Advanced CRC: Standard and New Targets

Prof.Dr.Hans-Joachim Schmoll

Department of Internal Medicine,

Chair, Div. Clinical Oncology Research

Martin Luther University, Halle-Wittenberg, Germany

Old and New Options for mCRC

- **chemotherapy:**
  - -iv/oral 5FU (Capecitabine, UFT, S1)
  - -Oxaliplatin
  - -Irinotecan
  - -Mitomycin C

NEW: **-TAS 102 last line, 2016**

- **Targeted drugs: Angiogenesis-/Stroma-Inhibitors**
  - **-** Bevacizumab
  - - Aflibercept (2.line)
  - - Regorafenib (3./4. line)

NEW: **- Ramicirumab, (2.), 3./4. line**

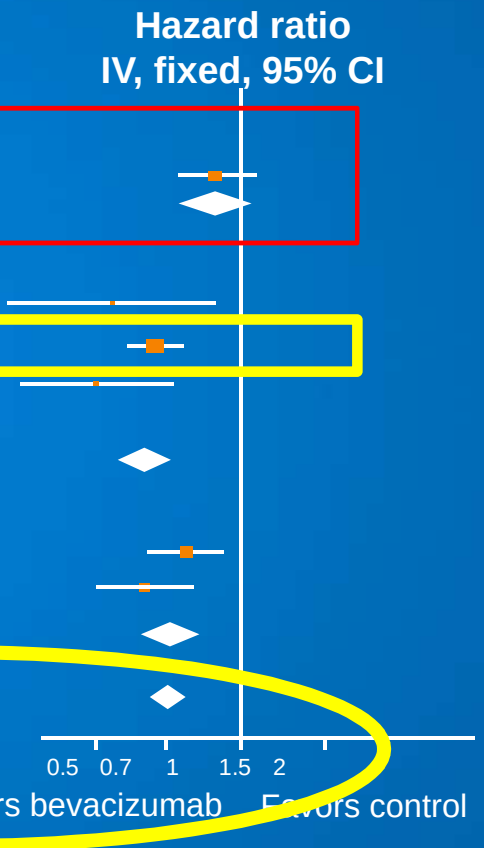
- **Targeted drugs: EGF-Receptor-Inhibitors**
  - - Cetuximab
  - - Panitumumab
  - **- Erlotinib (maintenance): wird nicht registriert**

NEW Targets:

- **- Her2: Trastuzumab+Lapatinib**
- **- B-raf: Dabrafenib, Vemurafenib**
- **- MEK: Trametinib**
- **- PD1: Nivolumab, Pembrolizumab, Atezolizumab (MSI high)**

Bevacizumab in 1st line mCRC – PFS

Study or subgroup	Hazard ratio IV, fixed, 95% CI
Infusional 5-FU	
Saltz 2008 (NO16966, FOLFOX4)	0.89 [0.74, 1.06]
Subtotal (95% CI)	**0.89 [0.74, 1.06]**
Bolus 5-FU	
Kabbinavar 2003 (5FU/LV)	0.54 [0.33, 0.88]
Hurwitz 2004 (AVF2107, IFL)	0.66 [0.58, 0.76]
Kabbinavar 2005 (5FU/LV)	0.50 [0.35, 0.73]
Stathopoulos 2010 (mIFL)	Not estimable
Subtotal (95% CI)	**0.63 [0.56, 0.72]**
Capecitabine-based regimens	
Saltz 2008 (NO16966, XELOX)	0.77 [0.65, 0.92]
Tebbutt 2010 (MAX, capecitabine)	0.63 [0.50, 0.80]
Subtotal (95% CI)	**0.72 [0.62, 0.83]**
Total (95% CI)	**0.71 [0.66, 0.77]**

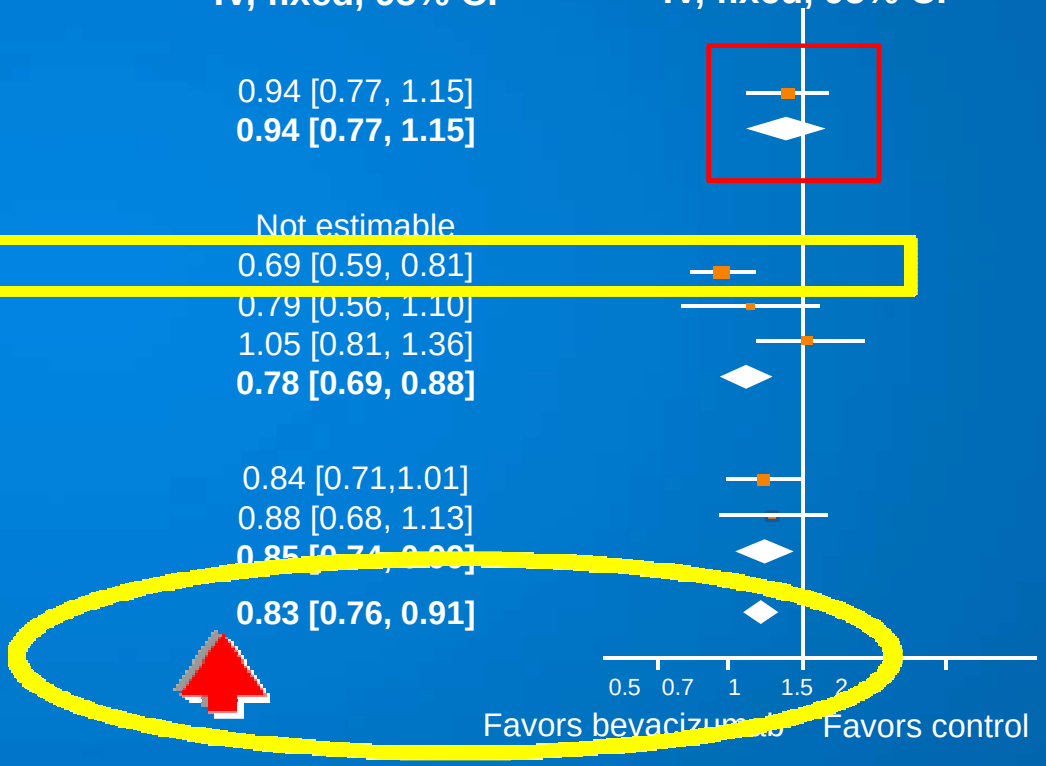


Macedo LT, et al. BMC Cancer 2012;12:89; Saltz LB, et al. J Clin Oncol 2008;26:2013–2019; Kabbinavar FF, et al. J Clin Oncol 2003;21:60–5; Hurwitz H, et al. N Engl J Med 2004;350:2335–2342; Kabbinavar FF, et al. J Clin Oncol 2005;23:3706–3712; Stathopoulos GP, et al. Oncology 2010;78:376–81; Tebbutt NC, et al. J Clin Oncol 2010;28:3191–3198

Bevacizumab in 1st line mCRC – OS

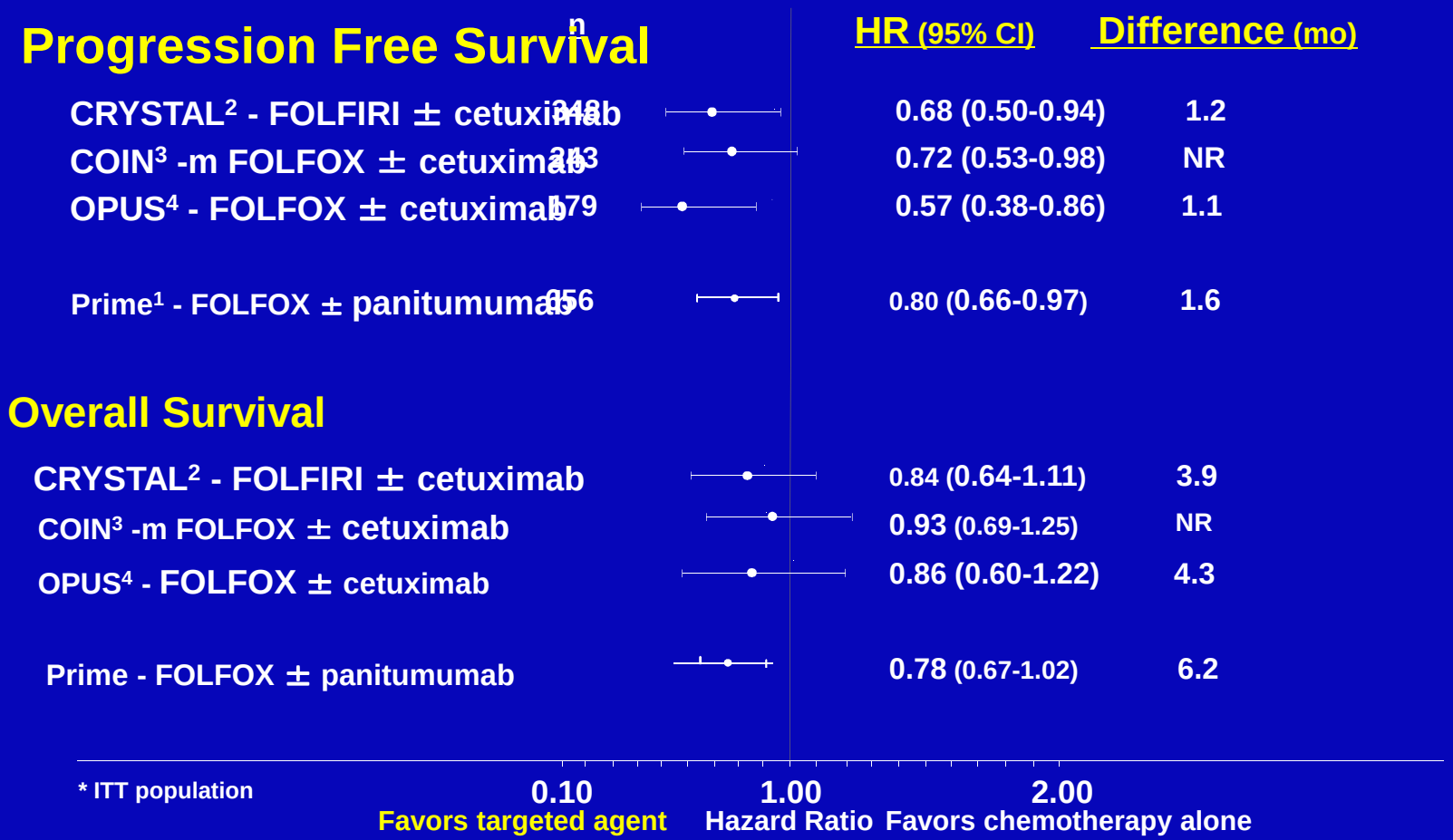
No significant OS benefit with BEV with standard infusional CT

Study or subgroup	Hazard ratio IV, fixed, 95% CI
Infusional 5-FU	
Saltz 2008 (NO16966, FOLFOX4)	0.94 [0.77, 1.15]
Subtotal (95% CI)	**0.94 [0.77, 1.15]**
Bolus 5-FU	
Kabbinavar 2003 (5FU/LV)	Not estimable
Hurwitz 2004 (AVF2107, IFL)	0.69 [0.59, 0.81]
Kabbinavar 2005 (5FU/LV)	0.79 [0.56, 1.10]
Stathopoulos 2010 (mIFL)	1.05 [0.81, 1.36]
Subtotal (95% CI)	**0.78 [0.69, 0.88]**
Capecitabine-based regimens	
Saltz 2008 (NO16966, XELOX)	0.84 [0.71,1.01]
Tebbutt 2010 (MAX, capecitabine)	0.88 [0.68, 1.13]
Subtotal (95% CI)	**0.85 [0.74, 0.98]**
Total (95% CI)	**0.83 [0.76, 0.91]**



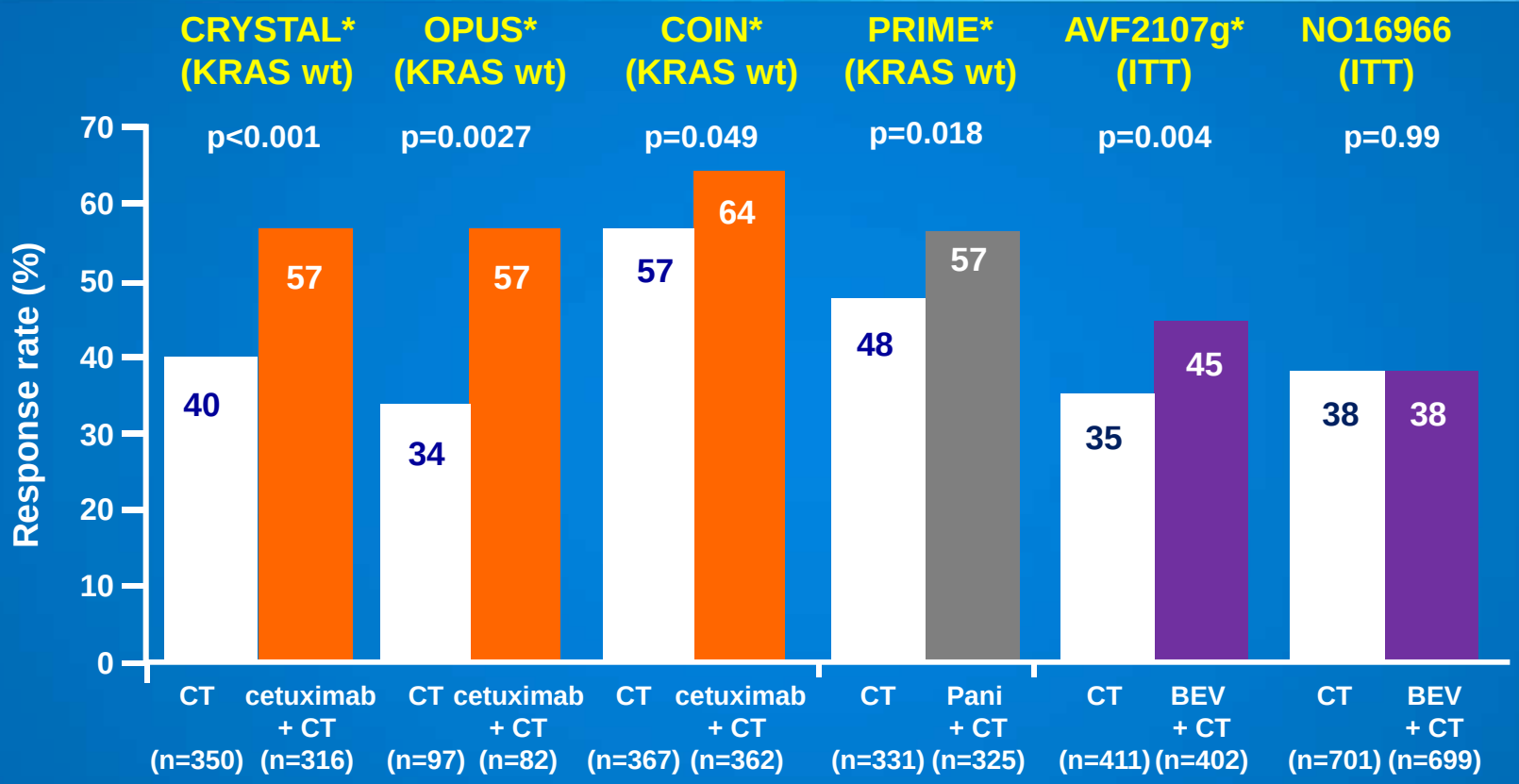
Macedo LT, et al. BMC Cancer 2012;12:89; Saltz LB, et al. J Clin Oncol 2008;26:2013–2019; Kabbinavar FF, et al. J Clin Oncol 2003;21:60–5; Hurwitz H, et al. N Engl J Med 2004;350:2335–2342; Kabbinavar FF, et al. J Clin Oncol 2005;23:3706–3712; Stathopoulos GP, et al. Oncology 2010;78:376–81; Tebbutt NC, et al. J Clin Oncol 2010;28:3191–3198

Anti-EGF-R with infusional FU



1. Douillard JY, et al. *J Clin Onc* 2010;*27:* 4697-4705, 2. Van Cutsem E, et al. *N Engl J Med* 2009; 360:1408-17, 3. Maughan T, et al. EJC 2009;7 (suppl) :a6LBA, 4. Bokemeyer C, et al. *Ann Onc* 2011; doi:10.1093/annonc/mdq632 ,

EGF-Rec.-AntikörperRR: Chemo-Doublets vsTriplets

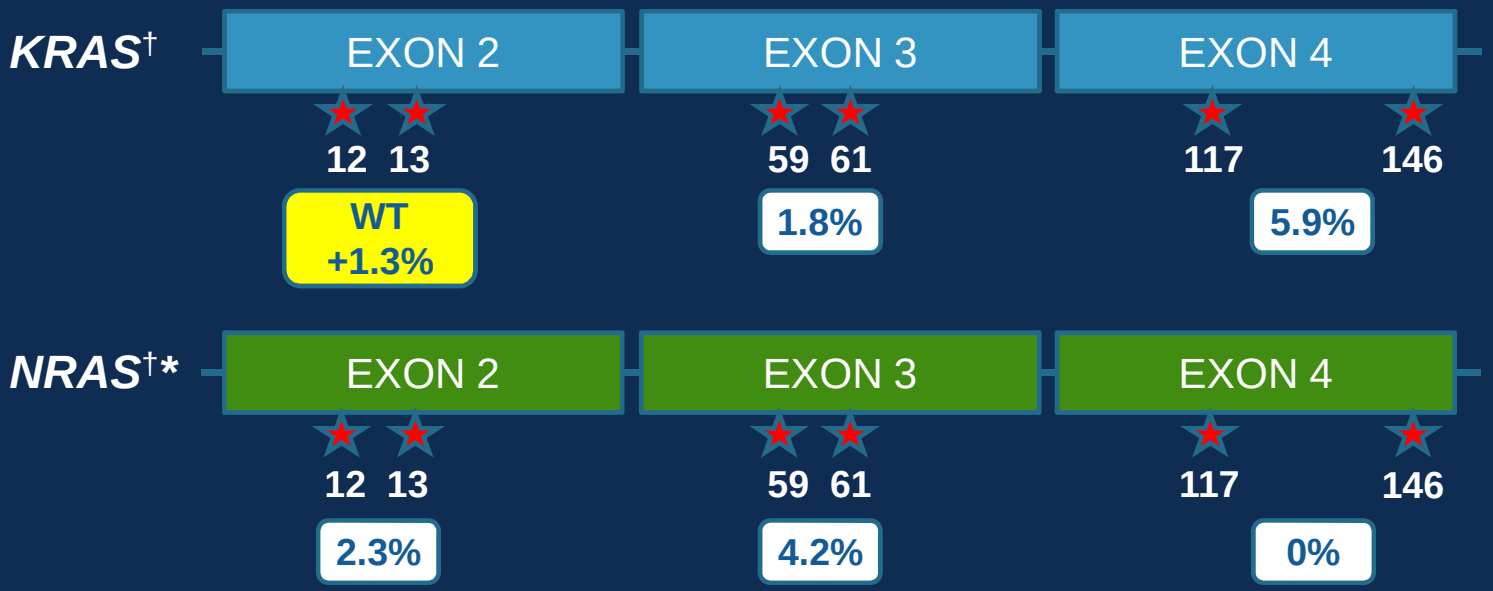


*Significant vs chemotherapy control

Van Cutsem E, et al. J Clin Oncol 2011;29:2011–2019; Bokemeyer C, et al. Ann Oncol 2011;7:1535–1546; Maughan TS, et al. Lancet 2011;377:2103–2114; Douillard J-Y, et al. ASCO 2011 (Abstract No. 3510); Hurwitz H, et al. N Engl J Med 2004;350:2335–2342; Saltz L, et al. J Clin Oncol 2008;26:2013–2019

RAS mutations: CALGB/SWOG 80405

670/1137 patients (59%) with *KRAS* codon 12/13 WT tumors evaluable
621/1137 analyzed (55%) analyzed
95/621 (15.3%) patients new ras mutation identified



†Percentages relate to fraction of *RAS* evaluable patients with mutations in particular exons;

*One patient had a mutation at both NRAS Exon1 codon12 and NRAS Exon3 codon61

RAS mutation rates: first-line studies

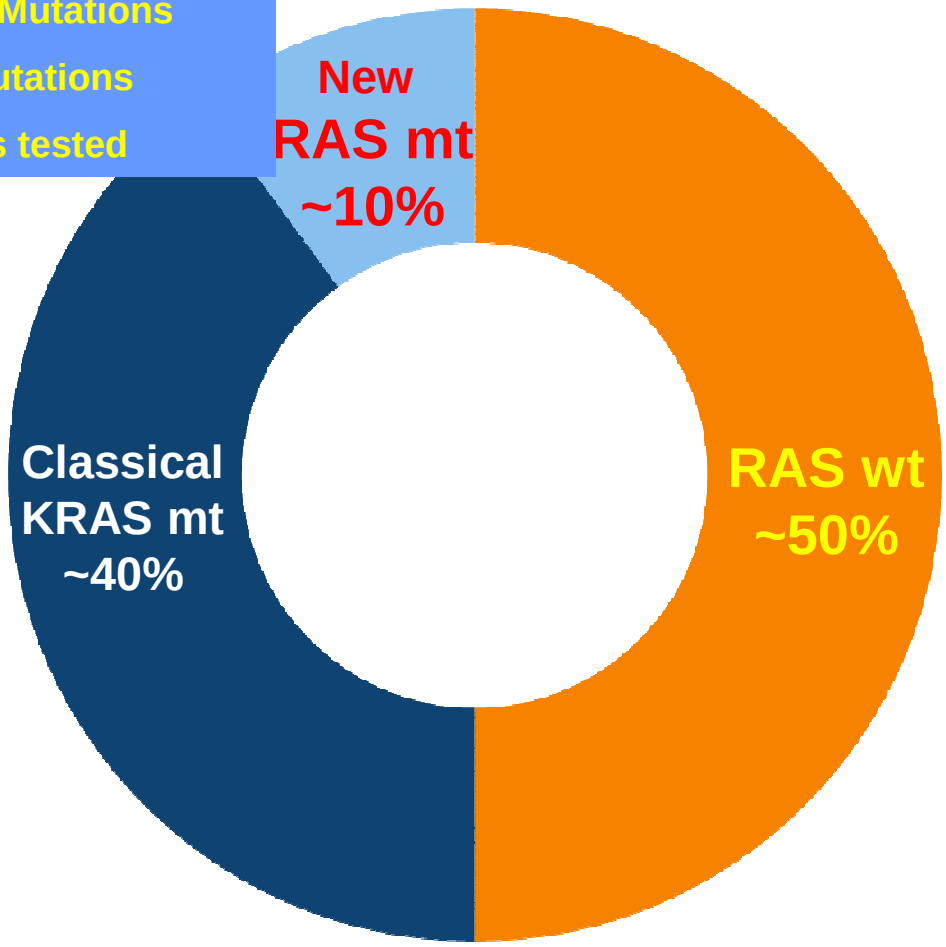
Patients with *KRAS* codon 12/13 wild-type tumors

Study	Evaluable patients*	Method	Other *RAS* mutations, %
CALGB/SWOG 80405	670	BEAMing††	15.3
OPUS	118	BEAMing†	26.3
CRYSTAL	430	BEAMing†	14.7
FIRE-3‡	407	Pyrosequencing	16.0
PRIME§	620	Dideoxy sequencing/WAVE	17.4
PEAK	221	Dideoxy sequencing/WAVE	23.1

