

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



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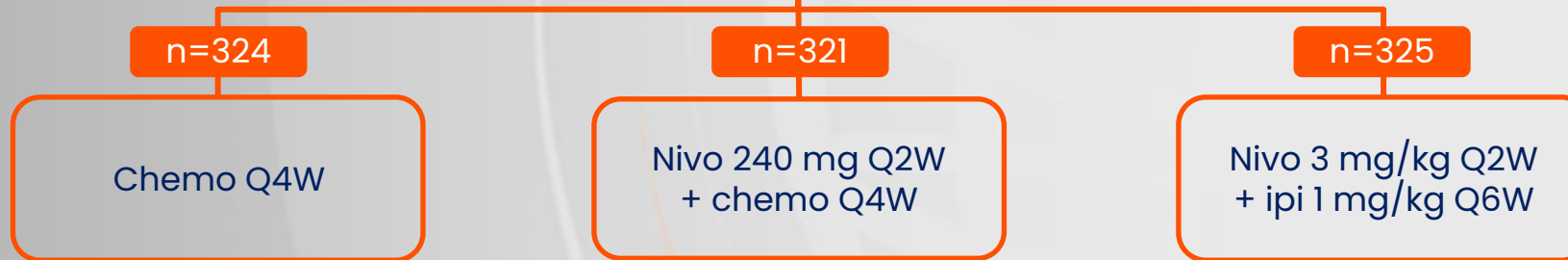
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CheckMate 648: Study design

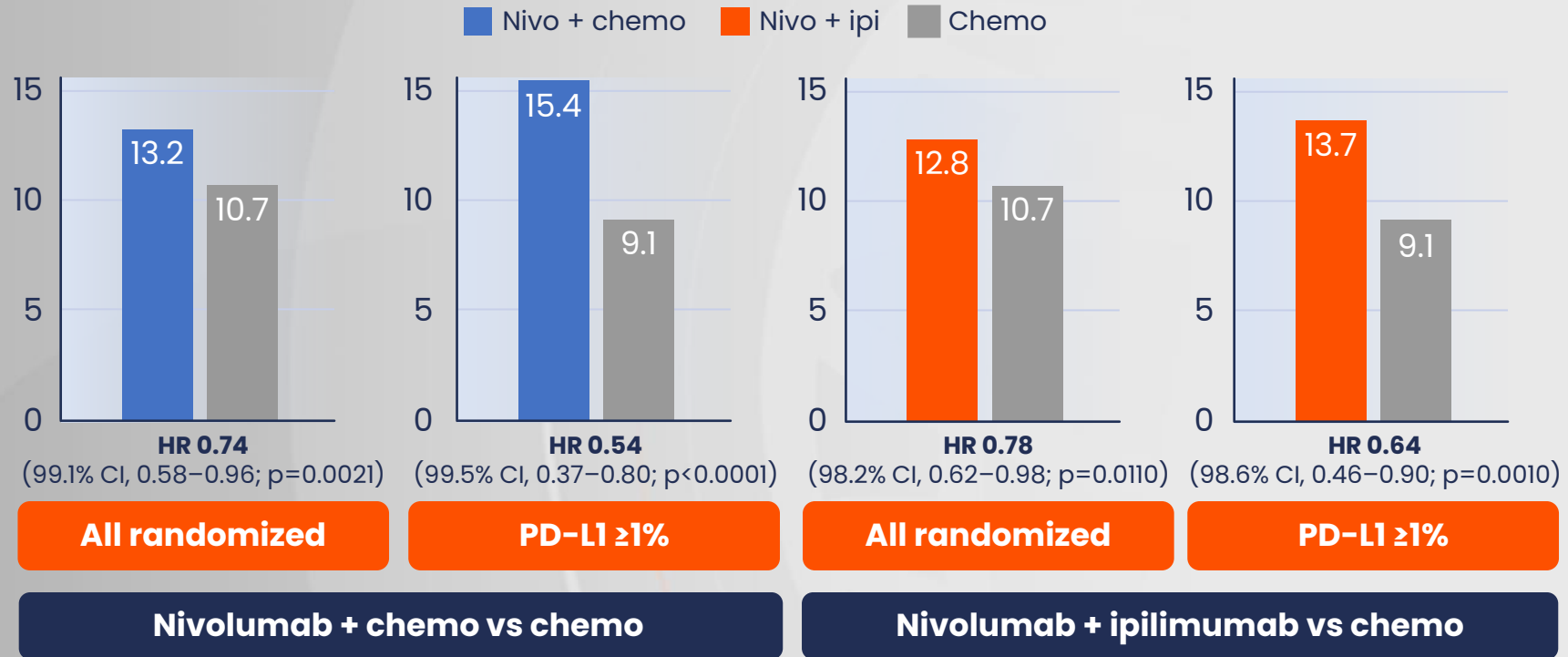


- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0 or 1
- No prior systemic treatment for advanced disease
- Measurable disease



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

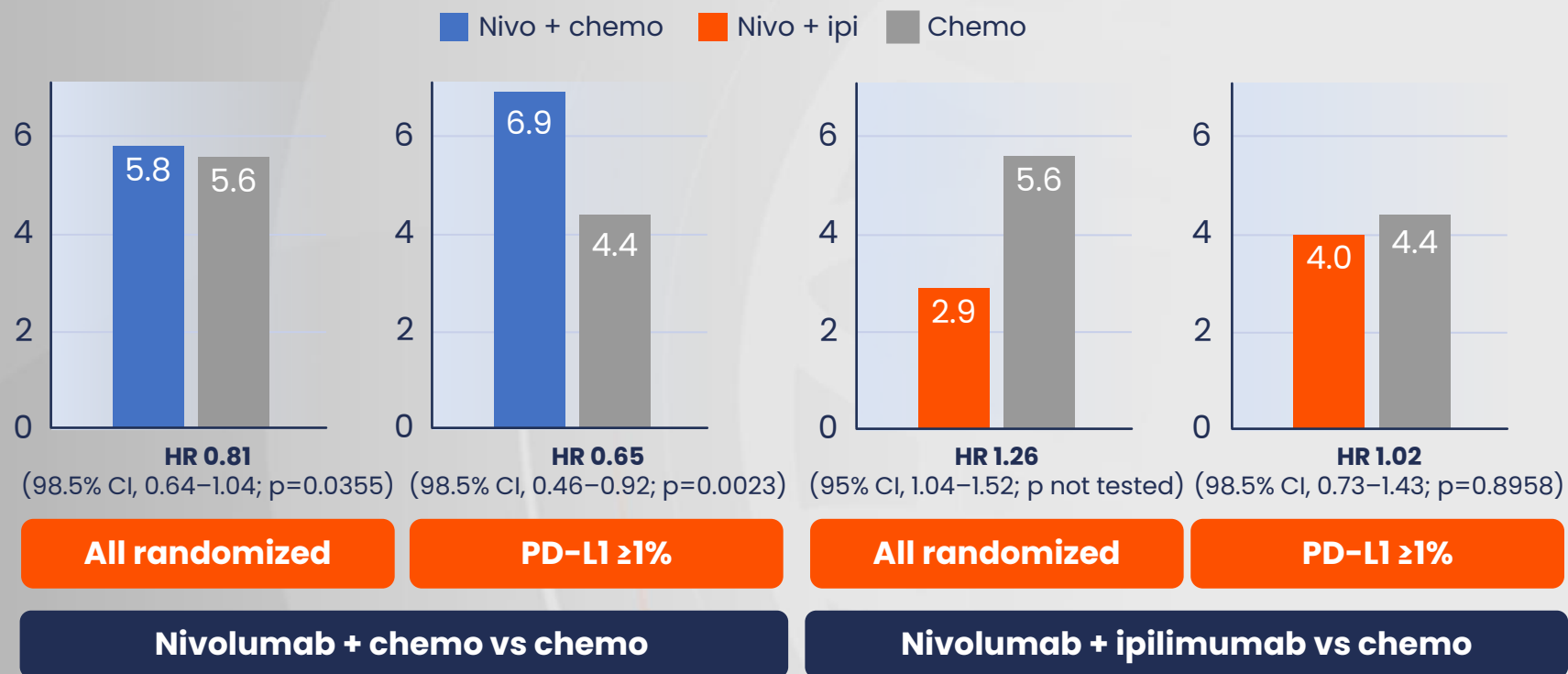
CheckMate 648: Median overall survival (months)



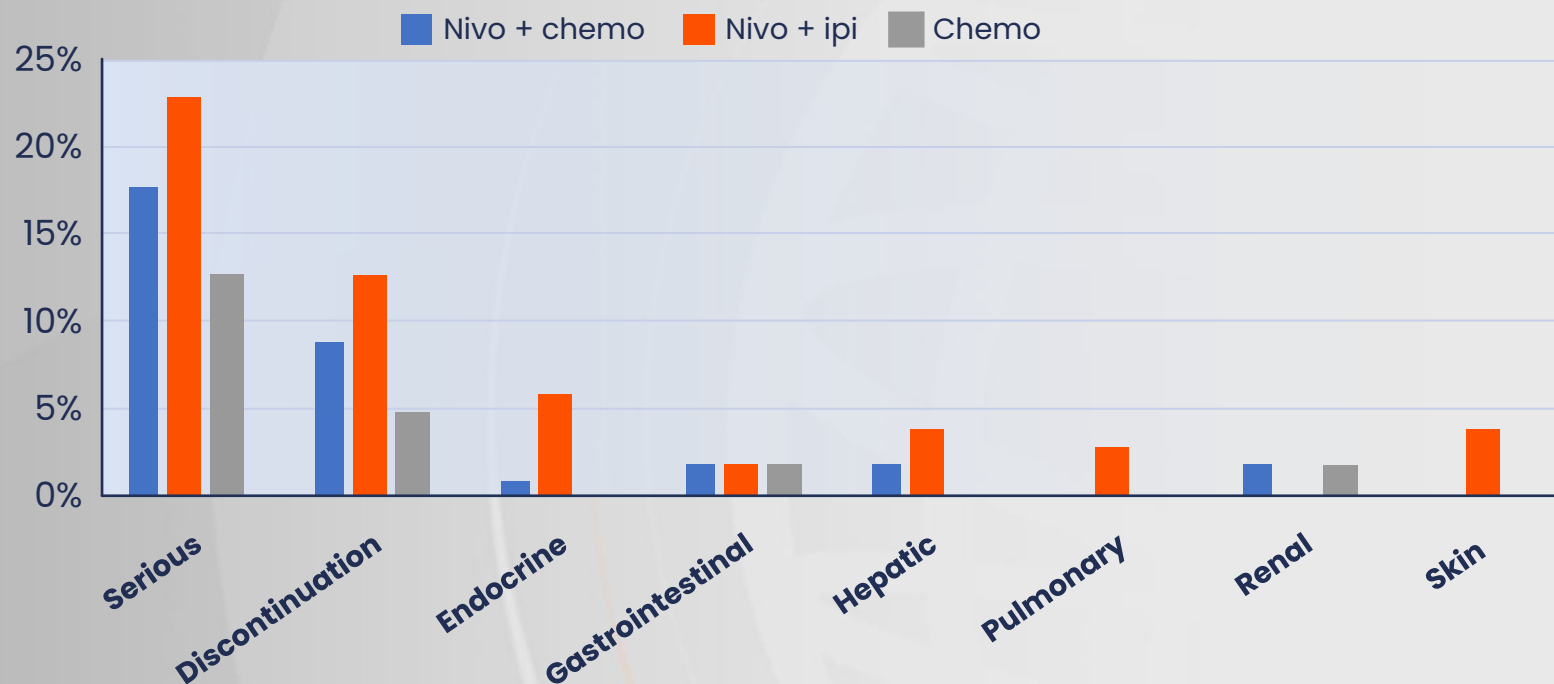
CI, confidence interval; HR, hazard ratio; PD-L1, programmed death-ligand 1.

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.

CheckMate 648: Median progression-free survival (months)



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



- For all randomized patients and those with PD-L1 $\geq 1\%$:
 - 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.

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

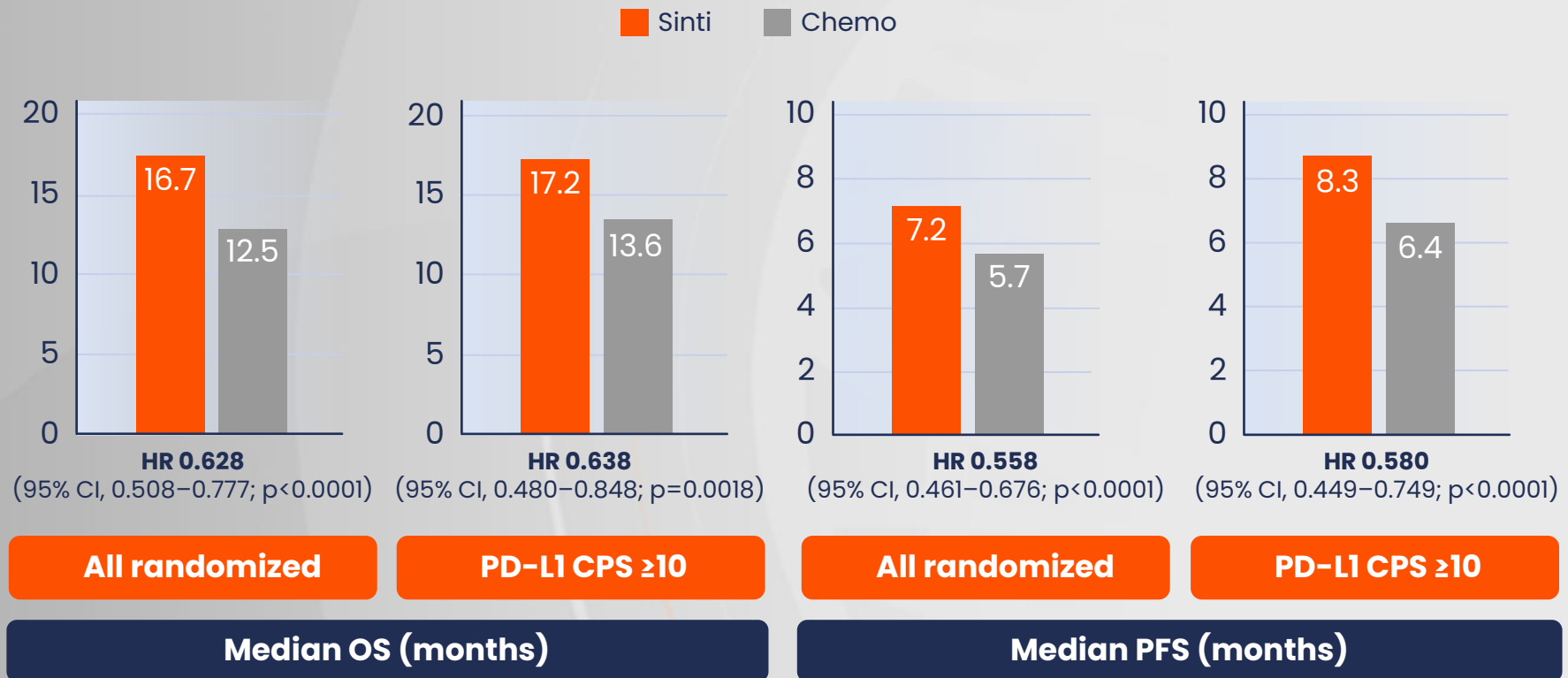
Placebo Q3W, for a maximum of 24 months + chemo Q3W for a maximum of 6 cycles

n=327

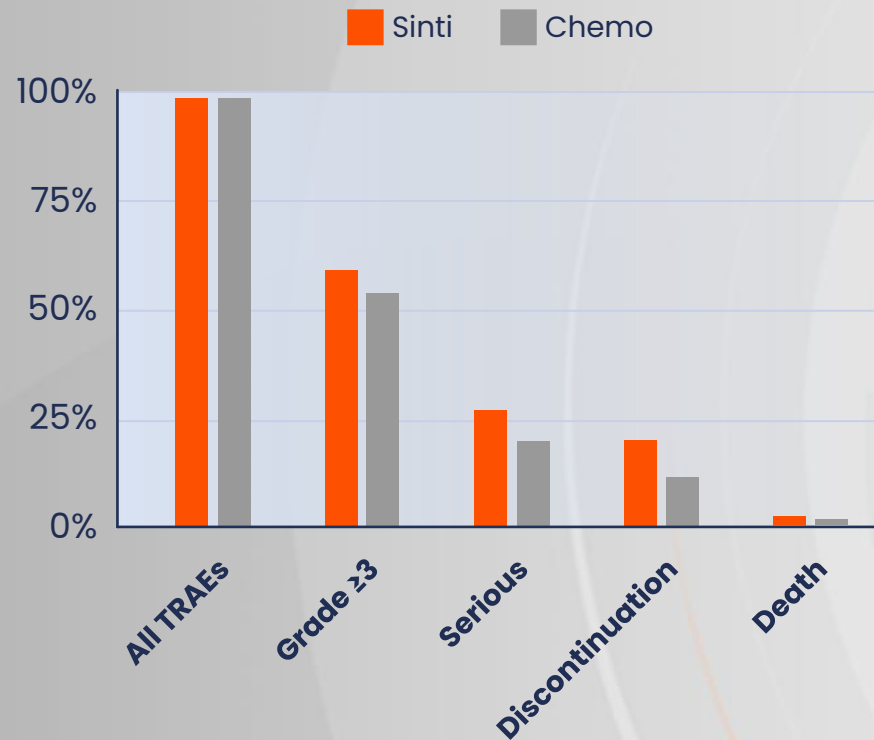
Sintilimab Q3W, for a maximum of 24 months + chemo Q3W for a maximum of 6 cycles

