City of Hope

THIRD ANNUAL
ISSPP Congress 2022
International Society for the Study of Pleura and Peritoneum

COLORECTAL CANCERS

Systemic Approaches to Colorectal Peritoneal Metastases

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Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Disclosures

- Consultant for Bayer, Daiichi Sankyo, Inc., Eisai, Exact Sciences, Foundation Medicine, Lilly, Merck, Natera, Servier, Seattle Genetics, Delcath Systems, QED, and Taiho Pharmaceutical Co, Ltd.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their products and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

The following CLC & IB components will be addressed in this presentation:

- Differences seen in this patient population.
- Disparity in data.

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Key Learning Objectives

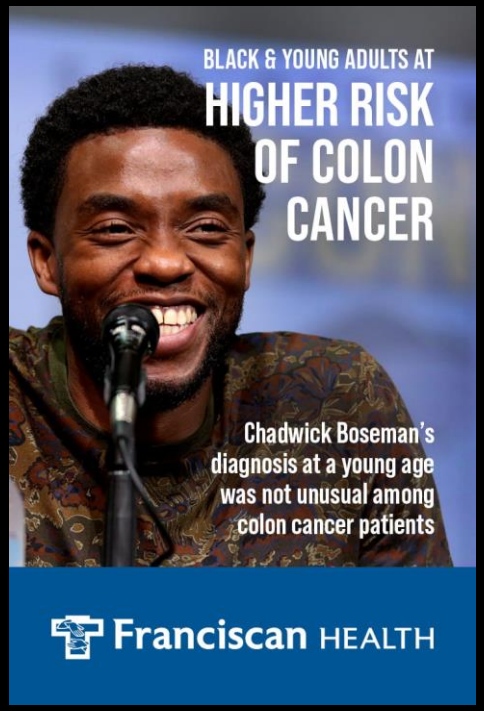
1. Understand what are the **systemic approaches** for patients with colorectal cancer
2. Understand that advances are coming in "**subsets of subsets**."
3. Understand what the **subset of patients with peritoneal metastasis** entails.

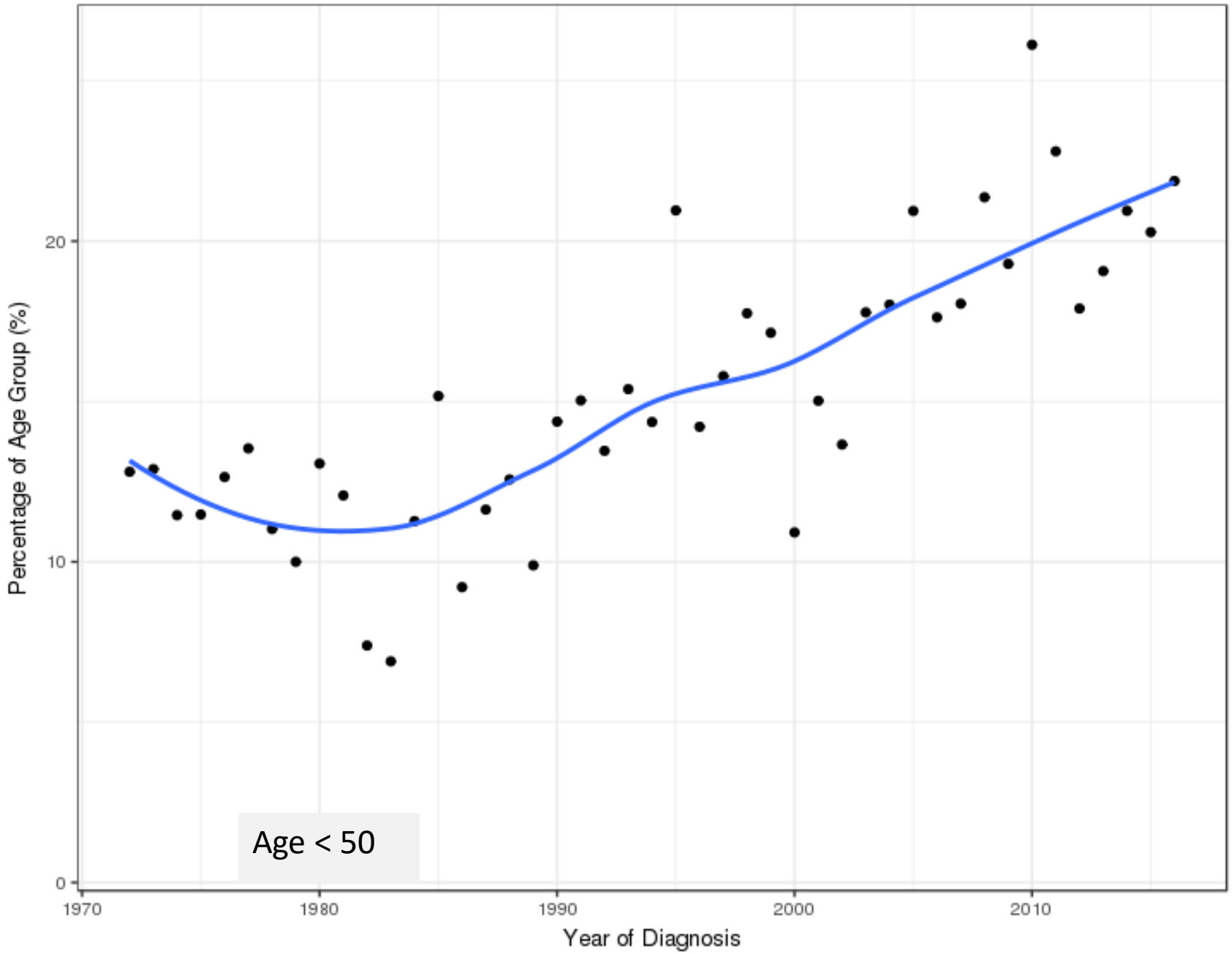
Trends and Biology

SECTIONS HOME SEARCH The New York Times

WELL | LIVE

More Young People Are Dying of Colon Cancer





@pashtoonkasi

Kasi PM, et al. Presented at ASCO 2018.Published: Clinical Colorectal Cancer March 2019; 18(1): e87-95

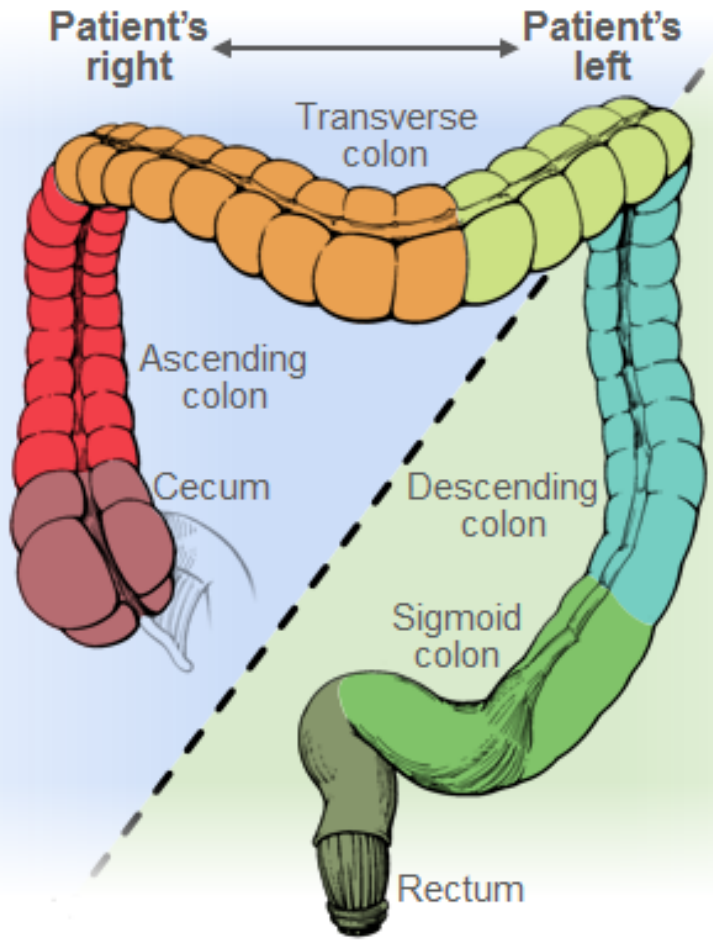
RIGHT vs. LEFT

MIDGUT DERIVATIVE

- females
- sessile serrated lesions
- mucinous tumors

Overall WORSE prognosis

- CIMP-high
- BRAF
- MSI-high
- CMS-1-MSI immune tumors
- CMS-3-metabolic tumors
- (KRAS)



HINDGUT DERIVATIVE

- males

Overall BETTER prognosis

- CMS-4-MSI mesenchymal
- CMS-2-canonical distally
- TP53
- APC

EGFR → RAS → $BRAF^{V600E}$ → MEK → ERK

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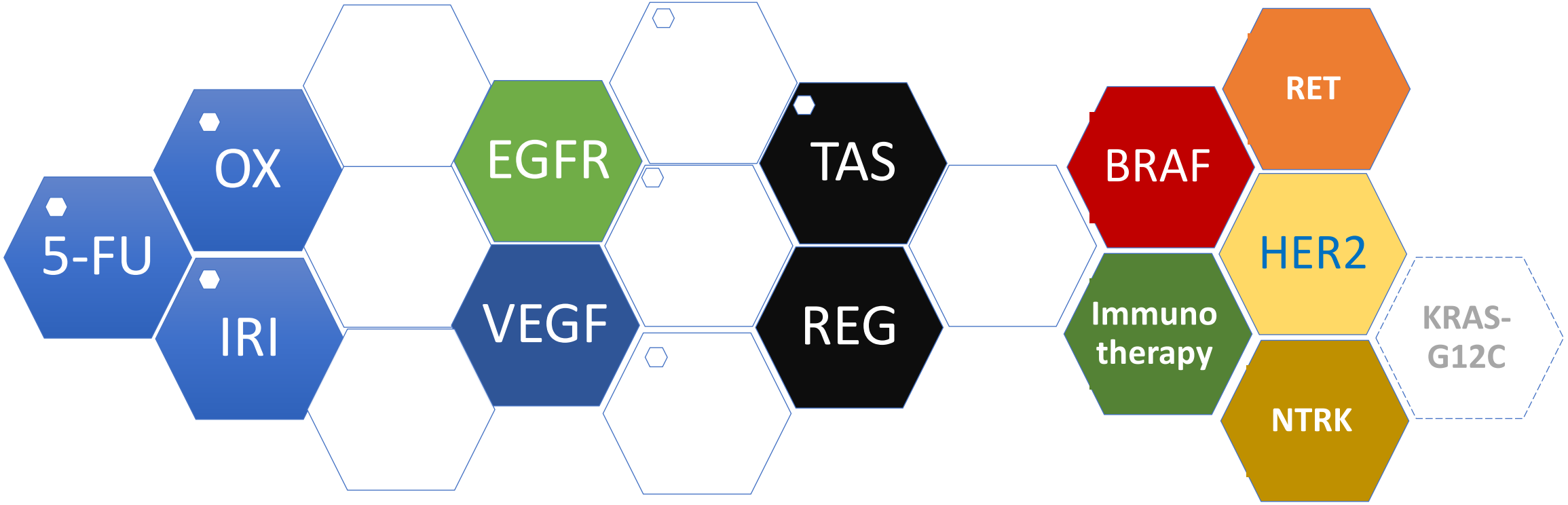
Kasi PM et al. Colorectal Cancer. Lancet Oct 2019.

Treatment options for patients with mCRC



Kasi PM et al. Colorectal Cancer. Lancet Oct 2019.

The consensus molecular subtypes of colorectal cancer

nature medicine

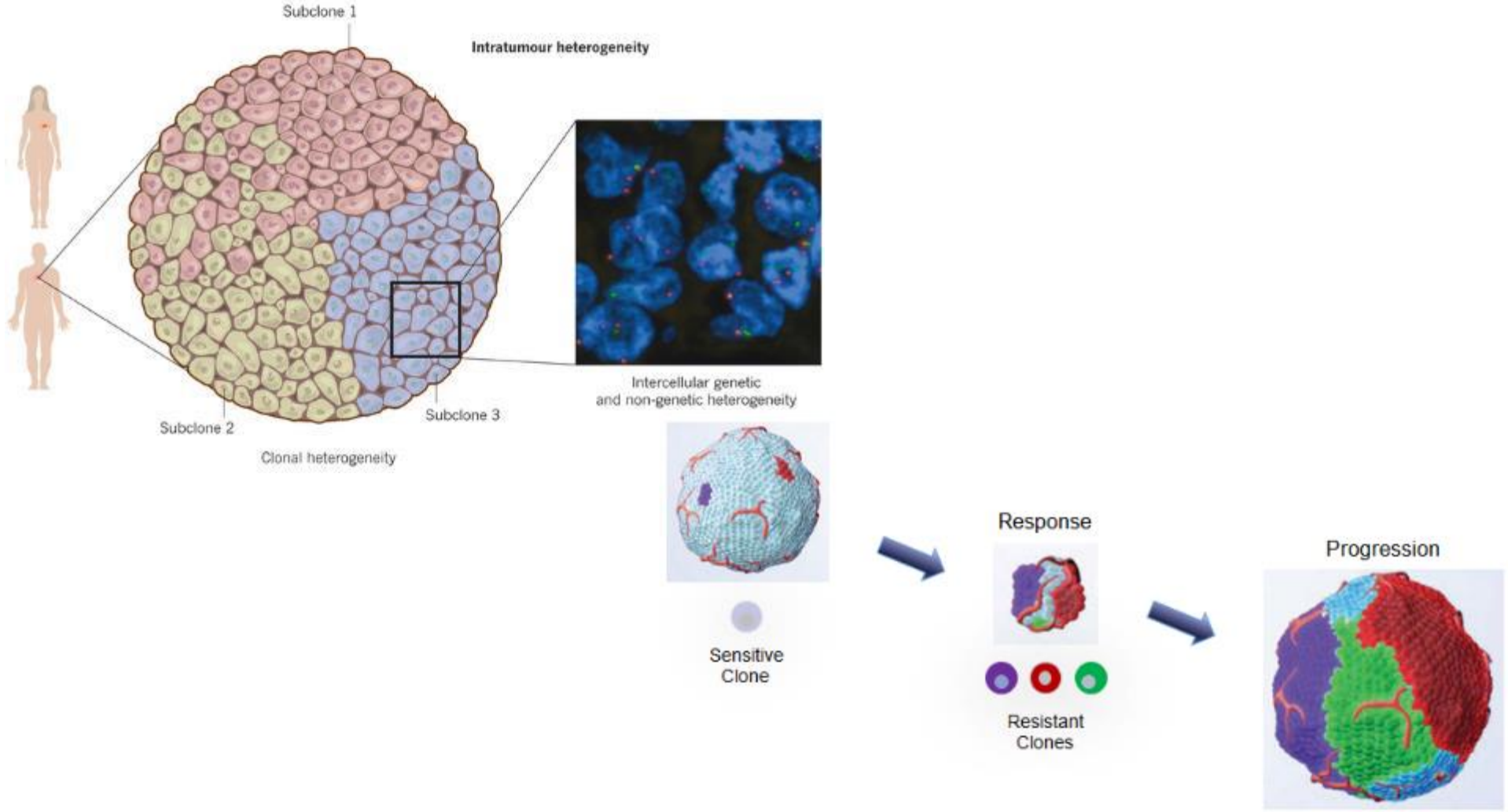
CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF-β activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

Nature Medicine **volume 21**, pages1350–1356 (2015

Heterogeneity

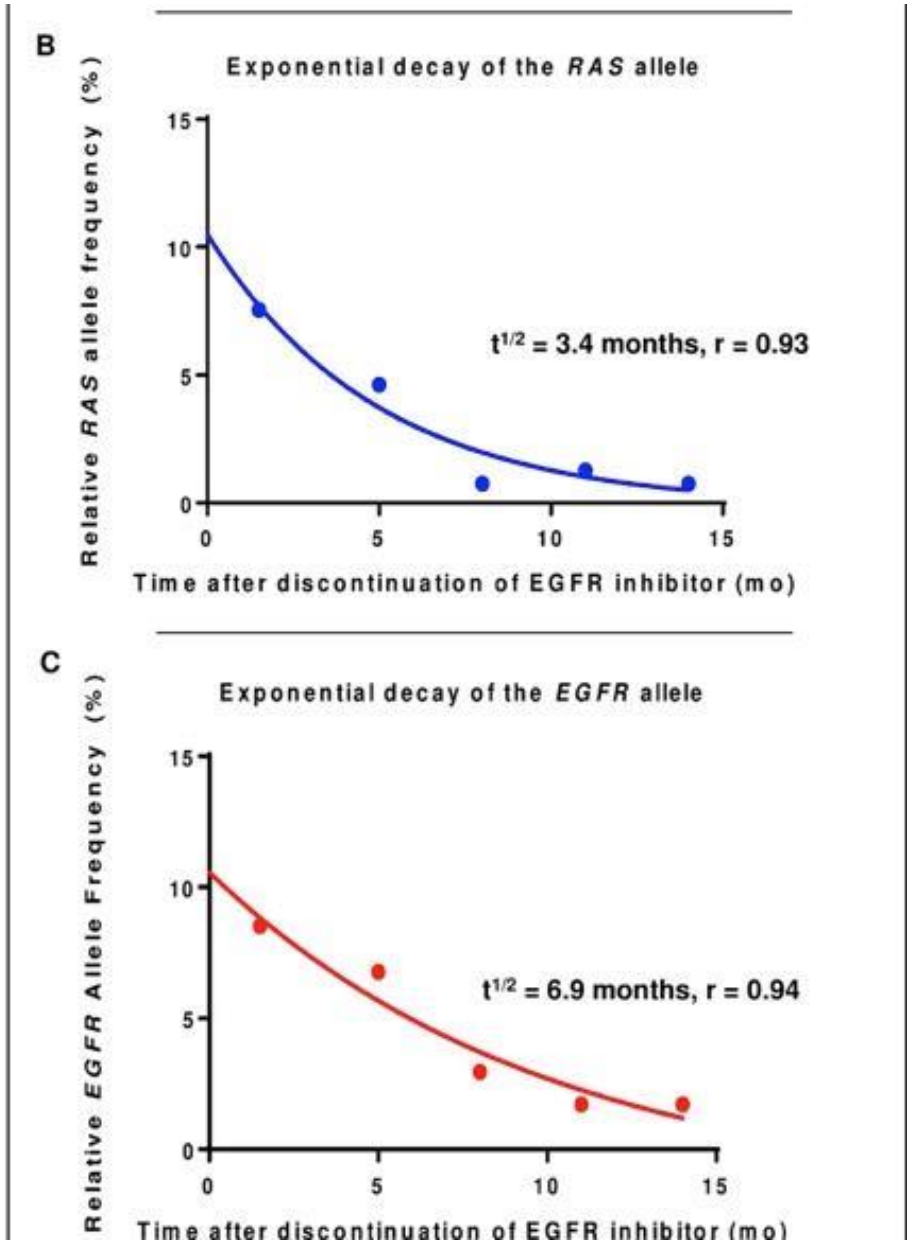
Intra-tumoral
and
Temporal

Intratumoral and temporal heterogeneity



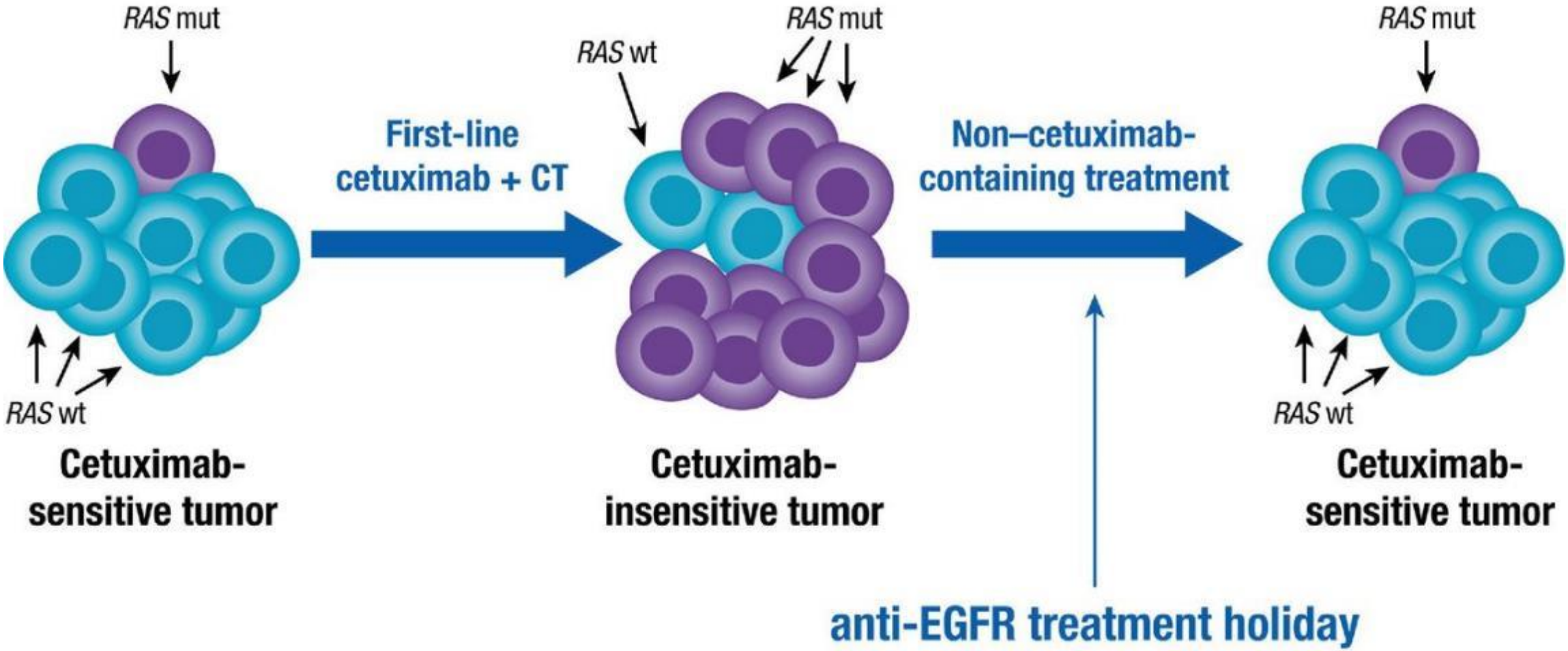
Burrell RA, et al. *Nature.* 2013;501:338.
Misale S, et al. *Cancer Discov*. 2014;4:1269.

Loss of EGFR and RAS Clones



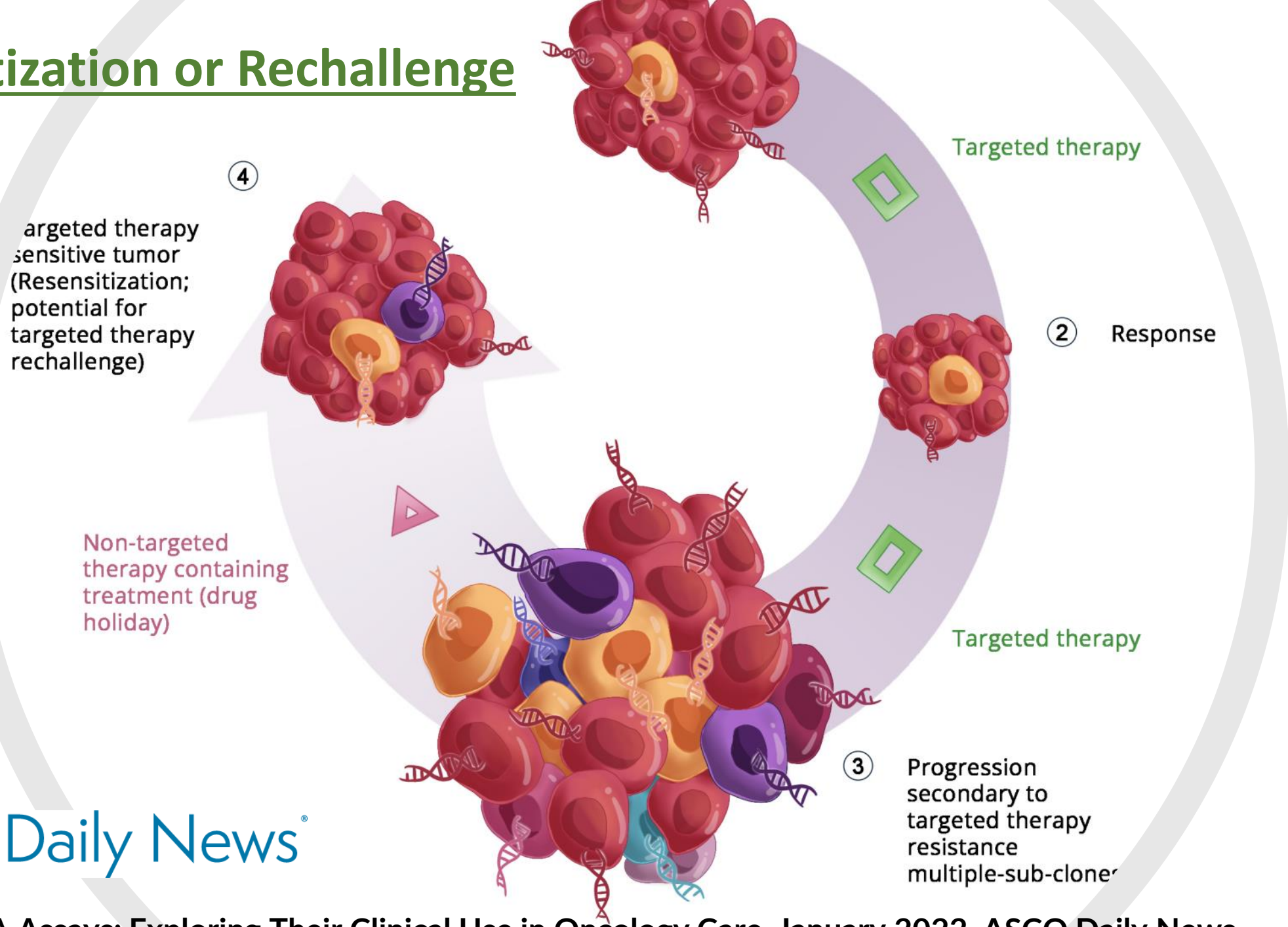
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Parseghian CM, et al. *J Clin Oncol.* 36, 2018 (suppl; abstr 3511).



Goldberg, et al. ESMO Open. *Cancer Horizons.* 2018 3(4).

