What is the Best Treatment for the First Line Treatment of Unresectable Metastatic Colorectal Cancer?

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Sunnybrook
HEALTH SCIENCES CENTRE

VELUT ARBOR ÆVO

Overview

Landscape

Trials of Chemo +/- Bev, Chemo +/-EGFR

Randomized Trials of Chemo+Bev vs Chemo+EGFRi

PEAK
FIRE3
CALGB 80405 / CRC.5

Case

50 yo woman - No medical problems

Presents with metastatic colorectal cancer with bilobar liver and bilateral lung metastases

Some RUQ pain and cough

ECOG 1

KRAS Exon 2 WT

Chemo + Bev

Chemo + EGFR Inhibitor

Case

50 yo woman - No medical problems

Presents with metastatic colorectal cancer with bilobar liver and bilateral lung metastases

Some RUQ pain and cough

ECOG 1

All Ras WT

Chemo + Bev

Chemo + EGFR Inhibitor

Chemo +/-
Bevacizumab

Statistically Significant Results in RED		RR (%)	Median PFS/TTP (mos)	Median OS (mos)
Combination Infusional Chemo	CapeOx/FOLFOX +/- Bev (Saltz, JCO 2008)	38 vs 38	9.4 vs 8.0 HR=0.83	21. 3 vs 19.8 HR=0.89
	FOLFIRI/FOLFOX +/- Bev (Passardi, ASCO 2013)	49 vs 48	9.6 vs 8.4 HR=0.87	*
Combination Bolus Chemo	IFL +/- Bev (Hurwitz, NEJM, 2004)	45 vs 35	10.6 vs 6.2 HR=0.54	20.3 vs 15.6 HR = 0.66
	Iri / 5FU Bolus q 3wks +/- Bev (Stathopolous, Oncology, 2010)	37 vs 35	NR	22.0 vs 25.0 HR=NR
	mIFL+/- Bev (Guan, Chinese Journal of Cancer, 2011)	35 vs 17	8.3 vs 4.2 HR=0.44	18.7 vs 13.4 HR=0.62
Fluoropyrimidine Monoptherapy	5FU/LV +/- Bev (pooled analysis) (Kabbinavar, JCO, 2005)	34 vs 24	8.8 vs 5.6 HR=0.63	17.9 vs 14.6 HR=0.74
	Cape+/- Bev (Tebutt, JCO, 2010)	38 vs 30	8.5 vs 5.7 HR=0.63	18.9 vs 16.4 HR=0.88
	Cape+/- Bev (Cunningham, Lancet Onc, 2013)	19 vs 10	9.1 vs 5.1 HR=0.53	20.7 vs 16.8 HR=0.79

Chemo +/-
EGFR Inhibitors

First Line Trials: KRAS WT (Significant Results in Red)	RR %	Median PFS/TTP (mos)	Median OS (mos)
CRYSTAL (FOLFIRI+/-Cetux) Van Cutsem, JCO 2011	59 vs 43	9.9 vs 8.7 (HR=0.68) (1	23.5 vs 20 (HR=0.80)
PRIME (FOLFOX+/-Pmab) Douillard, JCO 2009	55 vs 48	9.6 vs 8.0 (HR=0.80) (1	23.9 vs 19.7 (HR=0.80)
OPUS (FOLFOX +/- Cetux) Bokemeyer, JCO 2009	57 vs 34	8.3 vs 7.2 (HR=0.57)	22.8 vs 18.5 (HR=0.86)
COIN (CapeOx/FOLFOX+/-Cetux) Maughan, Lancet 2011	64 vs 57	8.6 vs 8.6 (HR.96)	17.0 vs 17.9 (HR=1.04)
Nordic VII (NORDIC FLOX+/-Cetux) Tveit JCO 2012	46 vs 47	7.9 vs 8.7 (HR 1.07)	20.1 vs 22.0 (HR=1.14)

What is the best 1st Line Therapy for KRAS WT Patients?

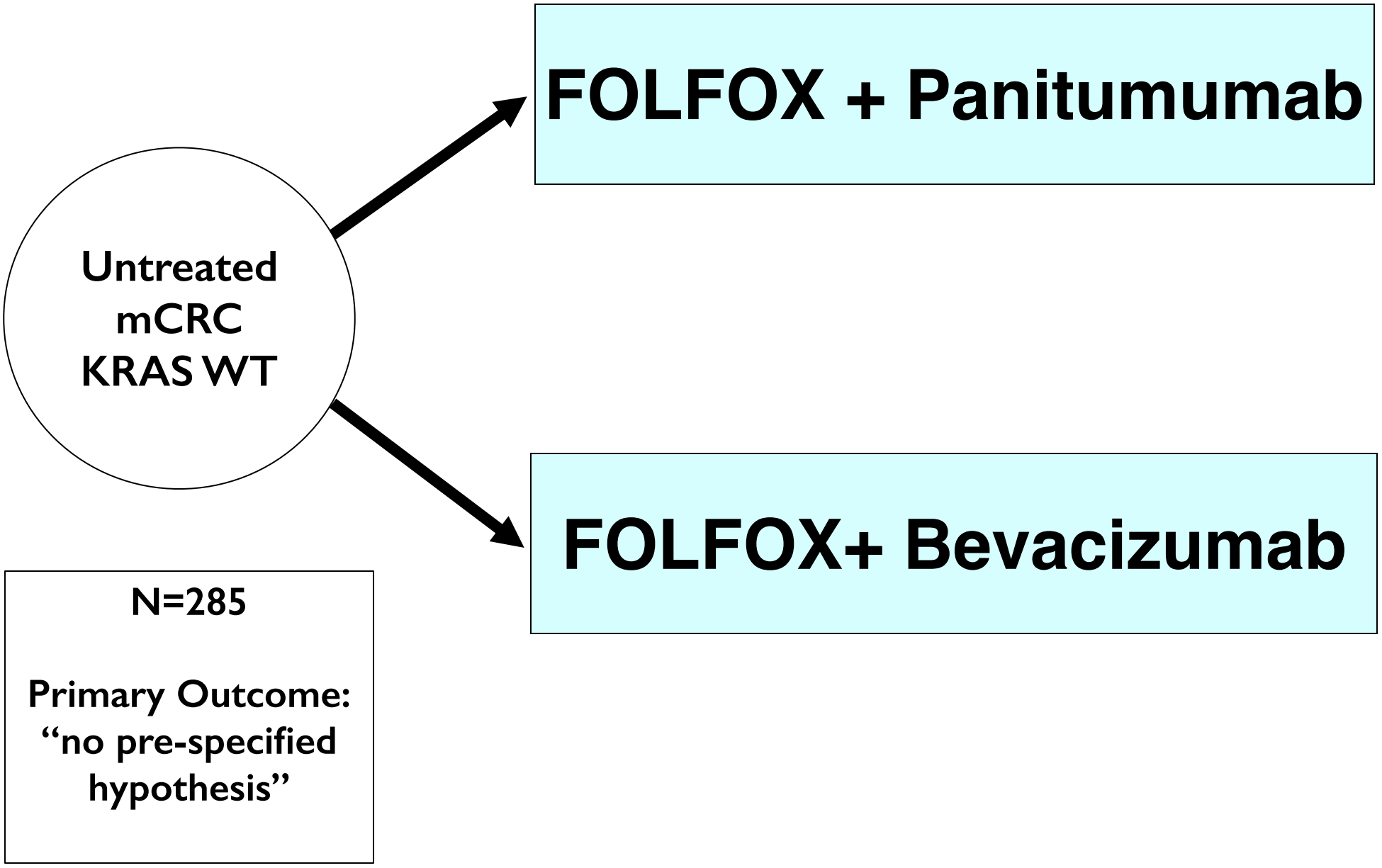
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

PEAK: A Randomized, Multicenter Phase II Study of Panitumumab Plus Modified Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOX6) or Bevacizumab Plus mFOLFOX6 in Patients With Previously Untreated, Unresectable, Wild-Type *KRAS* Exon 2 Metastatic Colorectal Cancer

Lee S. Schwartzberg, Fernando Rivera, Meinolf Karthaus, Gianpiero Fasola, Jean-Luc Canon, J. Randolph Hecht, Hua Yu, Kelly S. Oliner, and William Y. Go

PEAK

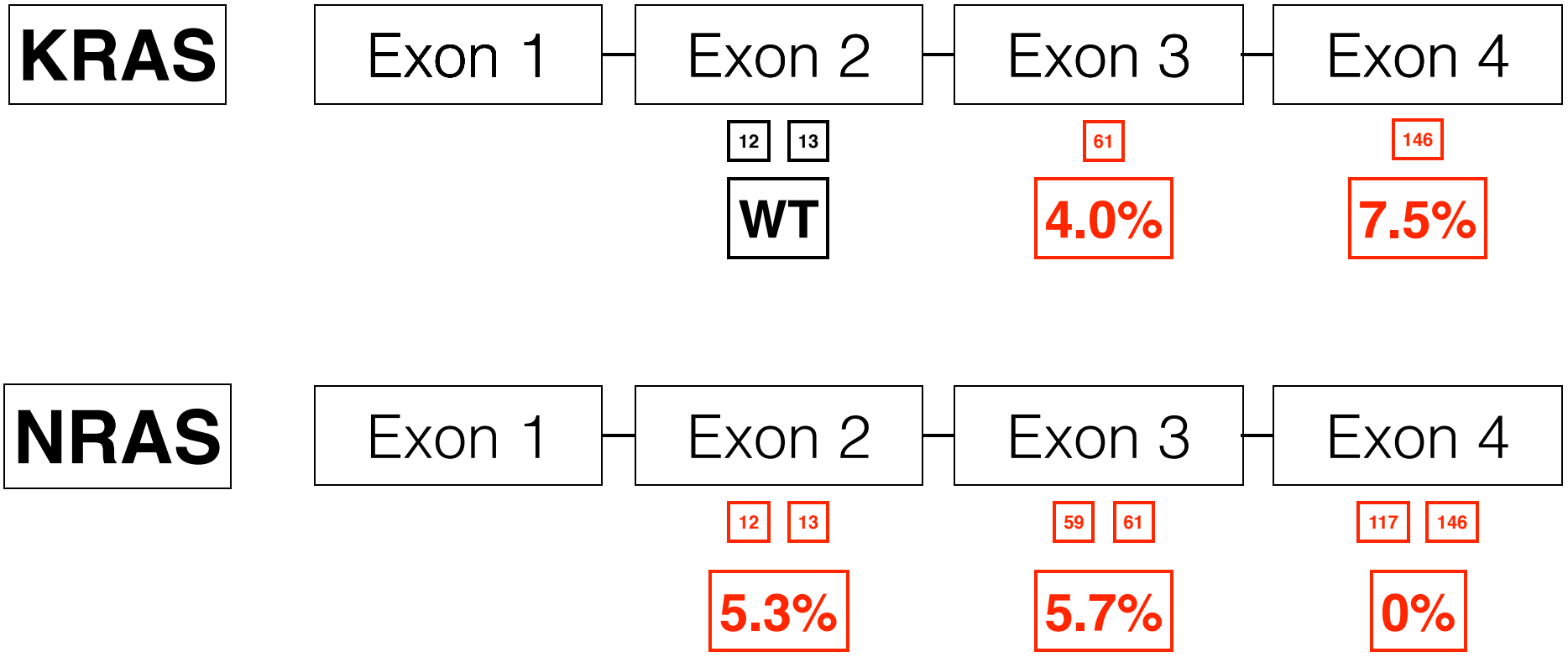

FOLFOX + Panitumumab
Untreated
mCRC
KRAS WT
FOLFOX+ Bevacizumab
N=285
Primary Outcome:
"no pre-specified
hypothesis"

