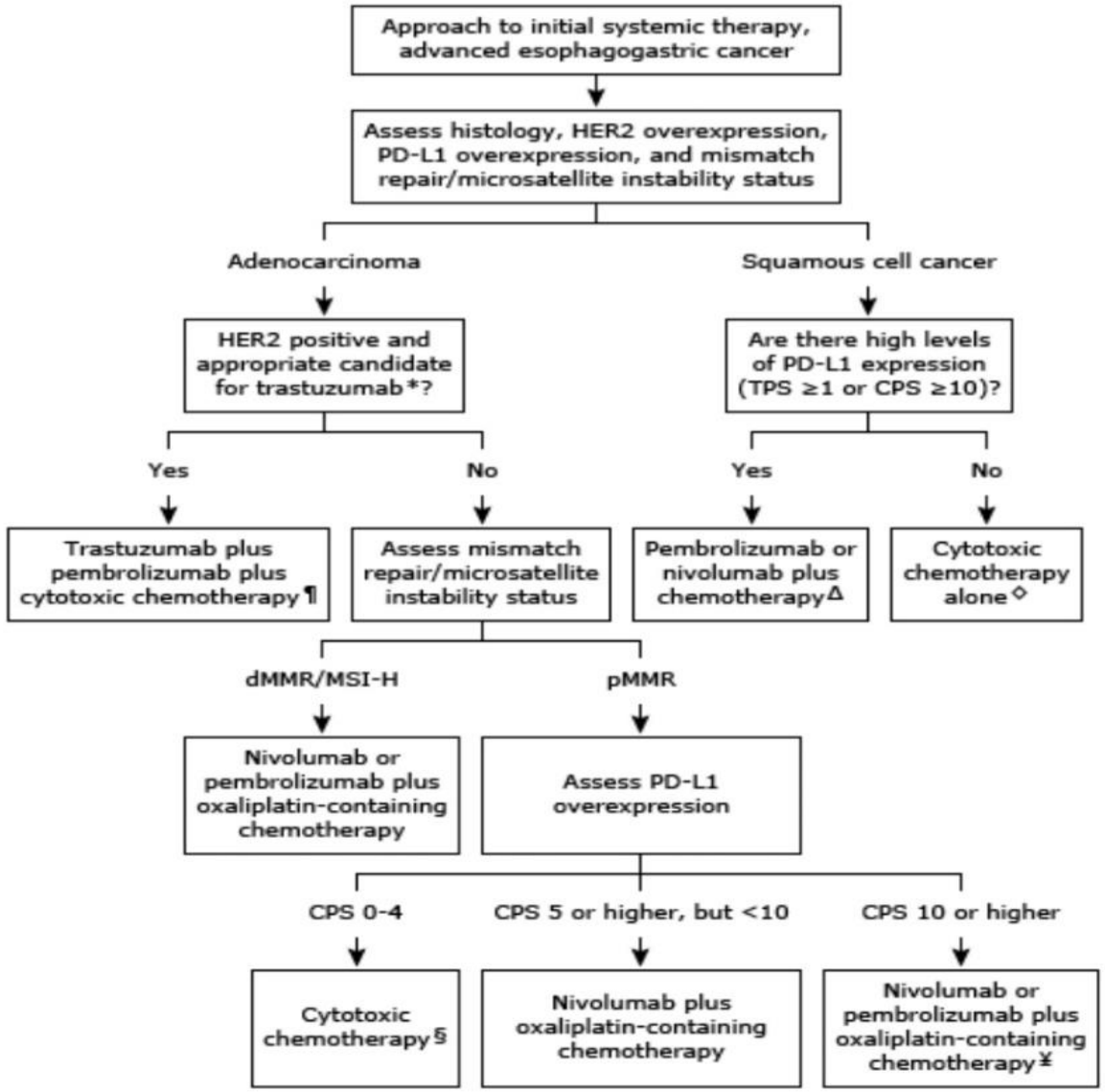
Novel and Targeted agents in Gastric Cancer

Dr Krishna Chaitanya MD DM
Associate Professor
Department of Medical Oncology
MNJIO RCC, Hyderabad

Initial approach to systemic treatment of esophagogastric cancer



Biomarker Testing in Gastroesophageal Cancers

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

NCCN. Clinical practice guidelines in oncology: gastric cancer. v.2.2022. nccn.org.

PD-L1 In Gastroesophageal Cancers

- 23% to 60% of gastric cancers are PD-L1 positive (tumor cells + tumor-infiltrating immune cells)[1-3]
- 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)

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

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.

Gastroesophageal Adenocarcinoma Algorithm for HER2 Testing by IHC

HER2 Level Assessment		Gastric		Breast Biopsy
Score	Overexpression	Surgical Specimen	Biopsy Specimen	
0	Negative	No reactivity or membranous reactivity in <10% of TC	No reactivity in any TC	No staining observed or membrane staining incomplete and faint/barely perceptible and in ≤10% of TCs
1+	Negative	Faint/barely perceptible membranous reactivity in ≥10% of TCs; cells reactive only in part of membrane	TC cluster with faint/barely perceptible membranous reactivity regardless of % of TCs stained	Incomplete membrane staining that is faint/barely perceptible and in >10% of TCs
2+	Equivocal	Weak to moderate complete, basolateral, or lateral membranous reactivity in ≥10% of TCs	TC cluster with weak to moderate complete, basolateral, or lateral membranous activity regardless of % of TCs stained	Weak to moderate complete membrane staining in >10% of TCs
3+	Positive	Strong complete, basolateral, or lateral membranous reactivity in ≥10% of TCs	TC cluster with strong complete, basolateral, or lateral membranous activity regardless of % of TCs stained	Circumferential membrane staining that is complete, intense, and in >10% of TCs

Bartley. JCO. 2017;35:446. Wolff. Arch Pathol Lab Med. 2018;142:1364.
NCCN. Clinical practice guidelines in oncology: gastric cancer. v.2.2022. nccn.org.

Simplified First-line Treatment Algorithm for Advanced Gastroesophageal Adenocarcinomas

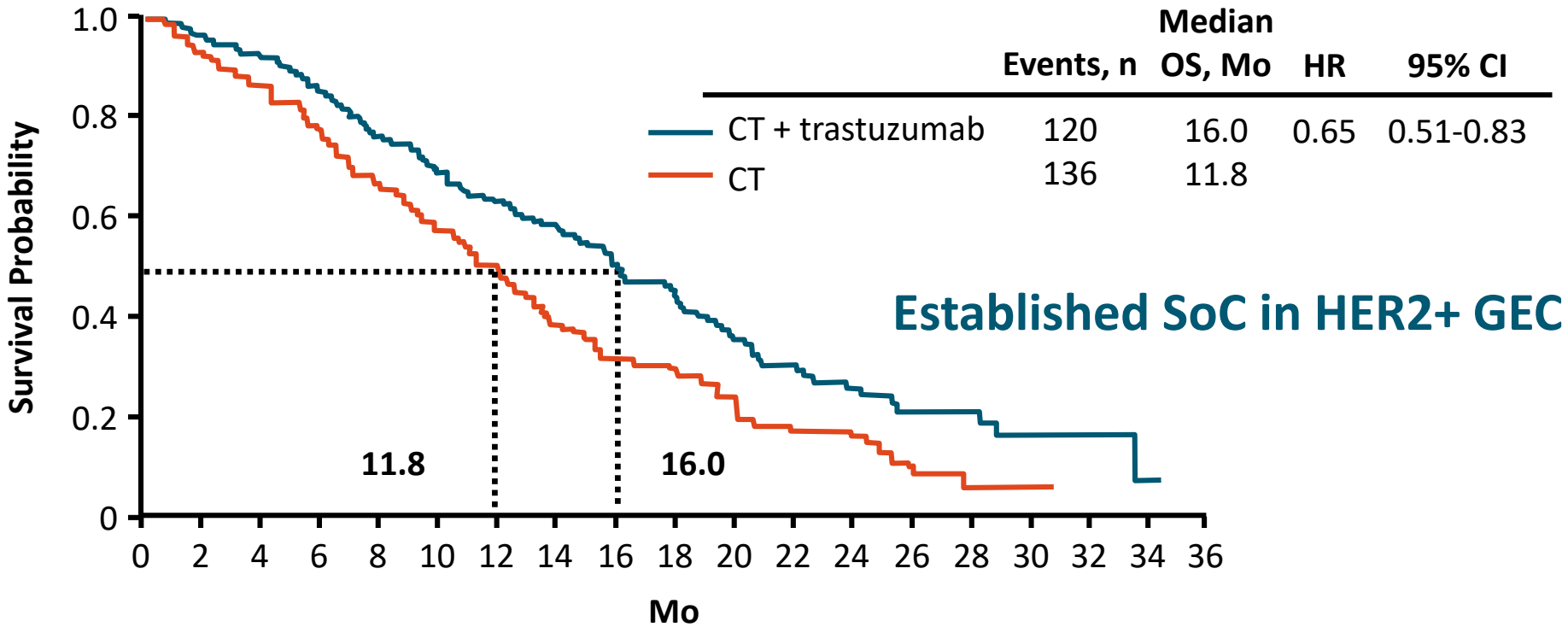
	No Biomarkers or HER2-	HER2+
Gastric	Fluoropyrimidine + platinum ± nivolumab (*CPS ≥5*; CheckMate 649)	Fluoropyrimidine + platinum + trastuzumab ± pembrolizumab (KEYNOTE-811)
Esophageal/ GEJ	Fluoropyrimidine + platinum ± nivolumab (*CPS ≥5*; CheckMate 649) Fluoropyrimidine + platinum ± pembrolizumab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

ToGA: First-line Trastuzumab + Chemotherapy in Advanced HER2+ Gastric Cancer

- Randomized phase III trial of 5-FU or capecitabine + cisplatin ± trastuzumab for patients with advanced gastric cancer (N = 584)

OS in Patients With IHC 3+ or FISH+ and IHC 2+ (Exploratory Analysis) (N = 446)

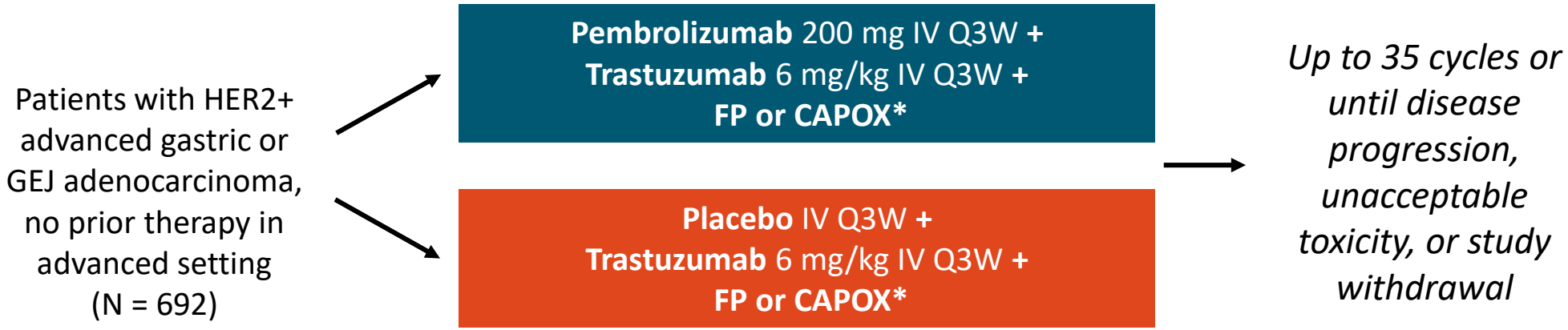


Established SoC in HER2+ GEC

Bang. Lancet. 2010;376:687.

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

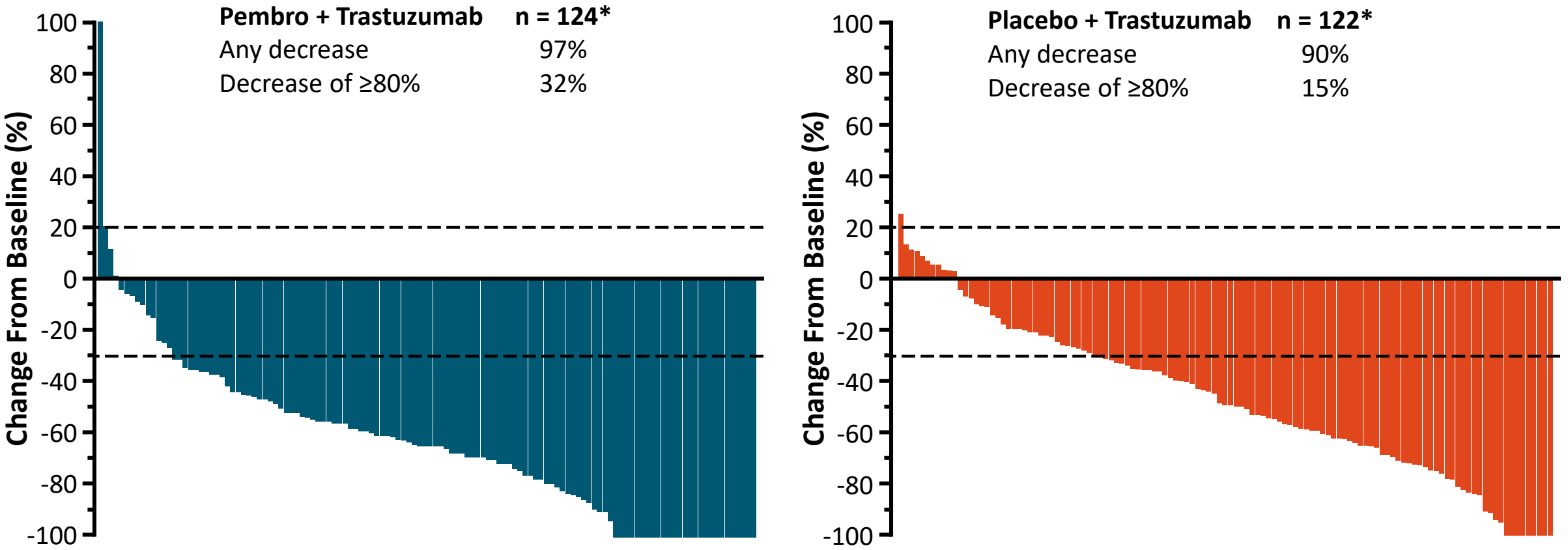
Janjigian. Nature. 2021;600:727.

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.

