
بسم الله الرحمن الرحيم

Immunotherapy of GI Cancers

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Why Does Cancer Occur?

- I now understand that cancer “happens” all the time in all of us
  - Most malignant cells are either cleared by the immune system, undergo DNA repair, or experience apoptosis
- That means that cancers that grow and need treatment, either:
  - Evade the immune system, or
  - Have broken DNA repair and apoptosis mechanisms

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Select Key Validated Biomarkers and Associated Therapies Across GI Cancers

Tumor Type	Molecular Testing Commonly Used (Associated Targeted Agents)
Colorectal	***BRAF* V600E mut** (encorafenib + cetuximab); ***HER2+*** (trastuzumab + pertuzumab or lapatinib; trastuzumab deruxtecan); **MSI-H/dMMR** (pembrolizumab; nivolumab ± ipilimumab)
Gastric/GEJ/esophageal	**PD-L1+** (nivolumab; pembrolizumab); ***HER2+*** (trastuzumab; trastuzumab deruxtecan; pembrolizumab + trastuzumab/fluoropyrimidine- and platinum-containing CT)
Pancreatic	***BRCA1/2* mut** (olaparib)
Cholangiocarcinoma	***FGFR2* mut** (pemigatinib; infigratinib), ***IDH1* mut** (ivosidenib)
Tumor agnostic	**MSI-H/dMMR** (pembrolizumab, dostarlimab); **TMB-H** (pembrolizumab); ***NTRK* fusion** (larotrectinib, entrectinib)

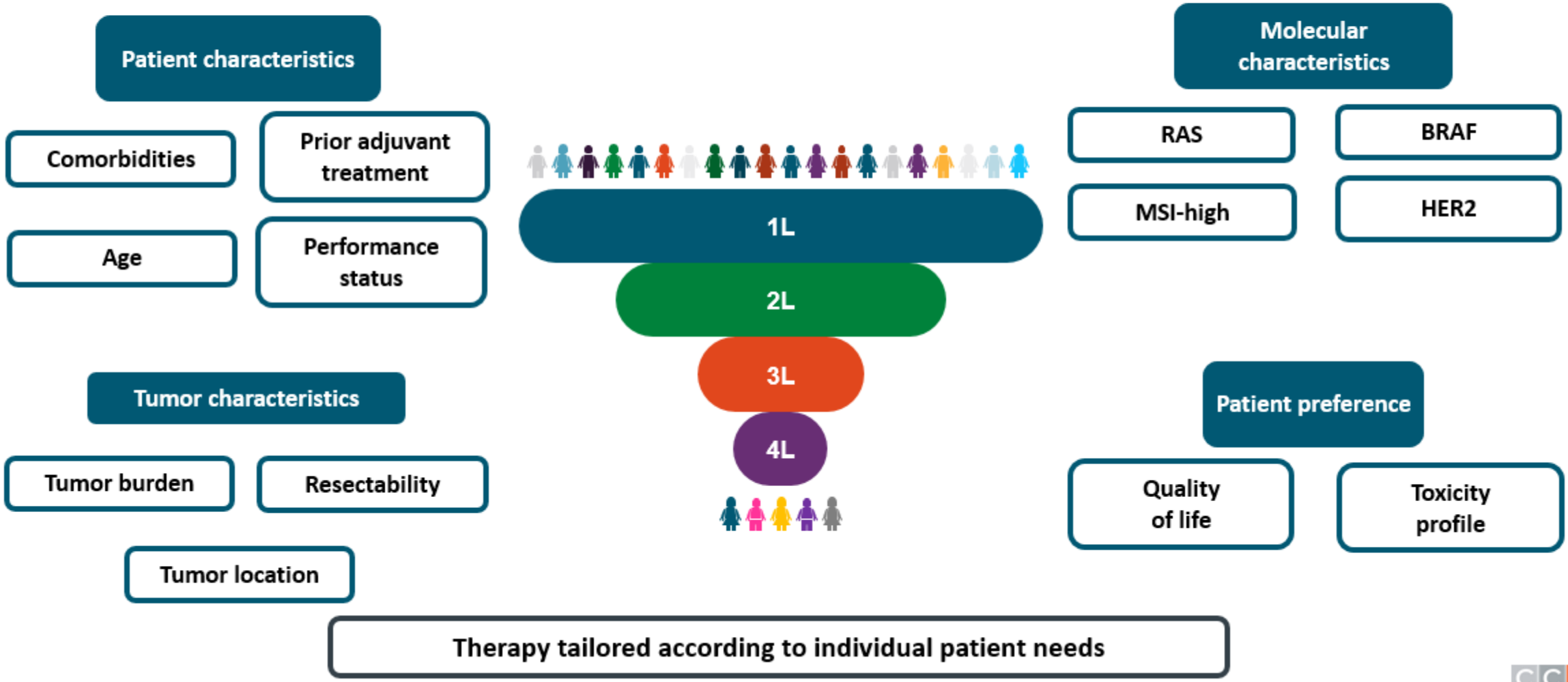
Adapted from Bedard. Lancet. 2020;395;1078.

Slide credit: clinicaloptions.com

Biomarker-Driven Treatment of Advanced Colorectal Cancer

STRONGERTOGETHER

What Influences Treatment Choices in mCRC?

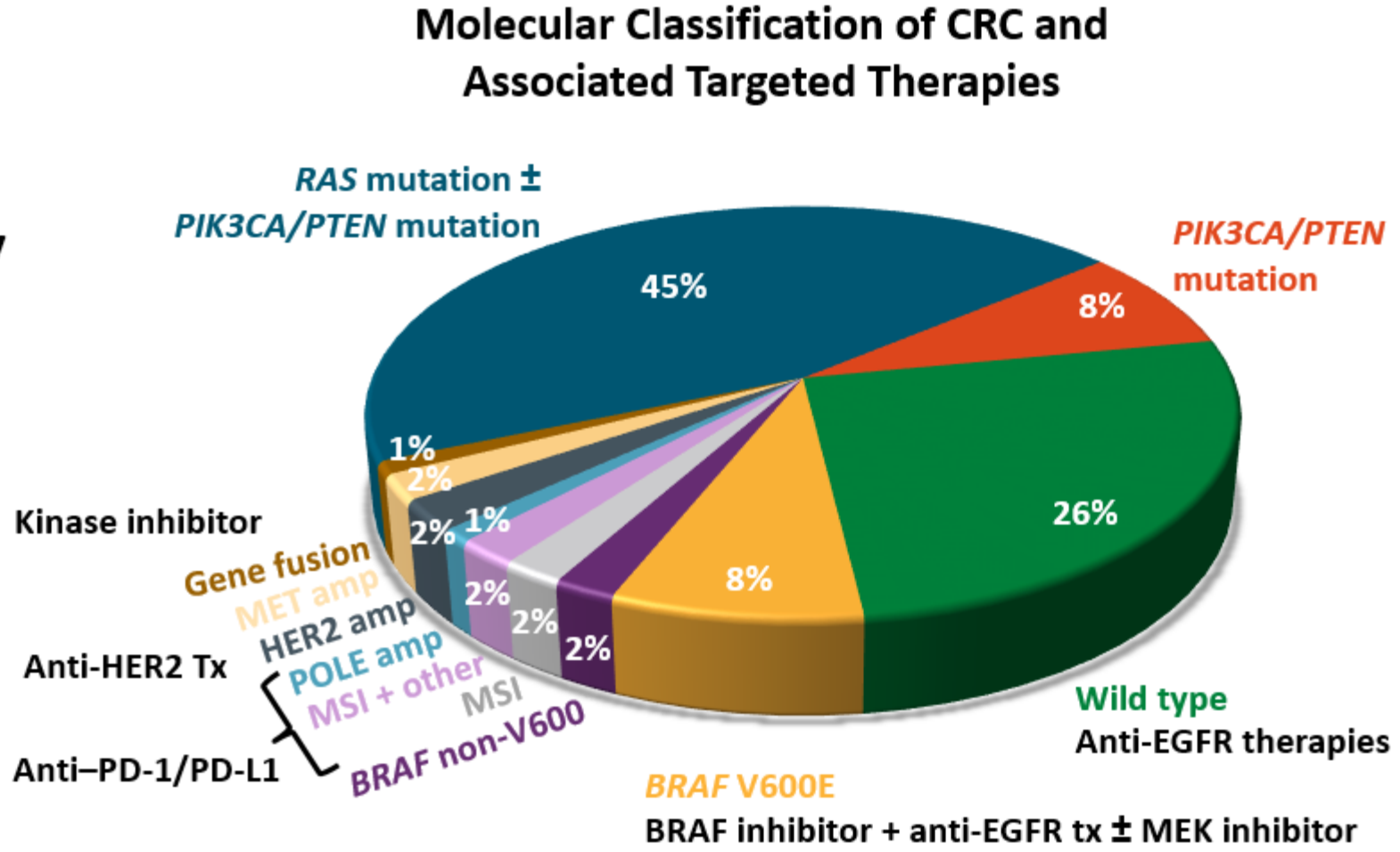


Modified from Van Cutsem. Ann Oncol. 2016;27:1386.

Slide credit: clinicaloptions.com

Biomarker Testing in CRC

- For all colon cancers:
  - **MMR**
  - **Microsatellite stability**
- Metastatic disease:
  - ***KRAS, NRAS, BRAF***
  - ***HER2* amplification**
  - **Panels: ± fusion, broad NGS**



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

Slide credit: clinicaloptions.com

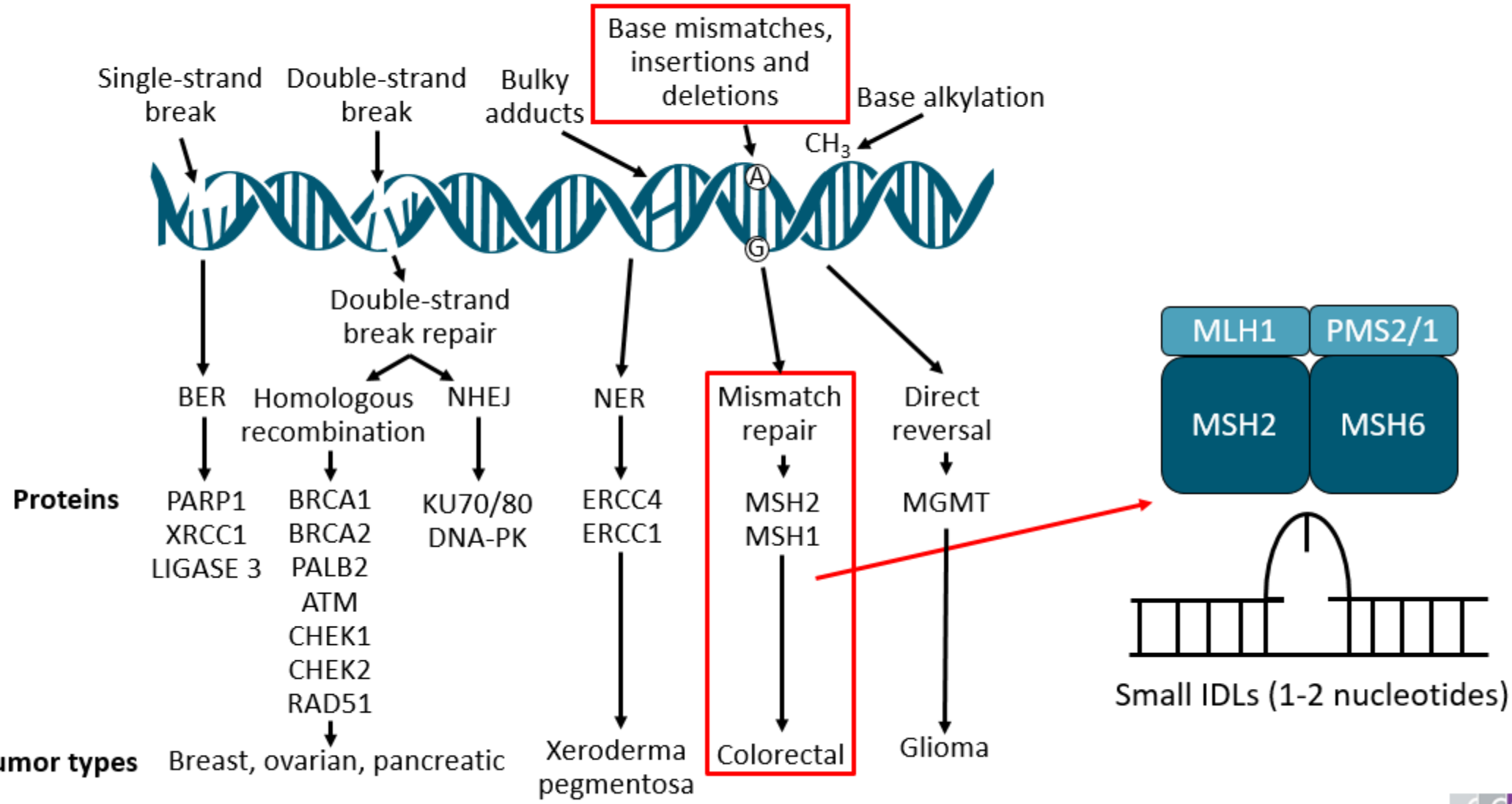
General Treatment Algorithm for Metastatic CRC

	BRAF/RAS wt	*RAS* mut	*BRAF* V600 mut	MSI-H/dMMR	*NTRK* fusion	*HER2* amplification
1L	*R side*: CT + bev *L side*: CT + EGFRi or bev[1-4]	CT + bev[5-7]	FOLFOXIRI + bev or Doublet + bev	Pembrolizumab	As with *BRAF/RAS* wt	
	Consider capecitabine + bev maintenance[9]					
2L	CT as with *RAS* mut; If bev: in 1L continue bev or change to EGFRi If EGFRi in 1L, bev	*If prior oxaliplatin*: irinotecan-based regimen + bev *If prior irinotecan*: oxaliplatin-based regimen + bev *If prior FOLFOXIRI*: regorafenib[11] or TAS-102 ± bev[12,13]	Consider encorafenib + EGFRi i[14]; otherwise, CT + bevacizumab	*If no prior PD-1i*: PD-1i ± CTLA-4i*; otherwise, CT/TT as with *BRAF/RAS* wt	*If no prior TRK inhibitor*: consider larotrectinib or entrectinib[15,16]; otherwise, CT/TT as with *BRAF/RAS* wt	Consider trastuzumab (+ pertuzumab or lapatinib) or trastuzumab deruxtecan[17-19]; otherwise, CT/TT as with *BRAF/RAS* wt
3L+	*If prior oxaliplatin- and irinotecan-based regimens*: regorafenib or TAS-102 ± bev					

CT, chemotherapy regimens, including oxaliplatin- and/or irinotecan-based regimens (eg, FOLFOX, FOLFIRI, FOLFOXIRI, CAPOX). EGFRi, EGFR inhibitors, including cetuximab or panitumumab.
*If prior PD-1i monotherapy only, can consider PD-1i + CTLA-4i.

1. Tejpar. JAMA Oncol. 2017;3:194. 2. Venook. JAMA. 2017;317:2392. 3. Loupakis. NEJM. 2014;371:1609. 4. Cremolini. Lancet Oncology. 2020;21:497.
5. Parikh. Clin Cancer Res. 2019;25:2988. 6. Douillard. NEJM. 2013;369:1023. 7. Van Cutsem. JCO. 2011;29:2011. 8. Overman. Lancet Oncol. 2017;18:1182.
9. Overman. JCO. 2018;36:773. 10. Van Cutsem. NEJM. 2020;383:2207. 11. Grothey. Lancet. 2013;381:303. 12. Mayer. NEJM. 2015;372:1909. 13. Pfeiffer. Lancet Oncology. 2020;21:412. 14. Tabernero. JCO. 2021;39:273. 15. Hong. Lancet Oncol. 2020;21:531. 16. Doebele. Lancet Oncol. 2020;21:271.
17. Sartore-Bianchi. Lancet Oncol. 2016;17:738. 18. Meric-Bernstam. Lancet Oncol. 2019;20:518. 19. Siena. Lancet Oncol. 2021;22:779.

DNA Repair Mechanisms



Lord. Nature. 2012; 481:287. Martin. Clin Cancer Res. 2010;16:5107.

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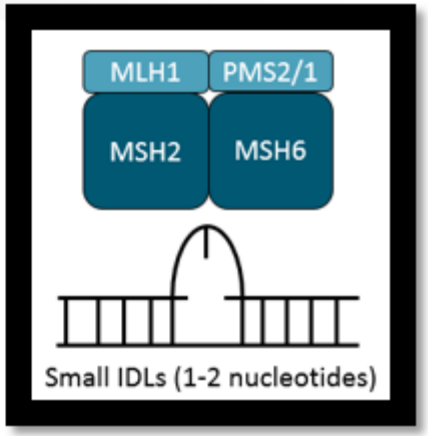
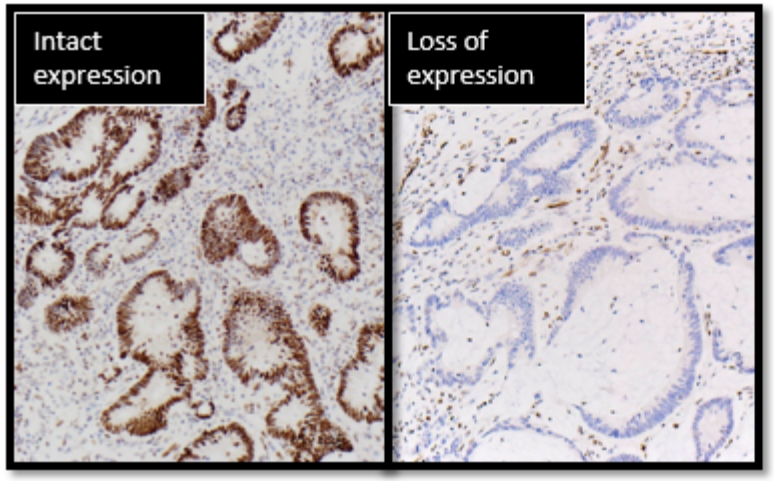
dMMR Testing: Methods



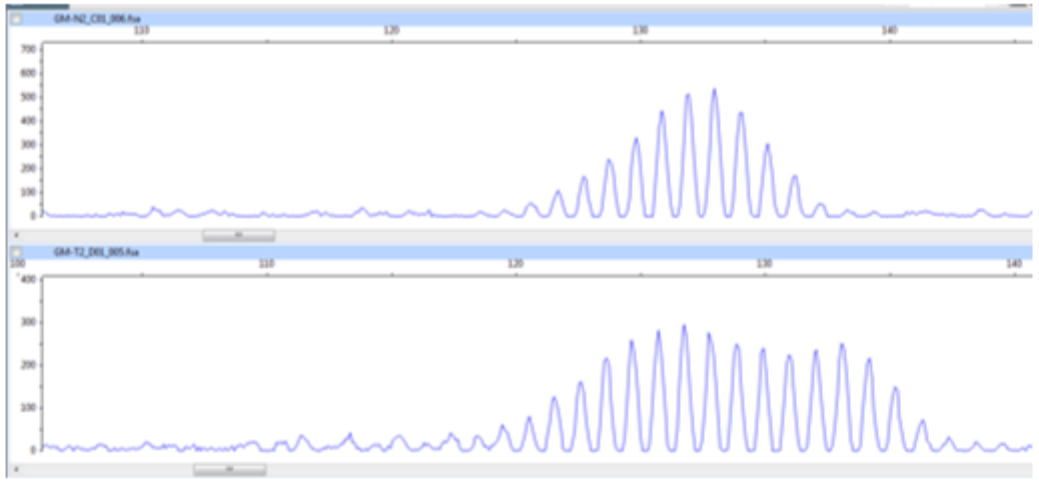
IHC

Complete loss of expression in one of the MMR proteins = MSI high



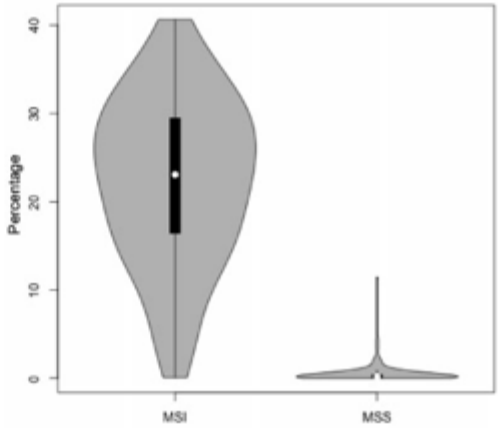
PCR

Panel of 5 or more microsatellites with allelic shift in 2 (> 30%) or more markers = MSI high



Next-Generation Sequencing

Differentiates microsatellite instable vs microsatellite stable samples



Niu. Bioinformatics. 2014;30:1015. Martin. Clin Cancer Res. 2010;16:5107.

Slide credit: clinicaloptions.com

Interpreting MSI Status

- A loss (ie, “reduced” or “deficient”) in any of these proteins—MLH1, MSH2, PMS2, and MSH6—suggests potential MSI-H status and warrants further testing with PCR to confirm MSI-H
- Some facilities only test for PMS2 and MSH6; the intact presence of these 2 markers alone is insufficient to rule out MSI-H status
- If all 4 proteins are intact (or “expressed,” “retained,” “present”) tumor is microsatellite stable and unlikely to respond to checkpoint inhibitor monotherapy . . . most of the time

Kawakami H, et al. Curr Treat Options Oncol. 2015;16:30.

Slide credit: clinicaloptions.com

Microsatellite Testing Options

- IHC and PCR can be used to determine microsatellite status and are likely equally efficacious

IHC

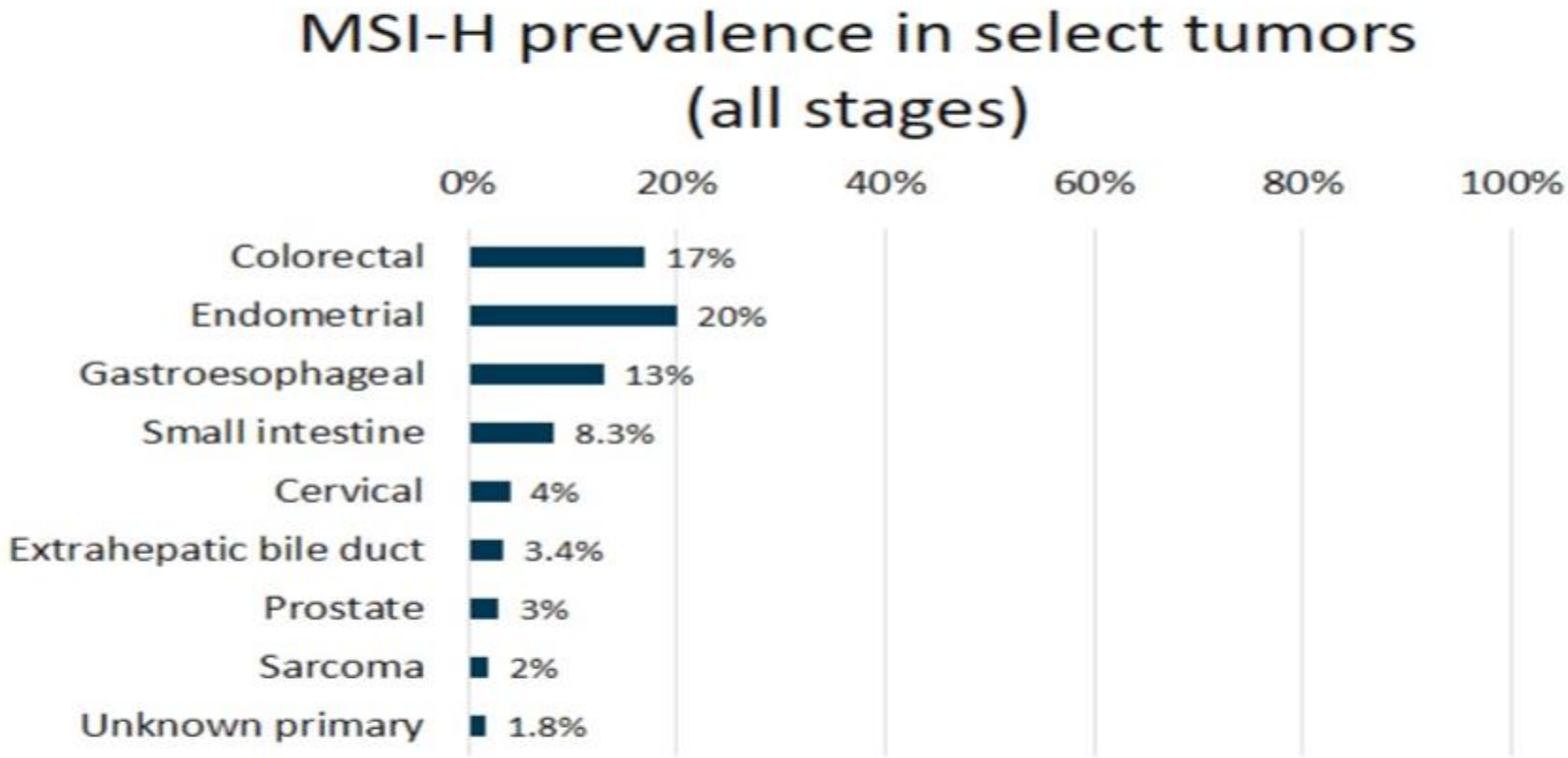
- Assesses for protein products of specific MMR genes (ie, *MLH1*, *MSH2*, *MSH6*, and *PMS2*)
- Classifies tumor as MSI or MSS
  - **MSI:** loss of at least 1 of MLH1, MSH2, MSH6, and/or PMS2 proteins, indicating tumor is MMR deficient
  - **MSS:** all proteins are retained, indicating tumor is pMMR
- When test report reads "positive for expression," it means MSS and should not be misinterpreted as MSI

PCR

- Assesses for 5 microsatellite markers and compares them with normal DNA from same patient
  - **2 mononucleotides:** BAT25 and BAT26
  - **3 dinucleotides:** D2S123, D5S346, and D17S250
- Classifies tumor as high (MSI-H), low (MSI-L), or stable (MSS)
  - **MSI-H:** ≥2 markers show instability
  - **MSI-L:** 1 marker shows instability
  - **MSS:** no markers show instability

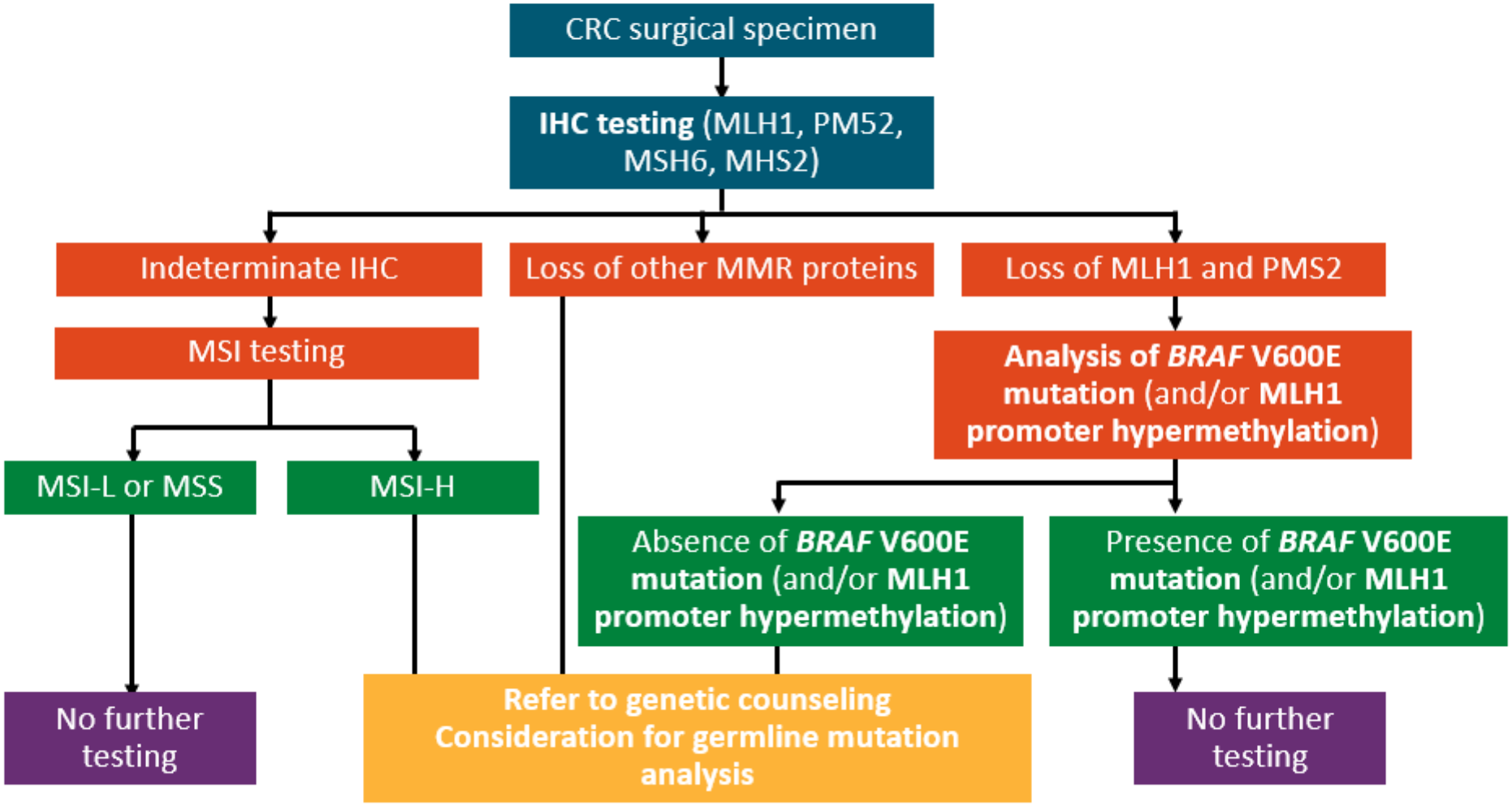
Kawakami H, et al. *Curr Treat Options Oncol*. 2015;16:30.

