Novel Advances for Esophageal, Gastric and GE Junction Tumors

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Current management strategies

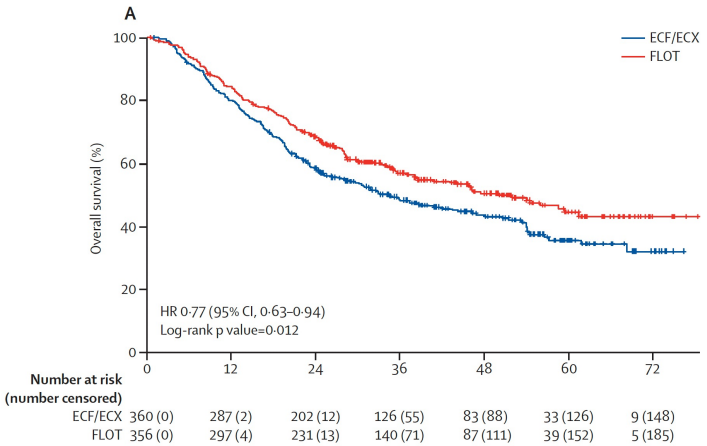
Treatment options	Esophageal SCC (ESCC)	Esophageal Adeno (AC)	GEJ AC	Gastric AC
Definitive ChemoXRT	X			
Neoadjuvant ChemoXRT + Surgery	X	X	X	
Chemo + Surgery + Chemo		X	X	X
Surgery + Chemo				X

Can we challenge the treatment paradigm?

Tepper J et al. J Clin Oncol. 2008 Mar 1;26(7):1086-92
Cunningham D et al. N Engl J Med. 2006 Jul 6;355(1):11-20
Leichman LP et al. J Clin Oncol. 2011 Dec 1;29(34):4555-60
Conroy T et al. Lancet Oncol. 2014 Mar;15(3):305-14

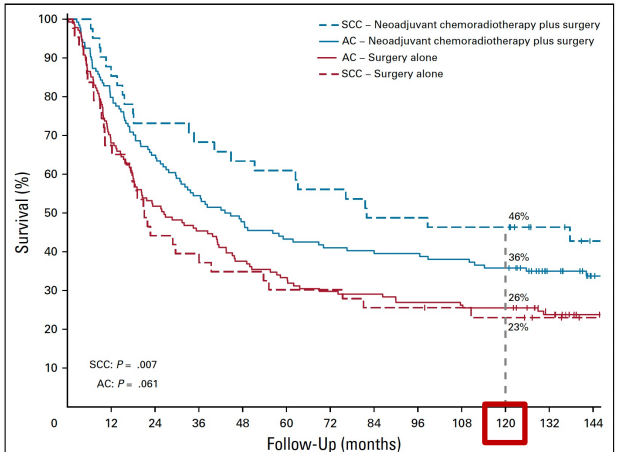
Neoadjuvant and Perioperative Strategies

FLOT4



FLOT4 (GEJ I-III 56% / Ga Ca 44%) mOS 50 mo

CROSS



ESCC 23%, ADC 75%

Al-Batran SE et al Lancet. 2019 May 11;393(10184):1948-1957

Eyck BM et al J Clin Oncol. 2021 Jun 20;39(18):1995-2004

Neo-AEGIS: FLOT Amendment June 2018

FLOT Regimen

- T docetaxel d1 50 mg/m² iv inf.
- O oxaliplatin d1 85 mg/m² iv inf.
- L leucovorin d1 200 mg/m² iv inf.
- F 5-FU d1 2.600 mg/m² iv 24h inf.
  - repeated every 2 weeks

Esophageal and GEJ adenocarcinoma:

Esophageal and AEG I-III

cT2-3N0-3M0

Non-inferiority (n= 540-powered as per first futility analysis Dec 2018)

R

EC(O)F(X) x 3 or FLOT x 4 → Surgery → EC(O)F(X) x 3 Or FLOT x 4

Arm A

362 evaluable patients, 178 CROSS, 184 MAGIC/FLOT (157/27)

Neo CRT (CROSS) wCP-RT(41.4Gy)+Surgery

Arm B

Primary endpoint: Overall survival

Secondary end points: Disease free survival; Time to treatment failure: TRG: R0: Toxicity: Postoperative complications; HR-QL

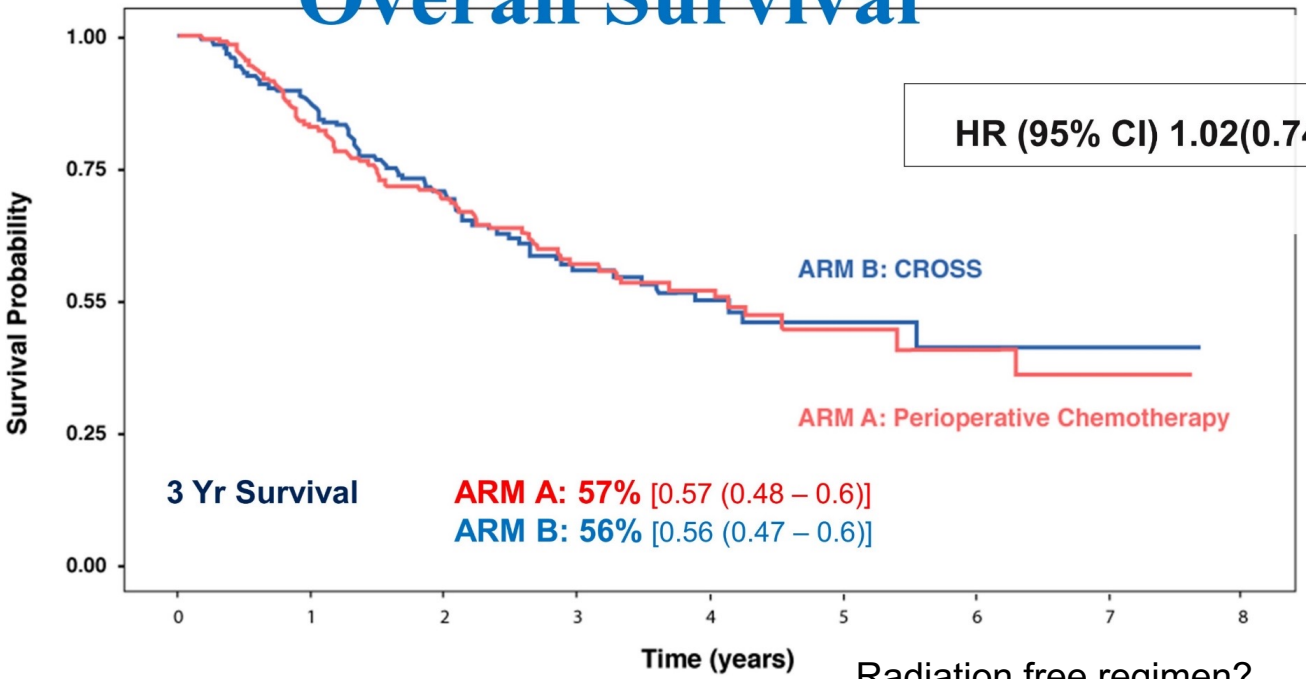
Al-Batran SE, et al. Lancet 2019; 393:1948-57

Results: Pathologic Response, TRG and R status

	ARM A (Chemo)	ARM B (CROSS)
ypN0	44.5%	60%
ypT3	59.6%	52%
Change from cN1-ypN+	-5%	-20%
R0	82%	95%
pCR	5%	16%
TRG1	5.3%	17.3%
TRG 2	6.7%	24.4%
Major Path Response	12%	31.7%
TRG 3	23.4%	32.1%
TRG 4	41.6%	22.4%
TRG 5	22.8%	3.8%

Slide Courtesy - Reynolds JV et al. J Clin Onc 2021 39:15_suppl, 4004-4004

Overall Survival



HR (95% CI) 1.02(0.74-1.42)

Radiation free regimen?

NUMBER AT RISK

ARM A:	180	132	90	55	37	14	9	7	0
ARM B:	175	139	92	52	25	11	7	6	0

ASCO Gastrointestinal Cancers Symposium

JCOG Japan Clinical Oncology Group

A randomized controlled phase III trial comparing two chemotherapy regimen and chemoradiotherapy regimen as neoadjuvant treatment for locally advanced esophageal cancer, JCOG1109 NExT study

Ken Kato[1], Yoshinori Ito[2], Hiroyuki Daiko[3], Soji Ozawa[4], Takashi Ogata[5], Hiroki Hara[6], Takashi Kojima[7], Tetsuya Abe[8], Takeo Bamba[9], Masaya Watanabe[10], Hirofumi Kawakubo[11], Yuichi Shibuya[12], Yasuhiro Tsubosa[13], Naoki Takegawa[14], Takeshi Kajiwara[15], Hideo Baba[16], Masaki Ueno[17], Ryunosuke Machida[18], Kenichi Nakamura[18], Yuko Kitagawa[11]

Japan Esophageal Oncology Group of Japan Clinical Oncology Group (JCOG)

PRESENTED BY: Ken Kato, National Cancer Center Hospital, Tokyo, Japan

JCOG1109 NExT: Study Design

Key eligibility criteria
- Histologically proven ESCC
- ECOG PS 0-1
- cStage IB, II, III (nonT4) (UICC TNM7th)
- Age 20-75 y.o.
- R0 esophagectomy is expected

Adjustment factors
- Institution
- cT1-2 / T3

Enrollment started 12/2012

R

Neoadjuvant CF
(5-fluorouracil + cisplatin)[a]
Q3W x 2 course **6 weeks**

Neoadjuvant DCF
(5-fluorouracil + cisplatin + docetaxel)[b]
Q3W x 3 course **9 weeks**

Neoadjuvant CF+RT
(5-fluorouracil + cisplatin + RT 41.4 Gy)[c]
Q4W x 2 course **8 weeks**

Transthoracic esophagectomy with regional lymphadenectomy (D2≤)[d]

Minimally invasive and open

Primary Endpoint: OS
Secondary endpoints:
PFS, % R0 resection, RR, pathCR and AEs.

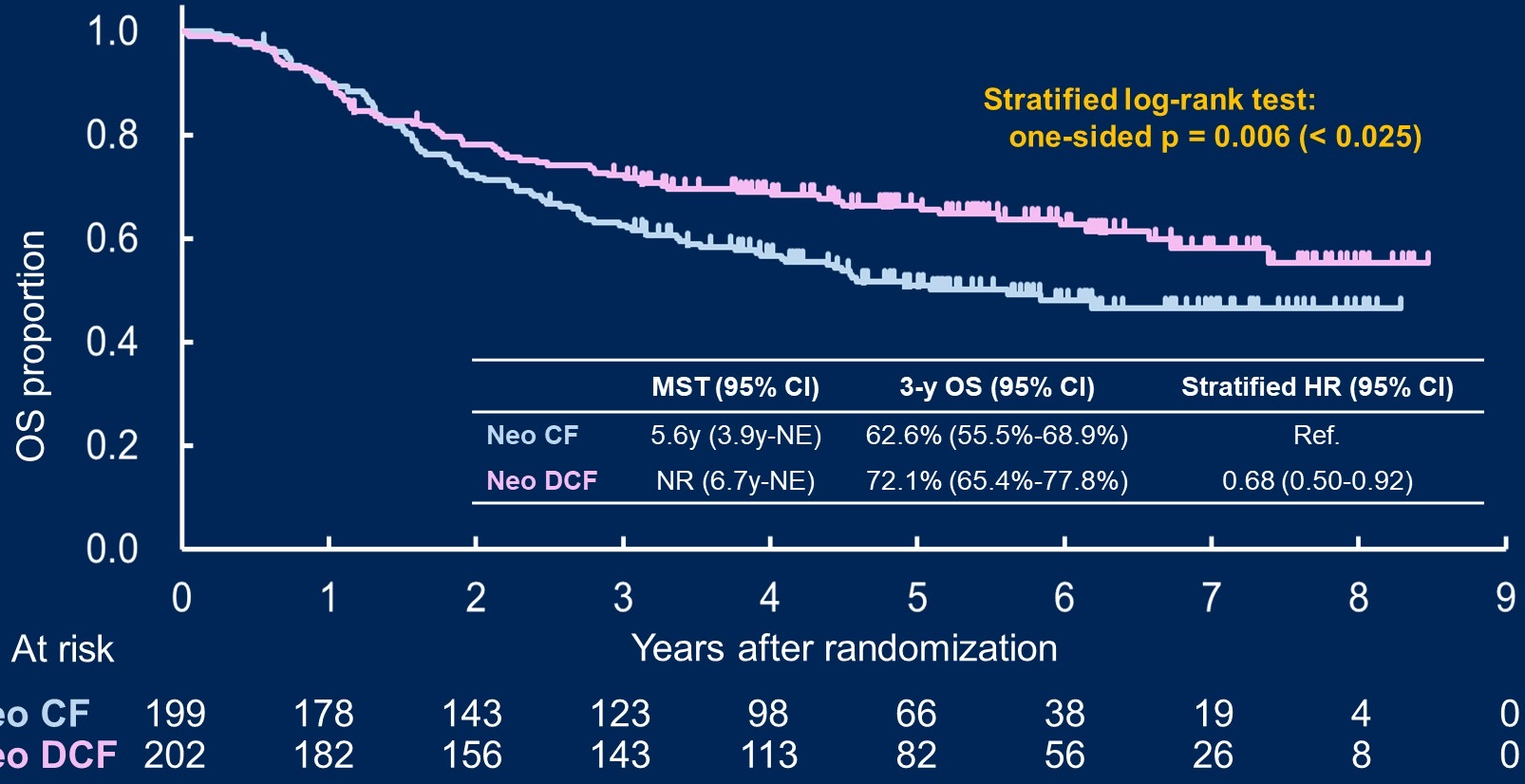
Minimium follow up 36 months

[a]5-FU 800 mg/m^2 IV days 1-5, cisplatin 80 mg/m^2 IV day1
[b]5-FU 750 mg/m^2 IV days 1-5, cisplatin 70 mg/m^2 IV day1, docetaxel 70 mg/m^2 IV (day1)
[c]5-FU 1000 mg/m^2 IV days 1-4, cisplatin 75 mg/m^2 IV day1

