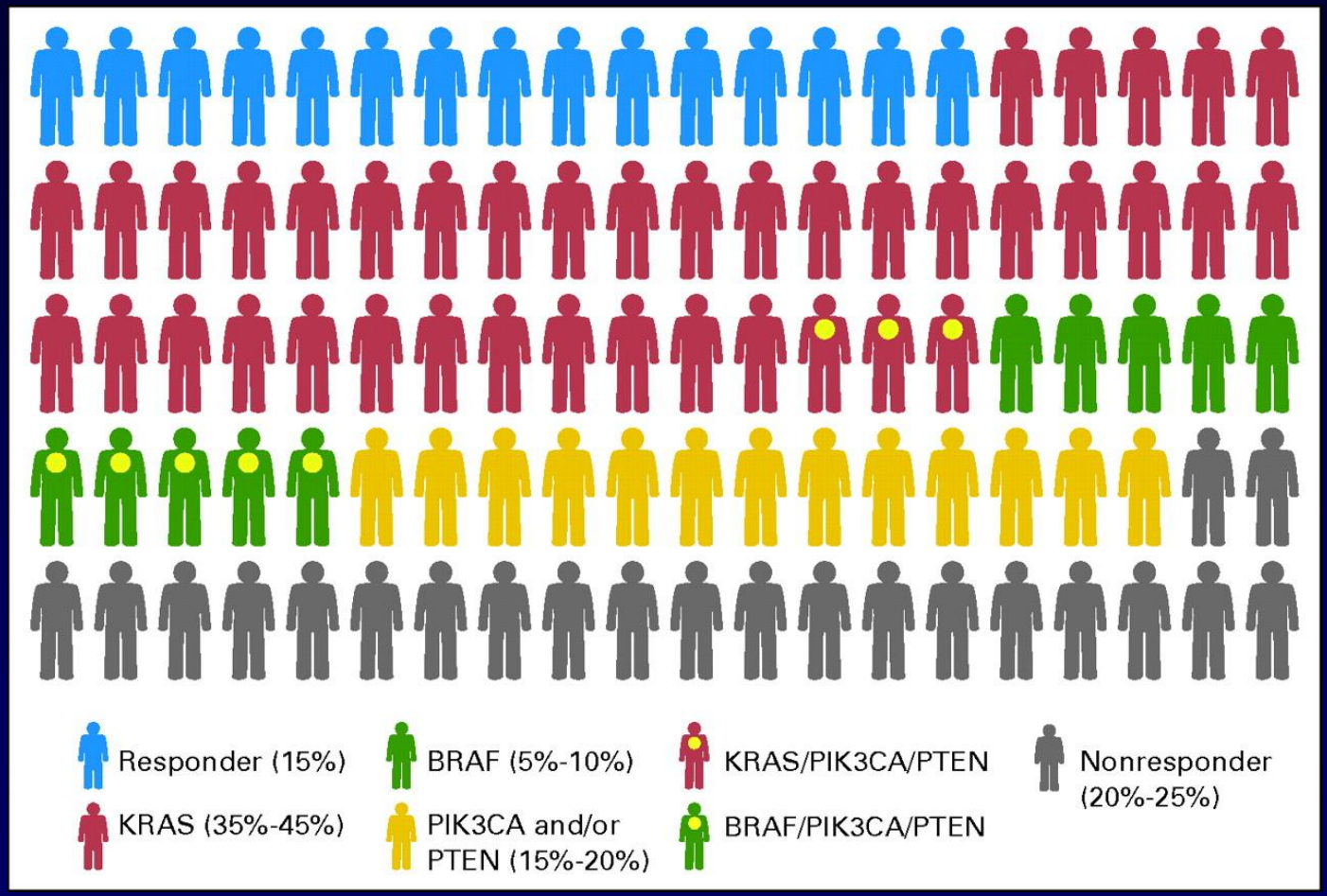
Ospedale S. Cuore Don Calabria

Inibitori di BRAF nel carcinoma del Colon Retto

Massimo Cirillo

Negrar 29 Novembre 2016

Graphic representation of a cohort of 100 patients with colorectal cancer treated with cetuximab or panitumumab

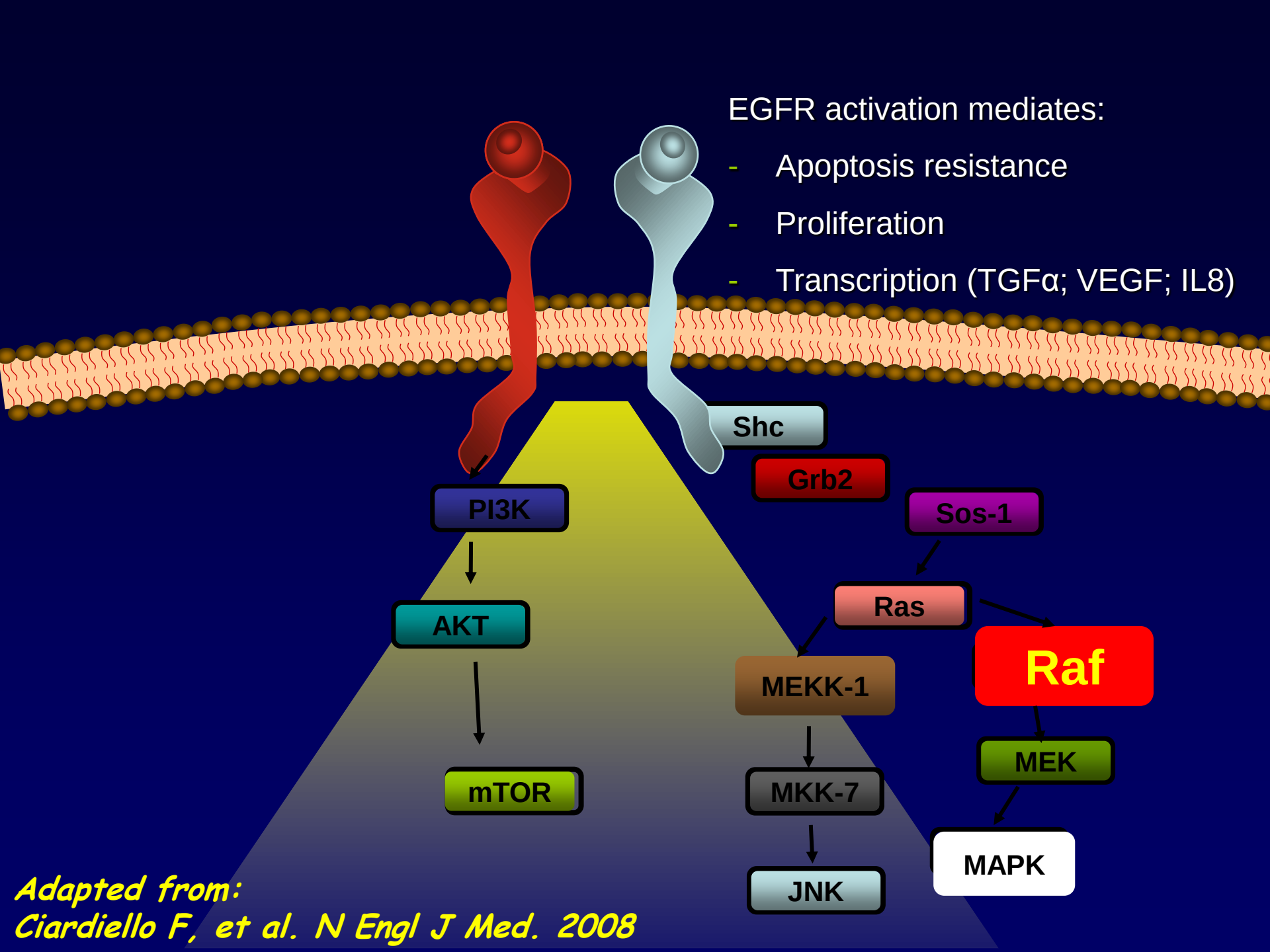


Bardelli A. et al. J Clin Oncol 2010

Di che cosa parliamo quando parliamo di BRAF-mutato nel carcinoma del colon retto ?

- **$BRAF^{V600E}$ mutato è presente nel 9-11% circa dei CCR metastatici**
- **maggiore frequenza nelle neoplasie prossimali (66% circa di BRAF mutati nella neoplasie localizzate nel colon dx)**
- **maggiore incidenza in donne (75%)**
- **maggiore incidenza di localizzazioni peritoneali e linfonodali**
- **minore incidenza di localizzazioni polmonari**
- **nessuna differenza in localizzazioni epatiche**
- **associazione con neoplasie MSI (30% dei tumori con MSI sono $BRAF^{V600E}$ mutati)**

- Van Cutsem E et al Ann Oncol 2016, Tran B. et al. Cancer 2011; Tveit KM et al J Clin Oncol 2011 ; Bledsoe JR et al Am J Surg Pathol 2014 ; Goldstein J et al. Ann Oncol 2014 -


EGFR activation mediates:
- Apoptosis resistance
- Proliferation
- Transcription (TGFα; VEGF; IL8)
Shc
Grb2
Sos-1
PI3K
Ras
AKT
Raf
MEKK-1
MEK
mTOR
MKK-7
MAPK
JNK
Adapted from:
Ciardiello F, et al. N Engl J Med. 2008

VOLUME 33 · NUMBER 35 · DECEMBER 10 2015

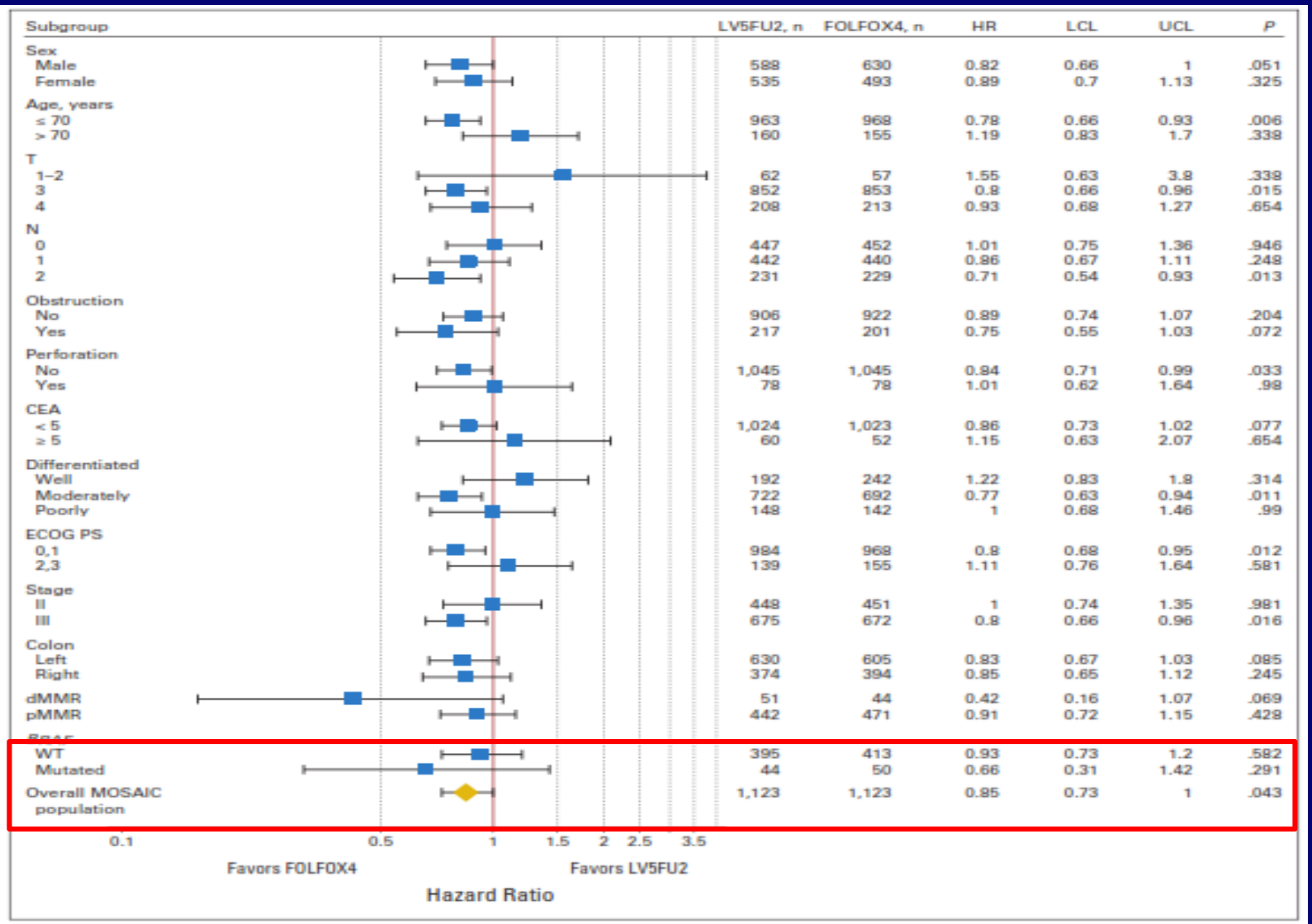
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to *BRAF* Mutation and Mismatch Repair Status of the MOSAIC Study

Thierry André, Armand de Gramont, Dewi Vernerey, Benoist Chibaudel, Franck Bonnetain,

