Goals of Palliative Therapy

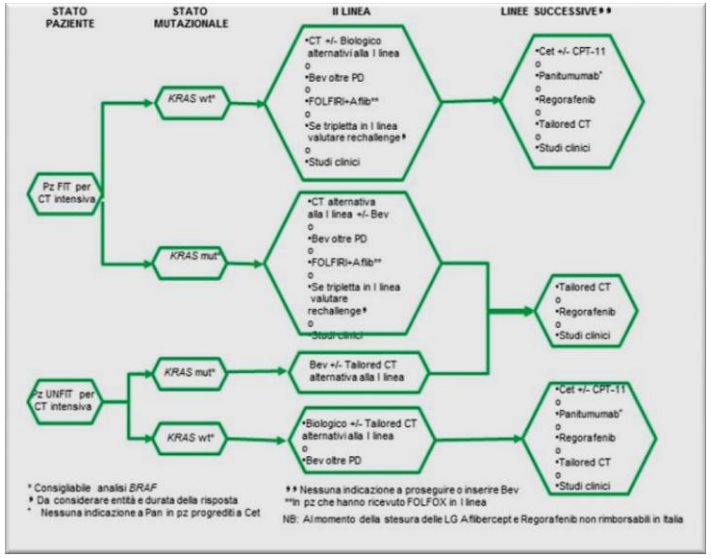
- Extend duration of life
- Maintain quality of life

…while using the least amount of therapy necessary to control the disease

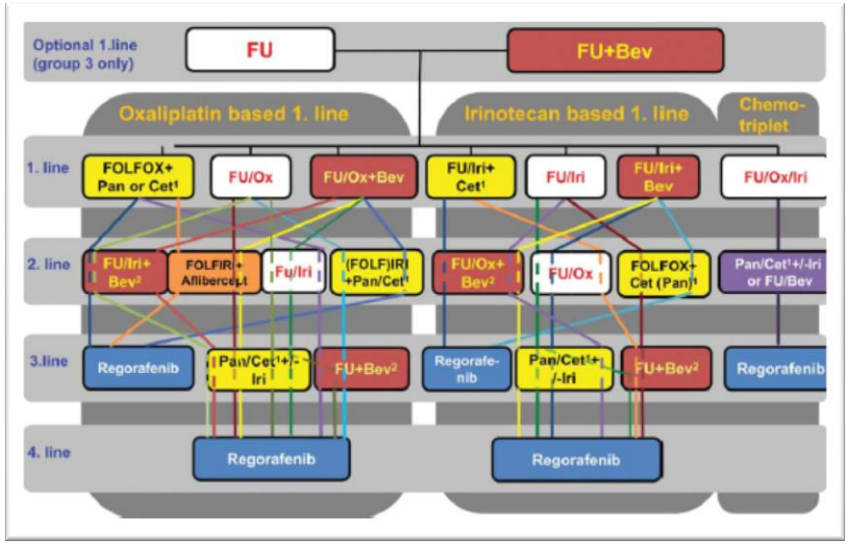
Searching for an ideal road..

…not always so linear!

AIOM 2014



ESMO 2012



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Colon Cancer

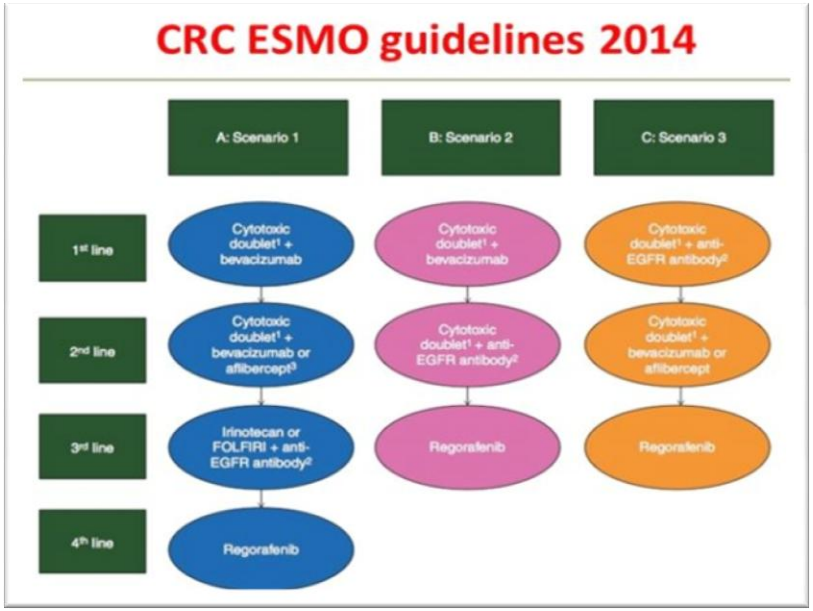
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEAS

Initial Therapy | Therapy After First Progression | Therapy After Second Prog

Patient appropriate for intensive therapy[2]

- 5-FU/leucovorin[18] or Capecitabine[19] ± bevacizumab[5,6,20]
  - FOLFOX[3] ± bevacizumab[5,6] or CapeOX[4] ± bevacizumab[5,6] or Irinotecan[10] + oxaliplatin ± bevacizumab[5,6] or Irinotecan[10] ± bevacizumab[5,6] or Irinotecan[10] ± ziv-aflibercept[11] or FOLFIRI[10] ± bevacizumab[5,6] or FOLFIRI[10] ± ziv-aflibercept[11] → Irinotecan[10] → (Cetuximab or panitumuma (KRAS/NRAS WT gene only irinotecan;[10] for patients not able to tole combination, consider sing (cetuximab or panitumuma (KRAS/NRAS WT gene only or Regorafenib[16]
  - FOLFOX[3] or CapeOX[4] → Regorafenib[16]
- or
- FOLFOXIRI ± bevacizumab[5,6] → (Cetuximab or panitumumab)[6,12-15] (KRAS/NRAS WT gene only)[8] + irinotecan;[10] for patients not able to tolerate combination, consider single-agent (cetuximab or panitumumab)[6,12-15] (KRAS/NRAS WT gene only)[8] or Regorafenib[16] → Regorafenib[16] (if not given previously) or Clinical trial or Best supportive care[17]

Additional options on



ESMO guidelines: continuum of care in mCRC patients

	Scenario 1	Scenario 2	Scenario 3
1L	CT doublet + bevacizumab	CT doublet + bevacizumab	CT doublet + anti-EGFR antibody
2L	CT doublet + bevacizumab or aflibercept	CT doublet + anti-EGFR antibody	CT doublet + bevacizumab or aflibercept
3L	Irinotecan or FOLFIRI + anti-EGFR antibody	Regorafenib	Regorafenib
4L	Regorafenib		

