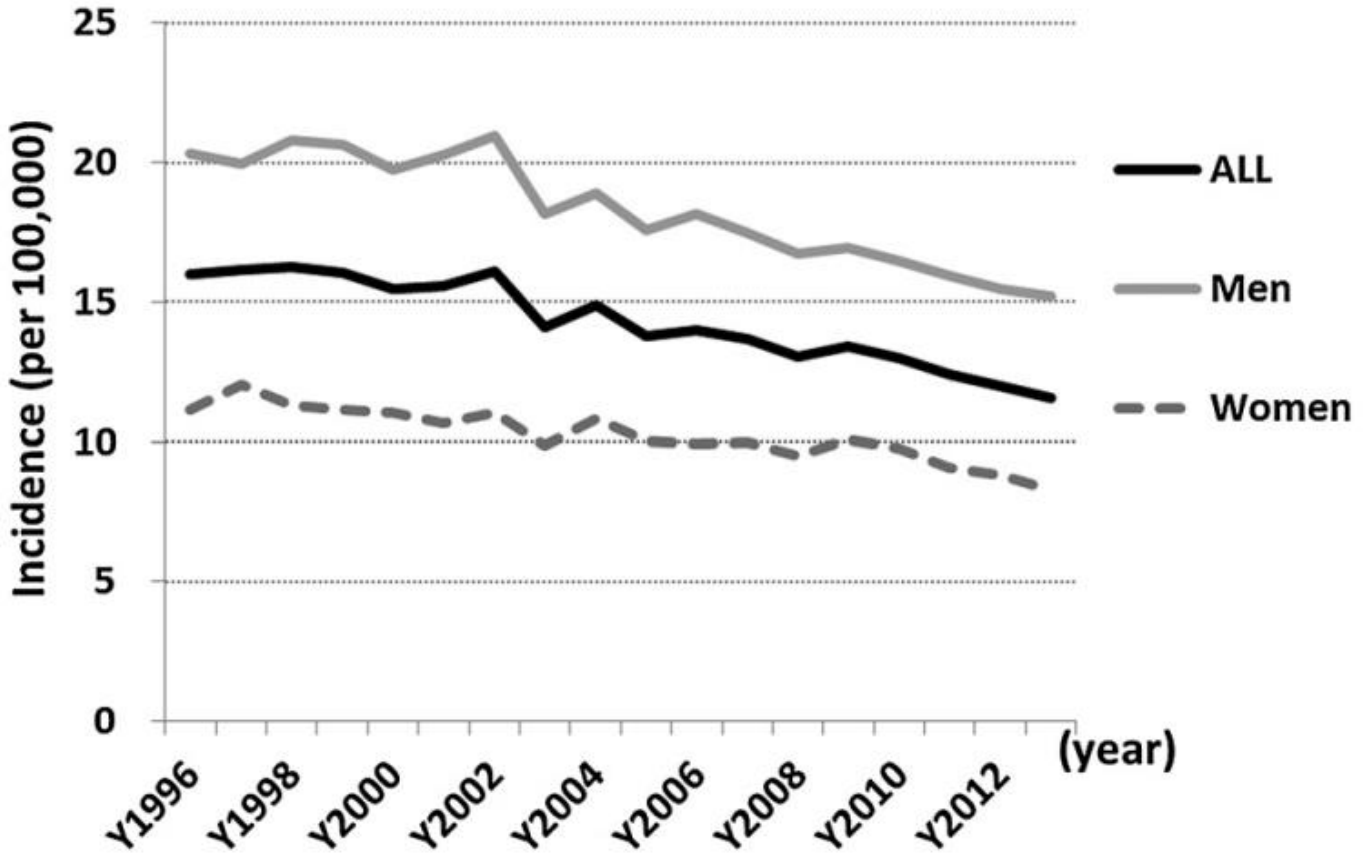
晚期胃癌治療趨勢
&
年紀對於治療的考量

2023/7/22
台中榮總內科部 血液腫瘤科
石宇軒

GC in the era of HP eradication

Taiwan Cancer Registry



Cancer Epidemiol Biomarkers Prev. 2019 Oct;28(10):1694-1703.

109年 癌登

10 大癌症（不含原位癌[4]）發生率（每 10 萬人口），民國 109 年

順位	ICD-O-3	原發部位	個案數（人）	粗發生率
1	C50	女性乳房	15,259	128.36 [5a]
2	C18-C21	結腸、直腸、乙狀結腸連結部及肛門	16,829	71.43
3	C33-C34	肺、支氣管及氣管	16,370	69.48
4	C61	攝護腺(前列腺)	7,178	61.49 [5b]
5	C22	肝及肝內膽管	10,982	46.61
6	C00-C14[3]	口腔、口咽及下咽	8,277	35.13
		口腔	5,418	23.00
		口咽	1,689	7.17
		下咽	1,170	4.97
7	C54	子宮體	3,032	25.51 [5a]
8	C73	甲狀腺	4,932	20.93
9	C56,C57.0-C57.4	卵巢、輸卵管及寬韌帶	1,824	15.34 [5a]
10	C16	胃	4,257	18.07
	C00-C80	全癌症	121,979	517.71

10 大癌症死亡率（每 10 萬人口），民國 109 年

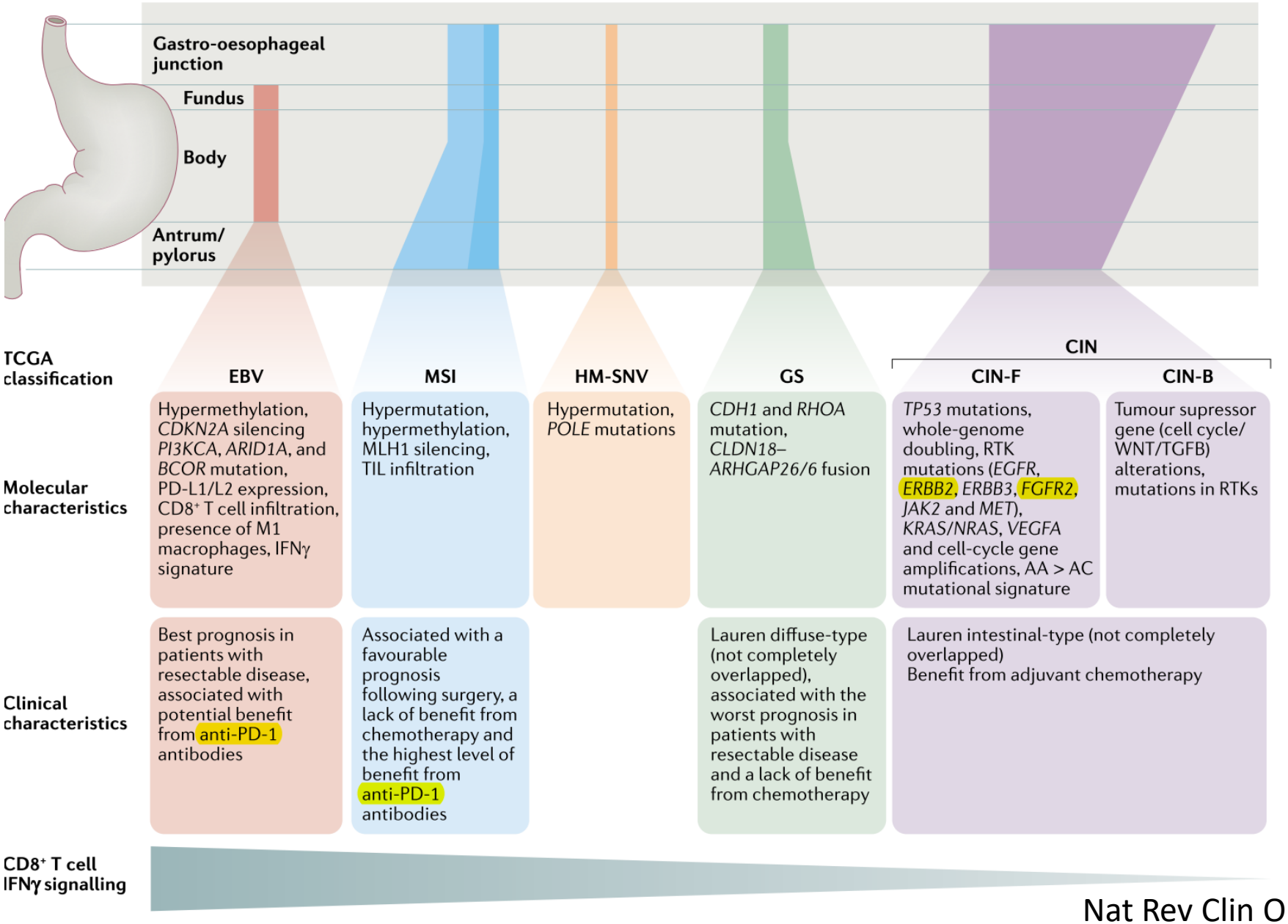
順位	ICD-10	原發部位	個案數（人）	粗死亡率
1	C33-C34	肺、支氣管及氣管	9,629	40.87
2	C22	肝及肝內膽管	7,773	32.99
3	C18-C21	結腸、直腸、乙狀結腸連結部及肛門	6,489	27.54
4	C50	女性乳房	2,655	22.33 [5a]
5	C00-C14[3]	口腔、口咽及下咽	3,380	14.35
6	C61	攝護腺(前列腺)	1,730	14.82 [5b]
7	C25	胰	2,450	10.40
8	C16	胃	2,339	9.93
9	C15	食道	1,954	8.29
10	C56,C57.0-C57.4	卵巢、輸卵管及寬韌帶	724	6.09 [5a]
	C00-C97	全癌症	50,161	212.90

109 年癌症個案數增加最多前 5 名

癌症部位	發生數		增加數	增加百分比*
	108 年	109 年		
1.甲狀腺	4,445	4,932	487	10.96%
2.女性乳房	14,856	15,259	403	2.71%
3.胃	3,938	4,257	319	8.10%
4.胰	2,803	3,012	209	7.46%
5.卵巢、輸卵管及寬韌帶	1,677	1,824	147	8.77%

*增加百分比=（當年發生數 － 前一年發生數）÷ 前一年發生數 ×100%

Molecular Classification



Nat Rev Clin Oncol 18, 473–487 (2021).

44 y/o Male, BW:64kg, BSA:1.7

Gastric cancer, adenocarcinoma, peritoneal metastasis, T4bN+M1, stage **IV**

2021/10

Initial Presentation

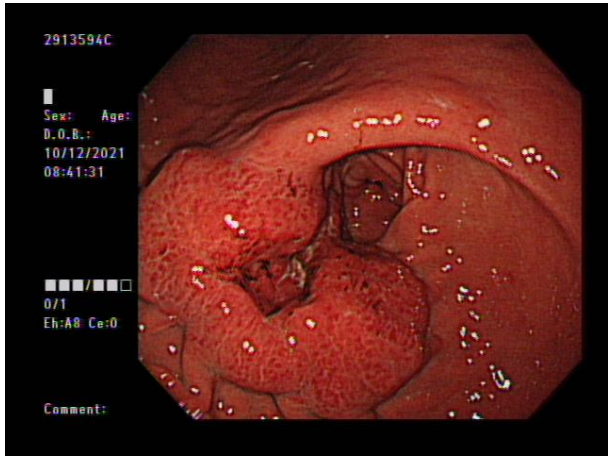
Epigastralgia
Vomiting
UGI scopy: huge ulcerative mass, adenocarinoma

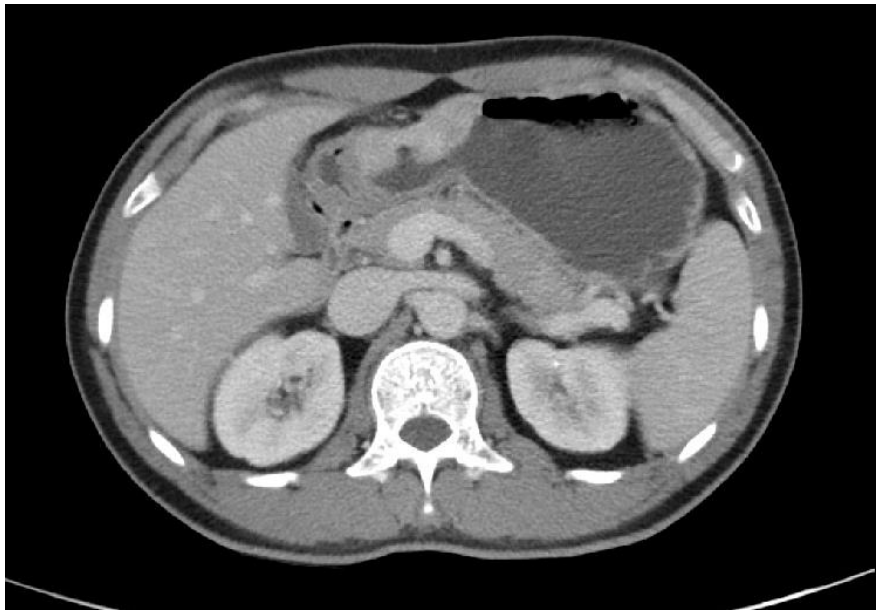
cT4aN+M1, stage **IV**

```
Pathologic diagnosis:
Peritoneum, permanent section of frozen specimen --- Metastatic
adenocarcinoma, poorly differentiated, in soft tissue.
```

HER2 IHC:2+, ISH: non-amplification

CPS: 2





Systemic Treatment of GC

Chemotherapy

Fluoropyrimidine

Platinum

Taxane

Irinotecan

Epirubicin

TAS-102

Target Therapy

HER2

VEGFR

CLDN 18.2

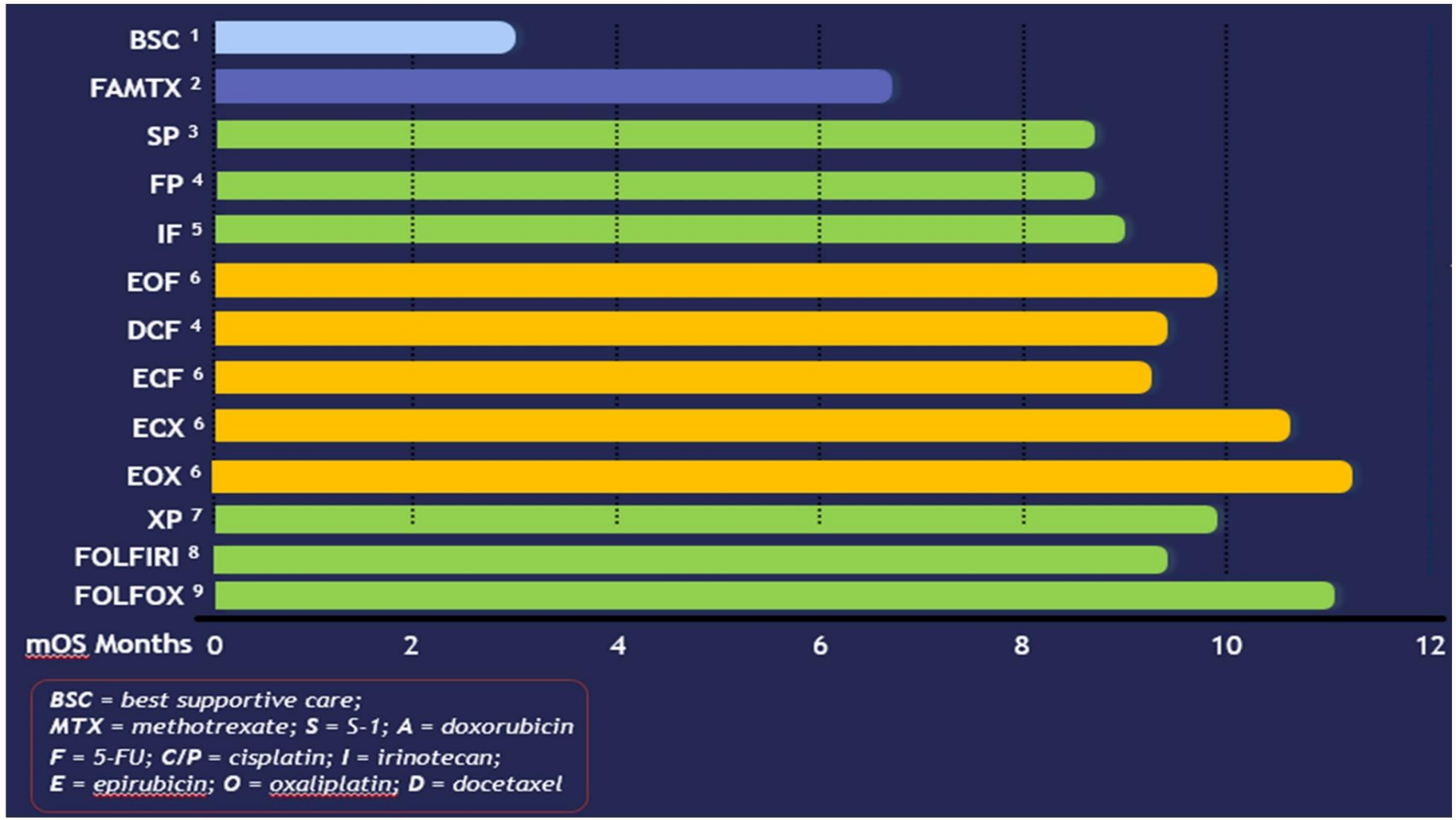
(FGFR2)

Immunotherapy

PD-1 inhibitor

(CTLA-4 inhibitor)

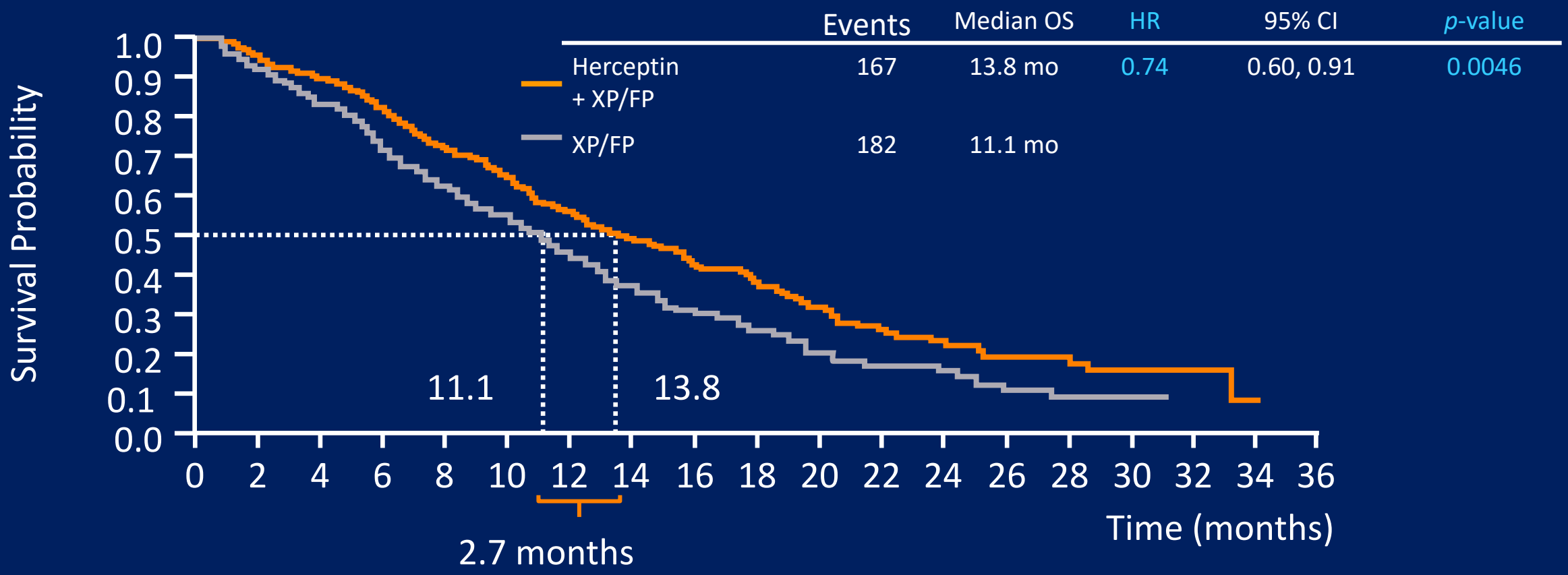
First Line Management of Advanced GEA



mOS = ~10-11m
1yr OS = ~40%
2yr OS = ~15-20%
5yr OS < ~2%

1. Murad AM et al. *Cancer.* 1993;72(1):37-41; 2. Vanhoefer U et al. *J Clin Oncol.* 2000;18(14):2648-2657; 3. Ajani JA et al. *J Clin Oncol.* 2010;28(9):1547-1553; 4. Van Cutsem E et al. *J Clin Oncol.* 2006;24(31):4991-4997; 5. Dank M et al. *Ann Oncol.* 2008;19(8):1450-1457; 6. Cunningham D et al. *N Engl J Med.* 2008;358(1):36-46; 7. Kang YK et al. *Ann Oncol.* 2009;20(4):666-673; 8. Guimbaud R et al. *J Clin Oncol.* 2014;32(31):3520-3526; 9. Shah MA et al. *JAMA Oncol.* 2017;3(5):620-627.

