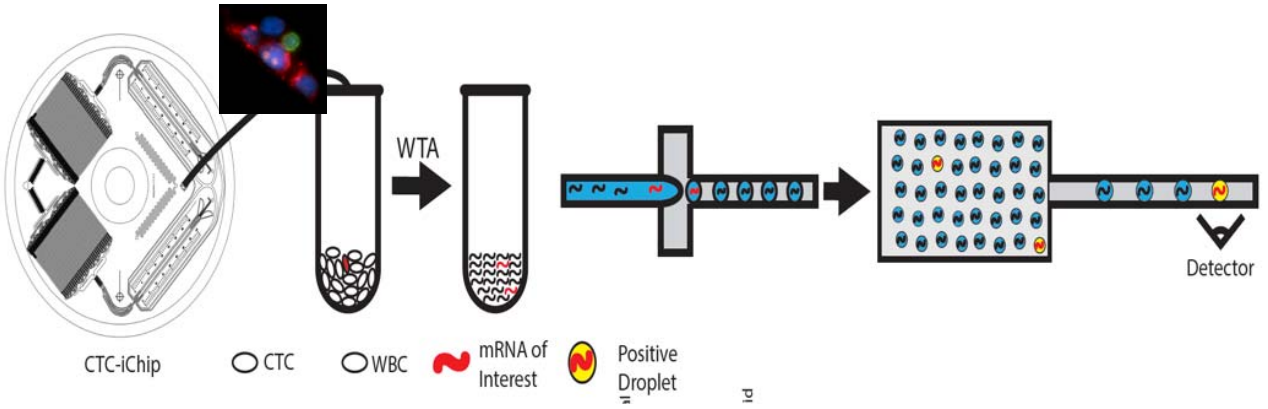
Developing a ***molecular signature of CTCs*** using RNA-digital PCR



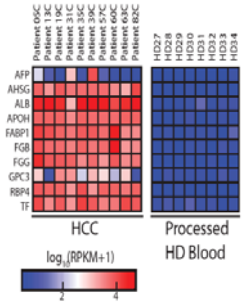
1. ***Automated*** and high throughput

Clinical applications of CTC detection

Developing a ***molecular signature of CTCs*** using RNA-digital PCR



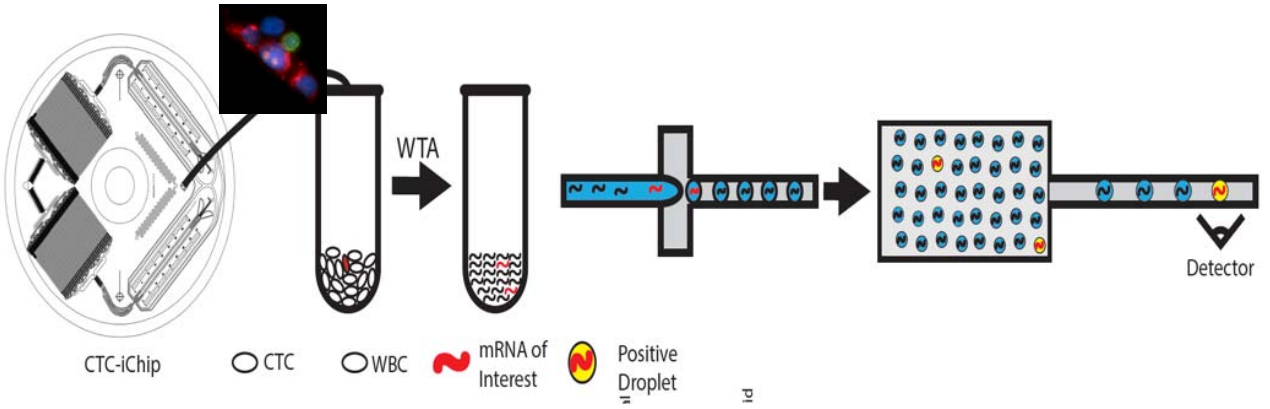
Liver cell transcripts



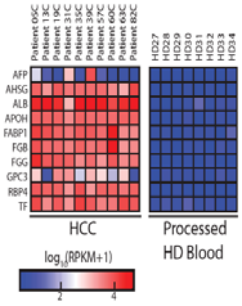
1. ***Automated*** and high throughput
2. ***Specific*** RNA lineage in blood cell background

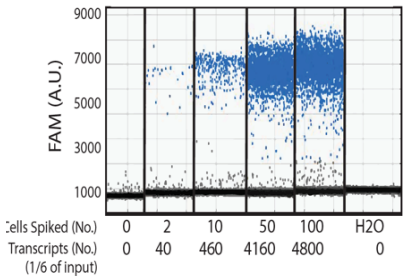
Clinical applications of CTC detection

Developing a ***molecular signature of CTCs*** using RNA-digital PCR



Liver cell transcripts

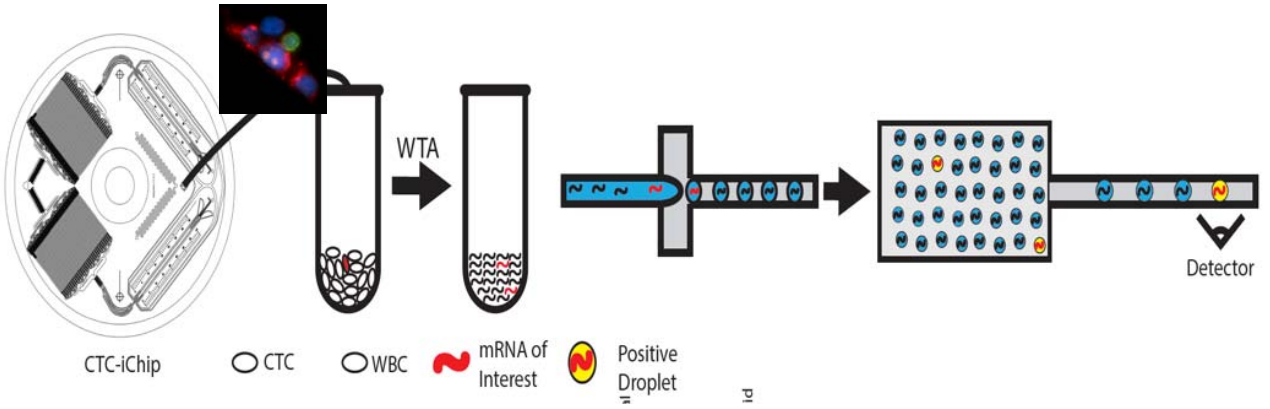




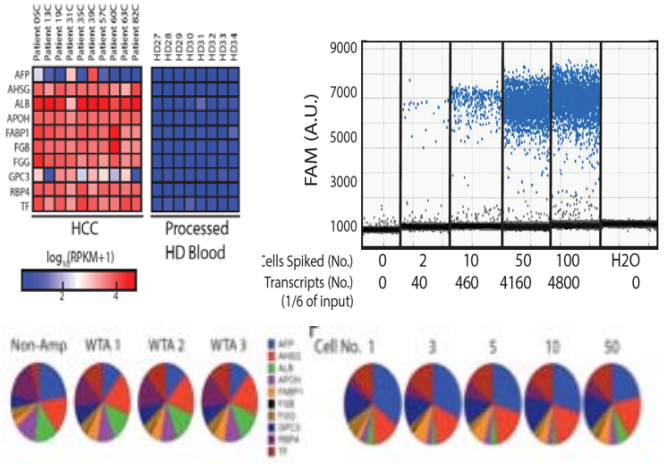
1. ***Automated*** and high throughput
2. ***Specific*** RNA lineage in blood cell background
3. ***Sensitive*** molecular amplification

Clinical applications of CTC detection

Developing a ***molecular signature of CTCs*** using RNA-digital PCR

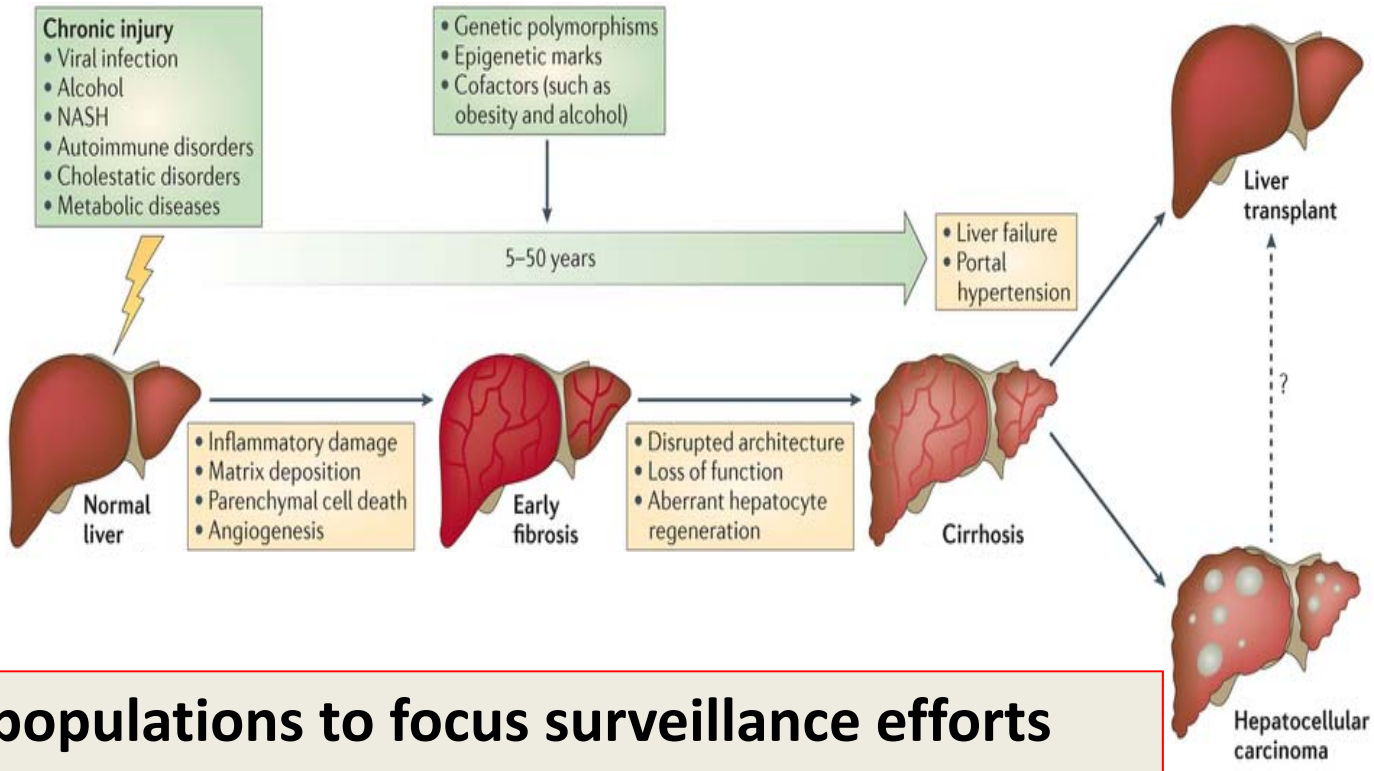


Liver cell transcripts



1. ***Automated*** and high throughput
2. ***Specific*** RNA lineage in blood cell background
3. ***Sensitive*** molecular amplification
4. Preserved marker **distribution**

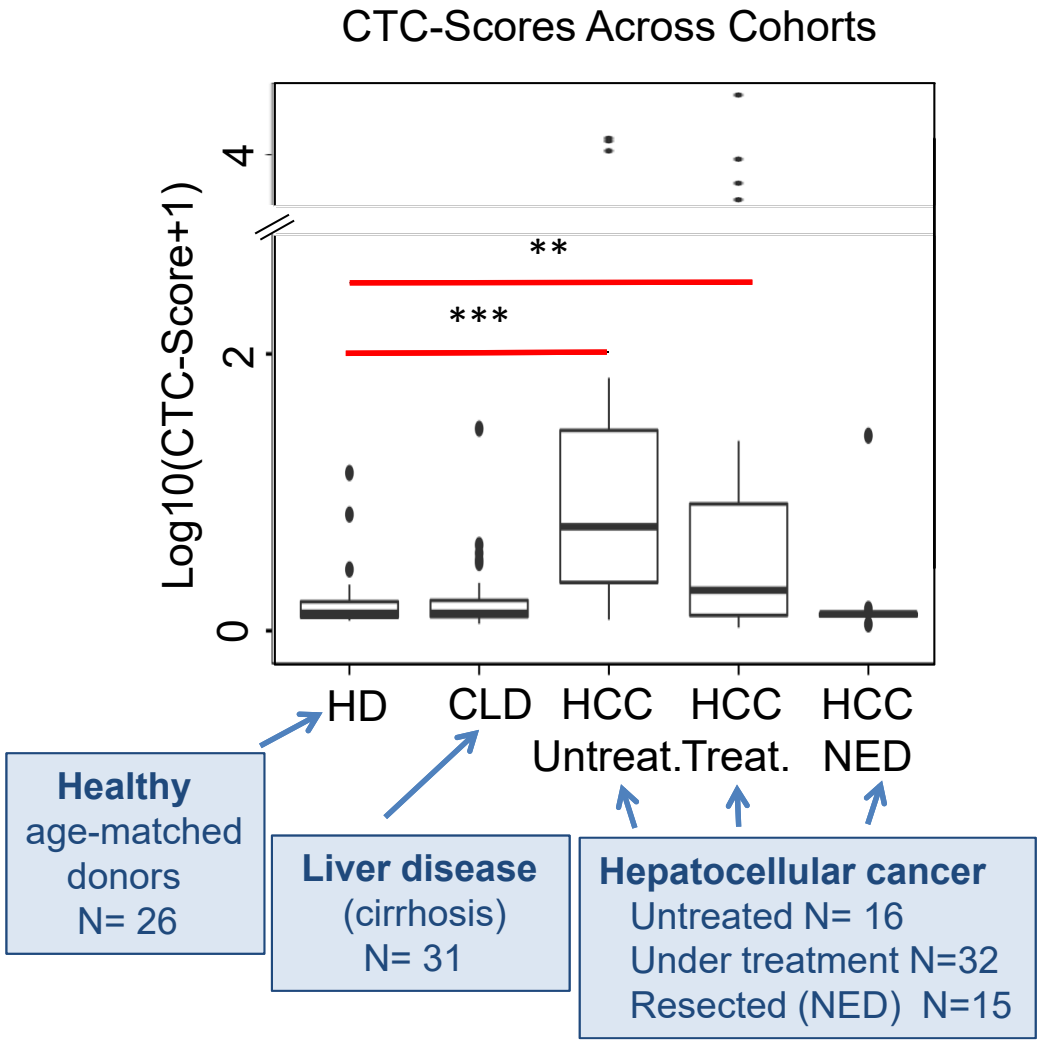
Proof of concept: Hepatocellular cancer

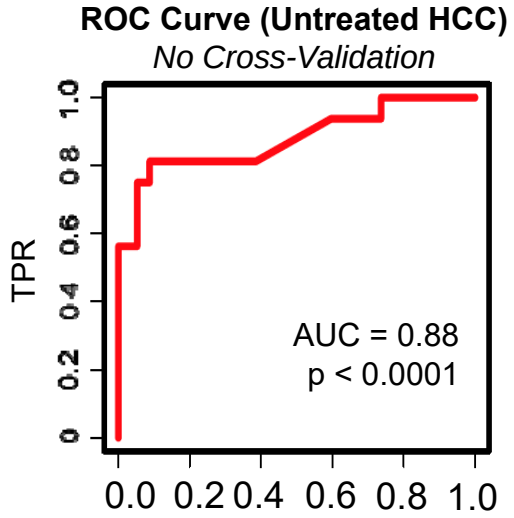


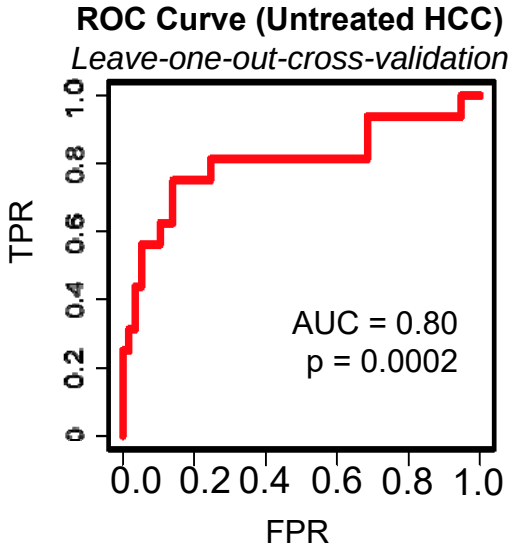
At-risk populations to focus surveillance efforts

- **80-90%** HCC occurs in cirrhosis
- HCC develops in **0.5 to 8%/year**, depending on risk
- 200M individuals at high risk from chronic hepatitis B

Hepatocellular carcinoma: Digital CTC detection



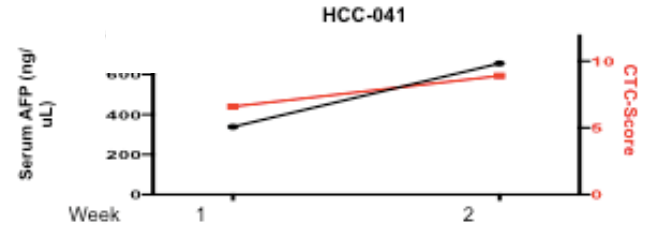




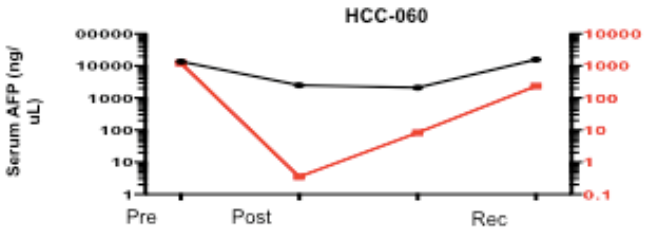
Kalinich, Bhan et al., PNAS 2017

Hepatocellular carcinoma: Monitoring response

Concordant with serum AFP

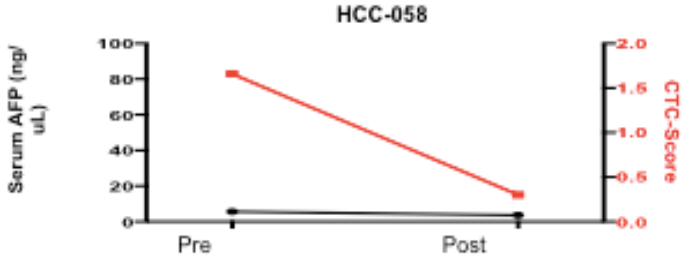


Progression

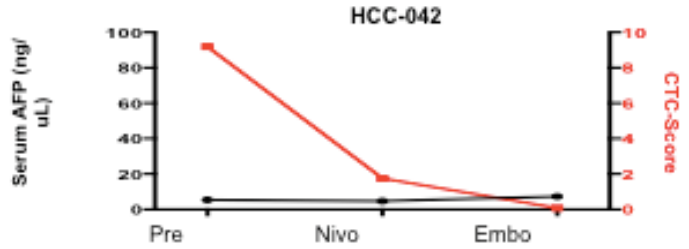


Surgical resection & recurrence

Informative when serum AFP is negative



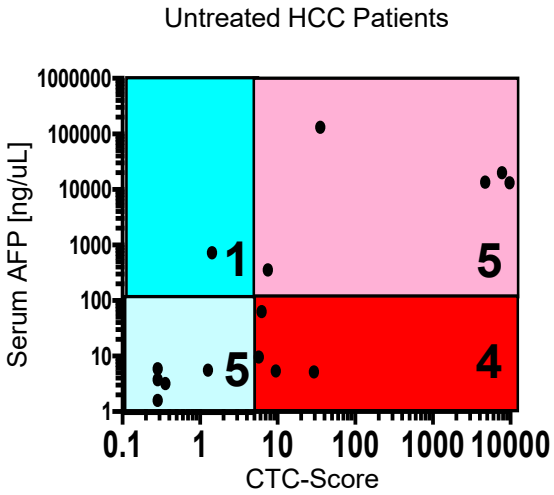
Surgical resection



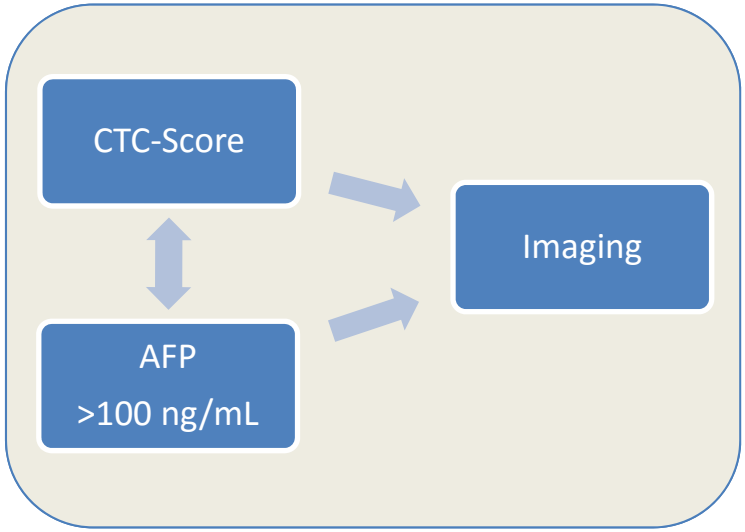
Immune Rx then embolization

Kalinich, Bhan et al., PNAS 2017

CTC-Score + AFP for early detection of liver cancer



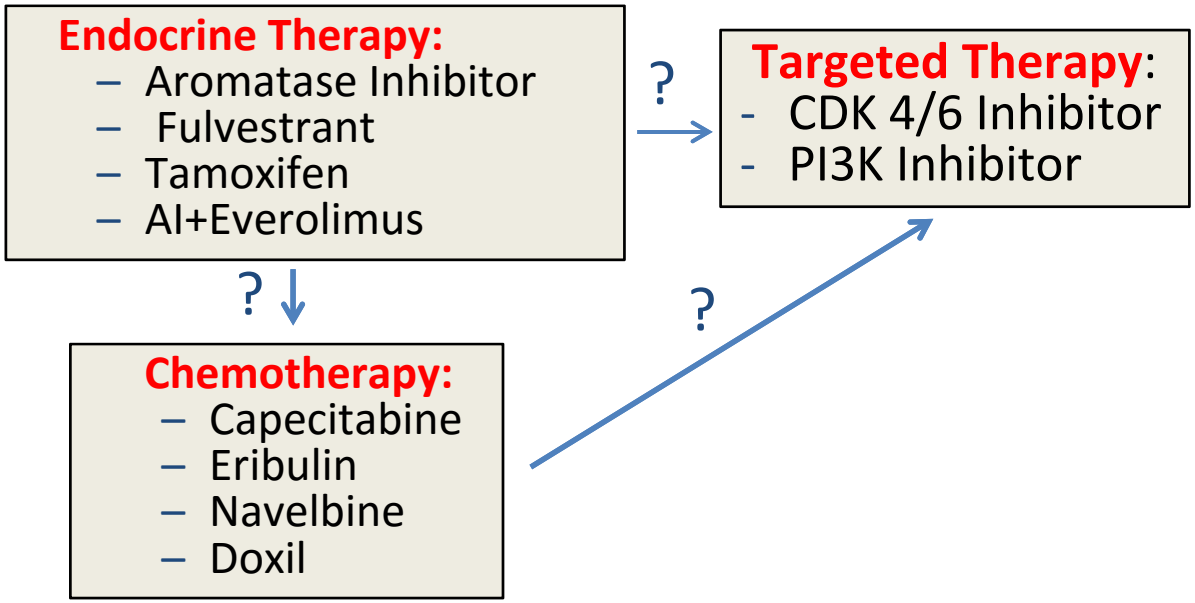
AFP+ CTC: **5**
AFP only: **1**
CTC only: 4
Combined: 10/15 of newly diagnosed HCC



Kalinich, Bhan et al., PNAS 2017

Proof of concept: *ER+* Breast cancer

2nd Line Treatment of ER+ Metastatic Breast Cancer



SESSION II:

Liquid Biopsies for Early Diagnosis

Session Chair: Carlos L. Arteaga, MD

Speakers:

Anne-Renee Hartman, MD

C. Ola Landgren, MD, PhD

Nicholas C. Turner, MD, PhD

Memorial Sloan Kettering Cancer Center

MRD Detection in Myeloma: Outcomes and Implications

Ola Landgren, M.D., Ph.D.
Chief of Myeloma Service, Memorial Sloan Kettering Cancer Center
Professor of Medicine, Weill Cornell Medical College, New York

Washington, DC, October 10, 2017

Memorial Sloan Kettering Cancer Center

Background

- With older myeloma drugs only a smaller fraction of patients obtained a complete response (CR)

- Using modern combination therapies, 100% of patients achieve a treatment response (overall response) with up to 80% of these patients reaching a CR

Landgren et al. *J Intern Med 2017*;281(4):365-382

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Background (*cont.*)

- Necessary and logical step forward, studies on minimal residual disease (MRD) and its correlation with clinical outcomes

- Both progression-free survival and overall survival have been associated with MRD

- In 2016 and 2017, two meta-analyses on MRD

Landgren et al. *J Intern Med 2017*;281(4):365-382

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ORIGINAL ARTICLE

Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: a meta-analysis

O Landgren[1], S Devlin[2], M Boulad[1] and S Mailankody[1]

Driven by access to better drugs, on average, newly diagnosed multiple myeloma patients have over 10 years overall survival. Using modern combination therapies—with or without the addition of high-dose melphalan and autologous stem cell transplantation—up to 80% of patients reach a complete response. As a logical and necessary step forward, clinical studies have explored strategies to detect minimal residual disease (MRD) and its correlation with clinical outcomes. In this context, MRD has been proposed as a regulatory end point for drug approval in newly diagnosed multiple myeloma. To better define the role of MRD negativity in relation to clinical outcomes, we undertook a meta-analysis including published clinical trials of newly diagnosed multiple myeloma patients. We applied a random effects model which weighted studies using the inverse–variance method. Studies were combined on the scale of the logarithm of the hazard ratio (HR) and the corresponding s.d. We found that MRD negativity (versus positivity) was associated with better PFS (HR = 0.35; 95% confidence interval (CI) 0.27–0.46; $P < 0.001$) and overall survival (HR = 0.48; 95% CI 0.33–0.70; $P < 0.001$). Our results show that MRD negativity is a strong predictor of clinical outcomes, supportive of MRD becoming a regulatory end point for drug approval in newly diagnosed multiple myeloma.

Bone Marrow Transplantation (2016) **51,** 1565–1568; doi:10.1038/bmt.2016.222; published online 5 September 2016

Research

JAMA Oncology | Original Investigation

Association of Minimal Residual Disease With Superior Survival Outcomes in Patients With Multiple Myeloma
A Meta-analysis

Nikhil C. Munshi, MD; Herve Avet-Loiseau, PhD; Andy C. Rawstron, PhD; Roger G. Owen, MD; J. Anthony Child, MD; Anjan Thakurta, PhD; Paul Sherrington, PhD; Mehmet Kemal Samur, PhD; Anna Georgieva, MD, PhD; Kenneth C. Anderson, MD; Walter M. Gregory, PhD

IMPORTANCE Numerous studies have evaluated the prognostic value of minimal residual disease (MRD) in patients with multiple myeloma (MM). Most studies were small and varied in terms of patient population, treatment, and MRD assessment methods.

Editorial page 18

Supplemental content

Landgren et al. *Bone Marrow Transplant 2016*;51(12):1565-1568;
Muschi et al. *JAMA Oncol. 2017*;3(1):28-35

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Methods

- On December 22, 2015, we conducted a systematic search for clinical trials of newly diagnosed multiple myeloma patients with information on MRD and clinical outcomes

- We applied the following MEDLINE (via PubMed), EMBASE, and Cochrane's Central Register of Controlled Trials (CENTRAL)

Landgren et al. *Bone Marrow Transplant 2016*;51(12):1565-1568

Methods (*cont.*)

- Total of 390 potential studies were first identified → review of individual abstracts

- 374 were not clinical trials with MRD testing in newly diagnosed multiple myeloma

- Defined 16 clinical trials of newly diagnosed multiple myeloma, MRD & clinical outcomes

Landgren et al. *Bone Marrow Transplant 2016*;51(12):1565-1568

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Statistical Methods

- Random effects model, which weighted studies using the inverse-variance method

- Studies were combined on the scale of the logarithm of the hazard ratio and the corresponding standard error

- The analysis used the package 'metafor' in R Statistical Platform, v 3.2.3

Landgren et al. *Bone Marrow Transplant 2016*;51(12):1565-1568

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Results

- Upon careful review of the 16 identified studies, the following were excluded:
  - 7 lacked HR estimates for MRD and PFS/OS
  - 4 used overlapping cohorts of patients (duplicates)
  - 1 lacked info on timing of MRD analysis

Landgren et al. *Bone Marrow Transplant 2016*;51(12):1565-1568

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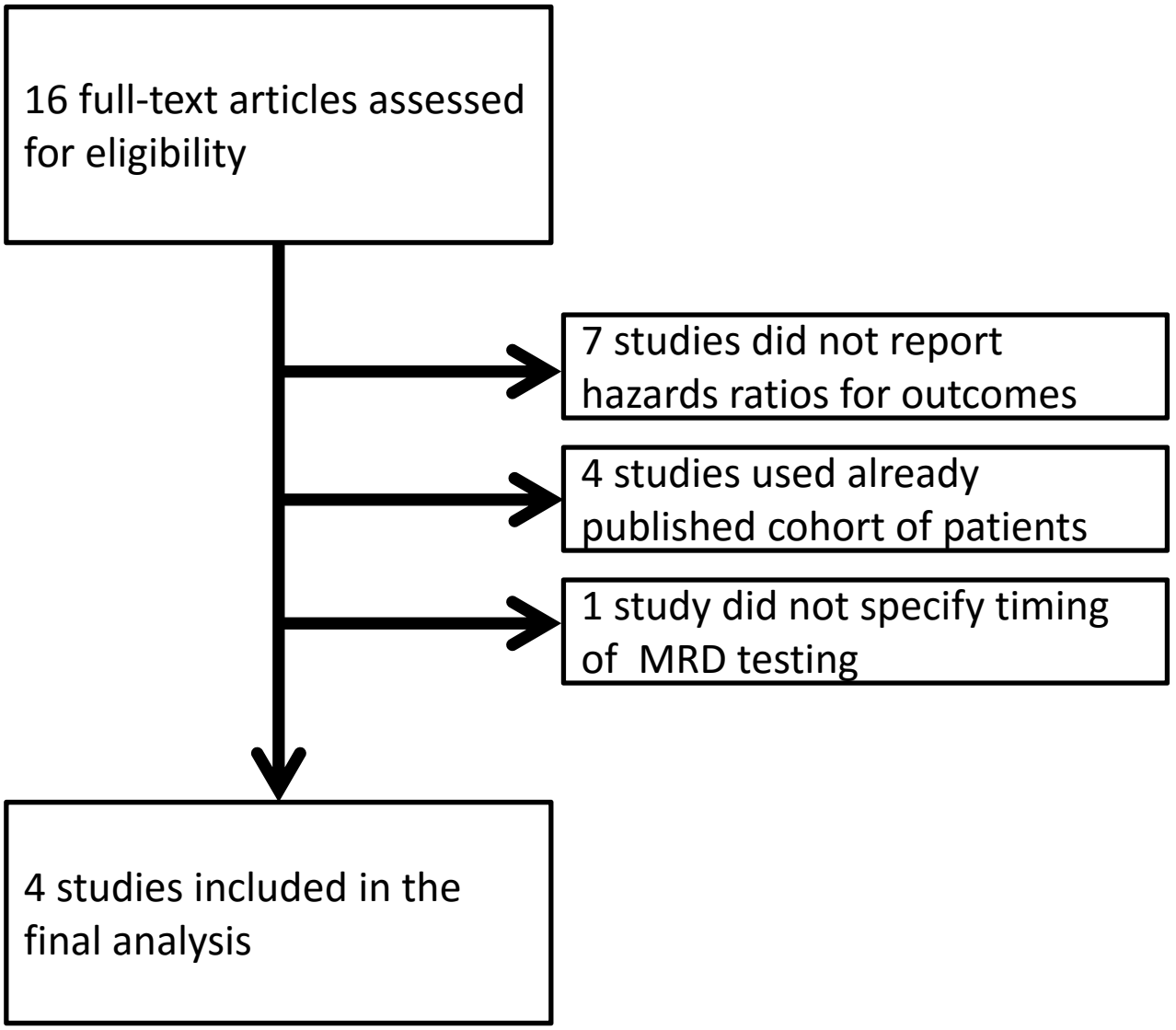

Adapted from Landgren et al. *Bone Marrow Transplant 2016*;51(12):1565-1568

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Results (*cont.*)

- Four studies with information on MRD status and HR for progression-free survival included in final analysis

- Three studies with overall survival data (however, one study had no deaths) so two studies provided HRs for MRD and overall survival

Landgren et al. *Bone Marrow Transplant 2016*;51(12):1565-1568

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Results (*cont.*)

- Main result of meta-analysis show that newly diagnosed multiple myeloma patients who obtained MRD negativity had better progression-free survival **(HR=0.35; 95% CI 0.27-0.46; P<0.001)**

Landgren et al. *Bone Marrow Transplant 2016*;51(12):1565-1568

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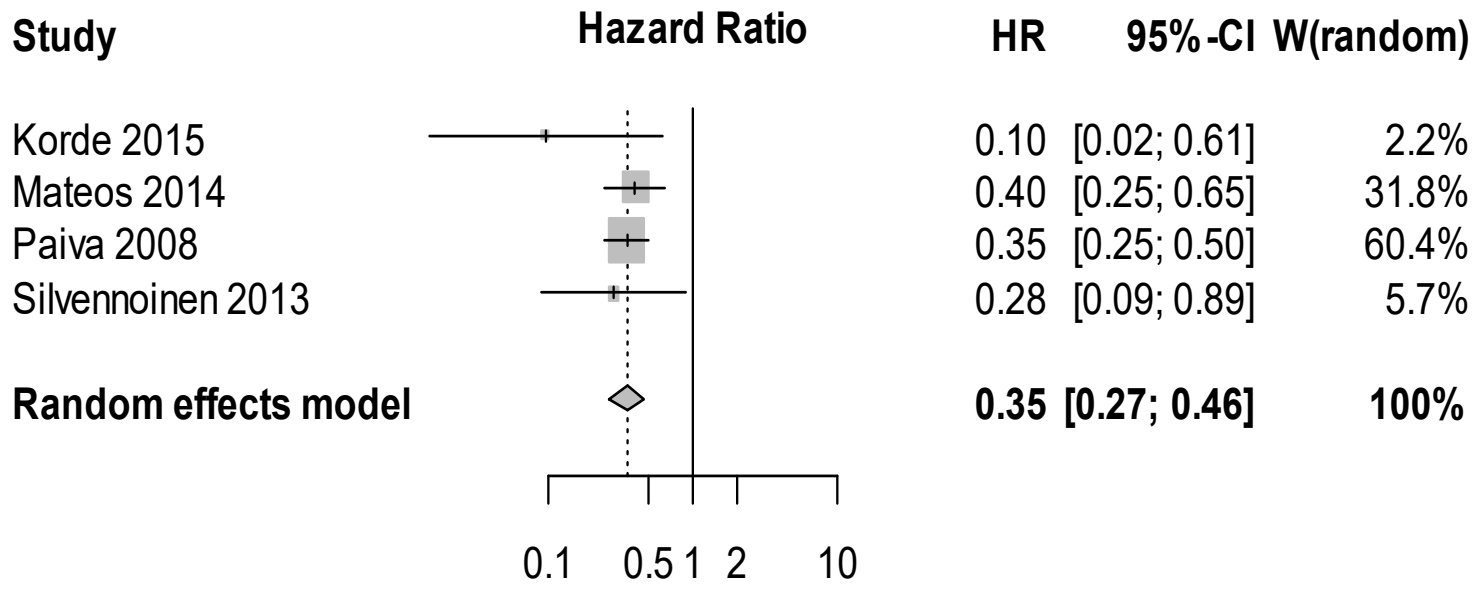
Results (*cont.*)

- Three studies used multiparameter flow-cytometry; one used allele-specific qPCR, both with a sensitivity of 1 in 10,000 cells (10^{-4}) or better for MRD

- Largest study (Paiva et al.) had 60.4% weight; while smallest study (Korde et al.) had 2.2% weight (W random)

Landgren et al. *Bone Marrow Transplant 2016*;51(12):1565-1568

MRD negativity (vs. MRD positivity) and progression-free survival*



A lower hazard ratio indicates decreased risk for each survival endpoint (i.e. MRD negativity associated with lower risk of progression)

Landgren et al. *Bone Marrow Transplant 2016*;51(12):1565-1568

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Results

- Only Paiva et al. and Mateos at al. studies provided HRs for MRD and overall survival

- Main result of meta-analysis show that newly diagnosed multiple myeloma patients who obtained MRD negativity had better overall survival **(HR=0.48; 95% CI 0.33-0.70; P<0.001)**

Landgren et al. *Bone Marrow Transplant 2016*;51(12):1565-1568

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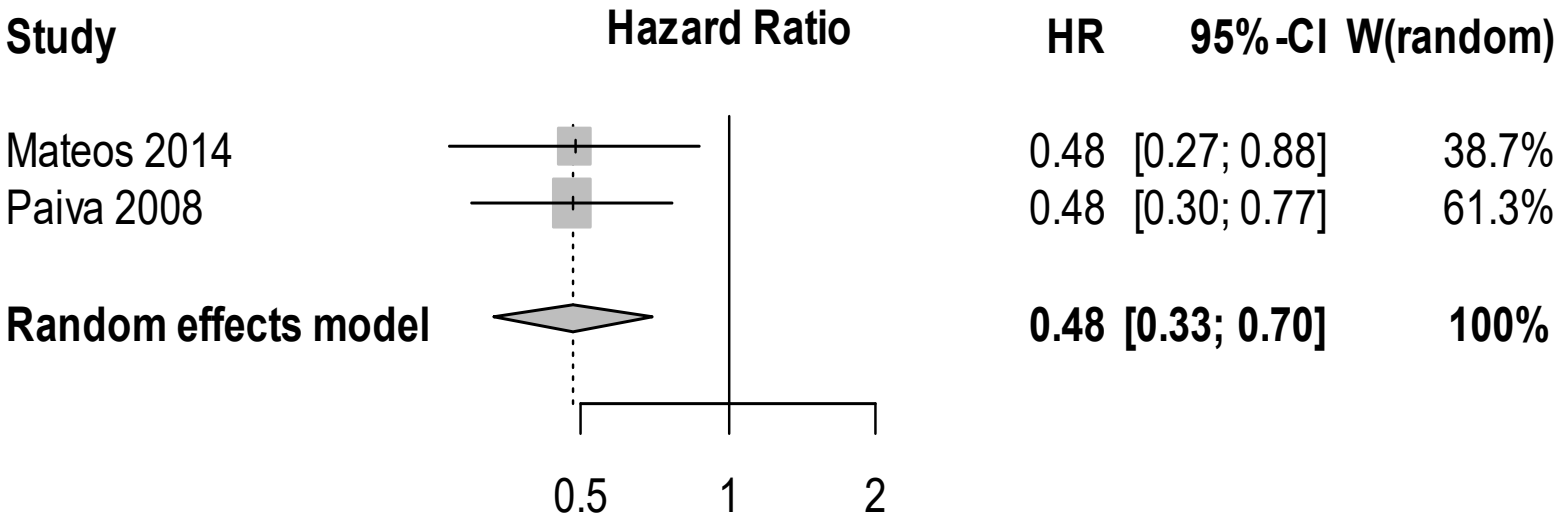
MRD negativity (vs. MRD positivity) and overall survival*



**A lower hazard ratio indicates decreased risk for each survival endpoint (i.e. MRD negativity associated with lower risk of dying)*

Landgren et al. *Bone Marrow Transplant 2016*;51(12):1565-1568

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Summary and implications

- Meta-analysis found MRD negativity associated with better progression-free survival and overall survival in newly diagnosed multiple myeloma

- MRD now part of updated 2016 IMWG criteria for treatment response evaluation

Kumar et al. *Lancet Oncol 2016*;17(8):e328-e346

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CCR FOCUS

New Developments in Diagnosis, Prognosis, and Assessment of Response in Multiple Myeloma

Ola Landgren[1] and S. Vincent Rajkumar[2]

Abstract

Over the past few years, the management of multiple my
loma has changed. We have new guidelines regarding how
set the diagnosis, when to initiate therapy, and how to monit
treatment response. In 2014, the updated International My
loma Working Group (IMWG) diagnostic criteria changed t
definition of multiple myeloma from being a disease defin
by symptoms to a disease defined by biomarkers. Toda
modern combination therapies have reported up to 60%
80% of patients reaching a complete response. As a logical a
necessary step forward, investigators have explored strategies

Box 2. Definition of MRD negativity based on 2016 IMWG criteria

MRD negativity

- Requires complete response
- Requires absence of aberrant clonal plasma in bone marrow aspirate, ruled out by an assay with a minimum sensitivity of 1 in 10^5 nucleated cells or higher (i.e., 10^{-5} sensitivity)[a]

NOTE: Adapted from ref. 6: *The Lancet Oncology*, Vol. 17, Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al., International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma, e328–46, © 2016, with permission from Elsevier.

[a]Based on flow cytometry or next-generation sequencing (such as the EuroFlow standard operation procedure for MRD detection in multiple myeloma, or other validated equivalent methods; LymphoSIGHT, or other validated equivalent method).

Landgren and Rajkumar. *Clin Cancer Res 2016*;22(22):5428-5433

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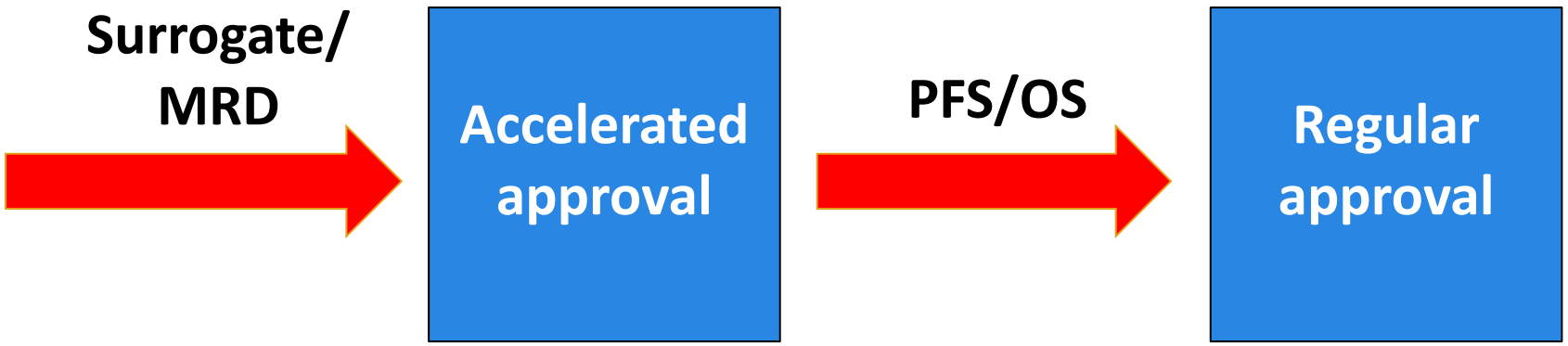
Regulatory implications of MRD testing in multiple myeloma?

MRD as a regulatory end-point

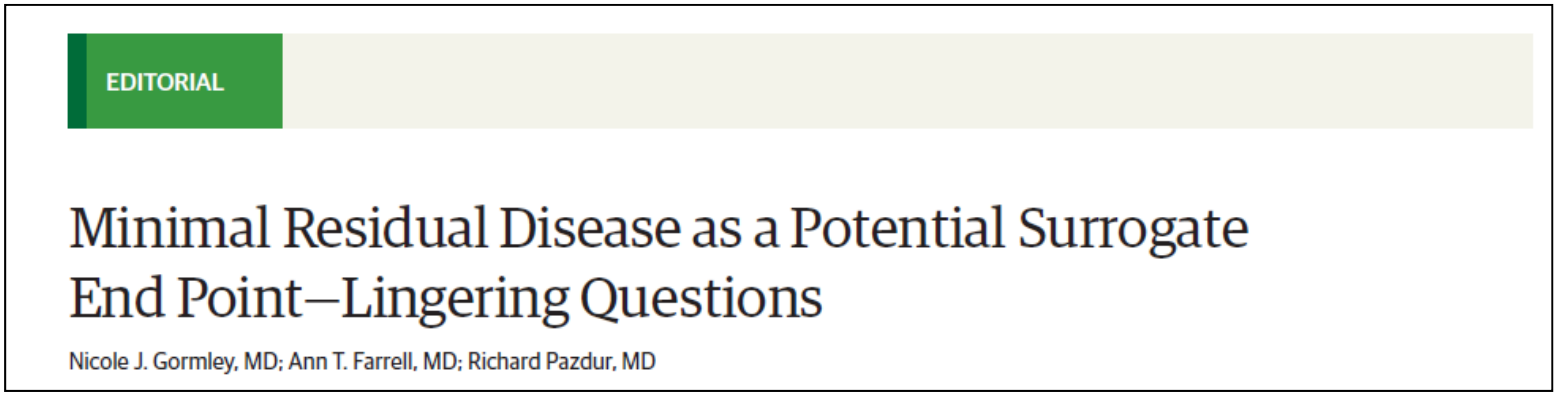
- Median PFS and OS in younger patients with newly diagnosed multiple myeloma is >5 and >10 years, respectively

- Urgent need for surrogate end-points to facilitate drug development and speed up patients' access to new drugs

MRD as a regulatory end-point: how do we get there?



Single trial model



- Level of MRD sensitivity is prognostic
- Newly diagnosed *vs.* relapsed patients
- Role of cytogenetics/FISH/sequencing
- Timing of MRD assessment
- Individual survival and censoring times

Gormley et al. *JAMA Oncol. 2017*;3(1):18-20

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Clinical implications of MRD testing in multiple myeloma?