VEGF = vascular endothelial growth factor

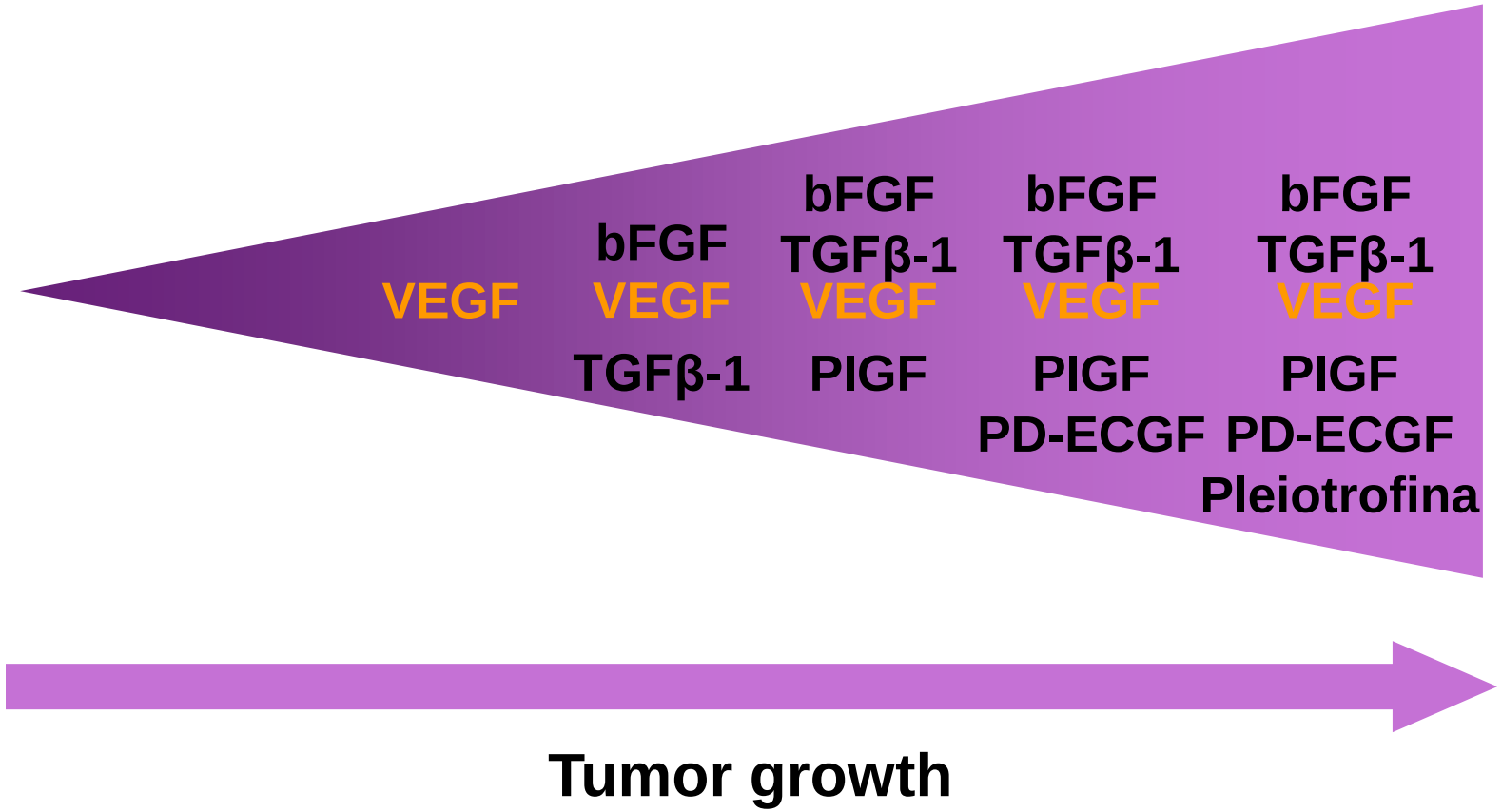
Van Cutsem, et al. Ann Oncol 2014

Regorafenib (Stivarga®) – Indicazione EMA *(30.8.2013)*

4.1 Therapeutic indications

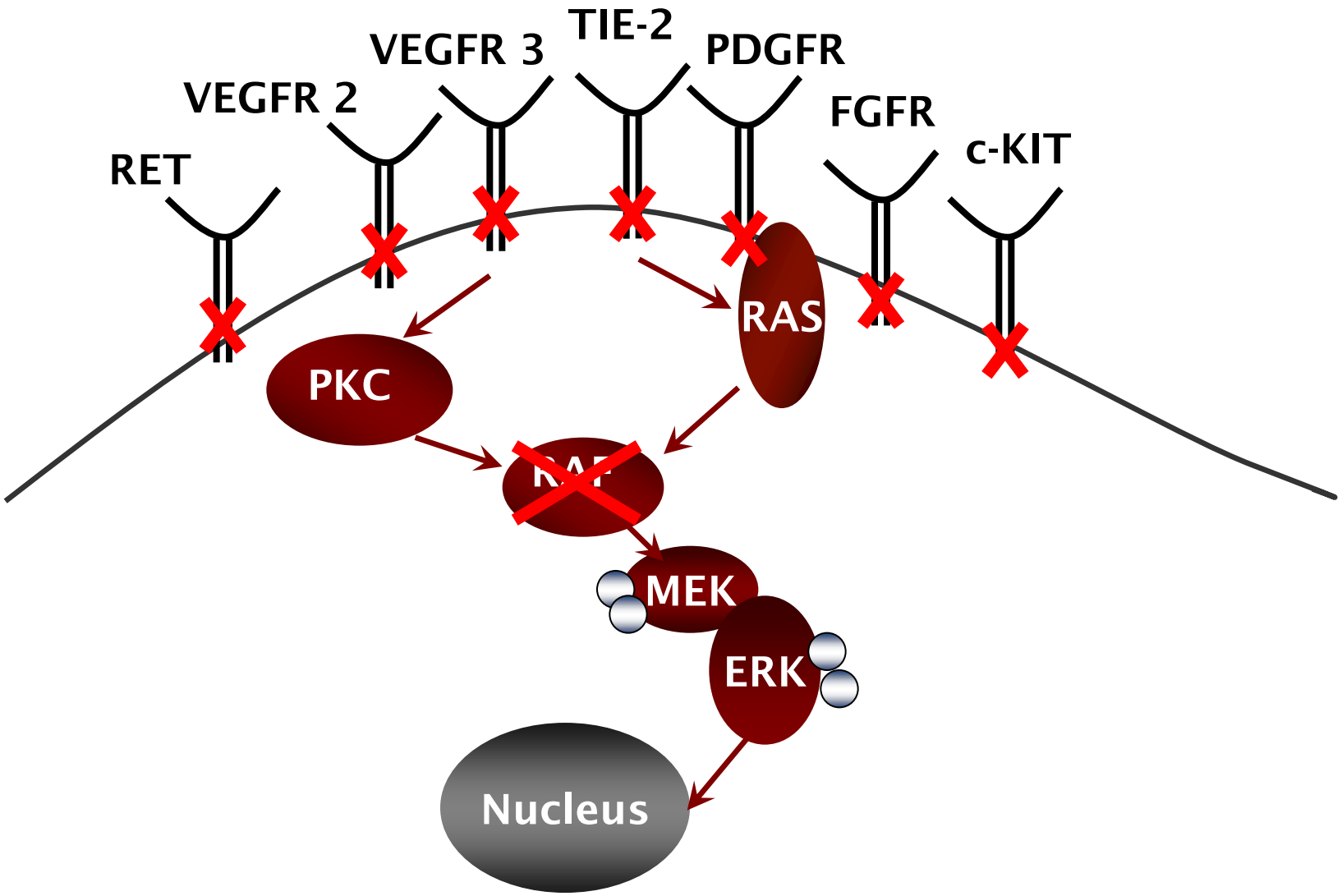
Stivarga is indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF and an anti-EGFR therapy.

VEGF expression along tumor natural history



Adapted from Folkman: Cancer. Principles and Practice of Oncology 2005

Regorafenib: multitarget mechanism of action



E quindi nell'era pre-Regorafenib nel 30-40% dei ns pz dopo …

- ~~Fluoropirimidine~~
- ~~Oxaliplatino~~
- ~~Irinotecano~~
- ~~Bevacizumab~~
- ~~Cetuximab/Panitumumab (solo WT)~~

… che fare?

Cosa facciamo/facevamo nell'era pre-Regorafenib

- **BSC**
- **Rechallenge**
- **Trattamenti locoregionali**
- **Altra chemioterapia sistemica (mitomicina-C, diversa fluoropirimidina, CT+beva, gemcitabina, raltitrexed, CT metronomica …)**

Cosa facciamo/facevamo nell'era pre-Regorafenib

- BSC
- **Rechallenge**
- Trattamenti locoregionali
- Altra chemioterapia sistemica (mitomicina-C, diversa fluoropirimidina, CT+beva, gemcitabina, raltitrexed, CT metronomica …)

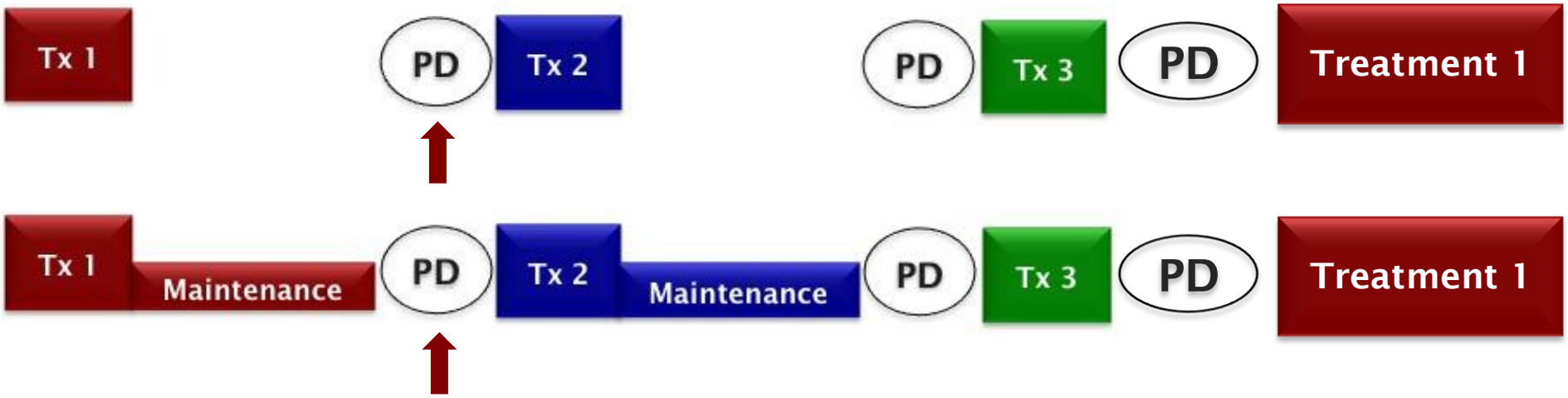
Reintroduzione di un trattamento precedentemente utilizzato in seguito al fallimento di ulteriori linee terapeutiche (diverso da strategie OPTIMOX-like)

Rechallenge = placebo?

