Le cancer colorectal métastatique
Une approche systémique

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25 octobre 2019

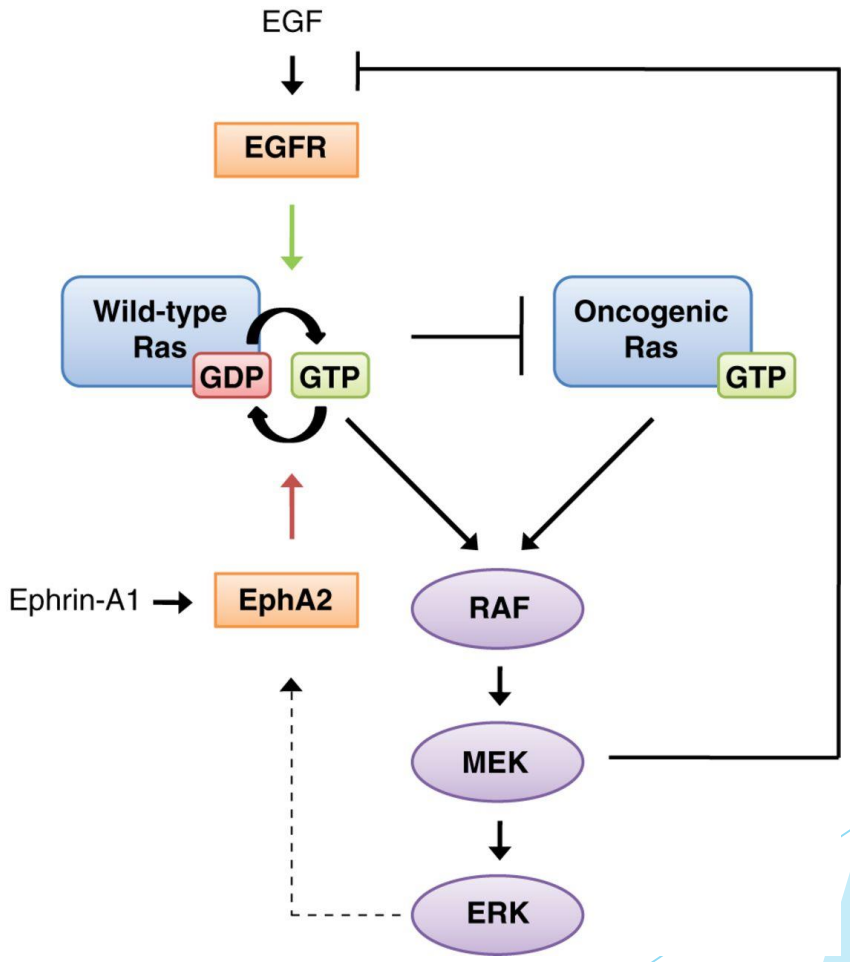
Objectifs de cette présentation

- Afin de mieux comprendre l'algorithme de traitement…..
  - Un peu de génétique moléculaire
- Sélectionner le bon traitement pour le bon patient
- Les principales lignes de traitements
- Les nouveautés
  - Dans le meilleur des monde, que pourrions-nous offrir à nos patients?

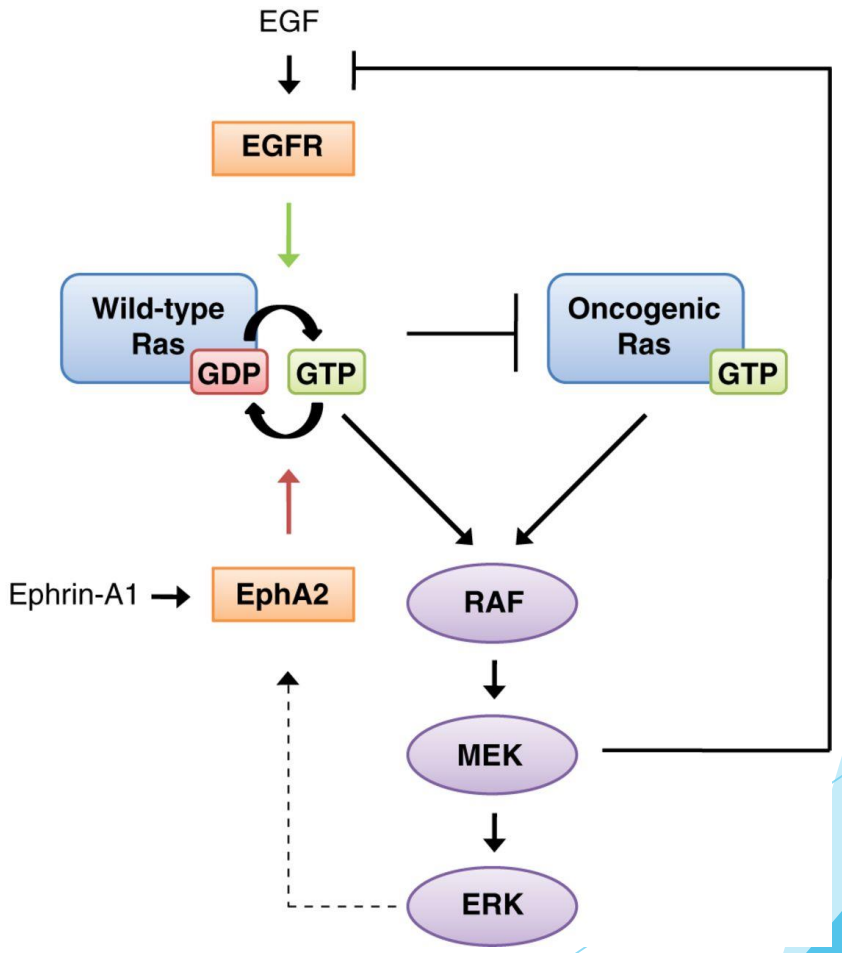
De plus en plus vers une médecine personnalisée

- Oncogène RAS
  - KRAS
  - NRAS
  - HRAS
- 50% des cas sporadiques

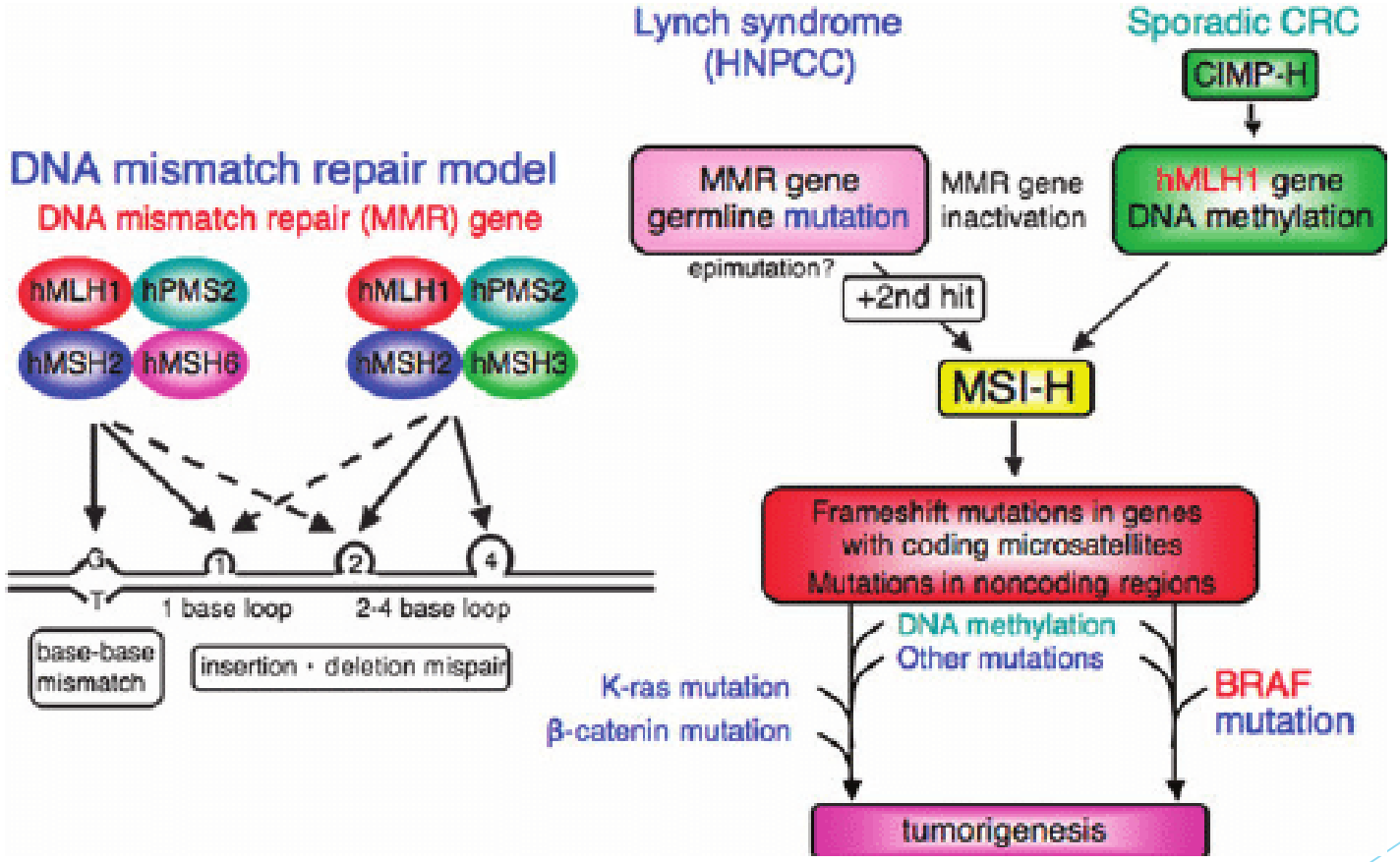
- Si RAS non muté, rechercher mutation BRAF V600E
  - Environ 10%



- Mutation BRAF
  - Si RAS non muté
  - Entre 8 et 12%
  - 2/3 côlon droit et confère un mauvais pronostic
    - Survie médiane 10,4 mois
  - 1/3 associé MSI-H
    - Survie médiane 34,7 mois

