ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI TUMORI

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Tracking clonal evolution and adapting therapy in metastatic colorectal cancer

Nicola Normanno

Tumor heterogenity and therapeutic strategies in mCRC

- **The concept of inter- and intra-tumor heterogeneity**
- **Intra-tumor heterogeneity in mCRC**
- **Clonal evolution and resistance to EGFR targeting therapies**

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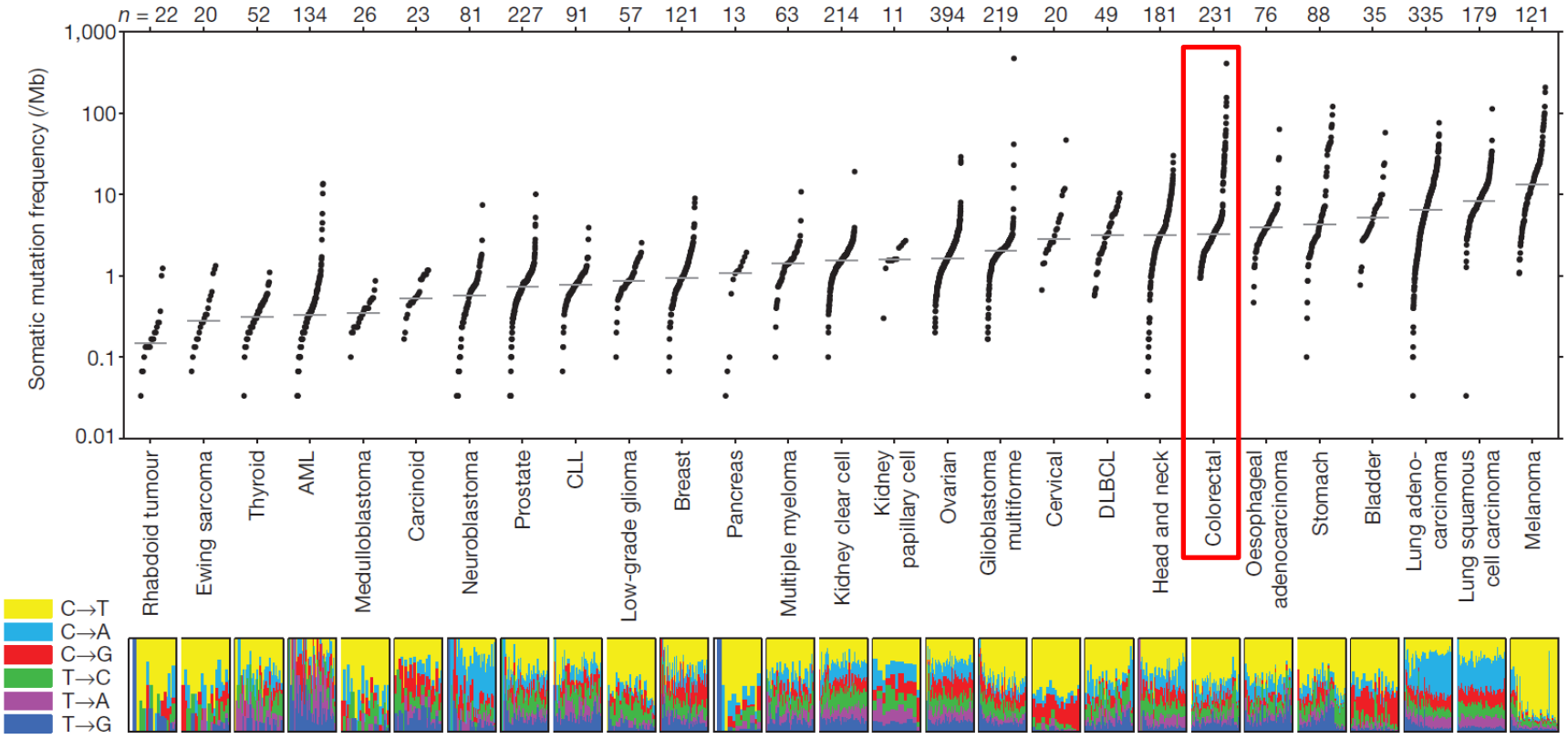
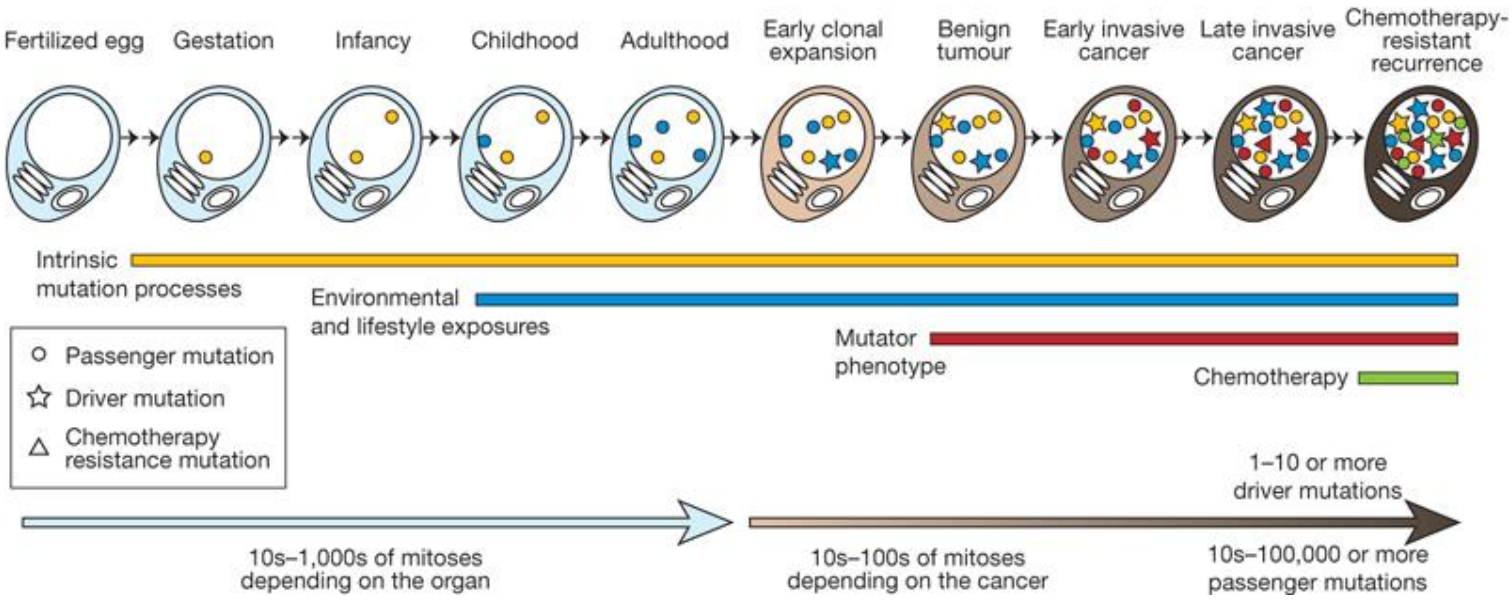
Somatic mutation frequencies in cancer



Lawrence Nature 2013

The cancer genome

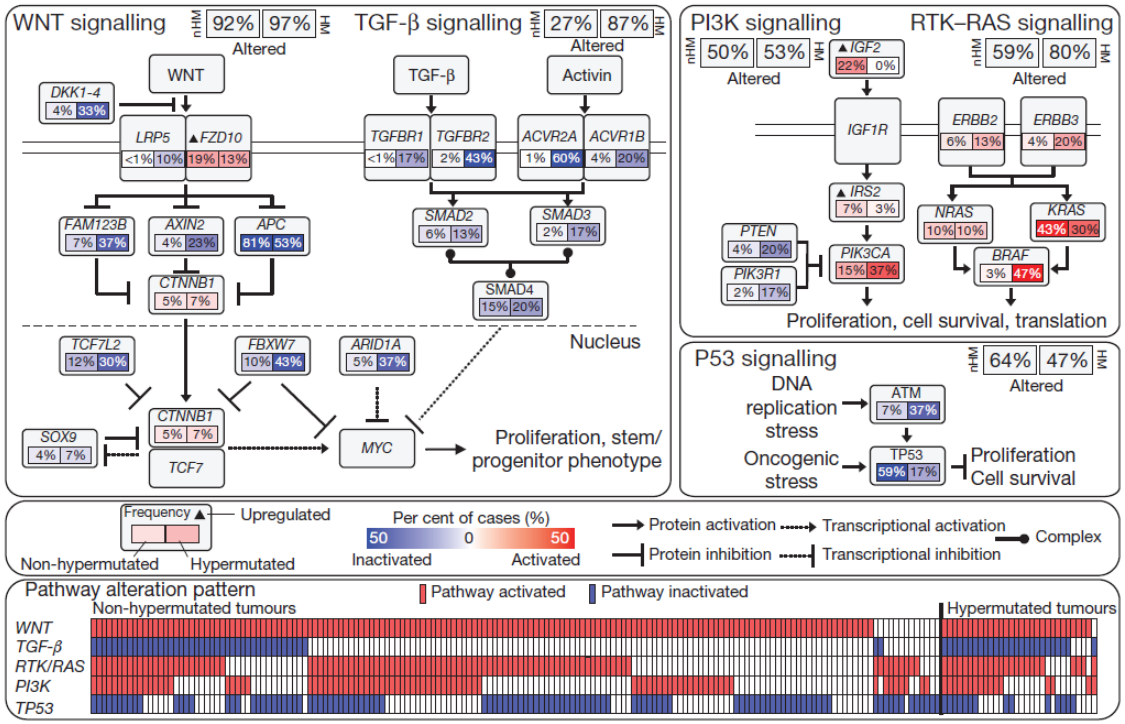


A **driver mutation** is causally implicated in oncogenesis. It has conferred growth advantage on the cancer cell and has been positively selected in the microenvironment of the tissue in which the cancer arises.

A **passenger mutation** has not been selected, has not conferred clonal growth advantage and has therefore not contributed to cancer development. Mutations without functional consequences often occur during cell division and will be carried along in the clonal expansion that follows.

MR Stratton *et al. Nature* **458**, 719-724 (2009) doi:10.1038/nature07943

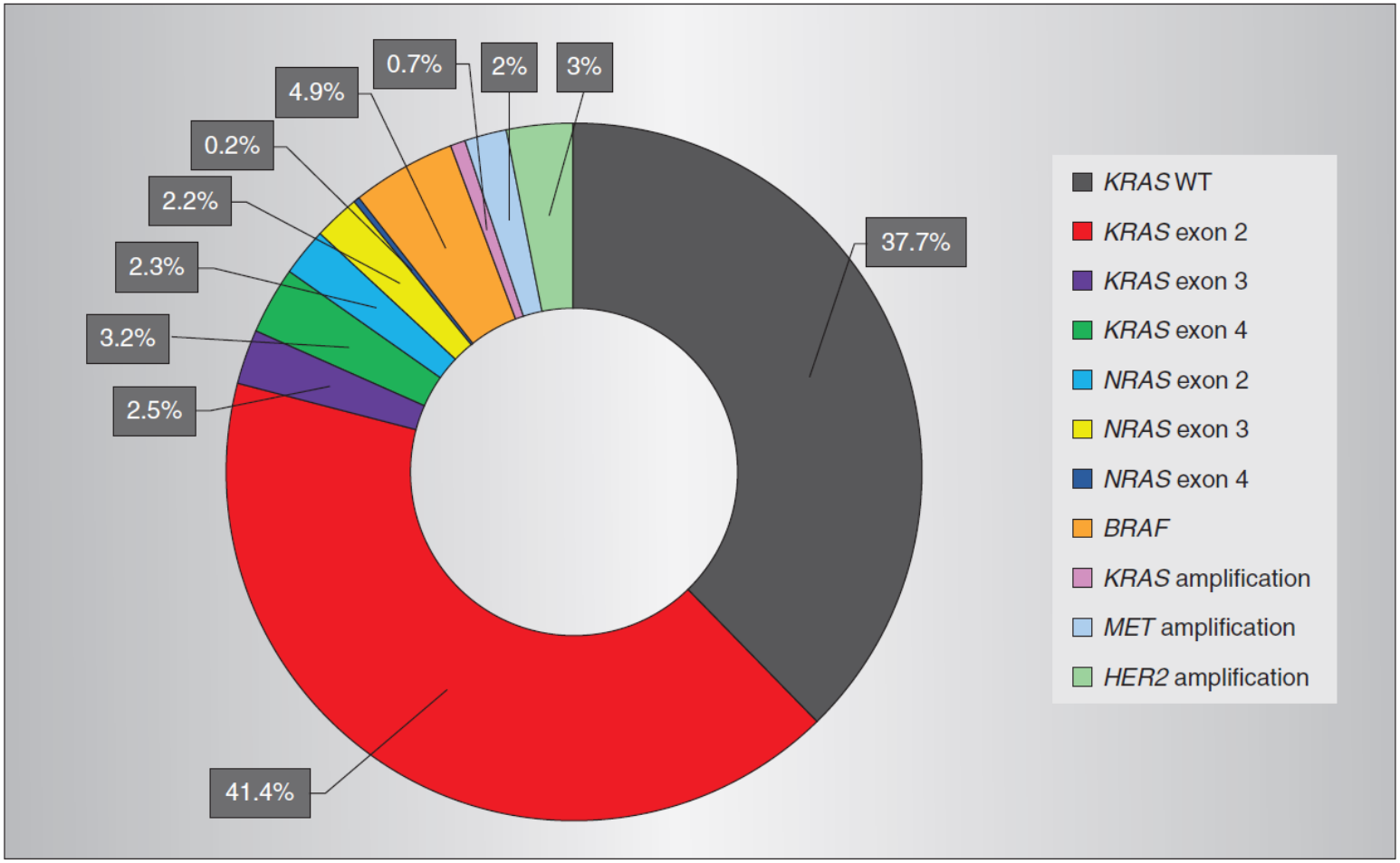
Genetic changes leading to deregulation of signalling pathways in CRC