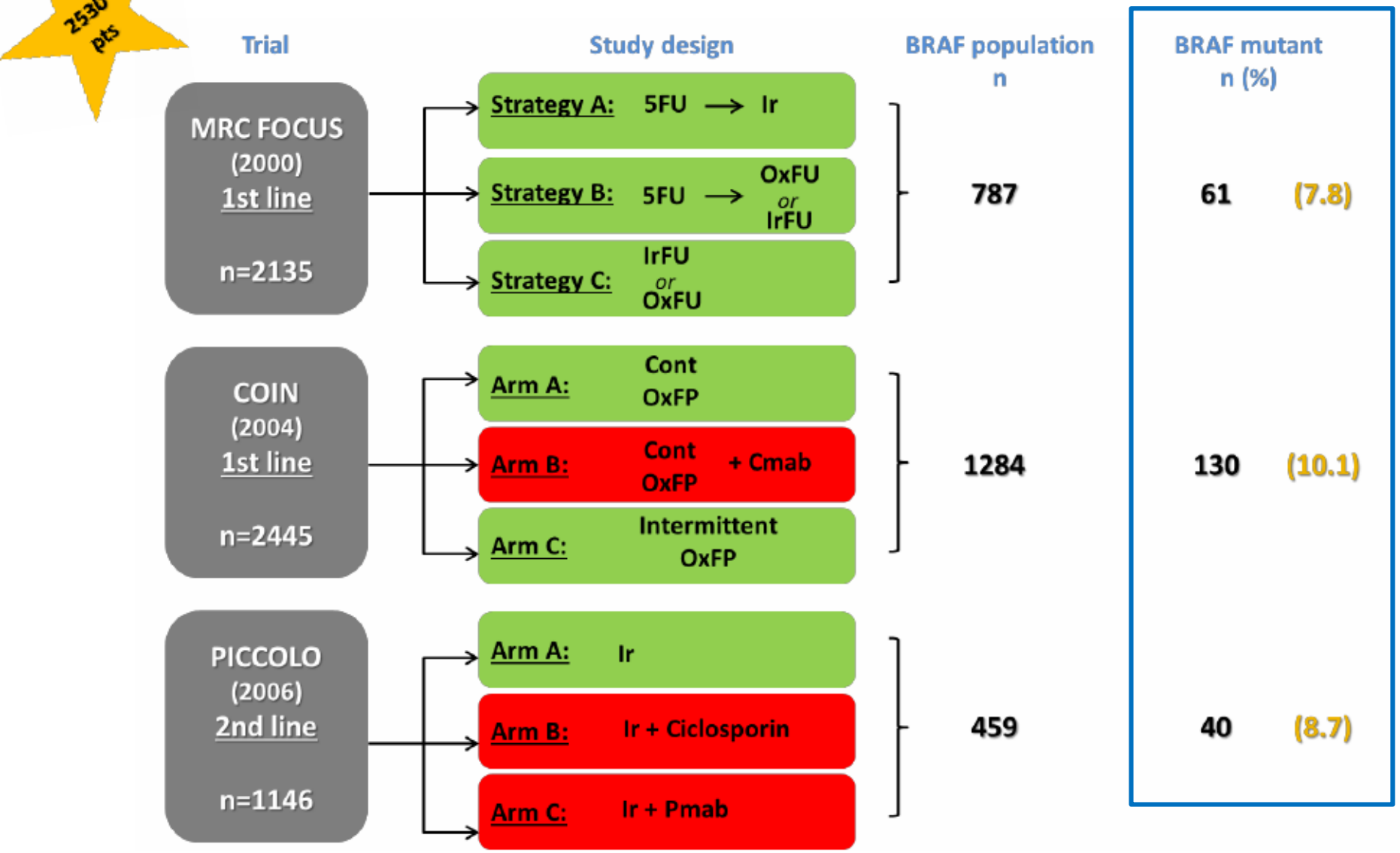
BRAF available in 902 /2248 pts
median Follow-up: 9.5 ys
BRAFmut: 94 pts (10.4%)



Exploring the poor outcome of BRAF mutant mCRC pts

2530 pts

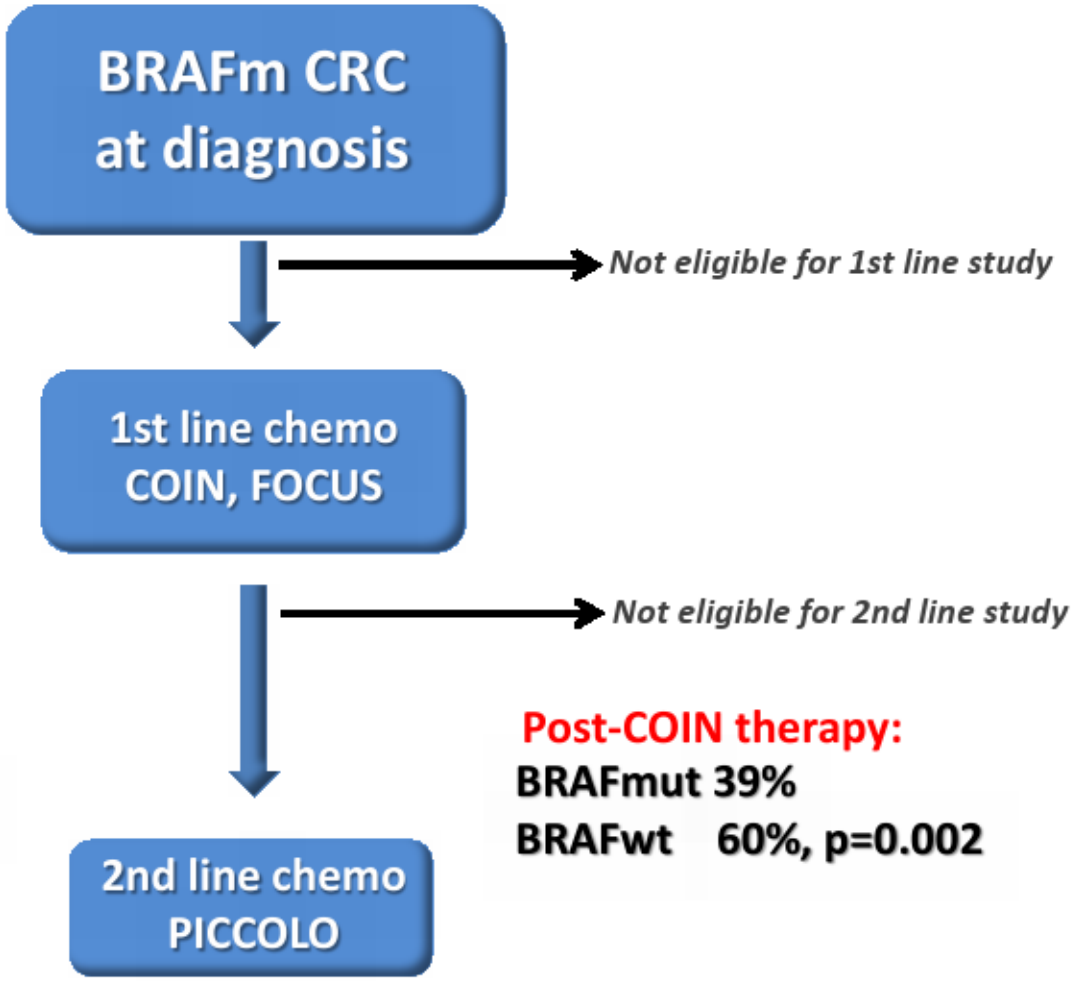
Meta-analysis of survival outcomes, adjusted for prognostic factors



Included in the analysis
Not included in the analysis

Seymour et al, Lancet 2007; Maughan et al, Lancet 2011; Adams et al, Lancet Oncol 2011; Seymour et al, Lancet Oncol 2013; Middleton et al, Eur J Cancer 2013; Seligmann et al, ASCO 2015 #3509

Exploring the poor outcome of BRAF mutant mCRC pts



mOS in 1st line
BRAFmut 10.8 mos
BRAF wt 16.4 mos
HR 1.48 p<0.001
No significant difference in PFS

Post-Progression survival significantly shorter if BRAFmut
FOCUS & COIN: 4.2 vs 9.2 mos
Adj HR 1.69 (1.41-2.06) p<0.001

Post-COIN therapy:
BRAFmut 39%
BRAFwt 60%, p=0.002

mOS in 2nd line
BRAFmut 6.9 mos
BRAF wt 10.2 mos
HR 1.17 p=0.33

Modified from Atreya, ASCO 2015
Colorectal Cancer Poster Discussion Session

Seligmann et al, ASCO 2015 #3509

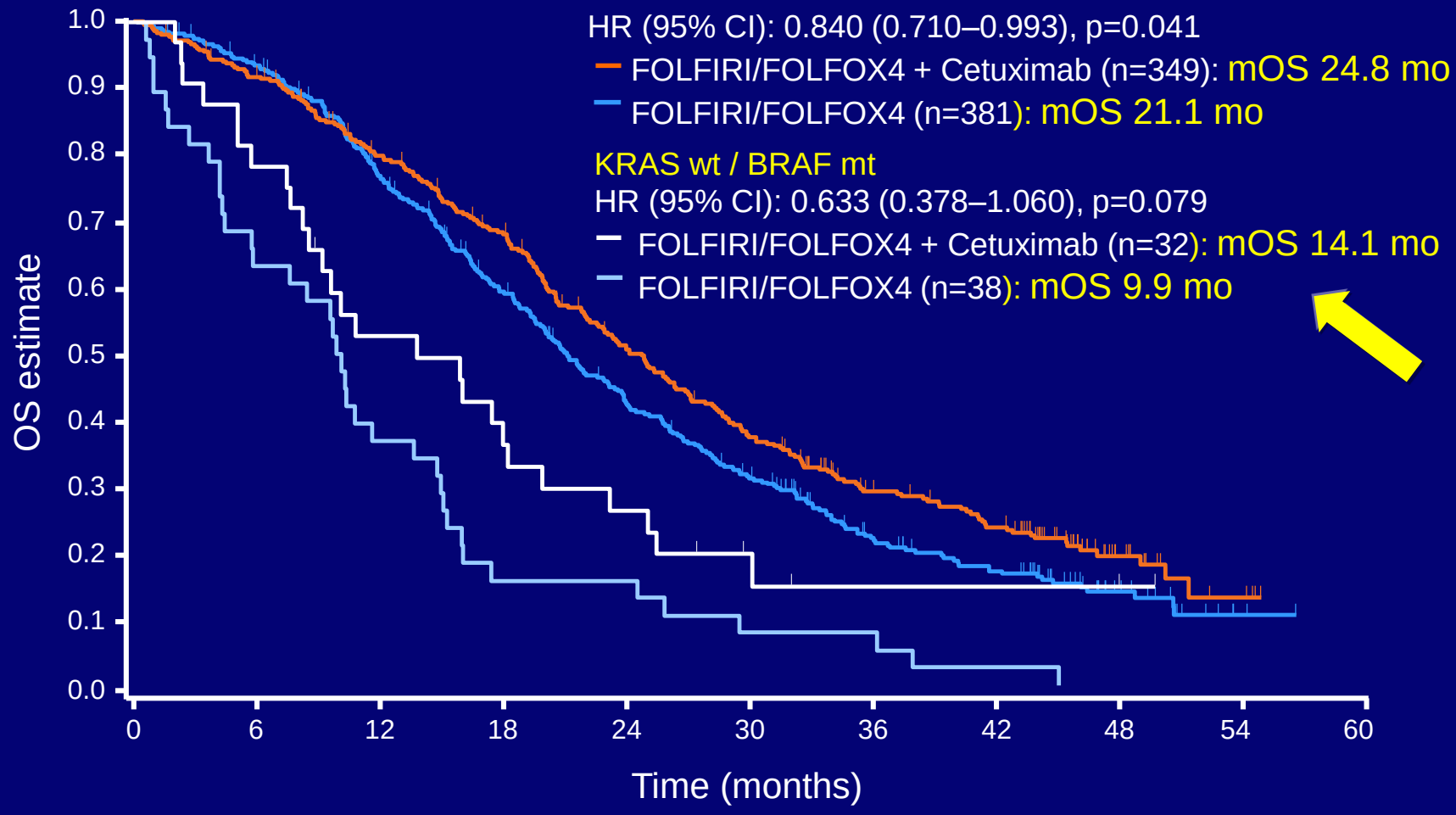
- Negli stadi precoci la presenza di BRAF mutato non riduce l'efficacia della chemioterapia adiuvante con Oxaliplatino

- Nella malattia metastatica la presenza di BRAF mutato rappresenta un fattore prognostico sfavorevole in termini di sopravvivenza con mOS di circa 10-11 mesi con chemioterapia standard (FU + Oxaliplatino/Irinotecan)

- nella malattia metastatica nei pazienti mutati si assiste ad un più veloce declino del PS e pertanto la probabilità di ricevere una seconda linea di terapia si riduce drasticamente

Esiste un ruolo dei farmaci anti EGFR ?

Pooled analysis of OS in patients with KRAS wt tumors according to BRAF mutation status
(KRAS wt/BRAF mut: 70 pts)



Bokemeyer C, et al. J Clin Oncol 2010; 28(Suppl. 15):Abstract No. 3506

ORIGINAL ARTICLE

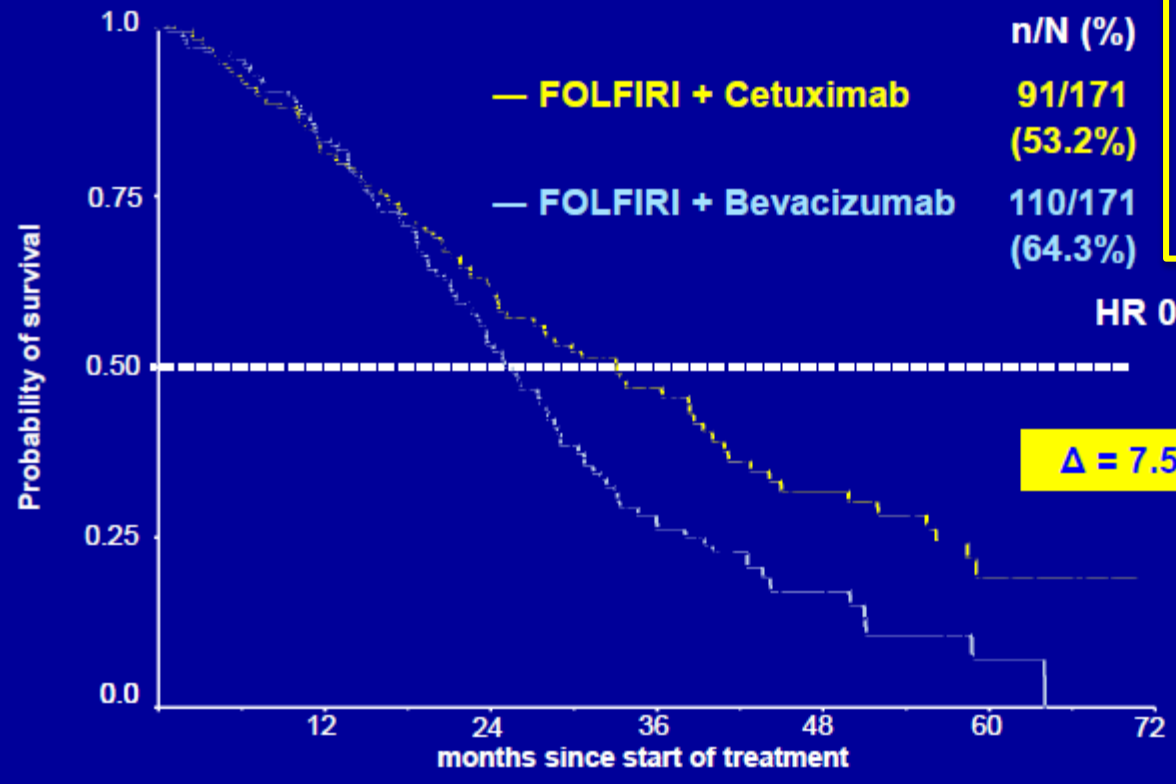
Panitumumab–FOLFOX4 Treatment and *RAS* Mutations in Colorectal Cancer

Table 3. Efficacy Results According to *RAS* and *BRAF* Mutation Status in the Primary-Analysis Population.*

