XXIV SIMPOSIO DE REVISIONES EN CÁNCER

"Tratamiento médico del cáncer en el año 2022"

Treatment Sequence in BRAFV600E mCRC

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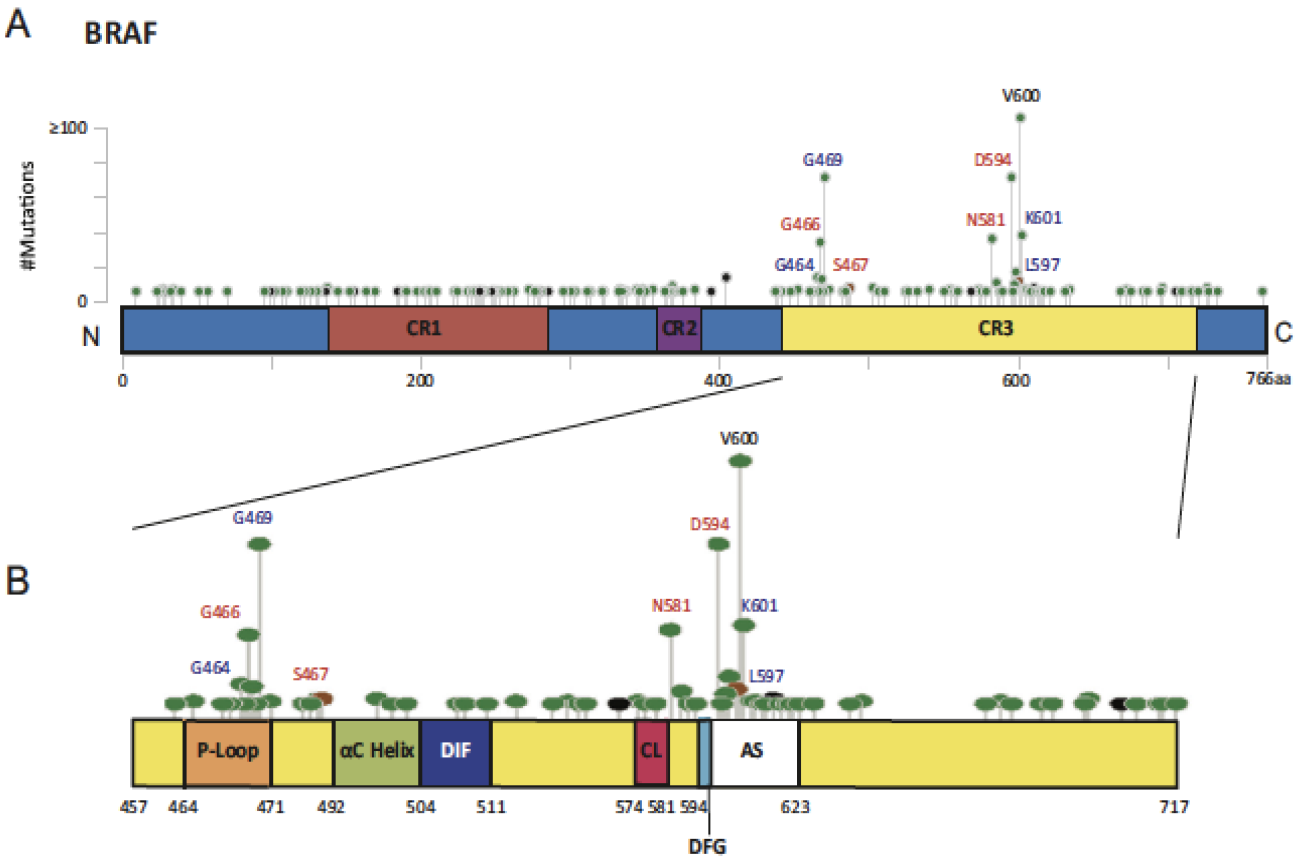
ARÁN

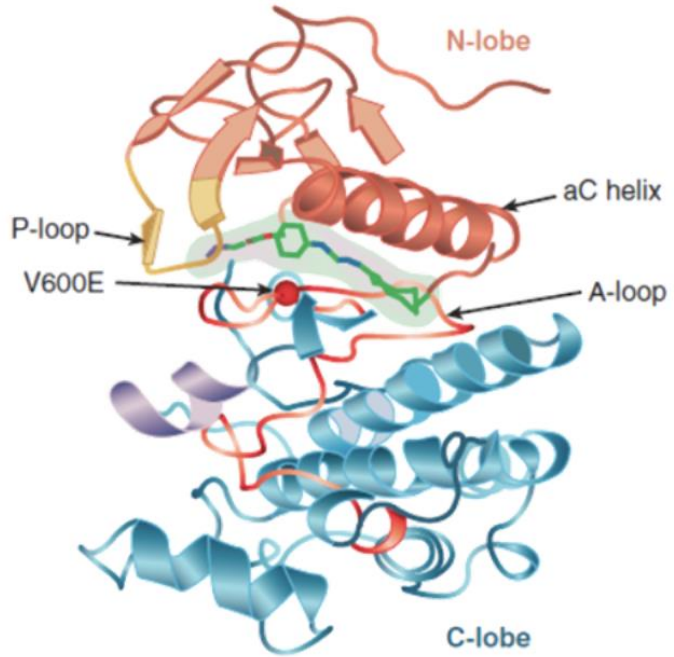
DISCLOSURES

- Personal financial interests, honoraria for advisory role, travel grants, research grants (past 5 years): Hoffman La-Roche, Sanofi Aventis, Amgen, Merck Serono, Servier, MSD, Pierre-Fabre, Bayer, Organon
- Institutional financial interests, my institution received honoraria due to my investigator contribution in clinical trials from: Hoffman La-Roche, Sanofi Aventis, Amgen, Merck Serono, MSD, Boehringer Ingelheim, AbbVie, Bristol Myers Squib, Array Pharmaceuticals, Pierre-Fabre, Novartis, Pfizer

