HÔPITAUX UNIVERSITAIRES PARIS OUEST

Hôpital européen Georges-Pompidou

Cancer colorectal un paysage qui change
Optimisation therapeutique au dela de la 2è ligne

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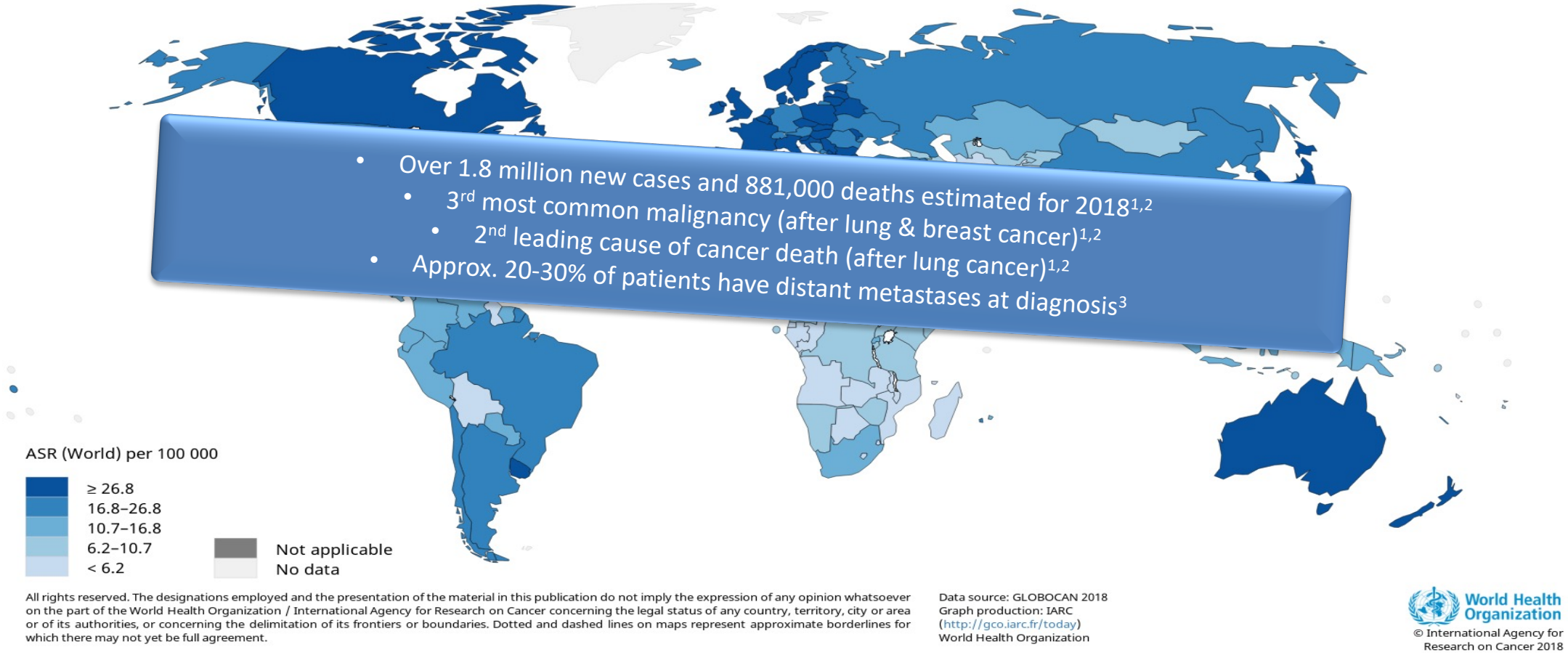
DISCLOSURE INFORMATION

Honoraria for speaker or advisory role for :

AMGEN, BMS, HallioDx, Lilly, Merck, MSD, Novartis, Pierre Fabre, Roche, Sanofi, Servier

Global perspective: Colorectal cancer

Estimated age-standardized incidence rates (World) in 2018, both sexes, all ages[1]

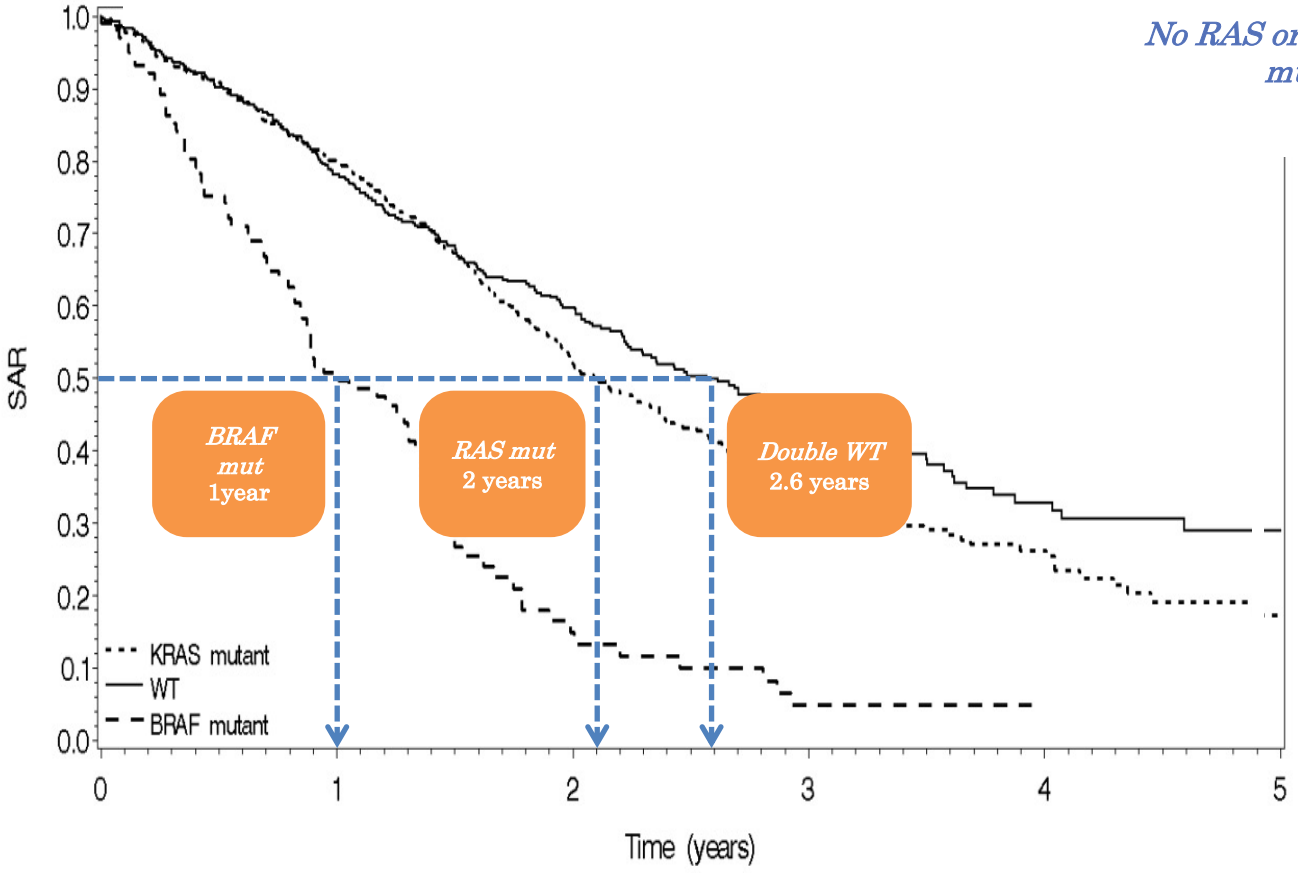


- Over 1.8 million new cases and 881,000 deaths estimated for 2018[1,2]
- 3rd most common malignancy (after lung & breast cancer)[1,2]
- 2nd leading cause of cancer death (after lung cancer)[1,2]
- Approx. 20-30% of patients have distant metastases at diagnosis[3]

