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

AMP workshop : 15th November 2017

Biomarker Driven Therapy in Colorectal Cancer: Established And Evolving Evidence

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Disclosures

- No relevant disclosures

Objectives

- Understand current management of mCRC as it pertains to biomarker guided therapy

Jemal et al. CA CANCER J CLIN 2014

Colorectal Cancer

Estimated New Cases

	Males			Females		
Prostate	180,890	21%		Breast	246,660	29%
Lung & bronchus	117,920	14%		Lung & bronchus	106,470	13%
Colon & rectum	70,820	8%		Colon & rectum	63,670	8%
Urinary bladder	58,950	7%		Uterine corpus	60,050	7%
Melanoma of the skin	46,870	6%		Thyroid	49,350	6%
Non-Hodgkin lymphoma	40,170	5%		Non-Hodgkin lymphoma	32,410	4%
Kidney & renal pelvis	39,650	5%		Melanoma of the skin	29,510	3%
Oral cavity & pharynx	34,780	4%		Leukemia	26,050	3%
Leukemia	34,090	4%		Pancreas	25,400	3%
Liver & intrahepatic bile duct	28,410	3%		Kidney & renal pelvis	23,050	3%
All Sites	**841,390**	**100%**		**All Sites**	**843,820**	**100%**

134,490

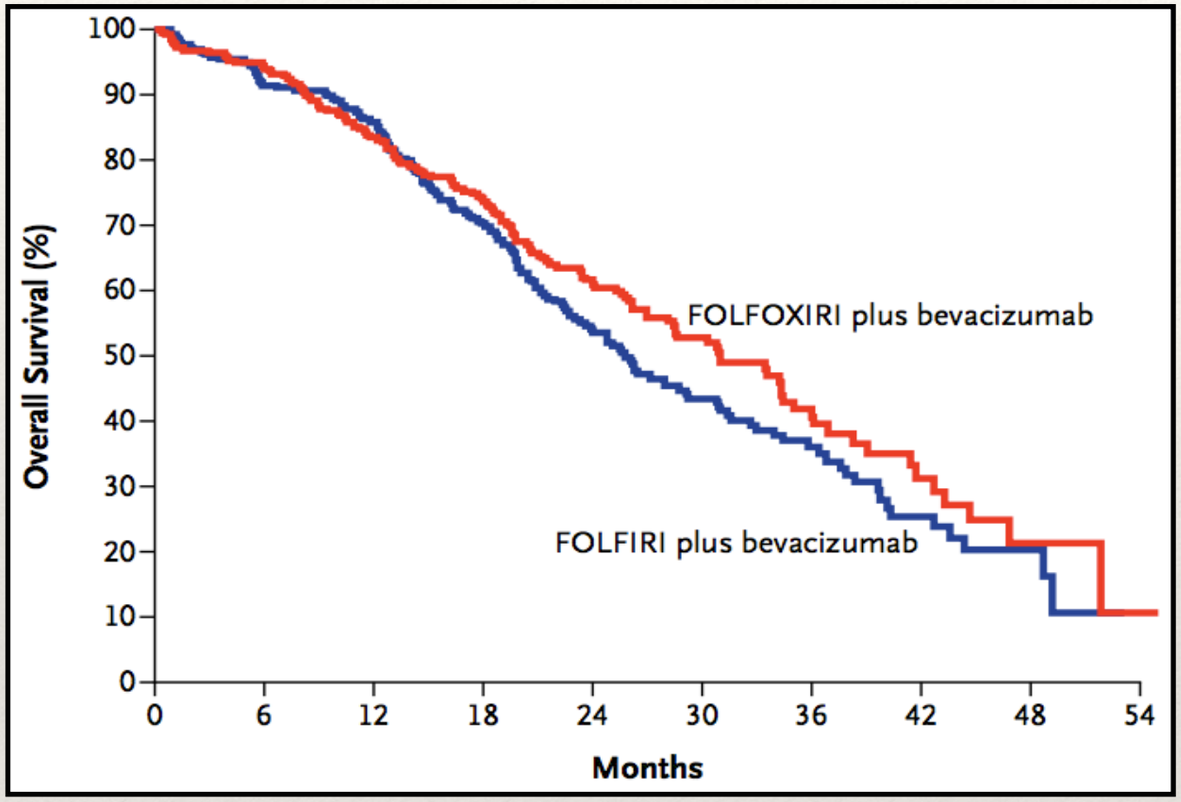
Estimated Deaths

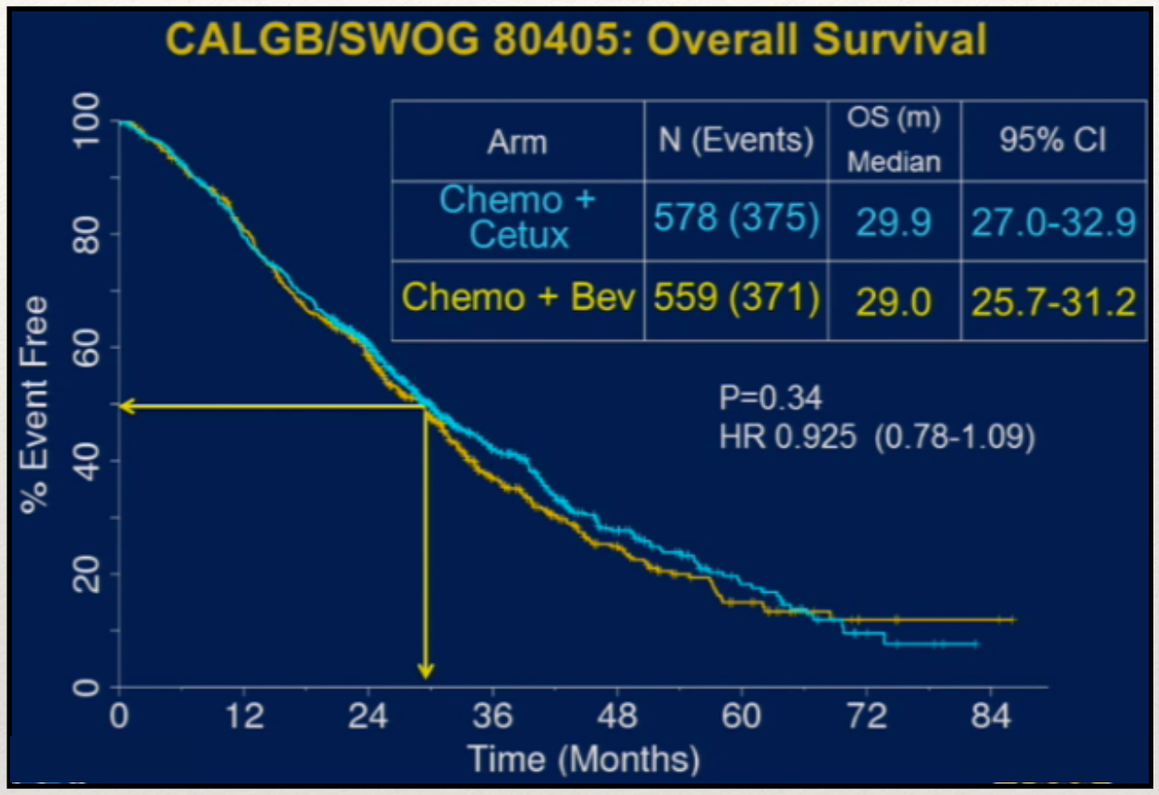
	Males			Females		
Lung & bronchus	85,920	27%		Lung & bronchus	72,160	26%
Prostate	26,120	8%		Breast	40,450	14%
Colon & rectum	26,020	8%		Colon & rectum	23,170	8%
Pancreas	21,450	7%		Pancreas	20,330	7%
Liver & intrahepatic bile duct	18,280	6%		Ovary	14,240	5%
Leukemia	14,130	4%		Uterine corpus	10,470	4%
Esophagus	12,720	4%		Leukemia	10,270	4%
Urinary bladder	11,820	4%		Liver & intrahepatic bile duct	8,890	3%
Non-Hodgkin lymphoma	11,520	4%		Non-Hodgkin lymphoma	8,630	3%
Brain & other nervous system	9,440	3%		Brain & other nervous system	6,610	2%
All Sites	**314,290**	**100%**		**All Sites**	**281,400**	**100%**

