Anti-EGFR Treatment in mCRC

The Right Patient at the Right Time

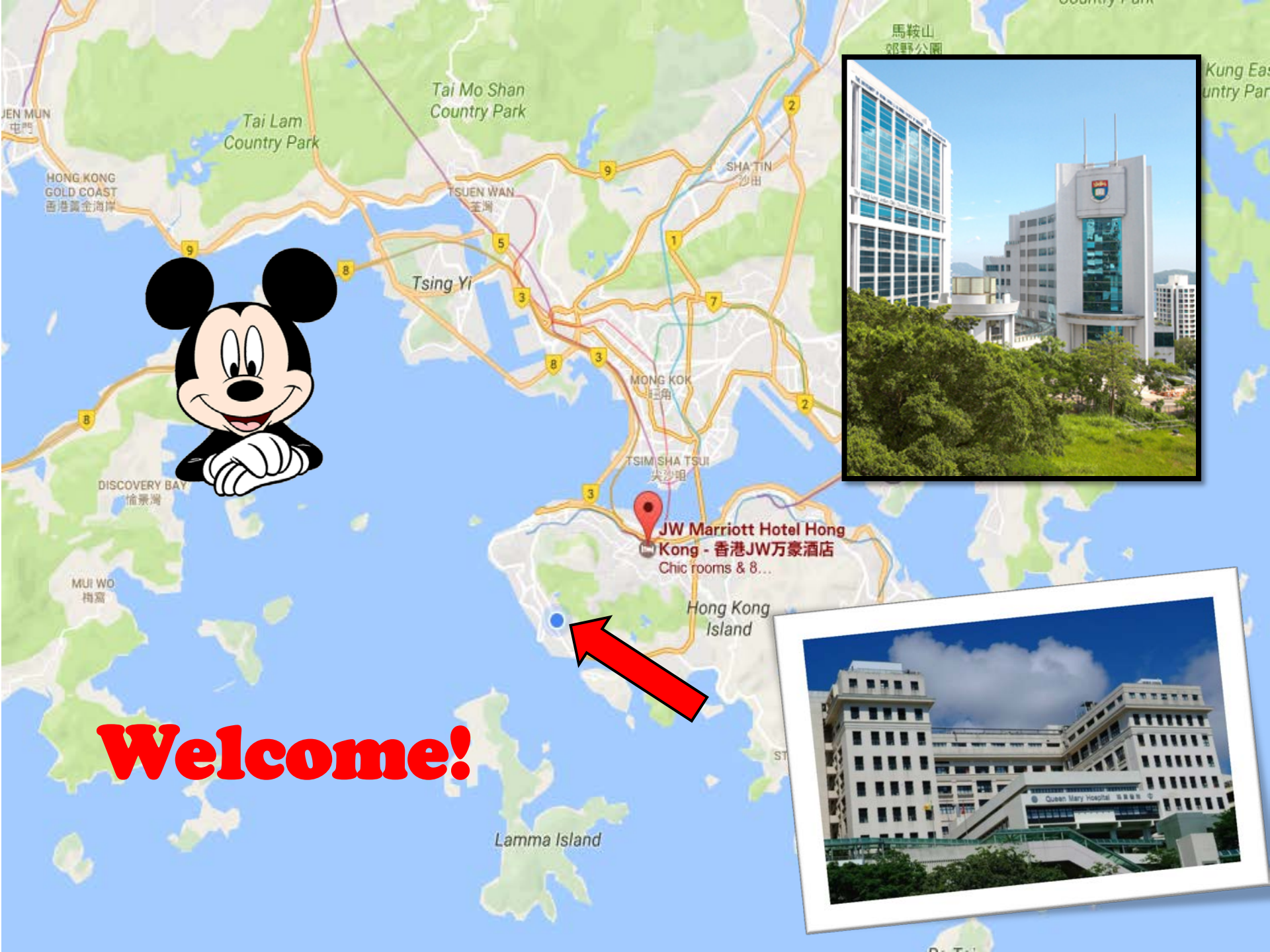
Dr. Lam Ka-On
Clinical Assistant Professor
Dept. of Clinical Oncology
LKS Faculty of Medicine
The University of Hong Kong
Queen Mary Hospital

Disclosure

Grants/Research Support: Bayer, Roche, Taiho

Advisory Board/Honoraria:

Amgen, Bayer, Eli Lilly, Merck, Roche, Sanofi-Aventis, Taiho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Country Park
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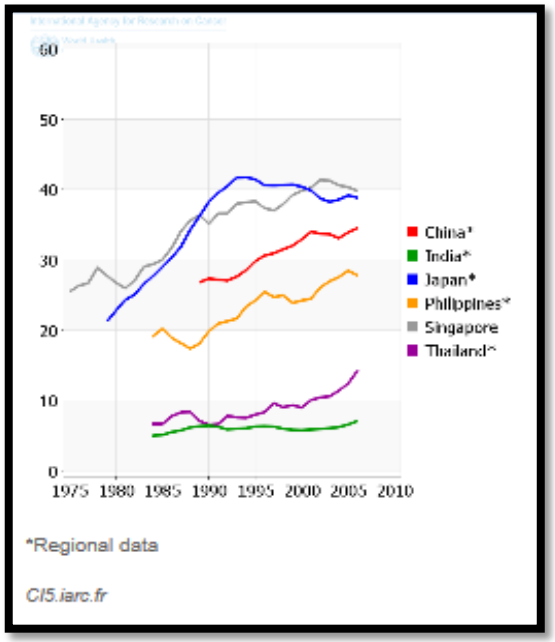
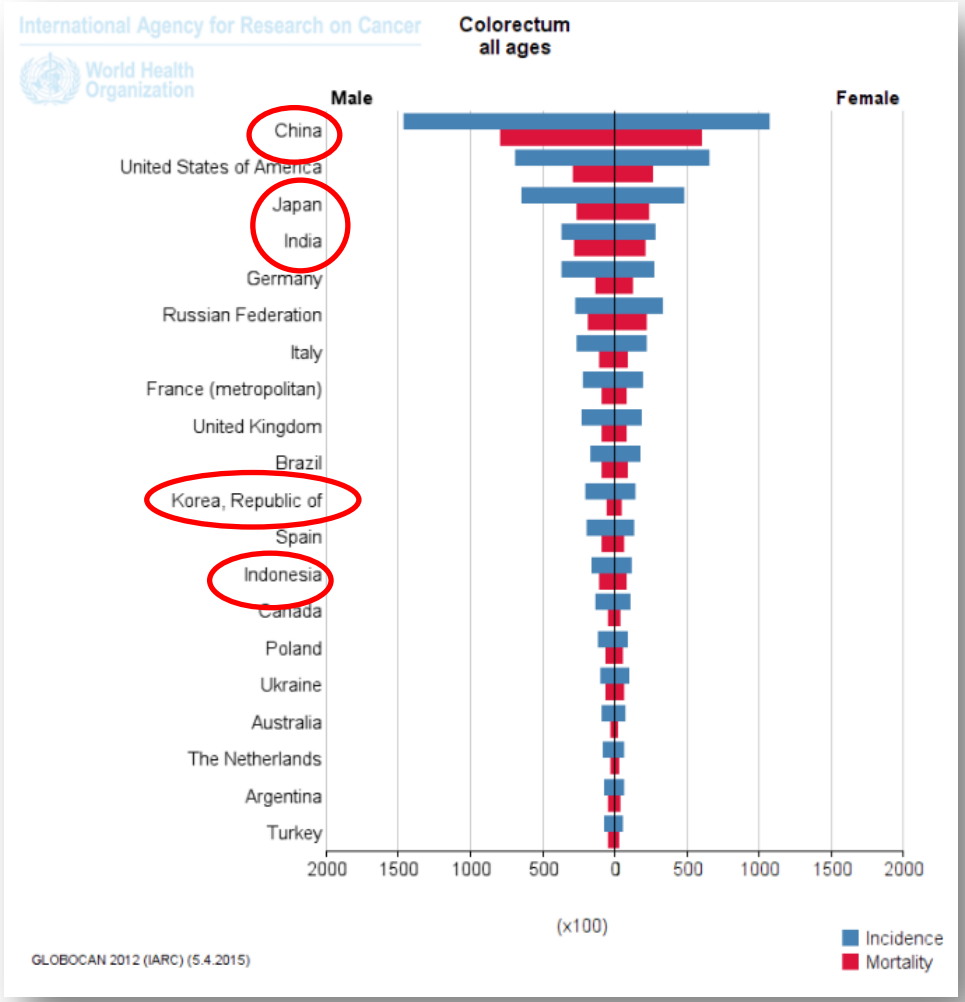
HONG KONG
GOLD COAST
TSUEN WAN
SHA TIN
Tsing Yi
MONG KOK
TSIM SHA TSUI
DISCOVERY BAY
JW Marriott Hotel Hong
Kong - 香港JW万豪酒店
Chic rooms & 8...
MUI WO
Hong Kong
Island
Lamma Island
Welcome!

Outline

- CRC as a healthcare burden in Asia
- Right Patients: Biomarkers, Sideness
- Right Time: Sequence, Maintenance, Beyond Progression, Rechallenge

CRC: Major Cancer Burden In Asia

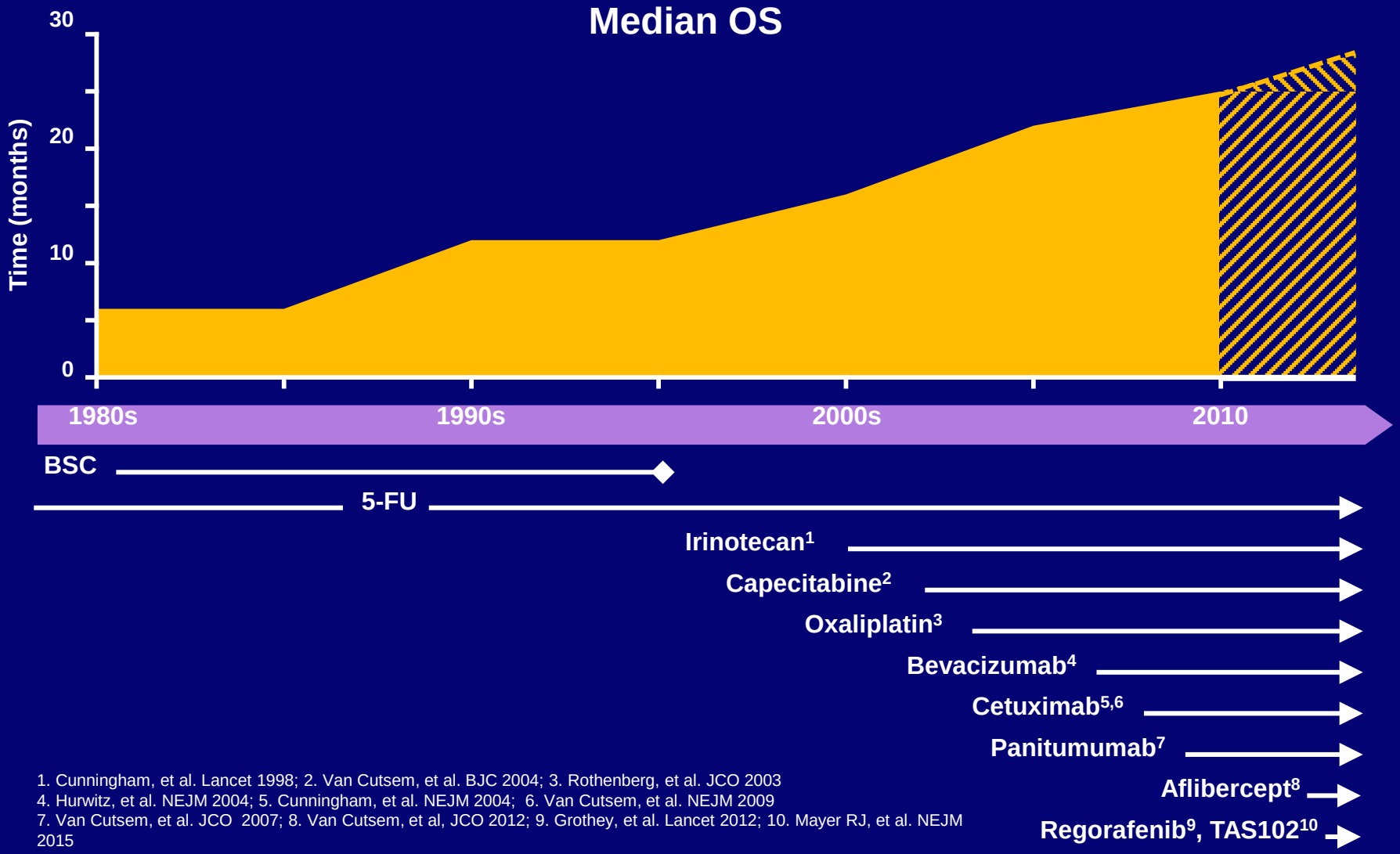




CRC in Hong Kong

	Hong Kong
Population	**7M**
Healthcare System	**Dual Public/ Private**
Health Care Expenditure (% of GDP)	**5.4**
Colorectal Cancer	
Incidence	**1st**
ASR (Male/ Female)	**41.8/ 26.4**
Reimbursement	**Only for potentially resectable cases**

