Biomarker-based Targeted Therapy for Colorectal Cancer: Recent Advances Toward Precision Medicine

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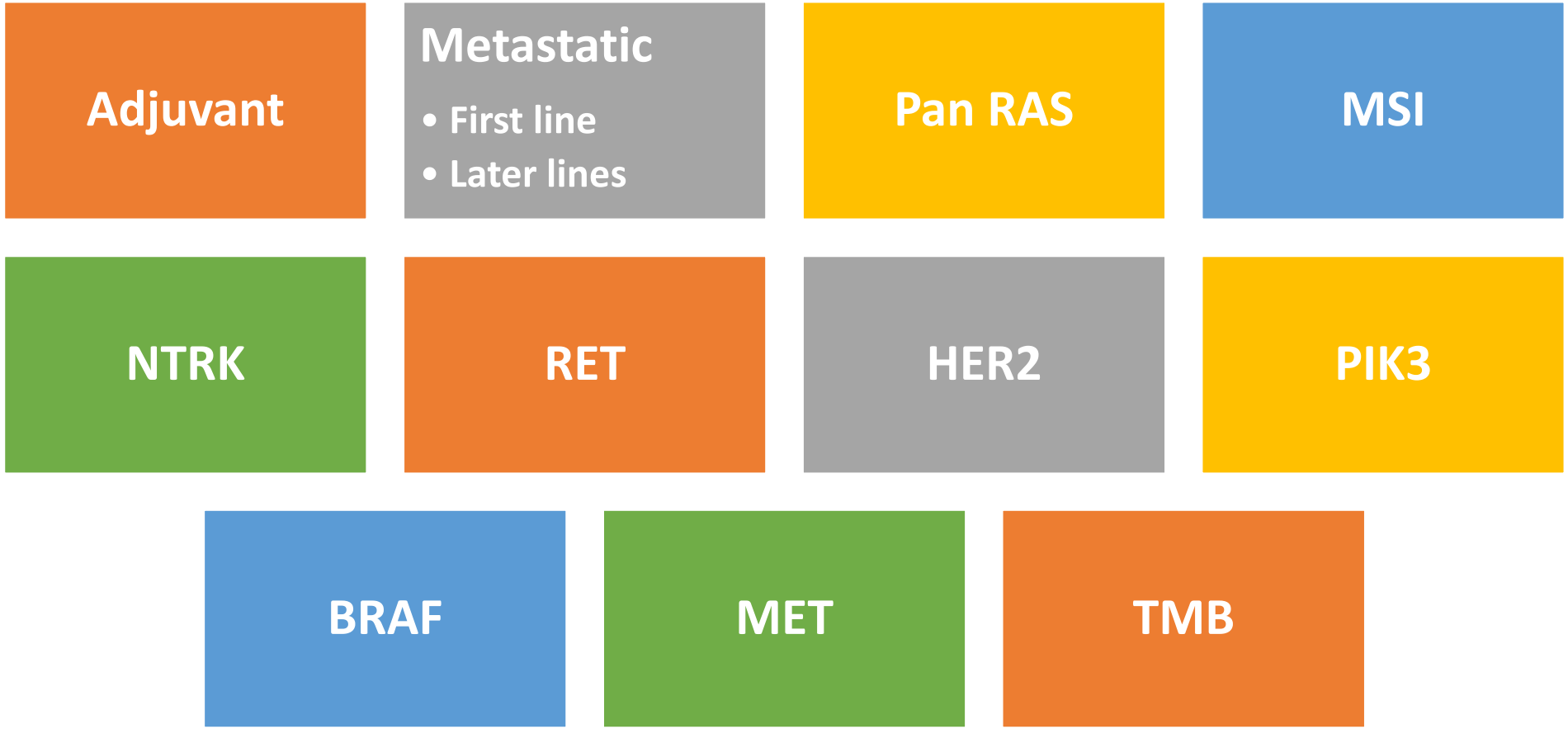
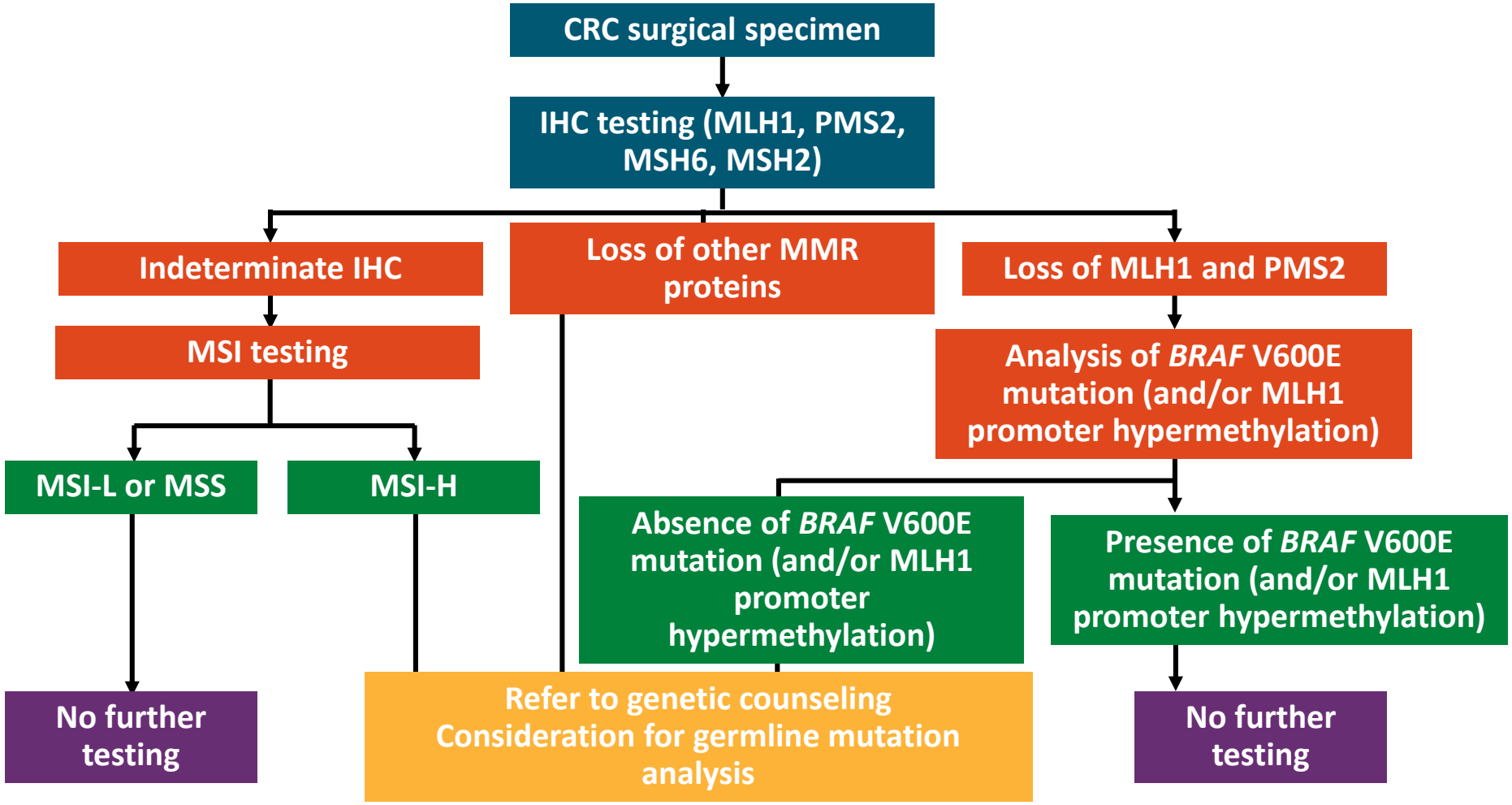
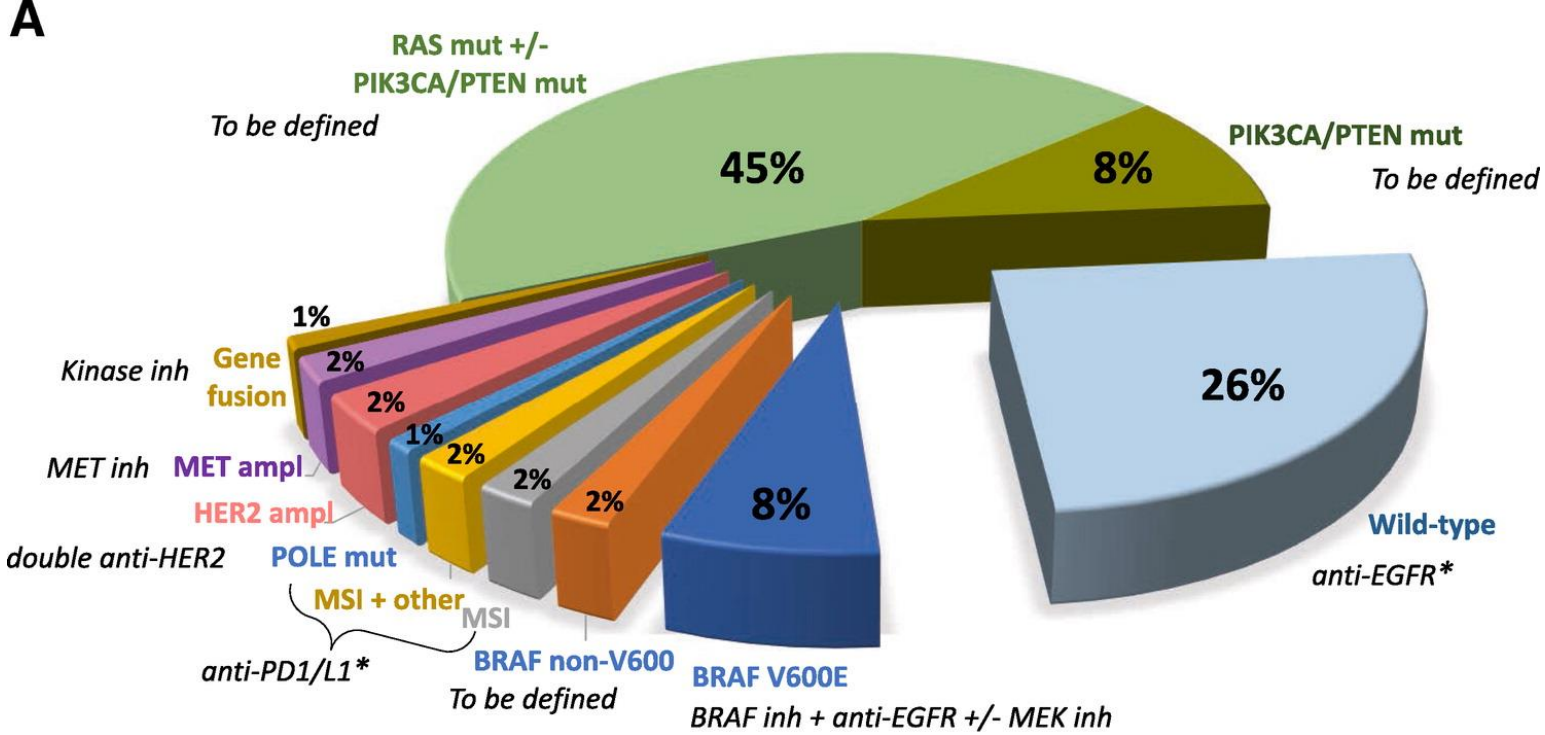
Biomarkers in CRC