Variable	Panitumumab–FOLFOX4	FOLFOX4 Alone	Hazard Ratio (95% CI)	P Value
No *RAS* or *BRAF* mutations				
No. of patients	228	218		
Months of progression-free survival — median (95% CI)	10.8 (9.4–12.4)	9.2 (7.4–9.6)	0.68 (0.54–0.87)	0.002
Months of overall survival — median (95% CI)	28.3 (23.7–NE)	20.9 (18.4–23.8)	0.74 (0.57–0.96)	0.02
No *RAS* mutation, *BRAF* mutation				
No. of patients	24	29		
Months of progression-free survival — median (95% CI)	6.1 (3.7–10.7)	5.4 (3.3–6.2)	0.58 (0.29–1.15)	0.12
Months of overall survival — median (95% CI)	10.5 (6.4–18.9)	9.2 (8.0–15.7)	0.90 (0.46–1.76)	0.76
***RAS* or *BRAF* mutation**				
No. of patients	296	305		
Months of progression-free survival — median (95% CI)	7.3 (6.3–7.7)	8.0 (7.5–9.0)	1.24 (1.02–1.49)	0.03
Months of overall survival — median (95% CI)	15.3 (12.7–17.6)	18.0 (15.9–20.8)	1.21 (0.99–1.47)	0.06
No *KRAS* mutation in exon 2, other *RAS* or *BRAF* mutation				
No. of patients	75	86		
Months of progression-free survival — median (95% CI)	6.7 (5.3–8.2)	7.3 (5.7–8.0)	1.05 (0.73–1.52)	0.80
Months of overall survival — median (95% CI)	14.5 (10.4–18.5)	15.8 (11.9–18.8)	1.14 (0.78–1.66)	0.51

- Douillard et al N.Engl.J.Med. 2013 -

Overall survival RAS* wild-type



	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	91/171 (53.2%)	33.1	24.5 – 39.4
— FOLFIRI + Bevacizumab	110/171 (64.3%)	25.6	22.7 – 28.6

HR 0.70 (95% CI: 0.53 – 0.92)
p (log-rank)= 0.011

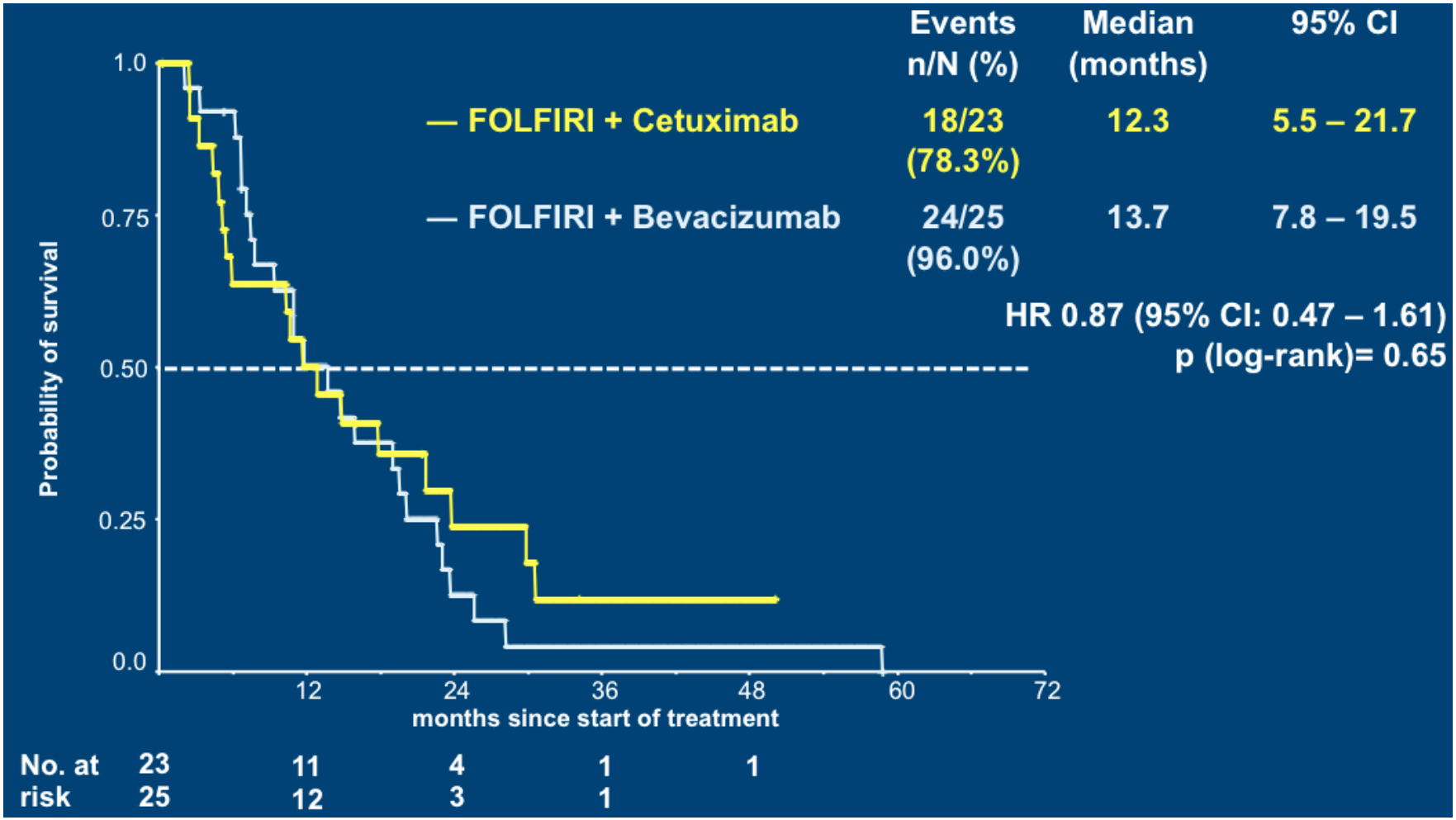
Δ = 7.5 months

No. at risk	171	128	71	39	20	6
	171	127	68	26	9	1

* KRAS and NRAS exon 2, 3 and 4 wild-type

- Heinemann Lancet Oncol 2014 -

FIRE-3: *BRAF* mut subgroup - OS



Stintzing et al, ASCO GI '14

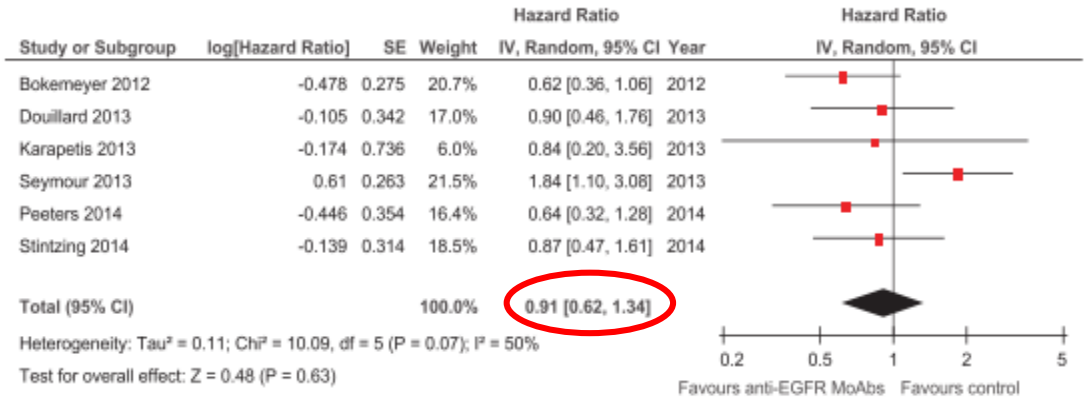


Fig. 2. Forest plots showing hazard ratio for overall survival for anti-epidermal growth factor receptor (EGFR) treatment in BRAF-mutated colorectal cancer patients.

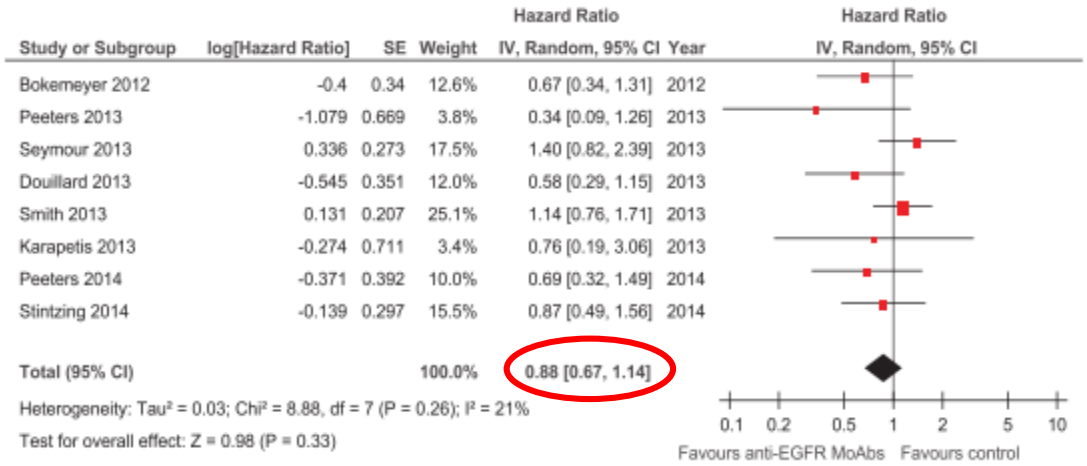


Fig. 3. Forest plots showing hazard ratio for progression-free survival for anti-epidermal growth factor receptor (EGFR) treatment in BRAF-mutated colorectal cancer patients.

Pietrantonio F. at al. Eur J Cancer 2015

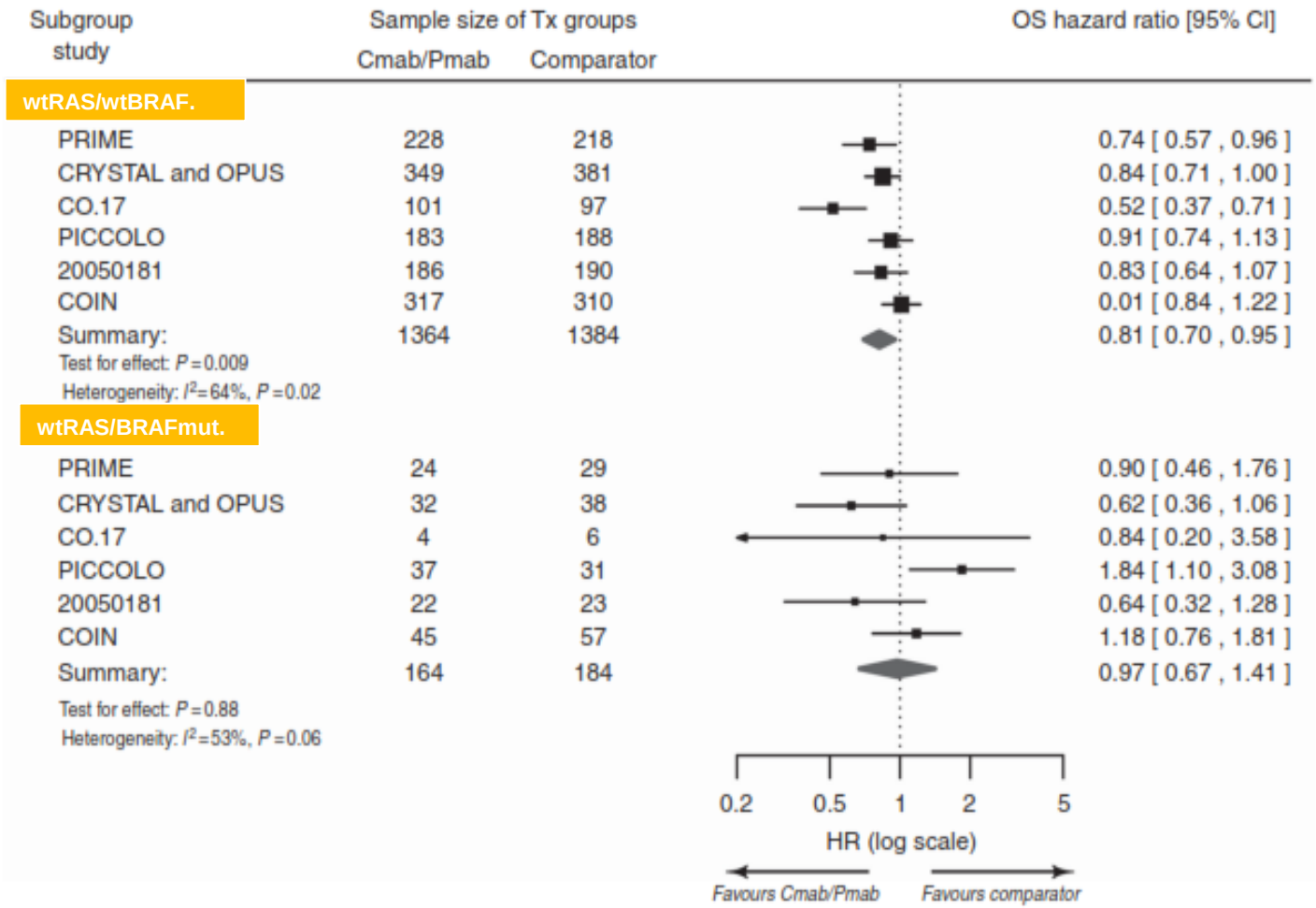


Figure 2. Forest plot of the overall survival benefit with anti-EGFR mAb therapy for subgroups defined by tumour *RAS* and *BRAF* mutations. Cmab = cetuximab; MT = mutant; Pmab = panitumumab; WT = wild type.