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

ORIENT-15: Key study endpoints



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

JUPITER-06: Study design



- Histologically or cytologically confirmed advanced or metastatic ESCC
- Treatment-naïve 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

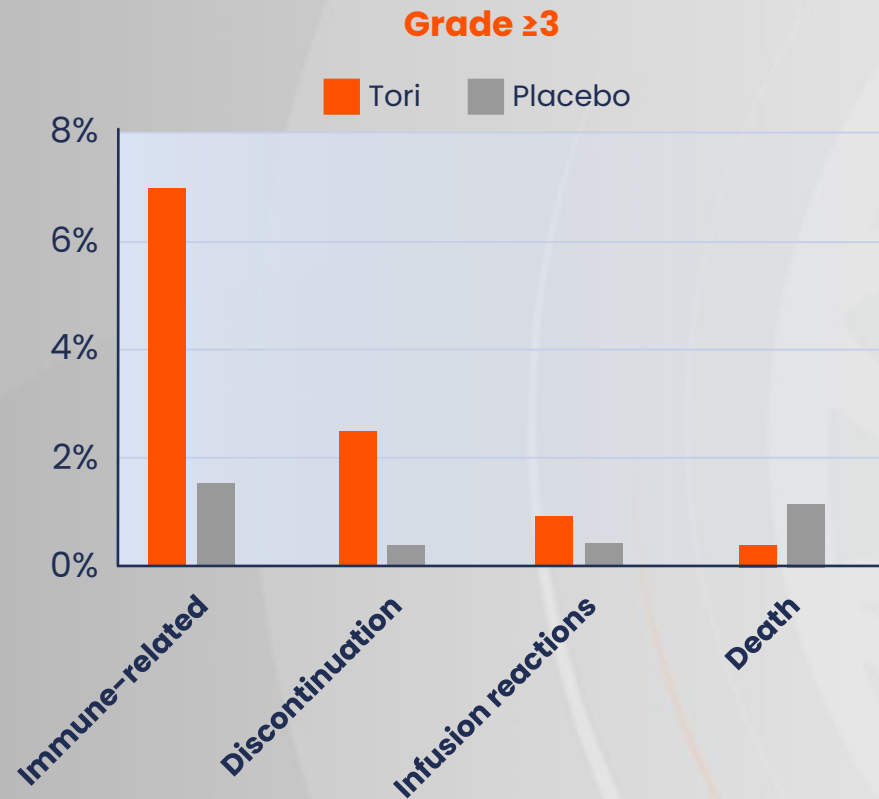
Randomized, double-blind, phase III study of toripalimab vs placebo in combination with first-line chemotherapy for treatment naïve advanced or metastatic ESCC

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; $p < 0.00001$)

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



TRAEs with $\geq 30\%$ 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

ESCORT-1st: Study design



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

n=298

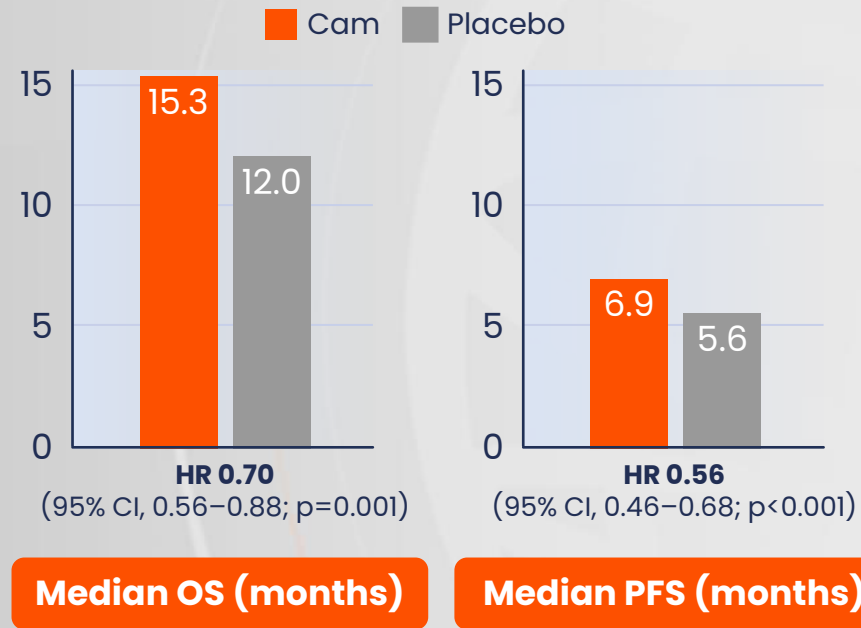
Placebo QW3 + chemo Q3W
+ chemo Q3W for ≤6 cycles

n=298

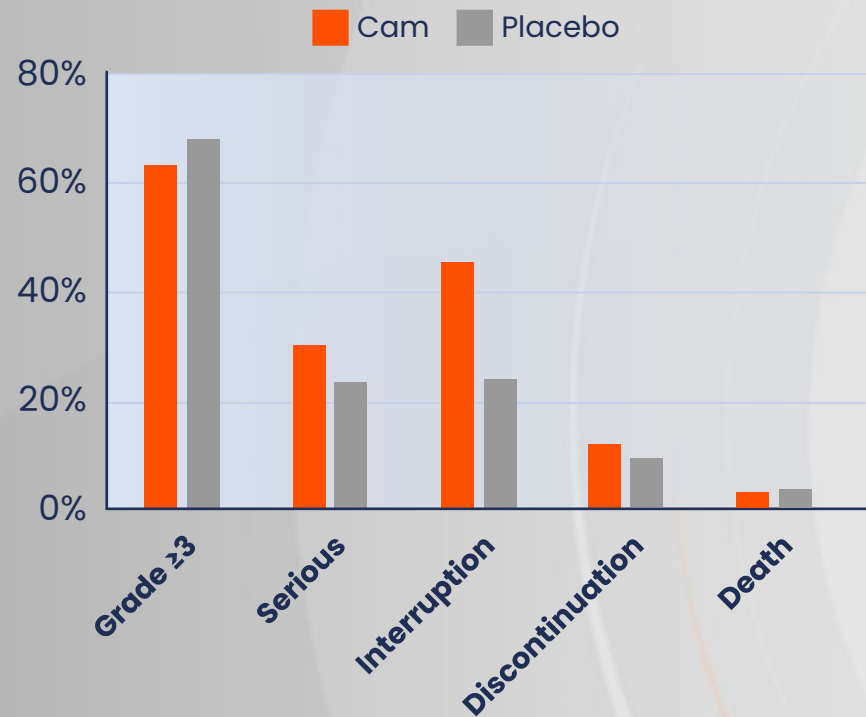
Camrelizumab 200 mg Q3W
+ chemo Q3W for ≤6 cycles

