Groupement d'hôpitaux Paris Centre
COCHIN
BROCA
HÔTEL-DIEU

FACULTÉ
DE MÉDECINE
PARIS DESCARTES

ASSISTANCE
PUBLIQUE
HÔPITAUX
DE PARIS

UNIVERSITÉ
PARIS DESCARTES

Stratégie thérapeutique au-delà de la 2ème ligne dans le CCRm

Romain Coriat

Service de gastroentérologie et d'oncologie digestive

CHU Cochin

romain.coriat@aphp.fr

L.FR.MKT.05.2017.3173

Stratégie CCR métastatique ?

Choix de traitement adapté au cas par cas :

Triade

Patient

"Fragiles" ou "à risque"

- **Age physiologique**
- **Comorbidités**
- **Isolement social**
- **Compliance incertaine** (fluoropyrimidines orales)

Maladie

Est-elle agressive ?

- **Symptômes tumoraux** (hépatalgies, carcinose péritonéale symptomatique, primitif symptomatique,…)
- **Statut de performance**
- **LDH**
- **Métastases hépatiques, péritonéales**
- **Métastases synchrones**
- **Métastases métachrones**
  - →Stade III initial
  - →Chimiothérapie adjuvante antérieure
  - →Intervalle libre court avant récidive métastatique
- **Mutations tumorales de BRAF et KRAS**

Traitement

Choix de la molécule,
CI chirurgicales, toxicités, stratégie

- **Choix de l'oxaliplatine : déconseillé si chimiothérapie adjuvante antérieure par oxaliplatine** (< 1 an)
- **Anti-EGFR : mutations tumorales de KRAS, NRAS et BRAF**
- **La maladie est elle résécable ? Avis chirurgical en RCP.**

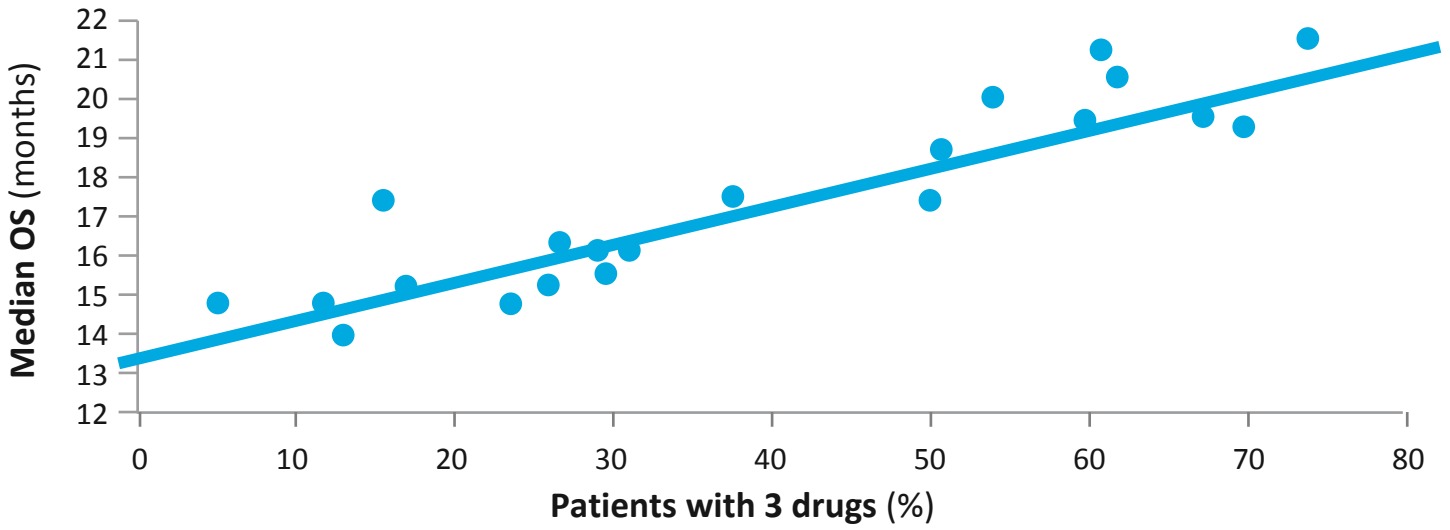
L.FR.MKT.05.2017.3173

Stratégie CCR métastatique ?

