Cancer Center

NCI-DESIGNATED COMPREHENSIVE CANCER CENTER

Update on Biomarker-Directed Therapy for Esophageal, Gastric, and Pancreas Cancer

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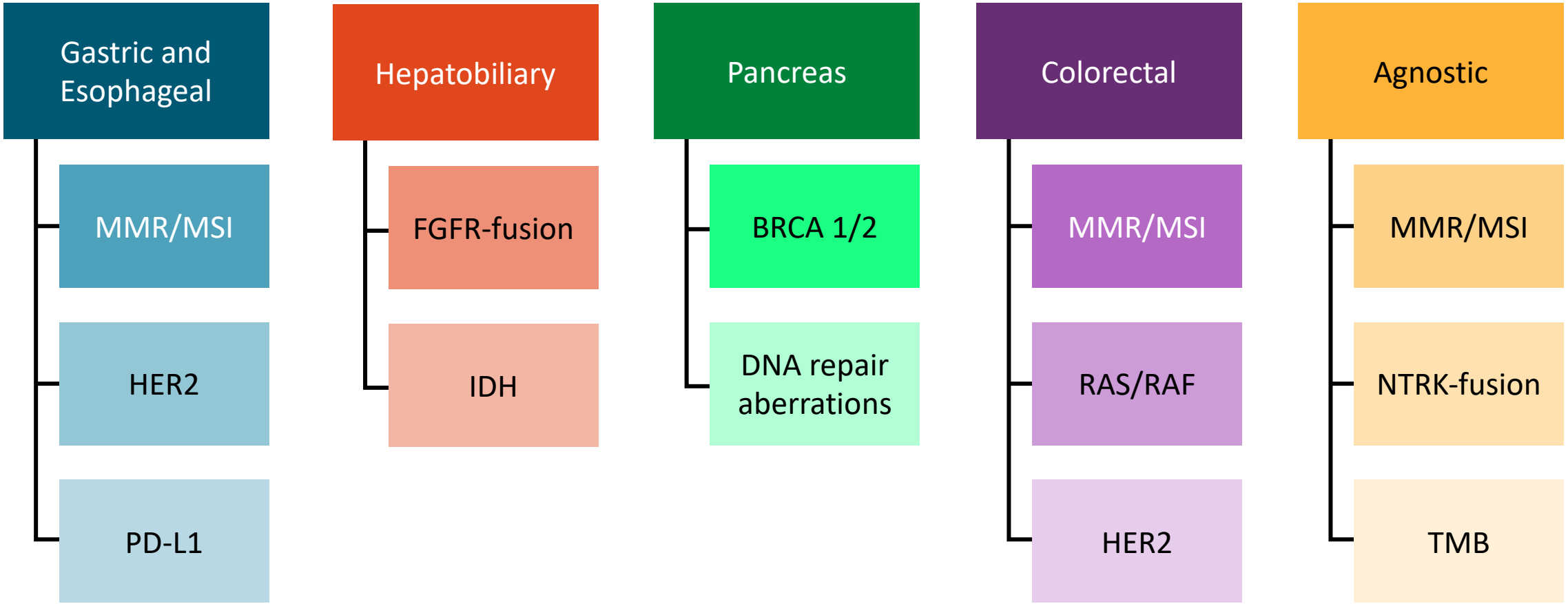
Key Biomarkers in GI Cancers



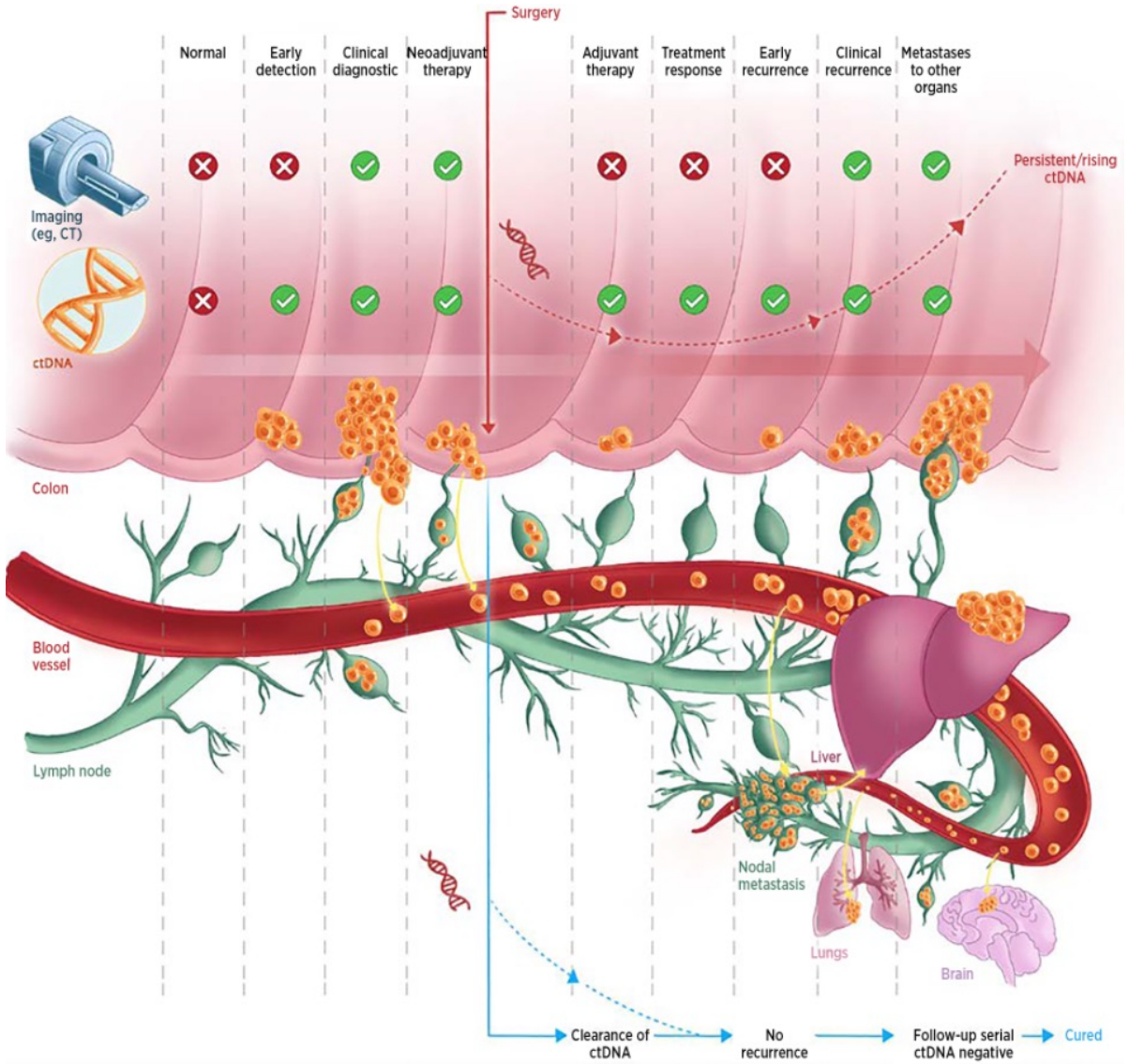
Slide credit: clinicaloptions.com

Biomarker Sequencing Approaches

	NGS	Single Gene Panel
Advantages	▪ Genetic variants in multiple targets (>600 genes) ▪ Sequence variants, CNV, rearrangements, indels, and fusions ▪ TMB and MSI ▪ Less cost per gene	▪ Easy to establish and validate ▪ Control tissue/blood not needed ▪ Sign out is less time consuming ▪ No problem with VUS ▪ May be more relevant in genetic screening to avoid VUS
Challenges	▪ Expertise to develop and validate the panel ▪ Normal tissue/blood ▪ Broader QI effort in day-to-day sign out ▪ VUS	▪ Limited target coverage ▪ Higher cost per gene ▪ May need multiple samples if testing performed in phases ▪ Cannot assess MSI

- Discussion: Is DNA enough for testing or should RNA be tested?

Potential Uses of ctDNA Assays



- Diagnosis
- Measurable Residual Disease
- Treatment Response
- Acquired Resistance

Kasi. ASCO Daily News 1.13.22. dailynews.ascopubs.org/do/10.1200/ADN.22.200792/full/.

Potential Advantages of Using ctDNA Assays to Assess Actionable Mutations

- Analysis of trial enrolment of patients with advanced GI cancers using ctDNA sequencing (GOZILA, n = 1687) vs tumor tissue sequencing (GI-SCREEN, n = 5621)

Key Findings

Outcome	GI-SCREEN (Tissue)	GOZILA (ctDNA)
Total screening duration, days	33	11
Pts enrolled in a trial, % (n/N)	4.1 (126/3055)	9.5 (60/632)
ORR, % (n/N)	16.7 (21/126)	20.0 (12/60)

Identification of Actionable Mutations

Success rate by tumor type, %	GI-SCREEN n = 5621	GOZILA n = 1687
CRC	92.3	100
GC	87.3	100
ESCC	86.2	99.1
PDAC	87.6	100
CCA	85.0	100
Others	84.7	100

Nakamura. Nat Med. 2020;26:1859.

Cases in Gastroesophageal and Pancreatic Cancers

Molecularly-Targeted Therapy Rapid Fire

Case Discussion

- 65-year-old patient presents with dysphagia. EGD reveals a GEJ mass – biopsy reveals moderately-differentiated adenocarcinoma, pMMR, HER2 amplified by IHC/FISH.
- CPS = 2.

- CT reveals multiple pulmonary and hepatic metastases.

- ECOG performance status = 0

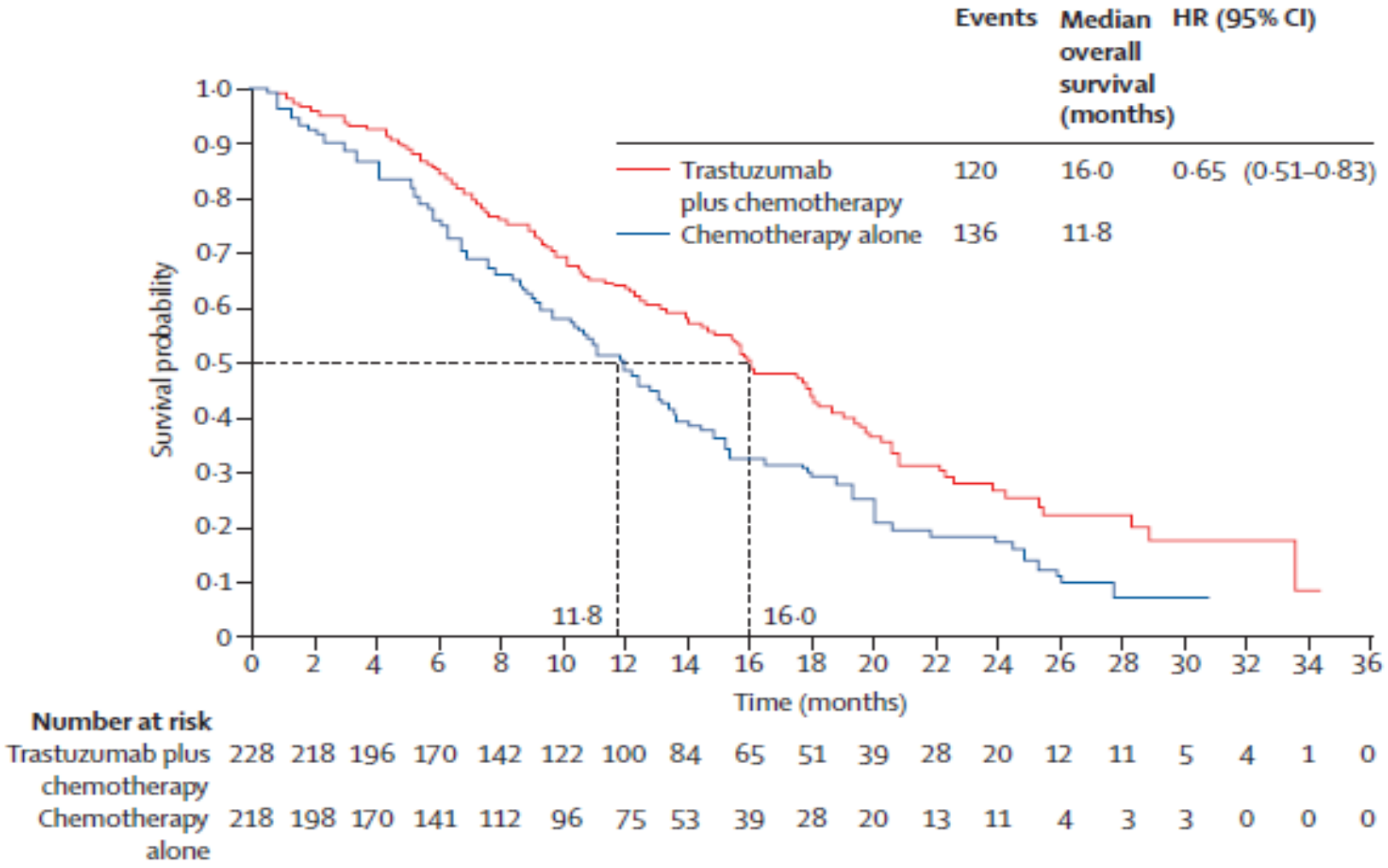
- What is your initial recommendation for systemic therapy?
  - FOLFOX and nivolumab
  - Carboplatin and paclitaxel
  - FOLFOX trastuzumab
  - FOLFOX trastuzumab pembrolizumab
  - Nivolumab and ipilimumab

First-Line HER2-Directed Clinical Trials

Clinical Trial	Regimen	Median OS, mos	HR	95% CI	*P* Value
ToGA[1]	5-FU or capecitabine + cisplatin + trastuzumab	13.8	0.74	0.60-0.91	.0046
	5-FU or capecitabine + cisplatin	11.1			
TRIO-013/LOGiC[2]	Capecitabine + oxaliplatin + lapatinib	12.2	0.91	0.73-1.12	.3492
	Capecitabine + oxaliplatin	10.5			
JACOB[3]	Capecitabine or 5-FU + cisplatin + trastuzumab + pertuzumab	17.5	0.84	0.71-1.00	.057
	Capecitabine or 5-FU + cisplatin + trastuzumab	14.2			

1. Bang YJ et al. *Lancet*. 2010;376:687-697; 2. Hecht JR et al. *J Clin Oncol*. 2016;34(5):443-451; 3. Tabernero J et al. *Lancet Oncol*. 2018;19(10):1372-1384.

