Belgian Symposium on the Integration of Molecular Biology Advances into Oncology Clinical Practice and Post-MASCC

Molecularly segmented colon cancer: Advances and Perspectives

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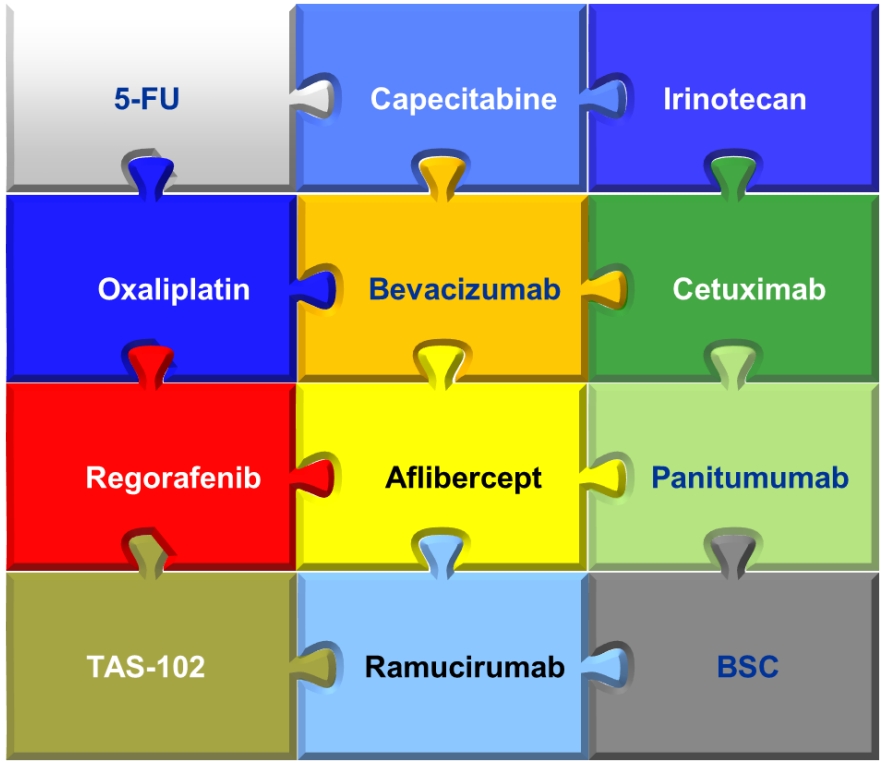
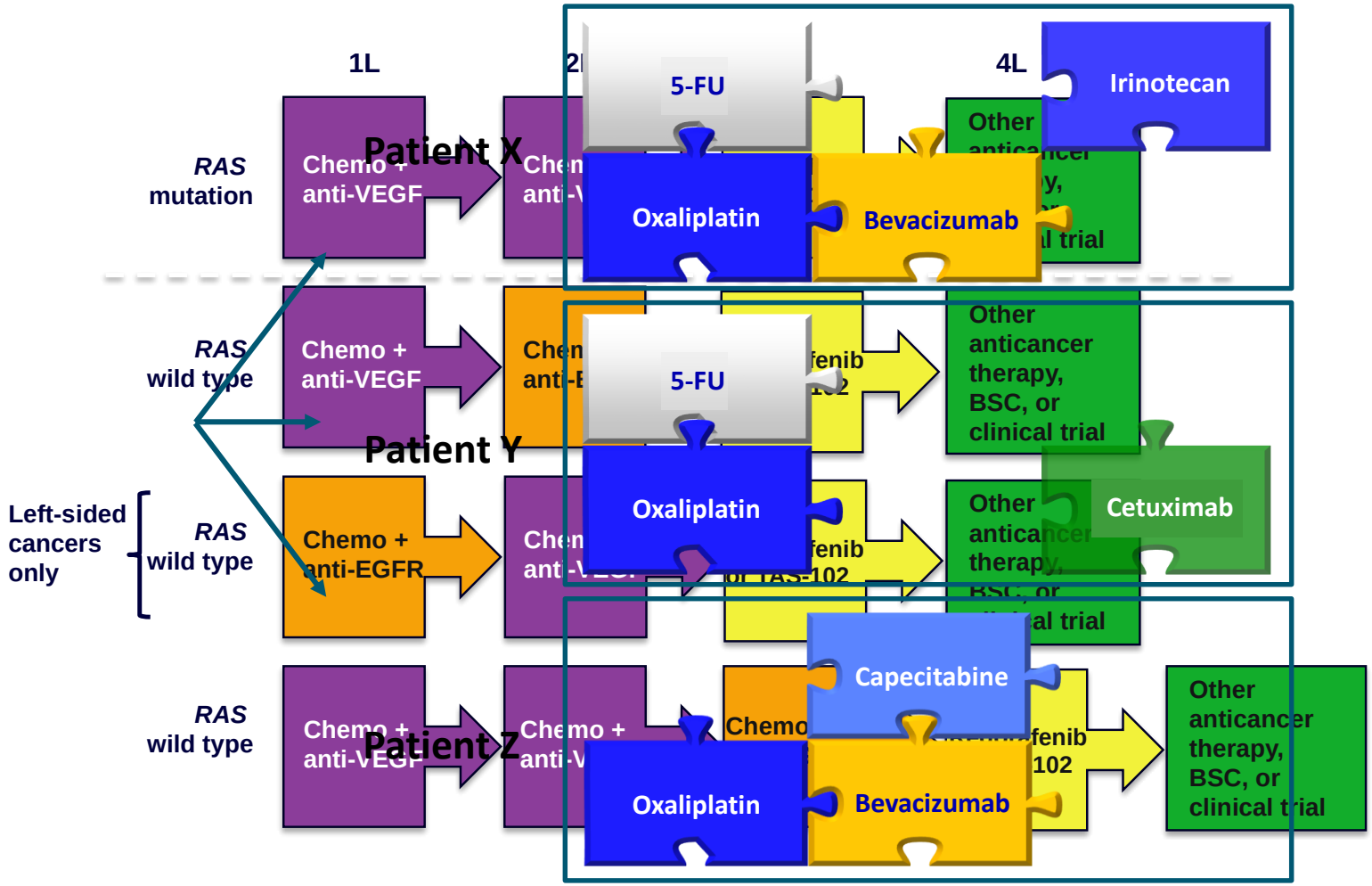
Disclosures

- **Consultancy, advisory board :**
  - **Bayer, Lilly, Roche, Sirtex, Pierre Fabre, Servier, Amgen, MSD**
- **Research Funding :**
  - **AstraZeneca, Bayer, Roche, Amgen, Teva, Merck, Sirtex**
- **Travel grants :**
  - **Bayer, Roche, Ipsen**

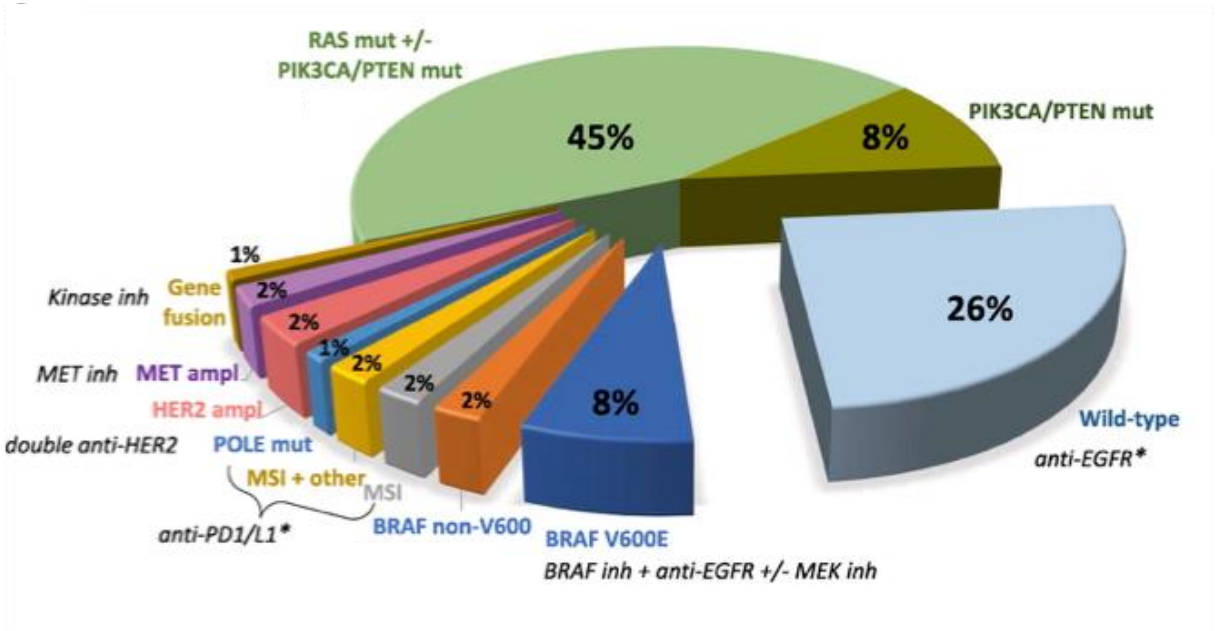
Metastatic CRC: path to personalized therapy?

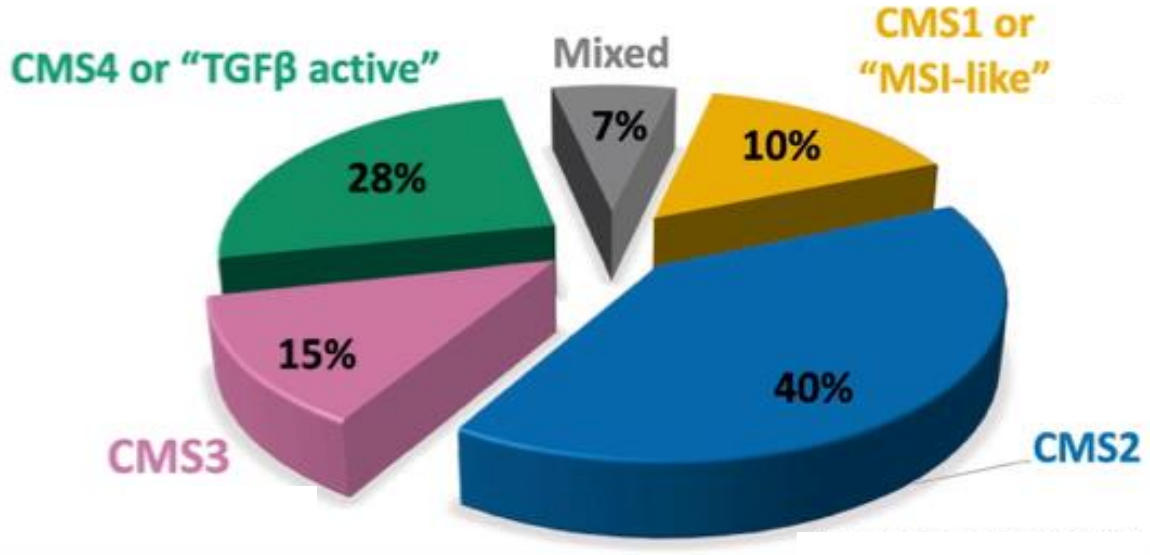




Van Cutsem et al. Ann Oncol 2016

Colon Cancer is More Than 1 Disease: Molecular Landscape



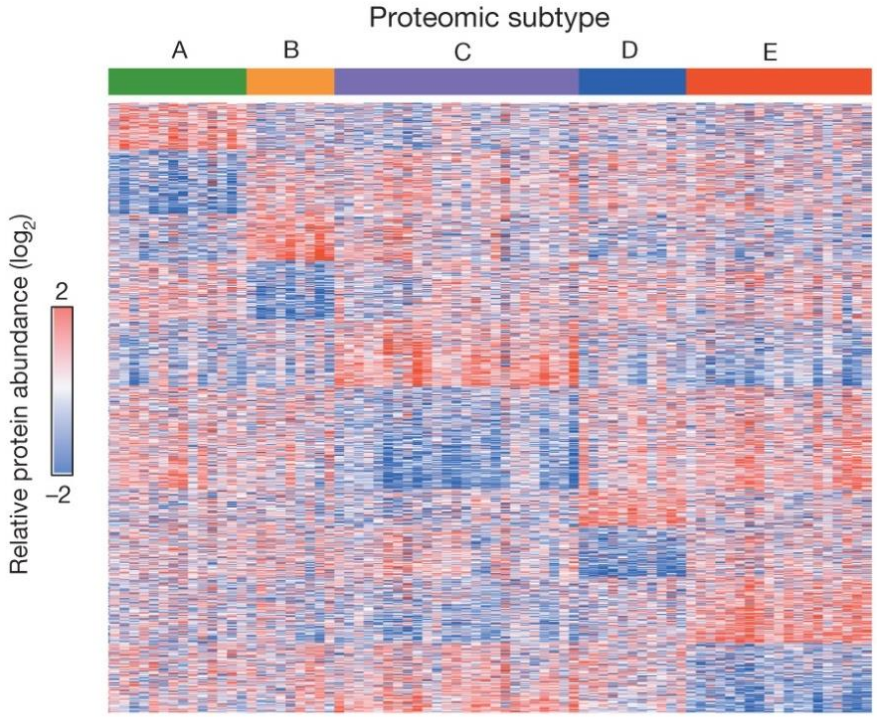


Genomics (DNA level)

Transcriptomics (RNA level)

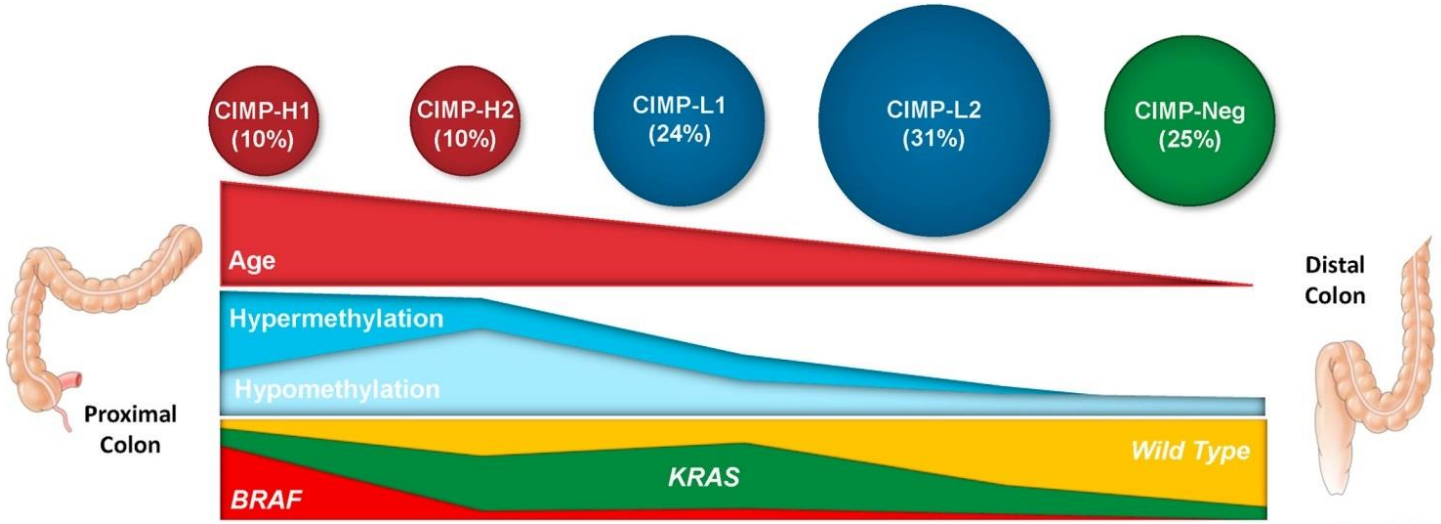
Dienstmann et al ASCO Educational Book 2018