- **Driver mutations can occur in different signaling pathways in CRC**
- **Some driver mutations are mutually exclusive, other can coexist in the same tumor cells**

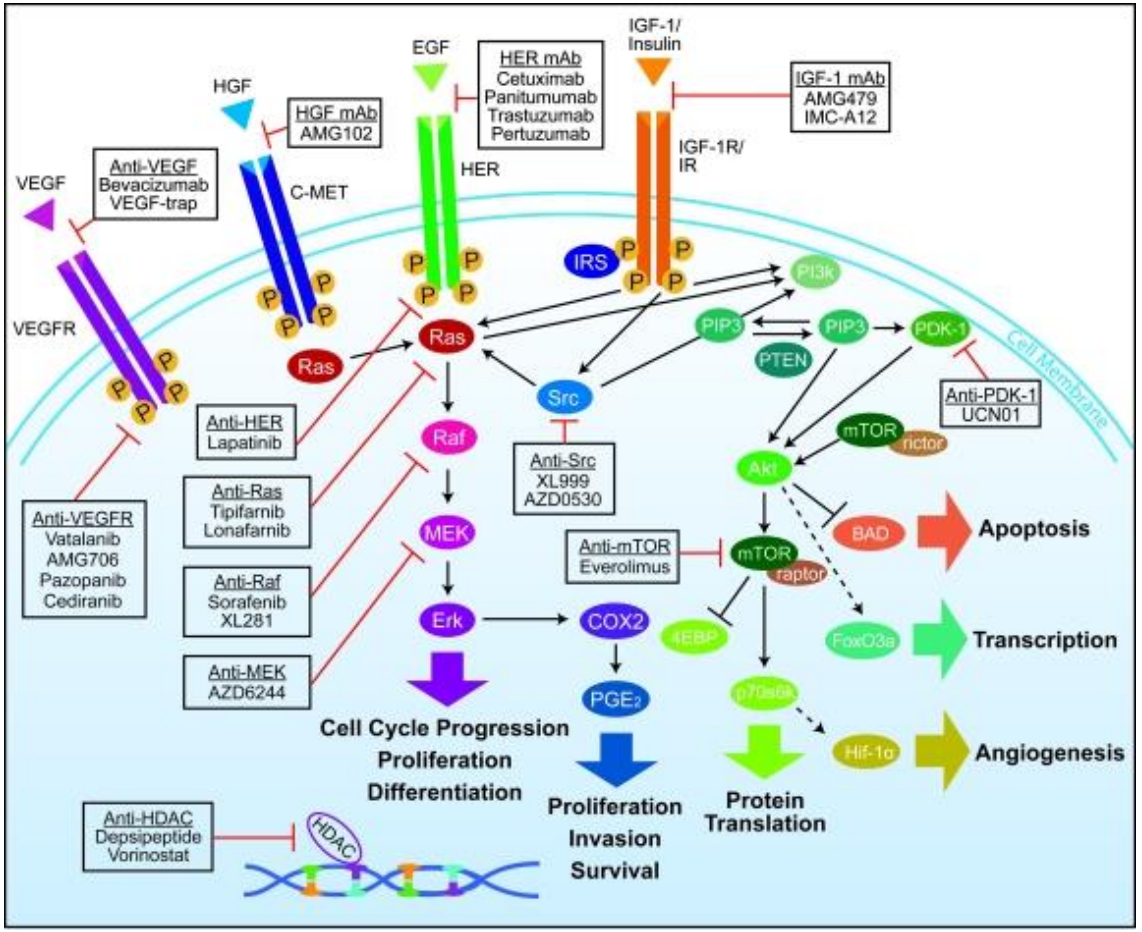
TCGA Nature 2012

Genetic alterations associated with de novo resistance to anti-EGFR therapies in mCRC



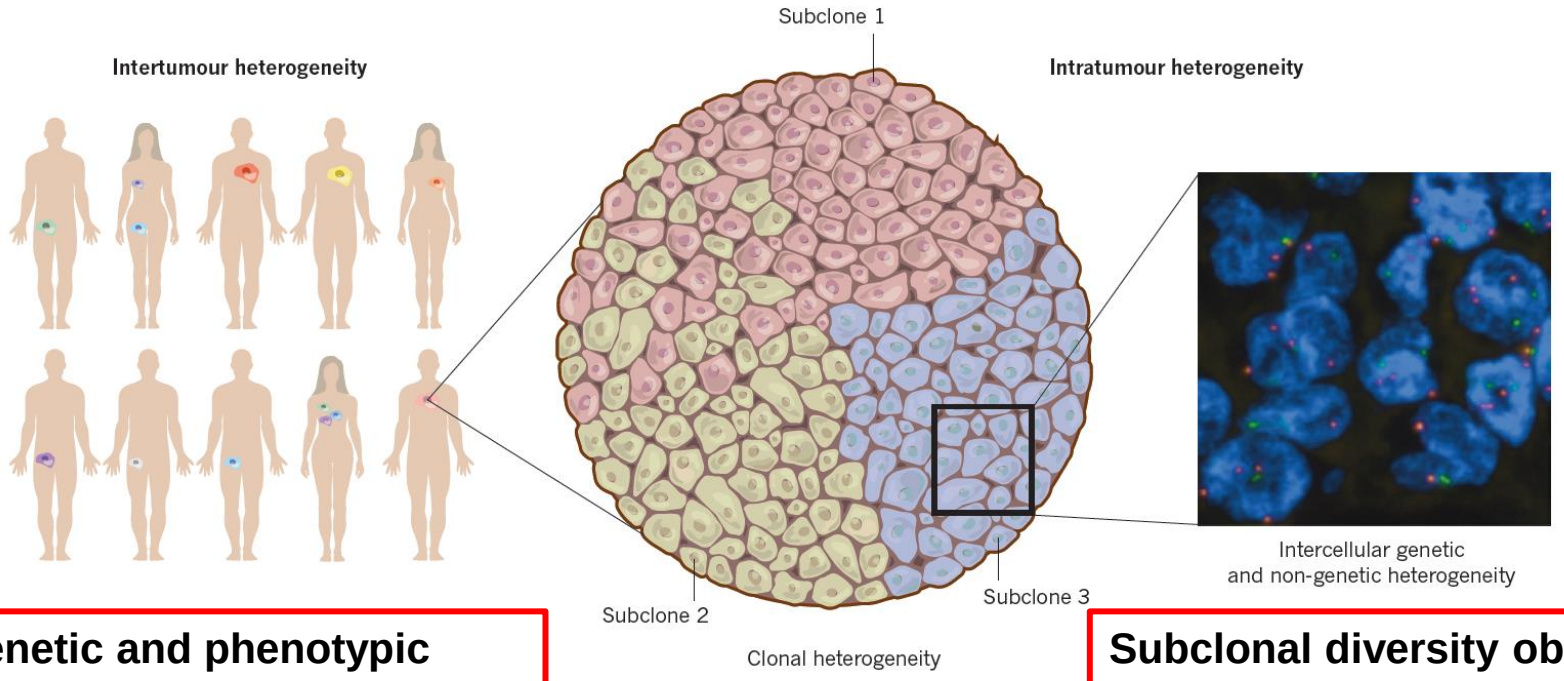
Misale Cancer Discov 2014

Novel targeted agents in CRC



The efficacy of targeted therapy depends on

TUMOR HETEROGENEITY

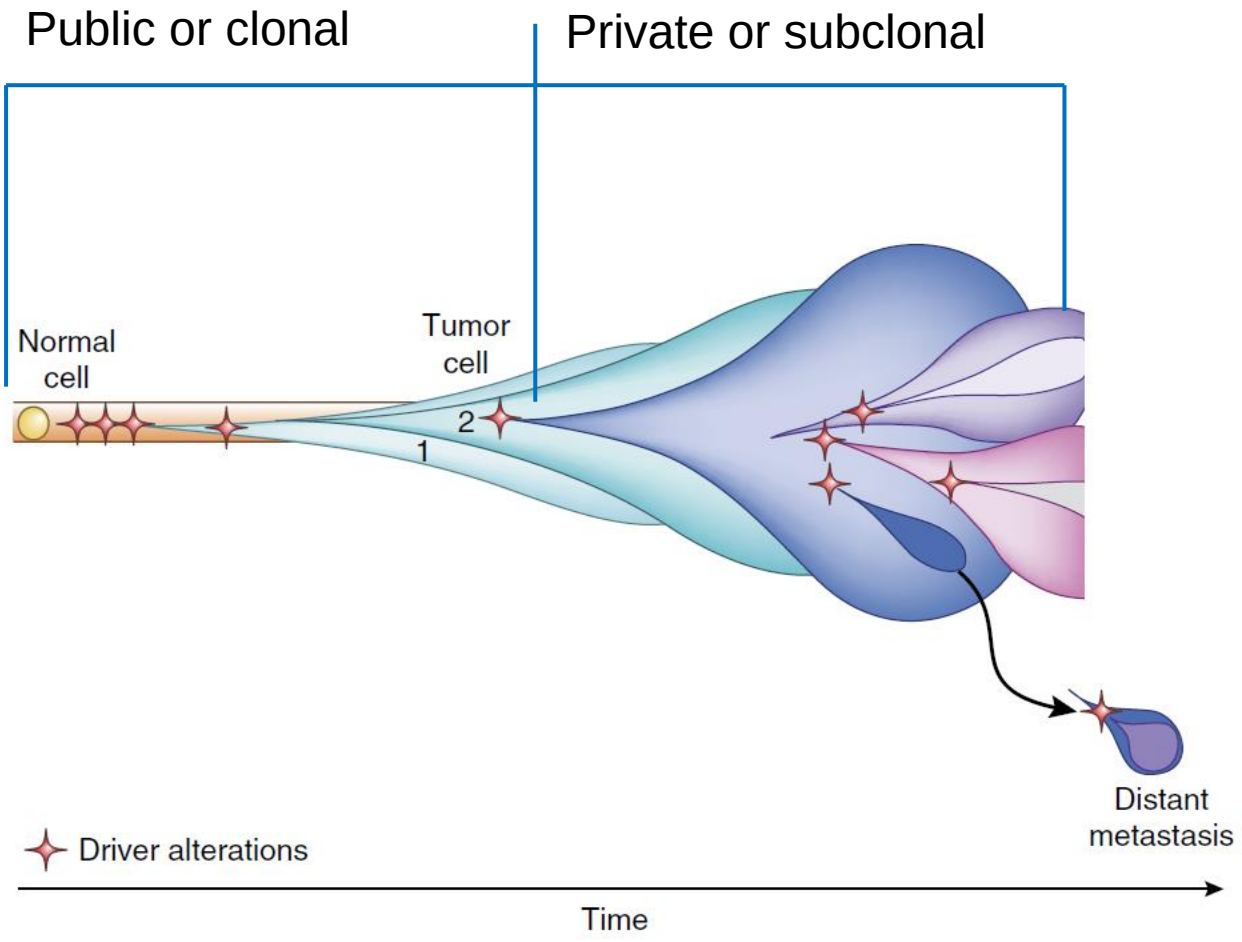


Genetic and phenotypic variation observed between tumors of different tissue and cell types, as well as between individuals with the same tumor type

