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2020 UPDATES: IMMUNOTHERAPY IN GASTROESOPHAGEAL CANCER

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- **Patients with metastatic gastric cancer**

mOS = 3 months (with only supportive care) up to 16 months with chemotherapies in clinical trials settings¹



There is still an unmet need to improve the treatment options for these patients

- **Benefit of ICI (anti-PD-1, -PD-L1, and -CTLA-4) therapies?**

Great success in treatment of melanoma, non-small cell lung cancer, and urothelial cancers¹



Initiation of investigations of these agents in gastroesophageal cancers

1. Terrero G and Lockhart AC, et al. Curr Oncol Rep. 2020;22(11):112
CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; mOS, median overall survival; PD-1, programmed death 1;
PD-L1, programmed death-ligand 1

BACKGROUND: KEY CLINICAL TRIALS INVESTIGATING ICI IN ADVANCED GASTROESOPHAGEAL CANCERS (1/2)

Treatment line	Name of trial	Trial phase	Drug(s) tested	Dose	Cancer type	N	Median PFS (m)	ORR (%)	Objective response (CR + PR)	Median OS (m)	1-year OS (%)
First-line	KEYNOTE-062	Phase 3	Pembrolizumab	200 mg IV Q3W	Advanced G/GEJ	256	2, 2.9^	14.8, 25^	NA	10.6, 17.4^	47, 57^
			Pembrolizumab + chemo	200 mg IV Q3W + standard doses		257	NA	48.6, 52.5^	NA	NA	NA
			Chemo + placebo	Standard doses		250	6.4, 6.1^	37.2, 37.8^	NA	11.1, 10.8^	46, 47^
First-line	KEYNOTE-059 (cohort 2 and 3)	Phase 2	Pembrolizumab (cohort 3)	200 mg IV Q3W	Advanced G/GEJ	31	NA	25.8	NA	NA	NA
			Pembrolizumab + chemo (cohort 2)	200 mg IV Q3W + standard doses		25	NA	60	NA	NA	NA
Second-line	KEYNOTE-061*	Phase 3	Pembrolizumab	200 mg IV Q3W	Advanced G/GEJ	196	1.5	NA	NA	9.1	NA
			Chemo	Standard doses		199	4.1	NA	NA	8.3	NA
Second-line	KEYNOTE-181†	Phase 3	Pembrolizumab	200 mg IV Q3W	Advanced ESCC	85^	3.2^	22^	NA	10.3^	48^
			Chemo	Standard doses		82^	2.3^	7^	NA	6.7^	23^
Second-line	ATTRACTION-3	Phase 3	Nivolumab	240 mg IV Q2W	Advanced ESCC	210	1.7	NA	NA	10.9	47
			Chemo	Standard doses		209	3.4	NA	NA	8.4	34
Beyond second-line	KEYNOTE-180†	Phase 2	Pembrolizumab	200 mg IV Q3W	Advanced ESCC	35^	NA	20^	NA	NA	NA
Beyond second-line	KEYNOTE-059† (cohort 1)	Phase 2	Pembrolizumab	200 mg IV Q3W	Advanced G/GEJ	259	NA	NA	15.5, 6.4	5.8, 4.9	NA
Beyond second-line	ATTRACTION-2	Phase 3	Nivolumab	240 mg IV Q2W	Advanced G/GEJ	330	NA	NA	NA	5.26	26.2
			Placebo	NA		163	NA	NA	NA	4.14	10.9
Beyond second-line	CHECKMATE-032	Phase 1/2	Nivolumab	3 mg/kg Q2W	Advanced G/GEJ	59	NA	NA	12	NA	39
			Nivolumab + Ipilimumab	1 mg/kg + 3 mg/kg Q3W		49	NA	NA	24	NA	35
			Nivolumab + Ipilimumab	3 mg/kg + 1 mg/kg Q3W		52	NA	NA	8	NA	24

^ = CPS ≥10; * Study did not show superiority of pembrolizumab to paclitaxel; † Led to FDA approval; **Bold** PD-L1-positive; at least CPS ≥1

1. Terrero G and Lockhart AC, et al. Curr Oncol Rep. 2020;22(11):112

CR, complete response; chemo, chemotherapy; CPS, combined positive score; ESCC, esophageal squamous cell carcinoma; FDA, Food and Drug Administration; G, gastric; GEJ, gastroesophageal junction; IV, intravenous; m, months; n, sample size; NA; not available; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks

BACKGROUND: CLINICAL TRIALS INVESTIGATING ICI IN ADVANCED GASTROESOPHAEGAL CANCERS (2/2)

Studies covered in the presentation	ICI under investigations	Target population
CheckMate-649	Nivolumab: human IgG4 monoclonal antibody that blocks PD-1	in patients with advanced gastric cancer, gastroesophageal junction tumour, or adenocarcinoma of the oesophagus
Keynote-590	Pembrolizumab: IgG4 isotype antibody that blocks PD-1	in patients with metastatic, recurrent, or advanced oesophageal and gastroesophageal junction cancer
CheckMate-577	Nivolumab (as an adjuvant treatment): human IgG4 monoclonal antibody that blocks PD-1	in patients with localised oesophageal and gastroesophageal junction tumours who received chemoradiotherapy followed by surgery and who showed residual pathology