Colon Cancer is More Than 1 Disease: Molecular Landscape



Proteomics (protein level)

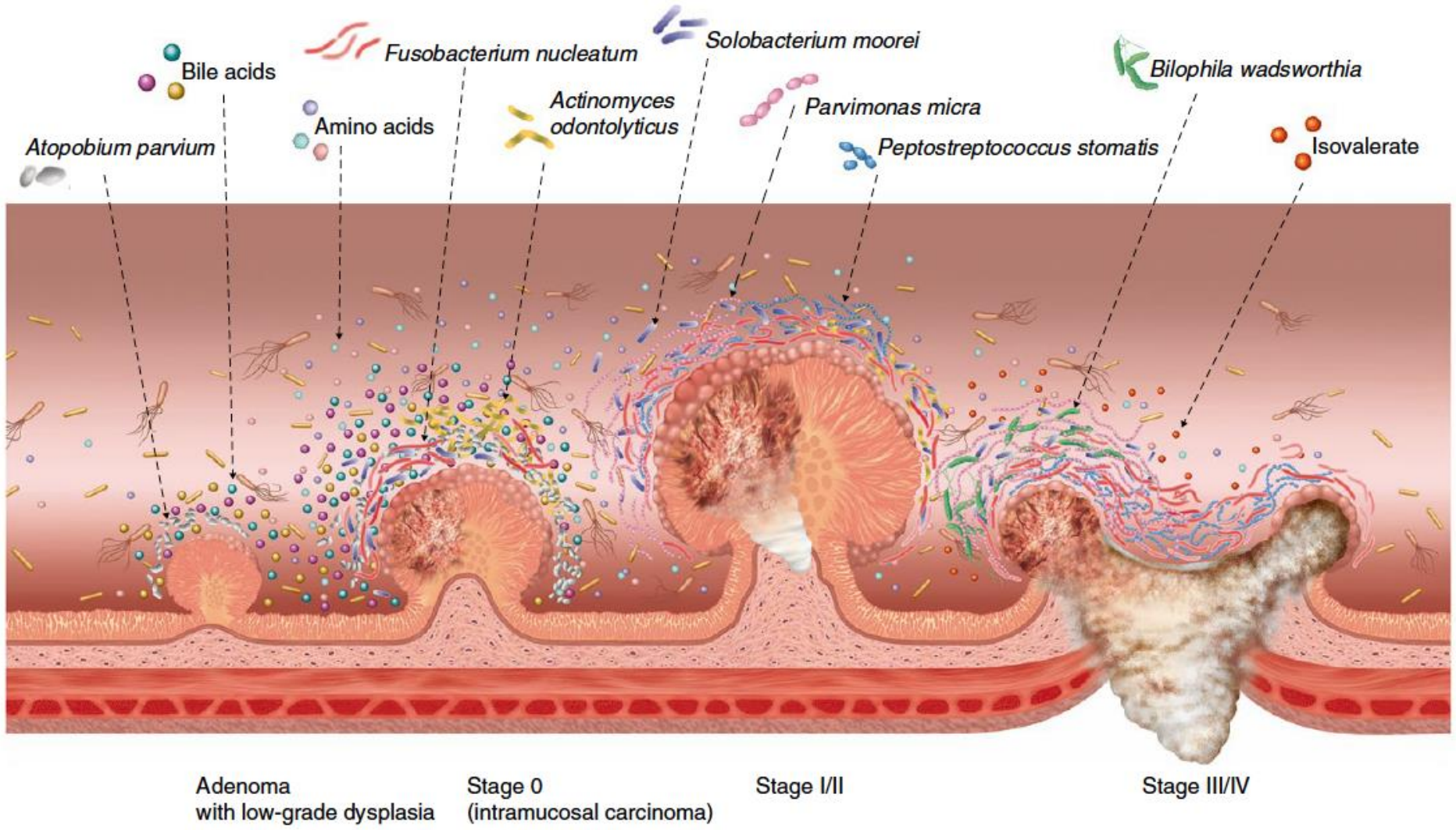
Zhang et al. Nature 2014



Epigenomics (changes in DNA and histone proteins)

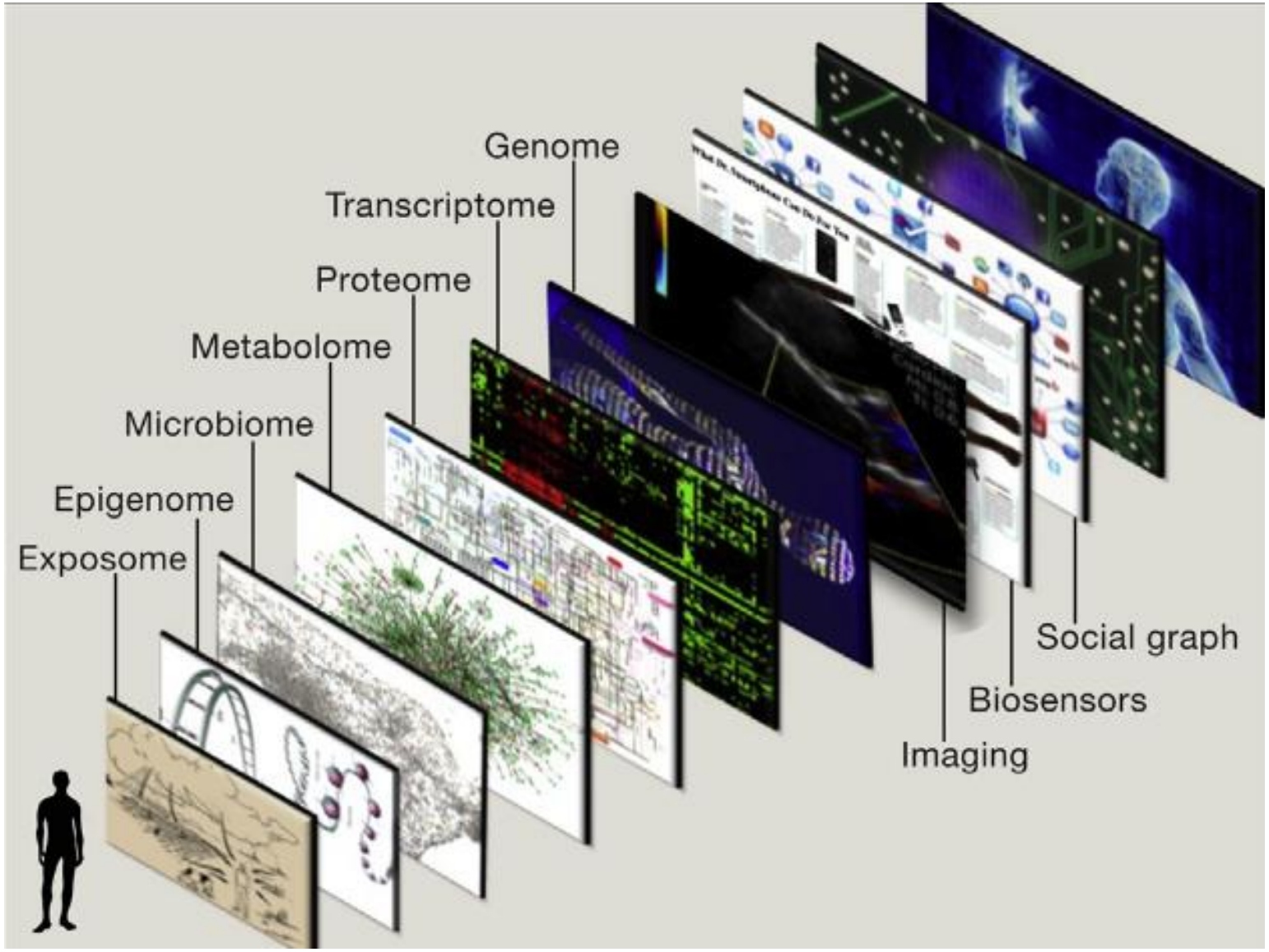
Fennell et al, Cellular and Molecular Gastroenterology and Hepatology 2019

