Current status of the treatment of metastatic colorectal cancer with EGFR inhibitors

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Ospedale Niguarda Cancer Center

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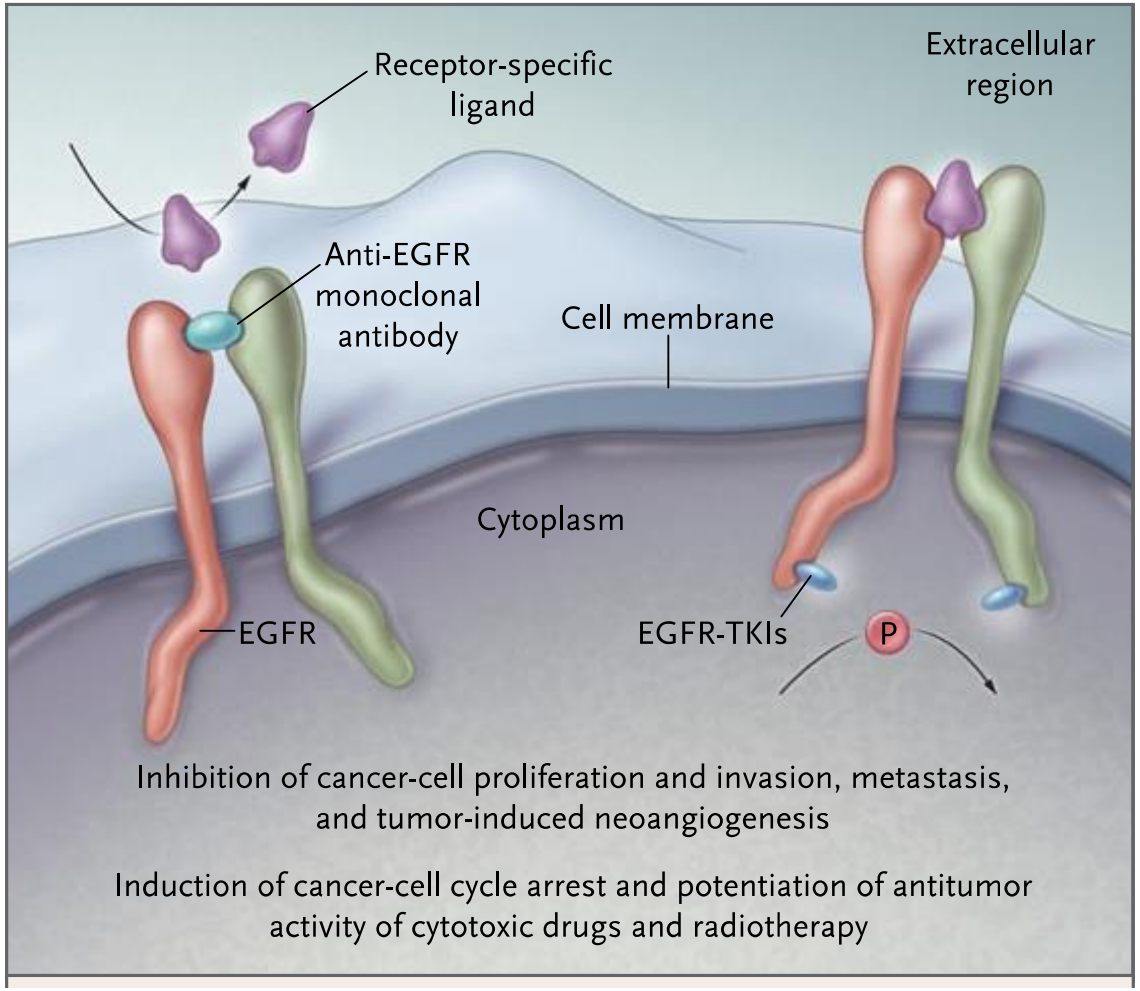
Regione Lombardia

UNIVERSITÀ DEGLI STUDI DI MILANO

DISCLOSURE SLIDE

- Advisory board member for Amgen, Bayer, Eli Lilly, Merck, Merrimack, Novartis, Roche, Sanofi.

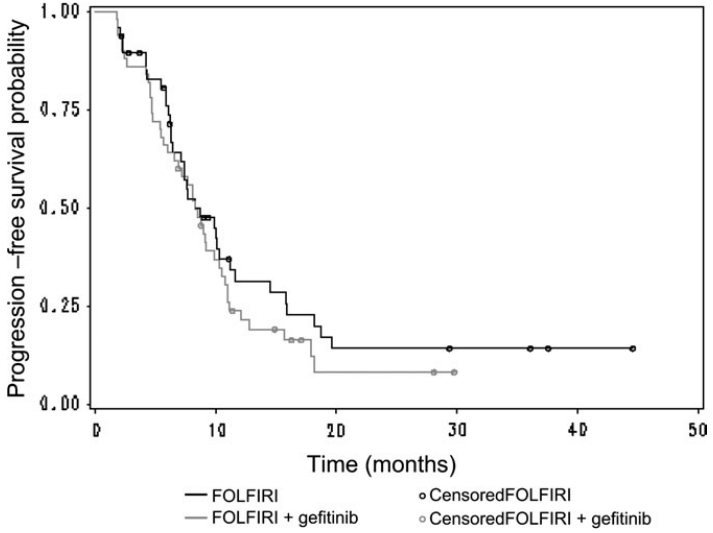
The two classes EGFR inhibitors developed for cancer therapy

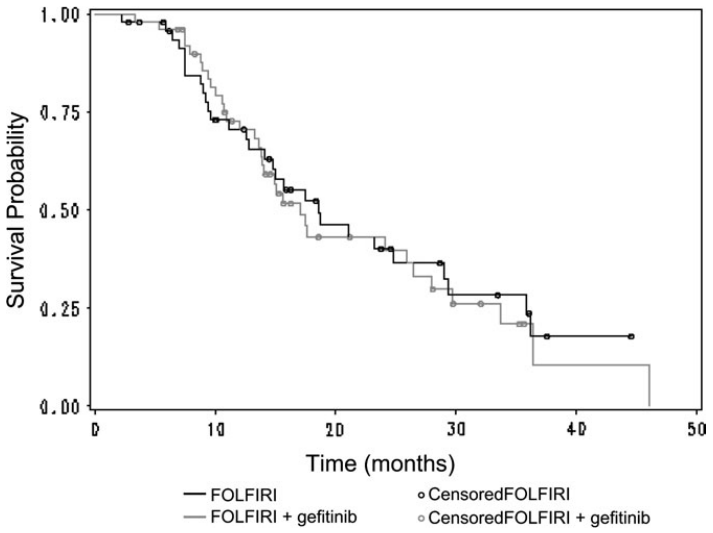


Ciardiello F. & Tortora G., NEJM 2008

A phase II randomized multicenter trial of gefitinib + FOLFIRI versus FOLFIRI in mCRC (designed in 2002)

	FOLFIRI (N = 48)		FOLFIRI + gefitinib (N = 51)	
	No.	%	No.	%
Overall response (CR + PR)	23	47.9	23	45.1
Stable disease	17	35.4	18	35.3
Disease control (CR + PR + SD)	40	83.3	41	80.4
Progressive disease	6	12.5	9	17.6
Not evaluable	2	4.2	1	2.0





Santoro et al, Ann Oncol 2008

Main EGFR-targeted monoclonal antibodies tested in the clinical setting

Denomination	Ig Isotype	Fraction of human Ig	ADCC
Cetuximab (C-225)	IgG_1	70% chimeric	+
Matuzumab (EMD72000)	IgG_1	90% humanized	+
Nimotuzumab (h-R3)	IgG_1	90% humanized	+
Necitumumab (LY3012211)	IgG_1	100% fully human	+
Zalutumumab (HuMax-EGFr)	IgG_1	100% fully human	+
Panitumumab (ABX-EGF)	IgG_2	100% fully human	-

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Zalutumumab (HuMax-EGFr)	IgG_1	100% fully human	+
Panitumumab (ABX-EGF)	IgG_2	100% fully human	-

European Medicines Agency (EMA) indications of EGFR-inhibitors for metastatic colorectal cancer in 2016

4.1 Therapeutic indications

Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer

- in combination with irinotecan-based chemotherapy,
- in first-line in combination with FOLFOX,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000558/WC500029119.pdf
accessed on February 28, 2016

4.1 Therapeutic indications

Vectibix is indicated for the treatment of adult patients with wild-type *RAS* metastatic colorectal cancer (mCRC):

- in first-line in combination with FOLFOX or FOLFIRI.
- in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).
- as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000741/WC500047710.pdf
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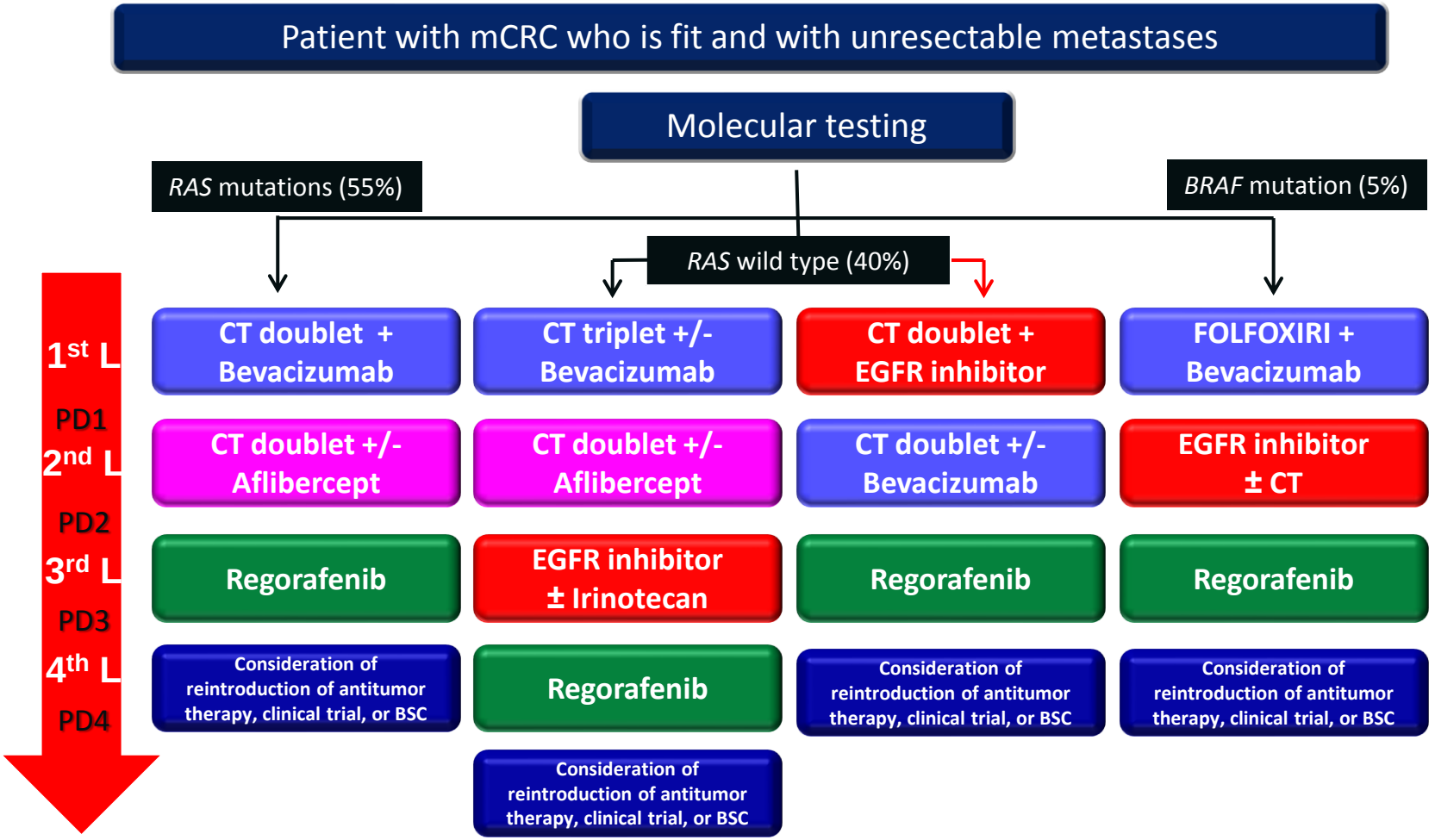
An algorithm for the medical management of mCRC based on clinical and molecular assessments



BSC, best supportive care; CT, chemotherapy; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; PD, progressive disease; VEGF, vascular endothelial growth factor; VEGF inhibitor, bevacizumab or aflibercept.

Adapted from Sridharan M, et al. http://www.cancernetwork.com/oncology-journal/colorectal-cancer-how-emerging-molecular-understanding-affects-treatment-decisions. 2014.

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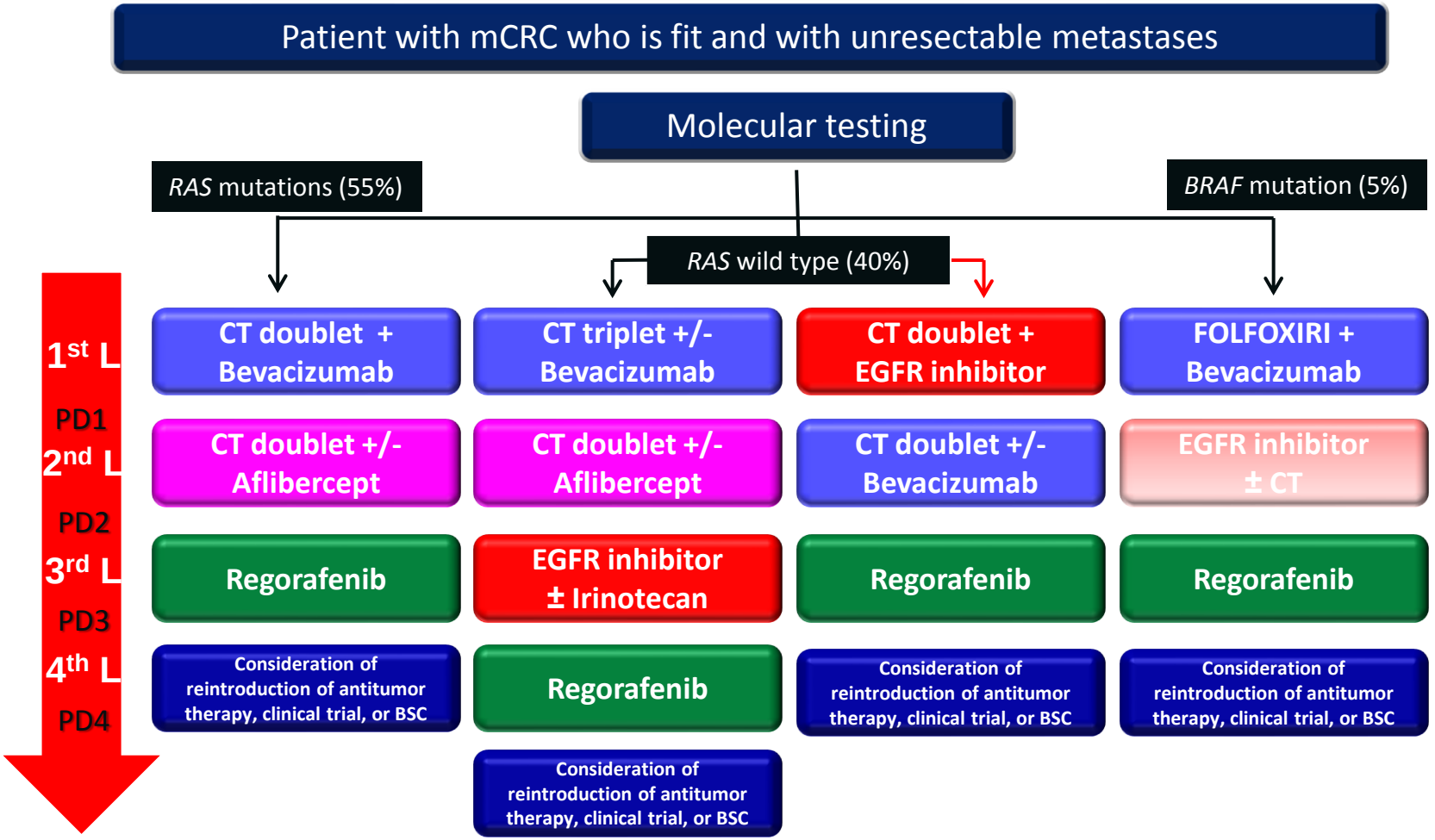

