Biologic Therapies – What and When?

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2023 UTHSC Surgical Oncology Annual Cancer Symposium
9/30/23

Disclosures

- No financial disclosures
- Presentation free of commercial bias

Goals

- Scope of metastatic colorectal cancer
- Current treatment approaches utilizing various biologic agents:
  - VEGF inhibitors
  - EGFR inhibitors
  - Immune check point inhibitors
  - BRAF inhibitors
  - HER2 inhibitors

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2020 Estimates

Estimated New Cases

Male			Female		
Prostate	191,930	21%	Breast	276,480	30%
Lung & bronchus	116,300	13%	Lung & bronchus	112,520	12%
Colon & rectum	78,300	9%	Colon & rectum	69,650	8%
Urinary bladder	62,100	7%	Uterine corpus	65,620	7%
Melanoma of the skin	60,190	7%	Thyroid	40,170	4%
Kidney & renal pelvis	45,520	5%	Melanoma of the skin	40,160	4%
Non-Hodgkin lymphoma	42,380	5%	Non-Hodgkin lymphoma	34,860	4%
Oral cavity & pharynx	38,380	4%	Kidney & renal pelvis	28,230	3%
Leukemia	35,470	4%	Pancreas	27,200	3%
Pancreas	30,400	3%	Leukemia	25,060	3%
All sites	**893,660**		**All sites**	**912,930**	

Estimated Deaths

Male			Female		
Lung & bronchus	72,500	23%	Lung & bronchus	63,220	22%
Prostate	33,330	10%	Breast	42,170	15%
Colon & rectum	28,630	9%	Colon & rectum	24,570	9%
Pancreas	24,640	8%	Pancreas	22,410	8%
Liver & intrahepatic bile duct	20,020	6%	Ovary	13,940	5%
Leukemia	13,420	4%	Uterine corpus	12,590	4%
Esophagus	13,100	4%	Liver & intrahepatic bile duct	10,140	4%
Urinary bladder	13,050	4%	Leukemia	9,680	3%
Non-Hodgkin lymphoma	11,460	4%	Non-Hodgkin lymphoma	8,480	3%
Brain & other nervous system	10,190	3%	Brain & other nervous system	7,830	3%
All sites	**321,160**		**All sites**	**285,360**	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

Table 8. Five-year Relative Survival Rates* (%) by Stage at Diagnosis, US, 2009-2015

	All stages	Local	Regional	Distant		All stages	Local	Regional	Distant
Breast (female)	90	99	86	27	Oral cavity & pharynx	65	84	66	39
Colon & rectum	64	90	71	14	Ovary	48	92	75	29
Colon	63	90	71	14	Pancreas	9	37	12	3
Rectum	67	89	71	15	Prostate	98	>99	>99	31
Esophagus	20	47	25	5	Stomach	32	69	31	5
Kidney†	75	93	70	12	Testis	95	99	96	73
Larynx	60	77	45	33	Thyroid	98	>99	98	56
Liver‡	18	33	11	2	Urinary bladder§	77	70	36	5
Lung & bronchus	19	57	31	5	Uterine cervix	66	92	56	17
Melanoma of the skin	92	99	65	25	Uterine corpus	81	95	69	17

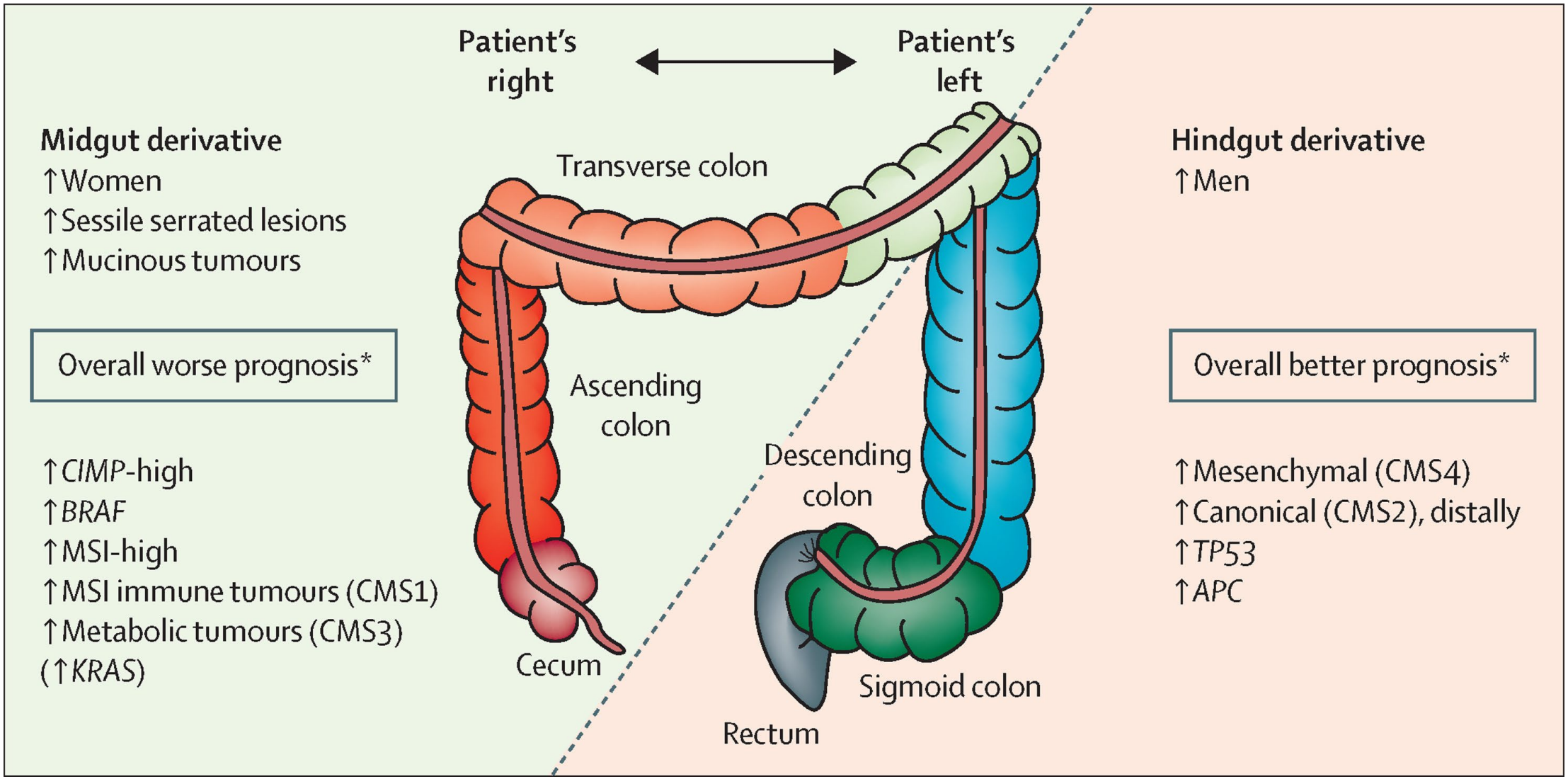
*Rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2009-2015, all followed through 2016. †Includes renal pelvis. ‡Includes intrahepatic bile duct. §Rate for in situ cases is 96%.

Local: an invasive malignant cancer confined entirely to the organ of origin. **Regional:** a malignant cancer that 1) has extended beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) involves regional lymph nodes; or 3) has both regional extension and involvement of regional lymph nodes. **Distant:** a malignant cancer that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis to distant organs, tissues, or via the lymphatic system to distant lymph nodes.

Source: Source: Howlader N, Noone AM, Krapcho M, et al (eds). *SEER Cancer Statistics Review, 1975-2016*, National Cancer Institute, Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER website, April 2019.

Pathophysiology

- Molecular features of right-sided (proximal) colon cancers are different from left-sided (distal) colon and rectal cancers
- Molecular, embryological, biological, and anatomical differences
  - Right: immunogenicity (MSI, RAS/BRAF, PIK3CA); midgut; worse clinical outcomes
  - Left: less immunogenic; canonical pathways (TP53); hindgut; better clinical outcomes
- Sidedness as a predictive marker of response to anti-EGFR drugs