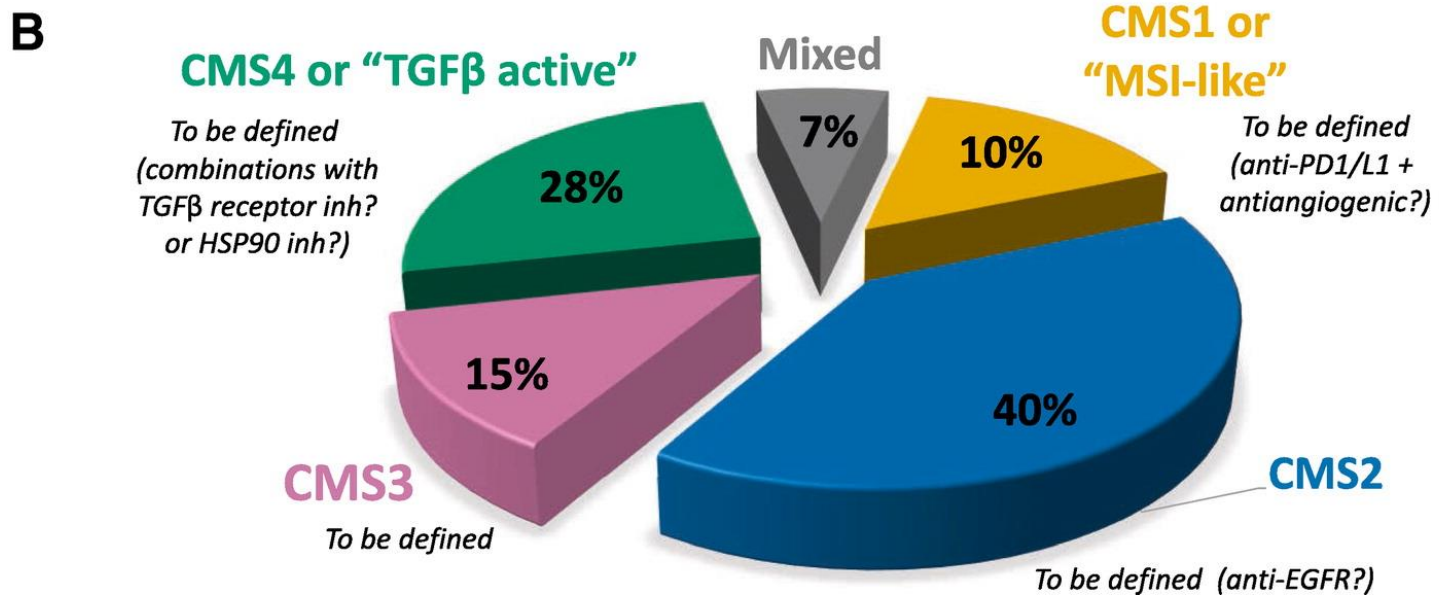
Algorithm for MMR/MSI Testing in CRC (Adjuvant)