CCR Perspectives in Regulatory Science and Policy

Clinical Cancer Research

The Role of Minimal Residual Disease Testing in Myeloma Treatment Selection and Drug Development: Current Value and Future Applications

Kenneth C. Anderson[1], Daniel Auclair[2], Gary J. Kelloff[3], Caroline C. Sigman[4], Hervé Avet-Loiseau[5], Ann T. Farrell[6], Nicole J. Gormley[6], Shaji K. Kumar[7], Ola Landgren[8], Nikhil C. Munshi[9], Michele Cavo[10], Faith E. Davies[11], Alessandra Di Bacco[12], Jennifer S. Dickey[13], Steven I. Gutman[14], Howard R. Higley[4], Mohamad A. Hussein[15,16], J. Milburn Jessup[17], Ilan R. Kirsch[18], Richard F. Little[3], Robert D. Loberg[19], Jens G. Lohr[9], Lata Mukundan[4], James L. Omel[20], Trevor J. Pugh[21], Gregory H. Reaman[6], Michael D. Robbins[22], A. Kate Sasser[23], Nancy Valente[24], and Elena Zamagni[10]

Abstract

Treatment of myeloma has benefited from the introduction of more effective and better tolerated agents, improvements in supportive care, better understanding of disease biology, revision of diagnostic criteria, and new sensitive and specific tools for disease prognostication and management. Assessment of minimal residual disease (MRD) in response to therapy is one of these tools, as longer progression-free survival (PFS) is seen consistently among patients who have achieved MRD negativity. Current therapies lead to unprecedented frequency and depth of response, developed to better understand the immune environment in myeloma and response to immunomodulatory agents while methods for molecular profiling of myeloma cells and circulating DNA in blood are also emerging. With the continued development and standardization of these methodologies, MRD has high potential for use in gaining new drug approvals in myeloma. The FDA has outlined two pathways by which MRD could be qualified as a surrogate endpoint for clinical studies directed at obtaining accelerated approval for new myeloma drugs. Most important-

Anderson et al. *Clin Cancer Res. 2017*;23(15):3980-3993

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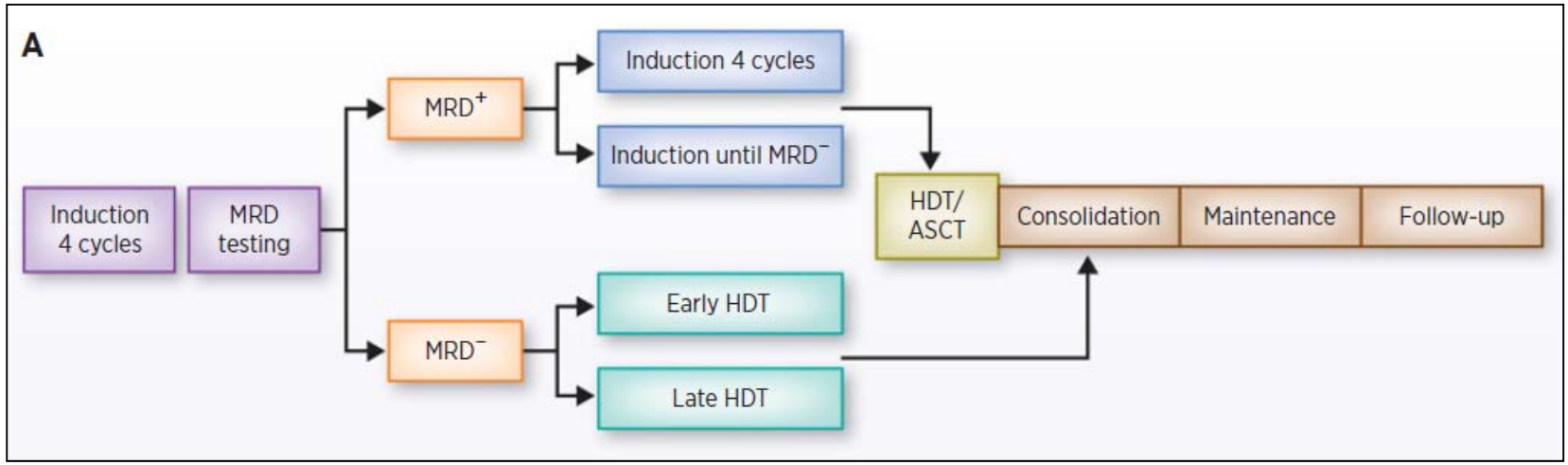
MRD negative after combination therapy



Hypothesis:

Early MRD negative

→ no upfront auto-transplant

Anderson et al. *Clin Cancer Res. 2017*;23(15):3980-3993

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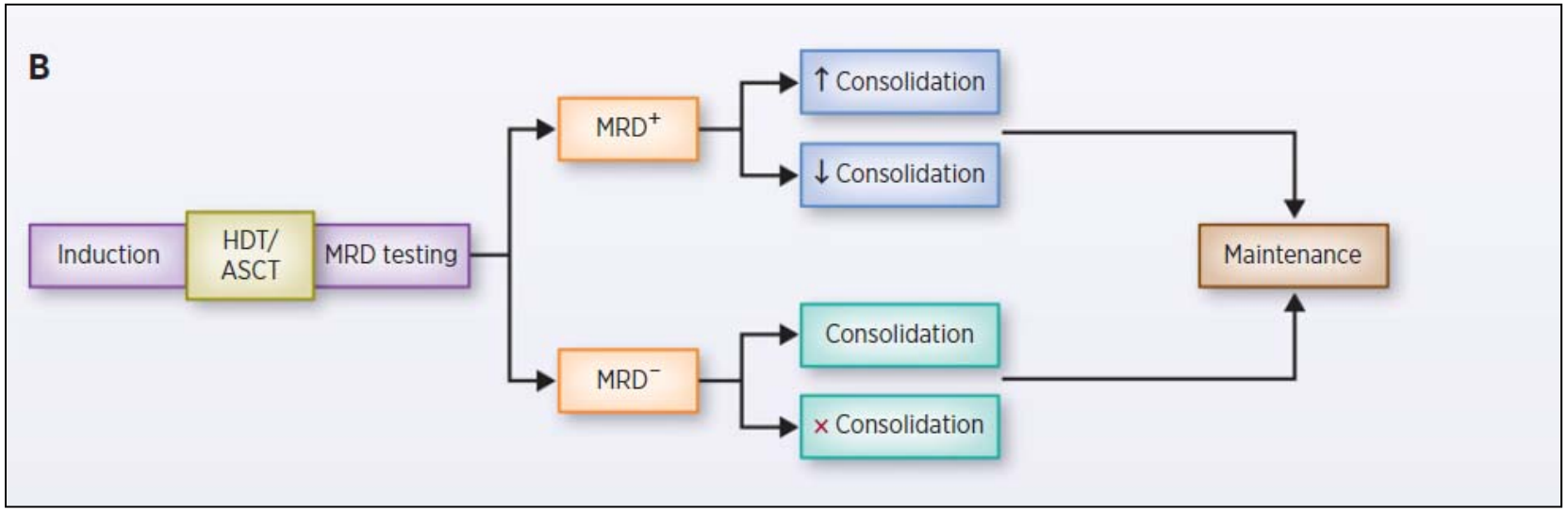
MRD negative after auto-transplant



<u>Hypothesis:</u>

MRD negative post-auto-transplant

→ no consolidation

Anderson et al. *Clin Cancer Res. 2017*;23(15):3980-3993

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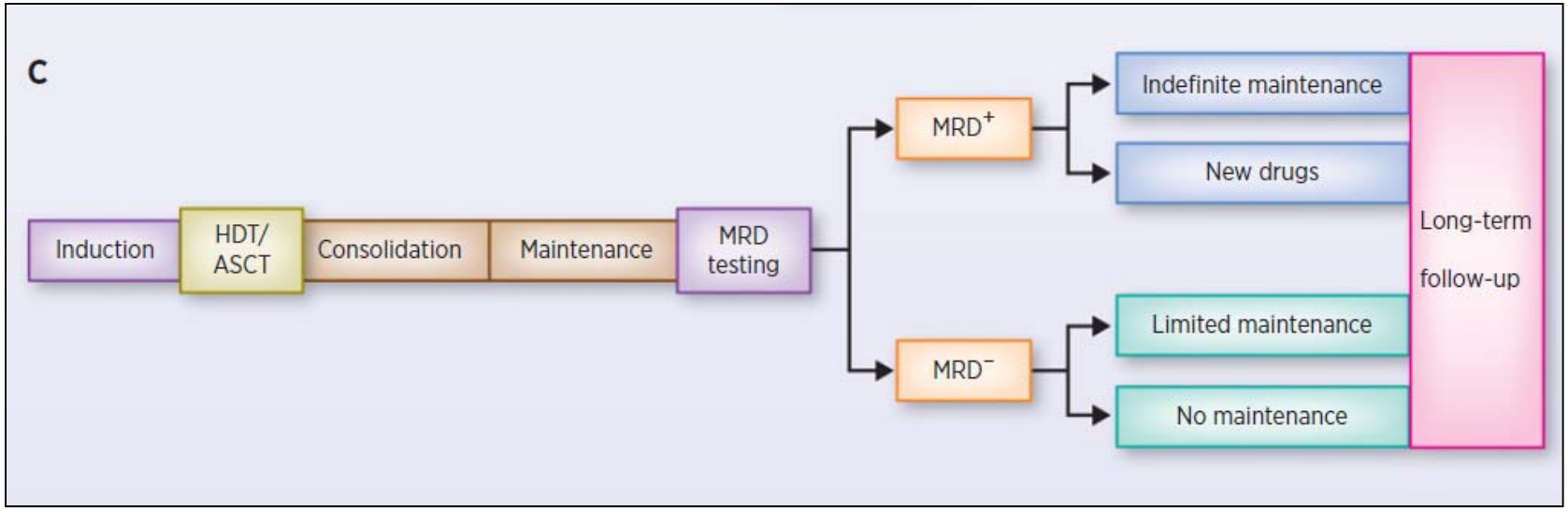
MRD negative after long maintenance



<u>Hypothesis:</u>

MRD negative extended period of time

→ stop maintenance

Anderson et al. *Clin Cancer Res. 2017*;23(15):3980-3993

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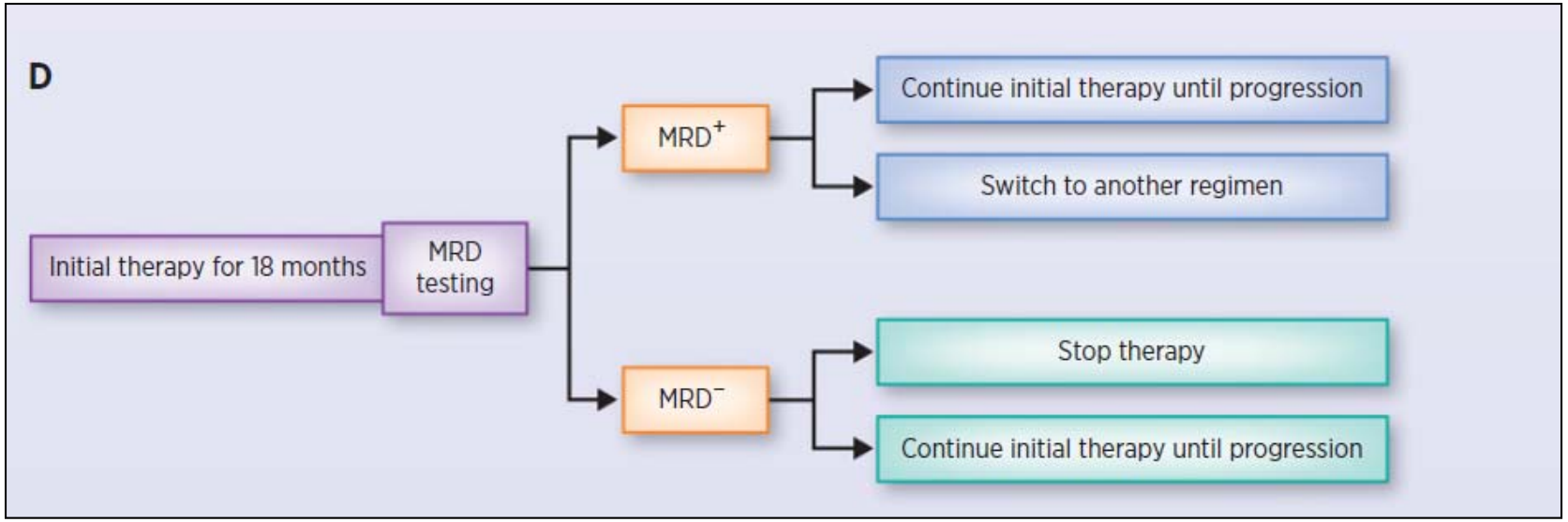
MRD negative non-transplant patients



Hypothesis:

MRD negative extended period of time

→ stop therapy

Anderson et al. *Clin Cancer Res. 2017*;23(15):3980-3993

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THIS WAY
THAT WAY

Emerging MRD patterns in myeloma

- Ongoing prospective studies suggest that MRD negativity is more important than treatment to become MRD negative

Newly diagnosed multiple myeloma

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 6, 2017 VOL. 376 NO. 14

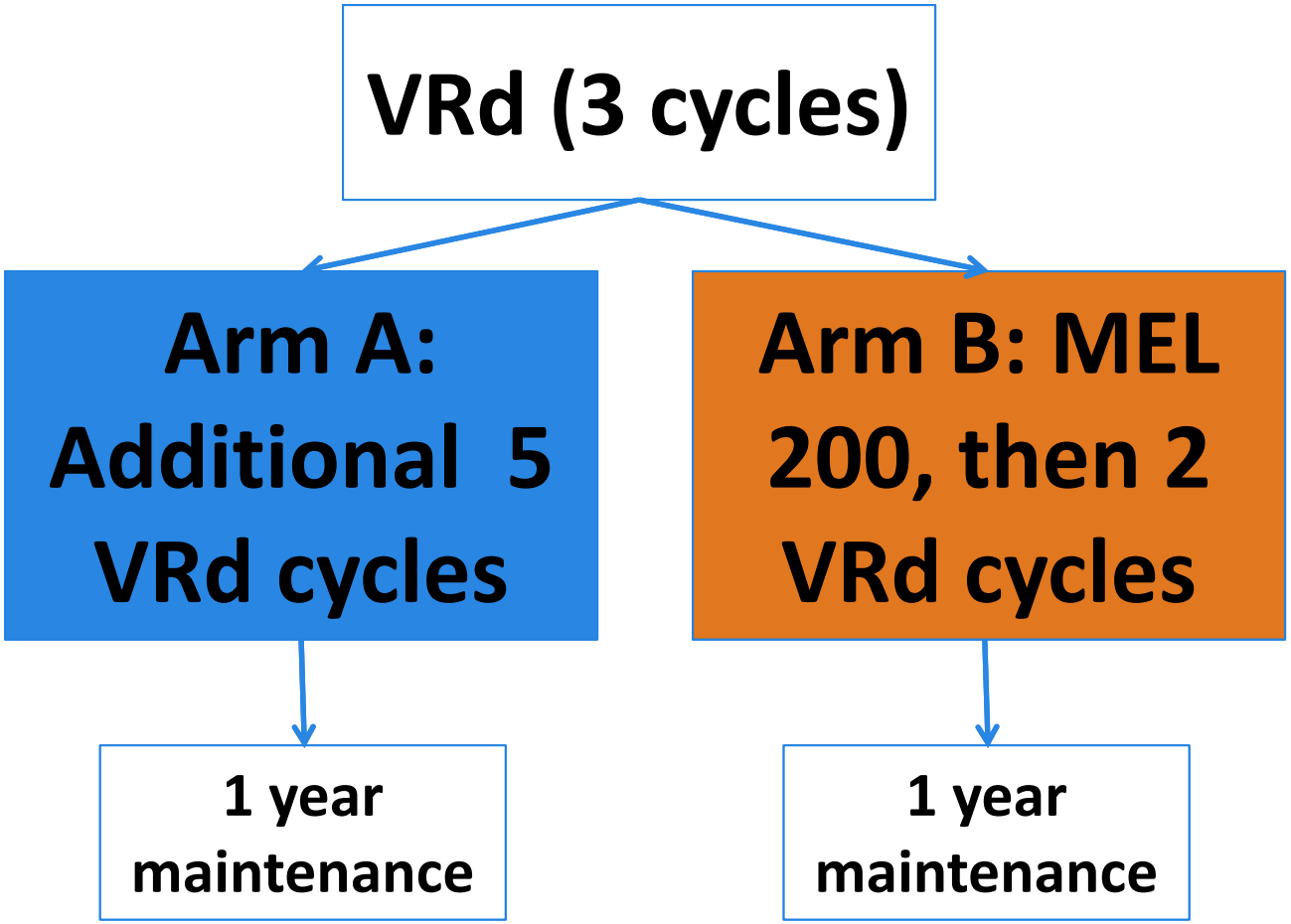
Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma

Michel Attal, M.D., Valerie Lauwers-Cances, M.D., Cyrille Hulin, M.D., Xavier Leleu, M.D., Denis Caillot, M.D., Martine Escoffre, M.D., Bertrand Arnulf, M.D., Margaret Macro, M.D., Karim Belhadj, M.D., Laurent Garderet, M.D., Murielle Roussel, M.D., Catherine Payen, M.D., Claire Mathiot, M.D., Jean P. Fermand, M.D., Nathalie Meuleman, M.D., Sandrine Rollet, M.S., Michelle E. Maglio, B.S., Andrea A. Zeytoonjian, B.S., Edie A. Weller, Ph.D., Nikhil Munshi, M.D., Kenneth C. Anderson, M.D., Paul G. Richardson, M.D., Thierry Facon, M.D., Hervé Avet-Loiseau, M.D., Jean-Luc Harousseau, M.D., and Philippe Moreau, M.D., for the IFM 2009 Study*

Attal M, et al. *NEJM 2017*

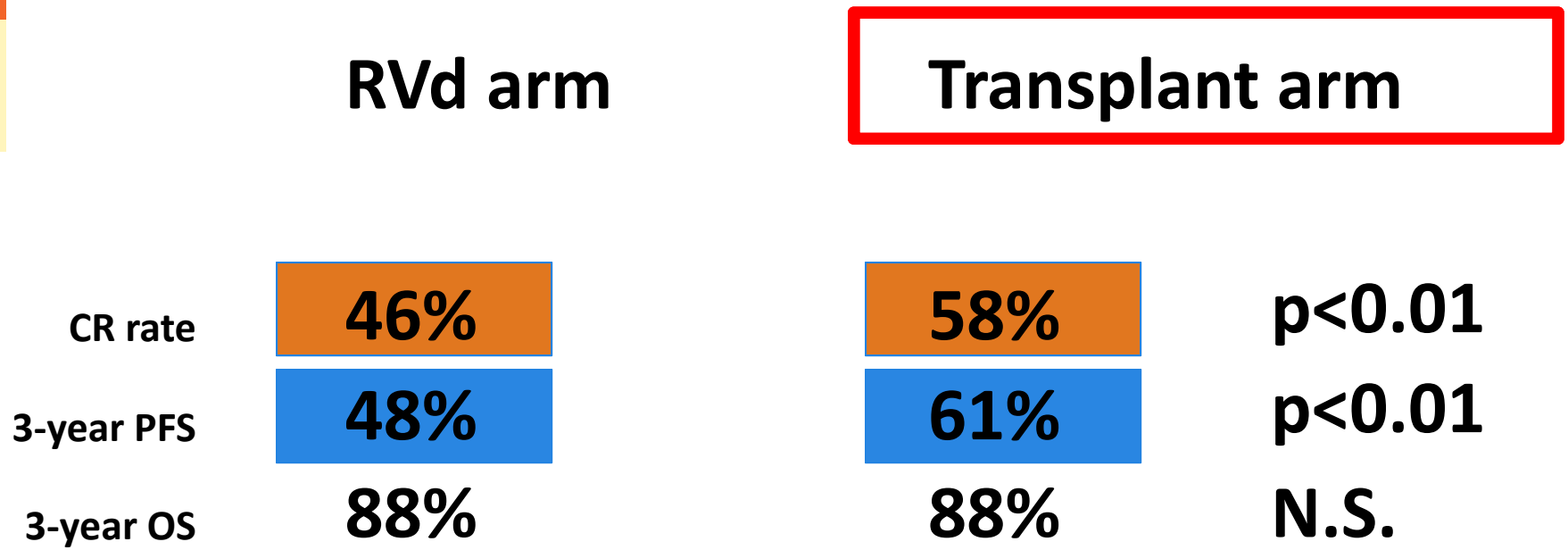
Memorial Sloan Kettering Cancer Center

Determination trial (IFM/DFCI 2009): newly diagnosed myeloma



Attal M, et al. *NEJM 2017*

Determination trial (IFM/DFCI 2009) shows HDM associated w/ longer PFS



Attal M, et al. *NEJM 2017*

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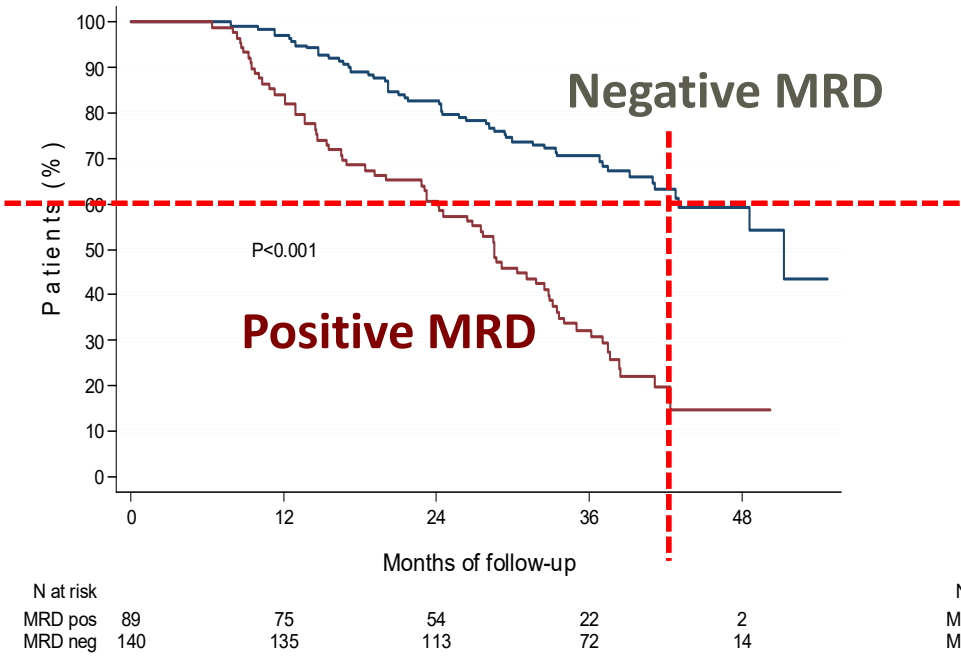
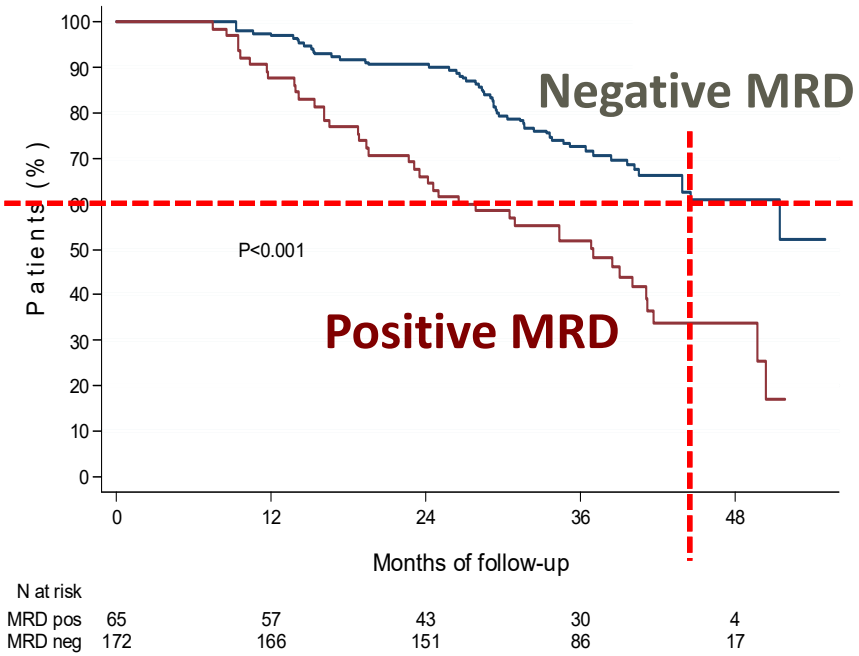
Determination trial (IFM/DFCI 2009) show MRD is valid

RVd arm, PFS



Transplant arm, PFS



Post consolidation (9/2015)

Figures adapted from Attal M, et al. *ASH 2015; 126, 391*

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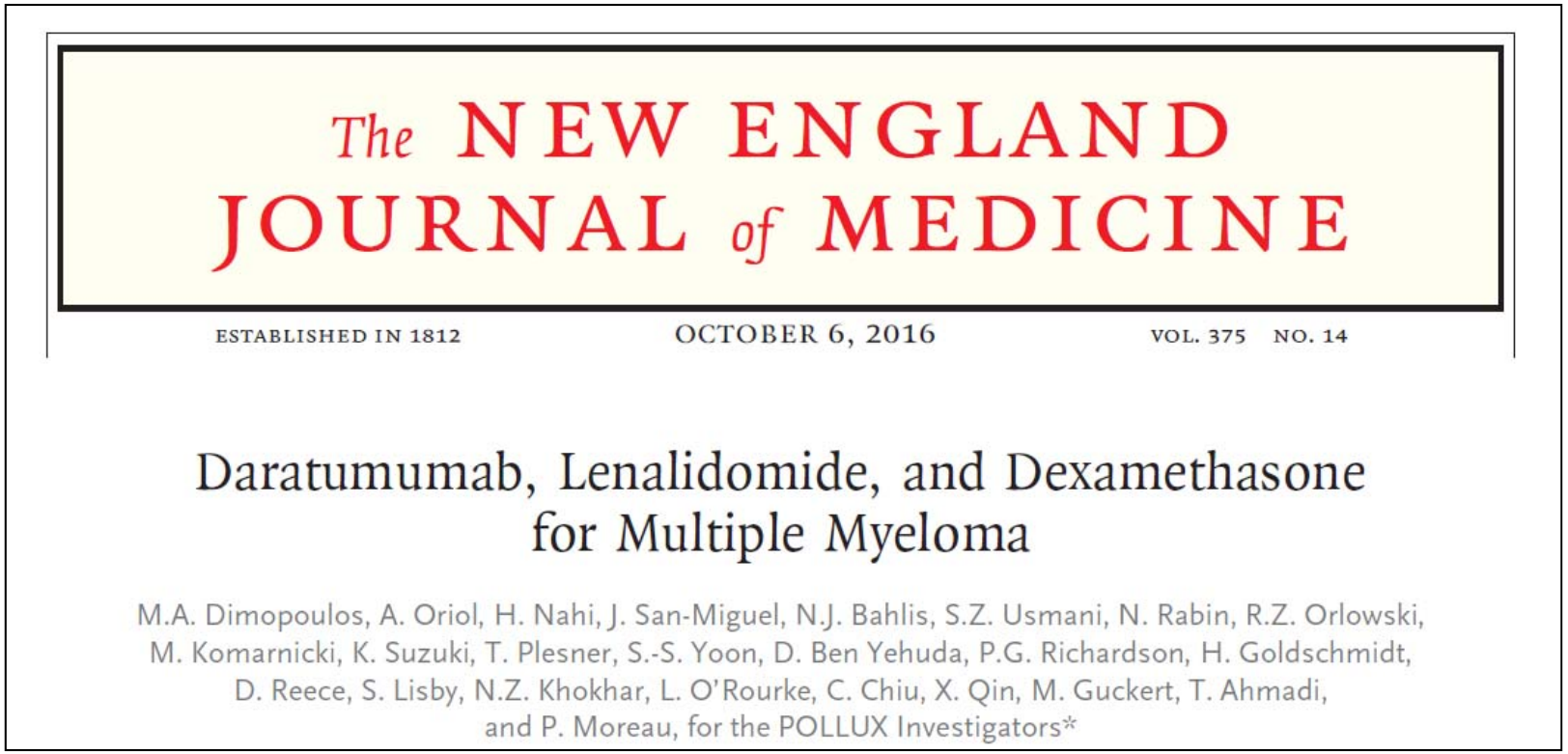
Relapsed/refractory multiple myeloma



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 6, 2016 VOL. 375 NO. 14

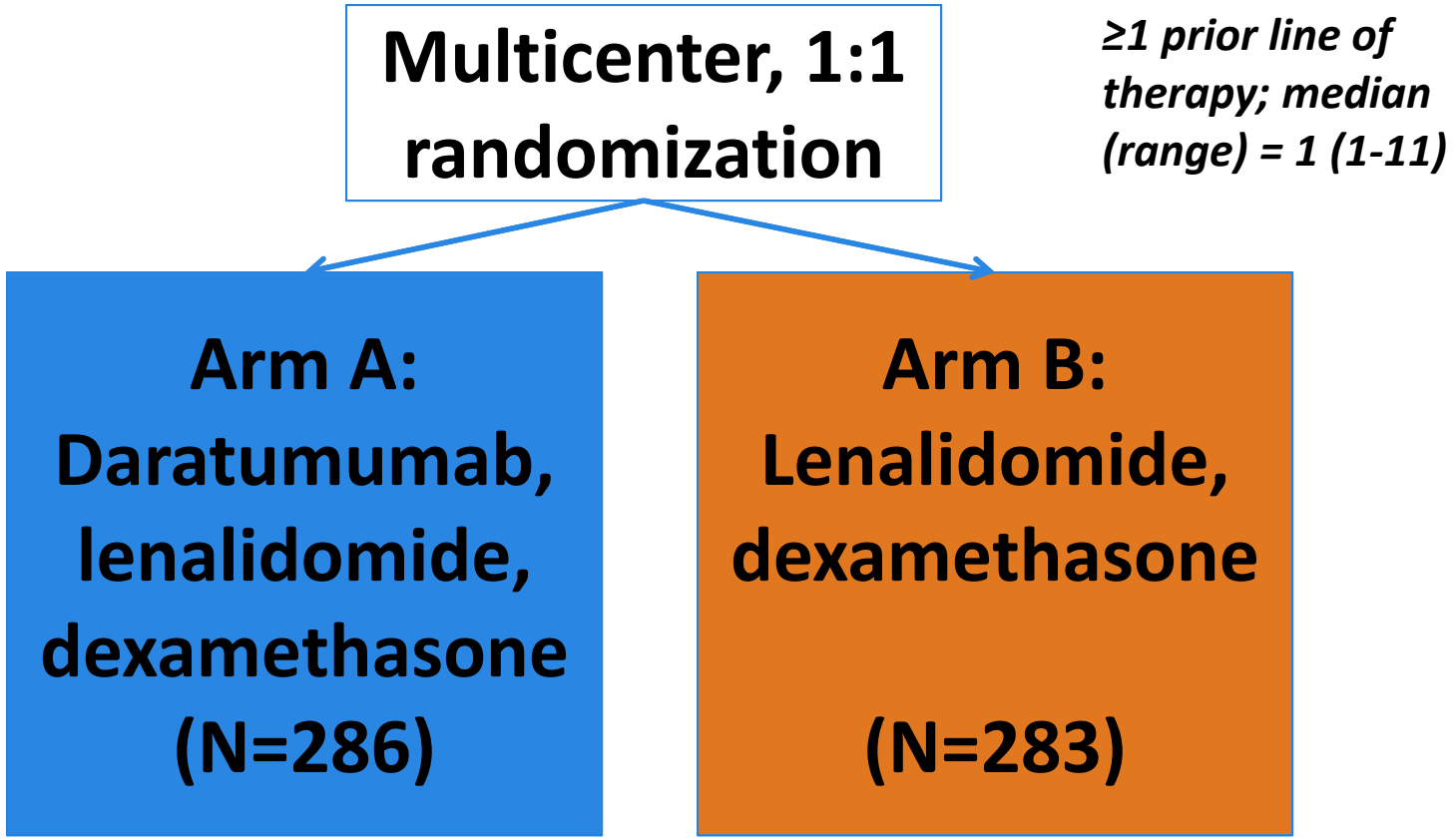
Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

M.A. Dimopoulos, A. Oriol, H. Nahi, J. San-Miguel, N.J. Bahlis, S.Z. Usmani, N. Rabin, R.Z. Orlowski, M. Komarnicki, K. Suzuki, T. Plesner, S.-S. Yoon, D. Ben Yehuda, P.G. Richardson, H. Goldschmidt, D. Reece, S. Lisby, N.Z. Khokhar, L. O'Rourke, C. Chiu, X. Qin, M. Guckert, T. Ahmadi, and P. Moreau, for the POLLUX Investigators*

Dimopoulos T, et al. *NEJM 2016*

Memorial Sloan Kettering Cancer Center

POLLUX phase 3 randomized trial: relapsed/refractory myeloma



MRD testing at suspected CR, and 3 and 6 months after CR

Dimopoulos T, et al. *NEJM 2016*

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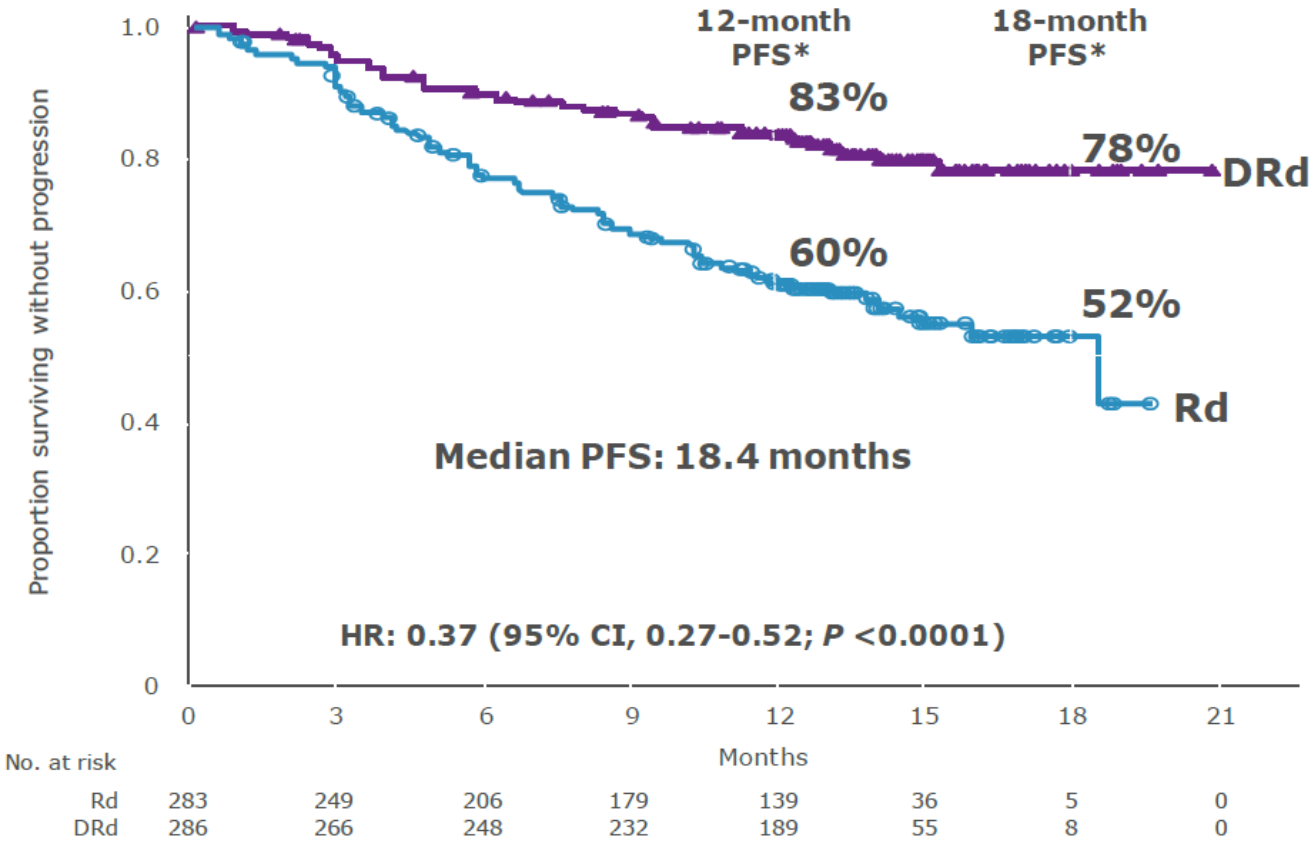
POLLUX study: PFS

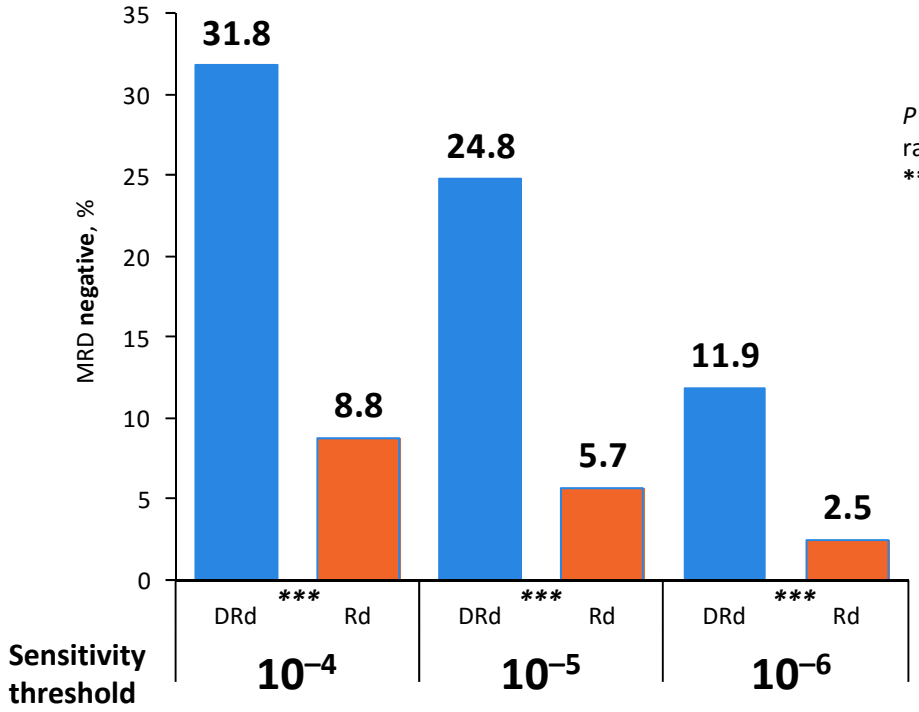


63% reduction in the risk of disease progression or death for DRd vs Rd

Dimopoulos T, et al. *NEJM 2016*

Memorial Sloan Kettering Cancer Center

Proportion of MRD-negative patients (10^{-4}, 10^{-5}, and 10^{-6}) on POLLUX

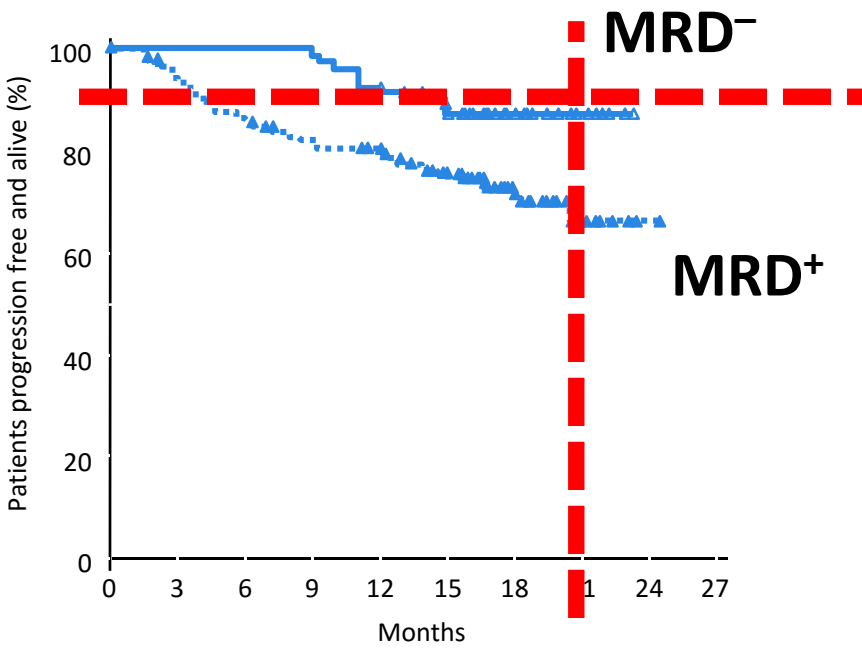


P values calculated using likelihood-ratio chi-square test.
*** ***P* <0.0001**

Avet-Loiseau H, et al. *ASH 2016*

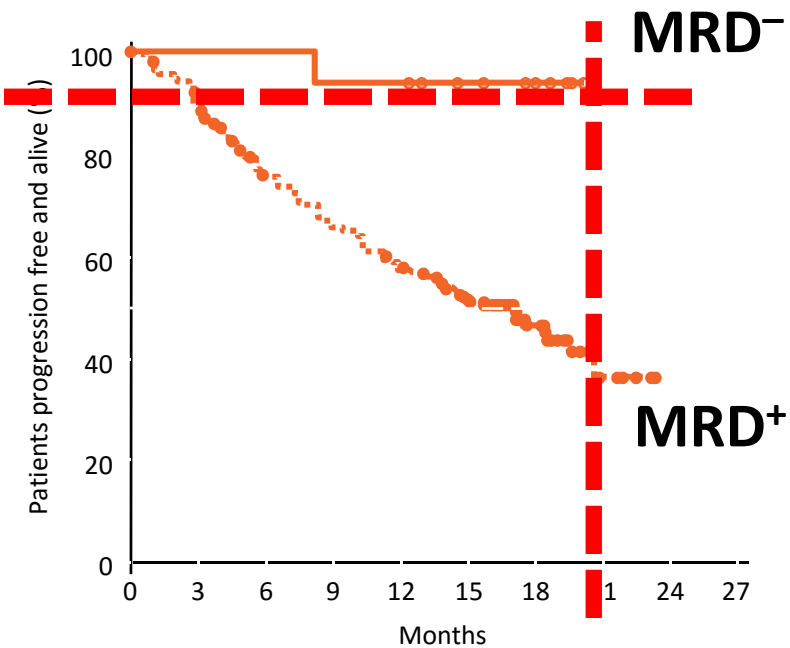
Memorial Sloan Kettering Cancer Center

PFS according to MRD status at 10^{-5}



Patients at risk										
Rd MRD negative	16	16	16	15	15	12	10	0	0	0
DRd MRD negative	71	71	71	70	66	57	28	6	0	0
Rd MRD positive	267	233	190	166	144	120	38	5	0	0
DRd MRD positive	215	195	178	167	161	137	54	9	1	0

Dara-Rev-dex



Patients at risk										
Rd MRD negative	16	16	16	15	15	12	10	0	0	0
DRd MRD negative	71	71	71	70	66	57	28	6	0	0
Rd MRD positive	267	233	190	166	144	120	38	5	0	0
DRd MRD positive	215	195	178	167	161	137	54	9	1	0

Rev-dex

Adapted from Avet-Loiseau H, et al. *ASH 2016*

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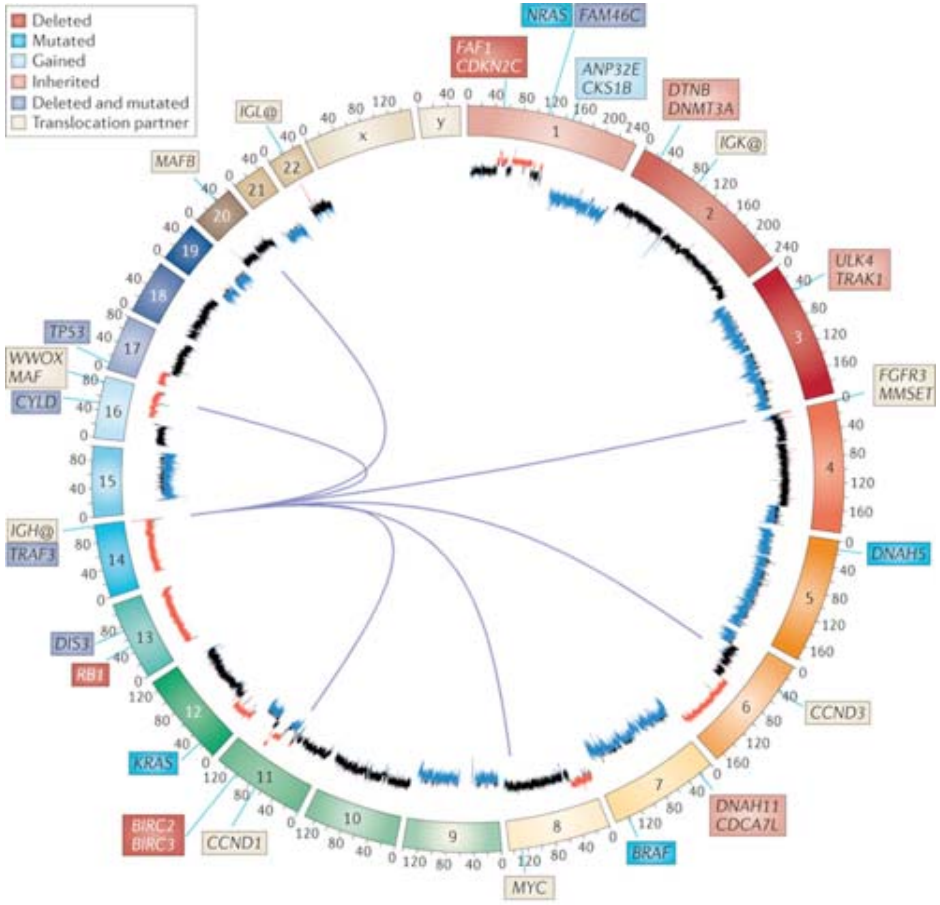
MRD>treatment modality?


