Novel Molecularly Targeted Therapies and Biomarkers in Advanced Colorectal Cancer

Michael S. Lee, MD
Assistant Professor of Medicine
University of North Carolina

UNC LINEBERGER

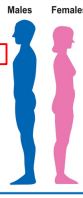
Objectives

- Discuss important clinicopathologic features underlying the biology of colorectal cancer
- Describe varying sequences of therapies in management of metastatic colorectal cancer
- Describe biomarkers that guide selection and personalization of therapies for patients with advanced colorectal cancer

Colorectal cancer is a leading cause of cancer death in the U.S.

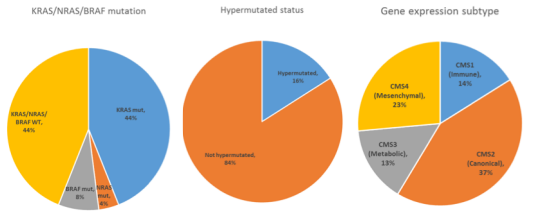
Estimated Deaths

Males			Females		
Lung & bronchus	83,550	26%	Lung & bronchus	70,500	25%
Prostate	29,430	9%	Breast	40,920	14%
Colon & rectum	27,390	8%	Colon & rectum	23,240	8%
Pancreas	23,020	7%	Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%	Ovary	14,070	5%
Leukemia	14,270	4%	Uterine corpus	11,350	4%
Esophagus	12,850	4%	Leukemia	10,100	4%
Urinary bladder	12,520	4%	Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%	Brain & other nervous system	7,340	3%
All Sites	**323,630**	**100%**	**All Sites**	**286,010**	**100%**

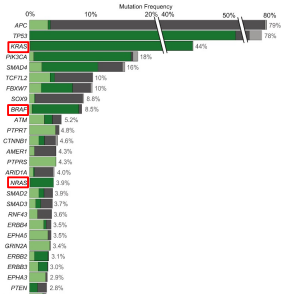


Siegel RL, et al. CA Cancer J Clin 2018; 68:7-30

Colorectal cancer is a biologically heterogeneous disease



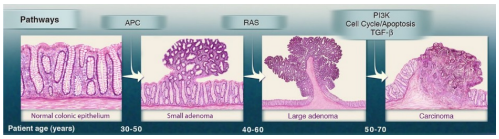
Oncogenic mutations common in key growth factor pathway proteins



Yaeger R, et al, Cancer Cell 2018;33:125-36.

Refined understanding of chromosomal and genomic instability

- The classic model of colorectal carcinogenesis…



is most representative of only a subset of colorectal cancers

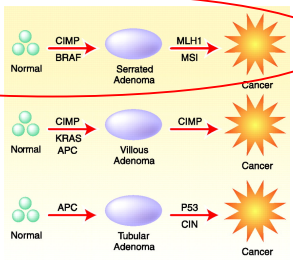
Vogelstein B, et al, Science 2013; 339:1546-58.

Microsatellite instability, hypermethylation, and chromosomal instability

Hypermethylation with microsatellite instability (10-20%)

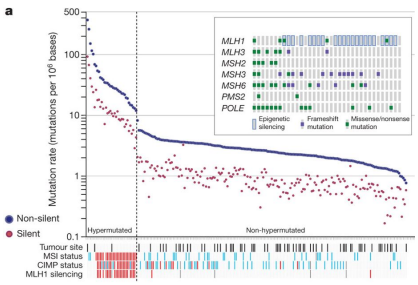
Hypermethylation with microsatellite stability (10-30%)

Chromosomal instability (50-70%)



Issa JP, Clin Cancer Res 2008; 14:5939-40.

Hypermutated tumors define a subgroup of colorectal cancers



The Cancer Genome Atlas Network. Nature 2012; 487:330-7

Multiple etiologies of hypermutated colorectal cancers

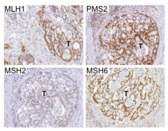
- Microsatellite instability due to deficiency of mismatch repair protein
  - Germline mutation (Lynch syndrome / HNPCC)
  - Epigenetic silencing via methylation of MLH1 promoter
- DNA polymerase ε (POLE) or δ (POLD1) proofreading domain mutation

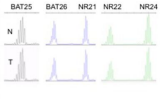
Yaeger R, et al, Cancer Cell 2018;33:125-36.

Tests for microsatellite instability / deficient mismatch repair

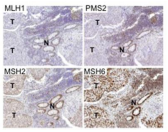
Immunohistochemistry | Polymerase chain reaction

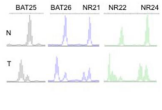
Microsatellite stable





Microsatellite unstable





There is 96% concordance between IHC and PCR, but 11.8% of MSI-High tumors by PCR had discordant IHC – often in cases of HNPCC where mutations do not abrogate nuclear staining.

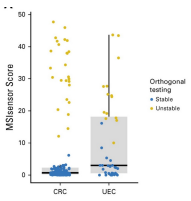
Bartley AN, et al, Cancer Prev Res (Phila) 2012; 5:320-7.