Characteristic	Panitumumab Plus mFOLFOX6 (n = 142)		Bevacizumab Plus mFOLFOX6 (n = 143)	
	No.	%	No.	%
Male sex	86	61	96	67
White race	131	92	127	89
Age, years				
Median	63		61	
Range	23-82		28-82	
≥ 65	62	44	53	37
≥ 75	15	11	11	8
ECOG PS				
0	89	63	91	64
1	53	37	51	36
Missing/unknown	0	0	1	< 1
Primary tumor diagnosis				
Colon	96	68	92	64
Rectum	46	32	51	36
No. of metastatic sites				
1	53	37	56	39
2	50	35	49	34
≥ 3	39	27	37	26
Missing/unknown	0	0	1	< 1
Liver-only metastatic disease	37	26	39	27
No. of metastatic organs				
Median	3		3	
Range	1-10		1-8	

PEAK KRAS Exon 2 WT

	FOLFOX+ Pmab (n=142)	FOLFOX+ Bev (n=143)
Response Rate %	58	54
PFS (mos)	10.9	10.1
OS (mos)	34	24

PEAK - Extended Ras Analysis



New RAS Mutations : 23%

PEAK KRAS Extended WT

	FOLFOX+ Pmab (n=82)	FOLFOX+ Bev (n=88)
Response Rate %	64	61
PFS (mos)	13.0	9.5
OS (mos)	41	29

Football Rob
$100

Jimmy Kimmel Rob
$30

Tuxedo Rob
$30

ROB FORD BOBBLEHEADS

CHOOSE FROM OUR SELECTION

T-SHIRTS, BOBBLEHEADS, TRAVEL MUGS
ARE ALSO AVAILABLE AT THE

ROB FORD CAMPAIGN OFFICE

2082 LAWRENCE AVE E

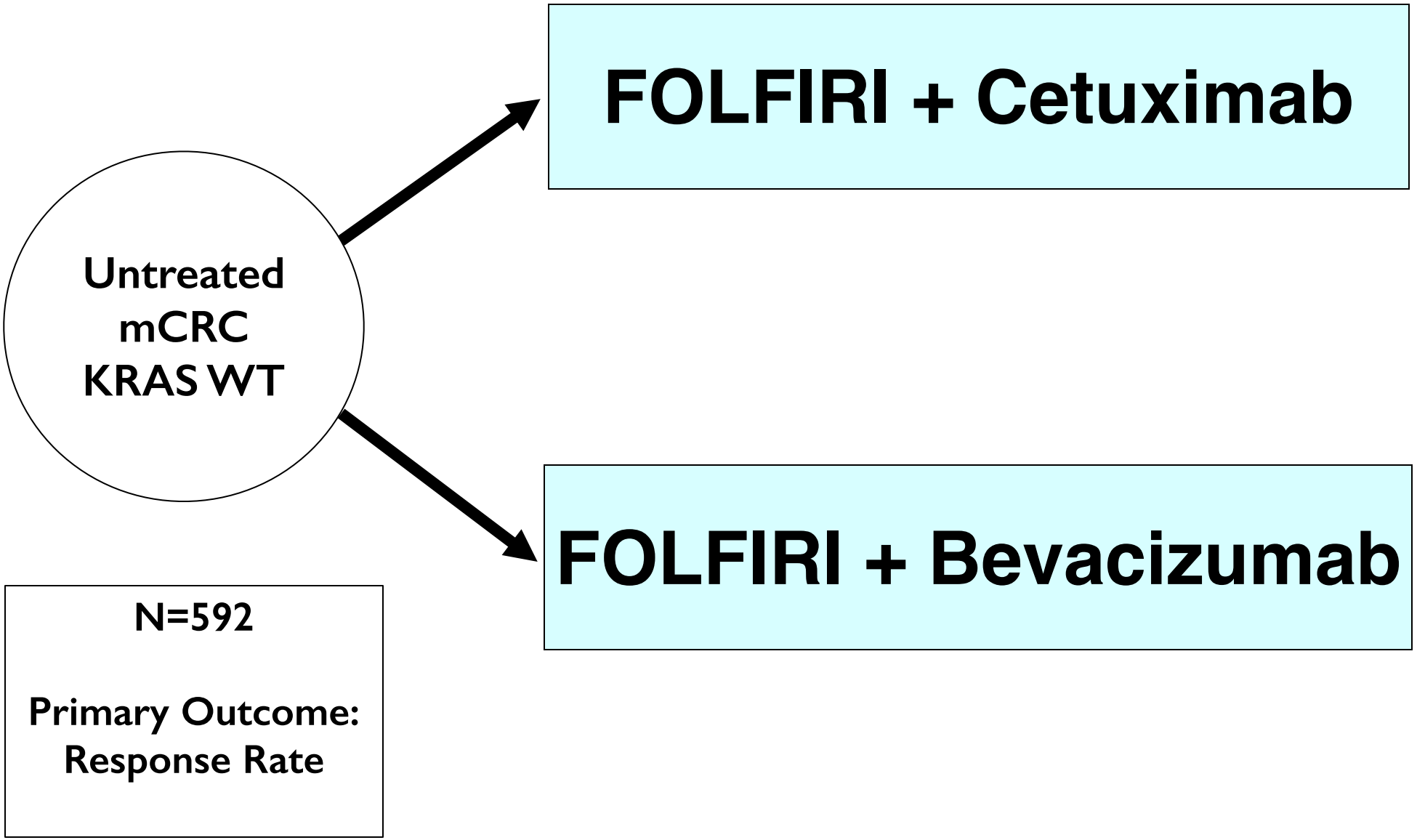
FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial

Volker Heinemann, Ludwig Fischer von Weikersthal, Thomas Decker, Alexander Kiani, Ursula Vehling-Kaiser, Salah-Eddin Al-Batran, Tobias Heintges, Christian Lerchenmüller, Christoph Kahl, Gernot Seipelt, Frank Kullmann, Martina Stauch, Werner Scheithauer, Jörg Hielscher, Michael Scholz, Sebastian Müller, Hartmut Link, Norbert Niederle, Andreas Rost, Heinz-Gert Höffkes, Markus Moehler, Reinhard U Lindig, Dominik P Modest, Lisa Rossius, Thomas Kirchner, Andreas Jung, Sebastian Stintzing

Lancet Oncol 2014; 15: 1065–75

Published Online
August 1, 2014

FIRE3


FOLFIRI + Cetuximab
Untreated
mCRC
KRAS WT
FOLFIRI + Bevacizumab
N=592
Primary Outcome:
Response Rate

	Intention-to-treat population	
	FOLFIRI plus cetuximab (n=297)	FOLFIRI plus bevacizumab (n=295)
Sex		
Men	214 (72%)	196 (66%)
Women	83 (28%)	99 (34%)
Age (years)	64·0 (38·0–79·0)	65·0 (27·0–76·0)
≤65	158 (53%)	160 (54%)
>65	139 (47%)	135 (46%)
≥70	90 (30%)	69 (23%)
ECOG performance status		
0	154 (52%)	158 (54%)
1	136 (46%)	133 (45%)
2	7 (2%)	4 (1%)
Laboratory values		
Leucocyte count ≥8 × 10⁹ per L	129 (43%)	118 (40%)
Alkaline phosphatase ≥300 U/L	40 (13%)	39 (13%)
Site of primary tumour		
Colon	168 (57%)	177 (60%)
Rectum	115 (39%)	106 (36%)
Colon and rectum	9 (3%)	12 (4%)
Unknown	5 (2%)	0
Number of metastatic sites		
1	119 (40%)	123 (42%)
≥2	174 (59%)	171 (58%)
Unknown	4 (1%)	1 (<1%)
Metastatic sites		
Liver	241 (81%)	240 (81%)
Liver only	93 (31%)	94 (32%)
Liver not affected	52 (18%)	54 (18%)
Previous treatment		
Surgery	249 (84%)	252 (85%)
Adjuvant chemotherapy	66 (22%)	56 (19%)
Radiotherapy	39 (13%)	40 (14%)