Choix du traitement

Regression plot and relationship between percentzge of patients (pts) receiving fluorouracil (FU)/leucovorin (LV), innotecan, and oxaliplatin (3 drugs in the course of their disease and the reported median overall survival (OS). Mathematical equitation of regression (based on a weighted model – solid line): median OS (months = 13.2 + (% pts with 3 drugs x 0.1). *P*= .0001, R2 = 0.85

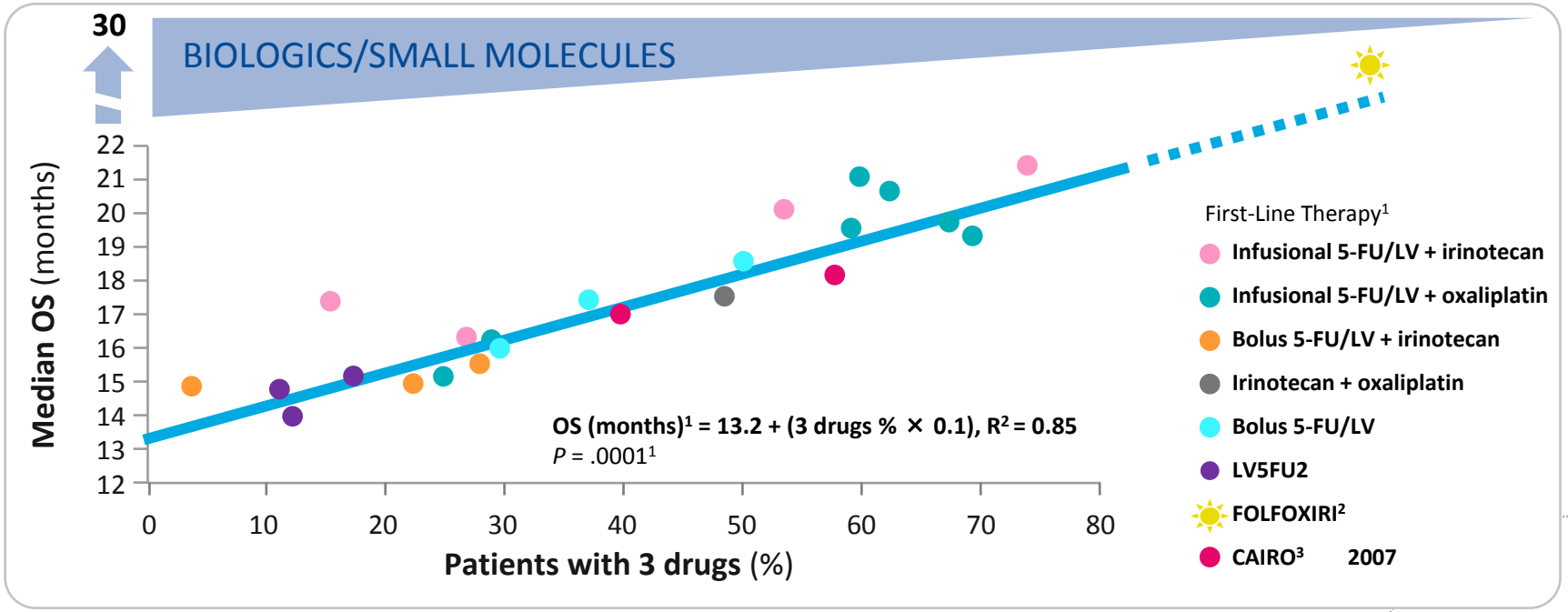
Overall Survival of Patients With Advanced Colorectal Cancer Correlates With Availability of Fluorouracil, Irinotecan, and Oxaliplatin Regardless of Whether Doublet or Single-Agent Therapy Is Used First Line



Grothey et al, JCO 2005

Exposure to as Many Agents as Possible Prolongs OS

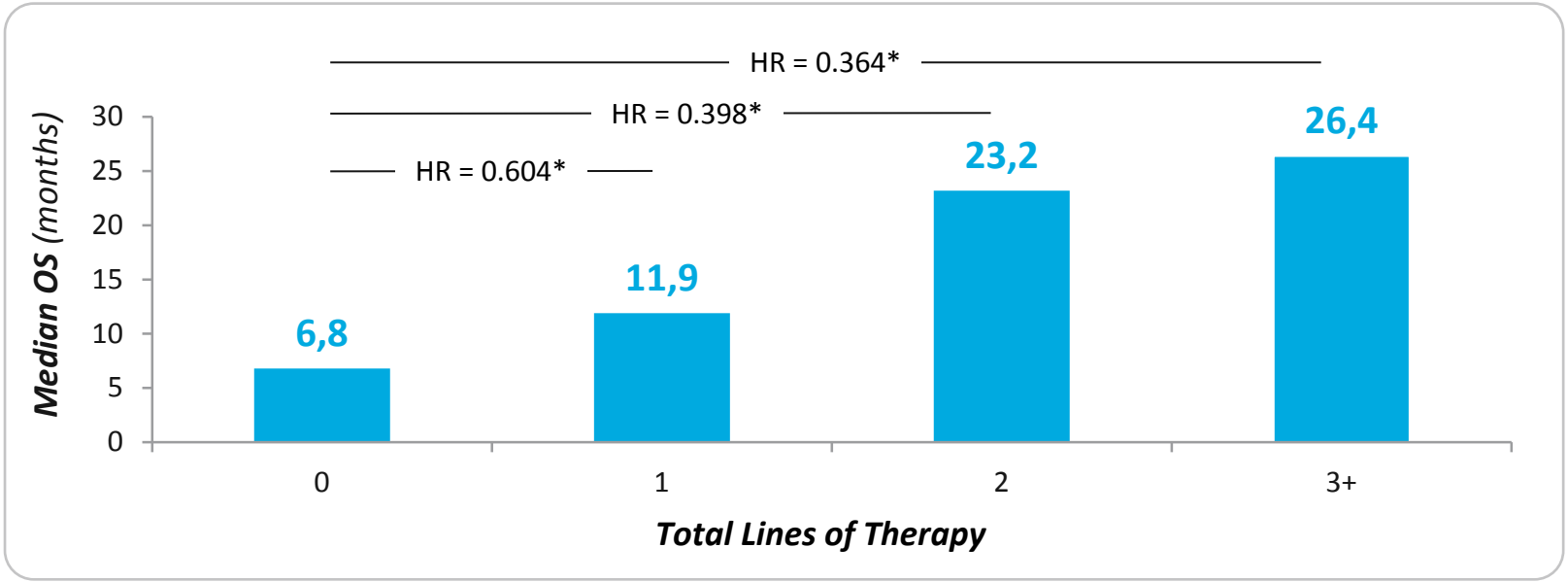
- Exposure to multiple chemotherapy agents is associated with prolonged OS
- Using multiple lines of therapy across a patient's disease course enables several different agents to be used