49,190

Loupakis et al. NEJM 2014; Venook et al. ASCO (Abstract) 2014

Prognosis





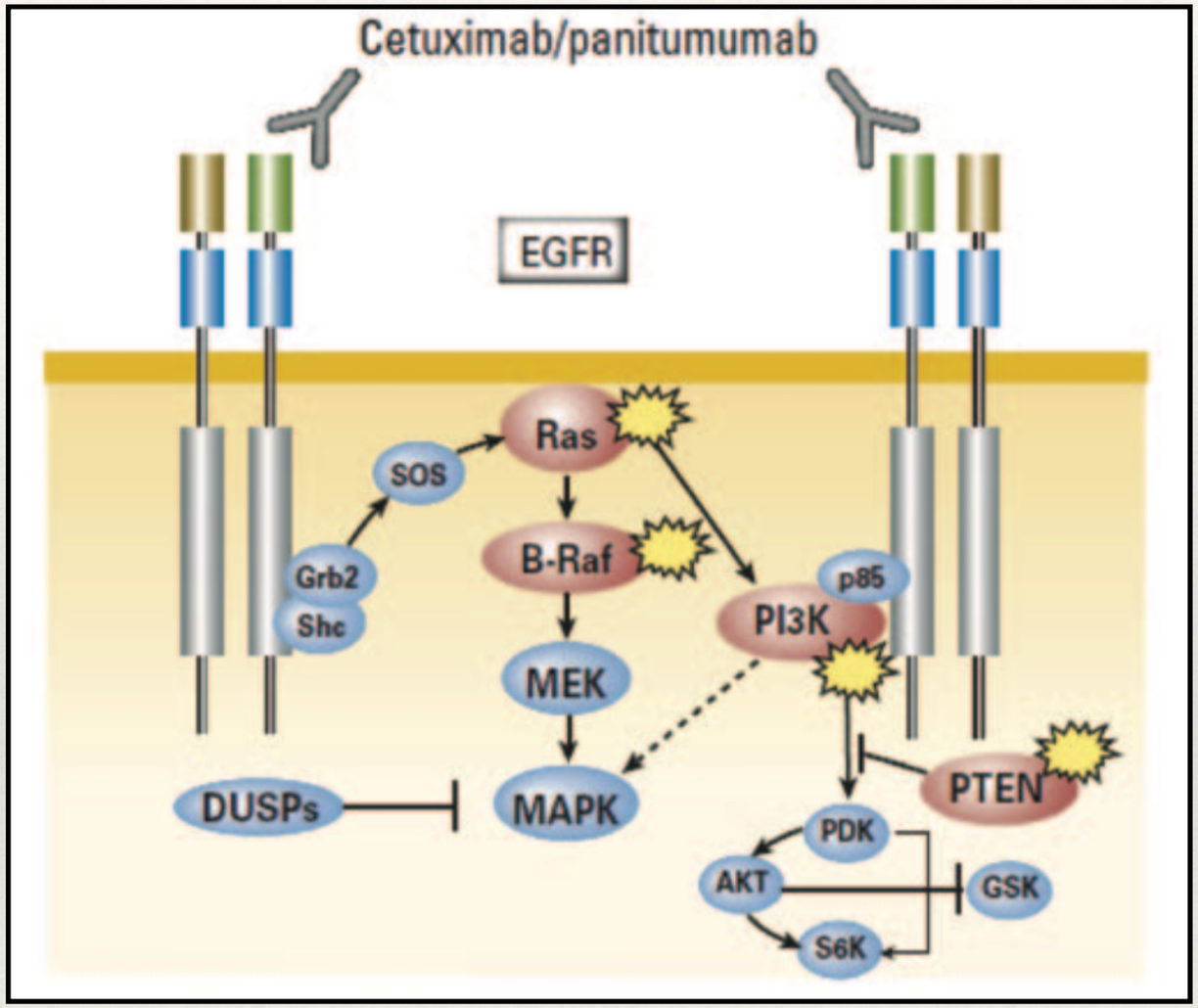
Median OS = 24-30 months

Biomarkers Driven Therapy in mCRC

Kelley et al. JNCCN 2011

Biomarkers in mCRC

- MSI-H
- EGFR Pathway:
  - Mutations:
    - KRAS/NRAS
    - BRAF
  - Amplification (HER2)
- CMS (Consensus Molecular Subtype)



MSI-H

Le et al. NEJM 2015

Colon Cancer & Immunotherapy

Phase 2 study of pembrolizumab, an anti–PD1 immune checkpoint inhibitor (N = 41)

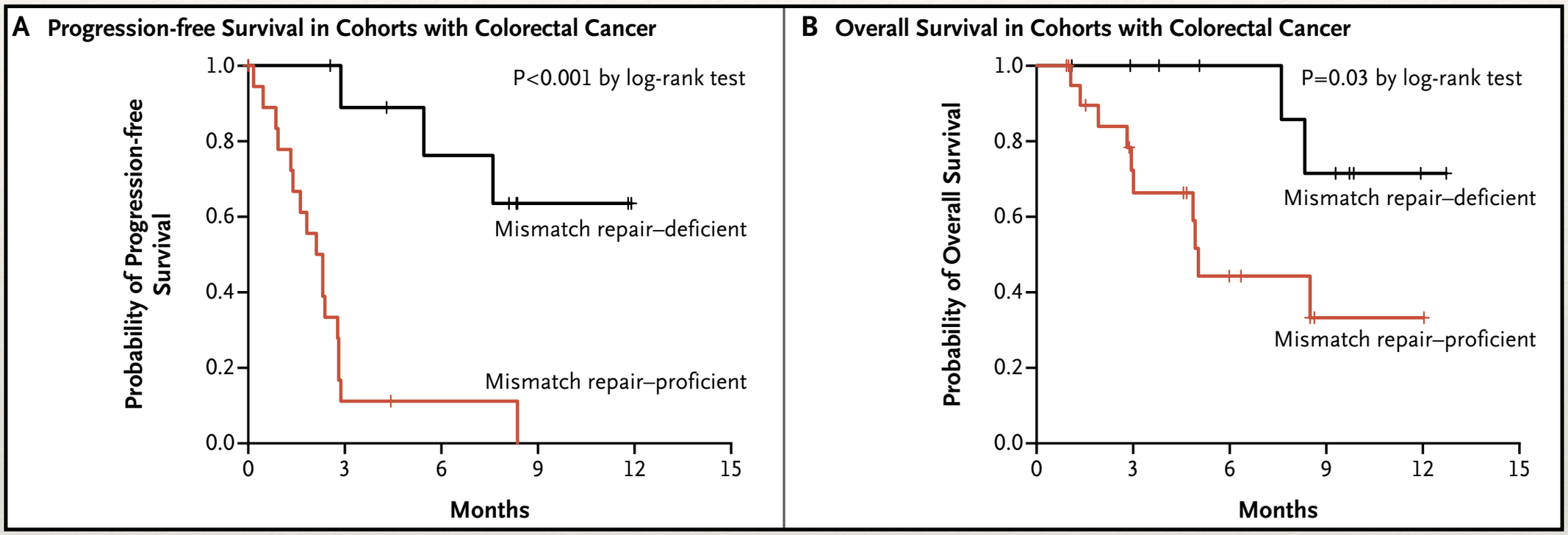


Table 2. Objective Responses According to RECIST Criteria.

Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

Listen to the FDA D.I.S.C.O. podcast about this approval

On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This is the FDA's first tissue/site-agnostic approval.

The approval was based on data from 149 patients with MSI-H or dMMR cancers enrolled across five uncontrolled, multi-cohort, multi-center, single-arm clinical trials. Ninety patients had colorectal cancer and 59 patients were diagnosed with one of 14 other cancer types. Patients received either pembrolizumab, 200 mg every 3 weeks, or pembrolizumab, 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity, or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or associated with a decline in performance status. A maximum of 24 months of treatment was administered.

