9TH ANNUAL PUERTO RICO WINTER CANCER SYMPSIUM 2020

NOVEL APPROACH FOR EARLY STAGES/LOCALLY ADVANCE ESOPHAGEAL AND GE JUNCTION TUMORS

PEDRO GIL SOLIVAN, MD

HEMATOLOGY-ONCOLOGY

SAN JUAN, PR

9TH ANNUAL PUERTO RICO WINTER CANCER SYMPOSIUM 2020

Speaker Bureau: Astrazeneca, BMS, Janssen, BI, Takeda, Caris, Biodexic

Consultancy: None

Royalties: None

Research: None

Employment: None

Stocks: None

Other: None

Clinical Anatomy

- Hollow muscular tube 25 cm in length which spans from the **cricopharyngeus** at the **cricoid cartilage** to **gastroesophageal** junction (Extends from C7-T10).

- Has 4 constrictions-
  - At starting(cricophyrangeal junction)
  - crossed by aortic arch(9'inch)
  - crossed by left bronchus(11'inch)
  - Pierces the diaphragm(15'inch)

- Histologically 4 layers: mucosa, submucosa, muscular & fibrous layer.

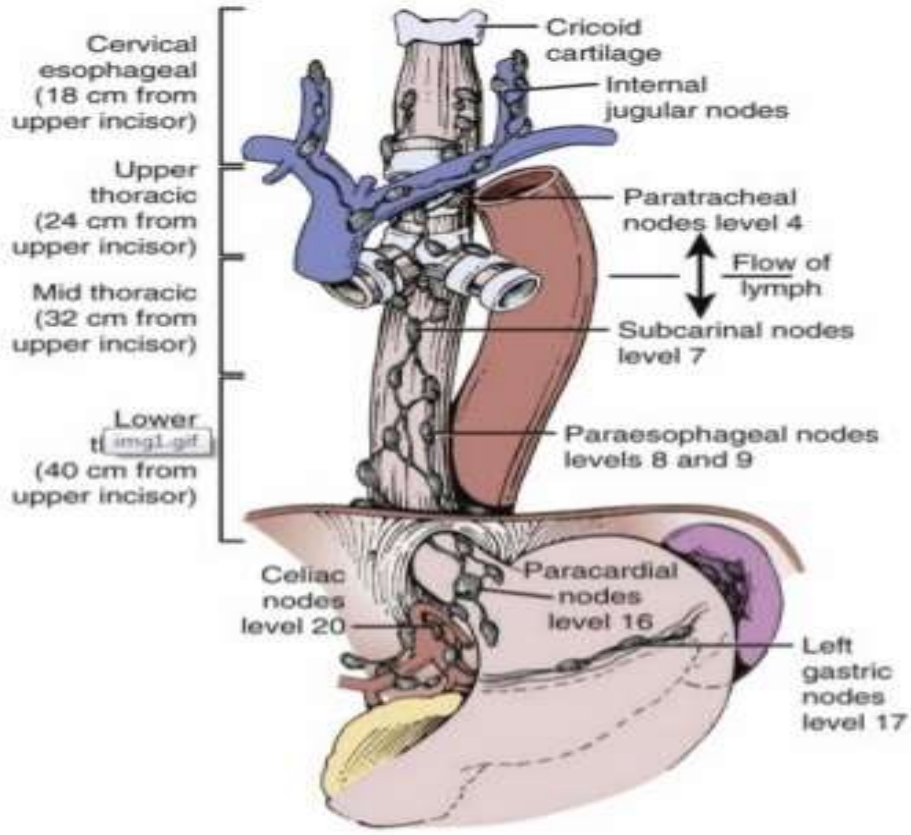
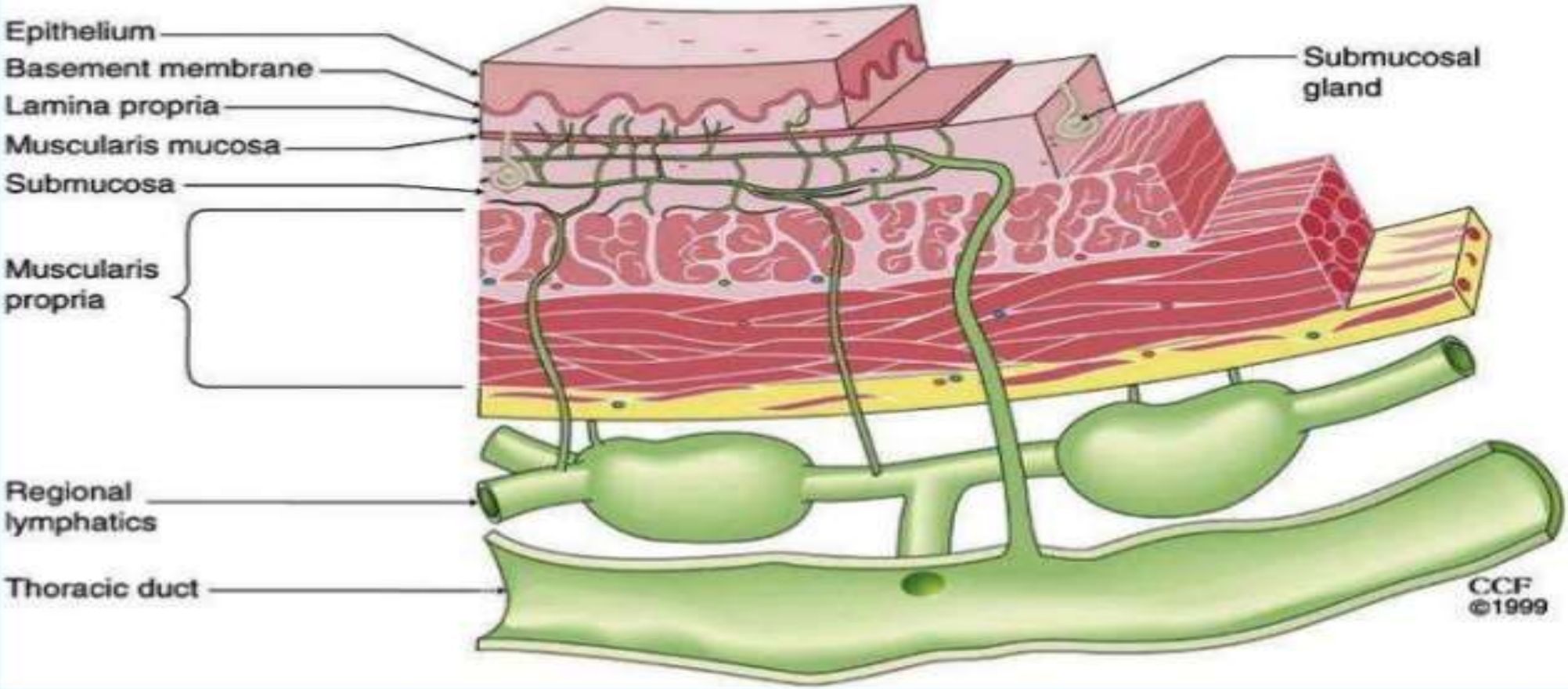
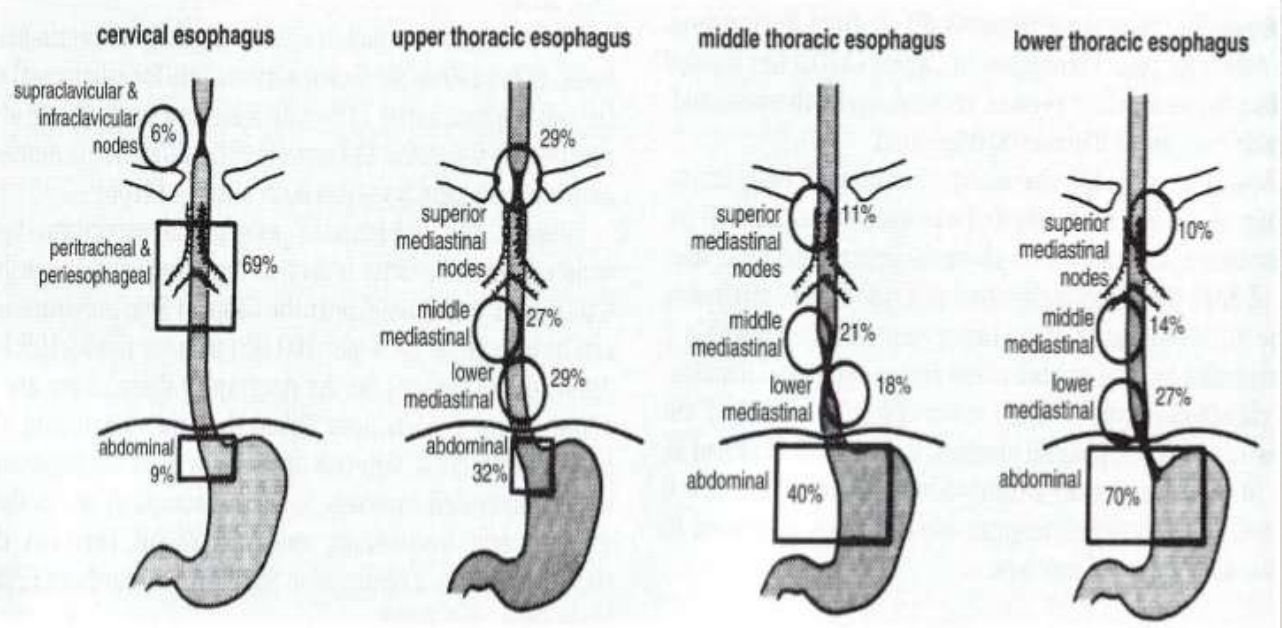


