Clinical and palliative care considerations for the patient with progressive mCRC

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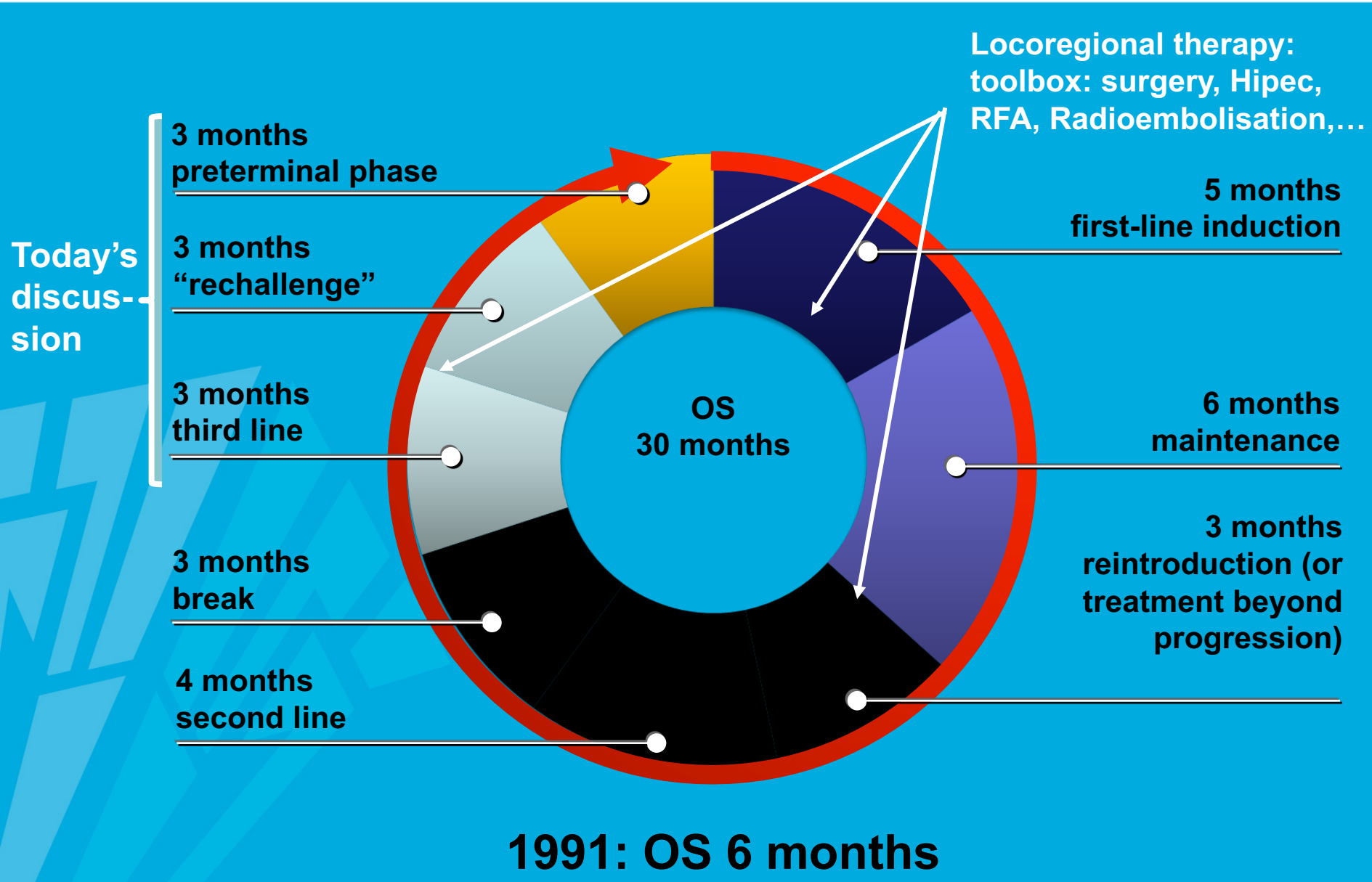
Disclosures

Contracted Research	Amgen Inc, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Ipsen Biopharmaceuticals Inc, Lilly, Merck, Novartis, Roche Laboratories Inc, Sanofi Genzyme

A classical case of mCRC in 2017
CONTINUUM OF CARE



1991: OS 6 months

Metastatic colorectal cancer

- **CHEMOTHERAPY: combination of cytotoxic and biological targeted drugs**

Cytotoxic agents

- ✓ 5-FU/capecitabine (S1)
- ✓ irinotecan
- ✓ oxaliplatin
- ✓ raltitrexed
- ✓ mitomycine
- ✓ trifluridine/tipiracil

Biological agents

- ✓ bevacizumab
- ✓ cetuximab
- ✓ panitumumab
- ✓ aflibercept
- ✓ ramucirumab
- ✓ regorafenib
- ✓ early: Sym004, dabrafenib, vemurafenib encorafenib, trametinib, binimetinib, nivolumab, pembrolizumab, atezolizumab, cobimetinib, napabucasin, alpelisib, bispecific antibodies (eg: RO6958688: antiCD3-CEA, crossMab RG7716 …), vantictumab, cabozantinib (nintedanib, MABp1, tremelimumab ….) …..