Nakamura et al, Jpn J Clin Oncol 2013;43(7)752–755

PRESENTED BY: Nataliya Uboha, MD, PhD

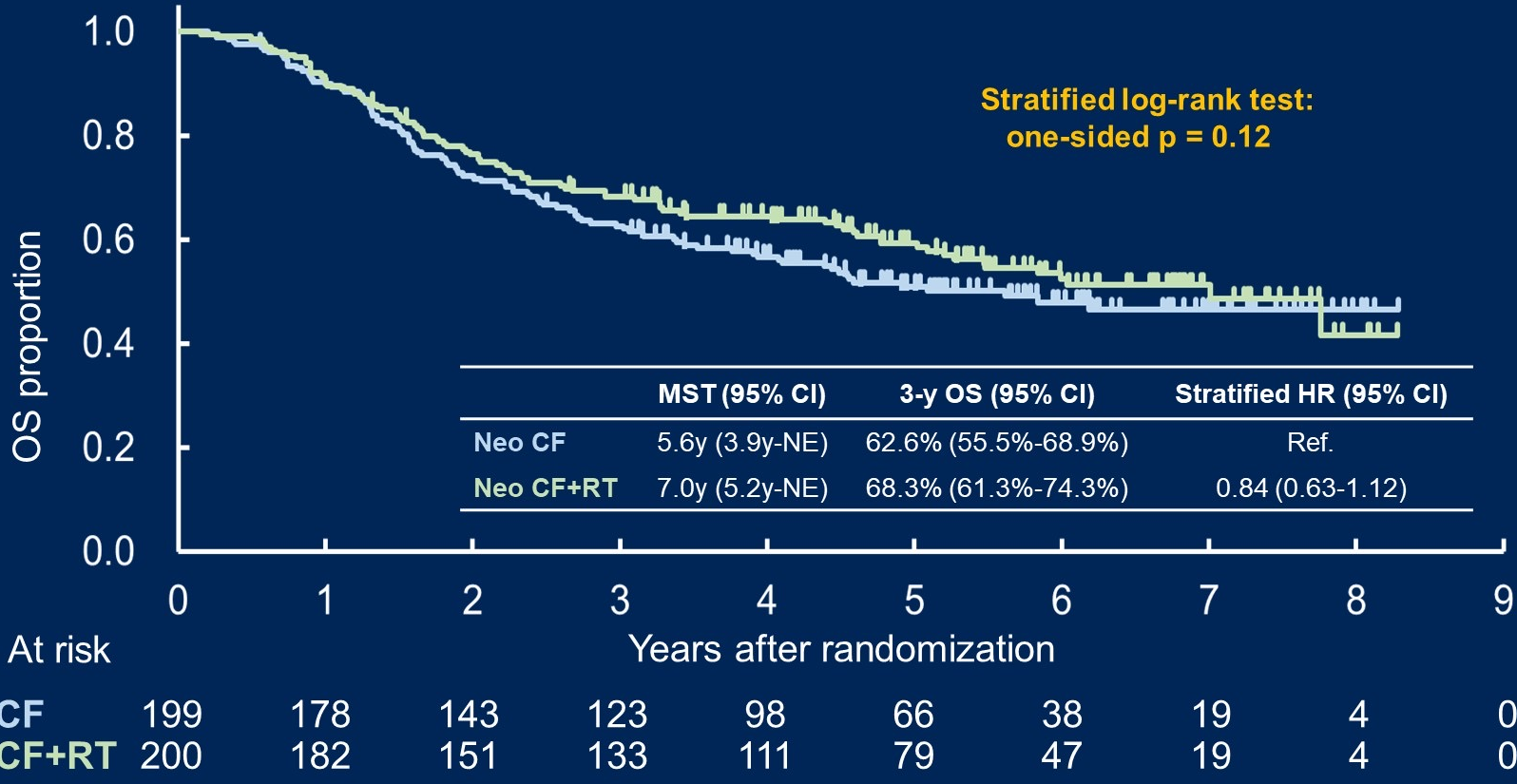
Overall survival: Neo CF vs Neo DCF



	MST (95% CI)	3-y OS (95% CI)	Stratified HR (95% CI)
Neo CF	5.6y (3.9y-NE)	62.6% (55.5%-68.9%)	Ref.
Neo DCF	NR (6.7y-NE)	72.1% (65.4%-77.8%)	0.68 (0.50-0.92)

PRESENTED BY: Ken Kato, National Cancer Center Hospital, Tokyo, Japan

Overall survival: Neo CF vs Neo CF+RT



	MST (95% CI)	3-y OS (95% CI)	Stratified HR (95% CI)
Neo CF	5.6y (3.9y-NE)	62.6% (55.5%-68.9%)	Ref.
Neo CF+RT	7.0y (5.2y-NE)	68.3% (61.3%-74.3%)	0.84 (0.63-1.12)

PRESENTED BY: Ken Kato, National Cancer Center Hospital, Tokyo, Japan

Conclusions

- ✓ Neoadjuvant DCF, but not neoadjuvant CF+RT significantly improved OS over neoadjuvant CF for locally advanced ESCC, with a manageable toxicity.
- ✓ Neoadjuvant DCF represents a new standard treatment for ESCC.

Radiation free regimen?

2022 ASCO® ANNUAL MEETING

Surgical and pathological outcome in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy vs. FLOT alone for resectable esophagogastric adenocarcinoma: interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK.

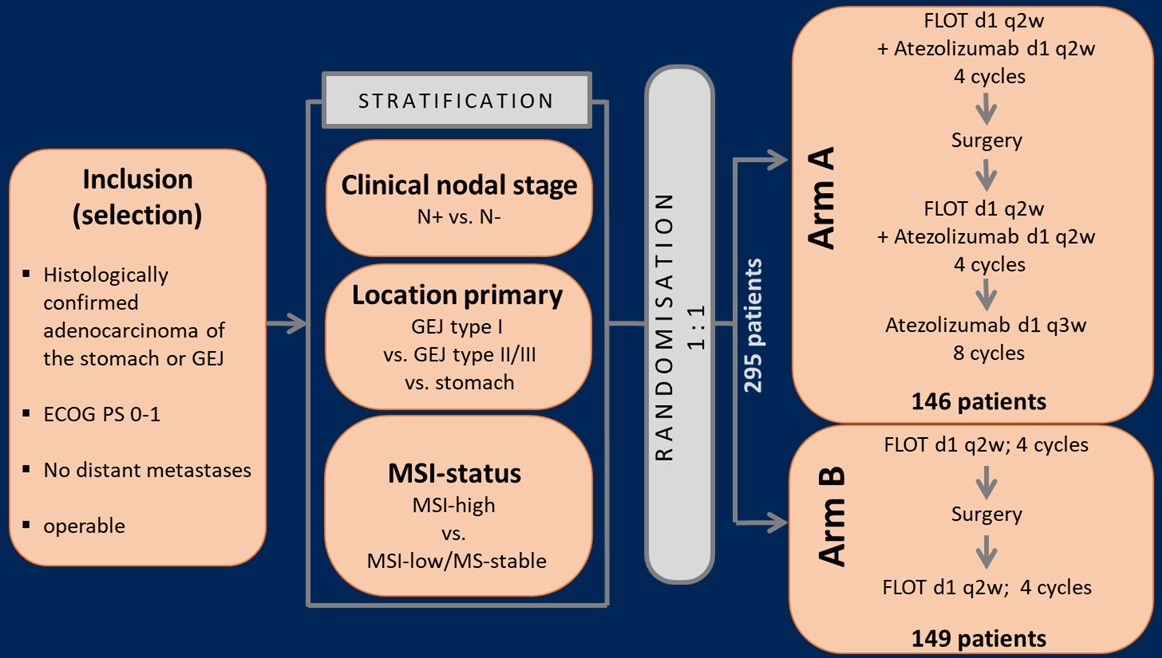
Salah-Eddin Al-Batran, Sylvie Lorenzen, Peter Thuss-Patience, Nils Homann, Michael Schenk, Udo Lindig, Vera Heuer, Albrecht Kretzschmar, Eray Goekkurt, Georg Martin Haag, Jorge Riera Knorrenschild, Claus Bolling, Ralf-Dieter Hofheinz, Stefan Angermeier, Thomas Jens Ettrich, Alexander Rheinhard Siebenhuener, Christina Kopp, Claudia Pauligk, Thorsten Oliver Götze, Timo Gaiser

On behalf of the FLOT-AIO Gastric Study Group

Presented by
Salah-Eddin Al-Batran, MD
Institute of Clinical Cancer Research IKF at Northwest Hospital
University Cancer Center (UCT) Frankfurt

Study Flow Chart

DANTE is an investigator-initiated phase-II trial with the potential to transition into a phase-III trial



Dosing Scheme

Arm A: FLOT + Atezolizumab

→ 4 pre- and post-operative cycles repeated every 2 weeks

- **Atezolizumab 840 mg i.v., d1**
- Docetaxel 50 mg/m² i.v., d1
- Oxaliplatin 85 mg/m² i.v., d1
- Leucovorin 200 mg/m² i.v., d1
- 5-FU 2600 mg/m² i.v., d1, 24 h inf.

→ 8 additional cycles **atezolizumab maintanance** repeated every 3 weeks

- Atezolizumab 1200 mg i.v., d1

Arm B: FLOT alone

→ 4 pre- and post-operative cycles repeated every 2 weeks

- Docetaxel 50 mg/m² i.v., d1
- Oxaliplatin 85 mg/m² i.v., d1
- Leucovorin 200 mg/m² i.v., d1
- 5-FU 2600 mg/m² i.v., d1, 24 h inf.