FIGURE Anatomy of the esophagus

The Esophageal Wall



Site-wise nodal involvement



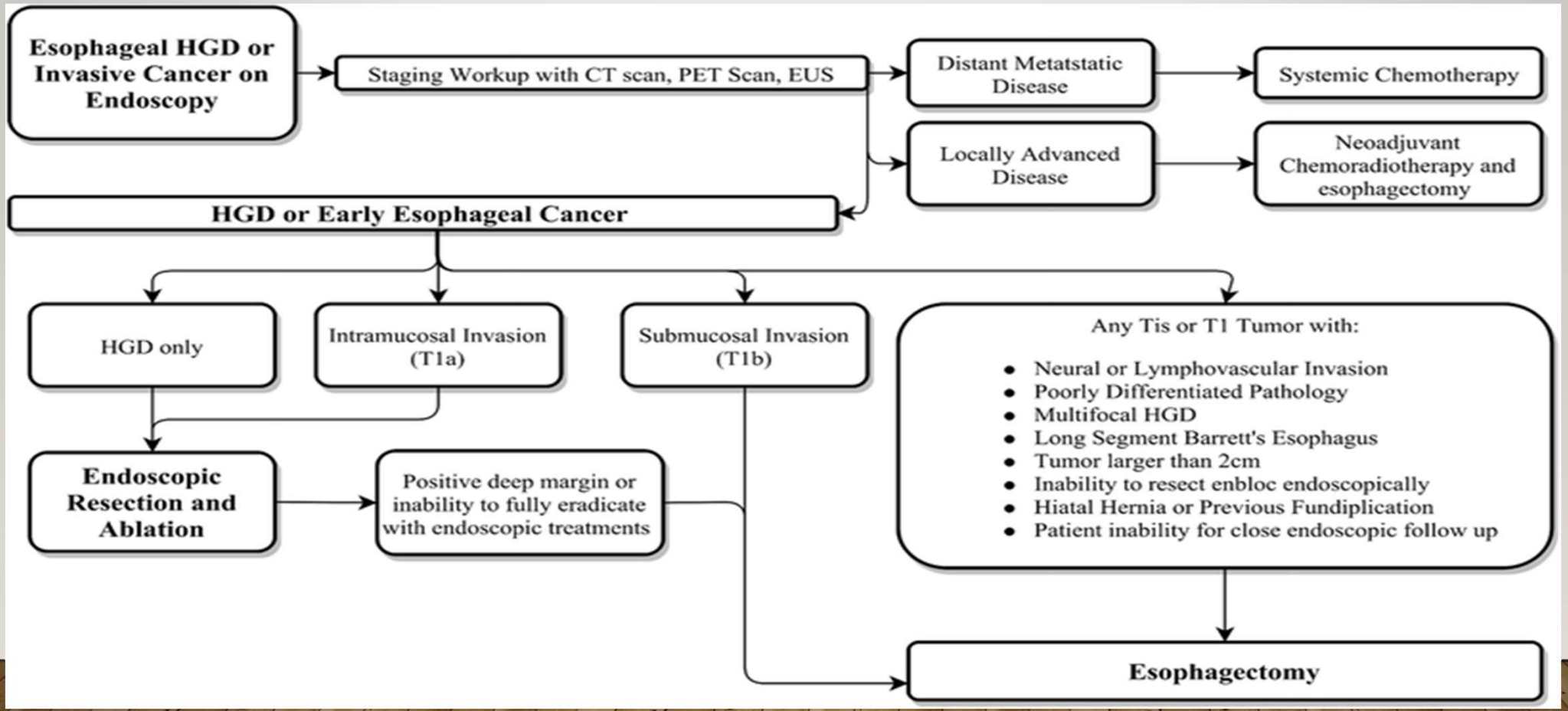
Geographical Distribution

- Carcinoma esophagus more common in China, Japan , India , South Africa Belgium ,Iran, U.K. France and Iceland

9TH ANNUAL PUERTO RICO WINTER CANCER SYMPOSIUM 2020

- Definition and Classification
  - Early esophageal cancers are
    - Tis (high grade dysplasia) and T1 lesions.
    - T1a- tumor invades lamina propria and muscularis mucosa
    - T1b- tumor invades submucosa.

9TH ANNUAL PUERTO RICO WINTER CANCER SYMPOSIUM 2020

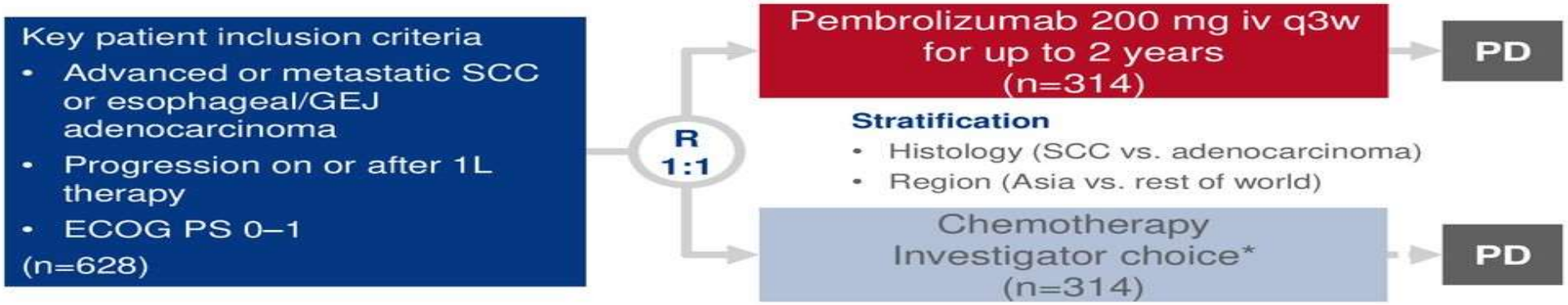


9TH ANNUAL PUERTO RICO WINTER CANCER SYMPOSIUM 2020

2: Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase III KEYNOTE-181 study – Kojima T, et al

Study objective

- To assess the efficacy and safety of pembrolizumab as a 2L treatment for patients with advanced or metastatic SCC and esophageal or GEJ adenocarcinoma in KEYNOTE-181



PRIMARY ENDPOINT

- OS in PD-L1 CPS ≥10, SCC, total population

SECONDARY ENDPOINTS

- PFS, ORR (RECIST v1.1), safety

*Paclitaxel 80–100 mg/m² D1, 8, 15 q4w; docetaxel 75 mg/m² q3w; or irinotecan 180 mg/m² q2w

Kojima T, et al. J Clin Oncol 2019;37(Suppl):Abstr 2

Pembrolizumab for Esophageal Cancer in Second-Line *KEYNOTE-181*

- Phase 3 study
- Patients with 1 of the following:
  - Advanced, metastatic adenocarcinoma or SCC of the esophagus
  - Siewert type 1 adenocarcinoma of the GEJ
- Pembrolizumab vs investigator's choice of chemo in second-line setting
- 628 patients; PD-L1 CPS ≥10

Patient Subgroup*	Pembrolizumab	Chemotherapy	*P* Value
mOS in PD-L1 positive, mo	9.3	6.7	.0074
mOS in SCC, mo	8.2	7.1	.0095
mOS in ITT, mo	7.1	7.1	.0560
Grade 3-5 TRAEs in ITT, %	18.2	40.9	

*Starting n for each patient subgroup in each treatment condition was different

Kojima T, et al. ASCO GI 2019. Abstract 2.

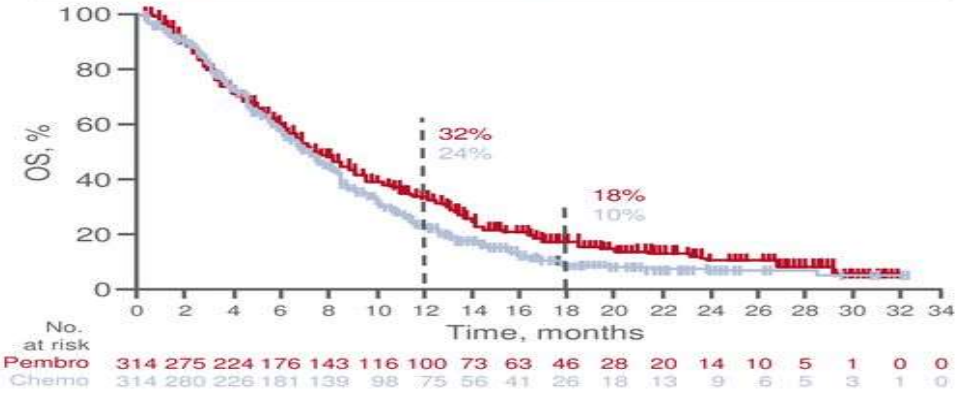
9TH ANNUAL PUERTO RICO WINTER CANCER SYMPOSIUM 2020

2: Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase III KEYNOTE-181 study – Kojima T, et al