"Old-fashion" strategy

PROGRESSION <u>ON</u> THERAPY

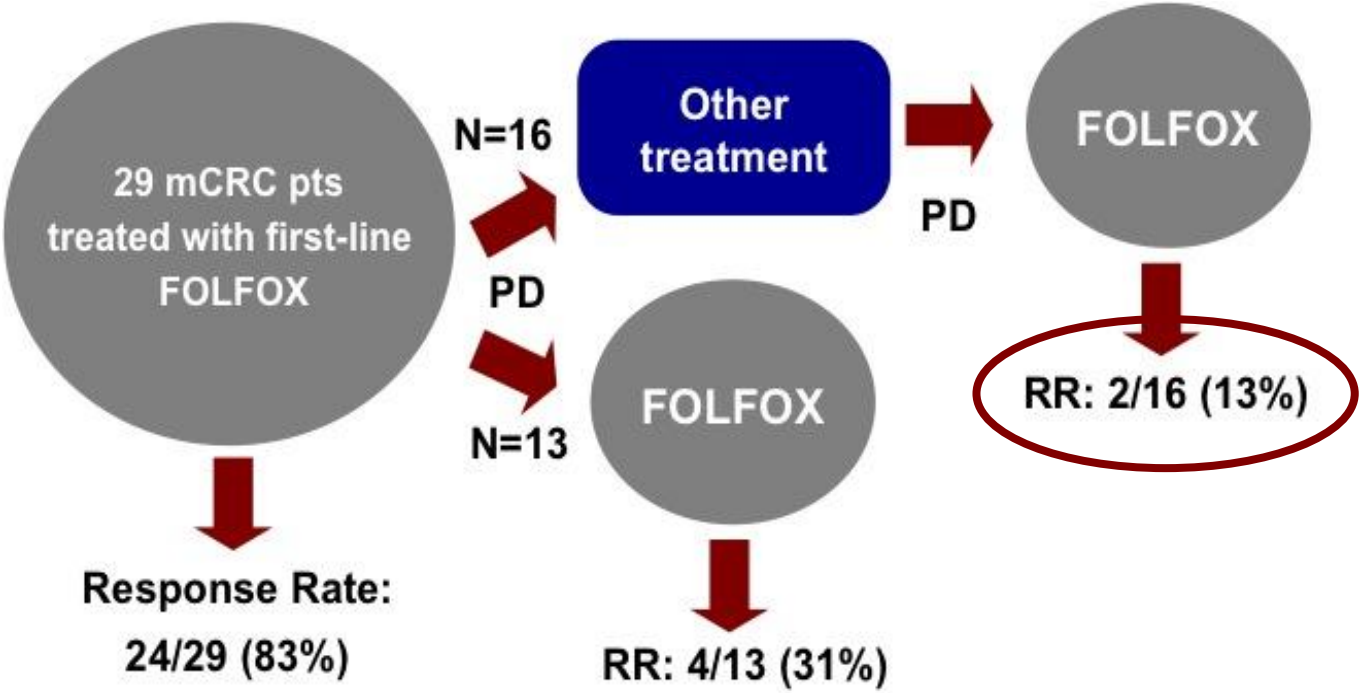
More "modern" strategies



PROGRESSION <u>OFF</u> THERAPY

Rechallenge con chemioterapia in linee avanzate

- **Prevalentemente con Oxaliplatino**
- **Scarse e limitate evidenze retrospettive**



Maindrault-Goebel et al, Ann Oncol '04

Cosa facciamo/facevamo nell'era pre-Regorafenib

- BSC
- Rechallenge
- **Trattamenti locoregionali**
- Altra chemioterapia sistemica (mitomicina-C, diversa fluoropirimidina, CT+beva, gemcitabina, raltitrexed, CT metronomica …)
-

Trattamenti locoregionali

Retrospective trials in chemorefractory mCRC pts with liver-limited/dominant disease

Treatment	N	Setting	ORR (%)	mPFS (mos)	mOS (mos)
5FU [HAI]	55	≥4th line	18	2.8	6.7
RTX [HAI] +OXA	17	3rd line	65	10.5	27.5
Oxa+Irino+5FU [HAI]	29	3rd line	35	4.5	18.0

Nishiofuku et al, Clin Colorectal Cancer 2010
Khouri et al, Anticancer Drug 2010
Bouchahda et al, Cancer 2009

Trattamenti locoregionali

Phase II and II randomized trials in chemorefractory mCRC pts with liver-limited/dominant disease

Treatment	Phase	N	Setting	ORR (%)	mPFS (mos)	mOS (mos)
Oxa+Irino+5FU [HAI] +Cet	II	35	≥3rd line	38	7.3	15.2
DEBIRI	II	55	≥3rd line	50	11.0	19.0
DEBIRI	II ran	74	≥3rd line	69	7.0	22.0
FOLFIRI				20	4.0	15.0
^{90}Yttrium SIRT	II	50	≥4th line	24	3.7	12.6
5FU	II ran	44	≥3rd line	0	2.1	7.3
^{90}Yttrium SIRT +5FU				10	4.5	10.0

Ducreux et al, ASCO 2013
Martin et al, Ann Surg Oncol 2011
Fiorentini et al, Anticancer Res 2013
Cosimelli et al, Br J Cancer 2010
Hendlisz et al, J Clin Oncol 2010

Cosa facciamo/facevamo nell'era pre-Regorafenib

- BSC
- Rechallenge
- Trattamenti locoregionali
- **Altra chemioterapia sistemica (mitomicina-C, diversa fluoropirimidina, CT+beva, gemcitabina, raltitrexed, CT metronomica …)**

Alltra chemioterapia sistemica

Retrospective trials in chemorefractory mCRC pts

Treatment	N	Setting	ORR (%)	mPFS (mos)	mOS (mos)
MMC+Cape	28	3rd line	4	2.0	6.0
MMC+Cape	61	3rd line	8	3.0	6.0
MMC +/- fluoropirimidine	109	≥3rd line	0	1.7	4.5
MMC+UFT	41	3rd line	7	2.5	6.0
MMC+UFT/5FU	22	≥3rd line	NR	3.0	7.0
Cape	20	3rd line	0	2.8	6.1
Cape	60	3rd line	7	2.8	9.7
Gem+Cape	39	≥3rd line	3	3.0	7.3

Rimassa et al, Tumori 2006; Scartozzi et al, Tumori 2006
Ferrarotto et al, Eur J Cancer 2012;
Vormittag et al, Anticancer Drug 2007
Alkis et al, J BUON 2011; Gubanski et al, Acta Oncol 2005
Lee et al, ASCO 2012; Salgado et al, Anticancer Res 2013

Altra chemioterapia sistemica

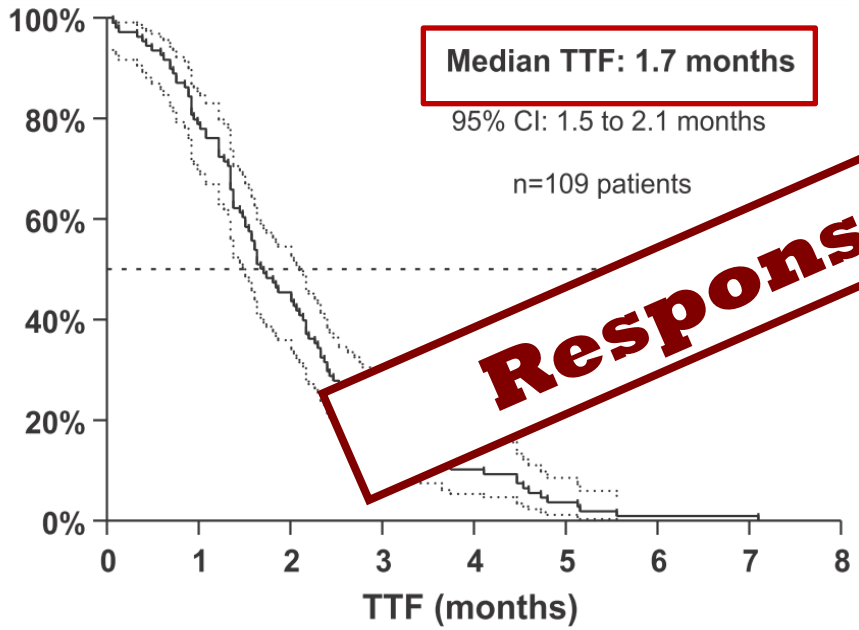
Phase II trials in chemorefractory mCRC pts

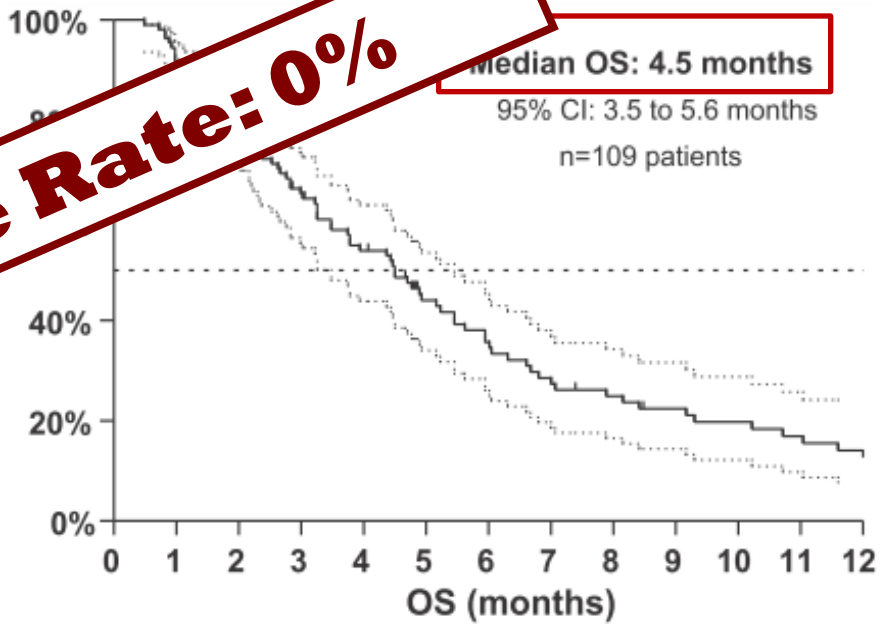
Treatment	N	Setting	ORR (%)	mPFS (mos)	mOS (mos)
MMC+RTX	21	3rd line	0	2.3	5.0
MMC+Cape	21	3rd line	5	2.6	6.8
MMC+UFT	21	3rd line	NR	NR	6.4
MMC+UFT	44	3rd line	9.3	5.0	7.5
Cape	28	3rd line	7	4.0	5.2
Gem+5FU	37	3rd line	11	4.2	8.9
Gem+Cape	49	3rd line	0	2.7	6.8
CTX+Cape	26	≥3rd line	4	2.1	6.0
S-1+Gem	36	3rd-4th line	17	3.7	10.0

Rosati et al, Anticancer Res 2003; Lim et al, Cancer Chemother Pharmacol 2005
Francois et al, J Chemother 2012; Michalak et al, J BUON 2005
Ardavanis et al, Anticancer Res 2006; Bitossi et al, Anticancer Res 2008
Spindler et al, Anticancer Res 2014; Marmorino et al, ASCO 2013; Sym et al, ASCO 2013

Real life experience : MD Anderson e centri brasiliani

Mitomycin C +/- fluoropirimidine in 109 refractory mCRC pts





Response Rate: 0%

Ferrarotto et al, Eur J Cancer 2012

Mitomicina C: profilo di tossicità

Toxicity	All grades ($n = 36$) (%)	Grade 3 (%)
Palmar-plantar erythema	50	16.7
Nausea/vomiting	44.5	8.3
Lethargy	94.5	5.6
Diarrhoea	52.8	2.8
Peripheral neuropathy	8.3	2.8
Fever	8.6	2.8
Stomatitis	33.3	0
Infection	11.1	0
Anaemia	61.1	8.3
Neutropenia	11.1	2.8
Thrombocytopenia	16.7	2.8

Chong et al, Br J Cancer 2005

Alternative a rego?

