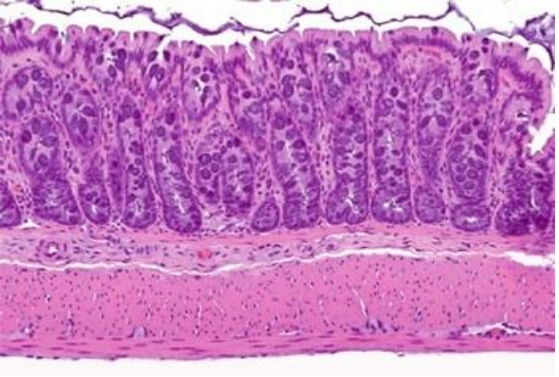
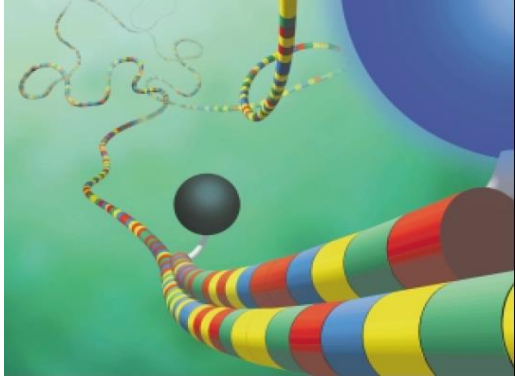




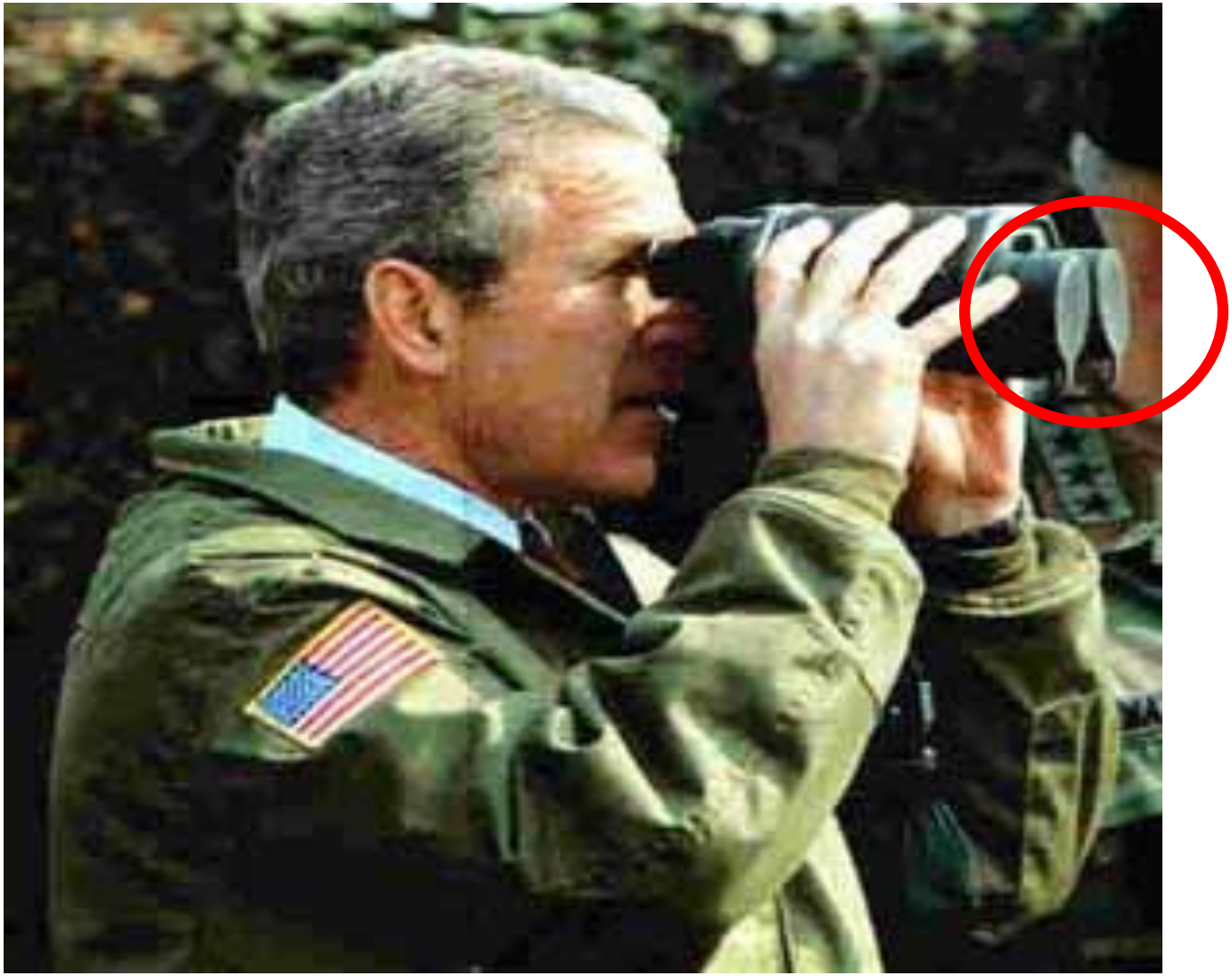
Tumor Sidedness or Molecular Targets in Metastatic Colorectal Cancer- what should we do in right-sided 'raps wt' tumors?

John Souglakos MD, PhD
Dep. Med. Oncology Univ. Hosp. of Heraklion
Lab of Translational Oncology, Med. School Univ. of Crete
johnsougl@gmail.com souglak@uoc.gr

The history of mCRC is full of dilemmas

- bolus vs. infusional 5FU
- 5FU +/- interferon-α
- 5FU vs p.o fluoropyrimidines
- **Irinotecan vs. Oxaliplatin**
- Cetuximab vs. Bevacizumab
- Cetuximab vs. Panitumumab
- Bevacizumab vs. Aflibercept
- …..to be continue

Open mindless vs. sidedness

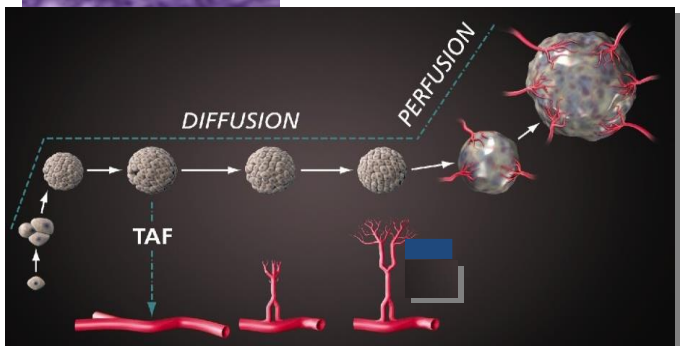


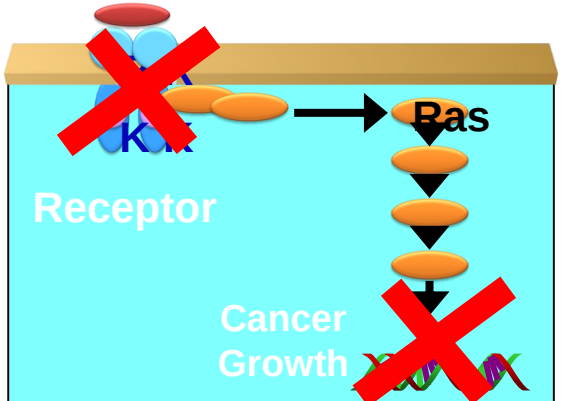
Biologics in 1st line therapy of mCRC

Two Main targets

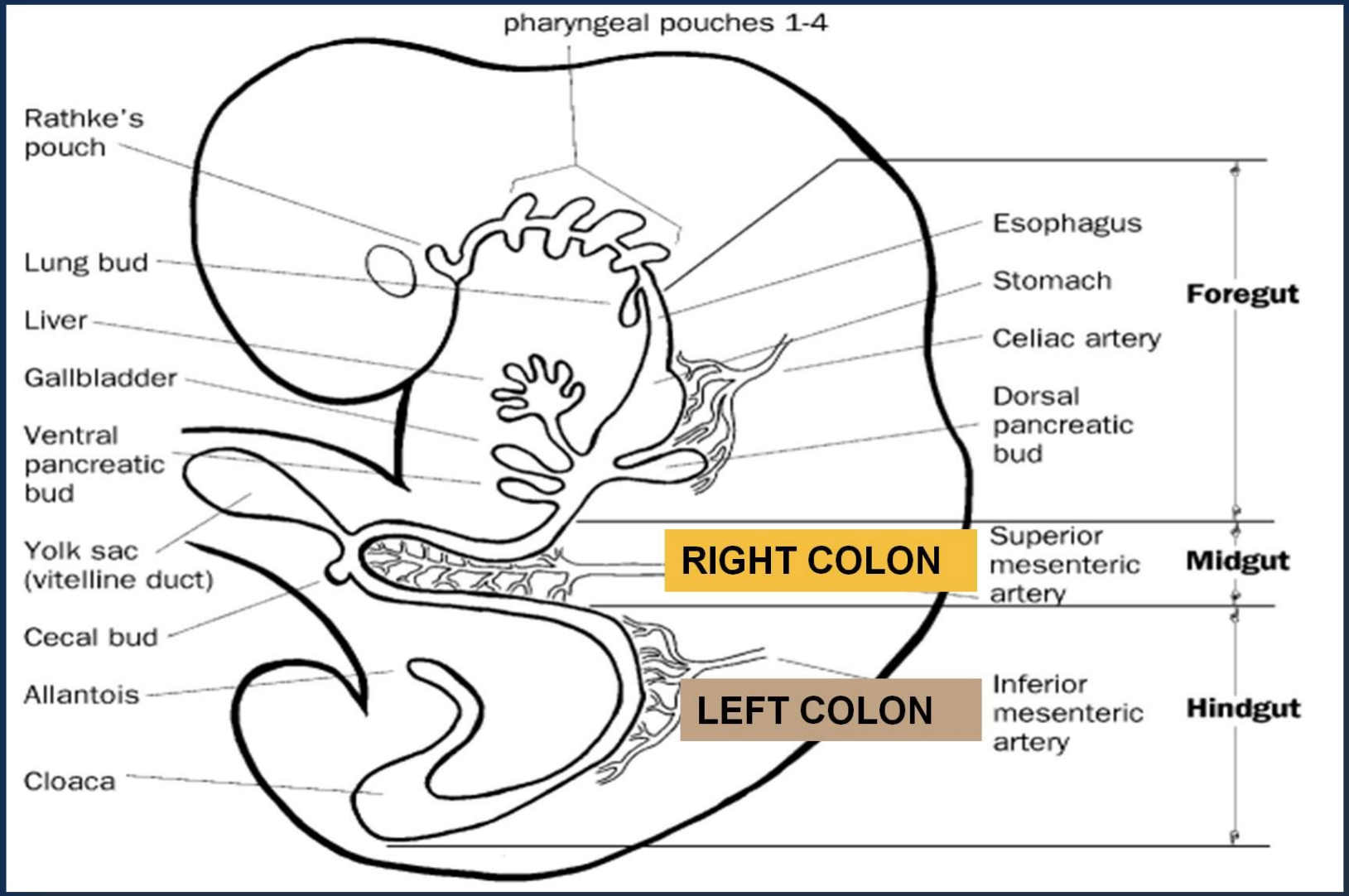
Targeting angiogenesis

Targeting the EGFR signaling





Embryology: The origin of the colon



Right vs. Left sided CRC: a really old story

Br. J. Cancer (1985), **52**, 629–632

1985

Short Communication

Evidence that c-*myc* expression defines two genetically distinct forms of colorectal adenocarcinoma

P.G. Rothberg[1], J.M. Spandorfer[1], M.D. Erisman[1], R.N. Staroscik[2], H.F. Sears[2], R.O. Petersen[3] & S.M. Astrin[1]

THE LANCET, AUGUST 12, 1989

1989

MULTIPLE GENETIC ALTERATIONS IN DISTAL AND PROXIMAL COLORECTAL CANCER

O. DELATTRE
D. J. LAW[1]
Y. REMVIKOS
X. SASTRE
A. P. FEINBERG[1]
S. OLSCHWANG
T. MELOT
R. J. SALMON
P. VALIDIRE
G. THOMAS

Colorectal Cancer: Evidence for Distinct Genetic Categories Based on Proximal or Distal Tumor Location

1990

José A. Bufill, MD

2008

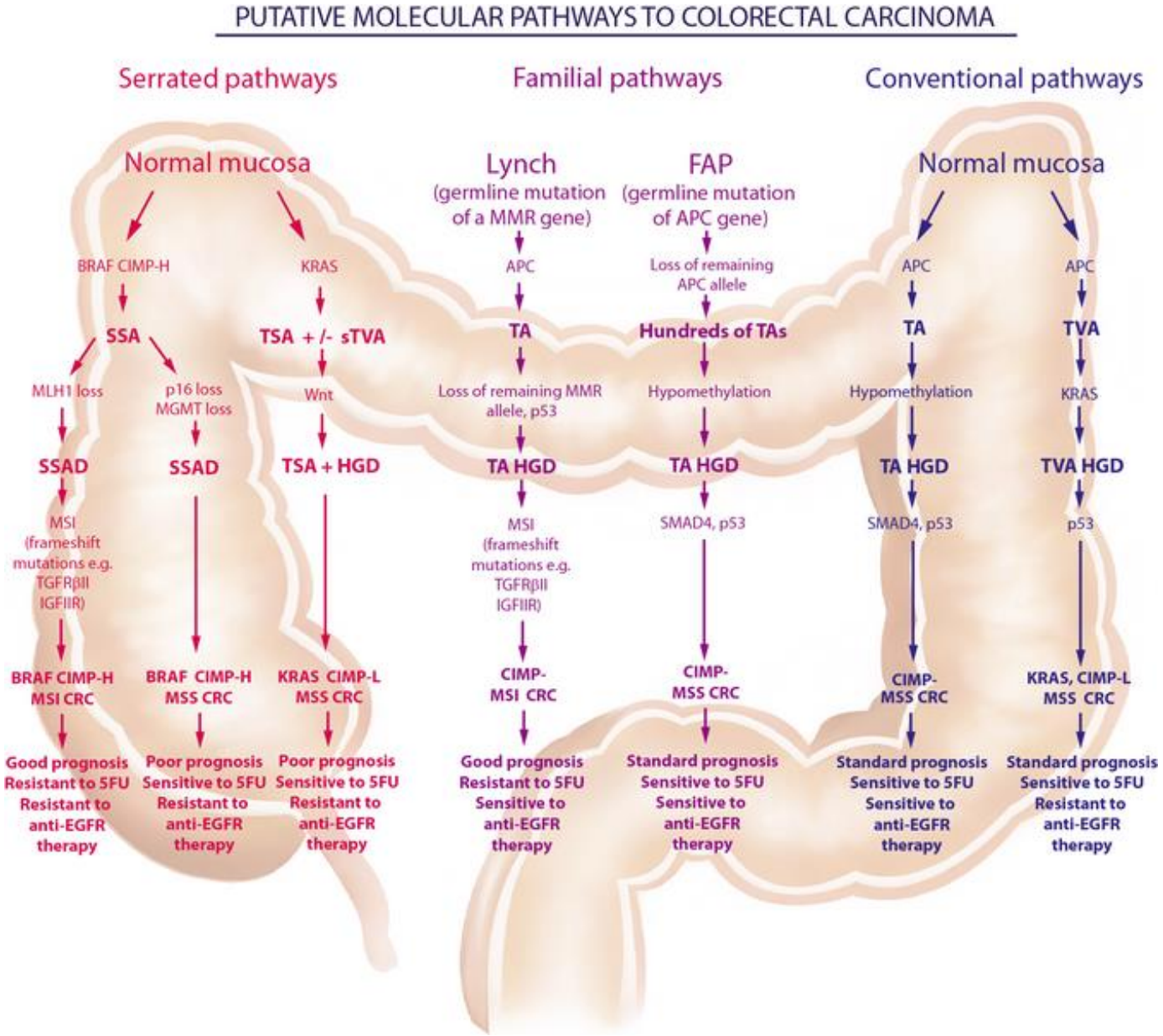
Is There a Difference in Survival Between Right- Versus Left-Sided Colon Cancers?