Subclonal diversity observed within a tumor (tumors are formed of different clones with different genetic and molecular features)

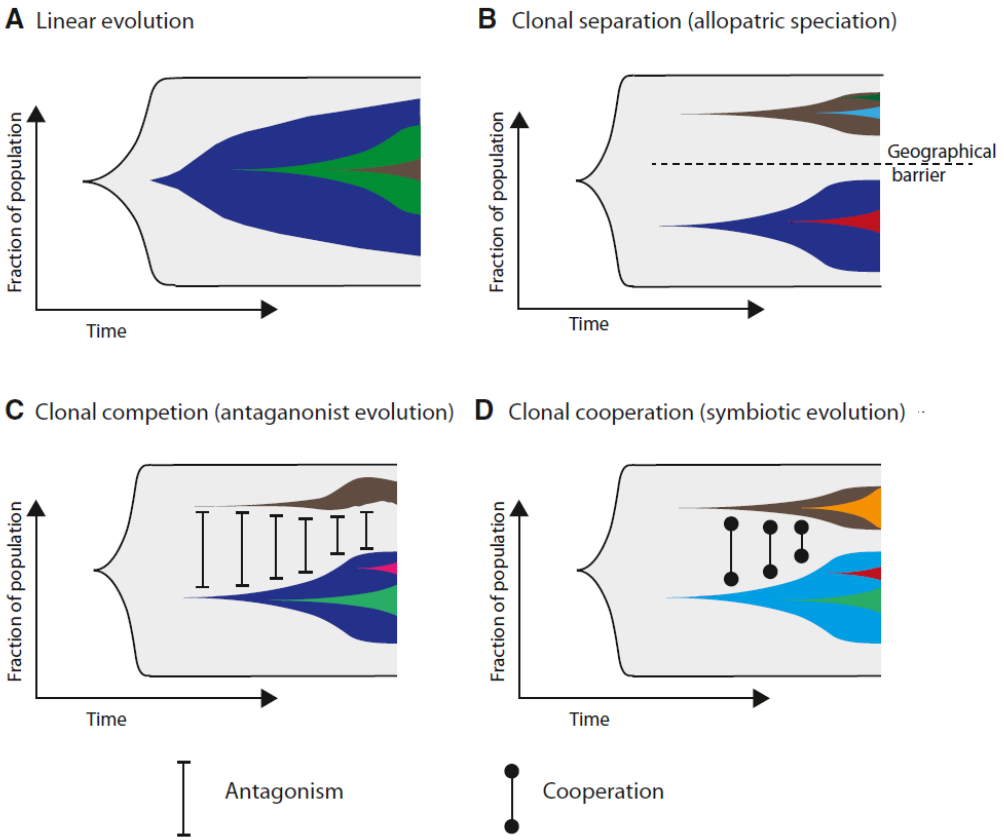
Burrell Nature 2013

The clonality of tumor evolution



Alizadeh Nat Med 2015

Modes of Tumor Evolution

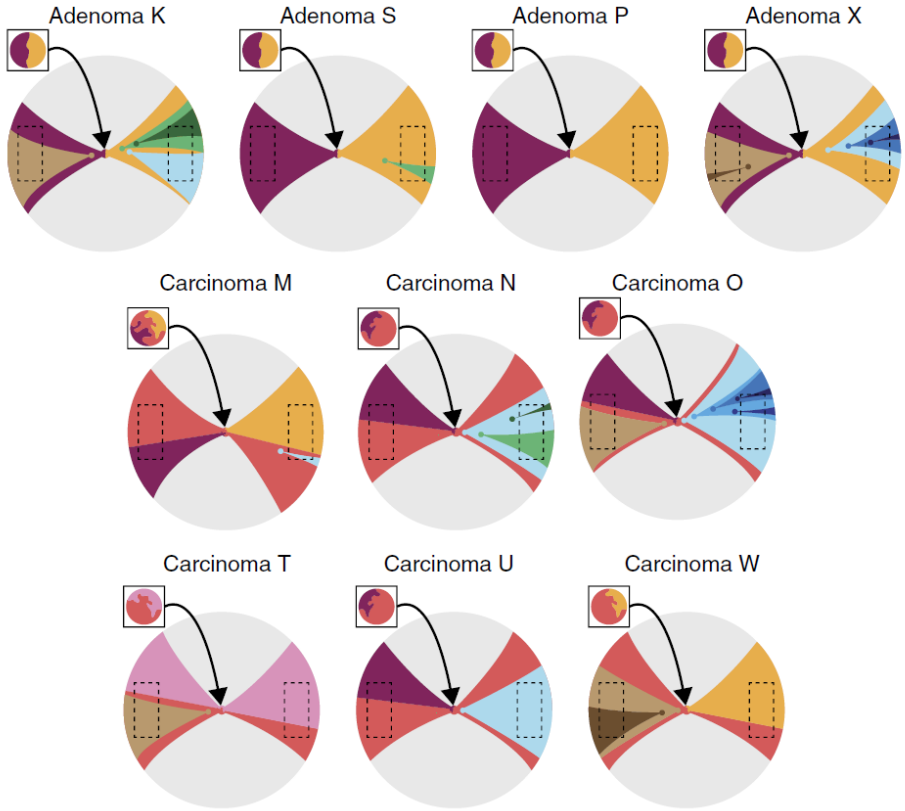


Tumor evolution is the result of genetic instability leading to accumulation of mutations that might provide growth advantage, and microenvironmental factors leading to clonal selection

McGranahan & Swanton Cancer Cell 2015

A Big Bang model of human colorectal tumor growth

- **Tumors grow predominantly as a single expansion producing numerous intermixed subclones that are not subject to stringent selection and where both public (clonal) and most detectable private (subclonal) alterations arise early during growth**
- **Most detectable intratumor heterogeneity (ITH) originates from early private alterations and not from later clonal expansions**

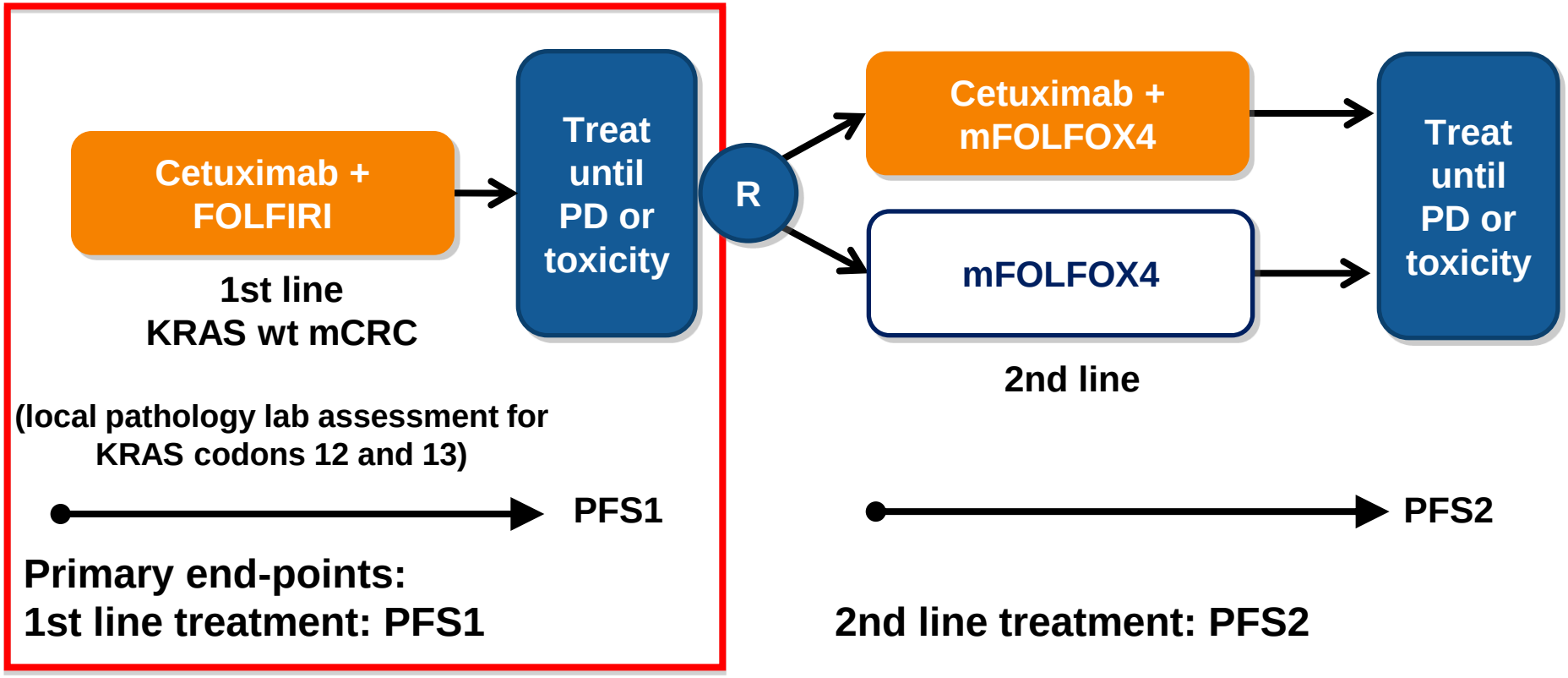


Sottoriva Nat Genetics 2015

Tumor heterogenity and therapeutic strategies in mCRC

- The concept of inter- and intra-tumor heterogeneity
- **Intra-tumor heterogeneity in mCRC**
- Clonal evolution and resistance to EGFR targeting therapies

CAPRI GOIM trial



- From July 2009 to June 2013: 340 patients enrolled for 1st line
- As of 31 August 2013, 151 pts have progressed and were randomized to ongoing 2nd line therapy (cetuximab + mFOLFOX4, n=76; mFOLFOX4, n=75)

Ciardiello, Normanno et al Ann Oncol 2014

22 multiple gene mutation analysis (Ion AmpliSeq™ Colon and Lung Cancer Panel)

- **Ion AmpliSeq™ technology enables rapid sequencing of hundreds of mutations with low allele frequency using 10 ng of DNA per reaction**
- **Ion AmpliSeq™ Colon and Lung Cancer Panel:**
  - **Covers known (> 500) and novel mutations in 91 hotspot regions in 22 genes relevant to colon and lung tumourigenesis:**
    - ***KRAS, EGFR, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MEK1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBXW7, FGFR3, NOTCH1, ERBB4, FGFR1, FGFR2***
  - **Clinical sensitivity 2% on hot spot mutations, 4% on other variants; average coverage > 1000 x**
  - **Developed and validated by the OncoNetwork Consortium**
    - **European collaborative effort of 8 Academic Cancer Translational Research Institutions**

Tops, Normanno N, et al. BMC Cancer 2015

22 multiple gene mutation analysis in mCRC treated with FOLFIRI + cetuximab

Gene	Number of cases (>2%) with mutations, n (%) (N=182 analyzed)	
TP53	72* (39.5%)	
KRAS	45^ (24.7%)	30 at codon 12 or 13 (16.5%); 16 at other (8.8%)
PIK3CA	24 § (13.2%)	16 at exon 9 (8.8%); 10 at exon 20 (5.5%)
BRAF	15 (8.2%)	10 at codon 600 (5.5%); 5 at other (2.7%)
NRAS	13 (7.1%)	
MET	7 (3.8%)	
FBXW7	9 (4.9%)	

*7 cases with double TP53 mutation; ^1 case with double KRAS mutation; § 2 cases with double PIK3CA mutation

- Mutations in genes EGFR, CTNNB1, FGFR3, SMAD4 occurred in 2 cases each (1.1%); mutations in genes ERBB2, FGFR2, PTEN occurred in 1 case each (0.55%)

Ciardiello, Normanno et al Ann Oncol 2014

First line efficacy data: KRAS/NRAS wt vs mt

Clinical activity of FOLFIRI + cetuximab	22 multiple gene mutation analysis (n=182)	KRAS/NRAS wt (n=124)	KRAS/NRAS mt (n=58)
Complete response, %	12/182 (6.6%)	8/124 (6.4%)	4/58 (6.9%)
Partial response, %	92/182 (50.5%)	69/124 (55.6%)	23/58 (39.7%)
Stable disease, %	61/182 (33.5%)	35/124 (28.2%)	26/58 (44.8%)
Progressive disease, %	17/182 (9.3%)	12/124 (9.7%)	5/58 (8.6%)
ORR, % (95% CI)	104/182 (57.1%) (52.0-66.4%)	77/124 (62.0%) (55.5-74.6%)	27/58 (46.6%) (39.9-57.5%)
Median PFS, months (95% CI)	9.8 (8.7–11.5)	11.1 (9.2–12.8)	8.9 (7.4–9.6)