In the past 3 decades, advances in the treatment of mCRC have led to improved OS



1. Cunningham, et al. Lancet 1998; 2. Van Cutsem, et al. BJC 2004; 3. Rothenberg, et al. JCO 2003
4. Hurwitz, et al. NEJM 2004; 5. Cunningham, et al. NEJM 2004; 6. Van Cutsem, et al. NEJM 2009
7. Van Cutsem, et al. JCO 2007; 8. Van Cutsem, et al, JCO 2012; 9. Grothey, et al. Lancet 2012; 10. Mayer RJ, et al. NEJM 2015

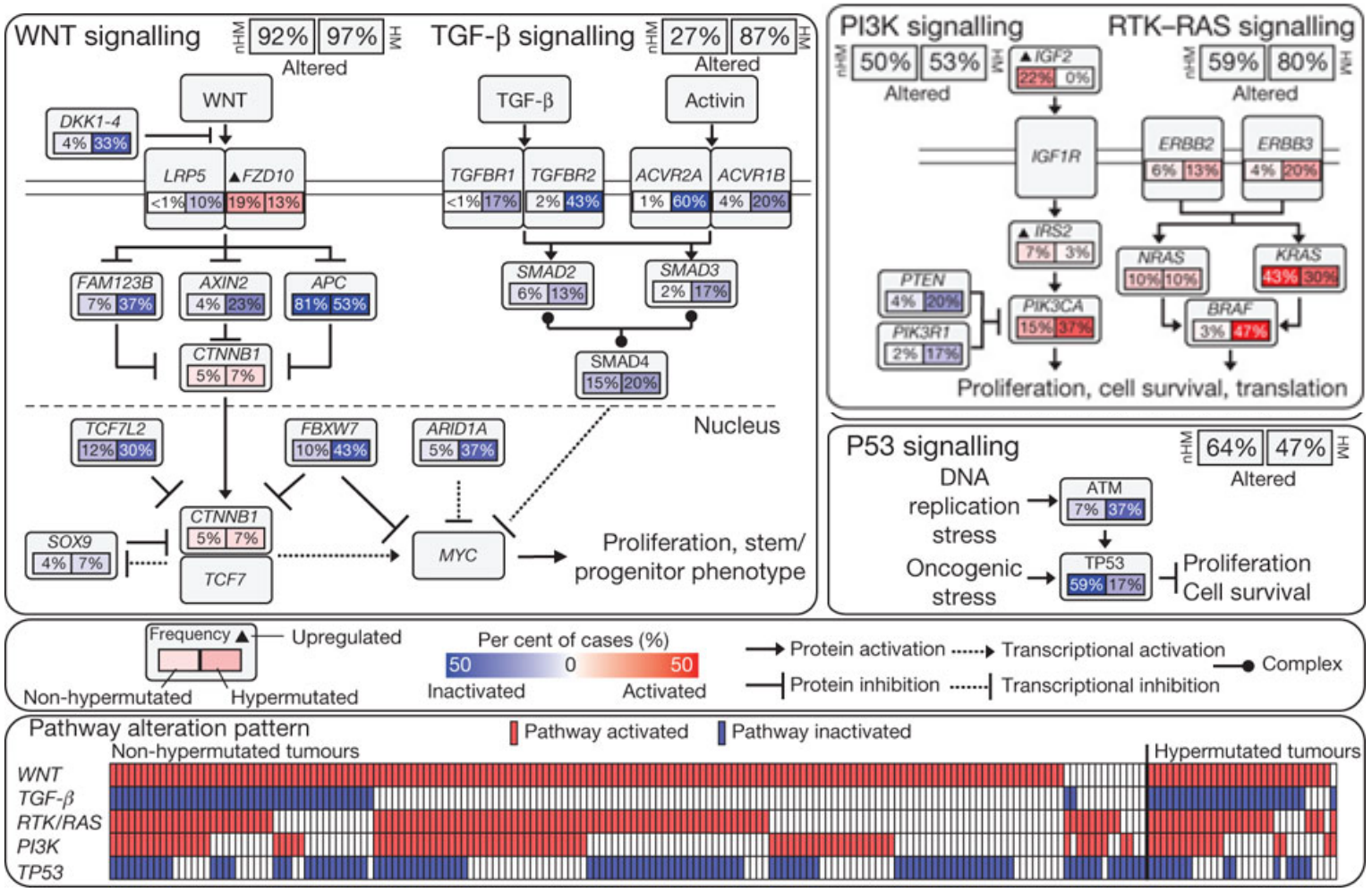
Treatment Access Across Asia

	Hong Kong	Japan	South Korea	Singapore	Taiwan	Thailand
Funding of treatment for unresectable metastatic disease						
Fluoropyrimidine	Public	Partly by national insurance	National insurance	Subsidised	National insurance	Public
Oxaliplatin	Public	Partly by national insurance	National insurance	Patient	National insurance	Patient (except civil servants)
Irinotecan	Public	Partly by national insurance	National insurance	Subsidised	National insurance	Patient (except civil servants who are covered)
Bevacizumab	Patient	Partly by national insurance	Patient	Patient	National insurance (only first line with chemotherapy)	Patient (except civil servants with preauthorisation)
Cetuximab	Patient (government care fund to help those who cannot afford)	Partly by national insurance	Patient	Patient	National insurance (only for refractory disease)	Patient (except in certain cases for civil servants)

Treatment access and affordability

Ku G, et al. Lancet Oncol 2012;13:e470-81

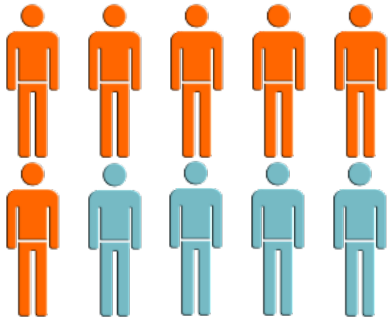
Dysfunctional Signalling Pathways in CRC



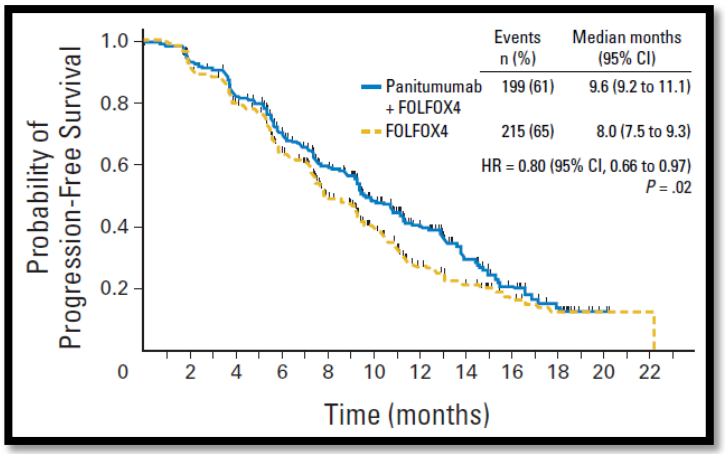
nature

The Cancer Genome Atlas Network Nature **487**, 330-337 (2012) doi:10.1038/nature11252

Defining The Biomarker

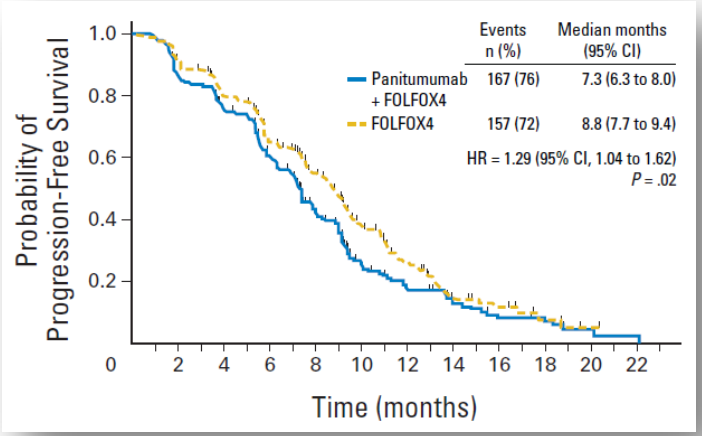


KRAS Wild-type



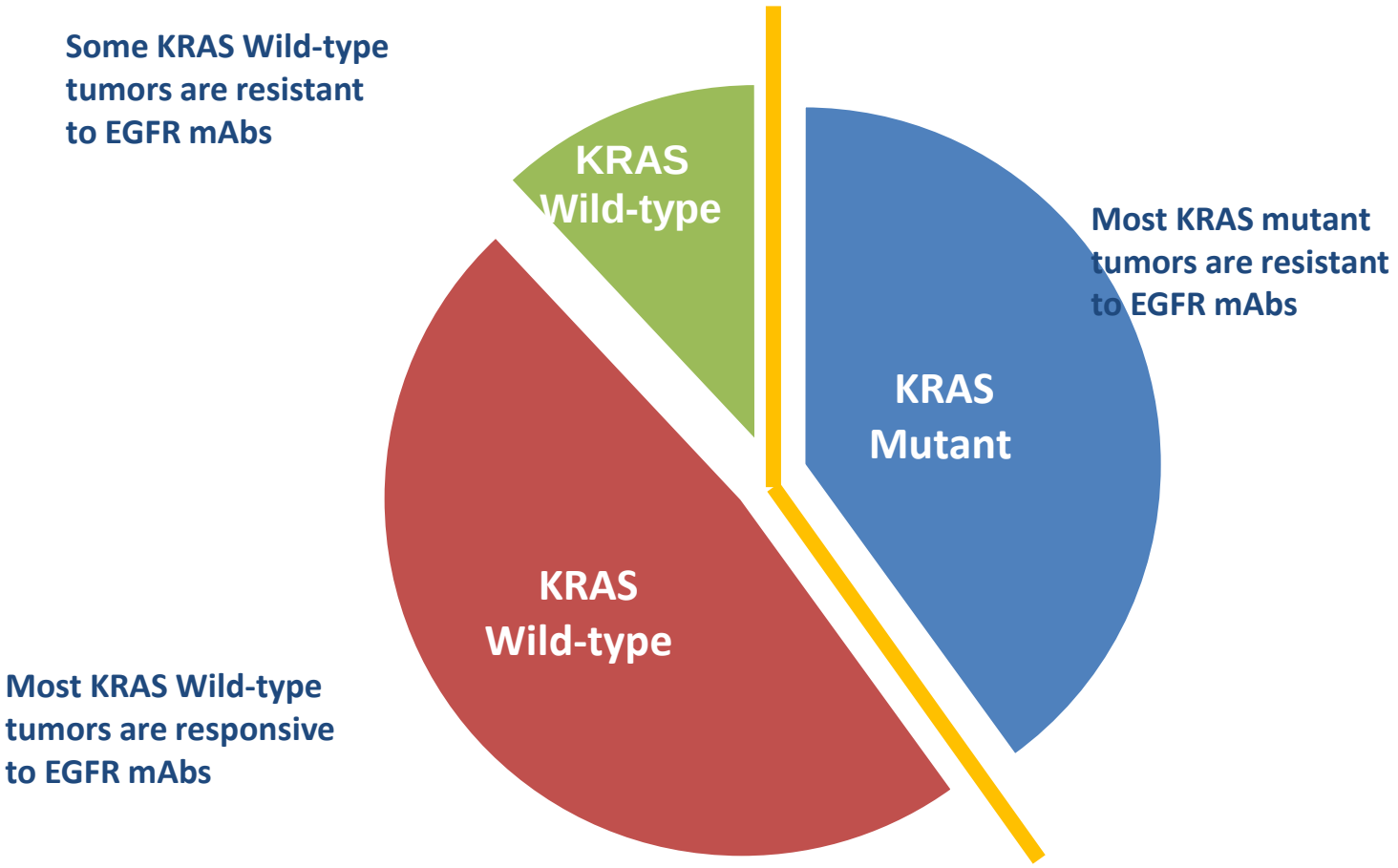
PRIME STUDY

KRAS Mutant



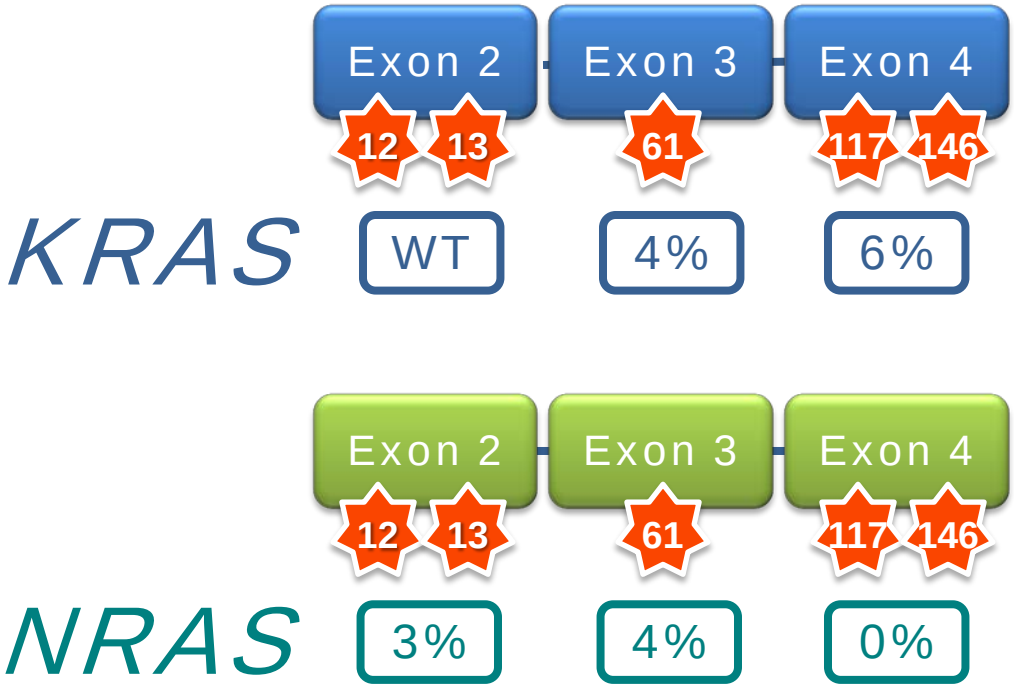
Douillard JY, et al. J Clin Oncol 2010;28:4697-4705