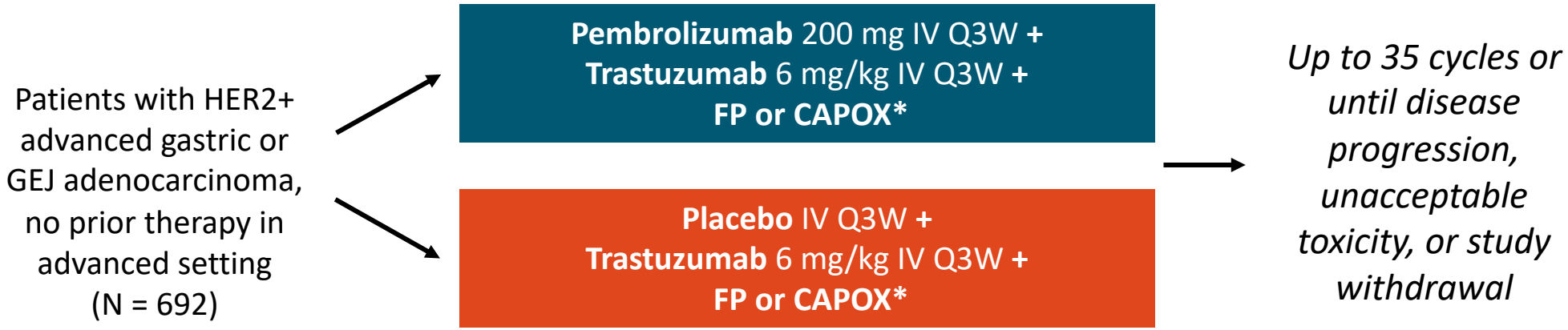
Improved OS in Patients With High HER2 Expression



Bang YJ et al. *Lancet*. 2010;376:687-697.

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

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

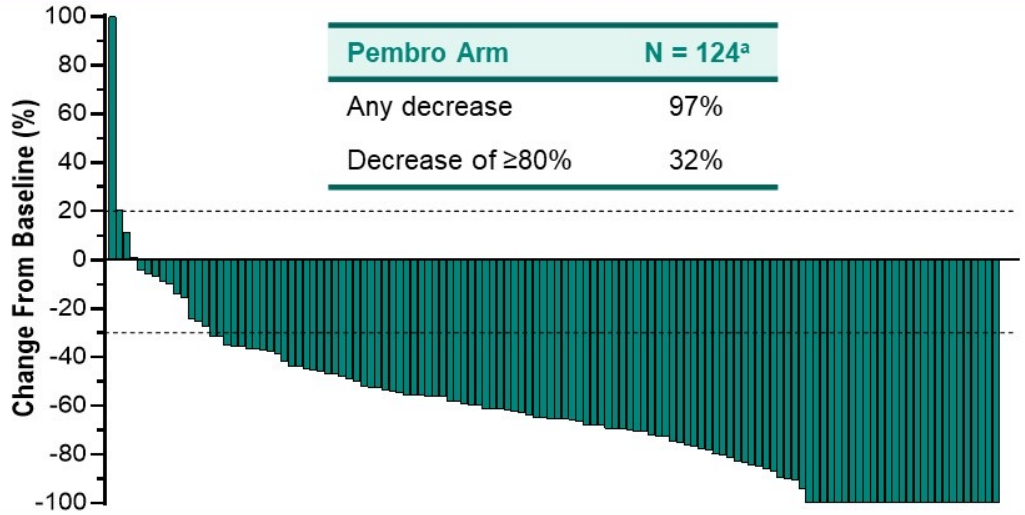


*Trastuzumab 8 mg/kg loading dose.
FP: 5-fluorouracil 800 mg/m^2 IV Days 1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W
CAPOX: capecitabine 1000 mg/m^2 BID Days 1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W

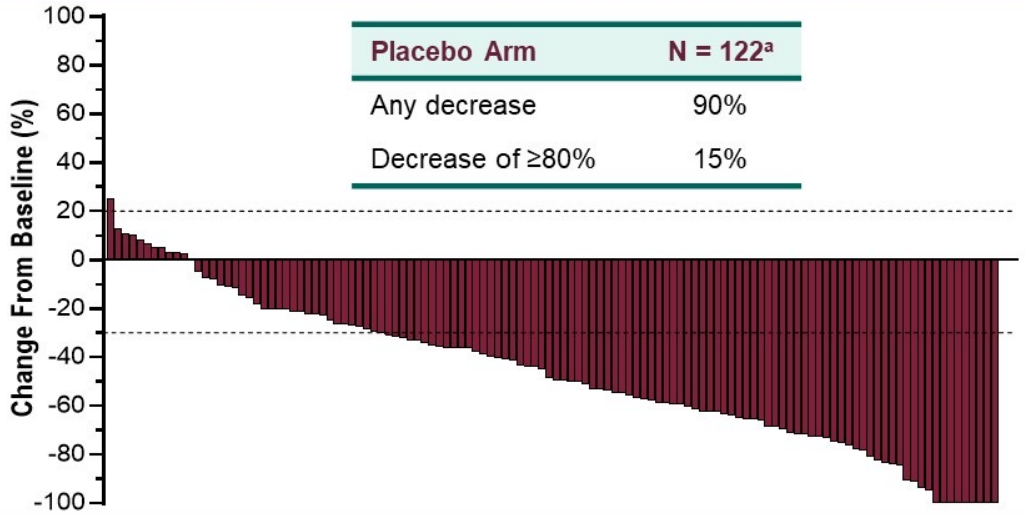
- Efficacy analysis: first 264 patients enrolled; safety analysis: 433 patients who received ≥1 dose of study medication
- Primary endpoints: OS, PFS per RECIST v1.1 by BICR; secondary endpoints: ORR and DoR per RECIST v1.1 by BICR, safety

Janjigian YY et al. *Nature*. 2021;600(7890):727-730.

Confirmed Response at IA1



Pembro Arm	N = 124[a]
Any decrease	97%
Decrease of ≥80%	32%



Placebo Arm	N = 122[a]
Any decrease	90%
Decrease of ≥80%	15%

ORR and DCR, % (95% CI)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	**74.4% (66.2-81.6)**	**51.9% (43.0-60.7)**
ORR difference[b]	**22.7% (11.2-33.7) *P* = 0.00006**	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)

Best Response, n (%)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
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[c]	Pembro Arm (N = 99)	Placebo Arm (N = 68)
Median[d]	10.6 mo	9.5 mo
Range	1.1+ to 16.5+	1.4+ to 15.4+
≥6-mo duration[d]	70.3%	61.4%
≥9-mo duration[d]	58.4%	51.1%

[a]Participants with RECIST-measurable disease at baseline and ≥1 post-baseline measurement evaluable for change from baseline in target lesions. [b]Calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors. [c]Calculated in participants with best response of CR or PR. [d]Kaplan-Meier estimation. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Janjigian YY et al. ASCO 2021. Abstract 4013.

Case Discussion

- Patient receives FOLFOX, trastuzumab, pembrolizumab in the frontline seting. After 9 months, patient has progression in the liver.

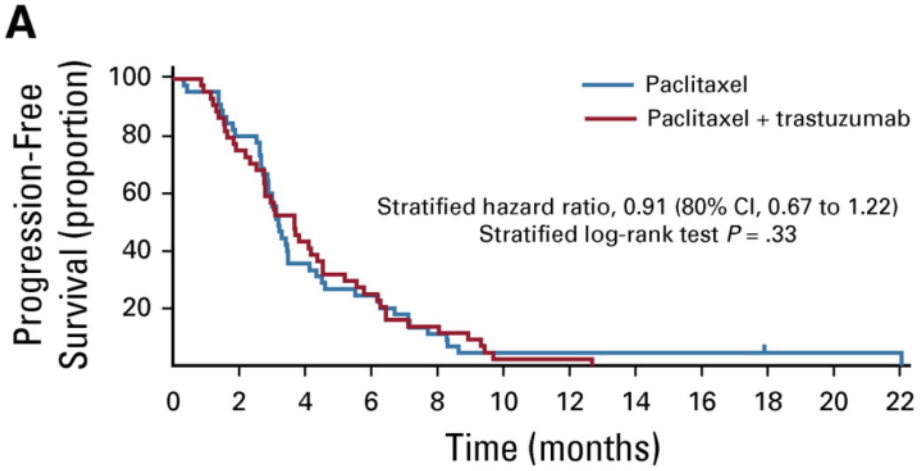
- What is your second line recommendation for systemic therapy?
  - FOLFIRI
  - FOLFIRI trastuzumab
  - Carboplatin and paclitaxel
  - Trastuzumab and Pertuzumab
  - Trastuzumab deruxtecan

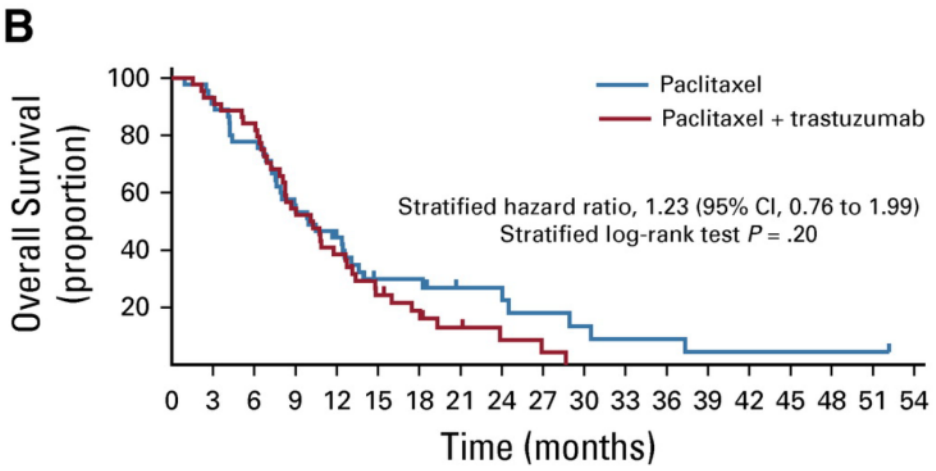
Second-Line HER2-Directed Clinical Trials

Clinical Trial	Regimen	Median OS, mos	HR	95% CI	*P* Value
TYTAN[1]	Paclitaxel + lapatinib	11.0	0.84	0.64-1.11	.1044
	Paclitaxel	8.9			
GATSBY[2]	Trastuzumab emtansine	7.9	1.15	0.87-1.51	.8589
	Paclitaxel or docetaxel	8.6			
T-ACT[3]	Paclitaxel + trastuzumab	10.0	1.2	0.75-2.0	.20
	Paclitaxel	10.0			

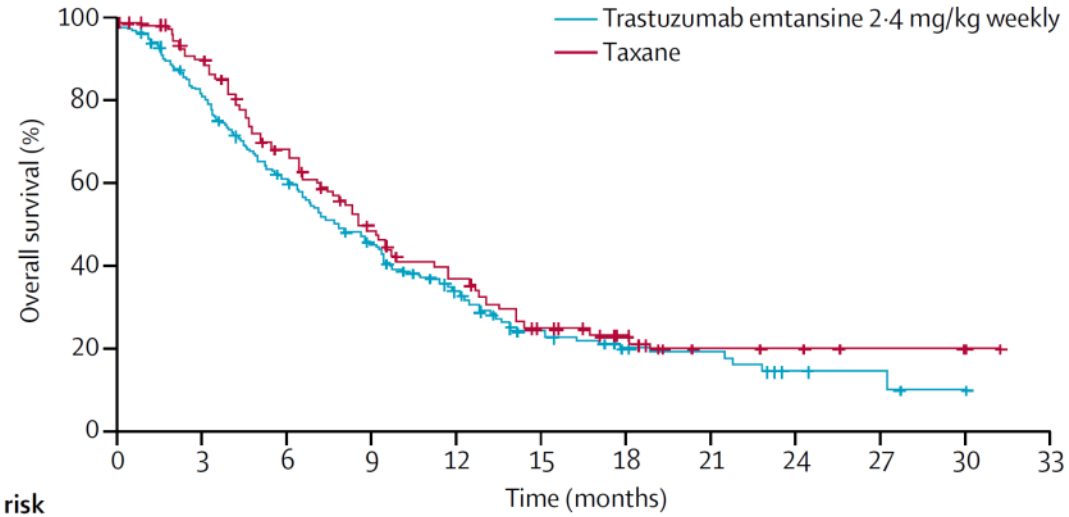
1. Satoh T et al. *J Clin Oncol*. 2014;32(19):2039-2049; 2. Thuss-Patience PC et al. *Lancet Oncol*. 2017;18:640-653;
3. Makiyama A et al. *J Clin Oncol.* 2020;38(17):1919-1927.