Resensitization or Rechallenge



ASCO Daily News®

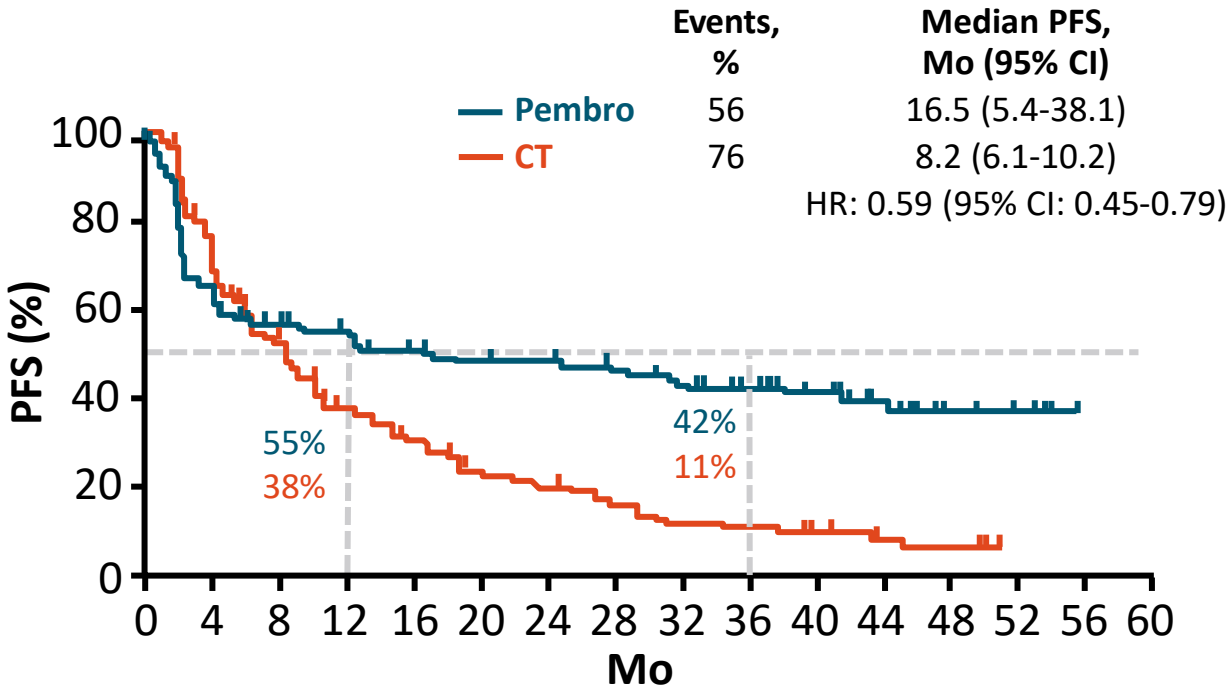
Kasi PM. ctDNA Assays: Exploring Their Clinical Use in Oncology Care. January 2022. ASCO Daily News.

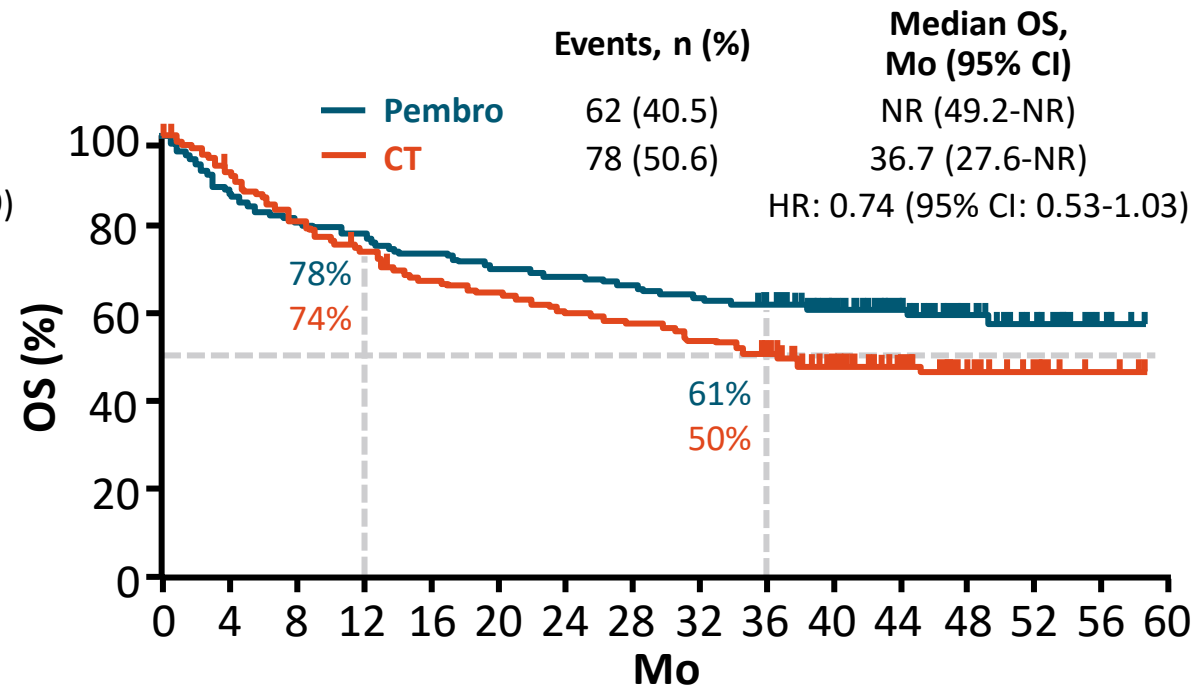
“Subsets of Subsets”

1 – dMMR/ MSI-High

KEYNOTE-177: First-line Pembrolizumab vs Chemotherapy in MSI-H/dMMR Metastatic CRC

- Randomized, open-label phase III study of pembrolizumab vs CT* for patients with treatment-naive MSI-H/dMMR mCRC (N = 307)





- ORR: pembrolizumab, 45%; CT, 33%

*mFOLFOX-6 ± bevacizumab or cetuximab or FOLFIRI ± bevacizumab or cetuximab.

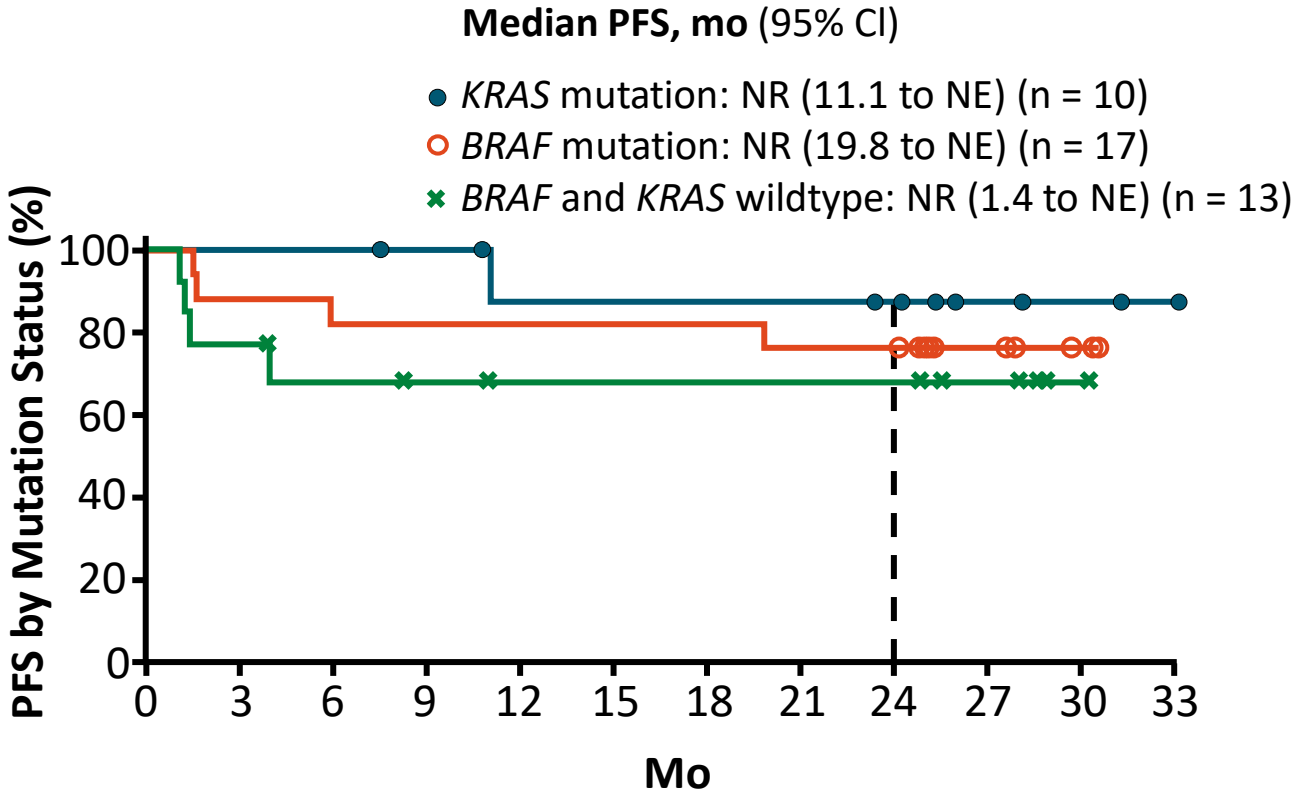
André. ASCO 2021. Abstr 3500.

Slide credit: clinicaloptions.com

CheckMate 142: First-line Nivolumab + Ipilimumab ± Chemotherapy in MSI-H/dMMR Metastatic CRC

1 – dMMR/ MSI-High

- Nonrandomized phase II study of nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W for patients with treatment-naive MSI-H/dMMR mCRC (N = 45)
- ORR: 69%
- Median OS, PFS: not reached at median follow-up of 24.2 mo
- 24-mo PFS: 74%
- 24-mo OS: 79%

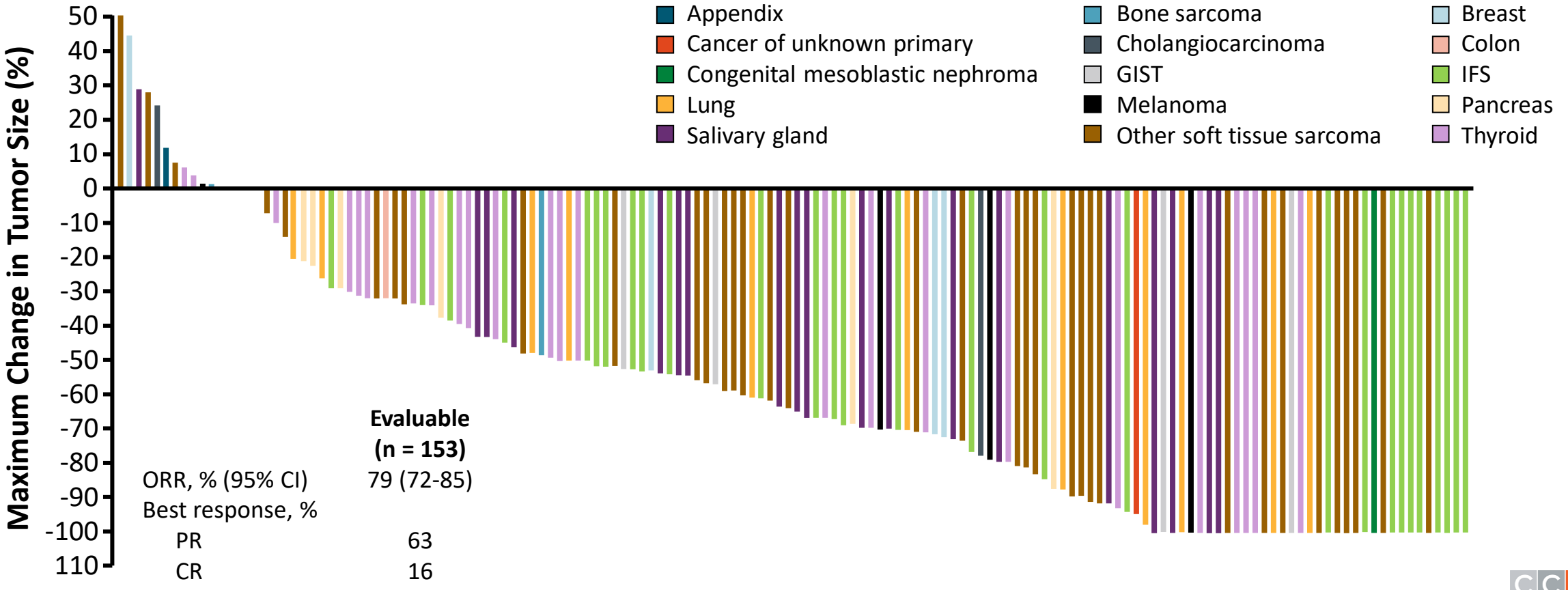


Lenz. JCO. 2022;40:161.

2 – NTRK fusion

Larotrectinib: Antitumor Activity Across Tumor Typ

- Analysis of 3 open-label trials (phase I, adults; phase I/II, children; phase II, adolescents/adults) assessing larotrectinib for treating advanced solid tumors with *NTRK* gene fusion (N = 159)



Hong. Lancet Oncol. 2020;21:531.

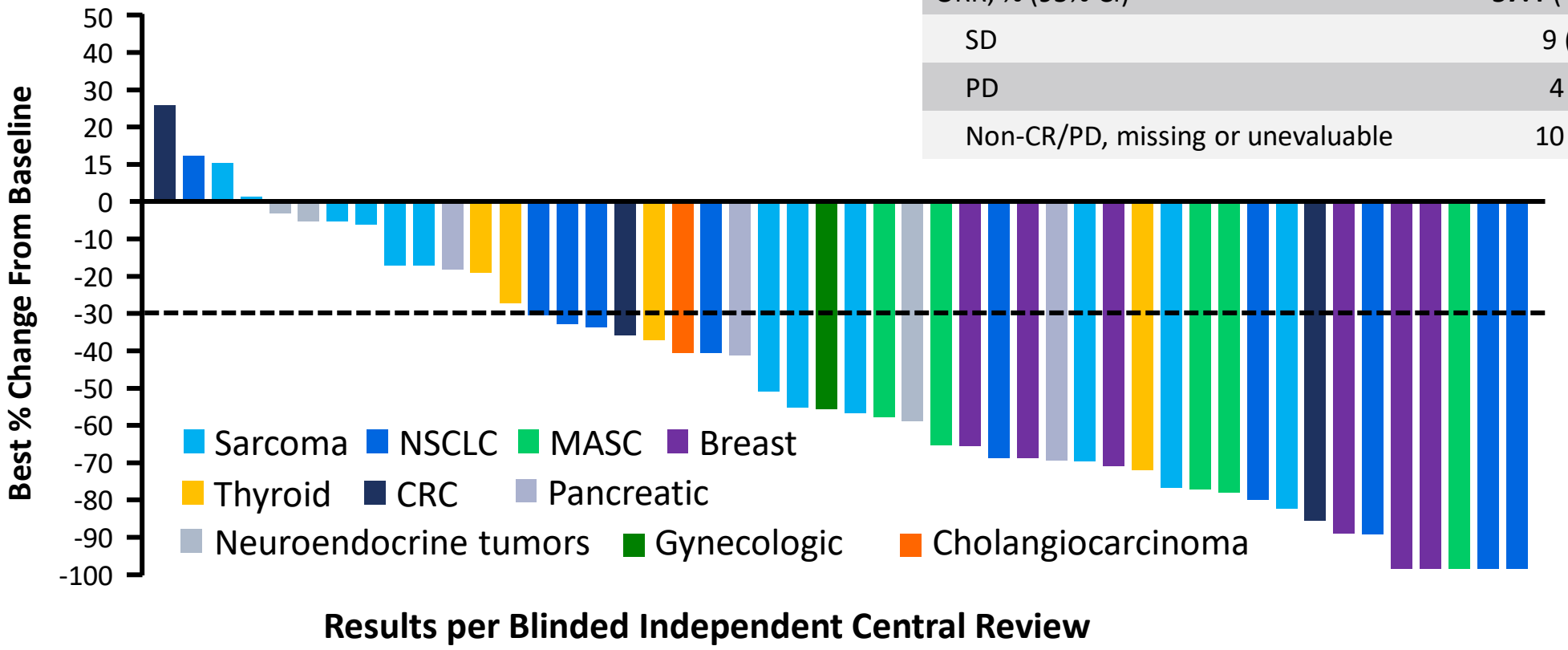
Slide credit: clinicaloptions.com

2 – NTRK fusion

Entrectinib: Antitumor Activity Across Tumor Types

- Analysis of 3 open-label trials (phase I or II trials in adults) assessing entrectinib for treating advanced solid tumors with *NTRK* gene fusion (N = 54)

	Patients (N = 54)
ORR, % (95% CI)	**57.4** (43.2-70.8)
SD	9 (16.7)
PD	4 (7.4)
Non-CR/PD, missing or unevaluable	10 (18.5)



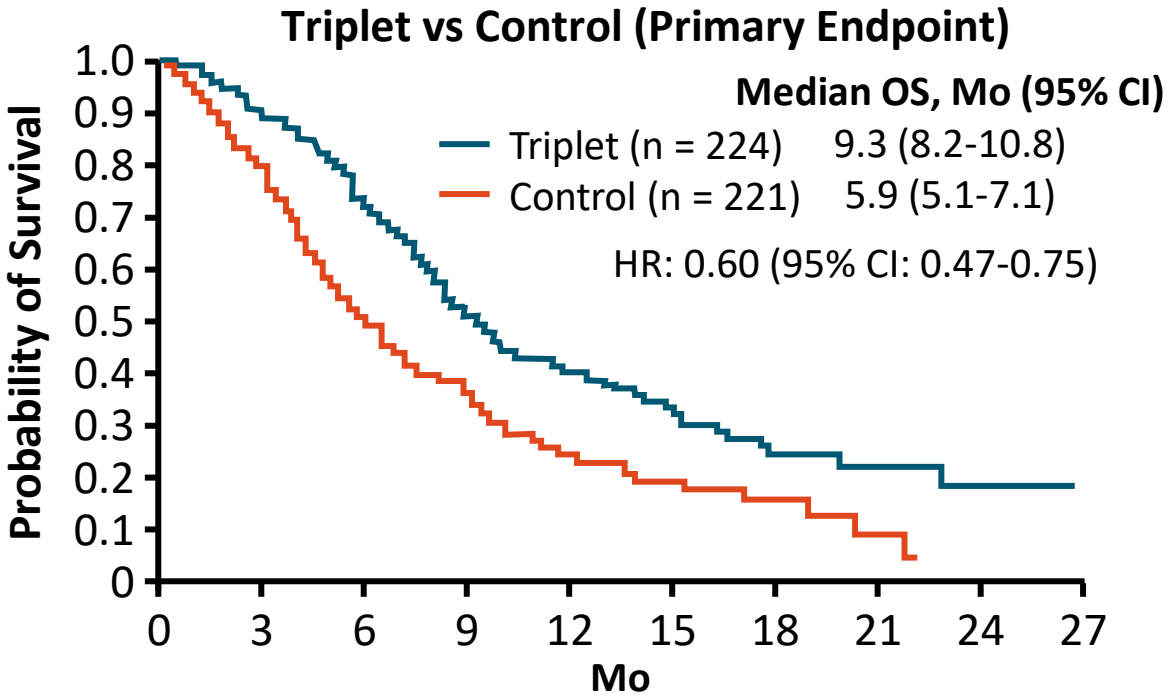
Doebele. Lancet Oncol. 2020;21:271.

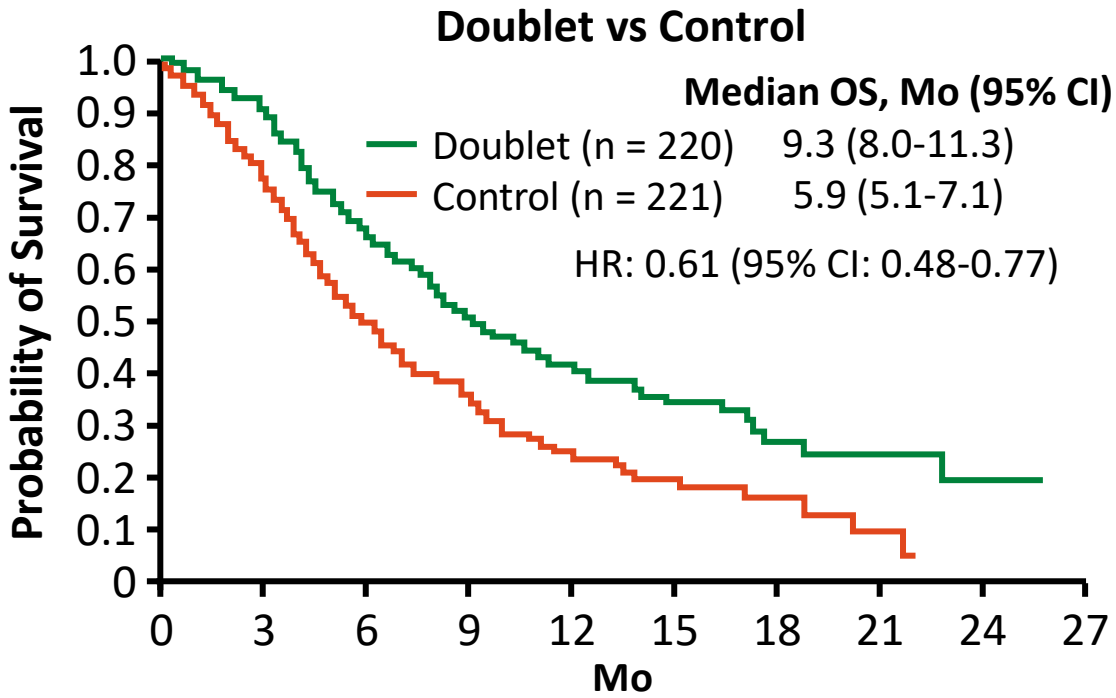
Slide credit: clinicaloptions.com

BEACON CRC: Encorafenib + Cetuximab ± Binimetin for *BRAF* V600E–Mutant mCRC

3 – BRAF-V600E

- Randomized phase III trial of encorafenib + cetuximab ± binimetinib for pts with *BRAF* V600E+ mCRC with PD after 1-2 prior regimens (no prior RAF/MEK/EGFR inhibitors





- ORR: triplet, 27%; doublet, 20%; control, 2% (triplet/doublet $P < .0001$ vs control)
- FDA indication: encorafenib + cetuximab for *BRAF* V600E–mutated mCRC after previous systemic therapy

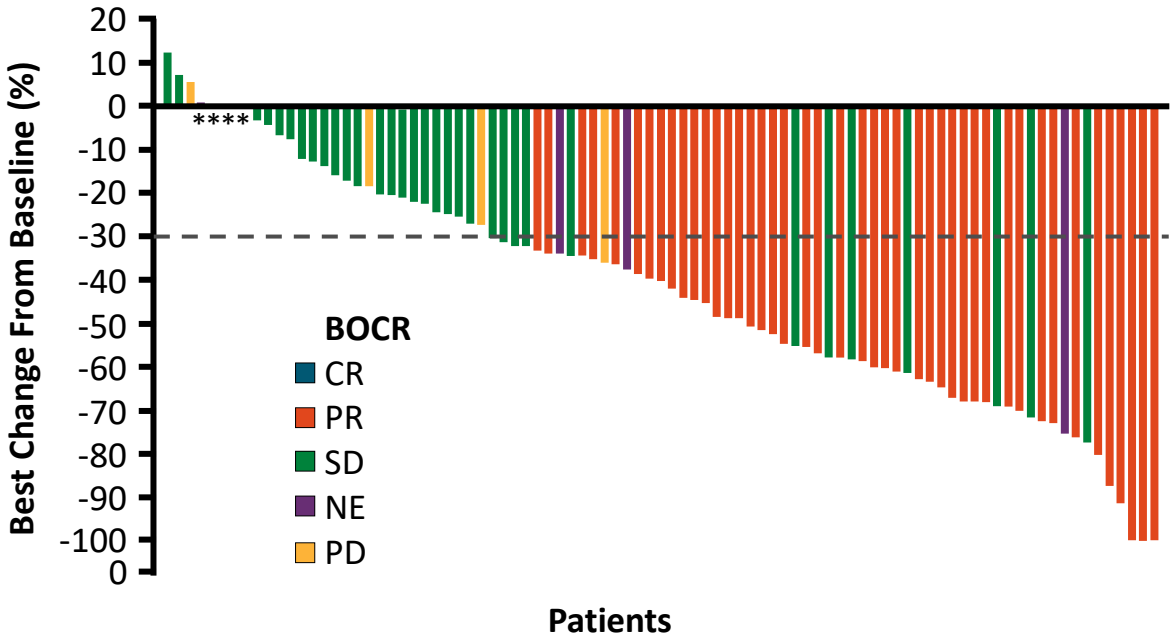
Kopetz. NEJM. 2019;381:1632. Tabernero. JCO. 2021;39:273.

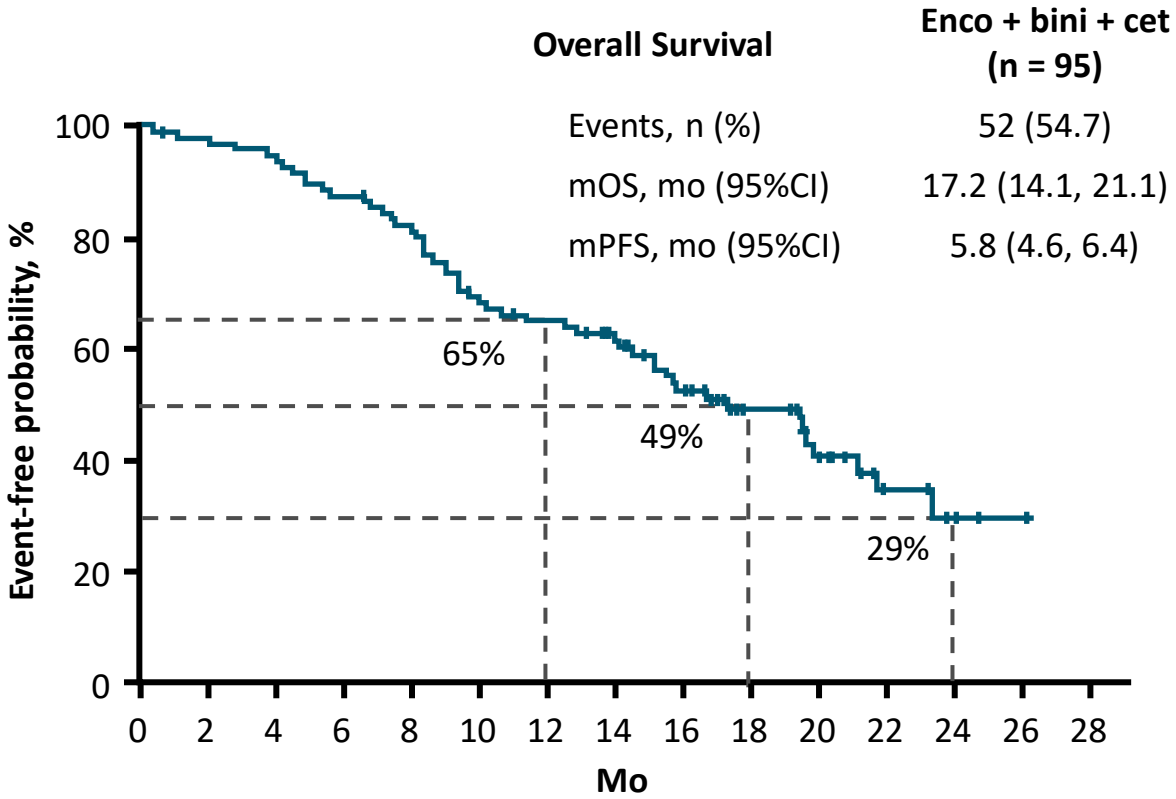
Slide credit: clinicaloptions.com

ANCHOR CRC: Phase II Study of First-line Encorafen Binimetinib + Cetuximab in *BRAF* V600E Mutant mCRC

3 – BRAF-V600E

- ORR: 48%; DCR: 88%





- Ongoing phase III BREAKWATER study (NCT04607421) in this population

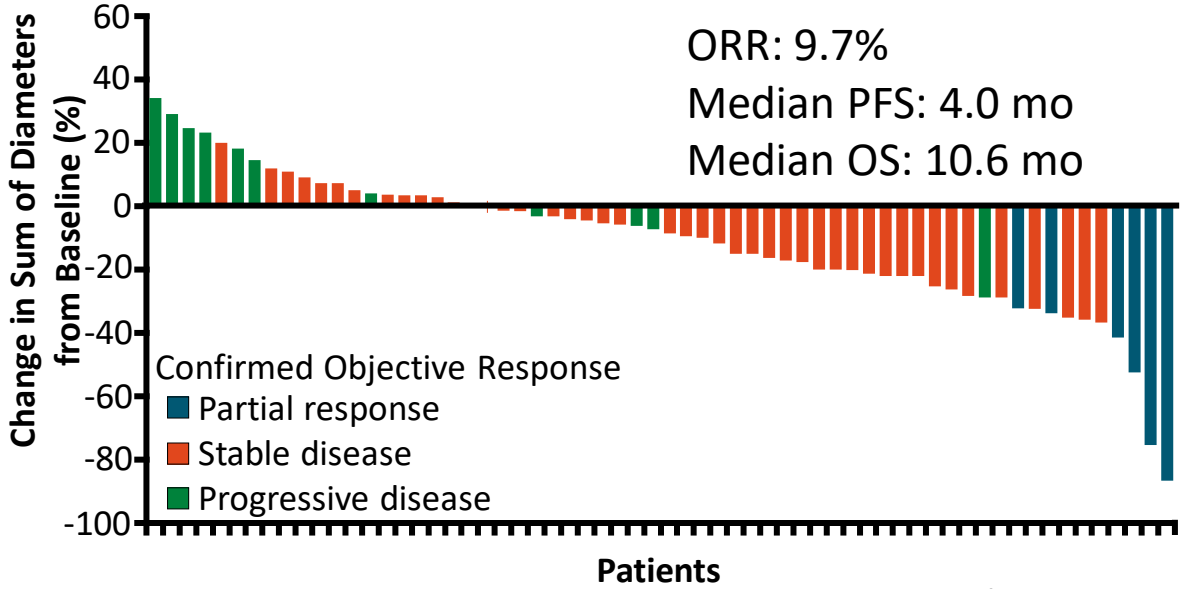
Van Cutsem. ESMO GI 2021. Abstr LB0-10.