Scarpa A, et al. Microsatellite Instability - Defective DNA Mismatch Repair: ESMO Biomarker Factsheet

UNC

Next generation sequencing to infer MSI

- 99.4% concordance with MSKCC sequencing panel



Middha S, et al, JCO Precis Oncol 2017

- 97% concordance with Foundation One sequencing (95 microsatellite loci).

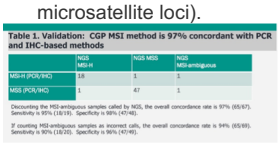


Table 1. Validation: CGP MSI method is 97% concordant with PCR and IHC-based methods

	NGS MSI-H	NGS MSS	NGS MSI-ambiguous
MSI-H (PCR/IHC)	18	1	1
MSS (PCR/IHC)	1	47	1

Discounting the MSI-ambiguous samples called by NGS, the overall concordance rate is 97% (65/67). Sensitivity is 95% (18/19). Specificity is 98% (47/48).

If counting MSI-ambiguous samples as incorrect calls, the overall concordance rate is 94% (65/69). Sensitivity is 90% (18/20). Specificity is 96% (47/49).

"The clinical validity of the qualitative MSI designation has not been established."

Hall MJ, et al. GI ASCO 2016

UNC

Case 1

- A previously healthy 60 year old male presents after colonoscopy for iron deficiency anemia revealed moderately differentiated adenocarcinoma in the ascending colon. He has no significant family history of colorectal cancers. Initial staging CT scans revealed multiple bilobar liver metastases and peritoneal carcinomatosis. The patient has an excellent performance status.

UNC

Poll

Which of the following tests is not recommended to send tumor tissue for?

A) BRAF codon 600 mutation
B) Assessment of microsatellite stability, by mismatch repair protein staining and/or MSI testing by PCR
C) PD-L1 immunohistochemistry using 22C3 antibody
D) KRAS exons 2, 3, and 4 mutations
E) NRAS exons 2, 3, and 4 mutations

Answer

Which of the following tests is not recommended to send tumor tissue for?

A) BRAF codon 600 mutation
B) Assessment of microsatellite stability, by mismatch repair protein staining and/or MSI testing by PCR
C) PD-L1 immunohistochemistry using 22C3 antibody
D) KRAS exons 2, 3, and 4 mutations
E) NRAS exons 2, 3, and 4 mutations

Case continued

- This patient with moderately differentiated adenocarcinoma of the ascending colon was found to have intact nuclear staining of MLH1, MSH2, MSH6, and PMS2 on immunohistochemistry. Testing for KRAS, NRAS, and BRAF mutations revealed no mutations.

Poll

Out of the following choices, which of the following treatments would be the best first-line therapy?

A) Pembrolizumab
B) FOLFIRI + Bevacizumab
C) FOLFOX + Panitumumab
D) CAPOX + Ziv-aflibercept
E) Trifluridine + Tipiracil

Answer

Out of the following choices, which of the following treatments would be the best first-line therapy?

A) Pembrolizumab
B) FOLFIRI + Bevacizumab
C) FOLFOX + Panitumumab
D) CAPOX + Ziv-aflibercept
E) Trifluridine + Tipiracil

First-line chemotherapy of metastatic colorectal cancer

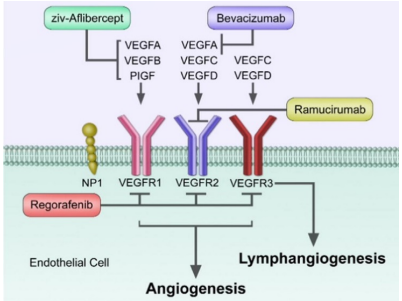
Chemo backbone
- FOLFOX or CAPOX
- FOLFIRI
- 5FU/leucovorin or capecitabine if less fit

+

Biologic agent
- Bevacizumab
- Anti-EGFR antibody (Cetuximab or Panitumumab) if RAS WT and left-sided primary

In certain circumstances
FOLFOXIRI ± bevacizumab

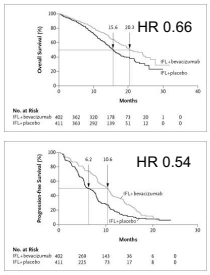
Anti-angiogenic therapies in colorectal cancer



Clarke JM, et al, Cancer Treat Rev 2014; 40:1065-72..

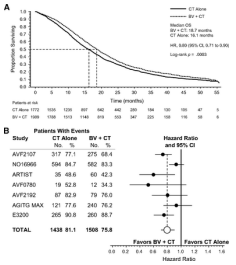
1L bevacizumab improves survival (in at least some trials)

AVF2107



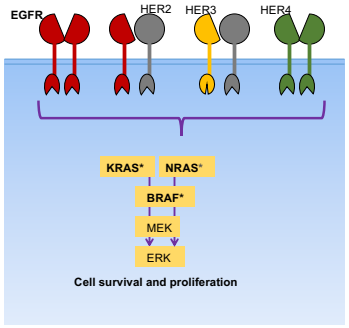
Hurwitz HI, et al, New Engl J Med 2004:350:2335-42.