Colon Cancer is More Than 1 Disease: Metagenomics



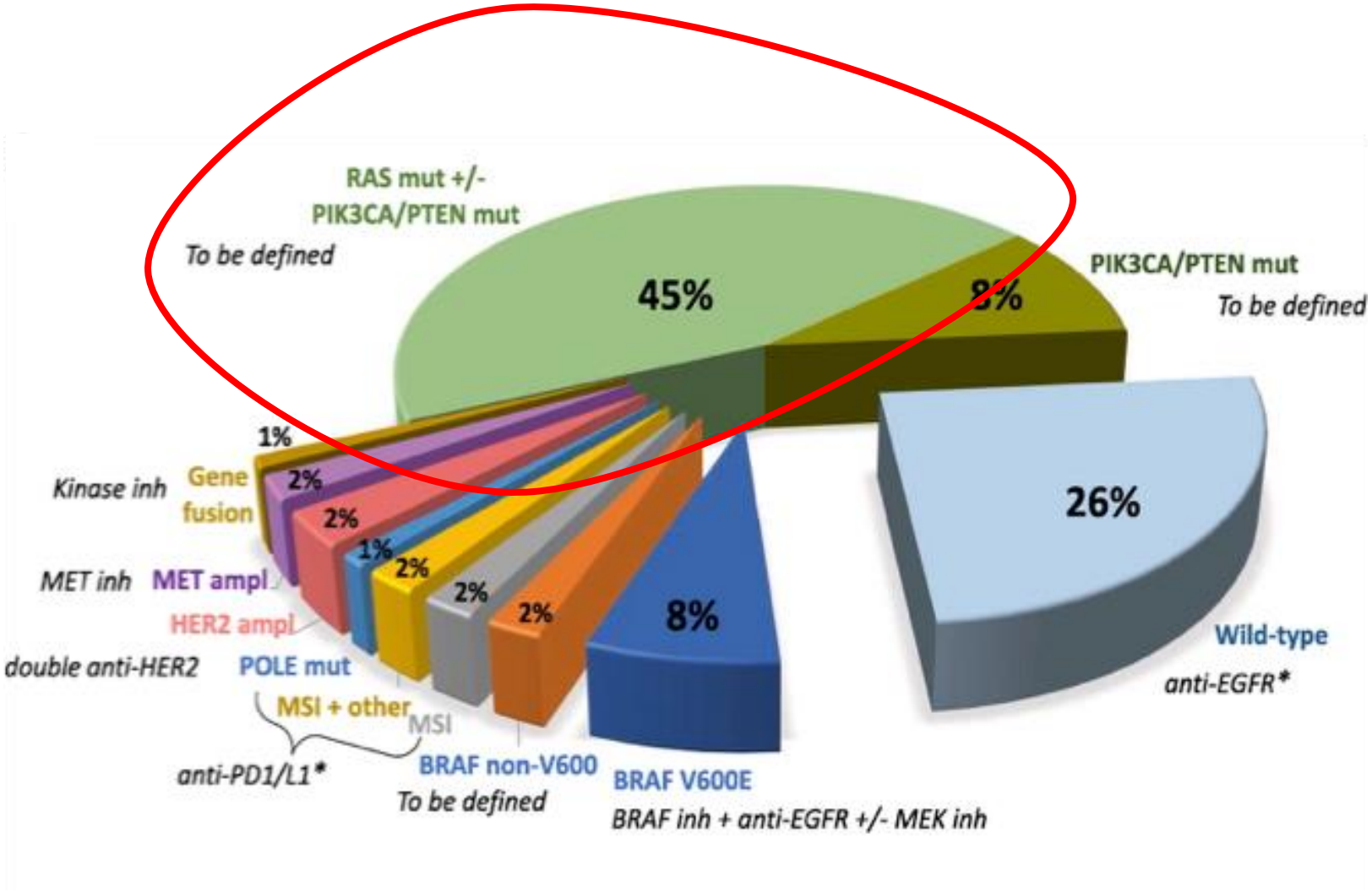
Yachida et al. Nature Medicine 2019

COMPLEX REALITY

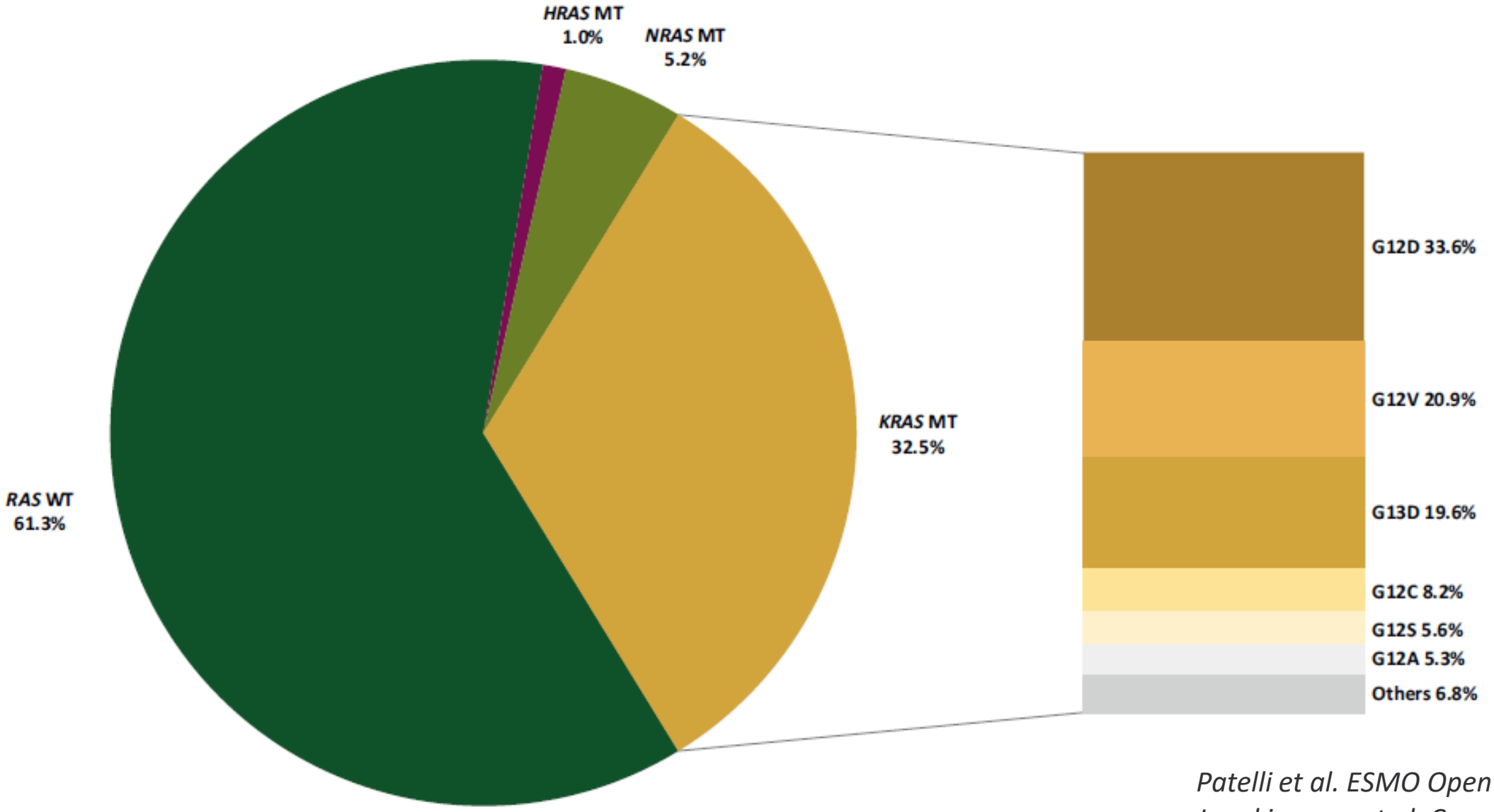


Topol Cell 2014

MOLECULARLY SEGMENTED CRC: RASmut



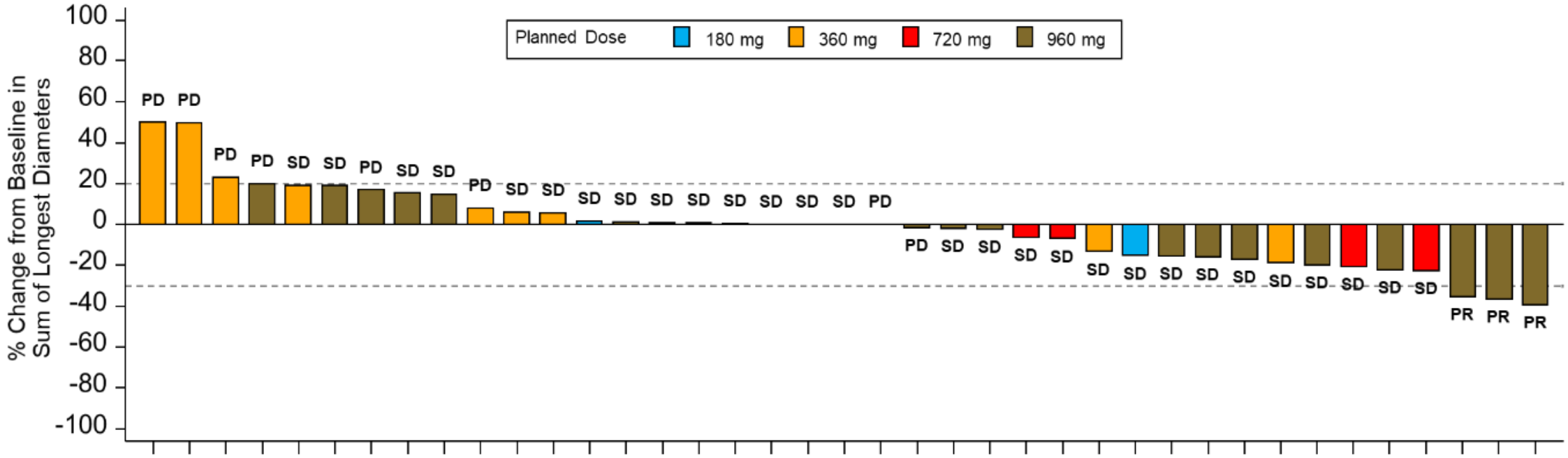
RAS mutations, deciphered



Patelli et al. ESMO Open 2022
Janakiraman et al. Cancer Res 2010
Hobbs et al. J Cell Science 2016

RAS… the undruggable protein

AMG 510 for KRASmut G12C: CODEBREAK 100 trial



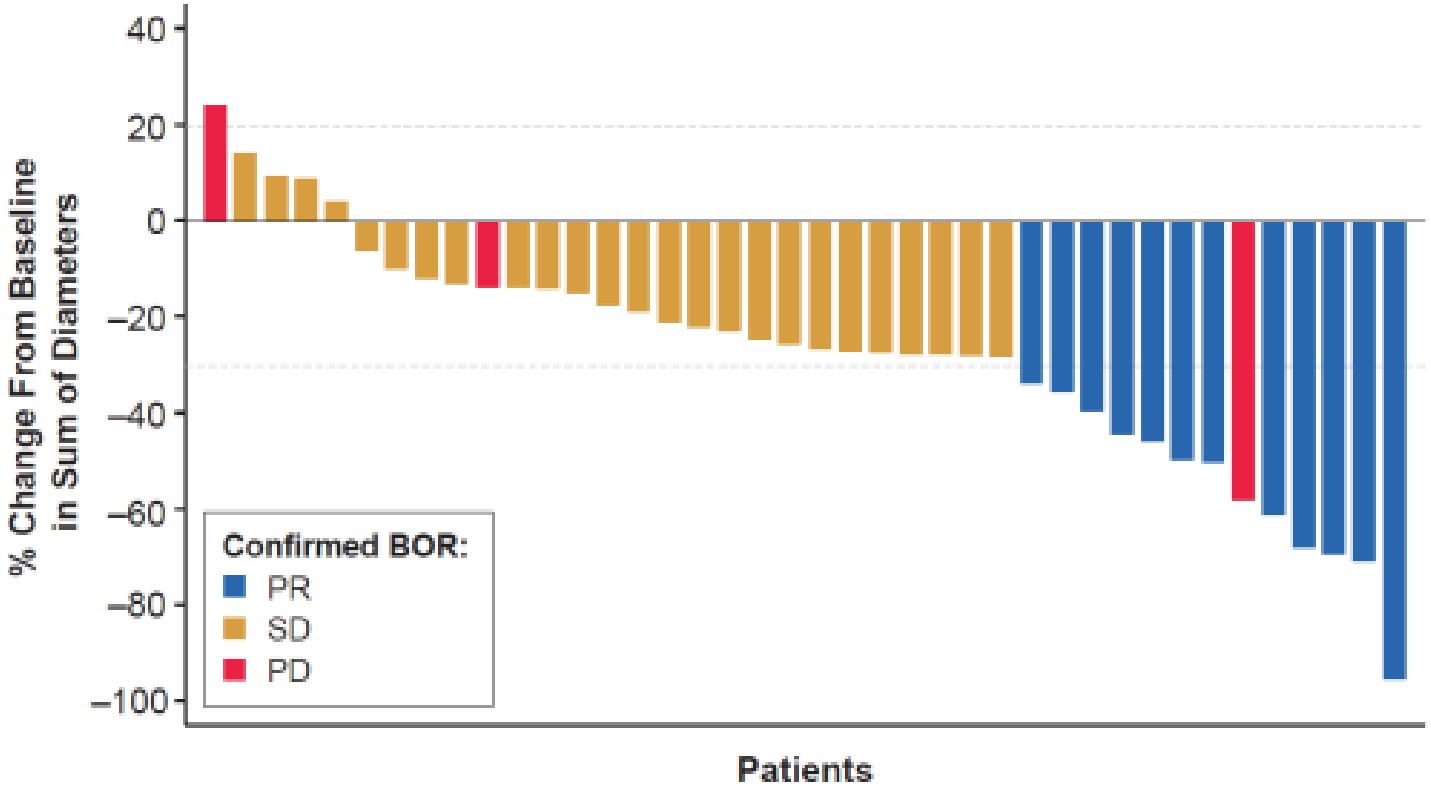
3/42 (7%) PR

32/42 (76%) DCR

Fakih et al. ASCO 2020

Hong et al. NEJM 2020

CODEBREAK 101 trial: Sotorasib + Panitumumab



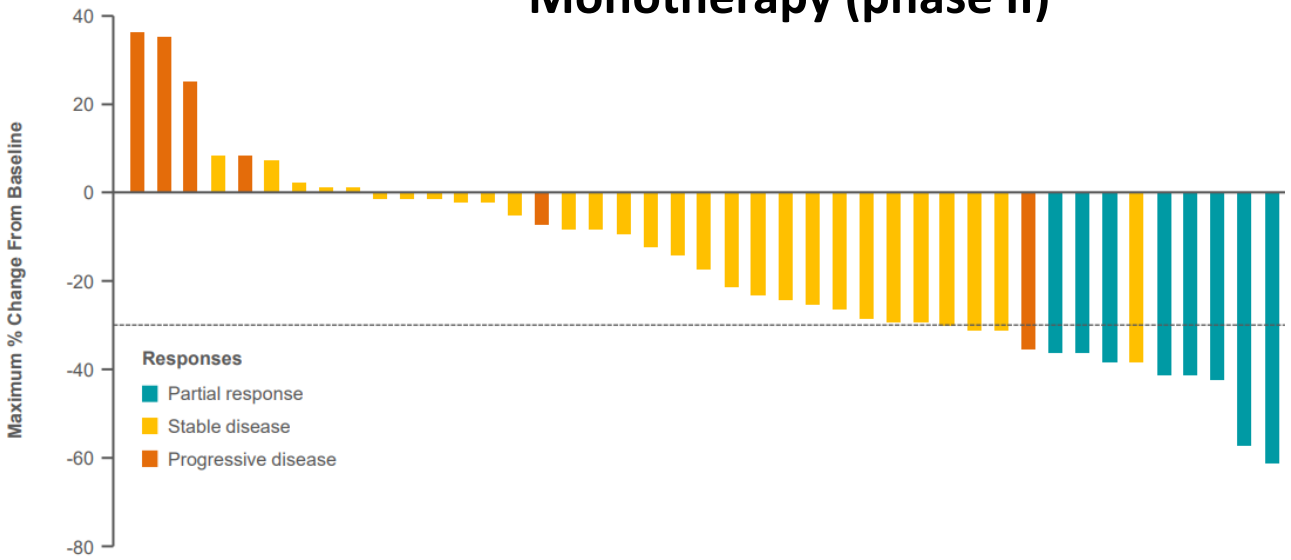
Response by investigator assessment	N = 40 n (%)
ORR confirmed (95% CI)	**12 (30)** (16.6, 46.5)
Complete response	0
Partial response	12 (30)
Stable disease*	25 (63)
Progressive disease	3 (8)
DCR (95% CI)	**37 (93)** (79.6, 98.4)

Data cutoff: June 24, 2022.
*Minimum requirement for stable disease was 5 weeks.
DCR, disease control rate; mCRC, metastatic colorectal cancer; ORR, objective response rate.

Kuboki et al ESMO 2022

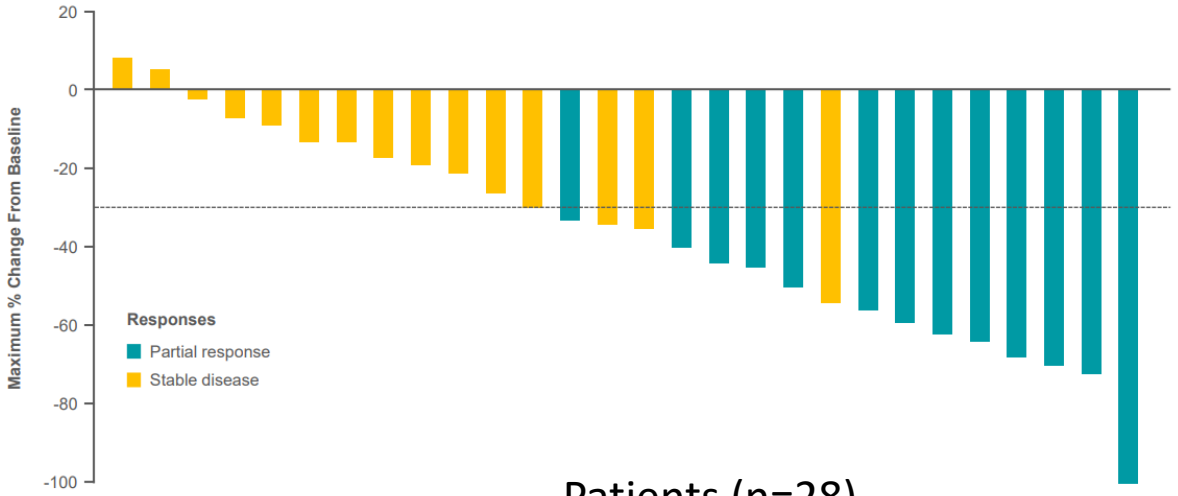
KRYSTAL-1 trial: Adagrasib in KRASG12c mut mCRC

Monotherapy (phase II)



Patients (n=43)
ORR 19% (8/43)
DCR 86% (37/43)

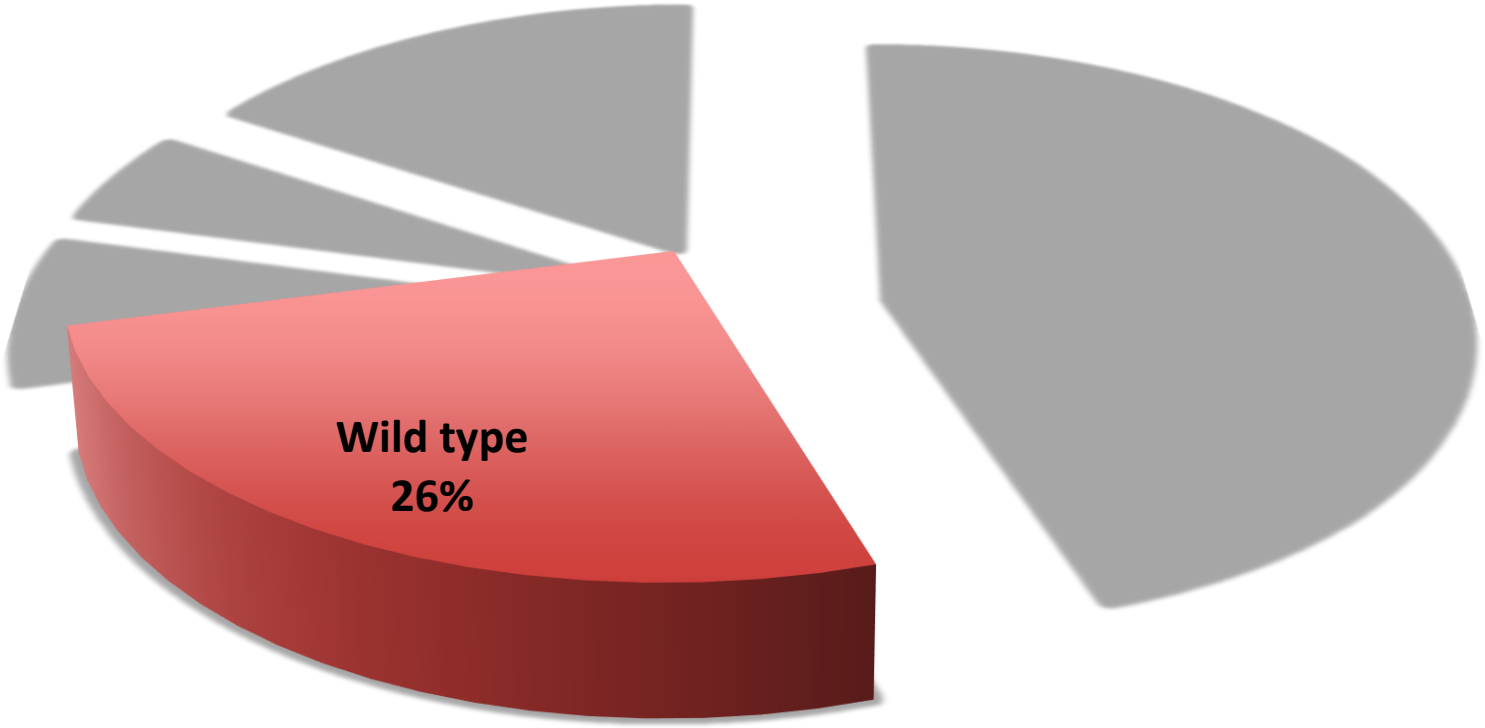
Combined with cetuximab (phase Ib)