Slide credit: clinicaloptions.com



Genomic markers and potential therapies



Transcriptomic markers and

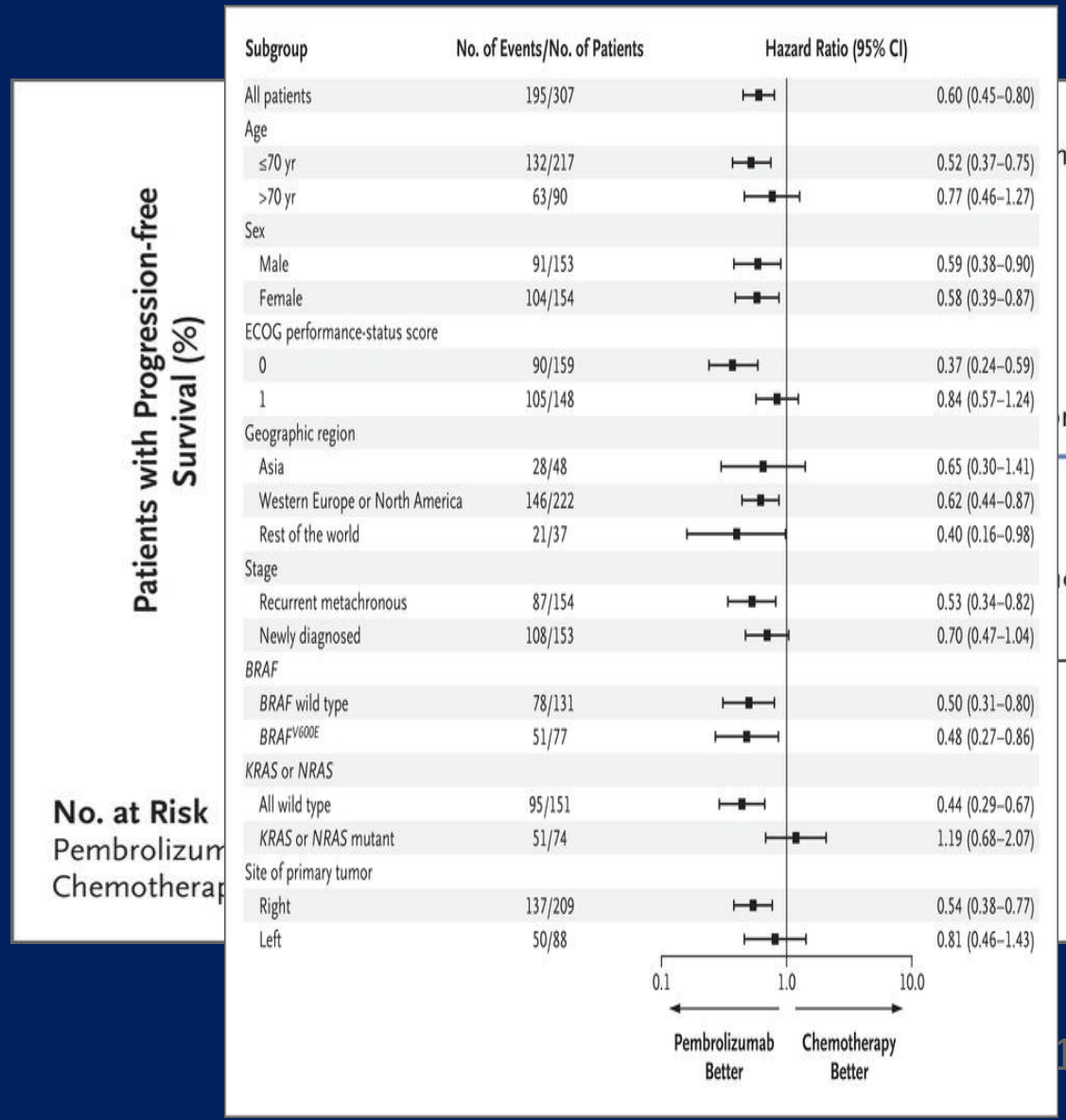
Pathway signatures

Dienstmann. Am Soc Clin Oncol Educ Book. 2018;38:231.

MSI-H/dMMR and Immune check point inhibitors

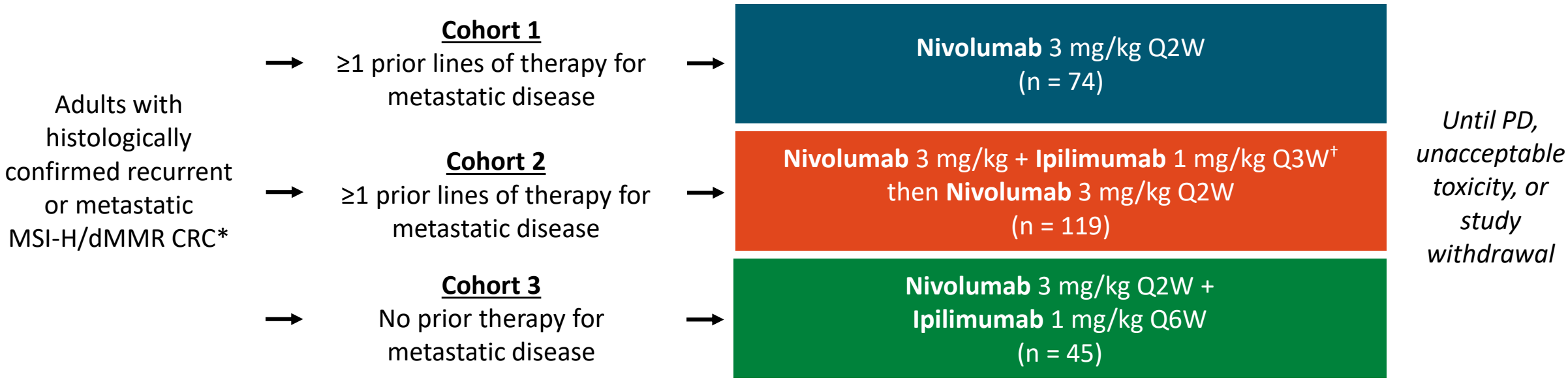
First line treatment

- Key note 177 - Pembro Vs Chemotherapy (n=307)
- mPFS 16.5 Vs 8.2 m
- Responses continued in 83% responders at 2 years in Pembro arm (Vs 35% in Chemo arm)



Nivolumab/ Ipi-Nivo
CheckMate 142 Extended Follow-up: Study Design

- Ongoing, multicohort, nonrandomized phase II study



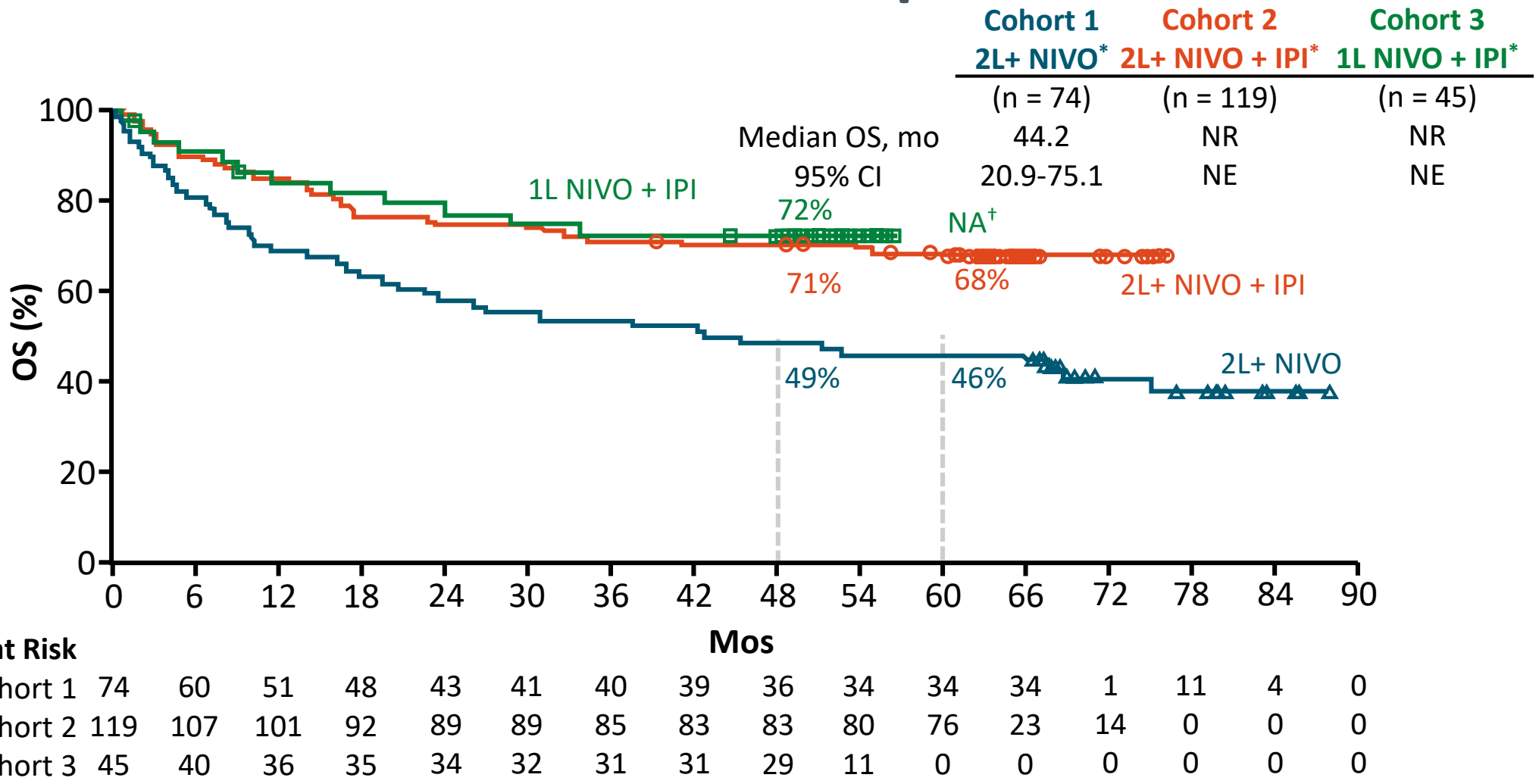
- **Primary endpoint:** ORR per investigator assessment (RECIST v1.1)
- **Secondary endpoints:** DCR, DoR, PFS per investigator and BICR, safety

*Locally assessed. †4 doses.