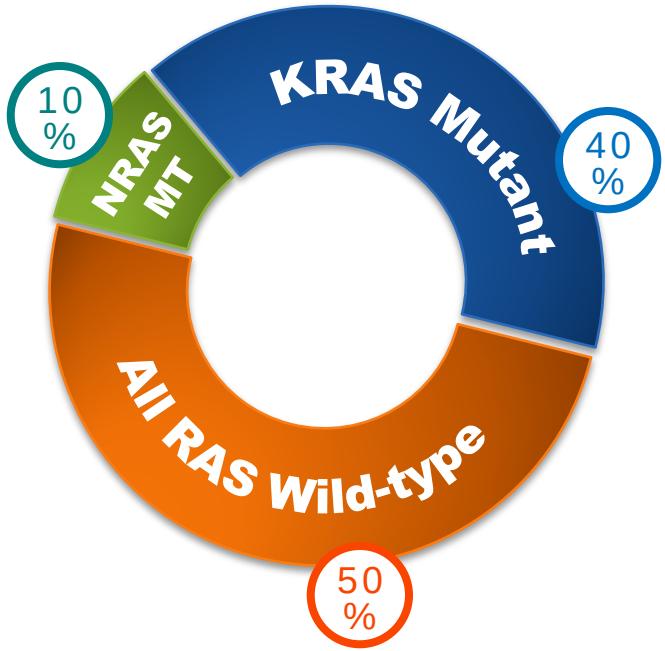
Kras (exon 2) mutation and Beyond



Detecting other alterations in the EGFR pathway that contribute to resistance may help select patients most likely to respond to treatment

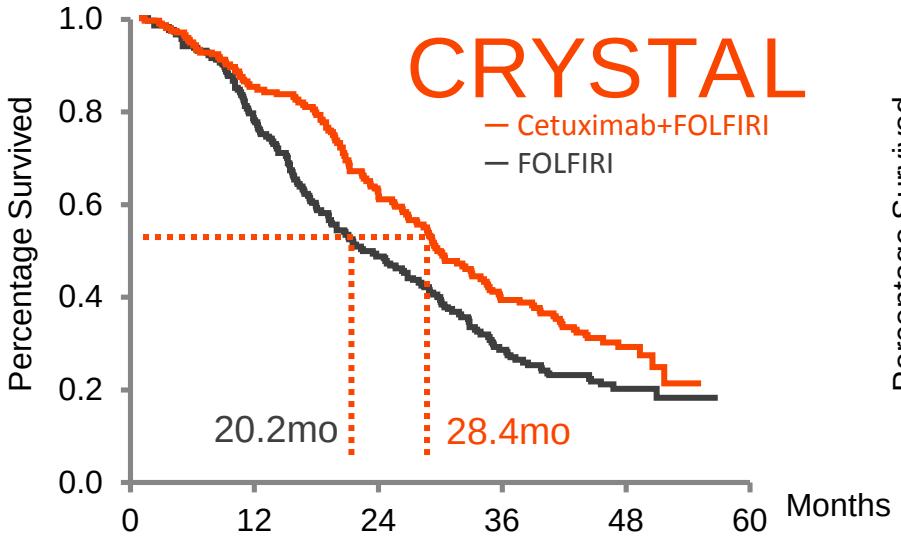
Prevalence of RAS Mutations

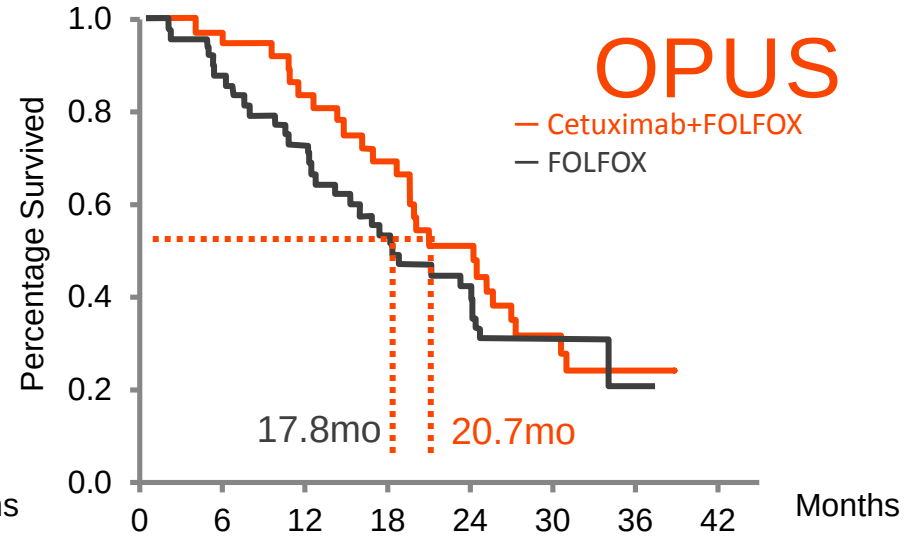


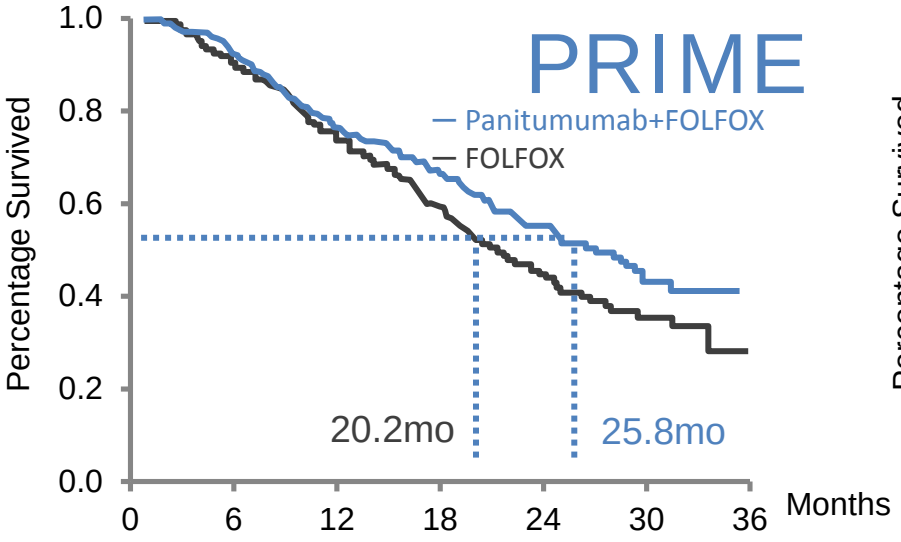


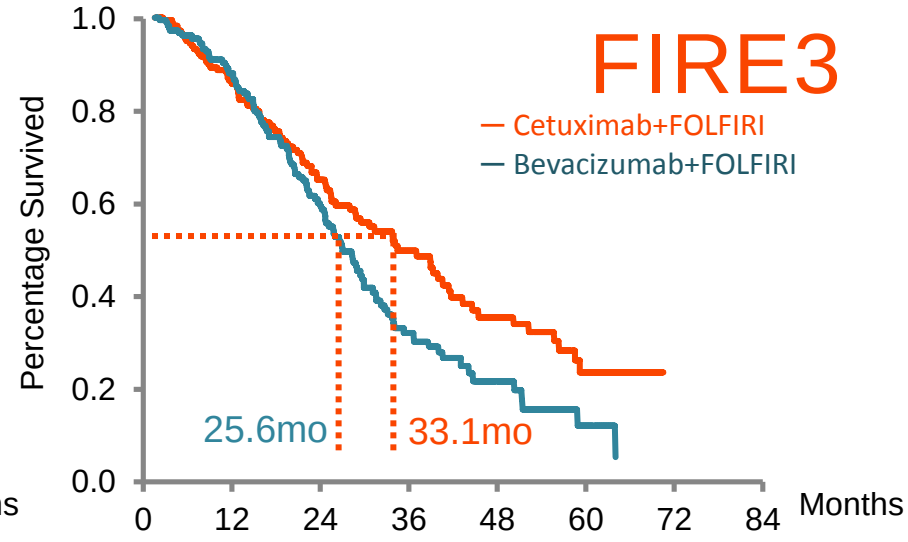
Douillard J-Y, et al. N Engl J Med 2013;369:1023–1034

OS of Latest Randomized Trials of Anti-EGFRs with RAS Mutation Analysis



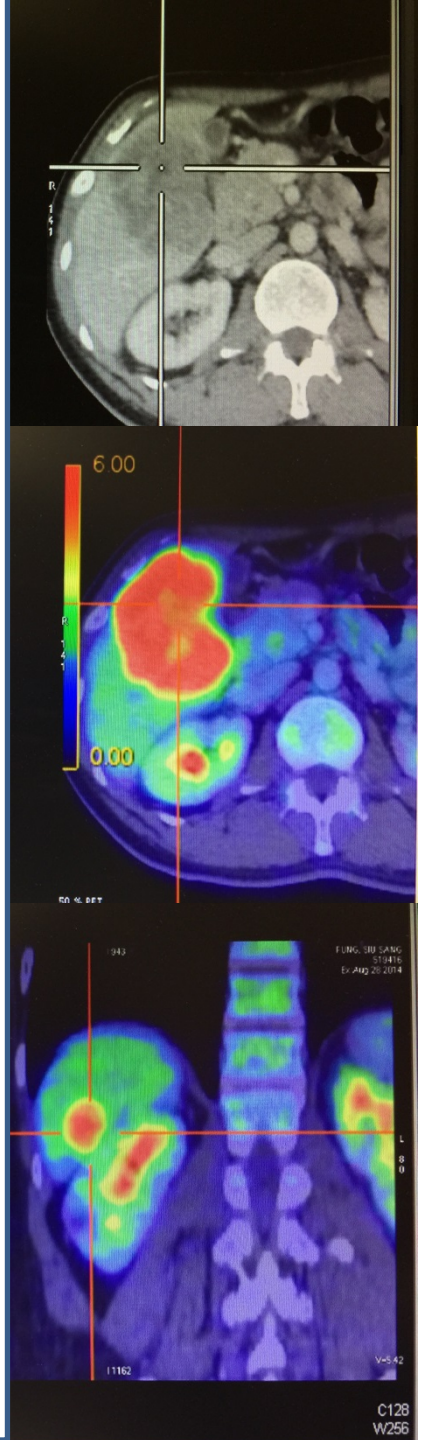






The Right Patient

- M/ 46
- Chronic smoker and drinker
- DM on diamicron
- Presented with diarrhoea and FOBT +ve
- CLN: circumferential sigmoid tumor
- Biopsy: adenoCA, RAS and BRAF wild type



The Right Patient

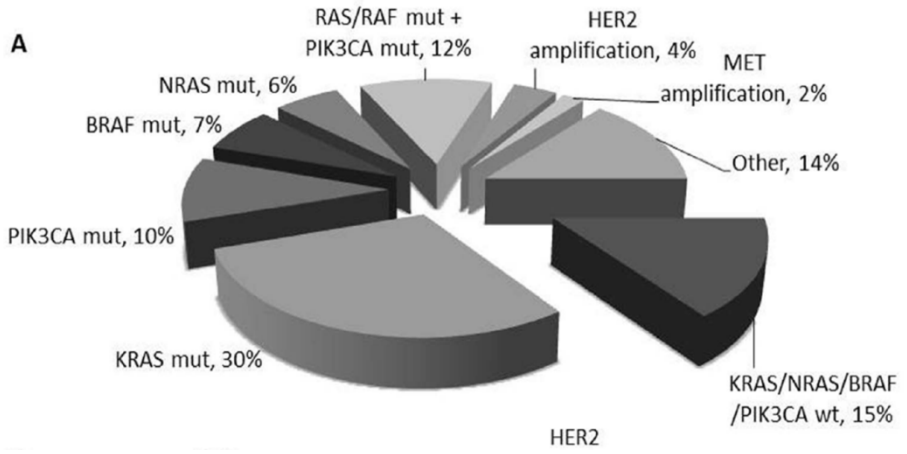
- PET/CT on 28 Aug 2014
  - Hypermetabolic sigmoid tumor
  - Multiple liver metastases at Seg 2, 5, 6
- CEA rapidly increasing: 604 to 1226 in 2 weeks
- MDT: to reassess after induction therapy
- Given Panitumumab + FOLFOX for 3 cycles since 4/9/2014