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

ESCORT-1st: Key endpoints – interim analysis



ESCOR-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

RATIONALE 302: Study design



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

n=256

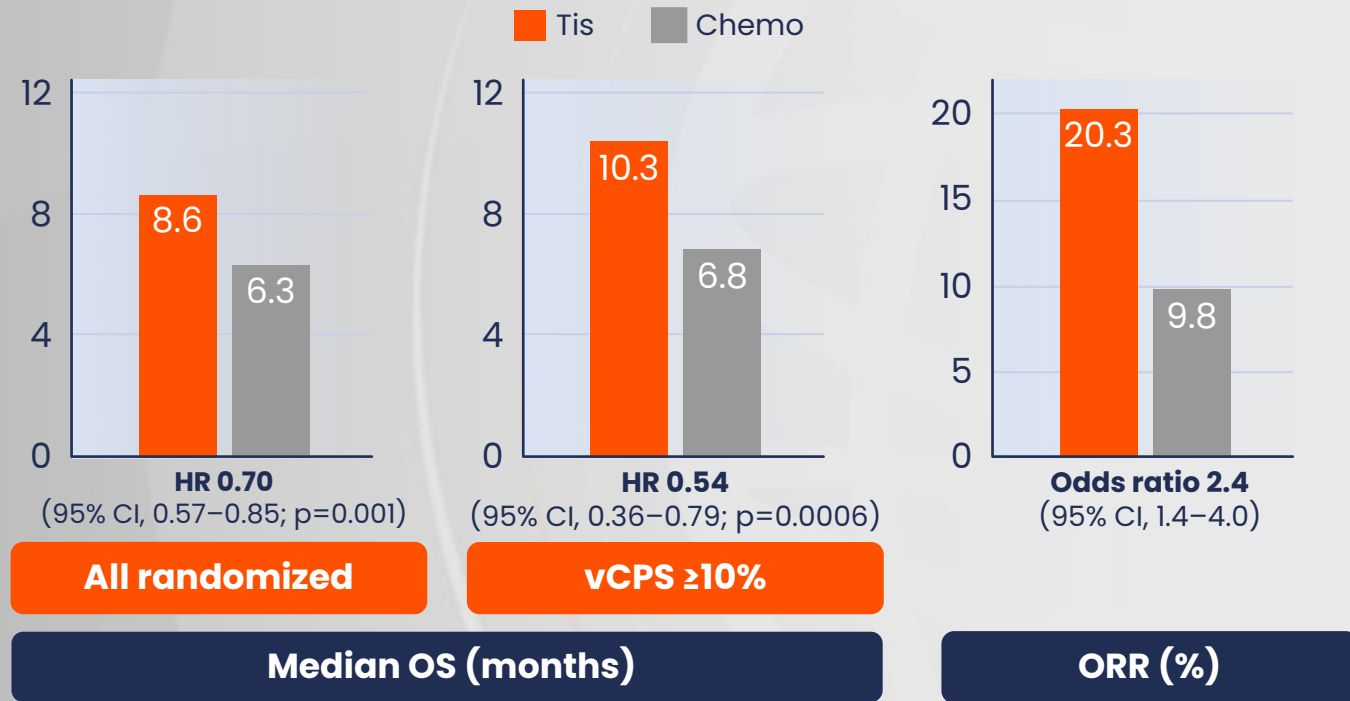
Investigator-chosen chemo

n=256

Tislelizumab 200 mg Q3W

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

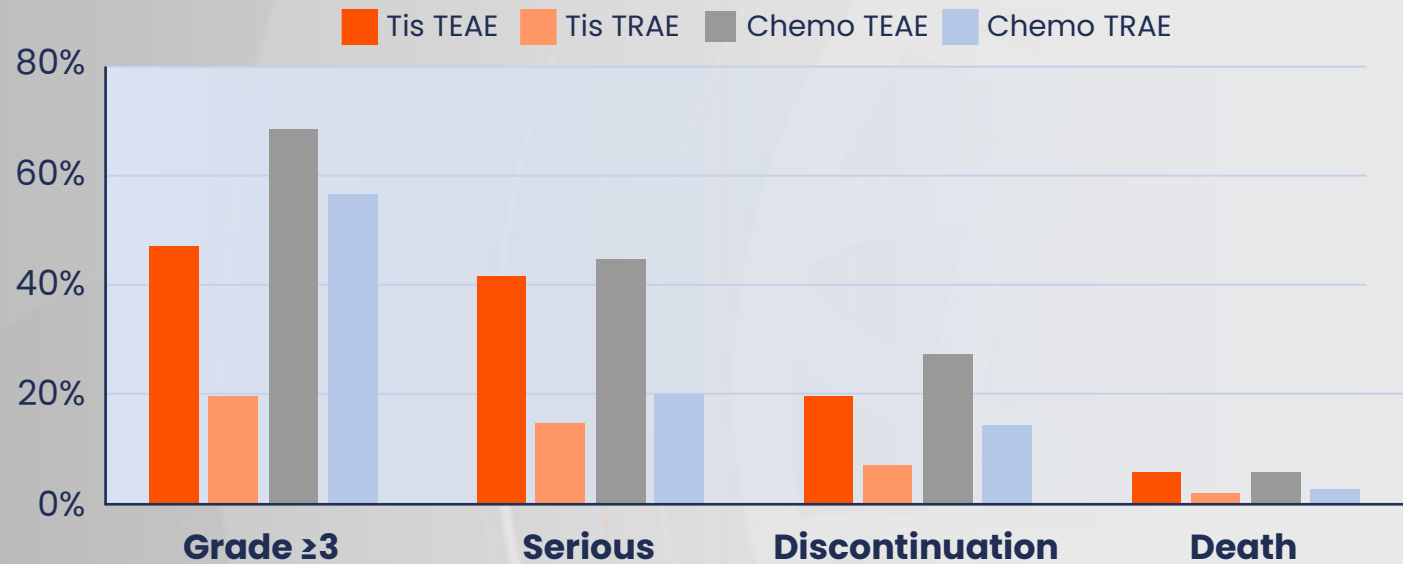
RATIONALE 302: Key endpoints



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

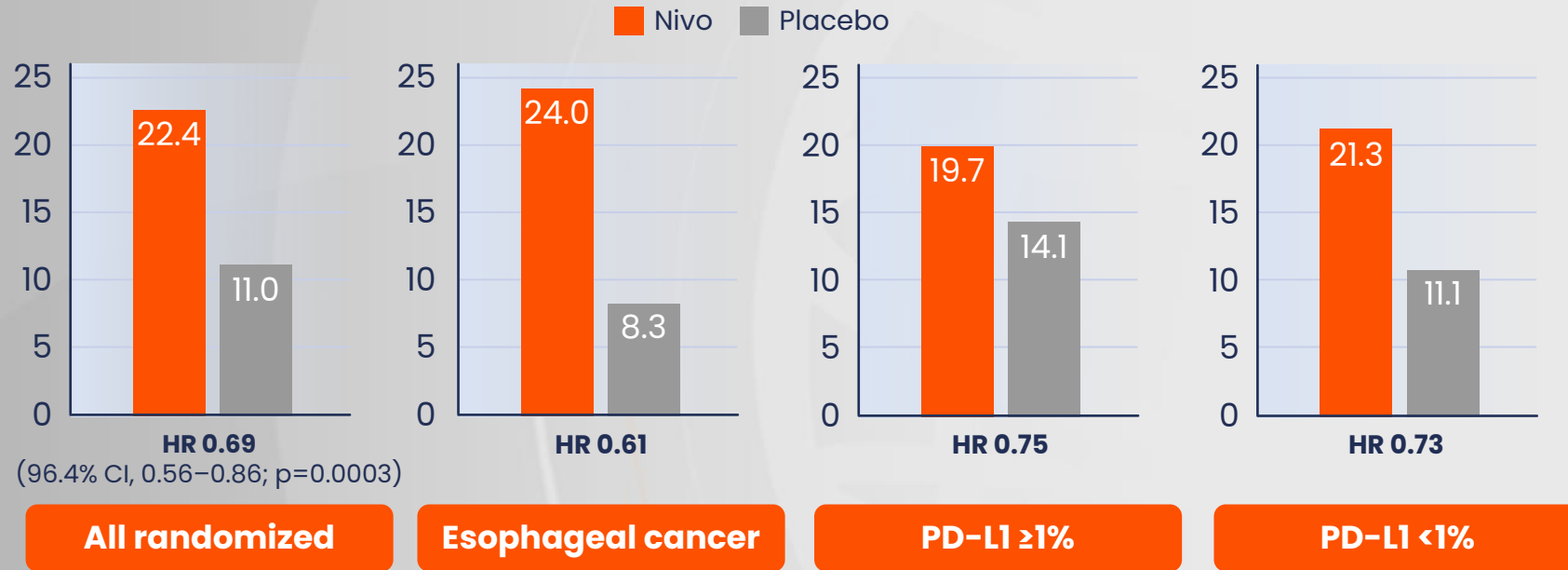
Placebo Q2W for 16 weeks
then Q4W

n=532

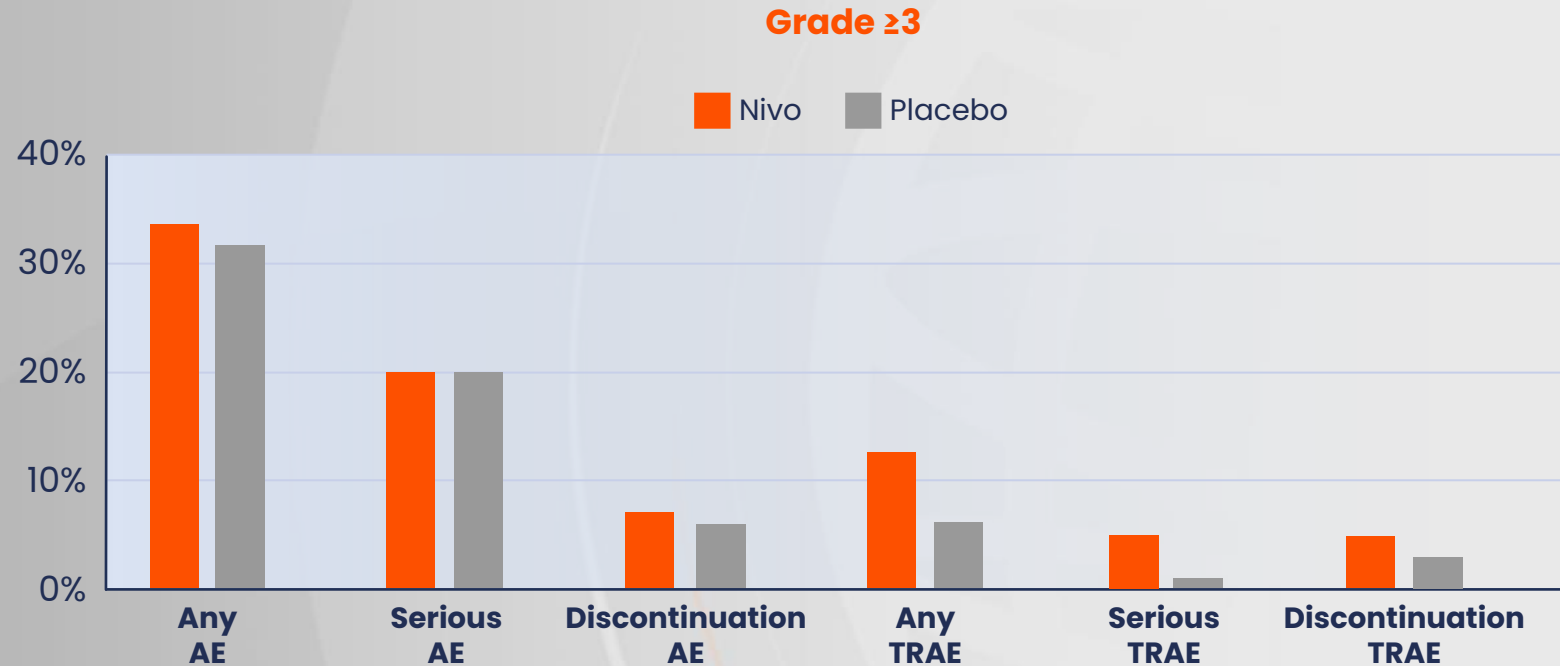
Nivolumab 240 mg Q2W for
16 weeks then 480 mg Q4W

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

CheckMate 577: Median disease-free survival (months)



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.

Summary and conclusions

Anti-PD-1 mAb	Outcome vs comparator*	Adjuvant	1L combo with chemo	2L mono
Nivo		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
Sint			<input checked="" type="checkbox"/>	
			<input checked="" type="checkbox"/>	
Tori			<input checked="" type="checkbox"/>	
			<input checked="" type="checkbox"/>	
Cam			<input checked="" type="checkbox"/>	
			<input checked="" type="checkbox"/>	
Tis				<input checked="" type="checkbox"/>
				<input checked="" type="checkbox"/>

 Efficacy  Safety

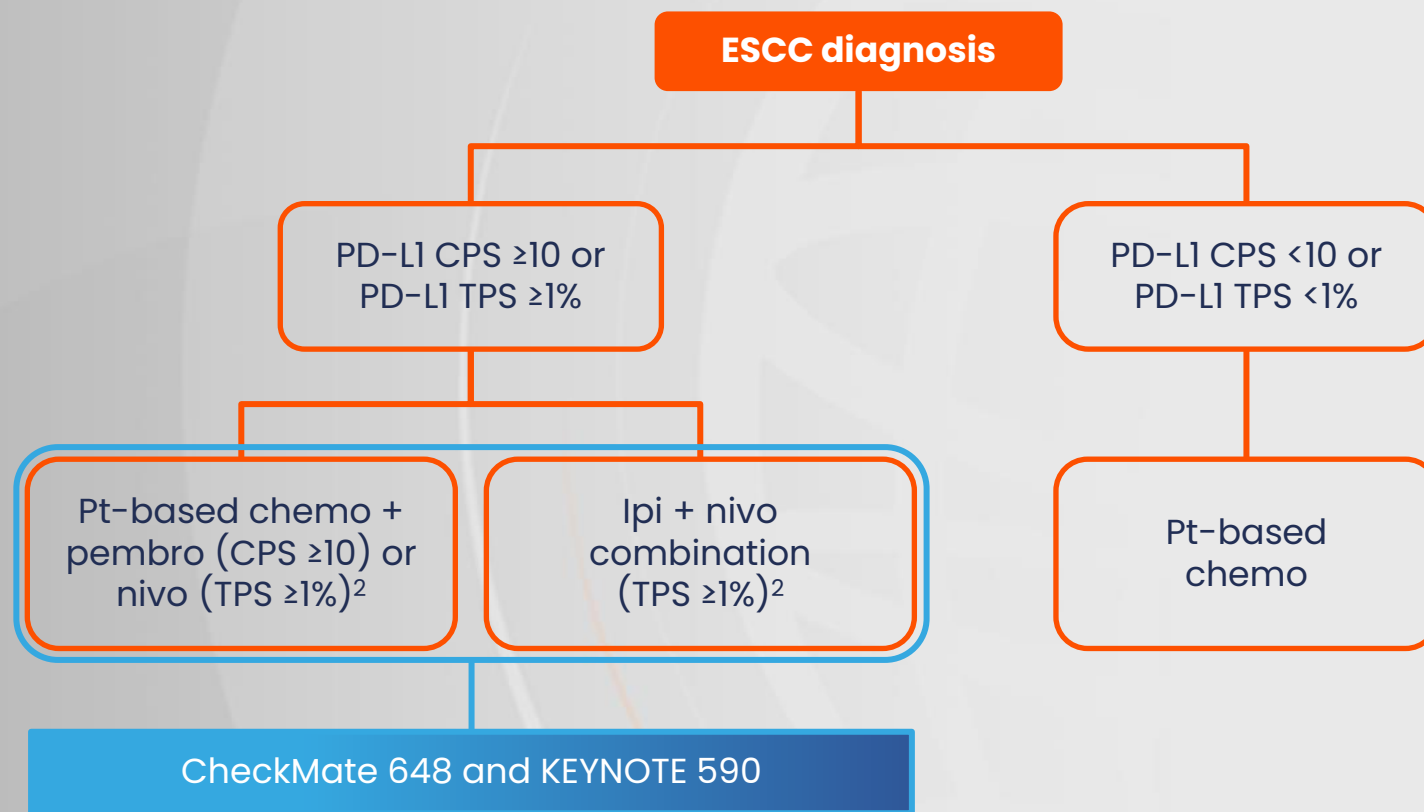
*Comparator arms were placebo, chemo or placebo + chemo.
Combo, combination; mAb, monoclonal antibody; mono, monotherapy.

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 line¹



New standards for care with checkpoint inhibitors: First line

	CheckMate 648 ¹		KEYNOTE 590 ²
PD-L1 expression	PD-L1 TPS \geq 1%		PD-L1 CPS \geq 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.

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

Nivo 240 mg Q2W +
chemo Q4W

n=325

Nivo 3 mg/kg Q2W +
ipi 1 mg/kg Q6W

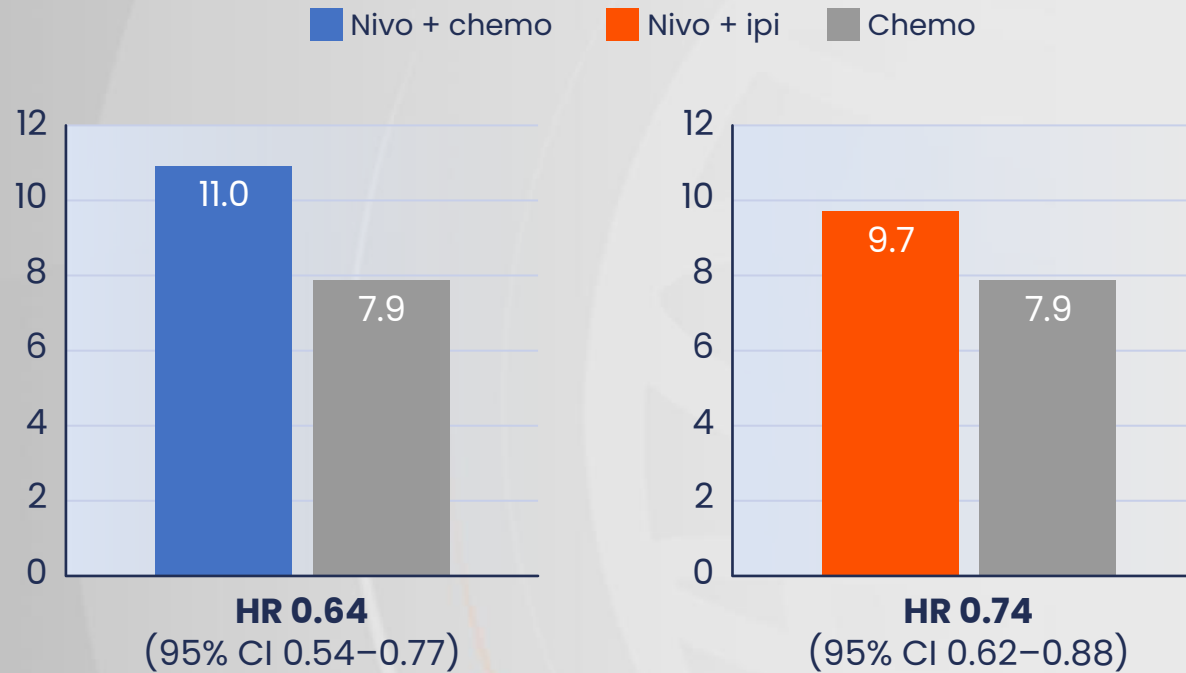
n=324

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.

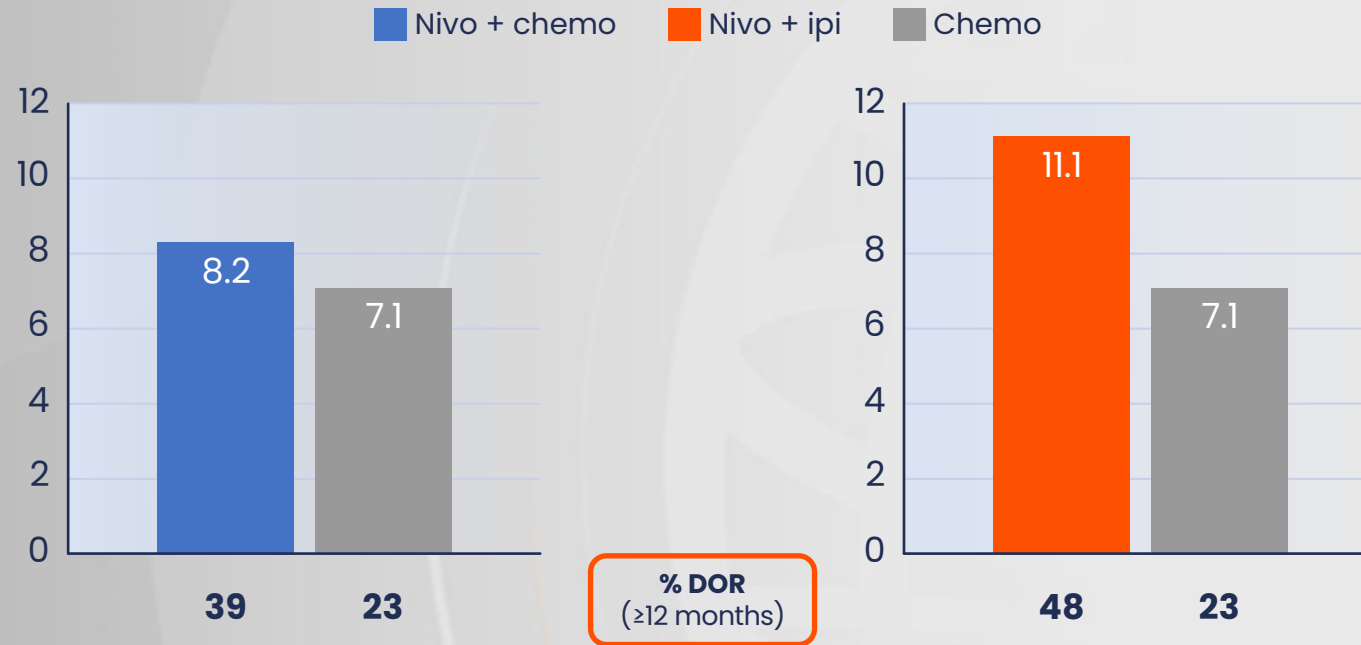
CheckMate 648: Median PFS2* (months)¹



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.