BRAF MUTATIONS

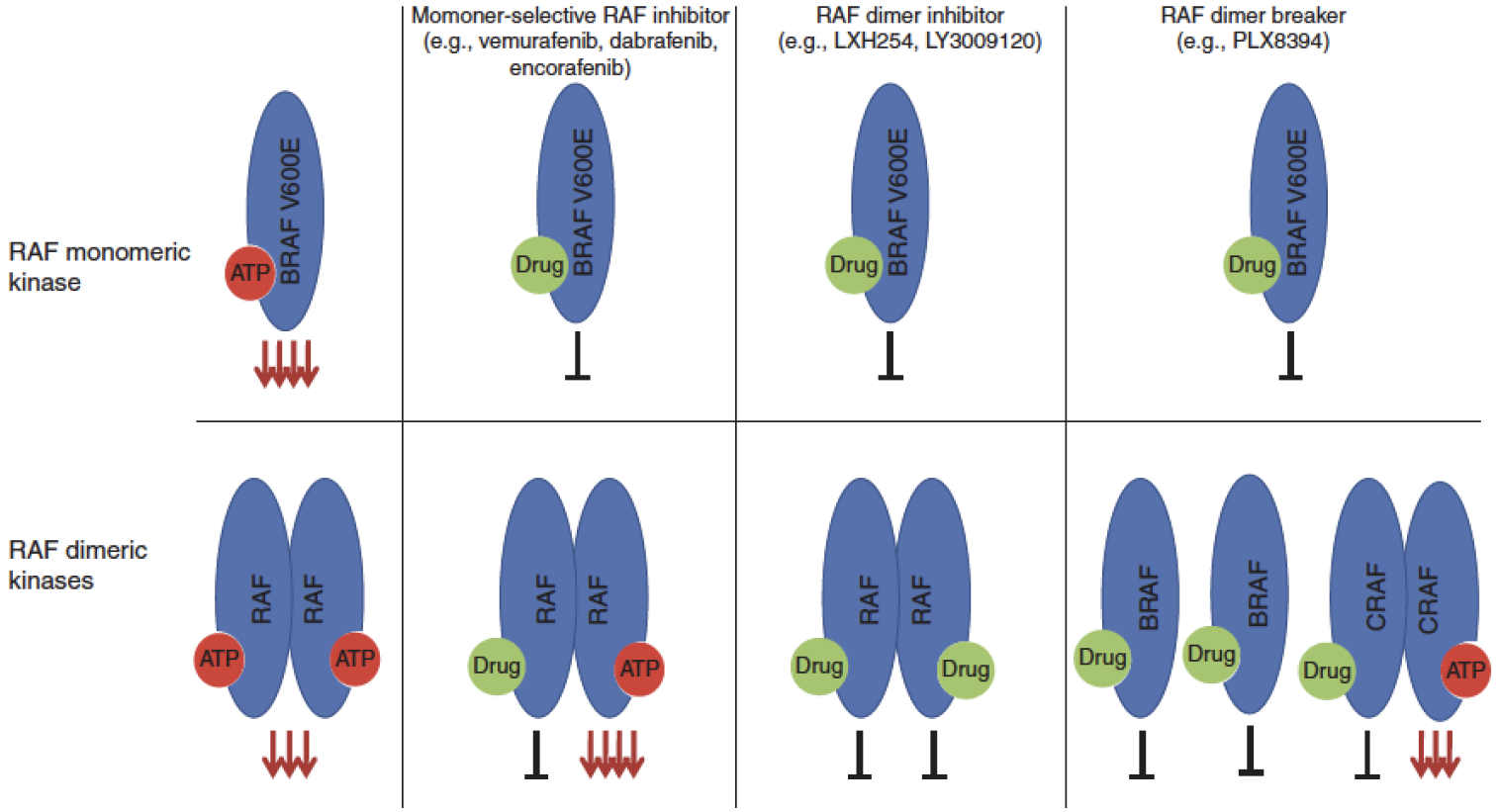


Dankner M et al. Oncogene 2017



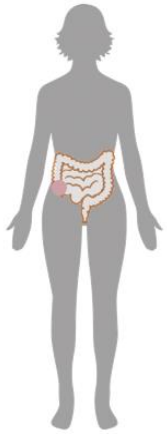
Picture adapated from Rodon J. ESMO OncPro 2018

RAF INHIBITION



Yaeger and Corcoran. Cancer Discovery, 2019

BRAFV600E mCRC: Clinical Features and Therapuetics



- BRAFV600E are Class I mt (>90% BRAF mt)[1,3]
- Up to 20% of CRC (<M1 disease)[1]
- Clinical Features: Older age, female sex, right sided CC, nodal and peritoneal spread[2]
- Pathological Features: Poor differentiation, mucinous histology, larger primary tumors[2]
- Molecular Features: Crossover of *BRAF* and sporadic MSI occurs in 30% of cases [3]
- Negative prognostic factor in mCRC (OS 8-20m)[4]
- Resistance to anti-EGFR therapies[5]

ADJUVANT CT

Recurrence

Resectable Disease

- ≤5% BRAF^{MT}CRC liver Surgery
- Poor OS reported (8-20m)[6,7]
- Worse RFS (Limited data in liver RFS)[6,7]
- Gagniere et al[7]:
  - ✓ 35BRAF^{MT}/1124 pt (2%)
  - ✓ Better Outcomes: N- primary tumors, CEA ≤ 200 µg/L, CRS < 4

Non-Resectable Disease

MSS / pMMR

FOLFOXIRI-Bevacizumab — FRONT LINE

- TRIBE[8]: FOLFOXIRI/bv (16 pt) vs FOLFIRI/bv (18 pt): OS 19m vs 10'7m, PFS 7'5 vs 5'5m
- Triplet Metanalisis[9]: FOLFOXIRI/BV (54 pt) vs control (61 pt) HR 1.11 (0.75 -1.73)

Doublets-Bevacizumab:

- IFL[10]: IFL-Bv (7 pt) vs IFL (3). OS 16 vs 8 m
- TML[11]: No available data

FOLFIRI-Aflibercept (Velour Trial)[12]: — 2^{d} LINE

- FOLFIRI/Afl (16 pt) vs FOLFIRI (20 pt):
- OS 10'3 m vs 5'5 m, PFS

FOLFIRI-Ramucirumab (Raise Trial)[13]:

- FOLFIRI/Ram (20 pt) vs FOLFIRI (21):
- OS 9 m vs 4'2 m, PFS

TIPIRACIL/TRIFLURIDINE (Recourse Trial)[15]: BRAF unknown in 85% pt

REGORAFENIB (Correct Trial)[16]: No specific efficacy data

REFRACTORY SETTING

MSI / dMMR

Keynote 177: — FRONT LINE

- Pembrolizumab (35 pt) vs SOC (44 pts),
- PFS HR 0'48[17], OS HR 0'72[18]

Checkmate 142 (Ph II)

- Nivolumab/Ipilimumab:
- 17 pts front line setting[19]: 24 m OS and PFS rate: 76'5%)
- 30 pt ≥1 prior lines[20]: RR 70%
- Nivolumab (≥1l, 12 pt)[21]: RR 25%

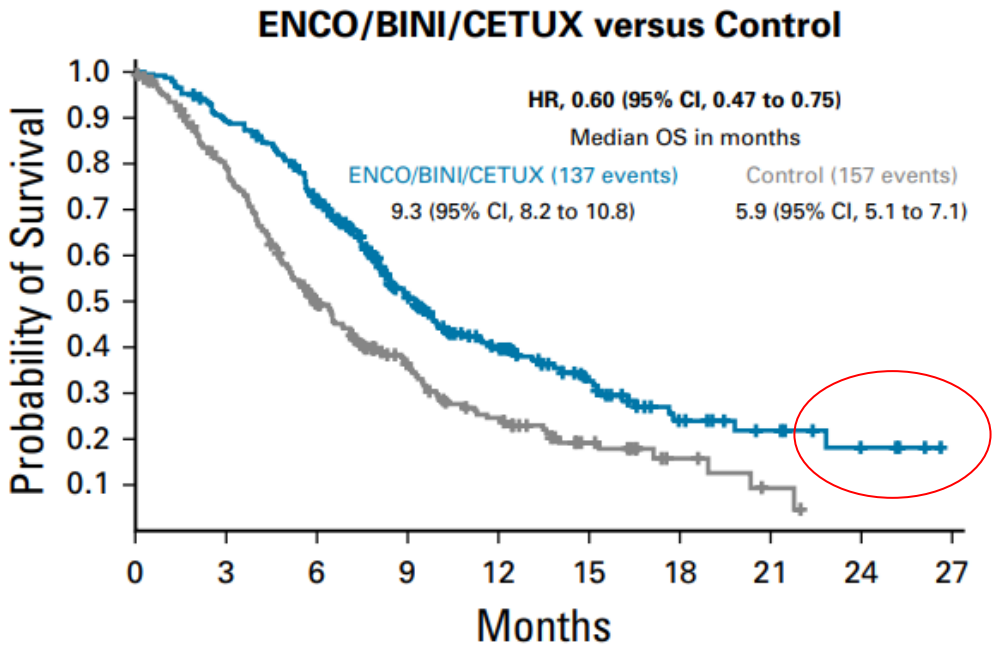
Keynote 164[22] (Ph II):

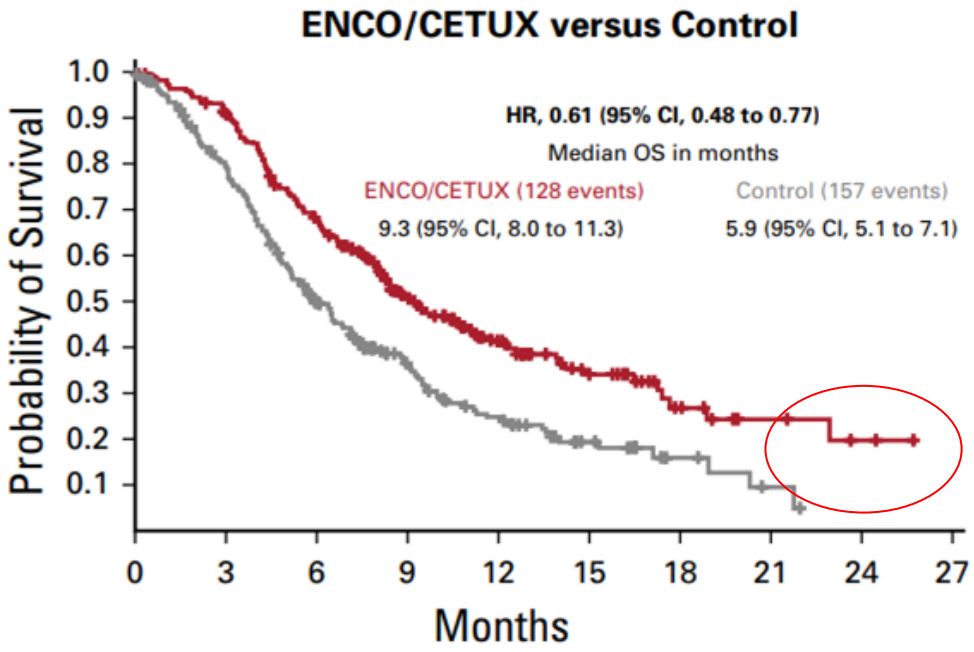
- Pembrolizumab 9pt
- Cohort A (≥2 Cohort B (≥1): 5 pts, RR 20%l), 9 pts, RR 55%