NCCN & Immunotherapy in CRC

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Colon Cancer

NCCN Guidelines Index
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Discussion

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 2 of 10)

Subsequent Therapy

FOLFIRI[10] ± (bevacizumab[15] [preferred][5,6] or ziv-aflibercept[15,16] or ramucirumab[15,16])
or
Irinotecan[10] ± (bevacizumab[15] [preferred][5,6] or ziv-aflibercept[15,16] or ramucirumab[15,16])

or

Irinotecan[10] + (cetuximab or panitumumab)*[6-8,17-19] (KRAS/NRAS WT only)
or
Regorafenib[20]
or
Trifluridine + tipiracil[20]
or
(Nivolumab or pembrolizumab)* (dMMR/MSI-H only)
See Subsequent therapy

Regorafenib[20]
or
Trifluridine + tipiracil[20]

Regorafenib[20]**
or
Trifluridine + tipiracil[20]**
or
Clinical trial
or
Best supportive care[21]

Previous oxaliplatin-based therapy without irinotecan

FOLFIRI[10] + (cetuximab or panitumumab)*[6-8,17-19] (KRAS/NRAS WT only)
or
Irinotecan[10] + (cetuximab or panitumumab)*[6-8,17-19] (KRAS/NRAS WT only)

or

(Nivolumab or pembrolizumab)* (dMMR/MSI-H only) → **See Subsequent therapy**

Regorafenib[20]
or
Trifluridine + tipiracil[20]
or
(Nivolumab or pembrolizumab)* (dMMR/MSI-H only)
See Subsequent therapy

***if neither previously given**
****if not previously given**

See footnotes COL-C 6 of 10

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN & Immunotherapy in CRC

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 1 of 10)

Initial Therapy

Patient appropriate for intensive therapy[2]

- **FOLFOX[3] ± bevacizumab[5,6]** or **CAPEOX[4] ± bevacizumab[5,6]** or **FOLFOX[3] + (cetuximab or panitumumab)[6-9] (KRAS/NRAS WT and left-sided tumors only)** → Progression → See COL-C 2 of 10
- **FOLFIRI[10] ± bevacizumab[5,6]** or **FOLFIRI[10] + (cetuximab or panitumumab)[6-9] (KRAS/NRAS WT and left-sided tumors only)** → Progression → See COL-C 3 of 10
- **FOLFOXIRI[10] ± bevacizumab[5,6]** → Progression → See COL-C 4 of 10
- **5-FU/leucovorin[11] ± bevacizumab[5,6,12]** or **Capecitabine[13] ± bevacizumab[5,6,12]** → Progression → See COL-C 5 of 10

Patient not appropriate for intensive therapy[2]

- **Infusional 5-FU + leucovorin ± bevacizumab[5]** or **Capecitabine[13] ± bevacizumab[5]** or **(Cetuximab or panitumumab)[7-9] (category 2B) (KRAS/NRAS WT and left-sided tumors only)** or **(Nivolumab or pembrolizumab) (dMMR/MSI-H only)[7]**
  - Improvement in functional status → Consider initial therapy as above[14]
  - No improvement in functional status → Best supportive care — See NCCN Guidelines for Palliative Care

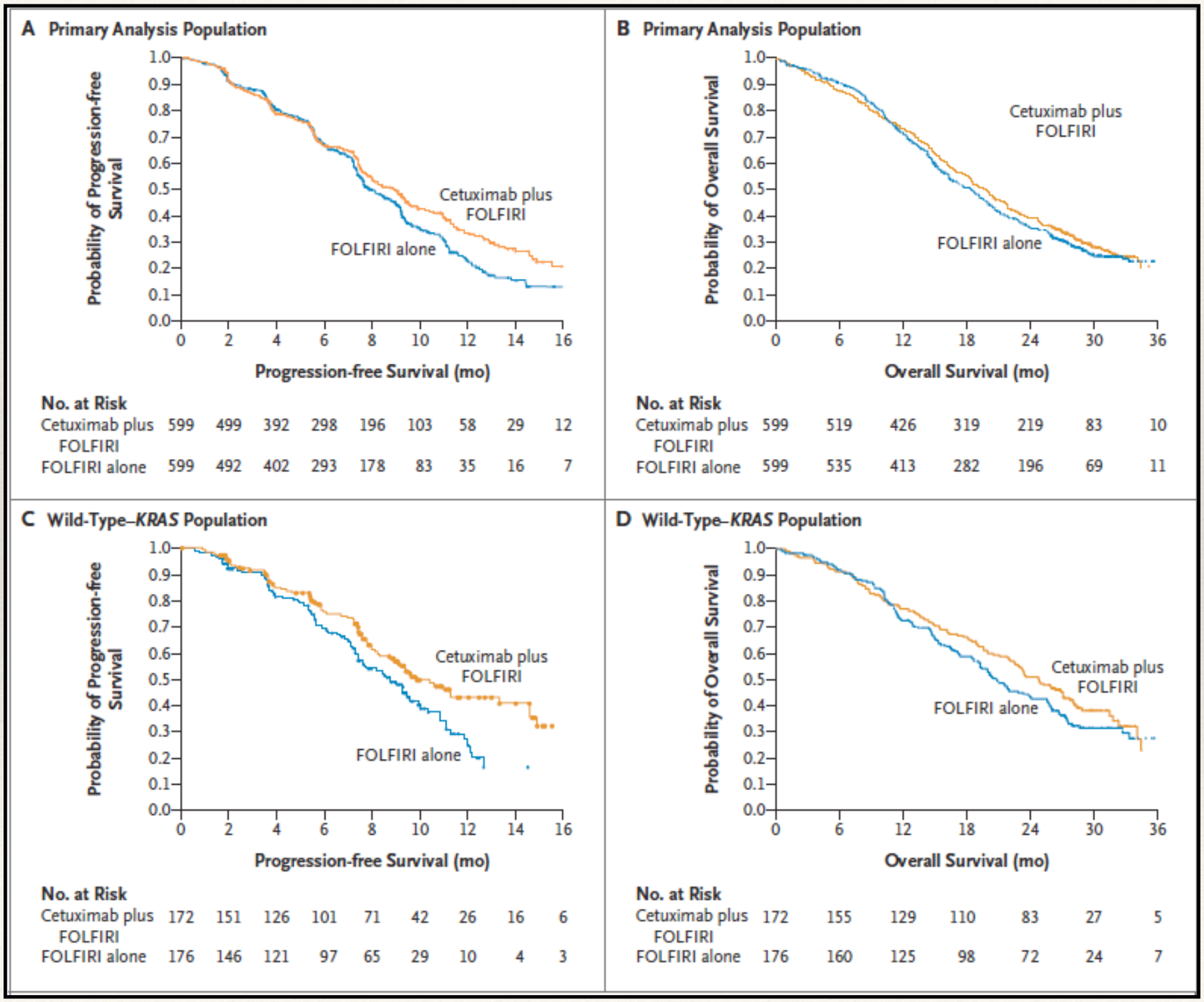
See footnotes COL-C 6 of 10

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

EGFR Pathway
(KRAS/NRAS Mutations)

Cunningham et al. NEJM 2004

Colon Cancer & Anti-EGFR Therapy



Douillard et al. NEJM 2013

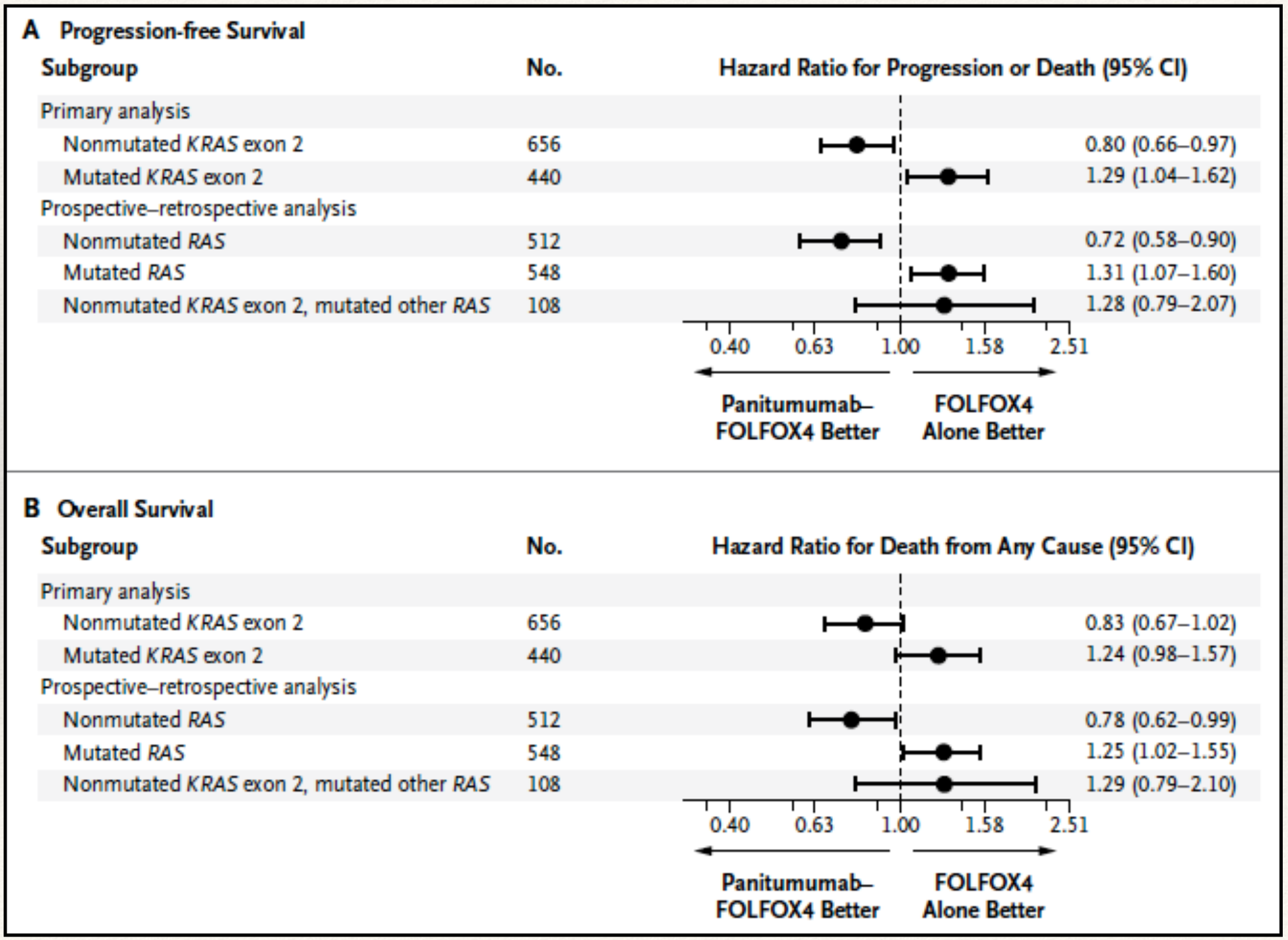
PRIME Analysis (Extended RAS)

