Emerging data with immunotherapy in esophageal squamous cell carcinoma and potential impact for clinical practice: Insights from 2021

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CheckMate 648: Study design

- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0 or 1
- No prior systemic treatment for advanced disease
- Measurable disease

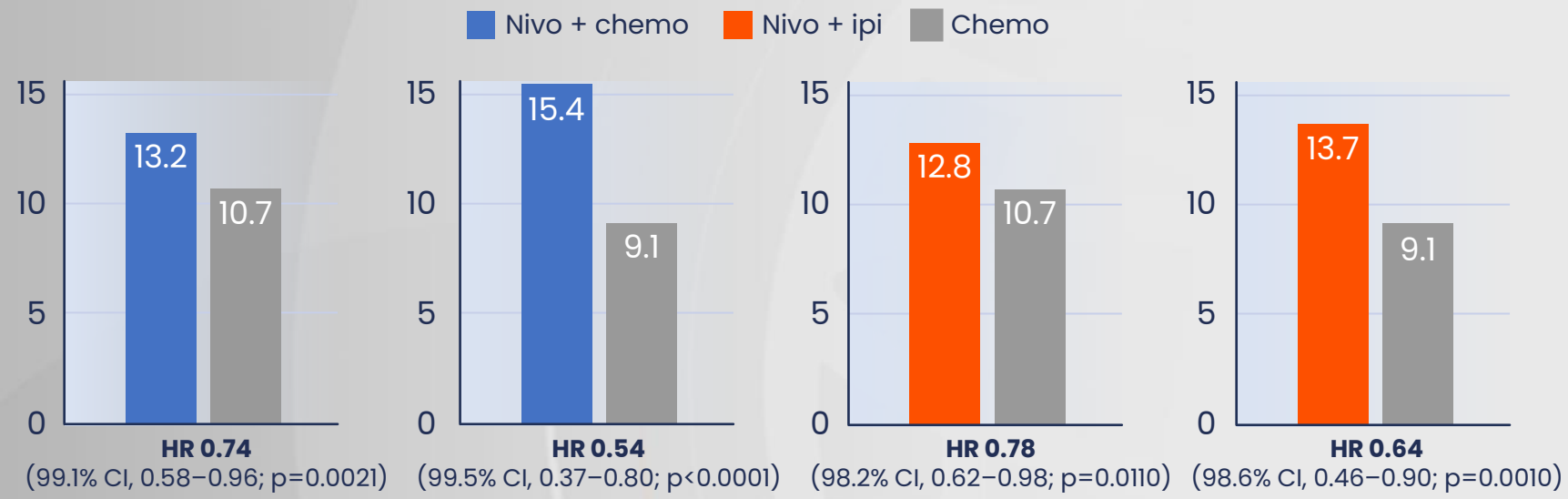
n=324	n=321	n=325
Chemo Q4W	Nivo 240 mg Q2W + chemo Q4W	Nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W

Nivolumab + ipilimumab or nivolumab + chemotherapy vs chemotherapy as first-line treatment for advanced ESCC

Chemo, chemotherapy; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; ipi, ipilimumab; nivo, nivolumab; PS, performance status; Q2/4/6W, once every 2/4/6 weeks.

1. Chau I, et al. *J Clin Oncol.* 2021;39(Suppl. 18):LBA4001; 2. Chau I, et al. Oral presentation at ASCO, 4–8 June 2021, Chicago, IL, USA: LBA7.

CheckMate 648: Median overall survival (months)



CI, confidence interval; HR, hazard ratio; PD-L1, programmed death-ligand 1.

1. Chau I, et al. *J Clin Oncol.* 2021;39(Suppl. 18):LBA4001; 2. Chau I, et al. Oral presentation at ASCO, 4–8 June 2021, Chicago, IL, USA: LBA7.

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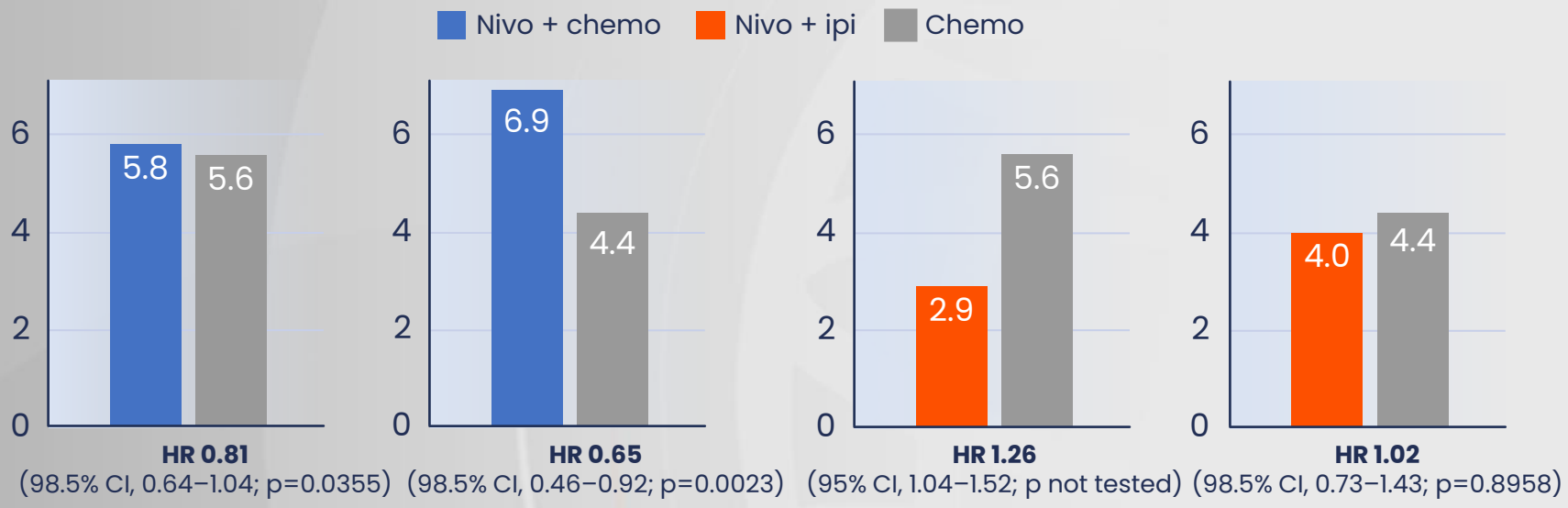
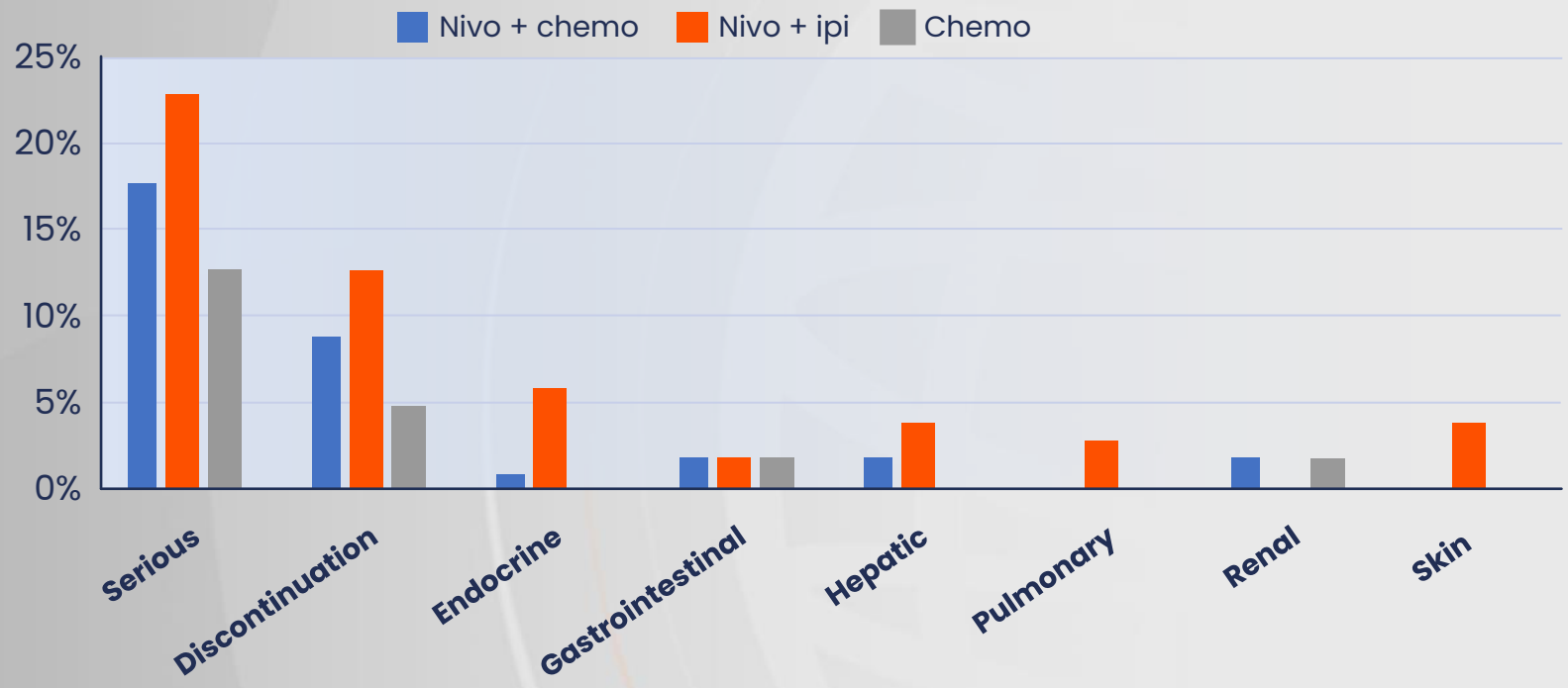
CheckMate 648: Median progression-free survival (months)



1. Chau I, et al. *J Clin Oncol.* 2021;39(Suppl. 18):LBA4001; 2. Chau I, et al. Oral presentation at ASCO, 4–8 June 2021, Chicago, IL, USA: LBA7.

CheckMate 648: Treatment-related adverse events (grade 3 or 4)*



- For all randomized patients and those with PD-L1 ≥1%:
  - Superior median OS with both IO combinations vs chemotherapy alone
  - Clinically meaningful PFS benefit with nivolumab + chemotherapy
- No new safety signals with either combined IO regimen

*Select treatment-related adverse events with potential immunologic aetiology that require frequent monitoring/intervention.
IO, immunotherapy.
1. Chau I, et al. *J Clin Oncol.* 2021;39(Suppl. 18):LBA4001; 2. Chau I, et al. Oral presentation at ASCO, 4–8 June 2021, Chicago, IL, USA: LBA7.

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ORIENT-15: Study design

- Unresectable locally advanced or metastatic ESCC
- ECOG PS 0 or 1
- ≥18 years old
- At least one measurable lesion

n=332

Placebo Q3W, for a maximum of 24 months + chemo Q3W for a maximum of 6 cycles

n=327

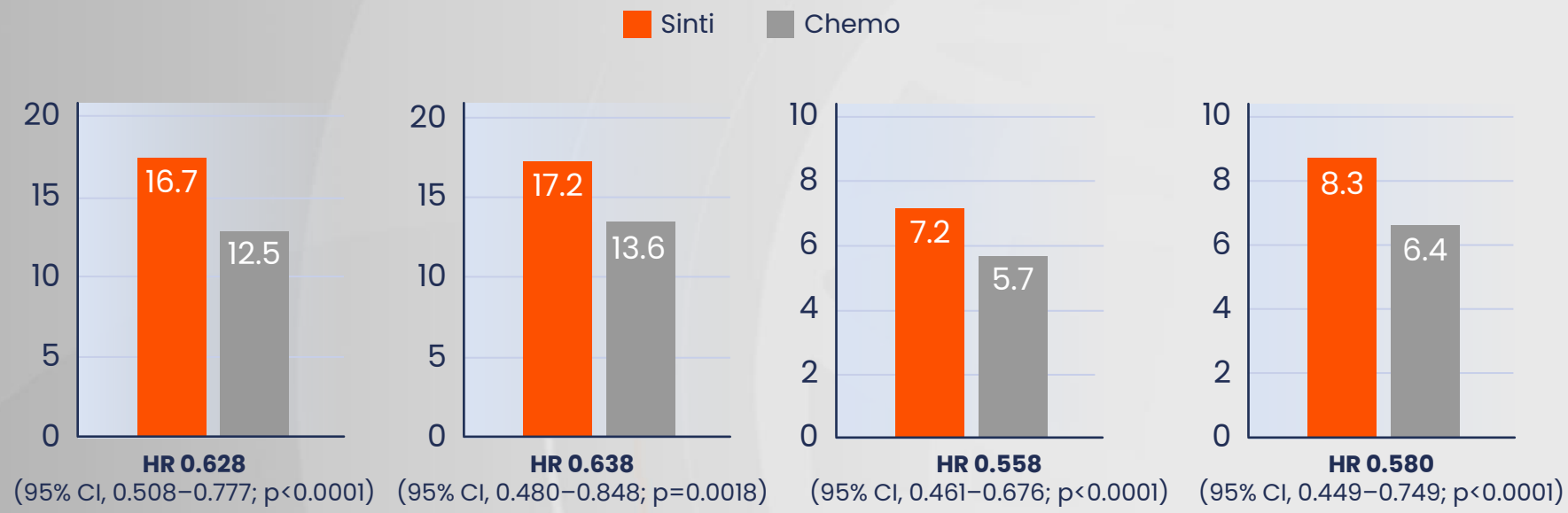
Sintilimab Q3W, for a maximum of 24 months + chemo Q3W for a maximum of 6 cycles

Sintilimab + chemotherapy vs chemotherapy as first-line therapy in patients with advanced or metastatic ESCC

Q3W, once every 3 weeks.

1. Shen L, et al. *Ann Oncol.* 2021;32(Suppl. 5):S1330; 2. Shen L, et al. Oral presentation at ESMO, 16–21 September 2021, Paris, France: LBA53.

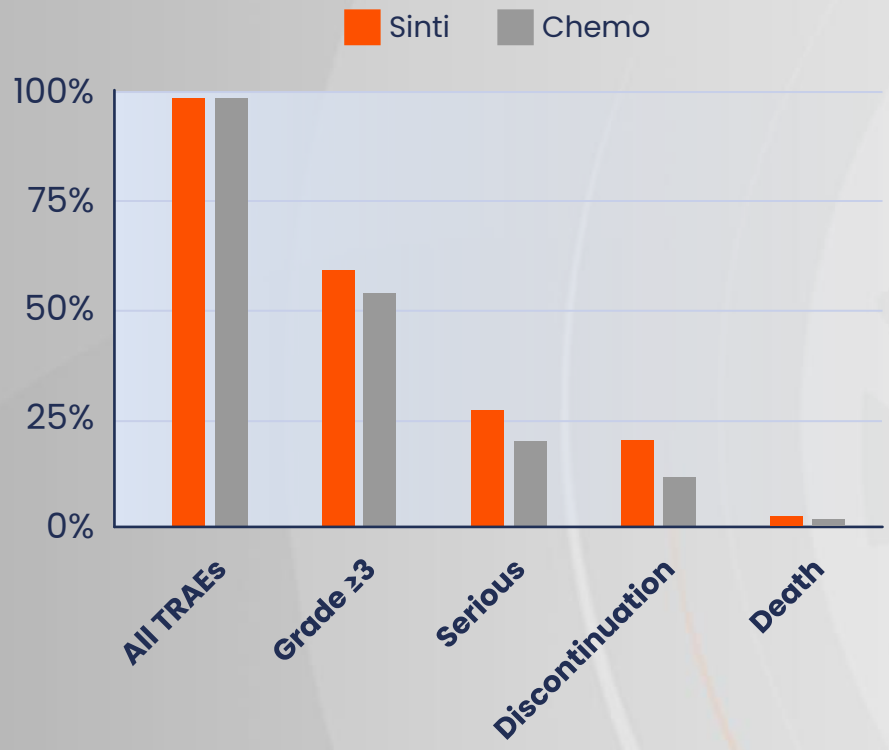
ORIENT-15: Key study endpoints



CPS, combined positive score; OS, overall survival; PFS, progression-free survival; sinti, sintilimab.

1. Shen L, et al. *Ann Oncol.* 2021;32(Suppl. 5):S1330; 2. Shen L, et al. Oral presentation at ESMO, 16–21 September 2021, Paris, France: LBA53.

ORIENT-15: Treatment-related adverse events



TRAEs with ≥15% incidence

Anaemia	Alopecia
Decreased WBCs	Decreased appetite
Decreased neutrophils	Hypoaesthesia
Nausea	Decreased platelets
Vomiting	Decreased weight
Asthenia	Rash

- Superior median overall survival and durable responses with sintilimab + chemotherapy than chemotherapy alone regardless of PD-L1 expression
- No new safety signals with the IO combination

TRAE, treatment-related adverse event; WBC, white blood cell.

1. Shen L, et al. *Ann Oncol.* 2021;32(Suppl. 5):S1330; 2. Shen L, et al. Oral presentation at ESMO, 16–21 September 2021, Paris, France: LBA53.

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JUPITER-06: Study design

- Histologically or cytologically confirmed advanced or metastatic ESCC
- Treatment-naive for metastatic disease
- ECOG PS 0 or 1
- Measurable disease

n=257

Placebo + chemo Q3W for up to 6 cycles followed by maintenance placebo Q3W

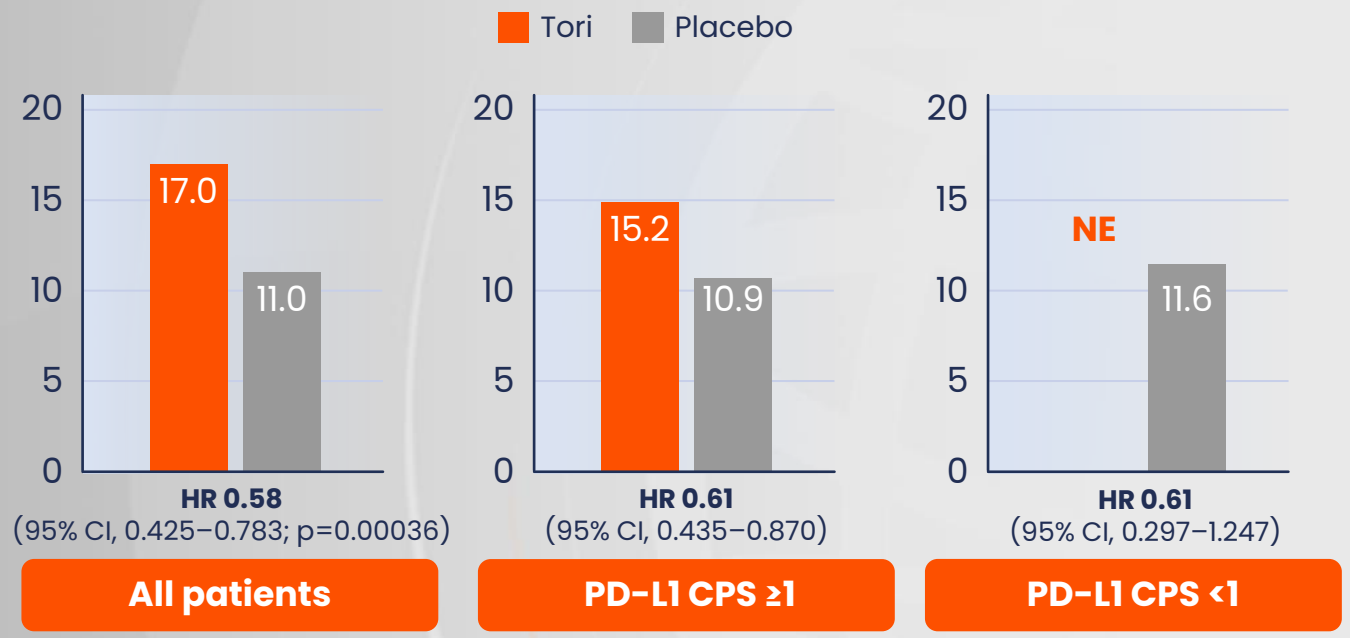
n=257

Toripalimab 240 mg + chemo Q3W for up to 6 cycles followed by maintenance 240 mg toripalimab Q3W

Randomized, double-blind, phase III study of toripalimab vs placebo in combination with first-line chemotherapy for treatment naive advanced or metastatic ESCC

1. Xu R, et al. *Ann Oncol.* 2021;32(Suppl. 5):S1040–75; 2. Xu R, et al. Oral presentation at ESMO, 16–21 September 2021, Paris, France: 1373MO.