Trastuzumab improved HER2+ GC OS



Bang & Van Cutsem et al 2010

First Line Management of Advanced GEA

HER2-
mOS = ~10-11m
1yr OS = ~40%
2yr OS = ~15-20%
5yr OS < ~2%

HER2+
mOS = ~14-16m
1yr OS = ~55-65%
2yr OS = ~25-30%
5yr OS < ~10-15%

1. Murad AM et al. *Cancer.* 1993;72(1):37-41; 2. Vanhoefer U et al. *J Clin Oncol.* 2000;18(14):2648-2657; 3. Ajani JA et al. *J Clin Oncol.* 2010;28(9):1547-1553; 4. Van Cutsem E et al. *J Clin Oncol.* 2006;24(31):4991-4997; 5. Dank M et al. *Ann Oncol.* 2008;19(8):1450-1457; 6. Cunningham D et al. *N Engl J Med.* 2008;358(1):36-46; 7. Kang YK et al. *Ann Oncol.* 2009;20(4):666-673; 8. Guimbaud R et al. *J Clin Oncol.* 2014;32(31):3520-3526; 9. Shah MA et al. *JAMA Oncol.* 2017;3(5):620-627; 10. Bang YJ et al. *Lancet.* 2010;376(9742):687-697.

Prevalence of HER2+ GC

Study	Country	*n*	% HER-2$^+$ (definition)	Association	Prognostic factor
Tanner et al. (2005) [8]	Finland	131	12.2 (FISH +)	Intestinal type	Yes
Park et al. (2006) [16]	Korea	182	15.9 (IHC 2+ or 3+)	Intestinal type	Yes
Kim et al. (2007) [12]	Korea	248	22.6 (IHC 2+ or 3+)	Differentiation Intestinal type	Yes
Hoffman et al. (2008) [14]	Germany, China, Mexico	168	13.6 (IHC 3+ or IHC 2+ and FISH +)	Intestinal type	Not done
Barros-Silva et al. (2009) [10]	Portugal	463	9.3 (IHC 2+ or 3+)	Intestinal type Expansive type	Yes
Begnami et al. (2011) [15]	Brazil	221	12 (IHC 2+ or 3+)	Differentiation Intestinal type	Yes
Hsu et al. (2011), current series	Taiwan	1,036	6.1 (IHC 3+ or IHC 2+ and FISH +)	Differentiation	No

Abbreviations: FISH, fluorescence in situ hybridization; HER-2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

6.1% in Taiwan CGMH report

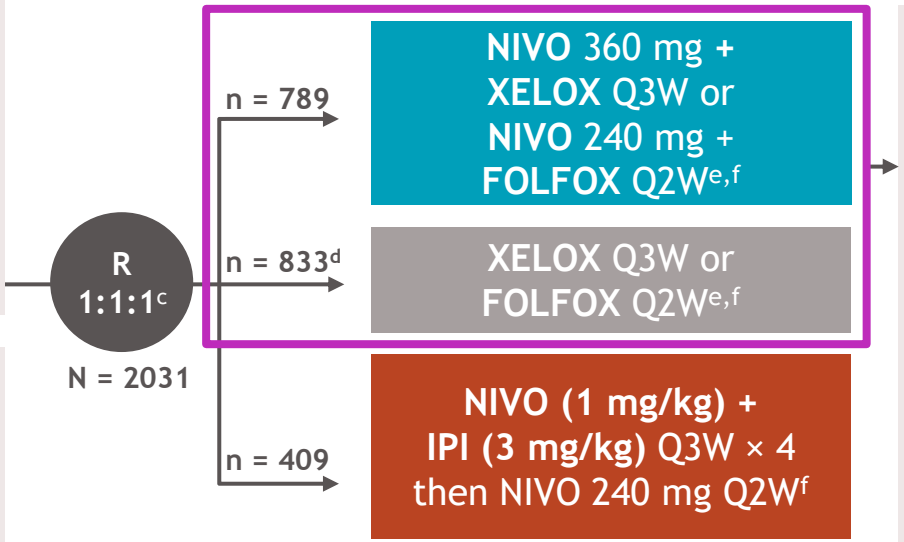
Oncologist. 2011;16(12):1706-13

CheckMate 649 study design

- CheckMate 649 is a randomized, open-label, global phase 3 study[a]

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0–1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



Dual primary endpoints:
- **OS** and **PFS**[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:
- **OS** (PD-L1 CPS ≥ 1, all randomized)
- **OS** (PD-L1 CPS ≥ 10)
- **PFS**[g] (PD-L1 CPS ≥ 10, ≥ 1, all randomized)
- **ORR**[g]

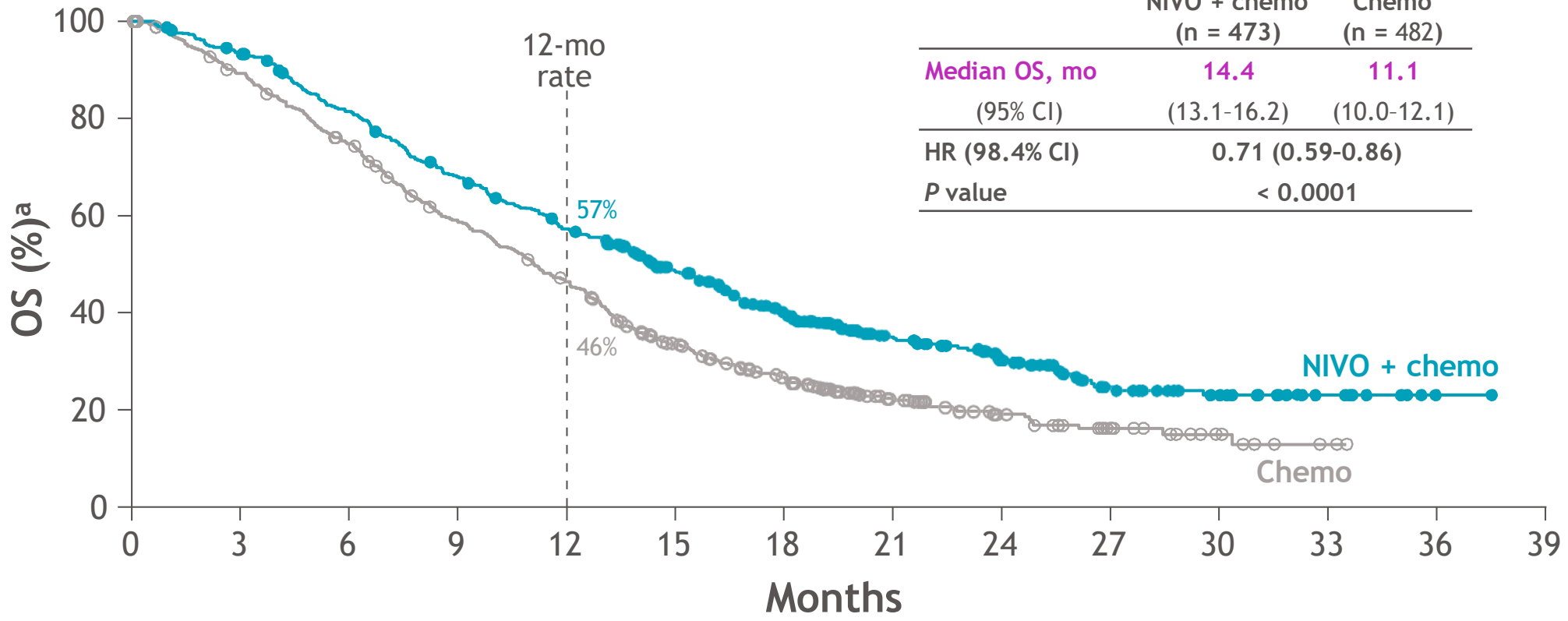
Exploratory endpoints:
- **Safety**
- **QoL**

- At data cutoff (May 27, 2021), the minimum follow-up[h] was 24.0 months in the NIVO + chemo arm

[a]ClinicalTrials.gov. NCT02872116; [b]Less than 1% includes indeterminate tumor cell PD-L1 expression; [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO + IPI arm was stopped early (June 5, 2018) based on DMC recommendation; patients already enrolled in the NIVO + IPI arm were allowed to remain on study; [d]Includes patients concurrently randomized to chemo vs NIVO + IPI (October 2016–June 2018) and to NIVO + chemo (April 2017-April 2019); [e]XELOX: oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1–14); FOLFOX: oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1–2); [f]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo or NIVO + IPI), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [g]BICR assessed; [h]Time from concurrent randomization of the last patient to clinical data cutoff. Janjigian YY, et al. *Lancet* 2021;398:27-40

Overall survival

Primary endpoint (PD-L1 CPS ≥ 5)



	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (98.4% CI)	0.71 (0.59-0.86)	
P value	< 0.0001	

No. at risk														
NIVO + chemo	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemo	482	421	350	271	211	138	98	56	34	19	8	2	0	0

- Superior OS, 29% reduction in the risk of death, and a 3.3-month improvement in median OS with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5

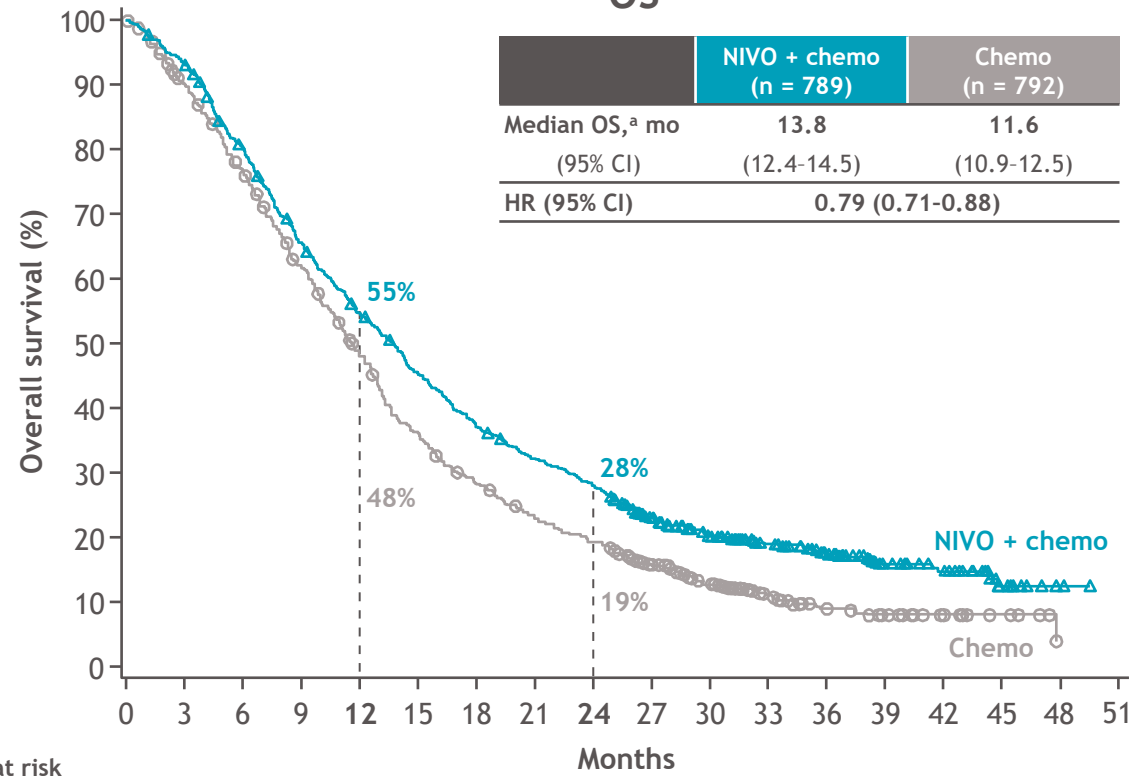
[a]Minimum follow-up 12.1 months.

Overall survival and progression-free survival

All randomized patients

OS

	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS,[a] mo	13.8	11.6
(95% CI)	(12.4-14.5)	(10.9-12.5)
HR (95% CI)	0.79 (0.71-0.88)	

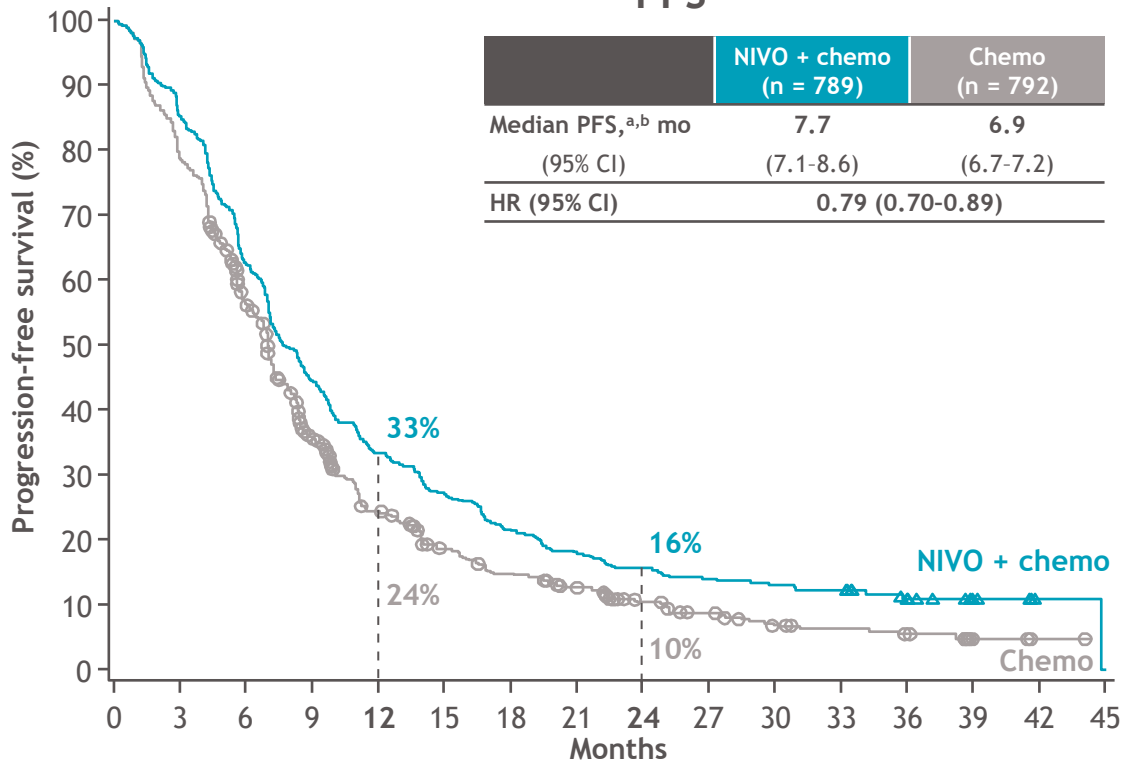


No. at risk

NIVO + chemo	789	733	624	508	422	349	287	246	212	156	115	84	57	33	25	9	2	0
Chemo	792	701	591	475	364	273	215	170	144	103	72	46	28	20	12	6	0	0

PFS

	NIVO + chemo (n = 789)	Chemo (n = 792)
Median PFS,[a,b] mo	7.7	6.9
(95% CI)	(7.1-8.6)	(6.7-7.2)
HR (95% CI)	0.79 (0.70-0.89)	



NIVO + chemo	789	640	431	295	209	166	126	96	74	53	37	25	11	6	1	0
Chemo	792	552	359	213	135	96	75	59	40	29	18	15	10	3	1	0

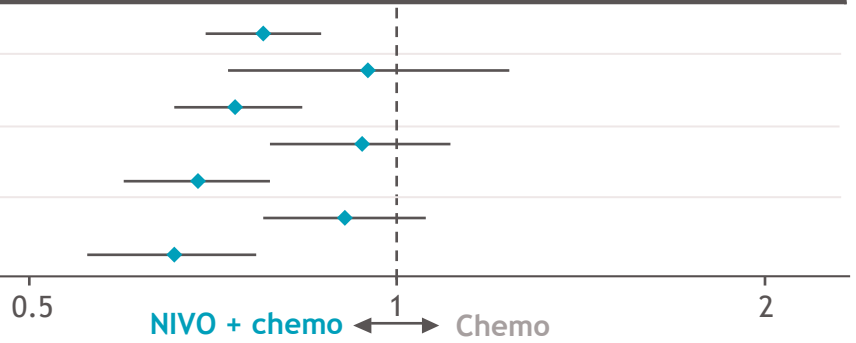
- Clinically meaningful improvement in OS and PFS with NIVO + chemo vs chemo was maintained with longer follow-up

[a]Minimum follow-up, 24.0 months. [b]Per BICR assessment. Janjigian YY et al. Oral presentation at ESMO; September 16–21, 2021; Virtual. Abstract LBA7

Efficacy subgroup analysis by PD-L1 CPS

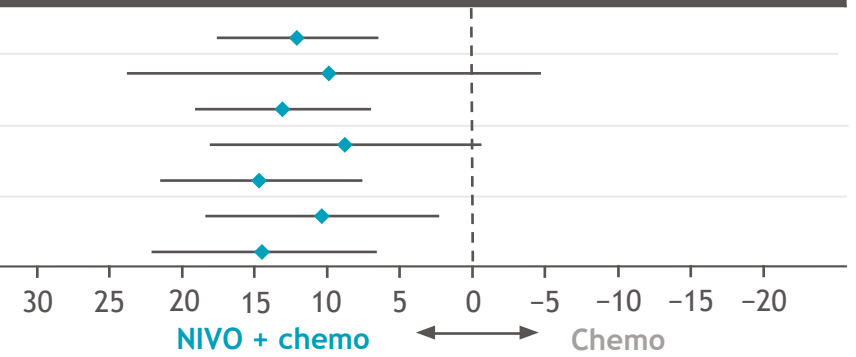
Overall survival

PD-L1 CPS[a]	Number of patients	Median, months		Unstratified HR[b]	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 1581)		13.8	11.6	0.78	
< 1	265	13.1	12.5	0.95	
≥ 1	1297	13.8	11.3	0.74	
< 5	607	12.4	12.3	0.94	
≥ 5	955	14.4	11.1	0.69	
< 10	795	12.4	12.5	0.91	
≥ 10	767	15.0	10.9	0.66	



Objective response rate

PD-L1 CPS[c]	Number of patients	Objective response rate, %		Unweighted ORR difference,[d] %	Unweighted ORR difference,[d] % (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 1210)		58	46	12	
< 1	179	51	41	10	
≥ 1	1017	59	46	13	
< 5	428	55	46	9	
≥ 5	768	60	45	15	
< 10	579	58	47	10	
≥ 10	617	59	44	15	



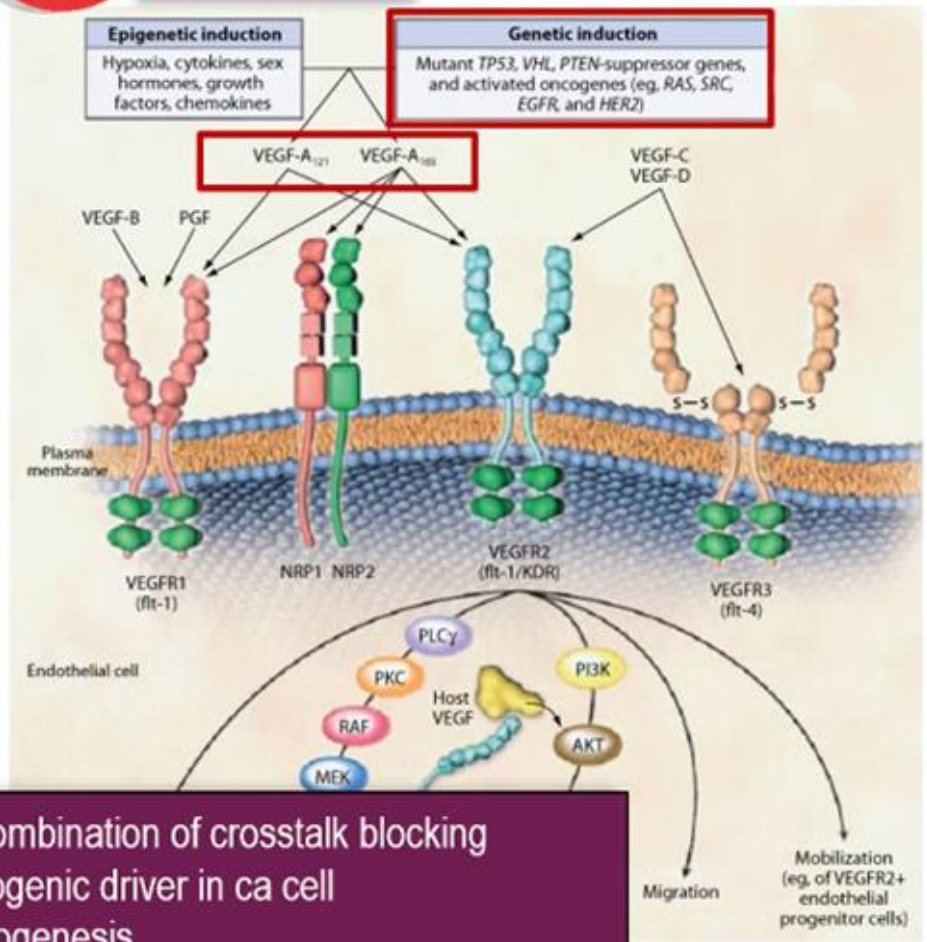
- OS benefit with NIVO + chemo was enriched at higher PD-L1 CPS cutoffs
- ORR was higher across all PD-L1 CPS subgroups vs chemo

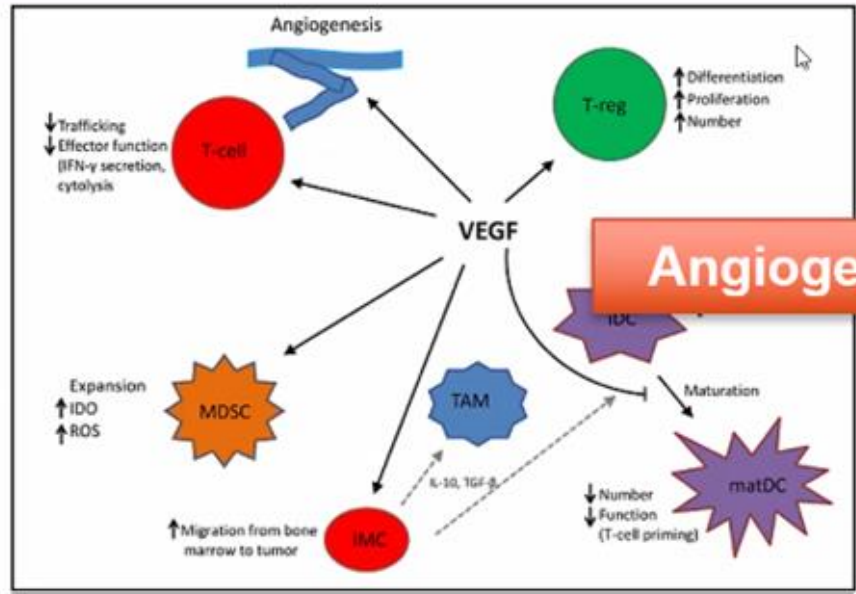
[a]PD-L1 CPS expression indeterminate/not evaluable/not reported, n = 19; [b]Unstratified HR for death (OS); [c]Randomized patients who had target lesion measurements at baseline, per BICR. PD-L1 CPS expression indeterminate/not evaluable/not reported, n = 14; [d]Percentages may not reflect an exact difference due to rounding.