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Current (2016) status of the treatment of mCRC with EGFR inhibitors

- Do panitumumab and cetuximab differ?
  - Anti-tumor effects
  - Side effects
  - Resistance
- Optimal use of EGFRi in the continuum of care
  - Combined with companion chemotherapy or monotherapy
  - First line versus subsequent lines of treatment(s)
  - Sequencing with anti-angiogenesis agent(s)
  - Rationale for repeated therapy (rechallenge with EGFRi)

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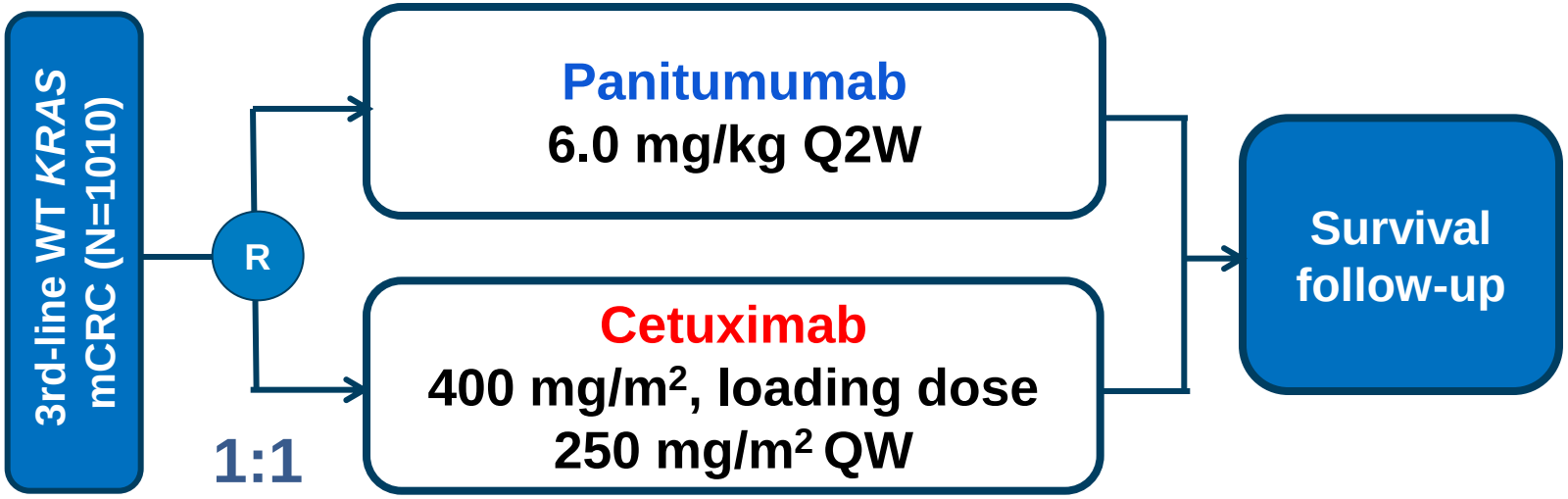
ASPECCT: phase 3 study of panitumumab versus cetuximab in previously treated WT *KRAS* mCRC

3rd-line, non-inferiority design



Primary endpoint: overall survival (OS)

Key secondary endpoints:

- **Progression-free survival (PFS)**
- **Objective response rate (ORR)**
- **Safety**

Plasma samples were collected for biomarker analysis = liquid biopsy

Price et al, Lancet Oncol 2014

ASPECCT: phase 3 study of panitumumab versus cetuximab in previously treated WT *KRAS* mCRC

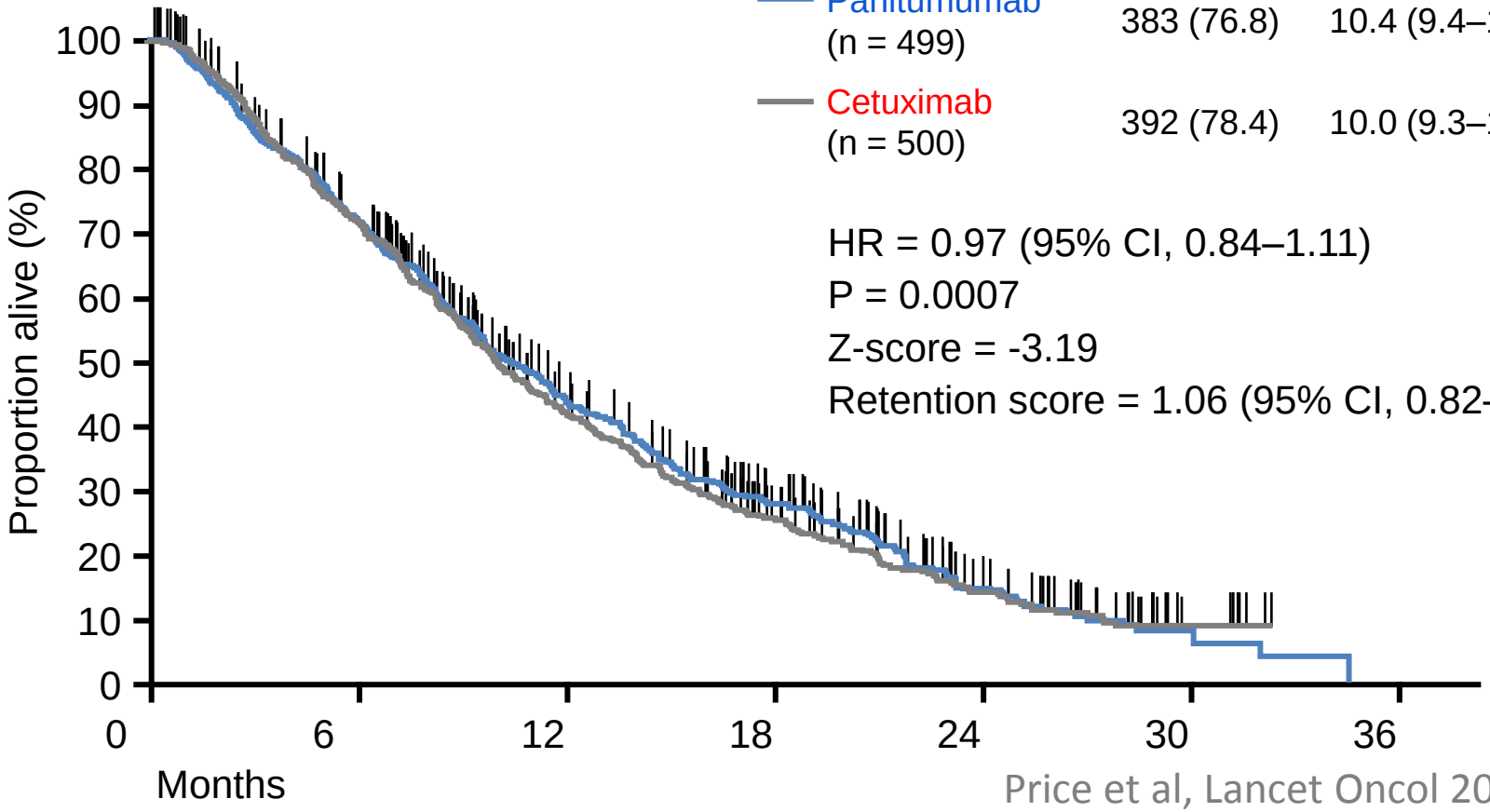
Efficacy	Panitumumab	Cetuximab	Hazard/odds ratio
Median OS, months (95% CI)	10.4 (9.4 - 11.6)	10.0 (9.3 - 11.0)	HR=0.97 (0.84 - 1.11)
Median PFS, months (95% CI)	4.1 (3.2 - 4.8)	4.4 (3.2 - 4.8)	HR=1.00 (0.88 - 1.14)
ORR, % (95% CI)	22.0 (18.4 - 26)	19.8 (16.3 - 23.6)	OR=1.15 (0.83 - 1.58)

Panitumumab was assessed to be non-inferior to cetuximab for OS based on a ≥50% retention rate of the OS benefit of cetuximab (*P* = 0.0007)

Price et al, Lancet Oncol 2014

ASPECCT: phase 3 study of panitumumab versus cetuximab in previously treated WT *KRAS* mCRC

Overall Survival



	Events n (%)	Median (95% CI) months
Panitumumab (n = 499)	383 (76.8)	10.4 (9.4–11.6)
Cetuximab (n = 500)	392 (78.4)	10.0 (9.3–11.0)

HR = 0.97 (95% CI, 0.84–1.11)
P = 0.0007
Z-score = -3.19
Retention score = 1.06 (95% CI, 0.82–1.29)

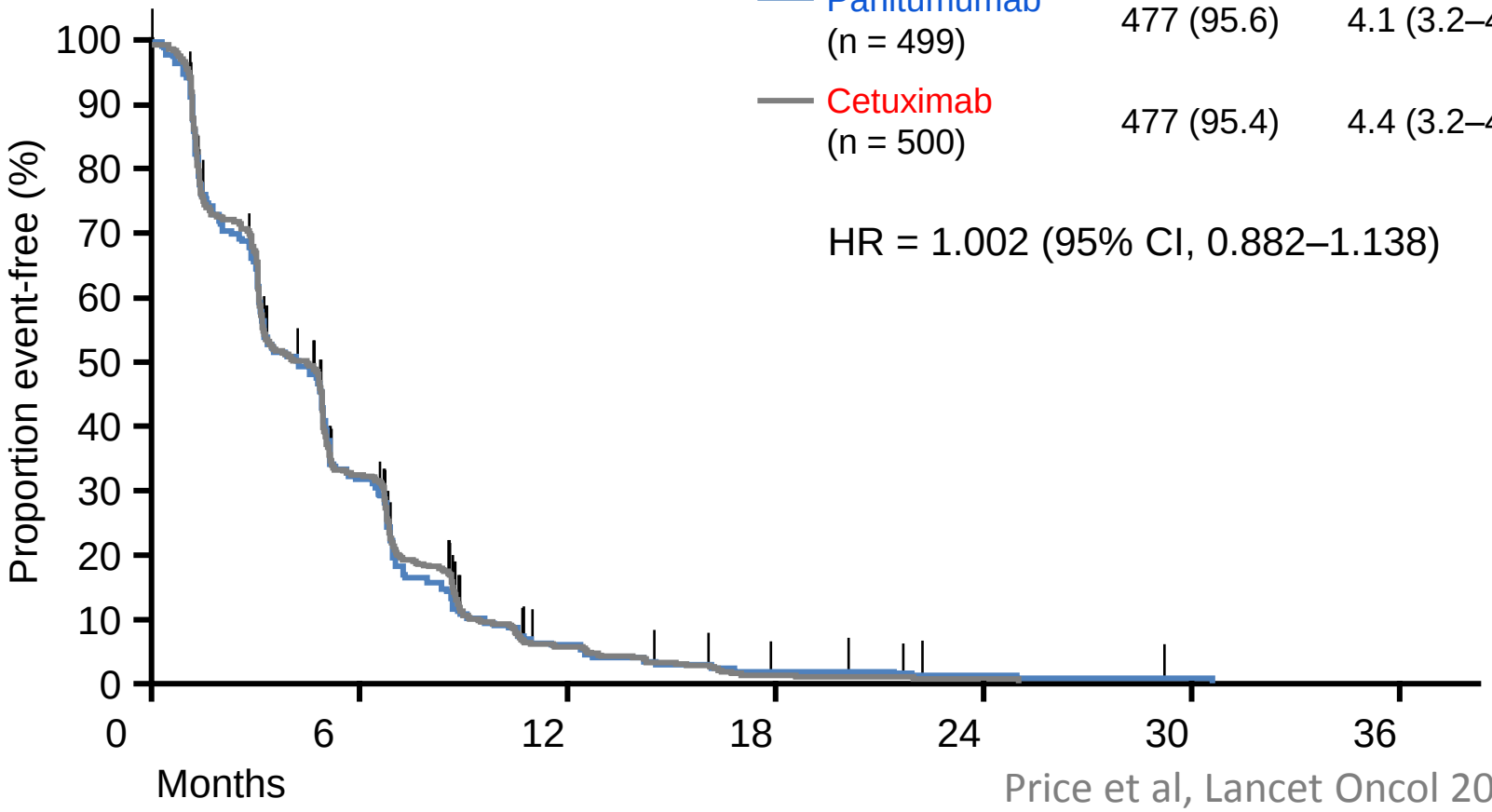
Price et al, Lancet Oncol 2014

ASPECCT: phase 3 study of panitumumab versus cetuximab in previously treated WT *KRAS* mCRC

Progression Free Survival

	Events n (%)	Median (95% CI) months
Panitumumab (n = 499)	477 (95.6)	4.1 (3.2–4.8)
Cetuximab (n = 500)	477 (95.4)	4.4 (3.2–4.8)

HR = 1.002 (95% CI, 0.882–1.138)



Price et al, Lancet Oncol 2014

ASPECCT: phase 3 study of panitumumab versus cetuximab in previously treated WT *KRAS* mCRC

Adverse events	Panitumumab		Cetuximab	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Infusion reactions, %	2.8	0.2	12.5	1.8
Skin toxicity, %	87	12.5	88	9.5
Hypomagnesaemia, %	29	7.3	19	2.6

Price et al, Lancet Oncol 2014

Current (2016) status of the treatment of mCRC with EGFR inhibitors

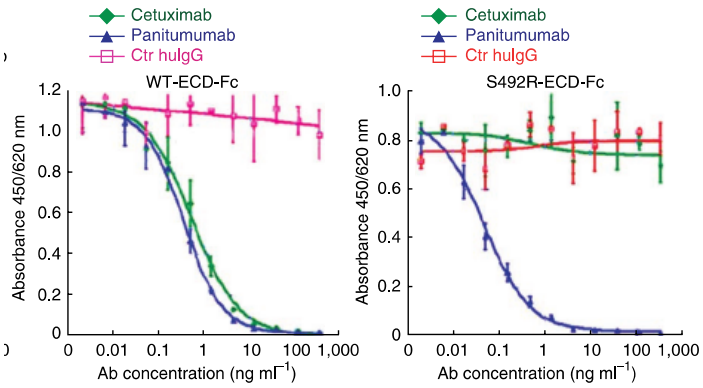
- Do panitumumab and cetuximab differ?
  - Anti-tumor effects: not different in EGFRi naive
  - Side effects: different in acute reactions and hypoMg
  - **Resistance**
- Optimal use of EGFRi in the continuum of care
  - Combined with companion chemotherapy or monotherapy
  - First line versus subsequent lines of treatment(s)
  - Sequencing with anti-angiogenesis agent(s)
  - Rationale for repeated therapy (rechallenge with EGFRi)