What have we been thinking about?

Molecular landscape in myeloma

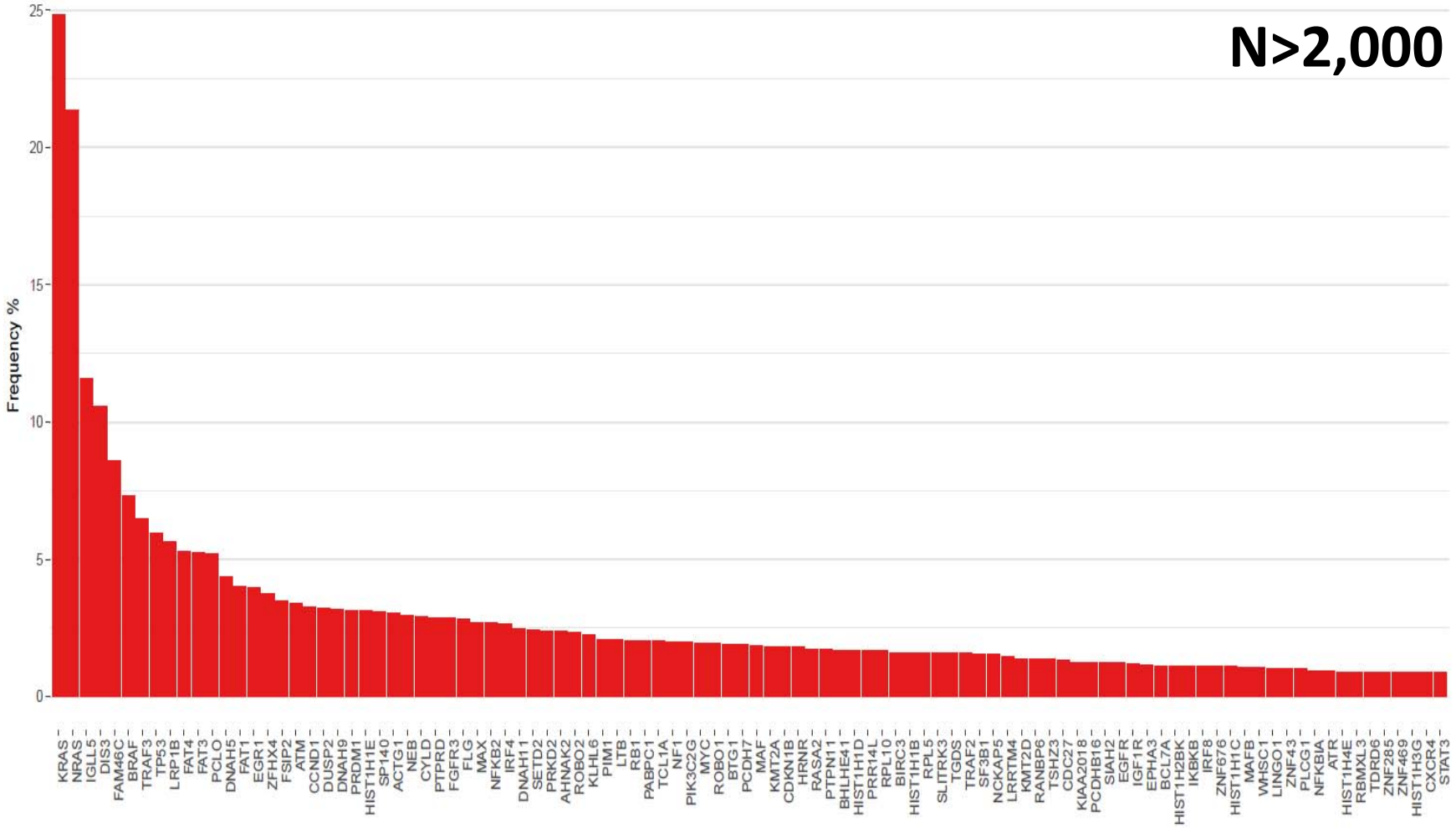


- IgH translocations
- Copy number variations
- Somatic mutations

myTYPE

Memorial Sloan Kettering Cancer Center

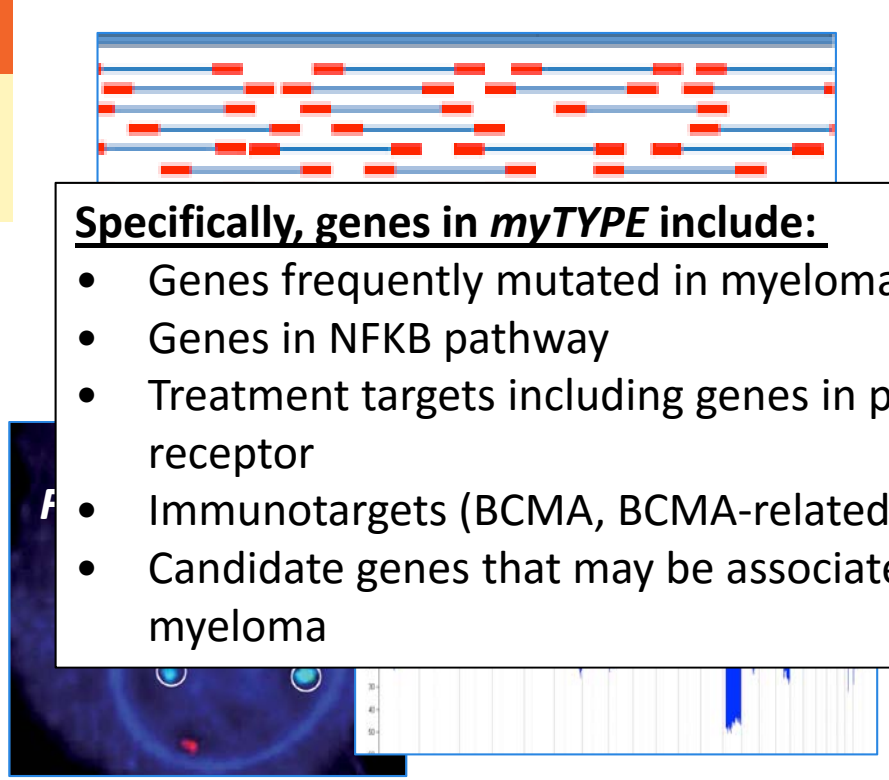
Frequently mutated genes in myeloma



Hultcrantz M, et al. *(in manuscript)*

Memorial Sloan Kettering Cancer Center

Targeted exome sequencing "*myTYPE*"



Specifically, genes in *myTYPE* include:

- Genes frequently mutated in myeloma
- Genes in NFKB pathway
- Treatment targets including genes in proteasome subunits and steroid receptor
- Immunotargets (BCMA, BCMA-related, CD38, PD1, PD-L1, and more)
- Candidate genes that may be associated with an increased risk of developing myeloma

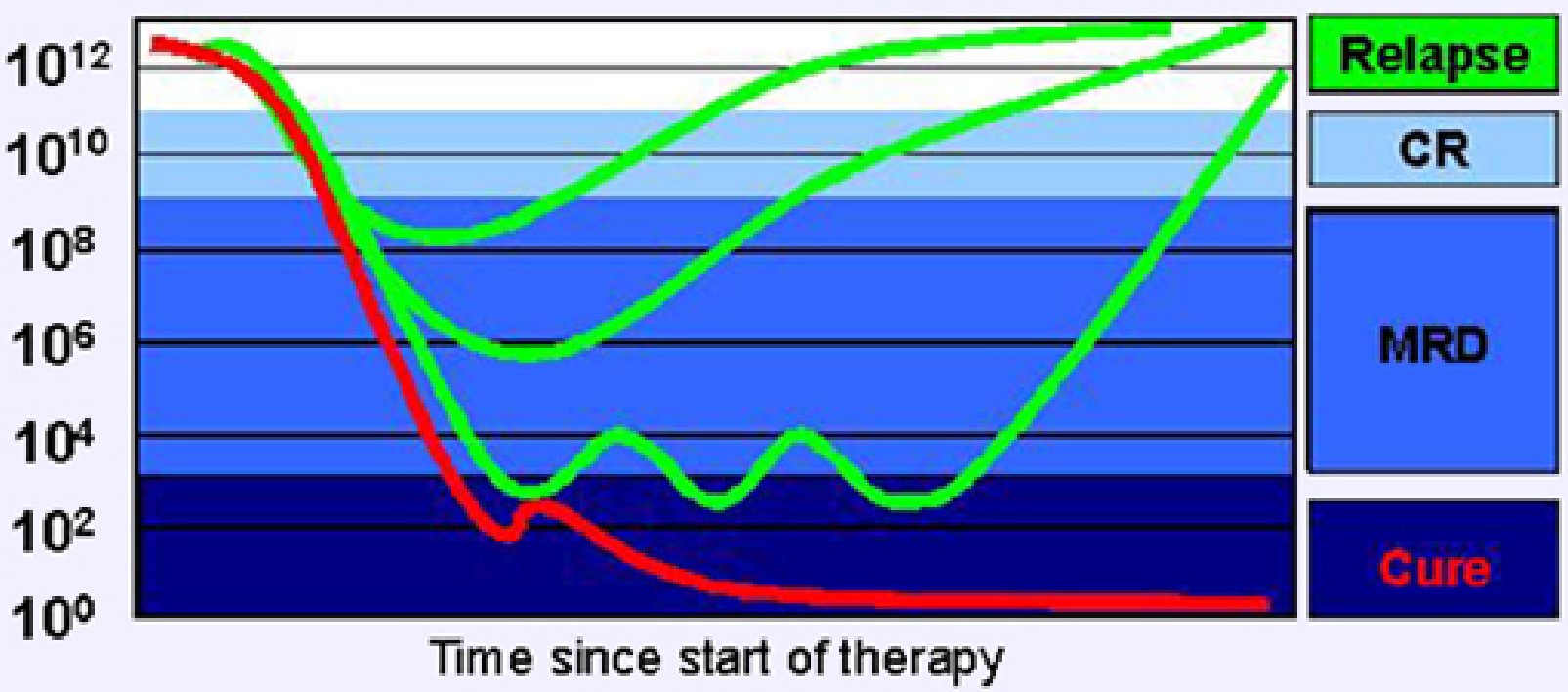
***myTYPE* is myeloma specific in terms of:**

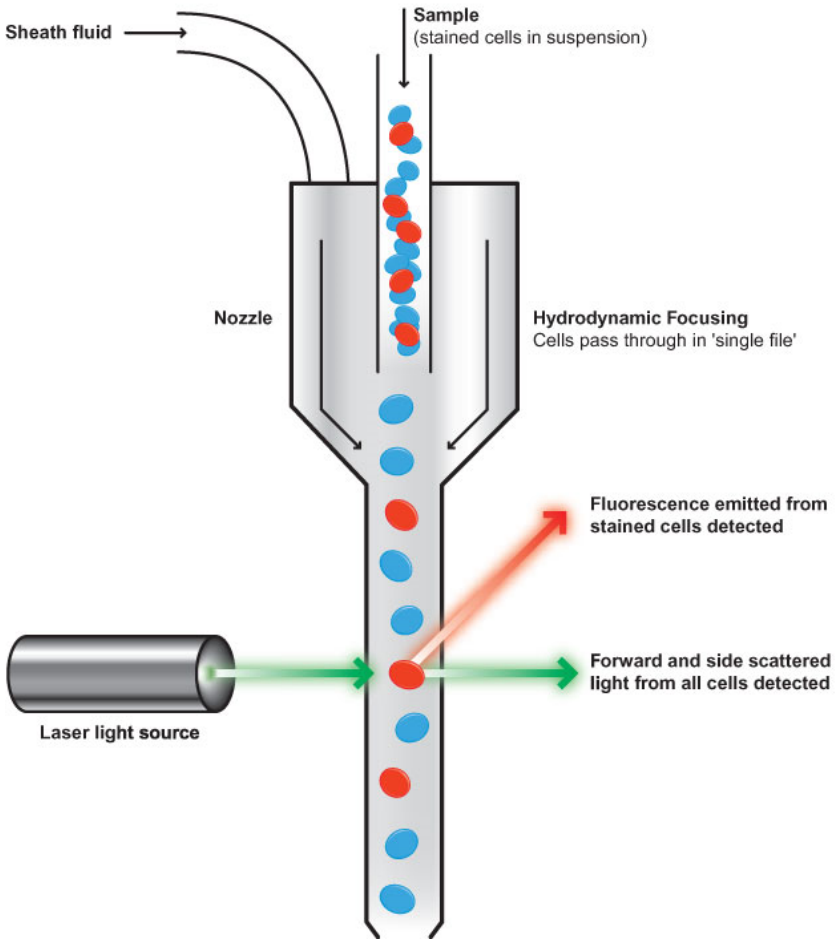
- **gene selection**
- **copy number SNPs for gene amplifications/deletions**
- **includes the IGH locus**

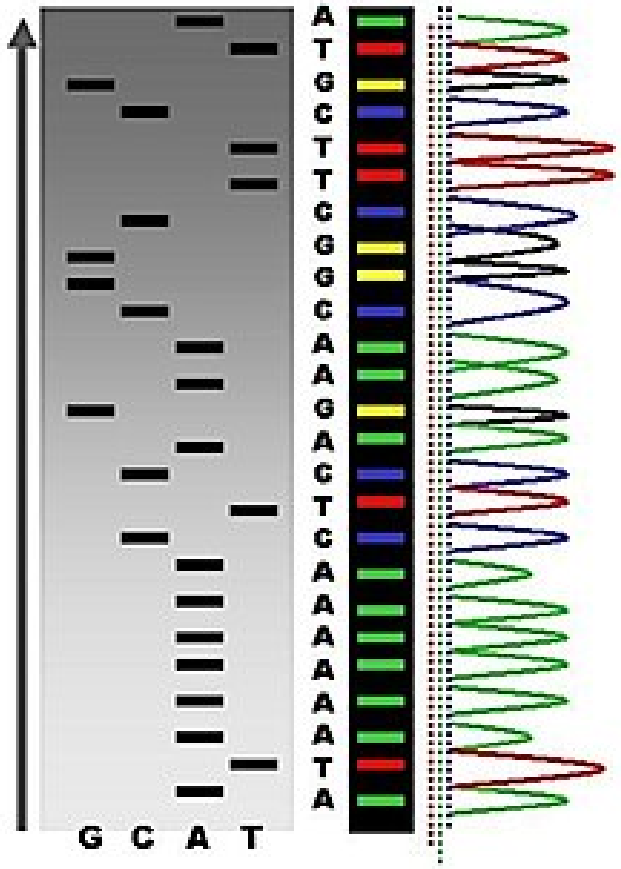
Hultcrantz et al. *(in manuscript)*

Memorial Sloan Kettering Cancer Center

Develop more sensitive MRD assays







1 cell in 100,000

1 cell in 1,000,000

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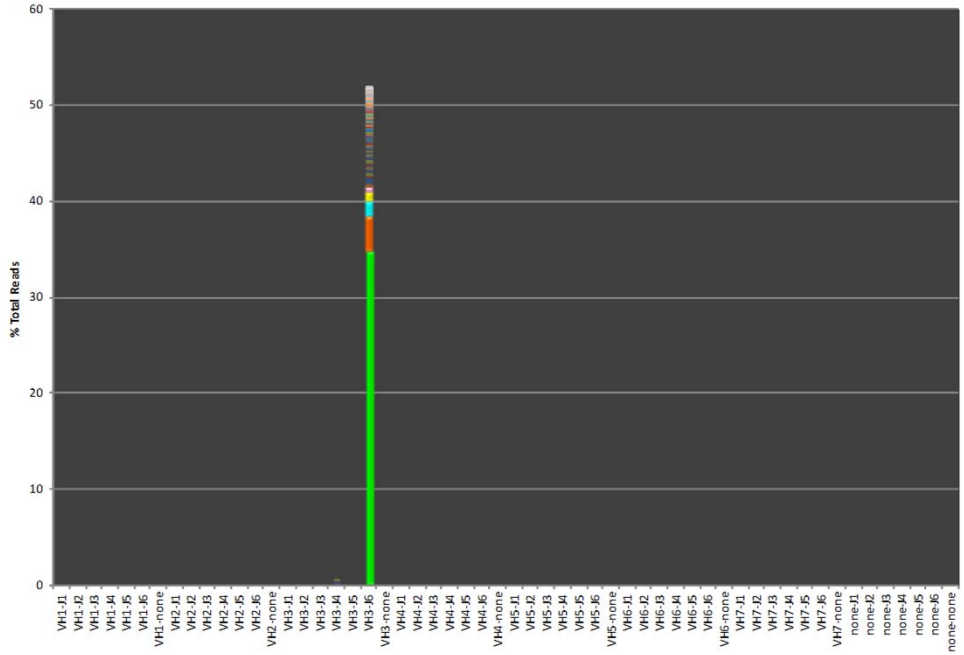
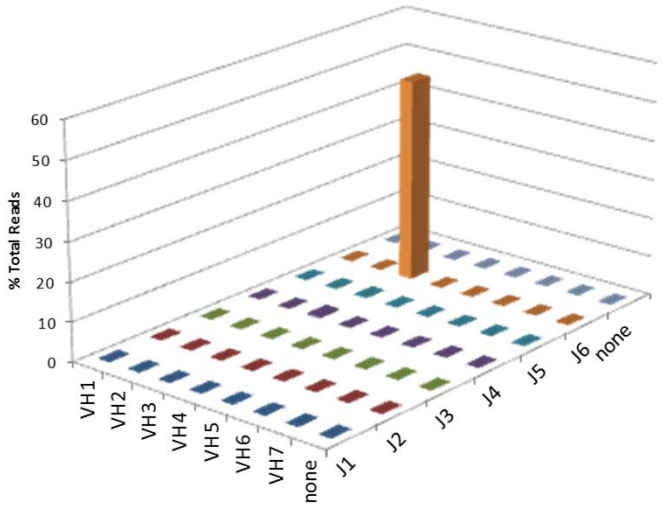
Clonal characterization

Rank	Sequence	Length	Merge count	V-gene	J-gene	% total reads	Cumulative %	Muta
1	GCCTCTGGATTCT	290	360462	IGHV3-11_05	IGHJ6_03	53.29	53.29	
2	CACCTTCTCTGGG	282	429	IGHV2-5_09	IGHJ5_02	0.06	53.35	
3	GCCTCTGGATTCA	178	263	IGHV3-NL1_01	IGHJ4_02	0.04	53.39	
4	GCCTCTGGGTTCA	211	260	IGHV3-73_02	IGHJ5_02	0.04	53.43	
5	GCCTCTGGATTCA	281	209	IGHV3-30_18	IGHJ6_03	0.03	53.46	
6	GCCTCTGGATTCA	251	205	IGHV3-30-3_01	IGHJ5_02	0.03	53.49	
7	GCCTCTGGATTCA	269	201	IGHV3-30_18	IGHJ4_02	0.03	53.52	
8	GCCTCTGGATTCA	268	199	IGHV3-7_03	IGHJ4_02	0.03	53.55	
9	GCCTCTGGATTCA	266	194	IGHV3-30_18	IGHJ4_02	0.03	53.58	
10	GTCTCTGGACTCA	296	194	IGHV3-30-3_01	IGHJ6_02	0.03	53.60	

GCCTCTGGATTCTCCTTCAGTGACTCCTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATTTCTTACATTACTACAAGTGGTAGTTACACAAAATACGCAGACTCT
GTGAAGGGCCGAGTCACCATCTCCAGAGACAACGCCAAGAACTCTCTGCATCTGCAAATGGACAGCCTGAGAGTCGACGACACGGCTCTTTACTACTGTGTGAGATGTCGGGGGGGGG
ACAACTCCTACCTTCGGCCCTACTACATGGACGTCTGGGGCAATGGGACCAC





Arcila M, et al and Landgren O (unpublished data)

Memorial Sloan Kettering Cancer Center

Disease monitoring post treatment

Rank	Sequence	Length	Merge count	V-gene	J-gene	% total reads	Cumulative %	Mutation rate to partial V-gene (%
1	GCCTCTGGATTCT	290	1428	IGHV3-11_05	IGHJ6_03	2.18	2.18	8.81
2	GCCTCTGGATTCA	254	1128	IGHV3-15_02	IGHJ5_02	1.72	3.90	0.00
3	GCCTCTGGATTCA	278	1011	IGHV3-30-3_01	IGHJ4_02	1.54	5.45	7.56
4	GCCTCTGGATTCA	290	973	IGHV3-7_03	IGHJ6_03	1.49	6.93	0.00
5	GCCTCTGGATTCA	290	892	IGHV3-48_01	IGHJ5_02	1.36	8.29	1.76
6	GCCTCTGGATTCA	278	885	IGHV3-23_04	IGHJ4_02	1.35	9.64	13.22
7	TCCTCTGGATTCA	284	866	IGHV3-9_01	IGHJ3_02	1.32	10.97	2.18
8	GCCTCTGGATTCA	308	856	IGHV3-49_04	IGHJ6_03	1.31	12.27	9.44
9	GCCTCTGGATTCA	284	832	IGHV3-30_18	IGHJ6_02	1.27	13.54	0.00
10	CGCTGTCTATGGT	294	826	IGHV4-34_02	IGHJ6_02	1.26	14.80	0.00

GCCTCTGGATTCTCCTTCAGTGACTCCTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATTTCTTACATTACTACAAGTGGTAGTTACACAAAATACGCAGACTCT
GTGAAGGGCCGAGTCACCATCTCCAGAGACAACGCCAAGAACTCTCTGCATCTGCAAATGGACAGCCTGAGAGTCGACGACACGGCTCTTTACTACTGTGTGAGATGTCGGGGGGGGGG
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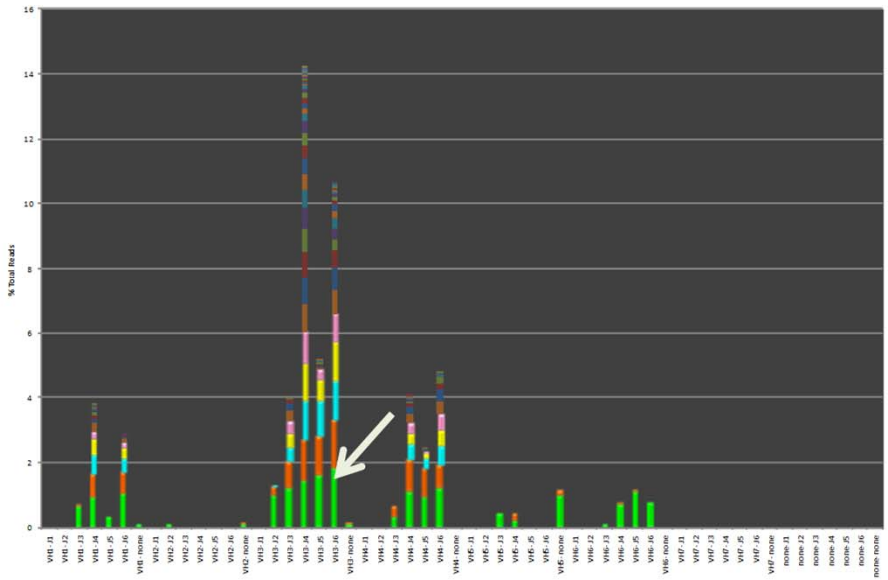
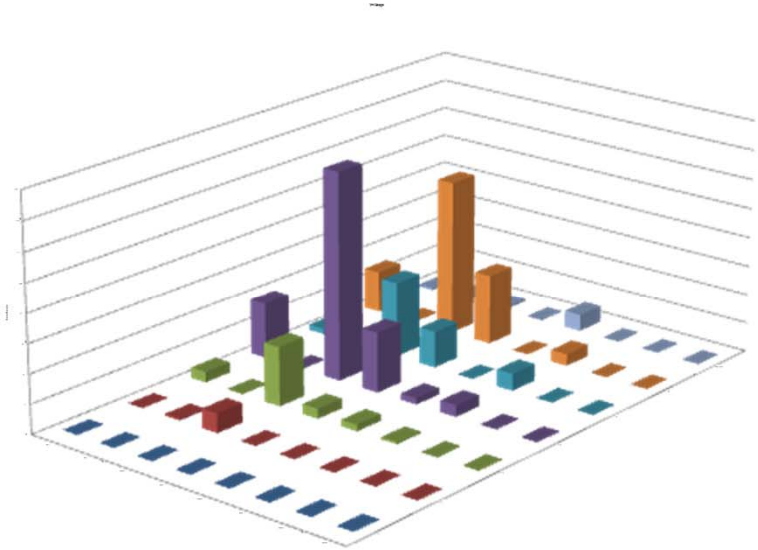
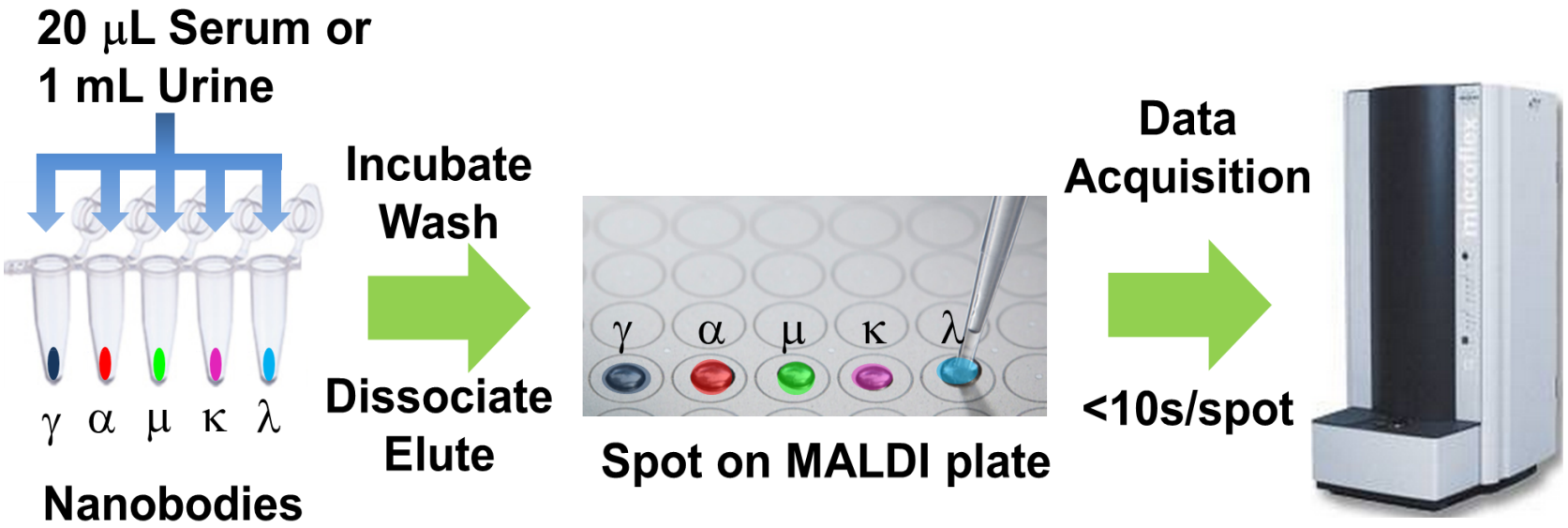




Arcila M, et al and Landgren O (unpublished data)

Memorial Sloan Kettering Cancer Center

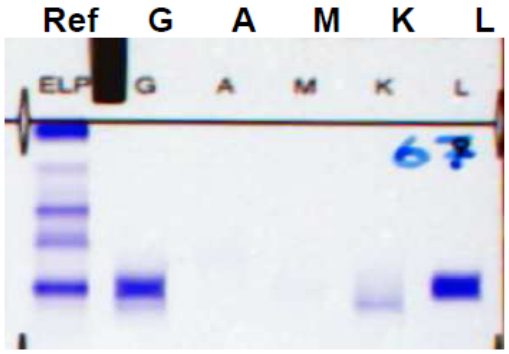
MALDI-TOF-MS analysis of monoclonal immunoglobulins



- Each sample is purified in 5 separate reactions using affinity matrix specific for individual heavy chains (IgG, IgA, IgM) or light chains (kappa, lambda)
- Immunoglobulins are eluted from beads and reduced to separate light chains and heavy chains

Mills et al. *Clinical Chem* 2016

Monoclonal immunoglobulins by MALDI

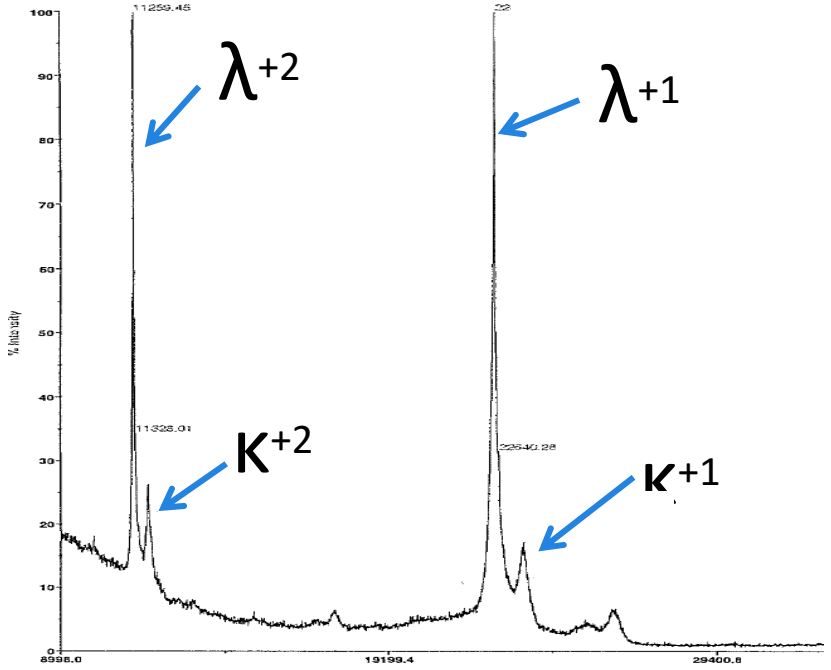


IFE Comment:

IgG Lambda monoclonal gammopathy.
Oligoclonal IgG Kappa band visible by immunofixation.

IgG-specific purification

Both kappa and lambda peaks observed



Thoren K, et al and Landgren O (unpublished data)

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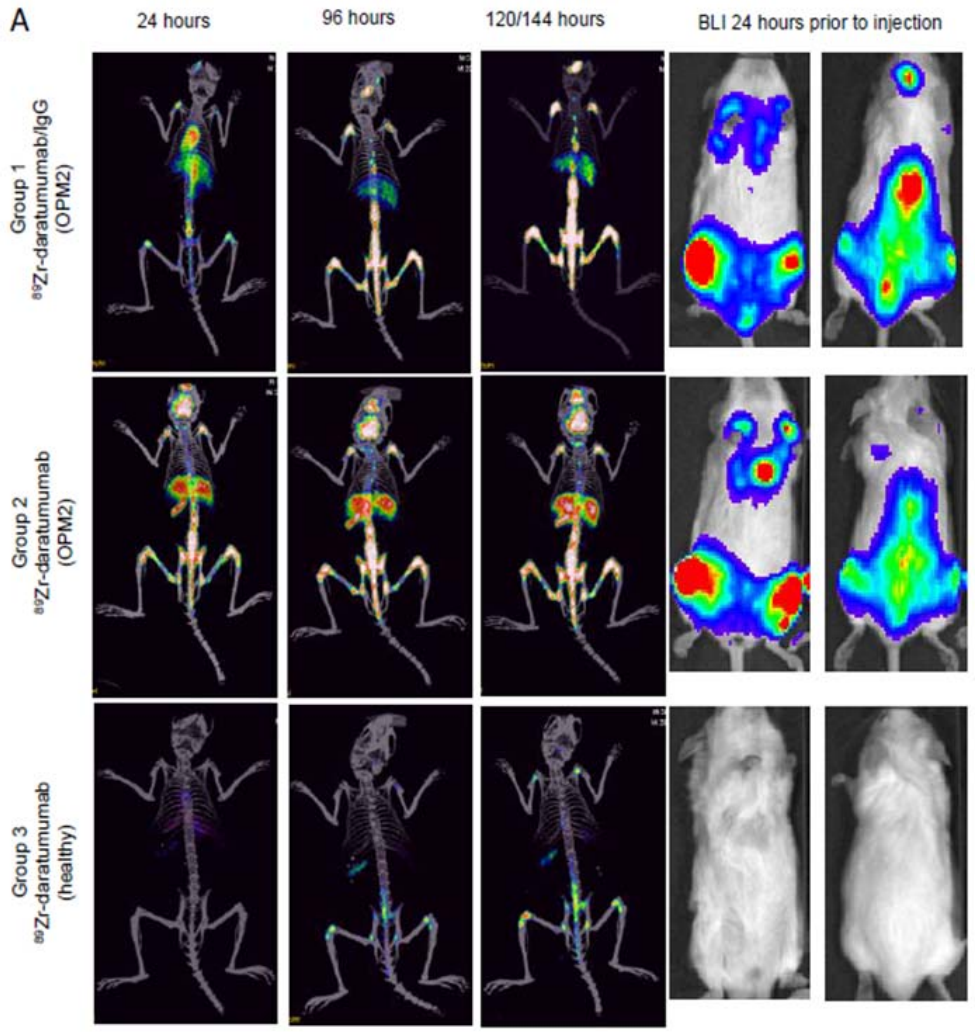
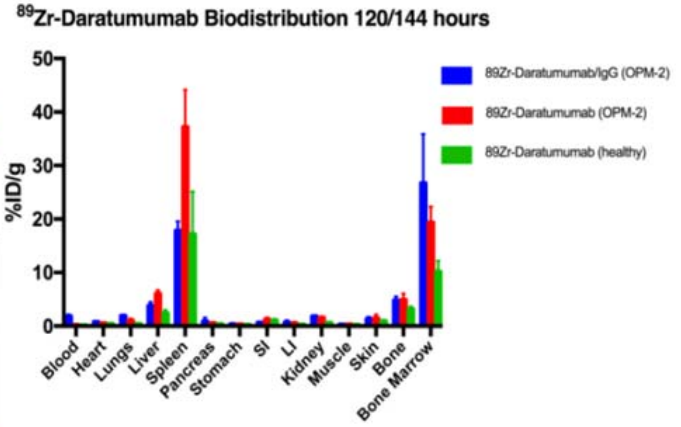
CD38 immuno-PET





Lewis J, Weber W, et al and Landgren O (unpublished data)

Memorial Sloan Kettering Cancer Center

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And many, many more!

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FDA
MMRF MULTIPLE MYELOMA Research Foundation
International Myeloma Foundation
LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers
Memorial Sloan Kettering Cancer Center

Thank you for your attention!

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Residual Disease Detection in Breast Cancer: Implications for Solid Tumors

Nicholas Turner

FDA-AACR workshop

The Royal Marsden NHS Foundation Trust

NHS

ICR The Institute of Cancer Research

Disclosures relevant to presentation

Research funding - Roche sequencing, Inivata, BioRad, Merck Sharpe Dohme, Roche/Genentech

Advisory board honoraria – Roche/Genentech

Residual Disease Detection in Breast Cancer: Implications for Solid Tumors

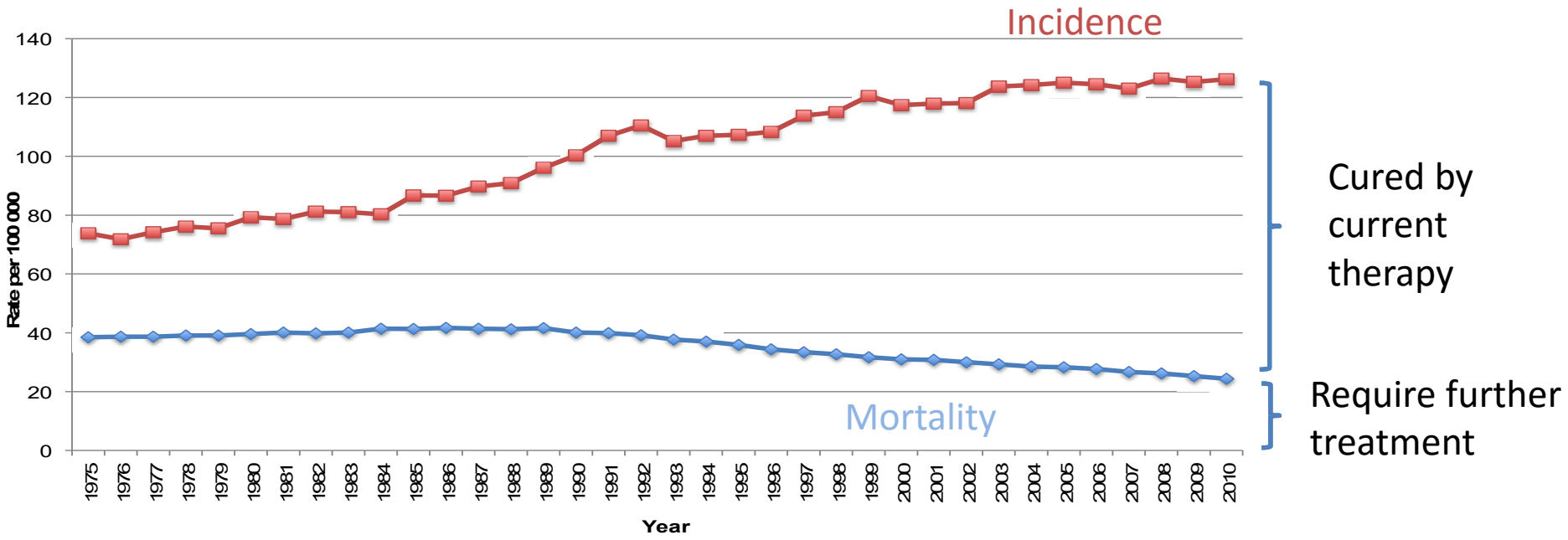
Background - identifying patients at risk of relapse despite current therapy

Current data in solid tumors for ctDNA residual disease detection

Future clinical trials design considerations

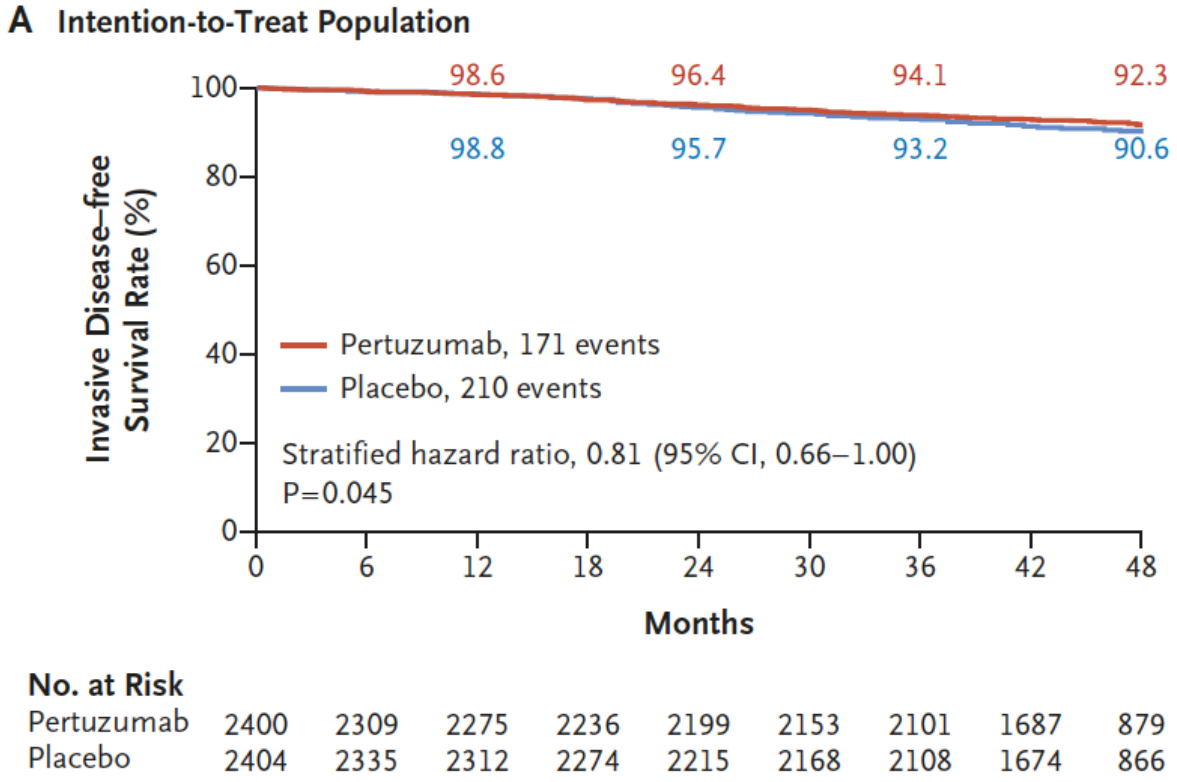
Progress in breast cancer management

UK Breast cancer incidence and mortality



http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/

Aphinity – pertuzumab adjuvant study

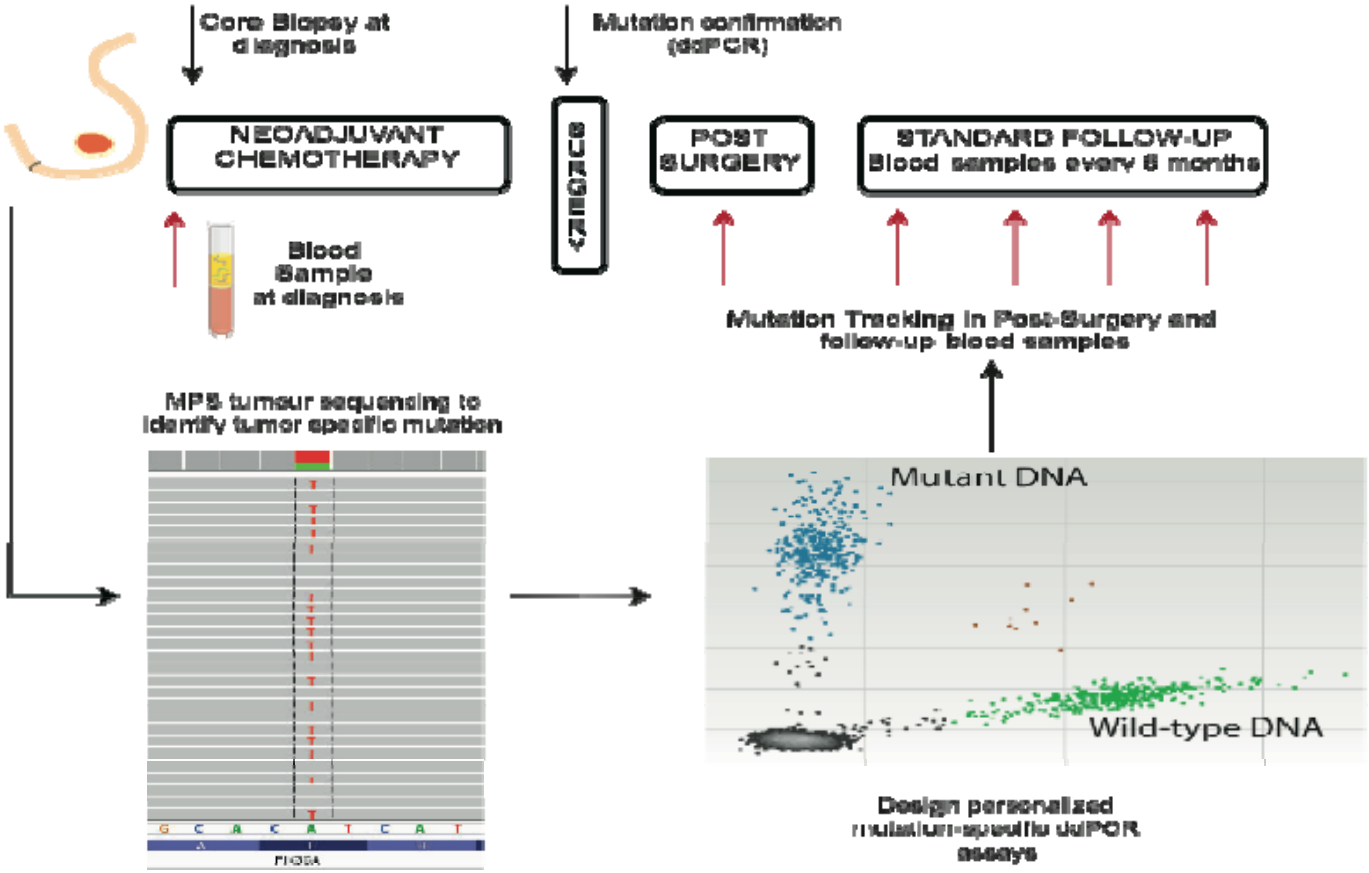


von Minkwitz et al NEJM 2017

Residual disease detection – breast cancer

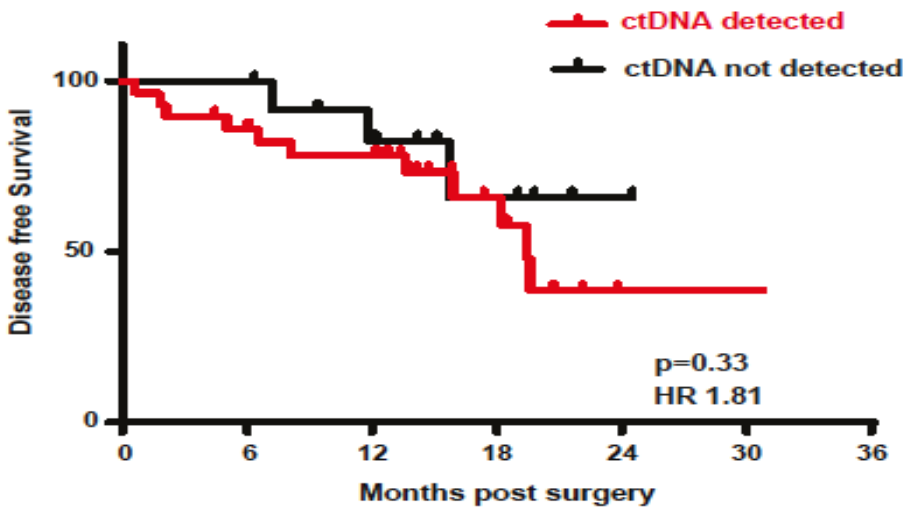
chemoNEAR study design

55 patients presenting with early stage breast cancer scheduled for standard neoadjuvant chemotherapy