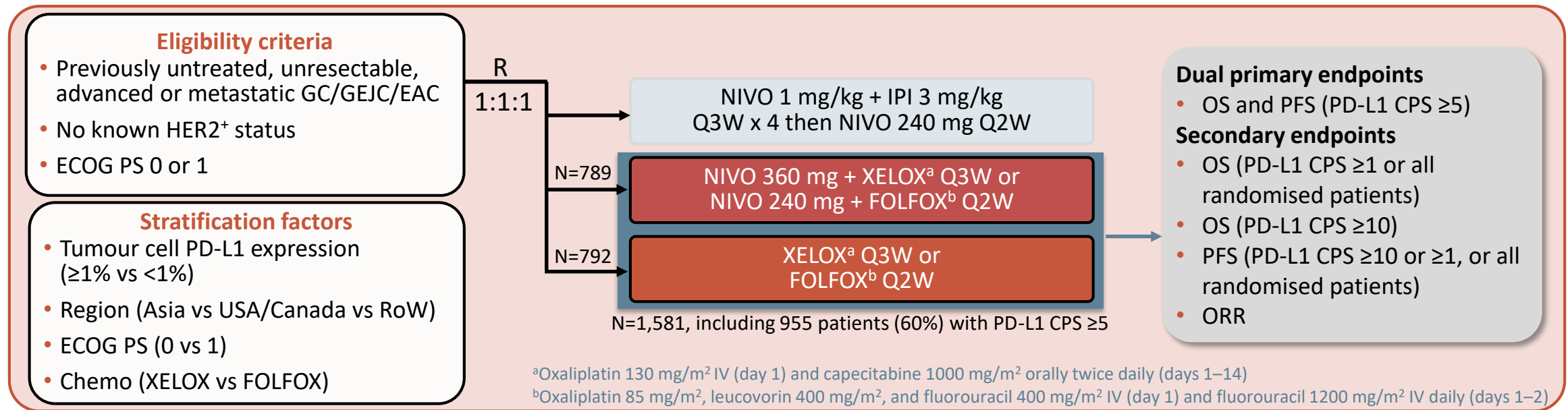


Those 3 clinical trials results are presented in more detail in this presentation

CheckMate-649

DESIGN OF THE STUDY

CheckMate-649 study (NCT02872116): randomised, open-label, Phase 3 study comparing OS in patients with GC or GEJC treated with nivolumab + ipilimumab or nivolumab + chemo compared with chemo alone



Moehler M. et al, reported during ESMO 2020 the first results of NIVO + chemo vs chemo

RESULTS: OS AND PFS

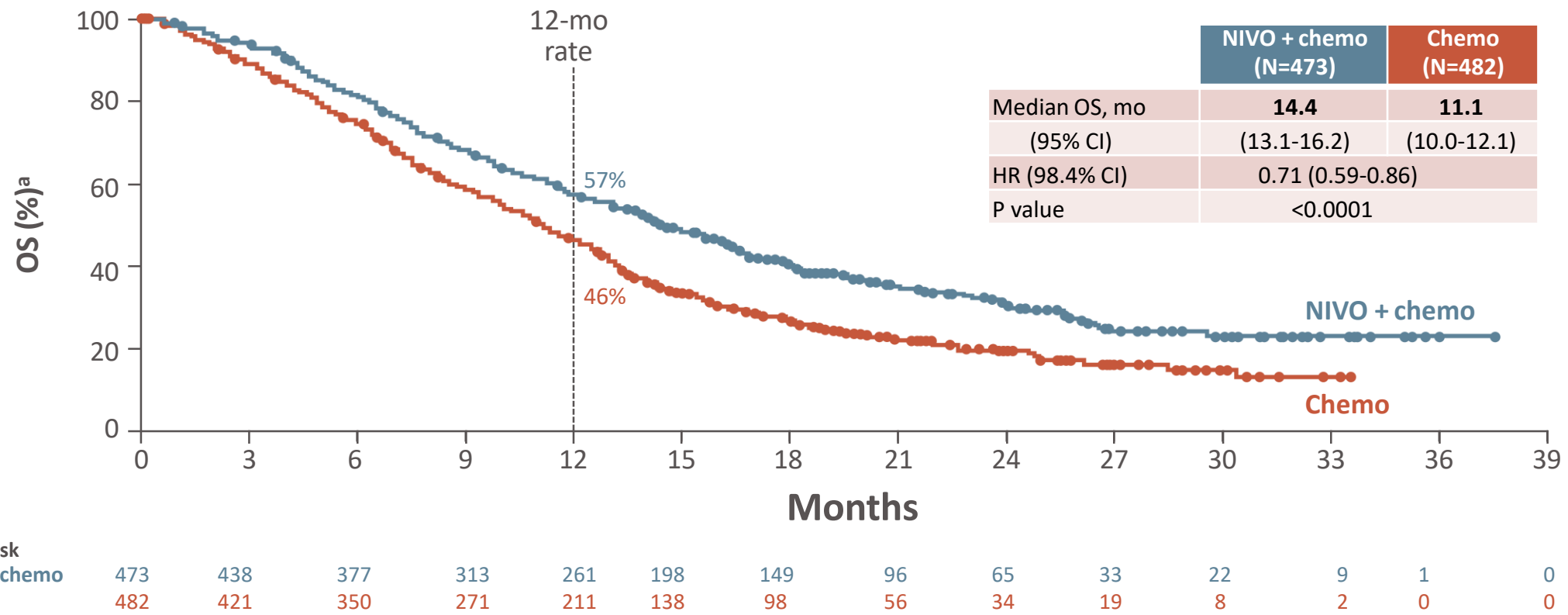
Data cut-off date: 27 May 2020 – minimum follow-up duration 12.1 months