Robert A. Meguid, MD, MPH,[1] Mark B. Slidell, MD, MPH,[2] Christopher L. Wolfgang, MD, PhD,[3] David C. Chang, PhD, MPH, MBA,[1] and Nita Ahuja, MD[3,4]

Mortality by Stage for Right- Versus Left-Sided Colon Cancer: Analysis of Surveillance, Epidemiology, and End Results–Medicare Data

2011

Jennifer M. Weiss, Patrick R. Pfau, Erin S. O'Connor, Jonathan King, Noelle LoConte, Gregory Kennedy, and Maureen A. Smith



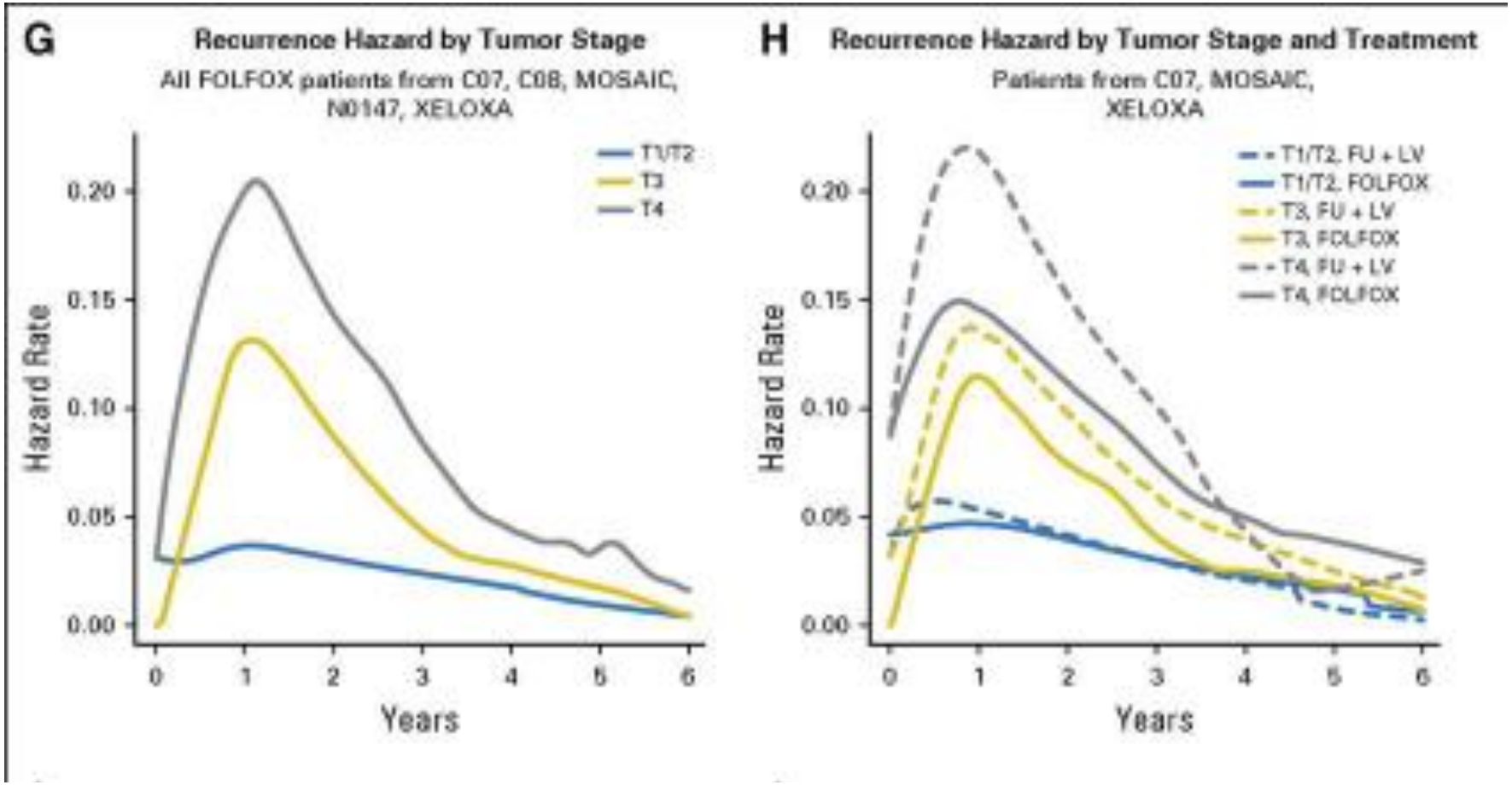
Histopathology JAN 2013 DOI: 10.1111/his.12055

Stage II

- For stage II colon cancer, the role of The benefit obtained by FU-based chemo may be attributed to subsets of patients:
  - Females
  - right-sided colon tumors

[1]Elsaleh H et al *Lancet*; 2000

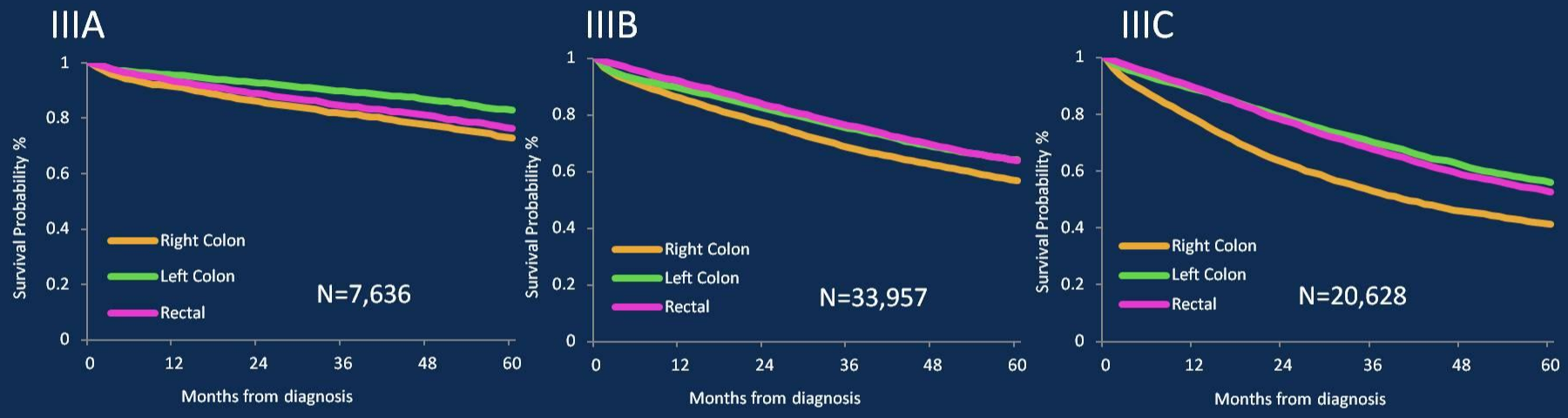
Risk of Death according to tumor location and treatment



Manish A. Shah et al. JCO 2016;34:843-853

Overall Survival for Stage III CRC

by tumor location and AJCC sub-stage



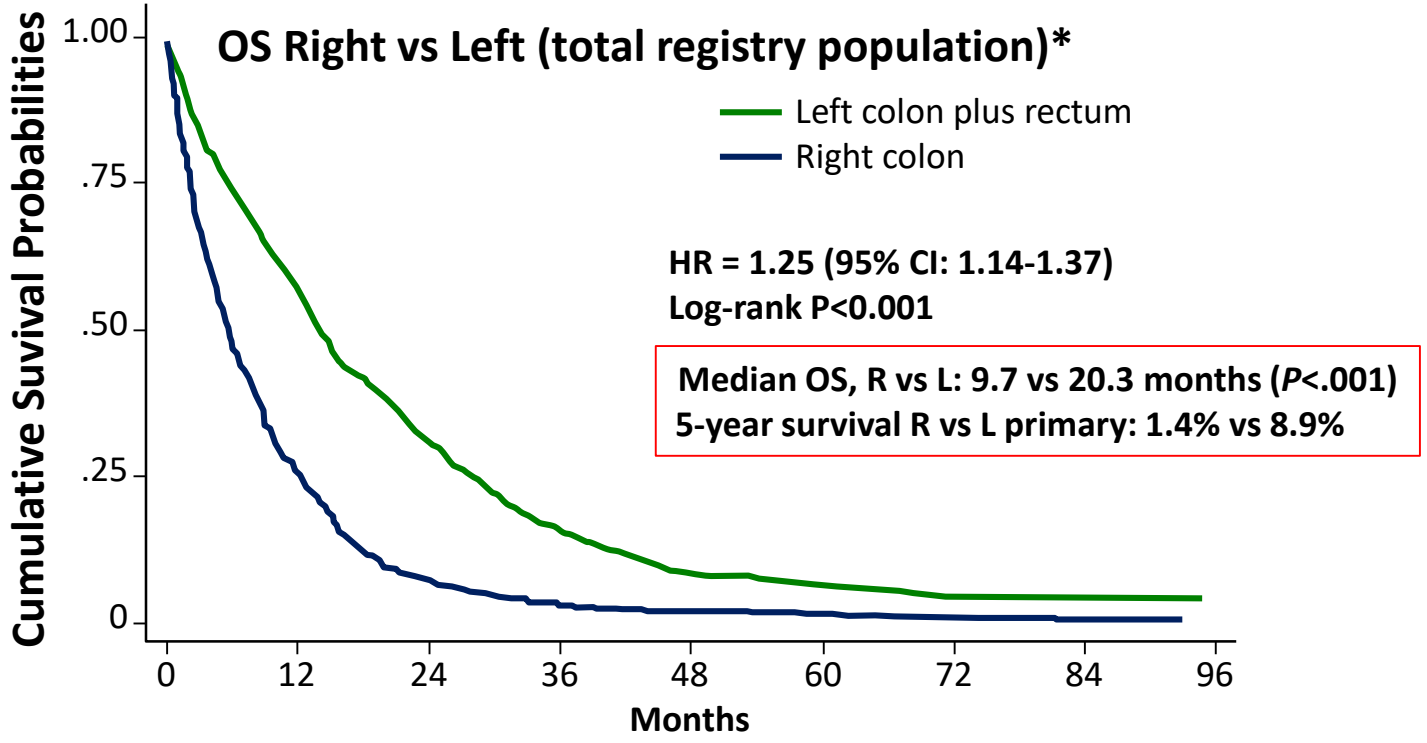
	Adj HR	95% CI
Right Colon vs. Left Colon	1.16	1.02-1.31
Rectal vs. Left Colon	1.39	1.23-1.57

	Adj HR	95% CI
Right Colon vs. Left Colon	1.03	0.99-1.07
Rectal vs. Left Colon	1.11	1.06-1.16

	Adj HR	95% CI
Right Colon vs. Left Colon	1.32	1.26-1.39
Rectal vs. Left Colon	1.10	1.04-1.16

Adjusted for age, gender, race, ethnicity, marital status , year of diagnosis (2004-2012, before 2004, substage information was not available)

South Australian mCRC Registry Data (N = 2,972)



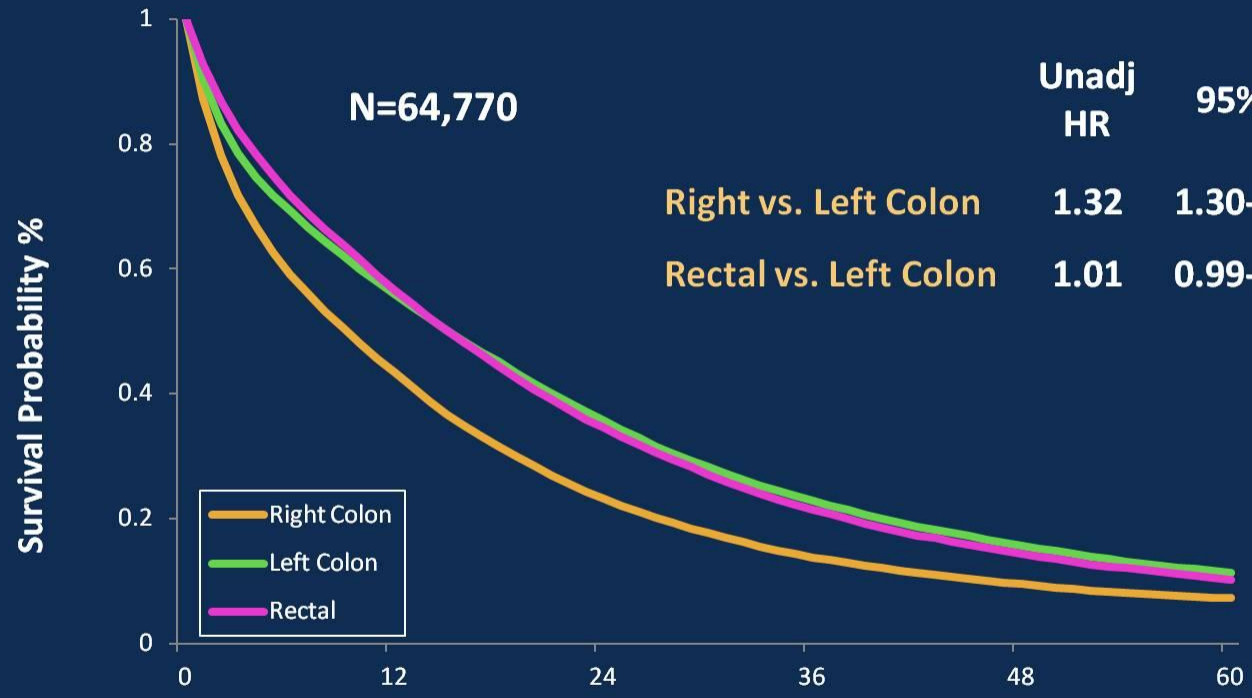
Left	1926	1138	659	364	206	127	56	23	0
Right	1046	479	233	143	89	62	43	25	0

*Including those who had no active therapy.

Price. 2015.

