"New treatment options for Gastrointestinal Malignancies"

ARUN NAGARAJAN, MD
VICE CHAIR NAPRC RECTAL CANCER MULTIDISCIPLINARY TEAM
GI MEDICAL ONCOLOGIST
CLEVELAND CLINIC WESTON, FLORIDA

"Upper GI Cancer: New Immunotherapy Approaches"

- Significant paradigm shift in management

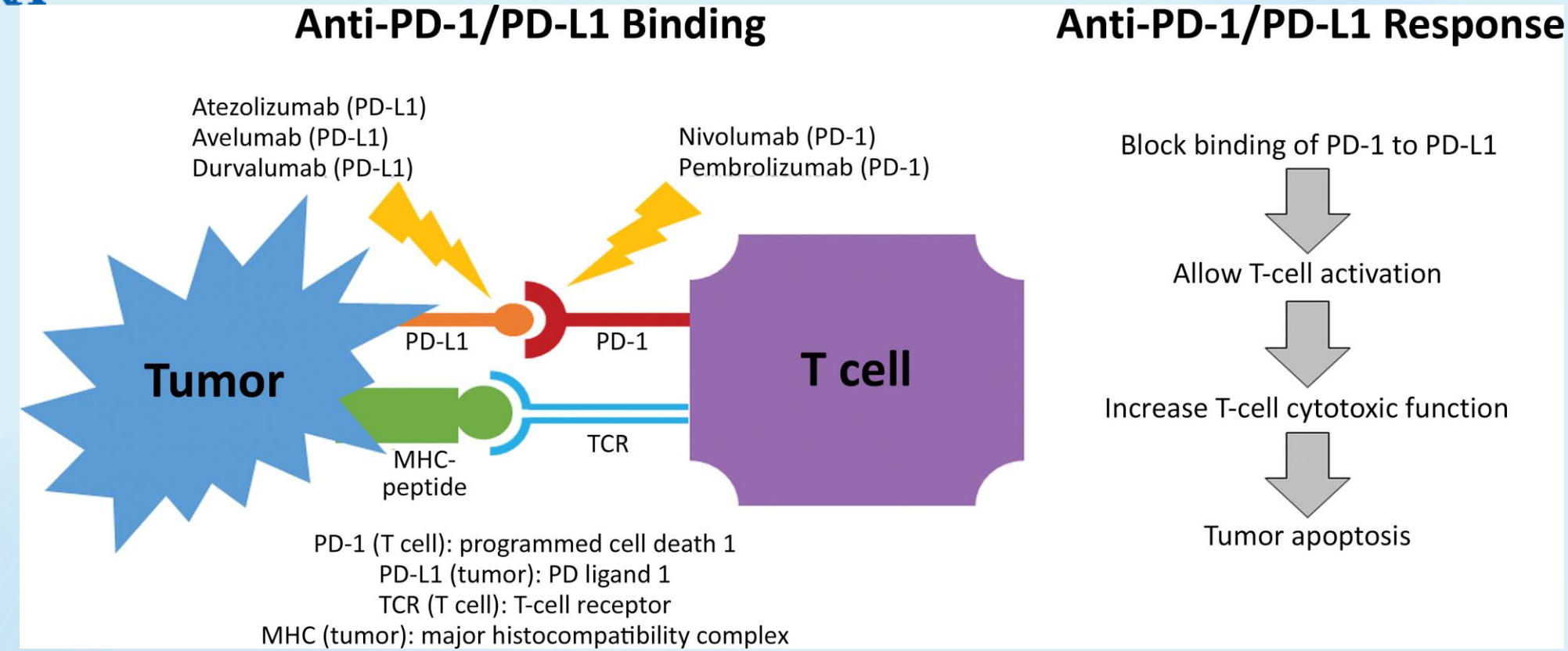

Figure 1a. Illustrations show the mechanisms of action (left) of ICIs and the downstream tumor effects (right) for PD-1 and PD-L1 **(a)** and CTLA-4 **(b)** inhibitors. *APC* = antigen-presenting cell, *B7-1/2* = ligands B7-1 and B7-2.

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NCCN Guidelines Version 4.2021
Esophageal and Esophagogastric Junction Cancers

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy

- Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Preferred Regimens

- HER2 overexpression positive adenocarcinoma[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,18]
- HER2 overexpression negative[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥ 5) for adenocarcinoma only (category 1)[e,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS 1-4) for adenocarcinoma only (category 2B)[e,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (PD-L1 CPS ≥ 10) for adenocarcinoma or squamous cell carcinoma[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (PD-L1 CPS 1-9) for adenocarcinoma only (category 2B)[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (PD-L1 CPS ≥ 10) (category 1) for adenocarcinoma or squamous cell carcinoma[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (PD-L1 CPS 1-9) for adenocarcinoma only (category 2B)[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin for adenocarcinoma or squamous cell carcinoma[21-23]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin for adenocarcinoma or squamous cell carcinoma[21,24-26]

Other Recommended Regimens

- HER2 overexpression positive adenocarcinoma[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab[a] and pembrolizumab[e,h,27]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] and pembrolizumab[e,h,27]
- Fluorouracil[b,i] and irinotecan[j,28]
- Paclitaxel with or without cisplatin or carboplatin [j,29-33]
- Docetaxel with or without cisplatin [j,34-37]
- Fluoropyrimidine [j,25,38,39] (fluorouracil[b] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b, j,40,41]

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy
- Dependent on prior therapy and PS

Preferred Regimens
- Nivolumab for esophageal squamous cell carcinoma (category 1)[e,h,43]
- Pembrolizumab[e,h]
  - For second-line therapy for esophageal squamous cell carcinoma, with PD-L1 expression levels by CPS of ≥10 (category 1)[44]
- Ramucirumab and paclitaxel for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[45]
- Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[46]
- Docetaxel (category 1)[36,37]
- Paclitaxel (category 1)[31,33,47]
- Irinotecan (category 1)[47-50]
- Fluorouracil[b,i] and irinotecan[48,51,52]
- Trifluridine and tipiracil for third-line or subsequent therapy for EGJ adenocarcinoma (category 1)[53]

Other Recommended Regimens
- Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[54]
- Irinotecan and cisplatin[22,55]
- Fluorouracil and irinotecan + ramucirumab for adenocarcinoma[b,i,56]
- Irinotecan and ramucirumab for adenocarcinoma[57]
- Docetaxel and irinotecan (category 2B)[58]

Useful in Certain Circumstances
- Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[59,60]
- Pembrolizumab[e,h] for MSI-H or dMMR tumors[61-63]
- Pembrolizumab[e,h] for TMB high (≥10 mutations/megabase) tumors[64]

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2021
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
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PRINCIPLES OF SYSTEMIC THERAPY

Preoperative Chemoradiation
(Infusional fluorouracil[b] can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin (category 1)[1]
- Fluorouracil[b] and oxaliplatin (category 1)[2,3]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[4,5]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Definitive Chemoradiation
(Infusional fluorouracil can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin[1]
- Fluorouracil[b] and oxaliplatin (category 1)[2,3]
- Fluorouracil and cisplatin (category 1)[11]

Other Recommended Regimens
- Cisplatin with docetaxel or paclitaxel[12-14]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Perioperative Chemotherapy
(Only for adenocarcinoma of the thoracic esophagus or EGJ)

Preferred Regimens
- Fluorouracil,[b] leucovorin, oxaliplatin, and docetaxel (FLOT)[8] (category 1)[c]
- Fluoropyrimidine and oxaliplatin[b,d]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[9]

Preoperative Chemotherapy
(Only for adenocarcinoma of the thoracic esophagus or EGJ)

- Fluorouracil and cisplatin (category 2B)[10]

Postoperative Therapy

Preferred Regimens
- Nivolumab only after preoperative chemoradiation with R0 resection and residual disease (category 1)[e,15]

Other Recommended Regimens
- Capecitabine and oxaliplatin[f,16]
- Fluorouracil[b] and oxaliplatin[f]

Postoperative Chemoradiation

- Fluoropyrimidine (infusional fluorouracil[b] or capecitabine) before and after fluoropyrimidine-based chemoradiation[17]

[b]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.

[c]Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit.

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy
- Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Preferred Regimens
- HER2 overexpression positive adenocarcinoma[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,11]
- HER2 overexpression negative[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)[g,h,12]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[13-15]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[13,16-18]

Other Recommended Regimens
- HER2 overexpression positive adenocarcinoma[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab[a] and pembrolizumab[g,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] and pembrolizumab[g,h,19]
- Fluorouracil[b,i] and irinotecan[j,20]
- Paclitaxel with or without cisplatin or carboplatin[j,21-25]
- Docetaxel with or without cisplatin[j,26-29]
- Fluoropyrimidine[j,17,30,31] (fluorouracil[b] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b,j,32,33]
- Docetaxel, carboplatin, and fluorouracil (category 2B)[j,34]

Useful in Certain Circumstances
- HER2 overexpression negative[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS 1-4) (category 2B)[g,h,12]

[a]An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy
• Dependent on prior therapy and PS
Preferred Regimens
• Ramucirumab and paclitaxel (category 1)[35]
• Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[36]
• Docetaxel (category 1)[28,29]
• Paclitaxel (category 1)[24,25,37]
• Irinotecan (category 1)[37-40]
• Fluorouracil[b,i] and irinotecan[38,41,42]
• Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[43]
Other Recommended Regimens
• Ramucirumab (category 1)[44]
• Irinotecan and cisplatin[14,45]
• Fluorouracil and irinotecan + ramucirumab[b,i,46]
• Irinotecan and ramucirumab[47]
• Docetaxel and irinotecan (category 2B)[48]
Useful in Certain Circumstances
• Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[49,50]
• Pembrolizumab[g,h] for MSI-H or dMMR tumors[51-53]
• Pembrolizumab[g,h] for TMB high (≥ 10 mutations/megabase) tumors[54]

"Upper GI Cancer: New Immunotherapy Approaches

LBA28_PR: KEYNOTE-059 update: Efficacy and safety of pembrolizumab alone or in combination with chemotherapy in patients with advanced gastric or gastroesophageal (G/GEJ) cancer – Wainberg ZA, et al

Study objective

- To evaluate the efficacy and safety of pembrolizumab alone or in combination with CT in patients with advanced gastric cancer

Key patient inclusion criteria

- Recurrent or metastatic gastric or GEJ adenocarcinoma
- **Cohort 1:** ≥2 prior lines of CT; PD-L1 positive or negative
- **Cohort 2:** No prior therapy; PD-L1 positive or negative
- **Cohort 3:** No prior therapy; PD-L1-positive

(n=315)

R

- Pembrolizumab 200 mg q3w monotherapy (n=259)
- Pembrolizumab 200 mg q3w + CT* [Japan only] (n=25)
- Pembrolizumab 200 mg q3w monotherapy (n=31)

≤35 cycles (~2 years) or PD/toxicity

PRIMARY ENDPOINTS

- Safety (all), ORR (cohorts 1 + 3)

SECONDARY ENDPOINTS

- ORR (cohort 2), DCR, PFS, OS

***Cisplatin 80 mg/m^2 D1 + 5FU 800 mg/m^2 D1–5 q3w or capecitabine 1000 mg/m^2 bid**

Wainberg ZA, et al. Ann Oncol 2017;28(Suppl 5):Abstr **LBA28_PR**

LBA28_PR: KEYNOTE-059 update: Efficacy and safety of pembrolizumab alone or in combination with chemotherapy in patients with advanced gastric or gastroesophageal (G/GEJ) cancer – Wainberg ZA, et al

Key results

Cohort 1	All (n=259)	PD-L1 positive (n=148)	PD-L1 negative (n=109)
ORR, % (95%CI)	12 (8, 17)	16 (11, 23)	6 (3, 13)
DCR, % (95%CI)	27 (22, 33)	34 (26, 42)	19 (12, 28)
mPFS, months (95%CI)	2.0 (2.0, 2.1)	2.1 (2.0, 2.1)	2.0 (1.9, 2.0)
mOS, months (95%CI)	5.5 (4.2, 6.5)	5.8 (4.4, 7.8)	4.6 (3.2, 6.5)

Cohort 2	All (n=25)	PD-L1 positive (n=15)	PD-L1 negative (n=8)
ORR, % (95%CI)	60 (39, 79)	73 (45, 92)	38 (9, 76)
DCR, % (95%CI)	80 (59, 93)	80 (52, 96)	75 (35, 97)
mPFS, months (95%CI)	6.6 (5.9, 10.6)	-	-
mOS, months (95%CI)	13.8 (8.6, NR)	-	-

Cohort 3	All (n=31)
ORR, % (95%CI)	26 (12, 45)
DCR, % (95%CI)	36 (19, 55)
mPFS, months (95%CI)	3.3 (2.0, 6.0)
mOS, months (95%CI)	20.7 (9.2, 20.7)

Wainberg ZA, et al. Ann Oncol 2017;28(Suppl 5):Abstr **LBA28_PR**

LBA28_PR: KEYNOTE-059 update: Efficacy and safety of pembrolizumab alone or in combination with chemotherapy in patients with advanced gastric or gastroesophageal (G/GEJ) cancer – Wainberg ZA, et al

Key results (cont.)