Ciardiello, Normanno et al Ann Oncol 2014

First line efficacy data: KRAS/NRAS/BRAF/PIK3CA wt vs mt

Clinical activity of FOLFIRI + cetuximab	22 multiple gene mutation analysis (n=182)	KRAS/RAS/ BRAF/PIK3CA wt (n=104)	KRAS/NRAS/ BRAF/PIK3CA mt (n=78)
Complete response, %	12/182 (6.6%)	8/104 (7.7%)	4/78 (5.1%)
Partial response, %	92/182 (50.5%)	59/104 (56.7%)	33/78 (42.3%)
Stable disease, %	61/182 (33.5%)	28/104 (26.9%)	33/78 (42.3%)
Progressive disease, %	17/182 (9.3%)	9/104 (8.6%)	8/78 (10.3%)
ORR, % (95% CI)	104/182 (57.1%) (52.0-66.4%)	67/104 (64.4%) (58.2-76.6%)	37/78 (47.4%) (39.0-61.2%)
Median PFS, months (95% CI)	9.8 (8.7–11.5)	11.3 (9.4–13.2)	7.7 (5.4–9.4)

Ciardiello, Normanno et al Ann Oncol 2014

Gene mutations were not mutually exclusive

Genes with >10 mutated cases	Total mutated cases, n (N=182 analyzed)	Cases with multiple mutations, n	Types of concomitant mutations (n)
KRAS	45	30*	TP53 (18), PIK3CA ex9 (9), PIK3CA ex20 (5), FBXW7 (5), BRAF (4), MET (1), EGFR (1), SMAD4 (1), FGFR3 (1), ERBB2 (1), PTEN (1)
NRAS	13	5	TP53 (3), PIK3CA ex9 (1), MET (1)
BRAF	15	12†	TP53 (9), KRAS (4), PIK3CA ex20 (3), FBXW7 (2), PIK3CA ex9 (1), SMAD4 (1), FGFR3 (1), FGFR2 (1)
PIK3CA ex9	16	14‡	KRAS (9), TP53 (8), PIK3CA ex 20 (2), NRAS (1), BRAF (1), MET (1), EGFR (1), ERBB2 (1)
PIK3CA ex20	10	7‡	KRAS (5), BRAF (3), TP53 (3), PIK3CA ex9 (2), FBXW7 (2), ERBB2 (1)
TP53	72	36	KRAS (18), BRAF (9), PIK3CA ex9 (8), FBXW7 (5), NRAS (3), PIK3CA ex20 (3), MET (1), EGFR (1), SMAD4 (1), CTNNB1 (1), FGFR3 (1), ERBB2 (1)

*11 cases with KRAS mutated tumors had >2 concomitant mutations (maximum 5 mutations)
†5 cases with BRAF mutated tumors had >2 concomitant mutations (maximum 4 mutations)
‡9 cases with PIK3CA mutated tumors had >2 concomitant mutations (maximum 4 mutations)

Ciardiello, Normanno et al Ann Oncol 2014

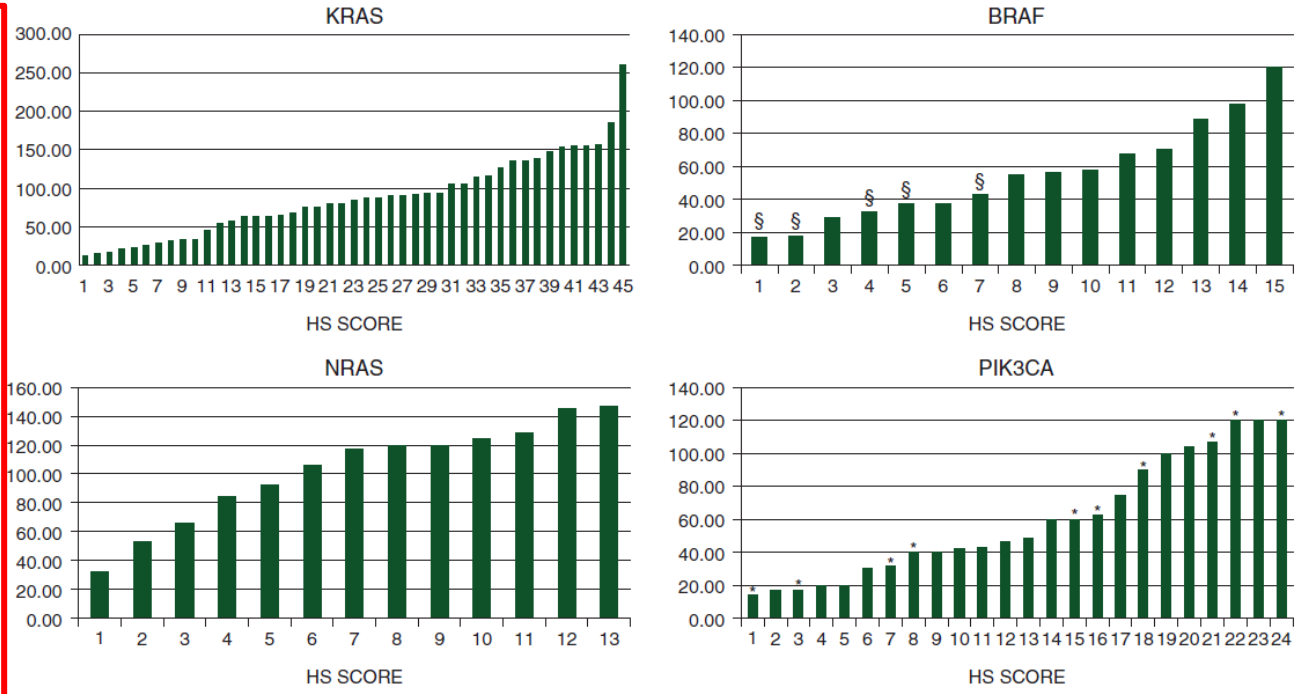
22 multiple gene mutation analysis in mCRC treated with FOLFIRI + cetuximab

Mutated cases (N=182 analyzed)	KRAS	NRAS	BRAF	PIK3CA ex9	PIK3CA ex20	MET	EGFR	SMAD4	CTNNB1	FGFR3	PTEN	ERBB2	FGFR2	FBXW7	TP53
KRAS (30/45)*			4	9	5	1	1	1		1	1	1		5	18
NRAS (5/13)*				1		1									3
BRAF (12/15)*	4			1	3			1		1			1	2	9
PIK3CA ex9 (14/16)*	9	1	1		2	1	1					1			8
PIK3CA ex20 (7/10)*	5		3	2								1		2	3
MET (4/7)*	1	1		1											1
EGFR (1/2)*	1			1											1
SMAD4 (2/2)*	1		1										1		1
CTNNB1 (2/2)*															1
FGFR3 (2/2)*	1		1												1
PTEN (1/1)*	1														
ERBB2 (1/1)*	1			1	1										1
FGFR2 (1/1)*			1					1							
FBXW7 (9/9)*	5		2		2										5
TP53 (36/72)*	18	3	9	8	3	1	1	1	1	1		1		5	

*cases with multiple mutations/total mutated cases

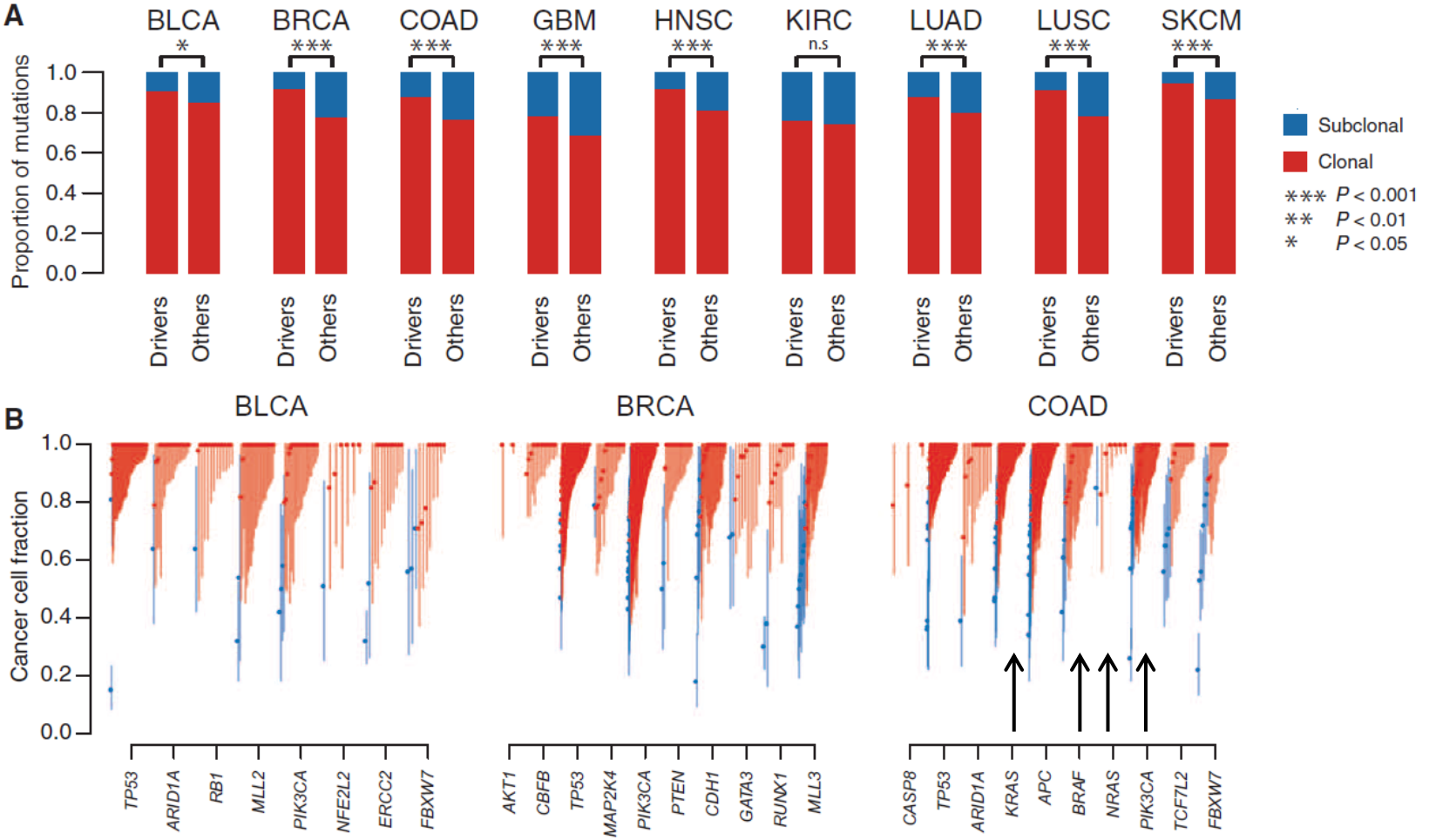
Heterogeneity Score (HS) in mCRC patients enrolled in the CAPRI trial

- 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

Clonal and subclonal mutations in different cancer types



McGranahan Sci Transl Med 2015

Heterogeneity Score (HS) among different mutant genes

	N.	Range	Mean	Median
KRAS	45	12-260	87,12	84,44
NRAS	13	35,5-146,67	102,77	117,14
BRAF	15	17,14-120	54,82	54,29
PIK3CA	24	14,29-120	59,47	47,33

Normanno et al Ann Oncol 2015

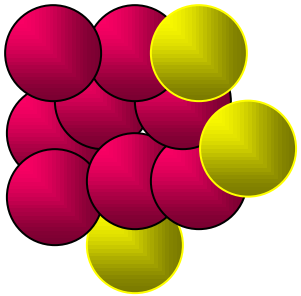
KRAS Heterogeneity Score (HS) and efficacy of treatment in the CAPRI trial

	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

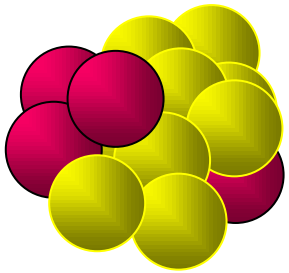
PD: Progressive Disease; SD: Stable Disease; PR: Partial Response;
CR: Complete Response