≥2^{d} LINE

1.Sorbye H et al. PLoS One 2015; 10(6): e0131046, 2.Tran B et al. Cancer 2011; 117: 4623-32, 3. Venderbosch S et al. Clin Cancer Res 2014; 20: 5322–5330, 4. Seligmann JF et al. Ann Oncol 2017; 28(3):562e8, 5. Rowland A et al. Br J Cancer 2015 Jun 9;112(12):1888-94, 6. Schirripa M et al. Br J Cancer 2015, 7. Gagniere J et al. Ann Surgery 2020, 8. Cremolini C et al. Lancet Oncol 2015 Oct;16(13):1306-15, 9. Cremolini C et al. J Clin Oncol 2020 Aug 20, 10. Ince W et al. J natls Cancer Inst 2005; 97: 981-989, 11. Bennouna J et al. Lancet Oncol 2013; 14: 29–37, 12. Wirapati P et al. J Clin Oncol 2017;35(suppl).Abstract 3538; 13. Yoshino T, et al. Ann Oncol 2018;30:124–31, 14. Kopetz S et al. 2019 Oct 24;381(17):1632-1643, 15. Van Cutsem et al. Eur J Cancer 2018, 16. Tabernero J et al. Lancet Oncol 2015 Aug;16(8):937-48, 17. Andre T et al. N Engl J Med 2020; 383:2207-2218, 18. Andre T et al. O-8. ESMO GI 2021, 19. Overman M et al, 20. Lenz HJ et al. J Clin Oncol 38, 15 suppl (May 20, 2020) 4040-4040, 21. Andre T et al. Abstract SO-27. ESMO GI 2021, 22. Le DT et al. J Clin Oncol. 2020 Jan 1; 38(1): 11–19

CAN WE IMPROVE PATIENT SELECTION





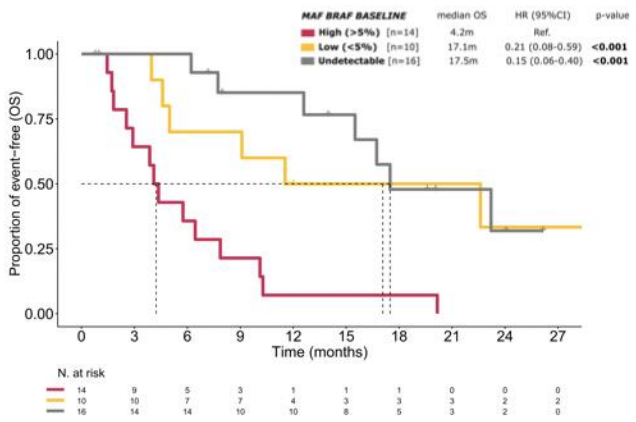
Near 20% of the patients in both arms (doublet and triplet) are still alive after 27 months

Tabernero J, JCO 2021

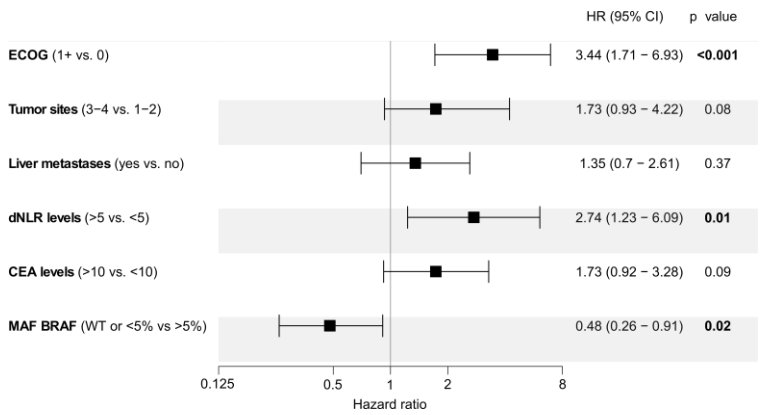
BRAFV600E CRC: Caveats and Pitfalls

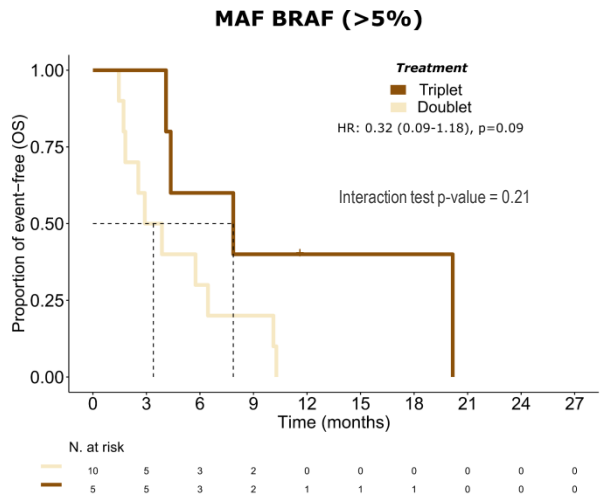
- Not all patients respond the same, some responses are short and the role of the triplet has not been established yet
- The integration of tumor burden features[1,2] as well as novel biomarkers like cfDNA BRAF MAF[3] could help to better define subgroups of patients with particular prognostic characteristics and potential therapeutic implications

Overall Survival Univariate Model



Overall Survival Multivariate Model



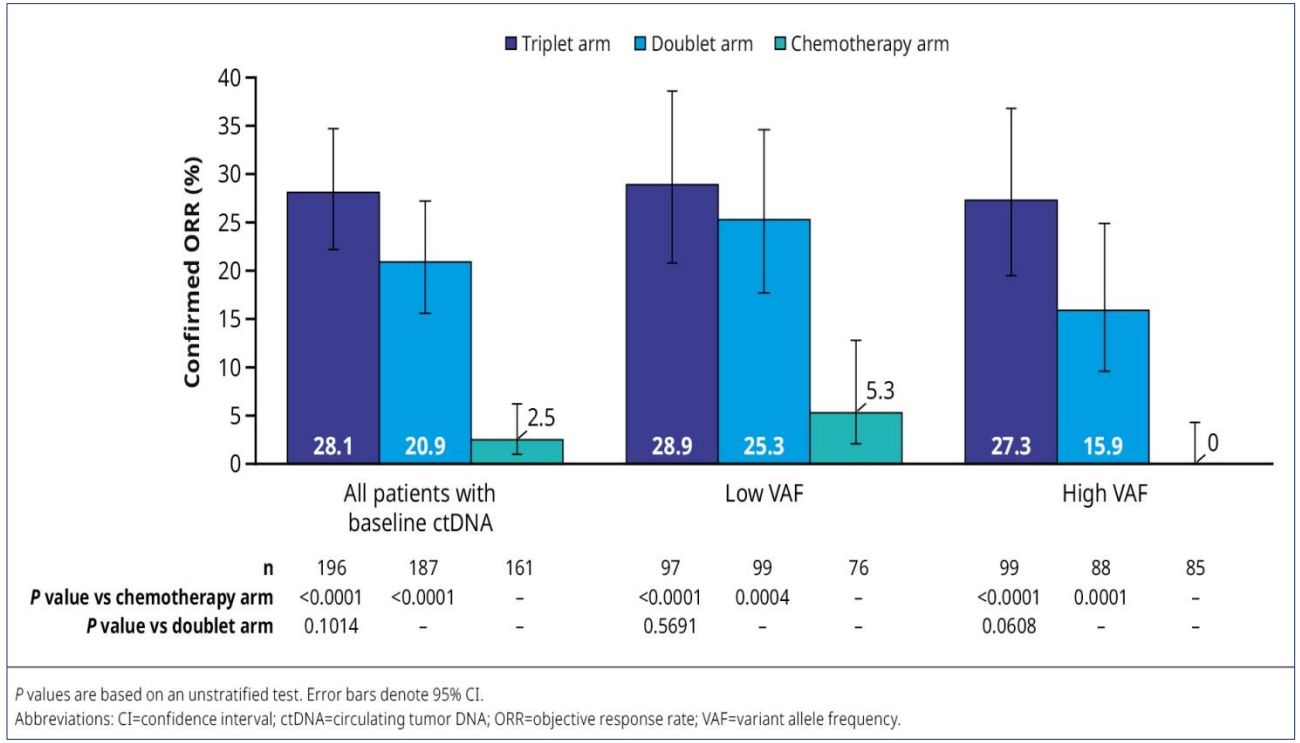


1. Loupakis F et al. European Journal of Cancer 118 (2019) 121-130, 2. Ros J et al. J Clin Oncol 38: 2020 (suppl; abstr 4112), 3. Elez E et al. ESMO GI LBA-3

