ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI TUMORI

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Current clinical applications of liquid biopsy

Nicola Normanno

Liquid biopsy in oncology: open questions

- **Can liquid biopsy be used for early diagnosis of cancer?**
- **Does liquid biopsy analysis provide prognostic information?**
- **Is liquid biopsy ready for the detection of predictive markers in clinical practice?**
- **Is liquid biopsy useful to monitor response to therapy?**

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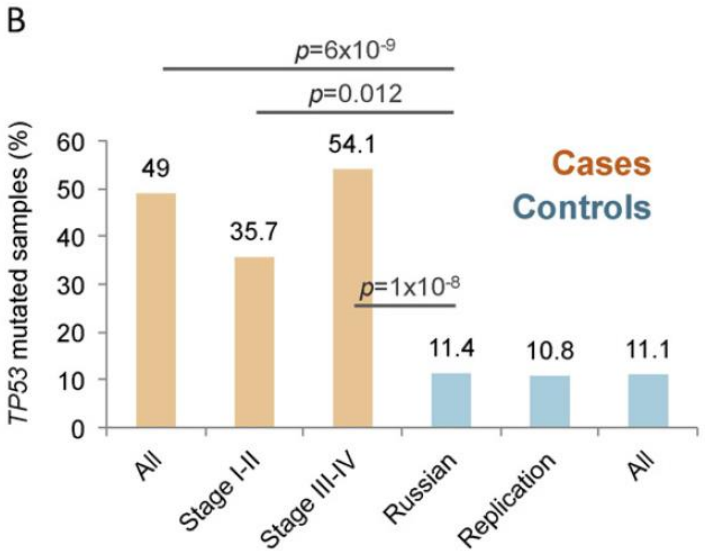
TP53 and KRAS Mutations in cfDNA of Healthy Subjects and Subsequent Cancer Occurrence

Table 1. Distribution of cancers among subjects of the GENAIR study tested for *TP53* and/or *KRAS2* mutations

Pathology	Total samples	*TP53*			KRAS2		
		Total samples tested (%)	Mutants (% of total tested)	OR (95% CI)	Total samples tested (%)	Mutants (% of total tested)	OR (95% CI)
Bladder	137	126 (92)	7 (5.5)	1.81 (0.66-4.87)	131 (95.6)	5 (3.8)	4.25 (1.27-14.15)
Lung	115	36 (31)	2 (5.5)	1.83 (0.36-9.44)	77 (67)	0 (0)	—
UADT	82	30 (36.6)	0 (0)	—	57 (69.5)	1 (1.7)	2.07 (0.23-18.7)
Leukemia	166	44 (26.5)	1 (2.3)	0.70 (0.09-5.61)	120 (72.3)	0 (0)	—
None	1,086	314 (30)	10 (3.2)	1 (Reference)	713 (65.7)	7 (1)	1 (Reference)
Total	1,586	550 (34.7)	20 (3.6)		1,098 (69)	13 (1.2)	

Gormally Cancer Res 2006

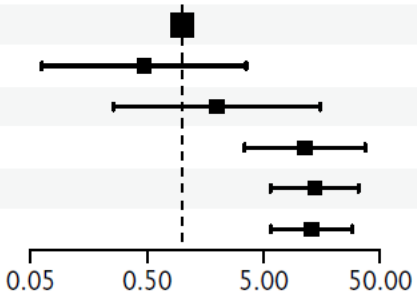


Fernandez-Cuesta EBioMedicine 2016

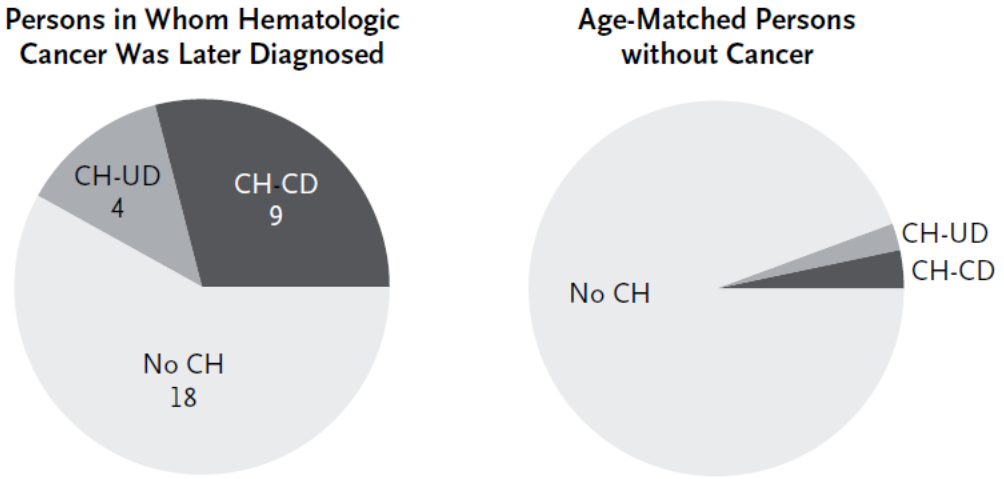
Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence

B

Category	No. of Patients	Hazard Ratio for Hematologic Cancer (95% CI)
No mutations	8783	1.00 (1.00–1.00)
One mutation	1122	0.47 (0.06–3.56)
Two mutations	237	1.99 (0.26–15.27)
CH-UD	170	11.34 (3.44–37.41)
CH-CD	269	13.73 (5.74–32.83)
CH	439	12.89 (5.78–28.72)



C



Clonal hematopoiesis with somatic mutations was observed in 10% of persons older than 65 years of age but in only 1% of those younger than 50 years of age.

Genovese NEJM 2014

Epi proColon® 2.0: Septin 9 methylation of cfDNA as marker for early detection of CRC

Method	Specificity	Sensitivity	Negative Predictive Value	Positive Predictive Value[4]
Epi proColon® 2.0 CE[1]	99.3%	80.6%	99.9%	45.7% 
Guaiac Fecal-Occult Blood Test[2]	97.7%	37.1%	99.6%	10.1% 
OC-Sensa Micro qFIT1x[3]	93.7%	69.2%	99.8%	7.5% 

- Results from 53 CRC cases and from 1457 subjects without CRC
- Sensitivity of 48.2% (95% CI 32.4% to 63.6%)
- For CRC stages I-IV, sensitivity was 35.0%, 63.0%, 46.0% and 77.4%, respectively
- Specificity was 91.5% (95% CI 89.7% to 93.1%)
- Sensitivity for advanced adenomas was low (11.2%)

Church Gut 2014

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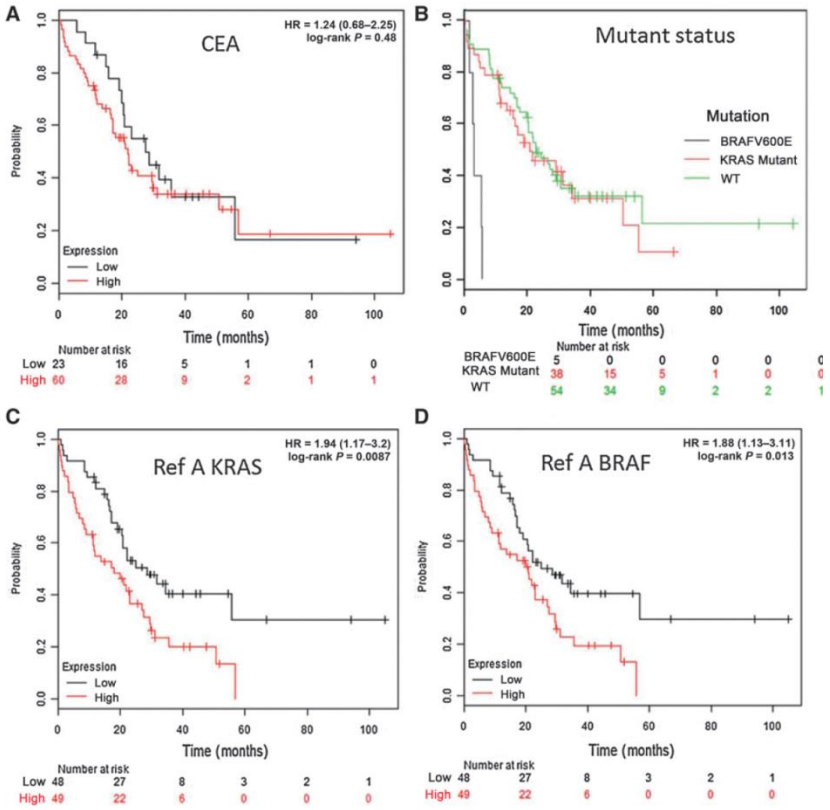
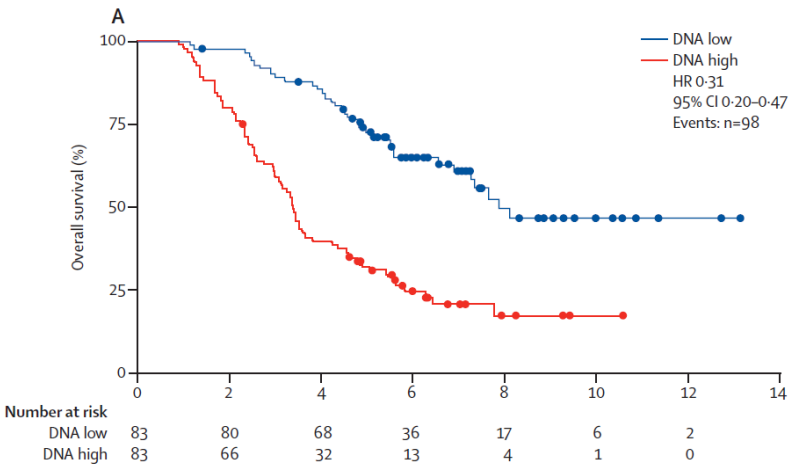
Association of baseline plasma DNA concentrations with overall survival in mCRC patients