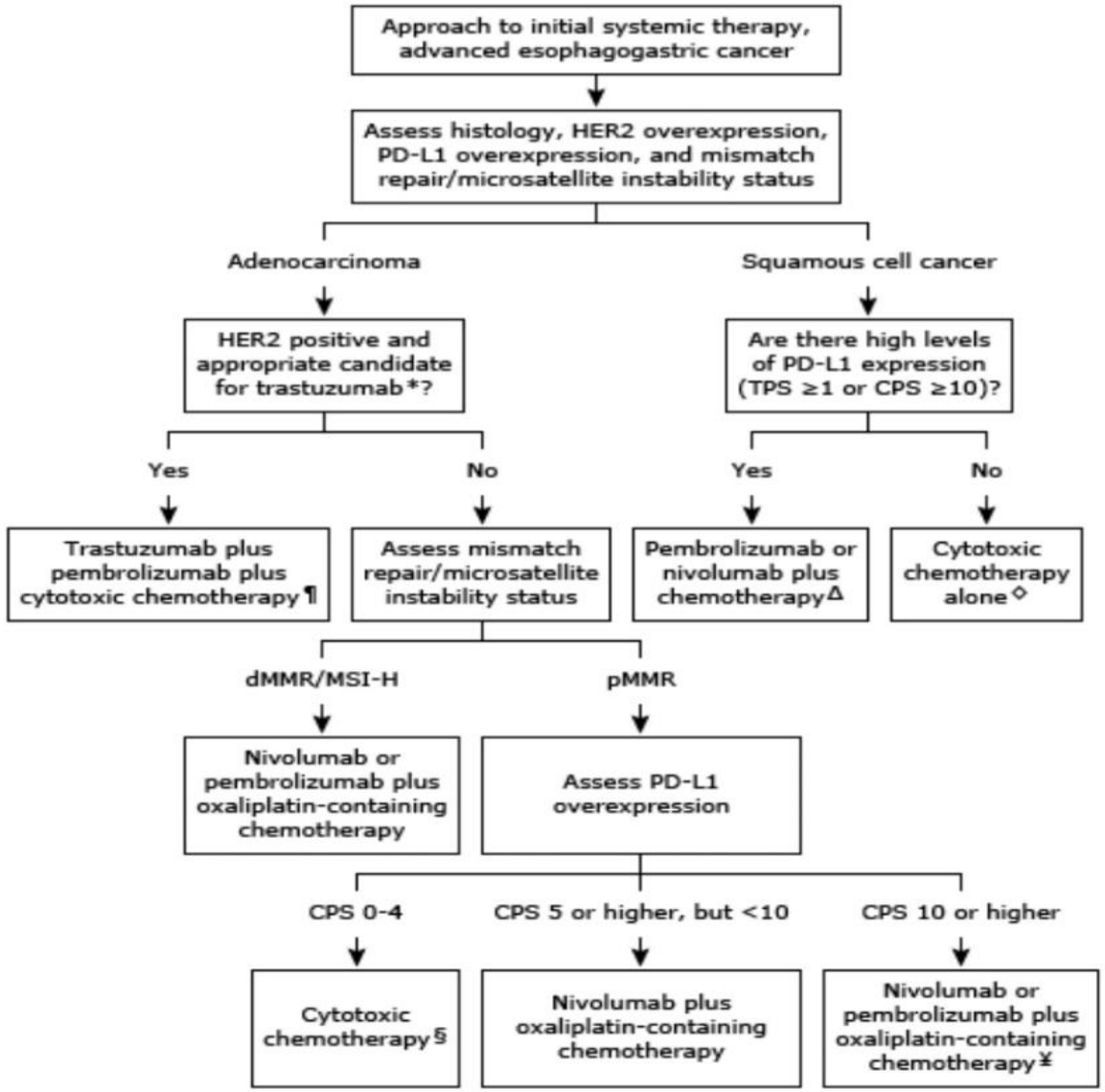
KEYNOTE-811: Response



*Participants with RECIST-measurable disease at baseline and ≥1 evaluable postbaseline measurement.

Janjigian ASCO 2021. Abstr 4013. Janjigian. Nature. 2021;600:727.

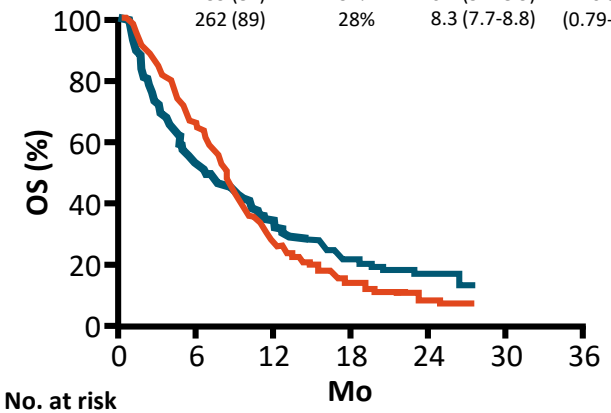
Initial approach to systemic treatment of esophagogastric cancer



PD-1 for 2L and Beyond MSI-H/dMMR

KEYNOTE-061: 2L Pembrolizumab vs Chemo

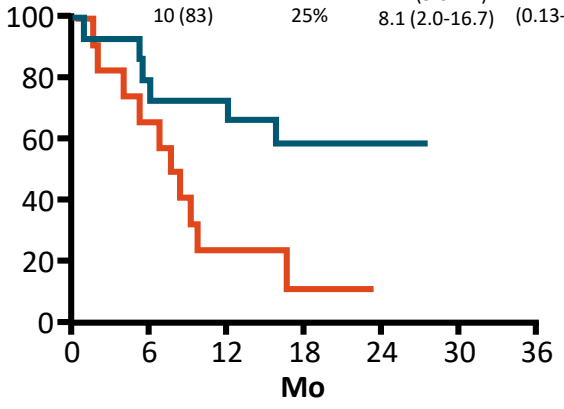
	Events n (%)	12-Mo Rate	Median, Mo (95% CI)	HR (95% CI)
Pembro	239 (81)	34%	6.7 (5.4-8.9)	0.94
Chemo	262 (89)	28%	8.3 (7.7-8.8)	(0.79-1.12)



No. at risk							
Pembro	296	155	101	53	16	0	0
Chemo	296	191	83	36	12	0	0

KEYNOTE-061: Pembrolizumab vs Chemo in MSI-H

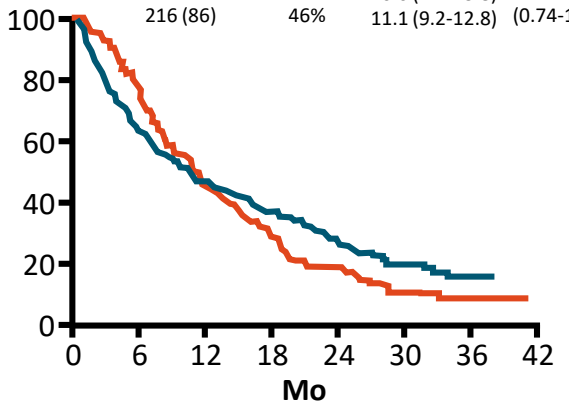
	Events n (%)	12-Mo Rate	Median, Mo (95% CI)	HR (95% CI)
Pembro	6 (40)	73%	NR (5.6-NR)	0.42
Chemo	10 (83)	25%	8.1 (2.0-16.7)	(0.13-1.31)



15	12	11	6	3	0	0
12	8	3	1	0	0	0

KEYNOTE-062: 1L Pembrolizumab vs Chemo

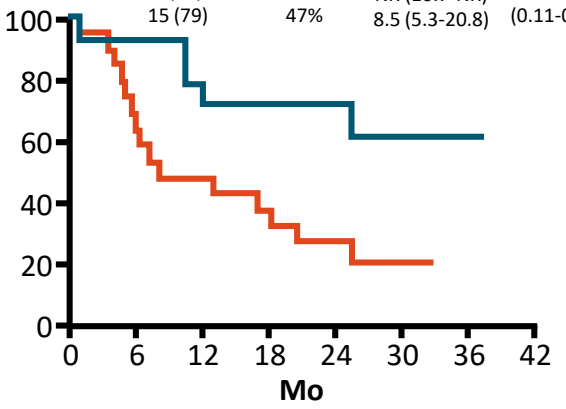
	Events n (%)	12-Mo Rate	Median, Mo (95% CI)	HR (95% CI)
Pembro	201 (79)	47%	10.6 (7.7-13.8)	0.91
Chemo	216 (86)	46%	11.1 (9.2-12.8)	(0.74-1.10)



256	162	120	94	59	23	4	0
250	192	114	75	38	15	2	0

KEYNOTE-062: Pembrolizumab vs Chemo in MSI-H

	Events n (%)	12-Mo Rate	Median, Mo (95% CI)	HR (95% CI)
Pembro	5 (36)	79%	NR (10.7-NR)	0.29
Chemo	15 (79)	47%	8.5 (5.3-20.8)	(0.11-0.81)



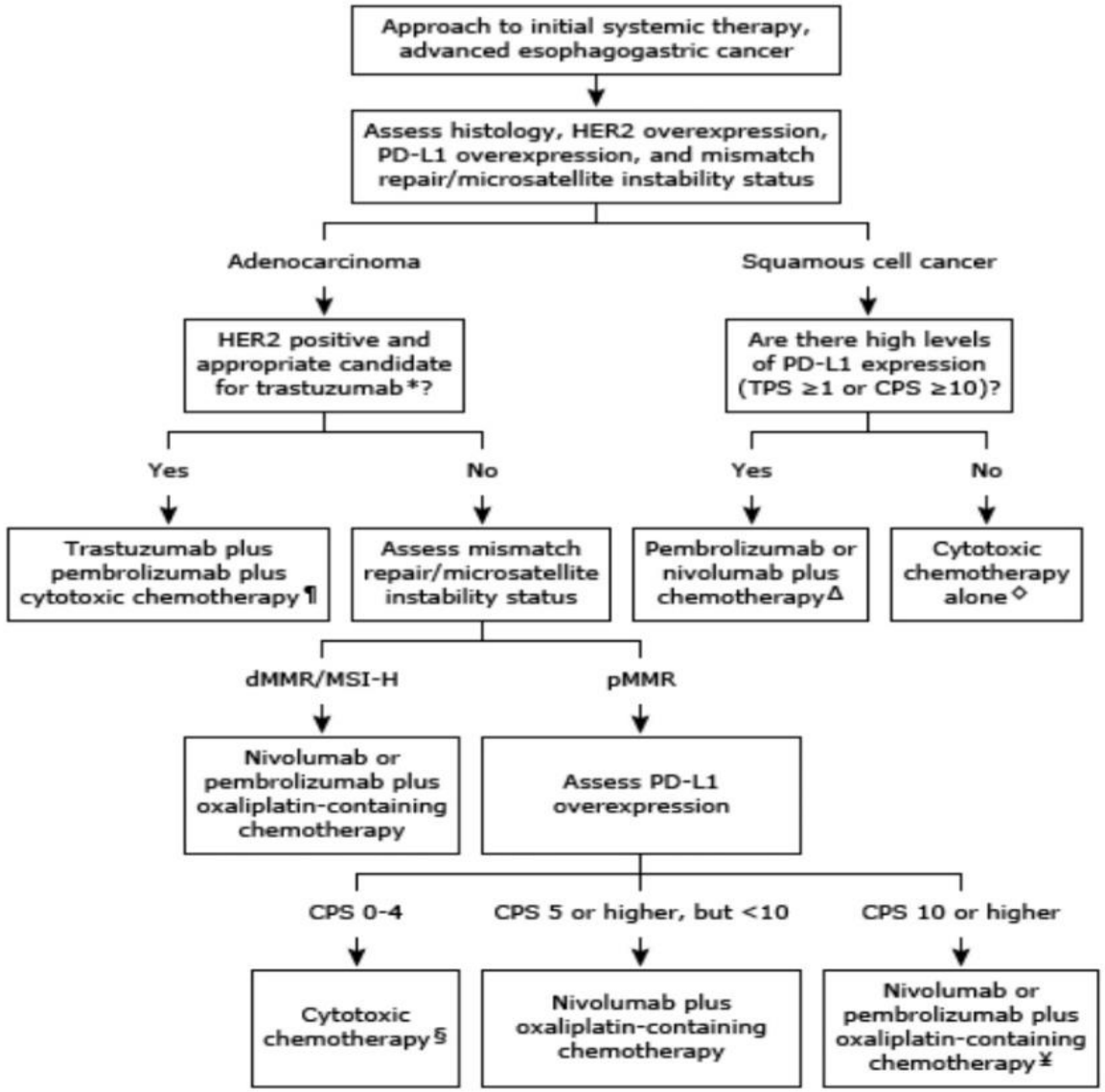
14	13	11	10	9	4	2	0
19	13	9	7	4	3	0	0

Response	Keynote-059 (3L+)	KEYNOTE-061 (2L)		KEYNOTE-062 (1L)	
	Pembro (n = 7)	Pembro (n = 15)	Chemo (n = 12)	Pembro (n = 14)	Chemo (n = 19)
ORR, n (%)	4 (57)	7 (47)	2 (17)	8 (57)	7 (37)
Median DOR, mo (range)	Not reached (20.0+ to 26.8+)	Not reached (5.5 to 26.0+)	Not reached (2.2+ to 12.2+)	21.2 (1.4+ to 33.6+)	7.0 (2.0 to 30.4+)

MSI-H or dMMR is strongly associated with improved outcomes with immune checkpoint inhibitor therapy
Activity is independent of the line of therapy

Chao. JAMA Oncol. 2021;7:895.