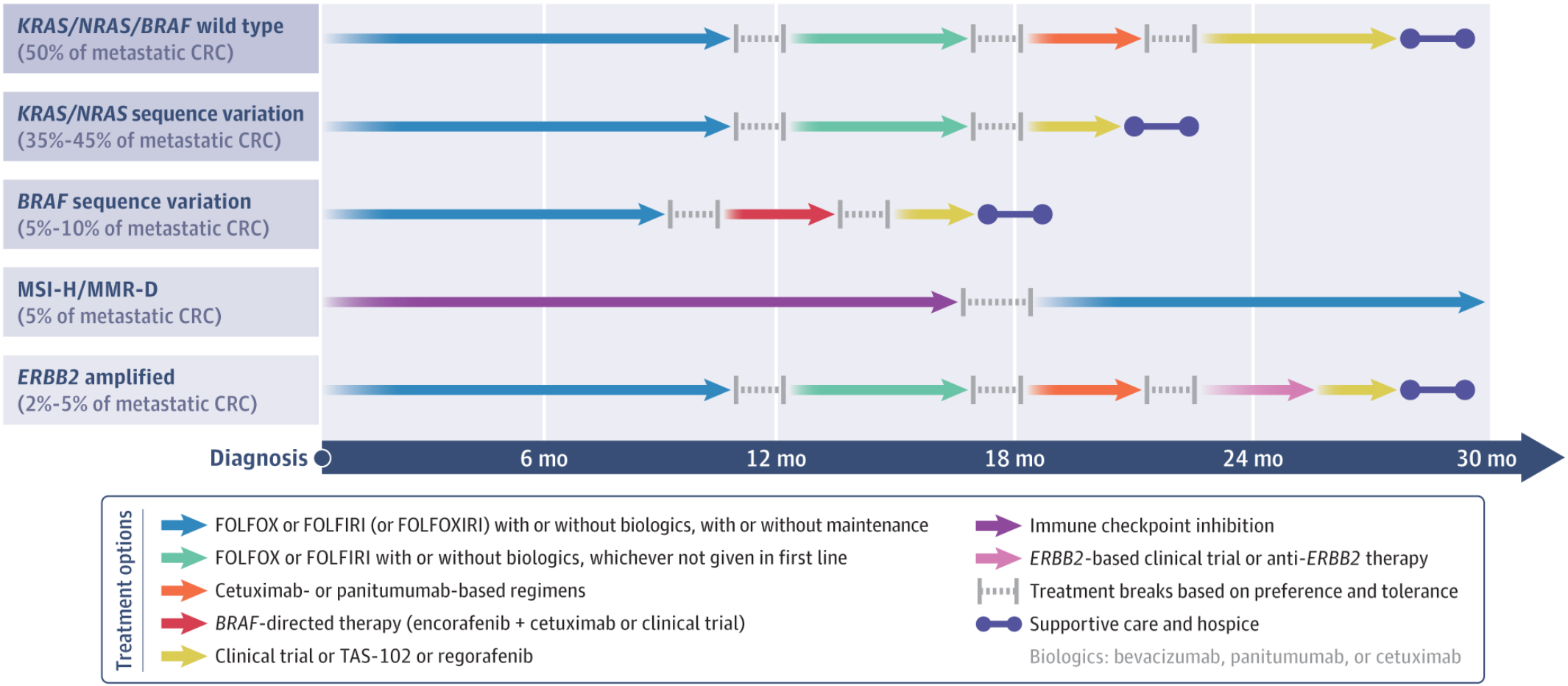


Evelien Dekker, Pieter J Tanis, Jasper L A Vleugels, Pashtoon M Kasi, Michael B Wallace. Colorectal cancer. The Lancet. Volume 394, Issue 10207. 2019.

Pathology/Molecular Studies

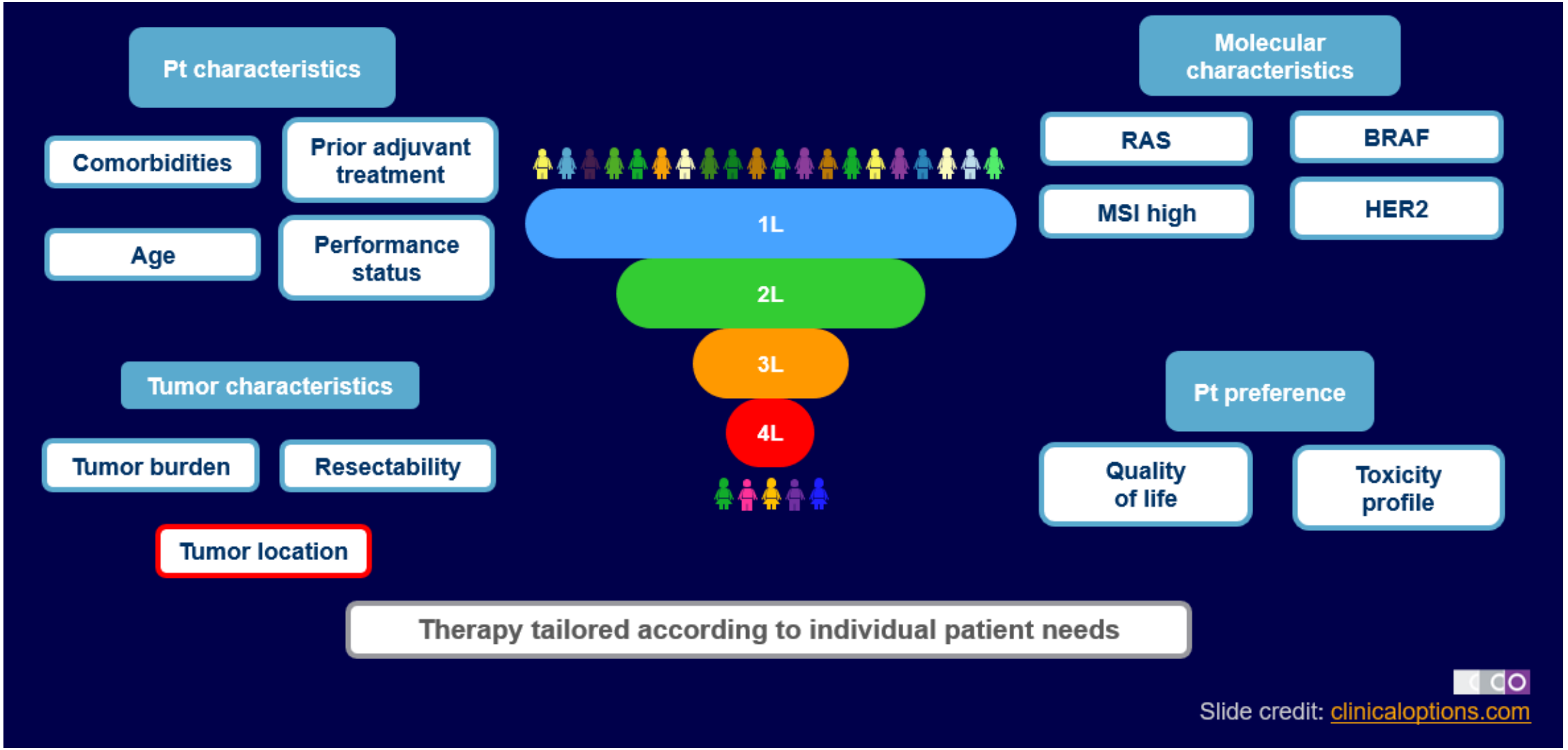
- Extended RAS testing (KRAS, NRAS)
- Mismatch repair proteins
  - MLH1, MSH2, MSH6, PMS2
- Microsatellite instability testing
- BRAF testing
- Next generation sequencing/multigene panels
  - NTRK
  - ERBB2