- **Other contributing factors to improved outcome: surgery,…**

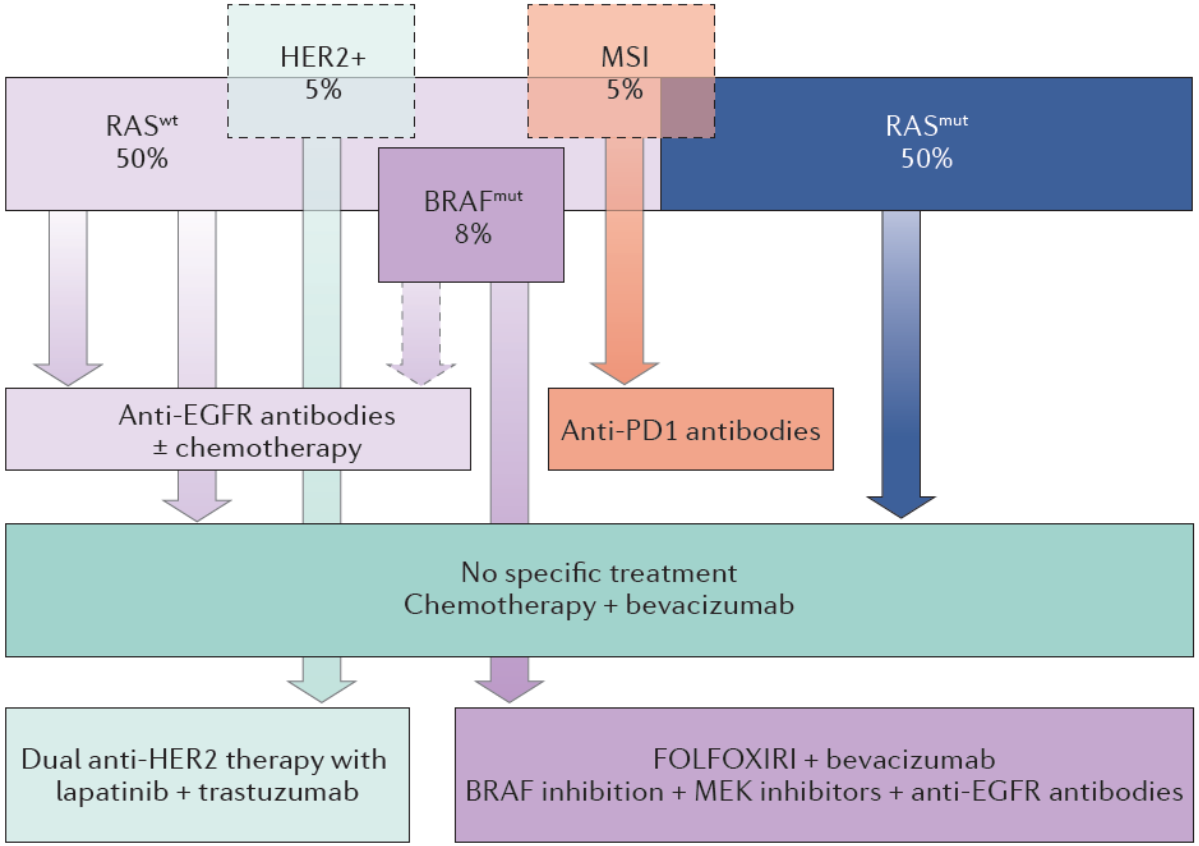


Figure 1| **Proposed landscape of molecularly targeted treatments for metastatic colorectal cancer.** The schematic summarizes the biomarker-based treatment options available and the typical proportions of patients in each biomarker subgroup. FOLFOXIRI, 5-fluorouracil, folinic acid, oxaliplatin, and irinotecan; MSI, microsatellite instability; mut, mutant, PD-1, programmed cell-death protein 1; wt, wild type.

Or clinical trial

Punt C et al, Nature Reviews Clinical Oncology. Online dec 6, 2016

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

Treatment of metastatic disease

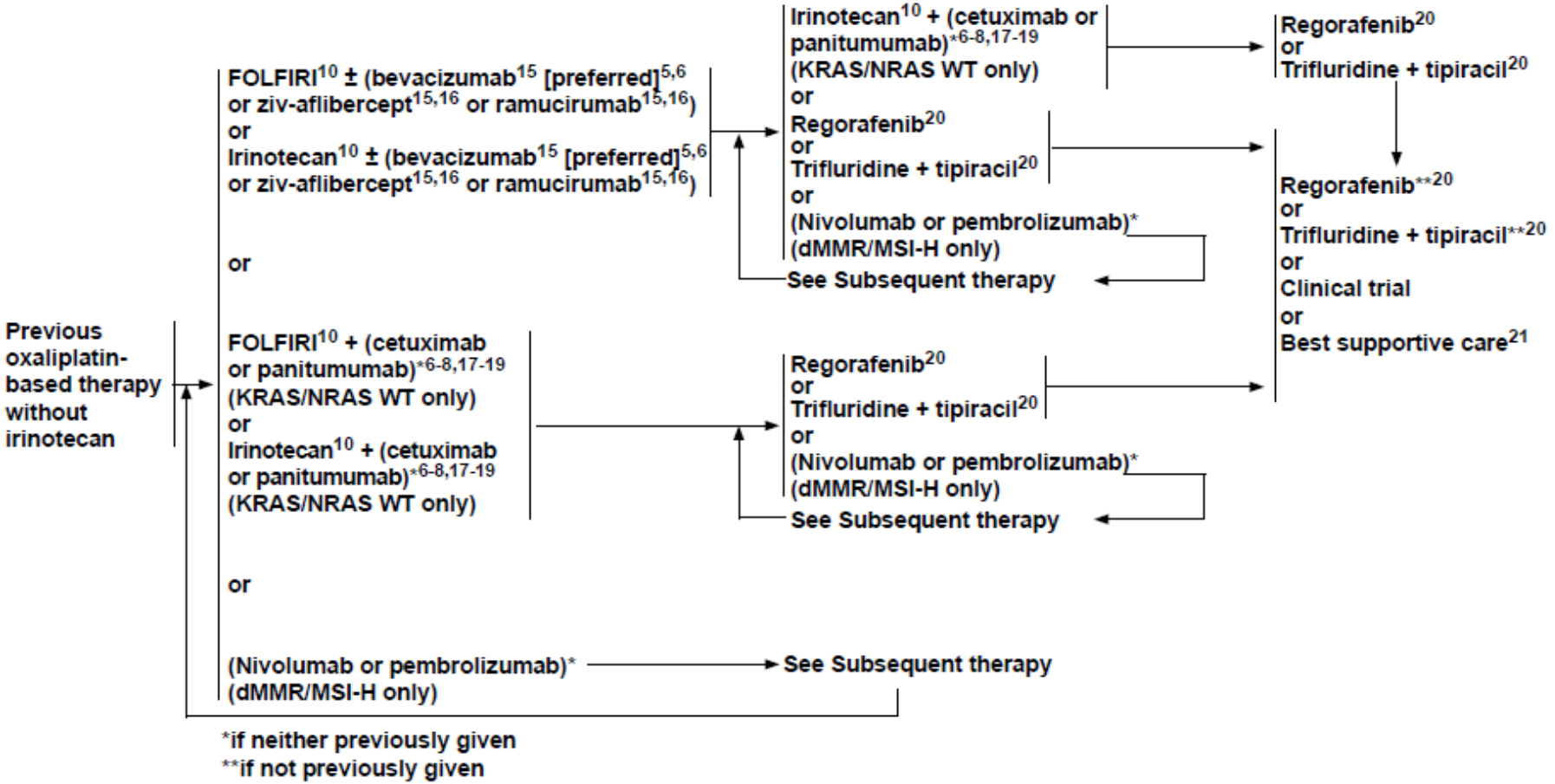
Table 7. Systemic therapy choices according to the Zurich treatment algorithm for patients with unresectable metastatic disease (excluding those with oligometastatic disease)