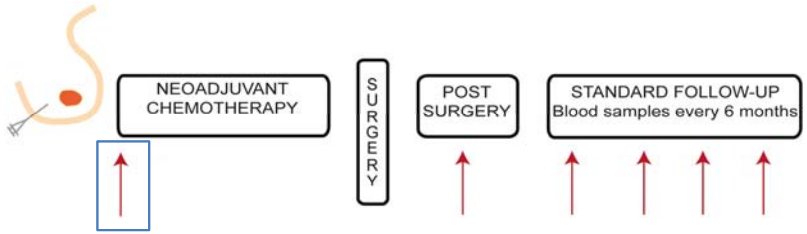


Garcia-Murillas *et al* Science Trans Med 2015

Predicting early relapse – baseline plasma



69% (29/42) mutation detected in baseline plasma



Garcia-Murillas *et al* Science Trans Med 2015

Biological factors associated with baseline ctDNA level

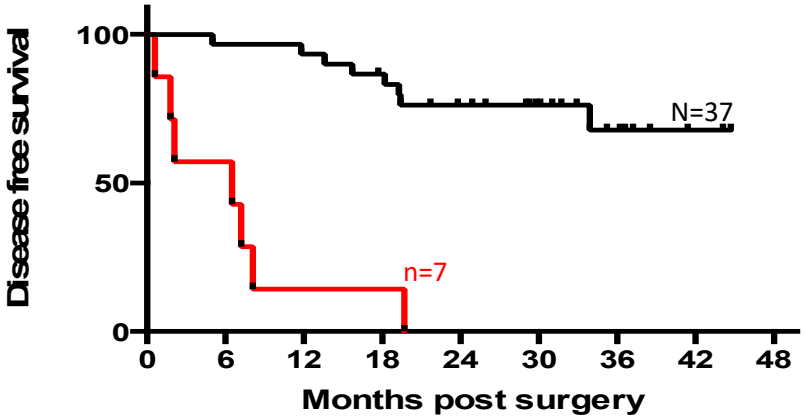
	Median ctDNA level copies per ml	*P* value	ctDNA detection (%)	*P* value
Clinical tumor size				
T1/2	3.878	0.42	64	0.42
T3/4	4.964		77	
Clinical node positive				
Yes	5.514	0.11	86	0.015
No	0.615		50	
Histological grade				
3	5.947	**0.03**	79	**0.015**
2	0		42	
ER status				
Positive	1.597	**0.011**	54	**0.016**
Negative	14.61		89	
HER2 status				
Positive	5.355	0.88	71	1
Negative	3.72		68	
Subtype				
TNBC	15.95	**0.027**	92	**0.033**
HER2+	5.355		71	
ER+HER2–	0		47	
Subsequent pCR				
Yes	4.679	0.49	75	0.65
No	4.345		67	

Garcia-Murillas *et al* Science Trans Med 2015

Predicting relapse with single post-surgical sample

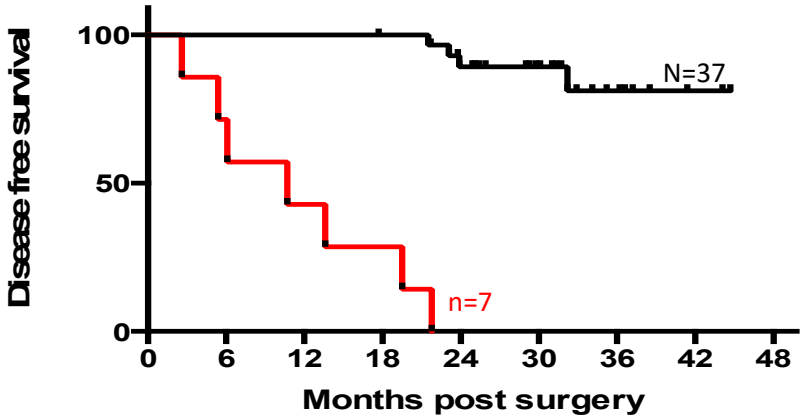
31.7 month median follow-up

Disease free survival

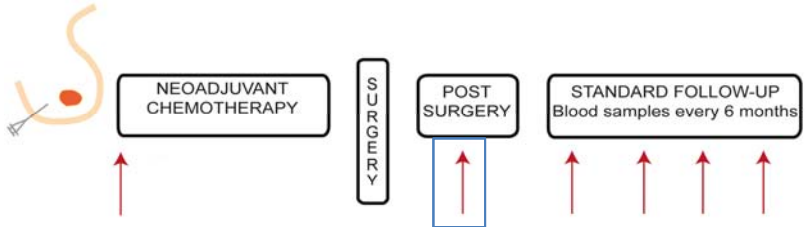


HR=13.6 95%CI (4.5, 41.2); p<0.001

Overall survival



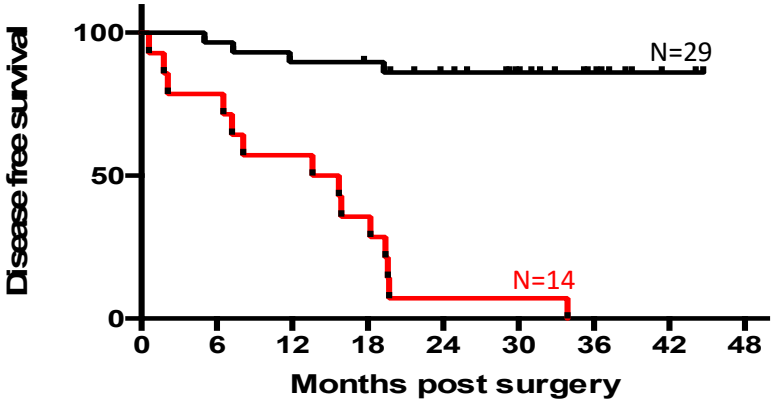
HR=84.7 95%CI (9.8, 730.4); p<0.001



Updated Turner *et al* SABCS 2016

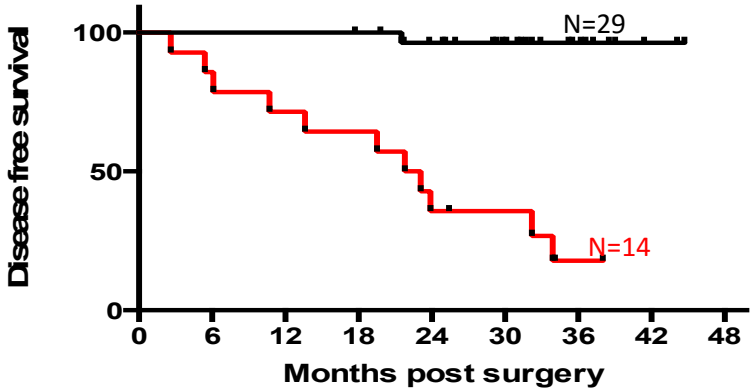
Predicting relapse with serial sample tracking

Disease free survival



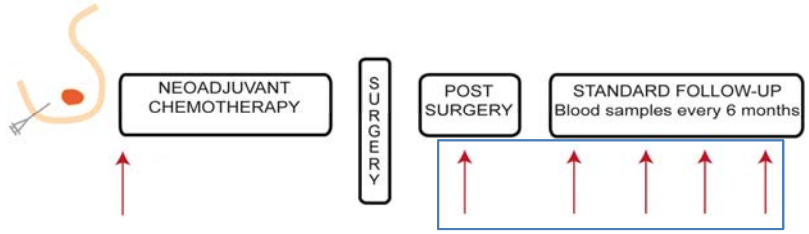
HR=25.7 05% CI(8.3, 79.8) p<0.001

Overall survival



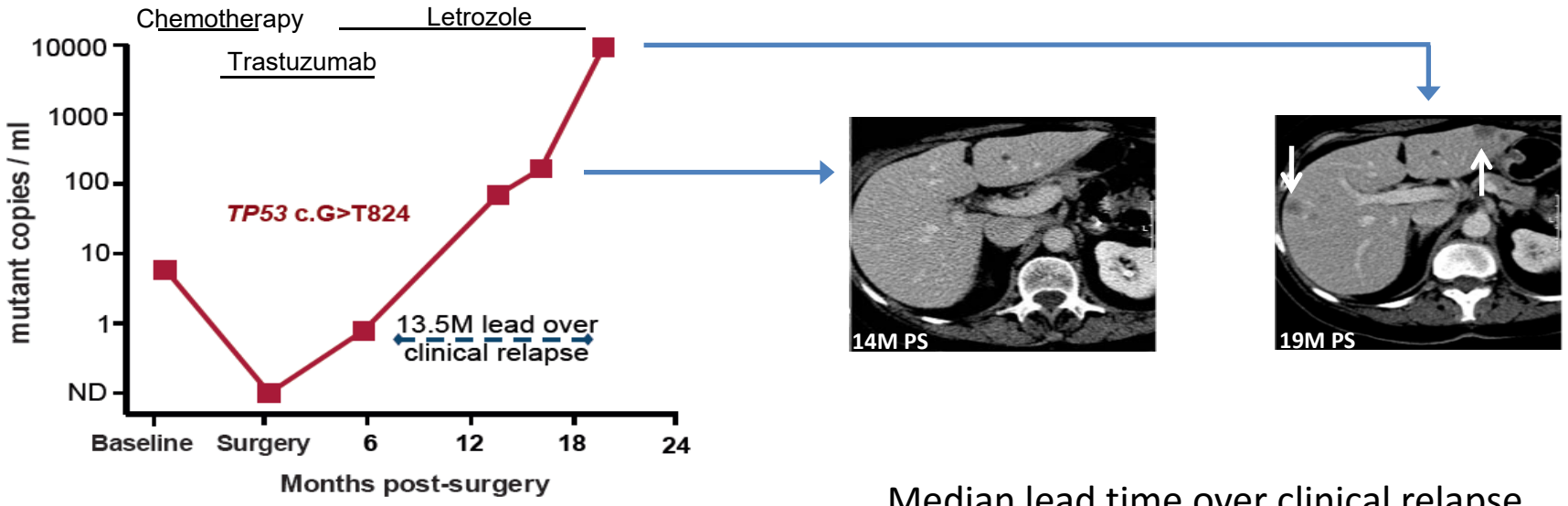
HR=47.1 05% CI(6.1, 366.1) p<0.001

100% positive predictive value for relapse



Updated Turner *et al* SABCS 2016

Lead time over clinical relapse

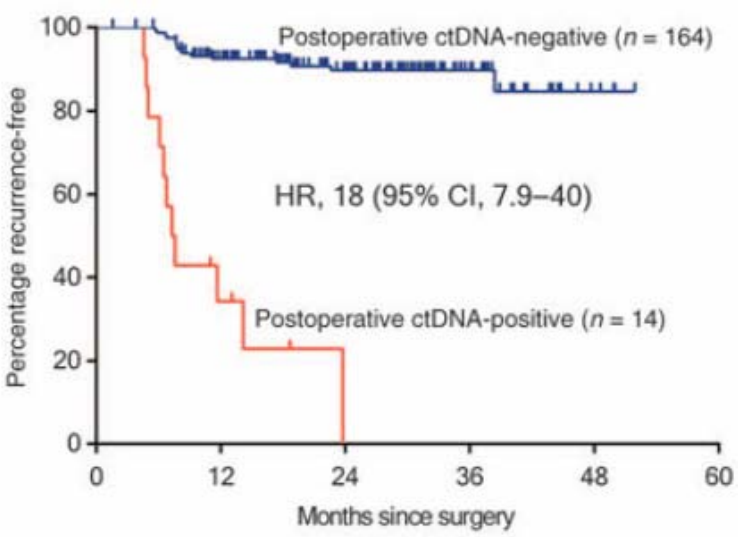


Median lead time over clinical relapse for all relapses 7.9 months

ER+ve HER2 +ve breast cancer
pathCR breast / nodes to neoadjuvant chemotherapy and trastuzumab

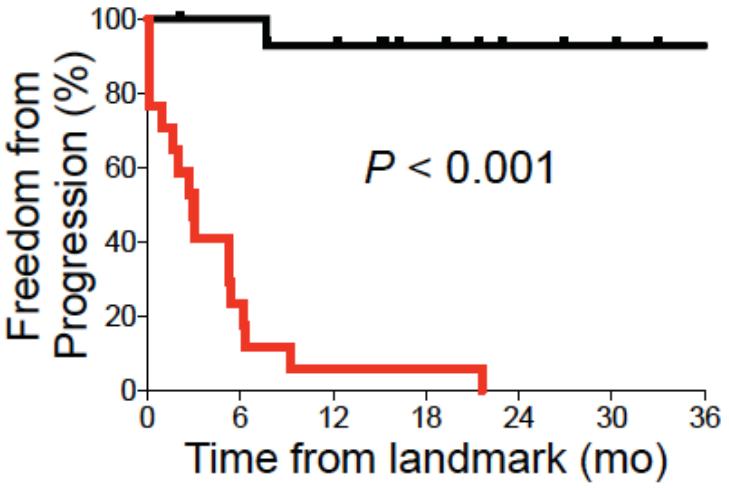
Residual disease detection – other tumor types

Colon cancer



Tie *et al* Science Trans Med 2016

Lung cancer



Chaudhuri *et al* Cancer Discov 2017

Common features of residual disease studies with current generation of assays

Very high positive predictive value

- detection of ctDNA implies a very high risk of future relapse

Lower negative predictive value of single post-operative samples

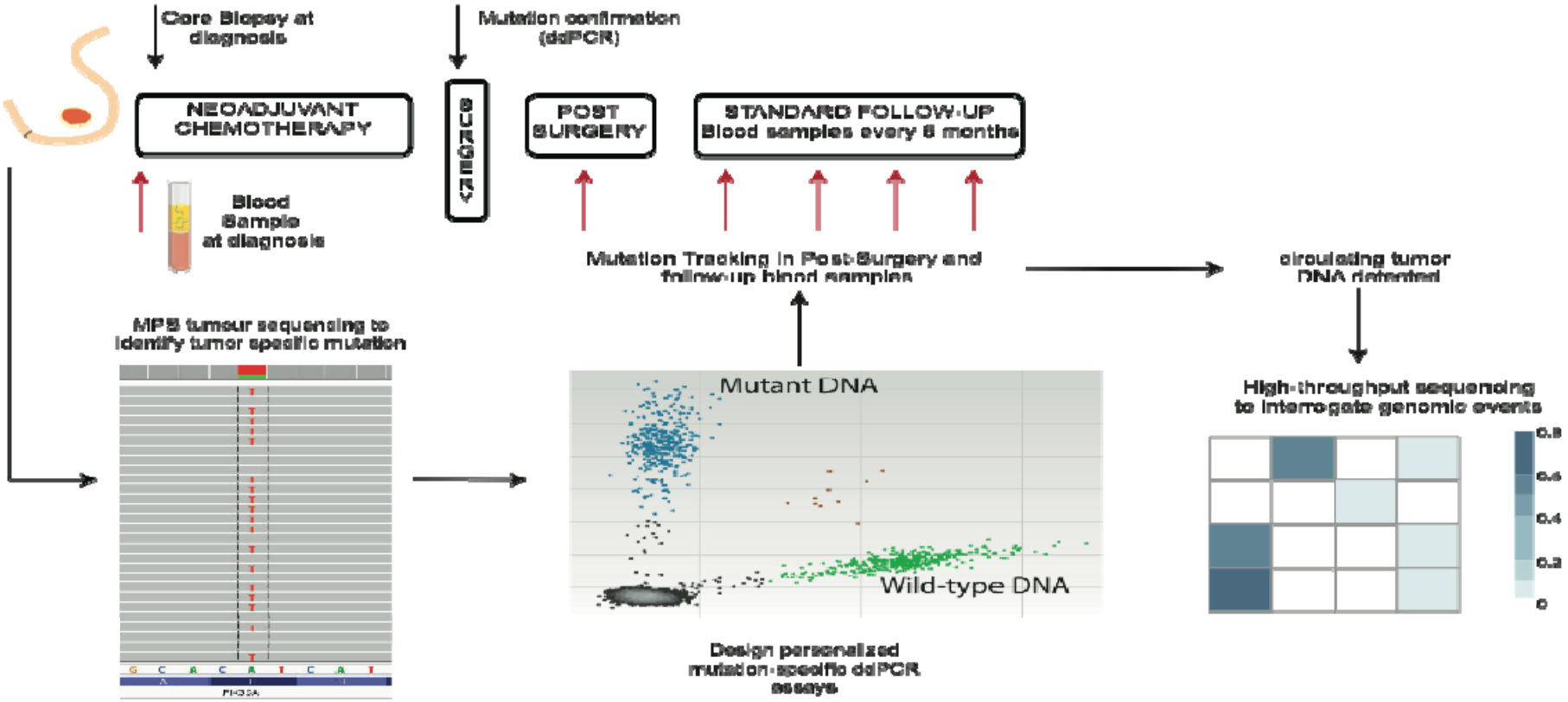
- Incomplete sensitivity to detect low level residual disease
- Serial sampling improves pick-up

Tie *et al* Science Trans Med 2016, Chaudhuri *et al* Cancer Discov 2017, Abbosh et al Nature 2017, Garcia-Murillas *et al* Science Trans Med 2015

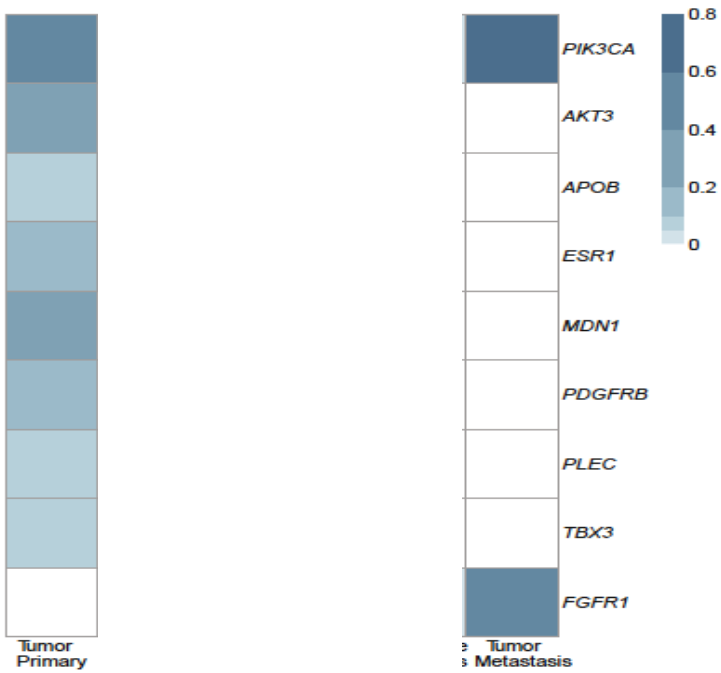
Challenges of clinical application

- Clonal selection of cancer – primary to metastasis
- Sanctuary/dark metastases
- Clonal hematopoesis
- What is being detected by the current generation of assays?

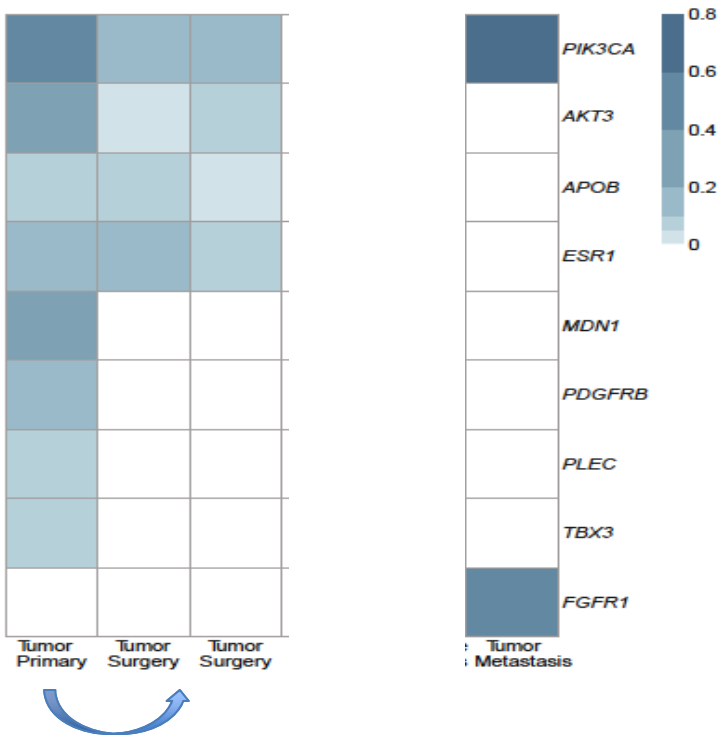
Sequencing circulating tumor DNA arising from micro-metastatic disease



Anticipating clonal selection in recurrence

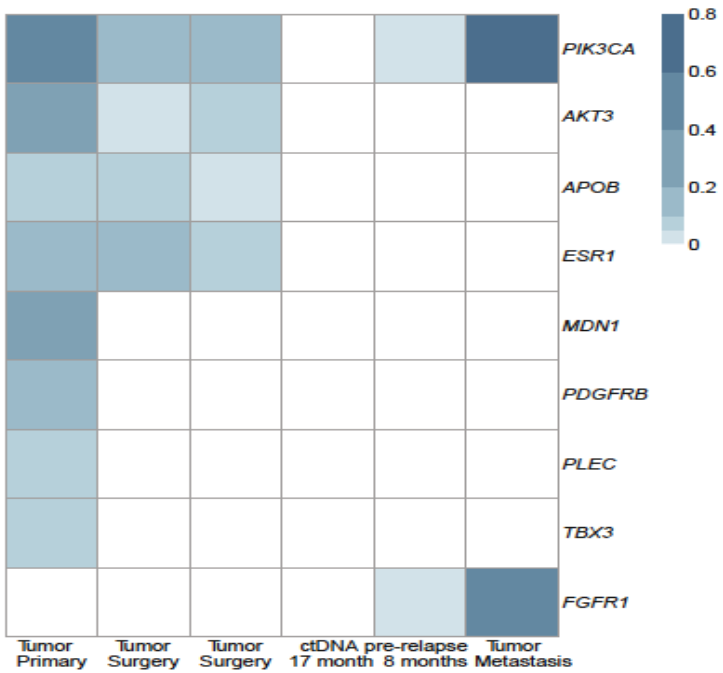


Anticipating clonal selection in recurrence

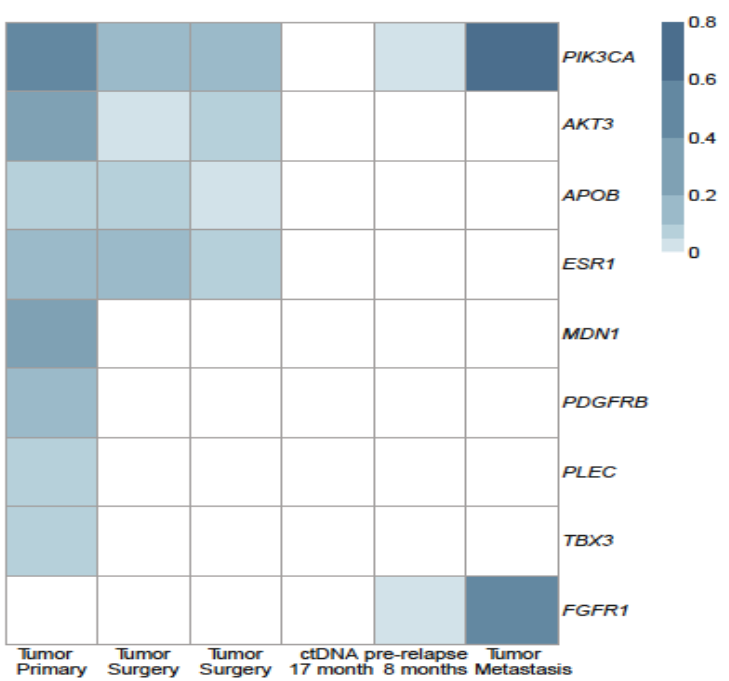


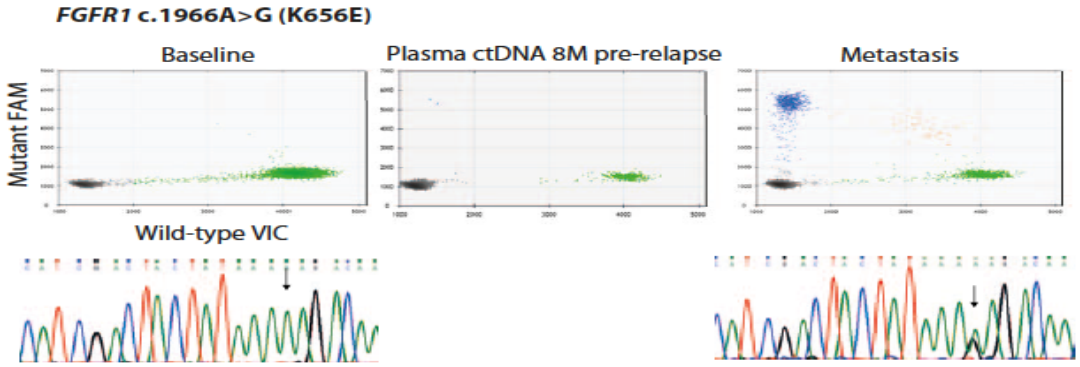
Reproducible selection by chemotherapy

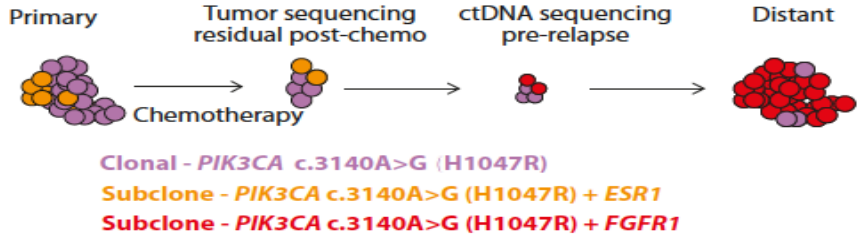
Anticipating clonal selection in recurrence



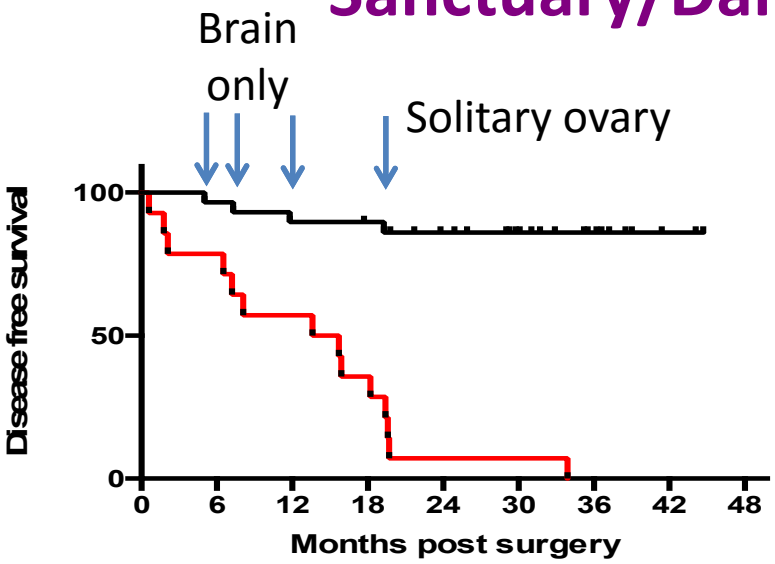
Anticipating clonal selection in recurrence







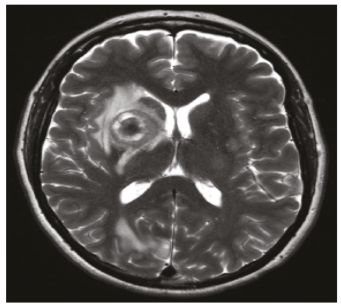
Sanctuary/Dark sites of metastasis



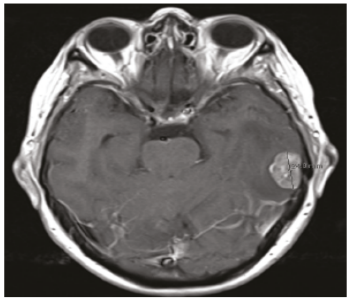
ctDNA detection

	+ve	-ve
Brain only	0	3
Extracranial	14	1

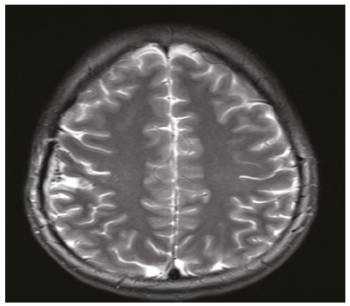
P=0.0049



A310012

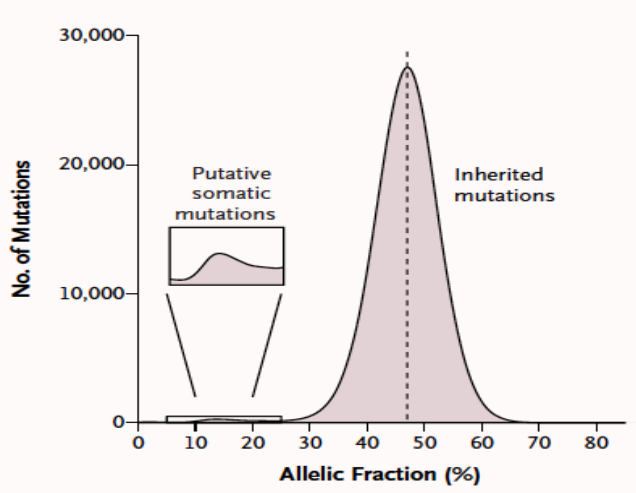


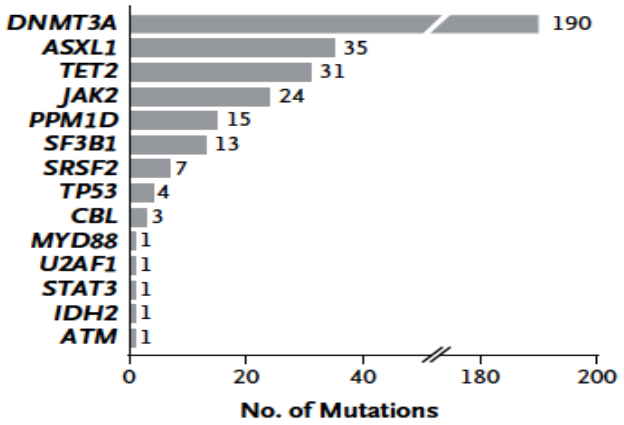
A310018

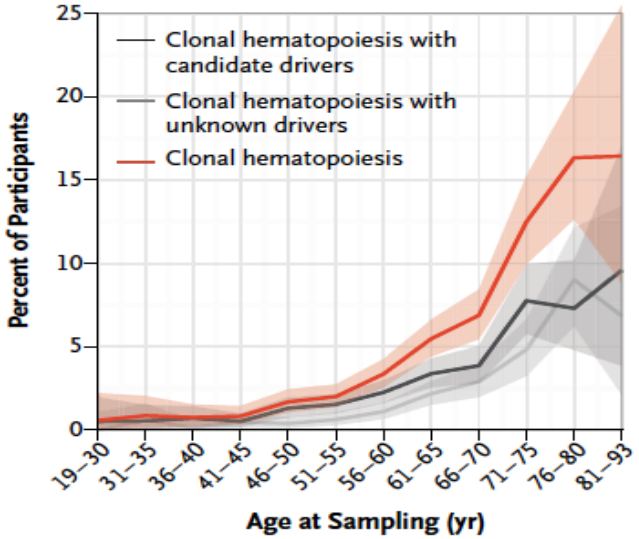


A310047

Clonal hematopoesis of indeterminate potential







Optimal strategies to exclude possible false positives from CHIP yet to be defined

Buffy coat sequencing
Multiple somatis mutation tracking

Genovese *et al* NEJM 2014

What do the current generation of assays detect?

Adjuvant setting

Metastatic setting

Micro-metastatic disease

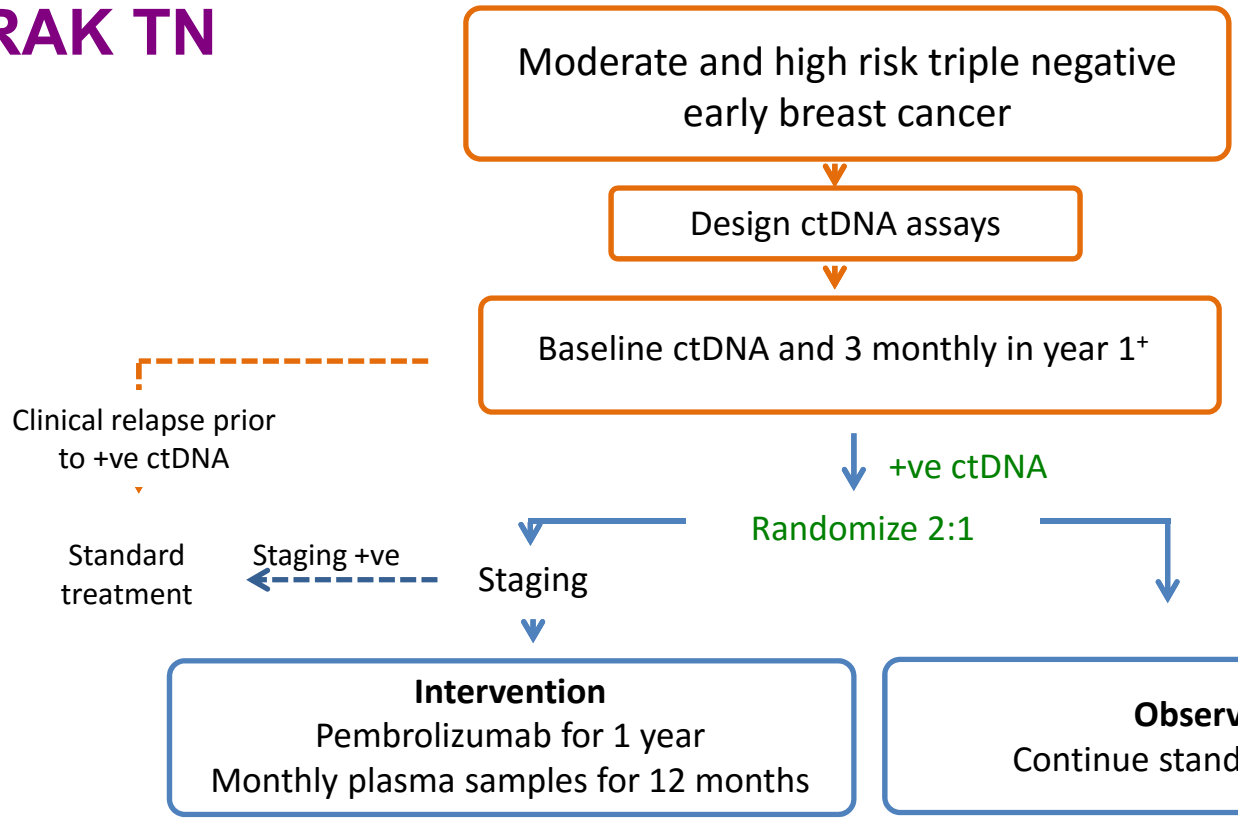
Macro-metastatic disease

Potentially curable

Where on this spectrum is ctDNA detected residual disease?

Incurable

cTRAK TN



150 patients

Blinded ctDNA surveillance and randomisation

Primary endpoint
ctDNA clearance at 12 months

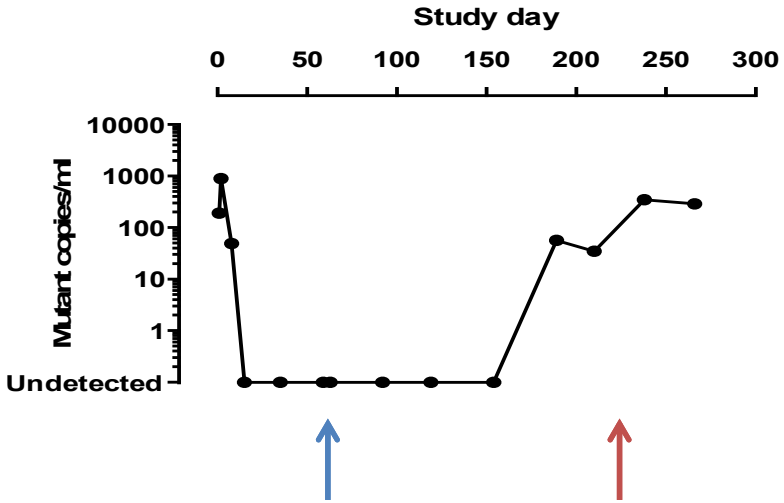
NHS National Institute for Health Research

The Royal Marsden Cancer Charity

Cancer Research UK

ctDNA clearance as a phase II endpoint

Timing of sampling may effect prediction of disease free survival



Patient on paclitaxel + AZD5363 from BEECH clinical trial

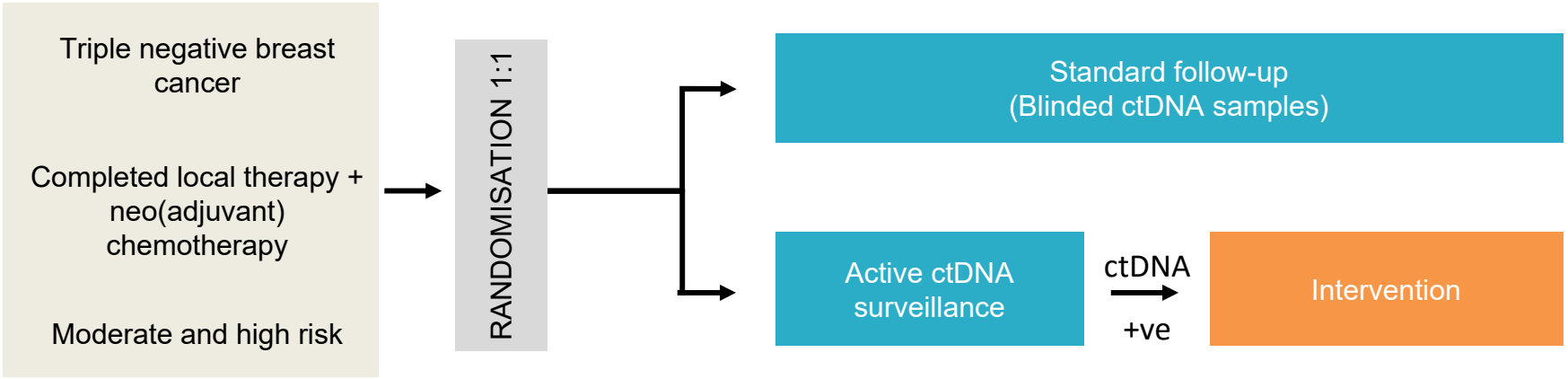
Early assessment - Treatment effective

Late assessment - Treatment ineffective

More robust predictor of DFS?