JUPITER-06: Median overall survival (months) – interim analysis



- PFS median 5.7 vs 5.5 months
  (HR, 0.58; 95% CI, 0.461–0.738; p<0.00001)

NE, not estimable; tori, toripalimab.

1. Xu R, et al. *Ann Oncol.* 2021;32(Suppl. 5):S1040–75; 2. Xu R, et al. Oral presentation at ESMO, 16–21 September 2021, Paris, France: 1373MO.

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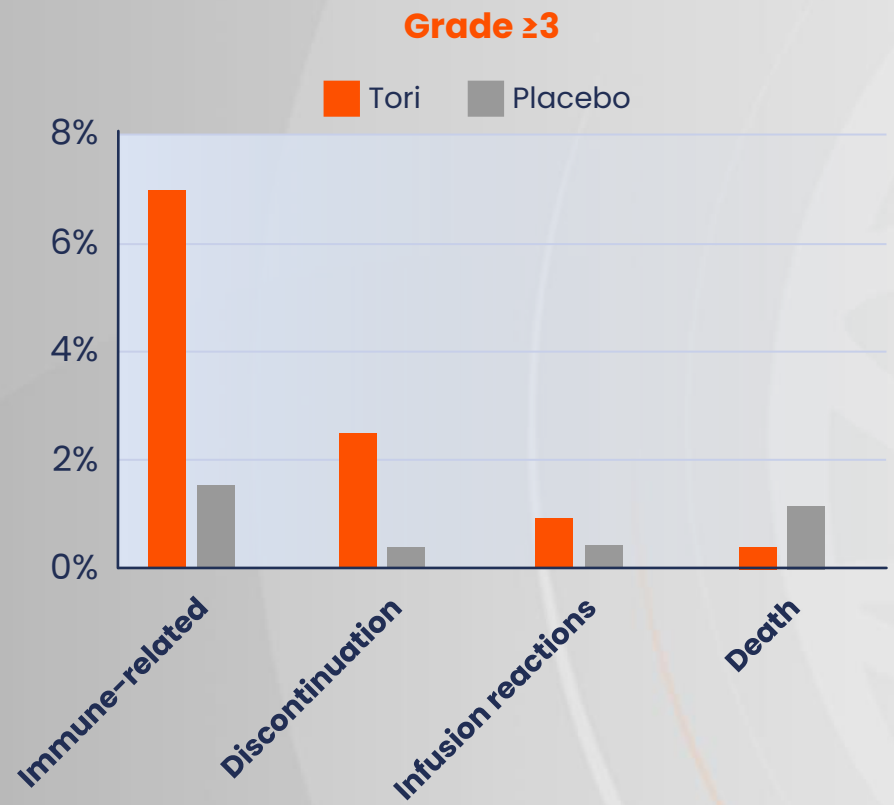
JUPITER-06: Treatment-related adverse events – interim analysis



TRAEs with ≥30% incidence

- Anaemia
- Leukopenia
- Neutropenia
- Nausea
- Peripheral neuropathy
- Fatigue
- Decreased appetite
- Alopecia
- Vomiting

- Superior OS and PFS with IO than chemo alone
- OS and PFS benefits were observed regardless of PD-L1 expression
- No new safety signals

1. Xu R, et al. *Ann Oncol.* 2021;32(Suppl. 5):S1040–75; 2. Xu R, et al. Oral presentation at ESMO, 16–21 September 2021, Paris, France: 1373MO.

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ESCORT-1st: Study design

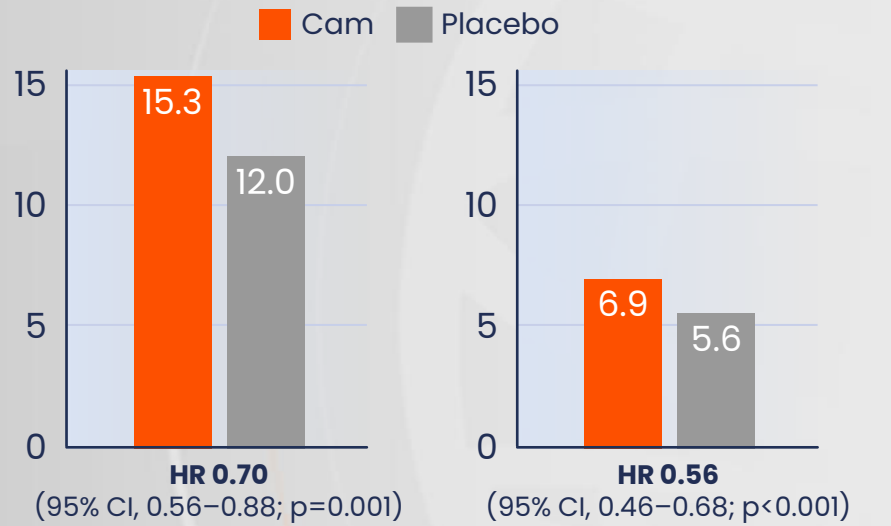
- Histologically or cytologically confirmed ESCC
- Treatment-naive
- Advanced or metastatic disease
- ECOG PS 0 or 1
- Measurable disease

n=298	n=298
Placebo QW3 + chemo Q3W + chemo Q3W for ≤6 cycles	Camrelizumab 200 mg Q3W + chemo Q3W for ≤6 cycles

Randomized, double-blind, placebo-controlled, phase III trial of camrelizumab + chemotherapy vs chemotherapy in patients with untreated advanced or metastatic ESCC

1. Xu R, et al. *J Clin Oncol.* 2021;39(Suppl. 15):4000; 2. Xu R, et al. Oral presentation at ASCO, 4–8 June 2021, Chicago, IL, USA: 4000.

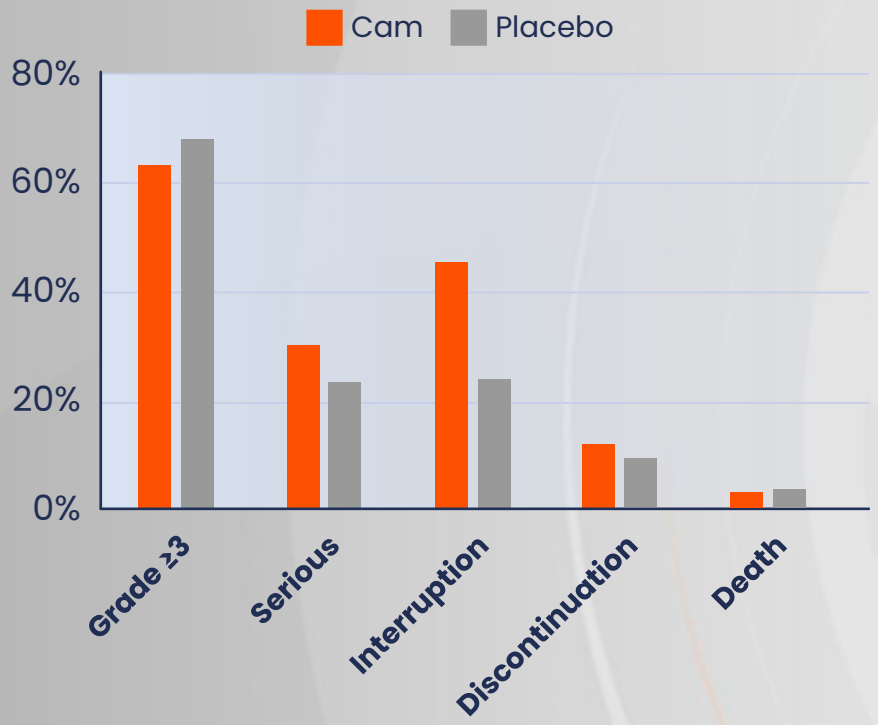
ESCORT-1st: Key endpoints – interim analysis



Cam, camrelizumab.

1. Xu R, et al. *J Clin Oncol.* 2021;39(Suppl. 15):4000; 2. Xu R, et al. Oral presentation at ASCO, 4–8 June 2021, Chicago, IL, USA: 4000.

ESCORT-1st: Treatment-related adverse events – interim analysis



TRAEs with ≥20% incidence

RCCEP	Alopecia
Anaemia	Decreased appetite
Decreased WBCs	Vomiting
Decreased neutrophils	Decreased platelets
Nausea	Decreased weight
Asthenia	Increased creatine

- Superior OS and PFS with IO than placebo + chemotherapy
- Manageable safety profile

RCCEP, reactive cutaneous capillary endothelial proliferation.

1. Xu R, et al. *J Clin Oncol.* 2021;39(Suppl. 15):4000; 2. Xu R, et al. Oral presentation at ASCO, 4–8 June 2021, Chicago, IL, USA: 4000.

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RATIONALE 302: Study design

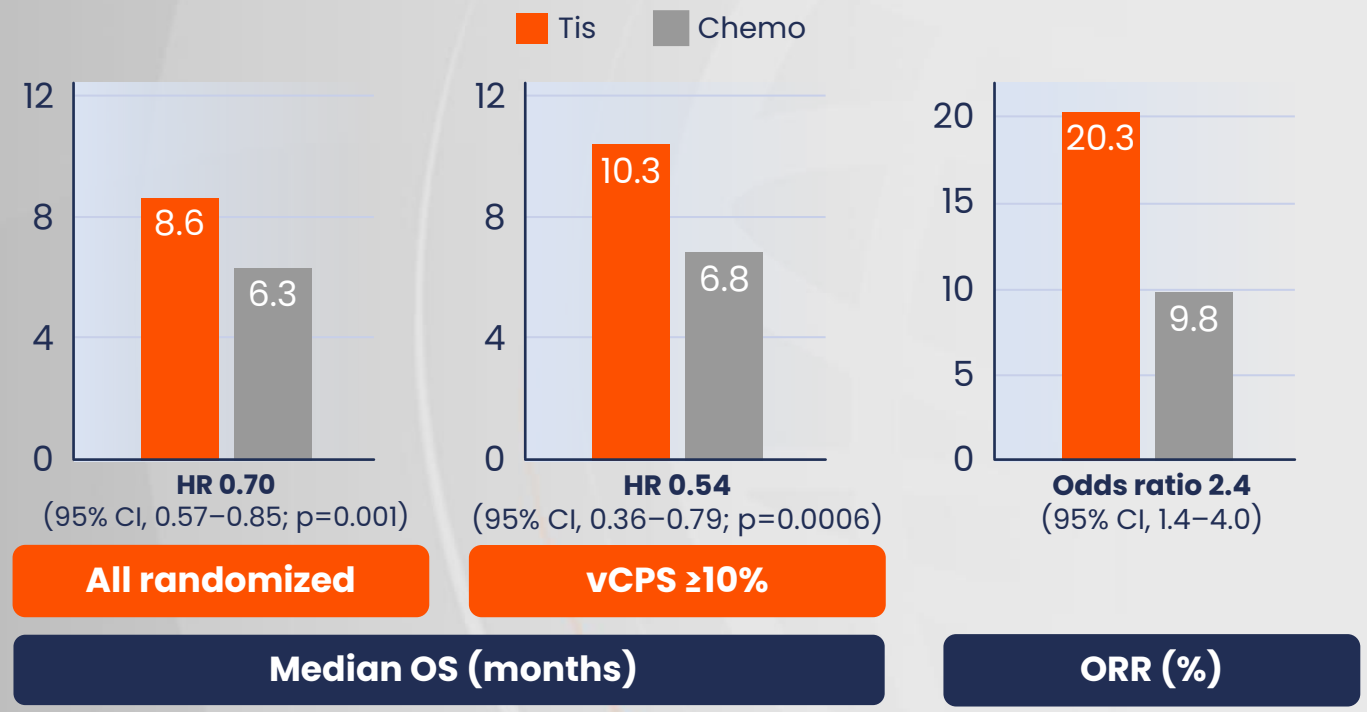
- Advanced or metastatic ESCC
- Progression during or after first-line systemic treatment
- ECOG PS 0 or 1

n=256	n=256
Investigator-chosen chemo	Tislelizumab 200 mg Q3W

Randomized, phase III study of second-line tislelizumab vs chemotherapy in advanced or metastatic ESCC

1. Shen L, et al. *J Clin Oncol.* 2021;39(Suppl. 15):4012; 2. Shen L, et al. Oral presentation at ASCO, 4–8 June 2021, Chicago, IL, USA: 4012.

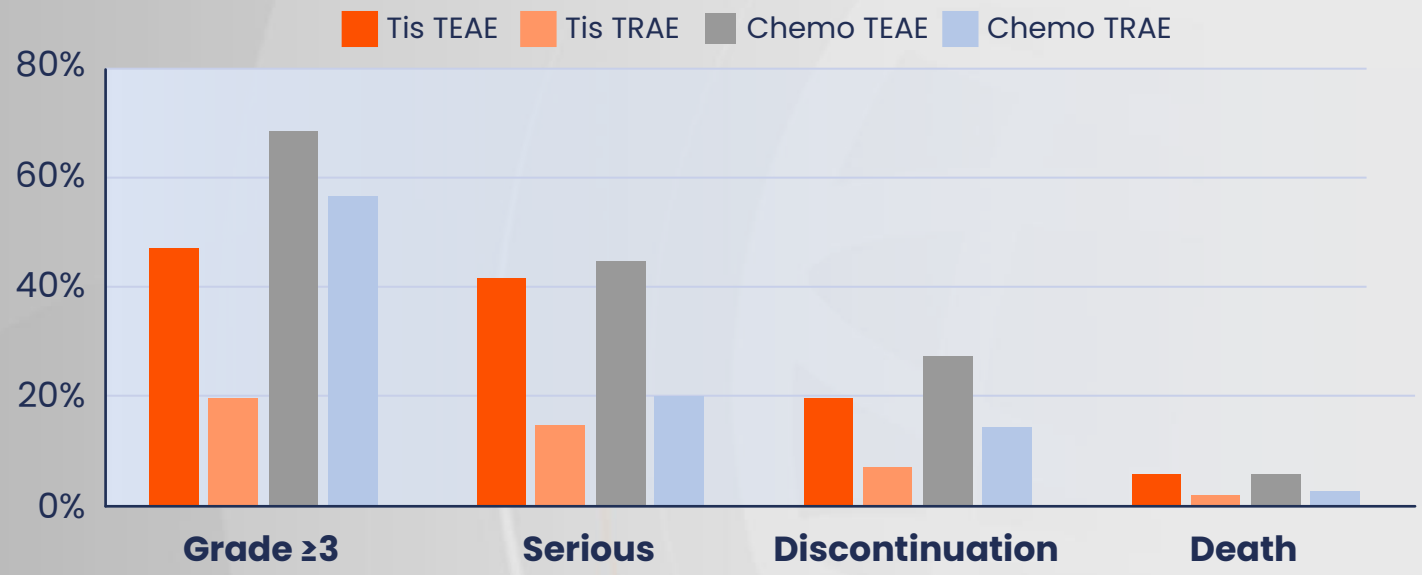
RATIONALE 302: Key endpoints



ORR, overall response rate; vCPS, visually estimated combined positivity score.

1. Shen L, et al. *J Clin Oncol.* 2021;39(Suppl. 15):4012; 2. Shen L, et al. Oral presentation at ASCO, 4–8 June 2021, Chicago, IL, USA: 4012.

RATIONALE 302: Treatment-emergent and -related adverse events



- Superior OS and more durable response with IO than chemotherapy alone
- OS benefit was observed regardless of PD-L1 expression
- No new safety signals

TEAE, treatment-emergent adverse event.

1. Shen L, et al. *J Clin Oncol.* 2021;39(Suppl. 15):4012; 2. Shen L, et al. Oral presentation at ASCO, 4–8 June 2021, Chicago, IL, USA: 4012.

CheckMate 577: Study design

- Stage II/III EC or GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant chemoradiotherapy and surgical resection
- Residual pathologic disease
- ECOG PS 0 or 1

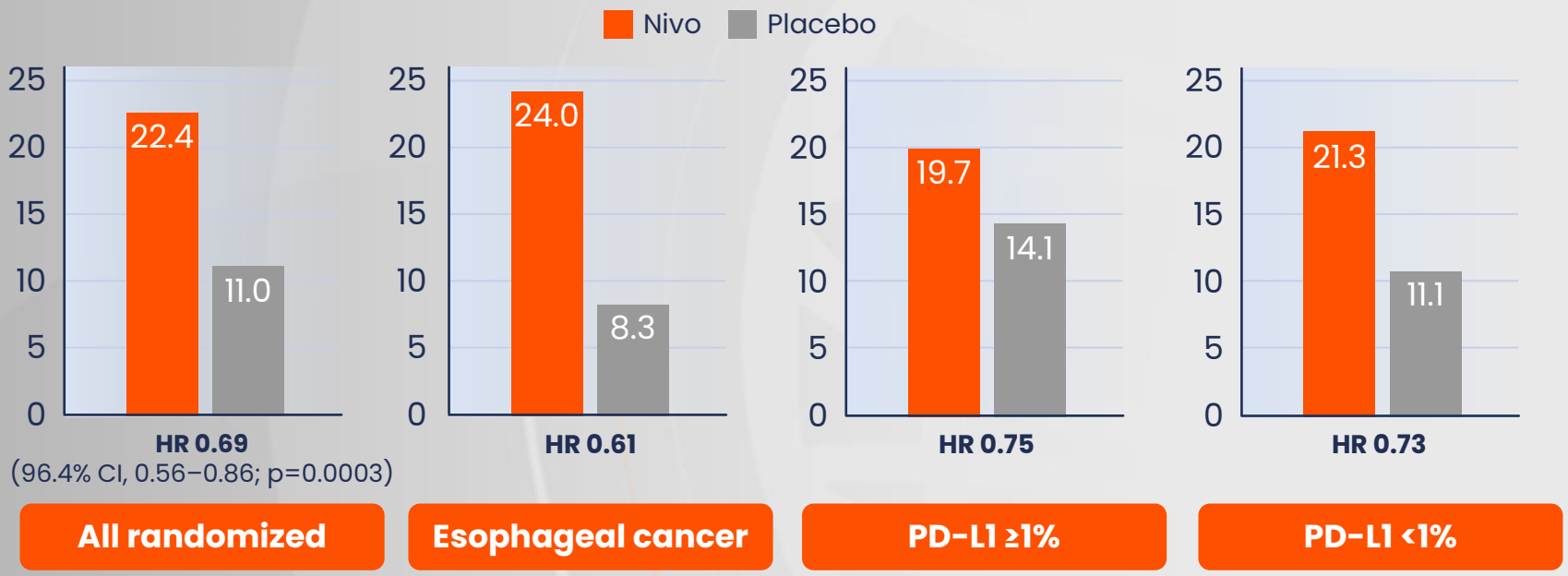
n=262	n=532
Placebo Q2W for 16 weeks then Q4W	Nivolumab 240 mg Q2W for 16 weeks then 480 mg Q4W

Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy

EC, esophageal cancer; GEJC, gastroesophageal junction cancer.