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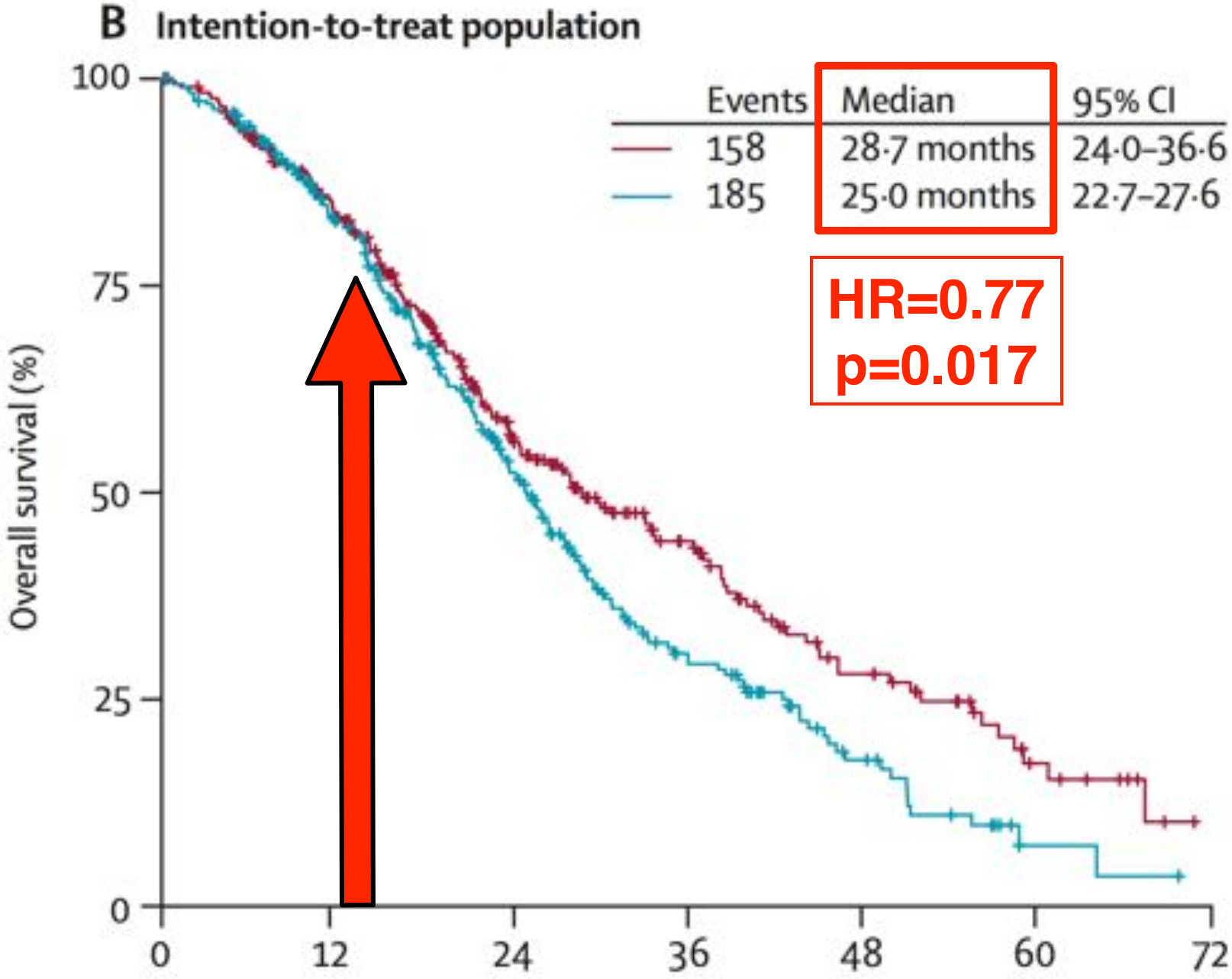
FIRE3 KRAS Exon 2 WT

N=592	FOLFIRI+ Cmab	FOLFIRI+ Bev
Response Rate %	62	58
PFS (mos)	10.0	10.3


B Intention-to-treat population
Events
Median
95% CI
158
28·7 months
24·0–36·6
185
25·0 months
22·7–27·6
HR=0.77
p=0.017
Overall survival (%)
100
75
50
25
0
0
12
24
36
48
60
72

FIRE3 2nd Line Treatment

	FOLFIRI+Cmab	FOLFIRI+Bev
Alive After First Line	260	250
Any 2nd Line Tx	78%	76%
Oxaliplatin	62%	63%
Irinotecan	16%	16%
Bevacizumab	47%	15%
Anti-EGFR	17%	41%

FIRE3

3rd Line Treatment

FOLFIRI + Cmab : 36%
FOLFIRI + Bev : 40%

FIRE3

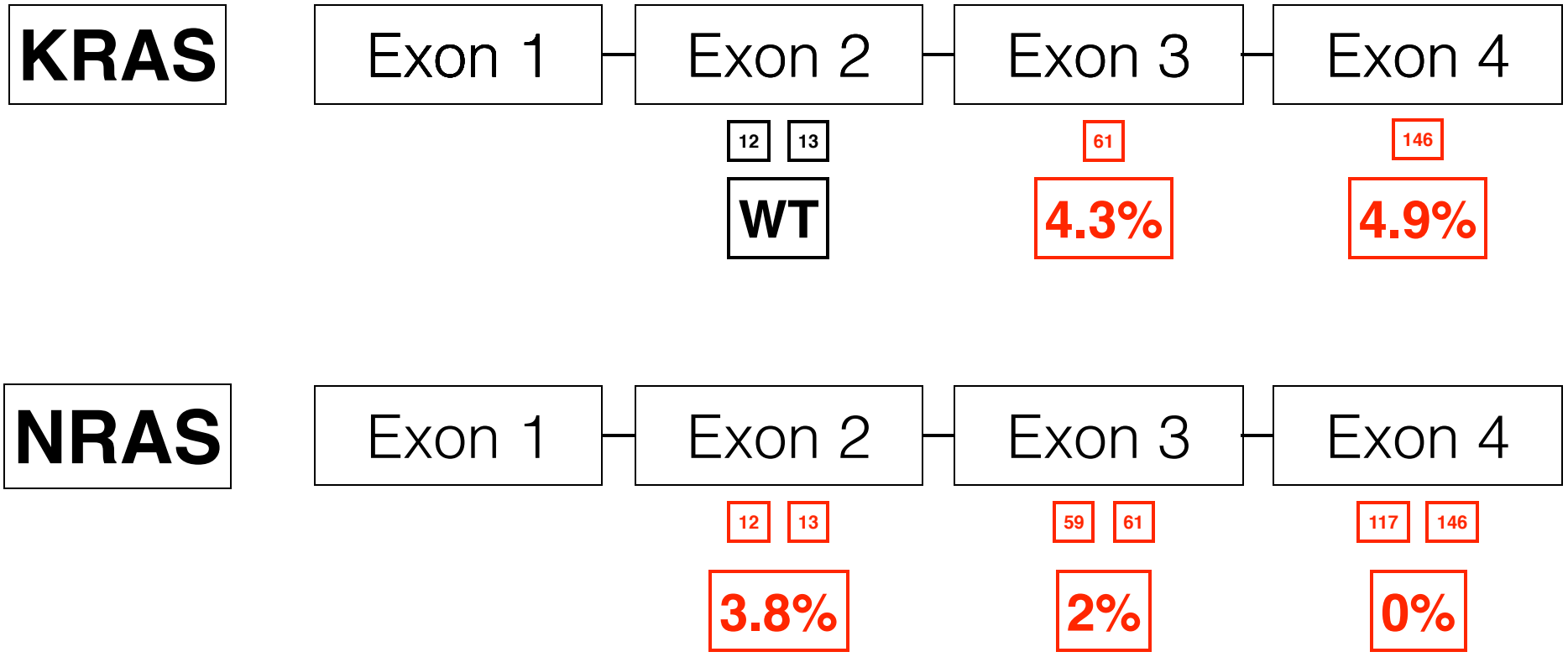
Off Tx
Because Eligible for Resection

FOLFIRI + Cmab : 36%
FOFIRI + Bev : 40%

FIRE3 - Toxcity

	FOLFIRI+ Cmab	FOLFIRI+ Bev
GR 3/4 Adverse Events	71%	64%
Discontinued Tx Because Drug Related Toxicity	15%	11%

FIRE3 - Extended Ras Analysis



New RAS Mutations : 15%

FIRE3 Extended RAS

	KRAS Exon 2 WT (N=592)		ALL RAS WT (N=342)	
	FOLFIRI+ Cmab	FOLFIRI+ Bev	FOLFIRI+ Cmab	FOLFIRI+ Bev
RR%	62.0	58.0	65.5	59.6
	Δ= 4.0%		Δ= 5.9%	
PFS (mos)	10.0	10.3	10.4	10.2
	Δ= -0.3 mos		Δ= 0.2 mos	
OS (mos)	28.7	25.0	33.1	25.6
	Δ= 3.7 mos		Δ= 7.5 mos	

FIRE 3 and PEAK

Trial results consistent despite different backbones

? Why OS benefit in absence of RR or PFS benefit?

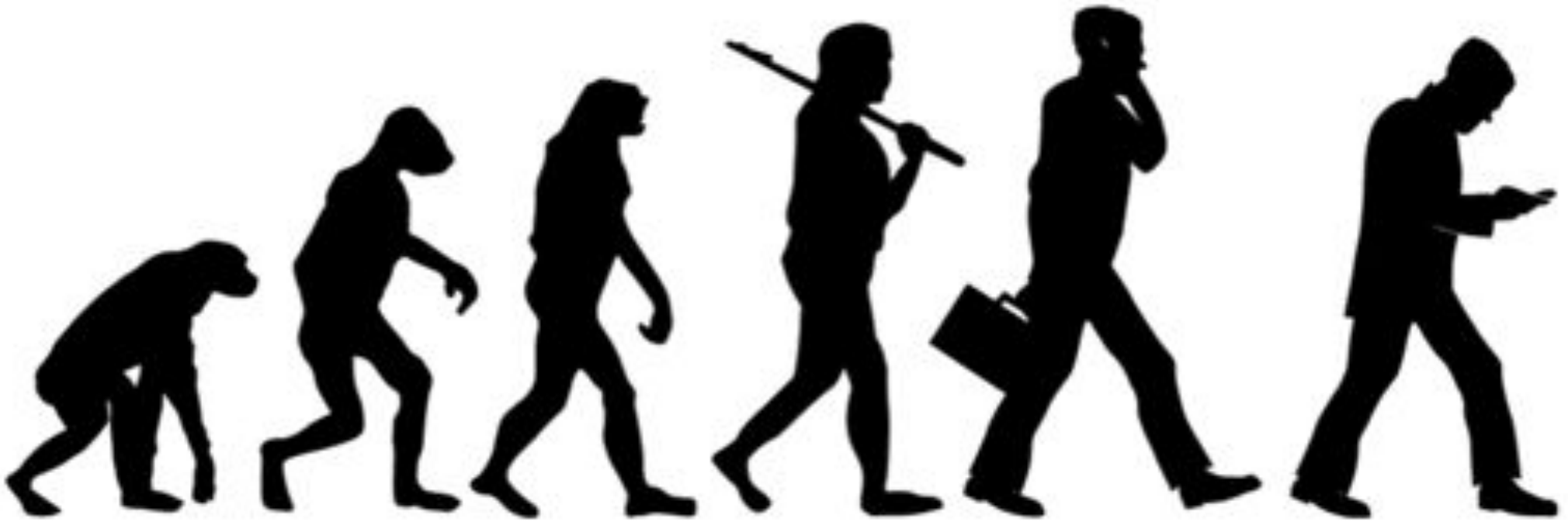
In the absence of a large randomized trial, powered for OS looking at the same question - I might be tempted to accept the findings of these trials….