Microsatellite Instability in Cancer



Luchini C, et al. *Ann Oncol.* 2019. [Epub ahead of print]

Algorithm for MSI Testing in CRC



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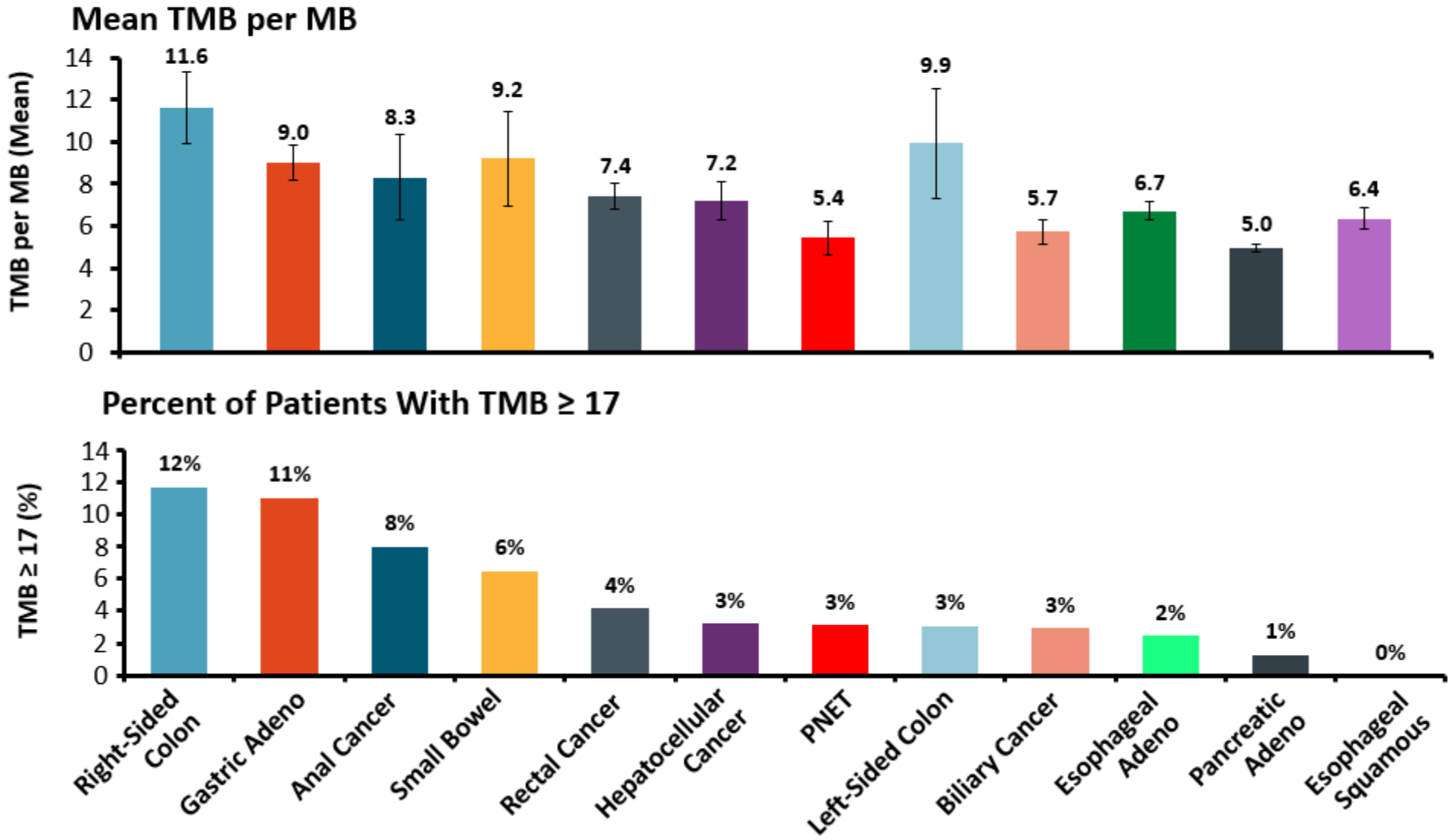
Relationship Between MSI and TMB

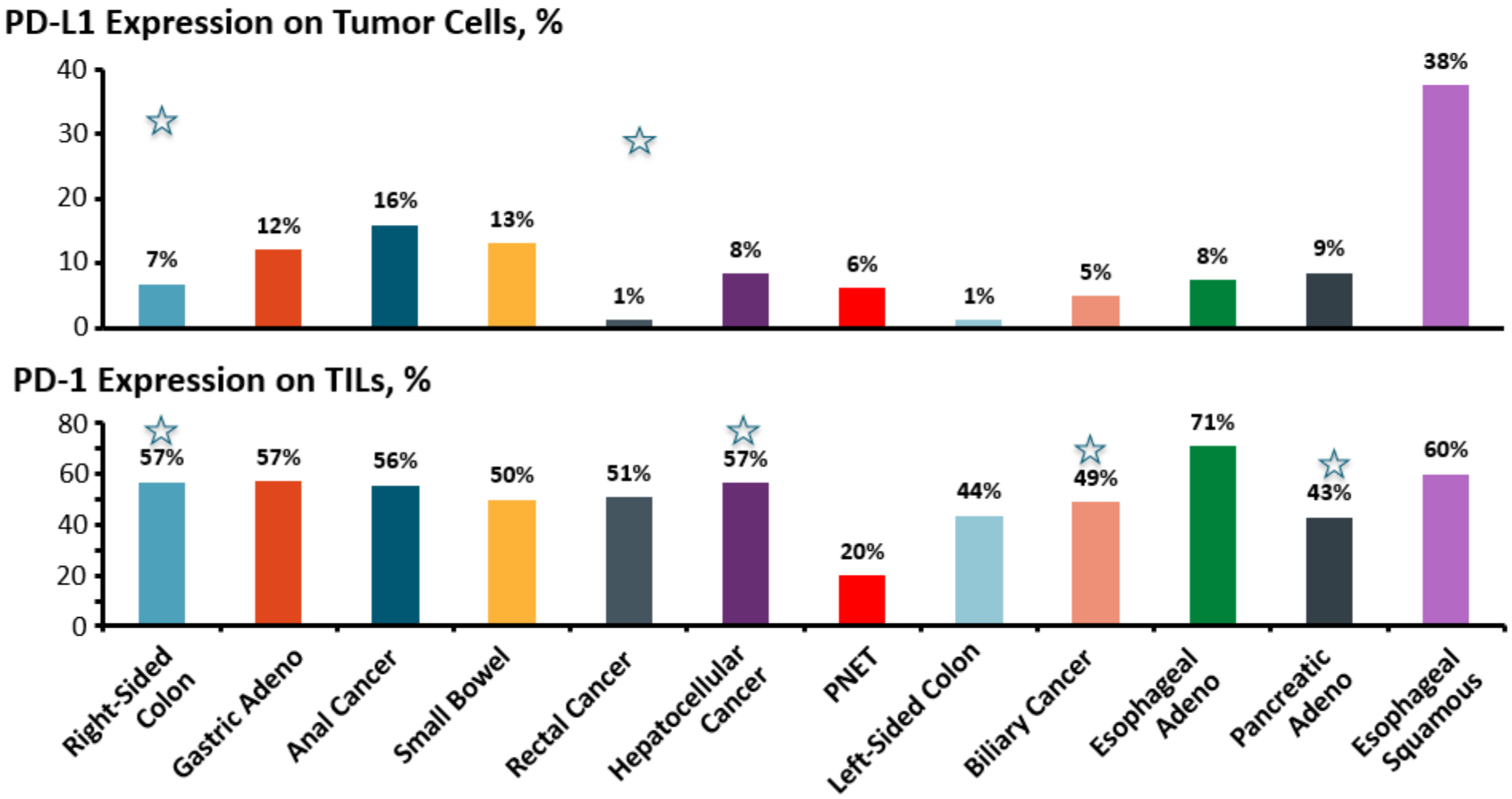
Tumor Mutation Burden Across GI Cancers



Salem ME, et al. ASCO GI 2017. Abstract 530.

Slide credit: clinicaloptions.com

PD-1/PD-L1 Expression Across GI Cancers

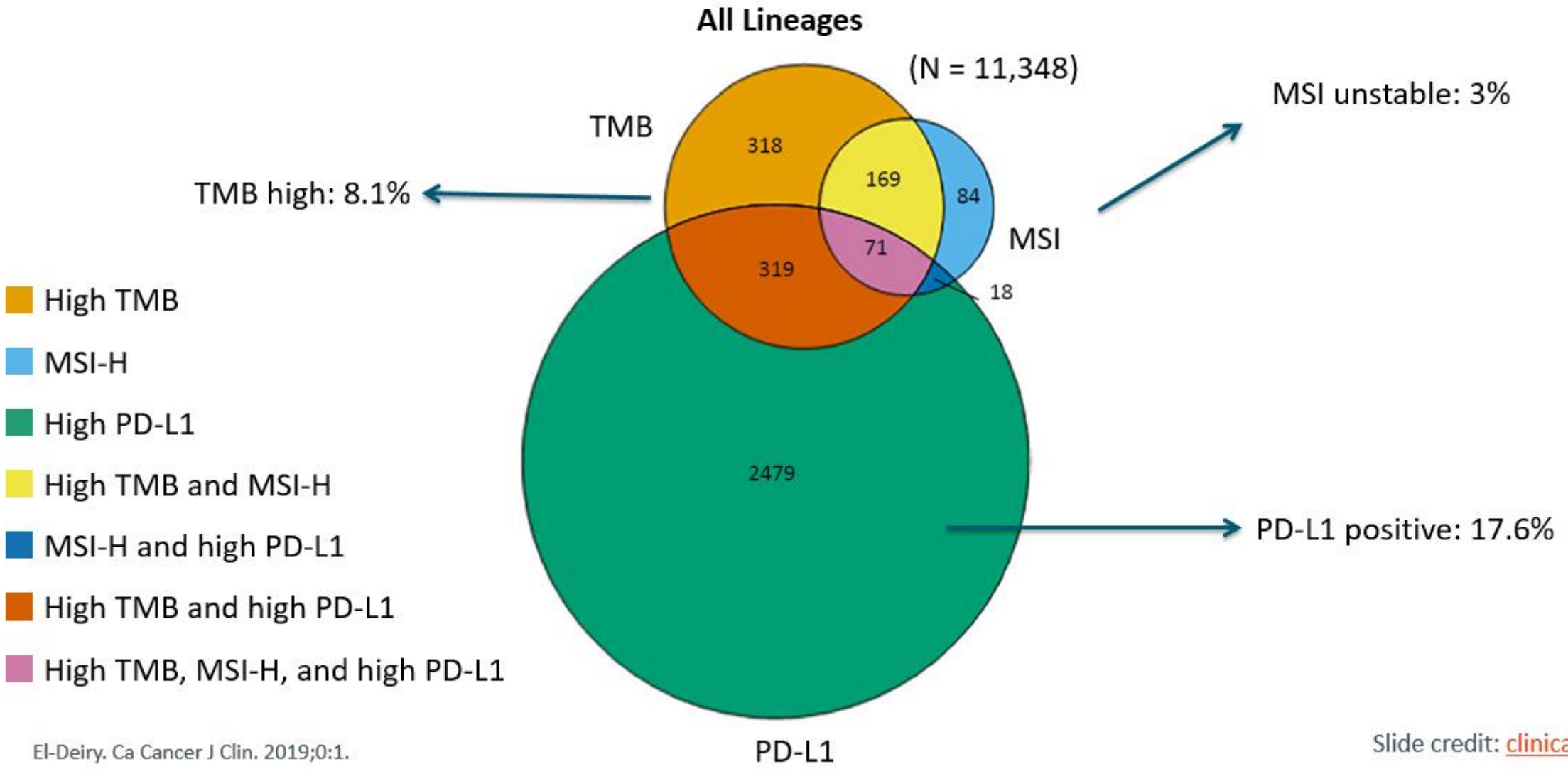


☆ = correlation of PD-1/PD-L1 expression with TMB ($P < .05$)

Salem ME, et al. ASCO GI 2017. Abstract 530.

Slide credit: clinicaloptions.com

Relationship Between MSI, TMB, and PD-L1



El-Deiry. Ca Cancer J Clin. 2019;0:1.

Slide credit: clinicaloptions.com

MSI and TMB: Conclusions

- TMB varies significantly across MSI-H tumors
- Loss of expression of the MSH2/MSH6 heterodimer by IHC associated with higher mean TMB than loss of the MLH1/PMS2 heterodimer
- MSI-H CRC carries the highest TMB compared with MSI-H endometrial cancers and others MSI-H solid tumors, consistent with the different prevalence of MSH2/6 protein loss
- These data support gene-specific and disease site–specific heterogeneity among MSI-H tumors, which may partially explain the different responses seen to immune checkpoint inhibitor therapy

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Current Indications for Immune Checkpoint Inhibitors in MSI-H/dMMR Cancer

- Pembrolizumab for **MSI-high/mismatch repair–deficient unresectable or metastatic CRC** with PD after a fluoropyrimidine, oxaliplatin, and irinotecan
- Pembrolizumab for **MSI-high/mismatch repair–deficient unresectable or metastatic solid tumors** with PD after prior treatment and no satisfactory alternative treatments
- Nivolumab ± ipilimumab for **MSI-high/mismatch repair–deficient metastatic CRC** with PD after a fluoropyrimidine, oxaliplatin, and irinotecan

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Tumor-Agnostic FDA Indications for Pembrolizumab in Solid Cancers

- Unresectable or metastatic **MSI-H or MMR deficient solid tumors** with PD after previous treatment with no satisfactory alternative treatment options
  - Assessed in several trials, including KEYNOTE-016, -164, -012, -028, -158, and -177
- Unresectable or metastatic **TMB-H (≥10 mut/Mb) solid tumors** with PD after previous treatment with no satisfactory alternative treatment options
  - KEYNOTE-158

Accelerated approvals.

Pembrolizumab PI.

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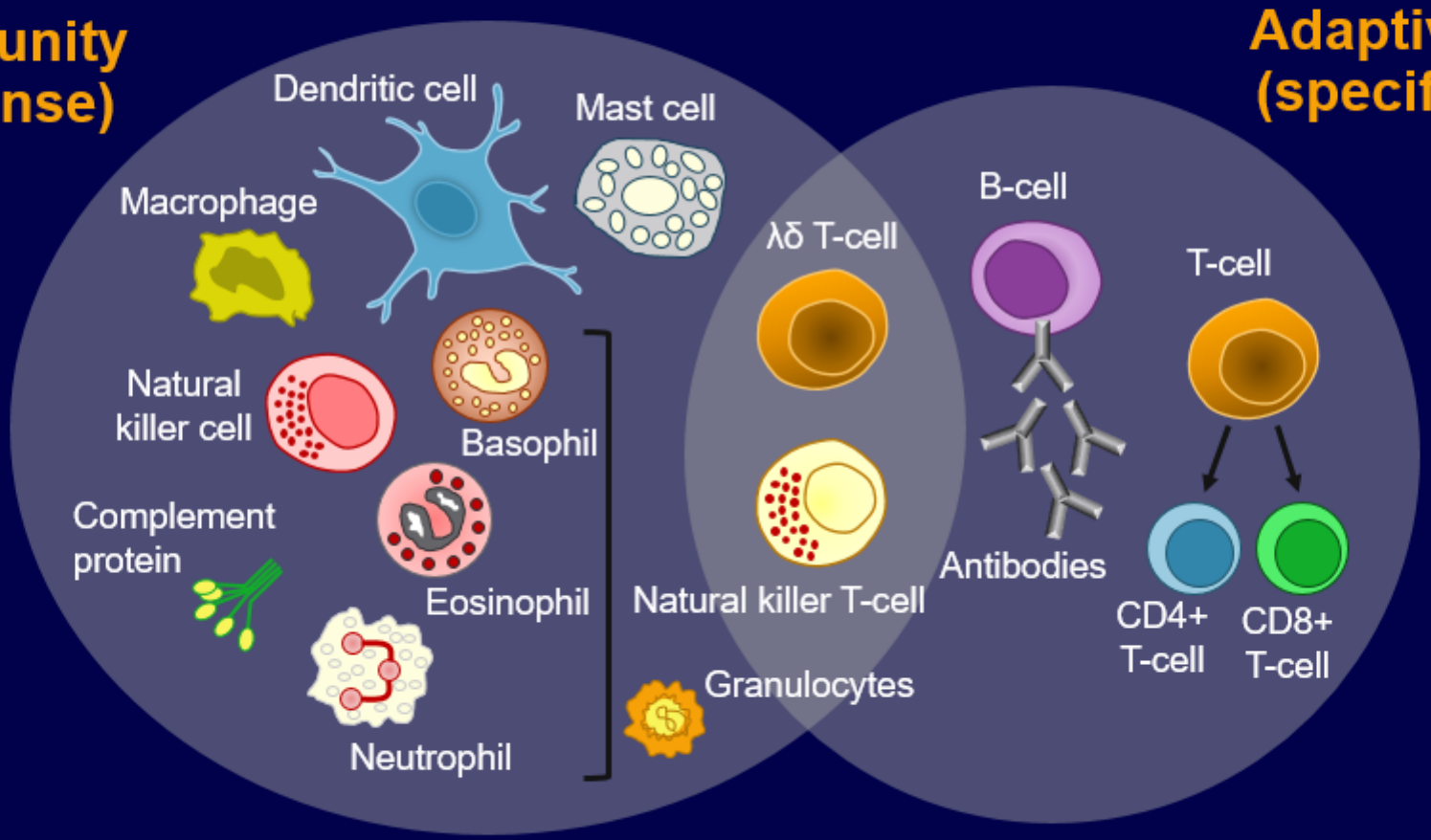
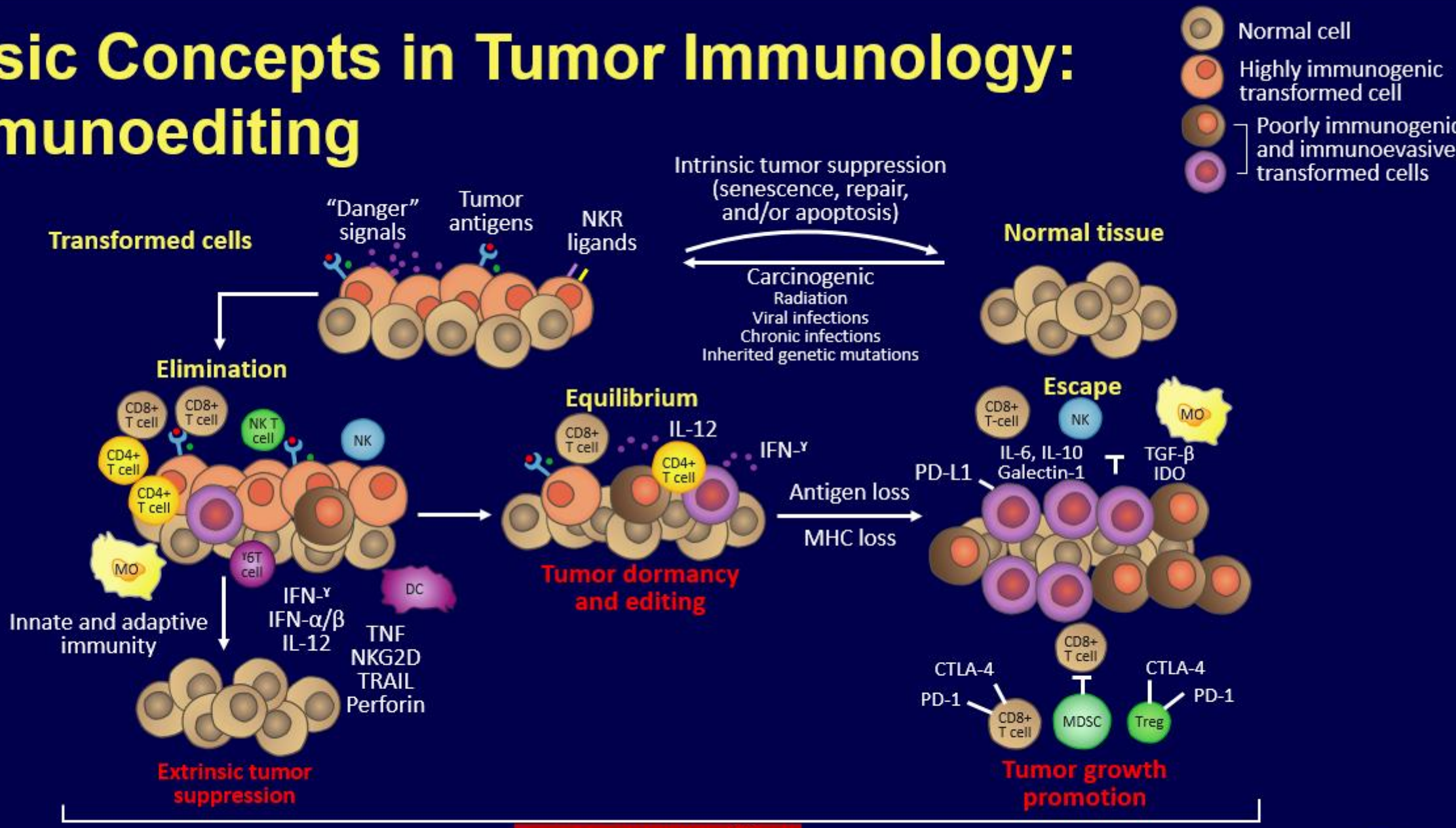
Immune System Function and Immune Response



Janeway CA Jr, et al. Immunobiology: the immune system in health and disease. 2001.

Slide credit: clinicaloptions.com

Basic Concepts in Tumor Immunology: Immunoediting



From Schreiber RD, et al. Science. 2011;331:1565-1570. Reprinted with permission from AAAS.

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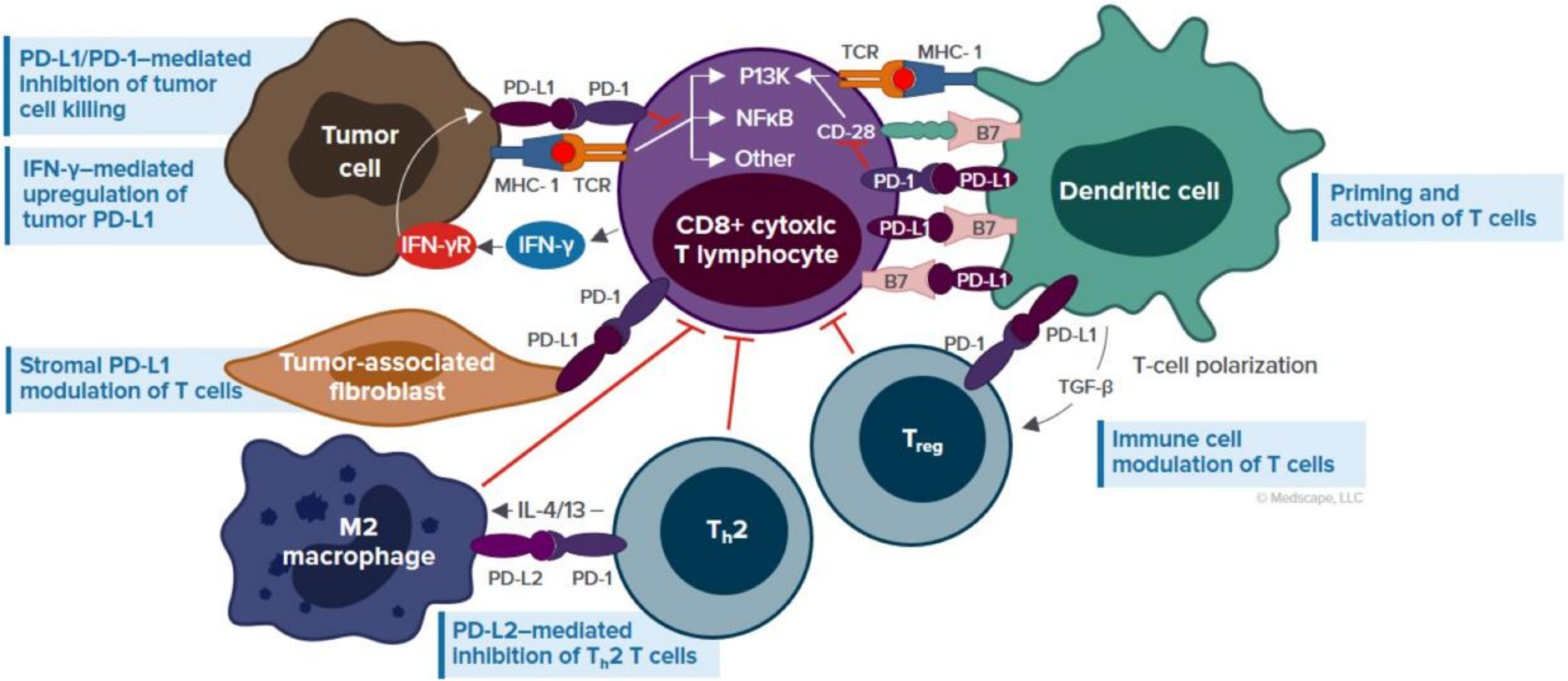
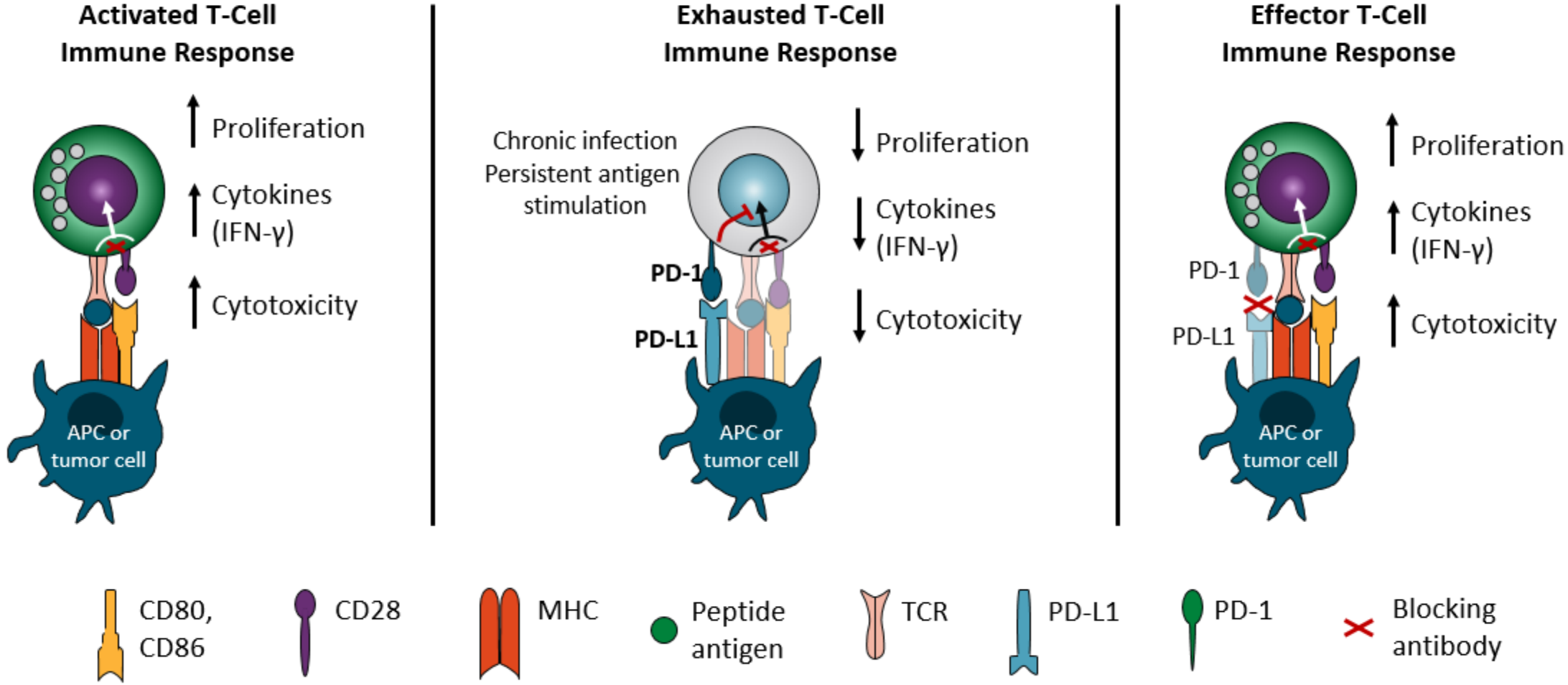
Immunologic Synapses Within Tumor Microenvironment

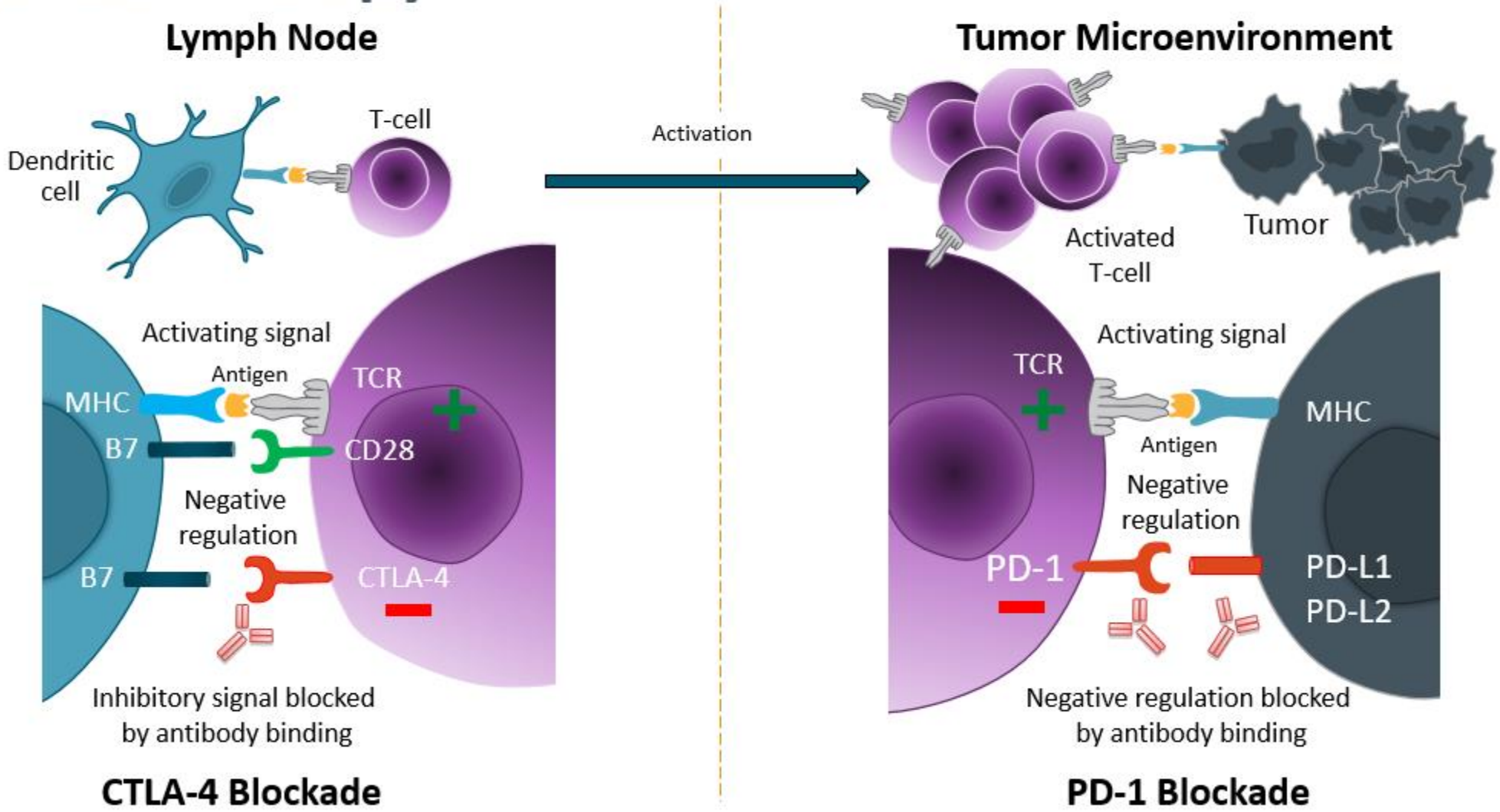


Sznol M, et al. Clin Cancer Res. 2013;19:1021-34.

T-Cell Exhaustion and Reinvigoration



Biologic Rationale for Immune Checkpoint Inhibition as Cancer Therapy



Adapted from Ribas. NEJM. 2012;366:2517.

