Unmet Needs and the Relevance of VEGFR in mCRC Pathophysiology

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Conflict of Interest Disclosure

- **Consulting Role or Advisory Board:** Amgen, Astra Zeneca, BMS, Daiichi-Sankyo, Incyte, Lilly, Merck Serono, MSD, Servier, Takeda, Astella

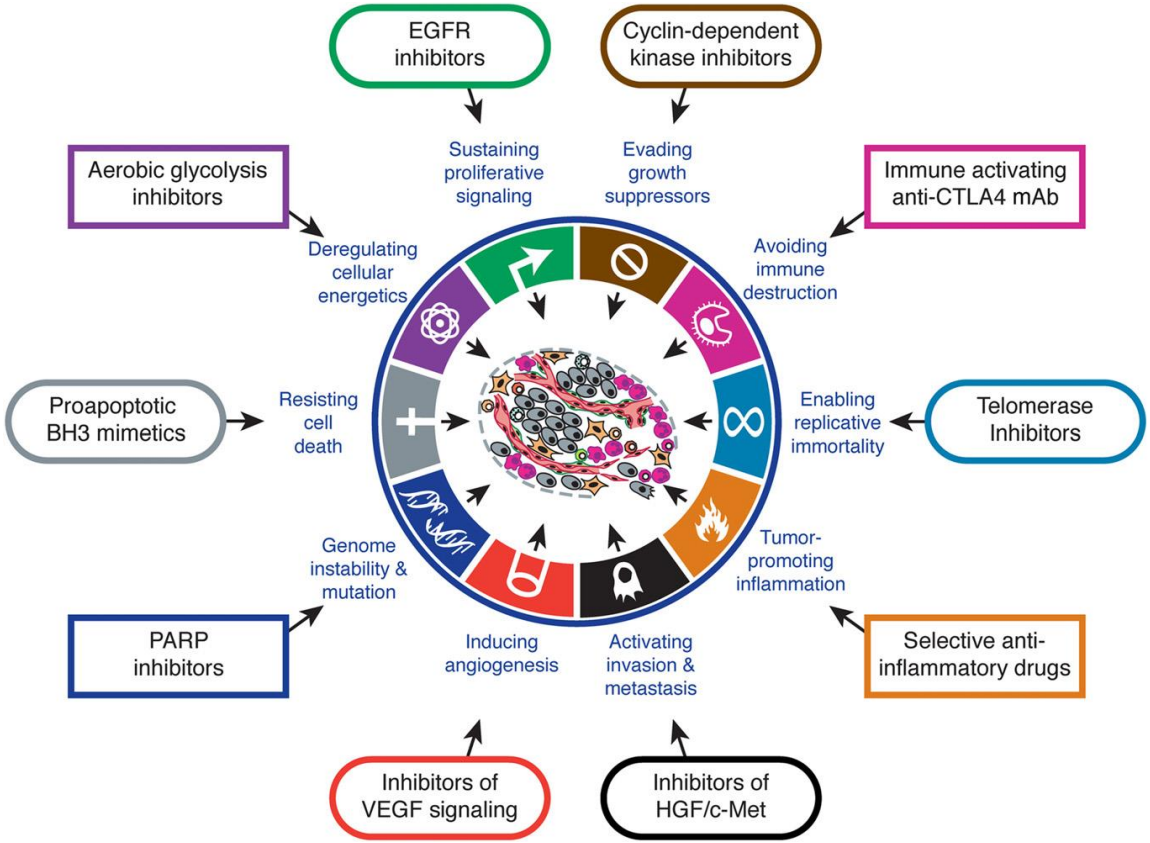
- **Speakers' Bureau:** Amgen, BMS, GSK, Lilly, Merck Serono, MSD, Pierre-Fabre, Roche, Servier

- **Research Funding:** Amgen, Astra Zeneca, Bayer, BMS, Lilly, Merck Serono, Roche

Unmet Needs in mCRC

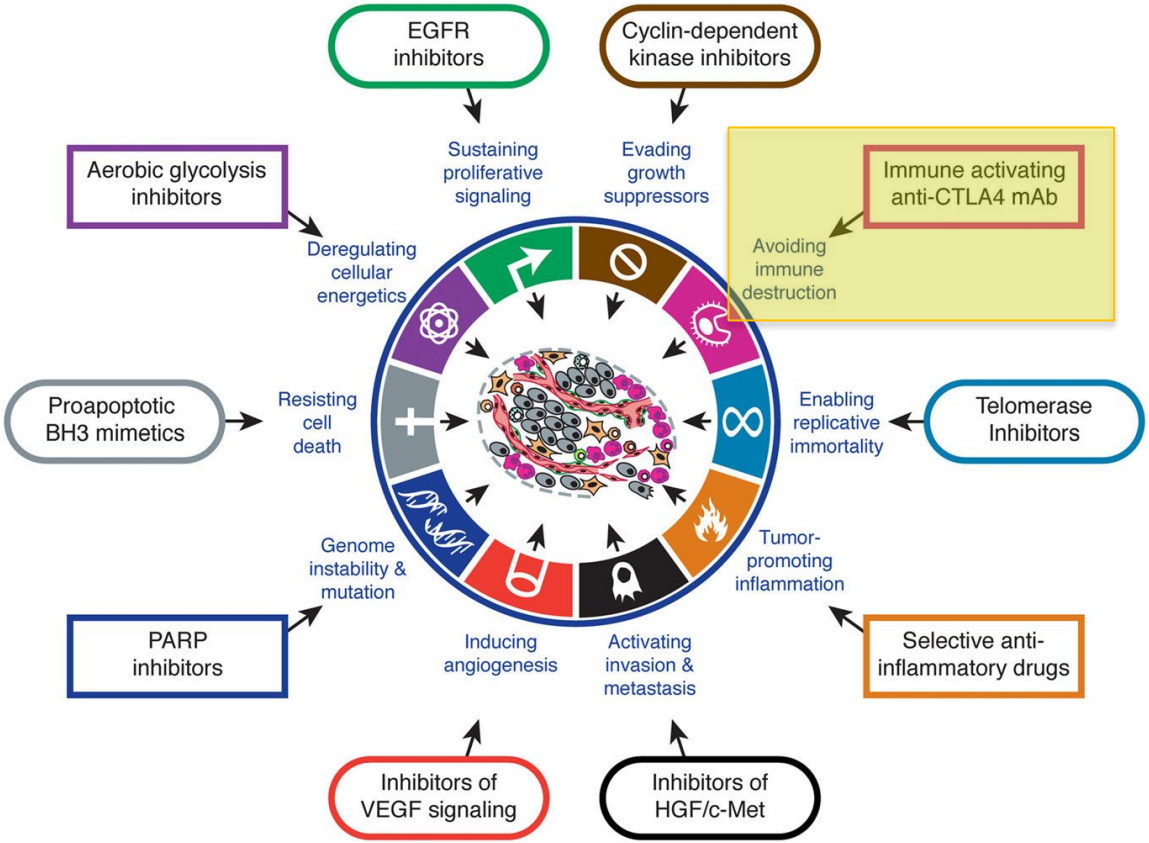
- **Except for MSI-H mCRC (~5%) treated with CPI, it is rare to completely cure advanced disease with current available therapies**
- **Survival prolongation and QoL maintenance are the goals of treatment**
- **A fine tuning of "biologics" combinations, chemo-intensity, sequence of therapies is the key to obtain the maximum benefit**

Biologics Combination



Hanahan D and Weinberg RA. *Cell.* 2011;144(5):646-674.

Biologics Combination



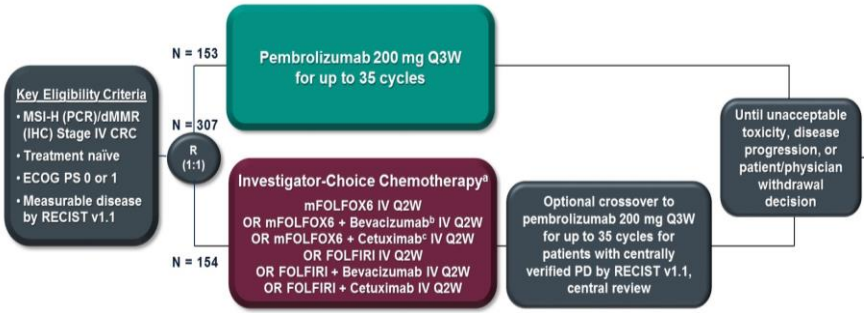
Hanahan D and Weinberg RA. *Cell.* 2011;144(5):646-674.