Molecular Subtype and Survival



JAMA. 2021;325(7):669-685. doi:10.1001/jama.2021.0106

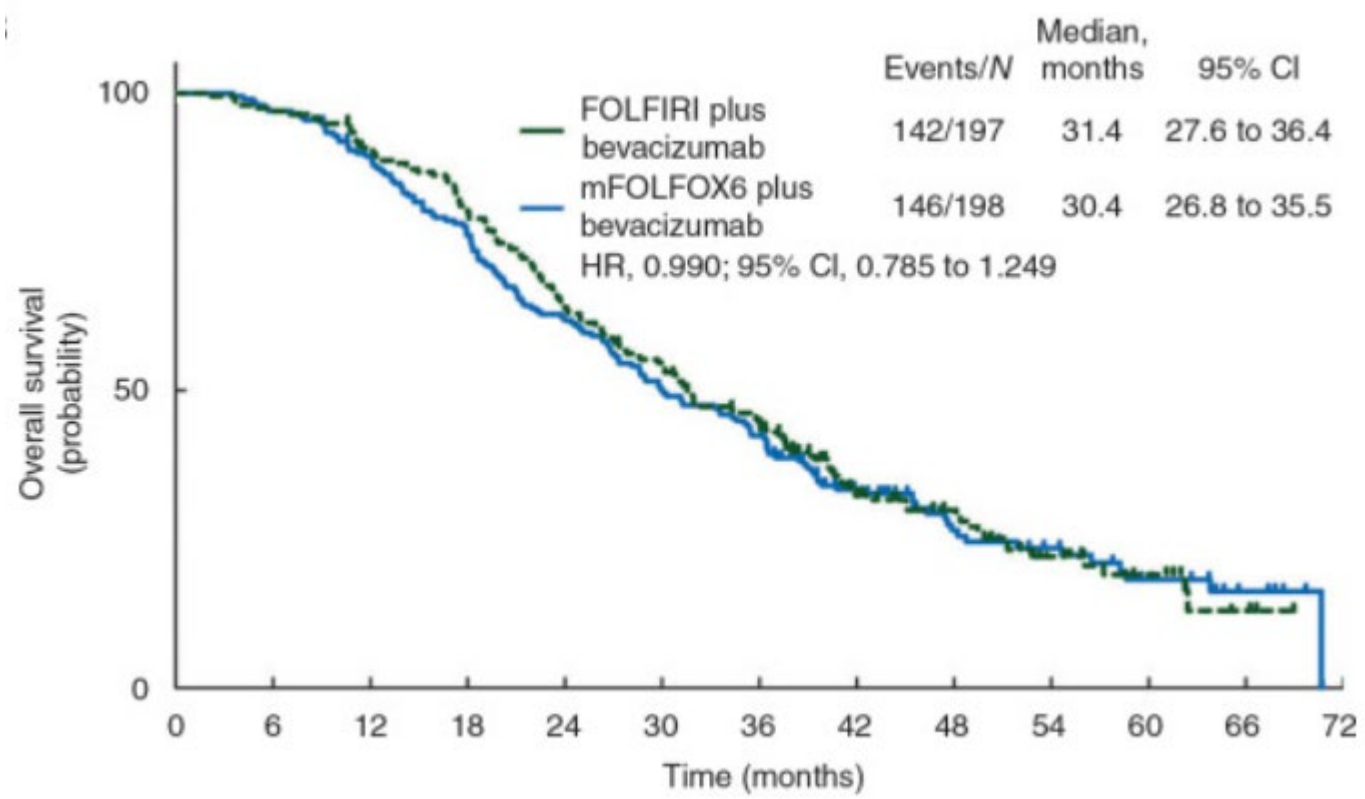
Treatment Options in Metastatic CRC



First Line Therapies – Chemotherapy

- Typically for MMR proficient/MSS tumors

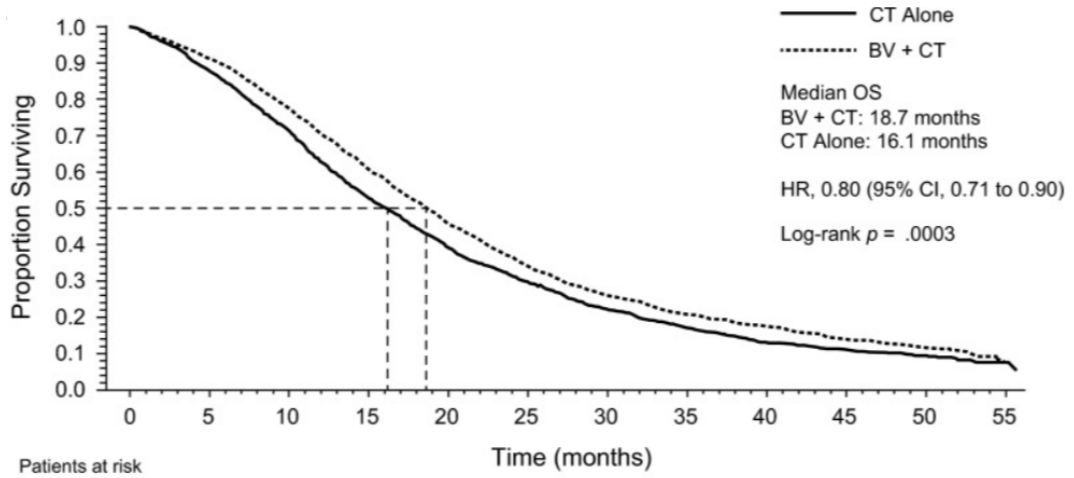
- Chemotherapy backbone
  - 5FU/LV, capecitabine
  - FOLFOX/CAPOX
  - FOLFIRI/CAPIRI
  - FOLFOXIRI



Ann Oncol. 2016;27(8):1539-1546

First Line Therapies – Biologic Therapies

- VEGF inhibitor - Bevacizumab - administered with either irinotecan or oxaliplatin containing chemotherapy

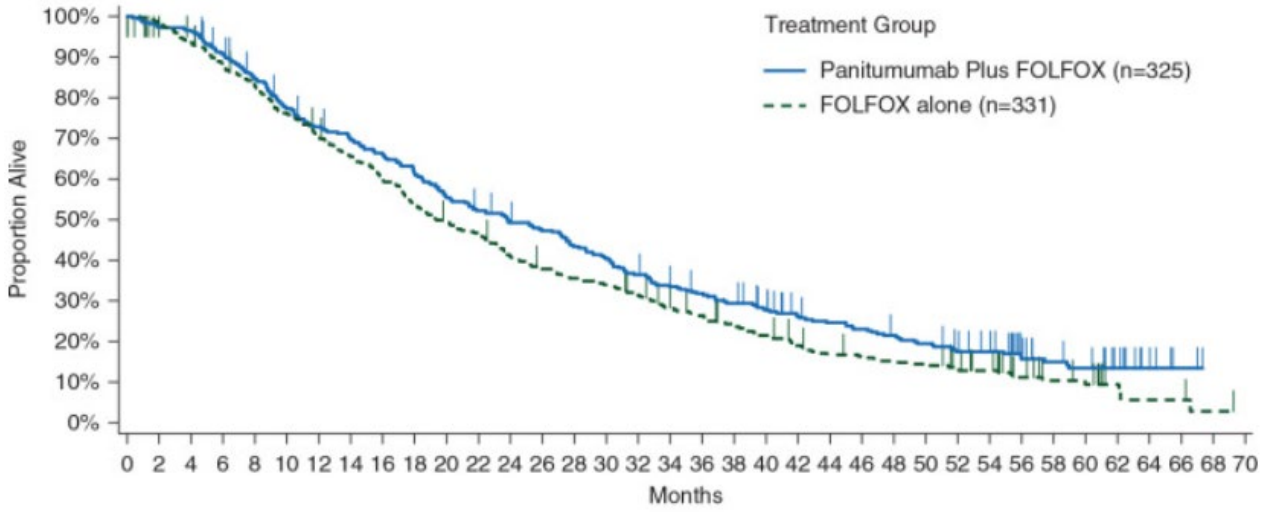


- improved PFS (HR, 0.79; *P* < .001) but not OS (HR, 0.92; *P* = .18)

Eur J Cancer. 2019;106:37-44.
Oncologist. 2013;18(9):1004-12. Epub 2013 Jul 23.

First Line Therapies – Biologic Therapies

- EGFR inhibitor – Cetuximab, Panitumumab – combined with chemotherapy
  - only effective for patients with left sided *KRAS/NRAS* wild-type metastatic CRC
  - Both considered interchangeable
  - Colon sidedness matters



Ann Oncol. 2014;25(7):1346-1355

First Line Therapies – Biologic Therapies

- EGFR vs VEGF inhibitors – how do you choose?

- CALGB/SWOG 80405: KRAS WT mCRC FOLFOX or FOLIRI + cetuximab or bevacizumab
  - No differences in OS (30.0 months for cetuximab vs 29.0 months for bevacizumab) or PFS (10.5 months vs 10.6 months)

JAMA. 2023;329(15):1271-1282

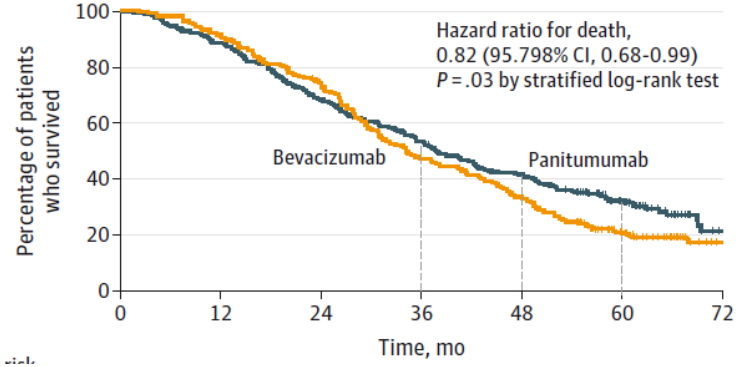
First Line Therapies – Biologic Therapies

- EGFR vs VEGF inhibitors – how do you choose?

A Overall survival

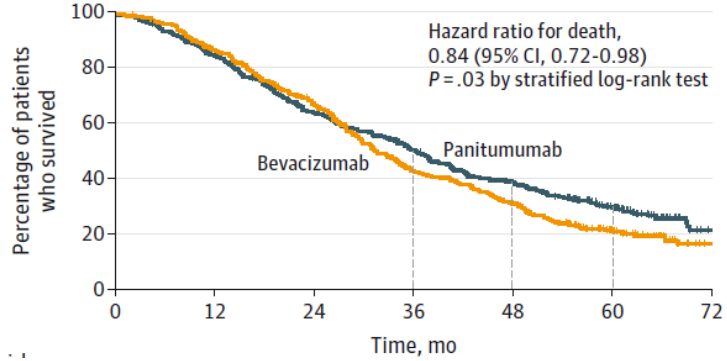
Participants with left-sided tumors

	No. (%) of patients with events	Median survival, mo (95.798% CI)
Panitumumab plus mFOLFOX6 (n = 312)	218 (69.9)	37.9 (34.1-42.6)
Bevacizumab plus mFOLFOX6 (n = 292)	230 (78.7)	34.3 (30.9-40.3)



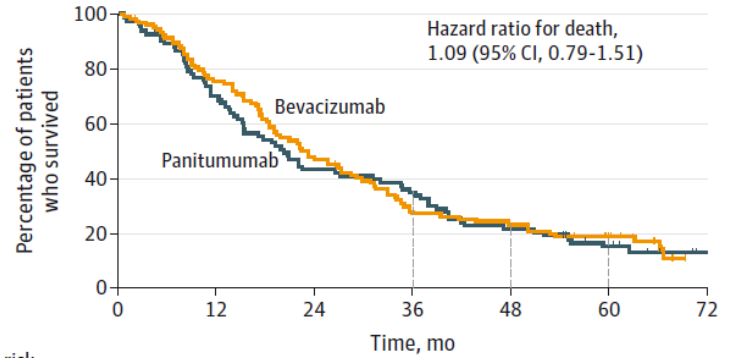
Overall study population

	No. (%) of patients with events	Median survival, mo (95% CI)
Panitumumab plus mFOLFOX6 (n = 400)	291 (72.8)	36.2 (32.0-39.0)
Bevacizumab plus mFOLFOX6 (n = 402)	322 (80.1)	31.3 (29.3-34.1)



Participants with right-sided tumors

	No. (%) of patients with events	Median survival, mo (95% CI)
Panitumumab plus mFOLFOX6 (n = 84)	71 (84.5)	20.2 (15.2-32.0)
Bevacizumab plus mFOLFOX6 (n = 103)	85 (82.5)	23.2 (18.5-29.1)