Crosstalk between cancer cells – endothelial cells – immune system

Her-2 +

Multiple blocking tumor with oncogenic driver (her-2) and immune checkpoints?
-> 1st line trials: PANTHERA(YCC, Korea), MSKCC, KN-811





Angiogenesis

- Promotes inhibitory immune cells
  - T_{reg}s / MDSCs/ TAMs
- Compromises APC & T eff… function
- Impairs lymphocyte trafficking

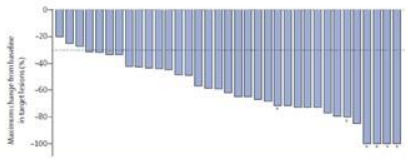
Immune suppression

Various combination of crosstalk blocking
- Oncogenic driver in ca cell
- Angiogenesis
- Immune checkpoint

Huang Y et al. Blood. 2007;110:624. Ott PA, et al. Front Oncol 2015;5:202, Motz GT et al. *Nat Rev Immunol.* 2011:11:702

Background

- Standard first-line therapy for HER2-positive metastatic gastric or gastroesophageal junction (G/GEJ) cancer is trastuzumab (anti–HER2) with a fluoropyrimidine and a platinum
- Phase 2 data suggested antitumor activity and manageable safety for adding pembrolizumab (anti–PD-1) to trastuzumab and chemotherapy
  - MSKCC study (N = 37): 91% ORR, 100% DCR, 70% 6-mo PFS, 80% 12-mo OS



Janjigian YY et al. *Lancet Oncol* 2020;21:821-31.
Figure reused with permission. © 2020 Elsevier.

  - PANTHERA (N = 43): 77% ORR, 98% DCR, 77% 6-mo PFS, 77% 12-mo OS

Rha SY et al. *J Clin Oncol* 2020;38:Abstr 3081.

KEYNOTE-811 Global Cohort

Double-Blind Phase 3 Study of Pembrolizumab + Trastuzumab and Chemotherapy vs Placebo + Trastuzumab and Chemotherapy as First-Line Therapy For HER2-Positive Unresectable or Metastatic G/GEJ Cancer (NCT03615326)

Patients
- Advanced G/GEJ adenocarcinoma
- No prior therapy in advanced setting
- HER2-positive

Stratification Factors
- Geographic region
- PD-L1 CPS
- Chemotherapy choice

R 1:1
N ≈ 692

Pembrolizumab 200 mg IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

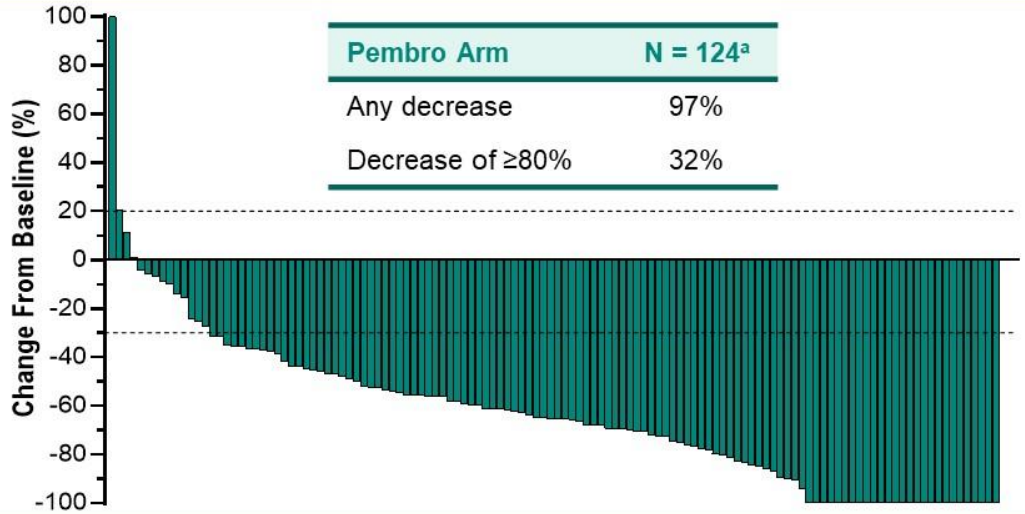
Placebo IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Dual Primary End Points
- OS
- PFS (RECIST v1.1 per BICR)

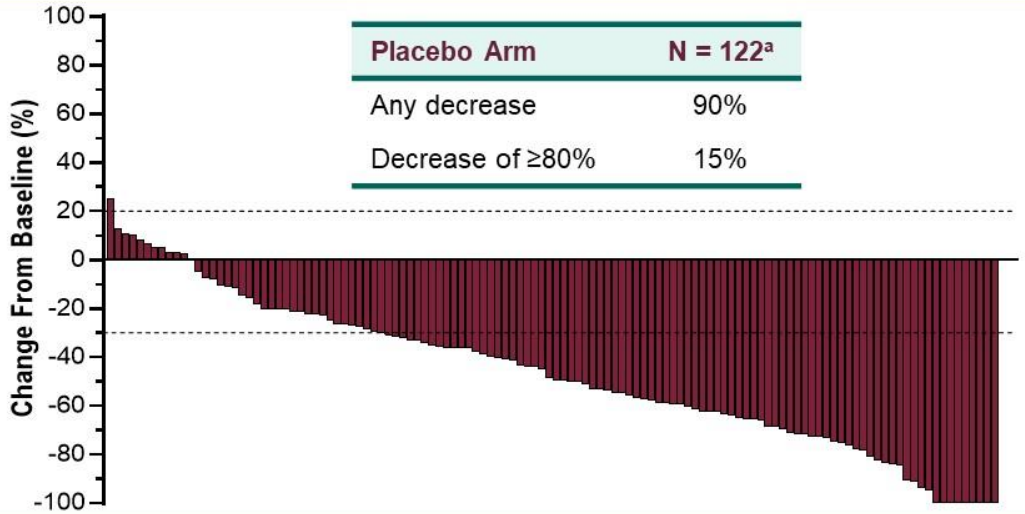
Secondary End Points
- ORR (RECIST v1.1 per BICR)
- DOR (RECIST v1.1 per BICR)
- Safety

[a]Trastuzumab dose: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP dose: 5-fluorouracil 800 mg/m² IV on D1-5 Q3W + cisplatin 80 mg/m² IV Q3W. CAPOX dose: capecitabine 1000 mg/m² BID on D1-14 Q3W + oxaliplatin 130 mg/m² IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100).

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%

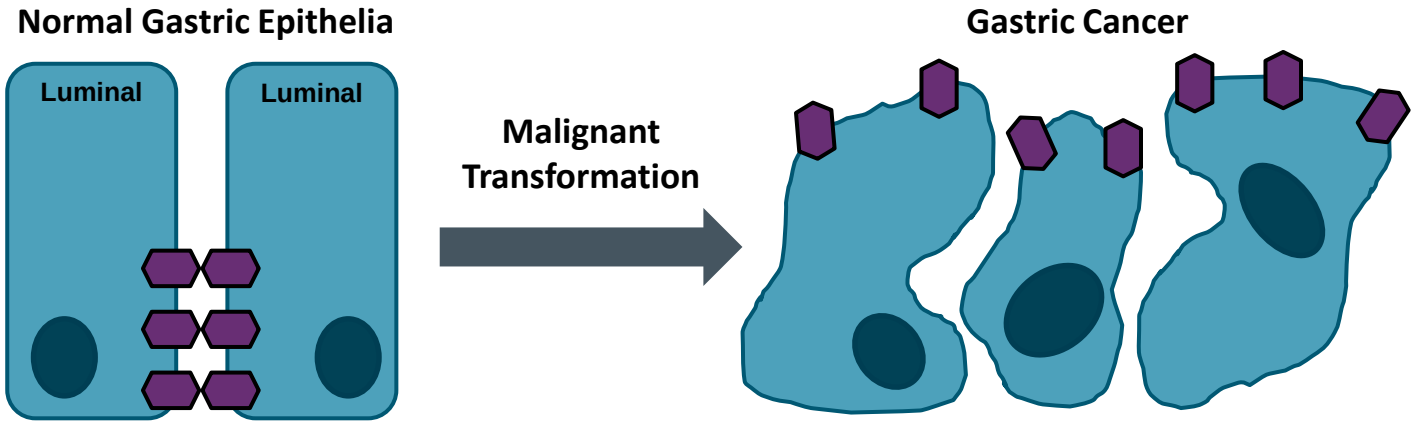
ORR and DCR, % (95% CI)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	**74.4% (66.2-81.6)**	**51.9% (43.0-60.7)**
ORR difference[b]	**22.7% (11.2-33.7) *P* = 0.00006**	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)

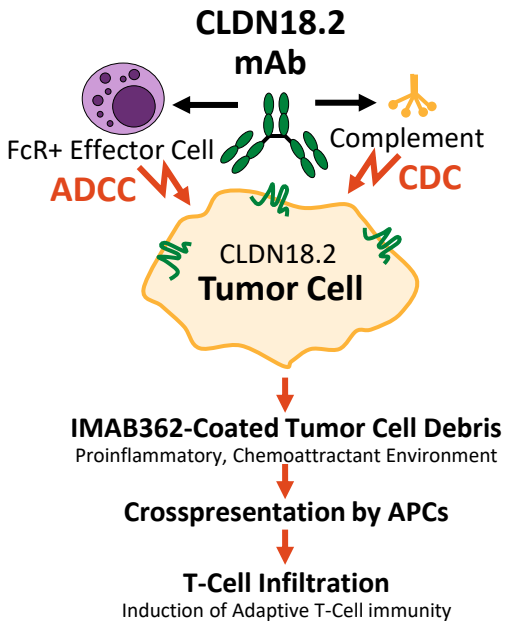
Best Response, n (%)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
CR	**15 (11%)**	**4 (3%)**
PR	**84 (63%)**	**64 (49%)**
SD	29 (22%)	49 (37%)
PD	5 (4%)	7 (5%)
Not evaluable	0	2 (2%)
Not assessed	0	5 (4%)

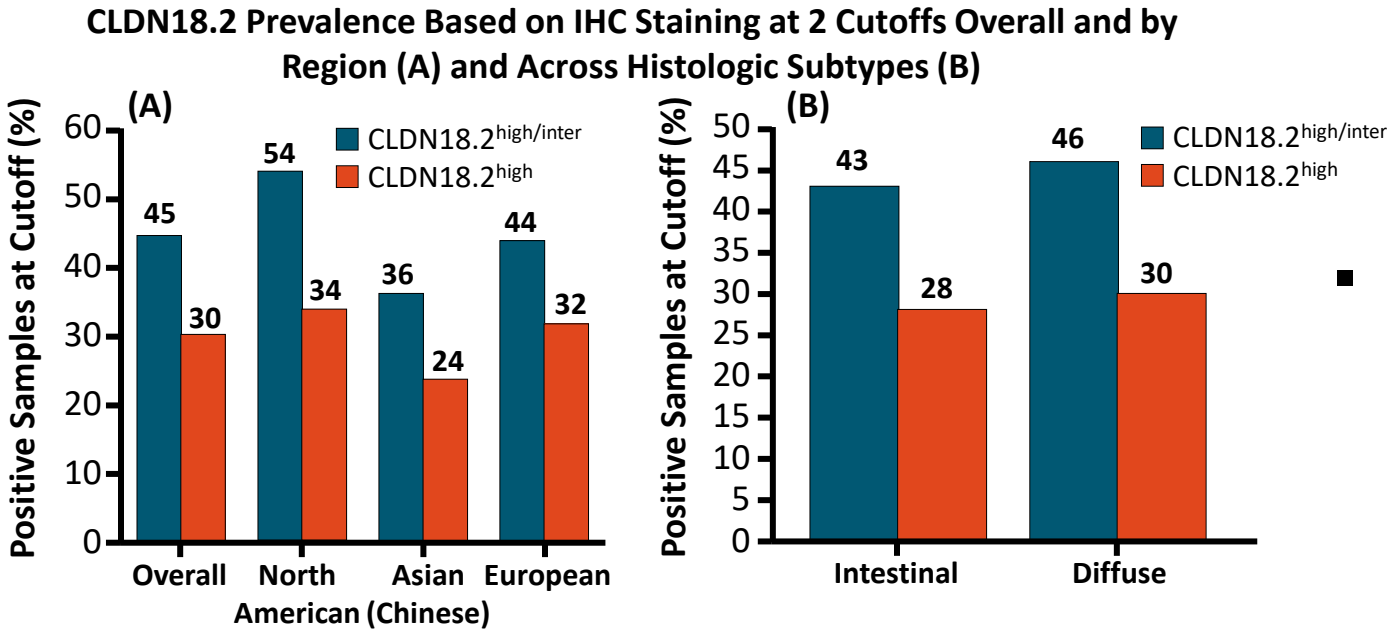
Duration of Response[c]	Pembro Arm (N = 99)	Placebo Arm (N = 68)
Median[d]	10.6 mo	9.5 mo
Range	1.1+ to 16.5+	1.4+ to 15.4+
≥6-mo duration[d]	70.3%	61.4%
≥9-mo duration[d]	58.4%	51.1%

[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.

Claudin18.2







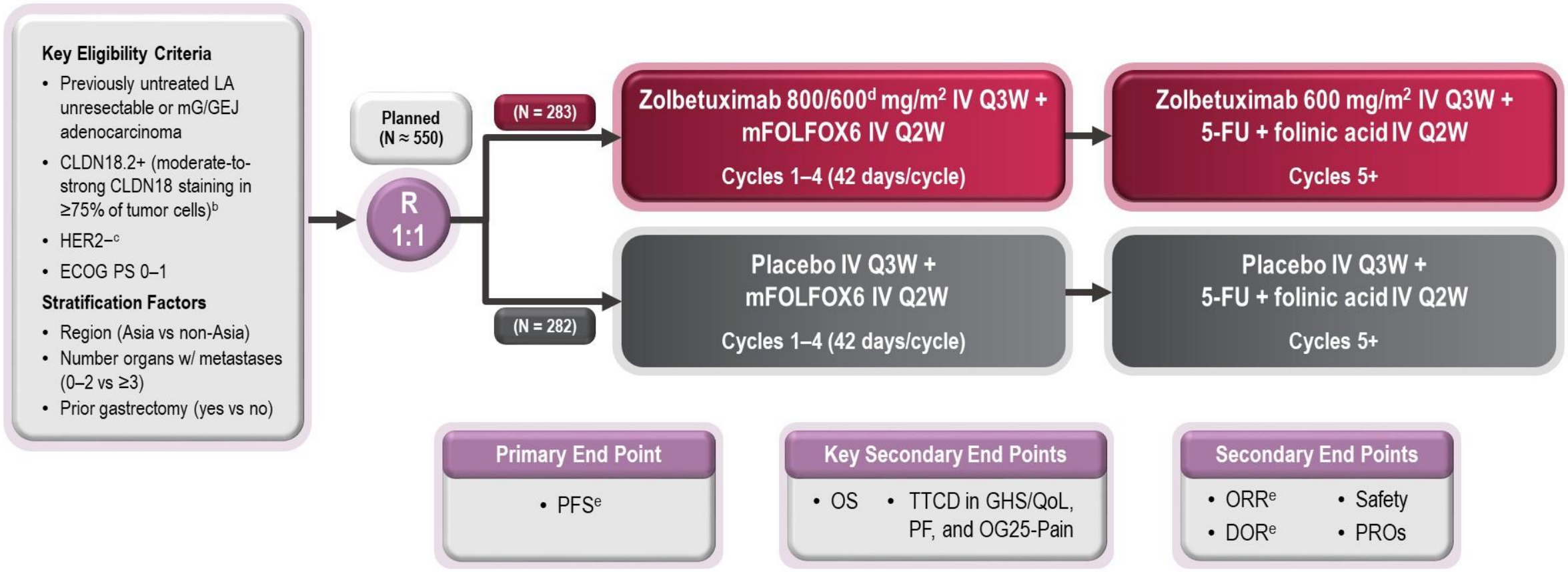
- Claudin18.2 is a major structural component of intercellular tight junctions
- Not routinely expressed in any normal tissue outside gastric mucosa (cancer-restricted antigen)
- Broadly expressed in several tumor types including gastric, GEJ, biliary, and pancreatic

Baek. Anticancer Res. 2019;39:6973.

Slide credit: clinicaloptions.com

Study Design: SPOTLIGHT

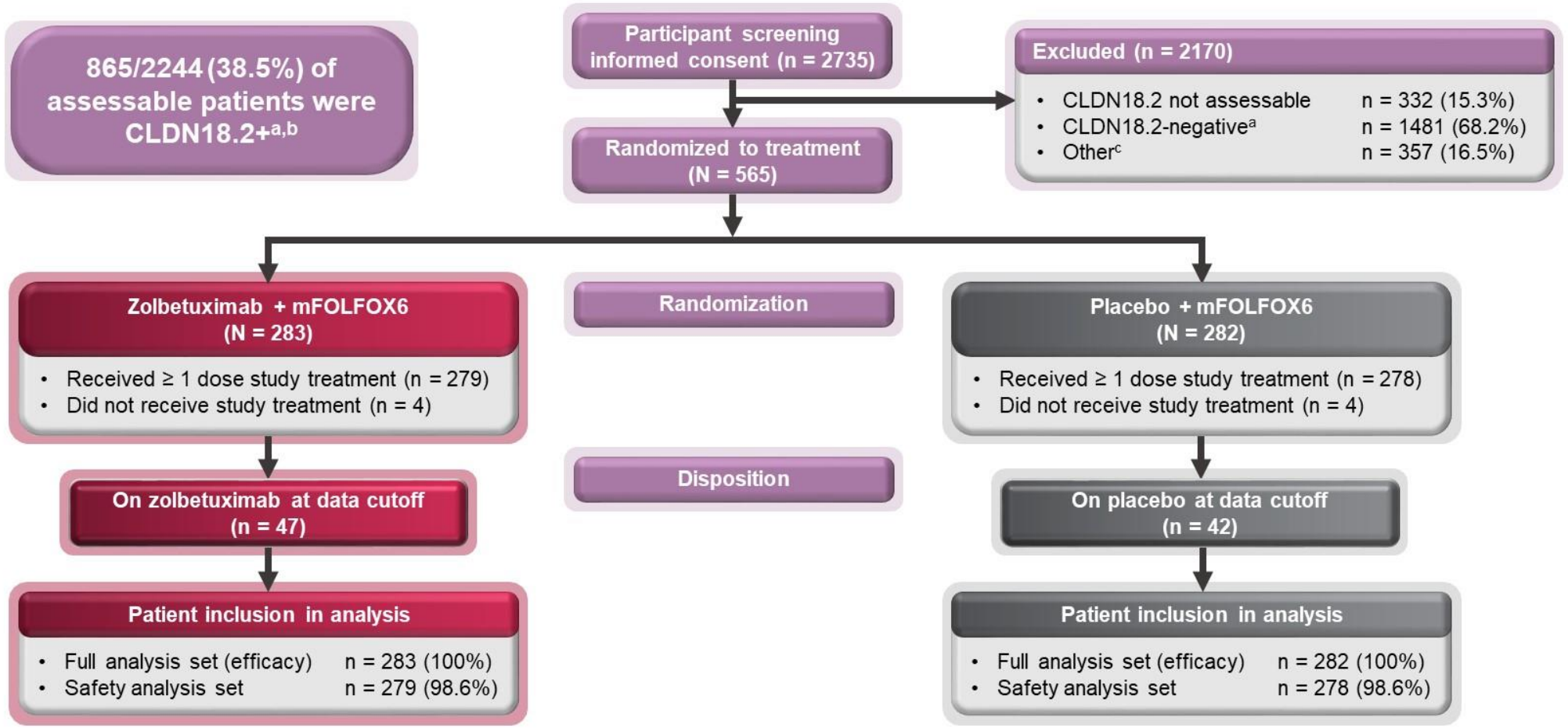
Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial



[a]Study was conducted at 215 sites in 20 countries across Australia, Asia, Europe, N. America, and S. America; [b]By central IHC using the analytically validated VENTANA CLDN18 (43-14A) RxDx Assay; [c]By central or local HER2 testing; [d]800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on cycle 1 day 22 and days 1 and 22 of subsequent cycles; [e]Per RECIST v1.1 by independent review committee.