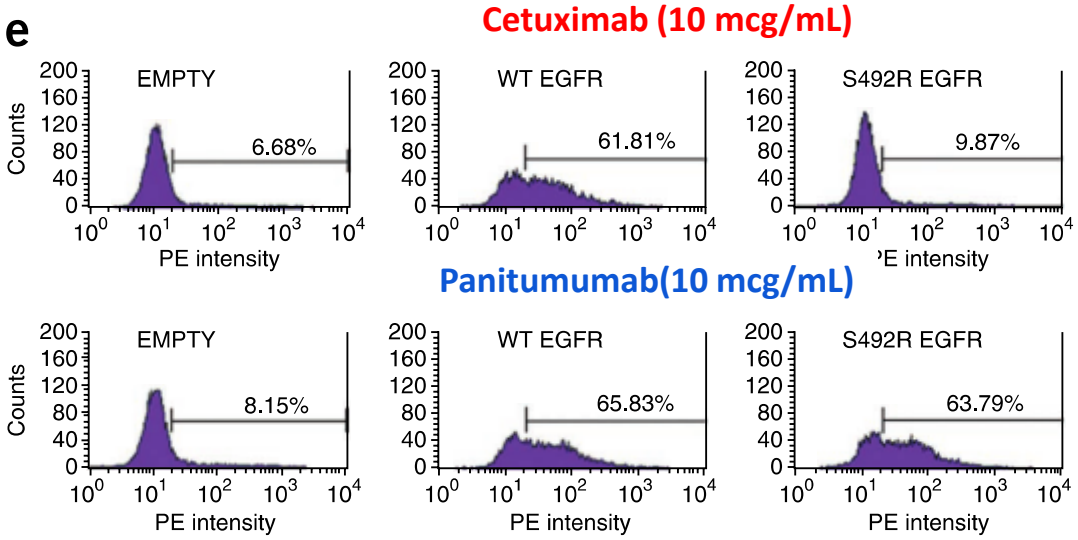
NATURE MEDICINE VOLUME 18 | NUMBER 2 | FEBRUARY 2012

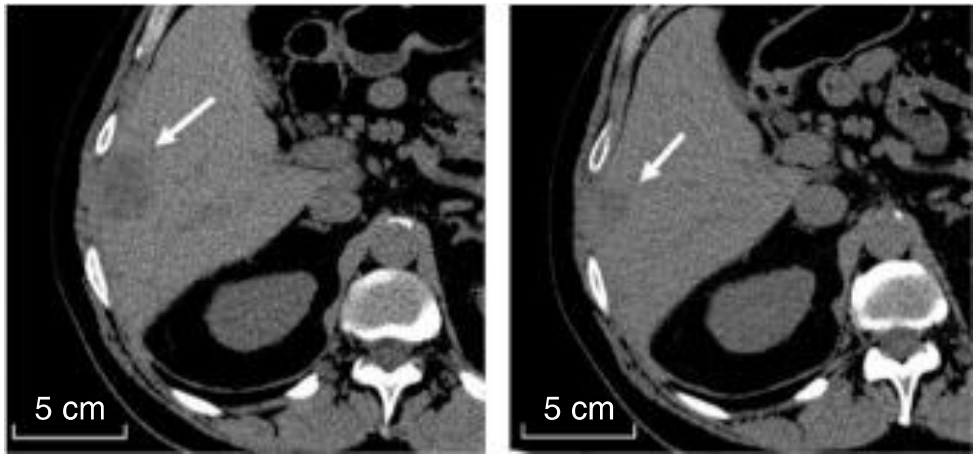
Identification of a mutation in the extracellular domain of the Epidermal Growth Factor Receptor conferring cetuximab resistance in colorectal cancer

Clara Montagut[1,2,9], Alba Dalmases[1,2,9], Beatriz Bellosillo[2,3], Marta Crespo[4], Silvia Pairet[2,3], Mar Iglesias[3,5], Marta Salido[3], Manuel Gallen[1,2], Scot Marsters[6], Siao Ping Tsai[6], André Minoche[7], Somasekar Seshagiri[6], Sergi Serrano[2,3,5], Heinz Himmelbauer[7], Joaquim Bellmunt[1,2,8], Ana Rovira[1,2], Jeff Settleman[6,9], Francesc Bosch[4,9] & Joan Albanell[1,2,5,9]

Antibodies against epidermal growth factor receptor (EGFR)—cetuximab and panitumumab—are widely used to treat colorectal cancer. Unfortunately, patients eventually develop resistance to these agents. We describe an acquired EGFR ectodomain mutation (S492R) that prevents cetuximab binding and confers resistance to cetuximab. Cells with this mutation, however, retain binding to and are growth inhibited by panitumumab. Two of ten subjects studied here with disease progression after cetuximab treatment acquired this mutation. A subject with cetuximab resistance harboring the S492R mutation responded to treatment with panitumumab.

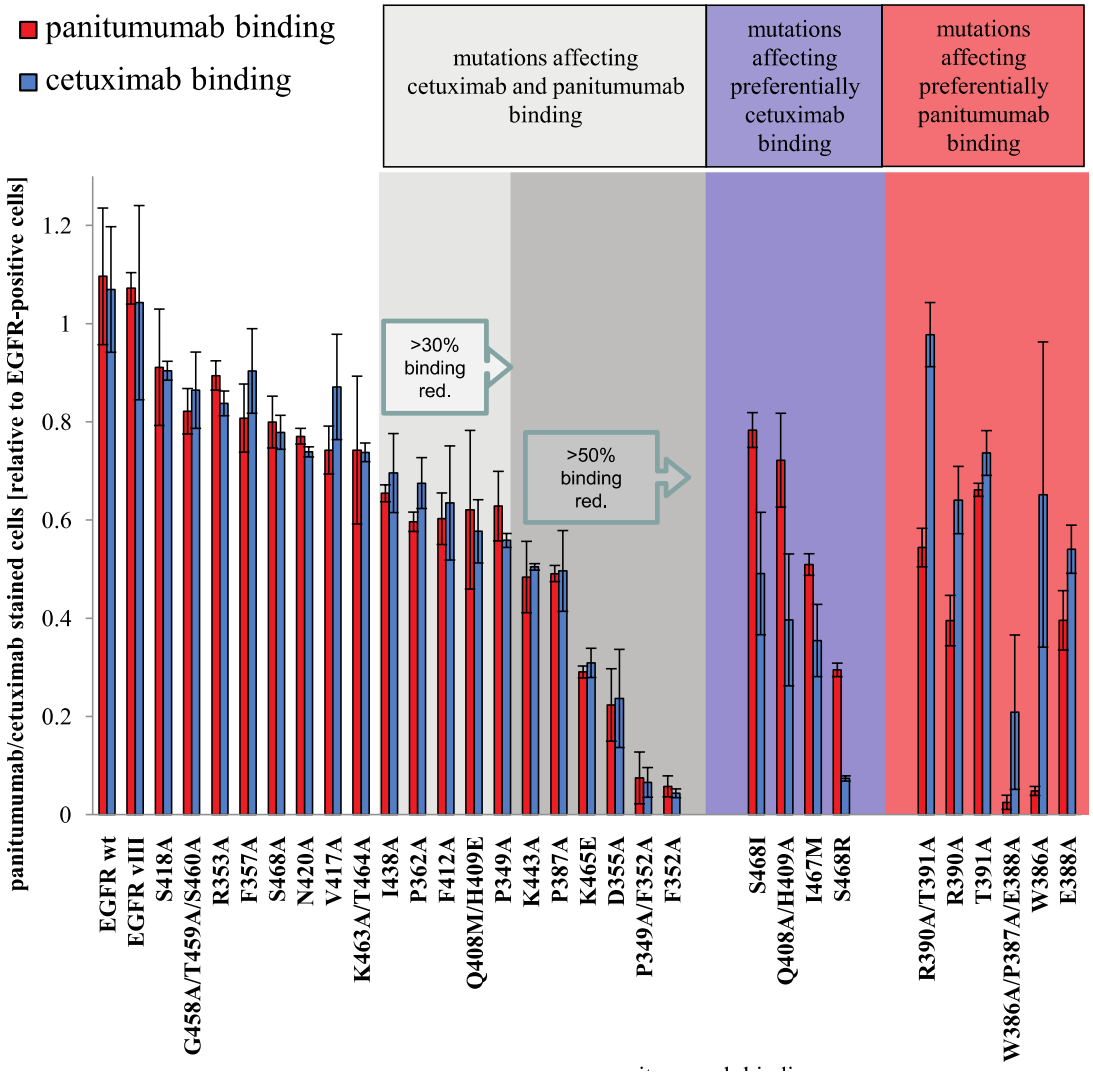






Montagut C et al, Nature Med 2012

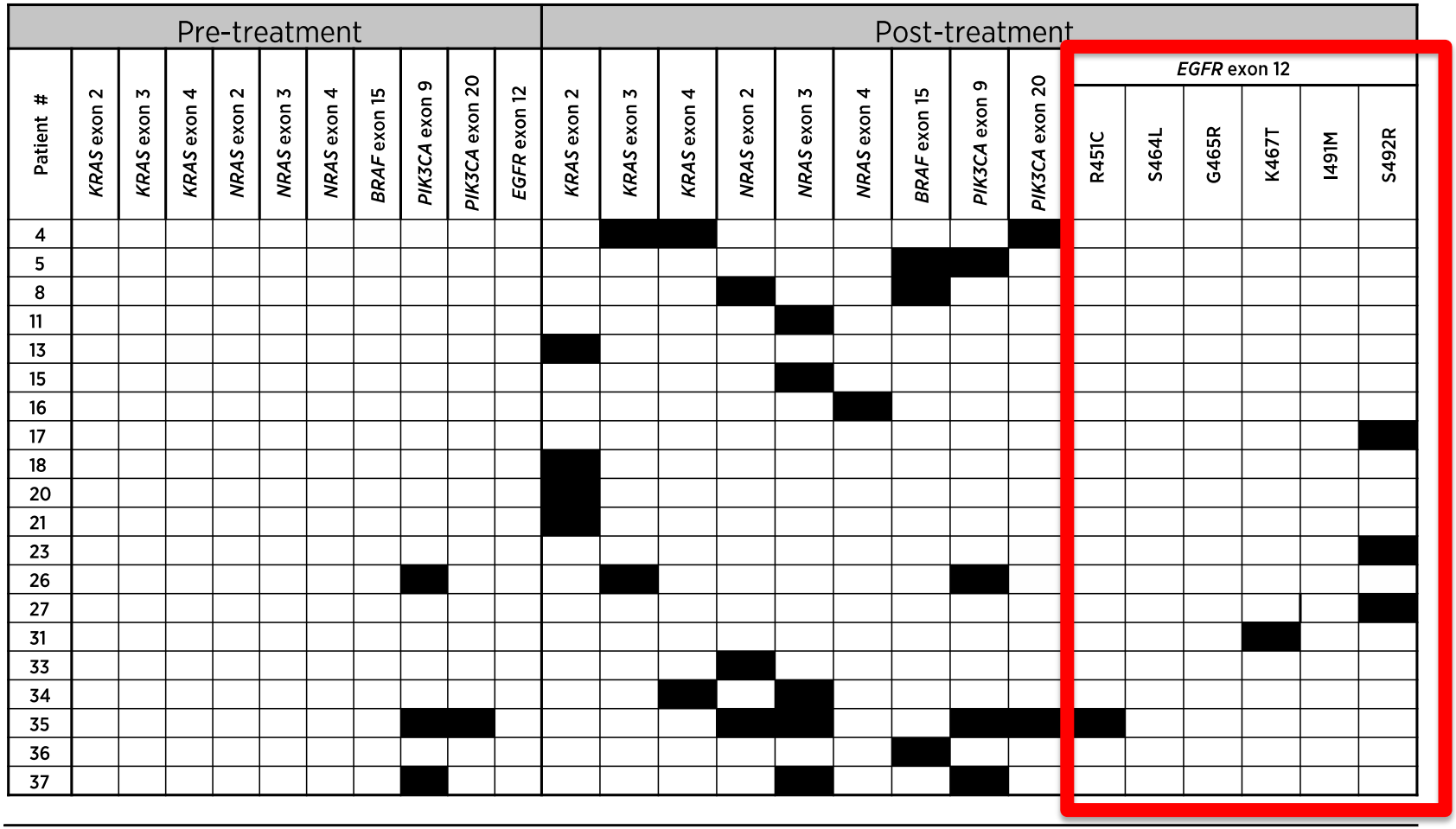
Functional dissection of the EGFR epitopes targeted by panitumumab or cetuximab



Evidence of 2 large, partially overlapping <u>functional EGFR epitopes</u> consisting of 17 critical amino acid positions. Four of these positions were selectively targeted by cetuximab (I467, S468, Q408, and H409), whereas another 4 were selectively recognized by panitumumab (W386, E388, R390, and T391).

Voigt M et al, Neoplasia 2012

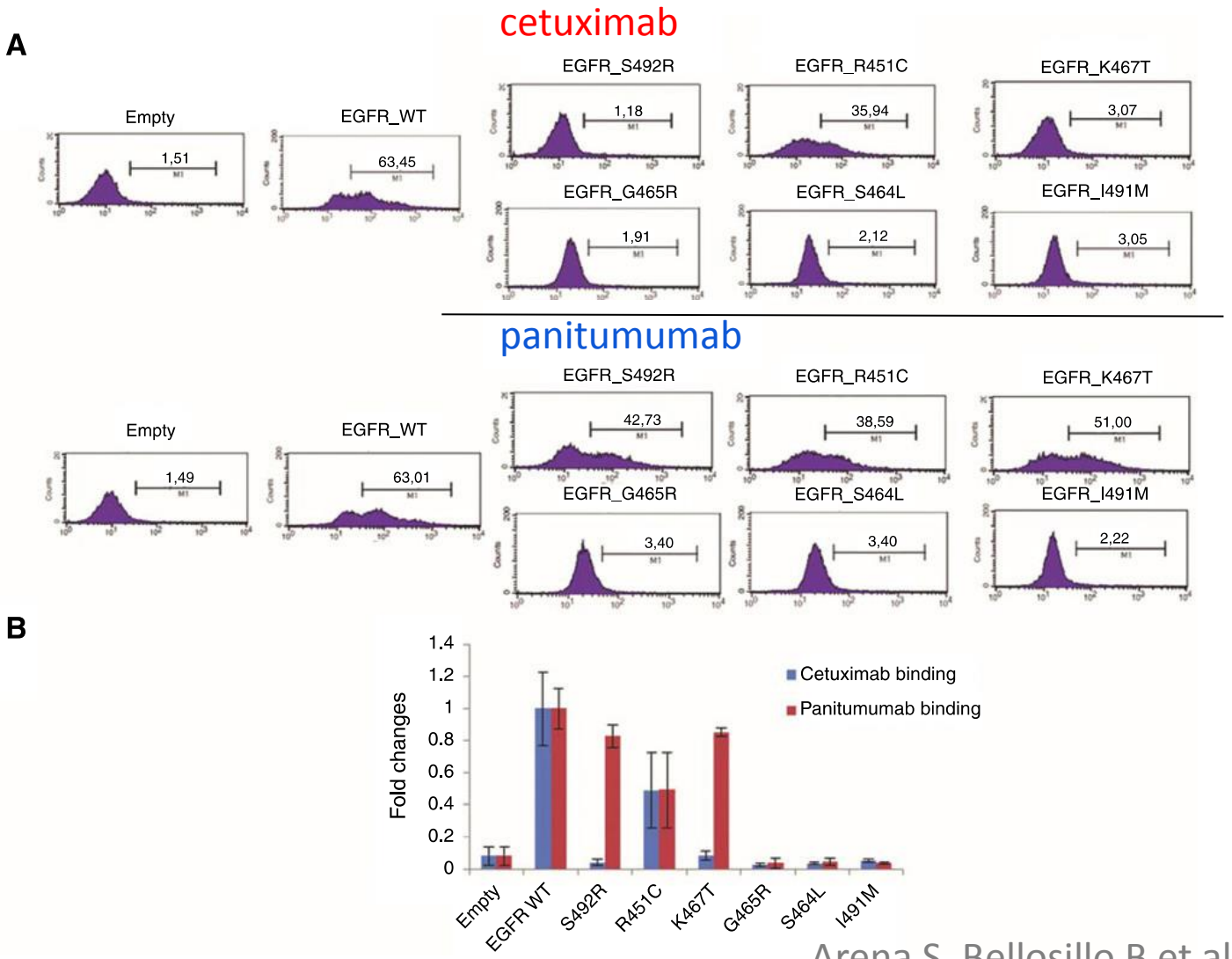
Upon progression of disease after cetuximab in mCRC
→ Emergence of multiple EGFR ectodomain mutations



NOTE: *KRAS*, *NRAS*, *BRAF*, *PIK3CA*, and *EGFR* mutations were analyzed in paired tissue samples obtained at diagnosis (pre-treatment) and at progression (post-treatment). Black boxes indicate the presence of mutations detected by clinical routine sequencing procedures.