1. Kelly RJ, et al. *J Clin Oncol.* 2021;39(Suppl. 15):4003; 2. Kelly RJ, et al. Oral presentation at ASCO, 4–8 June 2021, Chicago, IL, USA: 4003.

CheckMate 577: Median disease-free survival (months)



1. Kelly RJ, et al. *J Clin Oncol.* 2021;39(Suppl. 15):4003; 2. Kelly RJ, et al. Oral presentation at ASCO, 4–8 June 2021, Chicago, IL, USA: 4003.

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CheckMate 577: Adverse and treatment-related adverse events

- Adjuvant IO was superior to placebo in patients following neoadjuvant chemoradiotherapy
- Acceptable safety profile

AE, adverse event.

1. Kelly RJ, et al. *J Clin Oncol.* 2021;39(Suppl. 15):4003; 2. Kelly RJ, et al. Oral presentation at ASCO, 4–8 June 2021, Chicago, IL, USA: 4003.

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Summary and conclusions

Anti-PD-1 mAb	Outcome vs comparator*	Adjuvant	1L combo with chemo	2L mono
Nivo	Efficacy	☑	☑	
	Safety	☑	☑	
Sint	Efficacy		☑	
	Safety		☑	
Tori	Efficacy		☑	
	Safety		☑	
Cam	Efficacy		☑	
	Safety		☑	
Tis	Efficacy			☑
	Safety			☑

*Comparator arms were placebo, chemo or placebo + chemo.
Combo, combination; mAb, monoclonal antibody; mono, monotherapy.

Emerging data with immunotherapy in esophageal squamous cell carcinoma and potential impact for clinical practice: Insights from ASCO and ESMO GI 2022

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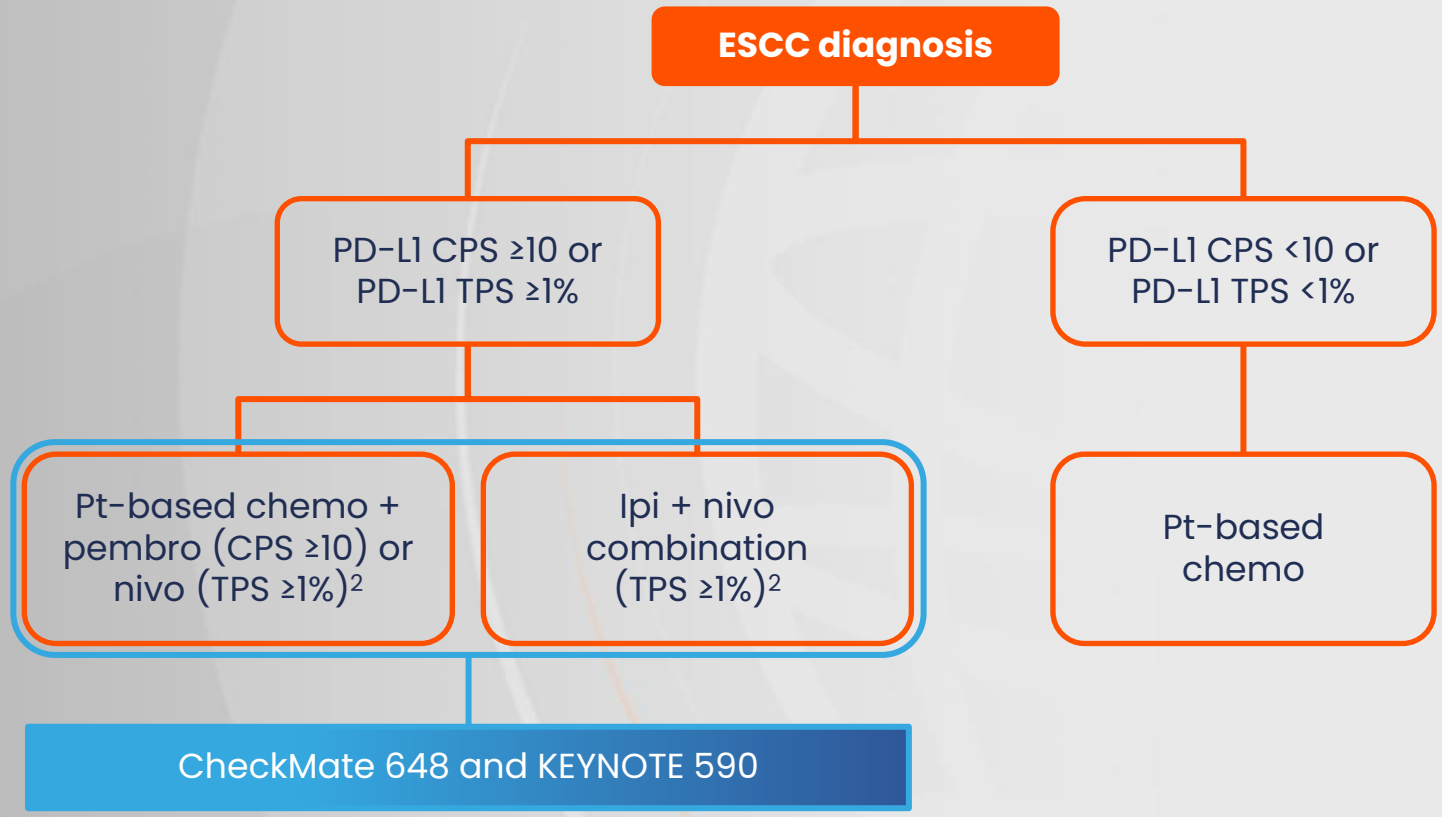
New standards for care with checkpoint inhibitors: First line[1]



Chemo, chemotherapy; CPS, combined positive score; EMA, European Medicines Association; ESCC, esophageal squamous cell carcinoma; ipi, ipilimumab; nivo, nivolumab; PD-L1, programmed death-ligand 1; pembro, pembrolizumab; Pt, platinum; SmPC, summary of product characteristics; TPS, tumour proportion score.

Smyth E. Presented at: ESMO Summit Latin America, Mexico City, 25–27 March 2022; 2. EMA SmPC for pembro and nivo. Available at: www.ema.europa.eu/ (accessed 7 June 2022).

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New standards for care with checkpoint inhibitors: First line

	CheckMate 648[1]		KEYNOTE 590[2]
PD-L1 expression	PD-L1 TPS ≥1%		PD-L1 CPS ≥10
Geography	Global Asia 70%		Global Asia ~50%
Treatment arm(s)	Nivo	Nivo + ipi	Pembro
Chemo arm(s)	Cisplatin + FP	None	Cisplatin + FP
Tumour type	ESCC		Adenocarcinoma 27% ESCC 73%
Primary endpoints	OS + PFS		OS + PFS

Chemo, chemotherapy; CPS, combined positive score; ESCC, esophageal squamous cell carcinoma; FP, fluoropyrimidine; ipi, ipilimumab; nivo, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1; pembro, pembrolizumab; PFS, progression-free survival; TPS, tumour proportion score.

1. Doki Y, et al. *N Engl J Med*. 2022;386:449-62; 2. Sun J-M, et al. *Lancet*. 2021;398:759–71.

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CheckMate 648 expanded analysis: Study design

Extended analysis included exploratory endpoints

- OS by baseline PD-L1 and PD-L1 CPS status
- PFS2*
- DOR
- Safety (onset and resolution of TRAEs with potential immunologic aetiology)

n=321	n=325	n=324
Nivo 240 mg Q2W + chemo Q4W	Nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W	Chemo Q4W

Nivo + ipi or nivo + chemo vs chemo as first-line treatment for advanced ESCC

*PFS2 is defined as the time from randomization to objective tumour progression on next-line treatment or death from any cause.
Chemo, chemotherapy; CPS, combined positive score; DOR, duration of response; ESCC, esophageal squamous cell carcinoma; ipi, ipilimumab; nivo, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q2/4/6W, once every 2/4/6 weeks.
Chau I, et al. *J Clin Oncol.* 2022;40(Suppl. 16):4035.

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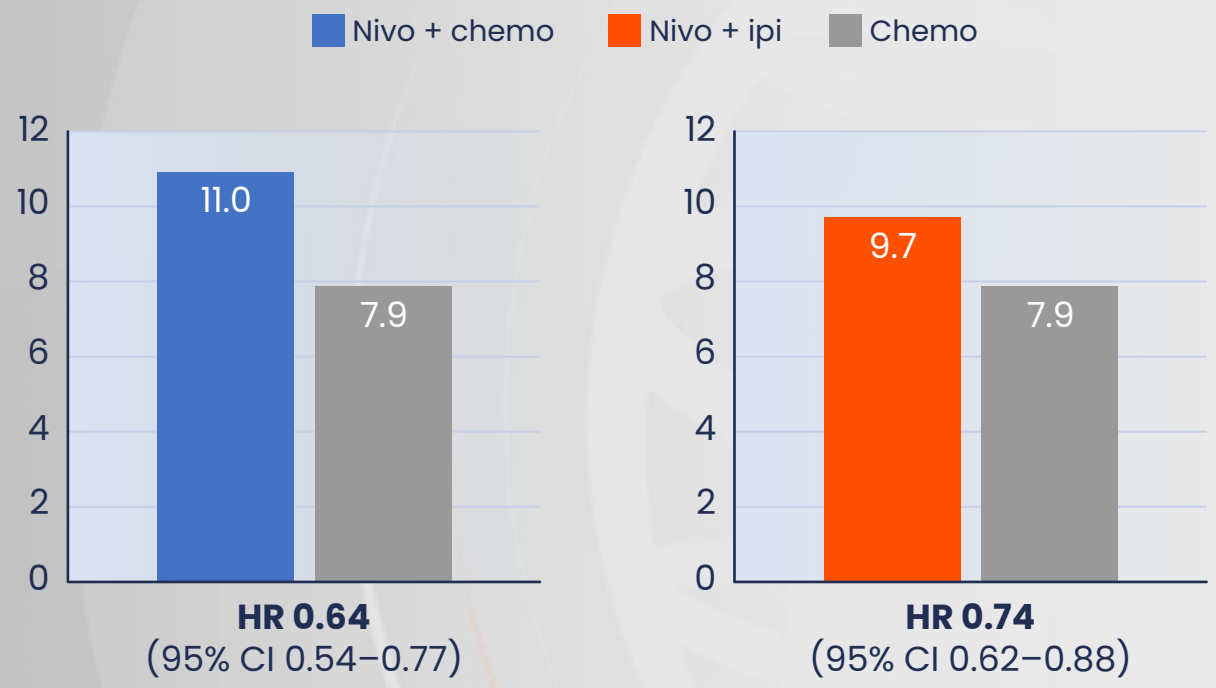
CheckMate 648: Median PFS2* (months)[1]



Favourable PFS2 observed with both nivo + chemo and nivo + ipi vs chemotherapy

*PFS2 is defined as the time from randomization to objective tumour progression on next-line treatment or death from any cause.
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; ipi, ipilimumab; nivo, nivolumab; PFS, progression-free survival.
1. Chau I, et al. *J Clin Oncol.* 2022;40(Suppl. 16):4035.

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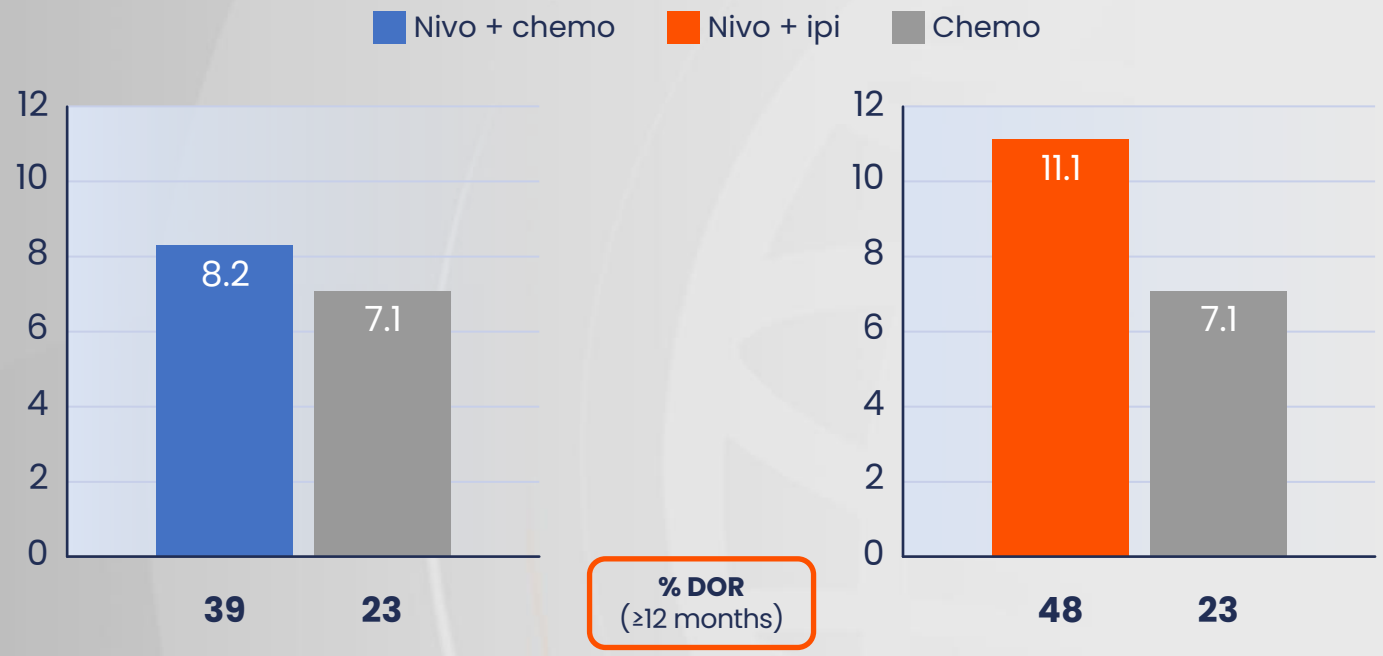
CheckMate 648: Median duration of response (months)



A larger proportion of responders had prolonged DOR (≥12 months) with nivo + chemo or nivo + ipi vs chemo alone

No new safety signals identified from initial analysis

TRAEs with potential immunologic aetiology resolved in most patients with appropriate management

Chemo, chemotherapy; DOR, duration of response; ipi, ipilimumab; nivo, nivolumab; TRAE, treatment-related adverse event.
Chau I, et al. *J Clin Oncol.* 2022;40(Suppl. 16):4035.

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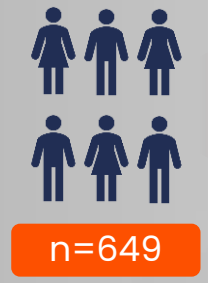
RATIONALE 306: Study design[1,2]



n=649

- Stage IV unresectable ESCC at first diagnosis, or locally advanced recurrent or metastatic ESCC
- 6-month treatment-free interval following prior definitive therapy
- No prior systemic treatment for unresectable advanced disease

1:1

n=326

Tis 200 mg Q3W + Pt-doublet chemo

Pt-doublet chemo arms comprised CIS-Pt or OX-Pt plus:

A 5-FU **B** CAP **C** PAC

n=323

PBO + Pt-doublet chemo

Tis + chemo vs chemo as first-line treatment for advanced ESCC

5-FU, 5-fluorouracil; CAP, capecitabine; chemo, chemotherapy; CIS, cisplatin; ESCC, esophageal squamous cell carcinoma; OX, oxaliplatin; PAC, paclitaxel; PBO, placebo; Pt, platinum; Q3W, once every 3 weeks; Tis, tislelizumab.

1. NCT03783442. Available at: https://clinicaltrials.gov/ (accessed 7 July 2022);
2. Yoon H, et al. Presented at: ESMO World Congress on Gastrointestinal Cancer, Barcelona, Spain. 29 June – 2 July 2022. Abstr. LBA1.

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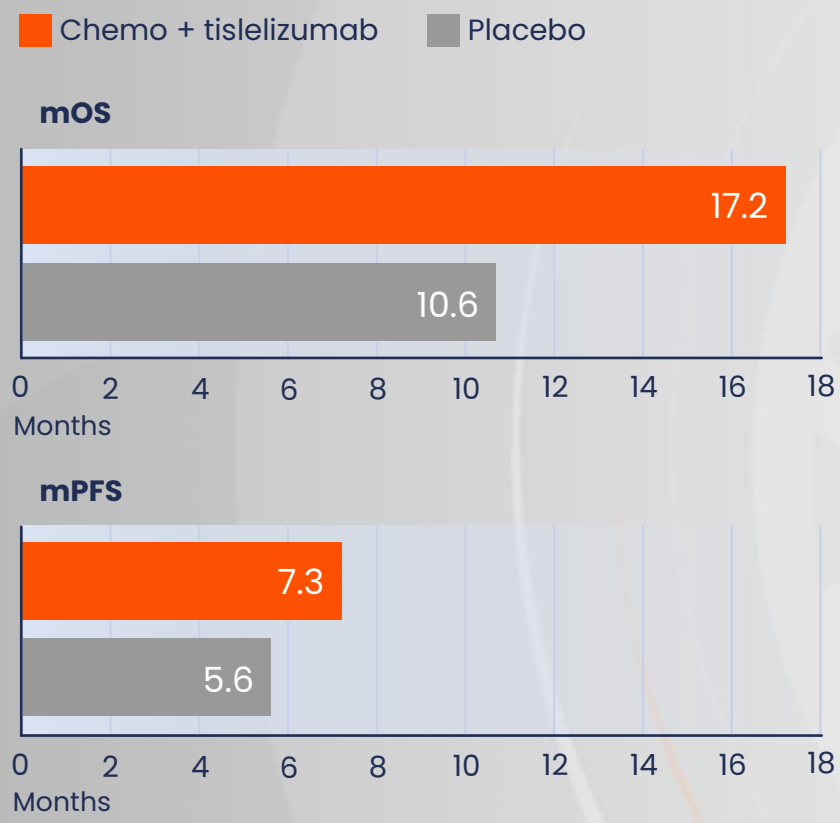
RATIONALE 306: Median survival outcomes (all randomized)



Risk of death: HR 0.66
(95% CI 0.54–0.80; p<0.0001)

34% reduced risk of death

Risk of progression: HR 0.62
(95% CI 0.52–0.75; p<0.0001)

38% reduced risk of progression

First-line tislelizumab + chemo achieved a statistically significant mOS benefit compared with placebo + chemo

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival.
Yoon H, et al. Presented at: ESMO World Congress on Gastrointestinal Cancer, Barcelona, Spain. 29 June – 2 July 2022. Abstr. LBA1.