BEACON BASELINE ctDNA ANALYSIS

	Low Baseline *BRAF* V600E ctDNA VAF			High Baseline *BRAF* V600E ctDNA VAF		
	Triplet Arm (n=97)	Doublet Arm (n=99)	Chemotherapy Arm (n=76)	Triplet Arm (n=99)	Doublet Arm (n=88)	Chemotherapy Arm (n=85)
Median (range) age, years	62 (26–85)	64 (30–91)	61.5 (27–91)	61 (28–77)	58.5 (30–81)	61 (27–81)
Male sex	37 (38.1)	54 (54.5)	30 (39.5)	53 (53.5)	42 (47.7)	39 (45.9)
ECOG performance status*						
0	61 (62.9)	58 (58.6)	41 (53.9)	42 (42.4)	35 (39.8)	34 (40.0)
1	36 (37.1)	40 (40.4)	35 (46.1)	57 (57.6)	51 (58.0)	51 (60.0)
Location of primary tumor†						
Left colon	35 (36.1)	39 (39.4)	26 (34.2)	32 (32.3)	31 (35.2)	23 (27.1)
Right colon	57 (58.8)	52 (52.5)	39 (51.3)	54 (54.5)	42 (47.7)	47 (55.3)
⩾3 organs involved	47 (48.5)	43 (43.4)	36 (47.4)	49 (49.5)	44 (50.0)	39 (45.9)
Liver metastases present	44 (45.4)	44 (44.4)	25 (32.9)	83 (83.8)	73 (83.0)	68 (80.0)
Primary tumor removed						
Completely resected	59 (60.8)	68 (68.7)	43 (56.6)	57 (57.6)	38 (43.2)	48 (56.5)
Partially resected or unresected	38 (39.2)	31 (31.3)	33 (43.4)	42 (42.4)	50 (56.8)	37 (43.5)
Prior systemic regimens for metastatic disease‡						
1	68 (70.1)	68 (68.7)	55 (72.4)	62 (62.6)	52 (59.1)	57 (67.1)
2	29 (29.9)	31 (31.3)	21 (27.6)	36 (36.4)	36 (40.9)	27 (31.8)
Microsatellite instability high§	9 (9.3)	9 (9.1)	5 (6.6)	10 (10.1)	6 (6.8)	5 (5.9)
Carcinoembryonic antigen >5 µg/L	66 (68.0)	63 (63.6)	55 (72.4)	91 (91.9)	70 (79.5)	82 (96.5)
C-reactive protein >10 mg/L	26 (26.8)	24 (24.2)	23 (30.3)	61 (61.6)	45 (51.1)	41 (48.2)

Data are n (%) unless noted otherwise.
*In the doublet arm, 1 and 2 patients with low and high VAF, respectively, had an ECOG performance status of 2; †For all other patients, the primary tumor was in both the left and right sides of the colon or at an unknown location; ‡Among patients with high VAF, 1 patient each in the triplet and chemotherapy arms had received ⩾3 prior regimens; §17.6% of patients in the analysis set were not evaluable or had missing microsatellite instability measurements by polymerase chain reaction.
Abbreviations: ctDNA=circulating tumor DNA; ECOG=Eastern Cooperative Oncology Group; VAF=variant allele frequency.



P values are based on an unstratified test. Error bars denote 95% CI.
Abbreviations: CI=confidence interval; ctDNA=circulating tumor DNA; ORR=objective response rate; VAF=variant allele frequency.

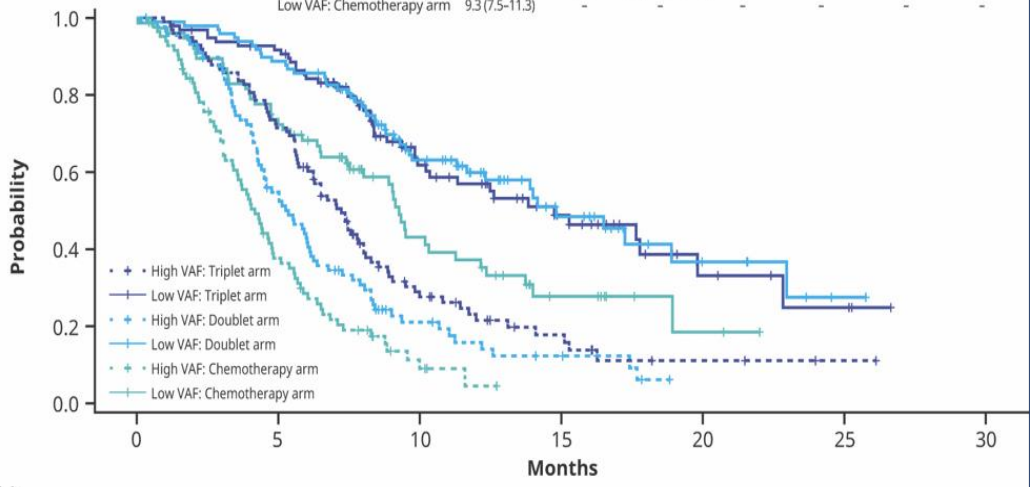
median BRAF V600E VAF: 7.4 (0–71.8), High VAF: ECOG 1, Liver M1, CEA>5, PCR>10

ORRs were greater, independent of VAF, in the triplet and doublet arms compared with the chemotherapy arm

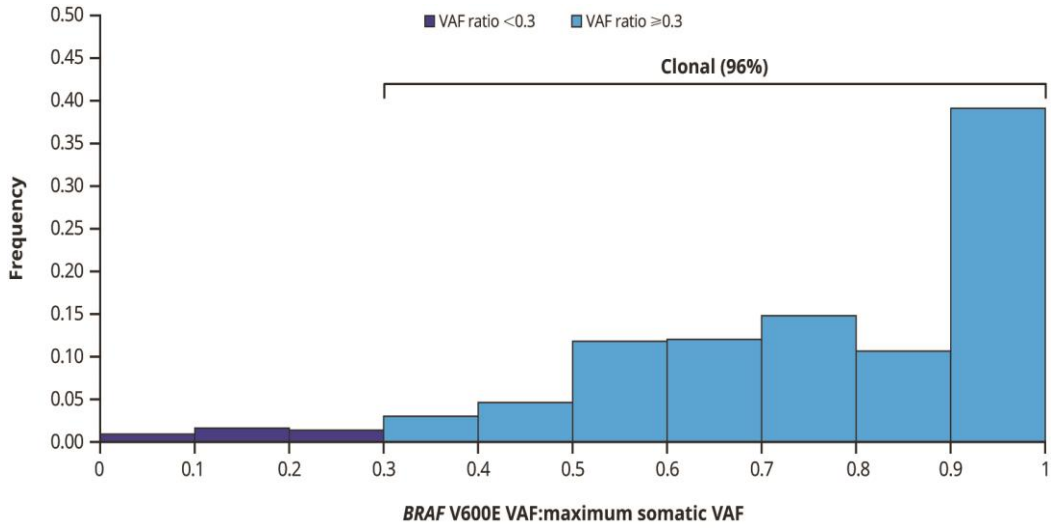
Kopetz S et al. J Clin Oncol 40, no. 4_suppl (Feb 01, 2022) 162-162

BEACON BASELINE ctDNA ANALYSIS

	Median (95% CI) OS, Months	vs Low VAF		vs Chemotherapy Arm		vs Doublet Arm	
		P Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)
High VAF: Triplet arm	7.2 (6.0–8.0)	<0.0001	2.61 (1.793–3.796)	<0.0001	0.46 (0.330–0.649)	0.0472	0.72 (0.523–0.996)
Low VAF: Triplet arm	14.8 (10.2–19.8)	-	-	0.0048	0.55 (0.361–0.832)	0.8018	1.06 (0.695–1.603)
High VAF: Doublet arm	5.4 (4.4–6.1)	<0.0001	3.75 (2.550–5.528)	0.0152	0.66 (0.473–0.923)	-	-
Low VAF: Doublet arm	14.8 (11.7–23.0)	-	-	0.0025	0.52 (0.345–0.796)	-	-
High VAF: Chemotherapy arm	4.2 (3.4–4.8)	<0.0001	2.99 (2.010–4.443)	-	-	-	-
Low VAF: Chemotherapy arm	9.3 (7.5–11.3)	-	-	-	-	-	-



Number at Risk							
High VAF: Triplet arm	99	70	21	9	3	1	0
Low VAF: Triplet arm	97	87	40	20	6	3	0
High VAF: Doublet arm	88	46	13	6	0	0	0
Low VAF: Doublet arm	99	87	45	19	6	1	0
High VAF: Chemotherapy arm	85	29	4	0	0	0	0
Low VAF: Chemotherapy arm	76	54	22	8	2	0	0