BUDDY GUY'S

CALGB/SWOG 80405: Phase III trial of FOLFIRI or FOLFOX with Bevacizumab or Cetuximab for patients w/ KRAS *wild type* untreated metastatic adenocarcinoma of the colon or rectum

A Venook, D Niedzwiecki, HJ Lenz,
F Innocenti, M Mahoney, B O'Neil,
J Shaw, B Polite, H Hochster,
R Goldberg, R Mayer, R Schilsky,
M Bertagnolli, C Blanke
for the ALLIANCE and SWOG

The Evolution of CALGB 80405 (aka CRC.5)



2004:

3 arm Trial Including Double Biologic (no KRAS)

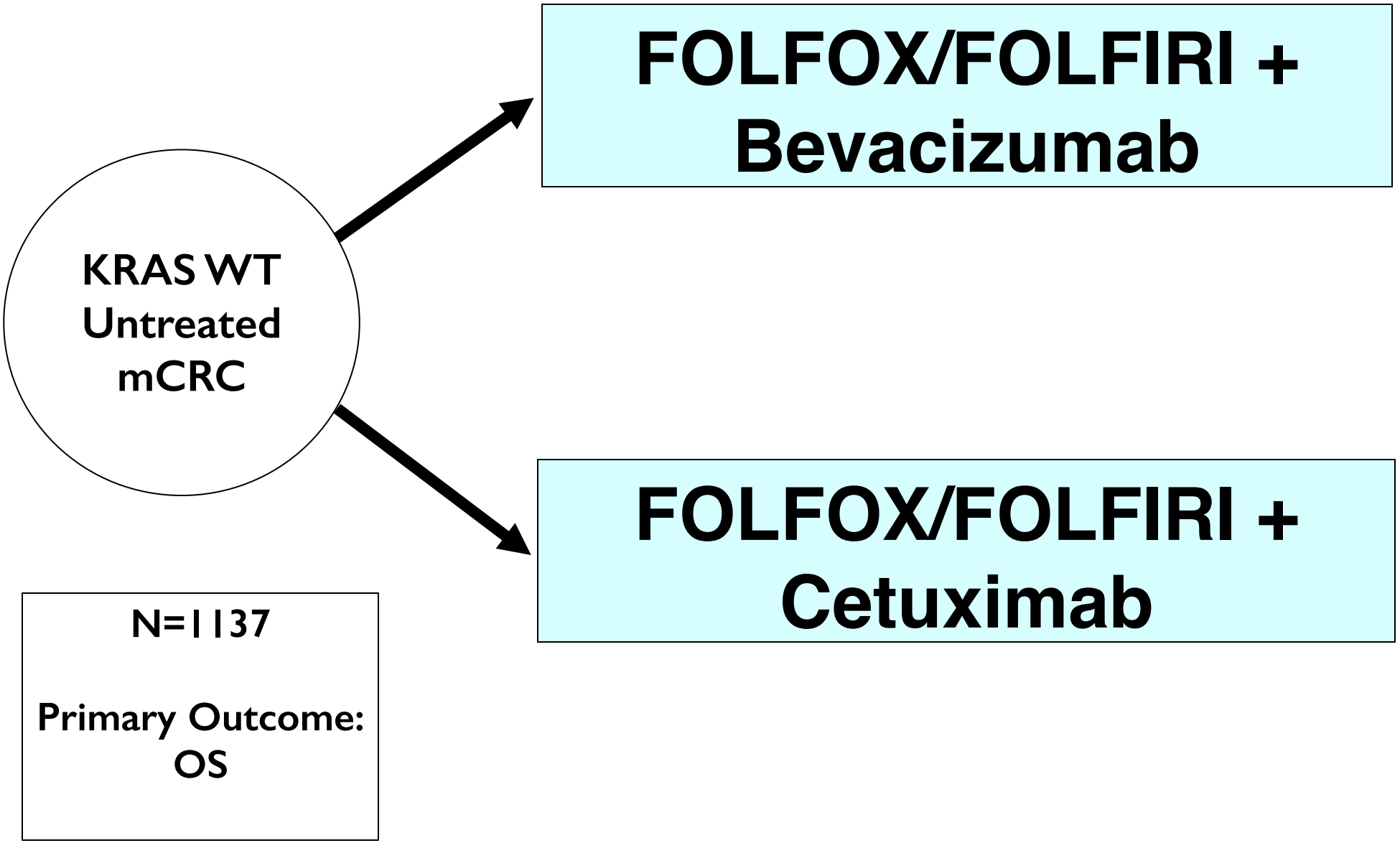
2008/9:

Closure / Amendment for KRAS

2010:

Closure of Double Biologic Arm

CALGB 80405 (CRC.5)



CALGB/SWOG 80405: Eligibility Criteria

- Untreated Metastatic CRC
- Tumor KRAS *wild type* codons 12 & 13
- > 12 months since adjuvant therapy
- ECOG 0-1
- Preserved organ function

AT ENROLLMENT

- CHOOSE: FOLFOX or FOLFIRI
- INTENT: **Palliative or Part of strategy to resect all metastases**

CALGB/SWOG 80405: Statistics

- Assumption: OS: 22 mos to 27.5 mos
  Δ 5.5 months
- 90% power to detect HR of 0.80 (2-sided α=0.05)

ACCRUAL GOAL = 1140 Actual **(1137)**

- **Estimate 326 eligible pre-amendment (333)**
  - ***KRAS wild type*, single biologic arm**
- **Estimate 814 post-amendment (804)**

CALGB/SWOG 80405: Patient Characteristics

	ARM A CHEMO + BEV N=559 (%)	ARM B CHEMO + CETUX N=578 (%)	TOTAL N=1137 (%)
Age median (range)	59 (21-85)	59 (20-89)	59 (20-89)
Male	348 (62.3)	349 (60.4)	697 (61.3)
Primary in place	157 (28)	154 (27)	311 (28)
Palliative Intent	465 (86.4)	458 (82.5)	923 (84.4)
FOLFOX / FOLFIRI (%)	73 / 27	74 / 26	73 / 27

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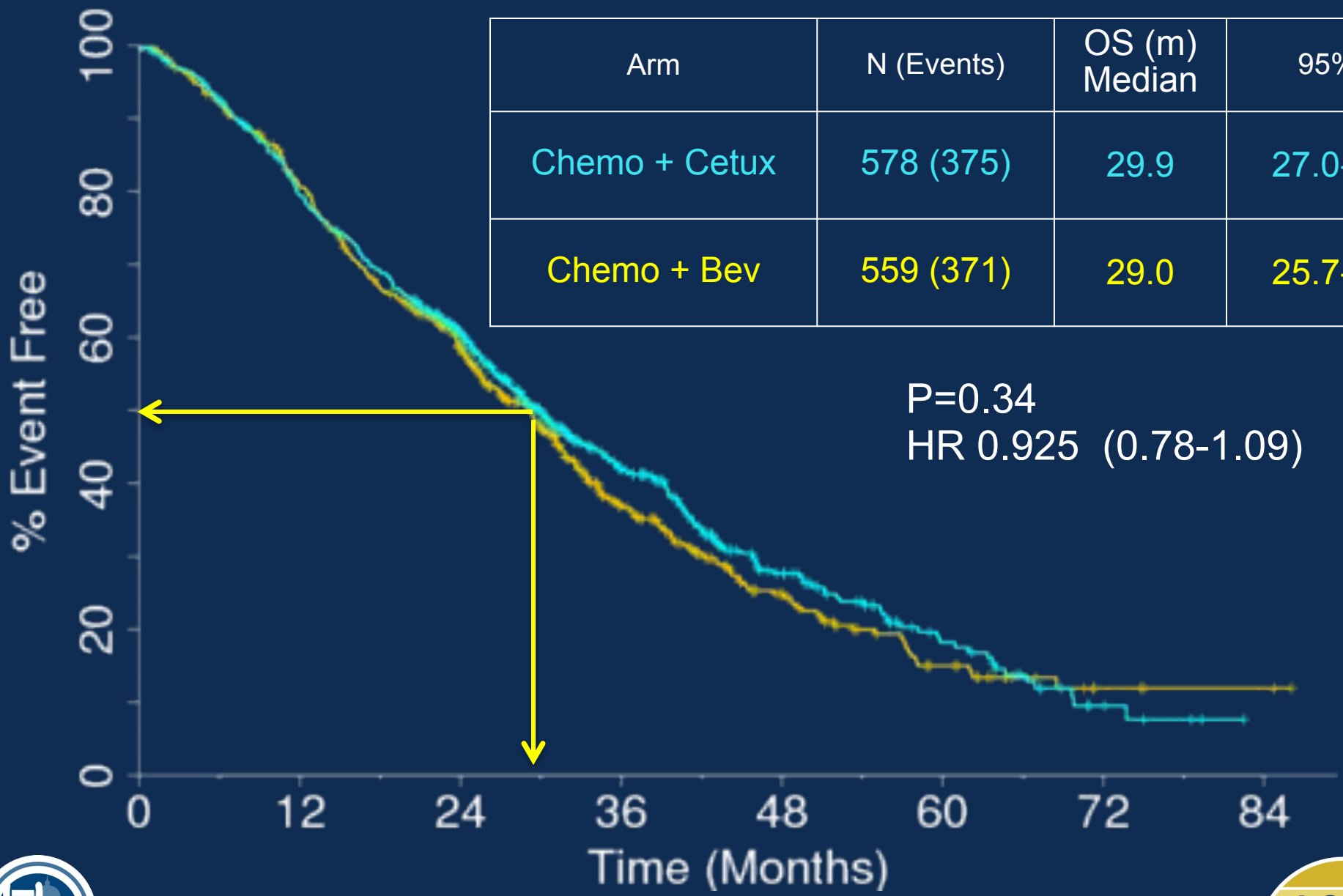
CALGB/SWOG 80405: Overall Survival