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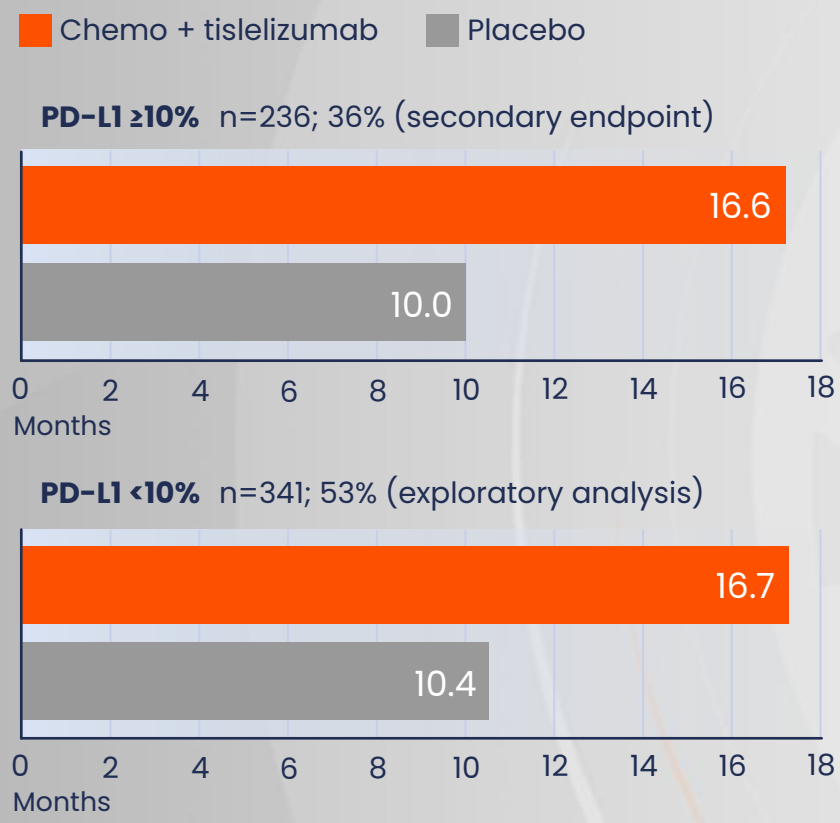
RATIONALE 306: Median overall survival by tumour PD-L1 status



Risk of death: HR 0.62
(95% CI 0.44–0.86; p=0.002)

38% reduced risk of death

Risk of death: HR 0.72
(95% CI 0.55–0.94)

28% reduced risk of progression

Tislelizumab + chemo achieved significant survival benefit regardless of tumour PD-L1 status

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; PD-L1, programmed death-ligand 1.
Yoon H, et al. Presented at: ESMO World Congress on Gastrointestinal Cancer, Barcelona, Spain. 29 June – 2 July 2022. Abstr. LBA1.

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RATIONALE 306: Safety outcomes

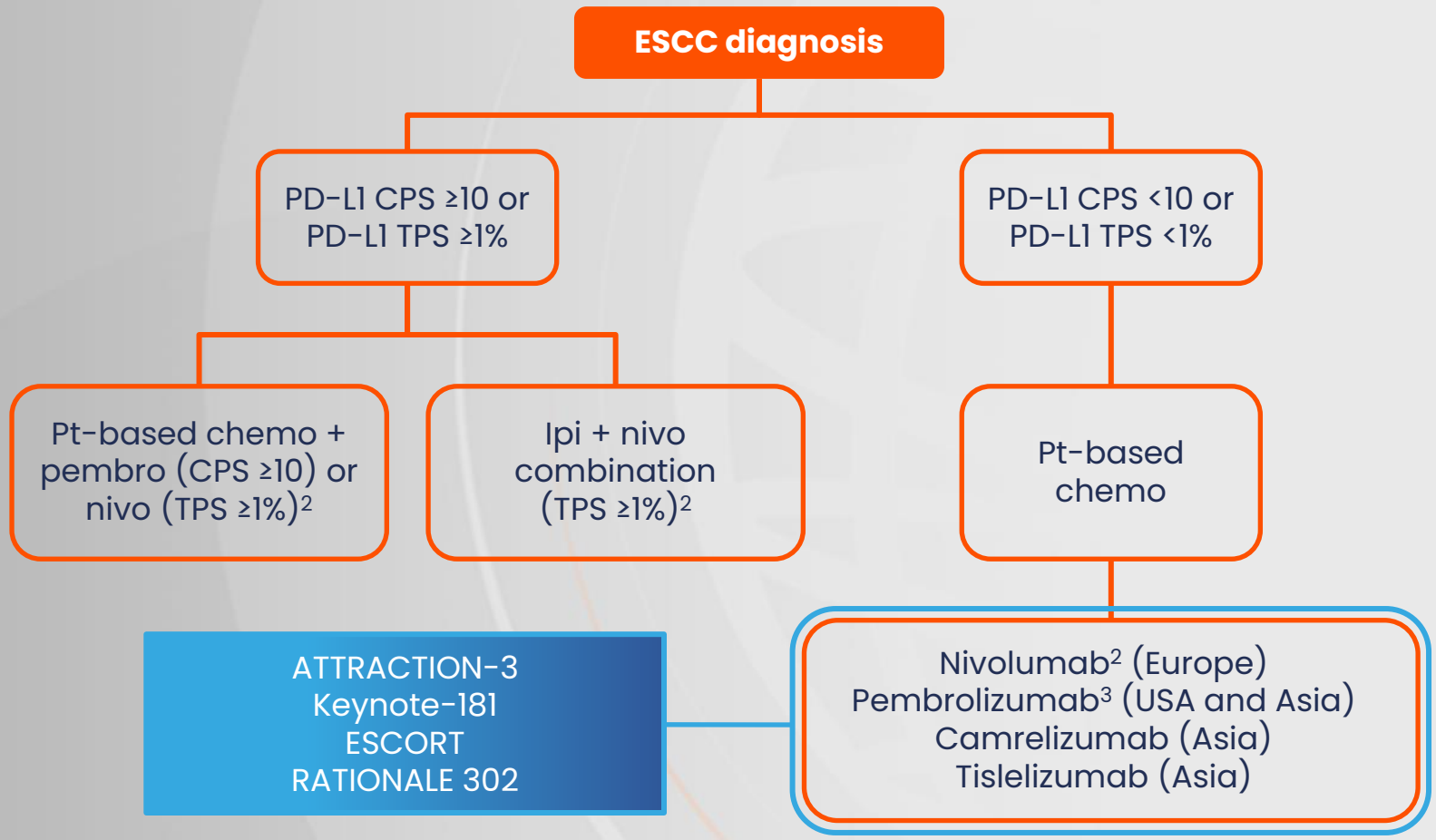
Most common TRAEs, %
(incidence ≥20%)

	Tislelizumab + chemo	Placebo + chemo
Anaemia	68	61
Neutropenia	78	80
Lymphopenia	55	65
Decreased appetite	39	38
Nausea	37	42
PNS	26	21
% Patients with ≥1 immune-mediated AE	22	6

Frequency of common TRAEs reported with tislelizumab + chemo were comparable with placebo + chemo

AE, adverse event; chemo, chemotherapy; PNS, peripheral sensory neuropathy; TRAE, treatment-related adverse event.
Yoon H, et al. Presented at: ESMO World Congress on Gastrointestinal Cancer, Barcelona, Spain. 29 June – 2 July 2022. Abstr. LBA1.

New standards for care with checkpoint inhibitors: Second line[1]



Chemo, chemotherapy; CPS, combined positivity score; ESCC, esophageal squamous cell carcinoma; EMA, European Medicines Association; FDA, Food and Drug Administration; ipi, ipilimumab; nivo, nivolumab; PD-L1, programmed death-ligand 1; pembro, pembrolizumab; PI, prescribing information; Pt, platinum; SmPC, summary of product characteristics; TPS, tumour proportion score.

1. Smyth E. Presented at: ESMO Summit Latin America, Mexico City. 25–27 March 2022; 2. EMA SmPC. Available at: www.ema.europa.eu/; 3. FDA PI. Available at: www.accessdata.fda.gov/scripts/cder/daf/index.cfm (links accessed 7 June 2022).

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Real-world study of anti-PD-1 second-line therapy: Study design

- Advanced or metastatic ESCC
- Initiated an anti-PD-1 second-line therapy between 1 January 2011 and 28 February 2021

N=60

- Patient characteristics
- Descriptive treatment patterns
- Duration of therapy
- Overall survival

Electronic health record-derived database analysis

ESCC, esophageal squamous cell carcinoma; PD-1, programmed death-1.
Ahn D, et al. *J Clin Oncol.* 2022;40(Suppl. 16):e16042.

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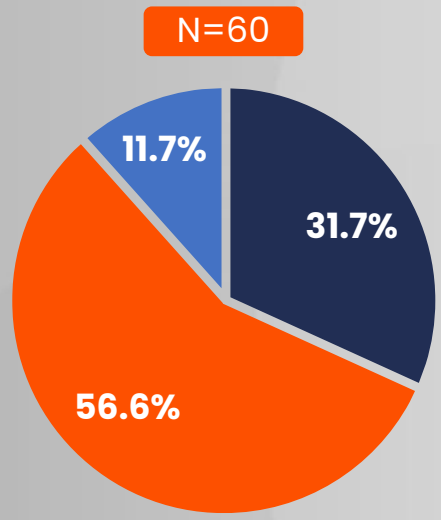
Real-world study of anti-PD-1 second-line therapy: Results



	DoT (days, range)	OS (days, range)
All patients	92 (0–650)	303 (214–450)
Nivolumab	63 (0–287)	310 (214–NR)
Pembrolizumab	92 (0–650)	325 (145–NR)
Pembrolizumab combination	102 (3–172)	259 (149–NR)

Consistent with trial findings, real-world data further validate that anti-PD-1 therapies as second-line treatment may be associated with improved survival in comparison with non-anti-PD-1 therapies

DoT, duration of therapy; OS, overall survival; NR, not reached; PD-1, programmed death-1.
Ahn D, et al. *J Clin Oncol.* 2022;40(Suppl. 16):e16042.

RATIONALE 302 health-related quality of life: Study design[1,2]

- Advanced or metastatic ESCC
- Progression during or after first-line systemic treatment
- ECOG PS 0 or 1

n=256

Tislelizumab 200 mg Q3W

n=256

Investigator-chosen chemo

Randomized, phase III study of second-line tislelizumab vs chemo in advanced or metastatic ESCC

Chemo, chemotherapy; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; PS, performance status; Q3W, every 3 weeks.

1. NCT03430843. Available at: https://clinicaltrials.gov/ (accessed 8 July 2022); 2. Van Cutsem E, et al. *J Clin Oncol.* 2022;40(Suppl. 4):268.

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RATIONALE 302: health-related quality of life endpoints

		Tislelizumab (N=256)		ICC (N=256)	
		Cycle 4	Cycle 6	Cycle 4	Cycle 6
QLQ–C30	GHS/QoL	0.0 (-2.5, 2.4)	-0.8 (-3.5, 2.0)	-5.8 (-8.8, -2.8)	-8.9 (-12.8, -4.9)
	Physical functioning	-4.0 (-6.3, -1.8)	-4.6 (-7.1, -2.1)	-6.6 (-9.3, -4.0)	-8.9 (-12.1, -5.6)
	Fatigue	3.5 (0.4, 6.6)	1.0 (-2.1, 4.2)	11.3 (7.5, 15.1)	6.4 (2.0, 10.9)
QLQ–OES18	Dysphagia	2.7 (-1.7, 7.1)	1.6 (-3.5, 6.6)	7.7 (2.2, 13.2)	1.9 (-5.5, 9.2)
	Reflux	-2.3 (-4.6, -0.1)	-1.8 (-4.7, 1.2)	1.8 (-1.1, 4.7)	-1.1 (-5.4, 3.2)
	Eating	0.0 (-2.8, 2.8)	-0.5 (-3.6, 2.6)	2.7 (-0.8, 6.2)	4.7 (0.3, 9.1)
	Pain	-1.6 (-3.4, 0.2)	-1.4 (-3.9, 1.0)	-1.1 (-3.6, 1.3)	0.2 (-3.6, 4.1)

EORTC, European Organisation For Research And Treatment Of Cancer; GHS/QoL, global health score/quality of life; ICC, investigator-chosen chemotherapy; QLQ-C30, EORTC Quality of Life Questionnaire-Core 30; QLQ-OES18, EORTC Quality of Life Questionnaire-Oesophageal Cancer Module.

Van Cutsem E, et al. *J Clin Oncol.* 2022;40(Suppl. 4):268.

Summary and conclusions

First-line treatment of ESCC
Tislelizumab has demonstrated potential to join nivolumab and pembrolizumab (in combination with chemotherapy) as a new standard of care

Second-line treatment of ESCC
Real-world and health-related QoL findings support anti-PD-1 use

ESCC, esophageal squamous cell carcinoma; QoL, quality of life; PD-1, programmed death-1.

Updated ESMO Clinical Practice Guideline for esophageal squamous cell carcinoma and insights from 2022 on potential future treatment options

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Clinical Consultant
Gastrointestinal Oncology
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Cambridge, UK

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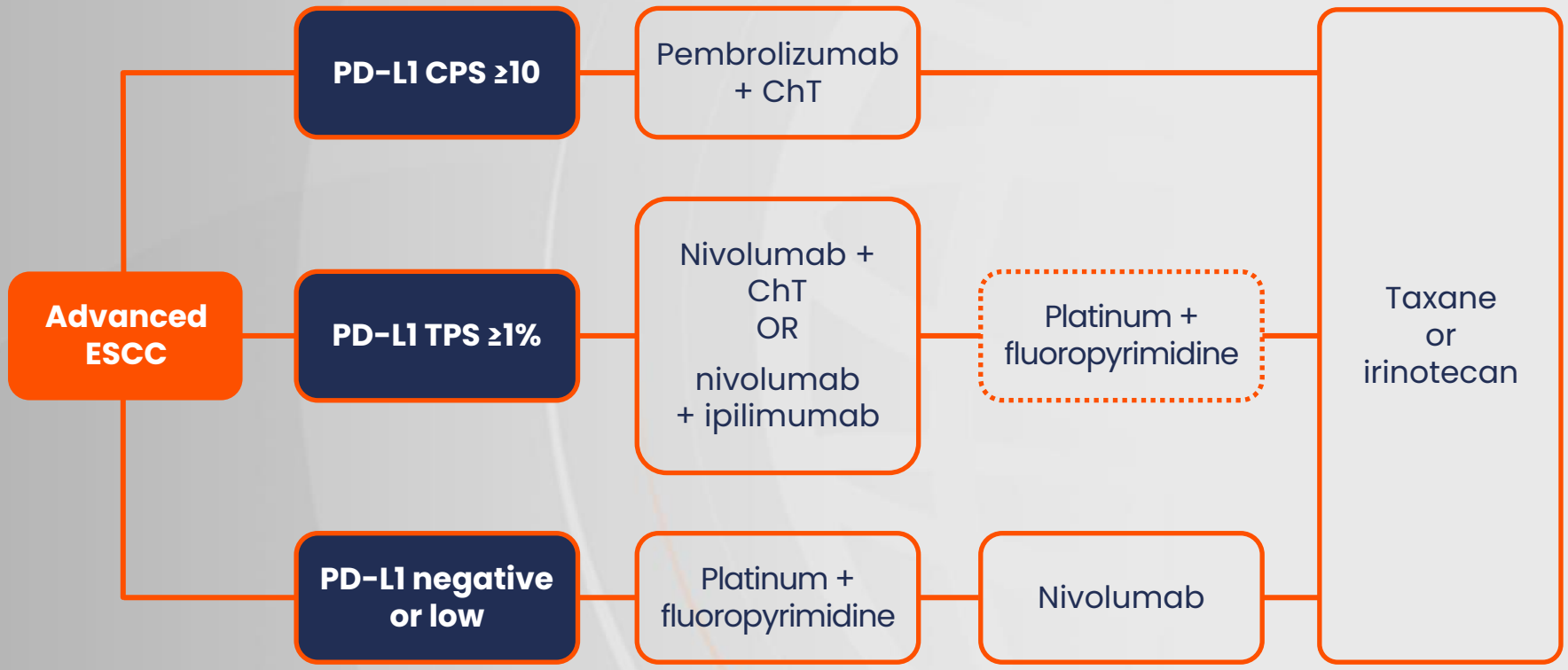
Treatment algorithm for advanced ESCC



CPS, combined positive score; ChT, chemotherapy; ESCC, esophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1; TPS, tumour proportion score.

Obermannová R, et al. *Ann Oncol*. 2022;33:992-1004.

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First-line chemotherapy for ESCC

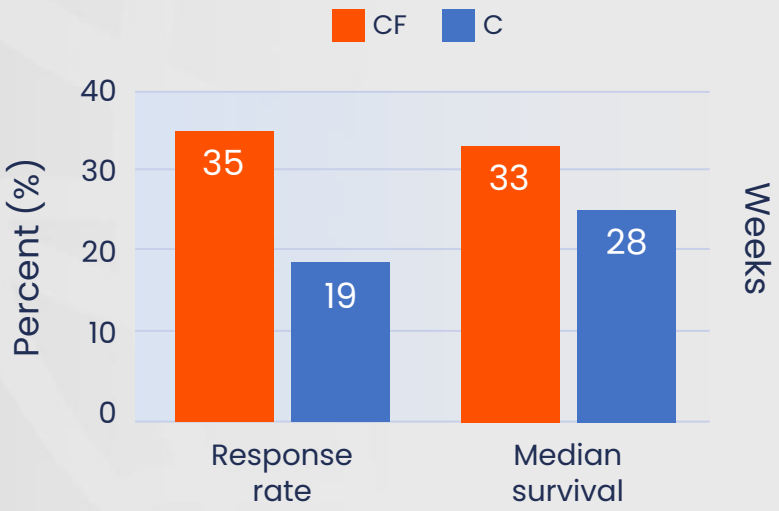
Advanced ESCC[1] → **PD-L1 negative or low** → Platinum + fluoropyrimidine

JCOG9407: Phase II study of cisplatin + 5-FU[2]

Overall response rate
33.3%
(95% CI 18.6–54.6)

1-year survival rate
33.3%
(95% CI 19.1–47.6)

Phase II study of cisplatin + 5-FU vs cisplatin alone[3]



5-FU, 5-fluorouracil; C, cisplatin; CET, cetuximab; CF, C + 5-FU; CI, confidence interval; ESCC, esophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1.

1. Obermannová R, et al. *Ann Oncol*. 2022;33:992–1004; 2. Hayashi K, et al. *Jpn J Clin Oncol*. 2001;31:419–23; 3. Bleiberg H, et al. *Eur J Cancer*. 1997;33:1216–20.