Pathological regression (local assessment)

Pathological Regression **FLOT + Atezolizumab (arm A) vs. FLOT (arm B)**	Becker Classification			
	TRG1a[1]		TRG1a/b[2]	
	A	B	A	B
All patients (N= 295; 146|149)	35 (24%)	23 (15%)	71 (49%)	58 (39%)
PD-L1 CPS ≥1 (N=170; 82|88)	20 (24%)	13 (15%)	42 (51%)	40 (46%)
PD-L1 CPS ≥5 (N=81; 40|41)	11 (28%)	8 (20%)	22 (55%)	18 (44%)
PD-L1 CPS ≥10 (N=53; 27|26)	9 (33%)	3 (12%)	18 (67%)	10 (39%)
MSI high (N=23; 8|15)	5 (63%)	4 (27%)	6 (75%)	7 (47%)

[1]pathological complete regression acc. to Becker
[2]pathological subtotal regression acc. to Becker

Pathological response (local vs. central assessment)

Pathological Regression **FLOT + Atezolizumab (arm A) vs. FLOT (arm B)**	Local assessment				Central assessment[1]			
	TRG1a[2]		TRG1a/b[3]		TRG1a[2]		TRG1a/b[3]	
	A	B	A	B	A	B	A	B
All patients (N= 295; 146|149)	35 (24%)	23 (15%)	71 (49%)	58 (39%)	37 (25%)	36 (24%)	72 (49%)	66 (44%)
PD-L1 CPS ≥1 (N=170; 82|88)	20 (24%)	13 (15%)	42 (51%)	40 (46%)	21 (26%)	20 (23%)	43 (52%)	41 (47%)
PD-L1 CPS ≥5 (N=81; 40|41)	11 (28%)	8 (20%)	22 (55%)	18 (44%)	13 (33%)	9 (22%)	21 (53%)	19 (46%)
PD-L1 CPS ≥10 (N=53; 27|26)	9 (33%)	3 (12%)	18 (67%)	10 (39%)	11 (41%)	5 (19%)	19 (70%)	13 (50%)
MSI high (N=23; 8|15)	5 (63%)	4 (27%)	6 (75%)	7 (47%)	5 (63%)	4 (27%)	6 (75%)	7 (47%)

[1]central assessment by one pathologist based on a representative tumor sample
[2]pathological complete regression acc. to Becker
[3]pathological subtotal regression acc. to Becker

Conclusion

- Perioperative FLOT plus atezolizumab is feasible and safe
- The addition of atezolizumab
  - improved downstaging (more patients in favorable pT and pN categories)
  - showed beneficial effects on path regression that seemed to be more pronounced with higher PD-L1 expression and in patients with MSI-high
- The analysis justifies the transition into a phase III trial

2021 ASCO ANNUAL MEETING

Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy: expanded efficacy and safety analyses from CheckMate 577

Ronan J. Kelly,[1] Jaffer A. Ajani,[2] Jaroslaw Kuzdzal,[3] Thomas Zander,[4] Eric Van Cutsem,[5] Guillaume Piessen,[6] Guillermo Mendez,[7] Josephine Feliciano,[8] Satoru Motoyama,[9] Astrid Lièvre,[10] Hope Uronis,[11] Elena Elimova,[12] Cecile Grootscholten,[13] Karen Geboes,[14] Jenny Zhang,[15] Samira Soleymani,[15] Ming Lei,[15] Prianka Singh,[15] James M. Cleary,[16] Markus Moehler[17]

[1]The Charles A. Sammons Cancer Center at Baylor University Medical Center, Dallas, TX; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Jagiellonian University, John Paul II Hospital, Cracow, Poland; [4]University Hospital of Cologne, Cologne, Germany; [5]University Hospitals Gasthuisberg, Leuven and KULeuven, Leuven, Belgium; [6]University of Lille, Claude Huriez University Hospital, Lille, France; [7]Fundacion Favaloro, Buenos Aires, Argentina; [8]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [9]Akita University Hospital, Akita, Japan; [10]CHU Pontchaillou, Rennes 1 University, Rennes, France; [11]Duke Cancer Institute, Durham, NC; [12]Princess Margaret Cancer Centre, Toronto, ON, Canada; [13]Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; [14]UZ Gent, Gent, Belgium; [15]Bristol Myers Squibb, Princeton, NJ; [16]Dana Farber Cancer Institute, Boston, MA; [17]Johannes-Gutenberg University Clinic, Mainz, Germany

Abstract number 4003 Slides Courtesy - Reynolds JV et al. J Clin Onc 2021 39:15_suppl, 4004-4004

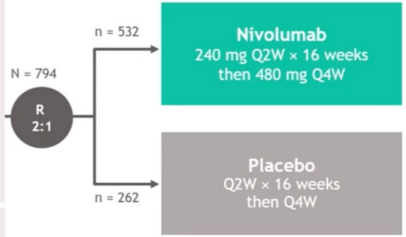
CheckMate-577

CheckMate 577 study design

- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria
- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

Stratification factors
- Histology (squamous versus adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 versus ypN0)
- Tumor-cell PD-L1 expression (≥ 1% versus < 1%[c])



Total treatment duration of up to 1 year[d]

Primary endpoint:
- DFS[e]

Secondary endpoints:
- OS[f]
- OS rate at 1, 2, and 3 years

Exploratory endpoints included:
- Safety
- DMFS[g]
- PFS2[h]
- QoL

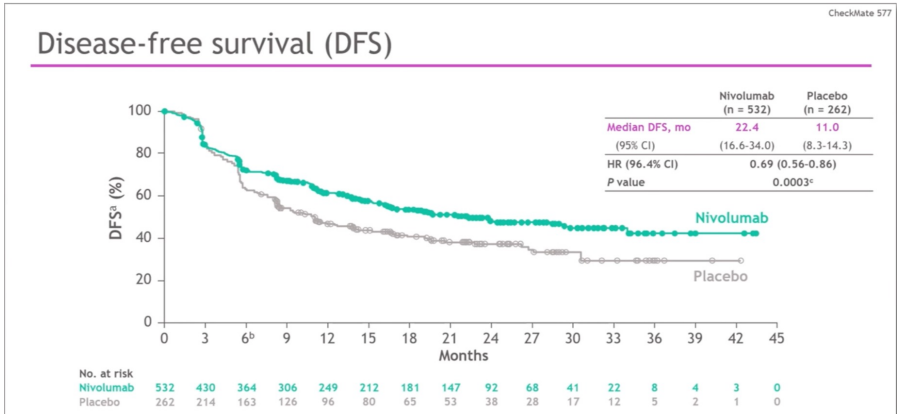
Baseline characteristics

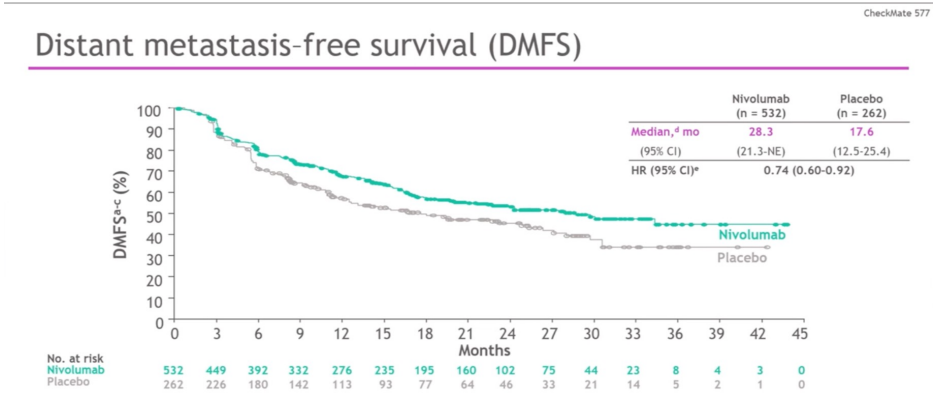
	Nivolumab (n = 532)	Placebo (n = 262)
Median age (range), years	62 (26-82)	61 (26-86)
Male, %	84	85
Race,[a] %		
White	81	82
Asian	16	13
ECOG PS, %		
0	58	60
1	42	40
Disease stage at initial diagnosis,[b] %		
II	34	38
III	66	62
Tumor location, %		
EC	60	59
GEJC	40	41
Histology,[c] %		
Squamous cell carcinoma	29	29
Adenocarcinoma	71	71
Pathologic lymph node status ≥ ypN1, %	57	58
Tumor-cell PD-L1 expression,[d,e] %		
≥ 1%	17	15
< 1%	70	75
Time from complete resection to randomization, %		
< 10 weeks	34	28
≥ 10 weeks	66	72

- In a post hoc analysis, a baseline PD-L1 CPS of 5 or higher was observed in 246 of 435 patients (57%) in the nivolumab arm and in 125 of 231 patients (54%) in the placebo arm

Slides Courtesy - Reynolds JV et al. J Clin Onc 2021 39:15_suppl, 4004-4004

CheckMate-577

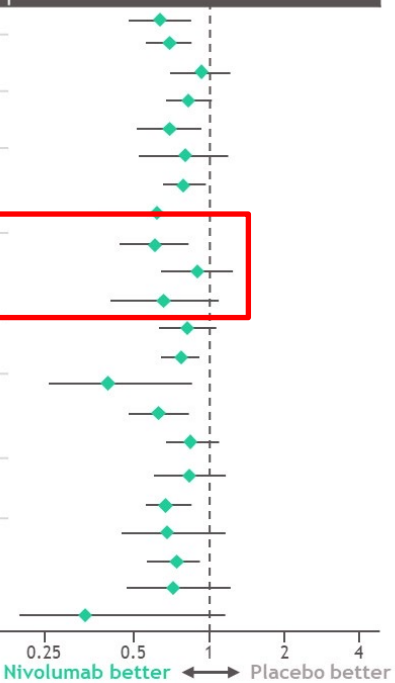




Slides Courtesy - Reynolds JV et al. J Clin Onc 2021 39:15_suppl, 4004-4004

Disease-free survival subgroup analysis

Category	Subgroup	Median DFS, mo		Unstratified HR
		Nivolumab	Placebo	
Overall	N = 794	22.4	11.0	0.70
Tumor location at initial diagnosis	Esophagus (n = 462)	24.0	8.3	0.61
	Gastroesophageal junction (n = 332)	22.4	20.6	0.87
Histologic type	Adenocarcinoma (n = 563)	19.4	11.1	0.75
	Squamous cell carcinoma (n = 230)	29.7	11.0	0.61
Tumor cell PD-L1 expression[a]	≥ 1% (n = 129)	19.7	14.1	0.75
	< 1% (n = 570)	21.3	11.1	0.73
	Indeterminate/nonevaluable (n = 95)	Not reached	9.5	0.54
PD-L1 CPS expression[a,b]	≥ 5 (n = 371)	29.4	10.2	0.62
	< 5 (n = 295)	16.3	11.1	0.89
	Missing/nonevaluable (n = 128)	Not reached	10.8	0.61
Pathologic lymph node status	ypN0 (n = 336)	Not reached	27.0	0.74
	≥ ypN1 (n = 457)	14.8	7.6	0.67
Pathological tumor status	ypT0 (n = 47)	34.0	5.2	0.35
	ypT1 or ypT2 (n = 308)	28.3	9.3	0.60
	ypT3 or ypT4 (n = 436)	18.9	14.1	0.84
Time from complete resection to randomization	< 10 weeks (n = 256)	24.0	14.1	0.84
	≥ 10 weeks (n = 538)	21.4	10.8	0.66
Radiotherapy dosage[b,c]	< 41.4 Gray (n = 92[d])	19.7	13.8	0.69
	41.4-50.4 Gray (n = 504)	24.0	11.1	0.73
	> 50.4 Gray (n = 152)	21.4	8.3	0.72
	Not reported (n = 41)	14.4	6.1	0.41



- Disease-free survival benefit was observed with nivolumab versus placebo across multiple subgroups

[a]PD-L1 expression determined from tumor tissue specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako), which for most patients, was obtained after completion of chemoradiotherapy; [b]Post hoc analysis; [c]Radiotherapies received from the start of concurrent CRT until complete resection. [d]10 patients (7 in the nivolumab group and 3 in the placebo group) received total exposure less than 40 Gray (following database lock, investigators amended the total dose of radiotherapy for 7 of these patients to 41.4-50.4 Gray).
Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203.