Slide credit: clinicaloptions.com

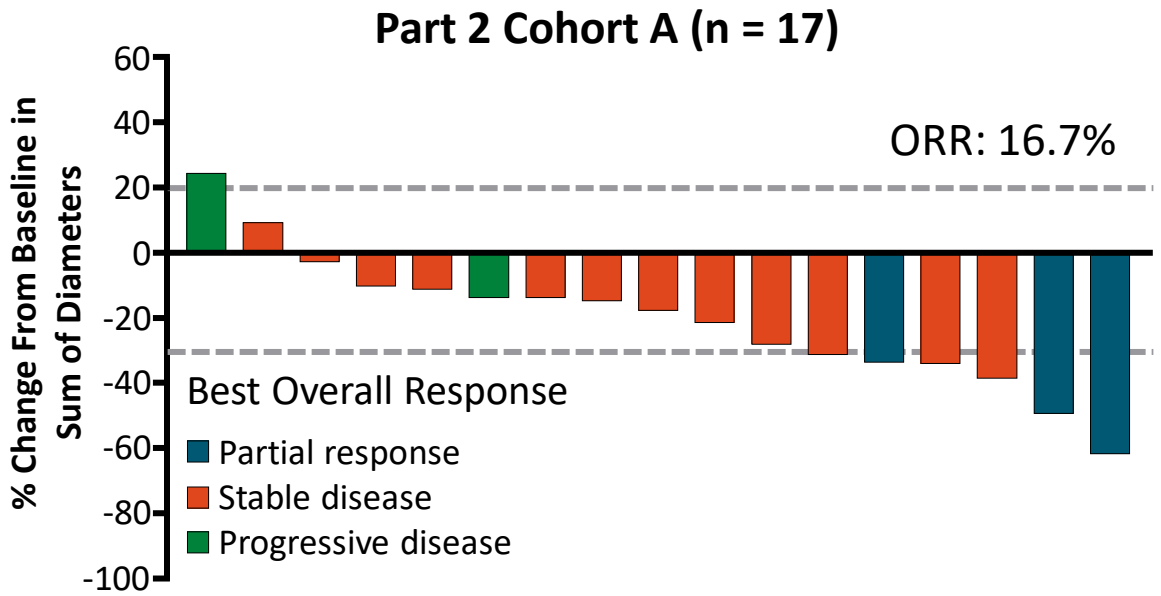
Targeting the "Undruggable": KRAS G12C Inhibitor Sotorasib for Previously Treated CRC

4 – KRAS-G12C

- CodeBreaK100: phase I/II trial of sotorasib for patients with *KRAS* G12C-mutated solid tumors (data from n = 62 patients with previously treated CRC in phase II)



- CodeBreaK101 Subprotocol H phase Ib: sotorasib + panitumumab for previously treated advanced *KRAS* G12C-mutated CRC



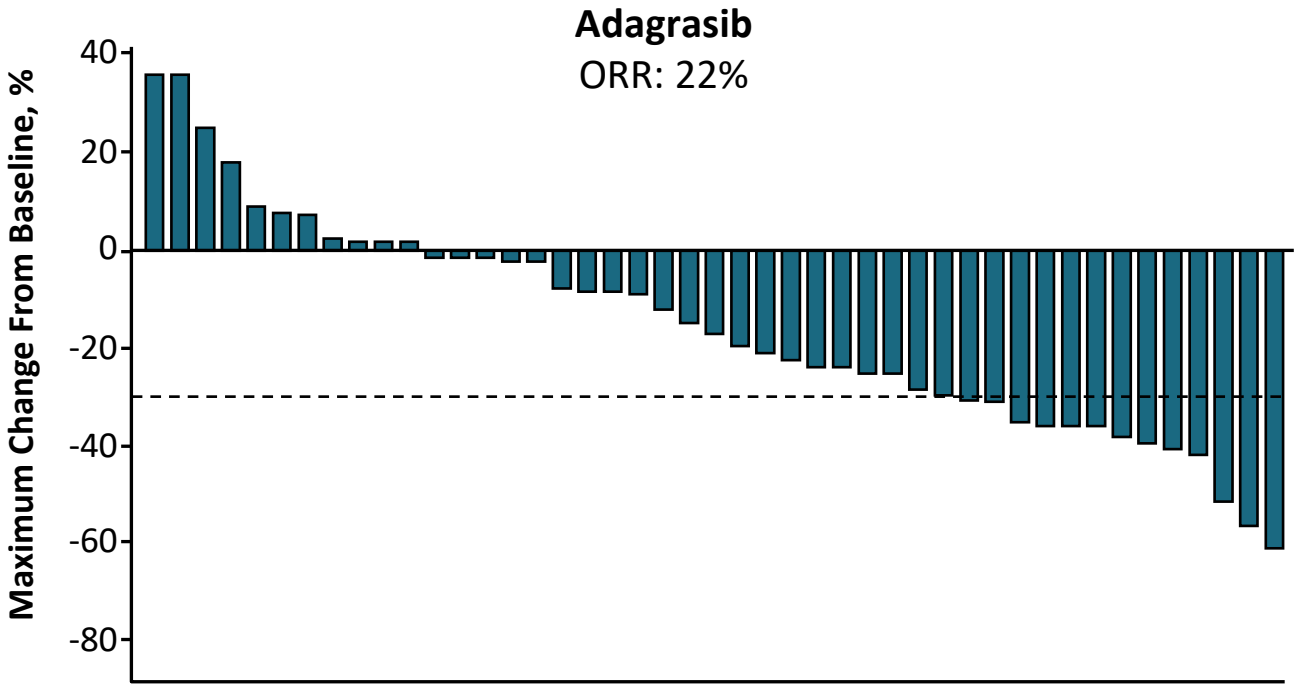
- Ongoing phase III CodeBreak 300 study (NCT05198934) of sotorasib + panitumumab vs TAS-102 or regorafenib in pts with previously treated KRAS G12C-mutated mCRC; additional earlier phase trials in pancreatic and other solid cancers

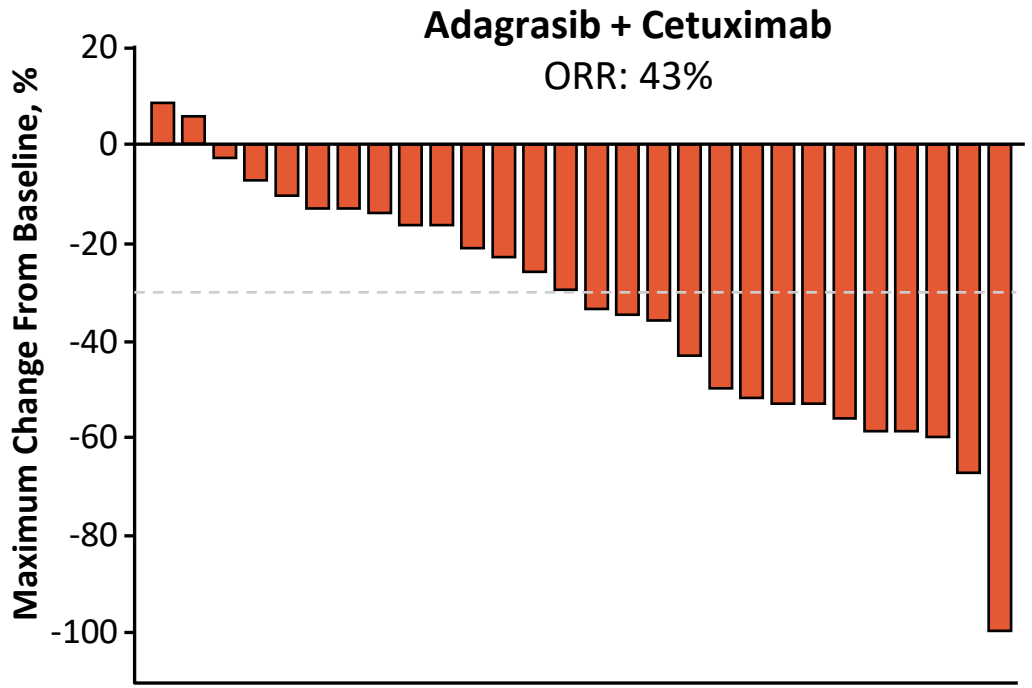
Fakih. Lancet Oncol. 2022;23:115. Fakih. ESMO 2021. Abstr 434P. NCT03600883.

Targeting the "Undruggable": KRAS G12C Inhibitor Adagrasib for CRC

4 – KRAS-G12C

- KRYSTAL-1: phase I/II trial of adagrasib ± cetuximabfor patients with *KRAS* G12C-mutated solid tumors (data from n = 78 patients with CRC)



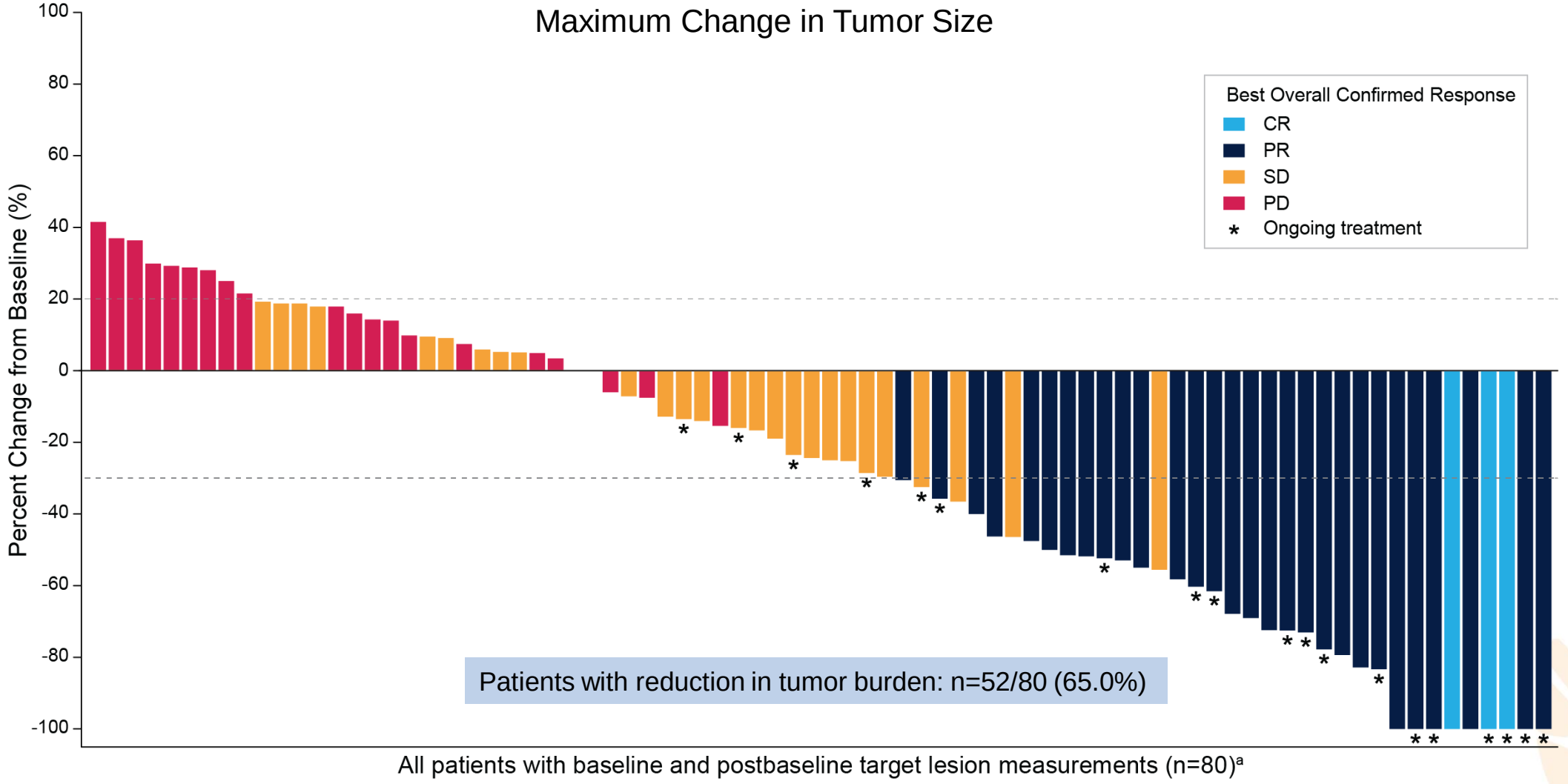


- Ongoing phase III KRYSTAL-10 study (NCT04793958) of adagrasib + cetuximab vs CT in pts with previously treated KRAS G12C-mutated mCRC; additional earlier phase trials in other solid cancers

Weiss. ESMO 2021. Abstr LBA6.

Tucatinib + Trastuzumab (Mountaineer): Change in Tu

5 – HER2-positive



a Four patients who did not have baseline and/or post-baseline target lesion measurements are excluded

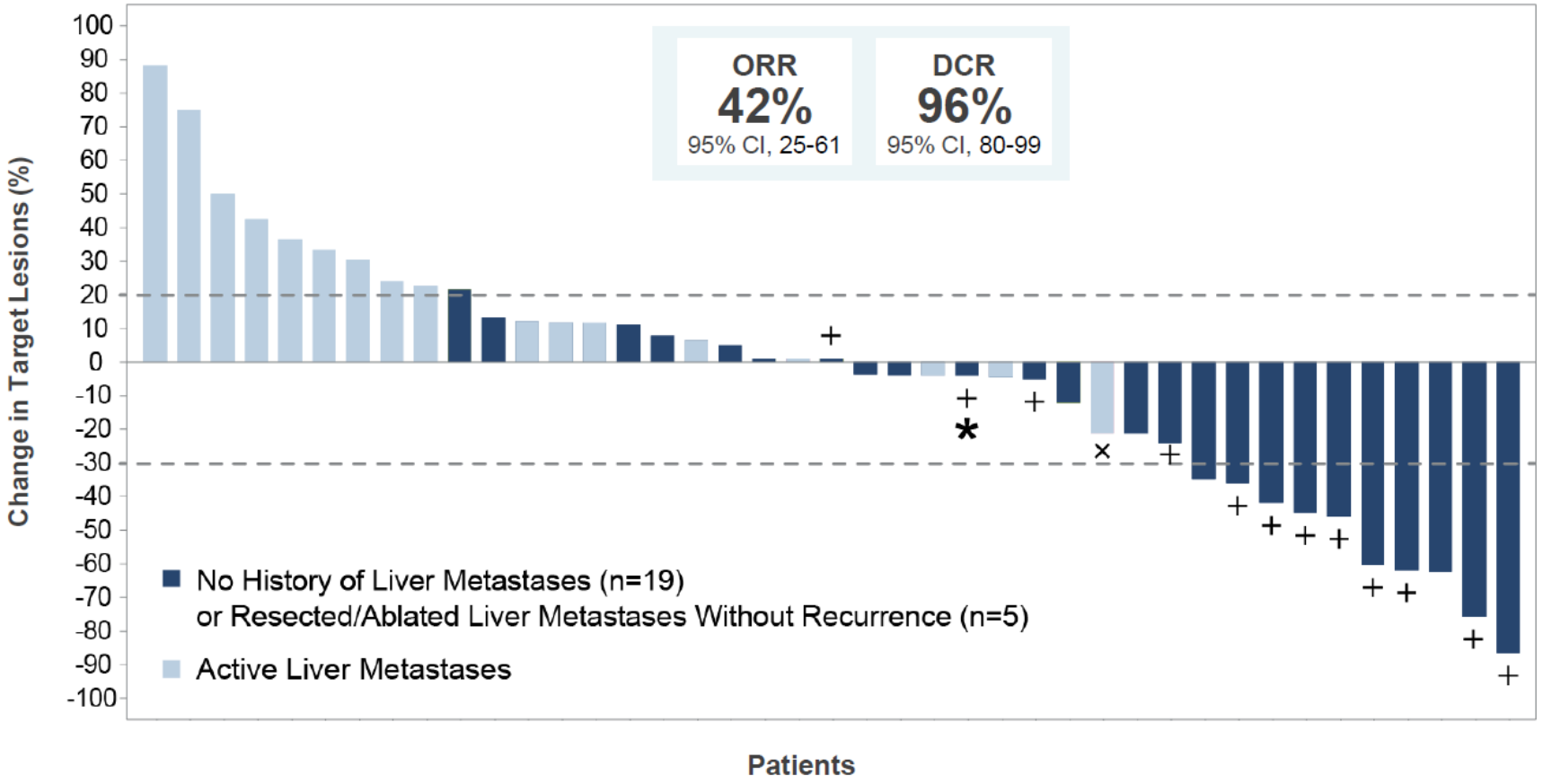
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Data cutoff: 28 Mar 2022

6 – Non-liver?

Exploratory Analysis by Liver Involvement

Enriched responses in patients without active liver metastases (n=24)



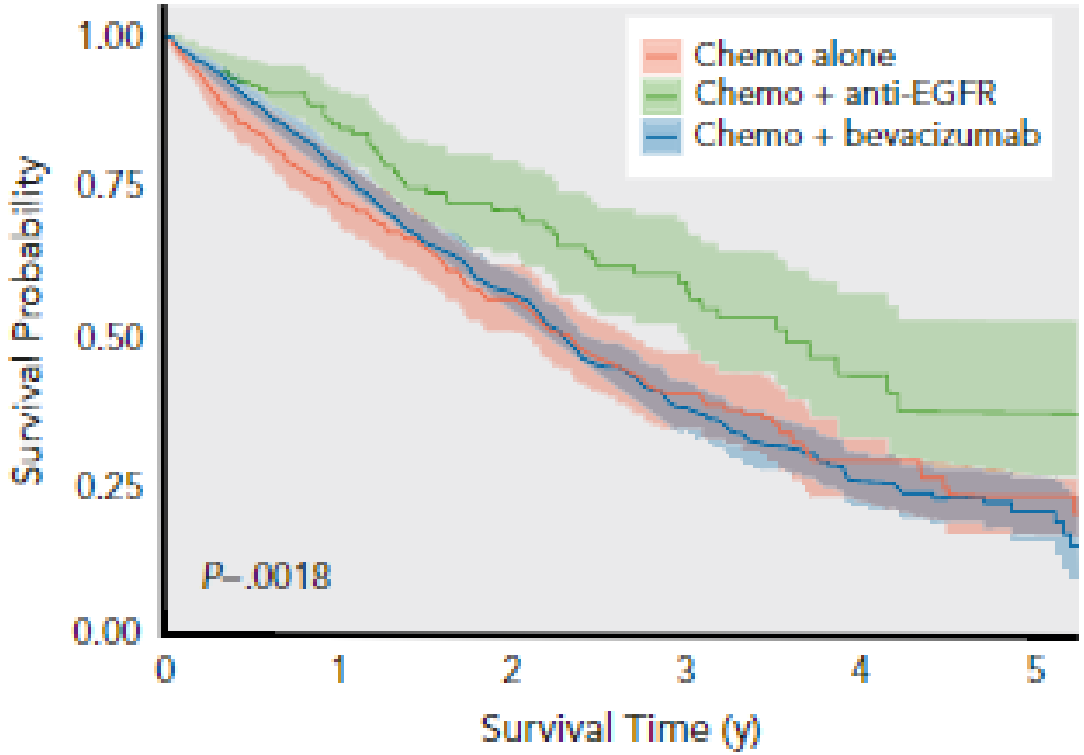
+ =Ongoing PR/SD * =Complete metabolic response by PET × =Progression of non-target lesions

Immunotherapy for MSS:
BOT+BAL:
CTLA4i+PD1i

17

Anthony B. El El-Khoueiry. ESMO WORLD GI 2022

7 – RAS/RAF-wildtype (LEFT)



Number at risk						
Chemo alone	456	238	130	66	26	8
Chemo + anti-EGFR	186	113	72	39	14	4
Chemo + bevacizumab	965	580	334	150	61	12

First-Line Therapy	
Chemotherapy alone	2
Chemotherapy + bevacizumab	27.5 (25.8–28.9)
Chemotherapy + anti-EGFR agent	42.9 (36.0–NR)

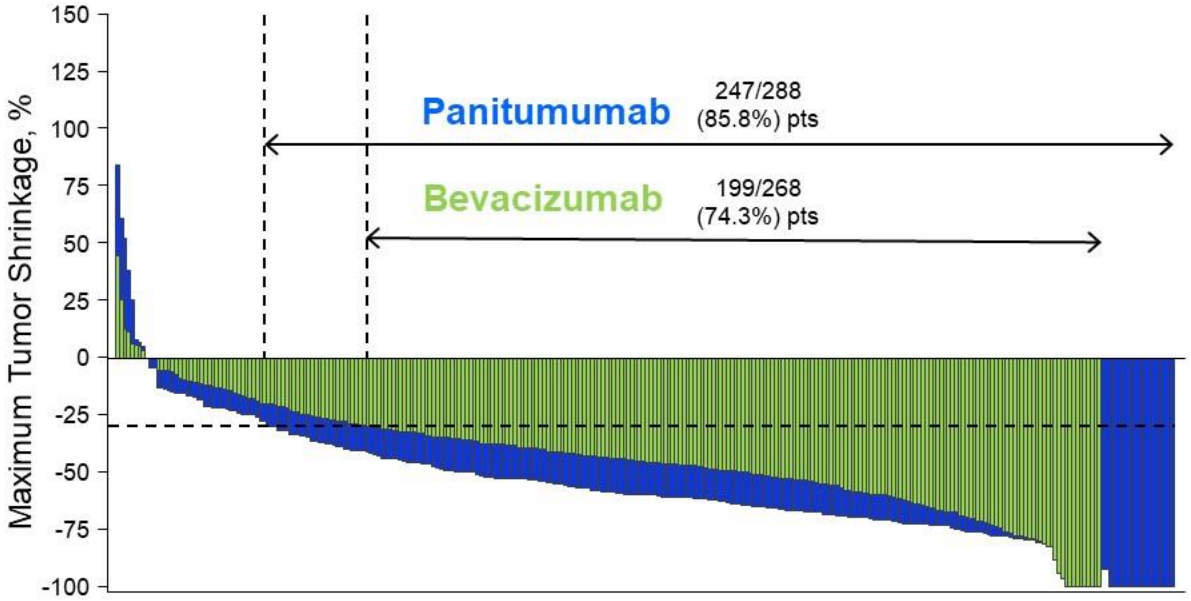
NCDB	**42.9**	27.5
CALGB 80405	**39.3**	32.6
PEAK	**43.4**	32.0
FIRE-3	**38.3**	28.0

Nevala-Plagemann C, et al. **Treatment Trends and Clinical Outcomes of Left-Sided RAS/RAF Wild-Type Metastatic Colorectal Cancer in the United States.** J Natl Compr Canc Netw. 2022 Feb 4:1-8. PMID: 35120306.

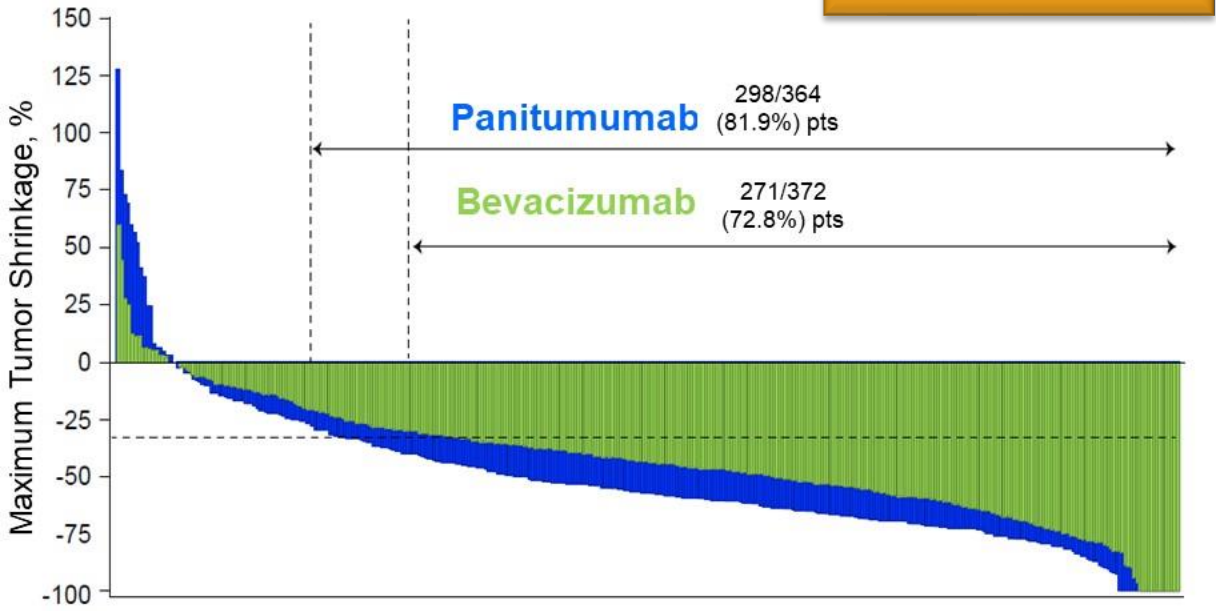
Other Efficacy Outcome: Depth of Response

7 – RAS/RAF-wildtype (LEFT)

Left-Sided Population



Overall Population



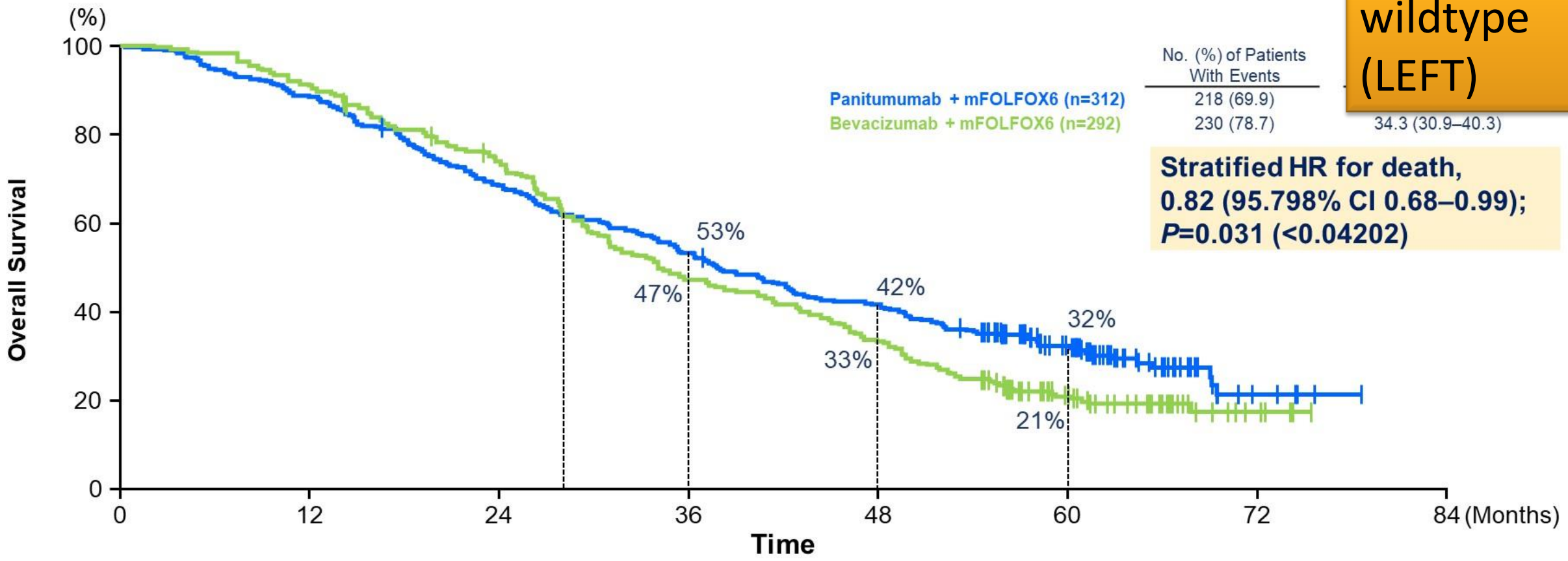
Horizontal dotted line at 30% indicates response per RECIST v1.1.