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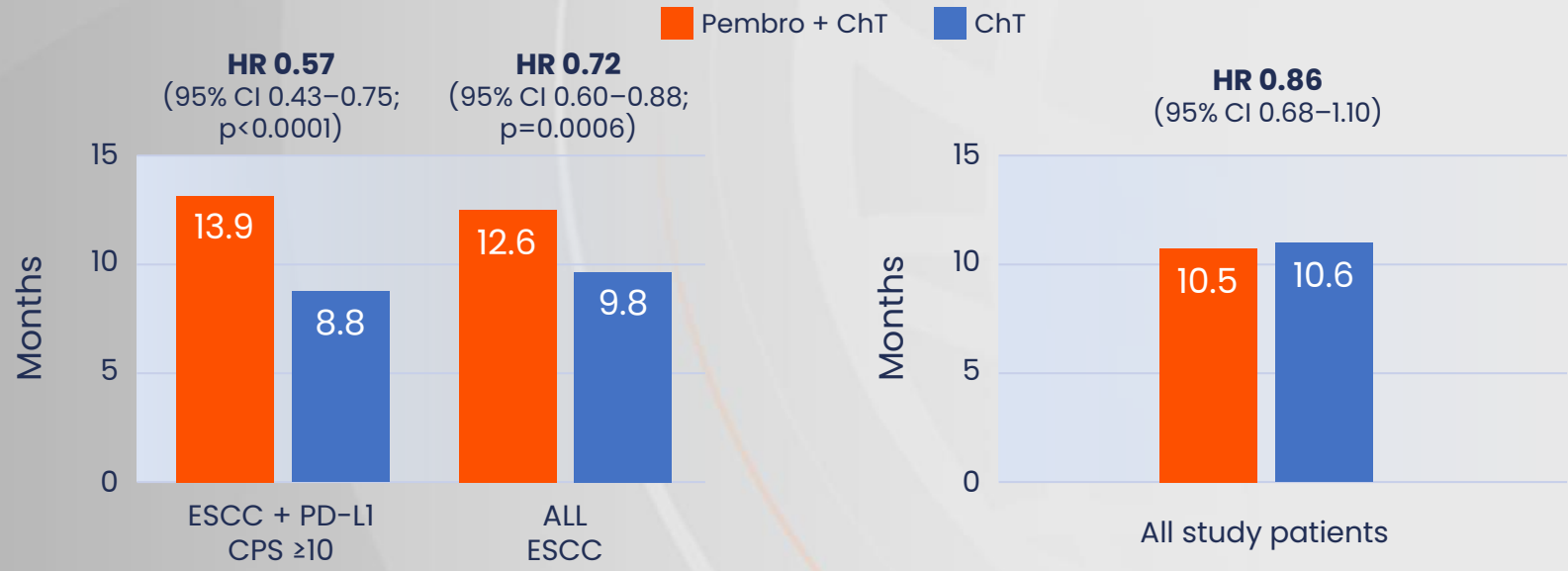
First-line immune checkpoint inhibitors ± chemotherapy for ESCC

Advanced ESCC[1] → **PD-L1 CPS ≥10** → Pembrolizumab + ChT

KEYNOTE-590: Phase III trial of pembrolizumab + chemotherapy vs placebo + chemotherapy[2]*

KEYNOTE-590: Post hoc analysis in patients with PD-L1 CPS <10[2†]



Median overall survival

*73% of study patients with ESCC; ~50% Asian. †32–34% of study patients with ESCC.
CI, confidence interval; CPS, combined positive score; ChT, chemotherapy; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab.

1. Obermannová R, et al. *Ann Oncol*. 2022;33:992-1004; 2. Sun J-M, et al. *Lancet*. 2021;398:759–71.

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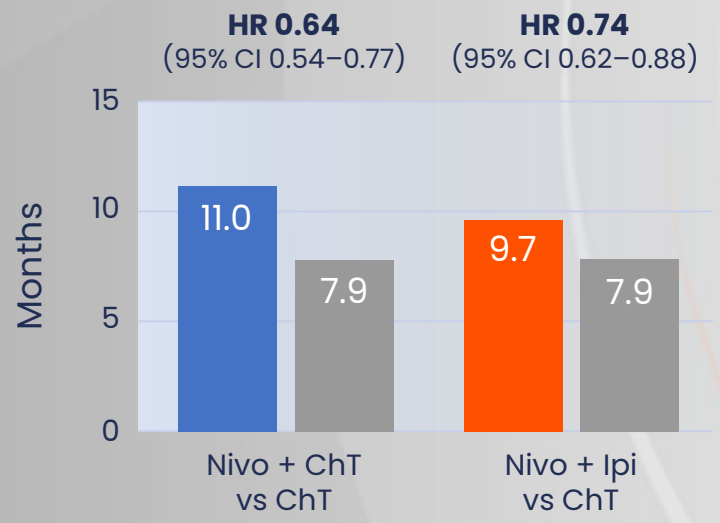
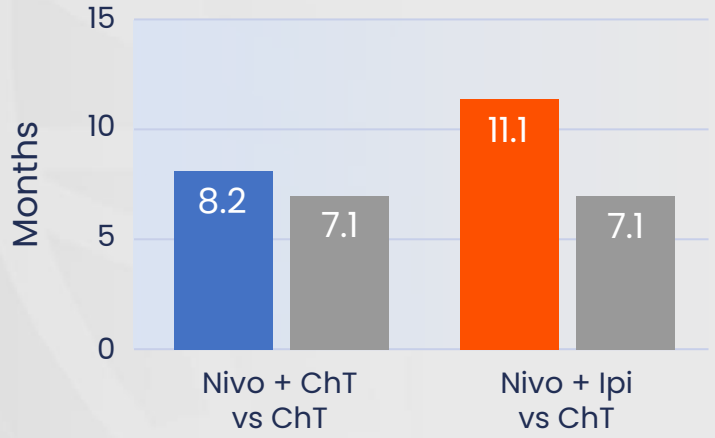
First-line immune checkpoint inhibitors ± chemotherapy for ESCC

Advanced ESCC[1] → **PD-L1 TPS ≥1%** → Nivolumab + ChT OR Nivolumab + ipilimumab

CheckMate 648: Phase III study of nivolumab + ipilimumab or nivolumab + chemotherapy vs chemotherapy[2,3]



Median progression-free survival 2*



Median duration of response

*PFS2 is defined as the time from randomization to objective tumour progression on next-line treatment or death from any cause.
CI, confidence interval; ChT, chemotherapy; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; Ipi, ipilimumab; Nivo, nivolumab; PD-L1, programmed death-ligand 1; TPS, tumour positivity score.
1. Obermannová R, et al. *Ann Oncol*. 2022;33:992-1004; 2. Chau I, et al. *J Clin Oncol*. 2022;40(Suppl. 16):4035; 3. Chau I, et al. Presented at ASCO, Chicago, IL, USA. 3–7 June 2022: #4035.

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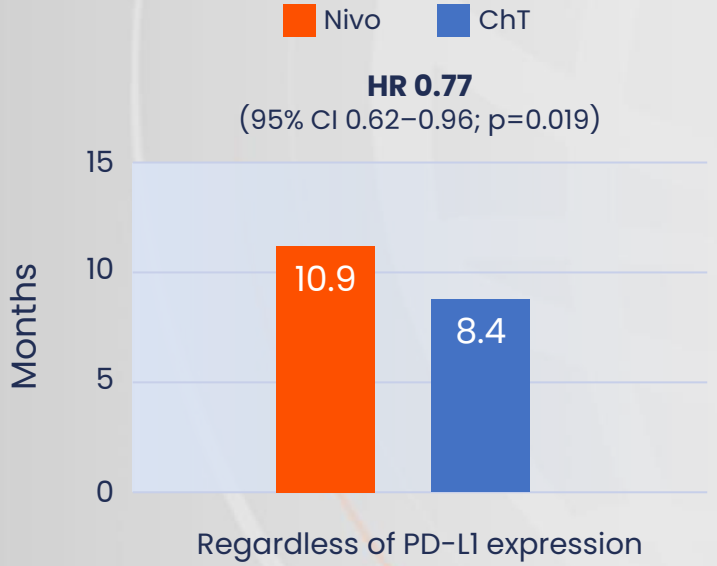
Second and subsequent lines of treatment for ESCC[1]

Advanced ESCC → **PD-L1 negative or low** → Platinum–fluoropyrimidine → Nivolumab

ATTRACTION-3: Phase III study of nivolumab vs chemotherapy following refractory disease or intolerance to previous chemotherapy[2]



Median overall survival

CI, confidence interval; CPS, combined positive score; ChT, chemotherapy; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; PD-L1, programmed death-ligand 1; Nivo, nivolumab.

1. Obermannová R, et al. *Ann Oncol*. 2022;33:992-1004; 2. Kato K, et al. *Lancet Oncol*. 2019;20:1506–17.

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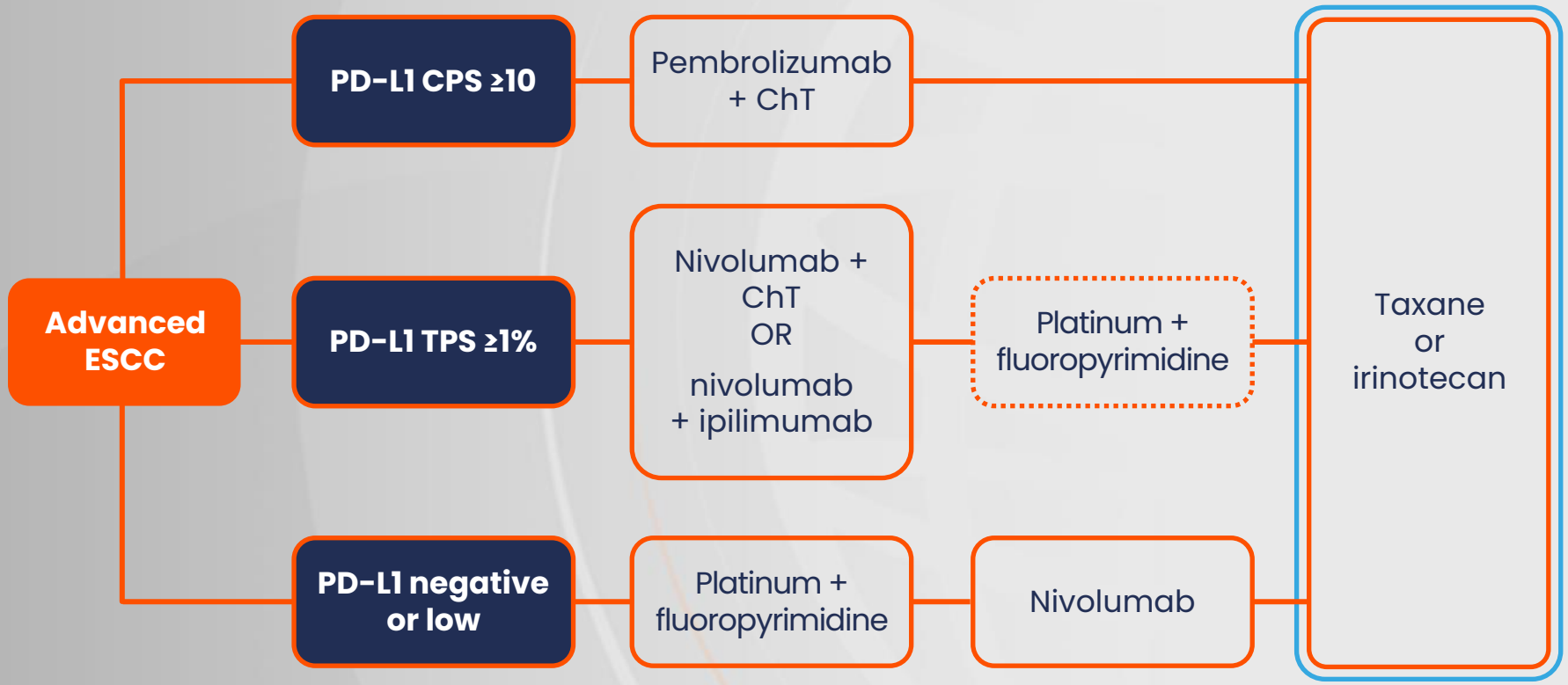
Second and subsequent lines of treatment for ESCC



CPS, combined positive score; ChT, chemotherapy; ESCC, esophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1; TPS, tumour proportion score.

Obermannová R, et al. *Ann Oncol*. 2022;33:992-1004.

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Second and subsequent lines of treatment for ESCC

Advanced ESCC[1] — Taxane or irinotecan

Phase II study of paclitaxel in patients who had previously received platinum-based chemotherapy[2]	Phase II study of single-agent docetaxel in patients with metastatic esophageal cancer*[3]	Phase II trial of irinotecan in cisplatin-refractory esophageal cancer‡[4]
ORR 44.2% (95% CI 30.5–58.7)	Partial response† 20% (95% CI 10–34)	Partial response† 15% (2 of 13 evaluable patients)
mOS 10.4 mo (95% CI 7.8–14.2)	mOS 8.1 mo (95% CI 6.6–11.3)	mOS 5 mo (95% CI 1.5–8.5)

*94% of patients with ESCC; †Response Evaluation Criteria in Solid Tumors criteria.; ‡50% of patients with ESCC.
CI, confidence interval; ESCC, esophageal squamous cell carcinoma;. mo, months; mOS, median overall survival; ORR, overall response rate.

1. Obermannová R, et al. *Ann Oncol*. 2022;33:992-1004; 2. Kato K, et al. *Cancer Chemother Pharmacol*. 2011;67:1265–72; 3. Muro K, et al. *Ann Oncol*. 2004;15:955-9; 4. Burkart C, et al. *Anticancer Res*. 2007;27:2845–8.

Summary: 2022 ESMO Clinical Practice Guideline

First-line treatment for advanced ESCC

- First-line chemotherapy with a platinum and fluoropyrimidine is recommended as a standard treatment for advanced untreated ESCC
  - Dose-reduced oxaliplatin + capecitabine is an alternative option for patients who are unsuitable for full-dose chemotherapy
- Pembrolizumab + chemotherapy is recommended for advanced, untreated ESCC
  - The greatest benefit is seen in patients with a PD-L1 CPS ≥10
- Nivolumab + chemotherapy is recommended in patients with tumours expressing PD-L1 with a TPS ≥1%

CPS, combined positive score; ESCC, esophageal squamous cell carcinoma; ESMO, European Society of Medical Oncology; PD-L1, programmed death-ligand 1; TPS, tumour proportion score.

Obermannová R, et al. *Ann Oncol*. 2022;33:992-1004.

Summary: 2022 ESMO Clinical Practice Guideline

Second and subsequent lines of treatment for advanced ESCC[1]

- Nivolumab is recommended for ESCC previously treated with platinum + fluoropyrimidine chemotherapy
- Where approved, pembrolizumab may be an option for patients with previously treated ESCC who have not received first-line treatment with immune checkpoint inhibitors and have a PD-L1 CPS ≥10
- Chemotherapy with a taxane or irinotecan can be considered in fit patients who have been previously treated with platinum + fluoropyrimidine and/or nivolumab or pembrolizumab

Chemotherapy plus nivolumab should be the standard of care for most patients[2]

- Chemotherapy may be avoided in selected patients, but careful counselling is needed to elaborate the risk of lower response and early progression[2]

CPS, combined positive score; ESCC, esophageal squamous cell carcinoma; ESMO, European Society of Medical Oncology; PD-L1, programmed death-ligand 1.

1. Obermannová R, et al. *Ann Oncol*. 2022;33:992-1004.; 2. Smyth EC, Lordick F. *Lancet Oncol*. 2022;23:1363-4.

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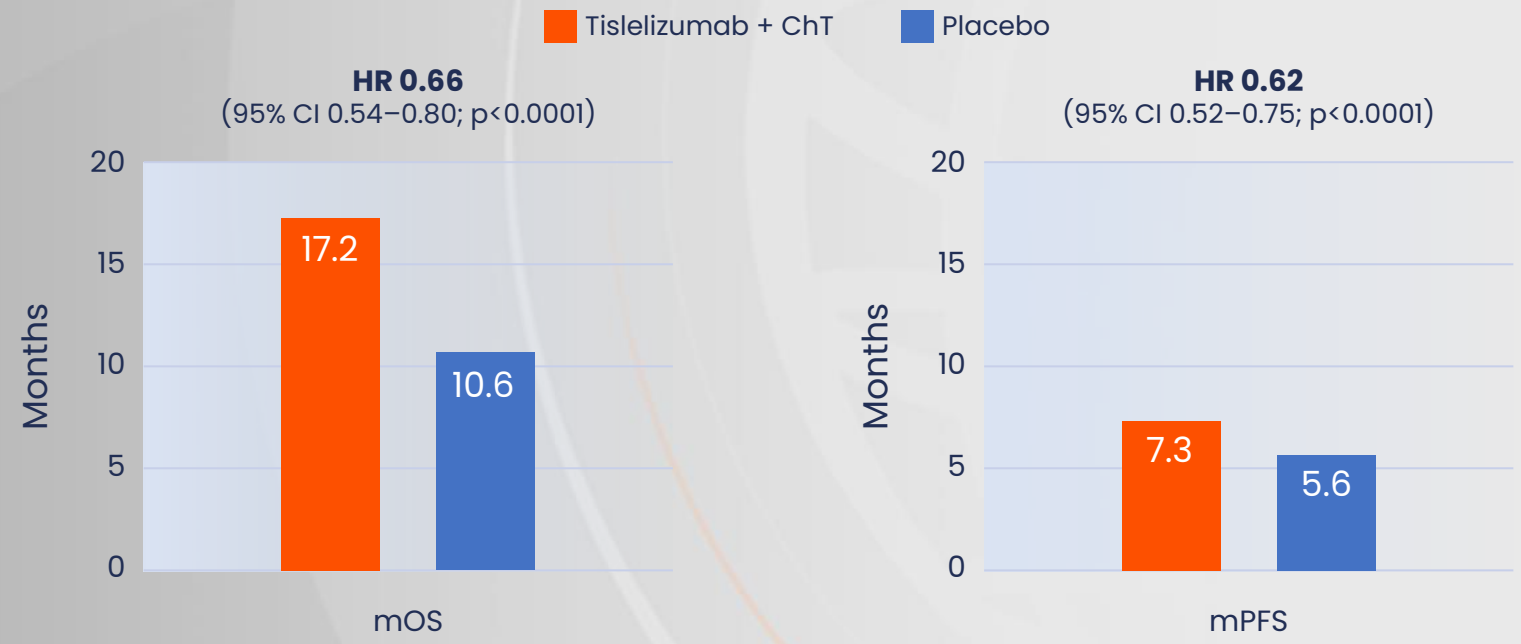
Potential change to standard of care in ESCC: First-line

RATIONALE-306: First-line tislelizumab + chemotherapy achieved a statistically significant OS and PFS benefit compared with placebo + chemotherapy[1]



ChT, chemotherapy; CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival.
1. Yoon H, et al. Presented at: ESMO World Congress on Gastrointestinal Cancer, Barcelona, Spain. 29 June – 2 July 2022. Abstr. LBA1.