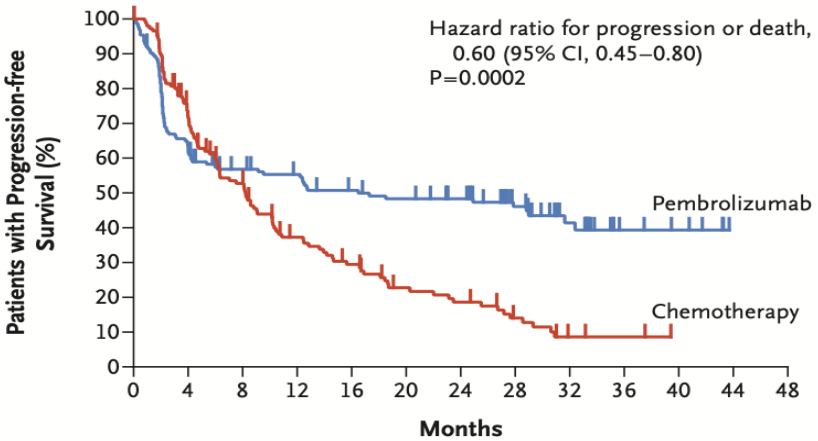
MSI-H mCRC, First Line, Pembrolizumab

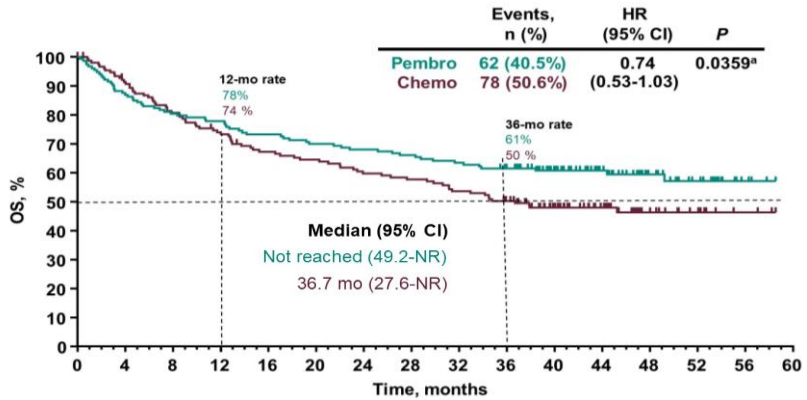
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 3, 2020 VOL. 383 NO. 23

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators*







André T et al. *N Engl J Med.* 2020;383(23):2207-2218.

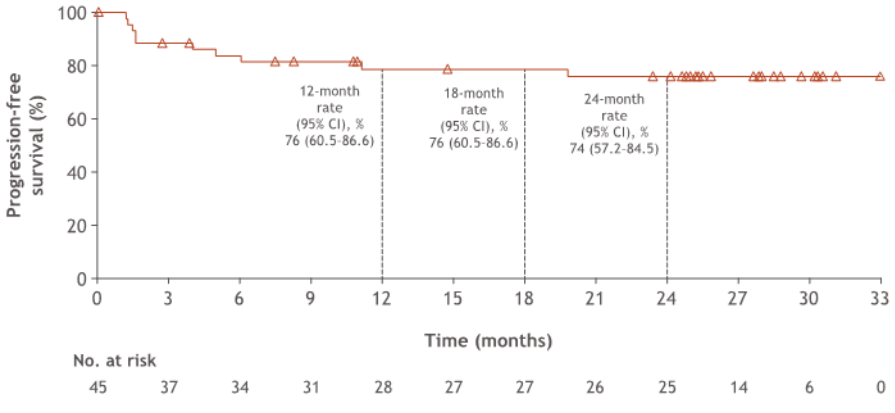
MSI-H mCRC, First Line, Nivolumab + Ipilimumab

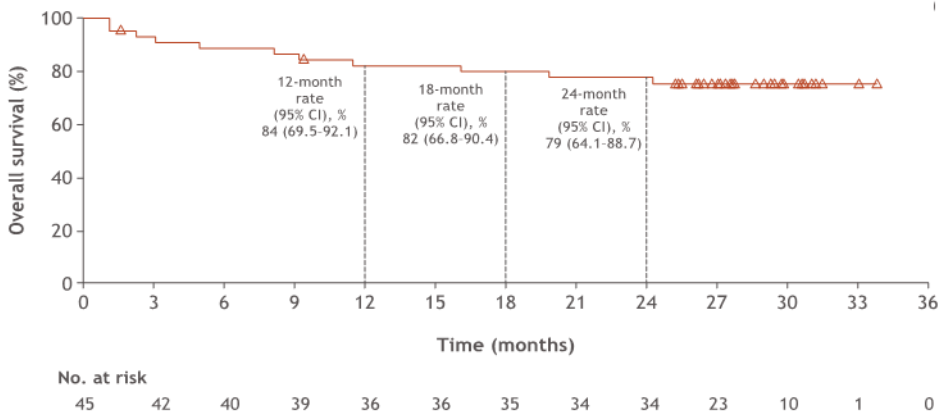
Journal of Clinical Oncology®

First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/ Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study

Heinz-Josef Lenz, MD[1]; Eric Van Cutsem, MD, PhD[2]; Maria Luisa Limon, MD[3]; Ka Yeung Mark Wong, PhD[4]; Alain Hendlisz, MD, PhD[5]; Massimo Aglietta, MD, PhD[6]; Pilar García-Alfonso, MD[7]; Bart Neyns, MD, PhD[8]; Gabriele Luppi, MD[9]; Dana B. Cardin, MD[10]; Tomislav Dragovich, MD, PhD[11]; Usman Shah, MD[12]; Sandzhar Abdullaev, MD, PhD[13]; Joseph Gricar, MS[13]; Jean-Marie Ledeine, MS[13]; Michael James Overman, MD[14]; and Sara Lonardi, MD[15]

	NIVO3 (Q2W) + IPI1 (Q6W) N = 45 Investigator assessed	
Data cutoff	July 2018	October 2019
Median follow-up (range), months	13.8 (9.0-18.5)	29.0 (24.2-33.7)
ORR,[a] n (%) [95% CI]	27 (60) [44 -74]	**31 (69)** [53-82]
Best overall response, n (%)		
CR	3 (7)	**6 (13)**
PR	24 (53)	25 (56)
SD	11 (24)	7 (16)
PD	6 (13)	6 (13)
Not determined	1 (2)	1 (2)
DCR,[b] n (%) [95% CI]	38 (84) [70.5-93.5]	38 (84) [70.5-93.5]
Median TTR (range), months	2.6 (1.2-13.8)	2.7 (1.2-27.7)
Median DOR (range), months	NR (1.4+ to 15.4+)	NR (1.4+ to 29.0+)





Lenz HJ et al. *J Clin Oncol.* 2022;40(2):161-170.

MSI-H mCRC, First Line, Nivolumab + Ipilimumab

Journal of Clinical Oncology®

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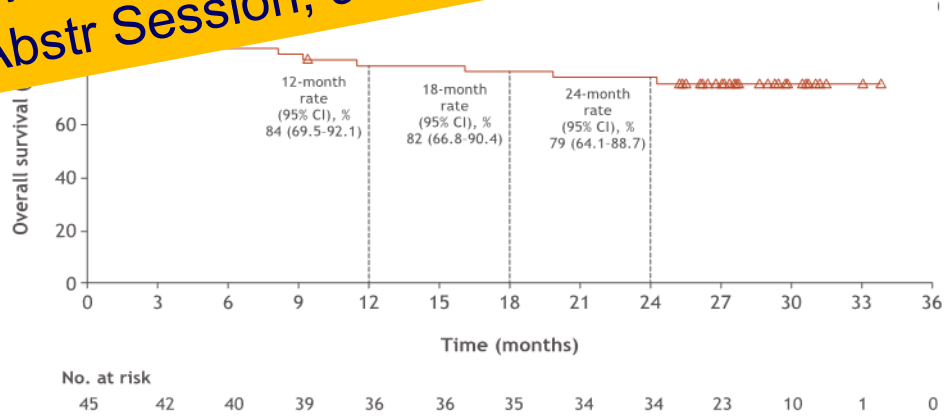
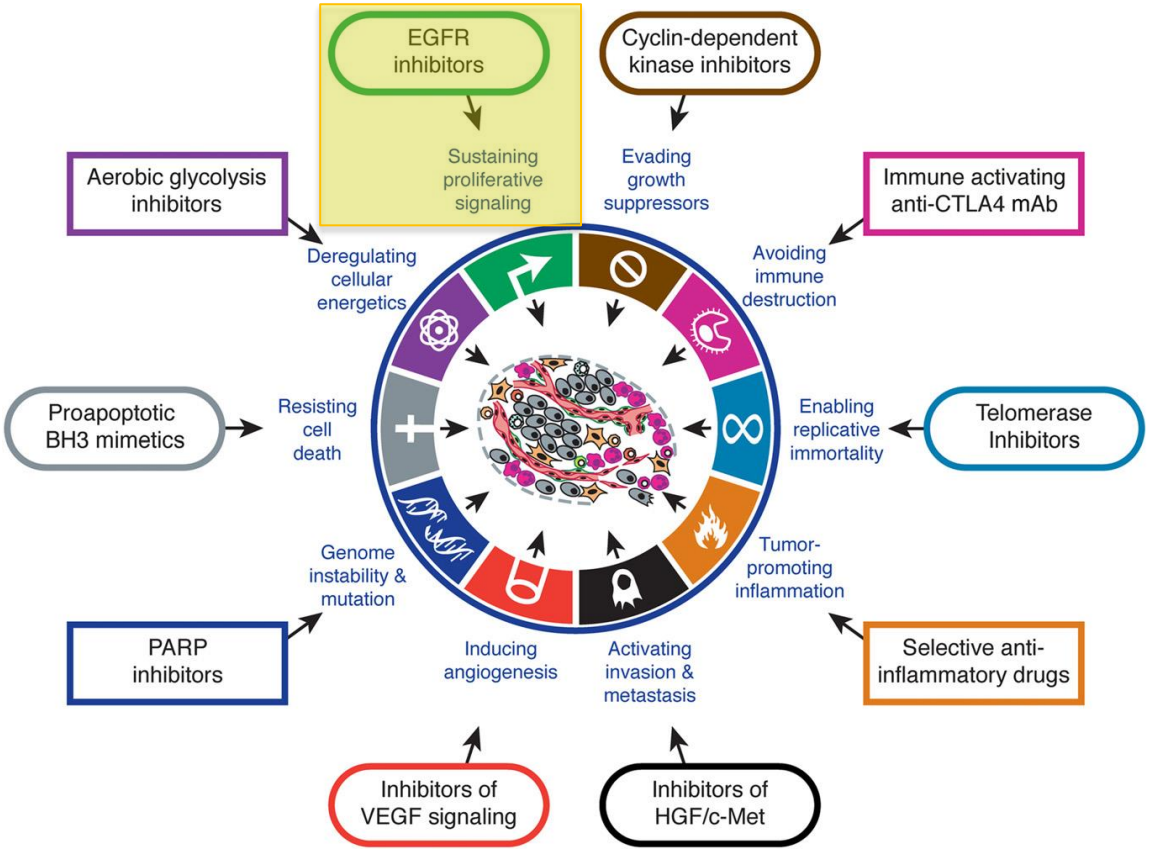
Stay tuned for CM 8HW first results presentation: Sat 20th, Rapid Oral Abstr Session, 9.15-10 AM



Lenz HJ et al. *J Clin Oncol.* 2022;40(2):161-170.