JAMA. 2023;329(15):1271-1282

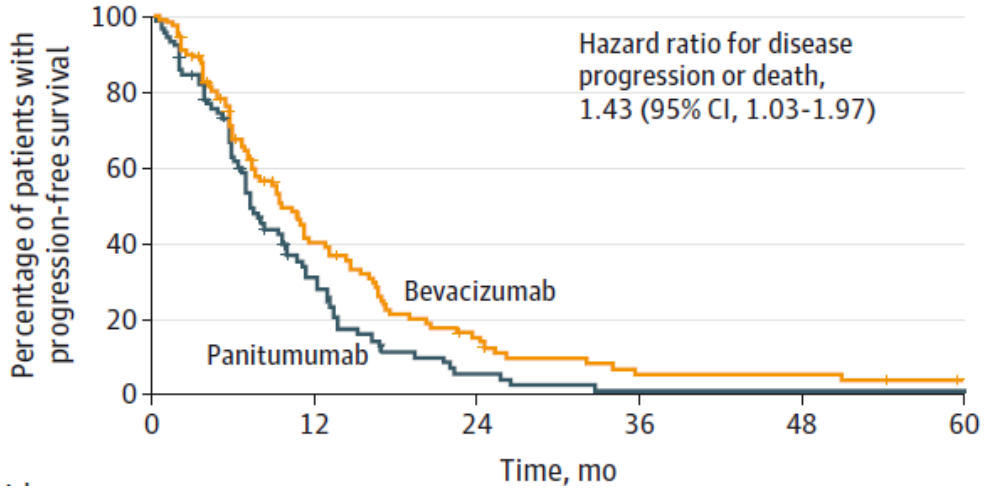
First Line Therapies – Biologic Therapies

- EGFR vs VEGF inhibitors – how do you choose?

B Progression-free survival

Participants with right-sided tumors

	No. (%) of patients with events	Median survival, mo (95% CI)
Panitumumab plus mFOLFOX6 (n = 84)	73 (86.9)	7.2 (6.6-9.9)
Bevacizumab plus mFOLFOX6 (n = 103)	85 (82.5)	9.4 (7.6-13.0)



JAMA. 2023;329(15):1271-1282

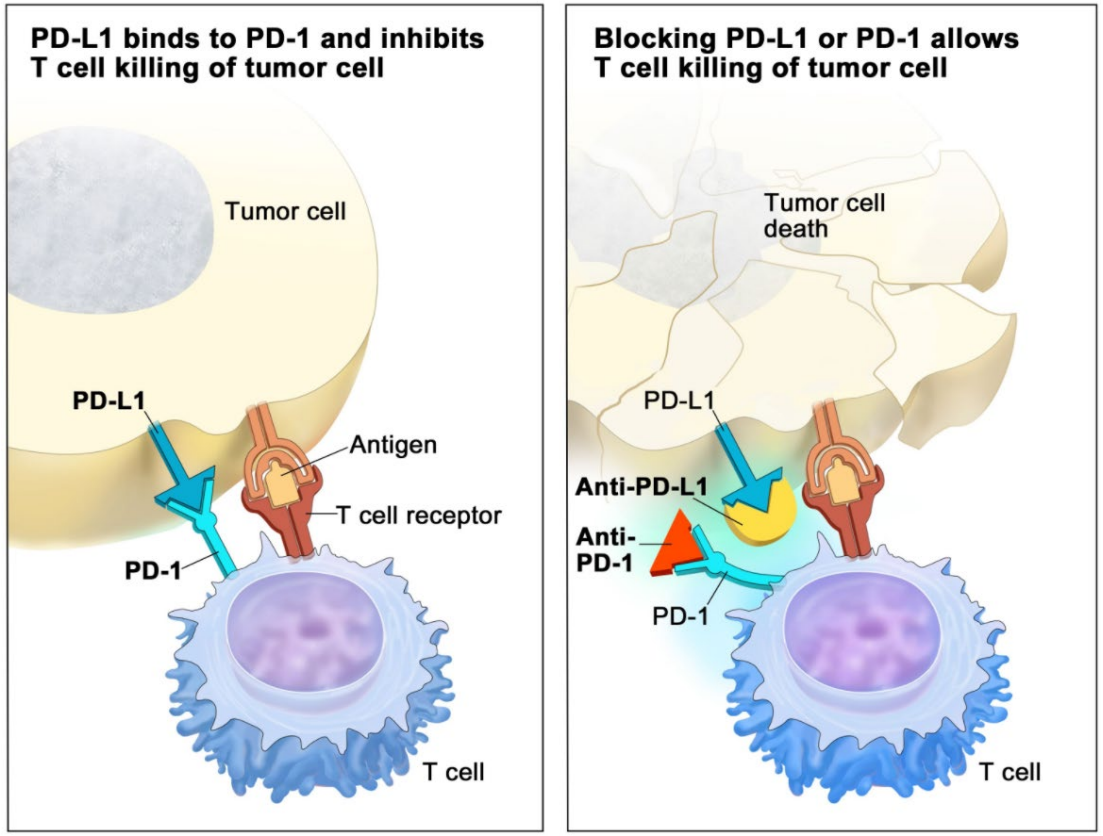
First Line Therapies – Biologic Therapies

- EGFR vs VEGF inhibitors – how do you choose?
- Sidedness is strongest factor to consider
- Resectability of oligometastatic disease

JAMA. 2023;329(15):1271-1282

First Line Therapies – Immune checkpoint inhibitors

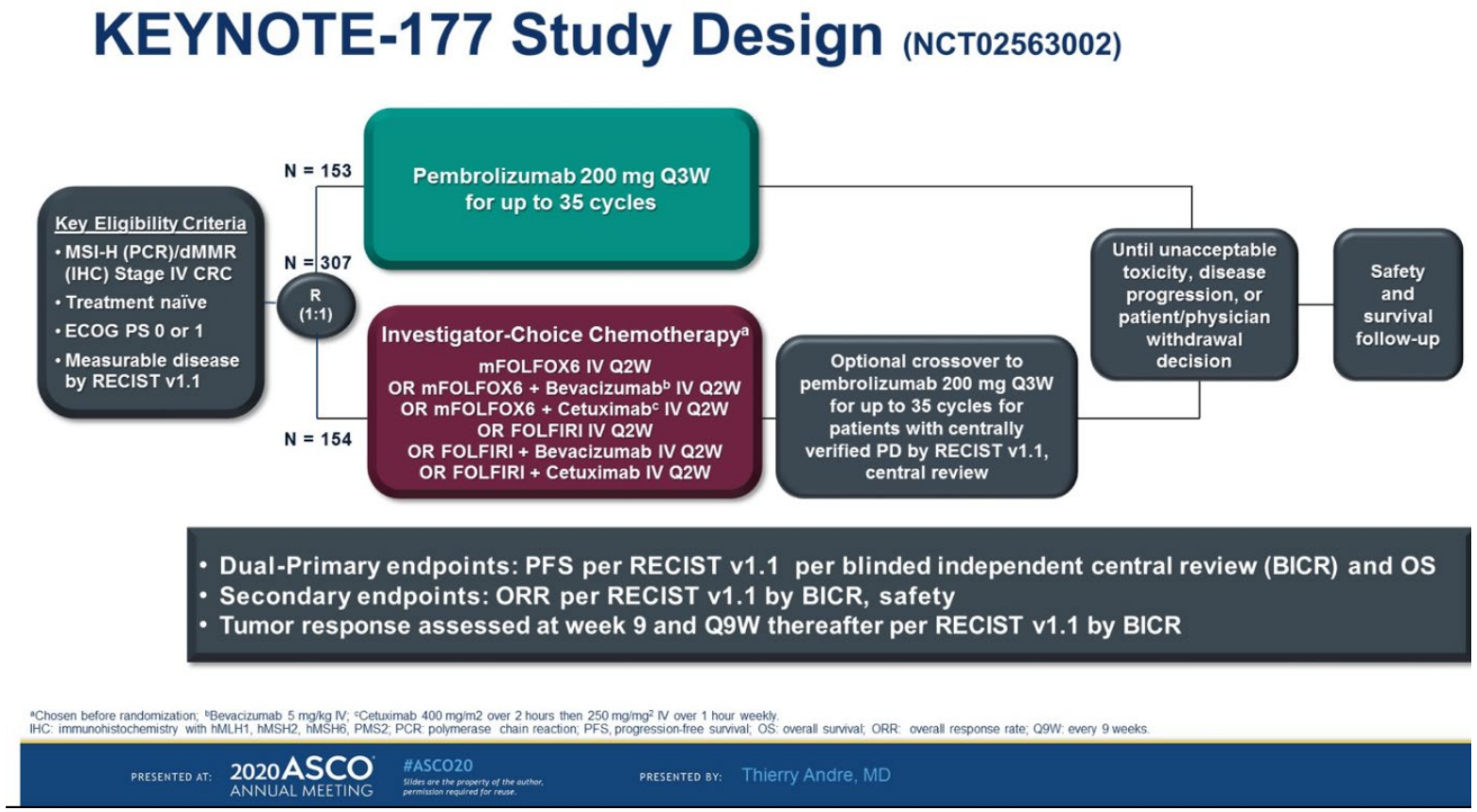
- Tumors that are MSI-High or mismatch repair protein deficient



https://www.cancer.gov/publications/dictionaries/cancer-terms/def/immune-checkpoint-inhibitor