1. Figure adapted from Grothey A and Sargent D. J Clin Oncol. 2005;23(36):9441-9442;
2. Cremolini C, et al. Lancet Oncol. 2016;16(13):1306-1315; 3. Koopman M, et al. Lancet. 2007;370(9582):135-142.

Median Survival Increases with Increased Lines of Therapy

SEER Medicare Database Analysis for mCRC (2003–2007; N = 5,129)



Patients should be exposed to all active and approved agents during their treatment

**P <.001. HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results.*

Hanna N, et al. J Clin Oncol. 2014;32(suppl 3): abstract 559.

L.ER.MKT.05.2017.3173

Stratégie CCRmétastatique au delà de la 2ème ligne ?

Choix de la 3ème ligne ?

Chimiothérapie+

- 5FU ✖
- Oxaliplatine ✖
- Irinotécan ✖
- Tomudex

Anti EGFR ✖

- Panitumumab
- Cetuximab

Anti VEGF

- Bevacizumab ✖

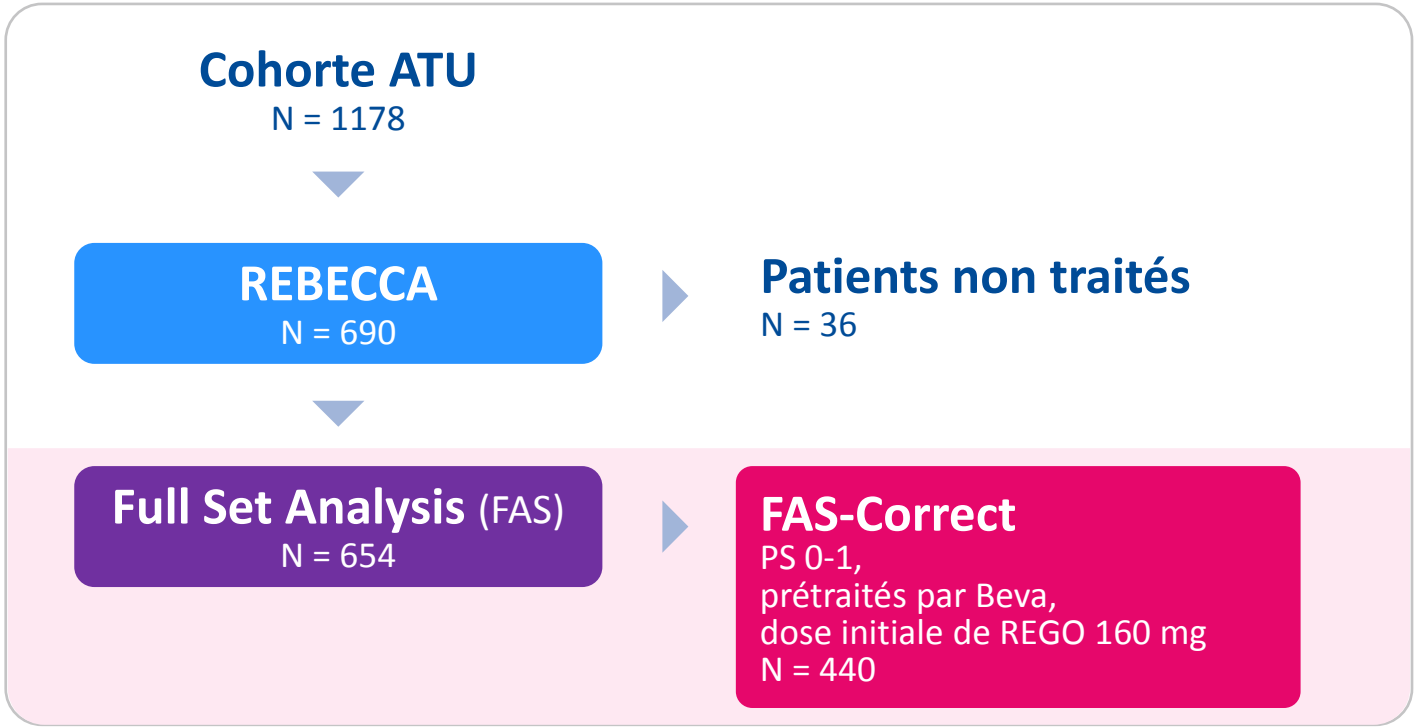
De l'ATU à REBECCA

REBECCA-1305: **RE**gorafeni**B** in m**E**tastatic **C**olorectal **C**ancer. The French Compassionate prograAm

- Etude non interventionnelle et multicentrique.
- **Objectif principal :** Estimer la survie globale des pts traités par regorafenib pour un CCRM dans le cadre de l'ATU
- **Objectifs secondaires**
  - → **Décrire les données initiales de la population traitée**
  - → **Estimer la durée de traitement, la survie sans progression**
  - → **Evaluer la dose-intensité du traitement, Décrire la tolérance au regorafenib**
  - → **Rechercher les potentiels facteurs pronostiques de survie sans échec, de survie sans progression et de survie globale**

A Adenis. BMC Cancer 2016 16:412

REBECCA : les populations de patients



A Adenis. BMC Cancer 2016 16:412

Principales caractéristiques des patients et de leur tumeur*

		FAS population
Age (years): median (range)		**64 (25 – 91)**
Age (years): n (%)	< 65 ≥ 65	**343 (52.4)** **311 (47.6)**
BMI (Kg/m²)		**24 (14.1 – 49.1)**
ECOG Performance Status: n (%)	0 1 2 3 Missing	**200 (30.7)** **383 (58.7)** **60 (9.2)** **9 (1.4)** **2**
Site of Primary tumour: n (%)	Colon Rectum Colon and rectum Missing	**445 (69.9)** **186 (29.9)** **5 (0.2)** **18**
Timing of metastases: n (%)	Synchronous Metachronous Missing	**416 (65.6)** **218 (34.4)** **20**
Delay from initial diagnosis of metastases (months): median (range)		**31 (0.8 – 156.5)**
Delay from initial diagnosis of metastases (months): n (%)	< 18 ≥ 18 Missing	**134 (20.6)** **518 (79.4)** **2**
KRAS mutational status: n (%)	Wild Mutated Missing	**291 (46.8)** **331 (53.2)** **32**
Initial dose of REG, mg/d, 3 w/4: n (%)	40 80 120 160 Missing	**3 (0.5)** **39 (6)** **89 (13.6)** **522 (79.9)** **1**

A Adenis. BMC Cancer 2016 16:412

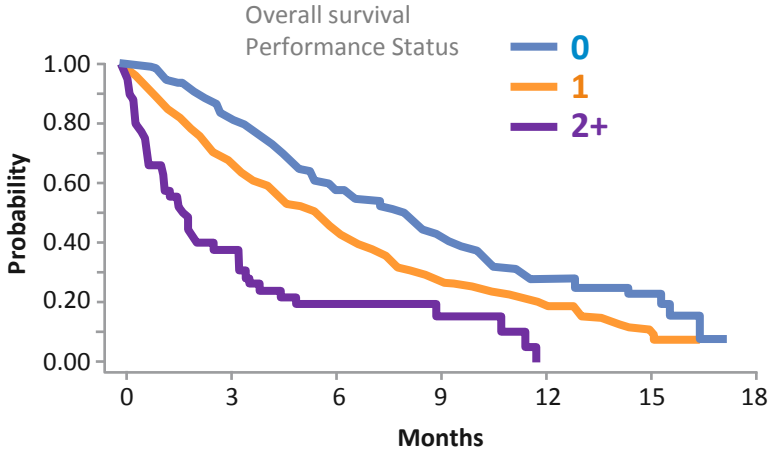
La survie : objectif principal

	FAS **N=654**	FAS-Correct N=440	CORRECT N=505
Survie médiane (IQR)	**5.6 m** (2.4-11.4 m)	**6.3 m** (2.9-11.4 m)	**6.4 m** (3.6-11.8 m)
% de survie à 12 m	**22%**	**22.8%**	**24%**