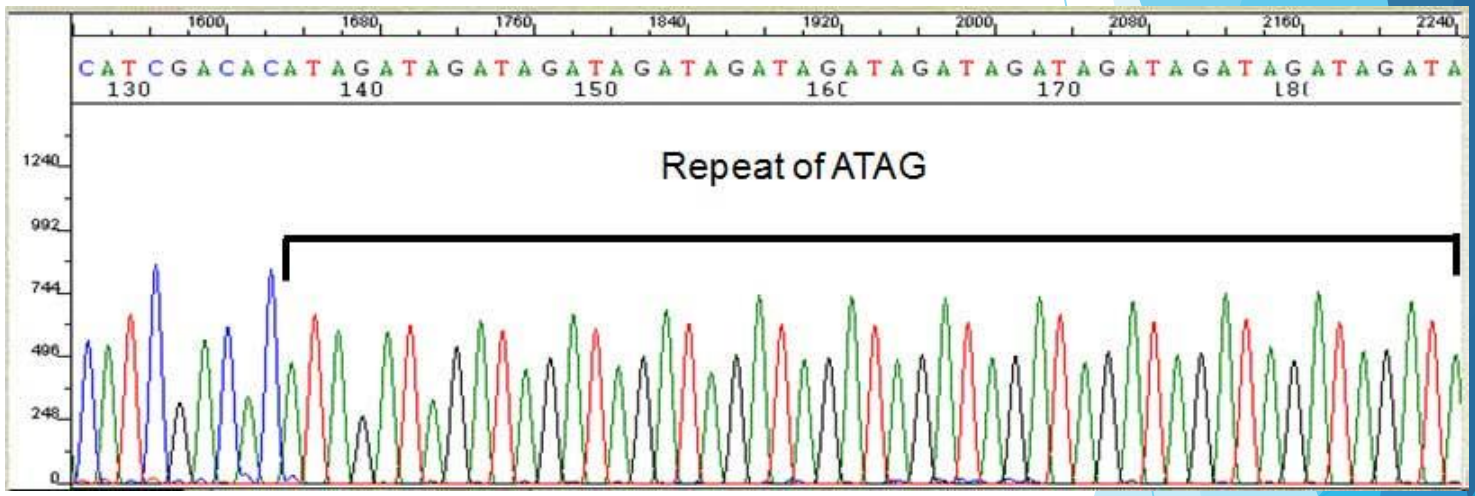


Gène de réparation de mésappariements (MMR)



Instabilités microsatellitaires élevées (MSI-H)

- 15% des cas sporadiques
- Côlon proximal
- Composante mucineuse prédominante
- Infiltration lymphocytaire
- Pauvrement différencié



Bien évaluer son patient

- L'âge chronologique n'est pas un bon marqueur du statut fonctionnel du patient
- Il existe plusieurs échelles pour évaluer le statut de performance des patients
  - ECOG
  - Karnofsky
  - Palliative Pronostic Scale

Eastern Cooperative Oncology Group (ECOG, Zubrod, World Health Organization) performance scale

Performance status	Definition
0	Fully active; no performance restrictions.
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work.
2	Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair >50% of waking hours.
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Adapted from: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649.

UpToDate®

Karnofsky Performance Status scale

Value	Level of functional capacity	Definition
100	Normal, no complaints, no evidence of disease	Able to carry on normal activity and to work; no special care needed
90	Able to carry on normal activity, minor signs or symptoms of disease	
80	Normal activity with effort, some signs or symptoms of disease	
70	Cares for self, unable to carry on normal activity or to do active work	Unable to work; able to live at home and care for most personal needs; various degrees of assistance needed
60	Requires occasional assistance but is able to care for most needs	
50	Requires considerable assistance and frequent medical care	
40	Disabled, requires special care and assistance	Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly
30	Severely disabled, hospitalization is indicated although death is not imminent	
20	Hospitalization is necessary, very sick, active supportive treatment necessary	
10	Moribund, fatal processes progressing rapidly	
0	Dead	

- Envisager soins de confort pour maintenir la qualité de vie chez les patients frêles, avec un indice de performance hypothéqué ou un ECOG 3-4.
- Les personnes âgées actives, « fit » et sans comorbidités devraient se voir offrir un traitement standard.
- Pour les patients en zone grise
  - Échelles d'évaluation gériatrique
    - Nombreuses
    - Parfois longues et/ou complexes
  - Consultation en oncogériatrie

CARG model for predicting chemotherapy toxicity in older adults

Risk factor	Prevalence		Grades 3 to 5 toxicity		OR	95% CI	Score
	No.	Percent	No.	Percent			
Age ≥72 years	270	54	163	60	1.85	1.22 to 2.82	2
Cancer type GI or GU	185	37	120	65	2.13	1.39 to 3.24	2
Chemotherapy dosing, standard dose	380	76	204	54	2.13	1.29 to 3.52	2
Number of chemotherapy drugs, polychemotherapy	351	70	192	55	1.69	1.08 to 2.65	2
Hemoglobin <11 g/dL (male), <10 g/dL (female)	62	12	46	74	2.31	1.15 to 4.64	3
Creatinine clearance (Jelliffe, ideal weight) <34 mL/min	44	9	34	77	2.46	1.11 to 5.44	3
Hearing, fair or worse	123	25	76	62	1.67	1.04 to 2.69	2
Number of falls in last six months, one or more	91	18	61	67	2.47	1.43 to 4.27	3
IADL: Taking medications, with some help/unable	39	8	28	72	1.50	0.66 to 3.38	1
MOS: Walking one block, somewhat limited/limited a lot	109	22	69	63	1.71	1.02 to 2.86	2
MOS: Decreased social activity because of physical/emotional health, limited at least sometimes	218	44	126	58	1.36	0.90 to 2.06	1

CARG: Cancer and Aging Research Group; OR: odds ratio; GI: gastrointestinal; GU: genitourinary; IADL: instrumental activities of daily living; MOS: Medical Outcomes Study.

From: Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011; 29:3457. Reprinted with permission.

Chimiothérapie vs soins de confort

- Soins de confort exclusifs
  - Médiane de survie 5-6 mois
- Chimiothérapie à l'ère de l'oxaliplatin et de l'irinotécan
  - Médiane de survie 30 mois

Quels traitements offrir à nos patients?

- 5FU
- Oxaliplatin
- Irinotecan
- Bevacizumab
- Cetuximab/Panitumumab
- Dabrafenib/Encorafenib/Vemurafenib ± Trametinib/Binimetinib
- Regorafenitb
- Trifluridine-tipiracil
- Nivolumab ± Ipilimumab/Pembrolizumab

- 5FU - fluoropyrimidine
  - Antimétabolite
  - Effet cytotoxique
- Irinotecan – inhibiteur de la topoisomérase I
  - Amène un bris de l'ADN simple brin empêchant la réplication de l'ADN
- Oxaliplatin – platins
  - Mécanisme d'action ± bien élucidé encore
  - Effet cytotoxique, inhibe la synthèse d'ADN

Effets secondaires – 5FU et capécitabine

- Syndrome main-pied
- Mucite
- Diarrhées
- Vasospasme coronarien

- Au Québec, dépistage variant de l'enzyme DPDY*2A recommandé d'emblée
  - Optionnel en Europe et aux États-Unis

Effets secondaires - irinotecan

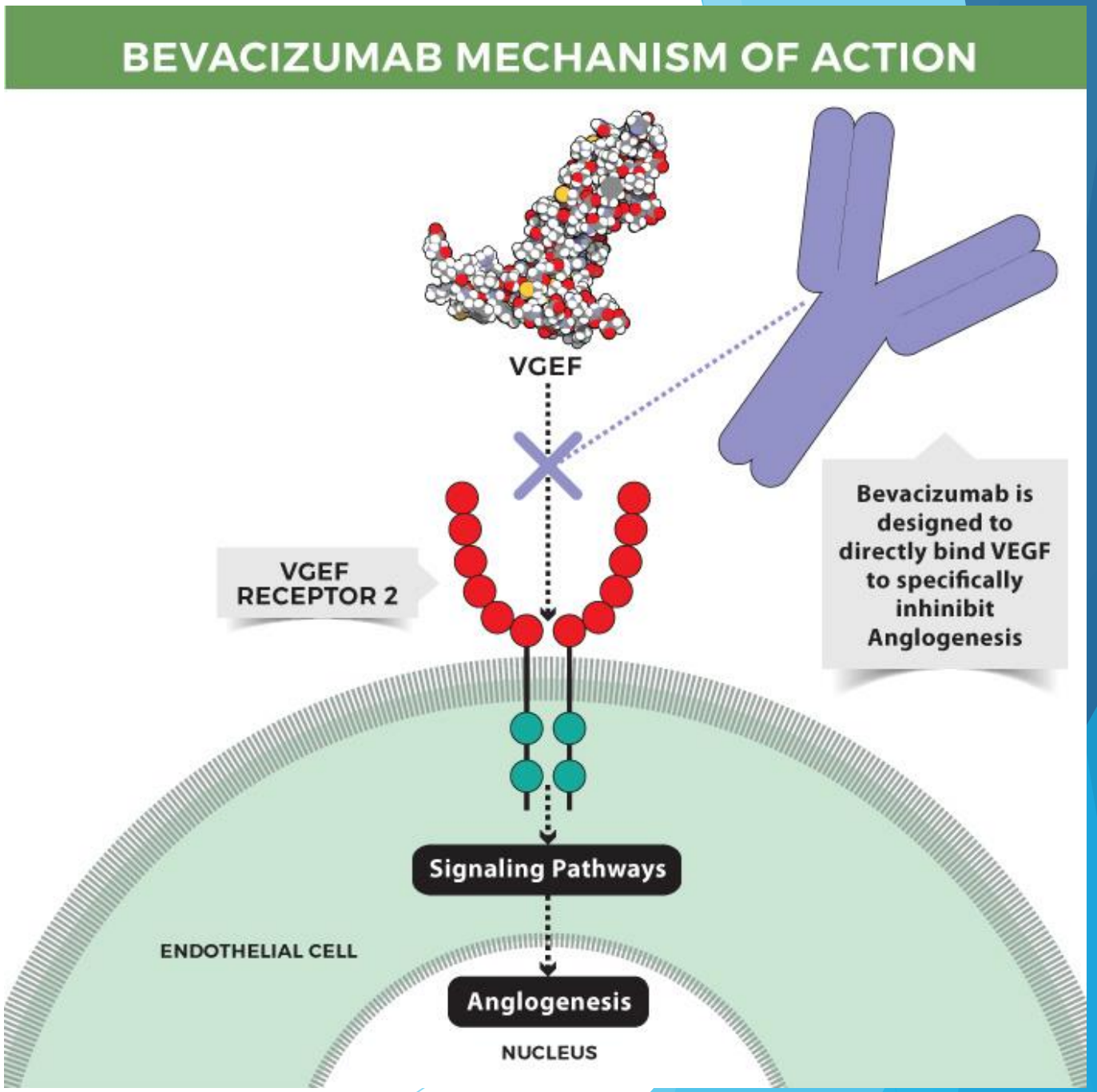
- Diarrhées
- Alopécie
- Neutropénie
- Pas de toxicité cumulative

