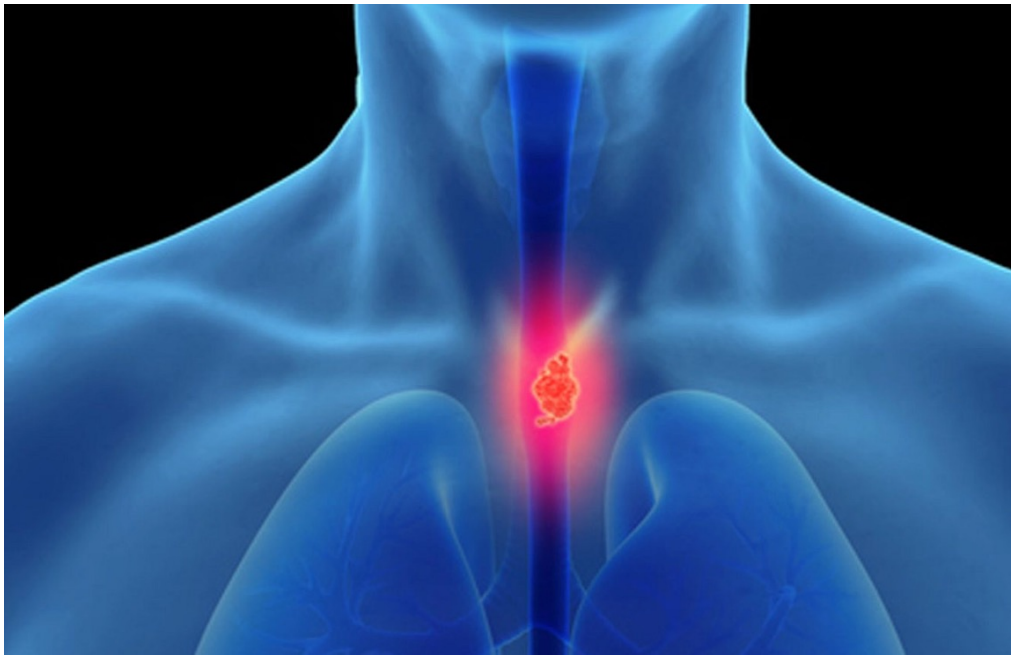

Treatment of Advanced Esophageal Cancer

Victor Hugo Fonseca de Jesus, MD, MSc
Medical oncologist

Grupo Oncoclínicas
Department of Gastrointestinal Medical Oncology
Florianópolis-SC

Centro de Pesquisas Oncológicas
Chair – Medical Oncology Department

Conflicts of interest

Advisory board	Honorarium	Consulting	Travel expenses	Research projects
MSD	BMS	Knight Medical	AstraZeneca	Astellas
Astellas	MSD	Bayer	Pfizer	
	Roche		Daiichi Sankyo	
	Pfizer			
	Sirtex			
	Merck			
	Daiichi Sankyo			
	Amgen			
	Servier			

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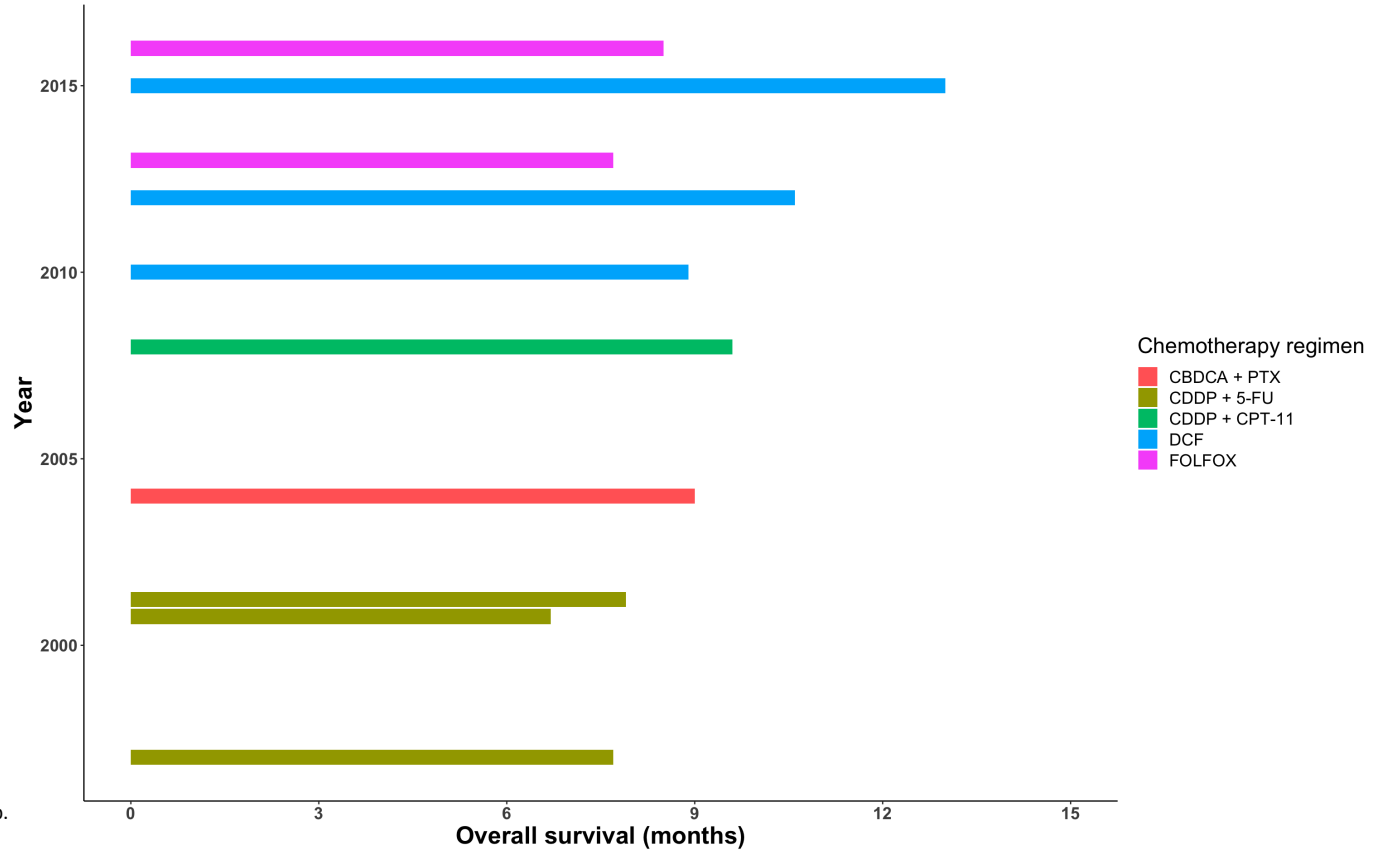
Advisory board	Honorarium	Consulting	Travel expenses	Research projects
MSD	**BMS**	Knight Medical	AstraZeneca	Astellas
Astellas	MSD	Bayer	Pfizer	
	Roche		Daiichi Sankyo	
	Pfizer			
	Sirtex			
	Merck			
	Daiichi Sankyo			
	Amgen			
	Servier			

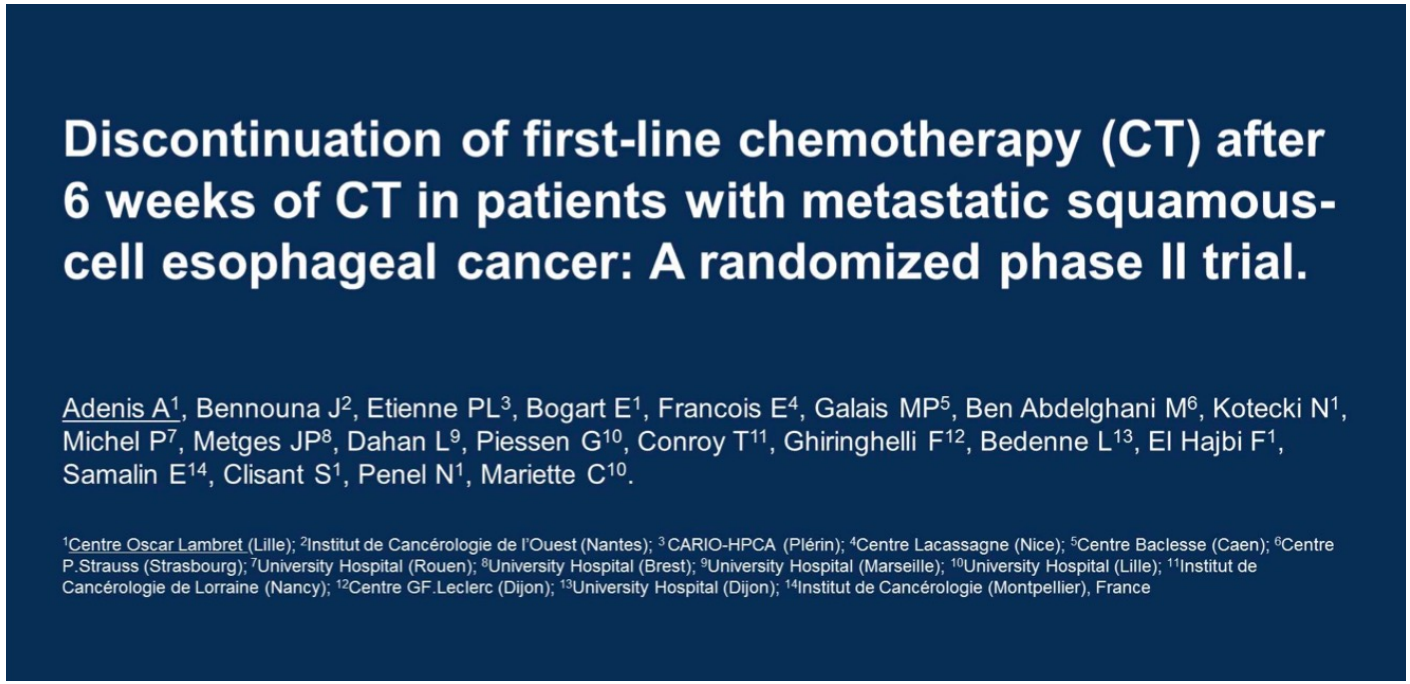
Systemic treatment of advanced EC

Limited role of systemic chemotherapy



1. Slide of presenter´s authorship.

Systemic treatment of advanced EC
Limited role of chemotherapy (E-DIS)



Discontinuation of first-line chemotherapy (CT) after 6 weeks of CT in patients with metastatic squamous-cell esophageal cancer: A randomized phase II trial.