TRAEs, n (%)	Cohort 1 (n=259)	Cohort 2 (n=25)	Cohort 3 (n=31)
Any	159 (61)	25 (100)	24 (77)
Grades ≥3	46 (18)	19 (76)	7 (23)
Anaemia	7 (3) [grade 3]	2 (8)	-
Fatigue	6 (2) [grade 3]	2 (8)	-
Dehydration	3 (1) [grade 3]	-	-
Neutropenia	-	6 (24)	-
Stomatitis	-	5 (20)	-
Decreased platelet count	-	2 (8)	-
Decreased appetite	-	2 (8)	-
Serious	29 (11)	-	-
Led to discontinuation	7 (3)	3 (12)	0 (0)
Led to death	2 (1)	0 (0)	1 (3)

Conclusions

- In patients with advanced gastric cancer, pembrolizumab continues to demonstrate promising anti-tumour activity:
  - As monotherapy in patients with PD after ≥2 prior lines of CT
  - In combination with CT in previously untreated patients
  - As monotherapy in previously untreated patients with PD-L1–positive tumours
- Responses were higher in patients with PD-L1–positive tumours in cohorts 1 and 2
- Safety was manageable and consistent with that of previous reports

FDA granted accelerated approval for Pembrolizumab **Third-Line Indication for GEJ/Gastric adenocarcinoma with CPS≥1** in 2017

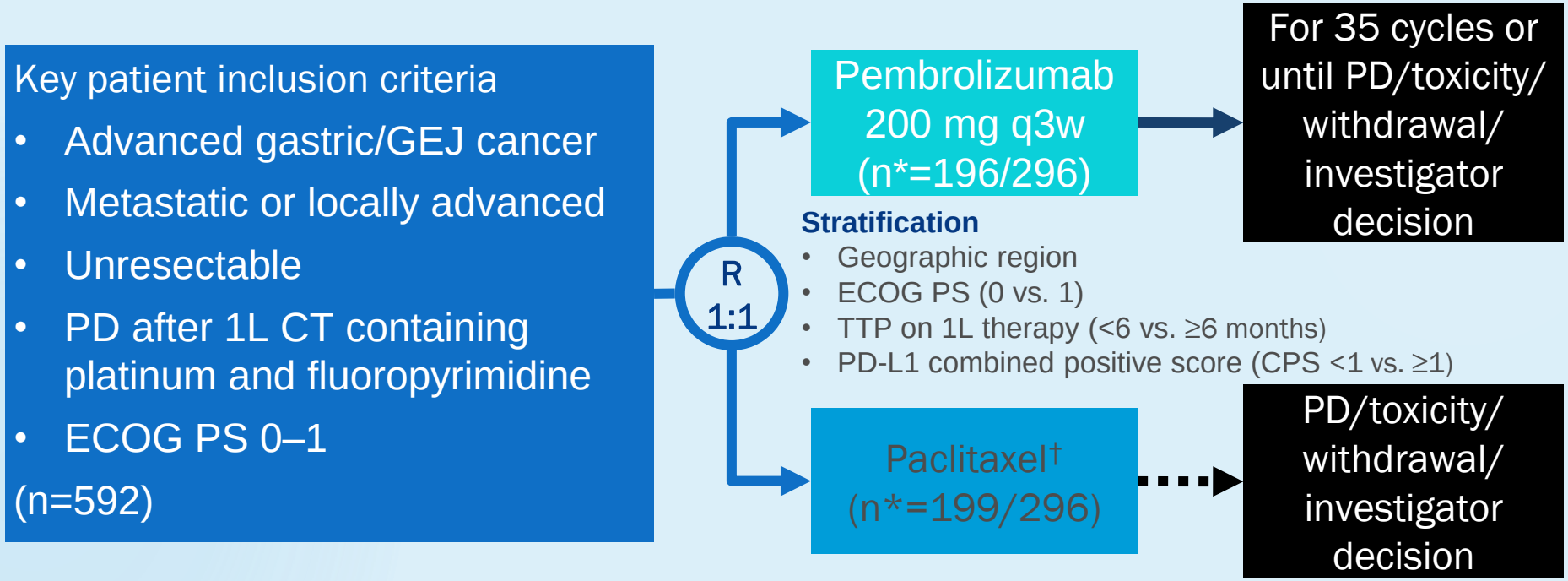
Wainberg ZA, et al. Ann Oncol 2017;28(Suppl 5):Abstr **LBA28_PR**

"Upper GI Cancer: New Immunotherapy Approaches

4062: Pembrolizumab (pembro) vs paclitaxel (PTX) for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase 3 KEYNOTE-061 trial – Fuchs CS, et al

Study objective

- **To assess the efficacy and safety of pembrolizumab vs. paclitaxel in previously treated patients with advanced gastric/GEJ cancer in the KEYNOTE-061 study**



PRIMARY ENDPOINT

- OS‡, PFS in CPS ≥1 population

SECONDARY ENDPOINTS

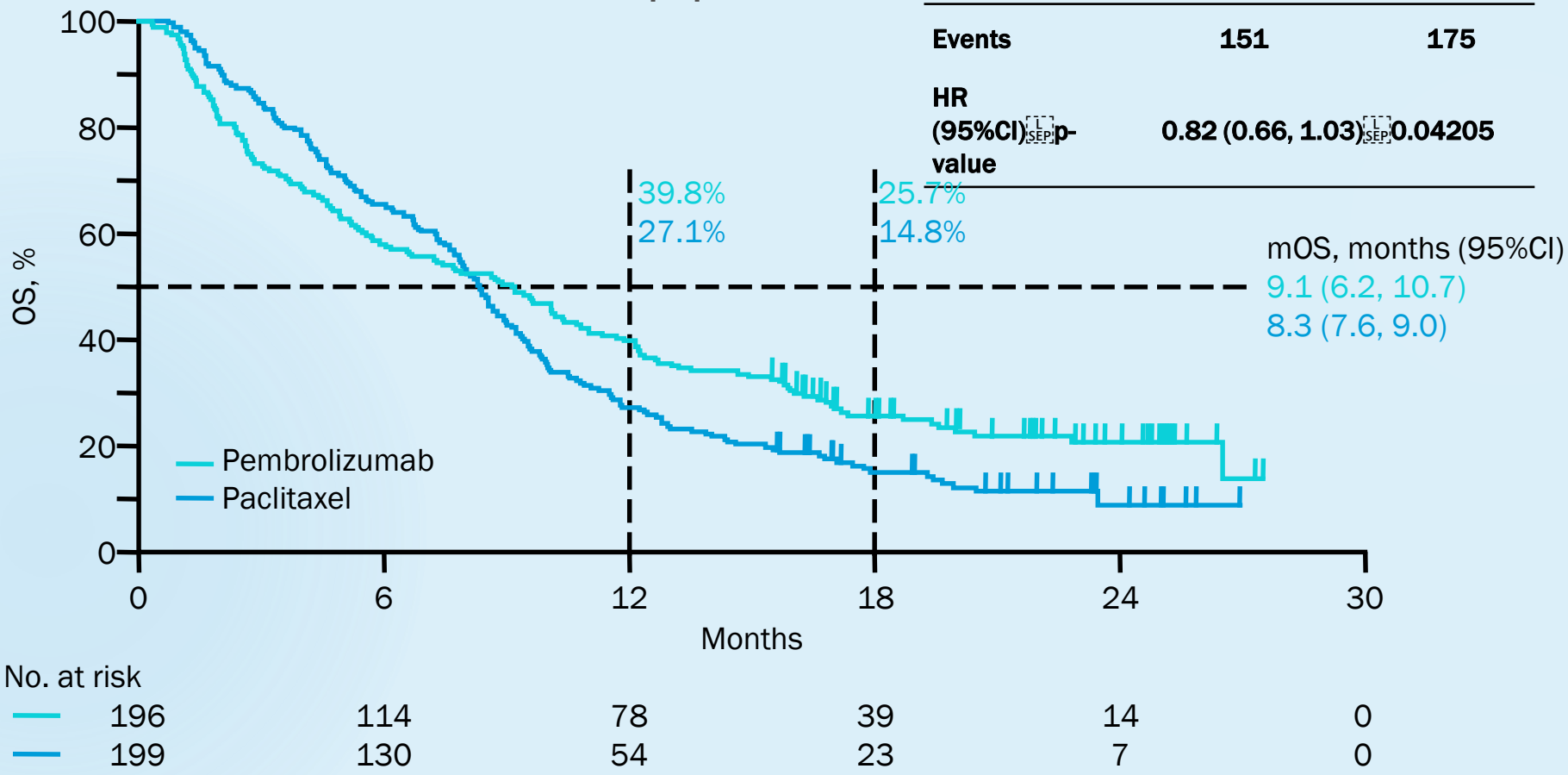
- ORR, DoR in CPS ≥1 population
- Safety in all patients

***n for CPS ≥1 population/all patients;**
†80 mg/m² d1,8,15 of 4-week cycle;
‡pre-specified significance threshold for OS: p≤0.0135

Presented by Shitara K
Fuchs CS, et al. J Clin Oncol 2018;36(suppl):abstr 4062

4062: Pembrolizumab (pembro) vs paclitaxel (PTX) for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase 3 KEYNOTE-061 trial – Fuchs CS, et al

Key results



	Pembrolizumab	Paclitaxel
Events	151	175
HR (95%CI); p-value	0.82 (0.66, 1.03); 0.04205	

Presented by Shitara K

Fuchs CS, et al. J Clin Oncol 2018;36(suppl):abstr 4062

4062: Pembrolizumab (pembro) vs paclitaxel (PTX) for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase 3 KEYNOTE-061 trial – Fuchs CS, et al

Key results (cont.)

	Pembrolizumab	Paclitaxel	HR (95%CI)
mOS, months (95%CI)			
ECOG PS 0	12.3 (9.7, 15.9)	9.3 (8.3, 10.5)	0.69 (0.49, 0.97)
ECOG PS 1	5.4 (3.7, 7.7)	7.5 (5.3, 8.4)	0.98 (0.73, 1.32)
mOS, months (95%CI)			
CPS <1	4.8 (3.9, 6.1)	8.2 (6.8, 10.6)	1.20 (0.89, 1.63)
CPS ≥1	9.1 (6.2, 10.7)	8.3 (7.6, 9.0)	0.82 (0.66, 1.03)
CPS ≥10	10.4 (5.9, 17.3)	8.0 (5.1, 9.9)	0.64 (0.41, 1.02)
mOS, months (95%CI) MSI-high tumours	NR (5.6, NR)	8.1 (2.0, 16.7)	0.42 (0.13, 1.31)
PFS, months (95%CI)			
CPS ≥1	1.5 (1.4, 2.0)	4.1 (3.1, 4.2)	1.27 (1.03, 1.57)
ORR, %			
CPS ≥1	15.8	13.6	-
MSI-high tumours	46.7	16.7	-
mDoR, months (range)			
CPS ≥1	18.0 (1.4+–26.0+)	5.2 (1.3+–16.8)	-

Presented by Shitara K

Fuchs CS, et al. J Clin Oncol 2018;36(suppl):abstr 4062

4062: Pembrolizumab (pembro) vs paclitaxel (PTX) for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase 3 KEYNOTE-061 trial – Fuchs CS, et al

Kev results (cont.)

AEs in all patients, n (%)	Pembrolizumab (n=294)	Paclitaxel (n=276)
TRAEs	155 (52.7)	232 (84.1)
Grade 3–5	42 (14.3)	96 (34.8)
Led to death	3 (1.0)	1 (0.4)
Led to discontinuation	9 (3.1)	15 (5.4)
Immune-mediated AEs/infusion reactions	54 (18.4)	21 (7.6)
Grade 3–5	10 (3.4)	5 (1.8)
Led to death	2 (0.7)	0

Conclusions

- **In previously treated patients with advanced gastric/GEJ cancer, the pre-specified significance threshold for OS was not reached for pembrolizumab vs. paclitaxel**
- **Improvements in OS with pembrolizumab were greater in patients with ECOG PS 0 vs. 1, PD-L1 CPS ≥10 vs. <1 or ≥1 and MSI-high tumours**
- **Pembrolizumab did not improve PFS or ORR vs. paclitaxel although was associated with more durable responses**
- **Fewer TRAEs were reported with pembrolizumab vs. paclitaxel**

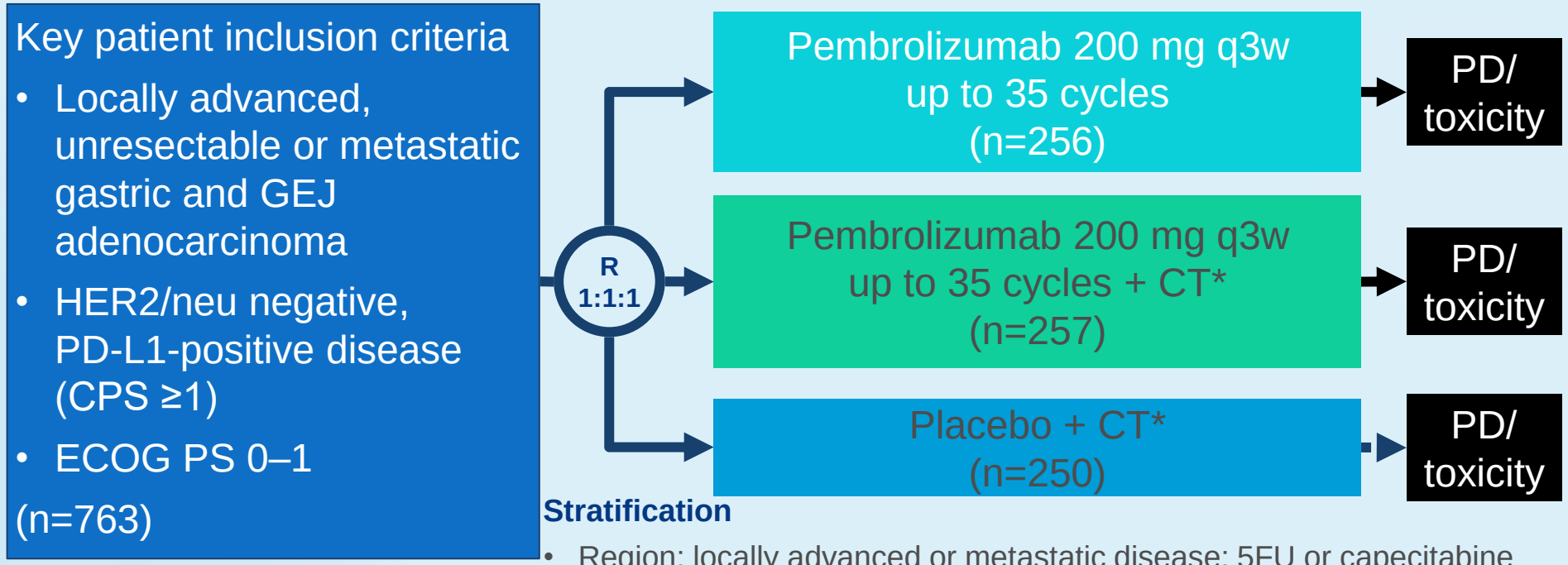
Presented by Shitara K
Fuchs CS, et al. J Clin Oncol 2018;36(suppl):abstr 4062

"Upper GI Cancer: New Immunotherapy Approaches

LBA4007: Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The phase III KEYNOTE-062 study – Tabernero J, et al

Study objective

- To assess the efficacy and safety of pembrolizumab with or without CT vs. CT alone in patients with advanced gastric and GEJ adenocarcinoma



PRIMARY ENDPOINTS

- OS, PFS

SECONDARY ENDPOINTS

- ORR, safety

*Cisplatin 80 mg/m^2 q3w + 5FU 800 mg/m^2/day for 5 days q3w (cisplatin may be capped at 6 cycles per country guidelines) or capecitabine bid D1–14 q3w

Tabernero J, et al. J Clin Oncol 2019;37(suppl):abstr LBA4007

LBA4007: Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The phase III KEYNOTE-062 study – Tabernero J, et al

Key results

Characteristic, n (%) [unless otherwise specified]	Pembrolizumab (n=254)	Pembrolizumab + CT (n=257)	CT (n=250)
Median age, years (range)	61.0 (20–83)	62.0 (22–83)	62.5 (23–87)
Male	180 (70)	195 (76)	179 (72)
ECOG PS 1	125 (49)	138 (54)	135 (54)
Metastatic disease	245 (96)	243 (95)	235 (94)
CPS ≥10	92 (36)	99 (39)	90 (36)
MSI-H	14 (5)	17 (7)	19 (8)
Region			
Europe/North America/Australia	148 (58)	148 (58)	147 (59)
Asia	62 (24)	64 (25)	61 (24)
Rest of World	46 (18)	45 (18)	42 (17)
Primary tumour location			
Stomach	176 (69)	170 (66)	181 (72)
GEJ	79 (31)	85 (33)	67 (27)
Backbone therapy[a]			
5FU	-	98 (38)	95 (38)
Capecitabine	-	159 (62)	155 (62)