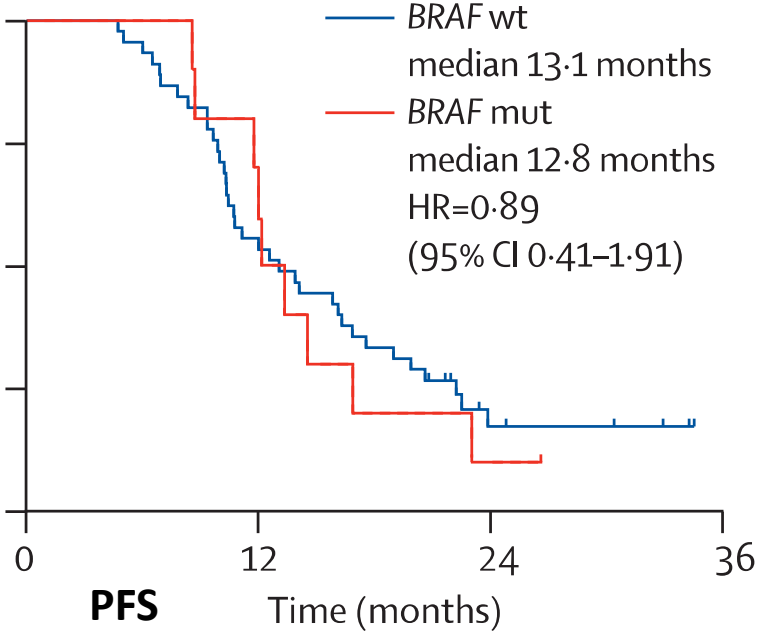
Test of interaction not statistically significative
P= 0.47

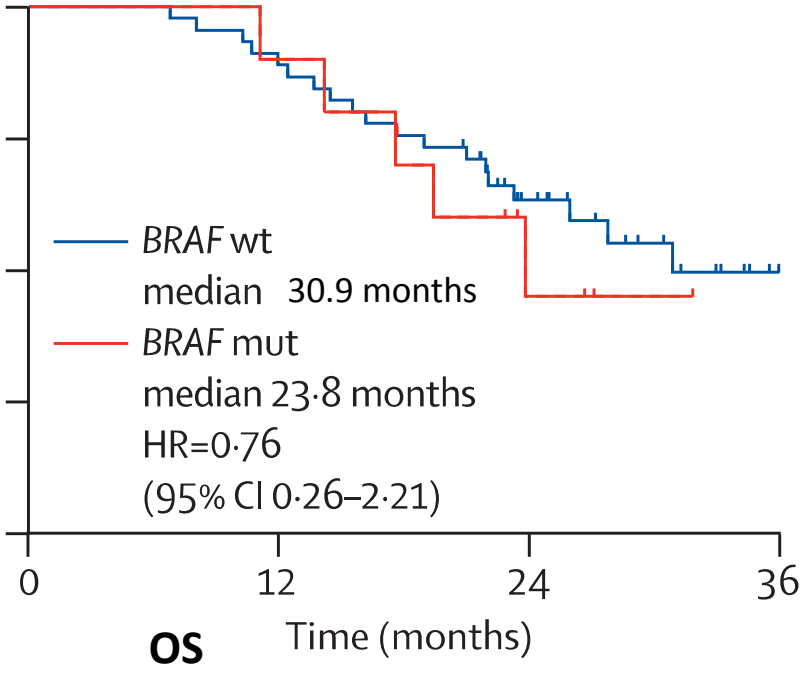
Rowland A. et al Br J Cancer 2015

FOLFOXIRI+Bev in *BRAF* mut

Retrospective analysis of phase II FOIB trial (10 pts BRAFmt/47 pts BRAFwt)

Bevacizumab with FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinate) as first-line treatment for metastatic colorectal cancer: a phase 2 trial





Masi et al. Lancet Oncol '10

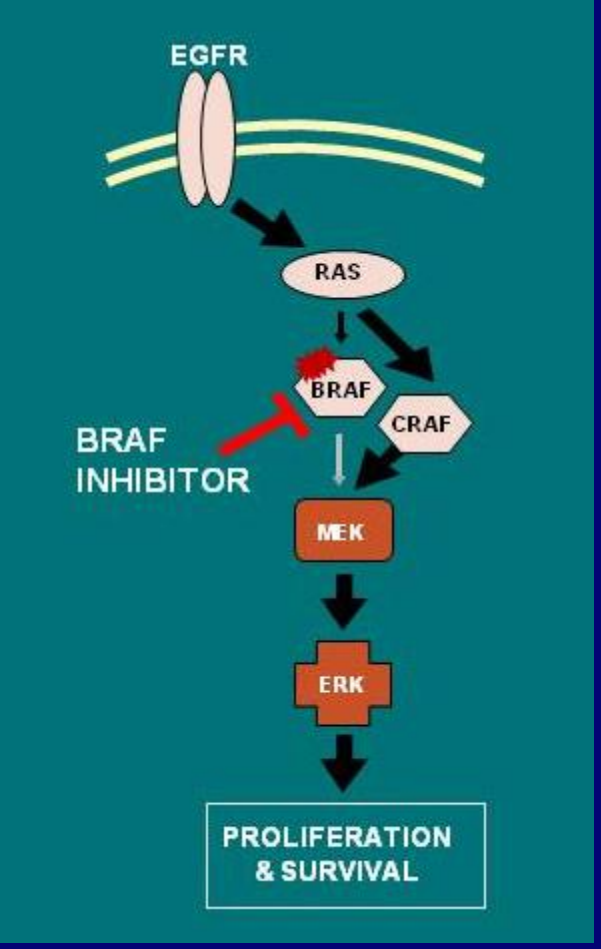
FOLFOXIRI+Bev in *BRAF* mut

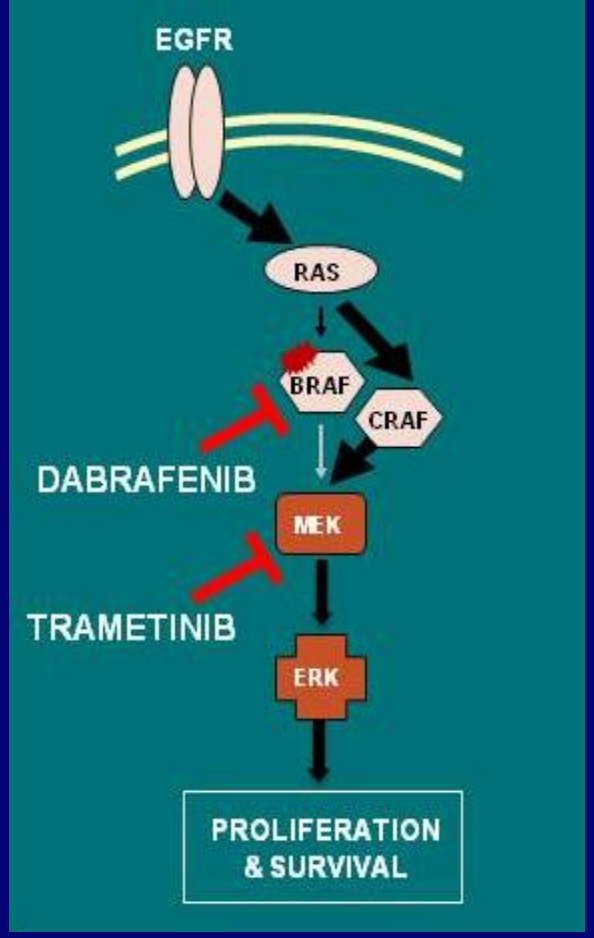
Subgroup analysis of phase III TRIBE trial

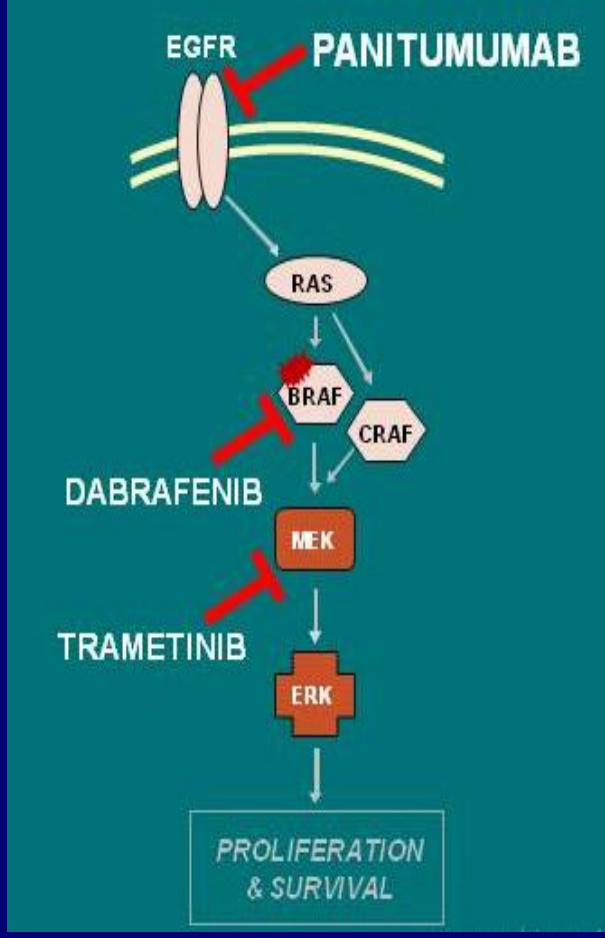
	N	FOLFIRI + bev Arm A Median PFS	FOLFOXIRI + bev Arm B Median PFS	HR [95% CI]
ITT population	508	9.7	12.1	0.75 [0.62-0.90]
***RAS* mutated**	218	9.5	12.0	0.82 [0.61-1.09]
***BRAF* mutated**	28	5.5	7.5	0.55 [0.26-1.18]
All wt patients	129	11.3	13.3	0.75 [0.52-1.10]

	N	FOLFIRI + bev Arm A Median OS	FOLFOXIRI + bev Arm B Median OS	HR [95% CI]
ITT population	508	25.8	31.0	0.79 [0.63-1.00]
***RAS* mutated**	218	23.1	30.8	0.86 [0.60-1.22]
***BRAF* mutated**	28	10.8	19.1	0.55 [0.24-1.23]
All wt patients	129	34.4	41.7	0.85 [0.52-1.39]

Cremolini et al, Lancet Oncol 2015







What's next ?

BRAF inibitori

BRAF/MEK inibitori

BRAF/EGFR inibitori

BRAF/MEK/EGFR inibitori

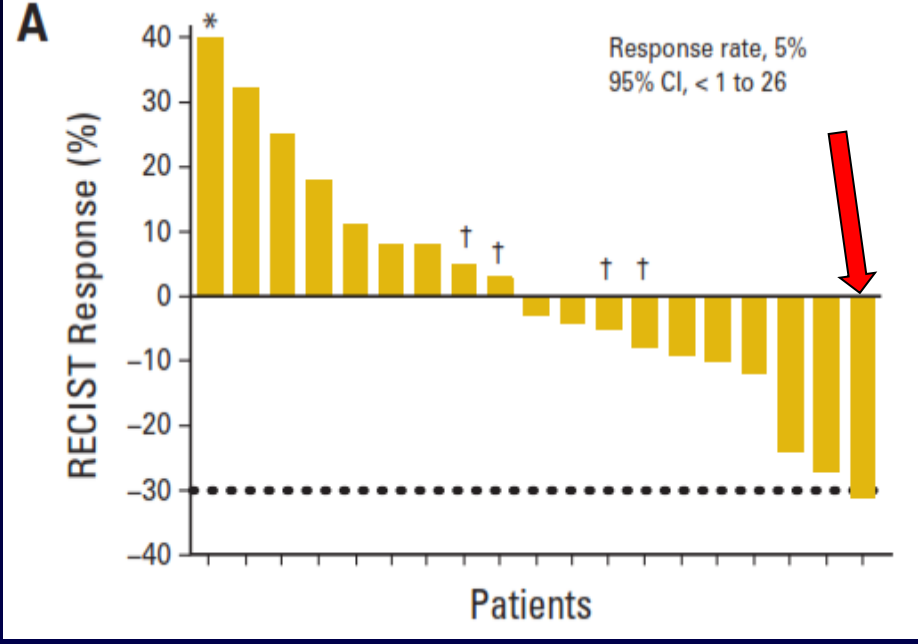
VOLUME 33 · NUMBER 34 · DECEMBER 1 2015

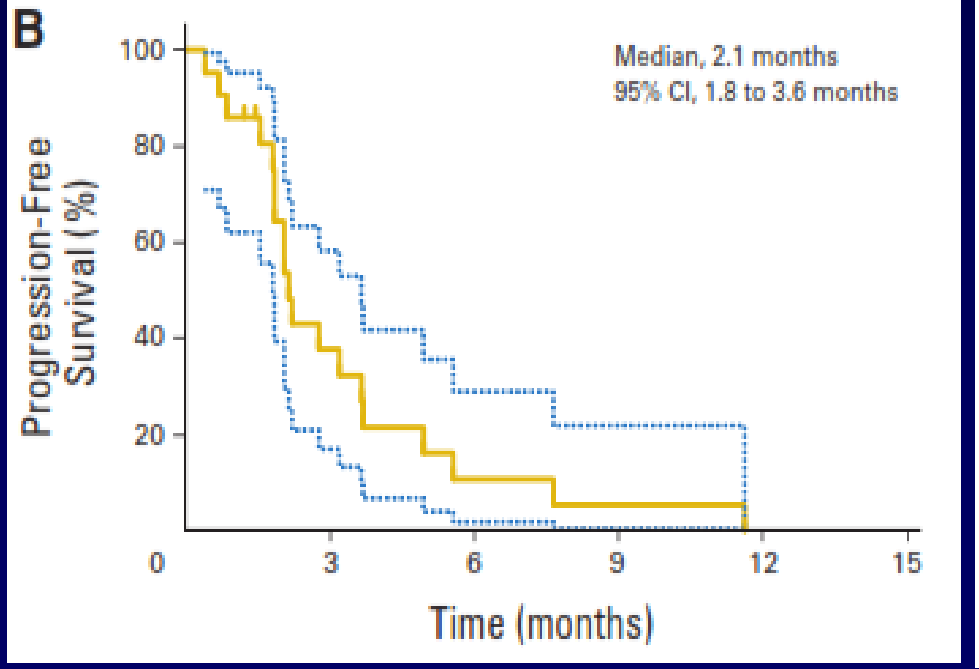
JOURNAL OF CLINICAL ONCOLOGY

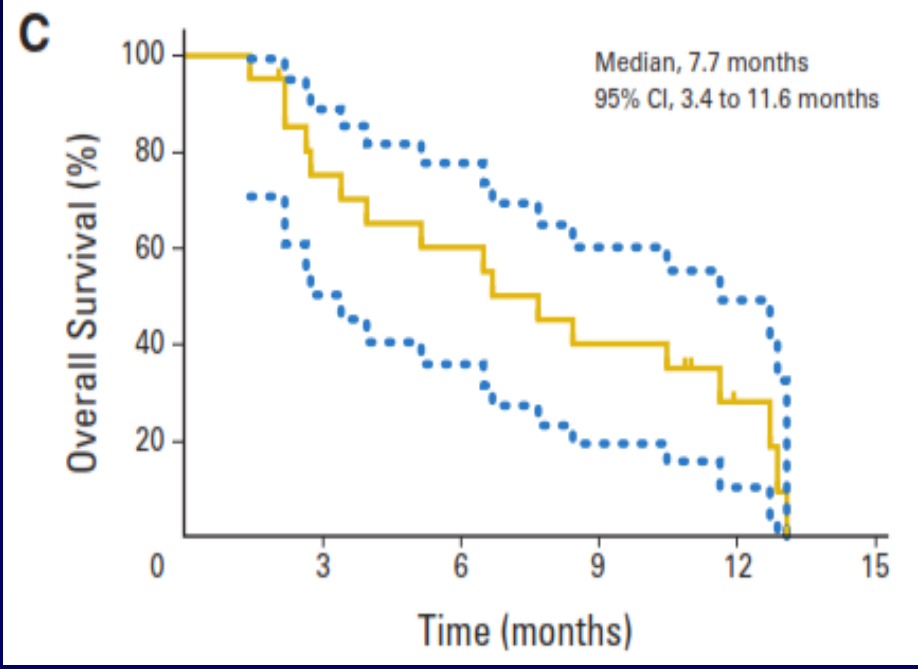
ORIGINAL REPORT

Phase II Pilot Study of Vemurafenib in Patients With Metastatic *BRAF*-Mutated Colorectal Cancer