Key results

OS in total population

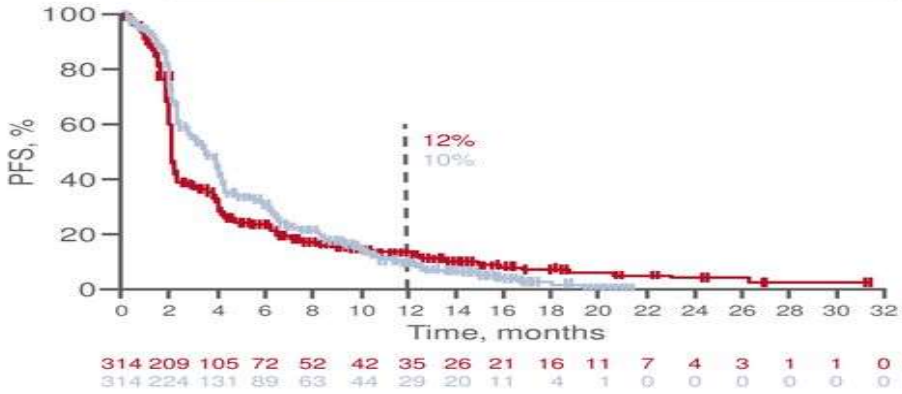
	Events, n	Median, mo (95%CI)	HR[a] (95%CI)	p-value
Pembrolizumab	314	7.1 (6.2, 8.1)	0.89 (0.75, 1.05)	0.0560
Chemotherapy	314	7.1 (6.3, 8.0)	–	



[a]Based on Cox regression model with treatment as a covariate stratified by region and histology

PFS in total population

	Median, mo (95%CI)	HR (95%CI)
Pembrolizumab	2.1 (2.1, 2.2)	1.11 (0.94, 1.31)
Chemotherapy	3.4 (2.8, 3.9)	



Kojima T, et al. J Clin Oncol 2019;37(Suppl):Abstr 2

EFFICACY RESULTS IN PATIENTS WITH RECURRENT OR METASTATIC ESCC (CPS ≥10) IN KEYNOTE-181

Endpoint	KEYTRUDA 200 mg every 3 weeks n=85	Chemotherapy N=82
OS		
Number (%) of patients with event	68 (80%)	72 (88%)
Median in months (95% CI)	10.3 (7.0, 13.5)	6.4 (4.8, 8.6)
Hazard ratio* (95% CI)	0.64 (0.46, 0.90)	
PFS		
Number (%) of patients with event	76 (89%)	76 (93%)
Median in months (95% CI)	3.2 (2.1, 4.4)	2.3 (2.1, 3.4)
Hazard ratio* (95% CI)	0.66 (0.48, 0.92)	
Objective Response Rate		
ORR (95% CI)	22 (14, 33)	7 (3, 15)
Number (%) of complete responses	4 (5)	1 (1)
Number (%) of partial responses	15 (18)	5 (6)
Median duration of response in months (range)	9.3 (2.1+, 18.8+)	7.7 (4.3, 16.8+)

9TH ANNUAL PUERTO RICO WINTER CANCER SYMPOSIUM2020

5: Safety and efficacy of durvalumab following trimodality therapy for locally advanced esophageal and GEJ adenocarcinoma: Early efficacy results from Big Ten Cancer Research Consortium study – Mamdani H, et al

Study objective

- To assess the efficacy and safety of durvalumab in patients with locally advanced esophageal or GEJ adenocarcinoma

Key patient inclusion criteria
- Locally advanced esophageal or GEJ adenocarcinoma
- ECOG PS 0–1

(n=24)

→ Preoperative CRT* followed by surgery (R0 resection)

→ Durvalumab 1500 mg iv† q4w for up to 1 year

PRIMARY ENDPOINT

- 1-year RFS

SECONDARY ENDPOINTS

- Safety

*Carboplatin/paclitaxel or cisplatin/5FU + definitive radiation;
†durvalumab started within 1–3 months of surgery

Mamdani H, et al. J Clin Oncol 2019;37(Suppl):Abstr 5

5: Safety and efficacy of durvalumab following trimodality therapy for locally advanced esophageal and GEJ adenocarcinoma: Early efficacy results from Big Ten Cancer Research Consortium study – Mamdani H, et al

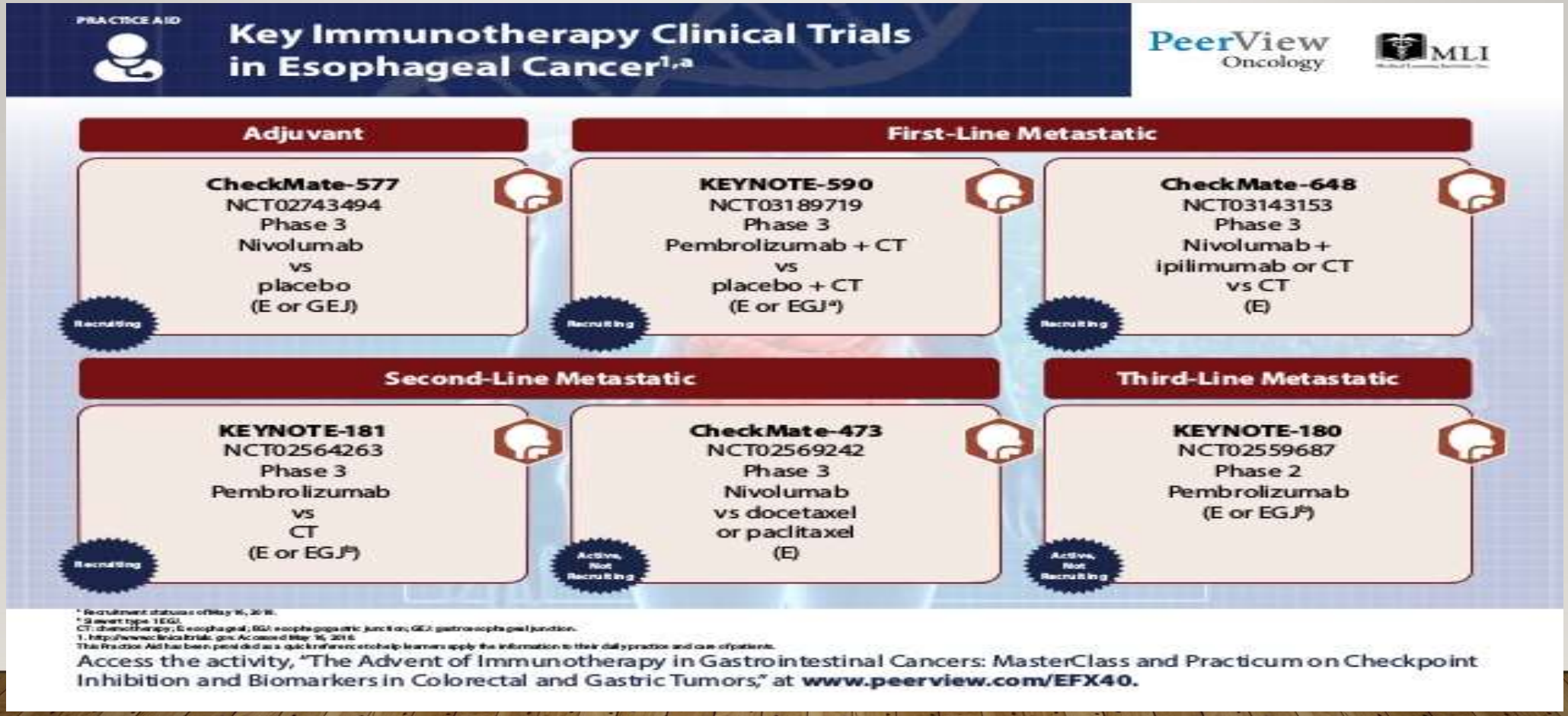
Key results (cont.)

AEs occurring in ≥10%, n (%)	Grade 1	Grade 2
Fatigue	6 (25.0)	2 (8.3)
Nausea	6 (25.0)	0 (0)
Cough	3 (12.5)	2 (8.3)
Diarrhea	3 (12.5)	1 (4.2)
Pruritus	3 (12.5)	1 (4.2)
Dyspnea	1 (4.2)	2 (8.3)

- Grade 3 AEs included hypoglycemia (n=1) and hyperglycemia (n=1)
- Grade 3 TRAEs leading to discontinuation occurred in 3 patients (1 pneumonitis, 1 hepatitis, 1 colitis)

Mamdani H, et al. J Clin Oncol 2019;37(Suppl):Abstr 5

9TH ANNUAL PUERTO RICO WINTER CANCER SYMPOSIUM 2020



•Nivolumab ± Ipilimumab

•in Patients With Advanced/Metastatic Chemotherapy-Refractory Gastric,

•Esophageal, or Gastroesophageal Junction Cancer:

•CheckMate 032 Study

Yelena Y. Janjigian,[1] Patrick A. Ott,[2] Emiliano Calvo,[3] Joseph W. Kim,[4] Paolo A. Ascierto,[5] Padmanee Sharma,[6] Katriina Peltola,[7] Dirk Jaeger,[8] Jeffrey Evans,[9] Filippo de Braud,[10] Ian Chau,[11] Marina Tschaika,[12] Christopher T. Harbison,[12] Weiguo Cai,[12] Johanna Bendell,[13] Dung T. Le[14]

[1]Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Dana-Farber Cancer Institute, Boston, MA; [3]START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain; [4]Yale Cancer Center, New Haven, CT; [5]Istituto Nazionale Tumori IRCCS, Naples, Italy; [6]The University of Texas MD Anderson Cancer Center, Houston, TX; [7]Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland; [8]National Center for Tumor Diseases, University Hospitals Heidelberg, Heidelberg, Germany; [9]Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK; [10]Fondazione IRCCS Istituto Tumori Milano, University of Milan, Milan, Italy; [11]Royal Marsden Hospital, London and Surrey, UK; [12]Bristol-Myers Squibb, Princeton, NJ; [13]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [14]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

BACKGROUND

- Nivolumab improved OS vs placebo in Asian patients with gastric/GEJ cancer with ≥ 2 prior treatments (ATTRACTION-2 phase 3 study)[1]
  - **27% vs 11% of patients alive at 1 year (HR, 0.63; *P* < 0.0001)**
- Nivolumab alone or in combination with ipilimumab led to encouraging results in a similar population of Western patients (CheckMate 032 phase 1/2 study)[2,3]
- Here we present **longer-term updated survival, efficacy, and safety** data from **CheckMate 032**

GEJ, gastroesophageal junction.