The Right Patient

- CEA 1226 to 133 after 1st cycle and then 39 after 3rd cycle
- Left hemicolectomy + Right hepatectomy + Segmentectomy on 20/11/2014
  - Pathology: ypT3N0M1 MD AdenoCA
- Received 6 months of postop therapy
- Yearly PET/CT showed no evidence of recurrence

Beyond RAS

- Activating RAS mutation predicts resistance to anti-EGFR mAbs
- Not all patients with RAS-wild type tumors respond to anti-EGFR mAbs
- And why…



Positive predictors

VOLUME 25 · NUMBER 22 · AUGUST 1 2007
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Expression of Epiregulin and Amphiregulin and *K-ras* Mutation Status Predict Disease Control in Metastatic Colorectal Cancer Patients Treated With Cetuximab

Shirin Khambata-Ford, Christopher R. Garrett, Neal J. Meropol, Mark Basik, Christopher T. Harbison, Shujian Wu, Tai W. Wong, Xin Huang, Chris H. Takimoto, Andrew K. Godwin, Benjamin R. Tan, Smitha S. Krishnamurthi, Howard A. Burris III, Elizabeth A. Poplin, Manuel Hidalgo, Jose Baselga, Edwin A. Clark, and David J. Mauro

From the Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton;

Gene copy number for epidermal growth factor receptor (EGFR) and clinical response to antiEGFR treatment in colorectal cancer: a cohort study

Mauro Moroni, Silvio Veronese,* Silvia Benvenuti,* Giovanna Marrapese, Andrea Sartore-Bianchi, Federica Di Nicolantonio, Marcello Gambacorta, Salvatore Siena, Alberto Bardelli*

Lancet Oncol 2005; 6: 279–86
Published online April 14, 2005
DOI 10.1016/S1470-2045(05)

VOLUME 25 · NUMBER 22 · AUGUST 1 2007
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

VOLUME 27 · NUMBER 30 · OCTOBER 20 2009
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Amphiregulin and Epiregulin mRNA Expression in Primary Tumors Predicts Outcome in Metastatic Colorectal Cancer Treated With Cetuximab

Bart Jacobs, Wendy De Roock, Hubert Piessevaux, Robin Van Oirbeek, Bart Biesmans, Jef De Schutter, Steffen Fieuws, Jo Vandesompele, Marc Peeters, Jean-Luc Van Laethem, Yves Humblet, Frederique Pénault-Llorca, Gert De Hertogh, Pierre Laurent-Puig, Eric Van Cutsem, and Sabine Tejpar

From the Department of Pathology, Digestive Oncology Unit, and Center for

Epidermal Growth Factor Receptor Gene Copy Number and Clinical Outcome of Metastatic Colorectal Cancer Treated With Panitumumab

Andrea Sartore-Bianchi, Mauro Moroni, Silvio Veronese, Carlo Carnaghi, Emilio Bajetta, Gabriele Luppi, Alberto Sobrero, Carlo Barone, Stefano Cascinu, Giuseppe Colucci, Enrico Cortesi, Michele Nichelatti, Marcello Gambacorta, and Salvatore Siena

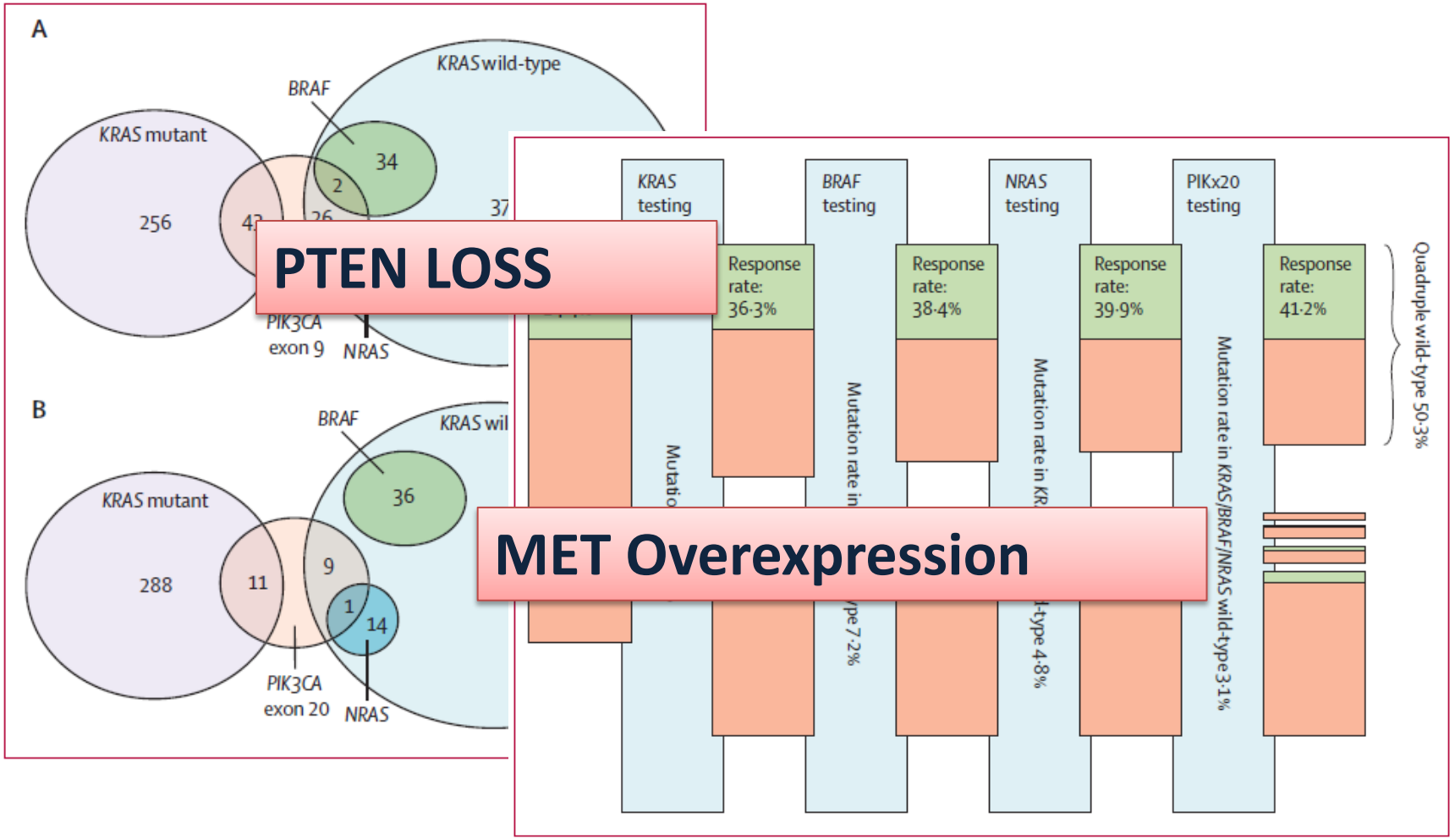
Cancer Therapy: Clinical

Clinical Usefulness of *EGFR* Gene Copy Number as a Predictive Marker in Colorectal Cancer Patients Treated with Cetuximab: A Fluorescent *In situ* Hybridization Study

Nicola Personeni,[1] Steffen Fieuws,[3] Hubert Piessevaux,[5] Gert De Hertogh,[2] Jef De Schutter,[4] Bart Biesmans,[4] Wendy De Roock,[4] An Capoen,[2] Maria Debiec-Rychter,[4] Jean-Luc Van Laethem,[6] Marc Peeters,[8] Yves Humblet,[7] Eric Van Cutsem,[1] and Sabine Tejpar[1]

Personeni N, et al. Clin Cancer Res 2008;14:5869-76. Moroni M, et al. Lancet Oncol 2005;6:279-86. Sartore-Bianchi A, et al. J Clin Oncol 2007;25:3238-45. Jacobs B, et al. J Clin Oncol 2009;27:5068-74. Khambata-Ford S, et al. J Clin Oncol 2007;25:3230-37.

Negative Predictors

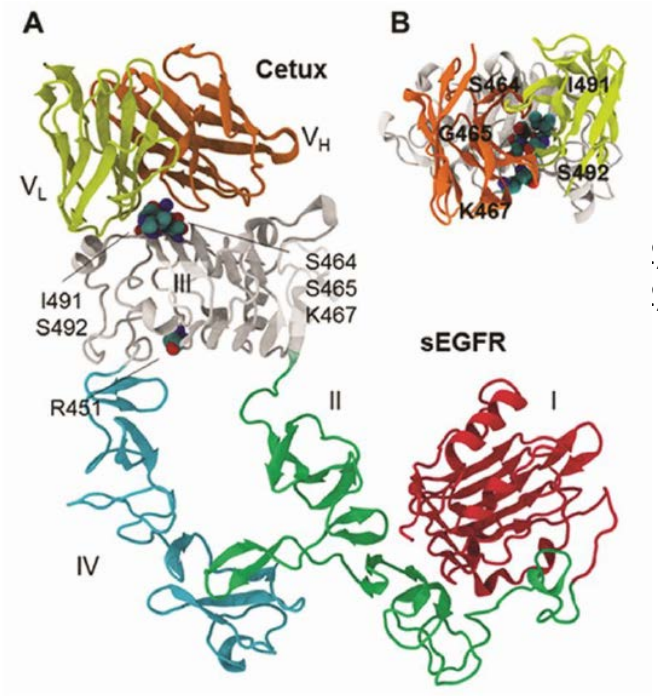


De Roock W, et al. Lancet Oncol 2010;11:753-62

Tumor Biology is Dynamic

Intrinsic tumor heterogeneity and treatment-related selection pressure

- Emergence of RAS mutatio
  - Circulating tumor DNA



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;486:537-540

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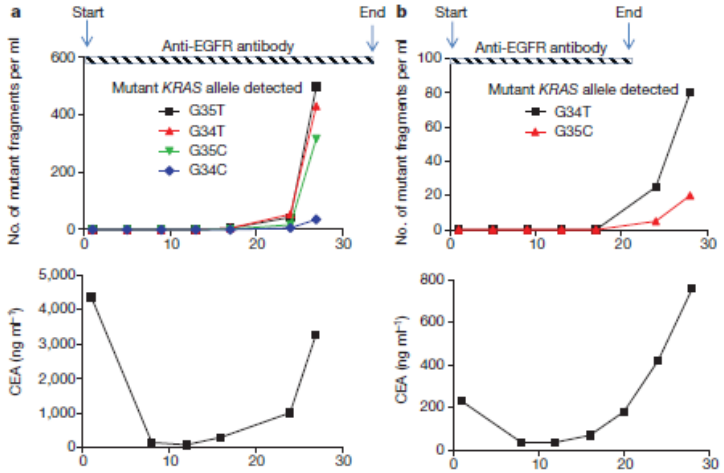

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13;3:658-673

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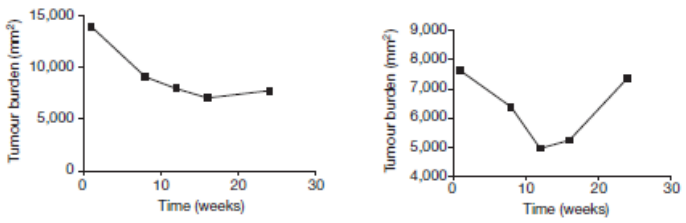

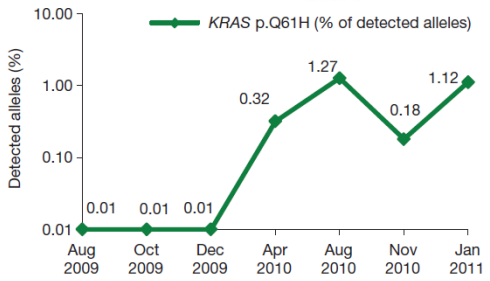

2;18:221-223

rena S, et

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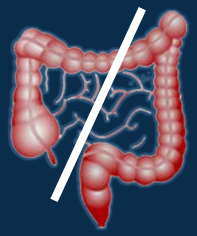
Right- and left-sided primary colon tumours have distinct biology[1]



Right-sided		Left-sided
Lower Increasing Female	**Incidence**	Higher Decreasing Male
Higher TNM stage Larger tumours More mucinous type	**Presentation**	Lower TNM stage Smaller tumours
MUTYH-associated polyposis	**Genetics**	Familial adenomatous polyposis
More active immune cells promoting immunogenicity	**Immunology**	Immunologically less active, promoting tolerogenesis
CIMP/MSI/BRAF positive tumours predominate	**Molecular pathway**	Chromosomal instability tumours predominate
Worse	**Survival**	Better

Review included six meta-analyses, 12 reviews, 62 observational studies and seven additional supporting articles
BRAF, v-raf murine sarcoma viral oncogene homolog B1; CIMP, cytosine-guanosine (CpG) island methylation phenotype; MSI, microsatellite instability; TNM, American Joint Committee on Cancer tumour–node–metastasis stage;