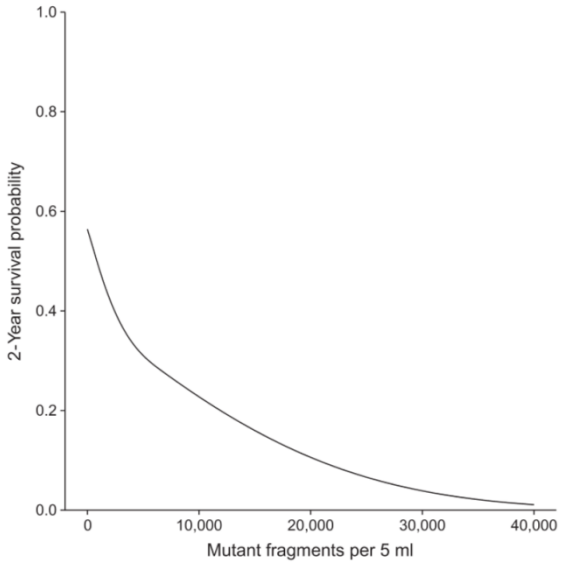


El Messaoudi CCR 2016

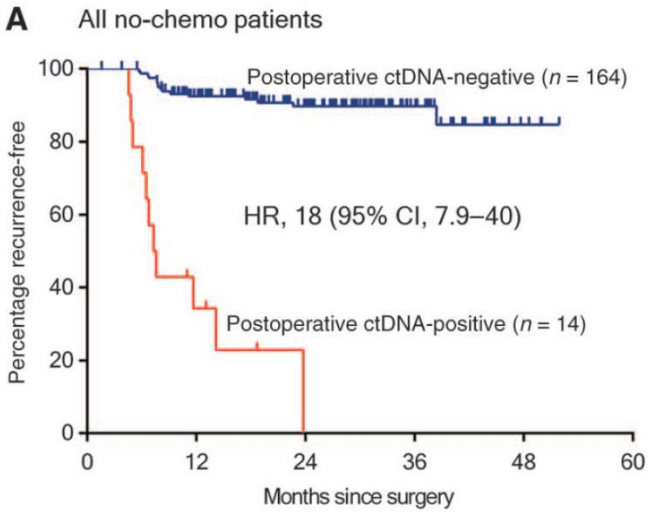
Tabernero Lancet Oncol 2015

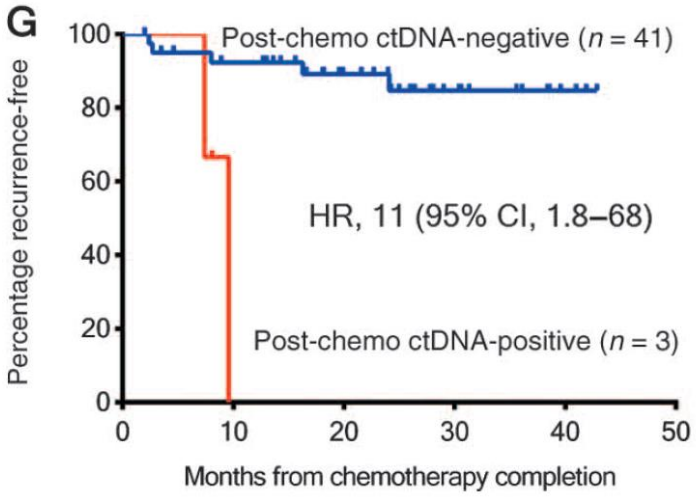


Bettegowda ST M 2014



ctDNA analysis predicts recurrence in patients with stage II colon cancer





HR 28, CI 11-68, p<0.001 at multivariate analysis

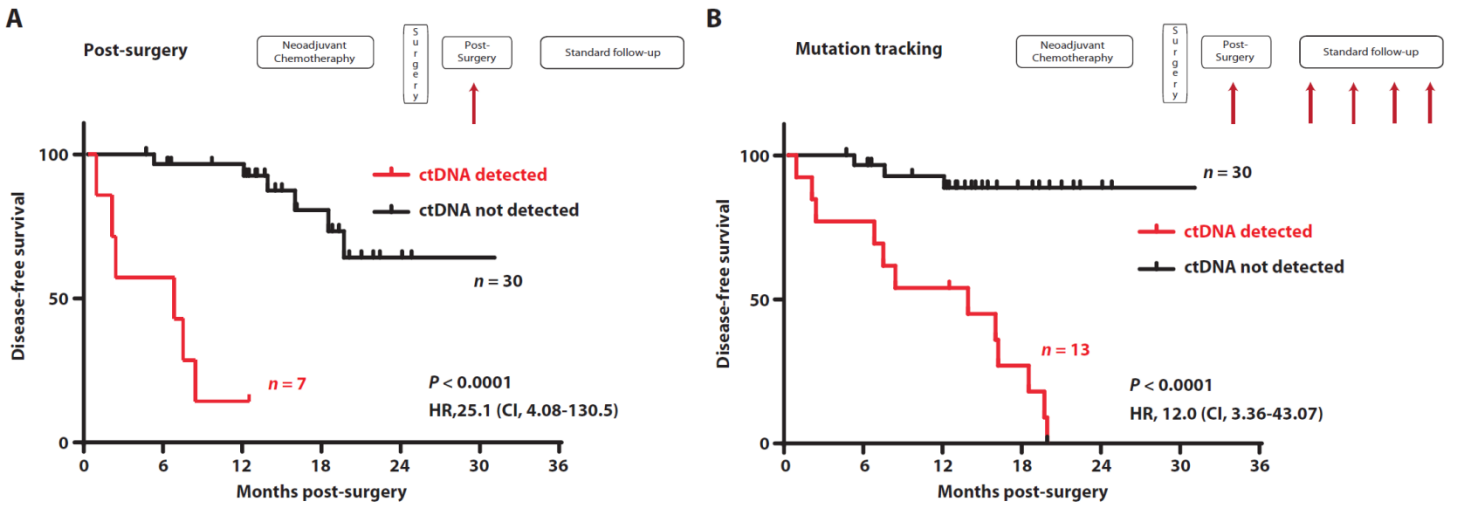
HR 14, CI 6.8-28, p<0.001 at multivariate analysis