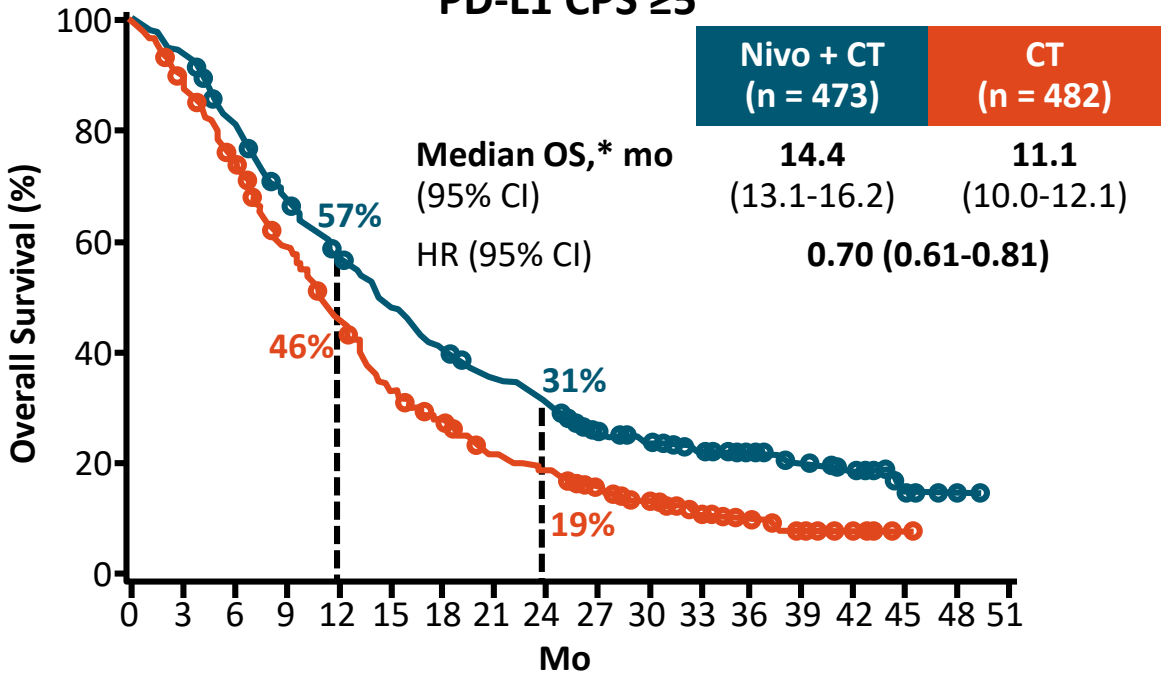
Initial approach to systemic treatment of esophagogastric cancer



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

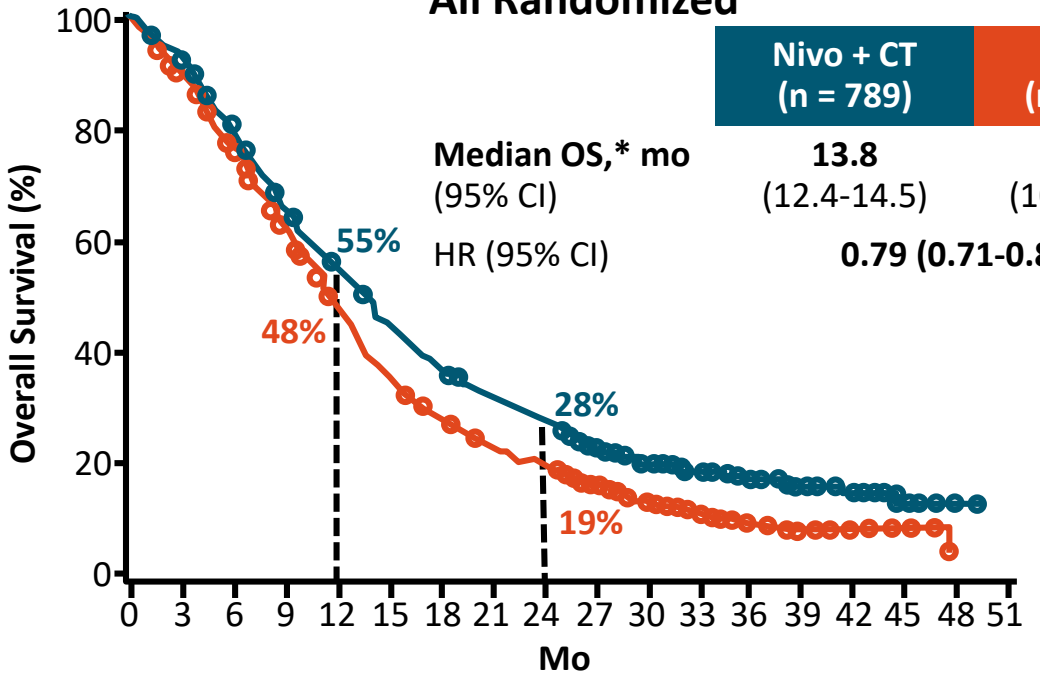
- Randomized phase III trial of nivolumab + ipilimumab, **nivolumab + chemo***, or **chemo*** for patients with previously untreated unresectable, advanced, or metastatic gastric/GEJ/esophageal adenocarcinoma (N = 1581)

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 = 1297)	All Randomized	CPS <5 (n = 607)
HR for OS	0.69	0.74	0.79	0.94

*XELOX or FOLFOX.

Janjigian. ESMO 2021. Abstr LBA7. Janjigian. Lancet. 2021;398:27. Shitara. ASCO GI 2022. Abstr 240.

CheckMate 649: OS Subgroup Analysis

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 1581)		13.8	11.6	0.78	
Age	< 65 (n = 961)	12.9	11.8	0.80	
	≥ 65 (n = 620)	14.4	11.3	0.76	
Sex	Male (n = 1100)	14.0	11.3	0.76	
	Female (n = 481)	12.8	12.1	0.85	
Region	Asia (n = 356)	16.3	12.8	0.78	
	United States (n = 263)	15.3	12.1	0.64	
	ROW (n = 962)	12.1	10.9	0.82	
ECOG PS	0 (n = 664)	16.8	14.2	0.81	
	1 (n = 913)	11.5	9.8	0.74	
Primary tumor location	GC (n = 1110)	14.2	11.3	0.75	
	GEJC (n = 260)	12.6	12.8	0.89	
	EAC (n = 211)	12.3	11.6	0.81	
Baseline tumor burden[a]	< Q3 (n = 904)	14.0	11.6	0.78	
	≥ Q3 (n = 308)	11.4	9.2	0.62	
Tumor cell PD-L1 expression[b]	< 1% (n = 1324)	13.4	12.0	0.84	
	≥ 1% (n = 253)	16.1	9.8	0.54	
Baseline albumin[c]	< LLN (n = 357)	9.2	8.8	0.94	
	≥ LLN (n = 1159)	14.7	12.5	0.74	
Baseline NLR[d]	< 4 (n = 929)	15.5	13.5	0.83	
	≥ 4 (n = 612)	9.8	8.2	0.71	
Peritoneal metastases[e]	Yes (n = 377)	9.3	10.0	0.98	
	No (n = 1155)	14.5	11.8	0.74	
Liver metastases[e]	Yes (n = 614)	12.5	10.6	0.70	
	No (n = 918)	14.2	12.3	0.85	
MSI status[f]	MSI-H (n = 44)	38.7	12.3	0.38	
	MSS (n = 1378)	13.8	11.5	0.78	
Chemotherapy regimen	FOLFOX (n = 828)	13.8	11.8	0.76	
	XELOX (n = 721)	13.8	11.7	0.81	

Shitara. ASCO GI 2022. Abstr 240.

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

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

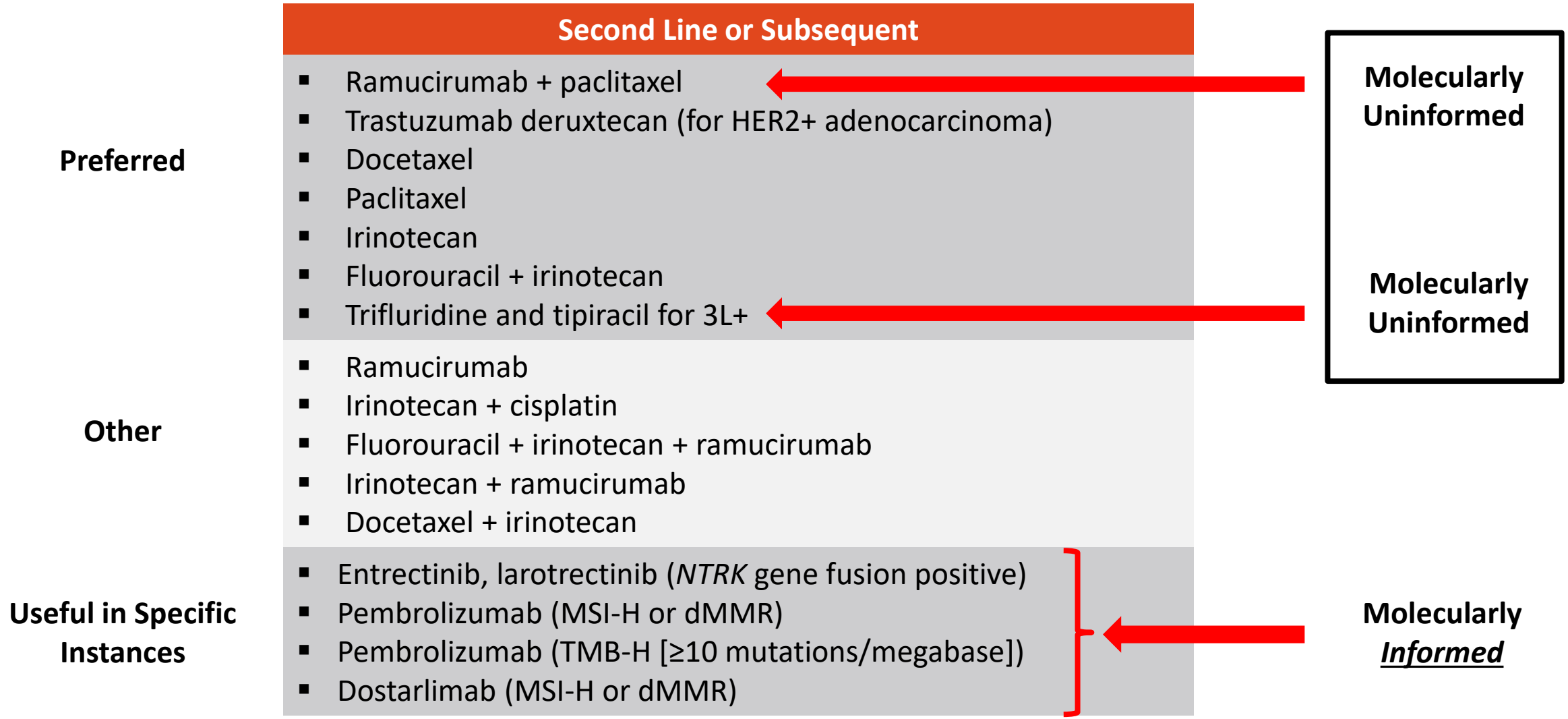
Outcome	All Patients			All Patients PD-L1 CPS ≥10			ESCC			ESCC PD-L1 CPS ≥10		
	Pembro + CT (n = 373)	CT (n = 376)	HR/ *P* Val	Pembro + CT (n = 186)	CT (n = 197)	HR/ *P* Val	Pembro + CT (n = 274)	CT (n = 274)	HR/ *P* Val	Pembro + CT (n = 143)	CT (n = 143)	HR/ *P* Val
Median OS,† mo	12.4	9.8	0.73/ <.0001	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.

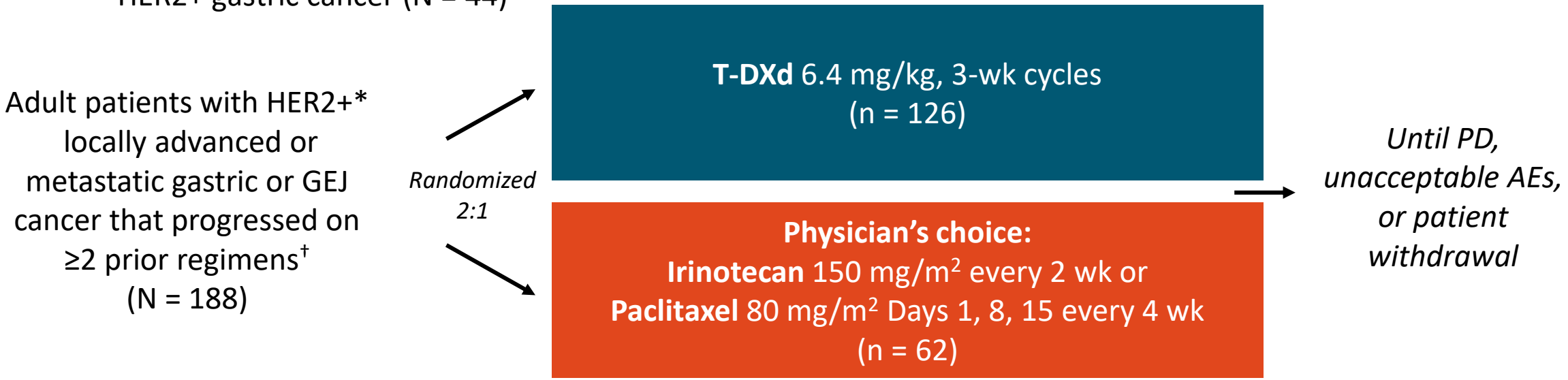
A Menu of 2L and Beyond for Gastric/GEJ



Adapted from NCCN. Clinical practice guidelines in oncology: gastric cancer. v.2.2022. nccn.org.

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

- Multicenter, open-label, randomized phase II study[1]
  - Phase I trial: T-DXd 5.4 or 6.4 mg/kg associated with 43.2% ORR, 12.8 mo mOS in patients with advanced HER2+ gastric cancer (N = 44)[2]



*HER2+ based on IHC 3+ or IHC 2+/ISH+ according to ASCO/CAP guidelines.
†Prior regimens included fluoropyrimidine, a platinum agent, and trastuzumab or approved biosimilar.

- Primary endpoint: ORR by ICR (RECIST v1.1); secondary endpoints: OS (key), DoR, PFS, DCR, confirmed ORR, safety

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

DESTINY-Gastric01: Response

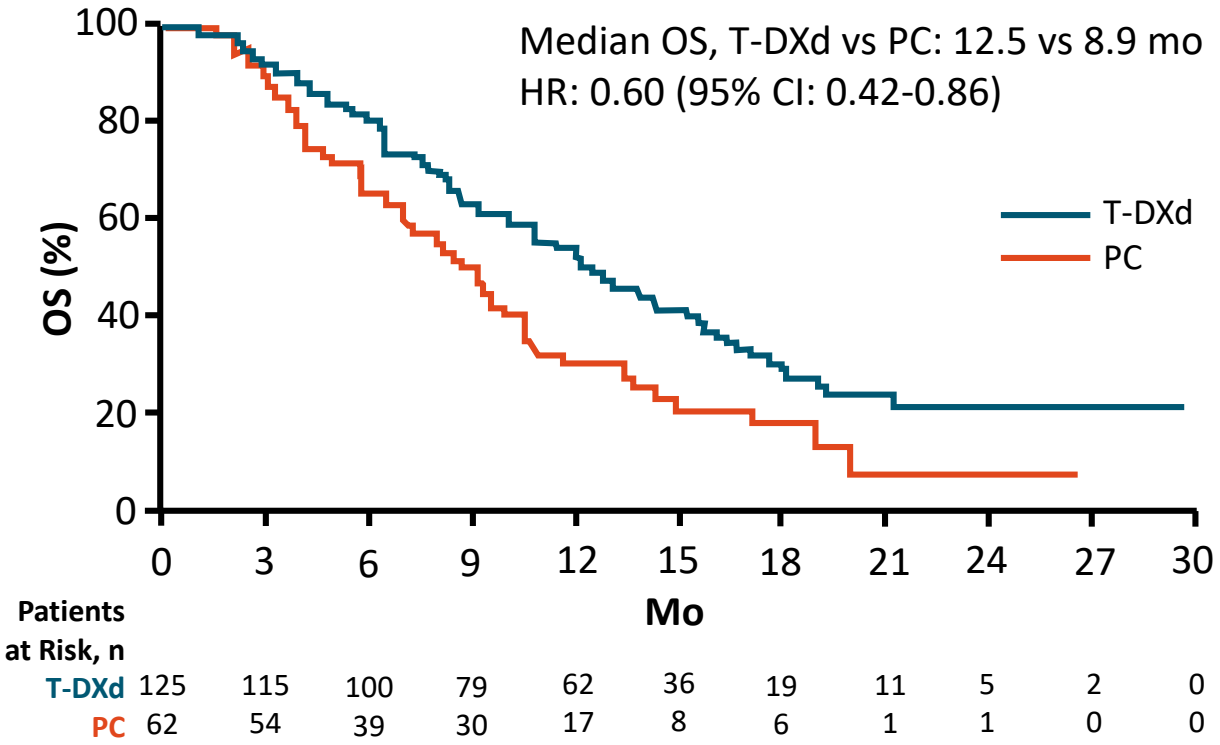
Response	T-DXd (n = 119)	PC (n = 56)	*P* Value
ORR* (CR + PR) by ICR, % (95% CI)	**51 (42-61)**	**14 (6-26)**	**<.0001**
▪ CR	9	0	
▪ PR	42	14	
▪ SD	35	48	
▪ PD	12	30	
▪ Not evaluable	2	7	
Confirmed DCR (CR + PR + SD), %	86	62	
Median confirmed DoR, mo	12.5	3.9	
Median time to response, mo	1.5	1.6	

*Primary endpoint.

