1st GBO Meeting

1st European Course for MDs in training
Going Beyond in Oncology

NOVEMBER, 28th 2018
MILANO

ROSA GRAND HOTEL MILANO
Piazza Fontana, 3

SESSION B
MEDICAL ONCOLOGY: CLINICAL ROUND

Should we be all «agnostic»?

Molecular tumor boards in the multidisciplinary oncology approach

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Disclosures

- Participation to Advisory Boards for Amgen, Bayer and Sanofi

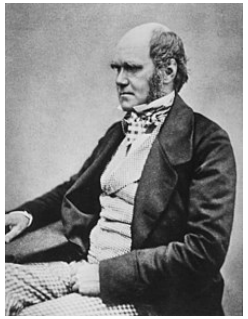
Tissue-agnostic versus tissue-driven oncology

agnostic

[ag-**nos**-tik]

adjective

4. of or relating to agnostics or their doctrines, attitudes, or beliefs.
5. asserting the uncertainty of all claims to knowledge.
6. not taking a stand on something, especially not holding either of two usually strongly opposed positions (often used in combination):
   to take an agnostic view of technological progress; fuel agnostic energy policies.
7. (especially of digital technology) not limited or dedicated to a particular device, system, etc. (often used in combination):
   platform agnostic software.



C. Darwin

T. Huxley

Tissue-agnostic cancer therapy: a therapy that has a specific molecular target unrelated to tissue origin

Tissue-agnostic versus tissue-driven oncology

- Choice of **chemotherapy** is traditionally based on **histologic classification**
- **Some molecular targets** are **confined to specific cell lineages** (such as estrogen receptors and CD20 in mammary epithelium and B-cell lymphoid, respectively). This tissue distribution restricts the clinical utility of selective estrogen receptor modulators and rituximab to breast and B-cell cancer, respectively
- However, **molecular alterations may be present in several cancer types**
- **Molecular or genetic alterations essential for the growth of cancer of one tissue** origin (based on preclinical studies in cell culture and animal models) **have been found to be important for another.** A therapy successful against a target in one cancer type may therefore prove effective for the same target in a different cancer type
- This concept is welcome because it is **based on scientific rationale**, **the pertinent biomarker assay to identify appropriate targets for treatment has been established**, **the pharmacology of an approved drug has been adequately delineated**, and **clinical trials that led to prior approval have established the optimal dosing and toxicity** associated with the therapy

Tissue-agnostic cancer therapy: examples

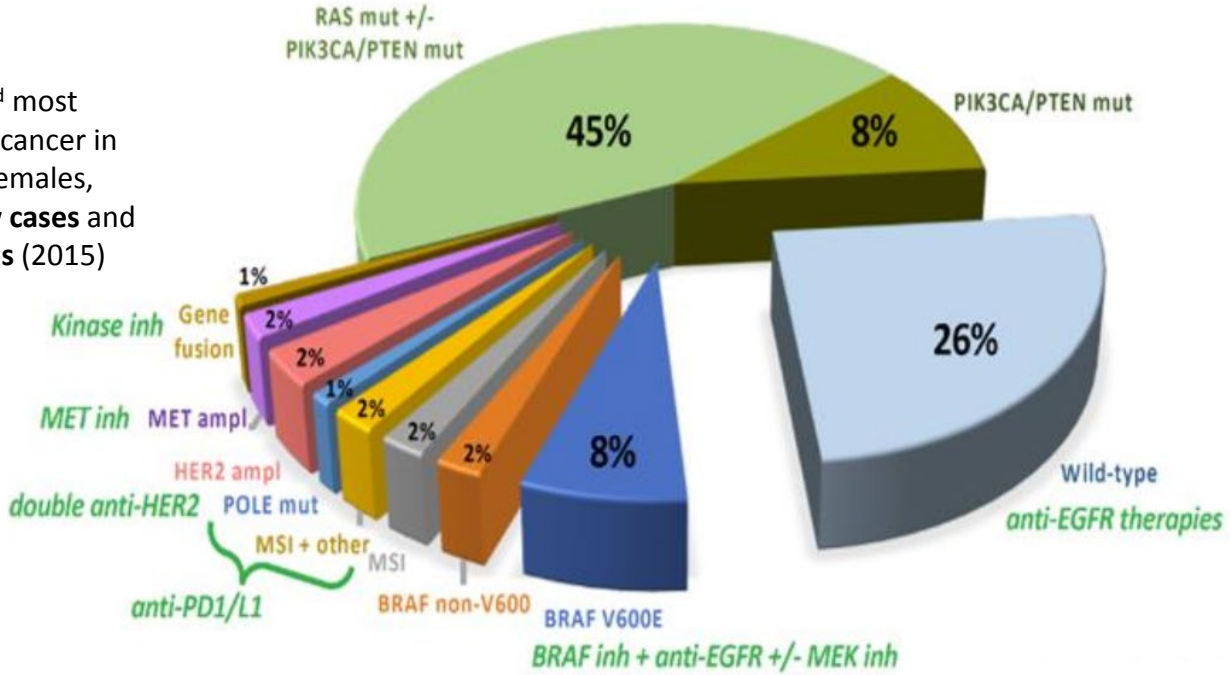
Biomarker	Therapeutic Target	Treatment Approach	Approved Pharmaceutical Agents	Cancer Types
BRAF V600 activating mutation	BRAF and MEKs	A BRAF inhibitor plus a MEK inhibitor	Vemurafenib, dabrafenib, trametinib, and cobimetinib	Cutaneous melanoma, NSCLC, and anaplastic thyroid cancer
HER2 gene amplification and protein overexpression	HER2	Anti-HER2 antibody	Trastuzumab	Breast and gastric/GE junction cancer
BRCA1/2 mutation	PARP-1	PARP-1 inhibitors	Olaparib, rucaparib, and niraparib	Ovarian and breast cancer
dMMR or MSI-H	Neoantigens	Anti–PD-1 antibody	Pembrolizumab	Colorectal, endometrial, biliary, gastric/GE junction, pancreatic, small intestine, breast and prostate cancer and other solid tumors

dMMR = mismatch repair deficiency; GE = gastroesophageal; HER2 = human epidermal growth factor receptor 2; MEK = mitogen-activated protein kinase/extracellular signal–regulated kinase; MSI-H = high microsatellite instability; NSCLC = non–small cell lung cancer; PARP-1 = poly adenosine diphosphate-ribose polymerase-1; PD-1 = programmed cell death protein 1.

Luoh and Flaherty *Ann Intern Med* 2018

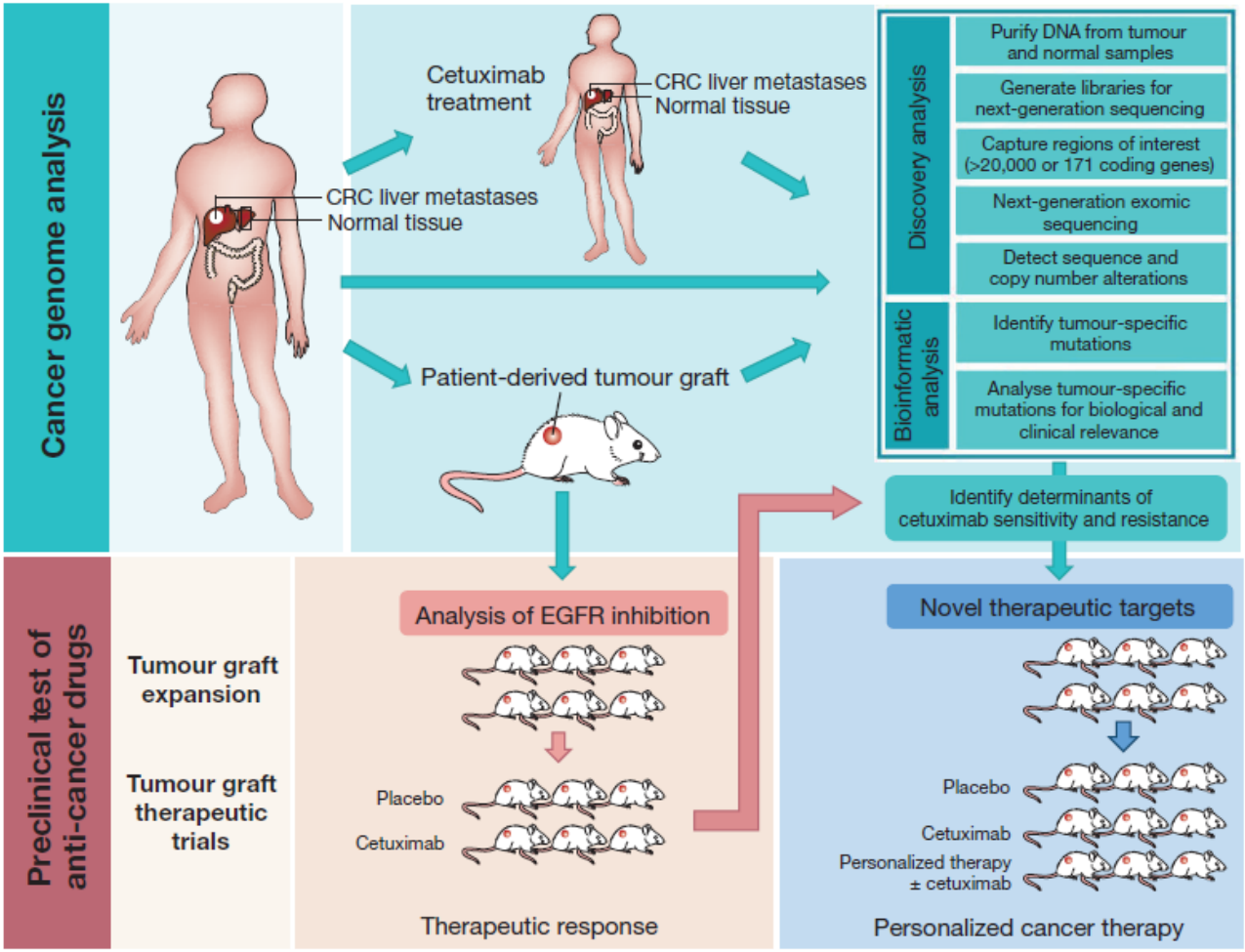
Tissue-agnostic cancer therapy: merits and hypes - the example of colorectal cancer

- "**Big killer cancer**"
- Globally, CRC is the 3rd most commonly diagnosed cancer in males and the 2nd in females, with **1.65 million new cases** and almost **835,000 deaths** (2015)



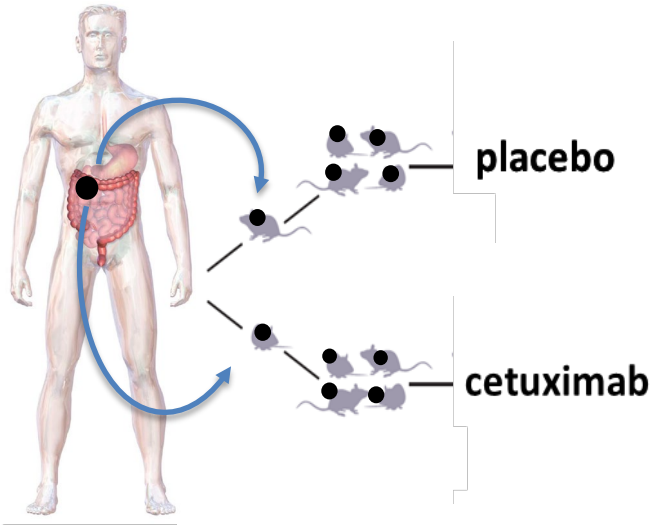
Dientsmann et al. ASCO ED Book 2018

The PDX platform to study anti-EGFR sensitivity

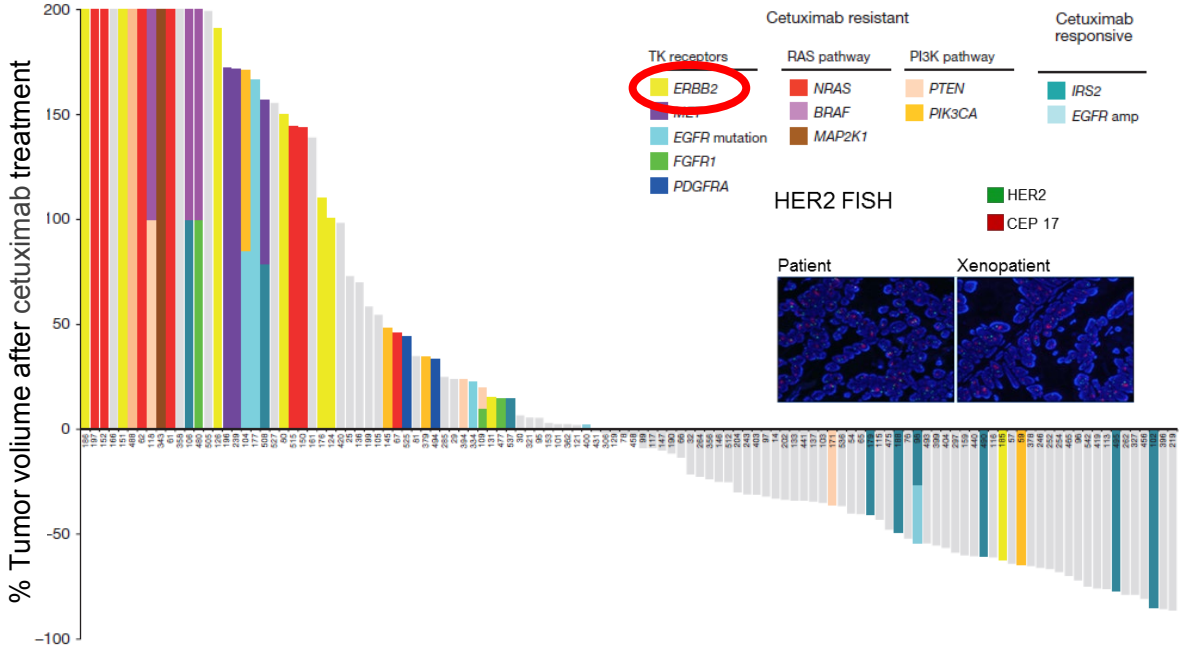


Bertotti et al, Nature 2015

The PDX model to unveil the genomic landscape of resistance/sensitivity to anti EGFR mAbs in WT mCRC