PRESENTED BY: Dr. Kohei Shitara

Patient Disposition



Data cutoff: September 9, 2022; Recruitment period: June 21, 2018–April 1, 2022.

[a]CLDN18.2+ was defined as moderate-to-strong CLDN18 staining in ≥75% of tumor cells by central IHC using the analytically validated VENTANA CLDN18 (43-14A) RxDx Assay. [b]These data exclude Chinese patients. [c]"Other" represents reasons including withdrawal by subject, laboratory findings, HER2-expression status, and ECOG PS score.

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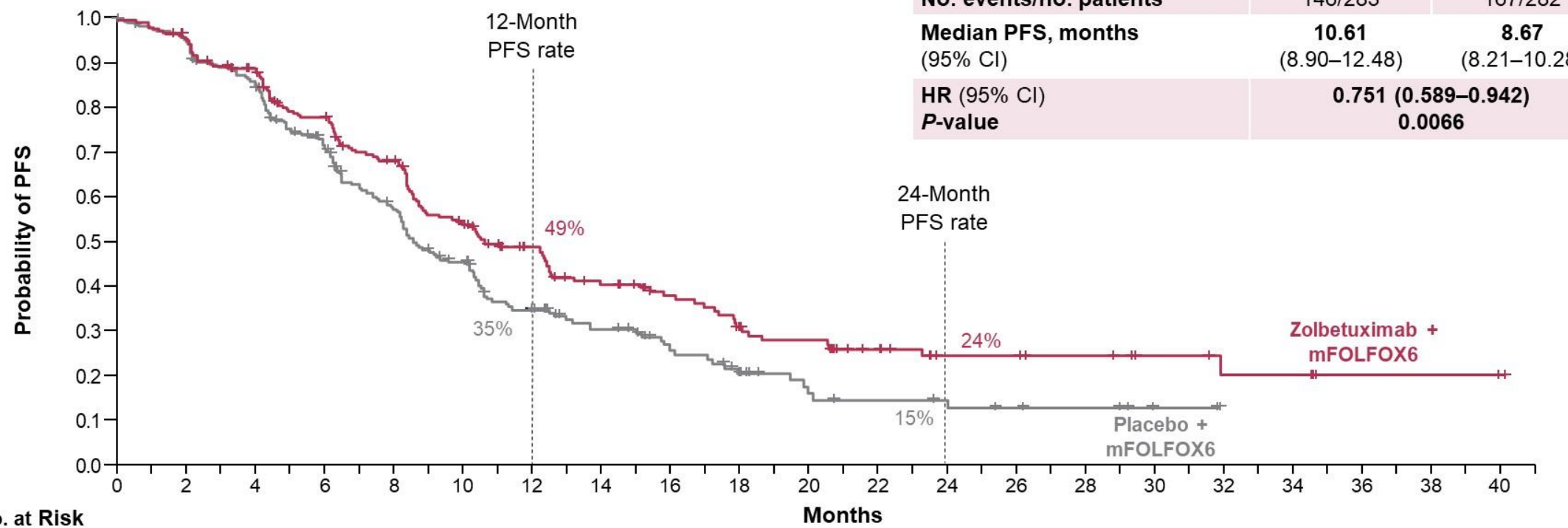
Primary End Point: PFS by Independent Review Committee[a]

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	146/283	167/282
Median PFS, months (95% CI)	**10.61** (8.90–12.48)	**8.67** (8.21–10.28)
HR (95% CI)	**0.751 (0.589–0.942)**	
***P*-value**	**0.0066**	



No. at Risk

Zolbetuximab + mFOLFOX6	283	263	254	232	226	190	187	148	143	108	102	84	78	59	56	53	43	40	33	28	28	21	19	17	12	12	12	10	10	9	7	7	5	5	5	2	2	2	2	2	1	0
Placebo + mFOLFOX6	282	273	260	237	226	183	168	136	122	91	83	60	56	43	40	38	26	25	19	14	12	9	9	9	8	7	6	5	5	4	2	2	0	0	0	0	0	0	0	0	0	0

- PFS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).

[a]Per RECIST version 1.1.

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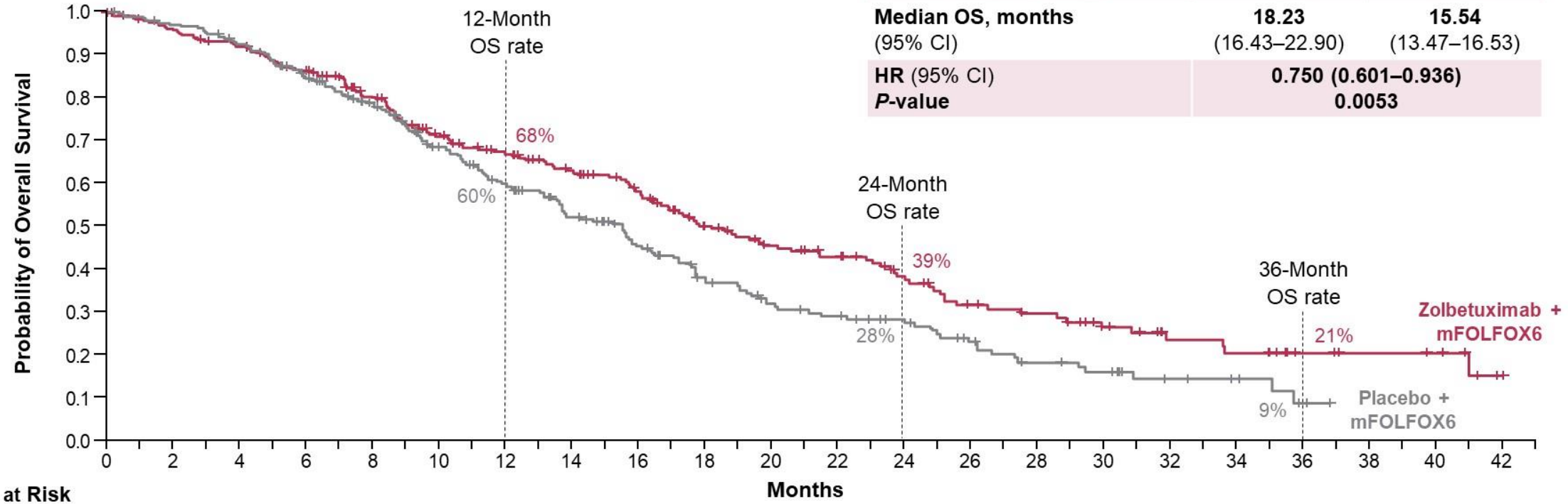
Key Secondary End Point: OS

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	149/283	177/282
Median OS, months (95% CI)	**18.23** (16.43–22.90)	**15.54** (13.47–16.53)
HR (95% CI)	**0.750 (0.601–0.936)**	
***P*-value**	**0.0053**	



No. at Risk

Zolbetuximab + mFOLFOX6	283	270	264	255	251	241	233	217	196	178	164	152	146	135	125	117	107	93	83	75	70	67	62	58	49	42	34	32	30	27	23	20	15	15	13	13	9	8	7	7	6	4	1	0
Placebo + mFOLFOX6	282	277	271	266	253	242	224	210	197	183	164	152	139	129	108	101	85	77	64	60	49	42	40	36	34	30	25	21	18	17	15	9	8	7	6	5	2	0	0	0	0	0	0	0

- OS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

Data cutoff: September 9, 2022; Median follow-up = 22.14 months (zolbetuximab + mFOLFOX6) vs 20.93 months (placebo + mFOLFOX6).

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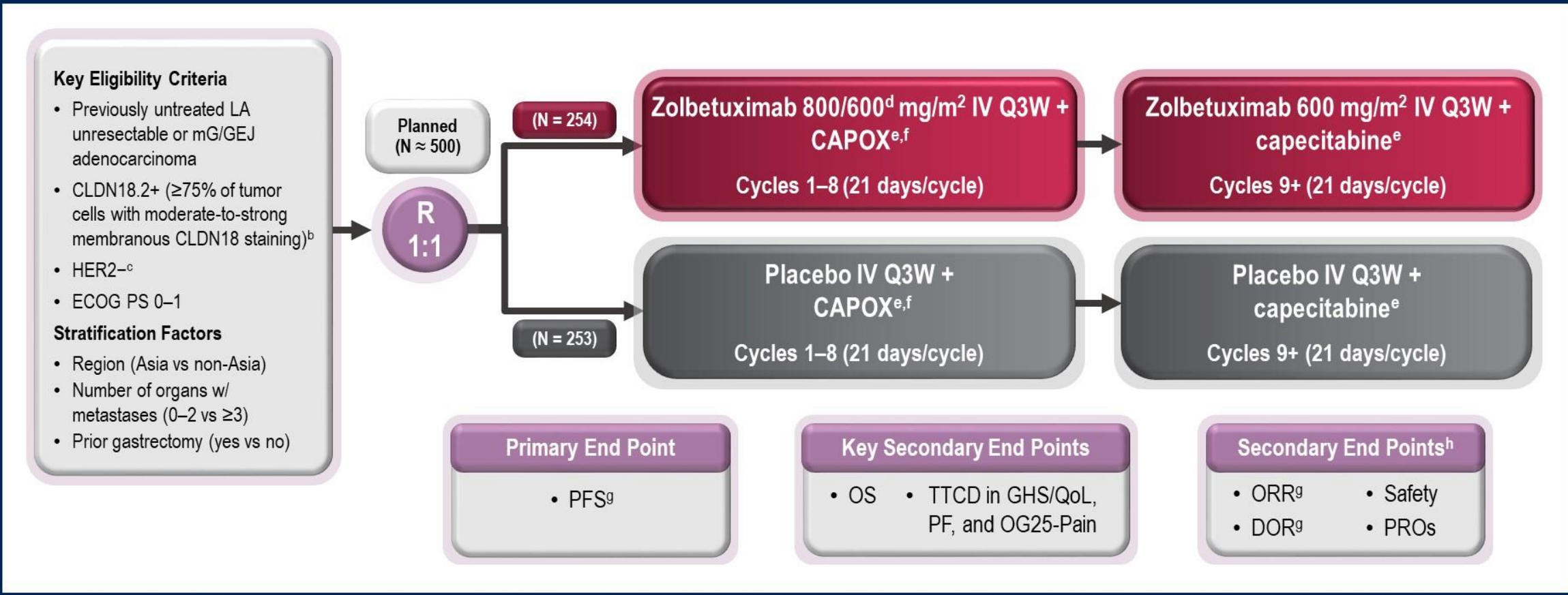
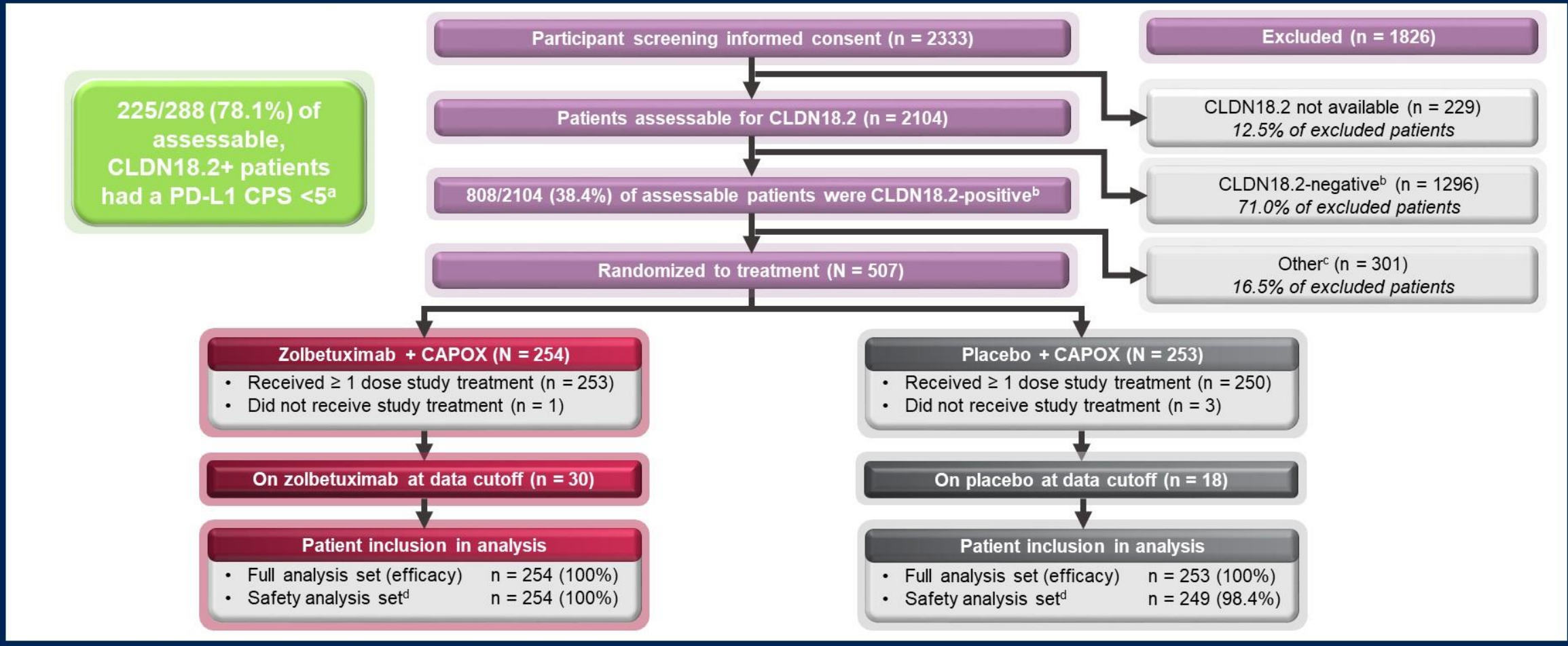
Study Design: GLOW

Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial



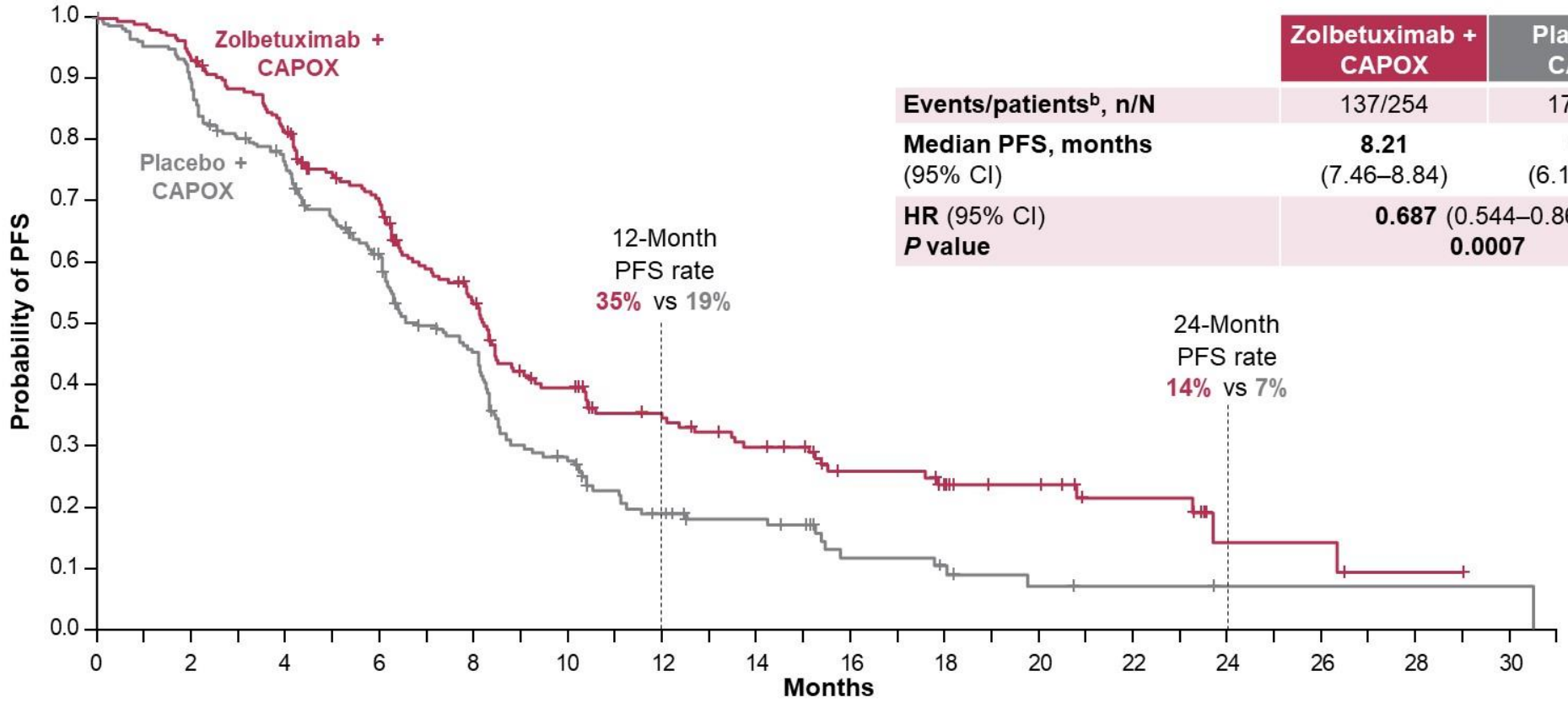
[a]Study was conducted at 166 sites in 18 countries across Asia, Europe, N. America, and S. America; [b]By central IHC using the investigational VENTANA CLDN18 (43-14A) RxDx Assay; [c]By central or local HER2 testing (IHC0–1, or IHC2/FISH–); [d]800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on day 1 of subsequent cycles; [e]1000 mg/m² capecitabine orally BID on days 1–14 of each cycle; [f]130 mg/m² oxaliplatin IV on day 1 of each cycle; [g]Per RECIST v1.1 by independent review committee; [h]Select secondary end points are included here.

Patient Disposition



Data cutoff: October 7, 2022; Recruitment period: November 28, 2018–October 7, 2022.
[a]As an ad hoc analysis using the Dako PD-L1 IHC 28-8 pharmDx assay for samples within test stability and with subject consent, and excluding patients from China; [b]"CLDN18.2-positive" was defined as ≥75% of tumor cells with moderate-to-strong membranous CLDN18 staining by central IHC using the investigational VENTANA CLDN18 (43-14A) RxDx Assay, and "CLDN18.2-negative" was defined as <75% of tumor cells with moderate-to-strong membranous CLDN18 staining; [c]"Other" represents reasons including withdrawal by subject, laboratory findings, HER2-expression status, and ECOG PS score; [d]One patient assigned to placebo + CAPOX received 1 dose of zolbetuximab as a protocol deviation and was moved to the zolbetuximab + CAPOX group for the safety analysis set.