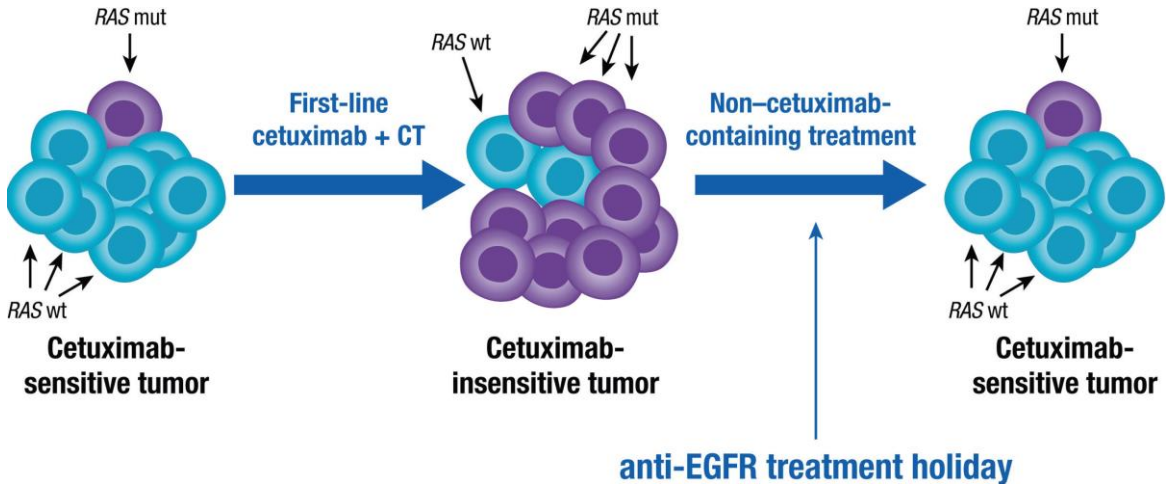
Patients (n=28)
ORR 46% (13/28)
DCR 100% (28/28)

Klempner et al ESMO 2022

Extended RAS/BRAF wild-type CRC



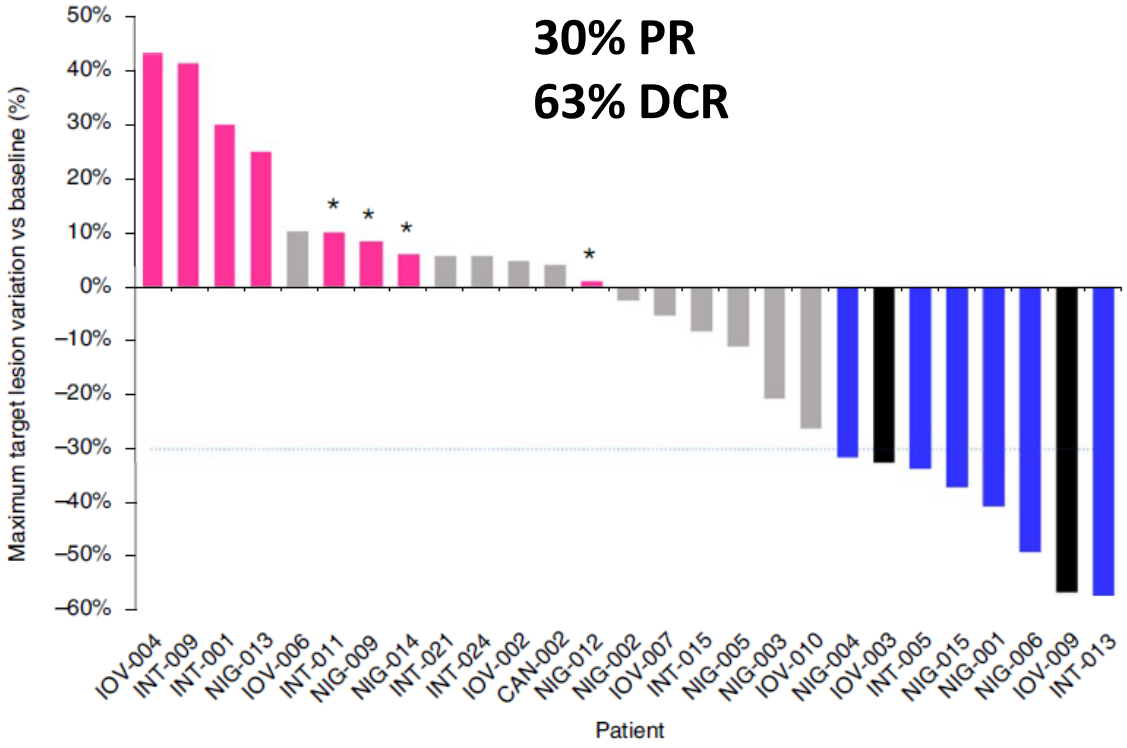
Rationale behind rechallenge with anti-EGFRs

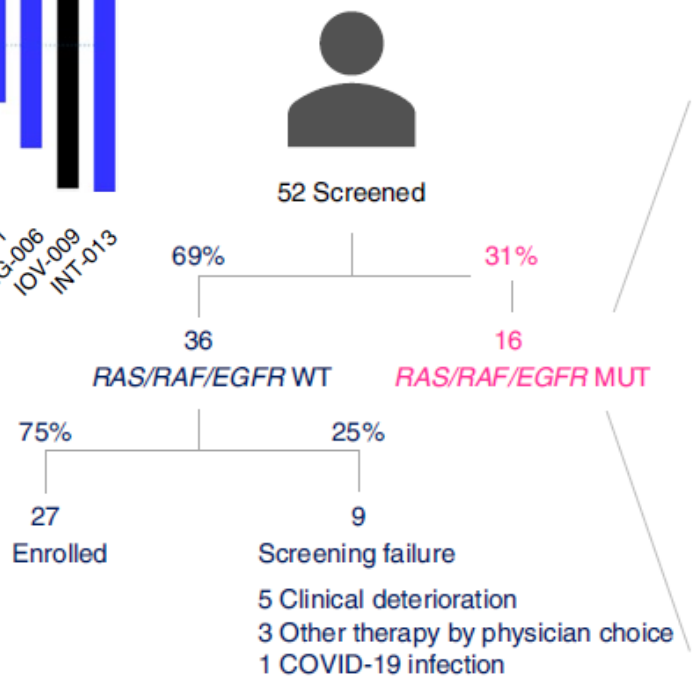


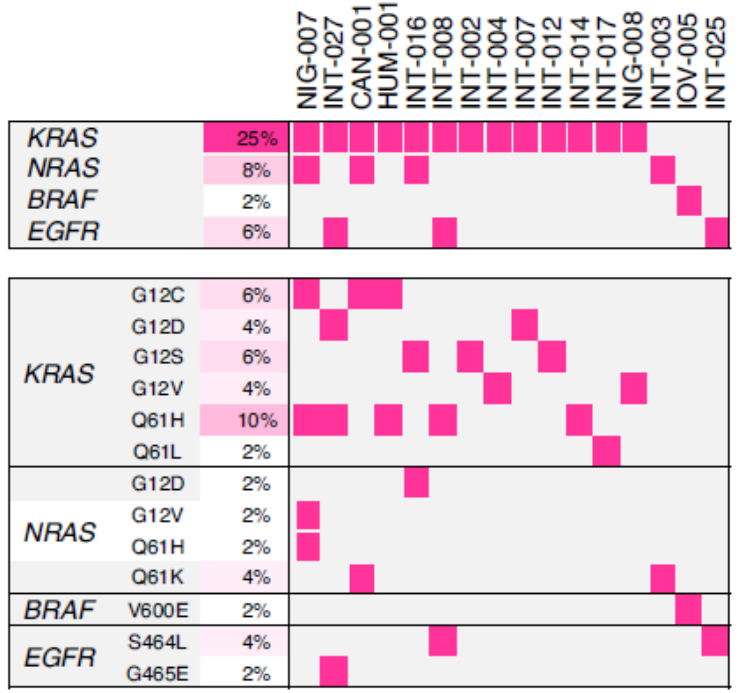
Study	Design	N pts	Treatment strategy	Median anti-EGFR interval (range)	ORR
Santini, 2012	Prosp	39	Cmab → Cmab	6.0 mos (2.0 - 12.0)	54%
Tsuji, 2016	Prosp	34	Cmab → Cmab	nr	3%
Nogueira, 2016	Retrosp	15	Cmab → Cmab	7.7 mos (1.6 - 30.0)	13%
Tanioka, 2017	Retrosp	14	Cmab → Cmab	13.1 mos (6.0 - 37.1)	21%
Cremolini, 2018	Prosp	28	Cmab → Cmab	nr	21%
Tsuji, 2018	Prosp	24	Pmab → Pmab	nr	8%
Osawa, 2018	Prosp	33	Cmab → Cmab	>4.0 mos	16%