Rechallenge

- **Toxic, ma non credo sempre placebo**

Trattamenti locoregionali

- **Toxic, complessi, ma non credo placebo in pz e centri molto selezionati**

Altra chemioterapia sistemica

- **Toxic, probabilmente placebo**

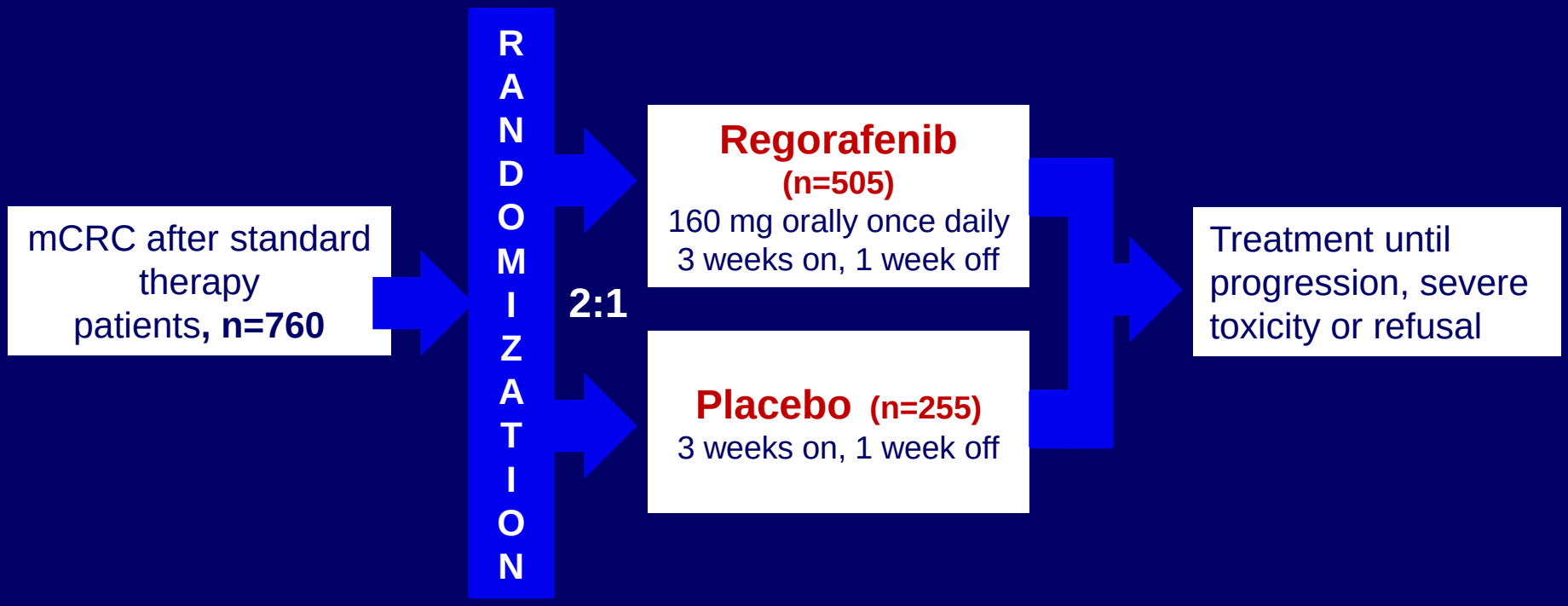
Results of a phase III randomized, double-blind, placebo-controlled, multicenter trial (CORRECT) of regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic colorectal cancer (mCRC) who have progressed after standard therapies

Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial

Axel Grothey, Eric Van Cutsem*, Alberto Sobrero, Salvatore Siena, Alfredo Falcone, Marc Ychou, Yves Humblet, Olivier Bouché, Laurent Mineur, Carlo Barone, Antoine Adenis, Josep Tabernero, Takayuki Yoshino, Heinz-Josef Lenz, Richard M Goldberg, Daniel J Sargent, Frank Cihon, Lisa Cupit, Andrea Wagner, Dirk Laurent, for the CORRECT Study Group†*

www.thelancet.com **Published online November 22, 2012 http://dx.doi.org/10.1016/S0140-6736(12)61900-X**

CORRECT trial design



- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - Stratification: prior anti-VEGF therapy, time from diagnosis of metastasis, geographical region
- Global trial: 16 countries, 114 centers
- **Primary endpoint: overall survival (OS)**
  - 90% power to detect 33.3% increase (hazard ratio [HR]=0.75), 1-sided overall α=0.025
- **Recruitment: May 2010 to March 2011**

Patient eligibility: key inclusion criteria

- Disease progression within **3 months** of last administration or intolerance of approved standard therapies, which had to include:
  - Fluoropyrimidine, oxaliplatin, irinotecan
  - Bevacizumab
  - Cetuximab or Panitumumab (if *KRAS* wild-type)

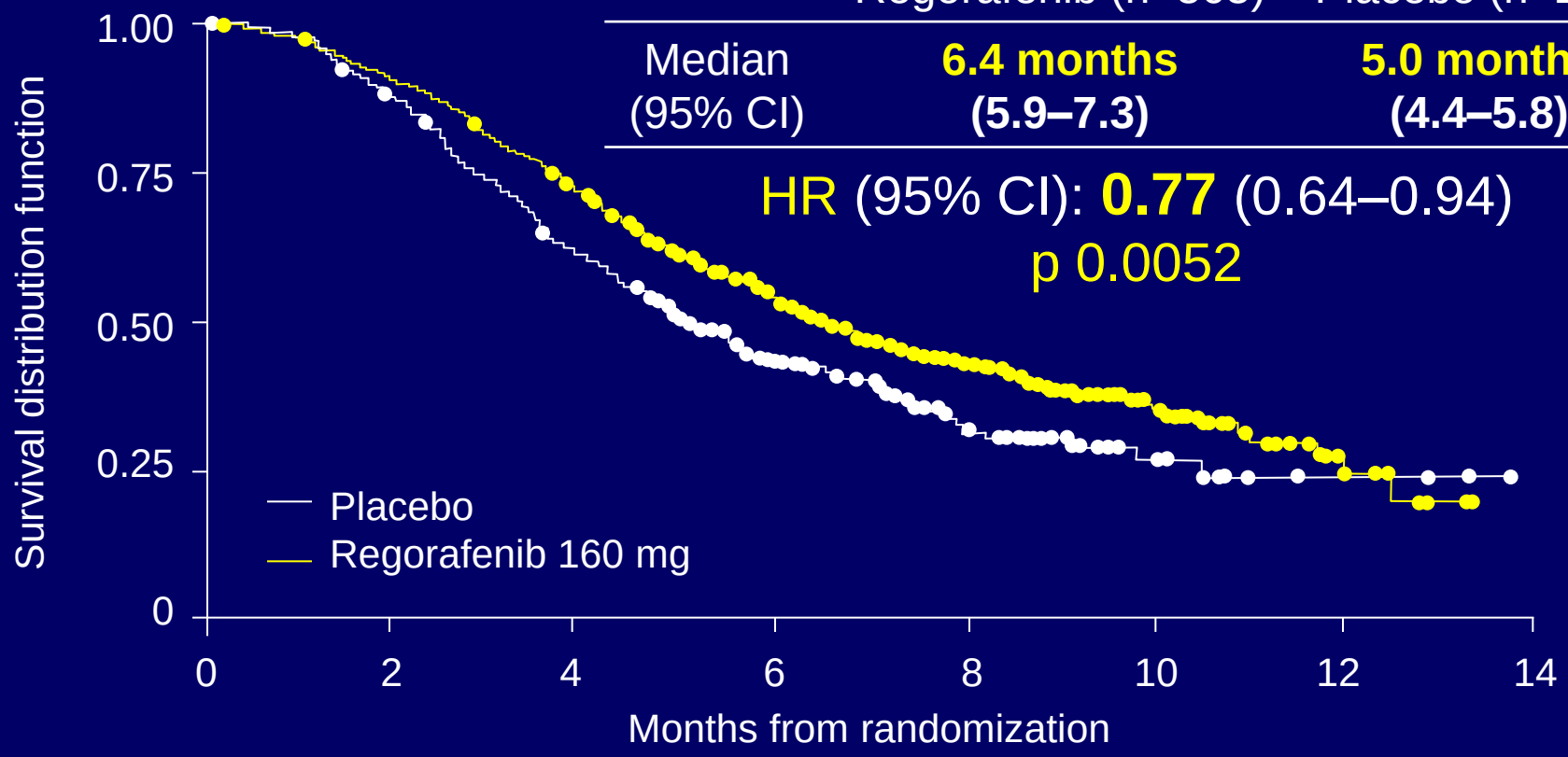
Patient demographics and baseline disease characteristics

	Regorafenib N=505	Placebo N=255
Age, median (range)	61 (22–82)	61 (25–85)
ECOG score 0, %	52.5	57.3
Region (North America, Western Europe, Israel, Australia), %	83.2	83.1
Colon as primary site of disease, %	64.0	67.5
***KRAS* mutation present, %**	**54.1**	**61.6**
≥4 prior treatment lines for metastatic disease, %	**48.5**	**47.1**
Prior Bevacizumab, %	**100**	**100**

Overall Survival (primary endpoint)