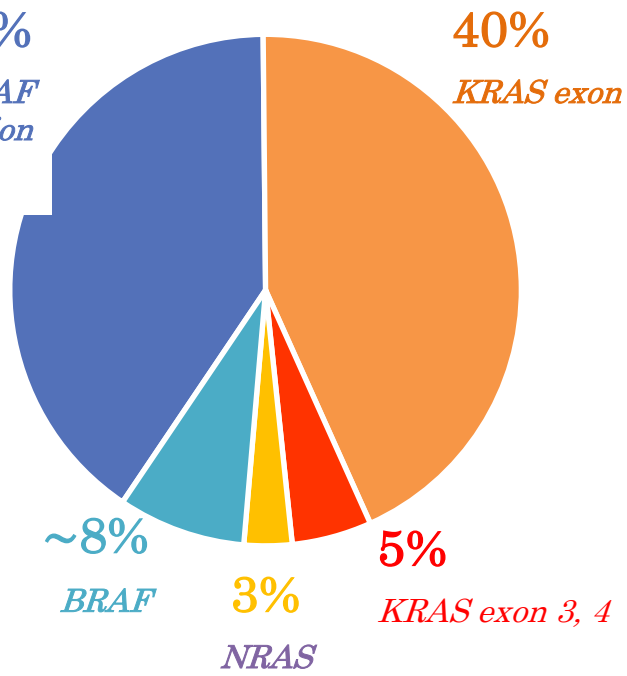
Highest rate is in Hungary at 51.8/100, 000 and is closely followed by South Korea at 44.5/ 100,

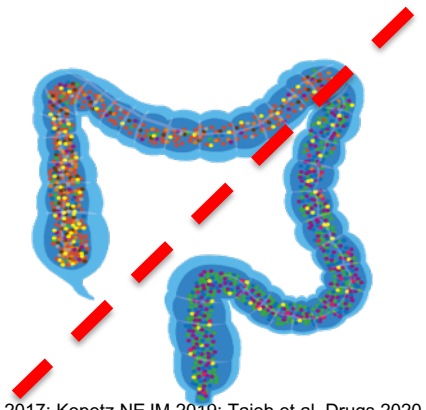
1. Source: http://gco.iarc.fr/today (accessed 21 Mar 2019);
2. Bray F, et al. CA Cancer J Clin 2018;68:394-424;
3. Siegel RL, et al. CA Cancer J Clin 2019;69:7–34

Profil moléculaire du cancer colorectal une histoire qui commence en 2006



KRAS mutant	467	341	184	78	32	9
WT	471	312	180	81	30	10
BRAF mutant	103	47	9	3	0	0





Lièvre et al. JCO 2008;
Douillard NEJM 2014; Arnold D et al Ann Oncol 2017; Taieb et al JNCI 2017; Kopetz NEJM 2019; Taieb et al. Drugs 2020. J Taieb ESMO Asia 2020

WT: wild-type. Mut: mutant

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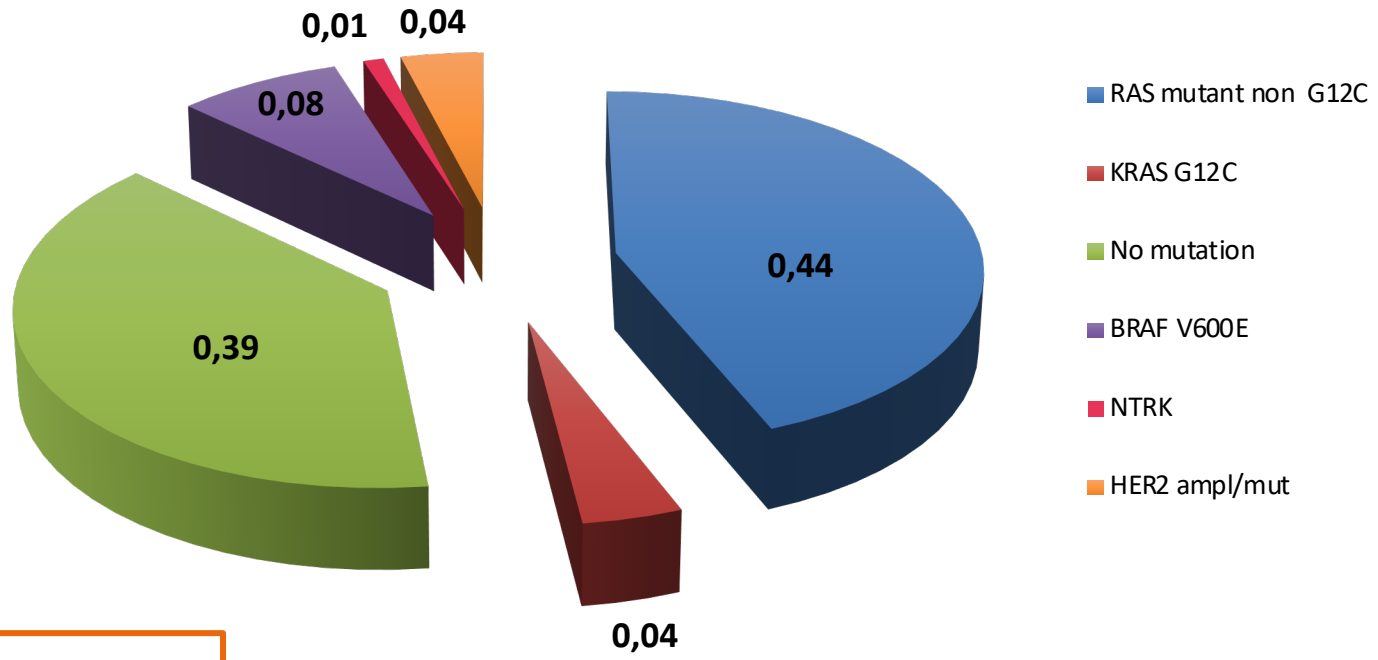
Mais le paysage change rapidement, on ne peut plus parler du cancer colorectal mais des cancers colorectaux

From KRAS exon 2 in the 2010 we have now to test for our mCRC patients :

- *KRAS* exon 2,3,4 (**including G12C**)
- *NRAS* exon 2,3,4
- *BRAF* V600E
- *HER2* ampl/mutations
- *NTRK* gene fusion
- *MSI/dMMR*
- *TMB* in *MSS/pMMR* ?



All with theranostic implications!

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BRAF V600E mutant – BEACON study