Arm	N (Events)	OS (m) Median	95% CI
Chemo + Cetux	578 (375)	29.9	27.0-32.9
Chemo + Bev	559 (371)	29.0	25.7-31.2



P=0.34
HR 0.925 (0.78-1.09)

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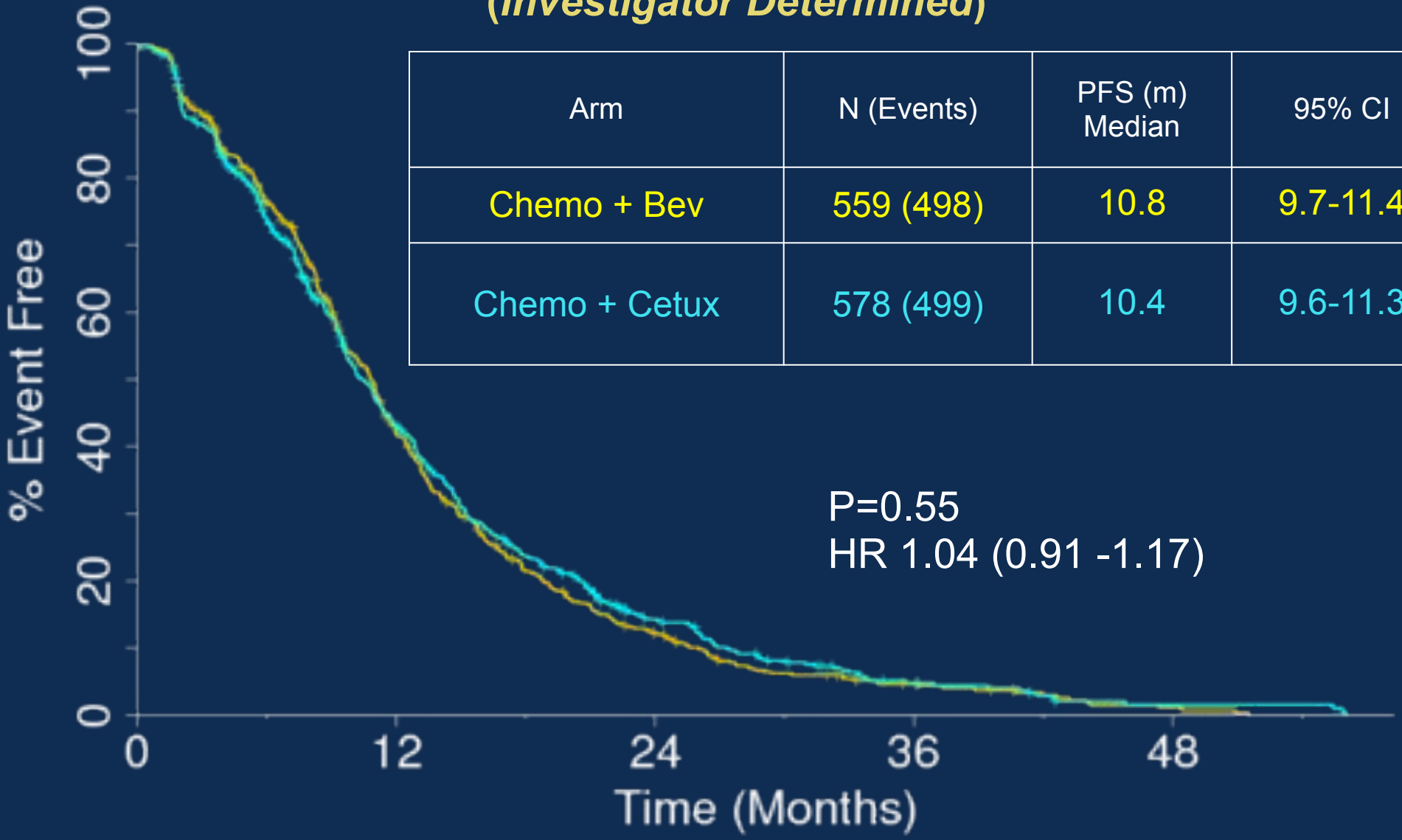
ASCO 50TH ANNUAL MEETING SCIENCE & SOCIETY

CALGB/SWOG 80405: Progression-Free Survival
(*Investigator Determined*)

Arm	N (Events)	PFS (m) Median	95% CI
Chemo + Bev	559 (498)	10.8	9.7-11.4
Chemo + Cetux	578 (499)	10.4	9.6-11.3



P=0.55
HR 1.04 (0.91 -1.17)

Federally Funded Research

Presented by:

PRESENTED AT:

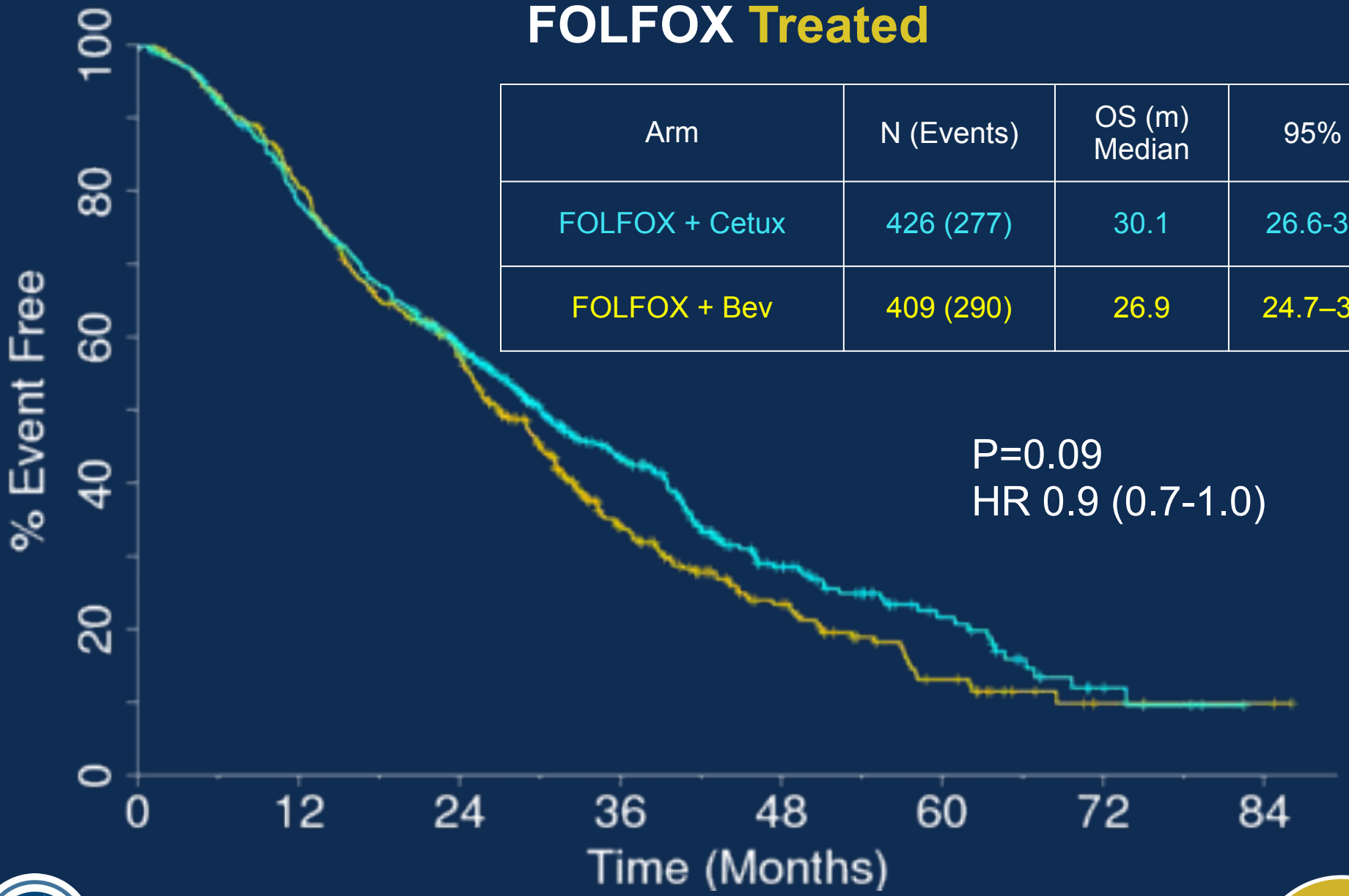
ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

OTHER SECONDARY OBJECTIVES

CALGB/SWOG 80405: Overall Survival

FOLFOX Treated

Arm	N (Events)	OS (m) Median	95% CI
FOLFOX + Cetux	426 (277)	30.1	26.6-34.8
FOLFOX + Bev	409 (290)	26.9	24.7–30.0



P=0.09
HR 0.9 (0.7-1.0)