mCRC patient-derived xenogratfs



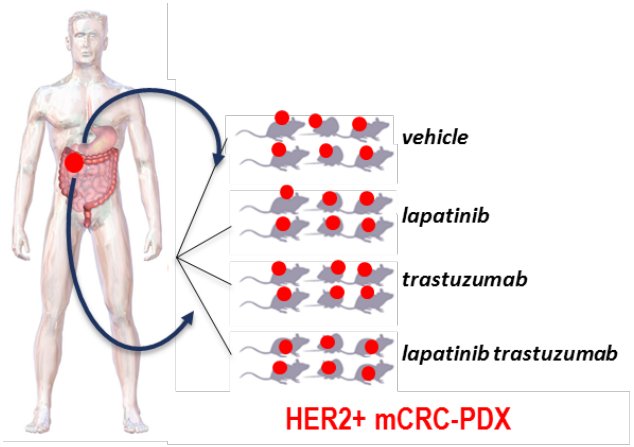
Bertotti A et al, Cancer Discovery 2011

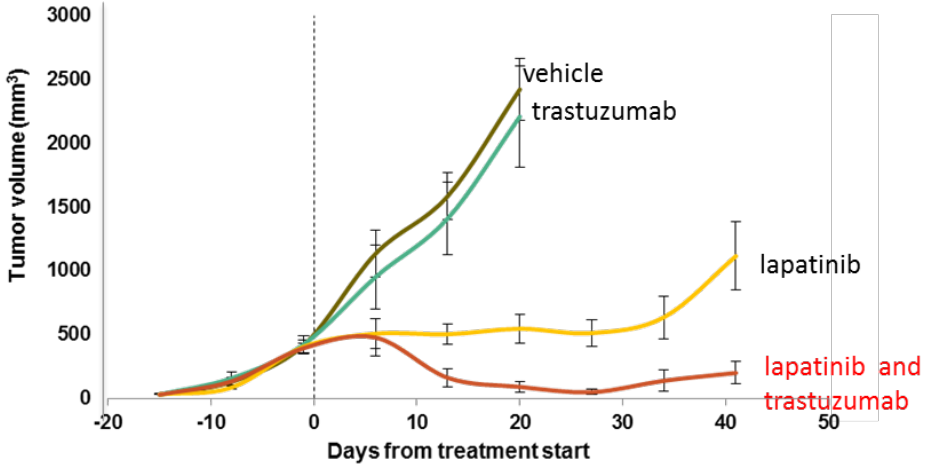
Bertotti A et al, Nature 2015

Approved HER2-directed therapies: breast and gastric

- **HER2 gene amplification** occurs in 15-20% of aggressive **breast** and **gastric** cancers, and is associated with poor prognosis.
- The standard of care for HER2-positive early **breast cancer** includes the HER2-targeting antibody, **trastuzumab**, **administered with chemotherapy**. In patients with advanced HER2-positive disease, the standard of care as first-line therapy includes dual blockade of HER2 with **trastuzumab and pertuzumab**, an antibody that binds to an alternative epitope of HER2. Other HER2-directed regimens include **lapatinib + capecitabine** and **T-DM1** that is an antibody-drug conjugate (ADC) in which trastuzumab is coupled to a derivative of the potent inhibitor of microtubule polymerization maitansine
- In **gastric cancer**, the combination of **trastuzumab + chemotherapy** is the standard of care for first-line treatment of HER2+ tumors, while lapatinib, T-DM1 or the combination of trastuzumab and pertuzumab did not provide registrative results

HER2-directed combinations in mCRC preclinical models

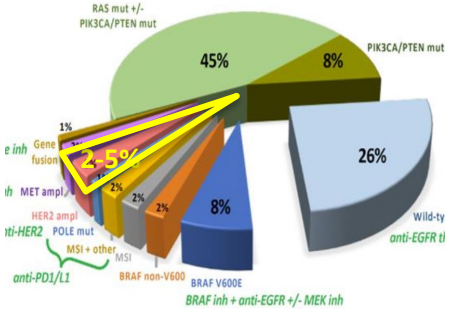




HER2+ mCRC-PDX are sensitive to dual HER2-blockade with lapatinib + trastuzumab but not to either drug alone

Bertotti A et al, Cancer Discovery 2011

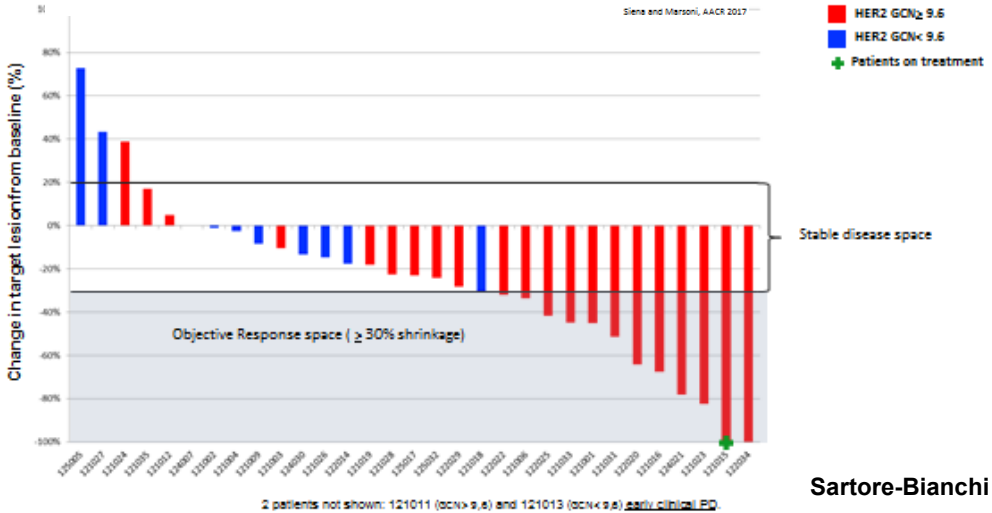
HER2-targeted therapy in mCRC



HERACLES A Trial - Patient characteristics

Clinical variables	N = 33	%	
Median age in years (range)	62 (40-86)		
Males / Females	28 / 5		
HER2 (IHC) 3+ / 2+	26 / 7		
Site of primary tumor			
Colon / Rectum	26 / 7		84% non-right colon
Proximal colon / Distal colon	5 /21		
Metastatic disease in multiple sites	29	87%	
Prior treatment			
Median number of prior lines (range)	5 (2-11)		
Patients with >3 prior lines	24	73 %	
Prior cetuximab or panitumumab	33	100 %	
Previous response to anti-EGFR moAbs	0	0 %	

Complete response	1 (4%, −3 to 11)
Partial response	7 (26%, 9 to 43)
Objective response	8 (30%, 14 to 50)
Disease control†	16 (59%, 39 to 78)
Duration of response (weeks)	38 (24 to 94+)

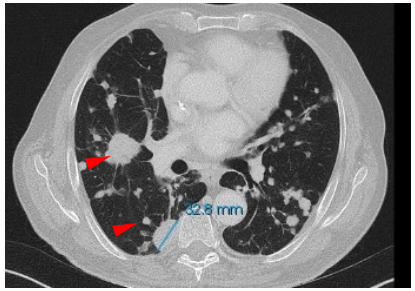


Sartore-Bianchi et al, Lancet Oncol 2016

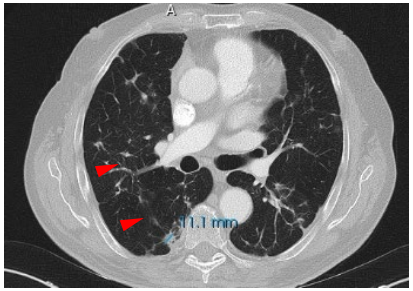
HERACLES A Trial

Representative CE-CT scans of 2 mCRC responders

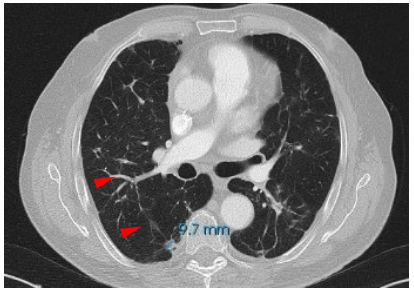
Patient #121016



baseline



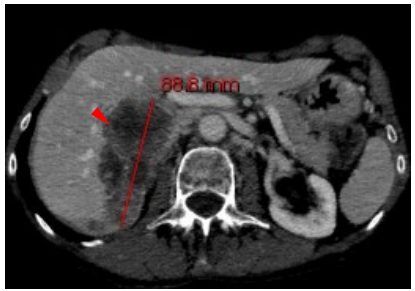
Week 8, PR



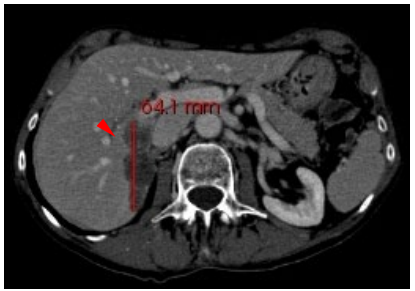
Week 54, PR

- 85 y-o male
- Left-sided RAS/BRAF WT CRC
- Multiple lung mets
- 4 previous line of Tx
- Her2 3+