Normanno et al Ann Oncol 2015

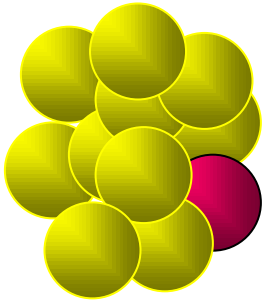
Resistance to anti-EGFR agents in CRC



Highly resistant: No RR, No Survival



Resistant: >RR, No Survival



Highly sensitive: >RR, >Survival

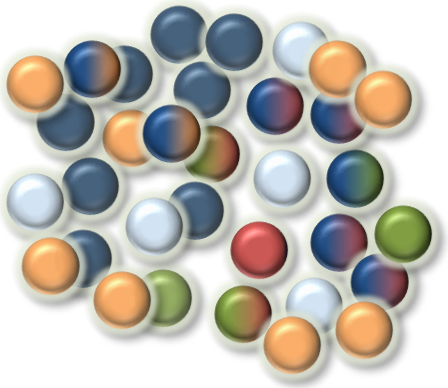
RAS Mutant **RAS WT**

Genotype of low (<33) KRAS HS tumors

ID Patient	KRAS HS Score	Additional Mutations
4553	12,00	NONE
4516	14,29	PIK3CA ex 20, BRAF V600E, FBXW7
4137	17,14	PIK3CA ex 9 and 20, ERBB2, TP53
3964	20,33	NONE
4139	22,86	PIK3CA ex9, TP53 (2 different mutations)
4141	25,71	PIK3CA ex9, BRAF ex11, TP53
4123	28,57	NONE
4124	30,00	PIK3CA ex9, TP53
4374	32,00	FGFR3
4166	32,00	TP53

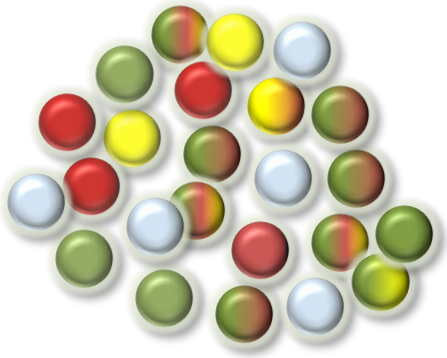
Heterogeneity Score (HS) and efficacy of treatment in the CAPRI trial

Case 177 (SD, PFS 5,9 mo)
70% tumor cells
HS 14,29 KRAS G13D
HS 17,14 PIK3CA ex20
HS 54,29 BRAF V600E
HS FBXW7 R465H 48,6



Normal
KRAS
BRAF
PIK3CA
FBXW7

Case 118 (PR, PFS 3,9 mo)
70% tumor cells
HS 22,86 KRAS G12D
HS 74,29 PIK3CA ex9
HS 57,14 TP53



Normal
KRAS
TP53
PIK3CA

Tumor heterogenity and therapeutic strategies in mCRC

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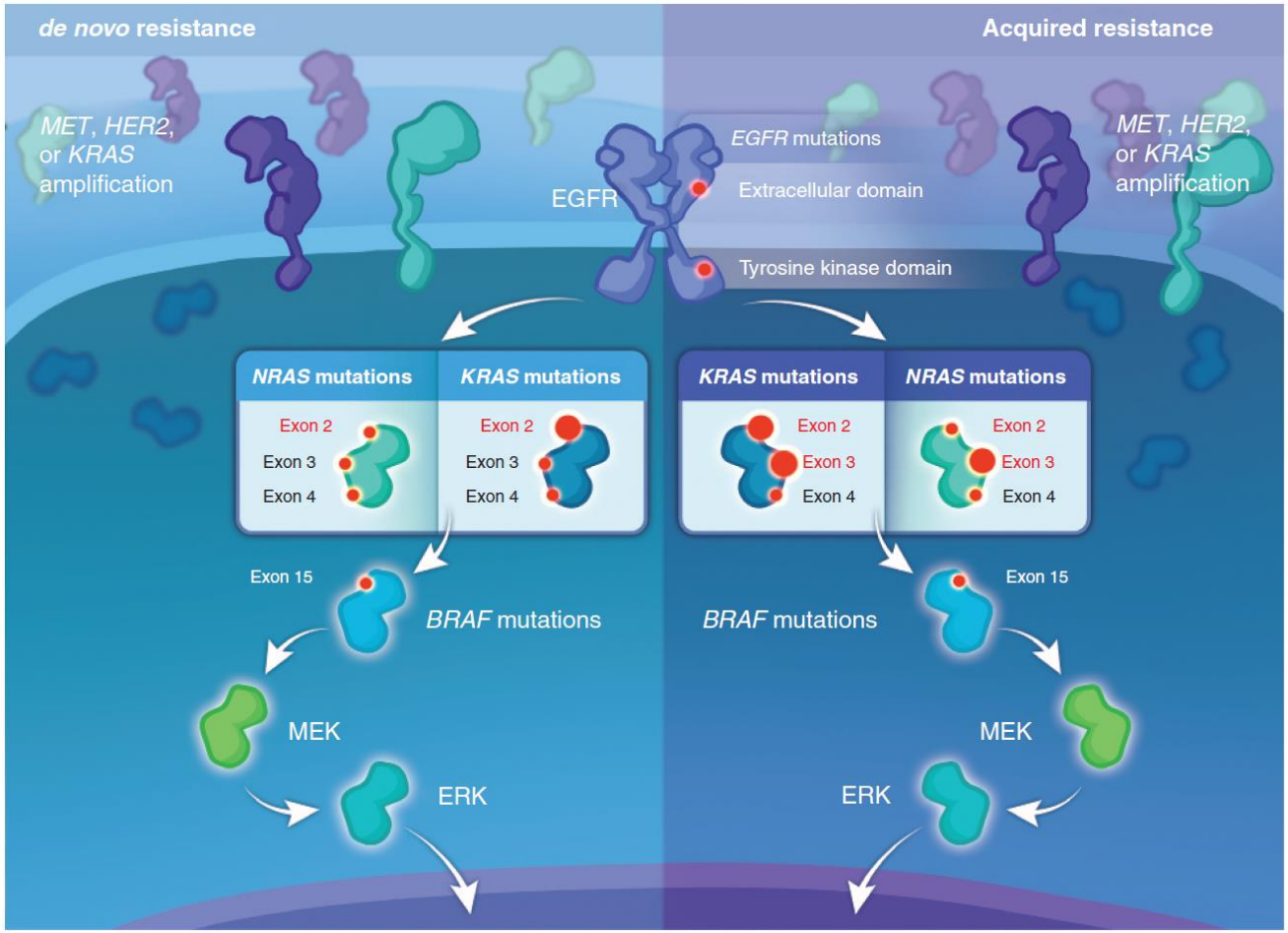
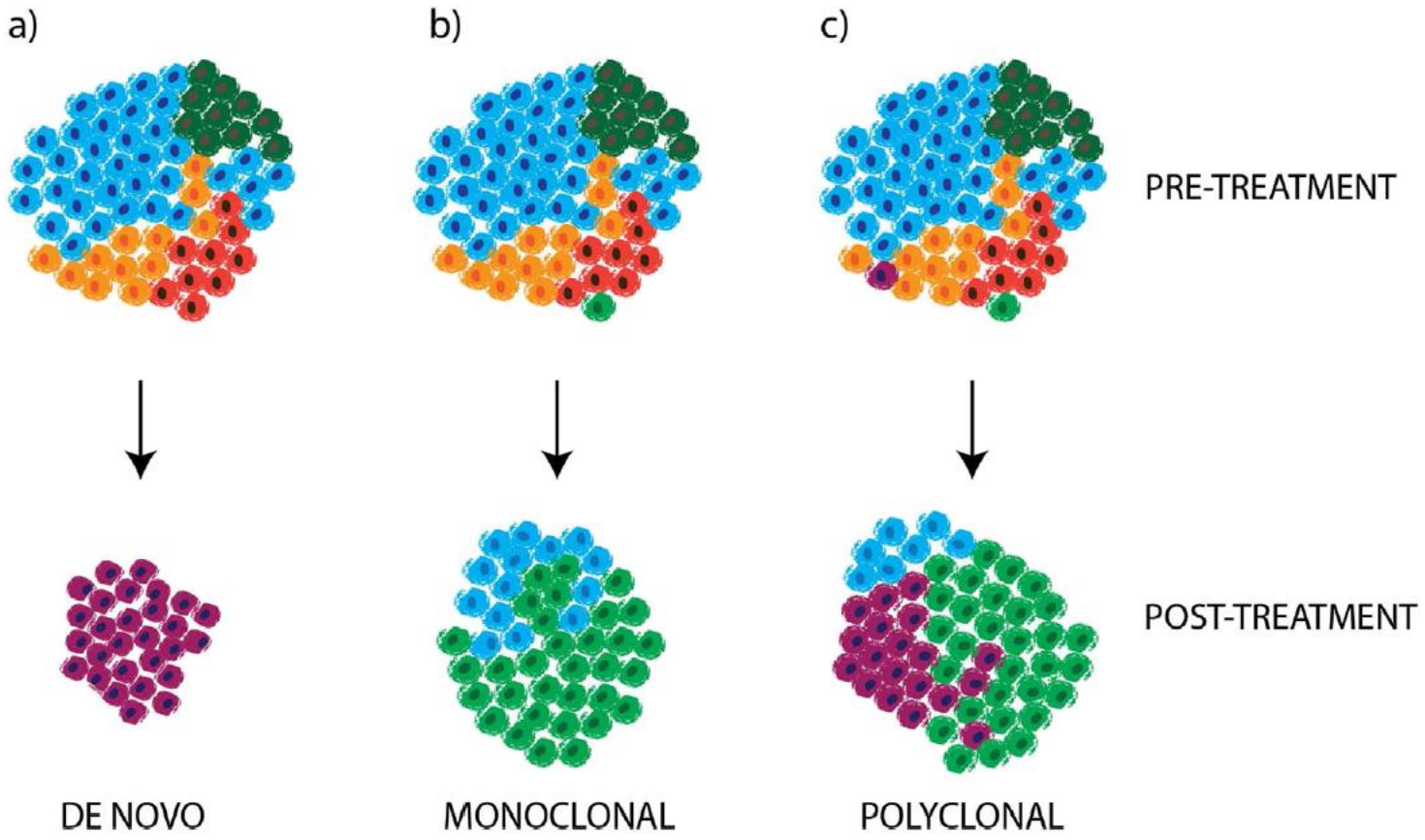
Mechanisms of primary and secondary resistance to anti-EGFR therapies in mCRC