Slide credit: clinicaloptions.com

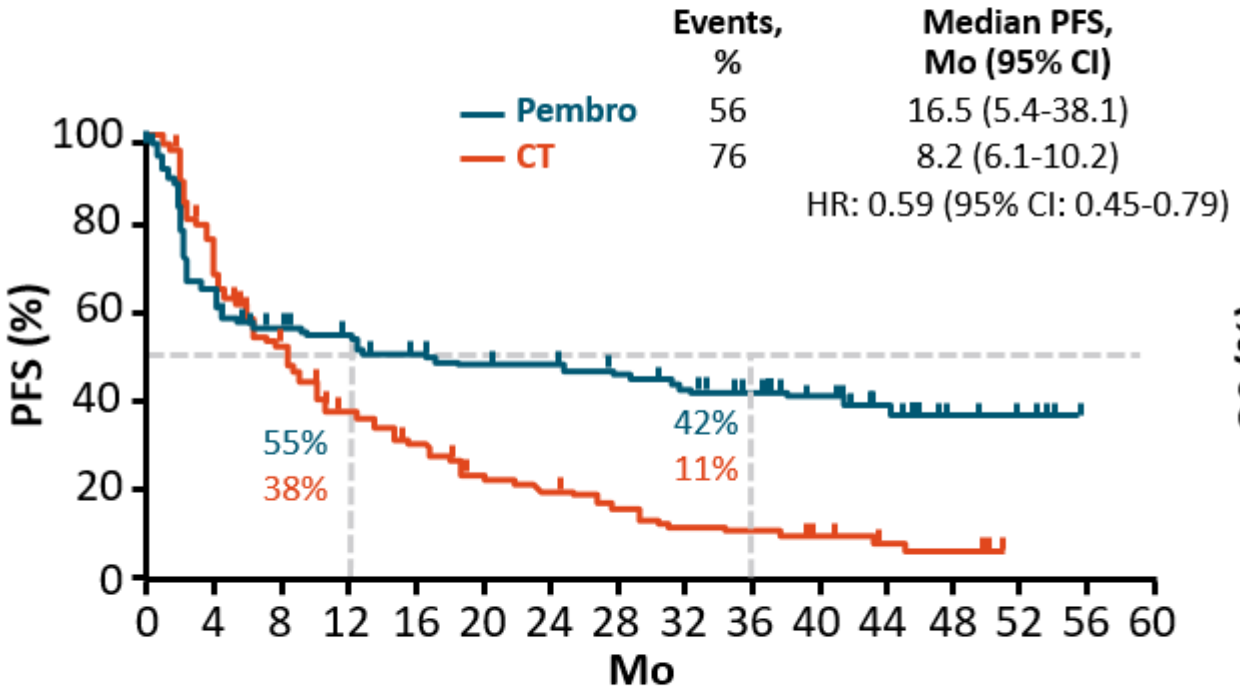
Tumor Agnostic and GI-Specific FDA Indications for MSI-H/dMMR Tumors

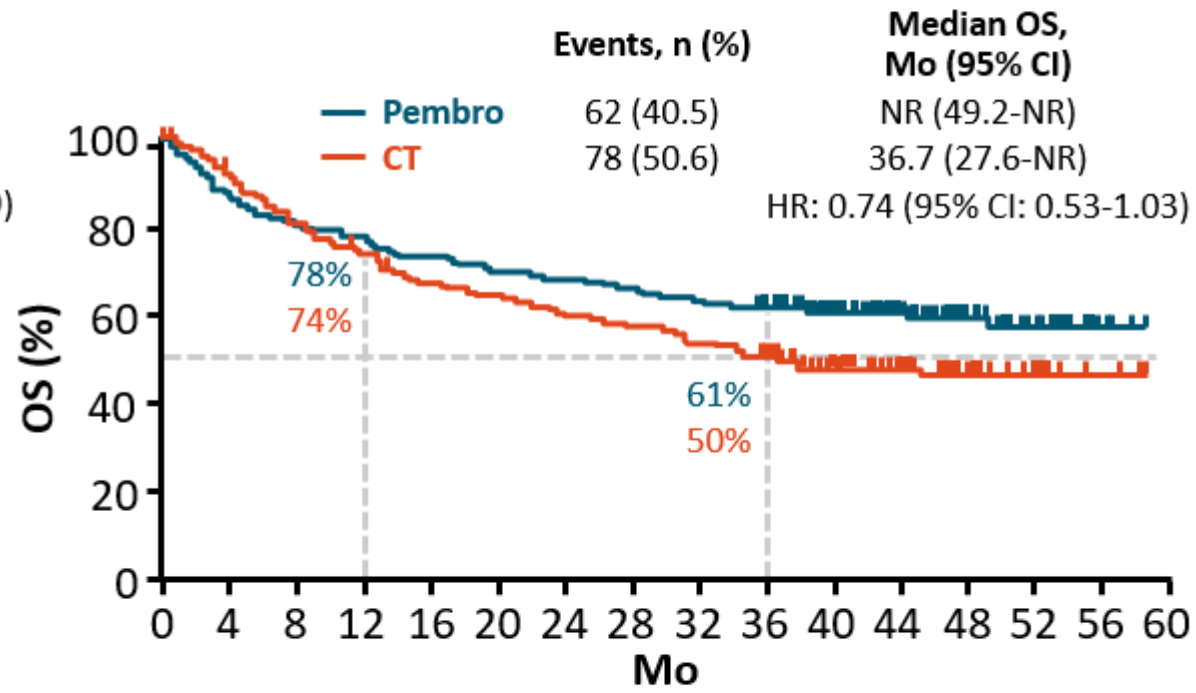
Treatment	Indication	Key Supporting Trials
Pembrolizumab	▪ Unresectable/metastatic **MSI-H or dMMR solid tumors** with PD after previous treatment with no satisfactory alternative treatment options ▪ Unresectable/metastatic **TMB-H (≥10 mut/Mb) solid tumors** with PD after previous treatment with no satisfactory alternative treatment options ▪ Unresectable/metastatic **MSI-H/dMMR CRC**	▪ KEYNOTE-016, -164, -012, -028, -158, -177 ▪ KEYNOTE-158 (ORR: 18%-45% in non-CRC GI cancers) ▪ KEYNOTE-177 (see next)
Dostarlimab	▪ Unresectable/metastatic **dMMR solid tumors** with PD after previous treatment with no satisfactory alternative treatment options	▪ GARNET (ORR: 36% in CRC and 43% in non-CRC GI cancers)
Nivolumab ± ipilimumab	▪ Metastatic **MSI-H/dMMR CRC** with PD after fluoropyrimidine, oxaliplatin, and irinotecan	▪ CheckMate-142 (ORR: 55% w/ nivo + ipi, 31% w/ nivo in recurrent CRC; 69% with nivo + ipi in mCRC with no prior treatment)

Nivolumab PI. Pembrolizumab PI. Dostarlimab PI. Marabelle. JCO. 2020;38:1. Andre. ASCO GI 2021. Abstr 9. Overman. JCO. 2018;36:773. Lenz. JCO. 2022;40:161.

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%

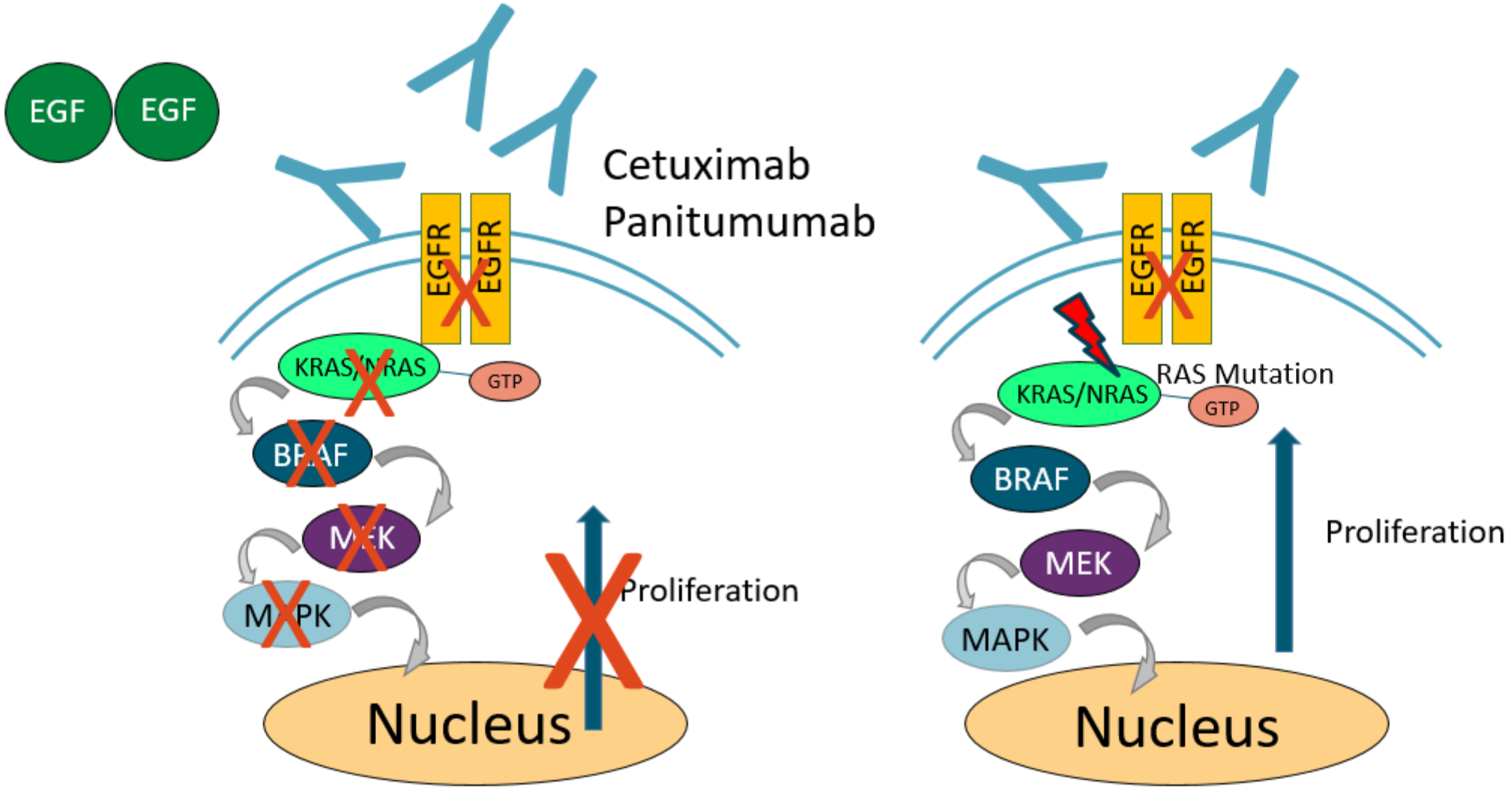
*mFOLFOX-6 ± bevacizumab or cetuximab or FOLFIRI ± bevacizumab or cetuximab.

André. ASCO 2021. Abstr 3500.

Slide credit: clinicaloptions.com

RAS and *BRAF* Mutations: Impact on Therapy

EGFR Inhibitors and Key Mutations in CRC



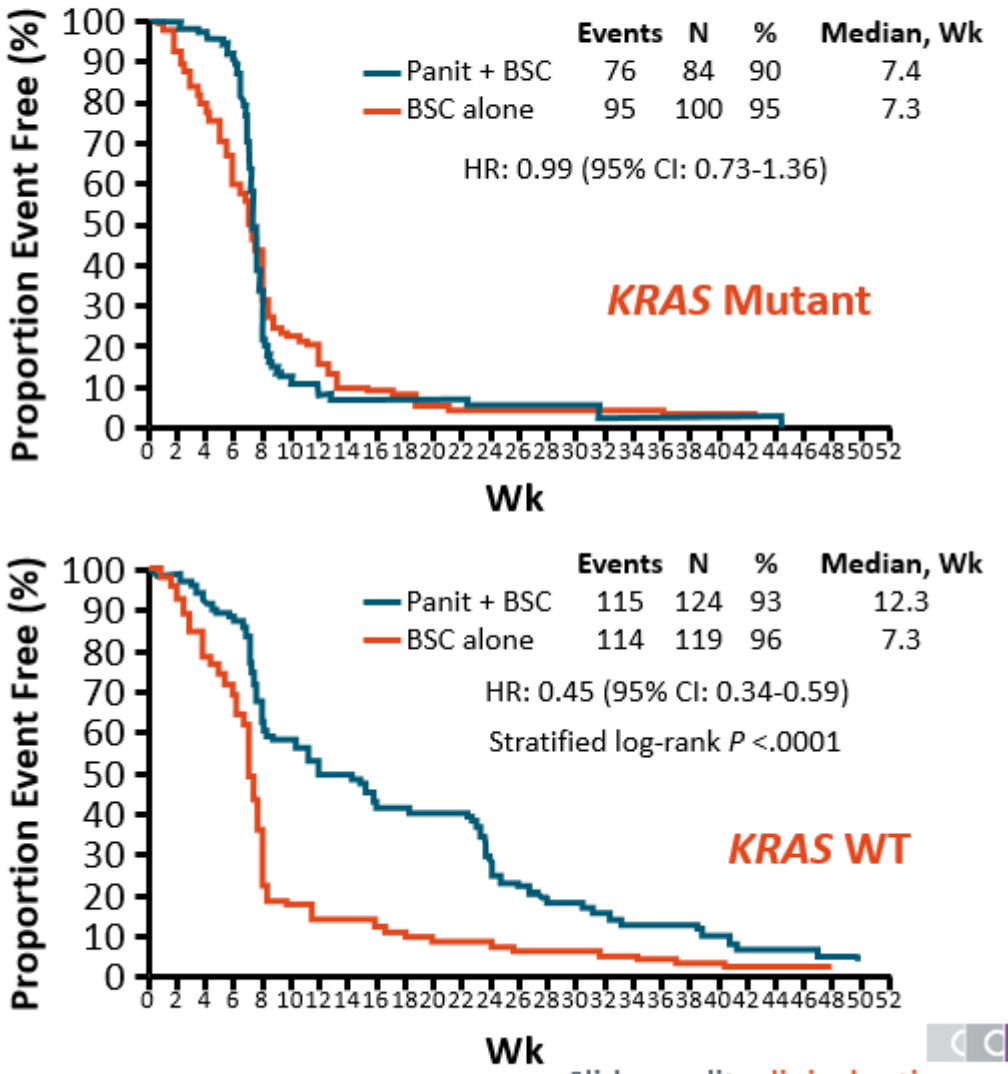
1. Porru. J Exp Clin Cancer Res. 2018;37:57. 2. Allegra. JCO. 2016;34:179.
3. Al-Shamsi. J Gastrointest Oncol. 2015;6:314. 4. Gong. J Gastrointest Oncol. 2016;7:687.

Slide credit: clinicaloptions.com

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]

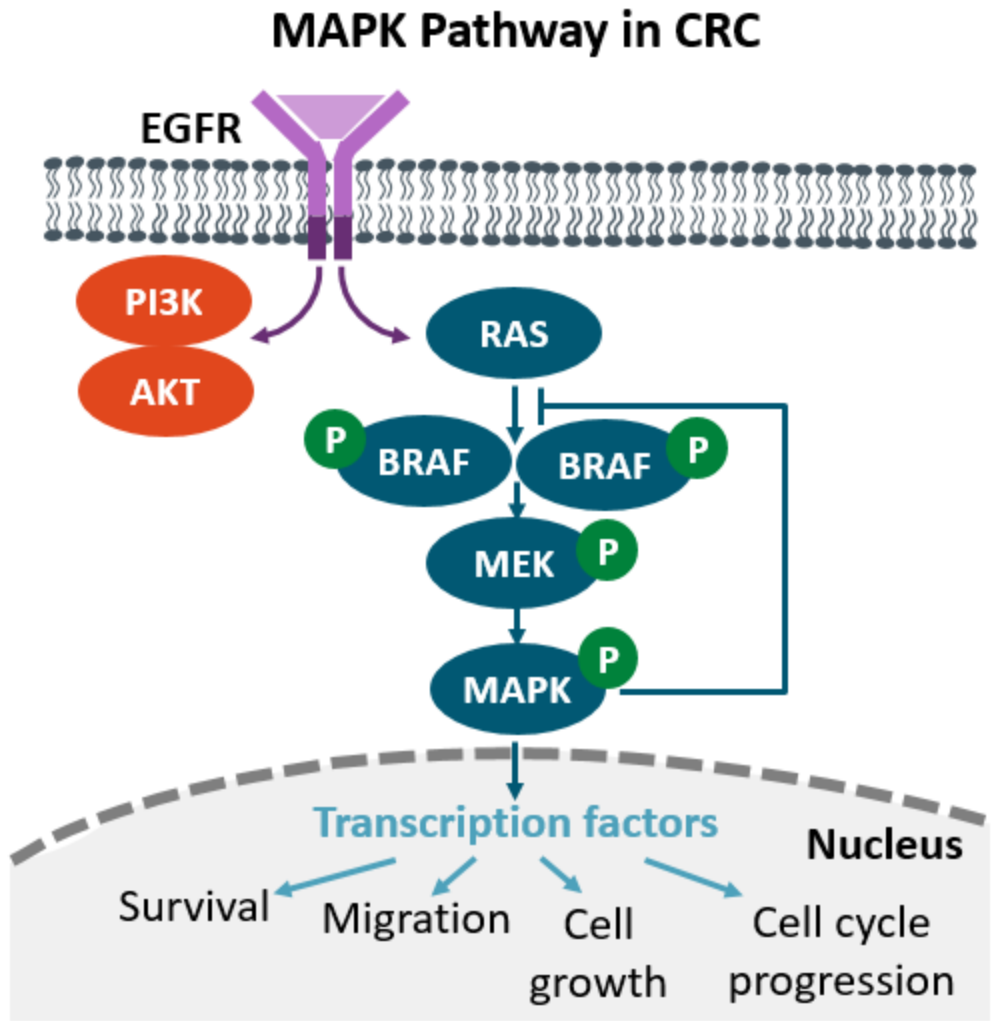


1. Porru. J Exp Clin Cancer Res. 2018;37:57. 2. Allegra. JCO. 2016;34:179.
3. Al-Shamsi. J Gastrointest Oncol. 2015;6:314. 4. Gong. J Gastrointest Oncol. 2016;7:687.

Slide credit: clinicaloptions.com

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

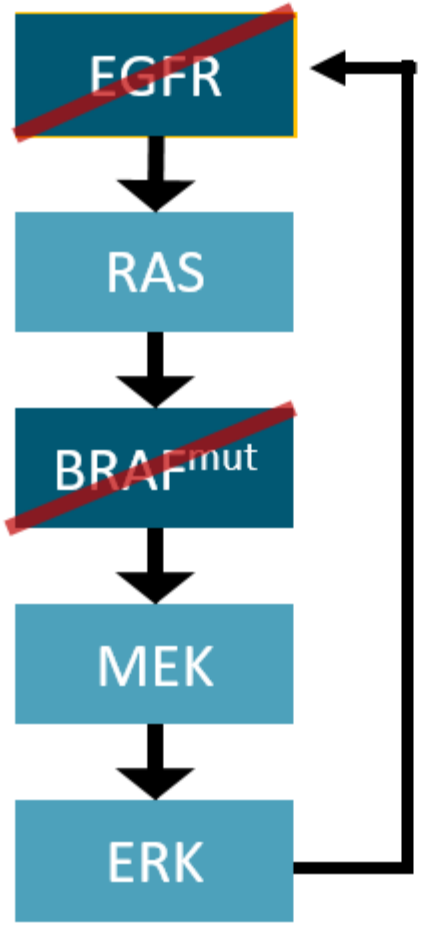


Turk. 2016;5. Larki. Cell J. 2017;19:113. Di Nicolantonio. JCO. 2008;26:5705. Artale. JCO. 2008;26:4217.

Slide credit: clinicaloptions.com

RAS and *BRAF* Mutations

- *KRAS, NRAS, HRAS* most frequently mutated oncogenes[1]
  - 90% of pancreatic cancers, 45% of colon cancers
  - *KRAS* most prevalent in these tumor types
  - In CRC, RAS testing is required before anti-EGFR therapy; patients with *KRAS* and *NRAS* mutations should not receive anti-EGFR therapy[2-4]
- *BRAF* mutations occur most frequently in exon 15 (V600E)
  - Found in ~10% of patients with CRC



BRAF inhibition releases negative feedback, activating EGFR signaling and restoring signaling

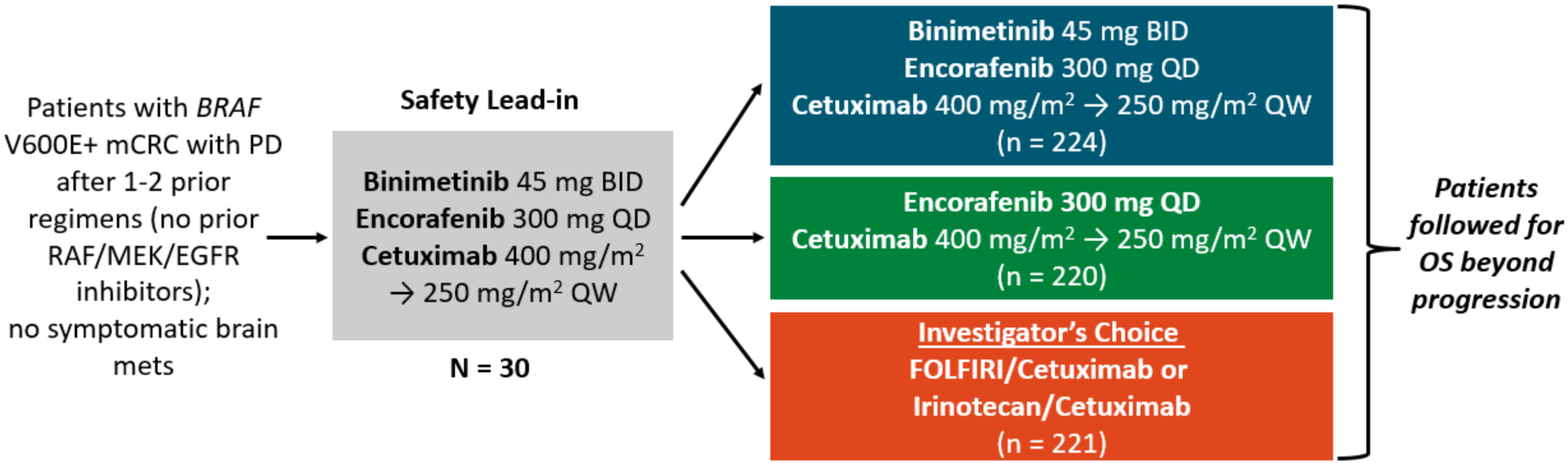
Dual BRAF/EGFR inhibition prevents this adaptive feedback mechanism

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. Hong. Cancer Disc. 2016.

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.

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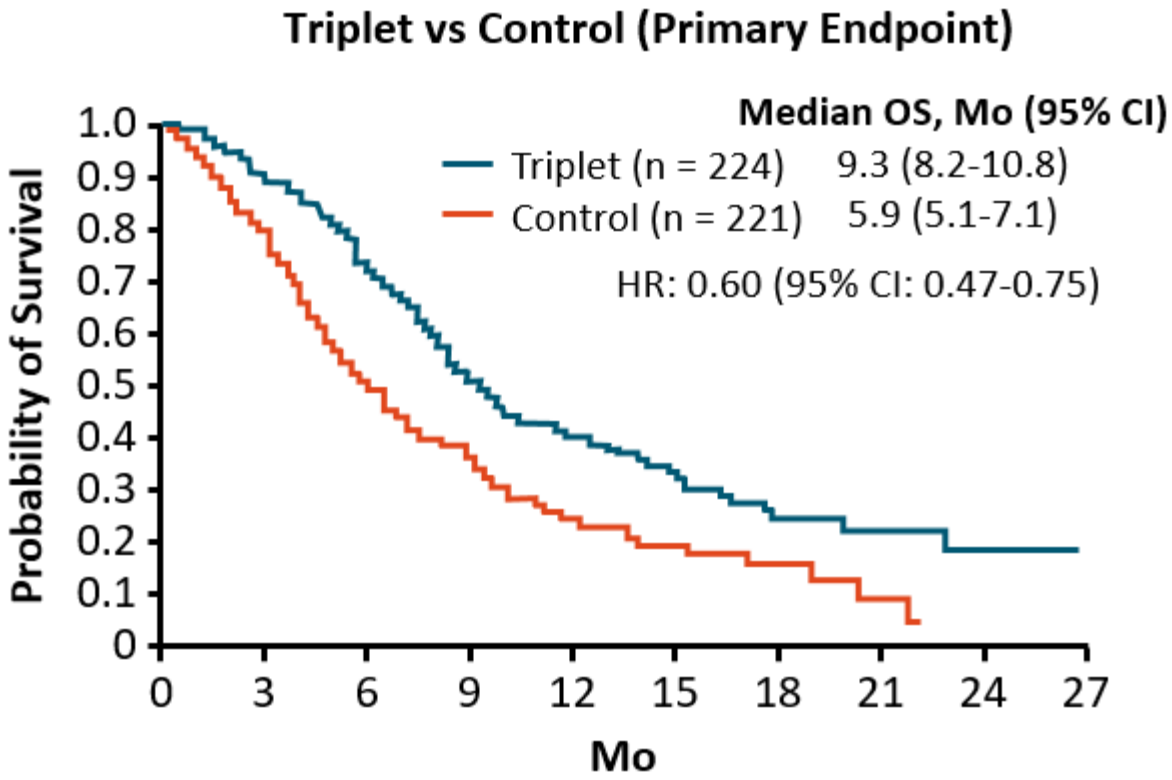
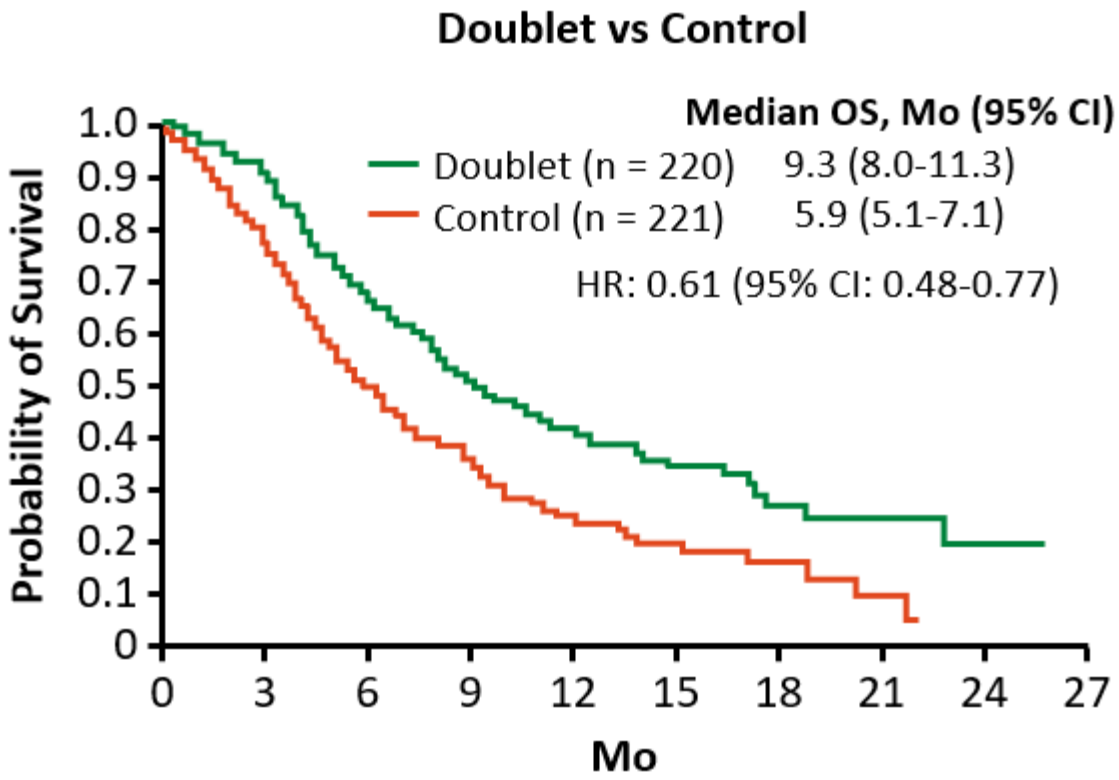
BEACON CRC: OS and ORR



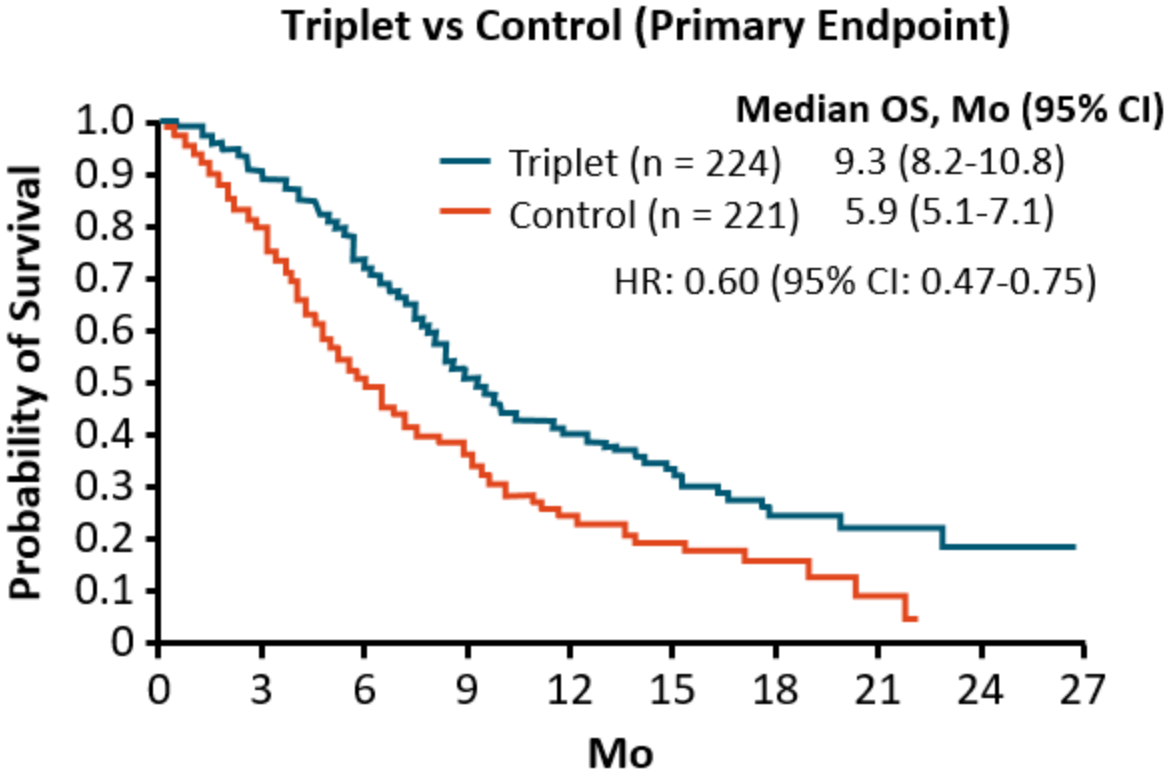


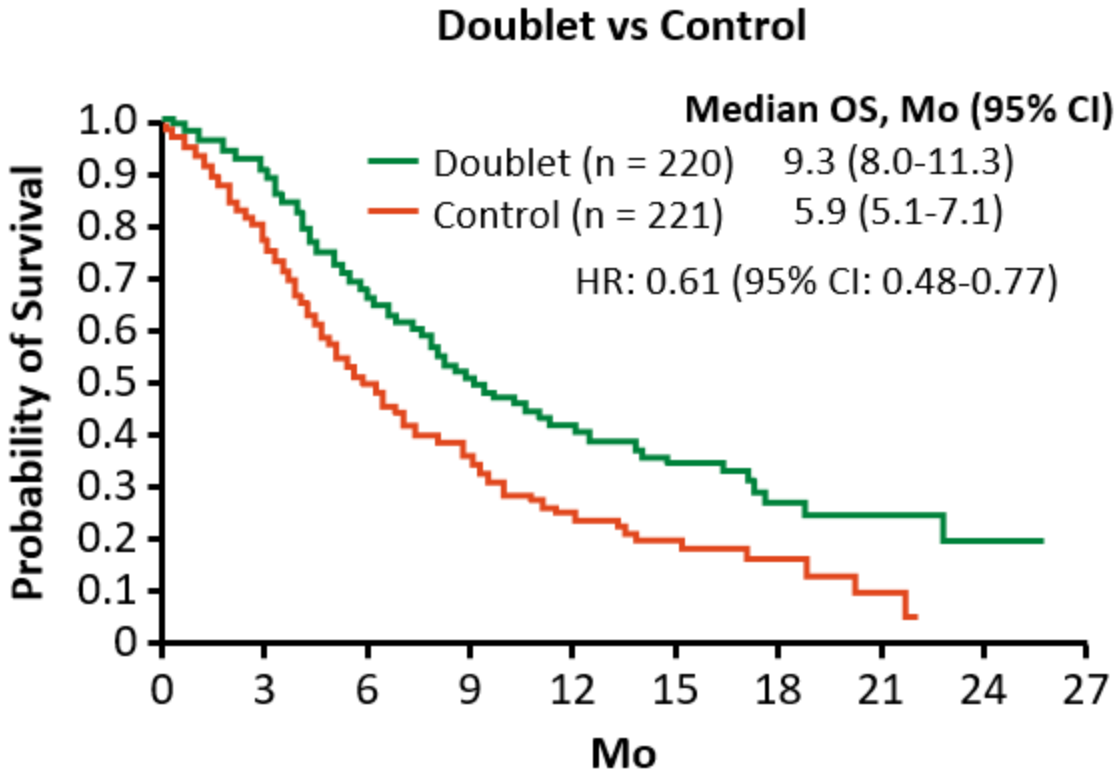
Confirmed Response by BICR	Triplet Regimen (n = 224)	Doublet Regimen (n = 220)	Control (n = 221)
ORR, % (95% CI)	27 (21-33)	20 (15-25)	2 (<1-5)
P value (vs control)	< .0001	< .0001	

Tabernero. JCO. 2021;39:273.