	Left-sided Population		Overall Population	
	Panitumumab + mFOLFOX6 (n=288)	Bevacizumab + mFOLFOX6 (n=268)	Panitumumab + mFOLFOX6 (n=364)	Bevacizumab + mFOLFOX6 (n=372)
Median, %	-59.4	-43.6	-57.3	-43.6

Depth of response was assessed in patients with measurable lesions at baseline.

Primary Endpoint-1; Overall Survival in Left-sided Popula

7 – RAS/RAF-wildtype (LEFT)



	No. (%) of Patients With Events	
Panitumumab + mFOLFOX6 (n=312)	218 (69.9)	
Bevacizumab + mFOLFOX6 (n=292)	230 (78.7)	34.3 (30.9–40.3)

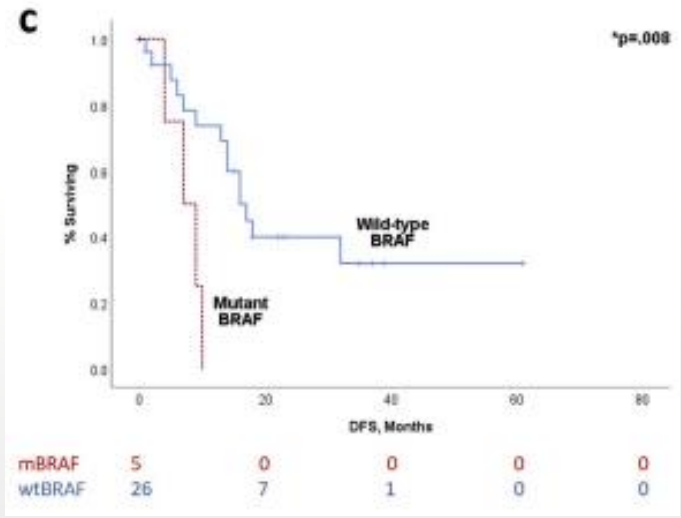
Stratified HR for death, 0.82 (95.798% CI 0.68–0.99); *P*=0.031 (<0.04202)

No. at risk								
Panitumumab	312	276	213	166	129	68	5	0
Bevacizumab	292	266	212	136	96	40	5	0

Subsets of Subsets

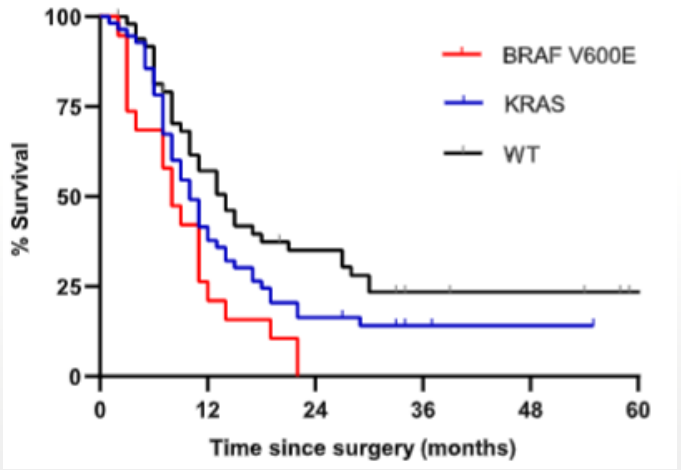
The Peritoneal Subset

BRAF



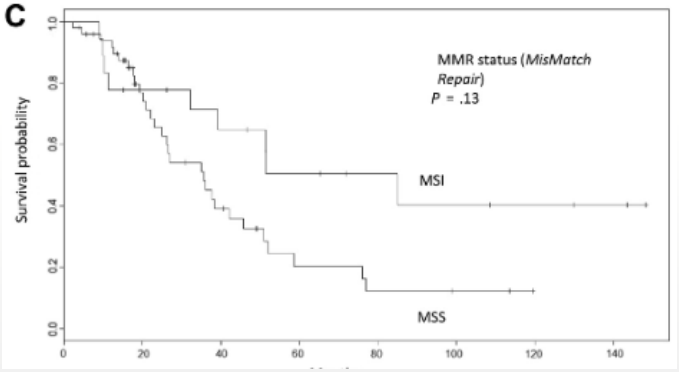
Solomon D. Surgeon. 2021 Dec;19(6):e379-e385. PMID: 33423919.

BRAF/KRAS

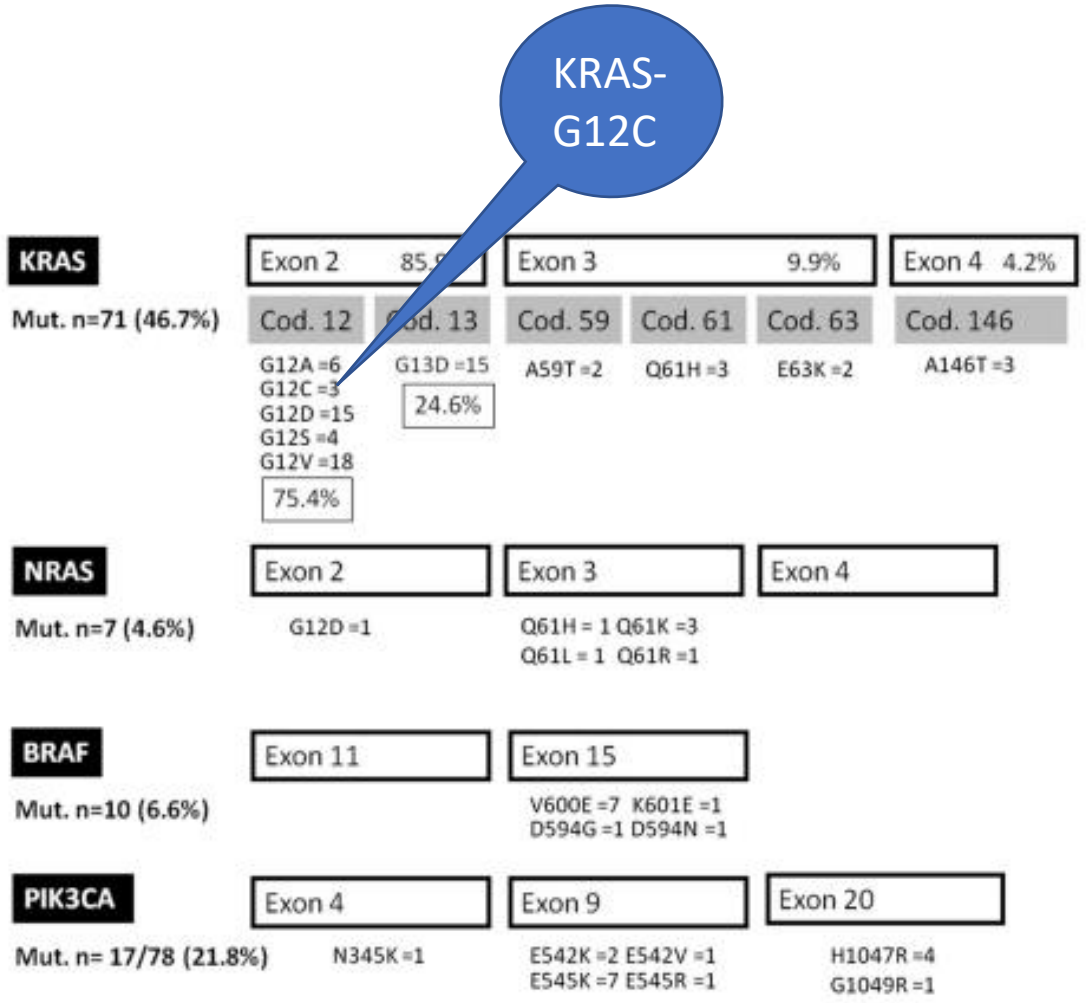


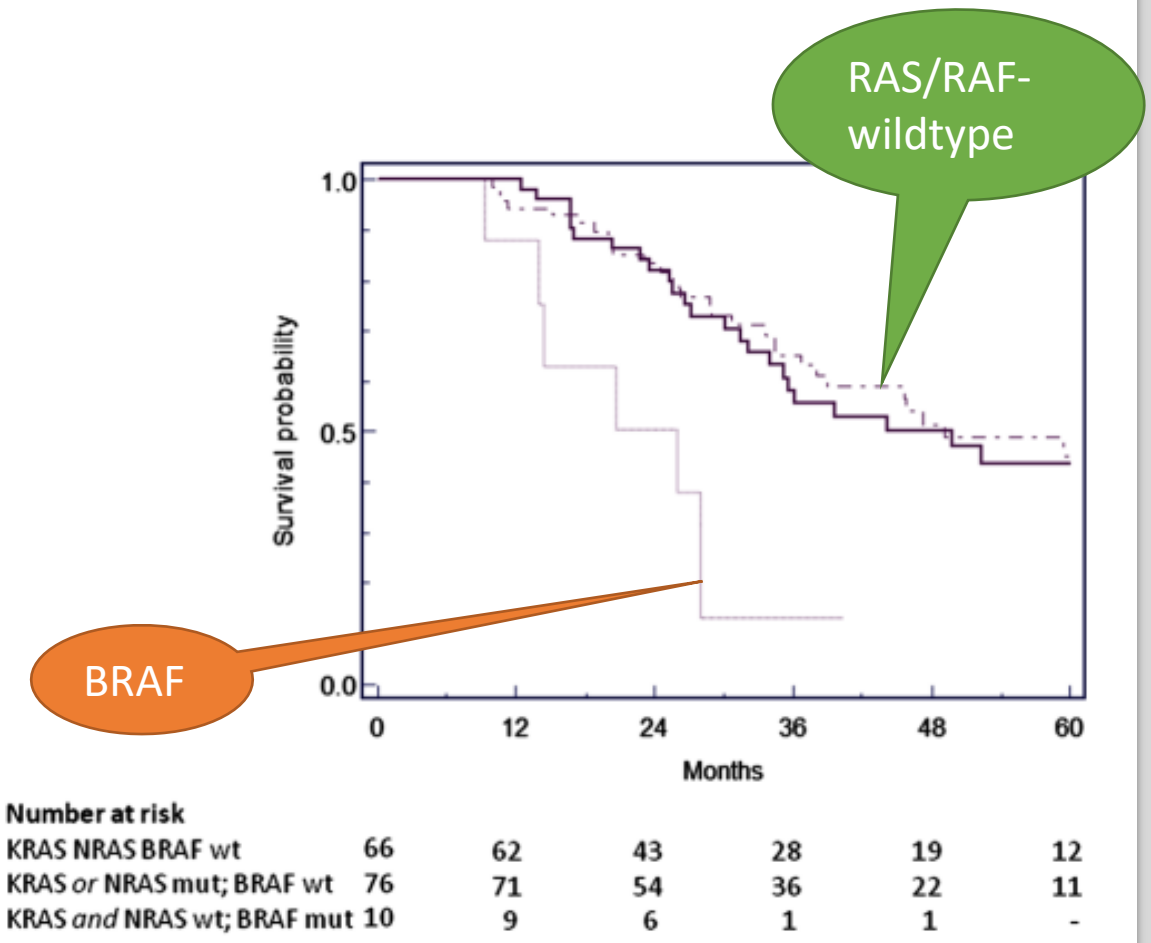
Flood MP. Eur J Surg Oncol. 2022 Jun 18:S0748-7983(22)00498-X. PMID: 35750576.

MMR/MSI

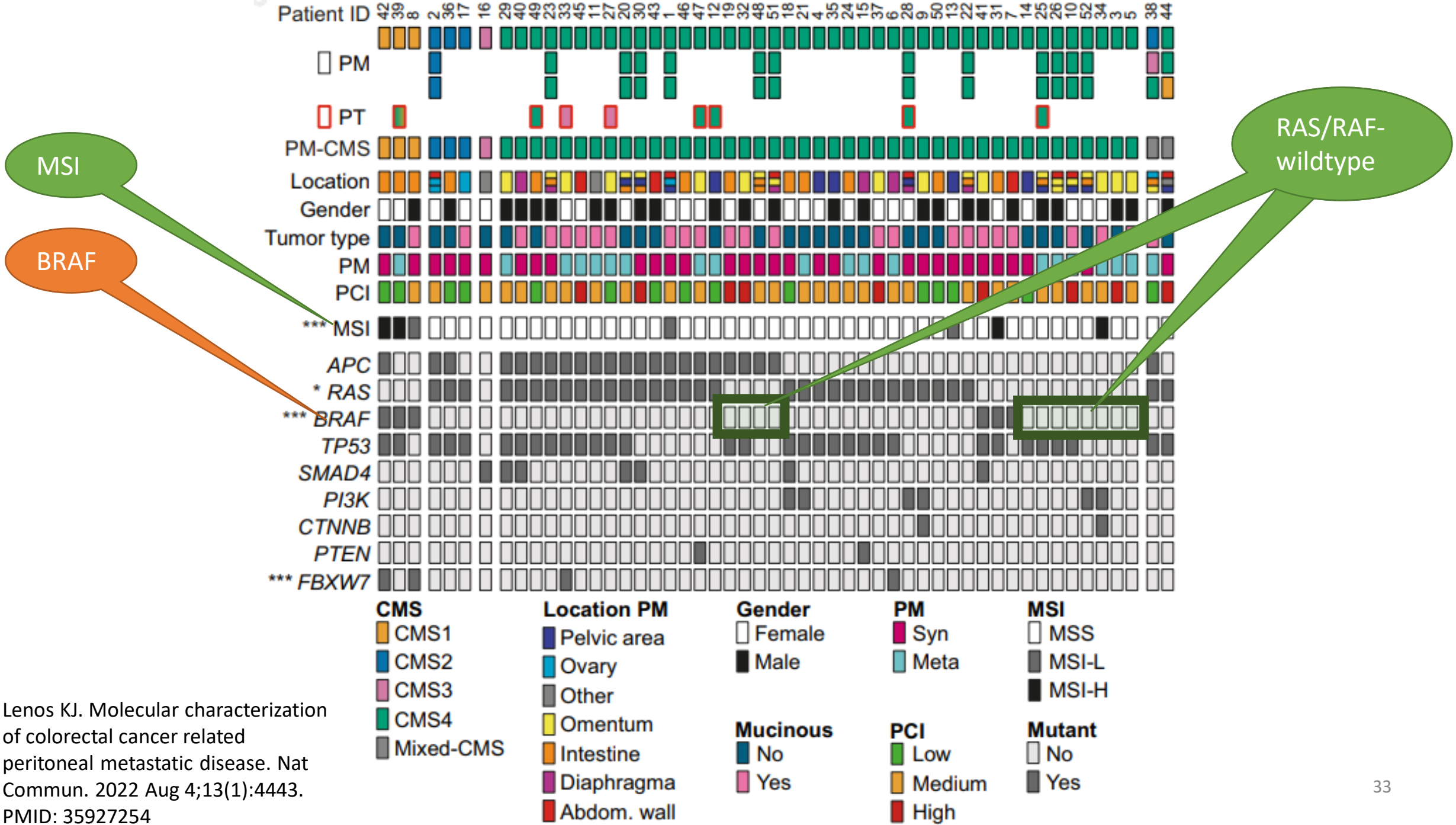


Massalou D, et al. Am J Surg. 2017 Feb;213(2):377-387. PMID: 27816197.





Baratti D, Kusamura. Prognostic Impact of Primary Side and RAS/RAF Mutations in a Surgical Series of Colorectal Cancer with Peritoneal Metastases. Ann Surg Oncol. 2021 Jun;28(6):3332-3342. PMID: 32974694.



Lenos KJ. Molecular characterization of colorectal cancer related peritoneal metastatic disease. Nat Commun. 2022 Aug 4;13(1):4443. PMID: 35927254

nature communications

Article

https://doi.org/10.1038/s41467-022-32198-z

Molecular characterization of colorectal cancer related peritoneal metastatic disease

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Check for updates

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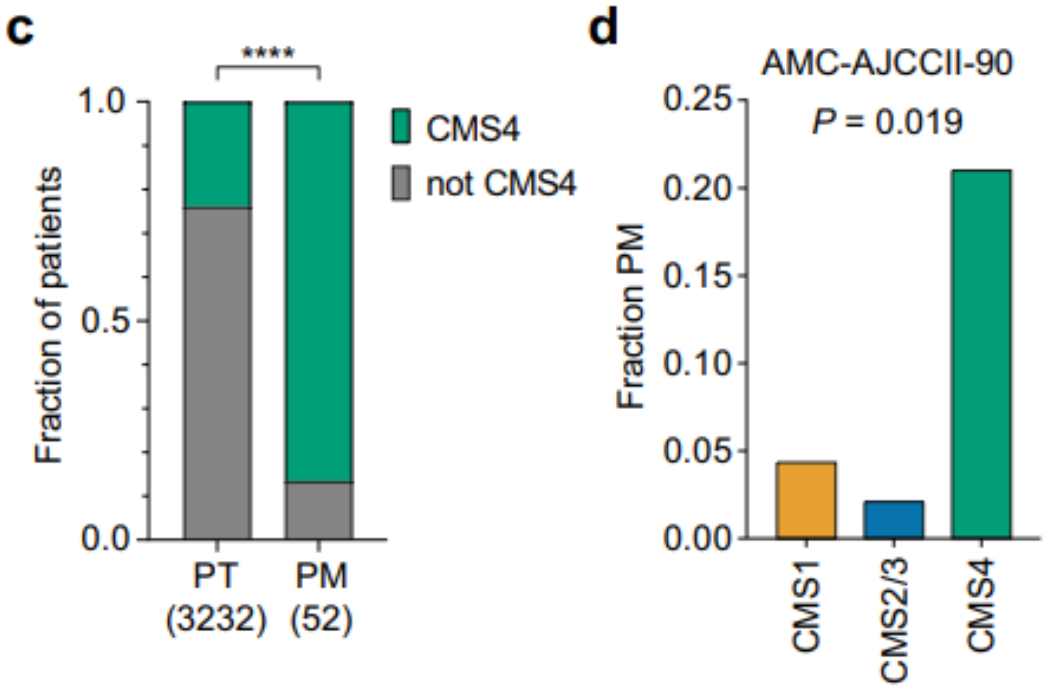


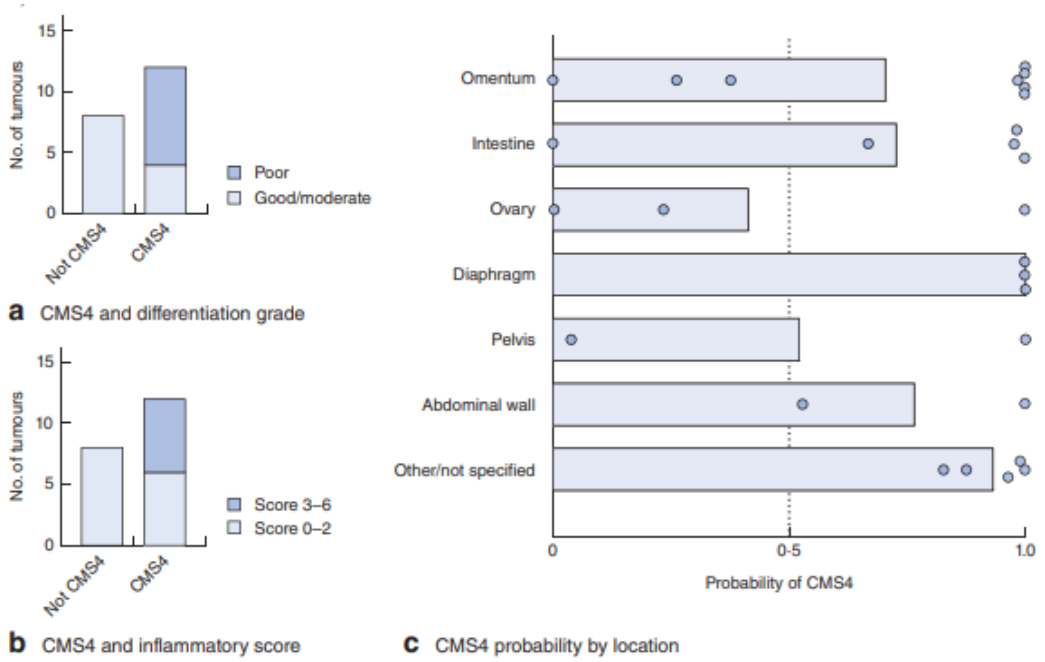
Lenos KJ. Molecular characterization of colorectal cancer related peritoneal metastatic disease. Nat Commun. 2022 Aug 4;13(1):4443. PMID: 35927254

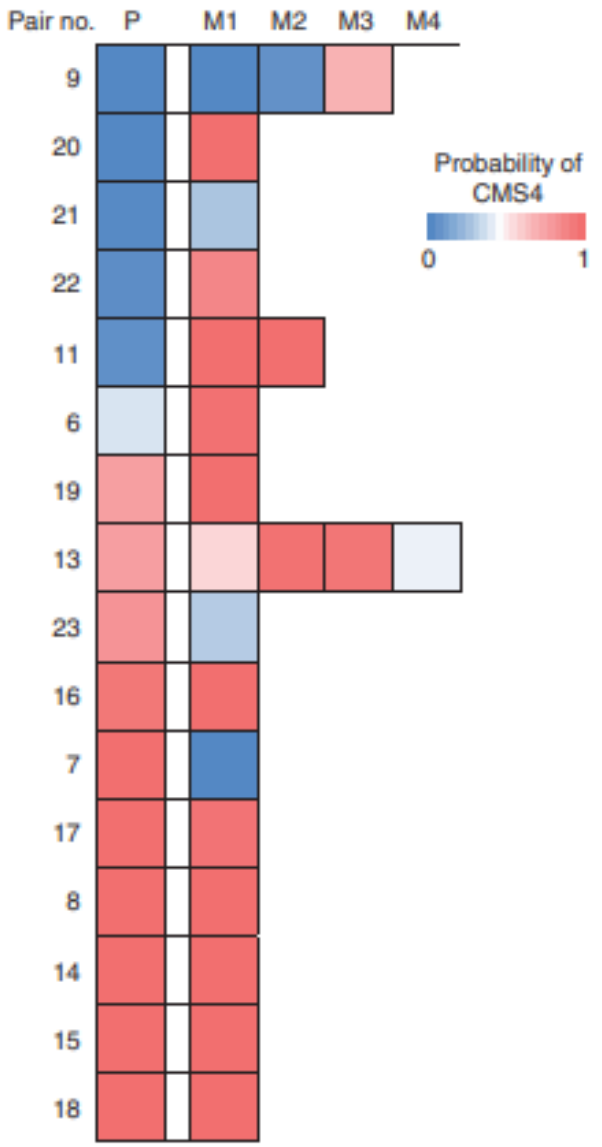
The consensus molecular subtypes of colorectal cancer

nature medicine

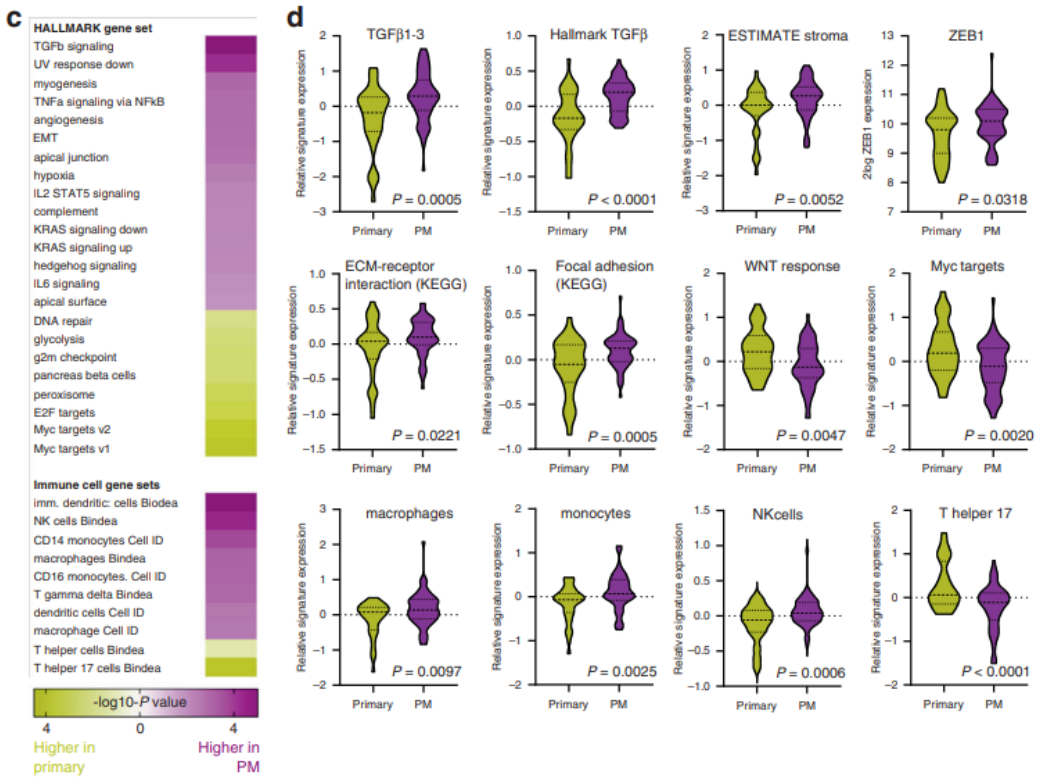
CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF-β activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

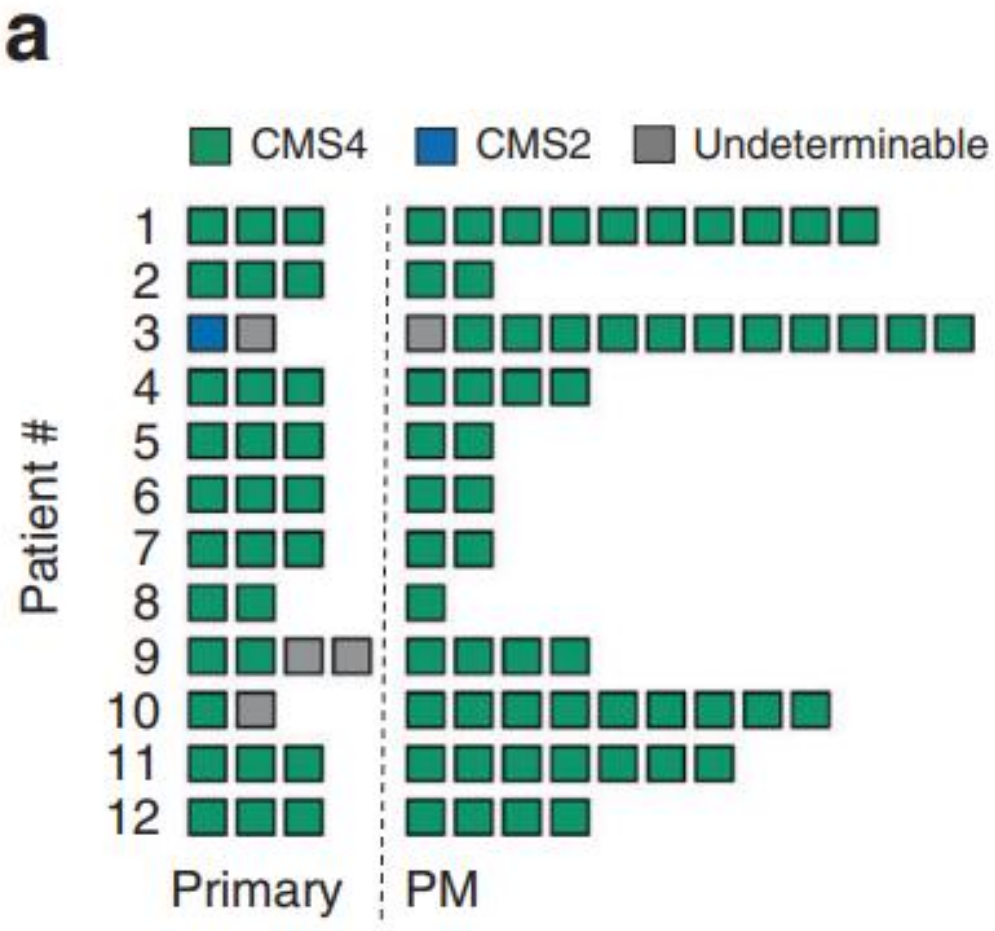
Nature Medicine **volume 21**, pages1350–1356 (2015





Ubink I. Histopathological and molecular classification of colorectal cancer and corresponding peritoneal metastases. Br J Surg. 2018 Jan;105(2):e204-e211. PMID: 29341165.