	Regorafenib (n=505)	Placebo (n=255)
Median (95% CI)	**6.4 months (5.9–7.3)**	**5.0 months (4.4–5.8)**

HR (95% CI): **0.77** (0.64–0.94)
p 0.0052



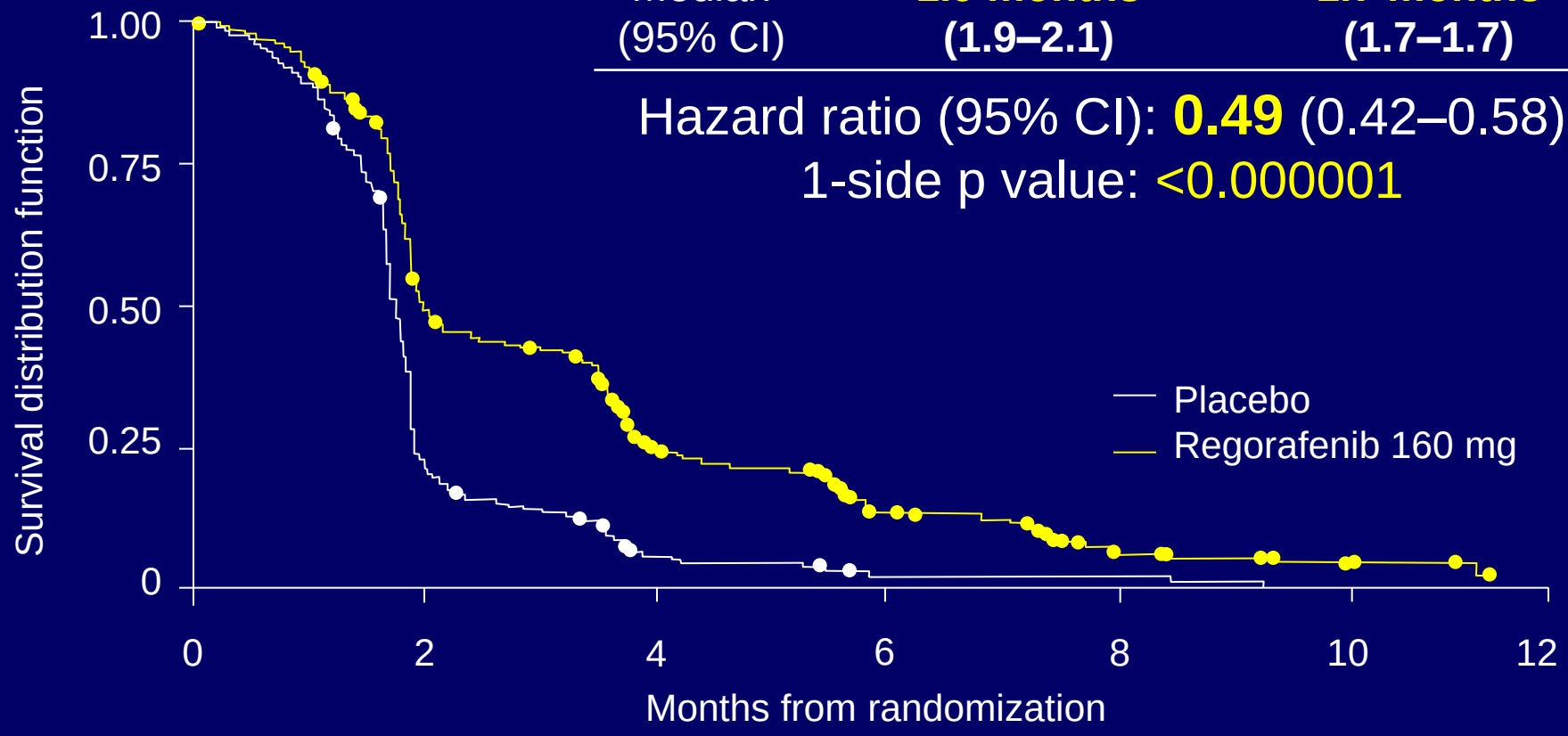
Patients at risk

Placebo	*221*	*150*	*75*	*32*	*9*	*3*
Regorafenib	*452*	*352*	*187*	*93*	*33*	*7*

Progression-Free Survival

	Regorafenib (n=505)	Placebo (n=255)
Median (95% CI)	**1.9 months (1.9–2.1)**	**1.7 months (1.7–1.7)**

Hazard ratio (95% CI): **0.49** (0.42–0.58)
1-side p value: <0.000001



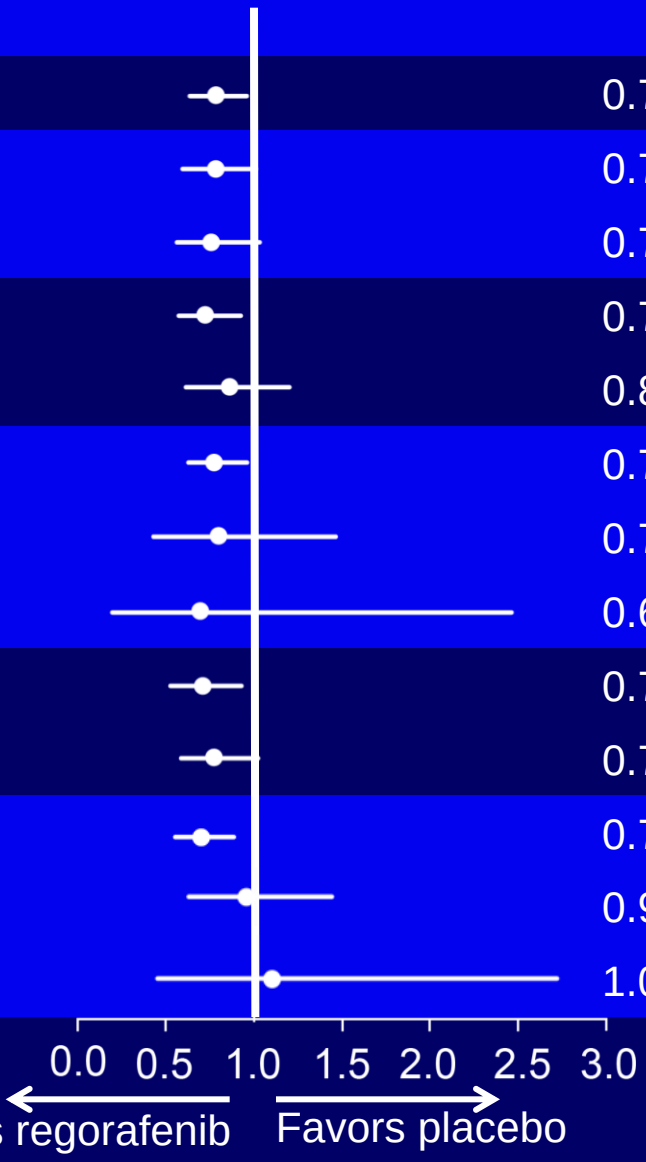
Patients at risk					
Placebo	*51*	*9*	*2*	*2*	*0*
Regorafenib	*238*	*98*	*42*	*12*	*3*

Overall Response

Best response, %	Regorafenib N=505	Placebo N=255
PR	**1.0**	**0.4**
SD	**42.8**	**14.5**
PD	**49.5**	**80.0**

Subgroup analysis of overall survival

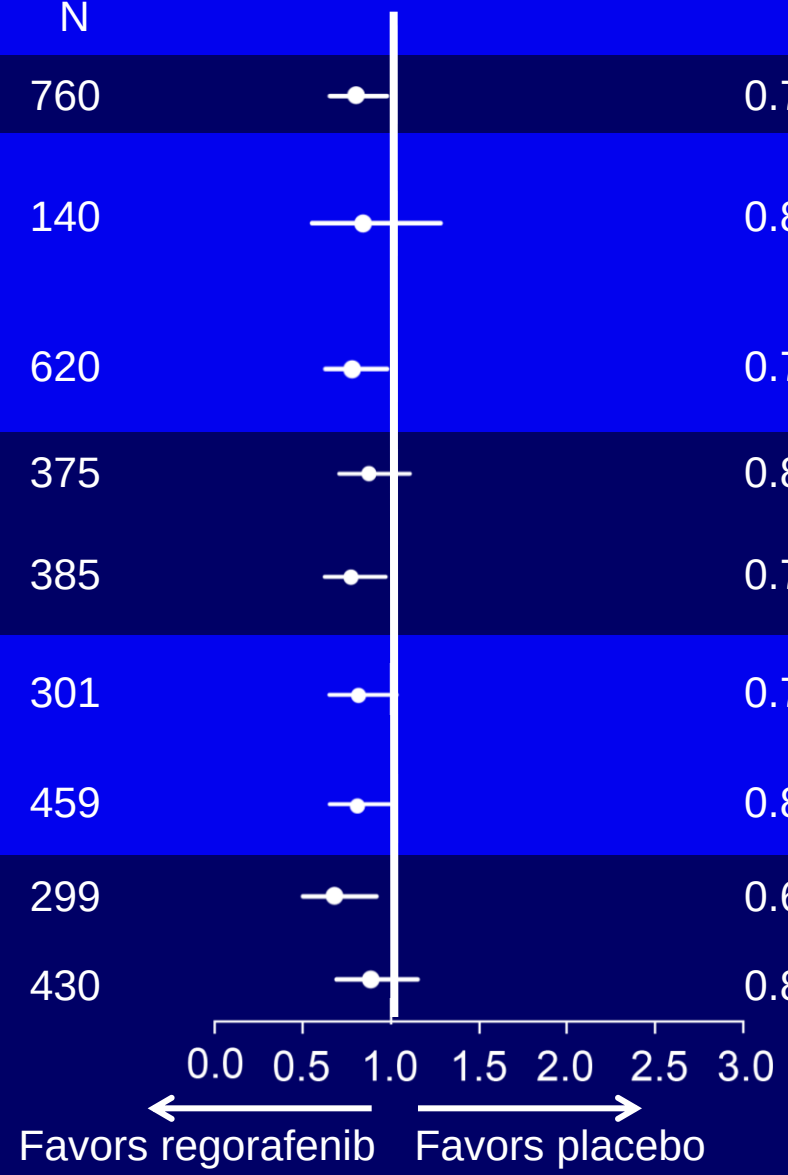
		N	HR (95% CI)
All patients		760	0.774 (0.636, 0.942)
Sex	Male	464	0.773 (0.599, 0.998)
	Female	296	0.751 (0.552, 1.022)
Age	<65 years	475	0.716 (0.561, 0.914)
	≥65 years	285	0.856 (0.614, 1.193)
Region	NA, WE, IS, AU	632	0.768 (0.622, 0.948)
	Asia	104	0.790 (0.429, 1.456)
	EE	24	0.694 (0.195, 2.466)
Baseline ECOG	0	411	0.702 (0.530, 0.929)
	1	349	0.773 (0.586, 1.020)
Primary site of disease	Colon	495	0.703 (0.557, 0.887)
	Rectum	220	0.953 (0.633, 1.436)
	Colon and rectum	44	1.091 (0.441, 2.697)