Primary End Point: PFS by Independent Review Committee[a]



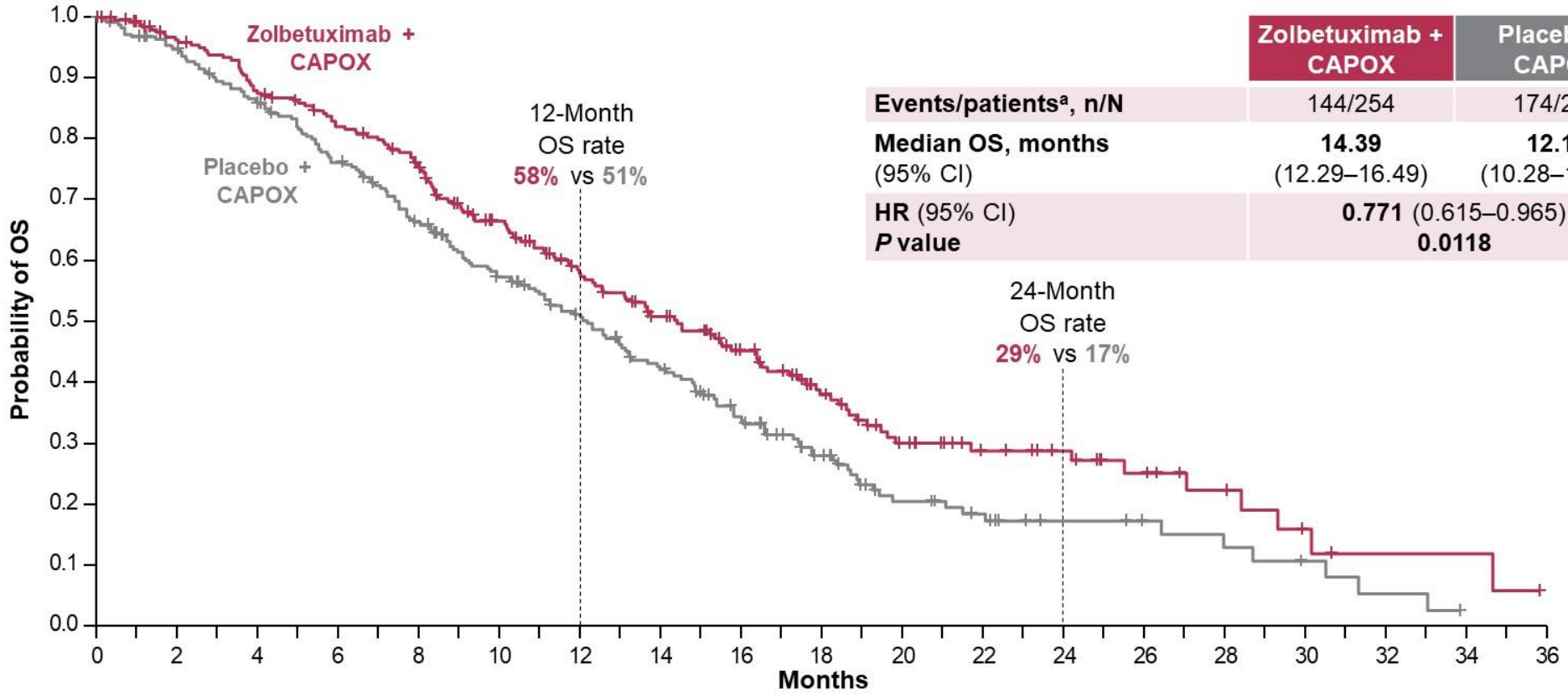
	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[b], n/N	137/254	172/253
Median PFS, months (95% CI)	**8.21** (7.46–8.84)	**6.80** (6.14–8.08)
HR (95% CI)	**0.687** (0.544–0.866)	
***P* value**	**0.0007**	

PFS was significantly longer in patients treated with zolbetuximab + CAPOX vs placebo + CAPOX

Data cutoff: October 7, 2022; Median follow-up = 12.62 months (zolbetuximab + CAPOX) vs 12.09 months (placebo + CAPOX).

[a]Per RECIST version 1.1; [b]117/254 (46.1%) patients assigned to zolbetuximab + CAPOX and 81/253 (32.0%) of patients assigned to placebo + CAPOX were censored.

Key Secondary End Point: OS



	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[a], n/N	144/254	174/253
Median OS, months (95% CI)	**14.39** (12.29–16.49)	**12.16** (10.28–13.67)
HR (95% CI)	**0.771** (0.615–0.965)	
***P* value**	**0.0118**	

OS was significantly longer in patients treated with zolbetuximab + CAPOX vs placebo + CAPOX
Subsequent anticancer therapies were administered to 47% of patients in the zolbetuximab arm and 55% in the placebo arm

Data cutoff: October 7, 2022; Median follow-up = 17.71 months (zolbetuximab + CAPOX) vs 18.43 months (placebo + CAPOX).

[a]110/254 (43.3%) patients assigned to zolbetuximab + CAPOX and 79/253 (31.2%) of patients assigned to placebo + CAPOX were censored.

PRESENTED BY: Manish A. Shah

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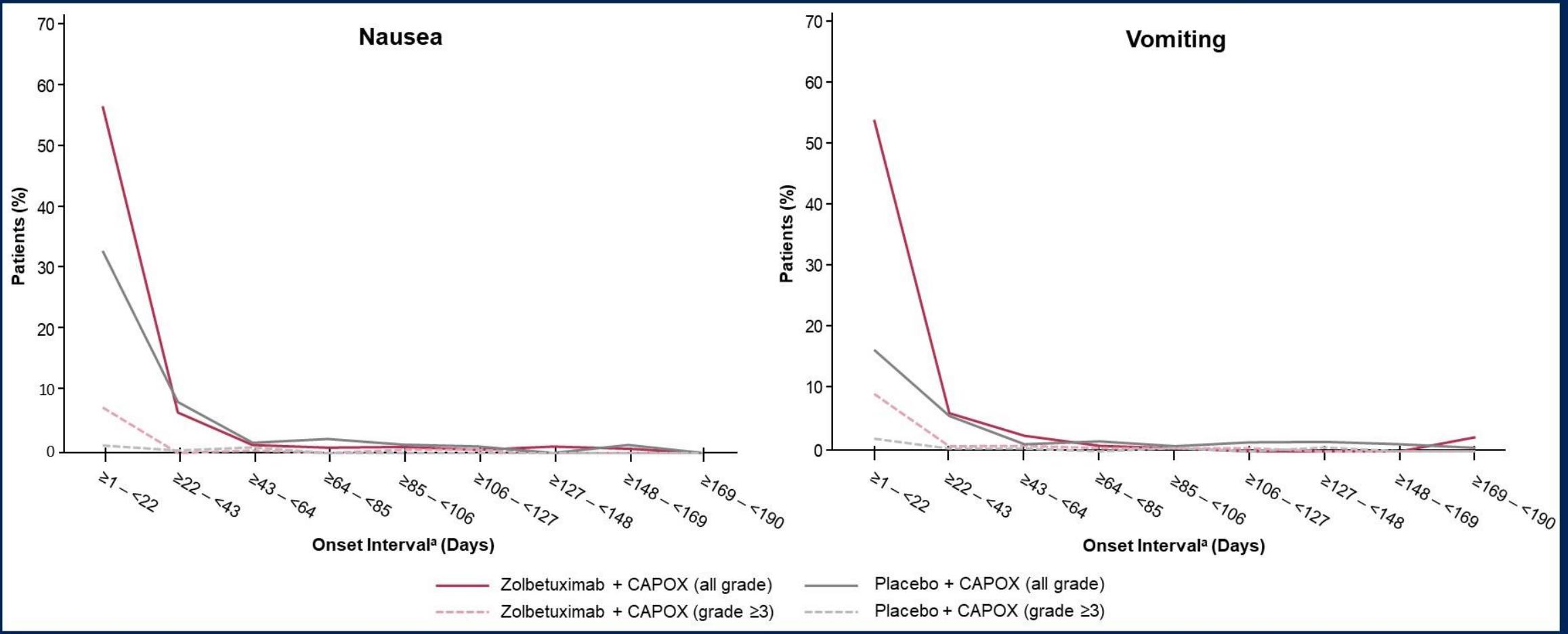
Safety: First Occurrence of Nausea and Vomiting



Nausea and vomiting first occurred most commonly during the first and second treatment cycles

[a]The onset interval was defined as the date of onset through the date of dose + 1.

PRESENTED BY: Manish A. Shah

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44 y/o Male, BW:64kg, BSA:1.7

Gastric cancer, adenocarcinoma, peritoneal metastasis, T4bN+M1

2021/10

Initial Presentation

Epigastralgia
Vomiting
UGI scopy: huge ulcerative mass, adenocarinoma

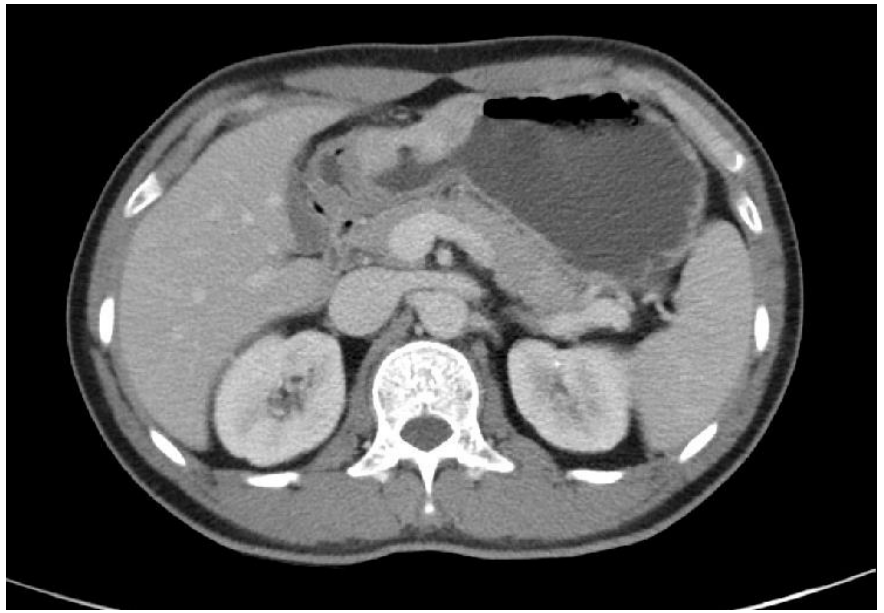
cT4aN+M1, stage **IV**

```
Pathologic diagnosis:
Peritoneum, permanent section of frozen specimen --- Metastatic
adenocarcinoma, poorly differentiated, in soft tissue.
```

HER2 IHC:2+, ISH: non-amplification

PDL1 CPS: 2

Claudin 18.2 positive (75% cutoff)



44 y/o Male, BW:64kg, BSA:1.7

Gastric cancer, adenocarcinoma, peritoneal metastasis, T4bN+M1

2021/10

Initial Presentation

Epigastralgia

Vomiting

UGI scopy: huge ulcerative mass, adenocarinoma

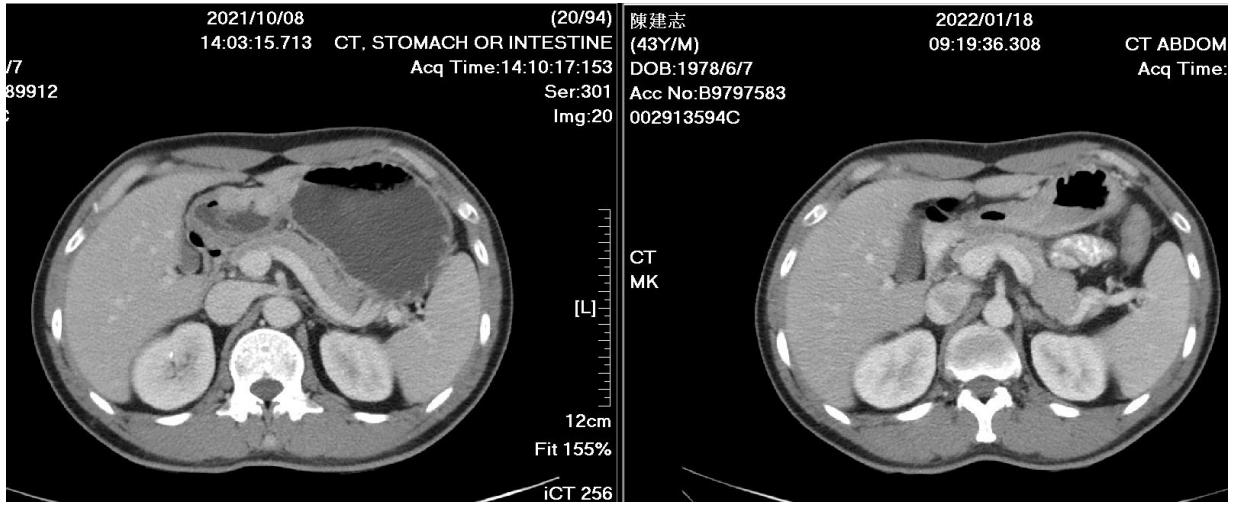
cT4bN+M0, stage **IVA**

2021/11-2022/1

Treatment

Zolbetuximab/ Placebo CapOx C3

Treatment response



44 y/o Male, BW:64kg, BSA:1.7

Gastric cancer, adenocarcinoma, peritoneal metastasis, T4bN+M1

2021/10	2022/1	2022/2	2022/3-
Initial Presentation Epigastralgia Vomiting UGI scopy: huge ulcerative mass, adenocarinoma	**Treatment** Zolbetuximab/ Placebo CapOx C3	**Treatment** Total gastrectomy HIPEC	**Treatment** Nivolumab CapOx Capecitabine maintenance
cT4bN+M0, stage **IVA**	**SD**	**ypT3N3a**	**Follow-up**

Treatment of Advanced Gastric Cancer

First line

Nivo/Pembro + Fluoropyrimidine + Platinum (CPS ≧ 5?)
HER2(+) → Trastuzumab (+Pembrolizumab) + C/T
Claudin 18.2(+) → Zolbetuximab + C/T

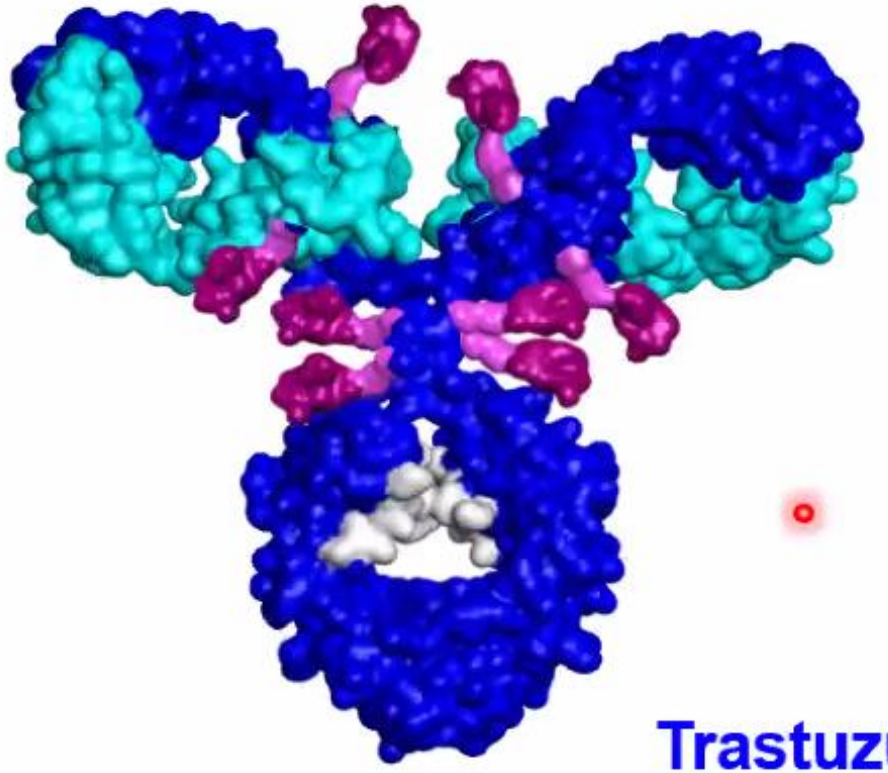
Second line

Ramucirumab + Paclitaxel
Taxane
Irinotecan
MSI-H/dMMR, TMB-H → Pembrolizumab

Third line

Nivolumab
TAS-102 Trifluridine/tipiracil
HER2(+) → Trastuzumab Deruxtecan
Irinotecan

T-DXd was designed with 7 key attributes



Trastuzumab Deruxtecan

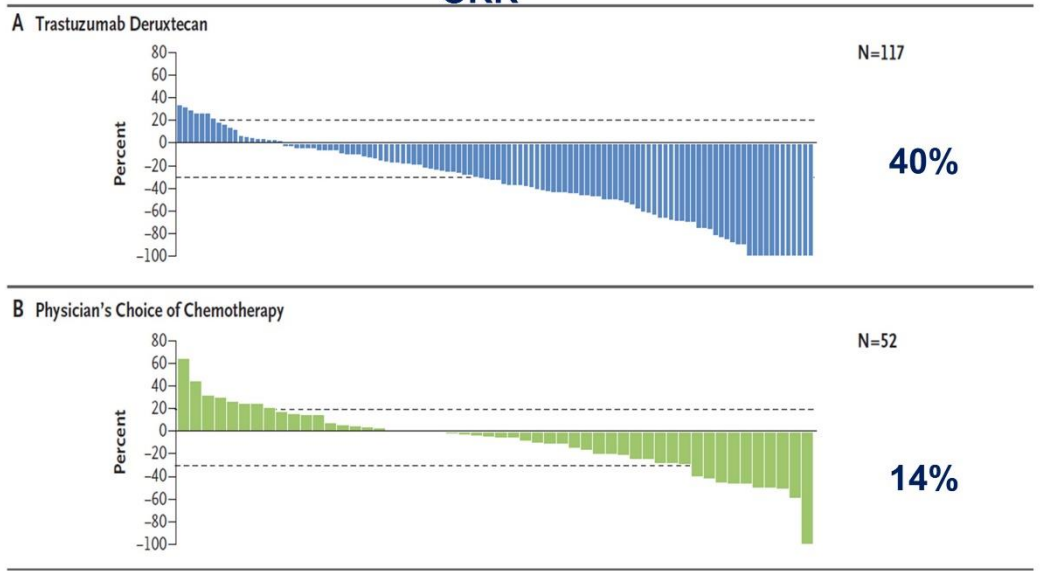
1. Topoisomerase I inhibitor payload[1-5]
2. High potency of payload based on a cell-free assay topoisomerase I-mediated DNA relaxation assay[1,2,3]
3. Payload with a short systemic $t_{1/2}$[1-5]
4. Highly membrane permeable, which may enable a bystander anti-tumour effect[4]
5. Stable linker-payload[1-5]
6. Designed to be cleaved by lysosomal enzymes overexpressed in tumour cells[5]
7. DAR of ~8[1-5]

- The clinical relevance of these features is under investigation.
- DAR=drug to antibody ratio; T-DXd=trastuzumab deruxtecan.
- 1. Krop I, et al. Presented at: SABCS 2019. 10–14 December. San Antonio, US. Abstract #GS1-03; 2. Iwata H, et al. Presented at: ASCO Annual Meeting; June 1–5, 2018; Chicago, IL. Abstract 2501; 3. Ogitani Y, et al. Clin Cancer Res. 2016;22:5097–5108; 4. Ogitani Y, et al. Cancer Sci. 2016;107:1039–1046 5. EMA. Enhertu® (trastuzumab deruxtecan) SmPC. Available from: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf. Accessed September 2022;

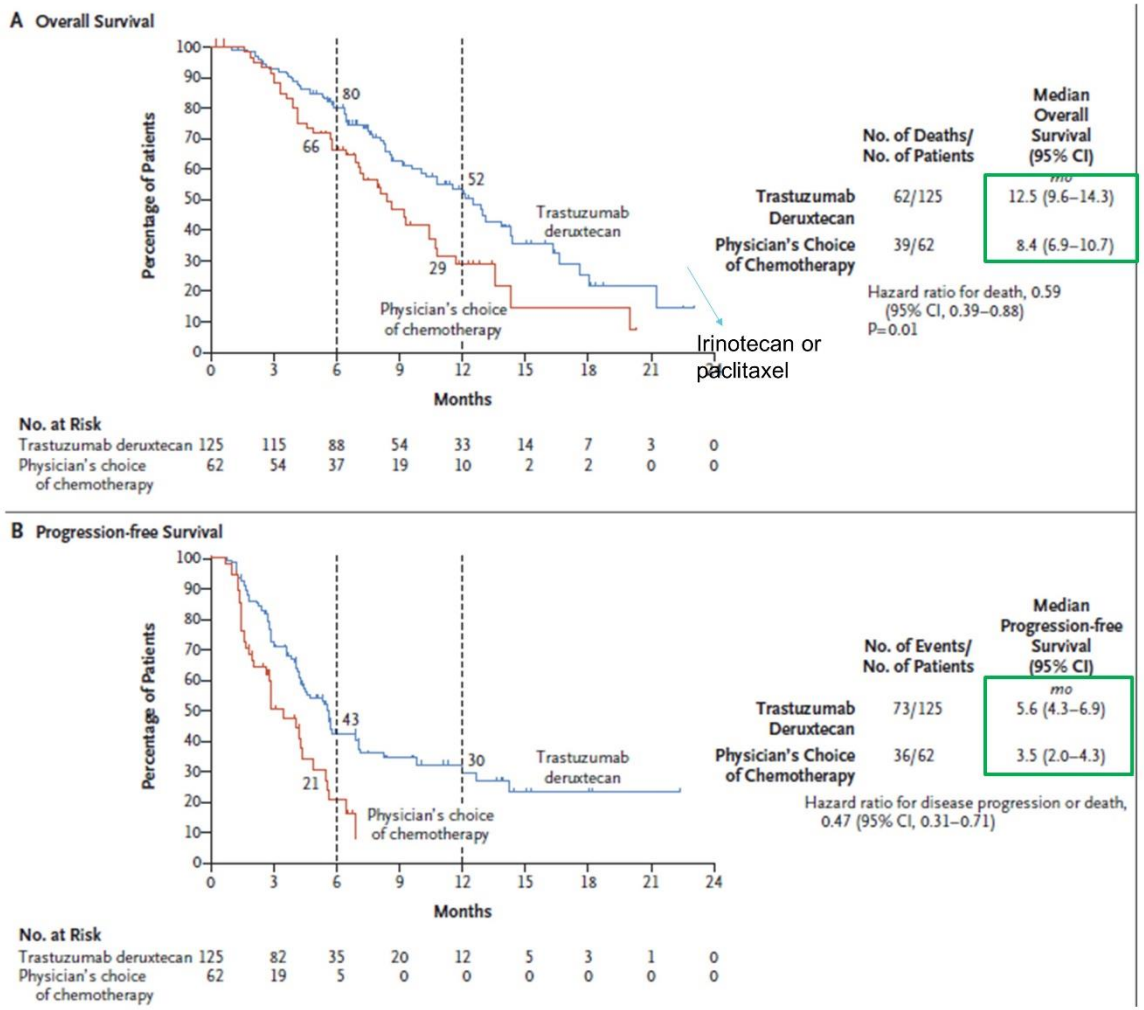
Third Line+ – Trastuzumab Deruxtecan

DESTINY Gastric01
Third line or higher
N= 125 pts
R 2:1 versus chemotherapy monotherapy
100% Asian