1. Lee GH, et al. Eur J Surg Oncol 2015;41:300–308

The Sideness Story

		R	L
CALGB	CET vs BEV	- 8.1	+ 5.4
FIRE III	CET vs BEV	- 4.7	+ 10.3
PEAK	PANI vs BEV	- 3.5	+ 11.4

R: Bev better than anti EGFR by 3.5 to 8.1 months

L: Anti EGFR better than BEV by 5.4 to 11.4 months

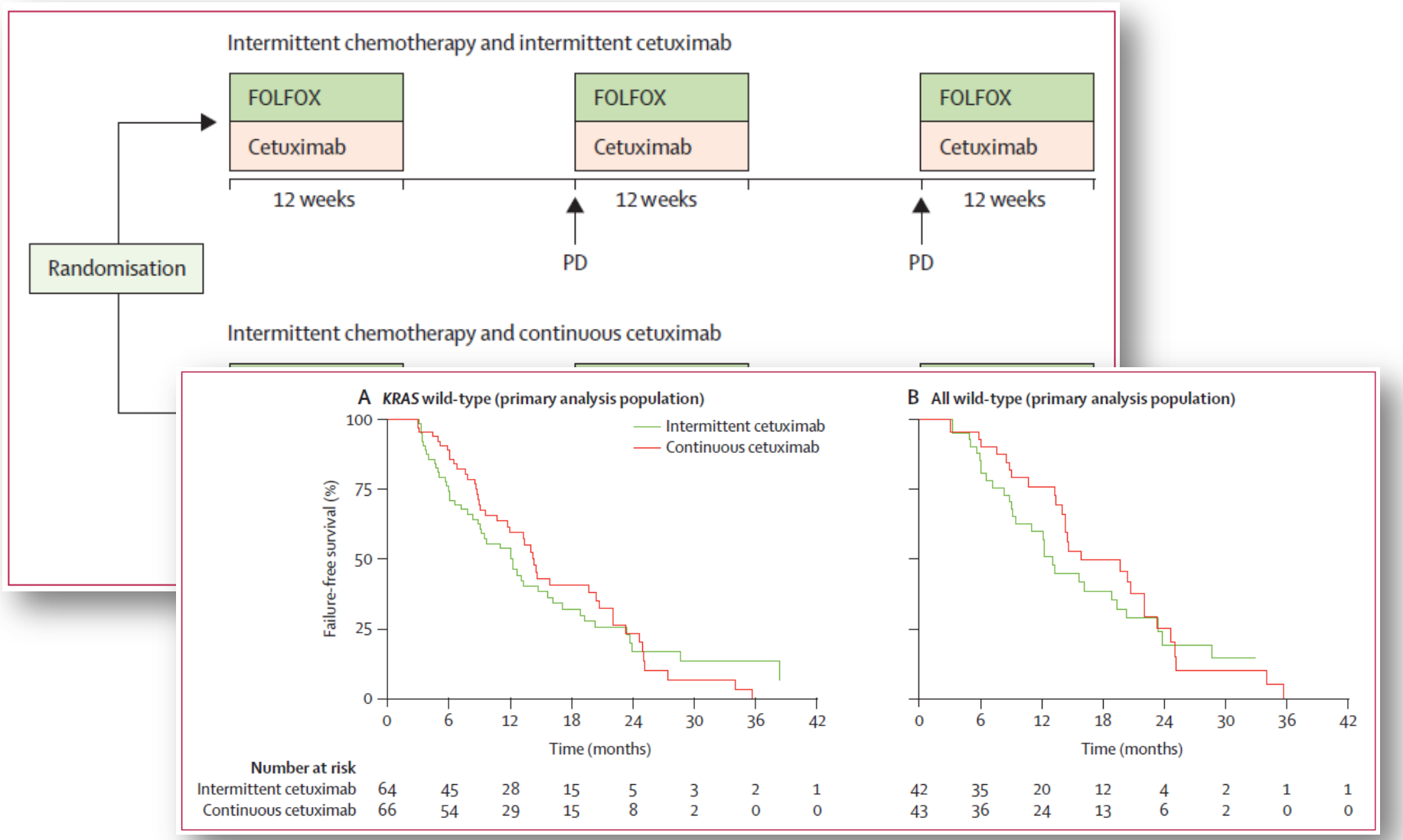
RIGHT TIME

Continuum of Care

- Sequence: Prof Tebbutt
- Maintenance
  - COIN B
  - Nordic VII
  - Nordic 7.5
  - MACRO II
- Beyond progression
- Rechallenge

MAINTENANCE

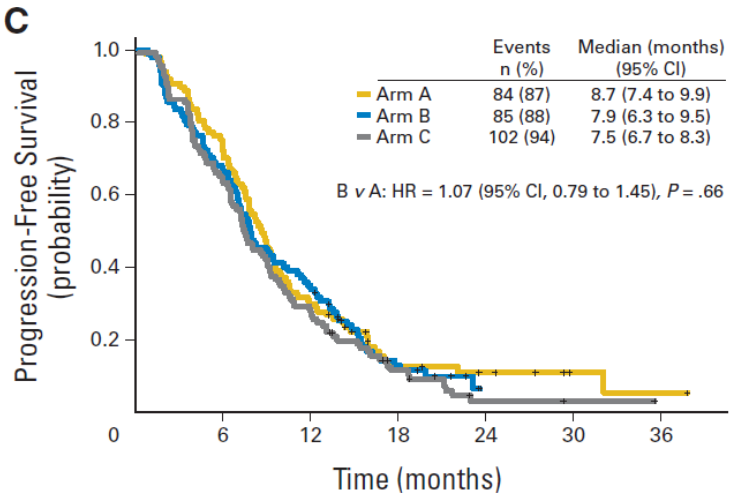
COIN B Study

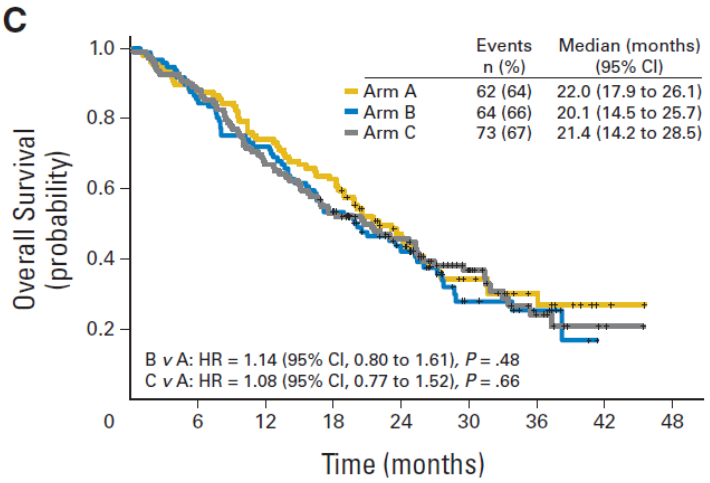


Wasan H, et al. Lancet Oncol 2014;15:631-39

Nordic VII

- Patients randomised to
  - FLOX (ARM A)
  - C + FLOX (ARM B)
  - C+ int. FLOX (ARM C)
- PFS and OS similar in all 3 study arms





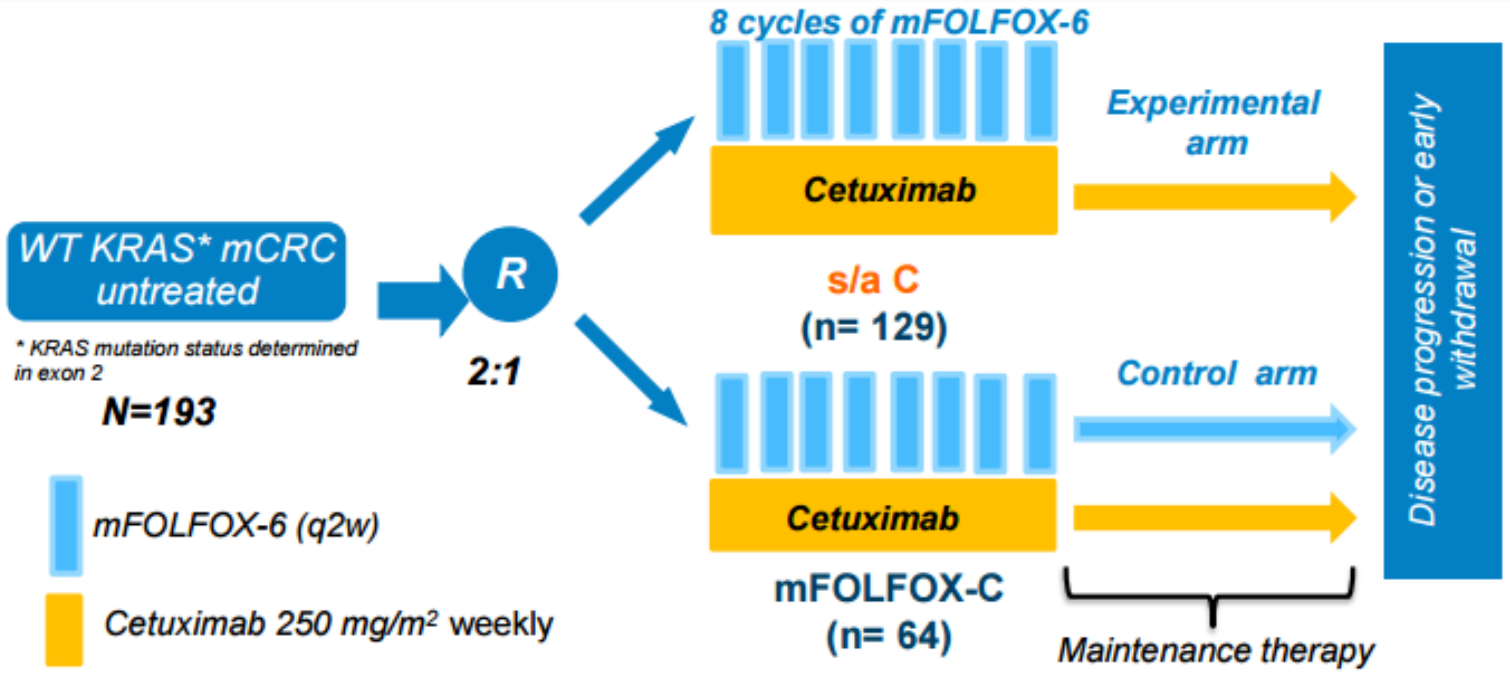
Tveit KM, et al. J Clin Oncol 2012;30:1755-1762

Nordic 7.5

- Multicentere phase II study
- 152 Kras wild-type patients
- C+ FLOX followed by maintenance C in 1st line after 16 weeks of FLOX
- RR: 62%
- mPFS: 8months
- mOS: 23.2months
- Conclusion: biweekly cetuximab was safely integrated in an intermittent chemotherapy strategy and might have added to a longer chemotherapy-free interval.

Pfeiffer P, et al. Clin Colorectal Cancer 2015;14:170-6

MACRO-2



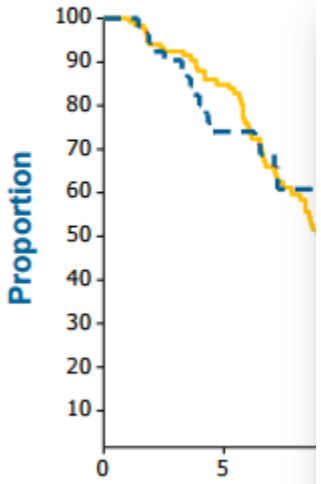
- Multicenter phase II study
- Non-inferiority of PFS at 9 months
- 193 Kras wild-type patients
- Randomised in 1st line setting:
- No significant difference in ORR, PFS
- or OS

	s/a C N = 129	FOLFOX-C N = 64
Patients free of progression at 9 months, n (%)	82 (63.6)	46 (71.9)
OR (95%CI)	0.6827 (0.3556 to 1.3108)	
P-value	0.25	

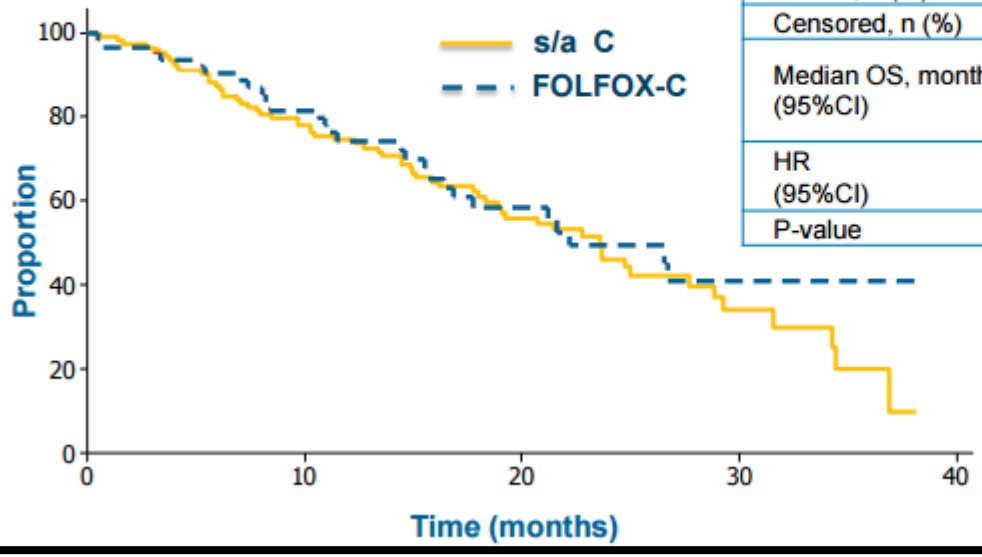
Garcia Alfonso P, et al. Abstract 4990 at ESMO 2014