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

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

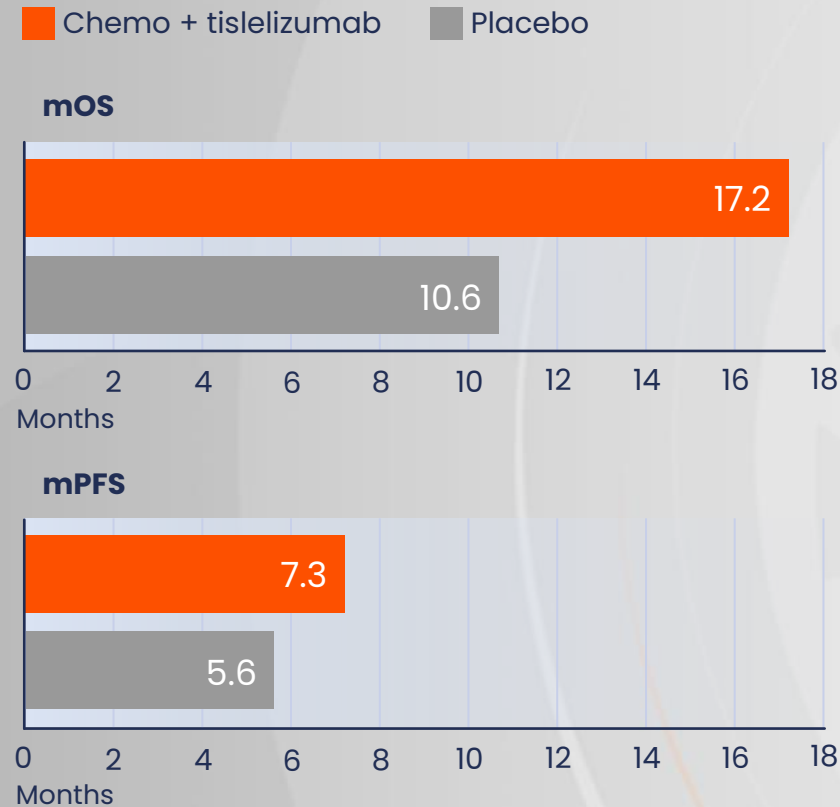
n=323

Pt-doublet chemo arms
comprised CIS-Pt or OX-Pt plus:
A 5-FU **B** CAP **C** PAC

PBO +
Pt-doublet chemo

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

RATIONALE 306: Median survival outcomes (all randomized)



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

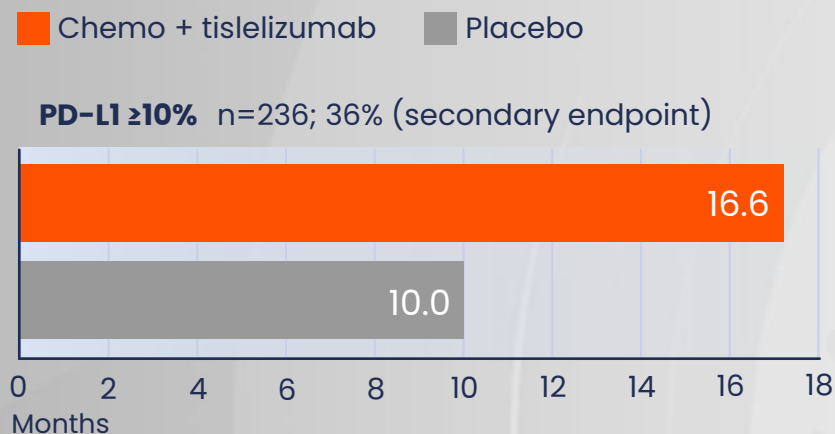
34% reduced risk of death

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

38% reduced risk of progression

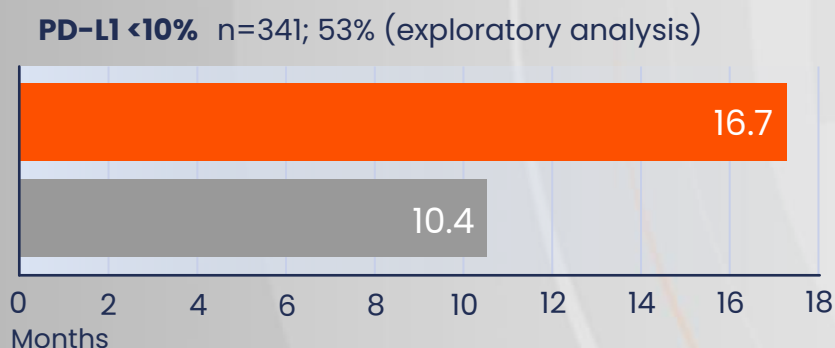
First-line tislelizumab + chemo achieved a statistically significant mOS benefit compared with placebo + chemo

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

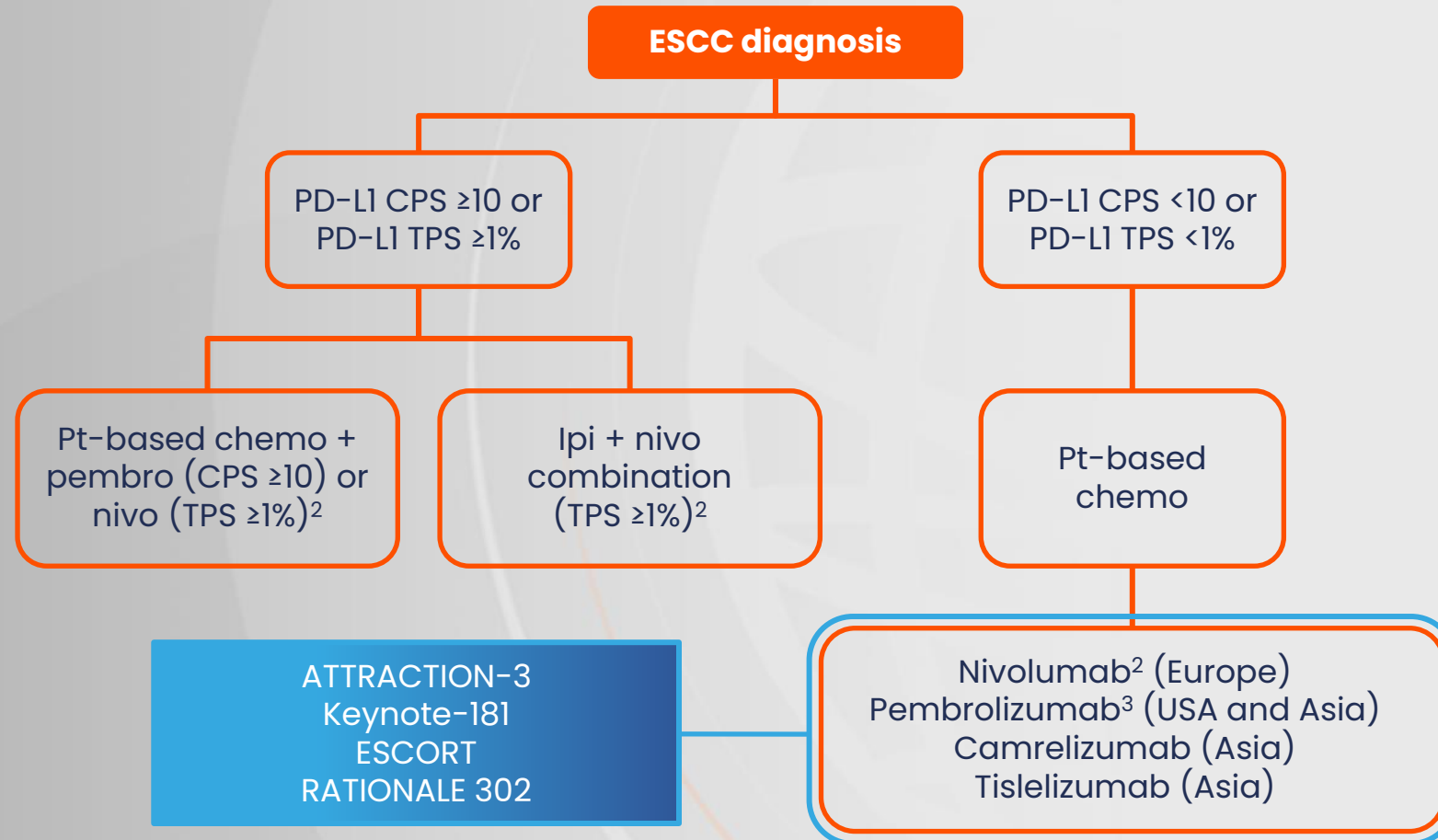
RATIONALE 306: Safety outcomes

Most common TRAEs, %
(incidence $\geq 20\%$)

	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

New standards for care with checkpoint inhibitors: Second line¹



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



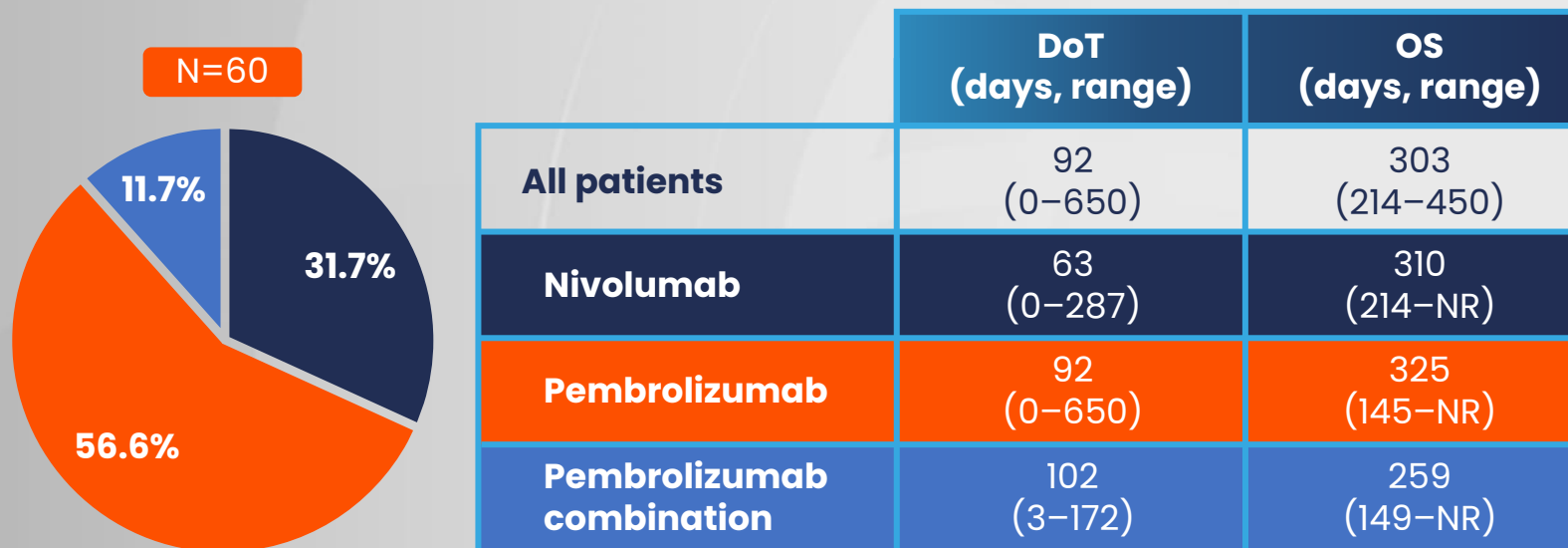
- Advanced or metastatic ESCC
- Initiated an anti-PD-1 second-line therapy between 1 January 2011 and 28 February 2021

N=60

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

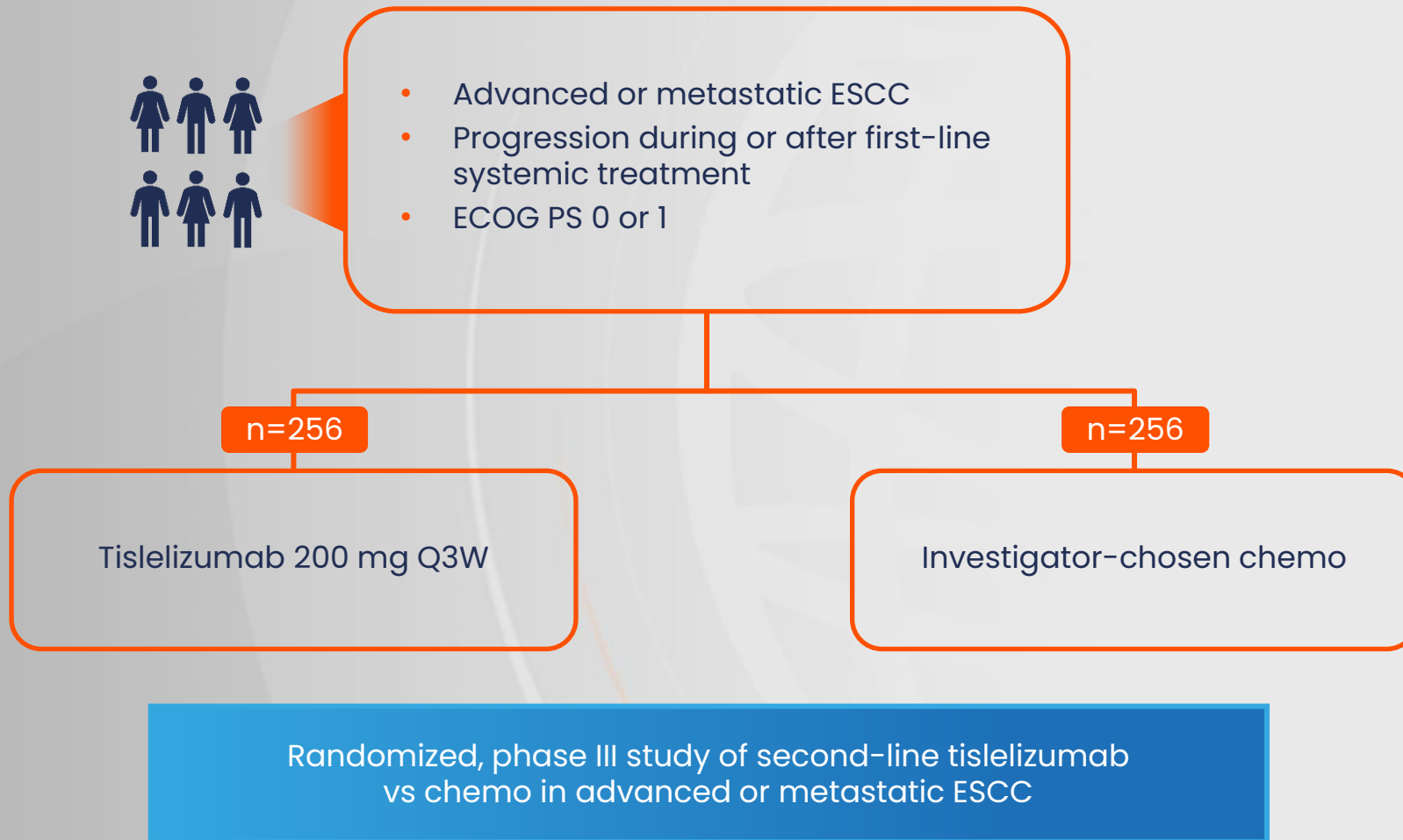
Electronic health record-derived database analysis