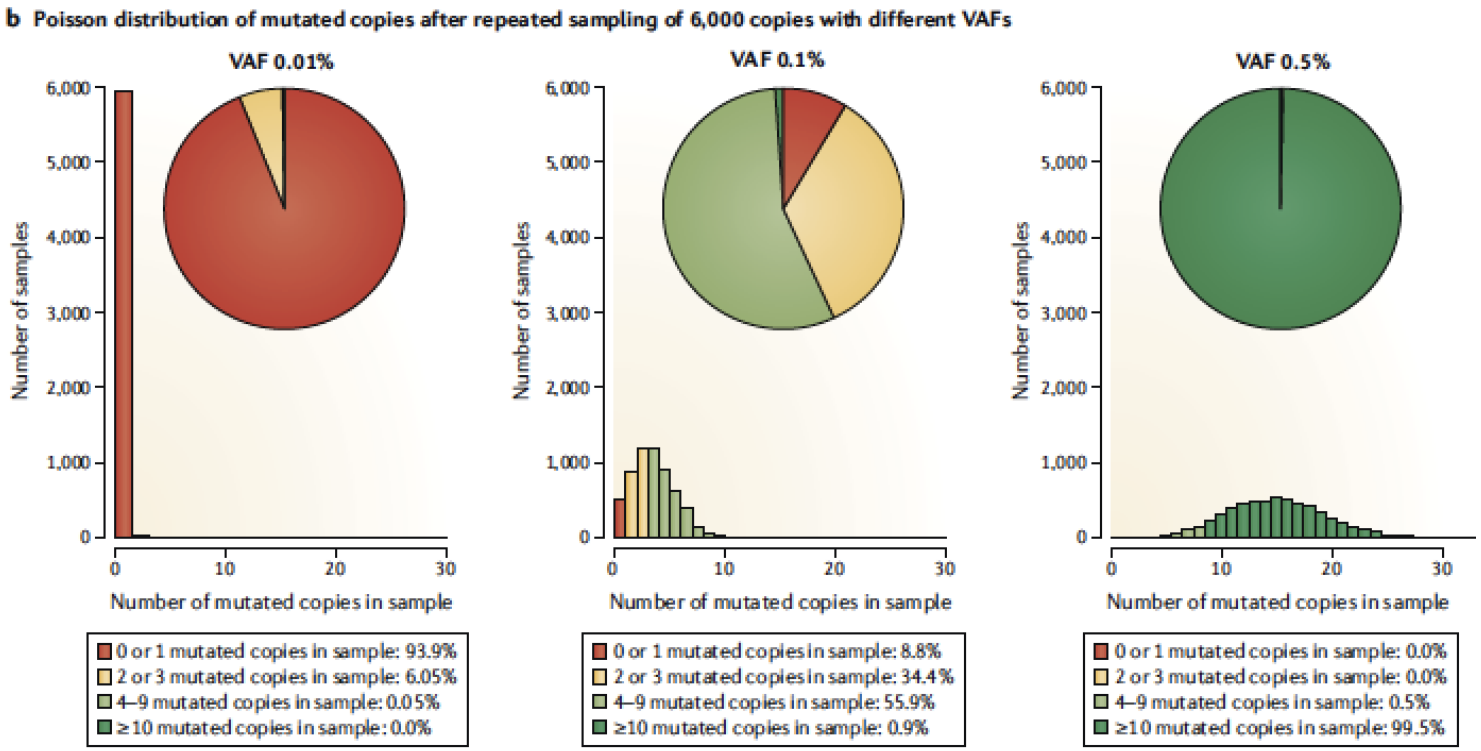
In all treatment arms, OS was longer in patients with low VAF than those with high VAF

BRAFV600E was predominantly clonal in patients with detectable *BRAF* V600E (≥0.3 VAF) by ctDNA genomic profiling

Kopetz S et al. J Clin Oncol 40, no. 4_suppl (Feb 01, 2022) 162-162

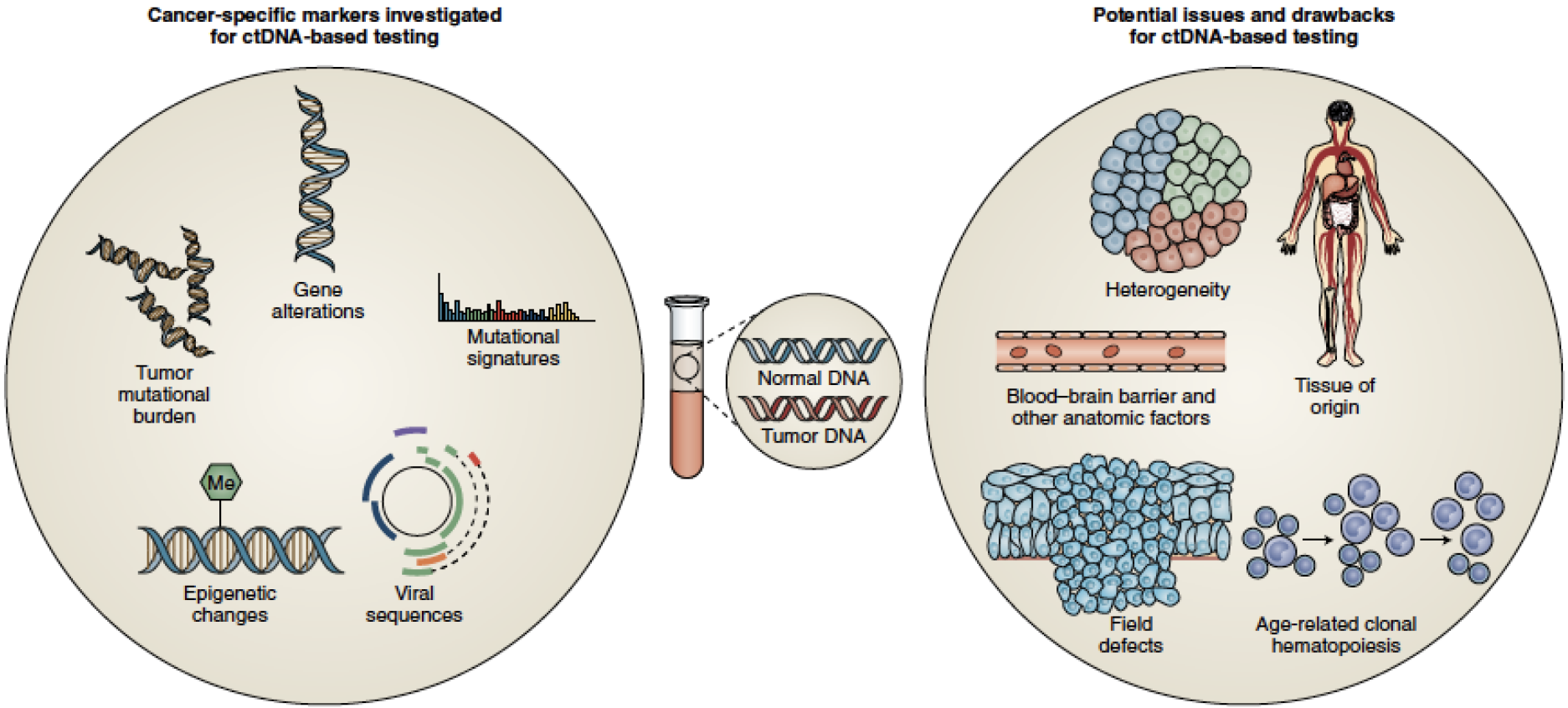
ctDNA: Analytical Validity

The amount of input cell- free DNA affects the ability to detect rare variants.



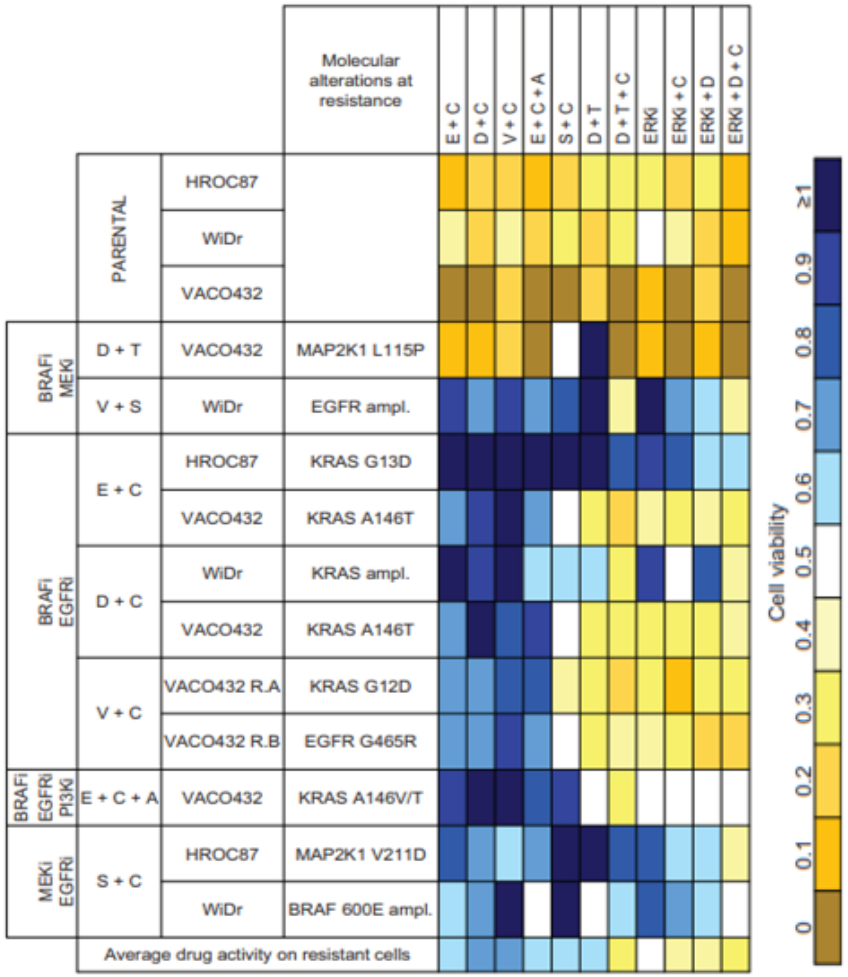
Heitzer, E et al. Current and future perspectives of liquid biopsies in genomics-driven oncology. Nat. Rev. Genet. 2019, 20, 71–88.