Slide credit: clinicaloptions.com

BEACON CRC: OS and ORR



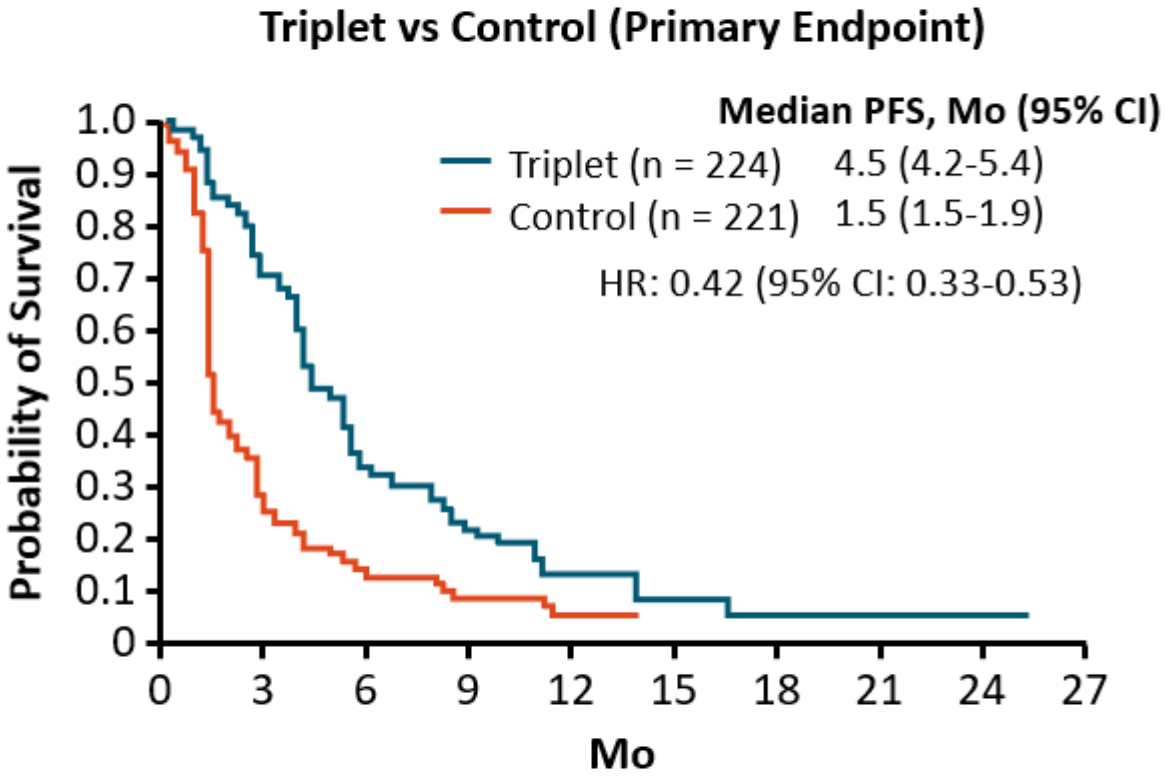


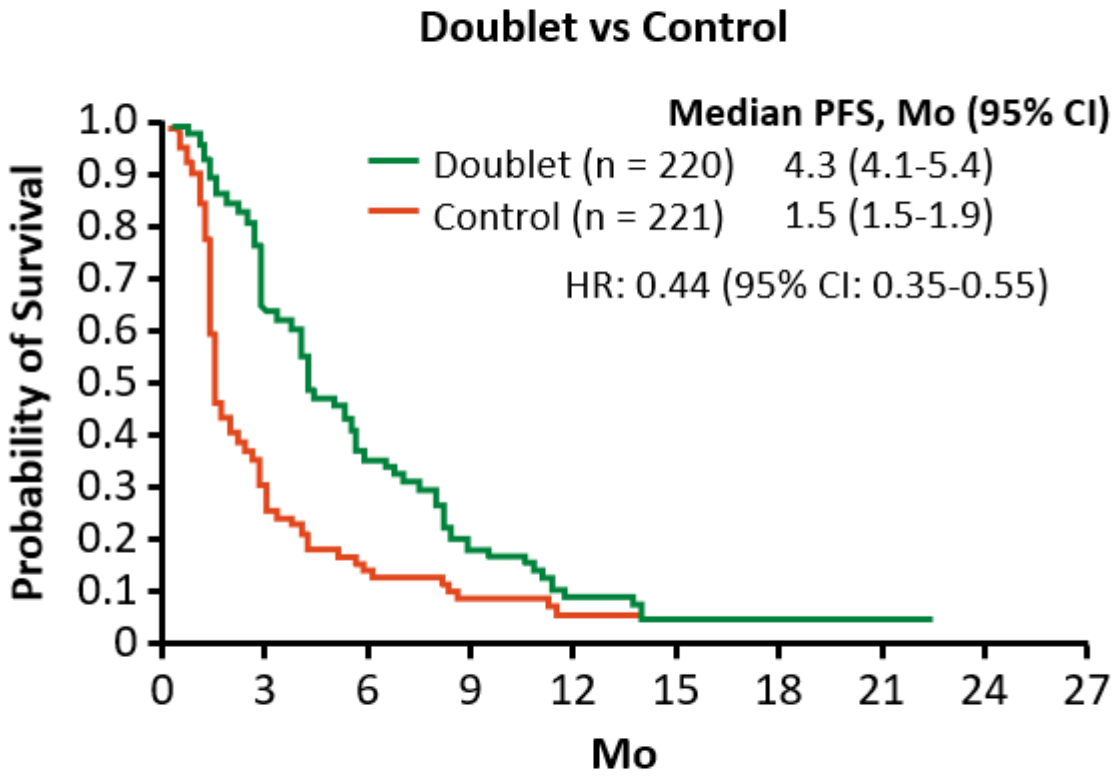
- FDA indication: encorafenib + cetuximab for *BRAF* V600E–mutated mCRC after previous systemic therapy

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

Slide credit: clinicaloptions.com

BEACON CRC: PFS (BICR)





- FDA/EMA indication: encorafenib + cetuximab for *BRAF* V600E-mutated mCRC after previous systemic therapy

Tabernero, Van Cutsem. JCO. 2021;39:273.

Slide credit: clinicaloptions.com

Ongoing Trials and Select Recent Data With BRAF and KRAS G12C Inhibitors in Advanced CRC

Regimen	Phase	Treatment	Population	Key Findings
Recent Data				
KRYSTAL-1 (NCT03785249)	I/II	Adagrasib ± cetuximab	Advanced *KRAS* G12C CRC, previous therapy	▪ A: ORR, 22%; DCR, 87% (n = 45) ▪ A + C: ORR, 43%; DCR, 100% (n = 28) ▪ Ongoing
Ongoing				
KRYSTAL-10 (NCT04793958)	III	Adagrasib + cetuximab vs CT	Advanced *KRAS* G12C CRC, previous 1L therapy	▪ Ongoing
BREAKWATER (NCT04607421)	III	Encorafenib + cetuximab ± CT vs CT	*BRAF* V600E–mutant mCRC, **no previous therapy**	▪ Ongoing

Weiss. ESMO 2021. Abstr LBA6.

Additional Biomarkers: *HER2* Amplification

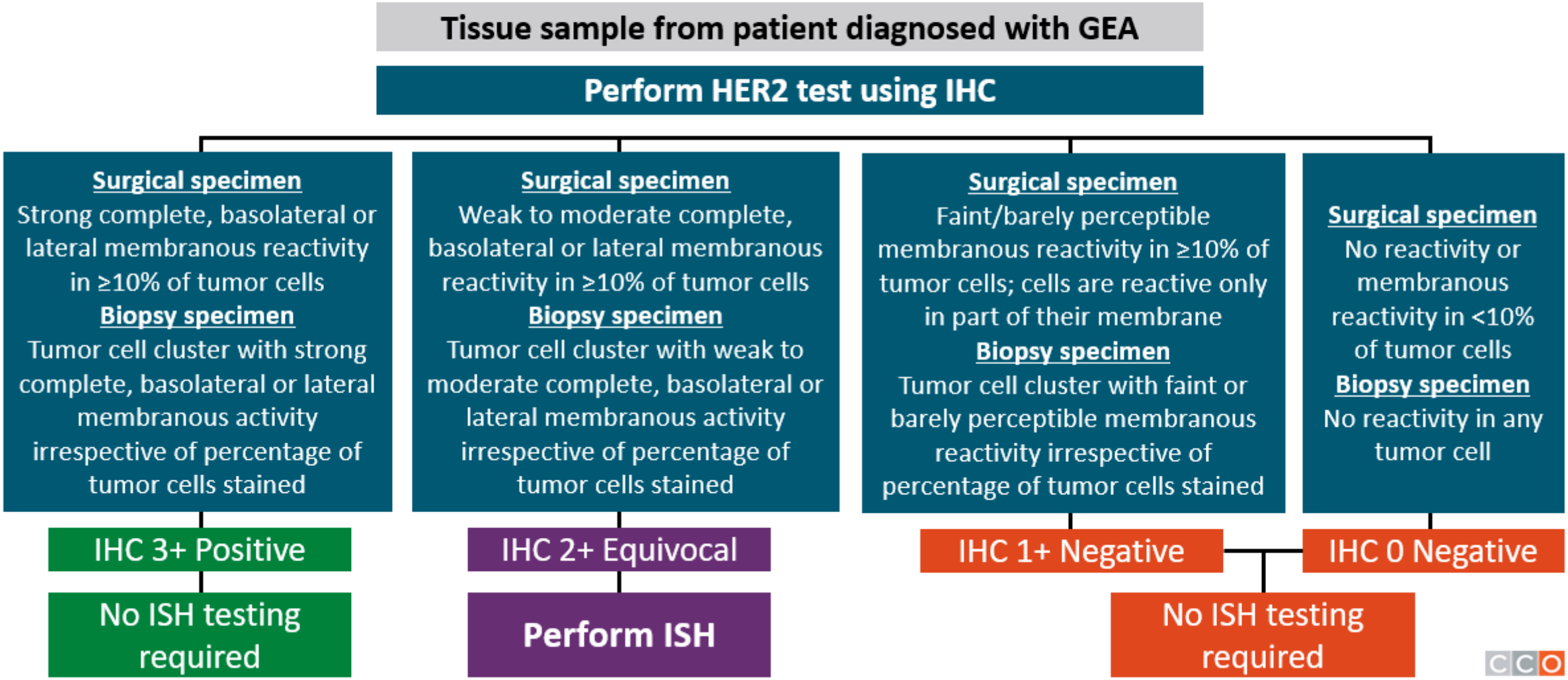
Genomic Alterations in *HER2/ERBB2* in Breast, Gastroesophageal, and Colorectal Cancers

Alterations, %	Breast	Gastro-esophageal	Colorectal
HER2 amplification	18	16	2-5
HER2 KD mutations	2	2	2
HER2 ECD mutations	<1	--	<1

- Mutually exclusive with *RAS/BRAF* mutations
- *HER2* amplification enriched in *KRAS*, *NRAS*, *BRAF*, and *PIK3CA* WT tumors

Press. JCO. 1997;15:2894. Press. Mol Cancer Ther. 2017;16:228. Ross. Cancer. 2018;124:1358. Wen. J Mol Diag. 2015;5:487. Ross. Cancer. 2016;122:2654. Valtorta. Mod Pathol. 2015;28:1481. Bertotti. 2011;1:508. Kuwada. Int J Cancer. 2004;109:291

Gastroesophageal Adenocarcinoma Algorithm for HER2 Testing by IHC



Bartley. JCO. 2017; 35:446.

Slide credit: clinicaloptions.com

ASCO/CAP Guideline for HER2 Testing

Group 1	Group 2	Group 3	Group 4	Group 5
Ratio ≥2	Ratio ≥2	Ratio <2	Ratio ≥2	Ratio <2
≥4 *HER2* signals/cell	<4 *HER2* signals/cell	≥6 *HER2* signals/cell	≥4 and <6 *HER2* signals/cell	≥4 *HER2* signals/cell

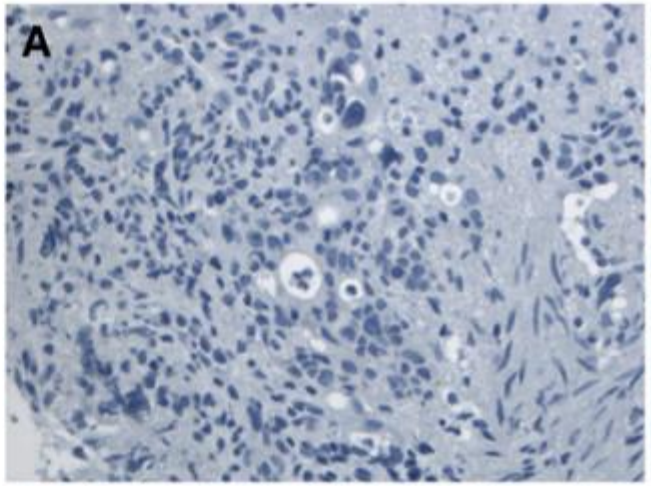
Dual Probe Assay	
HER2 Positive	**HER2 Negative**
Group 1	Group 2 AND concurrent IHC 0-1+ or 2+
Group 2 AND concurrent IHC 3+	Group 3 AND concurrent IHC 0-1+
Group 3 AND concurrent IHC 2+ or 3+	Group 4 AND concurrent IHC 0-1+ or 2+
Group 4 AND concurrent IHC 3+	Group 5

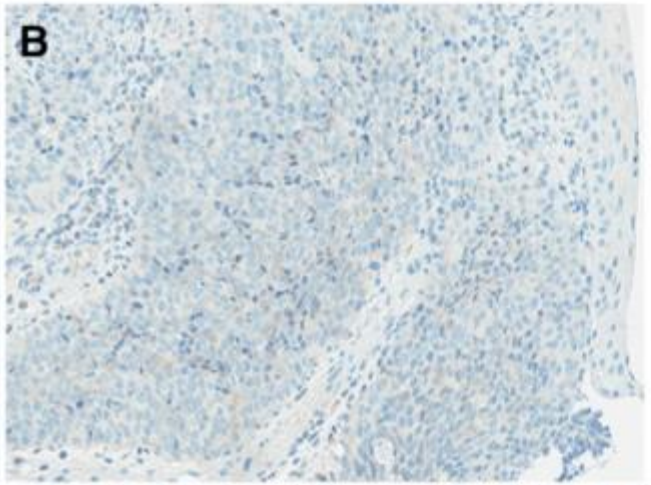
Wolff. Arch Pathol Lab Med. 2018;142:1364.

Slide credit: clinicaloptions.com

HER2 IHC in Representative Gastroesophageal Adenocarcinomas

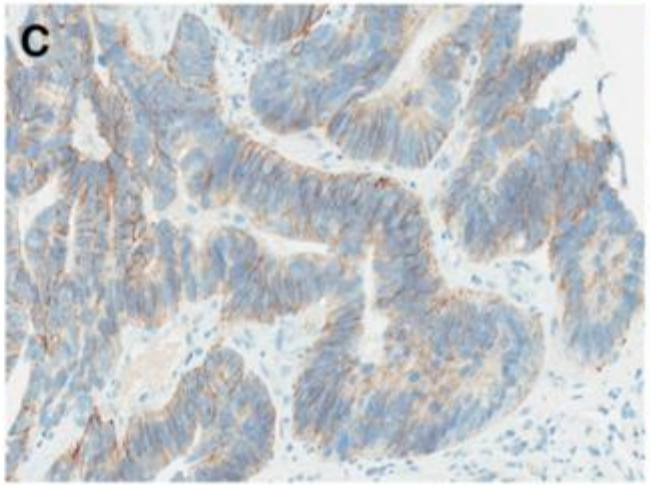
Negative 0

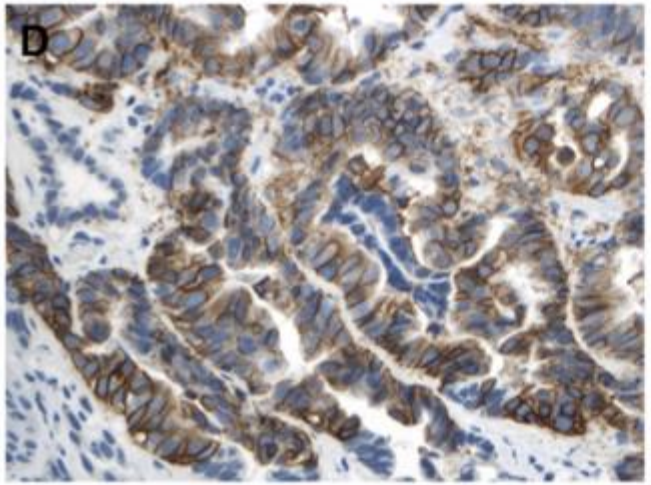




Negative 1+

Equivocal 2+



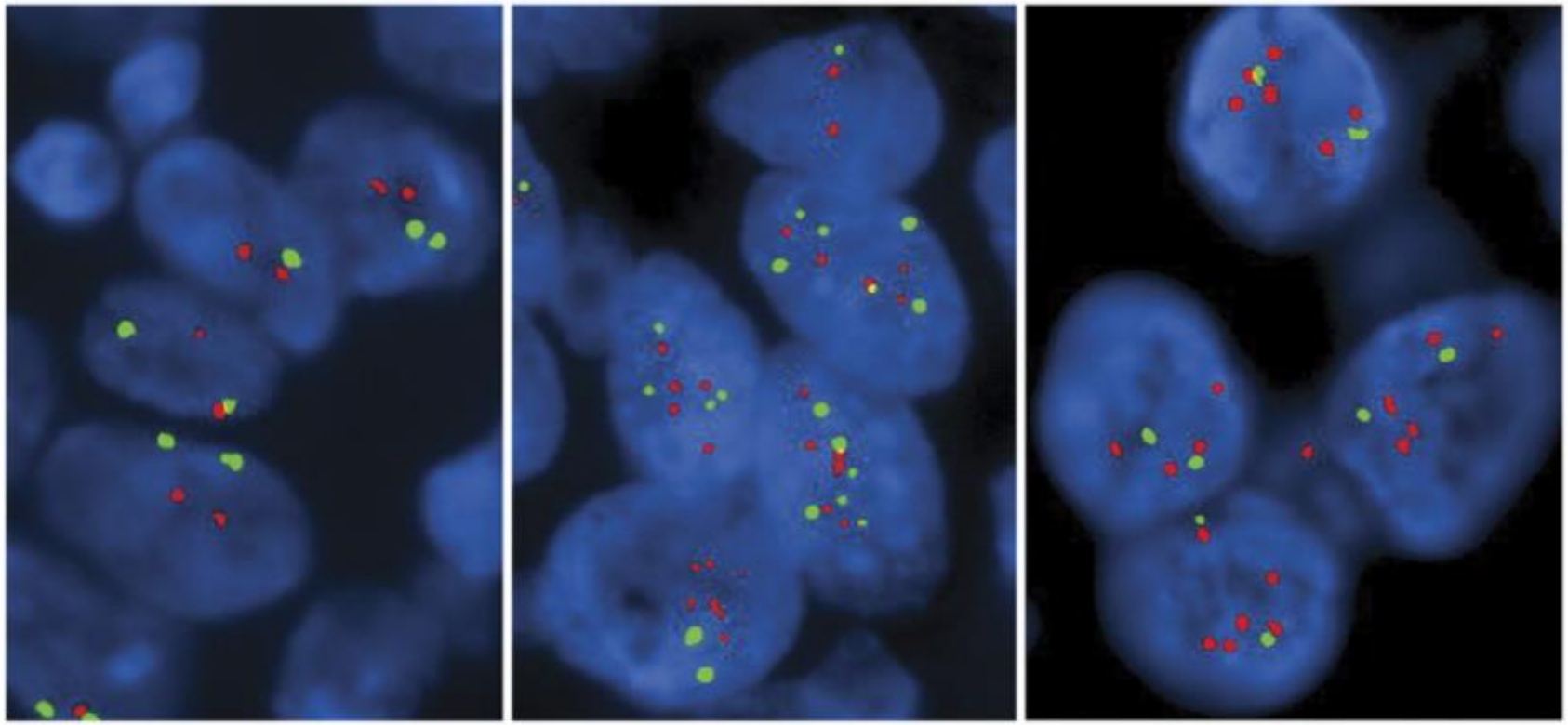


Positive 3+

Bartley. JCO. 2017;35:446.

Slide credit: clinicaloptions.com

HER2 and CEP17 FISH in Representative Gastroesophageal Adenocarcinomas



***HER2* Ratio = *HER2*/CEP17 =**	$\frac{1.9}{1.8} = 1.0$	$\frac{3.4}{2.7} = 1.3$	$\frac{5.2}{1.7} = 3.0$
	Not amplified	**Not amplified**	**"Amplified"**

Bartley. JCO. 2017;35:446.

Slide credit: clinicaloptions.com

Recent Data With HER2-Targeted Regimens for Advanced CRC

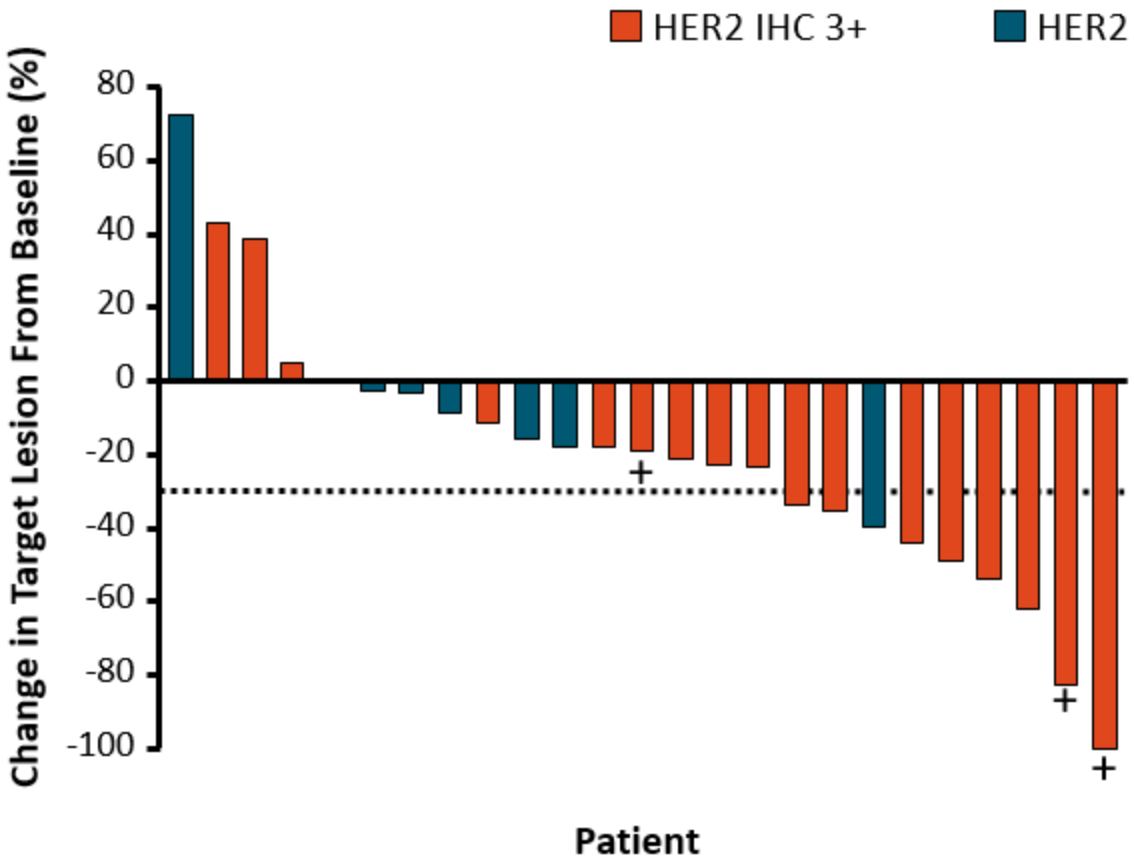
Regimen	Key Trials	Key Findings	Ongoing Trials
Trastuzumab + lapatinib	HERACLES ▪ For HER2+ mCRC with PD after standard treatment (phase II, N = 32)	▪ ORR: 28%	
Trastuzumab + pertuzumab	MyPathway ▪ For HER2+ mCRC refractory to standard treatment (phase II, N = 84)	▪ ORR: 31%	▪ Trastuzumab + pertuzumab vs CT (NCT03365882/S1613, ph II)
Tucatinib + trastuzumab	MOUNTAINEER ▪ For HER2+ mCRC that was previously treated (phase II, N = 26)	▪ ORR: 55%	▪ Ongoing as expanded pivotal trial (NCT03043313, ph II) ▪ Tucatinib + trastuzumab ± CT ± pembro (NCT04430738, ph I/II)
Trastuzumab deruxtecan	DESTINY-CRC01 ▪ For advanced CRC of varied HER2 expression with ≥2 prior regimens (phase II, N = 78)	▪ ORR: 45.3% if HER2+	▪ DESTINY-CRC02 (NCT04744831, ph II)

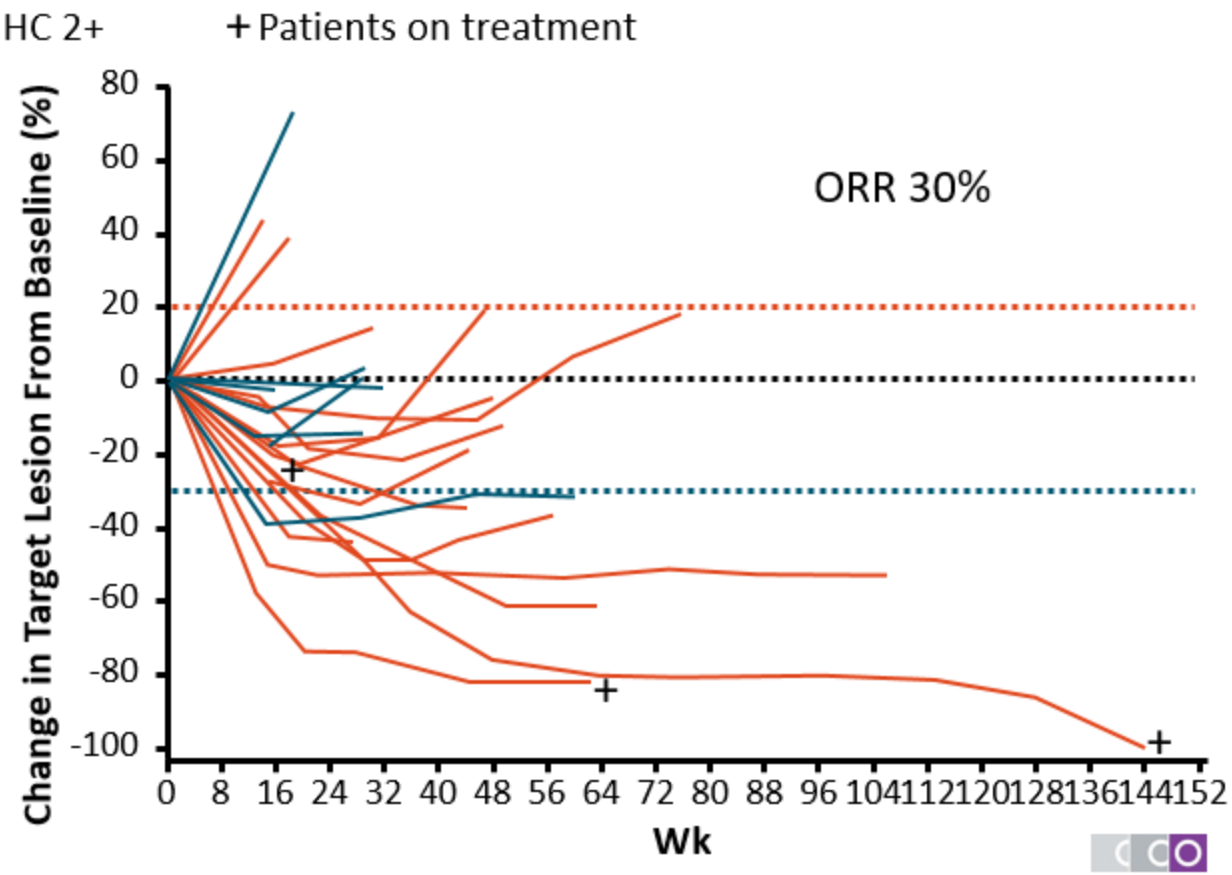
- Others: neratinib, zanidatamab

Tosi. Clin Colorectal Cancer. 2020;19:256. Meric-Bernstam. ASCO 2021. Abstr 3004. Strickler. ESMO 2019. Abstr 4795. Yoshino. ASCO GI 2022. Abstr 119.