Negative studies in refractory gastric cancer





	Taxane (n=117)	Trastuzumab emtansine 2·4 mg/kg weekly (n=228)
Median overall survival, months (95% CI)	8·6 (7·1–11·2)	7·9 (6·7–9·5)
Number of events	71 (60·7%)	164 (71·9%)
Unstratified hazard ratio (95% CI) weekly trastuzumab emtansine *vs* taxane	1·15 (0·87–1·51), p=0·86*	



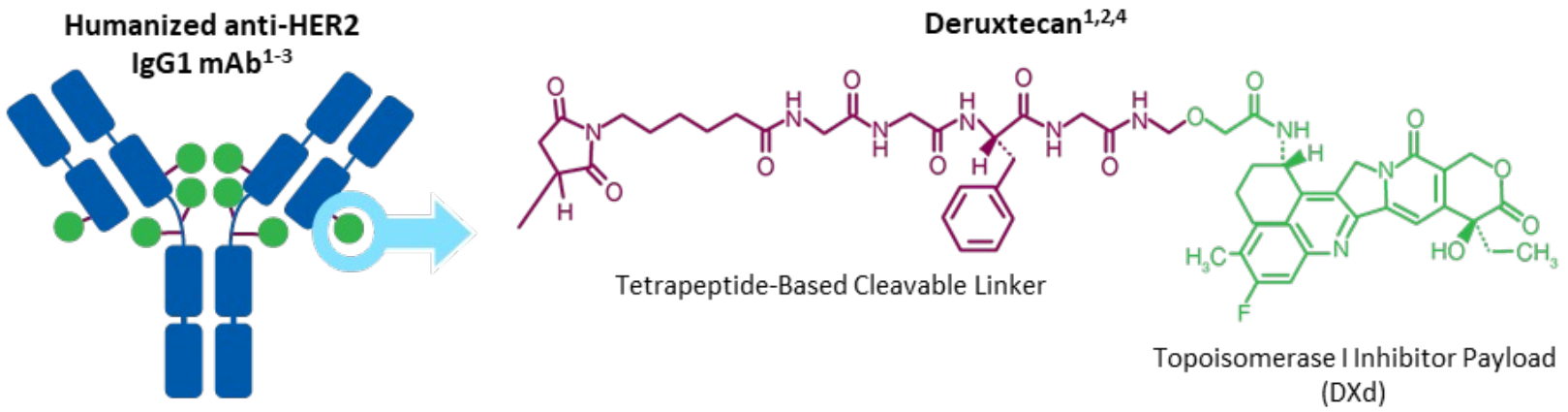
Thuss-Patience PC, et al. *Lancet*. 2017;18:640-53.
Makiyama A, et al. *J Clin Oncol.* 2020;38:1919-1927.

Prevent and conquer cancer. **Together**.

T-DXD Is A Novel ADC Designed To Deliver An Antitumor Effect

T-DXd is an ADC with 3 components

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



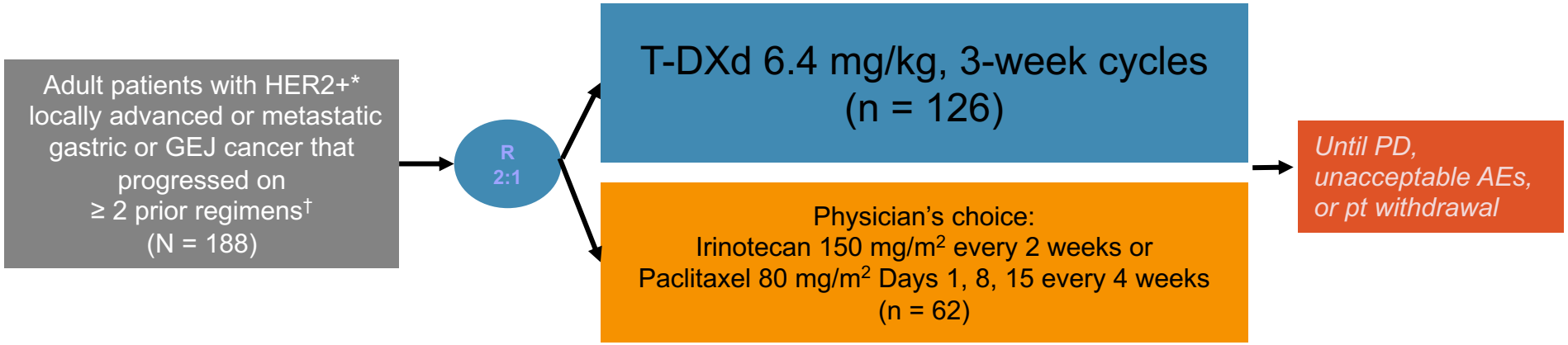
Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug-to-antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker payload
Tumor-selective cleavable linker
Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate.

1. Nakada T et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185; 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22(20):5097-5108; 3. Trail PA et al. *Pharmacol Ther.*2018;181:126-142; 4. Ogitani Y et al. *Cancer Sci.* 2016;107(7):1039-1046.

DESTINY-Gastric01: Study Design

- Multicenter, open-label, randomized phase II study



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

Stratified by region (Japan vs Korea), ECOG PS (0 vs 1), HER2 status (IHC 3+ vs IHC 2+/ISH+)

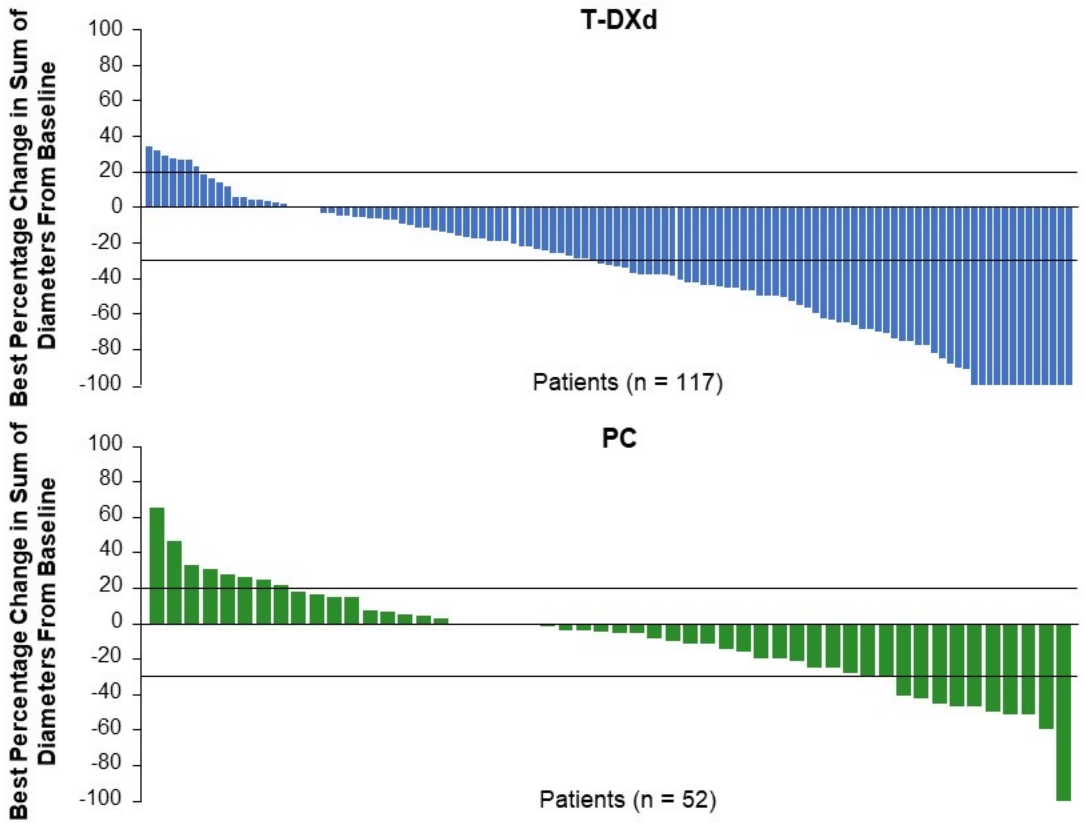
*HER2+ based on IHC 3+ or IHC 2+/ISH+ according to ASCO/CAP guidelines.
†Prior regimens included fluoropyrimidine, a platinum agent, and trastuzumab or approved biosimilar.

Shitara K et al. ASCO 2020. Abstract 4513; Shitara K et al. *N Engl J Med.* 2020; 382(25):2419-2430.

ORR and Other Efficacy Endpoints

	T-DXd n = 119	PC Overall n = 56
ORR (CR + PR) by ICR, n (%)[a]	**61 (51.3) 95% CI, 41.9-60.5**	**8 (14.3) 95% CI, 6.4-26.2**
	P < 0.0001[b]	
CR	11 (9.2)	0
PR	50 (42.0)	8 (14.3)
SD	42 (35.3)	27 (48.2)
PD	14 (11.8)	17 (30.4)
Not evaluable	2 (1.7)	4 (7.1)
Confirmed ORR (CR + PR) by ICR, n (%)[a]	50 (42.0) 95% CI, 33.0-51.4	7 (12.5) 95% CI, 5.2-24.1
CR	10 (8.4)	0
PR	40[c] (33.6)	7 (12.5)
SD	52 (43.7)	28 (50.0)
PD	14 (11.8)	17 (30.4)
Not evaluable	3 (2.5)	4 (7.1)
Confirmed DCR (CR + PR + SD), n (%)[a]	102 (85.7) 95% CI, 78.1-91.5	35 (62.5) 95% CI, 48.5-75.1
Confirmed DOR, median, months	12.5 95% CI, 5.6-NE	3.9 95% CI, 3.0-4.9
TTR, median, months	1.5 95% CI, 1.4-1.7	1.6 95% CI, 1.3-1.7

Best Percentage Change from Baseline in Tumor Size for Individual Patients[d]



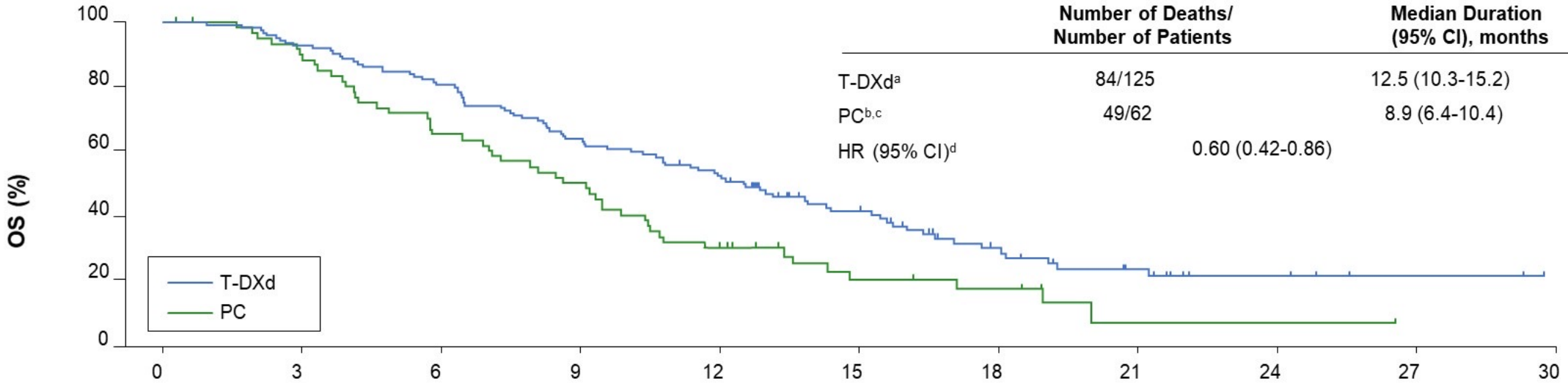
CR, complete response; DCR, disease control rate; DOR, duration of response; ICR, independent central review; NE, not estimable; ORR, objective response rate; PC, physician's choice; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TTR, time to response.