ORR



FDA approved 1/2021,
Label: recommend confirming persistent HER2+



Shitara *et al*. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. *NEJM* 2020

Treatment in Advanced Gastric Cancer

First line

Nivo/Pembro + Fluoropyrimidine + Platinum (CPS ≧ 5?)
HER2(+) → Trastuzumab (+Pembrolizumab) + C/T
Claudin 18.2(+) → Zolbetuximab + C/T

Second line

Ramucirumab + Paclitaxel
Taxane
Irinotecan
MSI-H/dMMR, TMB-H → Pembrolizumab

Third line

Nivolumab
TAS-102 Trifluridine/tipiracil
HER2(+) → Trastuzumab Deruxtecan
Irinotecan

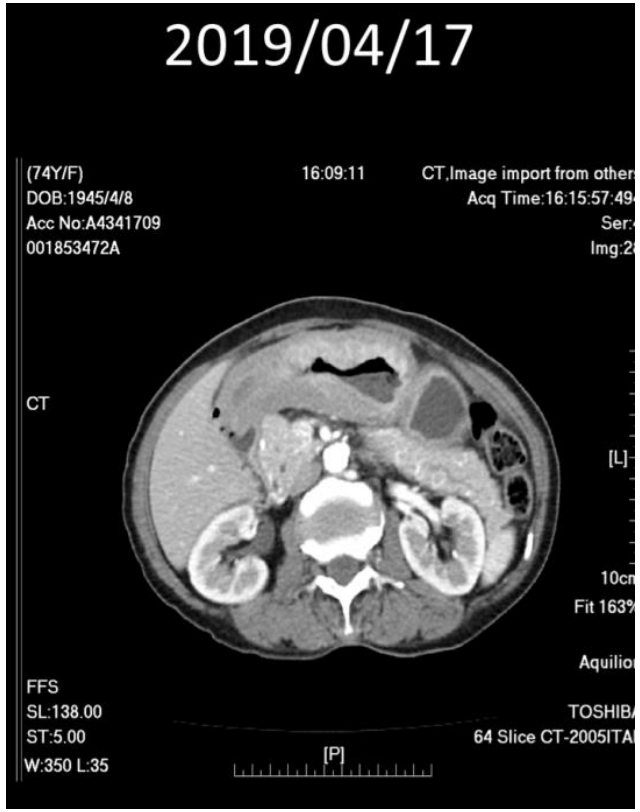
74 y/o Female, BW:33kg, BSA:1.16, ECOG PS: 2
Gastric cancer, adenocarcinoma, HER2(-), cT4bN+M0, stage **IVA**

2019/04

Initial Presentation

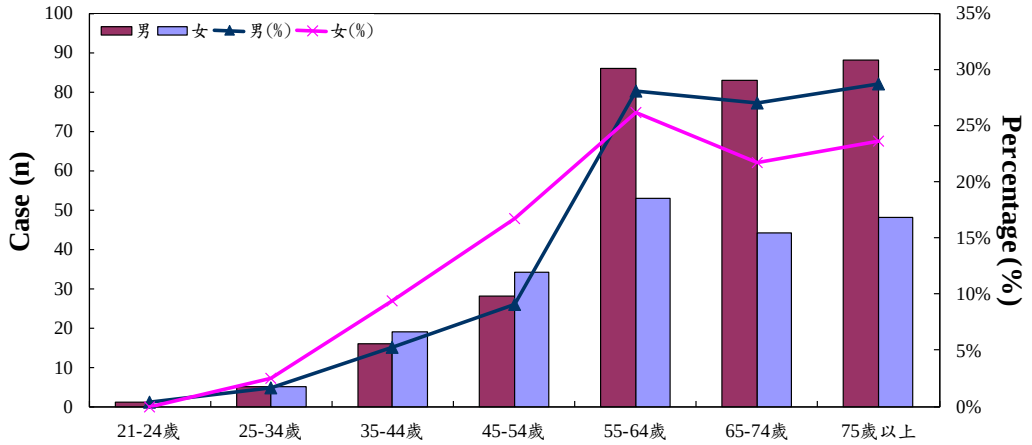
Epigastralgia
Vomiting
UGI scopy:
huge mass,
adeno

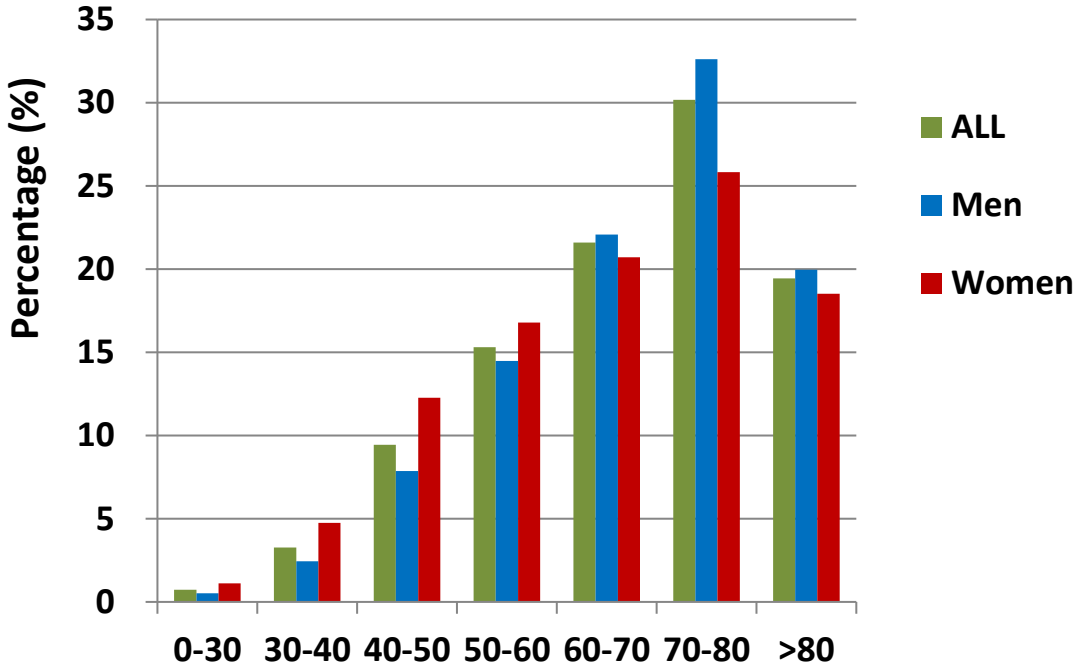
cT4bN+M0, stage **IVA**



Age Distribution of GC

VGHTC





- 台灣癌登 >40% >70 year-old
- Older patients, underrepresented in clinical trials

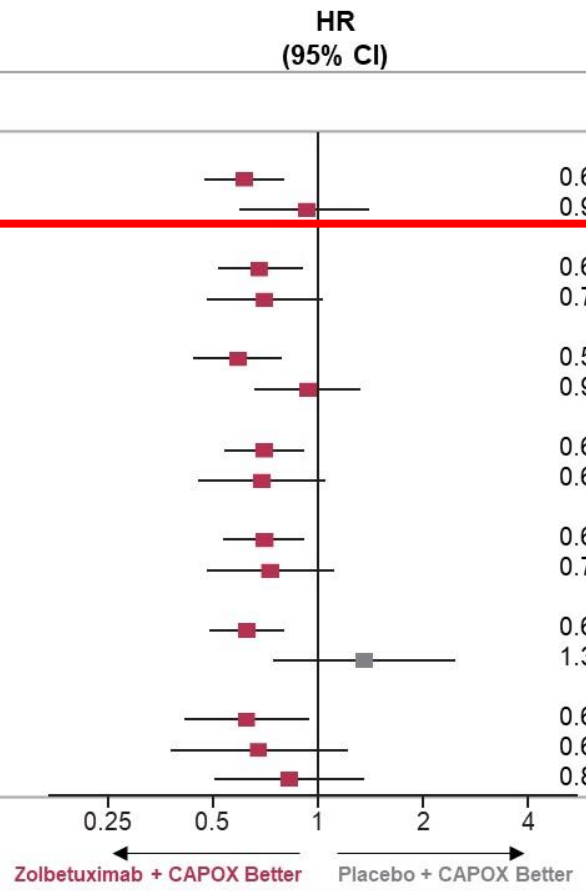
項　目	發生個案	
	男性	女性
個案數(人)	2,464	1,793
年齡中位數	69	69

Baseline Characteristics

		Zolbetuximab + CAPOX (N = 254)	Placebo + CAPOX (N = 253)
Age, years (range)	Median	61.0 (22–82)	59.0 (21–83)
Sex, n (%)	Male	159 (62.6)	156 (61.7)
Region, n (%)	Asia[a]	157 (61.8)	158 (62.5)
	Non-Asia	97 (38.2)	95 (37.5)
Organs with metastases, n (%)	0–2	189 (74.4)	188 (74.3)
	≥3	65 (25.6)	65 (25.7)
Prior gastrectomy, n (%)	No	179 (70.5)	178 (70.4)
	Yes	75 (29.5)	75 (29.6)
Primary site, n (%)	Stomach	219 (86.2)	209 (82.6)
	GEJ	35 (13.8)	44 (17.4)
Lauren classification, n (%)	Diffuse	87 (34.4)	100 (39.5)
	Intestinal	36 (14.2)	41 (16.2)
	Mixed/others/unknown[b]	130 (51.2)	112 (44.3)
ECOG PS[c], n (%)	0	108 (42.7)	108 (43.2)
	1	145 (57.3)	142 (56.8)

[a]76 patients assigned to zolbetuximab + CAPOX and 69 patients assigned to placebo + CAPOX were from China; [b]Patients with Lauren classification "unknown" represents patients with adenocarcinoma without Lauren classification; [c]One patient in the zolbetuximab arm and 3 patients in the placebo arm with ECOG PS missing at baseline who were enrolled with ECOG PS 0 or 1 at screening are not shown here (did not receive treatment and therefore did not have baseline measurements at cycle 1 day 1).

Primary End Point: PFS[a] Subgroup Analysis



Subgroup	HR (95% CI)	Zolbetuximab + CAPOX *Events/patients, n/N*	Placebo + CAPOX *Events/patients, n/N*
Age			
≤65 years	0.606 (0.463–0.794)	92/176	130/180
>65 years	0.917 (0.596–1.410)	45/78	42/73
Sex			
Male	0.679 (0.513–0.898)	92/159	110/156
Female	0.700 (0.474–1.035)	45/95	62/97
Region			
Asia[b]	0.583 (0.436–0.781)	82/157	109/158
Non-Asia	0.928 (0.645–1.336)	55/97	63/95
Number of metastatic sites			
0–2	0.691 (0.529–0.904)	97/189	125/188
≥3	0.682 (0.445–1.045)	40/65	47/65
Prior gastrectomy			
No	0.696 (0.533–0.909)	97/179	125/178
Yes	0.726 (0.472–1.114)	40/75	47/75
Primary site			
Stomach	0.619 (0.484–0.791)	116/219	149/209
GEJ	1.351 (0.731–2.496)	21/35	23/44
Lauren classification			
Diffuse	0.620 (0.411–0.936)	38/87	60/100
Intestinal	0.675 (0.375–1.217)	21/36	26/41
Mixed/other[c]	0.824 (0.499–1.358)	28/54	36/48

PFS was significantly longer in patients treated with zolbetuximab + CAPOX across most subgroups

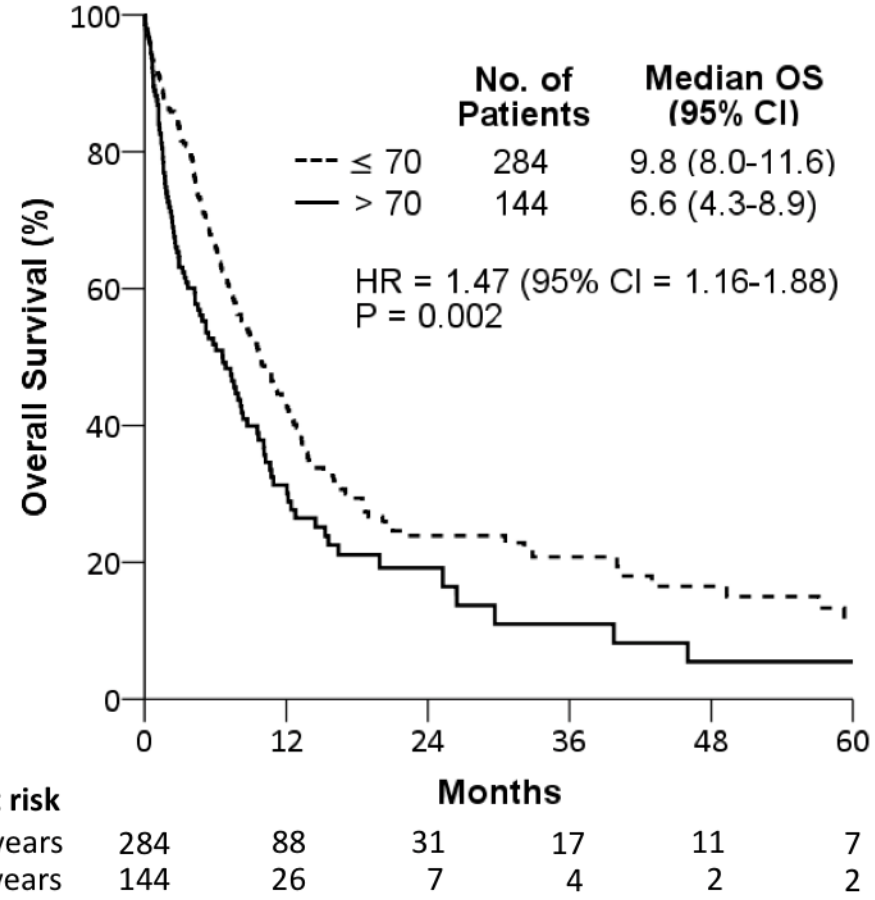
Data cutoff: October 7, 2022.
[a]Per RECIST version 1.1 by independent review committee; [b]76 patients assigned to zolbetuximab + CAPOX and 69 patients assigned to placebo + CAPOX were from China; [c]Patients with Lauren classification "Mixed/other" include those classified as "mixed" or "other," but does not include patients with an "unknown" or missing Lauren classification ("unknown" represents patients with adenocarcinoma without Lauren classification).

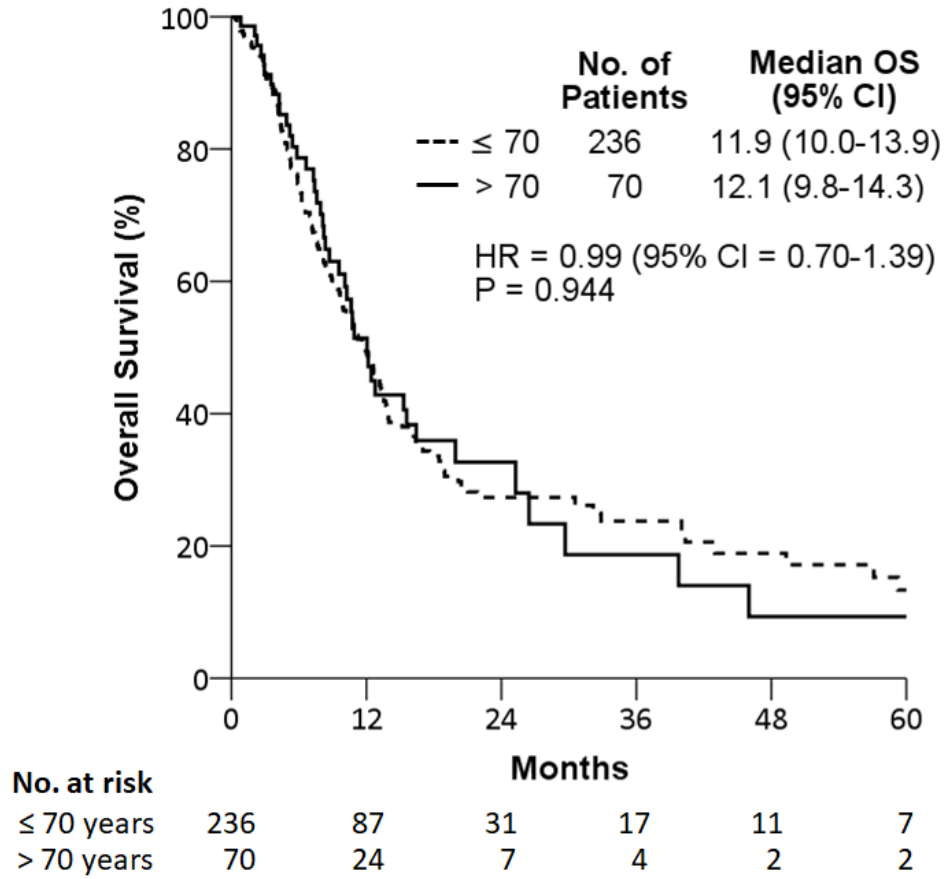
mGC in VGHTC

Overall patients

2009-2019 (n=428)

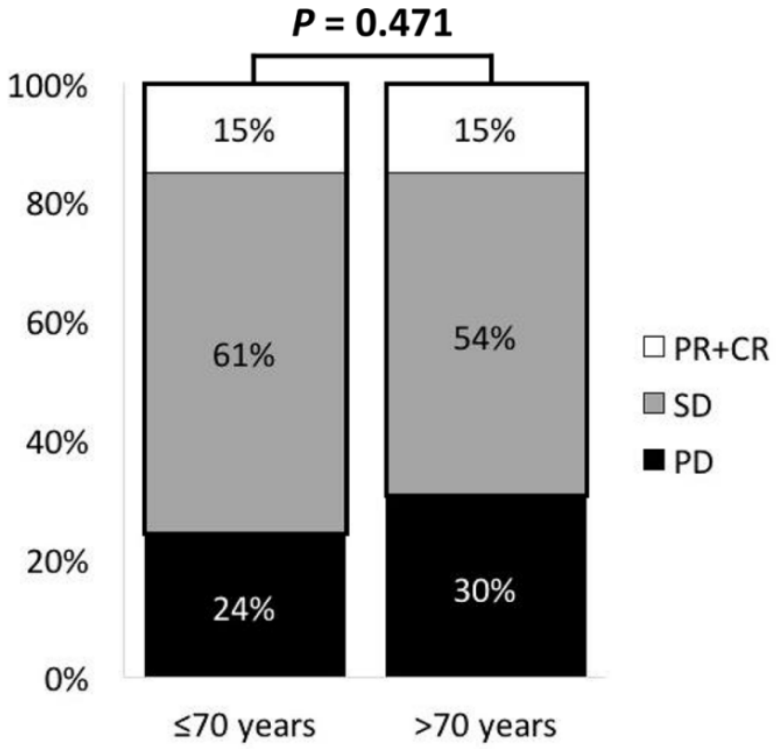
Patients with chemotherapy





Clin Med Insights Oncol. 2022 Sep 18;16

mGC in VGHTC
2009-2019

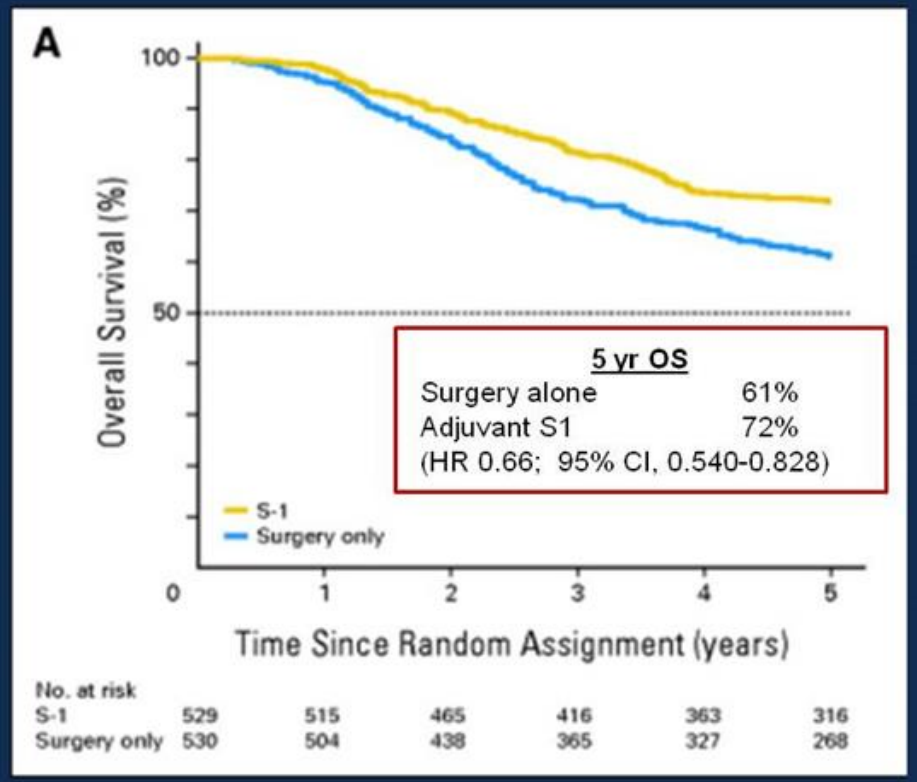


	GRADE 3-4				
	≤70YEARS (N=236)		>70YEARS (N=70)		*P*
Leukopenia, n (%)	14	(5.9)	1	(1.4)	.205
Neutropenia, n (%)	25	(10.6)	7	(10.0)	1.000
Anemia, n (%)	57	(24.2)	14	(20.0)	.574
Thrombocytopenia, n (%)	27	(11.4)	4	(5.7)	.242
Febrile neutropenia, n (%)	8	(3.4)	2	(2.9)	1.000