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



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

RATIONALE 302 health-related quality of life: Study design^{1,2}



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)

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

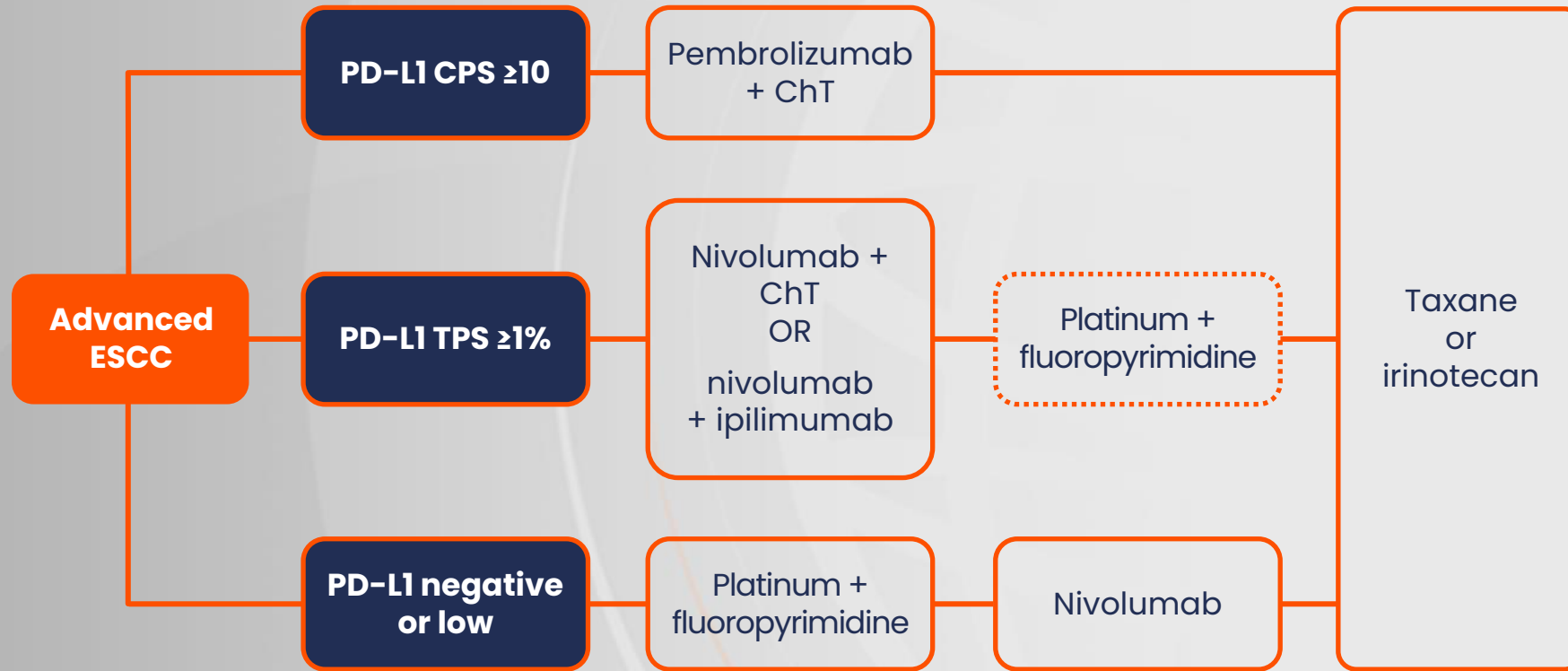
Real-world and health-related QoL findings support anti-PD-1 use

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



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Treatment algorithm for advanced ESCC



First-line chemotherapy for ESCC

Advanced ESCC¹

PD-L1 negative
or low

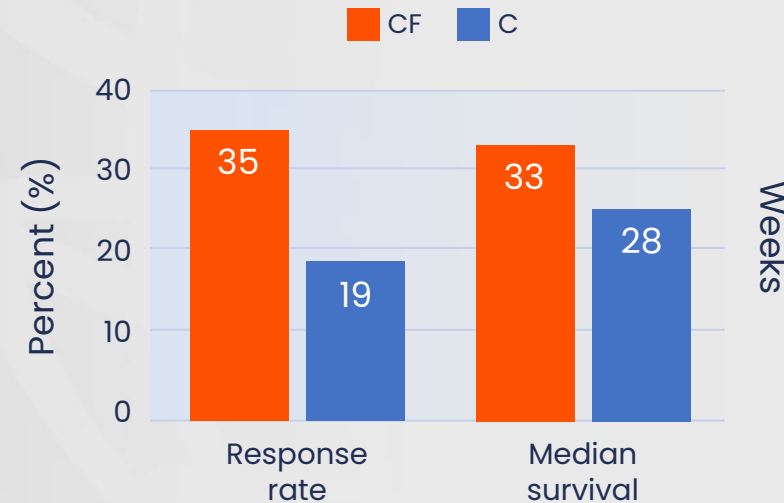
Platinum +
fluoropyrimidine

JCOG9407: Phase II study of
cisplatin + 5-FU²

Phase II study of cisplatin
+ 5-FU vs cisplatin alone³

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

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



First-line immune checkpoint inhibitors ± chemotherapy for ESCC

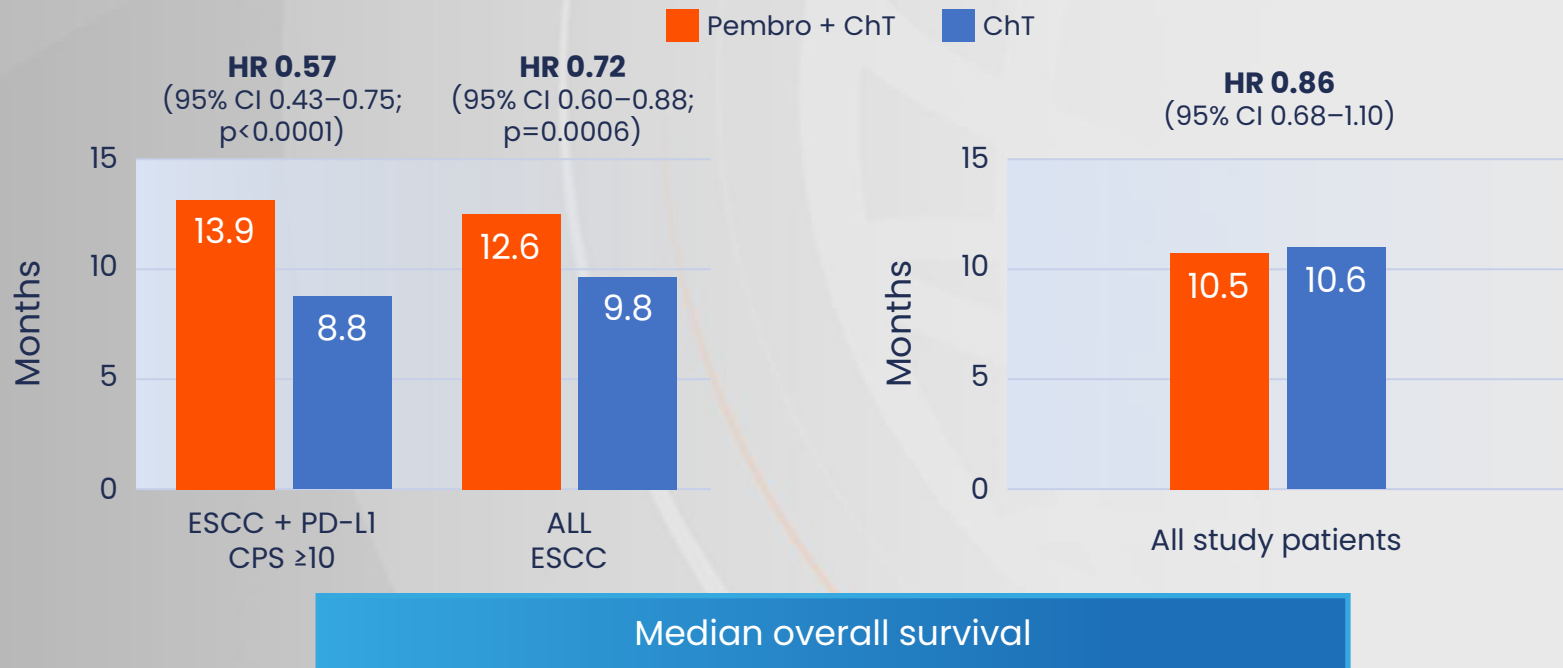
Advanced ESCC¹

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 [†]



*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.

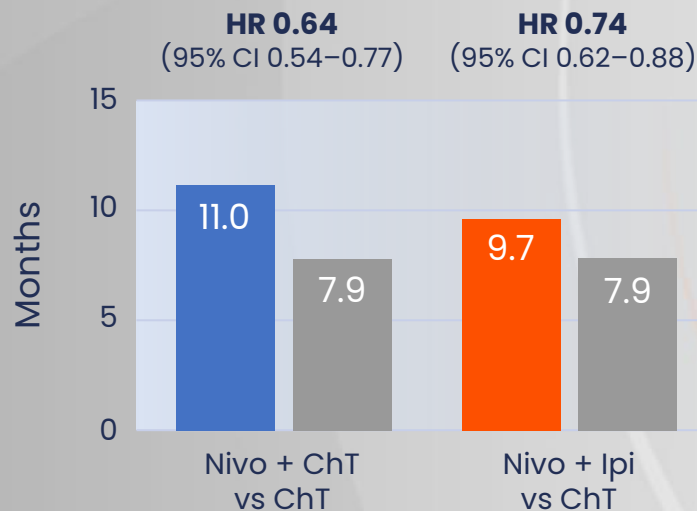
First-line immune checkpoint inhibitors ± chemotherapy for ESCC

Advanced ESCC¹

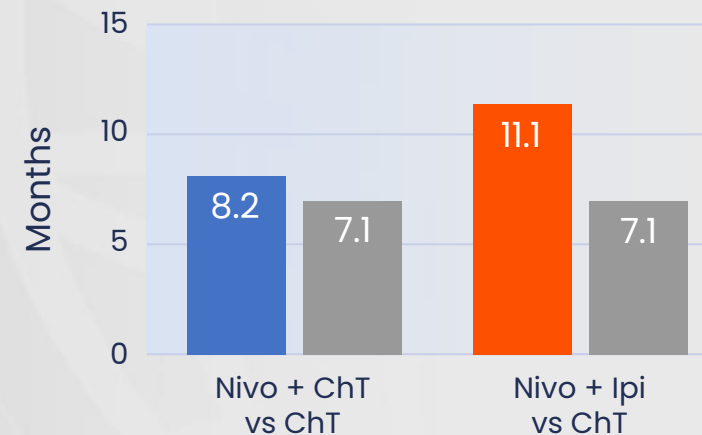
PD-L1 TPS ≥1%

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.

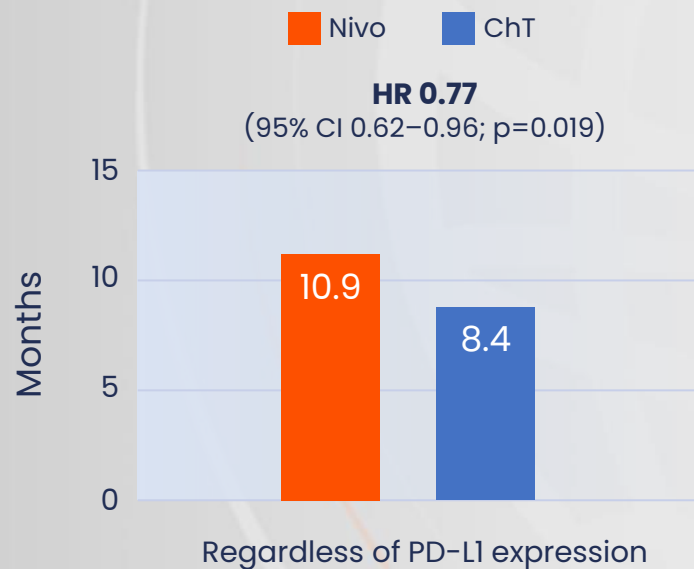
CI, confidence interval; ChT, chemotherapy; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; Ipi, ipilimumab; Nivo, nivolumab; PD-L1, programmed death-ligand 1; TPS, tumour positivity score.

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.

Second and subsequent lines of treatment for ESCC¹

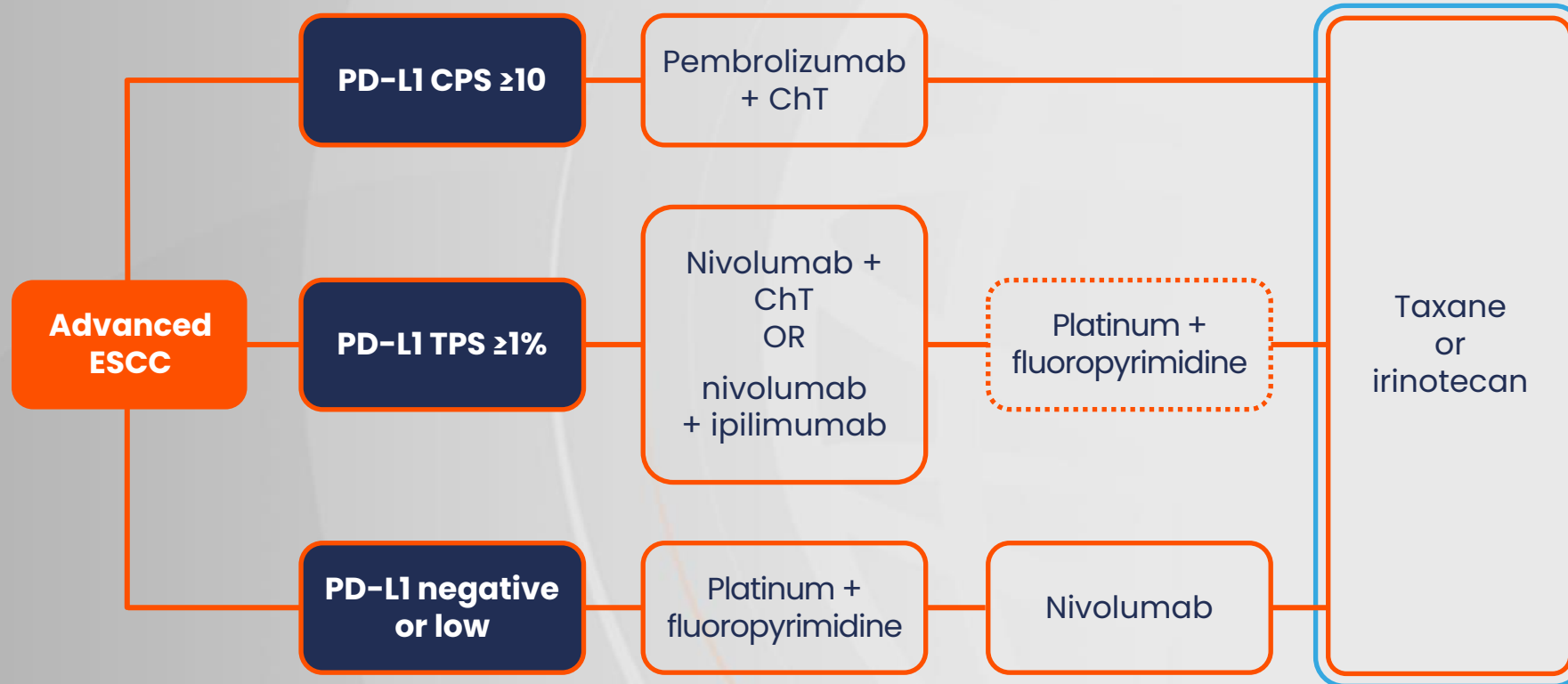


ATTRACTION-3: Phase III study of nivolumab vs chemotherapy following refractory disease or intolerance to previous chemotherapy²