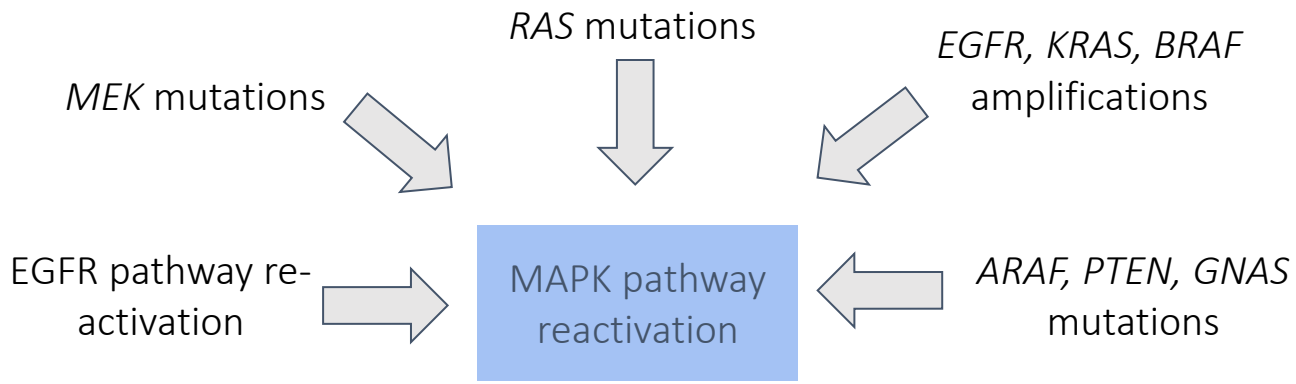
ctDNA: Analytical Validity



Cescon D et al. Nature Cancer 2020

TARGETING RESISTANCE

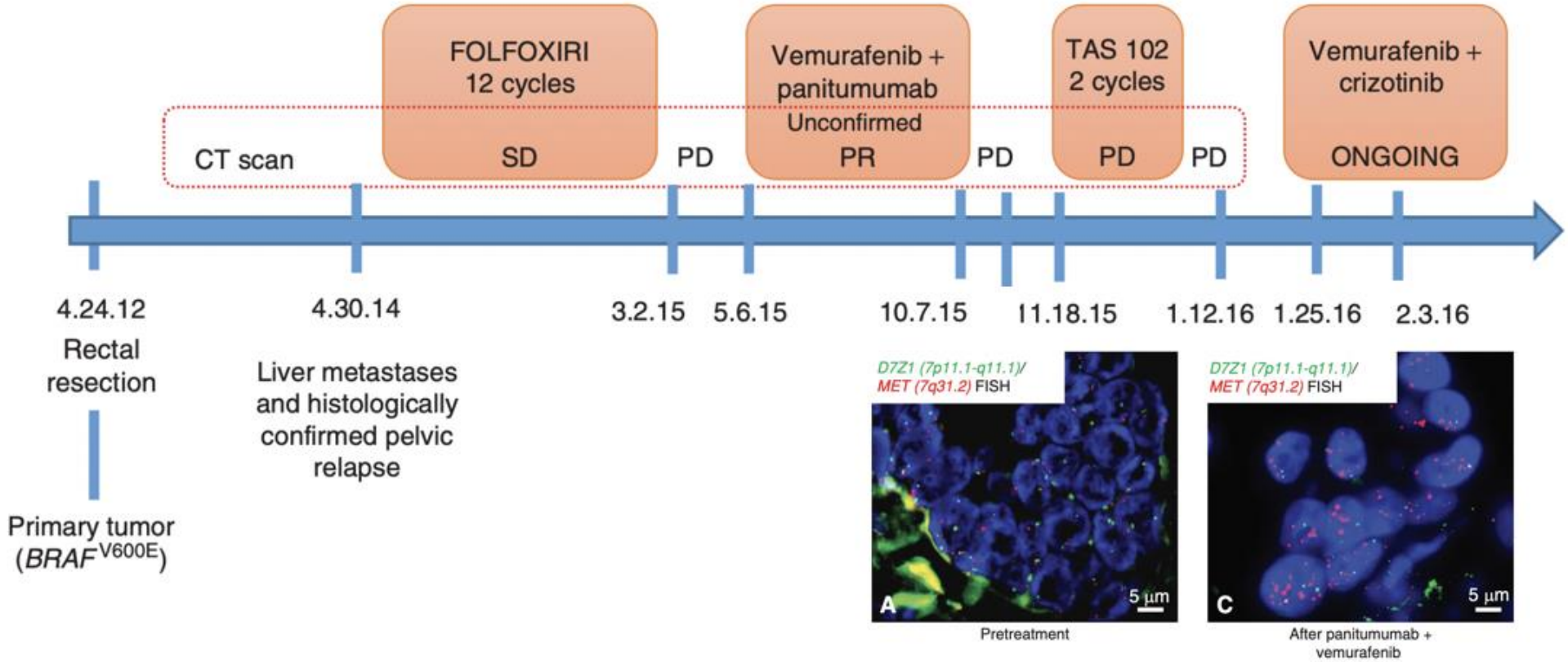




Acquired resistance to target therapy combinations can be overcomed by vertical MAPK pathway suppression

Hong DS, et al. Cancer Discov 2016, Oddo D, Clin Can Res 2016

TARGETING RESISTANCE

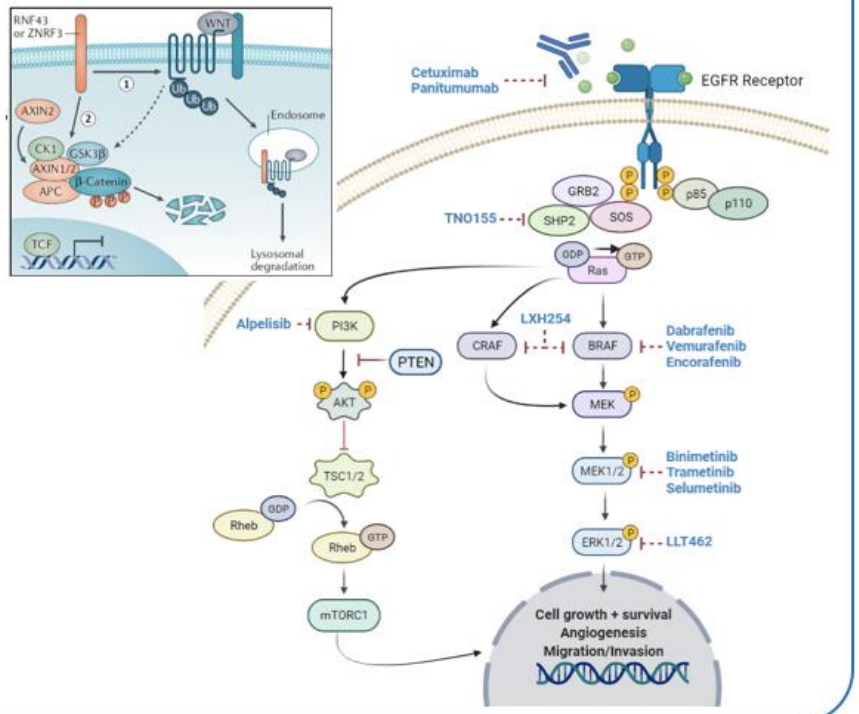


MET amplification is identified as a mechanism of resistance to EGFR and BRAF combination in BRAF -mutated CRC. Switching from EGFR to MET inhibition (maintaining BRAF inh), resulted in clinical benefit after the occurrence of MET-driven acquired resistance.