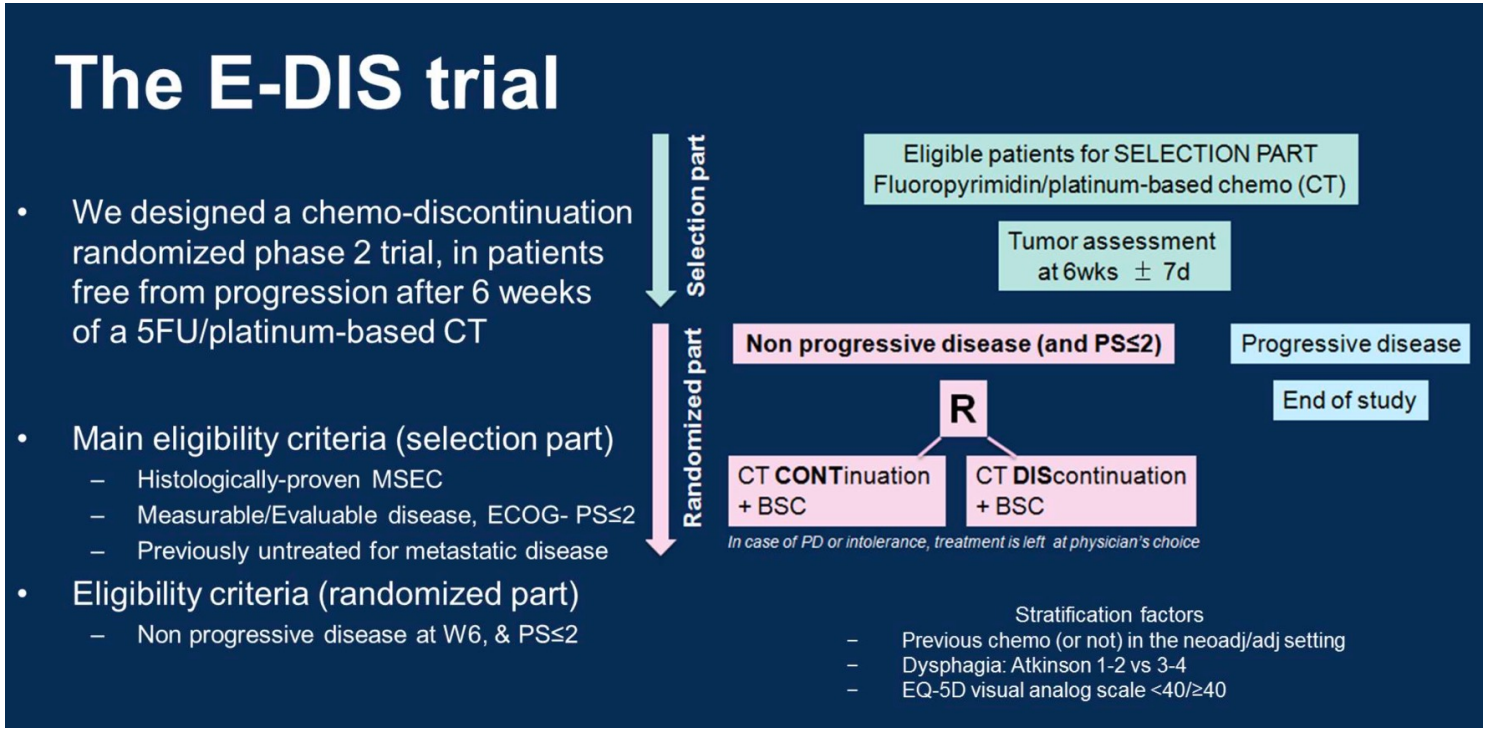
Adenis A[1], Bennouna J[2], Etienne PL[3], Bogart E[1], Francois E[4], Galais MP[5], Ben Abdelghani M[6], Kotecki N[1], Michel P[7], Metges JP[8], Dahan L[9], Piessen G[10], Conroy T[11], Ghiringhelli F[12], Bedenne L[13], El Hajbi F[1], Samalin E[14], Clisant S[1], Penel N[1], Mariette C[10].

[1]Centre Oscar Lambret (Lille); [2]Institut de Cancérologie de l'Ouest (Nantes); [3]CARIO-HPCA (Plérin); [4]Centre Lacassagne (Nice); [5]Centre Baclesse (Caen); [6]Centre P.Strauss (Strasbourg); [7]University Hospital (Rouen); [8]University Hospital (Brest); [9]University Hospital (Marseille); [10]University Hospital (Lille); [11]Institut de Cancérologie de Lorraine (Nancy); [12]Centre GF.Leclerc (Dijon); [13]University Hospital (Dijon); [14]Institut de Cancérologie (Montpellier), France

1. Adenis A, et al. J Clin Oncol 2016;34(suppl;abstr 4002).

Systemic treatment of advanced EC

Limited role of chemotherapy (E-DIS)



1. Adenis A, et al. J Clin Oncol 2016;34(suppl;abstr 4002).

Systemic treatment of advanced EC

Limited role of chemotherapy (E-DIS)

Results

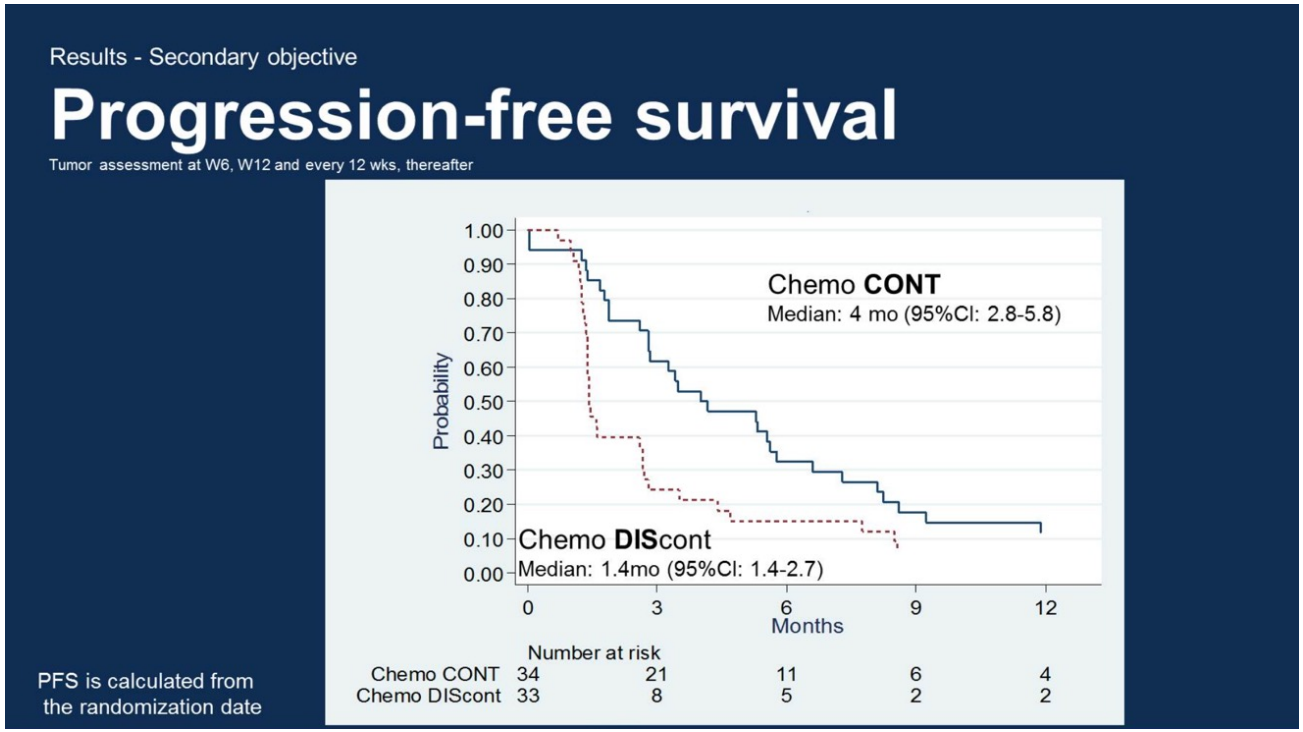
Study treatment

Chemo CONTinuation arm
Median number of cycles : 5 (1-20)
Mean (±SD) number of cycles: 7.2 (±5.3)

FU/platinum-based CT (Choice left to each physician's decision)	Selection part (Eligible & treated) n (%)	Chemo **CONT**inuation arm (Eligible & treated) n (%)
FU_{d1-4}-$CDDP_{d1}$, 4w	3/101 (3%)	0
$LVFU_{d1-2}$-$CDDP_{d1}$, 2w	18/101 (18%)	**7/31 (23%)**
FOLFOX, 2d/2w	76/101 (75%)	**24/31 (77%)**
$D_{d1}C_{d1}F_{d1-5}$, 3w	4/101 (4%)	0

1. Adenis A, et al. J Clin Oncol 2016;34(suppl;abstr 4002).

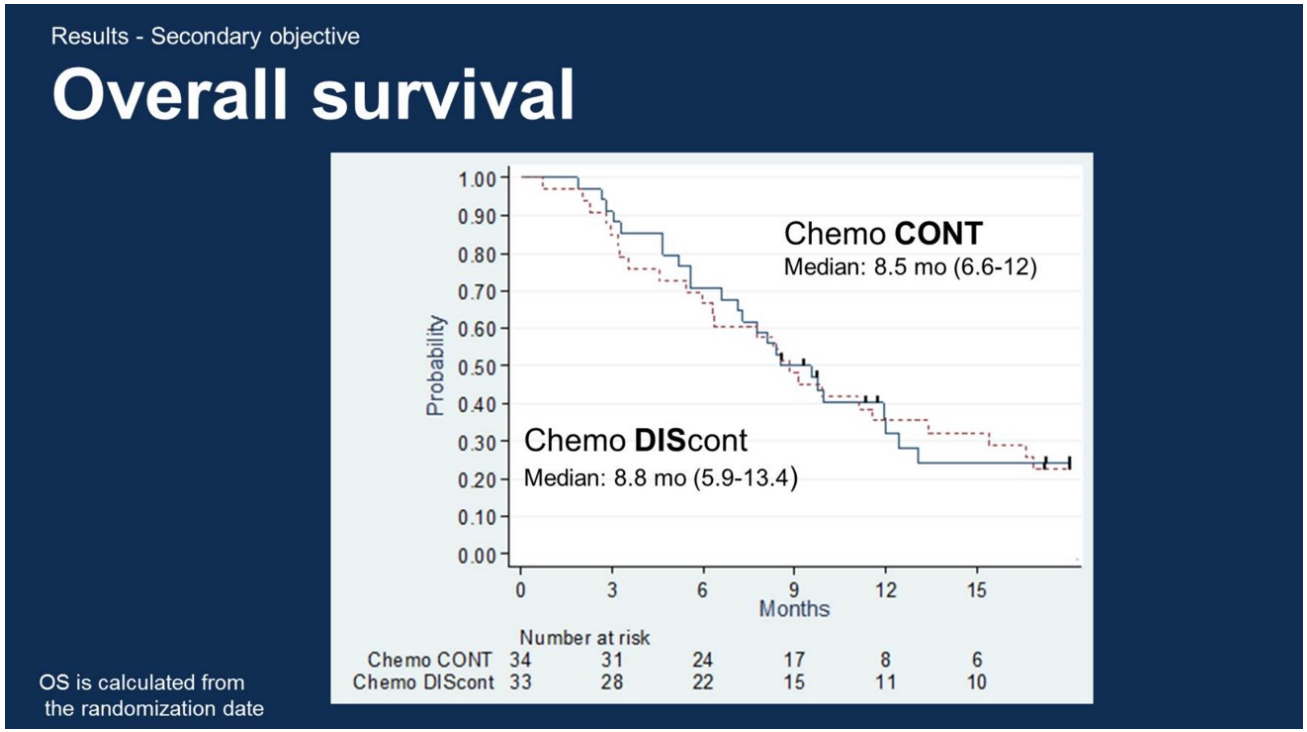
Systemic treatment of advanced EC
Limited role of chemotherapy (E-DIS)