Confirmed ORR: responses were confirmed by a follow-up scan ≥4 weeks after initial CR/PR. [a]Includes data for the response-evaluable set: all randomized patients who received ≥1 dose of study drug and had measurable tumors based on ICR at baseline (T-DXd, n = 119; PC overall, n = 56; irinotecan, n = 51; paclitaxel, n = 5). [b]Comparison between T-DXd and PC overall using Cochran-Mantel-Haenszel test stratified by region. [c]According to the procedure of the ICR, the adjudicator assessment was changed from PR to SD in 1 patient at data cutoff of the final OS analysis. [d]Includes patients who had both baseline and postbaseline target lesion assessments by ICR in both treatment arms. 6 patients were excluded from this analysis because they had no postbaseline tumor assessment (T-DXd, n = 2; PC, n = 4).

Line at 20% indicates progressive disease; line at –30% indicates partial response.

Overall Survival

Kaplan-Meier Analysis of OS



	Number of Deaths/ Number of Patients	Median Duration (95% CI), months
T-DXd[a]	84/125	12.5 (10.3-15.2)
PC[b,c]	49/62	8.9 (6.4-10.4)
HR (95% CI)[d]	0.60 (0.42-0.86)	

Subjects 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

As in the primary analysis (101 OS events; 54.0% maturity), in this updated analysis (133 OS events; 71.1% maturity), T-DXd showed superior antitumor activity compared to PC

HR, hazard ratio; OS, overall survival; PC, physician's choice; T-DXd, trastuzumab deruxtecan.
[a]In the T-DXd arm, 41 patients (32.8%) were censored.
[b]In the PC arm, 13 patients (21.0%) were censored.
[c]1 patient in the PC arm received crossover treatment of T-DXd.
[d]HR and corresponding 95% CI were estimated using Cox proportional hazards model stratified by region.

Overall Safety

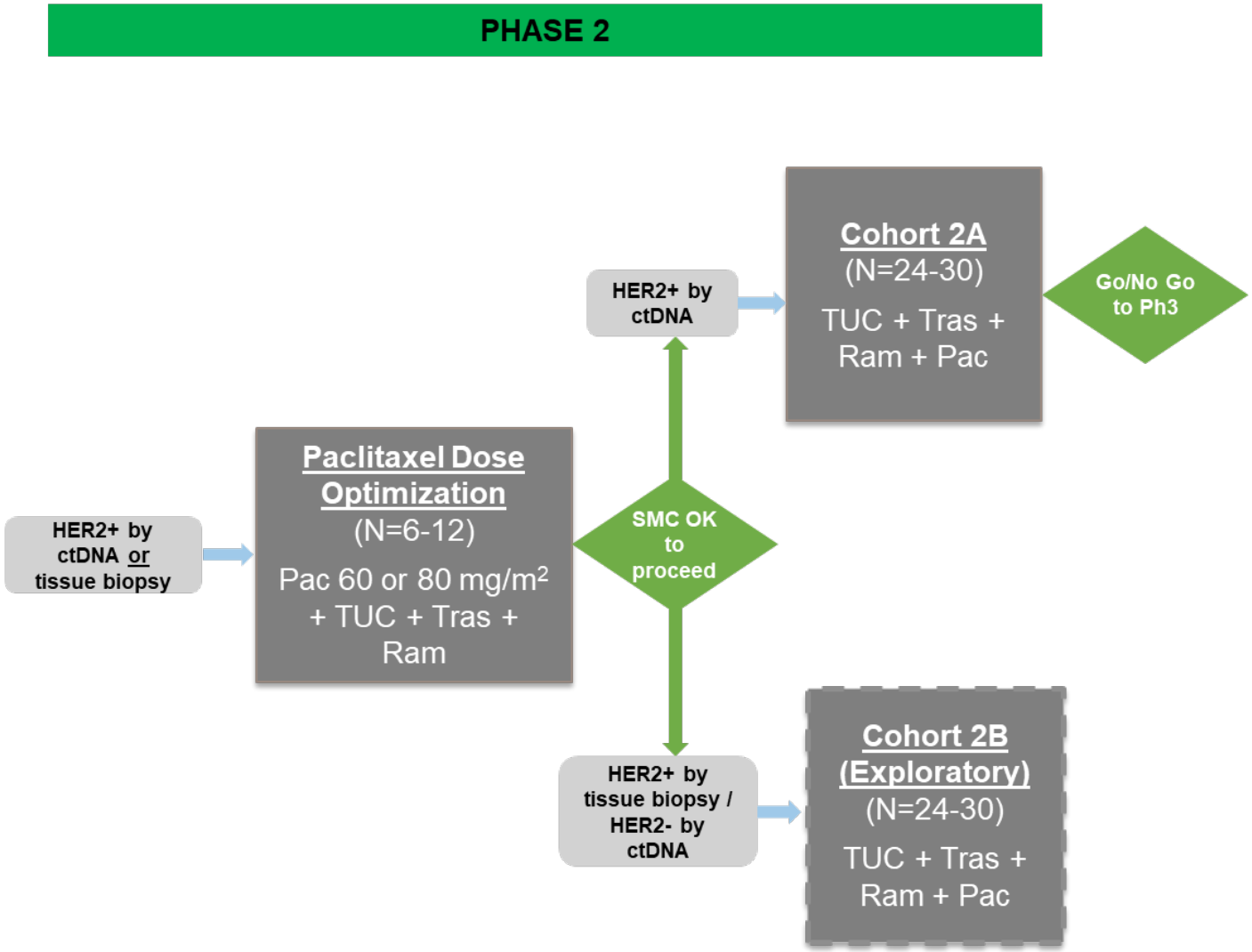
- Grade ≥3 AEs occurred in 85.6% of T-DXd patients versus 56.5% with PC
  - The most common were decreased neutrophil count (51.2% vs 24.2%), anemia (38.4% vs 22.6%), and decreased white blood cell count (20.8% vs 11.3%)
- 16 patients (12.8%) had T-DXd–related ILD/pneumonitis, as determined by an independent adjudication committee
  - There were 13 grade 1 or 2, 2 grade 3, 1 grade 4, and no grade 5 events
  - There were 4 ILD/pneumonitis events since the primary analysis; 1 grade 1 and 3 grade 2
  - Among the 16 total ILD/pneumonitis events, the median time to first onset was 102.5 days (range, 36-638)
  - There were no ILD/pneumonitis events in the PC arm
- There was 1 T-DXd-related death from pneumonia (non-ILD), as reported in the primary analysis
- There were no AE-related deaths in the PC arm

TEAEs in ≥20% of Patients Treated with T-DXd[a]

	T-DXd n = 125			PC Overall n = 62		
		Grade			Grade	
Preferred Term, %	Any	3	4	Any	3	4
Neutrophil count decreased[b]	64.8	38.4	12.8	35.5	16.1	8.1
Nausea	63.2	5.6	0	46.8	1.6	0
Decreased appetite	60.8	16.8	0	45.2	12.9	0
Anemia[c]	57.6	38.4	0	30.6	21.0	1.6
Platelet count decreased[d]	40.0	9.6	1.6	6.5	1.6	1.6
White blood cell count decreased[e]	38.4	20.8	0	35.5	8.1	3.2
Malaise	34.4	0.8	0	16.1	0	0
Diarrhea	32.8	2.4	0	32.3	1.6	0
Vomiting	26.4	0	0	8.1	0	0
Pyrexia	24.8	0	0	16.1	0	0
Constipation	24.8	0	0	24.2	0	0
Lymphocyte count decreased[f]	23.2	7.2	4.8	3.2	0	1.6
Alopecia	22.4	0	0	14.5	0	0
Fatigue	21.6	7.2	0	24.2	3.2	0

AE, adverse event; ILD, interstitial lung disease; PC, physician's choice; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent AE.
No additional TEAEs were observed in ≥20% of patients receiving PC. [a]There were no grade 5 events. [b]Includes preferred terms "neutrophil count decreased" and "neutropenia." [c]Includes preferred terms "hemoglobin decreased," "red blood cell count decreased," "anemia," and "hematocrit decreased." [d]Includes preferred terms "platelet count decreased" and "thrombocytopenia." [e]Includes preferred terms "leukopenia" and "white blood cell count decreased." [f]Includes preferred terms "lymphocyte count decreased" and "lymphopenia."
Shitara K et al. *J Clin Oncol.* 2020;38:4513.

MOUNTAINEER-02 Study



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Take Home Point:

Chemotherapy + trastuzumab + pembrolizumab is the new standard of care for metastatic HER2 amplified gastric or gastroesophageal junction adenocarcinoma in the frontline setting

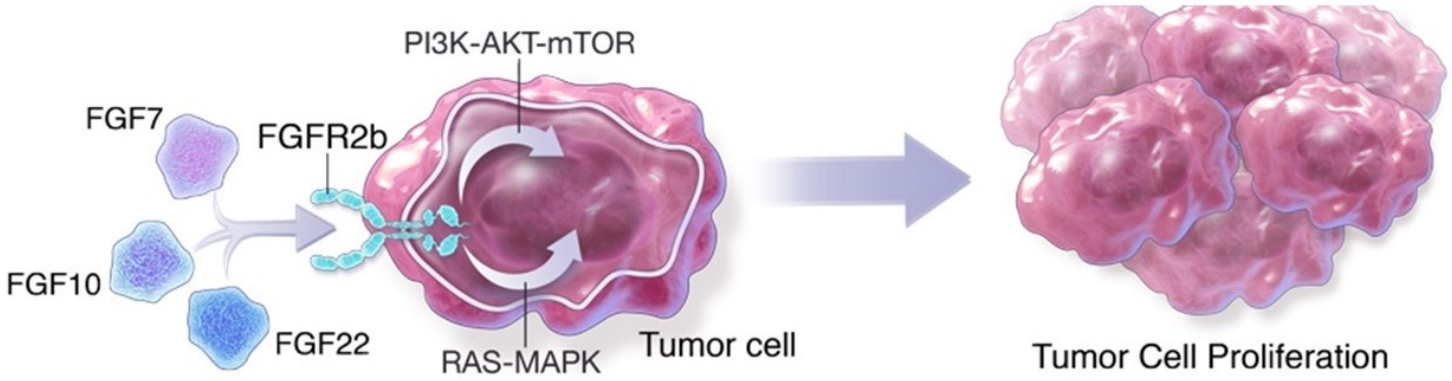
Trastuzumab deruxtecan is the new standard of care in the second-line setting and beyond for HER2-amplified gastric or gastroesophageal junction adenocarcinoma

Ongoing studies with tucatinib (MOUNTAINEER-02)

FGFR2 and Gastric Cancer

Fibroblast Growth Factor Receptor 2b (FGFR2b) in Cancer

- FGFR2b is a member of the FGFR family (FGFR1-4) and is a splice isoform of FGFR2
- FGFR2b overexpression: 3%-61% of gastric cancer depending on tumor stage and assay[1-4]



- FGFR tyrosine kinase inhibitors[5,6] have shown clinical benefit in cancers with FGFR mutations, fusions, or translocations

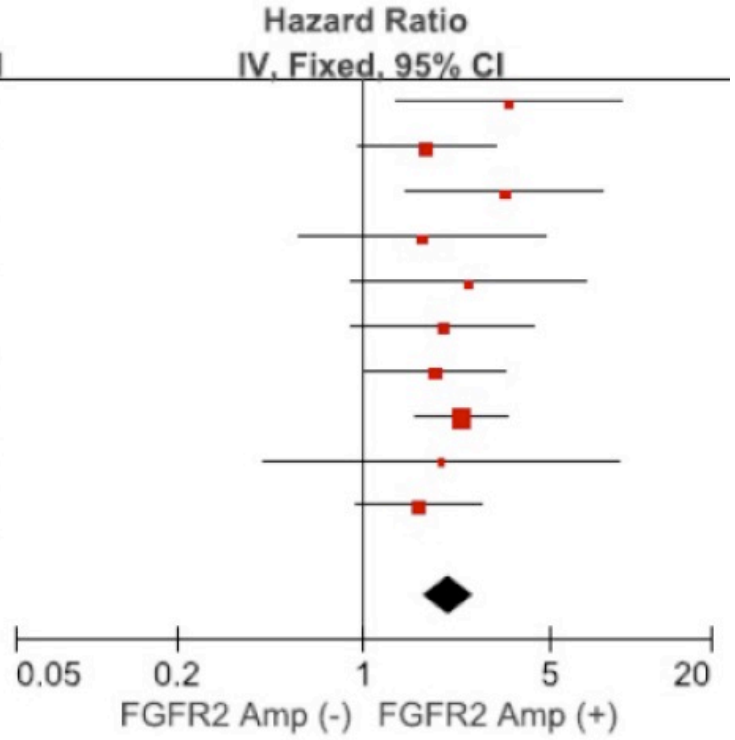
1. Han N et al. *Pathobiology.* 2015;82(6):269-279; 2. Ahn S et al. *Modern Pathol.* 2016;29(9):1095-1103; 3. Nagatsuma AK et al. *Gastric Cancer.* 2015;18(2):227-238; 4. Tokunaga R et al. *Oncotarget.* 2016;7(15):19748-19761; 5. Abou-Alfa GK et al. *Lancet Oncol.* 2020;21(5):671-684; 6. Loriot Y et al. *N Engl J Med.* 2019;381(4):338-348.