Meta-analysis



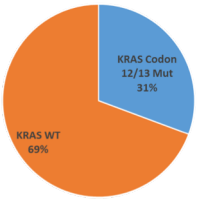
Hurwitz HI, et al, Oncologist 2013;18:1004-12.

Anti-EGFR therapies in RAS WT colorectal cancers



KRAS codons 12 and 13 mutations are most common

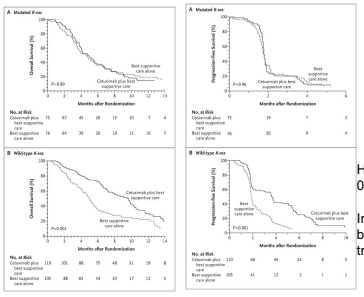
- Studies find 30-40% *KRAS* codon 12/13 mutations



KRAS mutation is predictive biomarker for resistance to anti-EGFR

HR 0.55 (95% CI 0.41-0.74)

Interaction p=0.01 between KRAS and treatment



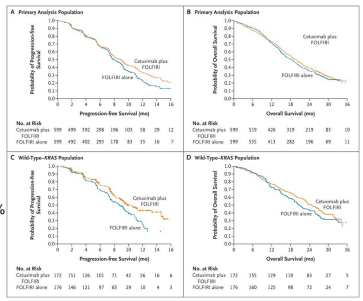
HR 0.40 (95% CI 0.30-0.54)

Interaction p<0.001 between KRAS and treatment

Karapetis CS, et al, N Engl J Med 2008; 359:1757-65

KRAS mutation is predictive biomarker for resistance to anti-EGFR

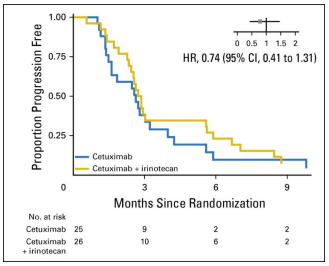
HR 0.68 (95% CI 0.50-0.94)



HR 0.84 (95% CI 0.64-1.11)

Van Cutsem E, et al, N Engl J Med 2009;360:1408-17

KRAS G13D mutant CRC is also not sensitive to anti-EGFR therapy

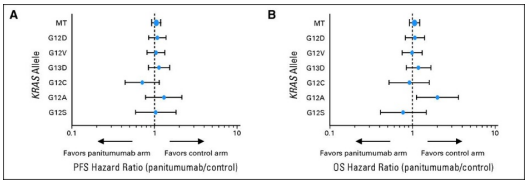


10% 6-mo PFS similar to best supportive care arm of CO.17

0% response rate with cetuximab monotherapy

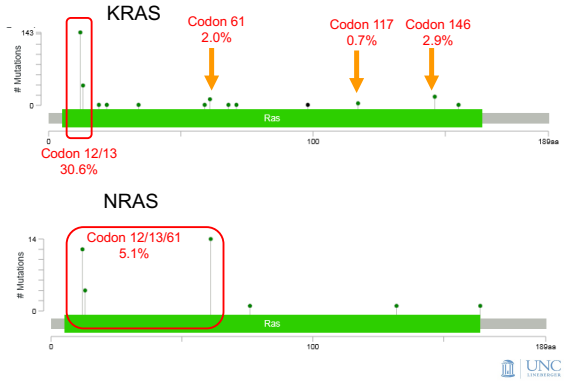
Segelov E, et al. J Clin Oncol 2016; 34:2258-64

KRAS G13D mutant CRC is also not sensitive to anti-EGFR therapy

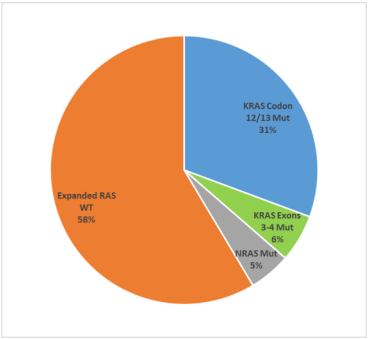


Peeters M, et al. J Clin Oncol 2013; 31:759-65

"Expansion" of RAS mutations



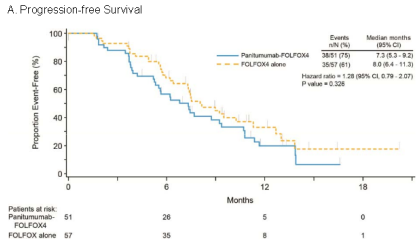
Expanded RAS mutations



- 16% of the KRAS codon 12/13 WT tumors have an expanded RAS mutation

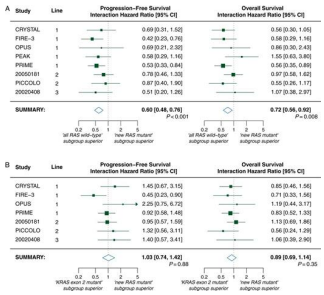
Expanded RAS mutation is negative predictive biomarker for anti-EGFR