1. Adenis A, et al. J Clin Oncol 2016;34(suppl;abstr 4002).

Systemic treatment of advanced EC

Limited role of chemotherapy (E-DIS)



1. Adenis A, et al. J Clin Oncol 2016;34(suppl;abstr 4002).

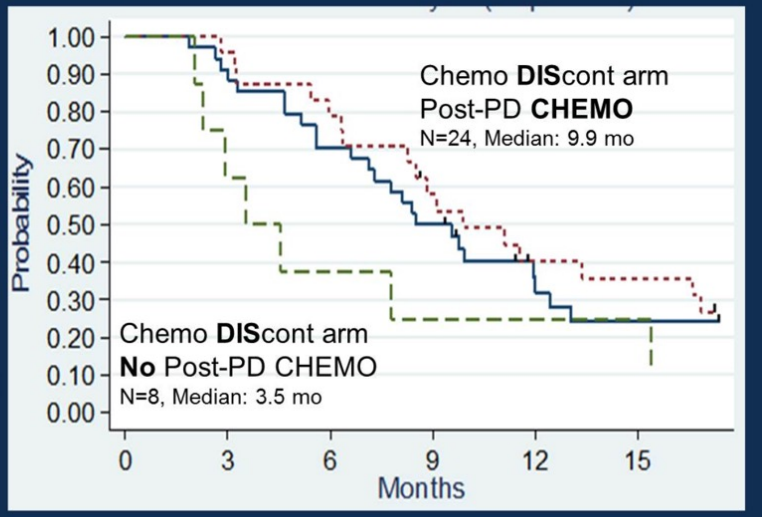
Systemic treatment of advanced EC

Limited role of chemotherapy (E-DIS)

Results

post hoc analysis

- 24/32 pts (missing data for 1 pt) in chemo **DIS**cont arm got some chemo as post progression treatment
- Consequently, as an unplaned, exploratory *post hoc* analysis, we split OS curves of pts from chemo **DIS**cont arm, according to whether or not they received post-progression chemo.



1. Adenis A, et al. J Clin Oncol 2016;34(suppl;abstr 4002).

Systemic treatment of advanced EC

Limited role of anti-EGFR mAb

original article

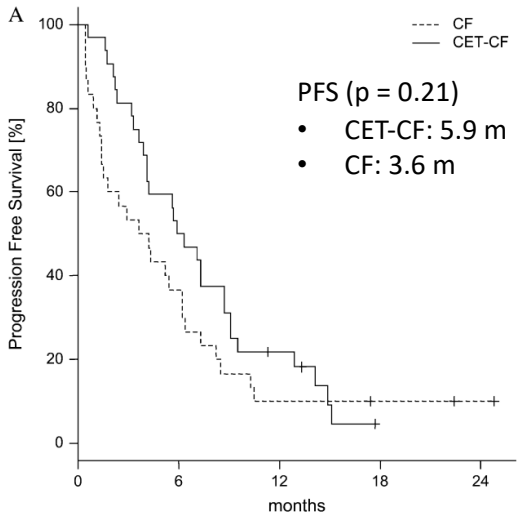
Annals of Oncology 20: 1667–1673, 2009
doi:10.1093/annonc/mdp069
Published online 23 June 2009

Cetuximab plus cisplatin–5-fluorouracil versus cisplatin–5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie

S. Lorenzen[1], T. Schuster[2], R. Porschen[3], S.-E. Al-Batran[4], R. Hofheinz[5], P. Thuss-Patience[6], M. Moehler[7], P. Grabowski[8], D. Arnold[9], T. Greten[10], L. Müller[11], N. Röthling[12], C. Peschel[1], R. Langer[13] & F. Lordick[14]*

[1]*Third Department of Internal Medicine (Hematology/Medical Oncology);* [2]*Department of Medical Statistics and Epidemiology, Technical University of Munich, Munich;* [3]*Department of Medicine, Hospital Bremen-Ost, Bremen;* [4]*Department of Hematology and Oncology, Krankenhaus Nordwest, Frankfurt am Main;* [5]*Department of Medicine III, University Hospital Mannheim, Mannheim;* [6]*Department of Hematology and Oncology, Charite, Medical University, Berlin;* [7]*First Medical Department, Johannes Gutenberg-University Mainz, Mainz;* [8]*Charite, Campus Benjamin Franklin, Berlin;* [9]*Department of Internal Medicine IV, Martin-Luther-University, Halle;* [10]*Department of Gastroenterology, Hepatology and Endocrinology, Center for Internal Medicine, Medical School of Hannover, Hannover;* [11]*Oncological main focus-practice Leer-Emden;* [12]*Munich Center for Clinical Studies, Munich;* [13]*Department of Pathology, Technical University of Munich, Munich and* [14]*National Center for Tumor Diseases, University of Heidelberg, Germany*

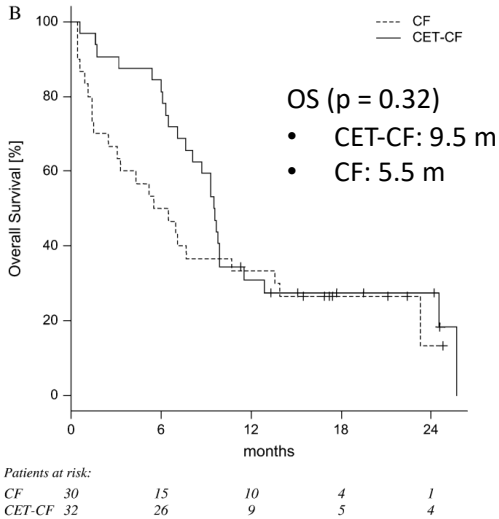
Progression-free survival



PFS (p = 0.21)

- CET-CF: 5.9 m
- CF: 3.6 m

Overall survival



OS (p = 0.32)

- CET-CF: 9.5 m
- CF: 5.5 m

Figure 2. Kaplan–Meier plots for progression-free survival (**A**) and overall survival (**B**) in the cetuximab, cisplatin and fluorouracil (CET–CF) and cisplatin and fluorouracil (CF) arm.

1. Lorenzen S, et al. Ann Oncol 2009;20:1667-1673.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

Nivolumab plus ipilimumab or nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced esophageal squamous cell carcinoma: first results of the CheckMate 648 study

Ian Chau,[1] Yuichiro Doki,[2] Jaffer A. Ajani,[3] Jianming Xu,[4] Lucjan Wyrwicz,[5] Satoru Motoyama,[6] Takashi Ogata,[7] Hisato Kawakami,[8] Chih-Hung Hsu,[9] Antoine Adenis,[10] Farid el Hajbi,[11] Maria Di Bartolomeo,[12] Maria Ignez Braghiroli,[13] Eva Holtved,[14] Ioannis Xynos,[15] Xuan Liu,[15] Ming Lei,[15] Kaoru Kondo,[15] Ken Kato,[16] Yuko Kitagawa[17]

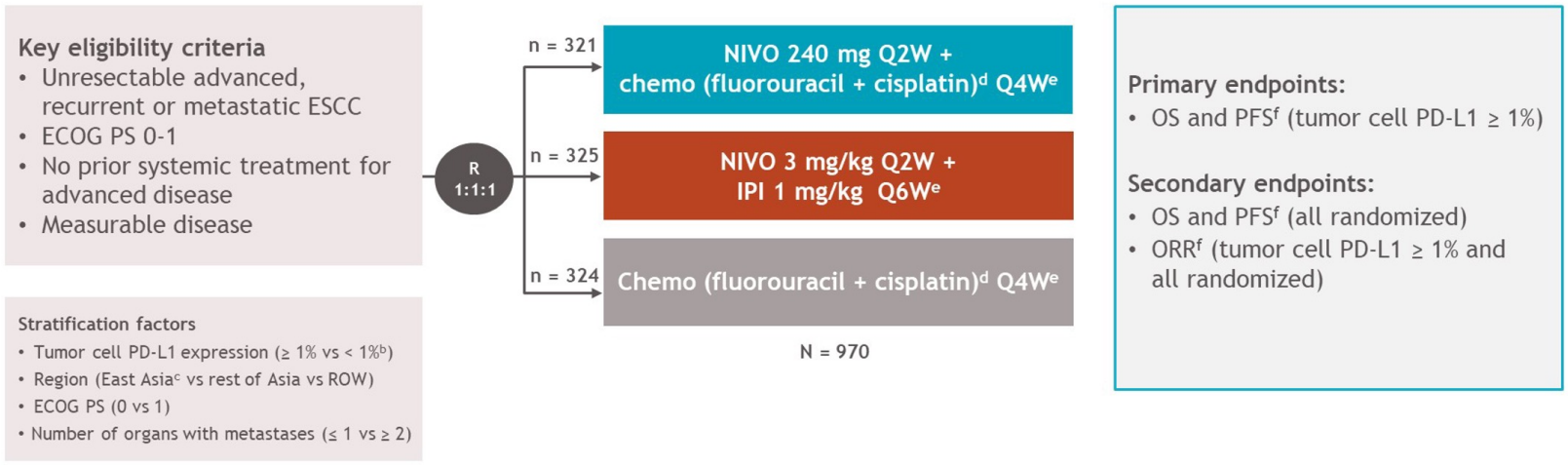
[1]Royal Marsden Hospital, London & Surrey, UK; [2]Osaka University Graduate School of Medicine, Osaka, Japan; [3]The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Affiliated Hospital Cancer Center, Academy of Military Medical Sciences, Beijing, China; [5]Klinika Onkologii i Radioterapii, Narodowy Instytut Onkologii, Warszawa, Poland; [6]Akita University Hospital, Akita, Japan; [7]Kanagawa Cancer Center, Kanagawa, Japan; [8]Kindai University Faculty of Medicine, Osakasayama, Japan; [9]National Taiwan University Hospital, Taipei, Taiwan; [10]Institut du Cancer de Montpellier, Montpellier, France; [11]Centre Oscar Lambret, Lille, France; [12]Fondazione IRCCS Instituto Nazionale dei Tumori, Milan, Italy; [13]Institute of Cancer of São Paulo, University of São Paulo, São Paulo, Brazil; [14]Odense University Hospital, Odense, Denmark; [15]Bristol Myers Squibb, Princeton, NJ; [16]National Cancer Center Hospital, Tokyo, Japan; [17]Keio University School of Medicine, Tokyo, Japan

1. Chau I, et al. ASCO 2021.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

- CheckMate 648 is a global, randomized, open-label phase 3 study[a]



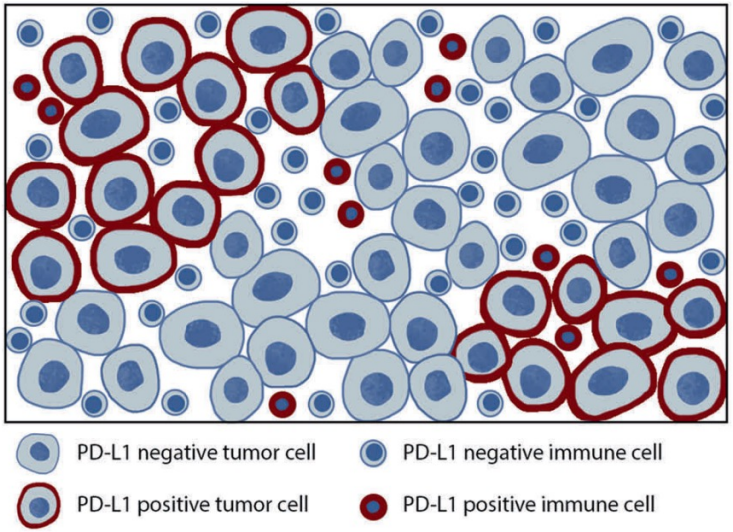
- At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months[g]

[a]ClinicalTrials.gov. NCT03143153; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]East Asia includes patients from Japan, Korea, and Taiwan; [d]Fluorouracil 800 mg/m^2 IV daily (days 1-5) and cisplatin 80 mg/m^2 IV (day 1); [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + IPI or NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given alone or in combination with IPI for a maximum of 2 years; [f]Per blinded independent central review (BICR); [g]Time from last patient randomized to clinical data cutoff.