Turner *et al* AACR 2015

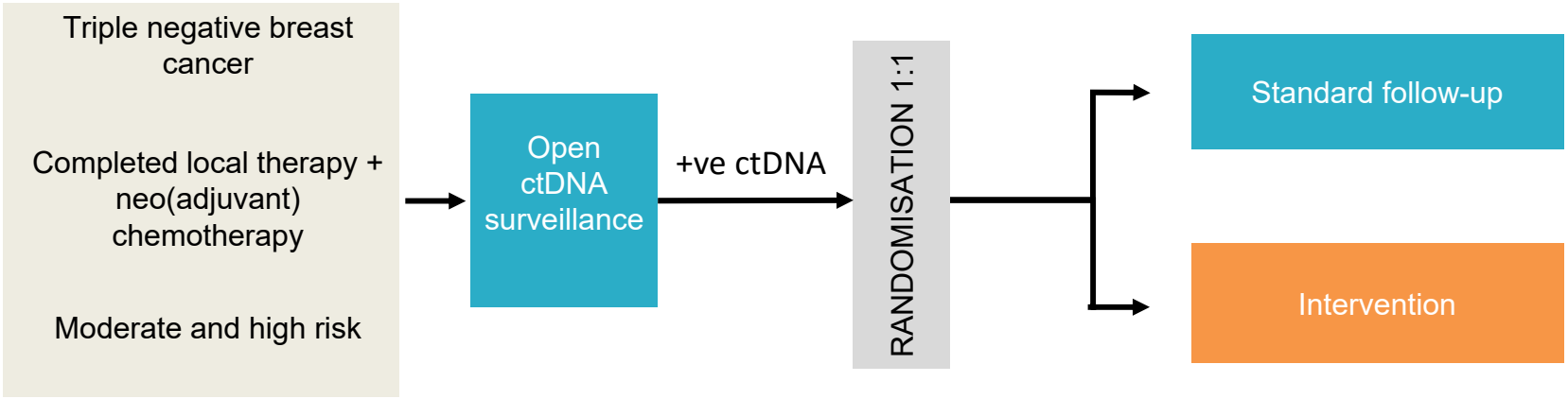
Challenges in phase III design



Issues

- Statistically inefficient
- Bias against intervention arm – ctDNA +ve patients know they are at risk of relapse, potentially resulting in more and earlier scans

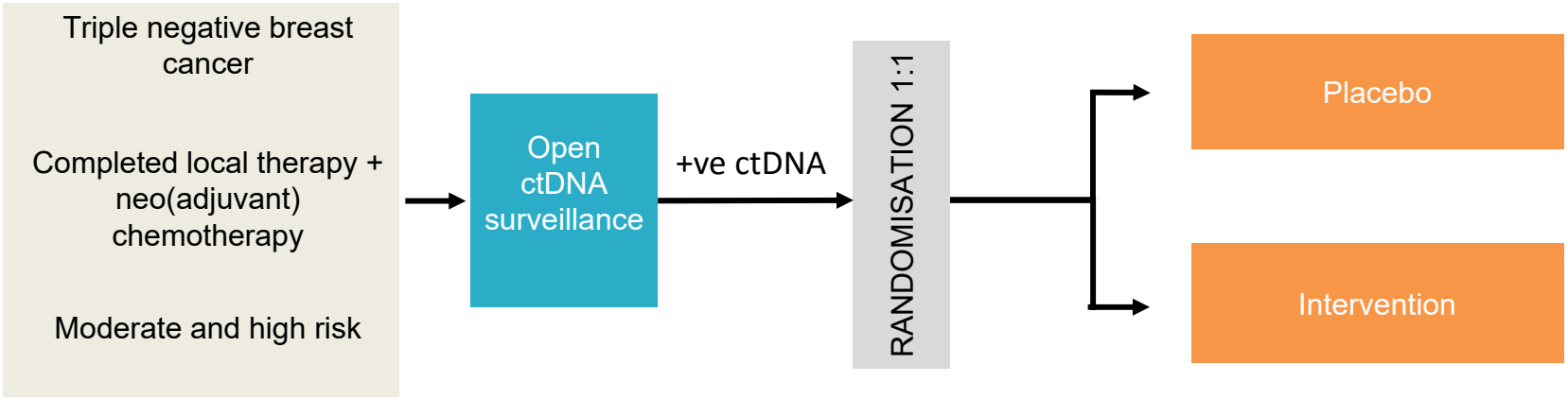
Challenges in phase III design



Issues

- **Statistically efficient but novel endpoint** - time from ctDNA detection to relapse
- **No bias against intervention** – ethically unacceptable to randomise to no treatment

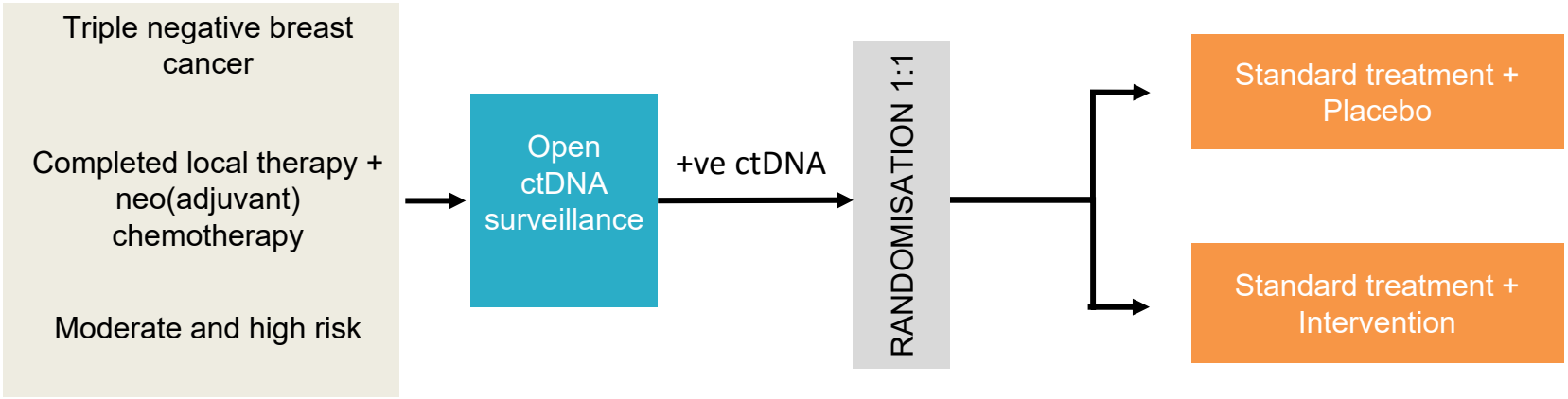
Challenges in phase III design



Issues

- **Statistically efficient but novel endpoint** - time from ctDNA detection to relapse
- **No bias against intervention** – ethically acceptable to randomise to placebo? AEs may unblind allocation

Challenges in phase III design



Issues

- **Statistically efficient, novel endpoints**
- **No bias against intervention** – provided appropriate standard therapy exists

Conclusions

ctDNA analysis identifies patients at high risk of relapse through detection of residual disease

ctDNA analysis may be used to identify targetable genetic events in residual disease, that may differ from the original primary

Clinical utility of ctDNA analysis in this setting requires prospective trials

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Molecular Oncology lab
Isaac Garcia-Murillas, Ros Cutts, Sarah Hrebien, Matthew Beaney, Inaki Comino-Mendez, Neha Chopra, Gaia Schiavon

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Dr Mohini Varughese (Musgrove Park)

MSKCC
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Academic Biochemistry Lab: Elizabeth Folkerd, Maria Afentakis, Kally Sidhu, Mitch Dowsett

Breakthrough Histopathology Lab: Frances Daley

U.S. FOOD & DRUG ADMINISTRATION

American Association for Cancer Research

PANEL DISCUSSION - SESSION II

Liquid Biopsies for Early Diagnosis

Session Chair: Carlos L. Arteaga, MD

Speakers:

Anne-Renee Hartman, MD

C. Ola Landgren, MD, PhD

Nicholas C. Turner, MD, PhD

SESSION III: Liquid Biopsies in Cancer Drug Development and Clinical Use

Session Chairs: Gideon M. Blumenthal, MD, and Pasi Jänne, MD, PhD

Speakers:

Pasi Jänne, MD, PhD

Gideon M. Blumenthal, MD

David Hyman, MD

Scott Kopetz, MD, PhD

Liquid Biopsies in Cancer Drug Development and Clinical Use: State of the Art for Lung Cancer

Pasi A. Jänne, M.D.,Ph.D.
Lowe Center for Thoracic Oncology
Dana Farber Cancer Institute

DANA-FARBER CANCER INSTITUTE

Belfer Center FOR APPLIED CANCER SCIENCE

HARVARD MEDICAL SCHOOL

Disclosure Information

Liquid Biopsies in Oncology Drug and Device Development

Pasi A. Jänne, MD, PhD

Consultant for: Astra Zeneca, Boehringer Ingelheim, Pfizer, Genentech/Roche, Chugai Pharmaceuticals, Merrimack Pharmaceuticals, Ariad, Ignyta, LOXO Oncology, Eli-Lilly

Research Support: Astellas, AstraZeneca, Daiichi-Sankyo, PUMA, Eli-Lilly

Stockholder in: Gatekeeper Pharmaceuticals

Other: LabCorp – post-marketing royalties from DFCI owned intellectual property on EGFR mutations

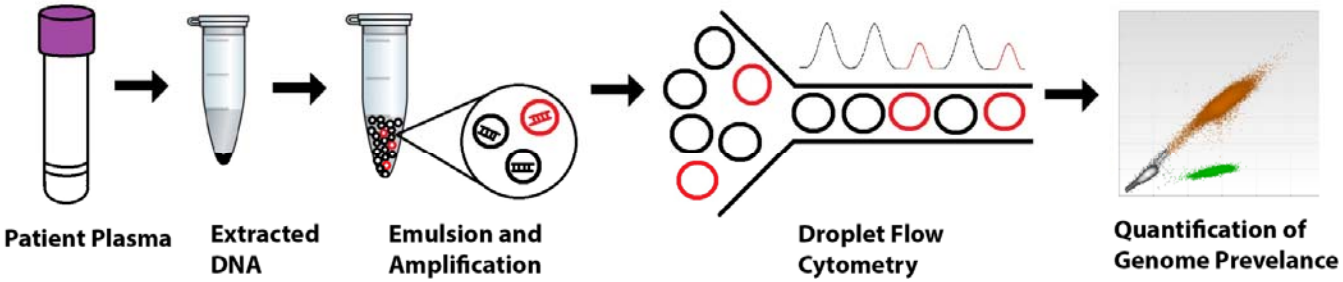
Liquid Biopsies – a tool to guide the treatment and study of lung cancer

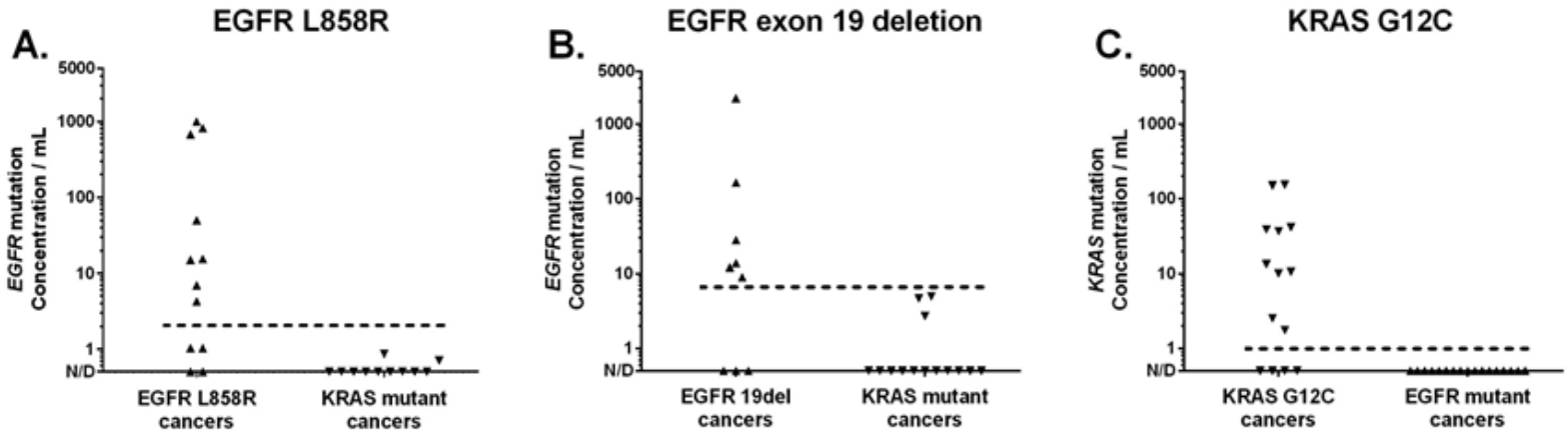
- Liquid biopsies as a non-invasive diagnostic tool
- Use of liquid biopsies to study the evolution of drug resistance
- Liquid biopsies as a pharmacodynamic tool for drug development

Liquid Biopsies – a tool to guide the treatment and study of lung cancer

- Liquid biopsies as a non-invasive diagnostic tool
- Use of liquid biopsies to study the evolution of drug resistance
- Liquid biopsies as a pharmacodynamic tool for drug development

Digital Droplet PCR for detection of tumor derived mutations in circulating free (cf) DNA

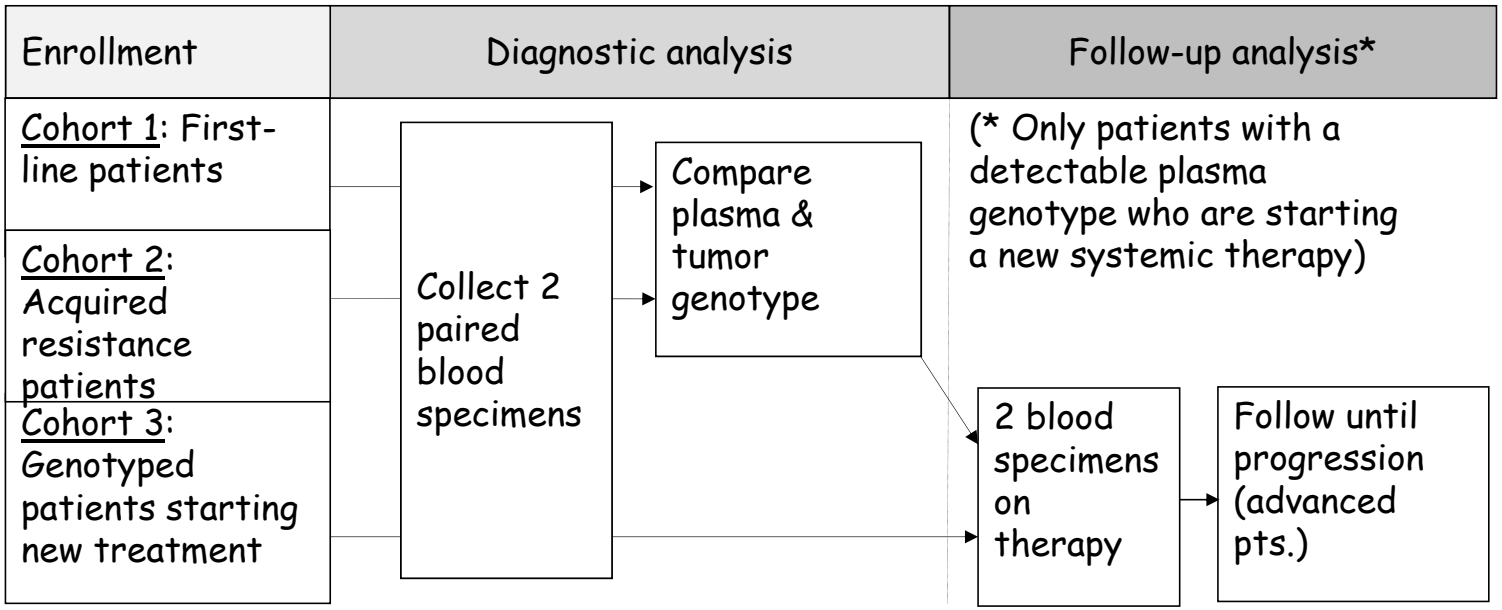




Assay validation against tumor genotypes allows definition of the analytical range

Oxnard et el. CCR 2014

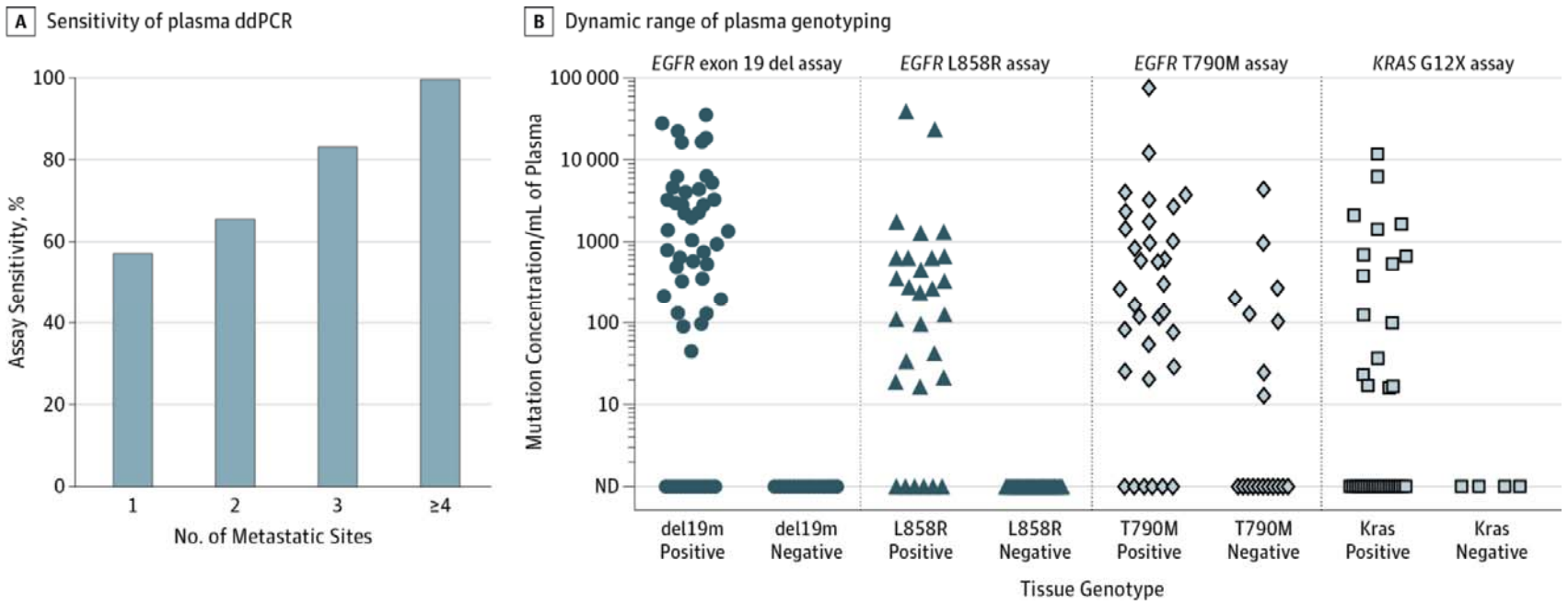
Prospective validation – DFCI# 14-147 Schema



Same day registration and initial blood draw

Adrian Sacher, Geoff Oxnard, Cloud Paweletz

Prospective validation of plasma genotyping for EGFR and KRAS mutations

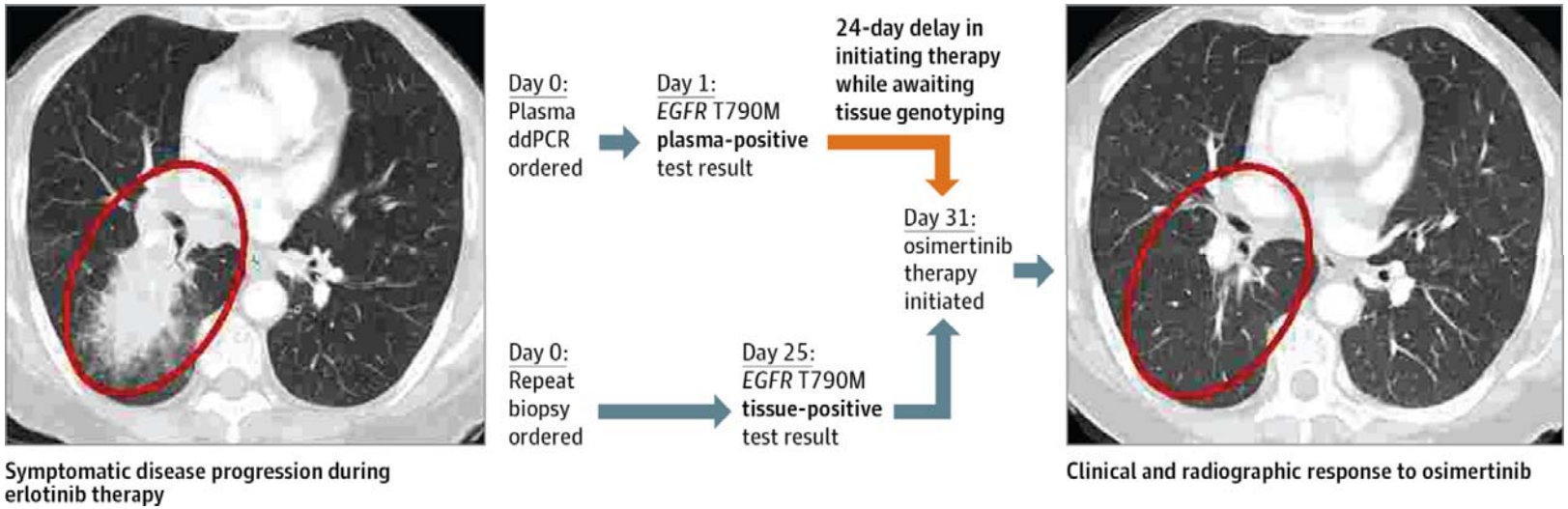


100% PPV for EGFR (del 19 and L858R) and KRAS mutations; 79% for T790M

Sensitivity: EGFR exon 19: 82%; L858R; 72%; T790M: 77%; KRAS: 64%

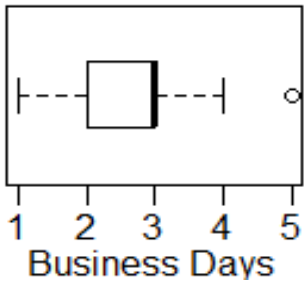
Sacher et al JAMA Oncology 2016

Plasma genotyping is faster than tissue based genotyping



Symptomatic disease progression during erlotinib therapy

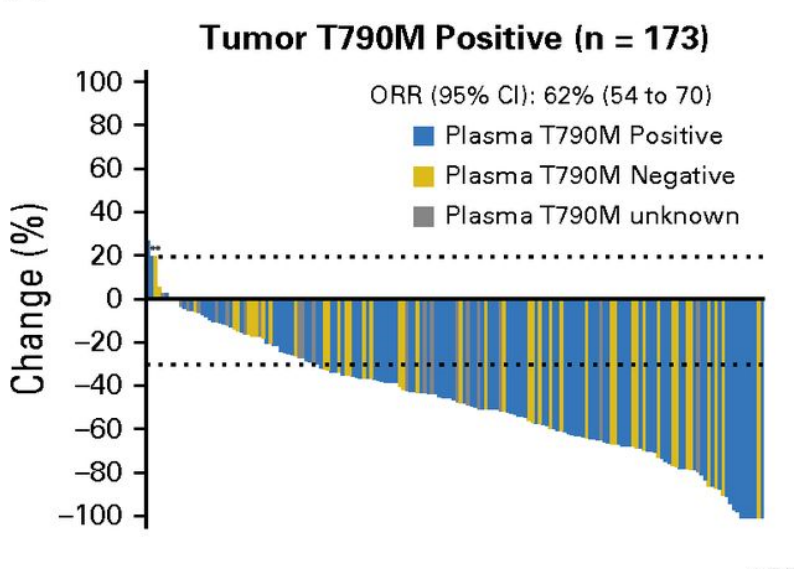
Clinical and radiographic response to osimertinib



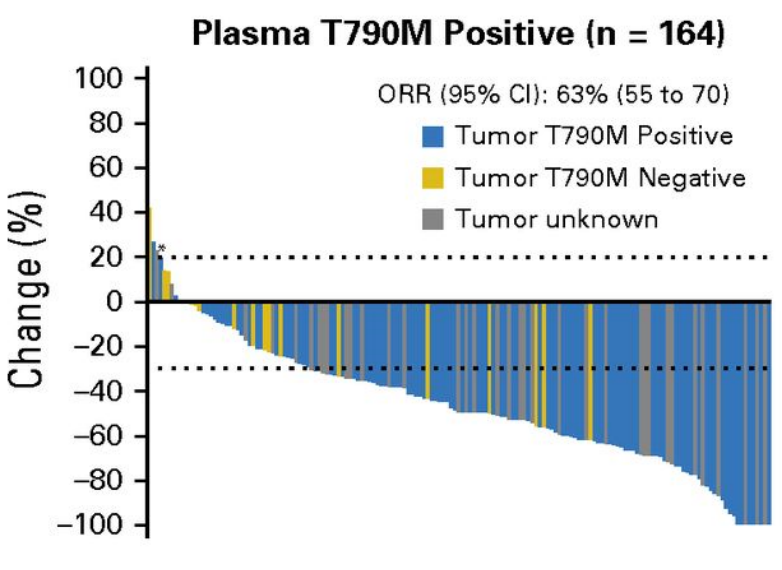
- Plasma ddPCR Turn around time (TAT): 3 days (range 1-7)
- Tissue genotyping TAT:
  - Newly diagnosed: 12 days (range 1 – 54)
  - EGFR acquired resistance: 27 days (range 1- 146)

Sacher et al JAMA Oncology 2016

Plasma genotyping can predict tumor response to osimertinib just as well as tumor genotyping



PFS: 10 months

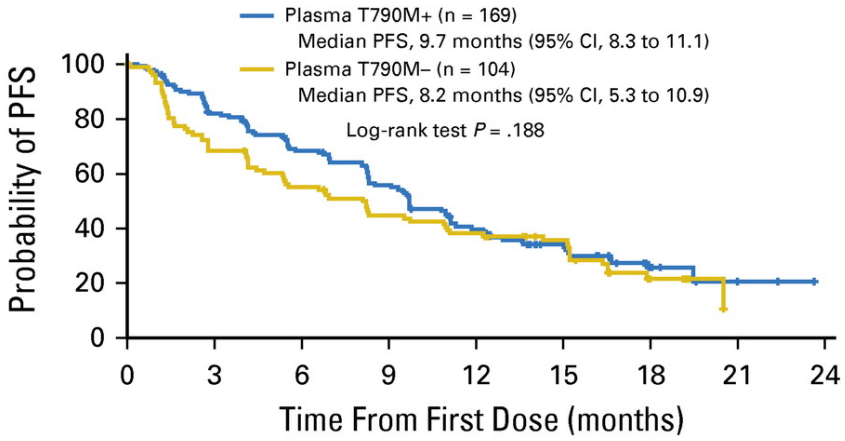


PFS: 10 months

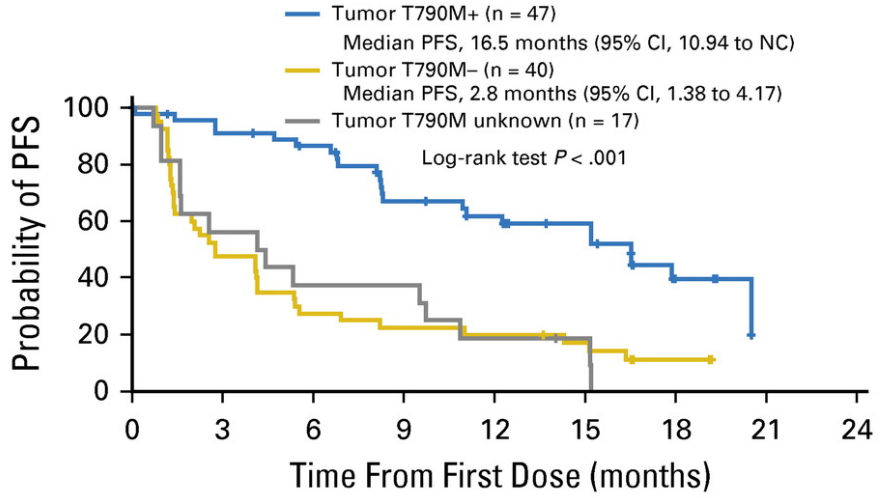
EGFR T790M cfDNA testing is now approved by the FDA

Oxnard et al. JCO 2016

Plasma based genotyping provides insight into tumor heterogeneity



No. at risk								
Plasma T790M+	167	130	102	79	53	31	9	2
Plasma T790M–	104	69	54	42	34	25	6	



No. at risk							
Tumor T790M+	47	41	37	27	23	17	4
Tumor T790M–	40	19	11	9	8	6	2
Tumor unknown	17	9	6	5	3	2	

Plasma T790M + vs -

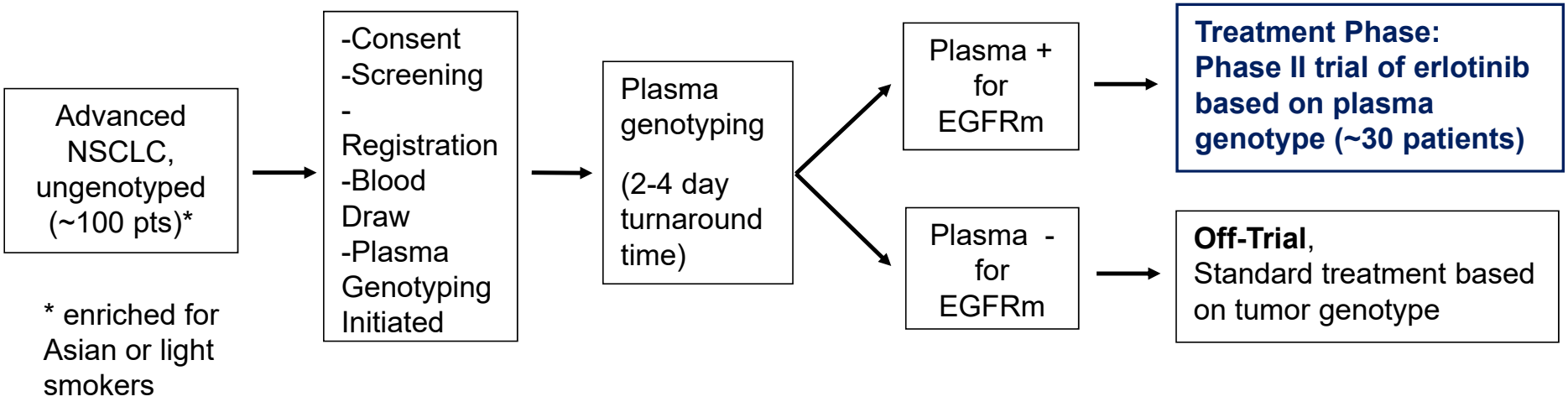
Tumor T790M + vs – in plasma T790M - patients

Plasma and Tumor testing can provide complementary information

Oxnard et al. JCO 2016

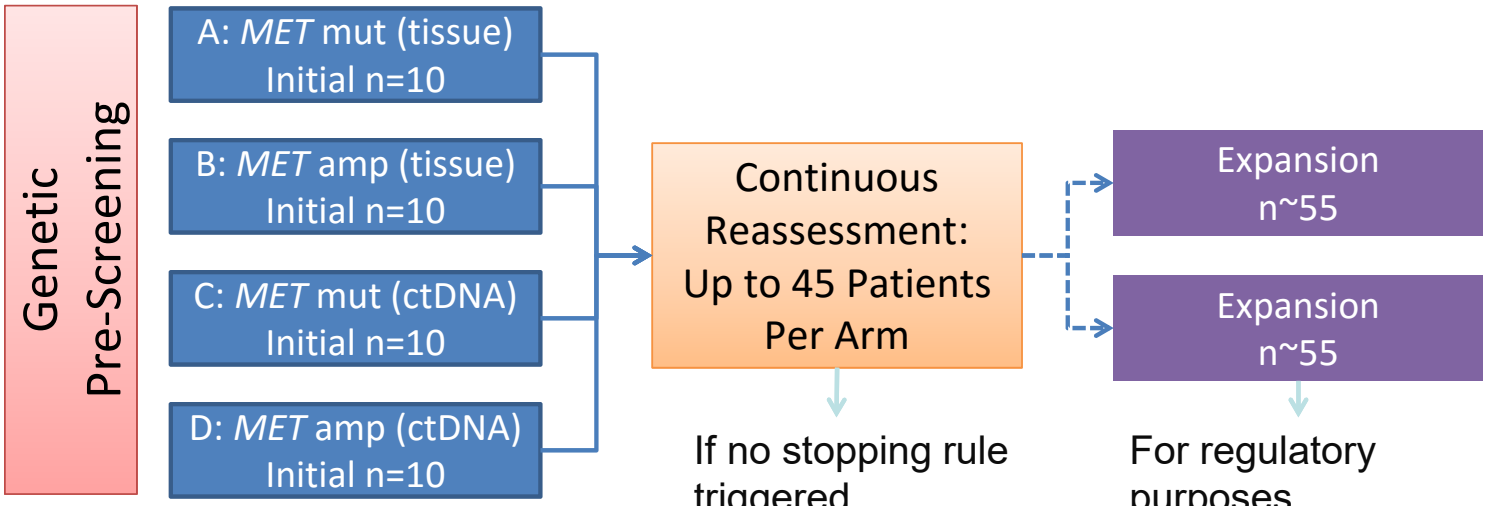
Clinical application of ddPCR

- We have launched plasma ddPCR as a clinical assay at DFCI/BWH for use in lung cancer care.
- Enrolling to a prospective trial which uses plasma EGFR genotyping for rapid initiation of erlotinib (NCT02770014)



PI: Geoff Oxnard - DFCI

AMETHYST-NSCLC: Study Design



If no stopping rule triggered, hypothesis testing will include 45 evaluable patients

For regulatory purposes

- Increase confidence interval around ORR
- Increase the size of safety database in the target patient population

amethyst NSCLC

Liquid Biopsies – a tool to guide the treatment and study of lung cancer

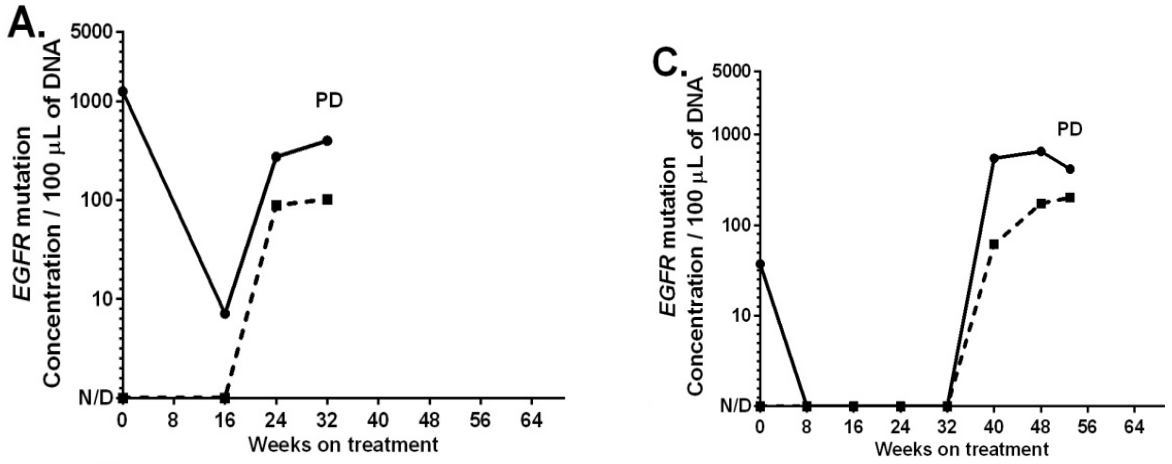
- Liquid biopsies as a non-invasive diagnostic tool
- Use of liquid biopsies to study the evolution of drug resistance
- Liquid biopsies as a pharmacodynamic tool for drug development

Non-invasive monitoring of evolution of drug resistance

Stage IV NSCLC
EGFR mutant
Treatment naive

Erlotinib
150 mg

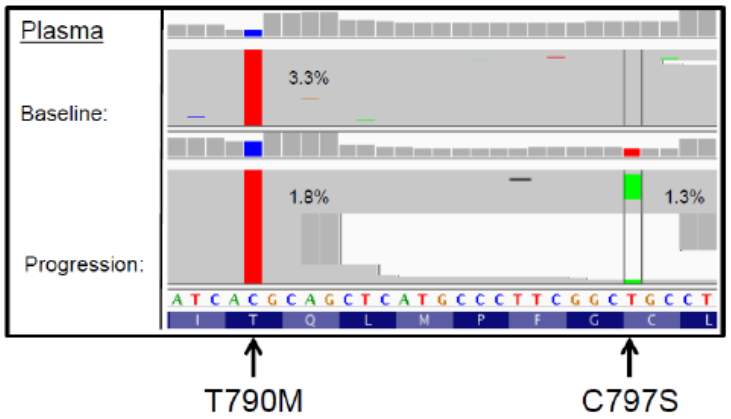
Biopsy at resistance
Circulating tumor cells
Plasma for cfDNA

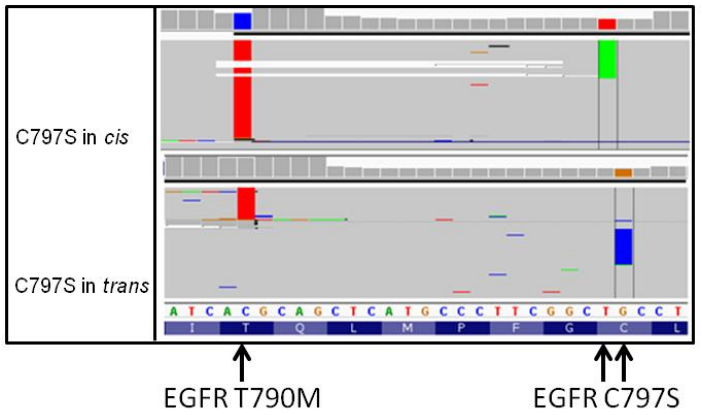


Serial monitoring for EGFR activating and EGFR T790M resistance mutation in erlotinib treated EGFR mutant patients

Oxnard et al. CCR 2014

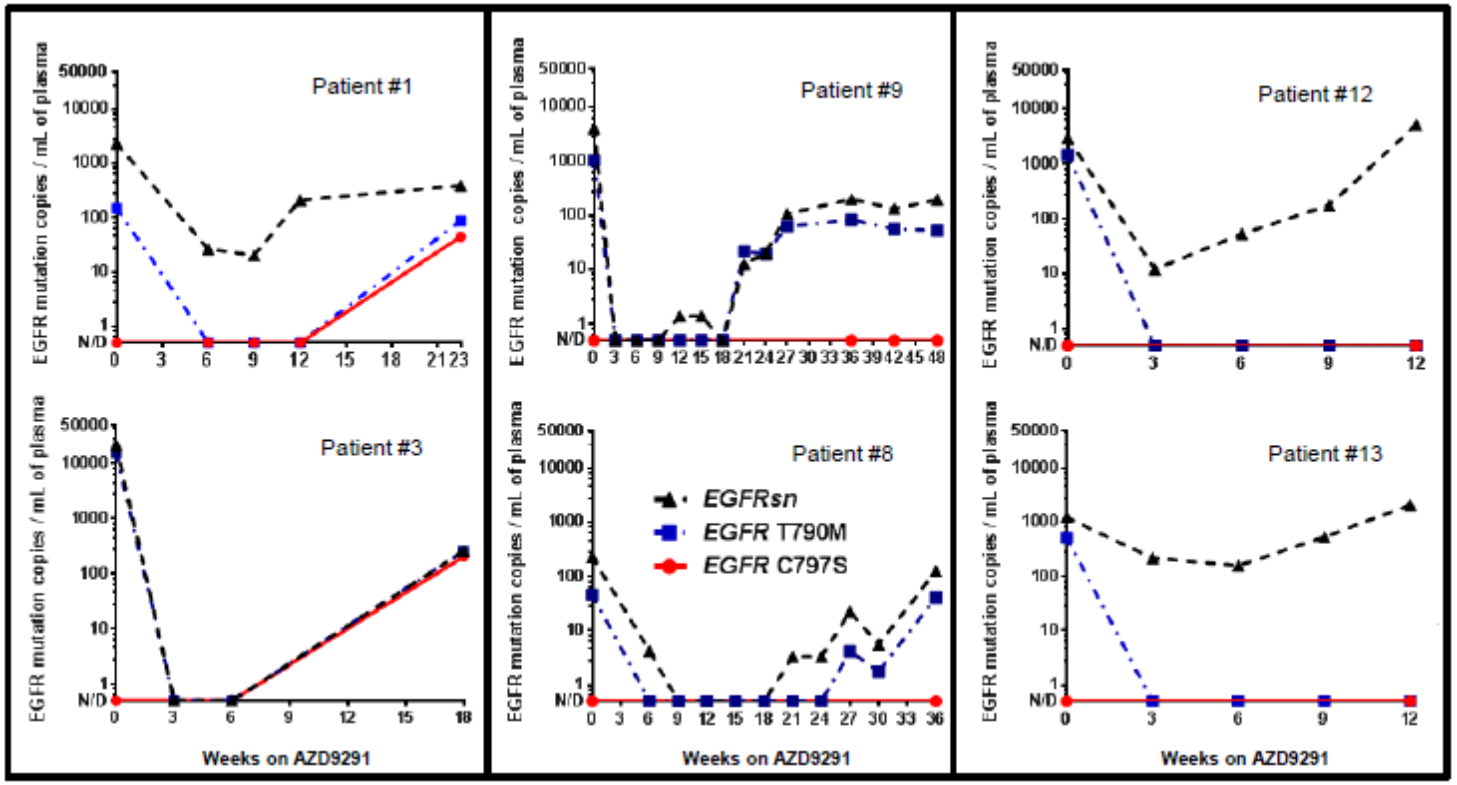
Identification of an acquired EGFR C797S mutation through NGS of cfDNA from an osimertinib relapsed patient





Thress et al, Nature Medicine, 2015

Serial ddPCR profiling of cfDNA reveals 3 molecular subtypes of acquired resistance to osimertinib



EGFR Activating Mutation
EGFR T790M
EGFR C797S

EGFR Activating Mutation
EGFR T790M

EGFR Activating Mutation
Loss of T790M

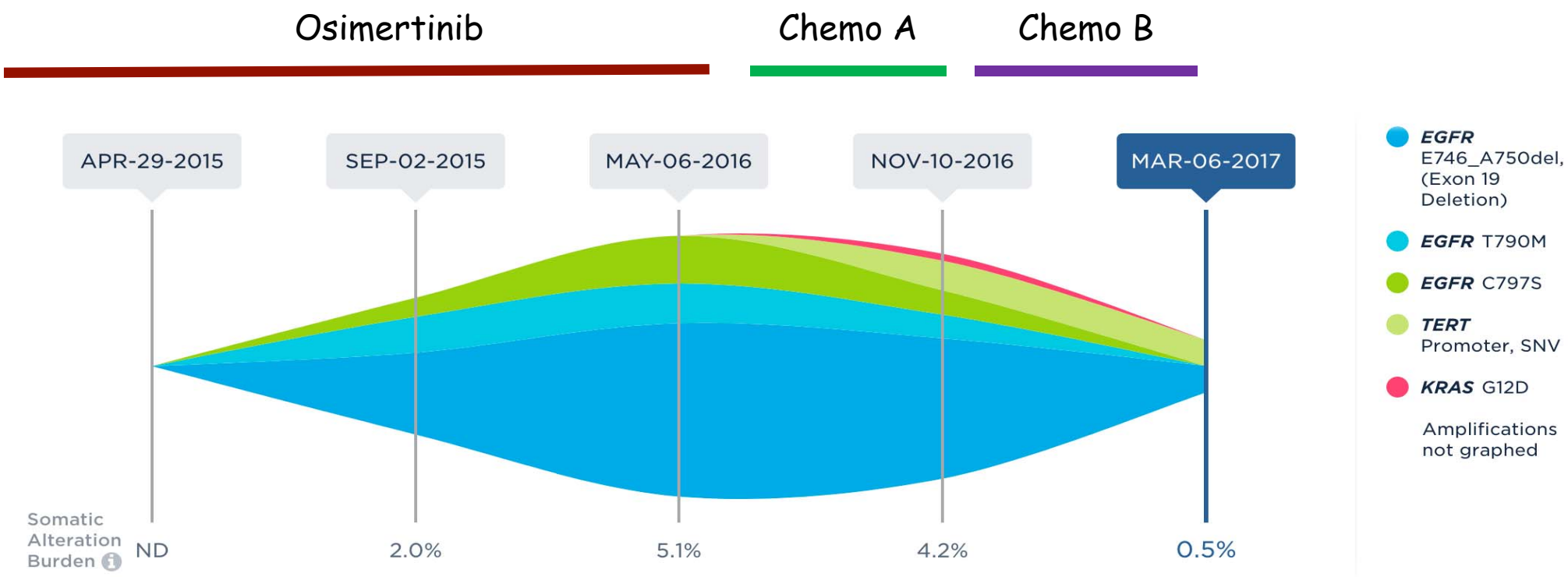
Thress et al, Nature Medicine, 2015

Detection of ALK fusion and multiple secondary mutations using NGS of cfDNA

Alteration		% cfDNA
TP53	*R337C*	2.7
ALK	*EML4-ALK fusion*	0.9
	G1128A	0.8
	L1198F	0.5
	F1174C	0.5
KRAS	*V8L*	0.4
	G12C	0.4

Courtesy of Guardant Health and Alice Shaw MD, PhD MGH Cancer Center

Tracking changes in allele frequencies of mutations using plasma NGS



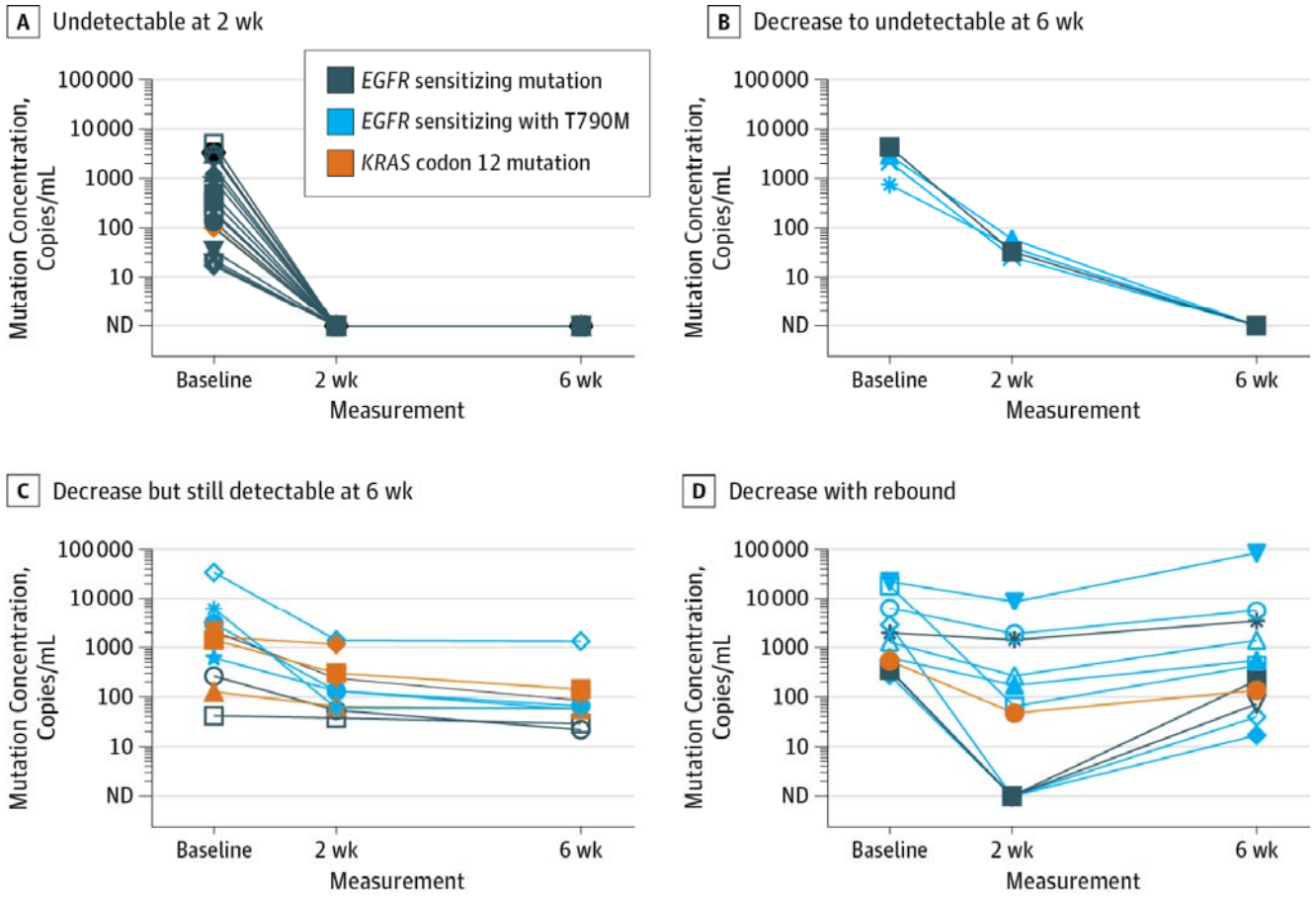
Liquid Biopsies – a tool to guide the treatment and study of lung cancer

- Liquid biopsies as a non-invasive diagnostic tool
- Use of liquid biopsies to study the evolution of drug resistance
- Liquid biopsies as a pharmacodynamic tool for drug development

Liquid biopsies as a pharmacodynamic tool for drug development

- Quantitative nature of ddPCR ideally suited to follow disease burden following treatment
- Opportunity to ask whether cfDNA clearance or persistence impacts duration of drug benefit
- Potential tool for dose finding in early stage clinical trials

Serial cfDNA analyses may be an early biomarker of treatment efficacy



Patients with complete cfDNA resolution

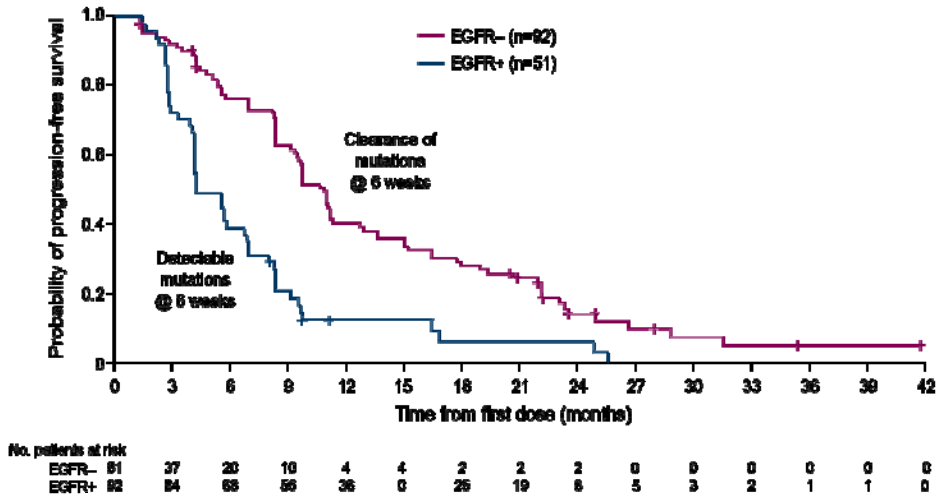
Treatment discontinuation rate
0% (0/23; 6 wks)
4% (1/23; 12 wks)

Patients without complete cfDNA resolution

Treatment discontinuation rate
33% (9/27; 6 wks)
56% (15/27; 12 wks)

Sacher et al. JAMA Onc 2016

Lack of plasma clearance of EGFR mutations is a poor prognostic marker

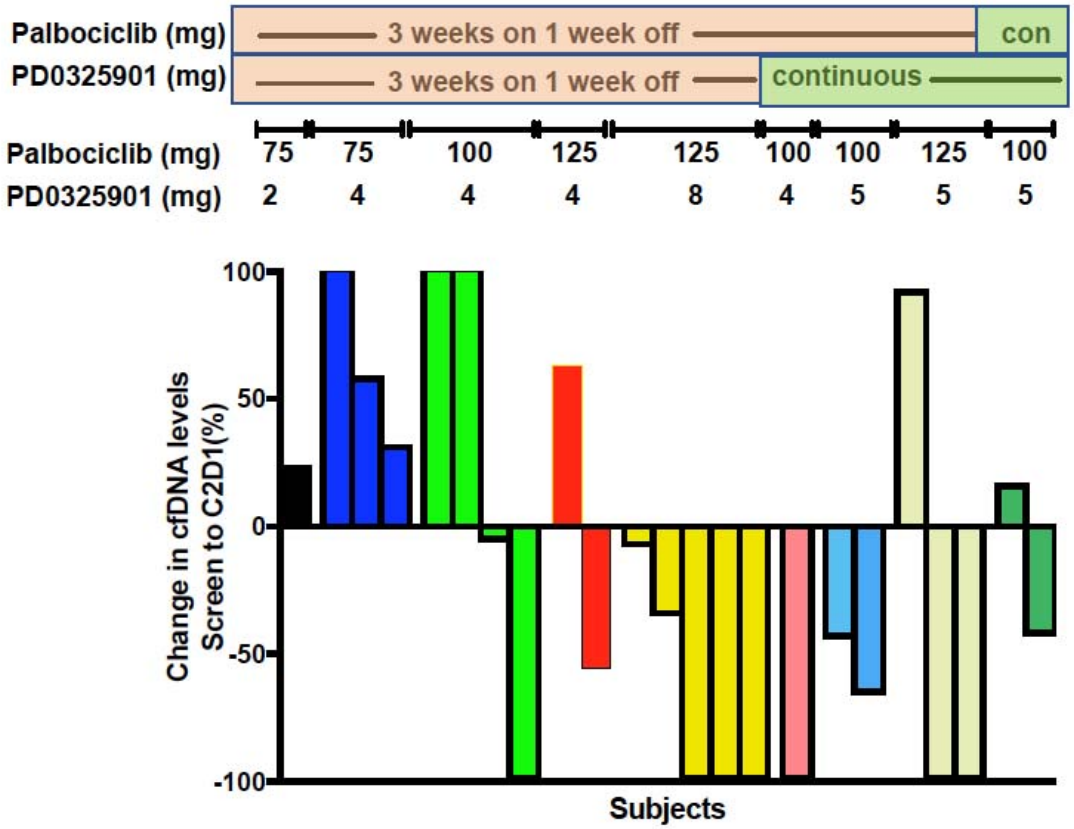


Group		Median PFS (95% CI)	ORR	P-value (log rank test)	Hazard ratio (95% CI)
Clearance of plasma EGFR mutations at 6 weeks	n=92	10.8 months 95% CI 9.3, 12.7	74%	<0.0001	2.64 (1.81, 3.84)
Detectable plasma EGFR mutations at 6 weeks	n=51	4.2 months 95% CI 4.1, 6.8	41%		

In this patient cohort (n=143), the overall median PFS was 8.3 months (95% confidence interval [CI] 6.9, 9.7).