Tie Sci Transl Med 2016

Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer

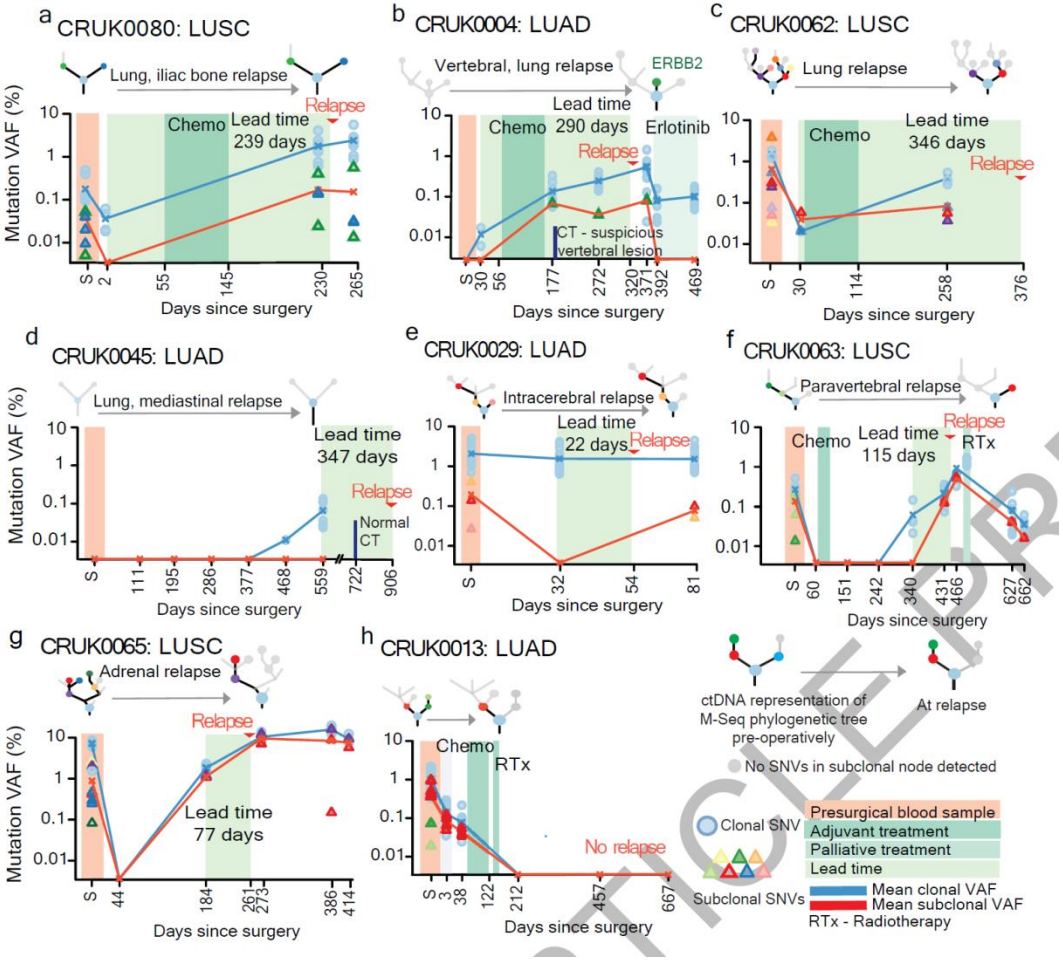
HR 25.1

HR 12



Garcia-Murillas Sci Transl Med 2016

Post-operative ctDNA detection predicts and characterizes NSCLC relapse



Abbosh Nature 2017

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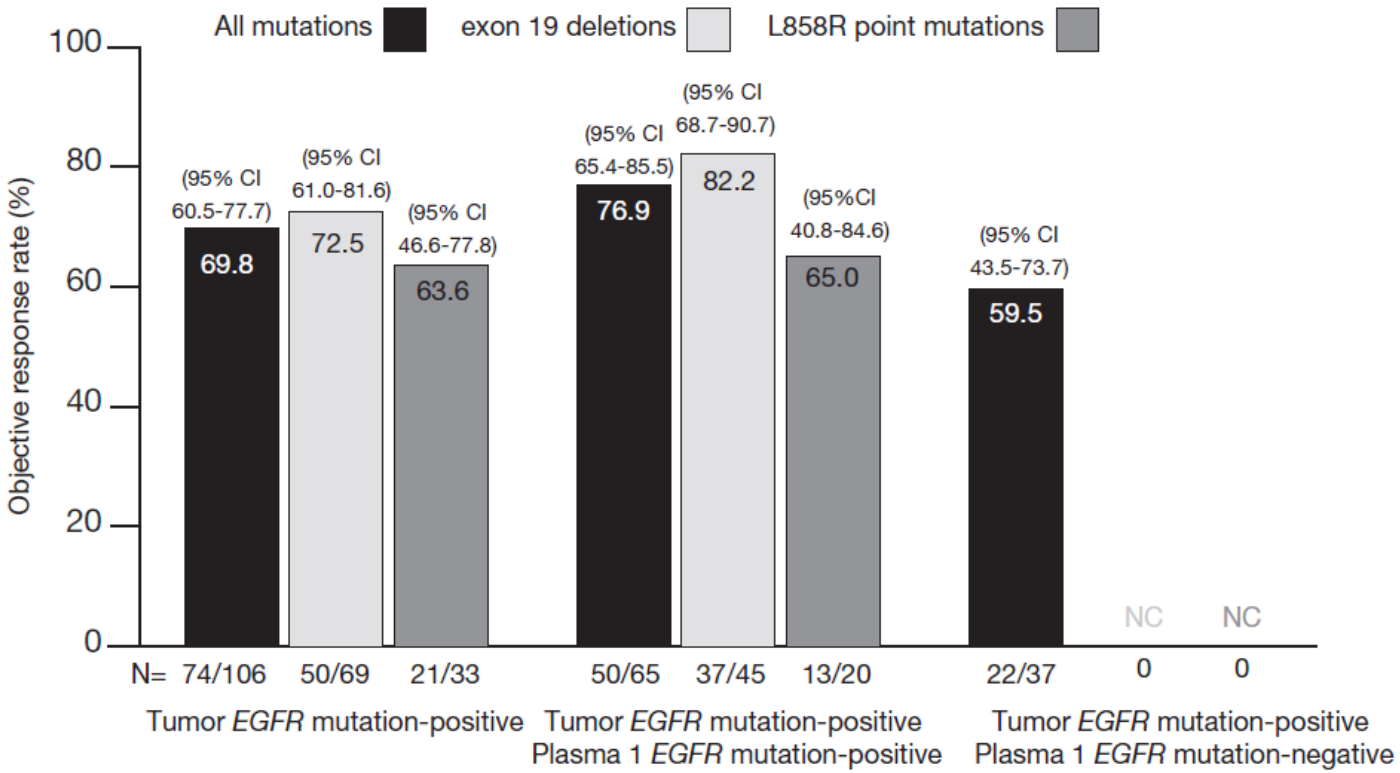
IFUM: ORR in tissue and/or plasma EGFR+ samples



Douillard JTO 2014

EGFR mutation status concordance

Same method used for >90 patients

Differences in concordance apparent between the three methods; with PPV acceptable for all

Concordance between matched tissue / cytology and plasma samples	PNA-LNA PCR Clamp (n=91)		Cycleave® (n=190)		QIAGEN therascreen® *EGFR* RGQ PCR Kit (n=138)	
	% (n/N)	95% CI	% (n/N)	95% CI	% (n/N)	95% CI
Concordance	83.5 (76/91)	74.3, 90.5	84.7 (161/190)	78.8, 89.5	94.9 (131/138)	89.8, 97.9
Sensitivity	51.7 (15/29)	32.5, 70.6	50.9 (29/57)	37.3, 64.4	72.7 (16/22)	49.8, 89.3
Specificity	98.4 (61/62)	91.3, 100.0	99.2 (132/133)	95.9, 100.0	99.1 (115/116)	95.3, 100.0
PPV	93.8 (15/16)	69.8, 99.8	96.7 (29/30)	82.8, 99.9	94.1 (16/17)	71.3, 99.9
NPV	81.3 (61/75)	70.7, 89.4	82.5 (132/160)	75.7, 88.0	95.0 (115/121)	89.5, 98.2

CI, confidence interval

Normanno WCLC 2015

OncoBEAM RAS CRC Assay

OncoBEAM RAS CRC is the first liquid biopsy test to achieve CE-Mark status for RAS testing in metastatic colorectal cancer

- Expanded RAS mutation analysis using BEAMing has been validated in anti-EGFR therapy clinical trials
  - Over 1,200 patients have been tested using the BEAMing platform in the OPUS, CRYSTAL, and CALGN/SWOG 80405 clinical trials
  - Expanded RAS testing was shown to improve the identification of mCRC patients eligible for anti-EGFR therapy

- Mutations Tested by OncoBEAM RAS CRC Kit:

Gene:	Exon 2	Exon 3	Exon 4
KRAS	G12S, G12R, G12C, G12D, G12A, G12V, G13D	A59T, Q61L, Q61R, Q61H, Q61H	K117N, K117N, A146T, A146V
NRAS	G12S, G12R, G12C, G12D, G12A, G12V, G13R, G13D, G13V	A59T, Q61K, Q61R, Q61L, Q61H, Q61H	K117N, K117N, A146T

Concordance of plasma and tissue RAS mutation results

	Tumor tissue RAS result						
	RAS	Mutant	WT	Total	PPA (95% CI)	NPA (95% CI)	OPA (95% CI)
Plasma ctDNA RAS result	Mutant	47	3	50	100 × 47/52 = 90.4%	100 × 43/46 = 93.5%	100 × 90/98 = 91.8%
	WT	5	43	48	(79%, 96%)	(82%, 98%)	(85%, 96%)
	Total	52	46	98			

Schmiegel Mol Oncol 2017

		Tissue RAS Result		
		Positive	**Negative**	**Total**
Plasma Ras Result	**Positive**	49*	5	54
	Negative	2	53	55
	Total	51	58	**109**

*1 positive in tissue and plasma but in different codons

Negative Agreement: 53/58: 91,4%

Positive Agreement: 49/51: 96,1%

Overall Agreement: 102/109: 93,6%

Vidal ESMO 2016

		Tissue SOC RAS result		
		Mutation detected	No mutation detected	Total
OncoBEAM RAS CRC Plasma RAS Result	Mutation detected	**31**	**3**	**34**
	No mutation detected	**2**	**28**	**30**
	Total	**33**	**31**	**64**

Overall Agreement = 92.2%

Positive Percent Agreement = 93.9%

Negative Percent Agreement = 90.3%

Saunders ESMO 2016

ESMO guidelines

recommendation 3: tissue selection.

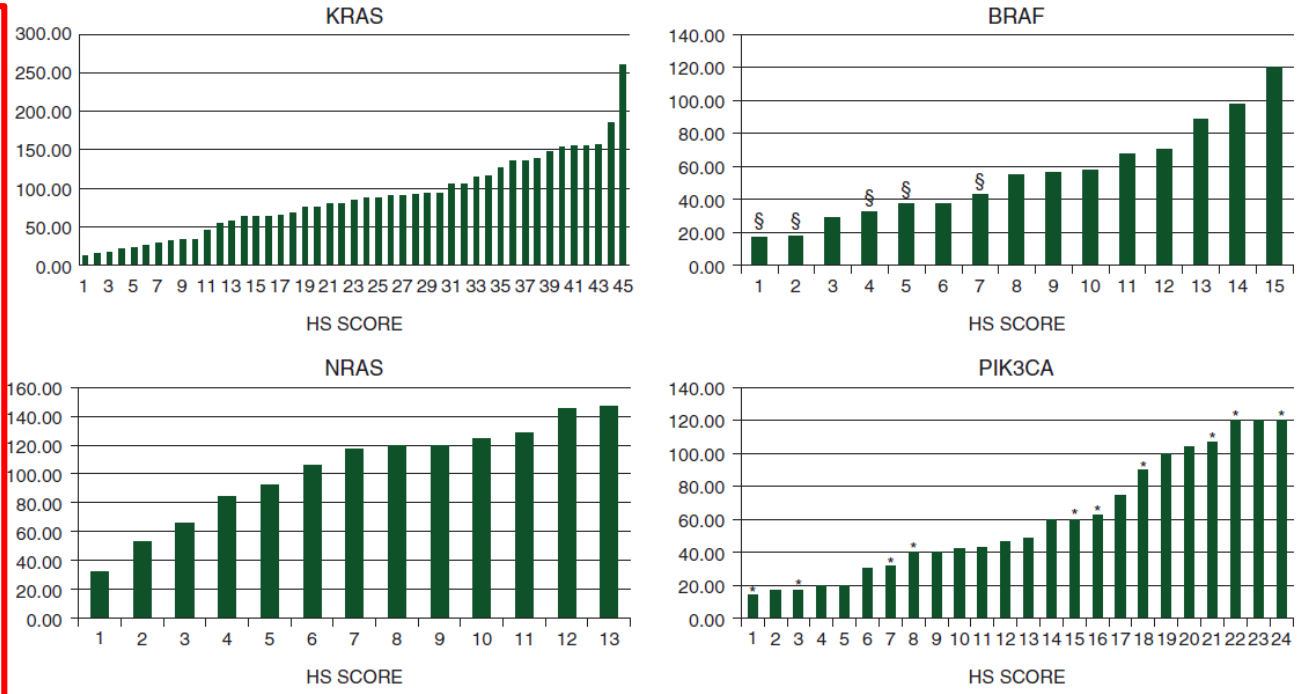
- Tissue from either the primary tumour or a liver metastasis may be used for *RAS* mutation testing [III, A].
- Other metastatic sites such as lymph node or lung metastases may be used only if primary tumour or liver metastases samples are not available [II, B].

Discordant rate primary vs	%
Liver	5
Lymph nodes	25
Lung	??