1. Kang YK, et al. ASCO-GI 2017 [abstract 2]; 2. Janjigian YY, et al. ASCO 2016 [abstract 4010]; 3. https://clinicaltrials.gov/ct2/show/study/NCT01928394 (Accessed April 21, 2017).

CHECKMATE 032 EG COHORT

Western patients with advanced/metastatic EG cancer with progression on ≥1 prior chemotherapy
N = 160

Nivolumab 3 mg/kg IV Q2W (NIVO 3)	**Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg IV Q3W* (NIVO 1 + IPI 3)**	**Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV Q3W* (NIVO 3 + IPI 1)**
Median (range) follow-up, mo†:		
28 (17 to 35)	**24 (21 to 33)**	**22 (19 to 25)**

Primary endpoint:

- ORR per RECIST v1.1

Secondary endpoints:

- OS, PFS, TTR, DOR
- Safety

Exploratory endpoint:

- PD-L1 tumor expression (Dako 28-8 pharmDx assay)

DOR, duration of response; EG, esophagogastric (including gastric/esophageal/gastroesophageal junction cancer); TTR, time to response.
* Nivolumab + ipilimumab administered for 4 cycles followed by nivolumab 3 mg/kg IV Q2W.
† Time from first dose to data cut-off; follow-up was shorter for patients who died prior to data cut-off.

BASELINE CHARACTERISTICS

Patients, n (%)	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
Age, median (range), years	60 (29 to 80)	53 (27 to 77)	58 (19 to 81)
≥65 years	17 (29)	10 (20)	17 (33)
Male	45 (76)	34 (69)	45 (87)
Race			
White	56 (95)	46 (94)	50 (96)
Black	3 (5)	1 (2)	1 (2)
Asian/other	0	2 (4)	1 (2)
Primary site			
Gastric	19 (32)	22 (45)	18 (35)
GEJ/esophageal	40 (68)	27 (55)	34 (65)
Number of prior regimens			
0	0	1 (2)	0
1	10 (17)	6 (12)	16 (31)
2	**20 (34)**	**19 (39)**	**16 (31)**
3	**19 (32)**	**11 (22)**	**13 (25)**
>3	**10 (17)**	**12 (24)**	**7 (13)**
PD-L1 tumor expression, n/N (%)*			
≥1%	16/42 (38)	10/42 (24)	13/43 (30)
<1%	**26/42 (62)**	**32/42 (76)**	**30/43 (70)**

* PD-L1 tumor expression rates reported according to the number of patients with quantifiable samples. PD-L1 was quantifiable in 71%, 86%, and 83% of patients in the NIVO 3, NIVO 1 + IPI 3, and NIVO 3 + IPI 1 treatment groups, respectively.

PATIENT DISPOSITION

Patients, n (%)	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
Continuing on study treatment	2 (3)	6 (12)	3 (6)
Not continuing on study treatment	57 (97)	43 (88)	49 (94)
Disease progression	**50 (85)**	**25 (51)**	**38 (73)**
AE related to study drug	2 (3)*	9 (18)†	7 (13)‡
AE unrelated to study drug	3 (5)	5 (10)	1 (2)
Patient withdrawal/noncompliance	2 (3)	4 (8)	3 (6)

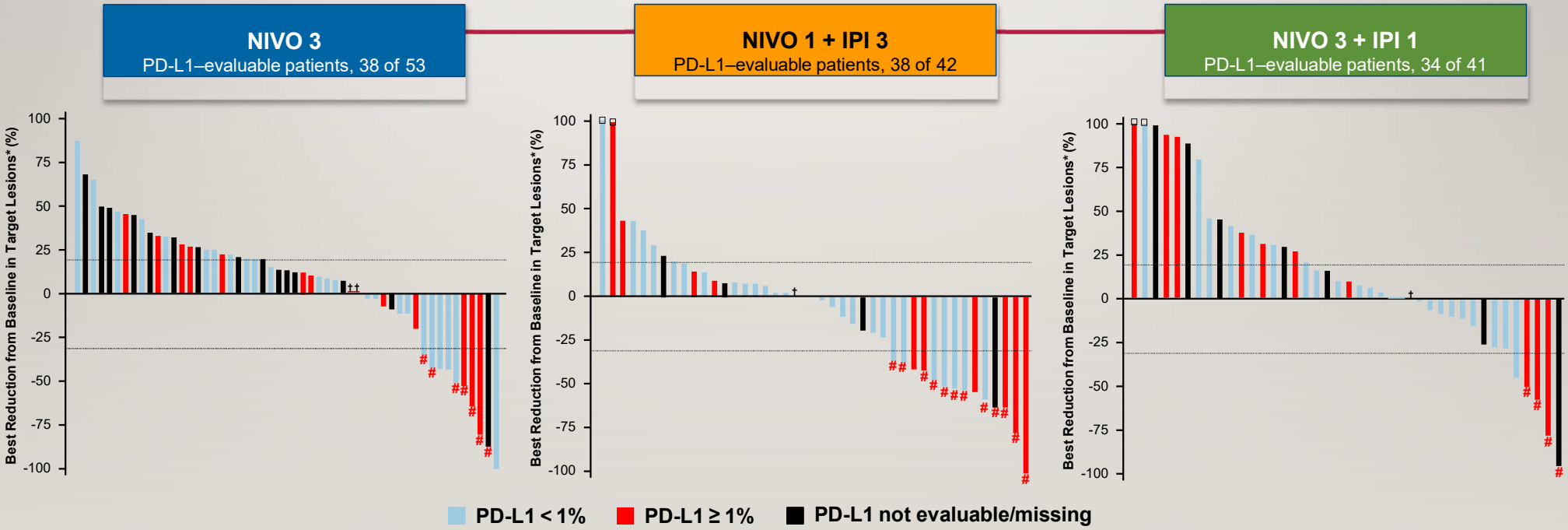
* Increased ALT/AST (n=1); pneumonitis (n=1).
† Increased ALT/AST (n=3); colitis (n=2); diarrhea (n=2); colitis, cystitis, and transaminitis (n=1); diarrhea and hyperthyroidism (n=1).
‡ Acute renal failure, autoimmune hepatitis, diarrhea, enteritis, increased ALT/AST, lymphocytic myocarditis, and pneumonitis (n=1 each).

OBJECTIVE RESPONSE

	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
ORR, n (%)*	**7 (12)**	**12 (24)**	**4 (8)**
[95% CI]	[5, 23]	[13, 39]	[2, 19]
BOR, n (%)*			
Complete response	1 (2)	1 (2)	0
Partial response	6 (10)	11 (22)	4 (8)
Stable disease	12 (20)	8 (16)	15 (29)
Progressive disease	34 (58)	23 (47)	24 (46)
Not evaluable	6 (10)	6 (12)	9 (17)
DCR, n (%)†	19 (32)	20 (41)	19 (37)
Median TTR (range), months	1.6 (1.2 to 4.0)	2.7 (1.2 to 14.5)	2.6 (1.3 to 2.8)
Median DOR (95% CI), months	7.1 (3.0, 13.2)	7.9 (2.8, NE)	NR (2.5, NE)

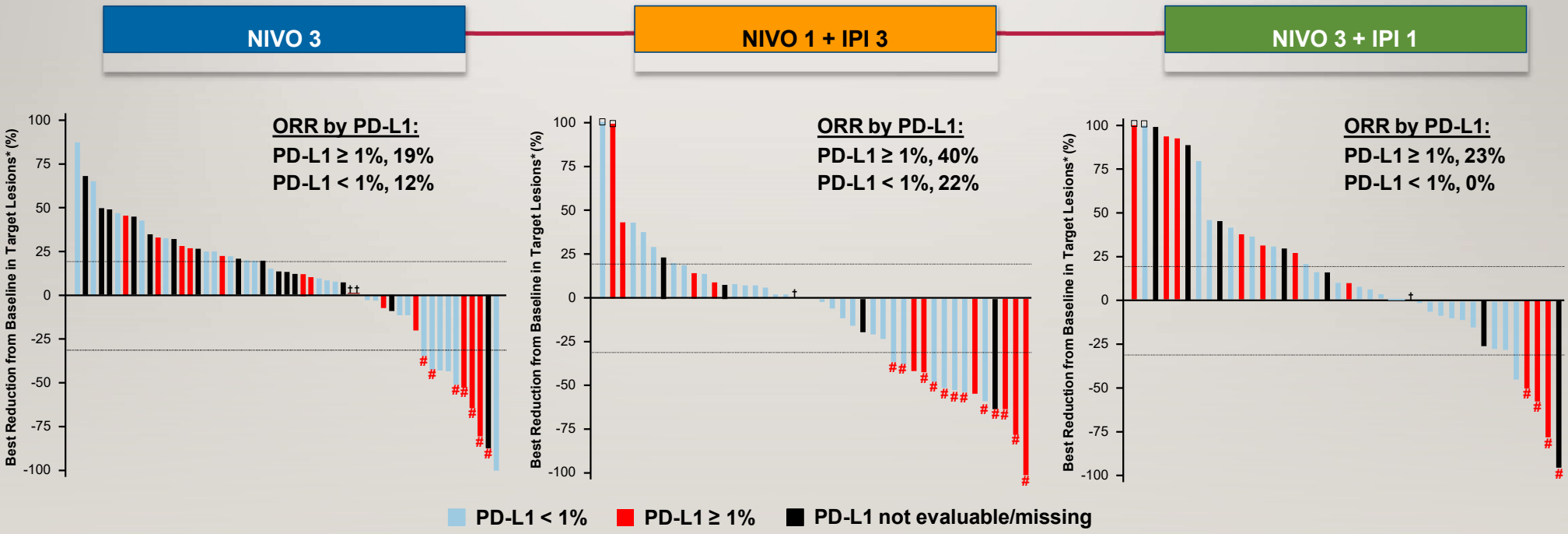
BOR, best objective response; DCR, disease control rate; NR, not reached, NE, not estimable.
* Investigator review.
† Patients with a BOR of complete response, partial response, or stable disease.