Arena S, Bellosillo B et al, Clin Cancer Res 2015S

Ectodomain EGFR mutations differentially affect binding to cetuximab and panitumumab



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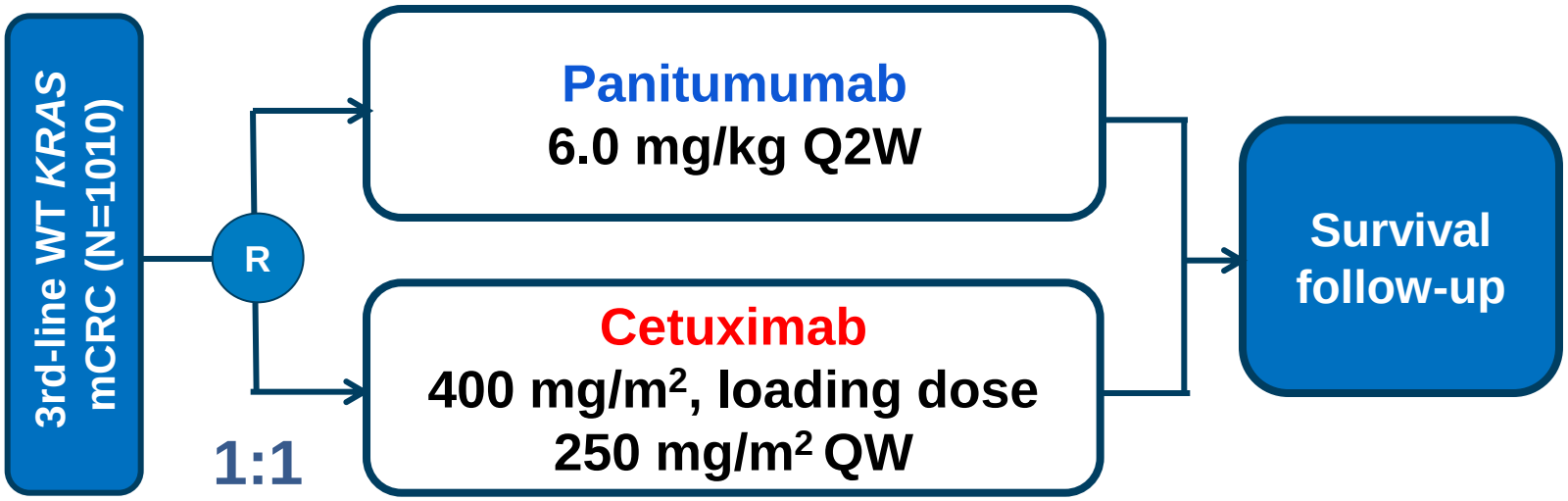

Primary endpoint: overall survival (OS)

Key secondary endpoints:

- **Progression-free survival (PFS)**
- **Objective response rate (ORR)**
- **Safety**

Plasma samples were collected for biomarker analysis = liquid biopsy

Price et al, Lancet Oncol 2014

Frequency of *EGFR* S492R mutations in the ASPECCT study based on plasma analysis using ddPCR

- No *EGFR* S492R mutations were identified in pre-treatment samples
- Safety follow-up plasma samples collected 4 weeks after last dose
  - Median duration of treatment was 14 weeks in both arms
- Testing was conducted without knowledge of treatment and the data analysis plan was finalized before any data was transferred
- 559 samples run
  - 13 failed samples based on Analytical Method Criteria (n=546)
  - Ascertainment was similar between arms
    - Cetuximab = 56.7%
    - Panitumumab = 52.6%

Treatment	WT	*EGFR* S492R	Frequency of *EGFR* S492R	95% CI	p Value
Cetuximab	**239**	**46**	**16.1%**	**12.1-20.9%**	**p<0.0001**
Panitumumab	**258**	**3**	**1.1%**	**0.2-3.3%**	

Price et al, ASCO 2015

Current (2016) status of the treatment of mCRC with EGFR inhibitors

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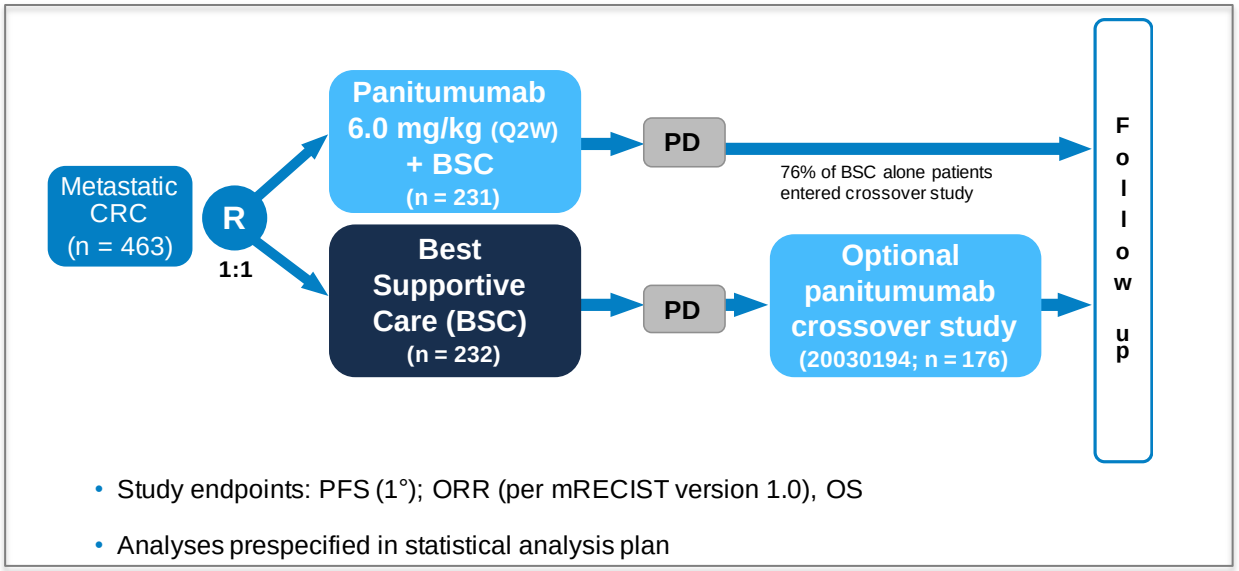
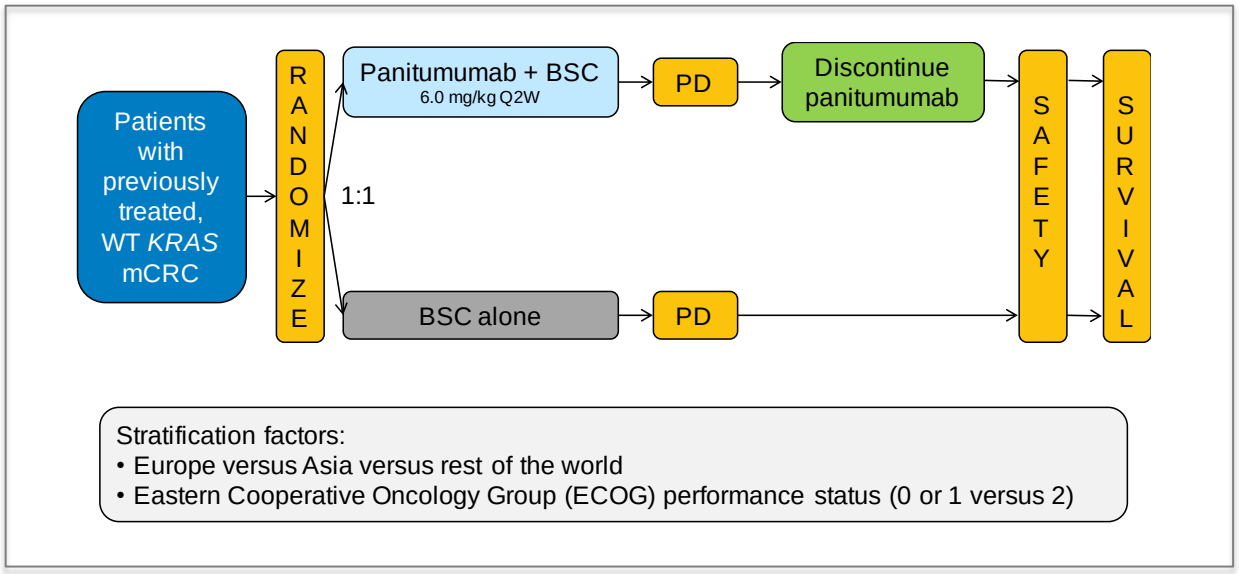
Panitumumab and BSC versus BSC alone in third and subsequent lines of therapy of mCRC



20020408 Study



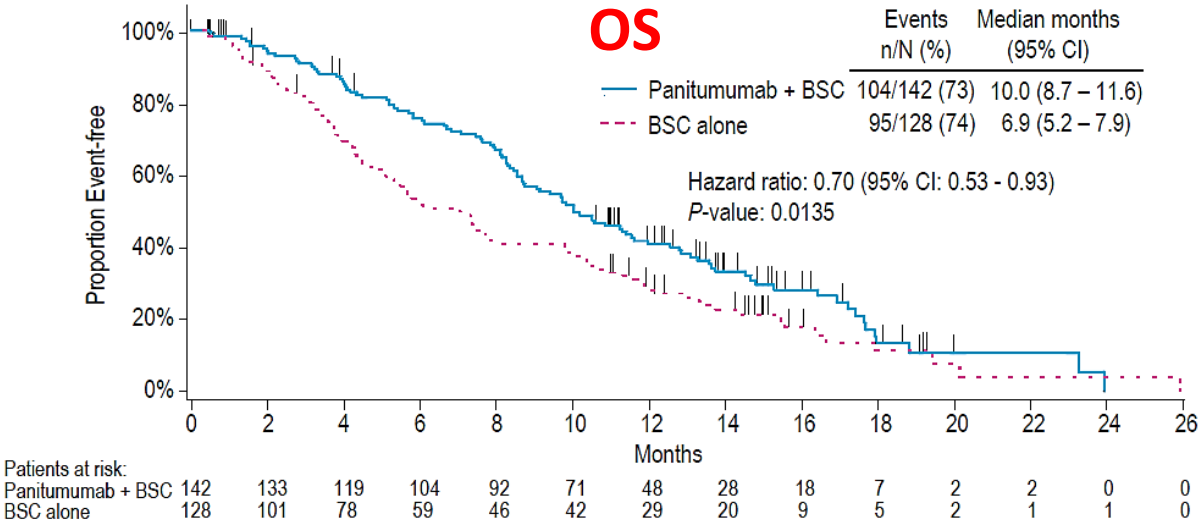
20100007 Study

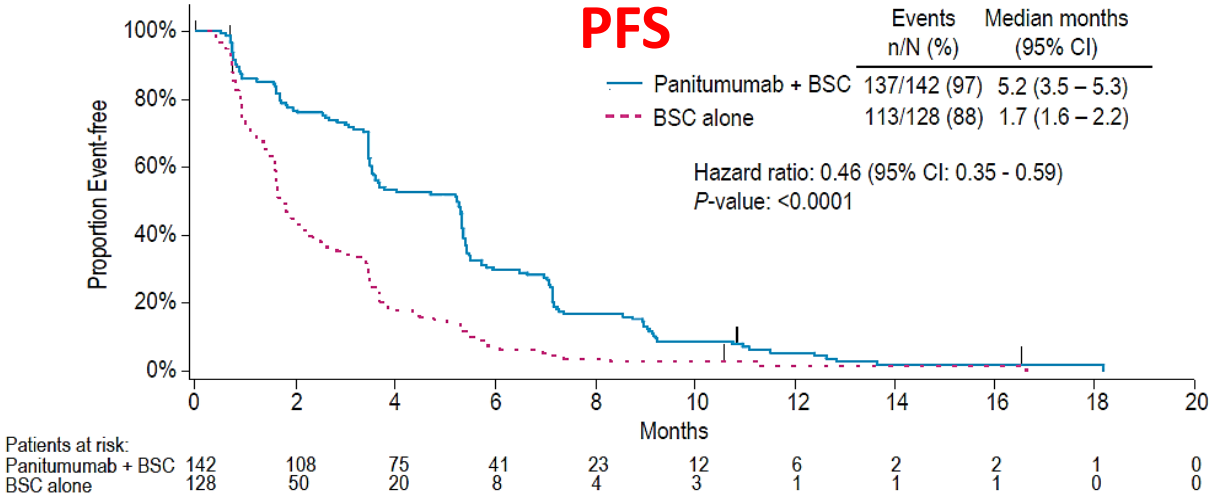
Panitumumab versus BSC (20100007 Study)
- **ORR in the w t *RAS* patients** -

	Wild-Type *RAS*	
	Panitumumab Plus BSC (n=142)	BSC Alone (n=128)
Objective response, n (%)		
Complete response	0 (0.0)	0 (0.0)
Partial response	44 (31.0)	3 (2.3)
Stable disease	62 (43.7)	26 (20.3)
Disease progression	31 (21.8)	62 (48.4)
Unevaluable/not done	5 (3.5)	37 (29.0)
Objective response rate, % (95% CI)	31.0 (23.5−39.3)	2.3 (0.5−6.7)
Odds ratio (95% CI)	20.00 (5.89−101.6)	
***P* value**	<0.0001	

Kim TW, et al. J Clin Oncol 2016;34(Suppl 4): abstract 642 (and poster).