Table 3. Efficacy Results According to *RAS* and *BRAF* Mutation Status in the Primary-Analysis Population.*

Variable	Panitumumab–FOLFOX4	FOLFOX4 Alone	Hazard Ratio (95% CI)	P Value
No *RAS* or *BRAF* mutations				
No. of patients	228	218		
Months of progression-free survival — median (95% CI)	10.8 (9.4–12.4)	9.2 (7.4–9.6)	0.68 (0.54–0.87)	0.002
Months of overall survival — median (95% CI)	28.3 (23.7–NE)	20.9 (18.4–23.8)	0.74 (0.57–0.96)	0.02
No *RAS* mutation, *BRAF* mutation				
No. of patients	24	29		
Months of progression-free survival — median (95% CI)	6.1 (3.7–10.7)	5.4 (3.3–6.2)	0.58 (0.29–1.15)	0.12
Months of overall survival — median (95% CI)	10.5 (6.4–18.9)	9.2 (8.0–15.7)	0.90 (0.46–1.76)	0.76
***RAS* or *BRAF* mutation**				
No. of patients	296	305		
Months of progression-free survival — median (95% CI)	7.3 (6.3–7.7)	8.0 (7.5–9.0)	1.24 (1.02–1.49)	0.03
Months of overall survival — median (95% CI)	15.3 (12.7–17.6)	18.0 (15.9–20.8)	1.21 (0.99–1.47)	0.06
No *KRAS* mutation in exon 2, other *RAS* or *BRAF* mutation				
No. of patients	75	86		
Months of progression-free survival — median (95% CI)	6.7 (5.3–8.2)	7.3 (5.7–8.0)	1.05 (0.73–1.52)	0.80
Months of overall survival — median (95% CI)	14.5 (10.4–18.5)	15.8 (11.9–18.8)	1.14 (0.78–1.66)	0.51

Douillard et al. NEJM 2013

PRIME Analysis (KRAS/NRAS)



Sequencing Anti-EGFR Therapy

Boeckx et. al. Ann Oncol 2017; Venook et. al. ASCO 2016

Sidedness & Anti-EGFR Therapy

		n patients		OS (m)		PFS (m)	
Study	Treatment	Left	Right	Left	Right	Left	Right
PRIME	Pmab + FOLFOX	156	26	32.5 (27.5, 37.6)	22.5 (8.1, 30.8)	12.9 (10.0, 14.9)	8.9 (5.5, 11.3)
	FOLFOX	148	32	23.6 (18.2, 27.7)	21.5 (10.8, 26.0)	9.3 (7.7, 10.8)	7.3 (4.2, 11.1)
	Adjusted HR[1]			0.68 (0.52, 0.87)	0.97 (0.55, 1.74)	0.69 (0.54, 0.88)	0.75 (0.42, 1.33)
	P-value			0.0027	0.9295	0.0028	0.3260
PEAK	Pmab + FOLFOX	52	13	43.4 (34.2, 63.0)	22.5 (8.4, 36.9)	14.6 (11.6, 18.1)	10.3 (6.1, 11.6)
	Bmab + FOLFOX	53	13	32.0 (26.9, 48.5)	23.3 (6.0, 29.0)	11.5 (9.3, 13.0)	12.6 (1.8, 18.4)
	Adjusted HR[2]			0.76 (0.45, 1.27)	0.64 (0.26, 1.58)	0.65 (0.43, 1.00)	0.90 (0.39, 2.07)
	P-value			0.2945	0.3326	0.0514	0.8092

SWOG 80405:
Cetuximab + Chemotherapy
vs.
Bevacizumab + Chemotherapy

	Right 1° Median OS (mos)	Left 1° Median OS (mos)	Log Rank p (adjusted*)
	N = 293	N = 732	
All pts	19.4	33.3	P < 0.001
Cet	**16.7**	**36.0**	P < 0.001
Bev	24.2	31.4	P = 0.017

EGFR Pathway
(BRAF Mutations)

Douillard et al. NEJM 2013

PRIME Analysis (BRAF Mutations)

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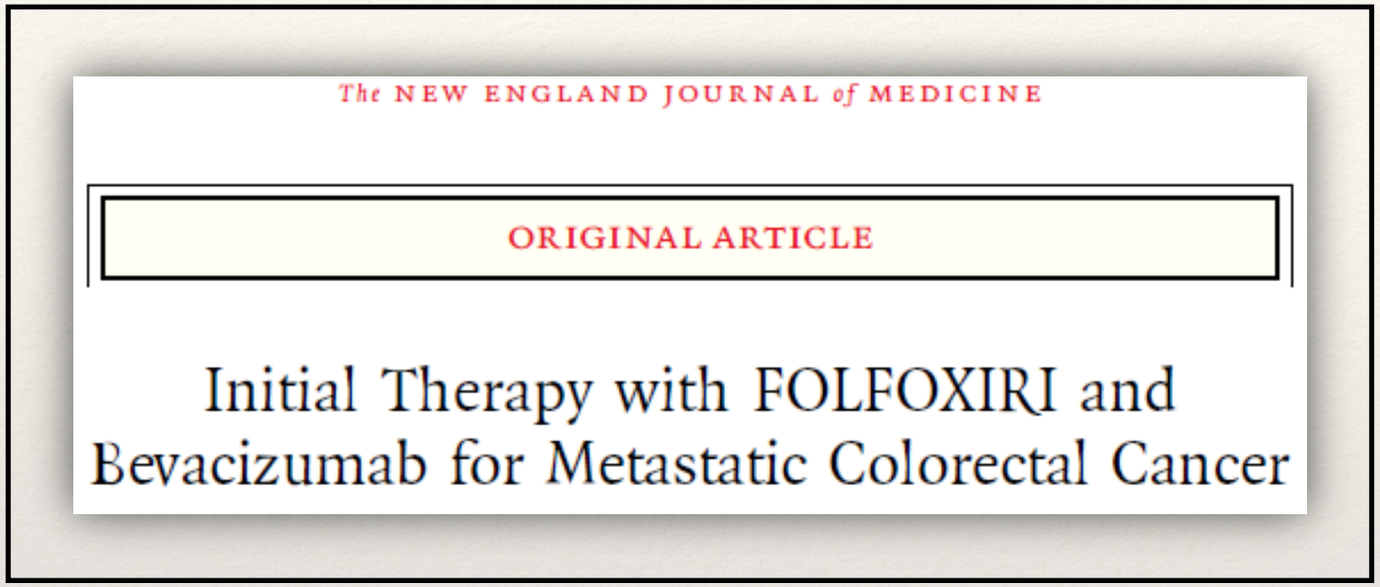
No. of patients	75	86		
Months of progression-free survival — median (95% CI)	6.7 (5.3–8.2)	7.3 (5.7–8.0)	1.05 (0.73–1.52)	0.80
Months of overall survival — median (95% CI)	14.5 (10.4–18.5)	15.8 (11.9–18.8)	1.14 (0.78–1.66)	0.51