Laoukili J. Peritoneal metastases from colorectal cancer belong to Consensus Molecular Subtype 4 and are sensitised to oxaliplatin by inhibiting reducing capacity. Br J Cancer. 2022 Jun;126(12):1824-1833. PMID: 35194192.

P - 9/24 **(56%)** had a high TMB ≥ 10 mut/Mb
T - 7/24 (30%)

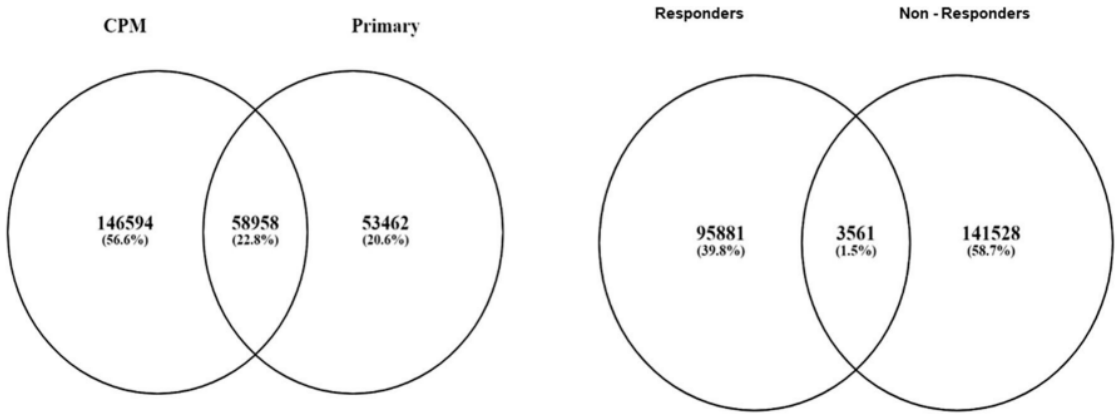
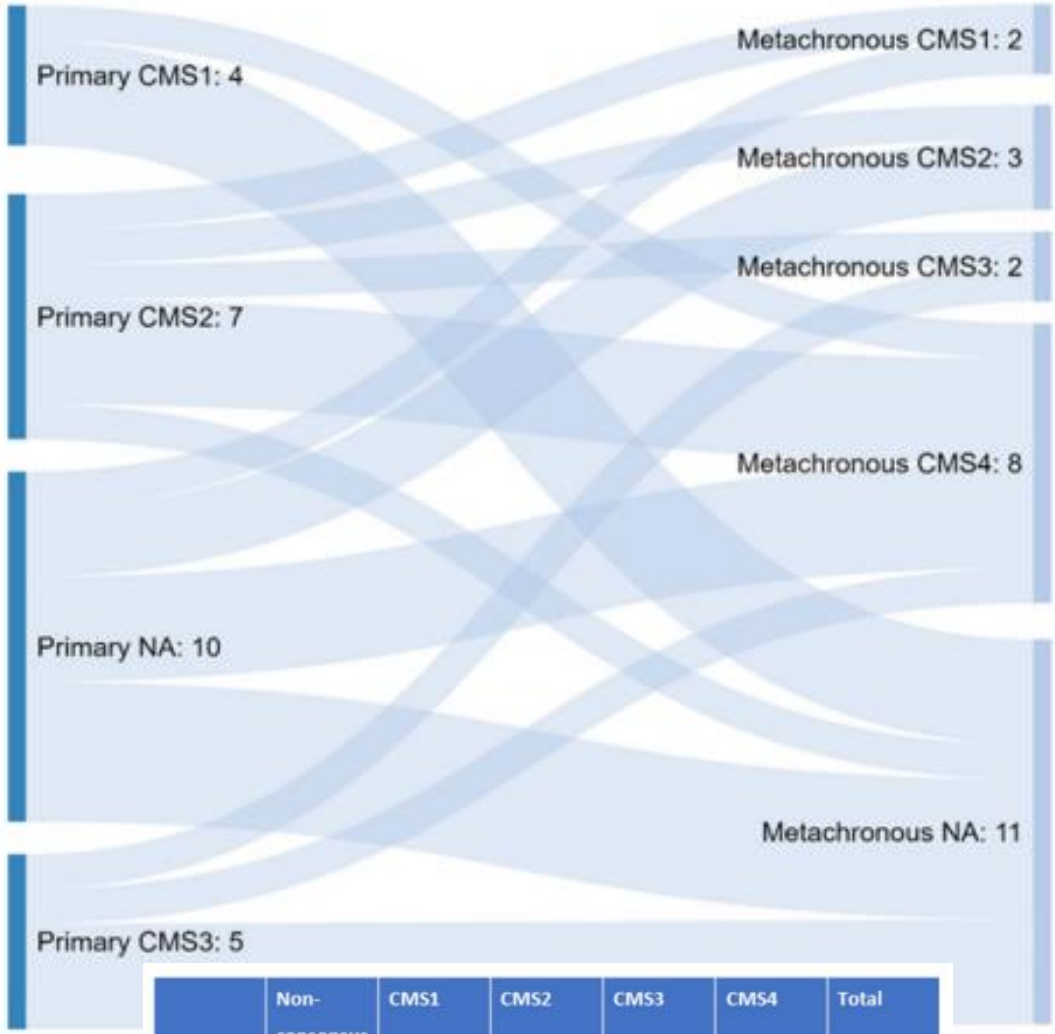


Figure 1. Venn diagrams depicting the frequency of mutations exclusive to and shared between primary CRC and matched CPM and responders and non-responders.

Chr	Position	Reference	Allele	*p* Value	FDR	Sample frequency (case)	Sample frequency (control)	Gene ID
4	93,084,410	C	G	0.007	0.53	62.5	0	*FAM13A*
18	11,552,313	G	C	0.023	0.53	50	0	*PIEZO2*

Table 2. Potential candidate variants, non-responders to CRS & HIPEC. CPM identified through Fisher exact test, genomics workbench (Chr, chromosome, FDR, false discovery rate).

Non-responders more commonly had a high TMB ≥ 10 mut/Mb **56%** vs. 44%; n = 145,089 variants in non-responders

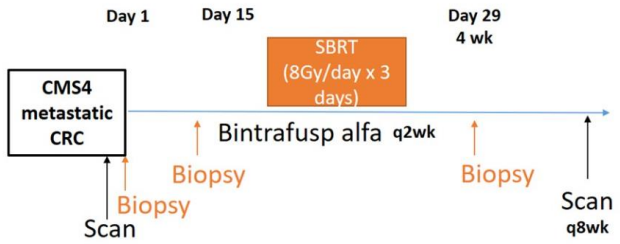


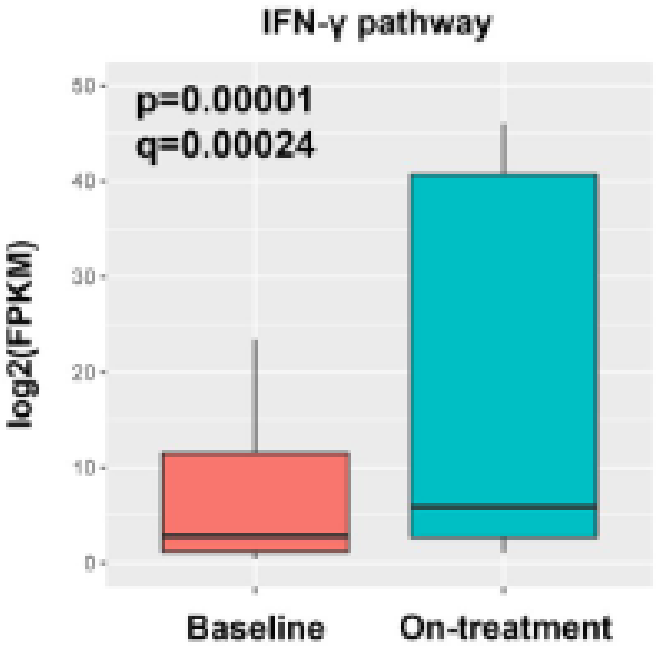
	Non-consensus	CMS1	CMS2	CMS3	CMS4	Total
Primary	10 (40)	4 (16)	6 (24)	5 (20)	0 (0)	25
CPM	12 (46)	1 (4)	3 (12)	2 (7)	8 (31)	26

Investigational Drug

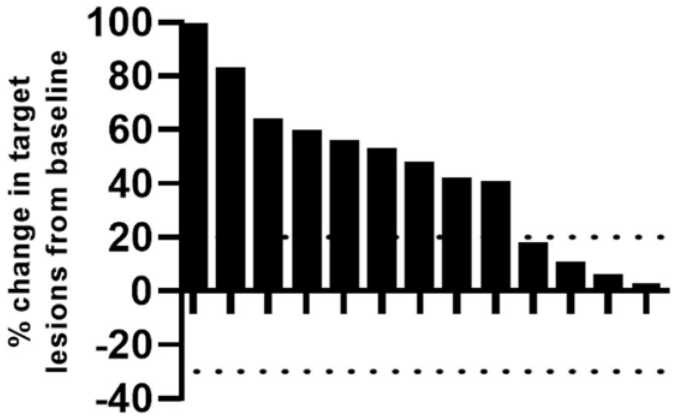
- **Bintrafusp alfa (M7824) is a first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF-β receptor II (a TGF-β "trap") fused to a human immunoglobulin G1 antibody blocking PD-L1, which has demonstrated clinical activity with a manageable safety profile in various solid tumors.**

Study Schema



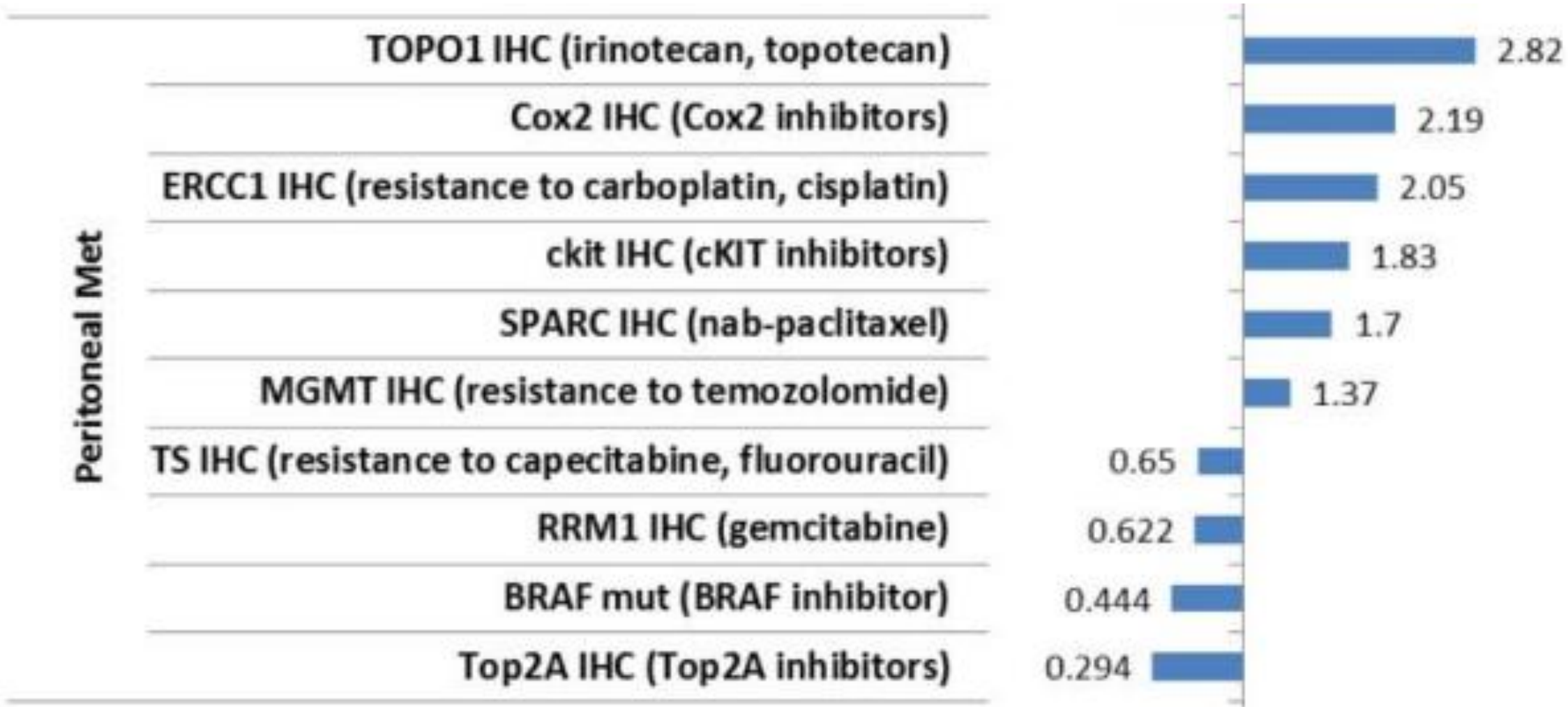


Best Response Rate



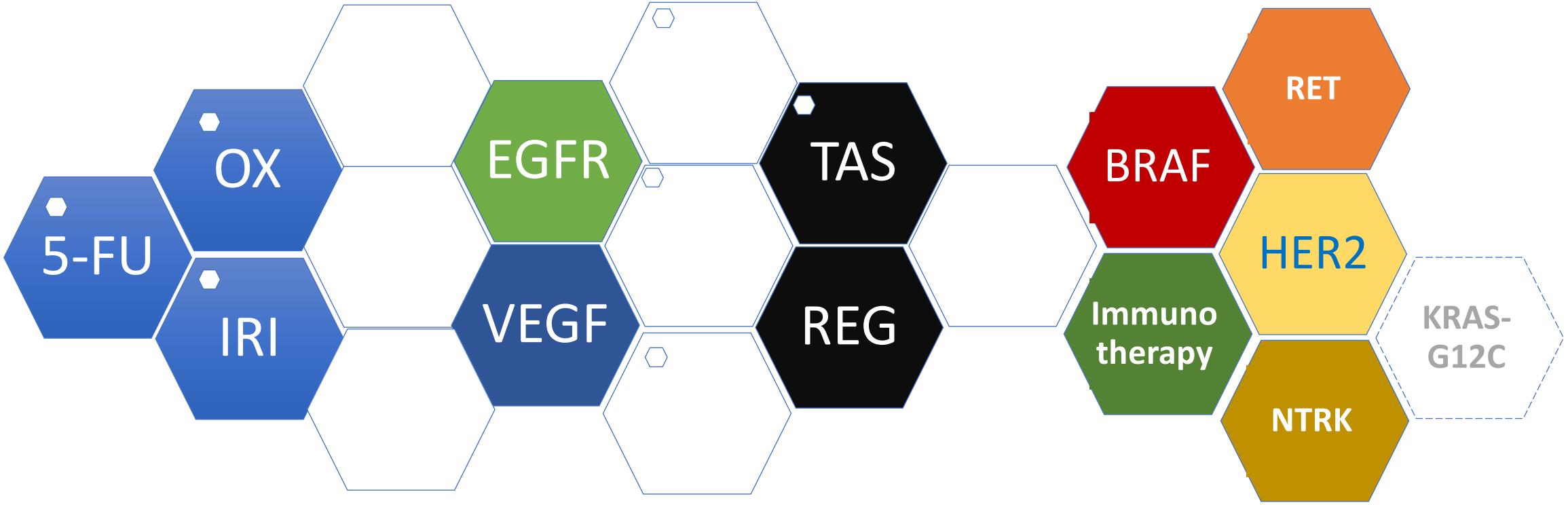
Agents associated with benefit	Biomarker	Primary CRC %	All Mets %	Metastasis to various sites							
				Lung Met %	Peritoneal Met %	Liver Met %	Bone Met %	Adrenal gland Met %	Brain met %	Ovarian Met %	Bladder Met%
trastuzumab	**Her2 IHC**	**1.8%**	(2.26%)	**4.0%**	(0.7%)	(2.3%)	(0.0%)	(0.0%)	(4.4%)	(2.9%)	(0.0%)
irinotecan; topotecan	**TOPO1 IHC**	**29.6%**	**52.00%**	**44.0%**	**54.3%**	**56.4%**	(50.0%)	(30.0%)	(31.8%)	**46.5%**	(20.0%)
temozolomide	**Low MGMT IHC**	**45.00%**	**38.25%**	**30.9%**	**37.00%**	(43.4%)	(57.1%)	**9.1%**	**21.00%**	**34.30%**	(20.0%)
cetuximab; panitumumab (lack of response)	**KRAS mutation**	**45.0%**	(46.77%)	**58.9%**	(48.1%)	(44.1%)	(55.6%)	**0.0%**	**65.0%**	**33.5%**	(16.7%)
imatinib	**cKIT IHC**	**6.4%**	**11.06%**	**10.7%**	**11.1%**	**12.1%**	(5.9%)	(25.0%)	(12.5%)	(6.2%)	(25.0%)
BRAF inhibitors	**BRAF mutation**	**14.6%**	**4.86%**	**2.4%**	**7.0%**	**4.4%**	(12.5%)	(0.0%)	(9.5%)	**5.5%**	(0.0%)
Cox2 inhibitors	**Cox2 IHC**	**68.3%**	(70.96%)	(67.4%)	**82.5%**	(64.3%)	**93.3%**	(80.0%)	(66.7%)	(73.0%)	(100.%)
oxaliplatin	**Low ERCC1 IHC**	**75.0%**	**70.98%**	(72.1%)	**59.5%**	(75.5%)	(68.4%)	(88.9%)	(73.7%)	(76.2%)	(100%)
nab-paclitaxel	**SPARC IHC**	**28.7%**	**34.20%**	(33.0%)	**41.0%**	(32.7%)	(33.3%)	(18.2%)	(29.2%)	(29.7%)	(20.0%)
fluoruracil; capecitabine	**Low TS IHC**	**65.4%**	**71.87%**	(67.1%)	**74.5%**	**73.0%**	(77.3%)	(50.0%)	(47.8%)	**74.2%**	(42.9%)
gemcitabine	**Low RRM1 IHC**	**55.2%**	**58.92%**	(58.8%)	**66.5%**	(53.5%)	(61.9%)	(50.0%)	(34.8%)	**69.0%**	(40.0%)
anthracyclines; etoposide	**TOPO2A IHC**	**80.4%**	**74.14%**	(81.4%)	**54.6%**	(82.4%)	(77.8%)	(66.7%)	**100.0%**	**68.0%**	(100.0%)
anthracyclines	**TOPO2A FISH**	**3.1%**	(6.78%)	(5.3%)	(0.0%)	**13.5%**	(0.0%)	(0.0%)	(0.0%)	(0.0%)	n/a
taxanes	**Low TUBB3 IHC**	**68.5%**	**57.23%**	(62.5%)	(58.5%)	**47.6%**	(0.0%)	(100.0%)	(100.0%)	(83.8%)	(100.0%)
cMET inhibitors	**cMET IHC**	**38.3%**	(44.01%)	(45.5%)	(41.0%)	**47.4%**	(20.0%)	(66.7%)	(50.0%)	(35.6%)	(0.0%)
PDGFR inhibitors	**PDGFR IHC**	**34.9%**	(29.69%)	(37.6%)	(36.1%)	**23.6%**	(33.3%)	(20.0%)	(33.3%)	(30.2%)	(25.0%)
cMET inhibitors	**cMET FISH**	**1.2%**	(2.37%)	(3.2%)	(0.0%)	(2.2%)	(0.0%)	**50.0%**	(0.0%)	(4.6%)	(33.3%)
PI3K/Akt/mTor inhibitors	**PIK3CA Mut**	**15.6%**	(11.74%)	(16.5%)	(12.6%)	(12.5%)	(0.0%)	(20.0%)	(0.0%)	**1.8%**	(0.0%)

El-Deiry WS,. Molecular profiling of 6,892 colorectal cancer samples suggests different possible treatment options specific to metastatic sites. Cancer Biol Ther. 2015;16(12):1726-37. PMID: 26553611.

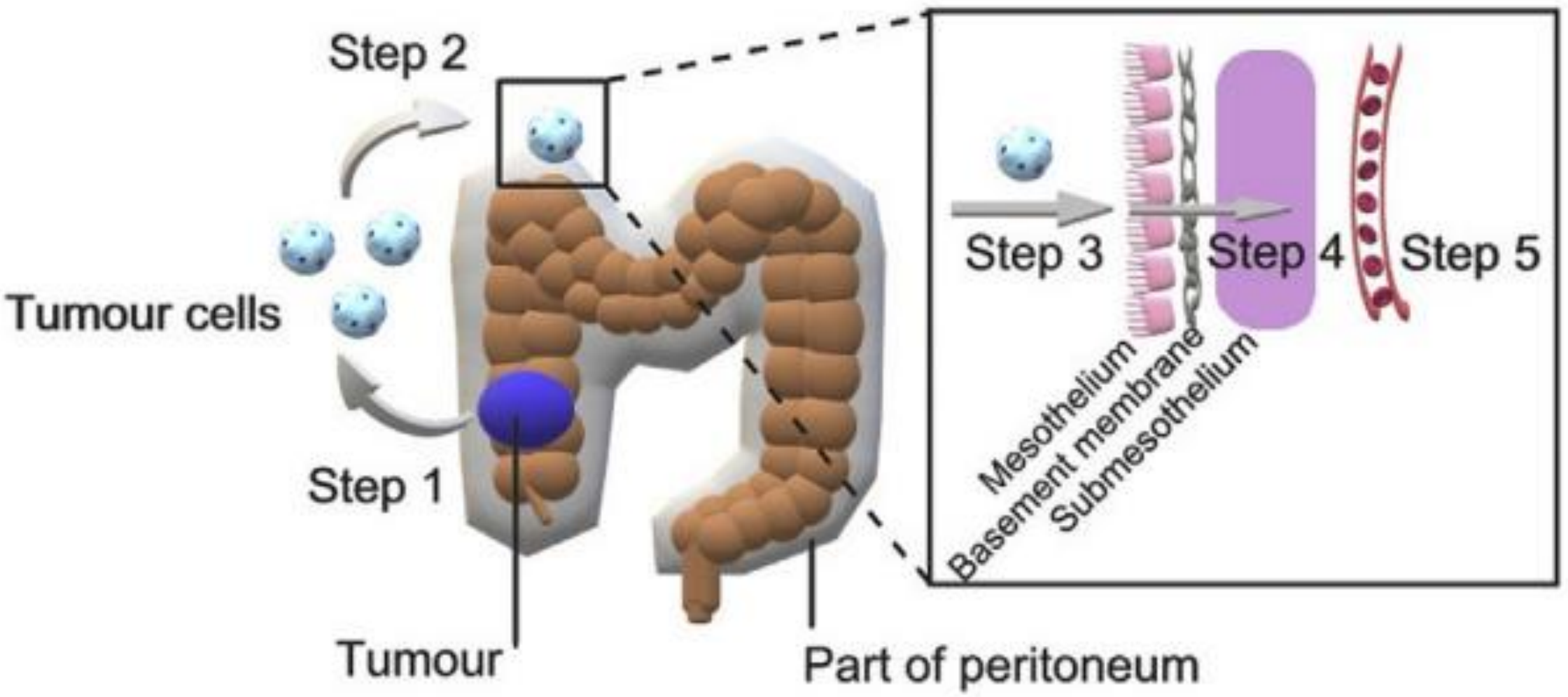


El-Deiry WS,. Molecular profiling of 6,892 colorectal cancer samples suggests different possible treatment options specific to metastatic sites. Cancer Biol Ther. 2015;16(12):1726-37. PMID: 26553611.

Treatment options for patients with mCRC



Kasi PM et al. Colorectal Cancer. Lancet Oct 2019.