NA (North America), WE (Western Europe),
IS (Israel), AU (Australia), EE (Eastern Europe)

Subgroup analysis of overall survival

		N	HR (95% CI)
All patients		760	0.774 (0.636, 0.942)
Time from first diagnosis of metastatic disease to randmization	<18 months	140	0.816 (0.532, 1.251)
	≥18 months	620	0.760 (0.609, 0.948)
Prior anticancer treatment	F, Ox, Iri, Bev	375	0.825 (0.625, 1.089)
	F, Ox, Iri, Bev, anti-EGFR	385	0.710 (0.538, 0.938)
Prior treatment lines for metastatic disease	≤3	301	0.709 (0.521, 0.967)
	>3	459	0.804 (0.624, 1.038)
KRAS mutation status (historical)	No	299	0.653 (0.476, 0.895)
	Yes	430	0.867 (0.670, 1.123)



F (fluoropyrimidine), Ox (oxaliplatin), Iri (irinotecan), Bex (bevacizumab)

Most frequent drug-related adverse events (>5% at grade 3 or greater)

Adverse event, %	Regorafenib, N=500			Placebo, N=253		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Hand-foot skin reaction	46.6	**16.6**	0	7.5	0.4	0
Fatigue	47.4	**9.2**	0.4	28.1	4.7	0.4
Hypertension	27.8	**7.2**	0	5.9	0.8	0
Diarrhea	33.8	**7.0**	0.2	8.3	0.8	0
Rash/desquamation	26.0	**5.8**	0	4.0	0	0

Drug-related AEs leading to permanent discontinuation

- Regorafenib 8.2 %
- Placebo 1.2 %

Drug-related grade 5 AEs: Regorafenib 1.0% Placebo 0%

Sobrero A et al. WCGI 2012;abstract O-0023.

Drug-related treatment-emergent adverse events occurring in ≥10% of patients

Adverse event, %	Regorafenib (n = 500)				Placebo (n = 253)			
	All grades	G 3	G 4	G 5*	All grades	G 3	G 4	G 5*
HFSR	46.6	16.6	0	0	7.5	0.4	0	0
Fatigue	47.4	9.2	0.4	0	28.1	4.7	0.4	0
Hypertension	27.8	7.2	0	0	5.9	0.8	0	0
Diarrhea	33.8	7.0	0.2	0	8.3	0.8	0	0
Rash/desquamation	26.0	5.8	0	0	4.0	0	0	0
Anorexia	30.4	3.2	0	0	15.4	2.8	0	0
Mucositis, oral	27.2	3.0	0	0	3.6	0	0	0
Thrombocytopenia	12.6	2.6	0.2	0	2.0	0.4	0	0
Fever	10.4	0.8	0	0	2.8	0	0	0
Nausea	14.4	0.4	0	0	11.1	0	0	0
Bleeding	11.4	0.4	0	0.4	2.8	0	0	0
Voice changes	29.4	0.2	0	0	5.5	0	0	0
Weight loss	13.8	0	0	0	2.4	0	0	0

HFSR, hand–foot skin reaction;
* Grade 5 drug-related AEs: 1.0% in regorafenib arm vs 0% in placebo arm

Van Cutsem E et al. ASCO 2012; abstract 3502

Health-related QoL analyses: time-adjusted area under the curve

- No significant difference in health-related QoL with regorafenib vs placebo

	Treatment group	Least-squares mean	(95% CI)
EORTC QLQ-C30	Placebo	58.13	(55.72, 60.53)
	Regorafenib	56.93	(54.79, 59.08)
EQ-5D index	Placebo	0.67	(0.64, 0.70)
	Regorafenib	0.67	(0.64, 0.70)
EQ-5D VAS	Placebo	61.84	(59.59, 64.09)
	Regorafenib	60.62	(58.62, 62.63)

VAS, visual analog scale

Van Cutsem E et al. ASCO 2012; abstract 3502

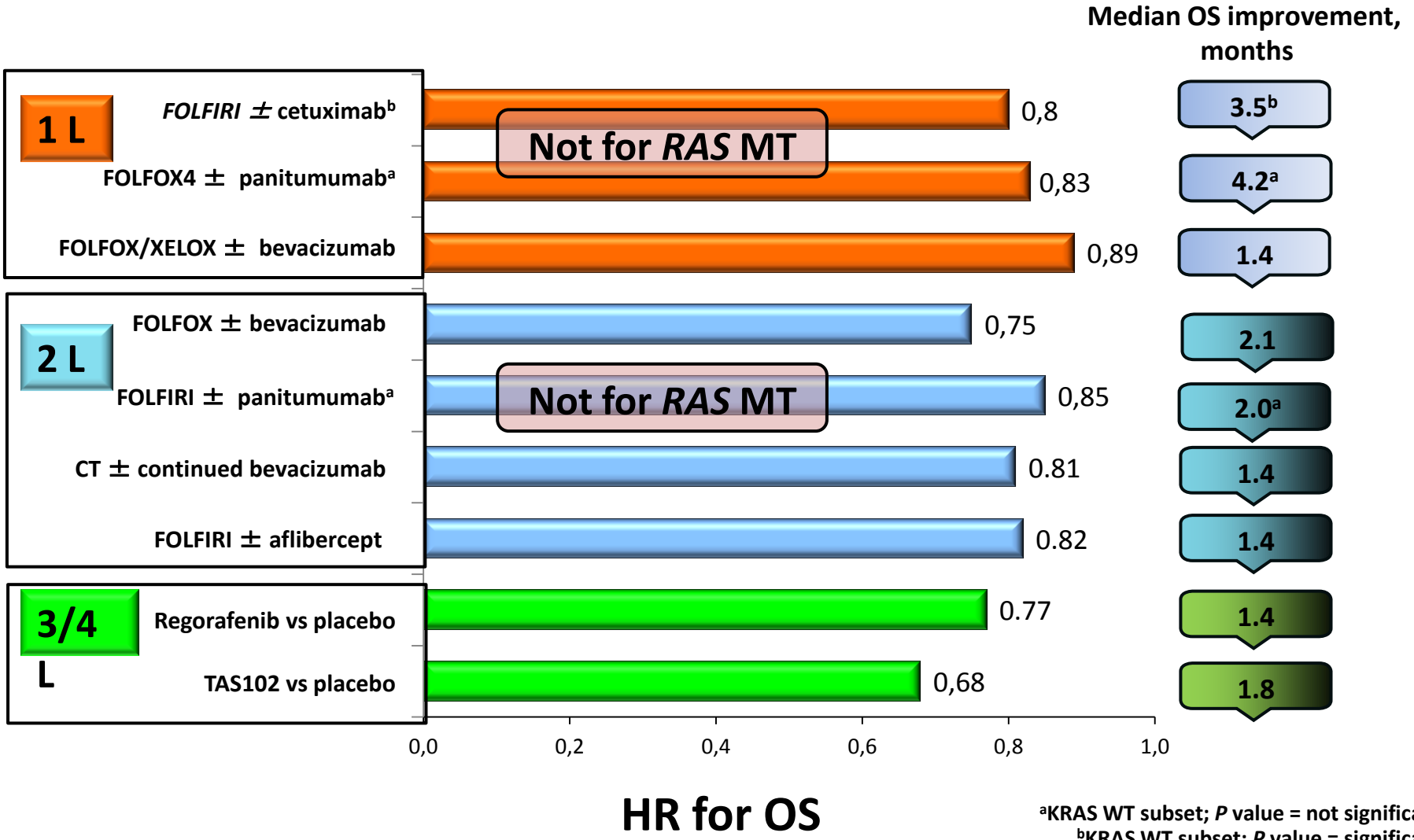
Conclusions

- The study is positive
  - The OS primary endpoint was reached (p=0.0052)
- The results are clinically relevant
  - **OS**: HR=0.77 - A modest effect, but nevertheless an incremental benefit in a difficult setting
  - **PFS:** HR=0.49, p<0.000001 - A "superstar " effect
  - Response rate was low, but expected
  - Fair toxicity
  - **First small-molecule multi-kinase inhibitor with proof of efficacy in CRC**
  - Potential new standard of care in this patient population