- Inferior PFS and OS among RAS mutated (KRAS exon 2 WT) CRC



Douillard JY, et al, New Engl J Med 2013; 369:1023-34

Expanded RAS mutation is negative predictive biomarker for anti-EGFR

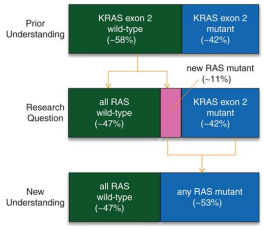


Atypical RAS mutations significantly associated with worse outcomes with anti-EGFR therapy (interaction p-value for PFS <0.001, for OS 0.008)

Sorich MJ, et al, Ann Oncol 2015; 26:13-21

Expanded RAS mutation testing is now standard of care

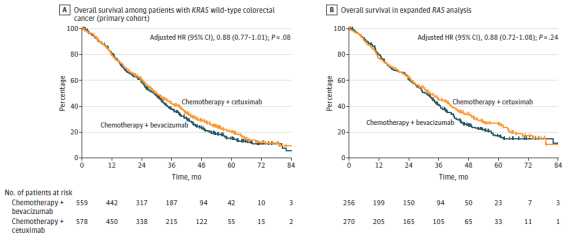
- Expanded RAS mutation (KRAS and NRAS codons 12, 31, 59, 61, 117, 146) is predictive for lack of benefit of anti-EGFR therapy



Sorich MJ, et al, Ann Oncol 2015; 26:13-21

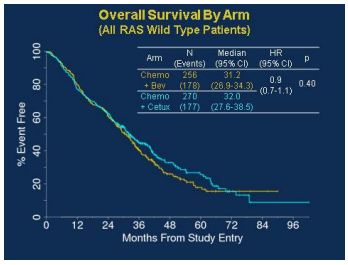
Is there an optimal first-line biologic for RAS WT colorectal cancer?

CALGB/SWOG 80405 showed no significant difference between bevacizumab vs cetuximab in KRAS wild-type cancer



Venook AP, et al, JAMA 2017; 317:2392-2401

80405 also showed no difference by expanded RAS WT



Lenz HJ, et al, Ann Oncol 2014; 25 suppl_4, abstract 501O

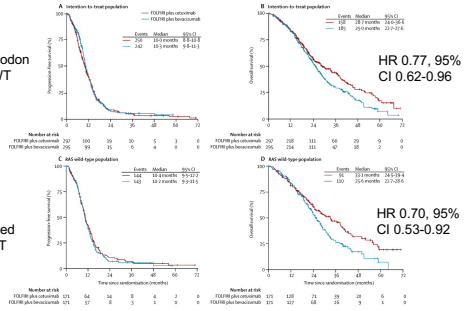
But FIRE-3 did show survival benefit in favor of cetuximab

KRAS codon 12/13 WT

HR 0.77, 95% CI 0.62-0.96

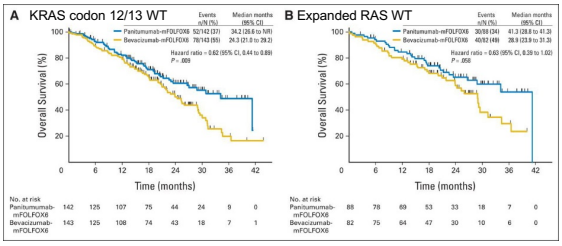
Expanded RAS WT

HR 0.70, 95% CI 0.53-0.92



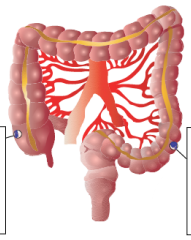
Heinemann V, et al, Lancet Oncol 2014; 15:1065-75

PEAK showed survival benefit in favor of panitumumab



Schwartzberg LS, et al, J Clin Oncol 2014; 32:2240-7.

Significant effect of right vs left sided primary tumor and anti-EGFR efficacy

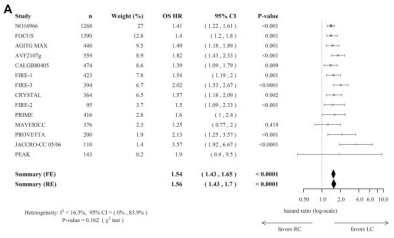


RIGHT COLON
Cecum
Ascending colon
Hepatic flexure
Transverse colon*

LEFT COLON
Splenic flexure
Descending colon
Sigmoid colon
Rectum

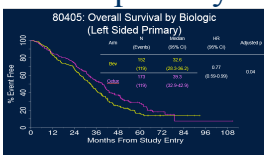
Adapted from Lee MS, et al, J Natl Compre Canc Netw 2017; 15:411-9