BEST REDUCTION IN TARGET LESIONS



* Investigator review.
\# Patients with confirmed response (complete or partial response).
† Patients with 0% best reduction in target lesion, including 3 patients with PD-L1 ≥1% (NIVO 3, n=2; NIVO 3 + IPI 1, n=1) and 1 patient with PD-L1 <1% (NIVO 1 + IPI 3).
□ change truncated to 100%

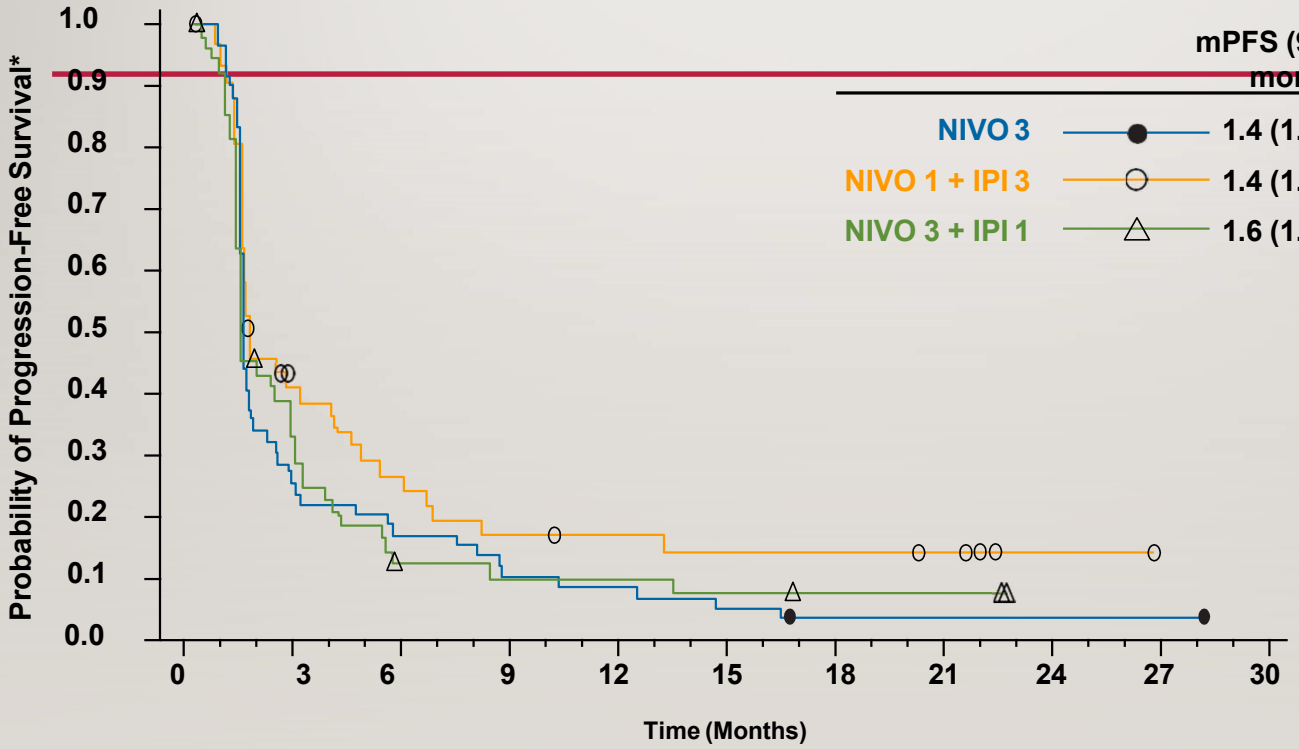
BEST REDUCTION IN TARGET LESIONS



- Responses were observed regardless of PD-L1 expression

* Investigator review.
# Patients with confirmed response (complete or partial response).
† Patients with 0% best reduction in target lesion, including 3 patients with PD-L1 ≥1% (NIVO 3, n=2; NIVO 3 + IPI 1, n=1) and 1 patient with PD-L1 <1% (NIVO 1 + IPI 3).
□ change truncated to 100%

PROGRESSION-FREE SURVIVAL



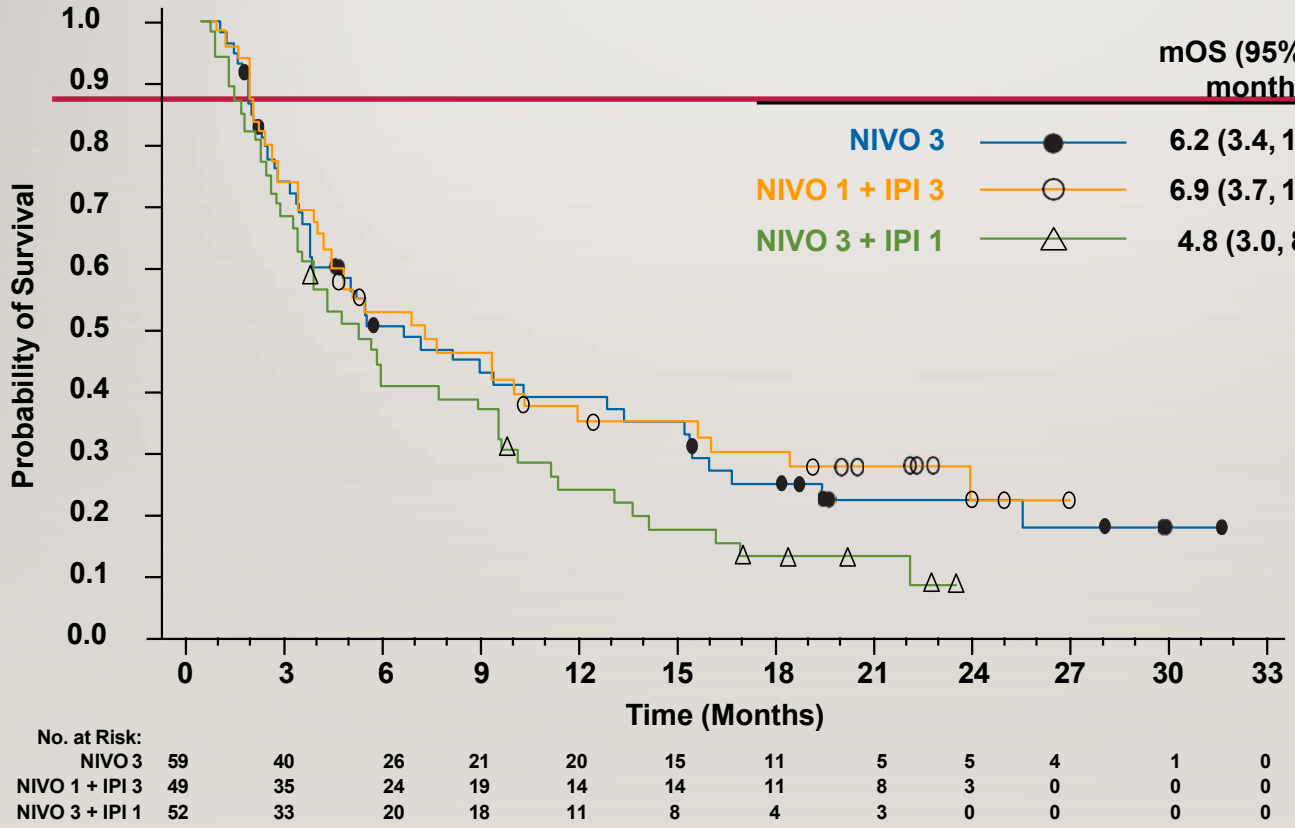
	mPFS (95% CI), months	6-month PFS rate, %	12-month PFS rate, %
NIVO 3	1.4 (1.2, 1.5)	17	8
NIVO 1 + IPI 3	1.4 (1.2, 3.8)	24	17
NIVO 3 + IPI 1	1.6 (1.4, 2.6)	12	10

No. at Risk:

NIVO 3	59	13	10	6	5	3	1	1	1	1	0
NIVO 1 + IPI 3	49	16	10	7	6	5	5	4	1	0	0
NIVO 3 + IPI 1	52	13	5	4	4	3	2	2	0	0	0

mPFS, median PFS
* Investigator review.

OVERALL SURVIVAL



	mOS (95% CI), months	12-month OS rate, %	18-month OS rate, %
NIVO 3	6.2 (3.4, 12.4)	39	25
NIVO 1 + IPI 3	6.9 (3.7, 11.5)	35	28
NIVO 3 + IPI 1	4.8 (3.0, 8.4)	24	13

No. at Risk:												
NIVO 3	59	40	26	21	20	15	11	5	5	4	1	0
NIVO 1 + IPI 3	49	35	24	19	14	14	11	8	3	0	0	0
NIVO 3 + IPI 1	52	33	20	18	11	8	4	3	0	0	0	0

mOS, median OS.