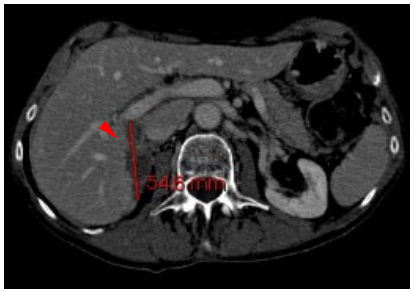
Patient #121023



baseline



Week 8, PR



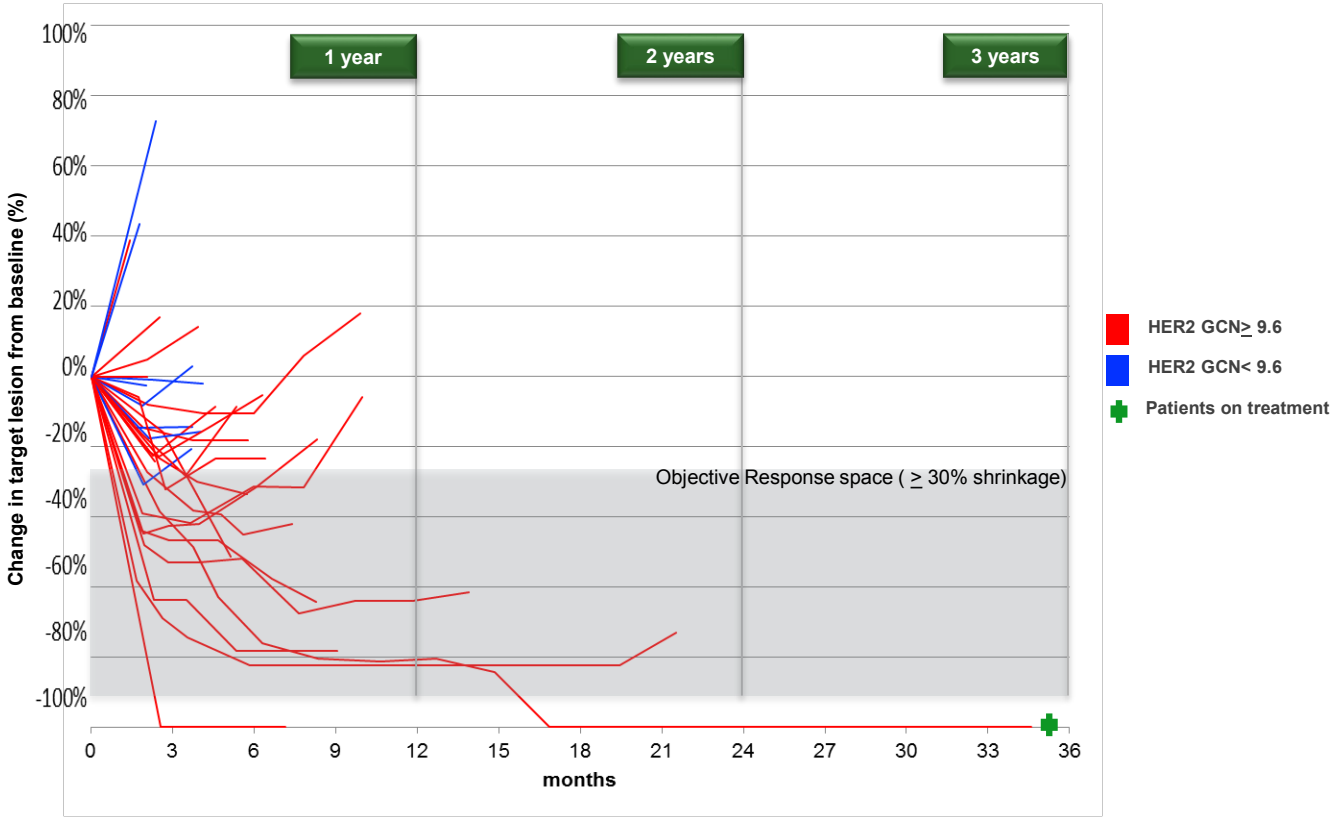
Week 24, PR

- 79 y-o male
- Rectal RAS WT cancer
- Multiple lung and liver mets
- 4 previous line of Tx/metastasectomy and local treatments

Sartore-Bianchi et al, Lancet Oncol 2016

HERACLES A Trial

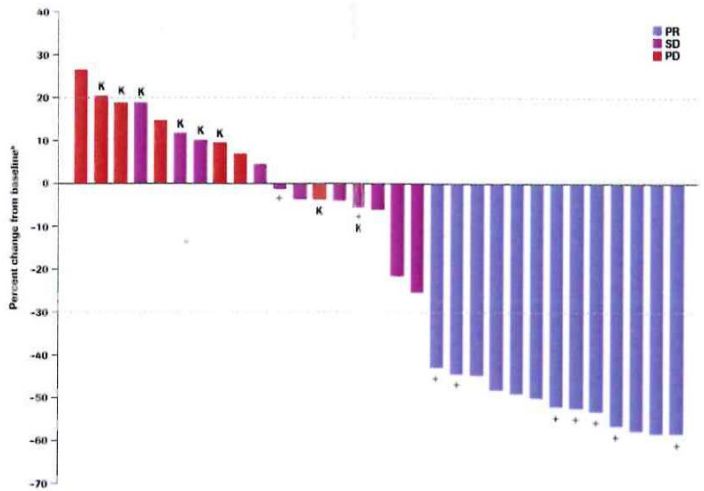
Spaghetti plot of tumor shrinkage trend and *HER2* copy number



2 patients not shown: 121011 (GCN> 9,6) and 121013 (GCN< 9,6) early clinical PD.

Anti-HER2 therapy in CRC cohort of MyPathway Trial

Figure 2. Best percent change from baseline in target lesion size in patients with HER2-amplified/overexpressed mCRC (n=31)[a]



+ indicates that treatment is ongoing, K indicates the patient has a KRAS mutation.
[a]Three patients are excluded from this plot: 2 patients (including 1 with a KRAS mutation) who discontinued treatment due to clinical progression without a post-baseline tumor assessment, and 1 who discontinued treatment due to a new lesion and who was missing three quarters of the target lesion assessments.
[b]"Percent change from baseline" represents the maximum reduction/minimum increase in the target lesion size from baseline. Patients with at least a 30% decrease in target lesion size qualify for PR. Patients with least a 20% increase in target lesion size, or the appearance of one or more new lesions, qualify for PD.

HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; PD, progressive disease; PR, partial response; SD, stable disease.

- ORR was higher in patients with wild-type versus mutated KRAS (52.0% versus 0%) and in patients with left-sided colon cancer (42.9%) or rectal cancer (45.5%) versus right-sided colon cancer (12.5%) (Table 2)

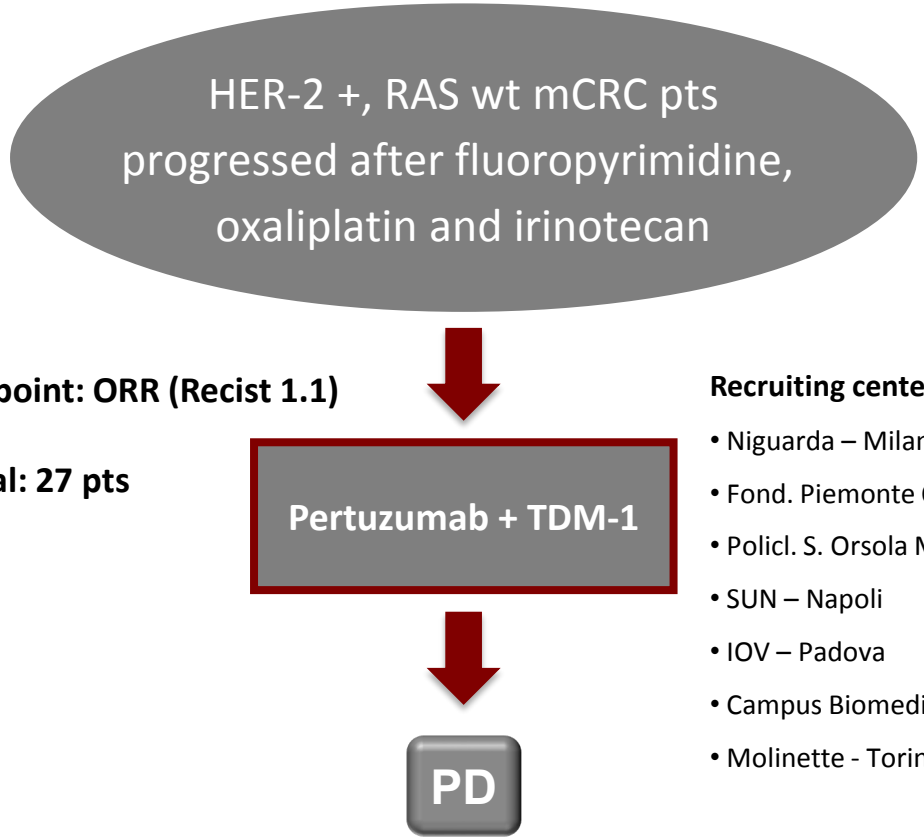
Table 3. Efficacy of Treatment With Trastuzumab Plus Pertuzumab in Patients With HER2 Amplification/Overexpression

Primary Site	No. of Patients	Response, No. (%) CR	PR	SD > 120 Days	ORR, % (95% CI)
Colorectal	37	0	14 (38)	4 (11)	38 (23 to 55)
Lung, non–small-cell	16	0	2 (13)	2 (13)	13 (2 to 38)
Bladder	9	1 (11)	2 (22)	2 (22)	33 (8 to 70)
Pancreas	9	0	2 (22)	1 (11)	22 (3 to 60)
Biliary	7	0	2 (29)	3 (38)	29 (4 to 71)
Ovary	8	0	1 (13)	0	13 (0 to 53)
Uterus	7	0	0	0	0
Salivary gland	5	0	4 (80)	0	80 (28 to > 99)
Other (11 sites)*	16	1 (6)	1 (6)	3 (19)	13 (2 to 38)
Total	114	2 (2)	28 (25)	16 (14)	26 (19 to 35)

NOTE. N = 114. Includes 12 patients with amplification/overexpression plus mutation.
Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.
*Responses occurred in patients with adenocarcinomas of the prostate (one) and skin (apocrine; one).

Hainsworth JD et al, *J Clin Oncol* 2018

HERACLES-B: Pertuzumab + TDM-1



Phase II

Primary endpoint: ORR (Recist 1.1)

Target accrual: 27 pts

Recruiting centers

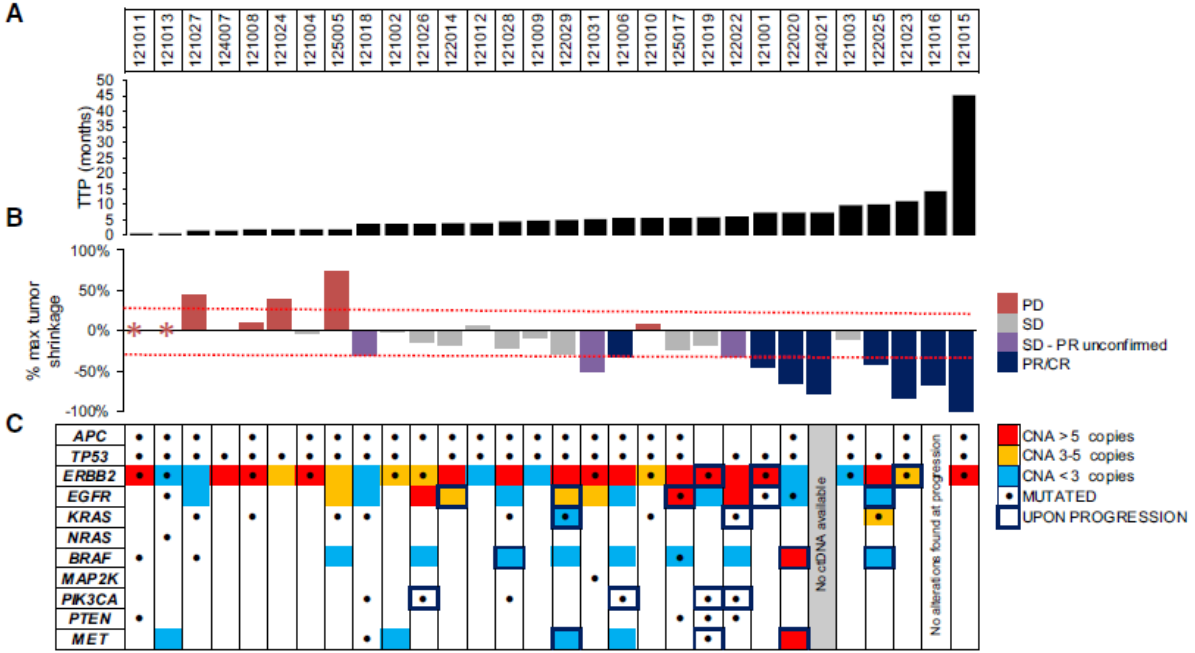
- Niguarda – Milano
- Fond. Piemonte Oncol. – Candiolo
- Policl. S. Orsola Malpighi – Bologna
- SUN – Napoli
- IOV – Padova
- Campus Biomedico – Roma
- Molinette - Torino

Siena S. et al, https://clinicaltrials.gov

Molecular Landscapes Predictive of Response and Primary Resistance to HER2 Blockade in mCRC

Cancer Cell

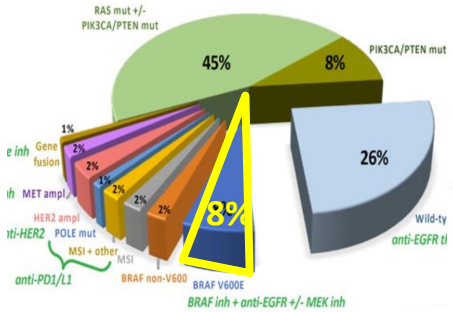
Radiologic and Genomic Evolution of Individual Metastases during HER2 Blockade in Colorectal Cancer