*For other tumor *RAS* mutations
†5% mutant/wild-type alleles diagnostic cutoff
††1% mutant/wild-type alleles diagnostic cutoff
‡*KRAS* codons 59 and 117 not considered
§*KRAS* and *NRAS* codon 59 not considered

PRIME-Trial: Among WT *KRAS* exon 2 patients, an additional 17% of tumours with *RAS* mutations were found

- -Rare additional KRAS Mutations
- -NRAS Mutations
- -All exons tested



Bevacizumab vs EGFR-inhibitors – 1.line treatment

ChemoBackbone +Cetuxi/Panitumumab

- Deeper response, probably higher resection chance in liver/lung mets?
- Only for 50% (ras-wild-type) of the patients !!!
- Major side effect: skin toxicity → reduced Qality of life
- No capecitabine possible, No bolus 5FU
- Panitumumab only with FOLFOX

Chemobackbone + Bevacizumab

- For all patients – no molecular subgroup!!!
- All types of 5FUBolus-, Infusion possible, but capecitabine more effective (?)
- **No clinically relevant toxicity**

ESMO guidelines 2012: Treatment goals and strategy determined by patient and tumor characteristics

Schmoll H-J, et al. Ann Oncol 2012

Group	Clinical presentation	Treatment goal	Treatment intensity
GROUP 0	Clearly R0-resectable liver and/or lung metastases	Cure, decrease risk of relapse	Nothing or moderate (neoadj.FOLFOX)
GROUP 1	Not R0-resectable liver and/or lung metastases only, may become resectable after induction CT	Maximum tumor shrinkage	Upfront most active combination
GROUP 2	Multiple metastases/sites, with rapid progression and/or tumor-related symptoms	Clinically relevant tumor shrinkage as soon as possible, control PD	Upfront active combination: at least doublet
GROUP 3	Multiple metastases/sites with no option for resection and/or initially asymptomatic with limited risk for rapid deterioration	Prevent further progression, low toxicity	Watchful waiting or sequential approach (triplet regimens only in selected patients)

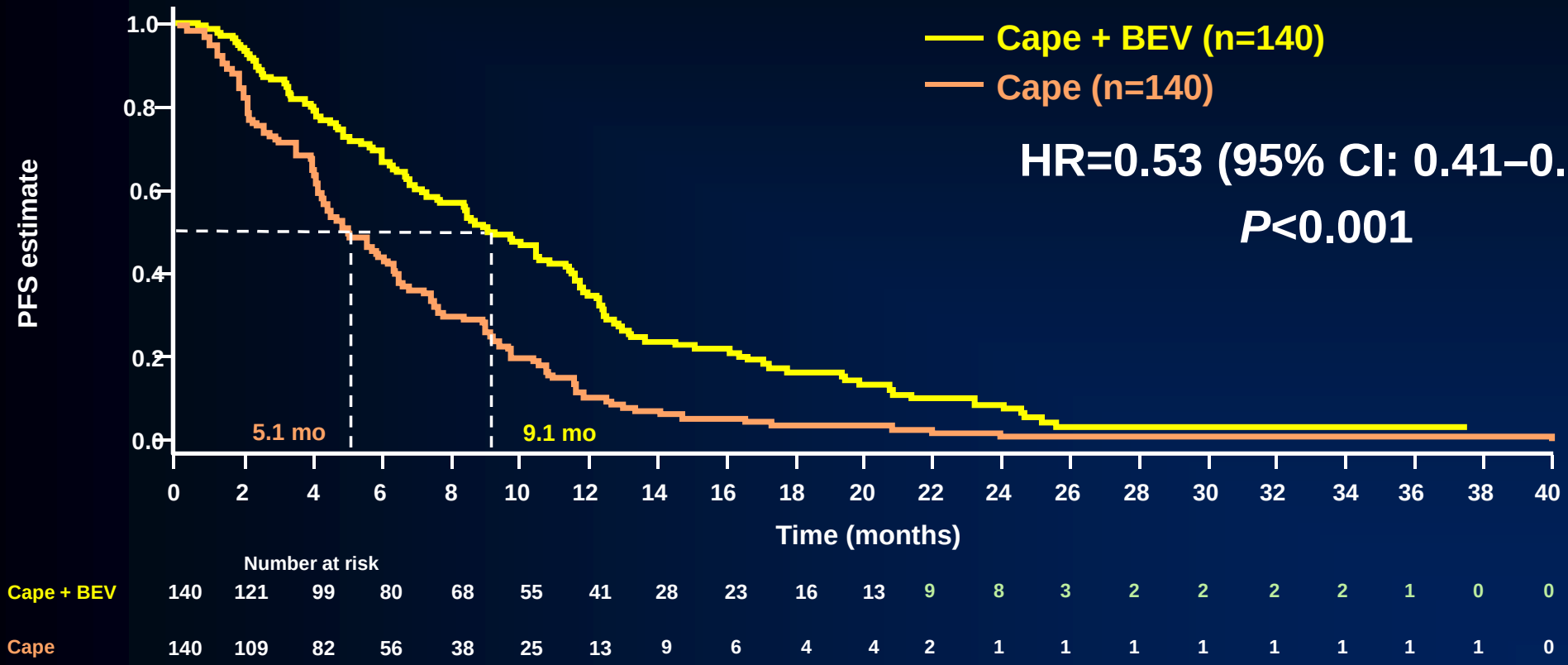
ESMO consensus 2012

(Schmoll H-J., Ann Oncol 2012)

	KRAS wt		KRAS mt	
1	FOLFIRI/FOLFOX + cet	+++	FOLFOX/XELOX + BEV	+++
	FOLFOX + pani	+++	FOLFOXIRI	++(+)
	FOLFIRI/XELIRI + BEV	++(+)	FOLFIRI/XELIRI + BEV	++(+)
	FOLFOX/XELOX + BEV	++(+)	FOLFOX/XELOX	+
	FOLFOXIRI	++(+)	FOLFIRI/XELIRI	+
	FOLFOX/XELOX or FOLFIRI/XELIRI	+	IRIS	+
	IRIS	+		
2	FOLFIRI + cet/FOLFOX+pani	+++	FOLFOX/XELOX + BEV	+++
	FOLFOX/XELOX + BEV	+++	FOLFOXIRI/XELIRI + BEV	++(+)
	FOLFIRI/XELIRI + BEV	++(+)	FOLFOX/XELOX	++
	FOLFOXIRI	+(+)	FOLFIRI/XELIRI	++
	FOLFOX + cet	+(+)	FOLFOXIRI	++
	FOLFOX/XELOX or FOLFIRI/XELIRI	+	IRIS	+
	IRIS	+		
3	FUFOL/capecitabine +/- BEV	+++	FUFOL/capecitabine +/- BEV	+++
	FOLFIRI/XELIRI or XELOX/FOLFOX	++	XELOX/FOLFOX	++
	IRIS	+	FOLFIRI/XELIRI	++
	Cet/pani (mono)	(+)	IRIS	+
	Watchful waiting/triplets (+/−BEV/cet/pani)	+*	Watchful waiting/triplets +/−BEV	+*

- Pani, panitumumab

AVEX – PFS
First-line Trial in Pts ≥70 yrs

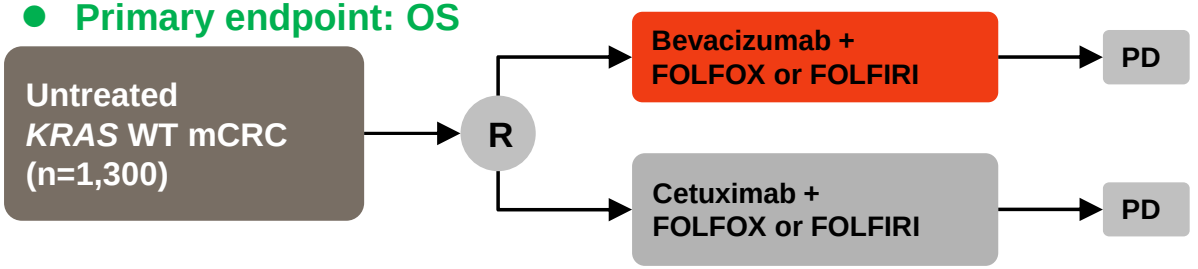


Cunningham et al, Lancet Oncol 2013

Ras-wild type tumors:
1. line: Head-to-head (H2H) Trials

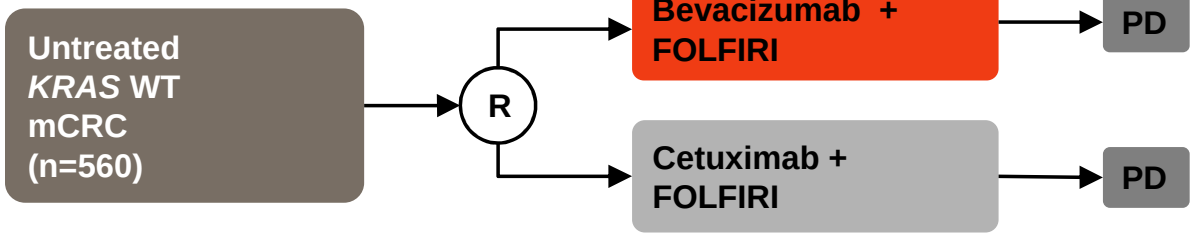
CALGB 80405 (phase III)

- Primary endpoint: OS



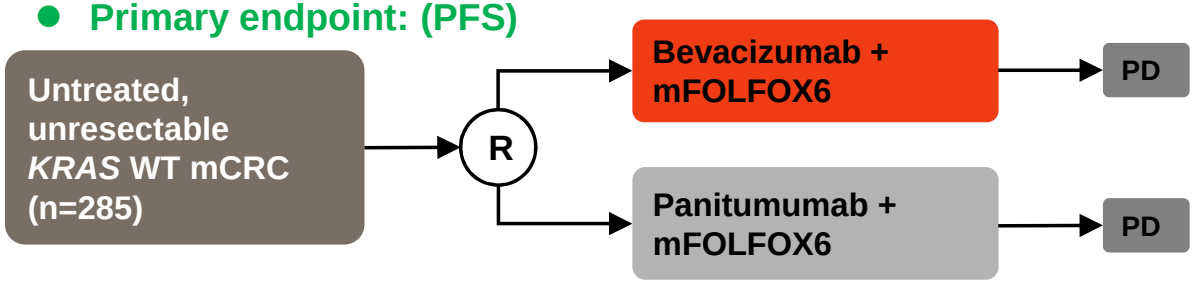
FIRE III (phase III)

- Primary endpoint: ORR



PEAK (phase II)

- Primary endpoint: (PFS)



CALGB vs FIRE III: H2H - comparison (all ras wt)

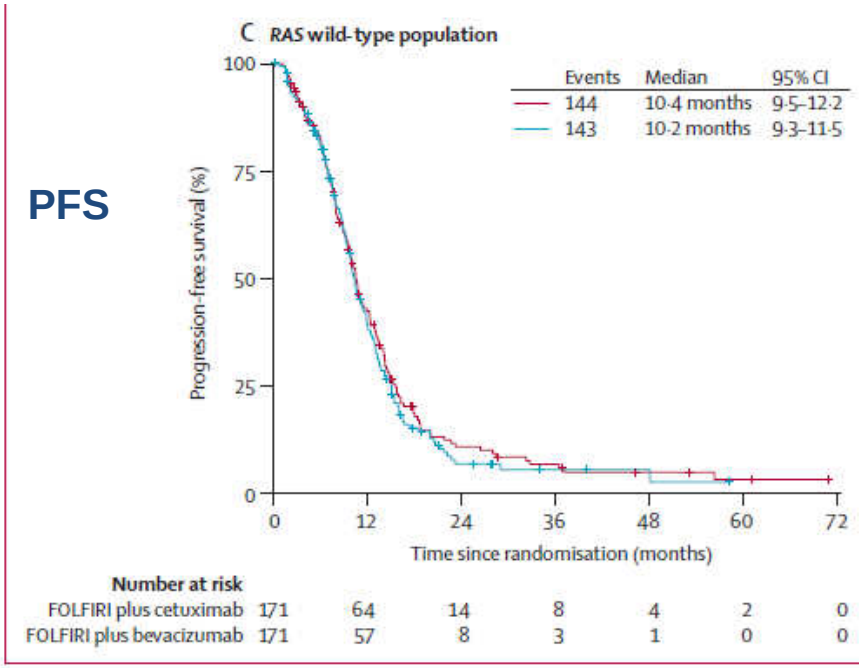
	CALGB 80405[1] Beva vs Cetuximab RAS WT (n=670)	FIRE 3[2,3] Beva vs Cetuximab RAS WT (n=342)
RR	53.8% vs 68.6% p<0.01	60% vs 65% ns. 56% vs 72% (eval. pts.) OR 2.01 p=0.003
Early Tumor Shrinkage	NA	68.2% vs 49.1% OR 2.22 p=0.0005
Deepness of Response	NA	48.9% vs 32.3% p<0.0001
PFS, months	11.3 vs 11.4 HR 1.1 p= 0.31	10.3 vs 10.2 HR 0.97 p=0.77
OS, months	31.2 vs 32.0 HR 0.90, p=0.40	33.1 vs 25.0 HR 0.697 p=0.0057

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

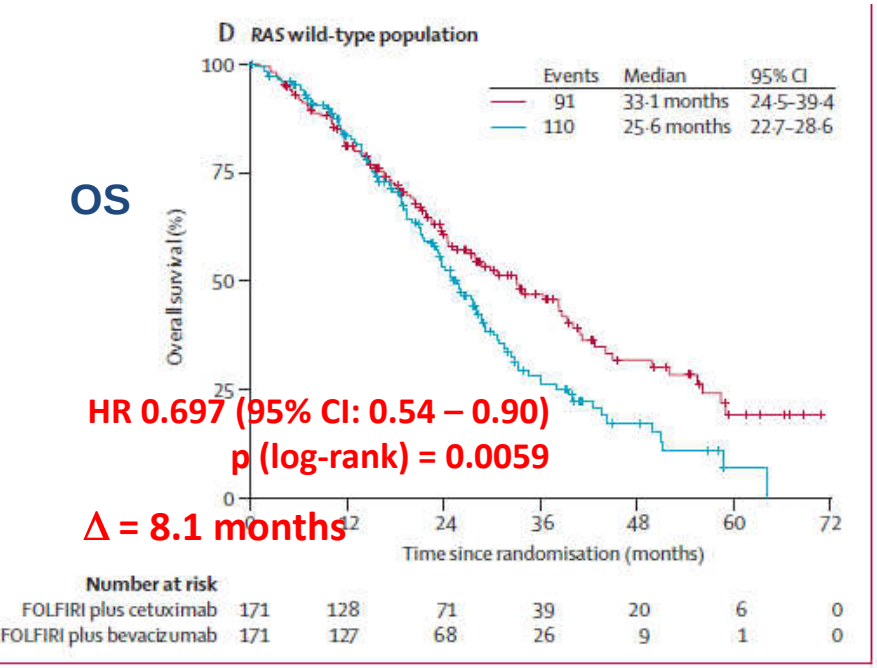
Volker Heinemann, Ludwig Fischer von Weikersthal, Thomas Decker, Alexander Kiani, Ursula Vehling-Kaiser, Salah-Eddin Al-Batran, Tobias Heintges, Christian Lerchenmüller, Christoph Kahl, Gernot Seipelt, Frank Kullmann, Martina Stauch, Werner Scheithauer, Jörg Hielscher, Michael Scholz, Sebastian Müller, 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

WTRas

PFS



OS



HR 0.697 (95% CI: 0.54 – 0.90)

p (log-rank) = 0.0059

Δ = 8.1 months

***Figure 2*: Kaplan-Meier estimates of progression-free and overall survival**

In the intention-to-treat (A and B) and RAS wild-type (C and D) populations, according to treatment group. FOLFIRI=fluorouracil, folinic acid, and irinotecan.

Volker Heinemann et al. 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, The Lancet Oncology, Volume 15, Issue 10, September 2014, Pages 1065-1075, ISSN 1470-2045, http://dx.doi.org/10.1016/S1470-2045(14)70330-4. (http://www.sciencedirect.com/science/article/pii/S1470204514703304)

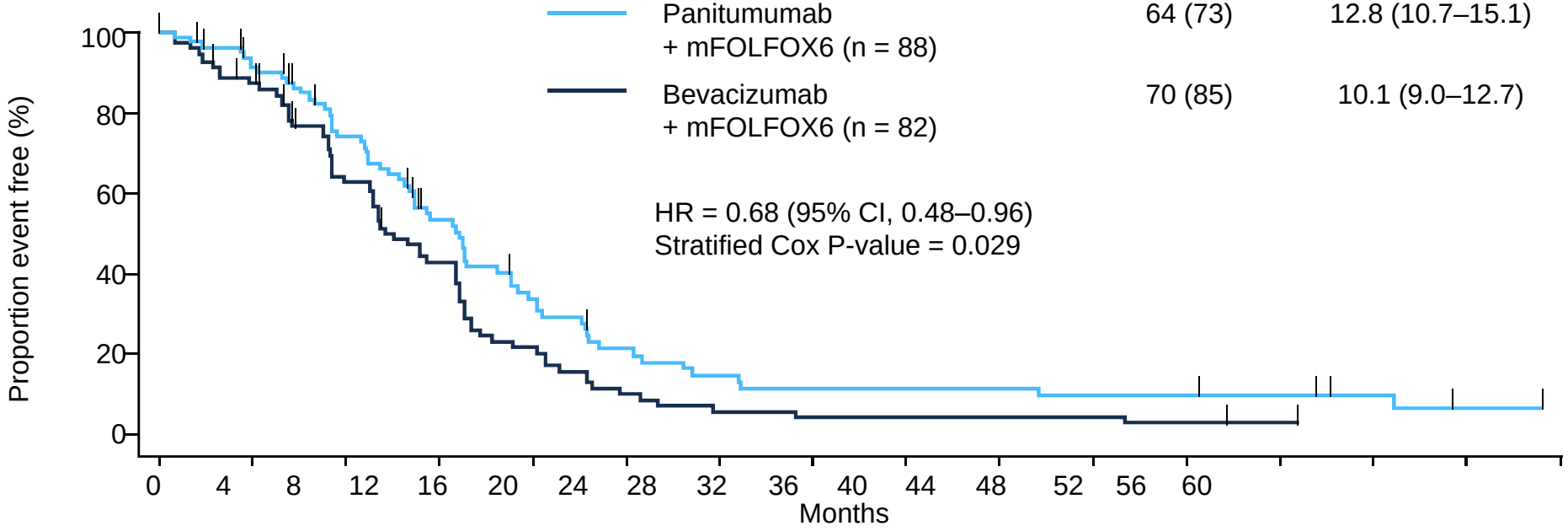
PEAK: FOLFOX + Panitumumab – final analysis

PFS (WT *RAS* population)

Rivera F, et al. Eur J Cancer 2015;51(Suppl 3):S1–S810:abstract 2014 (and poster).

Rrate 64% vs 60%

	Events n (%)	Median, months (95% CI)
Panitumumab + mFOLFOX6 (n = 88)	64 (73)	12.8 (10.7–15.1)
Bevacizumab + mFOLFOX6 (n = 82)	70 (85)	10.1 (9.0–12.7)

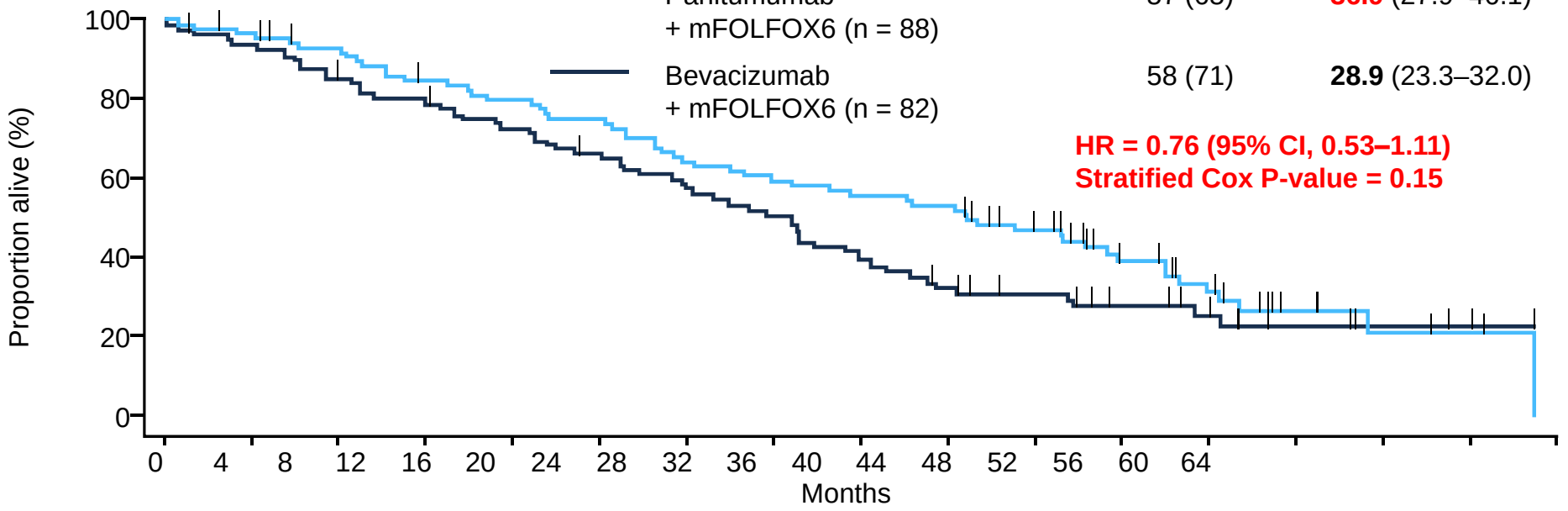


Pmab + mFOLFOX6	88	72	55	36	22	13	9	7	7	7	6	6	5	3	1	0
Bmab + mFOLFOX6	82	68	45	30	14	7	4	3	3	3	3	2	1	0	0	0

Censor indicated by vertical bar.
Pmab, panitumumab; Bmab, bevacizumab.

PEAK study: OS — WT *RAS* population

Rivera F, et al. Eur J Cancer 2015;51(Suppl 3):S1–S810:abstract 2014 (and poster).