A Adenis. BMC Cancer 2016 16:412

Facteurs associés à la survie

Le poids du PS 2



Overall Survival	**Hazard Ratio** (95%CI)	P
FAS Population		
ECOG Performance Status		**<0.001**
0 1 ≥ 2	**1** **1.54** (1.26 – 1.88) **3.43** (2.50 – 4.70)	
Time since initial diagnosis		**<0.001**
≥ 18 months < 18 months	**1** **1.72** (1.40 – 2.13)	
Initial daily dose of regorafenib		**0.042**
160 > 160	**1** **1.26** (1.01 – 1.57)	
Number of metastatic sites		**0.020**
< 3 3 +	**1** **1.29** (1.04 – 1.60)	
Liver metastases		**<0.001**
No Yes	**1** **1.61** (1.29 – 2.01)	
KRAS		**0.016**
Wild-type Mutated	**1** **1.25** (1.04 – 1.49)	

A Adenis. BMC Cancer 2016 16:412

Optimal Use of Regorafenib: Dosing Strategies and Patient Selection

Axel Grothey, MD

- **Dose d'AMM de 160mg**

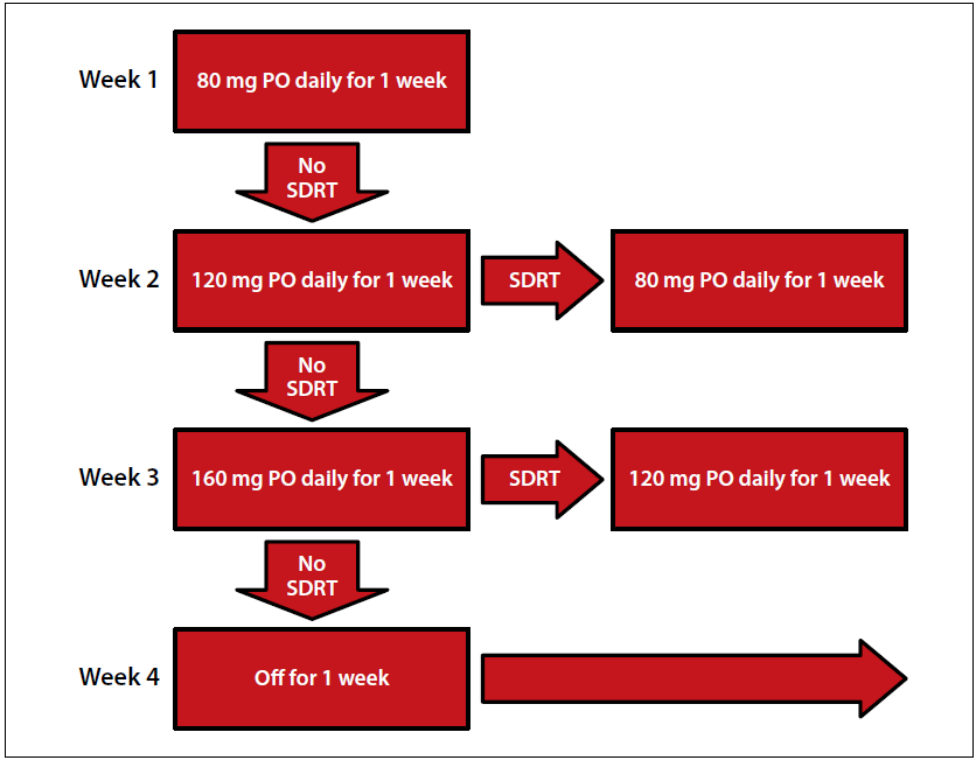


Figure 5. The toxicities associated with regorafenib in the first cycle of treatment can be minimized with an incremental dose-escalation protocol. PO, by mouth; SDRT, significant drug-related toxicities.

Grothey et al, Clin Adv Hem Onc 2016

Alternative en 3ème ligne ?

- **TAS-102 (trifluridine/tipiracil) …**
- **Pas d'implication de la DPD et peu/pas de la TS**

Table 3. Toxicity profile of TAS-102 in the Phase II and III studies.

Toxicity	Phase II study		Phase III study	
	Any grade (%)	*Grade 3–4 (%)*	*Any grade (%)*	*Grade 3–4 (%)*
Neutropenia	72	50	67	38
Leukopenia	76	28	77	21
Anemia	73	17	77	18
Thrombocytopenia	39	4	42	5
Fatigue	58	6	35	4
Diarrhea	38	6	32	3
Nausea	65	4	48	2
Febrile neutropenia	4	4	4	4
Vomiting	34	4	28	2
Anorexia	62	4	39	4

Adapted with permission from [6,50].

→ **Profil de toxicité :**
oui, c'est une chimio :
surveiller la NFS !