	PD-L1 CPS ≥5		PD-L1 CPS ≥1		All randomised patients	
	NIVO + chemo (N=473)	Chemo (N=482)	NIVO + chemo (N=641)	Chemo (N=655)	NIVO + chemo (N=789)	Chemo (N=792)
Median OS, months (95% CI)	14.4 (13.1-16.2)	11.1 (10.0-12.1)	14.0 (12.6-15.0)	11.3 (10.6-12.3)	13.8 (12.6-14.6)	11.6 (10.9-12.5)
HR (98.4% CI) ^a p value	0.71 (0.59-0.86) <0.0001		0.77 (0.64-0.92) 0.0001		0.80 (0.68-0.94) 0.0002	
12-month OS rate, %	57	46	56	47	55	48
Median PFS, months (95% CI)	7.7 (7.0-9.2)	6.0 (5.6-6.9)	7.5 (7.0-8.4)	6.9 (6.1-7.0)	7.7 (7.1-8.5)	6.9 (6.6-7.1)
HR (98% CI) ^b p value	0.68 (0.56-0.81) <0.0001		0.74 (0.65-0.85) NR		0.77 (0.68-0.87) NR	
12-month PFS rate, %	36	22	34	22	33	23

^a In the PD-L1 CPS ≥1 group and the all randomised patients group, the CI was 99.3%; ^b In the PD-L1 CPS ≥1 group and the all randomised patients group, the CI was 95%
chemo, chemotherapy; CI, confidence interval; CPS, combined positive score; HR, hazard ratio; NIVO, nivolumab; NR, not reported; OS, overall survival;
PD-L1, programmed death-ligand 1; PFS, progression-free survival
Source: Moehler M, et al. Ann Oncol. 2020;31(suppl_4):abstr LBA6

RESULTS: mOS IN PD-L1 CPS \geq 5

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



^a Minimum follow-up 12.1 months.

Source: Moehler M, et al. Ann Oncol 2020;31(suppl_4):abstr LBA6

chemo, chemotherapy; CI, confidence interval; CPS, combined positive score; HR, hazard ratio; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1

RESULTS: TREATMENT RELATED ADVERSE EVENTS

All treated patients ^a , n (%)	NIVO + chemo (N=782) ^b		Chemo (N=767) ^b	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAEs ^c	738 (94)	462 (59)	679 (89)	341 (44)
Serious TRAEs ^c	172 (22)	131 (17)	93 (12)	77 (10)
TRAEs leading to discontinuation ^c	284 (36)	132 (17)	181 (24)	67 (9)
12-month PFS rate, %	12 ^d (2)		4 ^e (<1)	

- The most common any-grade TRAEs (≥25%) across both arms were nausea, diarrhea, and peripheral neuropathy
- The incidence of TRAEs in patients whose tumors expressed PD-L1 CPS ≥5 was consistent with all treated patients across both arms

^a Patients who received ≥ 1 dose of study drug; ^b Assessed in all treated patients during treatment and for up to 30 days after the last dose of study treatment; ^c There were 4 grade 5 events in the NIVO + chemo arm, 1 case each of cerebrovascular accident, febrile neutropenia, gastrointestinal inflammation, and pneumonia. There were no grade 5 events in the chemo arm; ^d One event each of febrile neutropenia, gastrointestinal bleeding, gastrointestinal toxicity, infection, interstitial lung disease, intestinal mucositis, neutropenic fever, pneumonia, pneumonitis, pulmonitis, septic shock (capecitabine-related), and stroke. ^e One event each of diarrhea-associated toxicity, asthenia and severe hiporexy, pulmonary thromboembolism, and interstitial pneumonia

chemo, chemotherapy; CPS, combined positive score; NIVO, nivolumab; PD-L1, programmed death-ligand 1; TRAEs, Treatment related adverse events

Source: Moehler M, et al. Ann Oncol. 2020;31(suppl_4):abstr LBA6

RESULTS: BIOMARKER ANALYSIS

CheckMate-649

Secondary endpoints:
OS in PD-L1 CPS ≥ 1 and all randomised patients

	n	Hazard ratio	Δ	p value	
CPS ≥ 5	953	0.71 (0.59-0.86)	3.3	<0.0001	
CPS ≥ 1	1296	0.77 (0.64-0.92)	2.7	0.001	> 70% CPS ≥ 5
All patient	1581	0.80 (0.68-0.94)	2.2	0.002	> 60% CPS ≥ 5

- CPS ≥ 1 and “All patient” groups are enriched with immunogenic CPS ≥ 5 tumours
 - May not be representative of general GEA population¹
 - May be more sensitive to nivolumab than regular CPS ≥ 1 and “All patient” groups outside trial