	Events n (%)	Median, months (95% CI)
Panitumumab + mFOLFOX6 (n = 88)	57 (65)	**36.9** (27.9–46.1)
Bevacizumab + mFOLFOX6 (n = 82)	58 (71)	**28.9** (23.3–32.0)

HR = 0.76 (95% CI, 0.53–1.11)
Stratified Cox P-value = 0.15

Pmab + mFOLFOX6	88	84	78	70	66	62	53	49	46	44	34	22	15	7	3	2	0
Bmab + mFOLFOX6	82	76	69	63	57	51	44	39	31	23	19	14	10	5	3	2	0

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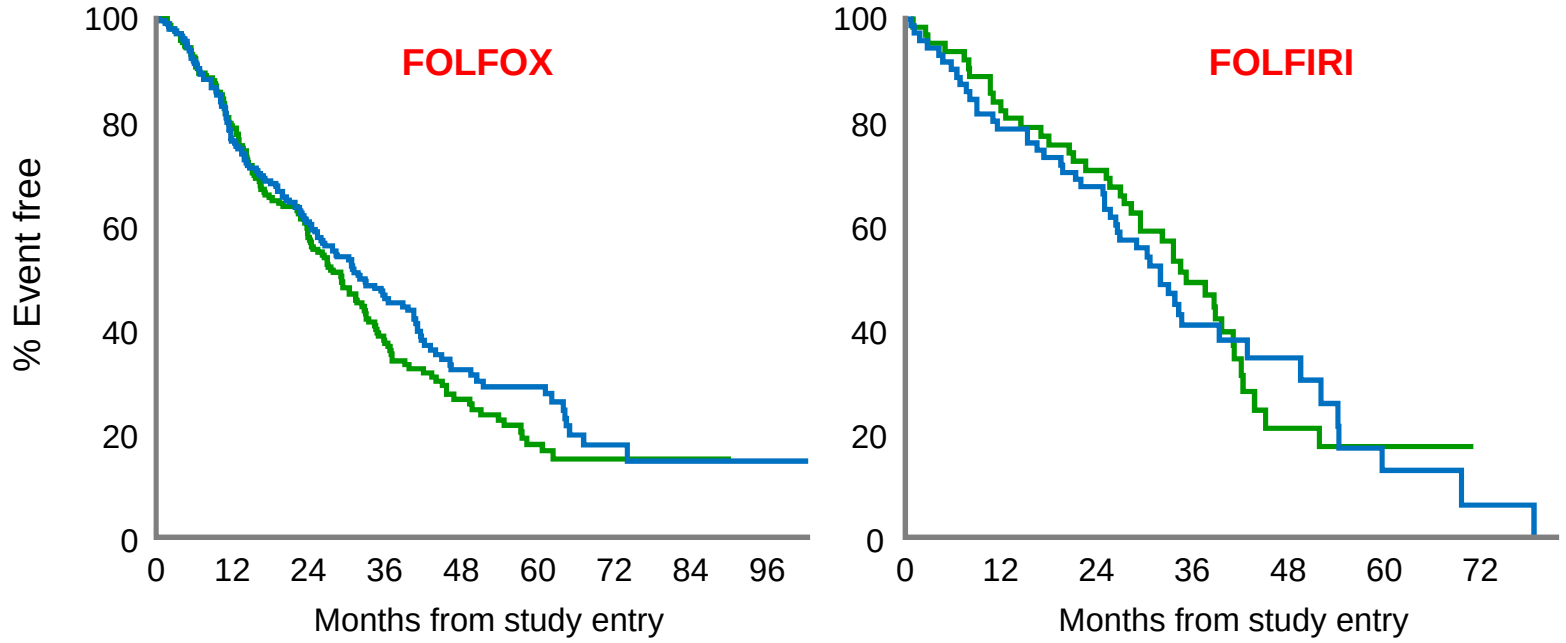
CALGB 80405*(all RAS wild type)*: OS by chemo-backbone

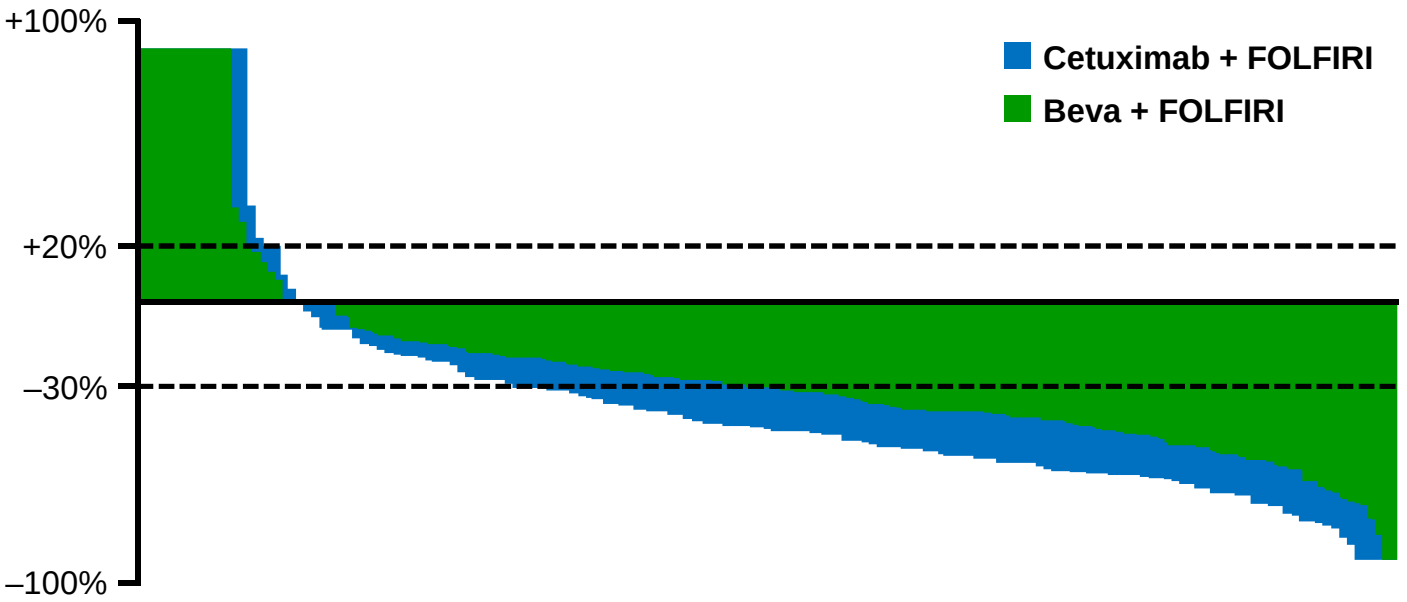
Lenz, et al. ESMO 2014. Abstract 501O



	FOLFOX			FOLFIRI		
Arm	**Median**	**HR (95% CI)**	**p**	**Median (95%**	**HR (95% CI)**	**p**
Chemo +Bev	**29.0 (24.0-32.8)**	**0.86 (0.6-1.1)**	**0.2**	**35.2 (28.3-41.3)**	**1.1 (0.7-1.6)**	**0.7**
Chemo +Cetux	**32.5 (26.1-40.4)**			**32.0 (25.6-42.9)**		

FIRE-3: *RAS* wild-type (n=330): Response

Stintzing, et al. ESMO 2014. Abstract LBA11

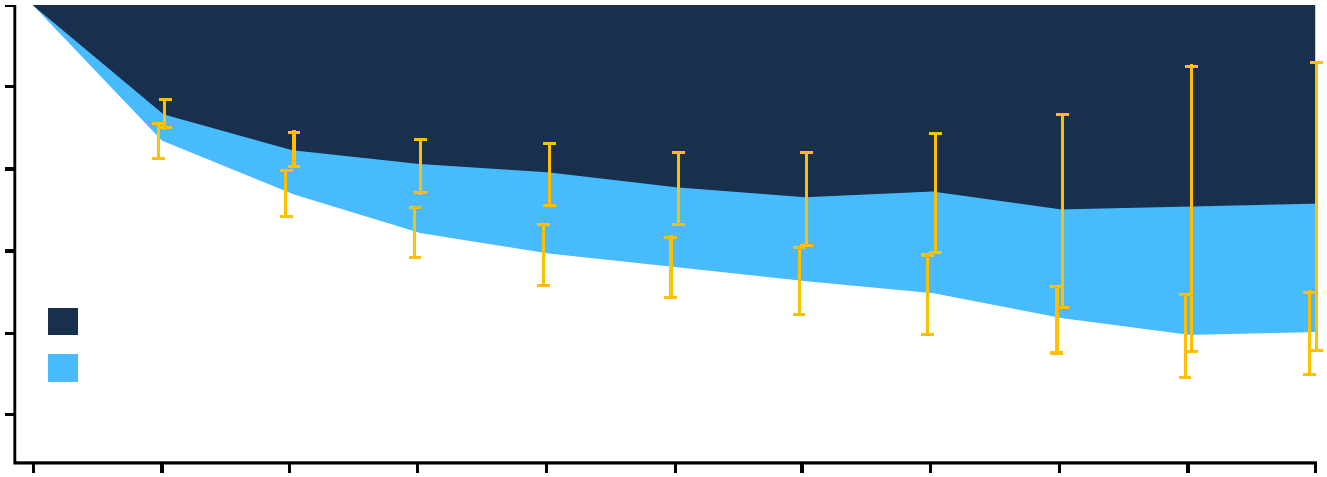


Median time to tumour nadir

FOLFIRI + Cetuximab	**15.0 weeks**
FOLFIRI + Beva	**15.7 weeks**

PEAK: FOLFOX 6 + Panitumumab or Bevacizumab (Rand. Phase II) N= 169
ras wildtype
Response: no difference (88% vs 81%)

Schwartzberg L, et al. J Clin Oncol 31, 2013



	Events n	Median, months
Panitumumab + mFOLFOX6 (n = 88)	73 %	12.8
Bevacizumab + mFOLFOX6 (n = 82)	85 %	10.1

HR = 0.68
Stratified Cox P-value = 0.029

CALGB 80405: patients resected (132) and NED (N=111)

Venook, et al. ESMO 2014. Abstract LBA10

	Chemo +	Chemo +	Total
Resected & NED	**45**	**66**	111
Response (CR, PR)	**82%**	**68%**	78%

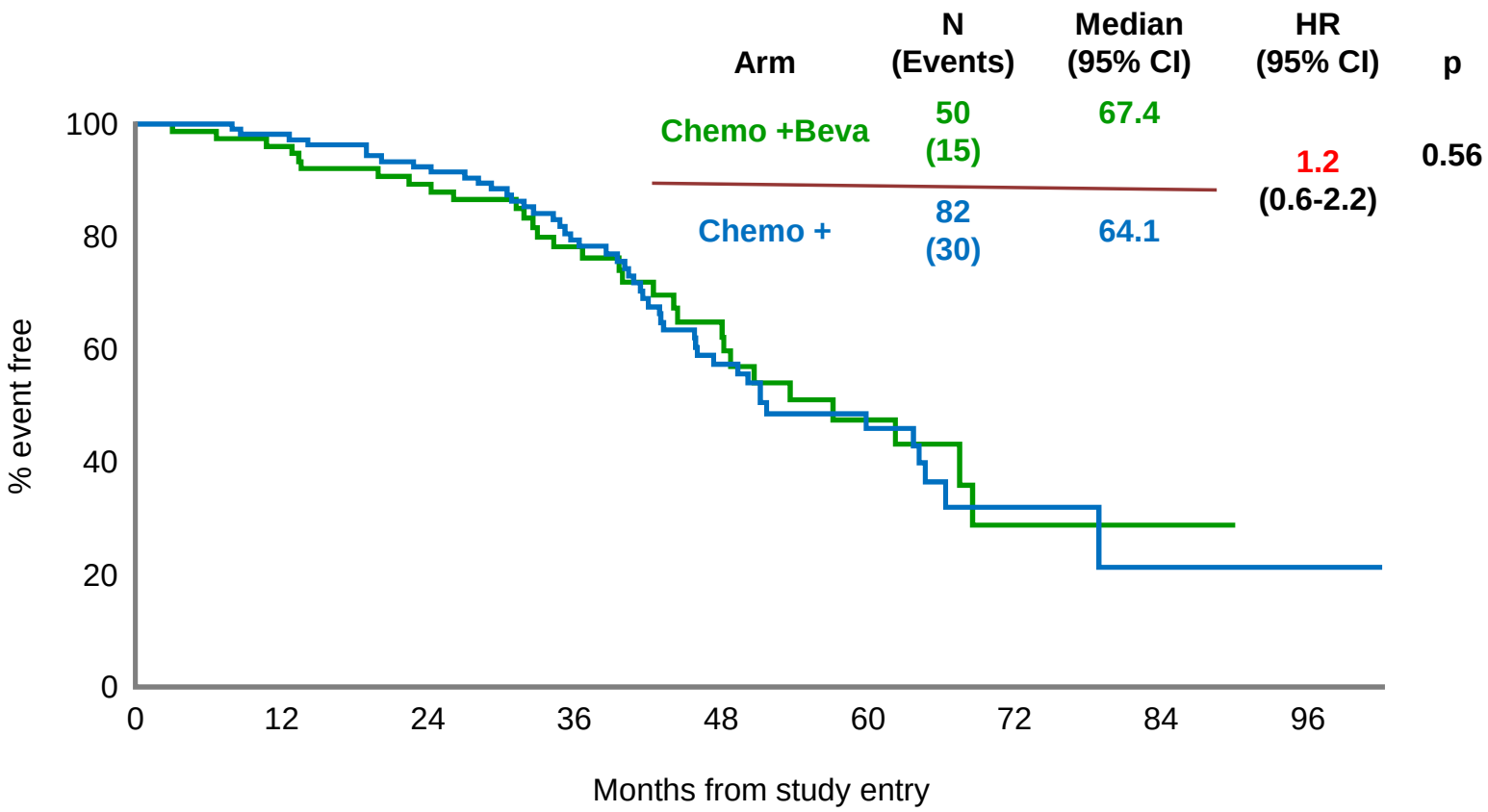
FIRE III: 12% vs 14% stopped Chemotherapy for surgery

**111/132 assessable for response

CALGB 80405 K-RAS wt: NED post-surgery (n=132)

OS

Venook, et al. ESMO 2014. Abstract LBA10

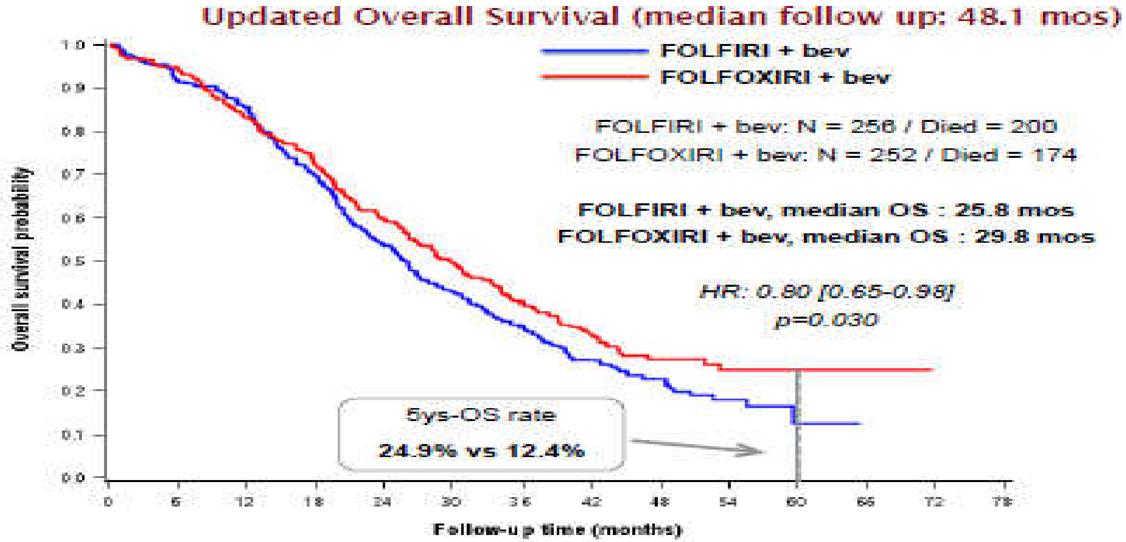


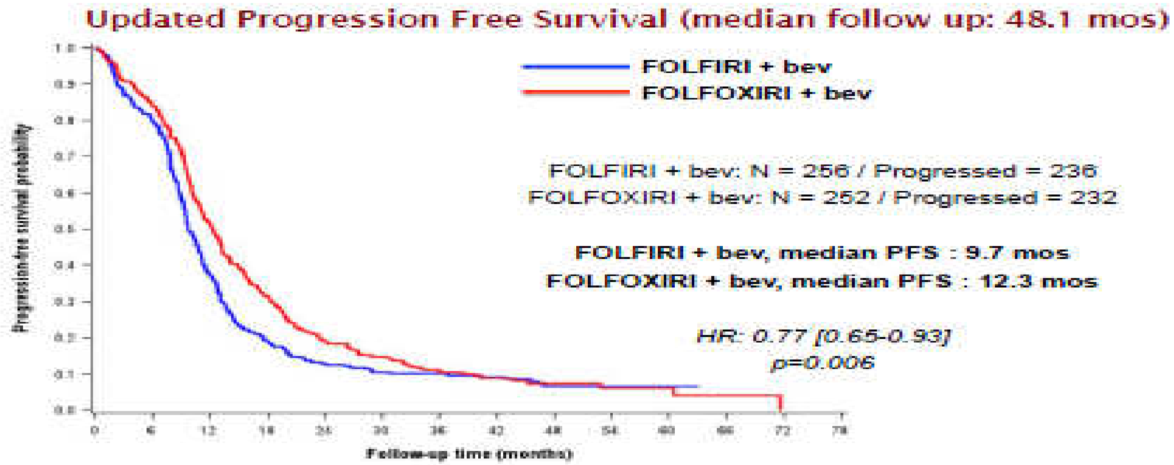
FOLFOXIRI plus bevacizumab (bev) versus FOLFIRI plus bev as first-line treatment of mCRC: updated survival results of the phase III TRIBE trial by the GONO group.

[illegible]

On behalf of the GONO (Gruppo Oncologico del Nord Ovest, Italy) investigators

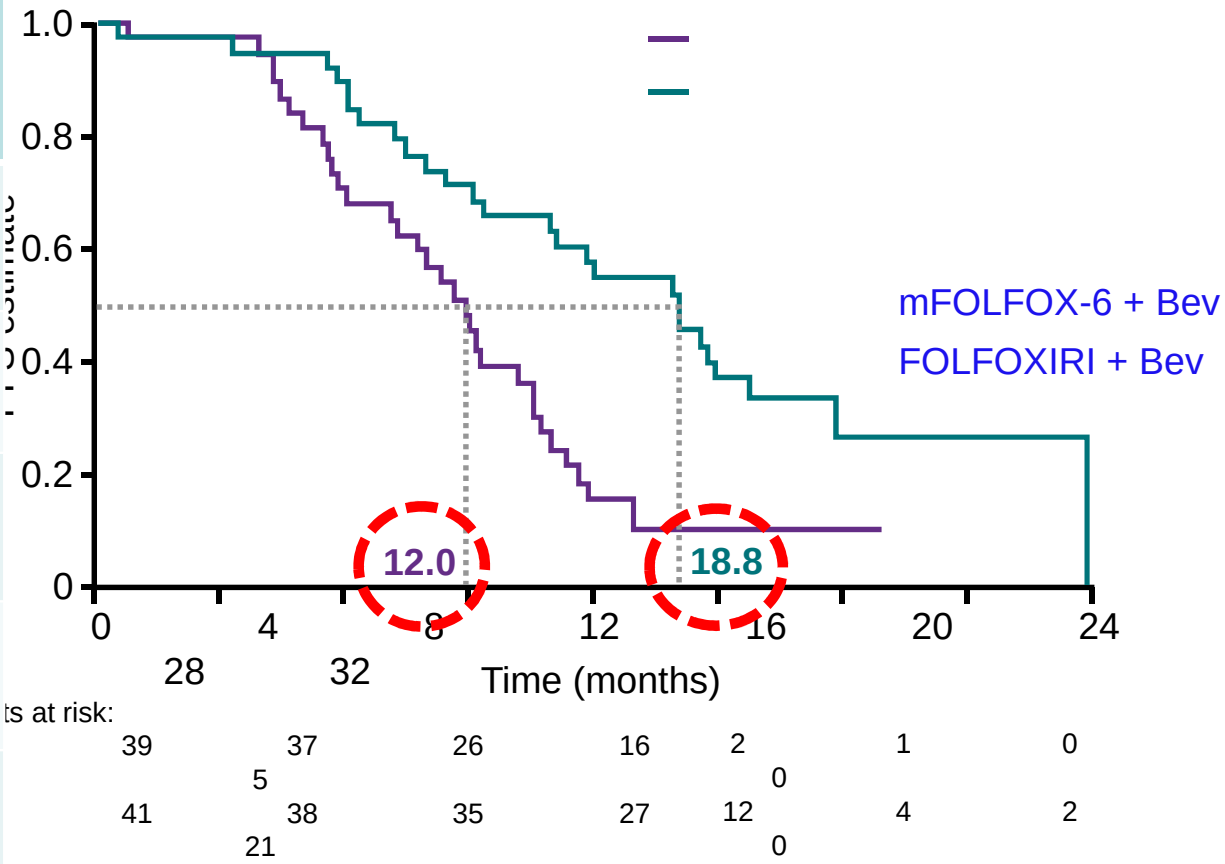
Best Resp.	FOLFIRI + bev N = 256	FOLFOXIRI + bev N = 252	*p*
Complete Resp.	3%	4%	
Partial	50%	61%	
Rate	**53%**	**65%**	***0.006***





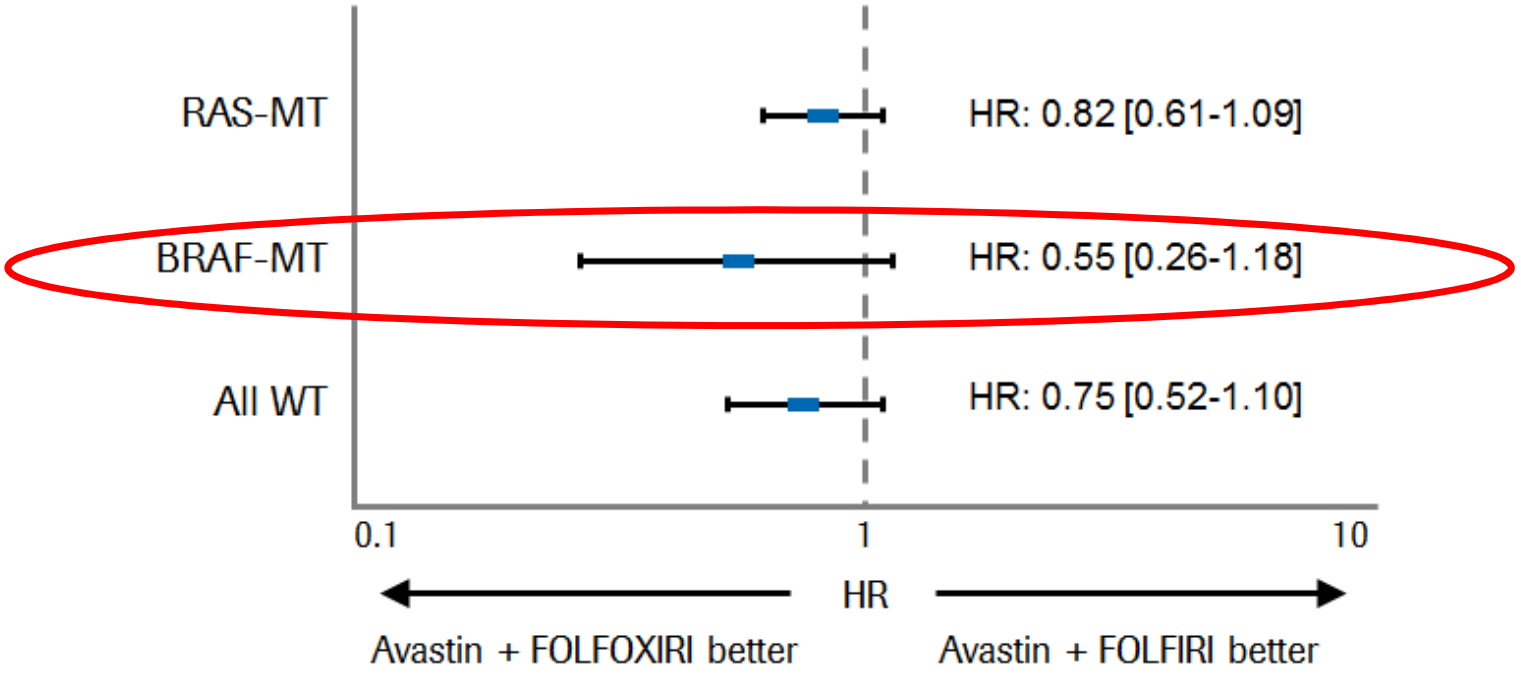
OLIVIA –Trial: FOLFOX+Beva +/- Irinotecan: PFS