Progression free-survival

	s/a C N = 129	FOLFOX-C N = 64
Events, n (%)	75 (58.1)	31 (48.4)
Censored, n (%)	54 (41.9)	33 (51.6)
Median PFS, months	8.9	9.8



Overall survival



	s/a C N = 129	FOLFOX-C N = 64
Events, n (%)	63 (48.8)	27 (42.1)
Censored, n (%)	66 (51.2)	37 (57.8)
Median OS, months (95%CI)	23.6 (18.3 to 28.9)	22.2 (16.4 –not estimable)
HR (95%CI)	1.151 (0.7330 to 1.8070)	
P-value	0.54	

	Evaluable RAS mutation status			Ras wild type			Ras mutated		
	Ras wild type N = 136	Ras mutated N = 33	HR/OR (95% CI; p-value)	Arm A N = 92	Arm B N = 44	HR/OR (95% CI; p-value)	Arm A N = 21	Arm B N = 12	HR/OR (95% CI; p-value)
mPFS, months	9.2	8.4	1.52 (0.91–2.53; 0.11)	9.1	9.8	0.86 (0.53–1.40; 0.54)	8.4	9.2	0.71 (0.25–2.06; 0.53)
mOS, months	25.1	17.6	1.75 (1.13–2.71; **0.01**)	24.8	26.7	0.80 (0.50–1.29; 0.37)	18.3	16.9	0.93 (0.41–2.07; 0.85)
ORR, %	52	24	3.41 (1.44–8.10; **0.004**)	54	48	1.30 (0.63–2.68; 0.47)	29	17	2.00 (0.33–11.97; 0.44)
PFS 9m rate, %	65	58	1.40 (0.64–3.03; 0.40)	63	70	0.72 (0.33–1.55; 0.40)	48	75	0.30 (0.06–1.45; 0.13)

*Fisher

Garcia Alfonso P, et al. Abstract 4990 at ESMO 2014
Aranda E, et al. Abstract 2122 at ECC 2015

Ongoing

- **VALENTINO: Panitumumab-based Maintenance in Patients With RAS Wild-type, Metastatic Colorectal Cancer**
- Fondazione IRCCS Istituto Nazionale dei Tumori, Milano (NCT02476045)
- Open label, randomized, multicenter, phase II
- Non-inferiority of PFS
- Induction FOLFOX-4 and panitumumab for 8 cycles. Then, in presence of disease control, they will receive at 1:1 ratio maintenance treatment **panitumumab alone** or **5-FU/LV plus panitumumab**

Ongoing

- **Randomized phase II study of maintenance treatment with 5-FU/FA plus panitumumab vs 5-FU/FA alone after induction (mFOLFOX6 plus panitumumab) in patients with RAS WT metastatic colorectal cancer**

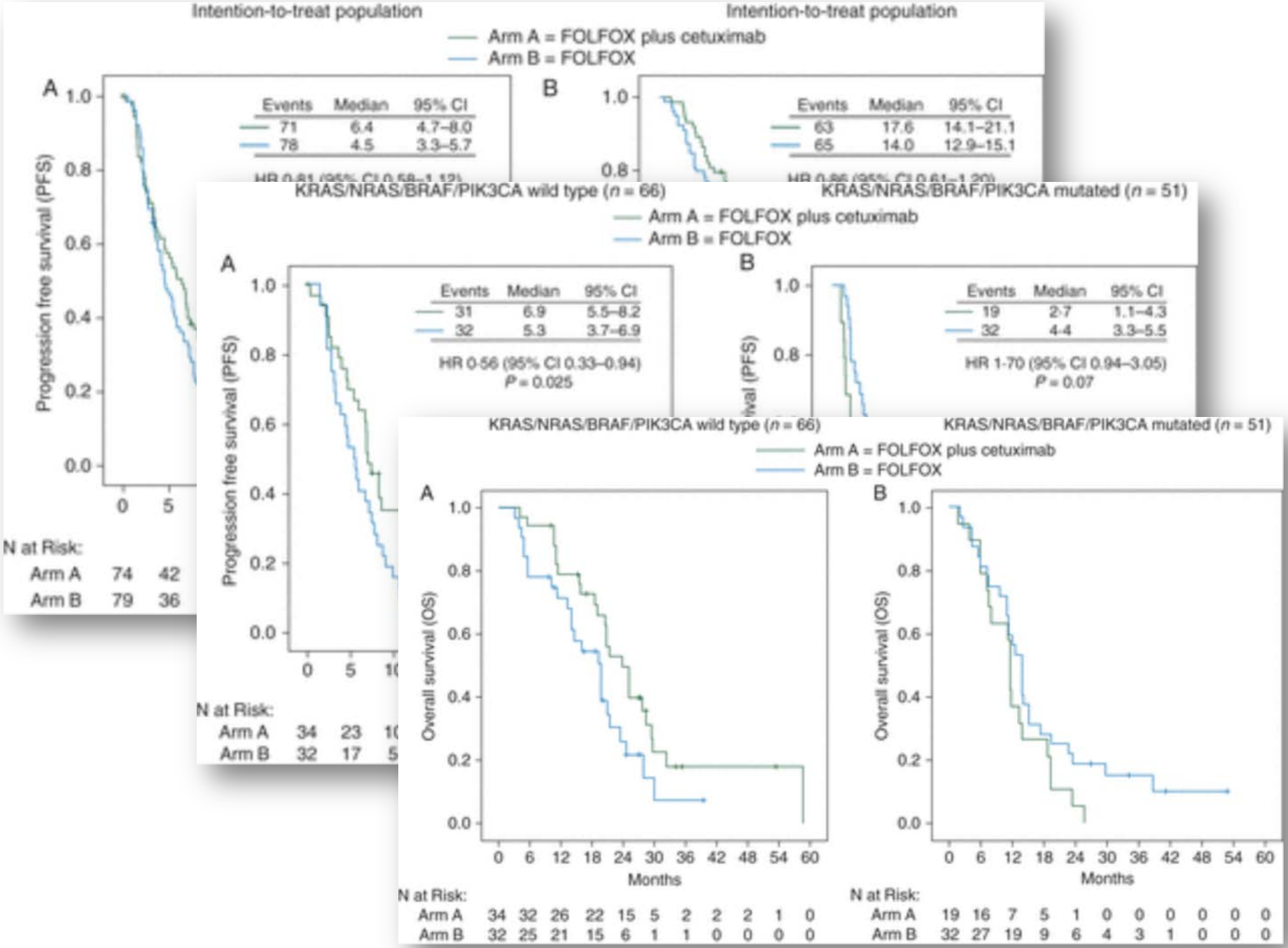
Modest DP, et al. Ann Oncol (2016) 27 (suppl_6): 605TiP

BEYOND PROGRESSION

CAPRI-GOIM

- **Cetuximab continuation after first progression in metastatic colorectal cancer (CAPRI-GOIM): a randomized phase II trial of FOLFOX plus cetuximab versus FOLFOX**
- Open-label, randomized phase II
- Failed 1st line cetuximab + FOLFIRI
- Primary end point: PFS

Ciardiello F, et al. Ann Oncol (2016) 27 (6): 1055-1061.


Intention-to-treat population
Arm A = FOLFOX plus cetuximab
Arm B = FOLFOX
A
Progression free survival (PFS)
Events Median 95% CI
71 6.4 4.7–8.0
78 4.5 3.3–5.7
N at Risk:
Arm A 74 42
Arm B 79 36
Intention-to-treat population
B
Events Median 95% CI
63 17.6 14.1–21.1
65 14.0 12.9–15.1
KRAS/NRAS/BRAF/PIK3CA wild type (n = 66)
KRAS/NRAS/BRAF/PIK3CA mutated (n = 51)
Arm A = FOLFOX plus cetuximab
Arm B = FOLFOX
A
Progression free survival (PFS)
Events Median 95% CI
31 6.9 5.5–8.2
32 5.3 3.7–6.9
HR 0·56 (95% CI 0·33–0·94)
P = 0.025
N at Risk:
Arm A 34 23
Arm B 32 17
B
Events Median 95% CI
19 2·7 1·1–4·3
32 4·4 3·3–5·5
HR 1·70 (95% CI 0·94–3·05)
P = 0.07
KRAS/NRAS/BRAF/PIK3CA wild type (n = 66)
KRAS/NRAS/BRAF/PIK3CA mutated (n = 51)
Arm A = FOLFOX plus cetuximab
Arm B = FOLFOX
A
Overall survival (OS)
Months
N at Risk:
Arm A 34 32 26 22 15 5 2 2 2 1 0
Arm B 32 25 21 15 6 1 1 0 0 0 0
B
Overall survival (OS)
Months
N at Risk:
Arm A 19 16 7 5 1 0 0 0 0 0 0
Arm B 32 27 19 9 6 4 3 1 0 0 0

Panitumumab
Beyond Progression on Cetuximab

- PANERB: 32 Kras wild type mCRC
  - Panitumumab after progression on cetuximab and irinotecan
  - ORR: 22% and DCR: 73% in 11 patients who had prior response to cetuximab
  - ORR: 7.7% and DCR: 15.4% in cetuximab resistant patients

- Wadlow RC, et al: similar single-arm PII study (n=20)
  - No response and DCR: 45%
  - mPFS 1.7m and mOS 5.2m
  - Panitumuab was well-tolerated

Metges J, et al. J Clin Oncol 28, 2010 (suppl;abstr e14000)
Wadlow RC, et al. The Oncologist Jan 2012:17;14-e34

Clinical Study

Single agent panitumumab in KRAS wild-type metastatic colorectal cancer patients following cetuximab-based regimens

Clinical outcome and biomarkers of efficacy

Filippo Pietrantonio, Federica Perrone, Pamela Biondani, Claudia Maggi, Andrea Lampis, Claudia Bertan, ...show all

Pages 1098-1103 | Received 10 Apr 2013, Accepted 02 Sep 2013, Published online: 04 Sep 2013

- Retrospective
- 30 patients at 9 Italian centers with clinical benefit from prior cetuximab regimen
  - ORR: 30% (40% in RAS/BRAF/PI3KCA wild type)
  - DCR: 67%
  - mPFS: 4.2months
  - mOS: 9.6months

Pietrantonio F, et al. Cancer Biol Ther 2013;14: 1098-1103

RECHALLENGE

Reintroduction vs Rechallenge

Reintroduction[1]

No progression of CRC while on therapy

Treatment was either of a set duration (eg, adjuvant) or was stopped for a planned break (eg, to reduce or manage AEs)

≠

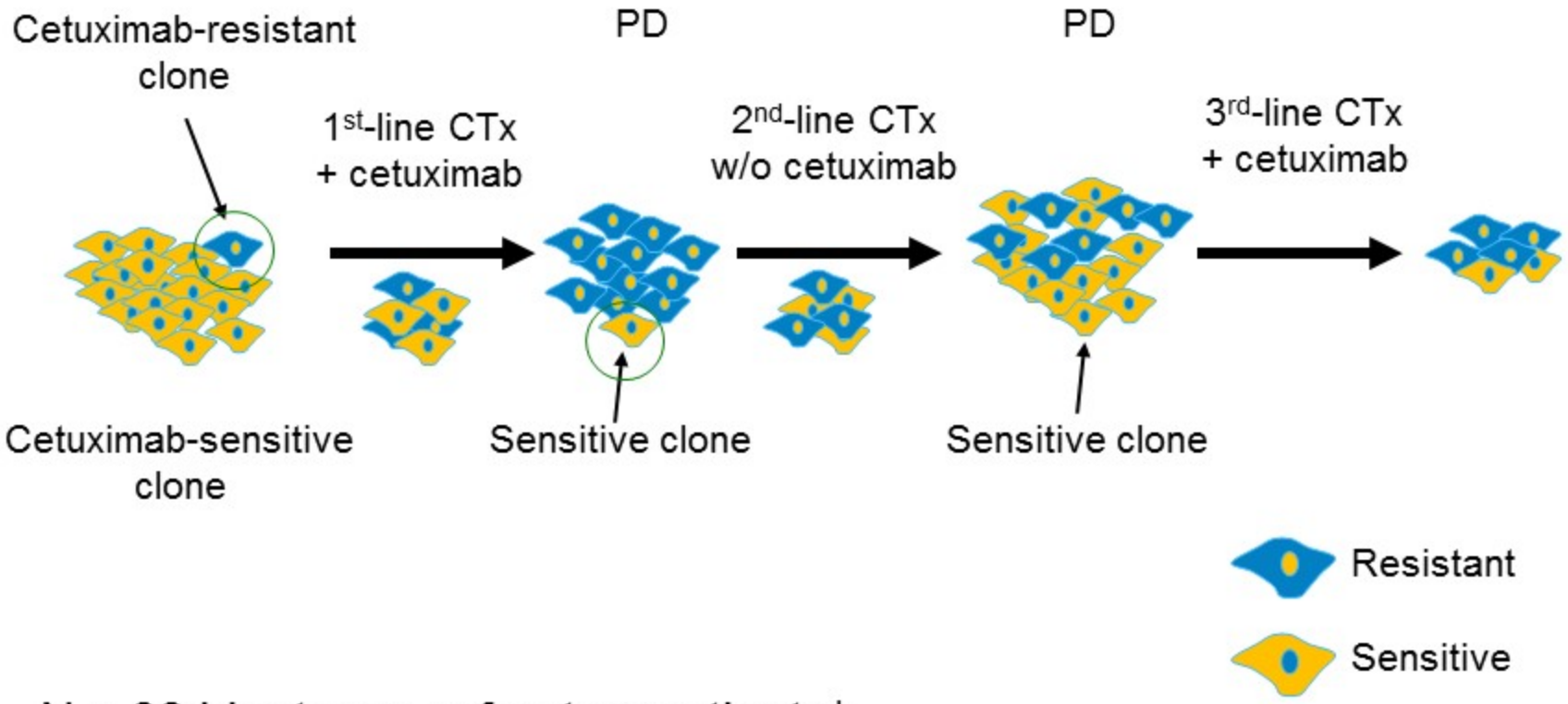
Rechallenge[2]