Slide Courtesy of Prof. E. Smyth

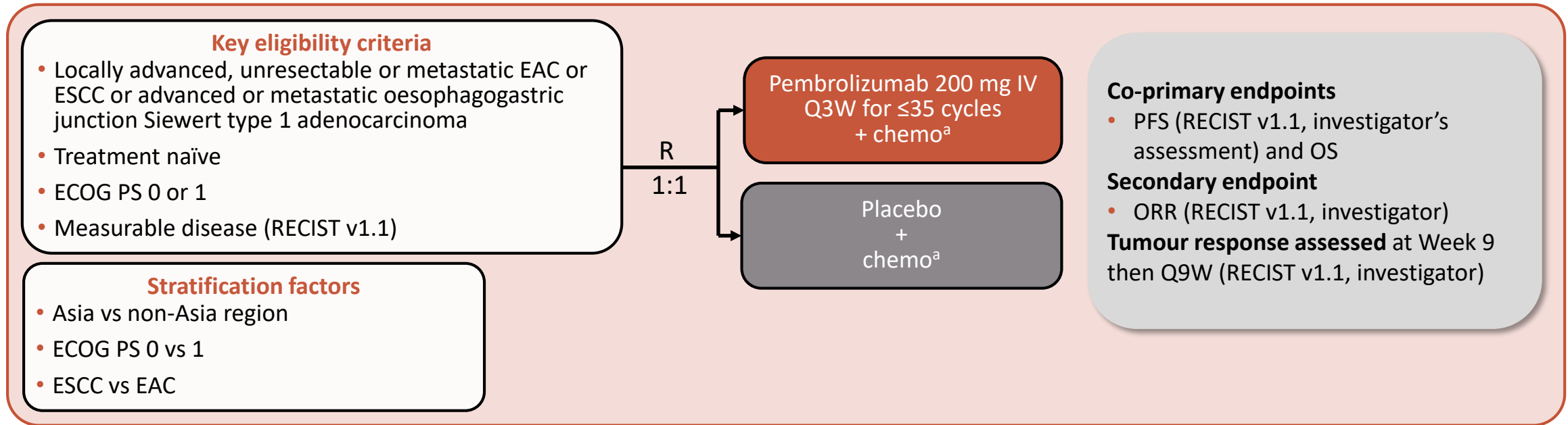
1. Hagi T, et al. Br J Cancer. 2020;123(6):965-972

CPS, combined positive score; GEA, gastroesophageal adenocarcinoma; OS; overall survival; PD-L1, programmed death-ligand 1

KEYNOTE-590

DESIGN OF THE STUDY

KEYNOTE-590 study (NCT03189719): a randomised, double-blind, placebo-controlled Phase 3 trial of first-line pembrolizumab + chemo vs placebo + chemo in advanced EAC or ESCC



Kato K. et al, reported primary results of pembrolizumab + chemo vs placebo + chemo during ESMO 2020

^a 5-fluorouracil 800 mg/m² IV on days 1-5 Q3W for ≤35 cycles + cisplatin 80 mg/m² IV Q3W for ≤6 cycles
chemo, chemotherapy; EAC, oesophageal adenocarcinoma; ECOG, Eastern Cooperative Oncology Group; ESCC, oesophageal squamous cell carcinoma; IV, intravenously;
ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W, every 3 weeks; Q9W, every 9 weeks; R, randomisation;
RECIST, Response Evaluation Criteria in Solid Tumours - Source: Kato K, et al. Ann Oncol. 2020;31(suppl_4):abstr LBA8

RESULTS: OS AND PFS

Data cut-off date: 2 July 2020 – median follow-up duration 10.8 months

Total population: 749 patients randomly assigned → 370 patients treated per arm

	ESCC		ESCC PD-L1 CPS ≥10		PD-L1 CPS ≥10		All patients	
	Pembro + chemo (N=274)	Chemo (N=274)	Pembro + chemo (N=143)	Chemo (N=143)	Pembro + chemo (N=186)	Chemo (N=197)	Pembro + chemo (N=373)	Chemo (N=376)
Median OS, months (95% CI)	12.6 (10.2-14.3)	9.8 (8.6-11.1)	13.9 (11.1-17.7)	8.8 (7.8-10.5)	13.5 (11.1-15.6)	9.4 (8.0-10.7)	12.4 (10.5-14.0)	9.8 (8.8-10.8)
HR (95% CI) p value	0.72 (0.60-0.88) 0.0006		0.57 (0.43-0.75) <0.0001		0.62 (0.49-0.78) <0.0001		0.73 (0.62-0.86) <0.0001	
12-month OS rate, %	51	38	55	34	54	37	51	39
24-month OS rate, %	29	17	31	15	31	15	28	16
Median PFS^a, months (95% CI)	6.3 (6.2-6.9)	5.8 (5.0-6.1)	NR (NR-NR)	NR (NR-NR)	7.5 (6.2-8.2)	5.5 (4.3-6.0)	6.3 (6.2-6.9)	5.8 (5.0-6.0)
HR (95% CI) p value	0.65 (0.54-0.78) <0.0001		NR (NR-NR) NR		0.51 (0.41-0.65) <0.0001		0.65 (0.55-0.76) <0.0001	
12-month PFS rate, %	24	12	NR	NR	30	9	25	12
18-month PFS rate, %	17	6	NR	NR	21	5	16	6