Category	Fit patients					
Treatment goal	Cytoreduction (tumour shrinkage)			Disease control (control of progression)		
Molecular profile	*RAS* wt	*RAS* mt	*BRAF* mt	*RAS* wt	*RAS* mt	*BRAF* mt
Third line						
Preferred choice (s)	CT doublet + EGFR antibody or irinotecan + cetuximab	Regorafenib or trifluridine/ tipiracil	Regorafenib or trifluridine/ tipiracil	CT doublet + EGFR antibody or irinotecan + cetuximab	Regorafenib or trifluridine/tipiracil	Regorafenib or trifluridine/tipiracil
Second choice	EGFR antibody monotherapy			EGFR antibody monotherapy		
Third choice	Regorafenib or trifluridine/ tipiracil			Regorafenib or trifluridine/ tipiracil		

Van Cutsem E, Cervantes A, Arnold D et al, ESMO Consensus 2016
Ann Oncol, July 2016

CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 2 of 10)

Subsequent Therapy



*if neither previously given
**if not previously given

See footnotes COL-C 6 of 10

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Table 4: Drivers for first-line treatment

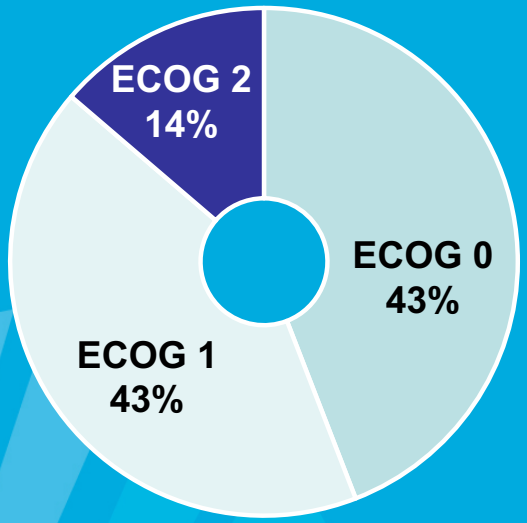
Tumour characteristics	Patient characteristics	Treatment characteristics
Clinical presentation: Tumour burden Tumour localisation	Age	Toxicity profile
Tumour biology	Performance status	Flexibility of treatment administration
RAS mutation status	Organ function	Socio-economic factors
BRAF mutation status	Comorbidities, patient attitude, expectation and preference	Quality of life

Patient and treatment characteristics become even more relevant in later lines

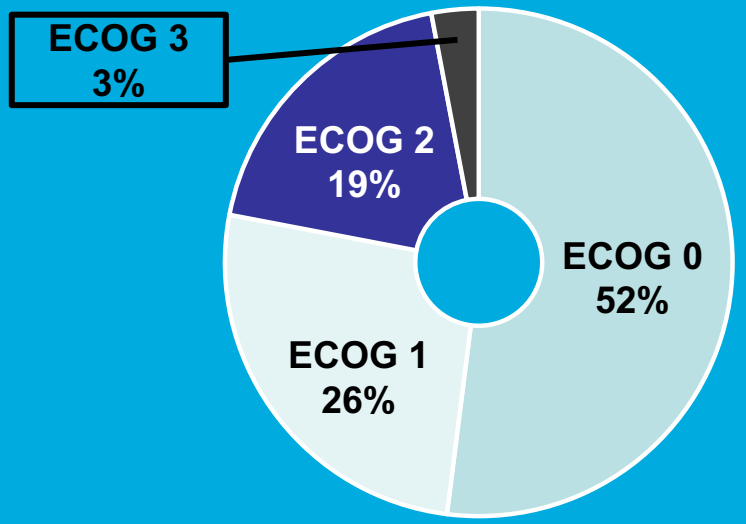
Van Cutsem E, Cervantes A, Arnold D et al, ESMO Consensus 2016
Ann Oncol, July 2016

A "snapshot" of third and fourth line treatment for mCRC in 2014 real world data for mCRC

3rd line treatment ECOG PS (%) patients



4th line treatment ECOG PS (%) patients



- A significant number of patients progressing beyond the 2nd or 3rd line of treatment are still fit for further therapy
- An Italian study assessed oncologists' clinical practice in the management of Italian mCRC patients, with a focus on the 3rd, 4th, and later lines of therapy.