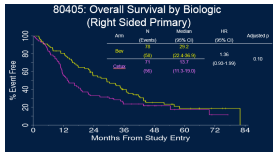
Right-sided CRC is a negative prognostic biomarker



Holch JW, et al, Eur J Cancer 2017; 70:87-98

Markedly worse survival among right-sided primary with 1L cetuximab



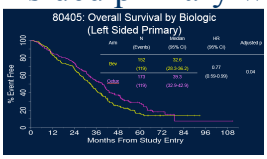


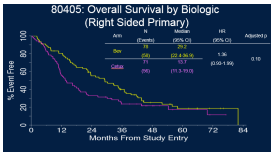
All RAS wt N=474	Right 1° Median OS (mos)	Left 1° Median OS (mos)	Hazard Ratio Left vs Right 95% CI (adjusted*)	P (adjusted*)
All pts	21.9	35.2	0.72 (0.56,0.92)	0.009
Cet	13.8	39.3	0.55 (0.39, 0.79)	0.001
Bev	29.2	32.6	0.88 (0.62, 1.25)	0.50

*Adjusted for biologic, protocol chemotherapy, prior adjuvant therapy, prior RT, age, sex, synchronous disease, in place primary, liver metastases

Venook AP, et al, J Clin Oncol 2016; 34 suppl15, abstract 3504

Markedly worse survival among right-sided primary with 1L cetuximab





BIOLOGIC	SIDE OF PRIMARY	HAZARD RATIO 95% CI	P (adjusted*)
Any biologic			
OS	Cetux v Bev; left Cetux v Bev; right	1.81 (1.15, 2.84)	$P_{adj} = 0.009$
PFS		1.94 (1.28, 2.95)	$P_{adj} = 0.001$
Cetux v Bev	Left		
OS		0.77 (0.59, 0.99)	0.04
PFS		0.84 (0.66, 1.06)	0.15
Cetux v Bev	Right		
OS		1.36 (0.93, 1.99)	0.10
PFS		1.64 (1.15, 2.36)	0.006

*Adjusted for biologic, protocol chemotherapy, prior adjuvant therapy, prior RT, age, sex, synchronous disease, in place primary, liver metastases

Venook AP, et al, J Clin Oncol 2016; 34 suppl15, abstract 3504

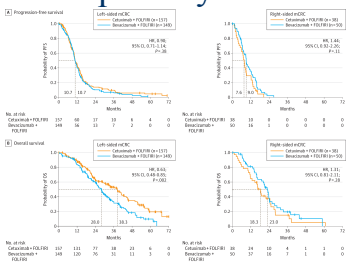
80405 Results with Expanded RAS and BRAF testing

	Left sided Median OS (95% CI)	Right sided Median OS (95% CI)	Log-rank p-value	Adjusted HR (95% CI)
Total population (n=728)	32.9 (30.7-35.3)	19.6 (7.0-23.6)	<0.0001	1.39 (1.03-1.88)
All RAS/BRAF WT (n=225)				
Bevacizumab (n=91)	38.7 (34.3-42.3)	34.4 (23.6-82.0)	0.918	0.62 (0.32-1.23)
Cetuximab (n=96)	40.3 (34.0-48.3)	18.4 (14.2-30.1)	0.003	1.68 (0.85-3.34)
BRAF Mutant				
Bevacizumab (n=23)	12.0 (4.8-14.5)	23.7 (7.9-36.9)	0.035	
Cetuximab (n=16)	9.6 (8.6-NE)	5.8 (1.9-11.7)	0.508	

Adjusted Cox proportional HR for side 1.392 (1.032-1.878)

Venook AP, et al, J Clin Oncol 2017; 35 suppl, abstract 3503

Markedly worse survival among right-sided primary with 1L cetuximab



Multivariate analysis showed sidedness remained significant even after accounting for BRAF mutation

Among right-sided CRC, FOLFIRI + cetuximab is also not superior to FOLFIRI alone by PFS (p=0.66) or OS (p=0.76)

Tejpar S, et al, JAMA Oncol 2017; 3:194-201.

Summary of First-Line Trials for all-RAS WT

	Right-sided Median OS	Left-sided Median OS
80405 (n=474)	**N=149**	**N=325**
Cetuximab	13.6 (11.3-19.0)	39.3 (32.9-42.9)
Bevacizumab	29.2 (22.4-36.9)	32.6 (28.3-36.2)
FIRE-3 (n=394)	**N=88**	**N=306**
Cetuximab	18.3	38.3
Bevacizumab	23.0	28.0
PEAK (n=143)	**N=36**	**N=107**
Panitumumab	17.5 (9.1-30.7)	43.4 (31.6-63.0)
Bevacizumab	21.0 (6.0-29.0)	32.0 (26.0-47.4)

Venook AP, et al, J Clin Oncol 2016; 34 suppl15, abstract 3504; Tejpar S, et al, JAMA Oncol 2017; 3:194-201; Boeckx N, et al, Ann Oncol 2017; 28:1862-8.