- Attention au syndrome de Gilbert qui ont un variant de l'enzyme UGT1A1

Effets secondaires - oxaliplatin

- Neutropénie, thrombopénie
- Neuropathie sensitive
  - Effet cumulatif
  - Plus fréquent une fois dose cumulative de 680 mg/m^2 atteinte, donc post 8 cycles de FOLFOX6m

- Bevacizumab – anticorps monoclonal
  - Dirigé vers le récepteur Vascular Endothelial Growth Factor
  - Inhibiteur de l'angiogenèse



Effets secondaires - bevacizumab

- Hypertension
- Protéinurie
- Thrombose artérielle
- Hémorragie
- Microperforation intestinale

- Contre-indications
  - Maladie artérielle thrombotique (AVC, infarctus, etc) < 6 à 12 mois
  - Attendre guérison des plaies si chirurgie (minimum 28 jours)
  - Histoire récente de saignement, surtout si hémoptysies
  - Métastases cérébrales?

Traitements de 1ère ligne

- L'importance du doublet
- FOLFIRI ou FOLFOX?

Annals of Oncology 27: 1539–1546, 2016
doi:10.1093/annonc/mdw206
Published online 13 May 2016

Randomized phase III study of bevacizumab plus FOLFIRI and bevacizumab plus mFOLFOX6 as first-line treatment for patients with metastatic colorectal cancer (WJOG4407G)

FOLFIRI-A vs FOLOFOX6m-A

- 402 patients enrôlés
- PFS
  - FOLFIRI-A 12,1 mois
  - FOLFOX6m-A 10,7 mois
- OS
  - FOLFIRI-A 31,4 mois
  - FOLFOX6m-A 30,1 mois
- RR
  - FOLFIRI-A 64%
  - FOLFOX6m-A 62%

Et si le patient refuse la pose d'un cathéter central?

- Pouvons-nous modifier le 5FU et perfusion continue par la capécitabine?

VOLUME 26 · NUMBER 12 · APRIL 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Study of Capecitabine Plus Oxaliplatin Compared With Fluorouracil/Folinic Acid Plus Oxaliplatin As First-Line Therapy for Metastatic Colorectal Cancer

Jim Cassidy, Stephen Clarke, Eduardo Díaz-Rubio, Werner Scheithauer, Arie Figer, Ralph Wong, Sheryl Koski, Mikhail Lichinitser, Tsai-Shen Yang, Fernando Rivera, Felix Couture, Florin Sirzén, and Leonard Saltz

- 2034 patients
- PFS
  - FOLFOX 8,5 mois
  - XELOX 8,0 mois
- OS
  - FOLFOX 19,6 mois
  - XELOX 19,8 mois
- Effets secondaires
  - FOLFOX plus de neutropénie/neutropénie fébrile
  - XELOX plus de diarrhées et de syndrome main-pied

British Journal of Cancer (2012) 106, 453–459

www.bjcancer.com

Randomised phase-II trial of CAPIRI (capecitabine, irinotecan) plus bevacizumab *vs* FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) plus bevacizumab as first-line treatment of patients with unresectable/metastatic colorectal cancer (mCRC)

- 333 patients
- PFS
  - FOLFIRI-A 10,0 mois
  - CAPIRI-A 8,9 mois
- OS
  - FOLFIRI-A 25,7 mois
  - CAPIRI-A 27,5 mois
- Effets secondaires
  - Plus de diarrhées, syndrome main-pied, neutropénie fébrile, retard de traitement et diminution de dose avec CAPIRI

Quelle est la place des anticorps monoclonaux?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 3, 2004 VOL. 350 NO. 23

Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer

Herbert Hurwitz, M.D., Louis Fehrenbacher, M.D., William Novotny, M.D., Thomas Cartwright, M.D., John Hainsworth, M.D., William Heim, M.D., Jordan Berlin, M.D., Ari Baron, M.D., Susan Griffing, B.S., Eric Holmgren, Ph.D., Napoleone Ferrara, M.D., Gwen Fyfe, M.D., Beth Rogers, B.S., Robert Ross, M.D., and Fairooz Kabbinavar, M.D.

- 813 patients
- PFS
  - IFL 6,2 mois
  - IFL + A 10,6 mois
- OS
  - IFL 15,6 mois
  - IFL + A 20,3 mois
- RR
  - IFL 34,8 %
  - IFL + A 44,8 %

Et si on ajoute un peu de biologie moléculaire à l'équation?

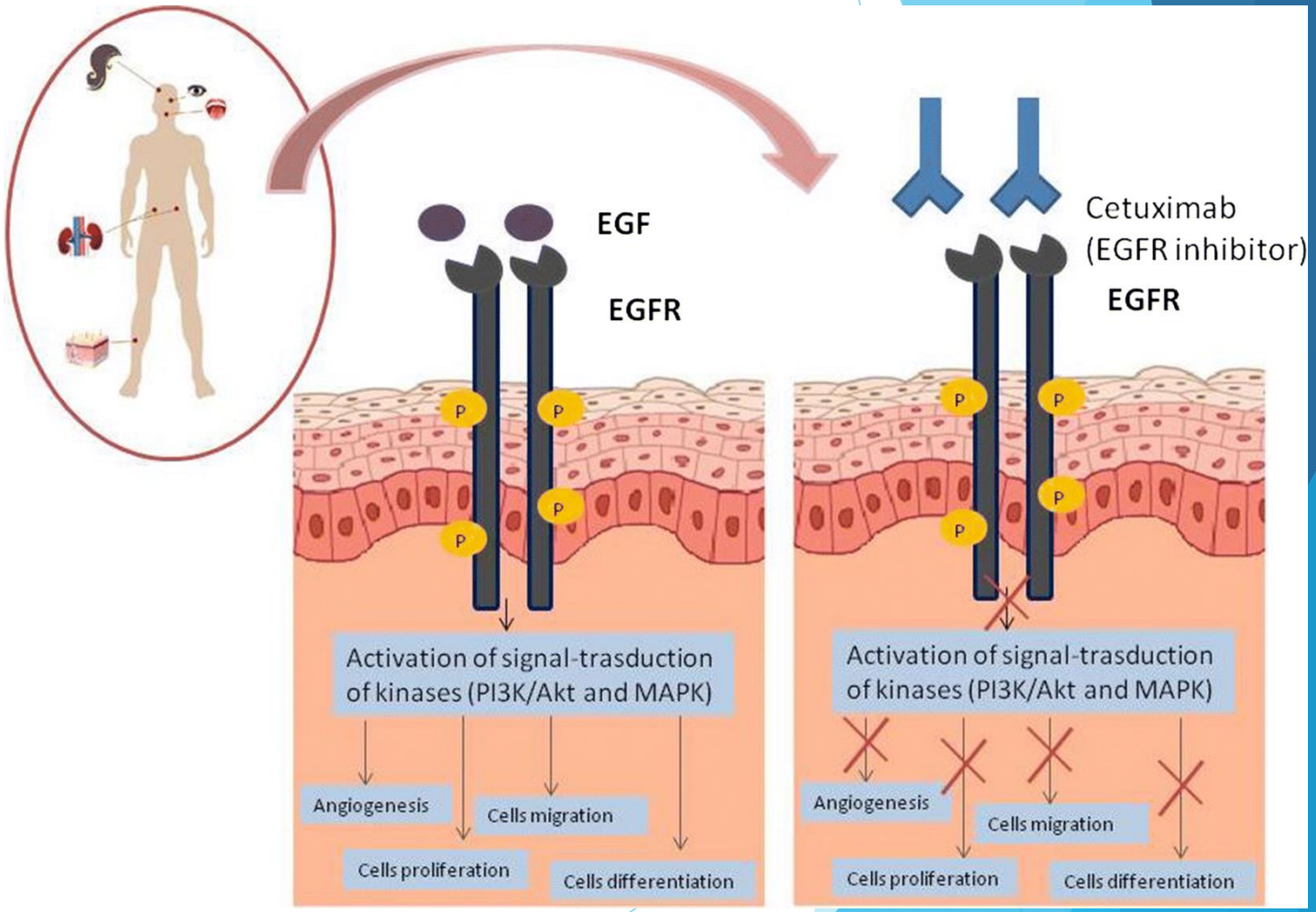
- Pour les patients RAS/BRAF non mutés?

FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final *RAS* wild-type subgroup of this randomised open-label phase 3 trial

Sebastian Stintzing, Dominik P Modest, Lisa Rossius, Markus M Lerch, Ludwig Fischer von Weikersthal, Thomas Decker, Alexander Kiani, Ursula Vehling-Kaiser, Salah-Eddin Al-Batran, Tobias Heintges, Christian Lerchenmüller, Christoph Kahl, Gernot Seipelt, Frank Kullmann, Martina Stauch, Werner Scheithauer, Swantje Held, Clemens Giessen-Jung, Markus Moehler, Andreas Jagenburg, Thomas Kirchner, Andreas Jung, Volker Heinemann, on behalf of the FIRE-3 investigators

Cetuximab/Panitumumab

- Anticorps monoclonaux dirigés vers Epidermal Growth Factor Receptor



Effets secondaires

- Cutanés
  - Érythème, prurit, rash acnéiforme, dermite exfoliative, paronychie
- Diarrhées
- Nausées, vomissements
- Hypomagnésémie
- Réactions infusionnelles: cetuximab > panitumumab

- ximab… chimérique
- umab… humain

- 400 patients
- PFS
  - FOLFIRI-A 10,2 mois
  - FOLFIRI-C 10,3 mois
- OS
  - FOLFIRI-A 25,0 mois — côlon gauche 28 mois — côlon droit 23 mois
  - FOLFIRI-C 33,1 mois — côlon gauche 38 mois — côlon droit 18,3 mois
- RR
  - FOLFIRI-A 56%
  - FOLFIRI-C 72%

On traite combien de temps?

VOLUME 24 · NUMBER 3 · JANUARY 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

OPTIMOX1: A Randomized Study of FOLFOX4 or FOLFOX7 With Oxaliplatin in a Stop-and-Go Fashion in Advanced Colorectal Cancer—A GERCOR Study

Christophe Tournigand, Andres Cervantes, Arie Figer, Gérard Lledo, Michel Flesch, Marc Buyse, Laurent Mineur, Elisabeth Carola, Pierre-Luc Etienne, Fernando Rivera, Isabel Chirivella, Nathalie Perez-Staub, Christophe Louvet, Thierry André, Isabelle Tabah-Fisch, and Aimery de Gramont

- 620 patients
- PFS
  - FOLFOX4 9,0 mois
  - FOLFOX7 8,7 mois
- OS
  - FOLFOX4 19,3 mois
  - FOLFOX7 21,2 mois
- RR
  - FOLFOX4 58,5%
  - FOLFOX7 59,2%
- Neuropathie sensitive
  - FOLFOX4 17,9%
  - FOLFOX7 13,3%

Choisir une deuxième ligne

FOLFOX  FOLFIRI

Bevacizumab  Cetuximab/Panitumumab

(si RAS/BRAF non mutés)

Choisir une troisième ligne

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cetuximab for the Treatment of Colorectal Cancer

Derek J. Jonker, M.D., Chris J. O'Callagh
John R. Zalcberg, M.D., Dongsheng
Scott R. Berry, M.D., Marianne K
R. John Simes, M.D., Niall C. Teb
Rafal Wierzbicki, M.D., Christiane Lang

VOLUME 25 · NUMBER 13 · MAY 1 2007

JOURNAL OF CLINICAL ONCOLOGY

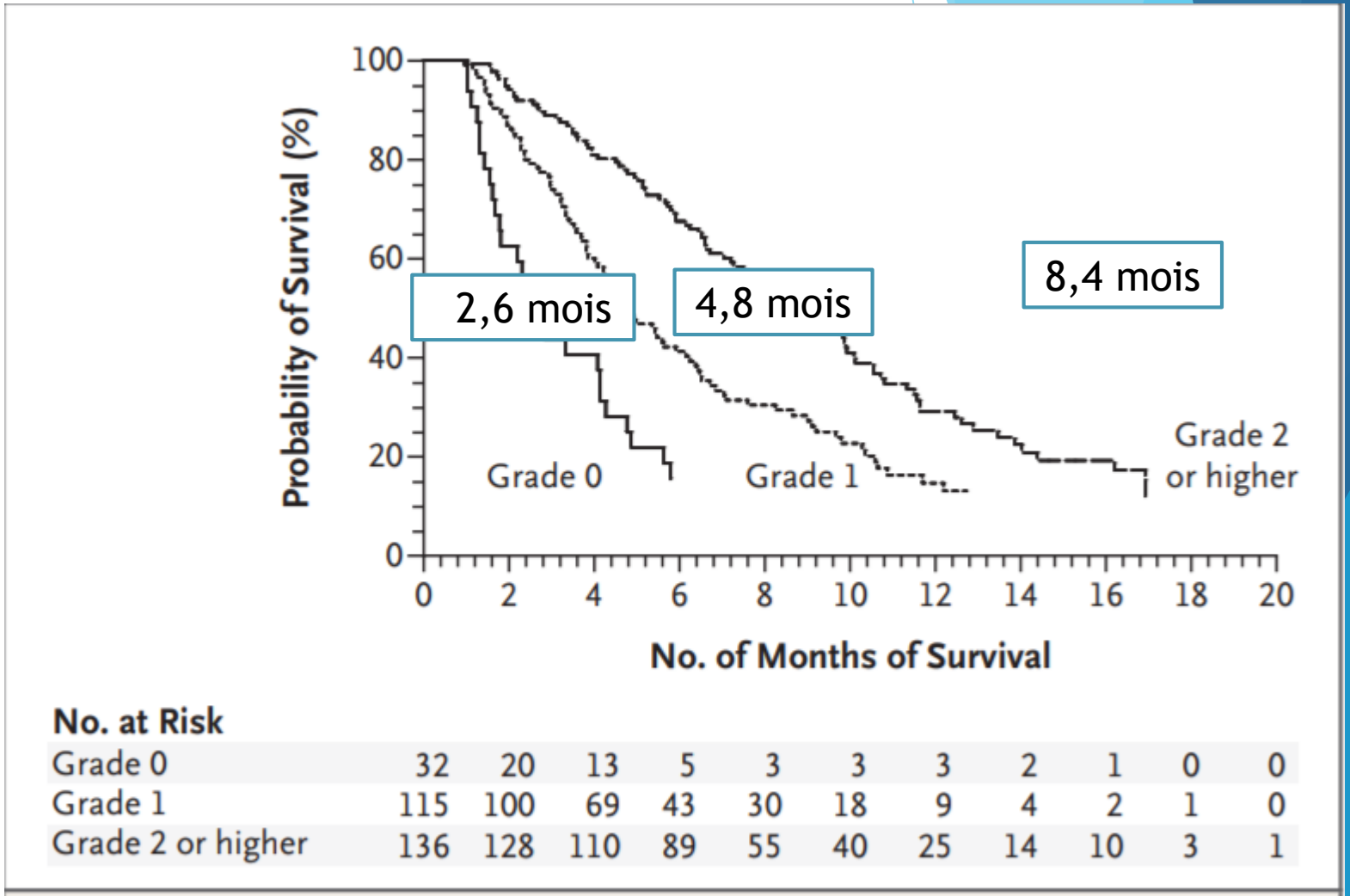
ORIGINAL REPORT

Open-Label Phase III Trial of Panitumumab Plus Best Supportive Care Compared With Best Supportive Care Alone in Patients With Chemotherapy-Refractory Metastatic Colorectal Cancer

Eric Van Cutsem, Marc Peeters, Salvatore Siena, Yves Humblet, Alain Hendlisz, Bart Neyns, Jean-Luc Canon, Jean-Luc Van Laethem, Joan Maurel, Gary Richardson, Michael Wolf, and Rafael G. Amado

Cetuximab vs soins de confort

- 572 patients
- OS
  - Cetuximab 6,1 mois
  - Soins de confort 4,6 mois



No. at Risk											
Grade 0	32	20	13	5	3	3	3	2	1	0	0
Grade 1	115	100	69	43	30	18	9	4	2	1	0
Grade 2 or higher	136	128	110	89	55	40	25	14	10	3	1

Figure 3. Overall Survival According to the Worst Grade of Rash in the Cetuximab Group.

- RR 22,9% vs 10,8%
- Temps médian à la progression
  - 4,1 mois vs 1,5 mois
- Temps médian de survie
  - 8,6 mois vs 6,9 mois

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cetuximab Monotherapy and Cetuximab plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer

David Cunningham, M.D., Yves Humblet, M.D., Ph.D., Salvatore Siena, M.D., David Khayat, M.D., Ph.D., Harry Bleiberg, M.D., Ph.D., Armando Santoro, M.D., Danny Bets, M.Sc., Matthias Mueser, M.D., Andreas Harstrick, M.D., Chris Verslype, M.D., Ph.D., Ian Chau, M.B., B.S., and Eric Van Cutsem, M.D., Ph.D.