Goldberg ESMO open 2018

The CHRONOS trial cDNA to guide rechallenge with anti-EGFR

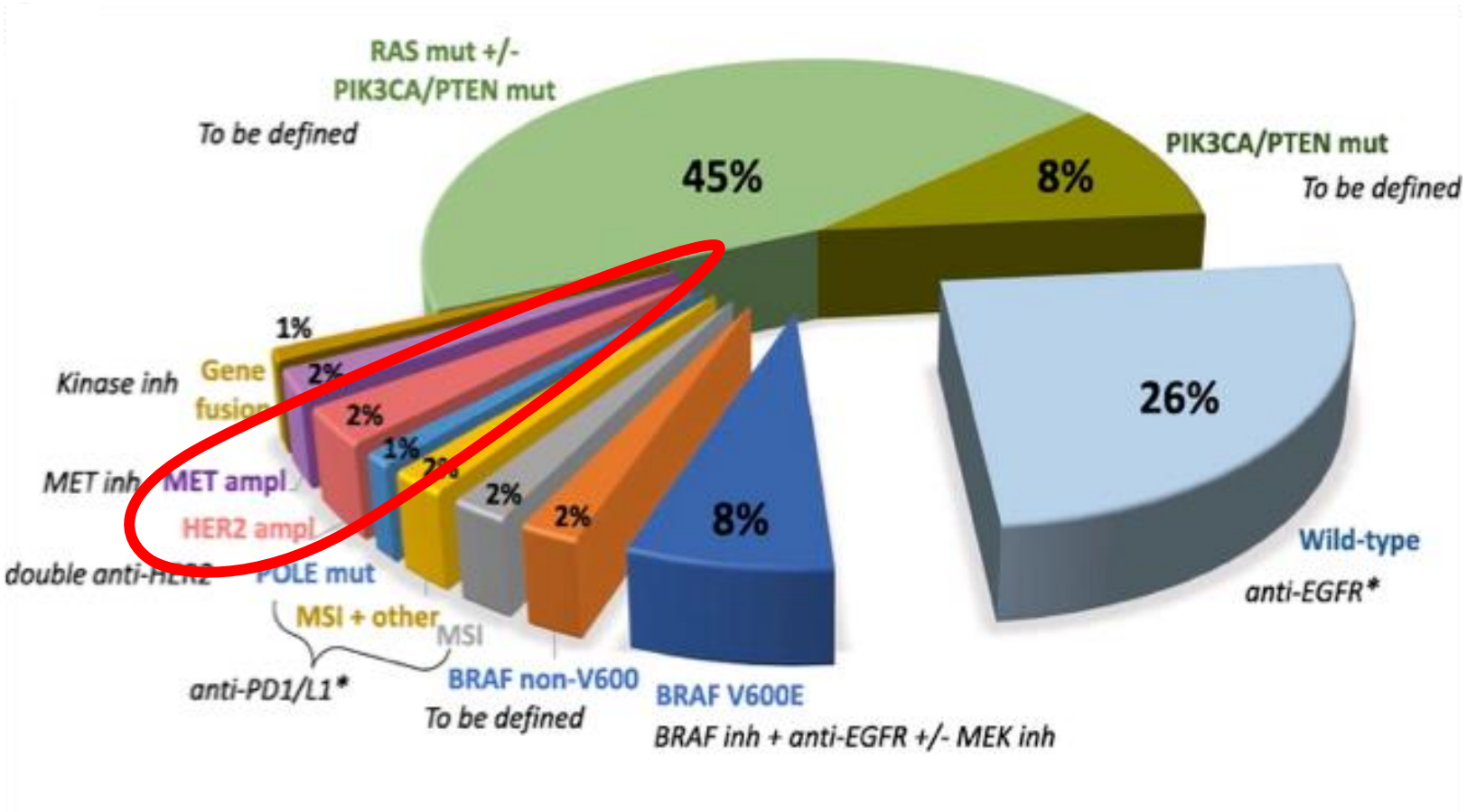




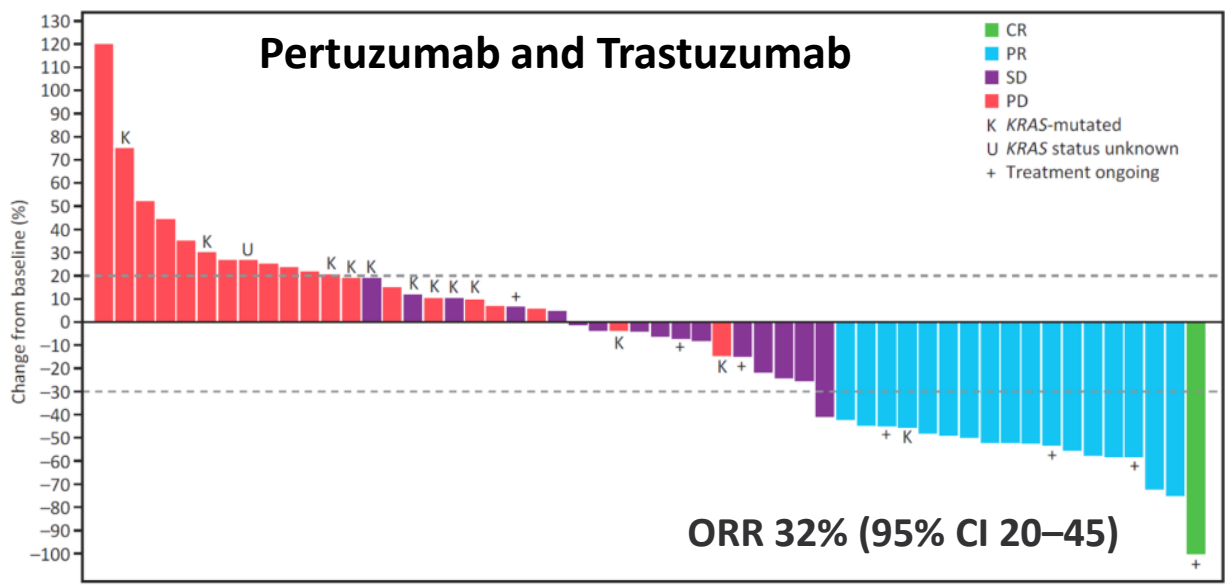


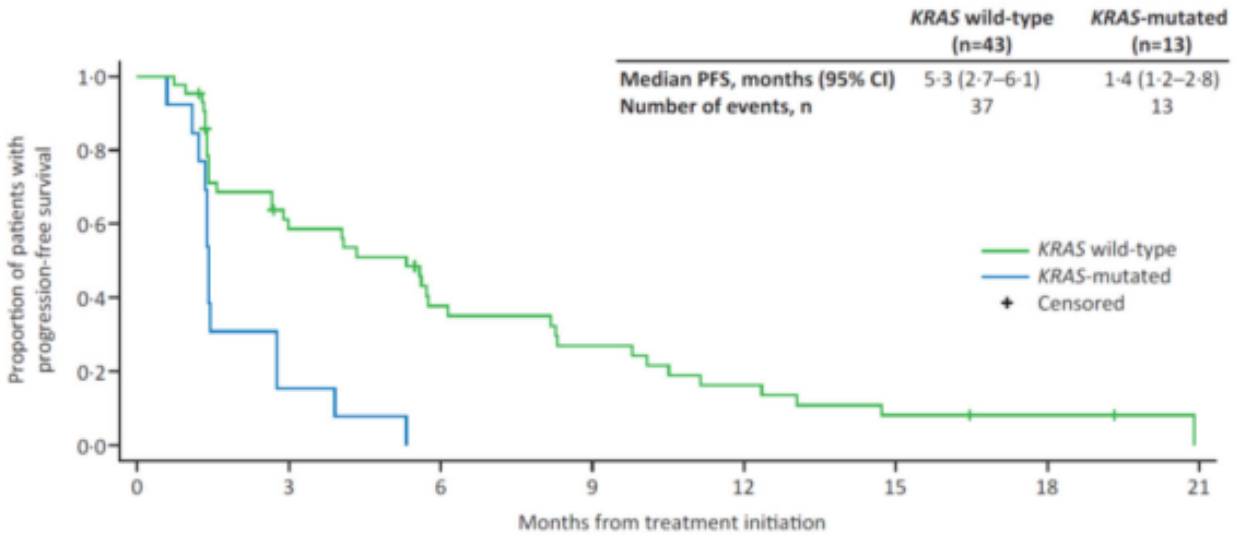
Sartore-Bianchi Nat Med 2022

MOLECULARLY SEGMENTED CRC: HER2 amplification

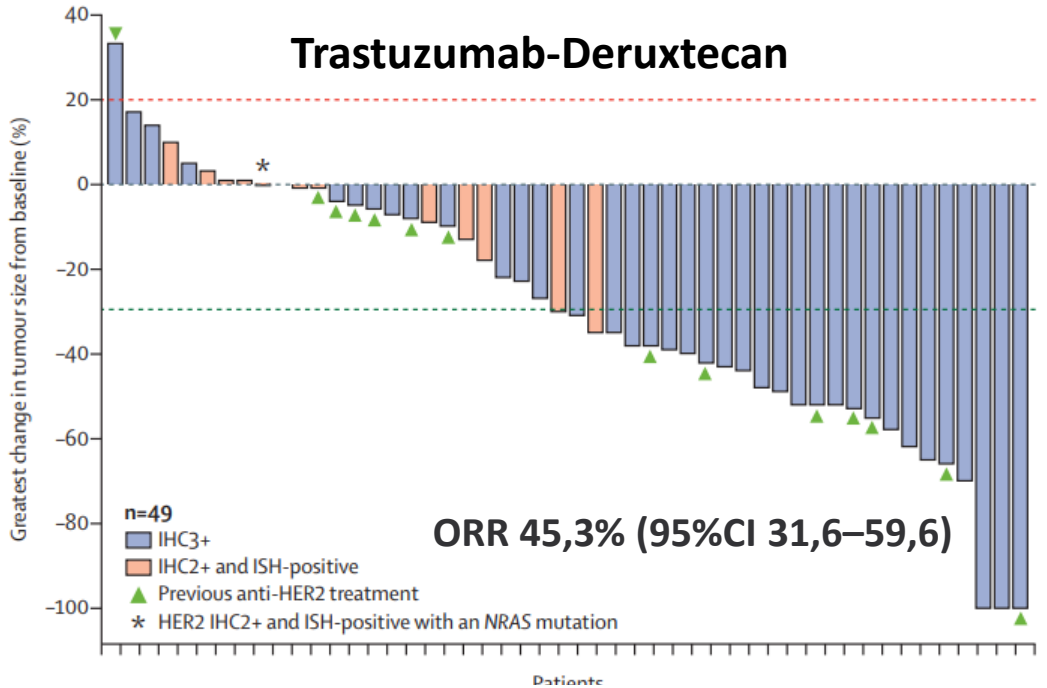


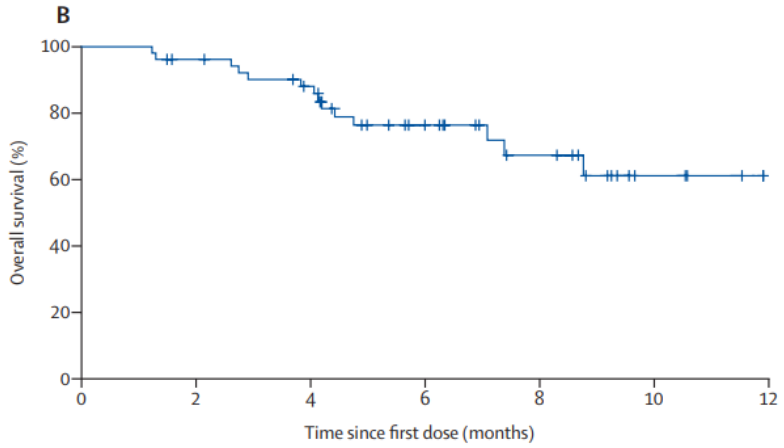
HER2-Oriented Therapies in HER2 amplified mCRC





Meric-Bernstam et al Lancet Oncol 2019

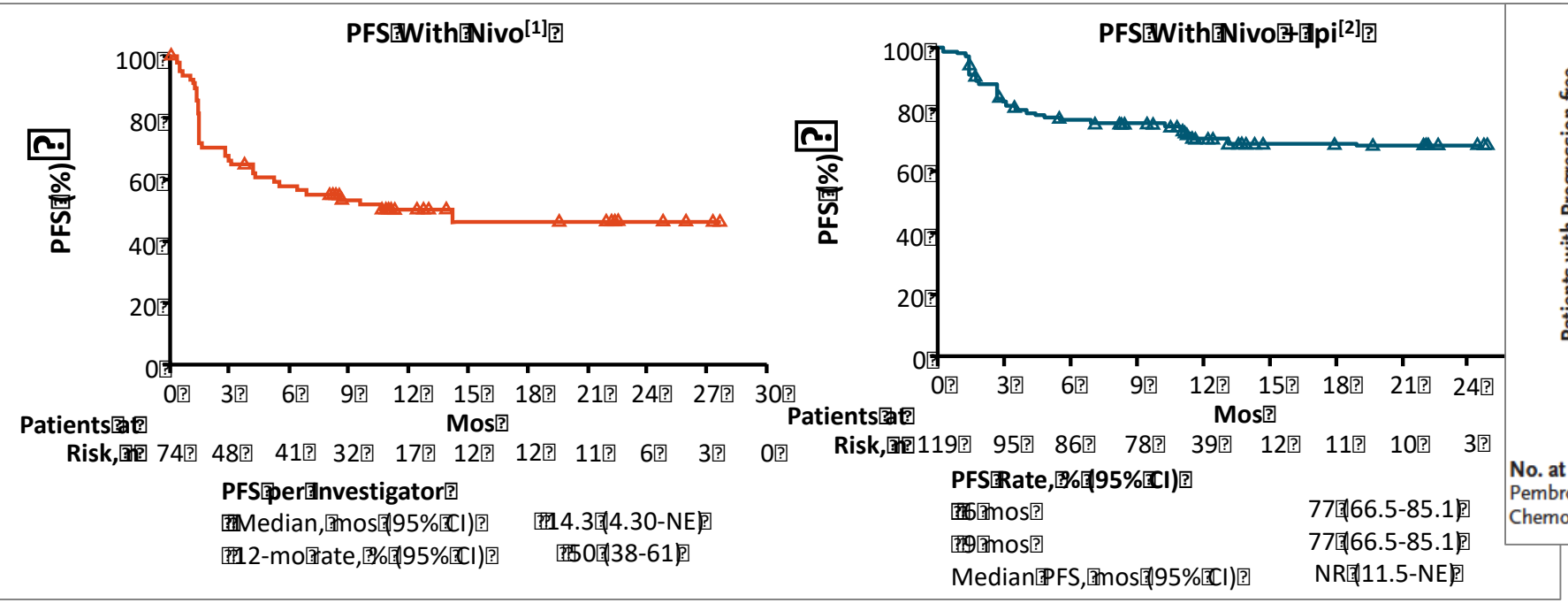


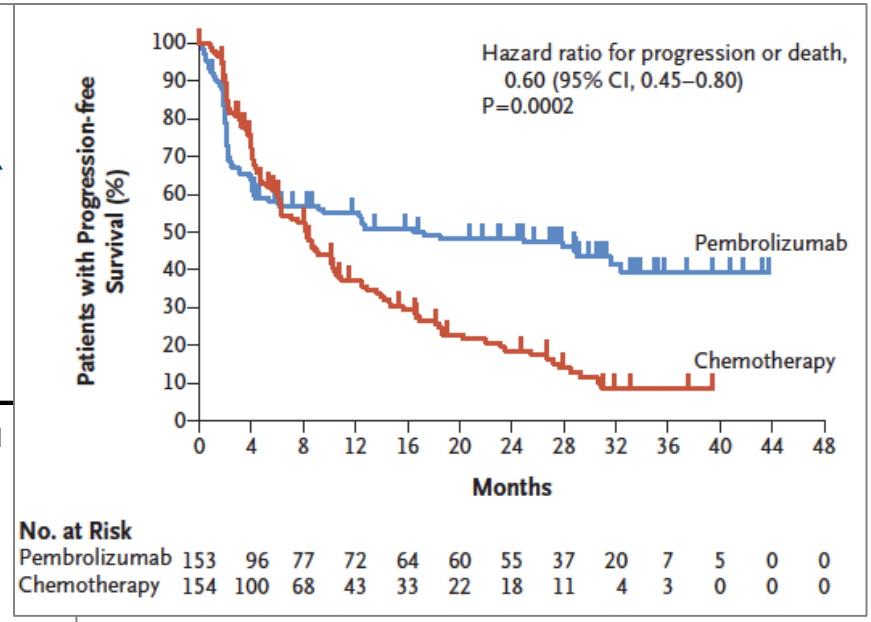


Siena et al Lancet Oncol 2021

MSI-H as positive predictive biomarker for immunotherapy

Immunotherapy in MSI-H CRC

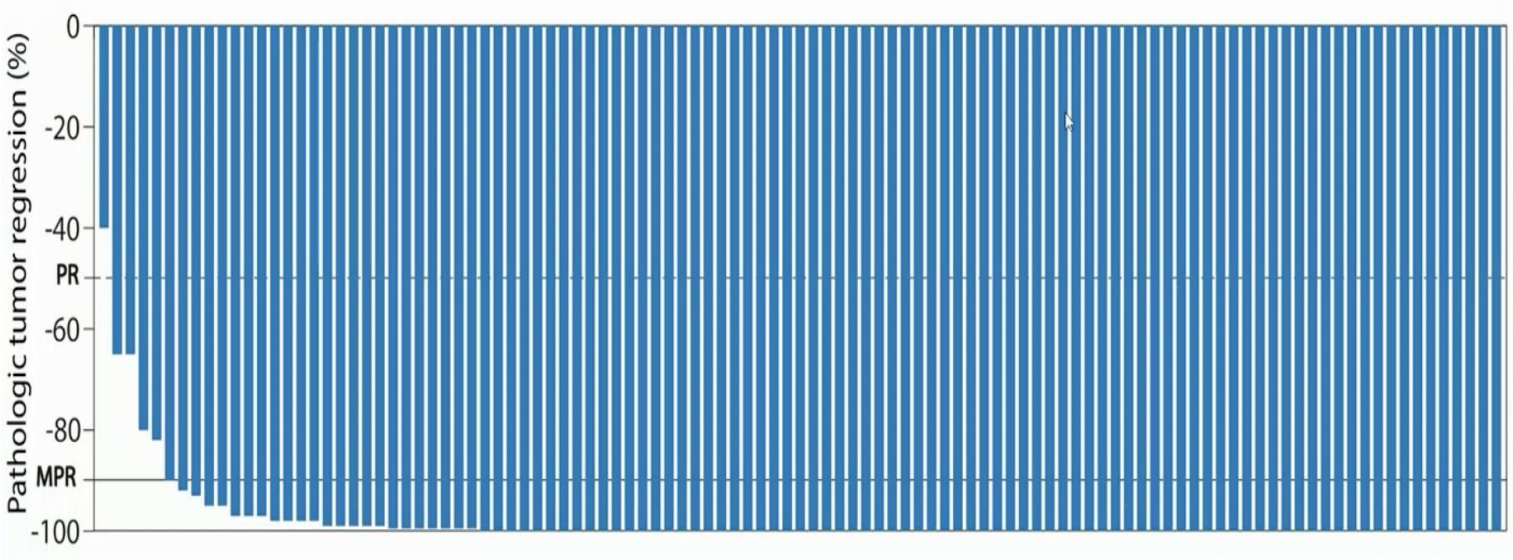




Overman et al. J Clin Oncol 2018

Andre et al. NEJM 2020

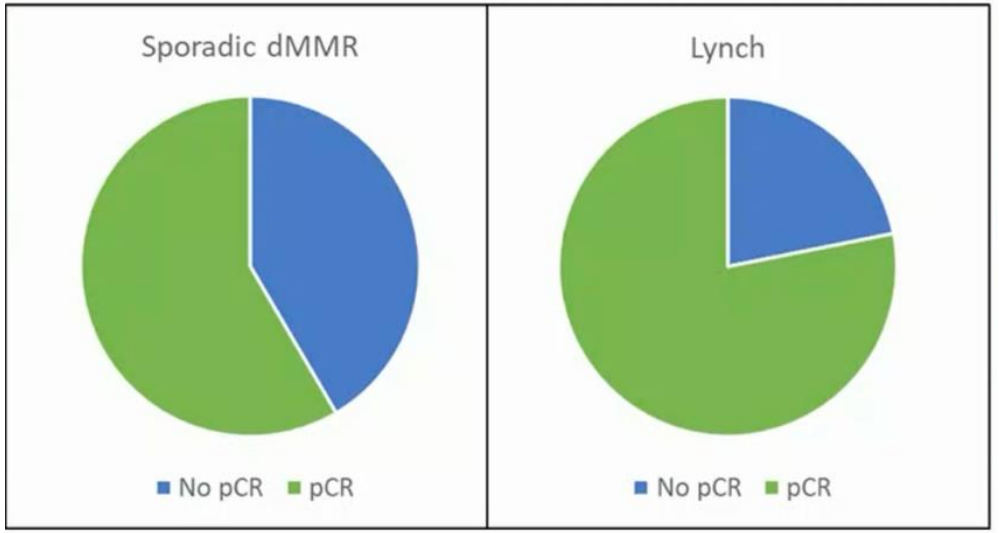
Combination immunotherapy early stage CRC: NICHE trial



pCR 67% - Major Path response 95%

	No pCR	pCR	
Sporadic tumor *n* = 65	27 (42%)	38 (58%)	p = 0.056
Lynch Syndrome *n* = 32	7 (22%)	25 (78%)	