Summary of First-Line Trials for all-RAS WT

	Right-sided Median OS	Left-sided Median OS	
80405 (n=474)	**N=149**	**N=325**	
Cetuximab	13.6 (11.3-19.0)	39.3 (32.9-42.9)	p=0.001
Bevacizumab	29.2 (22.4-36.9)	32.6 (28.3-36.2)	p=0.50
FIRE-3 (n=394)	**N=88**	**N=306**	
Cetuximab	18.3	38.3	p<0.001
Bevacizumab	23.0	28.0	p=0.04
PEAK (n=143)	**N=36**	**N=107**	
Panitumumab	17.5 (9.1-30.7)	43.4 (31.6-63.0)	p=0.007
Bevacizumab	21.0 (6.0-29.0)	32.0 (26.0-47.4)	p=0.004

Venook AP, et al, J Clin Oncol 2016; 34 suppl15, abstract 3504; Tejpar S, et al, JAMA Oncol 2017; 3:194-201; Boeckx N, et al, Ann Oncol 2017; 28:1862-8.

Summary of First-Line Trials for all-RAS WT

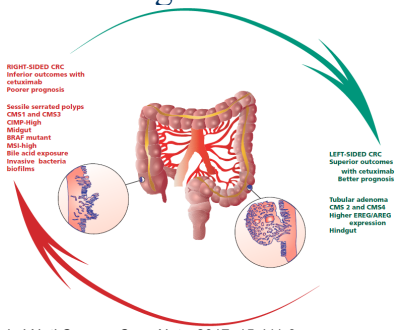
	Right-sided Median OS	Left-sided Median OS		
80405 (n=474)	**N=149**	**N=325**		
Cetuximab	13.6 (11.3-19.0)	39.3 (32.9-42.9)	p=0.04	Interaction p=0.009
Bevacizumab	29.2 (22.4-36.9) p=0.10	32.6 (28.3-36.2)		
FIRE-3 (n=394)	**N=88**	**N=306**		
Cetuximab	18.3	38.3	p=0.002	Interaction p=0.009
Bevacizumab	23.0 p=0.28	28.0		
PEAK (n=143)	**N=36**	**N=107**		
Panitumumab	17.5 (9.1-30.7)	43.4 (31.6-63.0)	p=0.31	
Bevacizumab	21.0 (6.0-29.0) p=0.33	32.0 (26.0-47.4)		

Venook AP, et al, J Clin Oncol 2016; 34 suppl15, abstract 3504; Tejpar S, et al, JAMA Oncol 2017; 3:194-201; Boeckx N, et al, Ann Oncol 2017; 28:1862-8.

Conclusions for selecting a first-line biologic therapy for RAS WT

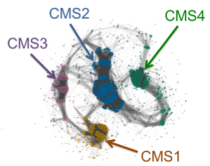
- Confirm wild-type in extended RAS (KRAS and NRAS exons 2,3,4)
- Do not use anti-EGFR based therapy for right-sided primary
- Consider first-line anti-EGFR (vs. bevacizumab) based therapy for left-sided primary
- If has BRAF mutation consider different strategy

Primary side is a clinical surrogate for biologic differences



Lee MS, et al, J Natl Compre Canc Netw 2017; 15:411-9

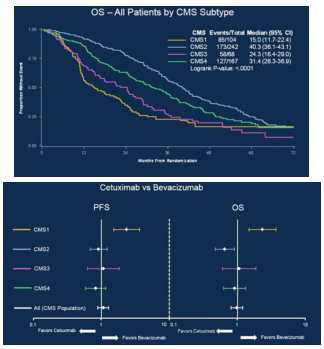
Consensus Molecular Subtypes (CMS) as a potential biomarker



CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF-β activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

Guinney J, et al, Nat Medicine 2015; 21:1350-6.

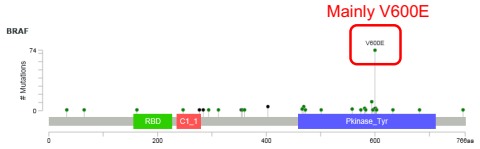
CMS classification is prognostic



Lenz HJ, et al, J Clin Oncol 2017; 35 suppl, abstract 3511

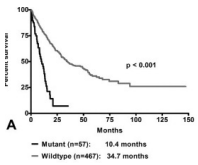
BRAF mutations are an important biomarker in colorectal cancer