Size of benefit (target delta) : a compromise

1. plausible to achieve
2. worthwhile if achieved

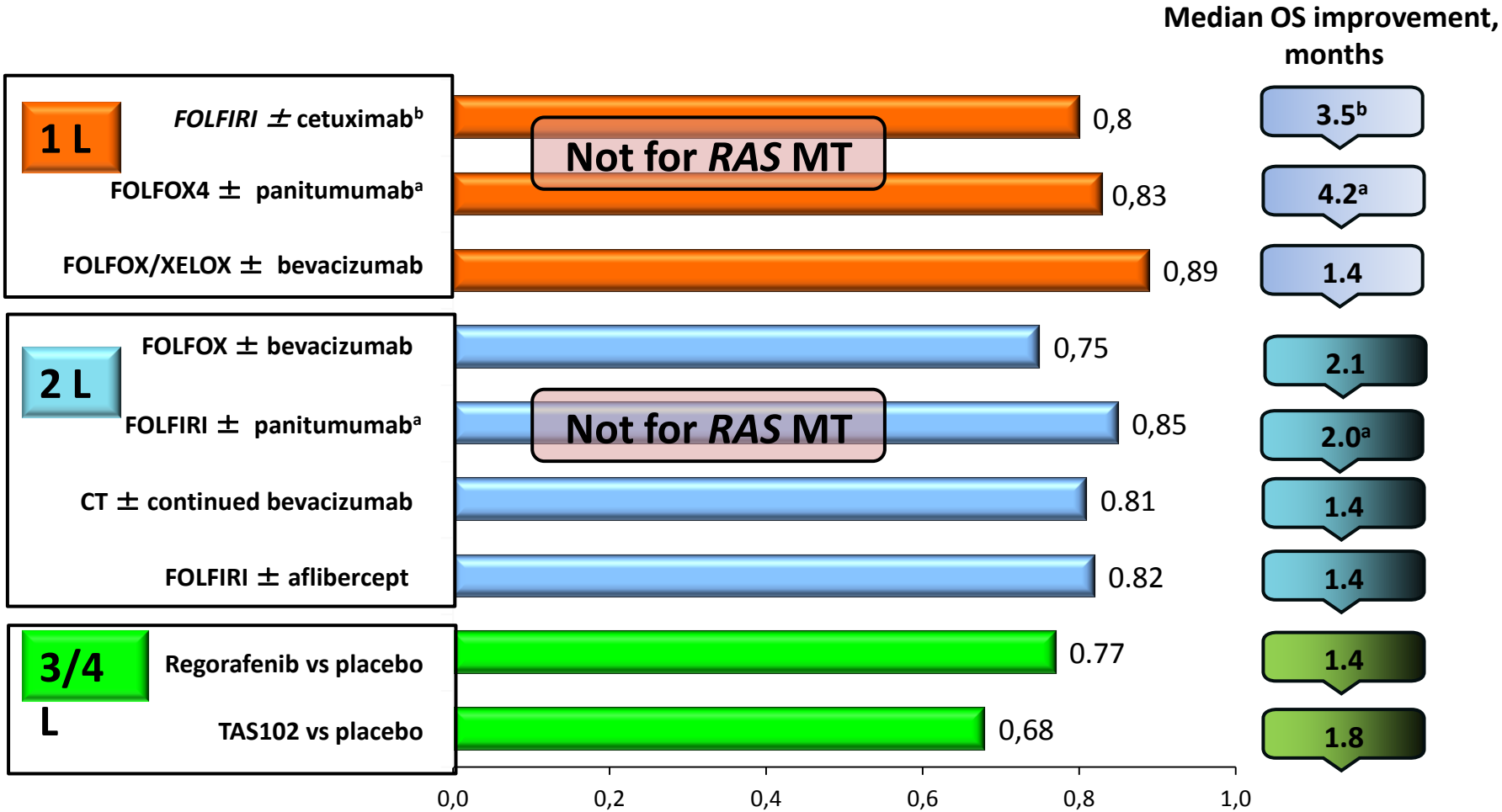
Proportional Impact on Magnitude of OS Benefit Achieved Across Lines of Therapy



[a]KRAS WT subset; *P* value = not significant.
[b]KRAS WT subset; *P* value = significant.

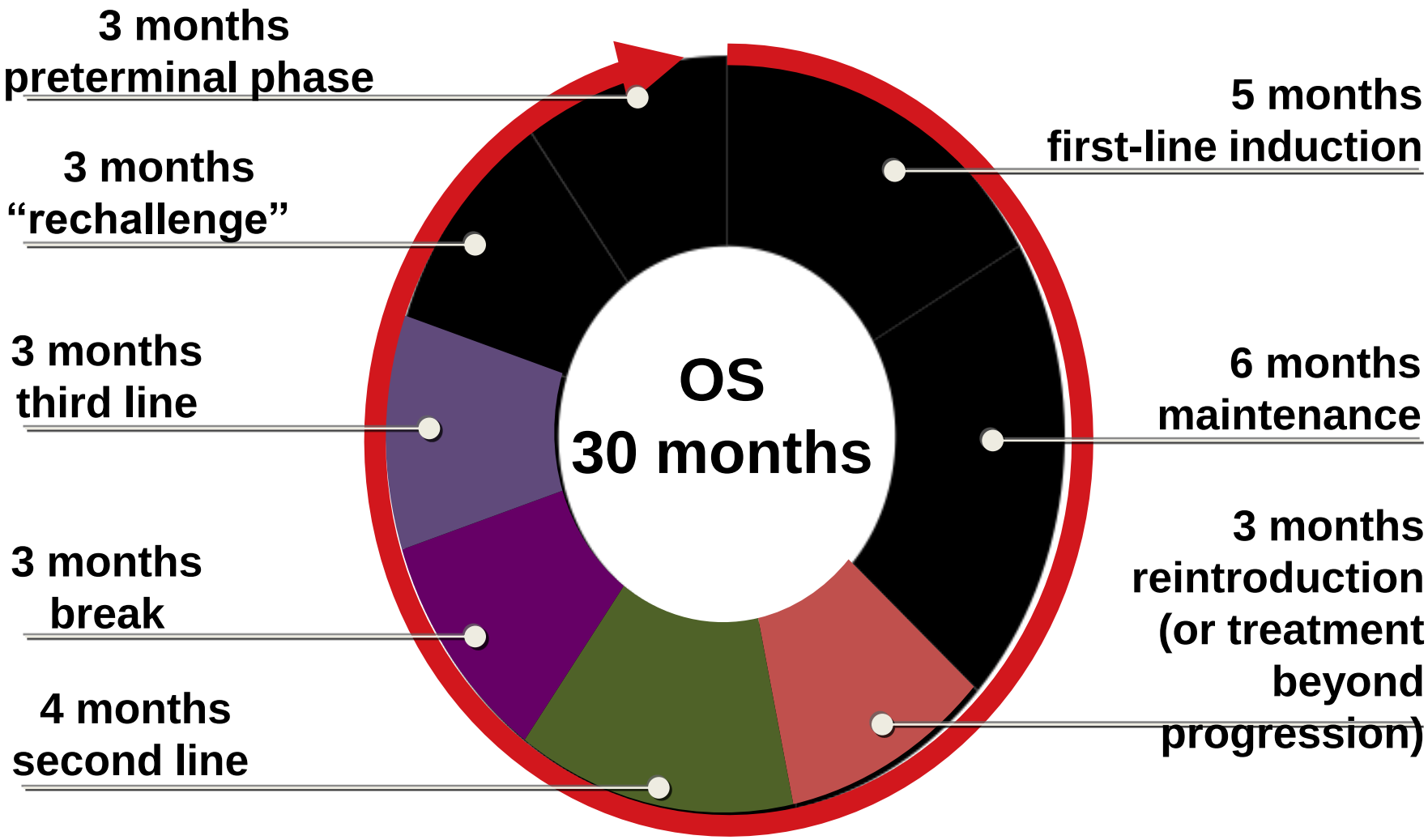
1. Saltz LB, et al. *J Clin Oncol.* 2008;26(12):2013-2019; 2. Douillard, J-Y, et al. *J Clin Oncol.* 2010;28(31):4697-4705; 3. Van Cutsem E, et al. *J Clin Oncol.* 2011;29(15): 2011 -2019; 4. Van Cutsem E, et al. *J Clin Oncol.* 2012;30(28):3499-3506; 5. Bennouna J, et al. *Lancet Oncol*. 2013;14(1):29-37; 6. Giantonio BJ, et al. *J Clin Oncol.* 2007;25(12)1539-1544; 7. Peeters M, et al. *J Clin Oncol* . 2010;28:4706-4713; 8. Grothey A, et al. *Lancet*. 2013;381:303-312. Van Cutsem E, et al. *ESMO 2014*

Proportional Impact on Magnitude of OS Benefit Achieved Across Lines of Therapy



Sobrero et al. Clin Cancer Res 2014:
Medium threshold for minimal clinically meaningful outcome
OS HR: 0.75, mOS +4 months

2015: A classical case of mCRC



Courtesy: Eric Van Cutsem

Regorafenib: Quesito clinico N. 1

E' raccomandato l'utilizzo di regorafenib per il trattamento dei pazienti adulti affetti da carcinoma metastatico del colon-retto con PS 0-1 pretrattati oppure non candidabili al trattamento con le terapie disponibili (chemioterapia a base di fluoropirimidina, una terapia anti-VEGF ed una terapia anti-EGFR)?