Van Cutsem Ann Oncol 2016

Heterogeneity Score (HS) in mCRC patients enrolled in the CAPRI trial

- The heterogeneity score (HS) was obtained by normalizing the frequency of mutant alleles for the fraction of neoplastic cells
- The HS virtually corresponds to the fraction of neoplastic cells that carry a specific mutation



Normanno N, et al. Ann Oncol 2015;26:1710–1714

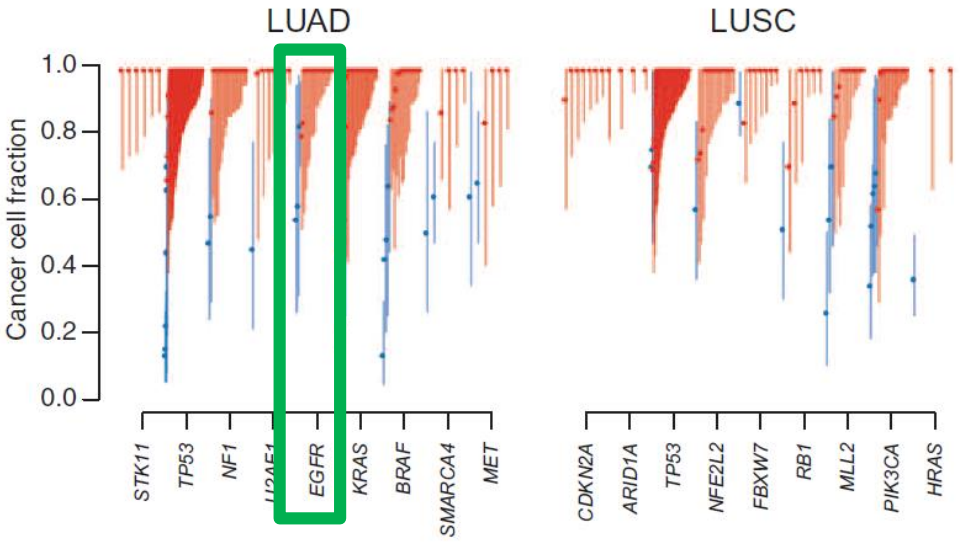
KRAS Heterogeneity Score (HS) and efficacy of treatment in the CAPRI trial

	N.	Responses	ORR (%)	Median PFS, months
HS<33	10	3 SD 6 PR 1 CR	70	7,97
HS>33	35	4 PD 15 SD 14 PR 2 CR	45,7	8,37

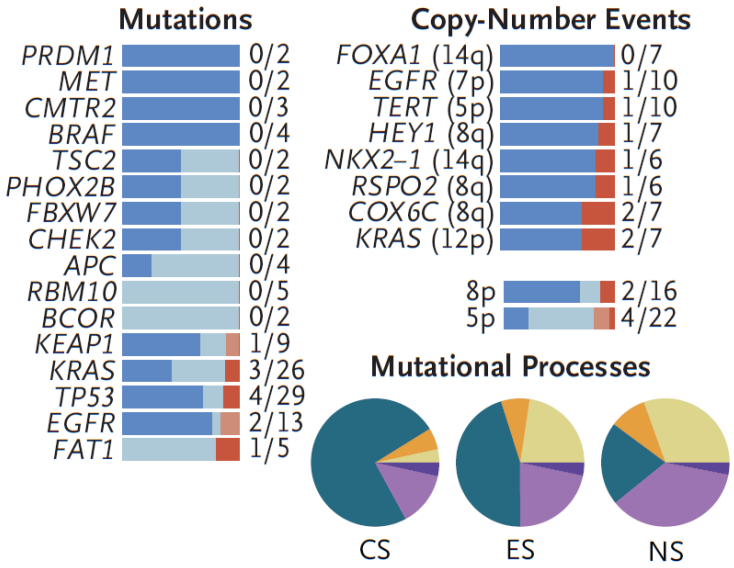
PD: Progressive Disease; SD: Stable Disease; PR: Partial Response;
CR: Complete Response

Normanno et al Ann Oncol 2015

Clonal and subclonal mutations in lung cancer



McGranahan Sci Transl Med 2015



Jamal-Hanjani NEJM 2017

NSCLC tumor and plasma samples analysis with the Oncomine Solid Tumour DNA: discordant cases

Case N.	Plasma analyses			Tissue analyses		
	NGS	Therascreen	ddPCR	NGS	Therascreen	ddPCR
L29	EGFR: p.E746_A750del (3,4%);	EGFR: wild type	EGFR: Del ex19 (4%)	-	EGFR: wild type	EGFR: Del ex19 (0.23%)
L33	EGFR: p.E746_A750del (1,6%); CTNNB1: p.S37C (12,3%)	EGFR: wild type	EGFR: Del ex19 (0.8%)	CTNNB1: p.S37C (13,3%)	EGFR: wild type	EGFR: Del ex19 (0.76%)

Rachiglio Oncotarget 2016

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Correlation between changes in ctDNA and response to chemotherapy

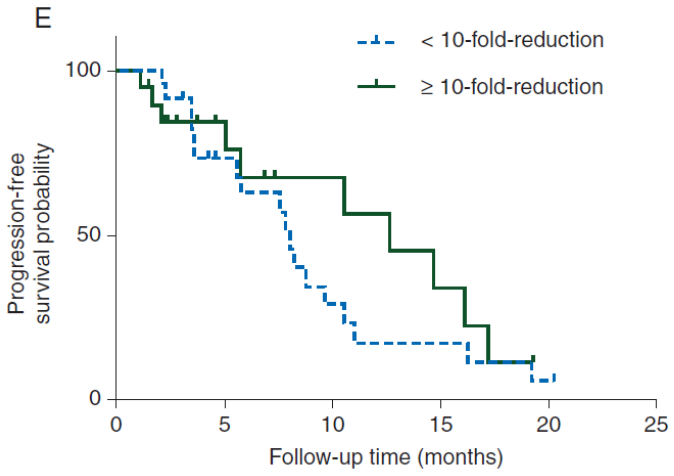
Table 2. Univariate association between tumor response at first imaging, CEA and ctDNA indices ($N = 42$)

Variable	Tumor response[a]		*P* value
	No response	Response	
Patients (*N*, %)	20 (47.6)	22 (52.4)	
CEA, pretreatment[b], median (IQR)	46 (18–660)	16.9 (10–89.5)	0.171
CEA after one cycle of chemotherapy, median (IQR)	50.4 (19–520)	11.3 (6.6–84.9)	0.173
Fold change in CEA, median (IQR)	0.92 (0.78–1.11)	0.91 (0.67–1.33)	0.884
ctDNA, pretreatment, median (IQR)	12.9 (0.6–29.7)	20.8 (2.7–34.5)	0.339
ctDNA after one cycle of chemotherapy, median (IQR)	3.7 (0.3–6.6)	0.4 (0.2–5.3)	0.182
Fold change in ctDNA (no. of patients, %)			*0.016*
<10-fold reduction	15 (75.0)	8 (36.4)	
≥10-fold reduction	5 (25.0)	14 (63.6)	

P value indicates a significance level of <0.05.

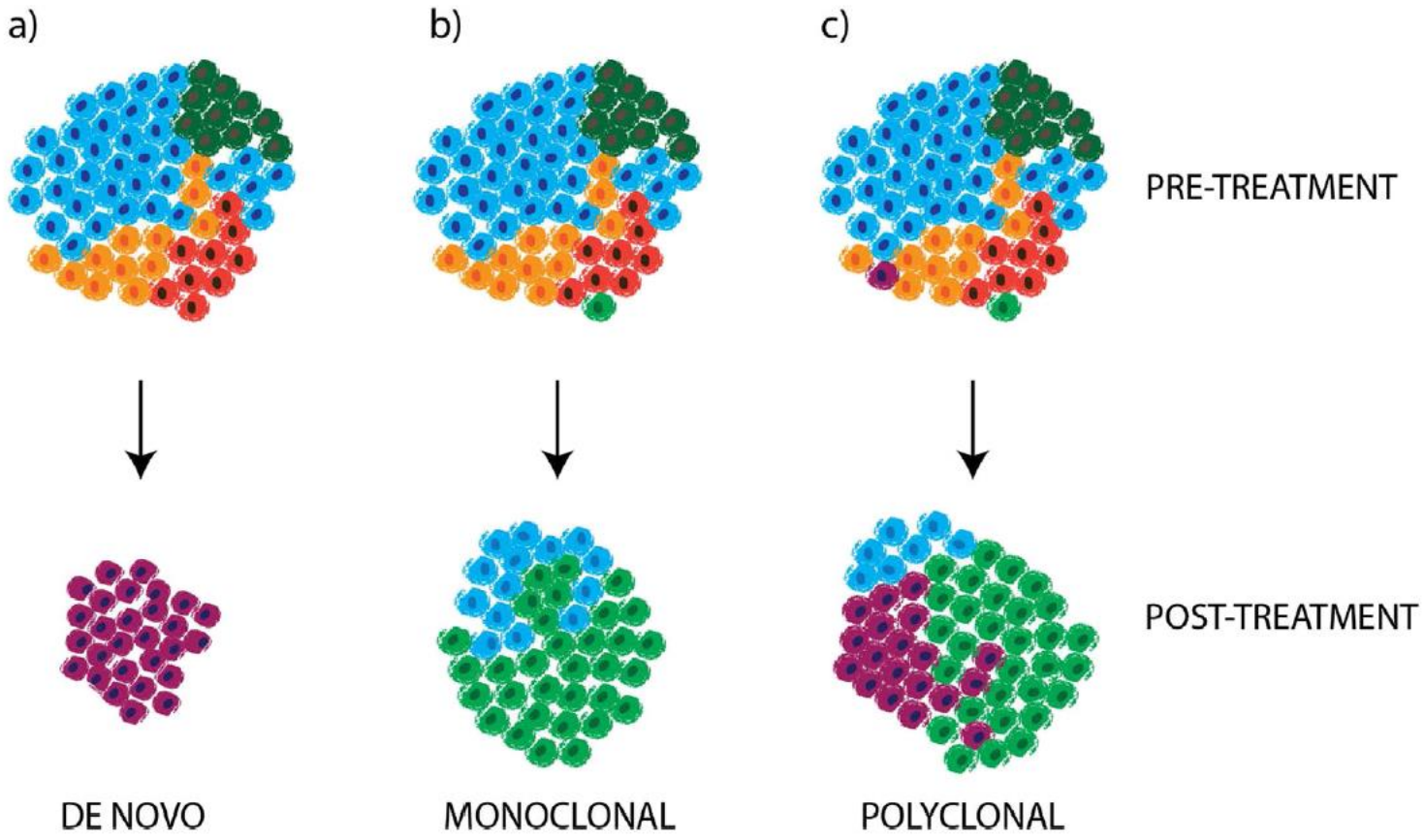
[a]Defined as ≥20% reduction in the sum of largest diameters according to standard RECIST criteria.

[b]CEA not collected before treatment in two patients.