Pts, %	mFOLFOX6 + Beva 39	FOLFOXIRI + Beva 41	Diffe r.	p
R0/1/2	48.7	61.0	12.3	0.271
R0/1	33.3	51.2	17.9	0.106
R0	23.1	48.8	25.7	0.017
ORR	61.5	80.5	18.9	0.061
PFS,	12.0	18.8	-	0.0002



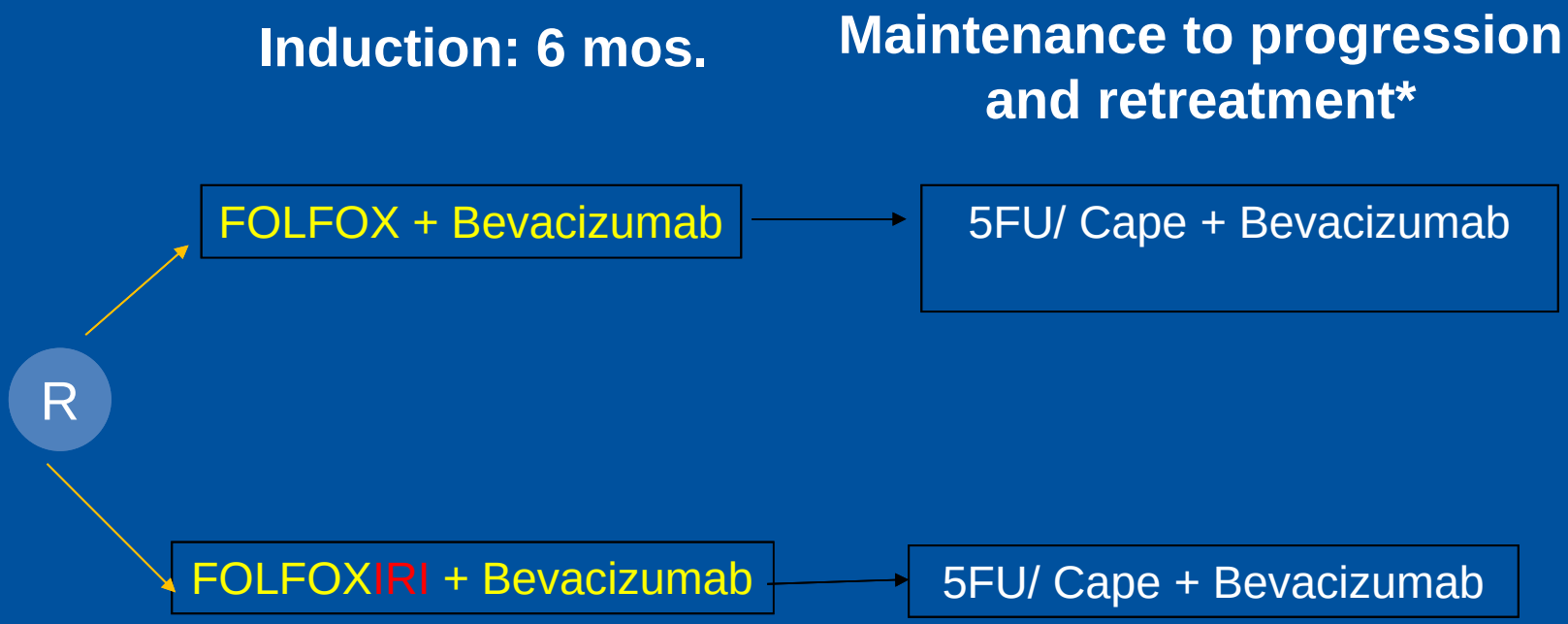
Gruenberger et al., J Clin Oncol 31, 2013 (suppl; abstr 3619)

TRIBE: large PFS benefit of FOLFOXIRI+Beva in BRAF-Mutation



Loupakis et al. ASCO 2014; Abstract 3519

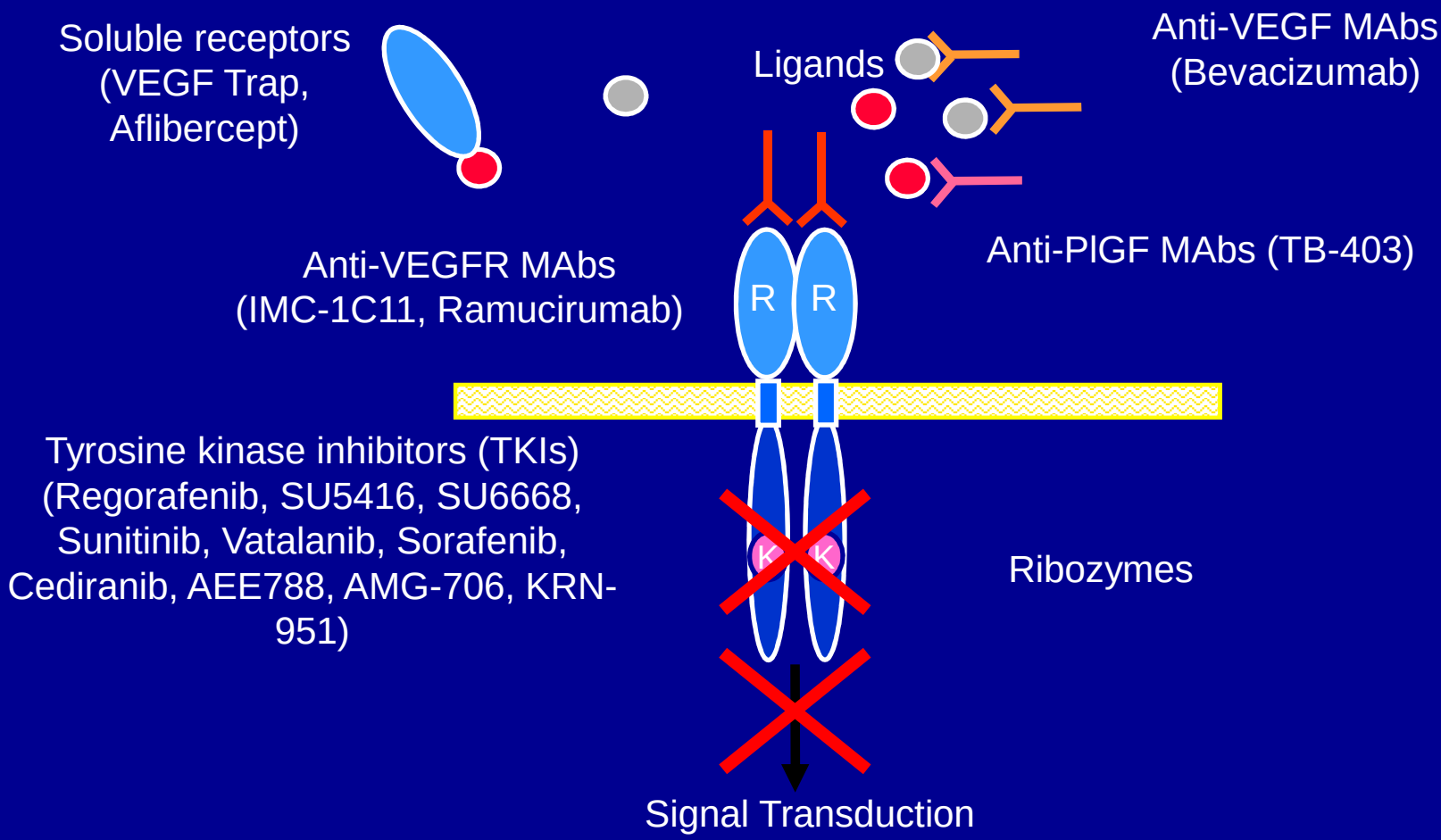
„CHARTA“ AIO 0209
random. phase II (N=240)



Strata 1,2,3 according to risk group

*after R0/1 resection maximum 12 months maintenance

Clinical anti-VEGF pathway therapies



Modified from Tabernero, J et al. Ann Oncol 2005

FOLFIRI +/-Ramicirumab 2.line (Tabernero et al)

RAISE: Study De

Ramicurimab — VEGFR2

- Ramicurimab is a fully humanized angiogenesis inhibitory antibody that targets VEGFR2 and prevents binding of VEGF
- Approved by FDA in April 2014 to treat gastric or GE junction cancer after it improved OS
- Known side-effects include diarrhea and hypertension

Progression during or after bevacizumab, oxaliplatin, and a fluoropyrimidine

RANDOMIZE (1:1)

Ramucirumab (8 mg/kg and FOLFIRI* every 2 weeks per cycle N=525

Placebo and FOLFIRI* every 2 weeks per cycle N=525

or unacceptable toxicity

Primary endpoint: Overall survival

Stratification factors:

- Geographic regions
- *KRAS* mutation status
- Time to disease progression after beginning first-line therapy

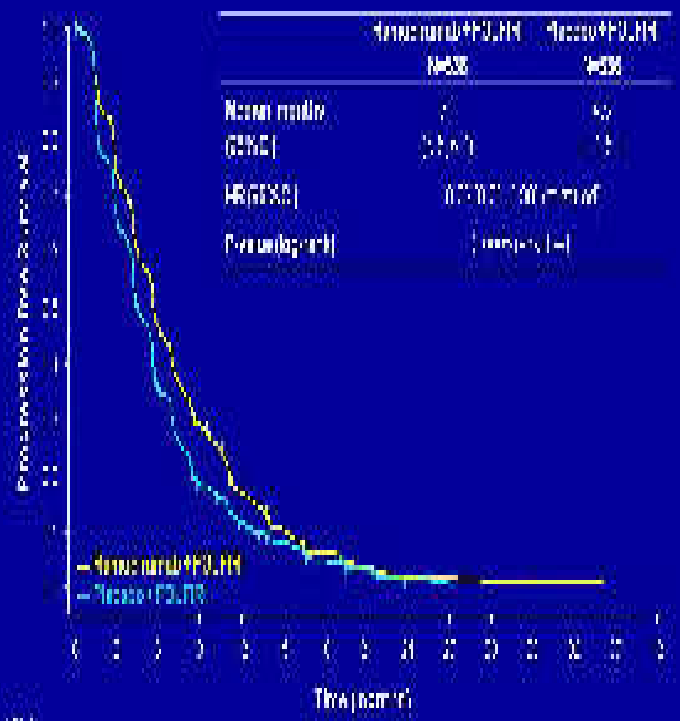
Secondary endpoints: PFS, ORR, PRO, Safety, PK, IG

Sample size assumptions

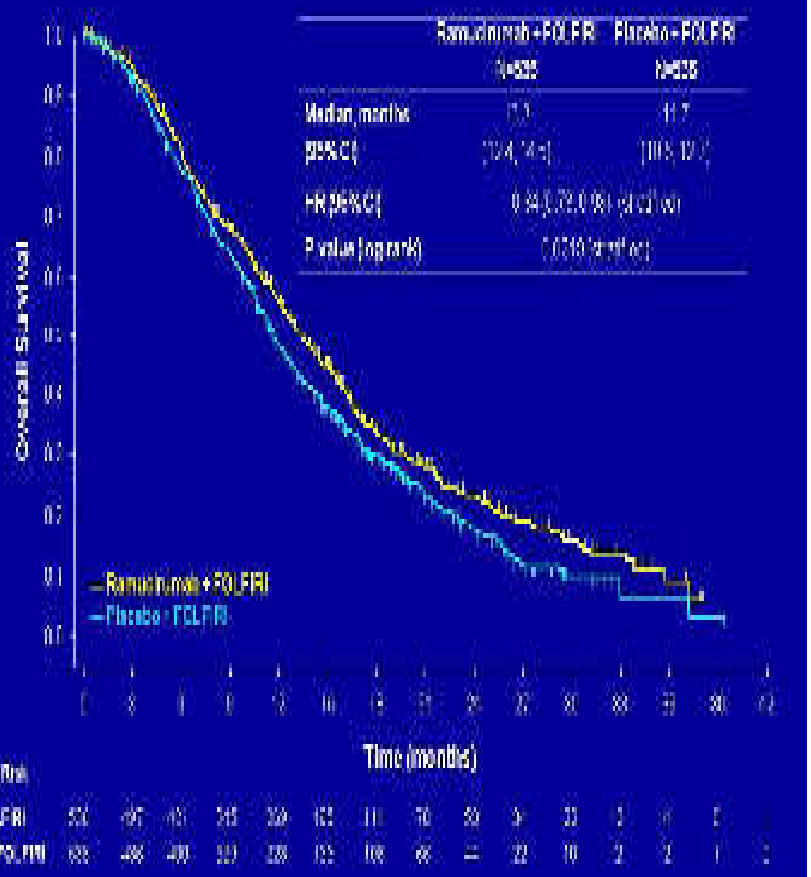
- Hazard ratio of 0.8
- Median overall survival of 10 months in the control arm vs 12.5 months with ramucirumab with a 2-sided α level of 0.05
- Enrollment of 1050 patients with 756 events for 85% power
- Gatekeeping from OS to PFS to ORR

Abbreviations: IG=immunogenicity; PFS=progression-free survival; PK=pharmacokinetics; OS=overall survival; ORR=objective response rate.
*Irinotecan: 180 mg/m²; Folinic acid: 400 mg/m² ; 5-Fluorouracil: 400 mg/m² bolus, followed by 2400 mg/m² administered intravenously over 46 to 48 hours (continuously).

RAISE: Progression-free Survival



RAISE: Overall Survival

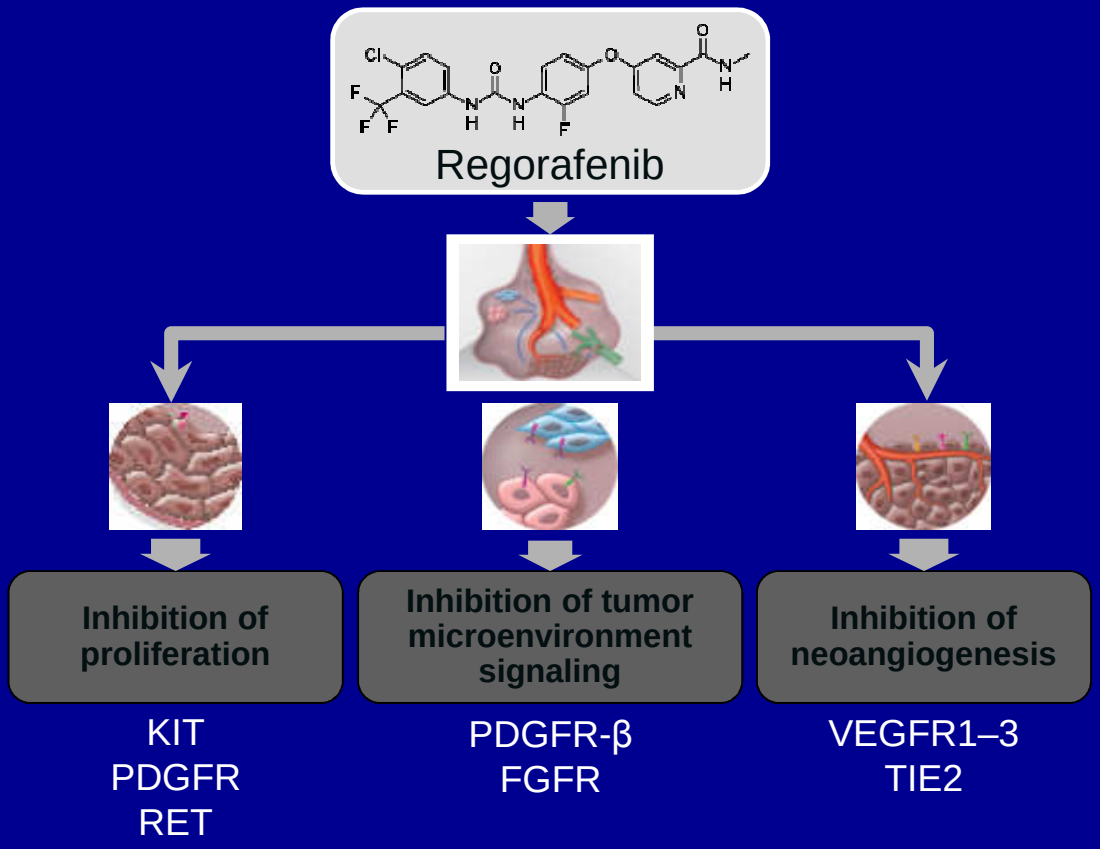


RAISE vs TML vs VELOUR summary of outcomes

	First Line		Second Line	PFS -/+	OS -/+
RAISE:	FOLFOX + Bev	→	FOLFIRI -/+ Ramicurimab	4.5/ 5.7 m	11.7/ 13.3 m
TML:	{FOLFOX or FOLFIRI} + Bev	→	{FOLFOX or FOLFIRI} -/+ Bev	4.1/ 5.7 m	9.8/ 11.2 m
VELOUR:	FOLFOX -/+ Bev	→	FOLFIRI -/+ ziv-Aflibercept	4.7/ 6.9 m	12.1/ 13.5 m

- Outcomes appear similar although designs not exactly the same
- Need randomized comparisons
- ? If there may be benefit from ziv or Ram beyond Bev & Ram or ziv (3rd line)
- ? If it may be worth trying to combine anti-angiogenics
  - Was too toxic in RCC but is this universally true with all agent combinations?

Regorafenib is an oral multikinase inhibitor targeting multiple tumor pathways[1–3]

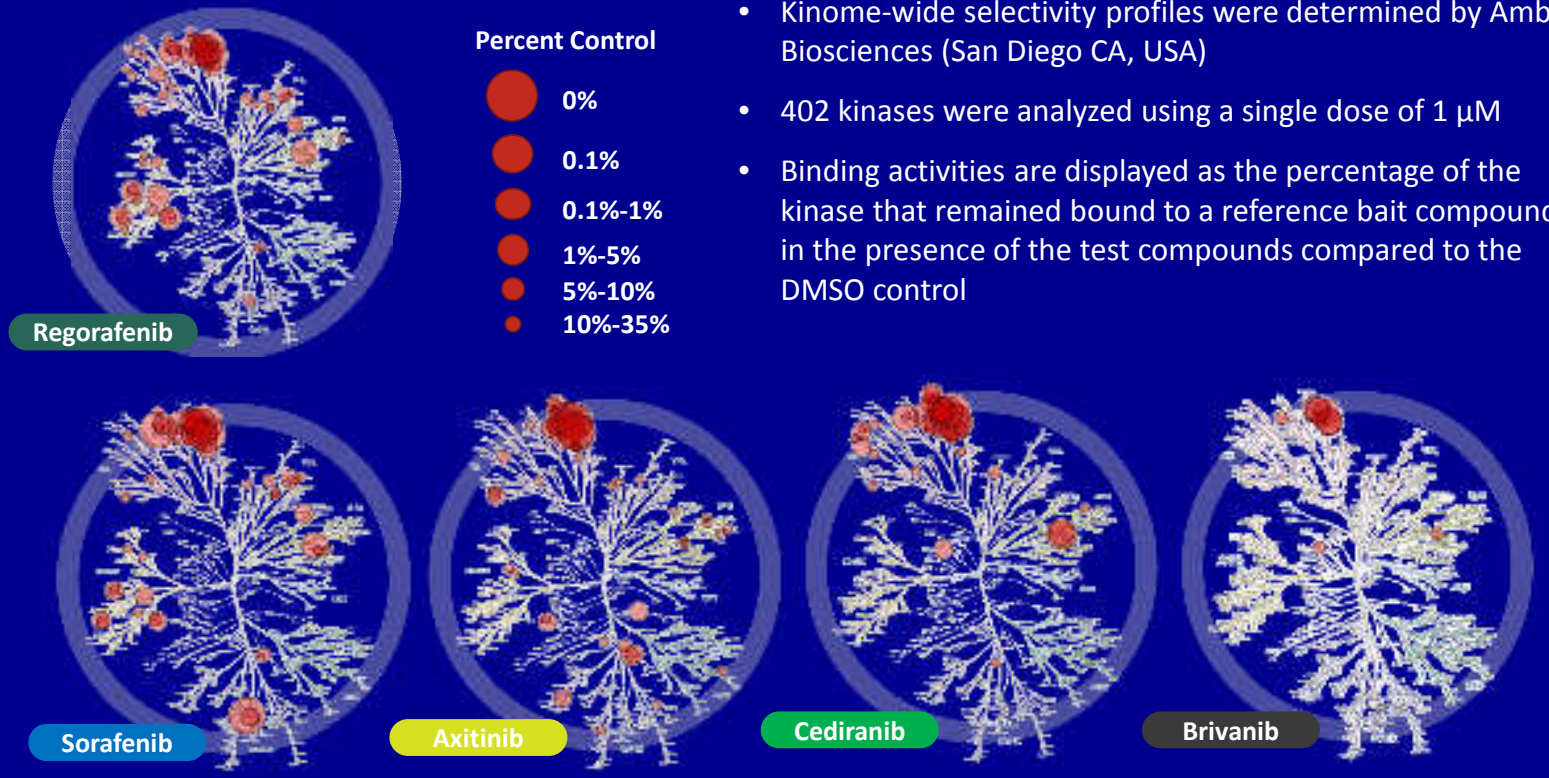


Biochemical activity	Regorafenib IC_{50} mean ± SD nmol/l (n)	
VEGFR1	13 ± 0.4	(2)
Murine VEGFR2	4.2 ± 1.6	(10)
Murine VEGFR3	46 ± 10	(4)
TIE2	311 ± 46	(4)
PDGFR-β	22 ± 3	(2)
FGFR1	202 ± 18	(6)
KIT	7 ± 2	(4)
RET	1.5 ± 0.7	(2)
RAF-1	2.5 ± 0.6	(4)
B-RAF	28 ± 10	(6)
$B\text{-}RAF^{V600E}$	19 ± 6	(6)

Slide adapted from that presented by
Professor E Van Cutsem at ASCO 2012 (abstract 3502)

1. Wilhelm SM et al. Int J Cancer 2011;129:245–-55;
2. Mross K et al. Clin Cancer Research 2012;18:2658–67;
3. Strumberg D et al. Expert Opin Invest Drugs 2012;21:879–89.