FGFR2 Amplification Reported in Up to 15% of Patients With Gastric Cancer and Is Associated With Worse Outcomes

Study or Subgroup	log[Hazard Ratio]	SE	FGFR2 Amp (+) Total	FGFR2 Amp (-) Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Jung (2012)	1.2528	0.4986	14	299	4.8%	3.50 [1.32, 9.30]
Matsumoto (2012)	0.5423	0.3038	11	256	13.0%	1.72 [0.95, 3.12]
Betts (2014)	1.2179	0.4339	3	168	6.4%	3.38 [1.44, 7.91]
Das (2014)	0.5056	0.5456	10	127	4.0%	1.66 [0.57, 4.83]
Shoji (2015)	0.9002	0.515	7	54	4.5%	2.46 [0.90, 6.75]
Su (2014) China	0.6831	0.4016	9	188	7.5%	1.98 [0.90, 4.35]
Su (2014) Korea	0.6259	0.308	15	341	12.7%	1.87 [1.02, 3.42]
Su (2014) UK	0.8442	0.2026	30	378	29.3%	2.33 [1.56, 3.46]
Tokunaga (2016)	0.6729	0.7795	21	119	2.0%	1.96 [0.43, 9.03]
Seo (2017)	0.4762	0.2768	16	311	15.7%	1.61 [0.94, 2.77]
Total (95% CI)			**136**	**2241**	**100.0%**	**2.09 [1.68, 2.59]**

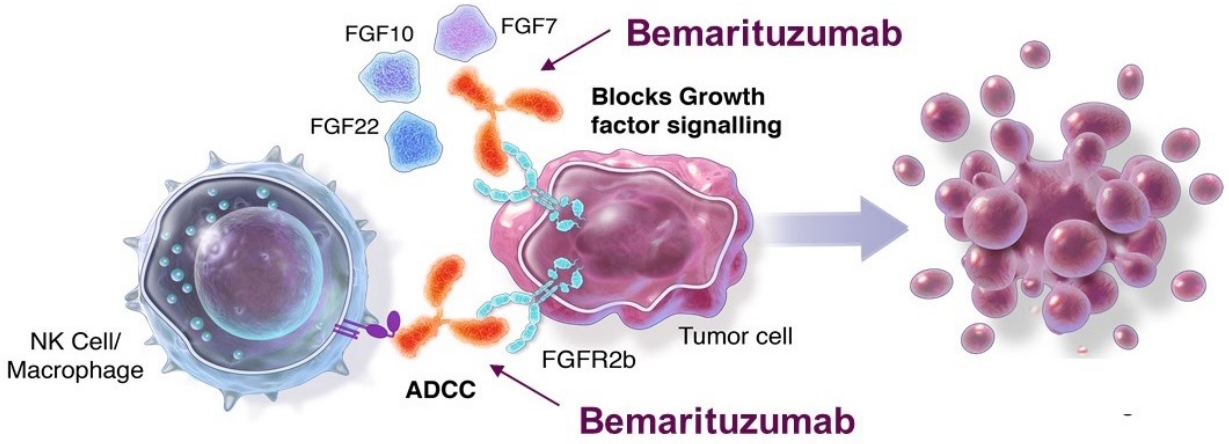
Heterogeneity: $Chi^2 = 4.31$, $df = 9$ ($P = 0.89$); $I^2 = 0\%$

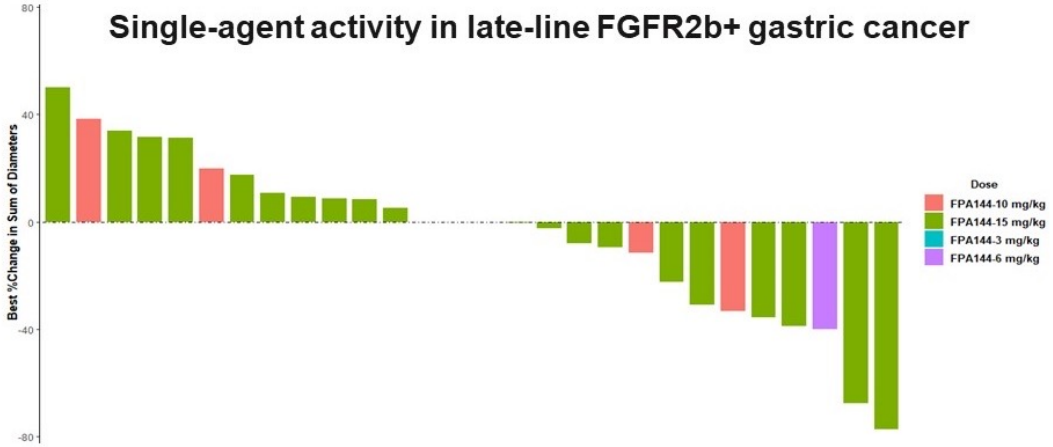
Test for overall effect: $Z = 6.71$ ($P < 0.00001$)



Kim HS et al. *J Cancer.* 2019;10(11):2560-2567.

Bemarituzumab Is an IgG1 Antibody Specific for the FGFR2b Receptor





- Confirmed ORR = 18% (n=28)[1]
- No dose-limiting toxicities
- Corneal adverse events in 3/28 patients
- Recommended Phase 2 dose: 15mg/kg Q2W with a single 7.5mg/kg dose on Cycle 1 Day 8[2]

1. Catenacci DVT et al. *J Clin Oncol.* 2020;38(21):2418-2426; 2. Tejani MA et al. ASCO GI 2019. Abstract 91.

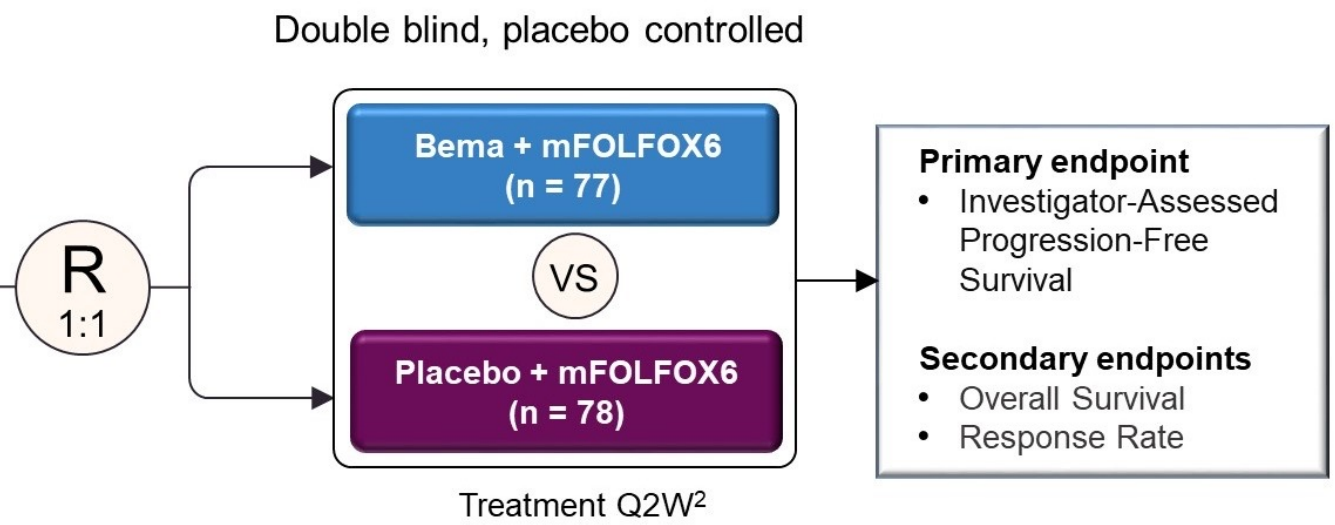
FIGHT Trial Design

Key Eligibility Criteria

- No prior therapy for unresectable locally advanced or metastatic gastric/GEJ adenocarcinoma
- RECIST v1.1 evaluable disease
- FGFR2b overexpression by IHC and/or *FGFR2* gene amplification by ctDNA
- ECOG 0/1
- HER2 not positive
- May receive 1 dose of mFOLFOX6

Stratification Factors

- Geographic region
- Single dose of mFOLFOX6 during screening
- Prior adjuvant or neo-adjuvant chemotherapy



Statistical Plan

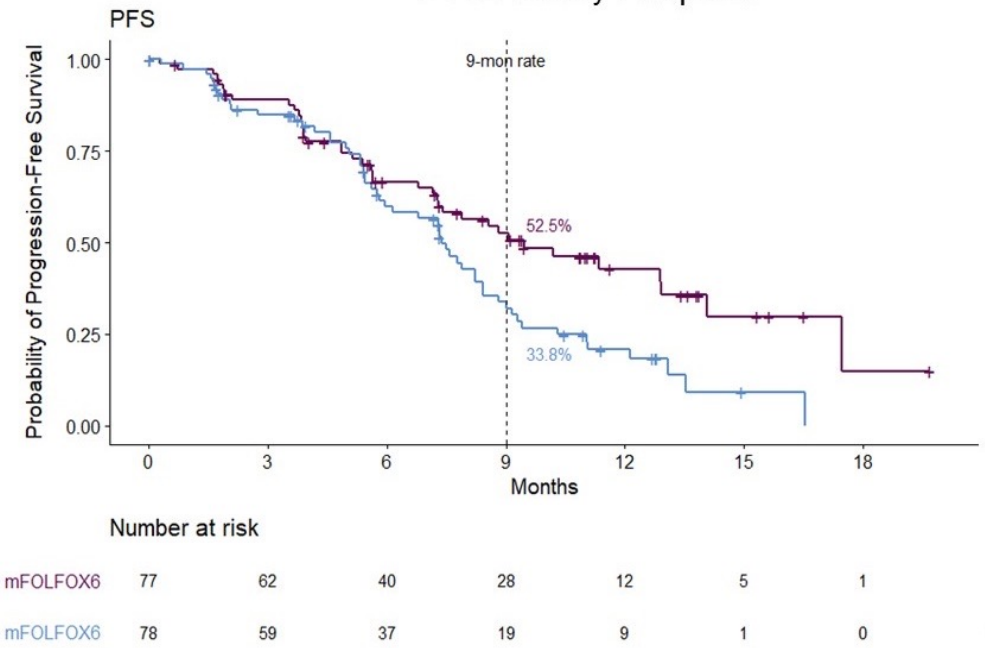
Trial initially designed as registrational Phase 3 (n=548) with 2-sided α 0.05
Amended after enrolling n = 155 to a proof-of-concept Phase 2 with pre-specified statistical assumptions of:

- Hierarchical sequential testing: PFS, then OS/ORR
- ≥84 events to demonstrate benefit at a HR≤0.76 for PFS at 2-sided α of 0.2

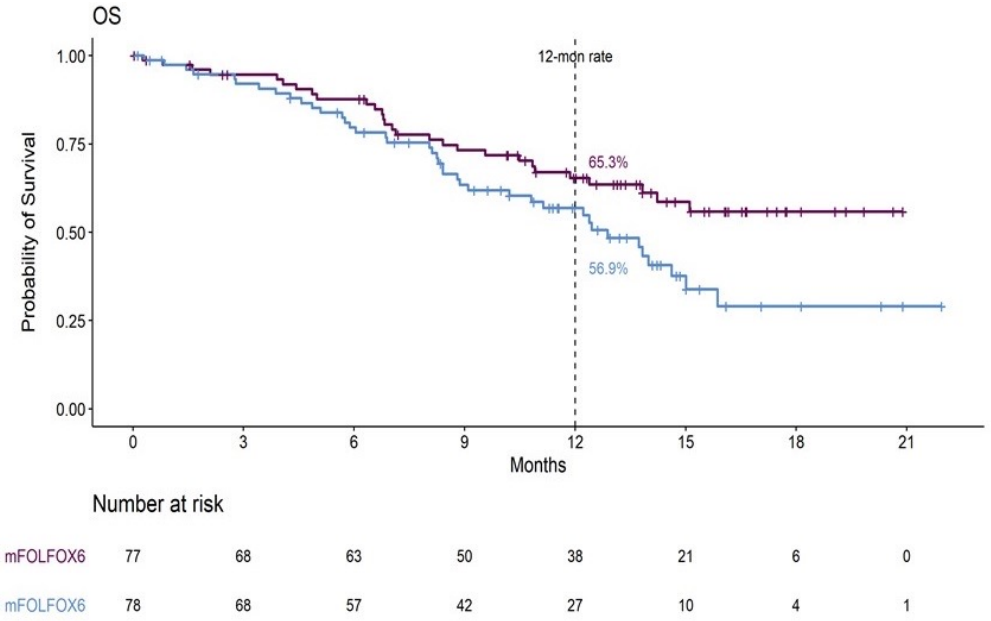
1 Central testing: Immunohistochemical stain (Ventana): cut-off any 2+/3+; circulating tumor DNA (PGDx): cut-off 1.5X
2 15mg/kg Q2W with a single 7.5mg/kg dose on Cycle 1 Day 8

Progression-Free Survival and Overall Survival: Intent to Treat

PFS Primary Endpoint



OS Key Secondary Endpoint



	Bema N = 77	Placebo N = 78
Median PFS, mo (95% CI)	9.5 (7.3, 12.9)	7.4 (5.8, 8.4)
	P=0.0727	
HR (95% CI)	0.68 (0.44, 1.04)	

	Bema N = 77	Placebo N = 78
Median OS, mo (95% CI)	NR (13.8, NR)	12.9 (9.1, 15.0)
	P=0.0268	
HR (95% CI)	0.58 (0.35, 0.95)	

Wainberg Z et al. ASCO GI 2021. Abstract 160.