Si RAS non muté / BRAF muté

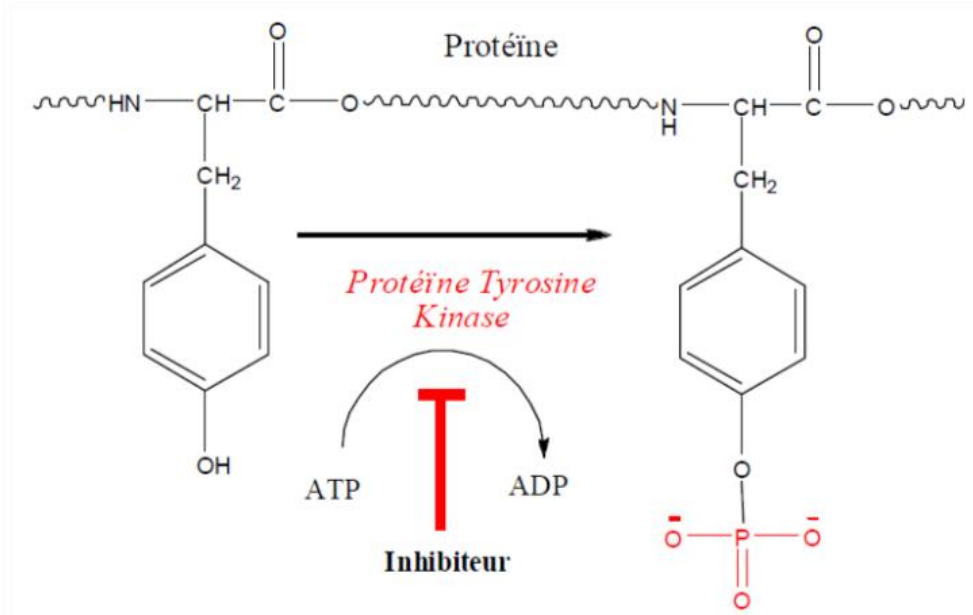
ORIGINAL ARTICLE

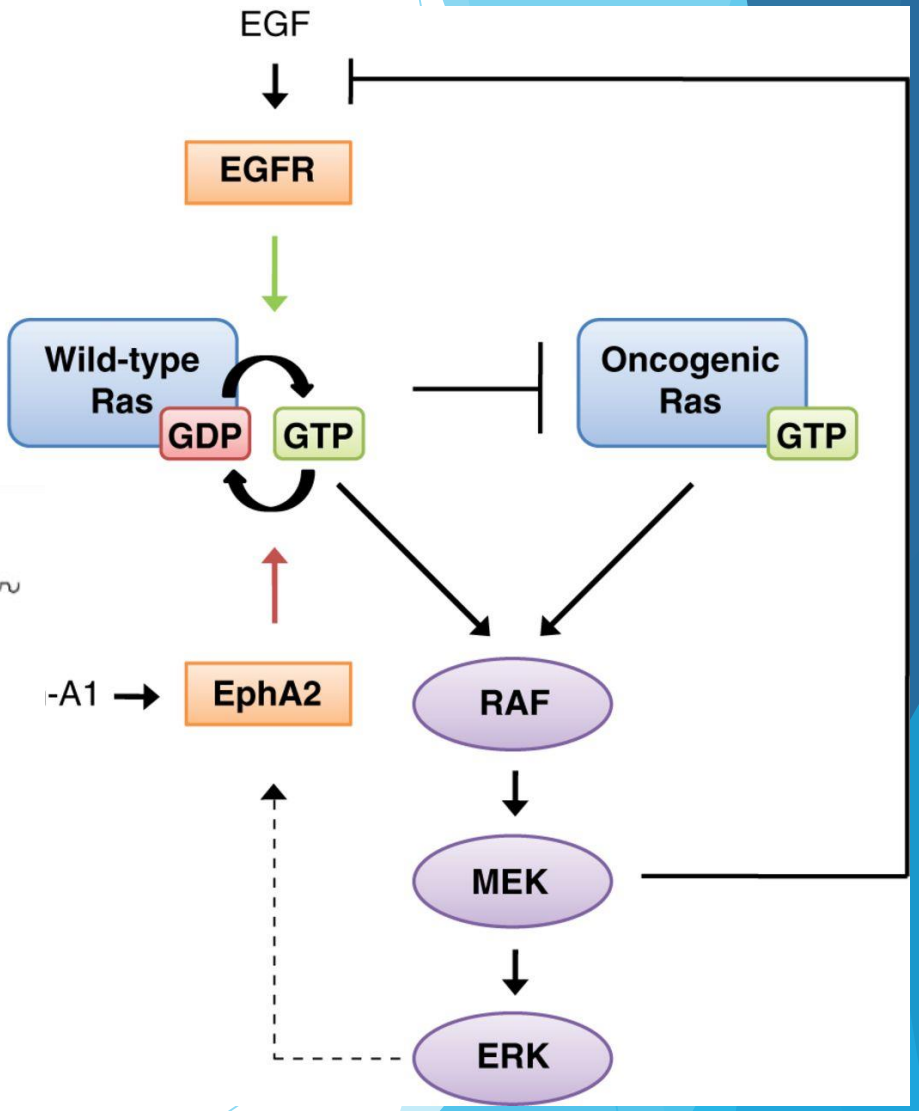
Encorafenib, Binimetinib, and Cetuximab in *BRAF* V600E–Mutated Colorectal Cancer

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

Inhibiteurs de tyrosine kinase EGFR

- Inhibiteurs BRAF
  - Dabrafenib
  - Vemurafenib
  - Encorafenib
- Inhibiteurs MEK
  - Trametinib
  - Cobimetinib
  - Binimetinib
- Combinaisons





Effets secondaires

Anti-BRAF

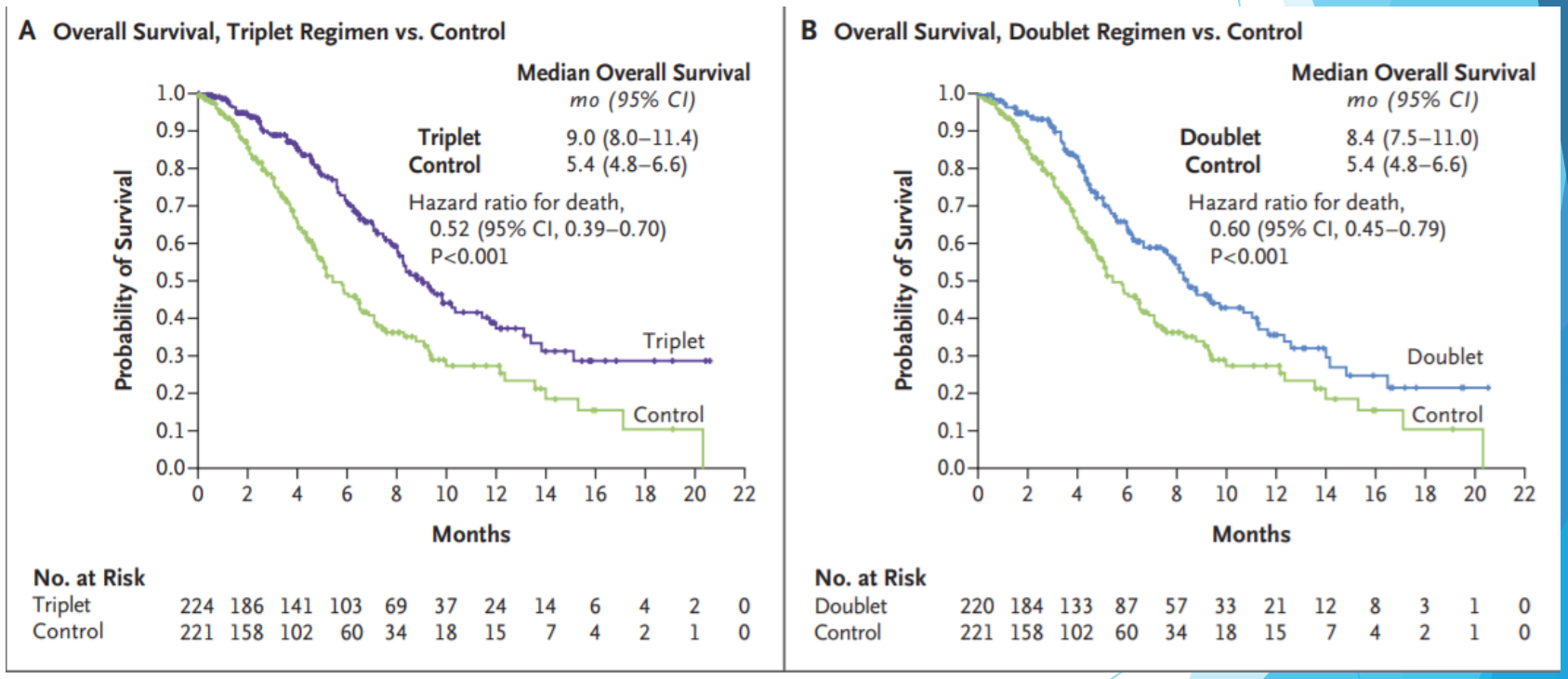
- Cutanés
  - Rash
  - Photosensibilité
  - Hyperkératose
- Arthrite
- Fatigue
- Nausées
- Diarrhées
- Tumeurs secondaires: kératoacanthomes

Anti-MEK

- Idem aux anti-BRAF
- Diminution FEVG
- Rétinopathie
- Diminuerait le risque de tumeurs cutanées en combinaison

Triplet – encorafenib, binimetinib, cetuximab
Doublet – encorafenib, cetuximab
Traitement standard (irino-c ou FOLFIRI-c)

- OS
  - Triplet 9,0 mois
  - Doublet 8,4 mois
  - Standard 5,4 mois
- RR 26% vs 20% vs 2%