Douillard et al. NEJM 2013

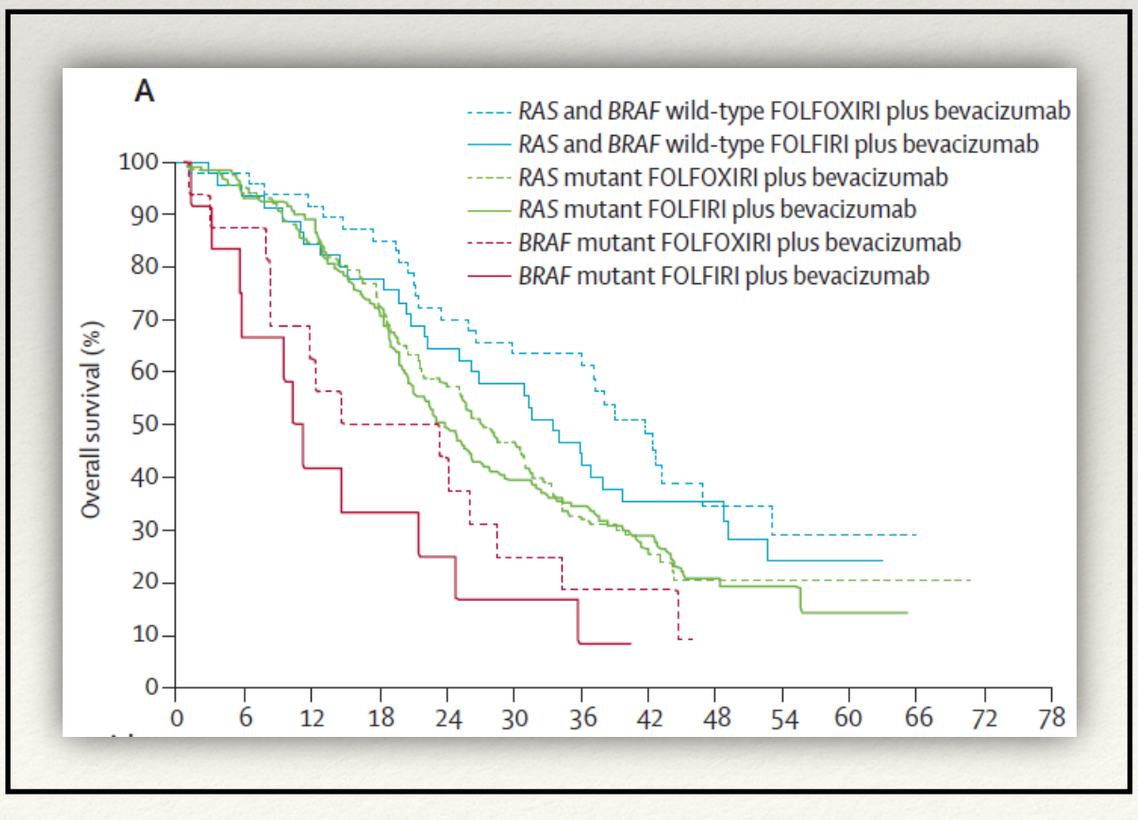
BRAF Mutant Therapy



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

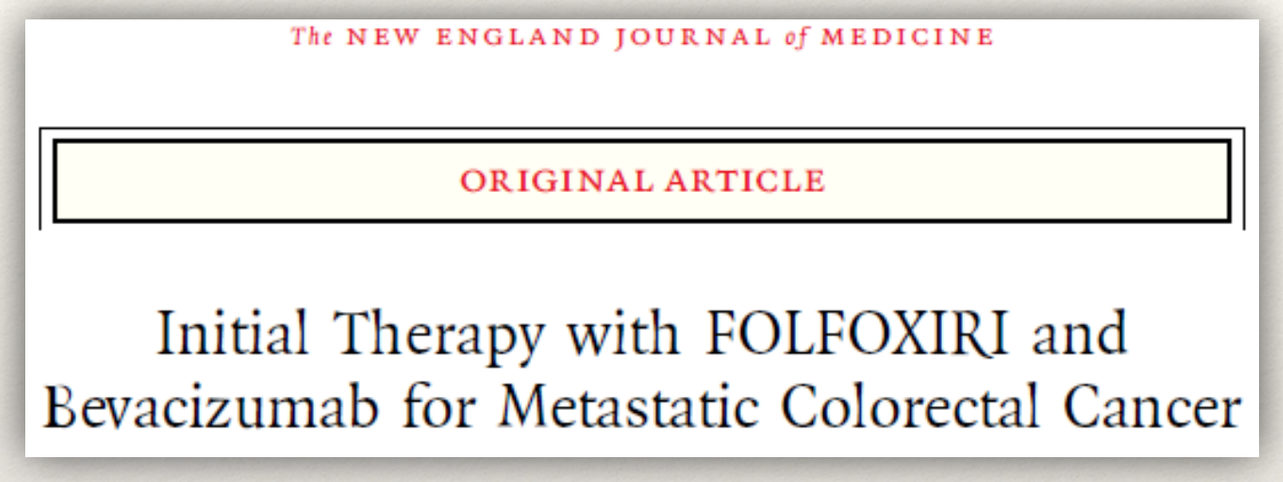
Initial Therapy with FOLFOXIRI and Bevacizumab for Metastatic Colorectal Cancer



- BRAF Mutant Patients in TRIBE
  - mPFS: 7.5 m (HR 0.57)
  - ORR: 56%
  - mOS: 19.0 (HR: 0.54)

Cremolini et. al. Lancet Oncol. 2015

BRAF Mutant Therapy



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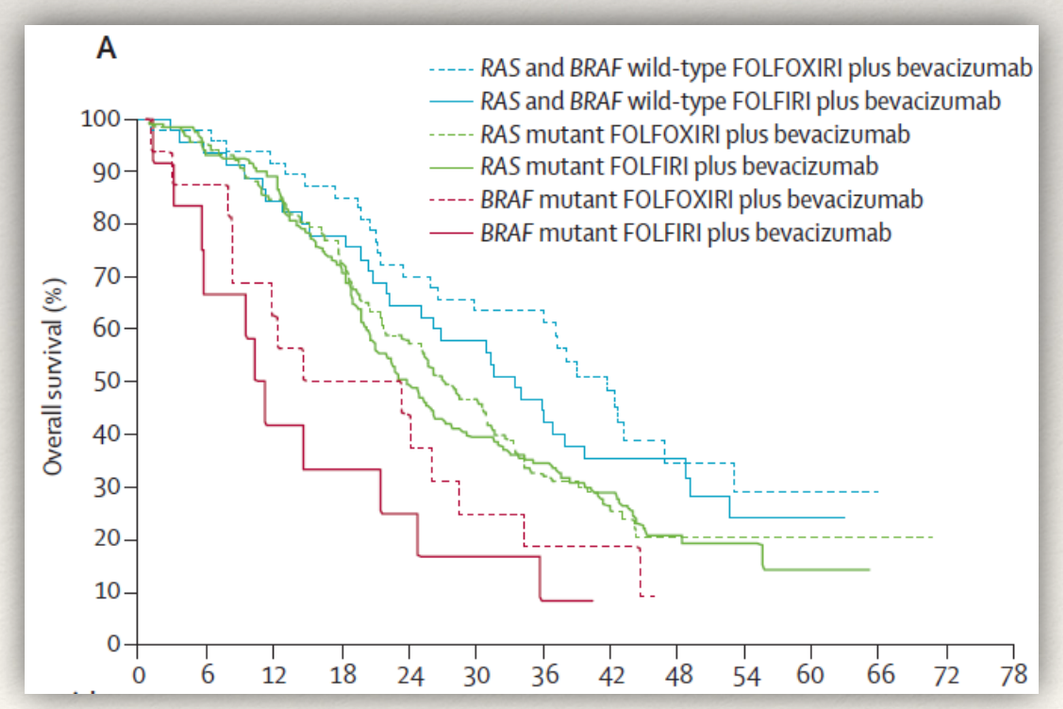
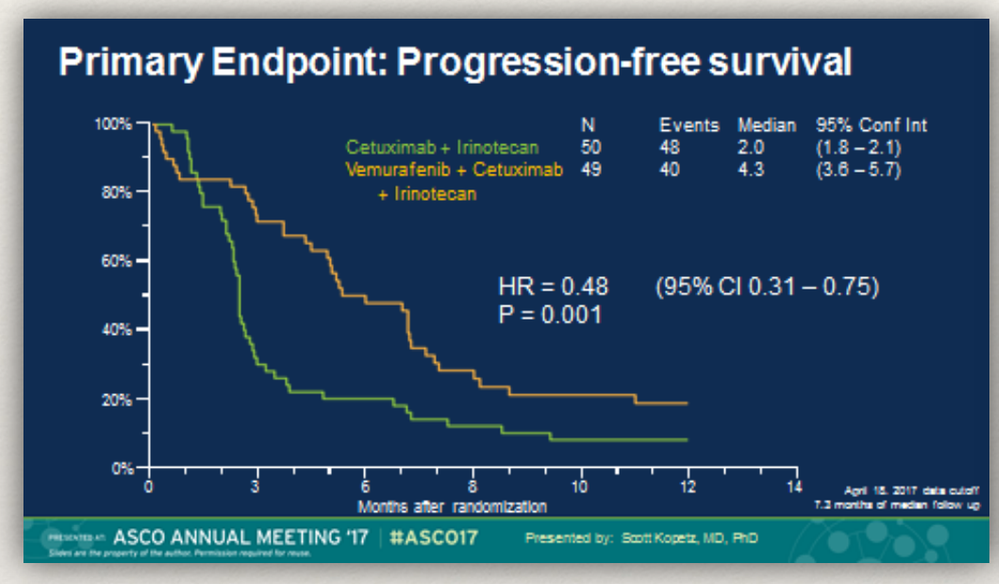