Slides Courtesy - Reynolds JV et al. J Clin Onc 2021 39:15_suppl, 4004-4004

Other novel therapies for early stage or locally advanced

Ongoing trials

NEONIPIGA Trial (Phase II) - Ipi/Nivo - Neoadjuvant for MSI/dMMR

RATIONALE 311 Trial (Phase III) - Tislelizumab - Definitive chemoradiation for ESCC

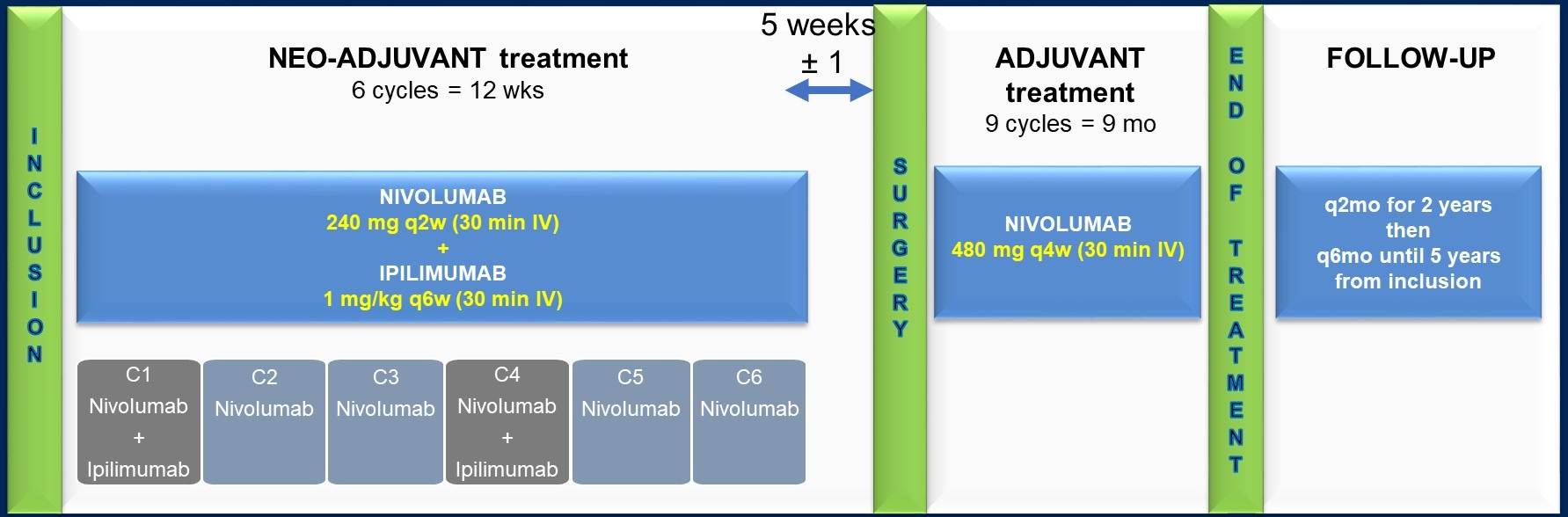
KUNLUN Trial (Phase III) - Durvalumab - Definitive chemoradiation for ESCC

NCT02844075 Trial (Phase II) - Pembrolizumab - Neoadjuvant chemoradiation for ESCC

NEONIPIGA: Study design/metods

- Phase II study evaluating efficacy of neo-adjuvant nivolumab and ipilimumab followed by adjuvant nivolumab in pts with resectable OGA MSI/dMMR, T2-T4 NxM0

- The primary objective was pathological complete response rate (pCRR).

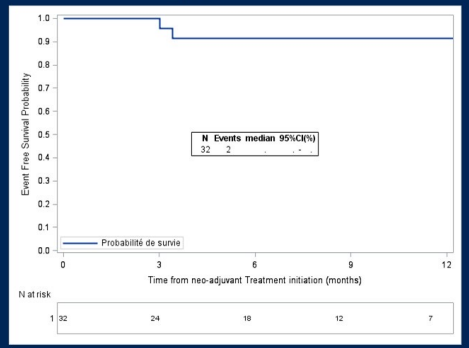


Slides Courtesy - Andre T et al. ASCO GI 2022

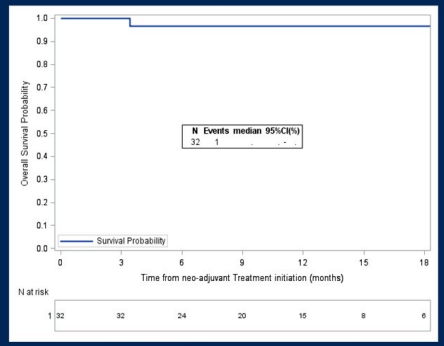
Results (2)

- With a median follow-up of 12 months (95%CI: 7.8-14.2), 2 patients had events (death or relapse)
  - one death at day 3 post surgery*
  - one progressive disease with metastatic disease PD after 6 cycles (surgery not performed)
  - 31 patients alive and 30 without relapse

EFS



OS



* History of severe cardio vascular co-morbidity and sudden death

Type of surgery (N=29)	N	%
R0	29	100
Total oesogastrectomy	1	3,5
Total gastrectomy	7	24
4/5 gastrectomy	9	31
Lewis-Santy procedure	11	38
Pancreaticoduodenectomy	1	3,5

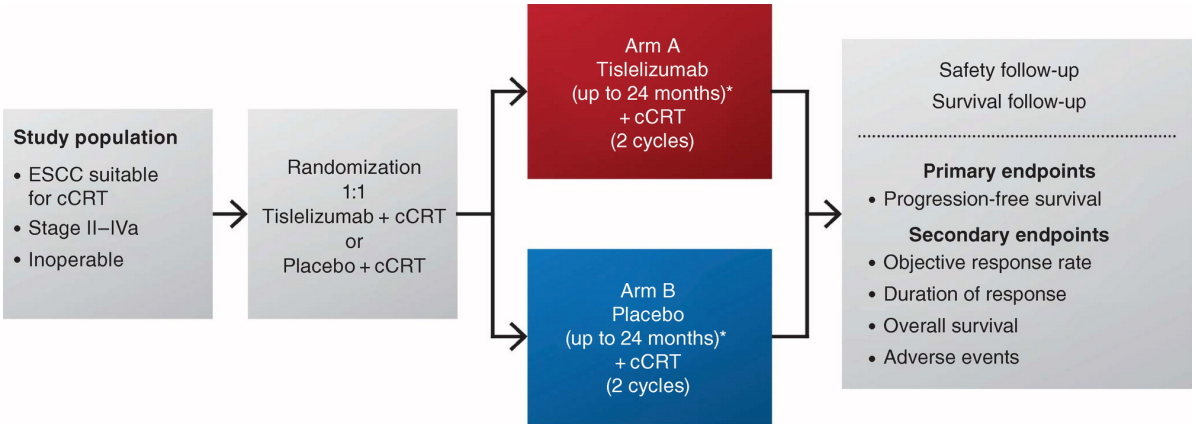
ypT stage (N=32)	
ypT0*	19
ypT1a	1
ypT1b	2
ypT2	2
ypT3	5
unknown**	3
ypN stage (N=32)	
ypN0	23
ypN1	6
unknown*	3

- * 2 patients ypT0 and y
- ** 3 patients without su

PRESENTED BY: Thierry André, MD

Slides Courtesy - Andre T et al. ASCO GI 2022

RATIONALE 311



Tislelizumab Q3W + paclitaxel on Day 1, for a total of 2 cycles + cisplatin on Day 1 to 3 of every cycle, for a total of 2 cycles + Radiotherapy

Yu R et al. Future Oncol. 2021 Nov;17(31):4081-4089

KUNLUN Trial

A Phase 3 randomized, double-blind, placebo-controlled, multicenter, global study of durvalumab with and after chemoradiotherapy in patients with locally advanced, unresectable esophageal squamous cell carcinoma: KUNLUN

Luhua Wang,[1] Ming Chen,[2] Ken Kato,[3] Lucjan Wyrwicz,[4] Elizabeth Smyth,[5] Anastasia Jiang,[6] Di Zhang,[6] Scott H. Robbins,[7] Philip He,[7] Alejandra Negro,[7] Nabil F. Saba[8]*

[1]Cancer Hospital of Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China; [2]Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, Guangdong, 510060, China; [3]National Cancer Center Hospital, Tokyo, Japan; [4]Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie, Warsaw, Poland; [5]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; [6]AstraZeneca, Shanghai, China; [7]AstraZeneca, Gaithersburg, MD, USA; [8]Winship Cancer Institute Emory University School of Medicine, Atlanta, GA, USA

*Presenting author

TPS373

Eligibility criteria

- Histologically or cytologically confirmed ESCC, and present with locally advanced disease (stage II-IVA)
- Unresectable or refusing surgery, and suitable for definitive chemoradiation therapy
- At least 1 evaluable lesion per RECIST 1.1
- Mandatory provision of available tumor tissue for PD-L1 expression analysis
- ECOG performance status of 0 or 1
- Adequate organ and marrow function
- Life expectancy >3 months

N = 600
Randomized 2:1

Group 1
Durvalumab with dCRT, followed by durvalumab for up to approximately 24 months

Group 2
Placebo with dCRT, followed by placebo for up to approximately 24 months

End points

Primary	Secondary
• PFS per RECIST 1.1	• OS • Safety and tolerability

ESCC, esophageal squamous cell carcinoma; dCRT, definitive chemoradiotherapy; OS, overall survival; PFS, progression-free survival.

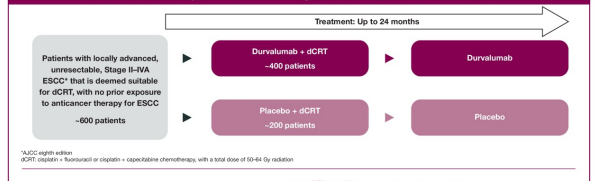
Introduction

- Esophageal cancer is the eighth most common cancer type and the sixth leading cause of cancer-related death worldwide.[1] Esophageal squamous cell carcinoma (ESCC) is the most common type of esophageal cancer, accounting for approximately 90% of cases globally[2]
- The current standard of care for patients with locally advanced, unresectable ESCC (American Joint Committee on Cancer [AJCC] eighth edition, Stage II–IVA) is definitive chemoradiotherapy (dCRT).[3] However, over half of patients still show disease progression within 2 years, and 5-year overall survival rate remains poor[4]

Rationale for durvalumab and concurrent dCRT in ESCC

- In preclinical models, the combination of an immune checkpoint inhibitor (programmed cell death ligand-1 [PD-L1] inhibitor) with chemoradiotherapy (CRT) has demonstrated synergistic antitumor activity[5]
- Subsequently, Phase 2 clinical study data demonstrated clinical benefits of combining a programmed cell death-1 (PD-1) inhibitor and preoperative CRT in patients with locally advanced ESCC[6]
- These findings support the evaluation of durvalumab, a PD-L1 inhibitor, in combination with and after CRT for the treatment of patients with locally advanced, unresectable ESCC[7]

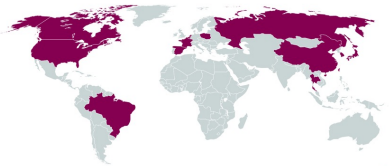
KUNLUN (NCT04550260) study design: Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study to evaluate durvalumab in combination with and after dCRT in patients with locally advanced, unresectable ESCC



*AJCC eighth edition
dCRT: cisplatin + fluorouracil or cisplatin + capecitabine chemotherapy, with a total dose of 50–64 Gy radiation

Enrollment start: Oct 2020
Expected study end: Oct 2026

- There are currently 14 countries participating in the KUNLUN study



Key inclusion criteria

- Age ≥18 years
- Histologically or cytologically confirmed, Stage II-IVA, unresectable ESCC that is deemed suitable for dCRT and not previously treated with anticancer therapy
- Availability of tumor sample (for PD-L1 expression analysis) <3 months prior to/at screening
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Adequate organ and marrow function

Key exclusion criteria

- Histologically or cytologically confirmed small cell esophageal carcinoma, esophageal adenocarcinoma, or other mixed carcinoma
- Prior anticancer treatment, including but not limited to chemotherapy and/or radiation therapy, immunotherapy, and investigational agents for ESCC
- Active infection including tuberculosis, hepatitis B, hepatitis C, or human immunodeficiency virus
- Contraindication to any of the study drugs

Study endpoints

1° Progression-free survival (per Response Evaluation Criteria In Solid Tumors v1.1 as assessed by Blinded Independent Central Review) for durvalumab plus dCRT versus placebo plus dCRT in all randomized patients and patients with PD-L1 high tumors

2° Overall survival; Safety and tolerability

References

1. World Health Organization International Agency for Research on Cancer. Globocan 2020: All cancers factsheet. Available at: https://gco.iarc.fr/today/fact-sheets-cancers
2. Abnet CC et al. Gastroenterology 2018; 154: 360–373.
3. Kitagawa Y et al. Esophagus 2019; 16: 1–24.
4. Chen Y et al. J Clin Oncol 2019; 37: 1695–1703.
5. Deng L et al. J Clin Invest 2014; 124: 687–695.
6. Hong MH et al. J Clin Oncol 2019; 37: Abstract 4027.
7. Akinleye A, Rasool Z. J Hematol Oncol 2019; 12: 92.

Abbreviations

AJCC, American Joint Committee on Cancer; CRT, chemoradiotherapy; dCRT, definitive chemoradiotherapy; ESCC, esophageal squamous cell carcinoma; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1

Disclosures

KK reports grants/research support from AstraZeneca, Bayer, Belgene, Bristol-Myers Squibb, Ono Pharma Healthcare, and Taiho; and honoraria from Taiho, outside the submitted work. LWy reports grants/research support from AstraZeneca, Bayer, Belgene, Bristol-Myers Squibb, and Merck Sharp and Dohme; and speakers' bureau from Novartis, outside the submitted work. ES reports grants/research support from Bristol-Myers Squibb; consultancy for Amgen, AMAL Therapeutics, AstraZeneca, Astellas, Celgene, Bristol-Myers Squibb, Merck, Novartis, Pfizer, Roche, Servier, and Zymeworks, outside the submitted work. NFS reports grants/research support from Bristol-Myers Squibb and Exelixis; and consultancy for Adum, BioMotiv, Eisai, GlaxoSmithKline, Kura, Merck, Merati, Pfizer, and Vaccinex, outside the submitted work. AJ, DZ, SHR, PH, and AN are employees of AstraZeneca and hold stock in AstraZeneca. LWa and ME have no disclosures to report.