Tie Ann Oncol 2015

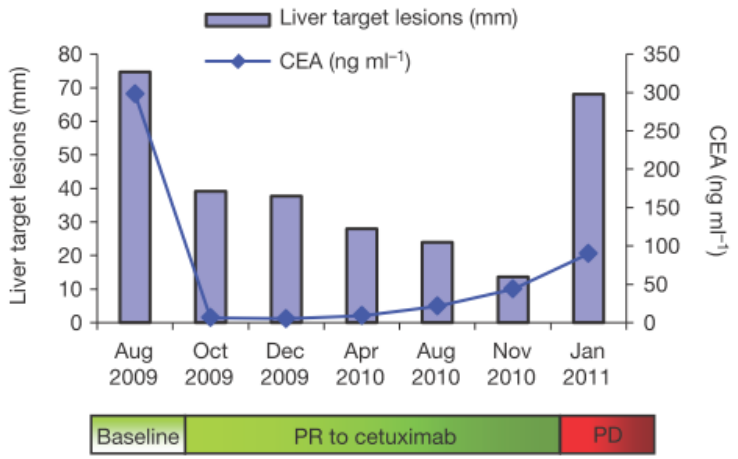
Clonal Evolution and Drug Resistance

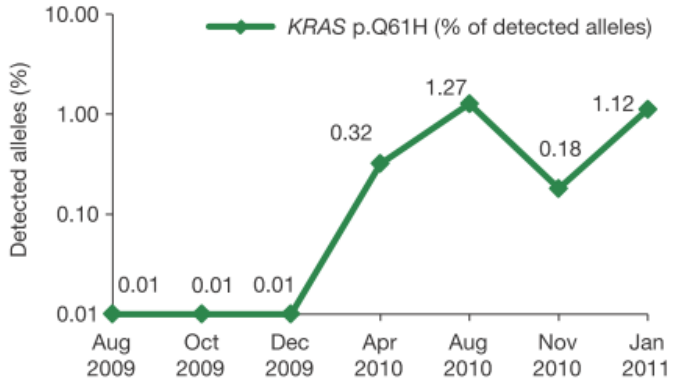


Burrell & Swanton Mol Oncol 2014

Potential further application of liquid biopsies

Monitoring for resistance to continue to personalize treatment





Initial response to cetuximab followed by PD in a patient with KRAS wild type tumor

Diagnosis of acquired resistance

Quantitative analysis of KRAS (Q61H) mutant DNA in plasma, as assessed by BEAMing

Misale S, et al. Nature 2012;486:532–536

Resistance mutations in mCRC according to liquid biopsy

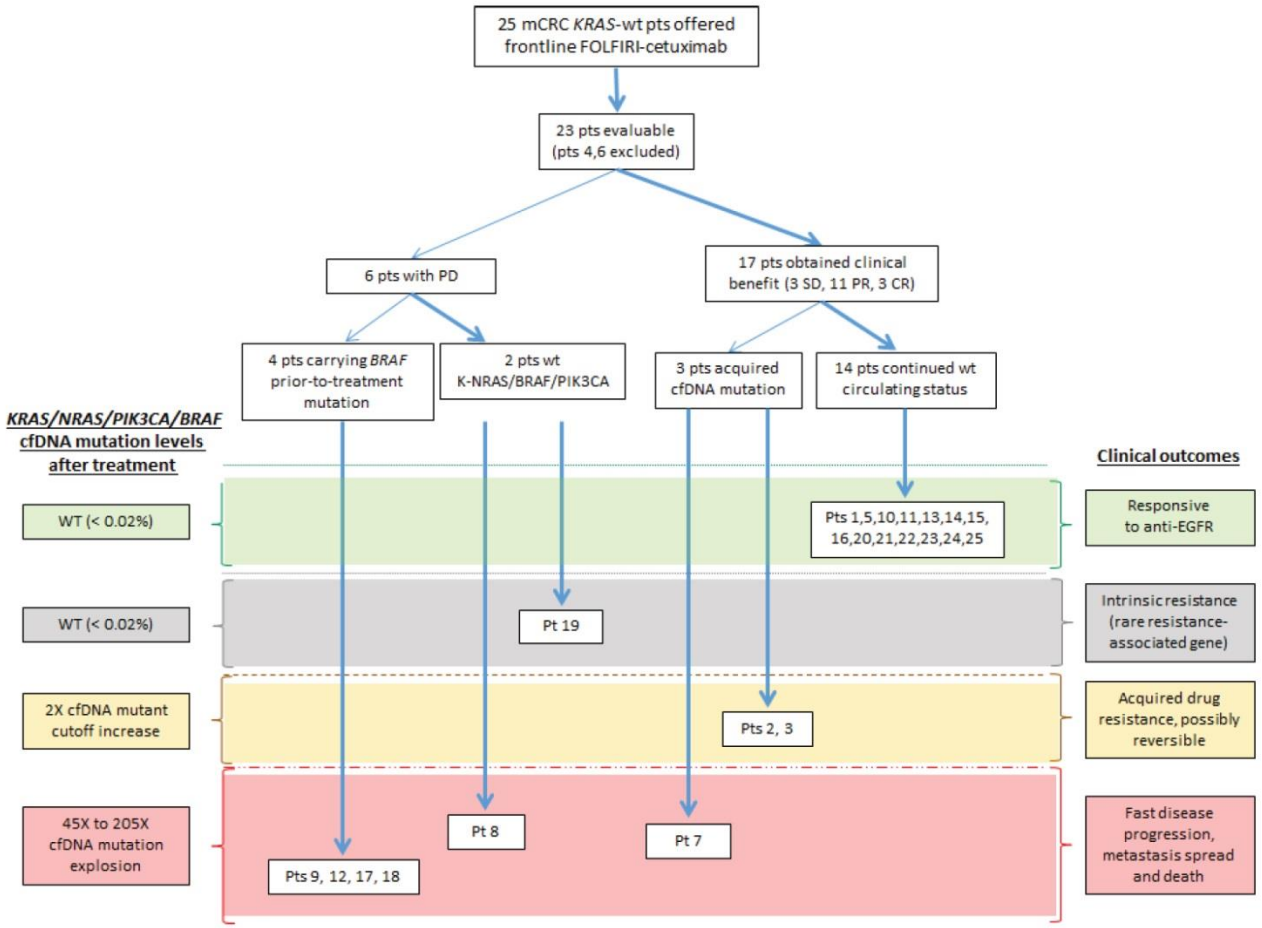
Publication	Method	(K)RAS mutations at progression n/N	%
Diaz et al. Nature 2012*[1]	PCR Ligation/ BEAMing	9/24	37.5
Misale et al. Nature 2012*[2]	NGS/BEAMing	2/3	66.6
Morelli et al. Ann Oncol 2015*[3]	BEAMing	27/62	43.5
Bettegowda et al. Sci Transl Med 2014[4]	PCR Ligation/ BEAMing/ SafeSeqS	23/24	95.8
Misale et al. Sci Transl Med 2014[5]	BEAMing	2/4	50.0
Siravegna et al. Nat Med 2015[6]	ddPCR	11/16	68.8
Tabernero et al. Lancet Oncol 2015*[7]	BEAMing	41/86	48

*only KRAS

1. Diaz L, et al. Nature 2012;486:537–540; 2. Misale S, et al. Nature 2012;486:532–536; 3. Morelli M, et al. Ann Oncol 2015;26:731–736; 4. Bettegowda C, et al. Sci Transl Med 2014;6(224):224ra24; 5. Misale S, et al. Sci Transl Med 2014;6(224):224ra26; 6. Siravegna G et al. Nature Med 2015;21(7):795–80; Tabernero J et al. Lancet Oncol 2015;16: 937–48

NGS, next-generation sequencing; PCR, polymerase chain reaction; ddPCR, droplet digital PCR

Liquid biopsy results and outcome for mCRC patients on cetuximab-FOLFIRI



Toledo Oncotarget 2016

Mechanisms of resistance to EGFR TKIs in NSCLC

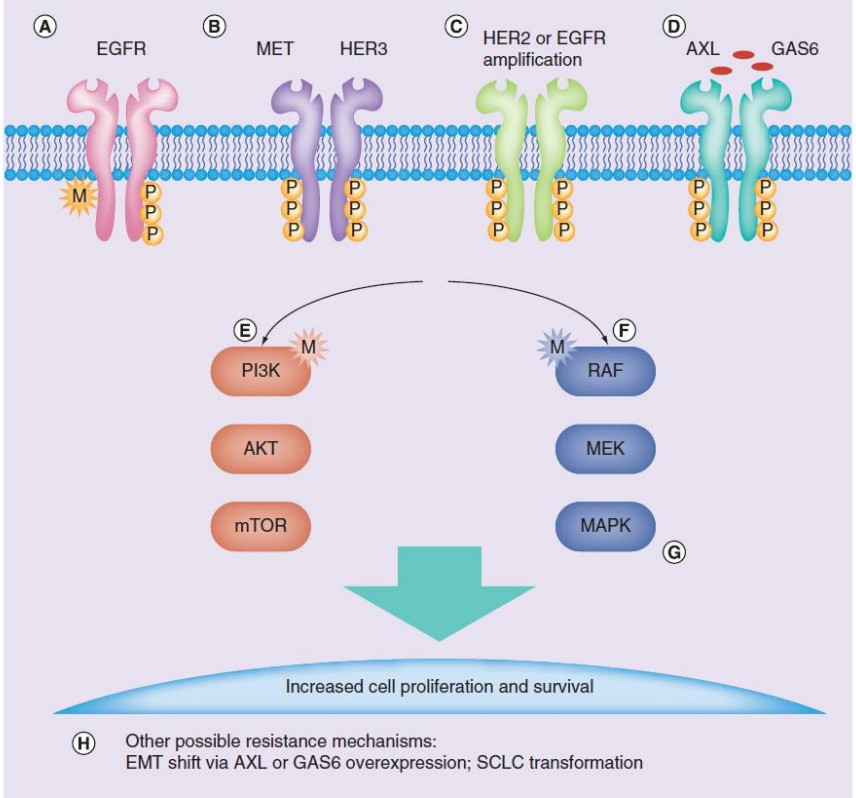


Table 1. Main mechanisms involved in acquired resistance to EGF receptor-tyrosine kinase inhibitors.

Molecular alteration	Frequency (%)†
T790M mutation	~50
MET amplification	5–20
EGFR amplification	8‡
HER2 amplification	5–13
MAPK1 amplification	4.8
PIK3CA mutations	5
BRAF mutations	1
AXL overexpression	20
GAS6 overexpression	25
EMT	1–2
SCLC transformation	5–14

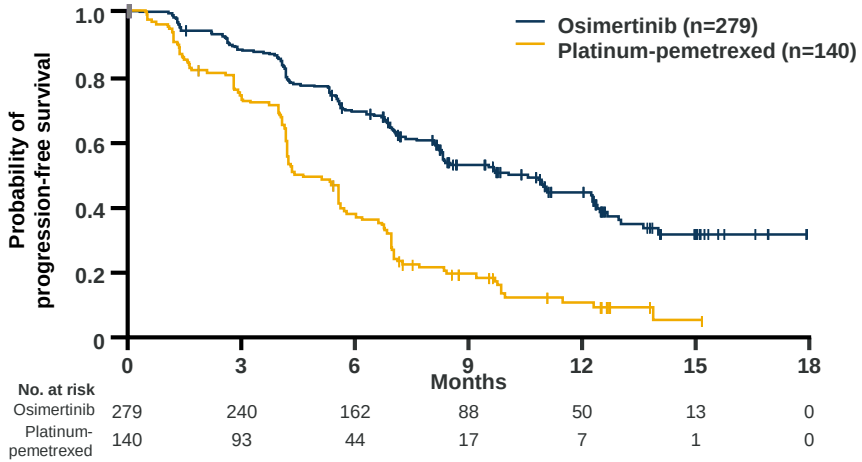
†Frequencies are derived from different studies [5,9,22,37–41].
‡*EGFR* amplification + T790M mutation [37].
EMT: Epithelial-to-mesenchymal transition; SCLC: Small-cell lung carcinoma.