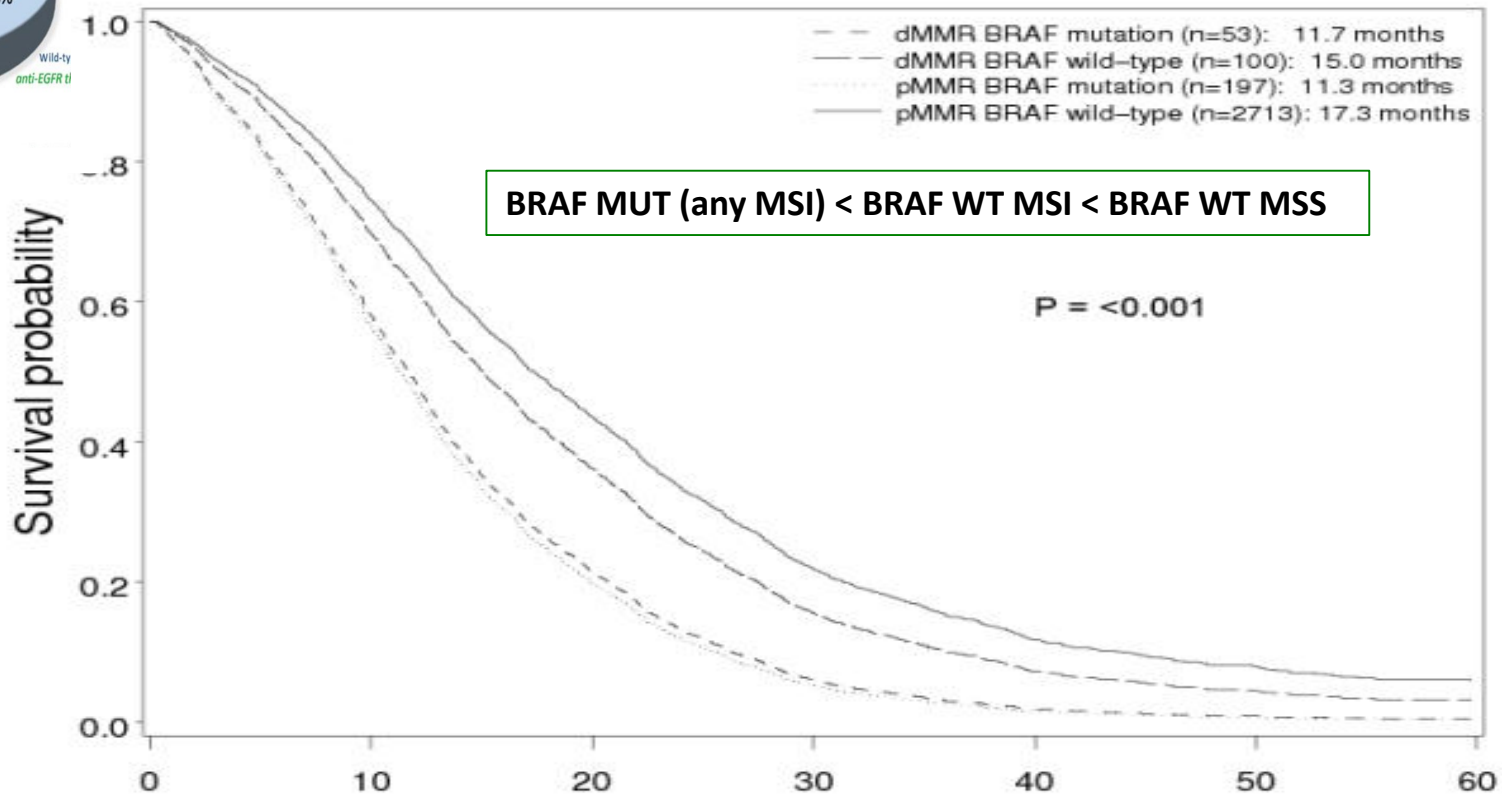


- Alterations in **RAS/RAF** at **baseline**:
  - ❑ 6/7 (86%) refractory patients
  - ❑ 3/22 (14%) cases with clinical benefit
- At **secondary resistance**:
  - ❑ emerging **KRAS** mutant clones and **BRAF** amplification were identified at progression in two SD patients and one PR case,
- **Other alterations** detected at **progression**:
  - ❑ **ERBB2 p.L755S and p.V777L,**
  - ❑ EGFR,
  - ❑ **PIK3CA**
  - ❑ PTEN

Siravegna et al, Cancer Cell 2018

Negative prognostic effect of BRAF in mCRC





BRAF MUT (any MSI) < BRAF WT MSI < BRAF WT MSS

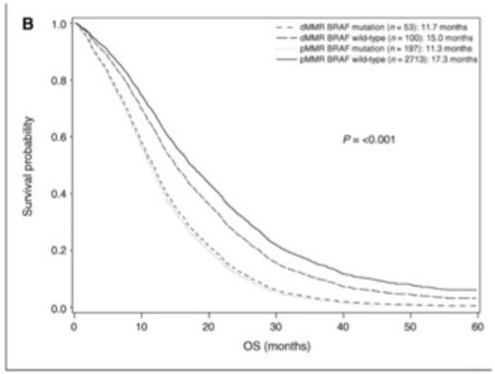
P = <0.001

Venderbosch et al, Clin Can Res 2014

Negative prognostic effect of BRAF in mCRC

B-RAF MUTATION

Prognosis and overlap with MSI



Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN and FOCUS studies Venderbosch et al 2014

MMR status	BRAF V600E mutation status, incidence and median OS		
	BRAF wild type	BRAF mutant	total
Deficient MMR	3.3% 15 mo	1.7% 11.7 mo	5%
Proficient MMR	88.6% 17.3 mo	6.4% 11.3 mo	95%
Total	91.9%	8.1%	3063

Non V600E mutations occur in another 2%

MD Anderson Jones ASCO 2017

	BRAF wt	V600E	Non V600E
Median OS	43.0 mo	11.4 mo	60.7 mo

Tim Maughan ESMO 2018

BRAF mutations in melanoma and CRC: differences

B-RAF mutations in melanoma and colorectal cancer: commonalities and differences with respect to frequency, demographics, risk factors, mutation-associated clinico-pathologic and molecular features and clinical implications.

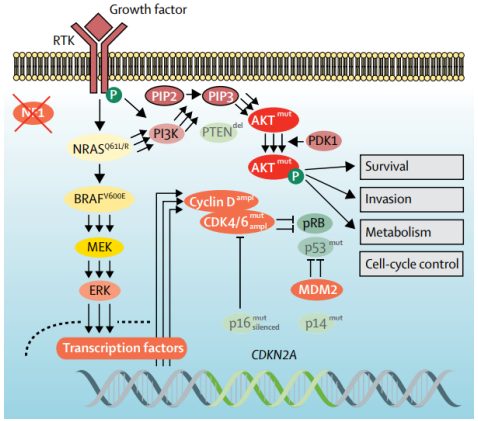
	Melanoma	Colorectal cancer
Frequency		
Cell lines	59%	18%
Unselected tumours	27–68%	5–22%
Extracutaneous tumours	0–11%	na
Potentially pre-malignant lesions	67–82%	6–100%
Demographic features		
Age	<55–60 years	>55–60 years
Sex	Male = female	Female > male
Lifestyle risk factors		
Sun exposure	Intermittent	na
Smoking	n.i.	Yes? (Men only?)
Diet	n.i.	No
Clinico-pathologic features		
Primary site	Trunk > extremities	Right colon > left colon
Histologic subtype	SSM/NM > LMM/AM	Poorly diff./mucinous
Molecular features		
Event in tumorigenesis	Early	Early
Concordance primary/metastasis	High	High
K-RAS mutations	Mutually exclusive	Mutually exclusive
MSI tumours	na	11–76%
CIMP+	na	18–89%
Clinical implication		
Prognostic role	No	Yes (poor outcome)
Predictive role	Yes (B-RAF inhibitors)	No

Abbreviations: SSM, superficial spread melanoma; NM, nodular melanoma; LMM, lentigo maligna melanoma; AM, acral melanoma; n.i., not investigated; and n.a., not applicable.

Approved BRAF-directed therapies: melanoma

Targeted therapy	Target	Year of approval by FDA
Vemurafenib	BRAFi	2011 (BRAFV600E)
Dabrafenib	BRAFi	2013 (BRAFV600E)
Vemurafenib + cobimetinib	BRAFi + MEKi	2015 (BRAFV600E or BRAFV600K)
Dabrafenib + trametinib	BRAFi + MEKi	2014 (BRAFV600E or BRAFV600K)
Trametinib	MEKi	2014 (BRAFV600E or BRAFV600K)

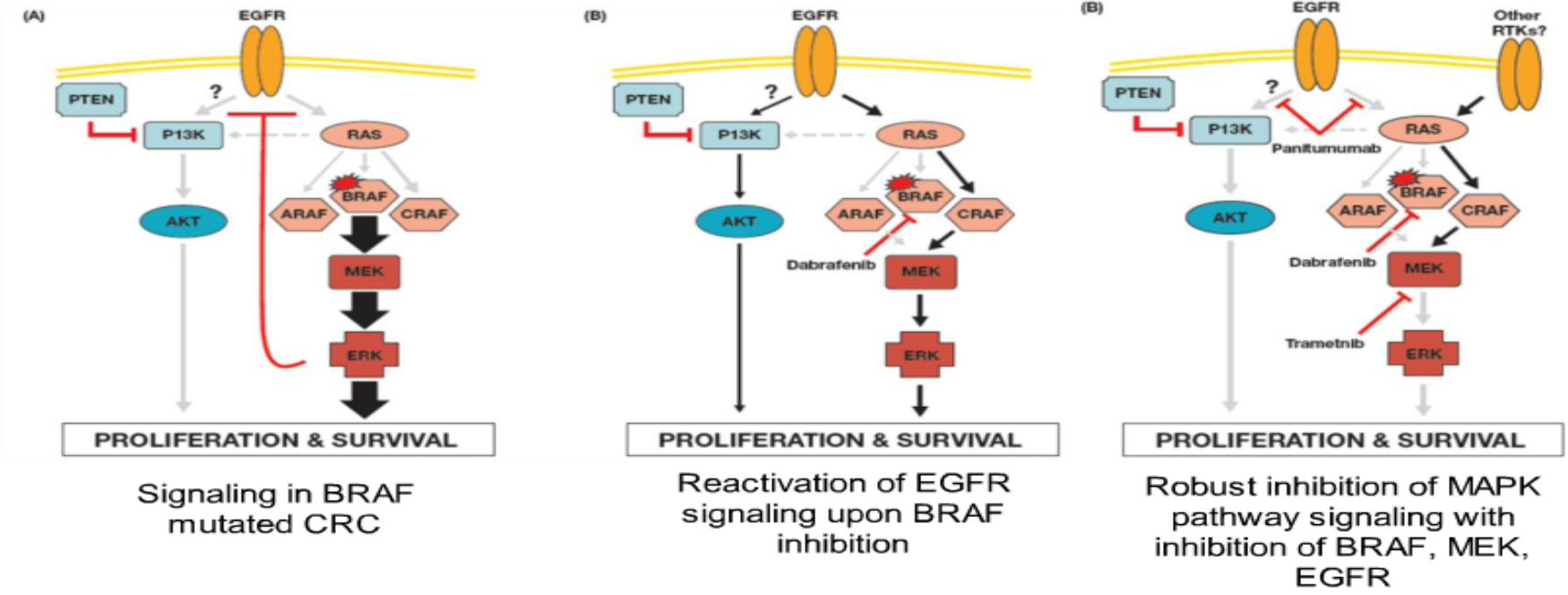
BRAFi BRAF inhibitor, *BRAF WT* BRAF wildtype, *CTLA-4* cytotoxic T-lymphocyte-associated protein 4, *MEKi* MEK inhibitor, *PD-1* programmed death-1



Variable	NSCLC (N = 20)	Colorectal Cancer		Cholangiocarcinoma (N = 8)	ECD or LCH (N = 18)	Anaplastic Thyroid Cancer (N = 7)
		Vemurafenib (N = 10)	Vemurafenib + Cetuximab (N = 27)			
Patients with ≥1 postbaseline assessment — no.	19	10	26	8	14	7
Complete response — no. (%)	0	0	0	0	1 (7)	1 (14)
Partial response — no. (%)	8 (42)	0	1 (4)	1 (12)	5 (36)	1 (14)
Stable disease — no. (%)	8 (42)	5 (50)	18 (69)	4 (50)	8 (57)	0
Progressive disease — no. (%)	2 (11)	5 (50)	7 (27)	3 (38)	0	4 (57)
Missing data — no. (%)‡	1 (5)	0	0	0	0	1 (14)
Overall response — no. (%) [95% CI]	8 (42) [20–67]	0	1 (4) [<1–20]	1 (12) [<1–53]	6 (43) [18–71]	2 (29) [4–71]