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)



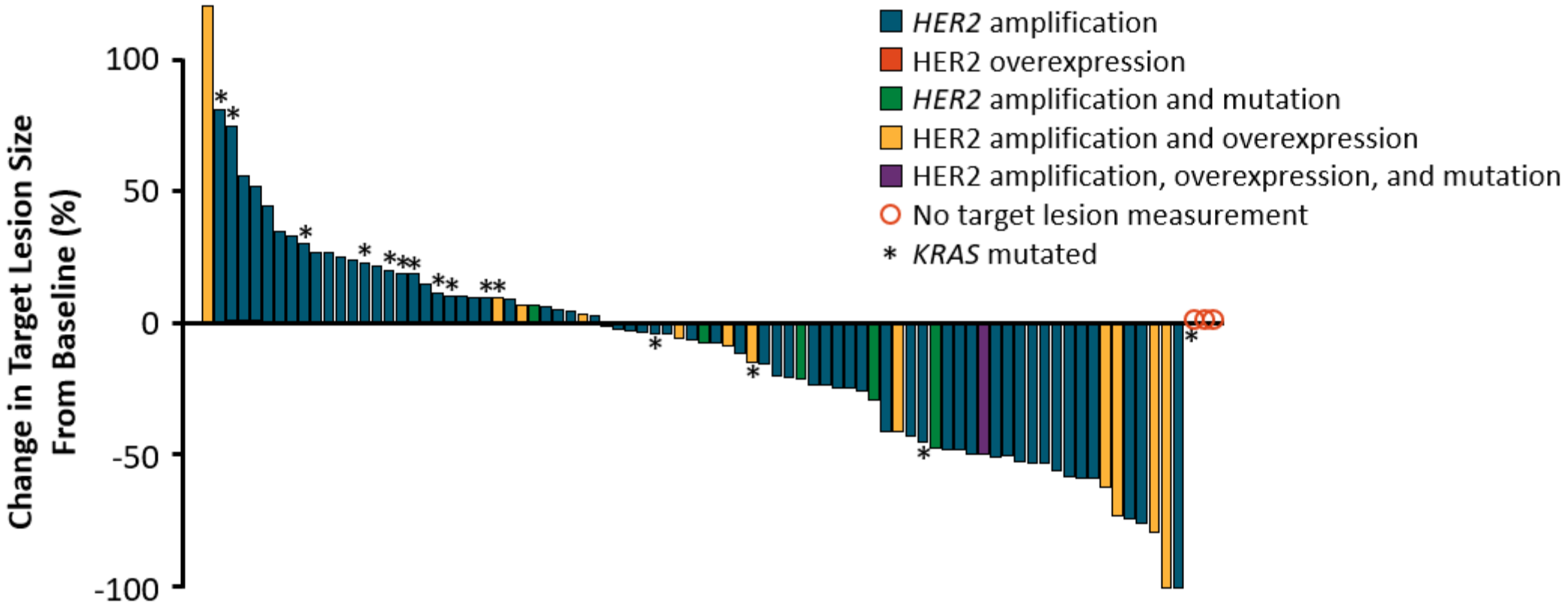


Sartore-Bianchi. Lancet Oncol. 2016;17:738.

Slide credit: clinicaloptions.com

MyPathway: Trastuzumab + Pertuzumab for HER2+ Metastatic CRC

- Open-label phase IIa basket study (n = 84 with CRC)



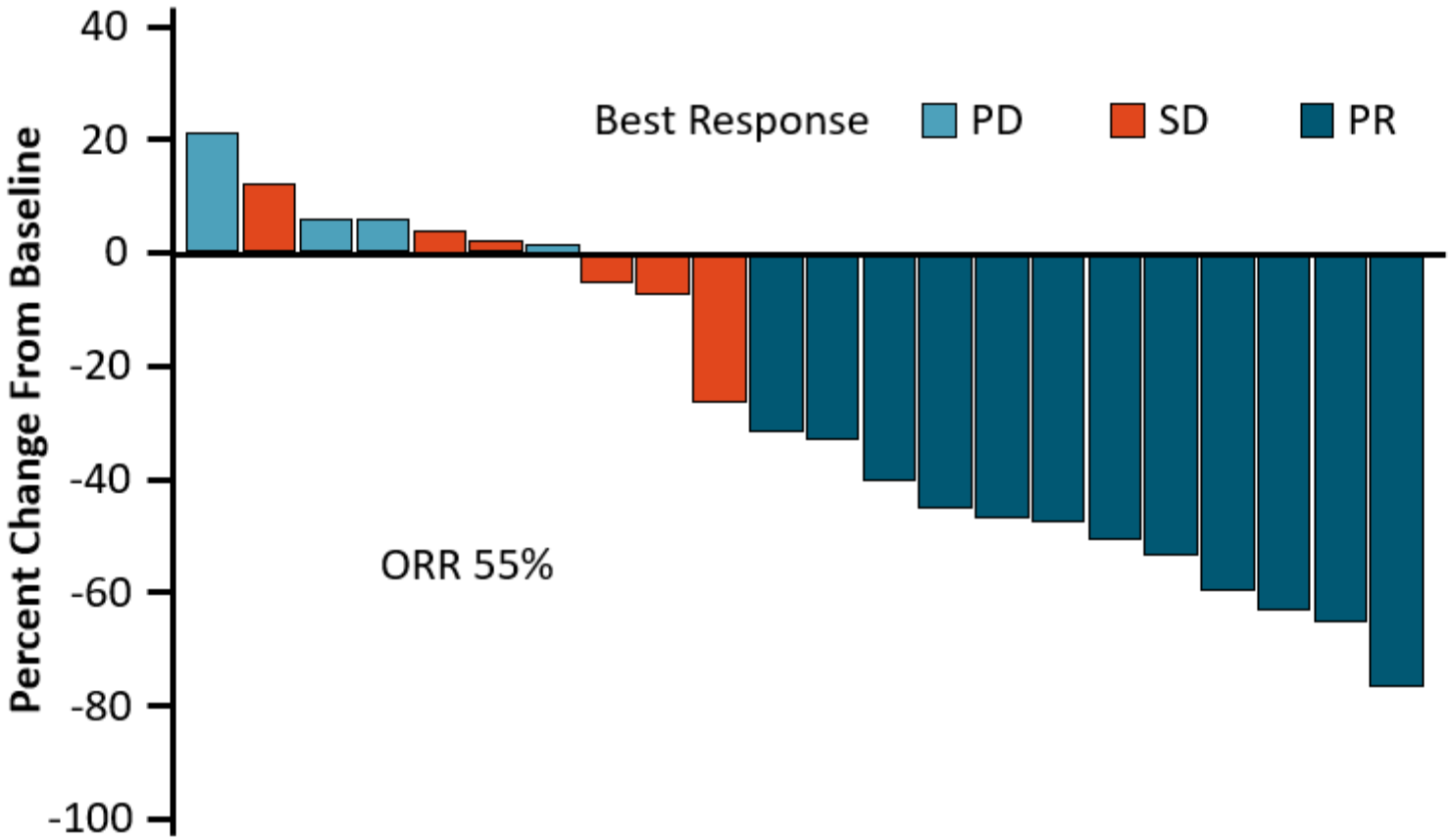
- ORR: 30.9% in *KRAS* wild-type (n = 68)

Meric-Bernstam. ASCO 2021. Abstr 3004.

Slide credit: clinicaloptions.com

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

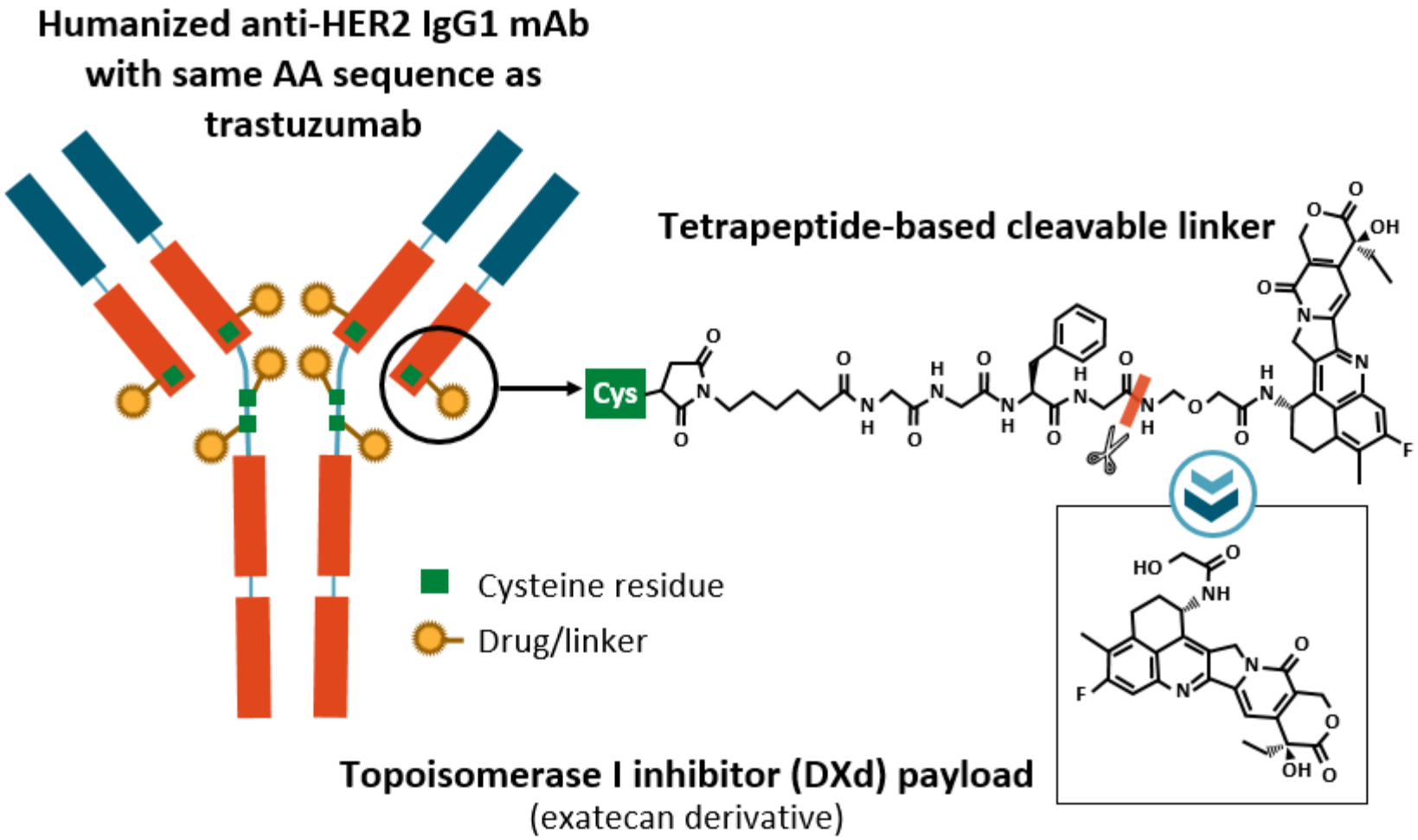
- Open-label, single-arm phase II study of tucatinib + trastuzumab for patients with previously treated, *RAS*-WT, *HER2*-amplified, metastatic or unresectable CRC (N = 26)



Strickler. ESMO 2019. Abstr 4795.

Slide credit: clinicaloptions.com

HER2-Targeted ADC: Trastuzumab Deruxtecan



- High drug:antibody ratio: ~8
- Stable linker-payload; tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life; bystander killing effect
- FDA indicated for adult patients with locally advanced or metastatic HER2+ gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126.
Ogitani. Cancer Sci. 2016;107:1039. Trastuzumab deruxtecan PI.

Slide credit: clinicaloptions.com

DESTINY-CRC01: Trastuzumab Deruxtecan for Patients With HER2-Expressing Metastatic Colorectal Cancer

- International, open-label, multicohort phase II trial

Patients with unresectable/metastatic CRC that is HER2 expressing† and *RAS/BRAF* wild type; received ≥2 previous regimens; previous anti-HER2 tx permitted; no history of or current/suspected ILD; ECOG PS 0/1 (N = 78)

Cohort A: HER2 Positive (IHC 3+ or IHC 2+/ISH+)

→ **T-DXd** 6.4 mg/kg Q3W (n = 53)

Cohort B*: HER2 IHC2+/ISH-

→ **T-DXd** 6.4 mg/kg Q3W (n = 7)

Cohort C*: HER2 IHC 1+

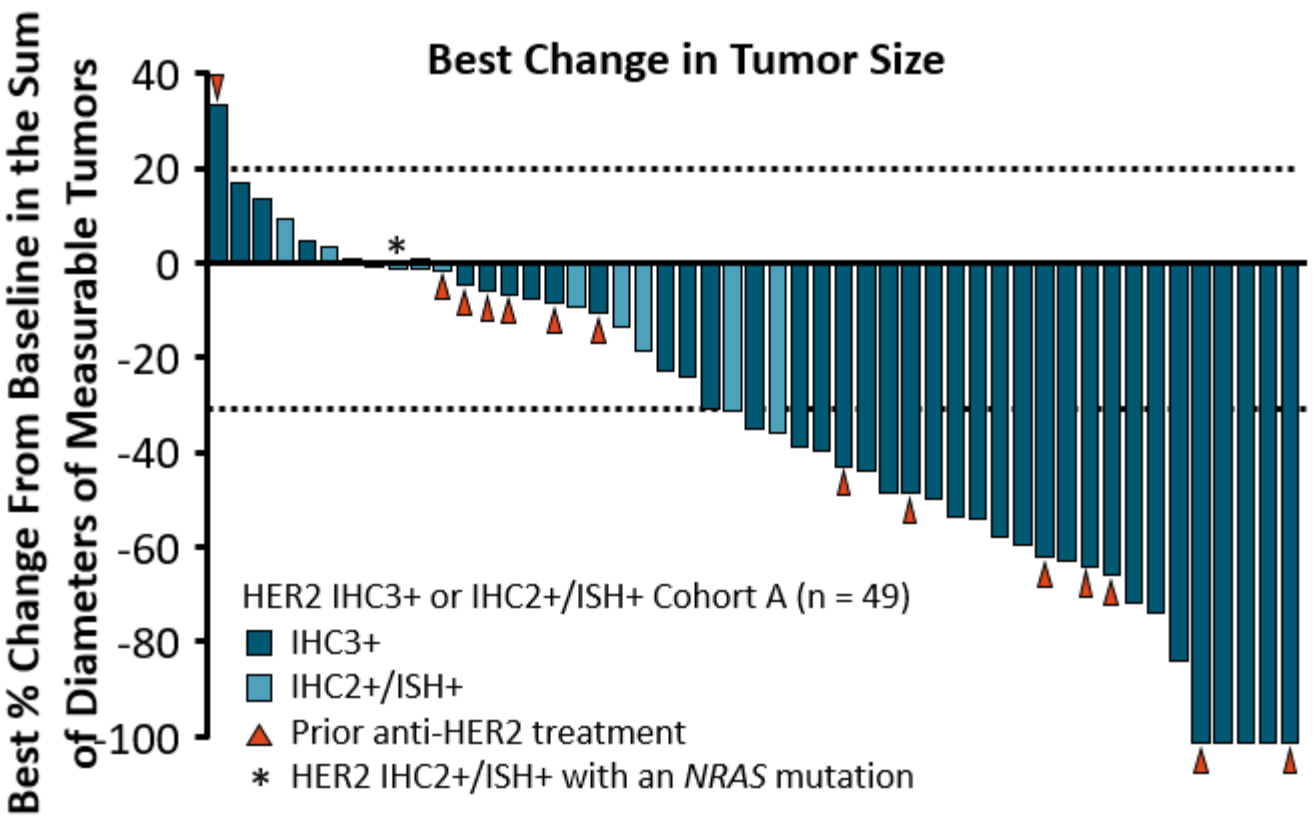
→ **T-DXd** 6.4 mg/kg Q3W (n = 18)

- Primary endpoint: confirmed ORR by ICR in Cohort A
- Secondary endpoints: DoR, DCR, ORR per investigator, PFS, OS, PK

*Cohorts B and C opened when futility monitoring performed after ≥20 patients enrolled on Cohort A had 12 wk of follow-up.
†Centrally confirmed.

Siena. Lancet Oncol. 2021;22:779.

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)

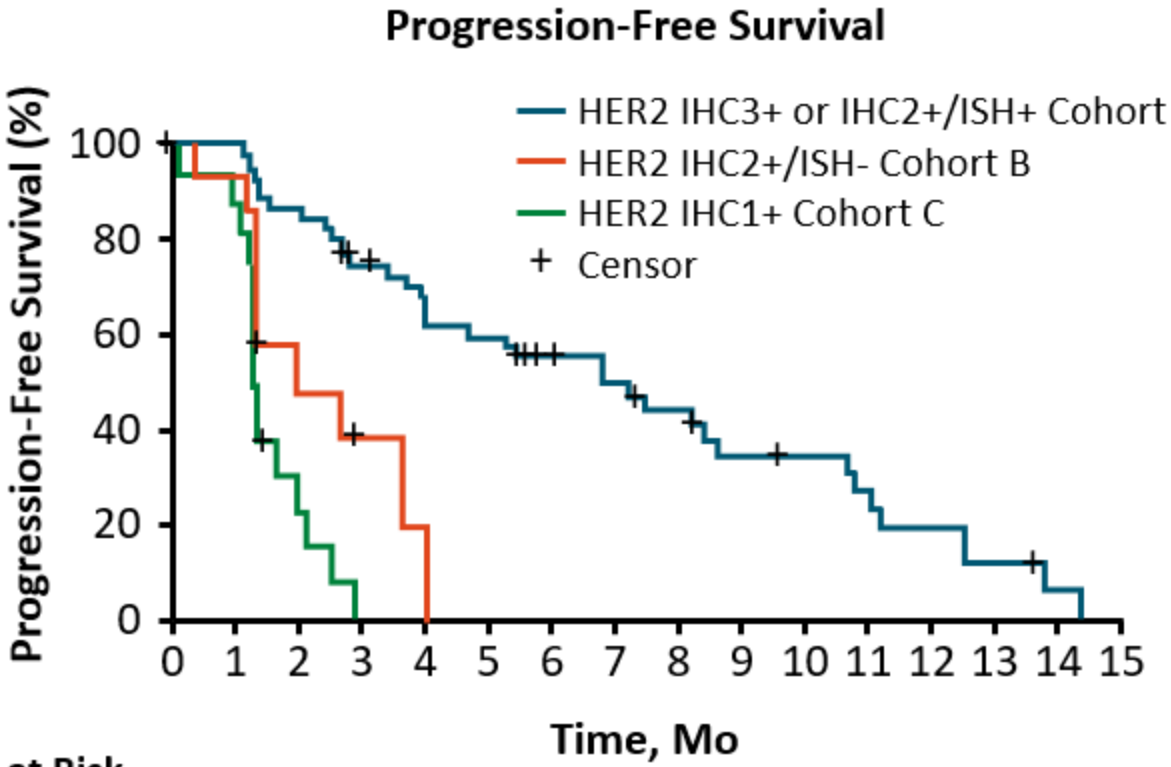
*Postbaseline scans missing.

- 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.

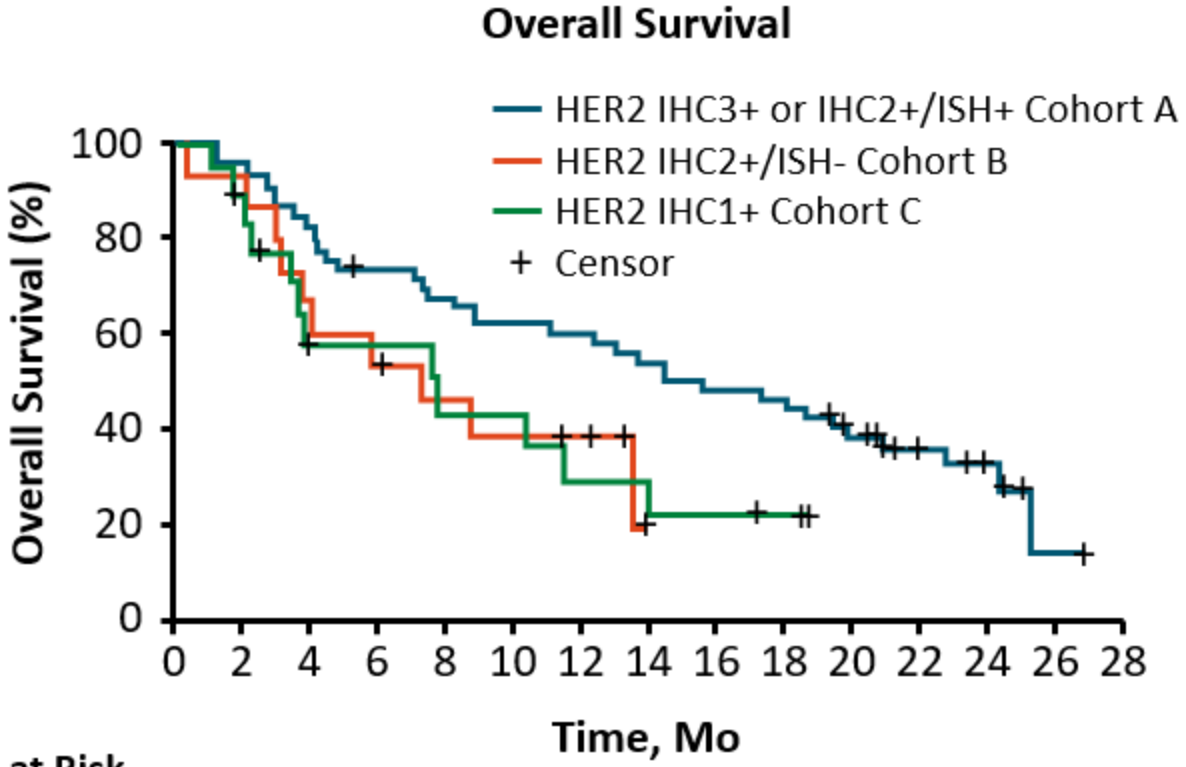
Slide credit: clinicaloptions.com

DESTINY-CRC01: PFS and OS by Cohort



No. at Risk

Cohort A	53	51	44	36	33	27	22	18	15	10	9	7	5	3	1	0
Cohort B	15	14	4	4	1	0	0	0	0	0	0	0	0	0	0	0
Cohort C	18	15	4	1	0	0	0	0	0	0	0	0	0	0	0	0



No. at Risk

Cohort A	53	51	44	36	35	32	31	28	25	24	18	12	6	1	0	
Cohort B	15	14	10	8	6	5	4	0	0	0	0	0	0	0	0	
Cohort C	18	15	8	8	6	6	4	3	3	2	0	0	0	0	0	

Yoshino. ASCO 2021. Abstr 3505.

Slide credit: clinicaloptions.com

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

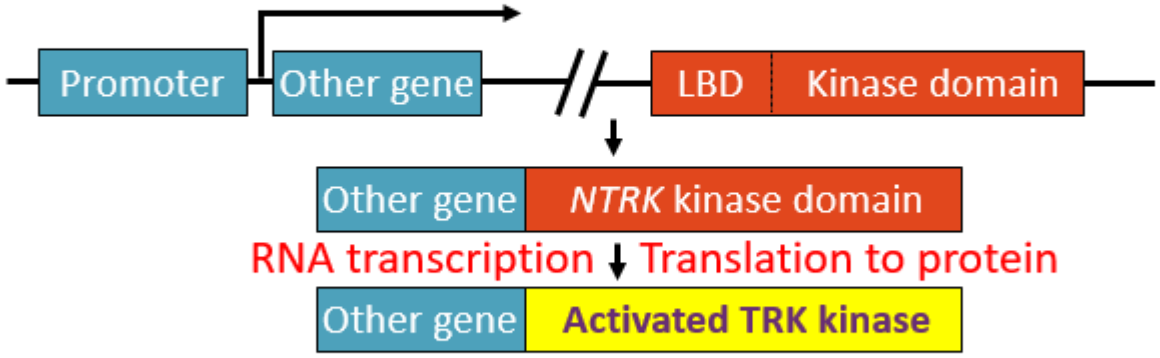
Slide credit: clinicaloptions.com

NTRK Genes and TRK Proteins: Roles in Normal Biology and Cancer

- ***NTRK*** genes and **TRK** receptors[1]:
  - In normal biology, expressed in neuronal tissue; roles in development, nervous system function via activation by neurotrophins
  - Rarely expressed in normal nonneuronal or cancerous tissues

Receptor[2-4]	Gene	Function
TRKA	*NTRK1*	Pain, thermoregulation
TRKB	*NTRK2*	Movement, memory, mood, appetite, weight
TRKC	*NTRK3*	Proprioception

- ***NTRK*** **gene fusions and TRK chimeric fusion proteins**[1]:
  - In-frame rearrangement of any *NTRK* gene links tyrosine kinase domain with upstream fusion partner to generate a chimeric RNA and TRK fusion protein
  - Uncontrolled TRK kinase function results[5]



1.Adapted from Amatu. ESMO Open. 2016;1:e000023. 2. Loewenthal. Pediatr Res. 2005;57:587. 3. Razzoli. Genes Brain Behav. 2011;10:424. 4. Inoue. Blood Cells Mol Dis. 2003;30:157. 5. Adapted from Hyman. ASCO 2017. Abstr LBA2501.

Slide credit: clinicaloptions.com

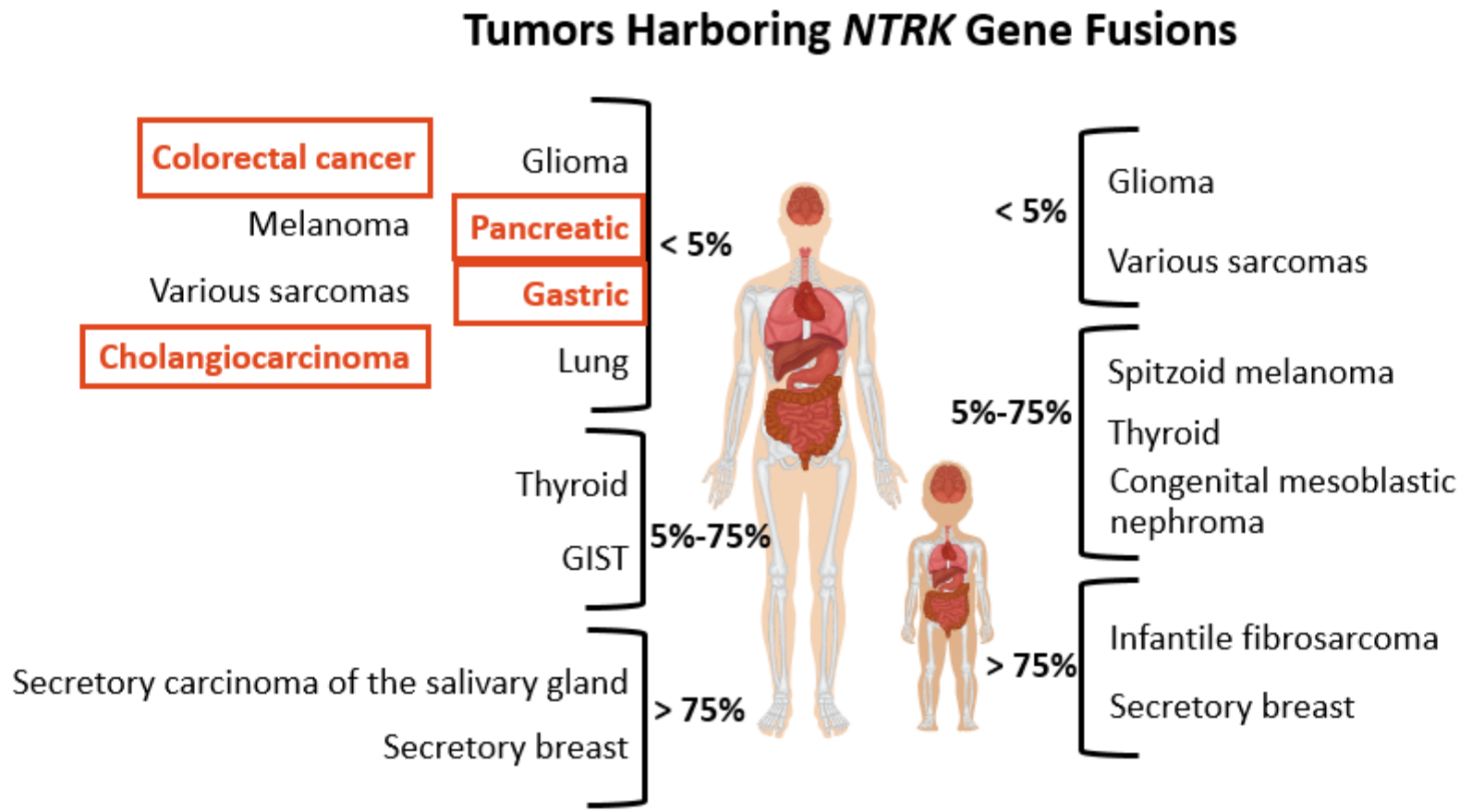
NTRK Gene Fusions in GI Cancers: Rare but Actionable

- *NTRK* gene fusions and TRK fusion chimeric proteins occur in <5% of GI cancers

Treatment	Tumor FDA Agnostic Indication
Larotrectinib	▪ Adult/pediatric patients with **solid tumors with a *NTRK* gene fusion** without a known acquired resistance mutation who are either metastatic or not candidates for surgical resection due to likely severe morbidity and who have no satisfactory alternative treatments or PD following treatment
Entrectinib	▪ Adult/pediatric patients (≥12 yr of age) with **solid tumors with a *NTRK* gene fusion** without a known acquired resistance mutation who are either metastatic or not candidates for surgical resection due to likely severe morbidity and who have no satisfactory alternative treatments PD following treatment

Larotrectinib PI. Entrectinib PI.

NTRK Gene Fusions in GI Cancers: Rare but Actionable



Hsaio. J Mol Diagn. 2019;21:553. Lasota. Am J Surg Pathol. 2020;44:162. Lee. Oncotarget. 2015;6:39028.
Chou. Mod Pathol. 2020;33:924. Hong. Lancet Oncol. 2020;21:531. Doebele. Lancet Oncol. 2020;21:271.

Slide credit: clinicaloptions.com

FDA-Approved TRK Inhibitors

Larotrectinib

- Adult and pediatric patients with **solid tumors with a *NTRK* gene fusion** without a known acquired resistance mutation who are either **metastatic or not candidates for surgical resection** due to likely severe morbidity and who have **no satisfactory alternative treatments or whose cancer has progressed following standard treatment**
- Second tissue-agnostic approval (after pembrolizumab)

Entrectinib

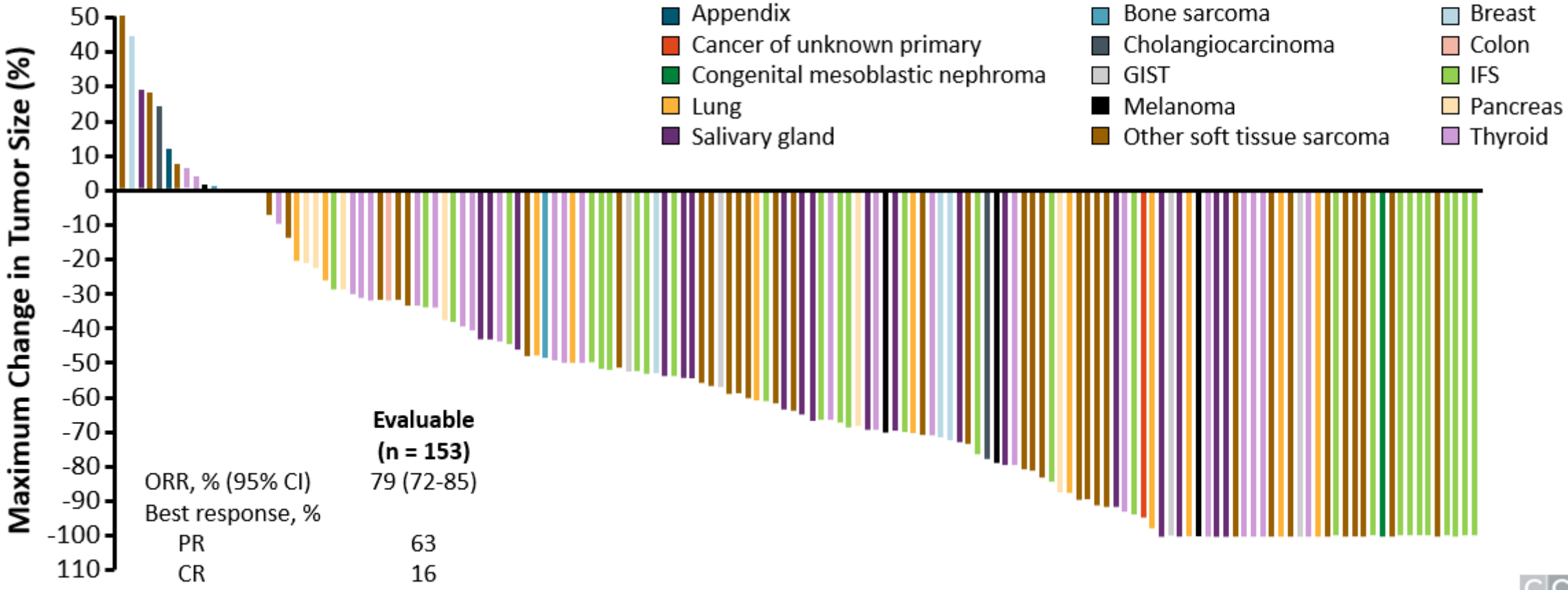
- Adult and pediatric patients with **locally advanced or metastatic *NTRK* fusion–positive solid tumors** without a known acquired resistance mutation who are either metastatic or not candidates for surgical resection due to likely severe morbidity and **who have no satisfactory alternative treatments or whose cancer has progressed following standard treatment**
- Third tissue-agnostic approval

Larotrectinib PI. 2018. Entrectinib PI. 2019.