Misale Cancer Discov 2014

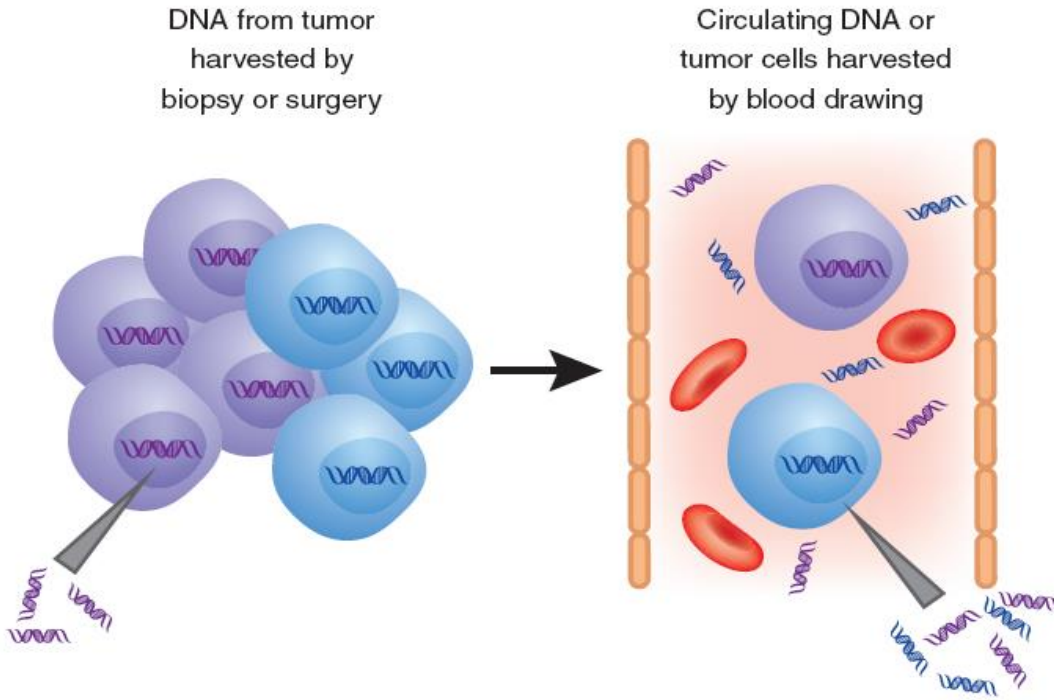
Clonal Evolution and Drug Resistance



Burrell & Swanton Mol Oncol 2014

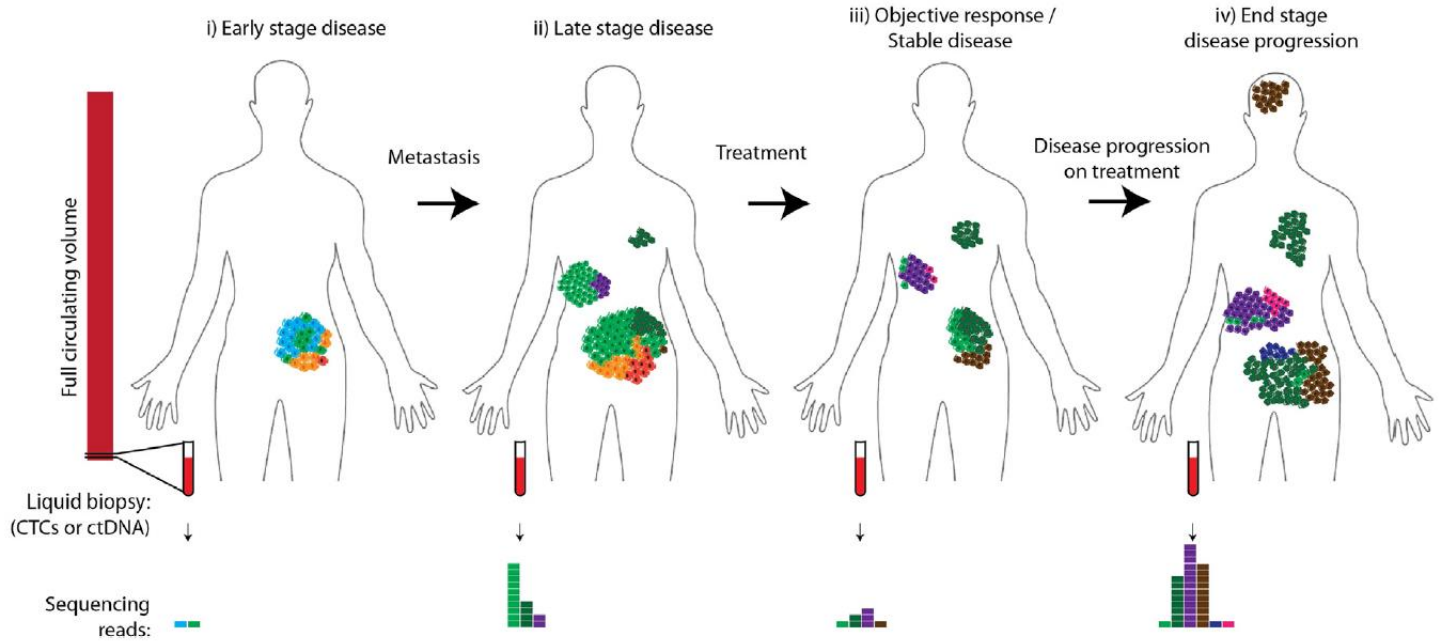
Different sources of tumor DNA

With the term liquid biopsy we refer to the possibility to perform tumor molecular profiling by using tumor-derived nucleic acids (DNA, RNA and miRNA) that can be isolated from the peripheral blood of cancer patients



Fleischacker & Schmidt Nat Med 2008

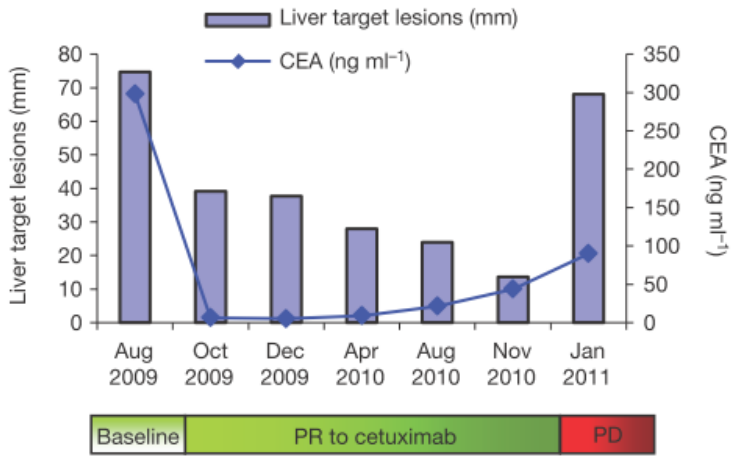
Liquid biopsy can represent temporal and spatial heterogeneity in cancer progression

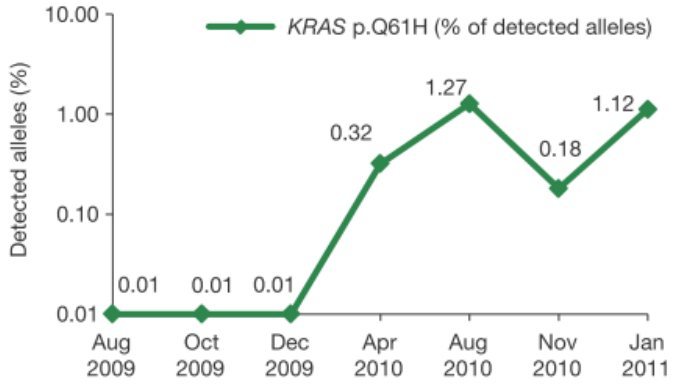


Burrell & Swanton Mol Oncol 2014

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

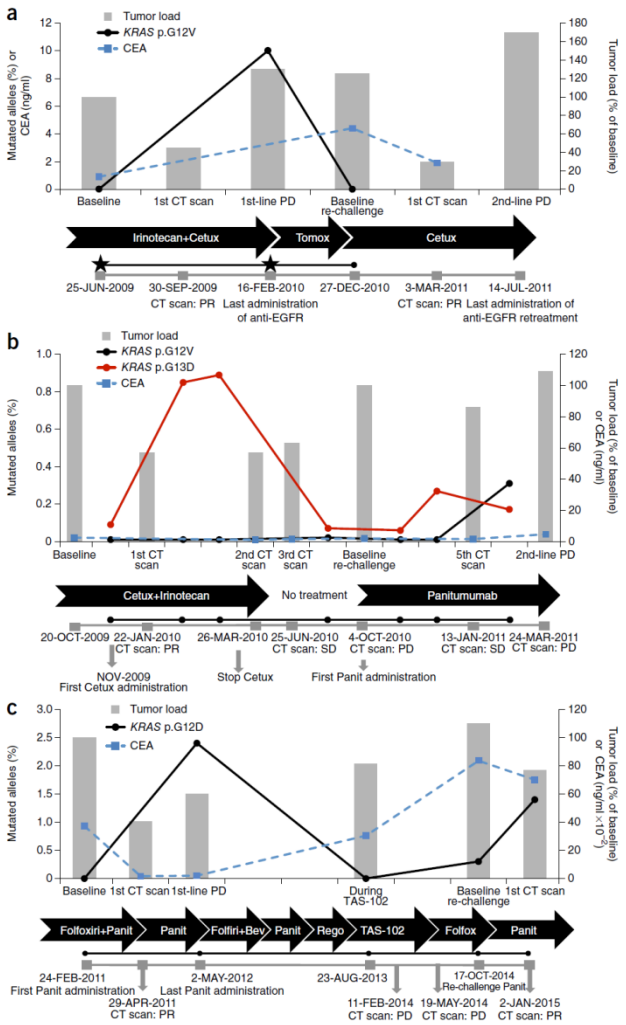
Publication	Method	(K)RAS mutations at progression	
		n/N	%
Diaz et al. Nature 2012*[1]	PCR Ligation/ BEAMing	9/24	37.5
Misale et al. Nature 2012*[2]	NGS/BEAMing	2/3	66.6
Morelli et al. Ann Oncol 2015*[3]	BEAMing	27/62	43.5
Bettegowda et al. Sci Transl Med 2014[4]	PCR Ligation/ BEAMing/ SafeSeqS	23/24	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

*only KRAS

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

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

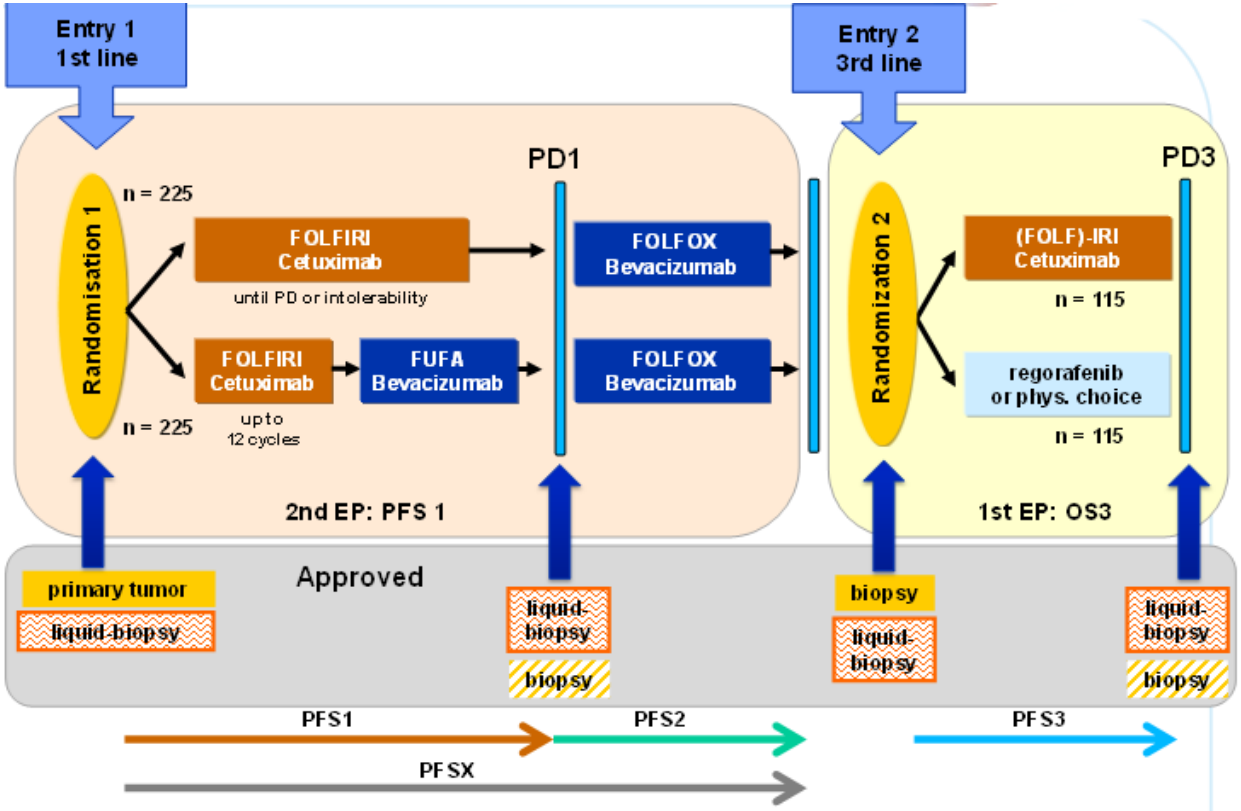
Changes in RAS+ DNA following treatment with EGFR MoAbs



- The levels of RAS mutant DNA in the peripheral blood increase before clinical progression and rapidly drop following suspension of anti-EGFR MoAbs
- Early detection of RAS mutation in blood might suggest resistance and induce to change therapy
- Drop in RAS mutation levels might indicate that patients will respond to re-challenging with EGFR MoAbs