Regorafenib Shows a Kinase Selectivity Profile That Is Distinct and Different from Other Multikinase Inhibitors

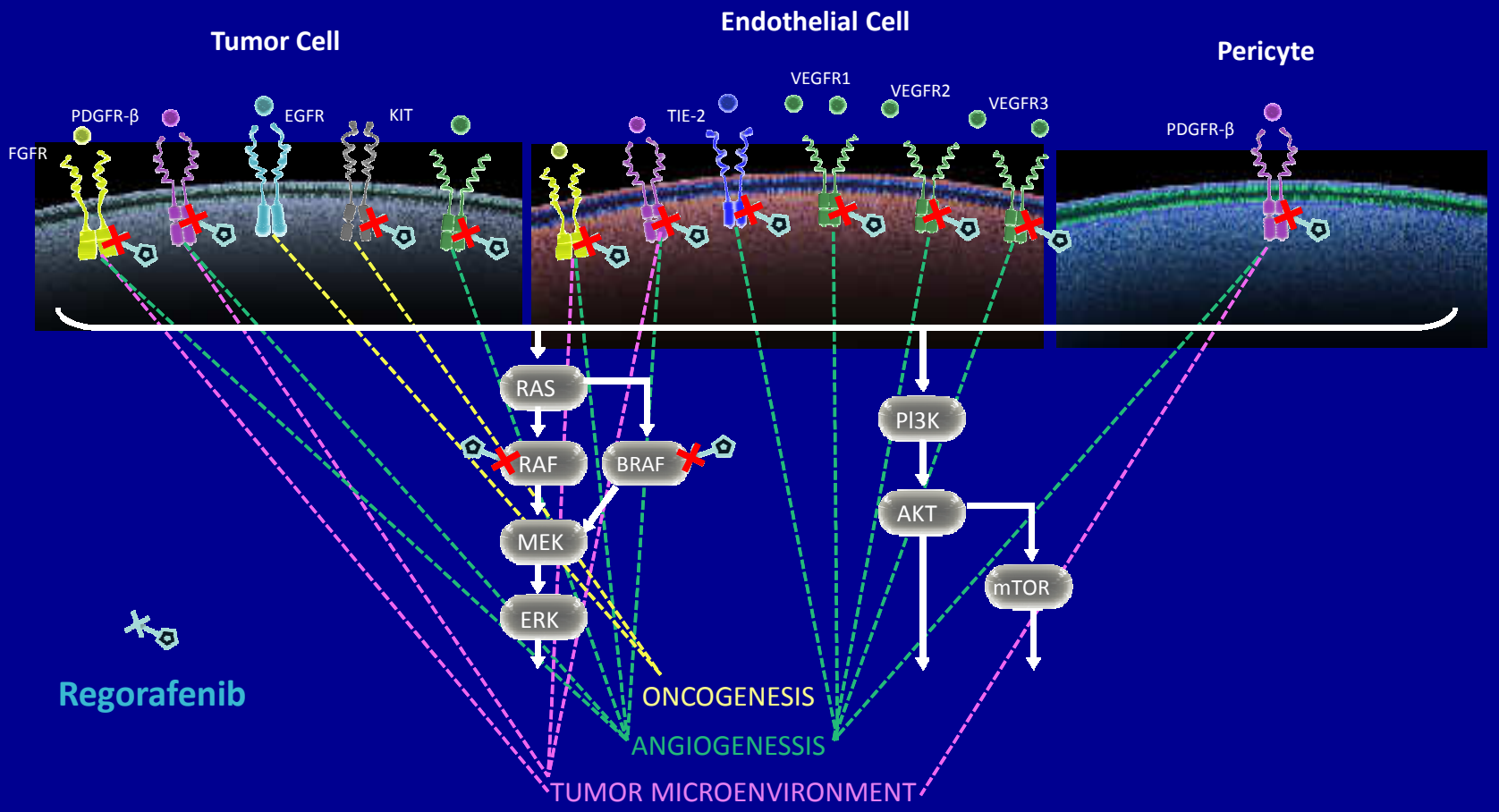


- Kinome-wide selectivity profiles were determined by Ambit Biosciences (San Diego CA, USA)
- 402 kinases were analyzed using a single dose of 1 µM
- Binding activities are displayed as the percentage of the kinase that remained bound to a reference bait compound in the presence of the test compounds compared to the DMSO control

DMSO, dimethyl sulfoxide.

Wilhelm SM, et al. *Int J Cancer.* 2011;129:245-255. Sorafenib PI. Wayne, NJ: Bayer HealthCare Pharmaceuticals; 2012.

Regorafenib, a Targeted Agent that Inhibits Multiple Pathways of Tumor Growth and Progression, Has Emerged as a New Direction for the Treatment of GIST and mCRC



G.SM.ON.09.2013.0810

Grothey A, et al. *Lancet*. 2013;381(9863):303-312; Wilhelm SM, et al. *Int J Cancer*. 2011;129:245-255.

CONCUR and CORRECT compared to RECOURSE

Clinical trial	Phase	Regimen	N	PFS (M)	HR (PFS)	OS (M)	HR (OS)	P value (OS)
10040030 study (IRC *)	rP2	TAS-102+BSC Placebo + BSC	112 57	2.0 1.0 **Δ1.0**	0.41	9.0 6.6 **Δ2.4**	0.56	0.0011
RECOURSE study	P3	TAS-102+BSC Placebo+BSC	534 266	2.0 1.7 **Δ0.3**	0.48	7.1 5.3 **Δ1.8**	0.68	0.0001
CONCUR study	P3	Regorafenib+BSC Placebo+BSC	136 68	3.2 1.7 **Δ1.7**	0.31	8.8 6.3 **Δ2.5**	0.55	0.0002
CORRECT study	P3	Regorafenib+BSC Placebo+BSC	505 255	1.9 1.7 **Δ0.2**	0.49	6.4 5.0 **Δ1.4**	0.77	0.0052

Yoshino T, et al. Lancet Oncology 2012: 13; 993-1001, Yoshino et al. WCGIC 2014. Abstract O-0022; Ann Onc Vol. 25 Suppl2, June 2014., Li et al. WCGIC 2014. Abstract O-0023; Ann Onc Vol. 25 Suppl2, June 2014, Grothey A et al. *Lancet* 2013

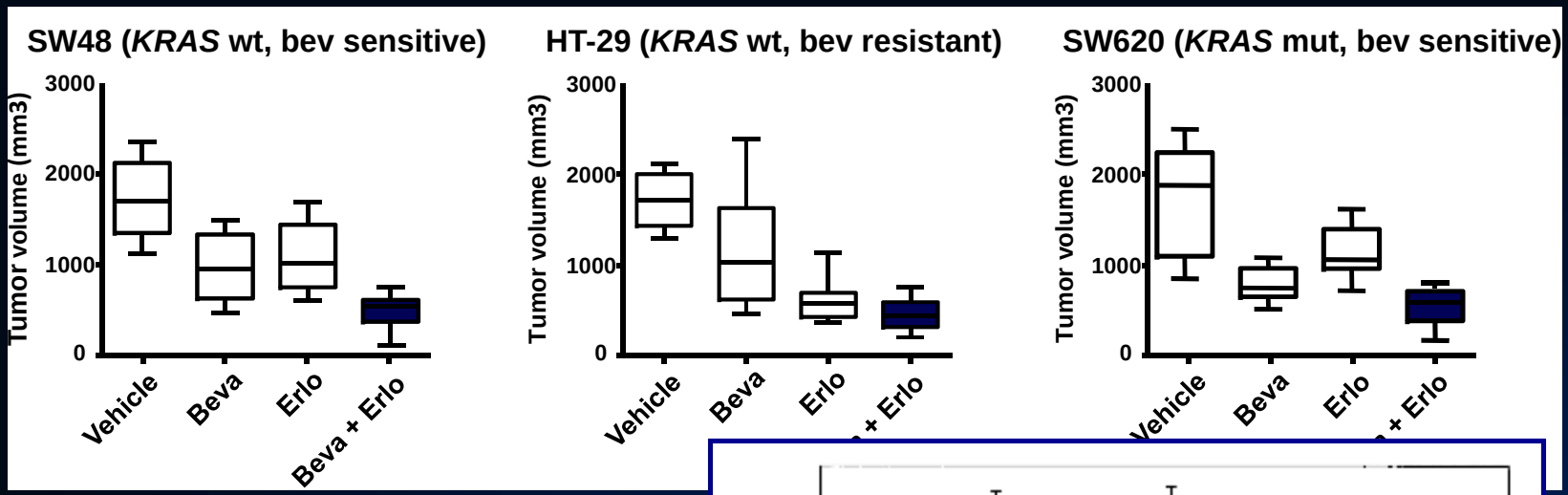
TAS-102

Most Frequent AEs (Grade 3)

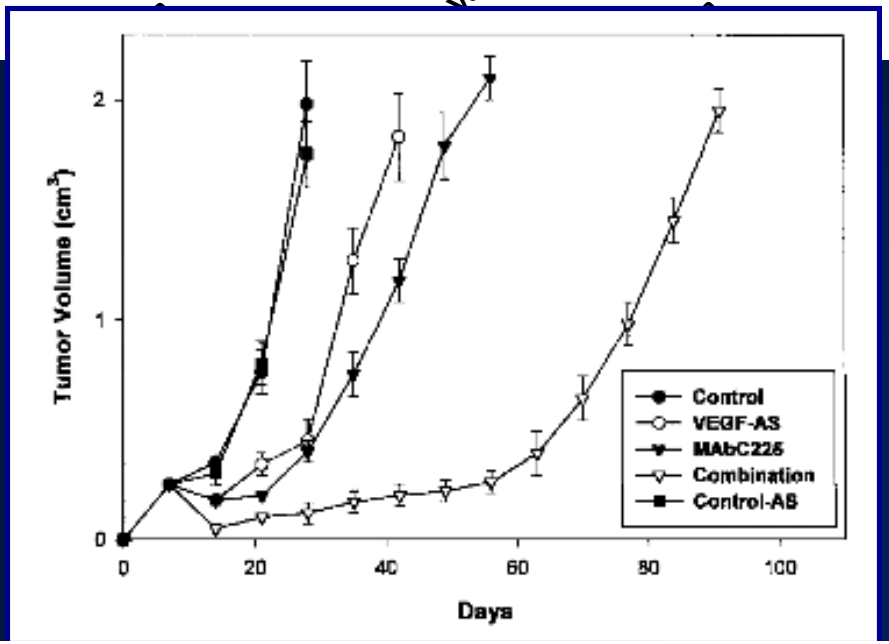
AE	TAS-102	Placebo
Neutropenia	34.9%	0%
Leukopenia	12.8%	0%
Anemia	16.5%	2.6%
Febrile neutropenia	3.8%	0%

Yoshino T, et al. *Ann Oncol.* 2014;25(suppl 2): Abstract 0-0022.

DREAM: Preclinical Rationale

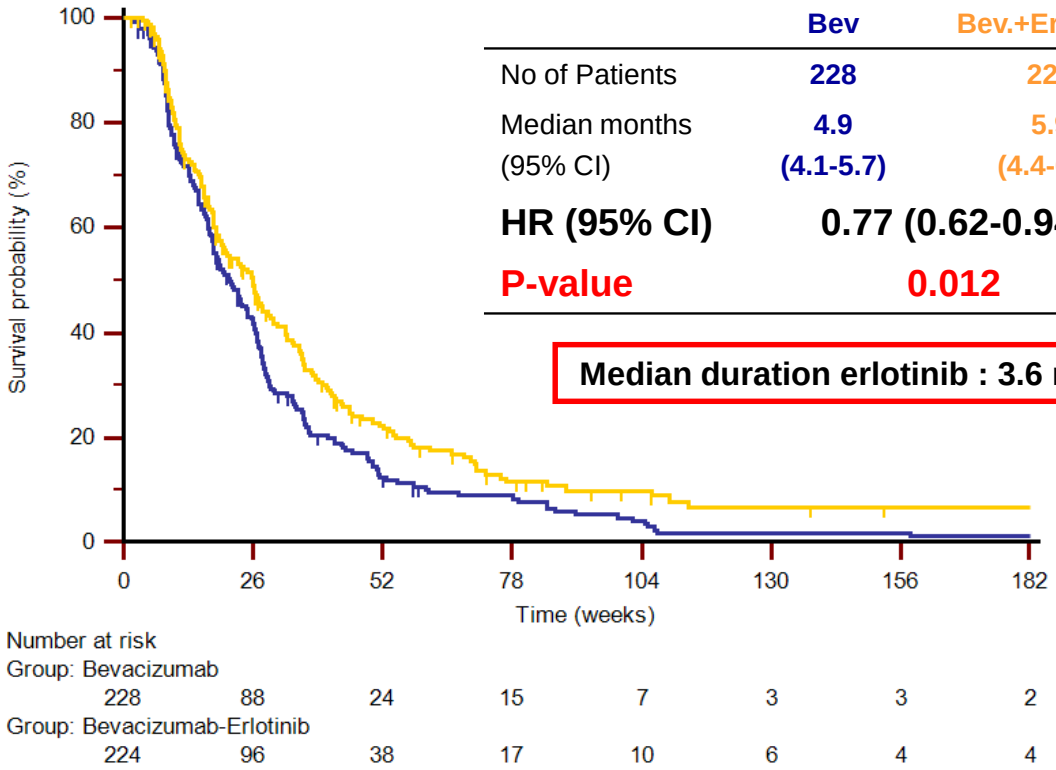


But we had previously also seen that anti-EGFR mAbs plus VEGFi worked in xenografts
(Ciardiello et al, CCR 2000)
…..but not in human together with chemotherapy……!!!!!



DREAM (N=453): Maintenance Beva +/- Erlotinib

PFS



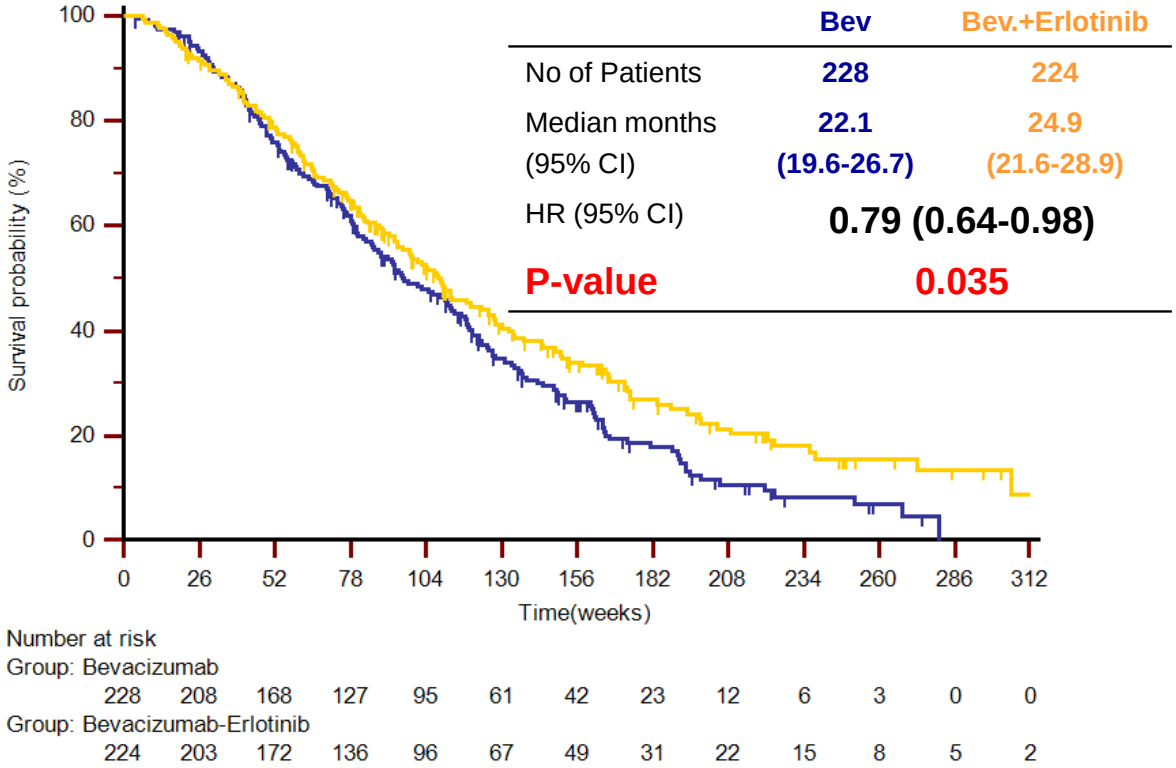
	Bev	Bev.+Erlotinib
No of Patients	228	224
Median months (95% CI)	4.9 (4.1-5.7)	5.9 (4.4-6.6)
HR (95% CI)	0.77 (0.62-0.94)	
P-value	0.012	

Median duration erlotinib : 3.6 months

Chibaudel et al, ESMO 2014

DREAM

OS

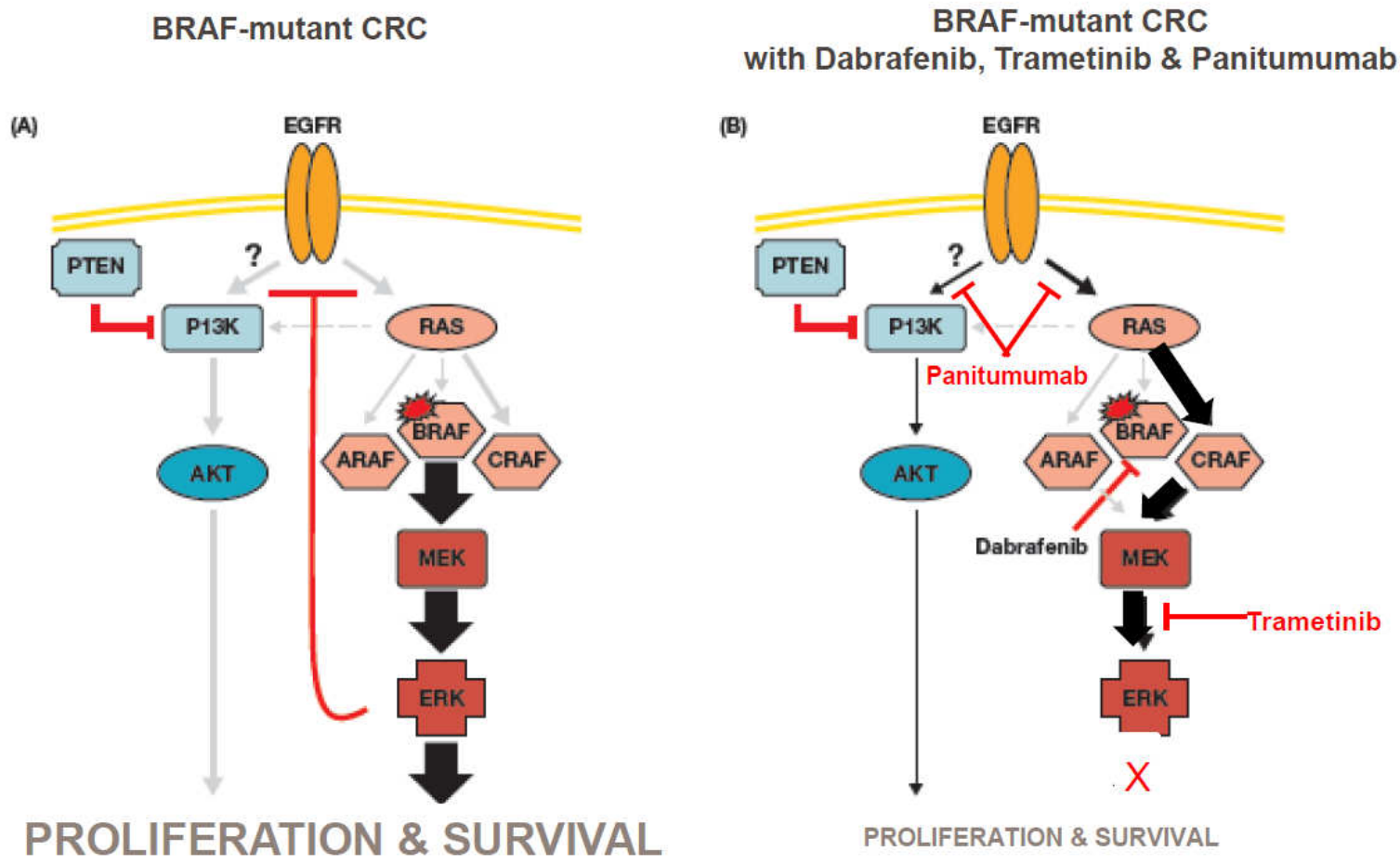


	Bev	Bev.+Erlotinib
No of Patients	228	224
Median months (95% CI)	22.1 (19.6-26.7)	24.9 (21.6-28.9)
HR (95% CI)	0.79 (0.64-0.98)	
P-value	0.035	