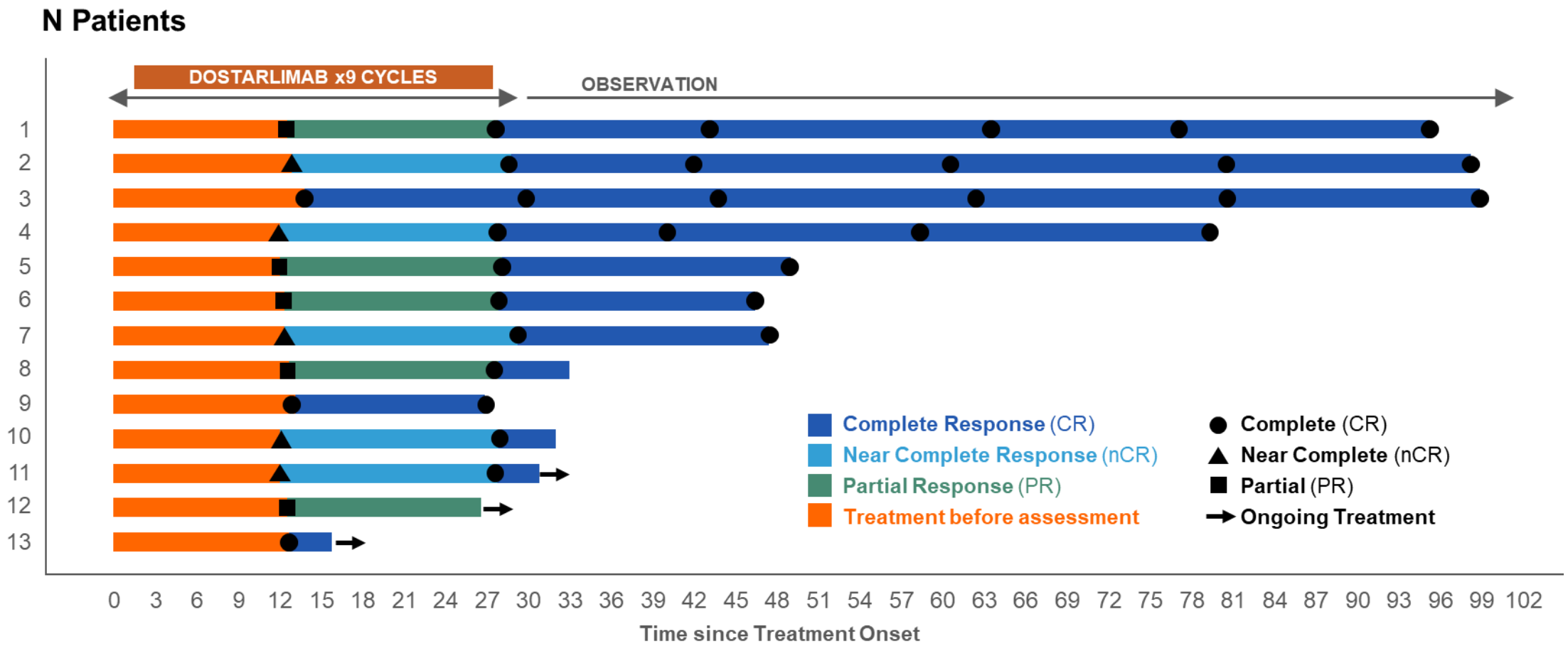
N totals 97 patients in the per protocol population for whom Lynch status was available at data cut-off



Chalabi et al. ESMO 2022
Chalabi, Nat Med 2020

Dostarlimab alone in locally advanced MSI-H Rectal Cancer

Radiological Responses



Lumish et al. ASCOGI 2022, Abs #16

Temozolomide in glioblastoma: hypermutation phenotype upon progression

Loss of the Mismatch Repair Protein MSH6 in Human Glioblastomas Is Associated with Tumor Progression during Temozolomide Treatment

Daniel P. Cahill,[1,2] Kymberly K. Levine,[1] Rebecca A. F... Linsey B. Reavie,[1] Tracy T. Batchelor,[3] P. Andrew Fu... A. John Iafrate,[1] and David N. Louis[1,4]

MSH6 Mutations Arise in Glioblastomas during Temozolomide Therapy and Mediate Temozolomide Resistance

Stephen Yip,[1,4] Jiangyong Miao,[1,4] Daniel P. Cahill,[1,2] A. John Iafrate,[1,3,4] Ken Aldape,[5] Catherine L. Nutt,[1,4] and David N. Louis[1,2,3,4]

A Hypermutation Phenotype and Somatic *MSH6* Mutations in Recurrent Human Malignant Gliomas after Alkylator Chemotherapy

Chris Hunter,[1] Raffaella Smith,[1] Daniel P. Cahill,[2] Philip Stephens,[1] Claire Stevens,[1] Jon Teague,[1] Chris Greenman,[1] Sarah Edkins,[1] Graham Bignell,[1] Helen Davies,[1] Sarah O'Meara,[1] Adrian Parker,[1] Tim Avis,[1] Syd Barthorpe,[1] Lisa Brackenbury,[1] Gemma Buck,[1] Adam Butler,[1] Jody Clements,[1] Ed Dicks,[1] Simon Forbes,[1] Matthew Gorton,[1] Kristian Gray,[1] Kelly Halliday,[1] Andy Jenkinson,[1] David Jones,[1] Andrew Menzies,[1] Janet Perry,[1] Rebecca Shepherd,[1] Alexandra Small,[1] ...ie West,[1] Sara Widaa,[1] Andy Yates,[1] ...Roy,[2] Kymberly K. Levine,[2] ...is,[2] Michael R. Stratton,[1,5]

Clinical Cancer Research

Mutational A... Origin and Th... of Recurrent ...

Brett E. Johnson,[1*] Tali Mazor,[1*] Chibo Hong,[1] Michael Barnes,[2] Koki Aihara,[3,4] Cory Y. McLean,[1†] Shaun D. Fouse,[1] Shogo Yamamoto,[3] Hiroki Ueda,[3] Kenji Tatsuno,[3] Saurabh Asthana,[5,6] Llewellyn E. Jalbert,[7] Sarah J. Nelson,[7,8] Andrew W. Bollen,[2] W. Clay Gustafson,[9] Elise Charron,[10] William A. Weiss,[1,9,10] Ivan V. Smirnov,[1] Jun S. Song,[11,12] Adam B. Olshen,[6,11] Soonmee Cha,[1] Yongjun Zhao,[13] Richard A. Moore,[13] Andrew J. Mungall,[13] Steven J. M. Jones,[13] Martin Hirst,[13] Marco A. Marra,[13] Nobuhito Saito,[4] Hiroyuki Aburatani,[3] Akitake Mukasa,[4] Mitchel S. Berger,[1] Susan M. Chang,[1] Barry S. Taylor,[5,6,11]‡ Joseph F. Costello[1]‡

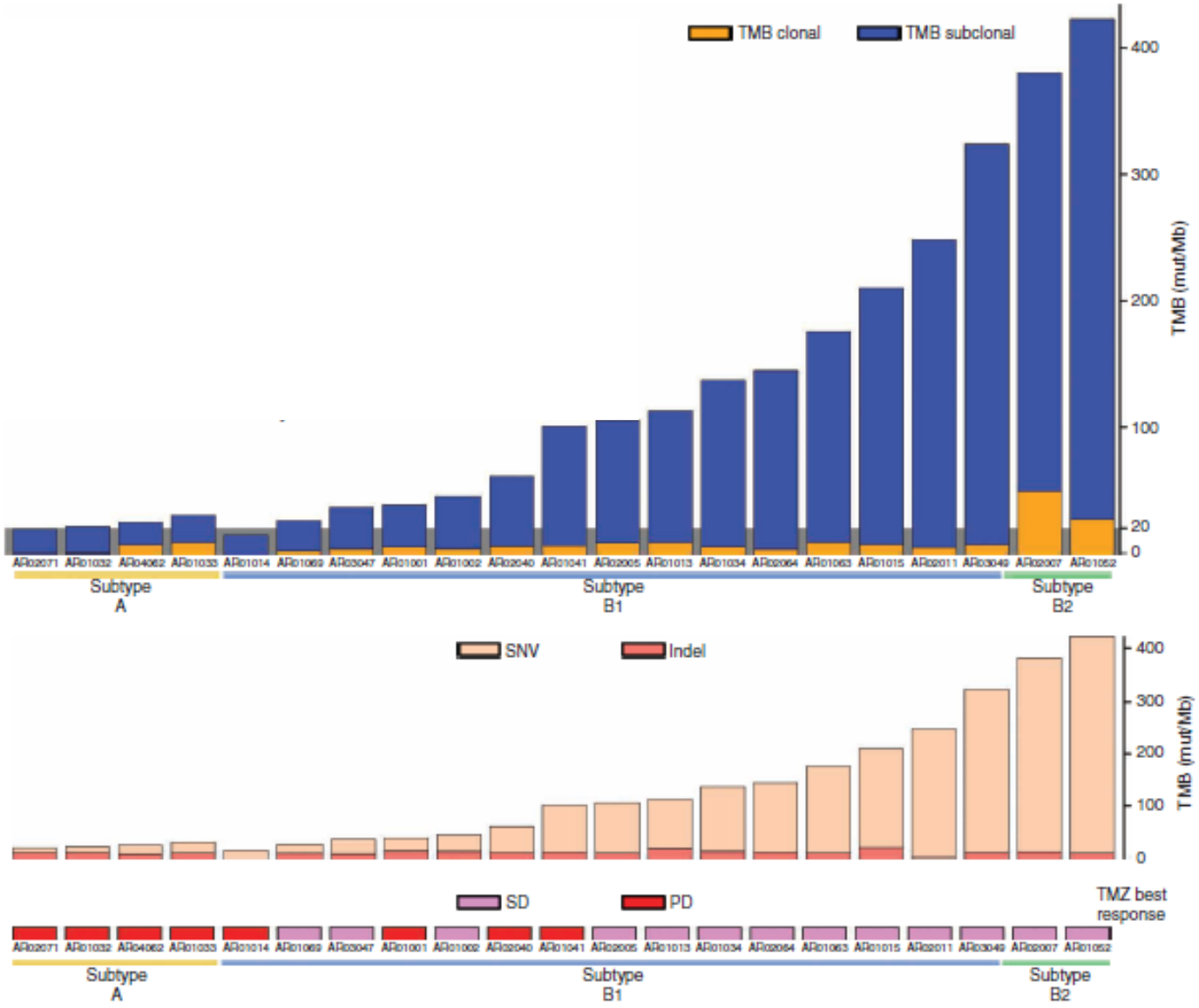
...ling of ... MMR-Deficient ...

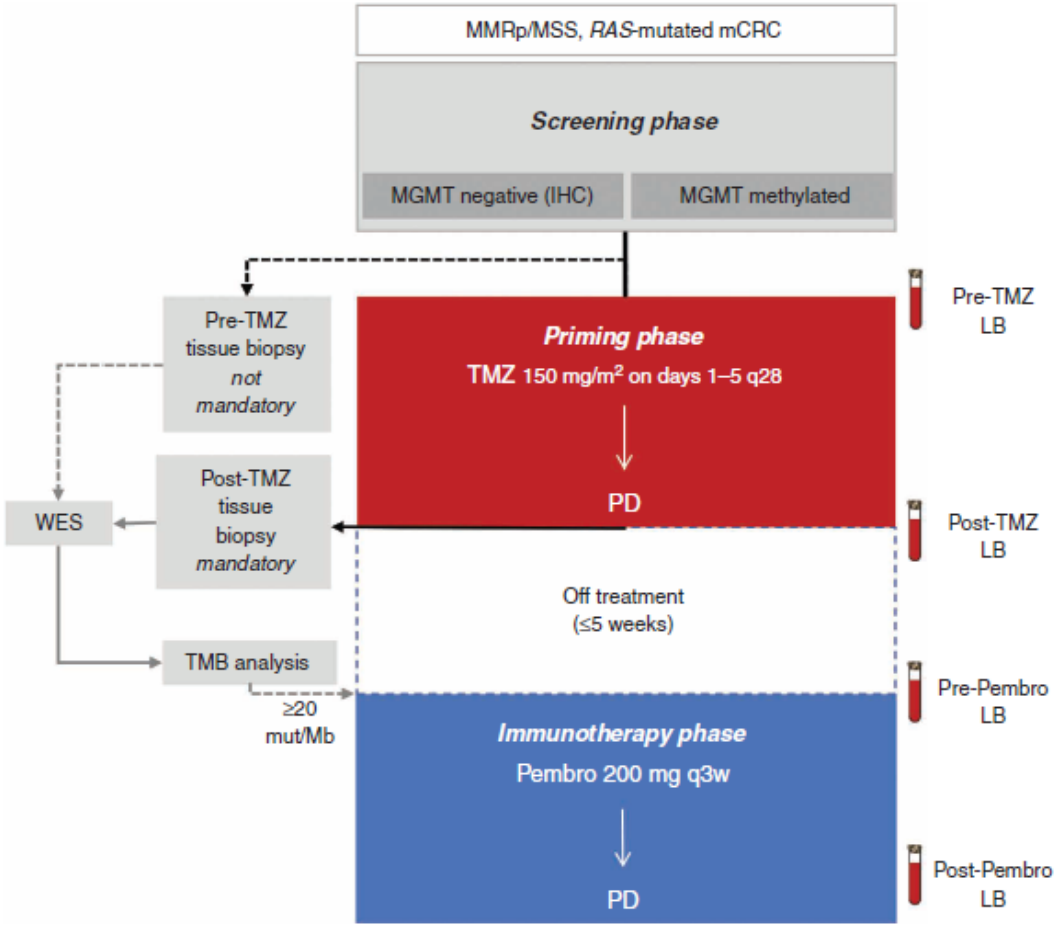
Stefano Indraccolo[1], Giuseppe Lombardi[2], Matteo Fassan[3], Lorenza Pasqualini[1], Silvia Giunco[1], Raffaella Marcato[1], Alessandra Gasparini[1], Cinzia Candiotto[1], Silvia Nalio[1], Pasquale Fiduccia[4], Giuseppe Nicolò Fanelli[3], Ardi Pambuku[2], Alessandro Della Puppa[5], Domenico D'Avella[6], Laura Bonaldi[1], Marina Paola Gardiman[7], Roberta Bertorelle[1], Anita De Rossi[1,8], and Vittorina Zagonel[2]

Does this mean that these tumours may become sensitive to immunotherapy…?