Biologics Combination



Hanahan D and Weinberg RA. *Cell.* 2011;144(5):646-674.

EGFR-i in RAS WT, Left Sided mCRC

	mPFS (mo)	mOS (mo)	ORR (%)
TRIPLETE**[1] [mFOLFOX6/pan] n = 191	12.7	NA	73
PARADIGM[2] [mFOLFOX6/pan] n = 312	13.1	37.9	80.2
FIRE-3[3] [FOLFIRI/cet] n = 157	10.7	38.3	68.8
CALGB80405[4] [chemo doublet*/cet] n = 173	12.7	39.3	69.4
PEAK[5] [mFOLFOX6/pan] n = 53	14.6	43.4	64.1

1. Rossini D et al. *J Clin Oncol.* 2022;40(25):2878-2888; 2. Watanabe J et al. *JAMA.* 2023;329(15):1271-1282; 3. Heinemann V et al. *Lancet Oncol.* 2014;15(10):1065-1075;
4. Venook AP et al. ASCO 2017. Abstract 3503; 5. Boeckx N et al. *Ann Oncol.* 2017;28(8):1862-1868.

Breakwater Trial: Encorafenib+Cetuximab in BRAFmut 1st Line mCRC

Safety Lead-In

Patients who have received ≤1 prior treatment for mCRC

Cohort 1 (n=30)
Encorafenib 300 mg QD
+ cetuximab 500 mg/m² Q2W
+ FOLFIRI Q2W in 28-day cycles

Cohort 2 (n=27)
Encorafenib 300 mg QD
+ cetuximab 500 mg/m² Q2W
+ mFOLFOX6 Q2W in 28-day cycles

Primary Endpoint
- Safety (frequency of DLTs)

Secondary Endpoints
- Safety (AEs, dose interruptions/ modifications/discontinuations)
- PKs (encorafenib, irinotecan, oxaliplatin, metabolites)
- Antitumor activity by investigator (ORR, DOR, TTR, PFS, OS)

R

Arm A (n≈235)
Encorafenib + cetuximab

Arm B (n≈235)
Encorafenib + cetuximab + mFOLFOX6

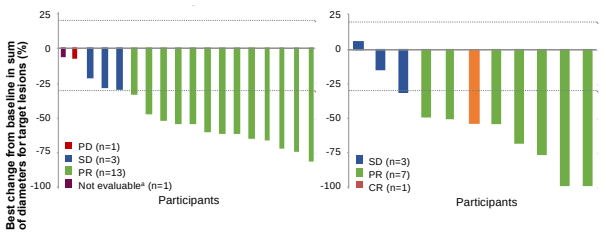
Control (n≈235)
mFOLFOX6/FOLFOXIRI/ CAPOX ± bevacizumab

Primary Endpoint
- PFS by BICR

Secondary Endpoints
- OS
- ORR, DOR, and TTR by BICR and by investigator
- PFS by investigator
- Safety
- PROs
- Biomarkers