Shitara. NEJM. 2020;382:2419. Yamaguchi. ASCO 2021. Abstr 4048.

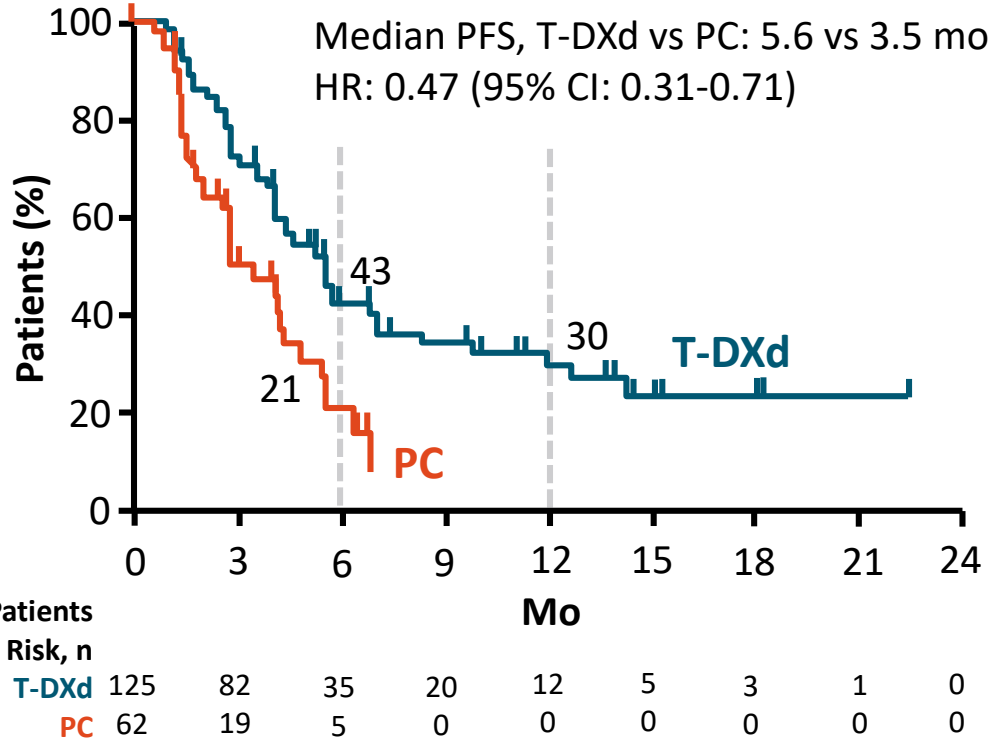
DESTINY-Gastric01: OS and PFS

OS



Patients at Risk, n											
T-DXd	125	115	100	79	62	36	19	11	5	2	0
PC	62	54	39	30	17	8	6	1	1	0	0

PFS



Patients at Risk, n								
T-DXd	125	82	35	20	12	5	3	1	0
PC	62	19	5	0	0	0	0	0	0

Shitara. NEJM. 2020;382:2419. Yamaguchi. ASCO 2021. Abstr 4048.

DESTINY-Gastric02: Trastuzumab Deruxtecan in HER2+ Advanced Gastric/GEJ Cancer After 1L Trastuzumab

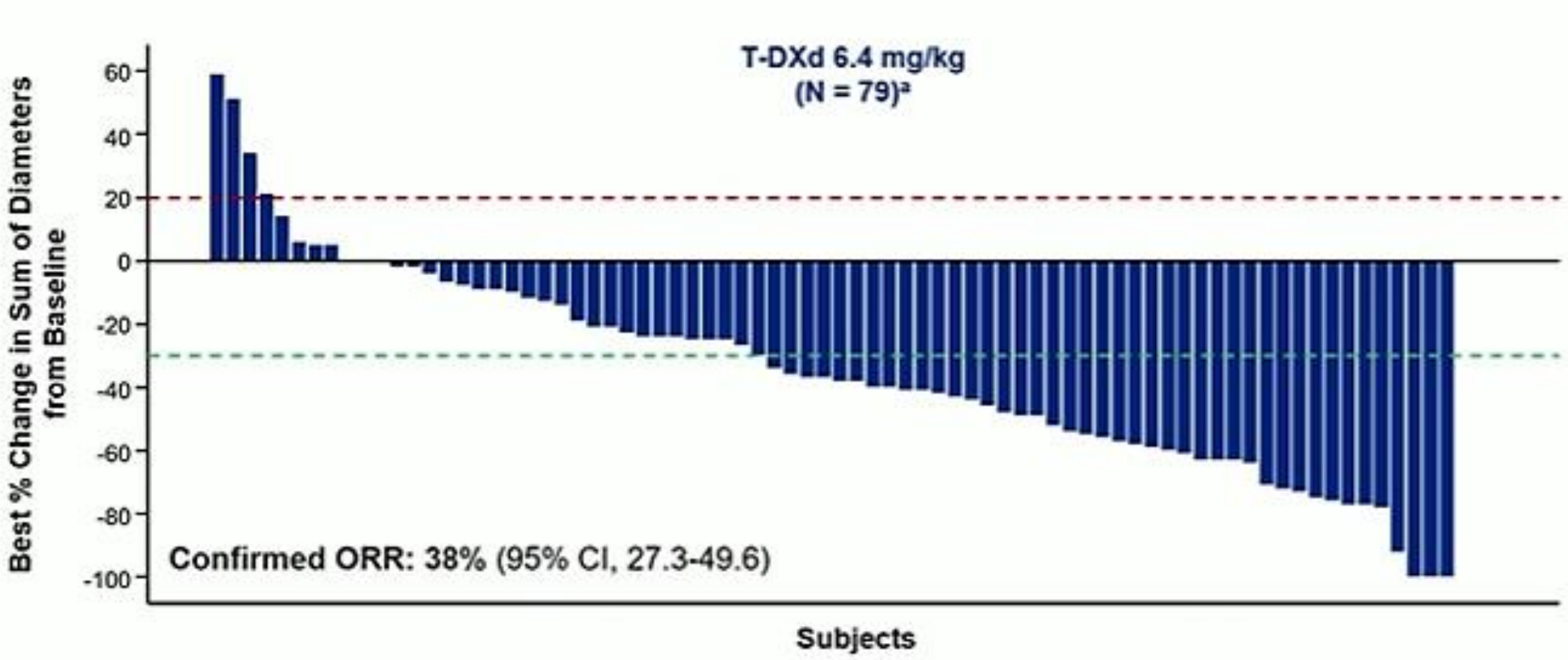
- Open-label phase II trial of T-DXd for patients in US, Europe with unresectable/metastatic gastric or GEJ cancer; HER2+* on biopsy after PD on 1L trastuzumab-containing regimen (N = 79)

Outcome	T-DXd (N = 79)
Confirmed ORR, n (%) (95% CI) ▪ CR, n (%) ▪ PR, n (%) ▪ SD, n (%) ▪ PD, n (%)	30 (38) (27.3-49.6) 3 (3.8) 27 (34.2) 34 (43.0) 13 (16.5)
Median DoR, mo (95% CI)	8.1 (4.1-NE)
Confirmed DCR, n (%) (95% CI)	64 (81.0) (70.6-89.0)
Median TTR, mo (95% CI)	1.4 (1.4-2.6)
Median PFS, mo (95% CI)	5.5 (4.2-7.3)
Median follow-up, mo (range)	5.7 (0.7-15.2)

*Defined as IHC 3+ or IHC 2+/ISH+.

Van Cutsem. ESMO 2021. Abstr LBA55.

DESTINY-Gastric02: Response



Van Cutsem. ESMO 2021. Abstr LBA55.

Select Novel HER2-Directed Strategies

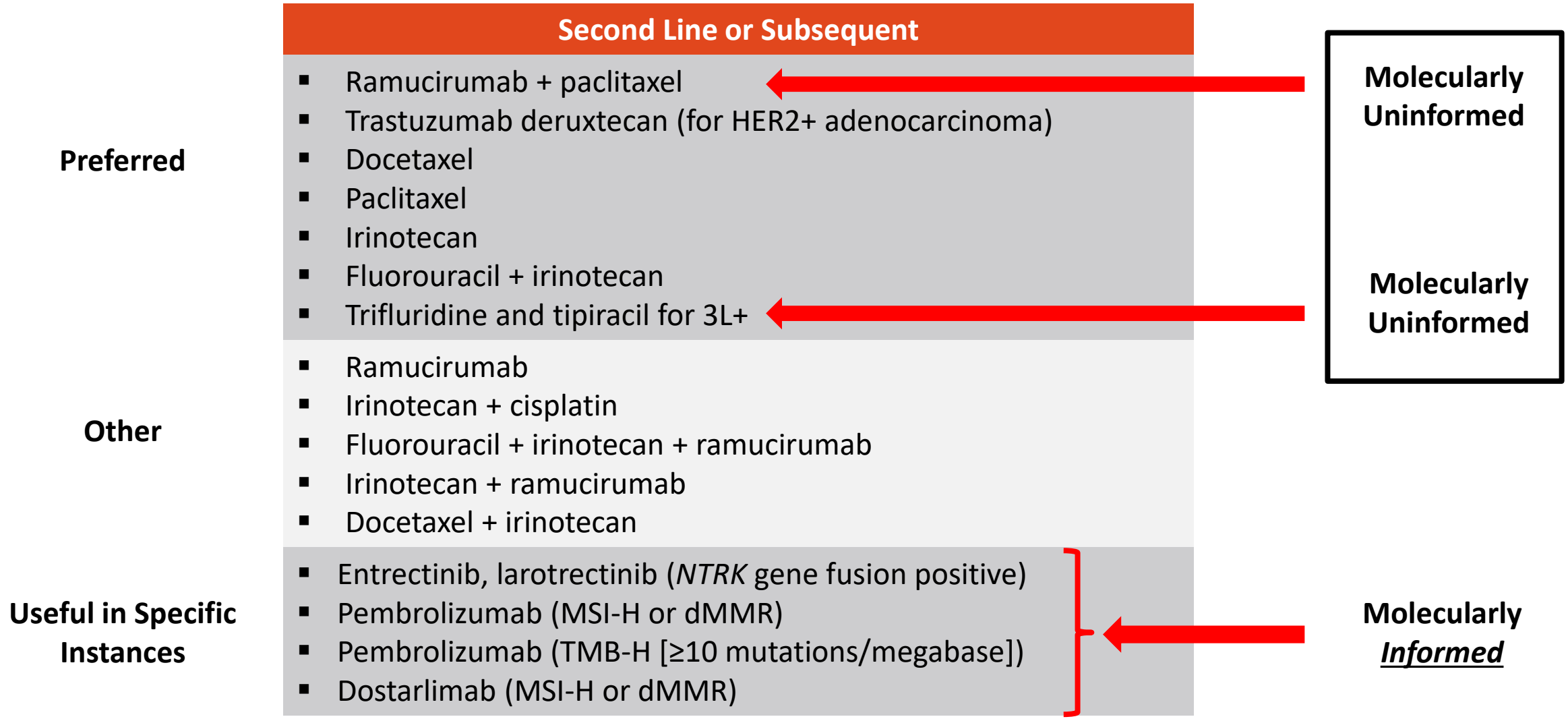
Strategy	Selected Agents
Antibody–drug conjugates	▪ Trastuzumab deruxtecan (DS-8201a) – US approval for adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen
Monoclonal antibodies (with augmented ADCC)	▪ Margetuximab
Bispecific antibodies	▪ Zanidatamab
Tyrosine kinase inhibitors	▪ Tucatinib ▪ Neratinib (+ trastuzumab or cetuximab)
Immunotherapy combinations	▪ Numerous

Select Investigational HER2-Targeted Agents for Advanced Gastroesophageal Cancers

Agent	MOA	Key Trial	
Margetuximab	HER2-targeted mAb	CP-MGAH22-05: phase Ib/II study of margetuximab + pembrolizumab for advanced HER2+ gastroesophageal cancers; ≥1 previous treatment with trastuzumab + CT (N = 95)	ORR: 29.03%; median PFS: 5.45 mo; median OS: 14.62 mo
Zanidatamab	HER2-targeted bispecific antibody	Phase Ib/II study of zanidatamab ± CT for advanced HER2+ gastroesophageal cancers; prior therapy (N = 52)	ORR: zan, 33%; zan + pac, 50%%; zan + cape, 57%

Bang. Ann Oncol. 2017;28:855. Catenacci. Lancet Oncol. 2020;21:1066. Meric-Bernstam. ASCO GI 2021. Abstr 164.