Slide credit: clinicaloptions.com

Larotrectinib: Antitumor Activity Across Tumor Types

- 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)



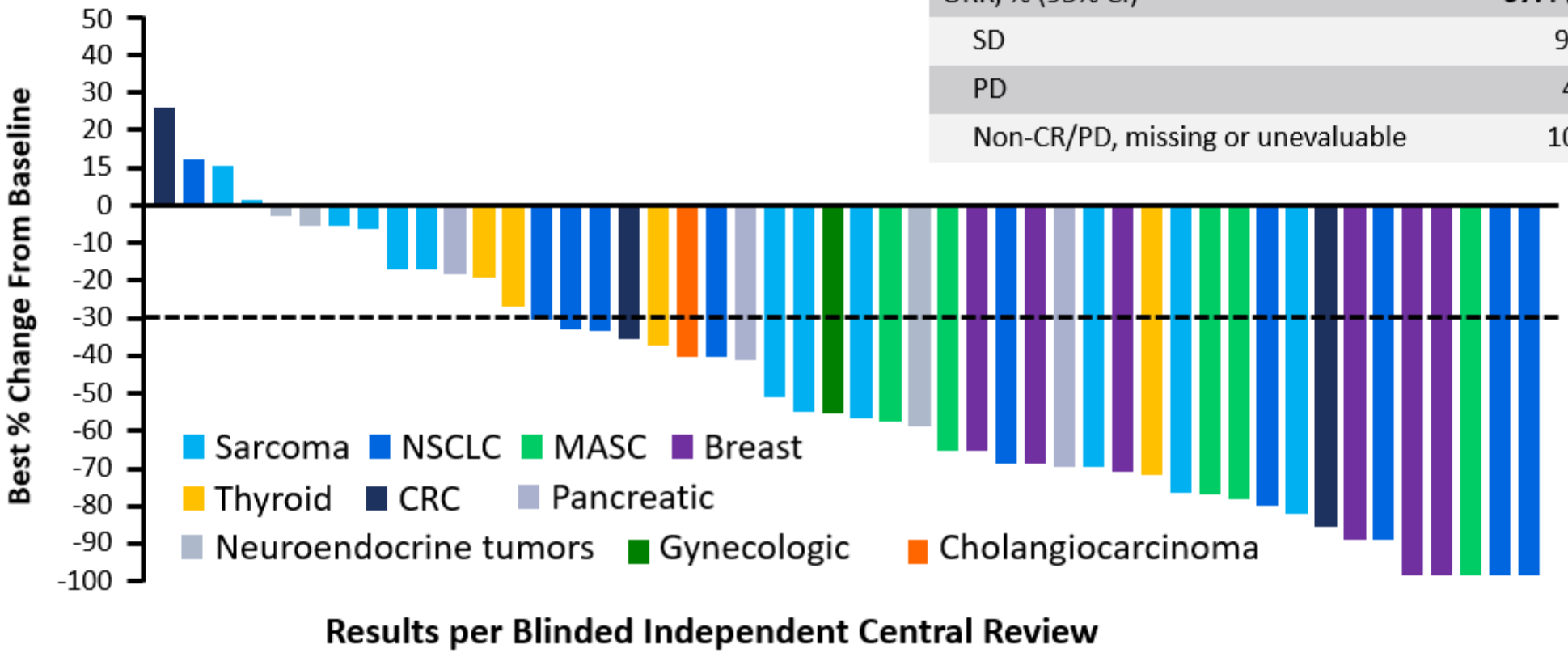
Hong. Lancet Oncol. 2020;21:531.

Slide credit: clinicaloptions.com

Entrectinib in *NTRK* Fusion+ Solid Tumors

- 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

Methods for Detection of *NTRK* Gene Fusions

	IHC	FISH	NGS
Advantages	✓ Rapid results ✓ Detects transcribed and translated events only ✓ Low cost as single test	✓ Rapid results	✓ Potential for multiplexed testing ✓ Less depletion of tissue ✓ Fusion partner/position defined
Disadvantages	– Depletion of tissue – Fusion partner/position unknown – Less well-validated currently	– Depletion of tissue – Fusion partner/position unknown – Can be difficult to interpret	– Longer wait time for results – Cost

DNA- vs RNA-Based NGS Diagnostic Approaches	
DNA-based NGS	**RNA-based NGS**
✓ Potential for multiplexed assessment for multiple different fusion targets	
– Detected fusions may or may not be expressed	✓ Detection of expressed transcripts
– Requires tiling through intronic regions	✓ Read directly through expressed transcripts
– Fusion positions inferred based on reads through genomic DNA	✓ Fusion positions are directly demonstrated

Jordan. Cancer Discov. 2017;7:596. Hyman. ASCO 2017. Abstr LBA2501. Farago. J Thorac Oncol. 2015;10:1670.
Hechtman. Am J Surg Pathol. 2017;41:1547. Meyerson. Nat Rev Genet. 2010;11:685. Zheng. Nature Med. 2014;20:1479.

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

Slide credit: clinicaloptions.com

Conclusions: Clinical Relevance and Use of Biomarkers

- Current precision therapies with clinical activity:

Alteration	Targeted Therapy
BRAF V600E mutation	Dual EGFR + BRAF inhibition (± MEK inhibitor)
HER2 amplification	Trastuzumab + lapatinib or pertuzumab
MSI-H/dMMR	Nivolumab ± ipilimumab, pembrolizumab
NTRK fusion	Larotrectinib or entrectinib

Biomarker-Driven Treatment of Gastric, Esophageal, and Gastroesophageal Junction Cancers

Biomarker Testing in Gastroesophageal Cancers

- What test results must we have?
  - *HER2* amplification (IHC/ISH)
  - MSI-H (PCR/NGS) or dMMR (IHC)
  - TMB-H (NGS)
  - PD-L1 examination (IHC)
  - *NTRK* fusion (NGS)
  - Comprehensive genomic profiling (if enough tissue)
- When should testing occur, and for whom?
  - All newly diagnosed patients with metastatic disease

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer v1.2022.

Slide credit: clinicaloptions.com

PD-L1 in Gastroesophageal Cancers

- 23% to 60% of gastric cancers are PD-L1+ (tumor cells + tumor-infiltrating immune cells)[1-3]
- Serial sections: HE and IHC; clone 22 C3
- Minimum 100 tumor cells in IHC slide
- Clinically relevant cutoffs >1%, >10%, and ~20%
- Higher response to PD-1 inhibitors in advanced gastroesophageal cancers with higher PD-L1 levels; pembrolizumab indications based on specific levels[4,5]

Assessing PD-L1 Levels (IHC Testing)

$$\textbf{Combined Positive Score} = \frac{\textbf{PD-L1 staining cells, n}\ \text{(tumor cells, lymphocytes, macrophages)}}{\textbf{Tumor cells evaluated, n}} \times 100$$

1. Herbst. Nature. 2014;515:563. 2. Salem. ASCO GI 2017. Abstr 530.
3. Liu. Pathol Res Pract. 2020;216:152881. 4. Wainberg. ASCO GI 2020. Abstr 427. 5. Pembrolizumab PI.

FDA-Approved Indications for Checkpoint Inhibitors in Advanced Gastroesophageal Cancers

Indication	Pembrolizumab	Nivolumab
Gastric	▪ **HER2+** locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma (with trastuzumab and fluoropyrimidine- and platinum-containing CT) as first-line therapy ▪ **PD-L1 CPS ≥1** recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma with PD on or after ≥2 previous therapies, including fluoropyrimidine- and platinum-containing CT and, if appropriate, HER2-targeted therapy	▪ Advanced or metastatic gastric or GEJ cancer and esophageal adenocarcinoma with fluoropyrimidine- and platinum-containing CT
Esophageal	▪ Locally advanced or metastatic esophageal or GEJ carcinoma: – With platinum- and fluoropyrimidine-based CT – For **PD-L1 CPS ≥10** *squamous* carcinoma after ≥1 line(s) of systemic therapy	▪ Unresectable advanced, recurrent, or metastatic esophageal *squamous* cell carcinoma after prior fluoropyrimidine- and platinum-based CT ▪ See above
Tumor agnostic	▪ **MSI-H or MMR deficient or TMB-H** (≥10 mut/Mb) unresectable or metastatic solid tumors with PD after previous treatment with no satisfactory alternative treatment options	

Pembrolizumab PI. Nivolumab PI.

Slide credit: clinicaloptions.com

Simplified First-line Treatment Algorithm for Advanced Gastroesophageal Adenocarcinomas

	No Biomarkers or HER2-	HER2+
Gastric	Fluoropyrimidine + platinum ± nivolumab (CPS ≥5; CheckMate 649)	Fluoropyrimidine + platinum + trastuzumab ± pembrolizumab (KEYNOTE-811)
Esophageal/ GEJ	Fluoropyrimidine + platinum ± nivolumab (CPS ≥5; CheckMate 649) Fluoropyrimidine + platinum ± pembrolizumab (CPS ≥10; KEYNOTE-590)	Fluoropyrimidine + platinum + trastuzumab ± pembrolizumab (KEYNOTE-811)

Janjigian. Nature. 2021;600:727. Janjigian. Lancet. 2021;398:27. Sun. Lancet. 2021;398:759.

Standard of Care for Gastroesophageal Cancers in 2021

Is chemoimmunotherapy the new standard of care?

YES – GEA CPS ≥5
YES – ESCC CPS ≥10
DEBATABLE – GEA CPS <5, CPS <10

What are the key biomarkers for anti-PD-1 therapy in gastric and esophageal cancer?

PD-L1 – standardization of PD-L1 assessment is critical
MSI – should be tested for all GEA patients
TMB – ↑ response rates, prospective validation lacking

Is there a difference in response to immune checkpoint blockade between Asian and non-Asian patients?

Asian patients show ↓ disease burden, ↑ PS compared with non-Asian patients
No definitive evidence of differential tumor or host biology

Esophageal or GEJ Adeno	Squamous Esophageal
Locally advanced Periop CT + surgery *or* CRT + surgery *then* **nivolumab** (high-risk adjuvant)	**Locally advanced** CRT + surgery **Nivolumab** (high-risk adjuvant resected)
1L Metastatic **Nivolumab** + CT (CPS ≥5) CT + Tmab (HER2+) CT alone (HER2–, CPS <5)	**1L Metastatic** **Pembrolizumab** + CT (?CPS)
2L Metastatic Taxane ± ramucirumab *or* irinotecan	**2L Metastatic** **Nivolumab** *or* **pembrolizumab** (CPS ≥10) *or* BSC
3L Metastatic Trifluridine-tipiracil *or* **nivolumab**	**3L Metastatic** Taxane *or* irinotecan *or* BSC

Smyth. Ann Oncol. 2021;32:590.

Slide credit: clinicaloptions.com

Additional FDA Indications for Immune Checkpoint Inhibitors in MSI-H/dMMR/PD-L1+ GI Cancers

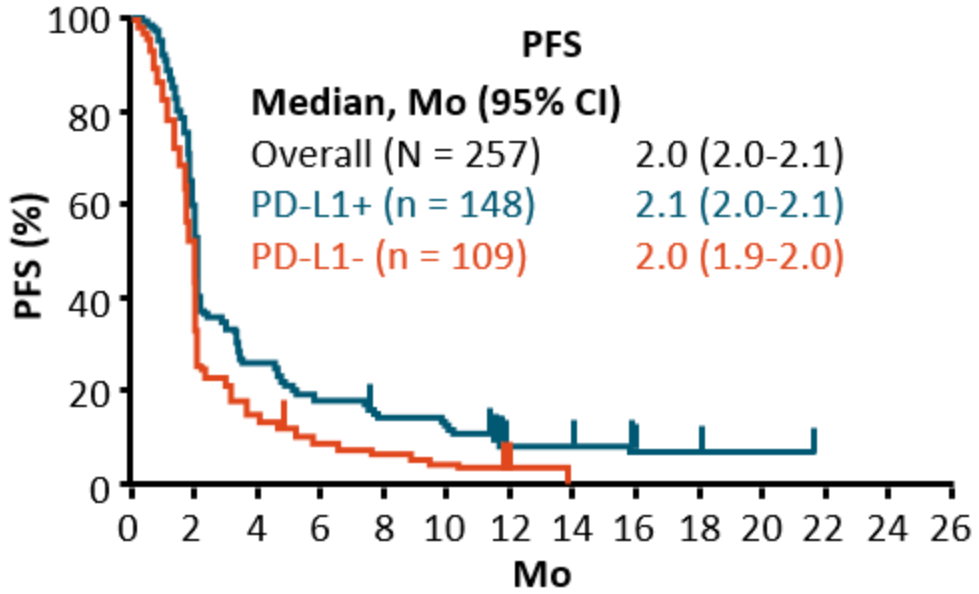
- Pembrolizumab for **MSI-high/dMMR unresectable or metastatic CRC**
- Nivolumab ± ipilimumab for **MSI-high/dMMR metastatic CRC** with PD after fluoropyrimidine, oxaliplatin, and irinotecan
- Pembrolizumab for **PD-L1 CPS ≥1 recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma** with PD on or after ≥2 previous therapies, including fluoropyrimidine- and platinum-containing CT and, if appropriate, HER2/neu-targeted therapy
- Pembrolizumab for **PD-L1 CPS ≥10 locally advanced or metastatic esophageal or GEJ squamous carcinoma** after ≥1 line(s) of systemic therapy

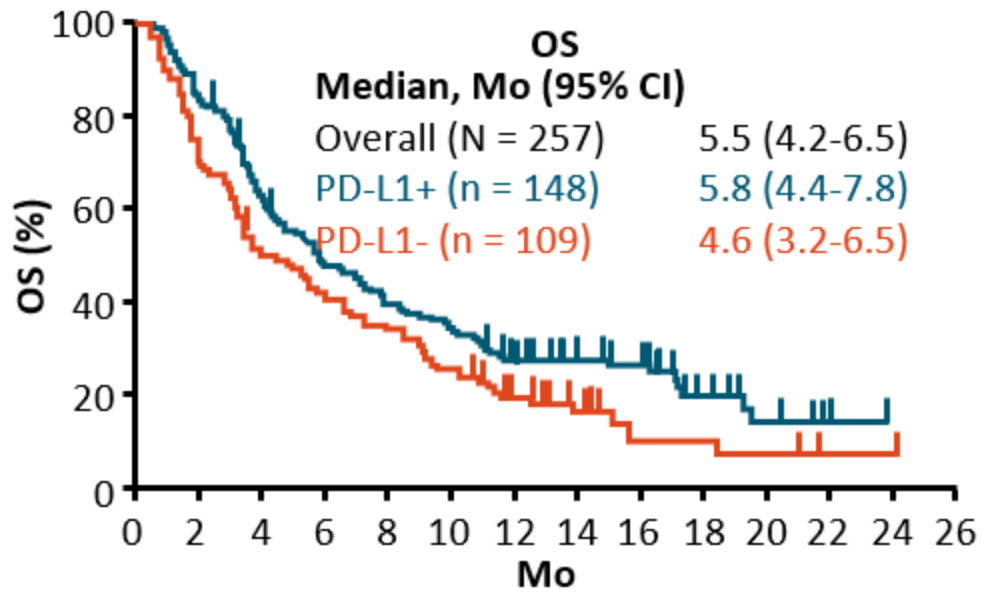
Nivolumab PI. Pembrolizumab PI.

Slide credit: clinicaloptions.com

KEYNOTE-059: Pembrolizumab for Gastric/GEJ Adenocarcinoma With ≥2 Prior Lines of CT

- Open-label phase II study of **pembrolizumab** for patients with recurrent or metastatic **gastric or GEJ** adenocarcinoma and **≥2 prior lines of CT** (cohort 1, N = 259)





Outcome	Overall	PD-L1		MSI Status	
		Positive (n = 148)	Negative (n = 109)	High (n = 7)	Non-H (n = 167)
ORR, % (95% CI)	11.6 (8.0-16.1)	15.5 (10.1-22.4)	6.4 (2.6-12.8)	57.1	9.0
Median DoR, mo (95% CI)	8.4 (1.6+ to 17.3+)	16.3 (1.6+ to 17.3+)	6.9 (2.4 to 7.0+)	--	--

Fuchs. JAMA Oncol. 2018;4:e180013. Wainberg. ESMO 2017. Abstr LBA28_PR.

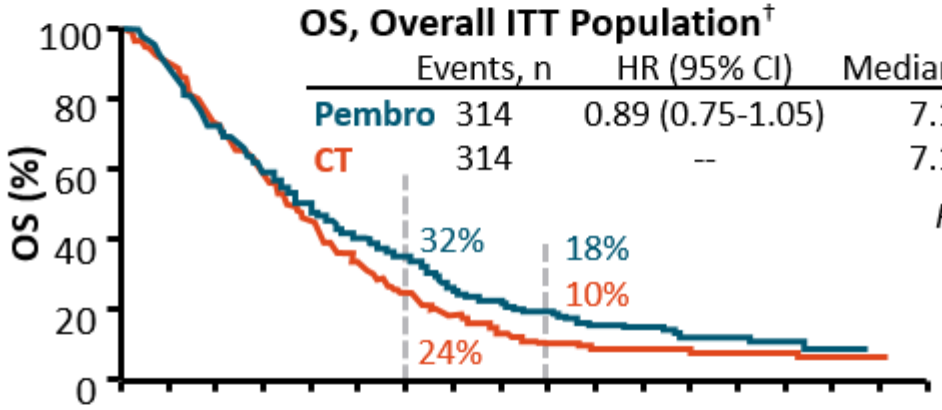
Slide credit: clinicaloptions.com

KEYNOTE-181: Second-Line Pembrolizumab vs Chemotherapy for Esophageal/GEJ Cancer

- Randomized phase III trial of **pembrolizumab** vs **investigator's choice CT*** for patients with advanced/metastatic **esophageal adenocarcinoma/SCC or GEJ adenocarcinoma** and **PD after 1L tx** (N = 628)

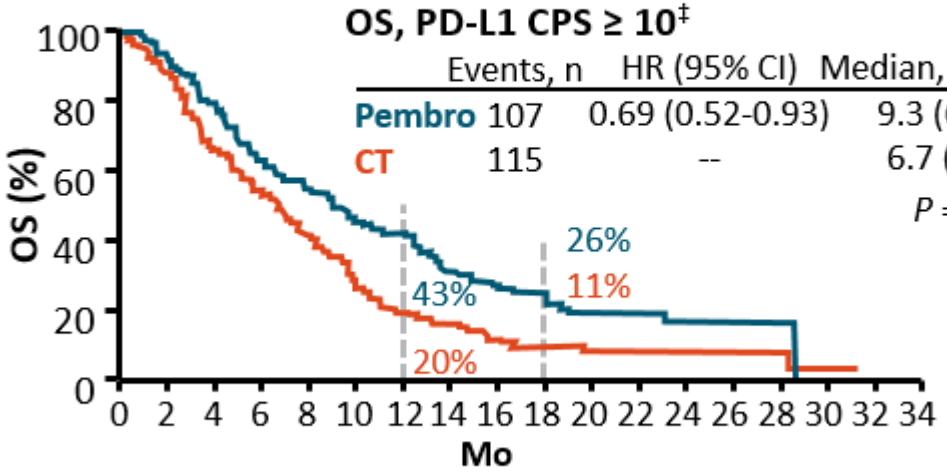
OS, Overall ITT Population†

	Events, n	HR (95% CI)	Median, Mo (95% CI)
Pembro	314	0.89 (0.75-1.05)	7.1 (6.2-8.1)
CT	314	--	7.1 (6.3-8.0)
			P = .0560



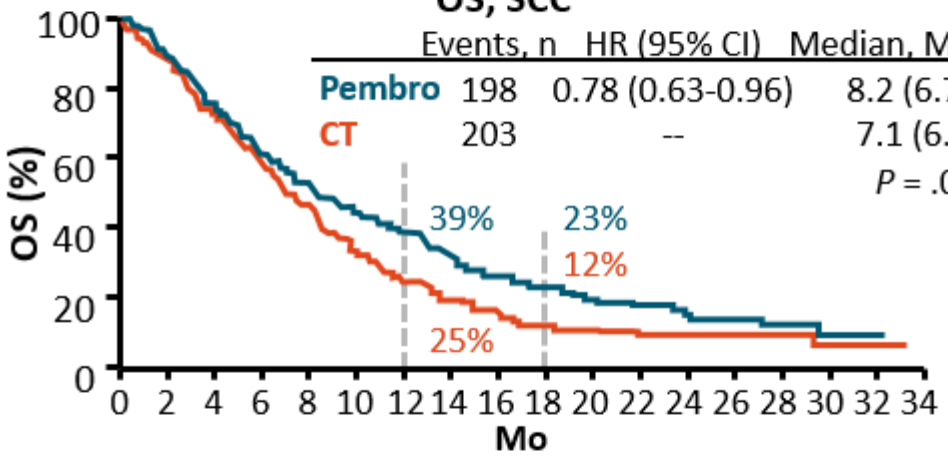
OS, PD-L1 CPS ≥ 10‡

	Events, n	HR (95% CI)	Median, Mo (95% CI)
Pembro	107	0.69 (0.52-0.93)	9.3 (6.6-12.5)
CT	115	--	6.7 (5.1-8.2)
			P = .0074



OS, SCC†

	Events, n	HR (95% CI)	Median, Mo (95% CI)
Pembro	198	0.78 (0.63-0.96)	8.2 (6.7-10.3)
CT	203	--	7.1 (6.1-8.2)
			P = .0095



ORR, %	Pembrolizumab	Chemotherapy	*P* Value
Total population	13.1	6.7	.0037
PD-L1 CPS ≥ 10	21.5	6.1	.0006
SCC	16.7	7.4	.0022

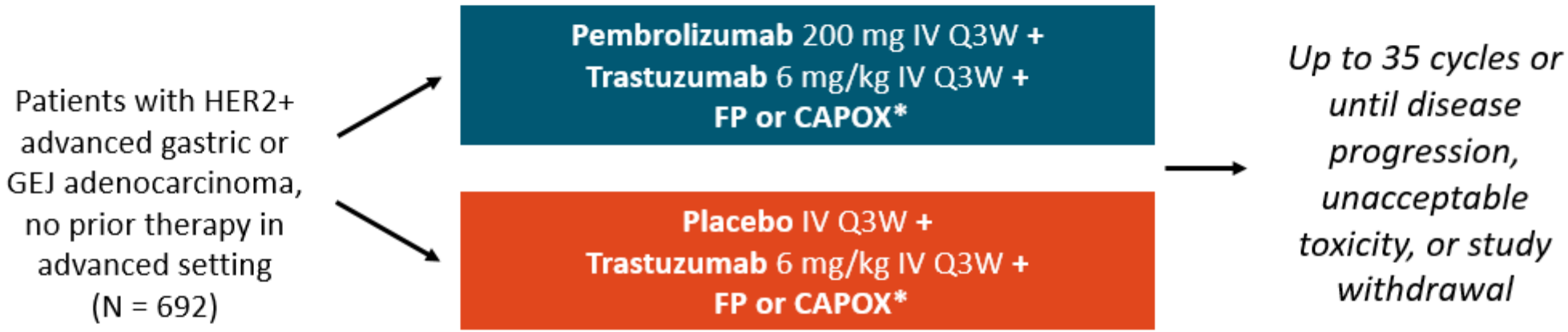
*Paclitaxel or irinotecan. †Did not meet primary endpoint per statistical prespecifications. ‡Met primary endpoint per statistical prespecifications.

Kojima. JCO. 2020;38:4138.

Slide credit: clinicaloptions.com

KEYNOTE-811: 1L Pembrolizumab + Trastuzumab + Chemotherapy in HER2+ Metastatic Gastric/GEJ Cancer

- Randomized, double-blind, placebo-controlled phase III study



*Trastuzumab 8 mg/kg loading dose.
FP: 5-fluorouracil 800 mg/m^2 IV Days 1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W.
CAPOX: capecitabine 1000 mg/m^2 BID Days 1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W.

- Efficacy analysis: first 264 patients enrolled; safety analysis: 433 patients who received ≥1 dose of study medication
- Primary endpoints: OS, PFS per RECIST v1.1 by BICR; secondary endpoints: ORR and DoR per RECIST v1.1 by BICR, safety

Janjigian. Nature. 2021;600:727.

KEYNOTE-811 Interim Analysis: Efficacy

Outcome	Pembrolizumab (n = 133)	Placebo (n = 131)
ORR, % (95% CI)	**74.4 (66.2-81.6)**	**51.9 (43.0-60.7)**
ORR difference*	**22.7 (11.2-33.7); *P* = .00006**	
DCR, % (95% CI)	96.2 (91.4-98.8)	89.3 (82.7-94.0)
Best response, n (%)		
▪ CR	15 (11)	4 (3)
▪ PR	84 (63)	64 (49)
▪ SD	29 (22)	49 (37)
▪ PD	5 (4)	7 (5)
▪ Not evaluable	0	2 (2)
▪ Not assessed	0	5 (4)
Duration of response†	(n = 99)	(n = 68)
▪ Median, mo (range)	10.6 (1.1+ to 16.5+)	9.5 (1.4+ to 15.4+)
▪ ≥6 mo duration, %	70.3	61.4
▪ ≥9 mo duration, %	58.4	51.1
Size reduction from baseline, n (%)	(n = 124)	(n = 122)
▪ Any decrease	97	90
▪ ≥80% decrease	32	15

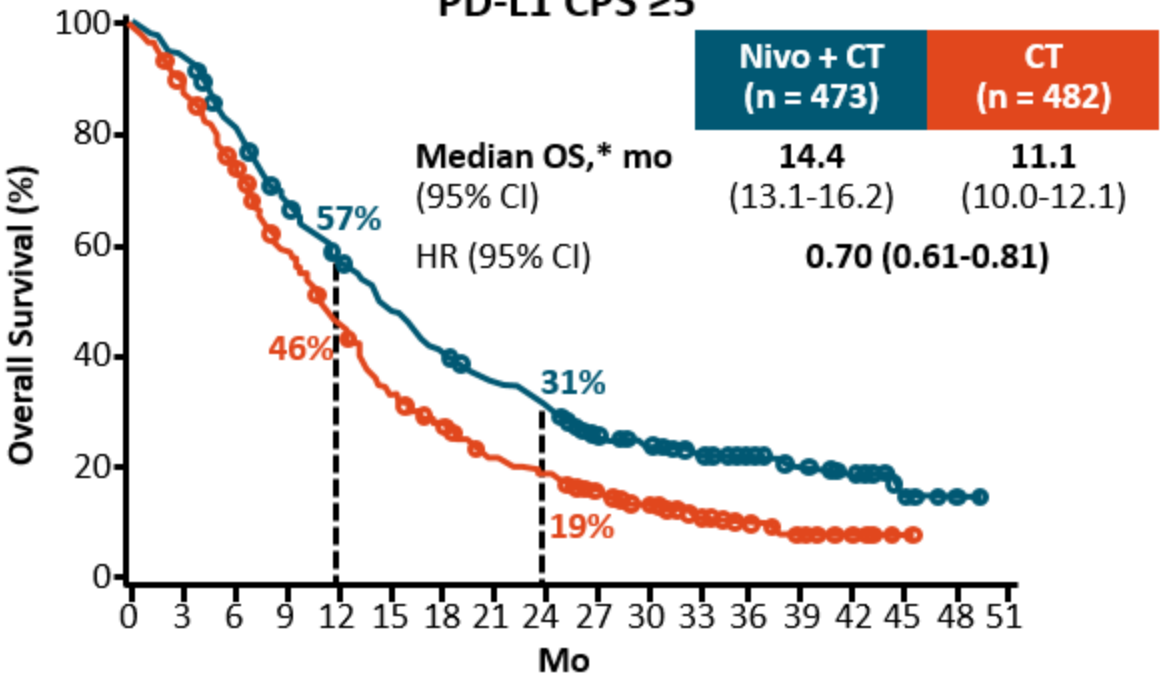
Janjigian. Nature. 2021;600:727.

Slide credit: clinicaloptions.com

CheckMate 649: First-line Nivolumab + Ipilimumab or CT vs CT in Gastroesophageal Cancer

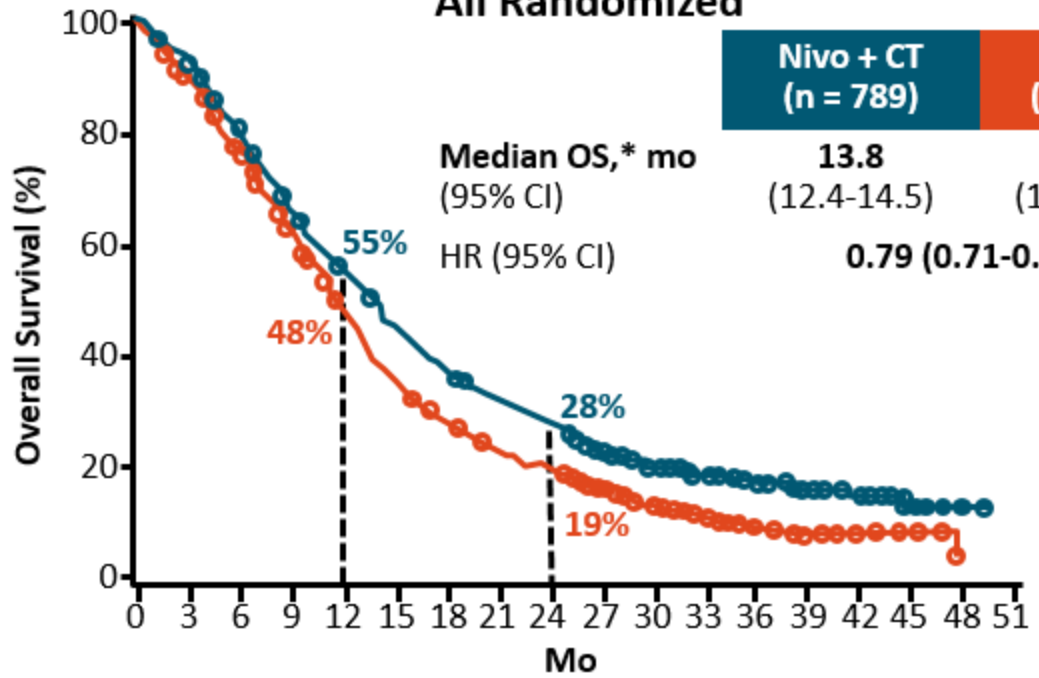
- Randomized phase III trial of nivolumab + ipilimumab, **nivolumab + CT**,* or **CT*** for patients with previously untreated unresectable, advanced, or metastatic gastric/GEJ/esophageal adenocarcinoma (N = 1581)

PD-L1 CPS ≥5



	Nivo + CT (n = 473)	CT (n = 482)
Median OS,* mo	**14.4**	**11.1**
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (95% CI)	**0.70 (0.61-0.81)**	

All Randomized



	Nivo + CT (n = 789)	CT (n = 792)
Median OS,* mo	**13.8**	**11.6**
(95% CI)	(12.4-14.5)	(10.9-12.5)
HR (95% CI)	**0.79 (0.71-0.88)**	

	CPS ≥5 (n = 955)	CPS ≥1 (n = 1296)	All Randomized	CPS <5 (n = 606)
HR for OS	0.70	0.76	0.79	0.94

*XELOX or FOLFOX.