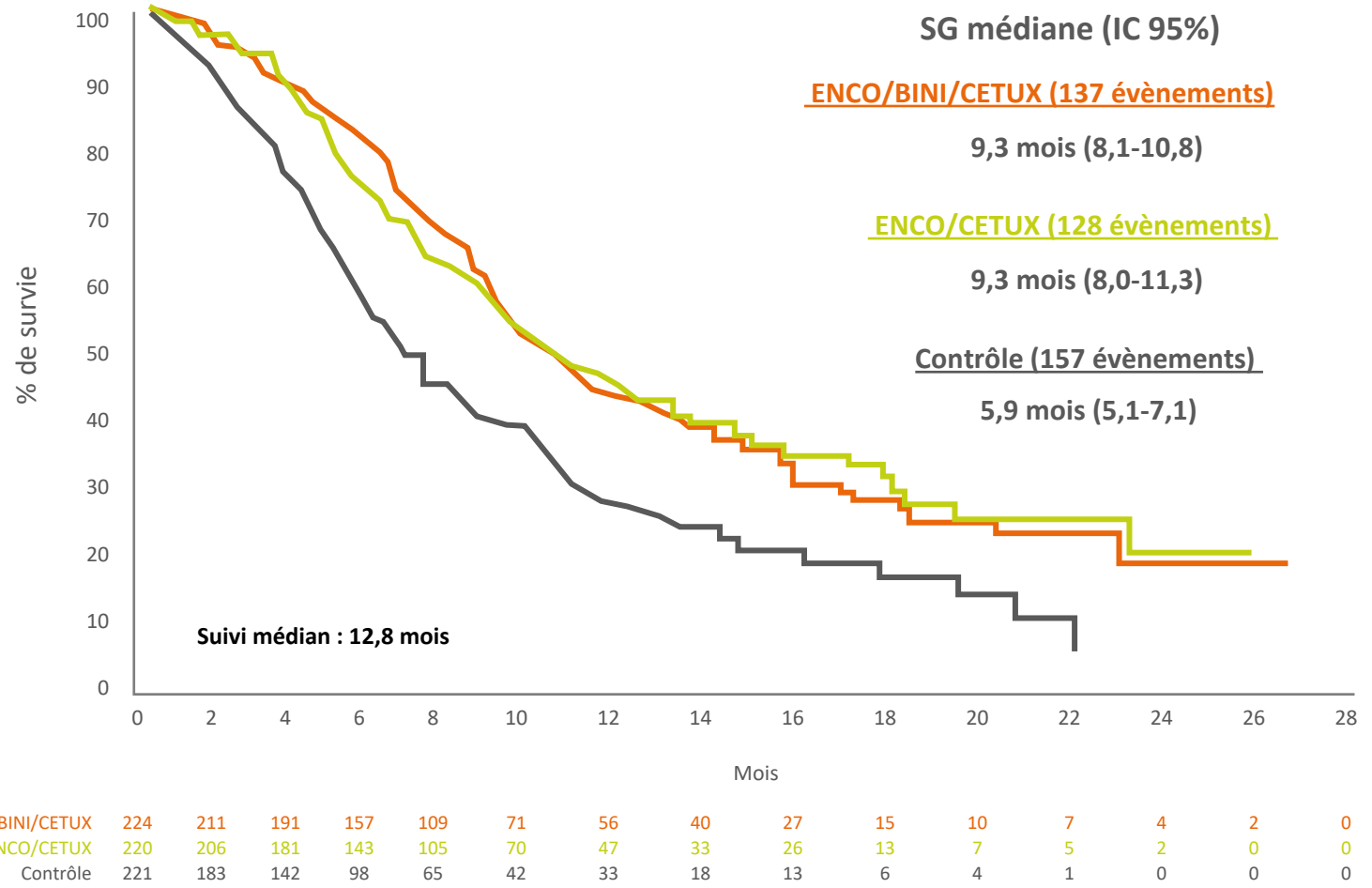
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Encorafenib, Binimetinib, and Cetuximab in *BRAF* V600E–Mutated Colorectal Cancer

S. Kopetz, A. Grothey, R. Yaeger, E. Van Cutsem, J. Desai, T. Yoshino, H. Wasan, F. Ciardiello, F. Loupakis, Y.S. Hong, N. Steeghs, T.K. Guren, H.-T. Arkenau, P. Garcia-Alfonso, P. Pfeiffer, S. Orlov, S. Lonardi, E. Elez, T.-W. Kim, J.H.M. Schellens, C. Guo, A. Krishnan, J. Dekervel, V. Morris, A. Calvo Ferrandiz, L.S. Tarpgaard, M. Braun, A. Gollerkeri, C. Keir, K. Maharry, M. Pickard, J. Christy-Bittel, L. Anderson, V. Sandor, and J. Tabernero

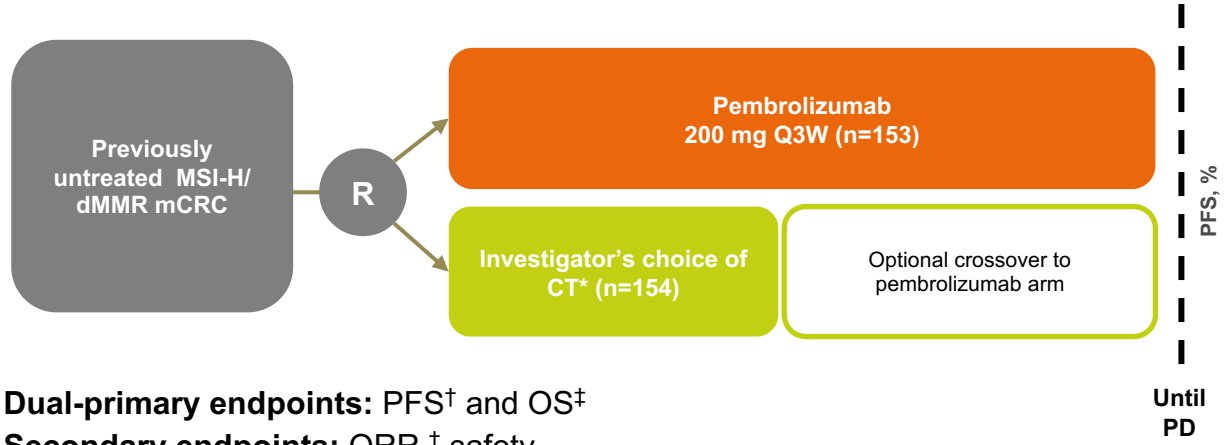
	Doublet	Triplet
Taux de RO	26%	20%
En L2	34%	22%
En L3	14%	16%



Scott Kopetz, et al., ASCO® 2020, Abs #4001

Pembrolizumab vs Chemotherapy for MSI-H/dMMR mCRC - KEYNOTE-177 Study

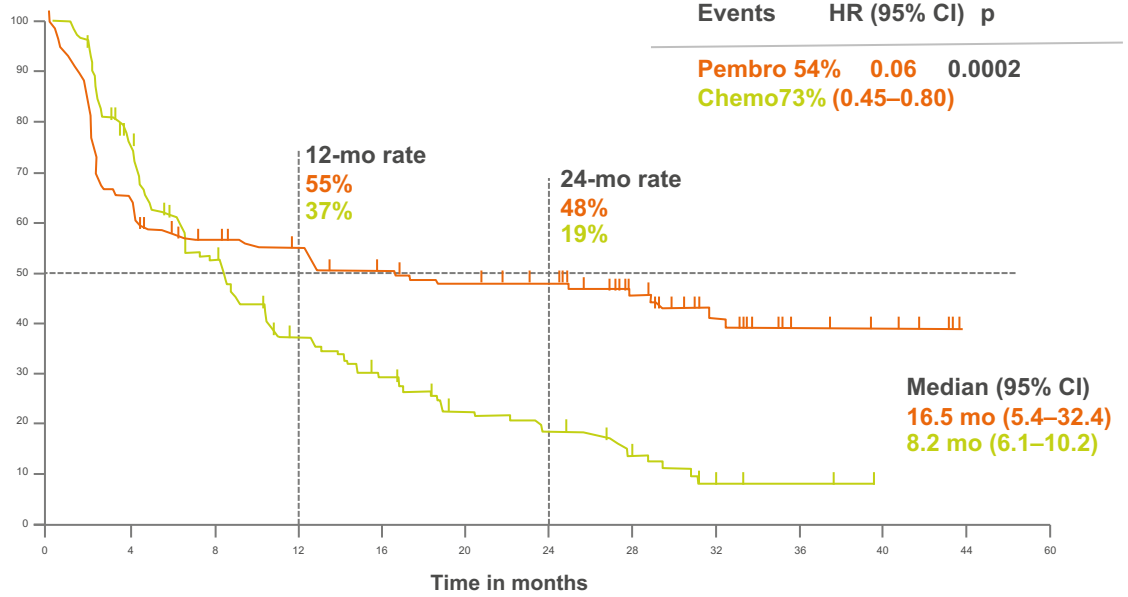
Open-label, randomized, Phase III trial (N=307)



Dual-primary endpoints: PFS† and OS‡
Secondary endpoints: ORR,† safety

* Choice of: FOLFOX ± cetuximab/bevacizumab or FOLFIRI ± cetuximab/bevacizumab
† per RECIST v1.1 per blinded independent central review
‡ Study will remain blinded for OS until 190 OS events achieved or 12 months after second interim analysis

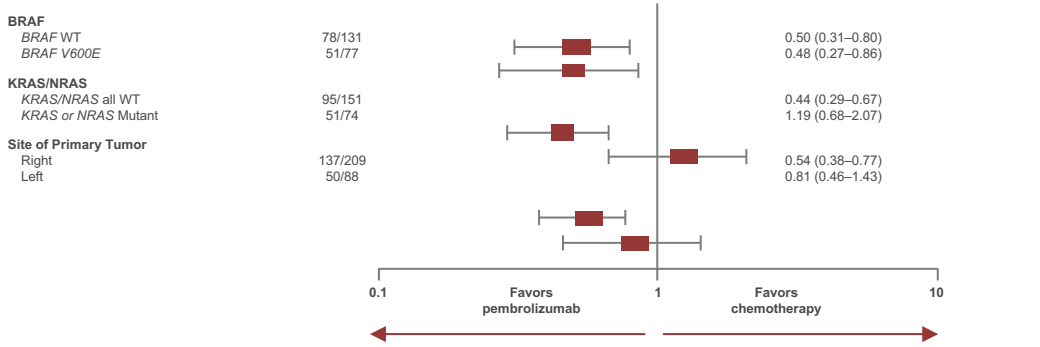
PFS



Safety

All grade Treatment related AEs: 80% with pembrolizumab vs **99%** with CT
Grade ≥3 Treatment related AEs: 22% with pembrolizumab vs **66%** with CT