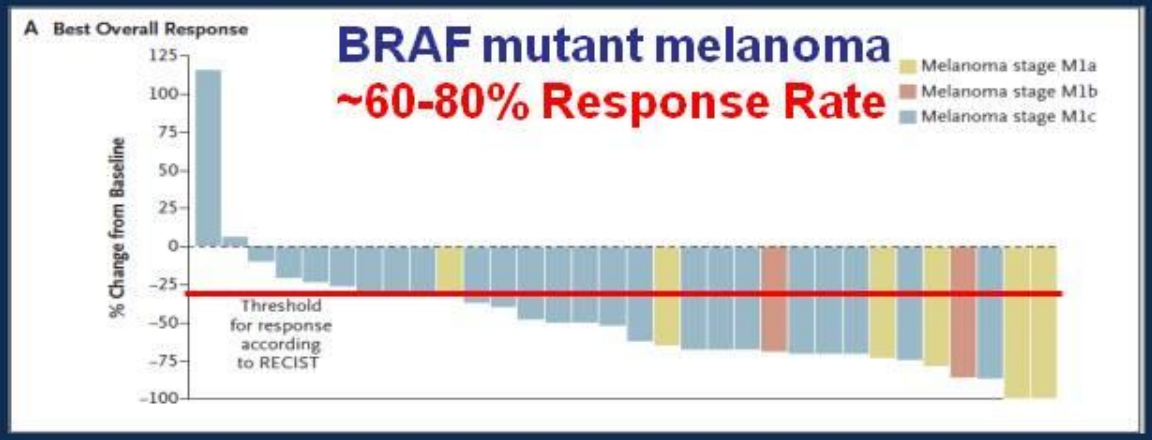
Scott Kopetz, Jayesh Desai, Emily Chan, Joel Randolph Hecht, Peter J. O'Dwyer, Dipen Maru, Van Morris, Filip Janku, Arvind Dasari, Woonbook Chung, Jean-Pierre J. Issa, Peter Gibbs, Brian James, Garth Powis, Keith B. Nolop, Suman Bhattacharya, and Leonard Saltz

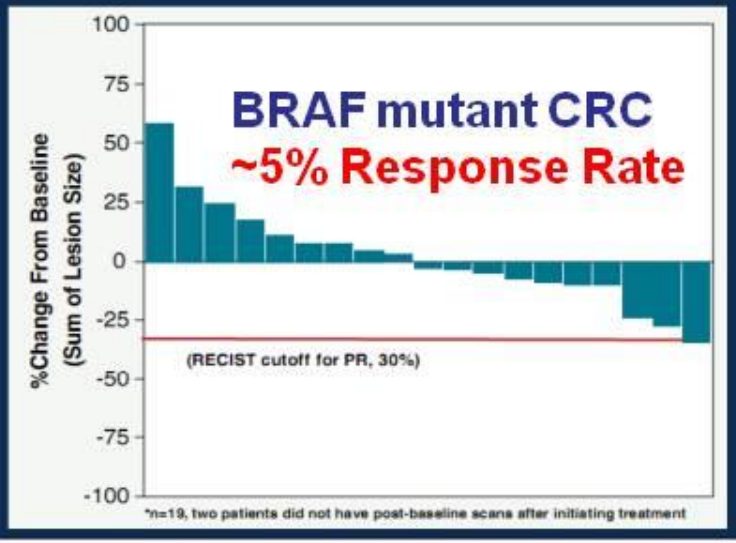






BRAF inhibition alone ineffective in BRAF-mutant CRC





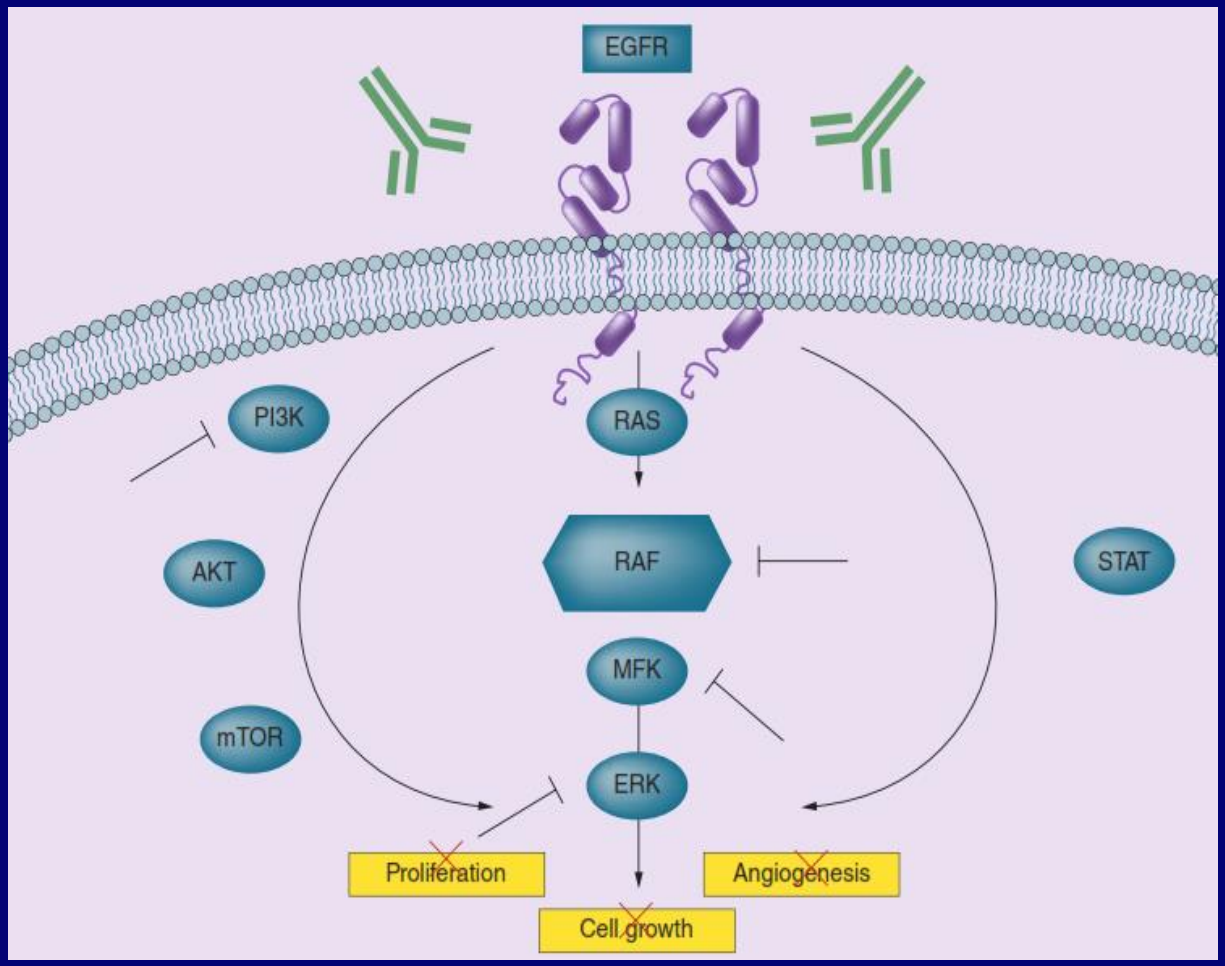
Flaherty *et al*, NEJM, 2010
Kopetz *et al*, ASCO, 2010

LETTER

doi:10.1038/nature10868

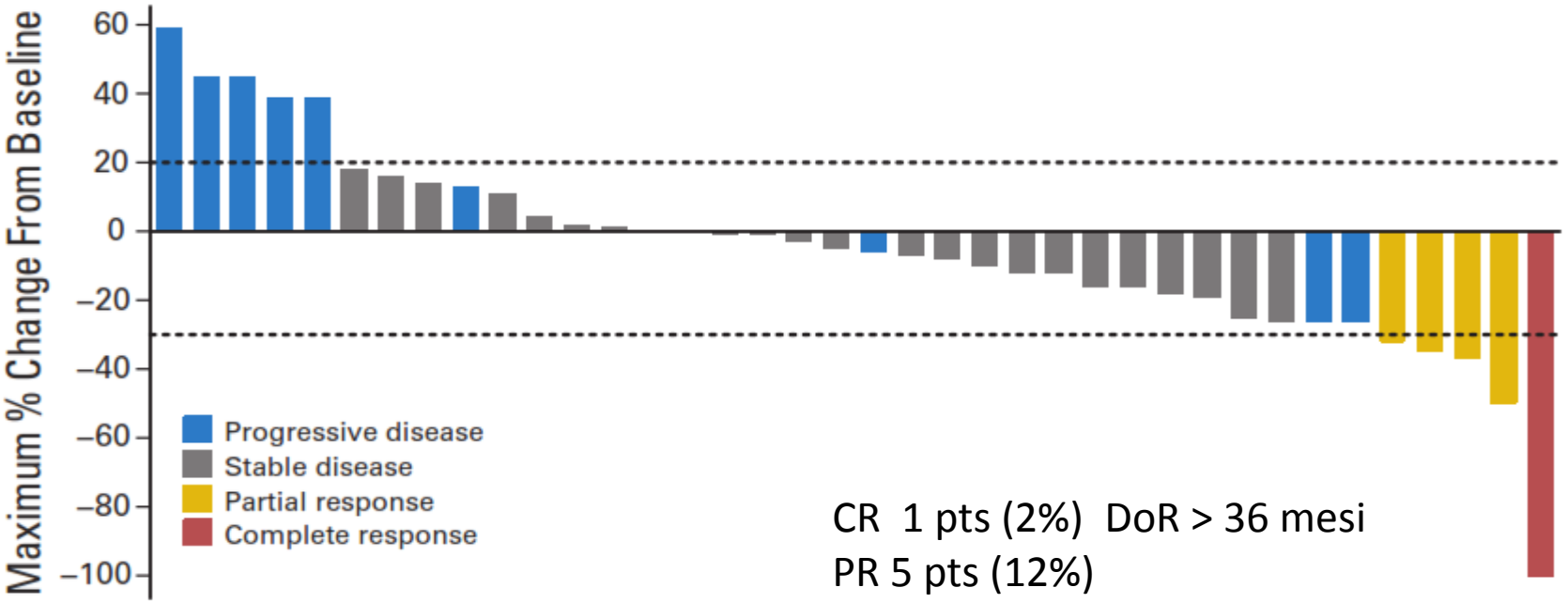
Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

Prahallad et al, Nature '12



Dabrafenib + Trametinib in pre-treated *BRAF* mut mCRC

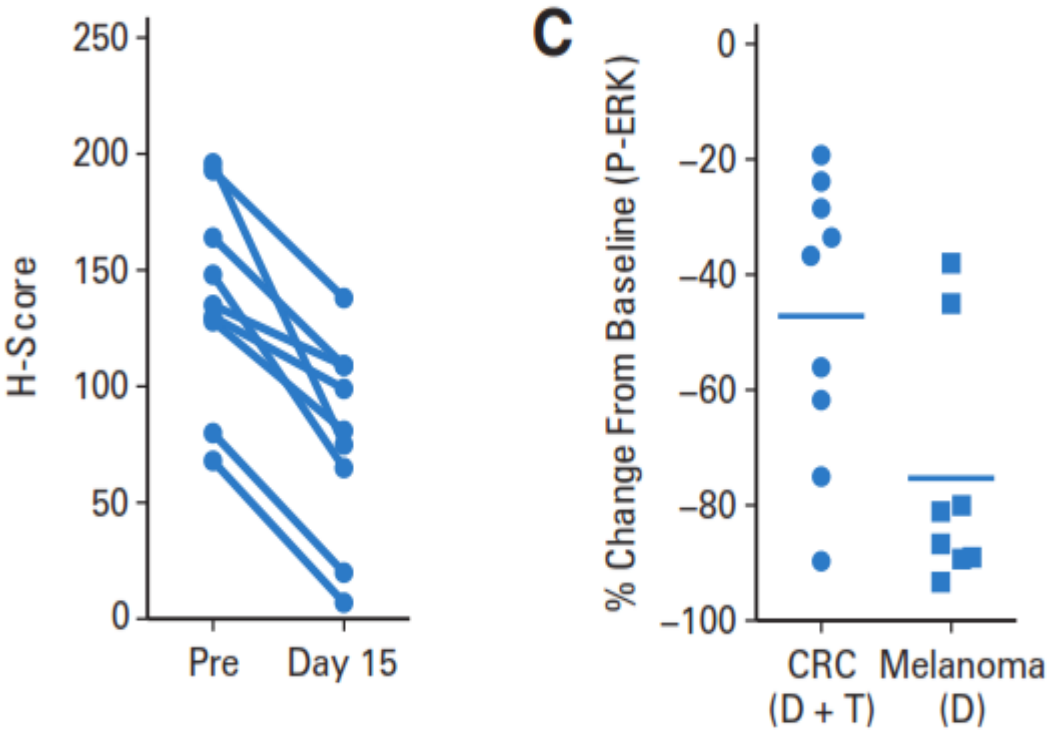
43 pts (36 pts ≥ 2 linee di terapia/20 pts trattati con anti EGFR



CR 1 pts (2%) DoR > 36 mesi
PR 5 pts (12%)
SD 24 pts (56%)
10 pts (23%) trattati > 6 mesi