Overman. ASCO 2022. Abstr 3510.

Slide credit: clinicaloptions.com

CheckMate 142 Extended Follow-up: OS



*Cohorts not randomized, nor was trial designed for formal comparison. †Median follow-up for cohort 3: 47.6 mo.

Overman. ASCO 2022. Abstr 3510. Reproduced with permission.

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PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

- Dostarlimab q 3 weeks for 6 cycles (n=12)
- If in CR at the end of 6 cycles, close follow up – No CT/RT
- The primary end points
  - Sustained clinical complete response 12 months
  - Path CR after completion of dostarlimab therapy with or without chemoradiotherapy
  - Overall response to neoadjuvant dostarlimab therapy with or without chemoradiotherapy
- All 12 patients had cCR (follow up range 6-25 m)

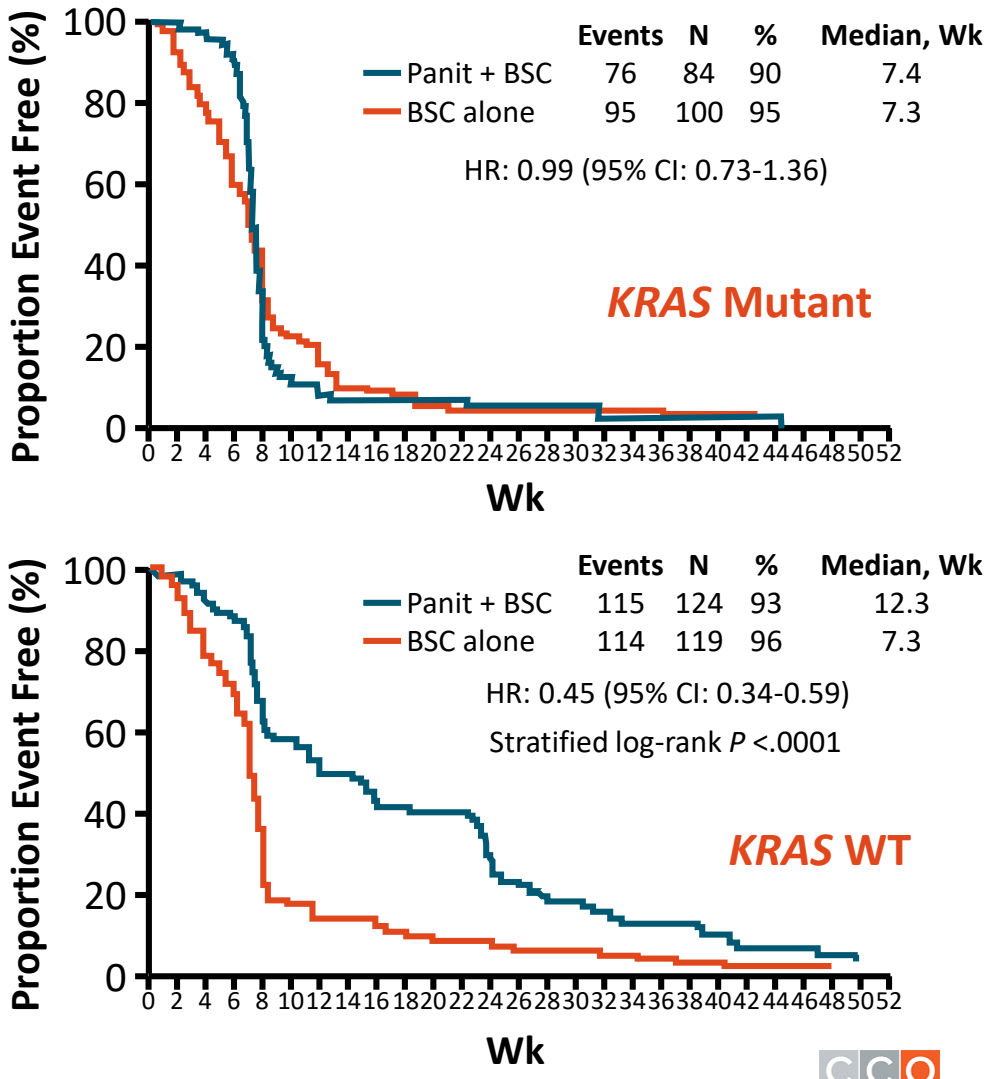
N Engl J Med 2022; 386:2363-2376

RAS and *BRAF* Mutations

RAS Mutations (*KRAS*, *NRAS*, *HRAS*)

- Most frequently mutated oncogenes[1]
  - 90% of pancreatic cancers, **45% of colon cancers,** 35% of lung cancers
  - *KRAS* most prevalent in these tumor types
- In CRC, RAS testing is required prior to anti-EGFR therapy (eg, cetuximab or panitumumab)
  - Patients with *KRAS* and *NRAS* mutations should not be treated with anti-EGFR therapy[2-4]
  - *HRAS* mutations are much less common (1.7%) but likely have the same negative predictive value

Panitumumab + BSC vs BSC[1]



1. Porru. J Exp Clin Cancer Res. 2018;37:57. 2. Allegra. JCO. 2016;34:179.
3. Al-Shamsi. J Gastrointest Oncol. 2015;6:314. 4. Gong. J Gastrointest Oncol. 2016;7:687.

Slide credit: clinicaloptions.com

PARADIGM Trial in KRAS WT 1L: OS (Primary Endpoint)

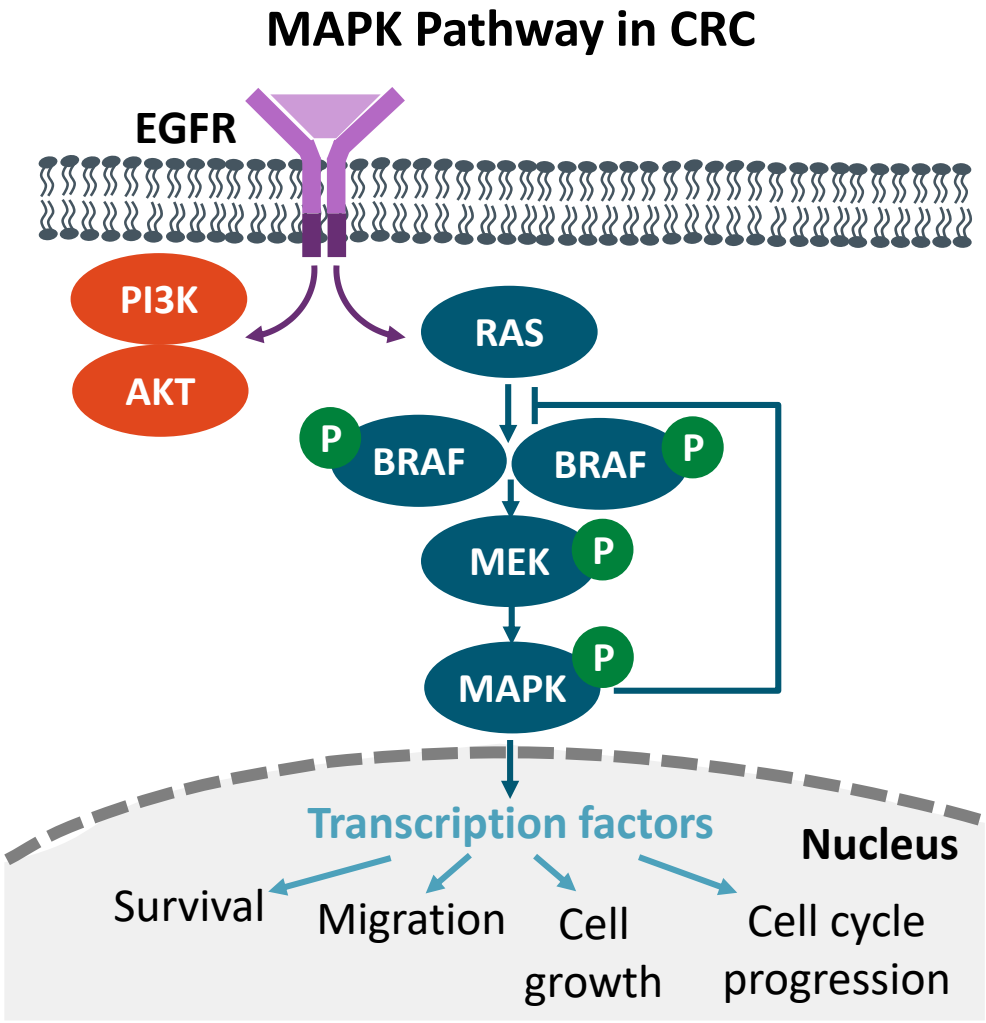
OS Outcome	Left-Sided Population		Overall Population	
	Panitumumab + mFOLFOX6 (n = 312)	Bevacizumab + mFOLFOX6 (n = 292)	Panitumumab + mFOLFOX6 (n = 400)	Bevacizumab + mFOLFOX6 (n = 402)
Patients with events, %	69.9	78.7	72.8	80.1
Median OS, mo	37.9	34.3	36.2	31.3
36-mo OS rate, %	53	47	50	42
48-mo OS rate, %	42	33	38	30
60-mo OS rate, %	32	21	29	20
HR	0.82; 95.798% CI: 0.68-0.99		0.84; 95% CI: 0.72-0.98	
P value	.031		.030	