Subgroup analysis of PFS



PFS: survie sans progression. AEs: effets indésirables. ORR: Taux de Réponse Objective. OS: survie global. PD: Progression de la maladie

Andre T, et al. ASCO; LBA4 and NEJM 2020

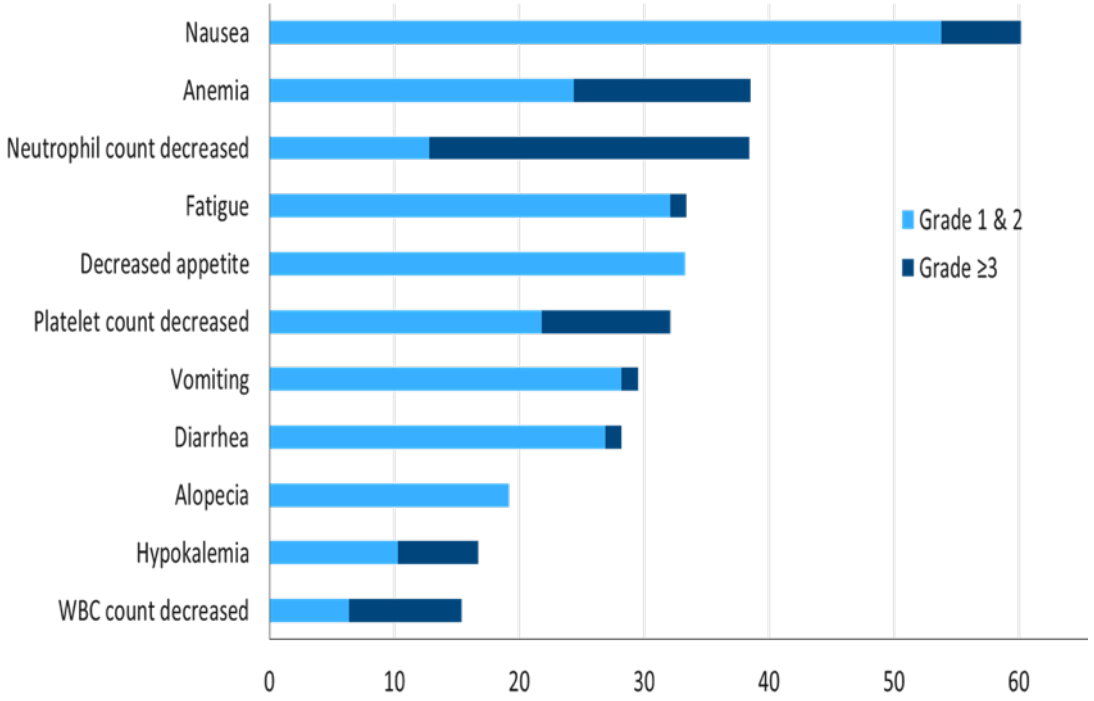
Traztuzumab-deruxtecan in HER2 amplified mCRC - DESTINY CRC01 study

53 patients RAS WT, BRAF WT, HER2 +++

Tolerability

6.4 % Interstitial lung disease including

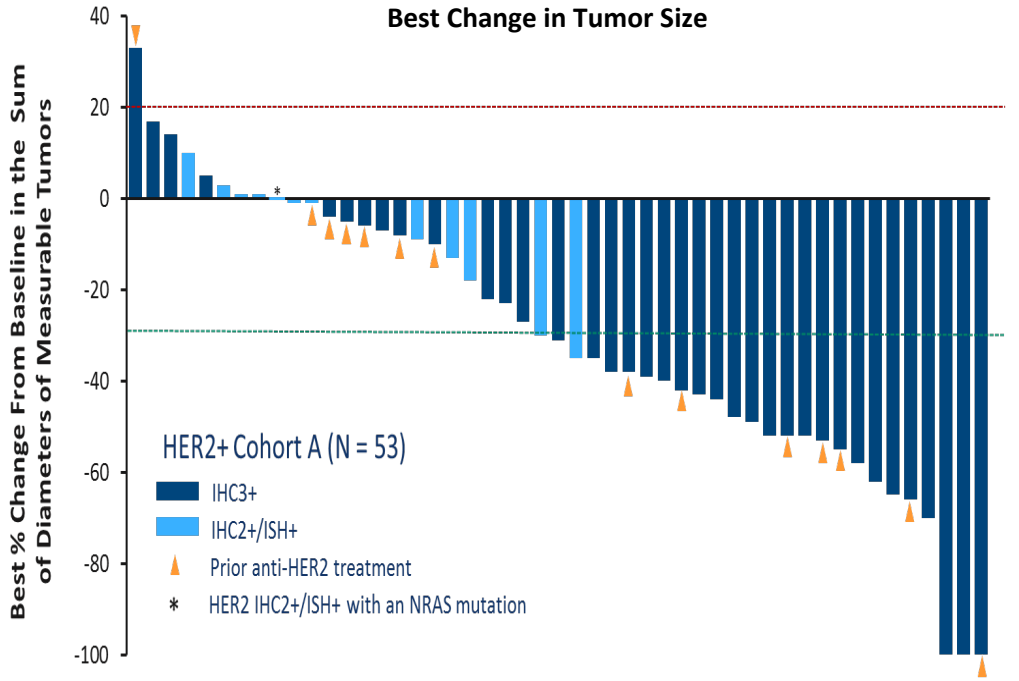
2.5% of toxic deaths due to ILD and pneumonitis



Efficacy

Primary endpoint ORR= 43.5%

DCR = 83%



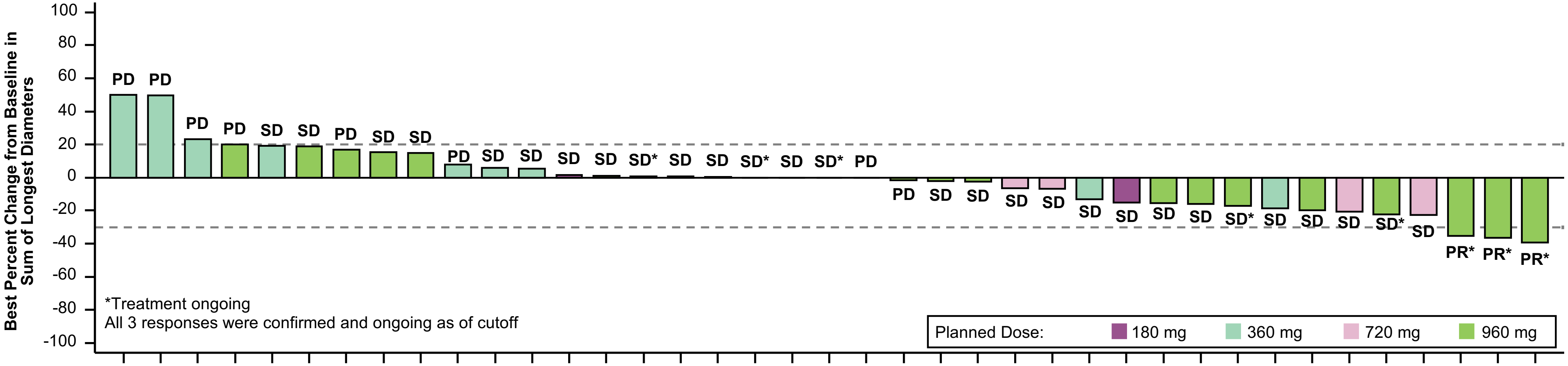
J Taieb ESMO Asia 2020

mCRC: Cancer colorectal métastatique. WT: wild-type DCR: Taux contrôle de la maladie. ORR: Taux de réponse objective.