OVERALL SURVIVAL BY PD-L1 STATUS

OS rate (95% CI), %	NIVO 3	NIVO 1 + IPI 3	NIVO 3 + IPI 1
Patients with PD-L1 ≥1%	**n = 16**	**n =10**	**n = 13**
12 months	34 (12, 57)	50 (18, 75)	23 (6, 47)
Patients with PD-L1 <1%	**n = 26**	**n = 32**	**n = 30**
12 months	45 (25, 62)	32 (16, 48)	25 (11, 42)

TREATMENT-RELATED ADVERSE EVENTS

Patients, n (%)	NIVO 3 n = 59		NIVO 1 + IPI 3 n = 49		NIVO 3 + IPI 1 n = 52	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAE	41 (69)	10 (17)	41 (84)	23 (47)	39 (75)	14 (27)
Serious TRAEs	**6 (10)**	**3 (5)**	**21 (43)**	**17 (35)**	**13 (25)**	**9 (17)**
TRAEs leading to treatment discontinuation	2 (3)	2 (3)	10 (20)	10 (20)	7 (13)	5 (10)
TRAEs in ≥15% of patients in any treatment arm						
ALT increased	5 (8)	2 (3)	8 (16)	7 (14)	5 (10)	2 (4)
AST increased	7 (12)	3 (5)	8 (16)	5 (10)	2 (4)	1 (2)
Decreased appetite	9 (15)	0	5 (10)	0	3 (6)	0
Diarrhea	9 (15)	1 (2)	15 (31)	7 (14)	5 (10)	1 (2)
Fatigue	20 (34)	1 (2)	14 (29)	3 (6)	10 (19)	0
Pruritus	10 (17)	0	9 (18)	1 (2)	12 (23)	0
Rash	5 (8)	0	10 (20)	0	8 (15)	0

- One grade 5 TRAE was reported (tumor lysis syndrome in a patient treated with NIVO 3 + IPI 1)

TRAE, treatment-related adverse event.

CONCLUSIONS

- Nivolumab alone or in combination with ipilimumab demonstrates clinical activity in patients with chemotherapy-refractory EG cancer irrespective of PD-L1 status
- Safety profile is consistent with prior reports[1-4]
- Nivolumab alone and in combination with ipilimumab are being investigated in phase 3 studies in patients with advanced EG cancer

1. Janjigian YY, et al. ASCO 2016 [abstract 4010]; 2. Larkin J, et al. *N Engl J Med.* 2015;373:23-34; 3. Wolchok JD, et al. *N Engl J Med.* 2013;369:122-133; 4. Antonia SJ, et al. *Lancet Oncol*. 2016;17:883-895.

ACKNOWLEDGMENTS

- The patients and families that made this trial possible
- The clinical study teams that participated in this trial
- Bristol-Myers Squibb, Inc. (Princeton, NJ) and Ono Pharmaceutical Co., Ltd. (Osaka, Japan)
- Dako for collaborative development of the PD-L1 28-8 pharmDx assay
- The study was supported by Bristol-Myers Squibb, Inc.
- All authors contributed to and approved the presentation; writing and editorial assistance was provided by Jonathan Morgan of Chrysalis Medical Communications, Inc., funded by Bristol-Myers Squibb, Inc.
- ClinicalTrials.gov identifier NCT01928394

Poster #, 383

Three-Year Follow-up of ATTRACTION-2: A Phase 3 Study of Nivolumab in Previously Treated Advanced Gastric or Gastric Esophageal Junction Cancer

Li-Tzong Chen[1], Yoon-Koo Kang[2], Taroh Satoh[3], Yee Chao[4], Ken Kato[5], Hyun Cheol Chung[6], Jen-Shi Chen[7], Kei Muro[8], Won Ki Kang[9], Takaki Yoshikawa[10], Sang Cheul Oh[11], Takao Tamura[12], Keun-Wook Lee[13], Narikazu Boku[5]

[1]National Institute of Cancer Research, National Health Research Institutes, and National Cheng Kung University Hospital, National Cheng Kung University, Tainan, Taiwan; [2]Department of Oncology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea; [3]Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan; [4]Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan; [5]Division of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [6]Division of Medical Oncology, Yonsei Cancer Center, Song-Dang Institute for Cancer Research, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea; [7]Division of Hematology and Oncology, Department of Internal Medicine, Linkou Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan; [8]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [9]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [10]Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan; [11]Division of Hematology and Oncology, Department of Internal Medicine, College of Medicine, Korea University, Seoul, South Korea; [12]Department of Medical Oncology, Faculty of Medicine, Kindai University, Osakasayama, Japan; [13]Division of Hematology and Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea

Background

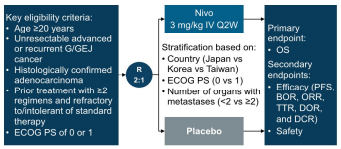
- Gastric/gastric esophageal junction (G/GEJ) cancer is the fifth most frequently diagnosed cancer and the third leading cause of cancer-related deaths worldwide[1]
- The incidence rates of G/GEJ cancer are markedly high in eastern Asia, including in Japan and Korea[1]
  - Korea has the highest rates of G/GEJ cancer worldwide for both sexes[1]
- Nivolumab, an immune checkpoint inhibitor, demonstrated survival benefits in the ATTRACTION-2 study in patients with unresectable advanced or recurrent G/GEJ cancer treated with ≥2 chemotherapy regimens[2]
  - Based on the results of the ATTRACTION-2 study,[2] nivolumab was approved in Japan,[3] Taiwan,[4] South Korea,[5] Singapore,[6] and Switzerland[7] as a third- or later-line therapeutic option in patients with unresectable advanced or recurrent G/GEJ cancer
  - Nivolumab is currently recommended as third- or later-line therapy for the treatment of gastric cancer according to the 2018 guidelines in Japan and Korea[8,9]
- Here, we report the 3-year survival update of the ATTRACTION-2 study (data cutoff: February 17, 2019)

Methods

Study design

- ATTRACTION-2 was a randomized, double-blind, placebo-controlled, phase 3 study conducted at 49 sites in Japan, South Korea, and Taiwan (**Figure 1**)

Figure 1. Study design and endpoints of ATTRACTION-2



Among the secondary efficacy endpoints, only PFS is reported in this presentation.
BOR, best overall response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; G/GEJ, gastric/gastroesophageal junction; IV, intravenous; Nivo, nivolumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; R, randomization; TTR, time to tumor response

Treatment

- Eligible patients were randomized in a 2:1 ratio to receive nivolumab (3 mg/kg intravenously every 2 weeks) or placebo until disease progression or unacceptable toxicity

Post hoc exploratory analysis

- Overall survival (OS) analyzed by best overall response (BOR: complete response [CR] + partial response [PR], progressive disease [PD], and stable disease [SD])
- Subgroup analysis of OS by treatment-related adverse events (TRAEs) of special interest (i.e., events with potential immunologic etiology)
- Landmark analysis: Subgroup analysis of OS by TRAEs of special interest in patients who continued nivolumab treatment for >2 months
- The duration of nivolumab treatment in patients with CR or PR with TRAEs of special interest is presented as a swimmer plot

Results

- A total of 493 patients were randomized to receive treatment with nivolumab (N=330) or placebo (N=163)

Demographics and baseline characteristics

- Patient demographics and baseline characteristics were comparable between the nivolumab and placebo groups (**Table 1**)

Table 1. Demographics and baseline characteristics

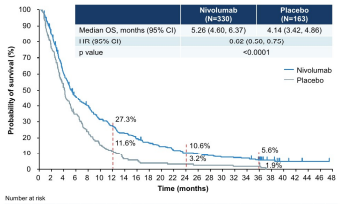
	Nivolumab 3 mg/kg (N=330)	Placebo (N=163)
Median age (IQR), years	62 (54–69)	61 (53–69)
<65 years, n (%)	189 (57.3)	95 (58.3)
Male, n (%)	229 (69.4)	119 (73.0)
Country, n (%)		
Japan	152 (46.1)	74 (45.4)
Korea	146 (44.2)	74 (45.4)
Taiwan	32 (9.7)	15 (9.2)
ECOG PS, n (%)		
0	95 (28.8)	48 (29.4)
1	235 (71.2)	115 (70.6)
Primary site of disease, n (%)		
Gastric	272 (82.4)	135 (82.8)
Gastric esophageal junction	30 (9.1)	12 (7.4)
Unknown	28 (8.5)	16 (9.8)
Prior gastrectomy, n (%)		
No	133 (40.3)	58 (35.6)
Yes	197 (59.7)	105 (64.4)
Organs with metastases (≥2), n (%)	246 (74.5)	119 (73.0)
Prior treatment regimens, n (%)		
2	69 (20.9)	29 (17.8)
3	137 (41.5)	62 (38.0)
≥4	124 (37.6)	72 (44.2)
Previous therapy, n (%)		
Any	330 (100.0)	163 (100.0)
Fluoropyrimidines	329 (99.7)	163 (100.0)
Platinum	311 (94.2)	157 (96.3)
Taxanes	284 (86.1)	140 (85.9)
Irinotecan	247 (74.8)	123 (75.5)
Ramucirumab	35 (10.6)	22 (13.5)

ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range

Efficacy

- The OS was significantly longer with nivolumab (median 5.26 months) vs placebo (median 4.14 months; hazard ratio [HR] [95% confidence interval (CI)]: 0.62 [0.50, 0.75], p<0.0001) (**Figure 2**)
- The estimated 3-year OS rate was numerically higher with nivolumab (5.6%) vs placebo (1.9%)
- A total of 15 patients in the nivolumab group and 3 patients in the placebo group survived >3 years. Two out of these 3 patients in the placebo group received nivolumab as subsequent post-progression therapy