Corcoran et al, JCO 2015

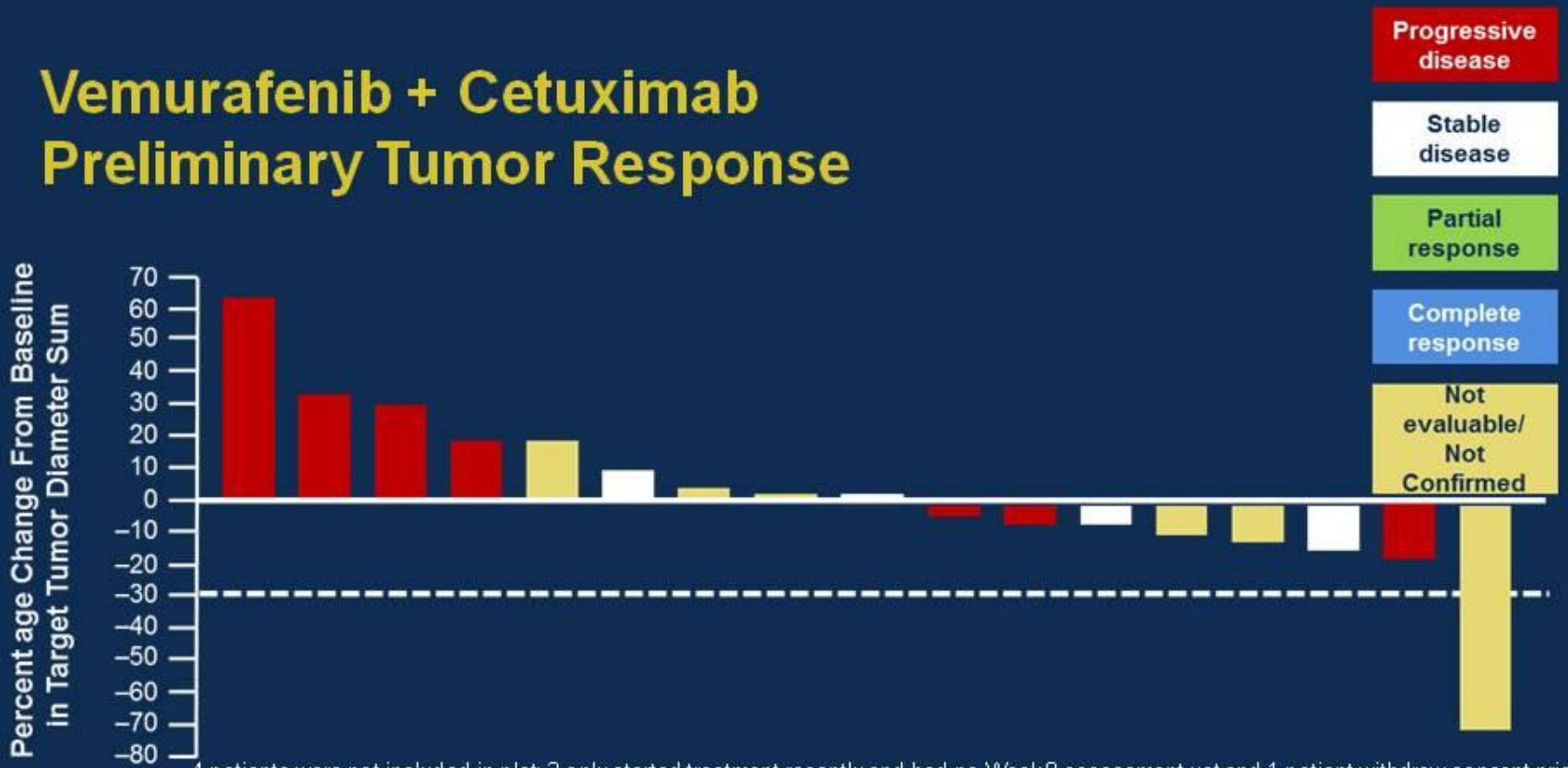
P-ERK H-score in 9 pts treated with Dabrafenib + Trametinib



MAPK signaling inibito nei pazienti valutati ma ad un livello inferiore rispetto a pazienti con Melanoma sottoposti a trattamento con solo Dabrafenib

- Corcoran et al, JCO 2015 -

Vemurafenib + Cetuximab Preliminary Tumor Response



4 patients were not included in plot: 3 only started treatment recently and had no Week 8 assessment yet and 1 patient withdrew consent prior to Week 8 treatment assessment.

Preliminary Best Overall Response and Clinical Benefit Rates in Vemurafenib + Cetuximab Cohort at Dose Level 3	
Response, n (%)	Patients (n=21)[a]
Complete response (CR)	0
Partial response (PR)	0
Stable disease (SD)	4 (19)
Progressive disease	7 (33)
Not available[b]	10 (48)
Patients with clinical benefit[c]	4 (19)
95% CI	5-42

[a]2 patients withdrew before vemurafenib administration and were not included in the maximum tolerated dose evaluation but are included in the safety and efficacy populations. [b]Of those not available, 1 withdrew consent before Week 8, and the remainder had not yet had a Week 8 evaluation, or their evaluation was not confirmed. [c]Patients with PR, CR, or SD.

Phase 1/2 Study of the MEK Inhibitor Trametinib, BRAF Inhibitor Dabrafenib, and Anti-EGFR Antibody Panitumumab in Patients With *BRAF* V600E-Mutated Metastatic Colorectal Cancer

C.E. Atreya, E. Van Cutsem, J.C. Bendell, T. André, J.H.M. Schellens, M.S. Gordon, A. McRee, P.J. O'Dwyer, K. Muro, J. Tabernero, R. van Geel, R. Sidhu, J.G. Greger, F. Rangwala, M. Motwani, Y. Wu, K.W. Orford, R.B. Corcoran

PRESENTED AT: ASCO Annual '15 Meeting

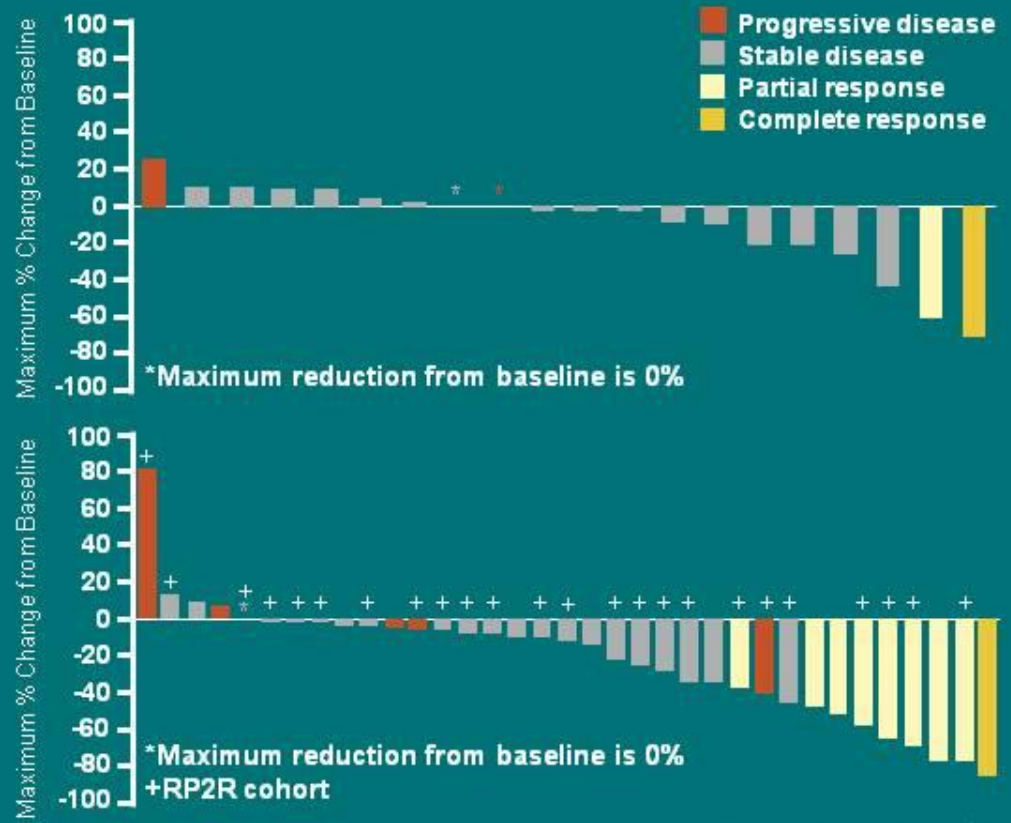
Presented By Chloe Atreya at 2015 ASCO Annual Meeting

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

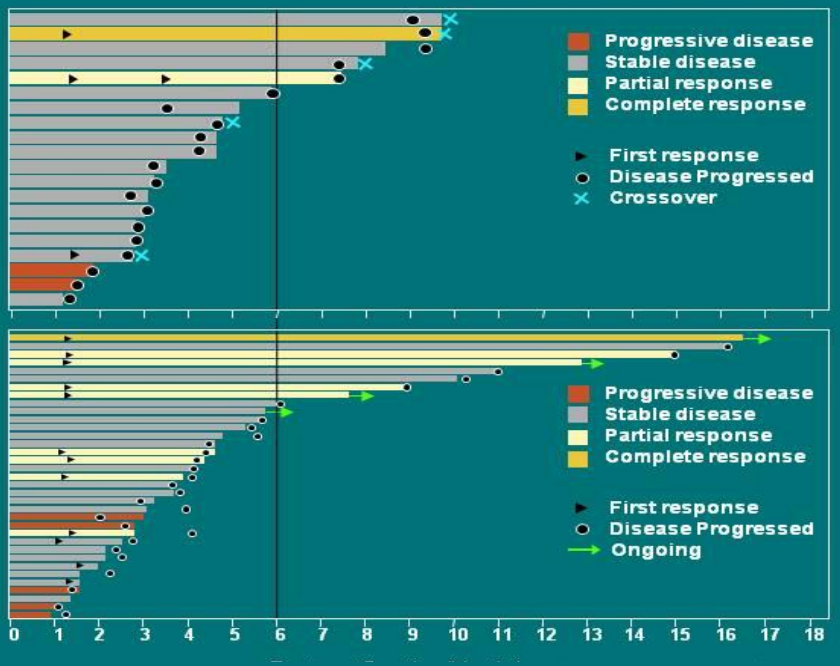
PRESENTED AT: ASCO Annual '15 Meeting

Duration on Study

D+P (N = 20)
> 6 months: 5 (25%)

D+P+T (N = 35)
> 6 months: 9 (26%)
> 1 year: 4 (11%)

Median Duration of Response:
5.4 mos (2.7, not available)

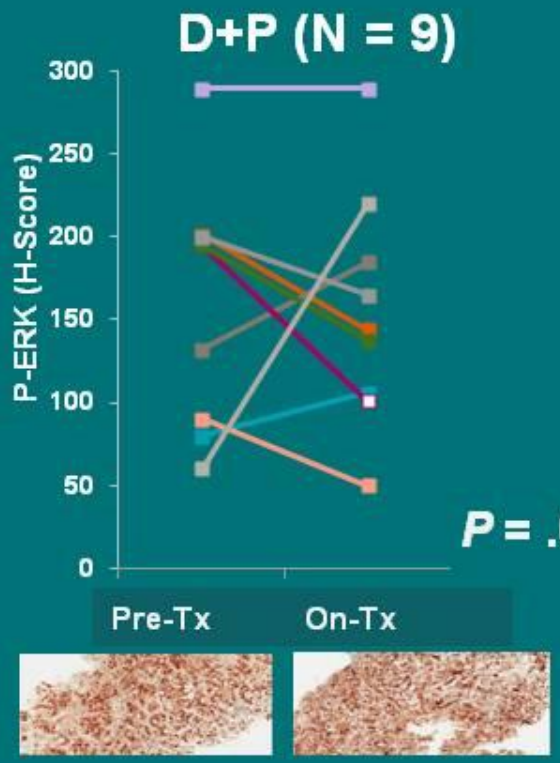


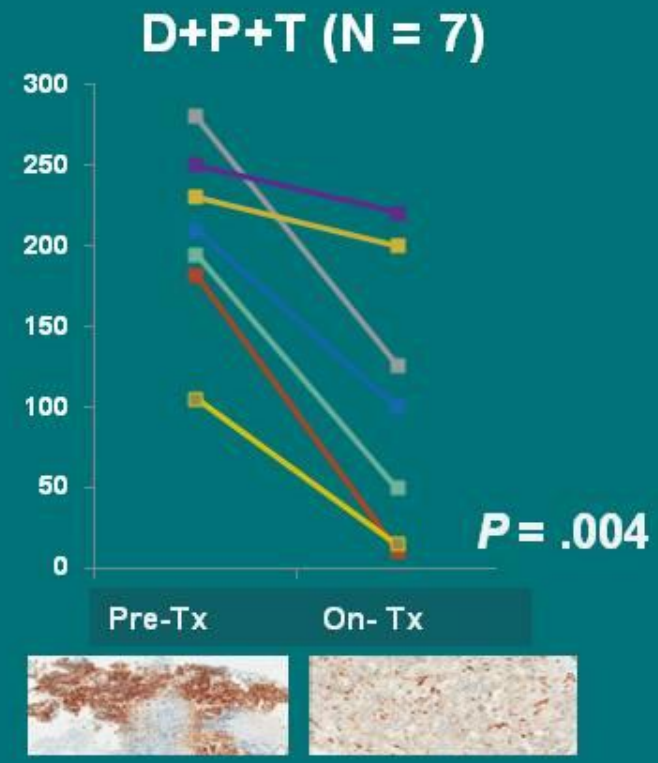
Investigator-Assessed Best Response (RECIST 1.1 Criteria)

	D 150mg BID P 6mg/kg Q2W (N = 20)	D 150mg BID P 6mg/kg Q2W T 2mg QD RP2R (N = 24)	D+P+T Total (N = 35)
Best Response With Confirmation, N (%)			
Complete response	1 (5%)	0	1 (3%)
Partial response	1 (5%)	5 (21%)	8 (23%)
Stable disease	16 (80%)	16 (67%)	21 (60%)
Progressive disease	2 (10%)	3 (13%)	5 (14%)
Response Rate (95% CI)	**2 (10%)** (1.2, 31.7)	**5 (21%)** (7.1, 42.2)	**9 (26%)** (12.5, 43.3)
Progression-Free Survival, months			
Median (95% CI)	**3.4** (2.6, 5.8)	**4.1** (2.6, 4.5)	**4.1** (2.8, 5.5)

Reduced Phosphorylated ERK (p-ERK) Staining by IHC on Paired Tumor Biopsies with D+T+P

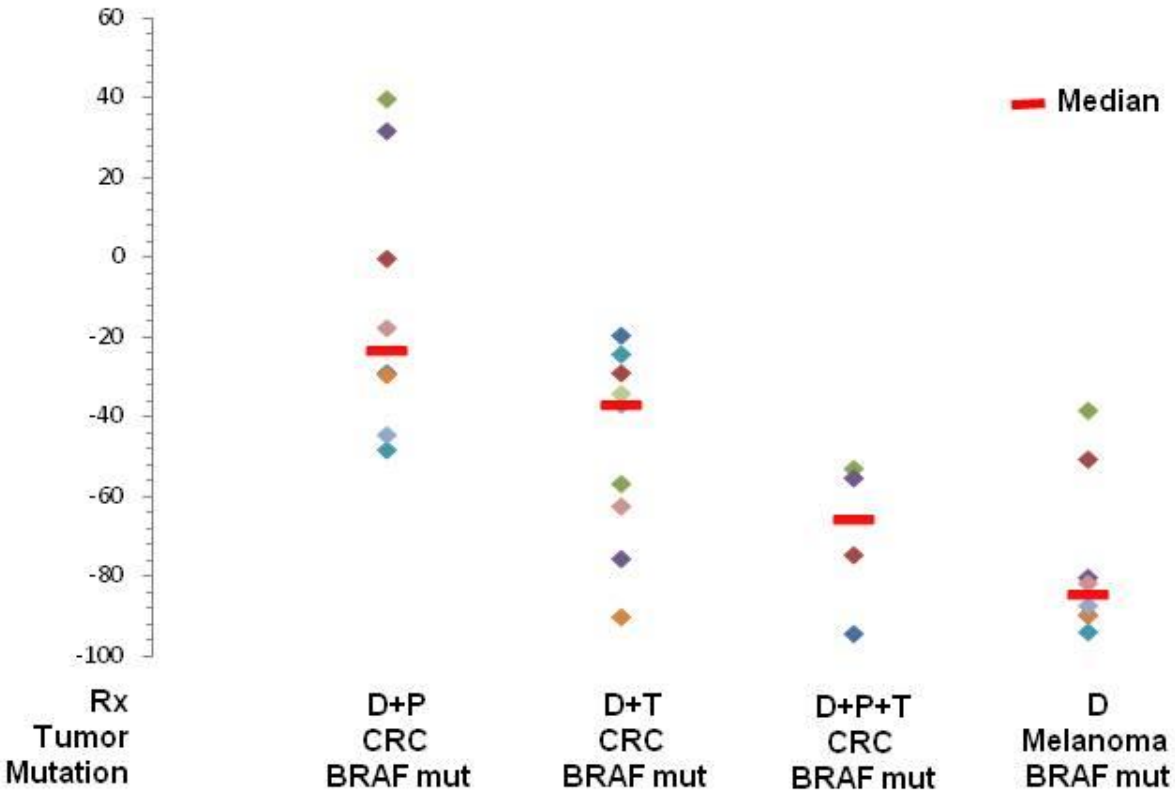
T-Test of H-Score





PRESENTED AT: ASCO Annual '15 Meeting

Comparison of p-ERK modulation using dabrafenib based combination therapies in BRAFm CRC and BRAFm melanoma



Treatment in BRAFm CRC was dabrafenib (150 mg BID) , trametinib (1.5-2 mg QD) and/or Panitumumab (4.5-6 mg every two weeks). Treatment in BRAFm melanoma was dabrafenib (70 -200 mg BID).