Panitumumab versus BSC (20100007 Study)
- OS and PFS in the w t *RAS* patients -





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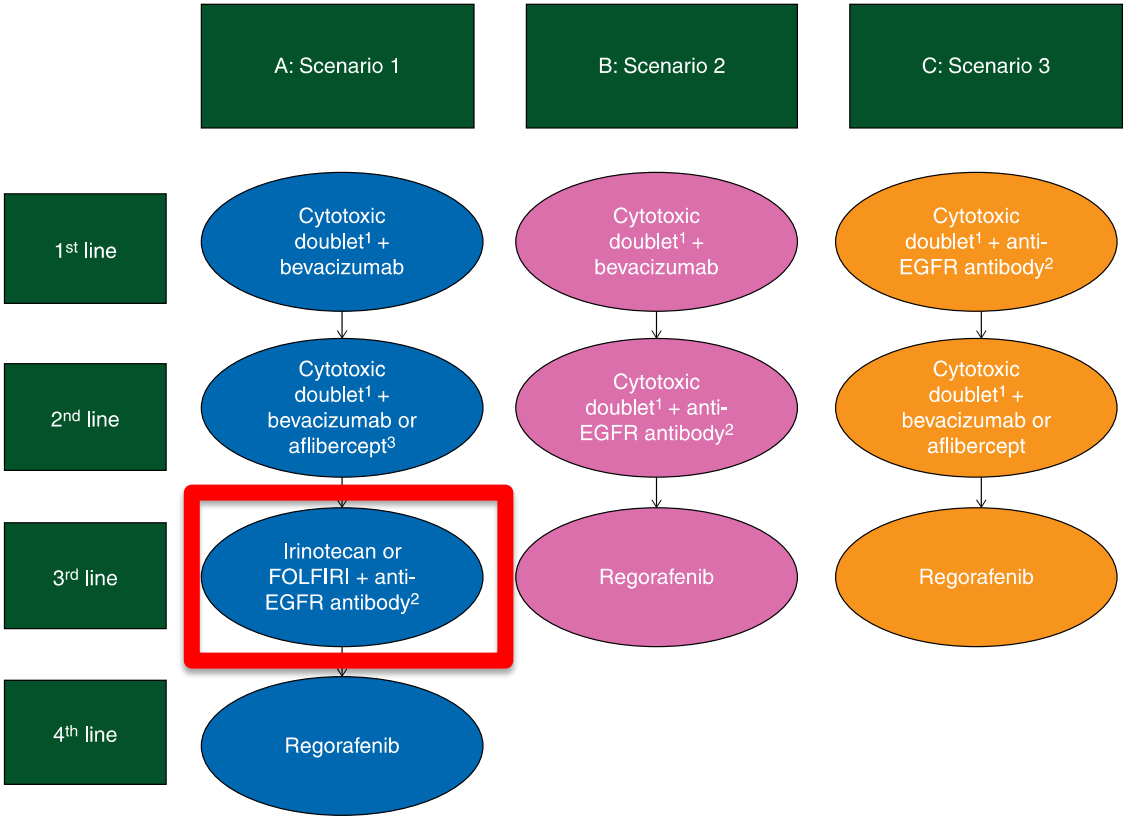
doi:10.1093/annonc/mdu260
Published online 4 September 2014

Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

E. Van Cutsem[1], A. Cervantes[2], B. Nordlinger[3] & D. Arnold[4], on behalf of the ESMO Guidelines Working Group*

[1]Digestive Oncology, University Hospitals Leuven, Leuven, Belgium; [2]Department of Hematology and Medical Oncology, INCLIVA, University of Valencia, Valencia, Spain; [3]Department of General Surgery and Surgical Oncology, Hôpital Ambroise Paré, Assistance Publique – Hôpitaux de Paris, Paris, France; [4]Klinik für Tumorbiologie, Freiburg, Germany



[1]cytotoxic doublets: fluoropyrimidine + oxaliplatin or irinotecan; [2]Ras wild type; [3]aflibercept only in combination with FOLFIRI

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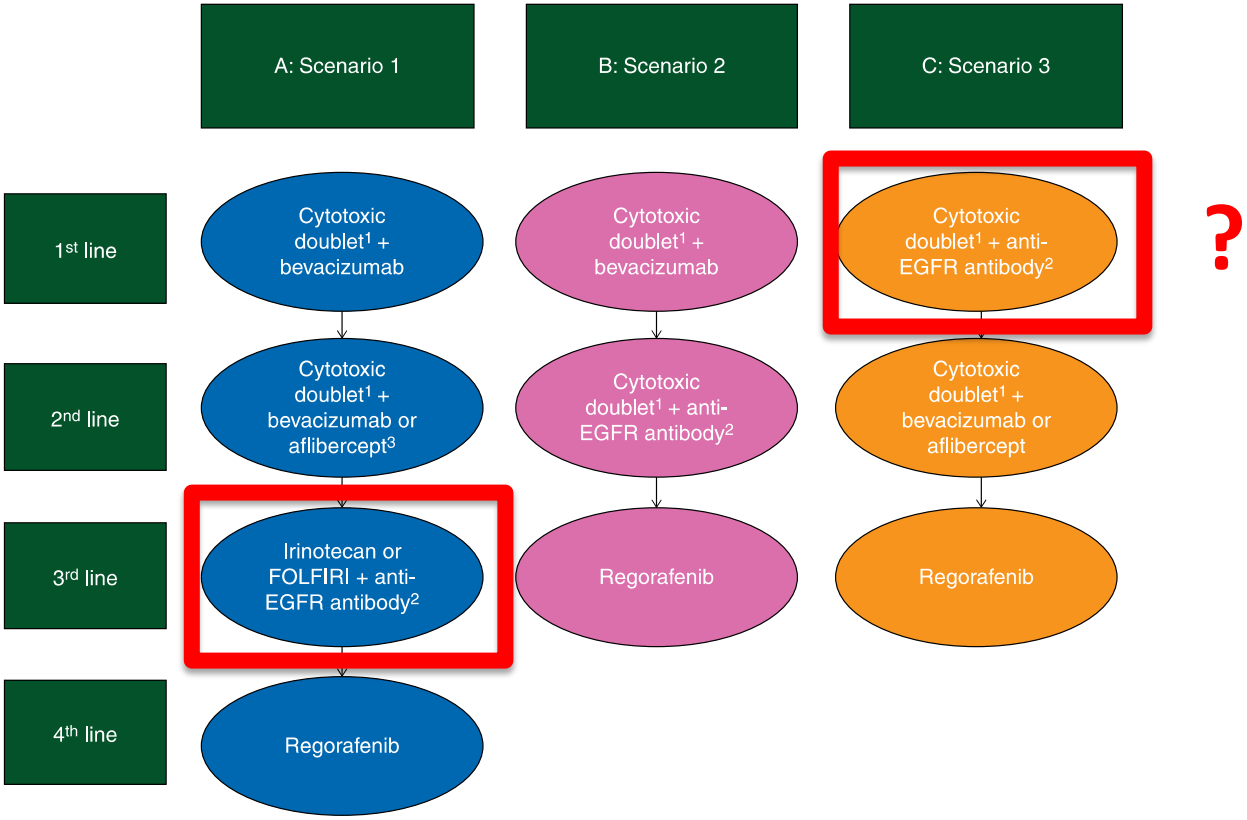

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Phase 3 trials of doublet CT plus an EGFR inhibitor or a VEGF inhibitor monoclonal antibody

Table 1 | Phase III trials of doublet chemotherapy plus a biologic agent in patients with mCRC

Trial	Study interventions (number of patients)	Primary end point	ORR (%)	Median PFS (months)	Median OS (months)
AVF2107g[9]	IFL + bevacizumab (*n* = 402) vs IFL (*n* = 411)	OS	45 vs 35 (*P* = 0.004)	10.6 vs 6.2 (HR 0.54, *P*<0.001)	20.3 vs 15.6 (HR 0.66, *P*<0.001)
NO16966[17]	Fluoropyrimidine–oxaliplatin + bevacizumab (*n* = 699) vs fluoropyrimidine–oxaliplatin (*n* = 701)	PFS	47 vs 49 (*P* = 0.31)	9.4 vs 8.0 (HR 0.83, *P* = 0.0023)	21.3 vs 19.9 (HR 0.89, *P* = 0.077)
NORDIC[77]*	FLOX+ cetuximab (*n* = 97) vs FLOX (*n* = 97)	OS	46 vs 47 (*P* = 0.89)	7.9 vs 8.7 (HR 1.07, *P* = 0.66)	20.1 vs 22.0 (HR 1.14, *P* = 0.48)
MRC COIN[78]*	Fluoropyrimidine–oxaliplatin + cetuximab (*n* = 362) vs fluoropyrimidine–oxaliplatin (*n* = 367)	PFS	64 vs 57 (*P* = 0.049)	8.6 vs 8.6 (HR 0.96, *P* = 0.67)	17.0 vs 17.9 (HR 1.04, *P* = 0.67)
CRYSTAL[21]‡	FOLFIRI + cetuximab (*n* = 178) vs FOLFIRI (*n* = 189)	PFS	66 vs 39 (*P*<0.0001)	11.4 vs 8.4 (HR 0.56, *P* = 0.0002)	28.4 vs 20.2 (HR 0.69, *P* = 0.0024)
PRIME[20]‡	FOLFOX+ panitumumab (*n* = 259) vs FOLFOX (*n* = 253)	PFS	NA	10.1 vs 7.9 (HR 0.72, *P* = 0.004)	25.8 vs 20.2 (HR 0.77, *P* = 0.009)
FIRE-3[29]‡	FOLFIRI + cetuximab (*n* = 171) vs FOLFIRI + bevacizumab (*n* = 171)	ORR	66 vs 60 (*P* = 0.32)	10.4 vs 10.2 (HR 0.93, *P* = 0.54)	33.1 vs 25.6 (HR 0.70, *P* = 0.011)
CALGB/ SWOG 80405[33]‡	FOLFOX or FOLFIRI + cetuximab (*n* = 270) vs FOLFOX or FOLFIRI + bevacizumab (*n* = 256)	OS	69 vs 54 (*P*<0.01)§	11.4 vs 11.3 (HR 1.10, *P* = 0.31)	32.0 vs 31.2 (HR 0.90, *P* = 0.40)

* In patients with *KRAS* (exon 2, codons 12 and 13)-wild-type tumours. ‡In patients with *RAS*-wild-type tumours (wild-type at exons 2, 3, and 4 of *KRAS* and *NRAS*). §Absolute number of patients evaluable in each arm was not available. Abbreviations: FLOX, bolus 5-fluorouracil, leucovorin (folinic acid), and oxaliplatin; FOLFIRI, 5-fluorouracil, folinic acid, and irinotecan; FOLFOX, 5-fluorouracil, folinic acid, and oxaliplatin; HR, hazard ratio; IFL, irinotecan, 5-fluorouracil, and leucovorin (folinic acid); mCRC, metastatic colorectal cancer; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Cremolini et al, Nature Rev Clin Oncol 2015

Phase 3 trials of doublet CT plus an EGFR inhibitor or a VEGF inhibitor monoclonal antibody

Table 1 | Phase III trials of doublet chemotherapy plus a biologic agent in patients with mCRC

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NO16966[17]	Fluoropyrimidine–oxaliplatin + bevacizumab (*n* = 699) vs fluoropyrimidine–oxaliplatin (*n* = 701)	PFS	47 vs 49 (*P* = 0.31)	9.4 vs 8.0 (HR 0.83, *P* = 0.0023)	21.3 vs 19.9 (HR 0.89, *P* = 0.077)
NORDIC7[77]*	FLOX + cetuximab (*n* = 97) vs FLOX (*n* = 97)	OS	46 vs 47 (*P* = 0.89)	7.9 vs 8.7 (HR 1.07, *P* = 0.66)	20.1 vs 22.0 (HR 1.14, *P* = 0.48)
MRC COIN[78]*	Fluoropyrimidine–oxaliplatin + cetuximab (*n* = 362) vs fluoropyrimidine–oxaliplatin (*n* = 367)	PFS	64 vs 57 (*P* = 0.049)	8.6 vs 8.6 (HR 0.96, *P* = 0.67)	17.0 vs 17.9 (HR 1.04, *P* = 0.67)
CRYSTAL[21]‡	FOLFIRI + cetuximab (*n* = 178) vs FOLFIRI (*n* = 189)	PFS	66 vs 39 (*P*<0.0001)	11.4 vs 8.4 (HR 0.56, *P* = 0.0002)	28.4 vs 20.2 (HR 0.69, *P* = 0.0024)
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Cremolini et al, Nature Rev Clin Oncol 2015

Table 1. Outcomes of Randomized Trials With EGFR mAbs Plus Chemotherapy in *KRAS* Wild-Type Colorectal Cancer

Trial	Fluoropyrimidine	Iri or Ox	EGFR mAb	Significant Improvement in RR	PFS	OS
First line						
CRYSTAL[4]	Inf + bolus FU	Iri	C	Yes	Yes	Yes
PRIME[5]	Inf + bolus FU	Ox	P	Yes	Yes	No
OPUS*[7]	Inf + bolus FU	Ox	C	Yes	Yes	No
COIN[9]	Inf + bolus FU	Ox	C	Yes	Yes	No
	Capecitabine	Ox	C	No	No	No
NORDIC[13]	Bolus FU	Ox	C	No	No	No
CAIRO2[21]	Capecitabine	Ox/Bev	C	Yes	No	No
Second line						
181[6]	Inf + bolus FU	Iri	P	Yes	Yes	No
PICCOLO[10]		Iri	P	Yes	Yes	No

Bev, bevacizumab; C, cetuximab; CAIRO, Capecitabine, Irinotecan, and Oxaliplatin in Advanced Colorectal Cancer; COIN, Continuous Chemotherapy Plus Cetuximab, or Intermittent Chemotherapy With Standard Continuous Palliative Combination Chemotherapy With Oxaliplatin and a Fluoropyrimidine in First-Line Treatment of Metastatic Colorectal Cancer; CRYSTAL, Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer; EGFR mAb, epidermal growth factor receptor monoclonal antibody; FU, fluorouracil; inf, infusional; Iri, irinotecan; NORDIC, 5-Fluorouracil/Folinate/Oxaliplatin (Eloxatin) (FLOX Regimen) Given Continuously or Intermittently, in Combination With Cetuximab (Erbitux) in First-Line Treatment of Metastatic Colorectal Cancer; OPUS, Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer; OS, overall survival; Ox, oxaliplatin; P, panitumumab; PFS, progression-free survival; PICCOLO, Panitumumab, Irinotecan & Ciclosporin in Colorectal Cancer Therapy; PRIME, Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy; RR, response rate.

*Randomized phase II trial.