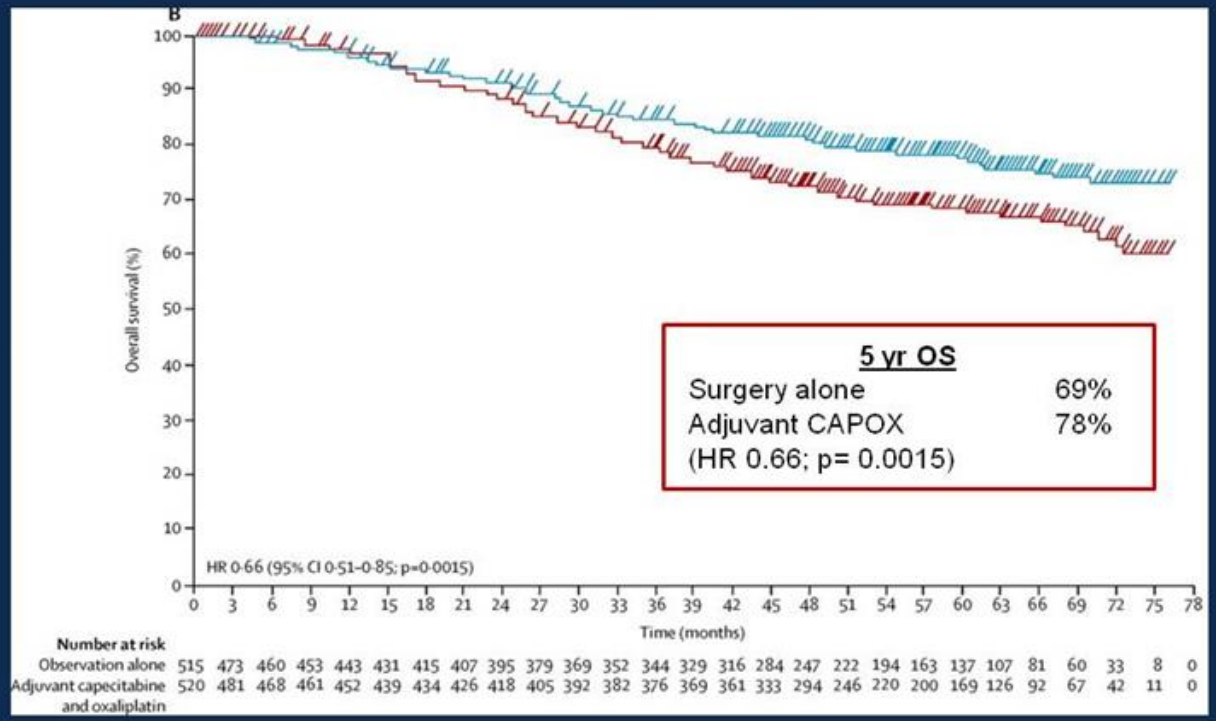
Clin Med Insights Oncol. 2022 Sep 18;16

Adjuvant chemotherapy following D2 gastrectomy is a standard of care in Asia

ACTS-GC



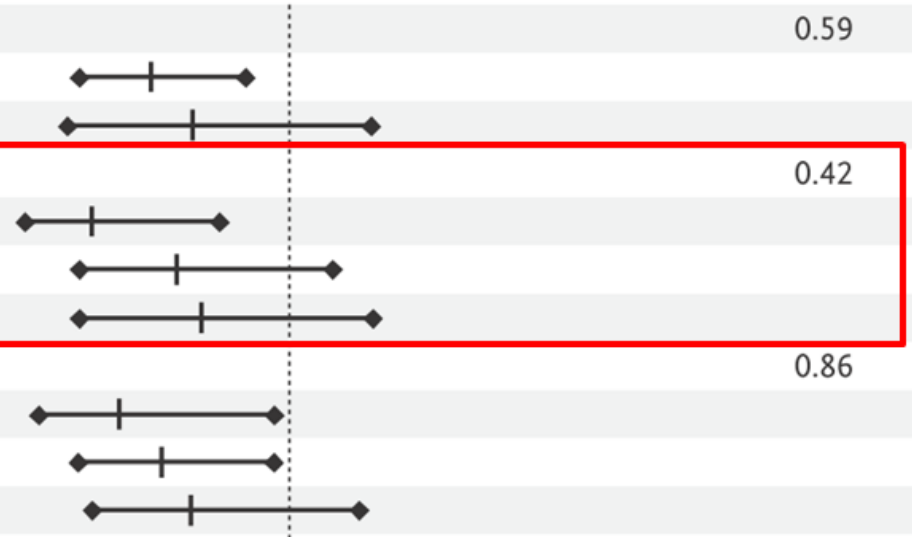
CLASSIC



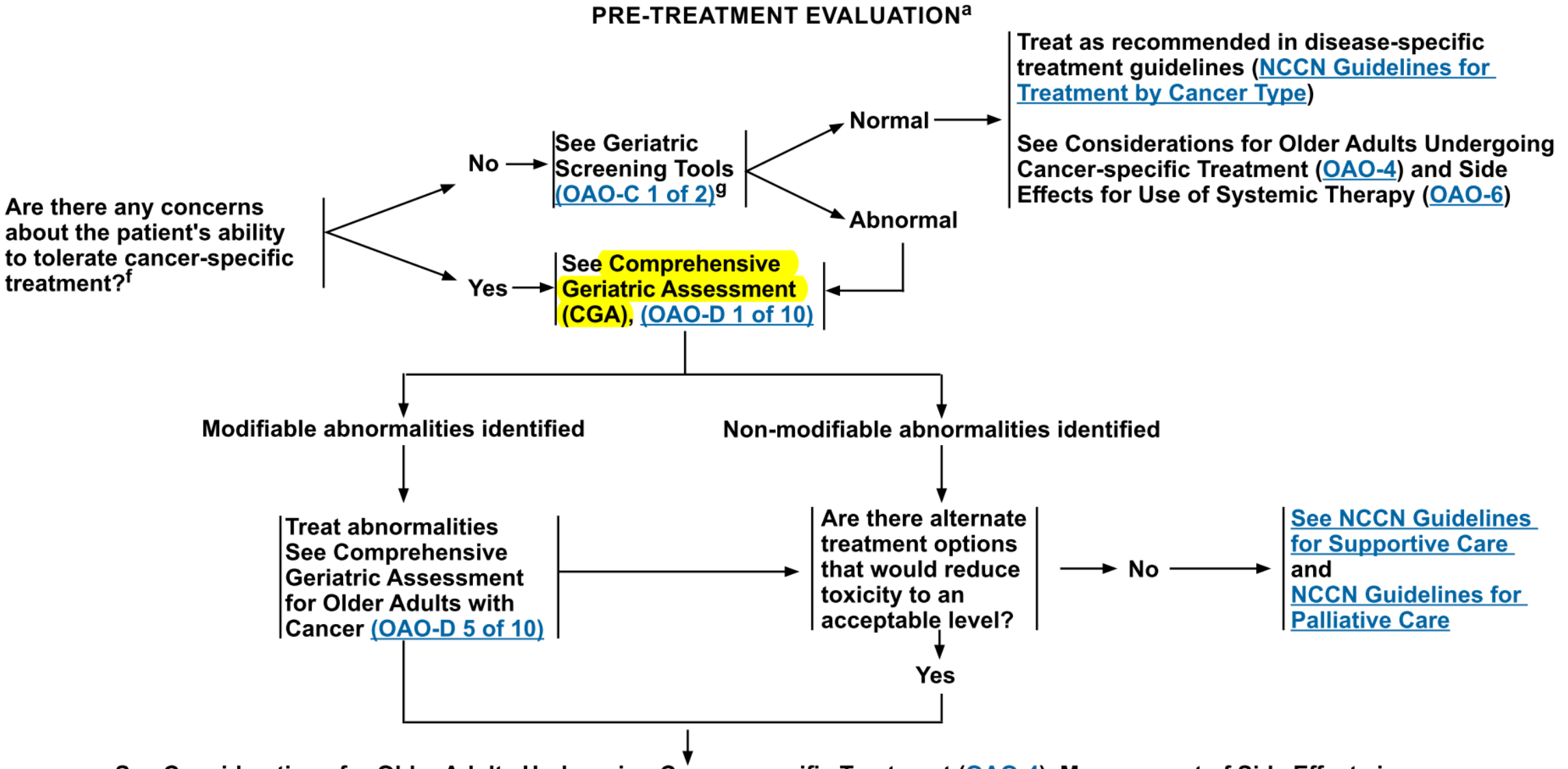
Sasako et al. J Clin Oncol 2011
Noh et al Lancet Oncol 2014

ACTS-GC

Baseline Characteristic	S-1 No. of deaths/total no. of patients	Surgery Only No. of deaths/total no. of patients	Hazard Ratio for Death (95% CI)	P Value for Interaction
Sex				0.59
Male	70/358	101/362		
Female	27/157	36/157		
Age				0.42
<60 yr	27/192	46/191		
60–69 yr	36/193	54/211		
70–80 yr	34/130	37/117		
Cancer stage (Japanese classification)				0.86
II	24/232	38/233		
IIIA	43/194	63/203		
IIIB	30/89	36/83		



N Engl J Med 2007; 357:1810-1820


PRE-TREATMENT EVALUATION[a]
Are there any concerns about the patient's ability to tolerate cancer-specific treatment?[f]
No
See Geriatric Screening Tools (OAO-C 1 of 2)[g]
Normal
Abnormal
Treat as recommended in disease-specific treatment guidelines (NCCN Guidelines for Treatment by Cancer Type)
See Considerations for Older Adults Undergoing Cancer-specific Treatment (OAO-4) and Side Effects for Use of Systemic Therapy (OAO-6)
Yes
See Comprehensive Geriatric Assessment (CGA), (OAO-D 1 of 10)
Modifiable abnormalities identified
Non-modifiable abnormalities identified
Treat abnormalities See Comprehensive Geriatric Assessment for Older Adults with Cancer (OAO-D 5 of 10)
Are there alternate treatment options that would reduce toxicity to an acceptable level?
No
See NCCN Guidelines for Supportive Care and NCCN Guidelines for Palliative Care
Yes
See Considerations for Older Adults Undergoing Cancer-specific Treatment (OAO-4), Management of Side Effects in Older Adults Undergoing Cancer-specific Treatment (OAO-6), and NCCN Guidelines for Supportive Care

Comprehenisve Geriatric Assessment

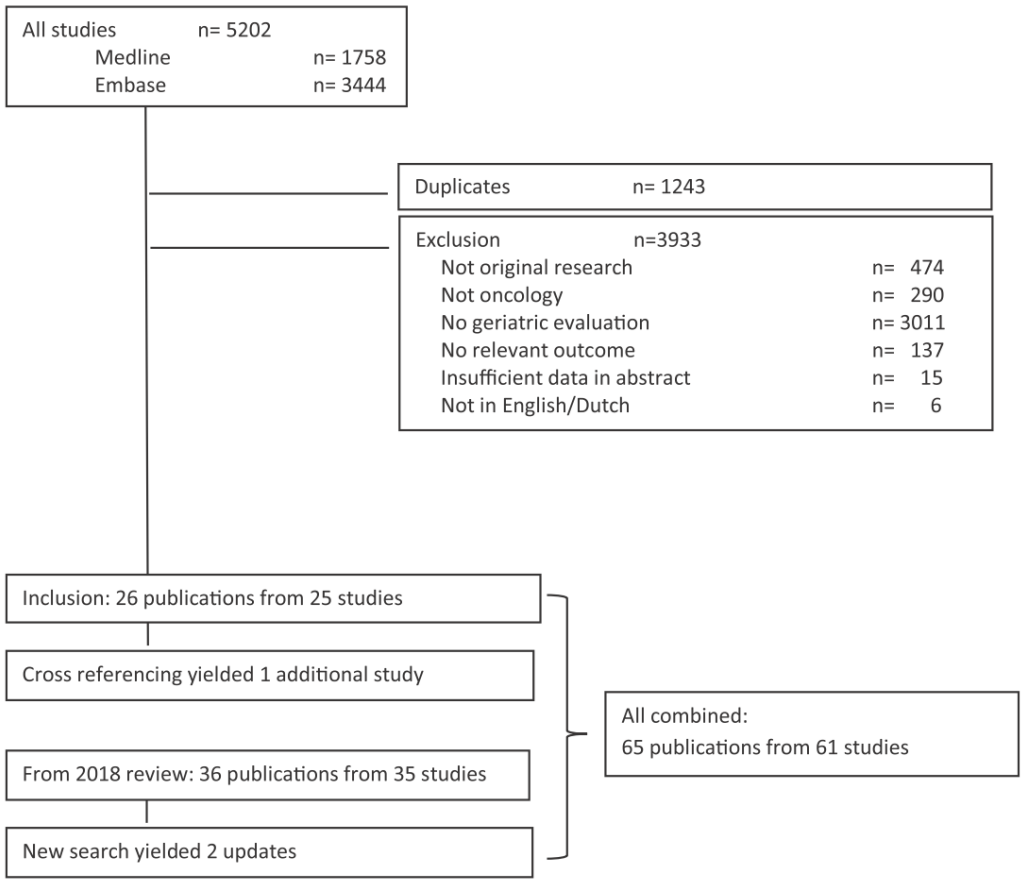
表一：常用的評估工具及施測所需時間[2,3]

問題	評估工具	平均施測所需時間(分)
視力障礙	Snellen 視力量表	2
聽力障礙	輕聲說話	1
日常生活活動功能	Katz 日常生活活動功能量表	2-4
	Lawton 工具性日常生活活動功能量表	3-5
行動/平衡	起身-行走測試	1
	Tinetti 平衡及步態評估表	5-15
認知障礙	簡短智能測驗	5-15
	畫時鐘測驗	2
憂鬱症	老年憂鬱量表(15 題簡式)	3-6
營養不良	身高/體重	2
尿失禁	詢問關於尿失禁問題	1

Formosan Journal of Medicine, 7(3), 2003

Geriatric assessment in the management of older patients with cancer – A systematic review (update)

Marije Hamaker [a,*], Cecilia Lund [b], Marthe te Molder [c], Pierre Soubeyran [d], Hans Wildiers [e], Lieke van Huis [f], Siri Rostoft [g,h]



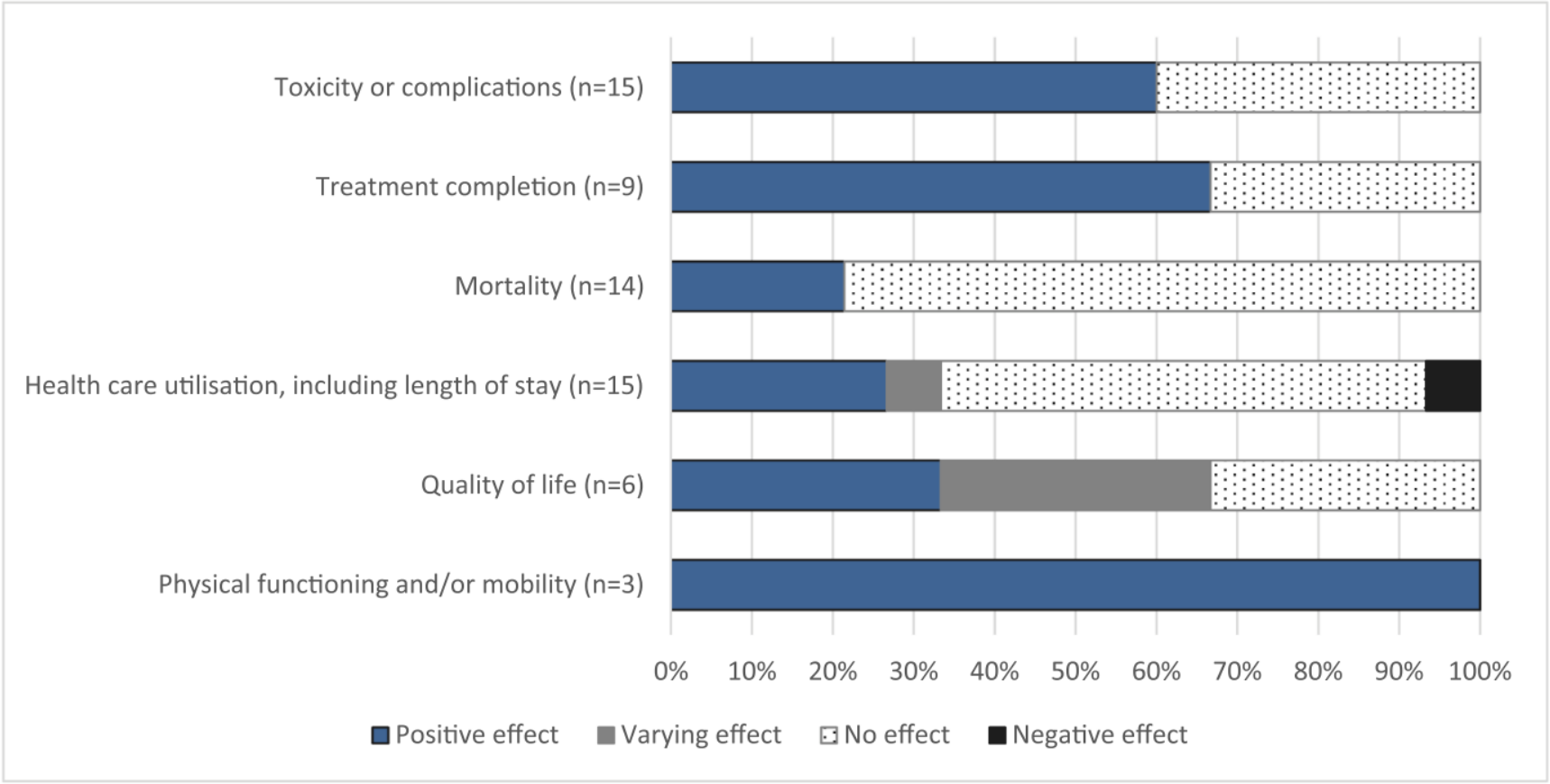
J Geriatr Oncol. 2022 Jul;13(6):761-777.

Main Goals of Geriatric Assessment

- Tailor the oncologic treatment decision
  - prevent both over- and undertreatment
  - improve outcome: complications/toxicity, rates, treatment completion, mortality
- Implement interventions
  - optimizing the patient ’ s health status
  - leading to better ability to tolerate treatment

J Geriatr Oncol. 2022 Jul;13(6):761-777.