Diapo: Dr O. Mir, Gustave Roussy
Uboha, Future Oncol 2015

TAS-102 vs. regorafenib ou anti-EGFR : pas de mécanisme de résistance croisée

Baseline characteristics of the intention-to-treat population

		TAS -102 (n=534)	Placebo (n=266)
Age, year	Median Range	**63** **27-82**	**63** **27-82**
Sex, n (%)	Male Female	**326 (61)** **208 (39)**	**165 (62)** **101 (38)**
ECOG PS, no (%)	0 1	**301 (56)** **233 (44)**	**147 (55)** **119 (45)**
Primary site of disease, %	Colon Rectum	**338 (63)** **196 (37)**	**161 (61)** **105 (39)**
***KRAS* mutation, n (%)**	No Yes	**262 (49)** **272 (51)**	**131 (49)** **135 (51)**
Time from diagnosis of metastases, n (%)	< 18 mo ≥ 18 mo	**111 (21)** **423 (79)**	**55 (21)** **211 (79)**
Number of prior regimen, n (%)	2 3 ≥ 4	**95 (18)** **119 (22)** **320 (60)**	**45 (17)** **54 (20)** **167 (63)**
Prior systemic anticancer agents , n (%)	Fluoropyrimidine Irinotecan Oxaliplatin Bevacizumab Anti-EGFR monoclonal antibody Regorafenib	**534 (100)** **534 (100)** **534 (100)** **534 (100)** **278 (52)** **91 (17)**	**266 (100)** **266 (100)** **266 (100)** **265 (>99)** **144 (54)** **53 (20)**

ORIGINAL ARTICLE

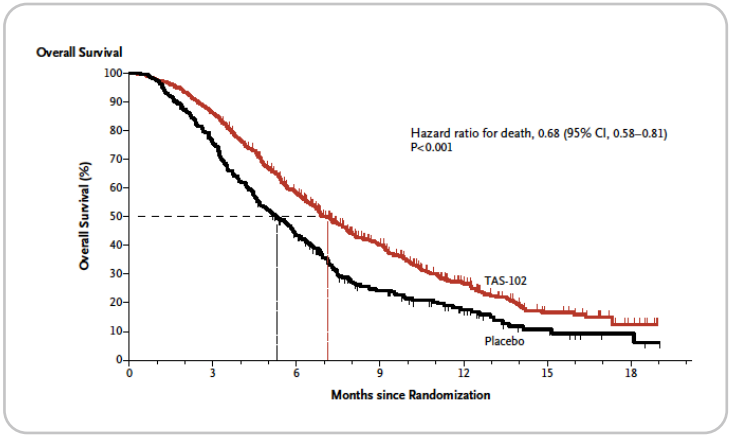
Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer

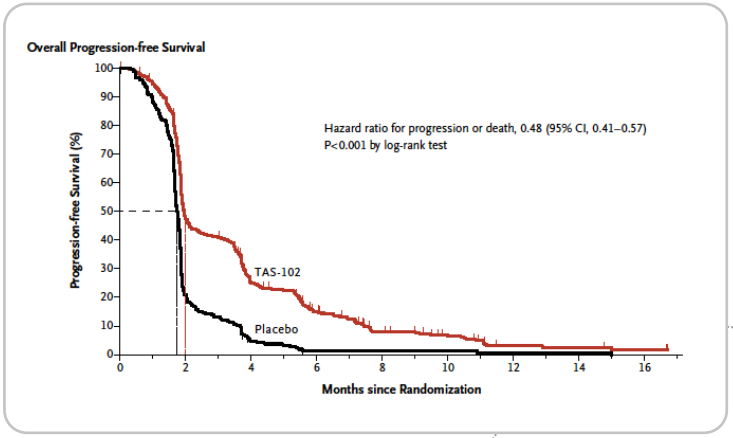
Mayer et al, NEJM 2015

ORIGINAL ARTICLE

Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer

Subgroup		N of patients	Hazard Ratio (95% CI)
All patients		800	0.68 (0.58-0.81)
Kras status	Wild type	393	0.58 (0.45-0.74)
	Mutant	407	0.80 (0.63-1.02)
Time since first diagnosis of first metastatic	< 18 months	166	0.84 (0.58-1.21)
	≥ 18 months	634	0.64 (0.53-0.78)
Age	< 65 years	448	0.74 (0.59-0.94)
	≥ 65 years	352	0.62 (0.48-0.80)
ECOG PS	0	448	0.73 (0.58-0.93)
	1	352	0.61 (0.48-0.79)
Primary tumor site	Colon	499	0.68 (0.55-0.85)
	Rectum	301	0.64 (0.48-0.85)
Prior use of regorafenib	Yes	144	0.69 (0.45-1.05)
	No	656	0.69 (0.57-0.83)
N. of prior regimens	2	140	1.05 (0.68-1.63)
	3	173	0.74 (0.51-1.08)
	≥ 4	487	0.59 (0.47-0.73)