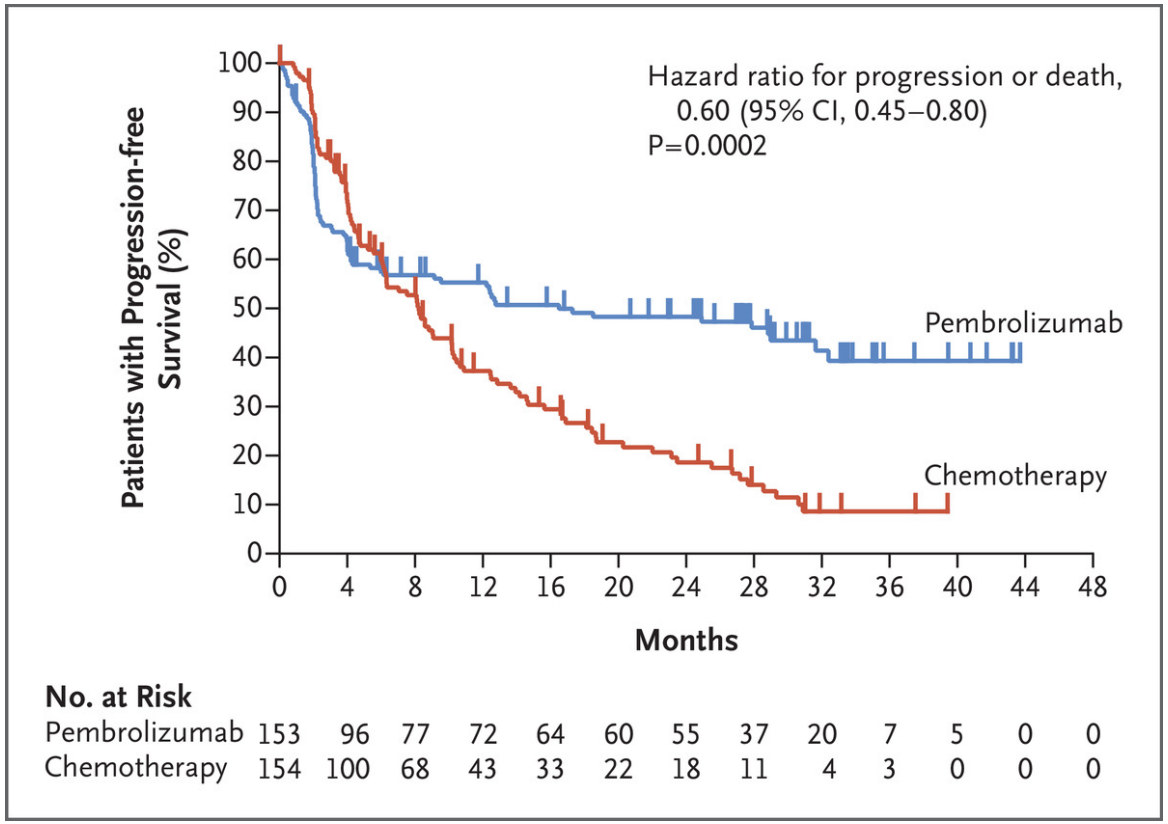
First Line Therapies – Immune checkpoint inhibitors

- Pembrolizumab – KEYNOTE-177



First Line Therapies – Immune checkpoint inhibitors

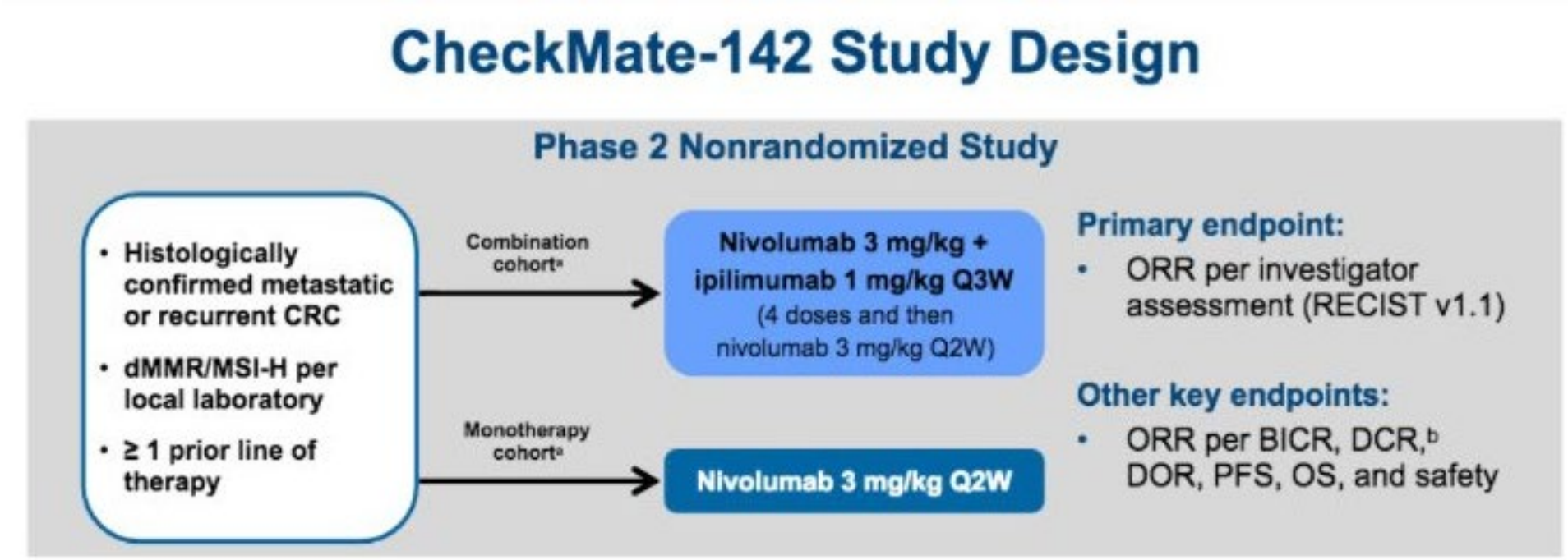
- Pembrolizumab – KEYNOTE-177
  - pembrolizumab was superior to chemotherapy with respect to progression-free survival (median, 16.5 vs. 8.2 months; hazard ratio, 0.60; 95% confidence interval [CI], 0.45 to 0.80; P=0.0002)



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

First Line Therapies – Immune checkpoint inhibitors

- Nivolumab/Ipilimumab – CheckMate-142



JCO. 2022 Jan 10;40(2):161-170

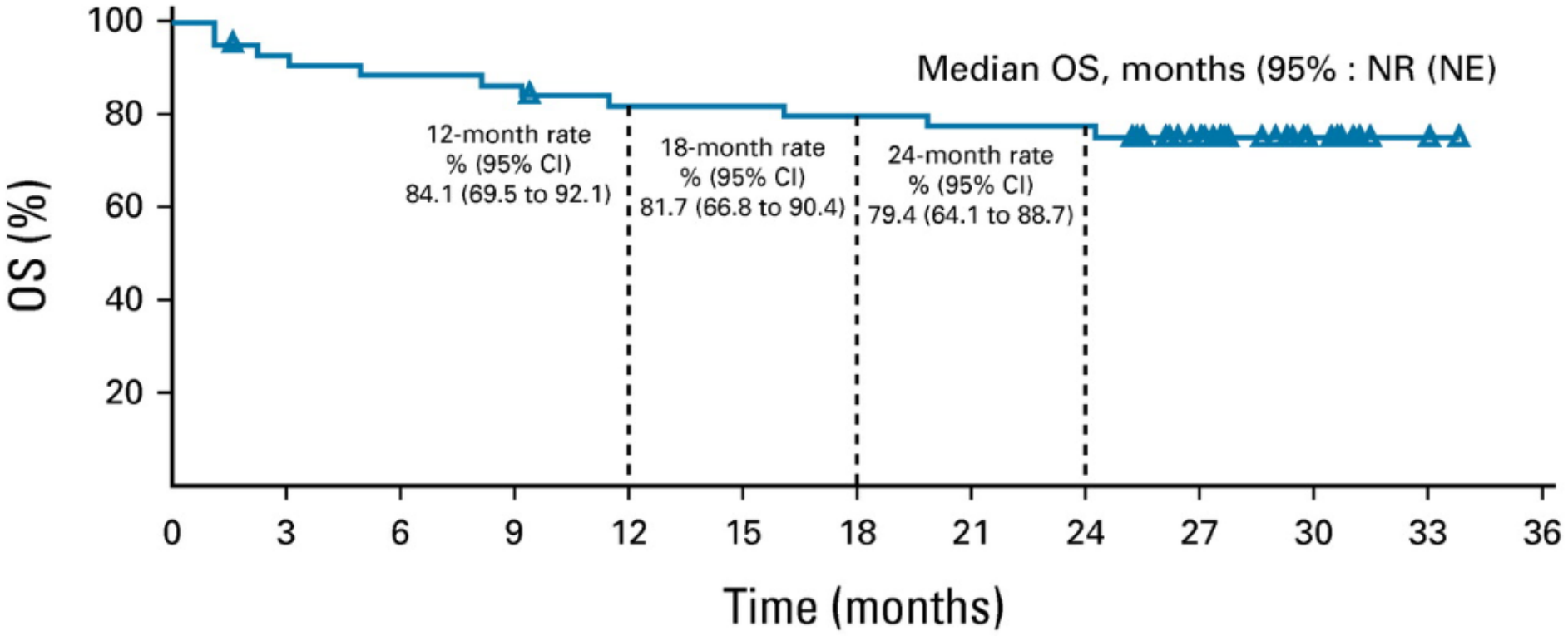
First Line Therapies – Immune checkpoint inhibitors

- Nivolumab – CheckMate-142
  - Objective response rate and disease control rate were 69% (95% CI, 53 to 82) and 84% (95% CI, 70.5 to 93.5), respectively, with 13% complete response rate
  - Median duration of response was not reached; 74% of responders had ongoing responses at data cutoff
  - Median progression-free survival and median overall survival were not reached with minimum follow-up of 24.2 months (24-month rates, 74% and 79%, respectively)