Acknowledgements

The authors would like to thank the patients, their families and caregivers, and all investigators involved in this study. This study is sponsored by AstraZeneca. Medical writing support, under the guidance of the authors, was provided by Elaine Groat, PhD, of CMC Connect, McCann Health Medical Communications (UK) and was funded by AstraZeneca in accordance with Good Publication Practice (GPP3) guidelines.

For more details on KUNLUN, please visit clinicaltrials.gov/ct2/show/record/NCT04550260

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ASCO GastroIntestinal Cancer Symposium, San Francisco, CA, USA, January 20–22, 2022

Wang L et al. ASCO GI 22

Novel therapies for advanced stage, unresectable disease

KEYNOTE-590 (Phase III) - Pembrolizumab + chemo - Metastatic ESCC/GEJ AC

CheckMate-649 Trial (Phase III) - Nivolumab + chemo - Metastatic GEJ or Gastric AC

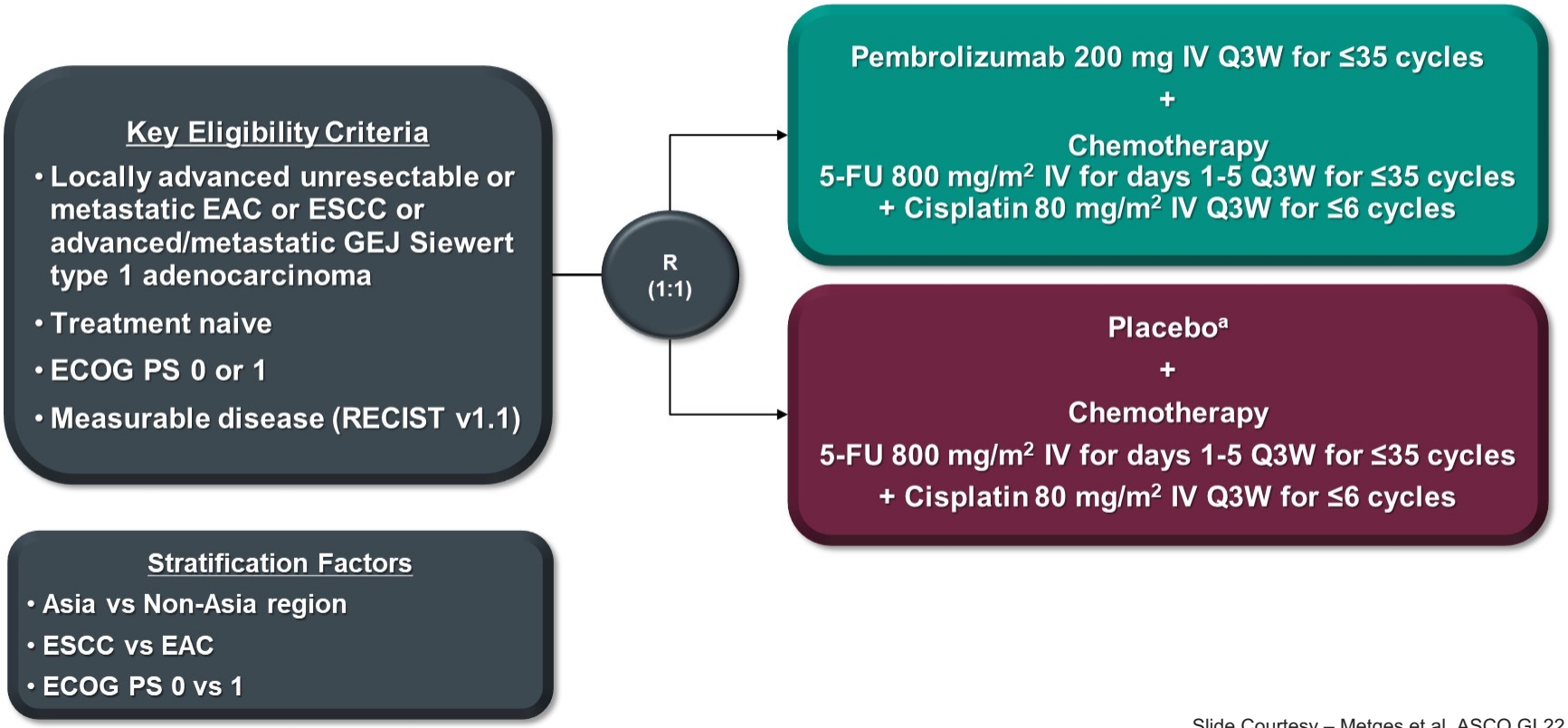
RATIONALE-302 Trial (Phase III) - Tislelizumab - 2L Metastatic ESCC

KEYNOTE-811 (Phase III) - Pembrolizumab + Transtuzumab + Chemo - Metastatic GEJ or Gastric AC

DESTINY-Gastric01 (Phase II) - Transtuzumab Deruxtecan - 2L Metastatic Gastric

JUPITER06 Trial (Phase III) - Toripalimab + chemo - Metastatic ESCC

KEYNOTE-590 Study Design (NCT03189719)



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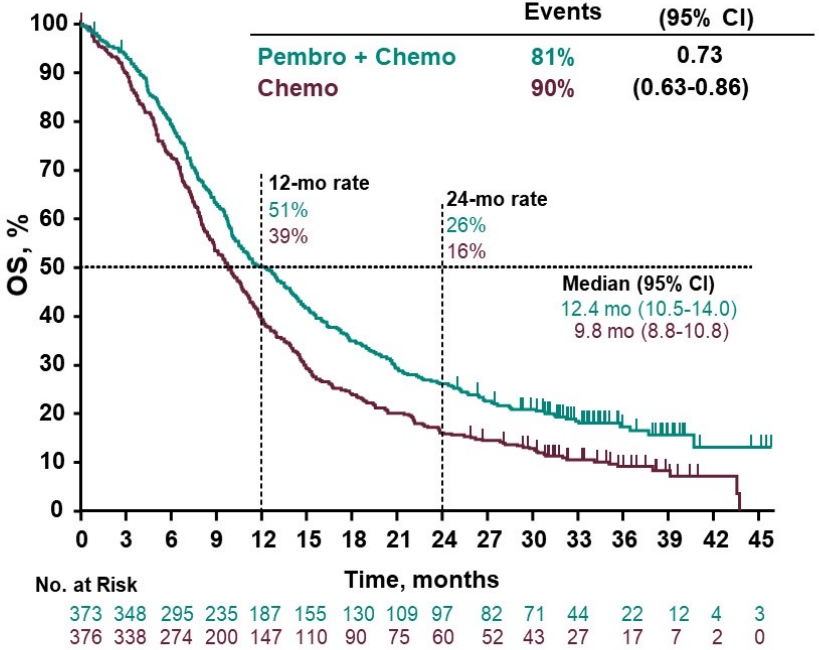
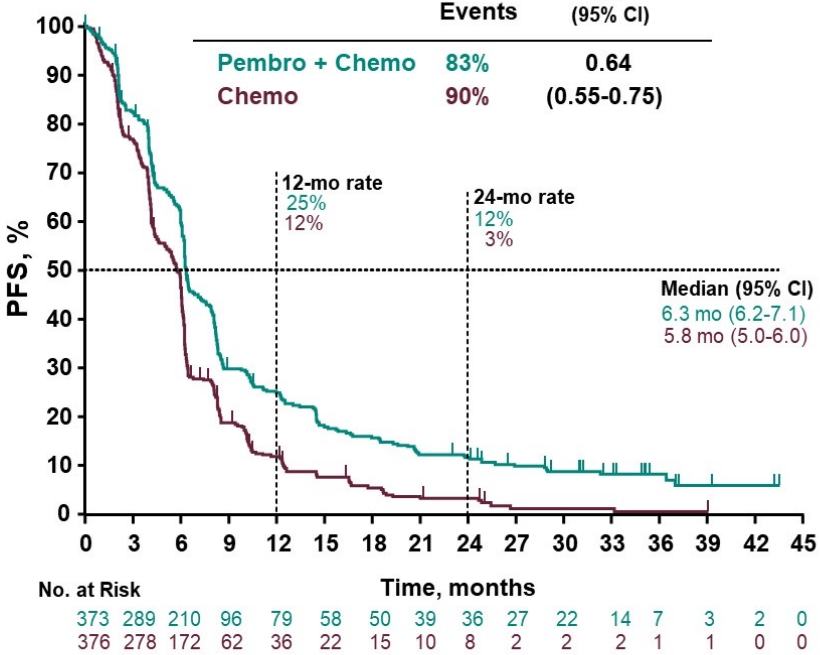
[a]Saline IV Q3W for ≤35 cycles. All treatments were continued for the specified number of cycles or until disease progression, intolerable toxicity, withdrawal of consent, or physician decision; EAC, esophageal adenocarcinoma; GEJ, gastroesophageal junction, ESCC, esophageal squamous cell carcinoma; Data cutoff: July 9, 2021.

Survival: All Patients

OS



PFS



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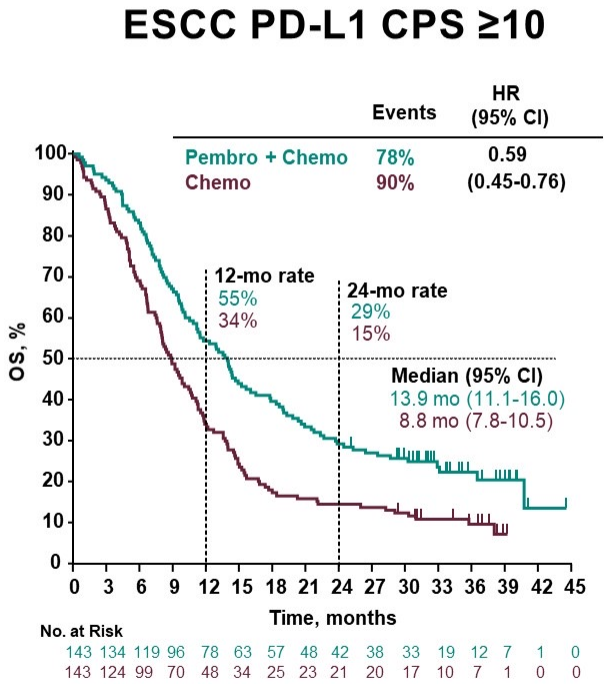
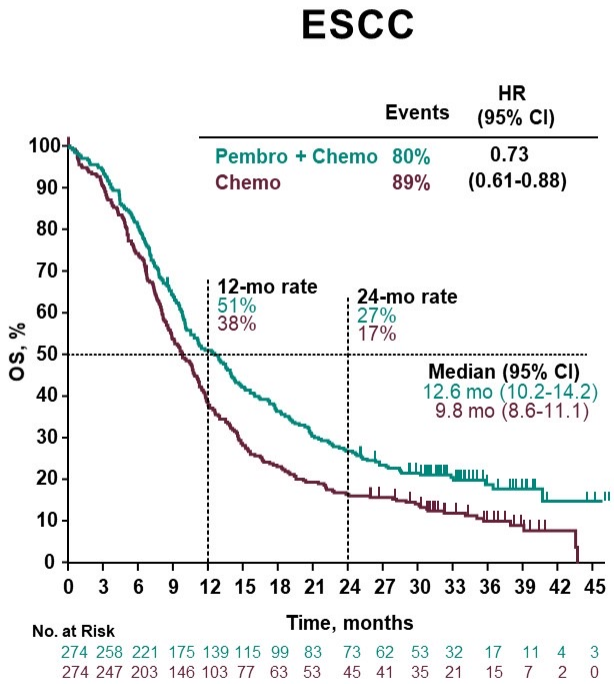
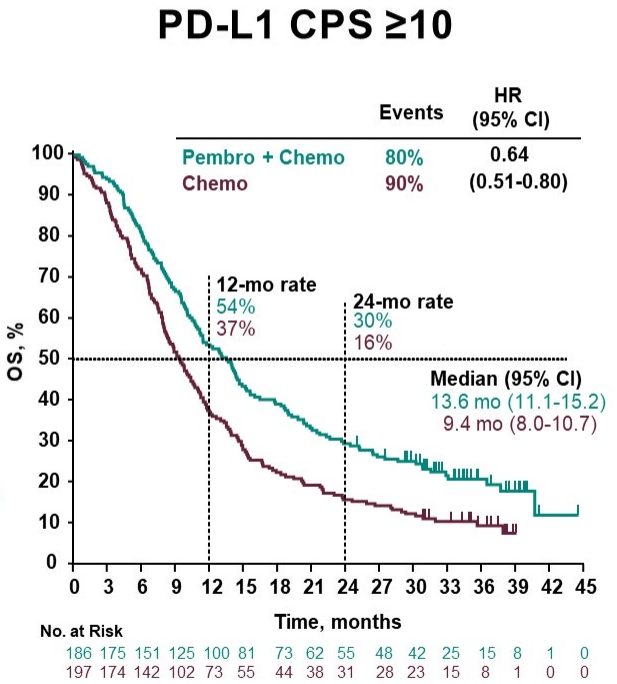
OS: Pre-specified Subgroups