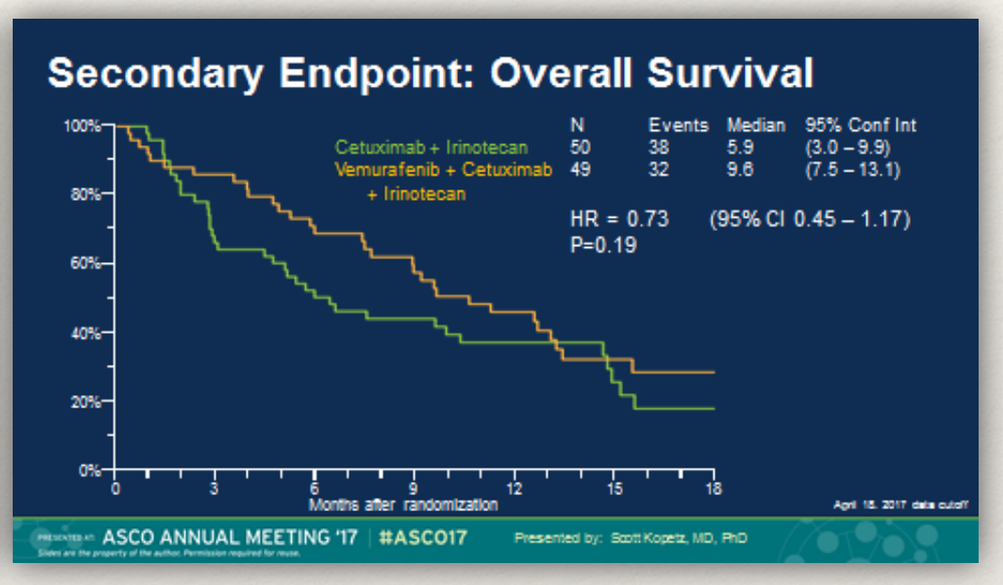
- BRAF Mutant Patients in TRIBE
  - mPFS: 7.5 m (HR 0.57)
  - ORR: 56%
  - mOS: 19.0 (HR: 0.54)

Kopetz et. al. ASCO 2017;

BRAF Mutant Therapy

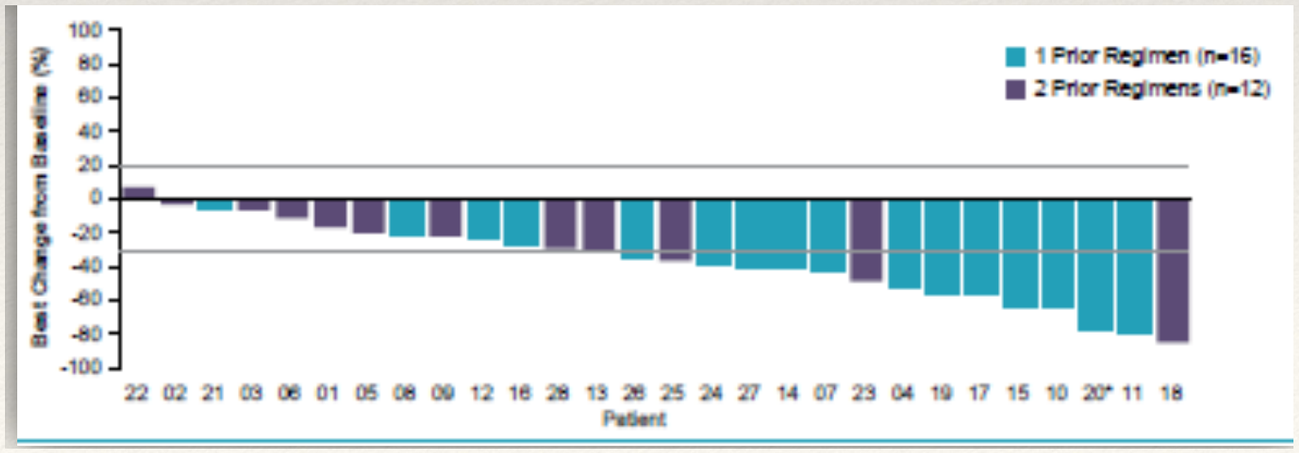
- Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant mCRC
- N = 105
- RR 16% vs. 4% (~ 40% had prior irinotecan)