No imbalances in Post-PD therapy

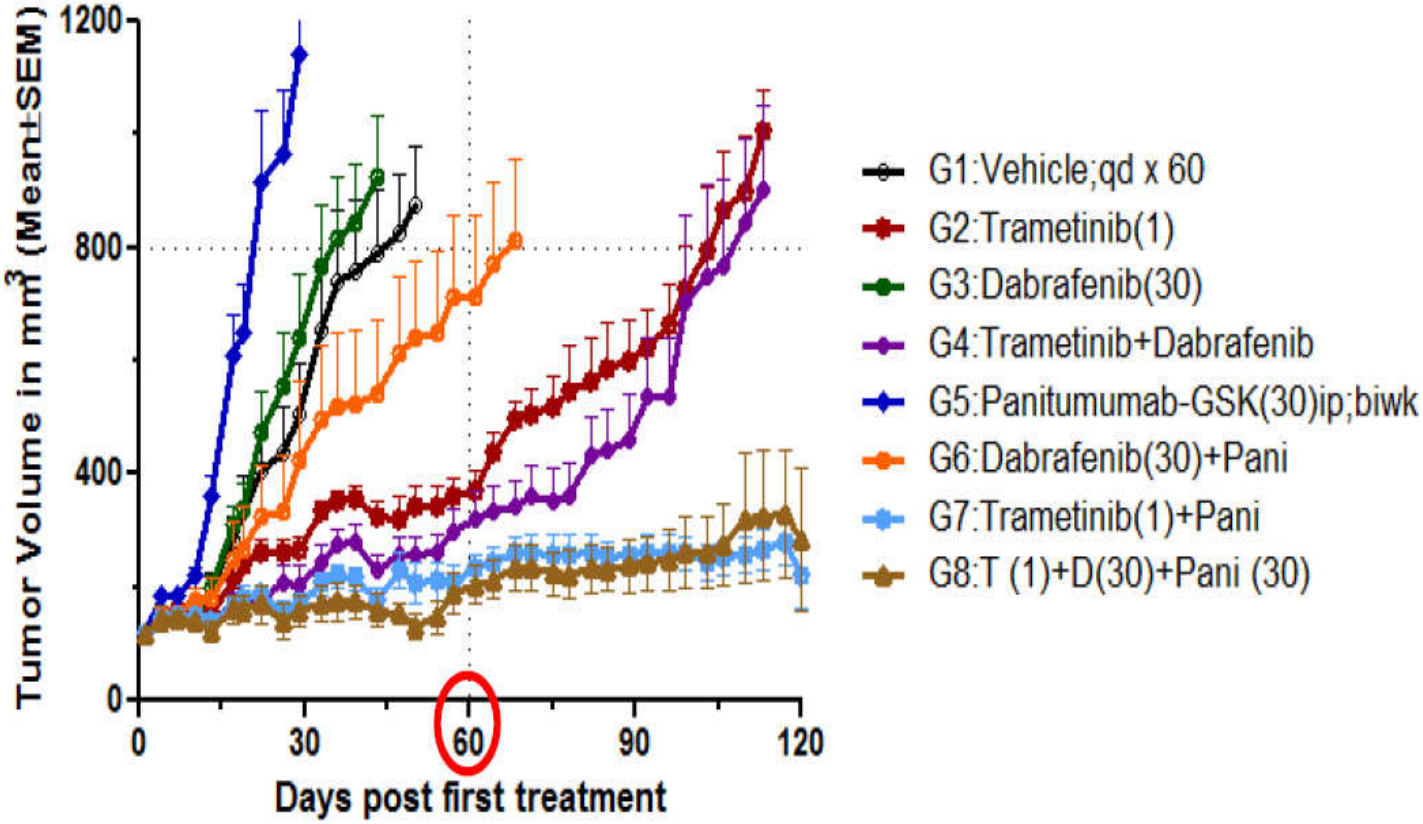
Chibaudel et al, ESMO 2014

Signaling Model for BRAF Mutant CRC

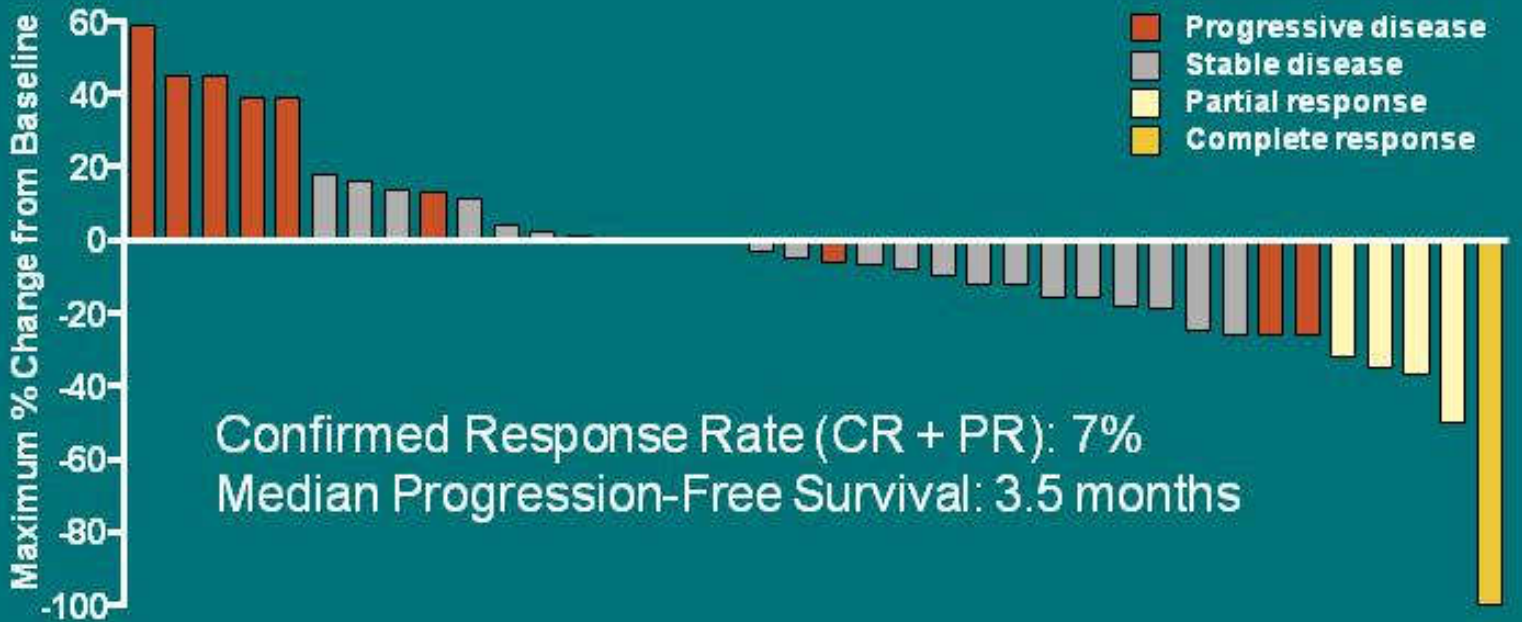


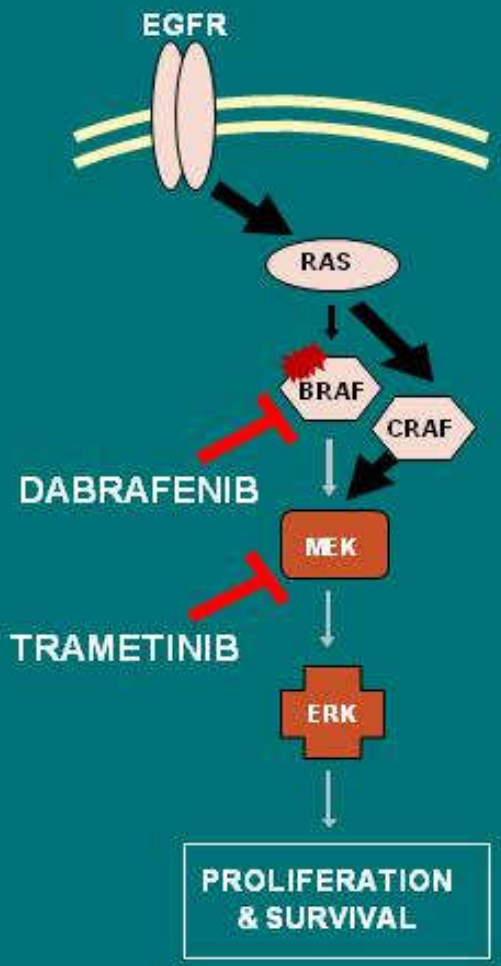
Combination of D+T+P and T+P Results in Most Significant Tumor Growth Delay

$BRAF^{V600E\_L584F}/PI3K^{wt}$ Co-012 CRC PDX model



Dabrafenib (D) + Trametinib (T): Limited Activity in BRAFm CRC





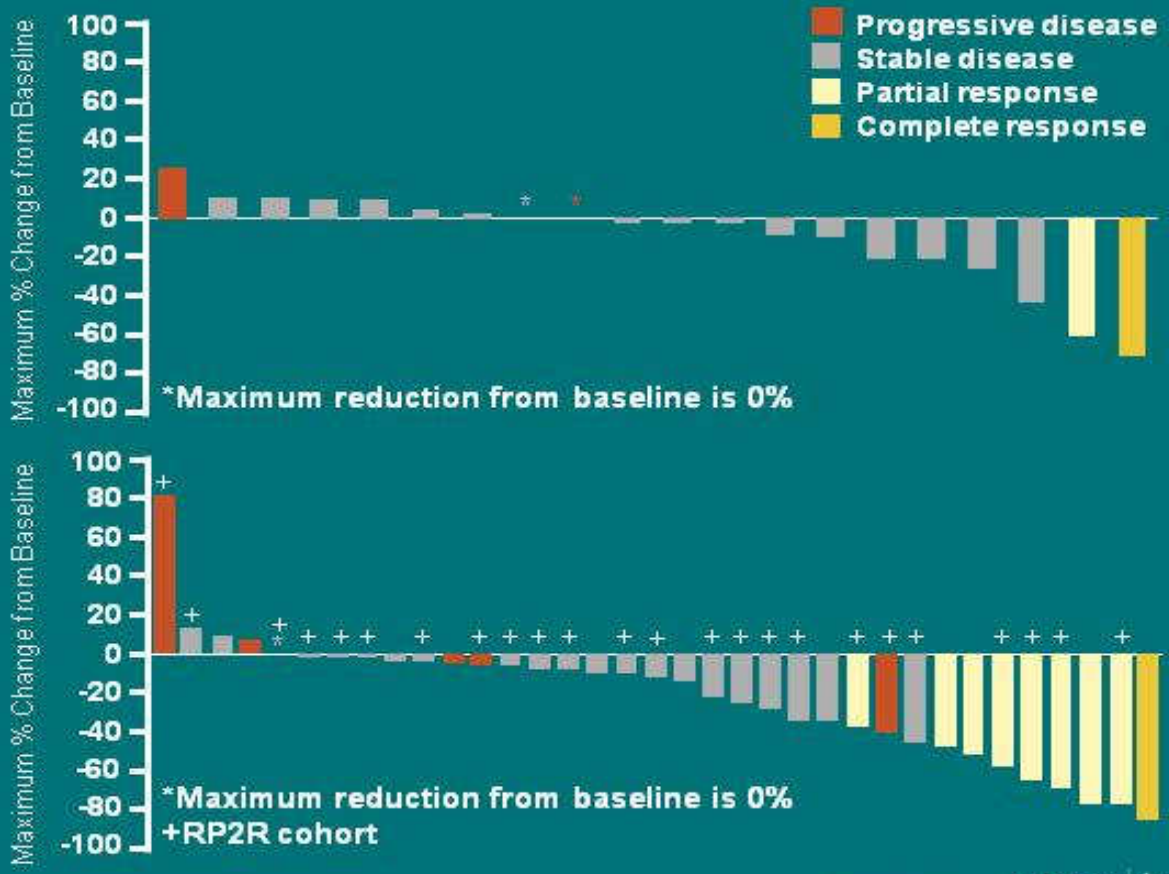
BRF113220 — Corcoran et al, *J Clin Oncol*, 2014

Best Response With Confirmation

Percent Change from Baseline at Maximum Reduction in Tumor Measurement

D+P (N = 20)
CR+PR: 2 (10%)
Stable disease: 16 (80%)

D+P+T (N = 35)
CR+PR: 9 (26%)
Stable disease: 21 (60%)

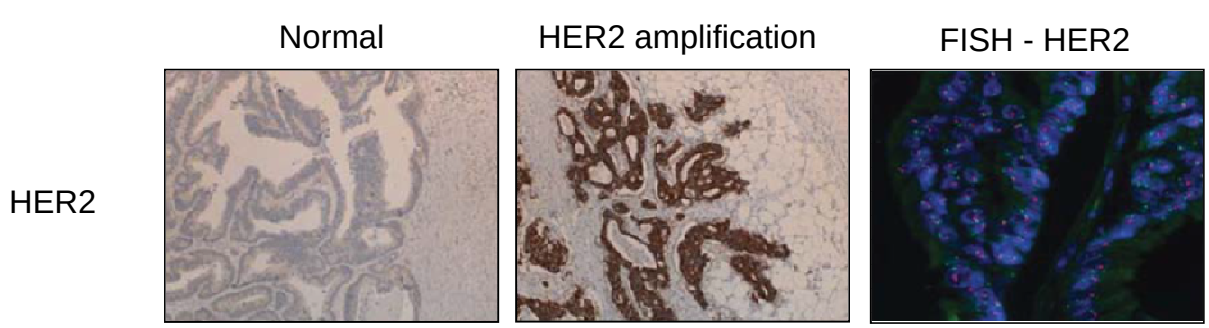


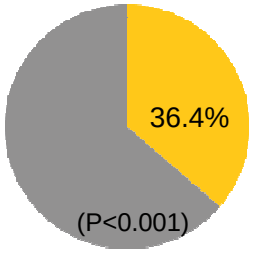
Color: confirmed response
Height of bar: best unconfirmed response

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Chloe Atreya at 2015 ASCO Annual Meeting

HER-2 amplification





Quadruple* wt
non-responders
(n=11 xenopatients)

**KRAS/NRAS/*
BRAF/PIK3CA

mCRC treated with cetuximab (DFCI)

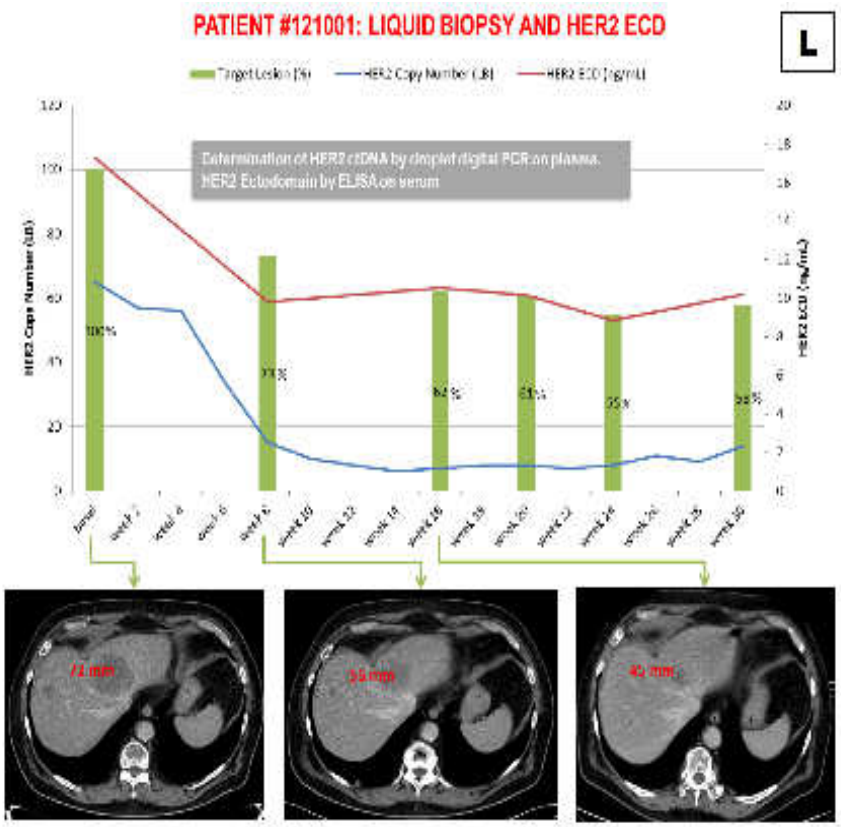
	HER-2 ampl	HER-2 non-ampl	
N	13	220	
mPFS (d)	89	149	p=NS
mOS (d)	307	515	p=0.0013

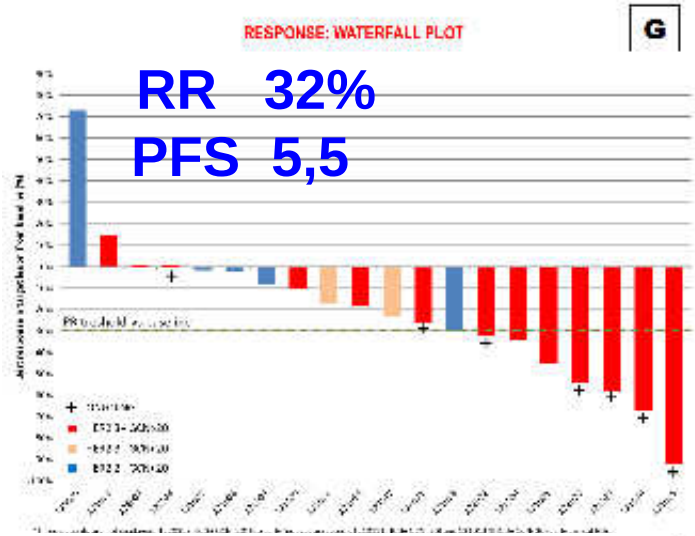
Bertotti A et al. Cancer Discov 2011;1:508-23

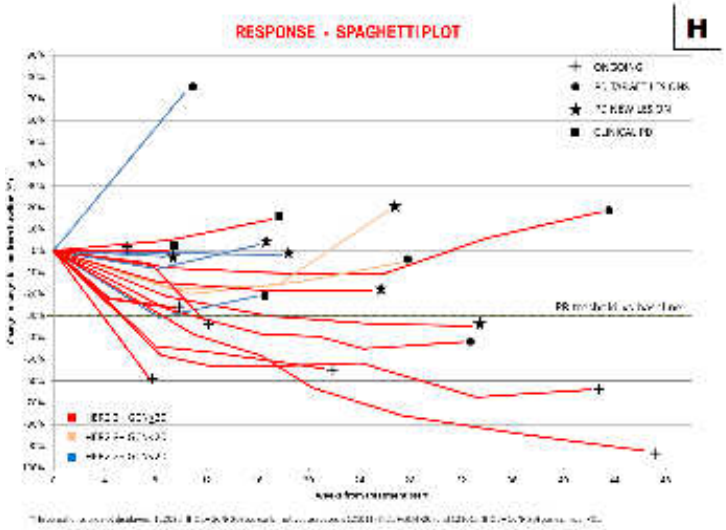
Yonesaka K et al. Sci Transl Med 2011;3:99ra86

Heracles-Trial: Trastuzumab + Lapatinib in HER2 +++ refractory CRC (Siena, S. et al.)

- 5% of pts
- N=23



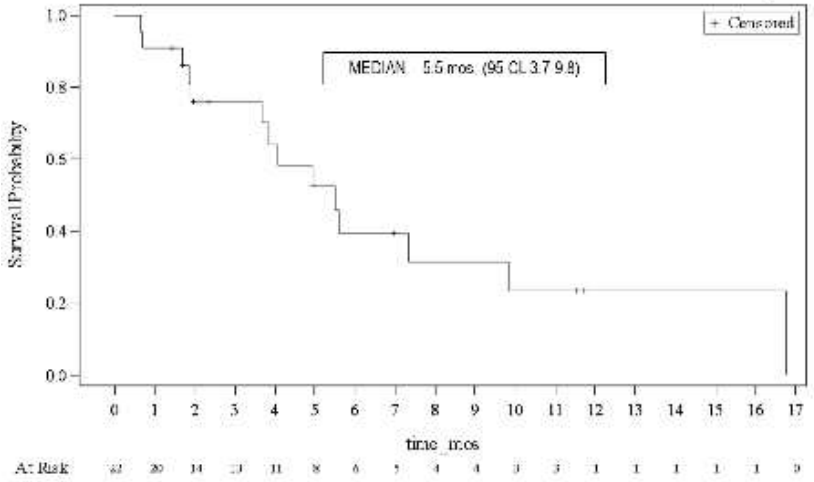




Heracles-Trial: Trastuzumab + Lapatinib in HER2 +++ refractory CRC (Siena, S. et al.)

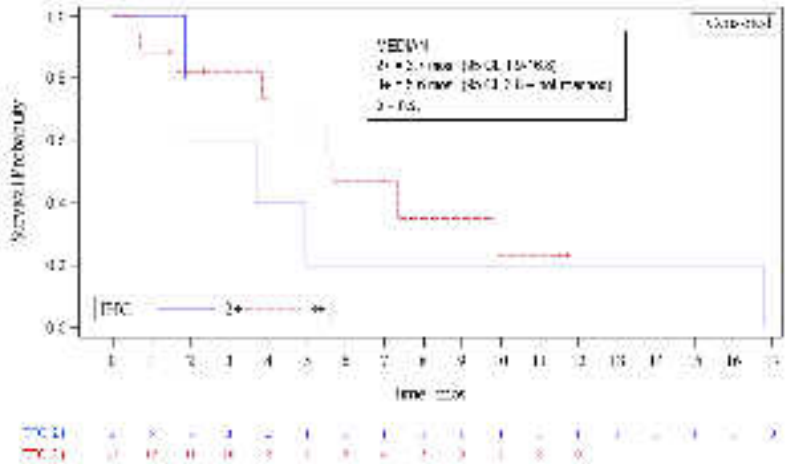
TIME TO PROGRESSION ALL PATIENTS

J1



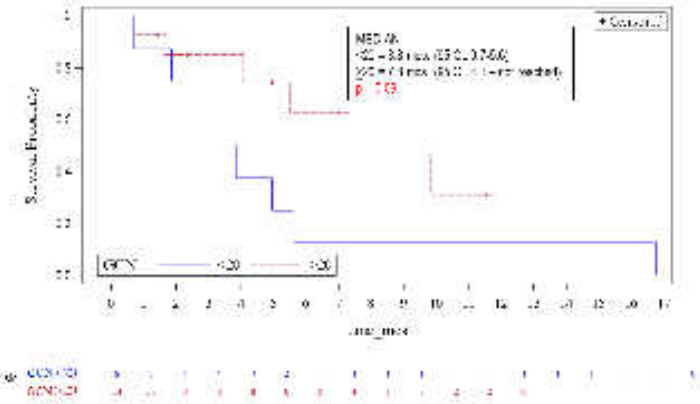
TIME TO PROGRESSION BY HER2 IHC SCORE

J2



TIME TO PROGRESSION BY HER2 GENE COPY NUMBER

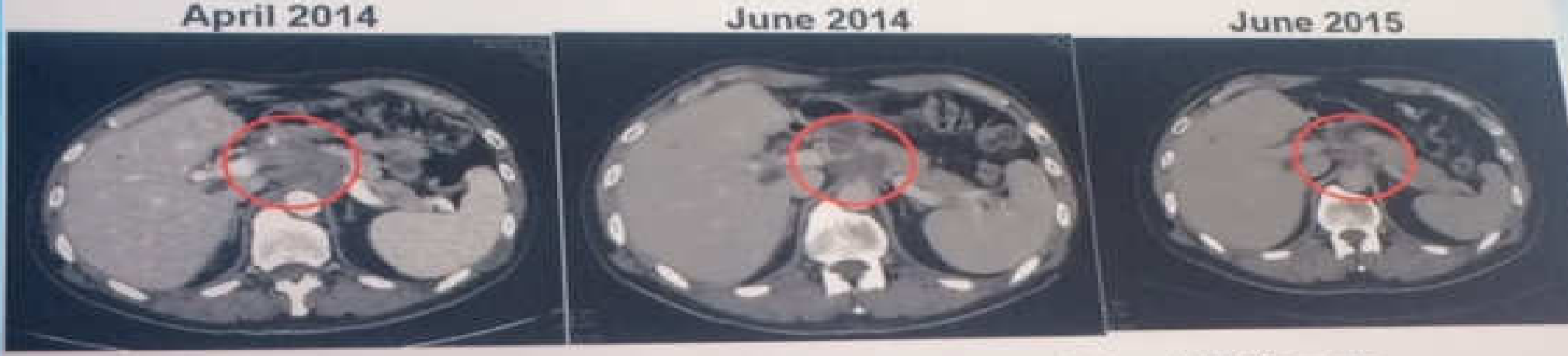
J3



ecco

Response in a Patient With MSI-H CRC

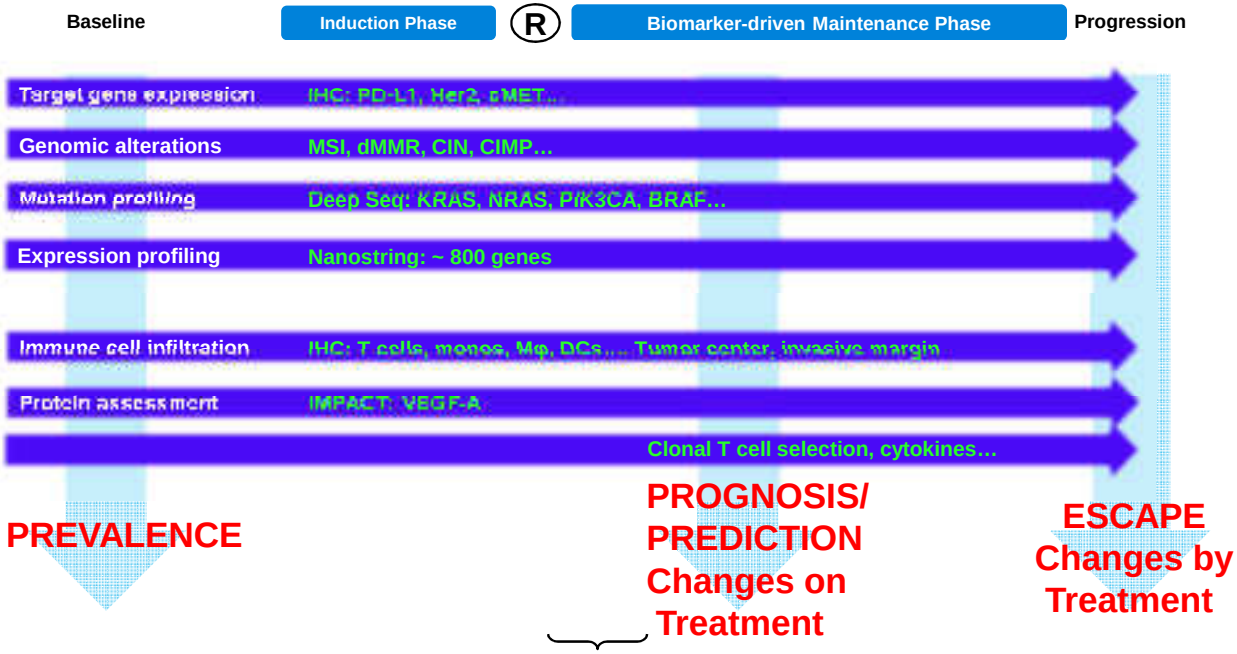
- Male aged 54 years, prior treatment with FOLFOX + cetuximab (with rapid progression) and FOLFIRI + bevacizumab with SD as best response.
- Presented with back pain secondary to celiac adenopathy
- Stereotactic core biopsy showed loss of *MLH1* by IHC, MSI-H confirmed by PCR, and *BRAF* mutation positive consistent with hypermethylation of *MLH1* promoter