Overall Survival for Stage IV CRC from SEER

by Tumor Location, 2000-2012 Diagnoses



	Unadj HR	95% CI	Adj HR	95% CI
Right vs. Left Colon	1.32	1.30-1.35	1.25	1.22-1.27
Rectal vs. Left Colon	1.01	0.99-1.03	0.83	0.81-0.85

Adjusted for age, gender, race, ethnicity, marital status, receipt of primary surgery, year of diagnosis

Curves truncated at 60 months

Presented by: D Schrag, MD

Presented By Deborah Schrag at 2016 ASCO Annual Meeting

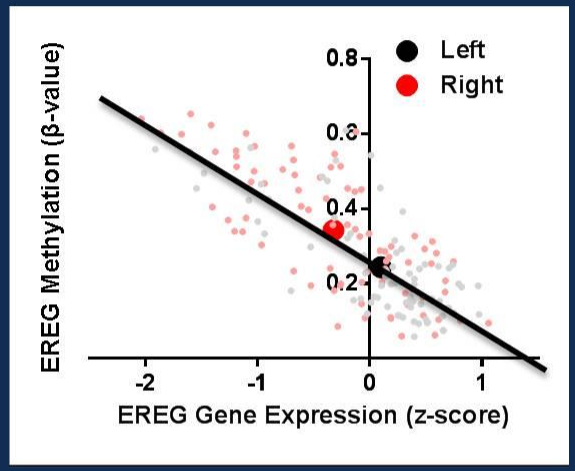
Age, MSI, *BRAF*, and Methylation (CIMP) are associated with right-sided primaries

	Right-Sided n=63 (32%)	Left-Sided n=135 (68%)	Odds Ratio	P-value
Median age	62 (30-81)	56 (24-76)	1.05 (1.02-1.08)	0.001
Male sex	37/63 (58.7%)	84/135 (62.2%)		0.64
White race	55/63 (87.3%)	103/135 (76.3%)		0.09
MSI-High	5/31 (16.1%)	2/71 (2.8%)	6.63 (1.21-36.3)	0.026
PIK3CA mutant	7/51 (13.7%)	19/112 (17.0%)		0.65
***BRAF* mutant**	22/61 (36.1%)	12/116 (10.3%)	5.45 (2.47-12.0)	0.00003
NRAS mutant	7/50 (14.0%)	14/107 (13.1%)		1.00
CIMP High	24/63 (38.1%)	28/135 (20.7%)	2.35 (1.22-4.54)	0.015

Low *EREG/AREG* expression in right-sided primaries

KRAS 12/13 WT	Right-sided	Left-sided	OR (95% CI)
*Low EREG/AREG**	37/49 (76%)	20/48 (42%)	4.32 (1.81-10.28)

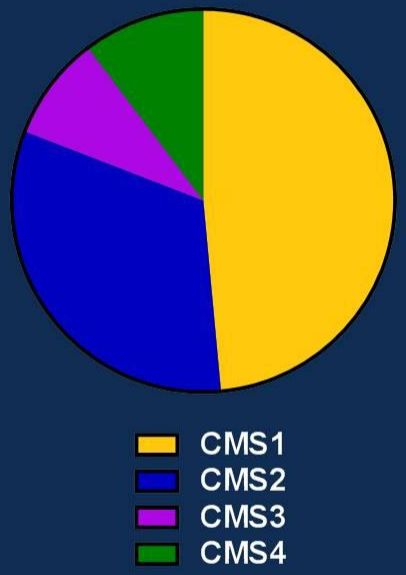
KRAS 12/13 WT	CIMP High	CIMP Low	OR (95% CI)
Low EREG/AREG	27/34 (79%)	32/69 (46%)	4.46 (1.71-11.61)



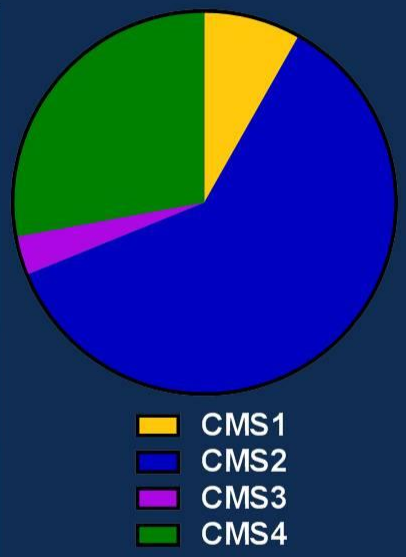
- *EREG/AREG* regulation is by methylation (*EREG* is in top 1% of methylation controlled genes)
- *EREG* and *AREG* biomarkers may be surrogates for broader hypermethylation biology

*High *EREG/AREG* defined as either *EREG* or *AREG* in top tertile, as per Seligmann J, et al. JAMA Oncol 2016

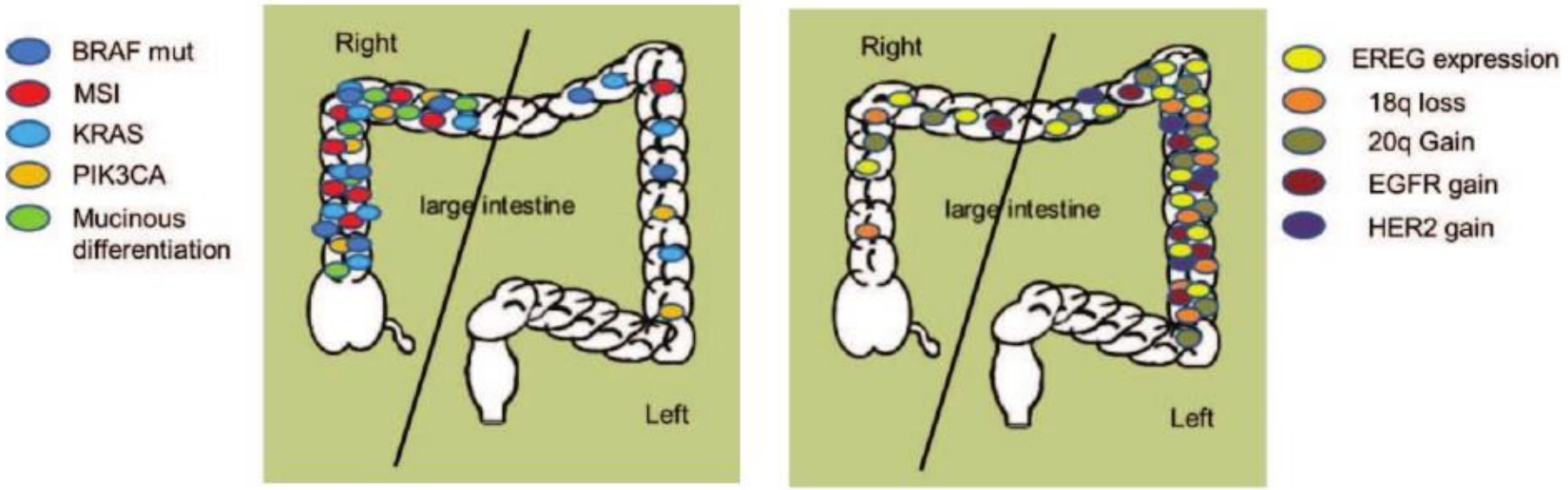
Right-sided primary is associated with CMS 1 & 3



Right-Sided		Left-Sided
33/68 (49%)	CMS 1 Immune	5/61 (8%)
22/68 (32%)	CMS 2 Canonical	37/61 (61%)
6/68 (9%)	CMS 3 Metabolic	2/61 (3%)
7/68 (10%)	CMS 4 Mesenchymal	17/61 (28%)

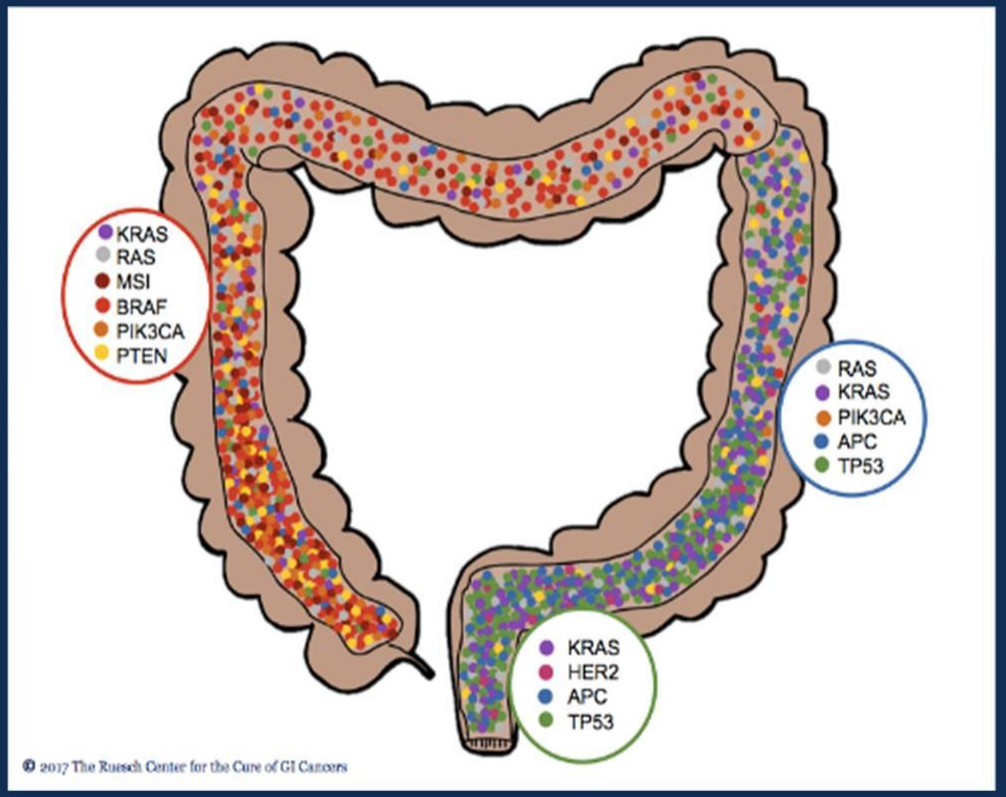


Are all colon cancers the same?

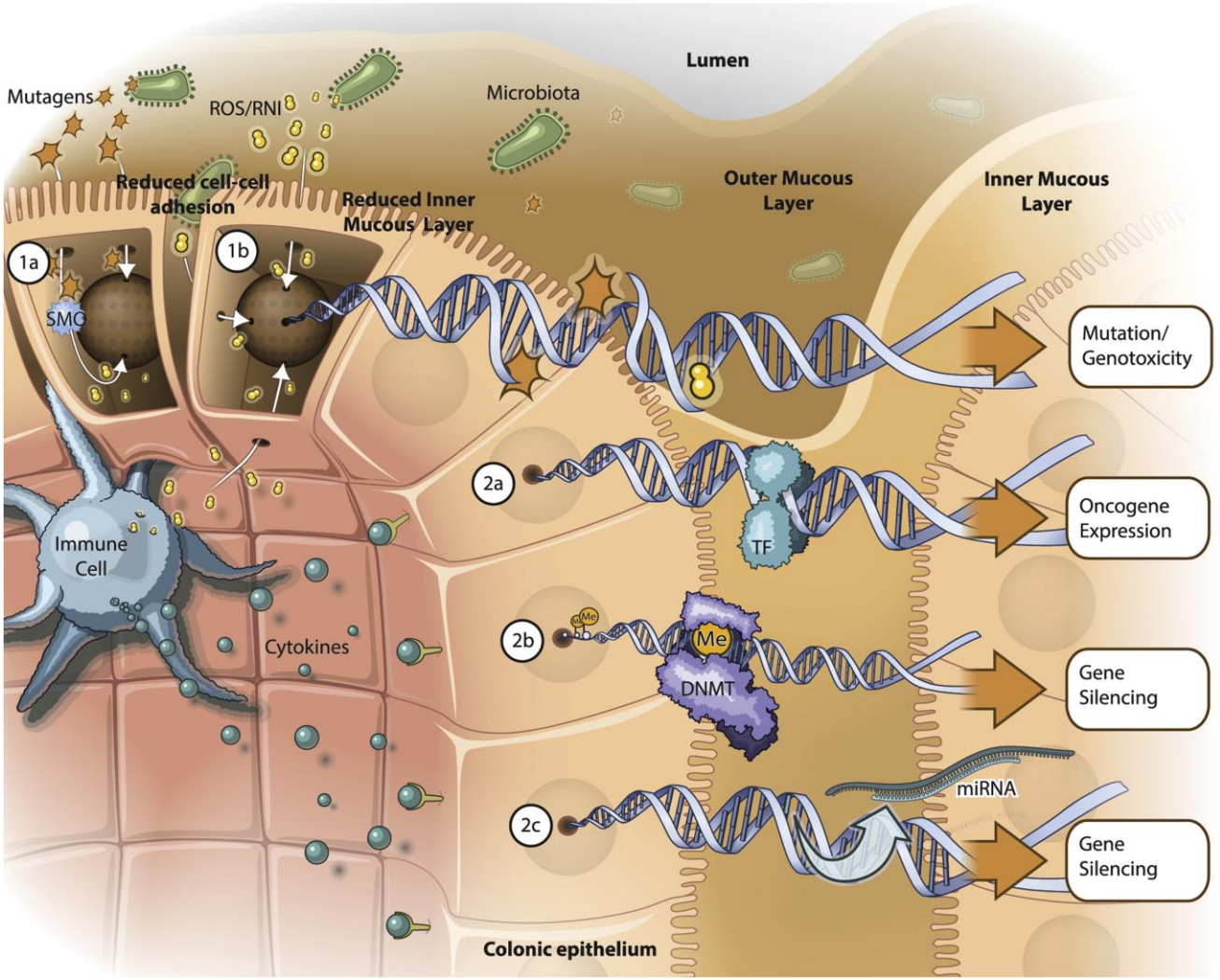


Missiaglia E ASCO 2013; Abstr # 3526

- CRCs carry a continuum of molecular alterations from right to left, rather than having a sharp, clear-cut distinction



The role of microbiota

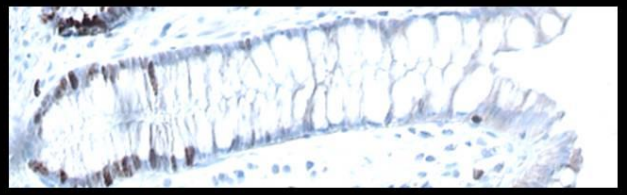


Bacterial biofilms are associated with colonic epithelial cell proliferation (Ki67)