- OS outcomes were generally consistent across patient subgroups in both left-sided and overall populations

Yoshino. ASCO 2022. Abstr LBA1.

BRAF Mutations in CRC

- BRAF: primary effector of RAS signaling
- *BRAF* mutations
  - Occur most frequently in exon 15 (V600E)
    - Accounts for majority of *BRAF* mutations
    - **Found in ~10% of patients with CRC**
  - Mutually exclusive with *RAS* mutations

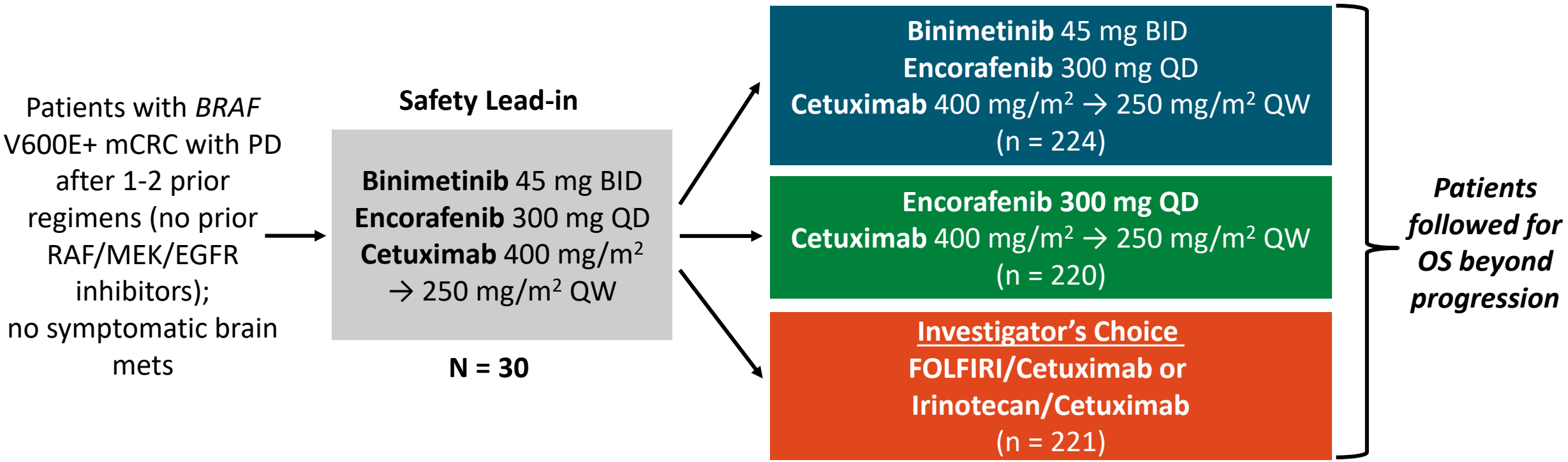


Turk. 2016;5. Larki. Cell J. 2017;19:113. Di Nicolantonio. JCO. 2008;26:5705. Artale. JCO. 2008;26:4217.

Slide credit: clinicaloptions.com

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

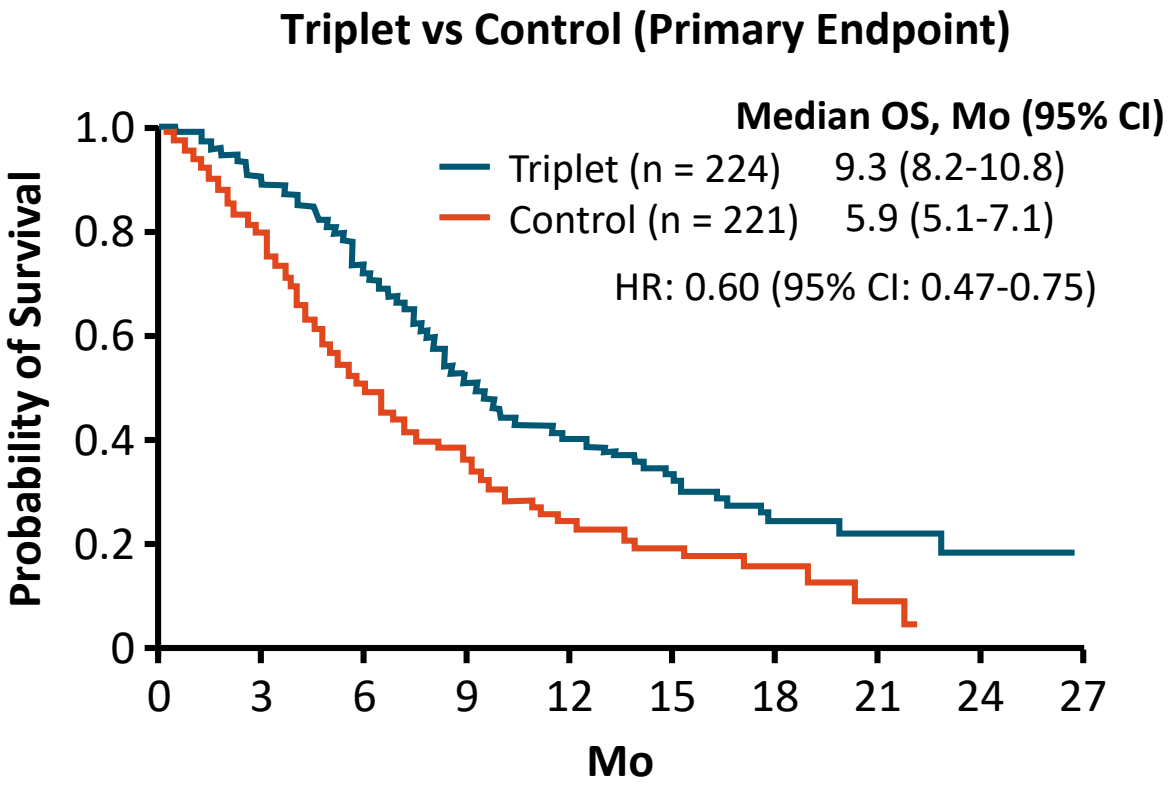
- A multicenter, randomized, open-label, 3-arm phase III trial