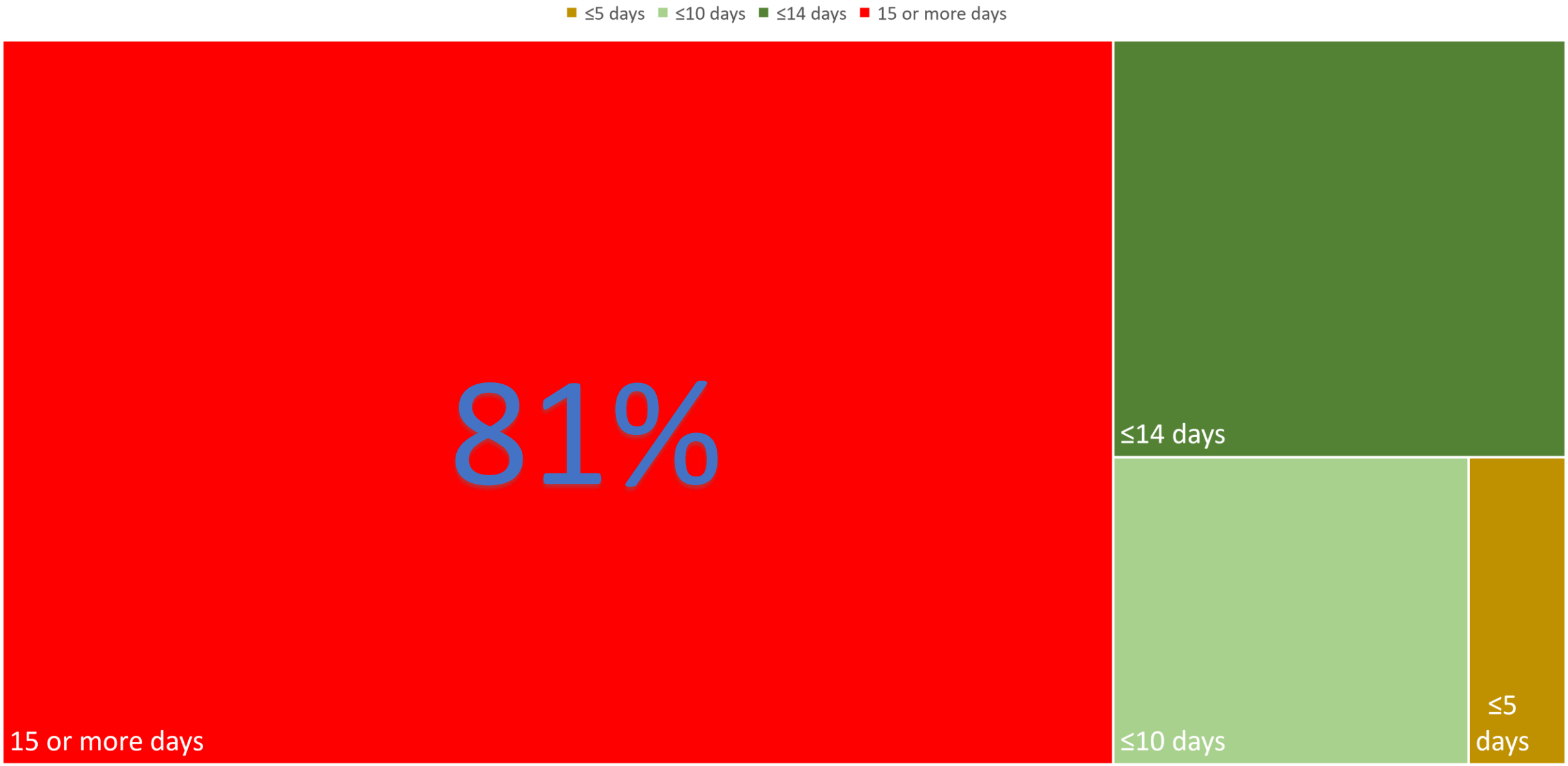


Baaten ICPA. Colorectal cancer peritoneal metastases: Biology, treatment and next steps. Eur J Surg Oncol. 2020 Apr;46(4 Pt A):675-683. PMID: 31806517.

Biomarkers

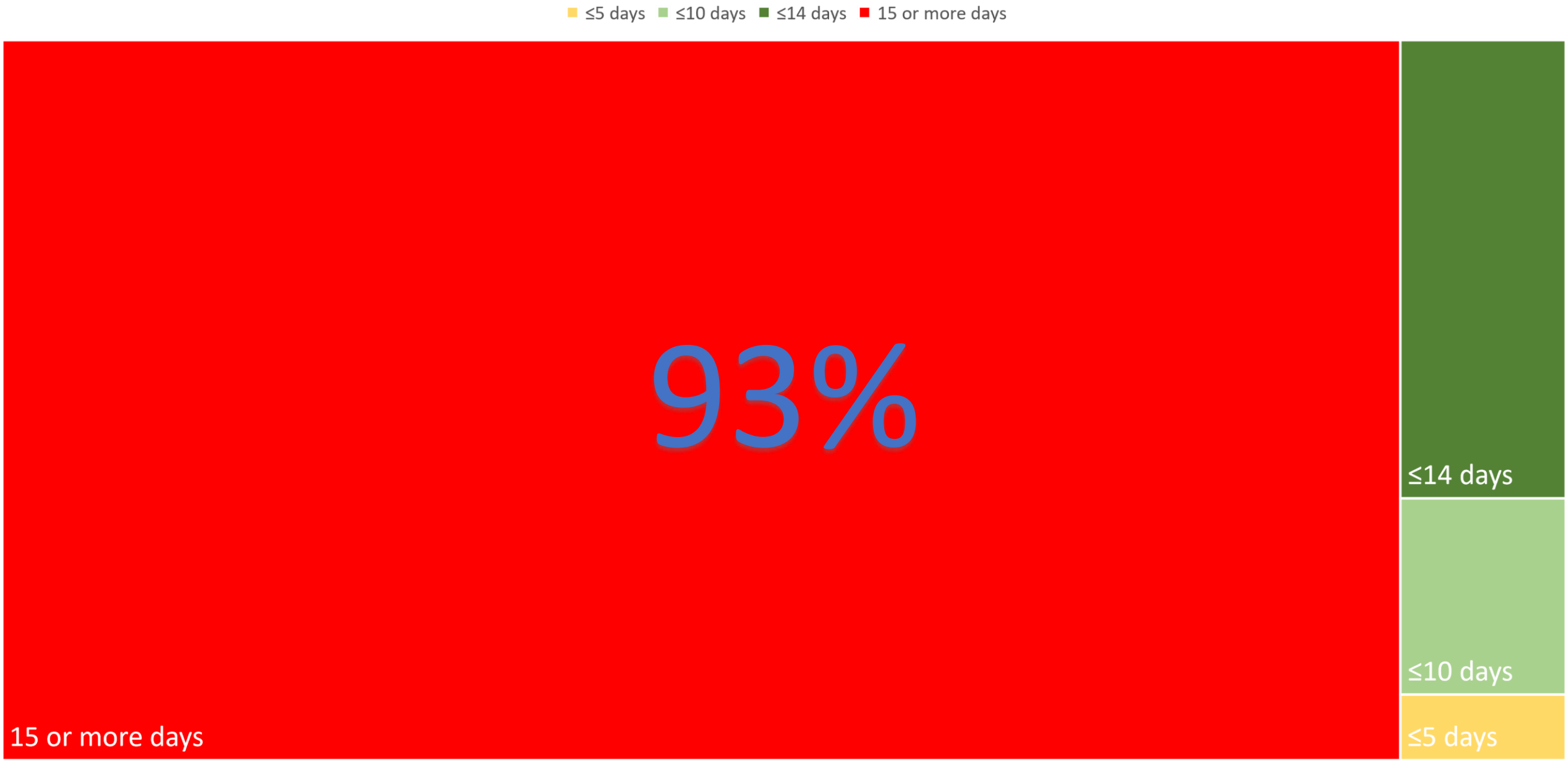
Testing patterns

RAS-testing and turnaround times



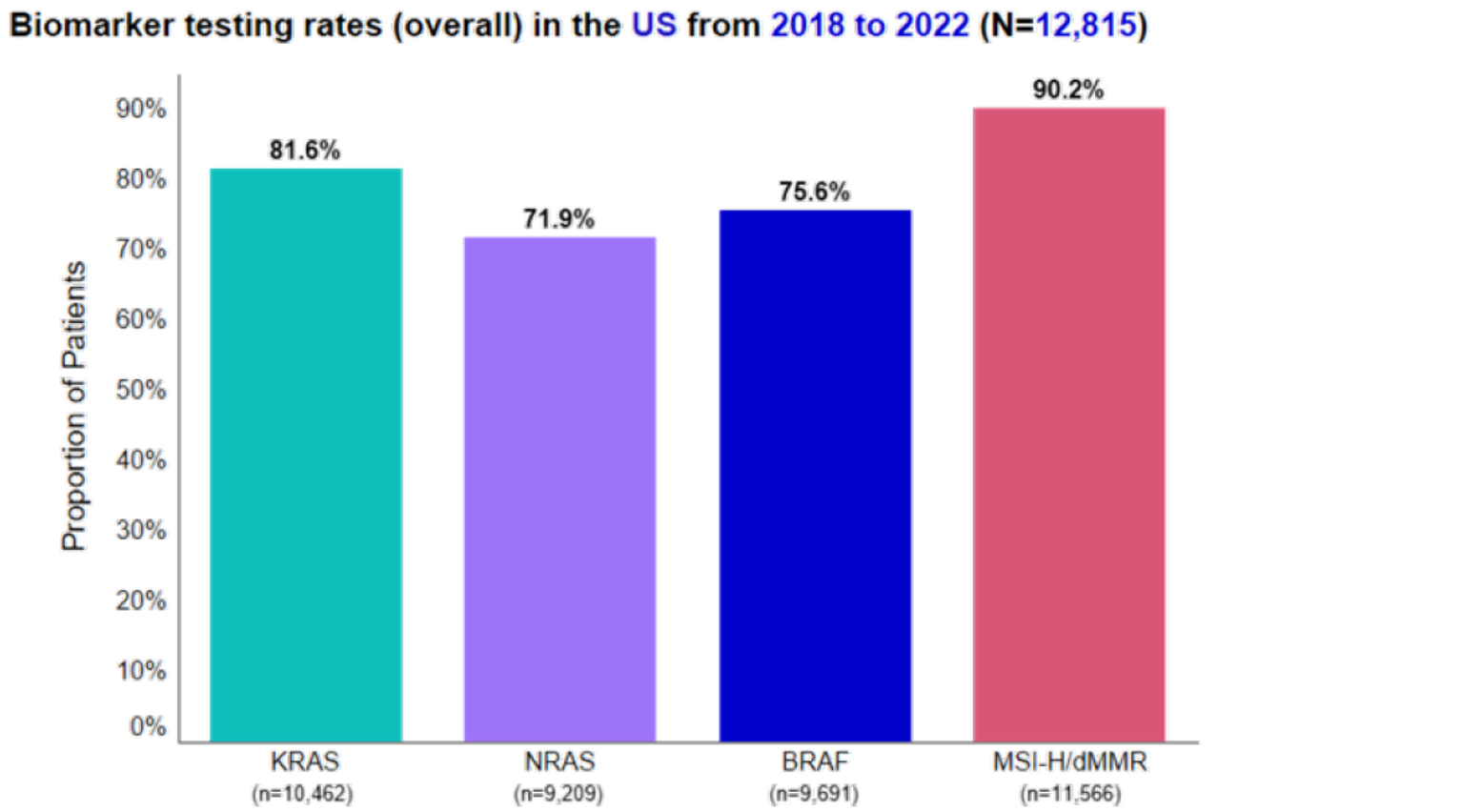
Sangaré L, Delli-Zotti K, Florea A, Rehn M, Benson AB, Lowe KA. An evaluation of *RAS* testing among metastatic colorectal cancer patients in the USA. Future Oncol. 2021 May;17(13):1653-1663. PMID: 33629919.

Time between testing and initiation of anti-EGFR



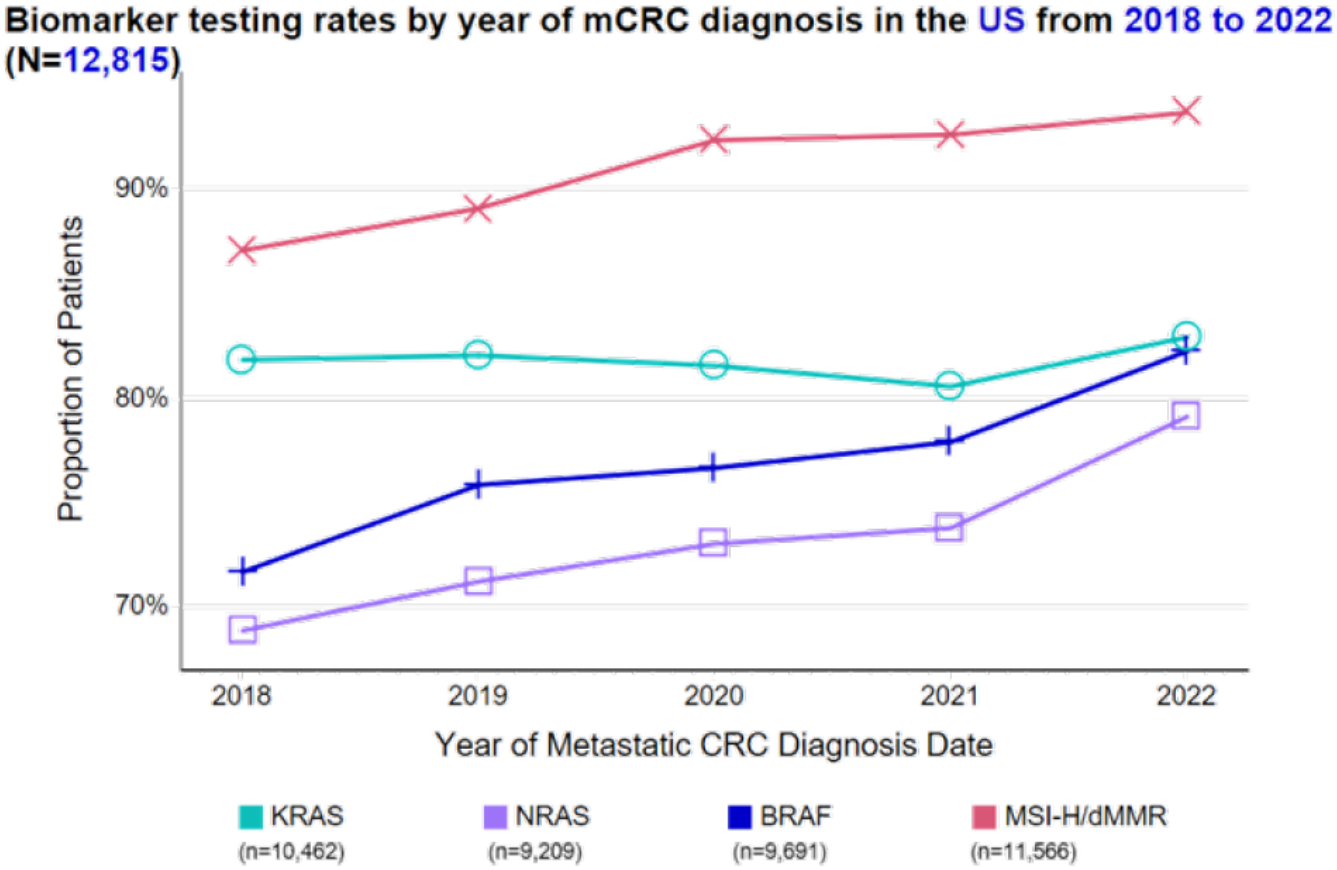
Sangaré L, Delli-Zotti K, Florea A, Rehn M, Benson AB, Lowe KA. An evaluation of *RAS* testing among metastatic colorectal cancer patients in the USA. Future Oncol. 2021 May;17(13):1653-1663. PMID: 33629919.

Overall Biomarker Testing Rates



N in slide title inclu s the entire mCRC population, regardless of biomarker testing status. N's in figure legend represent the number of mCRC patients with each respective biomarker test. Percentages show the number of patients tested for each biomarker among the entire mCRC population, by year of initial mCRC diagnosis. Data source: Flatiron(®) Health EHR Database .

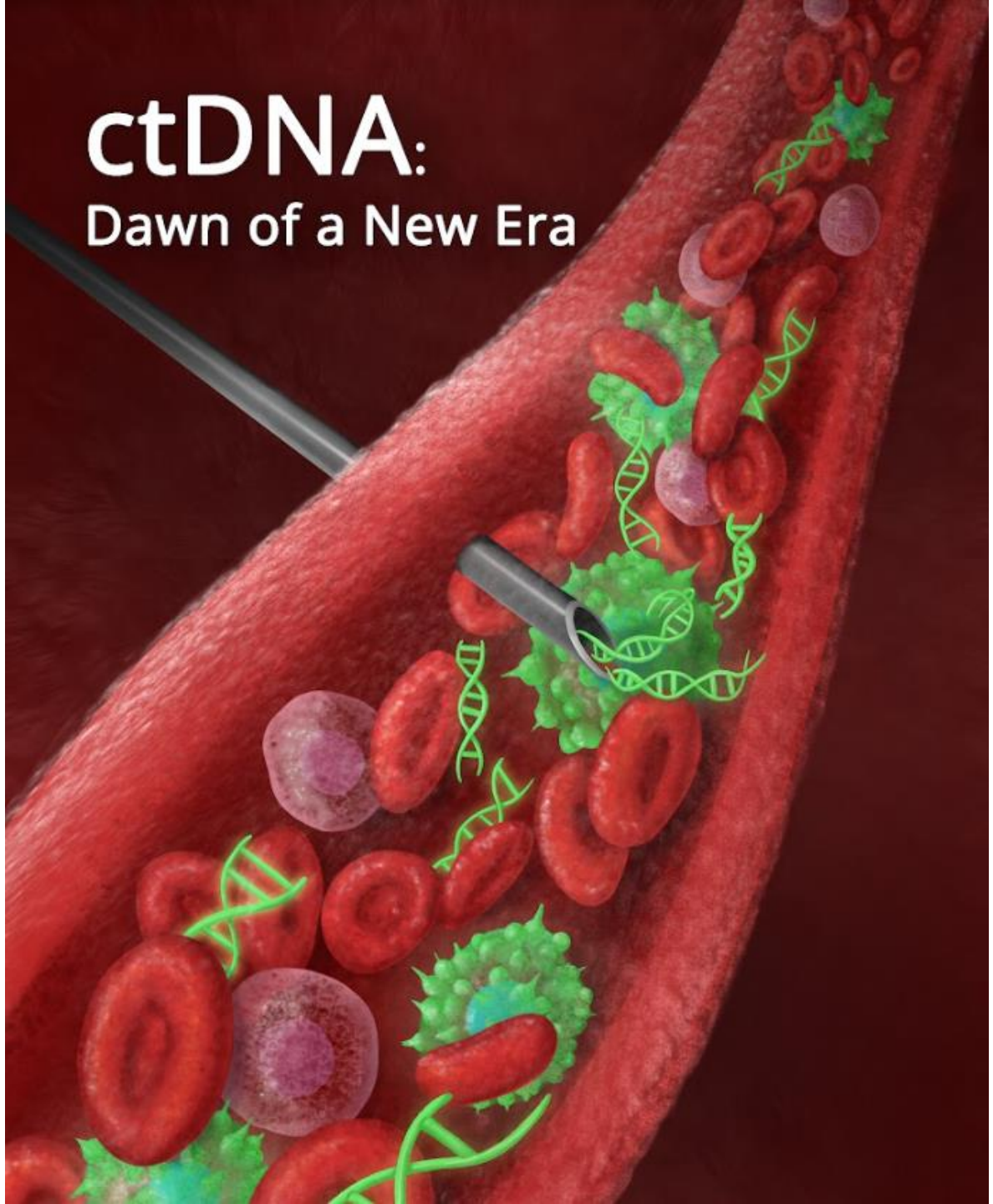
Biomarker Testing Rates by Year



N in slide title includes the entire mCRC population, regardless of biomarker testing status. N's in figure legend represent the number of mCRC patients with each respective biomarker test. Percentages show the number of patients tested for each biomarker among the entire mCRC population, by year of initial mCRC diagnosis. Data source: Flatiron(®) Health EHR Database .

Testing/Biomarkers

ctDNA

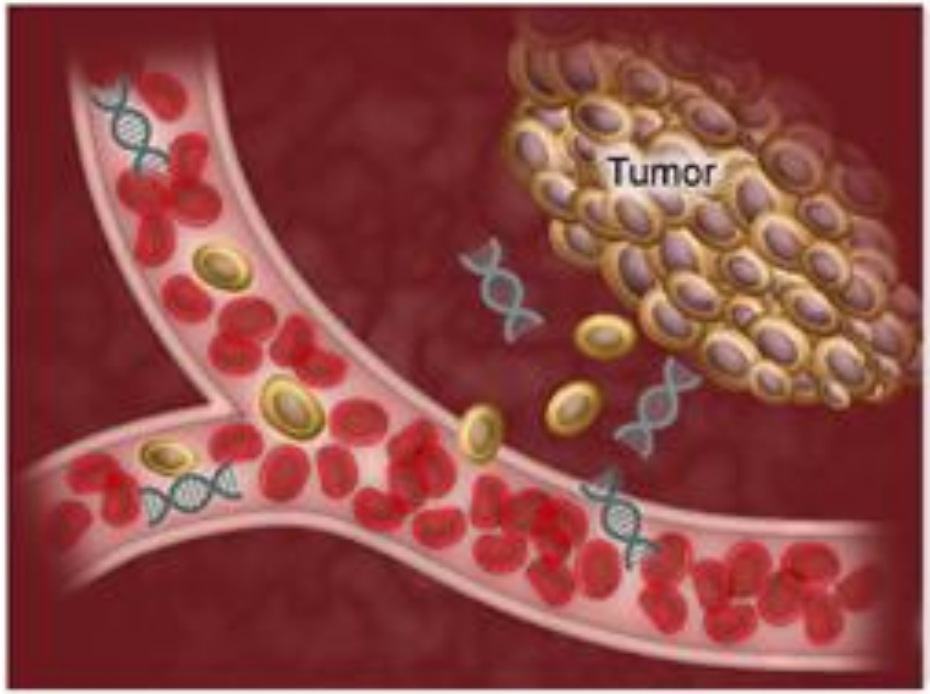


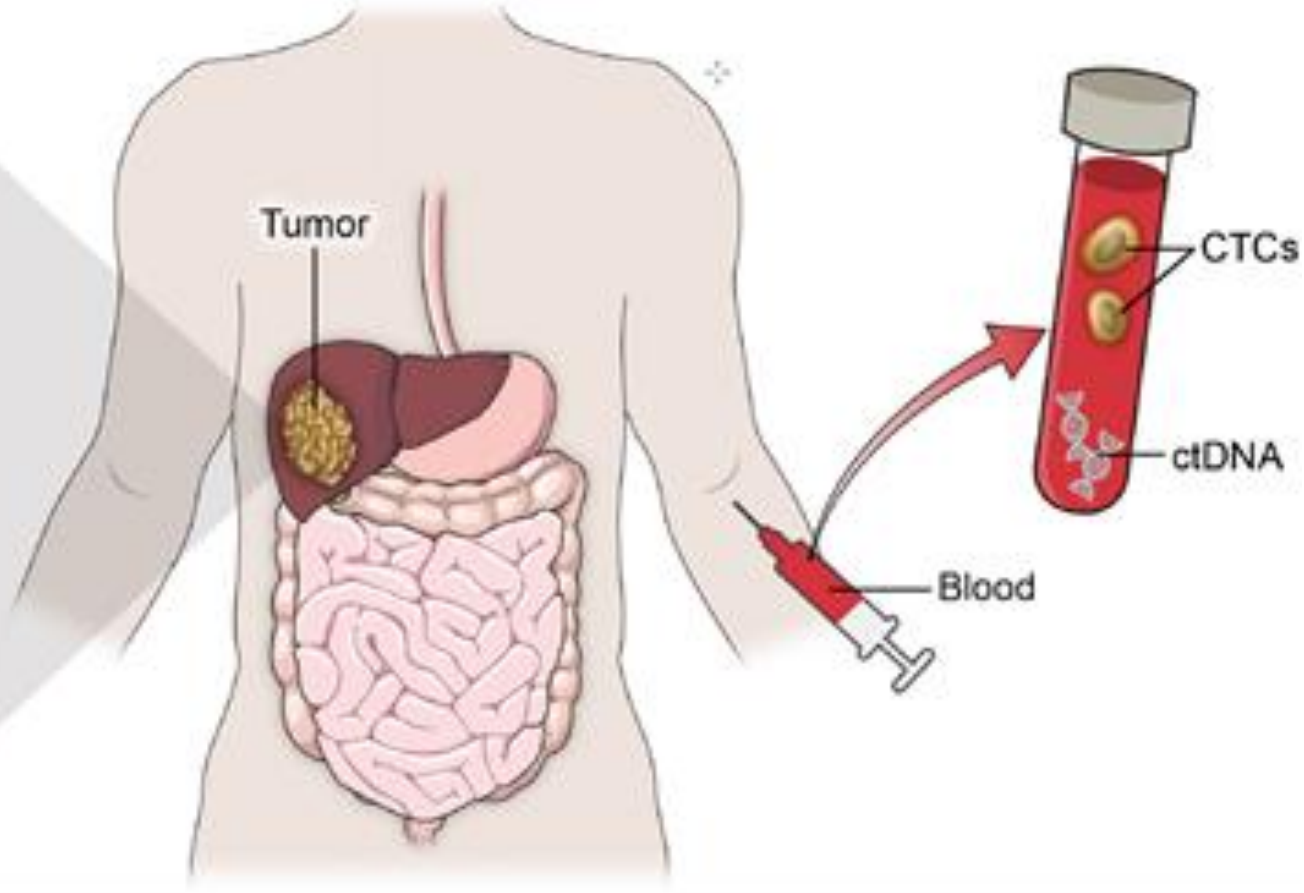
ctDNA: Dawn of a New Era

Location	Available On Demand
Time	Sat, Jun 4, 2022 | 9:00 AM – 10:30 AM EDT
Track(s)	Special Sessions