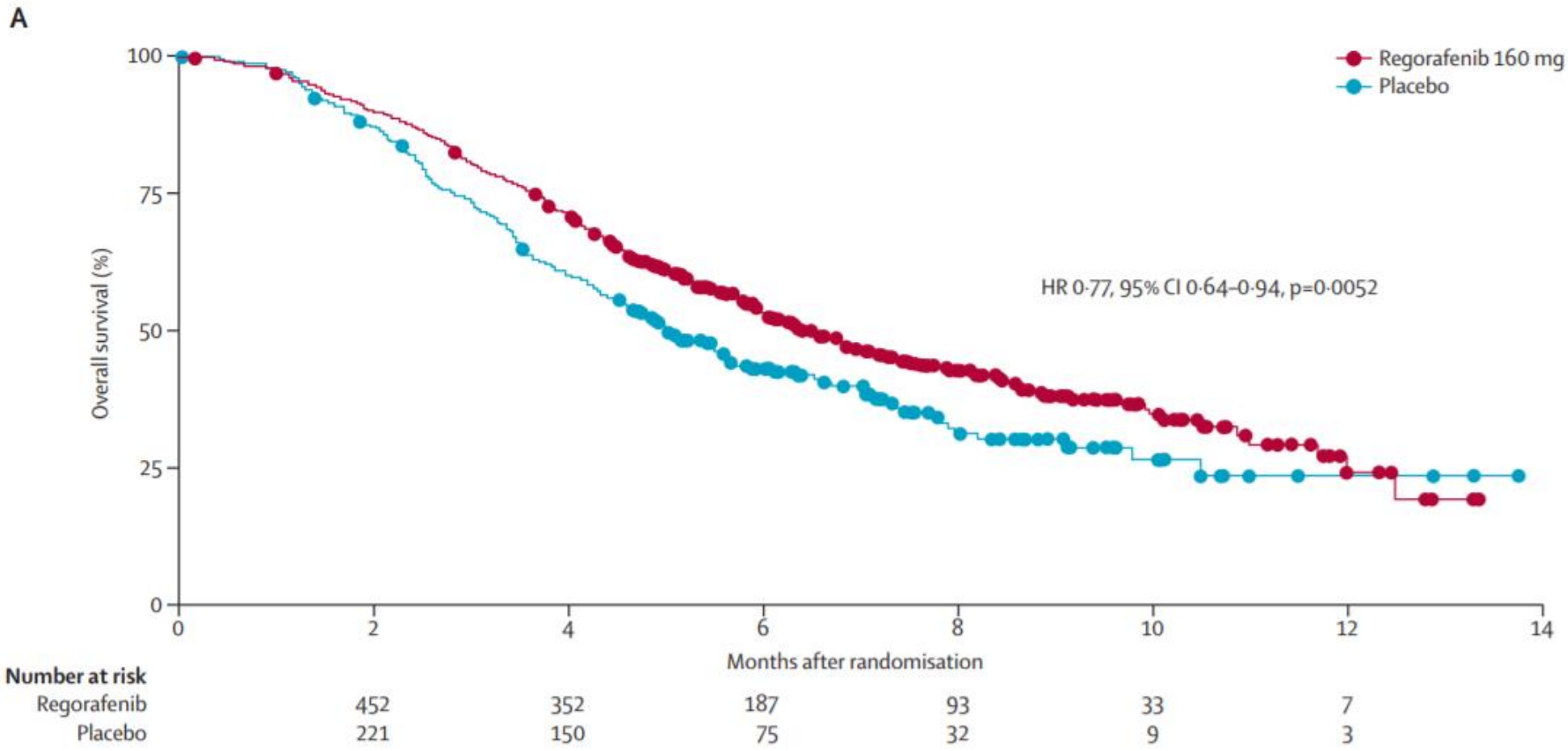


Inhibiteur de tyrosine kinase VEGFR

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†*

- 760 patients
- OS
  - Regorafenib 6,4 mois
  - Placebo 5,0 mois
- Effets secondaires
  - Fatigue
  - Syndrome main-pied, rash, mucite
  - Diarrhées
  - Anorexie, nausées
  - Hypertension



Trifluridine-tipiracil
Antimétabolites

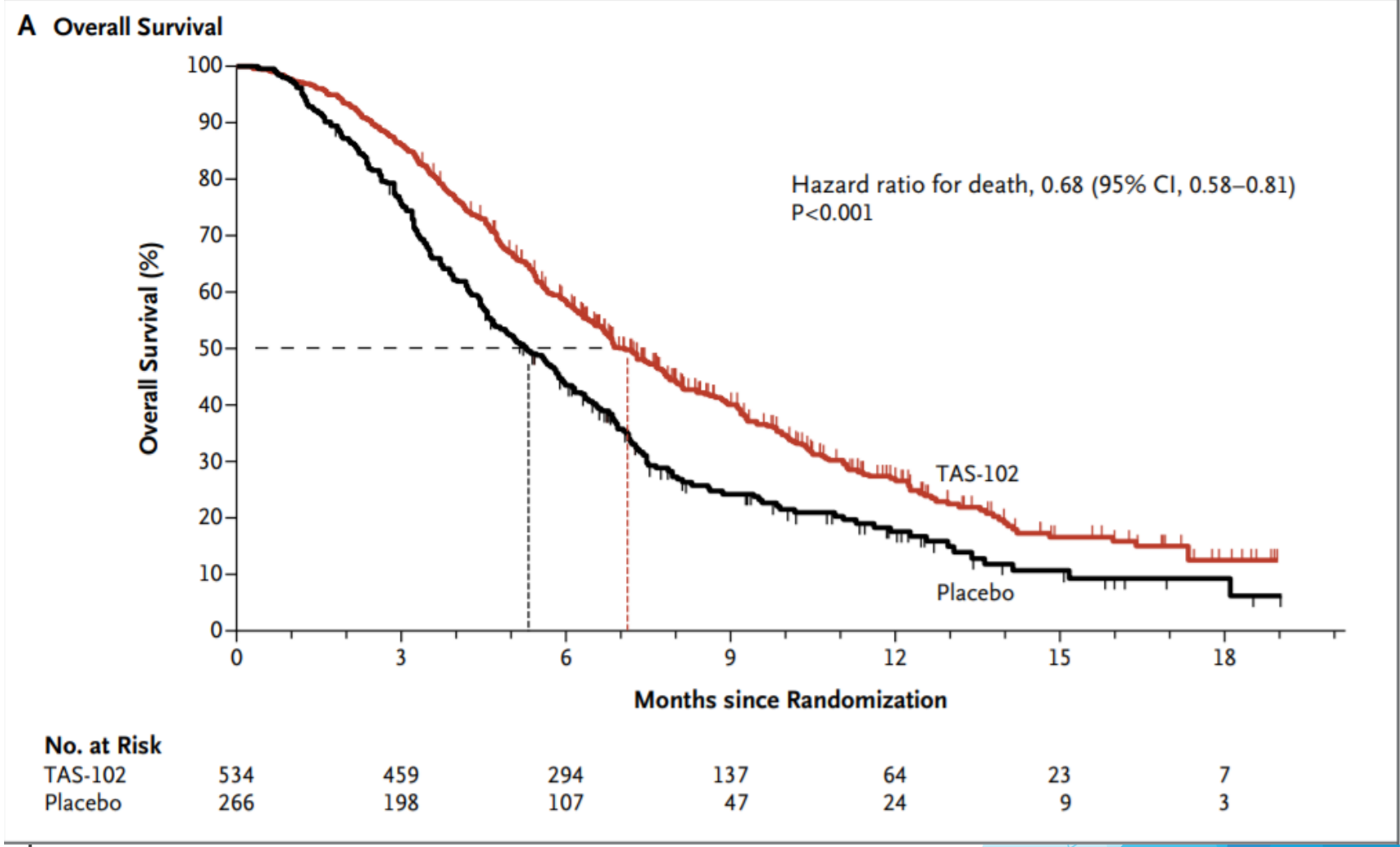
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer

Robert J. Mayer, M.D., Eric Van Cutsem, M.D., Ph.D., Alfredo Falcone, M.D., Takayuki Yoshino, M.D., Rocio Garcia-Carbonero, M.D., Ph.D., Nobuyuki Mizunuma, M.D., Ph.D., Kentaro Yamazaki, M.D., Yasuhiro Shimada, M.D., Josep Tabernero, M.D., Ph.D., Yoshito Komatsu, M.D., Ph.D., Alberto Sobrero, M.D., Eveline Boucher, M.D., Marc Peeters, M.D., Ph.D., Ben Tran, M.B., B.S., Heinz-Josef Lenz, M.D., Alberto Zaniboni, M.D., Howard Hochster, M.D., James M. Cleary, M.D., Hans Prenen, M.D., Ph.D., Fabio Benedetti, M.D., Hirokazu Mizuguchi, M.S., Lukas Makris, Ph.D., Masanobu Ito, M.S., and Atsushi Ohtsu, M.D., Ph.D., for the RECOURSE Study Group*

- 800 patients
- OS
  - TAS-102 7,1 mois
  - Placebo 5,3 mois
- Effets secondaires
  - Cytopénies
  - Nausées, vomissements
  - Diarrhées, douleur abdominale
  - Fatigue



Et les patients avec instabilités microsatellitaires?

Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study

Michael J Overman, Ray McDermott, Joseph L Leach, Sara Lonardi, Heinz-Josef Lenz, Michael A Morse, Jayesh Desai, A Rebecca A Moss, Monica V Goldberg, Z Alexander Cao, Jean-Marie Ledeine, Gregory A Maglinte, Scott Kopetz, Thierry*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

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Nivolumab ± Ipilimumab in Treatment of Patients With Metastatic Colorectal Cancer With and Without High Microsatellite Instability: CheckMate 142 Interim Results

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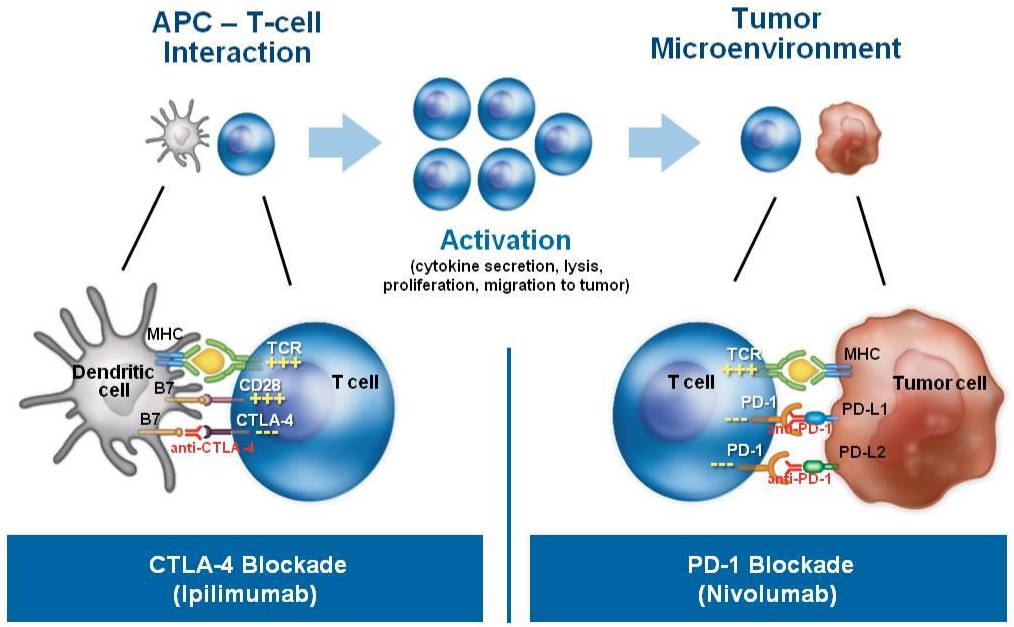
Ipilimumab and Nivolumab Mechanisms of Action