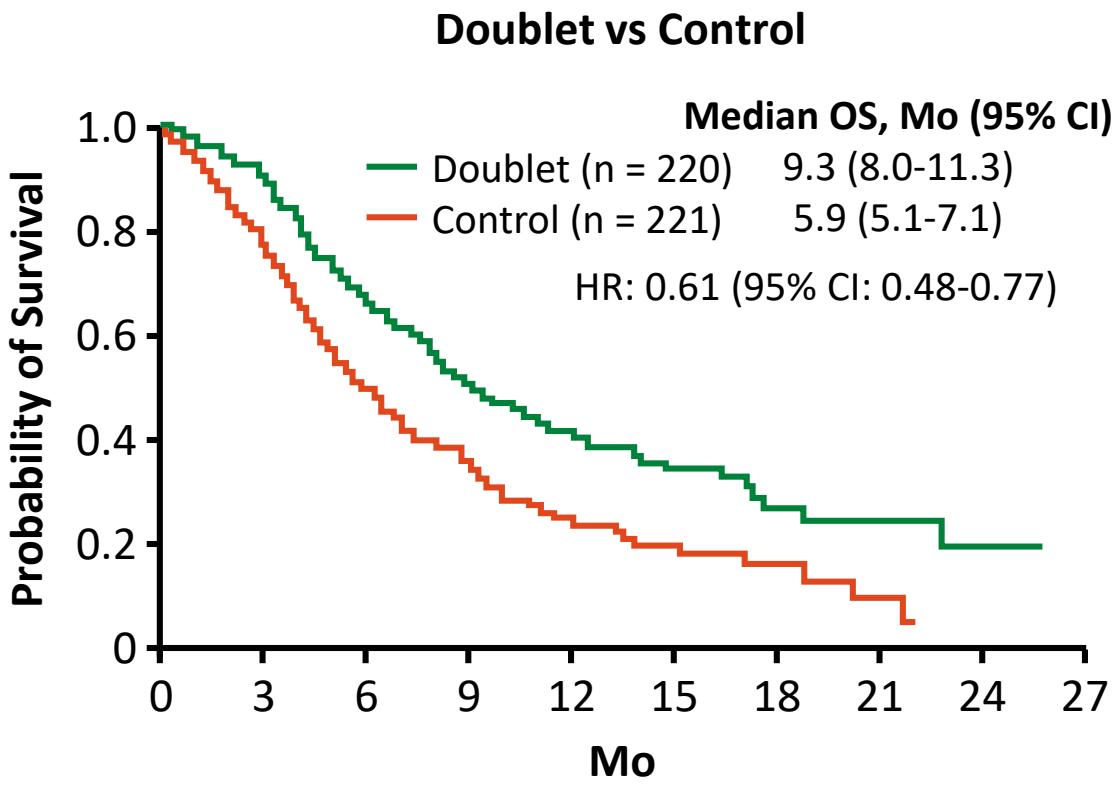


- Primary endpoints: OS and ORR for triplet vs control; secondary endpoints: OS and ORR for doublet vs control, triplet vs doublet; PFS; safety

Van Cutsem. JCO. 2019;10;37:1460. Kopetz. NEJM. 2019;381:1632. Tabernero. JCO. 2021;39:273. NCT02928224.

BEACON CRC: OS and ORR





Confirmed Response by BICR	Triplet Regimen (n = 224)	Doublet Regimen (n = 220)	Control (n = 221)
ORR, % (95% CI)	27 (21-33)	20 (15-25)	2 (<1-5)
P value (vs control)	<.0001	<.0001	

Tabernero. JCO. 2021;39:273.

Slide credit: clinicaloptions.com

KRAS G12C Inhibitors for Advanced CRC

Agent	Previous Data			Ongoing Trials
	Trial/Population	Combination	ORR (%)	
Sotorasib	CodeBreaK100 (phase I/II): previously treated *KRAS* G12C–mutated CRC	None	9.7	CodeBreak 300 (phase III, NCT05198934): sotorasib + panitumumab vs TAS-102 or regorafenib for previously treated *KRAS* G12C–mutated mCRC
	CodeBreaK101 (phase Ib): previously treated advanced *KRAS* G12C–mutated CRC	Panitumumab	16.7	
Adagrasib	KRYSTAL-1 (phase I/II): *KRAS* G12C–mutated CRC	± cetuximab	Monotherapy 22, + cetuximab, 43	KRYSTAL-10 (phase III, NCT04793958): adagrasib + cetuximab vs CT for previously treated *KRAS* G12C–mutated mCRC

Fakih. Lancet Oncol. 2022;23:115. Fakih. ESMO 2021. Abstr 434P. Weiss. ESMO 2021. Abstr LBA6.

Slide credit: clinicaloptions.com

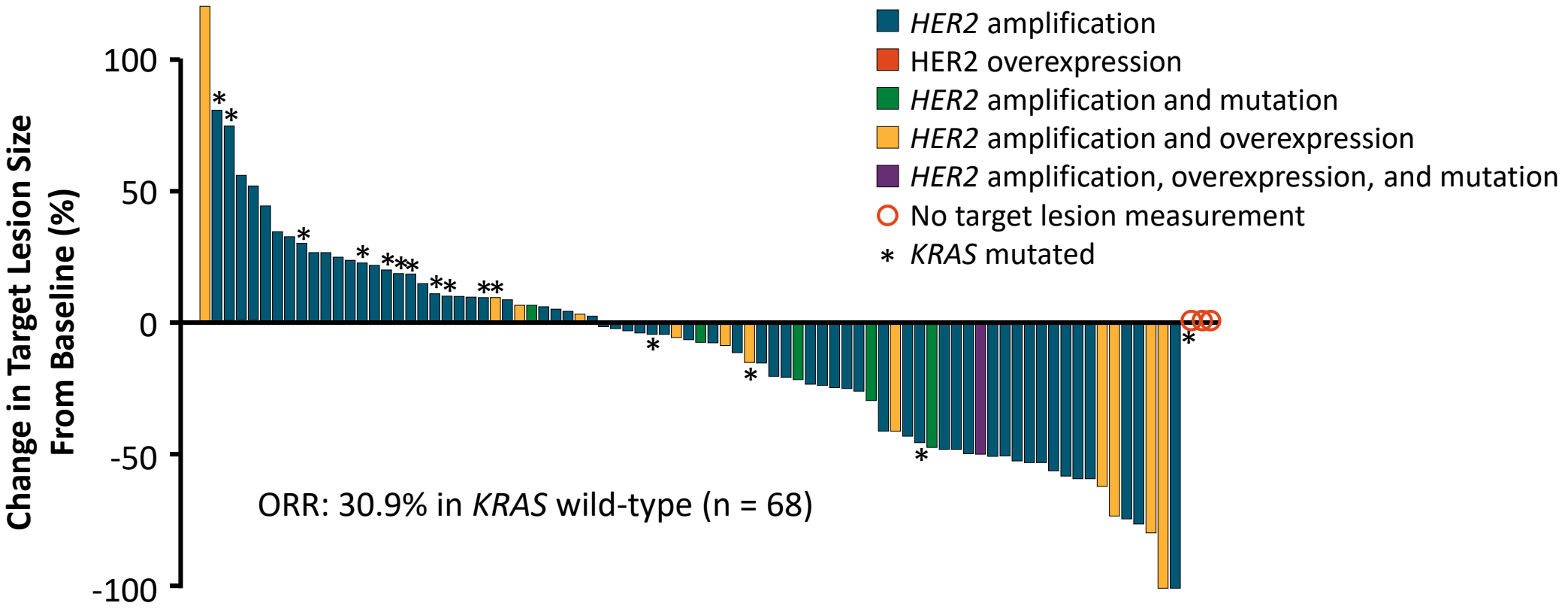
HER2 Amplification

HER2 Amplification in Patients With Colorectal Cancer

- 2.4 to 5.3 % by IHC or FISH
- Enriched in KRAS, NRAS, BRAF, PIK3 WT tumors (!!??)
- Clinical trials:
  - MyPathway (Basket trial)- T'mab + P'mab in mCRC
  - HERACLES – T'mab + Lapatinib
  - MOUNTAINEER- Tucatinib + T'mab
  - DESTINY CRC 01- TdDx

MyPathway: Trastuzumab + Pertuzumab for HER2+ mCRC

- Open-label **phase IIa** basket study (n = 84 with CRC) → ORR 26% (30% in KRAS WT); mOS 6m