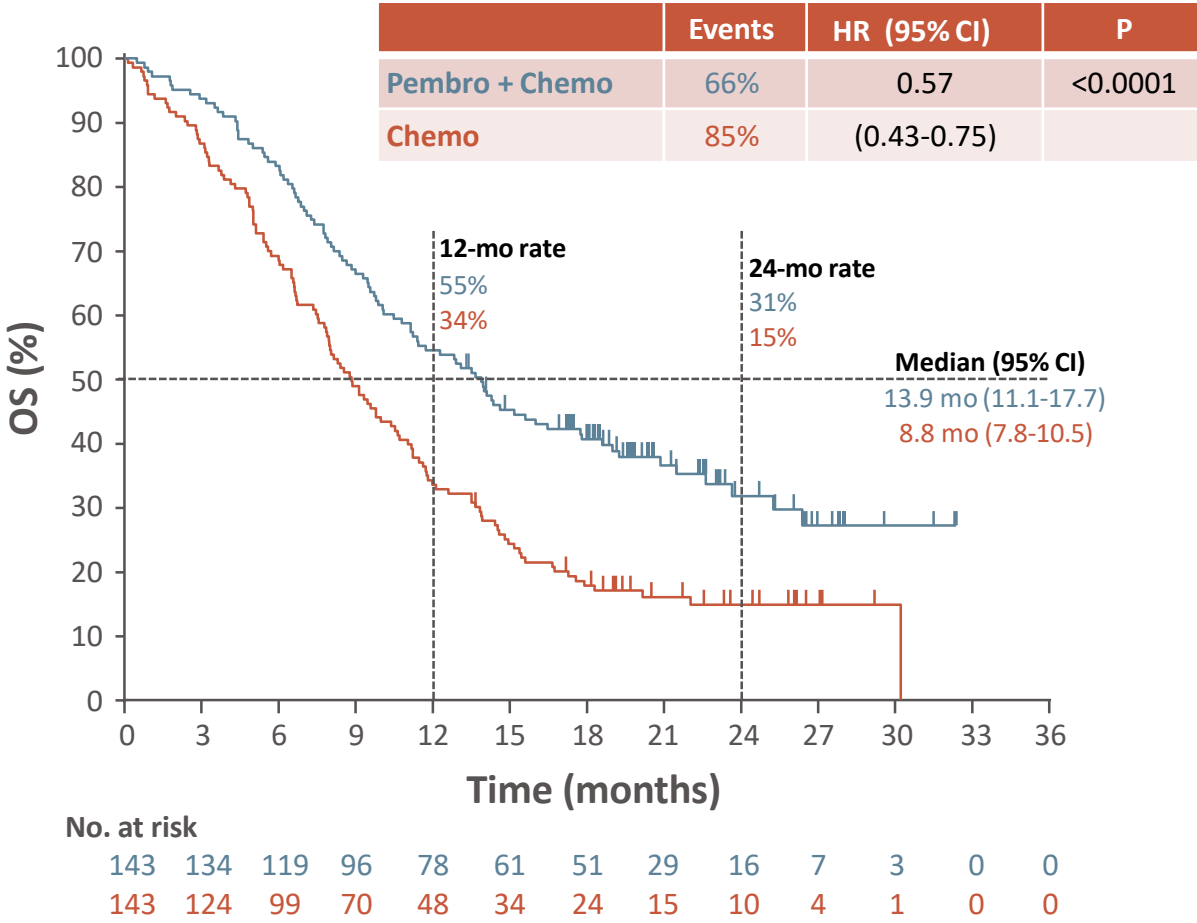
^a Per RECIST v1.1, investigator

chemo, chemotherapy; CI, confidence interval; CPS, combined positive score; ESCC, oesophageal squamous cell carcinoma; HR, hazard ratio; NR, not reported; OS, overall survival; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours - Source: Kato K, et al. Ann Oncol. 2020;31(suppl_4):abstr LBA8