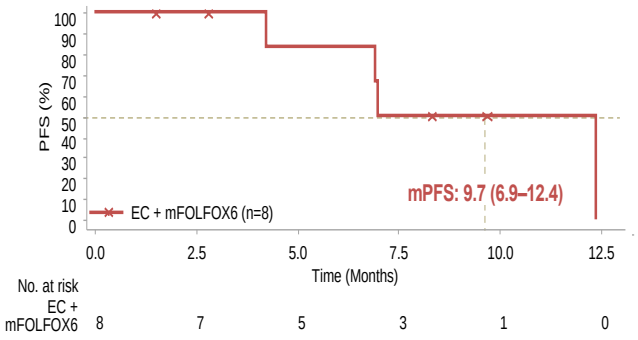
1L ORR

EC + mFOLFOX6	EC + FOLFIRI
n=19	n=12
68.4%	66.7%

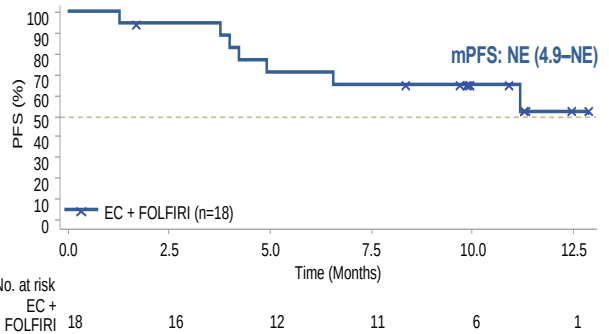


1L PFS

1L FOLFOX/enco/cet



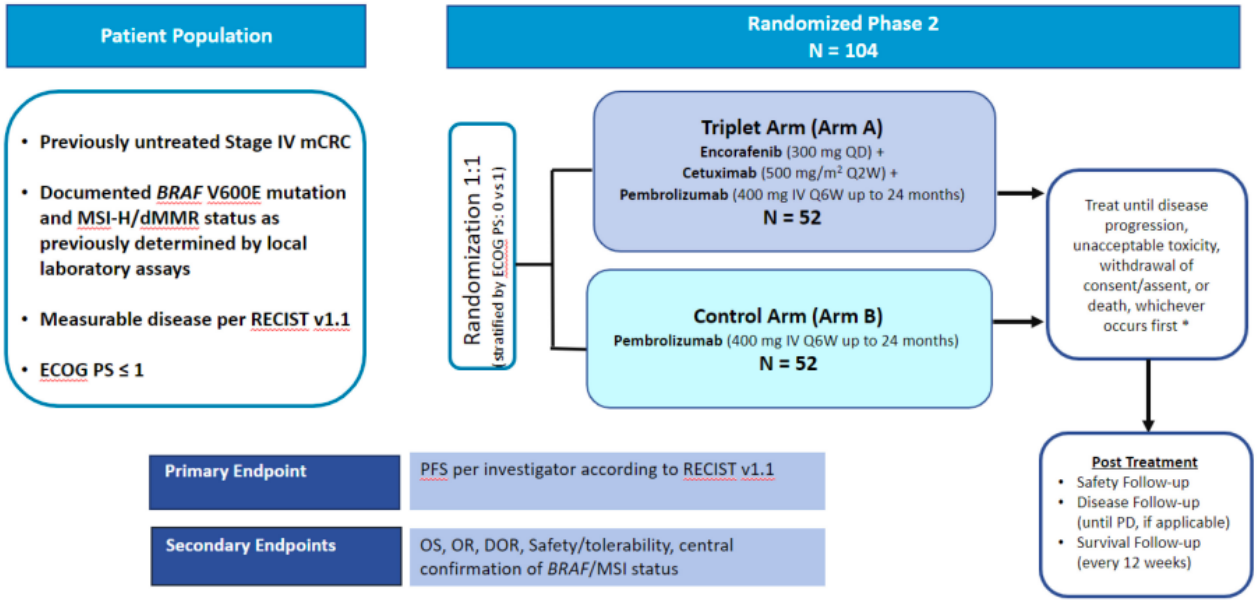
1L FOLFIRI/enco/cet



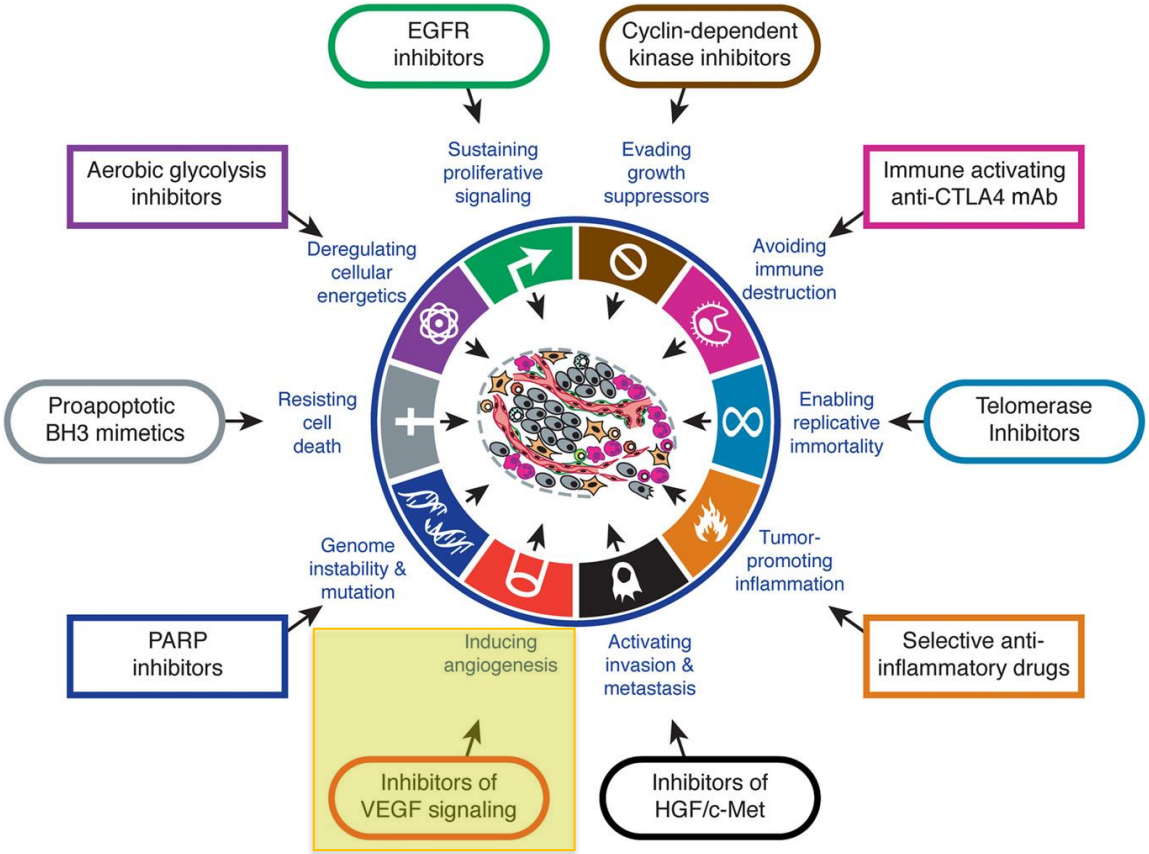
Tabernero J et al. ESMO 2022. Abstract LBA26.

MSI-H and BRAFmut 1st line mCRC

SEAMARK

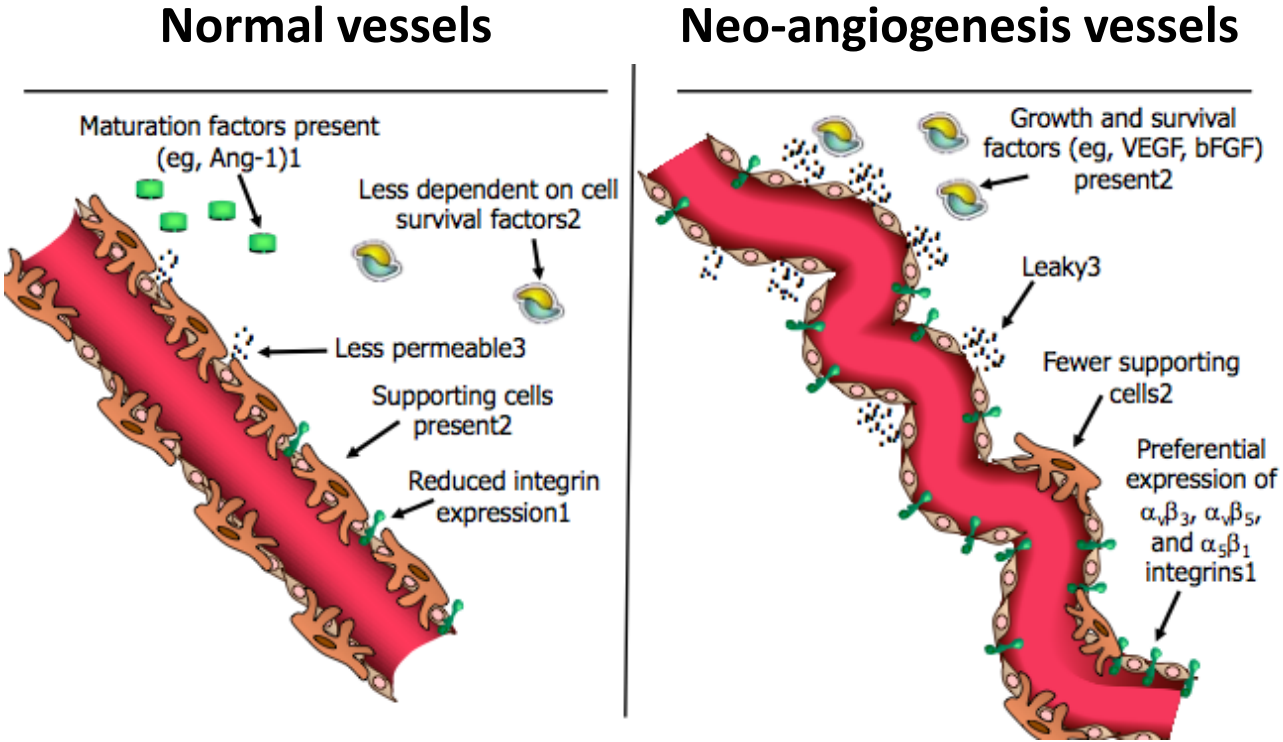


Biologics Combination



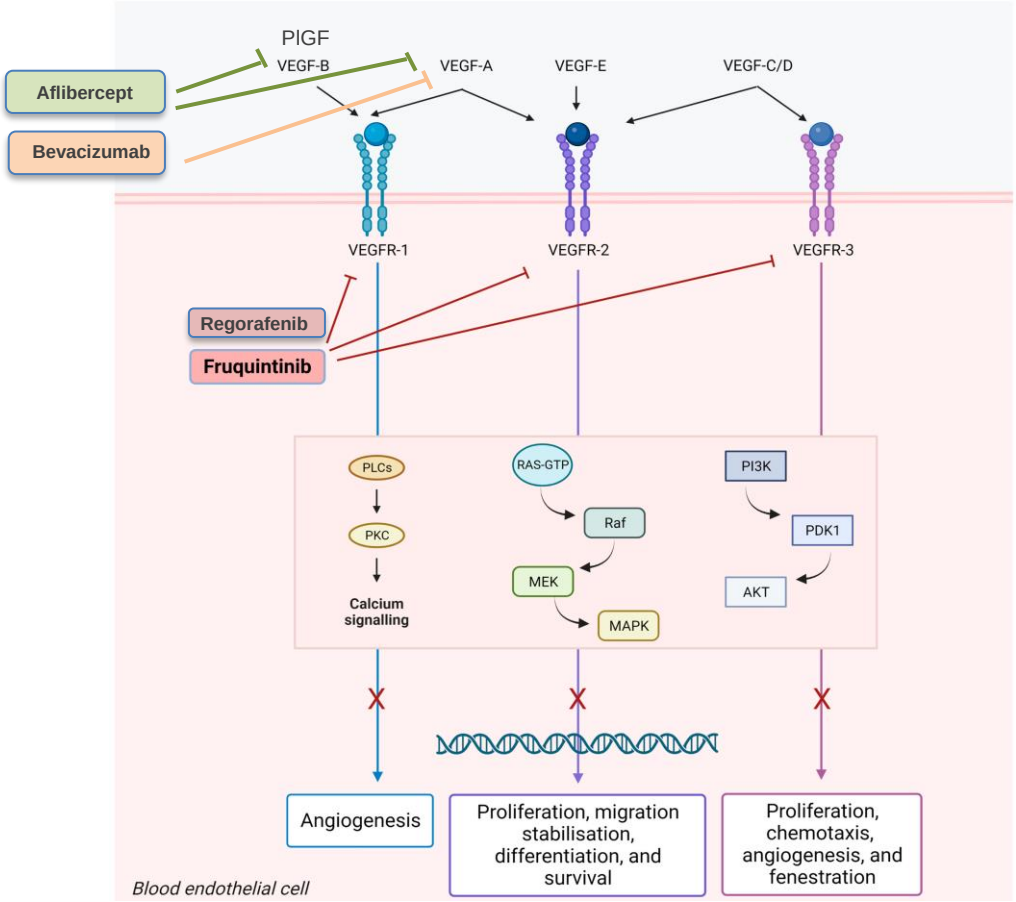
Hanahan D and Weinberg RA. *Cell.* 2011;144(5):646-674.

Neo-Angiogenesis in Cancer



Griffoen AW and Molema G. *Pharmacol Rev.* 2000;52(2):237-268; Blau HM and Banfi A. *Nat Med.* 2001;7(5):532-534; Jain RK. *Nat Med.* 2001;7(9):987-989.