Thress et al. *ASCO* 2017

KRAS Allelic Burden in Plasma (Cycle 1)



Geoff Shapiro & Cloud Paweletz; AACR 2017

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Lynette Sholl
Neal Lindeman

Belfer Center for Applied Cancer Science

Cloud Paweletz
Yanan Kuang
Nora Feeney
Bryan Ulrich
Allison O'Connell
Melissa Messineo

Session III Overview

- Biomarkers and surrogate endpoints
  - Gideon Blumenthal – FDA
- Use of cfDNA based genotyping for trial enrollment
  - David Hyman – MSKCC
- Use of cfDNA to guide the care of CRC patients
  - Scott Kopetz - MDACC

Optimizing Biomarkers for Oncology Drug Development

AACR-FDA Liquid Biopsies in Oncology II
October 10, 2017

Gideon M Blumenthal, MD
Deputy Division Director (Acting)
Office of Hematology and Oncology Products
U.S. Food and Drug Administration

Follow @FDAOncology on Twitter

Key points

- Basic definitions and types of biomarkers
- Examples of “validated” surrogate endpoints in drug development
- Methods to “validate” biomarkers and how to interact with agency

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Basic definitions and types of biomarkers

Some Definitions

- **Biomarker-** measured as indicator of biological/ pathogenic processes, or responses to exposures/ interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers
- **Endpoint-** a precisely defined variable intended to address a particular research question
- **Surrogate endpoint-** an endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. Should predict benefit or harm based on epidemiologic, therapeutic, pathophysiology, or other evidence

https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-S

Surrogate Endpoint: “reasonably likely” versus “established”

- **Accelerated Approval**: accept surrogate endpoint reasonably likely to predict clinical benefit
  - Serious conditions/ high unmet medical need
  - Better than available therapy
  - May require confirmatory studies
  - >90 AAs in Oncology since 1992, failure to confirm benefit is rare

- **Regular Approval**: established surrogates or improvement in direct measures of “feels, functions, survives”

Types of biomarkers

- **Susceptibility/risk** biomarkers
- **Diagnostic** biomarkers
- **Monitoring** biomarkers
- **Prognostic** biomarkers
- **Predictive** biomarkers
- **Pharmacodynamic/response** biomarkers
- **Safety** biomarkers

Biomarkers used frequently in Oncology drug development

- **Prognostic biomarkers** (e.g. mammaprint)
  - Useful for enrichment of high risk population, stratification
- **Predictive/Selection biomarkers** (e.g. EGFR/ ALK/ BRAF/ ROS1/ HER2/ ER/ PR/ IDH2/ cKIT/ PD-L1/ MSI-H)
  - Frequently requires contemporaneous approval of **companion diagnostic** if essential for safe and effective use
- **Pharmacodynamic/response biomarkers**
  - Used to assess proof of concept/ target engagement in the learning phase
  - Can be used as surrogate endpoints for go/no-go or for approval (accelerated or regular)

Factors considered in response biomarker assessment

- Risk introduced by its use
- Biologic rationale and understanding of its role in disease pathway
- Assay considerations (reliability, reproducibility, sensitivity, specificity)
  - See Session IV (Reena Philip)

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Examples of “validated” surrogate endpoints in drug development

Example #1 of validated surrogate endpoint: HIV-RNA

The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs

Jeffrey S. Murray, Michael R. Elashoff, Lauren C. Iacono-Connors, Therese A. Cvetkovich and Kimberly A. Struble

Objectives: To evaluate the utility of HIV RNA as an endpoint in antiretroviral efficacy studies.

Design: Data collected from antiretroviral efficacy trials were analyzed to explore relationships between clinical progression and the magnitude, nadir and duration of HIV RNA reductions. The proportion of patients suppressing HIV RNA below assay quantification, time to maximal virologic response, and loss of virologic response in relation to pretreatment characteristics were also analyzed.

Methods: Analyses were conducted using data from individual antiretoviral efficacy trials or groups of trials that studied similar types of drug regimens and used similar HIV RNA assays. Treatment regimens were pooled for most analyses. Clinical progression was defined as the occurrence of an AIDS-defining event (essentially Centers of Disease Control criteria) or death.

Results: Treatment-induced reductions in HIV RNA approximating total assay variability of about 0.5 $\log_{10}$ copies/ml were associated with decreases in the risk of clinical progression. Larger and more sustained reductions in HIV RNA were directly associated with lower risks for disease progression. Lower initial HIV RNA reductions were associated with more durable HIV RNA suppression.

Conclusions: For antiretoviral efficacy studies, plasma HIV RNA is a suitable study endpoint that is likely to predict a decreased risk for AIDS progression and death. Because greater and more sustained reductions in HIV RNA appear to confer greater reductions in clinical risk, maintaining maximal suppression of plasma HIV RNA, particularly below the limits of assay quantification, appears to be a rigorous benchmark for assessing the efficacy of antiretroviral regimens.

Lippincott Williams & Wilkins

AIDS 1999, **13**:797–804

- **Prior to 1997**
  - death or OI approval endpoint
- **After 1997**
  - 24-week HIV-RNA→ accelerated approval
  - 48-week HIV-RNA→ regular approval
- Combination antiretroviral therapy (cART) has transformed life expectancy

Example #2 of validated surrogate endpoint: BCR-ABL PCR in CML

Frequency of Major Molecular Responses to Imatinib or Interferon Alfa plus Cytarabine in Newly Diagnosed Chronic Myeloid Leukemia

Tim P. Hughes, M.D., Jaspal Kaeda, Ph.D., Susan Branford, Zbigniew Rudzki, Ph.D., Andreas Hochhaus, M.D., Martee L. Hensley, M.D., Insa Gathmann, M.Sc., Ann E. Bolton, B.Sc.N., Iris C. van Hoornissen, B.Sc.N., John M. Goldman, D.M., and Jerald P. Radich, M.D., for the International Randomised Study of Interferon versus STI571 (IRIS) Study Group*

ABSTRACT

BACKGROUND

In a randomized trial, 1106 patients with chronic myeloid leukemia (CML) in chronic phase were assigned to imatinib or interferon alfa plus cytarabine as initial therapy. We measured levels of BCR-ABL transcripts in the blood of all patients in this trial who had a complete cytogenetic remission.

METHODS

Levels of BCR-ABL transcripts were measured by a quantitative real-time polymerase-chain-reaction assay. Results were expressed relative to the median level of BCR-ABL transcripts in the blood of 30 patients with untreated CML in chronic phase.

RESULTS

In patients who had a complete cytogenetic remission, levels of BCR-ABL transcripts after 12 months of treatment had fallen by at least 3 log in 57 percent of those in the imatinib group and 24 percent of those in the group given interferon plus cytarabine (P=0.003). On the basis of the rates of complete cytogenetic remission of 68 percent in the imatinib group and 7 percent in the group given interferon plus cytarabine at 12 months, an estimated 39 percent of all patients treated with imatinib but only 2 percent of all those given interferon plus cytarabine had a reduction in BCR-ABL transcript levels of at least 3 log (P<0.001). For patients who had a complete cytogenetic remission and a reduction in transcript levels of at least 3 log at 12 months, the probability of remaining progression-free was 100 percent at 24 months, as compared with 95 percent for such patients with a reduction of less than 3 log and 85 percent for patients who were not in complete cytogenetic remission at 12 months (P<0.001).

CONCLUSIONS

The proportion of patients with CML who had a reduction in BCR-ABL transcript levels of at least 3 log by 12 months of therapy was far greater with imatinib treatment than with treatment with interferon plus cytarabine. Patients in the imatinib group with this degree of molecular response had a negligible risk of disease progression during the subsequent 12 months.

Hughes TP, Kaeda J, et al. NEJM 2003

Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS)

*Timothy P. Hughes,[1] *Andreas Hochhaus,[2] Susan Branford,[3] Martin C. Müller,[4] Jaspal S. Kaeda,[5] Letizia Foroni,[6] Brian J. Druker,[7] François Guilhot,[8] Richard A. Larson,[9] Stephen G. O'Brien,[10] Marc S. Rudoltz,[11] Manisha Mone,[11] Elisabeth Wehrle,[12] Vijay Modur,[13] John M. Goldman,[6] and Jerald P. Radich,[14] on behalf of the IRIS investigators

[1]Department of Haematology, SA Pathology, Royal Adelaide Hospital, Adelaide, Australia; [2]Abt Hämatologie und internistische Onkologie, Klinik für Innere Medizin II, Universitätsklinikum Jena, Jena, Germany; [3]Molecular Pathology, SA Pathology, Adelaide, Australia and School of Medicine, University of Adelaide, Adelaide, Australia; [4]III Medizinische Klinik, Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany; [5]Department of Hematology, Central Hospital of Coimbra, Coimbra, Portugal; [6]Haematology Department, Hammersmith Hospital, London, United Kingdom; [7]Knight Cancer Institute, Oregon Health & Science University, Portland, OR; [8]Centre d'Investigation Clinique CIC P 802, Inserm, Centre Hospitalier Universitaire de Poitiers, Poitiers, France; [9]University of Chicago, Chicago, IL; [10]Newcastle University Medical School, Newcastle, United Kingdom; [11]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [12]Novartis Pharma AG, Basel, Switzerland; [13]Novartis Institute of Biomedical Research, Cambridge, MA; and [14]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA

This study examines the prognostic significance of early molecular response using an expanded dataset in chronic myeloid leukemia patients enrolled in the International Randomized Study of Interferon and STI571 (IRIS). Serial molecular studies demonstrate decreases in *BCR-ABL* transcripts over time. Analyses of event-free survival (EFS) and time to progression to accelerated phase/blast crisis (AP/BC) at 7 years were based on molecular responses using the international scale (IS) at 6-, 12-, and 18-month landmarks. Patients with *BCR-ABL* transcripts > 10% at 6 months and > 1% at 12 months had inferior EFS and higher rate of progression to AP/BC compared with all other molecular response groups. Conversely, patients who achieved major molecular response [MMR: *BCR-ABL* (IS) ≤ 0.1%] by 18 months enjoyed remarkably durable responses, with no progression to AP/BC and 95% EFS at 7 years. The probability of loss of complete cytogenetic response by 7 years was only 3% for patients in MMR at 18 months versus 26% for patients with complete cytogenetic response but not MMR ($P < .001$). This study shows a strong association between the degree to which *BCR-ABL* transcript numbers are reduced by therapy and long-term clinical outcome, supporting the use of time-dependent molecular measures to determine optimal response to therapy. This study is registered at www.clinicaltrials.gov as NCT00006343. (*Blood*. 2010;116(19):3758-3765)

Hughes TP, Hochhaus, et al. Blood 2010

Example #2 of validated surrogate endpoint: BCR-ABL PCR in CML

	Dasatinib (N=259)	Imatinib (N=260)
MMR		
12 month	52%	34%
60 month	76%	64%

MMR (at any time) defined as BCR-ABL ratios <0.1% by RQ-PCR in peripheral blood samples standardized on the international scale. These are cumulative rates representing minimal follow-up for the time frame specified

	Nilotinib (N=282)	Imatinib (N=283)
MMR		
12 month	44%	22%
24 month	62%	38%
60 month	77%	60%

MMR defined as BCR-ABL/ABL ratios <0.1% by RQ-PCR in peripheral blood samples standardized on the international scale, which corresponds to a greater than or equal to 3 log reduction of BCR-ABL transcript from standardized baseline.

12 month MMR used as accelerated approval endpoint for imatinib-naïve 2nd Gen ABL KIs

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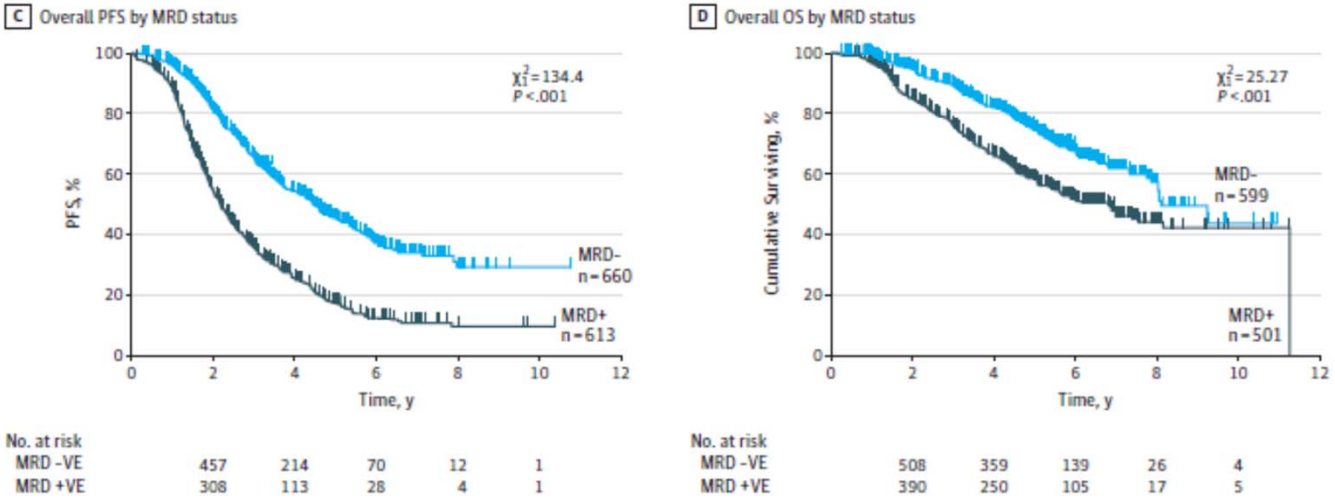
Methods to evaluate a candidate surrogate endpoint

Meta-analysis techniques

- **Individual-Patient level**

Association between candidate surrogate and clinical endpoint on individual level

Landmark approach to exclude “rapid progressors”



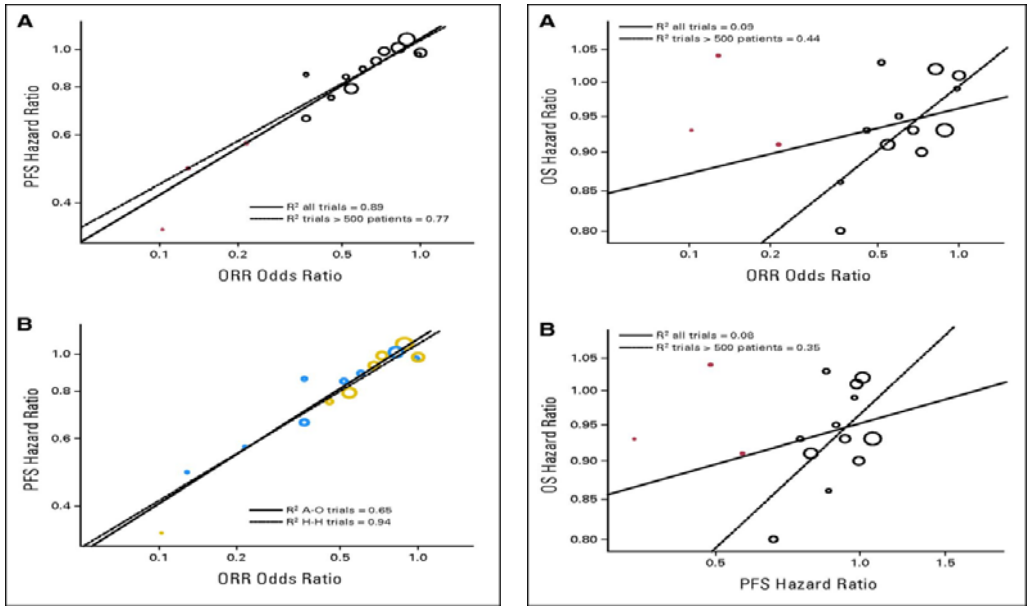
Munshi NC, Avet-Loiseau H et al. JAMA Oncology 2017

Meta-analysis techniques

- **Trial level Surrogacy**

Measures association of effect on surrogate with clinical endpoints between treatment arms in RCTs

Surrogate threshold effect- minimum treatment effect on surrogate necessary to predict effect on clinical endpoint(s)



Blumenthal GM, Karuri S, Zhang H, et al. J Clin Oncol. 2015 Mar 20;33(9):1008-14.

Opportunities to interact with the agency on "validating" surrogate endpoints

- CDER Biomarker Qualification Program
  - https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/default.htm
- Pre-IND or IND meeting
- Consortia (e.g. CTNeoBC pooled analysis for pCR neoadjuvant breast cancer see Cortazar *et al* Lancet 2014)

Parting thoughts

- Liquid biopsy technology has exciting potential applications for risk stratification, prediction, monitoring, surrogate endpoints for drug development and clinical practice
- Successful examples of establishing blood based tests as surrogate eps exist (HIV-RNA, BCR-ABL CML) though these are relatively “simple” diseases
- Requires careful planning, embedding as secondary endpoints into pivotal trials, data sharing, assay standardization, cooperation among stakeholders
- FDA OCE is a committed partner to advancing safe and effective LBx technologies for patients

Thank you!

Follow @FDAOncology on Twitter

Visit www.fda.gov/OCE

Memorial Sloan Kettering Cancer Center

Clinical Trial Enrollment based on cfDNA: Are We Ready for Liquid MATCH?

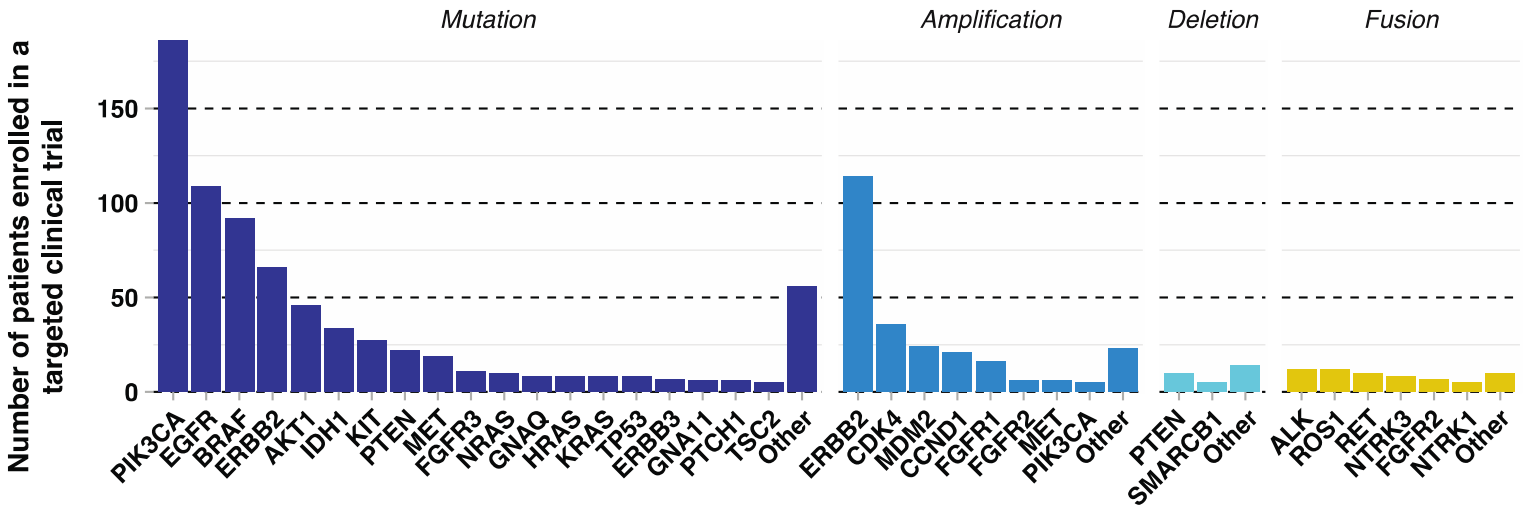
David Hyman, MD

Chief, Early Drug Development
Memorial Sloan Kettering Cancer Center

The Goal - Enrollment on Genomically Matched Trials

- MSK-Experience: 11% of patients with MSK-IMPACT (tumor based test) were enrolled on an MSK trial based on a target aberration

Total patients	5,009
…on any MSK trial	1,894 (38%)
…with a target aberration	527 (11%)

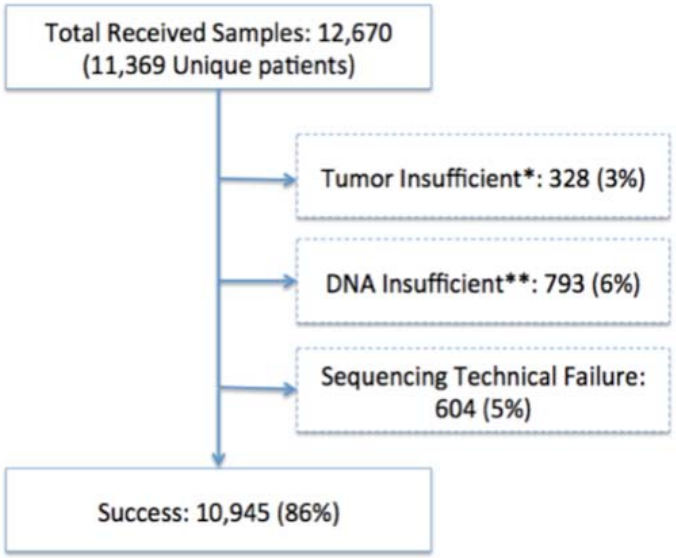


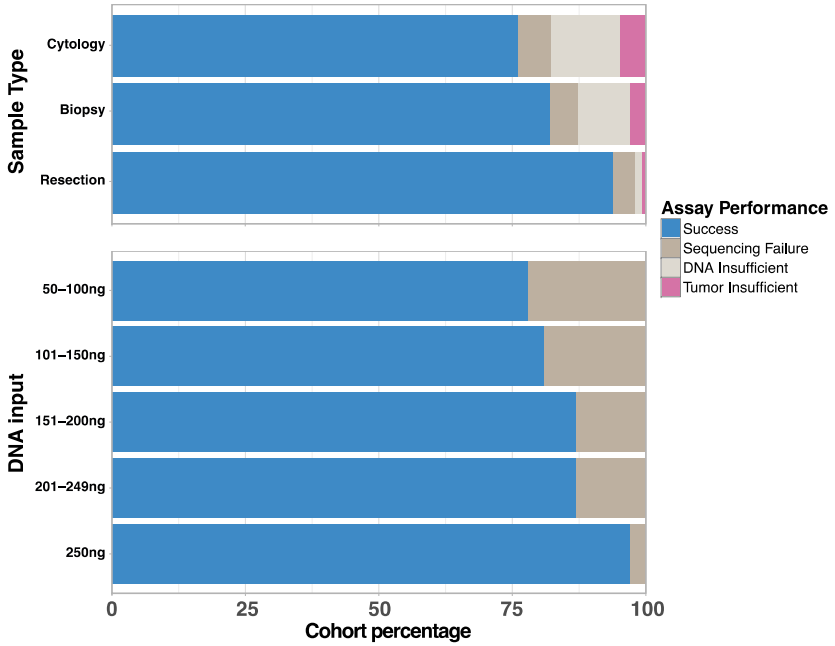
Zehir, Nat Med, 2017

Enrollment To Precision Medicine Studies Using cfDNA

- **Key Message**: Molecular allocation to targeted therapy studies based on cfDNA results is already a reality
- **Special Considerations**:
  - Technical feasibility / material availability / speed
  - Assay content
  - Additional technical considerations:
    - Somatic variant calling methodology
    - Gene Signatures from cfDNA – TMB, MSI, etc
    - Detection of non-missense mutations (fusions, indels, CNA)
    - Determining whether alteration represents a dominant clone
    - "Low shedders"
  - A unique opportunity: targeting acquired resistance

Tissue Adequacy for IMPACT Testing @MSK





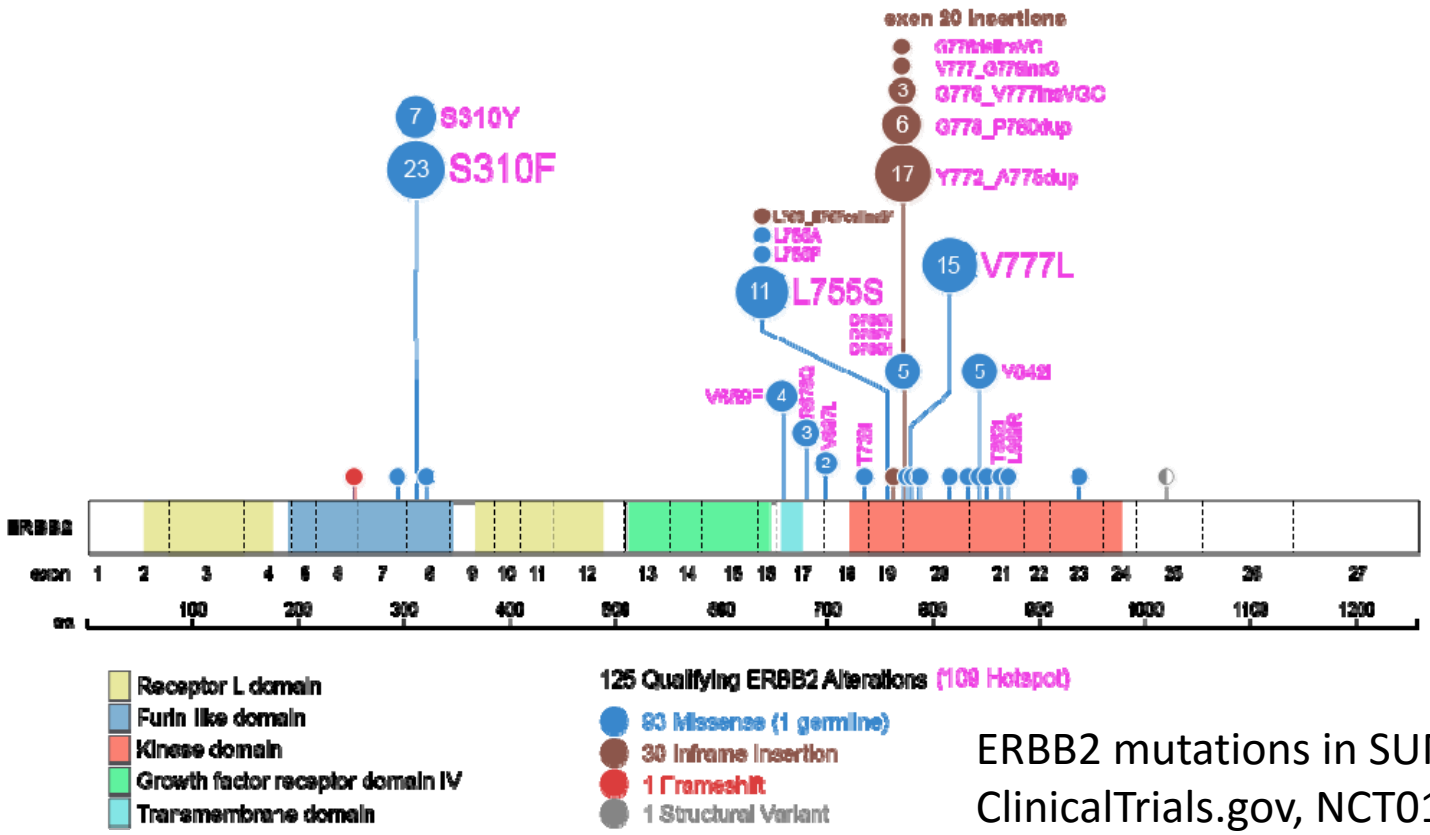
Not a major issue at our center…

…but MSK is likely not representative of the community experience

Assay Performance
Success
Sequencing Failure
DNA Insufficient
Tumor Insufficient

Zehir, Nat Med, 2017

Potentially Actionable ERBB2 Alterations Occur in Multiple Domains and Are of Multiple Classes



ERBB2 mutations in SUMMIT
ClinicalTrials.gov, NCT01953926

Hyman, AACR, 2017

How Much Content is Enough – cfDNA Assay @MSK

Gene List - Subject to Change

AKT1	CIC	FLT3	KNSTRN	NTRK2	RET	TGFBR2
ALK	CREBBP	FOXA1	KRAS	NTRK3	RHOA	TP53
APC	CTCF	FOXL2	MAP2K1	NUP93	RIT1	TP63
AR	CTNNB1	FOXO1	MAPK1	PAK7	ROS1	TSC1
ARAF	DICER1	FUBP1	MAX	PDGFRA	RRAS2	TSC2
ARID1A	DIS3	GATA3	MED12	PIK3CA	RXRA	U2AF1
ARID2	DNMT3A	GNA11	MET	PIK3CB	SETD2	VHL
ATM	EGFR	GNAQ	MLH1	PIK3R1	SF3B1	XPO1
B2M	EIF1AX	GNAS	MSH2	PIK3R2	SMAD3	
BCL2	EP300	H3F3A	MSH3	PMS2	SMAD4	
BCOR	ERBB2	HIST1H3B	MSH6	POLE	SMARCA4	
BRAF	ERBB3	HRAS	MTOR	PPP2R1A	SMARCB1	
BRCA1	ERCC2	IDH1	MYC	PPP6C	SOS1	
BRCA2	ESR1	IDH2	MYCN	PRKCI	SPOP	
CARD11	EZH2	IKZF1	MYD88	PTCH1	STAT3	
CBFB	FBXW7	INPPL1	NF1	PTEN	STK11	
CCND1	FGFR1	JAK1	NFE2L2	PTPN11	STK19	
CDH1	FGFR2	KDM6A	NOTCH1	RAC1	TCF7L2	
CDK4	FGFR3	KEAP1	NRAS	RAF1	TERT	
CDKN2A	FGFR4	KIT	NTRK1	RB1	TGFBR1	

Qualification Category	Exons in Category
Entire KD of OncoKB kinases	155
All exons of 25 most mutated TSG	497
≥1 OncoKB Level 1-4 variant	352
≥10 hotspot* mutations	189
>30 mutations	88
Fingerprint SNPs	31
Total	**1,312 exons**

- 128 genes
- 153,019 bp target territory
- 207,360 bp captured territory
- 1,728 probes
- Includes matched normal (buff coat)

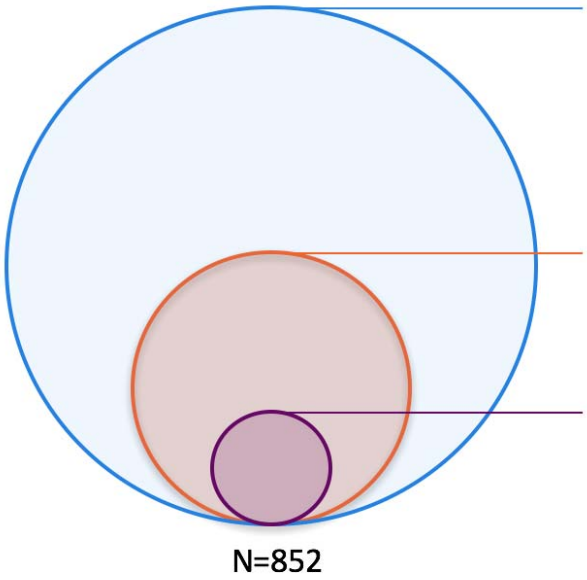
Courtesy of Mike Berger, Dana Tsui

*- Chang M, Nature Biotechnology, 2016

OncoKB
Precision Oncology Knowledge Base

Utility of Matched Normal Sequencing in Tumor and cfDNA Sequencing…

MSK-IMPACT Tumor Assay



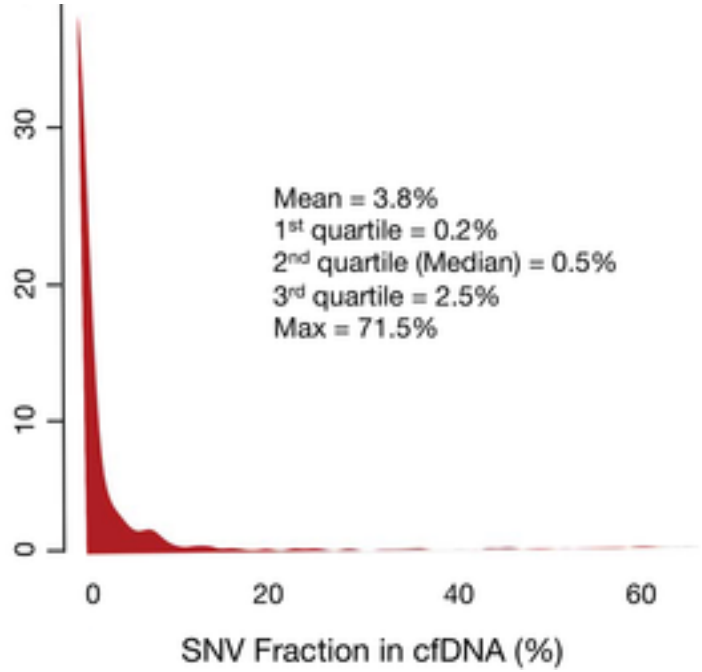
Unmatched
[Not in ExAC]
N=16,310

Matched
[Confirmed Somatic]
N=4,988 (30.6% of all variants)

Unmatched
[COSMIC variants]
N=874 (17.5% of true somatic mutations)

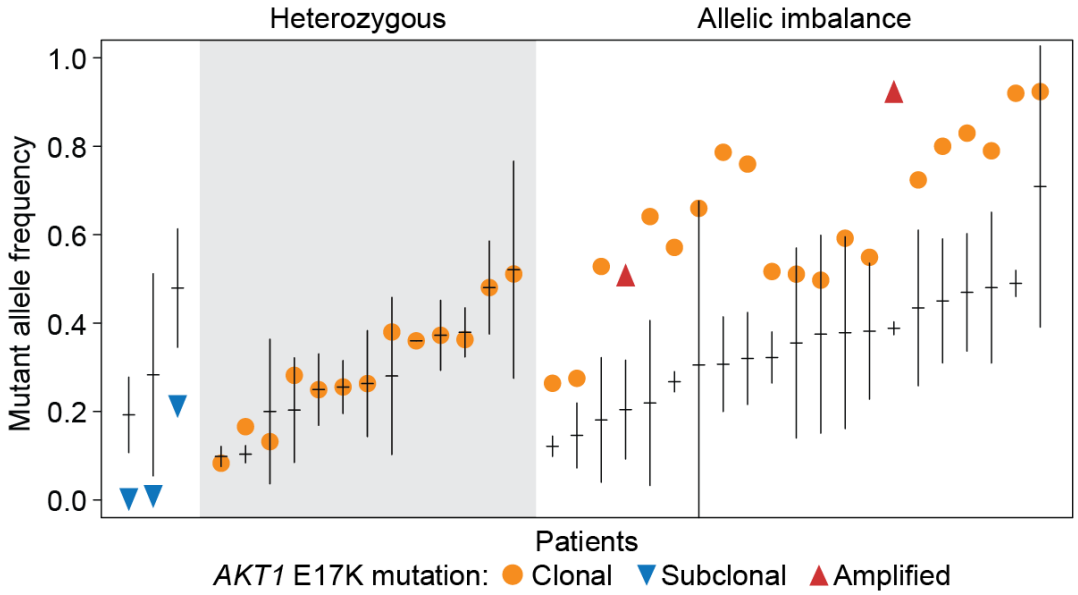
Zehir, Nat Med, 2017

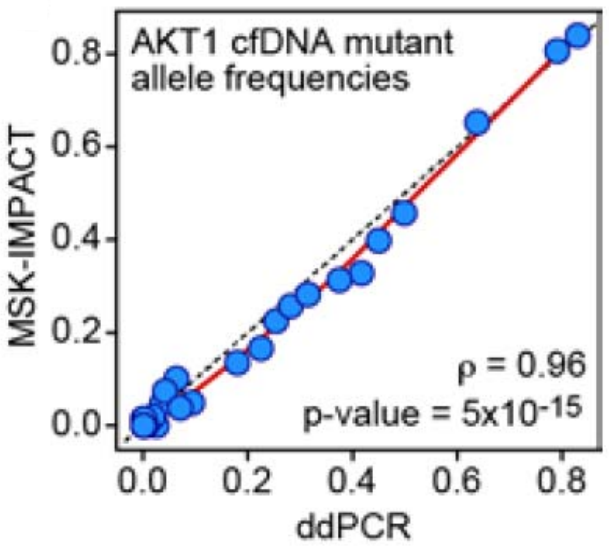
Commercial cfDNA Assay



Lanman RB, PLOS ONE 2015

...However Tumor Burden & Genomic Configuration of Allele Can Impact MAF in cfDNA

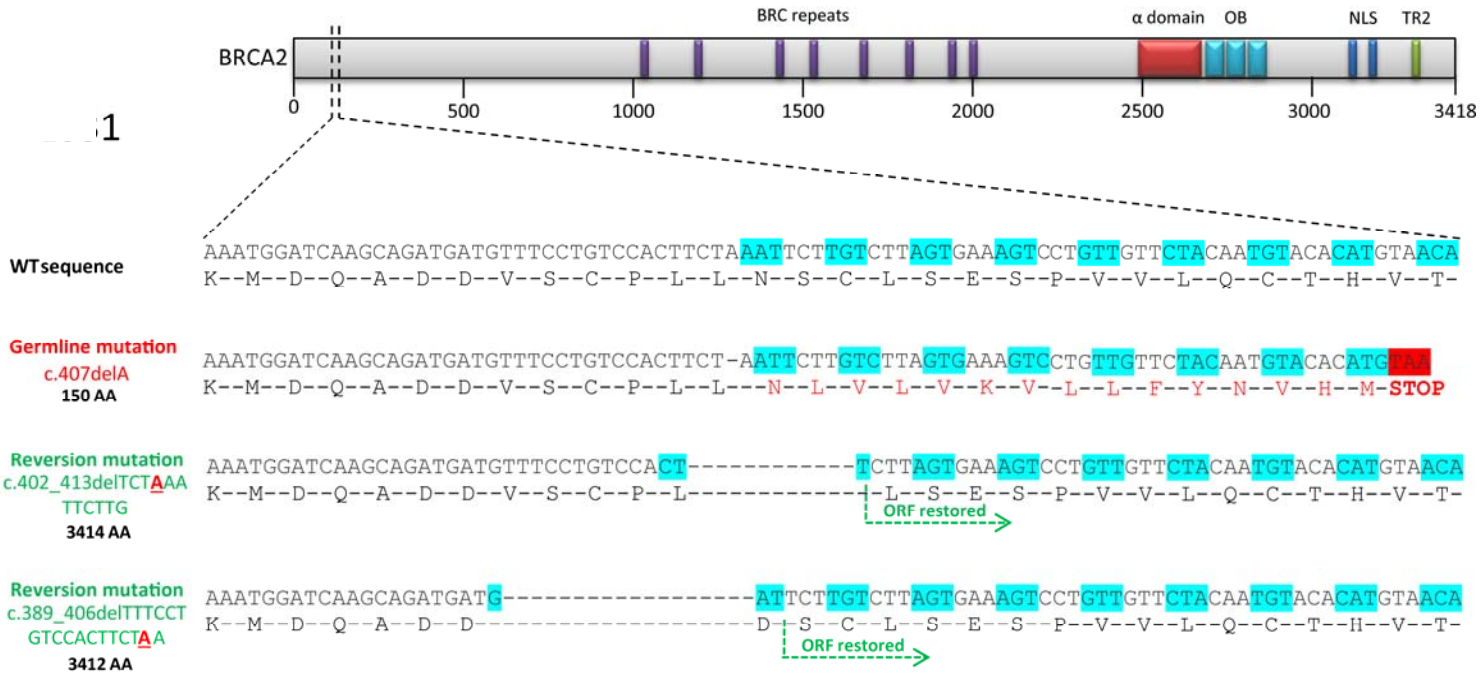




Hyman, JCO, 2017

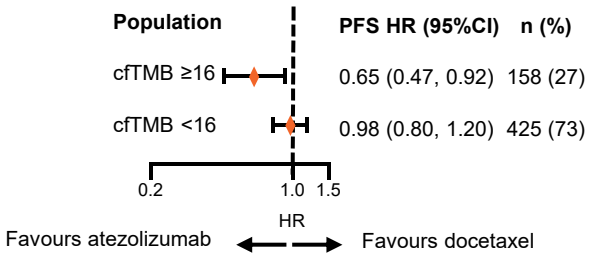
A Special Case: BRCA1/2 Reversion Mutations

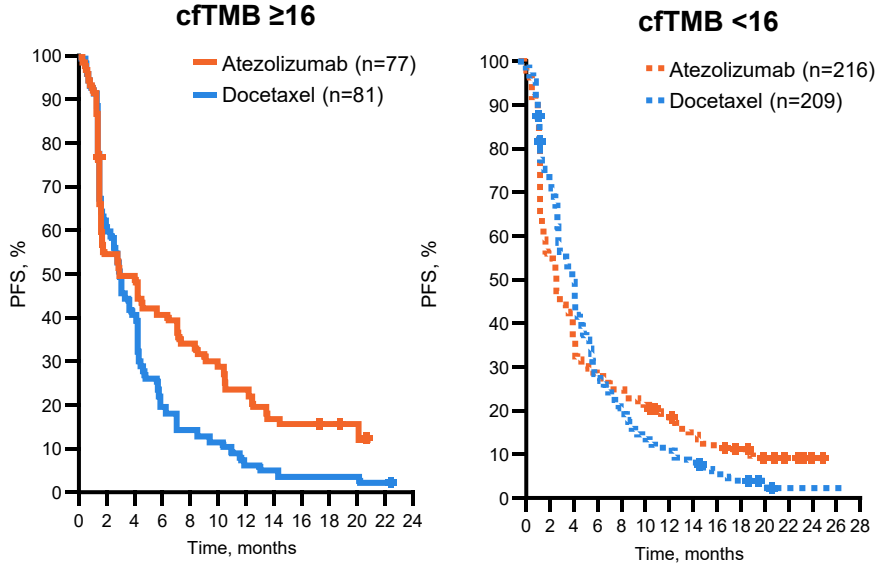
- Reporting just the reversion mutation and not the concurrent germline mutation could lead to misclassification of a resistant allele as a sensitizing one