Active treatment in later lines primarily reserved for "fit" (ECOG 0-1) patients

Heiman F, et al. Value Health 2014;17:A644 (PCN 171)

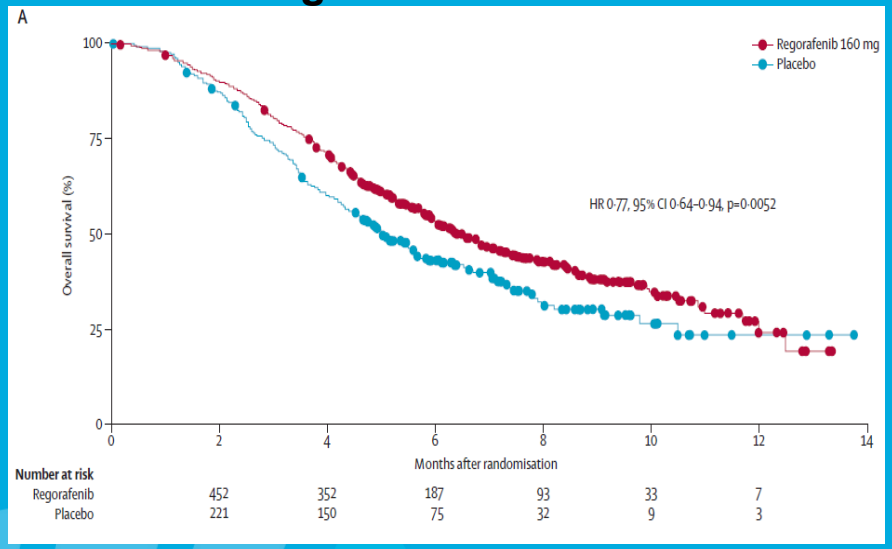
Later lines of treatment:
Which benefit?

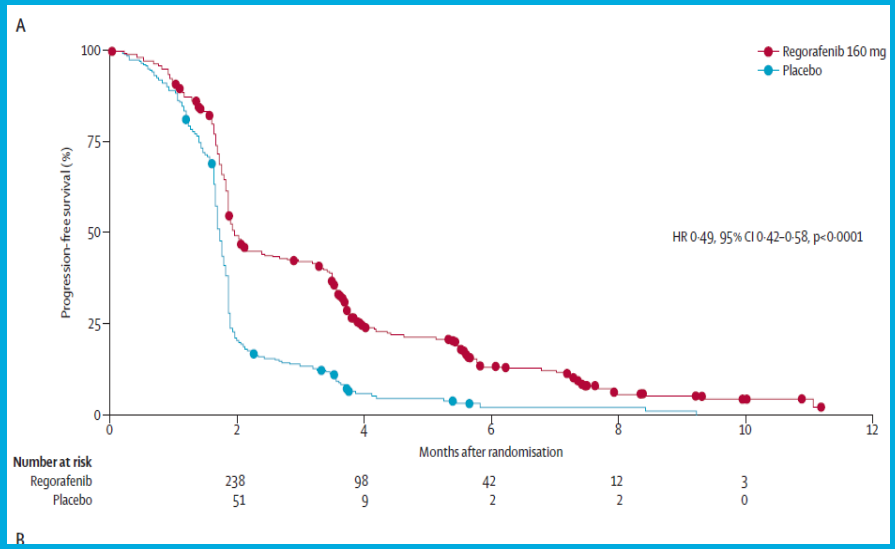
	CORRECT		CONCUR		CON-SIGN	RECOURSE		JAPANESE TRIAL		TERRA	
	Regora-fenib n=500	Plac n=253	Regora-fenib n=136	Plac n=68	Regora-fenib n=2864	TAS-102 n=533	Plac n=265	TAS-102 n=113	Plac n=57	TAS-102 n=271	Pla n=135
PFS	1.9	1.7	3.2	1.7	2.7	2.0	1.7	2.0	1.0	2.0	1.8
HR	0.49		0.31			0.48		0.41		0.43	
OS	6.4	5.0	8.8	6.3	NA	7.1	5.3	9.0	5.6	7.8	7.1
HR	0.77		0.55			0.68		0.56		0.79	

TAS-102 = trifluridine/tipiracil

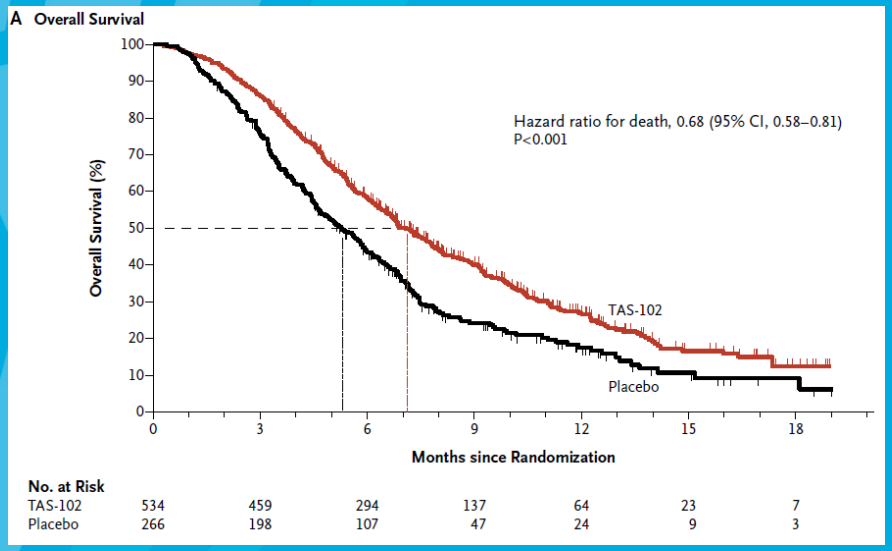
Regorafenib and trifluridine/tipiracil in refractory mCRC:

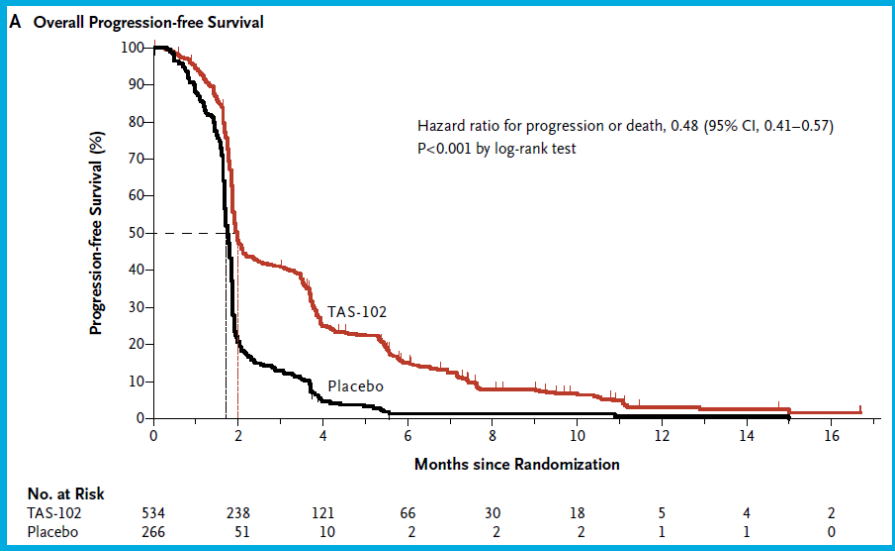
CORRECT: regorafenib





RECOURSE: trifluridine/tipiracil





Grothey, Van Cutsem E et al, Lancet 2013; Mayer R, Van Cutsem E, Ohtsu A et al NEJM, 2015

Later lines of treatment:

Grade ≥3 adverse events (%)

	CORRECT		CONCUR		CONSIGN	RECOURSE	
	Rego (n=505)	Placebo (n=255)	Rego (n=136)	Placebo (n=68)	Rego (2872)	TAS-102 (533)	Placebo (265)
HFS	17	<1	16	0	14	0	0
Fatigue	10	5	3	1	13	4	6
HT	7	1	11	3	15	NS	NS
Diarrhea	7	1	1	1	5	3	<1
Anemia	4	<1	7	0	5	18	3
Rash	6	0	4	0	<5	7	1
Bilirubin	13	8	11	4	13	9	12
Neutropenia	<1	0	4	0	1	38 (4*)	0

Rego = regorafenib; * Febrile neutropenia

Optimal Sequence in chemorefractory patients?

Regorafenib
Trifluridine/tipiracil →

or

Trifluridine/tipiracil
Regorafenib →

Clinical characteristics to decide upon regorafenib & trifluridine/tipiracil

- Selection criteria:
  - good PS, lower tumor burden, adequate organ function & bone marrow function
- Larger benefit in less heavily pretreated patients
- Markers of benefit: post-treatment:
  - Regorafenib: cavitation
  - Trifluridine/tipiracil: HFS, Neutropenia
- Biomarkers for regorafenib: not validated
  - CMS

CORRECT: Which Characteristics Correlate with Long PFS?

	All Patients (n = 505, 100%)	Long PFS* (n = 98, 19.4%)
Median age, years (range)	61 (22–82)	61 (34–82)
ECOG PS, %		
0	52	63
1	48	37
Primary tumor, %		
Colon	64	52
Rectum	30	37
Tumor metastatic sites, %		
1	19	30
2	36	38
3	27	16
KRAS status, %		
Mutant	54	47
Wild type	41	44
Time from diagnosis of metastatic disease, %		
<18 months	18	11
≥18 months	82	89
Mean treatment duration, months	2.8 ± 2.3**	6.3 ± 2.0
Mean planned dose, % ± SD	78.9 ± 19.9	81.4 ± 16.3
Mean daily dose, mg ± SD	147.1 ± 18.6	138.7 ± 22.0
Treatment modifications, % patients	76	91

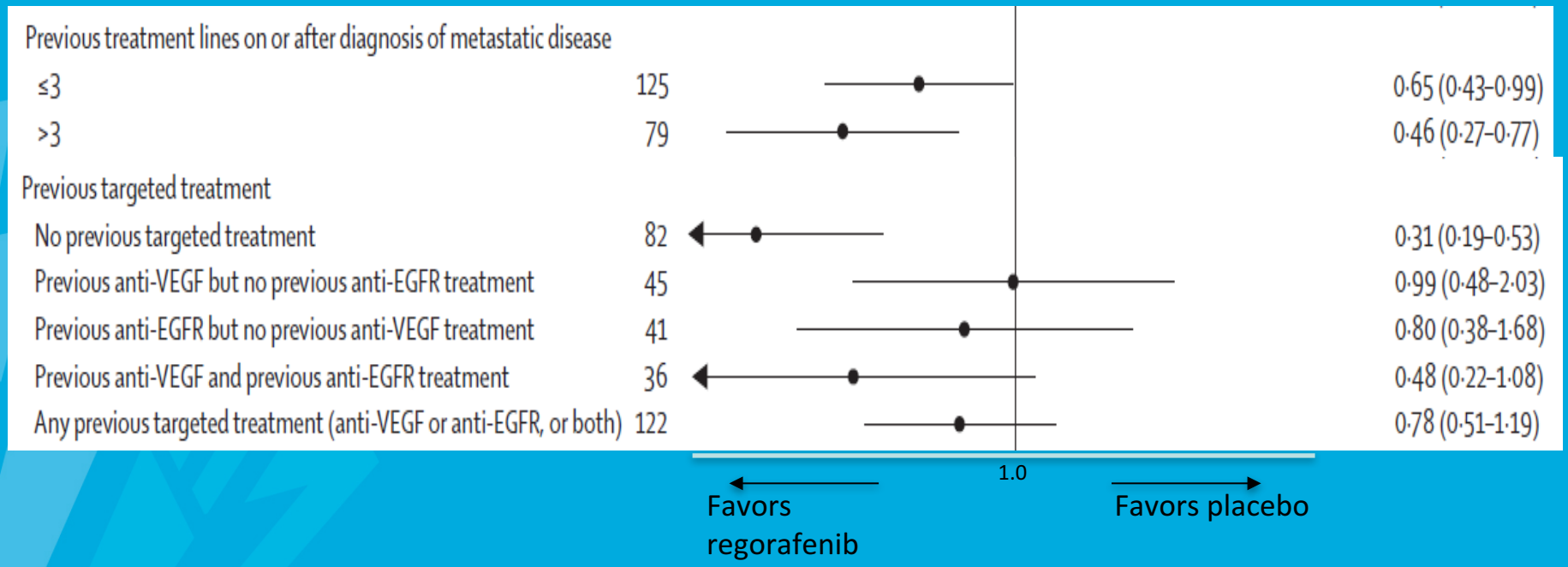
*Long-PFS: >4 months; median of 6 cycles regorafenib, 92% ≥5 cycles, and 20% >8 cycles; **Treated patients (n = 500).