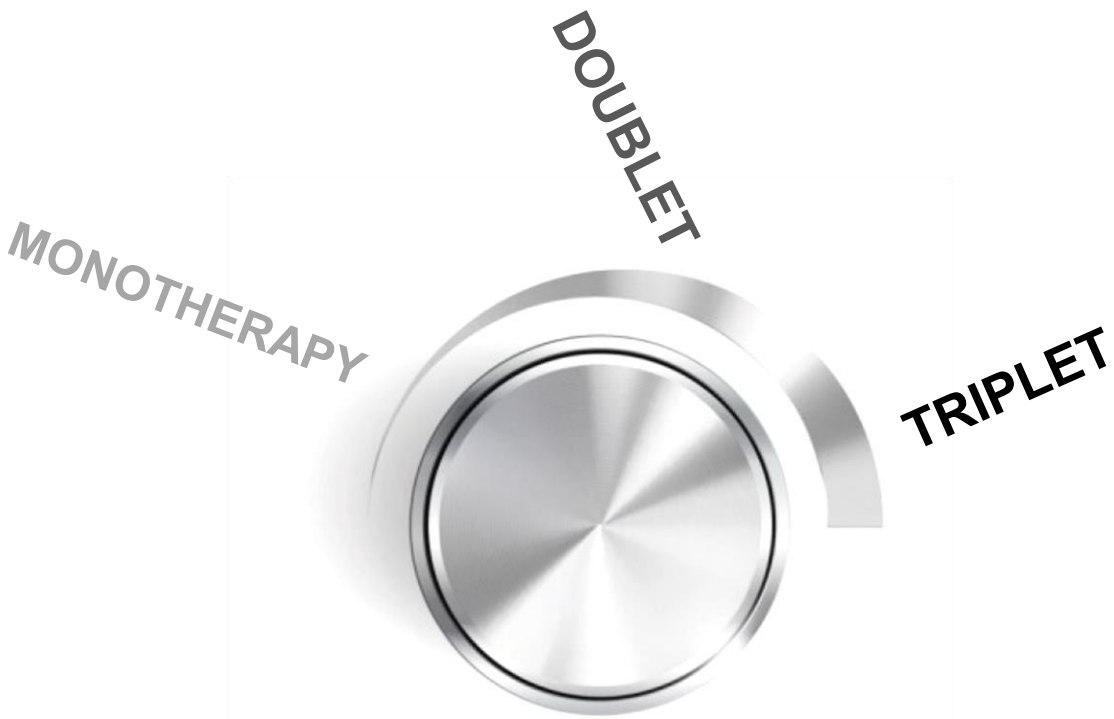
The Angiogenesis Pathway Is Extremely Complex



Modified from Lavacchi D et al. *Int J Mol Sci.* 2023;24(6):5840.

Chemo-intensity

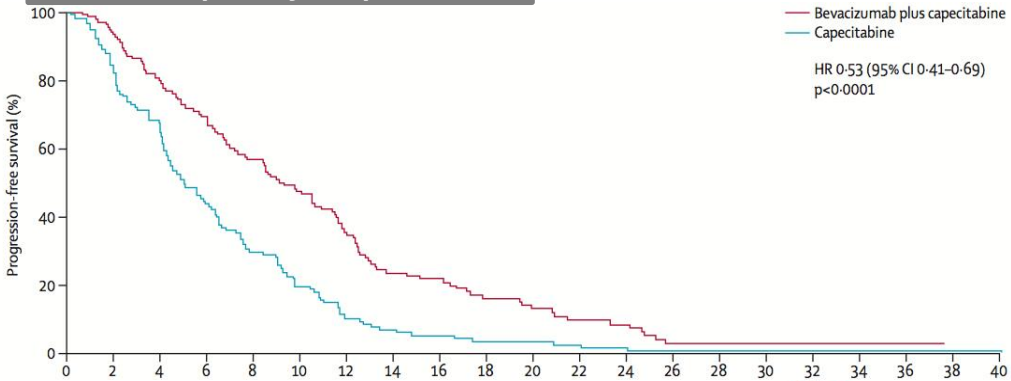
VEGFi +



PATIENT - age and fitness

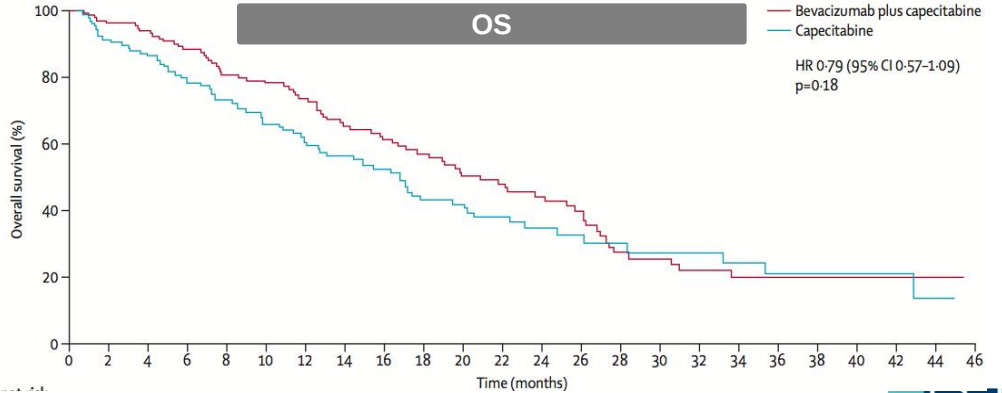
AVEX trial: FP Monotherapy Plus Bev, a Long-Lasting Standard

PFS: primary endpoint



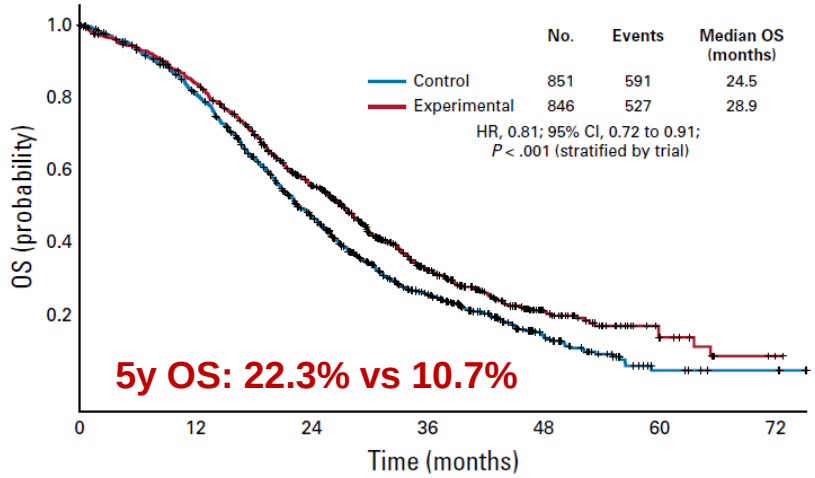
Not optimal candidates for a combination chemotherapy with irinotecan or oxaliplatin

OS



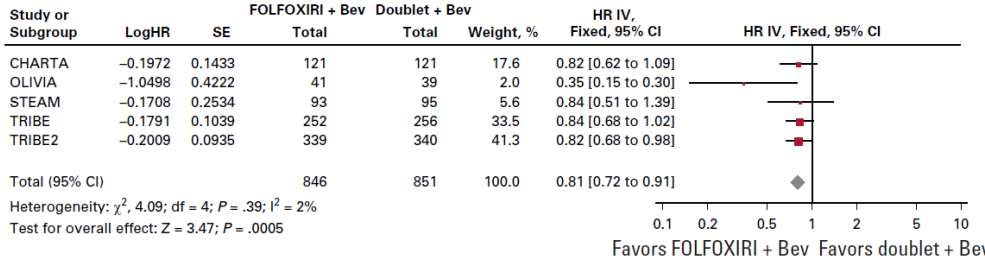
Cunningham D et al. *Lancet Oncol.* 2013;14(11):1077-1085

IPD-Based Metanalysis: FOLFOXIRI/Bev vs Doublets/Bev



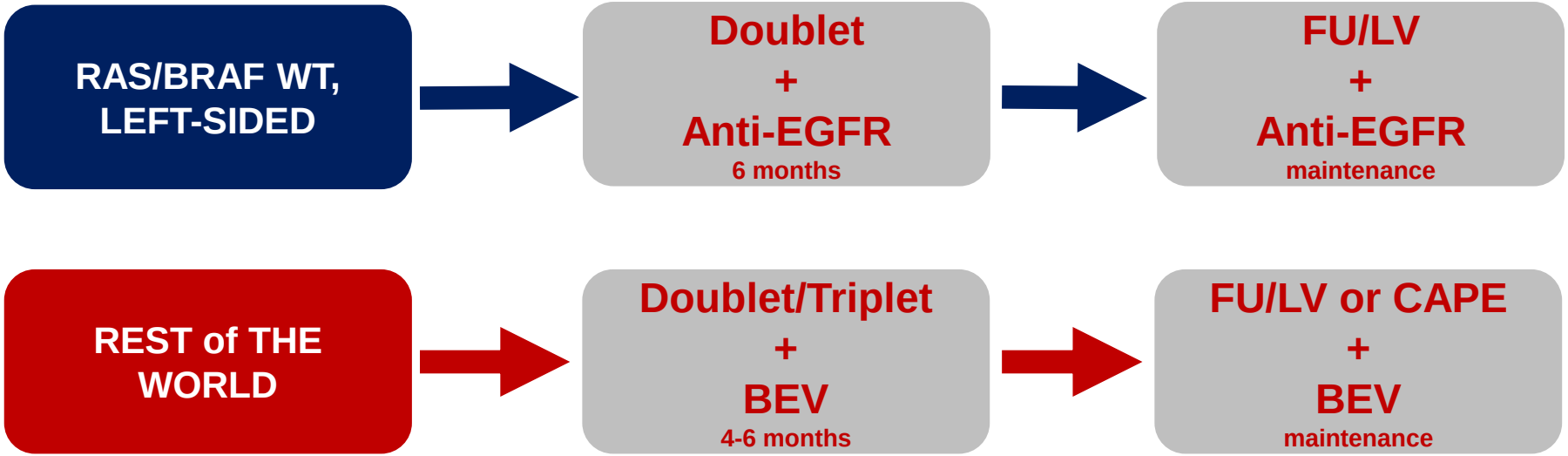
5y OS: 22.3% vs 10.7%

Metanalysis of 5 random studies
N= 1697



Cremolini C et al. *J Clin Oncol.* 2020; JCO2001225.