Grothey A & Lenz HJ, JCO 2012

Phase 3 trials of doublet CT plus an EGFR inhibitor or a VEGF inhibitor monoclonal antibody

Table 1 | Phase III trials of doublet chemotherapy plus a biologic agent in patients with mCRC

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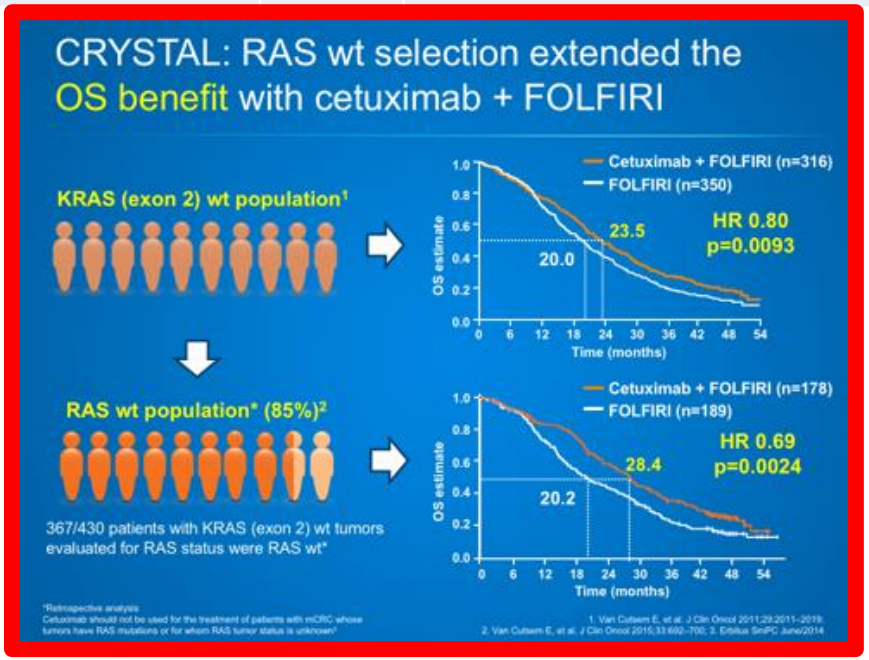
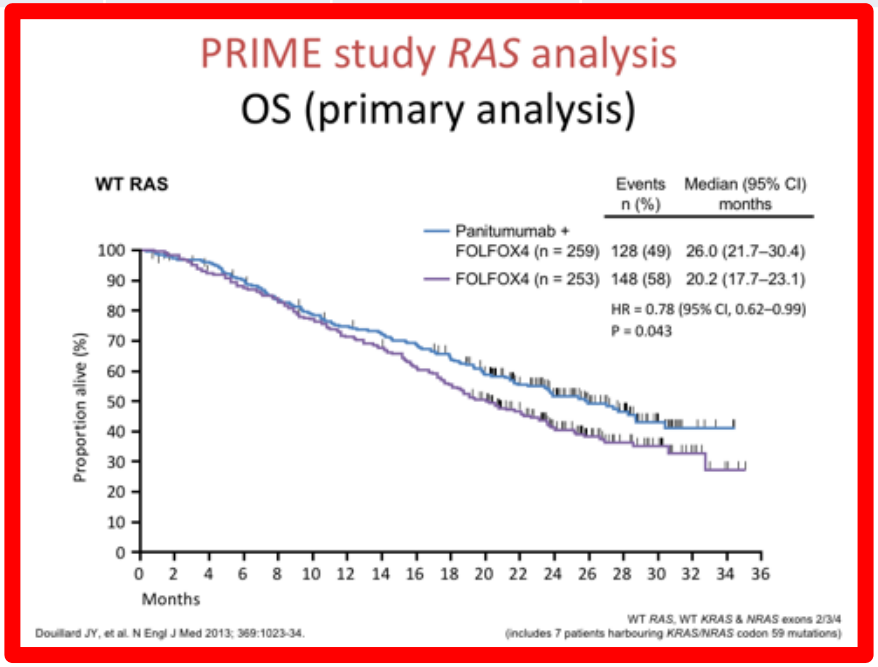
Cremolini et al, Nature Rev Clin Oncol 2015

Overall Survival benefit of chemotherapy + cetuximab or panitumumab in the 1st line therapy of mCRC

Trial	n	Treatment arm	OS, months	HR	Incremental gain, months
CRYSTAL[1]*	367	FOLFIRI + cetuximab FOLFIRI	**28.4** 20.2	0.69 p=0.0024	**8.2 ↑**
PRIME[2]*	512	FOLFOX + panitumumab FOLFOX	**26.0** 20.2	0.78 p=0.04	**5.8 ↑**



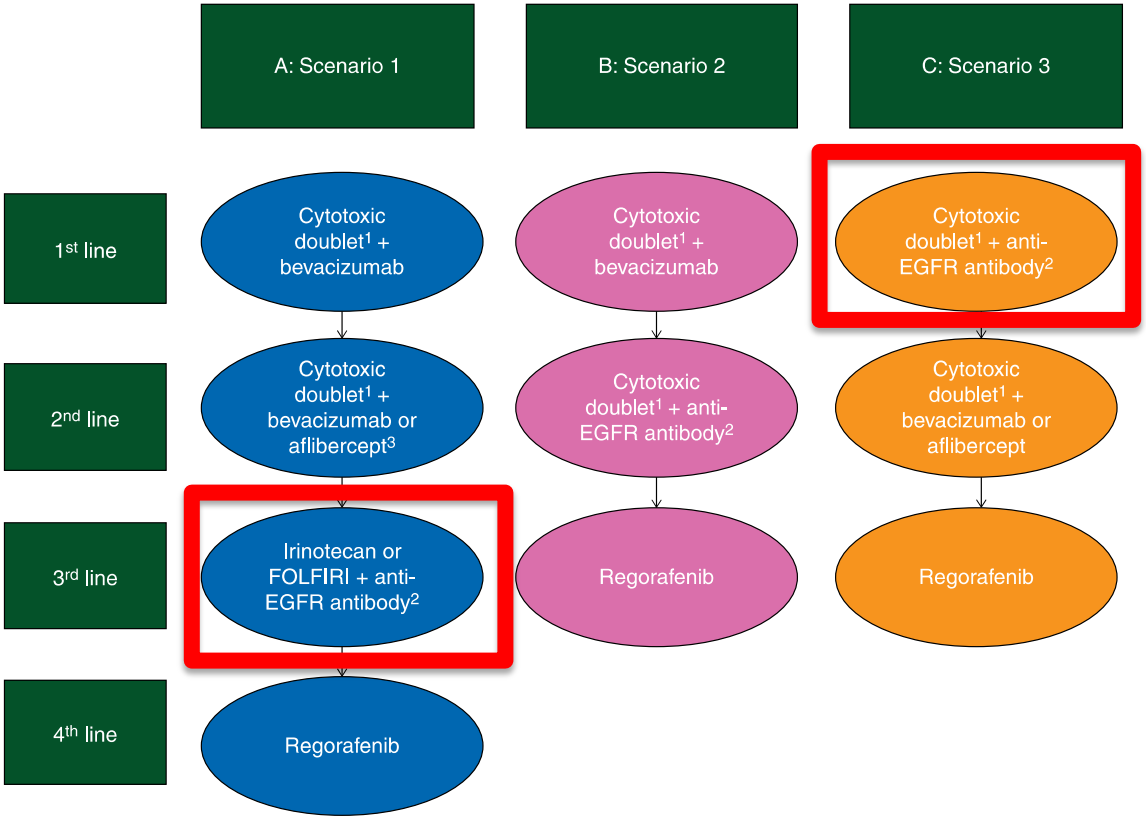


Annals of Oncology 25 (Supplement 3): iii1–iii9, 2014
doi:10.1093/annonc/mdu260
Published online 4 September 2014

Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

E. Van Cutsem[1], A. Cervantes[2], B. Nordlinger[3] & D. Arnold[4], on behalf of the ESMO Guidelines Working Group*

[1]Digestive Oncology, University Hospitals Leuven, Leuven, Belgium; [2]Department of Hematology and Medical Oncology, INCLIVA, University of Valencia, Valencia, Spain; [3]Department of General Surgery and Surgical Oncology, Hôpital Ambroise Paré, Assistance Publique – Hôpitaux de Paris, Paris, France; [4]Klinik für Tumorbiologie, Freiburg, Germany



[1]cytotoxic doublets: fluoropyrimidine + oxaliplatin or irinotecan; [2]Ras wild type; [3]aflibercept only in combination with FOLFIRI

Phase 3 trials of doublet CT plus an EGFR inhibitor or a VEGF inhibitor monoclonal antibody

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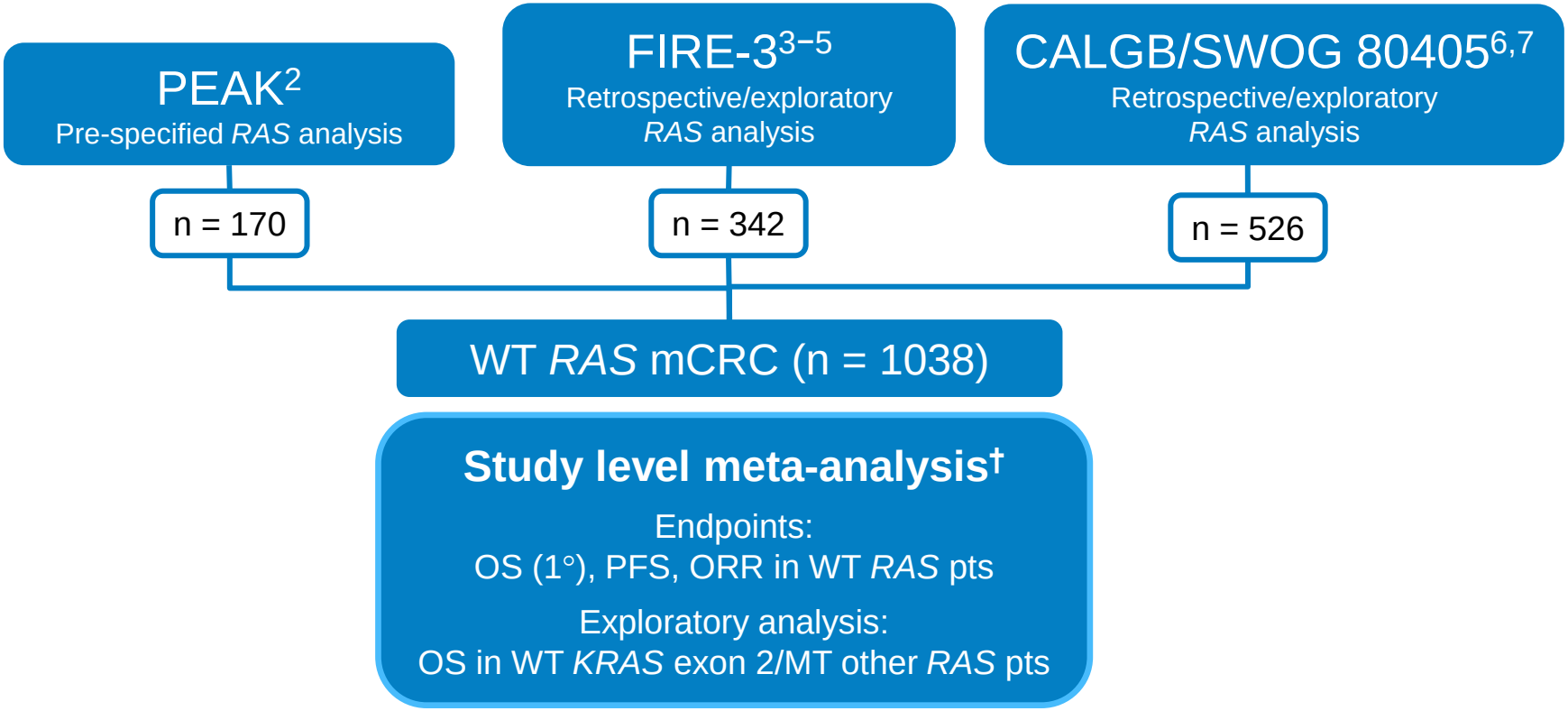
Cremolini et al, Nature Rev Clin Oncol 2015

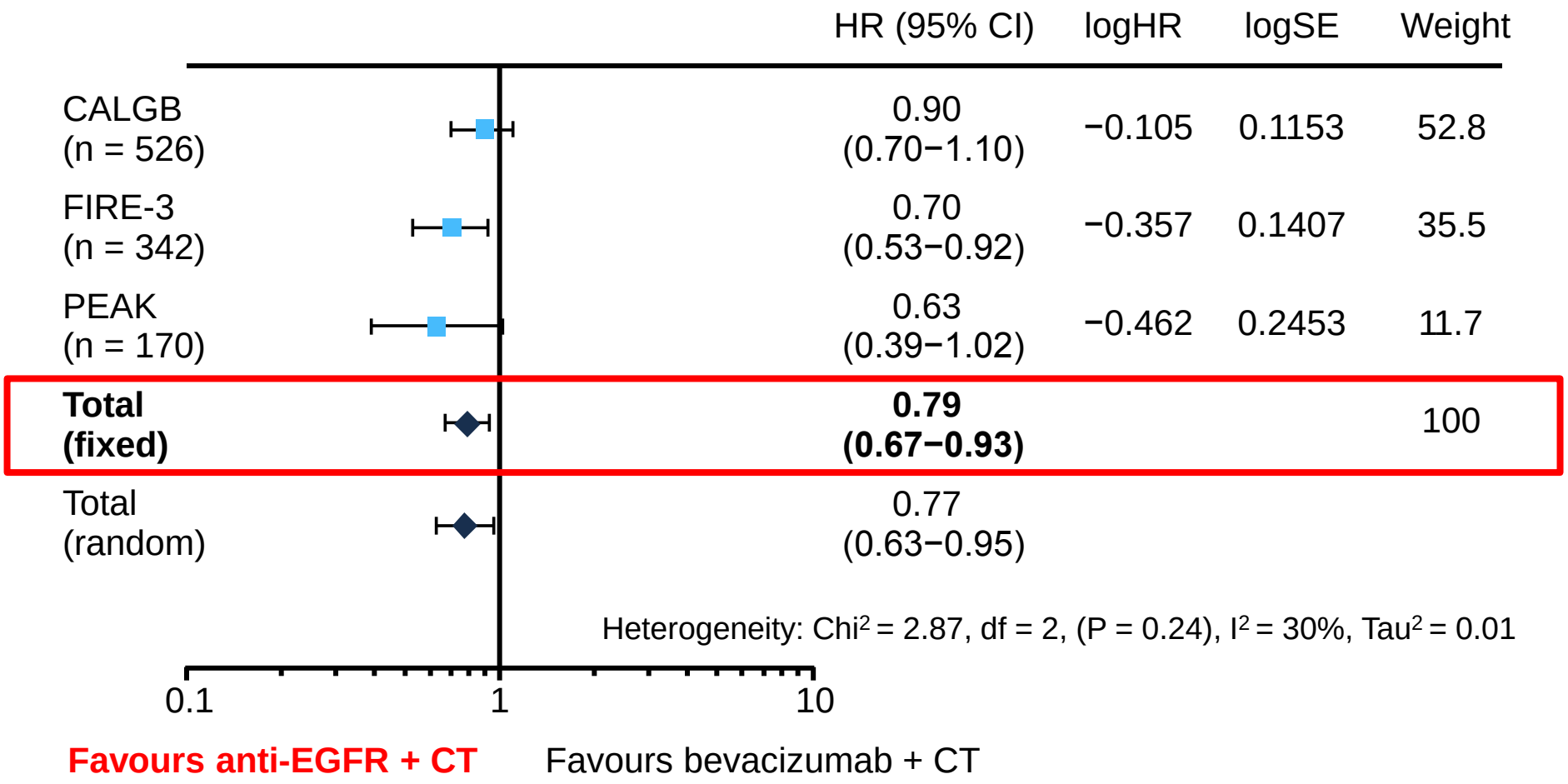
Meta-analysis based on head-to-head studies of 1st line CT + EGFRi versus CT + VEGFRi in w t RAS - List of studies -



1. Heinemann V, et al. Ann Oncol 2015;26(Suppl 4):abstract 150 (and poster);
2. Schwartzberg LS, et al. J Clin Oncol 2014;32:2240−7; 3. Stintzing S, et al. J Clin Oncol 2014;32(Suppl 3):abstract 445 (and oral presentation); 4. Heinemann V, et al. Ann Oncol 2014;25(Suppl 4):abstract O-0030 (and oral presentation);
5. Heinemann V, et al. Lancet Oncol 2014;15:1065−75; 6. Venook AP, et al. J Clin Oncol 2014;32(Suppl 5):abstract LBA3 (and oral presentation); 7. Lenz H, et al. Ann Oncol 2014;25(Suppl 4):abstract 501O (and oral presentation).

†Data cut-off December 2014.
CTx, chemotherapy;
H2H, head-to-head; MT, mutant;
ORR, objective response rate;
OS, overall survival;
PFS, progression-free survival;
VEGF, vascular endothelial growth factor.