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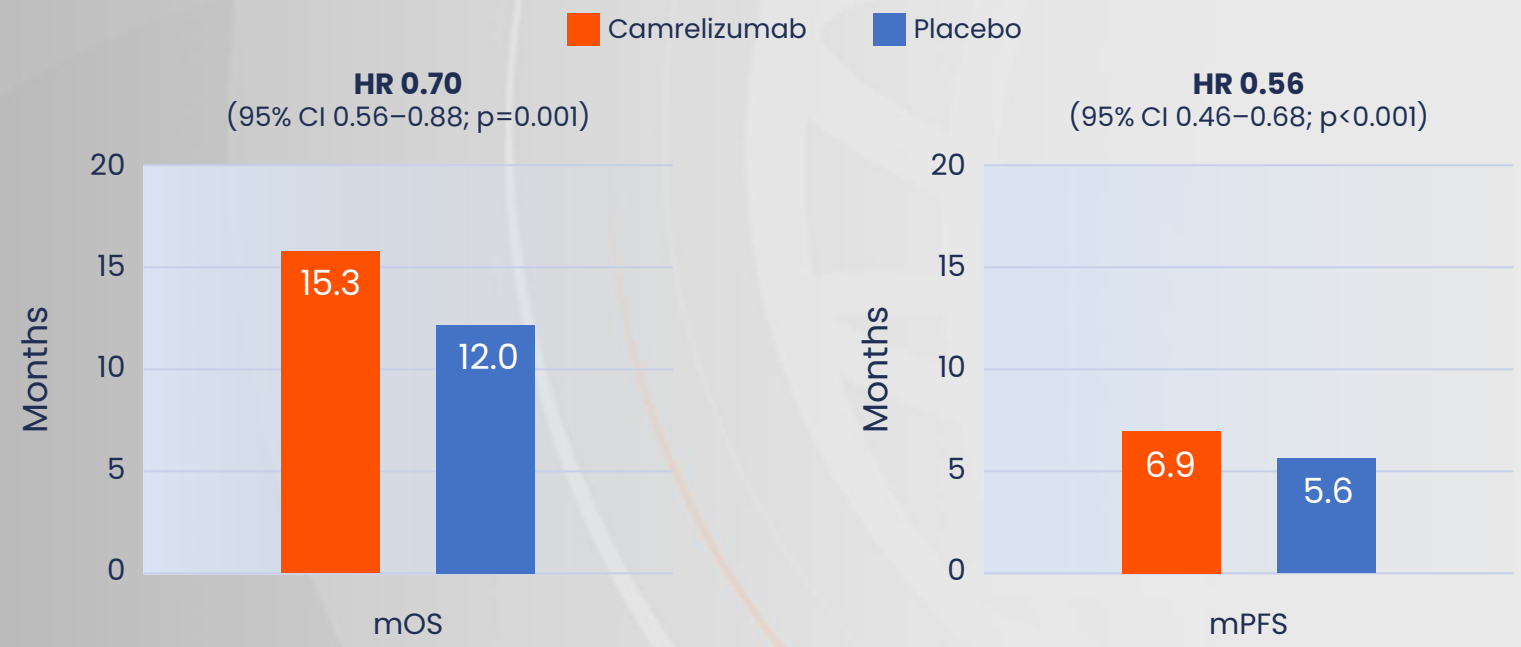
Potential change to standard of care in ESCC: First-line

ESCORT-1st: Camrelizumab + chemotherapy provided superior OS and PFS vs placebo + chemotherapy[1,2]



CI, confidence interval; HR, hazard ratio; m, median; OS, median overall survival; PFS, median progression-free survival.

1. Xu R, et al. *J Clin Oncol*. 2021;39(Suppl. 15):4000; 2. Xu R, et al. Oral presentation at ASCO, 4–8 June 2021, Chicago, IL, USA.

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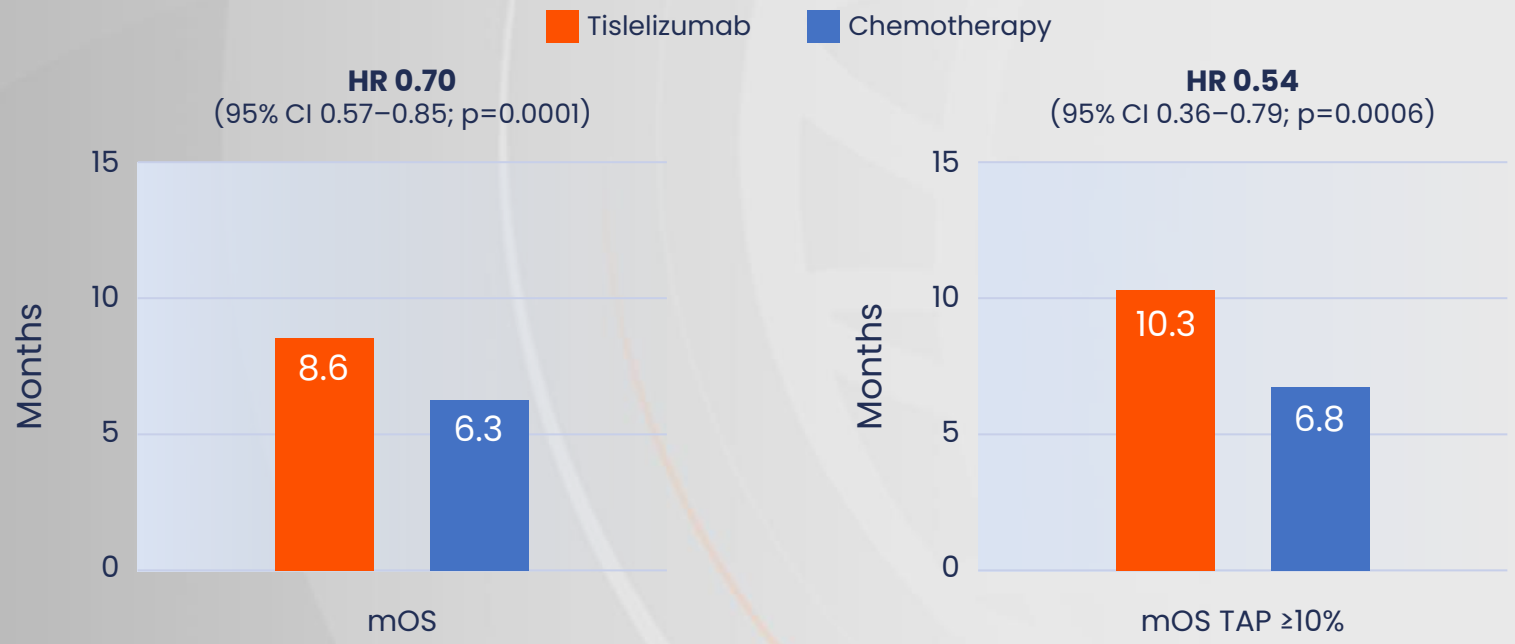
Potential change standard of care in ESCC: Second-line

RATIONALE-302: Tislelizumab significantly improved OS compared with chemotherapy as second-line therapy in patients with advanced or metastatic ESCC



ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; mOS, median overall survival; TAP, tumour area positivity.
Shen L, et al. *J Clin Oncol*. 2022;40:3065-76.

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Summary: New and emerging treatment options

First-line treatment for advanced ESCC

- **RATIONALE-306**: First-line tislelizumab + chemotherapy achieved a statistically significant mOS benefit compared with placebo + chemotherapy[1]
- **ESCORT-1st**: Camrelizumab + chemotherapy provided superior OS and PFS vs placebo + chemotherapy[2]

Second and subsequent lines of treatment for advanced ESCC

- **RATIONALE-302**: Tislelizumab significantly improved OS compared with chemotherapy as second-line therapy in patients with advanced or metastatic ESCC[3]

CPS, combined positive score; ESCC, esophageal squamous cell carcinoma; mOS, median overall survival; mPFS, median progression-free survival; PD-L1, programmed death-ligand 1.

1. Yoon H, et al. Presented at: ESMO World Congress on Gastrointestinal Cancer, Barcelona, Spain. 29 June – 2 July 2022. Abstr. LBA1; 2. Xu R, et al. *J Clin Oncol*. 2021;39(Suppl. 15):4000; 3. Shen L, et al. *J Clin Oncol*. 2022;40:3065-76.

Emerging data with immunotherapy in esophageal squamous cell carcinoma and potential impact for clinical practice: Insights from ESMO Asia 2022 and ASCO GI 2023

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Clinical Consultant
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ASTRUM-007: Study design[1,2]

N=551

- Double-blind phase III study
- Previously untreated, advanced, PD-L1 CPS ≥1 ESCC
- ECOG PS 0 or 1
- Randomization was stratified by PD-L1 expression level
- China-only study

2:1

n=368

Serplulimab 3 mg/kg
+ cisplatin 5-FU

n=183

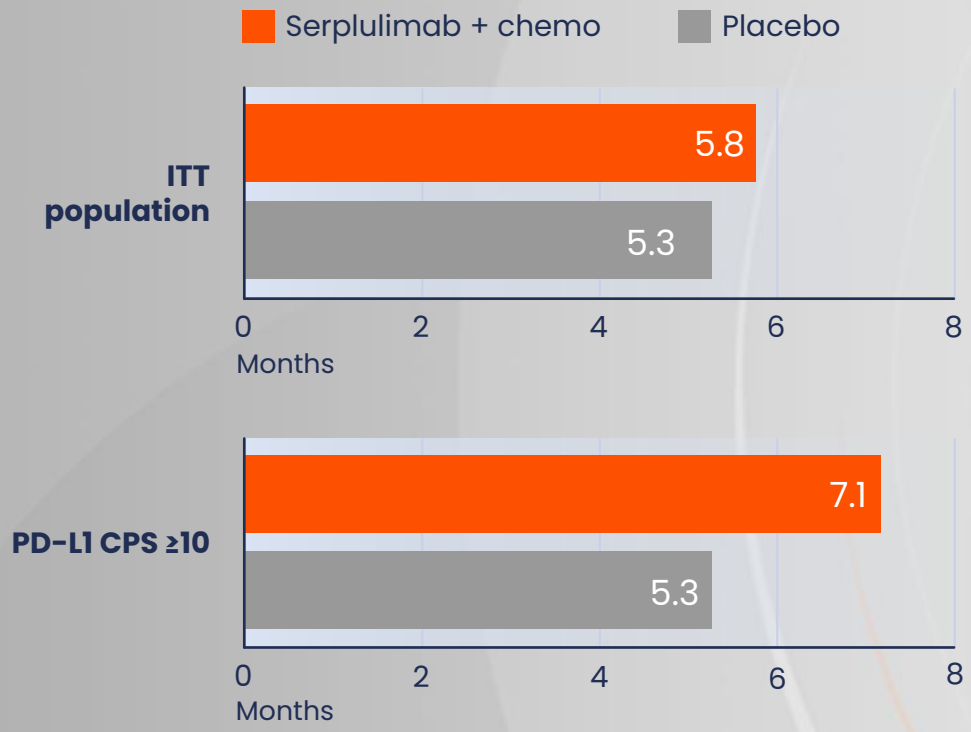
Placebo +
cisplatin 5-FU

Serplulimab + chemotherapy vs chemotherapy
as first-line treatment for advanced ESCC

5-FU, 5-fluorouracil; CPS, combined positivity score; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; PD-L1, programmed death-ligand 1; PS, performance status.

1. Huang J, et al. *Ann Oncol.* 2022;33(Suppl. 9):S1457-8; 2. Huang J, et al. Presented at: ESMO Asia Congress 2022, Singapore. 2–4 December 2022. Abstr. 69O.

ASTRUM-007: Median PFS (final analysis)[1,2]



HR 0.60
(95% CI 0.48–0.75; p<0.0001)

40% reduced risk of progression

HR 0.48
(95% CI 0.34–0.68; p<0.0001)

52% reduced risk of progression

Serplulimab + chemotherapy significantly improved PFS (final) compared with chemotherapy alone

Chemo, chemotherapy; CI, confidence interval; CPS, combined positivity score; HR, hazard ratio; ITT, intention to treat; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

1. Huang J, et al. *Ann Oncol.* 2022;33(Suppl. 9):S1457-8; 2. Huang J, et al. Presented at: ESMO Asia Congress 2022, Singapore. 2–4 December 2022. Abstr. 690.

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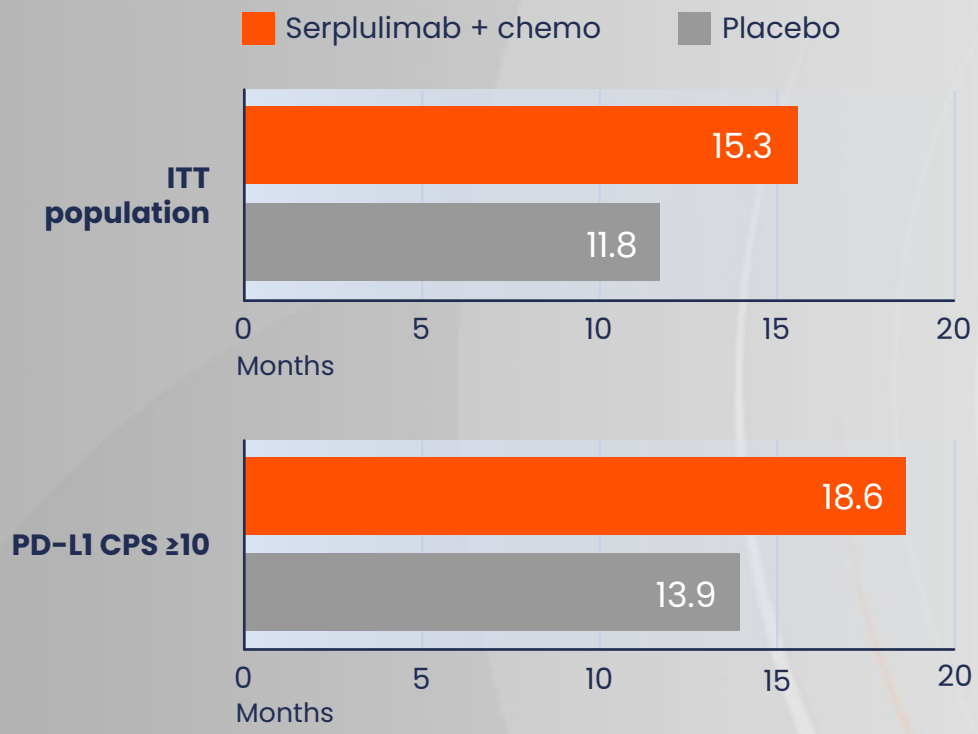
ASTRUM-007: Median OS (interim analysis)[1,2]



HR 0.68
(95% CI 0.53–0.87; p=0.0020)

32% reduced risk of death

HR 0.59
(95% CI 0.40–0.88; p=0.0082)

41% reduced risk of death

Serplulimab + chemotherapy significantly improved OS (interim) compared with chemotherapy alone

Chemo, chemotherapy; CI, confidence interval; CPS, combined positivity score; HR, hazard ratio; ITT, intention to treat; OS, overall survival; PD-L1, programmed death-ligand 1.

1. Huang J, et al. *Ann Oncol.* 2022;33(Suppl. 9):S1457-8; 2. Huang J, et al. Presented at: ESMO Asia Congress 2022, Singapore. 2–4 December 2022. Abstr. 69O.

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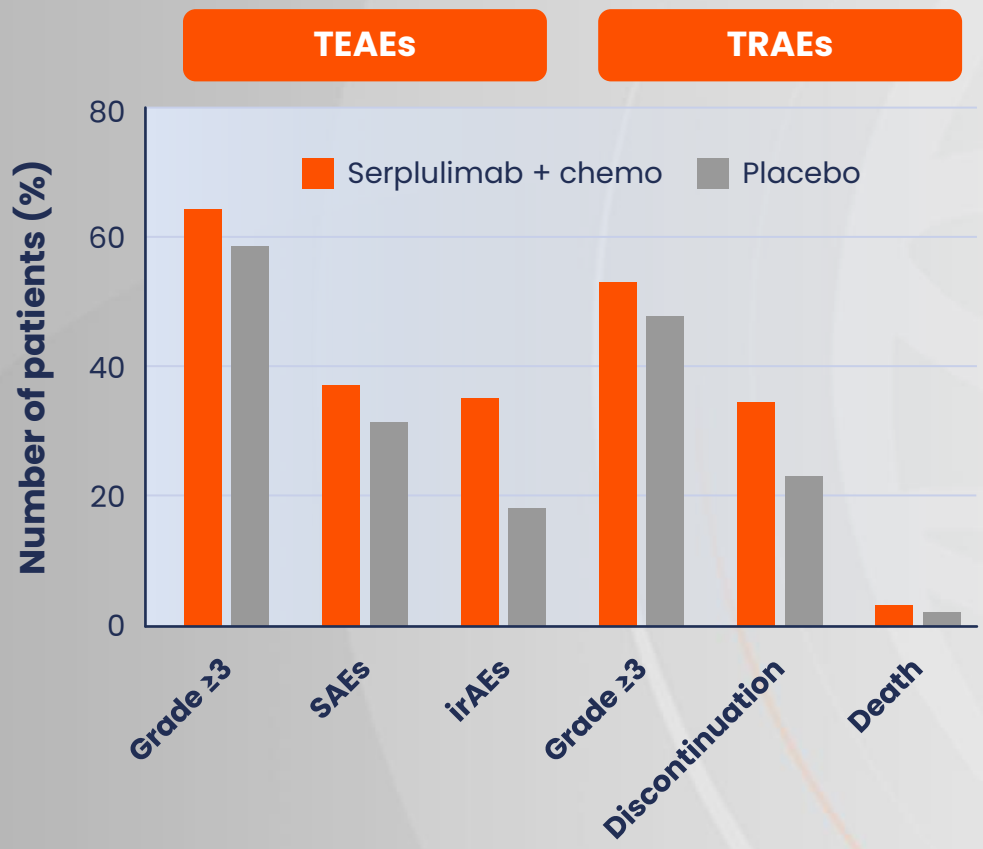
ASTRUM-007: Safety outcomes[1,2]



Most common irAEs
(serplulimab + chemo vs PBO)

• Hypothyroidism	10.7% vs 2.4%
• Dermatitis	6.3% vs 3.0%
• Hyperthyroidism	4.5% vs 2.4%

Interim results from ASTRUM-007 have led to the acceptance by China's National Medical Products Administration of a New Drug Application for serplulimab plus chemotherapy for locally advanced/recurrent or metastatic ESCC[3]

Chemo, chemotherapy; ESCC, esophageal squamous cell carcinoma; irAE, immune-related adverse event; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

1. Huang J, et al. *Ann Oncol.* 2022;33(Suppl. 9):S1457-8; 2. Huang J, et al. Presented at: ESMO Asia Congress 2022, Singapore. 2–4 December 2022. Abstr. 69O; 3. ESMO Daily Reporter. Available at: https://dailyreporter.esmo.org/esmo-asia-congress-2022/esmo-asia-congress-2022/serplulimab-plus-chemotherapy-prolongs-progression-free-survival-in-pd-l1-positive-oesophageal-squamous-cell-carcinoma (accessed February 2023).