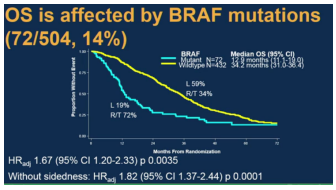
- 5-11% of CRCs are *BRAF* mutant



From Yaeger R, et al, Cancer Cell 2018; 33:125-36

BRAF mutation is a biomarker of very poor prognosis



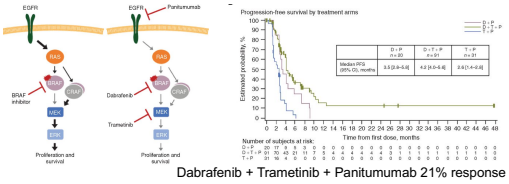


Tran B, et al, Cancer 2011; 117:4623-32

Innocenti F, et al, J Clin Oncol 2017; 35 suppl, abstract 3504

Targeted approaches to target BRAF V600 mutant CRC

- Seek clinical trials!
- Multilevel pathway inhibition is promising approach



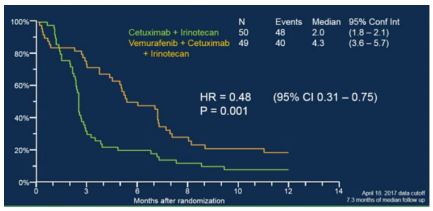
Dabrafenib + Trametinib + Panitumumab 21% response rate

- Ongoing phase III BEACON CRC trial of encorafenib + binimetinib +/- cetuximab vs chemo/cetuximab

Corcoran RB, et al, Cancer Discov 2018; 8:428-43

Targeted approaches to target BRAF V600 mutant CRC

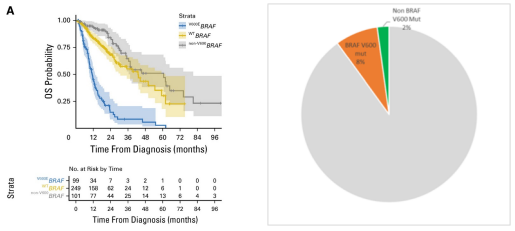
- Consider vemurafenib + cetuximab + irinotecan if no prior anti-EGFR therapy



- Median OS 9.6 mo vs 5.9 mo, HR 0.73 (0.45-1.17) but limited by crossover

Kopetz S, et al, J Clin Oncol 2017; 35 suppl, abstract 3505

BRAF mutations are not all equivalent



	Codons	% BRAF Mutations
Class I: Kinase activity activated	V600	78.4%
Class II: Kinase activity activated	G464, G466, G469, N581, L597, A598, K601,	6.1%
Class III: Kinase activity impaired	G466, **D594**, G596	15.5%

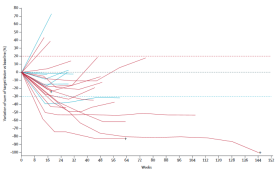
More dependent on receptor signaling in preclinical models; Clinical relevance unclear

Jones JC, et al, J Clin Oncol 2017; 35:2624-30

HER2 amplification appears targetable from preliminary trial data

HERACLES: Trastuzumab + Lapatinib

- ORR 30% (95% CI 13-47)
- PFS 21 wk (95% CI 16-32)



MyPathway: Trastuzumab + Pertuzumab

- ORR 37.5% (95% CI 21.1-56.2)

Hurwitz H, et al, J Clin Oncol 2017; suppl 4: Abstract 676

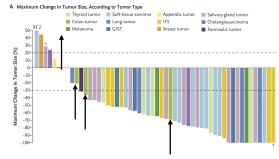
S1613: Randomized phase II trial of trastuzumab + pertuzumab vs cetuximab + irinotecan for HER2 amplified, RAS/BRAF WT previously treated metastatic CRC

Sartore-Bianchi A, et al, Lancet Oncol 2016;17:738-46

Rare but potentially actionable gene fusions in CRC

NTRK fusion

- 0.5% of CRC
- 4/55 subjects in the pivotal larotrectinib trial had colon cancer



Drilon A, et al, New Engl J Med 2018; 378:731-9

ALK fusion

- 0.2% of CRCs
- Case reports of responses with ceritinib

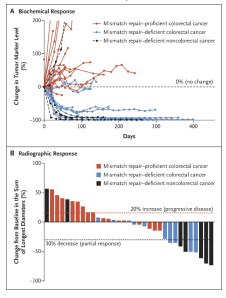
Yakirevich E, et al, Clin Cancer Res 2016;22:3831-40.

ALK, ROS1, and NTRK fusions are in 0.2-2.4% of CRC and are more common in elderly, right-sided, RAS WT, MSI-High cancers

Pietrantonio F, et al, J Natl Cancer Inst 2017; 109:

MSI-High is a key predictive biomarker for immune checkpoint inhibitors

KEYNOTE-016: pembrolizumab



Pembrolizumab granted accelerated FDA approval for MSI-High CRC following treatment with 5FU, oxaliplatin, irinotecan

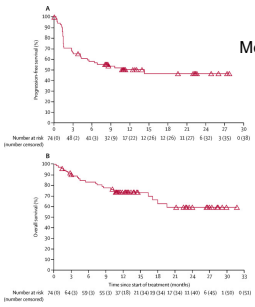
All MSI-High (n=149)	
Complete response rate	7.4%
Partial response rate	32.2%
ORR (95% CI)	39.6% (31.7-47.9)
Median duration of response	Not reached