Janjigian. ESMO 2021. Abstr LBA7. Janjigian. Lancet. 2021;398:27.

Slide credit: clinicaloptions.com

KEYNOTE-590: First-line Pembrolizumab + Chemotherapy vs Chemotherapy for Esophageal/GEJ Cancer

- Randomized phase III trial of **pembrolizumab + CT*** vs **CT*** for previously untreated patients with locally advanced unresectable or metastatic EAC, ESCC, or GEJA (N = 749)

Outcome	All Patients			All Patients PD-L1 CPS ≥10			ESCC			ESCC PD-L1 CPS ≥10		
	Pembro + CT (n = 373)	CT (n = 376)	HR/ *P* Val	Pembro + CT (n = 186)	CT (n = 197)	HR/ *P* Val	Pembro + CT (n = 274)	CT (n = 274)	HR/ *P* Val	Pembro + CT (n = 143)	CT (n = 143)	HR/ *P* Val
Median OS,† mo	12.4	9.8	0.73/ <.0001	13.5	9.4	0.62/ <.0001	12.6	9.8	0.72/ .0006	13.9	8.8	0.57/ <.0001
Median PFS,† mo	6.3	5.8	0.65/ <.0001	7.5	5.5	0.51/ <.0001	6.3	5.8	0.65/ <.0001	--	--	--

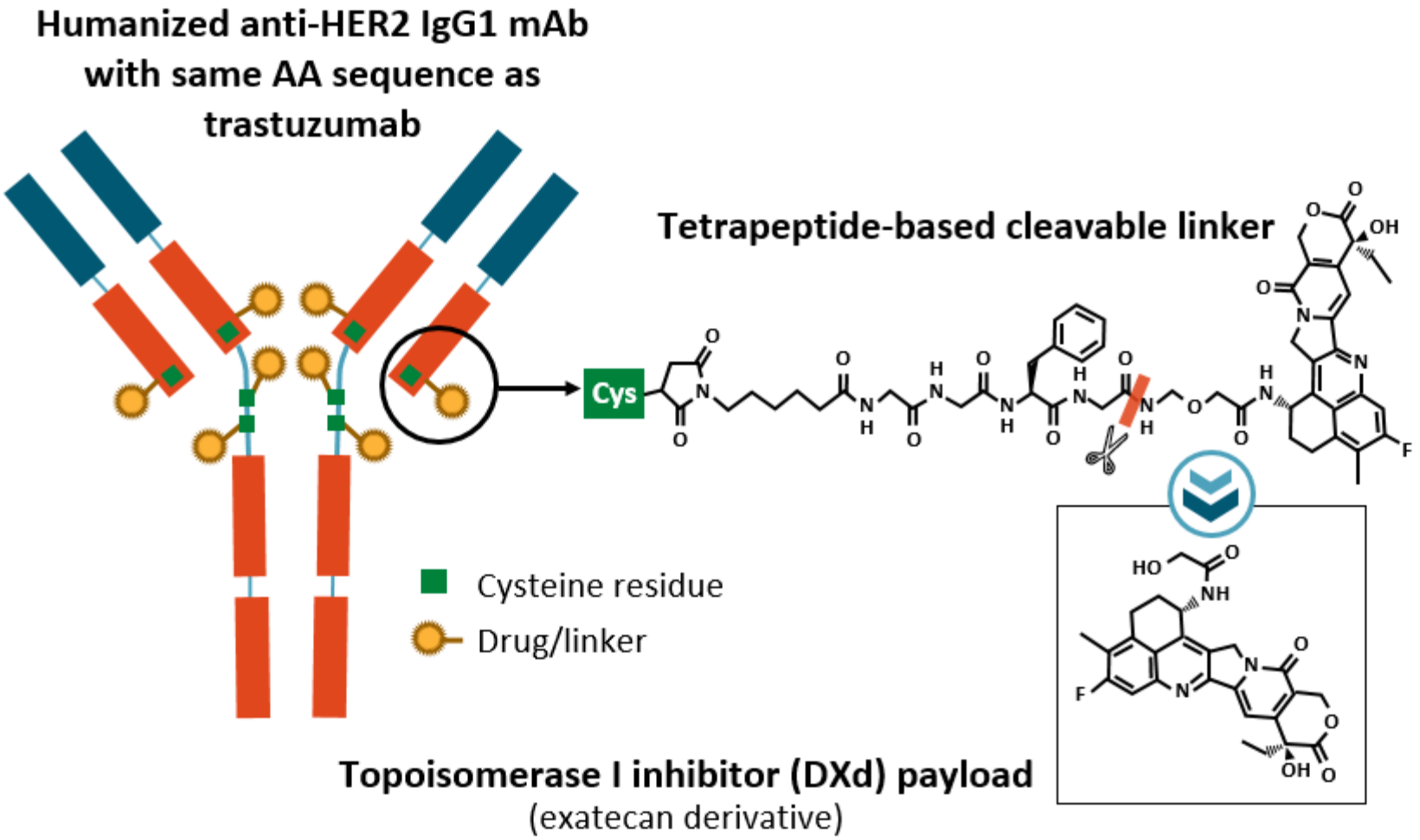
	CPS ≥10 (n = 383)	All Randomized	CPS <10 (n = 347)
HR for OS	0.62	0.73	0.86

*5-FU + cisplatin. †Primary endpoint.

Sun. Lancet. 2021;398:759.

Slide credit: clinicaloptions.com

HER2-Targeted ADC: Trastuzumab Deruxtecan



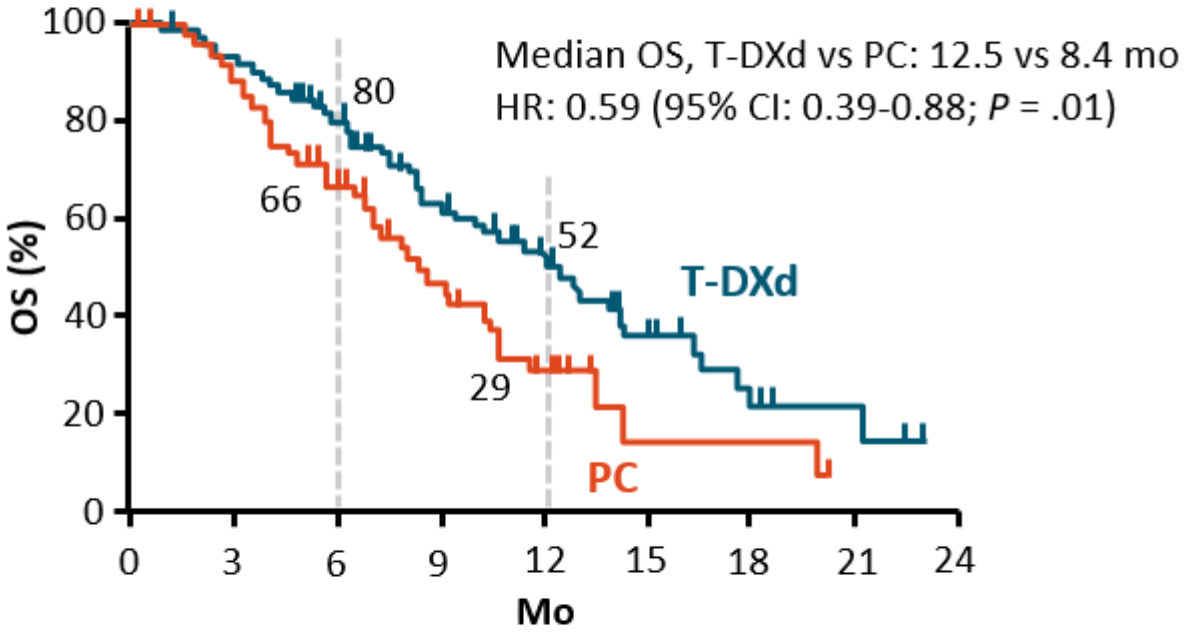
- High drug:antibody ratio: ~8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

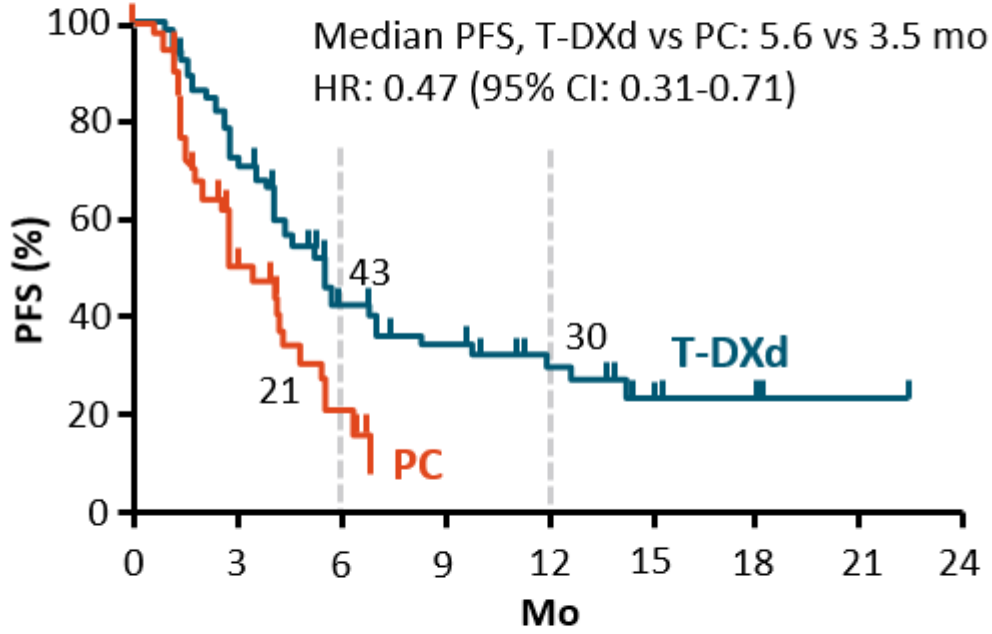
Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.

Slide credit: clinicaloptions.com

DESTINY-Gastric01: Trastuzumab Deruxtecan in Previously Treated, HER2+ Gastric/GEJ Adenocarcinoma

- Open-label, randomized phase II study of T-DXd vs irinotecan or paclitaxel for pts with HER2+ locally advanced or metastatic gastric or GEJ cancer that progressed on ≥2 prior regimens (N = 188)





- ORR: T-DXd, 54%; CT, 14%
- FDA approved for pts with locally advanced or metastatic HER2+ gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen

1. Shitara. Lancet Oncol. 2019;20:827. 2. Shitara. NEJM. 2020;382:2419.

Trastuzumab Deruxtecan Approval

- HER2-targeted antibody-drug conjugate
  - mAb has same AA sequence as trastuzumab; topoisomerase I inhibitor payload (exatecan derivative)
- Indicated for adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen

Trastuzumab deruxtecan PI.

Slide credit: clinicaloptions.com

Select Investigational Targeted Agents for Advanced Gastroesophageal Cancers

Agent	MoA	Key Trial	
Margetuximab	HER2-targeted antibody	CP-MGAH22-05: phase Ib/II study of margetuximab + pembrolizumab for previously treated advanced HER2+ GE cancers (N = 95)	ORR: 18%; median PFS: 3 mo; median OS: 13 mo
Zanidatamab	HER2-targeted bispecific antibody	Phase Ib/II study of zanidatamab ± CT for previously treated advanced HER2+ GE cancers (N = 52)	ORR: zan, 33%; zan + pac, 50%; zan + cape, 57%
Bemarituzumab	FGFR2b-targeted antibody	FIGHT: phase II study of first-line bemarituzumab vs placebo (both + mFOLFOX6) for advanced G/GEJ cancer with *FGFR2b* overexp/amp (N = 155)	Median OS, mo: bema, NR; placebo, 12.9 (HR: 0.58; *P* = .0268)
Zolbetuximab	CLDN18.2-targeted antibody	FAST: phase II study of first-line zolbetuximab + EOX vs EOX for advanced CLDN18.2+ G/GEJ cancer (N = 252)	Median OS, mo: zolb + EOX, 13; EOX, 8.3 (HR: 0.55; *P* <.0005)

Catenacci. Lancet Oncol. 2020;21:1066. Meric-Bernstam. ASCO GI 2021. Abstr 164.
Wainberg. ASCO GI 2021. Abstr LBA160. Sahin. Ann Oncol. 2021;32:609.

Selected Ongoing Phase III Trials for Advanced Gastroesophageal Cancer

Trial	Regimen	Population	Phase
MOUNTAINEER-02 (NCT04499924)	Tucatinib + trastuzumab vs placebo (both with ramucirumab + paclitaxel)	2L+, GC/GEJC, HER2+	II/III
MAHOGANY (NCT04082364)	Margetuximab + PD-1 inhibitor ± CT or margetuximab + CT ± dual checkpoint inhibitor or trastuzumab + CT	1L, GC/GEJC, HER2+	II/III
DESTINY-Gastric04 (NCT04704934)	Trastuzumab deruxtecan vs ramucirumab + paclitaxel	2L+, GC/GEJC, HER2+	III
FORTITUDE-101 (NCT05052801)	Bemarituzumab + mFOLFOX6 vs placebo + mFOLFOX6	1L, GC/GEJC, FGFR2+	III
GLOW (NCT03653507)	Zolbetuximab + CAPOX vs placebo + CAPOX	1L, GC/GEJC, CLDN18.2+	III
SPOTLIGHT (NCT03504397)	Zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6	1L, GC/GEJC, CLDN18.2+	III

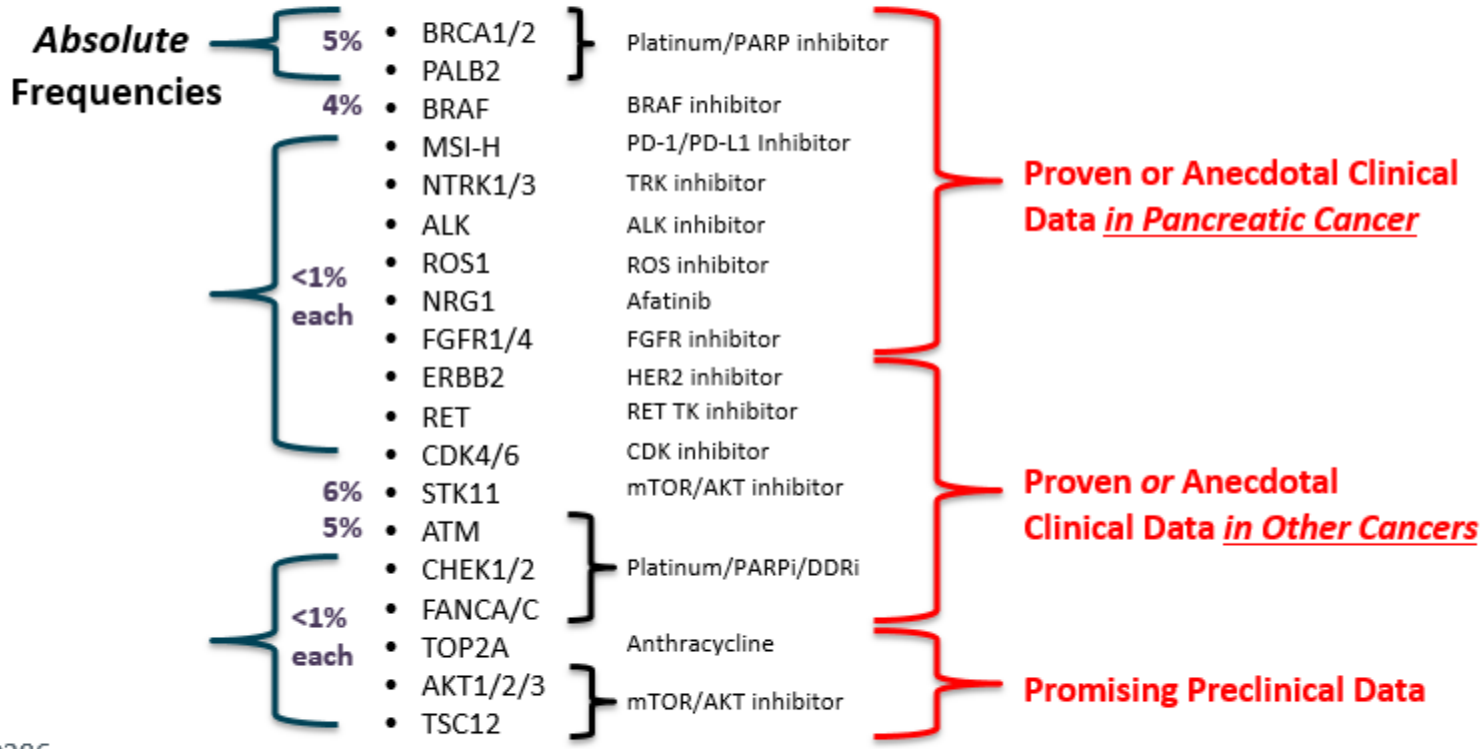
Slide credit: clinicaloptions.com

Biomarker-Driven Treatment of Pancreatic and Hepatobiliary Cancers

STRONGERTOGETHER

Pancreatic Cancers *DO* Harbor Actionable Mutations

- NGS efforts have consistently revealed that ≥25% of pancreatic cancers have potentially highly actionable molecular biomarkers



Singhi. Gastroenterology. 2019;156:2242. Pishvaian. Clin Cancer Res. 2018;24:5018. Heeke. JCO Precis Oncol. 2018;2018:10.1200/PO.17.00286. Aguire. Cancer Discov. 2018;8:1096. Witkiewicz. Nat Commun. 2015;6:6744. Lowery. Clin Cancer Res. 2017;23:6094. Waddell. Nature. 2015;518:495. Bailey. Nature. 2016;531:47. Biankin. Nature. 2012;491:399. Collisson. Nat Med. 2011;17:500. Pishvaian. Oncology (Williston Park). 2017;31:168. Jones. Clin Cancer Res. 2019;25:4674.

Slide credit: clinicaloptions.com

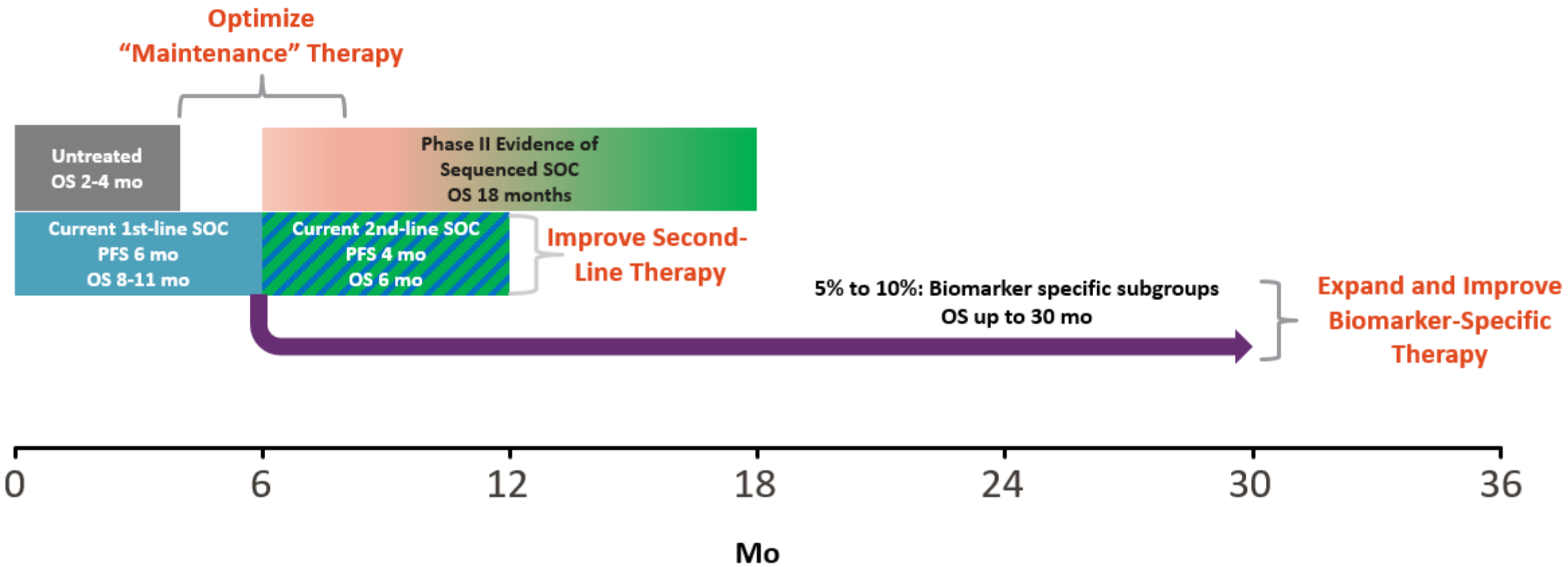
Pancreatic Cancer: Guideline Recommendations

- Germline testing recommended for any patient with PDAC
  - Multigene panel
- Tumor/somatic profiling recommended for all locally advanced/ metastatic patients who are candidates for anticancer therapy to identify uncommon actionable mutations
  - Tissue testing optimal
  - cfDNA backup if insufficient tissue

Tempero. J Natl Compr Canc Netw. 2021;19:439.

Slide credit: clinicaloptions.com

Metastatic Pancreatic Cancer Survival



Slide credit: clinicaloptions.com

Germline and Somatic Testing in Pancreatic Cancer: Guidelines Recommendation

Germline testing is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes

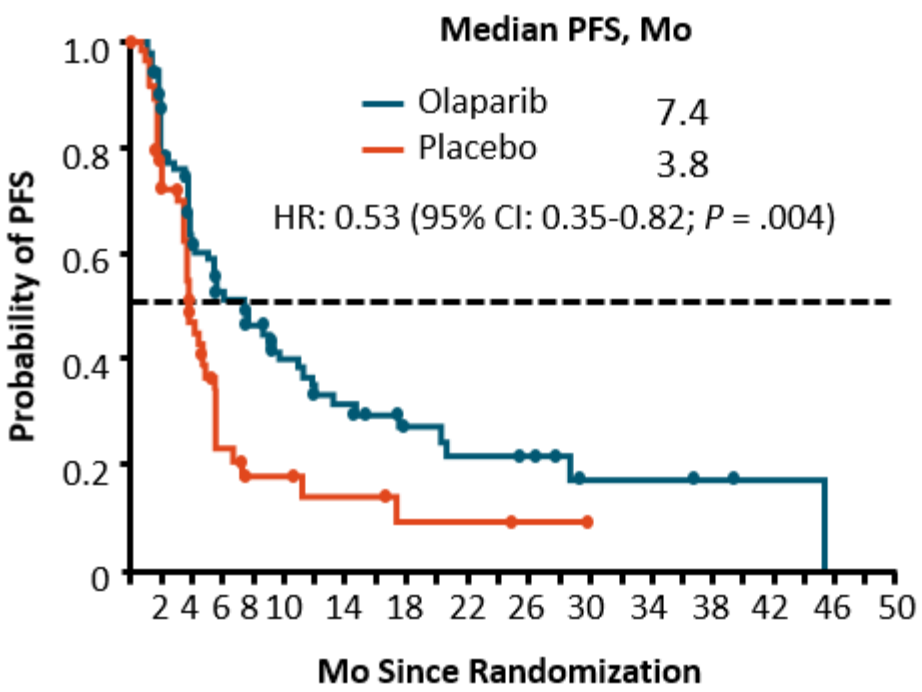
Tumor/somatic gene profiling is recommended for patients with locally advanced/metastatic pancreatic cancer (~80% of patients) who are candidates for anti-cancer therapy to identify uncommon but actionable mutations

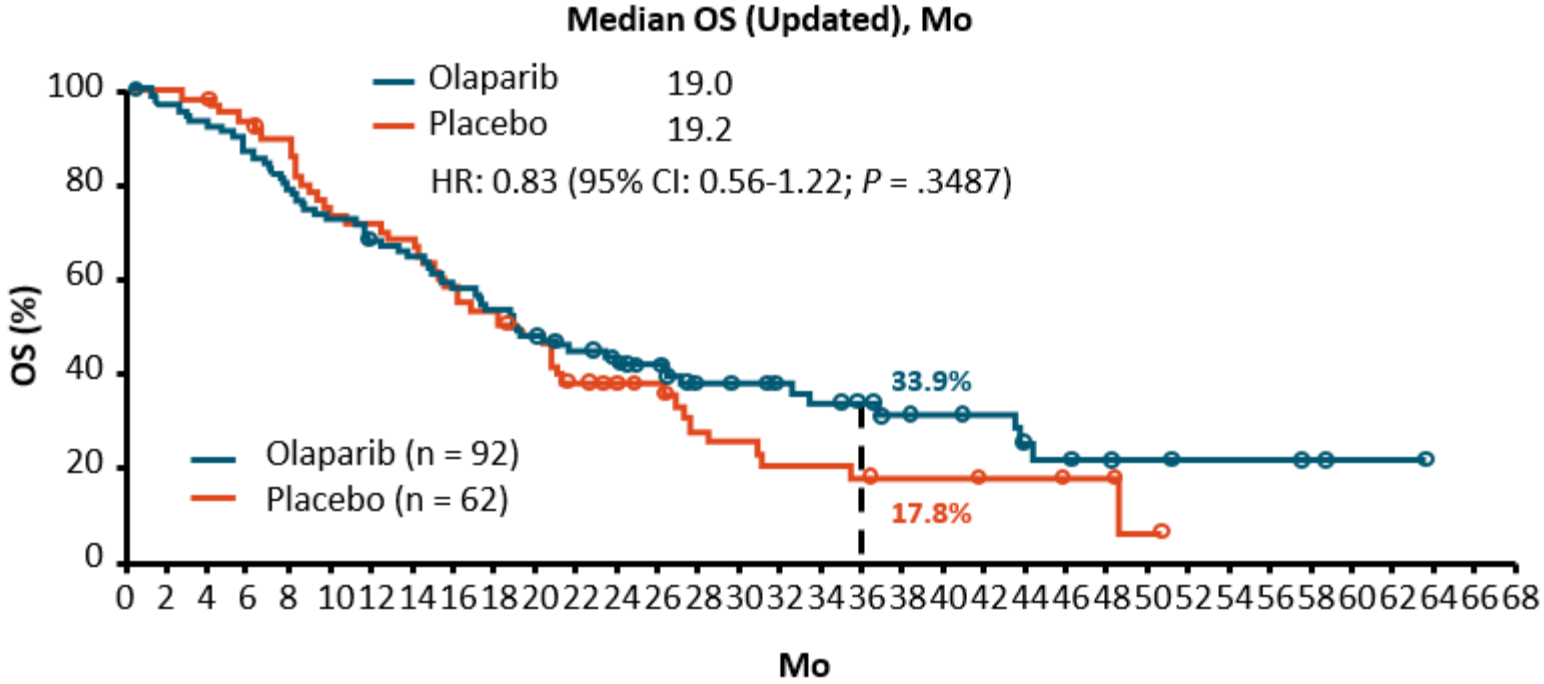
NCCN. Pancreatic Adenocarcinoma Guidelines. v2.2021. Sohal. JCO. 2020;JCO2001364.

Slide credit: clinicaloptions.com

POLO: Maintenance Olaparib vs Placebo After First-line, Platinum-Based Therapy in Metastatic Pancreatic Cancer

- Randomized phase III trial of maintenance olaparib or placebo for patients with metastatic pancreatic cancer and deleterious/suspected deleterious g*BRCA1/2* mutation, ≥16 wk of first-line platinum-based therapy without progression (N = 154)



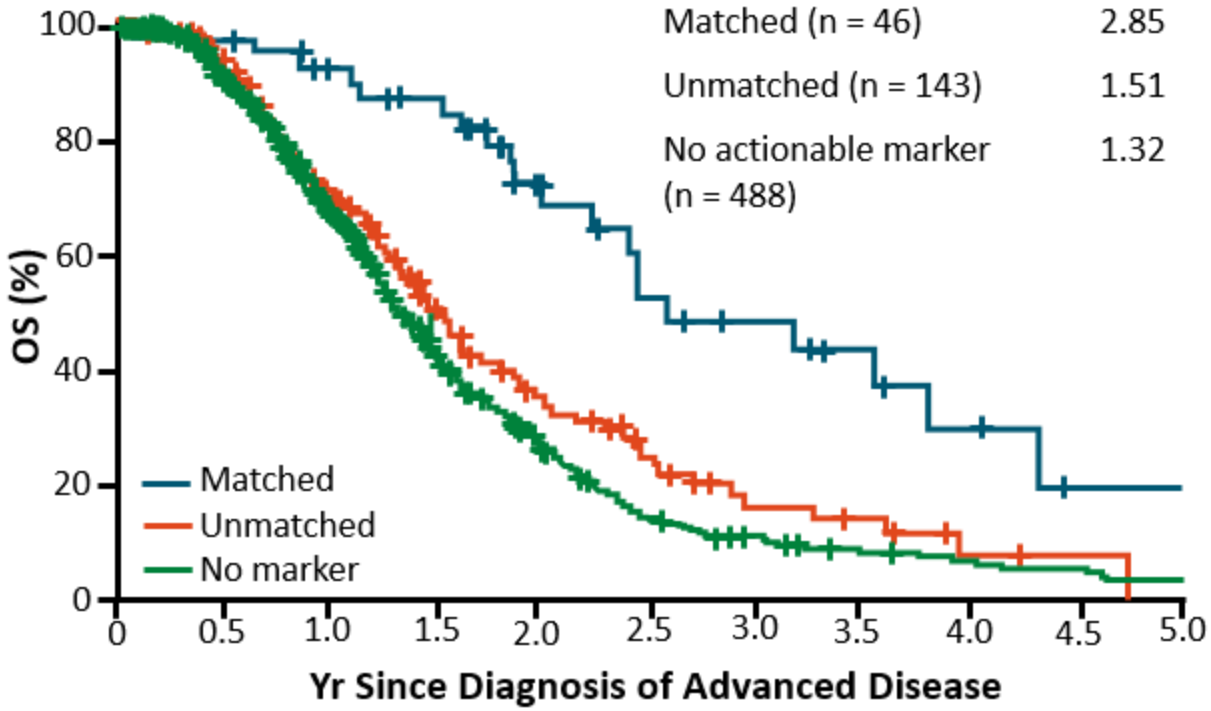


Golan. NEJM. 2019;381:317. Golan. ASCO GI 2021. Abstr 378.

Slide credit: clinicaloptions.com

Gold Standard: Overall Survival Benefit

- 1028 pancreatic cancer patients
  - All underwent molecular profiling w/NGS
- 677 patients with outcome information
  - 189 with actionable findings
    - 46 received molecularly matched therapy
    - 143 received "unmatched" therapy
  - 488 with no actionable findings
- Overall survival
  - **Matched 1 y > unmatched**
  - **Matched 1.3 y > no actionable marker**



Group	mOS, Yr
Matched (n = 46)	2.85
Unmatched (n = 143)	1.51
No actionable marker (n = 488)	1.32

Comparison	HR (95% CI)
Matched vs unmatched (highly actionable)	0.42 (0.26-0.68); *P* = .0004
Matched vs no actionable marker	0.34 (0.22-0.53); *P* <.0001

Pishvaian. Lancet Oncol. 2020;21:508.