To Make a Long Story Short… First-Line Treatment



And in second line?

The standard is… to switch chemo!

What Can We Do if First Line Doublet + Anti-EGFR?

Switch chemo and add antiVEGF!

(indirect evidences from E3200 and VELOUR trials, anti-EGFR registrative trials, head-to-head trials)

What Can We Do if First Line Doublet+BEV?

Switch chemo and continue antiVEGF!

(evidence from TML, VELOUR, RAISE trials)

How to Sequence Later on?

SELECTION!

(…if possible)

"Targeted" Options in Later Lines

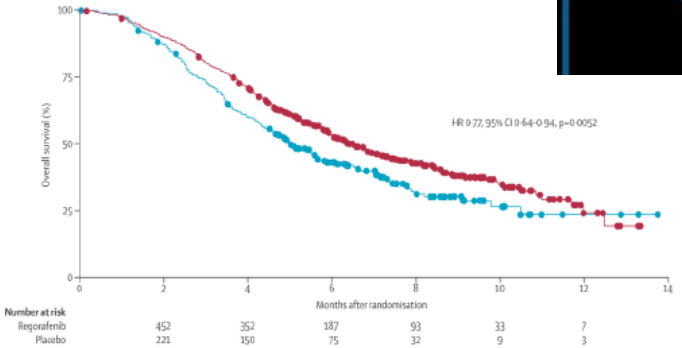
- ✓ **HER2+:** 3%, trastuzumab + lapatinib/pertuzumab/tucatinib, trastuzumab deruxtecan
- ✓ **Rearrangements:** 1%, larotrectinib, entrectinib
- ✓ **MGMTmet:** 20%, temozolomide + nivo-ipi
- ✓ **RAS wt ctDNA:** ? (superimposed to others), anti-EGFR rechallenge
- ✓ **KRAS G12C:** 3%, sotorasib + panitumumab, adagrasib + cetuximab

About 70% of patients has NO targets

If You Can Offer Third-Line Treatment..

REGORAFENIB

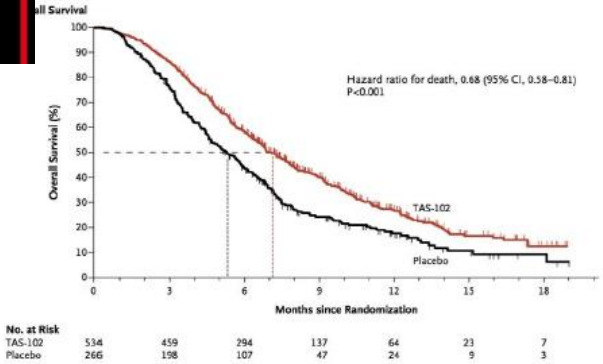
CORRECT trial



mOS 5.0 vs 6.4 mos
HR: 0.77

TAS-102

RECOURSE trial



mOS 5.3 vs 7.1 mos
HR: 0.68

Grothey A et al. *Lancet.* 2013;381(9863):303-312;
Mayer RJ et al. *N Engl J Med.* 2015;372(20):1909-1919.

A New "Sunlight" on the Third-Line Setting

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

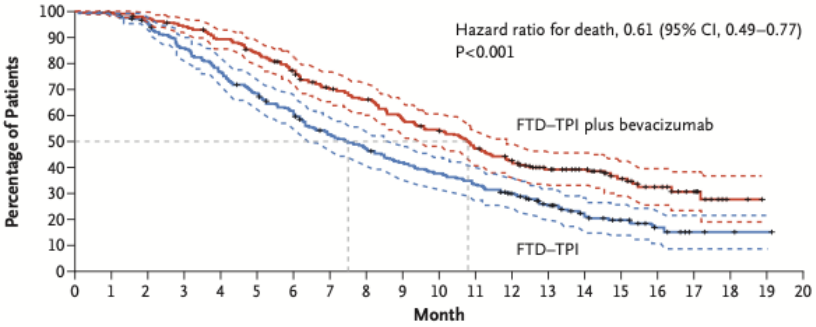
Trifluridine–Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer

Gerald W. Prager, M.D., Julien Taieb, M.D., Ph.D., Marwan Fakih, M.D., Fortunato Ciardiello, M.D., Ph.D., Eric Van Cutsem, M.D., Ph.D., Elena Elez, M.D., Ph.D., Felipe M. Cruz, M.D., Ph.D., Lucjan Wyrwicz, M.D., Ph.D., Daniil Stroyakovskiy, M.D., Ph.D., Zsuzsanna Pápai, M.D., Pierre-Guillaume Poureau, M.D., Gabor Liposits, M.D., Chiara Cremolini, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Dominik P. Modest, M.D., Karim A. Benhadji, M.D., Nadia Amellal, M.D., Catherine Leger, M.Sc., Loïck Vidot, M.Sc., and Josep Tabernero, M.D., Ph.D., for the SUNLIGHT Investigators*

3rd line mCRC

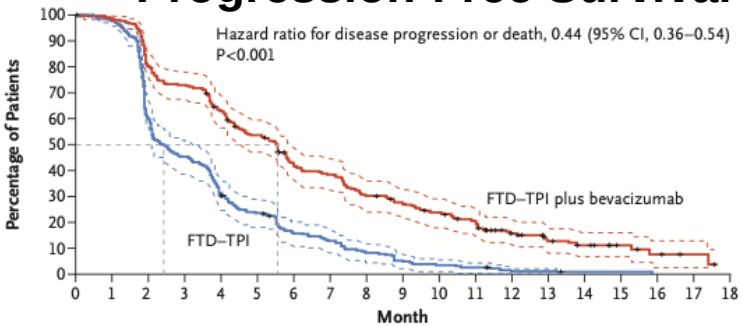
- Trifluridine Tipiracil
- Trifluridine Tipiracil + bev

Overall Survival



No. at Risk																				
FTD–TPI plus bevacizumab	246	244	239	230	217	203	183	160	149	131	119	104	88	69	52	37	24	13	2	0	0
FTD–TPI	246	242	230	205	184	163	143	120	108	95	85	76	63	44	24	16	10	5	2	1	0

Progression-Free Survival



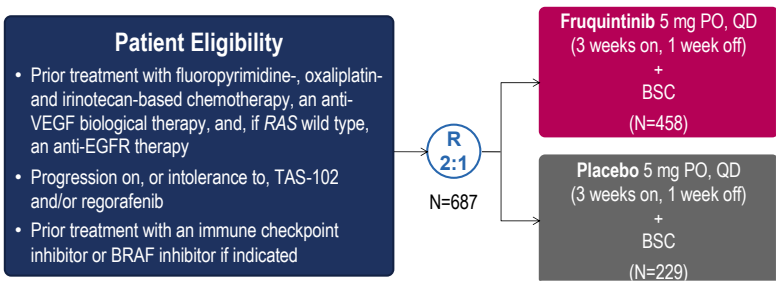
No. at Risk																			
FTD–TPI plus bevacizumab	246	242	198	179	153	128	99	89	70	61	52	43	25	18	13	7	4	2	0
FTD–TPI	246	236	147	109	74	56	36	29	19	12	8	6	2	2	1	1	0	0	0

Prager GW et al. *N Engl J Med.* 2023;388(18):1657-1667.

..and Finally…Some FRESCO!

Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study

Arvind Dasari, Sara Lonardi*, Rocio Garcia-Carbonero, Elena Elez, Takayuki Yoshino, Alberto Sobrero, James Yao, Pilar García-Alfonso, Judit Kocsis, Antonio Cubillo Gracian, Andrea Sartore-Bianchi, Taroh Satoh, Violaine Randrian, Jiri Tomasek, Geoff Chong, Andrew Scott Paulson, Toshiki Masuishi, Jeremy Jones, Tibor Csőszi, Chiara Cremolini, Francois Ghiringhelli, Ardaman Shergill, Howard S Hochster, John Krauss, Ali Bassam, Michel Ducreux, Anneli Elme, Laurence Faugeras, Stefan Kasper, Eric Van Cutsem, Dirk Arnold, Shivani Nanda, Zhao Yang, William R Schelman, Marek Kania, Josep Tabernero†, Cathy Eng†, on behalf of the FRESCO-2 Study Investigators‡*