JCO. 2022 Jan 10;40(2):161-170

First Line Therapies – Immune checkpoint inhibitors

- Nivolumab – CheckMate-142



JCO. 2022 Jan 10;40(2):161-170

Second Line therapies – Angiogenesis inhibitors

- Continuation of bevacizumab + chemotherapy backbone
- Aflibercept + FOLFIRI
  - Median OS was significantly longer in patients treated with aflibercept (13.5 versus 12.1 months) as was median PFS (6.9 versus 4.7 months)
  - Worse toxicity profile compared to bevacizumab
- Ramucirumab + FOLFIRI
  - Median OS was modestly but significantly greater with ramucirumab (13.3 versus 11.7 months), as was median PFS (5.7 versus 4.5 months)

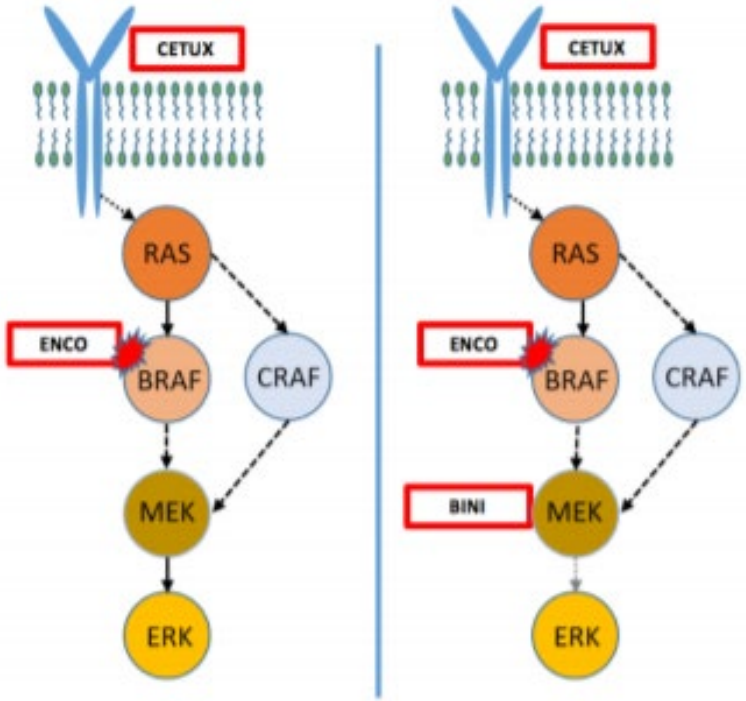
Lancet Oncol. 2013;14(1):29. Epub 2012 Nov 16

J Clin Oncol. 2012;30(28):3499. Epub 2012 Sep 4. Lancet Oncol. 2015;16(5):499. Epub 2015 Apr 12

Second Line therapies – BRAF V600E +

- *BRAF* V600E mutation occurs in approximately 10% of mCRC

MAPK Signaling in Colorectal Cancer[1]



1.Adapted From: Strickler JH. *Cancer Treatment Reviews*. 2017; 60:109-119

BEACON CRC Phase 3 Study Design[1]

Safety Lead-in Completed

ENCO 300 mg QD
+
BINI 45 mg BID
+
CETUX 400 mg/m² (initial) then
250 mg/m² QW

N=30

Phase 3 Currently Enrolling

R
1:1:1

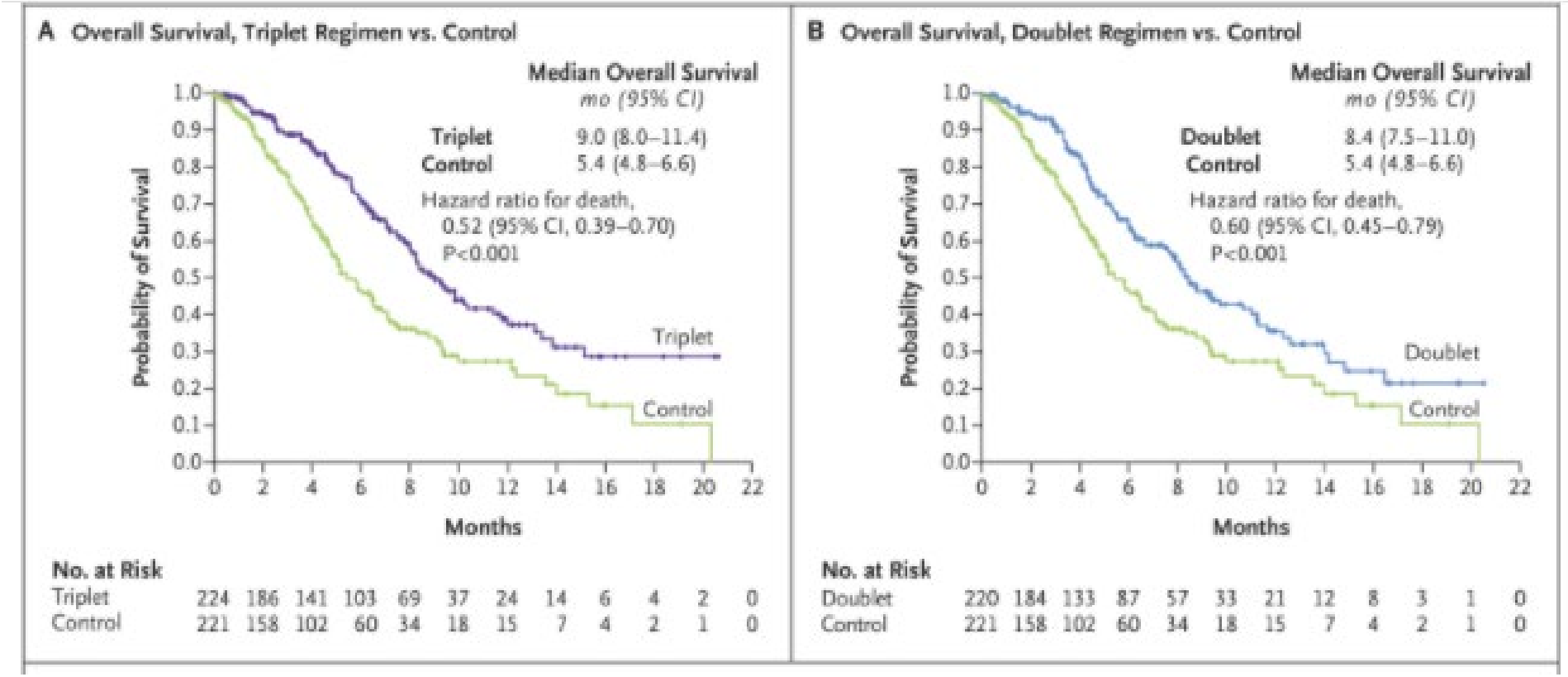
- Triplet therapy ENCO + BINI + CETUX n=205 → Disease progression
- Doublet Therapy ENCO + CETUX n=205 → Disease progression
- Control Arm FOLFIRI + CETUX, or IR + CETUX n=205 → Disease progression