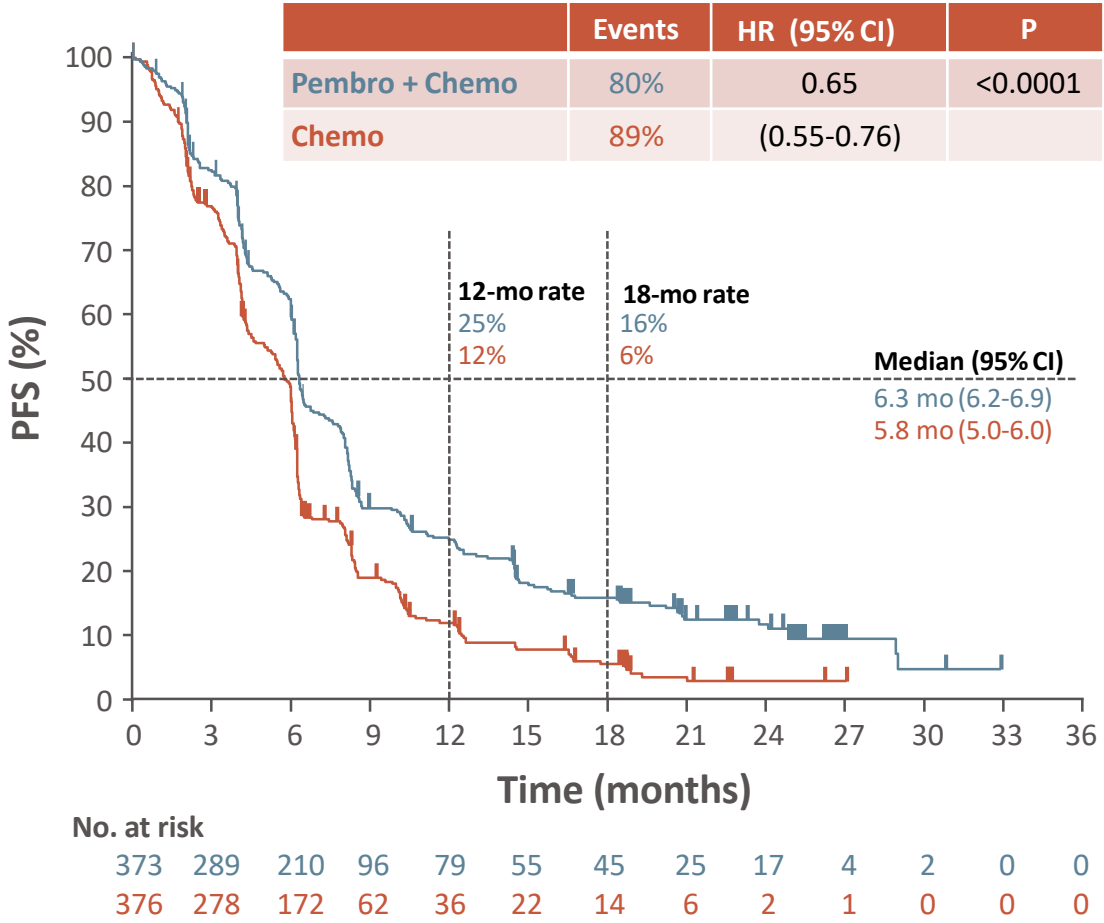
RESULTS: OS AND PFS



OS IN ESCC PD-L1 CPS ≥10

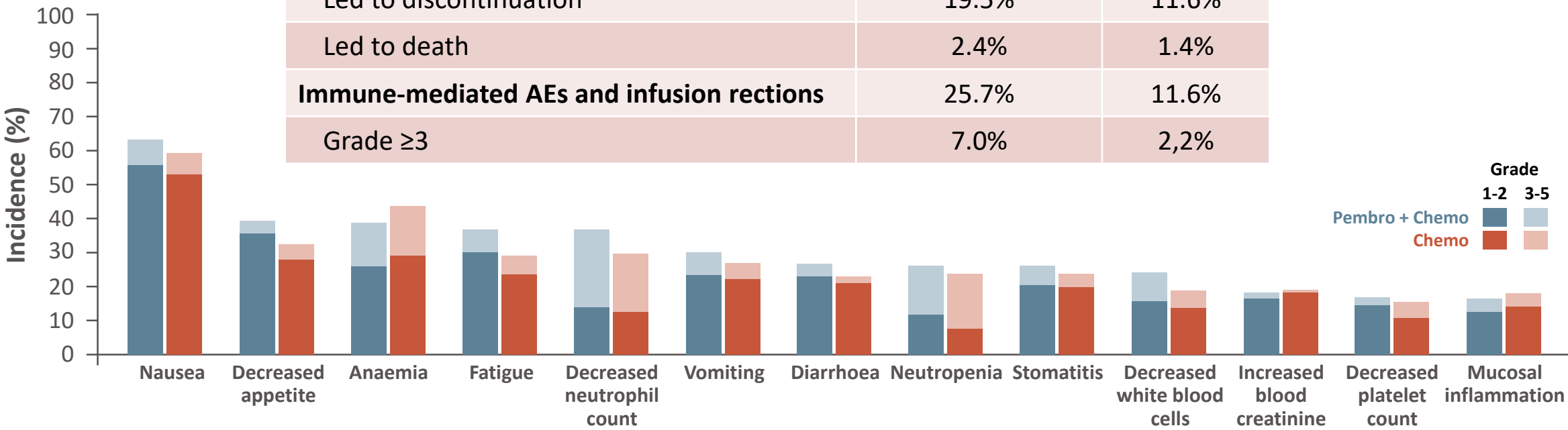


PFS IN ALL PATIENTS



RESULTS: ADVERSE EVENTS IN ALL TREATED PATIENTS

AEs	Pembro+Chemo (N=370)	Chemo (N=370)
Any	100%	99.5%
Treatment-related	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 AEs and infusion rections	25.7%	11.6%
Grade ≥3	7.0%	2,2%



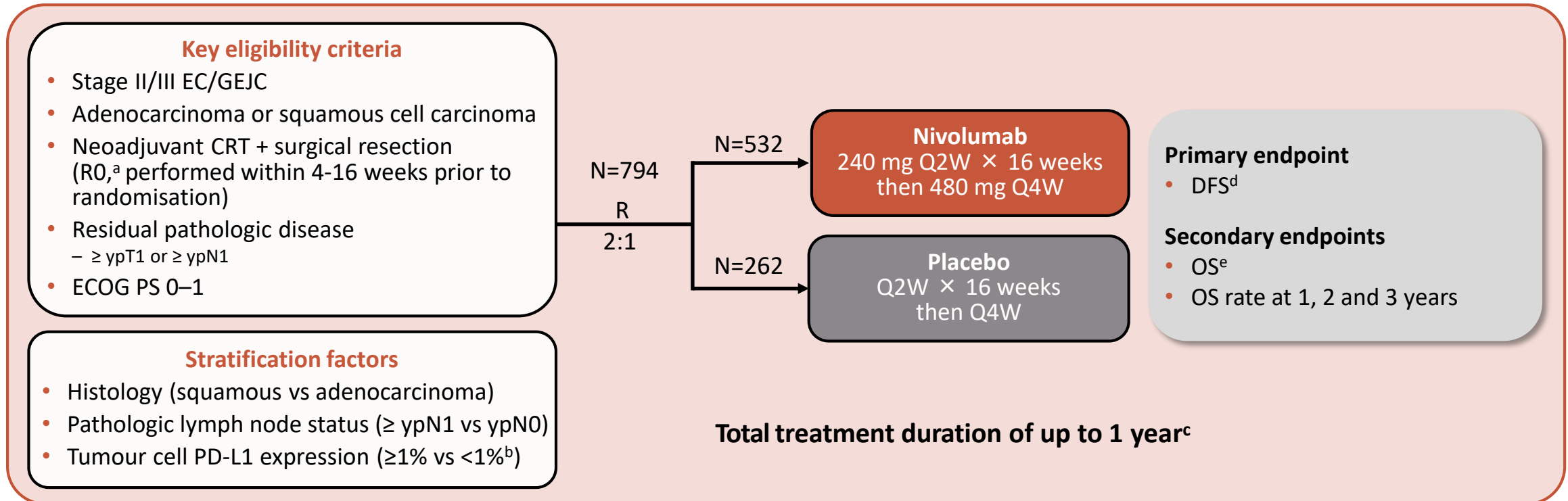
^a Treatment related events with ≥15% incidence in any treatment arm; Data cut-off: July 2, 2020.