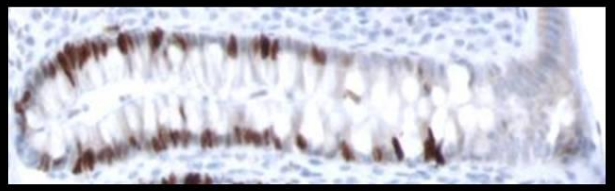
Colon Cancer Patient Distal Normal

Base — Crypt top

Biofilm negative mucosa



Biofilm positive mucosa

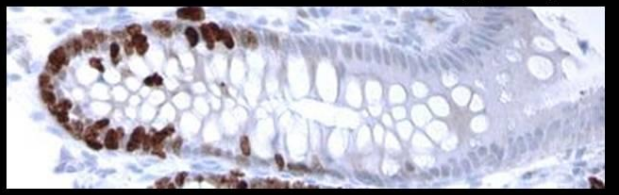


P<0.0001

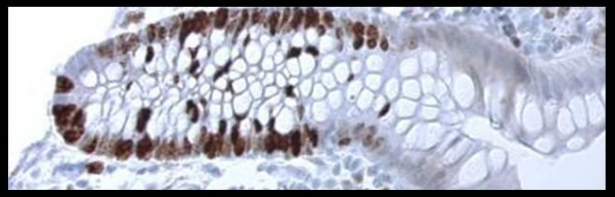
Colonoscopy Control Biopsy

Base — Crypt top

Biofilm negative mucosa



Biofilm positive mucosa



P<0.01

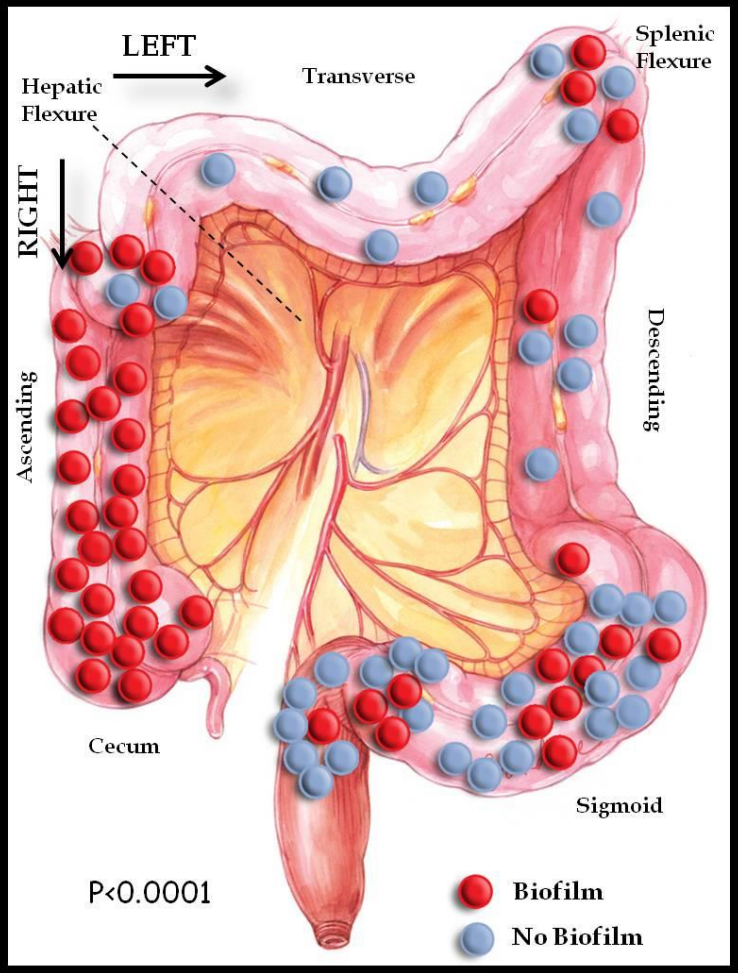
Also changes E-cadherin, IL-6, pStat3

All left samples

Sporadic right colon tumors are defined by bacterial biofilms

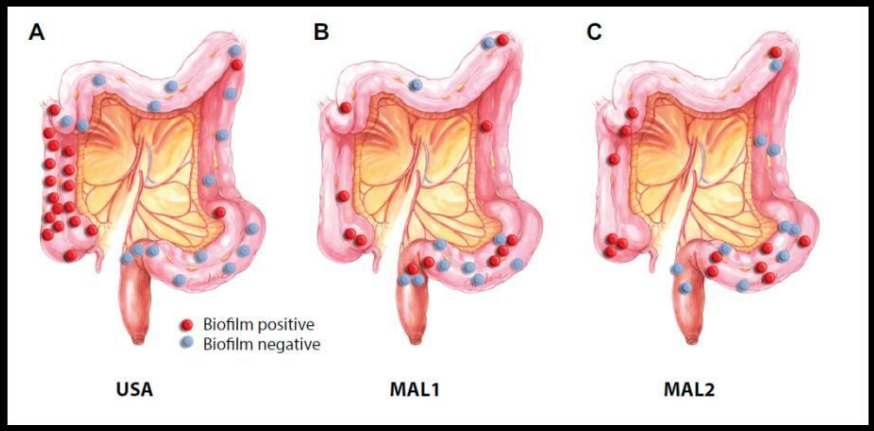
Johns Hopkins & University of Malaya cohorts

Julia Drewes



Dejea et al. PNAS, December 2014
Drewes, White et al submitted

N=36 N=21 N=23



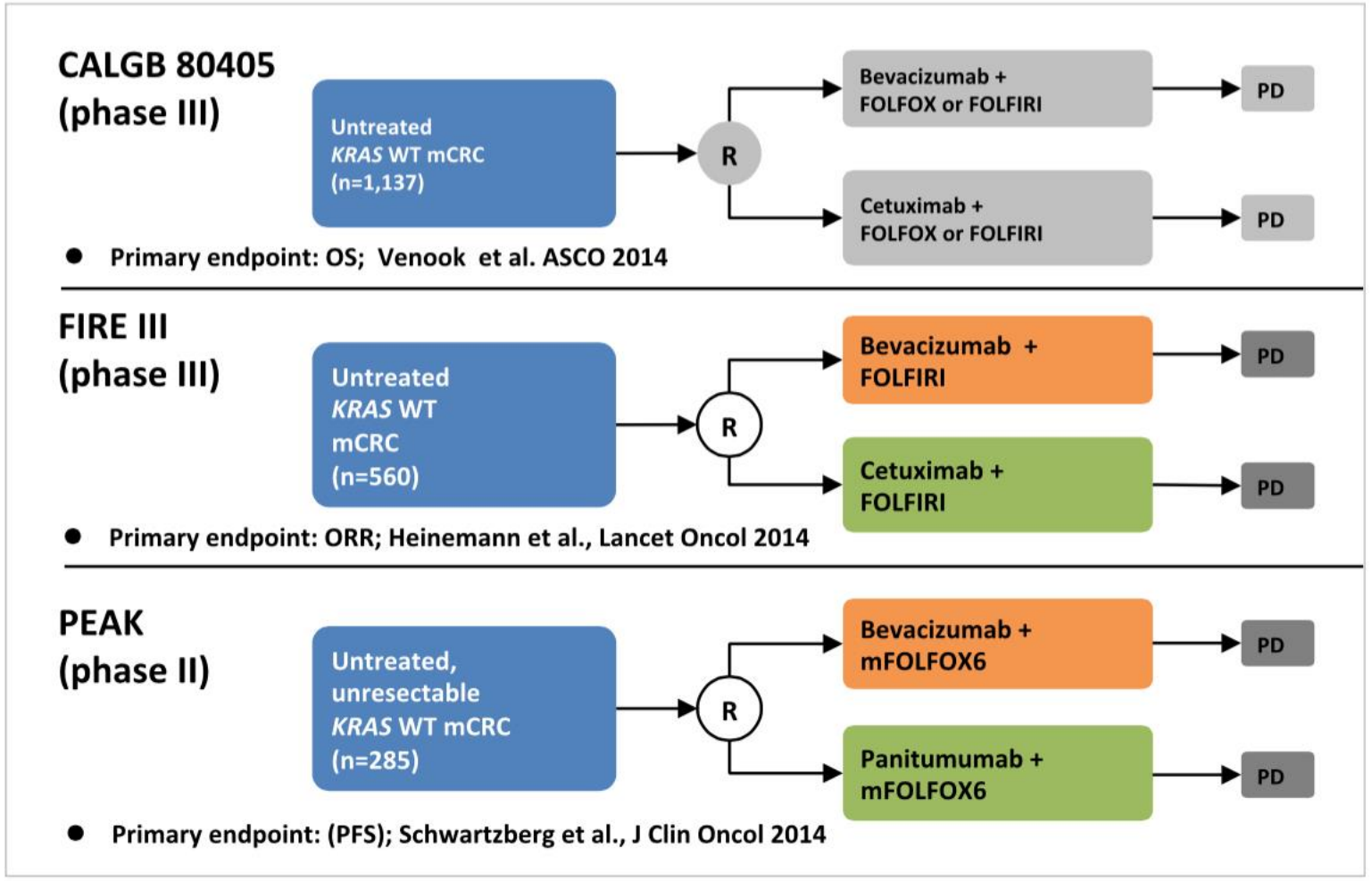
12% 33% 38%

Percent bf+ on left colon

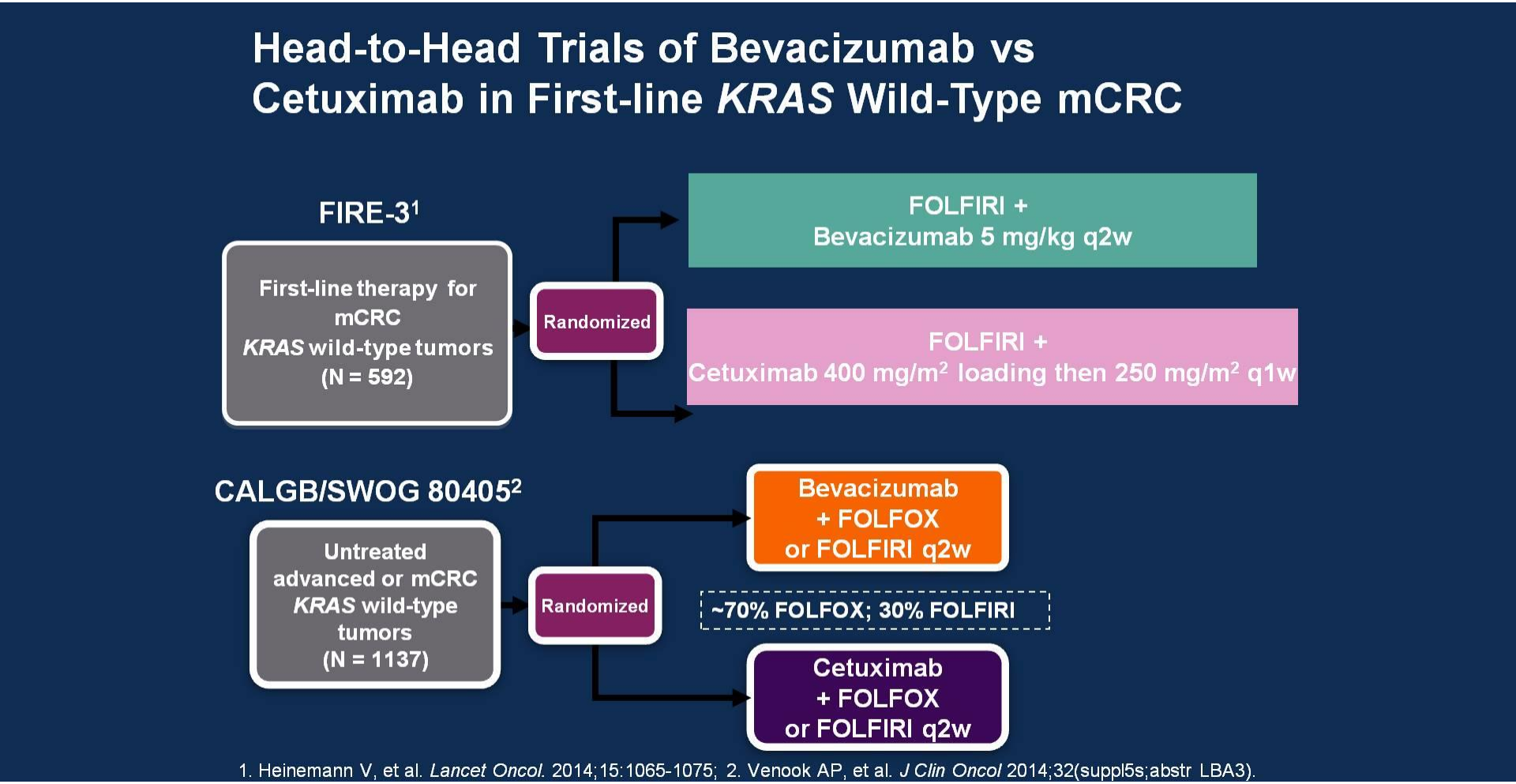
When biofilms are present, CRC and normal tissues are ~94% concordant for biofilms.

Diet, colon prep, other demographics, as yet, do not correlate with findings

Biologics Head to Head comparisons

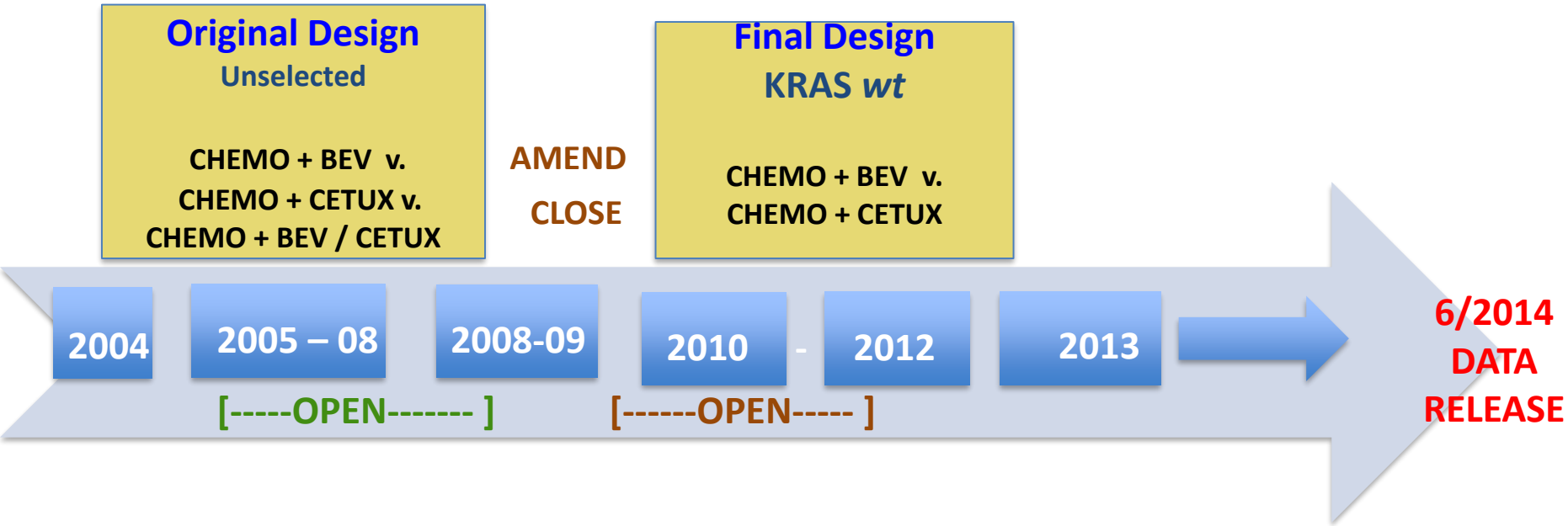


Phase III RCTs Anti-EGFR vs. Bevacizumab



1. Heinemann V, et al. *Lancet Oncol.* 2014;15:1065-1075; 2. Venook AP, et al. *J Clin Oncol* 2014;32(suppl5s;abstr LBA3).

CALGB / SWOG 80405: WHY DID IT TAKE TEN YEARS?