Hyman et al, New Engl J Med 2015

Molecular mechanisms underlying resistance to BRAF-directed single inhibition in mCRC

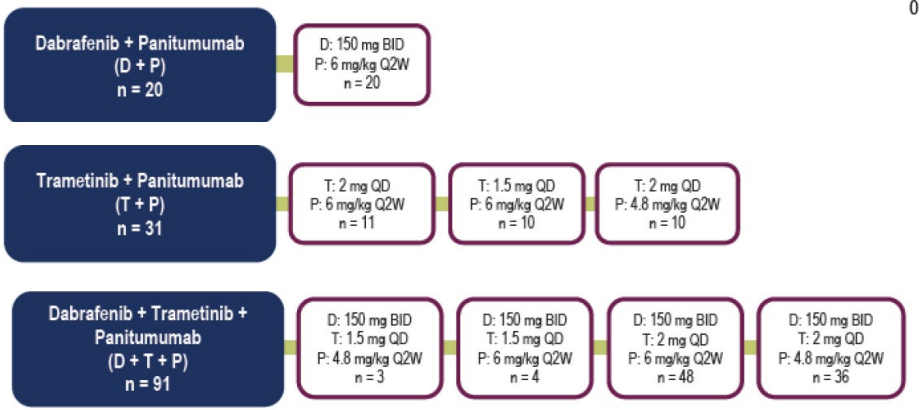


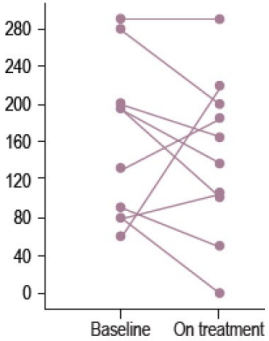
Prahallad Nature 2012; Corcoran, Cancer Discovery 2012; Coffee EM, CCR 2013; Mao M CCR, 2013

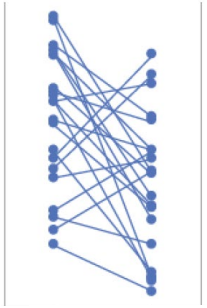
Drug combination

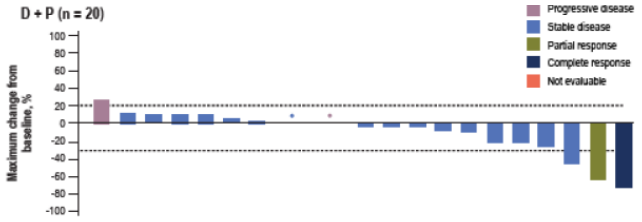
pERK

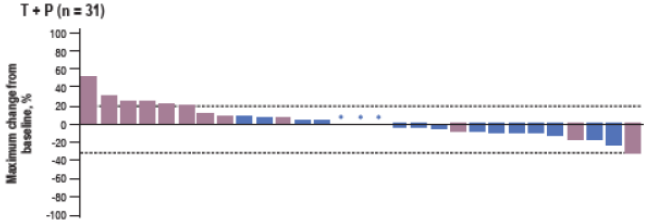
Waterfall plot

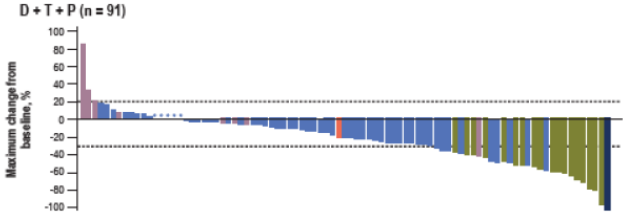












Corcoran et al, Combined BRAF, EGFR, and MEK Inhibition in Patients With *BRAF*$_{V600E}$-Mutant Colorectal Cancer. *Cancer Discovery* 2018

BRAF V600E predictive value in metastatic CRC

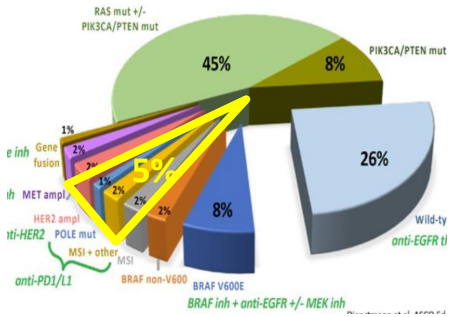
Prevalence ~ 8%

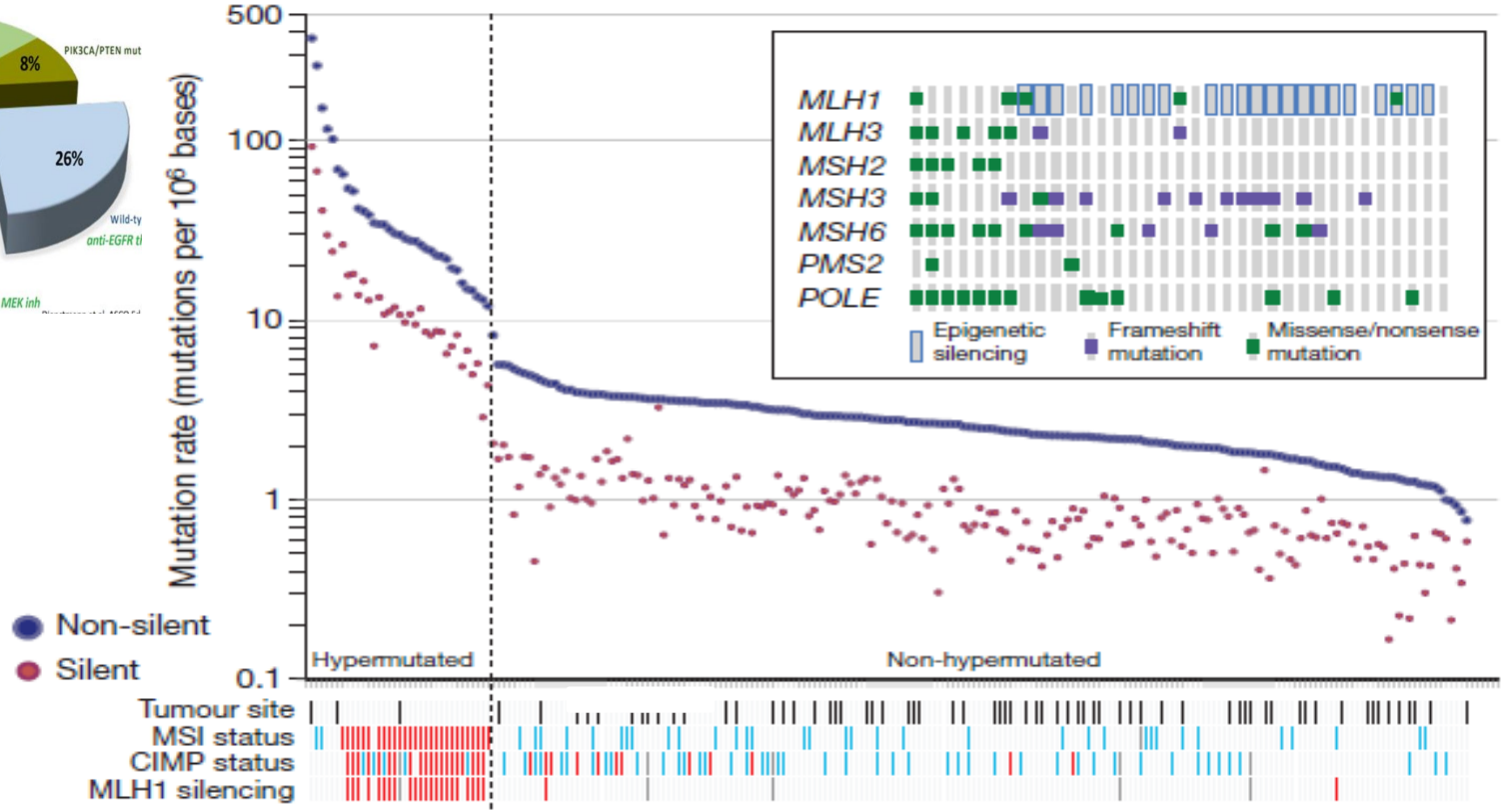
Regimen	N	PR/CR (%)	SD (%)	mPFS (m)
Vemurafenib[1]	21	5	33	2.1
Vemurafenib + Cetuximab[2]	27	4	69	3.7
Dabrafenib + Trametinib[3]	43	12	56	3.5
Dabrafenib + Panitumumab[4]	20	10	80	3.5
Dabrafenib + Trametinib + Panitumumab[4]	91	21	65	4.2
Encorafenib + Cetuximab[5]	42	23	54	3.7
Encorafenib + Alpelisib + Cetuximab[5]	49	32	61	4.3

[1]Kopetz S et al, JCO 2015; [2]Hyman D et al. NEJM 2015; [3]Corcoran R et al JCO 2015
[4]Corcoran R et al. Cancer Discov 2018; [5]Elez et al. ESMO GI 201

Tim Maughan ESMO 2018

MMR deficient CRCs are hypermutated

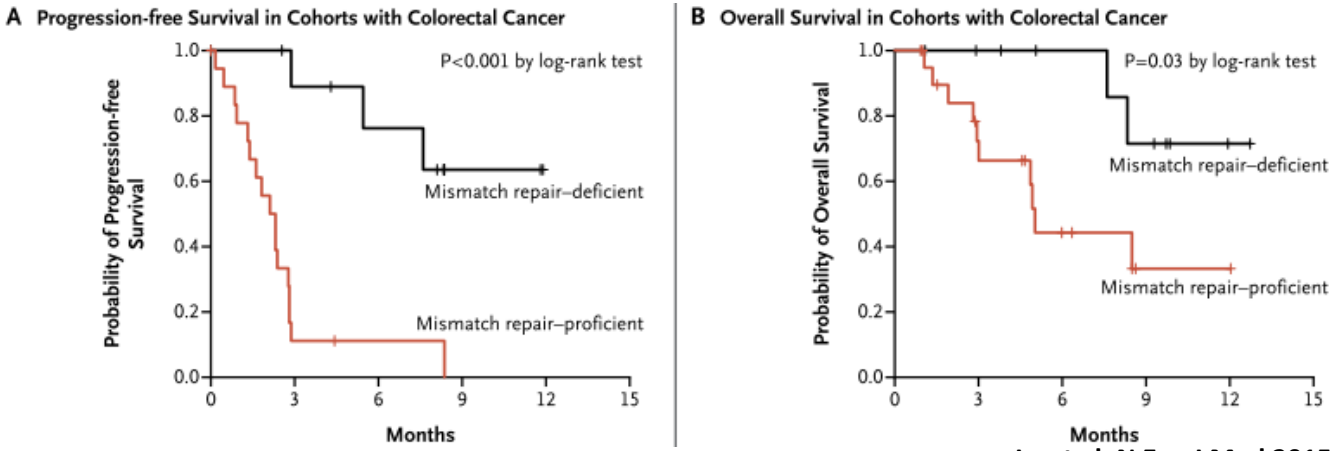




The Cancer Genome Atlas Network Nature 2012

MSI and immune checkpoint inhibition in mCRC

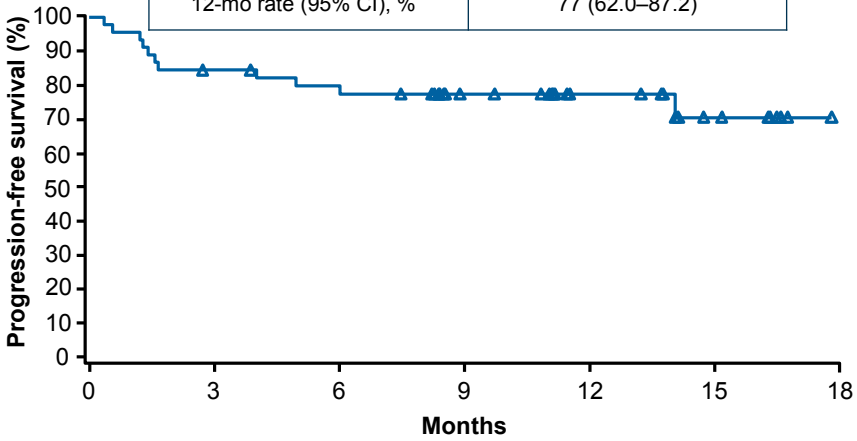
Type of response	MSI (n=10)	MSS (n=18)
Complete Response	0%	0%
Partial Response	40%	0%
Objective Response Rate	40%	0%
Disease Control Rate	90%	11%