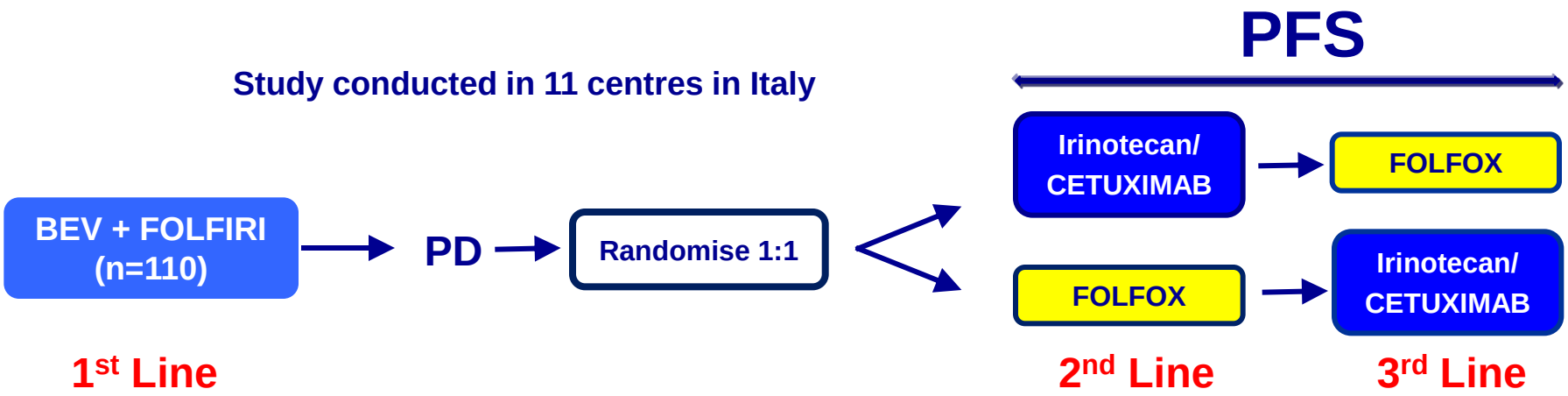
Meta-analysis based on head-to-head studies of 1st line CT + EGFRi versus CT + VEGFRi in w t RAS - Overall Survival -



Heinemann V, et al. Ann Oncol 2015;26(Suppl 4):abstract 150 (and poster).

†Primary endpoint. Weight is relative weight (%) from the fixed effect model.

COMETS: Study design



101 events were required to achieve a power of 80% of detecting a HR of 0.57 in favour of one of the two sequences, translating in an increase of median overall PFS from 4 to 7 months, with a type I error of 5%, two-sided, using the Mantel-Cox version of the log-rank test. 110 assessable patients were needed to reach the target number of events.

Primary endpoint	**Progression-free survival (PFS)**
Secondary endpoints	**Overall survival (OS) from randomisation;** **PFS 2° and 3° line;** **Overall response rate** **Safety**

Clinicaltrials.gov: NCT01030042
Research Funding Source: AIFA (Agenzia Italiana del Farmaco) Code FARM 6XB38F

Efficacy data according to arm

	Arma A (55 patients)	Arm B (55 patients)	Hazard ratio (95% CI)
Response rate (%)	19/52 (37%)	30/53 (57%)	p= 0.05 Fisher exact test
Overall median PFS (months)	9.9	11.3	HR 0.83 (0.56-1.24); p= 0.37
Overall median survival (months)	12.3	18.6	HR 0.79 (0.52-1.19); p= 0.26

Arm A: Cetuximab/irinotecan ⟶ FOLFOX

Arm B: FOLFOX followed by ⟶ Cetuximab/irinotecan

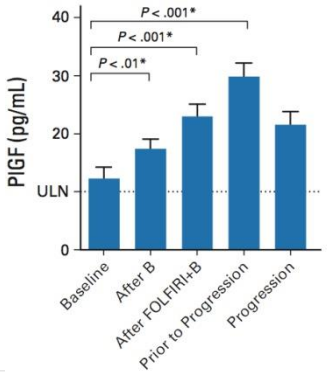
Cascinu S, et al. Eur J Cancer 2015;51(Suppl 3):abstract 2006 (and oral).

COMETS Conclusions

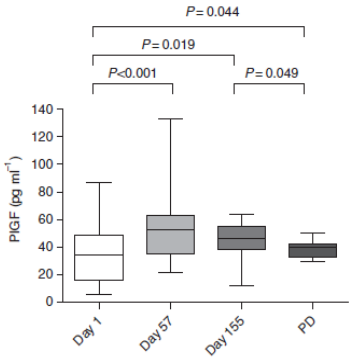
- In KRAS WT patients, Cmab seems to be less effective immediately after Bev
- Findings may support preclinical and clinical data suggesting that EGFR inhibition is not active after VEGF blockade
- Sequence of biological agents seems to be relevant as well as 1st-line choice
- In RAS WT pts Cmab should be given in 1st line or in 3rd line in patients progressing after 1st line bev

Cascinu S, et al. Eur J Cancer 2015;51(Suppl 3):abstract 2006 (and oral).

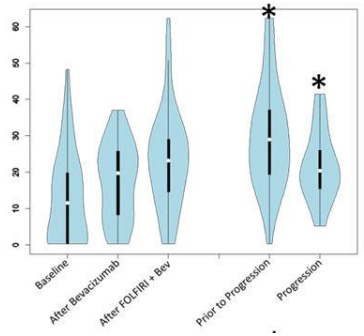
Pre-treatment with VEGFi therapy gives rise to overexpression of effectors of angiogenesis that hamper efficacy of subsequent EGFRi treatment



Kopetz et al. J Clin Oncol 2009



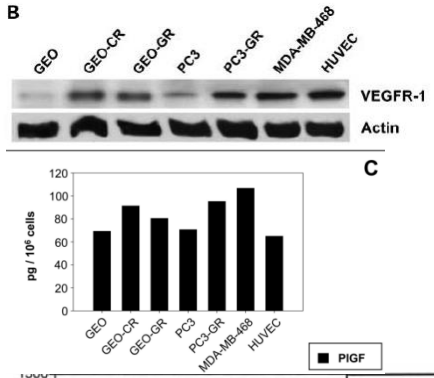
Loupakis et al. Br J Canc 2011



Lieu et al. Plos One 2013

Vascular Endothelial Growth Factor Receptor-1 Contributes to Resistance to Anti – Epidermal Growth Factor Receptor Drugs in Human Cancer Cells

Roberto Bianco,[1] Roberta Rosa,[1] Vincenzo Damiano,[1] Gennaro Daniele,[1] Teresa Gelardi,[1] Sonia Garofalo,[1] Valeria Tarallo,[2] Sandro De Falco,[2] Davide Melisi,[1] Roberto Benelli,[4] Adriana Albini,[5] Anderson Ryan,[6] Fortunato Ciardiello,[3] and Giampaolo Tortora[1]

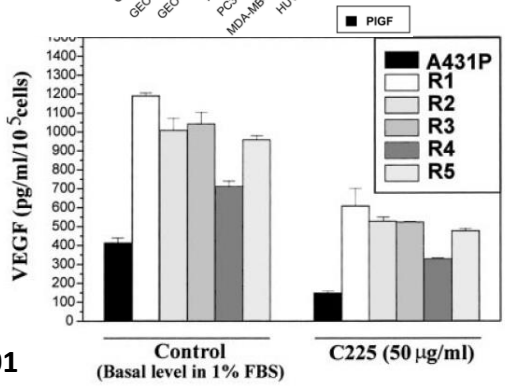


[CANCER RESEARCH 61, 5090–5101, July 1, 2001]

Acquired Resistance to the Antitumor Effect of Epidermal Growth Factor Receptor-blocking Antibodies *in Vivo*: A Role for Altered Tumor Angiogenesis[1]

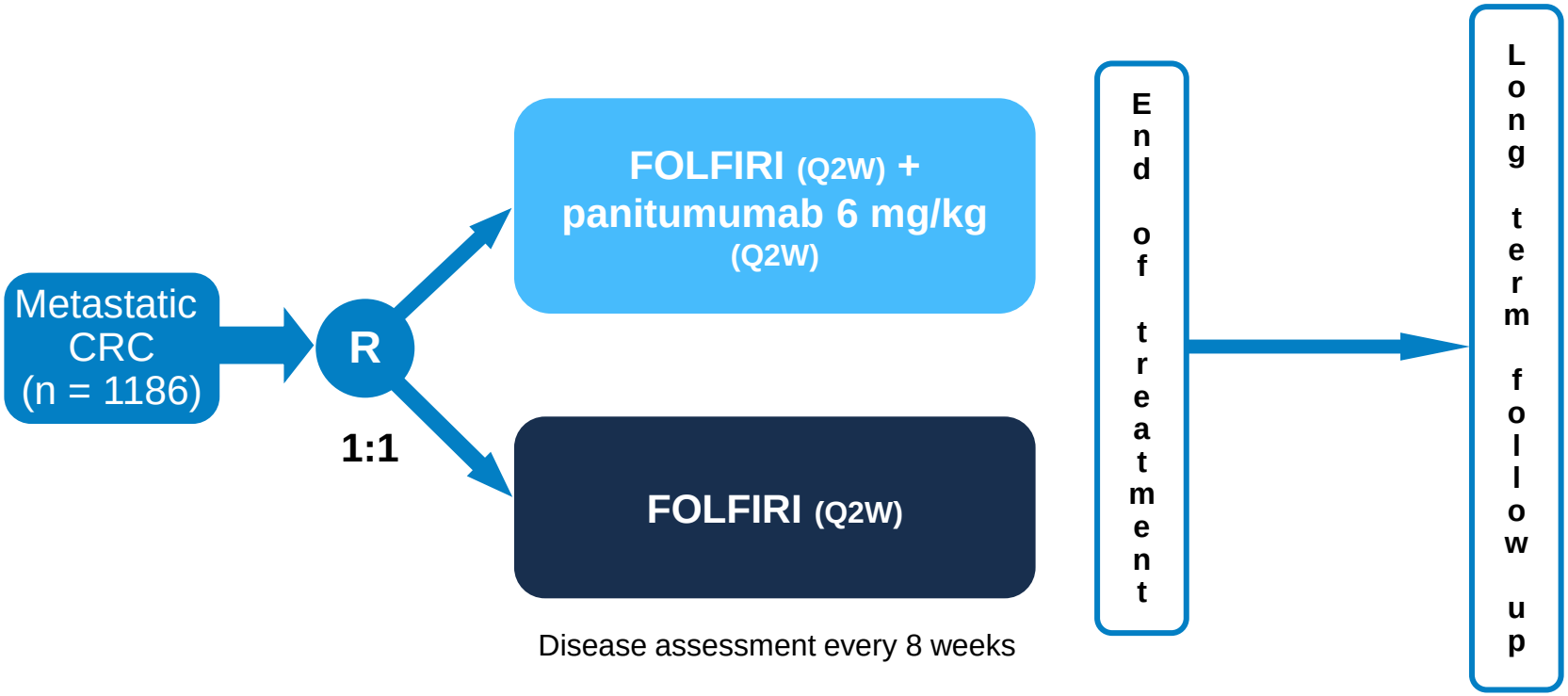
Alicia Viloria-Petit, Tania Crombet, Serge Jothy, Daniel Hicklin, Peter Bohlen, Jean Marc Schlaeppi, Janusz Rak, and Robert S. Kerbel[2]

Molecular and Cellular Biology Research [A. V-P., R. S. K.] and Department of Anatomic Pathology [S. J.], Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario M4N 3M5, Canada; Clinical Immunology Division, Center of Molecular Immunology, Havana, Cuba [T. C.]; ImClone Systems, Inc., New York, New York [D. H., P. B.]; Core Technology Department, Novartis Pharmaceuticals, Novartis Limited, Basel, Switzerland [J. M. S.]; and Hamilton Civic Hospitals Research Centre, Ontario, Canada [J. R.]



Bianco R, et al. Clin Cancer Res 2008;14:5069-5080; Viloria-Petit et al, Cancer Res 2001;61:5090-5101

20050181 study
FOLFIRI ± panitumumab in 2nd-line treatment of metastatic CRC

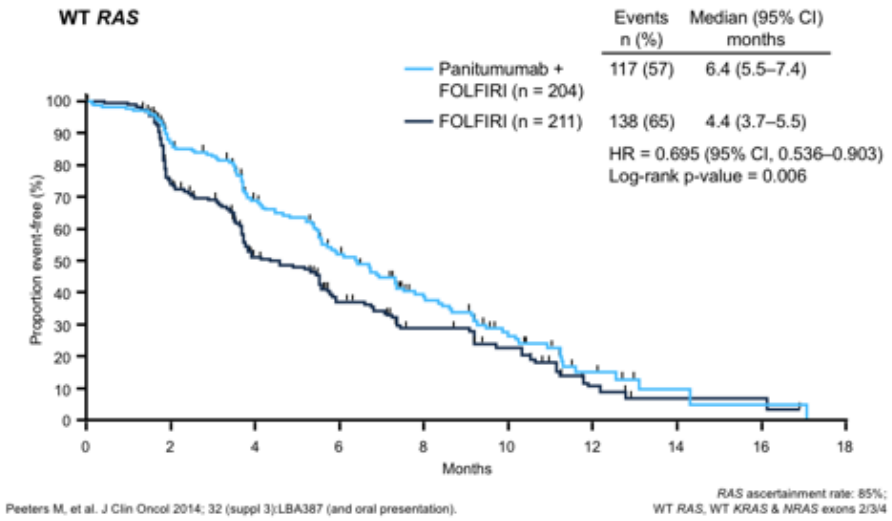


- Study endpoints: PFS and OS (1°), ORR, safety

Peeters M, et al. J Clin Oncol 2014; 32 (suppl 3):LBA387 (and oral presentation).

ORR, objective response rate

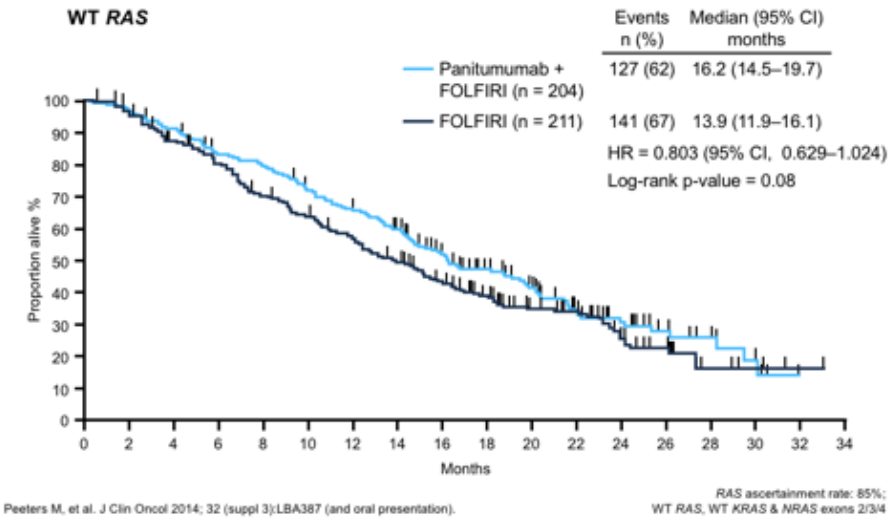
20050181 study *RAS* analysis
PFS (primary analysis)



Peeters M, et al. J Clin Oncol 2014; 32 (suppl 3):LBA387 (and oral presentation).

RAS ascertainment rate: 85%; WT *RAS*, WT *KRAS* & *NRAS* exons 2/3/4

20050181 study *RAS* analysis
OS (primary analysis)



Peeters M, et al. J Clin Oncol 2014; 32 (suppl 3):LBA387 (and oral presentation).