Hunter, Cancer Res 2006; Cahill, Clin Cancer Res 2007; Yip, Clin Cancer Res 2009; Johnson, Science 2014; Indraccolo, Clin Cancer Res 2019

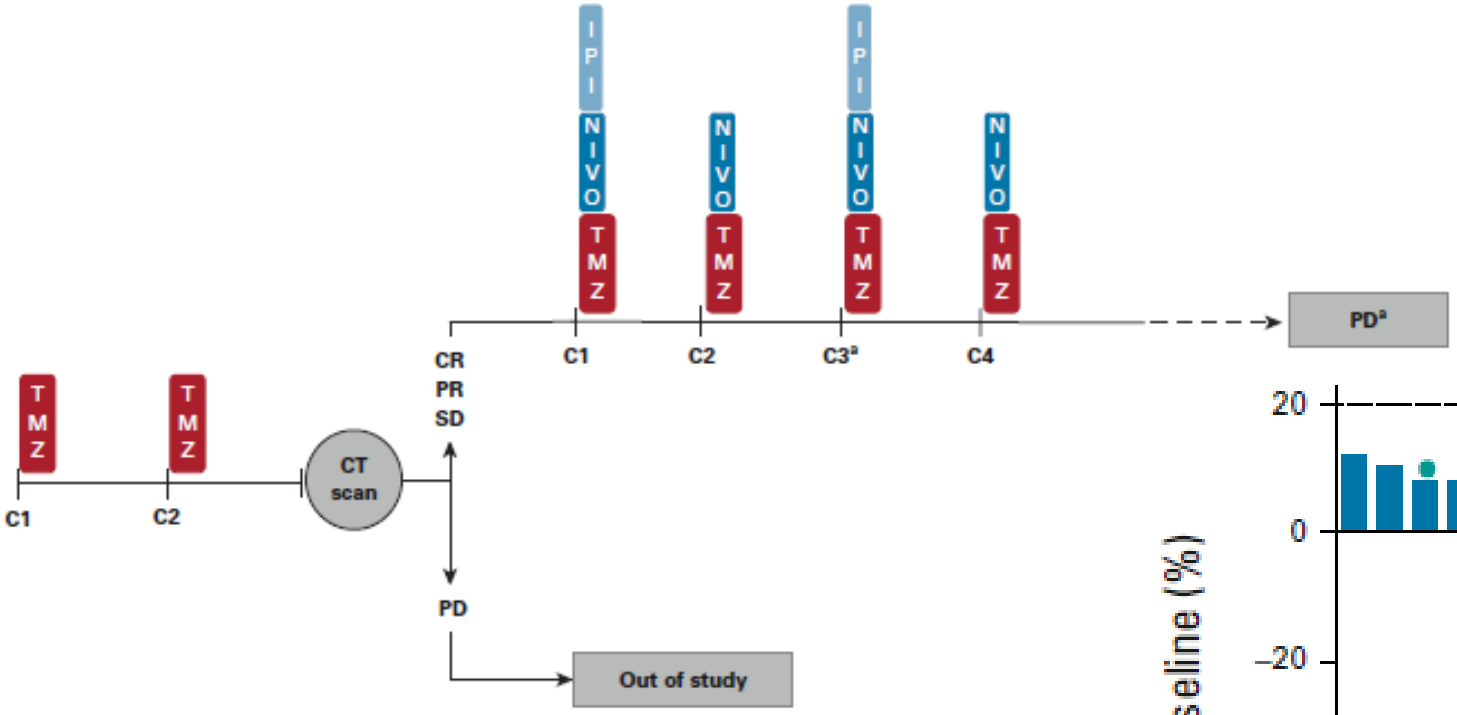
The ARETHUSA trial: Temozolomide priming for MSS mCRC

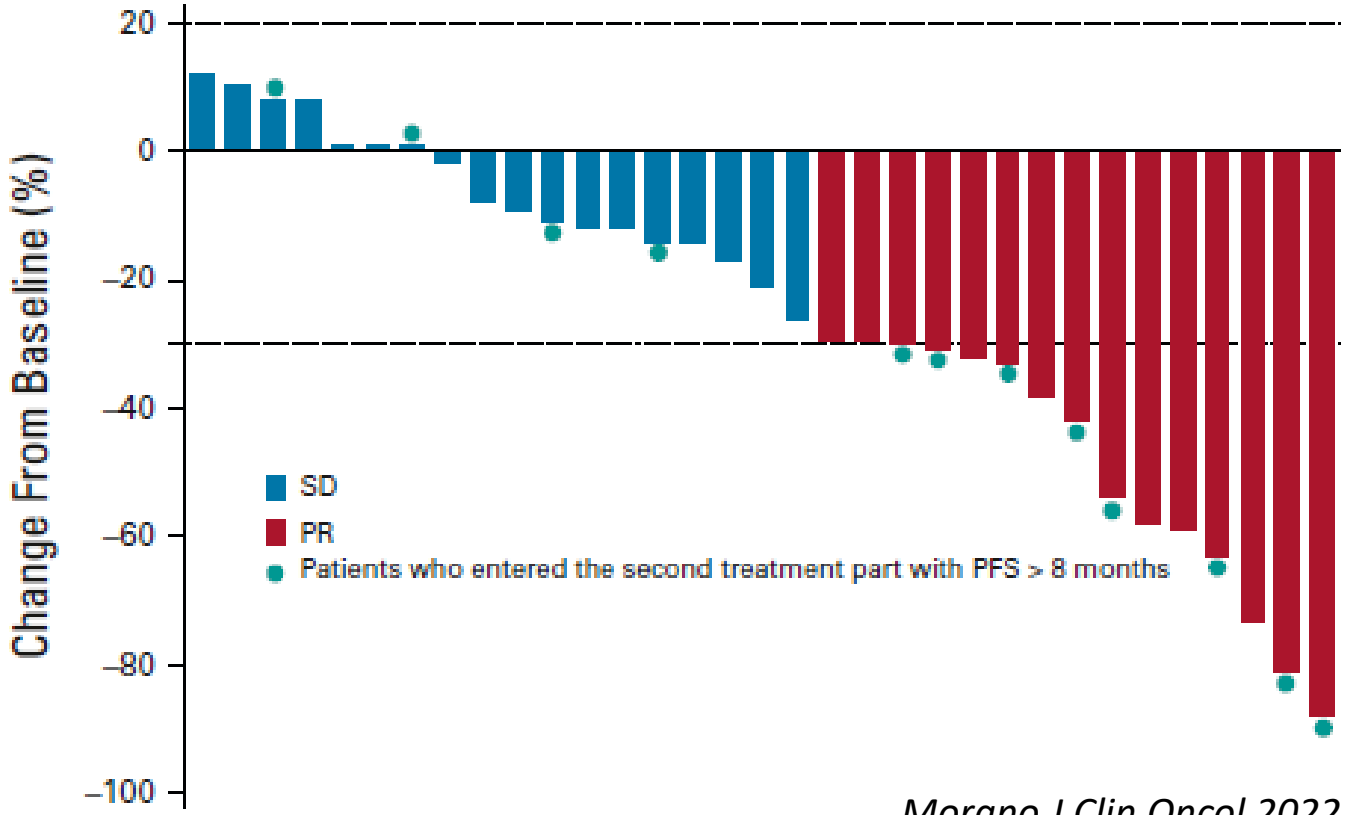




2022 Crisafulli Cancer Discov

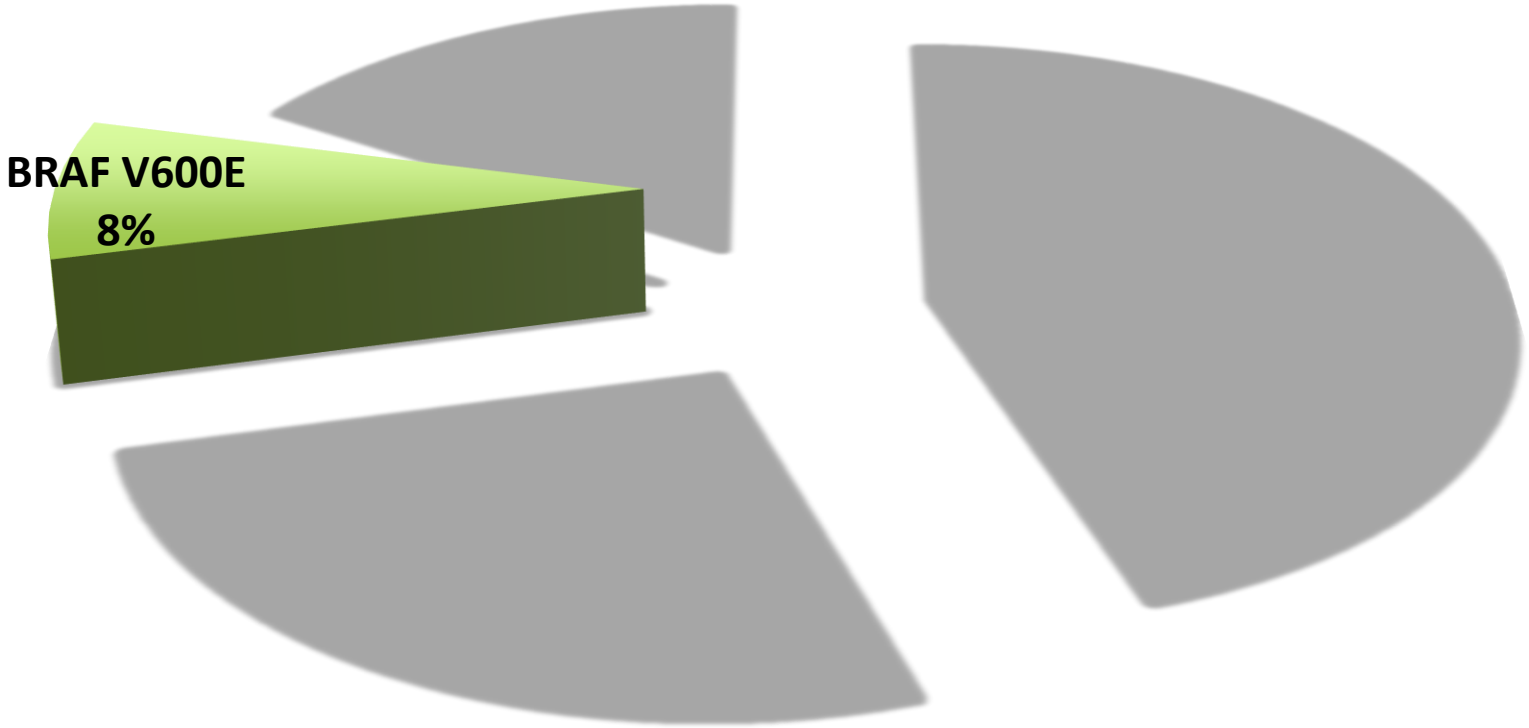
MAYA trial: TMZ and Ipi/Nivo MSS-MGMT hypermethyl mCRC