1
RAPPORTO RISCHIO/BENEFICIO
(RISULTATI DEGLI STUDI CLINICI PUBBLICATI)

EFFICACIA

OUTCOME CLINICI	DESCRIZIONE	VOTO
MOLTO RILEVANTI	Outcome clinici importanti ed essenziali ed entità del risultato clinicamente rilevante	4
RILEVANTI	Outcome clinici importanti ma non essenziali ed entità del risultato clinicamente rilevante OPPURE Outcome clinici importanti ed essenziali ed entità del risultato solo moderatamente rilevante	3
POCO RILEVANTI	Outcome clinici non importanti benché con entità del risultato clinicamente rilevante	2
MARGINALI	Qualsiasi Outcome clinico ed entità del risultato clinicamente non rilevante	1

TOLLERABILITA'

RISULTATI OTTENUTI	VOTO
BUONA	A
DISCRETA	B
SCARSA	C

BILANCIO BENEFICI/RISCHI

MOLTO FAVOREVOLE	4-A; 4-B
FAVOREVOLE	4-C; 3-A; 3-B
INCERTO	3-C; 2-A; 2-B
SFAVOREVOLE	2-C; 1-A; 1-B; 1-C

2

QUALITA' DELLE EVIDENZE*

vengono presi in considerazione esclusivamente gli RCT, per i quali si parte da un punteggio di 4 = ALTA; 3 = MODERATA; 2= BASSA; 1= MOLTO BASSA

Fattori che possono diminuire il livello di qualità delle evidenze	**Specificare se il limite è "assente" (0), "grave" (-1) o "molto grave" (-2)**		
Qualità di conduzione dello studio: ☐ errori o insufficiente attenzione a una assegnazione in cieco al braccio di trattamento o di controllo (allocation concealment) ☐ mancanza o problemi nella effettiva realizzazione della cecità, specie per outcome soggettivi ☐ perdita al follow up di una quota importante di pazienti originariamente inclusi negli studi o perdite al follow up asimmetriche nei due gruppi (attrition bias) ☐ esclusione dall'analisi dei soggetti/pazienti persi al follow up in diversi momenti dello studio (violazione del principio della intention to treat) ☐ interruzioni precoci degli studi a seguito di un eccesso di efficacia o tossicità, secondo modalità non previste dal protocollo	**0** (limiti assenti)	**-1** (limiti gravi)	**-2** (limiti molto gravi)
Incoerenza dei risultati /eterogeneità	**0** (risultati coerenti)	**-1** (incoerenza dei risultati)	**-2** (grave incoerenza dei risultati)
Incertezze circa la diretta trasferibilità dei risultati (es. età, dosaggio)	**0** (limiti assenti)	**-1** (alcune incertezze)	**-2** (importanti incertezze)
Imprecisione o dati insufficienti (i risultati sono imprecisi quando gli studi includono pochi pazienti e/o si verificano pochi eventi producendo così stime con ampi intervalli di confidenza) Per outcome continui: ☐ l'intervallo di confidenza al 95% include la totale mancanza di effetto ☐ il limite superiore o inferiore dell'intervallo di confidenza al 95% oltrepassa la differenza minima clinicamente rilevante per i benefici oppure per i danni (se questa non è nota o non è calcolabile, abbassare la qualità se il limite superiore o inferiore dell'intervallo di confidenza supera la dimensione dell'effetto di un valore di almeno 0,5, in una direzione o nell'altra)	**0** (limiti assenti)	**-1** (grave imprecisione)	**-2** (molto grave imprecisione)
Pubblicazione selettiva dei dati (Publication bias)	**0** (limiti assenti)	**-1** (fortemente sospettabile)	**-2** (molto fortemente sospettabile)

3
ALTERNATIVE DISPONIBILI
(Da Linee Guida / da Esperienza Clinica)

Giudizio sulle Alternative Terapeutiche

- **Disponibili**
- **Disponibili ma meno soddisfacenti**
- **Assenti o disponibili ma insoddisfacenti**

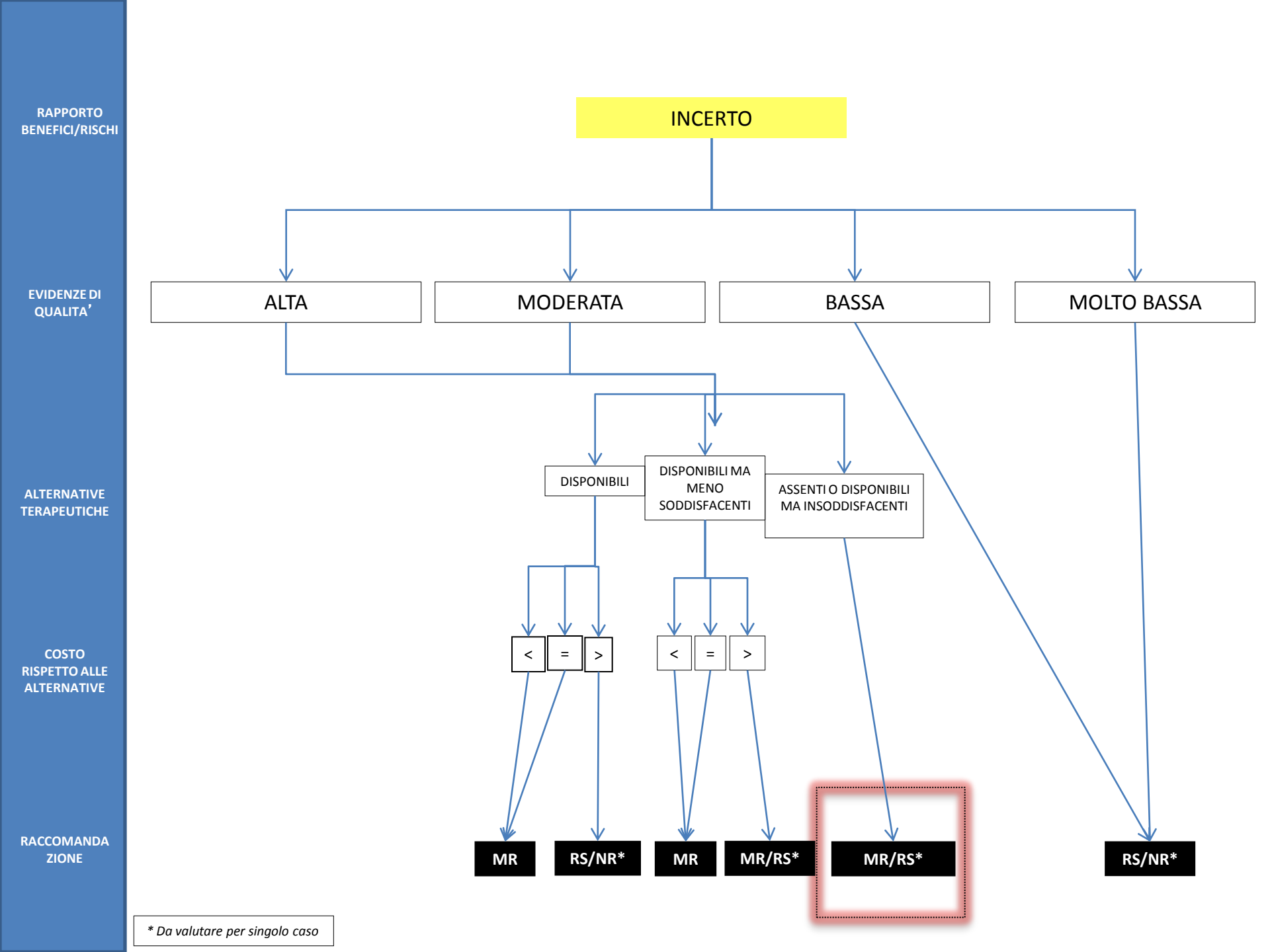
Le alternative considerate sono le migliori alternative disponibili e possono essere rappresentate sia dal comparator da studio clinico che dalla terapia normalmente utilizzata nella pratica clinica per la medesima indicazione.

4

SOSTENIBILITA' PER IL SSN

GIUDIZIO SUL COSTO RISPETTO ALLE ALTERNATIVE

- INFERIORE
- SOVRAPPONIBILE
- SUPERIORE
- ASSENZA DI ALTERNATIVE


RAPPORTO BENEFICI/RISCHI
INCERTO
EVIDENZE DI QUALITA'
ALTA
MODERATA
BASSA
MOLTO BASSA
ALTERNATIVE TERAPEUTICHE
DISPONIBILI
DISPONIBILI MA MENO SODDISFACENTI
ASSENTI O DISPONIBILI MA INSODDISFACENTI
COSTO RISPETTO ALLE ALTERNATIVE
<
=
>
<
=
>
RACCOMANDAZIONE
MR
RS/NR*
MR
MR/RS*
MR/RS*
RS/NR*
* Da valutare per singolo caso

Regorafenib: Quesito clinico N. 2

E' raccomandato l’utilizzo di regorafenib per il trattamento dei pazienti adulti affetti da carcinoma metastatico del colon-retto con PS ≥ 2 pretrattati oppure non candidabili al trattamento con le terapie disponibili (chemioterapia a base di fluoropirimidina, una terapia anti-VEGF ed una terapia anti-EGFR) ?

- **Raccomandazione: <u>NON RACCOMANDATO</u>**
- Raccomandazione formulata sulla base di:
- ***rapporto benefici/rischi:*** *non valutabile*
- ***evidenze considerate di qualità:*** *molto bassa*
- ***alternative terapeutiche:*** *--*
- ***costo rispetto alle alternative: --***

- *<u>Utilizzo atteso:</u>* sulla base della raccomandazione formulata, si prevede un tasso di utilizzo inferiore al 10% dei pazienti candidabili alla terapia.

News Release

May 12, 2014

Taiho Oncology's TAS-102 Meets Primary Endpoint of Improving Overall Survival in Global Phase III RECOURSE Trial in Refractory Metastatic Colorectal Cancer

-Company plans to pursue regulatory submissions-

Taiho Pharmaceutical Co., Ltd. (HQ: Tokyo, President: Masayuki Kobayashi) today announced results from its global Phase III RECOURSE trial on its oral combination anticancer drug TAS-102 (nonproprietary names: trifluridine and tipiracil hydrochloride) in refractory metastatic colorectal cancer (mCRC). The RECOURSE trial met its primary endpoint of demonstrating improvement in overall survival (OS) in patients with refractory mCRC whose disease had progressed after approved standard therapies. In this trial, TAS-102 appeared to be generally well tolerated and the toxicities were consistent with what was previously reported.