Federally Funded Research

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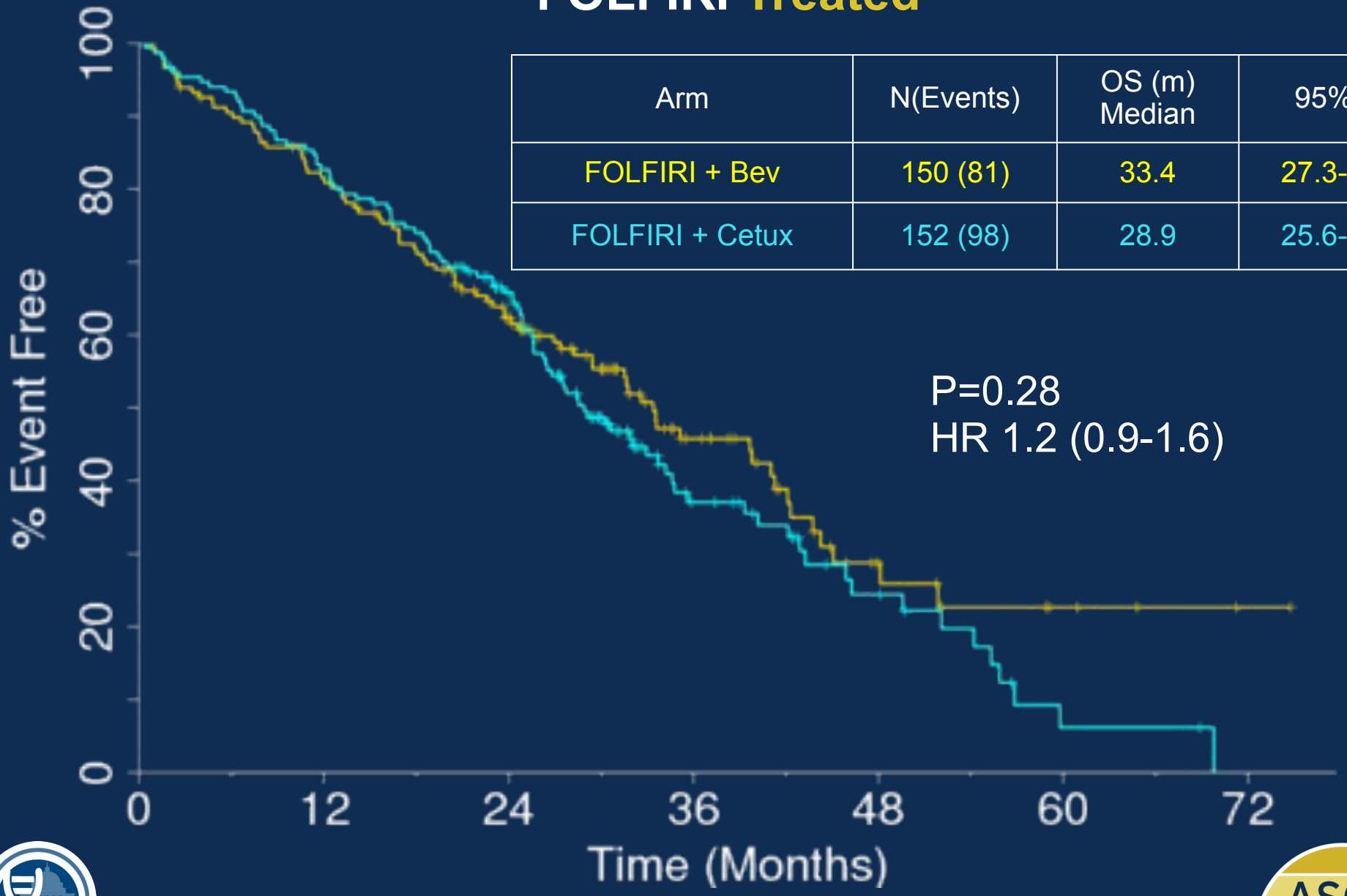
ASCO 50TH ANNUAL MEETING SCIENCE & SOCIETY

CALGB/SWOG 80405: Overall Survival
FOLFIRI Treated

Arm	N(Events)	OS (m) Median	95% CI
FOLFIRI + Bev	150 (81)	33.4	27.3-41.3
FOLFIRI + Cetux	152 (98)	28.9	25.6-34.2



P=0.28
HR 1.2 (0.9-1.6)

Federally Funded Research

Presented by:

PRESENTED AT:

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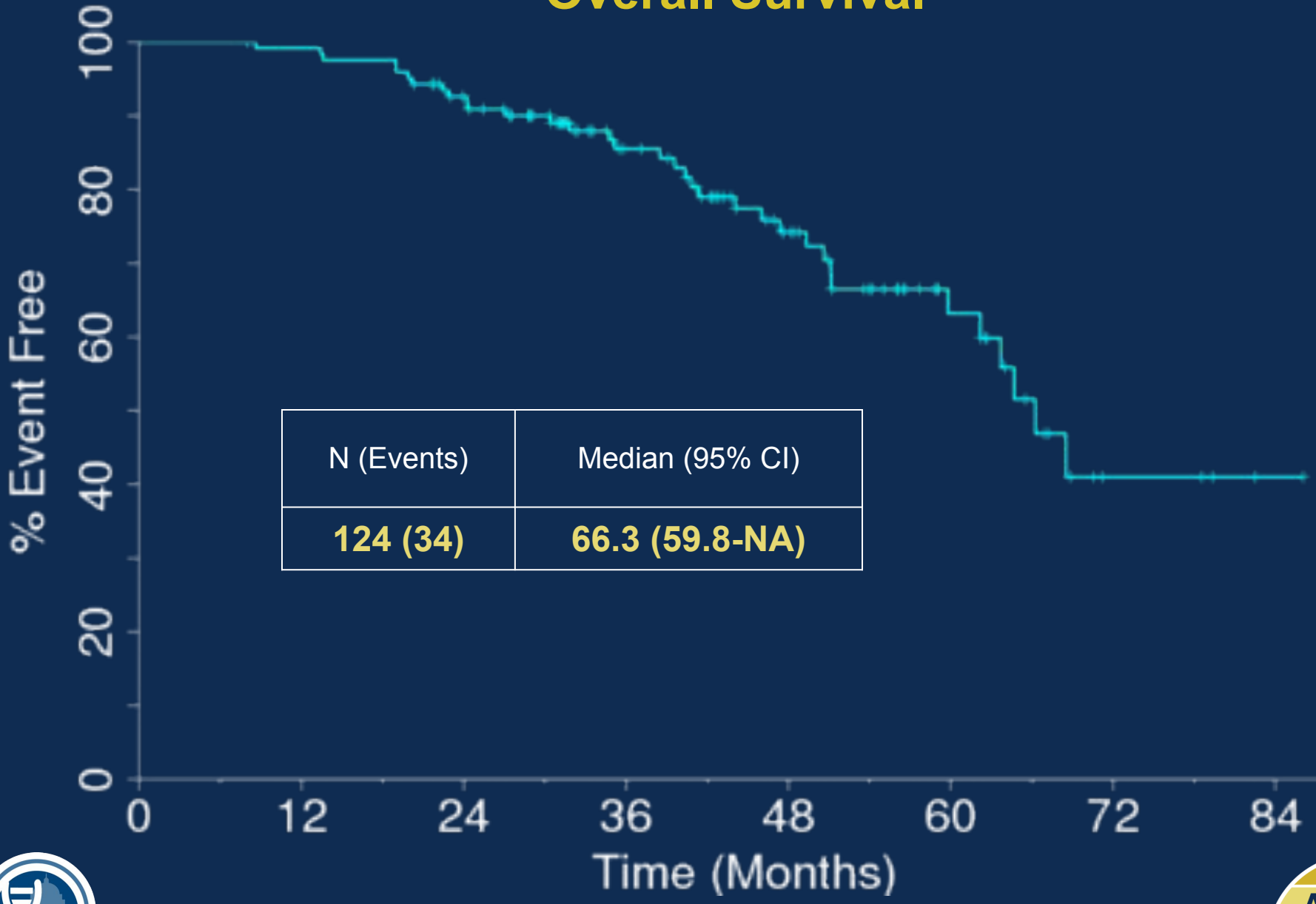
Patients Rendered Disease-Free

Overall Survival



N (Events)	Median (95% CI)
124 (34)	**66.3 (59.8-NA)**

Presented by:

PRESENTED AT:

ASCO 50TH ANNUAL MEETING SCIENCE & SOCIETY

Results – Safety

Toxicity	Chemo + Bev N (%)	Chemo + Cet N (%)
Grade 3	278 (52)	295 (54)
Hematologic	142 (26.6)	150 (27.4)
Non-Hem	234 (43.8)	259 (47.3)
Grade 4	66 (12.4)	75 (13.7)
Grade 5	7 (1.3)	3 (0.5)
Rash Gr 3	0	40 (7)
Diarrhea Gr ≥ 3	45 (8)	59 (11)
Neuropathy Gr ≥3	71 (14)	68 (12)
Hypertension Gr ≥3	35 (7)	3 (1)
VTE Gr ≥3	32 (6)	22 (4)
Cytokine Release	2 (<1)	11 (2)