1. Chau I, et al. ASCO 2021.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648



$$\text{TPS} = \frac{\text{No. PD-L1 positive tumor cells}}{\text{Total No. of viable tumor cells}} \times 100$$

$$\text{CPS} = \frac{\text{No. PD-L1 positive cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. of viable tumor cells}} \times 100$$

1. de Ruiter EJ, et al. Mod Pathol 2021;34:1125-32.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

Baseline characteristics

All randomized	NIVO + chemo (n = 321)	NIVO + IPI (n = 325)	Chemo (n = 324)[a]
Median age, years (range)	64 (40-90)	63 (28-81)	64 (26-81)
Male, %	79	83	85
Asian/non-Asian,[b] %	70/30	70/30	70/30
ECOG PS 1,[c] %	54	54	53
ESCC,[d] %	97	99	98
Tumor cell PD-L1 expression,[e] %			
≥ 1%	49	49	48
< 1%	51	51	52
Disease status at study entry, %			
De novo metastatic	57	60	58
Recurrent - locoregional	7	8	8
Recurrent - distant	22	22	19
Unresectable advanced	14	10	16
Number of organs with metastases[f]			
≤ 1	49	49	49
≥ 2	51	51	51
Current or former smoker, %	79	82	79

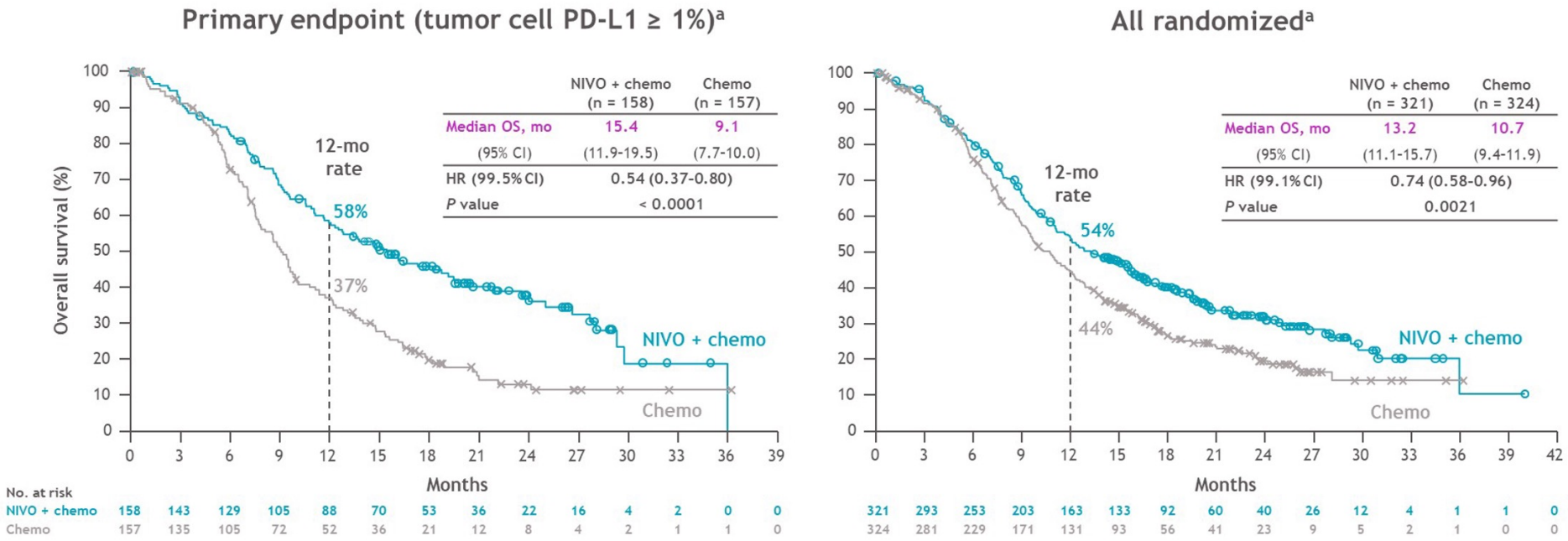
- Baseline characteristics were balanced across the 3 arms and were consistent with that of patients with tumor cell PD-L1 ≥ 1%

1. Chau I, et al. ASCO 2021.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

Overall survival: NIVO + chemo vs chemo



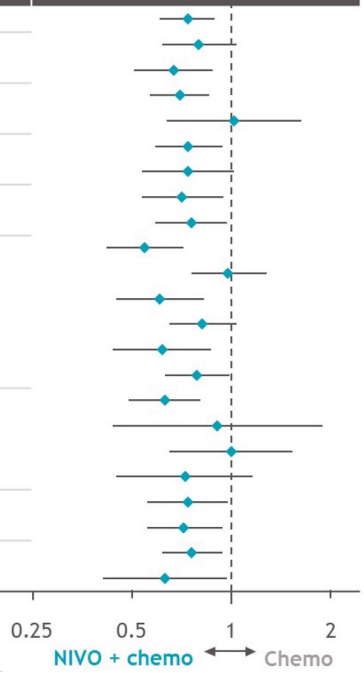
1. Chau I, et al. ASCO 2021.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

Overall survival subgroup analysis: NIVO + chemo vs chemo

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death
		NIVO + chemo	Chemo	
Overall (N = 645)		13.2	10.7	0.74
Age, years	< 65 (n = 333)	11.8	10.2	0.80
	≥ 65 (n = 312)	15.1	11.0	0.67
Sex	Male (n = 528)	12.5	10.0	0.70
	Female (n = 117)	15.2	14.8	1.02
Geographic region	Asian (n = 451)	15.5	11.9	0.74
	Non-Asian (n = 194)	10.5	8.5	0.74
ECOG PS[a]	0 (n = 300)	17.3	12.4	0.71
	1 (n = 344)	10.6	9.0	0.76
Tumor cell PD-L1 expression[b]	≥ 1% (n = 314)	15.4	9.2	0.55
	< 1% (n = 329)	12.0	12.2	0.98
	≥ 5% (n = 235)	13.7	9.5	0.61
	< 5% (n = 408)	12.8	11.1	0.82
	≥ 10% (n = 199)	14.7	9.5	0.62
	< 10% (n = 444)	12.3	10.8	0.79
Disease status at study entry	De novo metastatic (n = 371)	13.4	9.4	0.63
	Recurrent - locoregional (n = 46)	14.8	13.5	0.91
	Recurrent - distant (n = 132)	12.3	12.8	1.00
	Unresectable advanced (n = 96)	12.8	12.1	0.73
No. of organs with metastases	≤ 1 (n = 316)	15.7	11.6	0.74
	≥ 2 (n = 329)	11.1	9.6	0.72
Smoking	Current or former (n = 510)	12.3	10.0	0.76
	Never or unknown (n = 135)	15.7	11.1	0.63



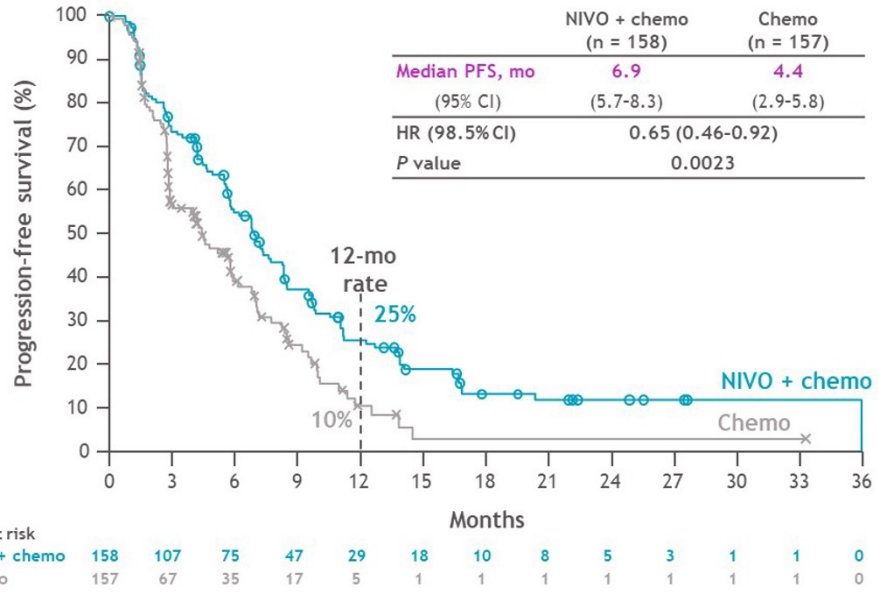
1. Chau I, et al. ASCO 2021.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

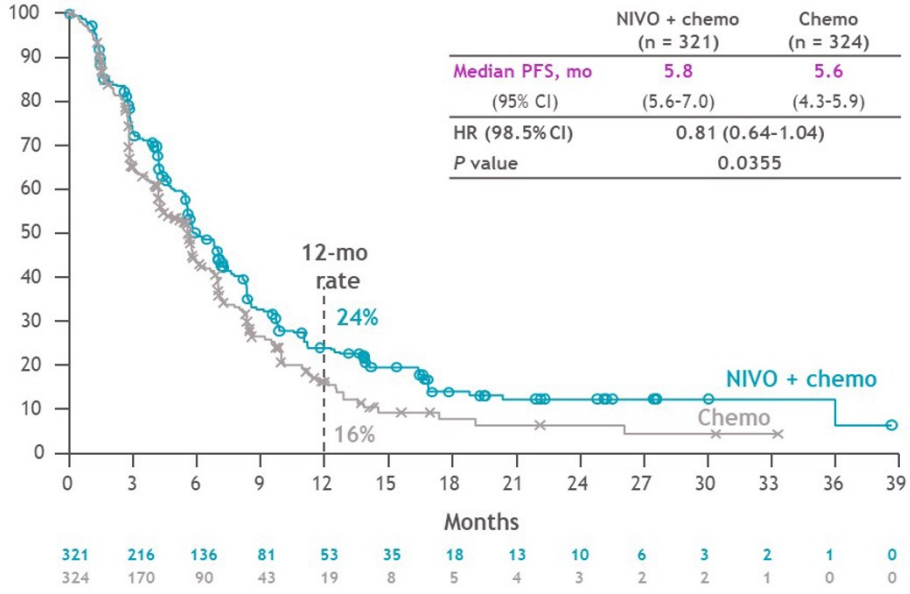
Progression-free survival: NIVO + chemo vs chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%; per BICR)[a]