Is FGFR2 Ready for Primetime?:

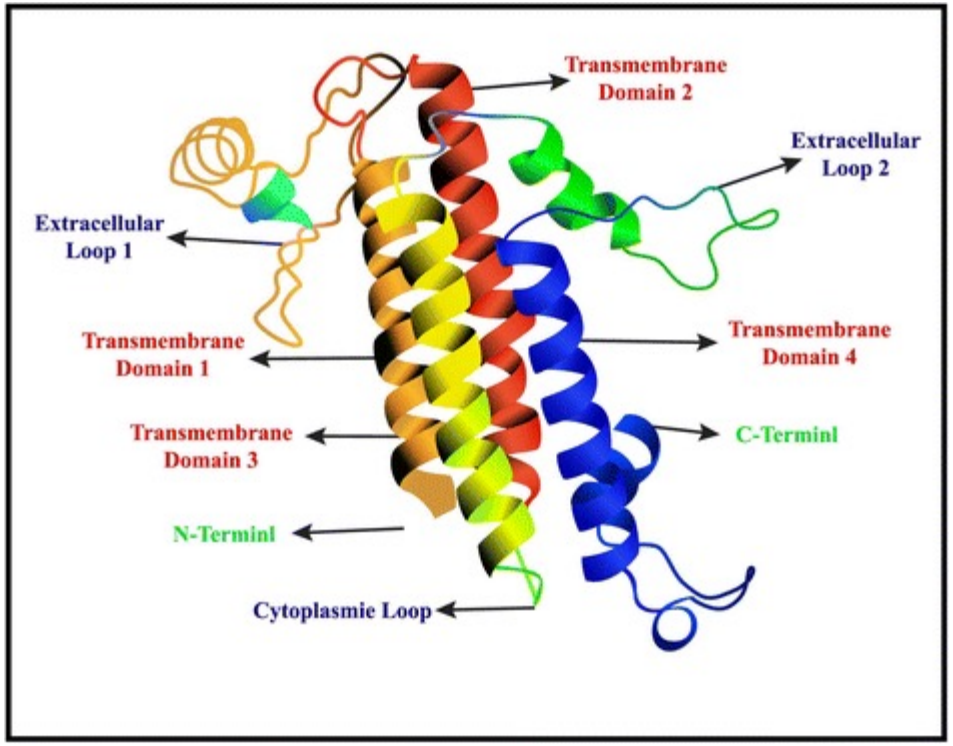
Potentially

Breakthrough designation granted by the FDA April 2021 based on a subset of patients from the FIGHT trial who showed at least 10% of tumor cells overexpression FGFR2b

Await results from the Phase III study

Claudin and Gastric Cancer

Claudin 18.2 – A New Target for Gastric Cancer?



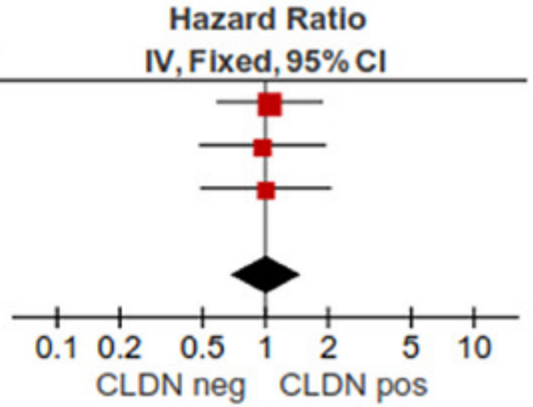
- Family of tight junction molecules involved in the regulation of permeability, barrier function
- With malignant transformation, epitopes of CLDN18.2 become exposed and available for binding
- CLDN18.2 appears altered in approximately 30-40% of gastric/GEJ cancers

Claudin 18.2 Expression Not Associated With Worse Outcomes

Study or Subgroup	log[Hazard Ratio]	SE	CLDN pos Total	CLDN neg Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Dottermusch 2019	0.045323	0.3	200	274	42.5%	1.05 [0.58, 1.88]	2019
Moentenich 2020	-0.03152	0.36	89	396	29.5%	0.97 [0.48, 1.96]	2020
Arnold 2020	0.004321	0.37	65	316	28.0%	1.00 [0.49, 2.07]	2020
Total (95% CI)			**354**	**986**	**100.0%**	**1.01 [0.69, 1.48]**	

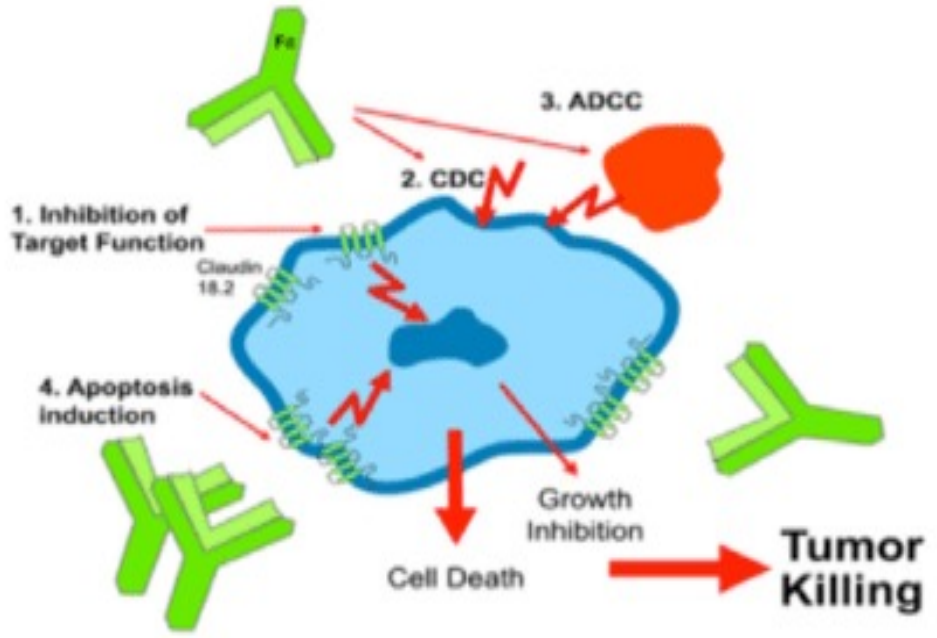
Heterogeneity: Chi² = 0.03, df = 2 (P = 0.99); I² = 0%

Test for overall effect: Z = 0.06 (P = 0.95)



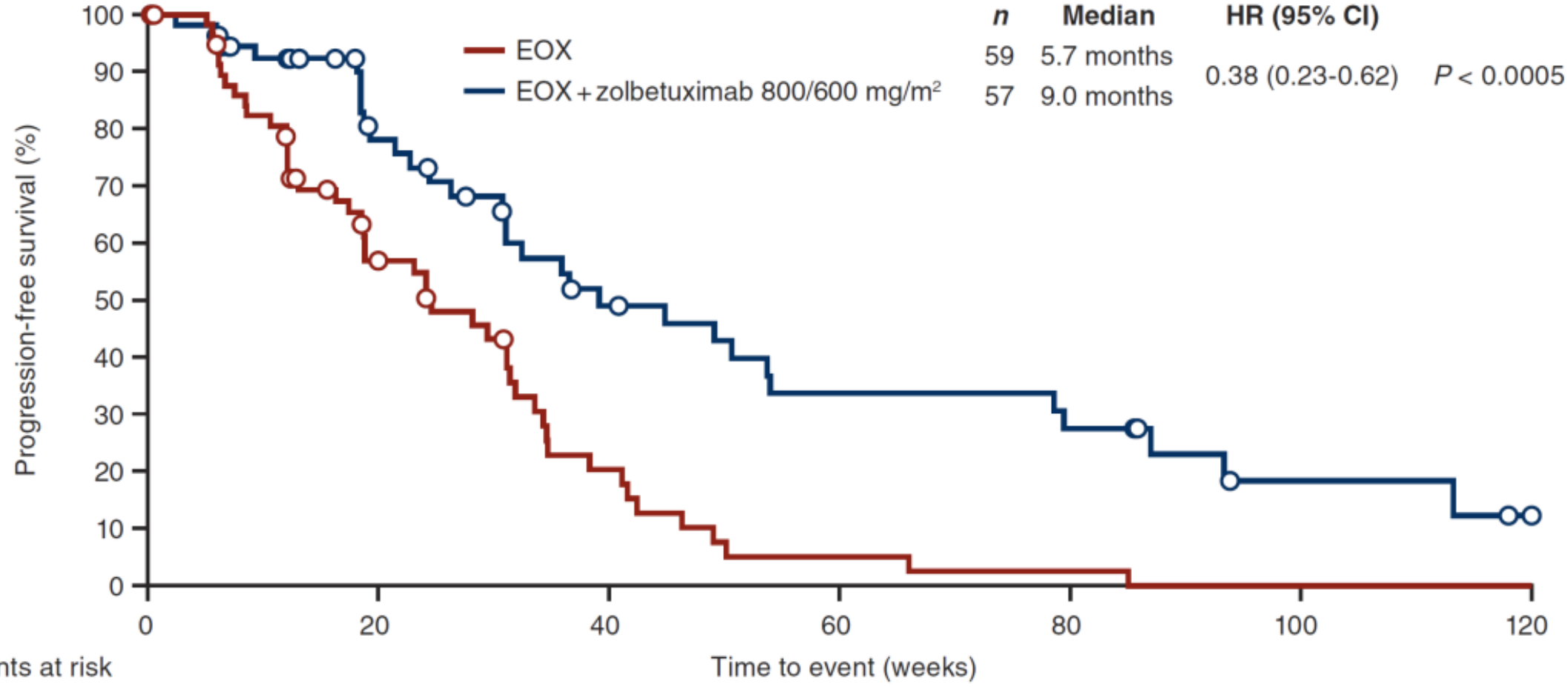
Ungureanu BS et al. *Fron Oncol.* 2021;11:643872.

Zolbetuximab (IMAB362)



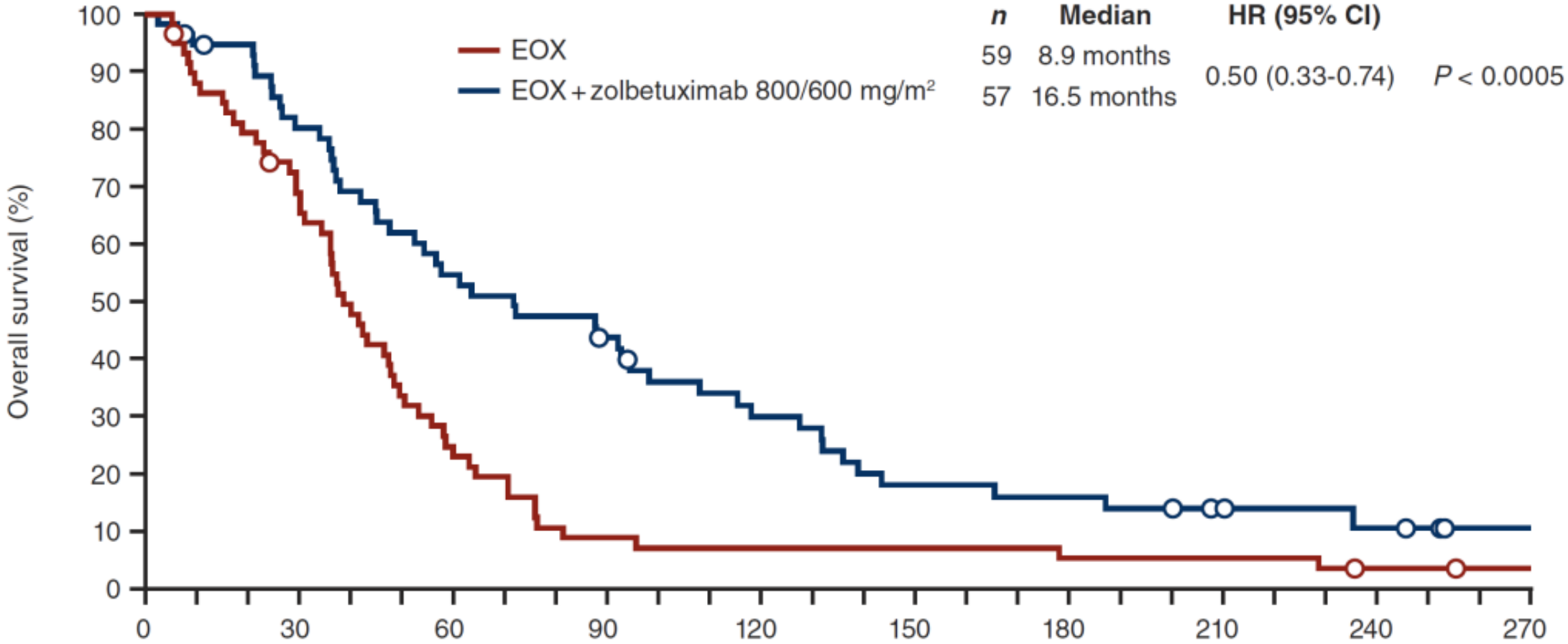
- Chimeric IgG1 backbone antibody
- Specific for CLDN 18.2
- Mechanism of action:
  - Antibody-dependent cellular cytotoxicity (ADCC)
  - Complement-dependent cytotoxicity (CDC)
  - In combination with chemotherapy:
    - Enhances T-cell infiltration
    - Induces pro-inflammatory cytokines

FAST: PFS Improved if ≥70% of Cells Positive for CLDN18.2



Sahin U et al. *Ann Oncol.* 2021;32(5):609-619.