[a]Per stratification; data cut-off: March 26, 2019

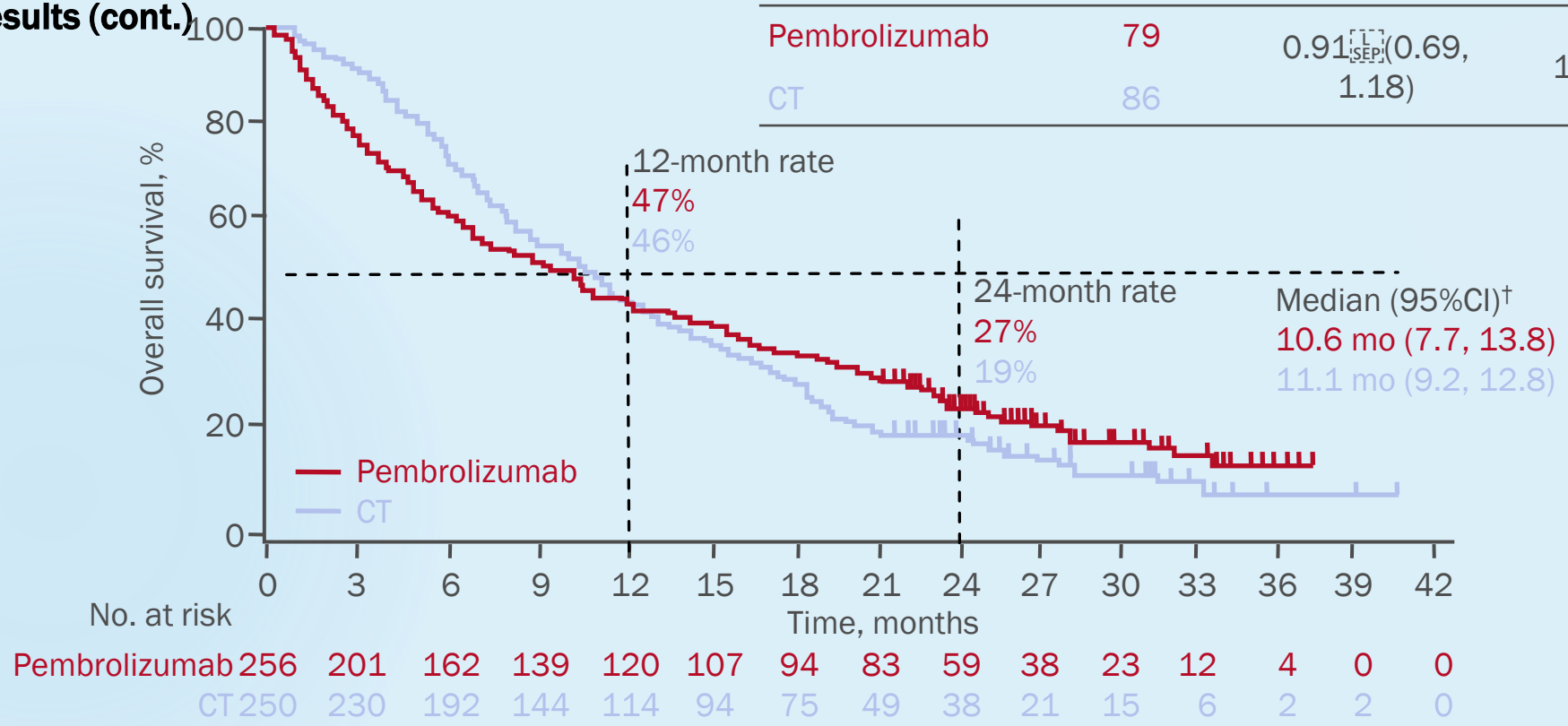
Tabernero J, et al. J Clin Oncol 2019;37(suppl):abstr LBA4007

LBA4007: Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The phase III KEYNOTE-062 study – Tabernero J, et al

Key results (cont.)

OS (CPS ≥1) for pembrolizumab vs. CT

	Events, %	HR (99.2%CI)	NI*
Pembrolizumab	79	0.91 (0.69, 1.18)	1.2
CT	86		



*Non-inferiority margin;†HR 0.91 (95%CI 0.74, 1.10)

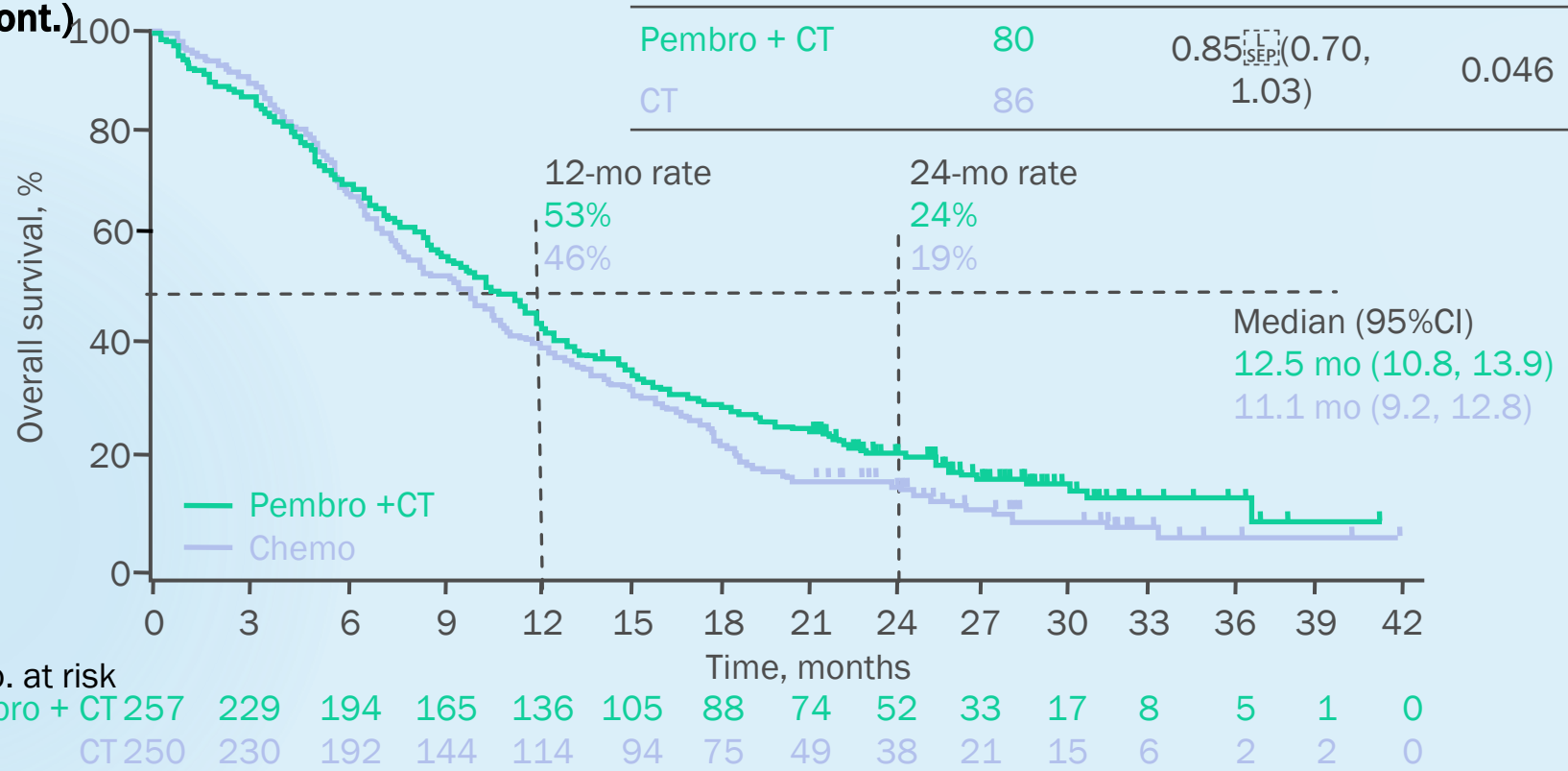
Tabernero J, et al. J Clin Oncol 2019;37(suppl):abstr LBA4007

LBA4007: Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The phase III KEYNOTE-062 study – Tabernero J, et al

Key results (cont.)

OS (CPS ≥1) for pembrolizumab + CT vs. CT

	Events, %	HR (99.2%CI)	p-value
Pembro + CT	80	0.85 (0.70, 1.03)	0.046
CT	86		



No. at risk

Pembro + CT	257	229	194	165	136	105	88	74	52	33	17	8	5	1	0
CT	250	230	192	144	114	94	75	49	38	21	15	6	2	2	0

Tabernero J, et al. J Clin Oncol 2019;37(suppl):abstr LBA4007

LBA4007: Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The phase III KEYNOTE-062 study – Tabernero J, et al

Key results (cont.)

Outcomes	CPS ≥1			CPS ≥10		
	Pembro	Pembro + CT	CT	Pembro	Pembro + CT	CT
OS						
Events	79	80	86	66	76	83
HR (95%CI) vs. CT	0.91 (0.69, 1.18)	0.85 (0.70, 1.03)	- -	0.69 (0.49, 0.97)	0.85 (0.62, 1.17)	- -
mOS, mo (95%CI)	10.6 (7.7, 13.8)	12.5 (10.8, 13.9)	11.1 (9.2, 12.8)	17.4 (9.1, 23.1)	12.3 (9.5, 14.8)	10.8 (8.5, 13.8)
PFS						
Events	88	83	89	80	79	89
HR (95%CI) vs. CT	1.66 (1.37, 2.01)	0.84 (0.70, 1.02)*	- -	1.10 (0.79, 1.51)	0.73 (0.53, 1.00)	- -
mPFS, mo (95%CI)	2.0 (1.5, 2.8)	6.9 (5.7, 7.3)	6.4 (5.7, 7.0)	2.9 (1.6, 5.4)	5.7 (5.5, 8.2)	6.1 (5.3, 6.9)
ORR, %	14.8	48.6	37.2	25.0	52.5	37.8
DoR, mo (range)	13.7 (1.4+–33.6+)	6.8 (1.4+–34.7+)	6.8 (1.4+–30.4+)	19.3 (1.4+–33.6+)	8.3 (1.6+–34.7+)	37.8 (1.5+–30.4+)

*p=0.039

Tabernero J, et al. J Clin Oncol 2019;37(suppl):abstr LBA4007

LBA4007: Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The phase III KEYNOTE-062 study – Tabernero J, et al

Key results (cont.)

TRAEs (CPS ≥1), %	Pembrolizumab (n=254)	Pembrolizumab + CT (n=250)	CT (n=244)
Any	54	94	92
Grade 3–4	16	71	68
Led to discontinuation	4	27	18
Led to death	1*	2†	1‡
Immune-mediated events and infusion reactions	21	24	8

Conclusions

- **In patients with advanced gastric or GEJ cancer with CPS ≥1, there was a comparable improvement in OS for those receiving 1L pembrolizumab vs. CT although there was a modest C improvement in those with CPS ≥10**
- **Pembrolizumab + CT also demonstrated some additional benefit to CT alone**
- **Pembrolizumab had a more favourable tolerability profile compared with CT and the safety prof for pembrolizumab + CT was manageable**

FDA's ODAC Votes Against Continuation of Pembrolizumab Third-Line Indication in Gastric/GEJ Cancer April 2021

*Pneumonitis, malignant neoplasm progression, pericardial effusion (n=1 each);
†febrile neutropenia, myocardial ischaemia, colitis, sepsis, malignant progression;
‡multiple organ failure, pneumonitis, pulmonary embolism (n=1 each)

Tabernero J, et al. J Clin Oncol 2019;37(suppl):abstr LBA4007

PRINCIPLES OF SYSTEMIC THERAPY

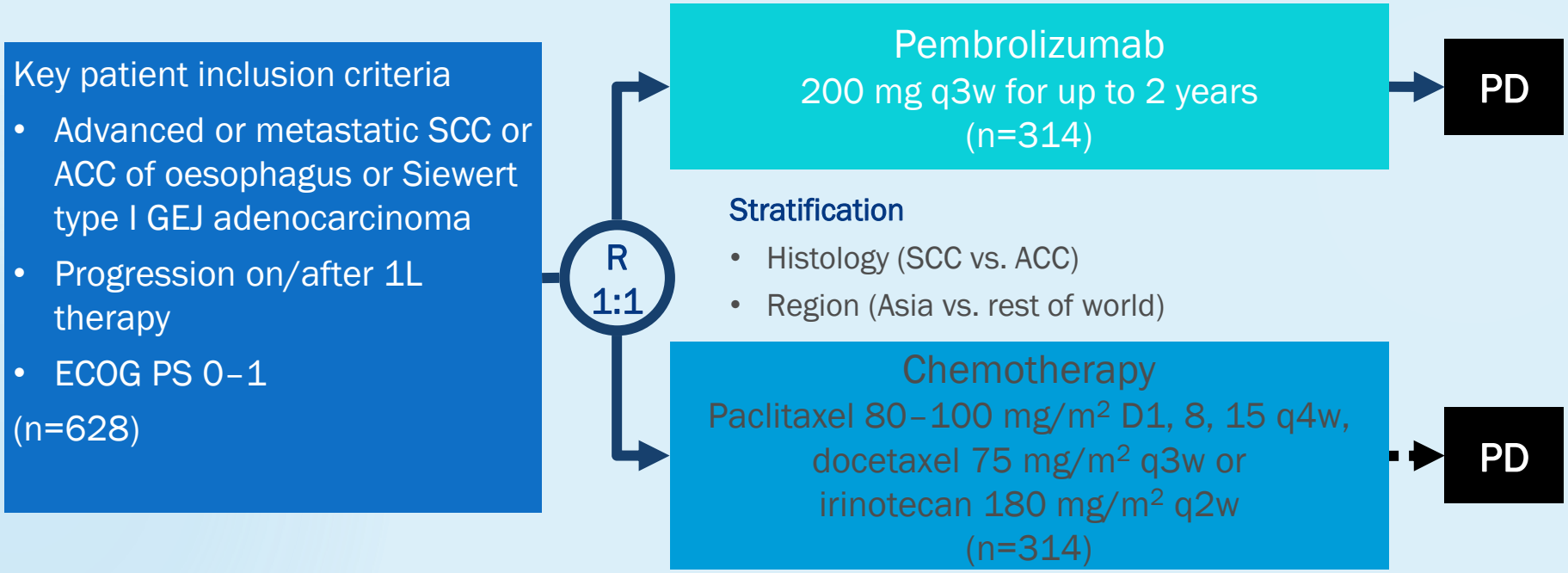
Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy
• Dependent on prior therapy and PS
Preferred Regimens
• Ramucirumab and paclitaxel (category 1)[35]
• Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[36]
• Docetaxel (category 1)[28,29]
• Paclitaxel (category 1)[24,25,37]
• Irinotecan (category 1)[37-40]
• Fluorouracil[b,i] and irinotecan[38,41,42]
• Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[43]
Other Recommended Regimens
• Ramucirumab (category 1)[44]
• Irinotecan and cisplatin[14,45]
• Fluorouracil and irinotecan + ramucirumab[b,i,46]
• Irinotecan and ramucirumab[47]
• Docetaxel and irinotecan (category 2B)[48]
Useful in Certain Circumstances
• Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[49,50]
• Pembrolizumab[g,h] for MSI-H or dMMR tumors[51-53]
• Pembrolizumab[g,h] for TMB high (≥ 10 mutations/megabase) tumors[54]

4010: Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase 3 KEYNOTE-181 study – Shah MA, et al

Study objective

- **To investigate the efficacy and safety of 2L pembrolizumab in patients with advanced or metastatic squamous cell carcinoma (SCC) or adenocarcinoma (ACC) of the oesophagus**