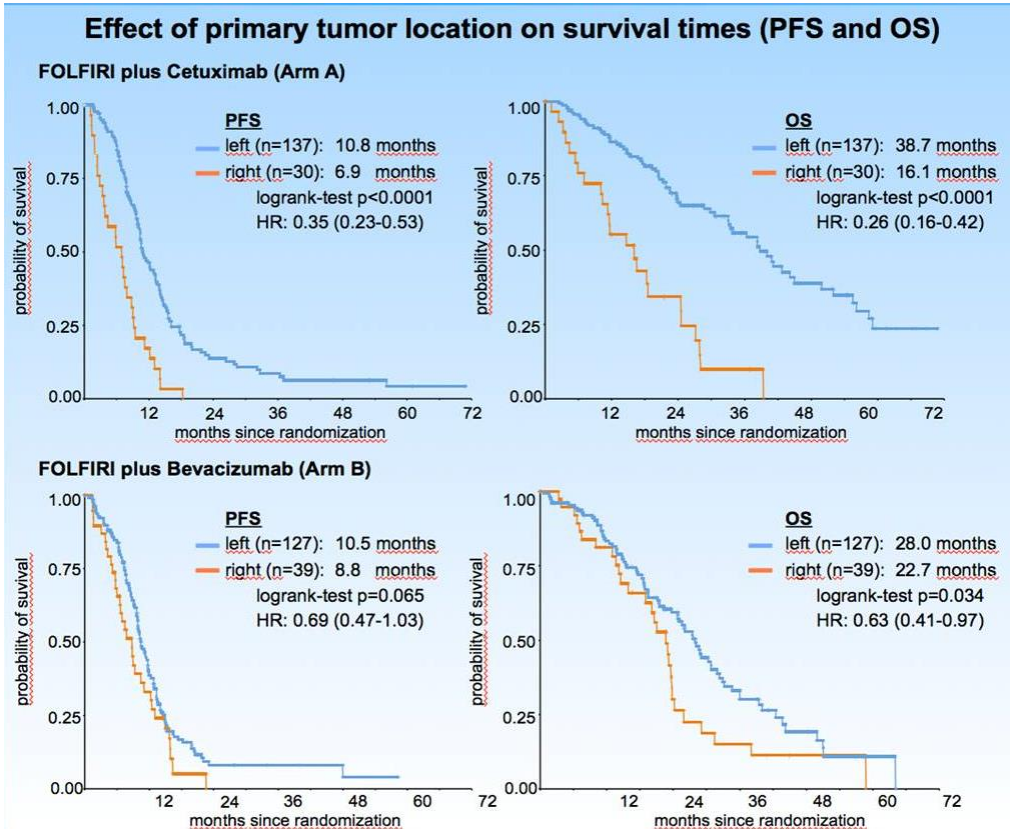
J. Tabernero, Post-Plenary Discussion II: Gastrointestinal Cancer, 2014 ASCO Annual Meeting

CALGB/SWOG 80405: Reason Treatment Discontinued

	ARM A CHEMO + BEV N=559 (%)	ARM B CHEMO + CETUX N=578 (%)	TOTAL N=1137 (%)
Progressive Disease	152 (27.2)	184 (31.8)	336 (29.6)
Other: AE / Withdrawal / change in therapy	315 (56.3)	316 (54.6)	631 (55.5)
Death on Study	15 (2.7)	12 (2.1)	27 (2.4)
On Study /data pending	72 (12.9)	60 (10.3)	132 (11.6)

A. Venook, LBA3, Plenary Session, Gastrointestinal Colorectal Cancer, 2014 ASCO Annual Meeting

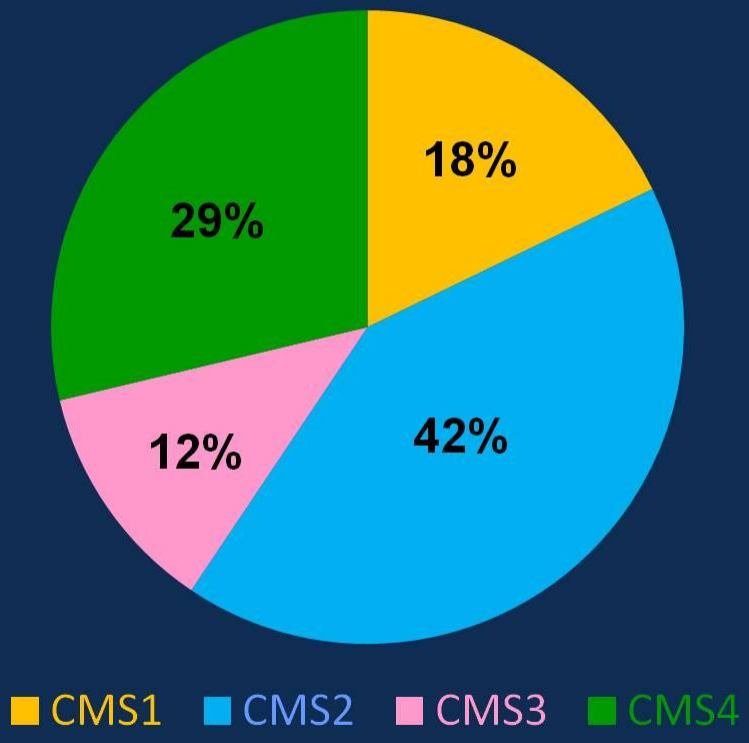
FIRE-3: Tumour Location is Clearly Prognostic

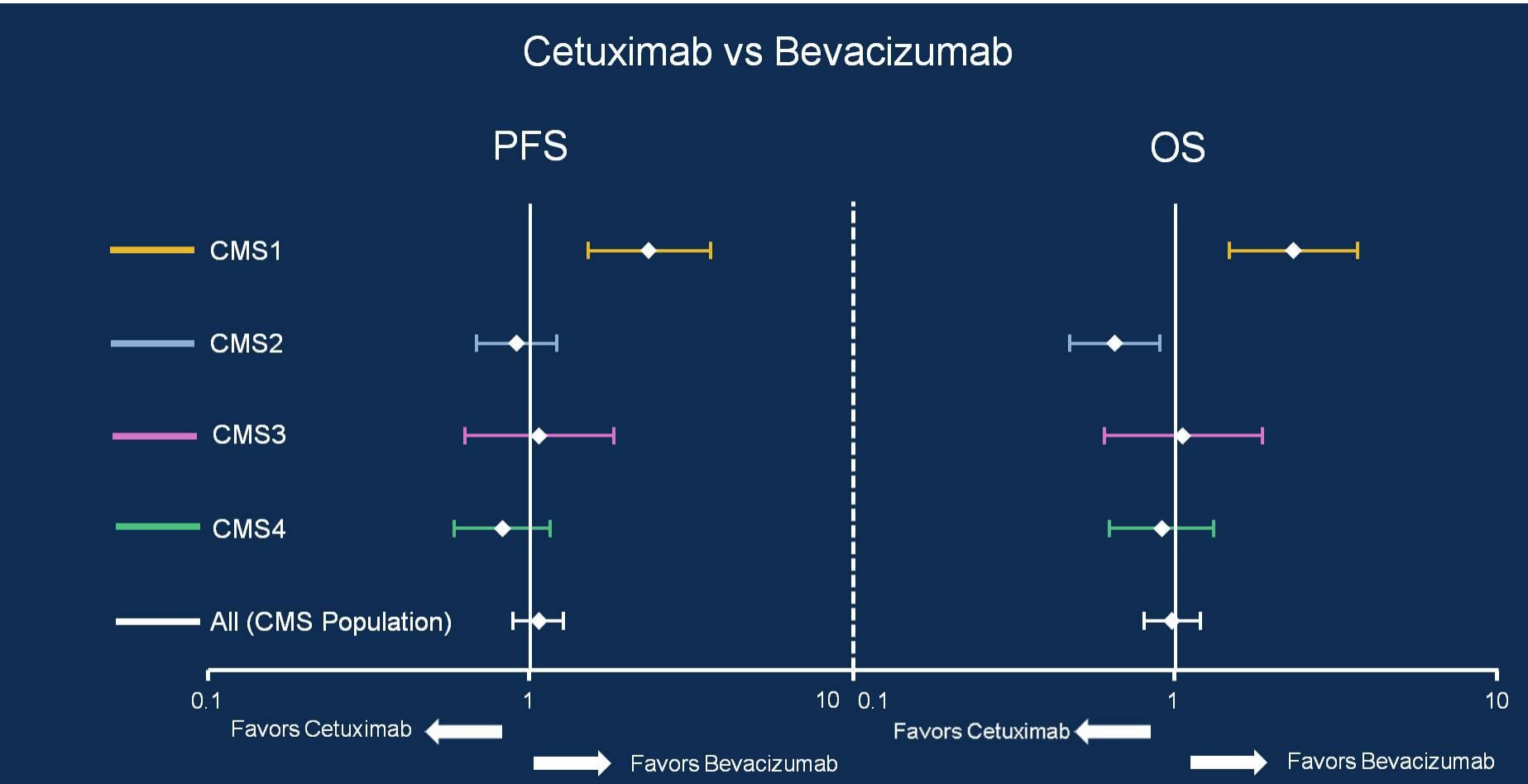


Multivariate Cox Regression Analysis: Location (left- vs right-side tumour)		
Treatment Arm	**OS – HR (*P* value)**	**PFS – HR (*P* value)**
FOLFIRI + Bevacizumab	1.04 (.89)	1.13 (.06)
FOLFIRI + Cetuximab	0.34 (<.0001)	0.43 (.0003)

Heinemann et all ASCO 2014

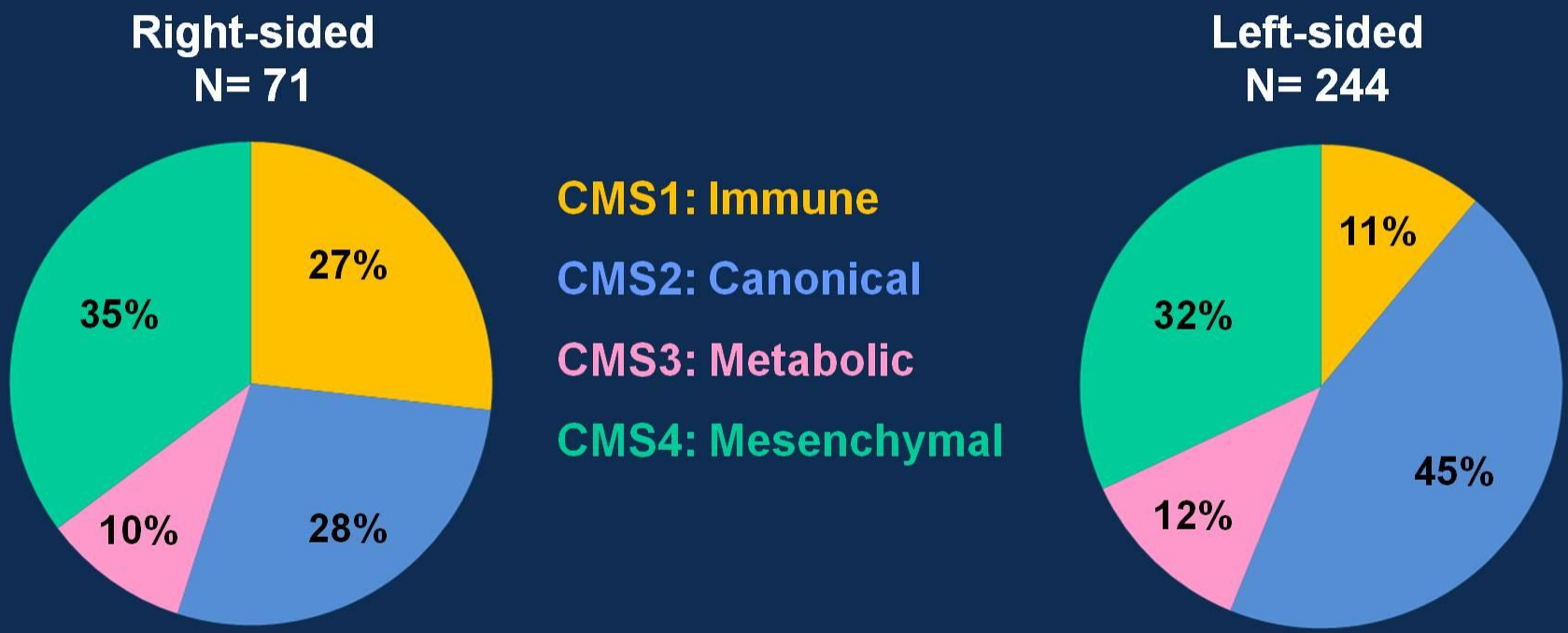
CMS Distribution in 80405



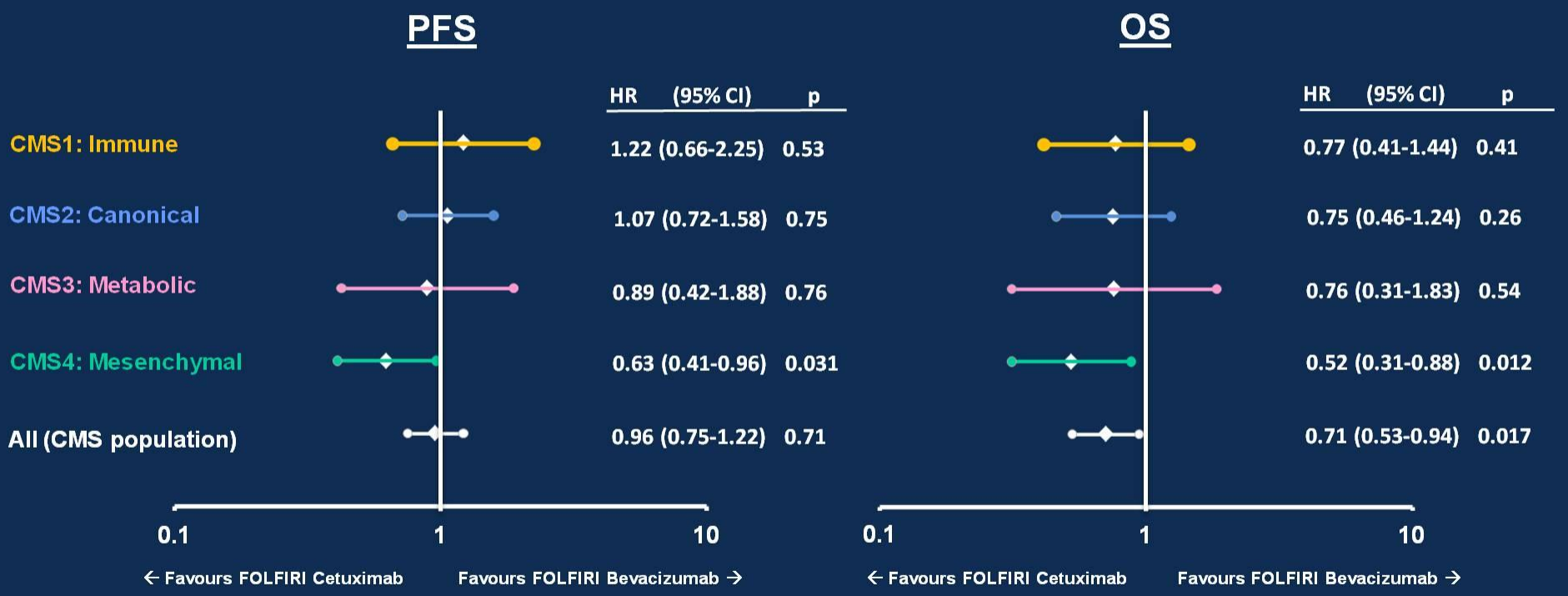


FIRE 3

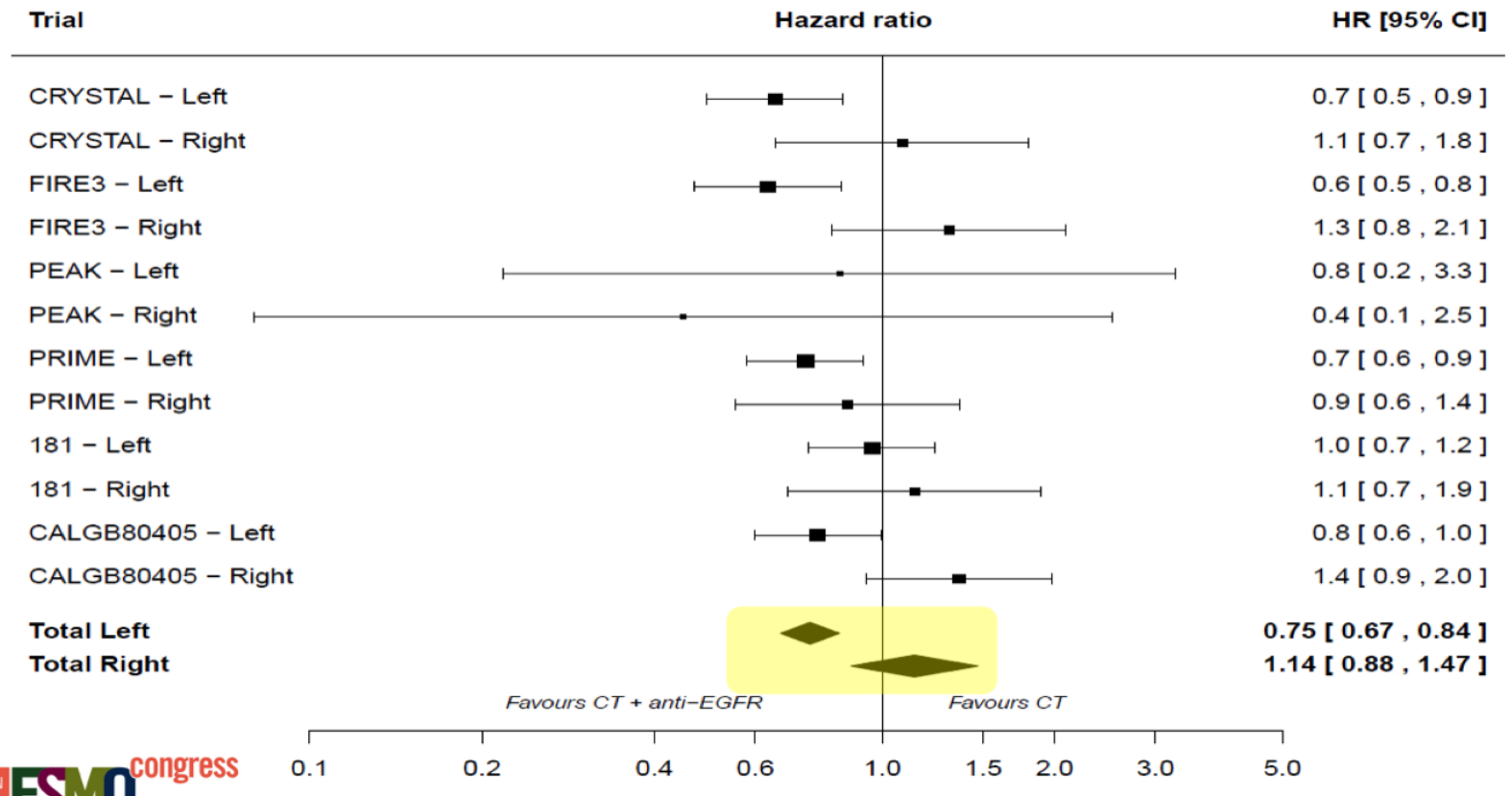
Distribution of CMS between in RAS wild-type left- vs. right sided primaries