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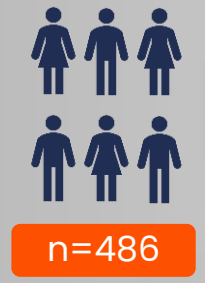
RATIONALE-306: Study design[1,2]



n=486

- Double-blind phase III study
- Unresectable locally advanced or metastatic ESCC
- No prior systemic treatment for advanced disease
- ECOG PS 0 or 1
- Measurable or evaluable disease per RECIST v1.1

1:1

n=243

Tis 200 mg Q3W +
Pt-doublet chemo

Pt-doublet chemo arms
comprised Cis-Pt or Ox-Pt plus
fluoropyrimidine or paclitaxel

n=243

PBO Q3W +
Pt-doublet chemo

Tislelizumab + chemotherapy vs chemotherapy
as first-line treatment for advanced ESCC

Chemo, chemotherapy; Cis, cisplatin; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; Ox, oxaliplatin; PBO, placebo; PS, performance status; Pt, platinum; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; Tis, tislelizumab.

1. Kato K, et al. *Ann Oncol.* 2022;33(Suppl. 9):S1458; 2. Kato K, et al. Presented at: ESMO Asia Congress 2022, Singapore. 2–4 December 2022. Abstr. 70O.

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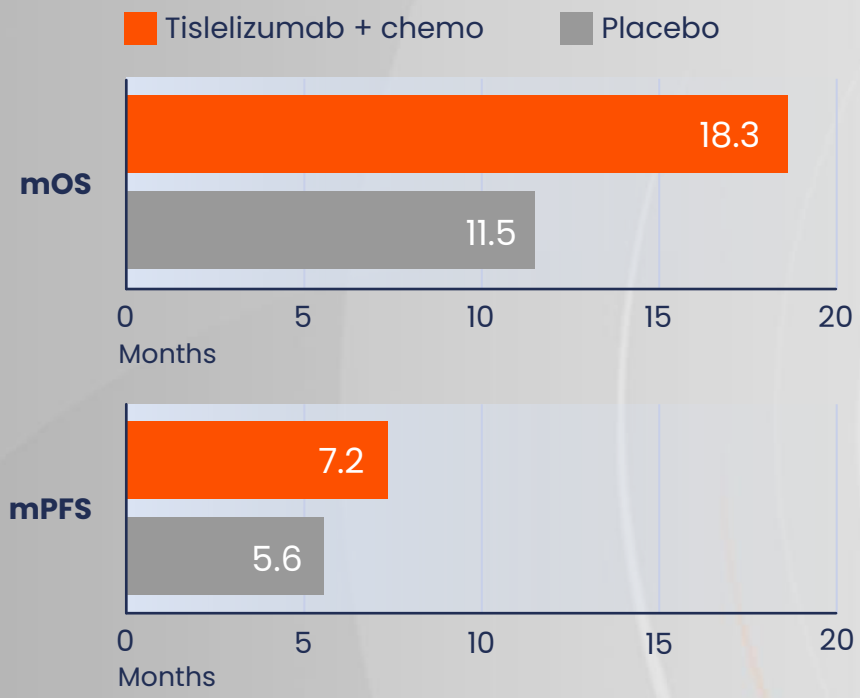
RATIONALE-306 Asia subgroup: Median survival outcomes[1,2]



HR 0.67
(95% CI 0.54–0.84)

33% reduced risk of death

HR 0.62
(95% CI 0.50–0.76)

38% reduced risk of progression

- Overall population: Tislelizumab + chemo vs placebo
  - mOS: 17.2 vs 10.6 months (HR 0.66; 95% CI 0.54–0.80)
  - mPFS: 7.3 vs 5.6 months (HR 0.62; 95% CI 0.52–0.75)
- Consistent with the overall population, there is a clinically meaningful improvement in OS in the Asia subgroup

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; m, median; OS, overall survival; PFS, progression-free survival.

1. Kato K, et al. *Ann Oncol.* 2022;33(Suppl. 9):S1458; 2. Kato K, et al. Presented at: ESMO Asia Congress 2022, Singapore. 2–4 December 2022. Abstr. 70O.

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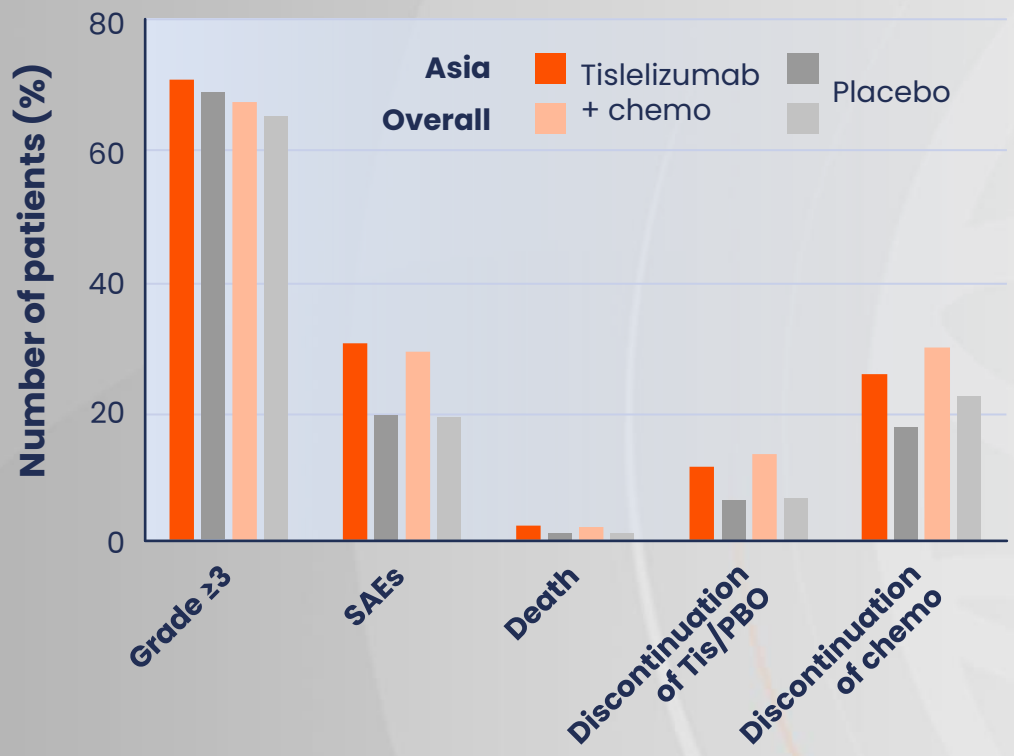
RATIONALE-306 Asia subgroup: Safety outcomes[1,2]



TEAEs with ≥20% incidence

Asia subgroup

- Anaemia
- Decreased neutrophil count
- Decreased white blood cell count
- Decreased appetite
- Nausea
- Decreased platelet count
- Vomiting

Overall

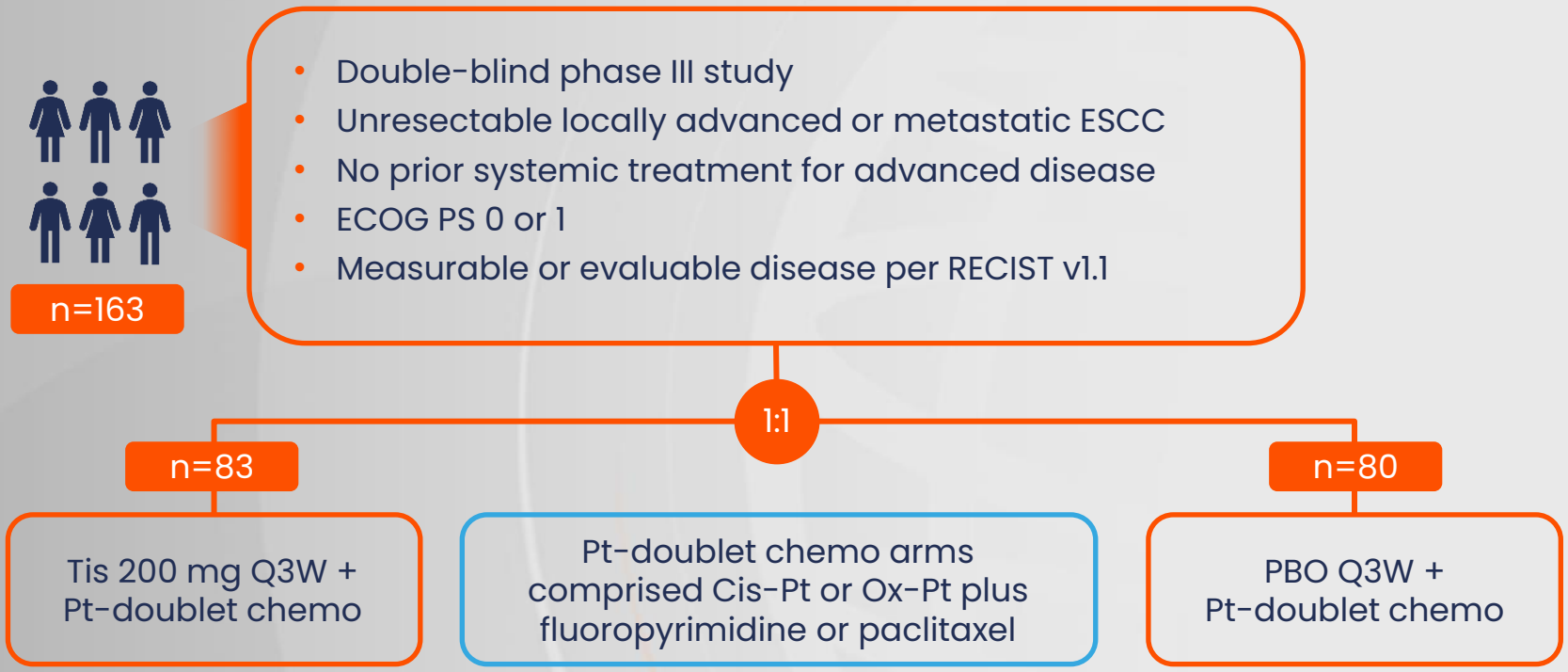
- Anaemia
- Decreased neutrophil count
- Decreased white blood cell count
- Decreased appetite
- Nausea

Tislelizumab + chemo had a manageable safety profile, consistent between the Asia subgroup and the overall population

Chemo, chemotherapy; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event; Tis, tislelizumab.

1. Kato K, et al. *Ann Oncol.* 2022;33(Suppl. 9):S1458; 2. Kato K, et al. Presented at: ESMO Asia Congress 2022, Singapore. 2–4 December 2022. Abstr. 70O.

RATIONALE-306: Study design[1,2]



Tislelizumab + chemotherapy vs chemotherapy as first-line treatment for advanced ESCC

Chemo, chemotherapy; Cis, cisplatin; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; Ox, oxaliplatin; PBO, placebo; PS, performance status; Pt, platinum; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; Tis, tislelizumab.

1. Raymond E, et al. *J Clin Oncol.* 2023;41(Suppl. 4):340; 2. Raymond E, et al. Presented at: 2023 ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, USA. 19–21 January 2023. Abstr. 340.

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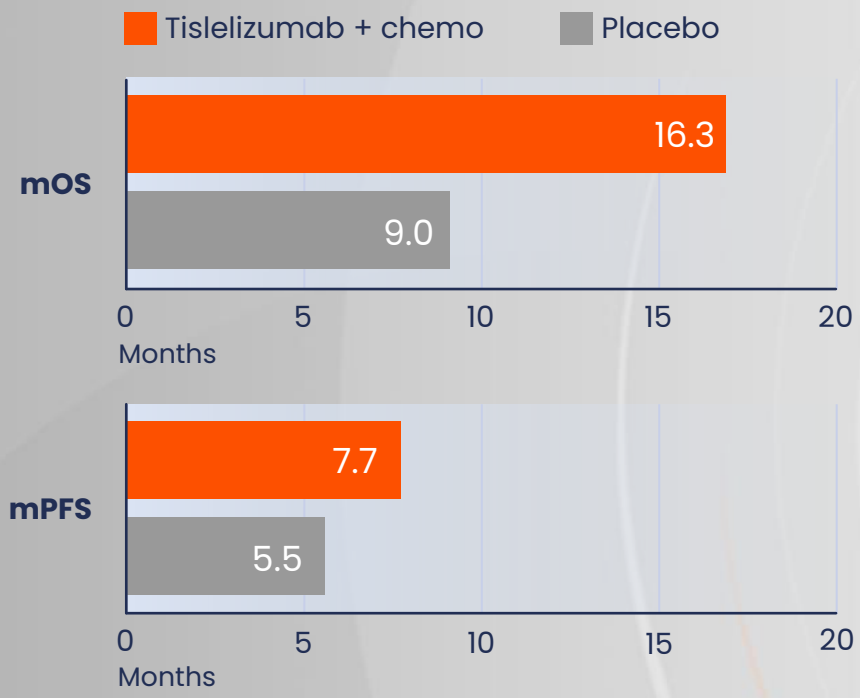
RATIONALE-306 non-Asia subgroup: Median survival outcomes[1,2]



HR 0.66
(95% CI 0.45–0.96)

34% reduced risk of death

HR 0.59
(95% CI 0.41–0.83)

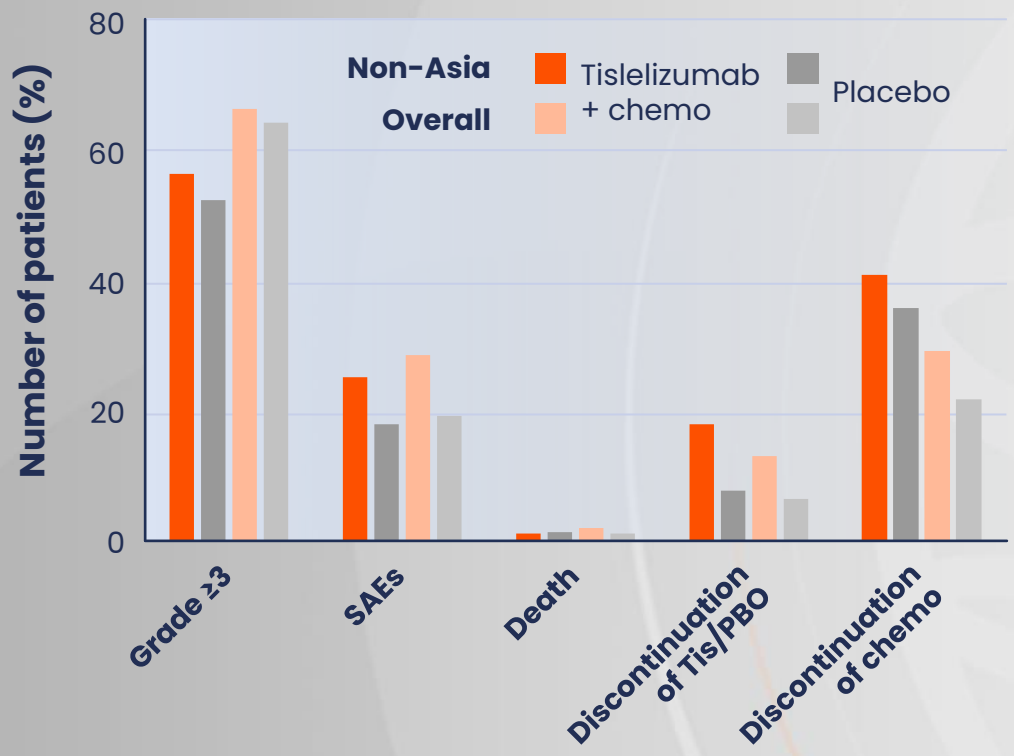
41% reduced risk of progression

- Overall population: Tislelizumab + chemo vs chemo
  - mOS: 17.2 vs 10.6 months (HR 0.66; 95% CI 0.54–0.80)
  - mPFS: 7.3 vs 5.6 months (HR 0.62; 95% CI 0.52–0.75)
- Consistent with the overall population, there is a clinically meaningful improvement in OS in the non-Asia subgroup

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival.

1. Raymond E, et al. *J Clin Oncol.* 2023;41(Suppl. 4):340; 2. Raymond E, et al. Presented at: 2023 ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, USA. 19–21 January 2023. Abstr. 340.

RATIONALE-306 non-Asia subgroup: Safety outcomes[1,2]



Most common grade ≥3 TRAEs
(tislelizumab + chemo vs PBO)

• Stomatitis	10.8% vs 9.0%
• Neutropenia	9.6% vs 16.7%
• Anaemia	6.0% vs 10.3%

Tislelizumab + chemotherapy had a manageable safety profile, with no new safety signals identified in the non-Asia subgroup vs the overall study population

Chemo, chemotherapy; PBO, placebo; SAE, serious adverse event; Tis, tislelizumab; TRAE, treatment-related adverse event.

1. Raymond E, et al. *J Clin Oncol.* 2023;41(Suppl. 4):340; 2. Raymond E, et al. Presented at: 2023 ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, USA. 19–21 January 2023. Abstr. 340.