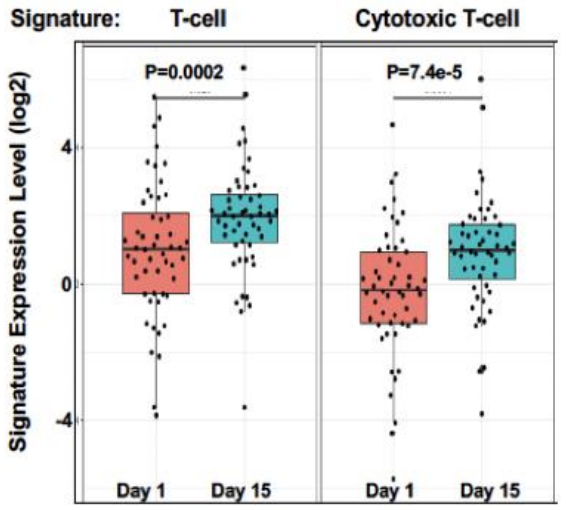
Oddo Brit Jour Can 2017

DEVELOPMENTAL THERAPEUTICS

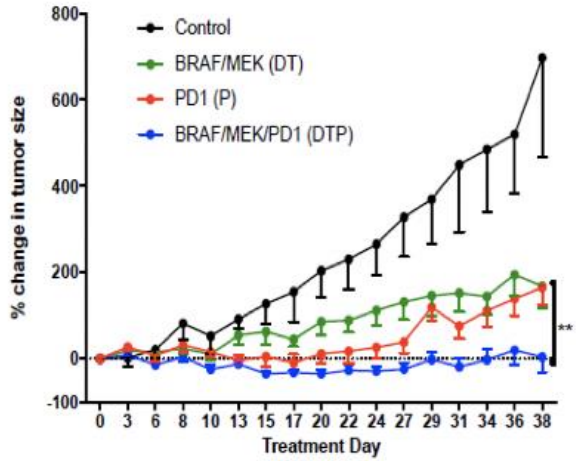
MAPK BLOCKADE



Potential cooperativity between BRAF-targeting and immune response



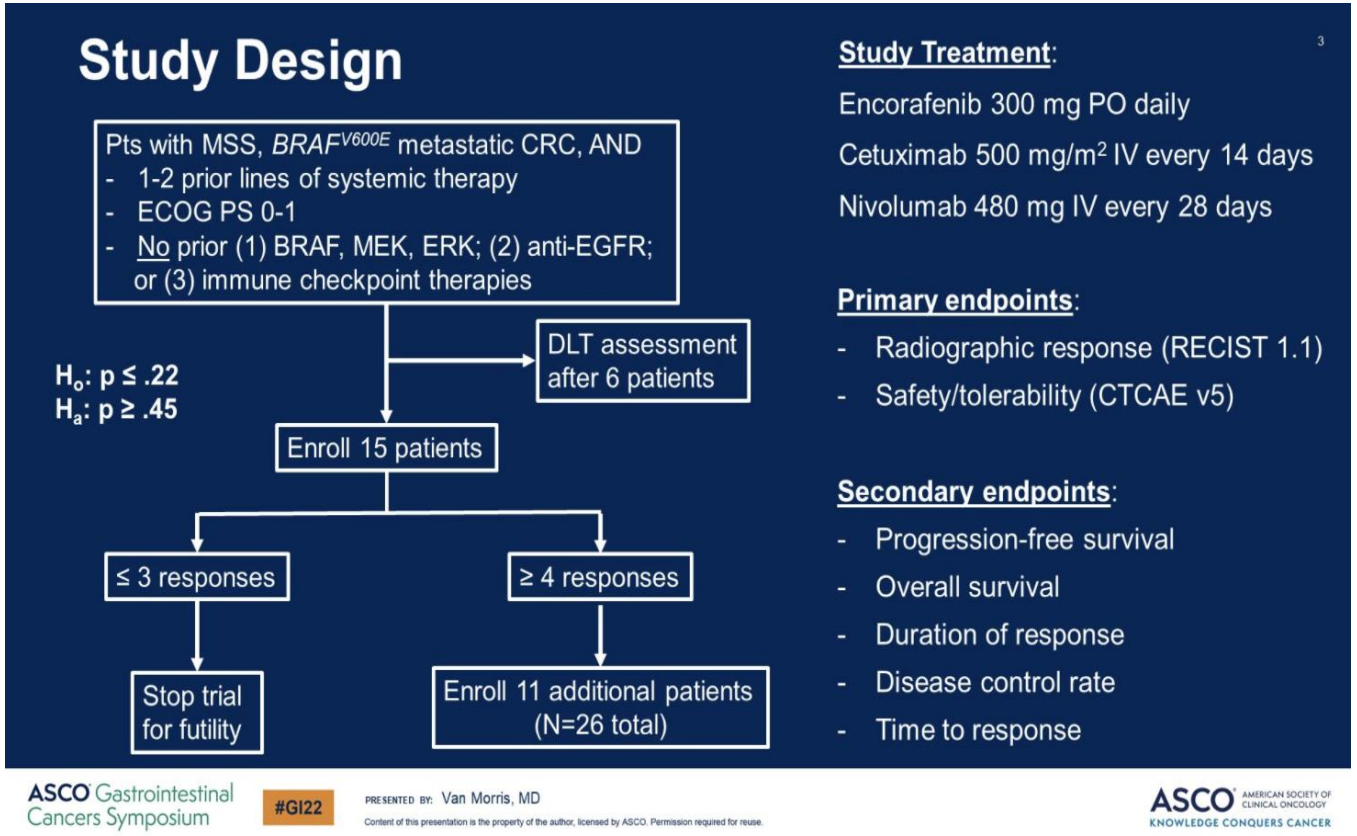
Increased T-cell infiltration after BRAF pathway blockade in paired patient tumor biopsies