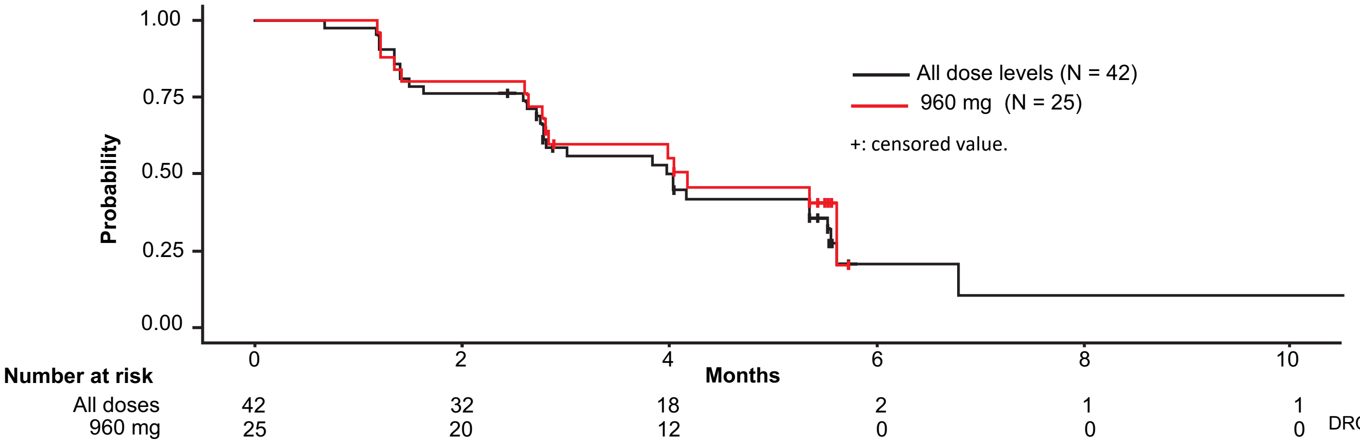
Siena et al. Lancet Oncol 2021

KRAS G12C inhibitors - AMG 510

Grade 3 treatment-related adverse events: Diarrhea (2/59, 3.4%) and Anemia (1/59, 1.7%)



Progression-Free Survival



Efficacy results	% or months
RR / DCR	7.1% / 76%
PFS: All doses / 960 mg	4.0/4.2 months

DRC: Taux de contrôle de la maladie. RR: Taux de réponse

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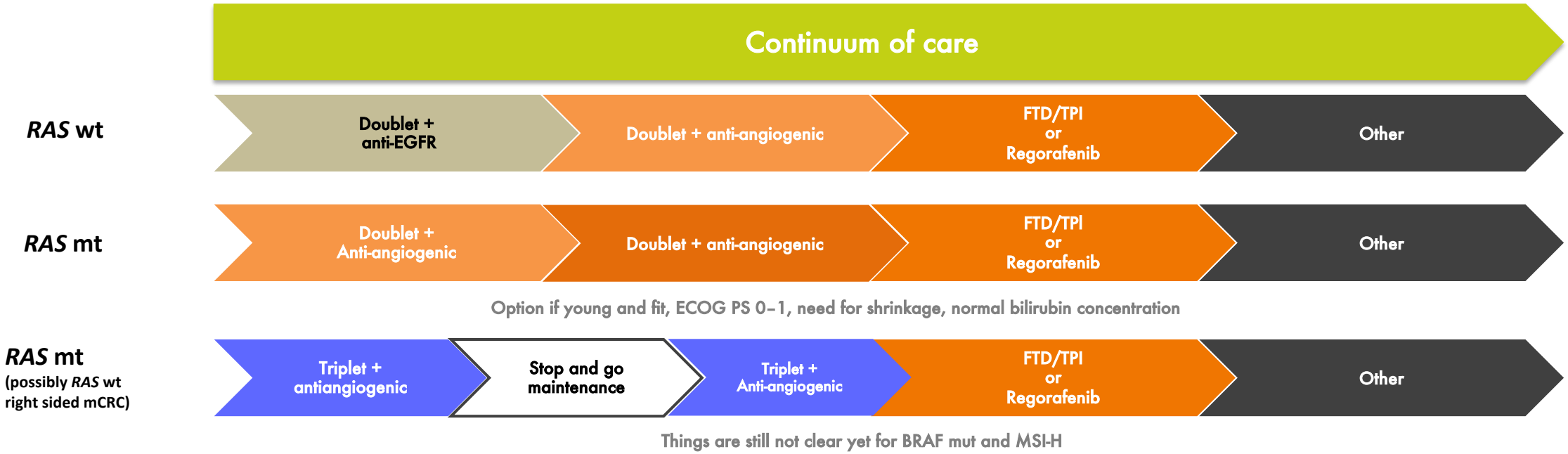
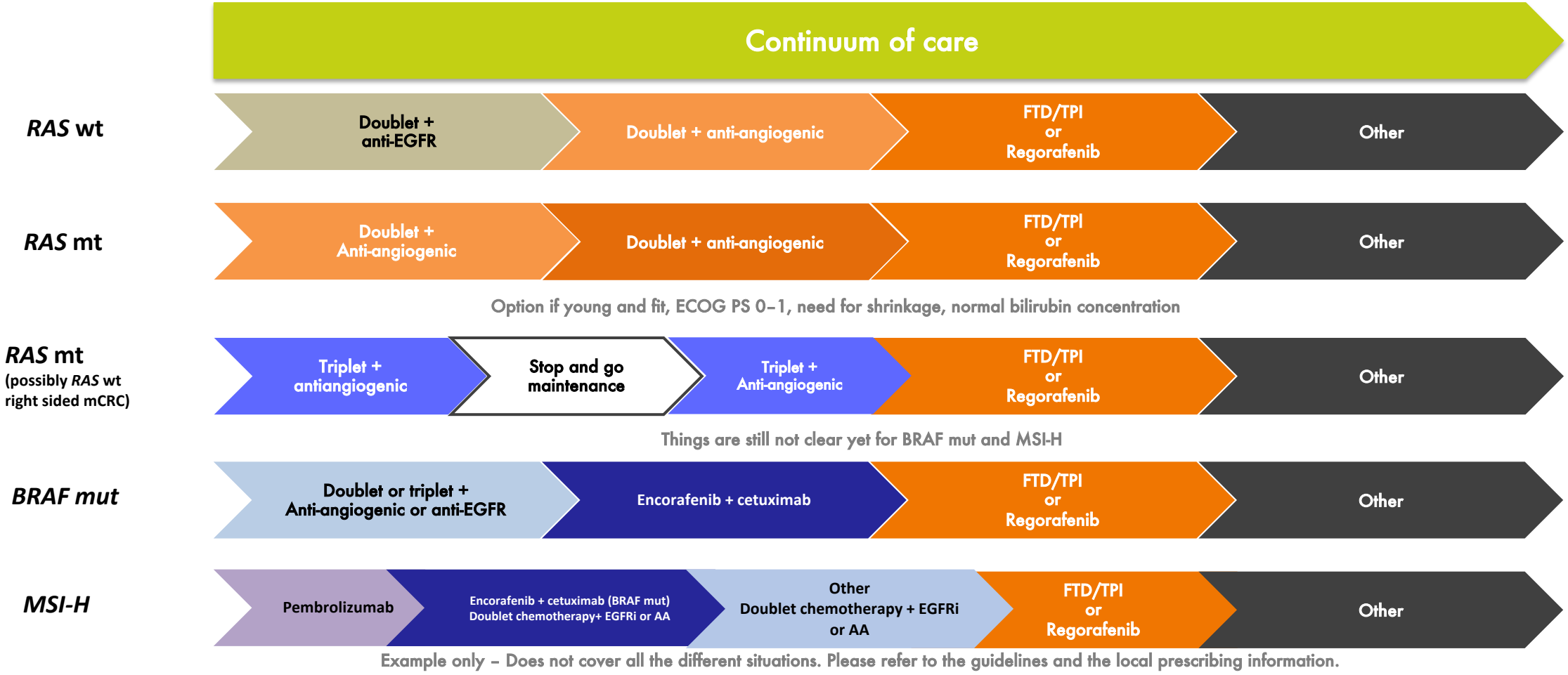
Therapeutic sequencing: to make it simple