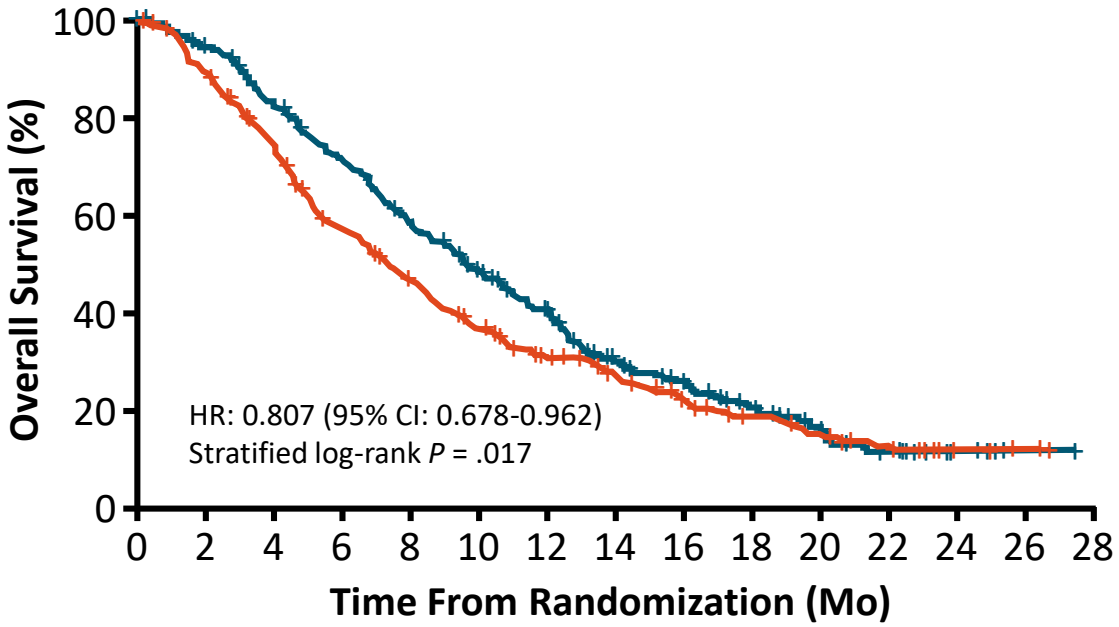
A Menu of 2L and Beyond for Gastric/GEJ

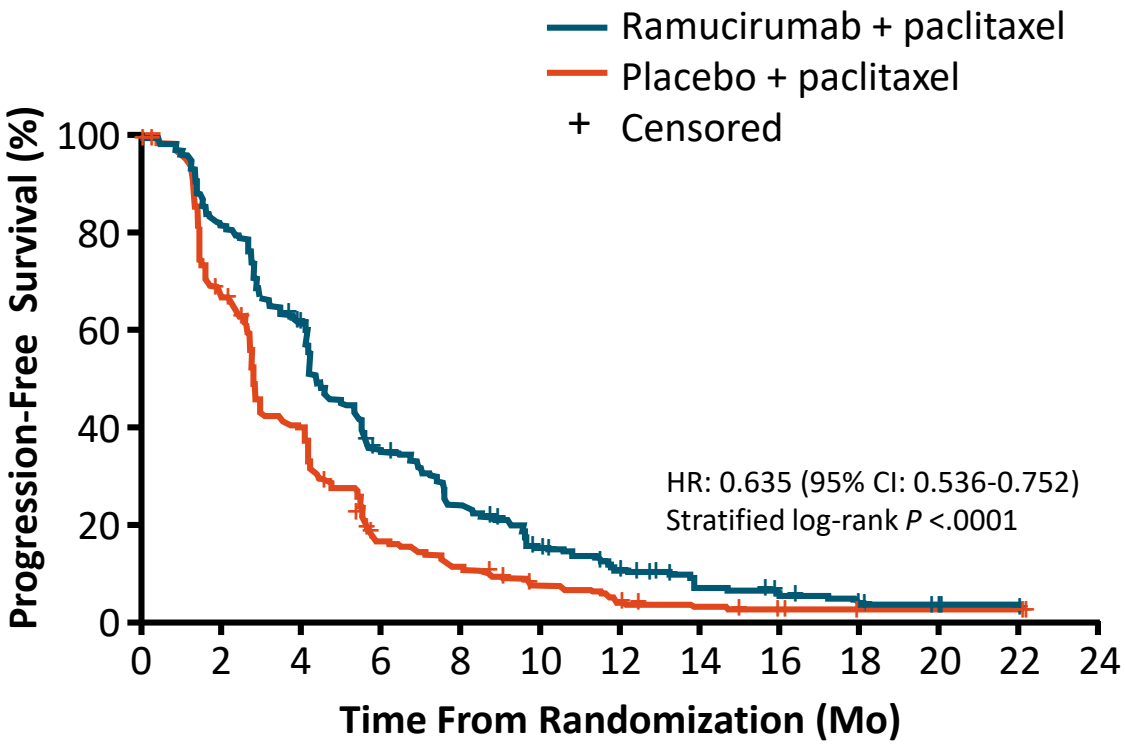


Adapted from NCCN. Clinical practice guidelines in oncology: gastric cancer. v.2.2022. nccn.org.

A Very Brief Refresher—RAINBOW

- 2L phase III RCT of Pac/Ram vs Pac (RAINBOW) in gastric/GEJ
- Median OS (primary endpoint): 9.6 mo vs 7.4 mo (HR: 0.80)
- Median PFS: 4.4 mo vs 2.9 mo (HR: 0.63)
- Overall response rate: 27% vs 16%





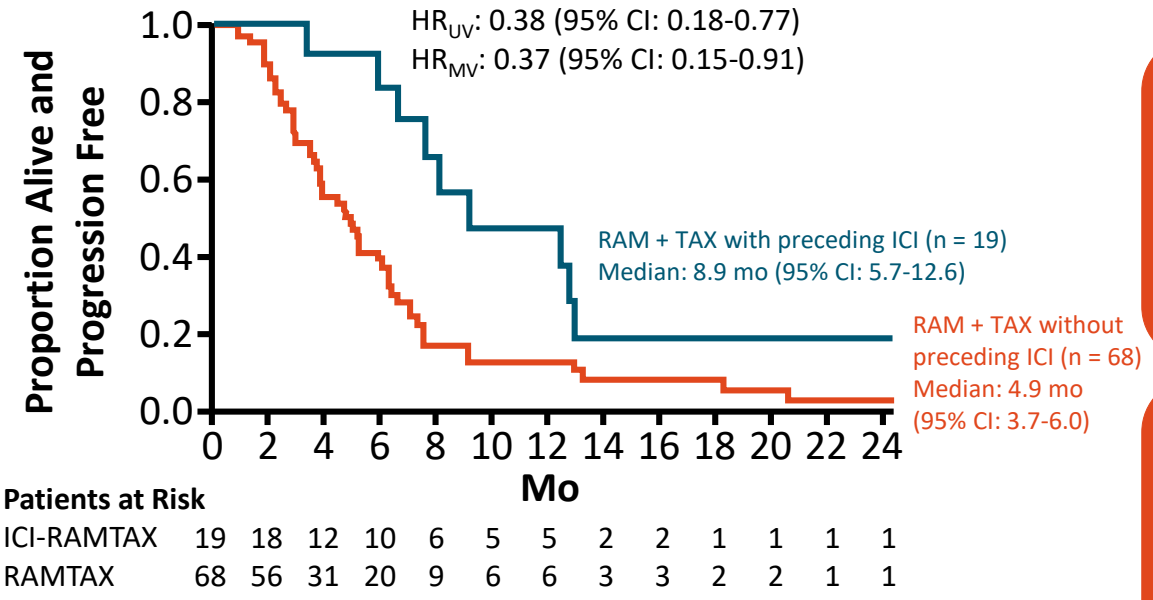
Patients at Risk, n															
Ramucirumab + paclitaxel	330	308	267	228	185	148	116	78	60	41	24	13	6	1	0
Placebo + paclitaxel	335	294	241	180	143	109	81	64	47	30	22	13	5	2	0

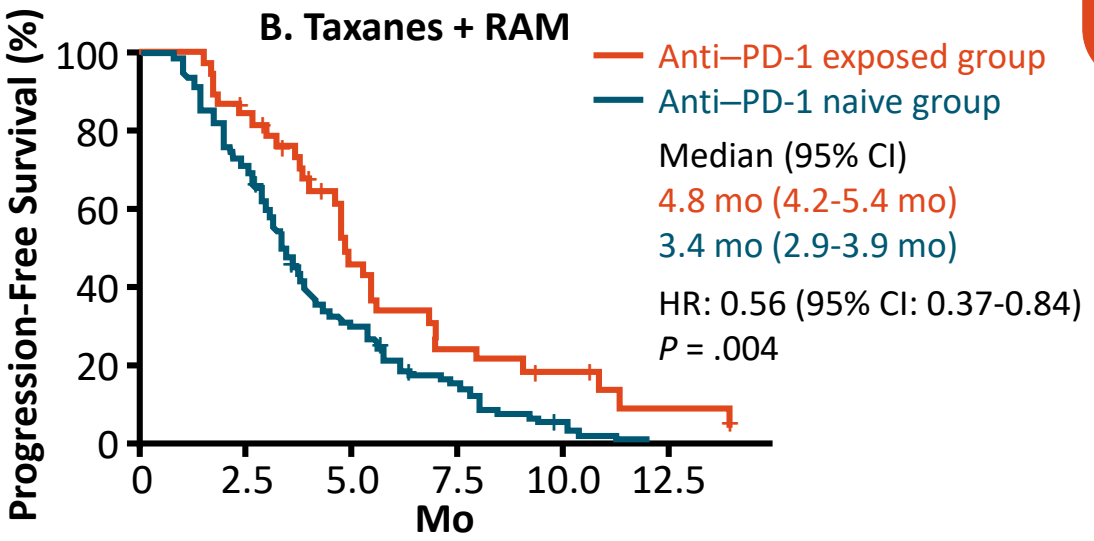
Ramucirumab + paclitaxel	330	259	188	104	70	43	28	15	11	7	3	1	-		
Placebo + paclitaxel	335	214	124	50	34	21	12	8	5	3	3	3	-		

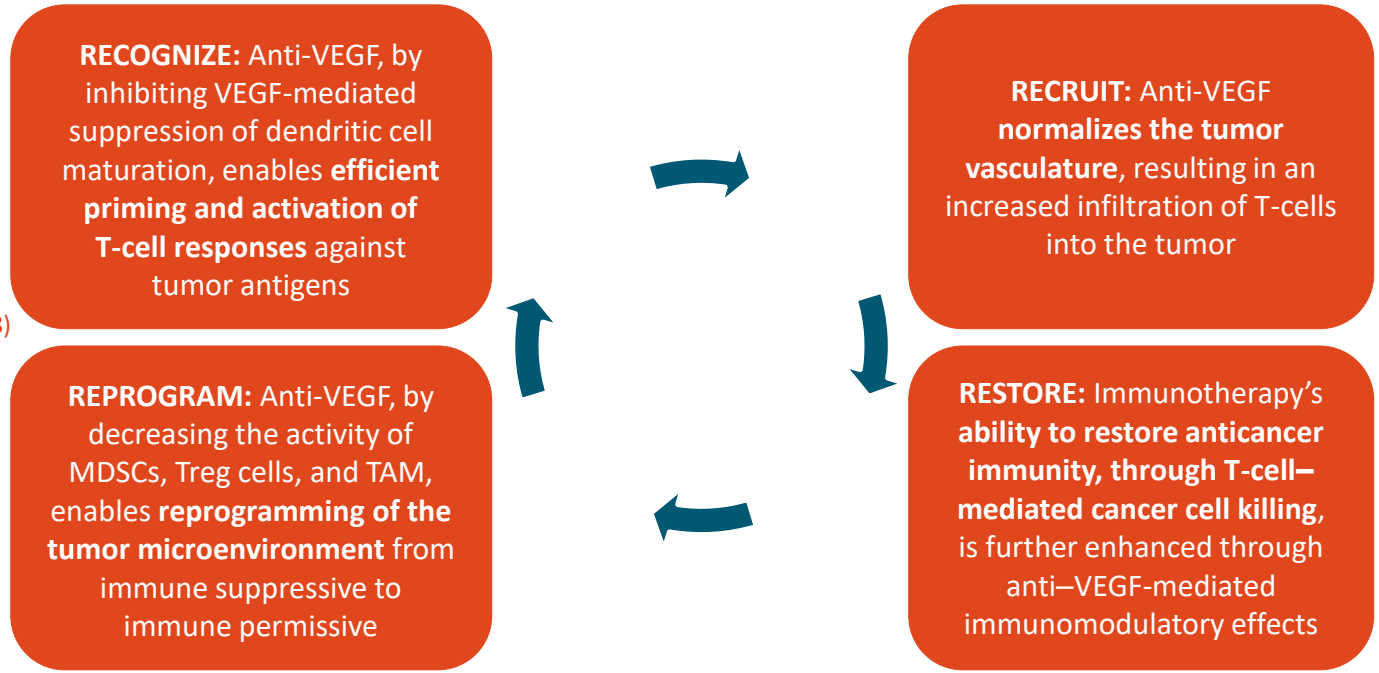
There is no phase III 2L trial to beat this

Wilke. Lancet Oncol. 2014;15:1224.

A RAINBOW After PD-1?





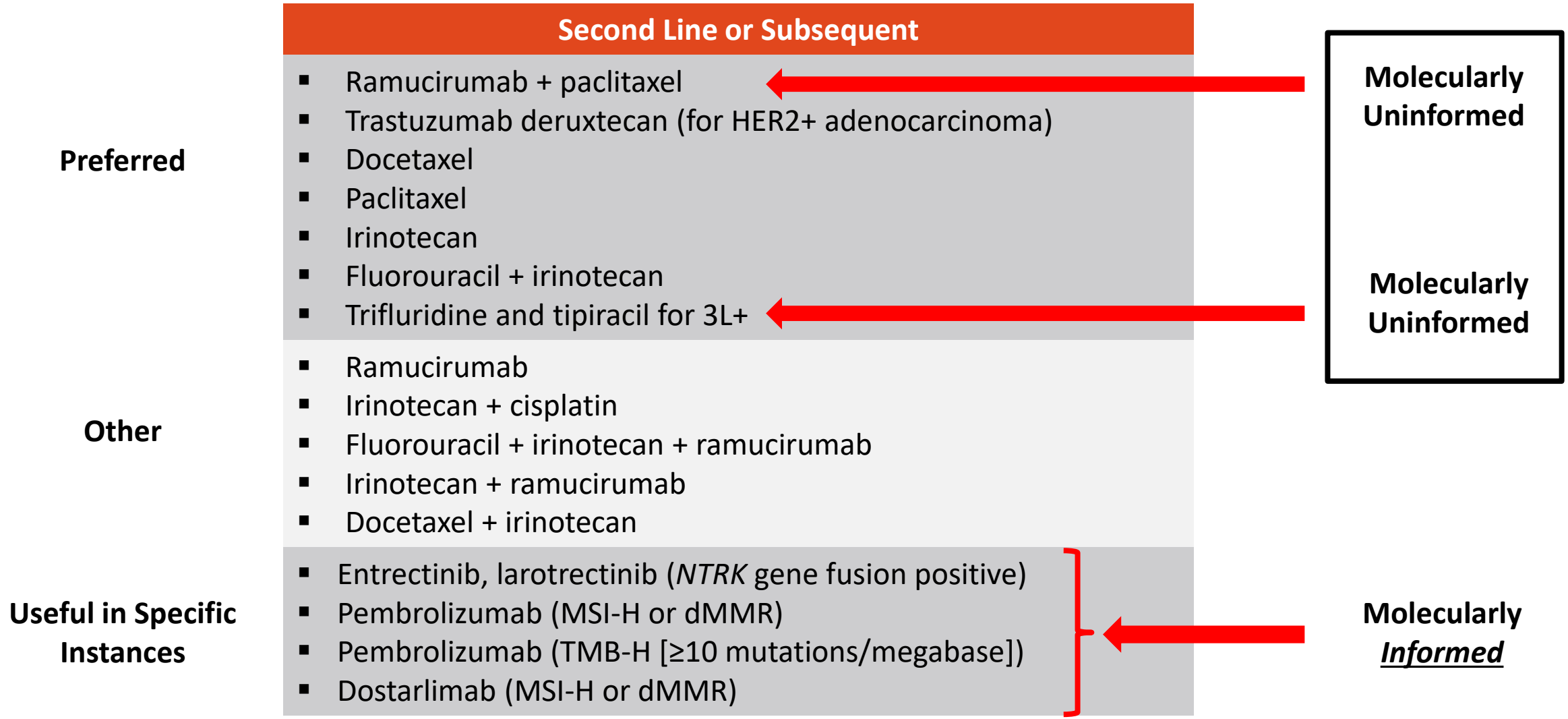


Paclitaxel/Ramucirumab Post PD-1

- Retrospective work in US and Asia
- ORR 58% to 60% in patients with PD-1 prior to paclitaxel + ramucirumab
- mPFS 5-12 mo
- Ongoing prospective trials

Kudo. Cancers (Basel). 2020;12:1089. Kankeu Fonkoua. Int J Cancer. 2021;149:378. Sasaki. ESMO Open. 2020;4:e000775.