BEACON Phase III Study

Encorafenib + Binimetinib + Cetuximab



HER2 Amplification

Raghav et al. ASCO 2016

HER2 Amplified Colon Cancer

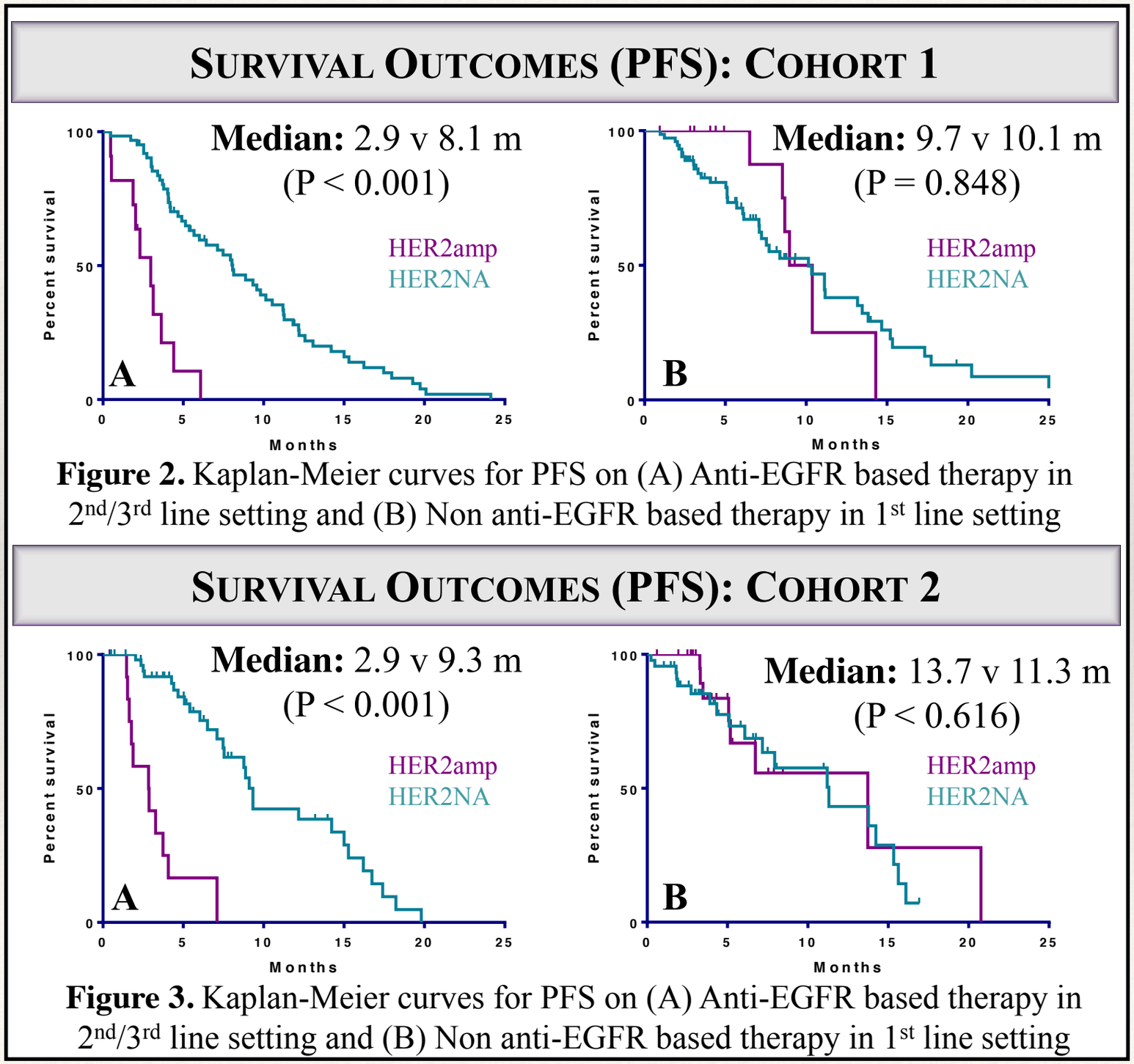
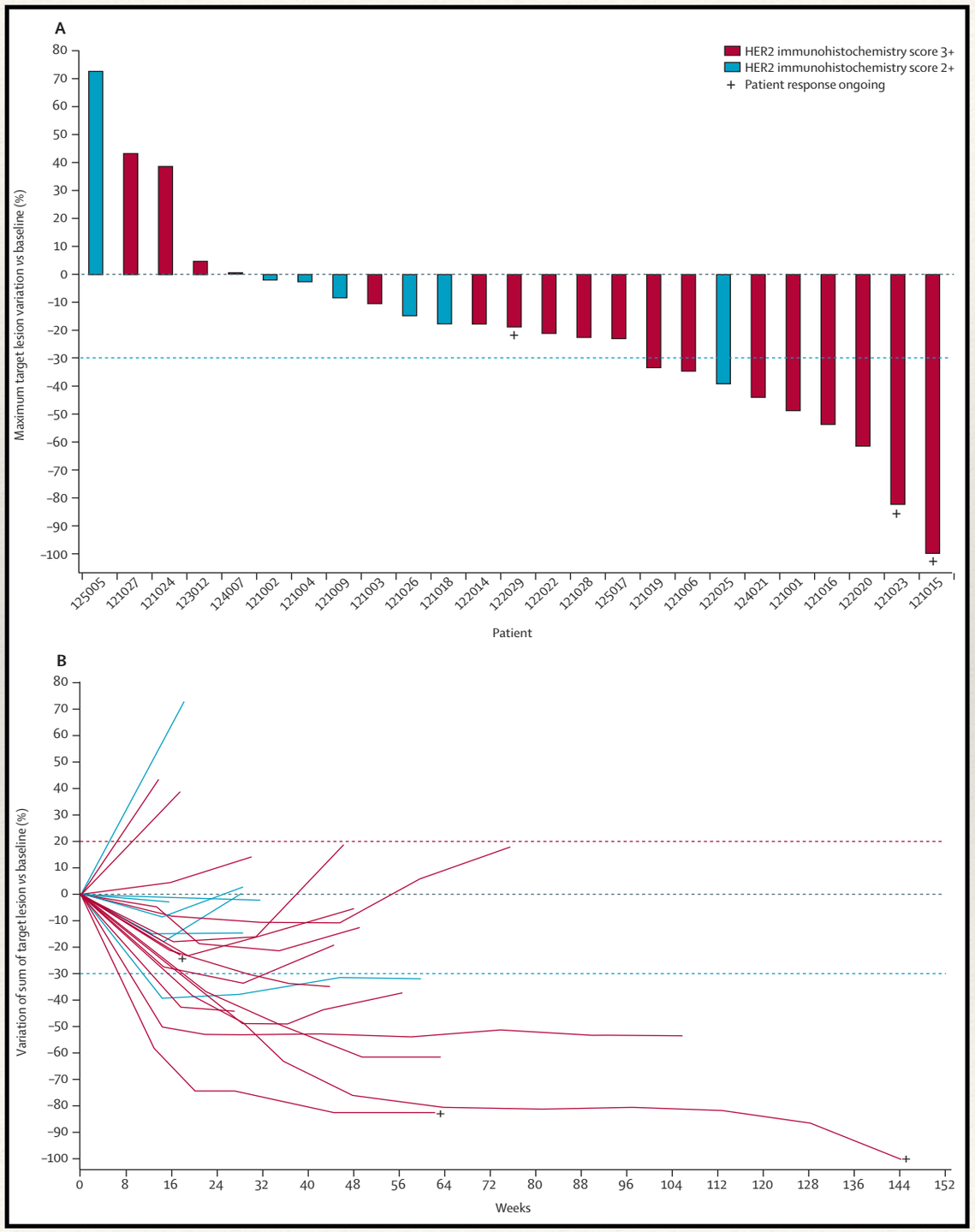


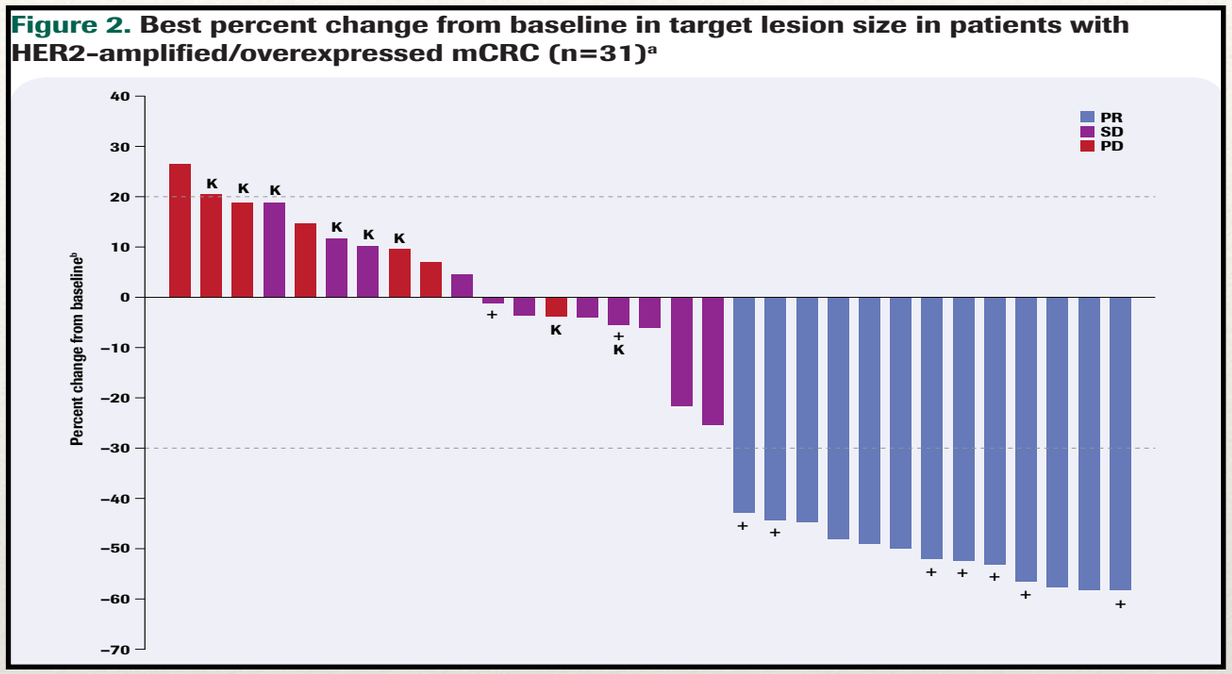
Figure 2. Kaplan-Meier curves for PFS on (A) Anti-EGFR based therapy in 2nd/3rd line setting and (B) Non anti-EGFR based therapy in 1st line setting

Figure 3. Kaplan-Meier curves for PFS on (A) Anti-EGFR based therapy in 2nd/3rd line setting and (B) Non anti-EGFR based therapy in 1st line setting