- PD-1 expression on TILs is associated with decreased cytokine production and effector function[1]
- Nivolumab is a fully human IgG4 immune checkpoint inhibitor antibody
  - Binds PD-1 receptors on T cells
  - Disrupts PD-L1/PD-L2 signaling to restore antitumor immunity[2-4]
- Nivolumab and the anti-CTLA-4 antibody, ipilimumab, enhance T-cell antitumor activity through distinct but complementary mechanisms[1-3,5]
- The combination of nivolumab and ipilimumab has demonstrated deep and durable responses in solid tumors[6,7]



1. Hamid O, et al. *Exp Opin Biol Ther.* 2013;13:847–861.
2. Brahmer JR, et al. *J Clin Oncol.* 2010;28:3167–3175.
3. Wang C, et al. *Cancer Immunol Res.* 2014;2:1–11.
4. Topalian SL, et al. *N Engl J Med.* 2012;366:2443–2454
5. Pardoll D, et al. *Nat Rev Cancer.* 2012;12:252-264.
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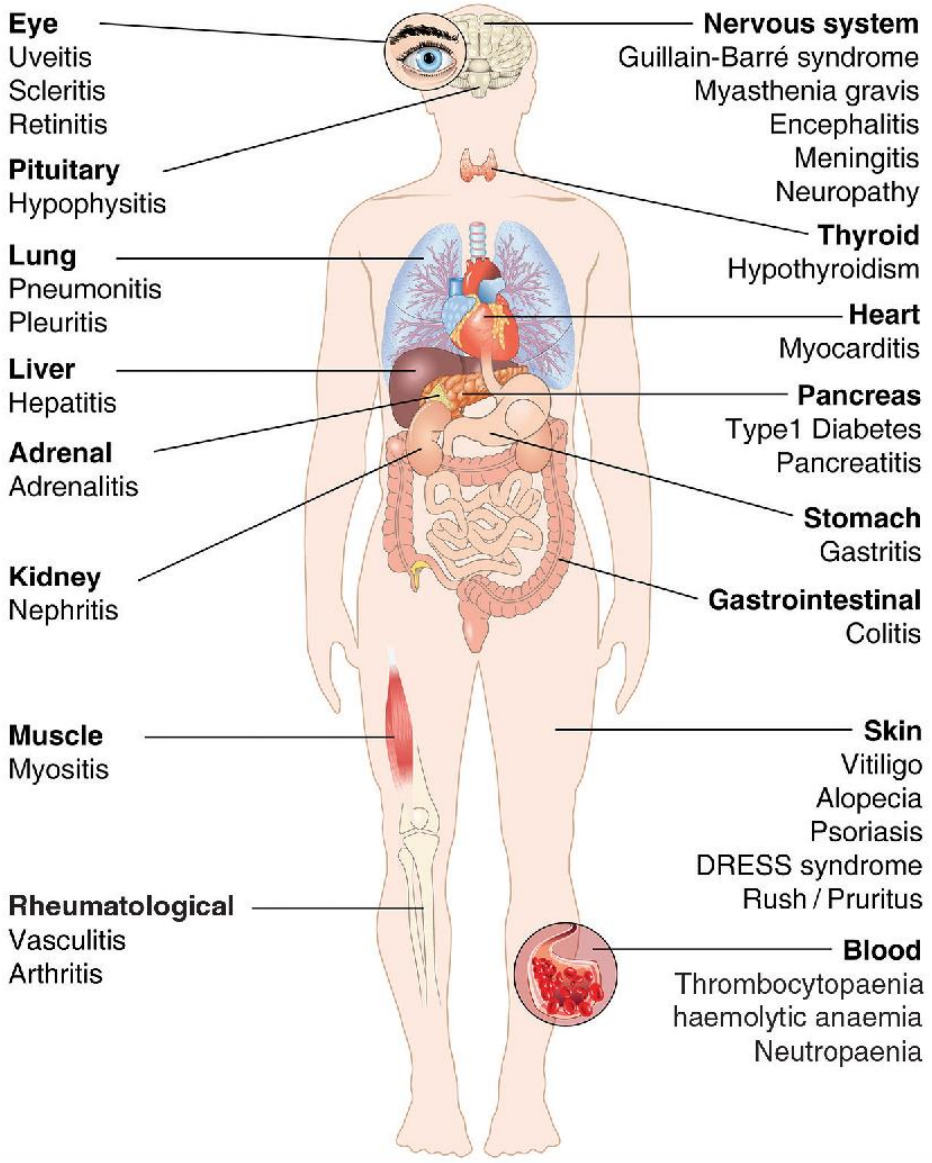
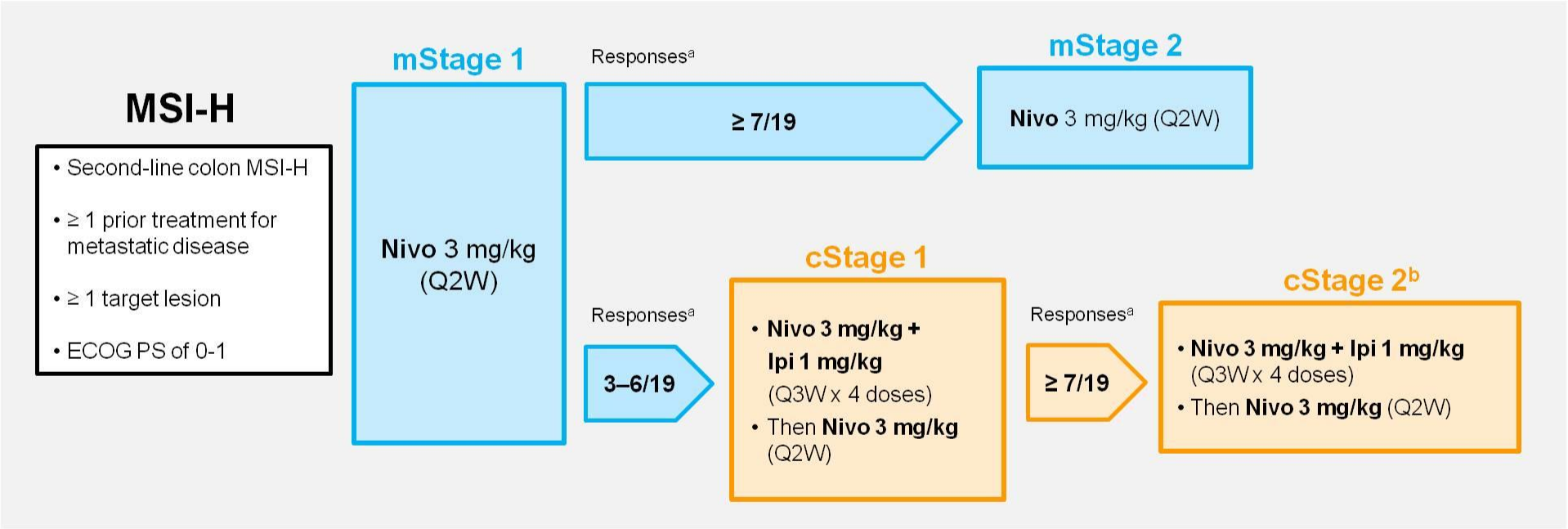
7. Postow MA, et al. *N Engl J Med.* 2015;372:2006–2017.

APC = antigen-presenting cell; MHC = major histocompatibility complex; TCR = T-cell receptor