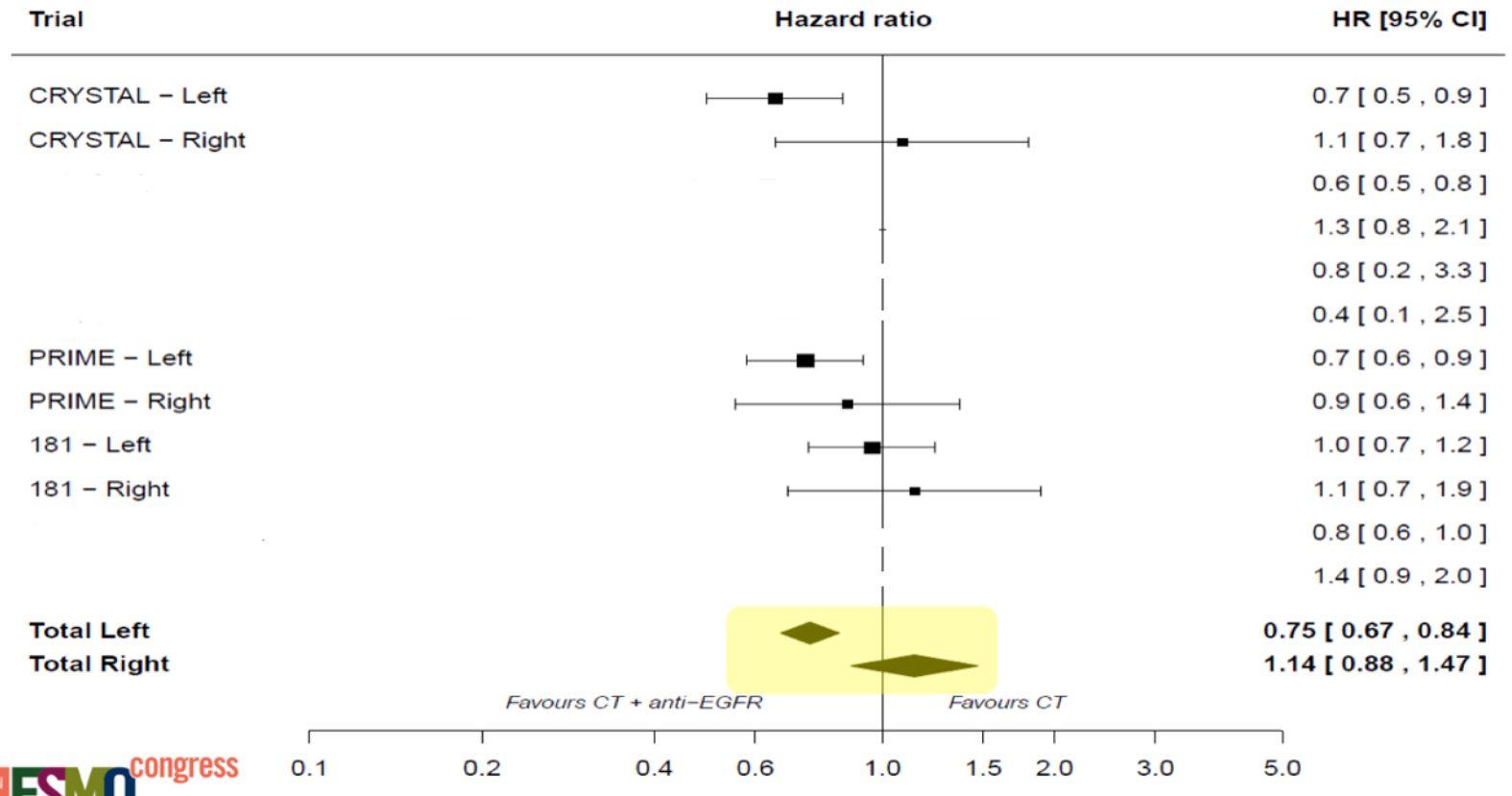
FOLFIRI cetuximab vs. FOLFIRI bevacizumab



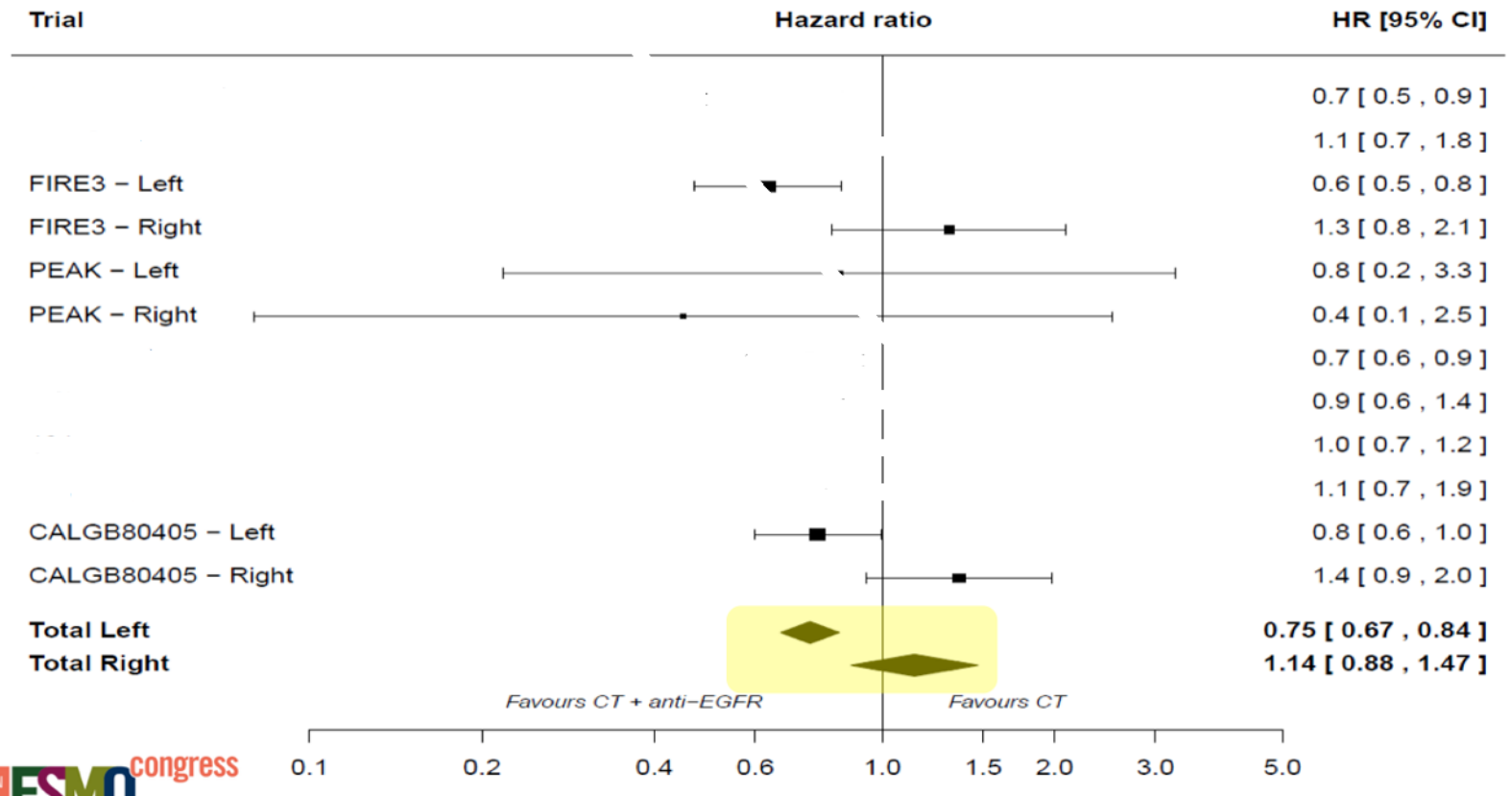
Predictive analysis: Overall Survival



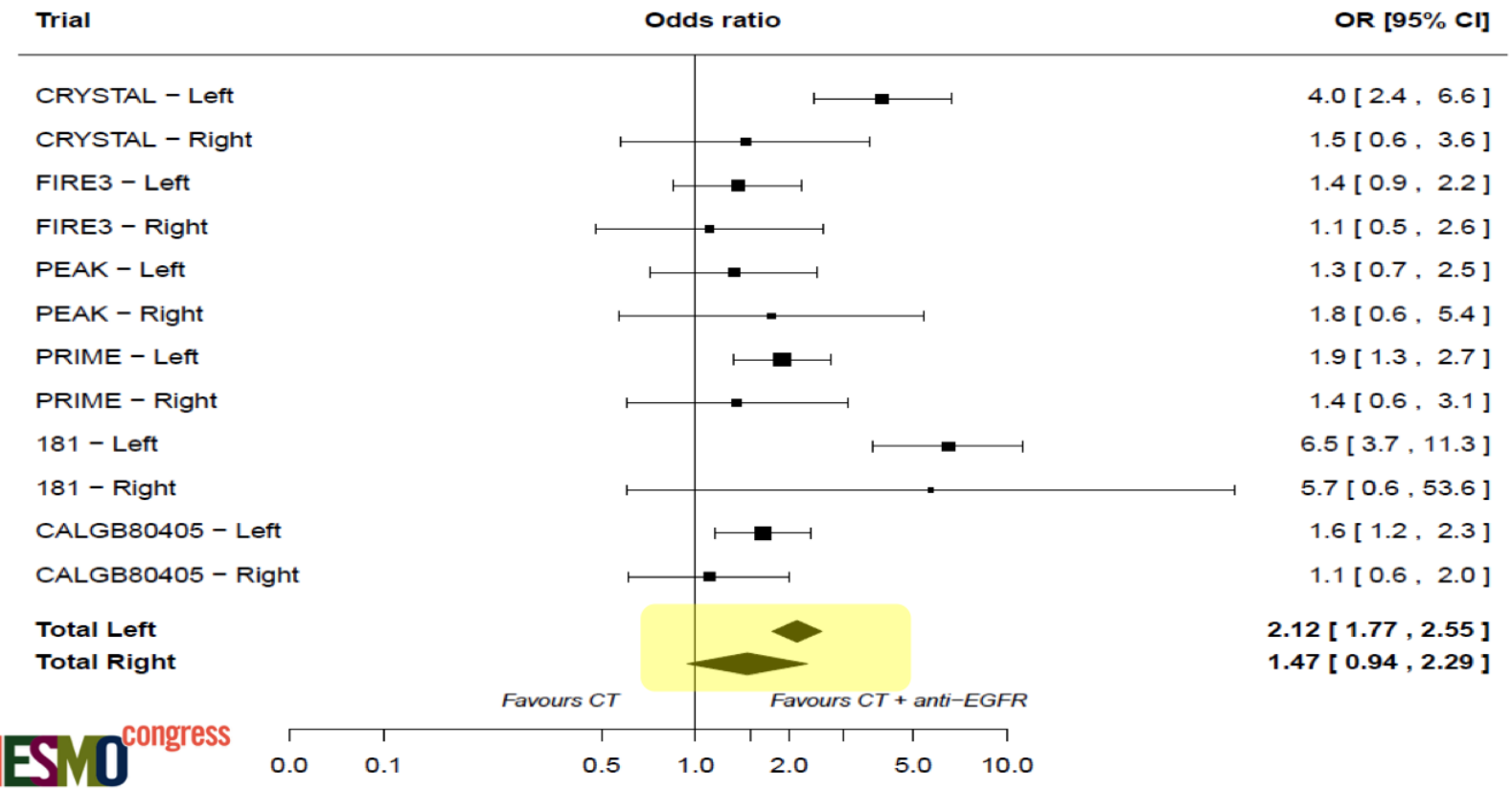
Predictive analysis: Overall Survival



Predictive analysis: Overall Survival



Predictive analysis: Overall response rate



If we put the data on FIRE

Potential Selection Bias

Out of 5741 patients randomized in the 6 trials, 2159 (37,6%) were included in this analysis (from 143 to 474 by trial)

Proportion of patients included run from 31,0% to 52,4%

Main reasons for missing data was KRAS status not evaluated

Patients with KRAS (RAS) mutation were excluded

For some patients information on tumour side was missing or not considered (transverse colon in CALGB 80405)

Not all randomized studies available for analysis (COIN, Scandinavian, etc, …)

TAILOR

Table 2. Effect of Primary Tumor Location on Efficacy in the *RAS* Wild-Type mITT Population