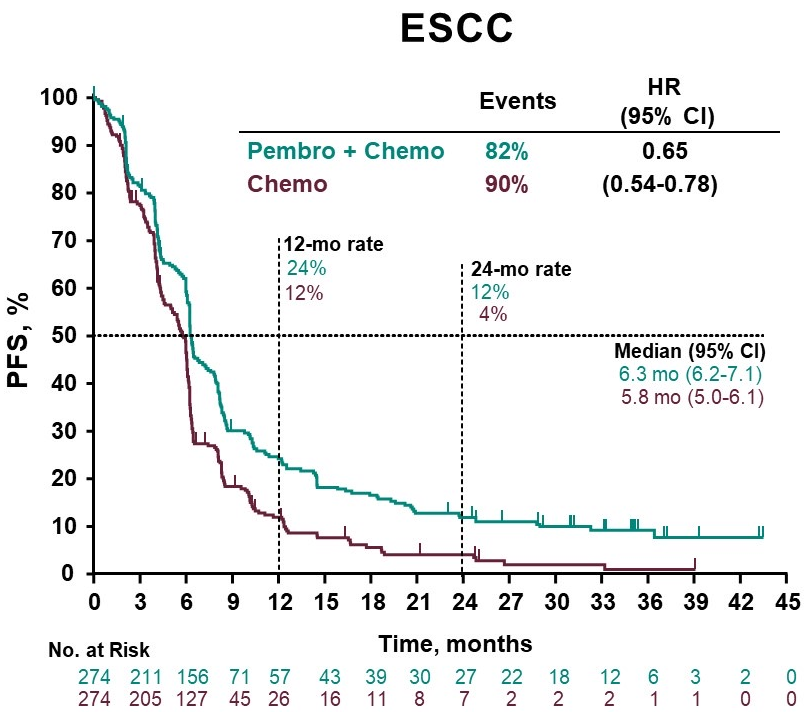


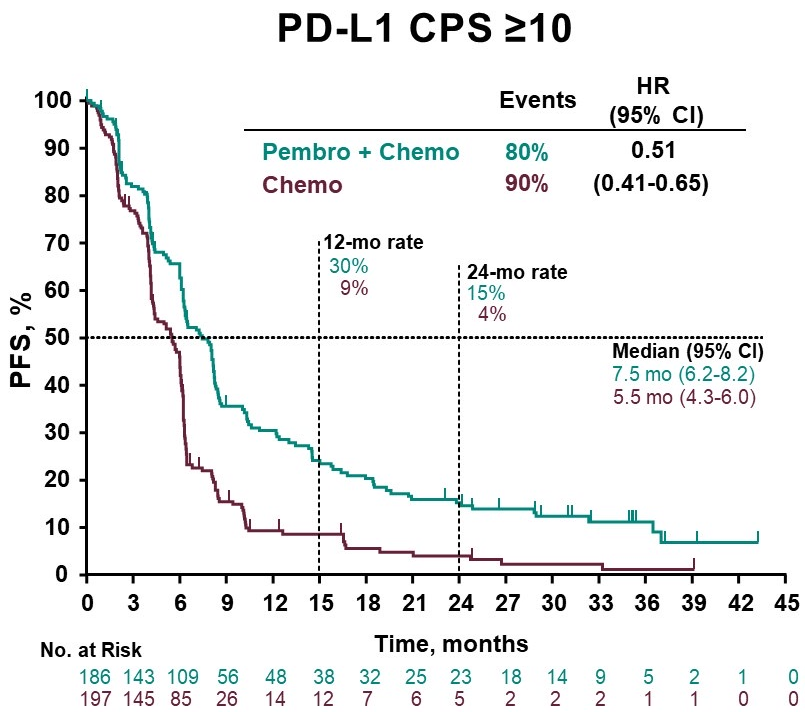




Data cut-off: July 9, 2021. Slide Courtesy – Metges et al. ASCO GI 22

PFS: Pre-specified Subgroups
(RECIST v1.1, investigator)





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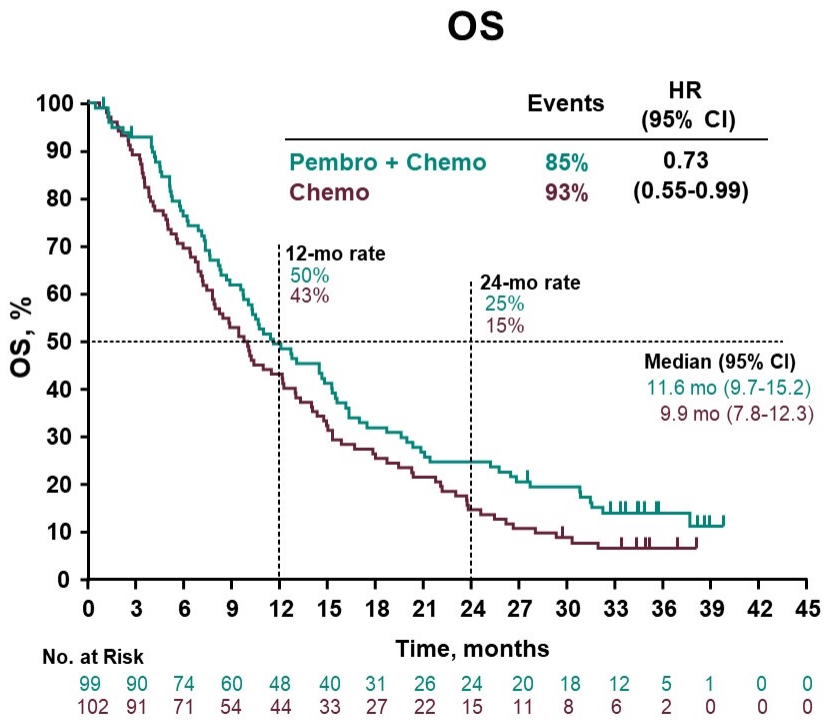
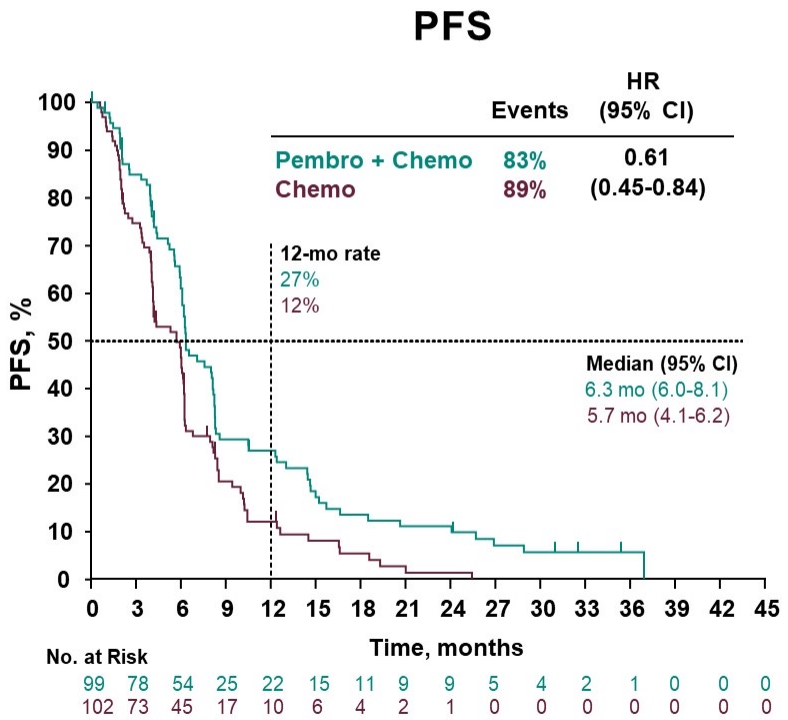
Survival: Adenocarcinoma





Data cut-off: July 9, 2021. Slide Courtesy – Metges et al. ASCO GI 22

Summary and Conclusions

- With an additional 12 months of follow-up, first-line pembrolizumab plus chemotherapy continued to provide clinically meaningful benefit in all patients with locally advanced and metastatic esophageal cancer including GEJ adenocarcinoma
  - OS: HR 0.73; PFS: HR 0.64 in all patients (12-month follow-up); OS: HR 0.73; PFS: HR 0.65 in all patients (IA1)
  - ORR: 45.0% vs 29.3% (12-month follow-up; IA1)
  - DOR: median 8.3 vs 6.0 months (12-month follow-up; IA1)
- Similar quality of life was maintained with pembrolizumab plus chemotherapy vs chemotherapy
- Comparable safety profile between the two treatment groups
  - No new safety signals detected
- These longer-term data further support first-line pembrolizumab plus chemotherapy as a new standard-of-care in patients with locally advanced and metastatic esophageal cancer including GEJ adenocarcinoma

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ASCO® Gastrointestinal Cancers Symposium

Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: expanded analyses from 24-month follow-up of CheckMate 649

Kohei Shitara,[1] Yelena Y. Janjigian,[2] Markus Moehler,[3] Marcelo Garrido,[4] Carlos Gallardo,[5] Lin Shen,[6] Kensei Yamaguchi,[7] Lucjan Wyrwicz,[8] Tomasz Skoczylas,[9] Arinilda Bragagnoli,[10] Tianshu Liu,[11] Mustapha Tehfe,[12] Elena Elimova,[13] Samira Soleymani,[14] Ming Lei,[14] Kaoru Kondo,[14] Mingshun Li,[14] Jaffer A. Ajani[15]

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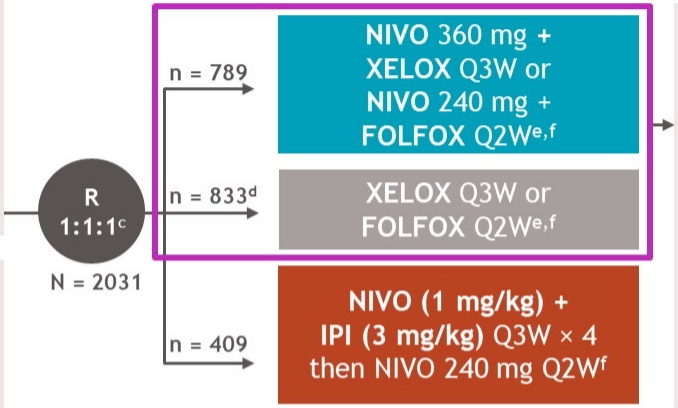
Abstract number 240

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.