Mayer et al, NEJM 2015

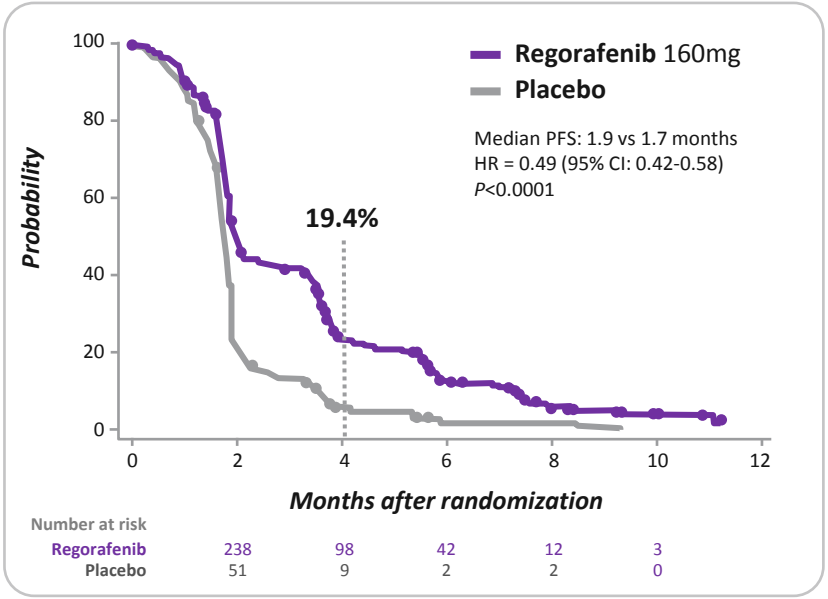
Stratégie CCR métastatique au delà de la 2ème ligne ?

Choix de la 3ème ligne ?

- **Le choix de la troisième ligne par un anti angiogénique de type régorafenib est validé dans le cancer colorectal métastatique.**
- **Le choix se base sur l'état général et l'évaluation des comorbidités. La dose d'AMM est de 160 mg par jour et justifie une surveillance clinique rapprochée.**
- **L'alternative, le TAS 102 est envisageable.**