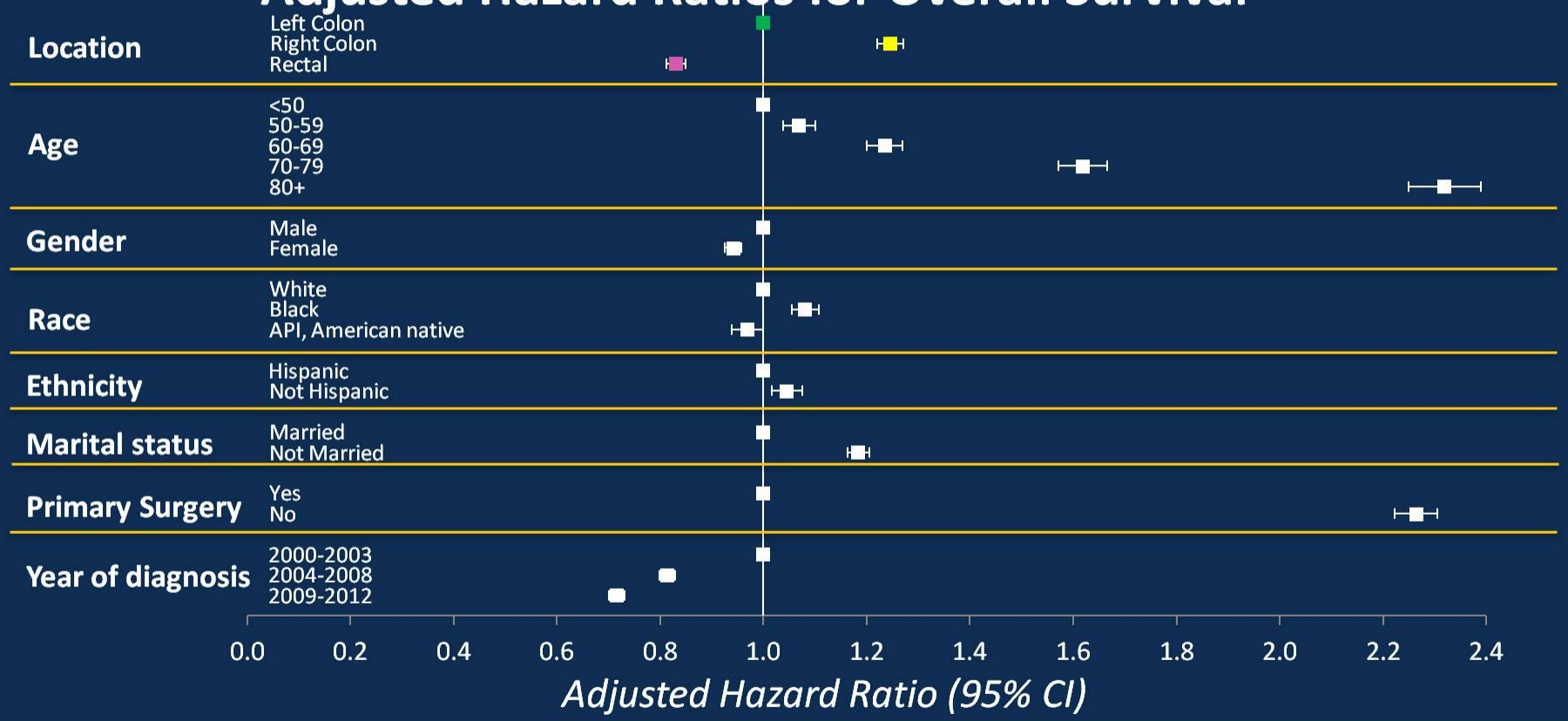
Population and Treatment Arm	No. of Patients	PFS (primary end point) HR (95% CI)	PFS *P* for HR (log-rank test)	PFS Median (months)	OS HR (95% CI)	OS *P* for HR (log-rank test)	OS Median (months)	ORR OR (95% CI)	ORR *P* for OR (Fisher's exact test)	ORR %
mITT*		0.69 (0.54 to 0.89)	.004		0.76 (0.61 to 0.96)	.020		2.41 (1.61 to 3.61)	< .001	
Cetuximab + FOLFOX-4	193			9.2			20.7			61.1
FOLFOX-4	200			7.4			17.8			39.5
Left sided		0.68 (0.50 to 0.91)	.009		0.69 (0.53 to 0.90)	.006		2.60 (1.64 to 4.14)	< .001	
Cetuximab + FOLFOX-4	146			9.2			22.0			66.4
FOLFOX-4	162			7.6			18.7			43.2
Right sided (transverse colon included)		0.67 (0.40 to 1.11)	.117		0.94 (0.58 to 1.51)	.787		2.58 (1.00 to 6.67)	.065	
Cetuximab + FOLFOX-4	45			7.4			11.3			44.4
FOLFOX-4	38			4.5			9.3			23.7
Right sided (transverse colon excluded)		0.77 (0.42 to 1.39)	.377		0.99 (0.56 to 1.76)	.975		2.44 (0.81 to 7.35)	.177	
Cetuximab + FOLFOX-4	32			7.4			11.3			43.8
FOLFOX-4	29			4.5			9.5			24.1

Abbreviations: FOLFOX-4, leucovorin, fluorouracil, and oxaliplatin; HR, hazard ratio; mITT, modified intent to treat; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
*Two patients in the cetuximab plus FOLFOX-4 arm were not evaluable for tumor location.

Qin S et al JCO Sep 2018

Stage IV CRC:

Adjusted Hazard Ratios for Overall Survival



Presented by: D Schrag, MD

Presented By Deborah Schrag at 2016 ASCO Annual Meeting

Clinical Cancer Research

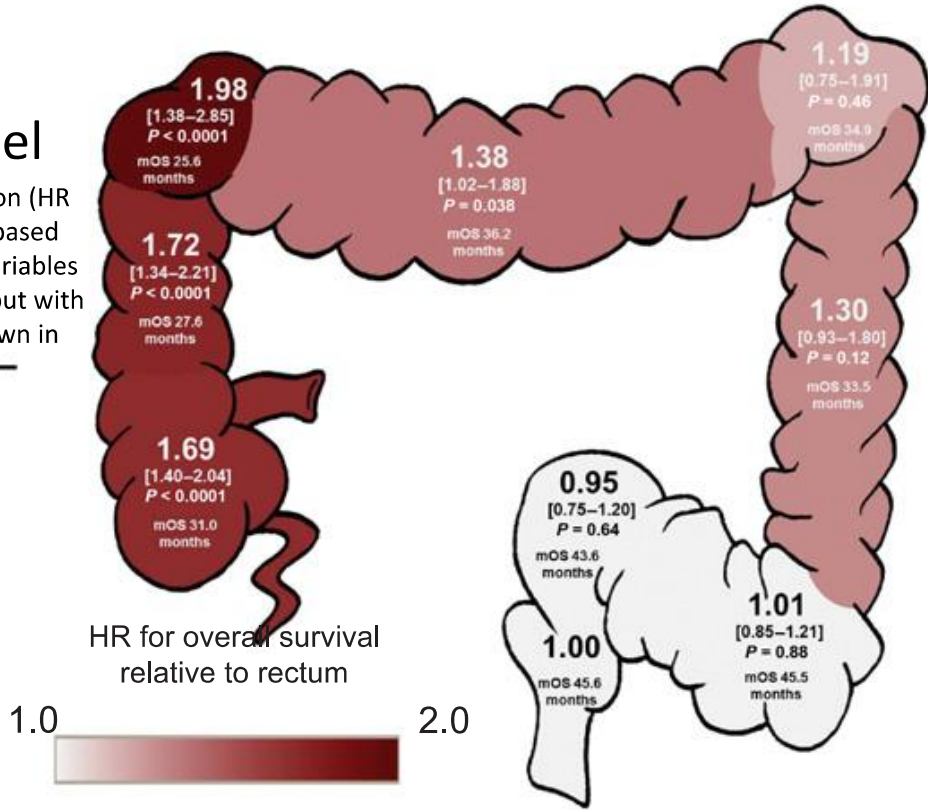
Classifying Colorectal Cancer by Tumor Location Rather than Sidedness Highlights a Continuum in Mutation Profiles and Consensus Molecular Subtypes

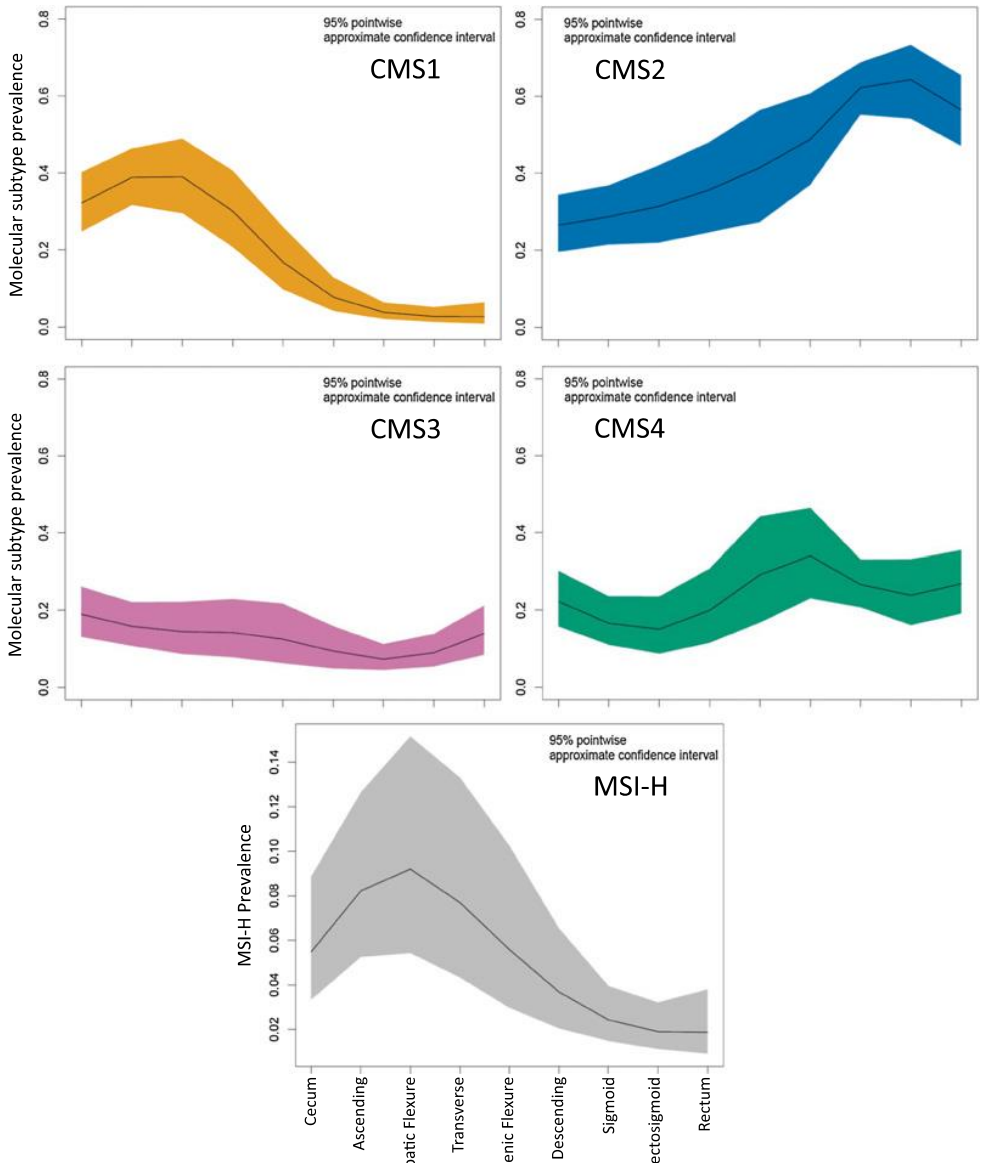
Jonathan M. Loree[1], Allan A.L. Pereira[1], Michael Lam[1], Alexandra N. Willauer[1],

B

Multivariate model

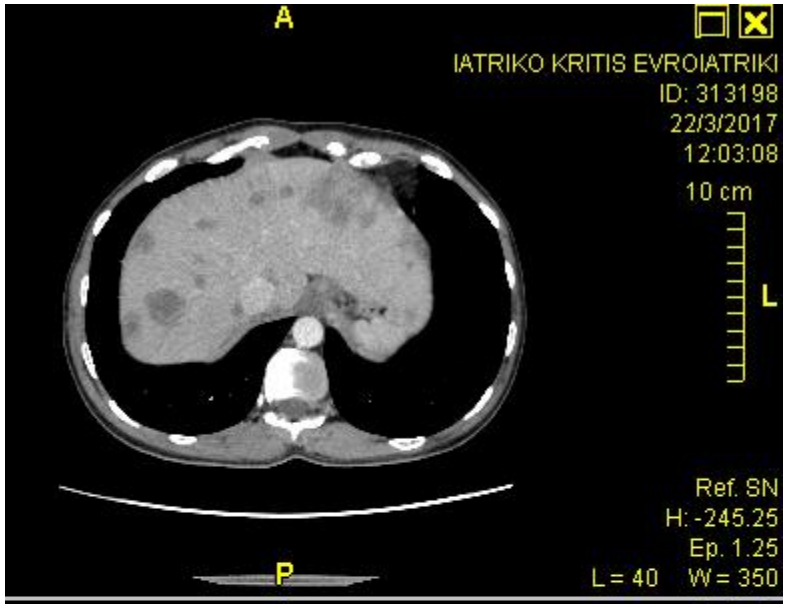
Model included primary tumor location (HR shown in graphic) and non-location based variables (HR in table below). Other variables considered for inclusion in the model but with P>0.1 during model creation are shown in ~~Supplementary Table 3.~~




95% pointwise
approximate confidence interval
CMS1
CMS2
CMS3
CMS4
MSI-H
Molecular subtype prevalence
MSI-H Prevalence
0.0
0.2
0.4
0.6
0.8
0.02
0.04
0.06
0.08
0.10
0.12
0.14
Cecum
Ascending
atic Flexure
Transverse
enic Flexure
Descending
Sigmoid
ectosigmoid
Rectum