PRIMARY ENDPOINT

- OS in SCC, PD-L1 CPS ≥10 and ITT populations

SECONDARY ENDPOINTS

- PFS, ORR, safety

Shah MA, et al. J Clin Oncol 2019;37(suppl):abstr 4010

4010: Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase 3 KEYNOTE-181 study – Shah MA, et al

Key results

Characteristic, n (%) [unless otherwise specified]	Pembrolizumab (n=314)	Chemotherapy (n=314)
Median age, years (range)	63 (23–84)	62 (24–84)
>65 years, n (%)	139 (44)	133 (42)
Male	273 (87)	271 (86)
Region		
Asia	121 (39)	122 (39)
Rest of World	193 (61)	192 (61)
ECOG PS 1	187 (60)	197 (63)
Tumour type		
SCC	198 (63)	203 (65)
ACC	116 (37)	111 (35)
PD-L1 status		
CPS ≥10	107 (34)	115 (37)
CPS <10	201 (64)	196 (62)
CPS not evaluable	6 (2)	3 (1)

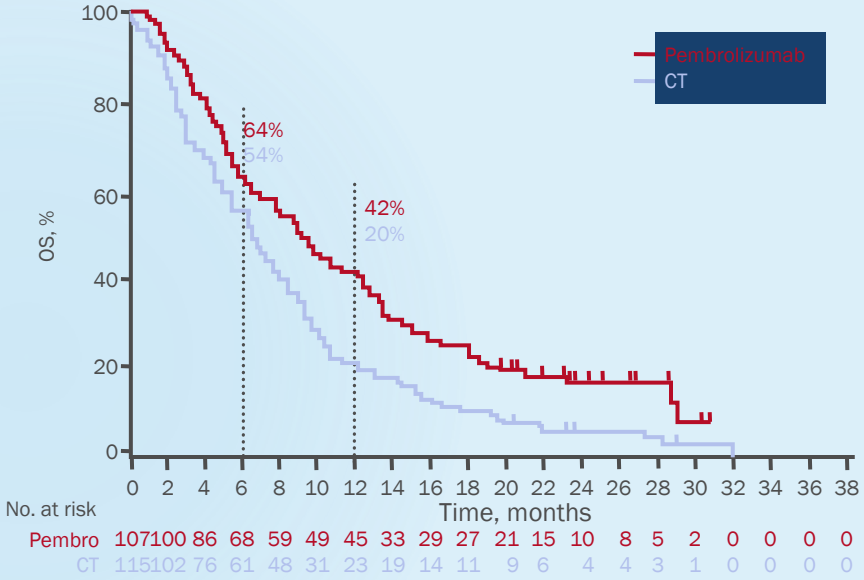
Shah MA, et al. J Clin Oncol 2019;37(suppl):abstr 4010

4010: Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase 3 KEYNOTE-181 study – Shah MA, et al

Key results (cont.)

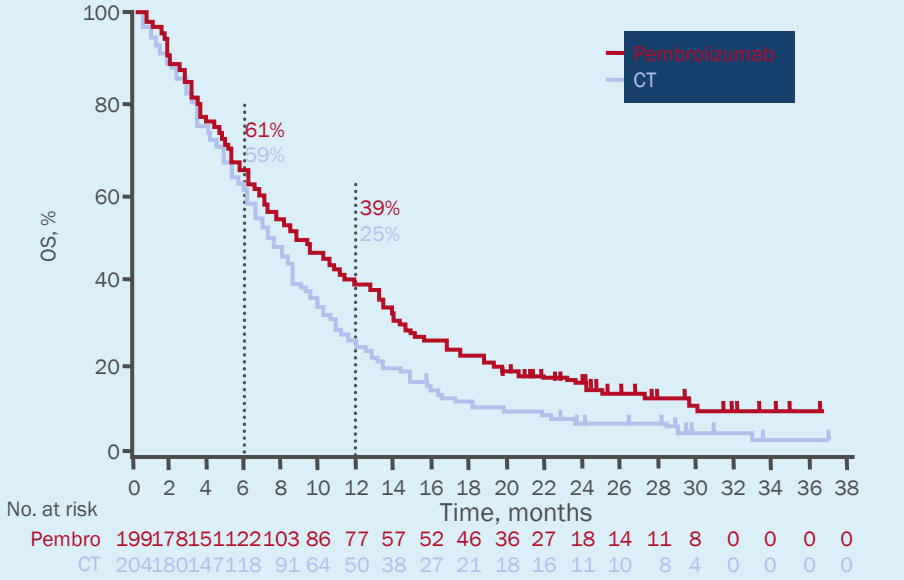
PD-L1 CPS ≥10

	Events	Median, mo (95%CI)	HR* (95%CI)	p-value†
Pembrolizumab	84	9.3 (6.6, 12.5)	0.67 (0.50, 0.89)	0.0029
CT	95	6.7 (5.1, 8.2)		



SCC population

	Events	Median, mo (95%CI)	HR* (95%CI)	p-value†
Pembrolizumab	86	8.2 (6.7, 10.0)	0.75 (0.61, 0.93)	0.0035
CT	93	7.1 (6.1, 8.2)		



*Based on Cox regression model with treatment as a covariate stratified by region and histology; †p-values are nominal

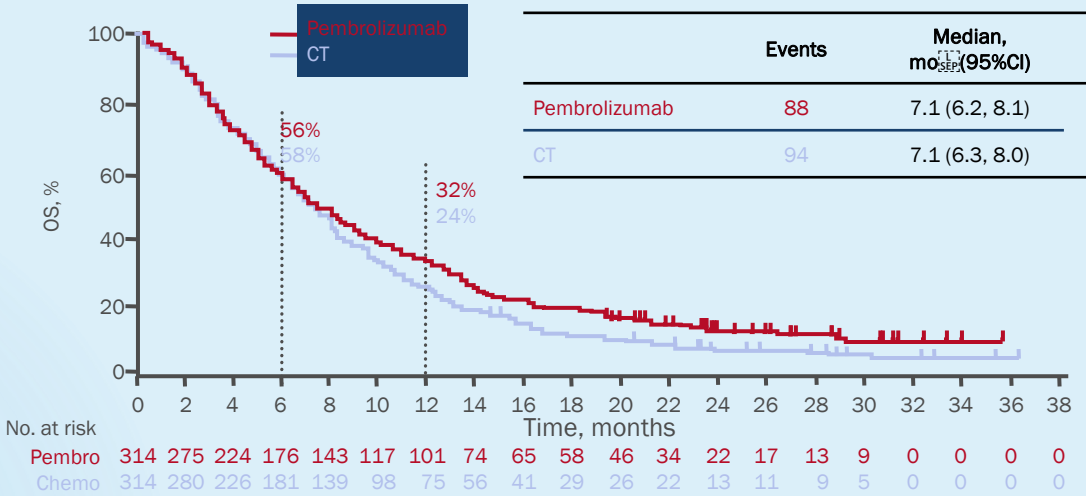
Shah MA, et al. J Clin Oncol 2019;37(suppl):abstr 4010

4010: Pembrolizumab versus chemotherapy as second-line therapy for esophageal cancer: Phase 3 KEYNOTE-181 study – Shah MA, et al

Cleveland Clinic

Key results (cont.)

ITT population



	Events	Median, mo (95%CI)	HR* (95%CI)	p-value†
Pembrolizumab	88	7.1 (6.2, 8.1)	0.85 (0.72, 1.01)	0.0031
CT	94	7.1 (6.3, 8.0)		

Conclusions

- In previously treated patients with advanced ACC of the oesophagus and PD-L1 CPS ≥10, pembrolizumab demonstrated improvement in OS after an additional four months of follow-up
- There were also clinically meaningful OS benefits in previously treated patients with advanced SCC of the oesophagus

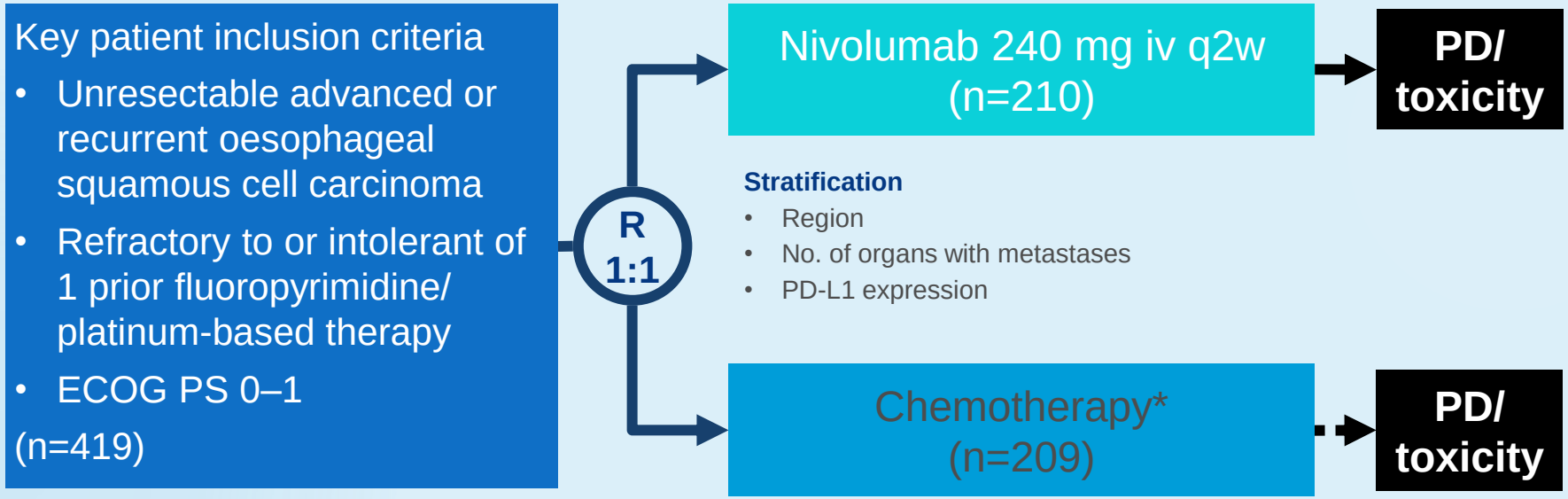
*Based on Cox regression model with treatment as a covariate stratified by region and histology; †p-values are nominal

Shah MA, et al. J Clin Oncol 2019;37(suppl):abstr 4010

LBA11: Nivolumab versus chemotherapy in advanced esophageal squamous cell carcinoma (ESCC): The phase 3 ATTRACTION-3 study – Cho BC, et al

Study objective

- **To investigate the efficacy and safety of nivolumab compared with chemotherapy in patients with advanced oesophageal squamous cell carcinoma**



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

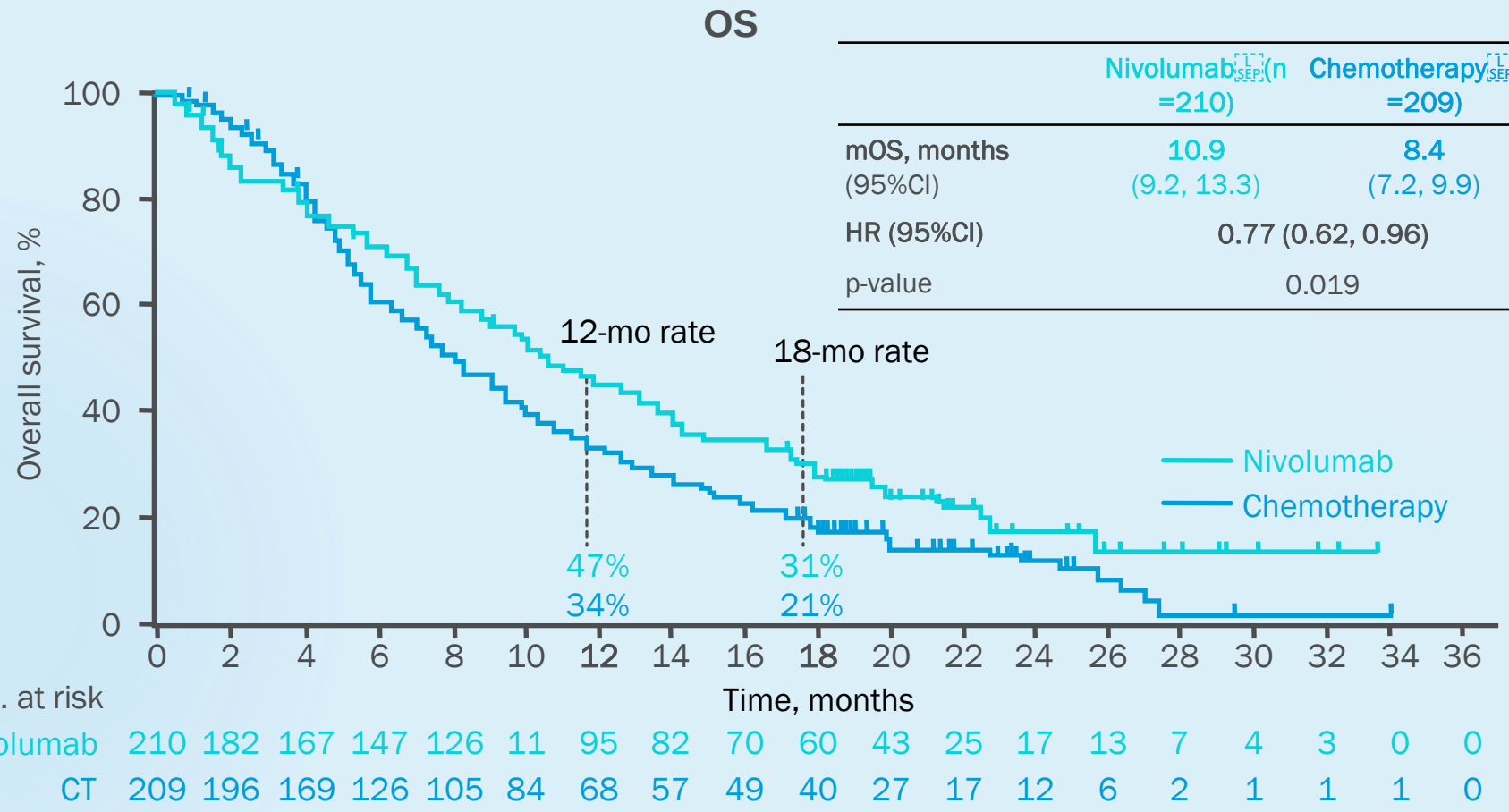
- PFS, ORR, DCR, TTR, DoR, HRQoL, safety

*Docetaxel 75 mg/m^2 q3w or paclitaxel 100 mg/m^2 iv qw 6-weeks on/1-week off

Cho BC, et al. Ann Oncol 2019;30(suppl):abstr LBA11

LBA11: Nivolumab versus chemotherapy in advanced esophageal squamous cell carcinoma (ESCC): The phase 3 ATTRACTION-3 study – Cho BC, et al

Key results



	Nivolumab (n=210)	Chemotherapy (n=209)
mOS, months (95%CI)	10.9 (9.2, 13.3)	8.4 (7.2, 9.9)
HR (95%CI)	0.77 (0.62, 0.96)	
p-value	0.019	