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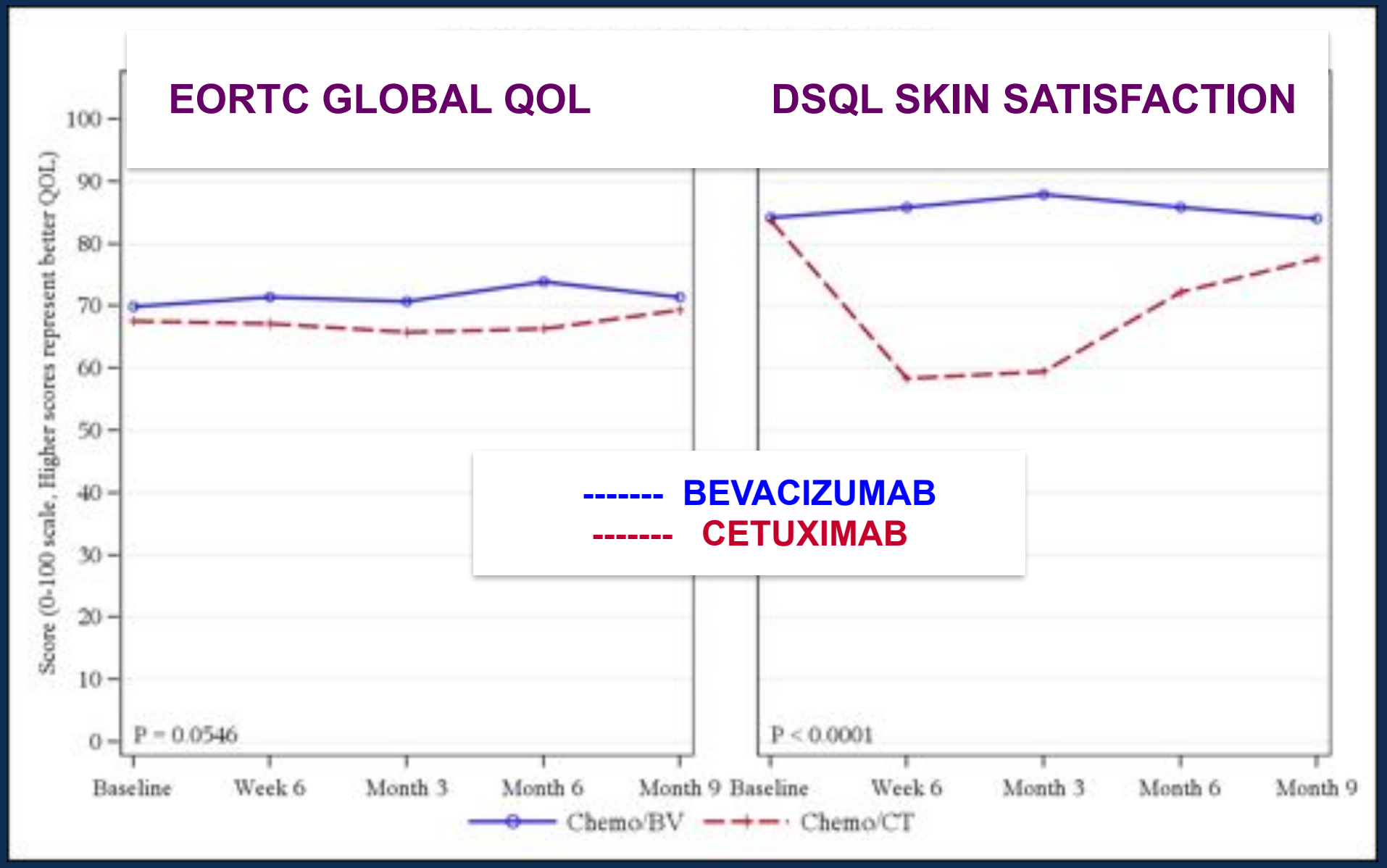
Grade 4	66 (12.4)	75 (13.7)
Grade 5	7 (1.3)	3 (0.5)
Rash Gr 3	0	40 (7)
Diarrhea Gr ≥ 3	45 (8)	59 (11)
Neuropathy Gr ≥3	71 (14)	68 (12)
Hypertension Gr ≥3	35 (7)	3 (1)
VTE Gr ≥3	32 (6)	22 (4)
Cytokine Release	2 (<1)	11 (2)

80405: Data Pending

- Response Rate
- Duration of therapy / dose intensity
- Analysis special subsets:
  - Patients rendered NED
  - Patients recur after adjuvant therapy
- Details 2nd and later treatments
- Concordance KRAS analysis: local v. central

Quality of Life and Symptoms

- Hypotheses: Cetuximab will reduce satisfaction with appearance and diminish overall quality of life
- Measures:
  - EORTC QLQ-C30
  - Dermatology-Specific Quality of Life (DSQL)
- Assessment Timepoints:
  - Baseline, 6 weeks, 3, 6 and 9 months



Slide courtesy of Dueck, Schrag, Naughton

Correlative Studies

Tumor / Plasma / Serum > 44000 samples

- Comprehensive Molecular Analysis
  - Expanded RAS
  - Next-generation sequencing
    - Tumor DNA screen / Cell free, circulating tumor DNA
    - Tumor RNA (nanostring platform)
  - Genome-wide association study on germline DNA
  - Tumor transcriptome
  - Plasma proteomics
- Model CRC: Systems Biology approach

SWOG: HJ Lenz ALLIANCE: F Innocenti

CALGB/SWOG 80405: Conclusions

- Overall survival on Chemo/Cetuximab is no different than on Chemo/Bevacizumab in 1st line treatment for patients with KRAS *wild type (codons 12 & 13)* metastatic colorectal cancer

- FOLFIRI or FOLFOX w/ either Bevacizumab or Cetuximab can be considered options for 1st line therapy of patients with KRAS *wt* metastatic CRC

CALGB/SWOG 80405: Conclusions

- Overall Survival > 29 months in both arms establishes a new benchmark for treatment of these patients. This was accomplished across a broad clinical trials network and suggests that the results apply in a variety of practice settings.

- Detailed analysis of selected subsets, e.g., long-term survivors may yield important biomarker information.

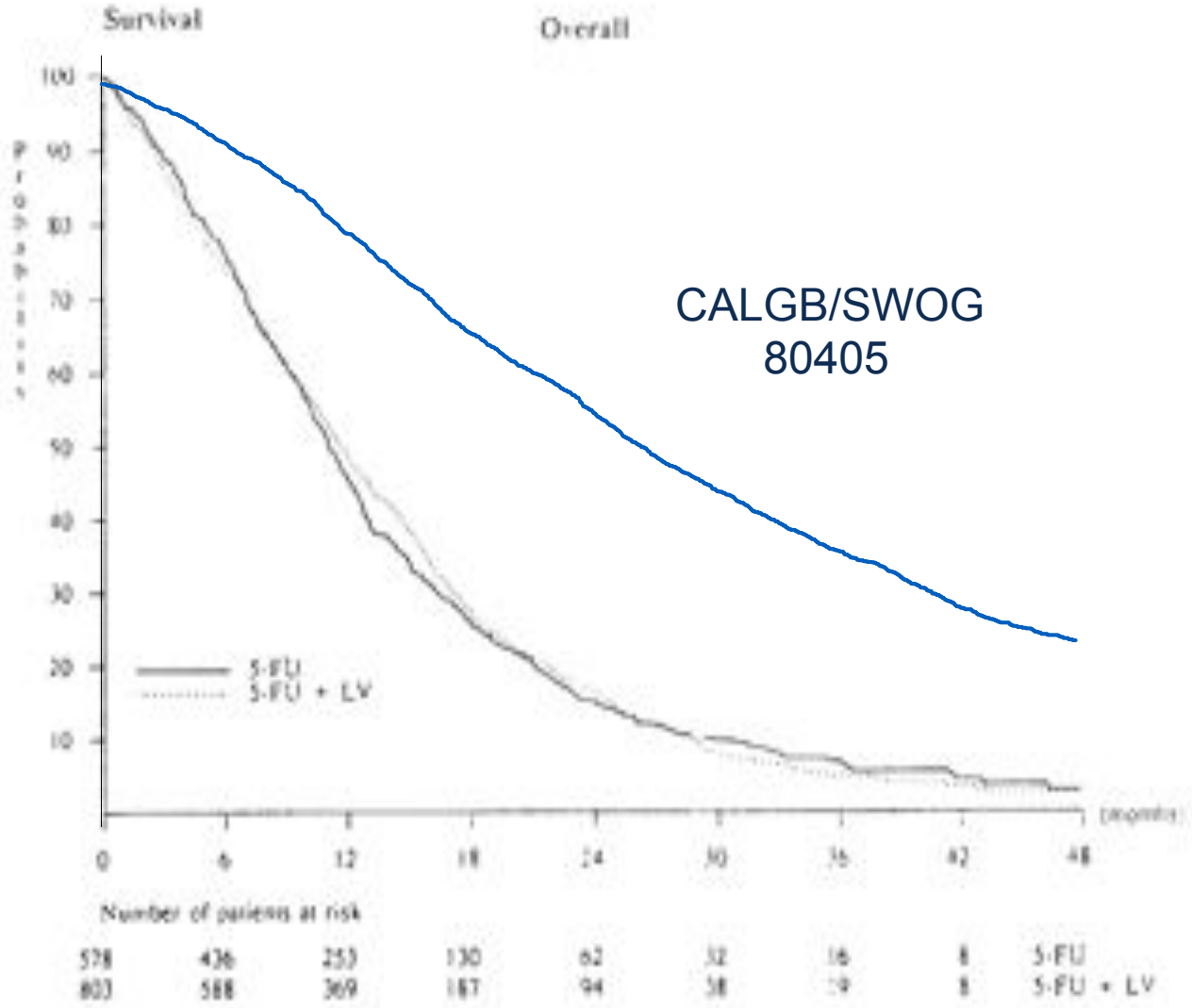
CALGB/SWOG 80405: Conclusions

- Some results appear contrary to findings in other studies, such as FOLFOX / Cetuximab and perhaps FOLFIRI / Bevacizumab. We await complete data to place in perspective.

- The clinical information and biospecimens from the patients in this study represent a rich resource and unique opportunity to gain a deeper understanding of CRC.

Colorectal Cancer: 20 Years Later

meta-analysis 1992 **80405 results**



CALGB/SWOG
80405

Fig 2. Overall survival.

J Clin Oncol, 1992

TAKE HOME MESSAGE

- Patients with KRAS *wild type* metastatic CRC have choices.
- First line therapy should reflect the patient's preference or concern for potential side effects.
- About 10% of patients will live > 5 years.

The puzzle of first-line treatment of mCRC

CALGB/SWOG 80405 study discussion

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ASCO 50TH ANNUAL MEETING SCIENCE & SOCIETY

CALGB 80405 and FIRE-3 Are they comparable?