Fenizia Future Oncology 2015

AURA3: osimertinib benefit in patients with plasma T790M-positive status is similar to patients with tumor tissue T790M-positive status[1,2]

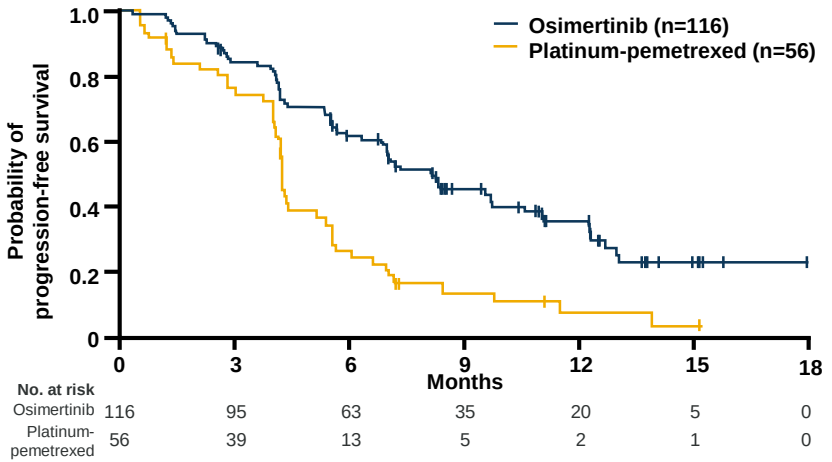
Tumor T790M-positive (intent-to-treat)*

	Osimertinib	Platinum-pemetrexed
Median PFS, months (95% CI)	10.1 (8.3, 12.3)	4.4 (4.2, 5.6)
PFS HR (95% CI)	0.30 (0.23, 0.41),* *P*<0.001	
ORR,† % (95% CI)	71 (65, 76)	31 (24, 40)



Plasma T790M-positive status

	Osimertinib	Platinum-pemetrexed
Median PFS, months (95% CI)	8.2 (6.8, 9.7)	4.2 (4.1, 5.1)
PFS HR (95% CI)	0.42 (0.29, 0.61)	
ORR,† % (95% CI)	77 (68, 84)	39 (27, 53)



Data cut-off April 15, 2016. Tick marks indicate censored data.

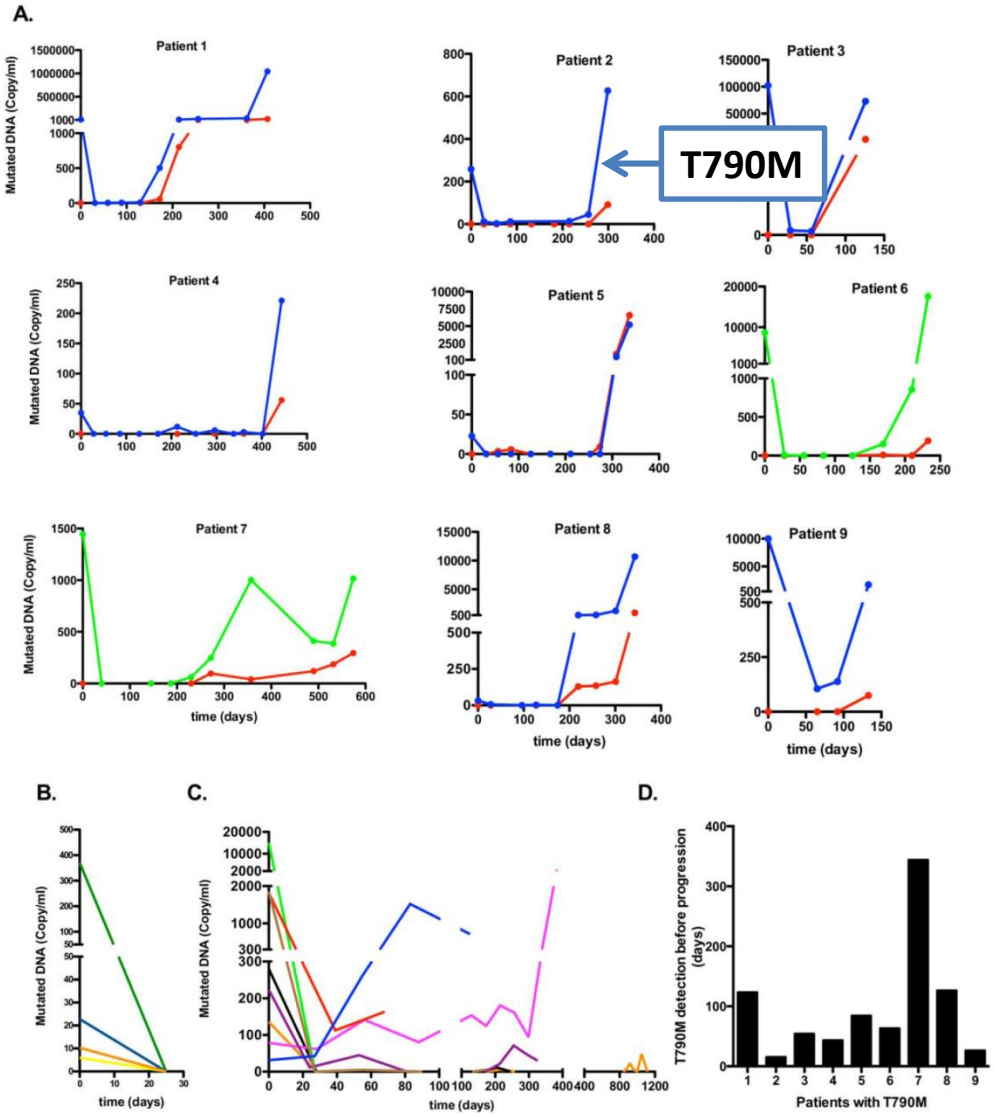
PFS is defined as time from randomization until date of objective disease progression or death. Progression included deaths in the absence of RECIST progression. Osimertinib administered 80 mg orally once daily. Platinum-pemetrexed group treatment consisted of: pemetrexed 500 mg/m^2 + carboplatin AUC5 or cisplatin 75 mg/m^2 Q3W for up to 6 cycles + optional maintenance pemetrexed for patients whose disease had not progressed after 4 cycles of platinum-pemetrexed. RECIST v1.1 assessments performed every 6 weeks until objective disease progression.

*PFS adjusted for ethnicity. All patients were selected using a tumor tissue test for *EGFR* T790M (by **cobas**® EGFR Mutation Test) from a biopsy after disease progression prior to study entry. †Response did not require confirmation per RECIST v1.1.

CI, confidence interval; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors

1. Mok TS, et al. *N Engl J Med.* 2017; 376:629-640. 2. Suppl. Info for: Mok TS, et al. *N Engl J Med.* 2017; 376:629-640.

Plasma EGFR mutations during treatment with EGFR TKIs (2)



Sorensen Cancer 2014

Testing T790M at progression of the disease

- T790M should be tested at the progression of the disease
- In patients with oligoprogression, it might be indicated to continue the treatment with the I/II generation TKI until clear progression
- In patients with limited disease (small tumor burden) the T790M test might result negative if performed with liquid biopsy
- In clinical practice, testing for the T790M should be performed when the doctor thinks it's time to change the therapy

AURA3: T790M mutation is detected in plasma of ~50% of patients with T790M in tumor tissue

- Patients with tissue sample available at screening (n=756)

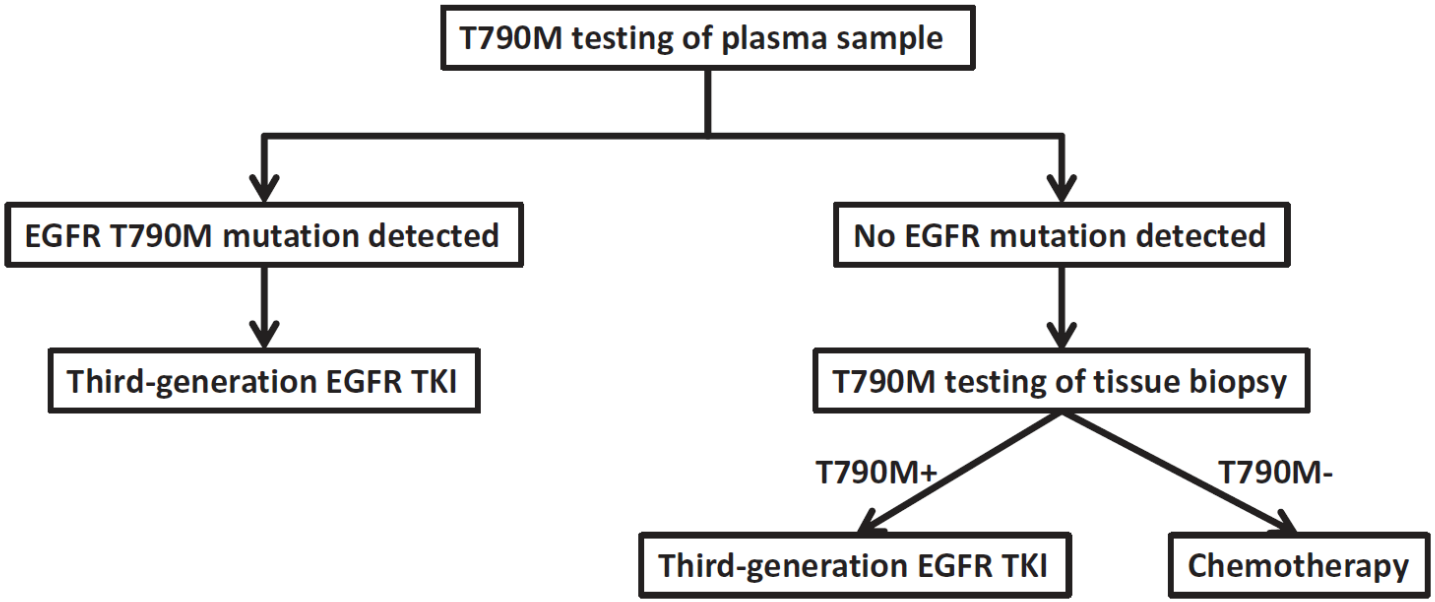
Plasma ctDNA test results, n	Tissue T790M positive (n=399)	Tissue Exon 19 deletion positive (n=427)	Tissue L858R positive (n=253)
Plasma positive	184	273	139
Plasma negative	175	60	67
No plasma test / invalid	37 / 3	91 / 3	47 / 0
Percent agreement using tissue test as reference, % (95% CI)*	**T790M**	**Exon 19 deletion**	**L858R**
Positive percent agreement (sensitivity)	**51 (46, 57)**	82 (77, 86)	68 (61, 74)
Negative percent agreement (specificity)	**77 (71, 83)**	98 (96, 100)	99 (98, 100)
Overall concordance	61 (57, 65)	89 (86, 91)	88 (85, 90)

- 51% sensitivity and 77% specificity for T790M detection using cobas® tissue test as reference
- High sensitivity and specificity is observed for Exon 19 deletion and L858R

Data cut-off April 15, 2016.
*Percent agreement of the **cobas**® plasma test with the **cobas**® tissue test. Positive percent agreement and negative percent agreement are used here as measures of test sensitivity and specificity, respectively, and calculated with invalid results excluded.