FAST: OS Improved if ≥70% of Cells Positive for CLDN18.2



Sahin U et al. *Ann Oncol.* 2021;32(5):609-619.

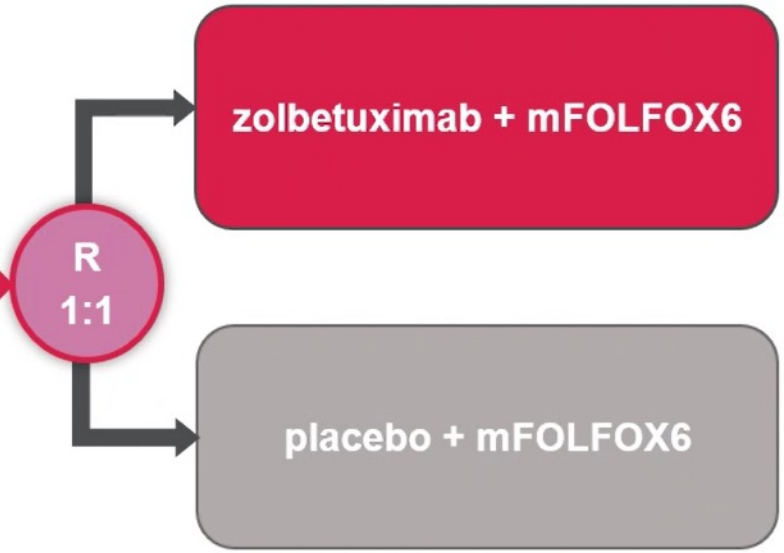
SPOTLIGHT - A Phase 3, Global, Multi-center, Double-blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus mFOLFOX6 Compared with Placebo Plus mFOLFOX6 as First-line Treatment of Subjects with Claudin (CLDN)18.2-positive, HER2-negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma[1]

Enrolling

Key Inclusion Criteria

- Histologically-confirmed Gastric or GEJ adenocarcinoma
- CLDN 18.2 positive*, HER2-negative
- Radiologically-confirmed, locally advanced, unresectable or metastatic disease

N ~ 550



Primary Endpoint
- PFS

Select Secondary Endpoints**
- OS
- ORR
- DOR
- Safety and tolerability
- Pharmacokinetics
- Incidence of ADA
- Quality of Life Analysis

* CLDN18.2 high expression (≥ 75% of tumor cells) demonstrating moderate to strong membranous staining by IHC testing

** A complete list of secondary endpoints can be found in the ClinicalTrials.gov website

Zolbetuximab (or placebo) and mFOLFOX6: administered in 42-day cycles.
Zolbetuximab: Day 1 of each cycle every 21 days
mFOLFOX6: Days 1, 15 and 29 of each cycle

After 12 mFOLFOX6 treatments, participants may continue to receive 5-FU and folinic acid at the investigator's discretion until subject meets study treatment discontinuation criteria.

Is Claudin 18.2 Ready for Primetime?:

Potentially

Awaiting results from a phase III study of first-line zolbetuximab + CAPOX vs placebo + CAPOX in Claudin 18.2+/HER2- advanced or metastatic gastric or gastroesophageal junction adenocarcinoma

GLOW and SPOTLIGHT studies

Wrap Up

- HER2 therapy is evolving with new treatment options for HER2+ gastric/GEJ adenocarcinomas
  - Chemo + pembrolizumab + trastuzumab
- FGFR2
  - Promising data with bemarituzumab
- Claudin 18.2
  - Promising data with zolbetuximab

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.

Germline BRCA alterations in pancreas cancer

Case: Patient With Metastatic Pancreatic Cancer With *BRCA2* Mutation

- 58-yr-old woman with no family history of cancer presented with pelvic pain
- Workup revealed metastatic pancreatic cancer with diffuse liver metastases; germline testing showed no inherited mutations
- She started first-line FOLFIRINOX and was able to complete 8 cycles of treatment with dose adjustments despite it being poorly tolerated
- Somatic tumor testing revealed a *BRCA2* mutation; results returned during cycle 2 of FOLFIRINOX
- Her disease burden improved after 8 cycles of FOLFIRINOX

Poll: What therapy would you recommend for this patient?

1. Continue FOLFIRINOX
2. Stop FOLFIRINOX and observe
3. PARPi maintenance therapy
4. 5-FU/capecitabine maintenance therapy
5. Uncertain

- 58-yr-old woman with metastatic pancreatic cancer with diffuse liver metastases; germline testing: no inherited mutations
- First-line FOLFIRINOX; completed 8 cycles with dose adjustments despite poor tolerance
- Somatic tumor testing: *BRCA2* mutation; results returned during cycle 2 of FOLFIRINOX
- Disease burden improved after 8 cycles of FOLFIRINOX

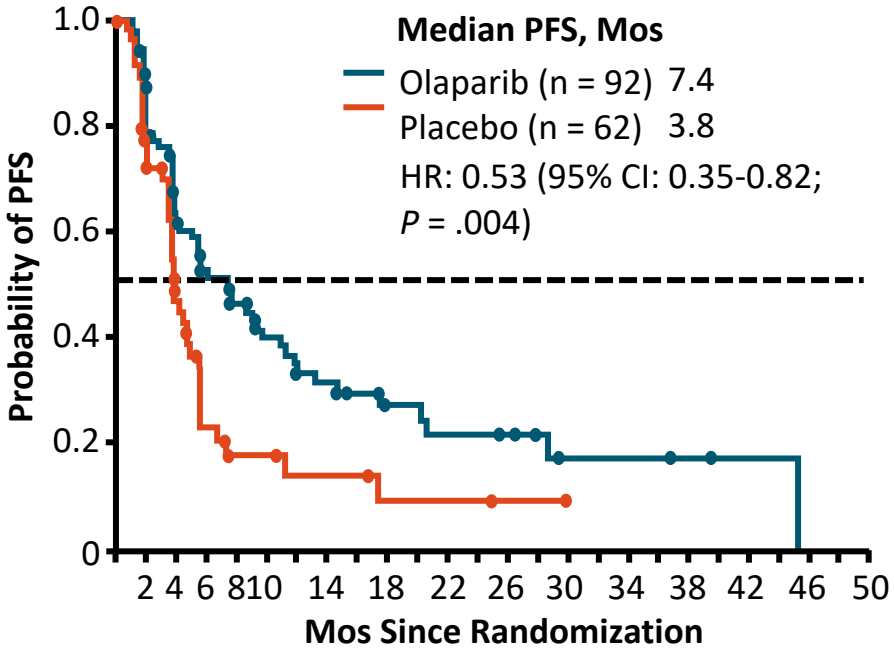
BRCA Mutations and Pancreas Cancer

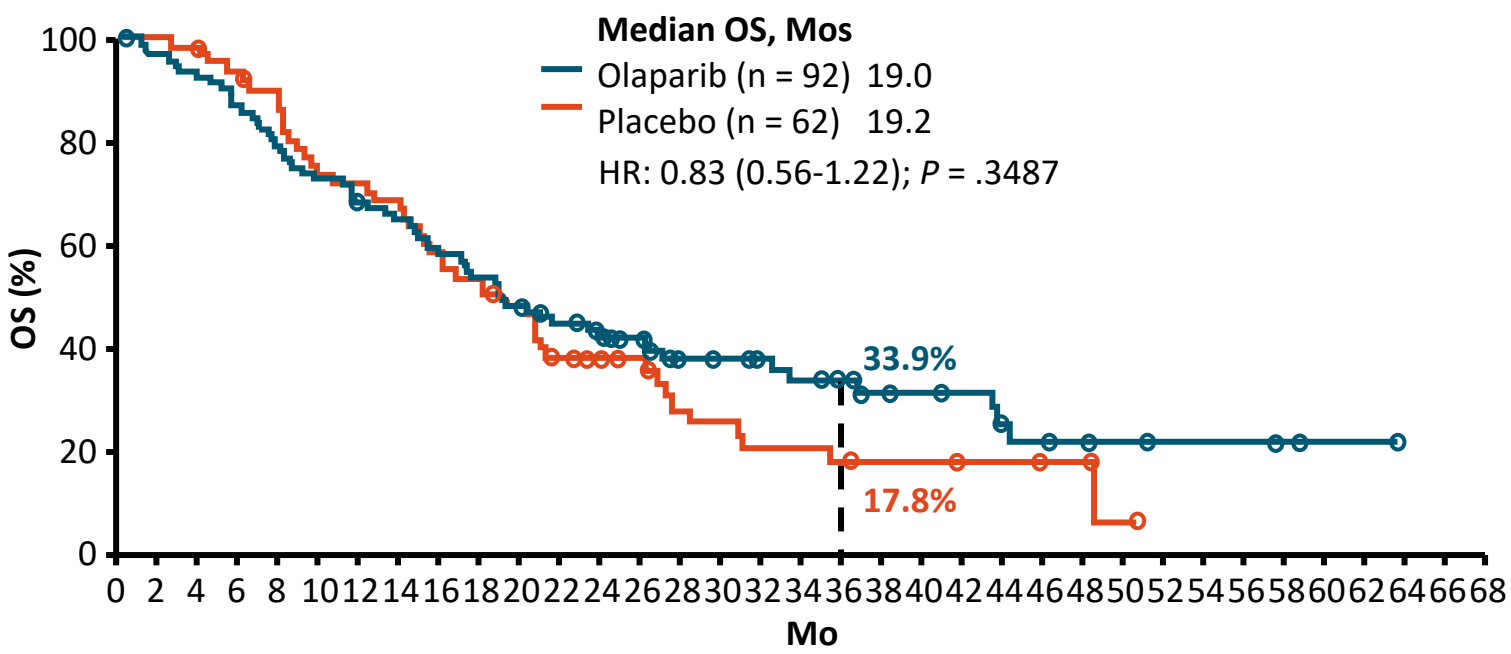
- Loss of function mutations in *BRCA1* and *BRCA2* are associated with an increased risk of pancreatic adenocarcinoma
  - 4% to 7% of patients have a germline *BRCA* mutation

- Clinical evidence suggests that platinum-based therapies may lead to improved outcomes
  - FOLFIRINOX or gemcitabine/cisplatin

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)

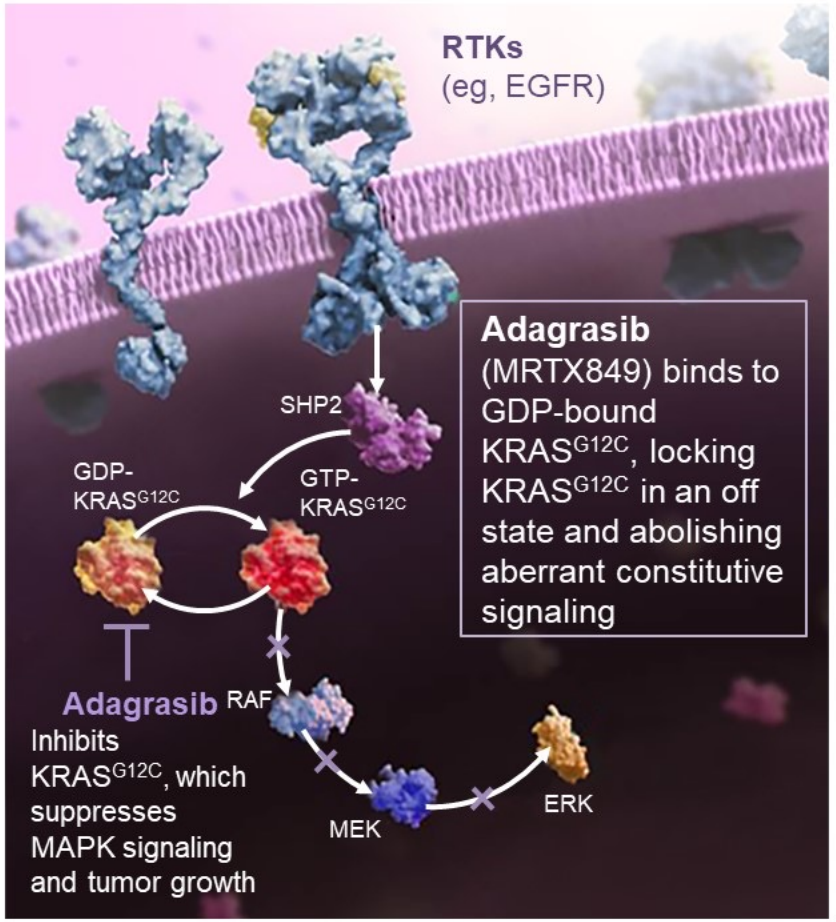




Golan. NEJM. 2019;381:317. Golan. ASCO GI 2021. Abstr 378.