Figure 2. OS over 3 years of follow-up

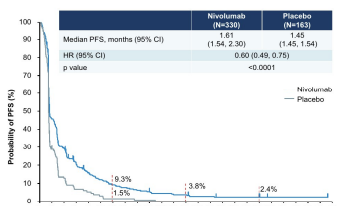


CI, confidence interval; HR, hazard ratio; OS, overall survival

PFS over 3 years of follow-up

- The progression-free survival (PFS) was longer with nivolumab (median 1.61 months) vs placebo (median 1.45 months; HR [95% CI]: 0.60 [0.49, 0.75], p<0.0001)
- The estimated 3-year PFS rate was numerically higher with nivolumab (2.4%) vs placebo (0%) (**Figure 3**)

Figure 3. PFS over 3 years of follow-up

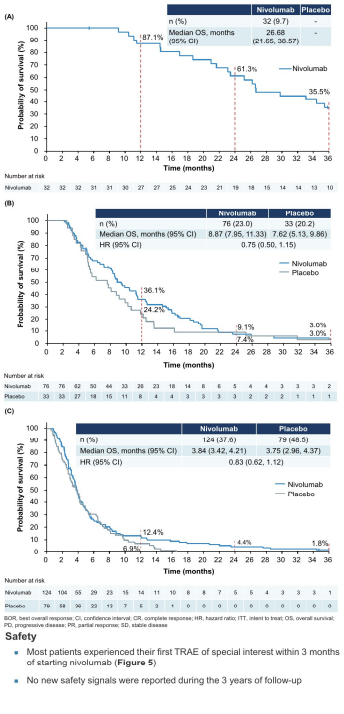


CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Subanalysis of OS by BOR

- The median OS was 26.68 months among patients with a CR or PR in the nivolumab group (**Figure 4A**). No patient in the placebo group had a CR or PR
- Even among patients with SD, the median OS was numerically longer with nivolumab vs placebo (**Figure 4B**)
- This analysis contains some biases

Figure 4. OS over 3 years of follow-up analyzed by BOR. (A) CR+PR, (B) SD, and (C) PD (ITT population)

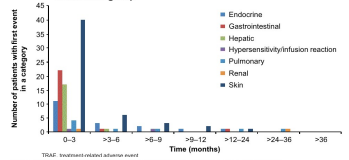


BOR, best overall response; CI, confidence interval; CR, complete response; HR, hazard ratio; ITT, intent to treat; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease

Safety

- Most patients experienced their first TRAE of special interest within 3 months of starting nivolumab (**Figure 5**)
- No new safety signals were reported during the 3 years of follow-up

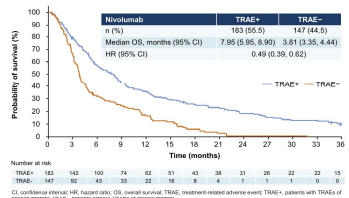
Figure 5. Onset of TRAEs of special interest over time in the nivolumab group



Subgroup analysis of OS by TRAEs of special interest

- In the nivolumab group (N=330), 183 (55.5%) patients experienced any TRAEs of special interest
- The median OS was 7.95 months for patients with these TRAEs and 3.81 months for patients without these TRAEs (**Figure 6**)

Figure 6. Subgroup analysis of OS by TRAEs of special interest

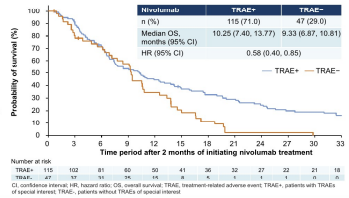


CI, confidence interval; HR, hazard ratio; OS, overall survival; TRAE, treatment-related adverse event; TRAE+, patients with TRAEs of special interest; TRAE−, patients without TRAEs of special interest

Landmark analysis

- Among 162 patients who continued nivolumab treatment for >2 months, the survival of 115 patients with TRAEs of special interest (median 10.25 months) was favorable compared with 47 patients without these TRAEs (median 9.33 months) (**Figure 7**)

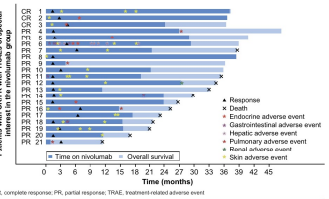
Figure 7. Landmark analysis: OS subgroup analysis by TRAEs of special interest in patients who continued nivolumab treatment for >2 months



CI, confidence interval; HR, hazard ratio; OS, overall survival; TRAE, treatment-related adverse event; TRAE+, patients with TRAEs of special interest; TRAE−, patients without TRAEs of special interest

- Among 32 patients with CR/PR, 21 experienced TRAEs of special interest and 11 did not experience these TRAEs
- Among 21 patients with these TRAEs, 9 experienced the TRAEs before the first response to nivolumab (**Figure 8**)

Figure 8. Duration of nivolumab treatment in patients with CR/PR with TRAEs of special interest (n=21) in the nivolumab group



CR, complete response; PR, partial response; TRAE, treatment-related adverse event

Conclusions

- Nivolumab demonstrated a statistically significant improvement in long-term OS compared with placebo in patients with previously treated advanced G/GEJ cancer
  - Median OS: 6.26 months in the nivolumab group vs 4.14 months in the placebo group
  - 3-year OS rate: 5.6% in the nivolumab group vs 1.9% in the placebo group
- The long-term survival benefit of nivolumab was most evident in patients with CR or PR
  - Even among patients with SD, the median OS was numerically longer with nivolumab vs placebo
- No new safety signals were observed in the 3-year long-term survival update
- Patients who experienced TRAEs of special interest with nivolumab had a longer median OS than those who did not
- All TRAEs of special interest did not precede before response to nivolumab
- All patients should be carefully monitored for the development of TRAEs of special interest during and after nivolumab treatment

References

1. Bray F, et al. CA Cancer J Clin. 2018;68:394–424.
2. Kang YK, et al. Lancet. 2017;390:2461–71.
3. Ono Pharmaceutical Co., Ltd. Press release, September 22, 2017. https://www.ono.co.jp/eng/news/pdf/ism_on170922.pdf. Accessed October 15, 2019.
4. Ono Pharmaceutical Co., Ltd. Press release, January 23, 2018. https://www.ono.co.jp/eng/news/pdf/ism_on180123.pdf. Accessed October 15, 2019.
5. Nam D. Korea Biomedical Review. August 20, 2019. http://www.koreabiomed.com/news/articleView.html?idxno=2883. Accessed October 15, 2019.
6. Singapore Health Sciences Authority. OPDIVO Product Insert. November 21, 2018. https://www.hsa.gov.sg/announcements/new-drug-indication-approvals/new-drug-indication-approval-nov-2018. Accessed October 15, 2019.
7. Swissmedic. OPDIVO Prescribing Information. www.swissmedicinfo.ch. Accessed October 15. 2019.
8. Japan Gastric Cancer Society, Tokyo, Kanehara & Co., Ltd., 2018. http://www.kanehara-shuppan.co.jp/books/detail.html?isbn=9784307203814. Accessed October 15, 2019.
9. Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel. J Gastric Cancer. 2019;19:1–48.

Acknowledgments

- We thank the patients and their families as well as the investigators and participating study teams for making this study possible
- This study was sponsored by Ono Pharmaceutical Co., Ltd., Osaka, Japan, and Bristol-Myers Squibb, Inc., Princeton, NJ
- Writing and editorial assistance was provided by Aninundha Chillar, MD, PhD, of Cactus Communications and was funded by Ono Pharmaceutical Co., Ltd., Osaka, Japan, and Bristol-Myers Squibb, Inc., Princeton, NJ

Email: leochen@nhri.org.tw

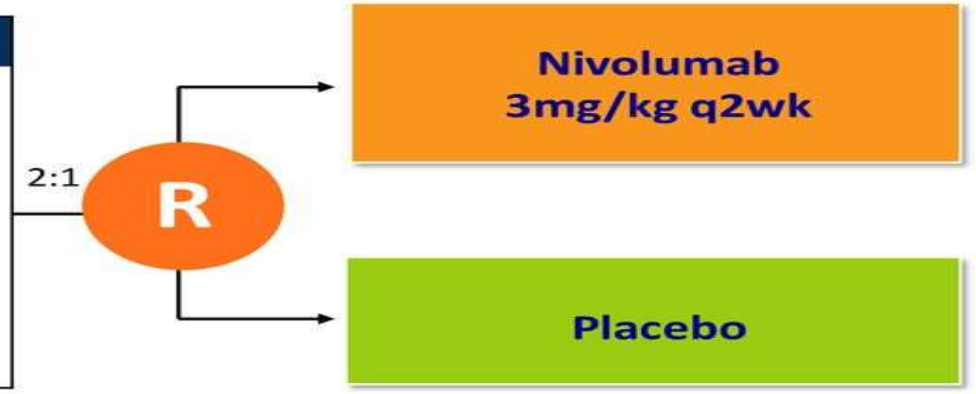
Presented at the 2020 Gastrointestinal Cancers Symposium (ASCO-GI), January 23-25, 2020, San Francisco, CA

ATTRACTION-2 Phase III Schema

Target Accrual: 493
Clinical Trial Identifier: NCT02267343

Eligibility

- Unresectable advanced or recurrent gastric or GEJ cancer
- Histologically confirmed adenocarcinoma
- Prior treatment with ≥2 regimens and refractory to/intolerant of standard therapy
- PS 0 or 1