Wu YL, et al. *J Thorac Oncol*. 2017; 12(S1), abstract MA08.03.

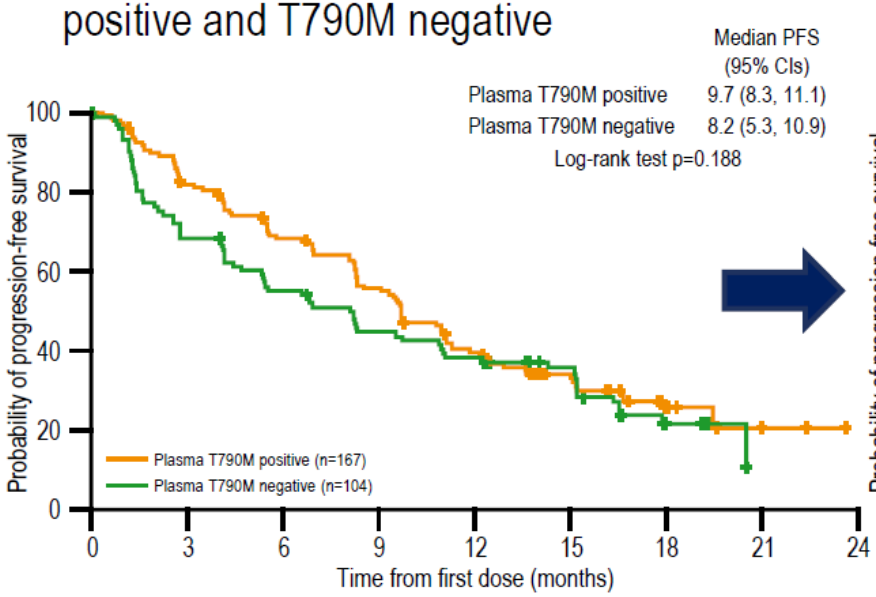
Algorithm of T790M testing in pts progressing after a I/II-generation TKI

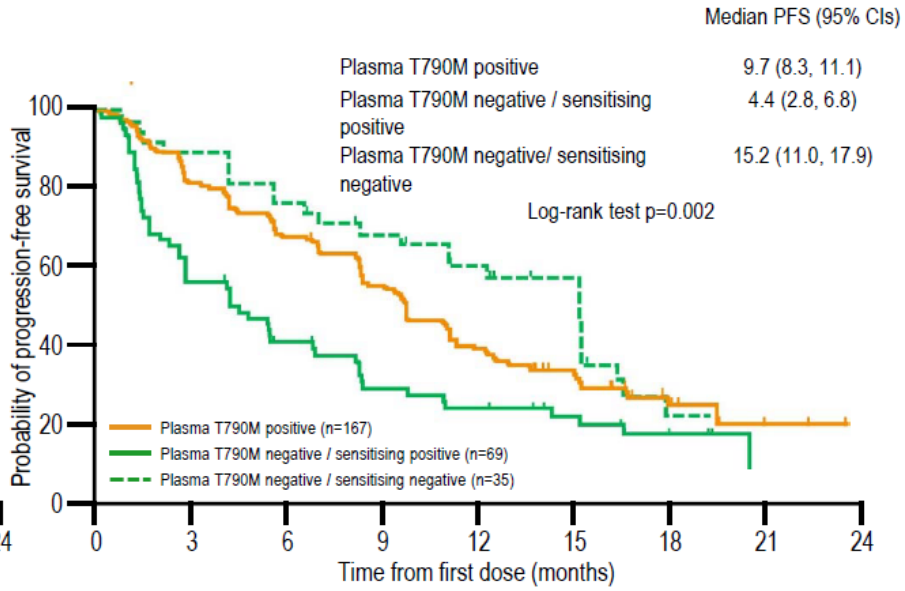


Normanno EOTT 2017

Detection of sensitising mutation as a control

- In the 104 patients with T790M negative plasma genotyping, we studied whether detection of the sensitising mutation helped to understand true negative versus false negative
  - Plasma T790M negative / sensitising positive: 38% ORR, 4.4 month median PFS
  - Plasma T790M negative / sensitising negative: 64% ORR,15.2 months median PFS
- If plasma T790M negative / sensitising negative are excluded from PFS analysis reflecting their unknown plasma T790M mutation status, a significant difference is seen between T790M positive and T790M negative





Data cut-off: 1 May 2015

Presented by Geoffrey R Oxnard at the 6th IASLC/ESMO European Lung Cancer Conference, 13–16 April 2016, Geneva, Switzerland; Abstract 135O_PR.

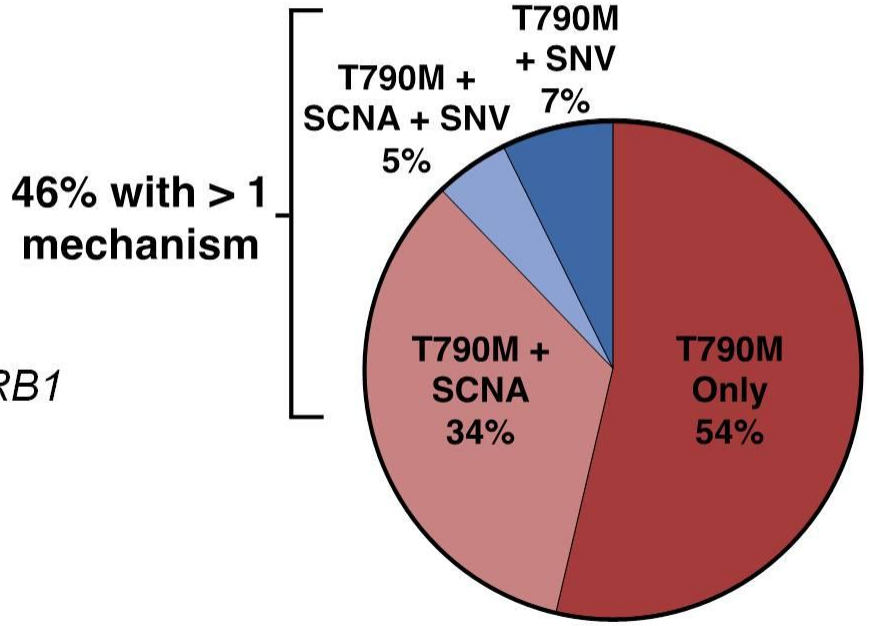
T790M plasma testing: clnical interpretation

Sensitizing	T790M	Interpretation
+	+	T790M positive: start treatment with 3° generation TKI
+	-	T790M negative: tissue biopsy recommended
-	+	T790M positive?: confirm with an orthogonal technique
-	-	Non informative: tissue biopsy strongly recommended

Normanno EOTT 2017

Heterogeneity of Resistance Mechanisms to First-line EGFR TKIs from a single sample source

- Baseline rociletinib plasma
  - *n* = 41 patients with detectable T790M
- 34% T790M+SCNA (copy number gain)
  - *MET* or *ERBB2*
- 7% T790M+SNV(s)
  - *EGFR*, *PIK3CA* or *RB1*
- 5% T790M+SCNA+SNV
  - SCNA in *MET* and SNV in *PIK3CA* or *RB1*



SNV=single nucleotide variant, SCNA=somatic copy number alteration

Detection of different mechanismsm of resistance to anti-EGFR moAbs in plasma of CRC patients