Bianchi et al. Lancet Oncol. 2016; Hurwitz et al. GI ASCO 2017

HER2 Amplified CRC Therapy

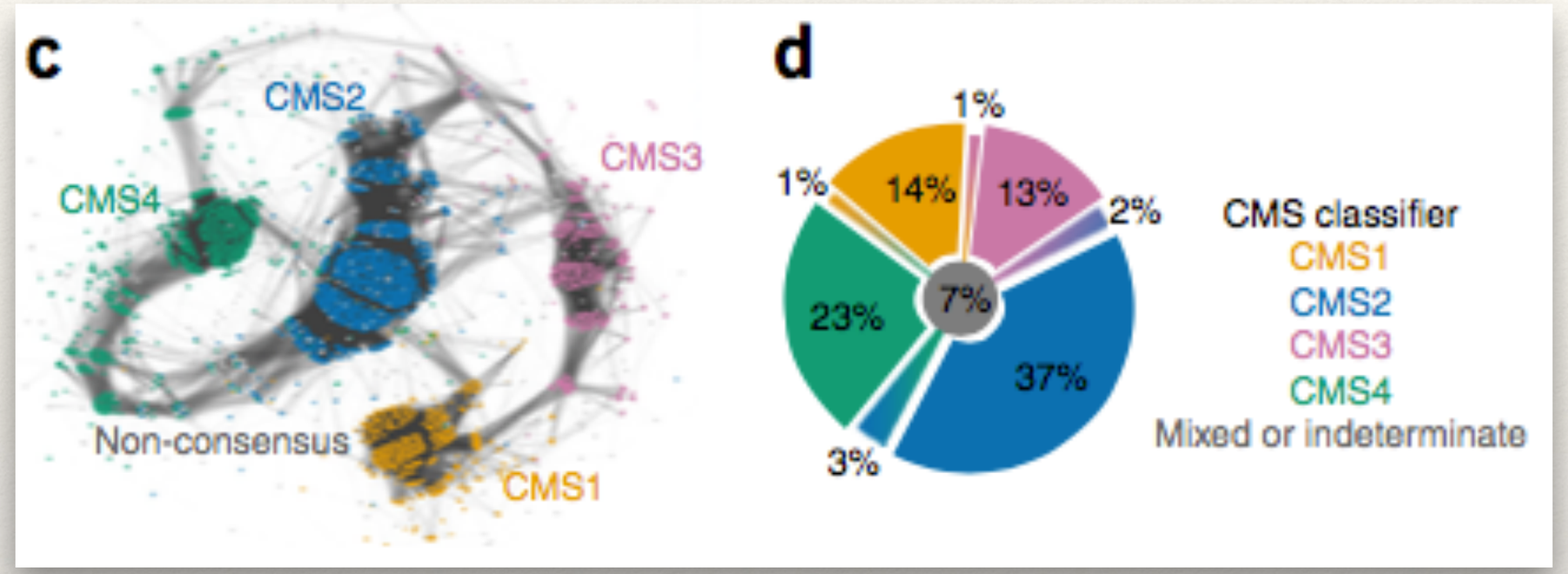




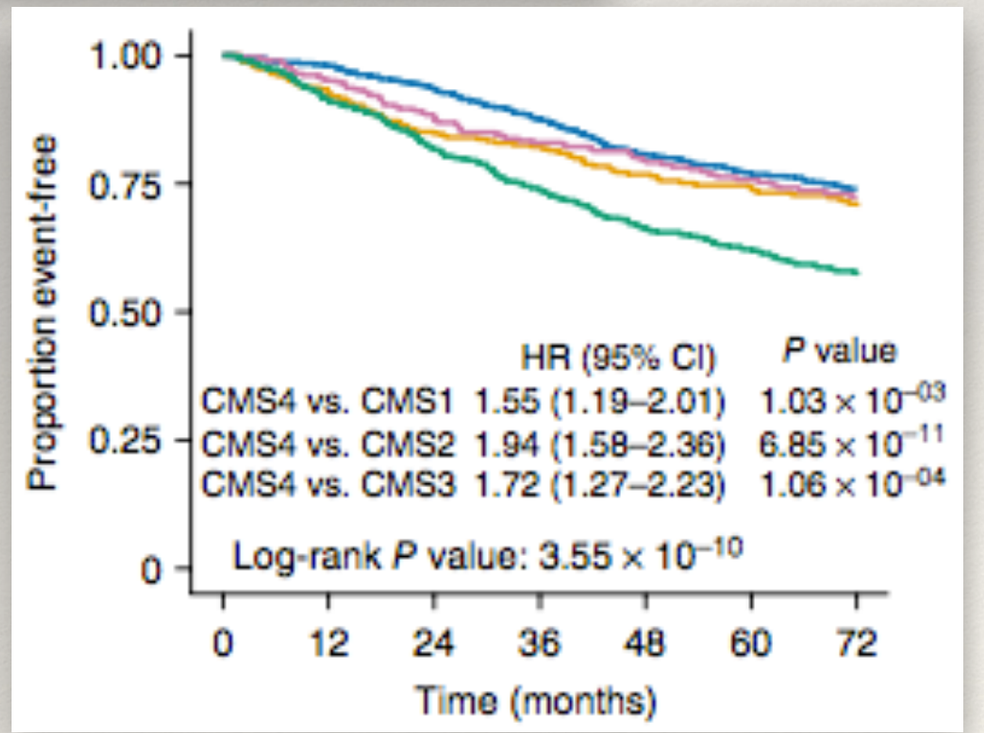
- **MyPathway Study**
- Trastuzumab + Pertuzumab
- **HERACLES Study**
- Trastuzumab + Lapatinib

CMS

Looking Beyond …



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



Biomarkers Testing in Clinics

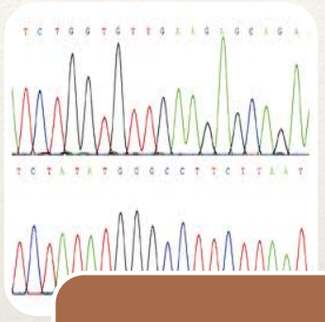
Overman et al. Ann of Oncol. 2015

Steps in Tissue Biomarker Testing

Ordering/ Consent

Tissue Acquisition

Block Selection, Extraction



Testing Completed

Office visit to return results

6 calendar days

23 calendar days

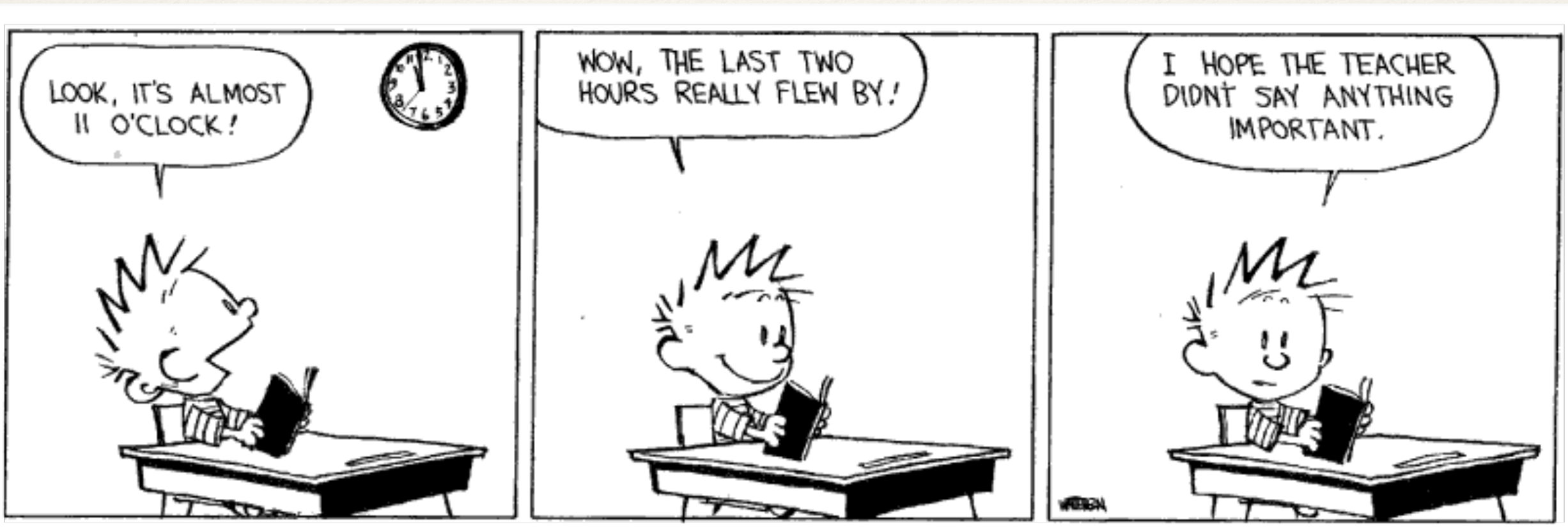
27 calendar days

Slide (Courtesy: Scott Kopetz, MD)

Summary

- All patients need to be tested for **KRAS, NRAS** mutations at diagnosis
- RAS wild type patients need to be tested for **BRAF** mutations due to their poor prognosis for early referral to clinical trials
- **MSI-H** should be tested in all patients with mCRC due to major treatment implication using immunotherapy
- **HER2 amplification** should be tested in RAS/BRAF wild type patients prior to anti-EGFR exposure to make an informed decision regarding toxicity/benefit and for referral to clinical trials
- Convenience of **"one-stop"** for testing will be attractive
- Tests need to be made available to treating oncologist as **rapid**ly as possible
- **Flexible** with regards to amount and type of patient specimen available

Questions


LOOK, IT'S ALMOST 11 O'CLOCK!
WOW, THE LAST TWO HOURS REALLY FLEW BY!
I HOPE THE TEACHER DIDN'T SAY ANYTHING IMPORTANT.