Continued follow-up for evaluation of OS

1. Clinicaltrials.gov/ct2/show/NCT02928224; https://clinicaltrials.gov/ct2/show/NCT02928224 (February 2018).

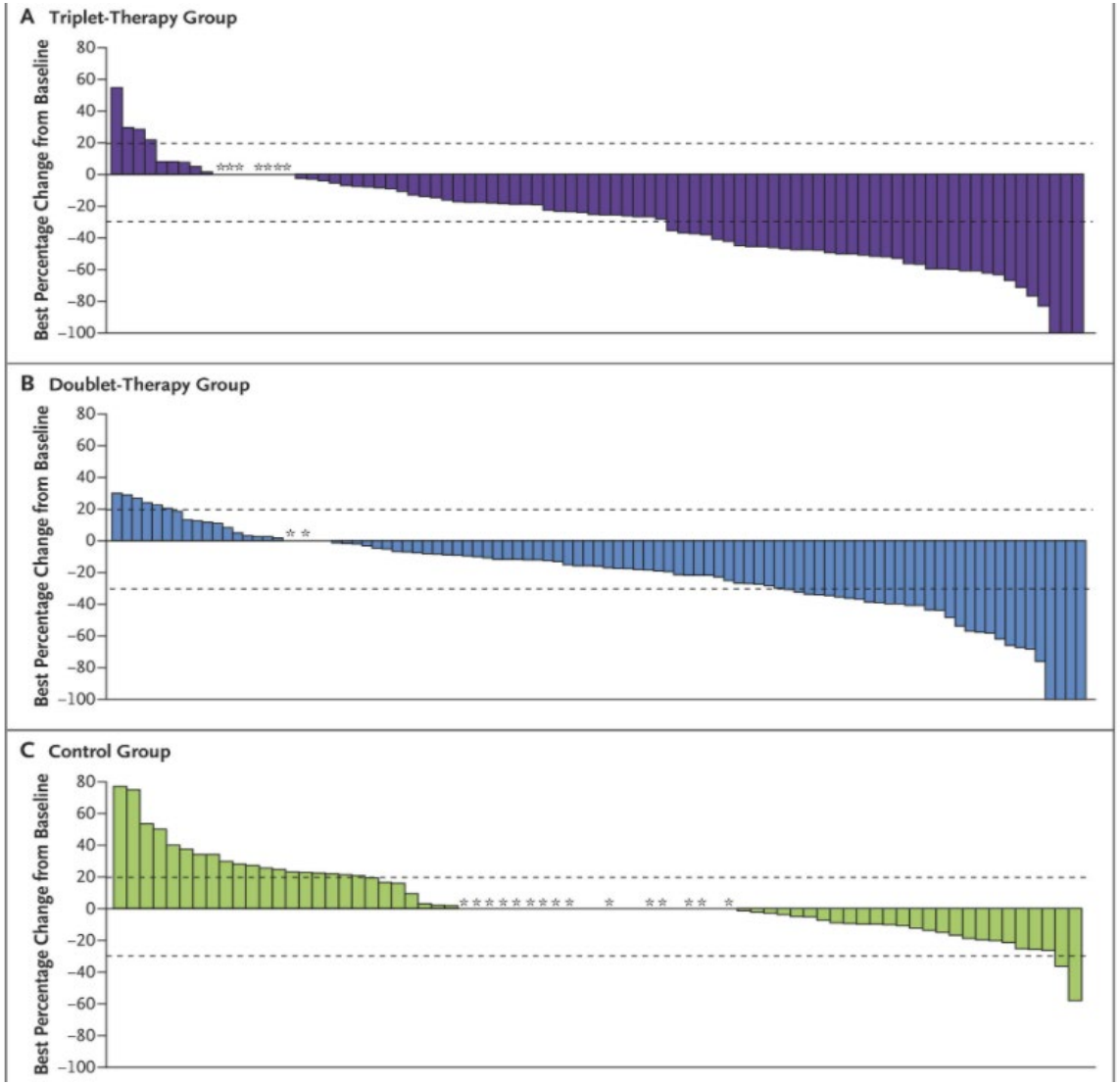
Second Line therapies – BRAF V600E +

- median OS 9.0 months in the triplet-therapy group vs 5.4 months in control group (HR for death, 0.52; P<0.001).



N Engl J Med. 2019;381(17):1632. Epub 2019 Sep 30.

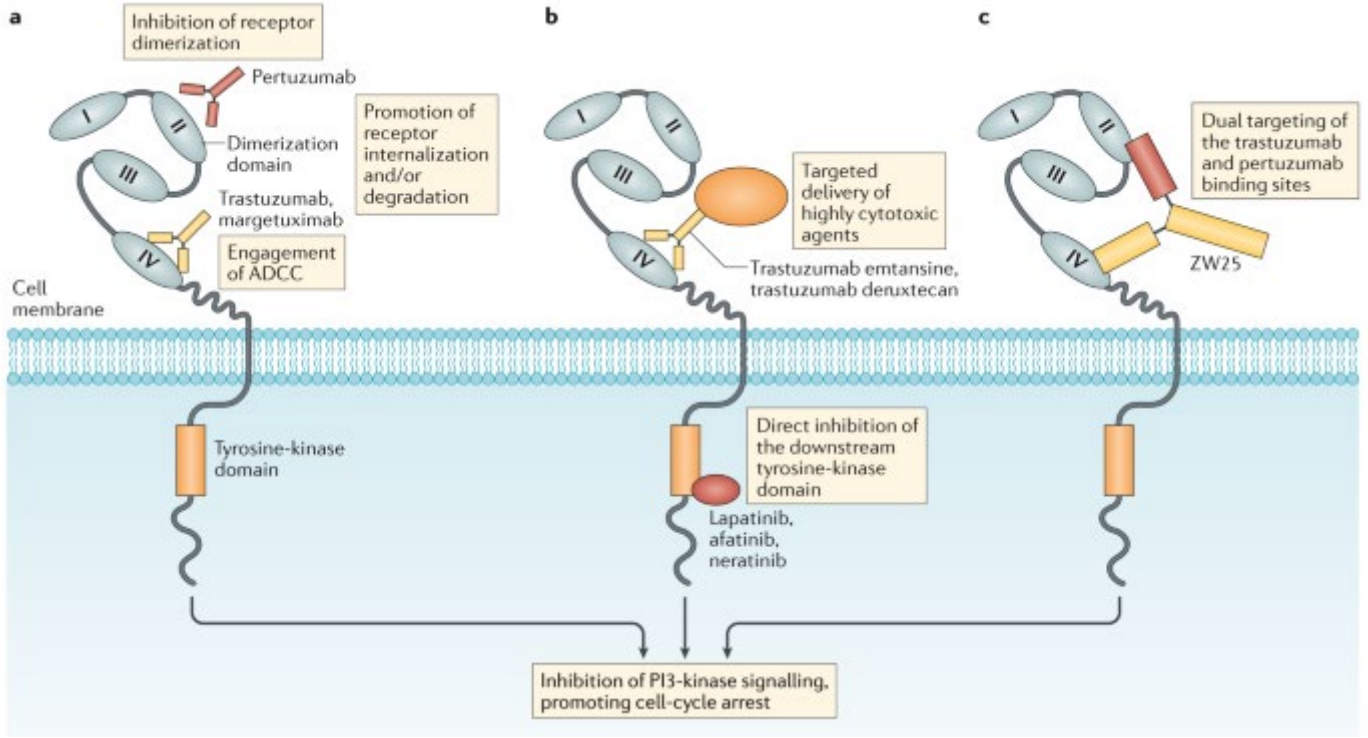
Second Line therapies – BRAF V600E +



N Engl J Med. 2019;381(17):1632. Epub 2019 Sep 30.

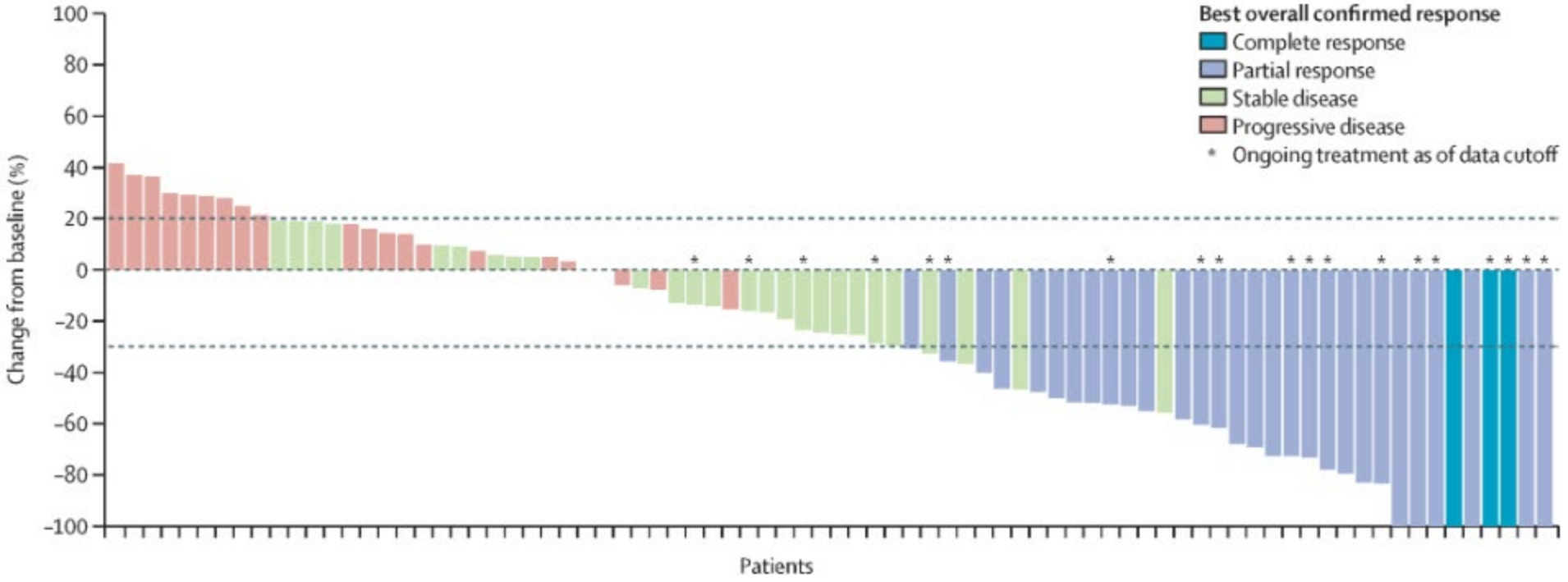
Second Line therapies – HER2 overexpressors

- ~ 3 to 5% of CRCs have amplification of the *HER2* oncogene or overexpress its protein product, HER2