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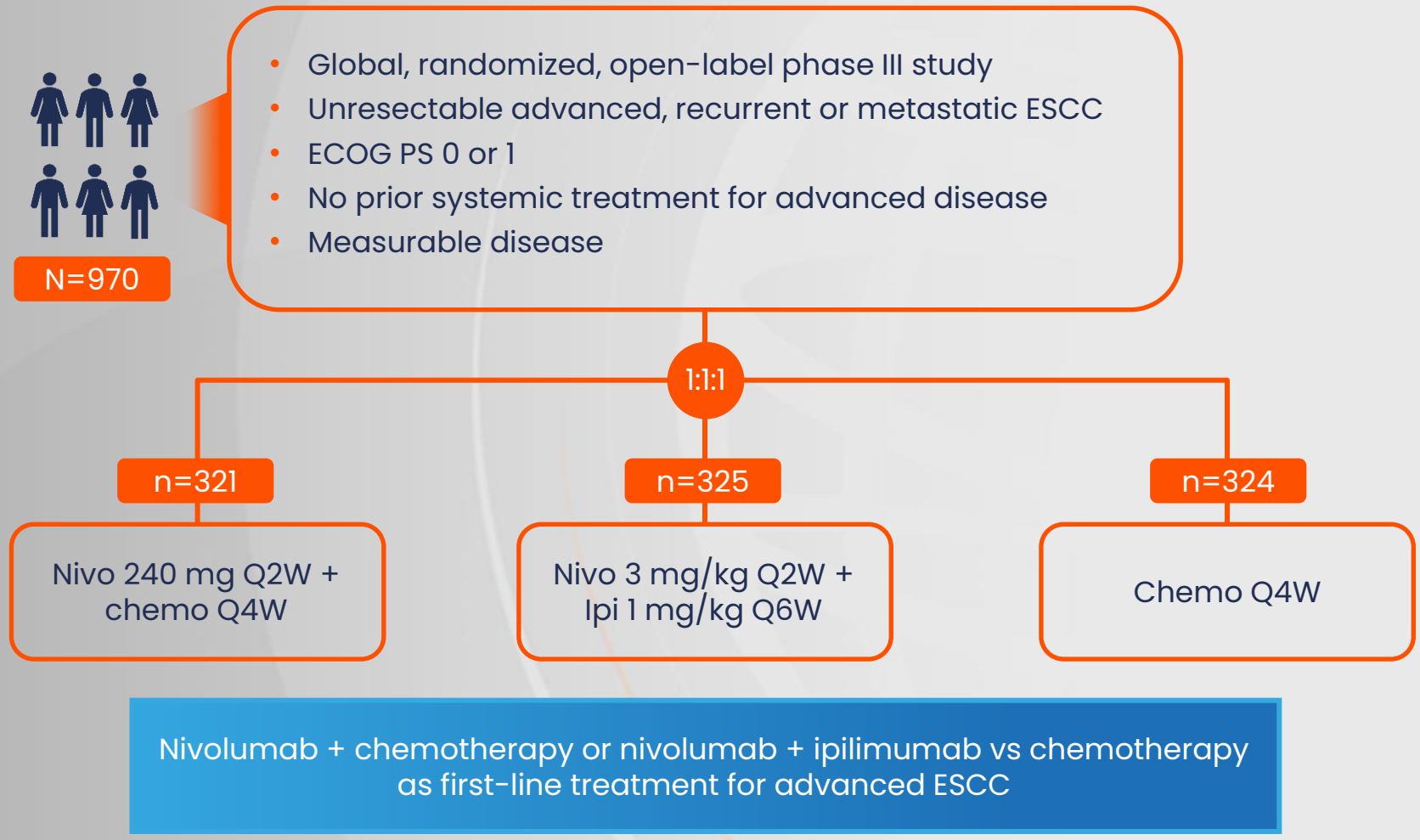
CheckMate 648: Study design[1-3]

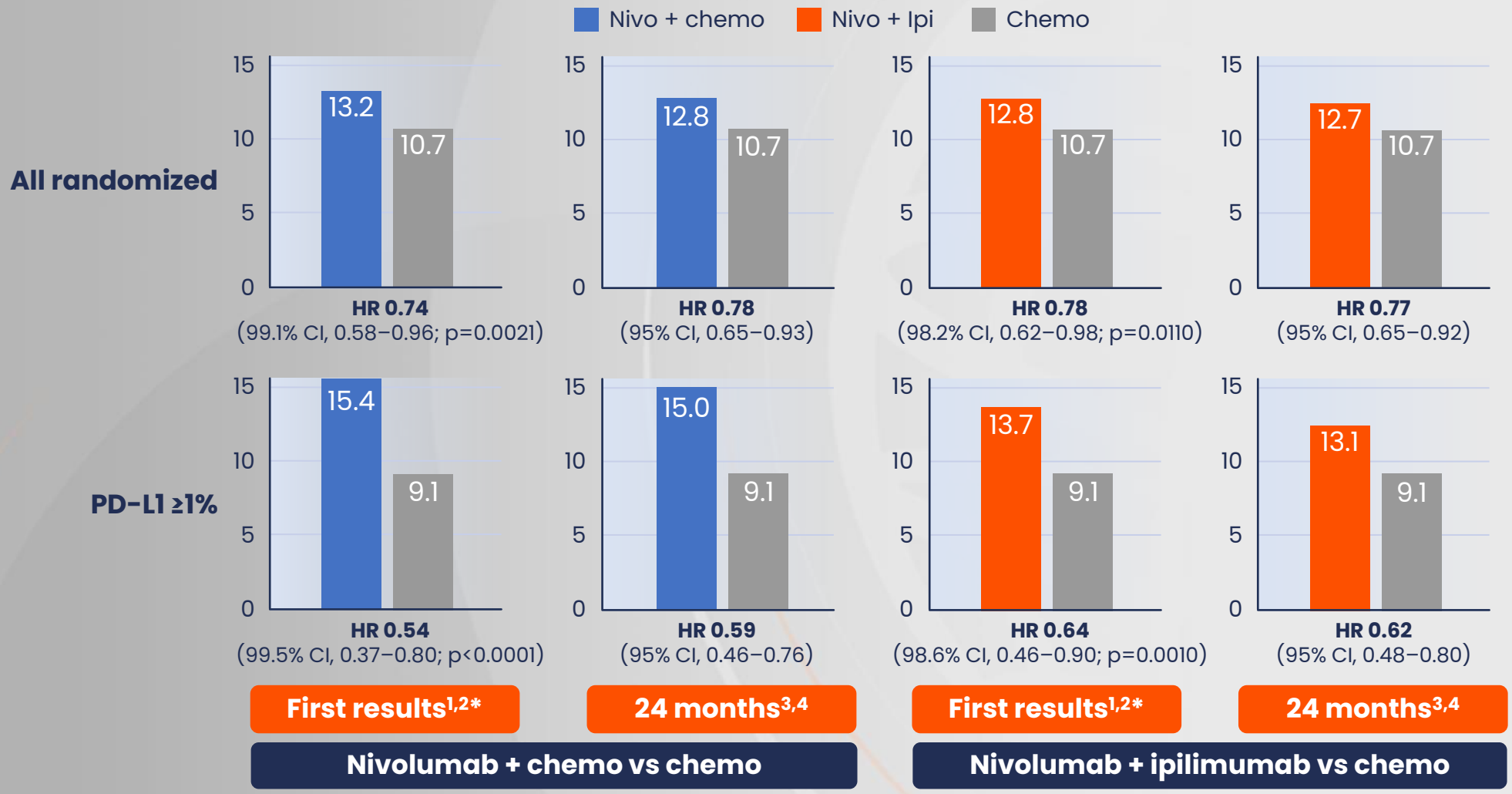


Nivolumab + chemotherapy or nivolumab + ipilimumab vs chemotherapy as first-line treatment for advanced ESCC

Chemo, chemotherapy; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; Ipi, ipilimumab; Nivo, nivolumab; PS, performance status; Q2/4/6W, once every 2/4/6 weeks.

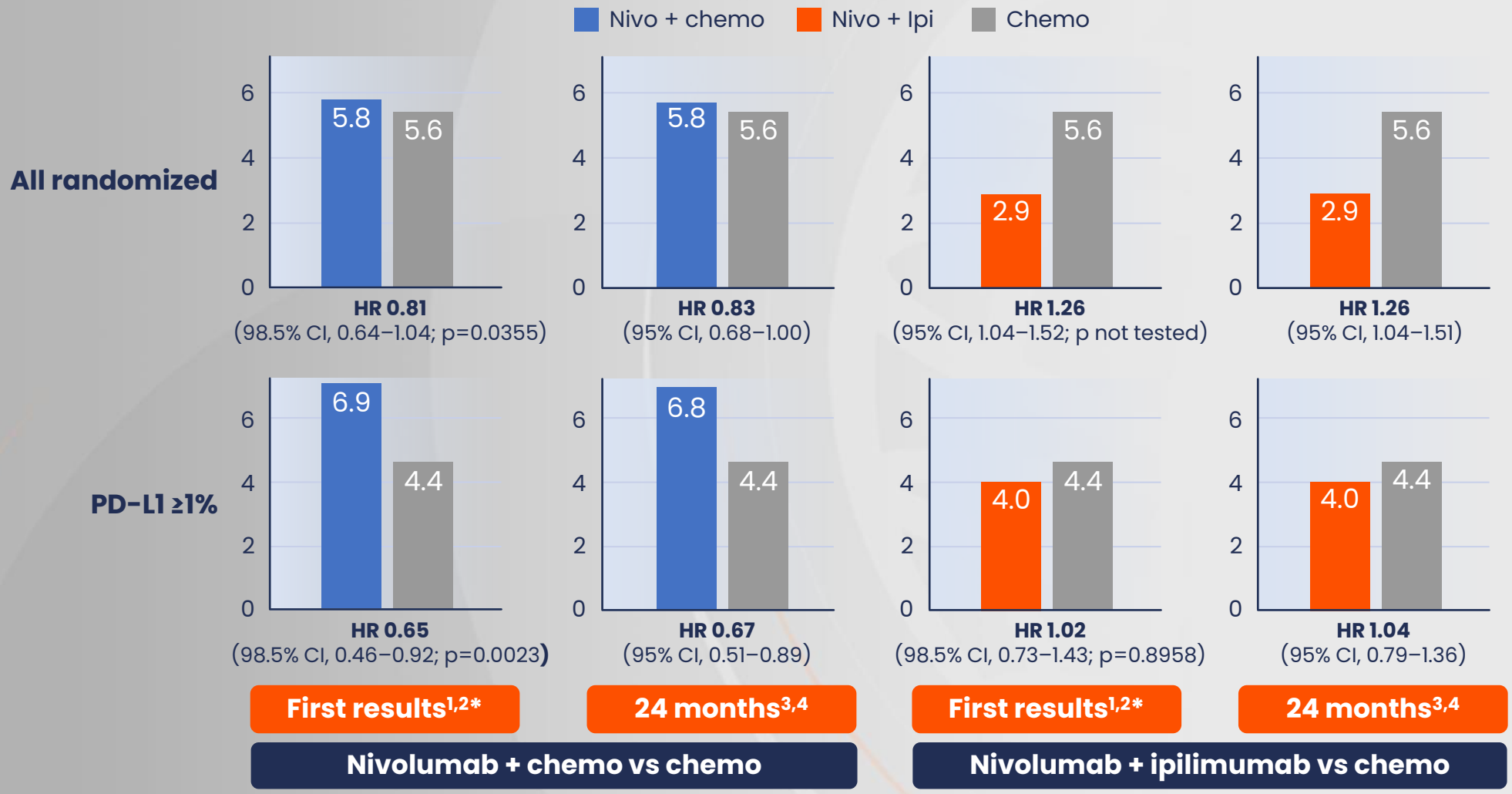
1. Kato K, et al. *J Clin Oncol.* 2023;41(Suppl. 4):290; 2. Kato K, et al. Presented at: 2023 ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, USA. 19–31 January 2023. Abstr 290.
3. Chau I, et al. Presented at: 2021 ASCO Annual Meeting, Chicago, IL, USA. 4–8 June 2021. Abstr LBA4001.

CheckMate 648 extended follow-up: mOS (months)



*Minimum follow-up 12.9 months.
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; Ipi, ipilimumab; mOS, median overall survival; Nivo, nivolumab; PD-L1, programmed death-ligand 1.
1. Kato K, et al. *J Clin Oncol.* 2023;41(Suppl. 4):290; 2. Kato K, et al. Presented at: 2023 ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, USA. 19–31 January 2023. Abstr 290;
3. Chau I, et al. *J Clin Oncol.* 2021;39(Suppl. 18):LBA4001; 4. Chau I, et al. Presented at: 2021 ASCO Annual Meeting, Chicago, IL, USA. 4–8 June 2021. Abstr LBA4001.

CheckMate 648 extended follow-up: mPFS (months)



*Minimum follow-up 12.9 months.
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; Ipi, ipilimumab; mPFS, median progression-free survival; Nivo, nivolumab; PD-L1, programmed death-ligand 1.
1. Kato K, et al. *J Clin Oncol.* 2023;41(Suppl. 4):290; 2. Kato K, et al. Presented at: 2023 ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, USA. 19–31 January 2023. Abstr. 290;
3. Chau I, et al. *J Clin Oncol.* 2021;39(Suppl. 18):LBA4001; 4. Chau I, et al. Presented at: 2021 ASCO Annual Meeting, Chicago, IL, USA. 4–8 June 2021. Abstr. LBA4001.

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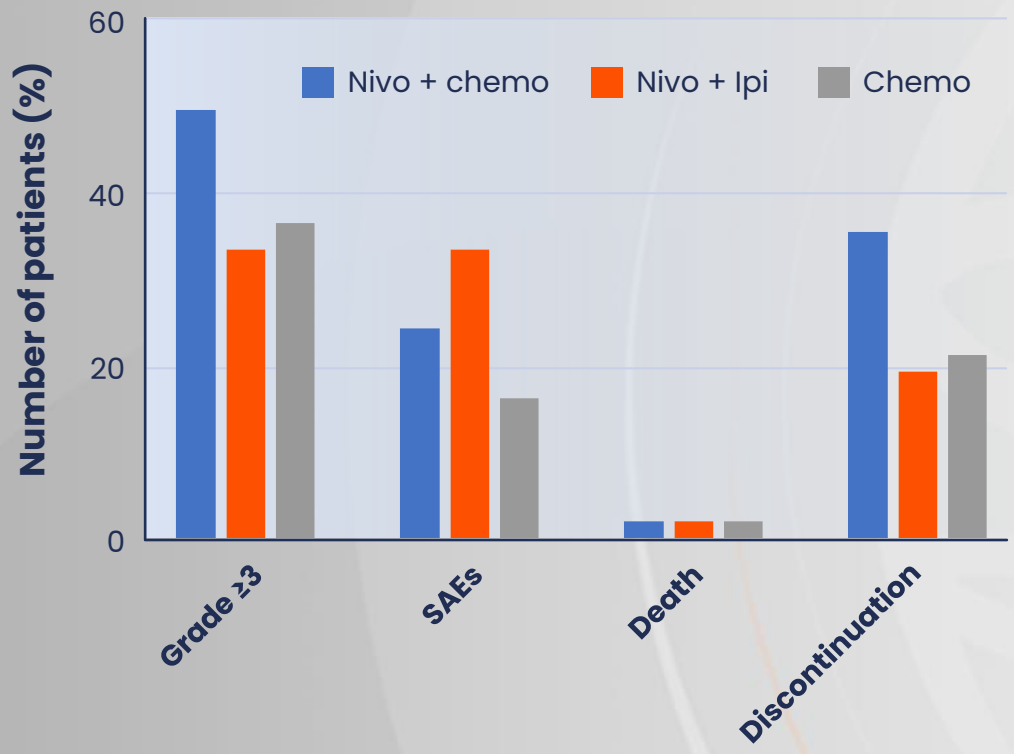
CheckMate 648 extended follow-up: Safety outcomes[1,2]



Most common any-grade TRAEs

- Nivo + chemo:
  - Nausea (59%)
  - Decreased appetite (43%)
  - Stomatitis (32%)
- Nivo + Ipi:
  - Rash (17%)
  - Pruritis (13%)
  - Hypothyroidism (13%)
- Chemo:
  - Nausea (52%)
  - Decreased appetite (43%)
  - Anaemia (22%)

After an extended follow-up period, no new safety signals were identified

Chemo, chemotherapy; Ipi, ipilimumab; Nivo, nivolumab; TRAE, treatment-related adverse event.

Kato K, et al. Presented at: 2023 ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, USA. 19–31 January 2023. Abstr. 290.

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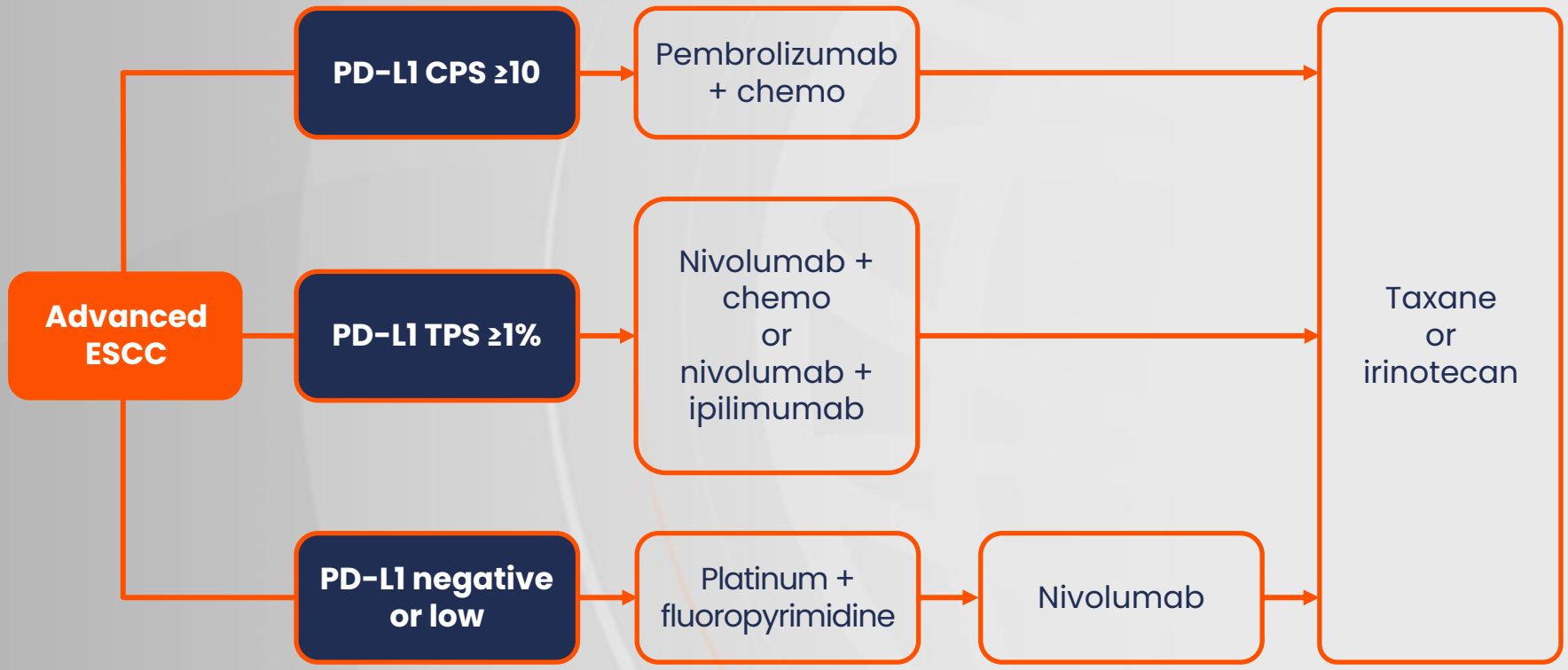
Latest ESMO treatment algorithm for advanced ESCC



CPS, combined positive score; chemo, chemotherapy; ESCC, esophageal squamous cell carcinoma; ESMO, European Society for Medical Oncology; PD-L1, programmed death-ligand 1; TPS, tumour proportion score.

Obermannová R, et al. *Ann Oncol*. 2022;33:992-1004.

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Summary: New and emerging treatment options

Anti-PD-1 mAb*	Adjuvant	First-line + chemo	Second-line mono
Nivolumab	☑ [1]	☑ [2]	☑ [3]
Pembrolizumab		☑ [4]	
Sintilimab		☑ [5]	
Toripalimab		☑ [6]	
Camrelizumab		☑ [7]	
Tislelizumab		☑ [8]	☑ [9]
Serplulimab		☑ [10]	

*Comparator arms were placebo, chemo or placebo + chemo. Chemo, chemotherapy; mAb, monoclonal antibody; mono, monotherapy; PD-1, programmed cell death protein 1.

1. Kelly RJ, et al. *N Engl J Med*. 2021;384:1191-1203; 2. Kato K, et al. Presented at: 2023 ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, USA. 19–31 January 2023. Abstr. 290; 3. Kato K, et al. *Lancet Oncol*. 2019;20:1506-17; 4. Kojima T, et al. *J Clin Oncol*. 2020;38:4138-48; 5. Shen L, et al. Presented at: ESMO Congress 2021, Paris, France. 16–21 September 2021. Abstr. LBA52; 6. Xu R, et al. Presented at: ESMO Congress 2021, Paris, France. 16–21 September 2021. Abstr. 1373MO; 7. Xu R, et al. Presented at: 2021 ASCO Annual Meeting, Chicago, IL, USA. 4–8 June 2021. Abstr. 4000; 8. Yoon H, et al. *Ann Oncol.* 2022;33 (Suppl. 4):S375; 9. Shen L, et al. Presented at: 2021 ASCO Annual Meeting, Chicago, IL, USA. 4–8 June 2021. Abstr. 4012; 10. Song Y, et al. *Nat Med.* 2023; online ahead of print.