Grothey A, et al. ASCO GI 2015. Abstract 710.

CONCUR Subgroup Analysis Further Suggests Greater Benefit in Less Heavily Pretreated Patients

Overall 204

OS HR: 0.55 (0.40—0.77)



Li J, et al. *Lancet Oncol*. 2015;16:619-629.

Importance of Imaging in Measuring Clinical Outcomes: Lung Metastasis Cavitation with Regorafenib

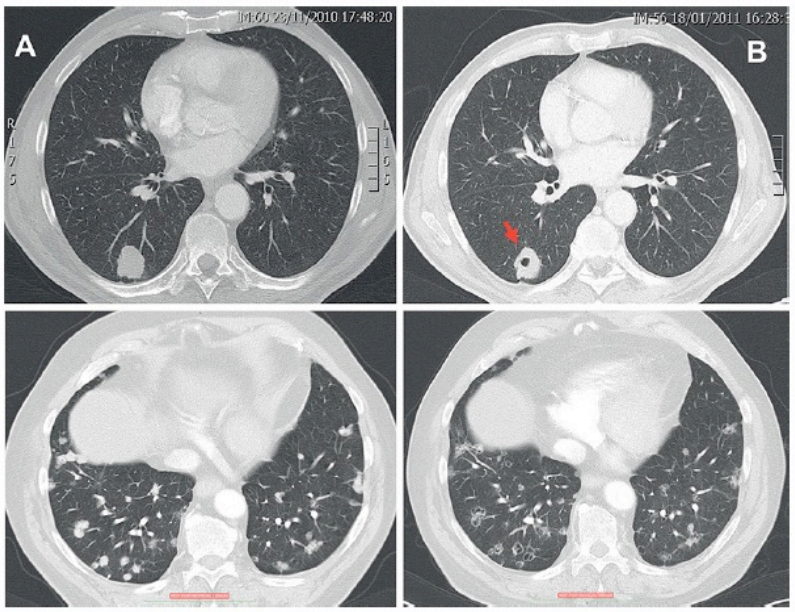


Figure 1 Baseline (A) and week 8 (B) CT displaying the onset of cavitation at week 8 in two patients treated with regorafenib. Upper: the arrow highlights single tumour metastases with cavitation. Lower: cavitation in multiple lung metastases.

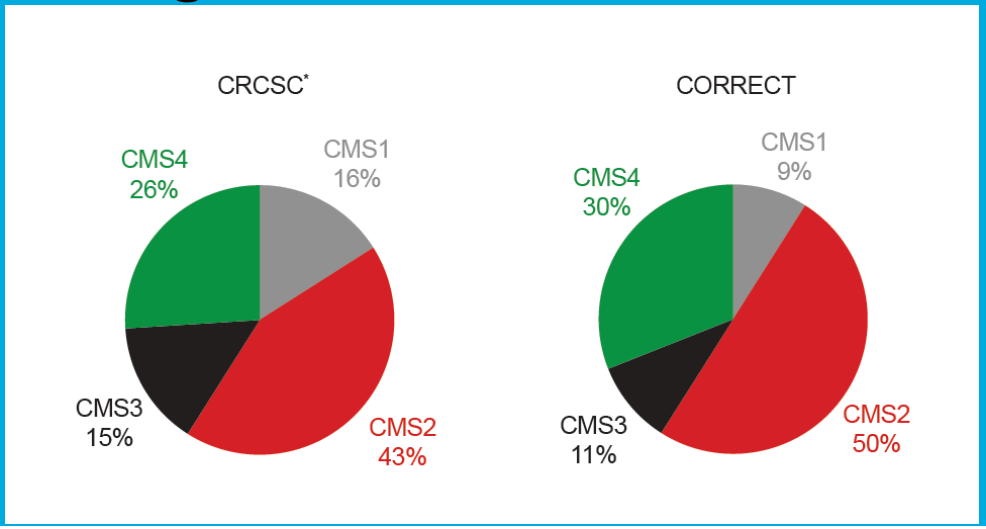
Table 2 Overall Survival

Survival	n	Months	*P*
Response on size criteria	3	10.60	.45
Stable disease or progressive disease on size	39	8.38	
Response or stable disease on size criteria	25	9.89	<.0001
Progressive disease on size criteria	17	6.44	
Response on density criteria	24	9.59	<.0001
No response on density criteria	18	7.04	
Response on corrected density criteria	22	9.09	.0016
No response on corrected density criteria	20	7.16	

Ricotta R et al, ESMO Open, 2017
Vanwynsberghe H et al, Clin Colorectal Cancer, 2017

Preliminary Analysis Suggests Greater Benefit with Regorafenib in CMS2 and CMS4

CMS4: Mesenchymal, CIN, MSI, TGF-β/ VEGF, NOTCH3



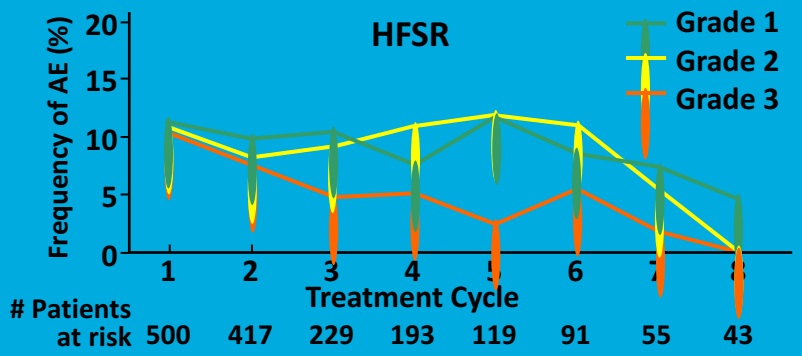
CMS2: Epithelial, MSS, high CIN, p53 mut, WNT/MYC