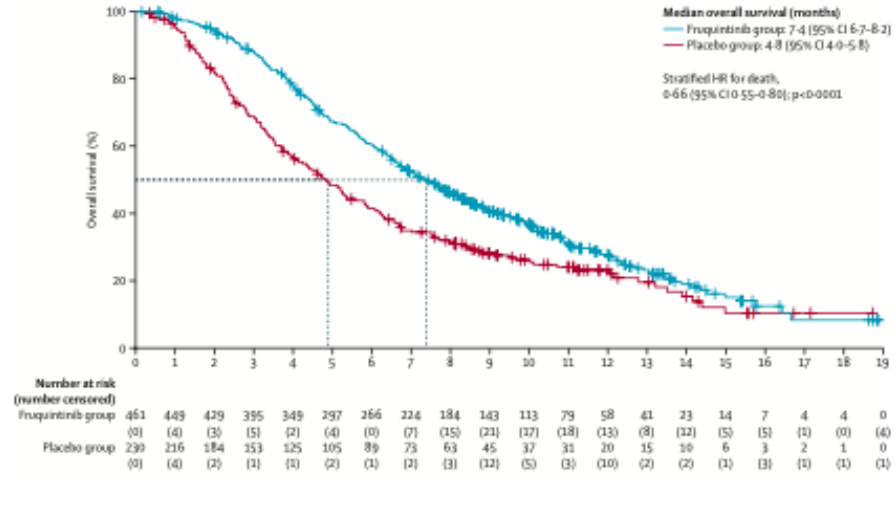


	Fruquintinib group (n=461)	Placebo group (n=230)	Treatment effect	Two-sided p value
Time-to-event endpoints				
Overall survival, months	7·4 (6·7–8·2)	4·8 (4·0–5·8)	0·66 (0·55–0·80)	<0·0001
Progression-free survival, months	3·7 (3·5–3·8)	1·8 (1·8–1·9)	0·32 (0·27–0·39)	<0·0001
Antitumour activity endpoints				
Best overall response*				
Complete response	0	0	..	..
Partial response	7 (2%)	0	..	..
Stable disease	249 (54%)	37 (16%)	..	..
Progressive disease	139 (30%)	143 (62%)	..	..
Not evaluable	6 (1%)	1 (<1%)	..	..
NA†	60 (13%)	49 (21%)	..	..
Objective response rate	7 (2%, 0·6–3·1)	0 (0%, 0·0–1·6)	2% (0·4–2·7)	0·059
Disease control rate	256 (56%, 50·9–60·1)	37 (16%, 11·6–21·5)	39%‡ (32·8–46·0)	<0·0001
Duration of response, months				
Median	10·7 (3·9–NE)	0 (NA)	..	..
Range	2·1–16·9§	NA	..	..

Dasari A et al. *Lancet.* 2023;402(101395):41-53.

Survival Outcome

Overall Survival



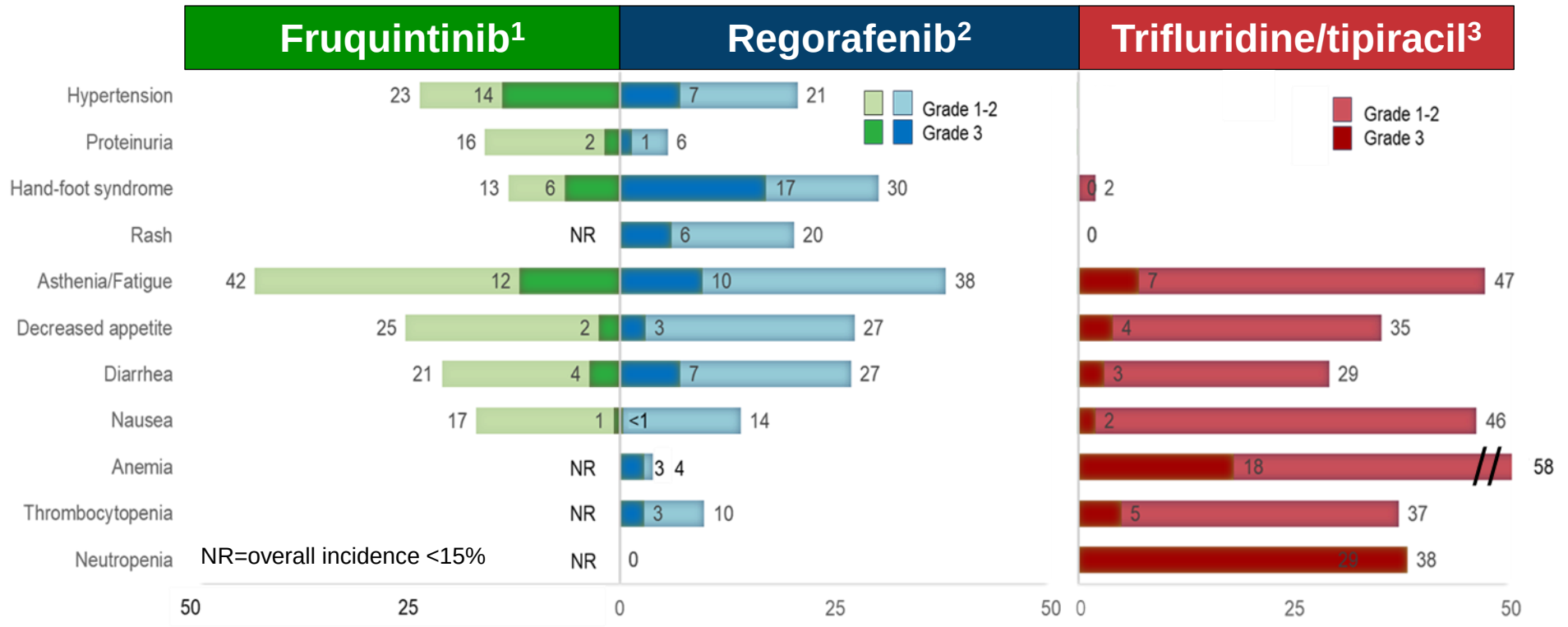
Progression-Free Survival

	Events/patients		Median overall survival (months)	
	Fruquintinib group	Placebo group	Fruquintinib group	Placebo group
Previous VEGF inhibitors				
Yes	306/445	167/221	7·4	4·9
No	11/16	6/9	10·0	3·5
Previous trifluridine–tipiracil or regorafenib				
Trifluridine–tipiracil	165/240	88/121	7·7	5·1
Regorafenib	25/40	12/18	10·2	8·2
Both	127/181	73/91	6·8	4·4

	Events/patients		Median progression-free survival (months)	
	Fruquintinib group	Placebo group	Fruquintinib group	Placebo group
Previous VEGF inhibitors				
Yes	377/445	206/221	3·7	1·9
No	15/16	7/9	5·9	1·6
Previous trifluridine–tipiracil or regorafenib				
Trifluridine–tipiracil	210/240	111/121	3·6	1·9
Regorafenib	29/40	16/18	3·6	1·9
Both	153/181	86/91	3·7	1·8

Dasari A et al. *Lancet.* 2023;402(101395):41-53.

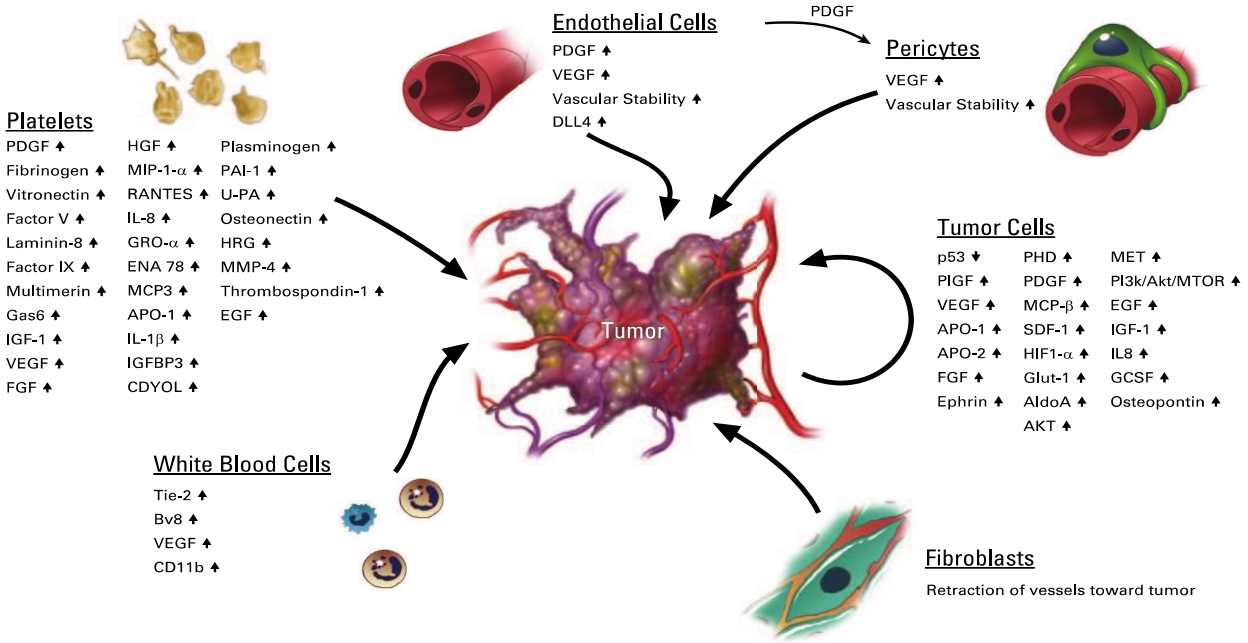
Safety Profiles



1. Dasari A et al. *Lancet.* 2023;402(101395):41-53; 2. Grothey A et al. *Lancet.* 2013;381(9863):303-312;
3. Mayer RJ et al. *N Engl J Med.* 2015;372(20):1909-1919.

Was Efficacy of Antiangiogenic Strategy in Late Line Expected?