MSI-High CRC (n=90)	
ORR	36%
Range of duration of response	1.6+ to 22.7+ mo

Le DT, et al, New Engl J Med 2015; 372:2509-20

MSI-High is a key predictive biomarker for immune checkpoint inhibitors

CheckMate 142: Nivolumab



Median PFS 14.3 mo (95% CI 4.30-NE)

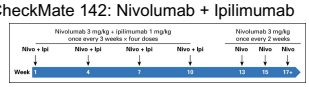
12-mo OS rate 73% (95% CI 62-82)

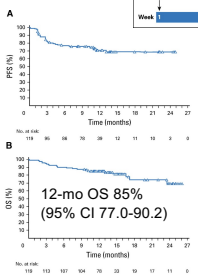
Nivolumab granted accelerated FDA approval for MSI-High CRC following treatment with 5FU, oxaliplatin, irinotecan

Overman MJ, et al, J Clin Oncol 2018; 36:773-9.

MSI-High is a key predictive biomarker for immune checkpoint inhibitors

CheckMate 142: Nivolumab + Ipilimumab





12-mo OS 85% (95% CI 77.0-90.2)

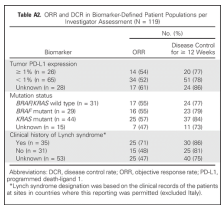


Table A2. ORR and DCR in Biomarker-Defined Patient Populations per Investigator Assessment (N = 119)

Biomarker	No. (%) ORR	No. (%) Disease Control for ≥ 12 Weeks
Tumor PD-L1 expression		
≥ 1% (n = 26)	14 (54)	20 (77)
< 1% (n = 65)	34 (52)	51 (78)
Unknown (n = 28)	17 (61)	24 (86)
Mutation status		
BRAF/*KRAS* wild type (n = 31)	17 (55)	24 (77)
BRAF mutant (n = 29)	16 (55)	23 (79)
KRAS mutant (n = 44)	25 (57)	37 (84)
Unknown (n = 15)	7 (47)	11 (73)
Clinical history of Lynch syndrome*		
Yes (n = 35)	25 (71)	30 (86)
No (n = 31)	15 (48)	25 (81)
Unknown (n = 53)	25 (47)	40 (75)

Abbreviations: DCR, disease control rate; ORR, objective response rate; PD-L1, programmed death-ligand 1.
*Lynch syndrome designation was based on the clinical records of the patients at sites in countries where this reporting was permitted (excluded Italy).

Nivolumab + Ipilimumab under consideration at FDA

Overman MJ, et al, J Clin Oncol 2018; 36:773-9.

What is the best approach for treatment of a newly diagnosed MSI-High CRC?

- Anti-PD1 therapy?
- Anti-PD1 + anti-CTLA4 therapy?

Clinical Trial	Line of therapy	Randomized Arms
KEYNOTE-177	Previously untreated	Pembrolizumab vs investigator's choice SOC
COMMIT (NRG-GI-004)	Previously untreated	mFOLFOX6+Bevacizumab vs Atezolizumab vs mFOLFOX6+Bevacizumab+Atezolizumab

The enigma of immuno-oncology in MSS colorectal cancer

- POLE mutant cancer may respond to pembrolizumab (Gong J, et al, J Natl Compr Canc Netw 2017;15:142-7)
- Recent negative phase III IMblaze370 trial of atezolizumab + cobimetinib vs atezolizumab vs regorafenib
- Key question is how to increase lymphocyte infiltration into "immune deserts" of T cell devoid tumors (Le DT, et al, Cancer Immunol Res 2017;5:942-9)

Summary of molecular biomarker testing guidelines for standard of care

- Test KRAS and NRAS codons 12, 13, 59, 61, 117, and 146 for patients being considered for anti-EGFR therapy
- Test for BRAF p.V600 mutation for prognostic stratification
  - Insufficient evidence for BRAF p.V600 mutation as predictive biomarker against anti-EGFR therapy
- Test for mismatch repair status for identification of patients at high risk for Lynch syndrome and/or prognostic stratification *(and for immune checkpoint inhibitor therapy)*
- Though metastatic/recurrent tissue is preferred for biomarker testing, in their absence, primary tumor tissue is acceptable and should be used.

Sepulveda AR, et al, J Clin Oncol 2017;35:1453-86 *(my addendum given subsequent FDA approval)*

Other non-standard potentially actionable findings for chemo-refractory patients

Always consider clinical trials!

Molecular Profile	Frequency	Therapy Options
BRAF V600E Mutant	5-11%	Cetuximab + Vemurafenib + Irinotecan *
BRAF non-V600 Mutant	<1%	? RTK inhibition for class III
HER2 Amplified	5%	Trastuzumab + Lapatinib Trastuzumab + Pertuzumab
NTRK fusion	<0.5%	TRK inhibitor
ALK fusion	<0.5%	? ALK inhibitor
POLE mutation with hypermutated status	<1%	? Anti-PD1 antibody

* Listed in NCCN guidelines
? Based on case reports or preclinical data, though compelling rationale