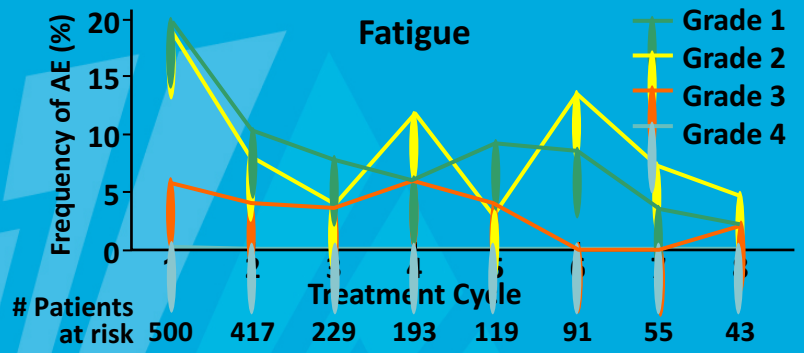
Molecular subtype	n	Overall survival		Progression-free survival	
		Hazard ratio	95% CI	Hazard ratio	95% CI
CMS1	24	1.116	0.290–4.690	0.850	0.321–2.252
CMS2	140	0.779	0.486–1.249	0.571	0.387–0.842
CMS3	32	1.047	0.399–2.749	0.287	0.112–0.737
CMS4	85	0.672	0.358–1.261	0.483	0.286–0.814
All samples	281	0.797	0.572–1.12	0.528	0.401–0.698

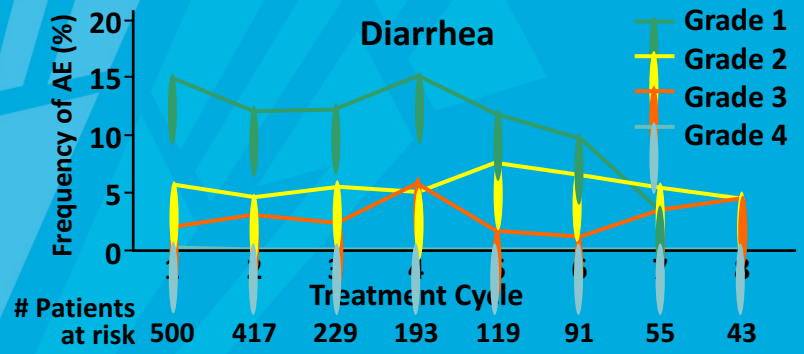
Extensive additional research is ongoing seeking biomarkers predictive for regorafenib clinical benefit

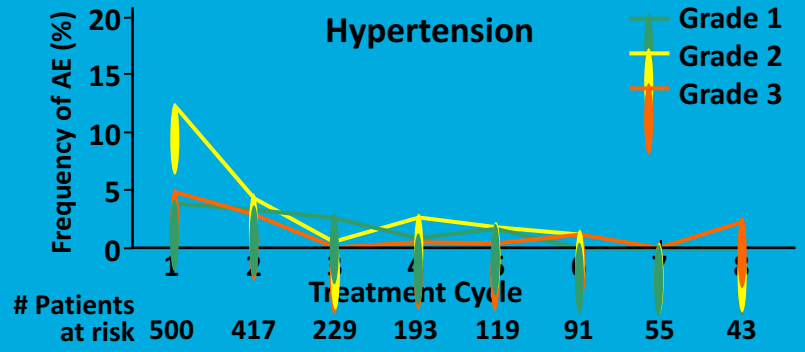
Teufel M, et al. *J Clin Oncol.* 2015;33(15 suppl): abstract 3558.

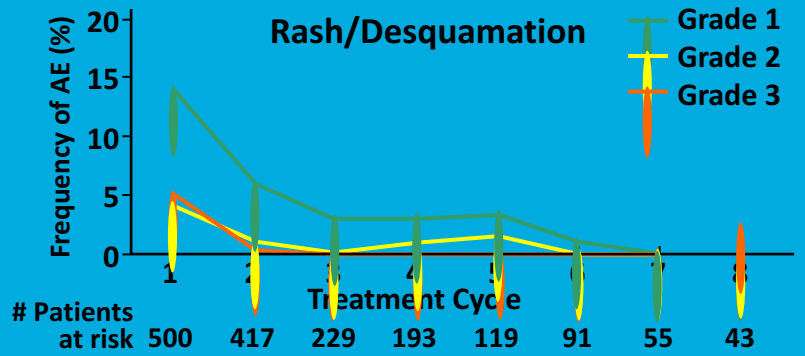
CORRECT study: Incidence of Grade 3 AEs decreases over time







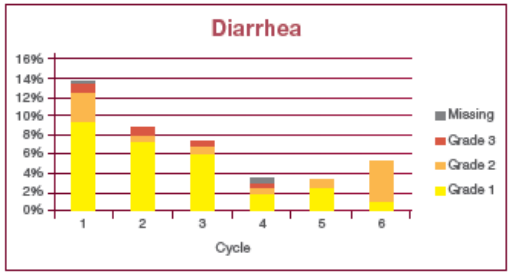


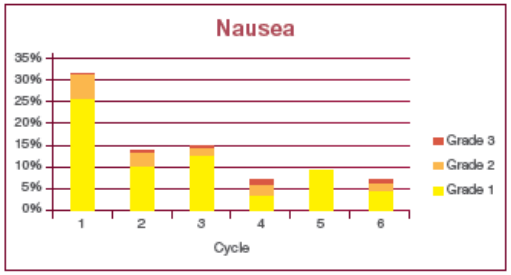


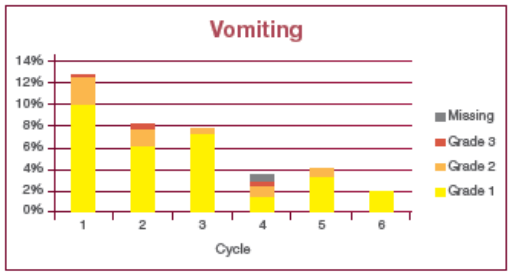
Grothey A, et al. ASCO GI; 2013. Abstract #467.