L.FR.MKT.05.2017.3173

Long-Term PFS in CORRECT:
19% of patients achieve >4-months PFS

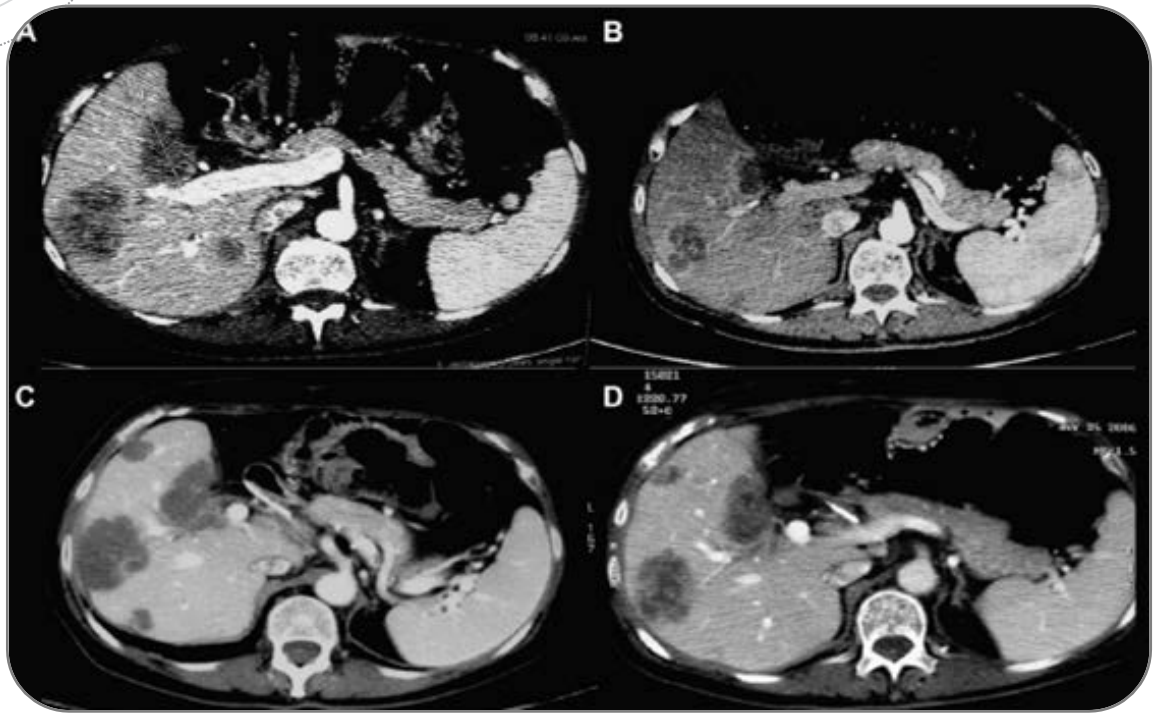


In CORRECT, 19% of regorafenib-treated patients had PFS >4 months

		Regorafenib	
		Long PFS > 4 months (n=98)	Short PFS ≤ 4 months (n=407)
Median age, years (range)		61 (34-82)	61 (22-82)
Age, %	< 65 years	65	60
	≥ 65 years	35	40
Male, %		64	61
Race, %	White	82	77
	Black	1	1
	Asian	11	16
	Other/not reported	6	6
Median Body mass index, kg/m^3		26	25
Primary site of disease, %	Colon	52	67
	Rectum	37	28
	Colon and rectum	10	5
ECOG PS, %	0	63	50
	1	37	50
KRAS mutation status, %	Wild-type	44	40
	Mutant	47	56
	Unknown	9	4
Liver metastases present, %		58	82
Number of tumor site, %	1	30	17
	2	38	35
	3	16	30
	4	7	11
	≥ 5	9	7
Prior treatment regimens on or after diagnosis of metastatic disease, %	1	3	3
	2	19	25
	3	22	25
	≥ 4	55	47
Time since first diagnosis of metastatic disease to randomization, %	< 18 months	11	20
	≥ 18 months	69	80

Grothey A ESMO 2016 abs 3568 516P
Grothey A et al. Lancet 2013

L’intérêt du maintien d’un anti angiogénique



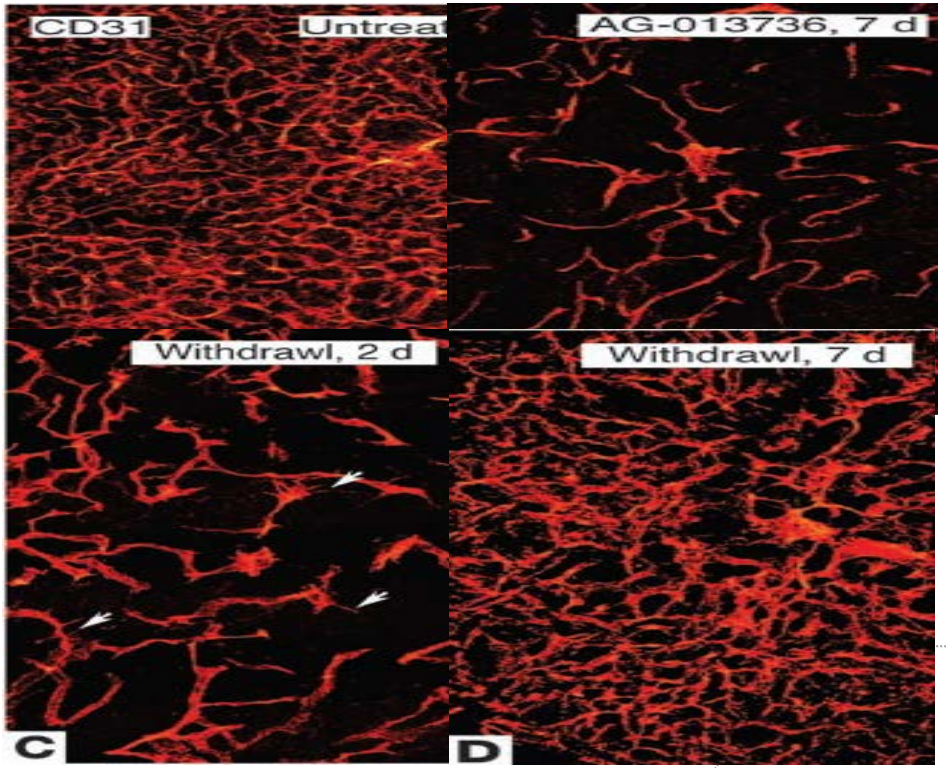
Reversible tumor growth acceleration following bevacizumab interruption in metastatic colorectal cancer