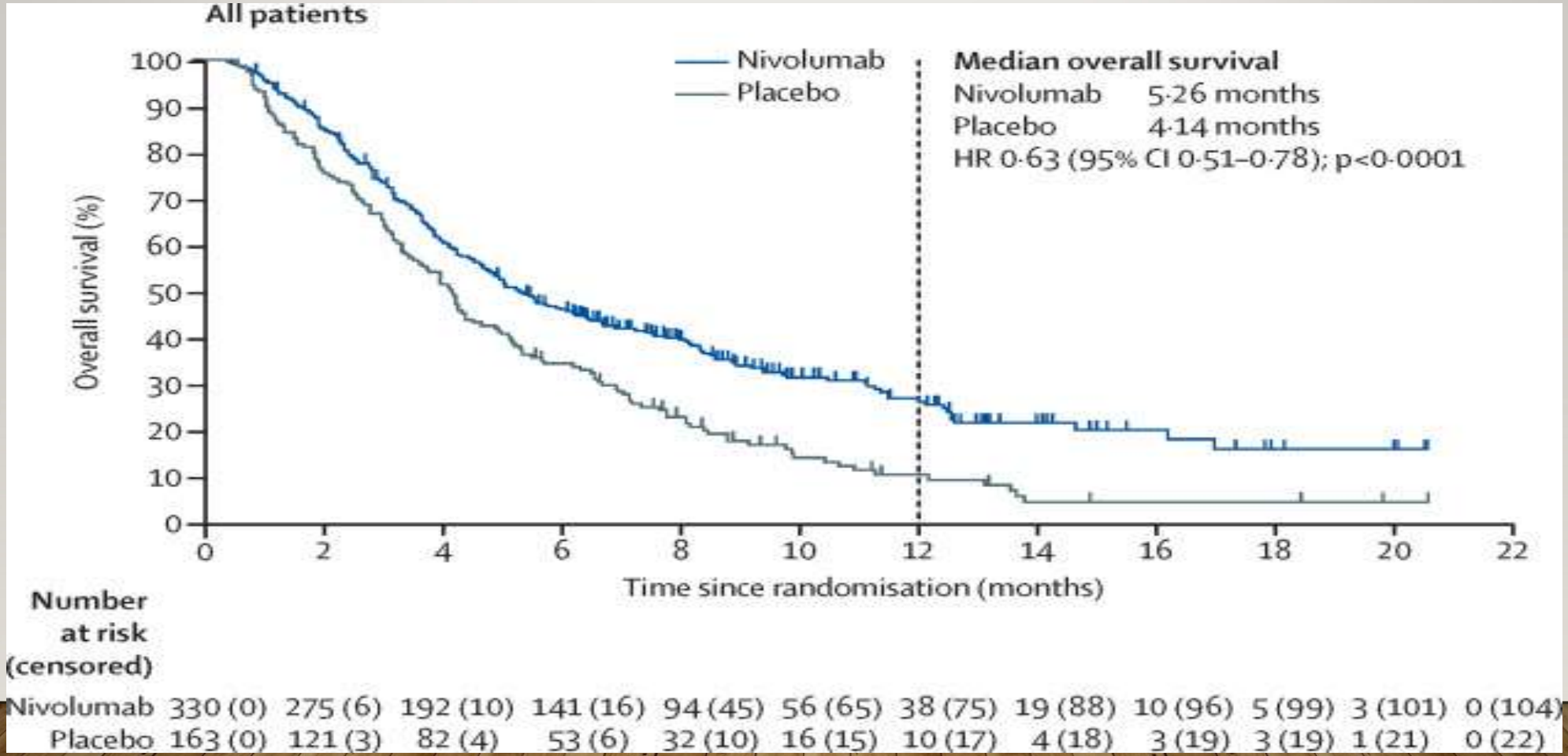
Primary endpoint: Overall survival

Patients were permitted to continue treatment beyond initial RECIST v1.1-defined disease progression, as assessed by the investigator, if receiving clinical benefit and tolerating treatment drug.

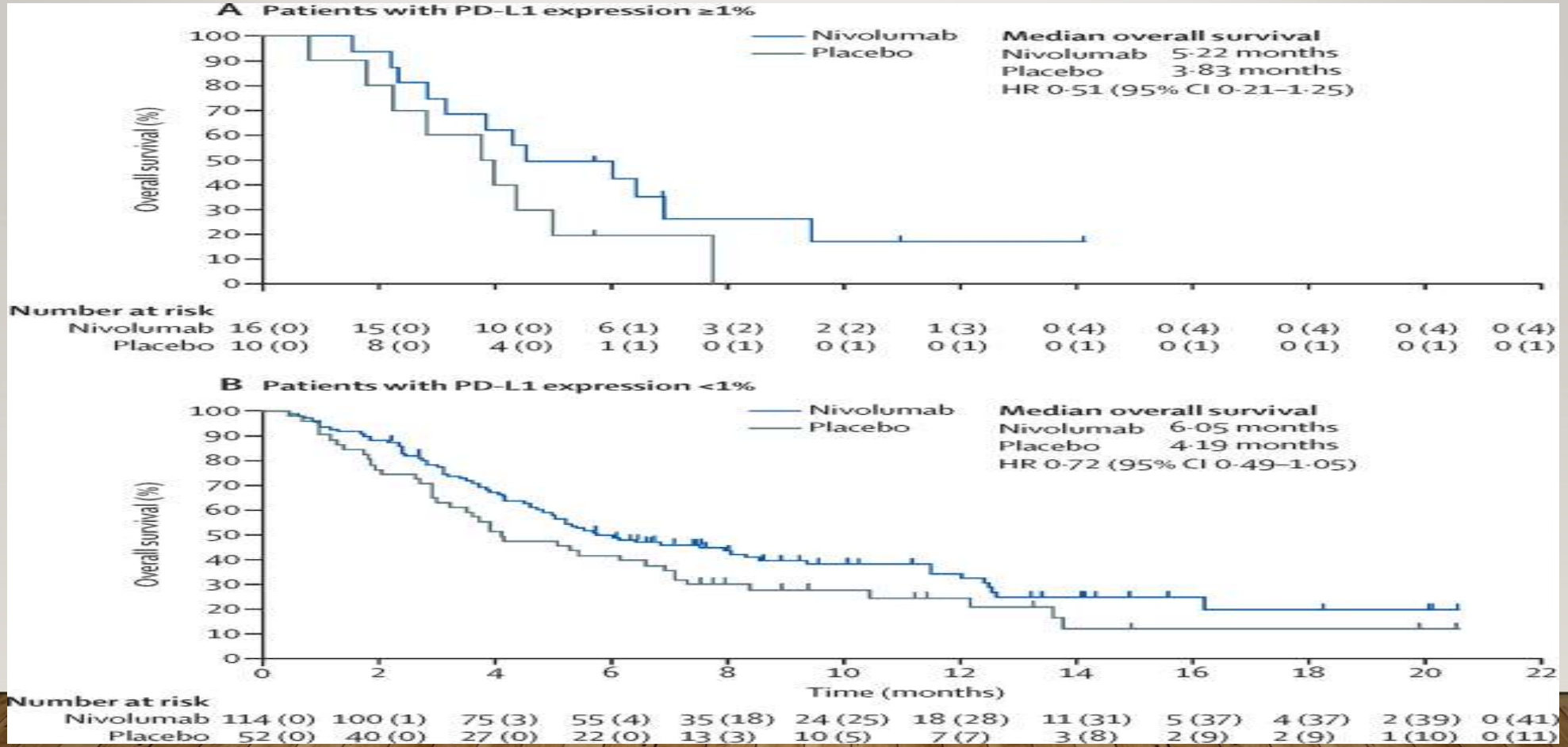
Kang YK et al. GI Cancers Symposium 2017;Abstract 02.

Research To Practice®

9TH ANNUAL PUERTO RICO WINTER CANCER SYMPSIUM 2020



9TH ANNUAL PUERTO RICO WINTER CANCER SYMPSIUM 2020 UAL PUERTO RICO WINTER CANCER



Immunotherapy Plus Chemotherapy
First-Line Setting

KEYNOTE-59 Cohort 2[a]

- Phase 2 study
- 25 patients with advanced G/GEJ cancer
- Pembrolizumab + 5-FU + cisplatin
- Higher ORR (PD-L1-positive): 69%
- mPFS: 6.6 mo
- mOS: 20.8 mo

ATTRACTION-4[b]

- Phase 2 study
- 40 patients with unresectable advanced or *HER2*-negative G/GEJ cancer
- Nivolumab + S-1 + SOX or CAPOX
- ORR (SOX): 57.1%
- ORR (CAPOX): 76.5%
- mOS (both groups): NR
- Proceeded to phase 3: nivolumab + SOX/CAPOX vs SOX/CAPOX alone

a. Bang YJ, et al. ASCO 2017. Abstract 4012.
b. Boku N, et al. *Ann Oncol*. 2019;30:250-258.

Conclusion

- Esophageal cancer is the 7th leading cause of cancer deaths.
- Adenocarcinoma now accounts for over 50% of esophageal cancer in the USA, due to association with GERD & obesity.
- Dysphagia and weight loss are the two most common presentations in patients with esophageal cancer.
- Endoscopic ultrasound (EUS) is necessary to accompany a complete workup for proper staging and diagnosis of esophageal cancer.
- Surgery is the standard of care for early-stage esophageal cancer.
- Preoperative chemotherapy and radiation is the standard option for locally advanced esophageal cancer in surgically eligible patients.

THE END