Second Line therapies – HER2 overexpressors

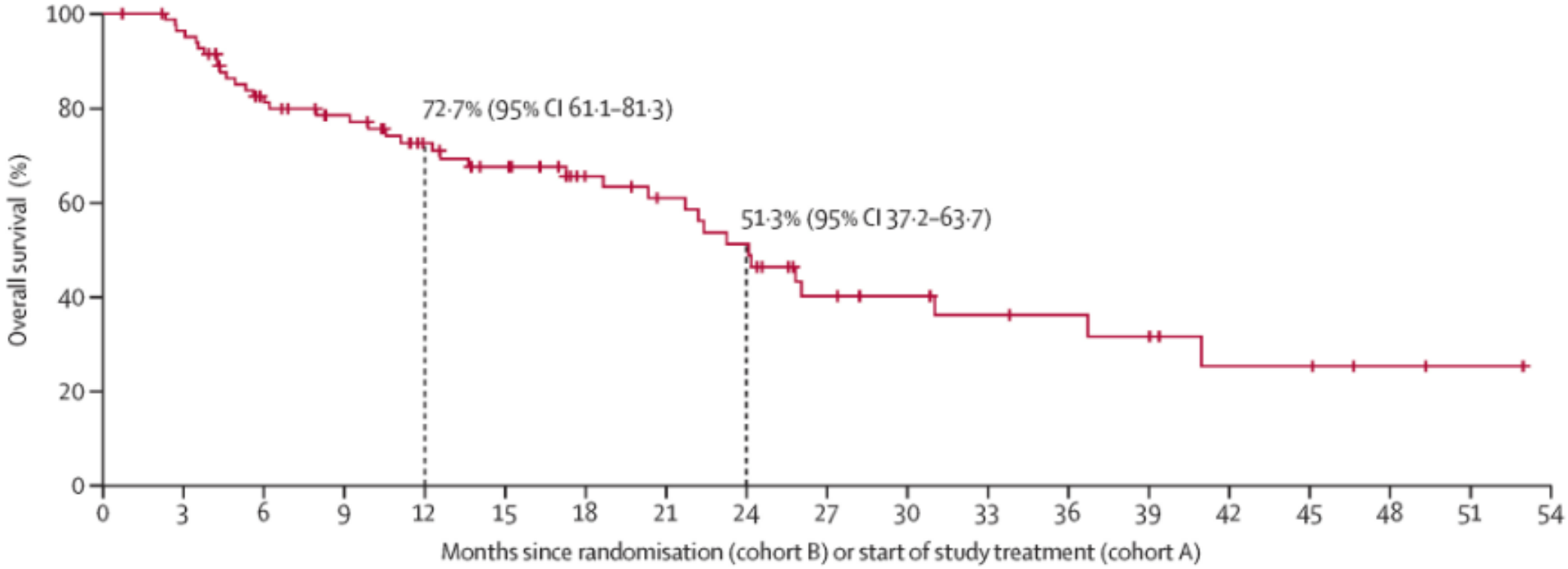
- Tucatinib plus trastuzumab - MOUNTAINEER



Lancet Oncol. 2023;24(5):496.

Second Line therapies – HER2 overexpressors

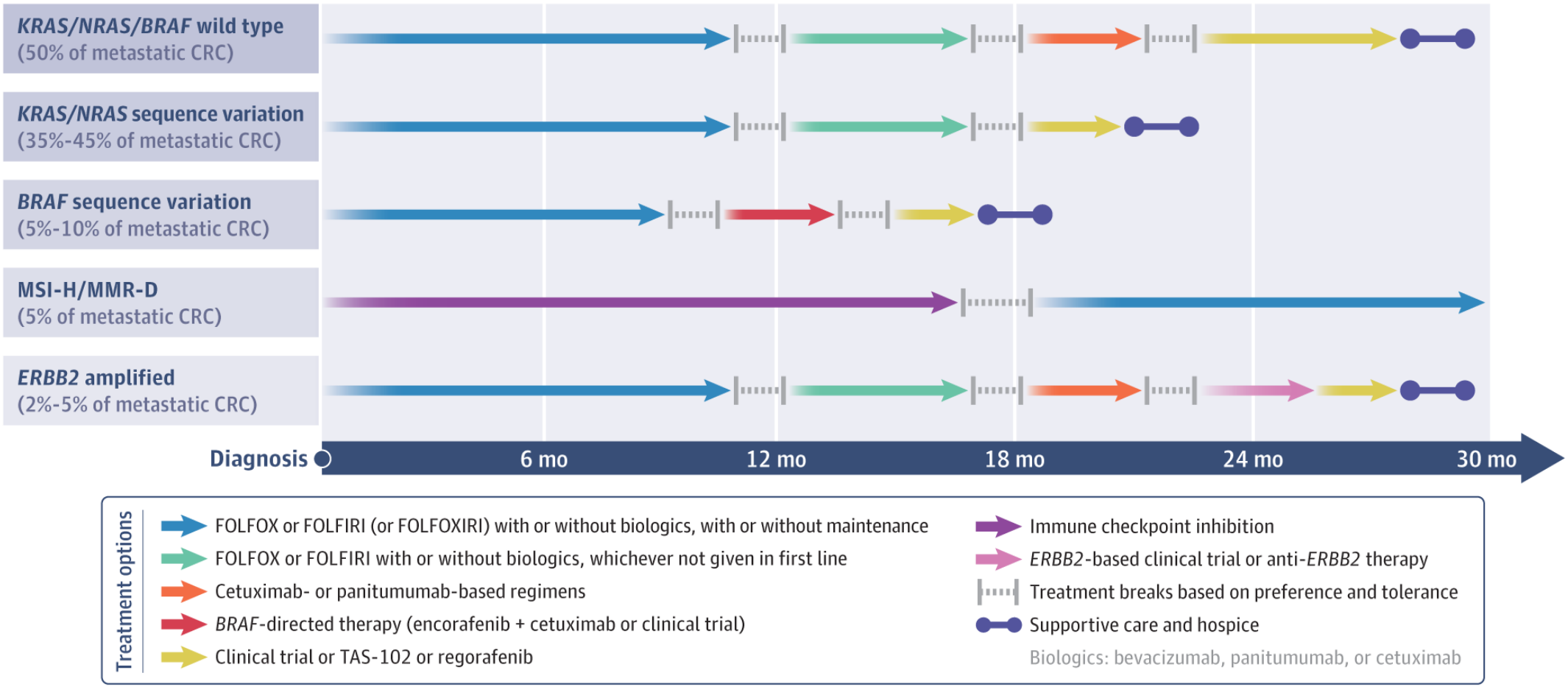
- Tucatinib plus trastuzumab - MOUNTAINEER



Lancet Oncol. 2023;24(5):496.

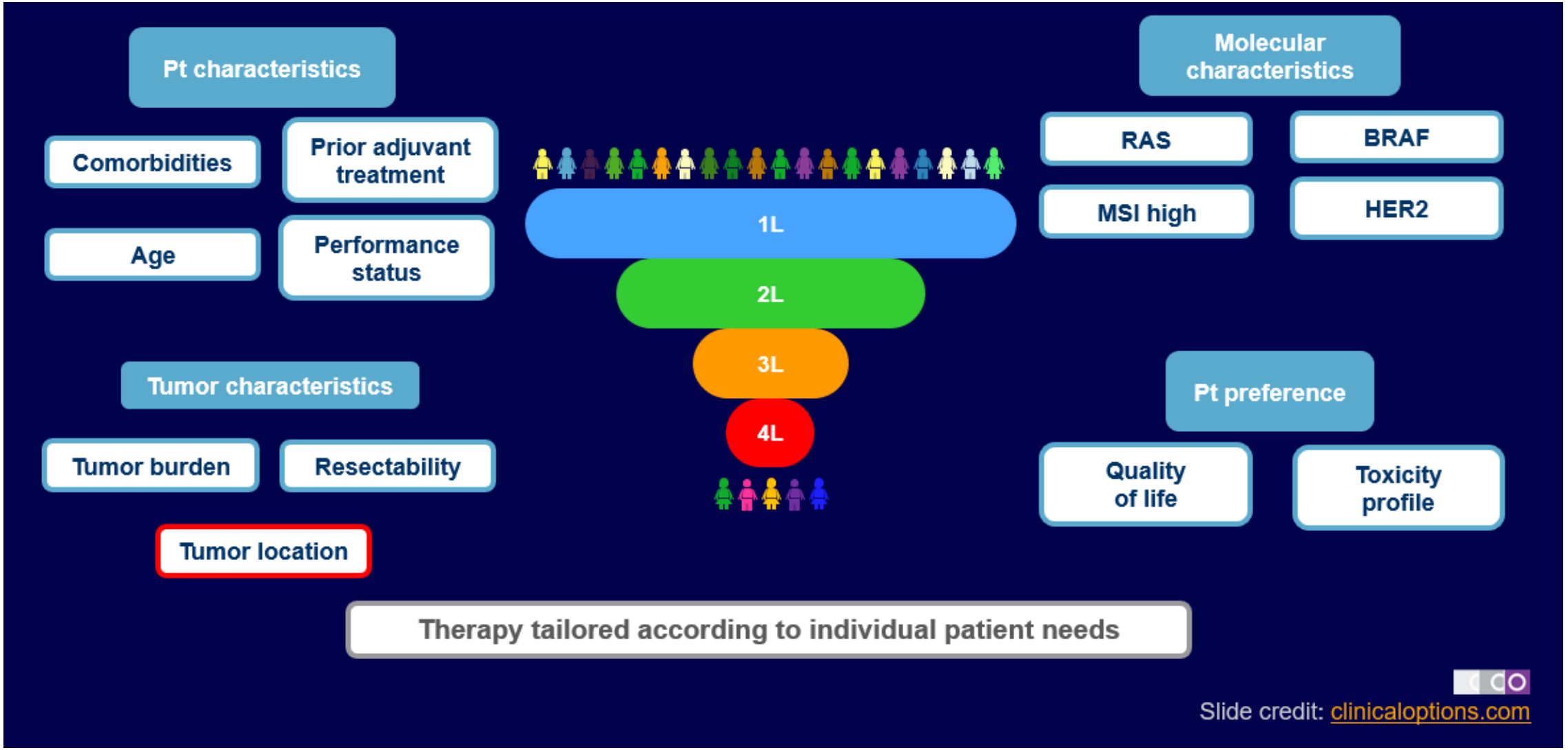
Second Line therapies – HER2 overexpressors

- Trastuzumab plus lapatinib – HERACLES
  - 30% (8/27) objective response; 44% (12/27) stable disease
- Trastuzumab plus pertuzumab – MyPathway
  - 26% (22/84) objective response
- Fam-trastuzumab deruxtecan – DESTINY-CRC01
  - 45% objective response (24/53)
  - Median PFS 7 months, median OS 16



JAMA. 2021;325(7):669-685. doi:10.1001/jama.2021.0106

Treatment Options in Metastatic CRC



Thank you!