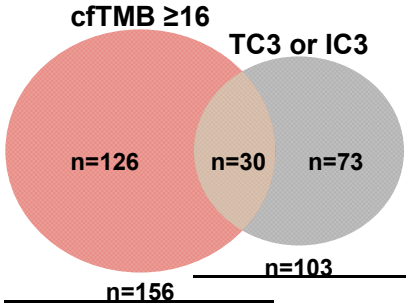


Weigelt, CRR, 2017

Moving Beyond Treatment Based on Individual Variants –Tumor Mutation from cfDNA





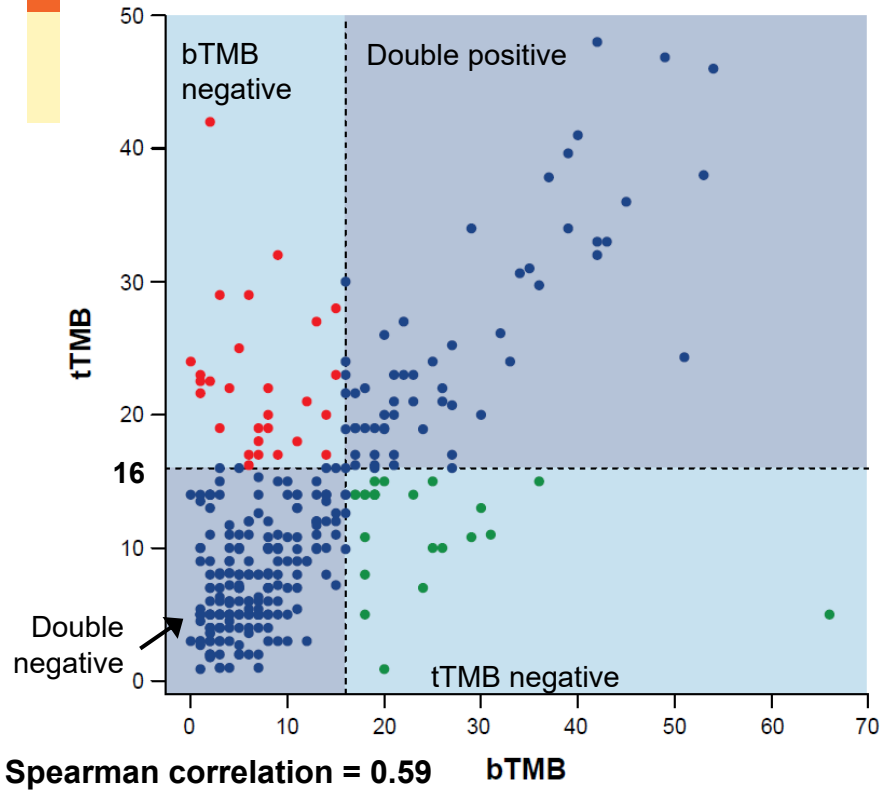


Biomarker evaluable population (n=229)

	PFS HR (95%CI)	OS HR (95%CI)
cfTMB ≥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)
cfTMB ≥16 and TC3 or IC3	0.38 (0.17, 0.85)	0.23 (0.09, 0.58)

Gandara DR et al. Ann Oncol 2017;28(suppl 5):Abstr 1295O

Comparison of Tissue-based TMB (tTMB) with Blood-based TMB (bTMB) (n=298)



Metric	Performance
PPA	64% (95% CI: 54, 74)
NPA	88% (95% CI: 83, 92)

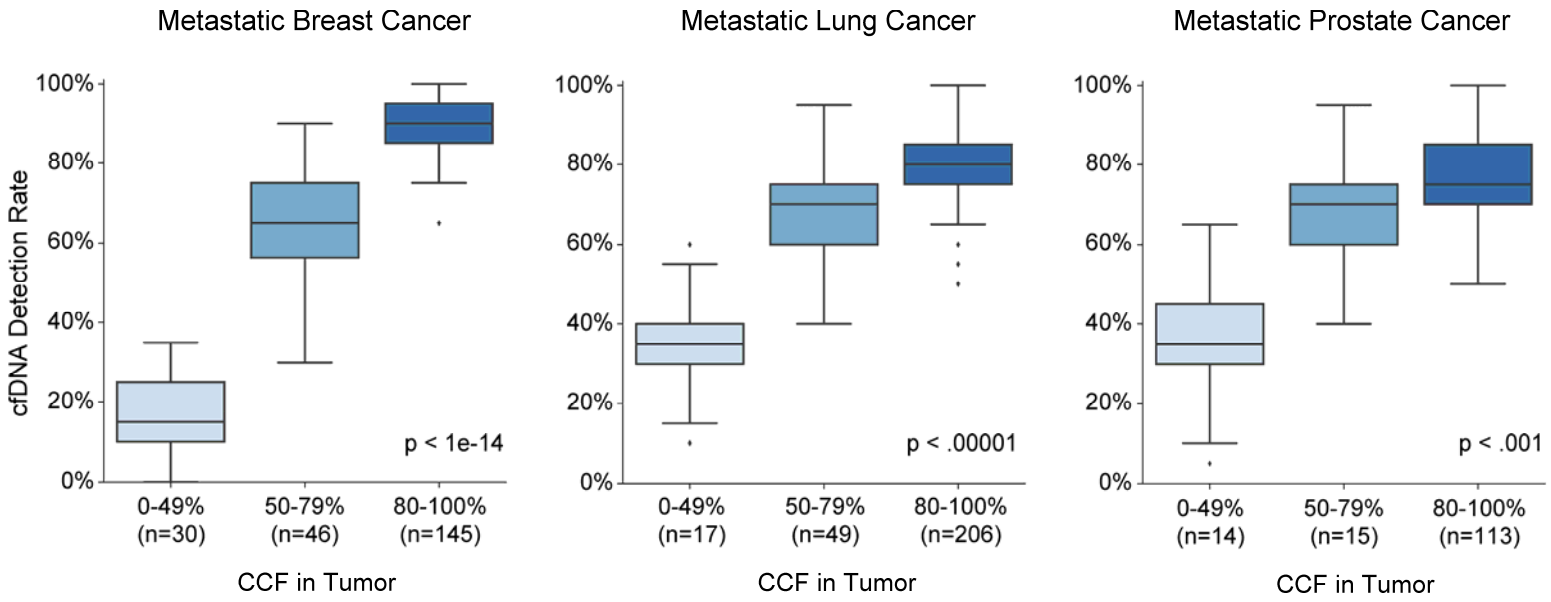
Factors Influencing PPA (*Cited by Investigators*):

- Tumor heterogeneity
  - Single-site biopsy vs. net ctDNA output
- Different computational methodologies
  - bTMB ≥ 0.5%, SNVs only
  - tTMB ≥ 5%, SNVs, fusions, insertions and deletions (indels)

…however, tumor burden and shedding dynamics may also be a factor

Gandara DR et al. Ann Oncol 2017;28(suppl 5):Abstr 1295O

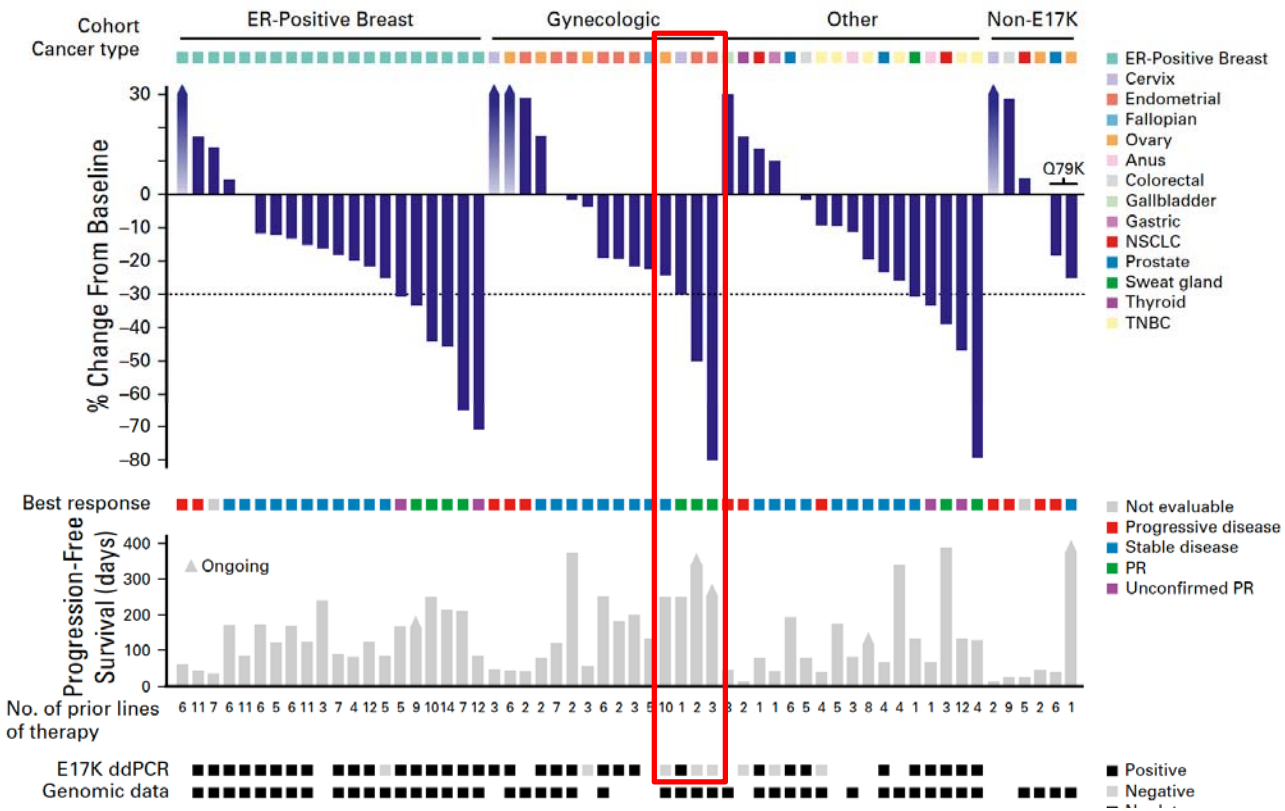
Impact of Variant Clonality in Tumor on Detection in cfDNA



- Clonal variants (CCF: 80-100%) in tissue more likely to be detected in cfDNA (p<.0001)
- Sometimes possible to infer variant clonality by comparing MAF across all calls

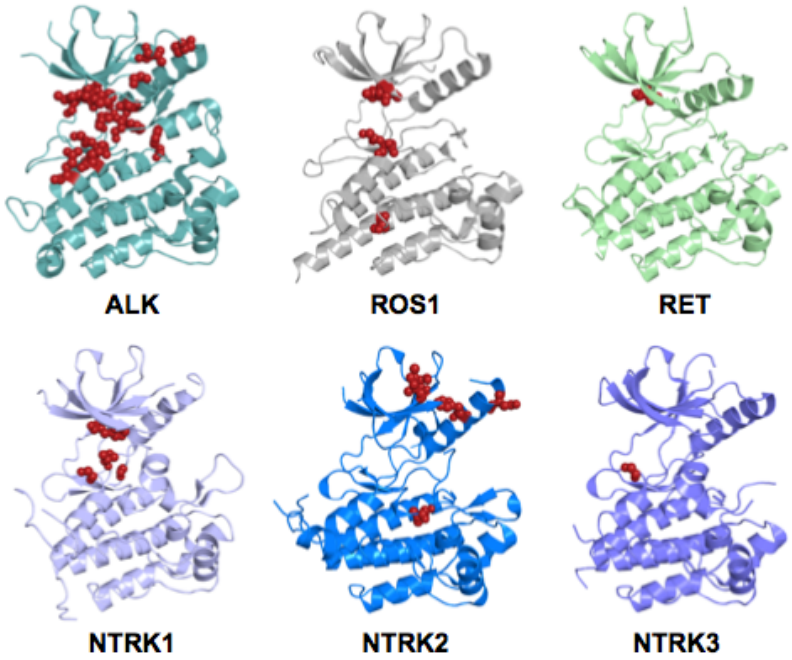
Razavi, ASCO 2017

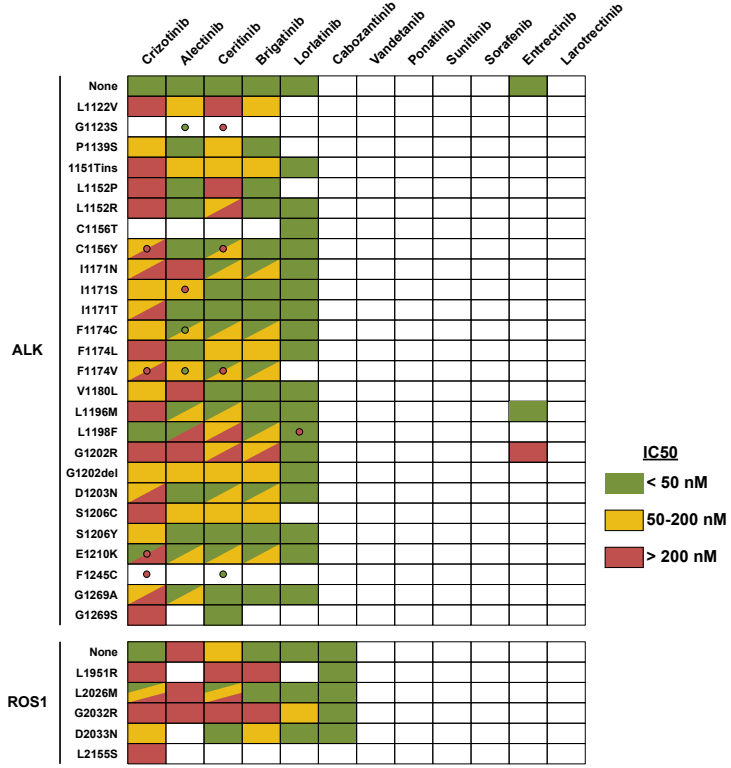
Another Consideration for Enrollment Based on cfDNA – “Low Shedding” Tumors



Hyman, *J Clin Oncol.* 2017 Jul 10;35(20):2251-2259

A Unique Opportunity for cfDNA – Targeting Acquired Resistance





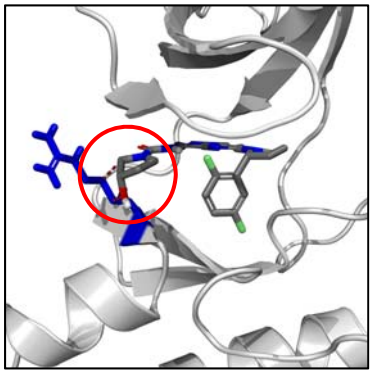
Acquired kinase domain mutations predominant driver of resistance in oncogenic fusions

Schram, Nat Rev Clin Onc 2017

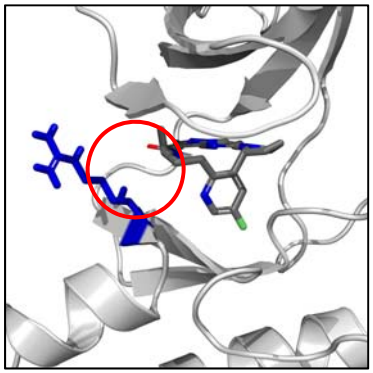
Solvent Front Mutations in TRK Fusion-Positive Cancers

TRKA G595R

Larotrectinib



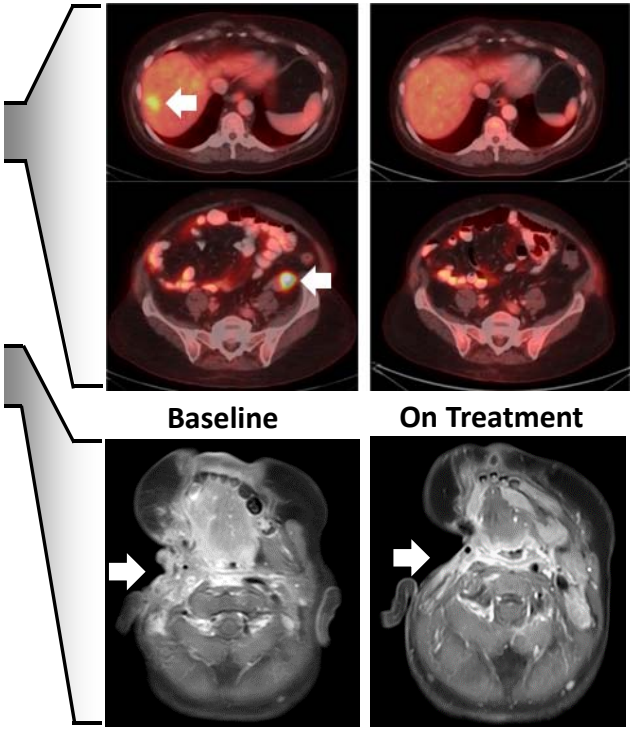
LOXO-195



Tumor type	Fusion	Resistance mutation
Colorectal	TPM3-NTRK1	TRKA G595R
Colorectal	LMNA-NTRK1	TRKA G595R
NSCLC	TPR-NTRK1	TRKA G595R
Sarcoma‡	TPM3-NTRK1	TRKA G595R
IFS	ETV6-NTRK3	TRKC G623R
Cholangio‡	LMNA-NTRK1	TRKA F589L* + GNAS Q227H

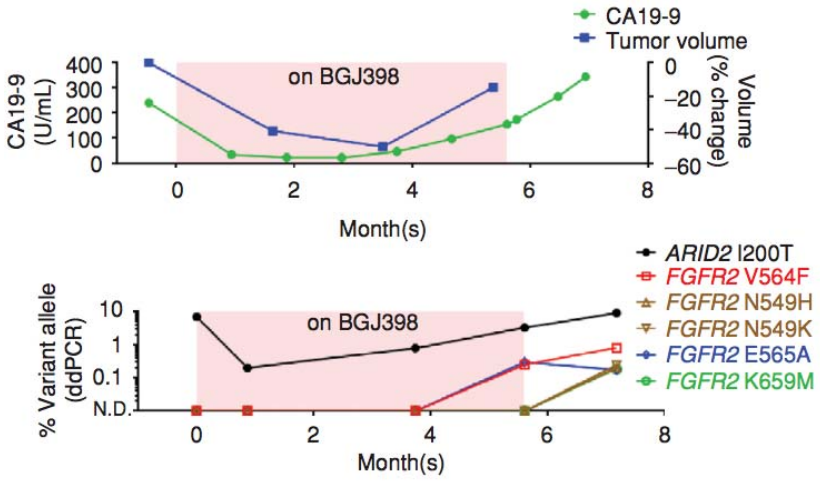
TRK solvent front mutations detected in 5 of 6 patients with acquired resistance. First 2 patients successfully treated with LOXO-195.

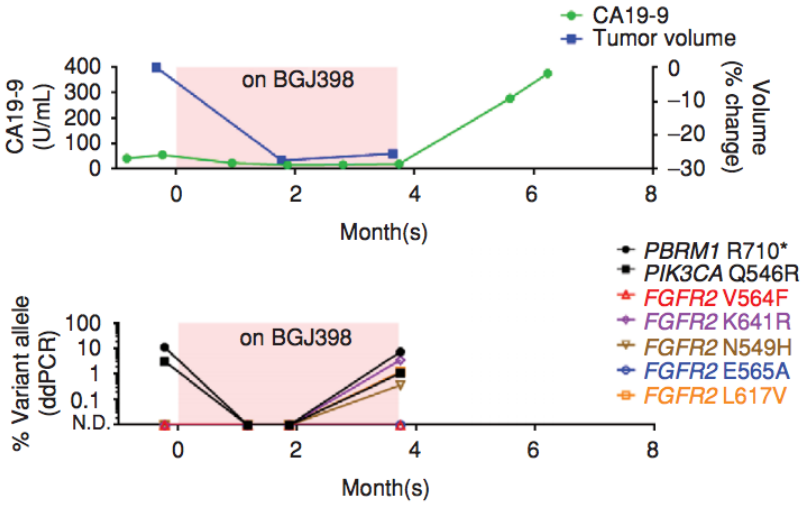
LOXO-195 Treatment



Hyman, ASCO 2017 & Drilon, Cancer Discovery 2017

Detecting Convergent Polyclonal Resistance Mechanism in cfDNA





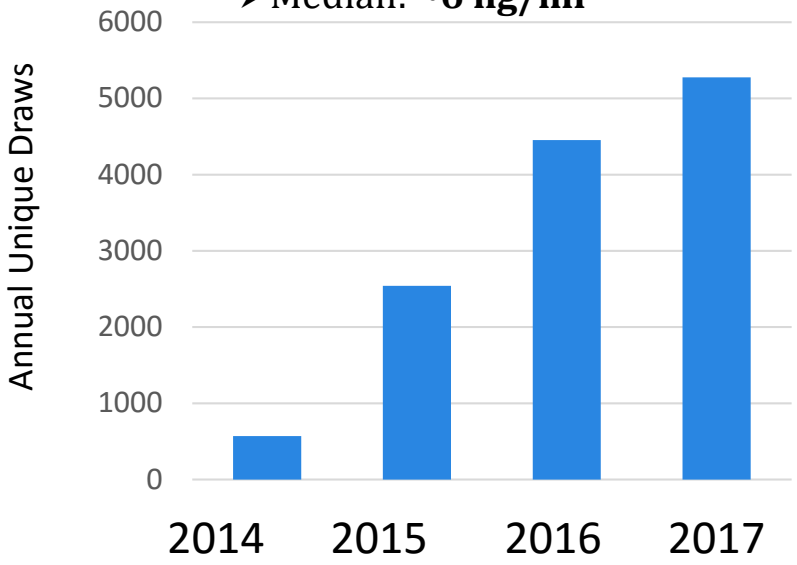
- Polyclonal on-target mutations drive resistance to FGFR inhibition in FGFR2-fusion positive cholangiocarcinomas
- MAF for most acquired resistance mutations <1%

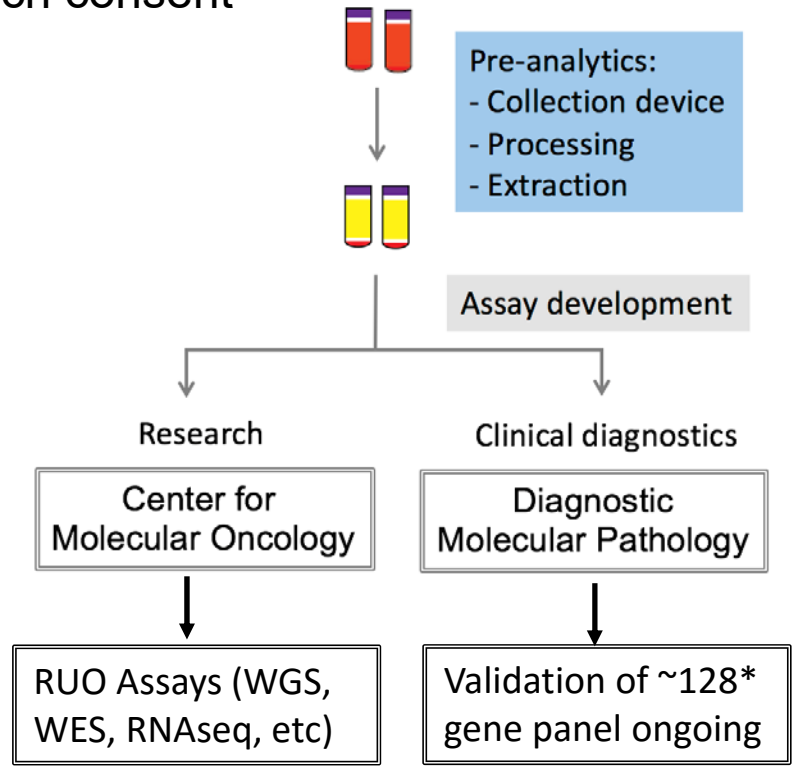
Goyal Cancer Discovery 2016

cfDNA Collection Strategy @MSK

Centralized CLIA laboratory for plasma processing and extraction
Managed under center-wide research consent

- Range: **<1 ~ 3300 ng/ml**
- Mean: **~22 ng/ml**
- Median: **~6 ng/ml**





Courtesy of Tsui, Samoila, Berger

*Subjecting to change

Conclusions – Clinical Trialist Perspective (1)

- Utility of single-analyte cfDNA testing limited to select scenarios (T790M)
- Broader cfDNA NGS operationally efficiency, especially in community
- Although genomic content smaller than tissue panels, remains generally adequate for most current individual targets (will scale over time)
- Technical validity of TMB, MSI, other signatures being evaluated
- May miss clinically actionable variants due to:
  - Low shedding
  - Lower analytic sensitivity for fusions > indels & CNA detection (compared to SNV)
  - Low disease burden patients / patients on active therapy
- Potential for detecting clinically relevant and irrelevant subclones (study eligibility must attempt to address this)

Conclusions (2)

- cfDNA results are already being regularly used to make treatment decisions for both:
  - Routine clinical practice
  - Clinical trial enrollment
- Therefore, optimal use requires an understanding of both:
  - Technology platform broadly
  - Characteristics of the individual platform utilized specifically

Acknowledgements

- José Baselga, MD, PhD
- Paul Sabbatini, MD
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  - Nikolaus Schultz PhD
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  - Sarat Chandarlapaty, MD
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  - Martin Voss, MD
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  - Gopa Iyer, MD
  - Mrinal Gounder, MD
  - John Gerecitano, MD, PhD
  - Wassim Abida, MD
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- Pathology
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- Data and Information Service
  - Stuart Gardos
  - Michael Eubank

NIH National Cancer Institute

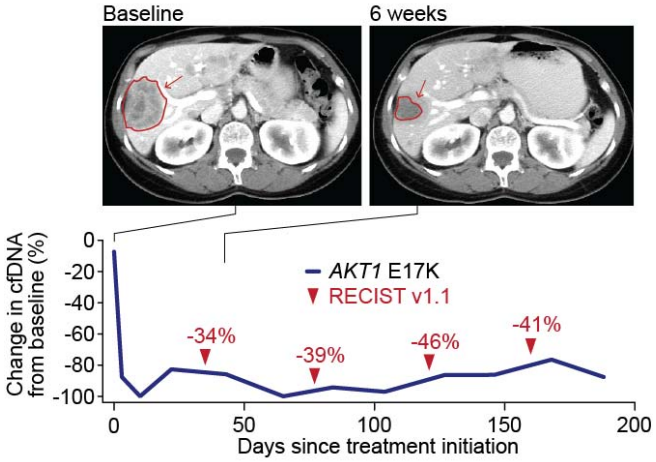
CYCLE FOR SURVIVAL
MEMORIAL SLOAN KETTERING | EQUINOX

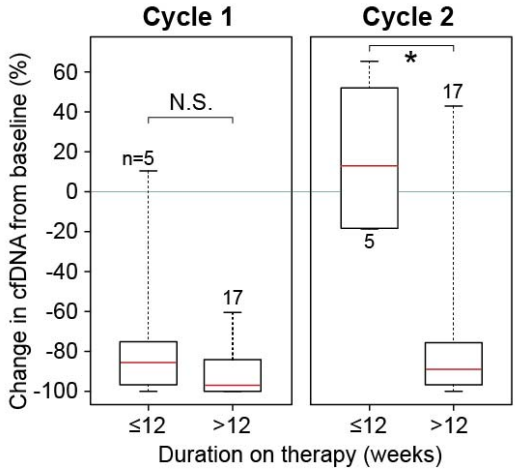
Erdheim-Chester Disease Global Alliance

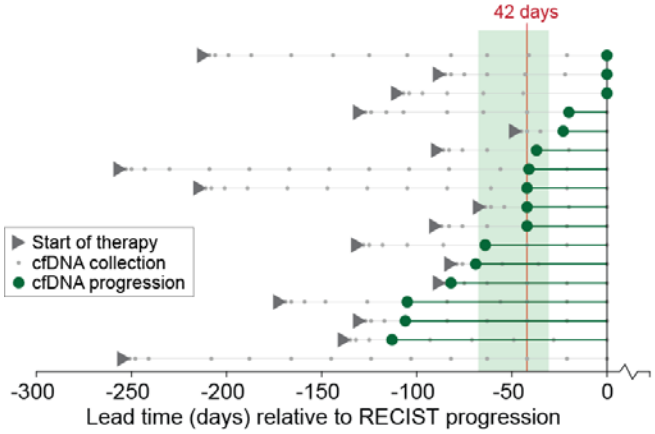
1884 THE SOCIETY of MEMORIAL SLOAN KETTERING CANCER CENTER

Center for Molecular Oncology

Implications for the Dynamic Nature of cfDNA







- Potential for treatment monitoring well documented
- Impacts timing of testing strategy when not being used to monitor response

Hyman, JCO, 2017

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

Clinical Care Based on cfDNA: What are the Opportunities and Needs?

Scott Kopetz, MD, PhD
Associate Professor, Deputy Chair, Translational Research
MD Anderson Cancer Center

Disclosures

Advisory board, research funding: Amgen, Roche/Genentech

Research funding: Biocartis, Sysmex

Stock Ownership: MolecularMatch, Navire

Advisory board: Amgen, Roche, Bayer, Array BioPharma, Genentech, Symphogen, EMD Serono, Merck, Karyopharm

Settings of interest for Liquid Biopsies

Screening

- Evaluation of asymptomatic population
- Limited by need for high specificity
- Asymptomatic clonal findings seen

Recurrence Detection

- Known cancer patients, often with known mutation profile of primary tumor
- Detect residual disease after resection or radiation/ablation

Metastatic Disease

- Tumor profiling
- Treatment response
- Resistance monitoring
- Heterogeneity assessment

Immediate Opportunities for Liquid Biopsies

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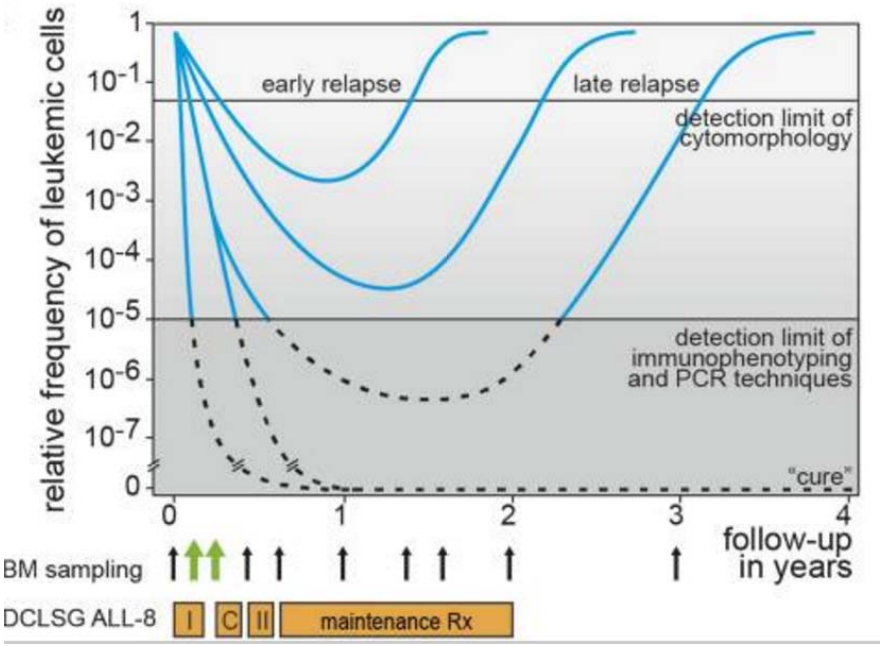
Minimal Residual Disease: "Stage IV MRD"

- Multiple studies have now demonstrated very high **specificity** for recurrent disease in patients with ctDNA detected in the "adjuvant" setting
- This is not a marker of high risk for recurrence, but defines molecular persistence of disease.
  - Stage I-III patients with ctDNA+ after definitive interventions should be considered as a Stage IV minimal residual disease, or Stage IV MRD



Well-established concept in hematologic malignancies

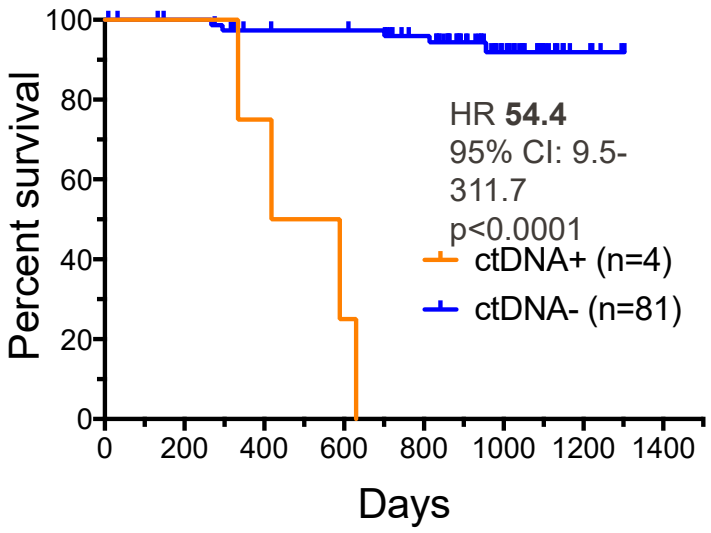
Van Dongen et al Blood, 2015

SafeSeq/Roche assay: Colorectal Cancer

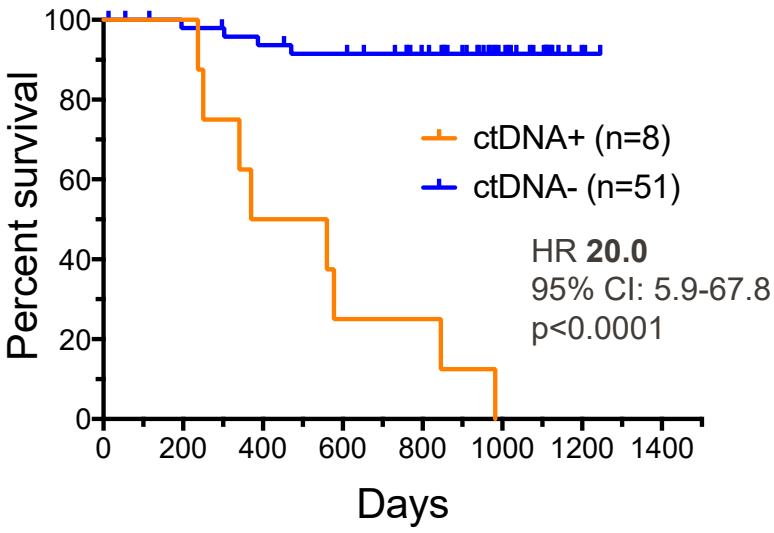
Assay with 197 genes; at least one mutation detected 99.3% of tumor tissue

ctDNA had 57% sensitivity for recurrence; 100% specificity

Stage II (5% prevalence of ctDNA+)



Stage III (16% prevalence of ctDNA+)



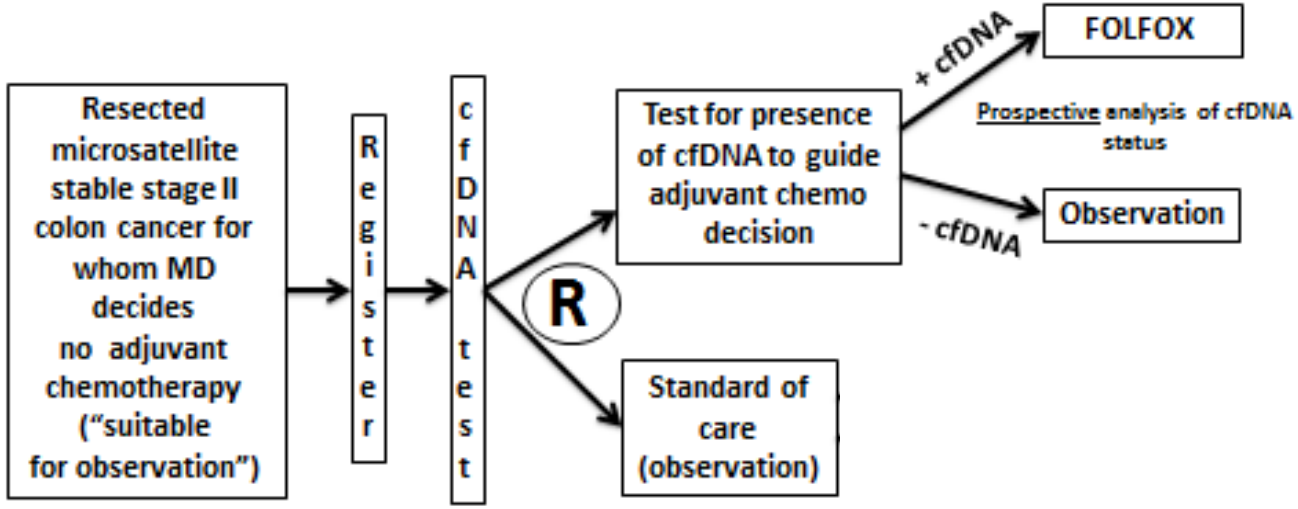
How does one demonstrate utility?

Diehn et al ASCO '17

NRG Stage II Adjuvant Study: CR1643

Evaluating early intervention for “Stage IV MRD”

Van Morris



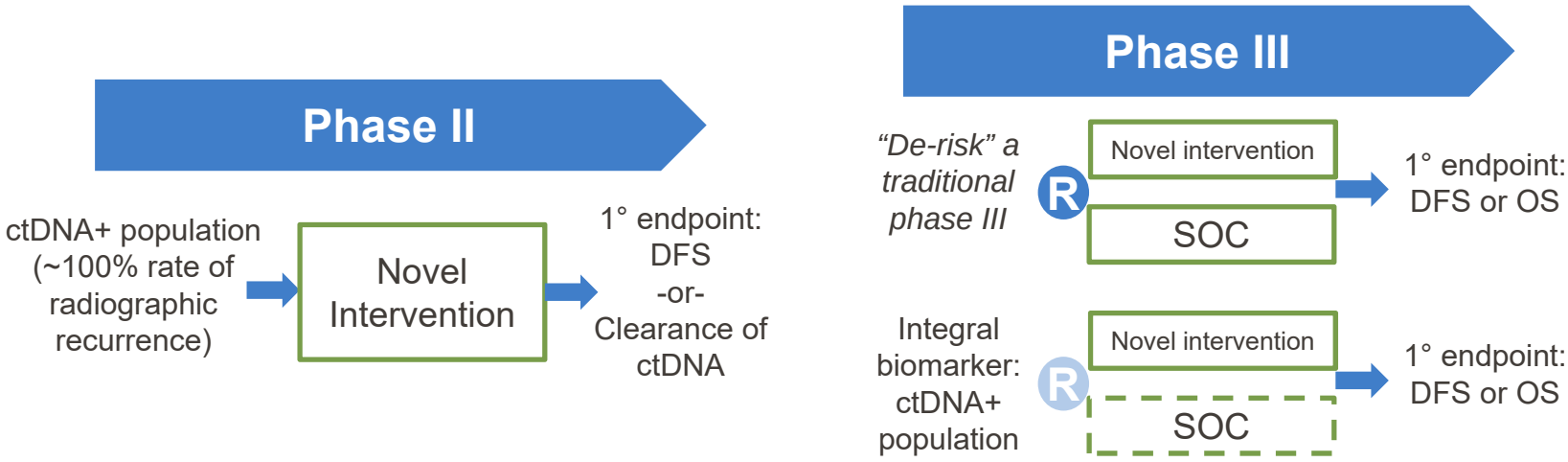
Primary objective: Clearance of cfDNA (to undetectable levels) for patients cfDNA+ at randomization

But are these the ~50% that we can’t cure with chemotherapy?

Morris, Kopetz

"Phase II" Adjuvant Studies

- This work enables proof-of-concept phase 2 studies
  - High event rates utilizing DFS endpoint
  - Alternative options for endpoint of clearance of ctDNA, where this is **necessary but not sufficient** for cure
- Smaller, lower risk studies for drug development



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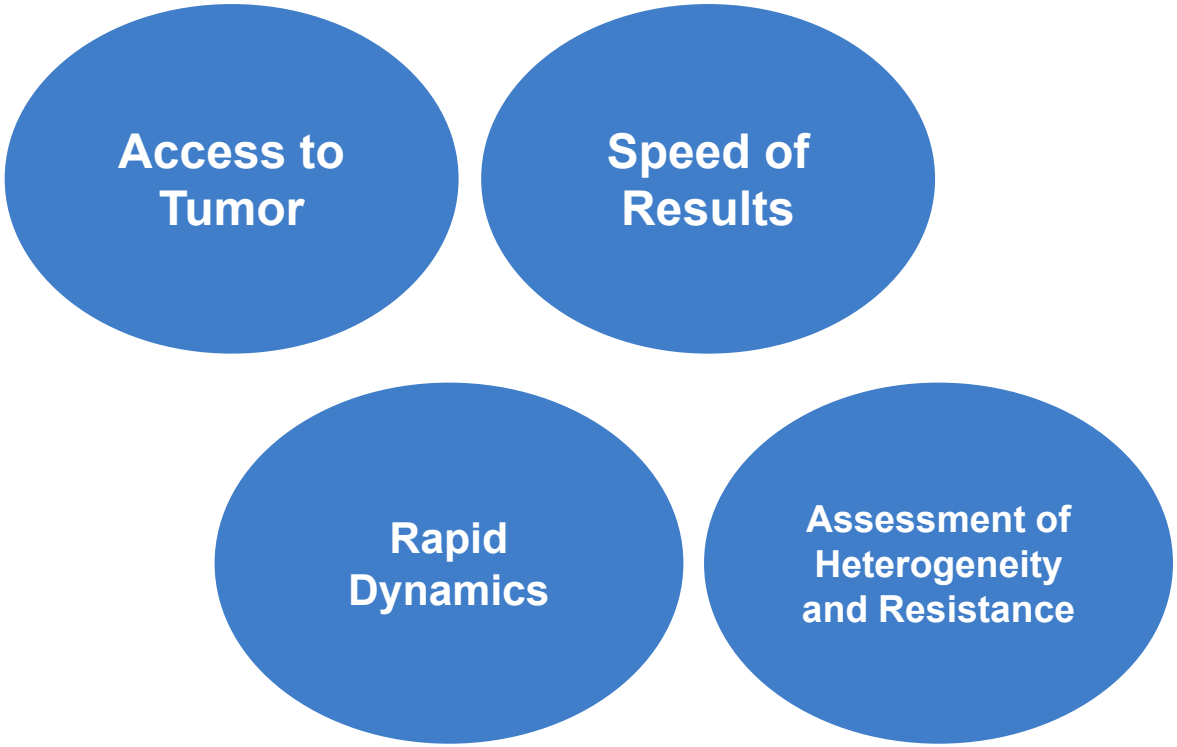
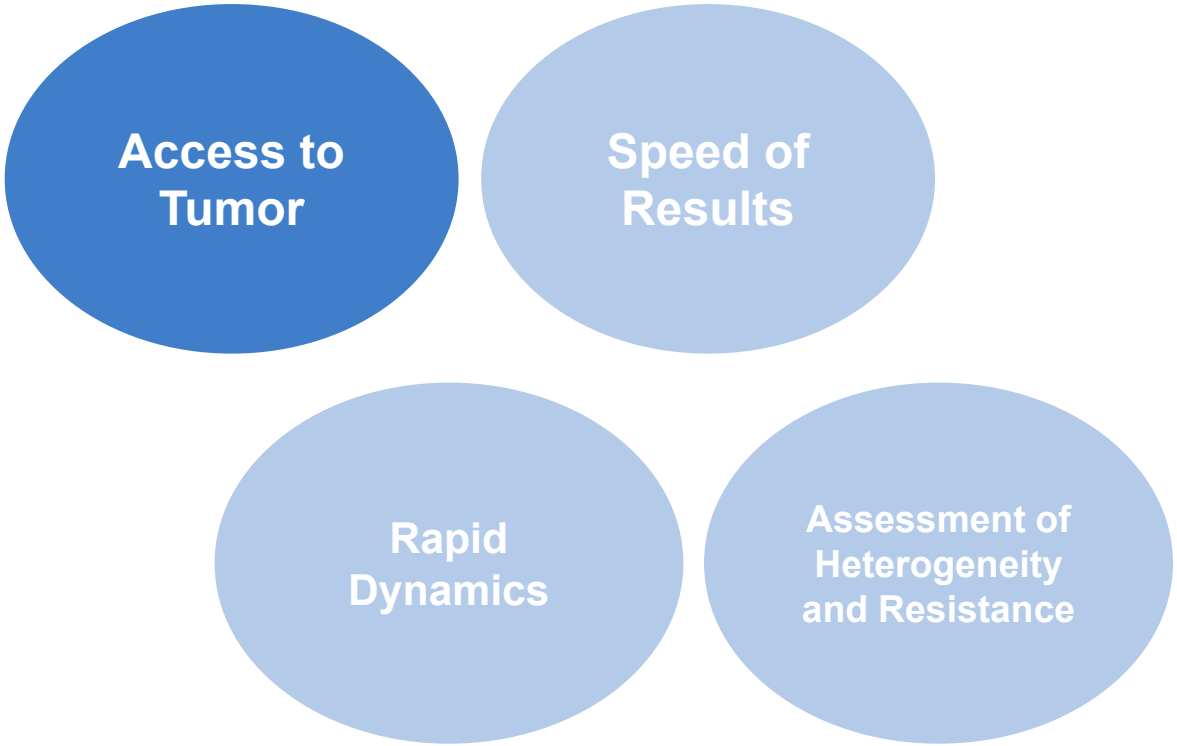
Utility of ctDNA



Utility of ctDNA



Biopsy for testing of metastatic disease: cost, risk, and time

Financial cost[1]

- Liver biopsy: ~$2,000-$7,000
- Lung biopsy: $8,869 average in Medicare database; $37,745 if complication

Biopsy risk[2]

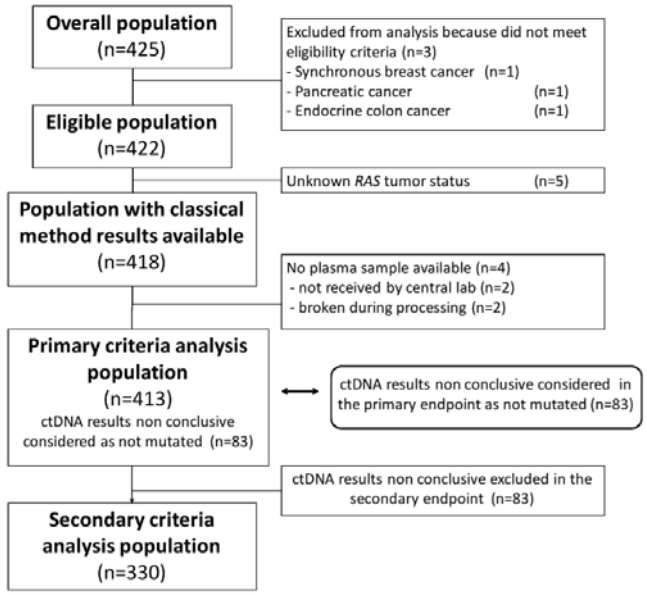
- Medicare analysis: 19% complication rate for intrathoracic biopsies
- MDACC series of 745 research biopsies[2]:
  - Intrathoracic biopsy complication rate= 17%
  - Overall complication rate= 5.2%

[1] Lokhandwala et al., presented at 2014 Chicago Multidisciplinary Symposium in Thoracic Oncology
[2] Overman et al., *J Clin Oncol*. 2013; 31(1) 17-22. Slide adapted from J. Strickler, Mol TriCon

Concordance of tissue and ctDNA in mCRC: 93% Accuracy

Prospective AGEO study:

425 patients were included in 14 French centers between 20 July 2015 – 13 December 2016.