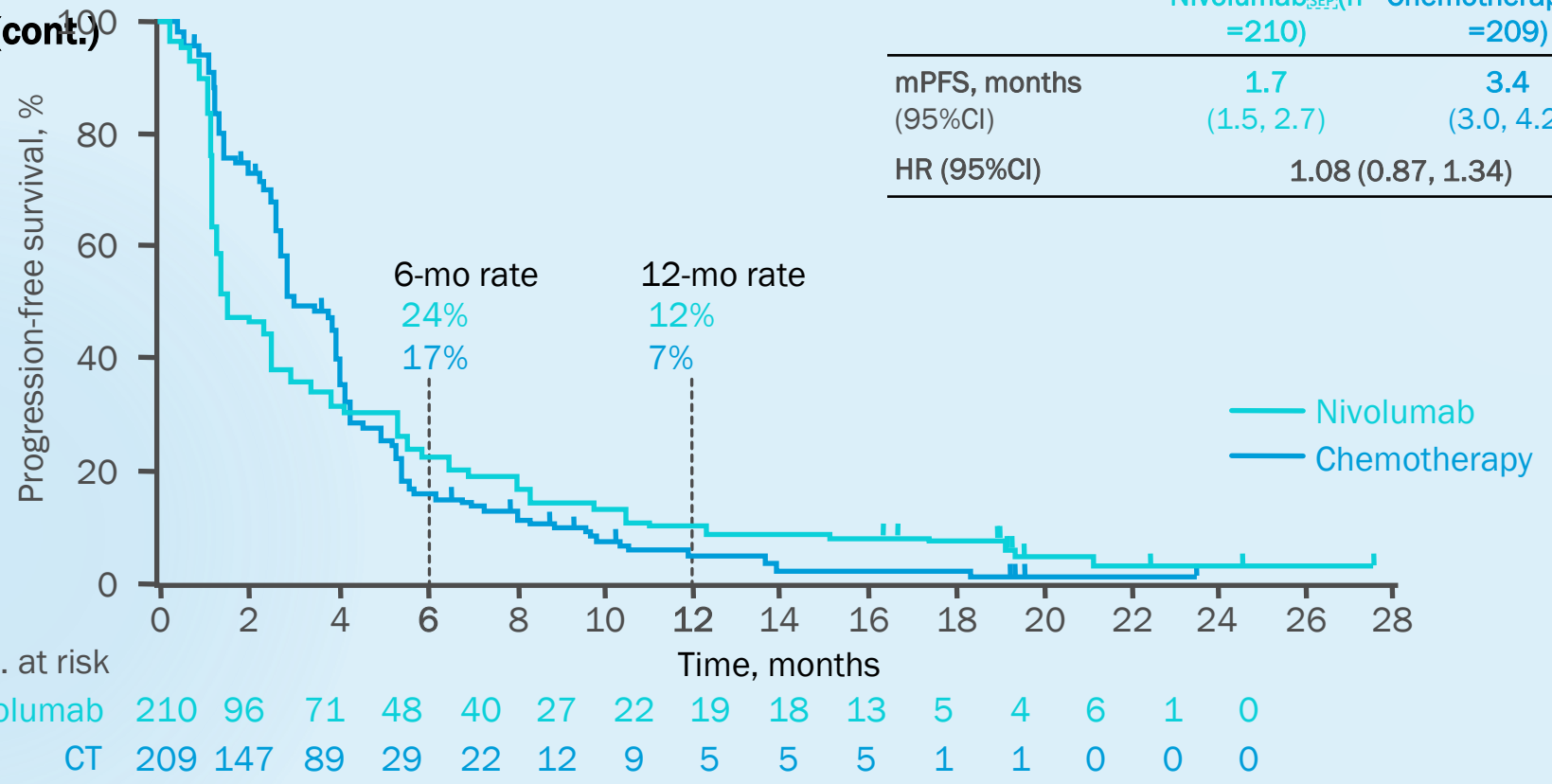
Cho BC, et al. Ann Oncol 2019;30(suppl):abstr LBA11

LBA11: Nivolumab versus chemotherapy in advanced esophageal squamous cell carcinoma (ESCC): The phase 3 ATTRACTION-3 study – Cho BC, et al

Key results (cont.)

PFS

	Nivolumab (n=210)	Chemotherapy (n=209)
mPFS, months (95%CI)	1.7 (1.5, 2.7)	3.4 (3.0, 4.2)
HR (95%CI)	1.08 (0.87, 1.34)	



Cho BC, et al. Ann Oncol 2019;30(suppl):abstr LBA11

LBA11: Nivolumab versus chemotherapy in advanced esophageal squamous cell carcinoma (ESCC): The phase 3 ATTRACTION-3 study – Cho BC, et al

Key results (cont.)

Select grade 3–4 TRAEs, n (%)	Nivolumab (n=209)	Chemotherapy (n=208)
Gastrointestinal	2 (1)	2 (1)
Hepatic	1 (<1)	4 (2)
Pulmonary	2 (1)	4 (2)
Renal	1 (<1)	0 (0)
Skin	4 (2)	2 (1)

Conclusion

- In patients with previously treated advanced oesophageal squamous cell carcinoma, nivolumab demonstrated a significant improvement in OS with a manageable safety profile compared with chemotherapy

Cho BC, et al. Ann Oncol 2019;30(suppl):abstr LBA11

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy
- Dependent on prior therapy and PS

Preferred Regimens
- Nivolumab for esophageal squamous cell carcinoma (category 1)[e,h,43]
- Pembrolizumab[e,h]
  - For second-line therapy for esophageal squamous cell carcinoma, with PD-L1 expression levels by CPS of ≥10 (category 1)[44]
- Ramucirumab and paclitaxel for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[45]
- Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[46]
- Docetaxel (category 1)[36,37]
- Paclitaxel (category 1)[31,33,47]
- Irinotecan (category 1)[47-50]
- Fluorouracil[b,i] and irinotecan[48,51,52]
- Trifluridine and tipiracil for third-line or subsequent therapy for EGJ adenocarcinoma (category 1)[53]

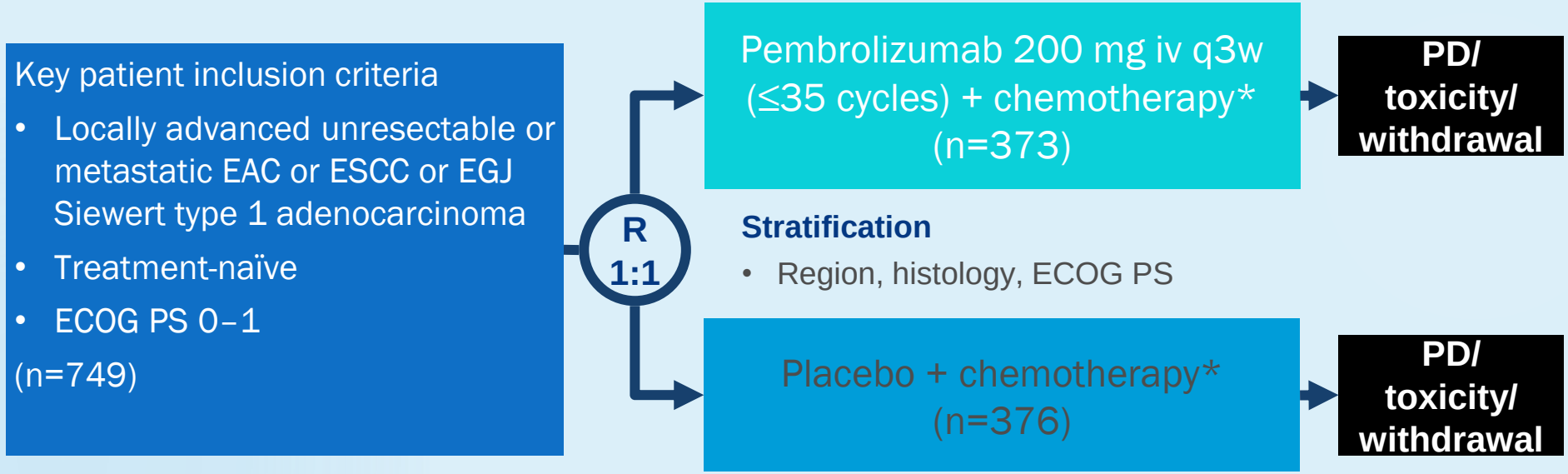
Other Recommended Regimens
- Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[54]
- Irinotecan and cisplatin[22,55]
- Fluorouracil and irinotecan + ramucirumab for adenocarcinoma[b,i,56]
- Irinotecan and ramucirumab for adenocarcinoma[57]
- Docetaxel and irinotecan (category 2B)[58]

Useful in Certain Circumstances
- Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[59,60]
- Pembrolizumab[e,h] for MSI-H or dMMR tumors[61-63]
- Pembrolizumab[e,h] for TMB high (≥10 mutations/megabase) tumors[64]

LBA8: Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase 3 KEYNOTE-590 study – Kato K, et al

Study objective

- **To evaluate the safety and efficacy of pembrolizumab + chemotherapy in patients with advanced esophageal cancer**



CO-PRIMARY ENDPOINTS

- OS and PFS (investigator-assessed, RECIST v1.1)
- ORR, safety

***5FU 800 mg/m² iv D1–5 q3w (≤35 cycles) + cisplatin 80 mg/m² (≤6 cycles). Data cut-off 02 July 2020.**

Kato K, et al. Ann Oncol 2020;31(suppl):abstr LBA8

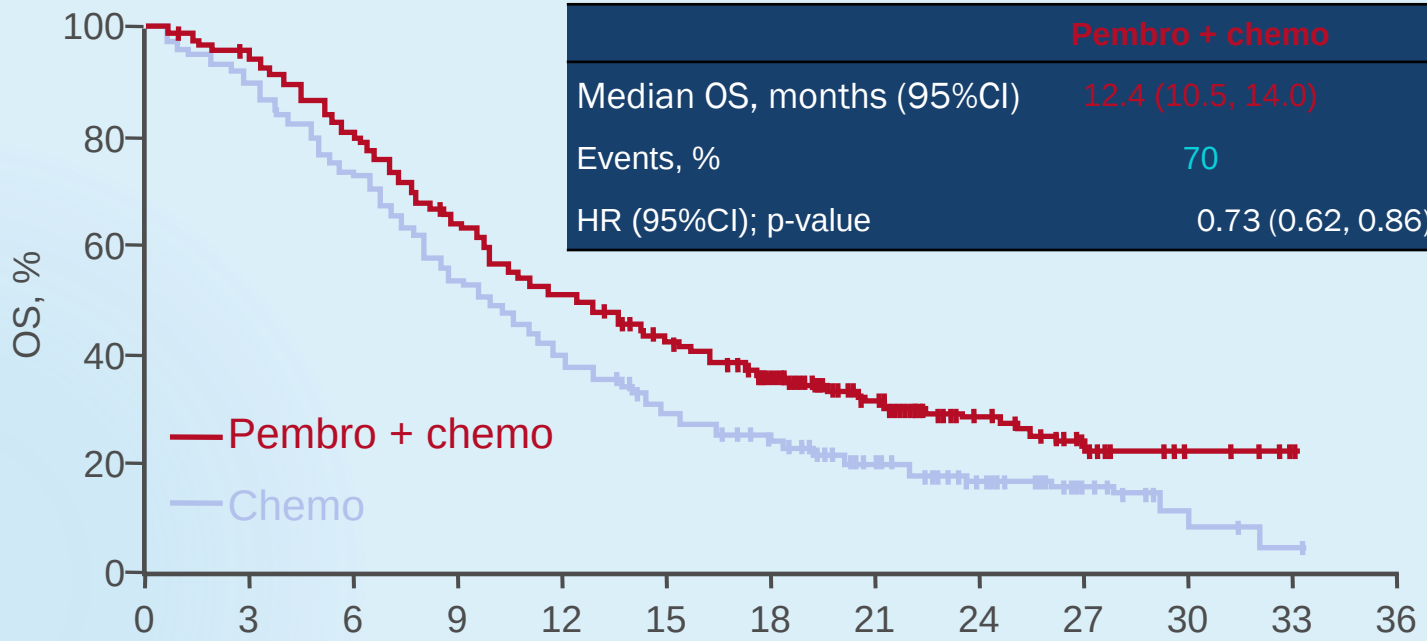
LBA8: Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase 3 KEYNOTE-590 study – Kato K, et al

PD-L1 CPS ≥ 10, median overall survival was **13.5 months vs 9.4 months** (HR = 0.62, 95% CI = 0.49–0.78, *P* < .0001)

Key results

Overall survival (all patients)

	Pembro + chemo	Chemo
Median OS, months (95%CI)	12.4 (10.5, 14.0)	9.8 (8.8, 10.8)
Events, %	70	82
HR (95%CI); p-value	0.73 (0.62, 0.86); <0.0001	



No. at risk

Pembro + chemo	373	348	295	235	187	151	118	68	36	17	7	2	0
Chemo	376	338	274	200	147	108	82	51	28	15	4	1	0

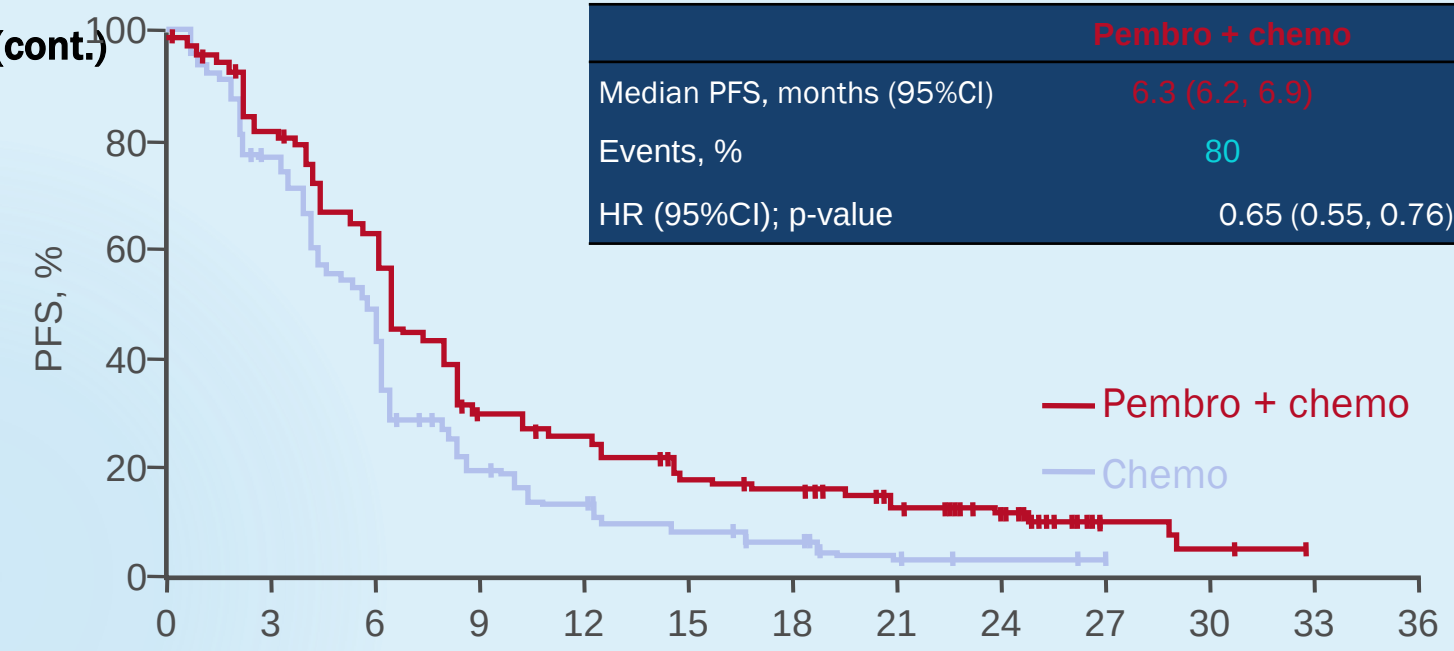
Kato K, et al. Ann Oncol 2020;31(suppl):abstr LBA8

LBA8: Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase 3 KEYNOTE-590 study – Kato K, et al

Key results (cont.)