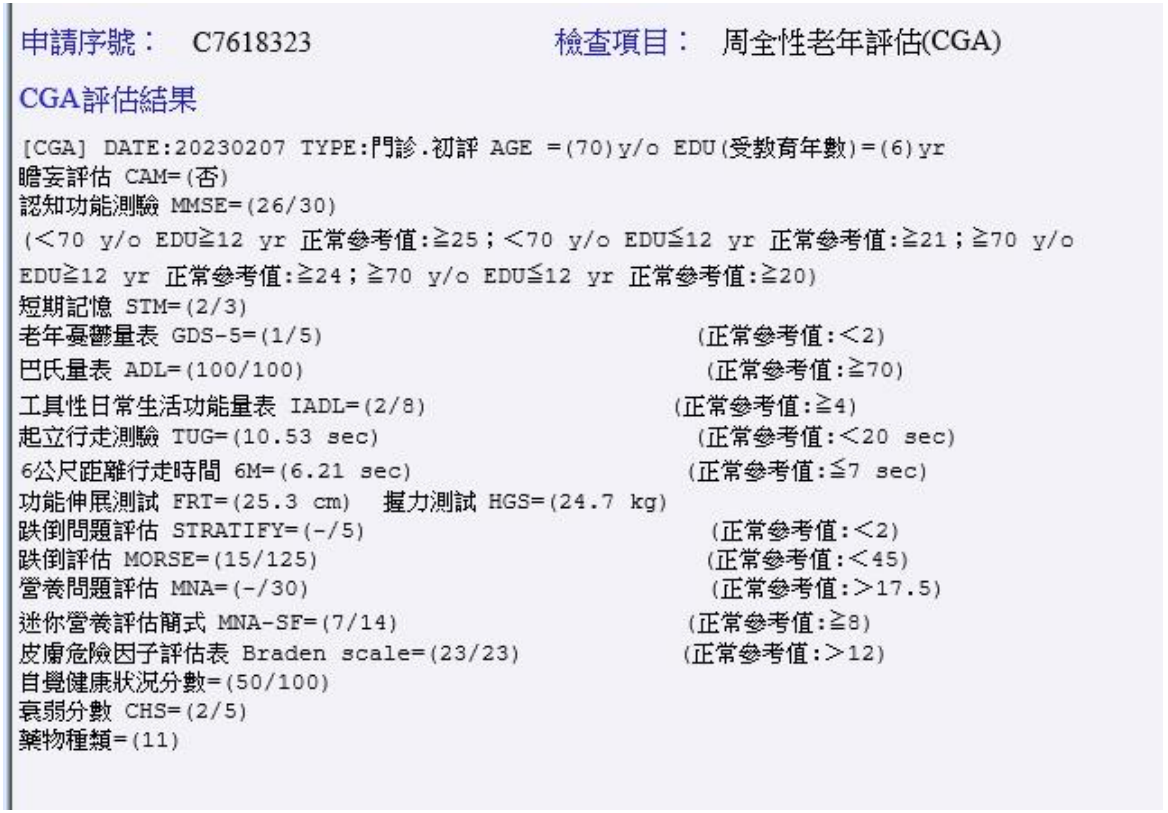
The Effect of Geriatric Assessment



J Geriatr Oncol. 2022 Jul;13(6):761-777.

高齡消化道癌症收案 (111-112年)

- Total: 27位
  - Male: 13, Female: 14
  - Median age: 73 y/o (range: 65-91 y/o)
  - Gastric cancer: 11
    pancreatic cancer: 15
    cholangiocarcinoma: 1



申請序號： C7618323　　檢查項目： 周全性老年評估(CGA)

CGA評估結果

[CGA] DATE:20230207 TYPE:門診.初評 AGE =(70)y/o EDU(受教育年數)=(6)yr
瞻妄評估 CAM=(否)
認知功能測驗 MMSE=(26/30)
(<70 y/o EDU≧12 yr 正常參考值:≧25；<70 y/o EDU≦12 yr 正常參考值:≧21；≧70 y/o EDU≧12 yr 正常參考值:≧24；≧70 y/o EDU≦12 yr 正常參考值:≧20)
短期記憶 STM=(2/3)
老年憂鬱量表 GDS-5=(1/5) (正常參考值:<2)
巴氏量表 ADL=(100/100) (正常參考值:≧70)
工具性日常生活功能量表 IADL=(2/8) (正常參考值:≧4)
起立行走測驗 TUG=(10.53 sec) (正常參考值:<20 sec)
6公尺距離行走時間 6M=(6.21 sec) (正常參考值:≦7 sec)
功能伸展測試 FRT=(25.3 cm)　握力測試 HGS=(24.7 kg)
跌倒問題評估 STRATIFY=(-/5) (正常參考值:<2)
跌倒評估 MORSE=(15/125) (正常參考值:<45)
營養問題評估 MNA=(-/30) (正常參考值:>17.5)
迷你營養評估簡式 MNA-SF=(7/14) (正常參考值:≧8)
皮膚危險因子評估表 Braden scale=(23/23) (正常參考值:>12)
自覺健康狀況分數=(50/100)
衰弱分數 CHS=(2/5)
藥物種類=(11)

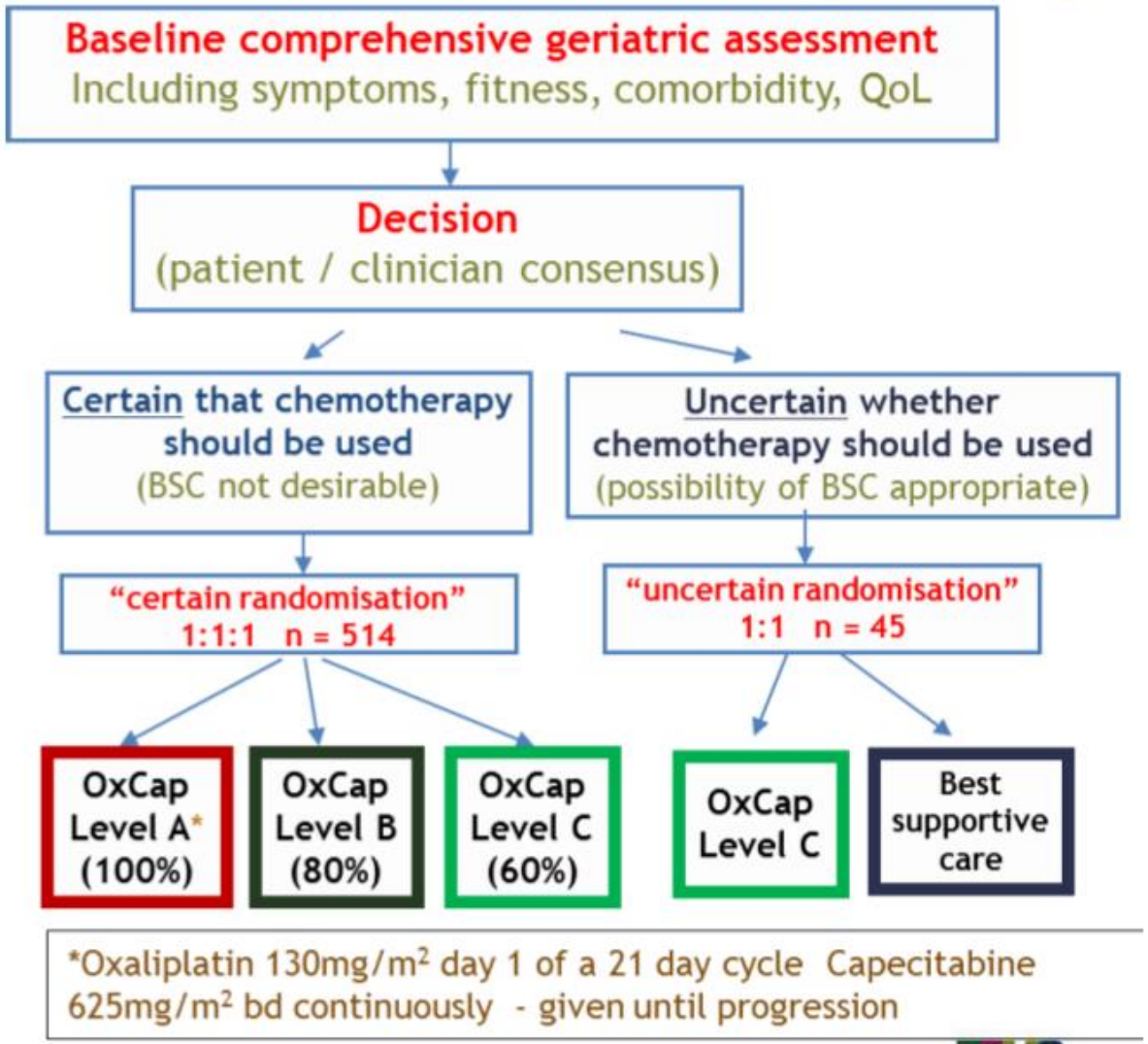
Item (total:27)	Number	Percentage %
認知功能障礙	3	11%
憂鬱情緒	6	22%
一個月內跌倒	3	11%
排便問題	12	44%
視力不良	13	48%
聽力不良	5	19%
睡眠問題	7	26%
營養不良	20	74%
多重藥物	27	100%

ELDERLY OR LESS FIT PATIENTS

GO2 Study

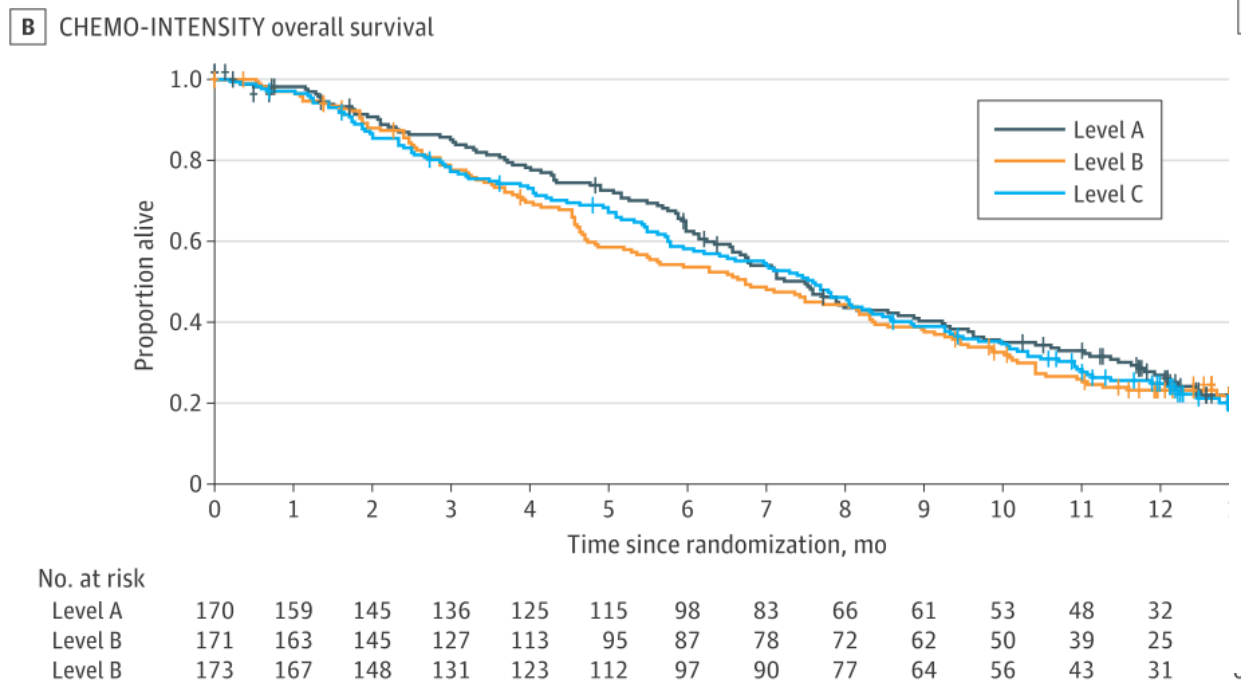
- **Phase III, randomised, multi-centre, prospective, controlled, open label, non-inferiority trial**

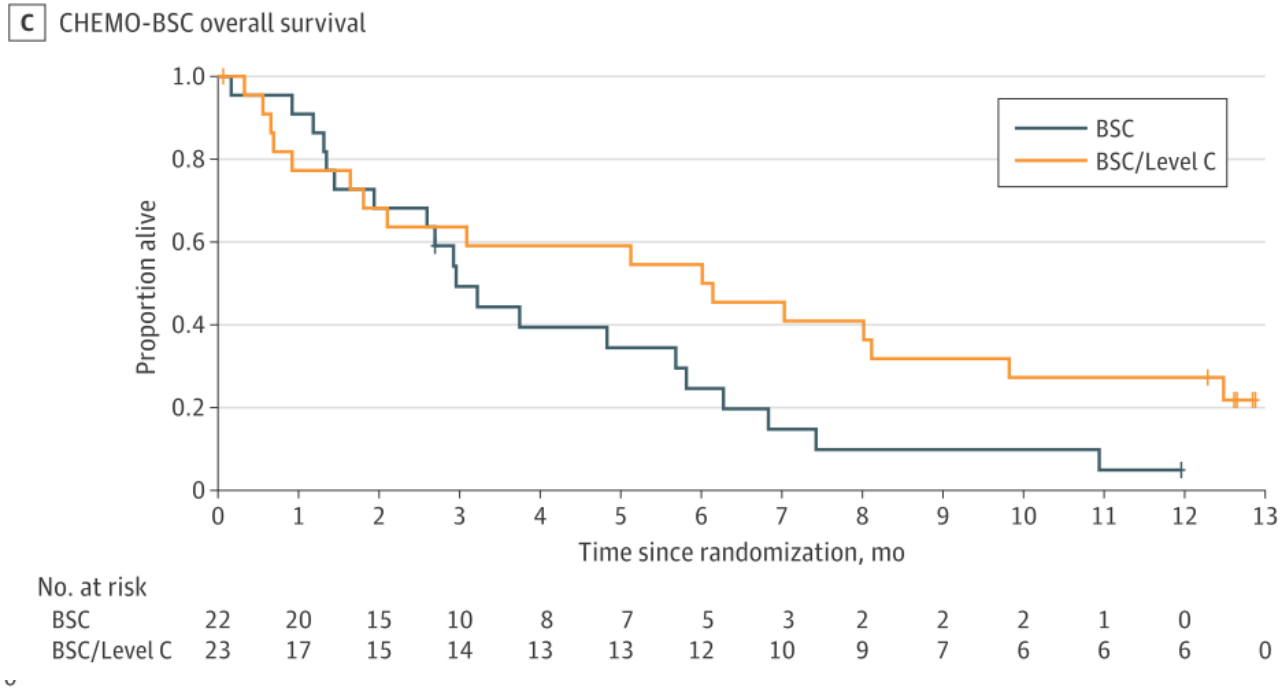
- Eligibility:
  - Not fit for full-dose 3-drug chemotherapy,
  - Suitable for reduced intensity chemotherapy.



Hall PS et al. *JAMA Oncol*. 2021 Aug 1;7(8):1249

Elderly/Less Fit Patients
GO2 Study





CapOx
Level A 100% of dose
Level B 80% of dose
Level C 60% of dose

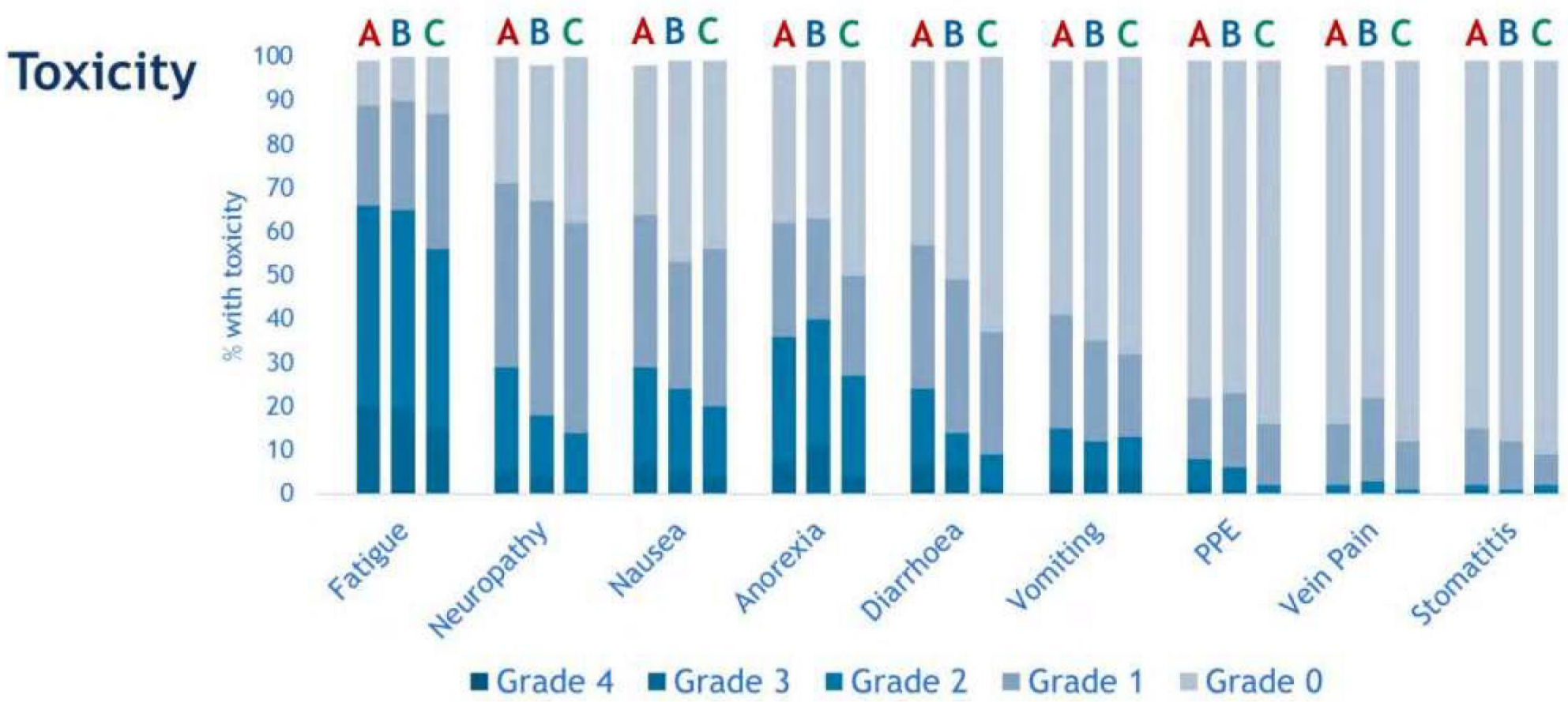
Noninferiority

median 6.1 vs 3.0 months
HR = 0.69 [95% CI, 0.32-1.48], P = 0.34

JAMA Oncol. 2021;7(6):869-877.

ELDERLY OR LESS FIT PATIENTS

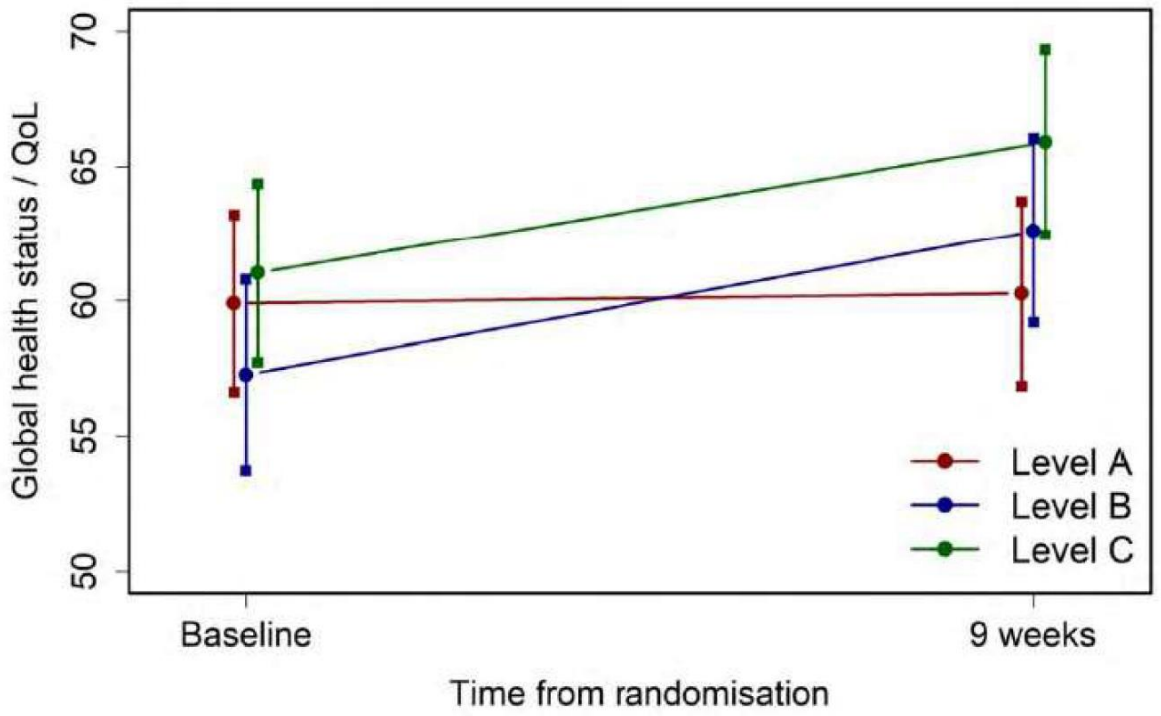
GO2 Study - Full vs Reduced-Intensity Chemotherapy



Hall PS et al. *JAMA Oncol*. 2021 Aug 1;7(8):1249

Elderly/Less Fit Patients

- Geriatric assessment
  - symptoms, fitness, comorbidities, QoL, family support
- Less-intensive therapy



JAMA Oncol. 2021;7(6):869-877.

Treatment of Advanced Gastric Cancer

First line

Nivo/Pembro + Fluoropyrimidine + Platinum (CPS ≧ 5?)
HER2(+) → Trastuzumab (+Pembrolizumab) + C/T
Claudin 18.2(+) → Zolbetuximab + C/T

Second line

Ramucirumab + Paclitaxel
Taxane
Irinotecan
MSI-H/dMMR, TMB-H → Pembrolizumab

Third line

Nivolumab
TAS-102 Trifluridine/tipiracil
HER2(+) → Trastuzumab Deruxtecan
Irinotecan

Thank you!!