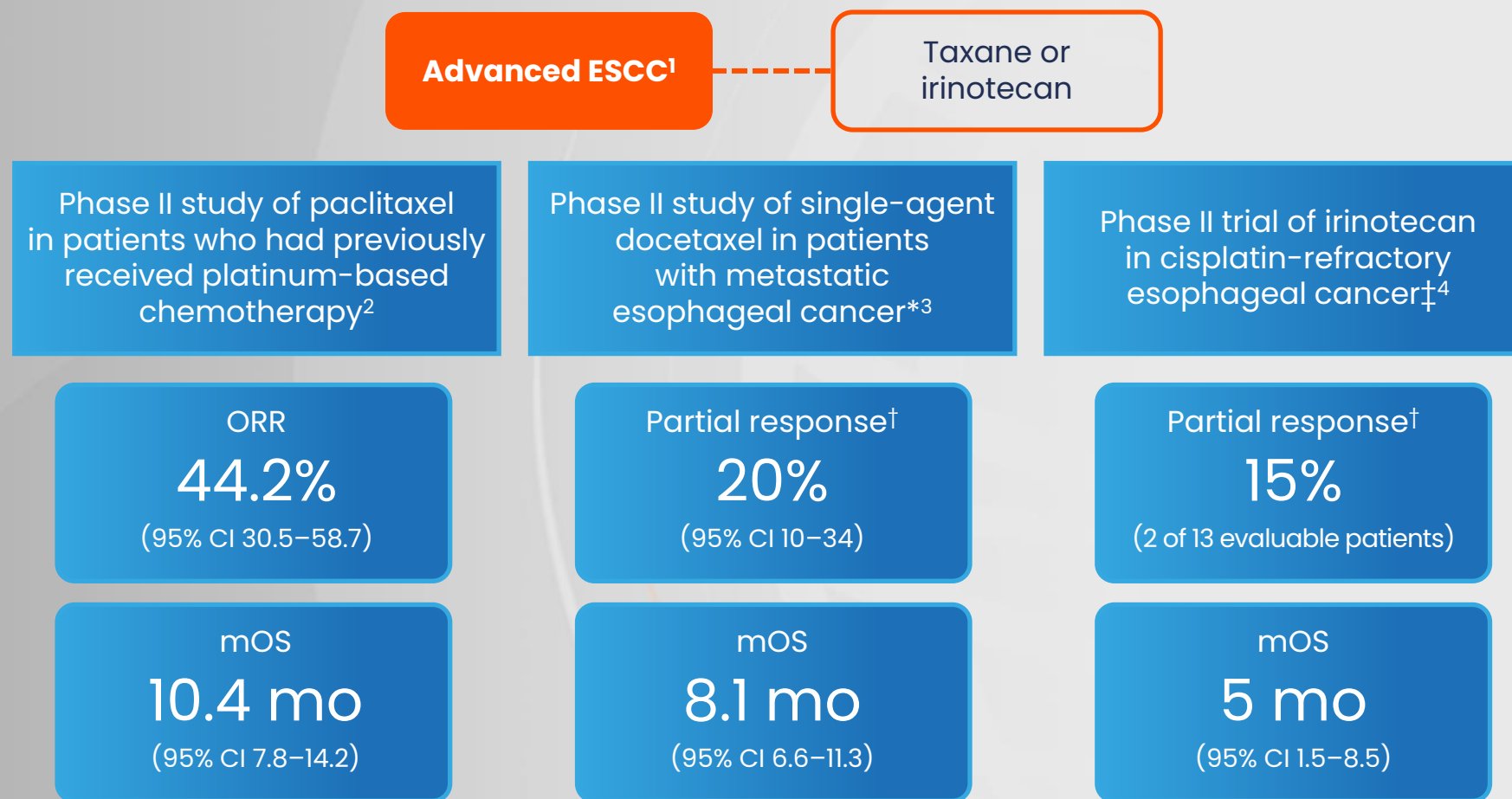


Median overall survival

Second and subsequent lines of treatment for ESCC



Second and subsequent lines of treatment for ESCC



*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 $\geq 1\%$

Summary: 2022 ESMO Clinical Practice Guideline

Second and subsequent lines of treatment for advanced ESCC¹

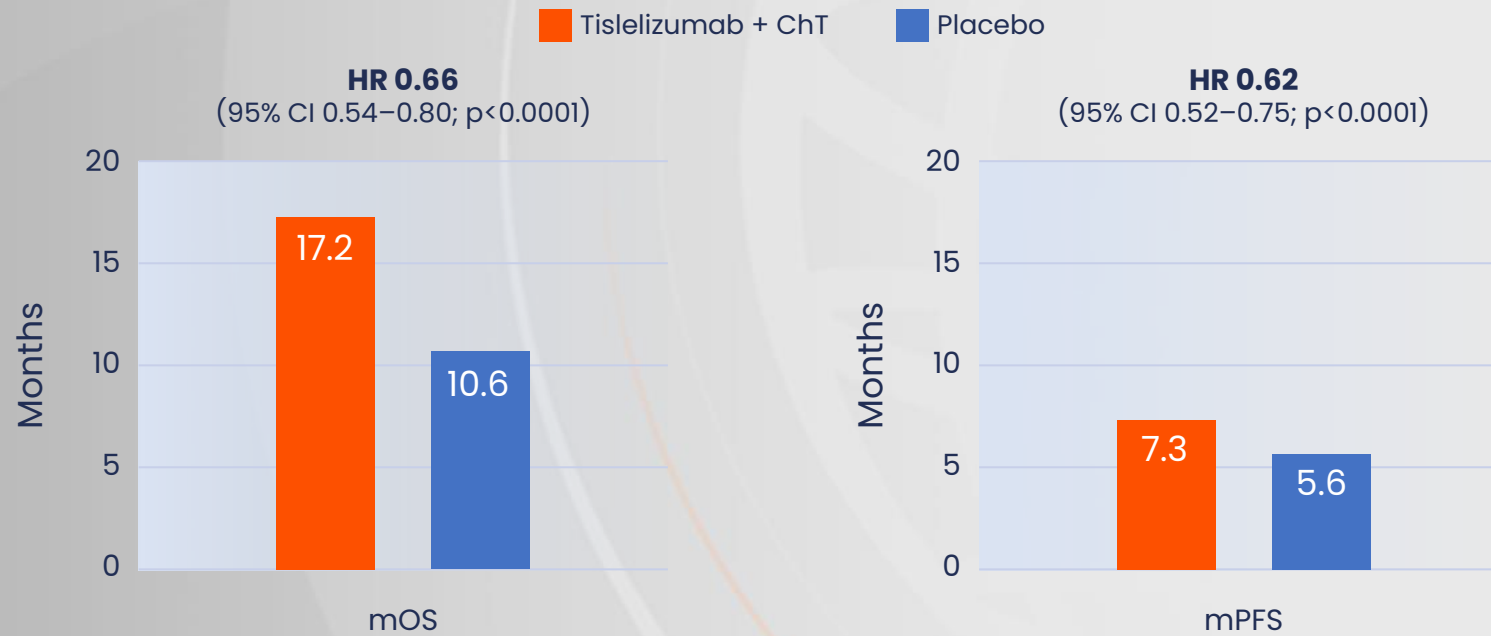
- Nivolumab is recommended for ESCC previously treated with platinum + fluoropyrimidine chemotherapy
- Where approved, pembrolizumab may be an option for patients with previously treated ESCC who have not received first-line treatment with immune checkpoint inhibitors and have a PD-L1 CPS ≥ 10
- Chemotherapy 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 patients²

- Chemotherapy may be avoided in selected patients, but careful counselling is needed to elaborate the risk of lower response and early progression²

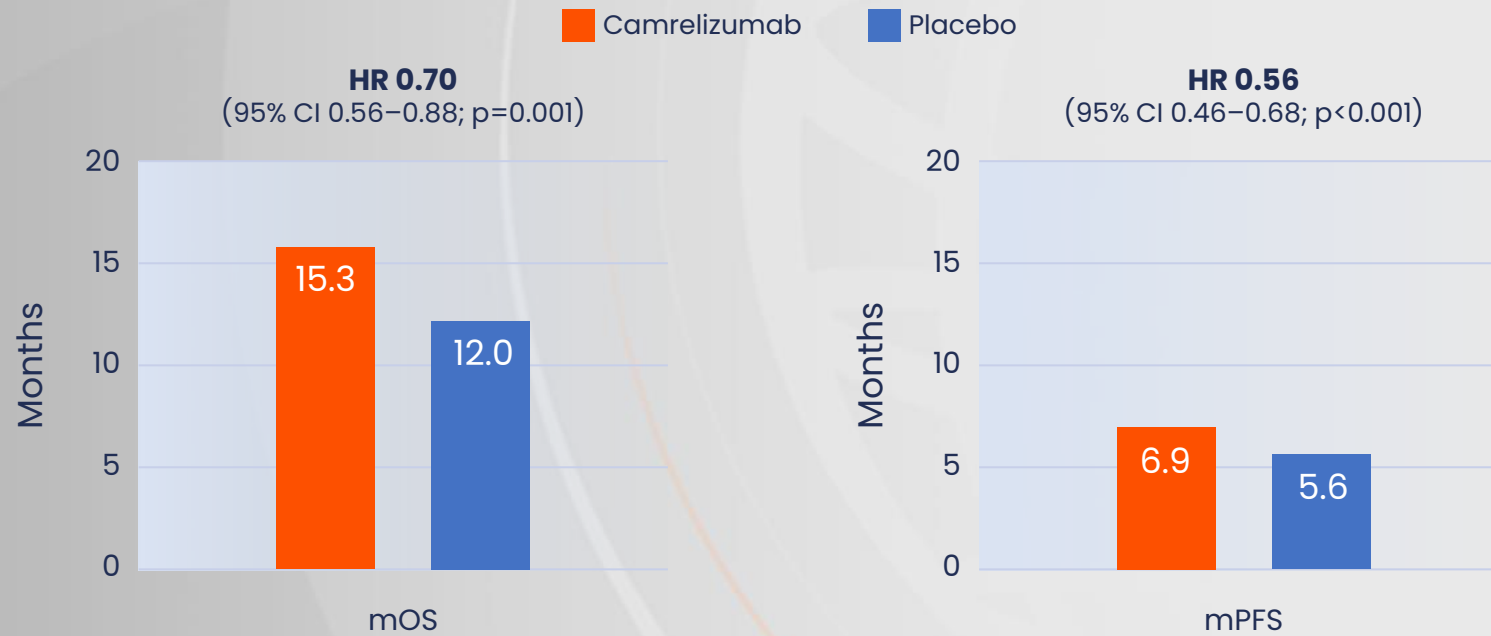
Potential change to standard of care in ESCC: First-line

RATIONALE-306: First-line tislelizumab + chemotherapy achieved a statistically significant OS and PFS benefit compared with placebo + chemotherapy¹



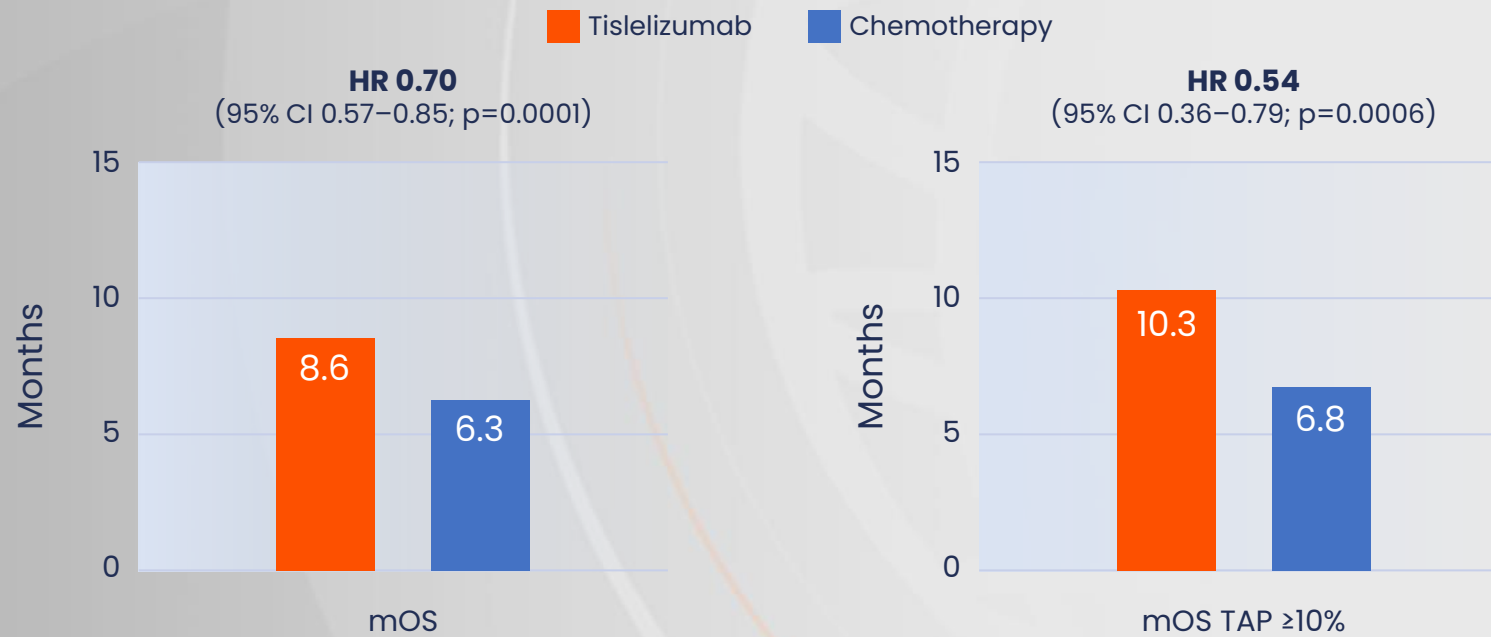
Potential change to standard of care in ESCC: First-line

ESCORT-1st: Camrelizumab + chemotherapy provided superior OS and PFS vs placebo + chemotherapy^{1,2}



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



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 + chemotherapy¹
- **ESCORT-1st:** Camrelizumab + chemotherapy provided superior OS and PFS vs placebo + chemotherapy²

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 ESCC³

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



Dr Elizabeth Smyth
Clinical Consultant
Gastrointestinal Oncology
Addenbrooke's Hospital
Cambridge, UK