Average, +/- SD for median pERK decrease in CRC was ***D+P (n= 8): -12 %*** (± 33.2%), -23; ***D+T (n=9): -47 %*** (± 24 %) , -36.7%; ***D+P+T (n=4): -69%*** (± 19.3%), -64.5%. Average +/- SD for pERK decrease in melanoma was ***D (n=8): -76 %*** (± 20 %), -84%.

Conclusions

1. Dabrafenib+Panitumumab+Trametinib (D+P+T) appears to be more active than D+P or D+T.
2. Dermatologic toxicity is significant, resulting in dose reductions and interruptions/delays.
3. D+P+T inhibits MAPK signaling (change in p-ERK) more strongly than D+P or D+T, but to a lesser degree than observed in BRAFm melanoma with D alone.

Grazie per l’attenzione

Summary of preliminary activity in studies of BRAFi-based therapy in BRAFmut CRC

Regimen	N=	PR/CR	SD	DCR
D + T	43	12%	51%	63%
D + P	15	13.3%	73.3%	86.6%
V + C	11	-	36.3%	36.3%
E + C	**24**	**29.2%**	**50%**	**79.2%**
D + T + P	**15**	**40%**	**40%**	**80%**
V + C + Ir	**8**	**50%**	**50%**	**100%**
E + C + BYL	20	30%	60%	90%

D = dabrafenib, T = trametinib, P = panitumumab, V = vemurafenenib, C = cetuximab, E = encorafenib, Ir = irinotecan, BYL = BYL719

Dabrafenib + Trametinib in pre-treated *BRAF* mut mCRC

LETTER

doi:10.1038/nature10868

Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

Prahallad et al, Nature '12

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

BRAF/MEK/EGFR Inhibitor Combination Study in Colorectal Cancer

This study is currently recruiting participants.

Verified August 2013 by GlaxoSmithKline

ClinicalTrials.gov Identifier:
NCT01750918

Dabrafenib + Trametinib + Panitumumab in *BRAF* mutant mCRC

TARGET ACCRUAL: 200 patients

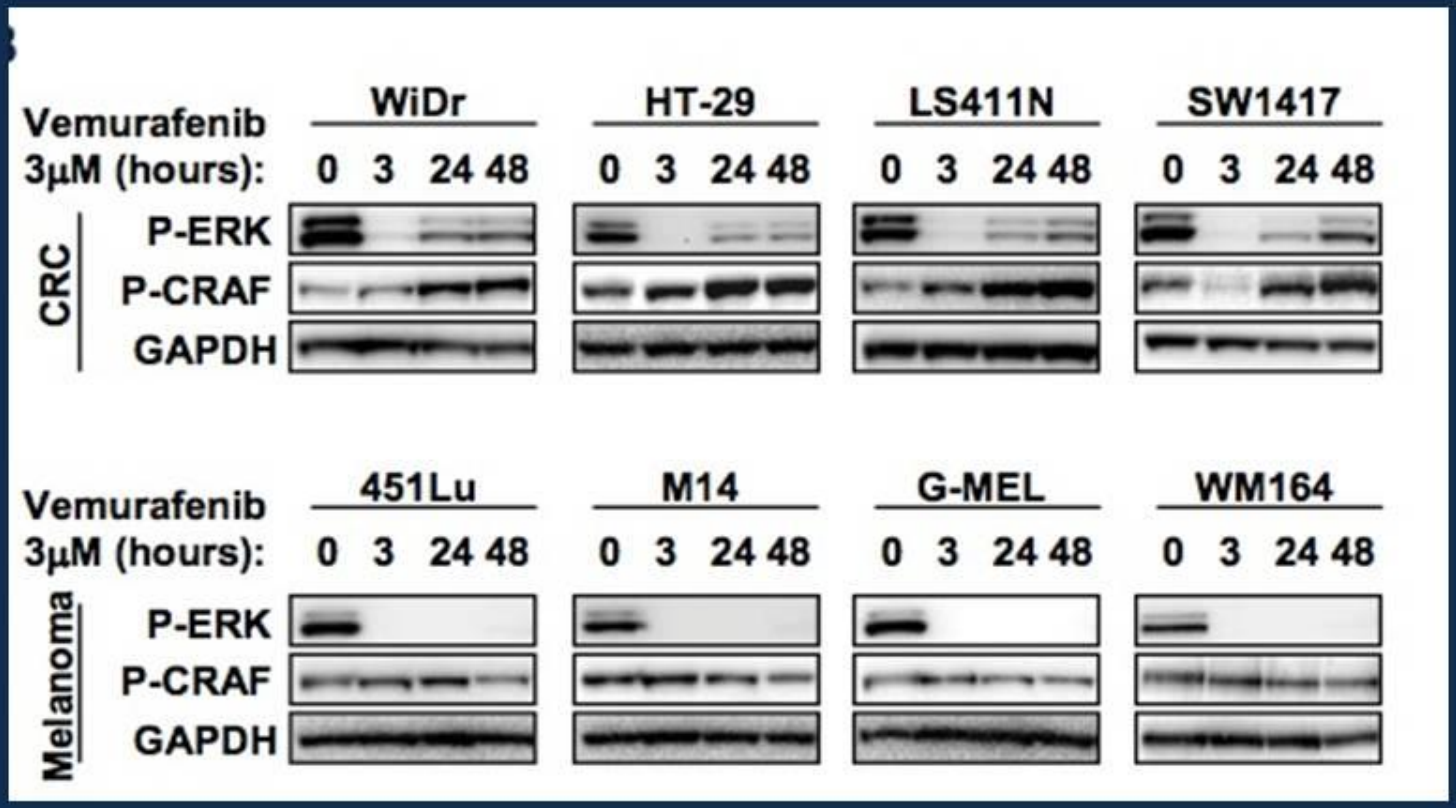
Therapeutic approaches to BRAF mutant colorectal cancer

Gary Middleton, University of Birmingham, UK

Discussant – Abstracts 3513 - 3519

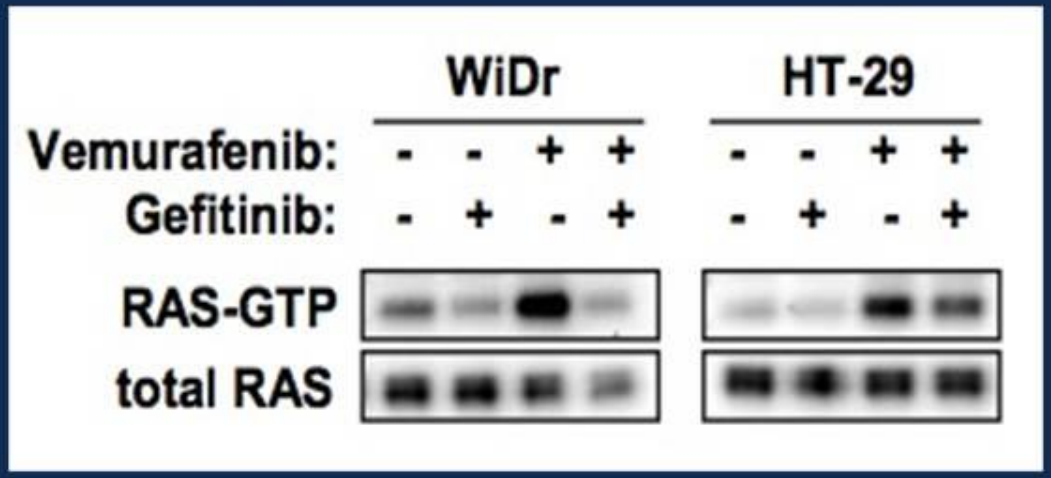
ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Incomplete suppression of P-ERK in BRAF-mutant colorectal cancers (CRC) is associated with decreased sensitivity to vemurafenib.



Corcoran R B et al. Cancer Discovery 2012;2:227-235

Combined inhibition of EGFR and RAF leads to sustained suppression of P-ERK and increased sensitivity in BRAF-mutant colorectal cancer cells.



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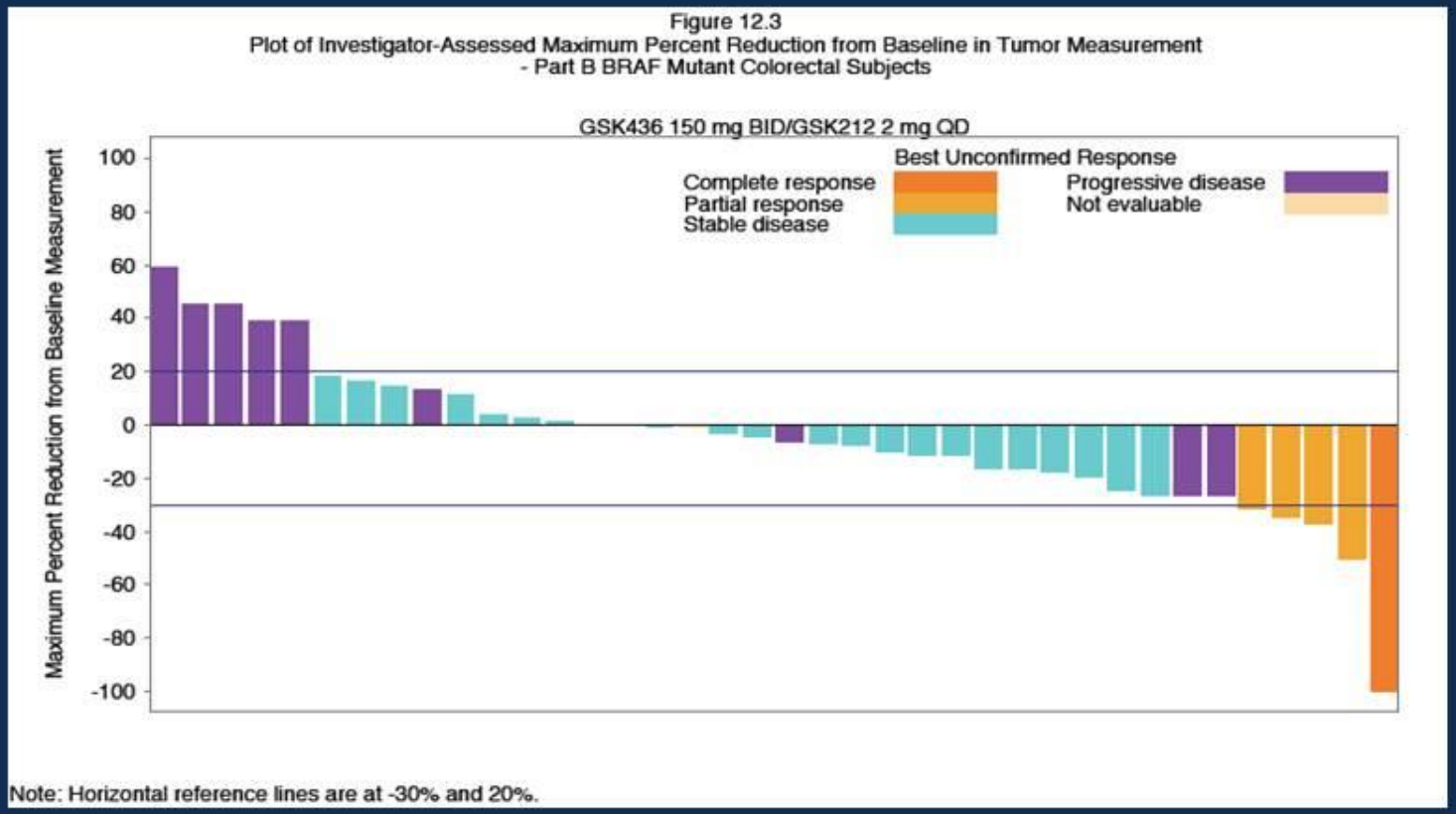
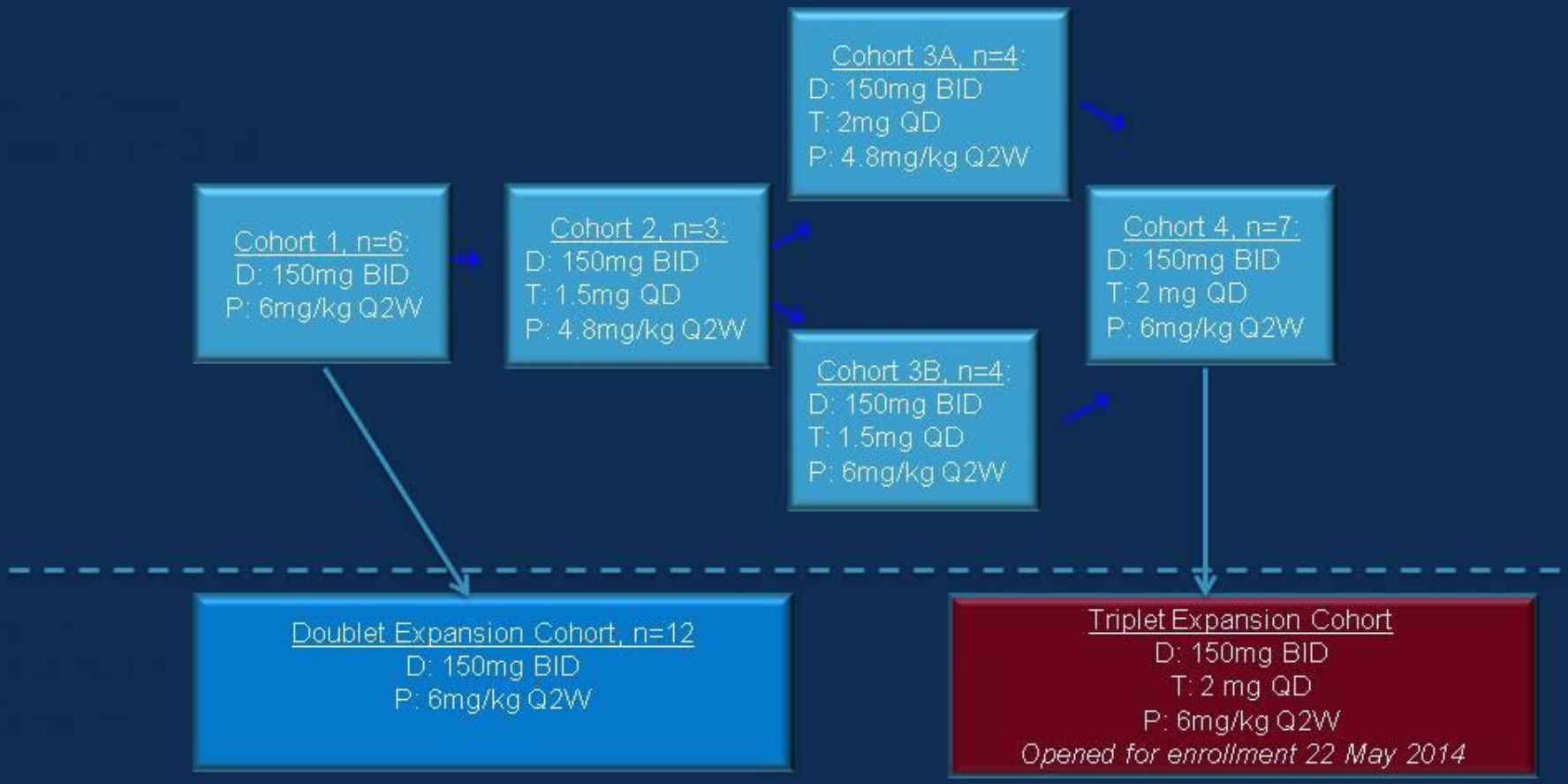
Waterfall plot of n=43 patients treated with dabrafenib and trametinb