Le et al, N Eng J Med 2015

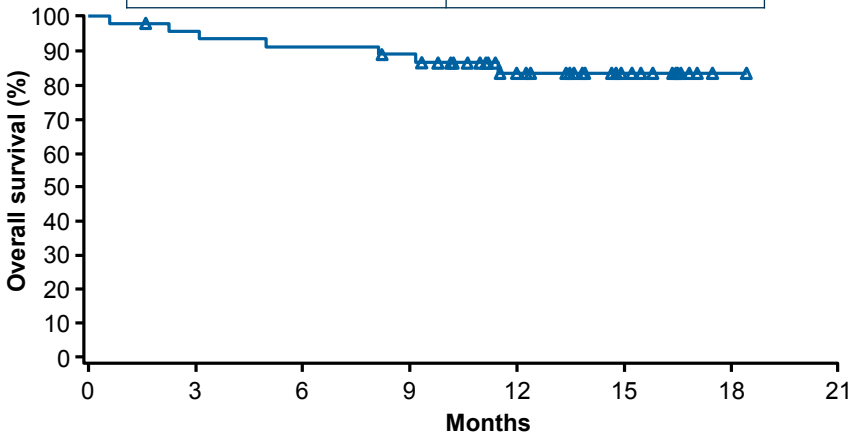
Progression-Free and Overall Survival

PFS[a]	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median PFS, months (95% CI)	NR (14.1–NE)
9-mo rate (95% CI), %	77 (62.0–87.2)
12-mo rate (95% CI), %	77 (62.0–87.2)



No. at risk	45	37	34	24	15	7	7

OS[a]	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median OS, months (95% CI)	NR (NE)
9-mo rate (95% CI), %	89 (74.9–95.1)
12-mo rate (95% CI), %	83 (67.6–91.7)

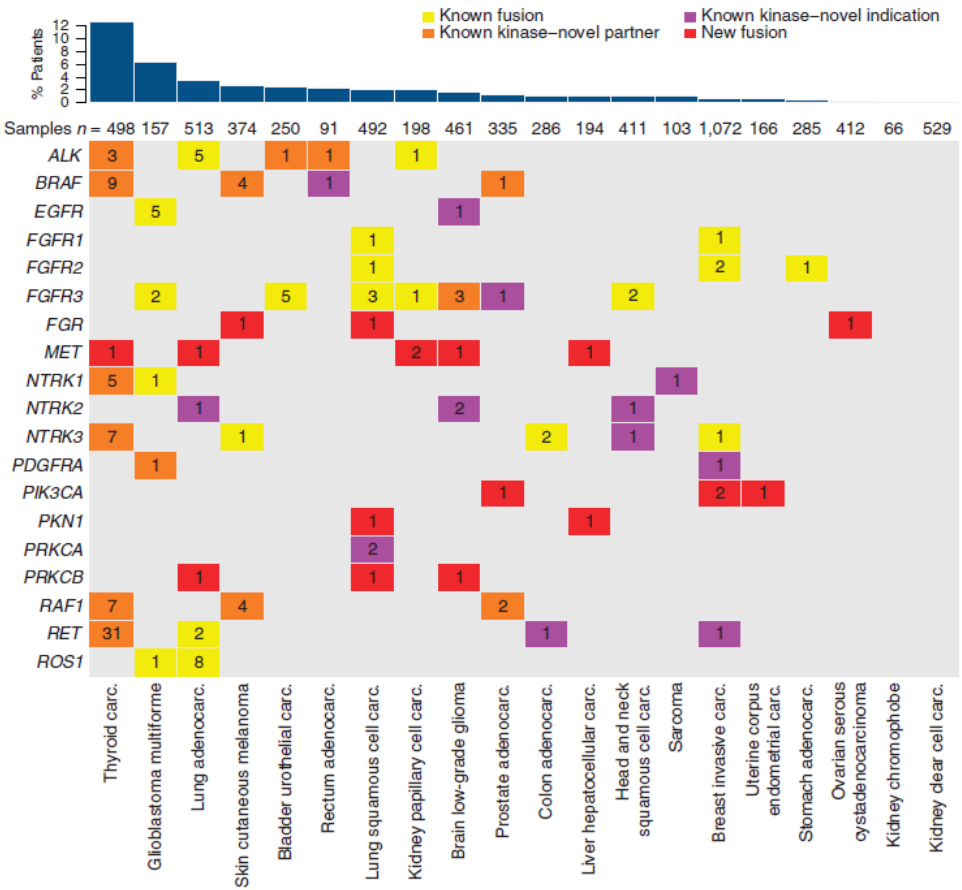


No. at risk	45	42	40	38	24	13	1	0

[a]Per investigator assessment.
mo = month; NE = not estimable; NR = not reached

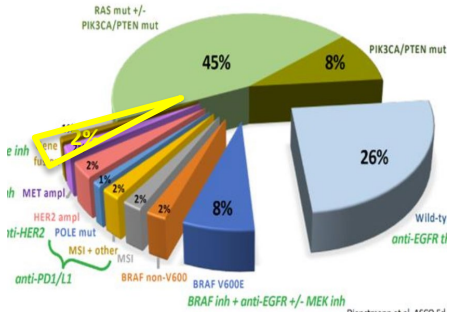
Lenz HJ et al, ESMO 2018

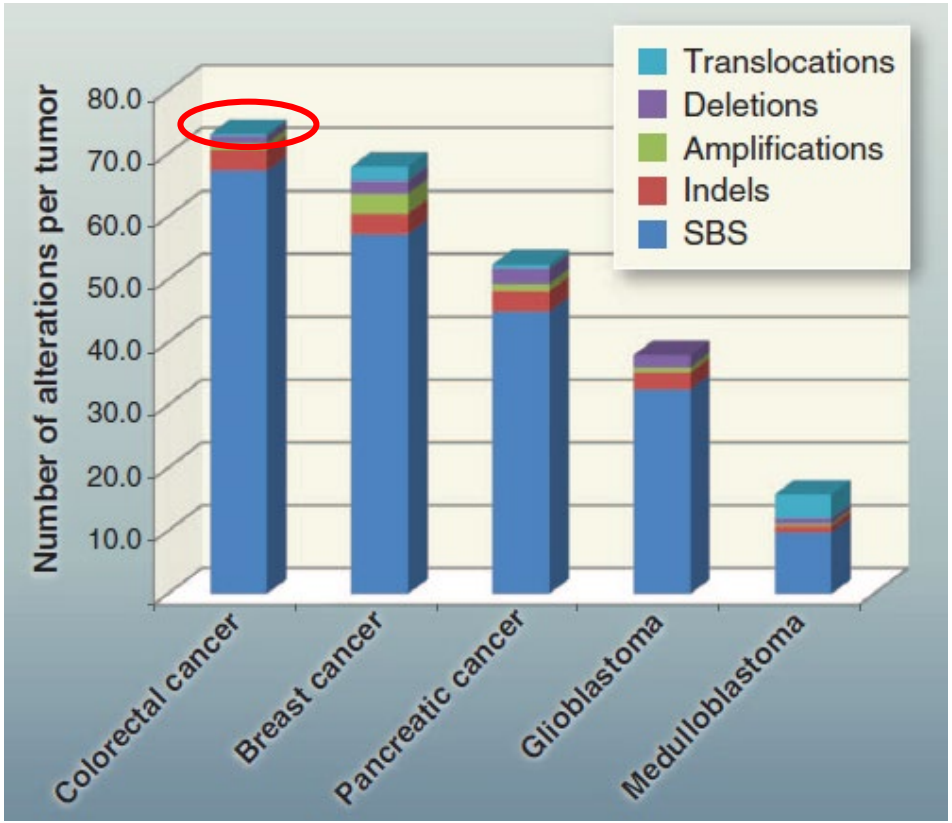
The landscape of recurrent kinase fusions in solid tumours



Stransky et al Nature Comm 2014

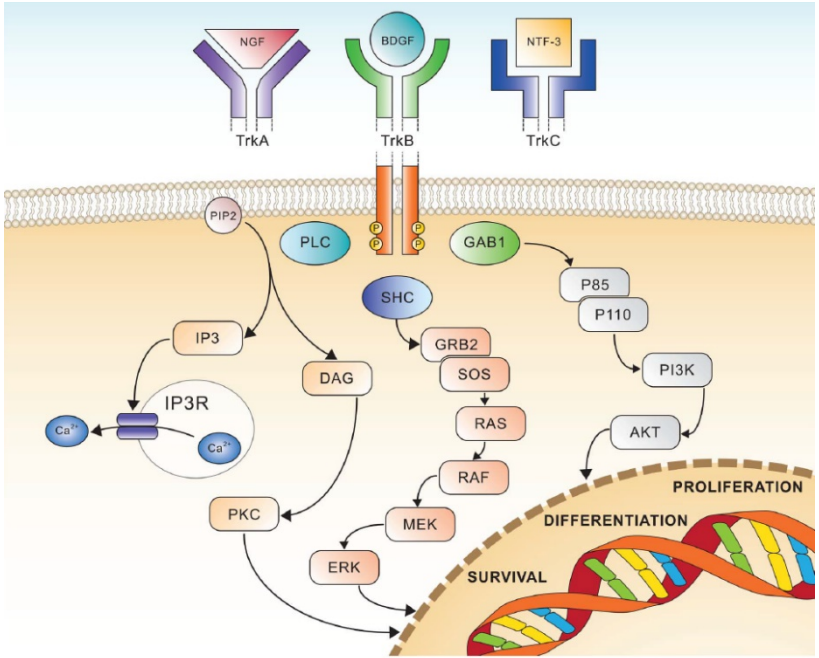
Gene fusions as uncommon oncogenic drivers in mCRC

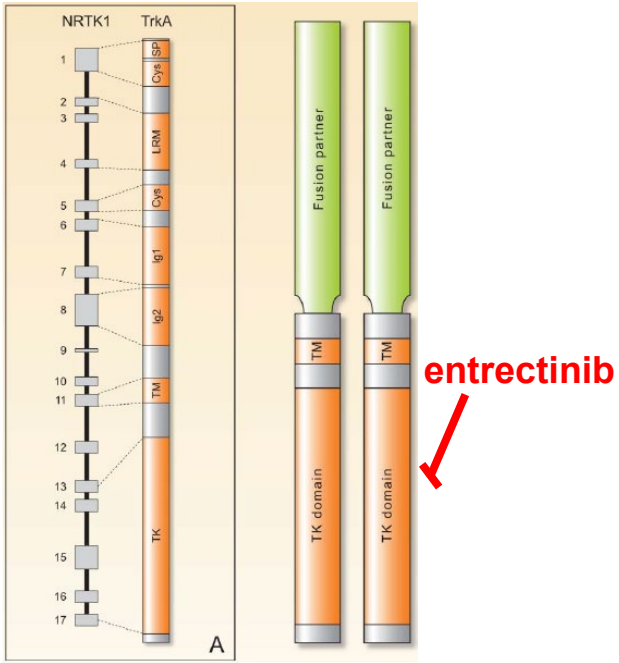




Bert Vogelstein, *Science* 2013

NTRK gene fusions as druggable targets in mCRC





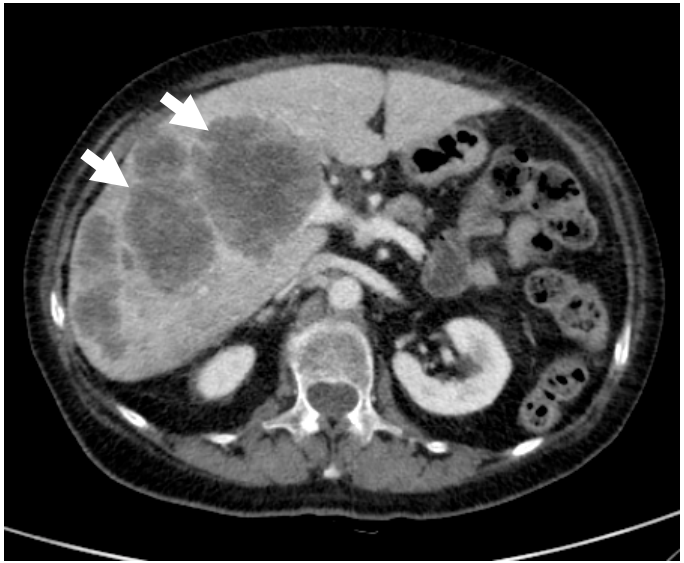
entrectinib

0.5% prevalence of NTRK fusions CRC

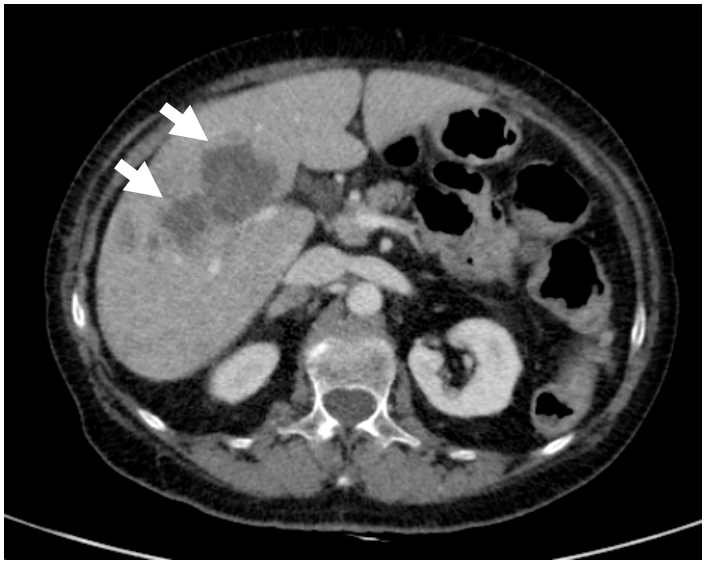
Amatu, Sartore-Bianchi & Siena, ESMO Open 2016