Therapeutic sequencing: to make it simple



Quelles avancées au delà de la 2è ligne

FTD/TPI, expériences à travers différents profils patients – Etude RECOURSE

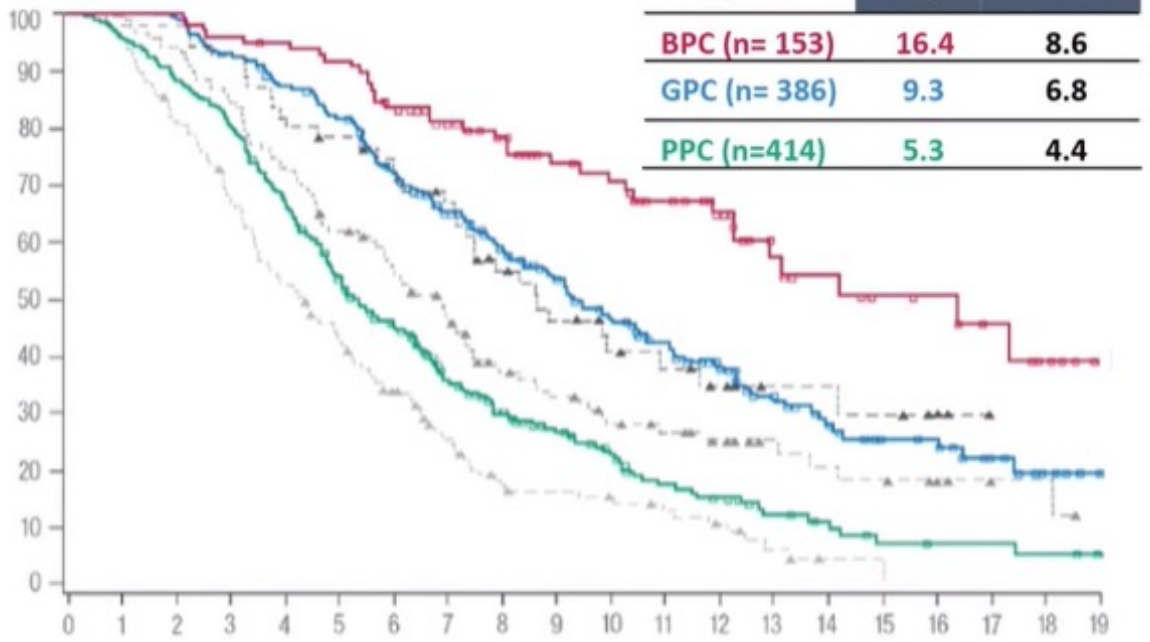
Faible masse tumorale et maladie indolente sans métastase hépatique
(BPC n=153)

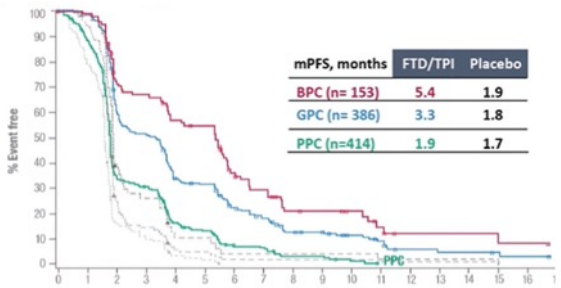
Faible masse tumorale et maladie indolente
- **<3 sites métastatiques**
- **diagnostic des métastases ≥18 mois**

(GPC n=386)

Forte masse tumorale et/ou maladie agressive
(PPC n=414)

mOS, months	FTD/TPI	Placebo
BPC (n= 153)	16.4	8.6
GPC (n= 386)	9.3	6.8
PPC (n=414)	5.3	4.4





BPC, Best prognosis (Forte masse tumorale et maladie agressive) CI, Intervalle de confiance; FTD/TPI, trifluridine tipiracil; HR, risque relatif; mOS, survie globale médiane; GPC; Good Prognosis (Faible masse tumorale et maladie indolente); PPC, Poor prognosis (Forte masse tumorale et maladie agressive)

Tabernero J, et al, ESMO Open 2020;5:e000752. doi:10.1136/ esmoopen-2020-000752

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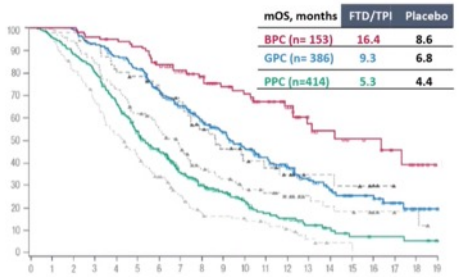
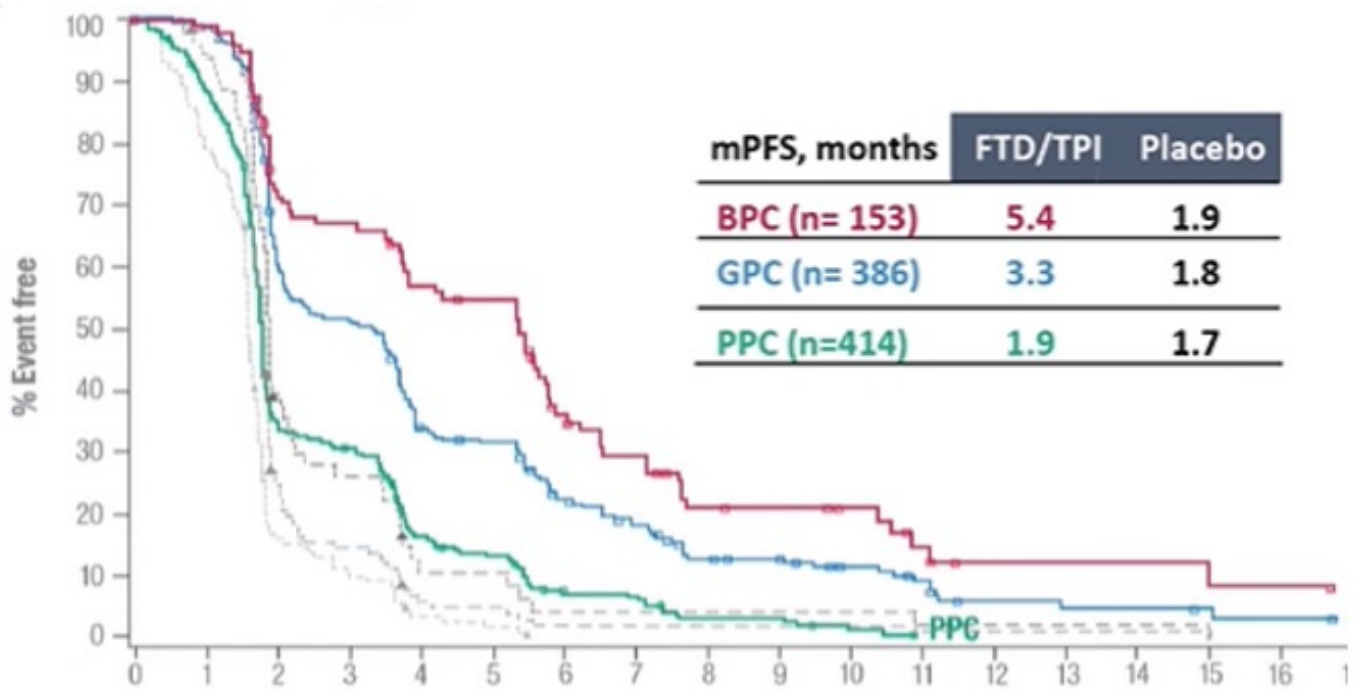
Forte masse tumorale et/ou maladie agressive (PPC n=414)





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Tabernero J, et al, ESMO Open 2020;5:e000752. doi:10.1136/ esmoopen-2020-000752