- Given stable abnormalities, patient recently underwent excision of left SC node
- Pathology report: lymph node tissue with extensive necrosis, xanthogranulomatous inflammation, and foreign body giant cell reaction

SCREEN Exploratory Biomarker Plan

Methods



Inform development beyond SCREEN

Inform disease understanding

Variations in genes regulating tumor-associated macrophages (TAMs) to predict outcomes of bevacizumab-based treatment in patients with metastatic colorectal cancer: results from TRIBE and FIRE3 trials

Y. Sunakawa[1,2*], S. Stintzing[3], S. Cao[4], V. Heinemann[3], C. Cremolini[5], A. Falcone[5], D. Yang[4], W. Zhang[1], Y. Ning[1], S. Stremitzer[1], S. Matsusaka[1], S. Yamauchi[1], A. Parekh[1], S. Okazaki[1], M. D. Berger[1], S. Graver[6], A. Mendez[1], S. J. Scherer[6], F. Loupakis[5] & H.-J. Lenz[1]

[1]Division of Medical Oncology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, USA; [2]Division of Medical Oncology, Department of Internal Medicine, Showa University Northern Yokohama Hospital, Yokohama, Japan; [3]Department of Hematology and Oncology, Klinikum der Universität München, Munich, Germany; [4]Department of Preventive Medicine, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, USA; [5]U.O. Oncologia Medica, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy; [6]Department of Physiological Chemistry, Biocenter, University of Wuerzburg, Wuerzburg, Germany

Received 19 July 2015; revised 8 September 2015; accepted 18 September 2015

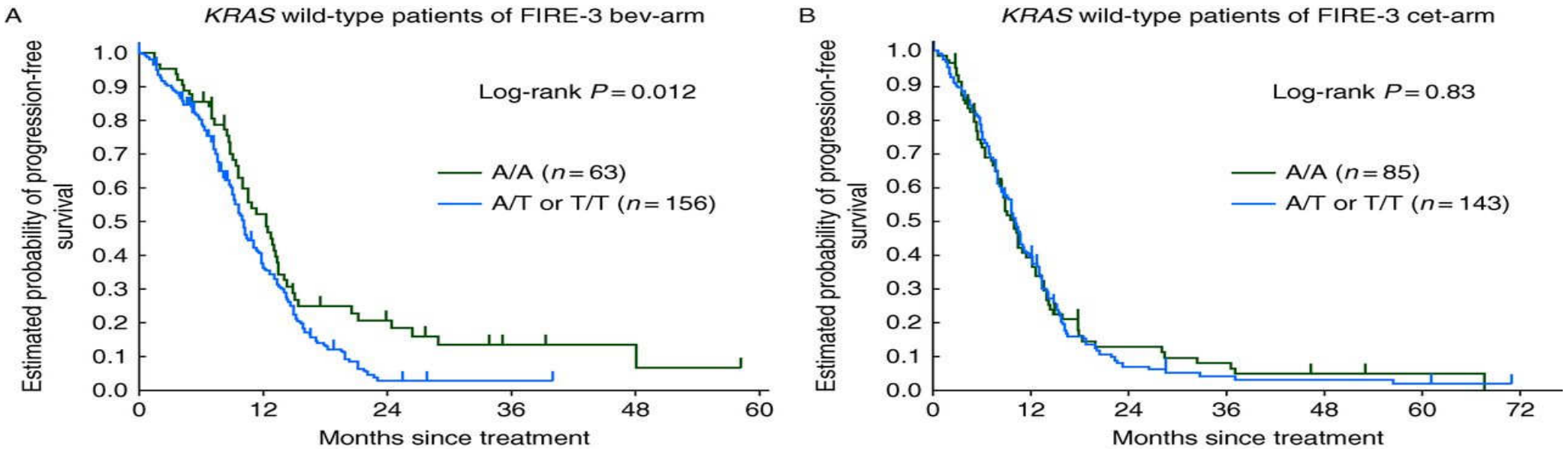
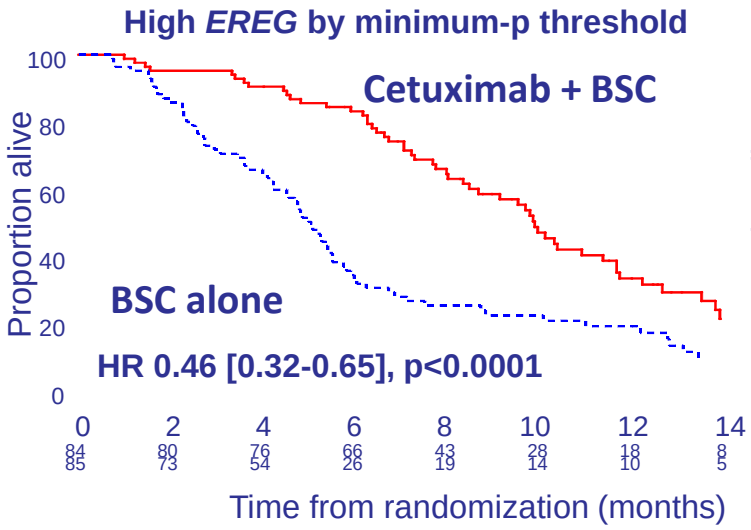


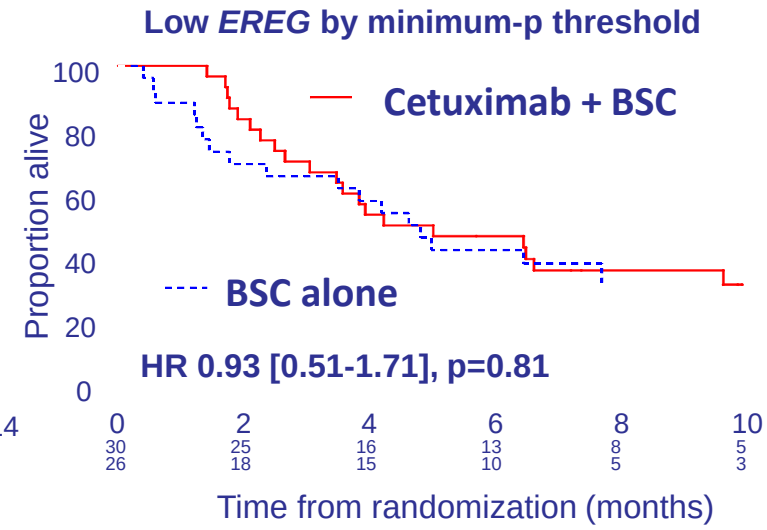
Figure 1. Probability of progression-free survival by *TBK1* rs7486100 in *KRAS* exon2 wild-type patients of FIRE-3 cohorts, (A) bevacizumab arm, (B) cetuximab arm.

Ann Oncol. 2015 Sep 28. pii: mdv474

Ligands: AREG, EREG, TGFalpha

- Combimarker: *K-Ras* wt and high EREG
  - Pre-especified threshold[1]
  - Minimum threshold: 169/384 (44%)
    - All comers → 394 (100%) HR: 0.7
    - K-Ras wt → 230 (58%) HR: 0.55
    - Combimarker → 169 (44%) HR: 0.46





[1]Khambata-Ford, S. et al. J Clin Oncol; 25:3230-3237, 2007
[2]Jonker, D et al. Proc ASCO 2009

A genetic variant in Rassf1a, a key regulator of Hippo pathway, predicts survival in two independent cohorts of mCRC patients treated with cetuximab-based chemotherapy

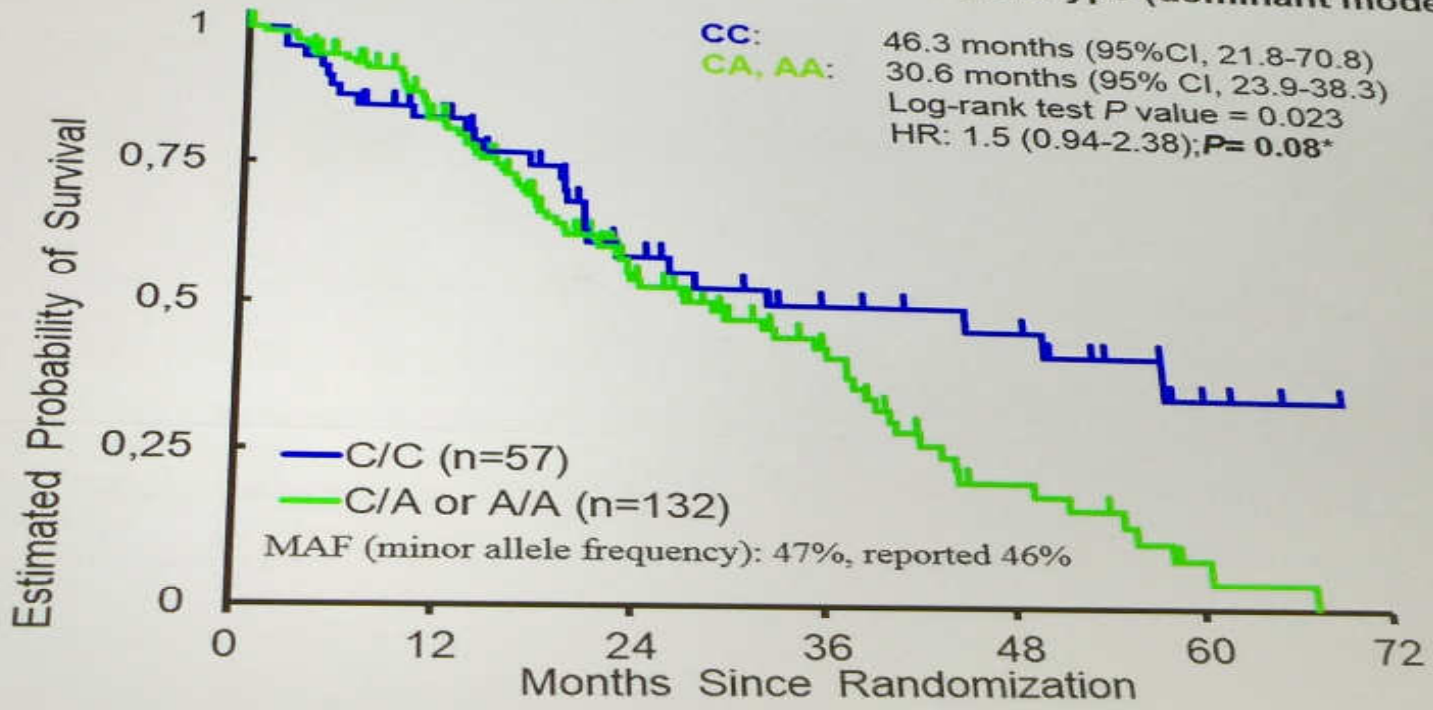
A. Sebio, S. Stintzing, V. Heinemann, W. Zhang, Y. Sunakawa, W. Ichikawa, A. Tsuji, T. Takahashi, A. Parek, D. Yang, S. Cao, Y. Ning, S. Stremitzer, S. Matsusaka, S. Okazaki, A. Barzi, Heinz-Josef Lenz

Santa Creu i Sant Pau Hospital, Barcelona, Spain

USC/Norris Cancer Center, Los Angeles, USA

Rassf1a rs2236947 associated with OS in wt Ras Fire3 (FOLFIRI/CET)

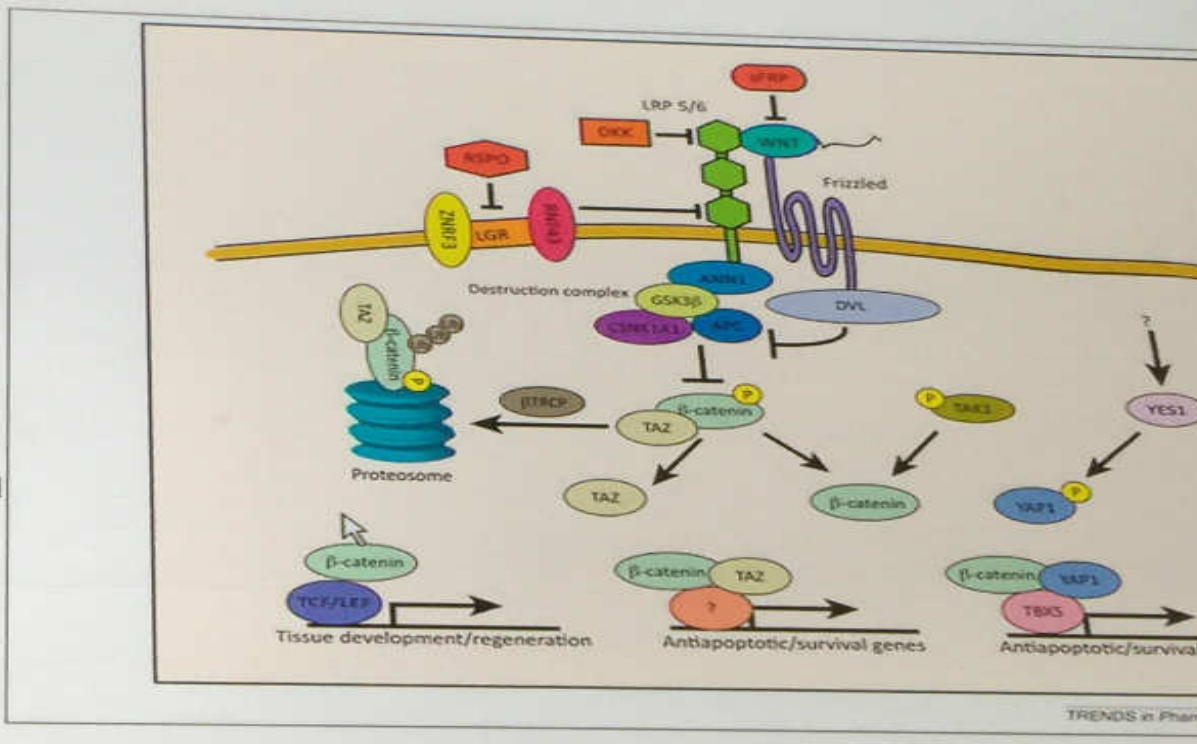
- 189 Ras wild-type patients (pts) from Fire-3 (FOLFIRI +Cetuximab arm)
- Overall Survival according to Rassf1a rs2236947 genotype (dominant model)



*Wald test in the multivariable Cox Regression model adjusting for sex, ECOG, and number of metastatic sites

AXIN1 and colorectal cancer

- The Wnt signaling is central to the biology of colorectal cancer
- AXIN1 and APC function in the assembly of a β-catenin destruction complex. Degradation of β-catenin is a key regulated step of the Wnt pathway
- AXIN1 acts as a tumor suppressor



Rosenbluh J, Trends Pharmacol Sci 2014

Genome-wide association study
ECCO/ESMO 2015 Vienna

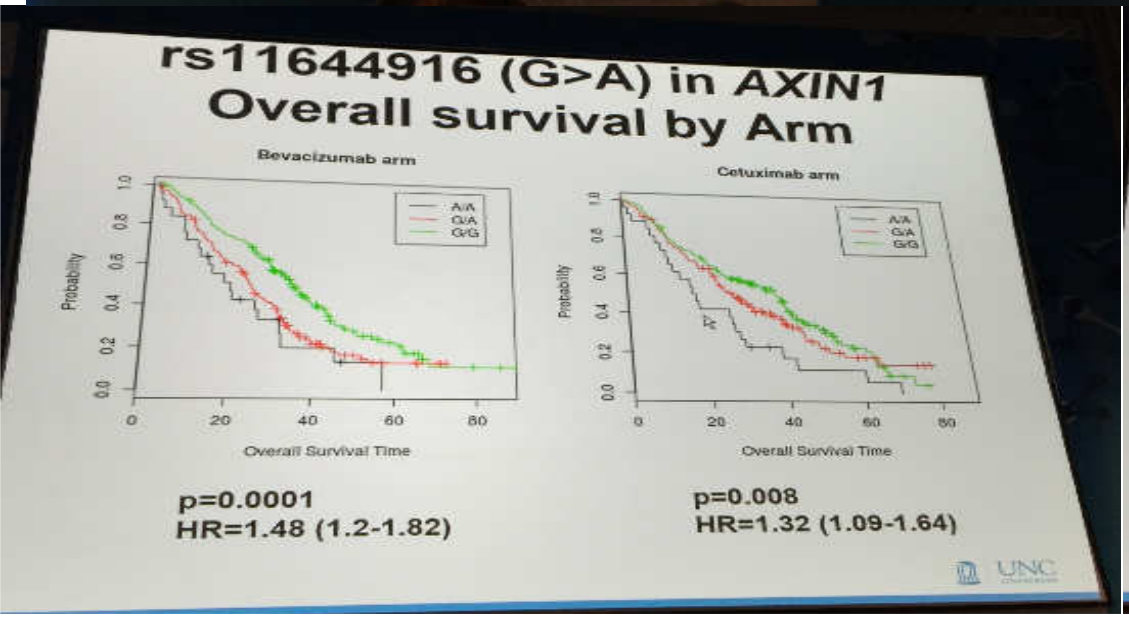
CALGB-Trial + FIRE III- Trial

		All Patients (N=1137)		GWAS Patients (N=609)	
		ARM A Chemo+BEV	ARM B Chemo+CETUX	ARM A Chemo+BEV	ARM B Chemo+CETUX
Sex	Male	348	349	189	187
	Female	211	229	120	113
Age	Median	59	59	59	59
	Range	22-85	21-90	22-84	23-84
Non-Caucasian		40	48	-	-
Primary in place		160	133	87	64
FOLFOX / FOLFIRI		245/79	256/90	157/45	155/47
Palliative Intent		466	459	258	236
Prior Radiation		81	79	46	33
Prior Adjuvant Chemo		50	52	33	26

Median OS in genotyped patients 29.6 months [95% CI: (26.9, 32.6), range: 0.46-73.72]

UNC

rs11644916 (G>A) in *AXIN1*
Overall survival by Arm

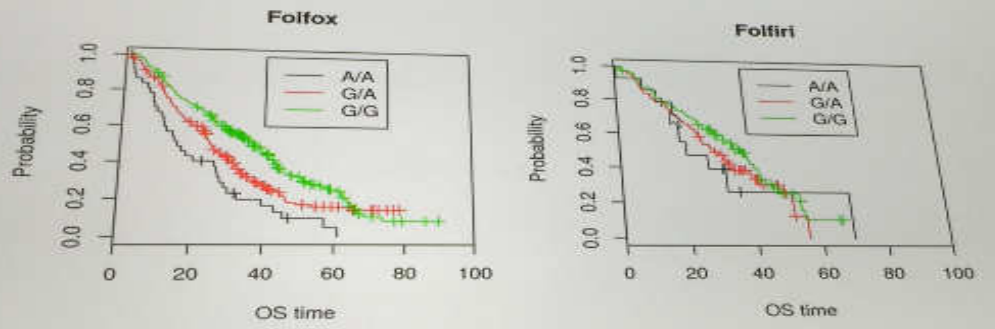


p=0.0001
HR=1.48 (1.2-1.82)

p=0.008
HR=1.32 (1.09-1.64)

UNC

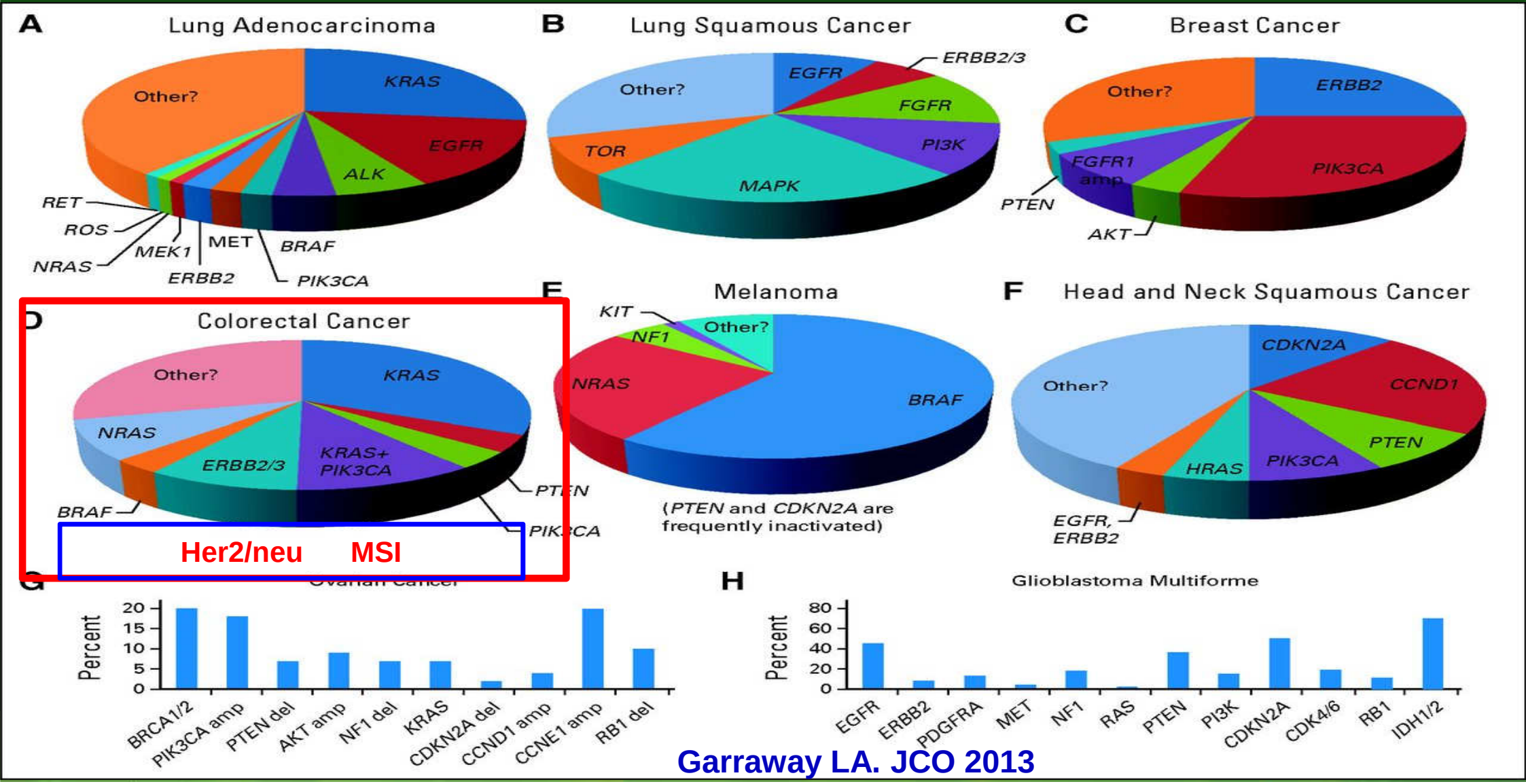
rs11644916 (G>A) in *AXIN1*
Overall survival by chemo



p=3.89x10^{-6}
HR=1.48 (1.25-1.74)

p=0.26
HR=1.19 (0.88-1.60)