NGS

		RAS status in plasma		
		No	Yes	Total
***RAS* status in tumor**	No	128 (38.8%)	8 (2.4%)	136 (41.2%)
	Yes	15 (4.6%)	179 (54.2%)	194 (58.8%)
	Total	143 (43.3%)	187 (56.7%)	330 (100%)

Kappa coefficient - $CI_{95\%}$: *0.86 [0.80-0.91]*
Accuracy % - $CI_{95\%}$: ***93.0 [89.7-95.5]***
Sensitivity % - $CI_{95\%}$: *92.3 [87.6 -95.6]*
Specificity % - $CI_{95\%}$: *94.1 [88.7-97.4]*

Positive Predictive Value % - CI95%: *95.7 [91.9-97.8]*
Negative Predictive Value % - CI95%: *89.5 [84.0-93.3]*

A subset of patients did not have detectable ctDNA:

Metachronous disease, peritoneal only, low tumor markers

Bachet et al ASCO ‘17

Is >90% Sensitivity Good Enough?
Context Dependent Implications of False Negatives

False positives are very rare, but false negatives are a limitation of ctDNA technology

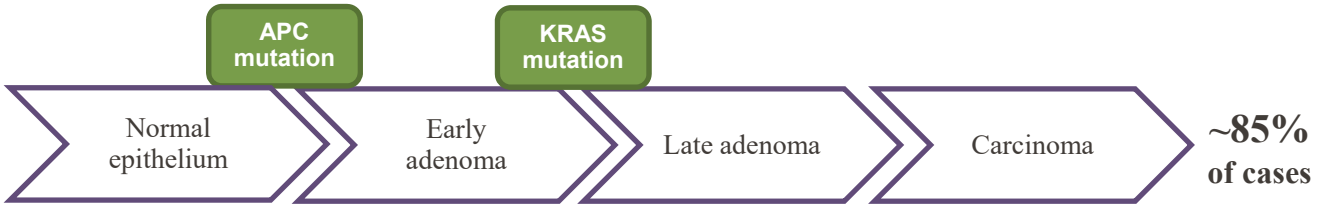
Missed opportunities for improved outcomes:

- EGFR mutations in lung cancer
- BRAF mutations in melanoma
- ALK, ROS fusions
- HER2 amplifications in breast, gastric, colon cancer

Exposure to agents with potential for harm:

- KRAS, NRAS mutations in colorectal cancer
  - Patients with these mutations in the tumors, when treated with EGFR inhibitors in combination with chemotherapy, can have *detrimental impact*

Interpreting RAS wild-type results in ctDNA: NGS panels



Informative negative

Truncal mutations were detected

-and-

Allelic frequency of these mutations are high enough that a truncal RAS mutations would have been detected

Uninformative negative

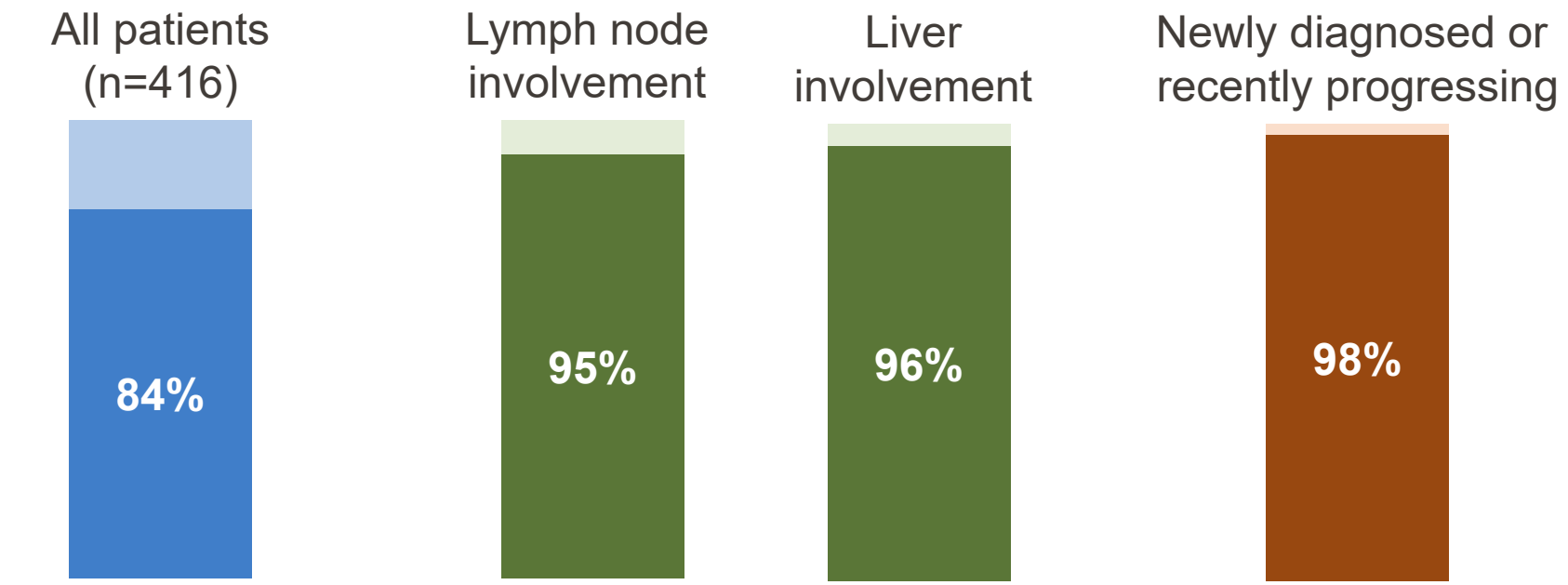
Truncal mutations were detected but near limit of assay sensitivity

-or-

No truncal mutations were detected

There is a need to better define "ctDNA negative" results in clinical reporting and clinical trials.

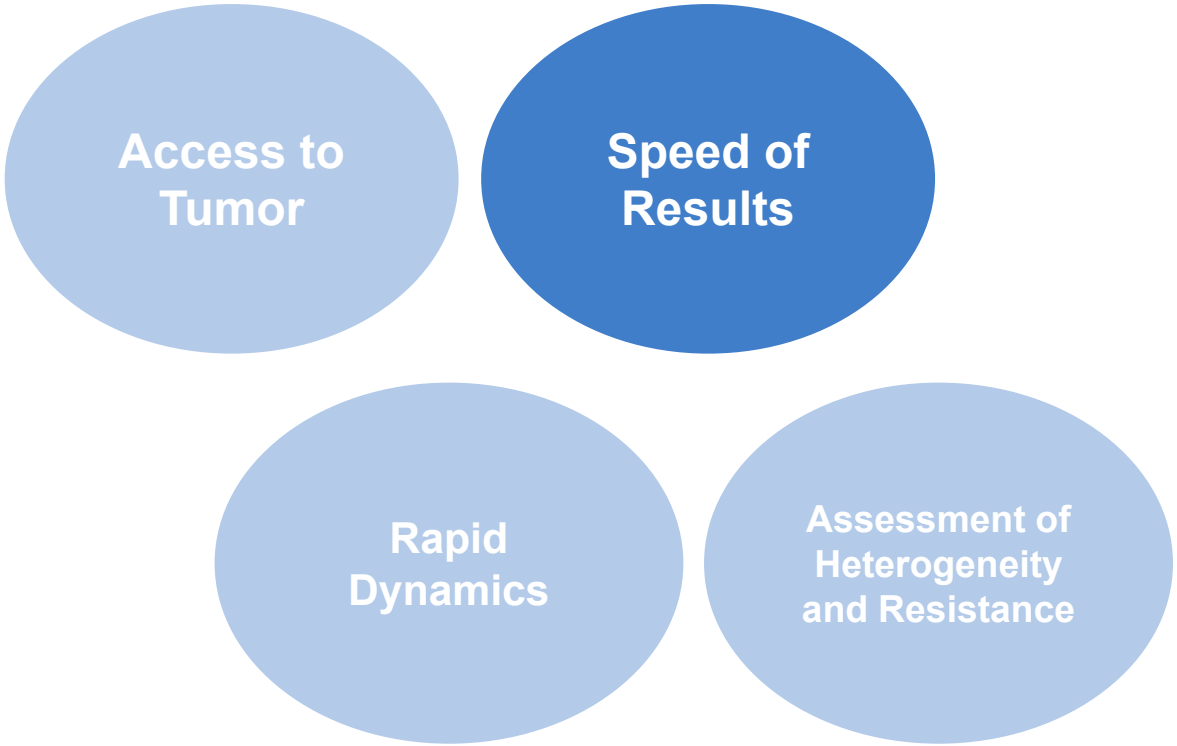
Optimal Time to Collect ctDNA: Detection rates are higher in mCRC patients with disease progression



Commercial NGS panel (Guardant)

Lima et al Unpublished

Utility of ctDNA



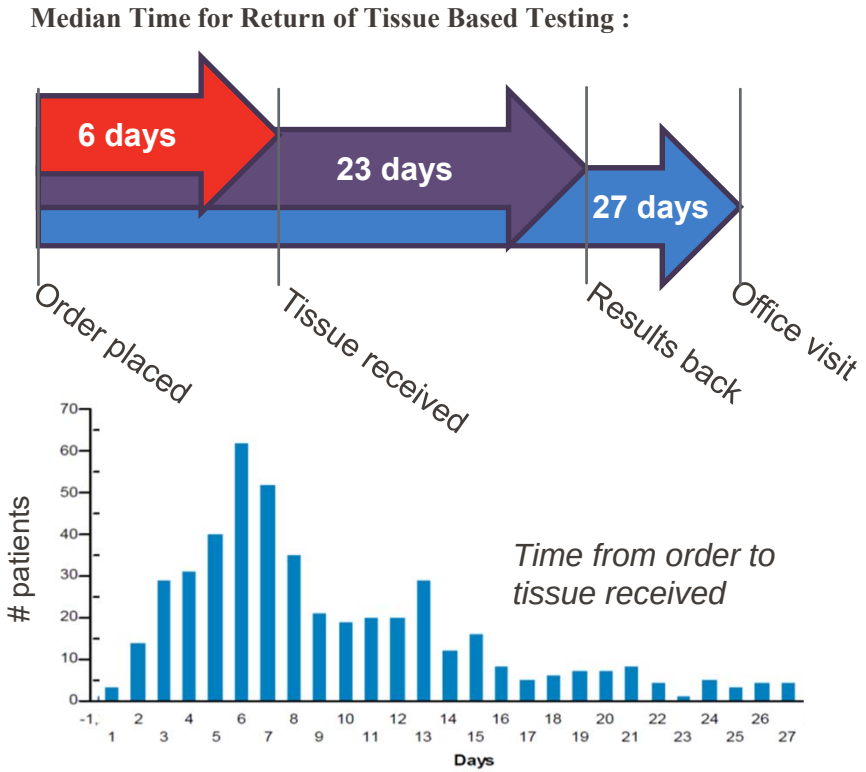
Timely Tissue Availability: mCRC

In the US, initial diagnosis is commonly performed in a different system than treatment

- 70% of patients in US have chemotherapy administered in a different system/location than surgery

Most patients do not have tissue for testing available at first visit.

Treatment decisions await molecular testing



(Overman et al Annals Oncol '15)

Utility of ctDNA for Treatment Refractory Patients:

Prospective MDACC Study

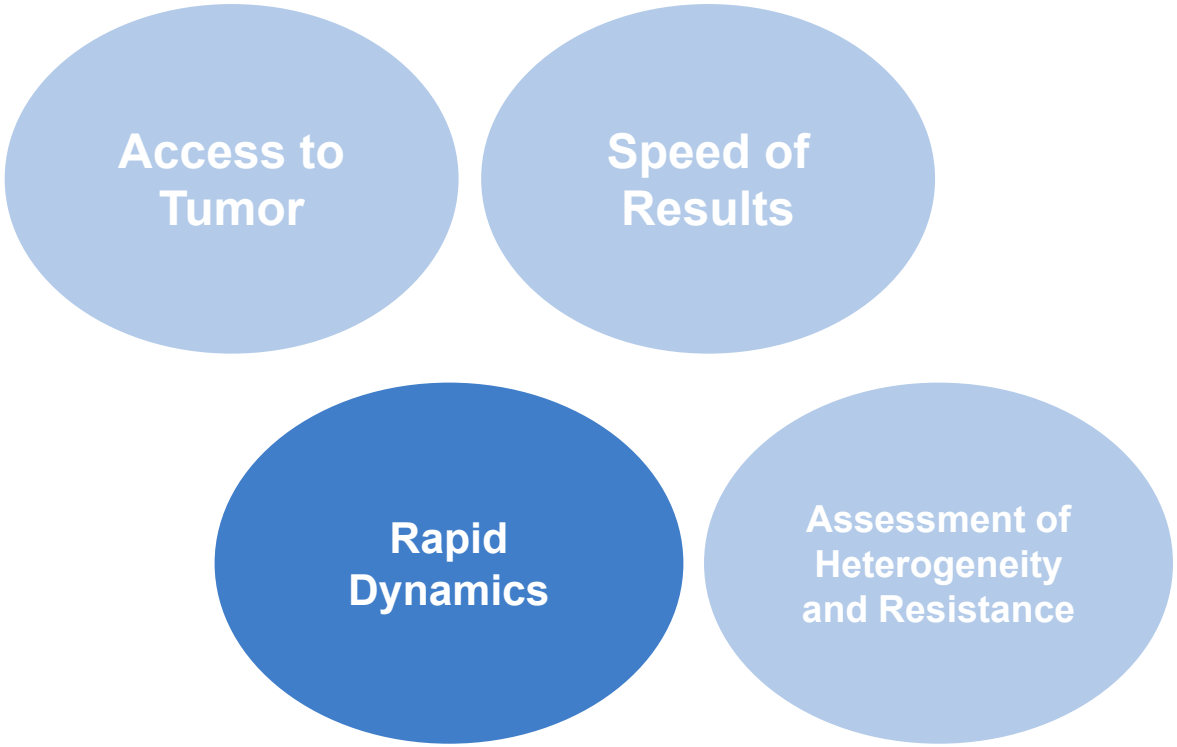
Decision Impact of Plasma Testing	Results (per case)
Plasma testing results available before tissue testing results	89%
Physicians felt plasma testing improved the quality of provided care	87%
Patients felt plasma testing improved satisfaction	97%
Patients had enrolled or were planning to enroll on a clinical trial based on the plasma results	56%

Allan Pereira

107 consecutive mCRC patients

Pereira et al PLOS One, 2016

Utility of ctDNA

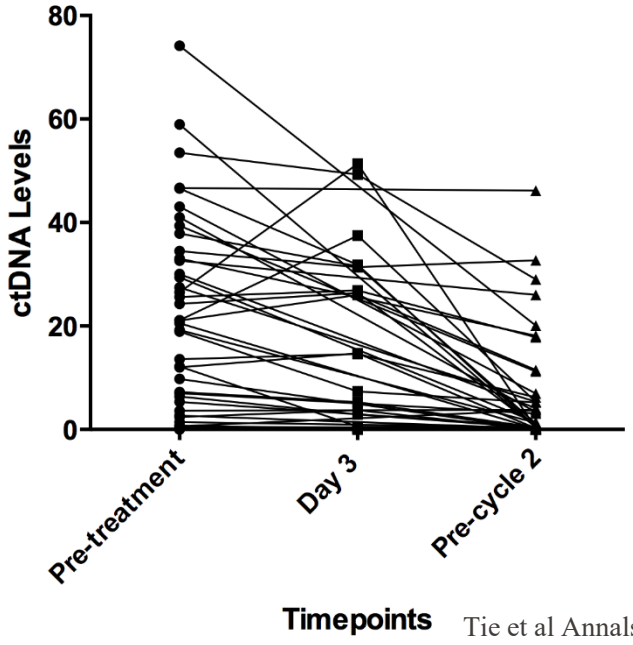


ctDNA as a rapid surrogate of tumor response

Half-life of ctDNA in circulation is measured in minutes/hours

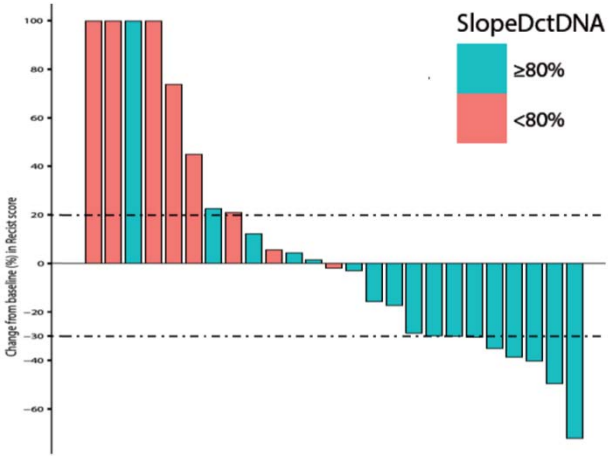
Protein markers (CEA) may have half-life of days, with post-treatment spikes

ctDNA levels fall >90% in 2 weeks in responding CRC patients

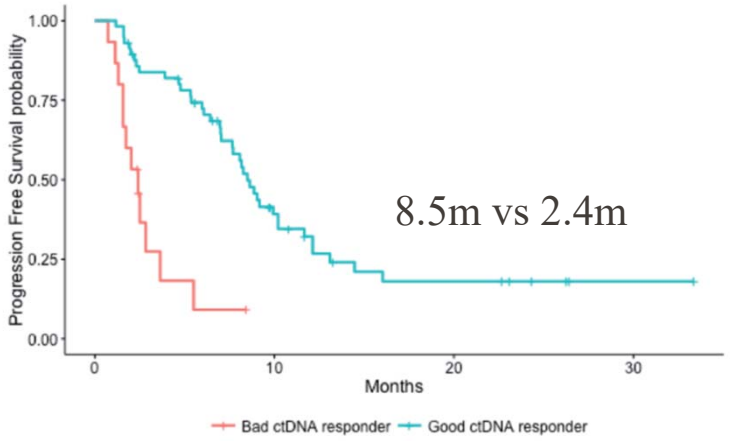


Tie et al Annals Oncology '15

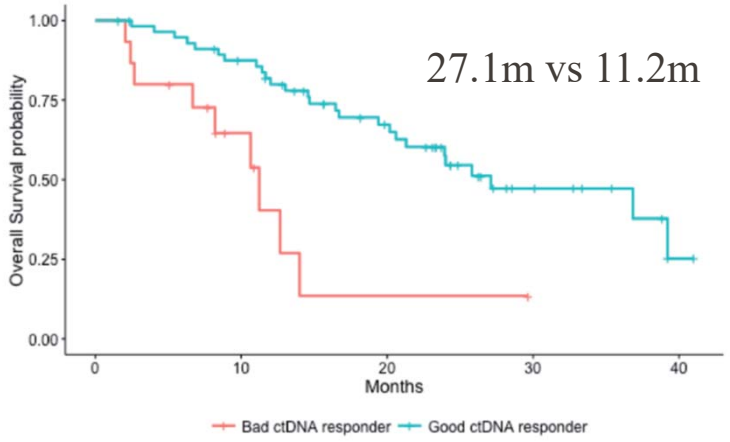
Early ctDNA response is associated with RECIST ORR, PFS, and OS (PLACOL study)



PFS



OS



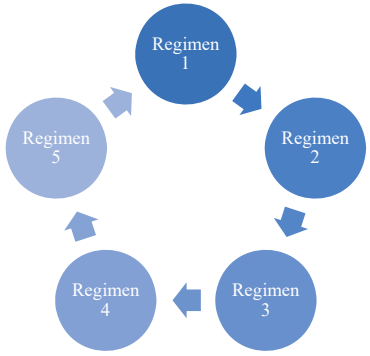
Garlan et al CCR '17

Where is early information on response useful?

Avoidance of toxicity in settings of limited benefit

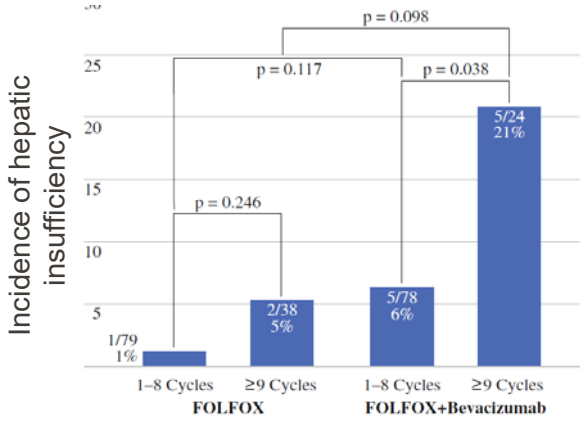
Line of Rx	Grade 3/4 adverse events	Response rates
First	60%	60%
Second	50%	15%
Third	55%	2%
Fourth	69%	2%

Change to alternate chemotherapy regimen



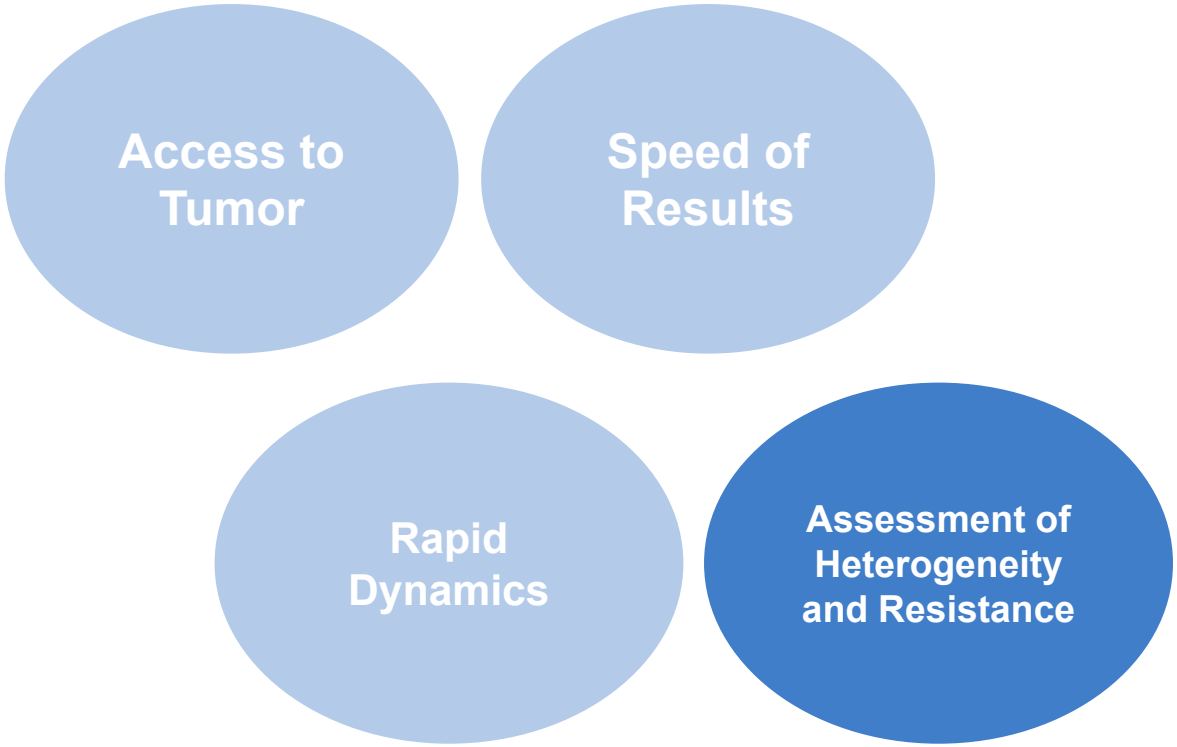
…but early change may not result in improved outcomes.

Conversion of unresectable to resectable disease… before organ toxicity



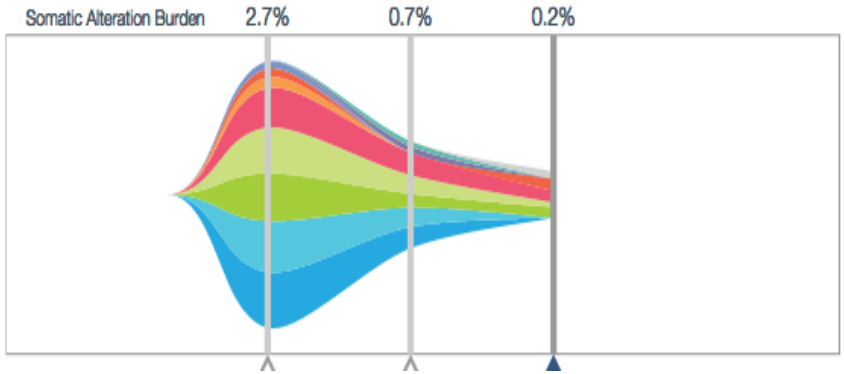
Substantial potential with upcoming trials for ctDNA to limit ineffectual therapies

Utility of ctDNA

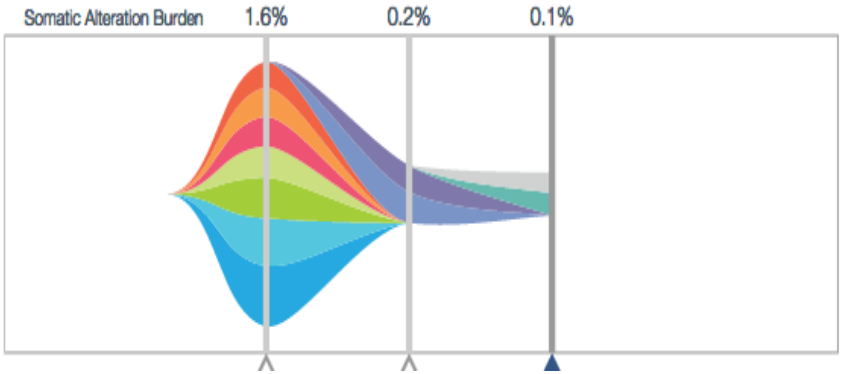


Clonal drift in mCRC with time/treatment

Change in total ctDNA levels without loss or gains of major mutant alleles



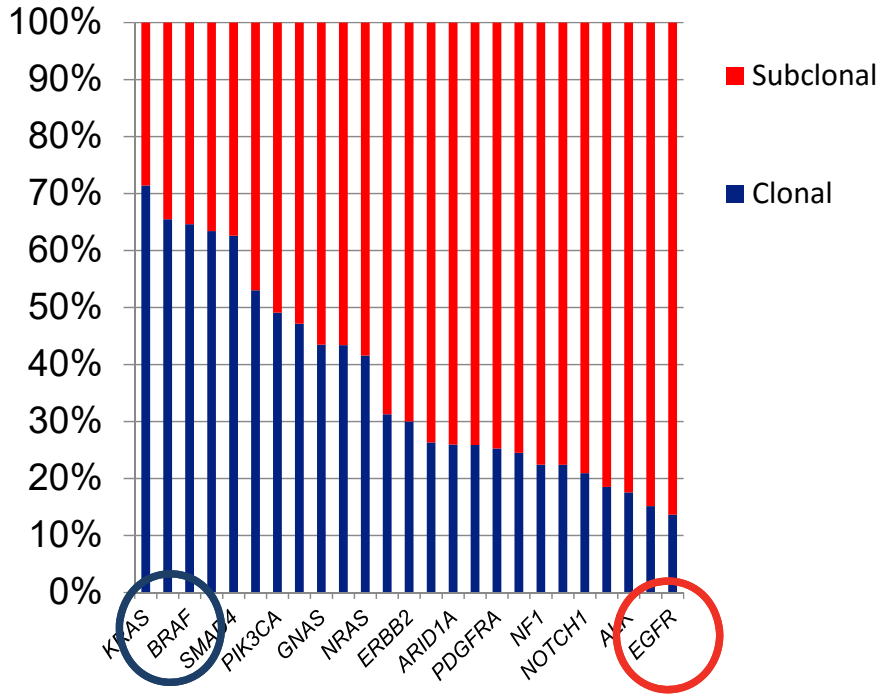
Loss and gain of new ctDNA mutant alleles at each of the subsequent analysis timepoints

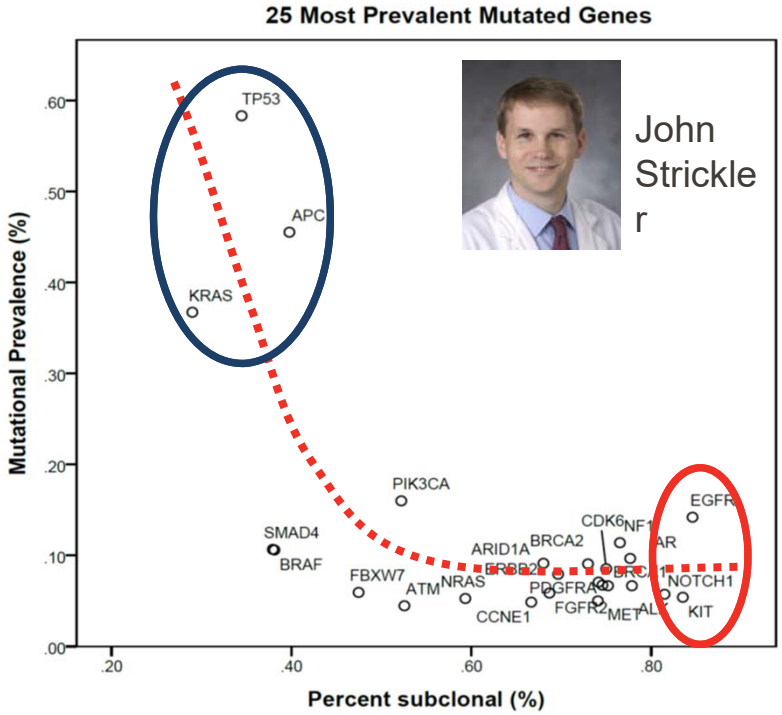


- **In 84 patients with metastatic CRC receiving serial monitoring, 87% had either gain (61%) or loss (63%) of clones over time**

Strickler et al., *J Clin Oncol*. 35, 2017 (suppl 4S; abstract 584). Presented at GI ASCO 2017.

Subclonal alterations tend to be infrequently mutated



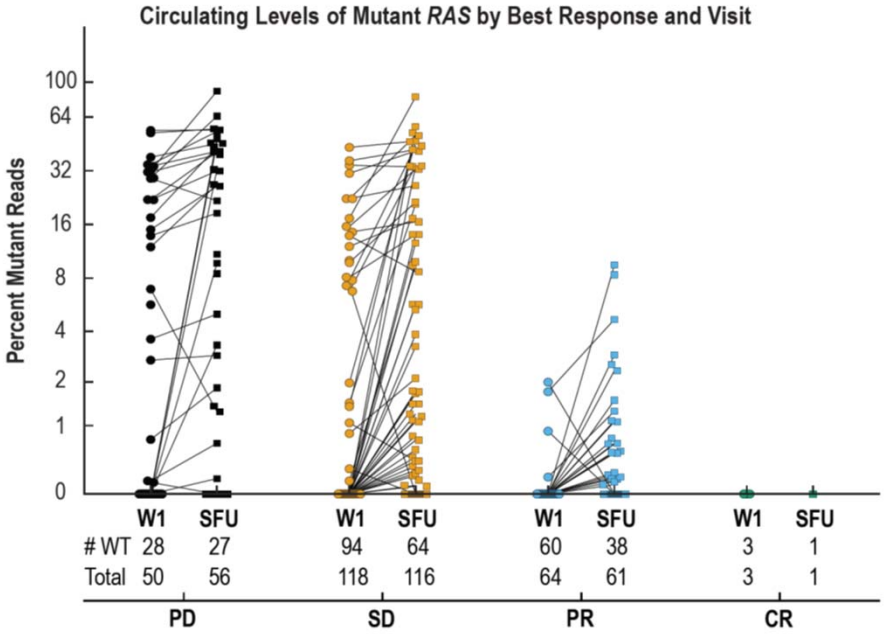


John Strickler

… and more likely to be variants of unknown significance

Stricker, et al GI ASCO ‘17, unpublished

Subclonal RAS mutations in ctDNA in tissue wildtype: Do these preclude response to EGFR?



ASPECCT study of single agent cetuximab and panitumumab:

N=1,010 patients (238 P-mab patients analyzed)

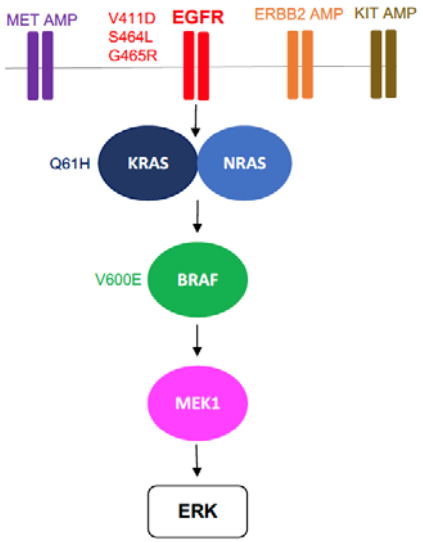
At baseline, RAS clones were detected in 20% of patients with SD, and 6% of patients with PR

Price, T et al ASCO '17

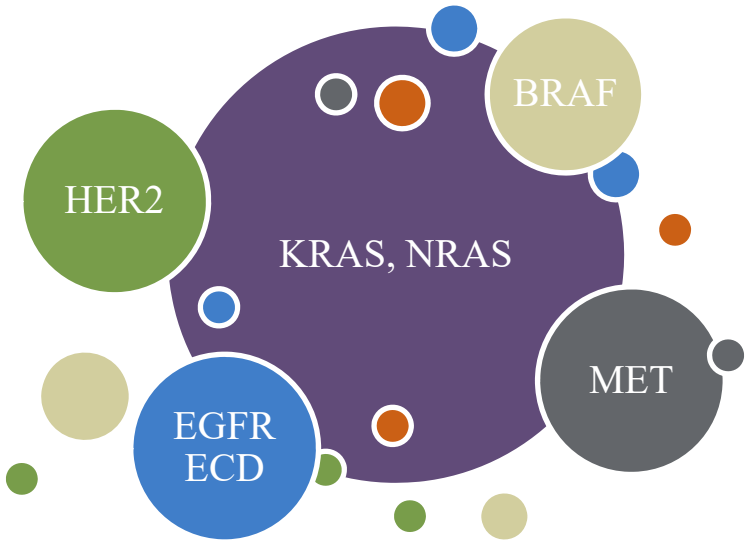
Not necessarily. Perhaps due to subclonality, and response of WT clones

ctDNA Detects Acquired Resistance Mutations after EGFR inhibition in CRC

Acquired mutations alter EGFR mAb binding, activate downstream signal transduction, or activate alternate RTK

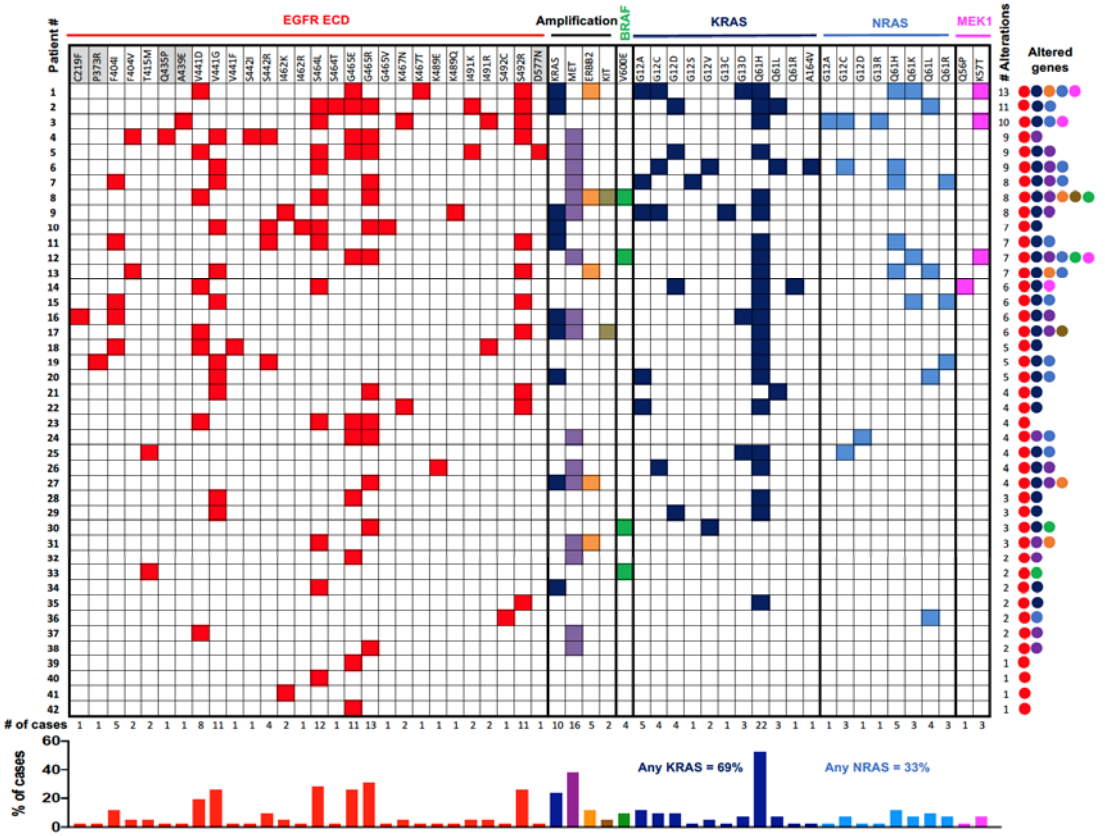


Multiple mechanisms can be detected in the same patient



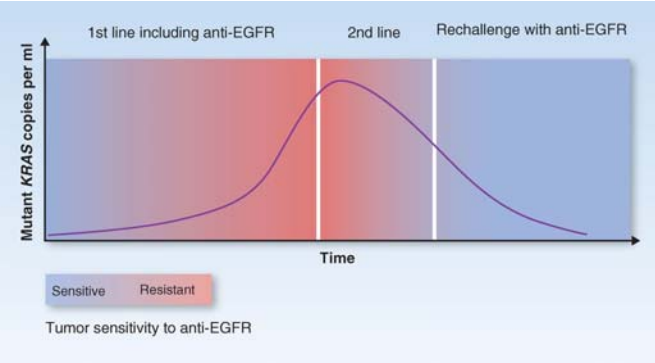
Strickler et al, submitted

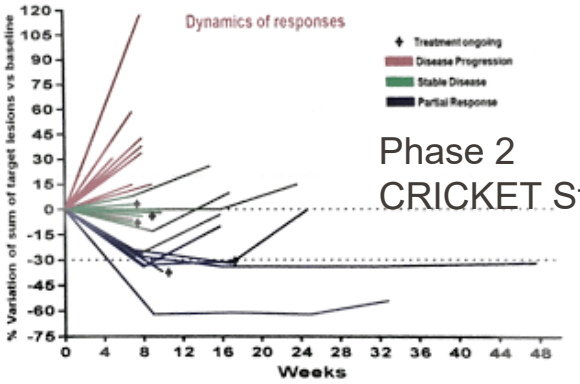
Resistance Mechanisms Rarely Travel Alone in CRC



Strickler et al, submitted

EGFR Resistance: Rechallenge Studies and Novel Therapies

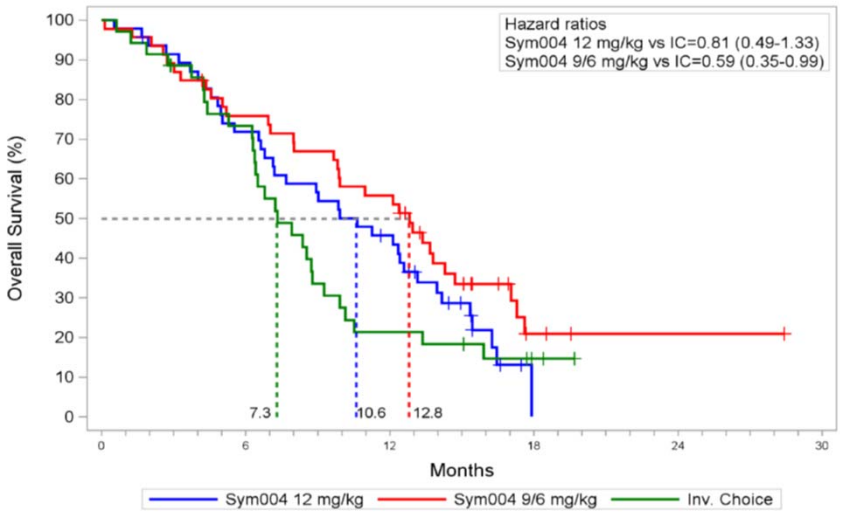




Phase 2
CRICKET Study

Rossini D et al., ESMO World GI 2017 -Abstract ID: PD-026, 30th June, 2017

Sym004 EGFR mAb RPhase 2: ctDNA selected to exclude of EGFR ECD mutations and RAS alleles frequency >20%



Tabernero et al ESMO '17
Amirouchene-Angelozzi et al Cancer Discovery '17

Conclusions

- There is a clinical need to solve several logistic issues in clinical care: access to tissue, access to timely results.
  - ctDNA is increasingly being used now for these indications.
- Studies using ctDNA for treatment response are planned and ongoing. However utility remains to be defined, and first applications may be in limiting ineffective therapies.
- Targeting resistance mechanisms are being studied in many settings, but may be influenced by heterogeneity.
- ctDNA for minimal residual disease offers immediate opportunities for clinic application, but utility needs to be demonstrated.

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- **Ryan Corcoran, MD, PhD**

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

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American Association for Cancer Research

SESSION III PANEL DISCUSSION

Liquid Biopsies in Cancer Drug Development and Clinical Use

Session Chairs: Gideon M. Blumenthal, MD, and Pasi Jänne, MD, PhD

Speakers:

Pasi Jänne, MD, PhD

Gideon M. Blumenthal, MD

David Hyman, MD

Scott Kopetz, MD, PhD

SESSION IV: Liquid Biopsy Test Development

Session Chair: Reena Philip, PhD

Speakers:

Eunice Lee, PhD

J. Carl Barrett, PhD

P. Mickey Williams, PhD

Meijuan Li, PhD

U.S. FOOD & DRUG ADMINISTRATION

Regulatory Perspective on Liquid Biopsy Diagnostics for Oncology Applications

FDA-AACR: Liquid Biopsies in Oncology Drug and Device Development II

Washington, DC

October 10, 2017

Eunice Lee, Ph.D.

Division of Molecular Genetics and Pathology (DMGP)

Office of In Vitro Diagnostics and Radiological Health (OIR)

Center for Devices and Radiological Health (CDRH)

Disclaimer

- Thoughts regarding new regulatory issues and policies are preliminary and do not represent finalized FDA policy.

- Questions related to specific diagnostic tests or platforms should be addressed through the Pre-Submission process.

Detection of Biomarkers for Cancer

Liquid Biopsy

Minimally Invasive

Convenient

Cost effective

- **Circulating cell-free nucleic acids**
- **Circulating tumor cells**
- **Exosomes**

Companion Diagnostics (CDx)

- Final Guidance issued on August 6, 2014
- CDx is defined as a test that provides information that is **essential** for the safe and effective use of a corresponding therapeutic
- > 40 IVD CDx approvals with corresponding therapeutics
  www.fda.gov/companiondiagnostics
- 1 approved liquid biopsy CDx

FDA Approved Liquid Biopsy Test for NSCLC

cobas EGFR Mutation Test v2 (using plasma specimens)

Two approvals:

- P150047 approved on June 1, 2016

  EGFR exon 19del and L858R mutations for **Tarceva (erlotinib)**

- P150044 approved on Sept. 28, 2016

  EGFR T790M mutation for **Tagrisso (osimertinib)**

Test previously approved for same indications using FFPE tissue specimens (P120019 and P120019/S007)

Practical Considerations for Liquid Biopsy Tests

cobas EGFR Mutation Test v2 (using plasma specimens)

Analytical

- Specimen collection and processing should be validated
- Samples should represent the intended use population; clinical specimens may be limiting
- Reference method/standards are lacking

Clinical

- Relevance to clinical outcomes should be demonstrated

Ongoing Challenges

- **To what extent can contrived samples be used in the validation studies?**
- **Is it possible for liquid biopsy tests to obtain follow-on claims to approved tissue tests?**
- **Are there additional considerations for validation of liquid biopsy NGS panels?**

Ongoing Challenges

- **To what extent can contrived samples be used in the validation studies?**
  - Clinical specimens should be used in key analytical studies, to the extent possible.
  - Contrived samples may supplement clinical samples, provided an appropriate functional characterization study is performed.
  - Clinical and contrived samples should be evaluated at 4-5 dilution levels between LoD and LoB for critical measures (e.g., input, variant allele frequency).

Ongoing Challenges

- **Is it possible for liquid biopsy tests to obtain follow-on claims to approved tissue tests?**
  - Follow-on CDx is expected to demonstrate comparable level of analytical and clinical performance for specific mutations as observed for the original companion diagnostic.
  - Clinical outcome based on liquid biopsy test results is ideal.
  - When enrollment is based on tissue, study population (e.g., line of therapy, tumor type and stage) and timing of blood sample collection should be considered.

Ongoing Challenges

- **Are there additional considerations for validation of liquid biopsy NGS panels?**
  - All variants with clinical claims should be included in the validation studies.
  - Representative variant approach for SNVs and indels.
  - Range of variant types should be included with consideration to sizes and genomic regions.

Resources

FDA Medical Device Database
https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm

FDA Companion Diagnostics Website
http://www.fda.gov/companiondiagnostics

In Vitro Companion Diagnostic Devices Guidance Document
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf

FDA-AACR Liquid Biopsy Public Workshop (July 19, 2016)
http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Pages/FDA-AACR-liquid-biopsies-in-oncology-drug-and-device-development.aspx#.WZDQXRvrupo

Pre-Submission Program Guidance Document
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

Email: Eunice.Lee@fda.hhs.gov

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