	NIVO + chemo (n = 158)	Chemo (n = 157)
Median PFS, mo	6.9	4.4
(95% CI)	(5.7-8.3)	(2.9-5.8)
HR (98.5% CI)	0.65 (0.46-0.92)	
P value	0.0023	

All randomized (per BICR)[a]



	NIVO + chemo (n = 321)	Chemo (n = 324)
Median PFS, mo	5.8	5.6
(95% CI)	(5.6-7.0)	(4.3-5.9)
HR (98.5% CI)	0.81 (0.64-1.04)	
P value	0.0355	

1. Chau I, et al. ASCO 2021.

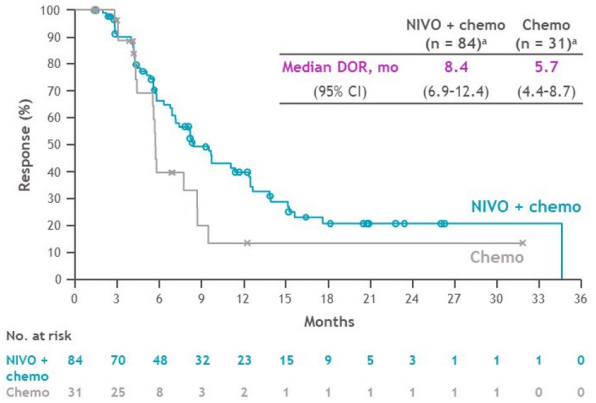
Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

Response and duration of response: NIVO + chemo vs chemo

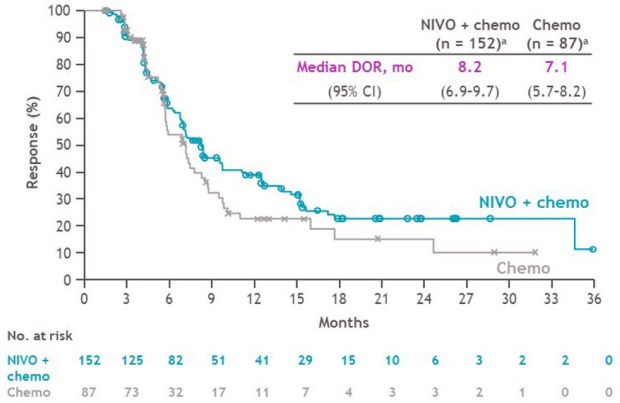
Tumor cell PD-L1 ≥ 1%

Response per BICR	NIVO + chemo (n = 158)	Chemo (n = 157)
ORR, % (95% CI)	53 (45-61)	20 (14-27)
CR	16	5
PR	37	15
SD	25	46
PD	14	15



All randomized

Response per BICR	NIVO + chemo (n = 321)	Chemo (n = 324)
ORR, % (95% CI)	47 (42-53)	27 (22-32)
CR	13	6
PR	34	21
SD	32	46
PD	13	12



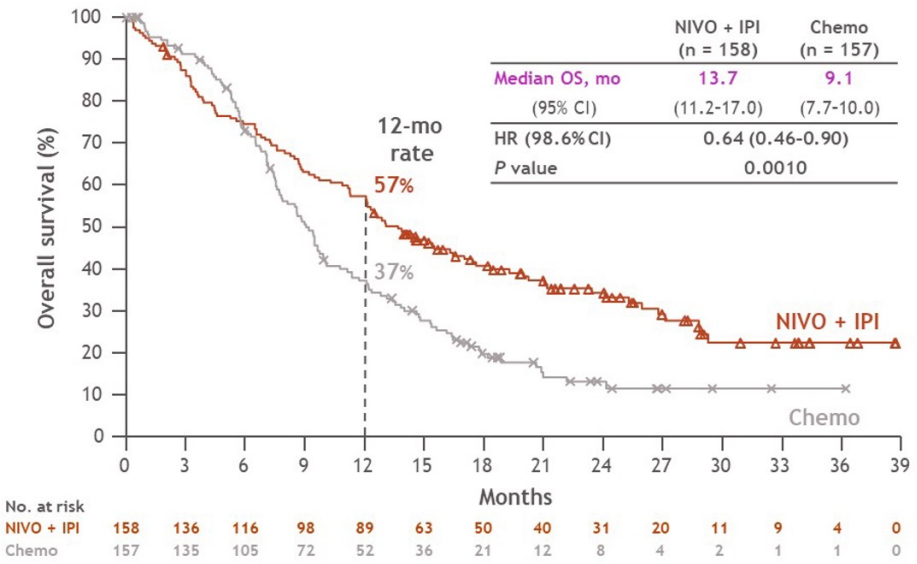
1. Chau I, et al. ASCO 2021.

Systemic treatment of advanced EC

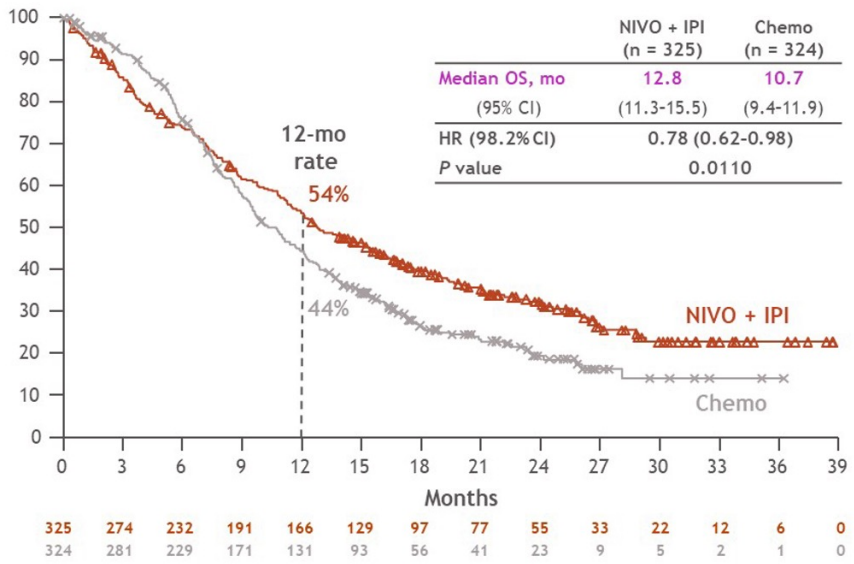
Immunotherapy – CheckMate 648

Overall survival: NIVO + IPI vs chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



All randomized[a]



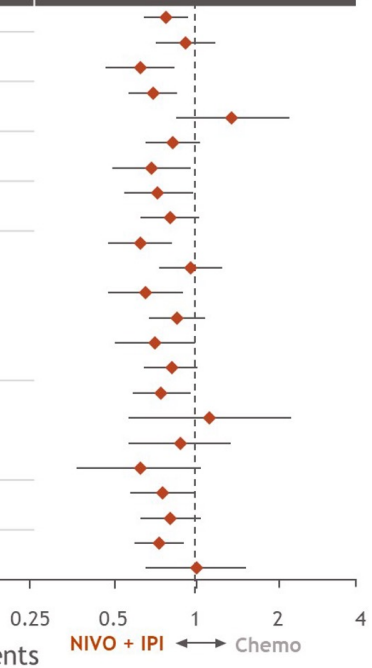
1. Chau I, et al. ASCO 2021.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

Overall survival subgroup analysis: NIVO + IPI vs chemo

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death
		NIVO + IPI	Chemo	
Overall (N = 649)		12.8	10.7	0.78
Age, years	< 65 (n = 351)	12.1	10.2	0.92
	≥ 65 (n = 298)	16.0	11.0	0.63
Sex	Male (n = 544)	13.7	10.0	0.70
	Female (n = 105)	11.7	14.8	1.36
Geographic region	Asian (n = 455)	13.7	11.9	0.83
	Non-Asian (n = 194)	11.4	8.5	0.69
ECOG PS[a]	0 (n = 300)	17.0	12.4	0.73
	1 (n = 348)	9.7	9.0	0.81
Tumor cell PD-L1 expression[b]	≥ 1% (n = 314)	13.7	9.2	0.63
	< 1% (n = 330)	12.0	12.2	0.96
	≥ 5% (n = 235)	13.0	9.5	0.66
	< 5% (n = 409)	12.4	11.1	0.86
	≥ 10% (n = 200)	13.0	9.5	0.71
	< 10% (n = 444)	12.5	10.8	0.82
Disease status at study entry	De novo metastatic (n = 383)	12.1	9.4	0.75
	Recurrent - locoregional (n = 50)	13.9	13.5	1.13
	Recurrent - distant (n = 133)	15.5	12.8	0.88
	Unresectable advanced (n = 83)	17.4	12.1	0.63
No. of organs with metastases	≤ 1 (n = 318)	16.0	11.6	0.76
	≥ 2 (n = 331)	10.3	9.6	0.81
Smoking	Current or former (n = 524)	14.4	10.0	0.74
	Never or unknown (n = 125)	9.8	11.1	1.01



- OS favored NIVO + IPI vs chemo across most prespecified subgroups in all randomized patients

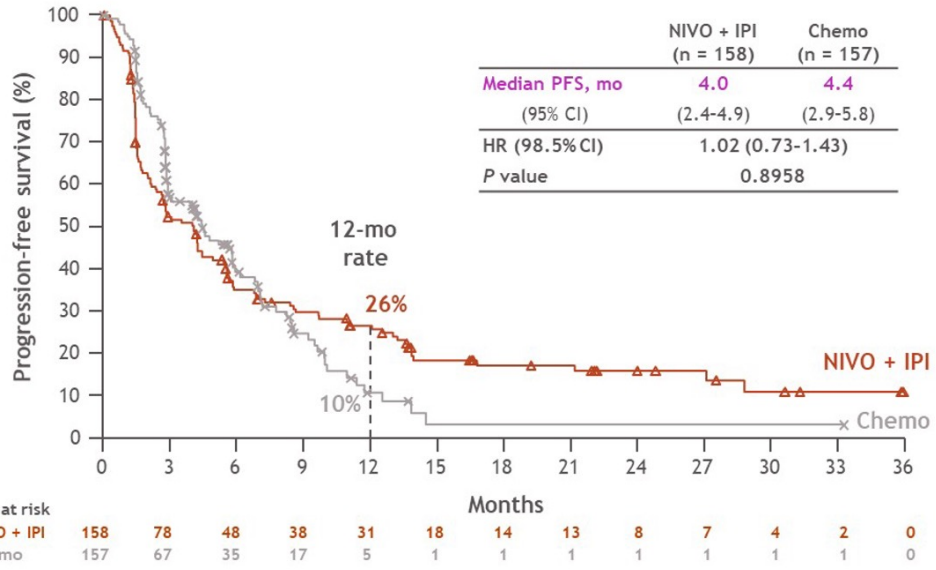
1. Chau I, et al. ASCO 2021.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