RAS ascertainment rate: 85%; WT *RAS*, WT *KRAS* & *NRAS* exons 2/3/4

	Panitumumab + FOLFIRI (n = 200)	FOLFIRI (n = 205)
ORR, n (%) (95% CI)	81 (41) (32%–48%)	21 (10) (6%–15

20050181 study *KRAS* exon 2 analysis
Demographics and disease characteristics

	WT *KRAS* (n = 597)		MT *KRAS* (n = 486)	
	Panitumumab + FOLFIRI (n = 303)	FOLFIRI (n = 294)	Panitumumab + FOLFIRI (n = 238)	FOLFIRI (n = 248)
Sex – men, n (%)	188 (62)	191 (65)	133 (56)	148 (60)
Age – years, median (min, max)	60 (28, 84)	61 (29, 86)	61 (29, 83)	64 (29, 86)
Race – white, n (%)	294 (97)	278 (95)	226 (95)	238 (96)
ECOG performance status, n (%)				
0-1	288 (95)	273 (93)	224 (94)	233 (94)
2	15 (5)	21* (7)	14 (6)	15 (6)
Primary tumour type, n (%)				
Colon	187 (62)	189 (64)	156 (66)	164 (66)
Rectal	116 (38)	105 (36)	82 (34)	84 (34)
Sites of metastatic disease, n (%)				
Liver only	51 (17)	59 (20)	37 (16)	35 (14)
Liver + other	205 (68)	189 (64)	166 (70)	172 (69)
Other only	47 (16)	44 (15)	34 (14)	39 (16)
Missing or unknown	0 (0)	2 (<1)	1 (<1)	2 (<1)
Prior oxaliplatin therapy, n (%)	204 (67)	191 (65)	164 (69)	169 (68)
Prior bevacizumab therapy, n (%)	55 (18)	60 (20)	45 (19)	43 (17)

Peeters M, et al. J Clin Oncol 2010; 28:4706-13.

*Included 1 patient with ECOG 3

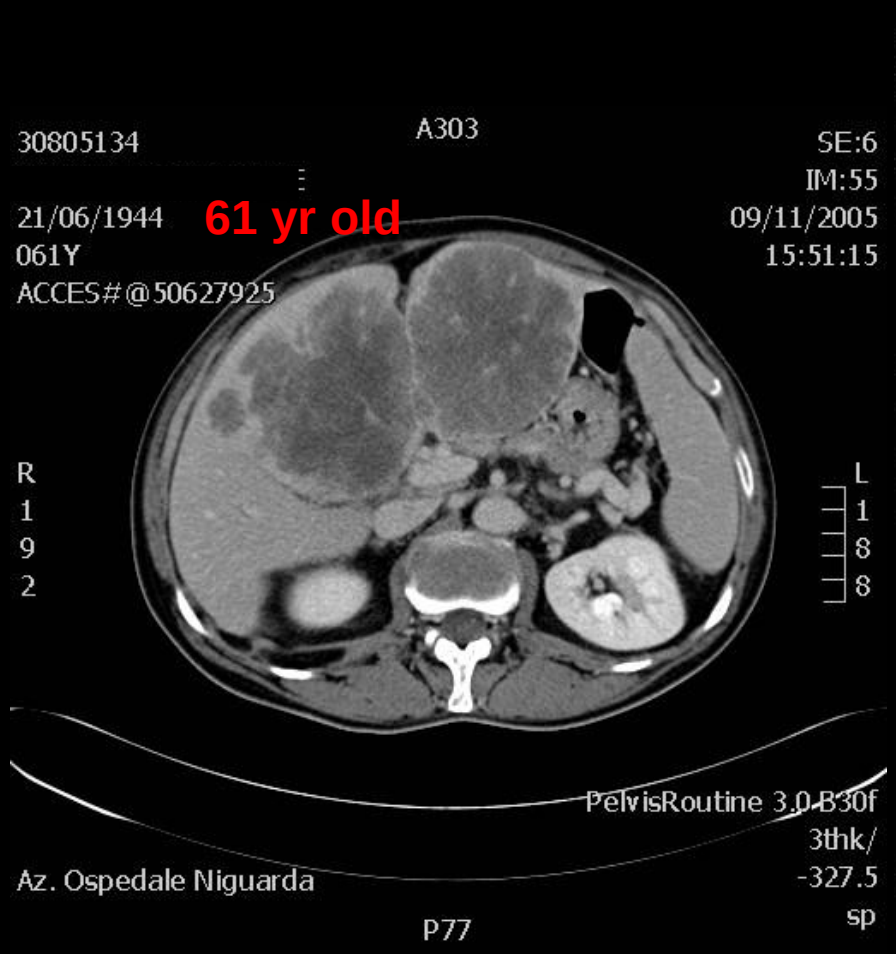
Current (2016) status of the treatment of mCRC with EGFR inhibitors

- **Panitumumab and cetuximab differ**
  - Anti-tumor effects
  - Side effects
  - Resistance
- **Optimal use of EGFRi in the continuum of care**
  - Combined with companion chemotherapy or monotherapy
  - First line versus subsequent lines of treatment(s)
  - **Sequencing with anti-angiogenesis agent(s)**
  - Rationale for repeated therapy (rechallenge)

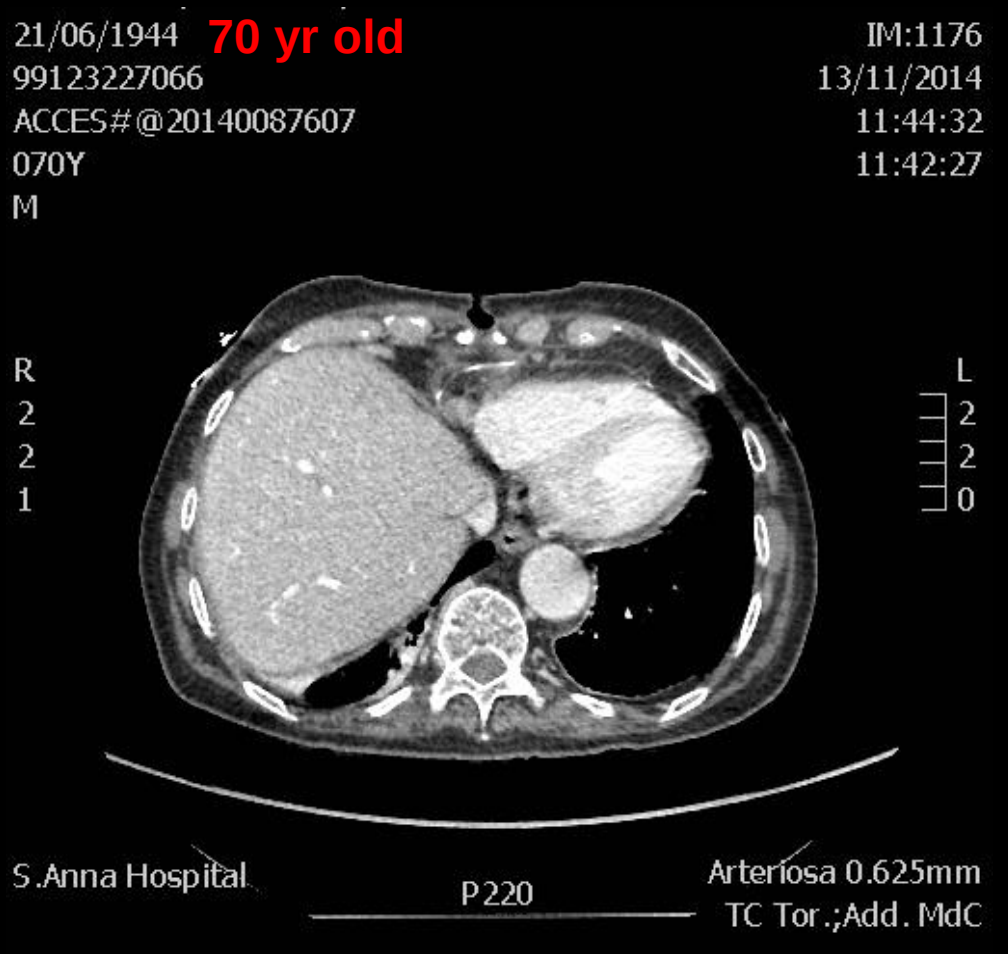
Current status of the treatment of metastatic colorectal cancer with EGFR inhibitors

Conclusions

Multidisciplinary therapies (med → surg → med, etc.) for metastatic colorectal cancer

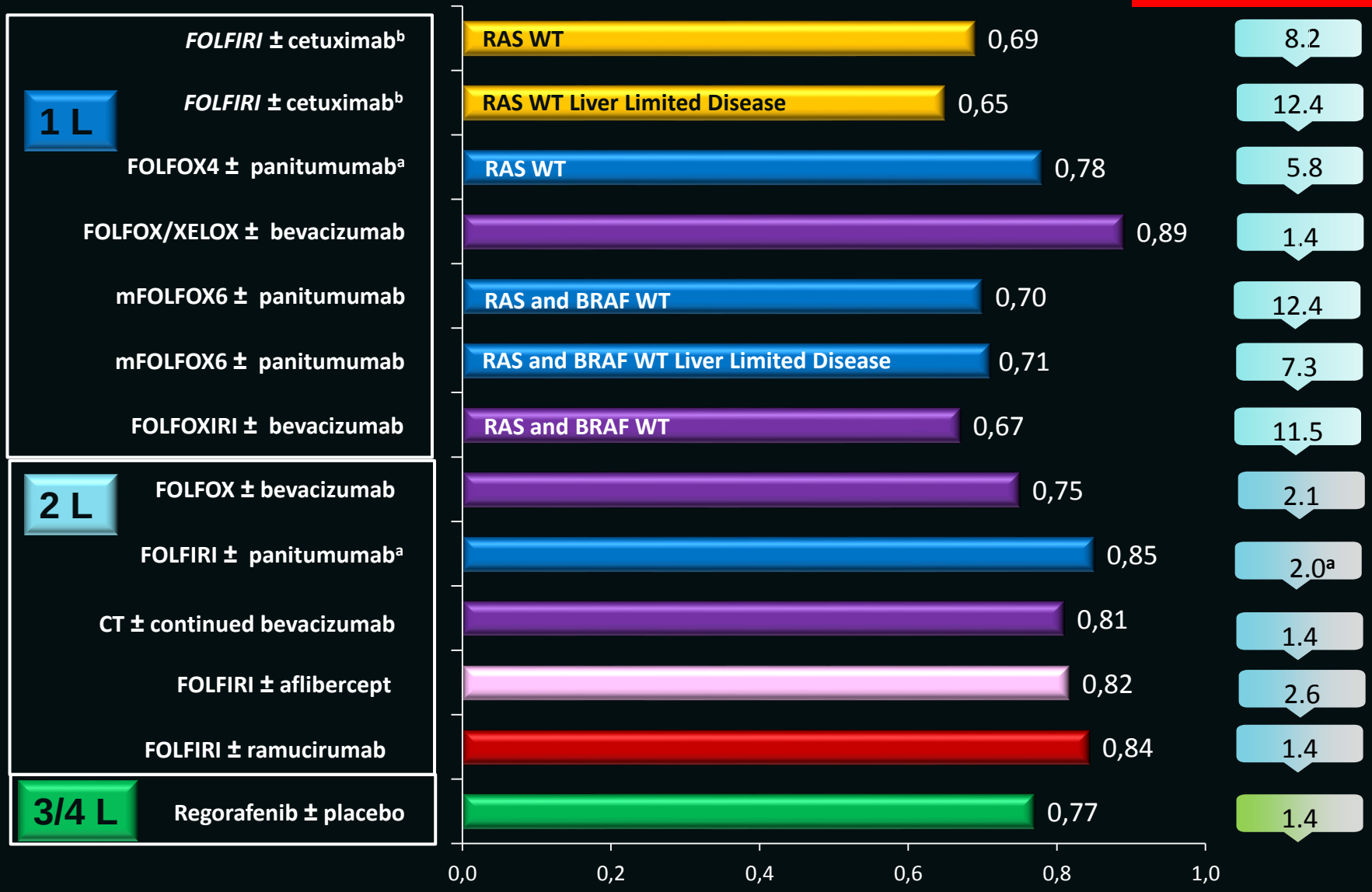


November 2005

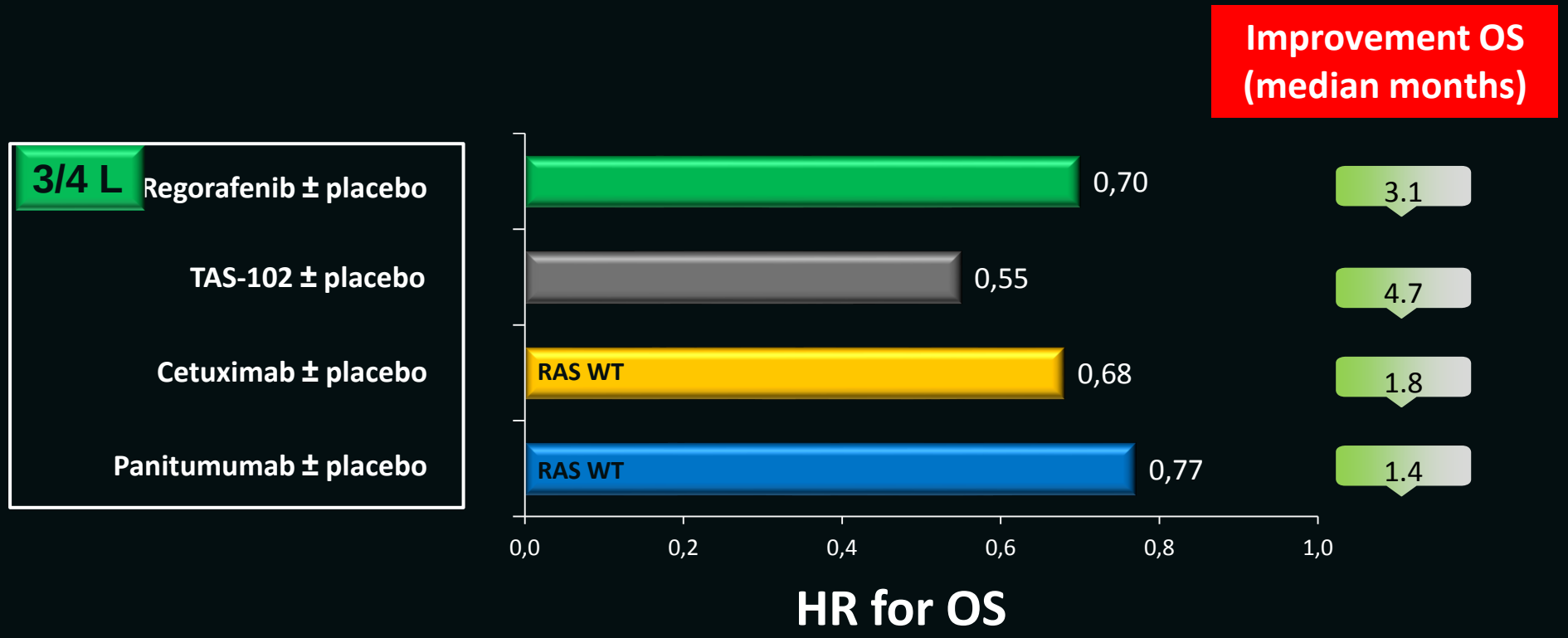


November 2014

Proportional impact on magnitude of OS benefit achieved across the continuum of care



Proportional impact on magnitude of OS benefit achieved across the continuum of care



Bench to bedside and viceversa collaboration
Ospedale Niguarda (Milano) & IRCC Candiolo (Torino)

Ospedale Niguarda Cancer Center

Sistema Socio Sanitario
Regione Lombardia

UNIVERSITÀ DEGLI STUDI DI MILANO

IRCC
INSTITUTE FOR CANCER RESEARCH AND TREATMENT

COLTHERES
colon therapy research consortium

5x1000
AIRC = RICERCA

AIRC
ASSOCIAZIONE ITALIANA
PER LA RICERCA SUL CANCRO

MOTRICOLOR

ROL
Rete Oncologica Lombarda

FONDAZIONE ONCOLOGIA NIGUARDA ONLUS

partnerships with big-, medium-, and small-size pharma