Adagrasib (MRTX849) is a Differentiated, Selective Inhibitor of KRAS^{G12C}

- KRAS mutations occur in approximately 90% of pancreatic cancer[1]; ~2% of these are KRAS^{G12C} mutations[2]
- The KRAS protein cycles between GTP-on and GDP-off states and has a protein resynthesis half-life of ~24 hours[3,4]
- Adagrasib, a covalent inhibitor of KRAS^{G12C}, irreversibly and selectively binds KRAS^{G12C} in its inactive, GDP-bound state
- Adagrasib was optimized for desired properties of a KRAS^{G12C} inhibitor[5]:
  - Long half-life of ~24 hours
  - Dose-dependent PK
  - CNS penetration
- Maintaining continuous exposure of adagrasib above a target threshold enables inhibition of KRAS-dependent signaling for the complete dose interval and maximizes depth and duration of antitumor activity



CNS, central nervous system; EGFR, epidermal growth factor receptor; PK, pharmacokinetics; RTK, receptor tyrosine kinase.

1. Prior IA, et al. *Cancer Res*. 2012;72(10):2457–2467. 2. Nollmann FI & Alexander Ruess D. *Biomedicines*. 2020;8(8):281. 3. Bos JL, et al. *Cell*. 2007;129:865–877. 4. Shukla S, et al. *Neoplasia*. 2014;16(2):115–128. 5. Hallin J, et al. *Cancer Discov*. 2020;10(1):54–71.

KRYSTAL-1 (849-001) Study Design

Key Eligibility Criteria

- Solid tumor with KRAS^{G12C} mutation
- Unresectable or metastatic disease
- Treated and/or stable brain metastases[a]

Phase 1
Dose Escalation[b]

- 600 mg BID Expansion
- 1200 mg QD[c]
- 600 mg QD[c]
- 300 mg QD[c]
- 150 mg QD[c]

Phase 1b
Dose Expansion and Combination[b]

- **Adagrasib** monotherapy in solid tumors
- **Adagrasib** brain metastases in solid tumors
- **Adagrasib** NSCLC treatment-naïve
- **Adagrasib** NSCLC prior KRAS^{G12C} inhibitor
- **Adagrasib** + pembrolizumab in NSCLC
- **Adagrasib** + afatinib in NSCLC
- **Adagrasib** + cetuximab in CRC
- **Adagrasib** + cetuximab in NSCLC / PDAC
- **Adagrasib** in NSCLC (tablet formulation)

Phase 2
Monotherapy and Combination Treatment

- **NSCLC**
  Adagrasib
- **CRC**
  Adagrasib
- **Other solid tumors (N=42)**[b,d]
  (GI tumors, n=30)
  Adagrasib
- **Treatment-Naïve NSCLC**
  Adagrasib: KRAS^{G12C} and STK11 mutation
- **CRC**
  Adagrasib +/- cetuximab

Phase 2 Endpoints **Primary:** ORR (RECIST 1.1) **Secondary:** DOR, PFS, OS, safety

- Previously reported data demonstrated clinical activity with adagrasib in patients with various KRAS^{G12C}-mutated solid tumors, including NSCLC, CRC and other tumors such as PDAC, ovarian and endometrial cancers, and cholangiocarcinoma[1–3]
- Here we report preliminary data from a Phase 2 cohort evaluating adagrasib 600 mg BID in patients with previously-treated GI tumors (n=30), excluding CRC, with a focus on PDAC (n=12) and other GI cancers (n=18), with a KRAS^{G12C} mutation

CRC, colorectal cancer; ctDNA, circulating tumor deoxyribonucleic acid; GI, gastrointestinal; NSCLC, non–small-cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.
1. Jänne PA et al. Presented at: 2020 EORTC-NCI-AACR Symposium; Oct 25, 2020. 2. Weiss J et al. Presented at: 2021 ESMO Congress; Sept 19, 2021. 3. Johnson ML et al. Presented at: 2020 EORTC-NCI-AACR Symposium; Oct 25, 2020.
[a]Most cohorts allow patients with brain metastases if adequately treated and stable; additional phase 1/1b cohort allows limited brain metastases; [b]KRAS^{G12C} mutation detected in tumor tissue and/or ctDNA; [c]Patients subsequently dose escalated up to 600 mg BID; [d]Solid tumors included GI tumors (n=30) and non-GI tumors (n=12).
Data as of 10 September 2021. ClinicalTrials.gov. NCT03785249.

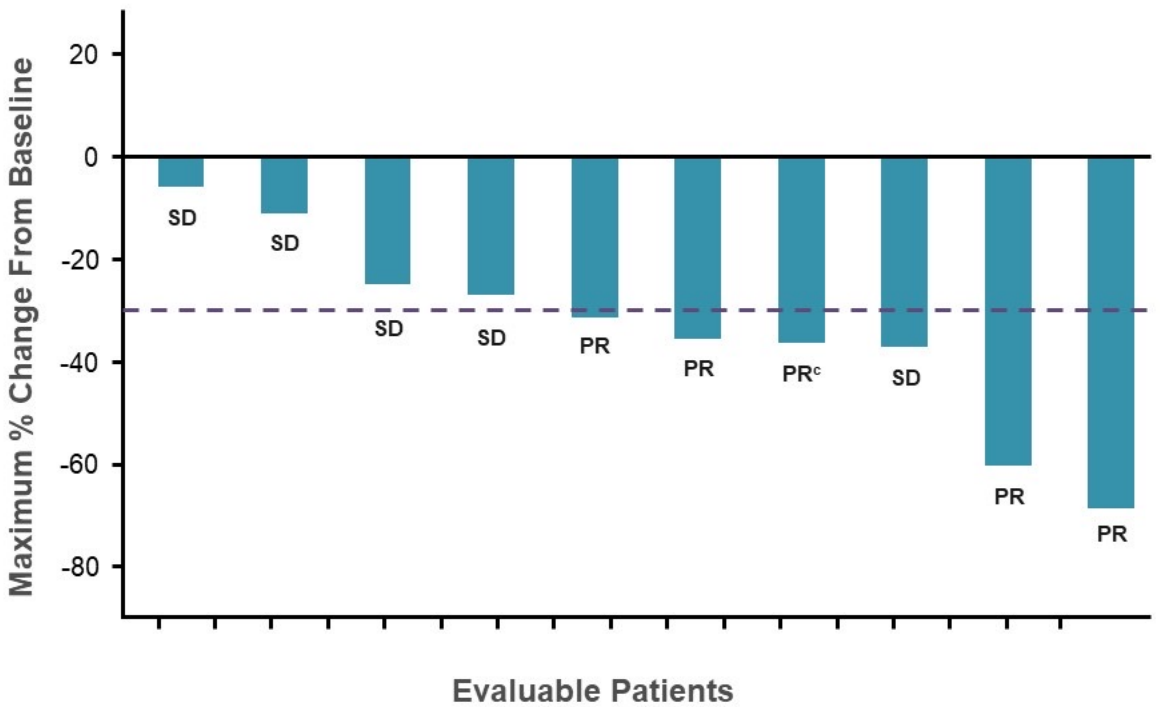
Adagrasib in Patients With PDAC and Other GI Tumors:[a] Objective Response Rate

Efficacy outcome[b], n (%)	PDAC (n=10)[c]	Other GI cancers (n=17)[d]	Overall GI cancers[a] (n=27)[c,d]
Objective response rate	5 **(50)**[e]	6 **(35)**[f]	11 **(41)**[g]
Best overall response			
Complete response (CR)	0 (0)	0 (0)	0 (0)
Partial response (PR)	5 (50)[e]	6 (35)[f]	11 (41)[g]
Stable disease (SD)	5 (50)	11 (65)	16 (59)
Disease control rate	10 **(100)**	17 **(100)**	27 **(100)**

A total of 30 patients were enrolled: 12 PDAC, 18 Other GI.
[a]Excluding CRC; [b]Based on investigator assessment of the clinically evaluable patients (measurable disease with ≥ 1 on-study scan); [c]Evaluable population (n=10) excludes 2 patients who had discontinued treatment prior to first scan due to unrelated adverse events and were not evaluable for clinical activity; [d]Evaluable population (n=17) excludes 1 patient who withdrew consent prior to the first scan; [e]Includes 1 unconfirmed PR as of data cut-off; [f]Includes 2 unconfirmed PR as of data cut-off; [g]Includes 3 unconfirmed PR as of data cut-off.
Data as of 10 Sept 2021 (median follow-up: overall, 6.3 months; PDAC, 8.1 months; other GI cancers: 6.3 months).

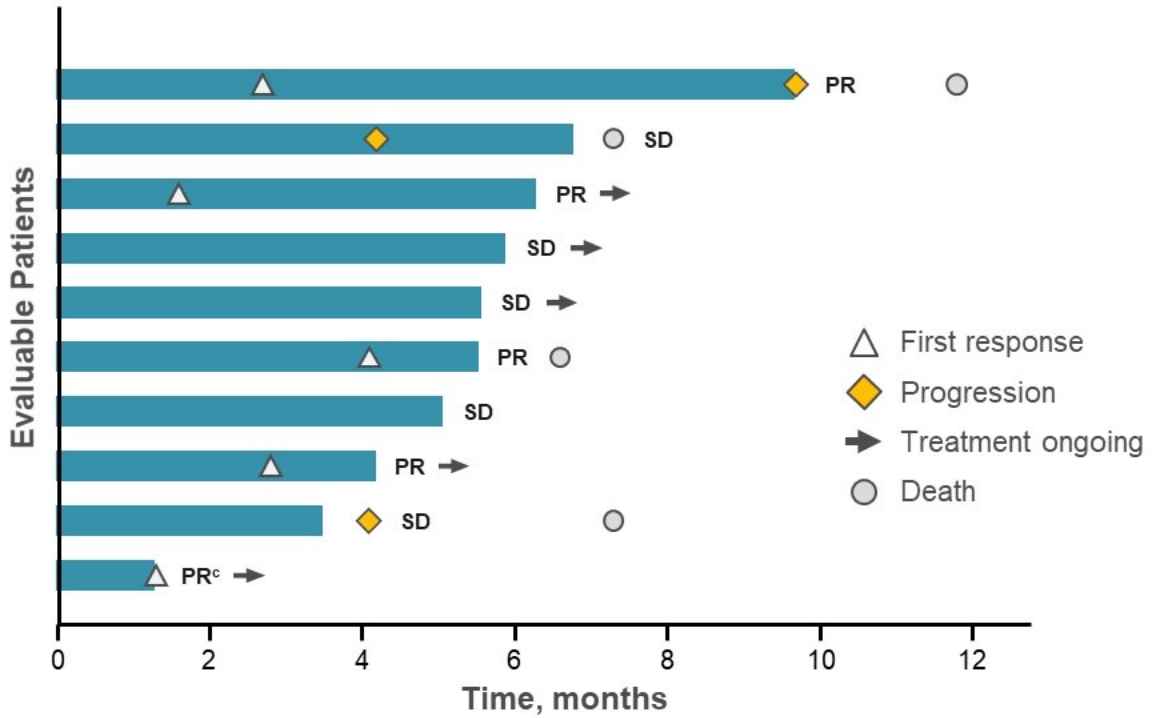
Adagrasib in Patients With Unresectable or Metastatic PDAC: Best Tumor Change From Baseline and Duration of Treatment

Best Tumor Change From Baseline (n=10)[a,b]



- Response rate: 50% (5/10), including 1 unconfirmed PR
- SD: 50% (5/10 patients)
- DCR: 100% (10/10 patients)

Duration of Treatment (n=10)[a,b]



- Median TTR: 2.8 months
- Median DOR: 6.97 months
- Median PFS: 6.6 months (95% CI 1.0–9.7)
- Treatment ongoing in 50% (5/10) of patients

DCR, disease control rate; DOR, duration of response; PR, partial response; SD, stable disease; TTR, time to response.
[a]Evaluable population (n=10) excludes 2 patients who had discontinued treatment prior to first scan due to unrelated adverse events and were not evaluable for clinical activity; [b]All results are based on investigator assessments; [c]At data cut-off, 1 patient had unconfirmed PR.
Data as of 10 Sept 2021 (median follow-up: 8.1 months).

Wrap Up

- Still a long way to go for molecularly-directed therapy for pancreas adenocarcinoma
- PARP inhibitors (olaparib) remains an FDA-approved therapy for patients with germline BRCA mutations
- Promising data with KRAS G12C inhibitors
- Continue to look for tissue agnostic treatment options
  - MSI-H, NTRK, BRAF V600E

Thank you!