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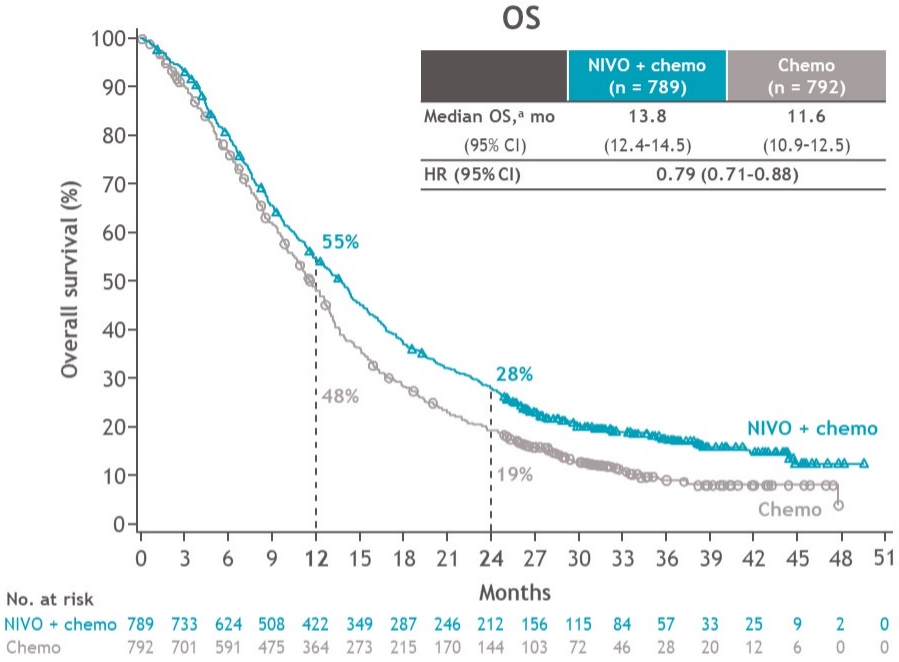
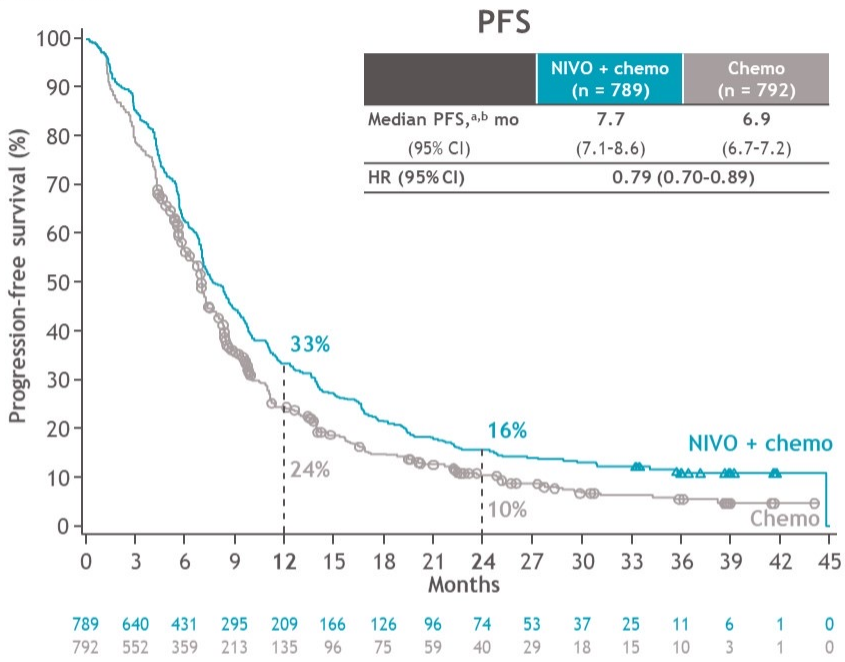
Overall survival and progression-free survival

All randomized patients





- 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.

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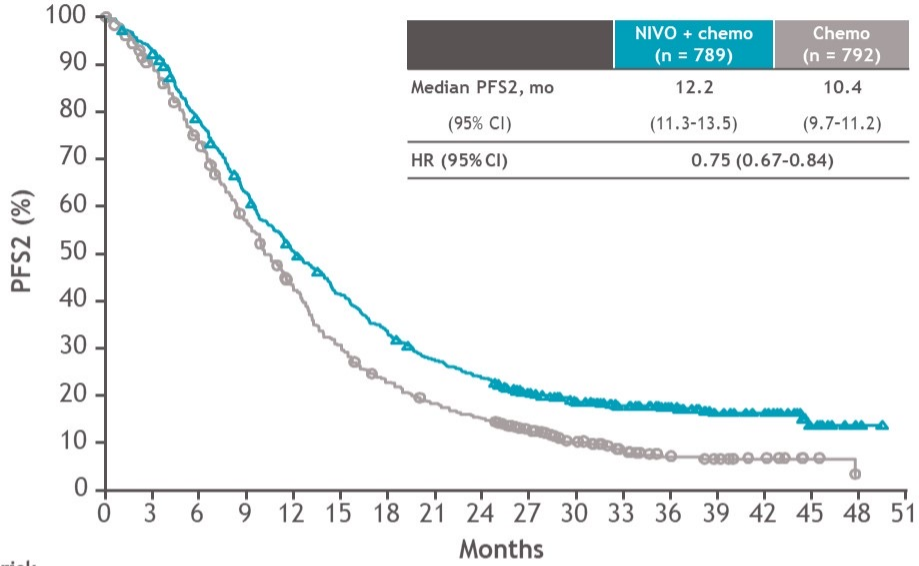
Progression-free survival 2 (PFS2)

All randomized patients



	NIVO + chemo (n = 789)	Chemo (n = 792)
Median PFS2, mo	12.2	10.4
(95% CI)	(11.3-13.5)	(9.7-11.2)
HR (95% CI)	0.75 (0.67-0.84)	

No. at risk

NIVO + chemo	789	731	609	488	390	317	257	210	182	139	104	76	53	31	25	9	2	0
Chemo	792	699	570	435	323	231	173	137	114	80	55	29	18	13	9	3	0	0

First subsequent therapy,[a] n (%)	NIVO + chemo (n = 789)	Chemo (n = 792)
Any subsequent therapy	325 (41)	346 (44)
Radiotherapy	32 (4)	28 (4)
Surgery	19 (2)	23 (3)
Systemic anticancer therapy[b]	290 (37)	329 (42)
Chemotherapy	267 (34)	297 (38)
Targeted therapy	92 (12)	76 (10)
Immunotherapy	8 (1)	27 (3)

- PFS2 favored NIVO + chemo vs chemo with a 25% reduction in risk of death or disease progression on subsequent therapy

PFS2, progression-free survival on subsequent therapy (time from randomization to progression after subsequent systemic therapy, initiation of second subsequent systemic therapy, or death, whichever was earlier). [a]Patients may have received more than 1 type of subsequent therapy. [b]Patients may receive multiple subsequent systemic therapies, out of which the first subsequent systemic therapies patients received are summarized in this table regardless of their timing relative to the subsequent radiotherapy and surgery.

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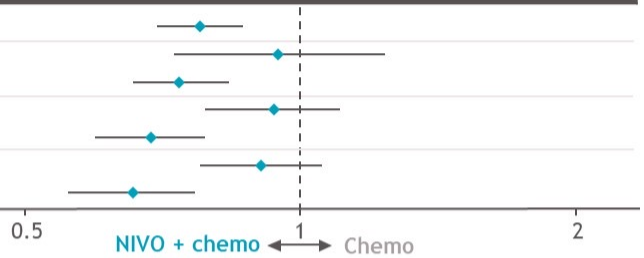
Efficacy subgroup analysis by PD-L1 CPS

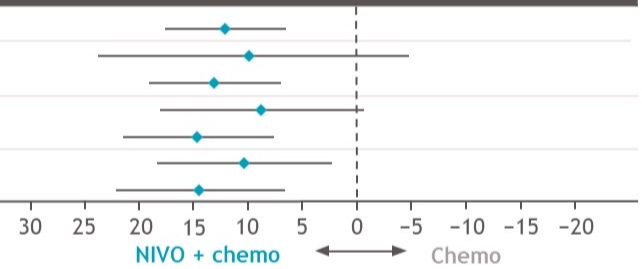
Overall survival

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.

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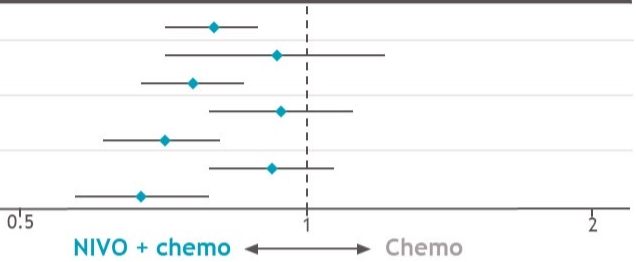
Efficacy subgroup analysis by PD-L1 CPS excluding MSI-H

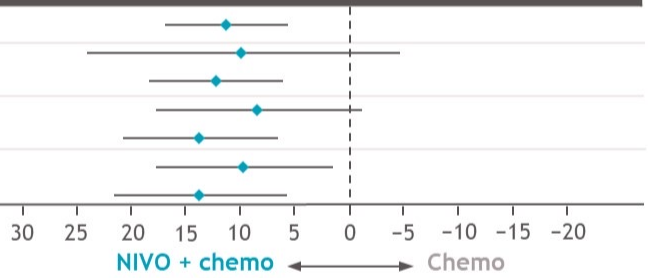
Overall survival

PD-L1 CPS[a]	Number of patients	Median, months		Unstratified HR[b]	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 1537)		13.5	11.6	0.80	
< 1	262	13.4	12.5	0.93	
≥ 1	1256	13.6	11.4	0.76	
< 5	597	12.4	12.1	0.94	
≥ 5	921	14.2	11.1	0.71	
< 10	779	12.4	12.6	0.92	
≥ 10	739	14.4	10.9	0.67	



Objective response rate

PD-L1 CPS[c]	Number of patients	Objective response rate, %		Unweighted ORR difference,[d] %	Unweighted ORR difference, % (95% CI)
		NIVO + chemo	Chemo		
Overall (n = 1172)		58	46	12	
< 1	176	52	41	11	
≥ 1	982	60	47	13	
< 5	418	55	46	9	
≥ 5	740	60	46	14	
< 10	563	57	47	10	
≥ 10	595	59	45	14	



- OS and ORR benefits were consistent with the all randomized population when excluding patients with MSI-H tumors[e]

[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; [e]Patients with MSI-H tumors, n = 44, patients with MSS tumors, n = 1377, patients with MSI-H status not reported/invalid, n = 160.

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Summary

- NIVO + chemo continued to demonstrate clinically meaningful improvement in efficacy vs chemo with an acceptable safety profile with longer follow-up in previously untreated patients with advanced GC/GEJC/EAC
  - Favorable PFS2
  - OS benefit across key subgroups and enriched at higher PD-L1 CPS cutoffs
  - Higher ORR across all evaluated PD-L1 CPS subgroups
  - More deep and more durable responses regardless of PD-L1 CPS ≥ 5 or < 5
  - OS and ORR benefit across PD-L1 CPS subgroups consistent with the all randomized population when excluding patients with MSI-H tumors
  - No new safety signals; TRAEs with potential immunologic etiology resolved in most patients with the use of established management algorithms
- These data further support the use of NIVO + chemo as standard 1L treatment in patients with advanced GC/GEJC/EAC

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What did the update tell us more about Keynote-590?

	First pub Data cutoff date July 2020, median follow-up 22 months			Update Data cutoff date July 2021 median follow-up 33 months		
Overall Survival	**Median**	**HR**	**24-mo rate**	**Median**	**HR**	**24-mo rate**
ESCC/PD-L1 CPS ≥10 (286)	13.9 vs. 8.8	0.57	31% vs. 15%	**13.9 vs. 8.8**	**0.59**	**29% vs. 15%**
ESCC (548)	12.6 vs. 9.8	0.72	29% vs. 17%	**12.6 vs. 9.8**	**0.73**	**27% vs 17%**
PD-L1 CPS ≥10 (383)	13.5 vs. 9.4	0.62	31% vs. 15%	**13.6 vs. 9.4**	**0.64**	**30% vs. 16%**
Adenocarcinoma (201 patients)	11.6 vs. 9.9	0.74	--------	**11.6 vs. 9.9**	**0.73**	**25% vs. 15%**
All patients (749)	12.4 vs. 9.8	0.73	28% vs. 16%	**12.4 vs 9.8**	**0.73**	**26% vs. 16%**
PFS						
All patients (749)	6.3 vs. 5.8	0.65	------	**6.3 vs. 5.8**	**0.64**	**12% vs. 3%**
ESCC	6.3 vs. 5.8	0.65	-----	**6.3 vs. 5.8**	**0.65**	**12% vs. 4%**
PD-L1 CPS ≥10	7.5 vs. 5.5	0.51	-----	**7.5 vs.5.5**	**0.51**	**15% vs. 4%**

What did the update tell use more about Checkmate 649?

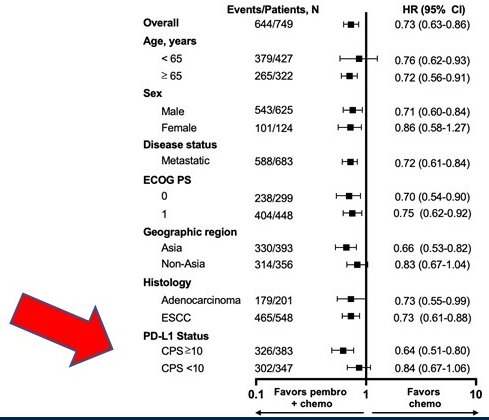
	First pub Data cutoff date July 2020, median follow-up 11.1/13 months			Update Data cutoff date May 27 2021 median follow-up 24 months		
Overall Survival	**Median (mo)**	**HR**	**12-mo rate**	**Median (mo)**	**HR**	**24-mo rate**
All patients (1581)	13.8 vs. 11.6	0.80	55% vs. 48%	13.8 vs. 11.6	0.79	28% vs. 19%
PD-L1CPS ≥5 (955)	14.4 vs. 11.1	0.71	57% vs. 46%	14.4 vs. 11.1	0.69	----------
PD-L1 CPS ≥1 (1297)	14.0 vs. 11.3	0.77	56% vs. 47%	13.8 vs. 11.3	0.74	----------
PD-L1 CPS ≥10 (767)				15 vs. 10.9	0.66	----------
PFS						
All patients	7.7 vs. 6.9	0.77	33% vs. 23%	7.7 vs. 6.9	0.79	16% vs. 10%
PD-L1 CPS ≥5	7.7 vs. 6.0	0.68	36% vs. 22%	---------	--------	
PD-L1 CPS ≥1	7.5 vs. 6.9	0.74	34% vs. 22%	---------	-------	--------
PD-L1CPS ≥10						

Does PD-L1 CPS matter?