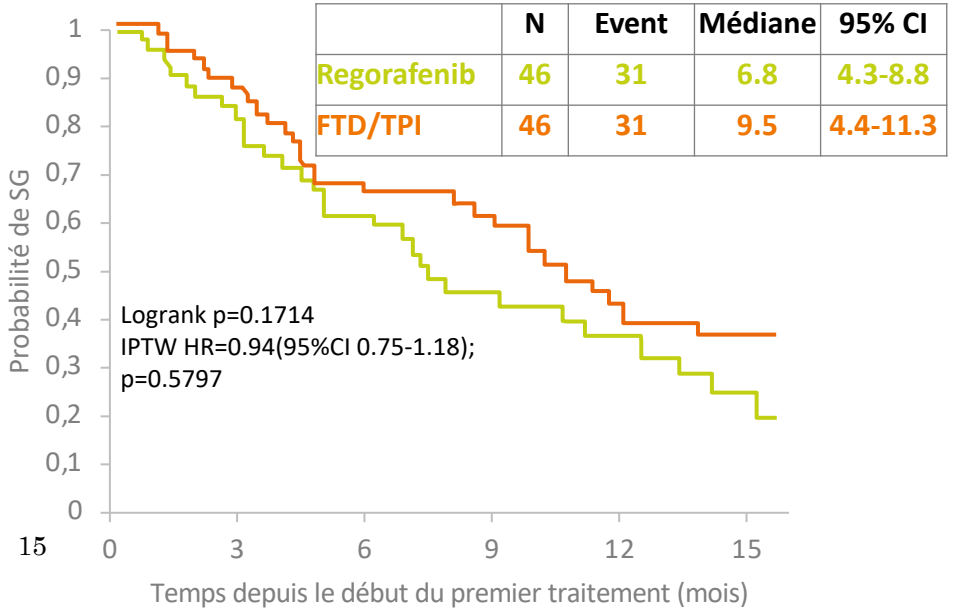
FTD/TPI et Rego en lignes avancées du CCRm – Etude de vie réelle TRIREG AGEO

237 patients recrutés prospectivement dans 12 centres français:

- mSG et mSSP respectivement de 6,6 et 2,4 mois avec FTD/TPI et 6,2 et 2,1 mois avec regorafenib
- Profils de tolérance similaires aux données publiées précédemment, mais réductions de dose significativement plus fréquentes dans le groupe Regorafenib (44% vs 27%, p = 0,008)
- 92 patients appariés (score de propension)

Survie Globale

	N	Event	Médiane	95% CI
Regorafenib	46	31	6.8	4.3-8.8
FTD/TPI	46	31	9.5	4.4-11.3



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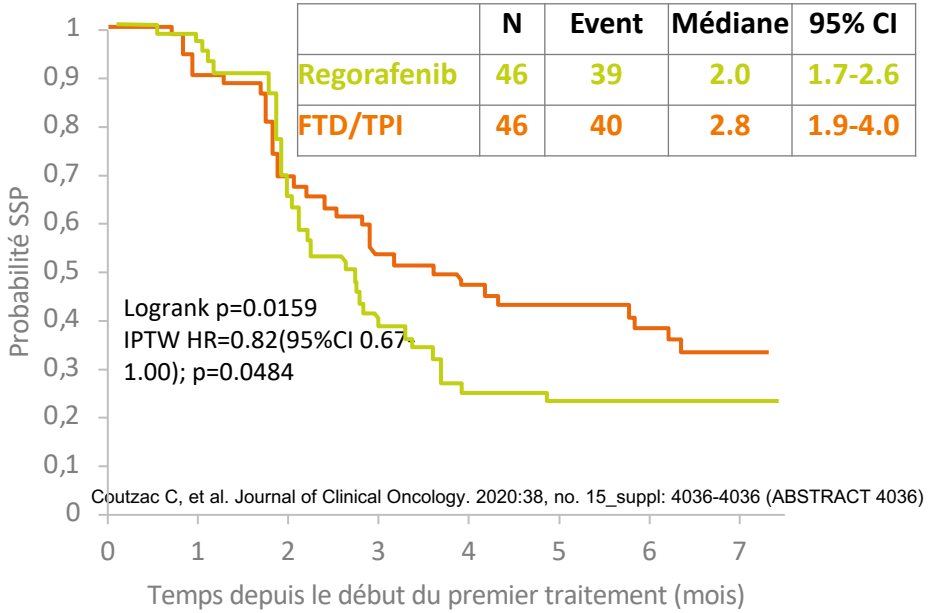
Survie Sans Progression

	N	Event	Médiane	95% CI
Regorafenib	46	39	2.0	1.7-2.6
FTD/TPI	46	40	2.8	1.9-4.0

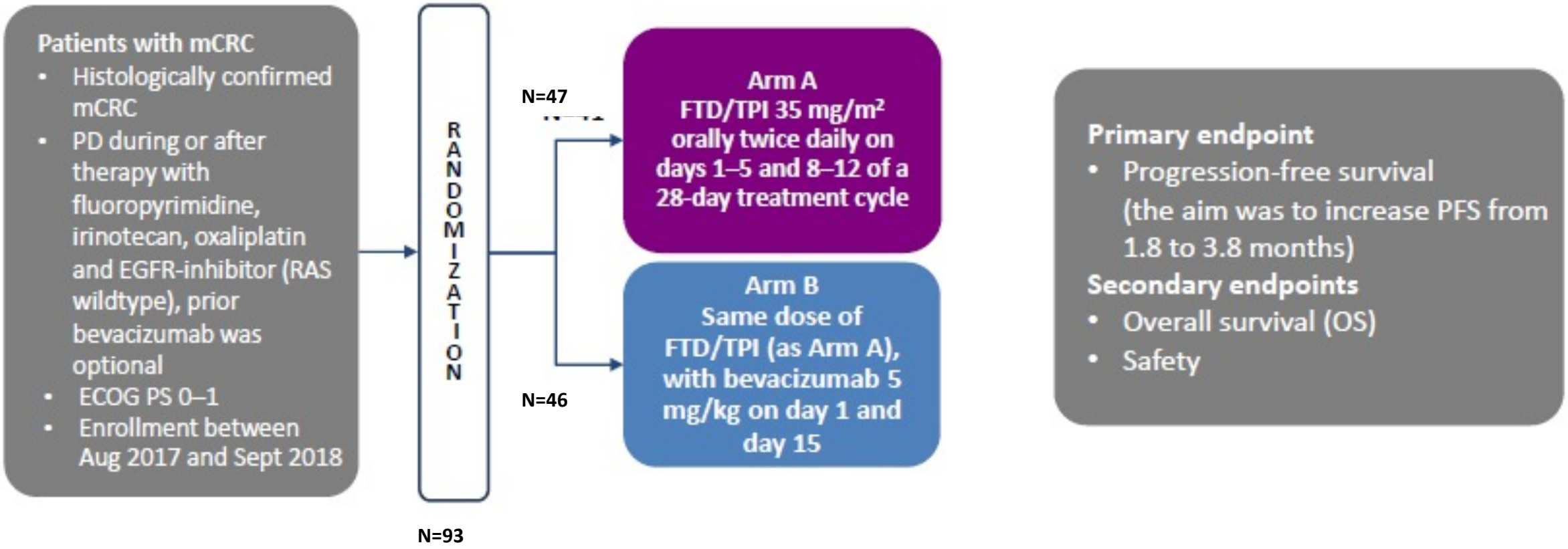


Coutzac C, et al. Journal of Clinical Oncology. 2020:38, no. 15_suppl: 4036-4036 (ABSTRACT 4036)

Coutzac et al. Clin Col Can 2021 (in press)