Siravegna Nat Med 2015

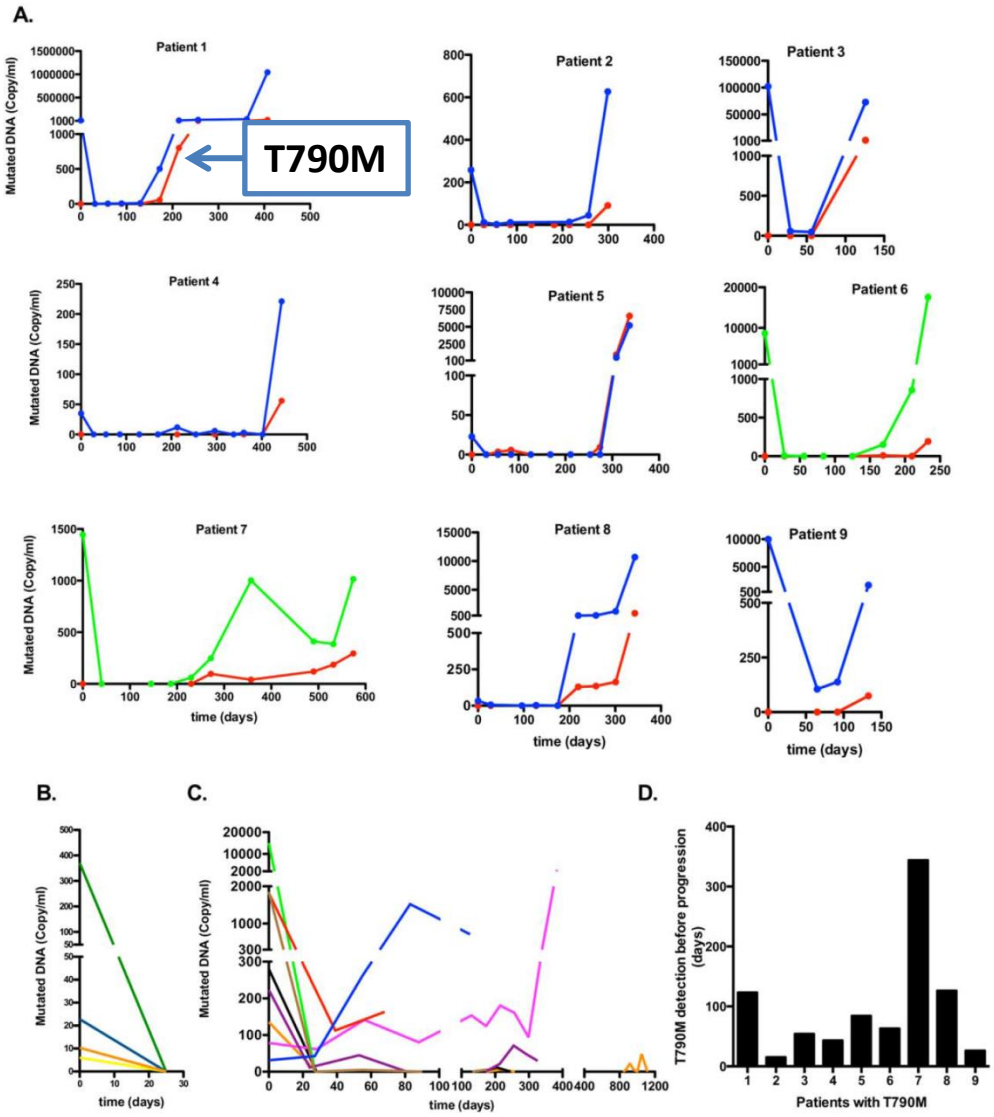
Ongoing study of cetuximab rechallenge
FIRE-4: Phase II randomized trial (Germany)



- **Estimated completion date: January 2022**
- **Primary endpoint is mOS of cetuximab rechallenge**
- **Prospective investigation of parameters of sensitivity and emergence of resistance**

- Available at 1. http://www.aio-portal.de/index.php/studien.html; 2. Erbitux SmPC June 2014

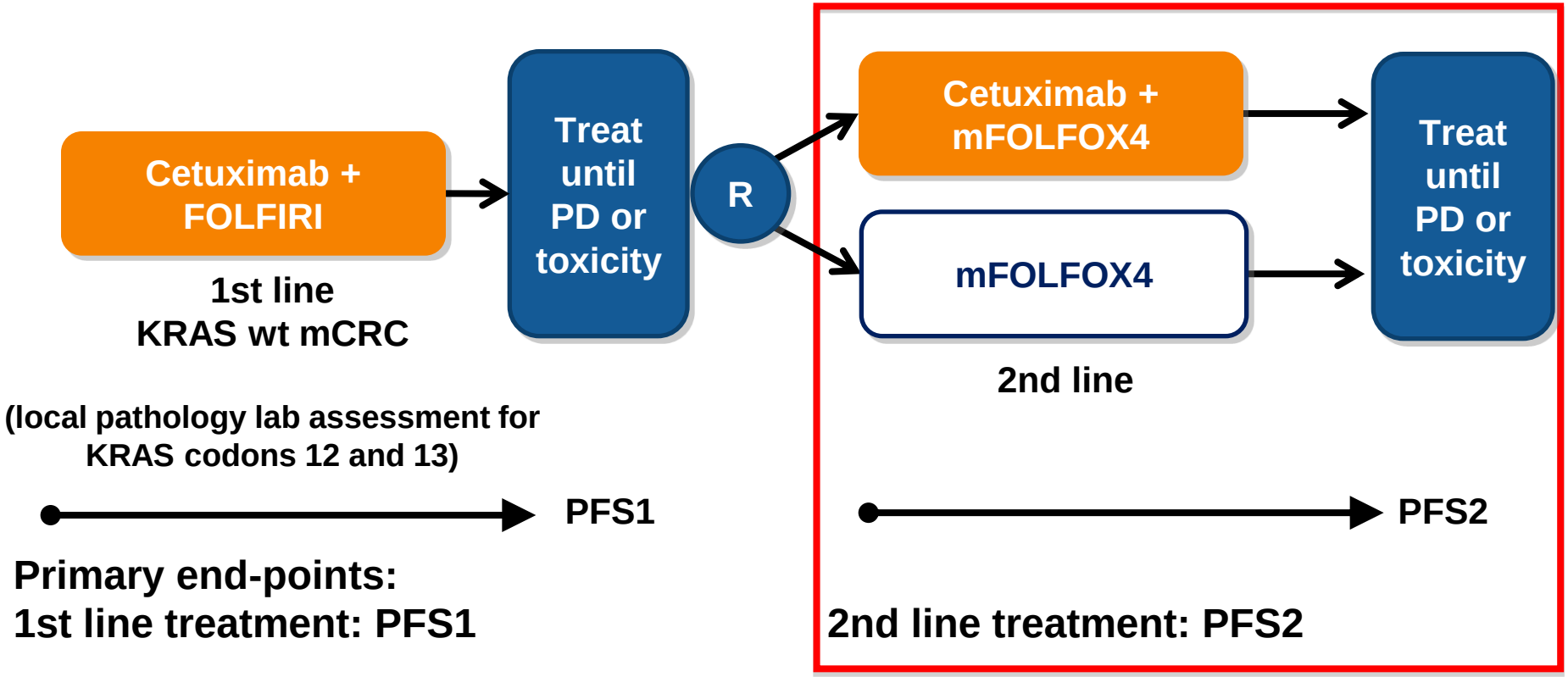
Plasma EGFR mutations during treatment with EGFR TKIs



In clinical practice, plasma testing for the T790M should be performed at the same time when tissue biopsy is indicated (i.e. at clinical progression of the disease)

Sorensen Cancer 2014

CAPRI GOIM trial



- From July 2009 to June 2013: 340 patients enrolled for 1st line
- As of 31 August 2013, 151 pts have progressed and were randomized to ongoing 2nd line therapy (cetuximab + mFOLFOX4, n=76; mFOLFOX4, n=75)

Ciardiello, Normanno et al Ann Oncol 2014

CAPRI GOIM trial: 2nd line cetuximab* + FOLFOX vs FOLFOX alone[1]

Population (n)	Cetuximab + FOLFOX vs FOLFOX, HR (95% CI), p value		
	ORR, %	Median PFS from 2nd line baseline, months	Median OS from 2nd line baseline, months
ITT KRAS (exon 2) wt (n=153)	22 vs 13 n/a NR	6.4 vs 4.5 0.81 (0.58–1.12) p=0.19	17.6 vs 14.0 0.86 (0.61–1.20) p=0.41
RAS wt (n=75)[§]	**26 vs 17 n/a NR**	**6.8 vs 5.5 0.80 (0.50–1.29) p=0.4**	**21.4 vs 19.8 0.78 (0.46–1.32) p=0.35**
RAS/BRAF/PIK3CA wt (n=66)[†]	**29 vs 9 n/a NR**	**6.9 vs 5.3 0.56 (0.33–0.94) p=0.025**	**23.7 vs 19.8 0.57 (0.32–1.02) p=0.056**
RAS/BRAF/PIK3CA mt (n=51)[†‡]	0 vs 22 n/a NR	2.7 vs 4.4 1.70 (0.94–3.05) p=0.07	11.6 vs 14.0 1.60 (0.89–2.96) p=0.10

*Cetuximab is not indicated for rechallenge therapy[2]
Cetuximab is approved in patients with RAS wt mCRC.[2] Cetuximab is not indicated for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown[2]
ITT, intention to treat; NR, not reported

1. Ciardiello F, et al. WCGC 2015 (Abstract No. LBA-09);
2. Erbitux SmPC June 2014

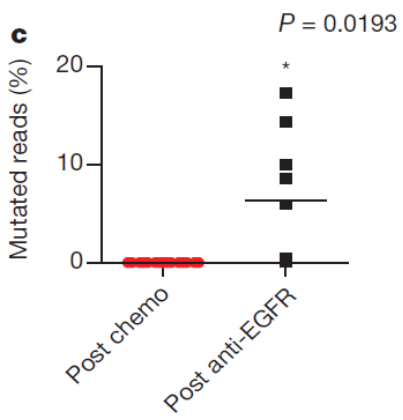
Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in CRC

a

	Chemotherapy-resistant tumours *KRAS* mutational status		
Patient ID	Mutation	Percentage	Reads*/events†
2	WT*	0%	0/30,000
7	WT*	0%	0/11,262
8	WT†	0.01%	5/76,200
9	WT†	0%	0/89,760
10	WT†	0%	0/34,500
11	WT†	0%	0/190,600
13	WT*	0%	0/18,277
14	WT*	0%	0/27,942
15	WT*	0%	0/43,279
16	WT*	0%	0/41,693
17	WT*	0%	0/30,174
18	WT*	0%	0/16,400
19	WT*	0%	0/29,578
21	WT*	0%	0/18,277

b

	Anti-EGFR-resistant tumours *KRAS* mutational status		
Patient ID	Mutation	Percentage	Reads*/events†
1	WT*	0%	0/12,123
2	G13D*	10%	859/8,556
4	G13D*	5.9%	461/7,764
5	G13D*	14.3%	1,037/7,247
6	G13D*	8.6%	651/7,577
7	WT*	0%	0/17,142
8	Q61H†	17.3%	5,960/190,200
9	G12D† G13D†	0.04% 0.44%	17/40,200 117/26,400
10	WT†	0%	0/50,300
11	WT† (KRAS amplified)	0%	0/30,400