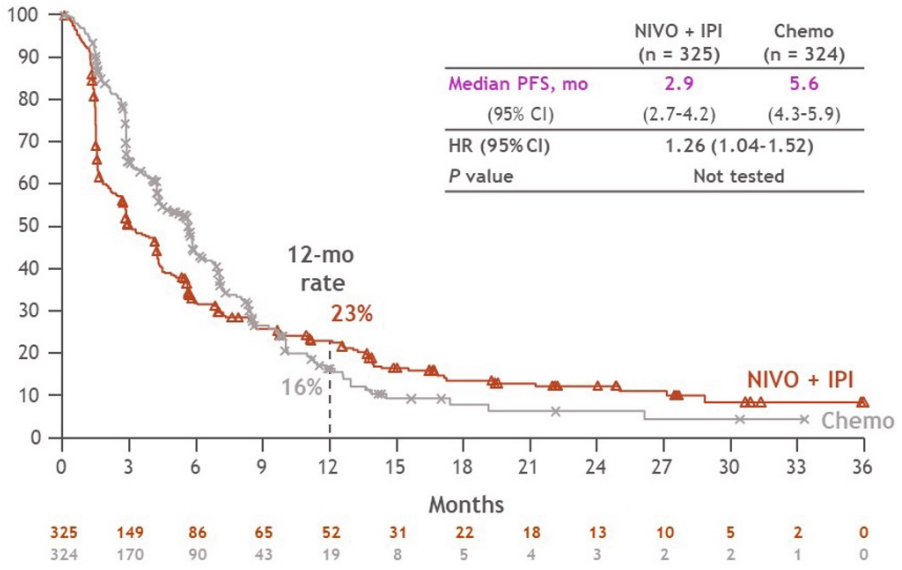
Progression-free survival: NIVO + IPI vs chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%; per BICR)[a]



	NIVO + IPI (n = 158)	Chemo (n = 157)
Median PFS, mo	4.0	4.4
(95% CI)	(2.4-4.9)	(2.9-5.8)
HR (98.5% CI)	1.02 (0.73-1.43)	
P value	0.8958	

All randomized (per BICR)[a]



	NIVO + IPI (n = 325)	Chemo (n = 324)
Median PFS, mo	2.9	5.6
(95% CI)	(2.7-4.2)	(4.3-5.9)
HR (95% CI)	1.26 (1.04-1.52)	
P value	Not tested	

1. Chau I, et al. ASCO 2021.

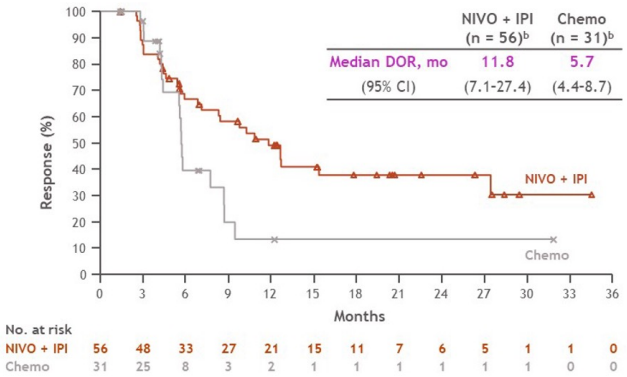
Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

Response and duration of response: NIVO + IPI vs chemo

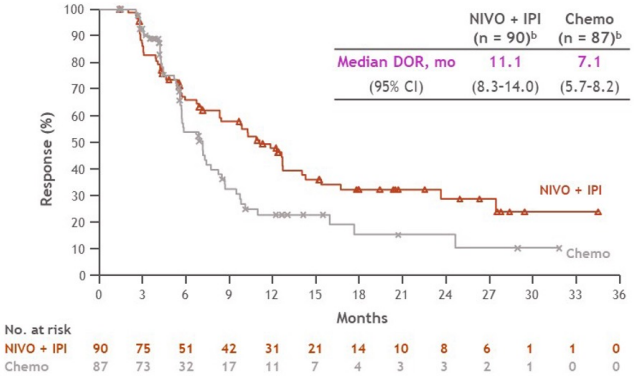
Tumor cell PD-L1 ≥ 1%

Response per BICR	NIVO + IPI (n = 158)	Chemo (n = 157)
ORR, % (95% CI)	35 (28-43)	20 (14-27)
CR[a]	18	5
PR[a]	18	15
SD	27	46
PD	30	15



All randomized

Response per BICR	NIVO + IPI (n = 325)	Chemo (n = 324)
ORR, % (95% CI)	28 (23-33)	27 (22-32)
CR	11	6
PR	17	21
SD	32	46
PD	32	12



1. Chau I, et al. ASCO 2021.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

Treatment-related adverse events

All treated,[a] n (%)	NIVO + chemo (n = 310)		NIVO + IPI (n = 322)		Chemo (n = 304)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAEs[b]	297 (96)	147 (47)	256 (80)	102 (32)	275 (90)	108 (36)
Serious TRAEs[b]	74 (24)	57 (18)	103 (32)	73 (23)	49 (16)	38 (13)
TRAEs leading to discontinuation[b,c]	106 (34)	29 (9)	57 (18)	41 (13)	59 (19)	14 (5)
Treatment-related deaths[d]	5 (2)[e]		5 (2)[f]		4 (1)[g]	

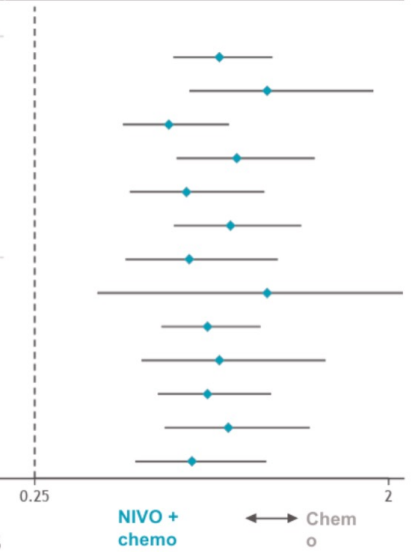
1. Chau I, et al. ASCO 2021.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

Overall survival by baseline PD-L1 status: NIVO + chemo vs chemo

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 645)		13.2	10.7	0.74	
Tumor cell PD-L1 expression[a]	< 1% (n = 329)	12.0	12.2	0.98	
	≥ 1% (n = 314)	15.4	9.2	0.55	
	< 5% (n = 408)	12.8	11.1	0.82	
	≥ 5% (n = 235)	13.7	9.5	0.61	
	< 10% (n = 444)	12.3	10.8	0.79	
	≥ 10% (n = 199)	14.7	9.5	0.62	
PD-L1 CPS[b,c]	< 1 (n = 51)	9.9	12.1	0.98	
	≥ 1 (n = 558)	13.8	9.8	0.69	
	< 5 (n = 188)	12.0	9.4	0.74	
	≥ 5 (n = 421)	15.2	11.1	0.69	
	< 10 (n = 329)	12.1	9.7	0.78	
	≥ 10 (n = 280)	16.1	11.6	0.63	



- HRs were below 1 favoring NIVO + chemo vs chemo across all PD-L1 expression subgroups
- Largest magnitude of benefit was observed in patients with tumor cell PD-L1 ≥ 1%, with no further enrichment in higher tumor cell PD-L1 expression subgroups

1. Chau I, et al. ESMO GI 2022.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

Response rate and duration of response: NIVO + chemo vs chemo

Response per BICR	All randomized		Tumor cell PD-L1 ≥ 1%		Tumor cell PD-L1 < 1%	
	NIVO + chemo (n = 321)	Chemo (n = 324)	NIVO + chemo (n = 158)	Chemo (n = 157)	NIVO + chemo (n = 163)	Chemo (n = 166)
ORR, % (95% CI)	47 (42-53)	27 (22-32)	53 (45-61)	20 (14-27)	42 (34-50)	34 (27-42)
Median DOR,[a,b] mo (95% CI)	8.2 (6.9-9.7)	7.1 (5.7-8.2)	8.4 (6.9-12.4)	5.7 (4.4-8.7)	6.9 (5.8-14.6)	7.2 (5.7-9.7)
DOR ≥ 12 mo,[a,b] % (95% CI)	39 (30-47)	23 (13-34)	40 (28-51)	13 (2-33)	38 (25-50)	27 (14-41)

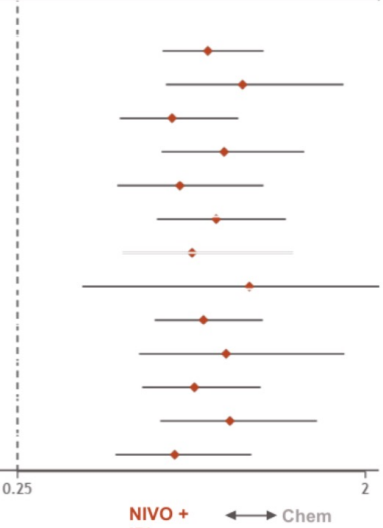
1. Chau I, et al. ESMO GI 2022.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

Overall survival by baseline PD-L1 status: NIVO + IPI vs chemo

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + IPI	Chemo		
Overall (N = 649)		12.7	10.7	0.78	
Tumor cell PD-L1 expression[a]	< 1% (n = 330)	12.0	12.2	0.96	
	≥ 1% (n = 314)	13.7	9.2	0.63	
	< 5% (n = 409)	12.4	11.1	0.86	
	≥ 5% (n = 235)	13.0	9.5	0.66	
	< 10% (n = 444)	12.5	10.8	0.82	
	≥ 10% (n = 200)	13.0	9.5	0.71	
PD-L1 CPS[b,c]	< 1 (n = 55)	11.5	12.1	1.00	
	≥ 1 (n = 546)	12.7	9.8	0.76	
	< 5 (n = 197)	11.4	9.4	0.87	
	≥ 5 (n = 404)	14.5	11.1	0.72	
	< 10 (n = 330)	11.2	9.7	0.89	
	≥ 10 (n = 271)	16.7	11.6	0.64	



- HRs were below 1 favoring NIVO + IPI vs chemo across all PD-L1 expression subgroups, except for CPS < 1 (n = 55; HR = 1)
- Largest magnitude of benefit was observed in patients with tumor cell PD-L1 ≥ 1%, with no further enrichment in higher tumor cell PD-L1 expression subgroups