Progression-free survival (all patients)

	Pembro + chemo	Chemo
Median PFS, months (95%CI)	6.3 (6.2, 6.9)	5.8 (5.0, 6.0)
Events, %	80	89
HR (95%CI); p-value	0.65 (0.55, 0.76); <0.0001	



No. at risk

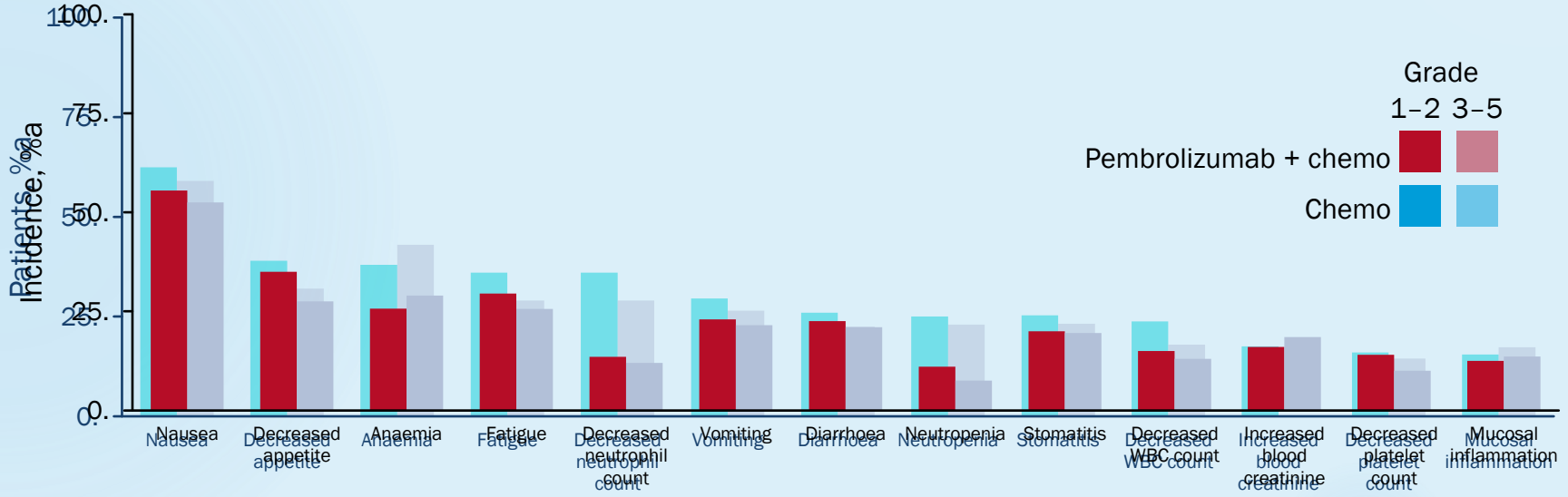
Pembro + chemo	373	289	210	96	79	55	45	25	17	4	2	0	0
Chemo	376	278	172	62	36	22	14	6	2	1	0	0	0

Kato K, et al. Ann Oncol 2020;31(suppl):abstr LBA8

LBA8: Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase 3 KEYNOTE-590 study – Kato K, et al

Key resu

AEs, %	Pembrolizumab + chemo (n=370)	Chemo (n=370)
Any AE	100	99.5
TRAE	98.4	97.3
Grade ≥3	71.9	67.6
Led to discontinuation	19.5	11.6
Led to death	2.4	1.4
Immune-mediated and infusion reactions	25.7	11.6
Grade ≥3	7.0	2.2



[a] TRAEs occurring in ≥15% of patients in any arm.

Kato K, et al. Ann Oncol 2020;31(suppl):abstr LBA8

LBA8: Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase 3 KEYNOTE-590 study – Kato K, et al

Conclusion

- **In patients with advanced esophageal cancer (Adeno and Squamous), 1L pembrolizumab + chemotherapy in CPS ≥ 10, demonstrated significant improvements in OS, PFS and ORR compared with chemotherapy alone and no new safety signals were observed**

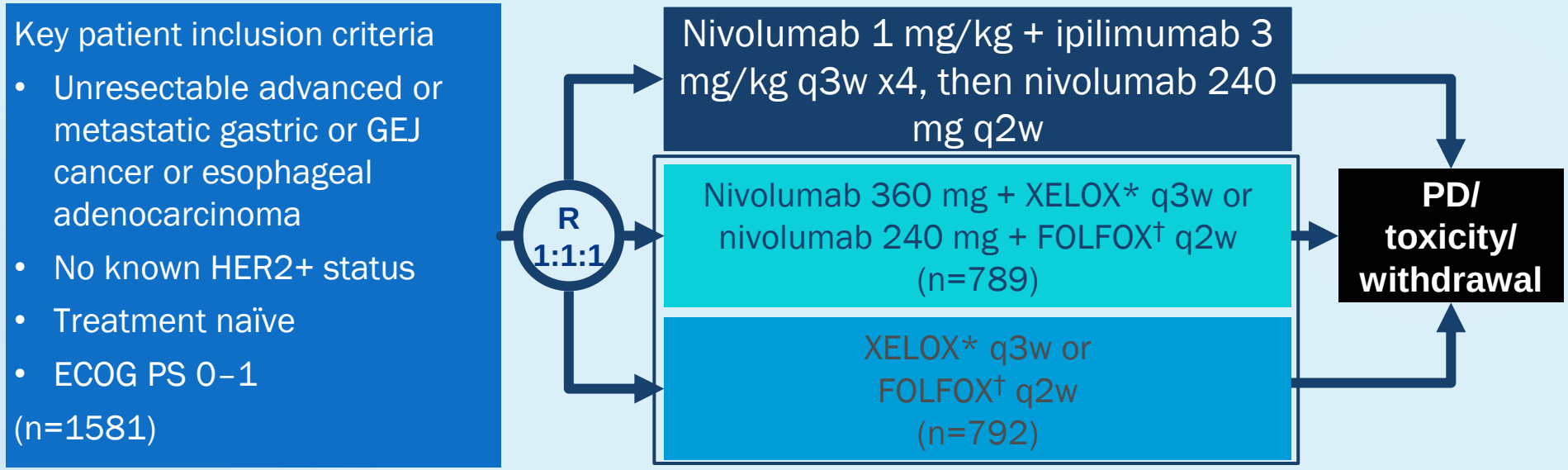
Kato K, et al. Ann Oncol 2020;31(suppl):abstr LBA8

"Upper GI Cancer: New Immunotherapy Approaches

4002: First-line (1L) nivolumab (NIVO) plus chemotherapy (chemo) versus chemo in advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): Expanded efficacy and safety data from CheckMate 649 – Moehler MH, et al

Study objective

- **To evaluate the efficacy and safety of nivolumab as a 1L treatment for patients with gastric or GEJ cancer or esophageal adenocarcinoma in the CheckMate 649 study**



Stratification

- Region, ECOG PS, chemotherapy regimen, PD-L1 expression

CO-PRIMARY ENDPOINTS

- OS and PFS (BICR) in PD-L1 CPS ≥5
- OS, PFS, ORR, safety

***Oxaliplatin 130 mg/m² iv D1 + capecitabine 1000 mg/m² po bid D1–14;** †oxaliplatin 85 mg/m², leucovorin 400 mg/m² + 5FU 400 mg/m² D1 then 5FU 1200 mg/m² iv D1–2

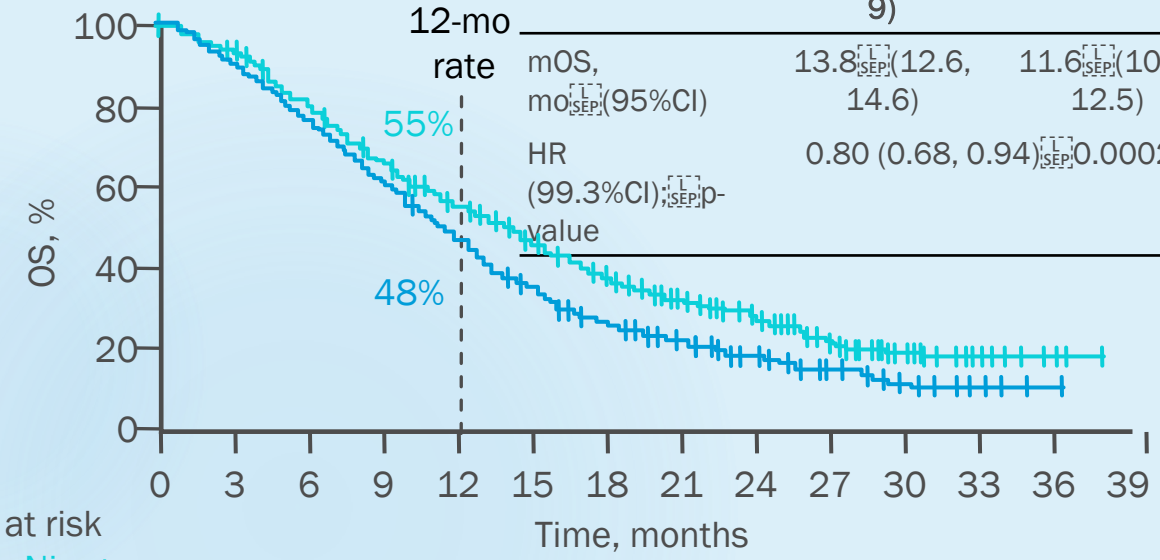
Moehler MH, et al. J Clin Oncol 2021;39(suppl):abstr 4002

4002: First-line (1L) nivolumab (NIVO) plus chemotherapy (chemo) versus chemo in advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): Expanded efficacy and safety data from CheckMate 649 – Moehler MH, et al

Overall survival

Key results

	Nivo + chemo (n=789)	Chemo (n=792)
mOS, mo (95%CI)	13.8 (12.6, 14.6)	11.6 (10.9, 12.5)
HR (99.3%CI); p-value	0.80 (0.68, 0.94); 0.0002	
12-mo rate	55%	48%

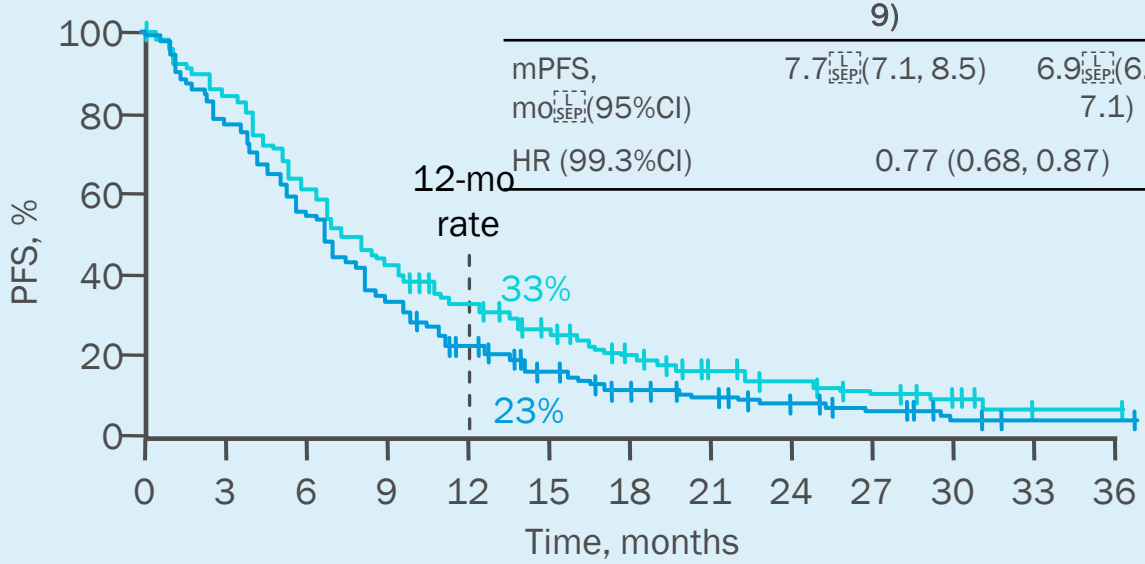


No. at risk

Nivo+ chemo	789	731	621	506	420	308	226	147	100	49	34	14	2	0
Chemo	792	697	586	469	359	239	160	94	59	35	15	7	2	0

Progression-free survival

	Nivo + chemo (n=789)	Chemo (n=792)
mPFS, mo (95%CI)	7.7 (7.1, 8.5)	6.9 (6.6, 7.1)
HR (99.3%CI)	0.77 (0.68, 0.87)	
12-mo rate	33%	23%



Nivo+ chemo	789	639	429	287	197	136	83	51	31	15	11	1	0	
Chemo	792	544	351	202	120	65	38	28	18	12	6	1	0	

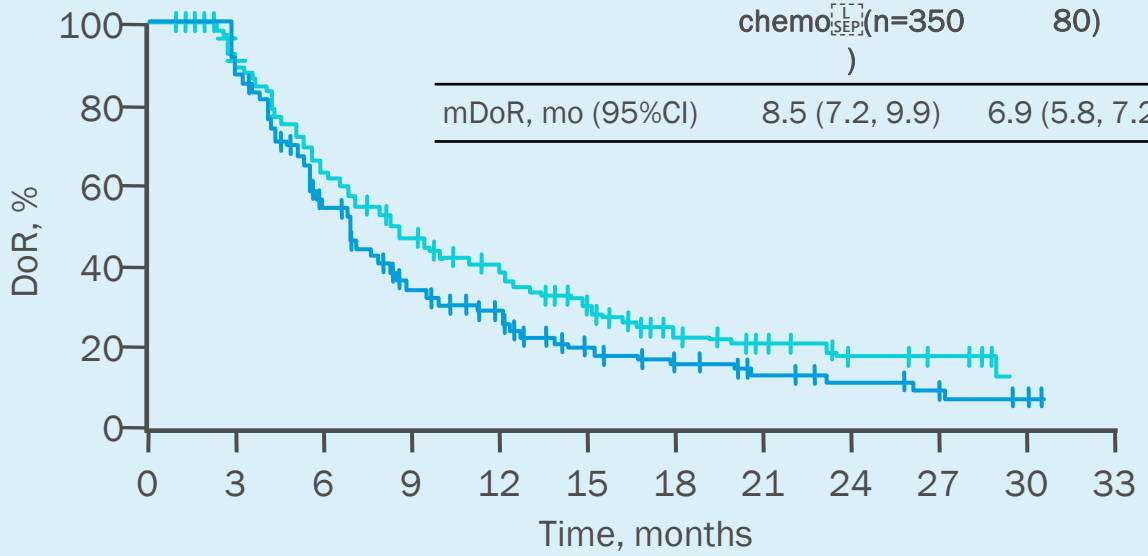
Moehler MH, et al. J Clin Oncol 2021;39(suppl):abstr 4002

4002: First-line (1L) nivolumab (NIVO) plus chemotherapy (chemo) versus chemo in advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): Expanded efficacy and safety data from CheckMate 649 – Moehler MH, et al

	Nivolumab + chemo (n=603)	Chemo (n=608)
BOR, %		
CR	10	6
PR	48	40
SD	28	33
PD	7	10
NE	7	11
ORR, % (95%CI)	58 (54, 62)	46 (42, 50)
Median TTR, mo (range)	1.5 (0.8–10.9)	1.5 (0.6–7.1)

Duration of response

	Nivo + chemo (n=350)	Chemo (n=280)
mDoR, mo (95%CI)	8.5 (7.2, 9.9)	6.9 (5.8, 7.2)



Nivo+ chemo	350	302	203	143	110	72	40	21	10	7	0	0
Chemo	280	233	137	77	55	30	20	10	7	5	2	0

Moehler MH, et al. J Clin Oncol 2021;39(suppl):abstr 4002

4002: First-line (1L) nivolumab (NIVO) plus chemotherapy (chemo) versus chemo in advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): Expanded efficacy and safety data from CheckMate 649 – Moehler MH, et al

Key results (cont.)