AE, adverse event; Chemo, chemotherapy; Pembro, pembrolizumab

CHECKMATE-577

DESIGN OF THE STUDY

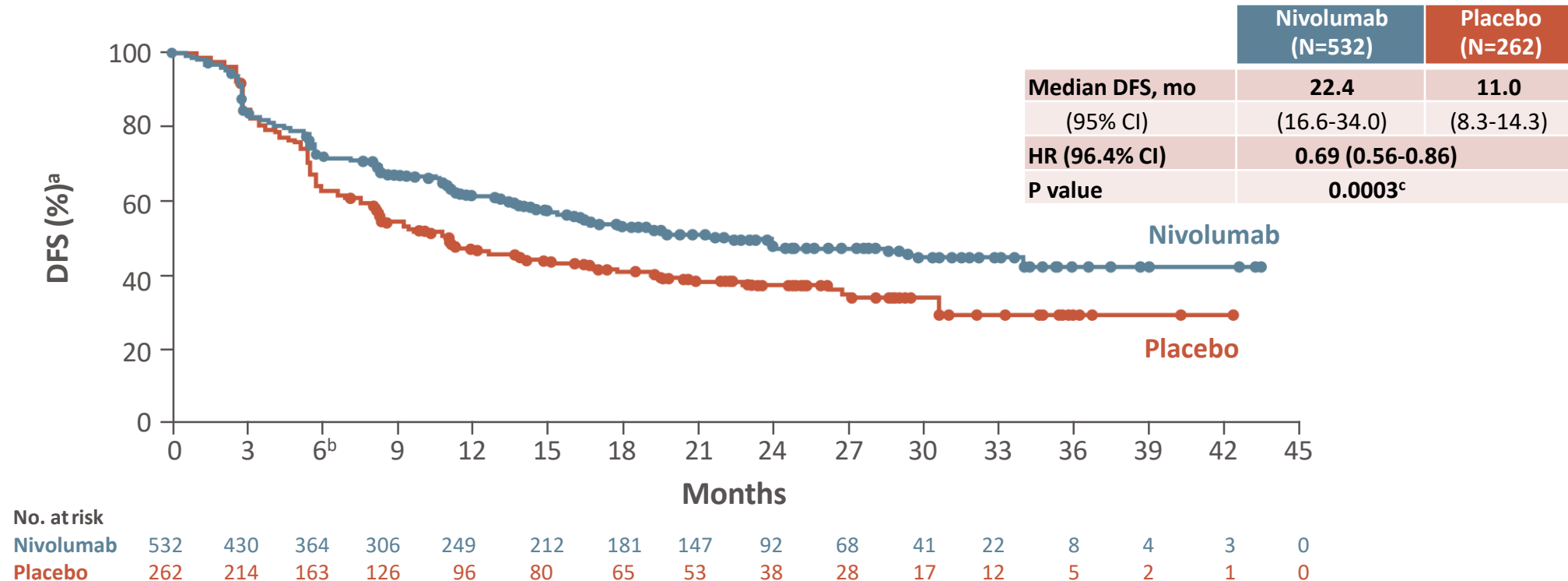
CheckMate-577 study (NCT02743494): randomised, multicentre, double-blind, Phase 3 study of adjuvant nivolumab or placebo in subjects with resected oesophageal, or gastroesophageal junction cancer



^a Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumour present within 1 mm of the proximal, distal, or circumferential resection margins; ^b <1% includes indeterminate/non evaluable tumour cell PD-L1 expression; ^c Until disease recurrence, unacceptable toxicity, or withdrawal of consent; ^d Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a pre-specified interim analysis; ^e The study will continue as planned to allow for future analysis of OS.

RESULTS: DFS

Clinical data cut-off date: 12 May 2020 (median follow-up 24.4 months (range, 6.2-44.9))



→ Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

^a Per investigator assessment; ^b 6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; ^c The boundary for statistical significance at the pre-specified interim analysis required the P value to be less than 0.036.