Reintroduction, after an intervening treatment, of the same therapy to which tumour has already proved to be resistant

The disease is challenged with the same regimen/agent in later-line treatment

Reintroduce/rechallenge as late as possible to allow for greater recovery from toxicity

Anti-EGFR rechallenge



- N = 39 irinotecan-refractory patients†
- ORR = 54%; PFS = 6.6 months

†Patients had clinical benefit (SD for ≥ 6 months or clinical response) after cetuximab- + irinotecan-based therapy, then PD during cetuximab-based therapy, followed by a new line of CTx and finally, after PD, retreatment with the same or another cetuximab- + irinotecan-based therapy.

Santini D, et al. Ann Oncol 2012;23:2313–8.
Siravegna G, et al. Nat Med 2015;21:795–801.

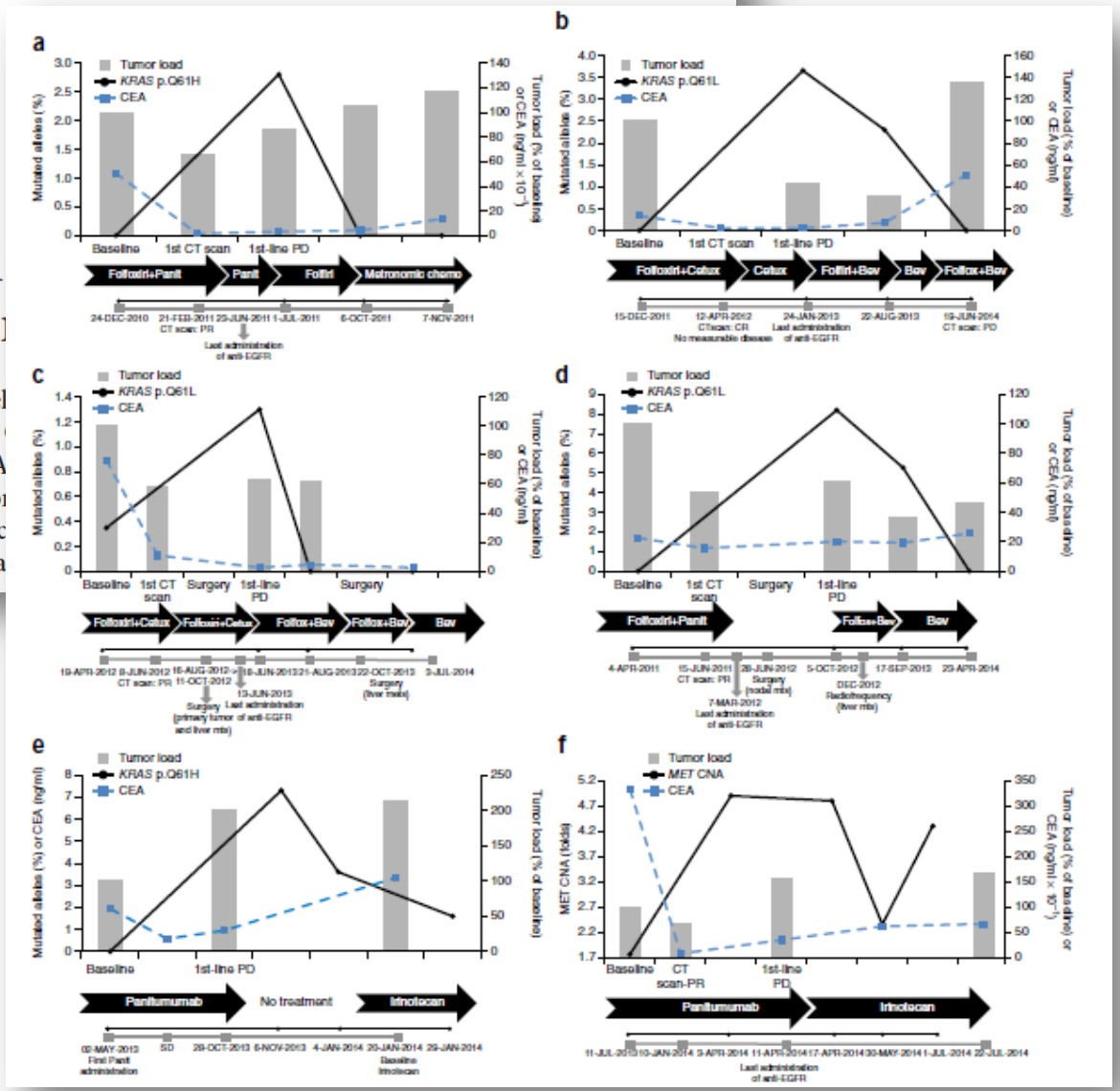
Rechallenge in mCRC

nature medicine

LETTERS

Clonal evolution and resi
blood of colorectal cance

Giulia Siravegna[1–3], Benedetta Mussolin[2], Michel
Giovanni Crisafulli[2], Agostino Ponzetti[5], Chiara
Simona Lamba[2], Sebastijan Hobor[2,10], Antonio A
Enzo Medico[1,2], Valentina Motta[4], Carlotta Anto
Alfredo Budillon[7], Clara Montagut[8], Patrizia Rac
Federica Di Nicolantonio[1,2], Fotios Loupakis[6], Sa



Rechallenge in mCRC

Annals of Oncology

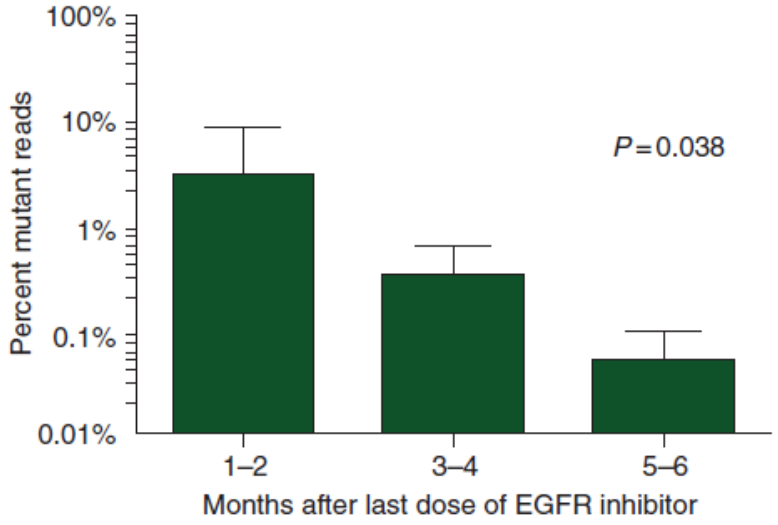
original articles

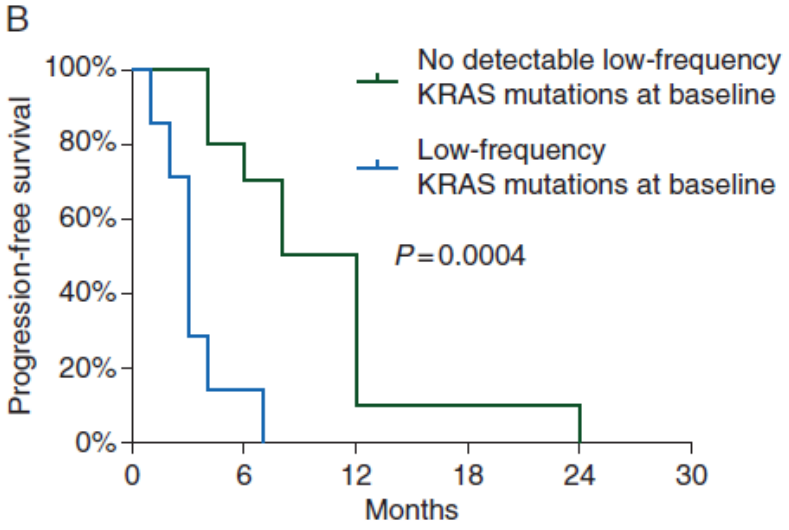
Annals of Oncology 26: 731–736, 2015
doi:10.1093/annonc/mdv005
Published online 26 January 2015

Characterizing the patterns of clonal selection in circulating tumor DNA from patients with colorectal cancer refractory to anti-EGFR treatment

M. P. Morelli[1], M. J. Overman[1], A. Dasari[1], S. M. A. Kazmi[1], T. Mazard[1], E. Vilar[1,2], V. K. Morris[1], M. S. Lee[1], D. Herron[1], C. Eng[1], J. Morris[3], B. K. Kee[1], F. Janku[4], F. L. Deaton[1], C. Garrett[1], D. Maru[5], F. Diehl[6], P. Angenendt[6] & S. Kopetz[1]*

Departments of [1]Gastrointestinal Medical Oncology; [2]Clinical Cancer Prevention; [3]Investigational Cancer Therapeutics; [4]Biostatistics; [5]Pathology, The University of Texas MD Anderson Cancer Center, Houston, USA; [6]Sysmex Inostics, Hamburg, Germany





Rechallenge in mCRC

Liu *et al. BMC Cancer* (2015) 15:713
DOI 10.1186/s12885-015-1701-3

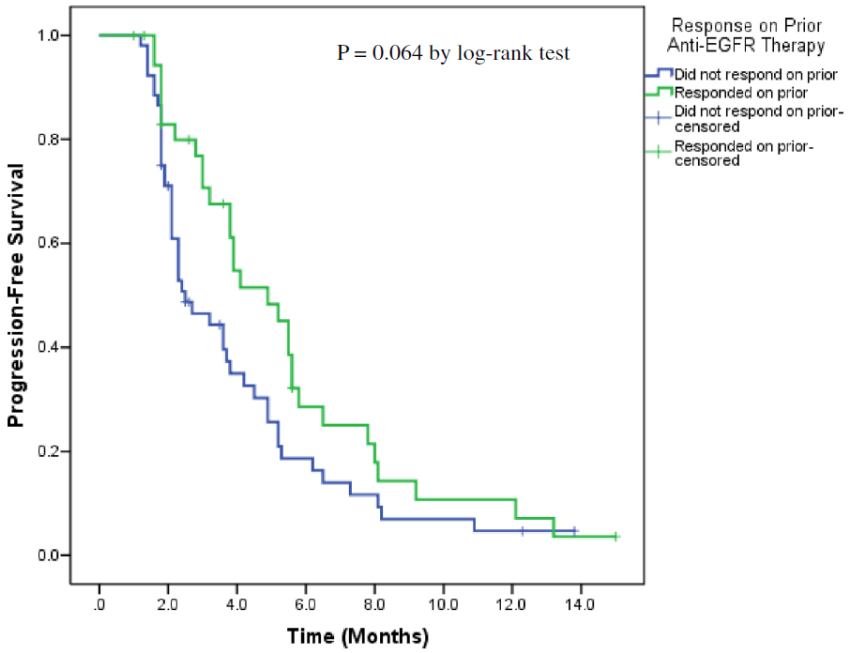
BMC Cancer

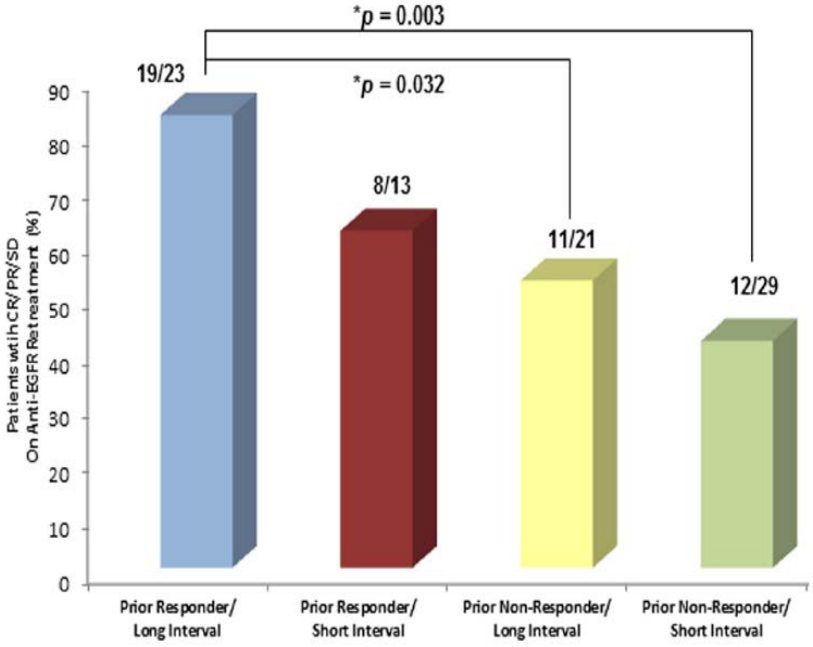
RESEARCH ARTICLE Open Access

CrossMark

Retreatment with anti-EGFR based therapies in metastatic colorectal cancer: impact of intervening time interval and prior anti-EGFR response