- *5 (12%) pts achieved partial response (PR) or better*
  (with or without confirmation)
  - 1 (2%) pt had a complete response (CR) ongoing >24 months
- 22 (51%) pts total achieved stable disease (SD) at first restaging
  - *11 (26%) pts had a minor response (10% to 30% tumor reduction)*
- *10 (23%) pts remained on study >6 months*

Study Design and Methods



Treatment- Related Adverse Events for Dabrafenib + Trametinib + Panitumumab, n=16

Adverse events, n (%)	Grade 1	Grade 2	Grade 3*
Acneiform rash	***4 (25%)***	***4 (25%)***	***1 (6%)***
Diarrhea	***7 (44%)***	***0***	***1 (6%)***
Fatigue	5 (31%)	1 (6%)	0
Vomiting	4 (25%)	2(13%)	1 (6%)
Decreased appetite	3 (19%)	1 (6%)	1 (6%)
Hypomagnesaemia	3 (19%)	2 (13%)	0
Skin fissures	3 (19%)	0	1 (6%)
Nausea	1 (6%)	3 (19%)	0
Dry skin	3 (19%)	1 (6%)	0
Rash (erythematous, pustular, or unspecified)	1 (6%)	2 (13%)	0
Erythema	1 (6%)	2 (13%)	0
Folliculitis	1 (6%)	2 (13%)	0
Hypokalaemia	2 (13%)	0	1 (6%)
Peripheral edema	2 (13%)	1 (6%)	0
Pyrexia	***2 (13%)***	***1 (6%)***	0
Maculopapular rash	2 (13%)	1 (6%)	0
Decreased weight	1 (6%)	2 (13%)	0
Increased alanine aminotransferase	2 (13%)	0	0
Increased aspartate aminotransferase	2 (13%)	0	0
Hypophosphatemia	1 (6%)	1 (6%)	0
Pruritus	1 (6%)	1 (6%)	0
Alopecia	2 (13%)	0	0
Dehydration	0	2 (13%)	0
Dry mouth	2 (13%)	0	0
Dysgeusia	2 (13%)	0	0
Pain of skin	1 (6%)	1 (6%)	0
Palmar-plantar erythrodysaesthesia syndrome	2 (13%)	0	0
Decreased ejection fraction	0	1 (6%)	0
Skin exfoliation	1 (6%)	0	0

Therapeutic Implications

Enhance pathway blockade to maxise inhibition of pERK

double pathway blockade (**Corcoran, 3517**)

highly potent BRAFi with slow off - rate (**van Geel, 3514**)

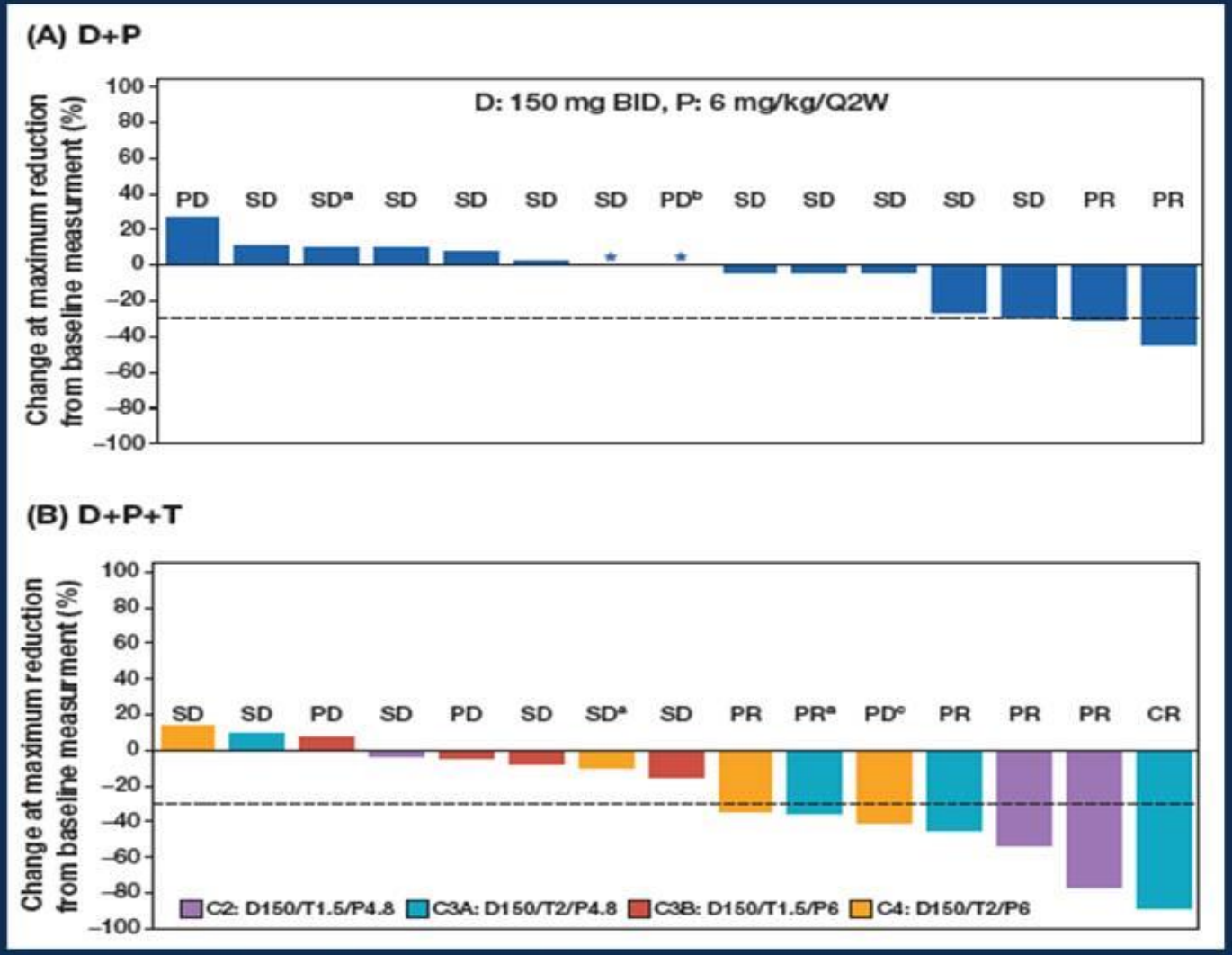
Block EGFR-mediated pathway reactivation

combined BRAFi/EGFRi (**Tabernero, 3518; Bendell, 3515; van Geel, 3514; *Hong, 3516***)

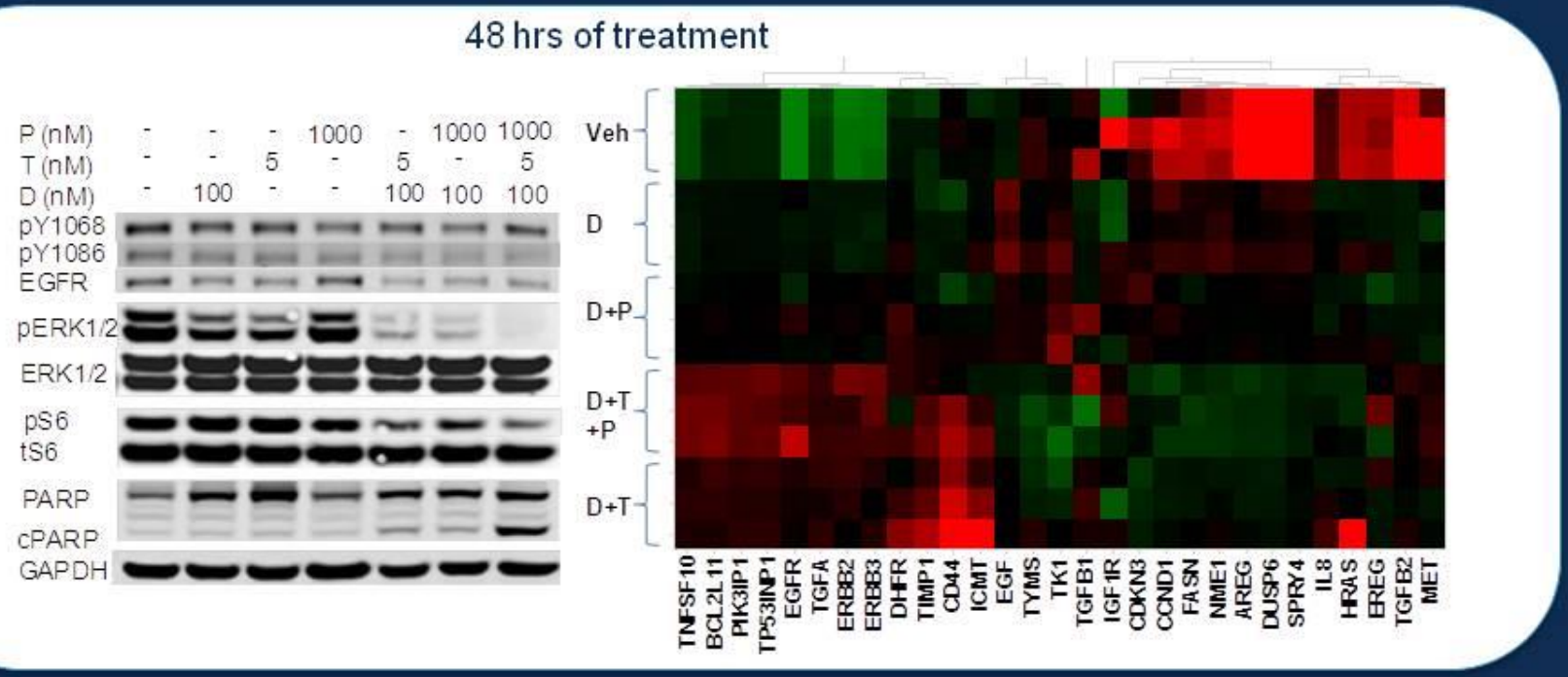
Combining both approaches

triple blockade (BRAFi/MEKi/EGFRi) (**Bendell, 3515)**

Maximum Tumor Response



Combined inhibition of BRAF/MEK and EGFR enhanced durable blockage of pERK/pS6 and apoptosis induction in HT29 BRAF^{V600E} CRC cells



- Triple combo of dabrafenib , trametinib and panitumumab induced strong apoptosis measured by cPARP which was associated with more effective inhibition of pERK/pS6 in HT 29 cells.
- Combined inhibition of BRAF/MEK and EGFR more effectively increased expression of genes involved in apoptosis induction TNFSF10 (TRAIL), BCL2L11 (BIM), PIK3INP1 and TP53INP1; and decreased CCND1 and MAPK signaling genes DUSP6, SPRY4, IL8 etc in HT29 cells.

Encorafenib + Cetuximab (+BYL719) – Best ORR

	Dual Combination CTX (250 mg/m²)					Triple Combination CTX (250 mg/m²)				
	ENC 100 mg n = 2 (%)	*ENC 200 mg n = 7 (%)*	ENC 400 mg n = 9 (%)	ENC 450 mg n = 8 (%)	All dual N = 26 (%)	ENC 200 mg + BYL 100 mg n = 3 (%)	ENC 200 mg + BYL 200 mg n = 7 (%)	*ENC 200 mg + BYL 300 mg n = 9 (%)*	ENC 300 mg + BYL 200 mg n = 6 (%)	All Triple N = 25 (%)
Evaluable patients	2	***5***	9	8	***24***	3	5	6	6	***20***
CR	0	***0***	0	0	0	0	0	0	0	0
PR	1 (50.0)	***2[a] (40.0)***	2[b] (22.2)	2[c] (25.0)	***7[d] (29.2)***	1 (33.3)	1 (20.0)	2[e] (33.3)	2[f] (33.3)	***6[g] (30.0)***
SD[h]	1 (50.0)	***1 (20.0)***	5 (55.6)	5 (62.5)	***12 (50.0)***	2 (66.7)	3 (60.0)	4 (66.7)	3 (50.0)	***12 (60.0)***
PD	0	***1 (20.0)***	1 (11.1)	1 (12.5)	3 (12.5)	0	0	0	0	0
Unknown	0	***1 (20.0)***	1 (11.1)	0	2 (8.3)	0	1 (20.0)	0	1 (16.7)	2 (10.0)
ORR (≥ PR)	1 (50.0)	***2[a] (40.0)***	2[b] (22.2)	2[c] (25.0)	7[d] (29.2)	1 (33.3)	1 (20.0)	2[e] (33.3)	2[f] (33.3)	6[g] (30.0)
DCR (≥ SD)	2 (100)	***3 (60.0)***	7 (77.8)	7 (87.5)	***19 (79.2)***	3 (100)	4 (80.0)	6 (100)	5 (83.3)	***18 (90.0)***