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

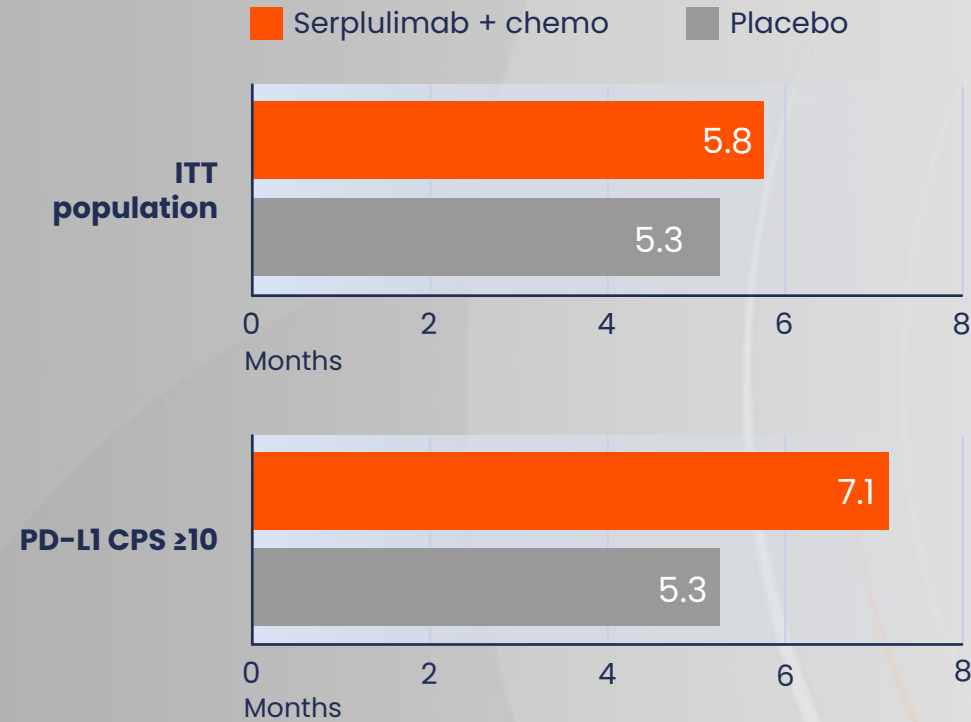
Serplulimab 3 mg/kg
+ cisplatin 5-FU

n=183

Placebo +
cisplatin 5-FU

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

ASTRUM-007: Median PFS (final analysis)^{1,2}



HR 0.60
(95% CI 0.48–0.75; p<0.0001)

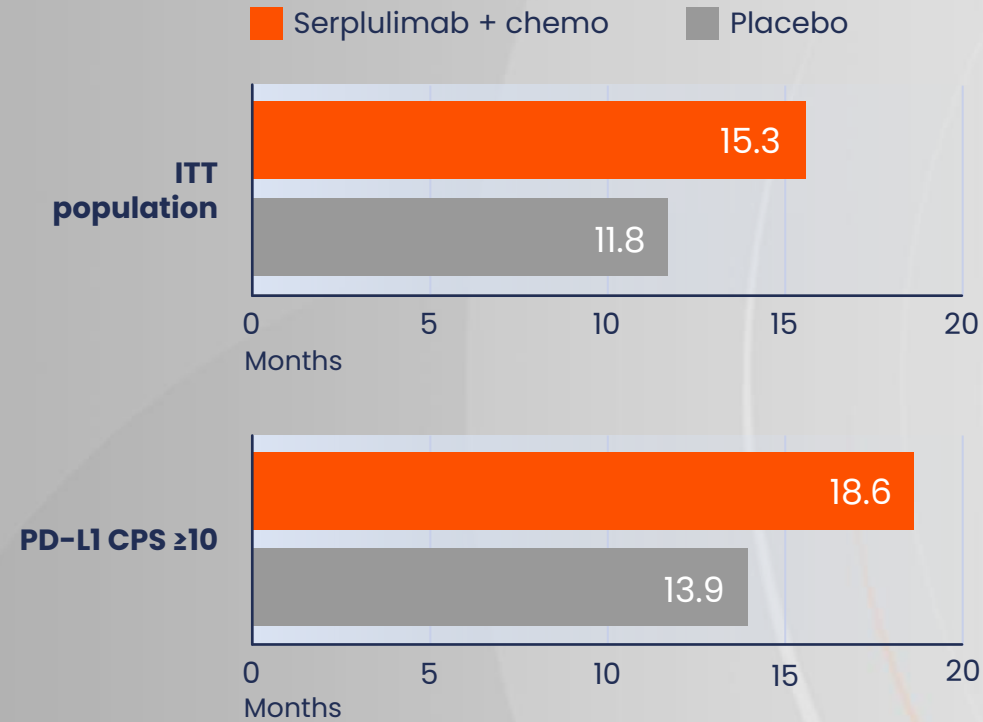
40% reduced risk of progression

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

ASTRUM-007: Median OS (interim analysis)^{1,2}



HR 0.68
(95% CI 0.53–0.87; p=0.0020)

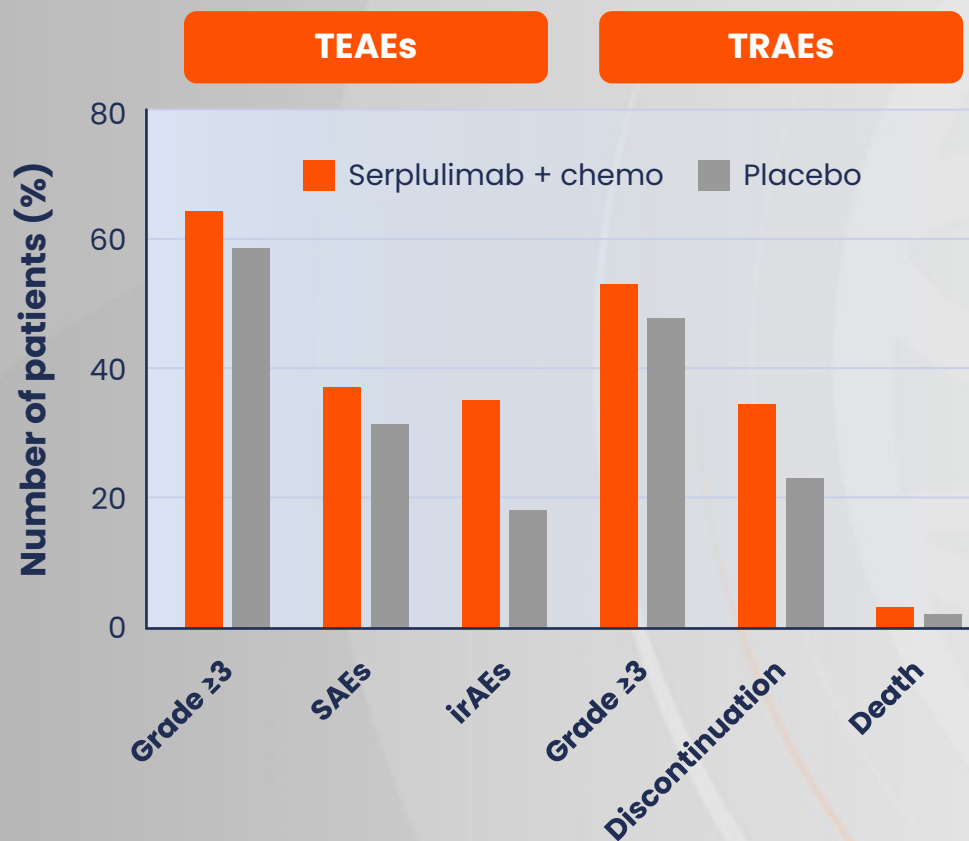
32% reduced risk of death

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

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 ESCC³

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

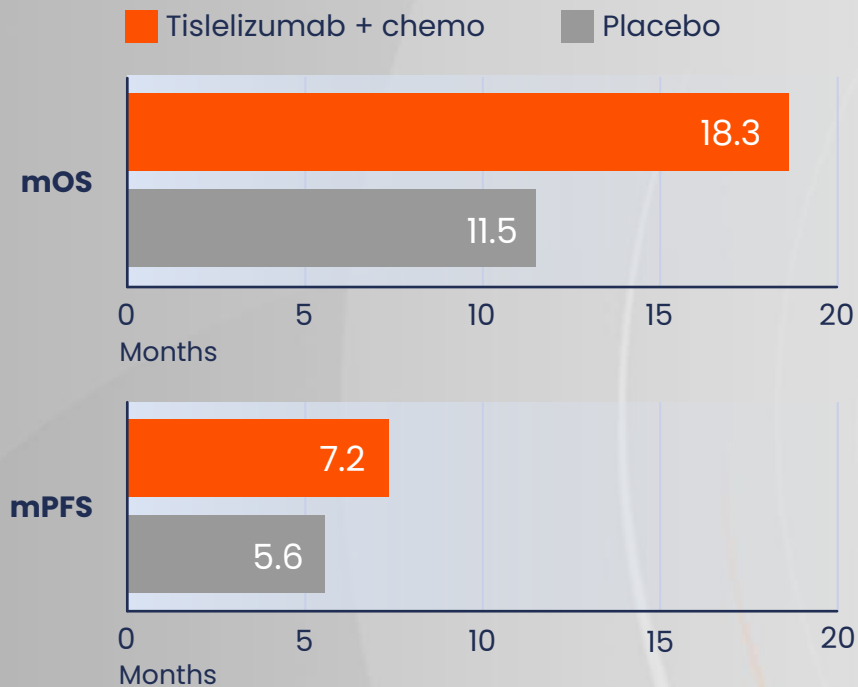
Pt-doublet chemo arms
comprised Cis-Pt or Ox-Pt plus
fluoropyrimidine or paclitaxel

n=243

PBO Q3W +
Pt-doublet chemo

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

RATIONALE-306 Asia subgroup: Median survival outcomes^{1,2}



HR 0.67
(95% CI 0.54–0.84)

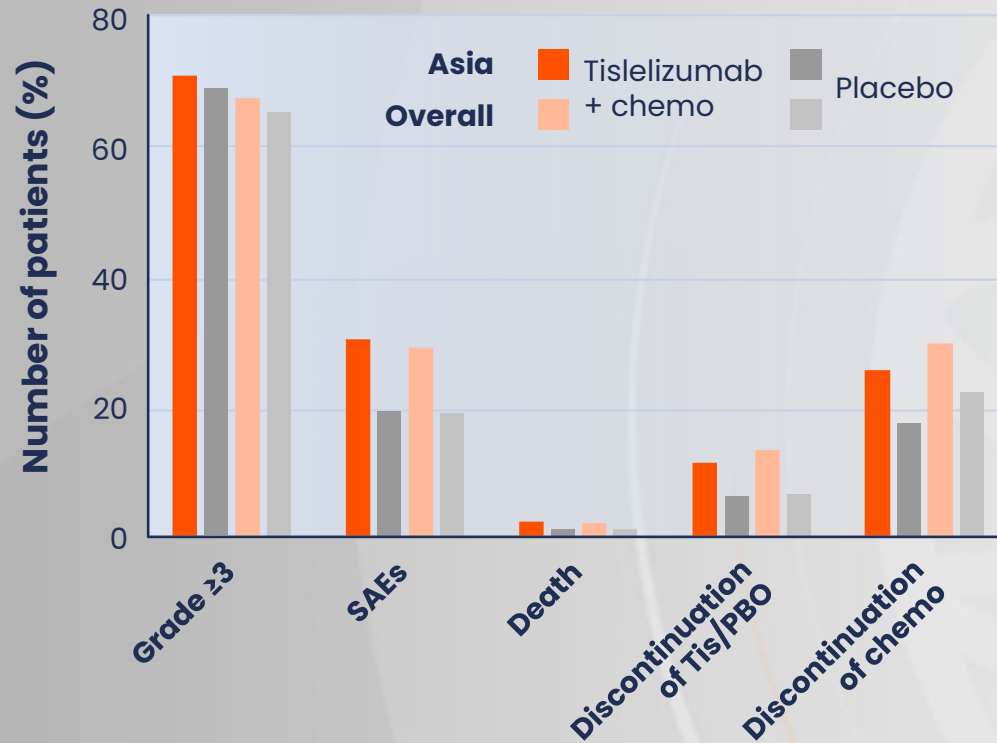
33% reduced risk of death

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

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

RATIONALE-306: Study design^{1,2}



n=163

- 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=83

Tis 200 mg Q3W +
Pt-doublet chemo

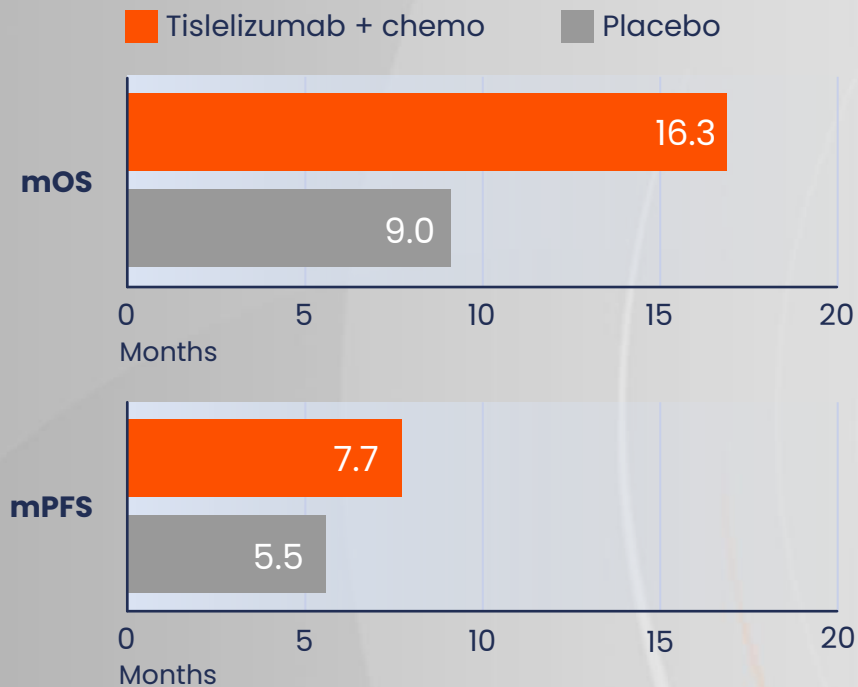
Pt-doublet chemo arms
comprised Cis-Pt or Ox-Pt plus
fluoropyrimidine or paclitaxel

n=80

PBO Q3W +
Pt-doublet chemo

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

RATIONALE-306 non-Asia subgroup: Median survival outcomes^{1,2}



HR 0.66
(95% CI 0.45–0.96)

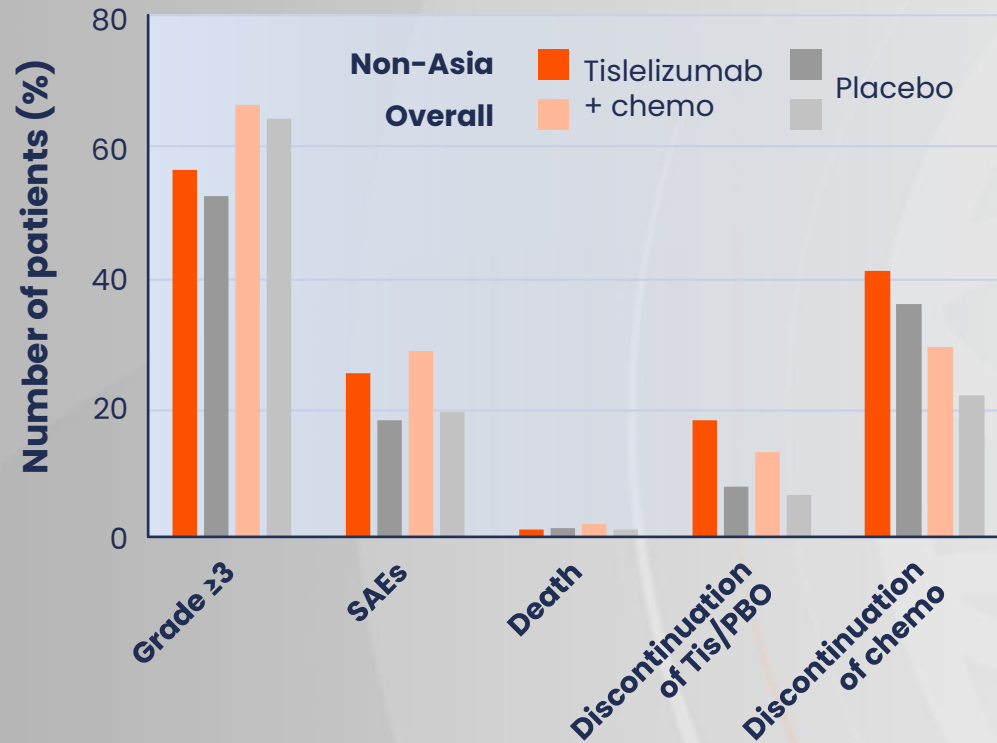
34% reduced risk of death

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

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

CheckMate 648: Study design¹⁻³



N=970

- Global, randomized, open-label phase III study
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0 or 1
- No prior systemic treatment for advanced disease
- Measurable disease