Misale Nature 2012

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

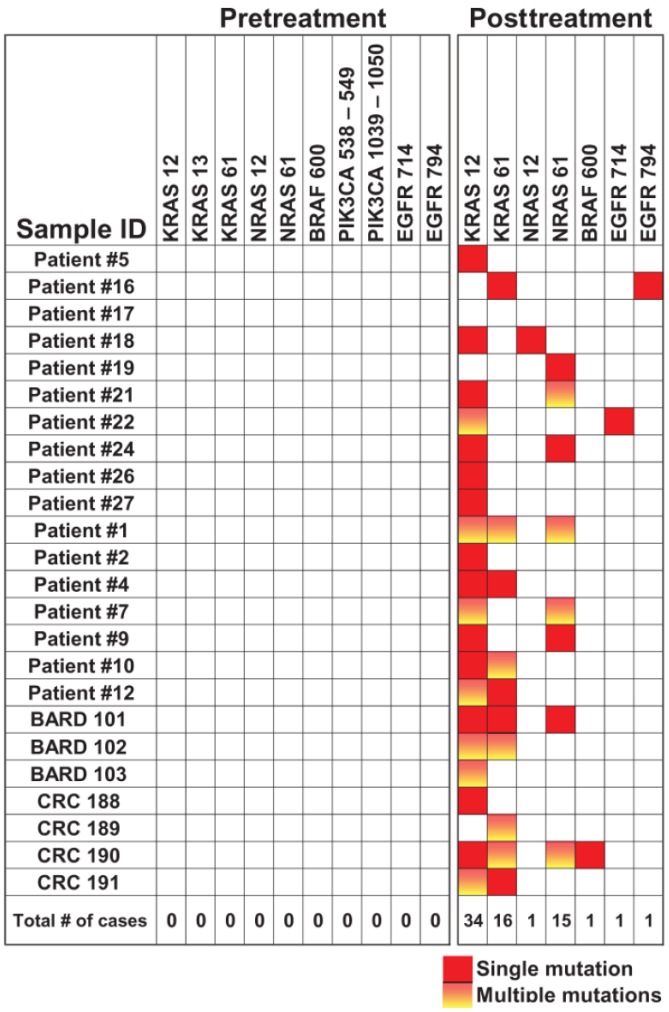


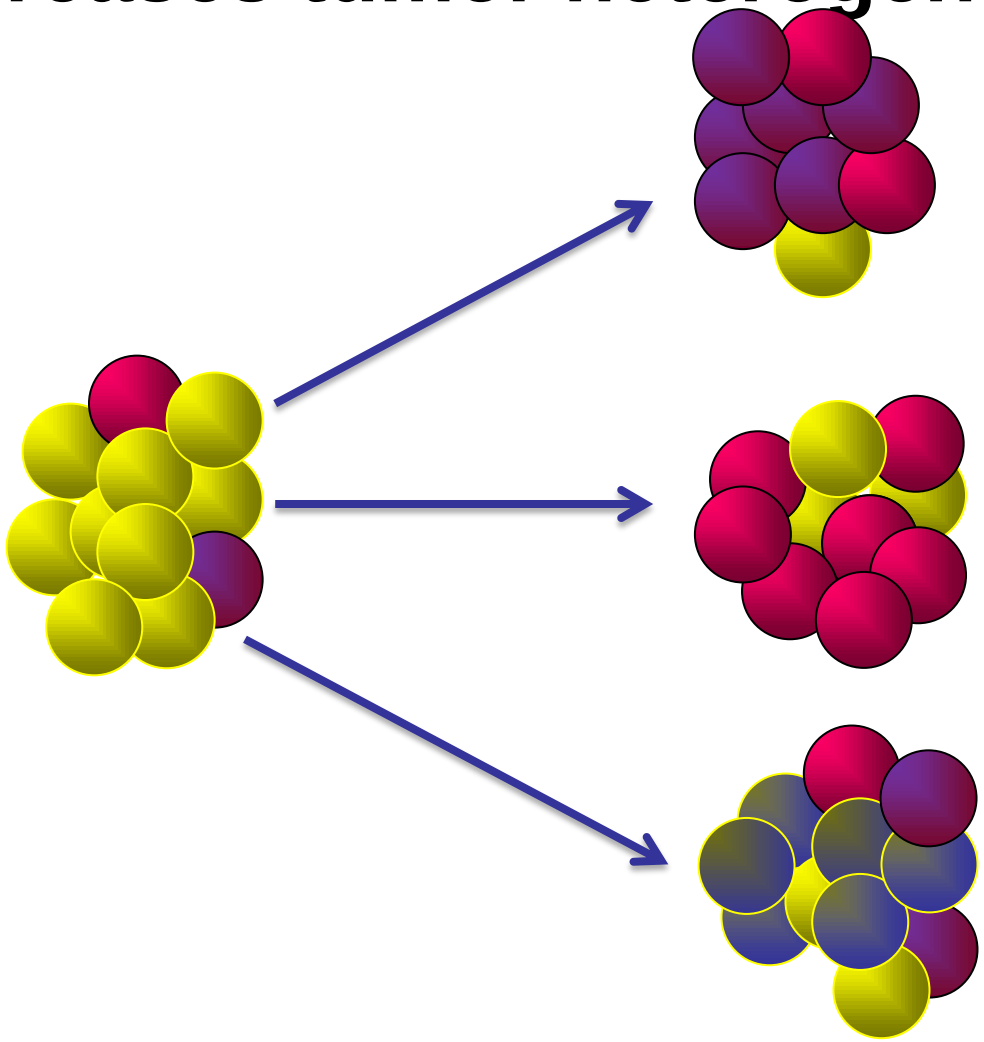
Table 1 Identification of genetic alterations associated with resistance to anti-EGFR antibodies in plasma samples

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

Resistance to anti-EGFR agents in CRC increases tumor heterogeneity



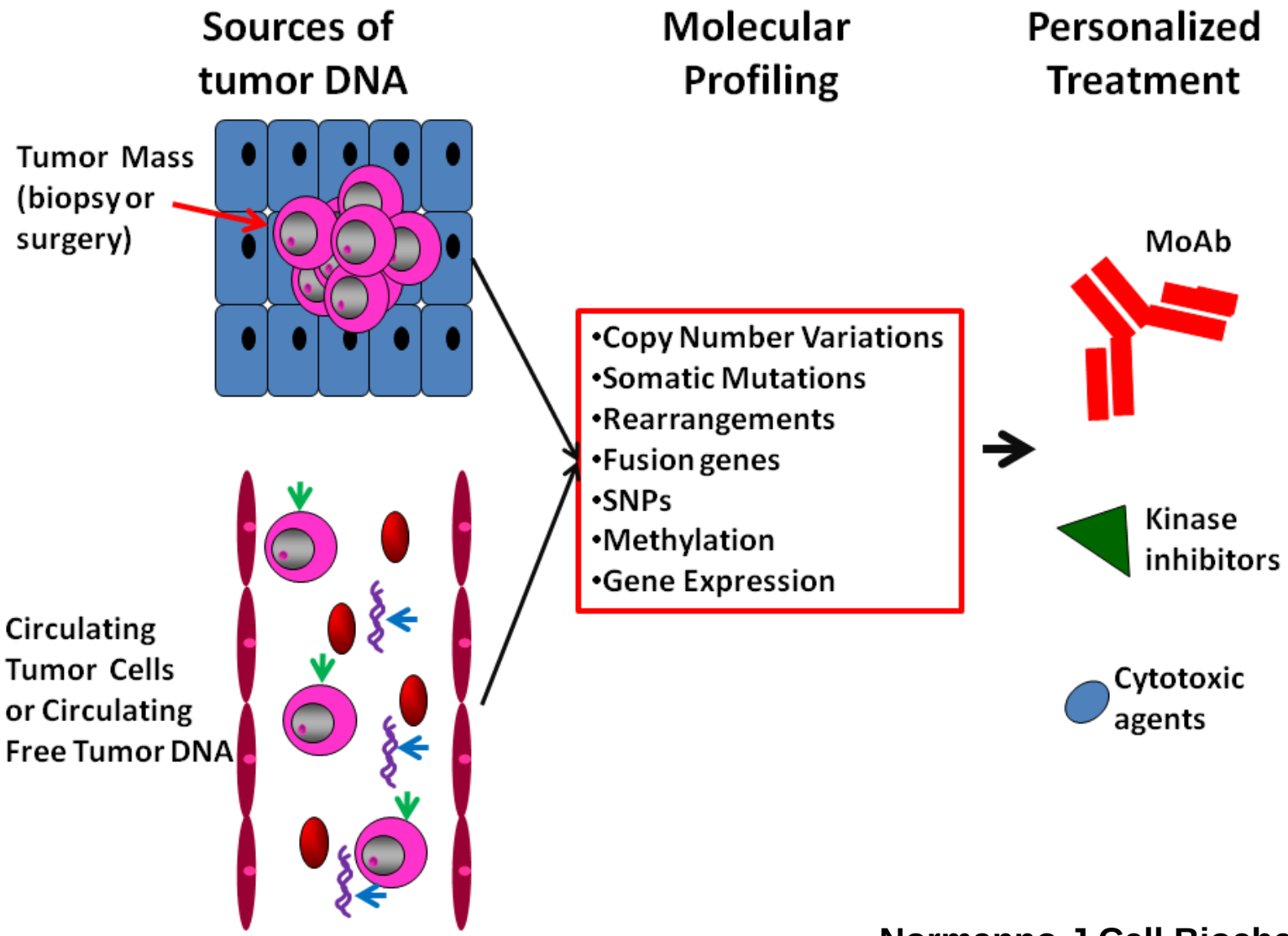
RAS WT

RAS Mutant

Other EGFR resistance mutations

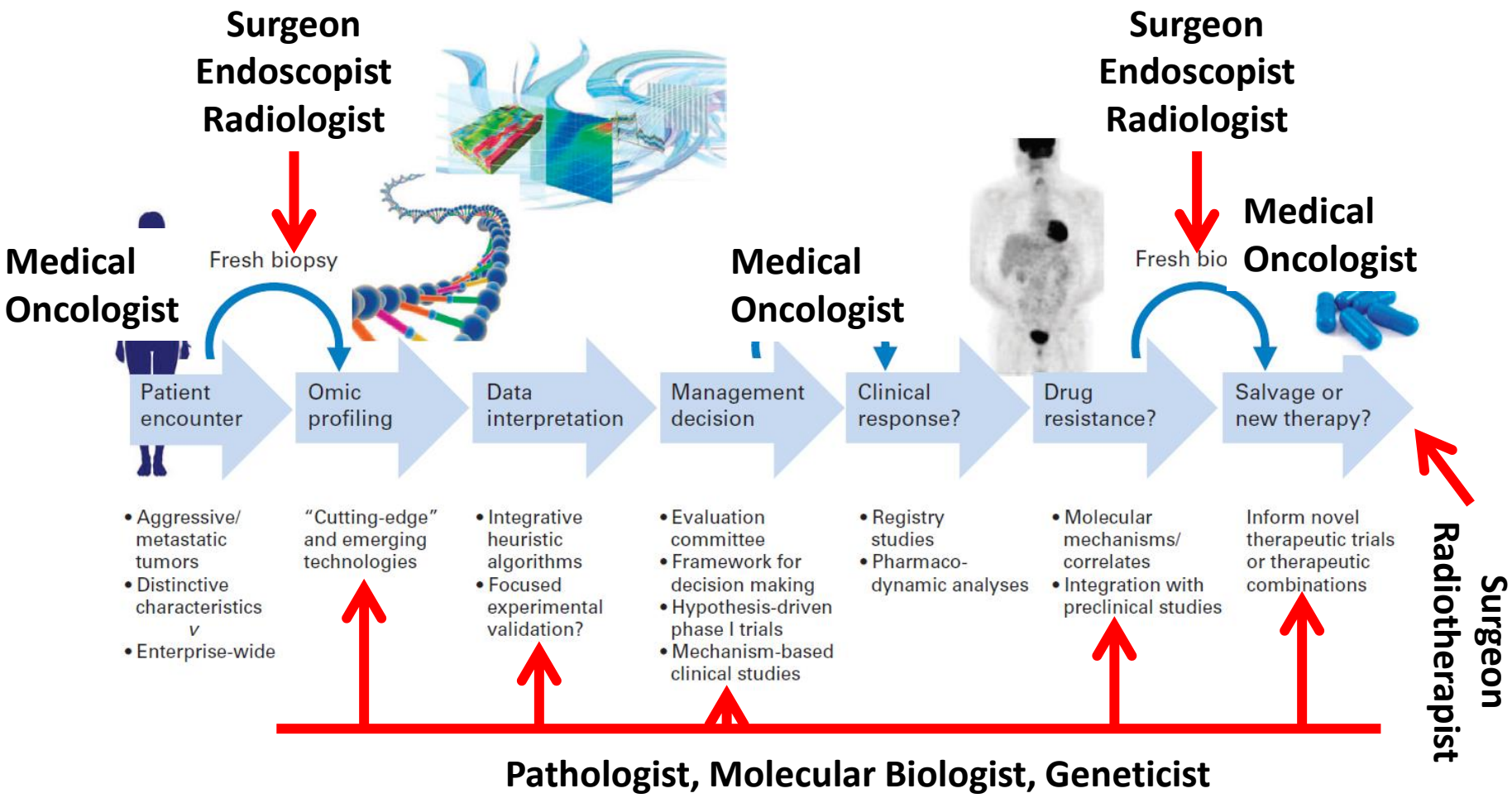
Chemotherapy resistant

The future of biomarker testing



Normanno J Cell Biochem 2013

Genomics-Driven Oncology



Garraway JCO 2013

Take home messages

- **Inter- and intra-tumor heterogeneity is a common phenomenon in CRC**
- **Intra-tumor heterogeneity is likely to be involved in the acquired resistance to targeted therapies**
- **Treatment of CRC with targeted therapies increases tumor heterogeneity**
- **Liquid biopsy can allow to track tumor clonal evolution and design novel therapeutic strategies that need to be assessed in clinical trials**

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