Effets secondaires - immunothérapie

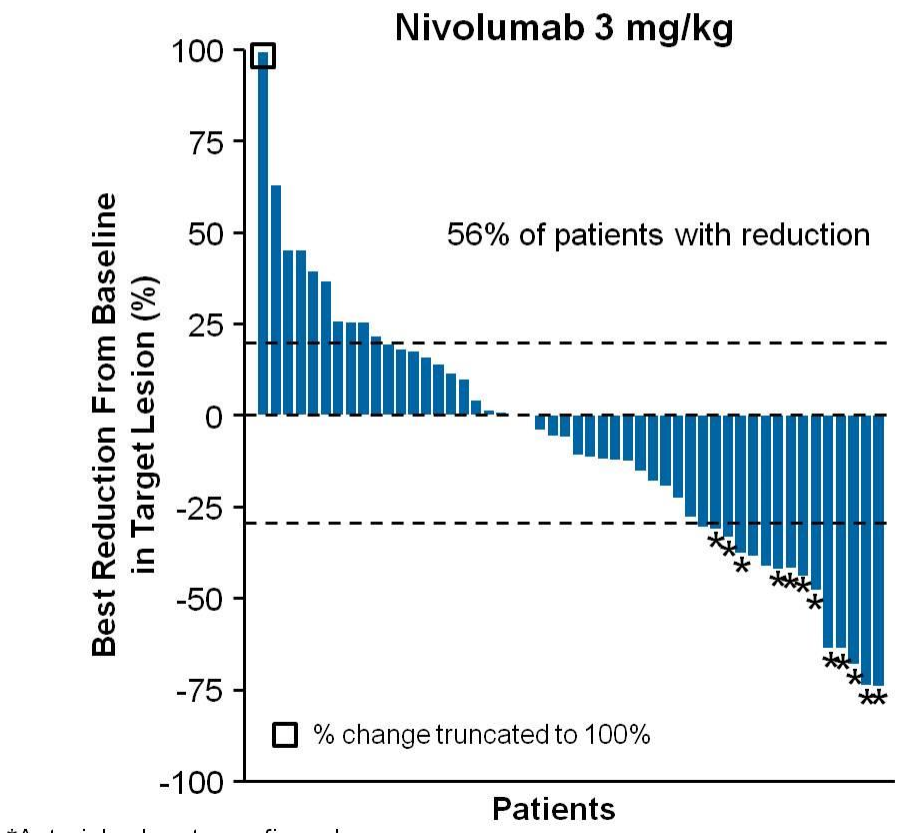


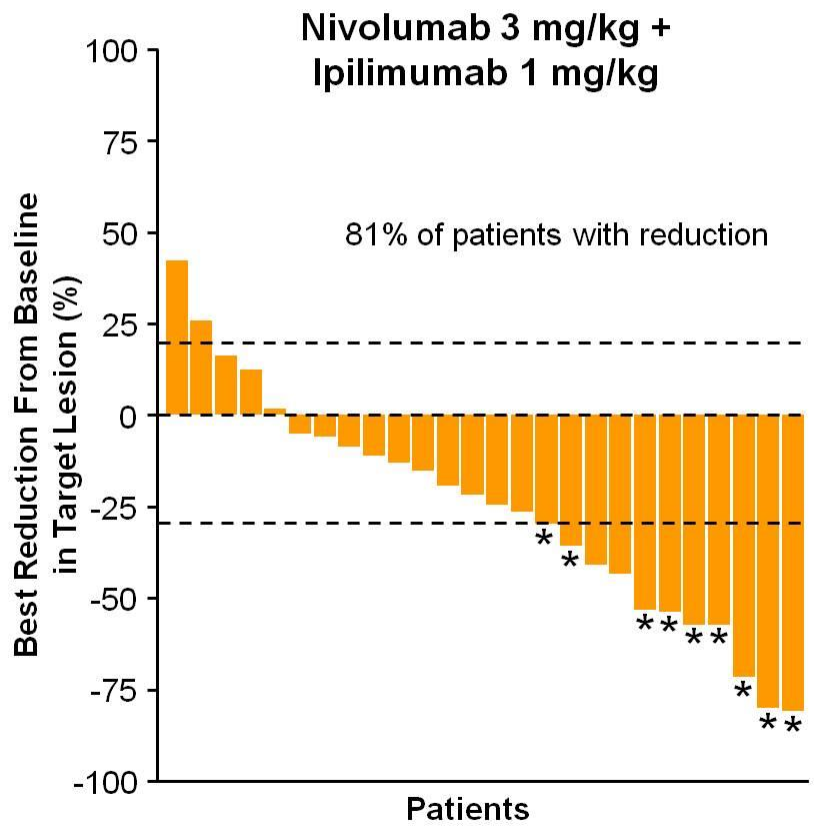
Phase 2 CheckMate 142 Study Design: MSI-H Cohort



[a]In patients with centrally confirmed MSI-H status
[b]Currently enrolling
cStage 1 = combination therapy stage 1; cStage 2 = combination therapy stage 2; Ipi = ipilimumab; mStage 1 = monotherapy stage 1; mStage 2 = monotherapy stage 2; Nivo = nivolumab; Q2W = every 2 weeks; Q3W = every 3 weeks

Best Reduction in Target Lesion Size in Patients With MSI-H



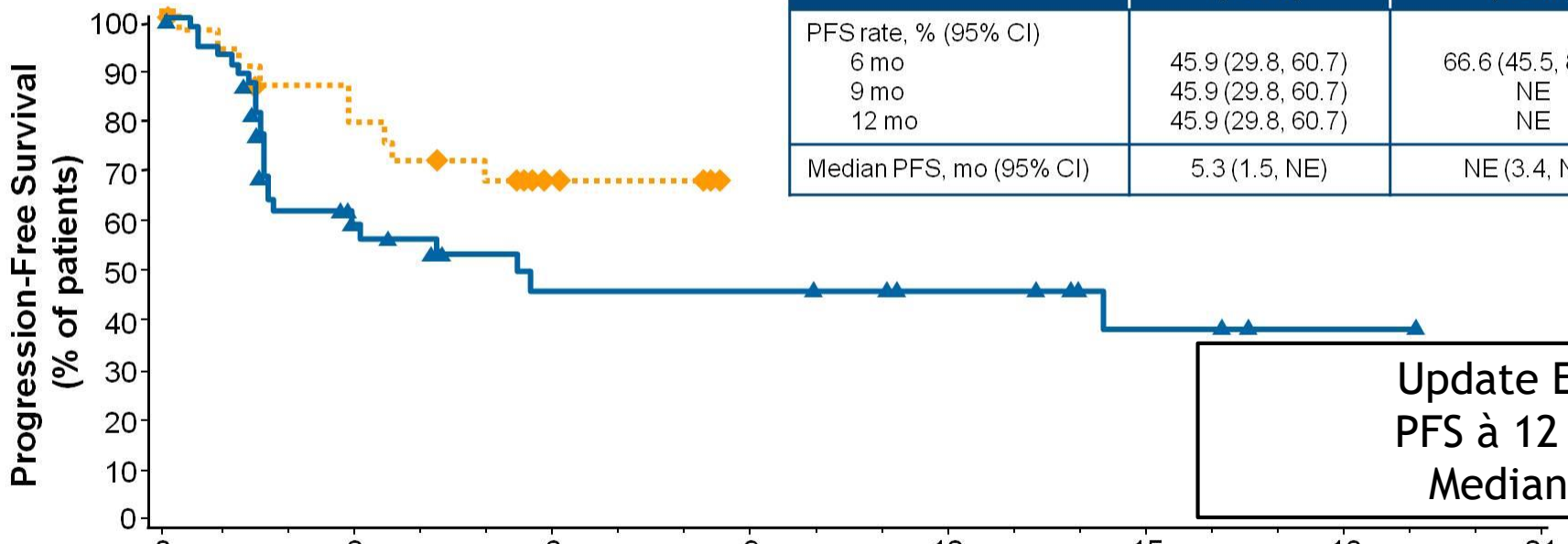


*Asterisks denote confirmed responses

Investigator-Assessed PFS in Patients With MSI-H

Nivolumab ± Ipilimumab in Metastatic CRC

	Nivolumab 3 mg/kg (n = 70)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 30)
PFS rate, % (95% CI)		
6 mo	45.9 (29.8, 60.7)	66.6 (45.5, 81.1)
9 mo	45.9 (29.8, 60.7)	NE
12 mo	45.9 (29.8, 60.7)	NE
Median PFS, mo (95% CI)	5.3 (1.5, NE)	NE (3.4, NE)



Update ESMO 2018
PFS à 12 mois: 77%
Median PFS: NE

No. at Risk								
Nivolumab	70	19	13	13	9	5	1	0
Nivolumab + Ipilimumab	30	21	7	0	0	0	0	0

NE = not estimable

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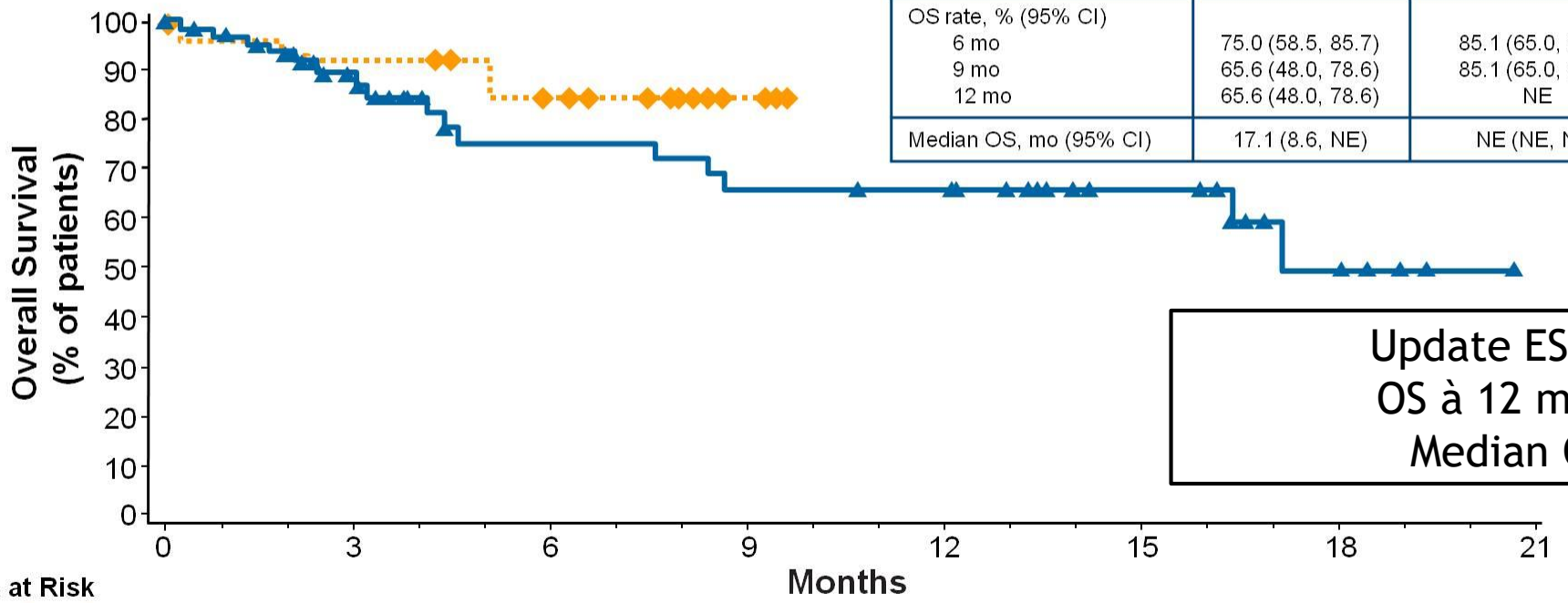
OS in Patients With MSI-H

Nivolumab ± Ipilimumab in Metastatic CRC

	Nivolumab 3 mg/kg (n = 70)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 30)
OS rate, % (95% CI)		
6 mo	75.0 (58.5, 85.7)	85.1 (65.0, 94.2)
9 mo	65.6 (48.0, 78.6)	85.1 (65.0, 94.2)
12 mo	65.6 (48.0, 78.6)	NE
Median OS, mo (95% CI)	17.1 (8.6, NE)	NE (NE, NE)



No. at Risk							
Nivolumab	70	34	24	21	20	12	5	0
Nivolumab + Ipilimumab	30	26	21	4	0	0	0	0

NE = not estimable

Update ESMO 2018
OS à 12 mois: 83%
Median OS: NE

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