Grade 3–4 TRAEs, n (%)	Nivolumab + chemotherapy (n=782)
Endocrine	5 (<1)
Gastrointestinal	43 (5)
Hepatic	29 (4)
Pulmonary	14 (2)
Renal	6 (<1)
Skin	26 (3)

Conclusions

- **In patients with advanced gastric/GEJ cancer or esophageal (Adenocarcinoma only), 1L nivolumab + chemotherapy in CPS ≥ 5, demonstrated significant improvement in OS and durable responses compared with chemotherapy alone and had an acceptable safety profile**

Moehler MH, et al. J Clin Oncol 2021;39(suppl):abstr 4002

NCCN Guidelines Version 4.2021
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy

- Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Preferred Regimens

- HER2 overexpression positive adenocarcinoma[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,18]
- HER2 overexpression negative[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥ 5) for adenocarcinoma only (category 1)[e,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS 1-4) for adenocarcinoma only (category 2B)[e,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (PD-L1 CPS ≥ 10) for adenocarcinoma or squamous cell carcinoma[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (PD-L1 CPS 1-9) for adenocarcinoma only (category 2B)[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (PD-L1 CPS ≥ 10) (category 1) for adenocarcinoma or squamous cell carcinoma[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (PD-L1 CPS 1-9) for adenocarcinoma only (category 2B)[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin for adenocarcinoma or squamous cell carcinoma[21-23]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin for adenocarcinoma or squamous cell carcinoma[21,24-26]

Other Recommended Regimens

- HER2 overexpression positive adenocarcinoma[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab[a] and pembrolizumab[e,h,27]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] and pembrolizumab[e,h,27]
- Fluorouracil[b,i] and irinotecan[j,28]
- Paclitaxel with or without cisplatin or carboplatin [j,29-33]
- Docetaxel with or without cisplatin [j,34-37]
- Fluoropyrimidine [j,25,38,39] (fluorouracil[b] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b, j,40,41]

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy
- Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Preferred Regimens
- HER2 overexpression positive adenocarcinoma[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,11]
- HER2 overexpression negative[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)[g,h,12]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[13-15]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[13,16-18]

Other Recommended Regimens
- HER2 overexpression positive adenocarcinoma[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab[a] and pembrolizumab[g,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] and pembrolizumab[g,h,19]
- Fluorouracil[b,i] and irinotecan[j,20]
- Paclitaxel with or without cisplatin or carboplatin[j,21-25]
- Docetaxel with or without cisplatin[j,26-29]
- Fluoropyrimidine[j,17,30,31] (fluorouracil[b] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b,j,32,33]
- Docetaxel, carboplatin, and fluorouracil (category 2B)[j,34]

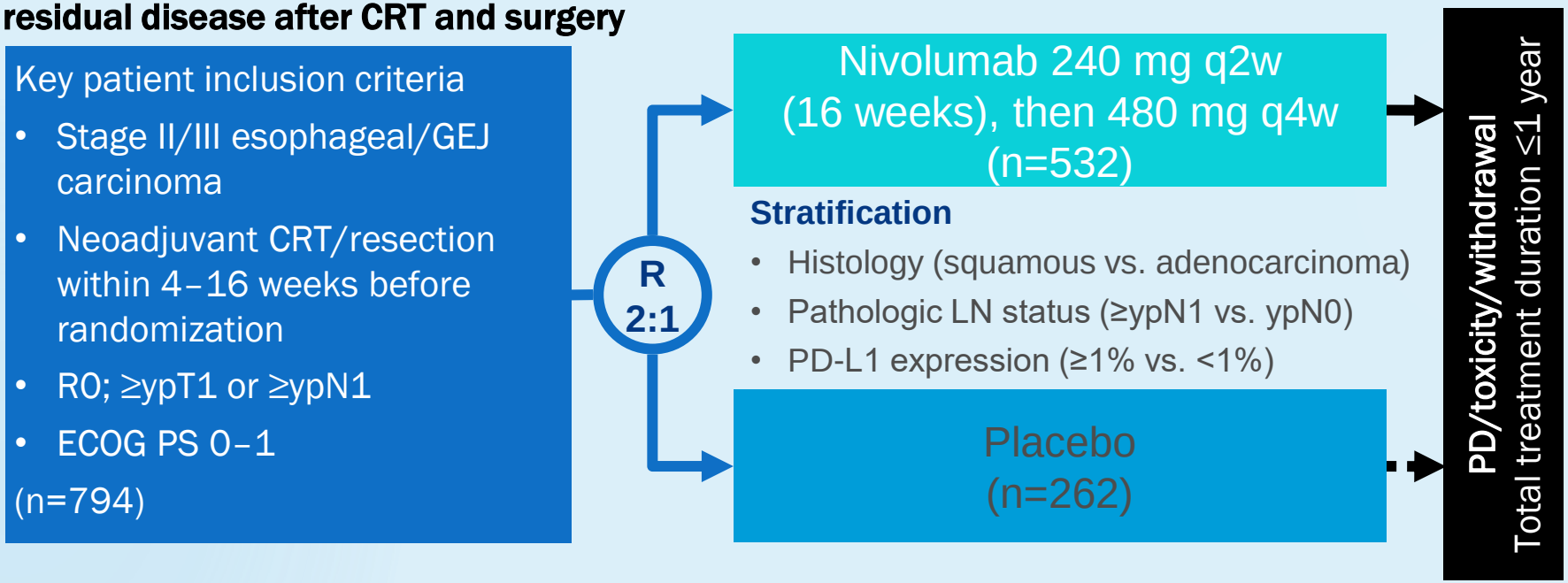
Useful in Certain Circumstances
- HER2 overexpression negative[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS 1-4) (category 2B)[g,h,12]

[a]An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

LBA9: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study – Kelly RJ, et al

Study objective

- **To evaluate the safety and efficacy of adjuvant nivolumab in patients with esophageal/GEJ cancer and residual disease after CRT and surgery**



PRIMARY ENDPOINT

- DFS

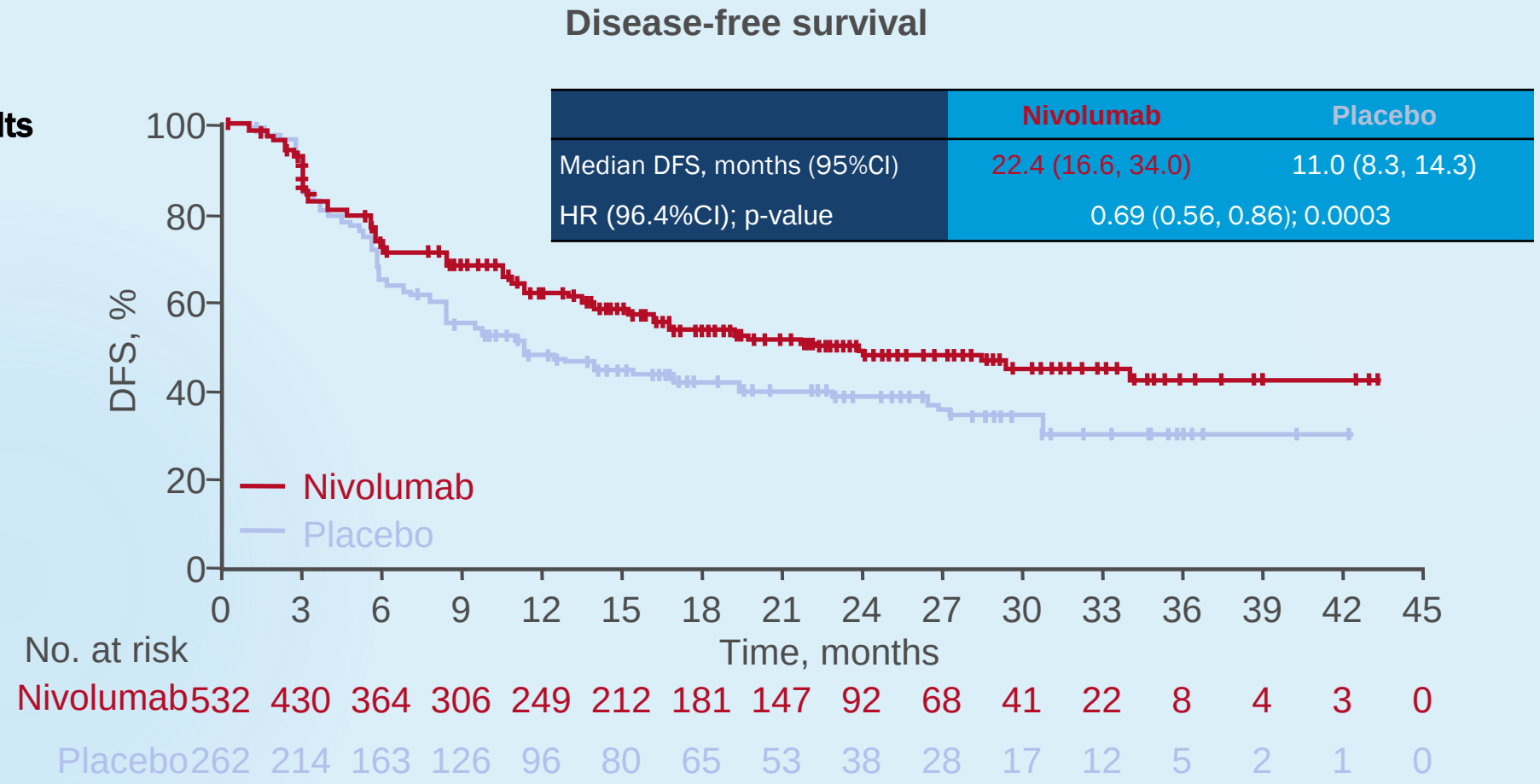
SECONDARY ENDPOINTS

- OS, safety

Kelly RJ, et al. Ann Oncol 2020;31(suppl):abstr LBA9

LBA9: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study – Kelly RJ, et al

Key results



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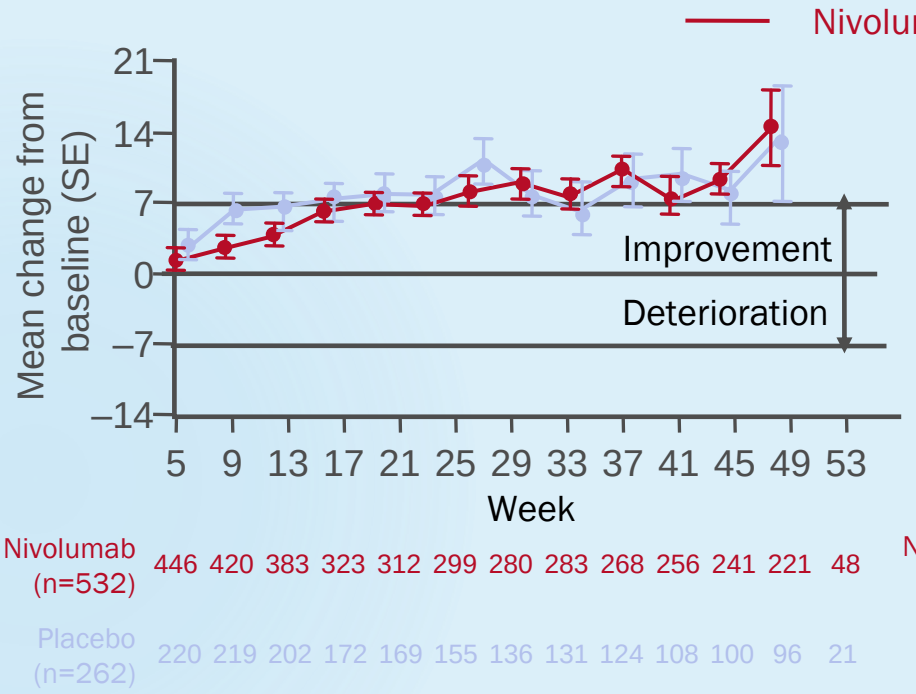
LBA9: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study – Kelly RJ, et al

Overall health status using EQ-5D-3L

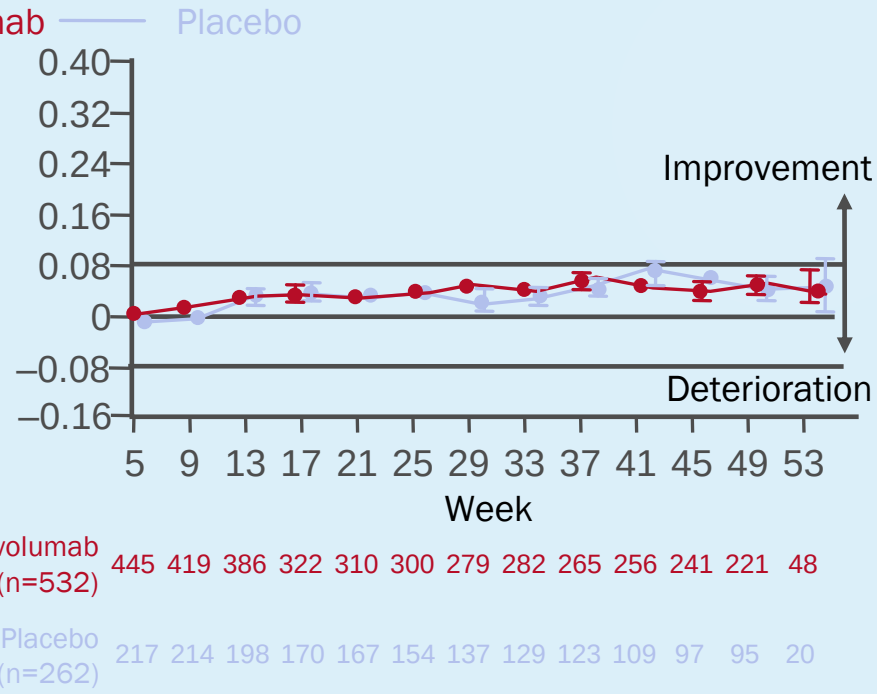
Key results (cont.)