[1] *Cacheux w et al, Annals of oncology, 2008*

L'intérêt du maintien d'un anti angiogénique

Bevacizumab et persistance de la trame vasculaire

- **Anti VEGF : vascularisation tumorale**
- **Réversibilité de l'action des anti VEGF**
- **Nécrose tumorale**
- **Diminution de la vascularisation**
- **Persistance des péricytes**
- **Reprise plus rapide de la vascularisation à l'arrêt des anti VEGF.**



[1] *Mancuso et al, JCI 2006*

Le cancer colorectal métastatique

Les recommandations ESMO

Strategic scenario in the continuum of care of metastatic colorectal cancer

	SCENARIO 1	SCENARIO 2	SCENARIO 3
1st line	Cytotoxic doublet[1] + bevacizumab	Cytotoxic doublet[1] + bevacizumab	Cytotoxic doublet[1] + anti-EGFR antibody[2]
2nd line	Cytotoxic doublet[1] + bevacizumab or aflibercept[3]	Cytotoxic doublet[1] + anti-EGFR antibody[2]	Cytotoxic doublet[1] + bevacizumab or aflibercept
3rd line	Irinotecan or FOLFIRI + anti-EGFR antibody[2]	Regorafenib or TAS-102	Regorafenib or TAS-102
4th line	Regorafenib or TAS-102		

[1] Cytoxic doublets: fluoropyrimide + oxaliplatin or irinotecan; [2] Ras wild type; [3] Aflibercept only in combination with FOLFIRI