Trifluridine/tipiracil and onset of AEs

Figure 3. Incidence of treatment-related AEs and hematological abnormalities by cycle during the first 6 cycles







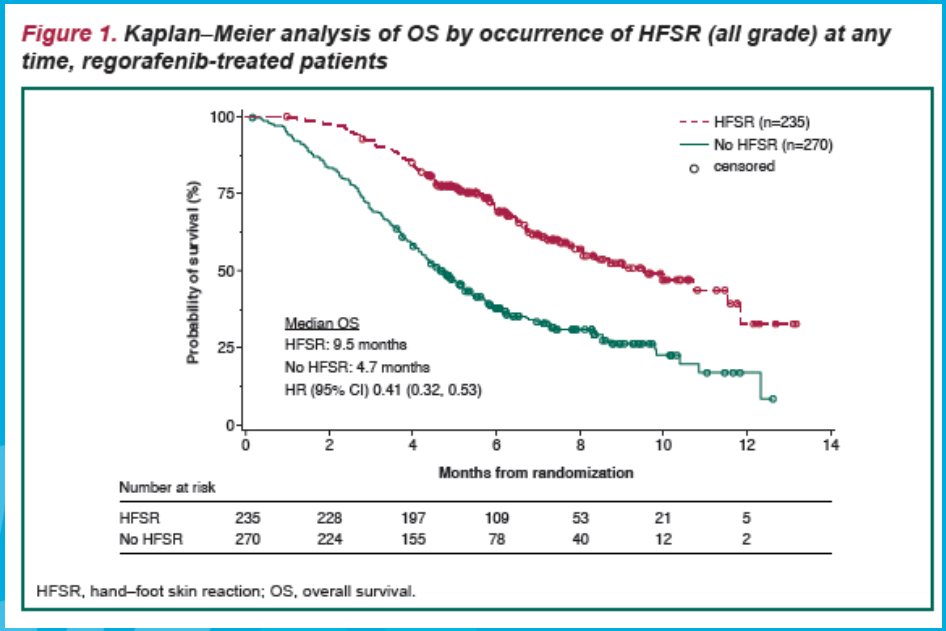
Incidence is calculated in ongoing patients, e.g., at cycle n, X% of patients had related diarrhea, nausea or vomiting among the patients who initiated cycle n. Values are cited as missing when an AE is reported but the grade is not provided.

Table 3. Median times to nadir for grade ≥3 hematological abnormalities and median time to grade ≥3 non-hematological adverse events in RECOURSE (over the whole treatment duration)

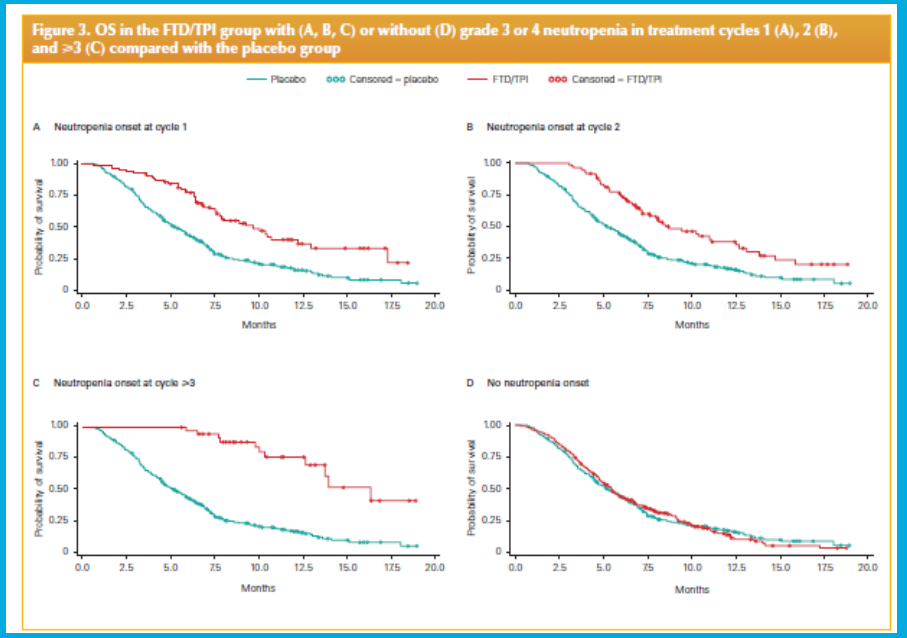
Adverse event (grade ≥3)	Median (range) time to nadir, days
Hematological adverse event	
Anemia	69 (9–442)
Neutropenia	63 (17–446)
Thrombocytopenia	92 (9–388)
Non-hematological adverse events	
Diarrhea	38 (14–74)
Nausea	36 (2–167)
Vomiting	35 (12–36)

Van Cutsem E et al,
ASCO GI 2017 - poster

Markers of benefit



Regorafenib and HFSR



Trifluridine/tipiracil and neutropenia

Grothey A, Van Cutsem E et al, ASCO 2017 - poster

Ohtsu A et al, ASCO GI 2017 poster

OPTIMAL DOSE

- **Regorafenib**
  - ✓ Label: 160 mg/d
  - ✓ More optimal: 120 mg/d?

- **Trifluridine/tipiracil**
  - ✓ 35 mg/m^2 BID PO
    d1–5, 8–12 q4w
  - ✓ More optimal regimen ??
  - ✓ In combination towards d1-5, 15-19 q4w ??