Visual analogue scale



Nivolumab (n=532)	446	420	383	323	312	299	280	283	268	256	241	221	48
Placebo (n=262)	220	219	202	172	169	155	136	131	124	108	100	96	21

Utility index



Nivolumab (n=532)	445	419	386	322	310	300	279	282	265	256	241	221	48
Placebo (n=262)	217	214	198	170	167	154	137	129	123	109	97	95	20

Kelly RJ, et al. Ann Oncol 2020;31(suppl):abstr LBA9

LBA9: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study – Kelly RJ, et al

Key results (cont.)

AEs, n (%)	Nivolumab (n=532)		Placebo (n=260)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any AE	510 (96)	183 (34)	243 (93)	84 (32)
Any TRAE	376 (71)	71 (13)	119 (46)	15 (6)
Serious TRAE	40 (8)	29 (5)	7 (3)	3 (1)
TRAE leading to discontinuation	48 (9)	26 (5)	8 (3)	7 (3)
Selected TRAE				
Endocrine	93 (17)	5 (<1)	6 (2)	0
Gastrointestinal	91 (17)	4 (<1)	40 (15)	3 (1)
Hepatic	49 (9)	6 (1)	18 (7)	4 (2)
Pulmonary	23 (4)	6 (1)	4 (2)	1 (<1)
Renal	7 (1)	1 (<1)	2 (<1)	0
Skin	130 (24)	7 (1)	28 (11)	1 (<1)

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LBA9: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study – Kelly RJ, et al

Key results (cont.)

AEs, n (%)	Nivolumab (n=532)		Placebo (n=260)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
TRAEs occurring in ≥10% of patients in either arm				
Fatigue	90 (17)	6 (1)	29 (11)	1 (<1)
Diarrhoea	88 (17)	2 (<1)	39 (15)	2 (<1)
Pruritus	53 (10)	2 (<1)	9 (3)	0
Rash	52 (10)	4 (<1)	10 (4)	1 (<1)

Conclusion

- **In patients with esophageal/GEJ carcinoma and pathological residual disease after neoadjuvant CRT and surgery, adjuvant nivolumab demonstrated significant and clinically meaningful improvement in DFS compared with placebo and was generally well-tolerated**

Kelly RJ, et al. Ann Oncol 2020;31(suppl):abstr LBA9

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2021
Esophageal and Esophagogastric Junction Cancers

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Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Preoperative Chemoradiation
(Infusional fluorouracil[b] can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin (category 1)[1]
- Fluorouracil[b] and oxaliplatin (category 1)[2,3]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[4,5]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Definitive Chemoradiation
(Infusional fluorouracil can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin[1]
- Fluorouracil[b] and oxaliplatin (category 1)[2,3]
- Fluorouracil and cisplatin (category 1)[11]

Other Recommended Regimens
- Cisplatin with docetaxel or paclitaxel[12-14]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Perioperative Chemotherapy
(Only for adenocarcinoma of the thoracic esophagus or EGJ)

Preferred Regimens
- Fluorouracil,[b] leucovorin, oxaliplatin, and docetaxel (FLOT)[8] (category 1)[c]
- Fluoropyrimidine and oxaliplatin[b,d]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[9]

Preoperative Chemotherapy
(Only for adenocarcinoma of the thoracic esophagus or EGJ)

- Fluorouracil and cisplatin (category 2B)[10]

Postoperative Therapy

Preferred Regimens
- Nivolumab only after preoperative chemoradiation with R0 resection and residual disease (category 1)[e,15]

Other Recommended Regimens
- Capecitabine and oxaliplatin[f,16]
- Fluorouracil[b] and oxaliplatin[f]

Postoperative Chemoradiation

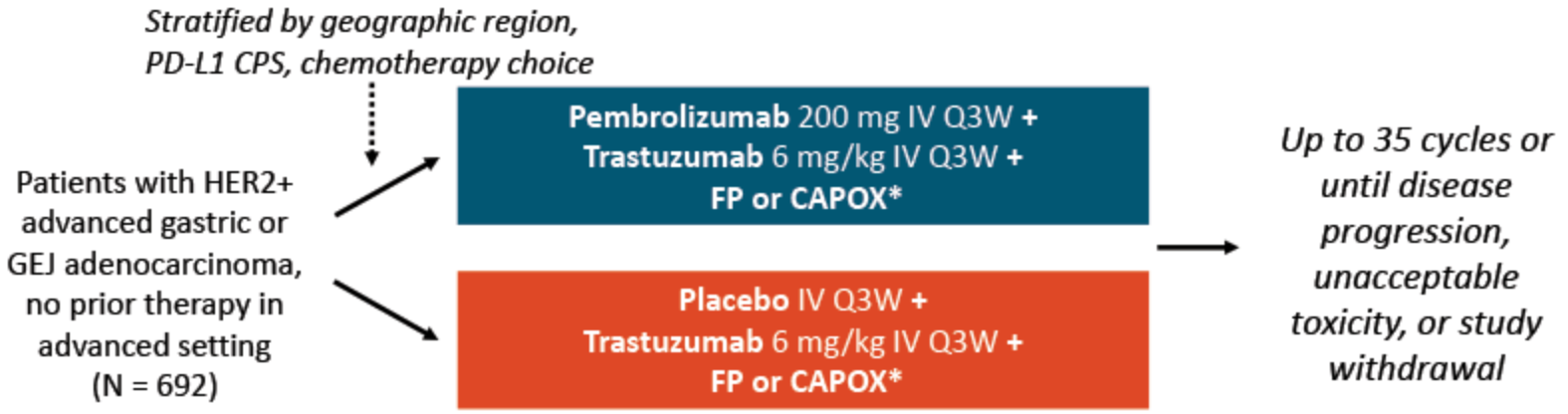
- Fluoropyrimidine (infusional fluorouracil[b] or capecitabine) before and after fluoropyrimidine-based chemoradiation[17]

[b]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.

[c]Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit.

KEYNOTE-811: Pembrolizumab + Trastuzumab + CT for HER2+ Advanced Gastroesophageal Cancer

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



*Trastuzumab 8 mg/kg loading dose.
FP: 5-fluorouracil 800 mg/m² IV Days 1-5 Q3W + cisplatin 80 mg/m² IV Q3W
CAPOX: capecitabine 1000 mg/m² BID Days 1-14 Q3W + oxaliplatin 130 mg/m² IV Q3W

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

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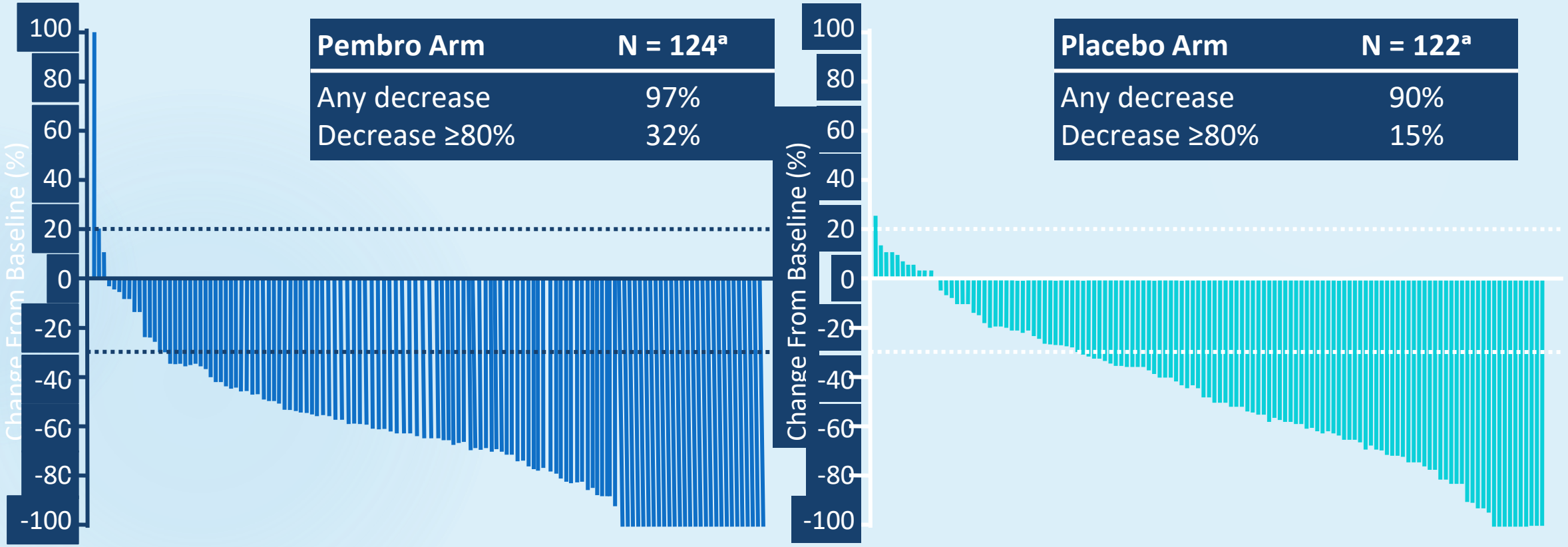
Characteristic		Efficacy Population	
		Pembrolizumab (n = 133)	Placebo (n = 131)
Median age, yr (range)		62 (19-84)	61 (32-83)
Male, n (%)		112 (84)	103 (79)
Region of enrollment	▪ Australia/EU/Israel/N America ▪ Asia ▪ Rest of world	41 (31) 40 (30) 52 (39)	45 (34) 39 (30) 48 (37)
ECOG PS 1, n (%)		68 (51)	72 (5Stomach as 5)
Stomach as primary location		96 (72)	89 (68)
Histological subtype	▪ Diffuse ▪ Intestinal ▪ Indeterminate	28 (21) 81 (61) 24 (18)	26 (20) 63 (48) 42 (32)
PD-L1 CPS ≥1		117 (88)	111 (85)
HER2 status	▪ IHC 2+, ISH positive ▪ IHC 3+	24 (18) 109 (82)	28 (21) 103 (79)
Chemotherapy	▪ CAPOX ▪ FP	114 (86) 19 (14)	115 (88) 16 (12)

Outcome	Efficacy Population	
	Pembrolizumab (n = 133)	Placebo (n = 131)
ORR, % (95% CI)	74.4 (66.2-81.6)	51.9 (43.0-60.7)
ORR difference*	22.7 (11.2-33.7); *P* = .00006	
DCR, % (95% CI)	96.2 (91.4-98.8)	89.3 (82.7-94.0)
Best response, n (%)		
▪ CR	15 (11)	4 (3)
▪ PR	84 (63)	64 (49)
▪ SD	29 (22)	49 (37)
▪ PD	5 (4)	7 (5)
▪ Not evaluable	0	2 (2)
▪ Not assessed	0	5 (4)
Duration of response†	(n = 99)	(n = 68)
▪ Median, mo (range)	10.6 (1.1+ to 16.5+)	9.5 (1.4+ to 15.4+)
▪ ≥6 mo duration, %	70.3	61.4
▪ ≥9 mo duration, %	58.4	51.1
Size reduction from baseline, n (%)	(n = 124)‡	(n = 122)‡
▪ Any decrease	97	90
▪ ≥80% decrease	32	15

KEYNOTE-811 Interim Analysis: Target Lesion Change From Baseline



KEYNOTE-811 Interim Analysis: Safety

AEs, %	Pembrolizumab (n = 217)	Placebo (n = 216)
Any grade	97	98
Gr ≥3	57	57
Serious	31	38
Led to death	3	5
Led to discontinuation	24	26

	Any	Gr ≥3	Any	Gr ≥3
Incidence >20%				
▪ Diarrhea	53	7	44	8
▪ Nausea	49	5	44	6
▪ Anemia	41	9	44	9
▪ Decreased appetite	31	2	32	4
▪ Vomiting	31	5	27	2
▪ Decreased platelets	24	8	28	7
▪ Fatigue	24	4	20	3
▪ Decreased neutrophils	24	7	25	7
▪ Peripheral neuropathy	23	3	19	1
▪ Increased AST	21	<1	13	<1

Immune-Mediated AEs and Infusion Reaction,* %	Pembrolizumab (n = 217)	Placebo (n = 216)
Any grade	34	21
Gr ≥3	10	3
Serious	9	3
Led to death	1	<1
Led to discontinuation	6	2

	Any	Gr ≥3	Any	Gr ≥3
Incidence ≥2 patients				
▪ Infusion reactions	18	3	13	1
▪ Pneumonitis	5	1	1	0
▪ Colitis	5	3	2	2
▪ Hypothyroidism	5	0	3	0
▪ Hyperthyroidism	4	0	3	0
▪ Hypophysitis	1	<1	0	0
▪ Hepatitis	1	1	1	0
▪ Severe skin reactions	1	1	0	0

*Events considered regardless of attribution to treatment by investigator.
Related terms included in addition to specific terms listed.

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KEYNOTE-811 Interim Analysis: Conclusions

- Adding pembrolizumab to trastuzumab/CT led to a 22.7% improvement in ORR vs placebo + trastuzumab/CT as first-line treatment for patients with advanced HER2+ gastric or gastroesophageal junction cancer
- Responses with pembrolizumab + trastuzumab/CT were deeper and more durable than those achieved with placebo + trastuzumab/CT
- Safety profile was similar between treatment arms with no unexpected safety concerns associated with pembrolizumab
- Investigators suggest pembrolizumab + trastuzumab/chemotherapy may be a possible new treatment option for previously untreated, unresectable or metastatic HER2+ gastric or gastroesophageal junction cancer

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Esophageal and Esophagogastric Junction Cancers

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy

- Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Preferred Regimens

- HER2 overexpression positive adenocarcinoma[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,18]
- HER2 overexpression negative[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥ 5) for adenocarcinoma only (category 1)[e,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS 1-4) for adenocarcinoma only (category 2B)[e,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (PD-L1 CPS ≥ 10) for adenocarcinoma or squamous cell carcinoma[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (PD-L1 CPS 1-9) for adenocarcinoma only (category 2B)[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (PD-L1 CPS ≥ 10) (category 1) for adenocarcinoma or squamous cell carcinoma[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (PD-L1 CPS 1-9) for adenocarcinoma only (category 2B)[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin for adenocarcinoma or squamous cell carcinoma[21-23]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin for adenocarcinoma or squamous cell carcinoma[21,24-26]

Other Recommended Regimens

- HER2 overexpression positive adenocarcinoma[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab[a] and pembrolizumab[e,h,27]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] and pembrolizumab[e,h,27]
- Fluorouracil[b,i] and irinotecan[j,28]
- Paclitaxel with or without cisplatin or carboplatin [j,29-33]
- Docetaxel with or without cisplatin [j,34-37]
- Fluoropyrimidine [j,25,38,39] (fluorouracil[b] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b, j,40,41]

Summary and Clinical Implications

- Adjuvant Nivolumab in Esophageal and GEJ after C/RT -> R0, T+ or N+
- First Line Esophageal and GEJ - Chemo+ Nivolumab for CPS ≥ 5 (Adeno only)
  First Line Esophageal and GEJ - Chemo + Pembrolizumab for CPS ≥ 10 (Adeno and Squamous)
- Second line Esophageal cancer – Nivolumab (Squamous only)
  - Pembrolizumab (Squamous only CPS ≥ 10)
- First line Gastric cancer - Chemo + Nivolumab for CPS ≥ 5
- Second and third line Gastric cancer – Immunotherapy not approved unless MSI-H or TMB ≥ 10
- Metastatic HER 2+, Esophageal/GEJ/Gastric adeno ca- Chemo + Trastuzumab + Pembrolizumab