Slide credit: clinicaloptions.com

cfDNA/ctDNA in Pancreatic Cancer

- Sensitivity is not too high[1,2]
  - *KRAS* mutation detection: 30% to 75%
- But specificity is very high[2]
  - Concordance with *KRAS* mutations in tissue: 90% to 100%
- Can be used to track outcomes on serial samples
  - Decrease in mutated *KRAS* an early indicator of response to therapy[3]
- Might be useful as a prognostic and/or predictive marker[3-5]
  - Median OS: 3.2 mo for detectable vs 8.4 mo for undetectable ctDNA[4]

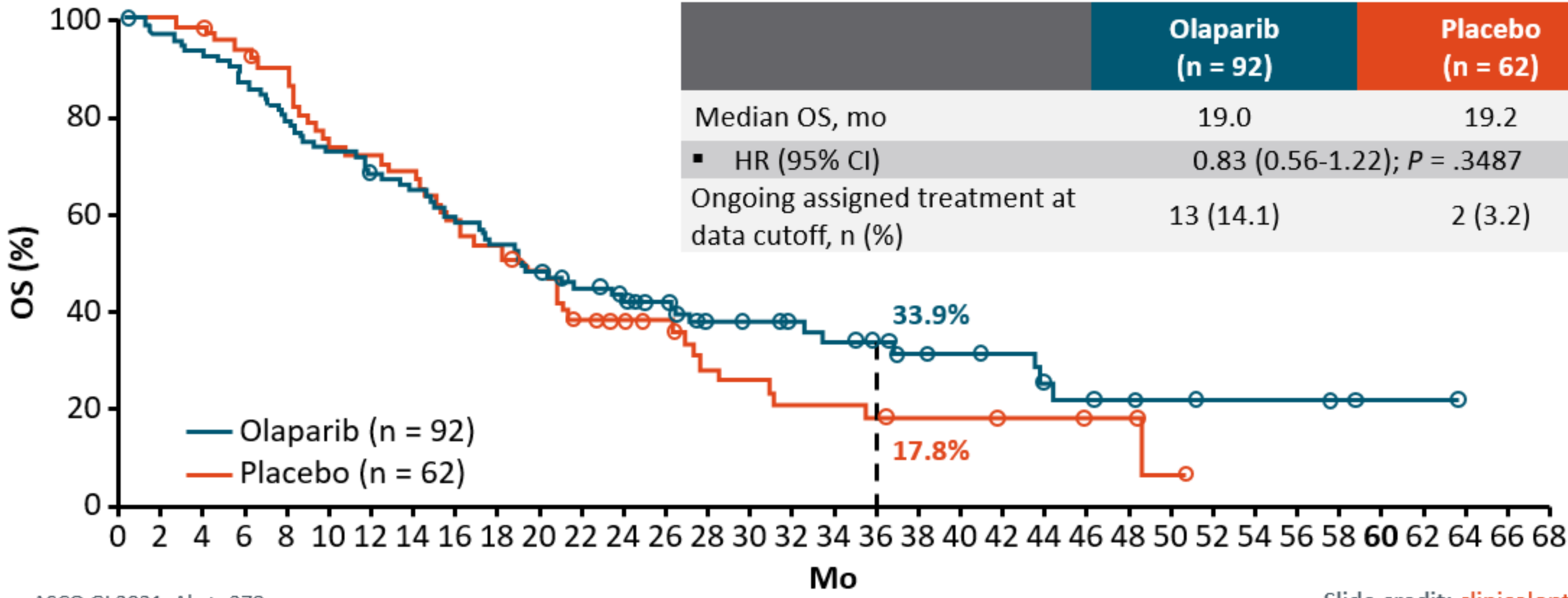
1. Pishvaian. Oncotarget. 2016;8:83446. 2. Kruger. Ann Oncol. 2018;29:2348. 2019;13:1623. 3. Nakano. Br J Cancer. 2018;118:662.
4. Strijker. Int J Cancer. 2019;146:1445. 5. Lee. Mol Oncol. 2019;13:1623.

Slide credit: clinicaloptions.com

POLO: Maintenance Olaparib vs Placebo After First-line Platinum-Based Therapy in Metastatic Pancreatic Cancer

- Randomized phase III trial of maintenance olaparib or placebo for patients with metastatic pancreatic cancer and deleterious/suspected deleterious g*BRCA1/2* mutation, ≥16 wk of first-line platinum-based therapy without progression (N = 154)

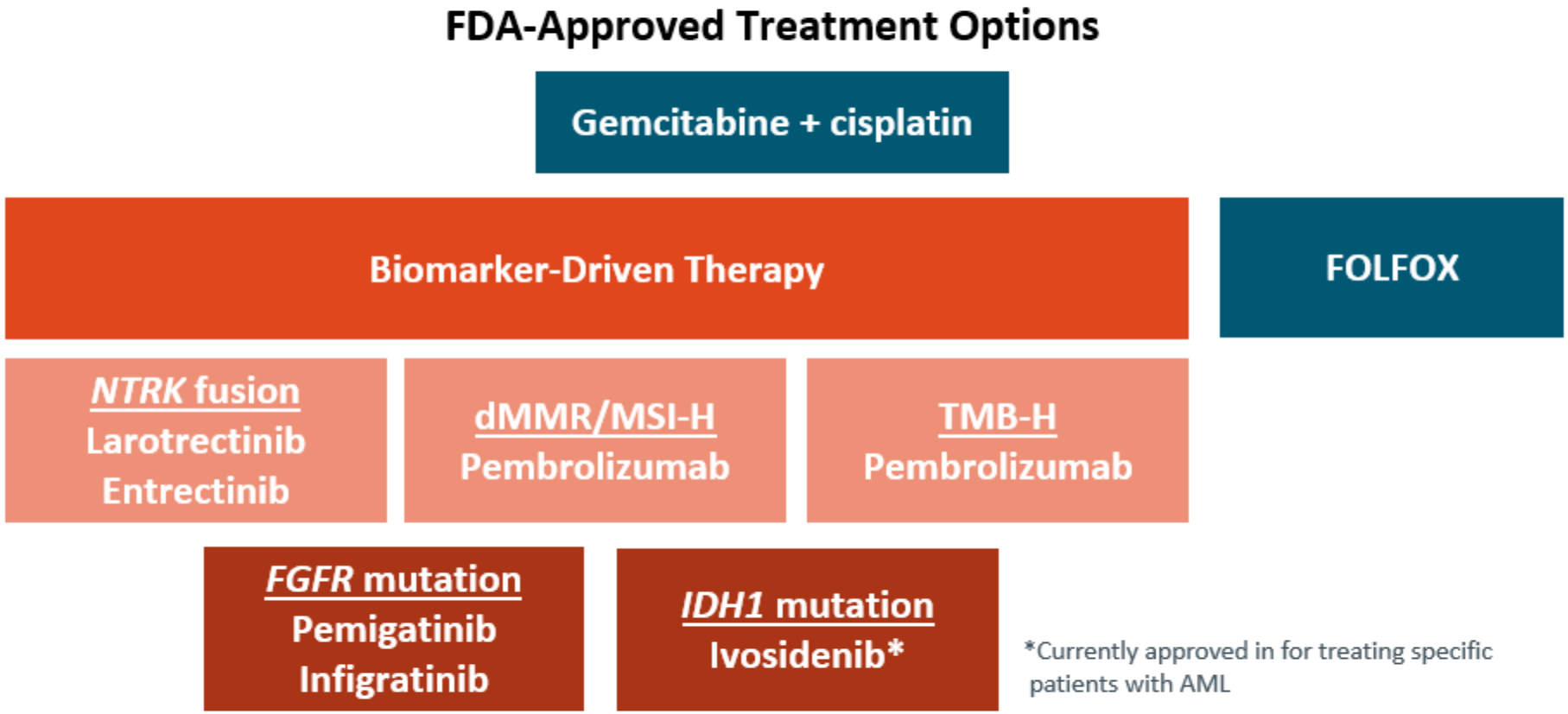
	Olaparib (n = 92)	Placebo (n = 62)
Median OS, mo	19.0	19.2
▪ HR (95% CI)	0.83 (0.56-1.22); *P* = .3487	
Ongoing assigned treatment at data cutoff, n (%)	13 (14.1)	2 (3.2)



Golan. ASCO GI 2021. Abstr 378.

Slide credit: clinicaloptions.com

Select Treatments for Advanced BTC



- Currently being assessed: gemcitabine + cisplatin + nab-paclitaxel or immunotherapy; TKIs + immunotherapy; Nal-IRI plus 5-FU/LV; trastuzumab (*HER2* amplified); dabrafenib + trametinib (*BRAF* V600E mutation)

NCCN. Hepatobiliary Cancer Guidelines. v3.2021.

Slide credit: clinicaloptions.com

Cholangiocarcinoma: Target-Rich Disease

Genetic Abnormality, n (%)	Intrahepatic CCA (n = 55)	Extrahepatic CCA (n = 20)	Odds Ratio	*P* Value	95% CI
TP53	16 (29.1)	9 (45)	0.506	.268	0.154-1.669
KRAS	13 (23.6)	8 (40)	0.469	.244	0.138-1.626
ARID1A	11 (20)	1 (5)	4.678	.164	0.599-214.83
HER2	1 (1.8)	5 (20)	0.058	.004	0.001-0.576
PBRM1	6 (10.9)	1 (5)	2.305	.667	0.252-112.51
BAP1	5 (9.1)	2 (10)	0.901	1	0.132-10.26
FBXW7	3 (5.5)	3 (15)	0.333	.333	0.041-2.719
SMAD4	2 (3.6)	5 (25)	0.333	.333	0.01-0.804
IDH	13 (23.6)	0	Infinite	.01	1.274-INF
MAP-ERK pathway	19 (34.5)	11 (55)	0.437	.121	0.133-1.389
mTOR pathway	14 (25.5)	8 (40)	0.517	.258	0.154-1.776
DNA repair pathway	9 (16.4)	8 (40)	0.299	.058	0.081-1.094
FGF pathway	7 (12.7)	1 (5)	2.741	.673	0.316-131.27
Chromatin modification pathway	18 (32.7)	3 (15)	2.724	.157	0.659-16.364

Churi. PLoS One. 2014;9:e115383.

Slide credit: clinicaloptions.com

Targeted Approaches for BTC

Target	~Frequency in CC	Drug	Benefit	Status
MSI-H/dMMR	3%	Pembrolizumab	ORR: 40%[1]	Tumor agnostic approval
TMB >10 mut/Mb	2.4%	Pembrolizumab	ORR: 29%[1]	Tumor agnostic approval
NTRK fusion	1%	Larotrectinib	ORR: 75%[2]	Tumor agnostic approval
FGFR2 fusion	14% (intrahepatic)	Pemigatinib or infigratinib	ORR: 37% (pemigatinib)[3]; 23% (infigratinib)[4]	Cholangiocarcinoma approval
IDH1 mutation	10%-20% (intrahepatic)	Ivosidenib	PFS HR: 0.37[5]	Cholangiocarcinoma approval
BRAF V600E	4%	Dabrafenib/trametinib	ORR: 41% (ROAR)[6]	Open-label basket study
HER2	9% of BTC*†	Pertuzumab/trastuzumab	ORR: 23% (MyPathway)[7]	Open-label basket study
RET	1%	Pralsetinib	Responses[8]	2/2 PR in basket trial
BRCA1/2, DDR	20%*	PARP inhibitor	Responses reported	Case reports
ROS1	1%	Crizotinib	Response reported	Case reports

Most common in *extrahepatic or †GB.

1. Pembrolizumab PI. 2. Lenvatinib PI. 3. Pemigatinib PI. 4. Infigratinib PI. 5. Ivosidenib PI. 6. Subbiah. Lancet Oncol. 2020;21:1234.
7. Javle. Lancet Oncol. 2021;22:1290. 8. Subbiah. ASCO 2020. Abstr 109. Thornblade. Cancers (Basel). 2021;13:4062.

Select Ongoing Randomized Trials of Immunotherapy/Targeted Therapy for BTC

Trial	Regimens	Phase	Population
TOPAZ-1 (NCT03875235)	Gemcitabine + cisplatin ± durvalumab	III	Previously untreated unresectable/ metastatic BTC (planned N = 757)
KEYNOTE-966 (NCT04003636)	Gemcitabine + cisplatin ± pembrolizumab	III	Previously untreated unresectable/ metastatic BTC (planned N = 1048)
S1815 (NCT03768414)	Gemcitabine + cisplatin ± nab-paclitaxel	III	Previously untreated advanced BTC (planned N = 452)
IMbrave151 (NCT04677504)	Gemcitabine + cisplatin + atezolizumab ± bevacizumab	II	Previously untreated unresectable/ metastatic BTC (planned N = 150)
HERIZON-BTC-01 (NCT04466891)	Zanidatamab	II	Previously treated advanced/ metastatic HER2+ BTC (planned N = 100)
NCT04042831	Olaparib	II	Advanced BTC with DDR alterations (planned N = 36)
NCT03639935	Rucaparib + nivolumab	II	Previously treated advanced/ metastatic BTC (planned N = 35)

Slide credit: clinicaloptions.com

Rationale for Immunotherapy in HCC (cont)

The liver is tolerogenic

- Tolerates foreign antigens
- Increases risk of viral infection, which can lead to chronic liver damage
  - Decreases liver function
  - Increases cirrhosis
  - Increases cancer risk

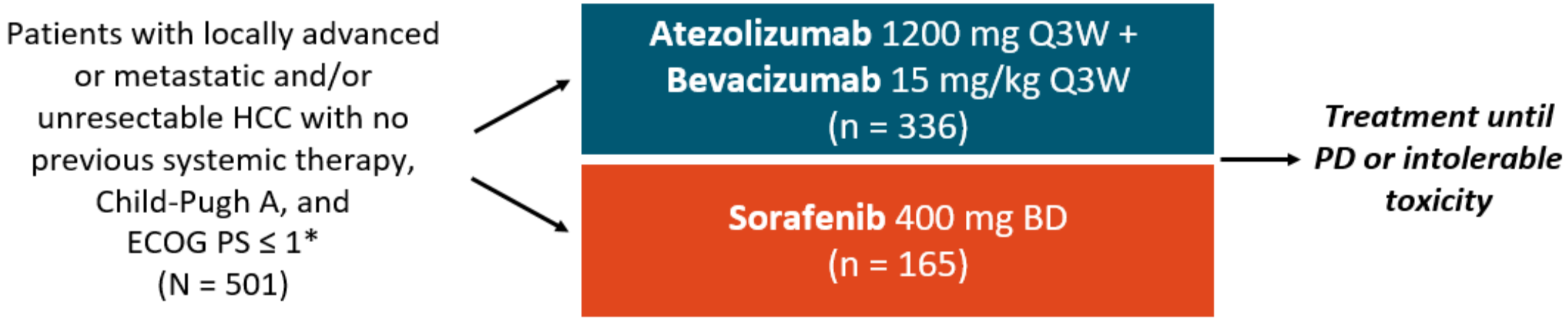
HCC may be considered 2 concurrent diseases: cancer and liver disease

- Patients are frail and may not tolerate some therapies
- Effective but well tolerated treatment options are needed

Johnston MP, Khakoo SI. *World J Gastroenterol.* 2019;35:2977-2989.

IMbrave150: Atezolizumab + Bevacizumab vs Sorafenib for First-line Treatment of HCC

- Multicenter, randomized, open-label phase III trial[1]
  - GO30140: randomized phase Ib study showed potential benefit of atezolizumab + bevacizumab for patients with advanced HCC (ORR 36%)[2]



- Coprimary endpoints: OS and PFS

*Trial included subgroups of high-risk patients excluded from other contemporary phase III trials: ~ 40% had macrovascular invasion; specifically included patients with 50% hepatic involvement or main portal vein invasion or invasion of the portal vein branch contralateral to the primarily involved lobe.

1. Finn. NEJM. 2020;382:1894. 2. Lee. Lancet Oncol. 2020;21:808.

Slide credit: clinicaloptions.com

Combining VEGF and PD-1/PD-L1 Inhibitors

Atezolizumab (PD-L1 Inhibitor)

- Promotes T-cell activation by allowing B7.1 costimulation
- Restores anticancer immunity with activity further enhanced through VEGF-mediated immunomodulatory effects

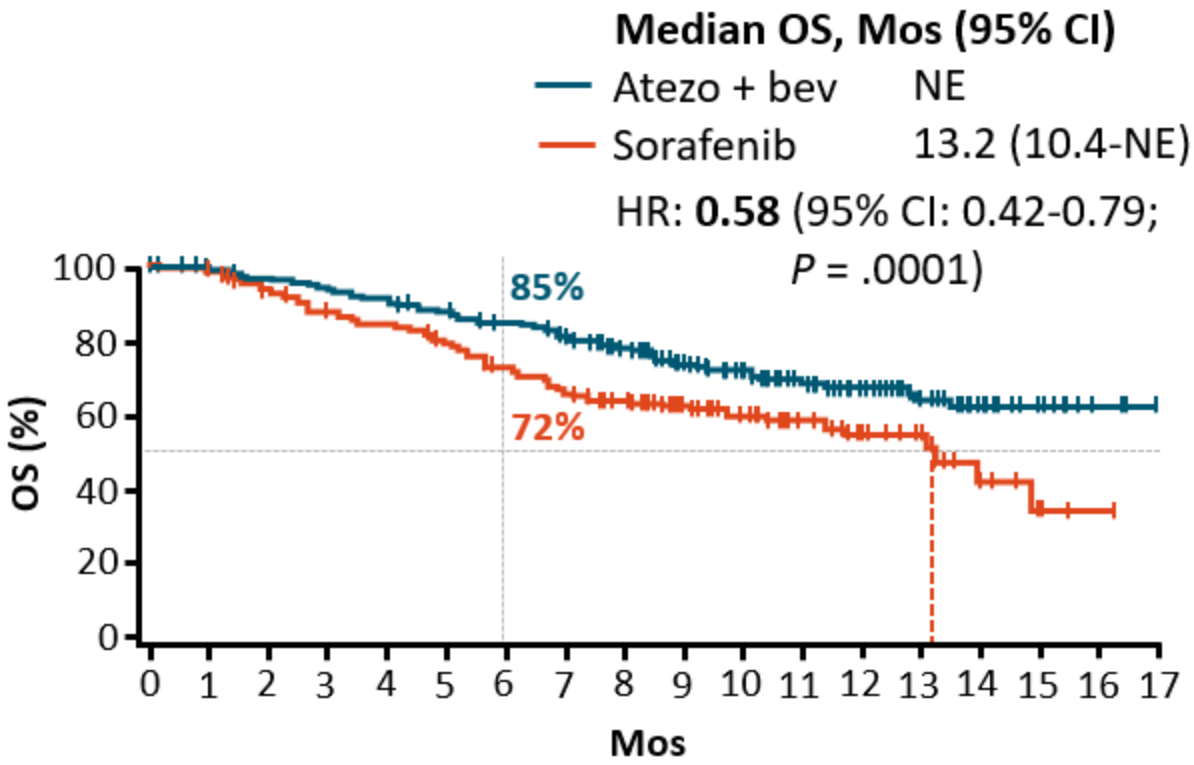
Bevacizumab (VEGF Inhibitor)

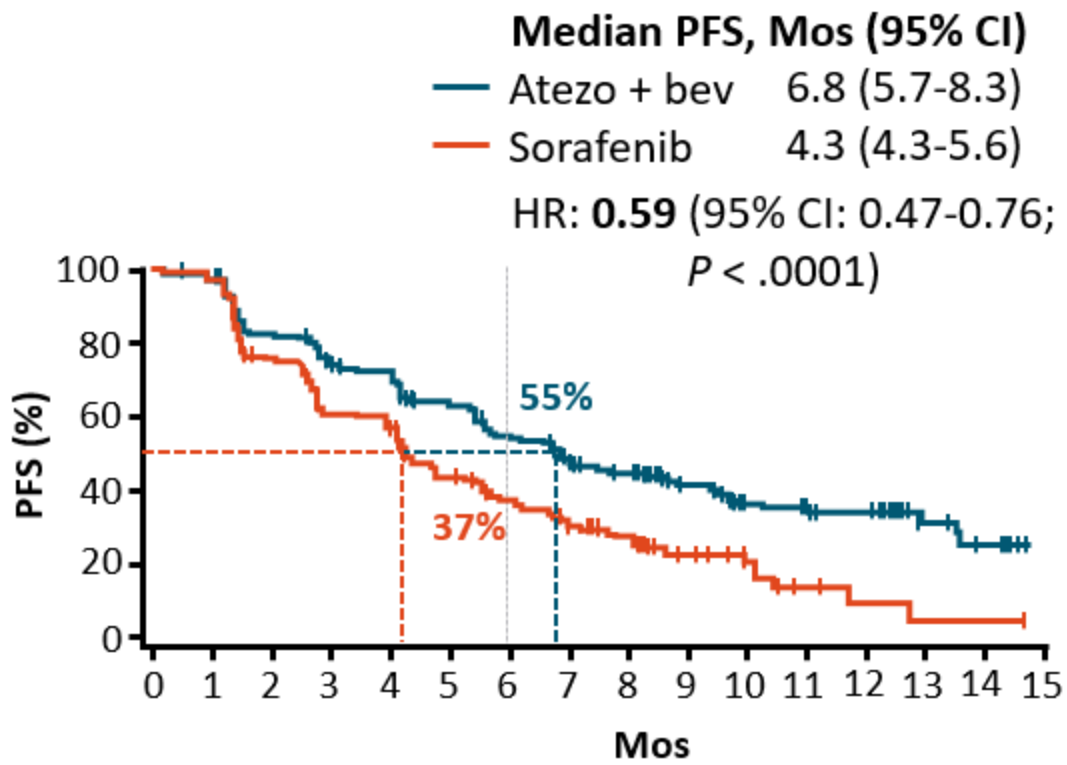
- Promotes DC maturation
- Normalizes tumor vasculature, increasing T-cell infiltration
- Decreases activity of immunosuppressive cells (MDSCs, Tregs)

- **In combination, bevacizumab may enhance efficacy of atezolizumab by reversing VEGF-mediated immunosuppression to promote T-cell infiltration into tumor**

Chen. Immunity. 2013;39:1. Hegde. Semin Cancer Biol. 2018;52:117. Wallin. Nat Commun. 2016;7:12624.

IMbrave150: OS, PFS, and Response





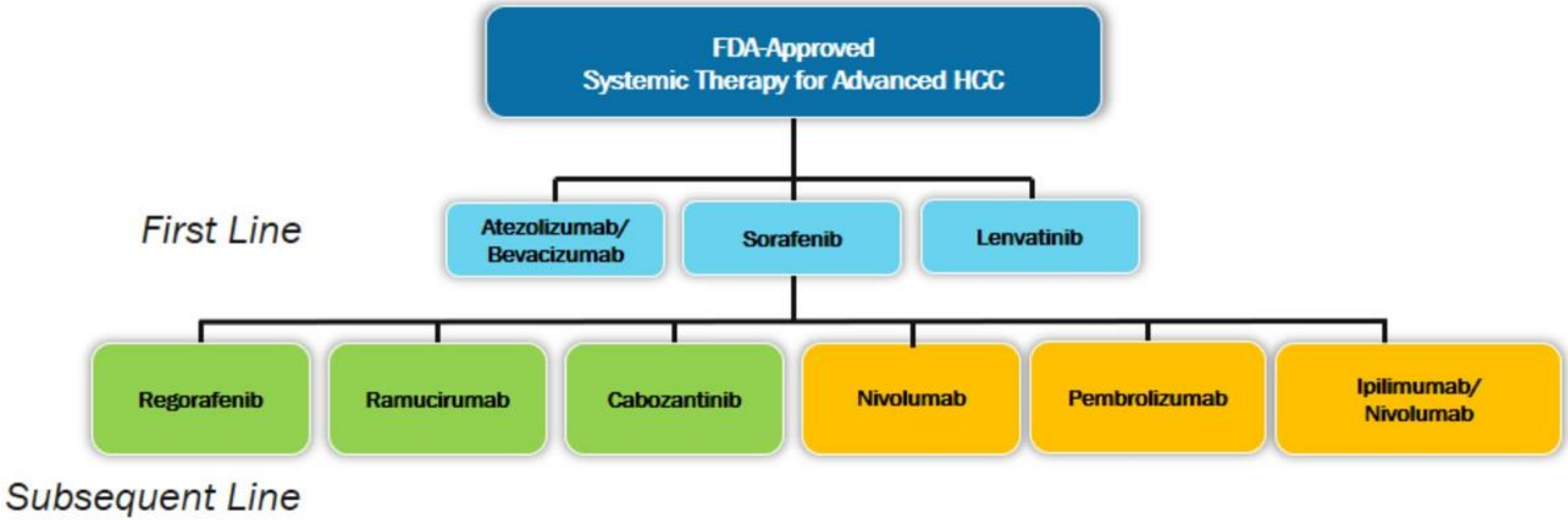
- ORR by HCC-specific modified RECIST with atezo + bev vs sorafenib: 33.2% vs 13.3%; CR rate, 10.2% vs 1.9%

Median follow-up: 8.6 mos.

Finn. NEJM. 2020;382:1894.

Slide credit: clinicaloptions.com

Treatment Landscape of Advanced HCC



NCCN Guidelines. Hepatobiliary Cancers. 2021.

NCCN Guidelines for HCC

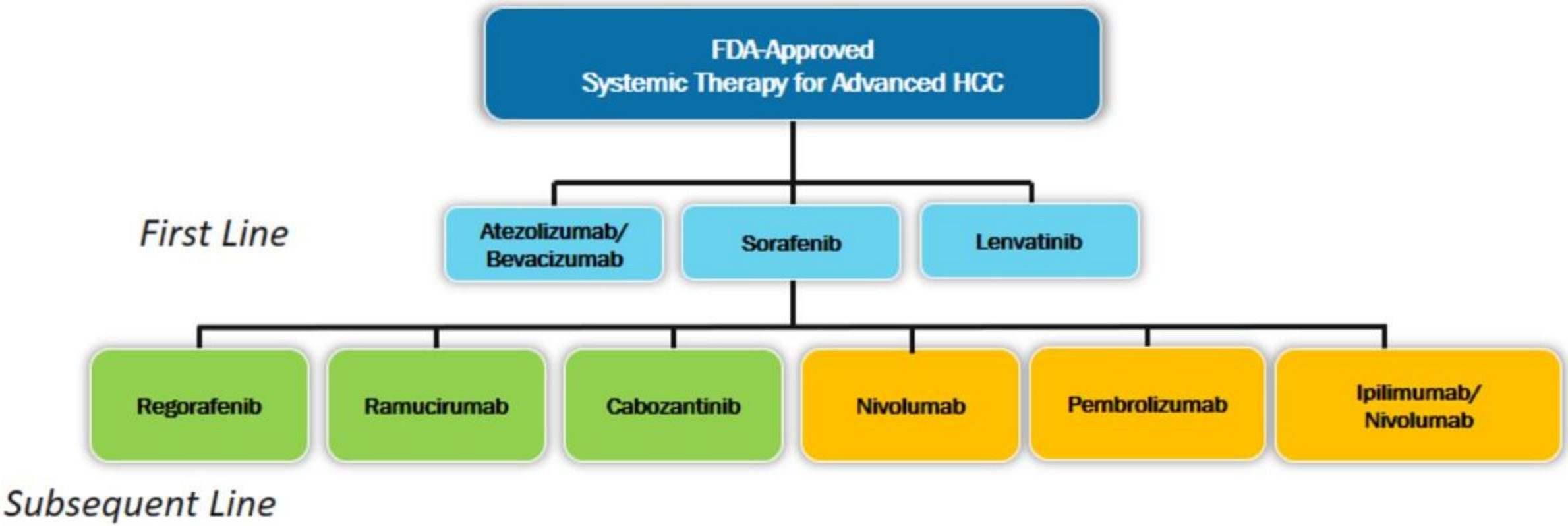
First-line Systemic Therapy

Preferred regimens	Other recommended regimens	Useful in certain circumstances
• Atezolizumab-bevacizumab (Child-Pugh Class A only) (category 1)	• Sorafenib (Child-Pugh Class A [category 1] or B7) • Lenvatinib (Child-Pugh Class A only) (category 1)	• Nivolumab (if ineligible for TKIs or other antiangiogenic agents) (category 2B) • FOLFOX (category 2B)

Subsequent-line therapy if disease progression	Other recommended regimens
• Regorafenib (Child-Pugh Class A only) (category 1) • Cabozantinib (Child-Pugh Class A only) (category 1) • Ramucirumab (AFP ≥ 400 ng/mL only) (category 1) • Lenvatinib (Child-Pugh Class A only) • Sorafenib (Child-Pugh Class A or B7)	• Nivolumab (Child-Pugh Class A or B) • Nivolumab-ipilimumab (Child-Pugh Class A only) • Pembrolizumab (Child-Pugh Class A only) (category 2B)

NCCN. Hepatobiliary cancers. 2021.

Treatment Landscape of Advanced HCC



NCCN Guidelines. Hepatobiliary Cancers. V2.2021.

NCCN Guidelines for HCC

1L systemic therapy		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Atezolizumab-bevacizumab (Child-Pugh Class A only) (category 1)	• Sorafenib (Child-Pugh Class A [category 1] or B7) • Lenvatinib (Child-Pugh Class A only) (category 1)	• Nivolumab (if ineligible for TKIs or other antiangiogenic agents) (Child-Pugh Class A or B; category 2B) • FOLFOX (category 2B)

Subsequent-line therapy if disease progression	Other recommended regimens
• Regorafenib (Child-Pugh Class A only) (category 1) • Cabozantinib (Child-Pugh Class A only) (category 1) • Ramucirumab (AFP ≥ 400 ng/mL only) (category 1) • Lenvatinib (Child-Pugh Class A only) • Sorafenib (Child-Pugh Class A or B7)	• Nivolumab (Child-Pugh Class B only) • Nivolumab-ipilimumab (Child-Pugh Class A only) • Pembrolizumab (Child-Pugh Class A only) (category 2B) • Dostarlimab-gxly for MSI-H/dMMR tumors (category 2B)

1L, first-line; AFP, alpha-fetoprotein; dMMR, deficient mismatch repair; HCC, hepatocellular carcinoma; MSI-H; microsatellite instability-high; TKI, tyrosine kinase inhibitor.

NCCN Guidelines®. Hepatobiliary cancers (v5.2021) 2021. Accessed November 1, 2021.

Immunotherapy for Advanced HCC

Nivolumab

- PD-1 inhibitor
- FDA-approved (2017) as second-line treatment of HCC in patients previously receiving sorafenib[a]
  - Phase 1/2 CheckMate 040 study; ORR: 15%[b]

Nivolumab + Ipilimumab

- Ipilimumab is a CTLA-4 blocking antibody
- FDA-approved (2020) as second-line treatment of HCC in patients previously on sorafenib[c]
  - Phase 1/2 CheckMate 040 study; ORR: 31%[d]

Pembrolizumab

- PD-1 inhibitor
- FDA-approved (2018) as second-line treatment of HCC in patients previously receiving sorafenib[e]
- Phase 1/2 study KEYNOTE-224: ORR 17%

a. Opdivo® (nivolumab). [PI]. 2018; b. El-Khoueiry AB, et al. *Lancet*. 2017;389:2492-2502; c. US FDA Drug Approvals. Fda.gov/drugs. Accessed March 21, 2020. d. Yau T, et al. *J Clin Oncol*. 2019;37(suppl): Abstract 4012. e. Keytruda® (pembrolizumab) [PI]. 2021; f. Zhu AX, et al. *Lancet Oncol*. 2018;19:940-952.

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