FTD/TPI + beva en lignes avancées du CCRm
Phase 2 danoise

Design et objectifs

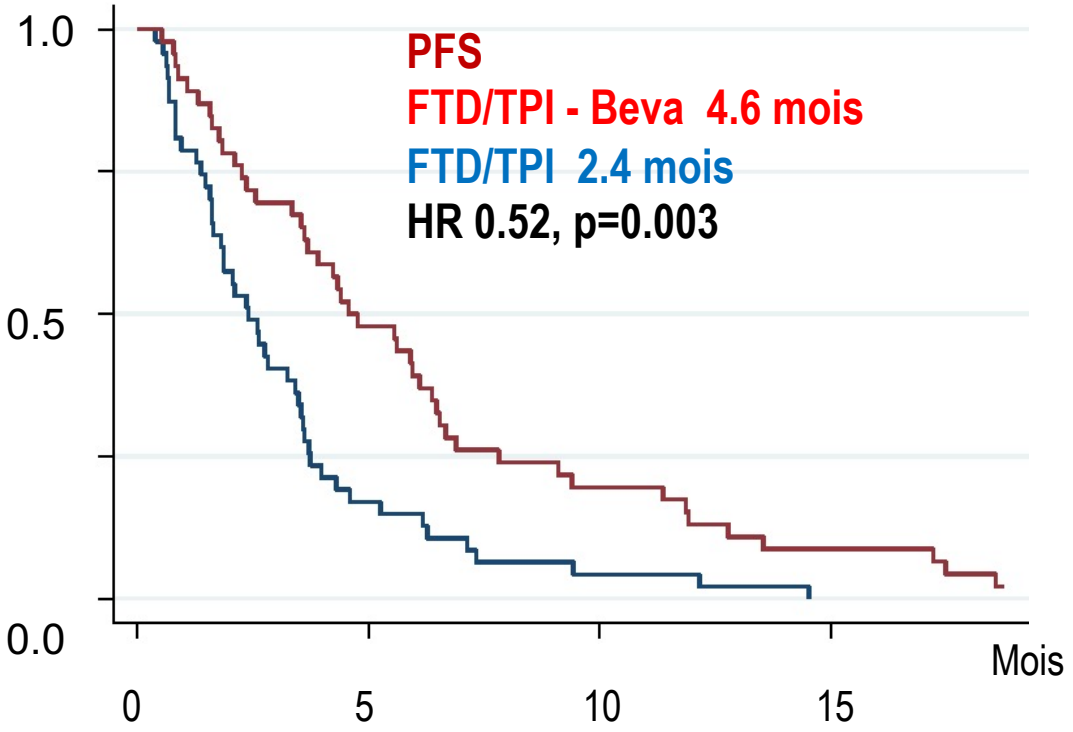


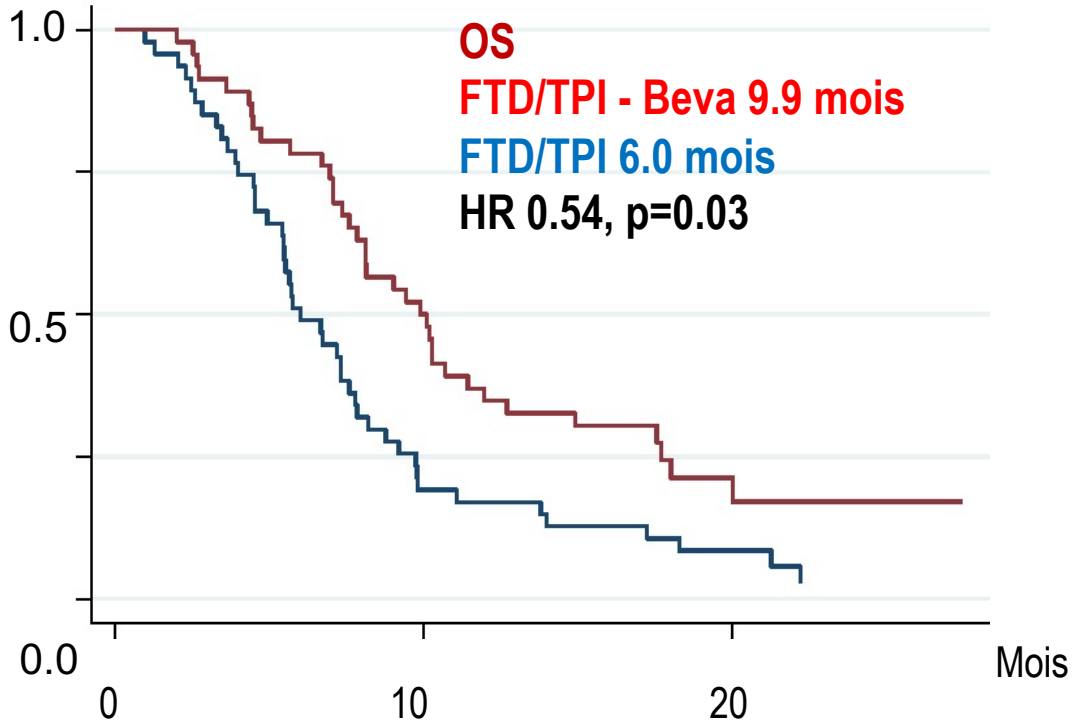
FTD/TPI, trifluridine/tipiracil. PFS: survie sans progression. mCRC/CCRm: Cancer colorectal métastatique.
ECOG PS: Eastern Cooperative Oncology Group performance status

EudraCT 2016-005241-23
Pfeiffer et al, ESMO GI 2019 & Lancet Oncol 2020

FTD/TPI + beva en lignes avancées du CCRm
Phase 2 danoise

FTD/TPI + bevacizumab est désormais recommandé comme option de traitement en L3 du CCRm par les recommandations américaines (NCCN)



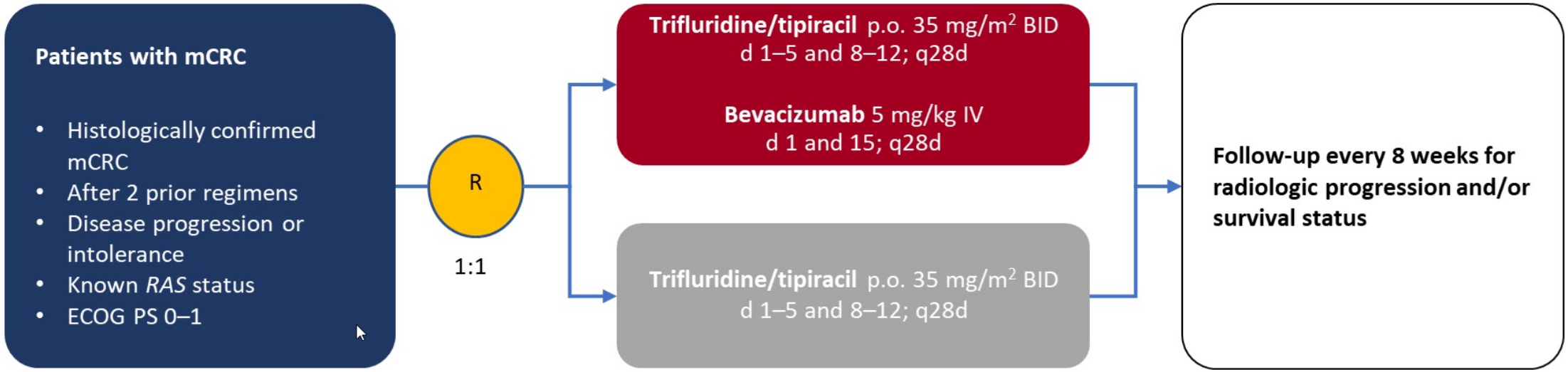


Significativement + de neutropénie Grade 3-4 (67% vs 38% des patients) et de thrombopénie tous grades (39% vs 17%) dans la bras FTD/TPI + Beva

OS: survie globale. FTD/TPI: trifluridine/tipiracil. PFS: survie sans progression. CCRm: Cancer colorectal métastatique

EudraCT 2016-005241-23
Pfeiffer et al, Lancet Oncol 2020 & ESMO GI 2020

FTD/TPI + beva en lignes avancées du CCRm – Phase 3 SUNLIGHT



Primary end point: OS

Secondary end points: PFS, ORR, DCR, safety, QoL

Stratification factors:

Geographic region (North America, EU, ROW)

Time since diagnosis of first metastasis (<18 months, ≥18 months)

RAS status (wild type, mutant)

mCRC=CCRm: cancer colorectal métastatique, ROW: Reste du monde. BID: deux fois/jour. ECOG PS, Eastern Cooperative Oncology Group performance status.
FTD/TPI: trifluridine/tipiracil.

NCT04737187
J. Tabernero et al. Future Oncology 2021


Merci pour votre attention