Partial response in patient with TRKA rearranged chemorefractory mCRC

- 73 y-o female
- Left-sided RAS/BRAF WT CRC
- Her2-
- Multiple liver mets
- 3 previous line of Tx



Pre-treatment
March 20, 2014



Post-treatment
April 23, 2014

Sartore-Bianchi et al. J Natl Cancer Inst 2015

OXFORD

JNCI J Natl Cancer Inst (2016) 108(1): djv306

doi:10.1093/jnci/djv306
First published online November 12, 2015
Brief Communication

BRIEF COMMUNICATION

Sensitivity to Entrectinib Associated With a Novel LMNA-NTRK1 Gene Fusion in Metastatic Colorectal Cancer

Andrea Sartore-Bianchi, Elena Ardini, Roberta Bosotti, Alessio Amatu, Emanuele Valtorta, Alessio Somaschini, Laura Raddrizzani, Laura Palmeri, Patrizia Banfi, Erica Bonazzina, Sandra Misale, Giovanna Marrapese, Antonella Leone, Rachele Alzani, David Luo, Zachary Hornby, Jonathan Lim, Silvio Veronese, Angelo Vanzulli, Alberto Bardelli, Marcella Martignoni, Cristina Davite, Arturo Galvani, Antonella Isacchi, Salvatore Siena

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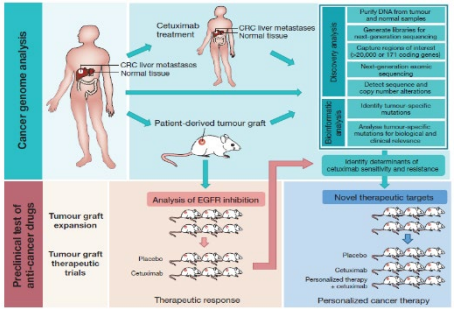
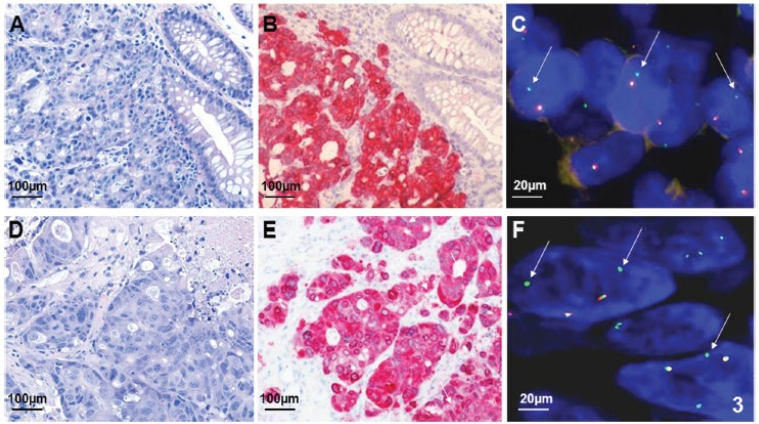
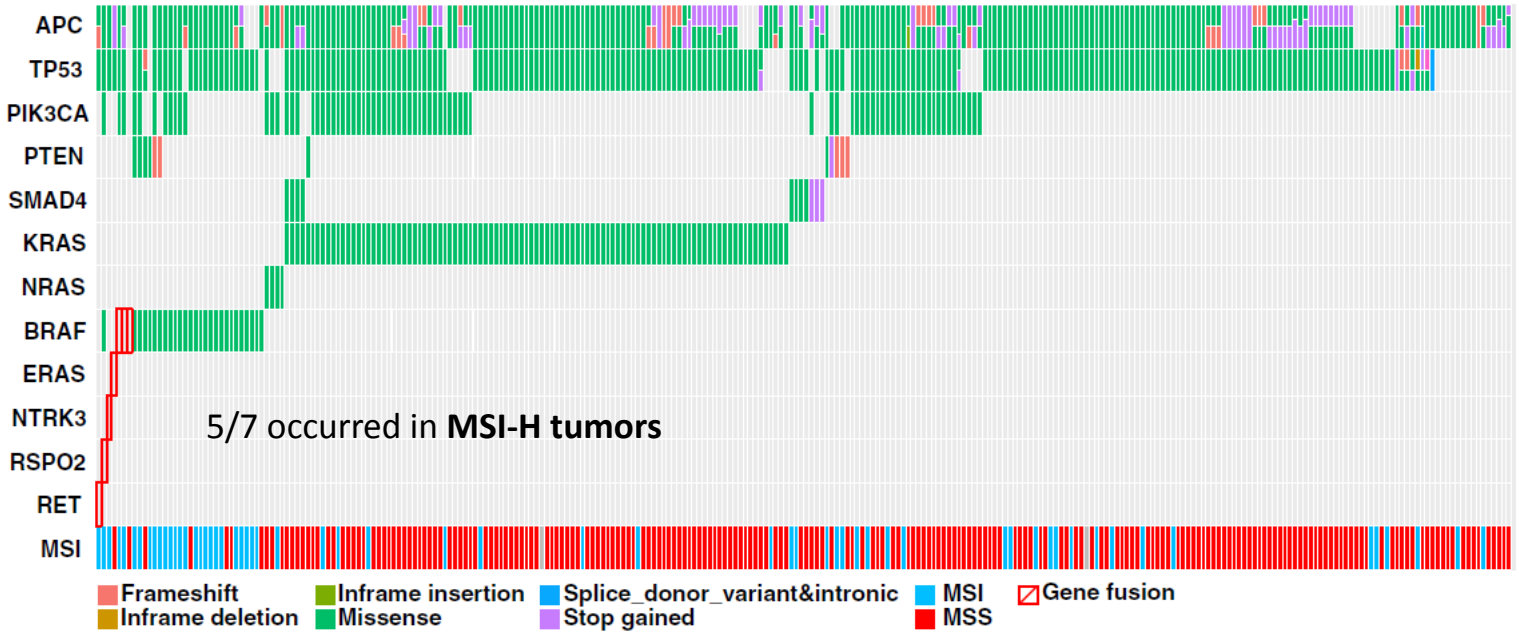




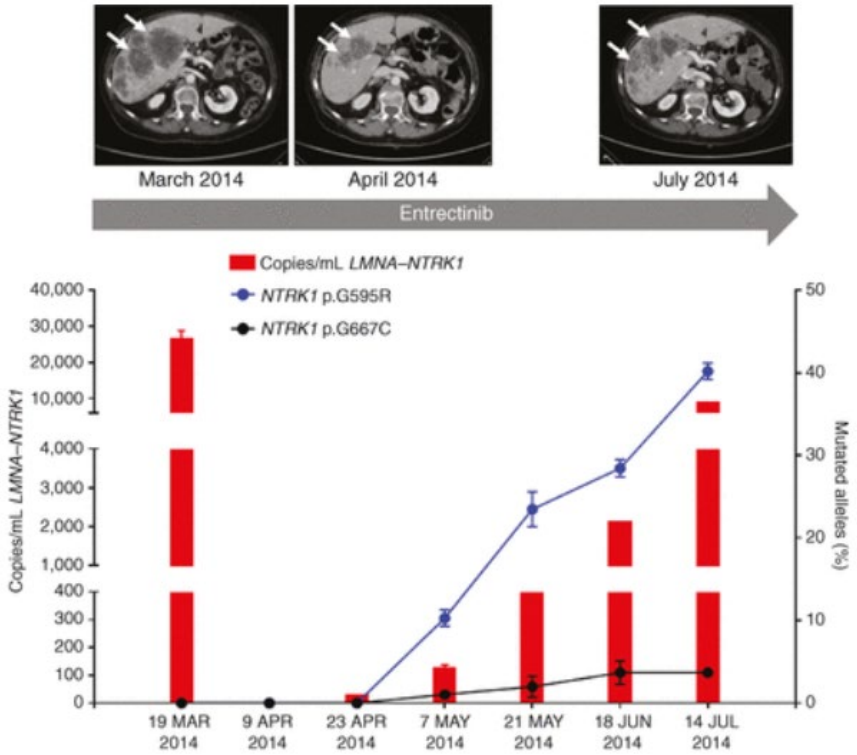
Histologic, immunohistochemical, and fluorescence in situ hybridization analyses of primary tumor (A-C) and patient-derived xenograft from liver metastasis (D-F) of a CRC patient showing LMNA-NTRK1 gene fusion

Oncogenic gene fusions and association with MSI status and mutations in mCRC

- **278** primary colon cancers
- **2.5%** had a relevant gene fusion (kinase fusions 1.8%)
- Oncogenic fusions occurred only in lymph node-negative **BRAF/KRAS WT tumors**



Kloosterman et al., Cancer Res 2017



NTRK1+ patient responding to entrectinib but rapidly experiencing secondary resistance entrectnib and rapi

Sartore Bianch et al JNCI 2016
Russo et al Cancer Discov. 2016

Tissue-agnostic approaches: opportunities and *caveats*

Opportunities

- **Genomic medicine** has been **advancing rapidly** since the introduction of **massive parallel sequencing/next generation sequencing (NGS) technologies**. Many **commercial vendors** as well as academic institutions have been offering **extensive molecular testing for cancer care in a clinical setting**, including cancer-related gene mutation analysis, copy number variation (CNV), gene rearrangement analysis, and RNA expression signatures.

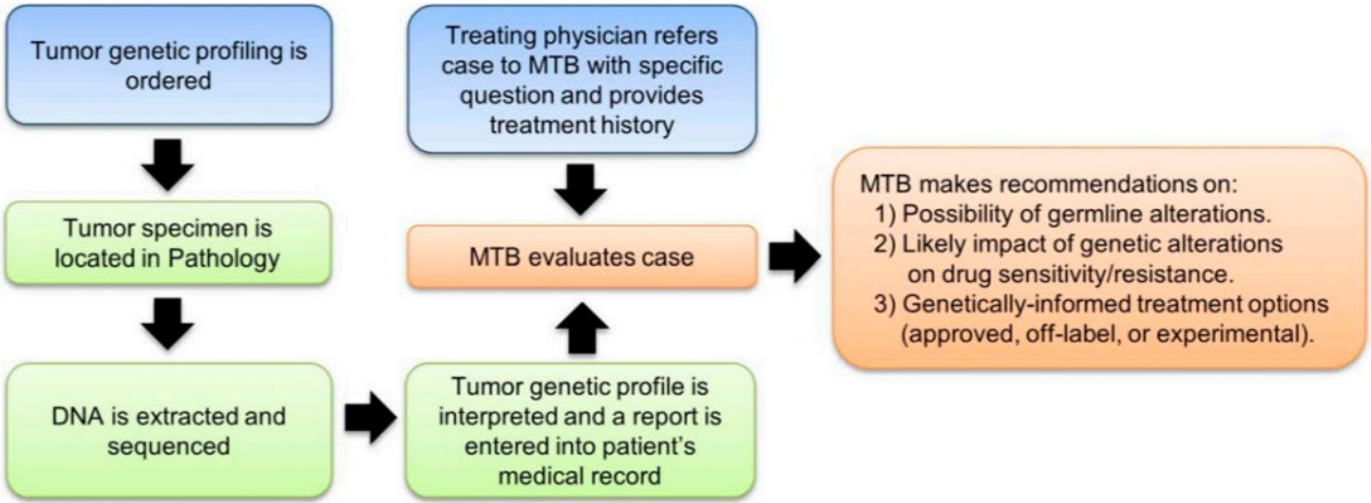
- Finding a **driver gene mutation** can lead to **specific targeted therapies**, which forms the basis for **personalized / precision medicine and tissue-agnostic approaches.**

Caveats

- NGS is a powerful tool and **while the cost** associated with the **assay is declining**, NGS still requires **extensive informatics support** for data analysis.
- The **variability among** the current available **test options and complex results** may be **confusing to clinicians and pathologists**.