Case # 1

- Female 34, single mother of 1 child, unemployed accouter
- Vague abdominal pain
- Colonoscopy tumor in ascending colon
- Adenocarcinoma *KRAS, NRAS, BRAF wt.*
- CEA 243
- Otherwise fit
- FOLFOXIRI + Panitumumab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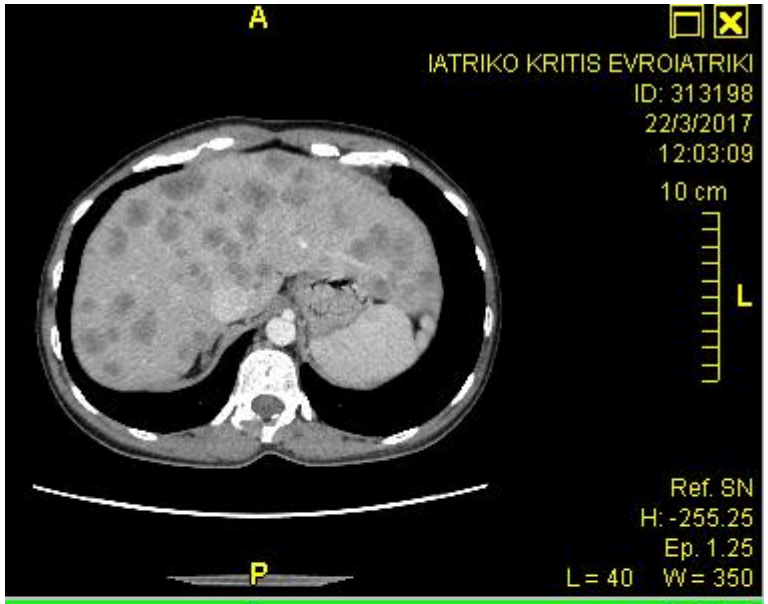
10 cm
L
Ref. SN
H: -245.25
Ep. 1.25
L = 40 W = 350
P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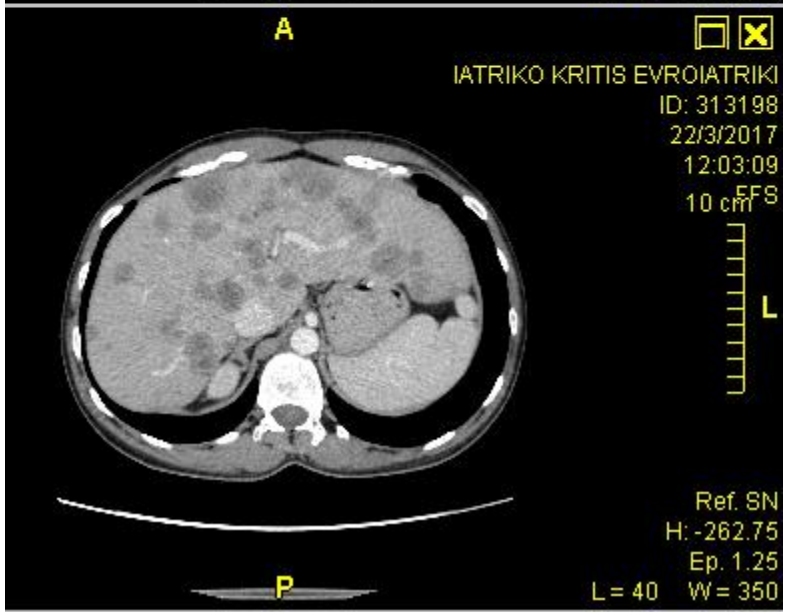
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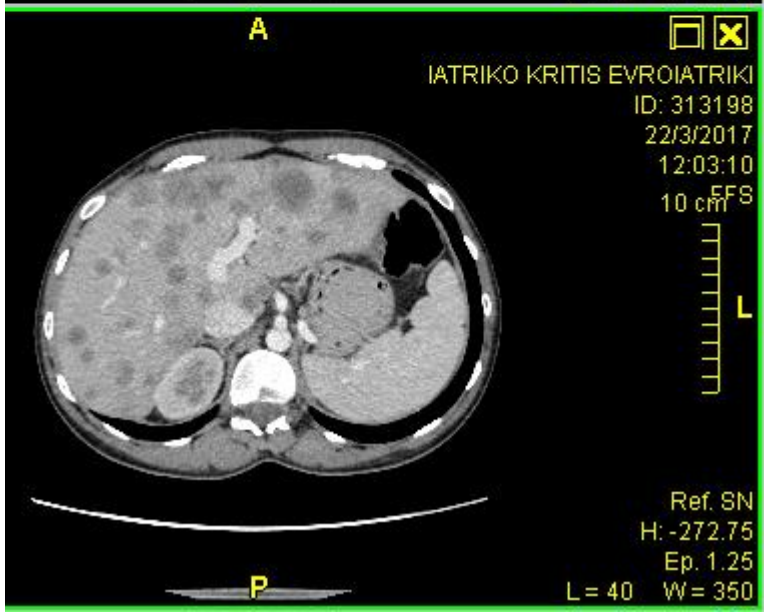
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22/3/2017
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EFS
L
Ref. SN
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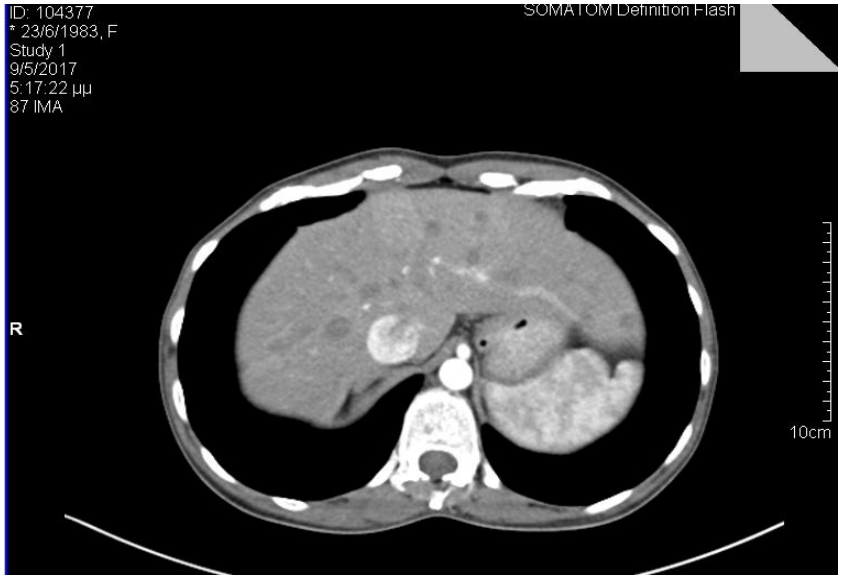
Ep. 1.25
L = 40 W = 350
P

CEA 19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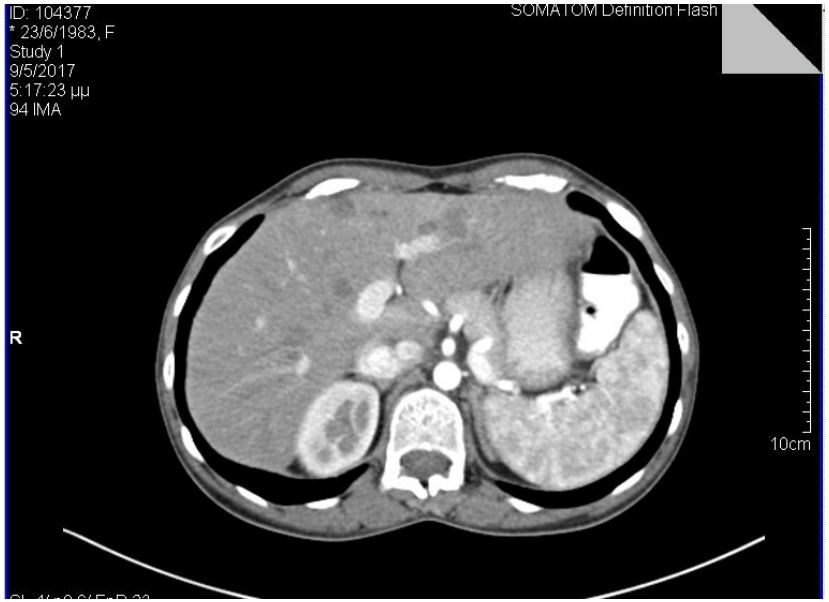
* 23/6/1983, F
Study 1
9/5/2017
5:17:22 µµ
87 IMA
SOMATOM Definition Flash
R
10cm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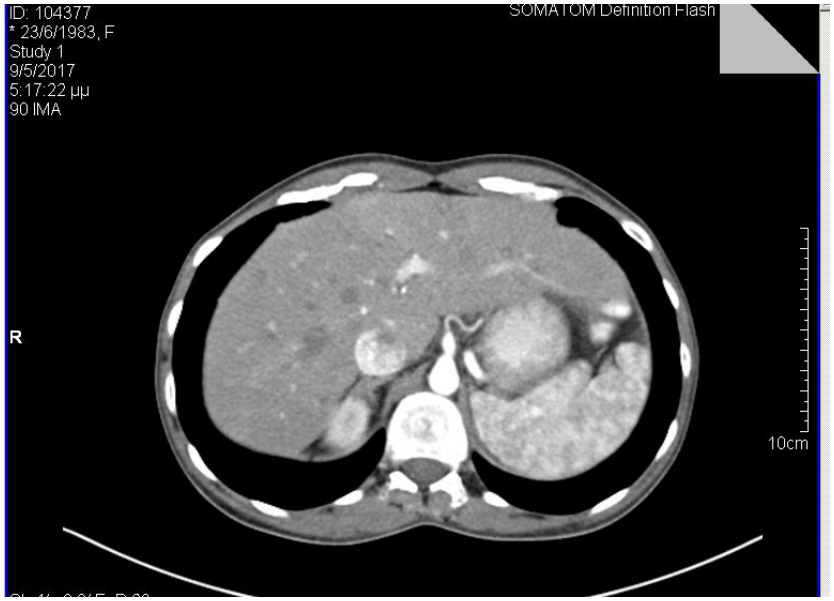
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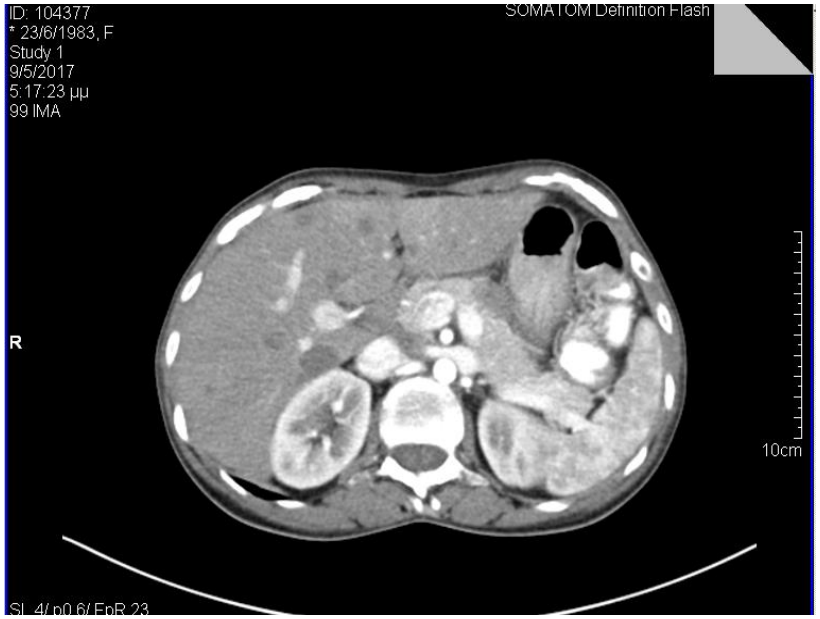
SOMATOM Definition Flash
R
10cm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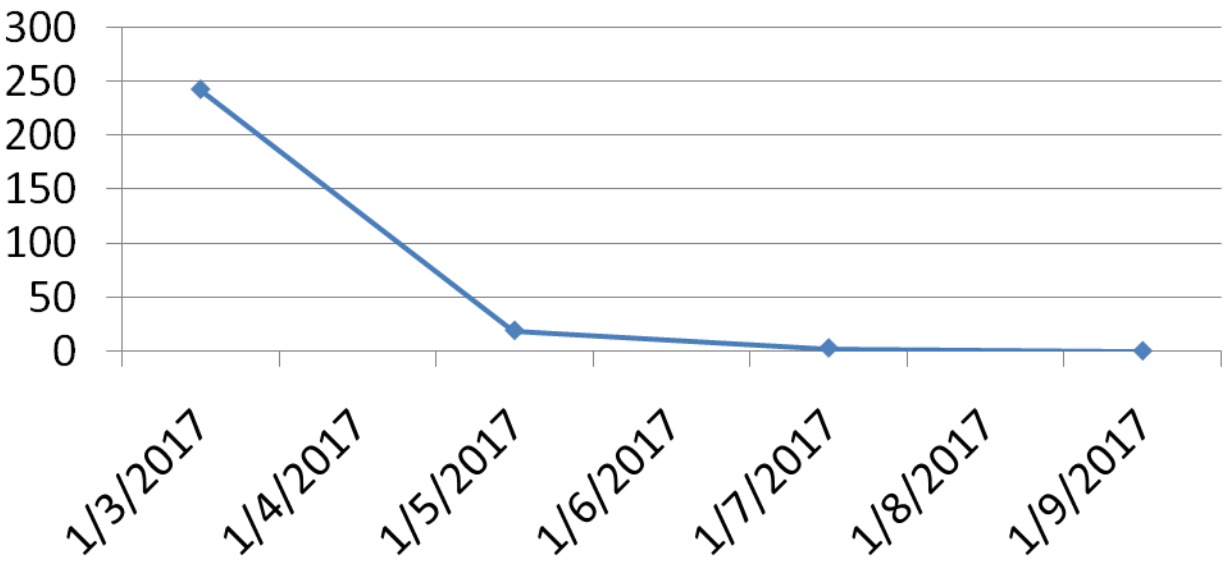
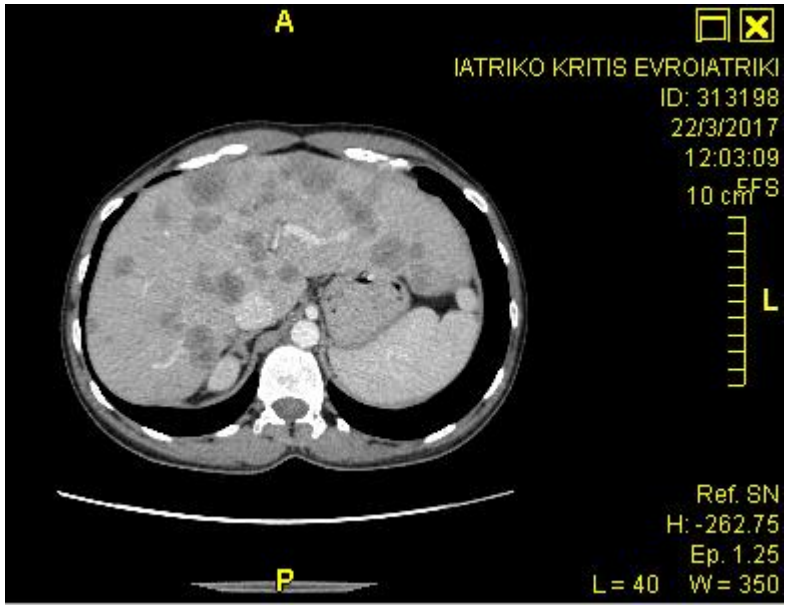
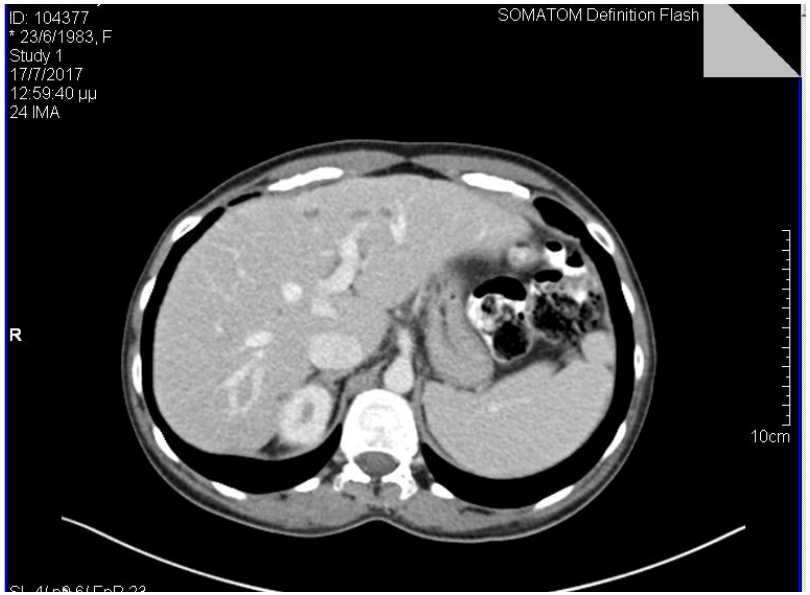
* 23/6/1983, F
Study 1
9/5/2017
5:17:23 µµ
99 IMA
SOMATOM Definition Flash
R
10cm





March 2017



October 2017

October 2017

- Colonoscopy small polypoid mass with central scar 3 cm in max diameter

- PET CT
- One met in segment VI (Suva 7.4)
- Right colectomy and Hepatectomy (right + ablation)

Case 2

- 64y female otherwise healthy
- May 2016 acute + vomiting
- CT: obstructive ileus, liver mets
- Colostomy, liver mets and peritoneal metastasis mucinous adenocarcinoma of the rectum pT4,N2,M1b
- 1st oncologic evaluation 3 months later
- New scan with significant disease progression

Case # 2

- *BRAF*^{V600E}mutant tumor

- MSI-H (4/5 markers, IHC MHL1 -)

Case # 2

- FOLFIRI + AFLIBERCEPT
- continuous response for 6 months (>50% reduction)
- Relapse after 10 months
- Start Pembrolizumab
  - 2 years on treatment with objective response and asymptomatic

Sidedness mCRC: existing knowledge

- Molecular marker and intention to are the main determinants for treatment decisions
- Confirmed prognostic associations
  - FIRE 3, CALGB, SEERs

- Unknown
  - predictive value
  - Effect of micro-environment
  - Effect of microbiota

- Distinct molecular surrogates

- Hypothesis generation post-hoc unplanned analysis

What am I Doing in RAS-RAF wt. tumors

Treatment goal		Right sided	Left sided
Cytoreduction		Doublet (or even triplet with anti-EGFR)	
Prolongation of PFS			
	Non-maintenance planning	Doublets + bev	Doublet + anti-EGFR
	Maintenance planning	Doublets (or fluoropyrimidine+ bev)	

University of Crete