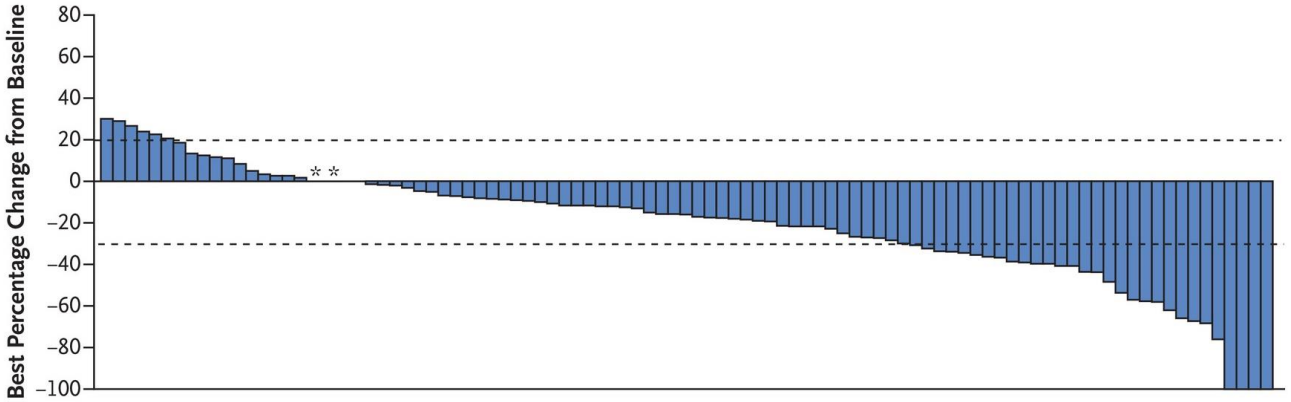
Morano J Clin Oncol 2022

BRAF mutations

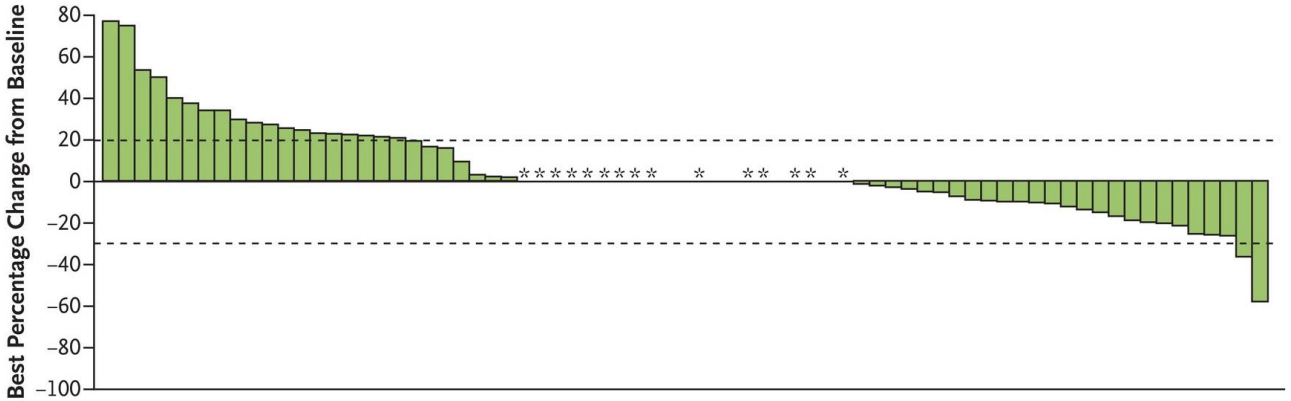


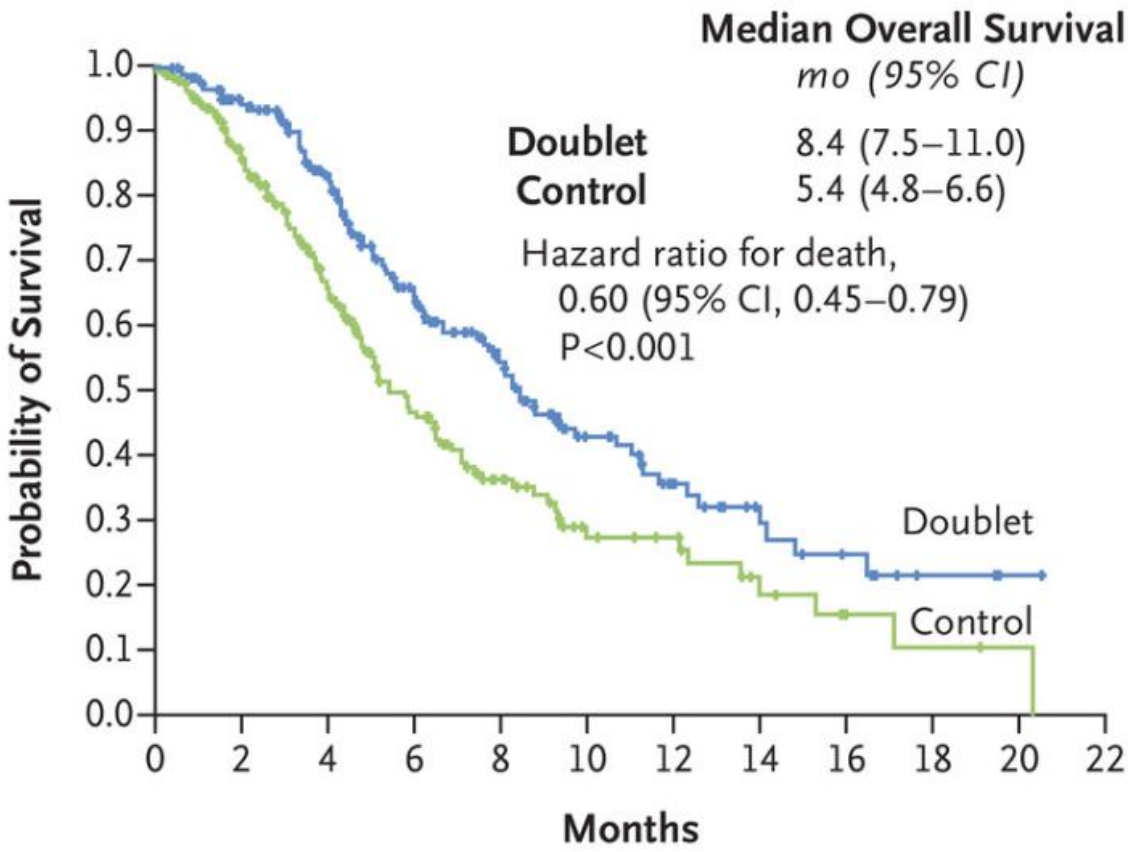
BRAF-EGFR inhibition in BRAFV600E mCRC: Beacon

Encorafenib+Cetuximab



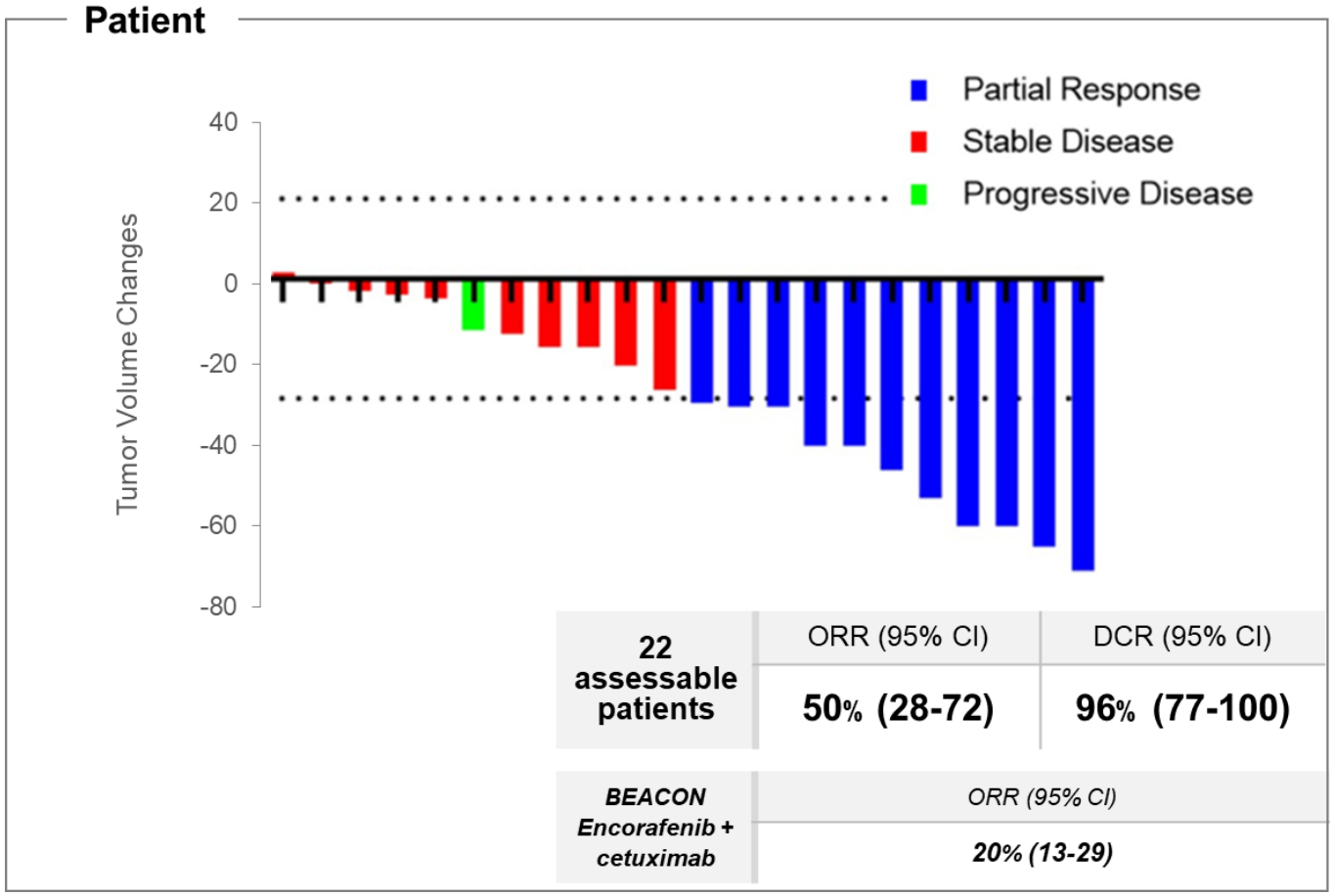
Control (Iri+Cetuximab or Folfiri+Cetuximab)





Kopetz et al, N Engl J Med 2019

Encorafenib/cetux + Nivolumab in BRAFm V600E MSS CRC

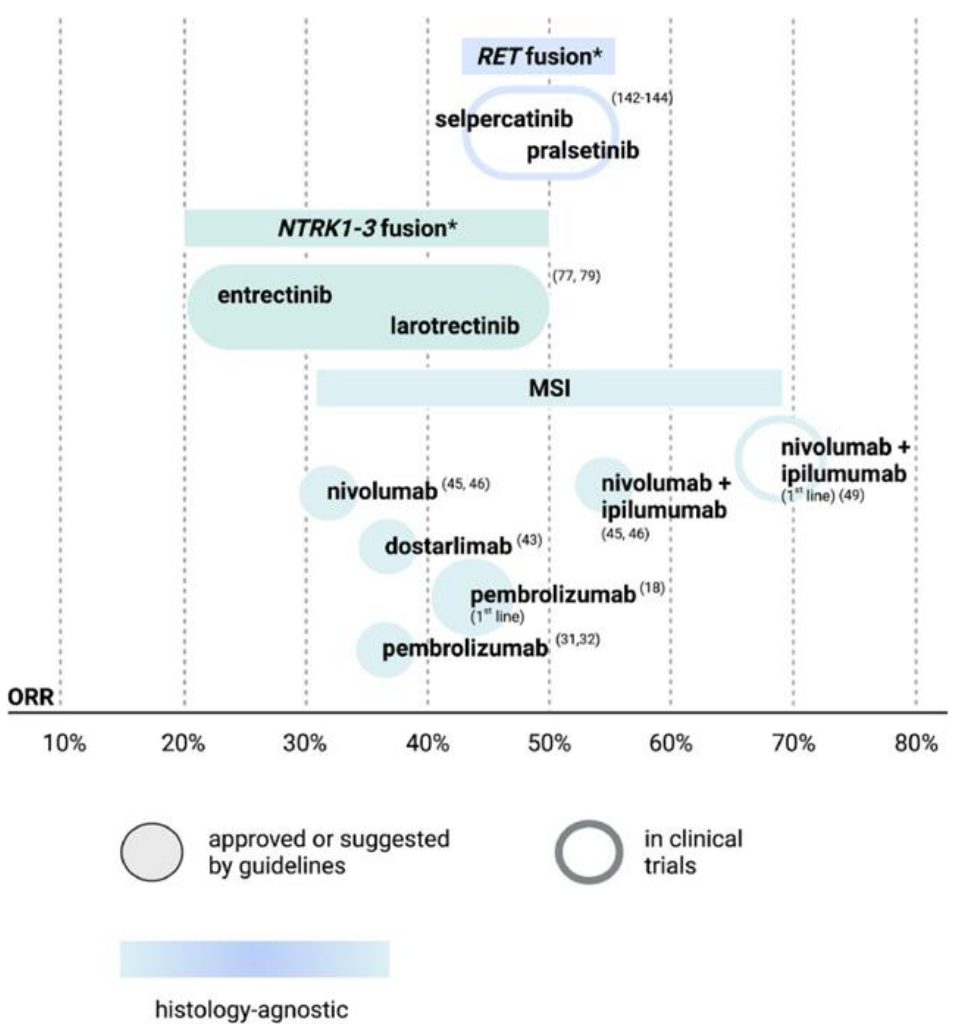


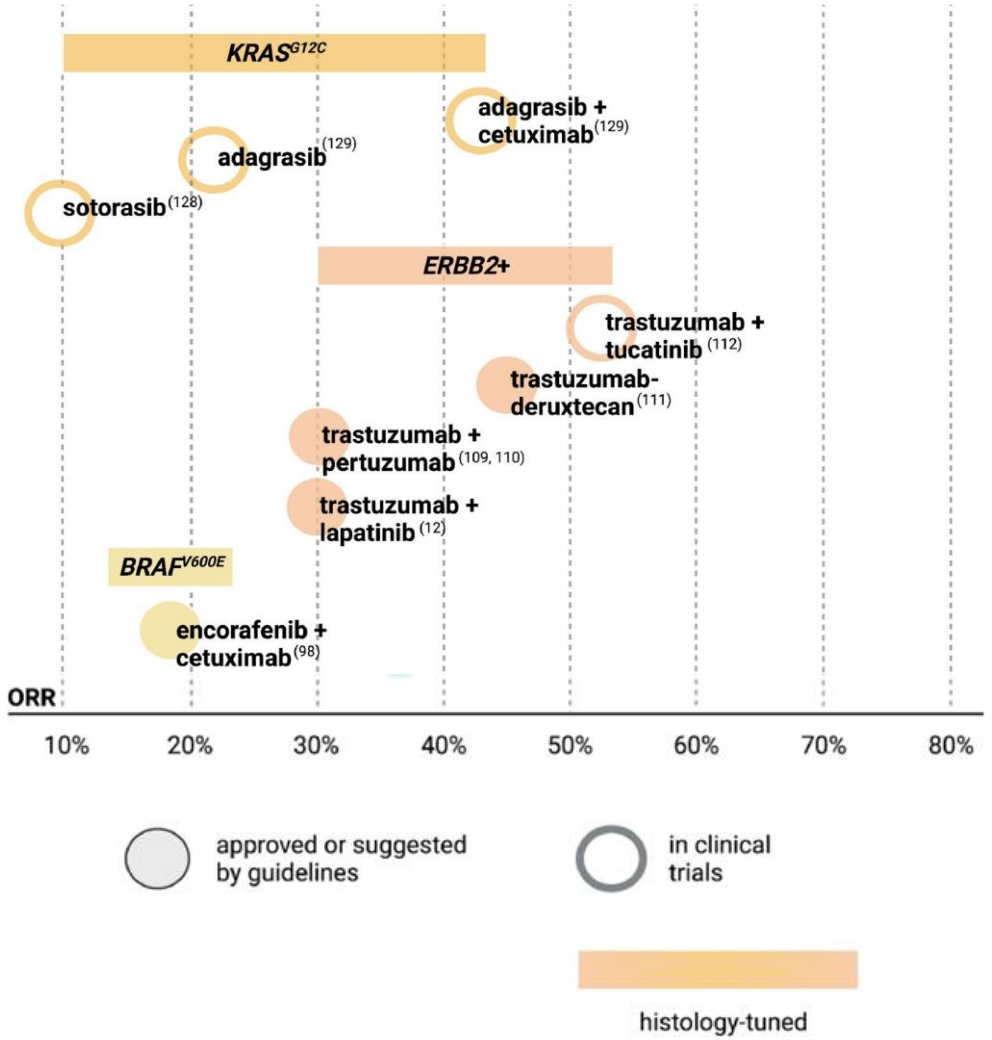
Study	mPFS (95%CI)	mOS (95%CI)	
Encora/Cetux/ Nivo	7.7 months (5.6-NA)	15.1 months (7.7-NA)	*
Beacon	4.2 months (3,7-5,4)	8,4 (7,5-11,0)	*

**historical comparison without scientific value*

Russo et al Science 2019
Morris et al. ASCOGI 2022, Abs #12

Histology-agnostic and Histology-tuned Developments in CRC





Sartore-Bianchi et al Dig Liver Dis 2022

CONCLUSIONS

One Size Does Not Fit All