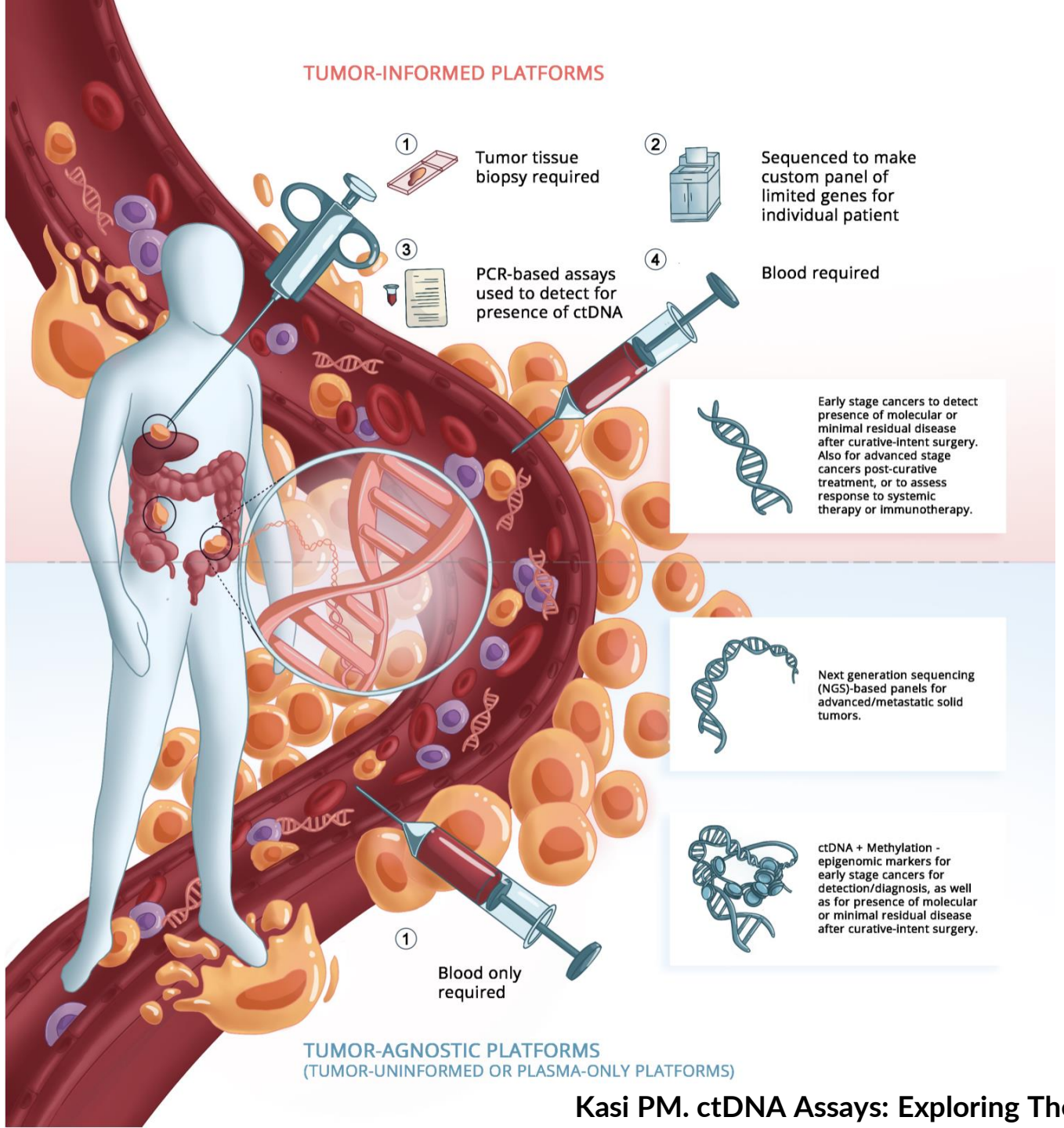
2022 ASCO® ANNUAL MEETING

ADVANCING EQUITABLE CANCER CARE THROUGH INNOVATION





@pashtoonkasi



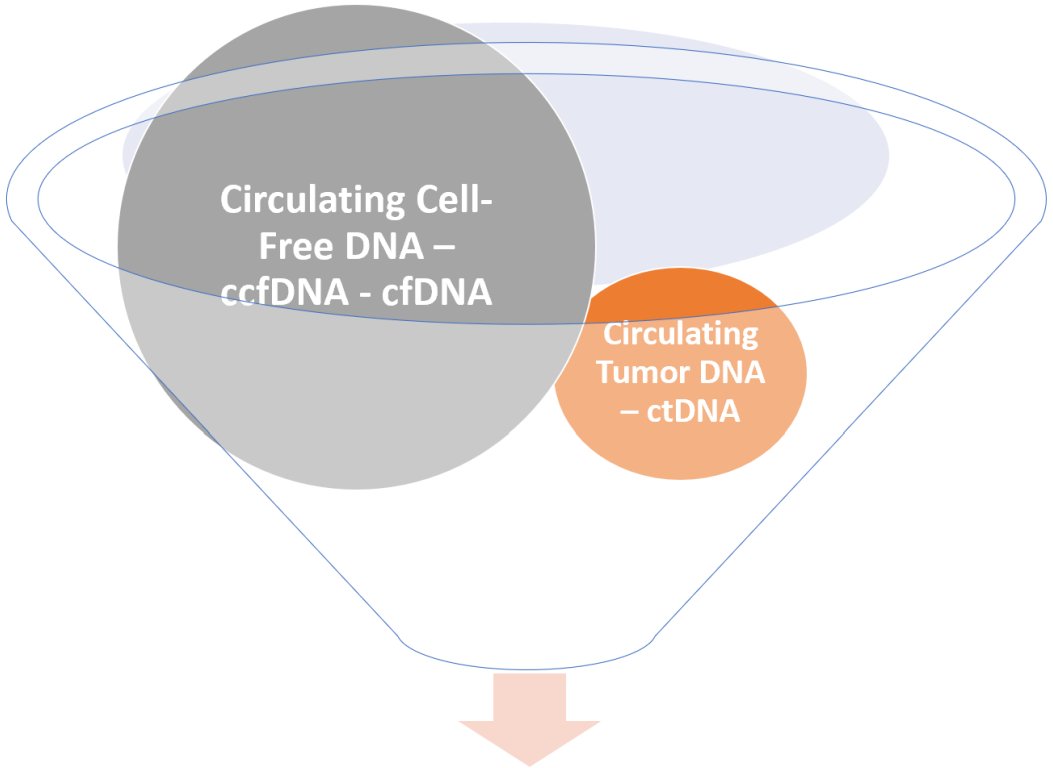
Tumor-informed Platforms Versus Tumor-agnostic (tumor-uninformed or plasma-only) Platforms

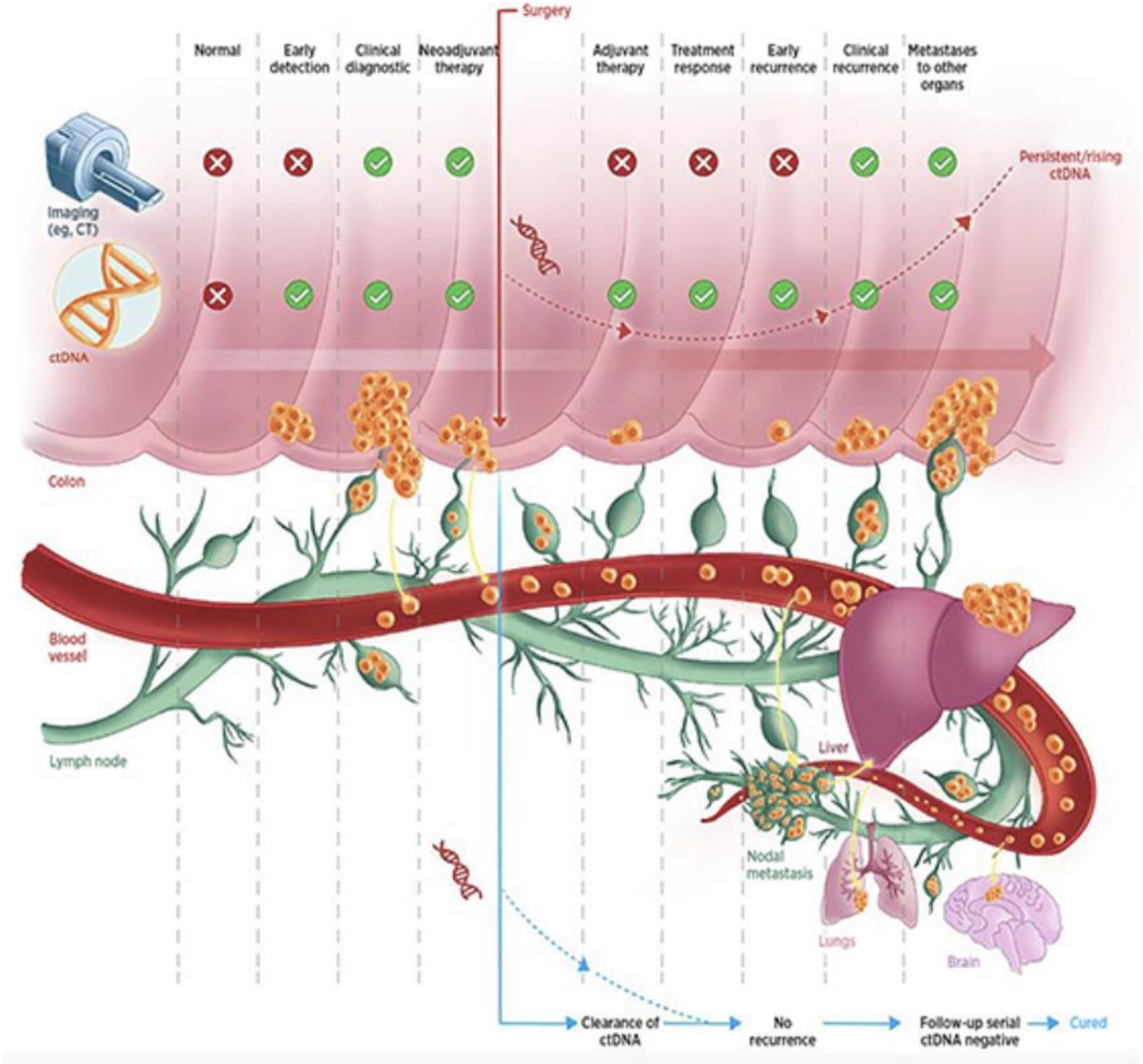
ASCO Daily News®

Kasi PM. ctDNA Assays: Exploring Their Clinical Use in Oncology Care. January 2022. ASCO Daily News.

Plasma MSI (microsatellite instability)

- Detected
- Not Detected (ND)



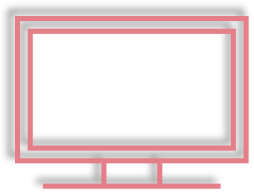


- Diagnosis
- Minimal Residual Disease
- Treatment Response
- Acquired Resistance

ASCO Daily News®

Kasi PM. ctDNA Assays: Exploring Their Clinical Use in Oncology Care. January 2022. ASCO Daily News.

nature medicine



14 + 19 = 33 days !

GI-SCREEN (tissue) $n = 5,621$

Median 14 days

Median 19 days

GOZILA (ctDNA) $n = 1,687$

Median 4 days

Median 7 days

4 + 7 = 11 days ✓

$P < 0.0001$

Interval between enrollment and sample reception

Time from receiving samples to reporting results

0 5 10 15 20 25 30 35

Time (days)

	GI-SCREEN (N = 5,621)	GOZILA (N = 1,687)
CRC	2543/2754 (92.3%)	654/654 (100.0%)
GC	979/1121 (87.3%)	260/260 (100.0%)
ESCC	307/356 (86.2%)	107/108 (99.1%)
PDAC	546/623 (87.6%)	363/363 (100.0%)
CCA	347/408 (85.0%)	188/188 (100.0%)
Others	304/359 (84.7%)	114/114 (100.0%)

NILE Study

"cfDNA analysis as the first genomic testing approach would have **identified 87%** of the 89 biomarker-positive participants, compared with a rate of **67% using tissue testing** first."

AACR 2019

Noninvasive versus Invasive Lung Evaluation

NATURE MEDICINE | VOL 26 | DECEMBER 2020 | 1859–1864

nature medicine

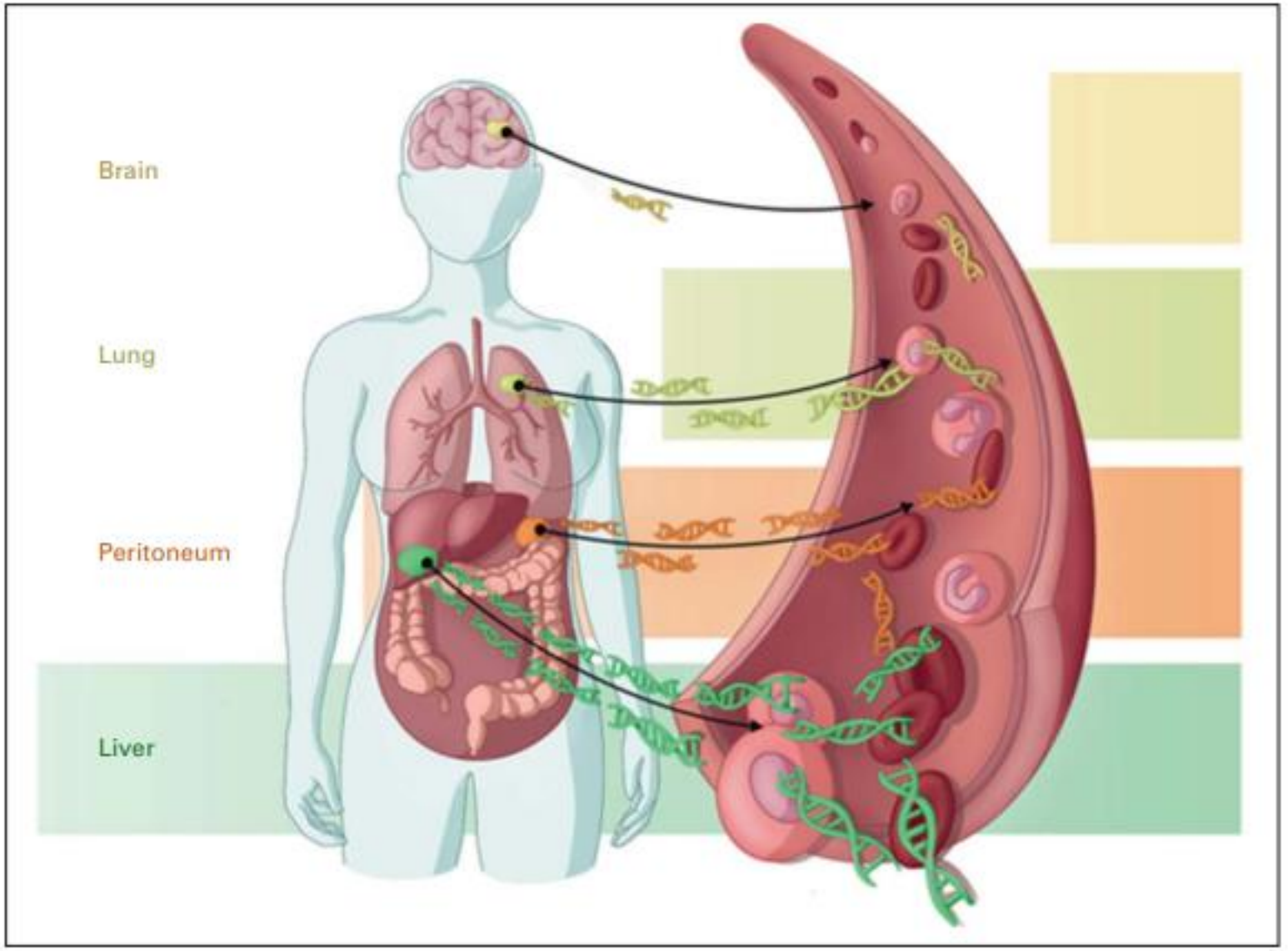
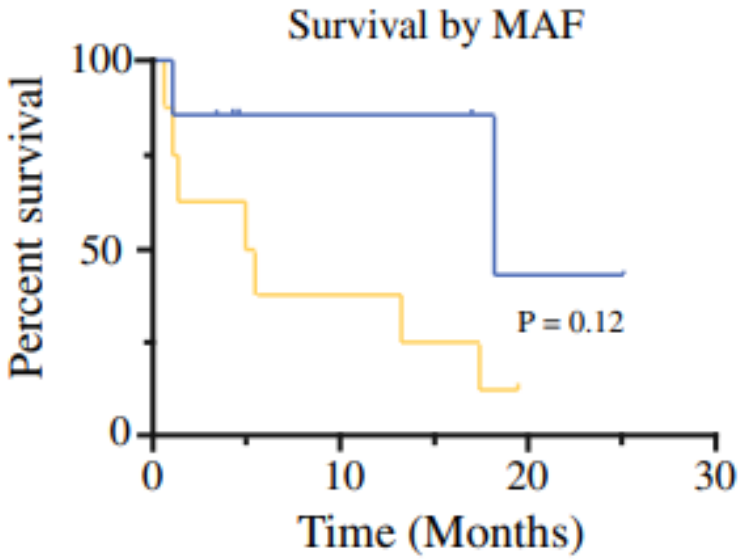


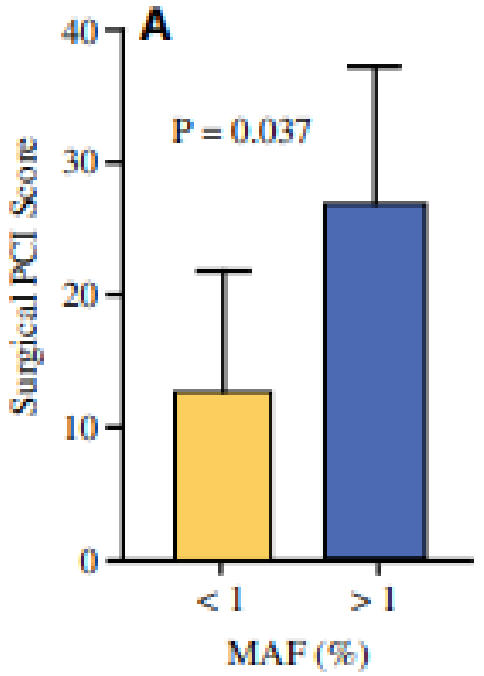
FIG 1. Shedding and amount of detectable circulating tumor DNA varies by location of metastatic site. Liver metastases appear to shed the most DNA, followed by the peritoneum and lung.

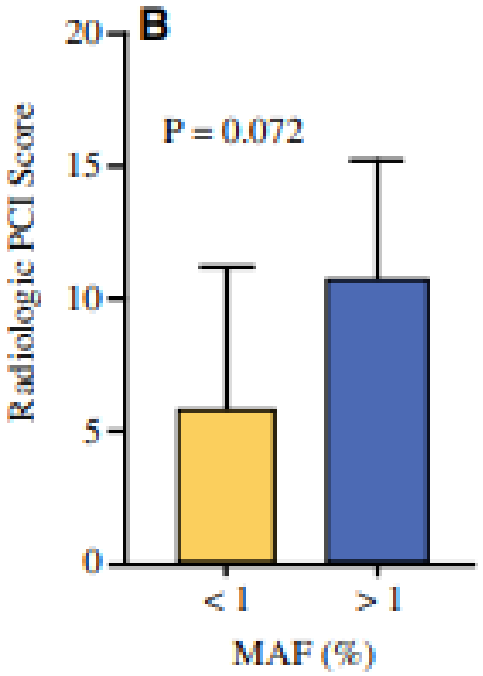
Kasi PM, Fehringer G, Aleshin A, Kopetz S. Reply to F. Dayyani et al. **JCO Precis Oncol**. 2022 Jul;6:e2200275. doi: 10.1200/PO.22.00275. PMID: 35834757.

18.2 months vs.
5.2 months



"ptDNA"





Patients with MAF > 1% had significantly higher surgical PCI scores (27 versus 13)

Patients with MAF > 1% had significantly higher radiological PCI scores (11 versus 6)

Ann Surg Oncol (2020) 27:5065–5071
https://doi.org/10.1245/s10434-020-08832-9

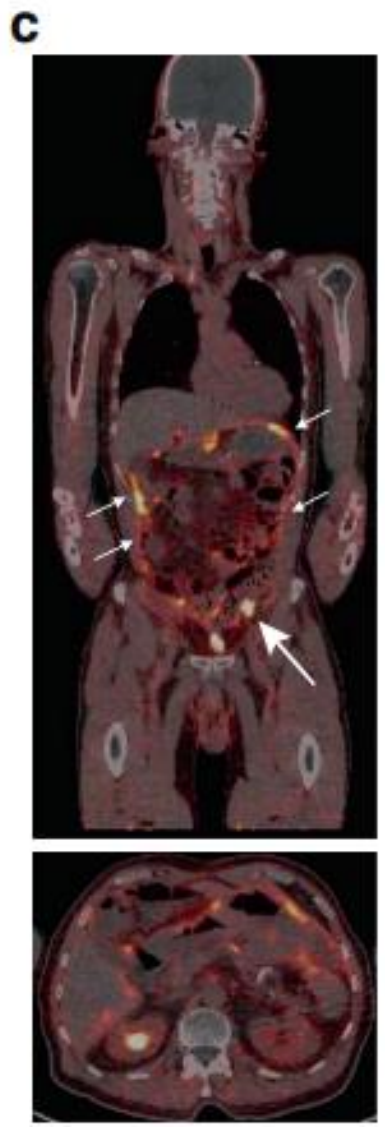
Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

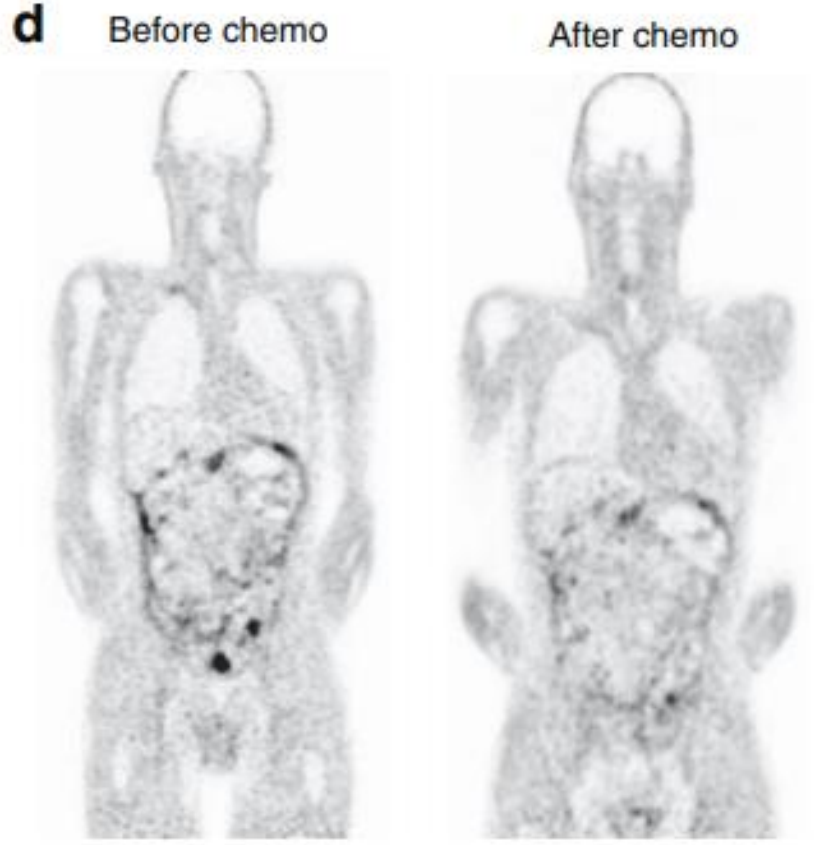
ORIGINAL ARTICLE – TRANSLATIONAL RESEARCH

Peritoneal Cell-Free Tumor DNA as Biomarker for Peritoneal Surface Malignancies

Katie M. Leick, MD, MS[1], Austin G. Kazarian, BS[1], Maheen Rajput, MD[2], Ann Tomanek-Chalkley, BS[1], Ann Miller, PhD[1], Hannah R. Shrader, BA, BS[1], Ashley McCarthy, BS, MPH[3], Kristen L. Coleman, PhD[3], Pashtoon M. Kasi, MD, MS[3,4], and Carlos H. F. Chan, MD, PhD[1,3]

[1]Department of Surgery, University of Iowa, Iowa City, IA; [2]Department of Radiology, University of Iowa, Iowa City, IA; [3]Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA; [4]Internal Medicine, University of Iowa, Iowa City, IA





Fibroblast activation protein (FAP) identifies Consensus Molecular Subtype 4 in colorectal cancer and allows its detection by 68Ga-FAPI-PET imaging

Strating E. Fibroblast activation protein identifies Consensus Molecular Subtype 4 in colorectal cancer and allows its detection by ^{68}Ga-FAPI-PET imaging. Br J Cancer. 2022 Jul;127(1):145-155. PMID: 35296803.

City of Hope

THIRD ANNUAL
ISSPP Congress 2022
International Society for the Study of Pleura and Peritoneum

COLORECTAL CANCERS

Systemic Approaches to Colorectal Peritoneal Metastases

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Director, Precision Medicine Research for Liquid Biopsies
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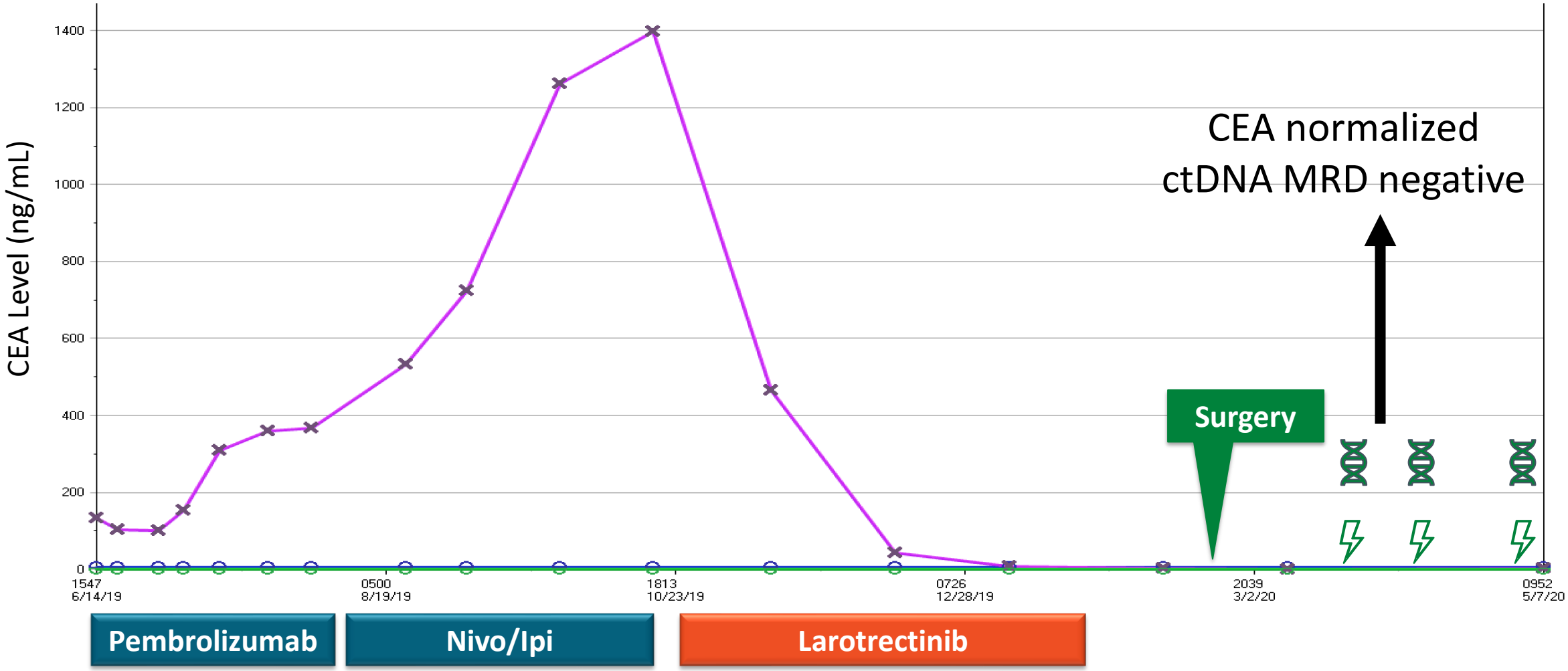
Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Backup Slides

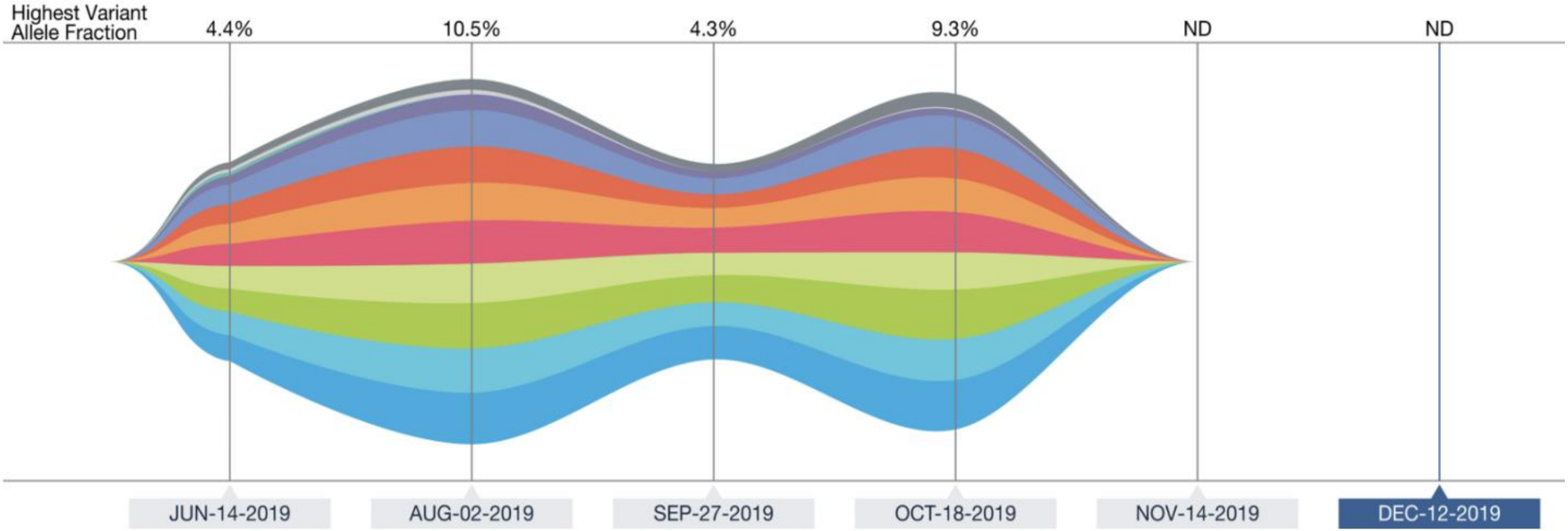
Case presentation: Patient With MSI-H/*NTRK* Fusion+ CRC