A Menu of 2L and Beyond for Gastric/GEJ

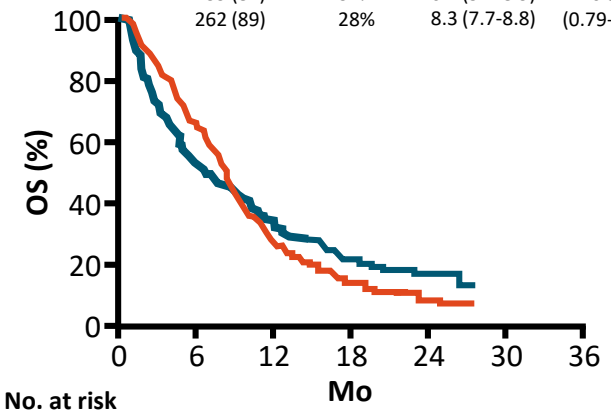


Adapted from NCCN. Clinical practice guidelines in oncology: gastric cancer. v.2.2022. nccn.org.

PD-1 for 2L and Beyond MSI-H/dMMR

KEYNOTE-061: 2L Pembrolizumab vs Chemo

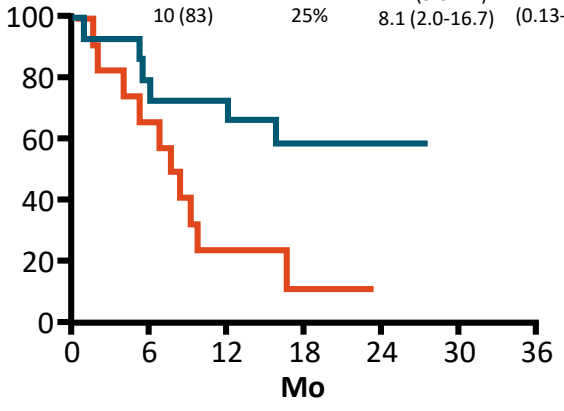
	Events n (%)	12-Mo Rate	Median, Mo (95% CI)	HR (95% CI)
Pembro	239 (81)	34%	6.7 (5.4-8.9)	0.94
Chemo	262 (89)	28%	8.3 (7.7-8.8)	(0.79-1.12)



No. at risk							
Pembro	296	155	101	53	16	0	0
Chemo	296	191	83	36	12	0	0

KEYNOTE-061: Pembrolizumab vs Chemo in MSI-H

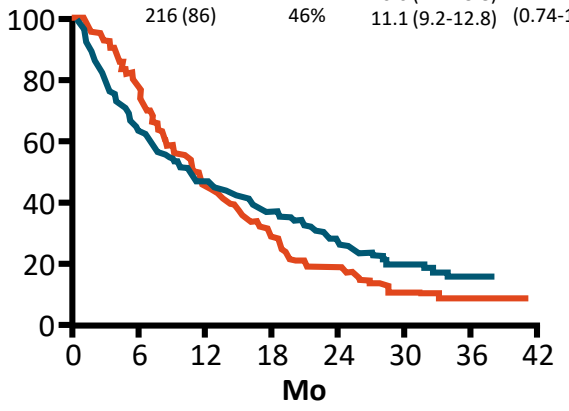
	Events n (%)	12-Mo Rate	Median, Mo (95% CI)	HR (95% CI)
Pembro	6 (40)	73%	NR (5.6-NR)	0.42
Chemo	10 (83)	25%	8.1 (2.0-16.7)	(0.13-1.31)



15	12	11	6	3	0	0
12	8	3	1	0	0	0

KEYNOTE-062: 1L Pembrolizumab vs Chemo

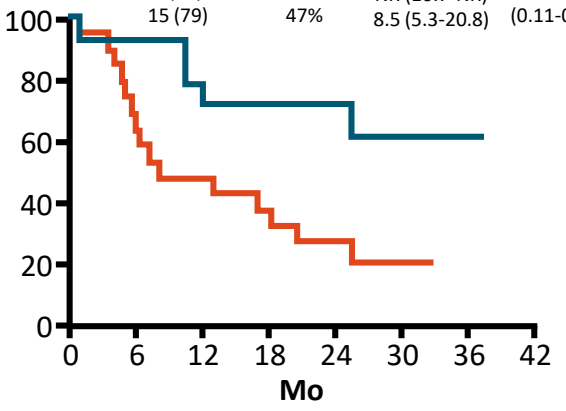
	Events n (%)	12-Mo Rate	Median, Mo (95% CI)	HR (95% CI)
Pembro	201 (79)	47%	10.6 (7.7-13.8)	0.91
Chemo	216 (86)	46%	11.1 (9.2-12.8)	(0.74-1.10)



256	162	120	94	59	23	4	0
250	192	114	75	38	15	2	0

KEYNOTE-062: Pembrolizumab vs Chemo in MSI-H

	Events n (%)	12-Mo Rate	Median, Mo (95% CI)	HR (95% CI)
Pembro	5 (36)	79%	NR (10.7-NR)	0.29
Chemo	15 (79)	47%	8.5 (5.3-20.8)	(0.11-0.81)



14	13	11	10	9	4	2	0
19	13	9	7	4	3	0	0

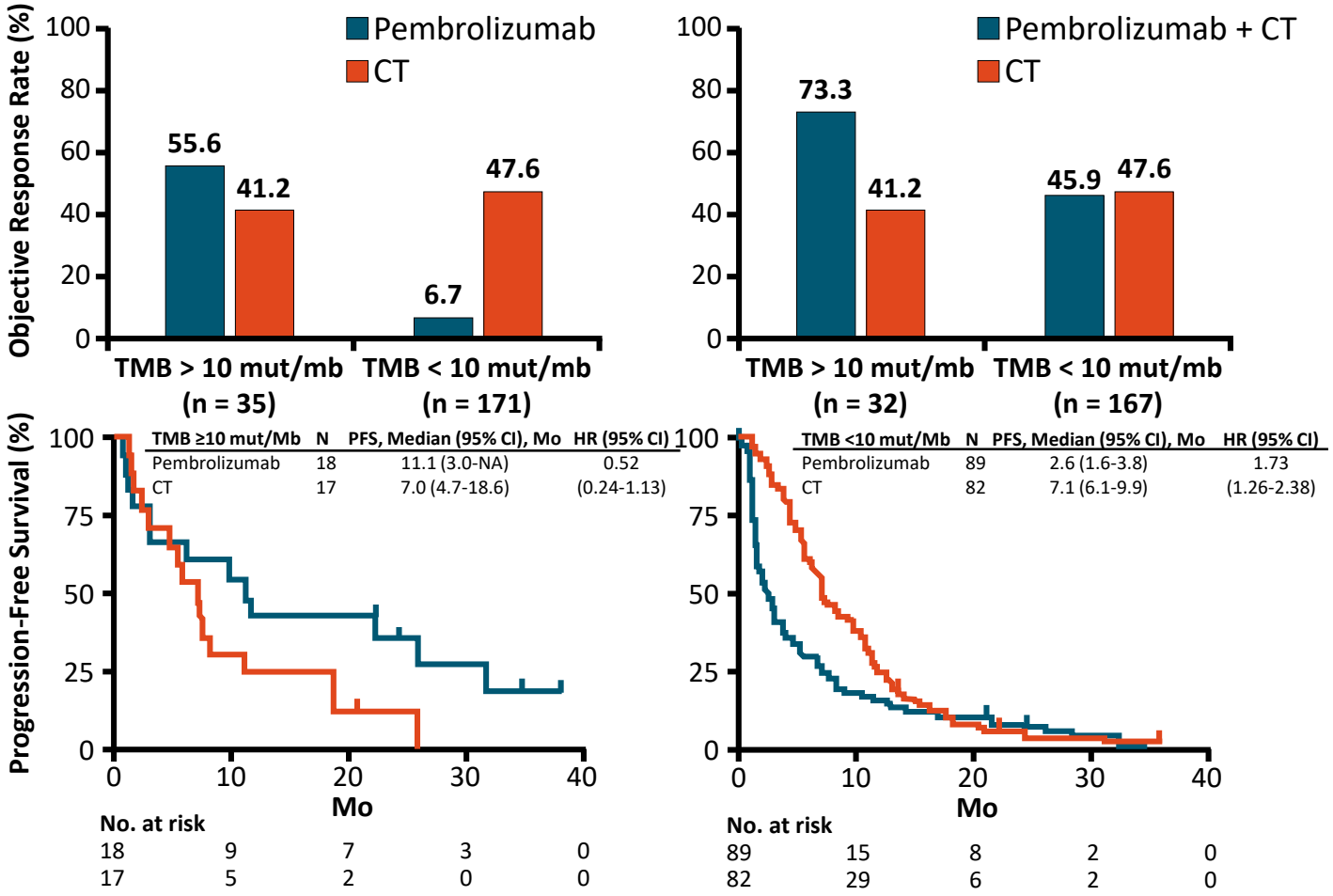
Response	Keynote-059 (3L+)	KEYNOTE-061 (2L)		KEYNOTE-062 (1L)	
	Pembro (n = 7)	Pembro (n = 15)	Chemo (n = 12)	Pembro (n = 14)	Chemo (n = 19)
ORR, n (%)	4 (57)	7 (47)	2 (17)	8 (57)	7 (37)
Median DOR, mo (range)	Not reached (20.0+ to 26.8+)	Not reached (5.5 to 26.0+)	Not reached (2.2+ to 12.2+)	21.2 (1.4+ to 33.6+)	7.0 (2.0 to 30.4+)

MSI-H or dMMR is strongly associated with improved outcomes with immune checkpoint inhibitor therapy
Activity is independent of the line of therapy

Chao. JAMA Oncol. 2021;7:895.

Into Murkier Waters—TMB-High

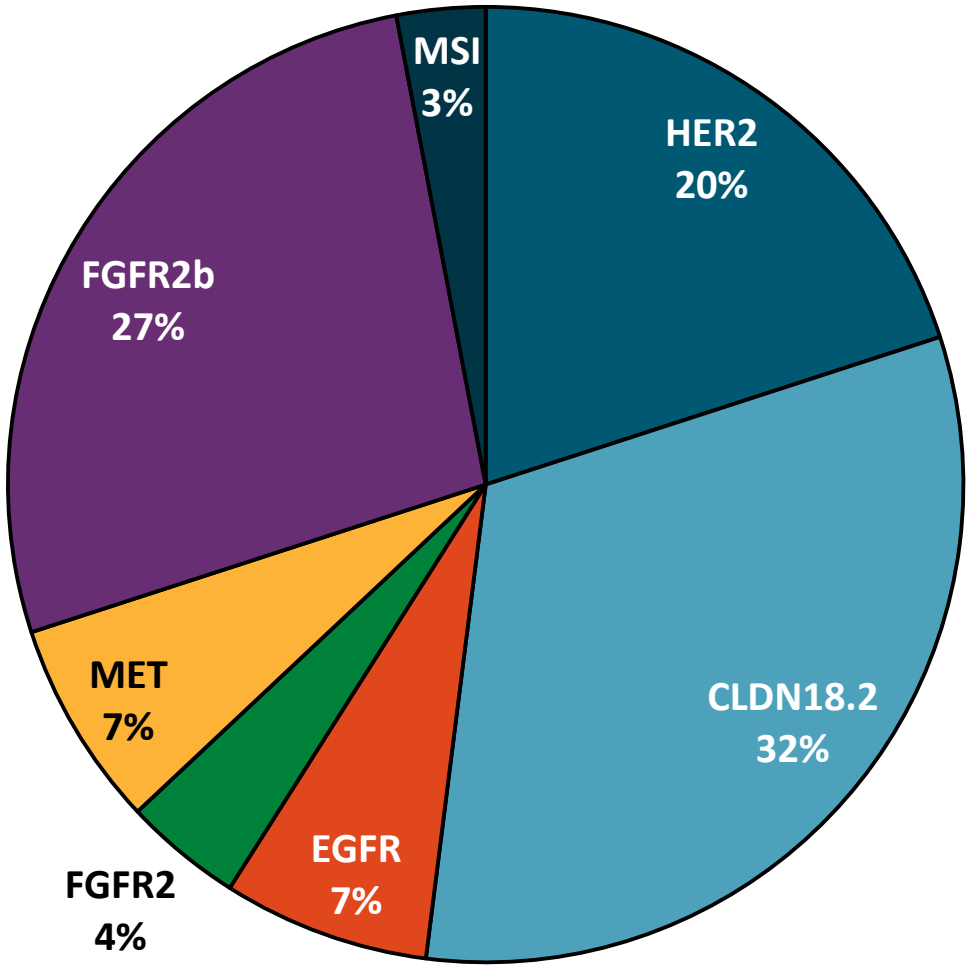
- **FDA 6/16/2020:** accelerated approval for pembrolizumab for unresectable or metastatic TMB-H (≥10mut/Mb) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment option



- TMB ≥10 Mut/Mb is seen in ~10%-15% of gastric cancers (KEYNOTE-062 data)
- ~45% of TMB-H also were MSI-H
- TMB and PD-L1 CPS do not have a tight correlation (r = 0.23)
- After removing patients with MSI-H tumors, association between TMB-H and PFS/OS no longer significant

Lee. Clin Cancer Res. 2022 [Epub].