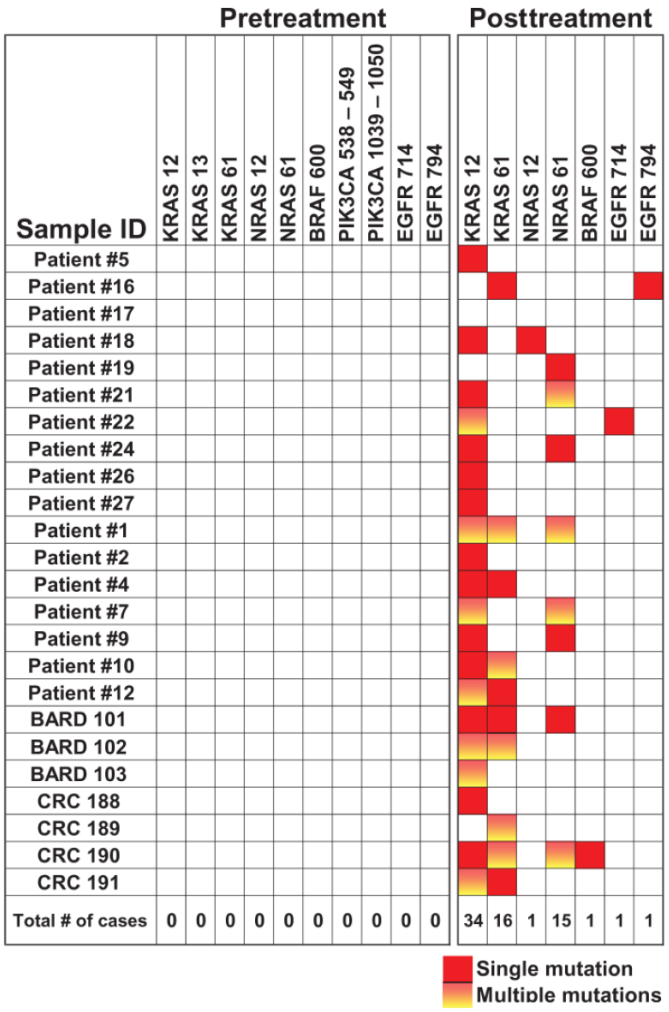


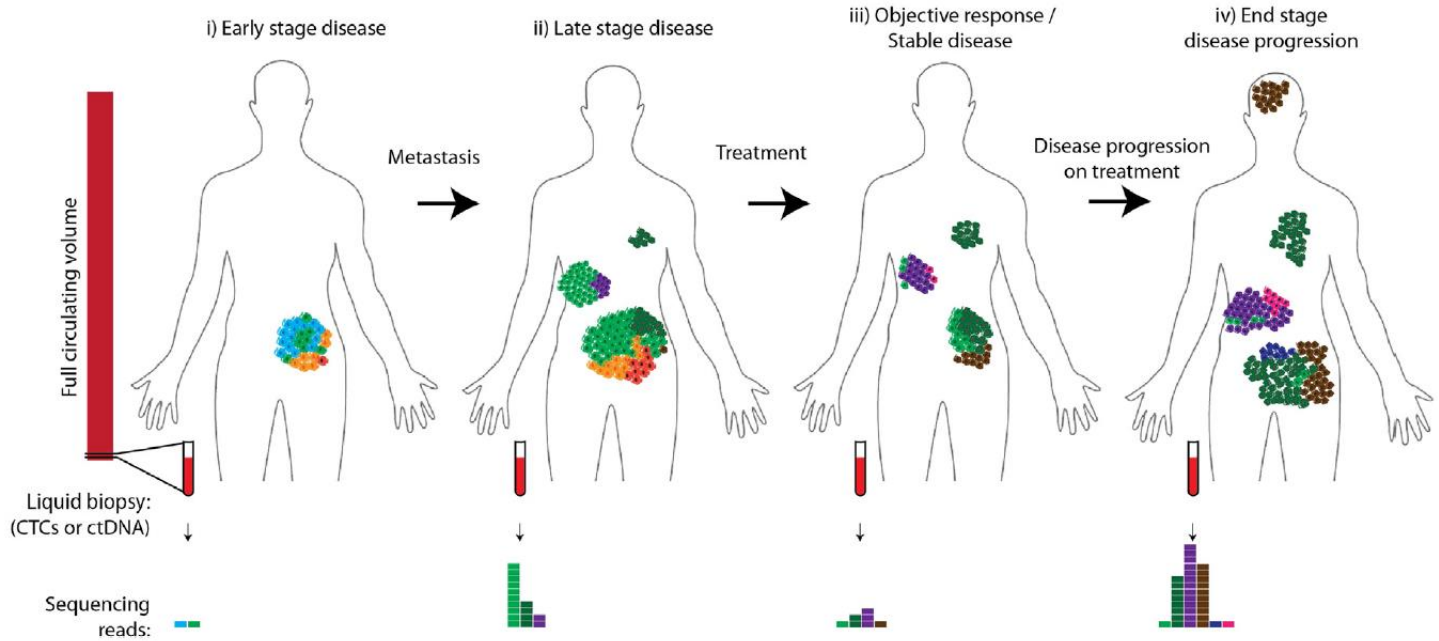
Table 1 Identification of genetic alterations associated with resistance to anti-EGFR antibodies in plasma samples

Patient ID	Therapy	Resistance	Plausible genetic mechanism	Oncogenic alteration in COSMIC database
MOLI-CRC02	Cetux + Irino	Primary	*NRAS* p.Q61L	YES
ONCGH-CRC01	Cetux + Irino	Primary	*ERBB2* amplification*	YES
MOLI-CRC16	Cetux + Folfiri	Primary	*FLT3* amplification*	YES
MOLI-CRC07	Cetux + Folfiri	Primary	N.I.	–
ONCGH-CRC11	Cetux + Folfiri	Primary	*ERBB2* amplification*	YES
MOLI-CRC06	Panit	Primary	*NRAS* p.G12D	YES
MOLI-CRC15	Panit + Folfox4	Primary	*ERBB2* amplification*	YES
ONCG-CRC13	Panit	Primary	*MAP2K1* p.K57N*	YES
ONCG-CRC41	Panit	Primary	N.I.	–
ONCGH-CRC06	Cetux + Irino	Primary	*ERBB2* amplification*	YES
			FLT3 amplification*	
ONCG-CRC67	Panit	Acquired	*MET* amplification*	YES
ONCG-CRC57	Panit	Acquired	*KRAS* p.G12A	YES
			KRAS p.G12D	
			KRAS p.G13D	
AOUP-CRC04	Panit + Folfoxiri	Acquired	*KRAS* p.Q61H	YES
MOLI-CRC04	Cetux + Folfiri	Acquired	*KRAS* p.Q61H	YES
AOUP-CRC05	Panit + Folfoxiri	Acquired	*KRAS* p.G12D	YES
ONCG-CRC69	Cetux; then Panit	Acquired	*KRAS* p.G12V	YES
			KRAS p.G13D	
AOUP-CRC01	Cetux + Folfoxiri	Acquired	*KRAS* p.Q61L	YES
MGH-CRC02	Cetux	Acquired	*KRAS* amplification	YES
AOUP-CRC06	Cetux + Folfoxiri	Acquired	*KRAS* p.Q61L	YES
AOUP-CRC03	Panit + Folfoxiri	Acquired	*KRAS* p.Q61L	YES
AOUP-CRC02	Panit + Folfoxiri	Acquired	*KRAS* p.Q61H	YES
ONCG-CRC70	Panit + Irino	Acquired	*KRAS* p.Q61H	YES
			EGFR p.S464L	
			EGFR p.G465R	
ONCG-CRC71	Panit	Acquired	*KRAS* p.Q61H	YES
ONCG-CRC72	Panit	Acquired	*MET* amplification*	YES
			EGFR p.G465R	
			EGFR p.G465E	
MOLI-CRC12	Cetux + Folfox4	Acquired	N.I.	–
ONCG-CRC73	Panit	Acquired	*MET* amplification*	YES

Bettegowda Sci Transl Med 2014

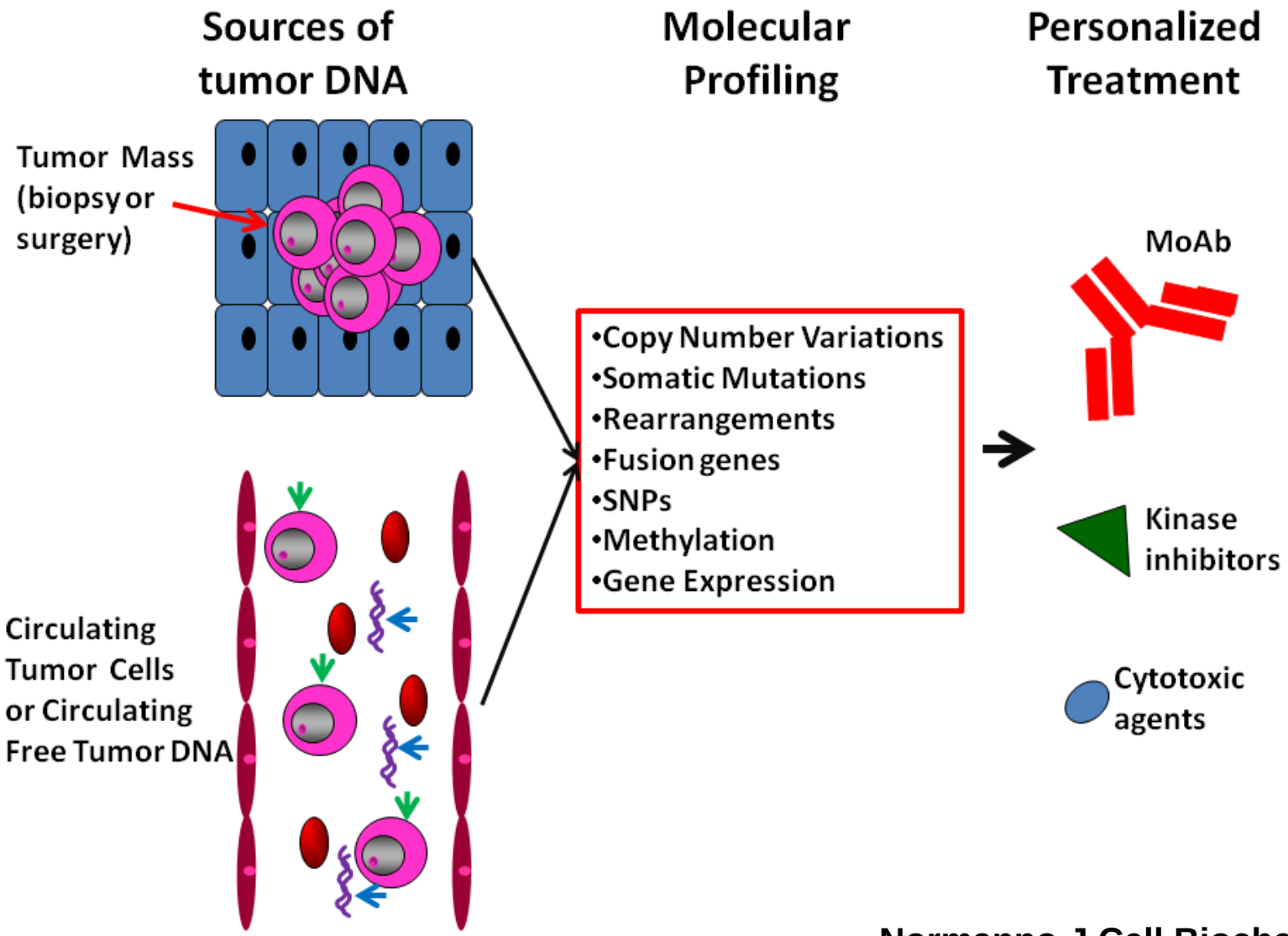
Siravegna Nat Med 2015

Liquid biopsy can represent temporal and spatial heterogeneity in cancer progression



Burrell & Swanton Mol Oncol 2014

The future of biomarker testing



Normanno J Cell Biochem 2013

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