- The **integration** of these test results **into clinical care** has been **largely left up to the treating physician**.
- **Proper utilization** of these assays must be ensured to **maximize benefits to the patient** while also being **cost-effective**.
- In the absence of these standards, **efforts to investigate molecular targets may not favorably impact clinical care** and potentially could **drive up healthcare costs.**

Molecular tumor boards



www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 16), pp: 27145-27154

Research Paper

Experience with precision genomics and tumor board, indicates frequent target identification, but barriers to delivery

Alan H. Bryce[1,2,3,*], Jan B. Egan[3,*], Mitesh J. Borad[1,2,3], A. Keith Stewart[1,2,3], Grzegorz S. Nowakowski[3,4], Asher Chanan-Khan[3,5], Mrinal M. Patnaik[3,4], Stephen M. Ansell[3,4], Michaela S. Banck[3,6], Steven I. Robinson[3,6], Aaron S. Mansfield[3,6], Eric W. Klee[3,7], Gavin R. Oliver[3,7], Jennifer B. McCormick[7], Norine E. Huneke[3], Colleen M. Tagtow[3], Robert B. Jenkins[8], Kandelaria M. Rumilla[8], Sarah E. Kerr[9], Jean-Pierre A. Kocher[3,7], Scott A. Beck[3], Martin E. Fernandez-Zapico[10], Gianrico Farrugia[3,11], Konstantinos N. Lazaridis[3,11], Robert R. McWilliams[3,6,12]

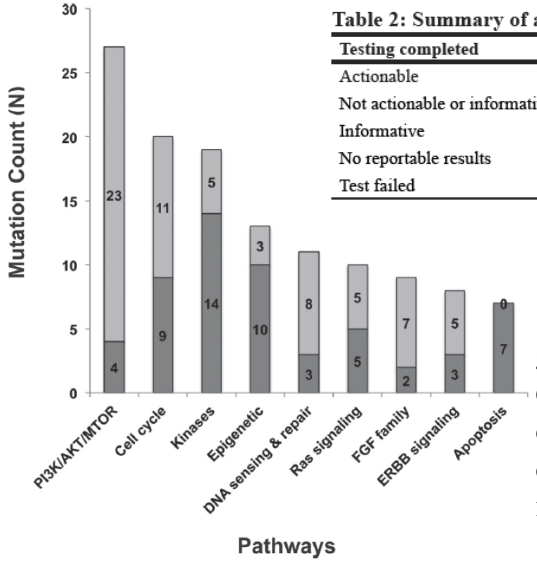
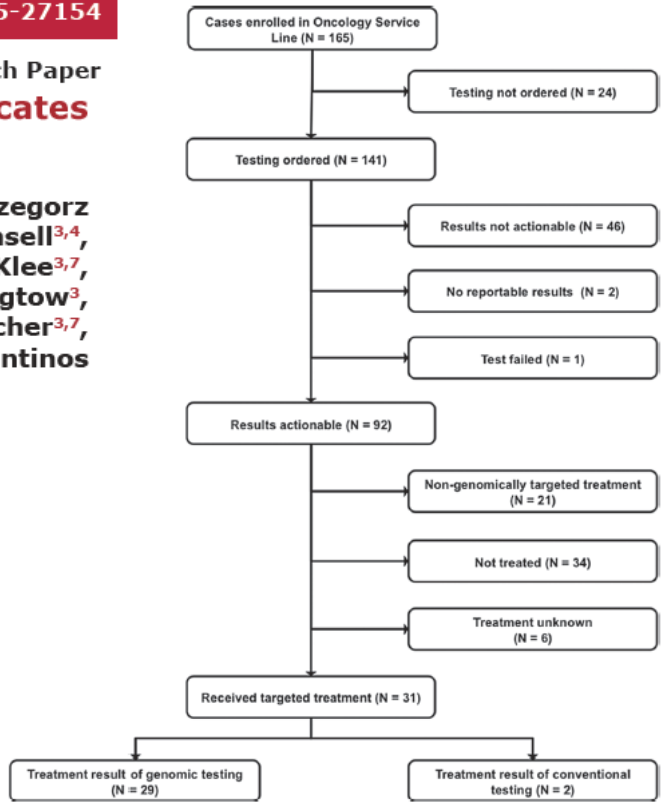


Table 2: Summary of actionable and informative results

Testing completed	*N* (%)
Actionable	92 (65%)
Not actionable or informative	35 (25%)
Informative	11 (8%)
No reportable results	2 (1%)
Test failed	1 (< 1%)

…Fully realizing the potential of tumor genomics to benefit clinical care remains challenging as surveys by ourselves and others indicate the use of genomic testing in oncology practice, but discomfort with interpreting results.



Targ Oncol
DOI 10.1007/s11523-017-0505-6

ORIGINAL RESEARCH ARTICLE

Pooled Analysis of Clinical Outcome of Patients with Chemorefractory Metastatic Colorectal Cancer Treated within Phase I/II Clinical Studies Based on Individual Biomarkers of Susceptibility: A Single-Institution Experience

Andrea Sartore-Bianchi[1] · Alessio Amatu[1] · Erica Bonazzina[1] · Stefano Stabile[1] · Laura Giannetta[1] · Giulio Cerea[1] · Ilaria Schiavetto[1] · Katia Bencardino[1] · Chiara Funaioli[1] · Riccardo Ricotta[1] · Tiziana Cipani[1] · Michele Schirru[1] · Valentina Gambi[1] · Laura Palmeri[1] · Giulia Carlo-Stella[1] · Francesca Rusconi[1] · Sara Di Bella[1] · Giovanni Burrafato[1] · Andrea Cassingena[1] · Emanuele Valtorta[1] · Calogero Lauricella[1] · Federica Pazzi[1] · Alessandra Gambaro[1] · Silvia Ghezzi[1] · Giovanna Marrapese[1] · Emiliana Tarenzi[1] · Silvio Veronese[1] · Mauro Truini[1] · Angelo Vanzulli[1,2] · Salvatore Siena[1,2]

Pie chart showing molecular targets in the pooled patients population (n=80)

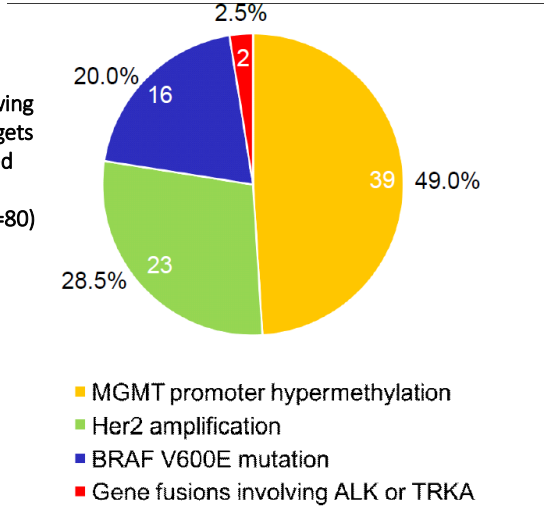


Table 1 Distribution of patients in clinical trials with actionable molecular alterations treated with matched targeted agents included in the pooled analysis

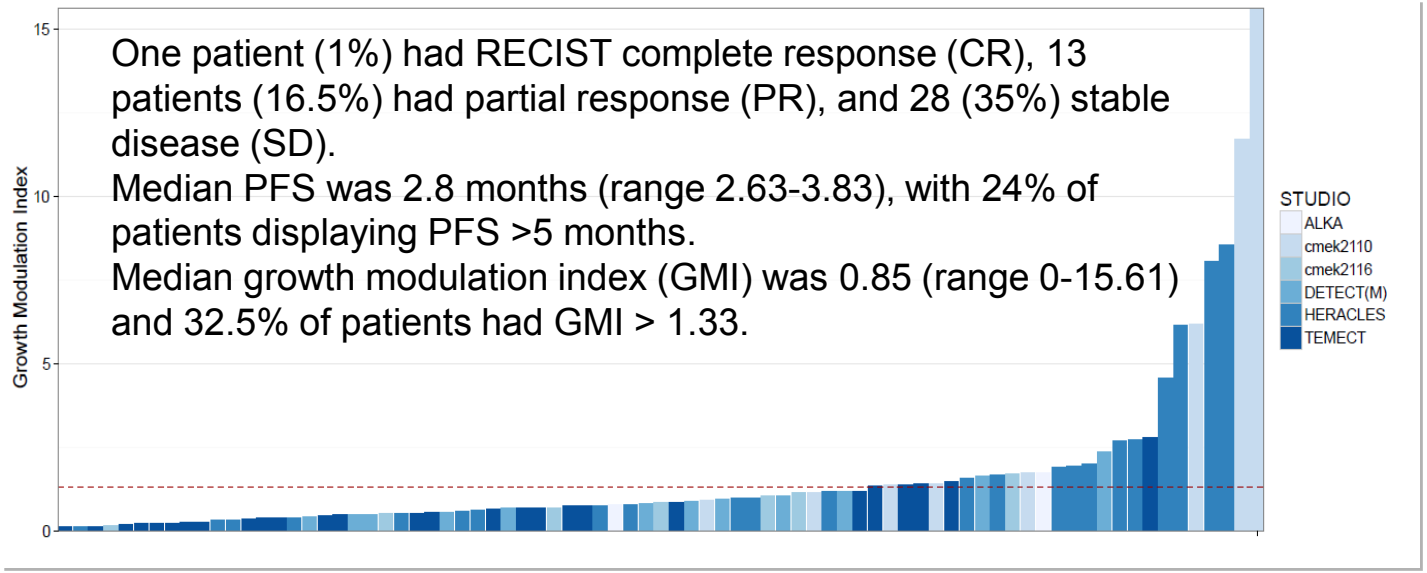
Biomarker	Study drug(s)	EudraCT N°	Patients (*n*)
MGMT promoter hypermethylation	Temozolomide [9]	2012–003338-17	27
HER2 amplification	Trastuzumab + lapatinib [10]	2012–002128-33	23
MGMT promoter hypermethylation	Dacarbazine [11]	2011–002080-21	12
BRAF mutation	MEK162 + LGX818 [NCT01543698]	2011–005875-17	9
BRAF mutation	MEK162 + panitumumab [NCT01927341]	2013–001986-18	7
NTRK or *ALK* gene fusions	Entrectinib [12]	2012–000148-88	2

Treatment of metastatic colorectal cancer (mCRC) patients driven by selection according to individual tumor molecular characteristics is expected to provide enhanced clinical benefit.

In this single-institution retrospective analysis, 3.9% of 2044 patients were found to harbor biomarkers for *ad hoc* phase I-II clinical studies, including *MGMT* promoter hypermethylation, *HER2* amplification, $BRAF^{V600E}$ mutation, and gene fusions involving *ALK* or *NTRK*.

14 patients had an objective response, and 28 stable disease. Median progression-free survival (PFS) was 2.8 months, with 24% of patients displaying PFS >5 months.

Sartore-Bianchi et al, *Targ Oncol* 2017



Our single institution case series indicates that, in a **heavily pretreated mCRC** population, about **5% of tumors display a potential actionable molecular context suitable for phase I/II trials with matched therapeutics**. Response rate and progression-free survival in our cohort were similar to earlier settings. The presence of a *KRAS* mutation exerts an overall negative impact, and it was among exclusion criteria in some studies. Application of molecular selection in mCRC is challenging and improves clinical outcome even in later lines of treatment.

Sartore-Bianchi et al, *Targ Oncol* 2017

Conclusions

- **Matching unique features of cancer types with effective therapies** is a cornerstone of **precision medicine**
- Recent advances have found that the success of biomarker-driven cancer therapy may be relevant across sites of origin (**tissue-agnostic approach**) such as the case for immunotherapy with immune checkpoint inhibitors in MSI-H tumors
- However, **the context of susceptibility to cancer therapy may vary depending on the primary histology**
- Therefore, we should be agnostic on making an absolute dichotomy of tissue-driven and tissue-agnostic approaches!
- Integration of **tumor molecular boards** would enhance application of precision medicine and make more tissue-agnostic biomarker therapies reaching the bedside

Thank You

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