NGS—the Right Tool for the Job

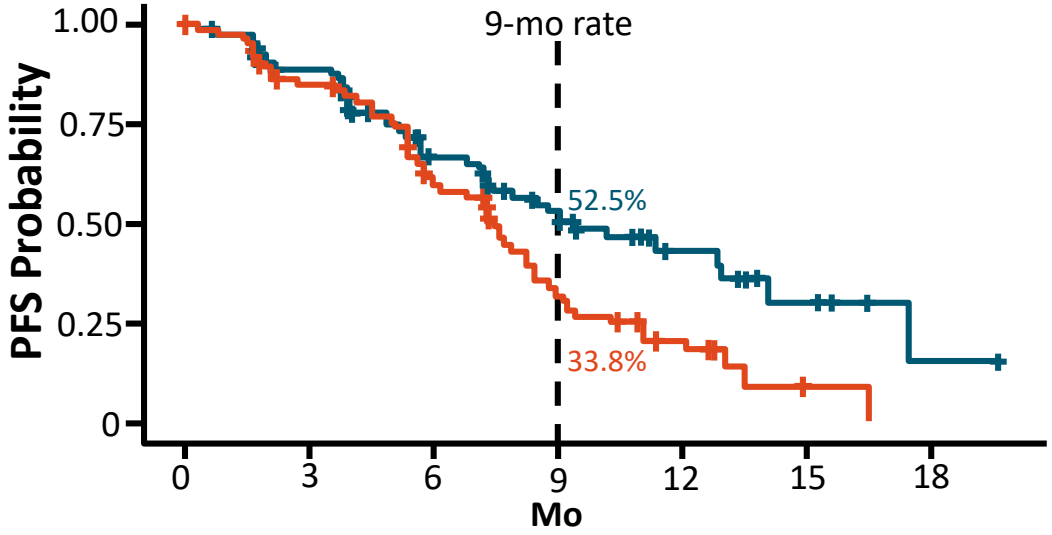


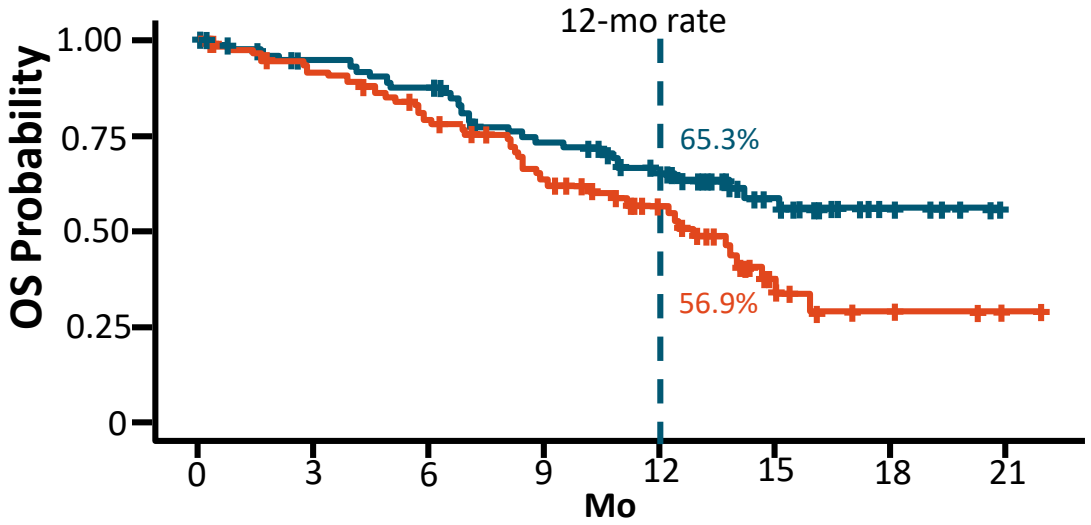
- HER2 status: NGS, FISH, IHC
- MSI status: NGS, PCR, IHC
- PD-L1 score: IHC
- NTRK status: NGS, IHC, FISH
- TMB level: NGS
- CLDN18.2 expression: IHC
- FGFR2 status: NGS, FISH, IHC
- $EGFR_{amp}$ status: NGS, FISH
- MET_{amp} status: NGS, FISH

Lee. J Pathol Transl Med. 2017;51:103. Schoemig-Markieffka. Gastric Cancer. 2021;24:1115.
Cai. J Transl Med. 2019;17:189. Baek. Anticancer Res. 2019;39:6973. Ahn. Mod Pathol. 2016;29:1095.

FIGHT: First-line Bemarituzumab + mFOLFOX6 vs Placebo + mFOLFOX6 in Advanced Gastric/GEJ Cancer

- Randomized phase II trial of bemarituzumab (anti-FGFR2b antibody) or placebo + (both + mFOLFOX6) for patients with no prior therapy and unresectable locally advanced or metastatic gastric/GEJ adenocarcinoma with *FGFR2b* overexpression/amplification (N = 155)





	Bema + mFOLFOX6 (n = 77)	Placebo + mFOLFOX6 (n = 78)	
Median PFS, mo	9.5	7.4	HR 0.68; *P* = .0727)
Median OS, mo	Not reached	12.9	HR 0.58; *P* = .0268)

- Ongoing phase III: FORTITUDE-101 (bemarituzumab + mFOLFOX6, NCT05052801)

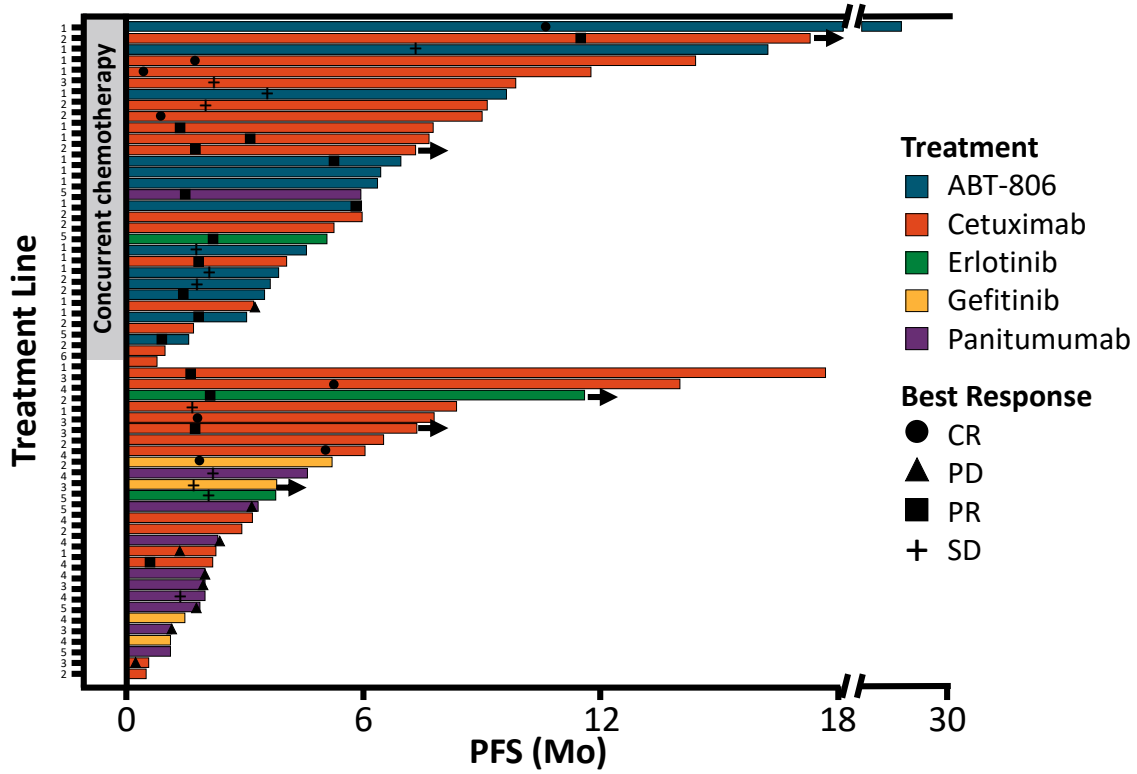
Wainberg. ASCO GI 2021. Abstr LBA160.

EGFR—Revisiting an Older Target

- EGFR amplification is seen in 5% to 8% of EAC/GEJ
- Prior negative trials impacted by patient selection
- Subgroup analysis suggest EGFRamp may benefit from EGFRi

Maron. Cancer Discov. 2018;8:696.

EGFR—Revisiting an Older Target

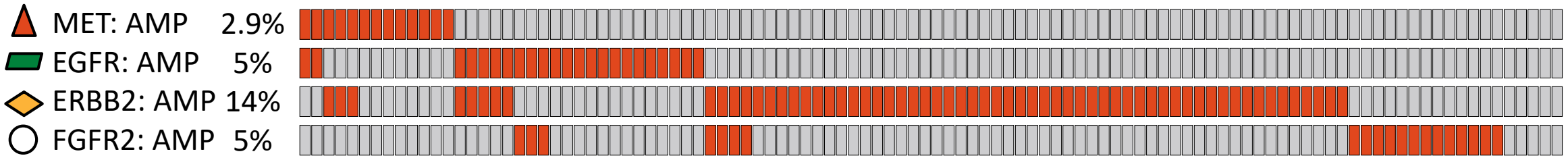


Treatment Line, n/N (%)	1	2	3	4	5
Overall	11/17 (65)	7/15 (43)	28 (25)	4/16 (25)	24/56 (43)
EGFRi + chemo	9/14 (64)	5/10 (50)	0/1 (0)	2/3 (67)	16/28 (57)
EGFRi	2/3 (67)	2/5 (40)	2/7 (29)	2/13 (15)	8/28 (29)

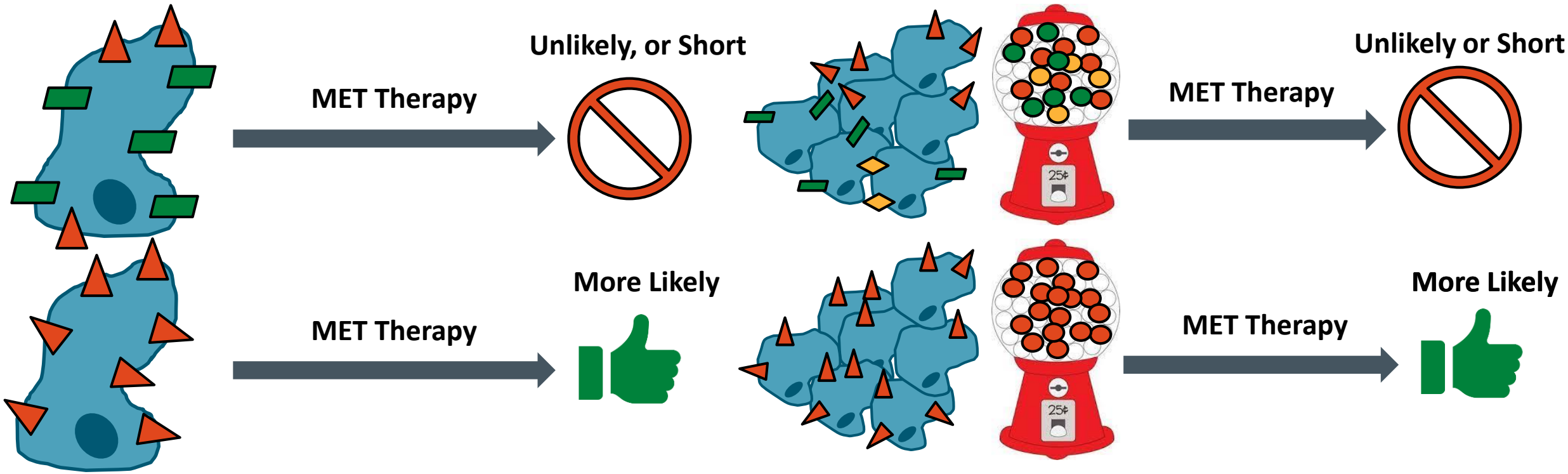
Maron. JCO. 2022;[Online].

- EGFR is a therapeutic target in EAC/GEJ
- Well suited toward combinatorial approaches
- Activity seen independent of line of therapy (c/w driver)
- Ongoing phase II trials examining bispecific Ab amivantamab in EGFR and/or METamp GEA

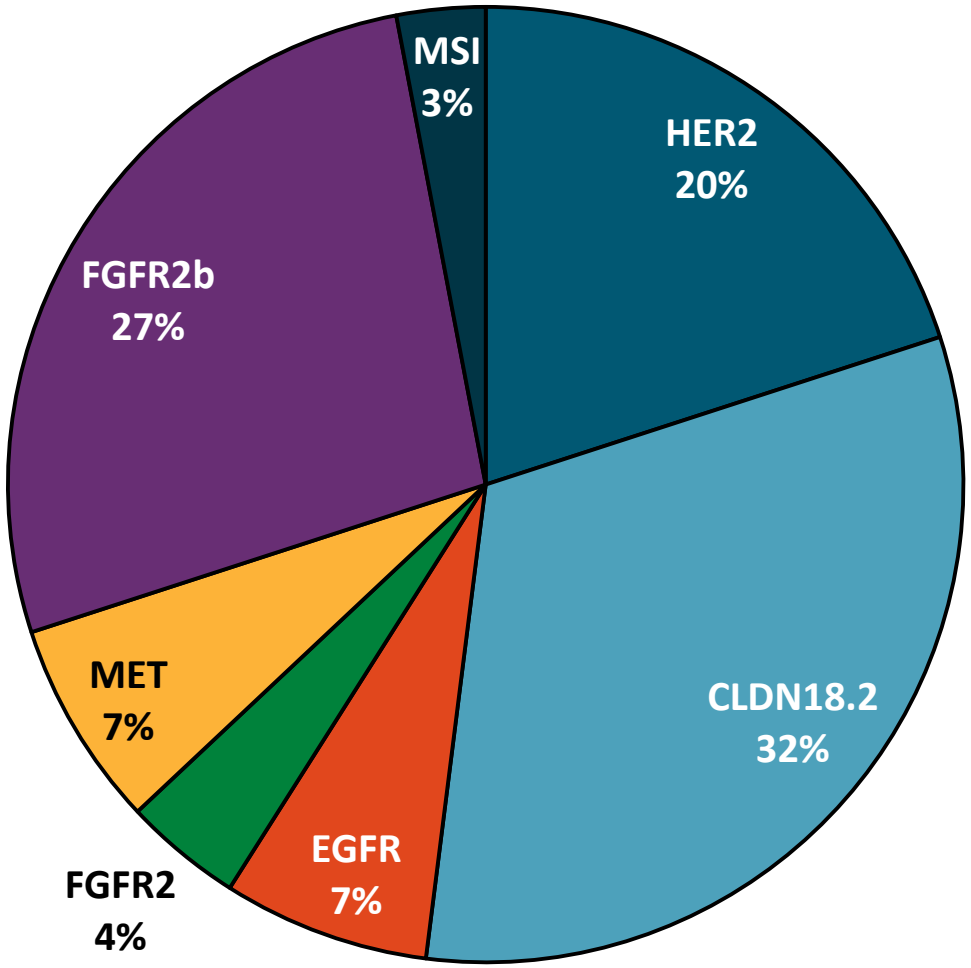
MET—Still a Viable Target?