CHECKMATE 649

KEYNOTE-590

OS in Key Subgroups: All Patients



Efficacy subgroup analysis excluding patients with MSI-H tumors[a]

Overall survival

PD-L1 CPS[b]	Number of patients	Median, months		Unstratified HR[c]	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 1537)		13.5	11.6	0.80	
< 1	262	13.4	12.5	0.93	
≥ 1	1256	13.6	11.4	0.76	
< 5	597	12.4	12.1	0.94	
≥ 5	921	14.2	11.1	0.71	
< 10	779	12.4	12.6	0.92	
≥ 10	739	14.4	10.9	0.67	

0.5 1 2

NIVO + chemo ← → Chemo

In reality, the benefit may only be driven by a specific subpopulation. For instance, if we say that patients with PD-L1 CPS ≥1 (1256) have a benefit with immunotherapy we have to consider that they include also patients with PD-L1 ≥ 5 (921) or 10 (739).

PRESENTED BY: Stefano Cascinu, MD

Pembrolizumab Plus Trastuzumab and Chemotherapy for HER2+ Metastatic Gastric or Gastroesophageal Junction Cancer: Initial Findings of the Global Phase 3 KEYNOTE-811 Study

Yelena Y. Janjigian,[1] Akihito Kawazoe,[2] Patricio Yañez,[3] Suxia Luo,[4] Sara Lonardi,[5] Oleksii Kolesnik,[6] Olga Barajas,[7] Yuxian Bai,[8] Lin Shen,[9] Yong Tang,[10] Lucjan S. Wyrwicz,[11] Kohei Shitara,[2] Shukui Qin,[12] Eric Van Cutsem,[13] Josep Tabernero,[14] Lie Li,[15] Chie-Schin Shih,[15] Pooja Bhagia,[15] Hyun Cheol Chung,[16] on behalf of the KEYNOTE-811 Investigators

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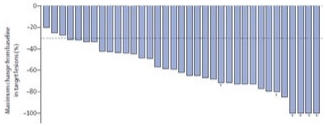
Background

- 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

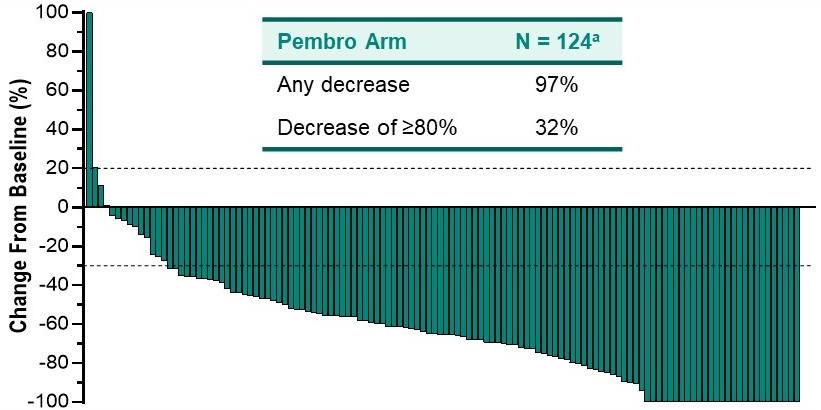
Placebo IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

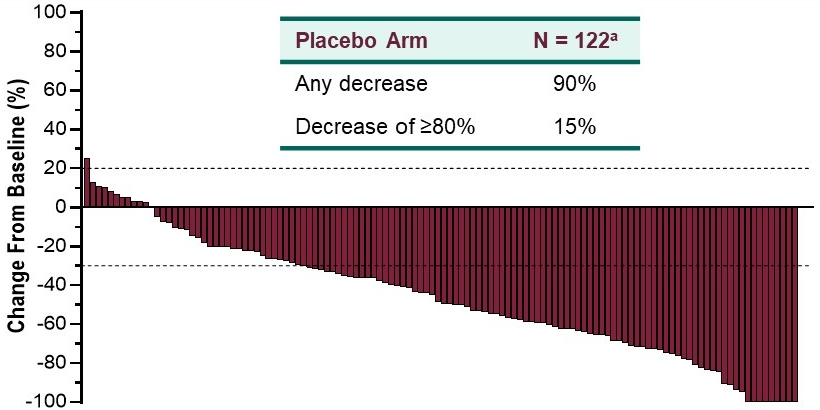
Dual Primary End Points
- OS
- PFS (RECIST v1.1 per BICR)

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/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX dose: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 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





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.

Summary of KEYNOTE-811 IA1

- Pembrolizumab plus trastuzumab and chemotherapy provided a 74.4% ORR that resulted in a statistically significant, clinically meaningful 22.7% improvement in ORR compared with placebo plus trastuzumab and chemotherapy
- Responses to pembrolizumab plus trastuzumab and chemotherapy were deeper and more durable
- AE incidence was similar between arms, and the observed AEs were as expected with no new safety concerns identified
- Study is continuing as planned, and analyses of OS and PFS will be performed in the future in accordance with the analysis plan

Key Takeaway

- Pembrolizumab plus trastuzumab and chemotherapy is a potential new treatment option for previously untreated, unresectable or metastatic, HER2-positive gastric or gastroesophageal junction cancer

Acknowledgments

- Participants, families, investigators, and personnel from 168 sites in 20 countries
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Poster

bit.ly/3u92jUa

Audio

bit.ly/3eORd0u

ASCO Gastrointestinal Cancers Symposium

Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2–Positive Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma: Final Overall Survival (OS) Results From a Randomized, Multicenter, Open-Label, Phase 2 Study (DESTINY-Gastric01)

Kensei Yamaguchi

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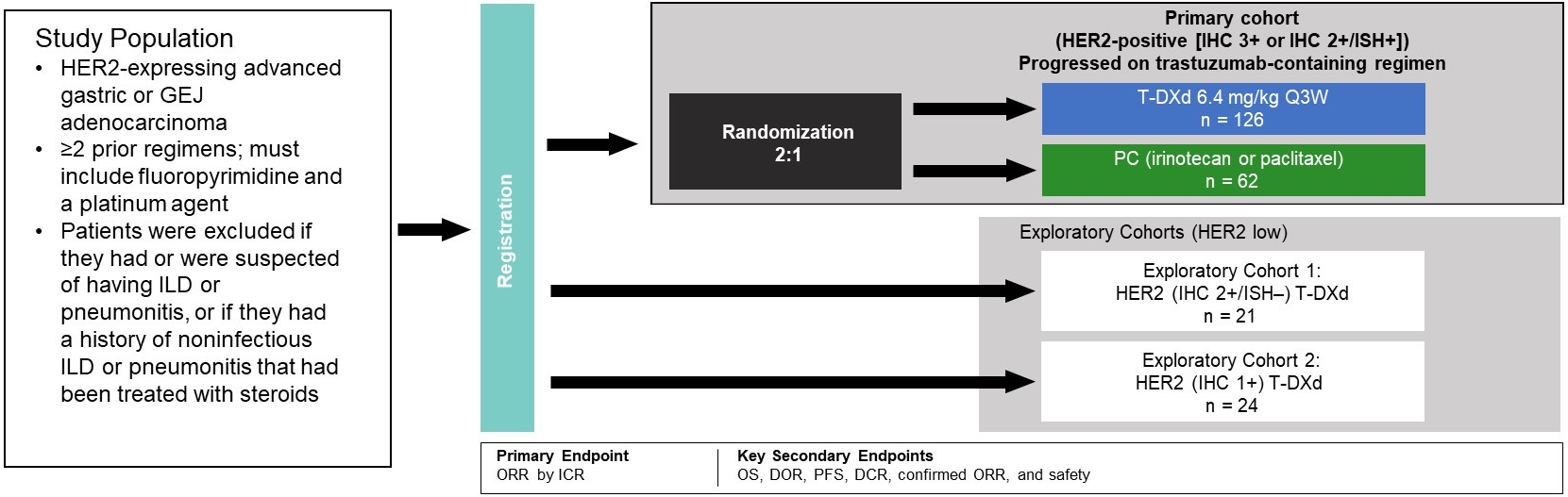
ON BEHALF OF THE DESTINY-GASTRIC01 INVESTIGATORS

Additional authors: Yung-Jue Bang, Satoru Iwasa, Naotoshi Sugimoto, Min-Hee Ryu, Daisuke Sakai, Hyun Cheol Chung, Hisato Kawakami, Hiroshi Yabusaki, Jeeyun Lee, Kaku Saito, Yoshinori Kawaguchi, Takahiro Kamio, Akihito Kojima, Masahiro Sugihara, Kohei Shitara

DESTINY-Gastric01 Study Design

An open-label, multicenter phase 2 study (NCT03329690)



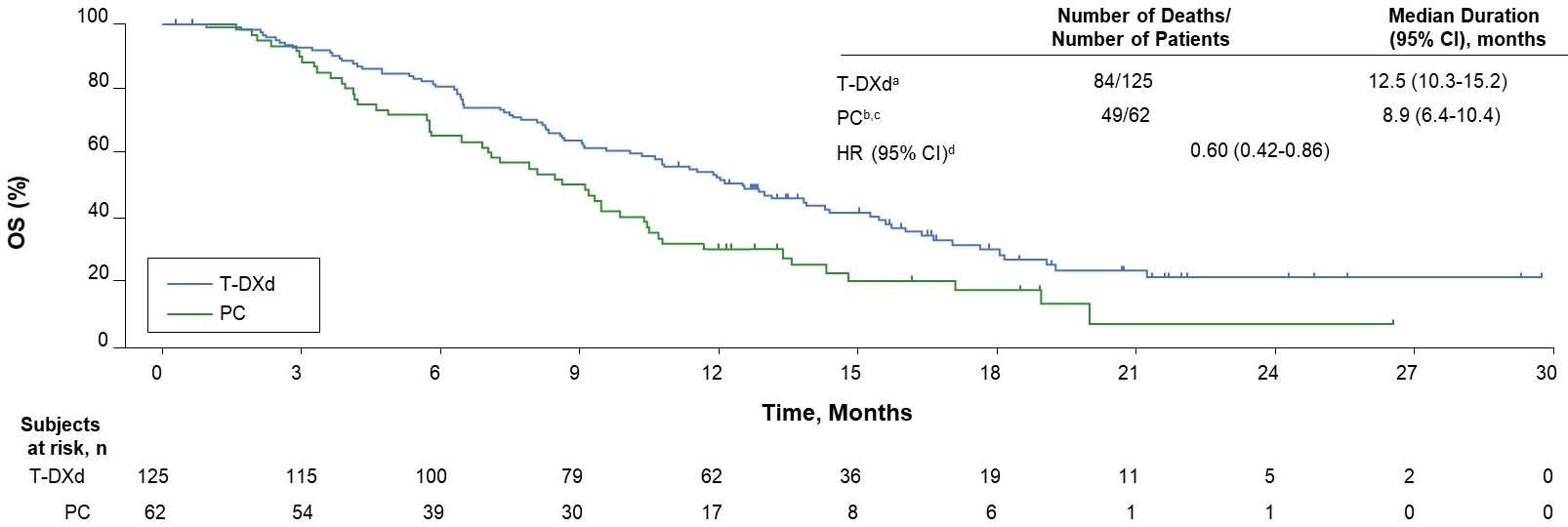
- Patients were stratified by country, ECOG PS score, and HER2 status
- In the primary analysis (data cutoff: Nov 8, 2019; 101 OS events; median survival follow-up, 12.3 months), T-DXd showed statistically significant benefit vs standard chemotherapy in ORR and OS
- Key secondary endpoint of OS was to be statistically evaluated hierarchically if the primary endpoint was statistically significant
- Data cutoff: June 3, 2020 (133 OS events; median survival follow-up: 18.5 months)

DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PC, physician's choice; PFS, progression-free survival; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.

Shitara K et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med*. 2020;382:2419-2430.

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.