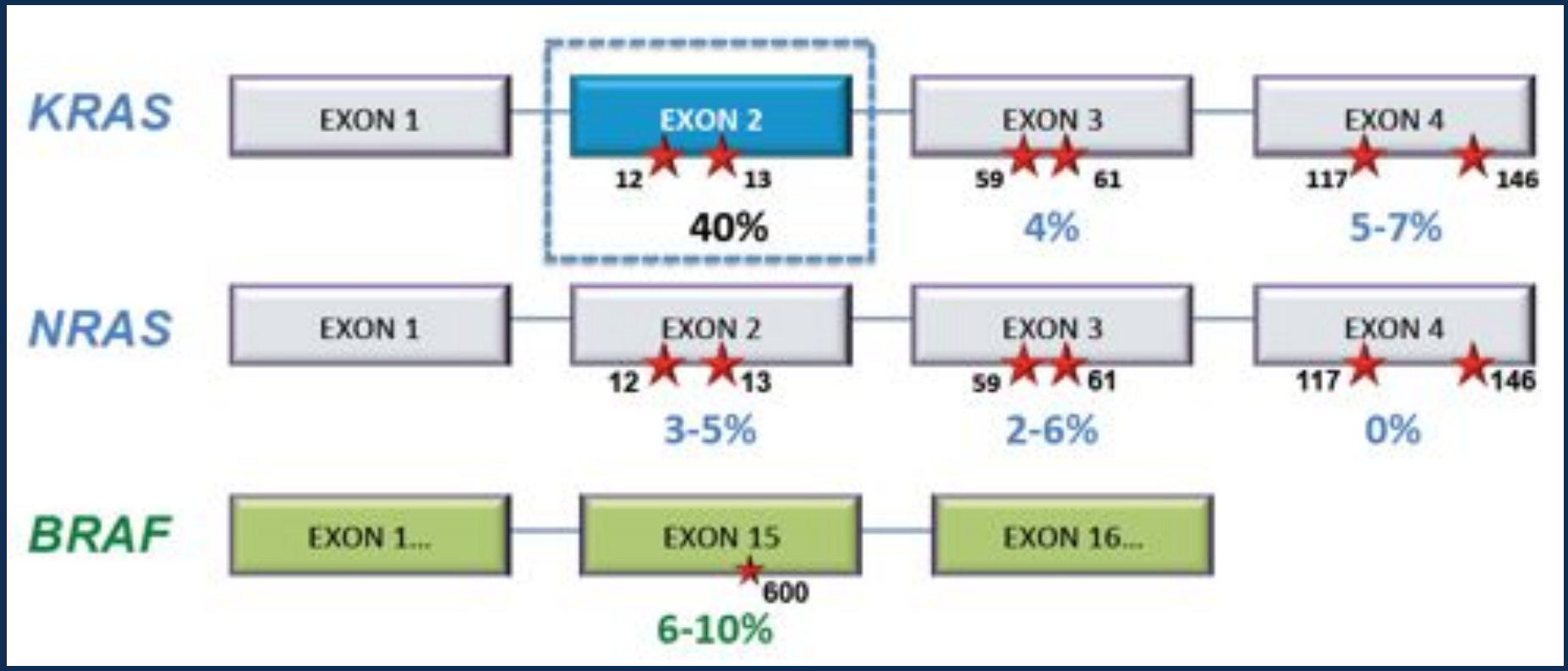
	CALGB 80405 N = 1137	FIRE-3 N = 592
Study population	*Untreated* KRAS exon 2 wt mCRC*	*Untreated** KRAS exon 2 wt mCRC*
ECOG PS	*0–1*	*0–1; 2 (1.5%)*
Primary tumor in place	*28%*	*12%*
Age, median	*59*	*64*
Countries	*US*	*Germany/Austria*
Chemotherapy	*FOLFOX (73%) / FOLFIRI (27%)*	*FOLFIRI (100%)*
Primary endpoint	*OS*	*ORR*
≥2nd	*88%*	*77%*

* >12 months since prior adjuvant chemotherapy
** >6 months since prior adjuvant chemotherapy

[1]Venook A, JCO 2014 (LBA)
[2]Heinemann V, JCO 2013 (LBA3506)

Could expanded RAS analysis change the results?

Analysis of PRIME[1], PEAK[2] and FIRE-3[3] studies



Among KRAS ex 2 wt patients, an additional **14-20%** of tumors with other RAS mutations were found

[1]Douillard JY, NEJM 2013; [2]Schwartzberg L, JCO 2013 (A 3631); [3]Stintzing S, EJC 2013

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Could expanded RAS analysis change the results?

Study		WT KRAS ex 2	WT All RAS	↓ HR
PRIME (+/- Panitumumab)				
	N	***656***	***512***	
	PFS HR / p	***0.8 / 0.02***	***0.72 / 0.04***	***-0.08***
	OS HR / p	***0.83 / 0.072***	***0.78 / 0.043***	***-0.05***
FIRE-3 (Cetuximab vs Bevacizumab)				
	N	***592***	***342***	
	PFS HR / p	***1.06 / 0.54***	***0.93 / 0.54***	
	OS HR / p	***0.77 / 0.017***	***0.7 / 0.011***	***-0.07***
PEAK (Panitumumab vs Bevacizumab)				
	N	***285***	***170***	
	PFS HR / p	***0.84 / 0.22***	***0.66 / 0.03***	***-0.18***
	OS HR / p	***0.62 / 0.009***	***0.63 / 0.058***	

[1]Douillard JY, NEJM 2013; [2]Schwartzberg L, JCO 2013 (A 3631); [3]Stintzing S, EJC 2013 (Proc ECCO)

Could expanded RAS analysis change the results?

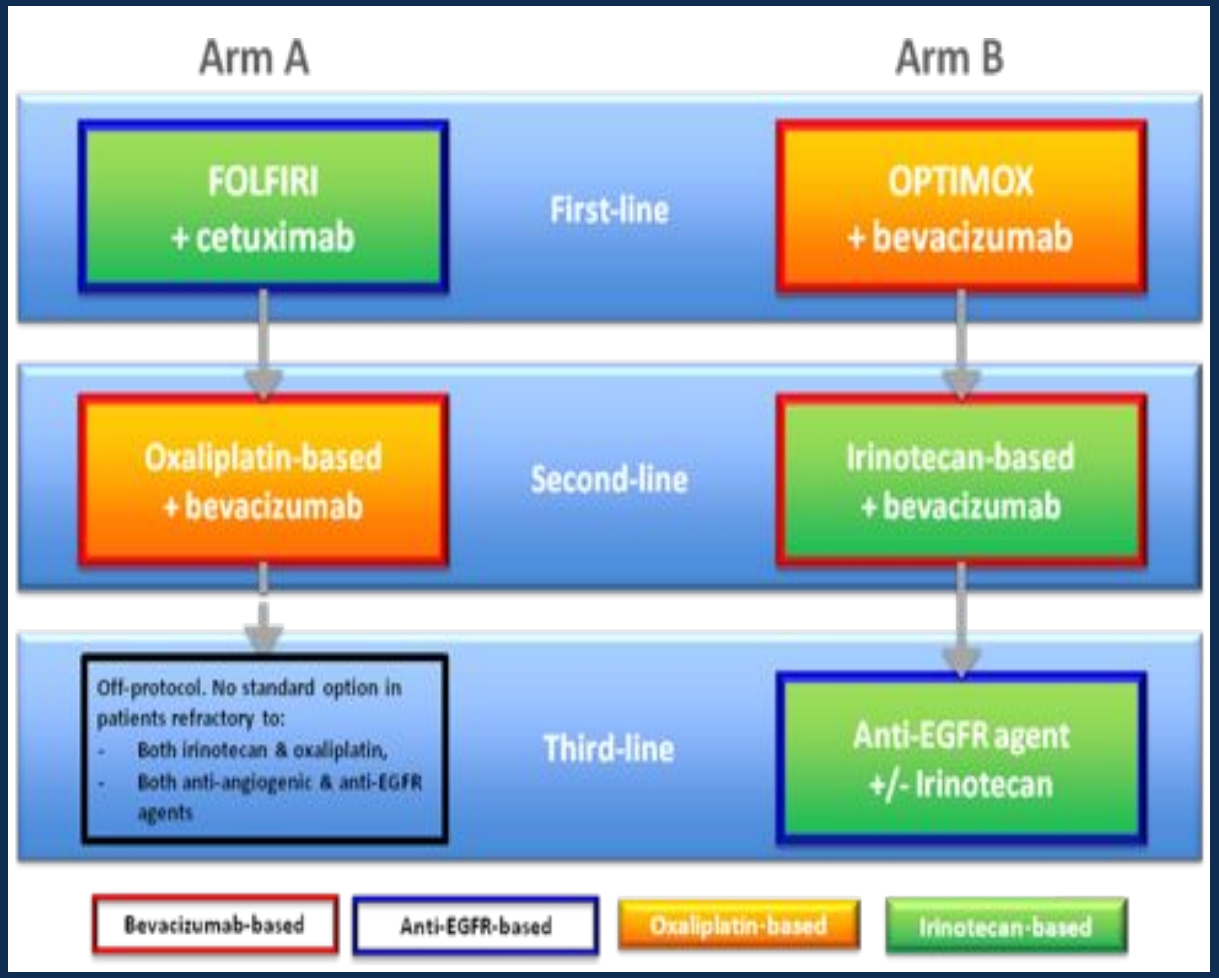
- **CALGB 80405** study (speculative):
  - KRAS ex 2 wt → All RAS wt
  - N: 1137 pts → 900 - 975 pts
  - OS HR: 0.92 → 0.87 – 0.85

Conceptual challenges

1. Specific regimen sequence, does it matter?
   – No conclusive evidence[1]

[1]Larsen, Pharmacol Ther 2011

GERCOR Strategic 1 Design



- Phase III superiority study (arm B > arm A)
- Sample size: N = 474
- Primary endpoint: Duration of disease control (DDC)

My Take

Await:

Expanded RAS

Info on resections by arm

Info on second / third line treatments by arm

Other molecular analyses

My Take

- **Pending further results :**

  Given the largest trial, and the only one powered for OS did not demonstrate an improvement in OS and/or QOL

  This data suggests that we should not change our current standard of Chemo + Bev for patients with unresected mCRC

Case

50 yo woman - No medical problems

Presents with metastatic colorectal cancer with bilobar liver and bilateral lung metastases

Some RUQ pain and cough

ECOG 1

All Ras WT

Chemo + Bev

Chemo + EGFR Inhhibitor

CASE

60 yo woman

Presents to ER with R Arm Weakness

CT Head : L MCA territory stroke

Microcytic, Hypochromic Anemia: Hb 81

CASE

Transfused,

Admitted to a 4 month history of
progressive fatigue,
15 kg weight loss, no hematochezia

CASE

Investigations:

Colonoscopy : Caecal tumour

Biopsy Adenocarcinoma

KRAS WT (codon 12,13)

CT Chest Abdo Pelvis:

Multiple Small Bilateral Lung Mets

Peritoneal Mets

Bilobar Liver Mets

CASE

1 month later : Persistent mild R arm weakness - with rehab functioning well

Hb 100 and stable

Neurology – Cleared for treatment

CASE

You live in a province that funds all chemo and biologic options

But…

Expanded ras analysis is not available

What treatment would you recommend:

Chemo

Chemo + Bev

Chemo + Cetux

CASE

You are now in a place that has funding of all biologics and extended Ras testing

She is all Ras WT

What treatment would you recommend:

Chemo

FOLFIRI + Cetuximab

FOLFOX + Pmab

CapeOx + Cetuximab

FOLFOX + Cetuximab