RESULTS: SAFETY-NIVOLUMAB WELL TOLERATED

Patients, n (%)	Nivolumab ^a (N=532)		Placebo ^a (N=260)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AEs^b	510 (96)	183 (34)	243 (93)	84 (32)
Serious AEs	158 (30)	107 (20)	78 (30)	53 (20)
AEs leading to discontinuation	68 (13)	38 (7)	20 (8)	16 (6)
Any TRAEs^{b,c}	376 (71)	71 (13)	119 (46)	15 (6)
Serious TRAEs ^c	40 (8)	29 (5)	7 (3)	3 (1)
TRAEs leading to discontinuation ^c	48 (9)	26 (5)	8 (3)	7 (3)
TRAEs in ≥10% of treated patients in either arm^b				
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)

^a Patients who received ≥1 dose of study treatment; ^b Events reported between first dose and 30 days after last dose of study drug ; ^c Only 1 grade 5 TRAE was recorded in either arm (cardiac arrest in the nivolumab arm that was reported as not treatment related after database lock).

Source: Kelly RJ, et al. Ann Oncol. 2020;31(suppl_4):abstr LBA9

AE, adverse event; TRAE, treatment-related adverse event

CONCLUSIONS

KEY FINDINGS

- Based on CheckMate-649 results, NIVO + chemo represents a **new potential standard of care in the first-line treatment of advanced GC/GEJC/EAC in patients with CPS ≥ 5**
- Based on KEYNOTE-590 results, Pembro + chemo could be considered a **new potential first-line treatment option for patients with locally advanced and metastatic oesophageal cancer, especially ESCC (70% of the population) or tumours with PD-L1 CPS ≥ 10 (50% of the population)**
- Based on CheckMate-577 results, **NIVO as adjuvant therapy** in patients treated with chemo-radiotherapy and curative surgery has the potential to become a **new standard of care**
- The **safety profile** of the 3 therapies seems **acceptable and well tolerated**

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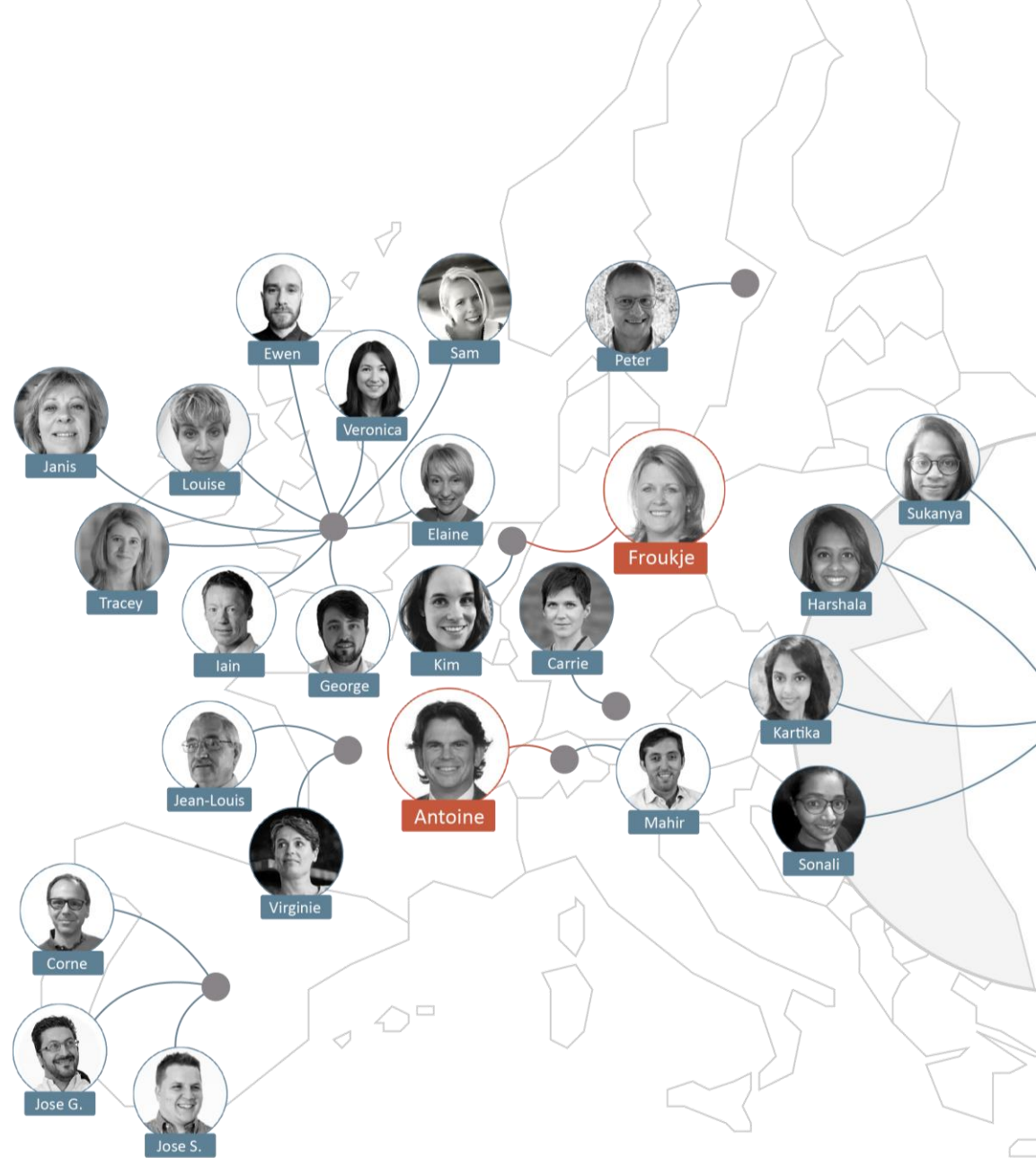
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