Genetic Alteration Amplification No alterations



NGS—the Right Tool for the Job



- HER2 status: NGS, FISH, IHC
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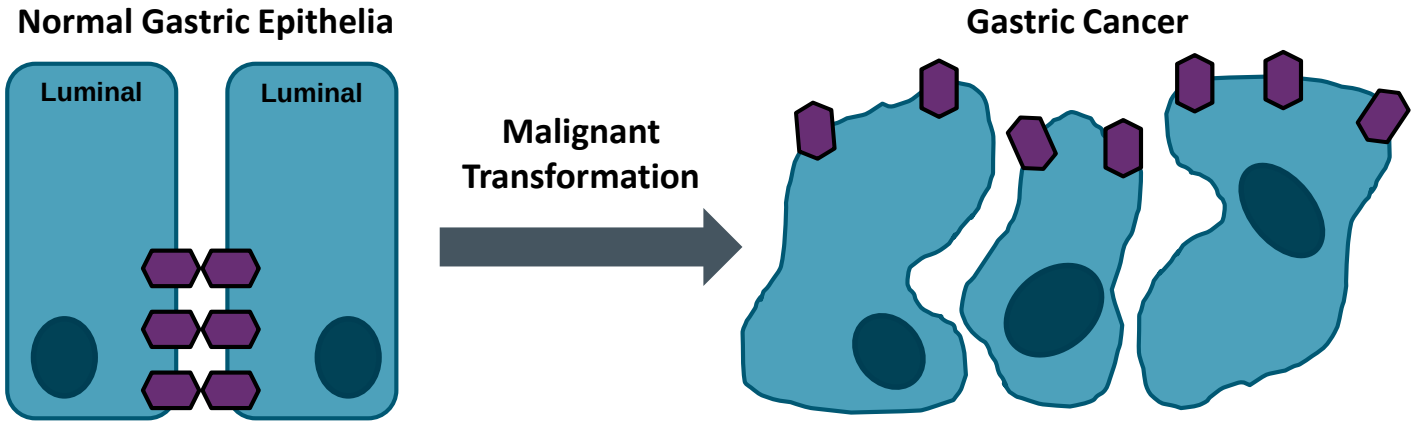
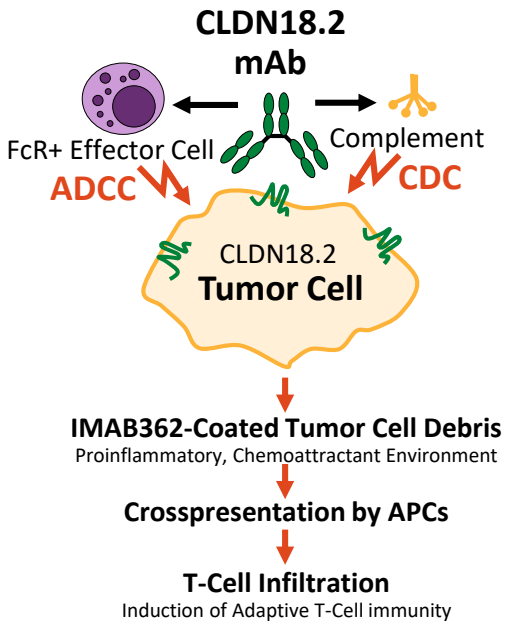
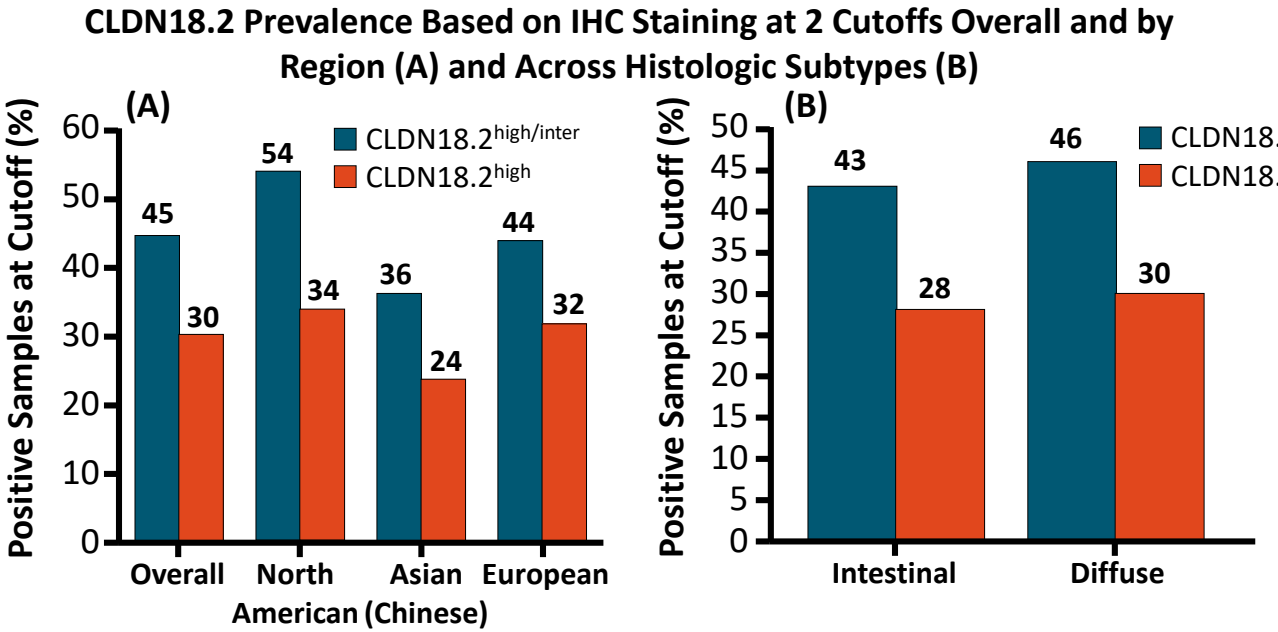
Lee. J Pathol Transl Med. 2017;51:103. Schoemig-Markieffka. Gastric Cancer. 2021;24:1115.
Cai. J Transl Med. 2019;17:189. Baek. Anticancer Res. 2019;39:6973. Ahn. Mod Pathol. 2016;29:1095.

Claudin18.2—Leveraging Biology







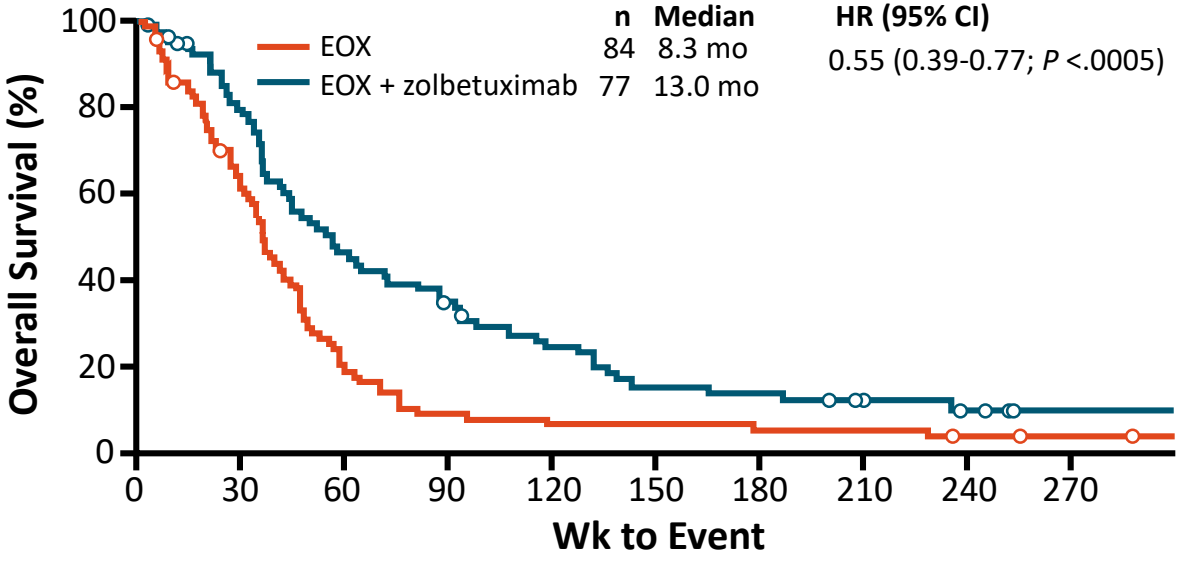
- Claudin18.2 is a major structural component of intercellular tight junctions
- Not routinely expressed in any normal tissue outside gastric mucosa (cancer-restricted antigen)
- Broadly expressed in several tumor types including gastric, GEJ, biliary, and pancreatic

Baek. Anticancer Res. 2019;39:6973.

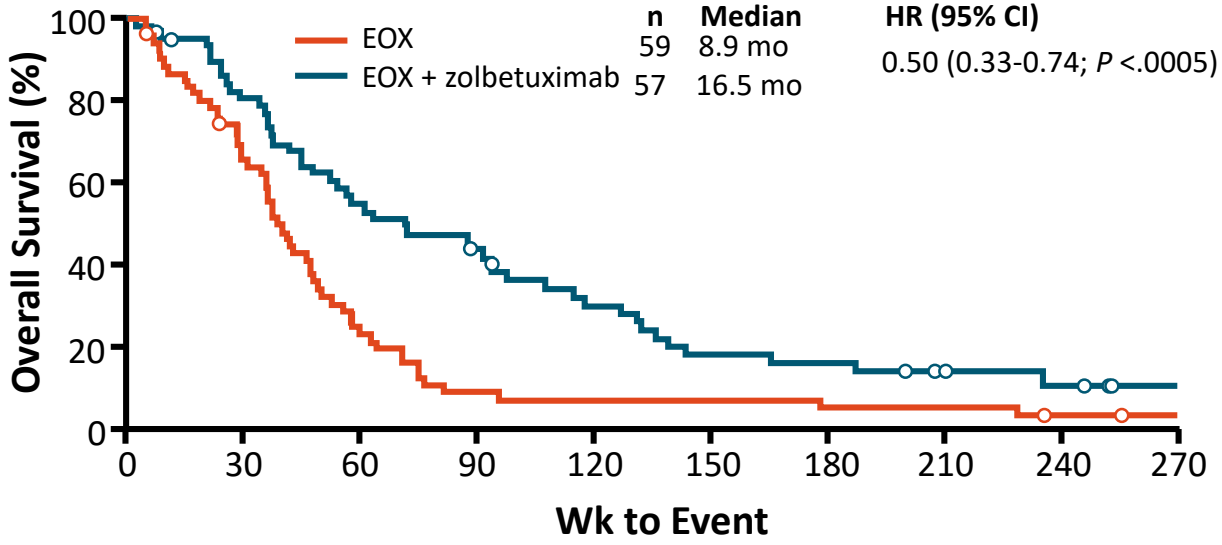
FAST: First-line Zolbetuximab (IMAB362) + EOX for Advanced CLDN18.2+ Gastric/GEJ Adenocarcinoma

- Randomized phase II study of first-line zolbetuximab + EOX vs EOX for patients with locally advanced, inoperable, recurrent, or metastatic CLDN18.2+ gastric or GEJ adenocarcinoma (N = 252)

OS in Overall Population*



OS in High CLDN18.2 Expressors†



*Patients with ≥40% of tumor cells positive for CLDN18.2. †Patients with ≥70% of tumor cells positive for CLDN18.2.

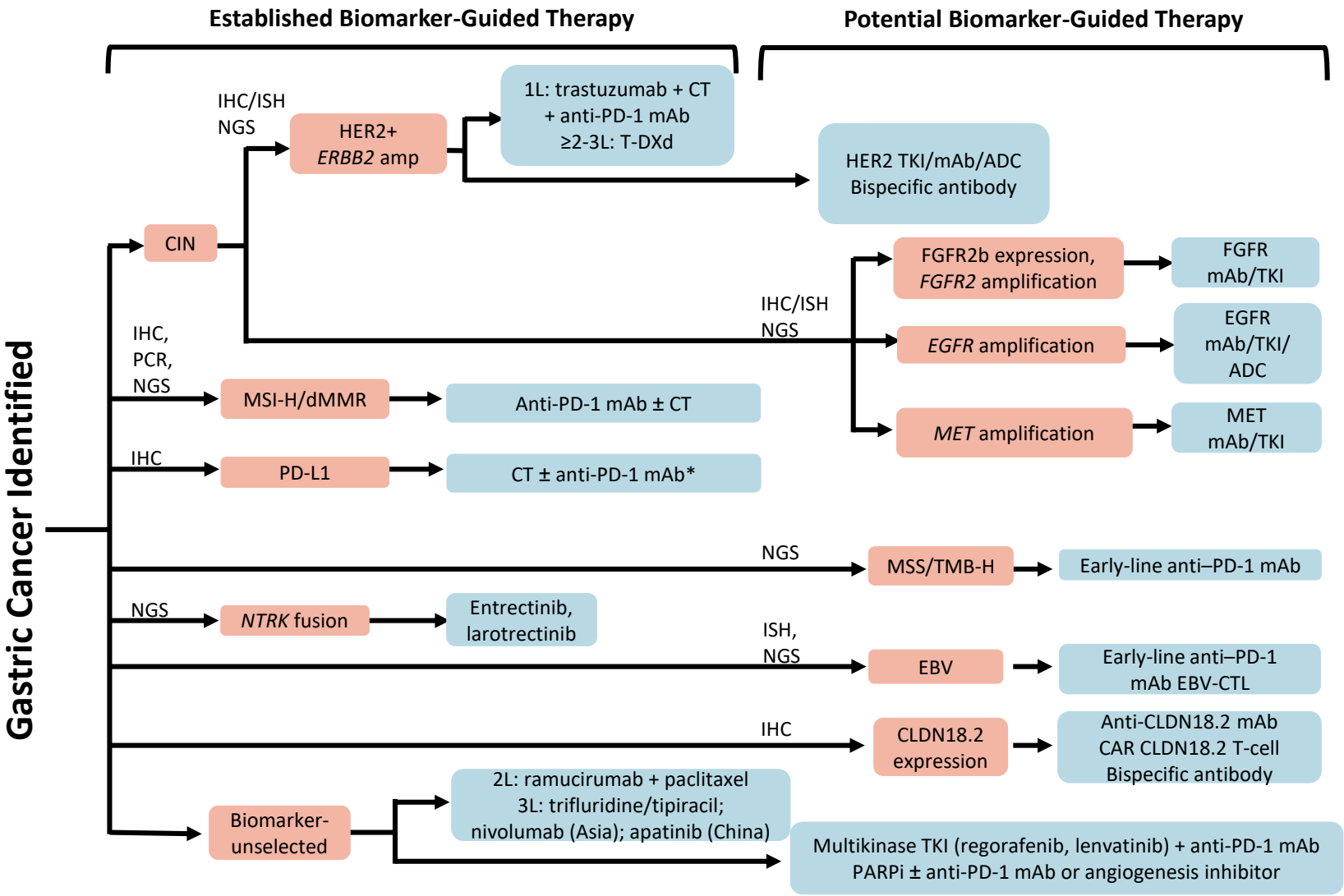
- Ongoing: Spotlight (FOLFOX6 ± zolbetuximab, NCT03504397); GLOW (CapeOx ± zolbetuximab, NCT03653507)

Sahin. Ann Oncol. 2021;32:609.

Summary

- The treatment landscape for upper GI cancers has changed significantly in the past 5 yr, with novel approaches available for patients with resectable disease and numerous targeted therapies now approved for advanced disease
- Gastroesophageal cancers should be tested for *HER2* amplification, MSI-H/dMMR, and PD-L1 elevation, which can inform use of PD-1 inhibitor combinations and HER2 targeting agents

Hopefully, the Near Future



- It's all about the biomarkers
- Trials are how we advance care
- NGS is a tool to interrogate multiple biomarkers in parallel
- CLDN18.2, EGFR, MET, TROP2, novel IO combinations, cellular therapies ALL warrant further study in later-line patients

Adapted from Shitara. Nat Rev Clin Oncol. 2021;18:473.

*Consideration for anti-PD-1 mAb based on PD-L1 testing results