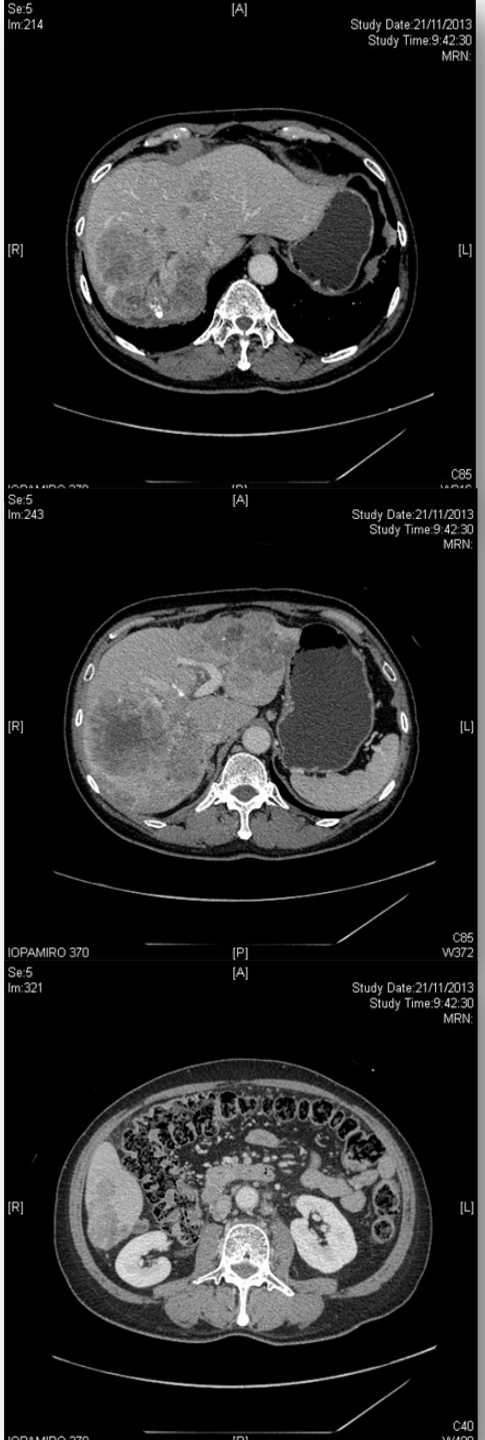
X. Liu[1], G. C. George[1], A. M. Tsimberidou[1], A. Naing[1], J. J. Wheler[1], S. Kopetz[2], S. Fu[1], S. A. Piha-Paul[1], C. Eng[2], G. S. Falchook[1], F. Janku[1], C. Garrett[2], D. Karp[1], R. Kurzrock[3], R. Zinner[1], K. Raghav[2], V. Subbiah[1], K. Hess[4], F. Meric-Bernstam[1], D. S. Hong[1*†] and M. J. Overman[2*†]





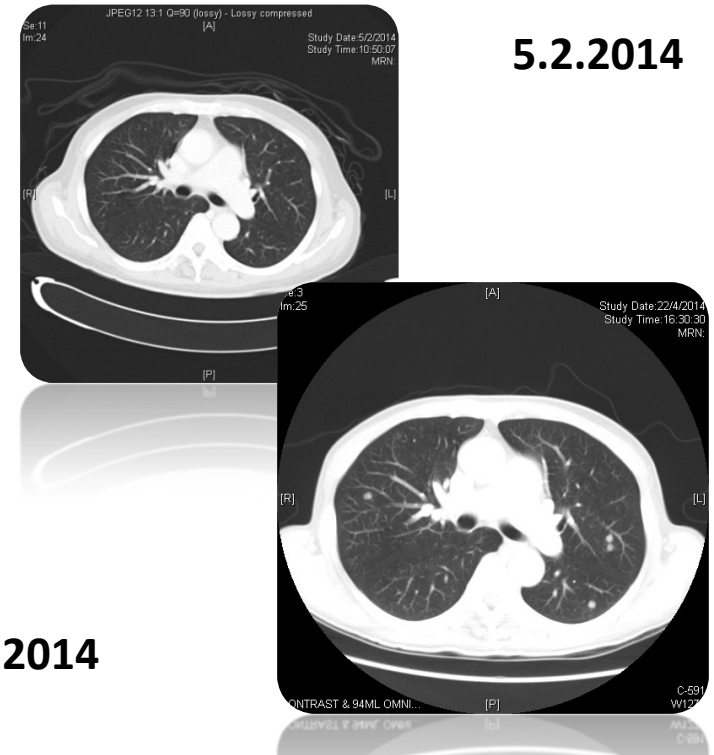
Heterogeneity and Reprogramming

- M/ 57. Good past health
- CA colon with synchronous distant LNs, lung and liver metastases diagnosed in 8/ 2011
- RAS wild type. Primary not resected
- Treatment
  - 9/2011-2/2012: XELOX + Bevacizumab x 7 cycles ->PD
  - 3/2012-10/2012: FOLFIRI + C225 x 12 cycles ->PR
  - 10/2012-3/2013: Drug holiday
  - 3/2013-6/2013: FOLFIRI + C225 x 7 cycles ->PD
  - 6/2013-10/2013: FOLFIRI + Bevacizumab x 8 ->PD
  - 12/2013-2/2014: Regorafenib -> PD



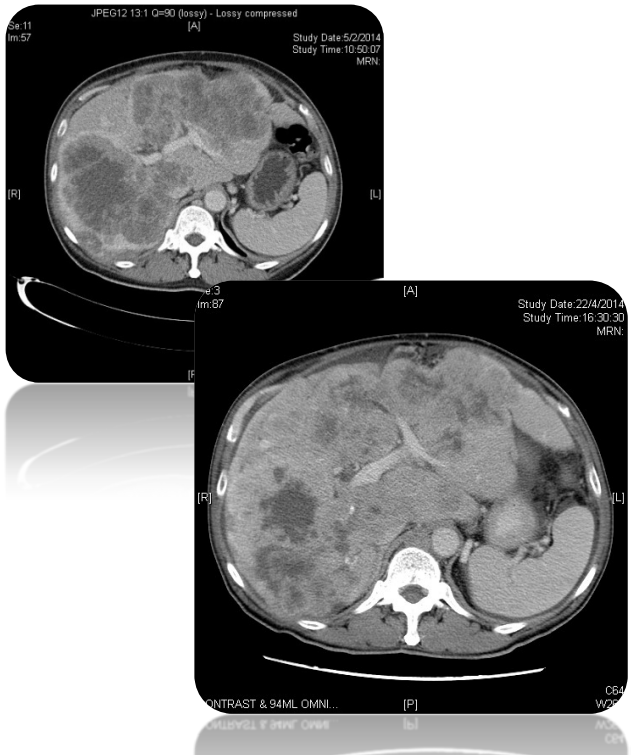
Heterogeneity and Reprogramming

- Started single agent Panitumumab 6mg/m^2 Q2W
  - Mild improvement in LFT
  - CEA: 8972 -> 4946 -> 2943 -> 2815 -> 2756 -> 3315
- Transient improvement for 8 weeks but then rapid downhill with liver failure and succumb in 5/2014



5.2.2014

22.4.2014



NOVEL STRATEGY

Novel Approach

- Vertical blockade: Cetuximab + erlotinib

  Weickhardt AJ, et al. J Clin Oncol 2012;30:1505-12.

- Glycoengineered anti-EGFR mAb that enhance ADCC: GA201

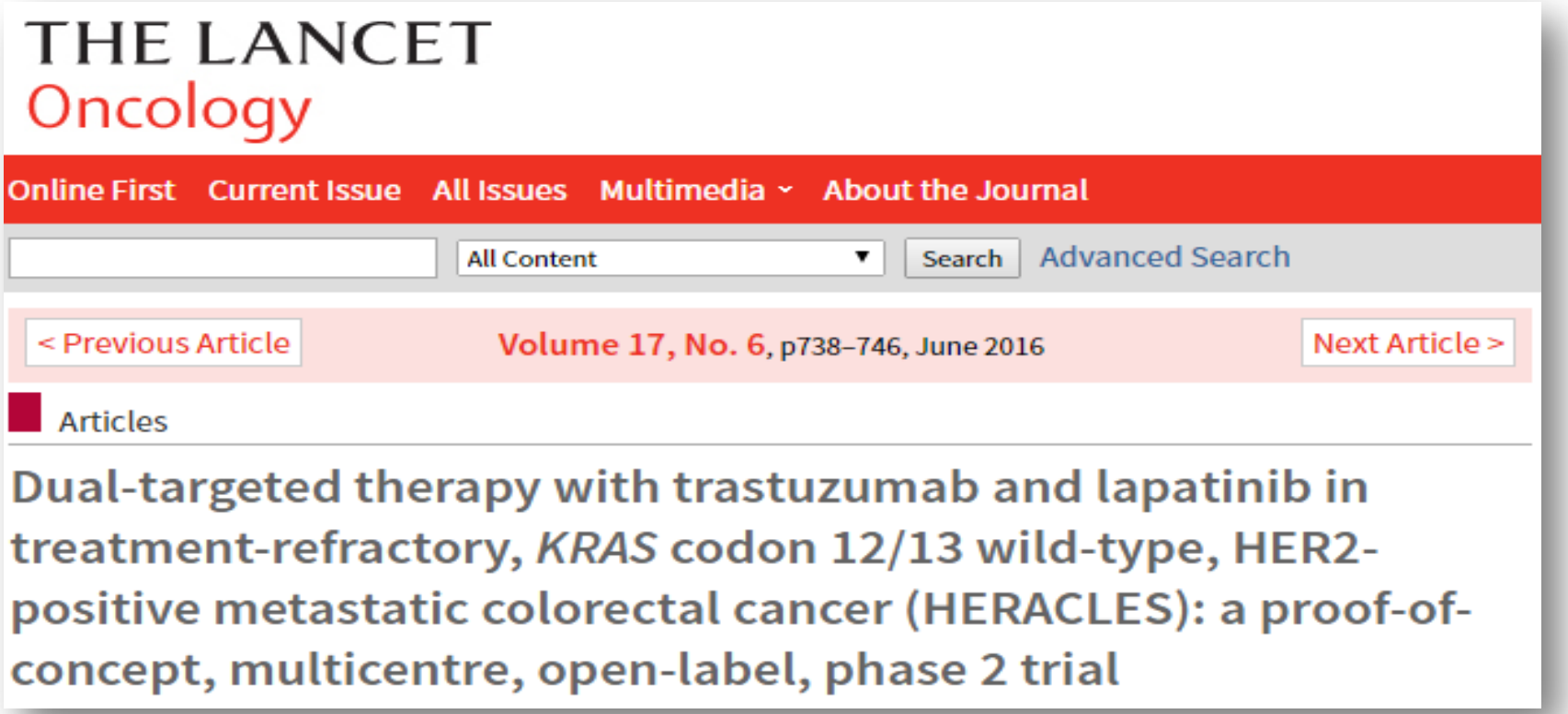
  Paz-Ares LG, et al. J Clin Oncol 2011;29:3783-90

- Novel mixture of Abs directed against distinct epitopes on the extracellular domain of EGFR: Sym004

  Lida M, et al. Neoplasia 2013;15:1196-206

- Inhibition of multiple pathways: MEK, HER2, HER3, PI3K, BRAF, IGF, HGF, c-MET

- Combination with immunotherapy



- Kras exon 2 wild type mCRC: 5% Her2 +ve (48/ 914)
- 27 were treated with trastuzumab weekly + laptinib weekly until PD
- RR: 30% (CR: 4% and PR: 26%)
- SD: 44% and DCR: 74%
- G3 AEs: 22%

Conclusion

- Right patient?
  - Complexity of intracellular signaling
  - Dynamic of tumor biology

- Right time?
  - Continuum of care
  - Novelty

THANK YOU