- 43-yr-old woman initially diagnosed with pT4aN0 colon cancer that was MMR proficient
- Patient deferred chemotherapy; a right lower quadrant mass later recurred, with carcinomatosis and ascites
  - Laboratory findings: dMMR/MSI-H, TMB-high, *TPR-NTRK1* fusion, HER2 negative

Case 1 Continued: Patient With MSI-H/*NTRK* Fusion+ CRC



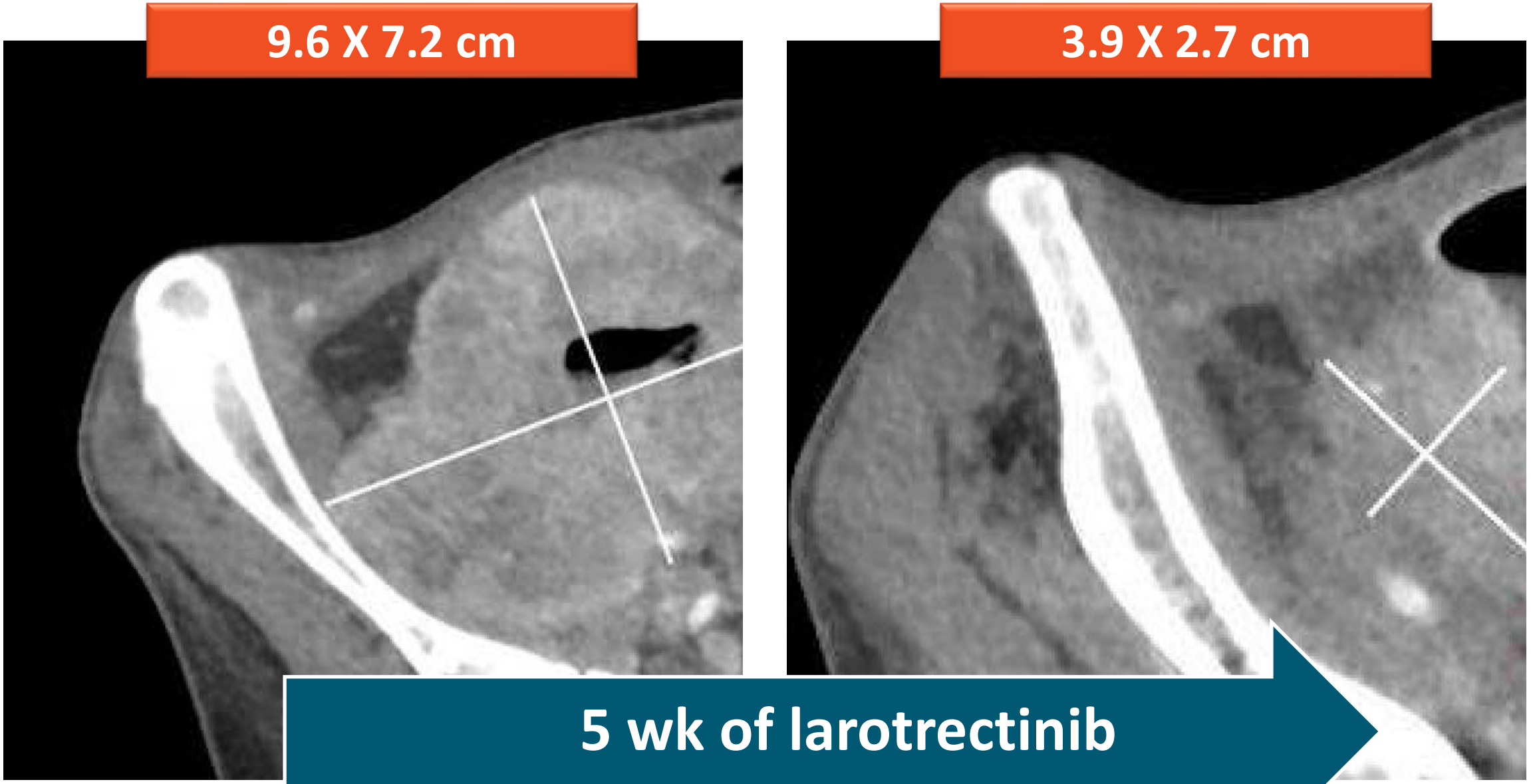
Case 1 Continued: Patient With MSI-H/*NTRK* Fusion+ CRC

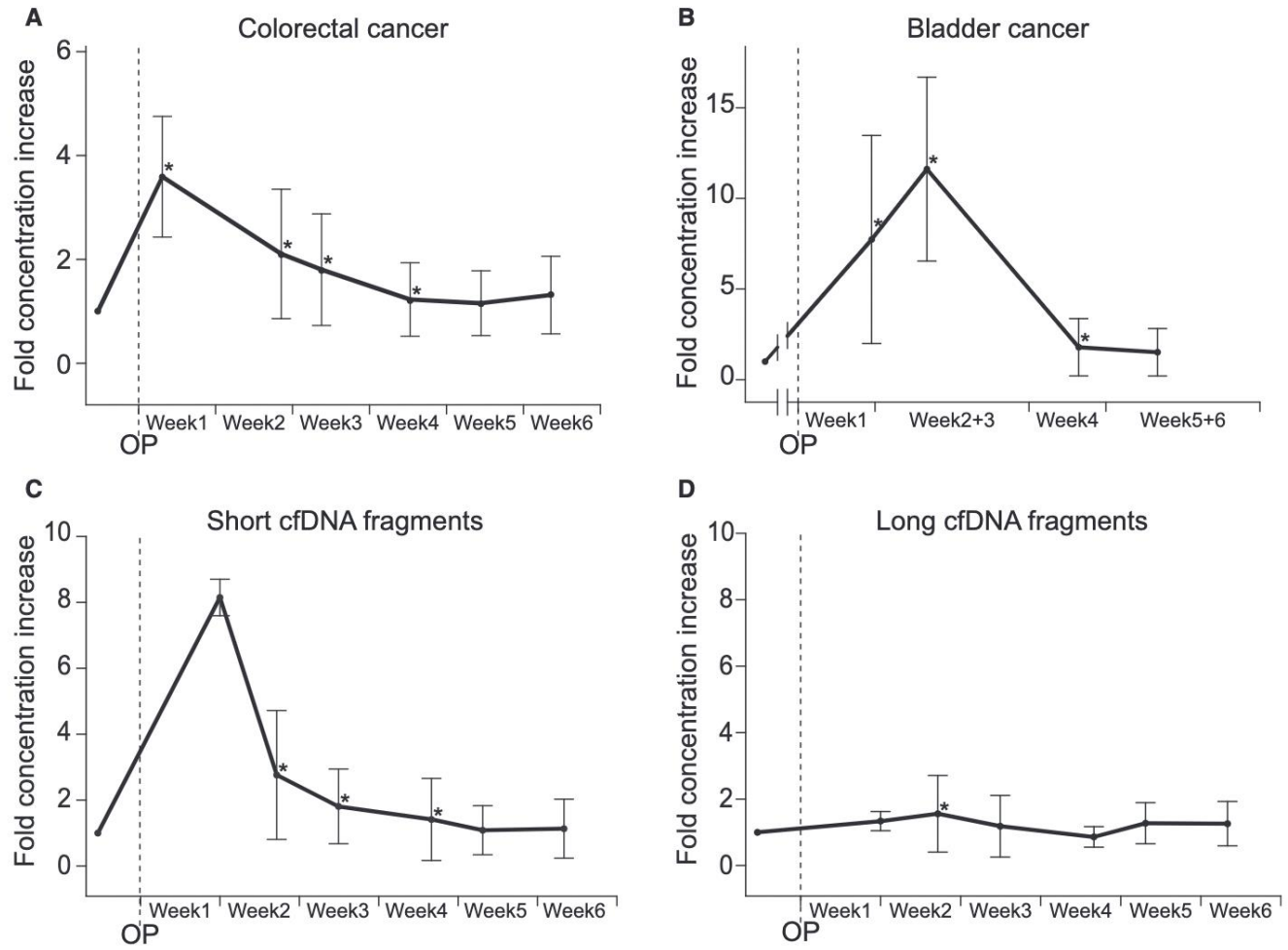


Pembrolizumab | Nivo/Ipi | Larotrectinib

Microsatellite status: MSI-High

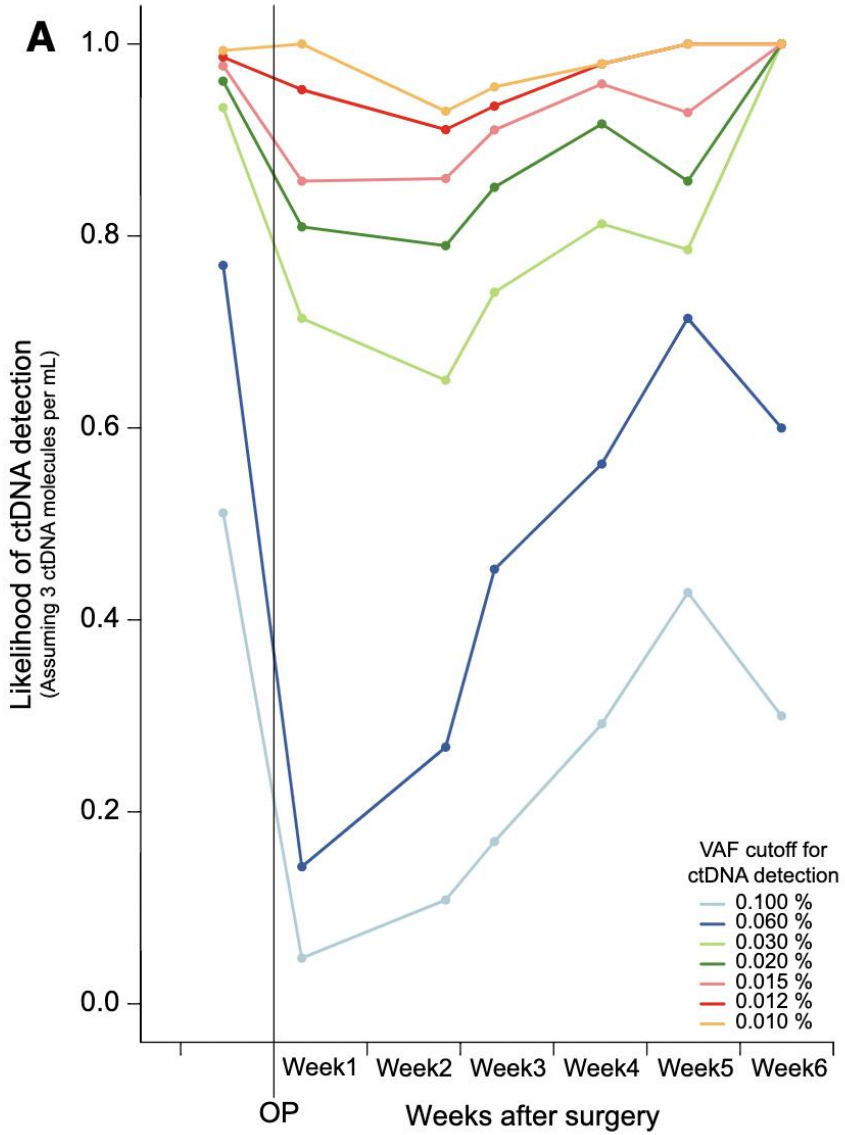
DETECTED | NOT DETECTED


9.6 X 7.2 cm
3.9 X 2.7 cm
5 wk of larotrectinib



Surgical trauma induced **cfDNA** affects **ctDNA** detection

Henriksen TV. **The effect of surgical trauma on circulating free DNA levels in cancer patients-implications for studies of circulating tumor DNA**. Mol Oncol. 2020 Aug;14(8):1670-1679.



cfDNA affects

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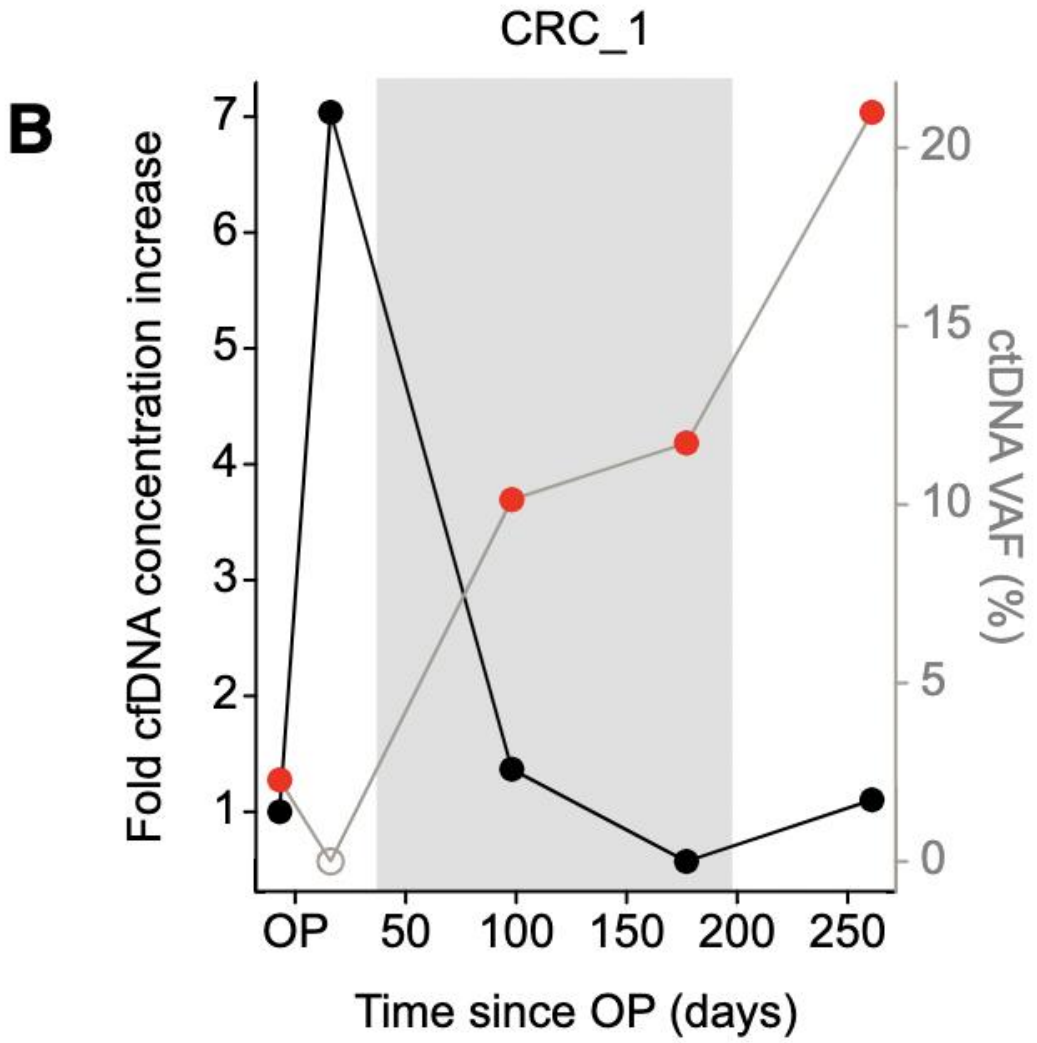
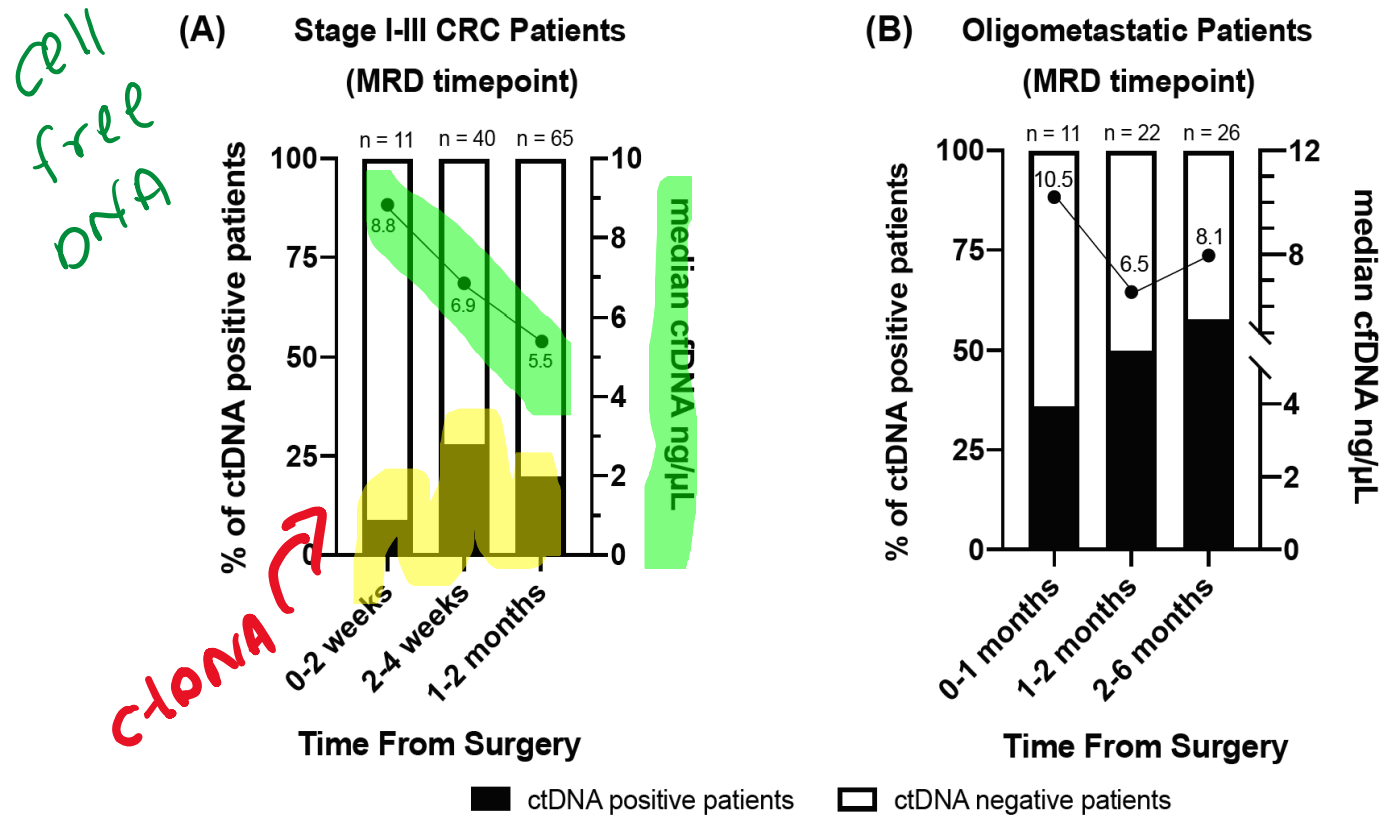


cfDNA affects
ctDNA
detection

Henriksen TV. **The effect of surgical trauma on circulating free DNA levels in cancer patients-implications for studies of circulating tumor DNA**. Mol Oncol. 2020 Aug;14(8):1670-1679.

Figure 2. Percentage of MRD positive cases vs. timing from surgery in locoregionally advanced and oligometastatic CRC patients



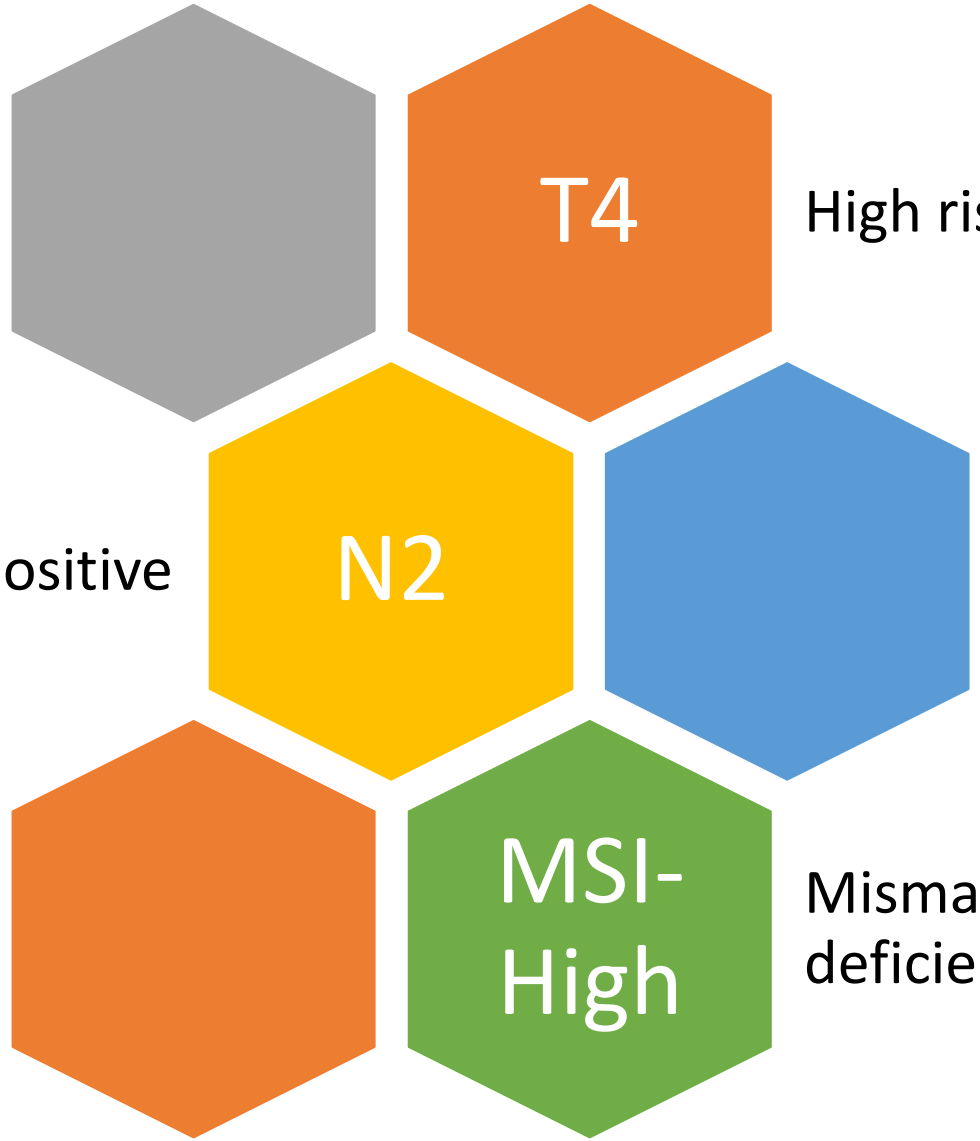
Tumor-informed assessment of molecular residual disease and its incorporation into practice for patients with early and advanced-stage colorectal cancer (CRC-MRD Consortia).

Kasi PM et al. ASCO 2020. *Journal of Clinical Oncology* 38, no. 15_suppl (May 20, 2020) 4108-4108.

Timing is key

Finding the needle in the haystack

Immediate post-operative period – bigger haystack



High risk

Node positive

Mismatch repair deficiency

Table 1 Summary of targets with possibility for clinical implementation in PM in the future

Promising target in PM	Biological relevance in PM	Difference with CRLM	Prognostic relevance	Possible therapeutic implications
IGF-1	Growth factor	Yes, >2-fold change in mRNA [74]	Not clear	Monoclonal antibody Figitumumab [107, 108]
KLK7	Anoikis Evasion	Not clear	Yes, worse overall survival in CRC [45, 46]	Inhibition of KLK7 would lead to less evasion of anoikis [40]. However, interaction with α5β1 integrin, thus integrin inhibitors such as Volociximab may also be of interest [42, 43].
HIF1	Angiogenesis	Yes, >2-fold change in mRNA [74]	Not clear, trend was observed	HIF1 inhibitors could potentially be of interest in PM. HIF1 upregulation seems also to be specific for PM [74, 109]
VEGF	Angiogenesis	No	Yes, high VEGF expression correlated to worse survival [86]	Currently anti-VEGF antibody therapies already in use in clinical setting, very promising for clinical application [87].
Cyr61	Angiogenesis	No	Not clear	Is the ligand for α5β3. If possibility for blocking this interaction blocking of attachment to peritoneal surface ensues and subsequent angiogenesis is inhibited [33].
TWIST	Detachment and motility	No	Not clear	In experimental model blocking of TWIST showed less migration, invasion and adhesion to peritoneal surface. In theory powerful inhibition of PM formation [20].
c-MET	Detachment and motility	No	Yes, higher expression of c-MET correlated to worse survival [24]	In multiple experimental models blocking of c-MET showed marked inhibition of dissemination. Theoretically attractive therapeutic target [25].
EGFR	Detachment and motility	No	Not clear	Cetuximab is a clinical grade antibody already widely in use for metastasized CRC. No clinical data on specific EGFR inhibition in PM is available.
Integrins	Adhesion molecule	Not clear	Not clear	In multiple experimental models blocking of integrins showed marked inhibition of dissemination. Theoretically attractive therapeutic target [44, 77, 78]. Several integrin inhibitors currently under development [42, 43].
ICAM-1	Adhesion molecule	Not clear	Not clear	Highly experimental, dubious if therapeutically significant. Theoretically blocking of ICAM-1 leads to less PM due to less attachment to peritoneum [56].
Ep-CAM	Adhesion molecule	Not clear	Yes, higher expression of Ep-CAM correlated to worse survival [60]	Dubious if therapeutically significant. Theoretically blocking of Ep-CAM leads to less PM due to less attachment to peritoneum.
CD44	Adhesion molecule	Not clear	Yes, exon v6 variant in advanced disease [62, 63]	Highly experimental, dubious if therapeutically significant. Blocking of CD44 does not completely block attachment to peritoneum in experimental model [61].
MMPs	Proteolytic enzyme	No	Yes, higher expression of MMP7 in primary tumour independent risk factor for PM [16].	In experimental model, treatment with Batimastat showed inhibition of PM. However serious adverse events reported, thus no clinical studies to date [72].

Target expressed in HIPEC patient material from PM of CRC	Possible clinical implementation
IGF-1 [74, 107, 108]	Therapeutic
TIMP2 [16, 74]	Possible stratification tool
HIF1 [74, 84]	Possible stratification tool Therapeutic
VEGF [86, 87]	Possible stratification tool Therapeutic

de Cuba EM. Understanding molecular mechanisms in peritoneal dissemination of colorectal cancer : future possibilities for personalised treatment by use of biomarkers. Virchows Arch. 2012 Sep;461(3):231-43.PMID: 22825001.