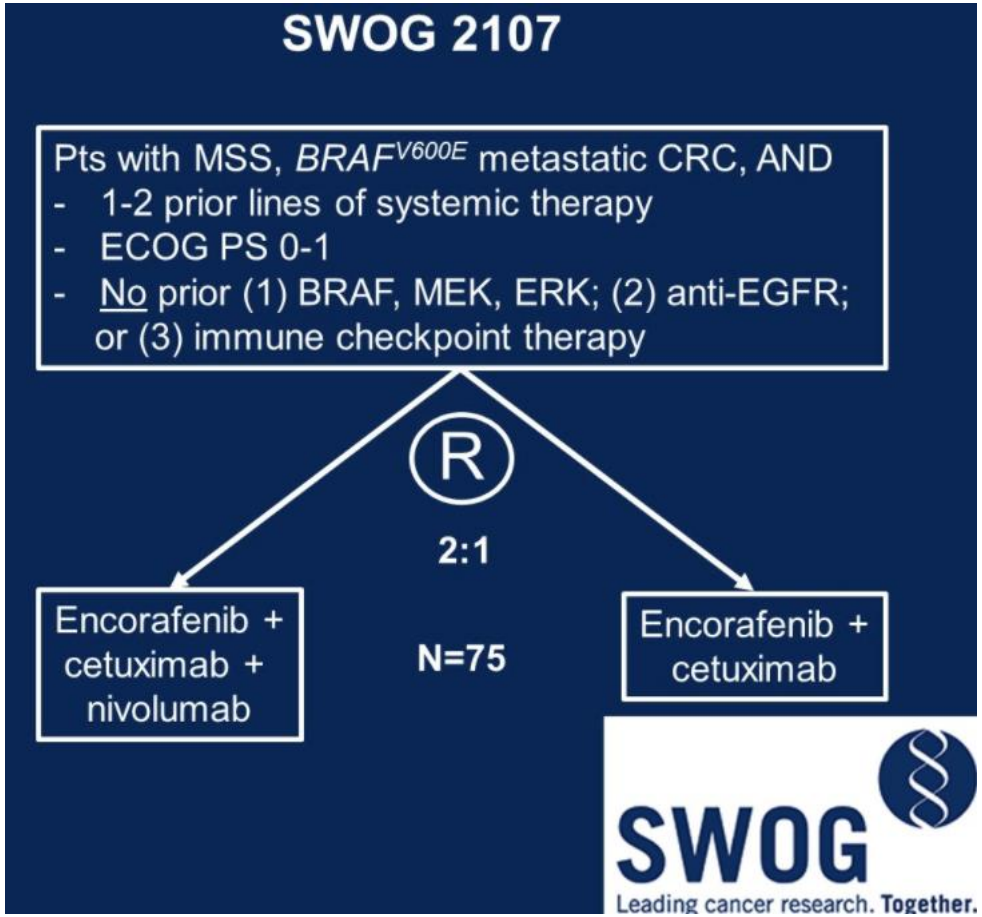


PD-1/BRAF/MEK inhibition in mouse models

1. Bugter JM et al. Nat Rev Cancer 2021 Jan;21(1):5-21, 2. Modified from Corcoran et al, WCGI Congress (2020)

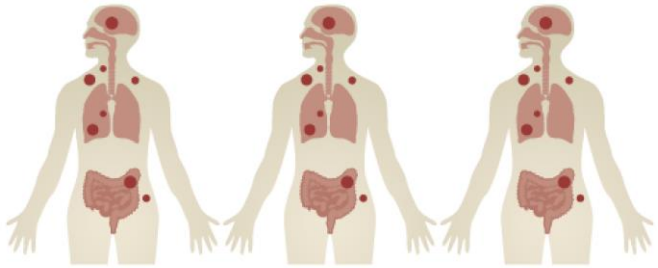
DEVELOPMENTAL THERAPEUTICS





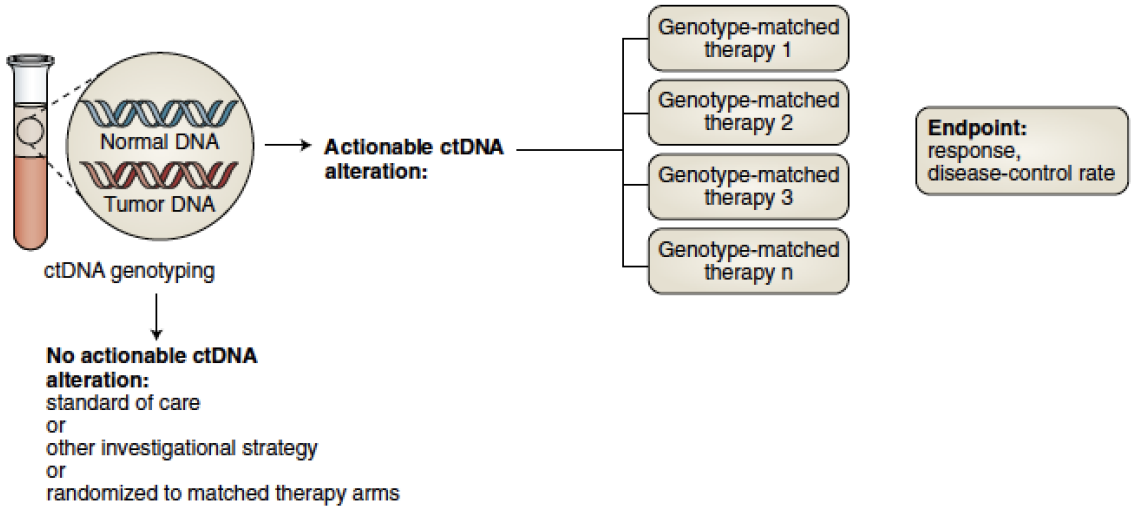
Morris V et al. J Clin Oncol 40, no. 4_suppl (February 01, 2022) 12-12

ctDNA: 100% potential

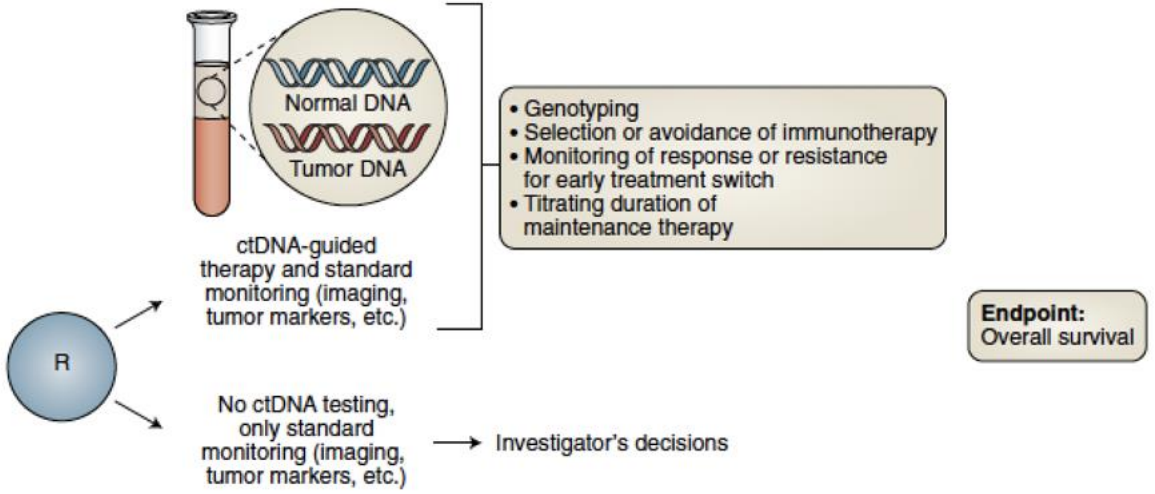


Patients with recurrent and/or metastatic cancer: same histology or alterations

Precision Therapy Umbrella Study

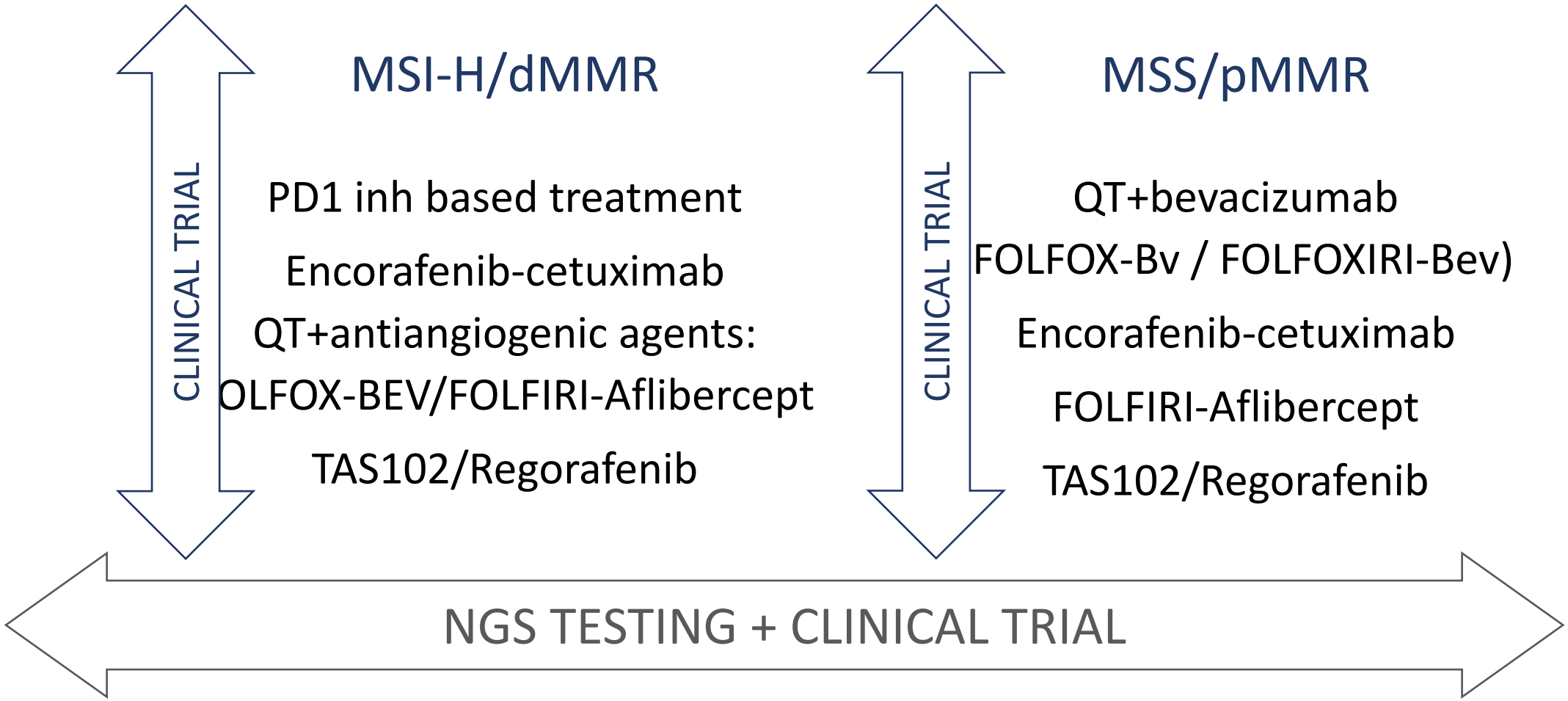


Pragmatic Trial Design



Cescon D et al. Nature Cancer 2020

ment Sequence in BRAFV600E mCRC



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Javier Gonzalo PhD
Alena Gros PhD
Paolo Nuciforo MD PhD
Cristina Pérez
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