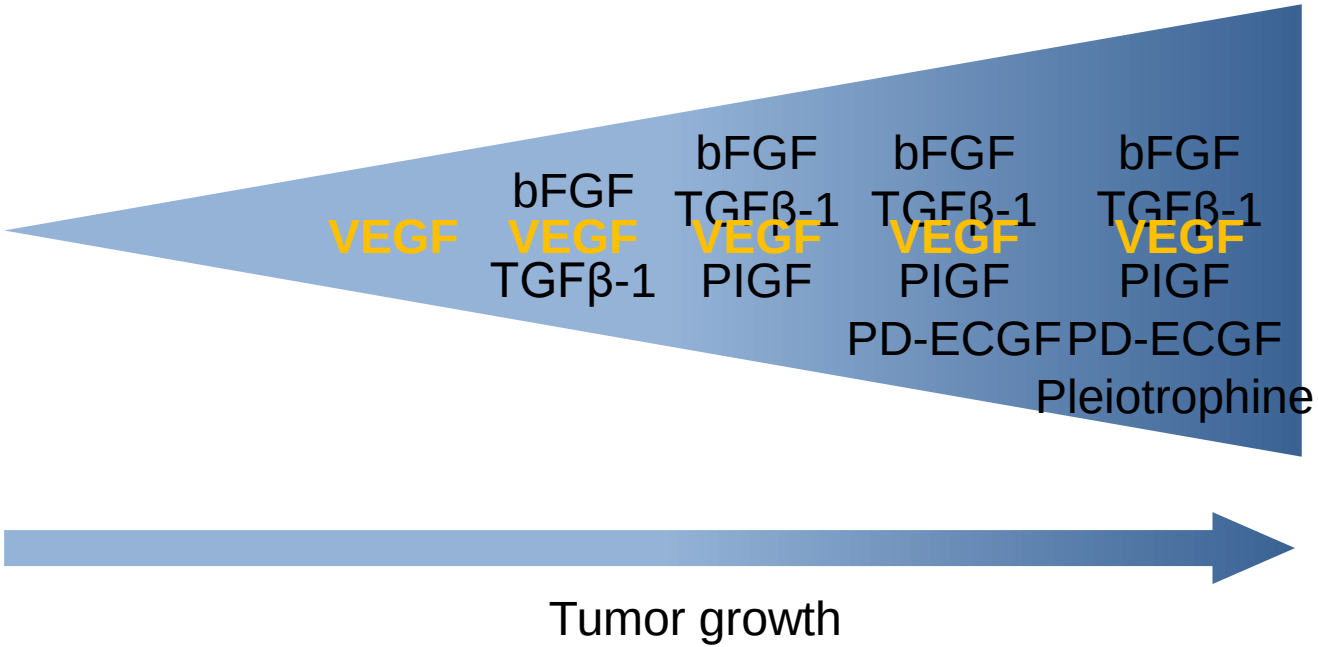
Resistance to antiangiogenesis therapy: multiple mechanisms of escape



Bottsford-Miller JN et al. *J Clin Oncol.* 2012;30(32):4026-4034.

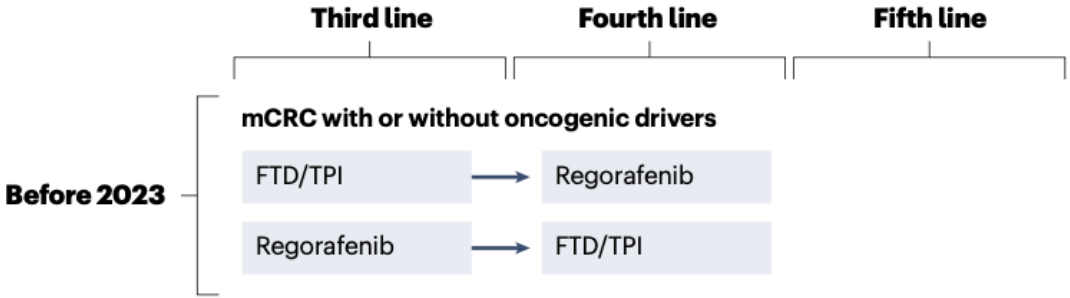
Continuous Relevance of VEGF-Mediated Signal

VEGF is expressed from the early to the late phase of disease



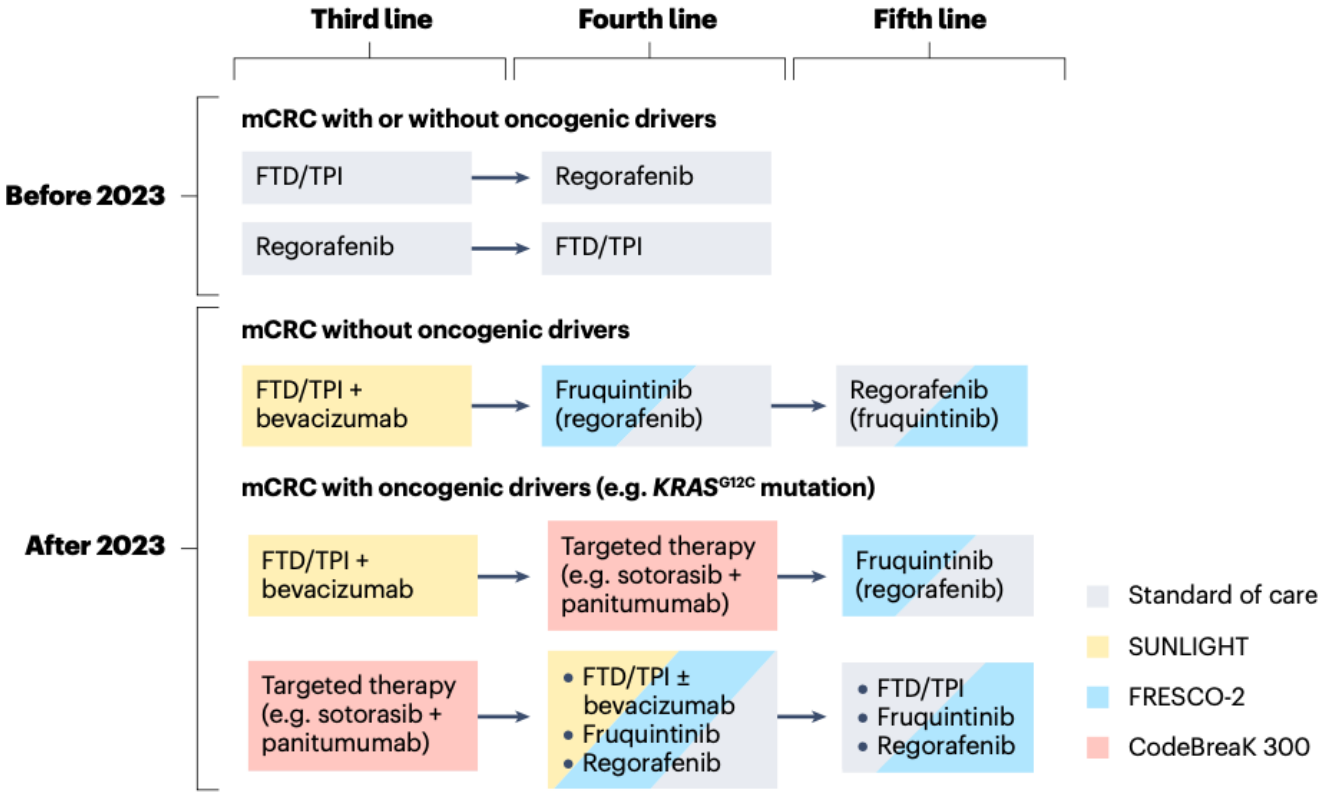
Adapted from Folkman: Cancer. Principles and Practice of Oncology 2005.

Advanced Lines Treatment Algorithm Proposal



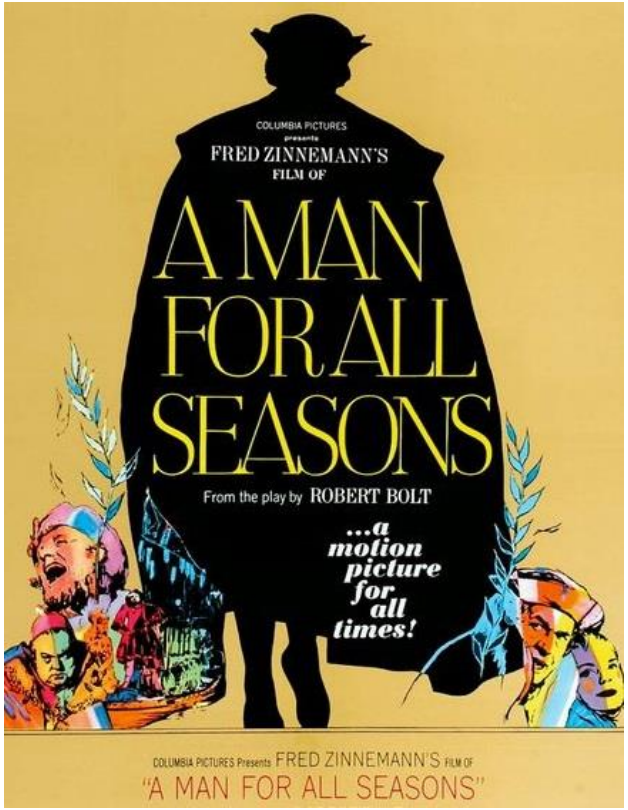
Lonardi S and Pietrantonio F. *Nat Rev Gastroenterol Hepatol.* 2023. Online ahead of print.

Advanced Lines Treatment Algorithm Proposal



Lonardi S and Pietrantonio F. *Nat Rev Gastroenterol Hepatol.* 2023. Online ahead of print.

VEGF Pathway Inhibition..



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