All cancers are becoming rare cancers



Garraway LA. JCO 2013

FOCUS 4 trial design

N=1550

Start 2013

MRC Clinical Trials Unit

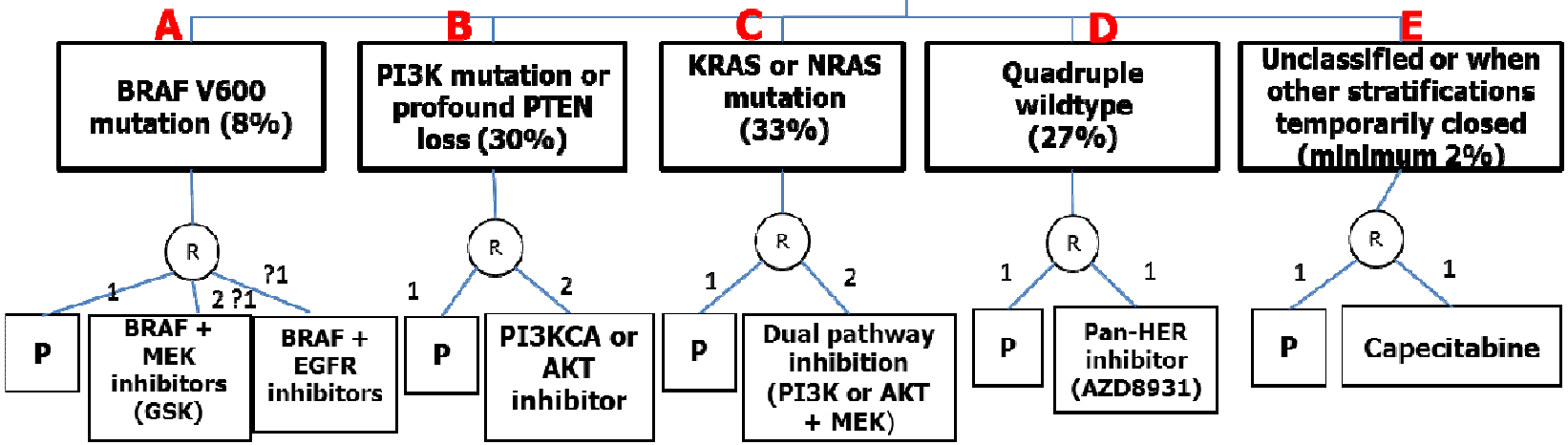
Eligible pts: 1st line mCRC
Fit for chemo, platelets < 400k
consent to biomarker analysis

Any standard chemo
16 weeks
(response = SD, PR or CR)

Biomarker panel
on FFPE tumour block
B-RAF, K-RAS, NRAS, PI3K mutation;
EREG, DUSP4/6 mRNA; DNA MMR, PTEN IHC

Optional biopsy of metastatic site

Consents to stratified randomisation



On progression - recommence first line chemotherapy

Stage II/III primary outcome measure: PFS between randomisation to interval therapy (recommence 1st line chemo)

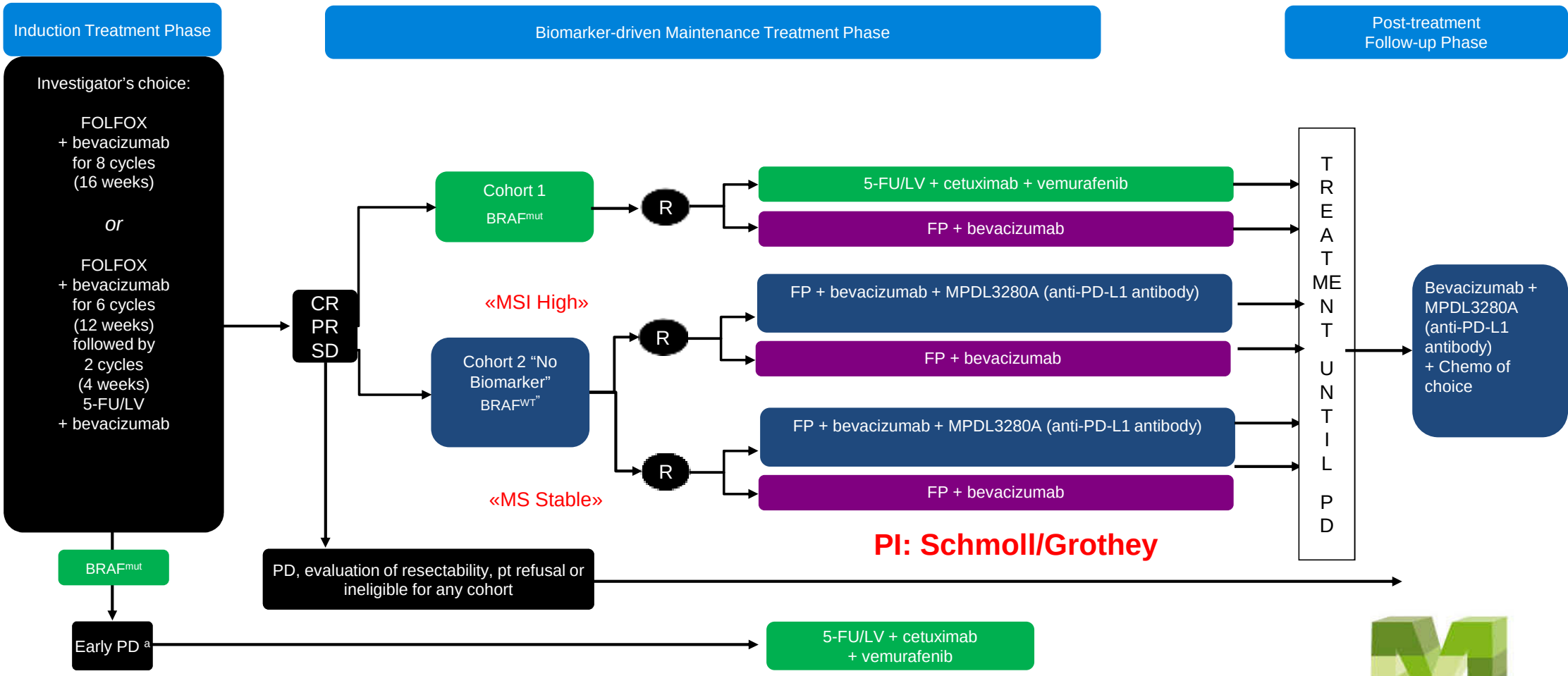
Decision points for each stratified cohort:
- 1st, 2nd and 3rd interim analyses for Lack of Activity (based on PFS)
- 4th analysis for PFS efficacy (target HR 0.5 or 0.65 depending on cohort/agent)

PFS: HR= 0.65

For biomarker selected cohorts that pass 3rd PFS Lack of Activity stage ($\alpha = 0.1$): test specificity of biomarker selection in a separate cohort of patients *without* the selection biomarker

For larger cohorts that pass 4th PFS Efficacy stage: Continue to phase III with final efficacy analysis on an OS endpoint

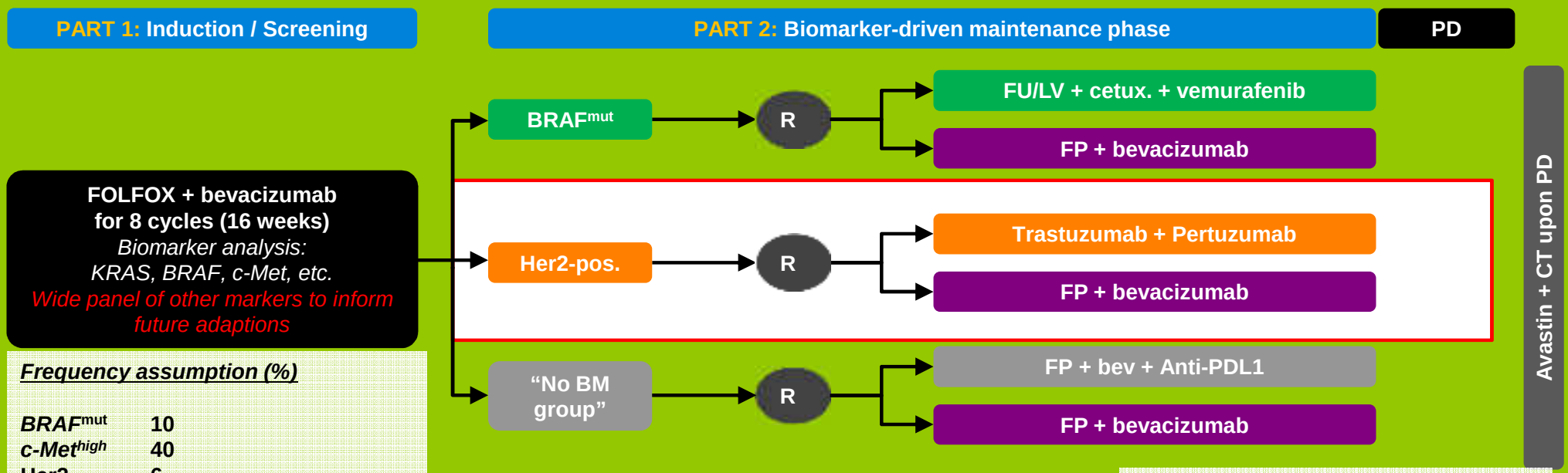
MODUL "NEW" COHORT Proposals 09 2015
-> prospective stratification for "MSI+" + NGS



FP = fluoropyrimidine (5-FU or capecitabine)

a. Patients who progress early and who are not BRAF^{mut} will enter the Post-treatment Follow-up Phase with initiation of 2nd-line treatment per Investigator discretion

MODUL Update of HER2 pos. cohort



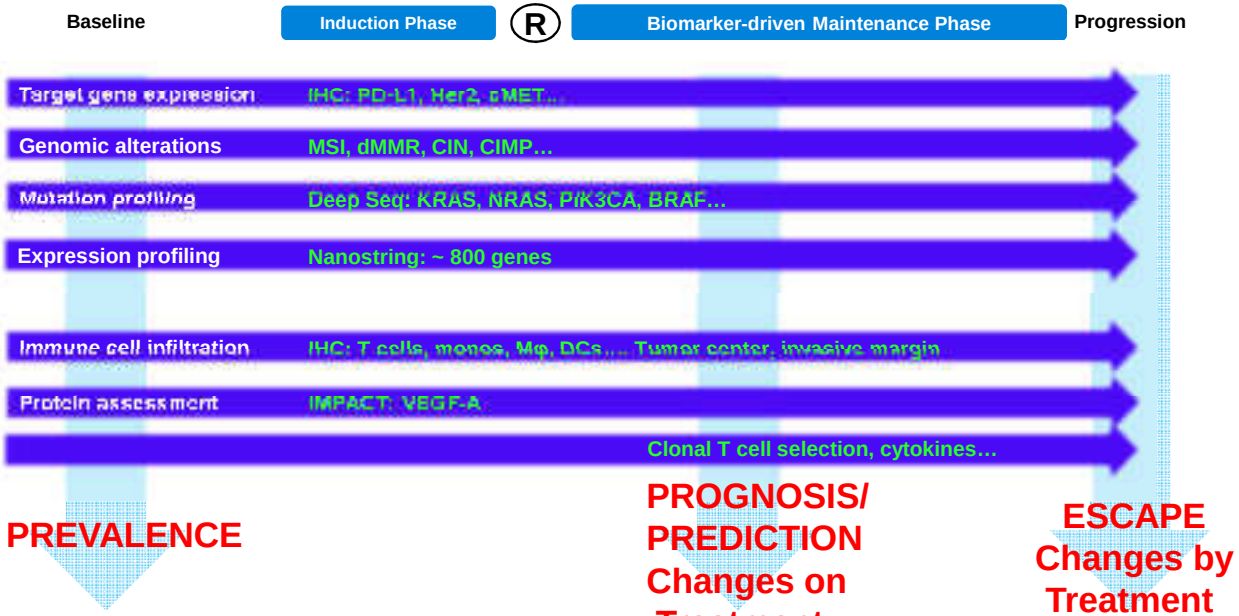
- **Sponsor: Roche, in close collaboration with international study groups**
- 1600+ patients to be randomised, open depending on future adaptions
- Primary EP: Early Response (Waterfall Plots) and PFS (Phase 2 level investigation for each randomisation); Secondary EP: OS, ORR, safety, QoL, biomarker, etc

Suggesting dosing: (***According to MyPathway Study NCT02091141***):

- **Pertuzumab** 840 mg IV loading dose, then 420 mg IV Q3W
  +
- **Trastuzumab** 8 mg/kg IV loading dose, then 6 mg/kg, IV Q3W

SCREEN Exploratory Biomarker Plan

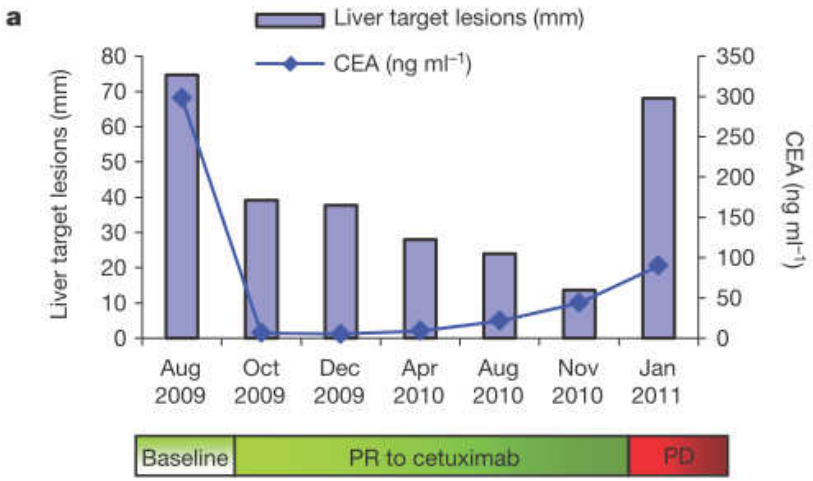
Methods



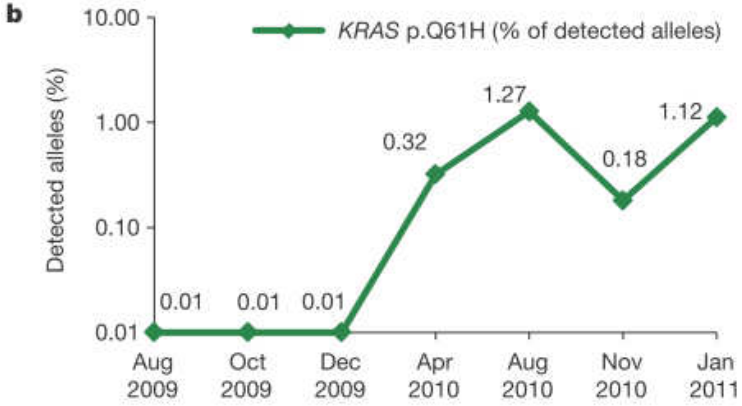
Inform development beyond SCREEN
Inform disease understanding

KRAS mut/ampl under pressure

Initial response to cetuximab followed by PD

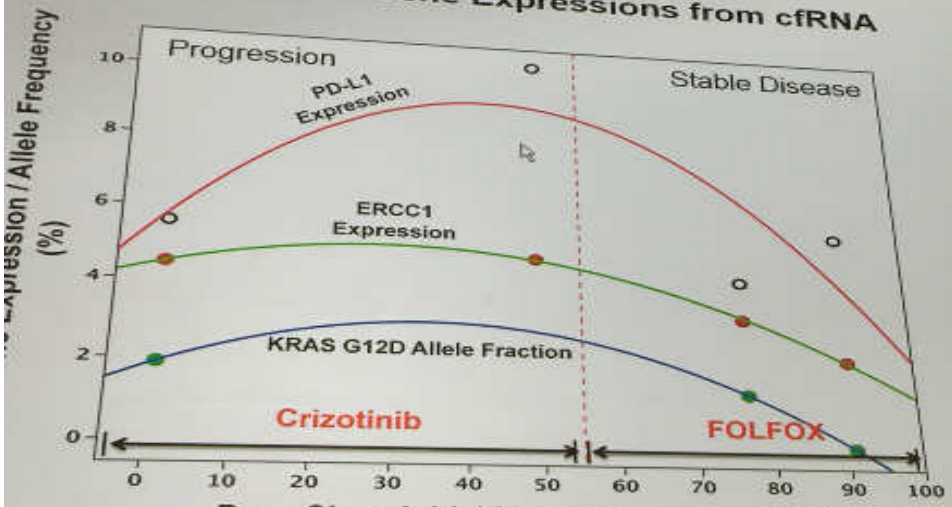


Quantitative analysis of KRAS(Q61H) mutant DNA in plasma, as assessed by BEAMing

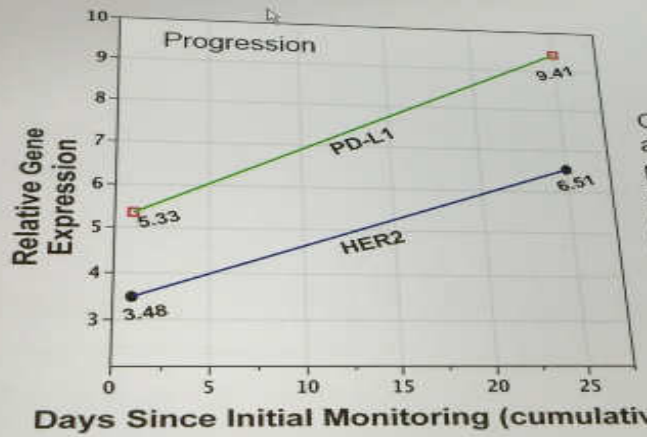


Misale S, et al. Nature 2012
Diaz E, et al. Nature 2012

RC Patient : KRAS Mutation AF% and Relative Gene Expressions from cfRNA



Gastric Patient: HER2 Negative by FISH:



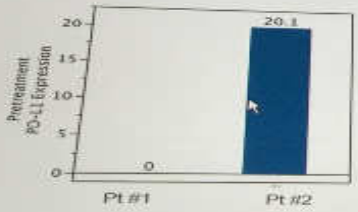
Cell-free RNA analysis provides two additional targets for therapy.

…parallel, PD-L1 and HER2 relative gene expressions nearly double in 25-day …erval

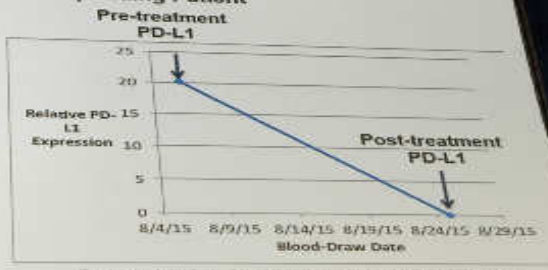
Cell-Free RNA Analysis: NSCLC

Measurement of Relative Expression of PD-L1 in Cancer Patient's Plasma from cfRNA

Positive PD-L1 cfRNA and response to nivolumab



Expected decrease in PD-L1 during treatment for Responding Patient



Danenberg, K., et al, IASLC Presentation, Sept. 2015

Summary: Transitioning from Tissue to Blood

Testing must consist of DNA and RNA components

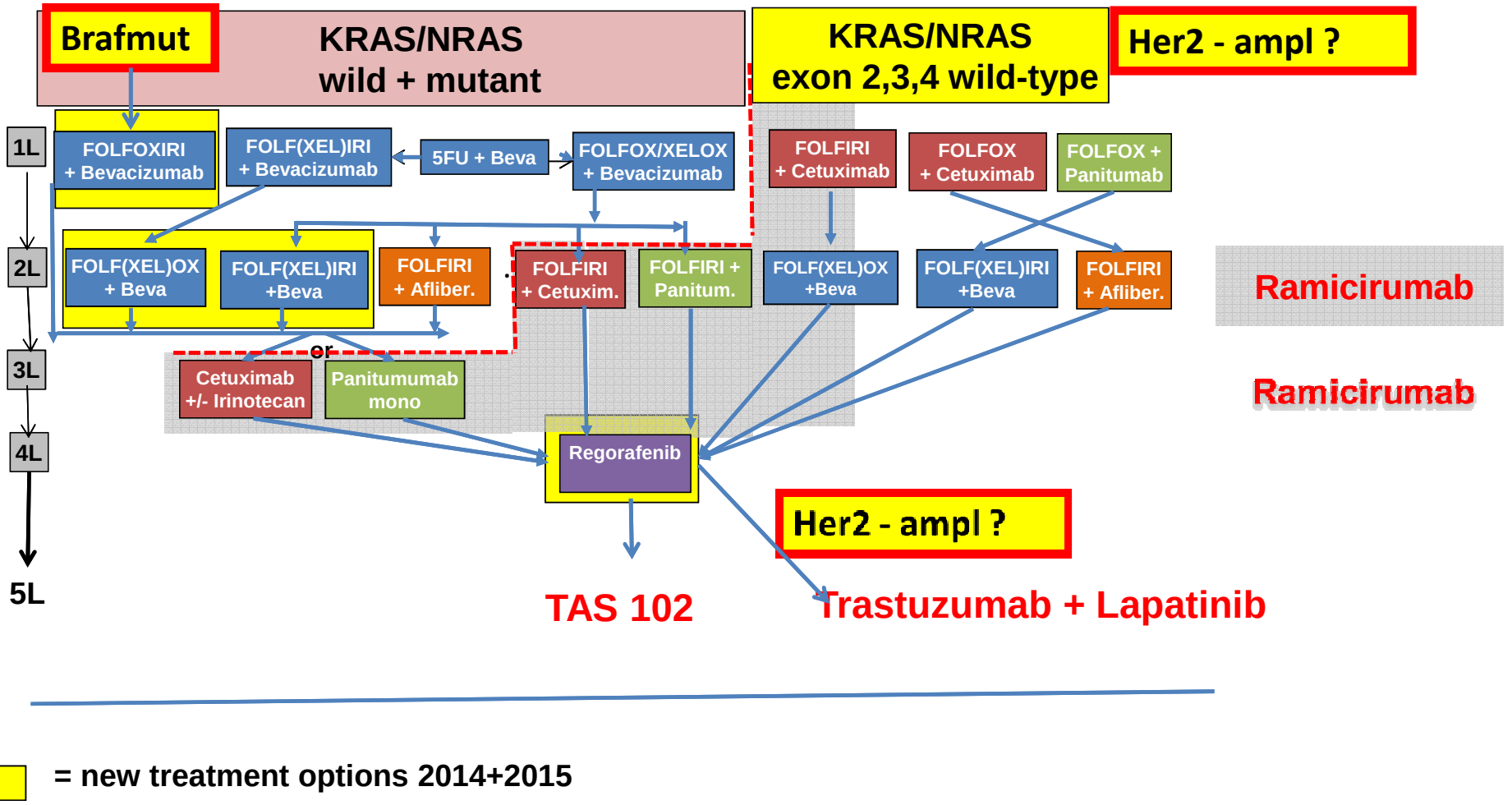
DNA Mutations — Replace Tissue Based DNA Mutation Tests with Cell-Free DNA Blood Tests

RNA Expression — Replace Tissue - IHC and FISH Tests with Cell-Free RNA Blood Tests

From ambient temperature shipped blood

CRC Treatment Algorhythm 2015

modif. from: Schmoll, HJ & Stein, A: Nature Reviews Clin Oncol 2/2014



= new treatment options 2014+2015