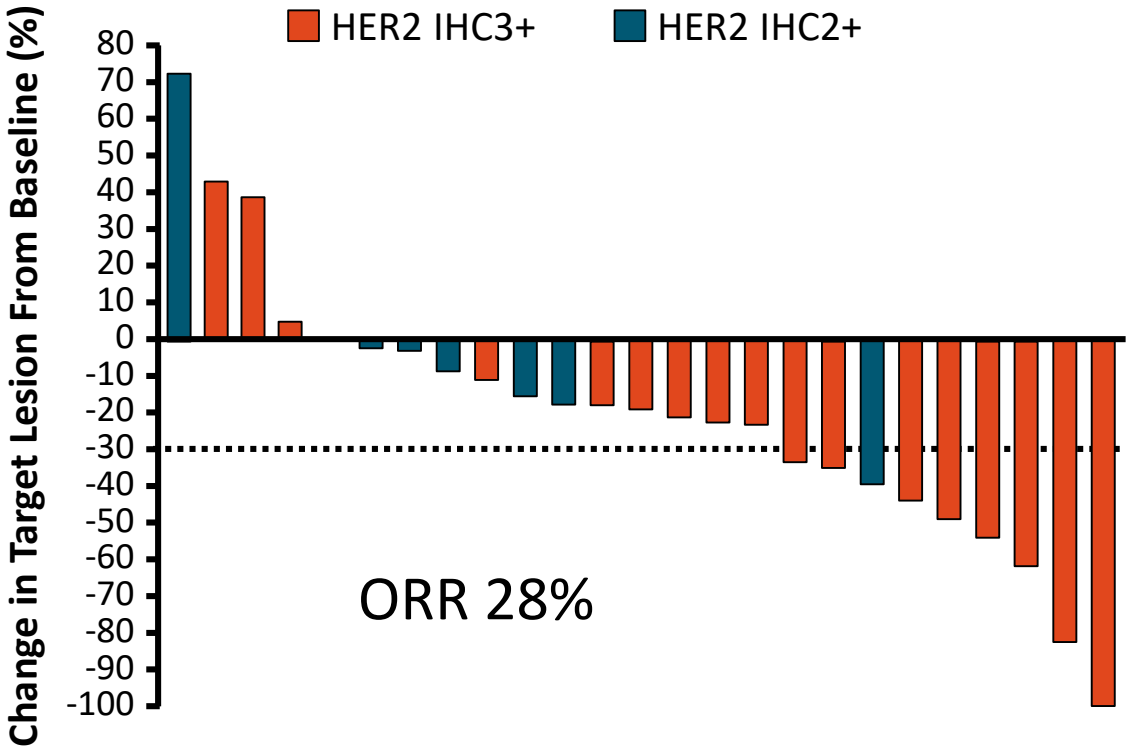
- Key investigation: S1613 (NCT03365882); randomized phase II study of trastuzumab + pertuzumab vs cetuximab + irinotecan for previously treated advanced HER2+ CRC (no previous HER2 treatment)

Meric-Bernstam. ASCO 2021. Abstr 3004.

Slide credit: clinicaloptions.com

HERACLES: Trastuzumab + Lapatinib for Previously Treated mCRC

- Multicenter, open-label **phase II** trial of trastuzumab + lapatinib for patients with HER2+/*KRAS* exon 2 WT metastatic CRC; PD on/within 6 mo of approved standard treatment for CRC* (N = 27)

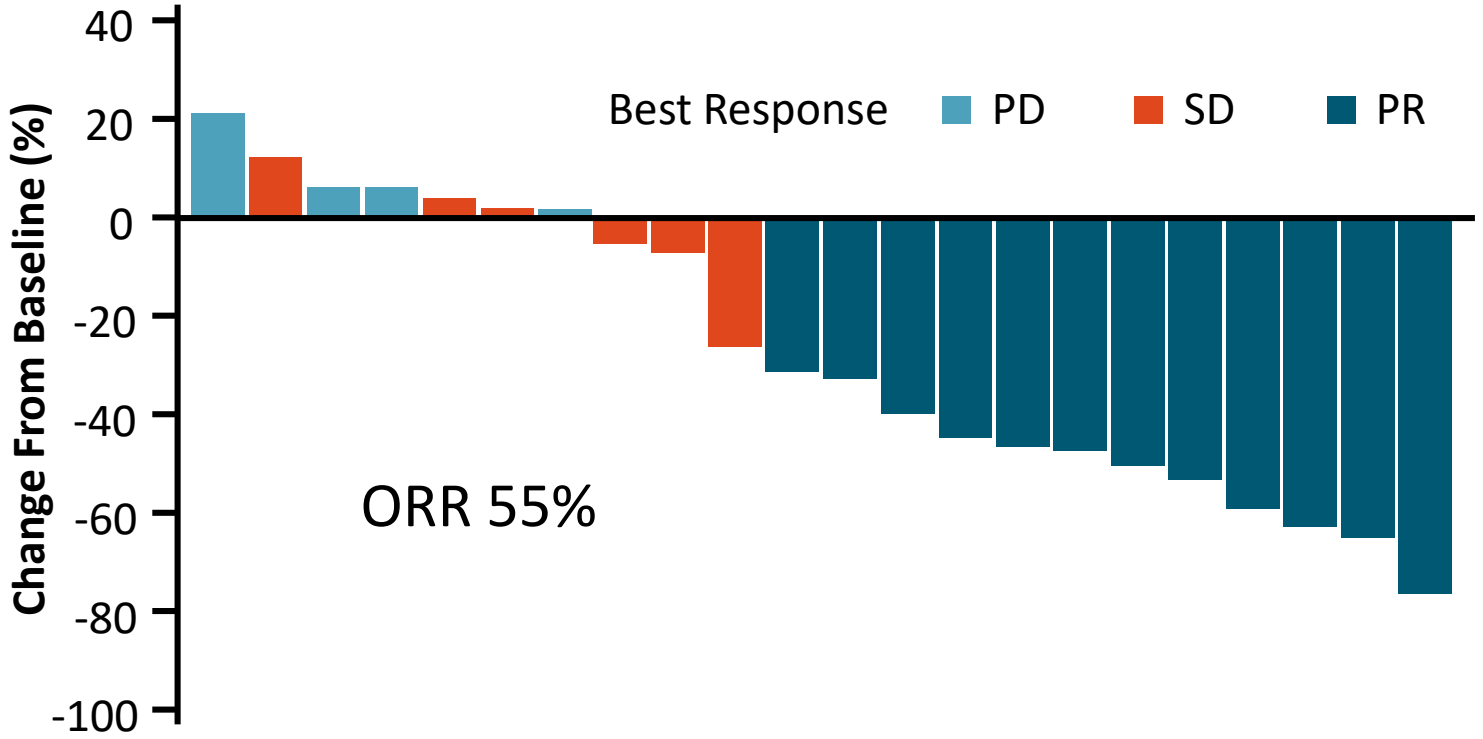


Sartore-Bianchi. Lancet Oncol. 2016;17:738. Tosi. Clin Colorectal Cancer. 2020;19:256.