1:1:1

n=321

Nivo 240 mg Q2W +
chemo Q4W

n=325

Nivo 3 mg/kg Q2W +
Ipi 1 mg/kg Q6W

n=324

Chemo Q4W

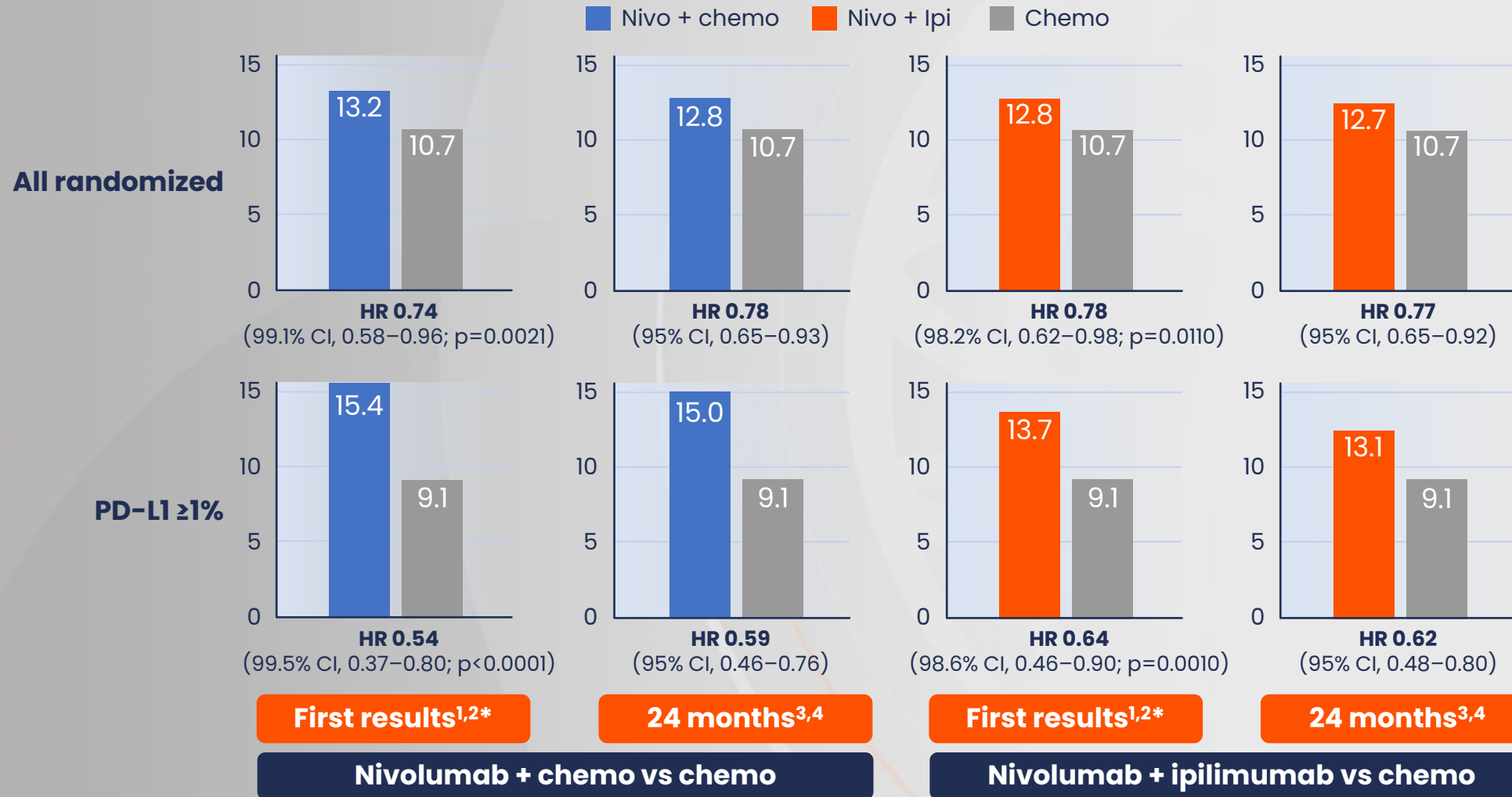
Nivolumab + chemotherapy or nivolumab + ipilimumab vs chemotherapy
as first-line treatment for advanced ESCC

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)



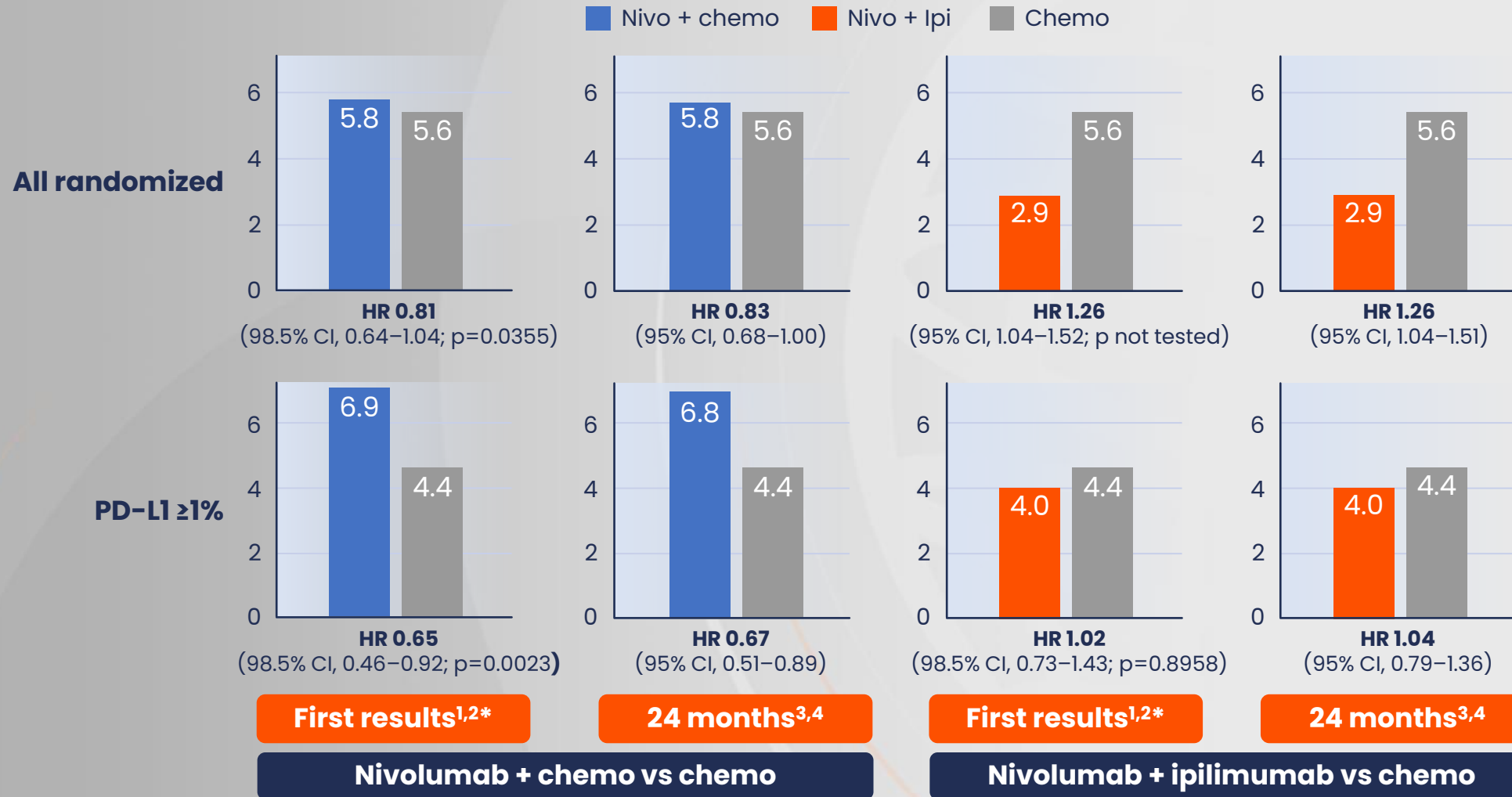
*Minimum follow-up 12.9 months.

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.

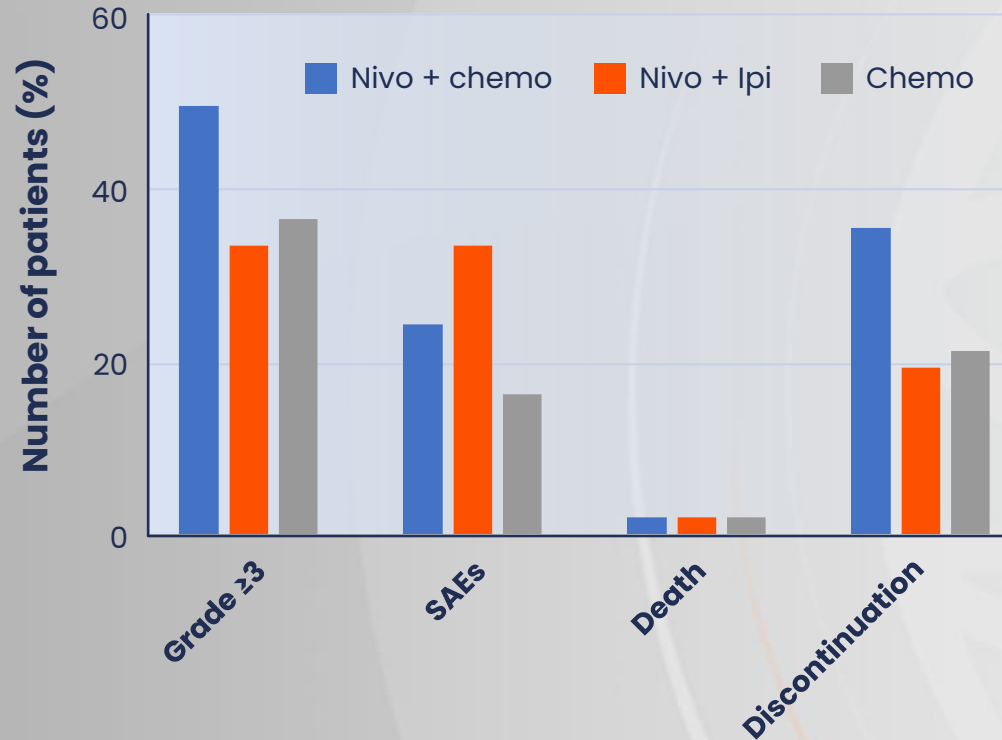
CheckMate 648 extended follow-up: mPFS (months)



*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.

CheckMate 648 extended follow-up: Safety outcomes^{1,2}

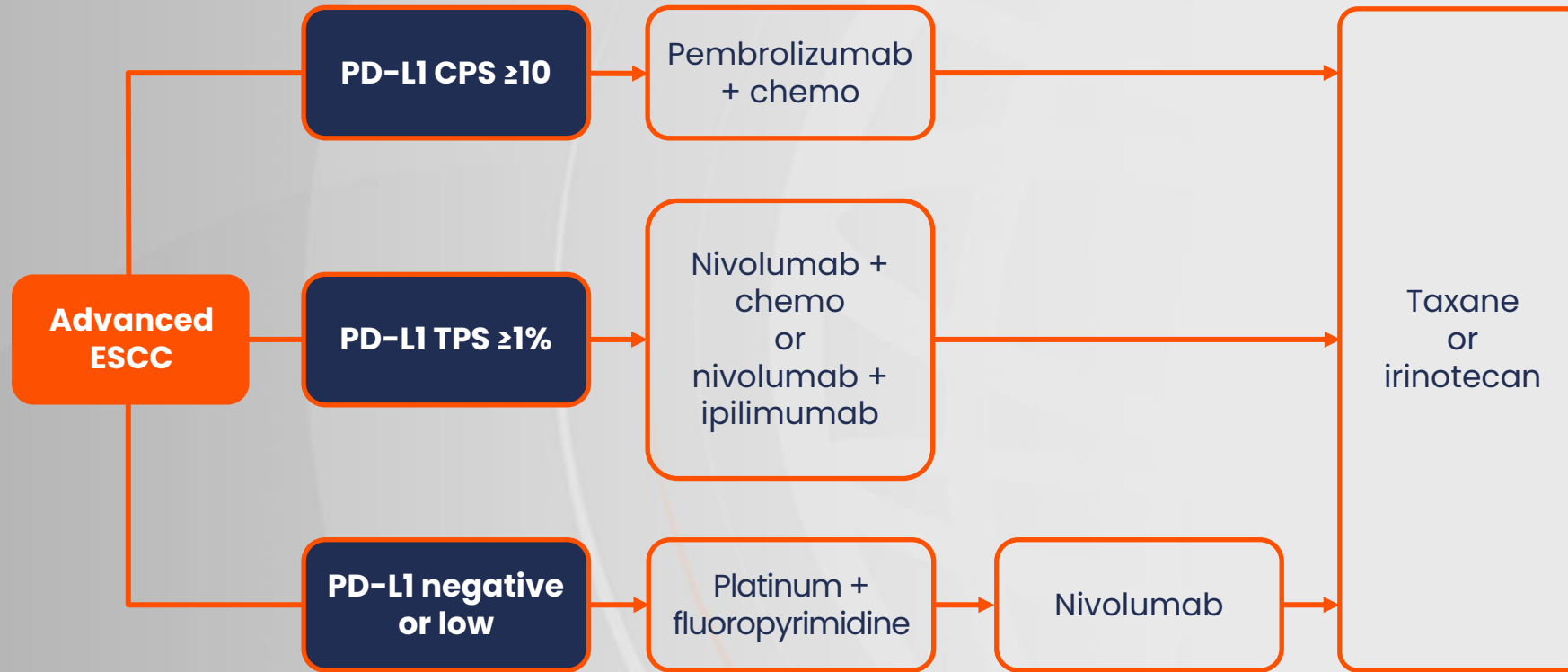


Most common any-grade TRAEs

- 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

Latest ESMO treatment algorithm for advanced ESCC



Summary: New and emerging treatment options

Anti-PD-1 mAb*	Adjuvant	First-line + chemo	Second-line mono
Nivolumab	<input checked="" type="checkbox"/> ¹	<input checked="" type="checkbox"/> ²	<input checked="" type="checkbox"/> ³
Pembrolizumab		<input checked="" type="checkbox"/> ⁴	
Sintilimab		<input checked="" type="checkbox"/> ⁵	
Toripalimab		<input checked="" type="checkbox"/> ⁶	
Camrelizumab		<input checked="" type="checkbox"/> ⁷	
Tislelizumab		<input checked="" type="checkbox"/> ⁸	<input checked="" type="checkbox"/> ⁹
Serplulimab		<input checked="" type="checkbox"/> 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.