1. Chau I, et al. ESMO GI 2022.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648

Response rate and duration of response: NIVO + IPI vs chemo

Response per BICR	All randomized		Tumor cell PD-L1 ≥ 1%		Tumor cell PD-L1 < 1%	
	NIVO + IPI (n = 325)	Chemo (n = 324)	NIVO + IPI (n = 158)	Chemo (n = 157)	NIVO + IPI (n = 164)	Chemo (n = 166)
ORR, % (95% CI)	28 (23-33)	27 (22-32)	35 (28-43)	20 (14-27)	20 (14-27)	34 (27-42)
Median DOR,[a,b] mo (95% CI)	11.1 (8.3-14.0)	7.1 (5.7-8.2)	11.8 (7.1-27.4)	5.7 (4.4-8.7)	11.1 (5.7-14.3)	7.2 (5.7-9.7)
DOR ≥12 mo,[a,b] % (95% CI)	48 (36-58)	23 (13-34)	49 (35-62)	13 (2-33)	47 (28-64)	27 (14-41)

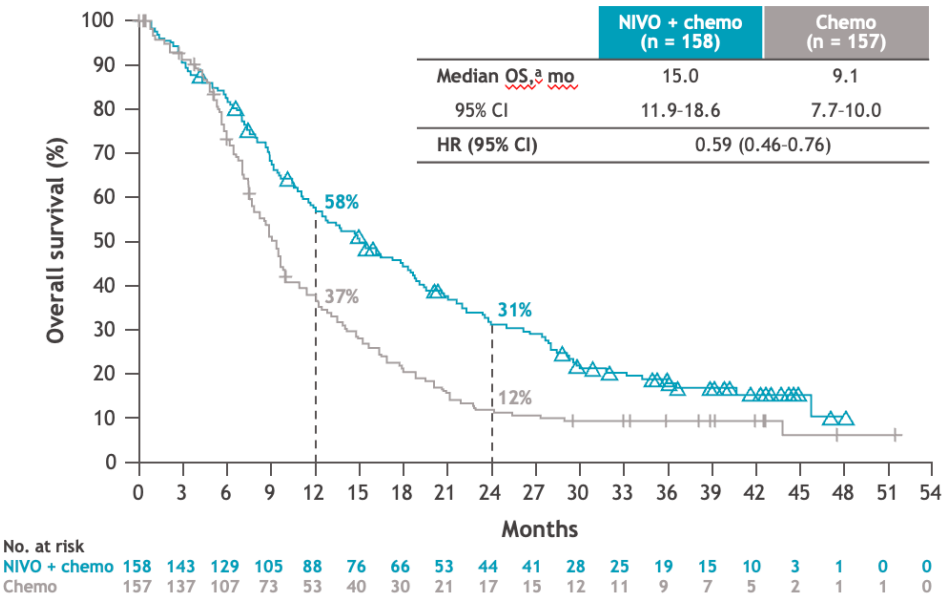
1. Chau I, et al. ESMO GI 2022.

Systemic treatment of advanced EC

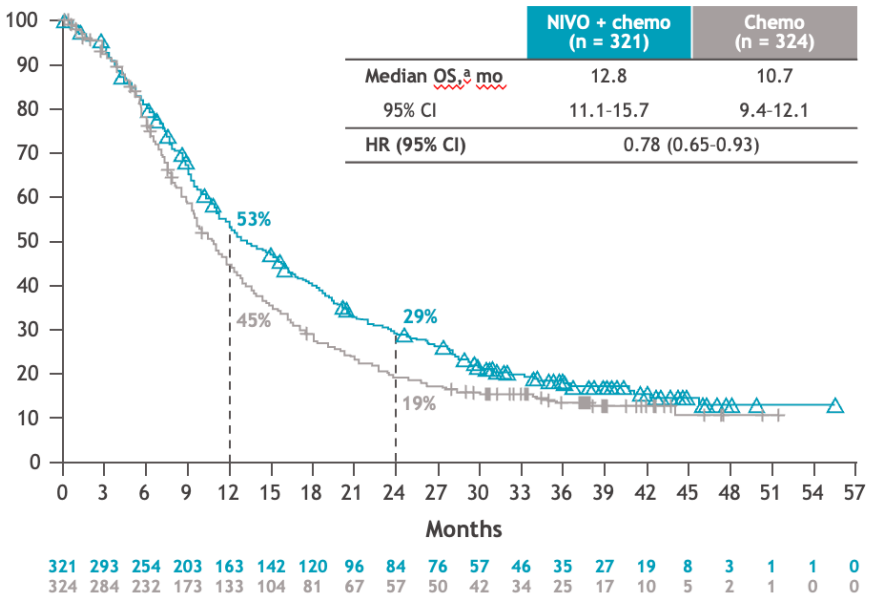
Immunotherapy – CheckMate 648 (29-m follow-up)

OS with NIVO + chemo vs chemo: 29-month follow-up

Tumor cell PD-L1 ≥ 1%



All randomized



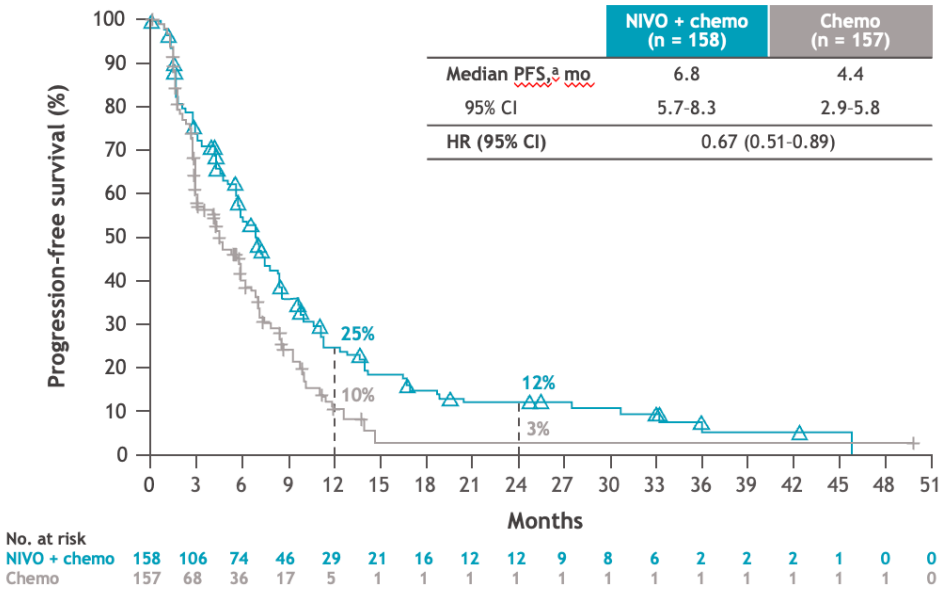
1. Kato K, et al. ASCO GI 2023.

Systemic treatment of advanced EC

Immunotherapy – CheckMate 648 (29-m follow-up)

PFS with NIVO + chemo vs chemo: 29-month follow-up

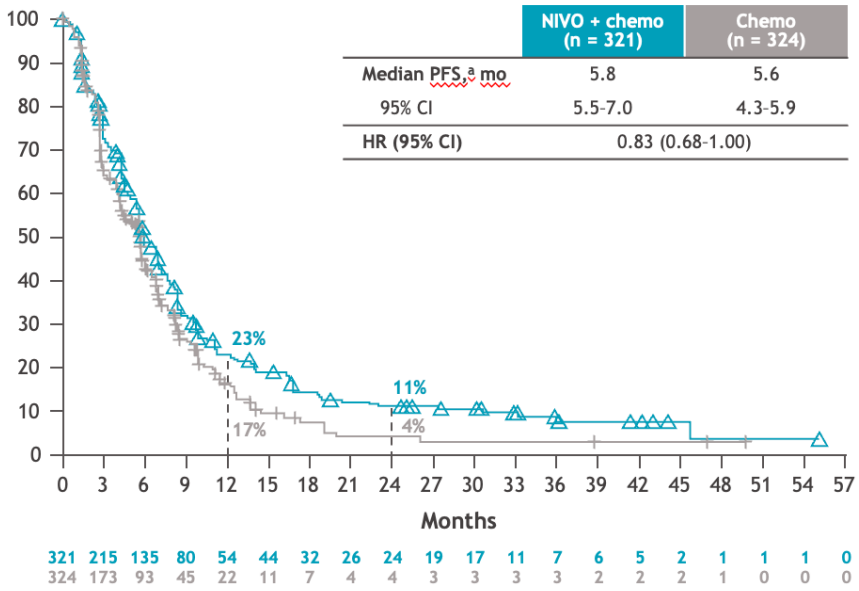
Tumor cell PD-L1 ≥ 1% (per BICR)



	NIVO + chemo (n = 158)	Chemo (n = 157)
Median PFS,[a] mo	6.8	4.4
95% CI	5.7-8.3	2.9-5.8
HR (95% CI)	0.67 (0.51-0.89)	

No. at risk																		
NIVO + chemo	158	106	74	46	29	21	16	12	12	9	8	6	2	2	2	1	0	0
Chemo	157	68	36	17	5	1	1	1	1	1	1	1	1	1	1	1	1	0

All randomized (per BICR)



	NIVO + chemo (n = 321)	Chemo (n = 324)
Median PFS,[a] mo	5.8	5.6
95% CI	5.5-7.0	4.3-5.9
HR (95% CI)	0.83 (0.68-1.00)	

NIVO + chemo	321	215	135	80	54	44	32	26	24	19	17	11	7	6	5	2	1	1	1	0
Chemo	324	173	93	45	22	11	7	4	4	3	3	3	3	2	2	2	1	0	0	0

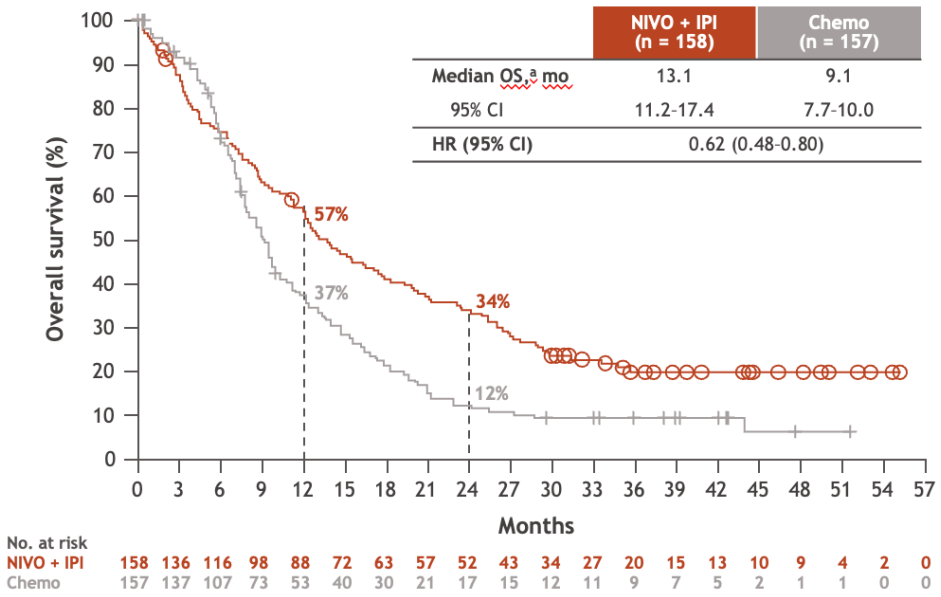
1. Kato K, et al. ASCO GI 2023.