Slide credit: clinicaloptions.com

MOUNTAINEER: Tucatinib + Trastuzumab in *HER2*-Amplified mCRC

- Open-label, single-arm **phase II study** of tucatinib + trastuzumab for patients with previously treated, *RAS*-WT, *HER2*-amplified, metastatic or unresectable CRC (N = 26)

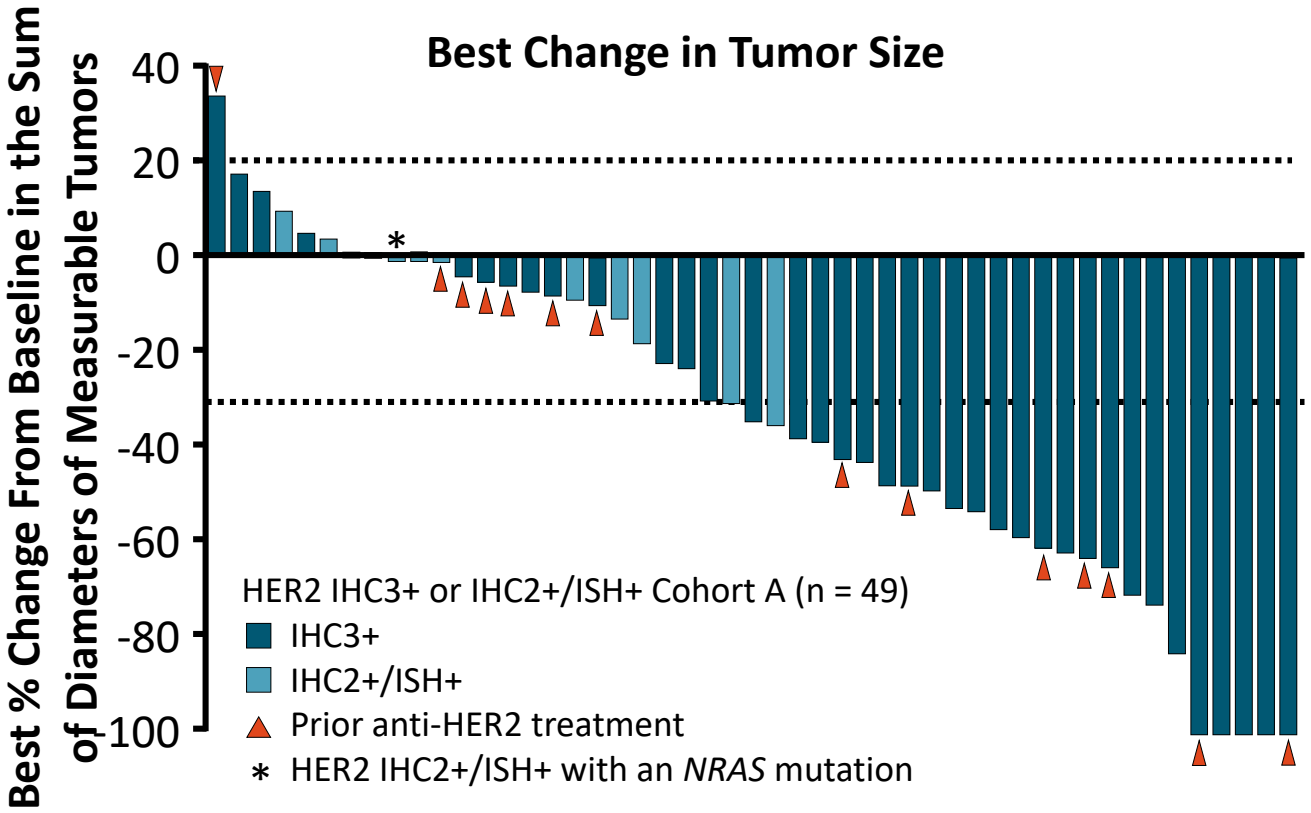


- Key investigations: MOUNTAINEER-03 (NCT05253651); randomized phase III study of tucatinib + trastuzumab + mFOLFOX6 vs SoC as first-line treatment for HER2+ mCRC

Strickler. ESMO 2019. Abstr 4795.

Slide credit: clinicaloptions.com

DESTINY-CRC01: Best Change in Tumor Size and Response With Trastuzumab Deruxtecan in HER2+ CRC Cohort A



Response, n (%)	HER2+ Cohort A (n = 53)
Confirmed ORR by ICR (primary endpoint)	24 (45.3)
▪ CR	0
▪ PR	24 (45.3)
▪ SD	20 (37.7)
▪ PD	5 (9.4)
▪ NE	4 (7.5)*
DCR, % (95% CI)	83.0 (70.2-91.9)
Median DoR, mo (95% CI)	7.0 (5.8-9.5)

*Postbaseline scans missing.

- Tumor shrinkage generally detected by Mo 2 and sustained or deepened over time
- No confirmed responses by ICR in cohorts B and C

Yoshino. ASCO 2021. Abstr 3505. Siena. Lancet Oncol. 2021;22:779.

Slide credit: clinicaloptions.com

NTRK fusions in GI cancers- Rare but actionable

- Less than 5%
- Methods to detect:
  - IHC
  - FISH
  - NGS
- FDA approved drugs- Tumour agnostic-
  - Larotrectinib
  - Entrectinib
  - Selitrectinib
  - Repotrectinib
- ORRs- 40 to 70%

Table S1. Biomarkers and molecular targets for precision medicines and corresponding ESCAT scores

Biomarker or genomic alteration	Method of detection	Drug match	ESCAT score[a,b]
MSI or dMMR[1]	PCR or IHC	Pembrolizumab in first-line treatment	I-A
RAS mutations[2, 3] Including any mutation at exon 2, 3, 4 in KRAS and NRAS	dPCR or NGS	Cetuximab or panitumumab (EGFR inhibitors) to be avoided	Not applicable
***BRAF* V600E mutations**[4]	Sanger sequencing, dPCR or NGS	Encorafenib–cetuximab to be used in second or further lines of treatment	I-A
***HER2* amplification**[5]	IHC, ISH or NGS	Double HER2 blockade to be used in *RAS* wild-type and *HER2* amplified tumours	II-B
***NTRK* mutations or fusions**[6, 7]	Sanger sequencing or NGS	*NTRK* inhibitors (larotrectinib, entrectinib)	I-C
ALK or ROS1 fusions[7]	Sanger sequencing or NGS	ALK or ROS1 inhibitors (entrectinib)	III-A

Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up†

ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) scores .. Eg..

I-A :: Strongest evidence and recommendation

Select Ongoing Biomarker-Based Trials in CRC

- Many ongoing biomarker-based studies

Study	Phase	Treatment	Population
BREAKWATER (NCT04607421)	III	Encorafenib + cetuximab ± CT vs CT	*BRAF* V600E-mutant mCRC
KRYSTAL-10 (NCT04793958)	III	Adagrasib + cetuximab vs CT	Advanced *KRAS* G12C CRC, previous 1L therapy
DESTINY-CRC02 (NCT04744831)	II	Trastuzumab deruxtecan	Advanced HER2+ CRC, prior therapy
S1613 (NCT03365882)	II	Trastuzumab + pertuzumab vs cetuximab + irinotecan	Advanced HER2+ CRC, ≤2 prior lines of therapy

Slide credit: clinicaloptions.com

Select Ongoing Studies of Immune Checkpoint and TRK Inhibitors

Study	Phase	Treatment	Population
CheckMate 8HW (NCT04008030)	III	Nivolumab ± ipilimumab vs CT	mCRC with dMMR/MSI-H
NCT04895722	III	Pembrolizumab or pembrolizumab/quavonlimab	mCRC with dMMR/MSI-H
NAVIGATE (NCT02576431)	II	Larotrectinib	Advanced solid tumors with *NTRK* fusion
STARTRK-2 (NCT02568267)	II	Entrectinib	Advanced solid tumors with *NTRK* fusion or *ROS1/ALK* rearrangement
NCT03215511	I/II	Selitrectinib	Advanced solid tumors with *NTRK1/2/3* fusion and prior TRK inhibitor, no satisfactory treatment options
TRIDENT-1 (NCT03093116)	I/II	Repotrectinib	Patients aged ≥12 yr, advanced solid tumors with *NTRK1/2/3*, *ROS1*, or *ALK* fusion
NCT04094610	I/II	Repotrectinib	Children and young adults, advanced malignancies with *NTRK1/2/3*, *ROS1*, or *ALK* fusion

Besse. AACR-NCI-EORTC 2021. Abstr LB6546.

Slide credit: clinicaloptions.com

Summary and take home

- Personalization and individualization of treatment for mCRC leads to improved outcomes
- Biomarker analyses in all patients with mCRC is extremely relevant
- ctDNA analysis may become more relevant in near future
- Relevant markers leading to change in therapeutic strategy in mCRC:
  - MSI-H/MSS---dMMR/pMMR
  - *RAS*
  - *BRAF* V600E mutation
  - HER2: IHC 3+ or amplification
  - *NTRK* fusion
  - Other mutations/alterations: anecdotal reports

Thank you!!

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