Systemic treatment of advanced EC

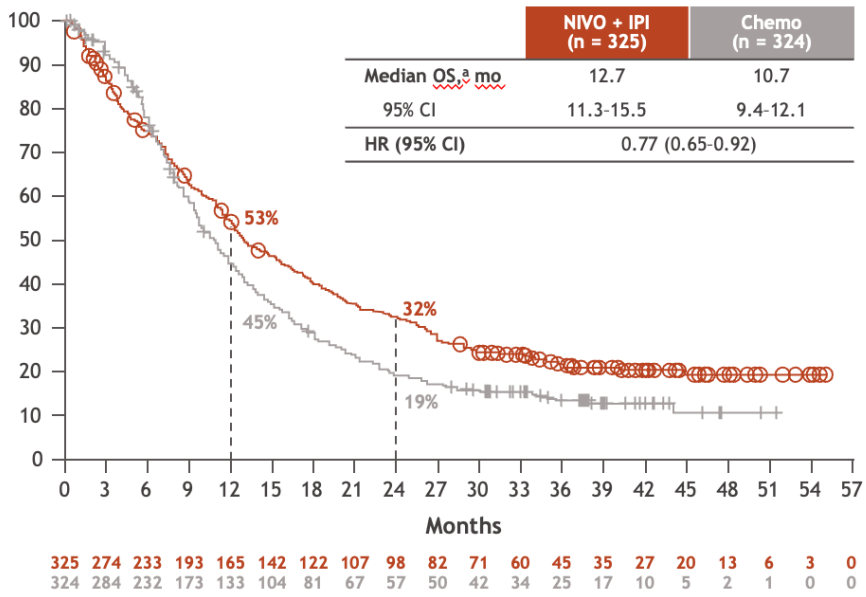
Immunotherapy – CheckMate 648 (29-m follow-up)

OS with NIVO + IPI vs chemo: 29-month follow-up

Tumor cell PD-L1 ≥ 1%



All randomized



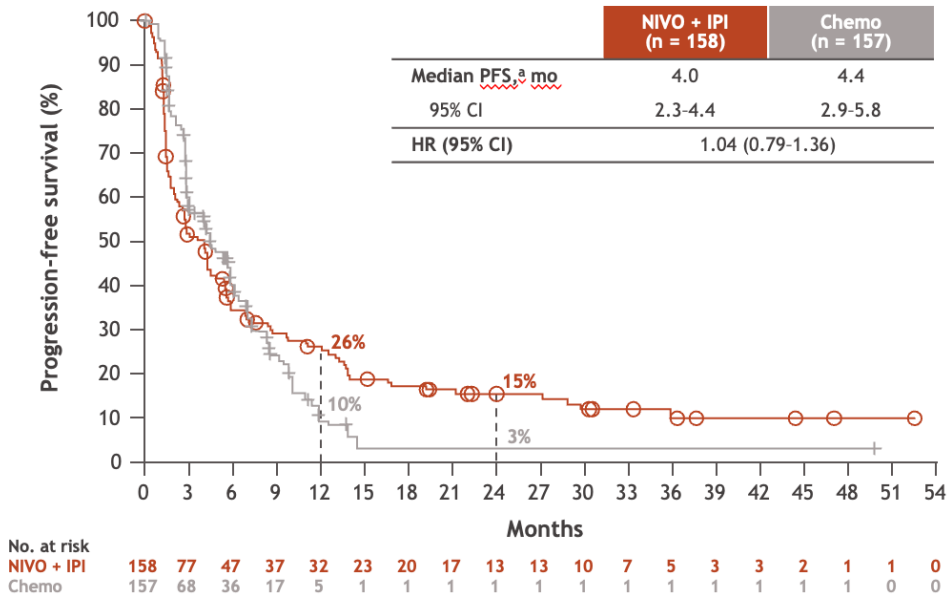
1. Kato K, et al. ASCO GI 2023.

Systemic treatment of advanced EC

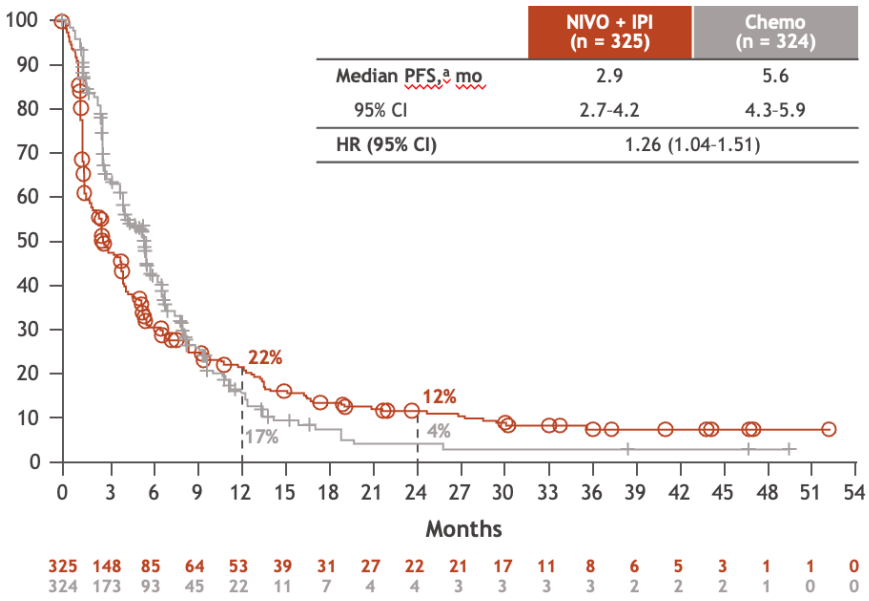
Immunotherapy – CheckMate 648 (29-m follow-up)

PFS with NIVO + IPI vs chemo: 29-month follow-up

Tumor cell PD-L1 ≥ 1% (per BICR)



All randomized (per BICR)



1. Kato K, et al. ASCO GI 2023.

Systemic treatment of advanced EC

Immunotherapy – KEYNOTE-590

Pembrolizumab Plus Chemotherapy Versus Chemotherapy as First-Line Therapy in Patients With Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study

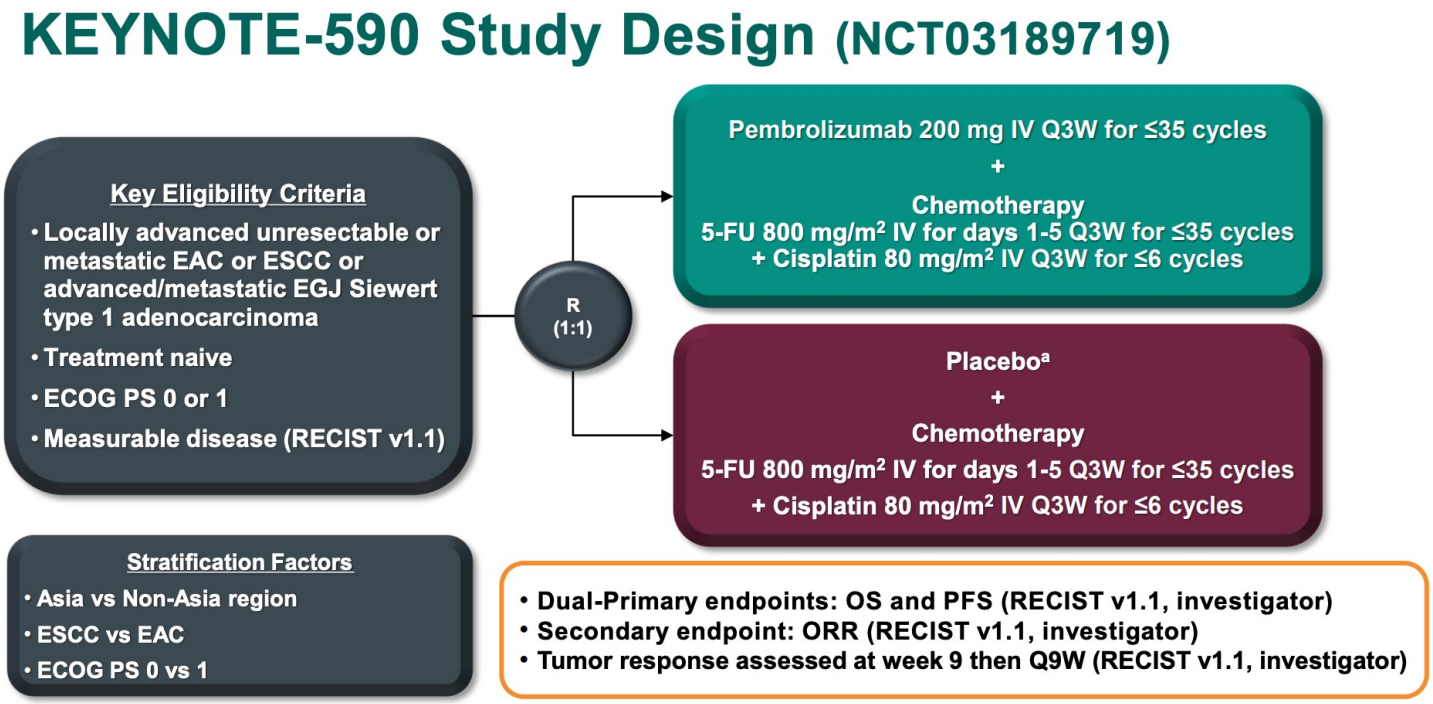
Ken Kato,[1] Jong-Mu Sun,[2] Manish A. Shah,[3] Peter Enzinger,[4] Antoine Adenis,[5] Toshihiko Doi,[6] Takashi Kojima,[6] Jean-Philippe Metges,[7] Zhigang Li,[8] Sung-Bae Kim,[9] Byoung Chul Cho,[10] Wasat Mansoor,[11] Shau-Hsuan Li,[12] Patrapim Sunpaweravong,[13] Maria Alsina Maqueda,[14] Eray Goekkurt,[15] Qi Liu,[16] Sukrut Shah,[16] Pooja Bhagia,[16] Lin Shen[17]

[1]National Cancer Center Hospital, Tokyo, Japan; [2]Samsung Medical Center, Sungkyunkwan University Seoul, Republic of Korea, [3]Weill Cornell Medical College, New York, NY, USA; [4]Dana Farber Cancer Institute, Boston, MA, USA; [5]IRCM, Inserm, Université Montpellier, ICM, Montpellier, France; [6]National Cancer Center Hospital East, Kashiwa, Japan;[7]CHU Brest – Institut de Cancerologie et d'Hematologie ARPEGO Network, Brest, France; [8]Shanghai Chest Hospital Esophageal Disease Center, Shanghai, China; [9]Asan Medical Center, Seoul, Republic of Korea; [10]Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea; [11]Christie Hospital NHS Trust, Manchester, United Kingdom; [12]Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan;[13]Prince of Songkla University Hospital, Songkhla, Thailand; [14]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [15]Hematology Oncology Practice Eppendorf, and University Cancer Center Hamburg, Hamburg, Germany; [16]Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; [17]Peking University Cancer Hospital & Institute; Beijing, China

1. Kato K, et al. ESMO 2020.

Systemic treatment of advanced EC

Immunotherapy – KEYNOTE-590

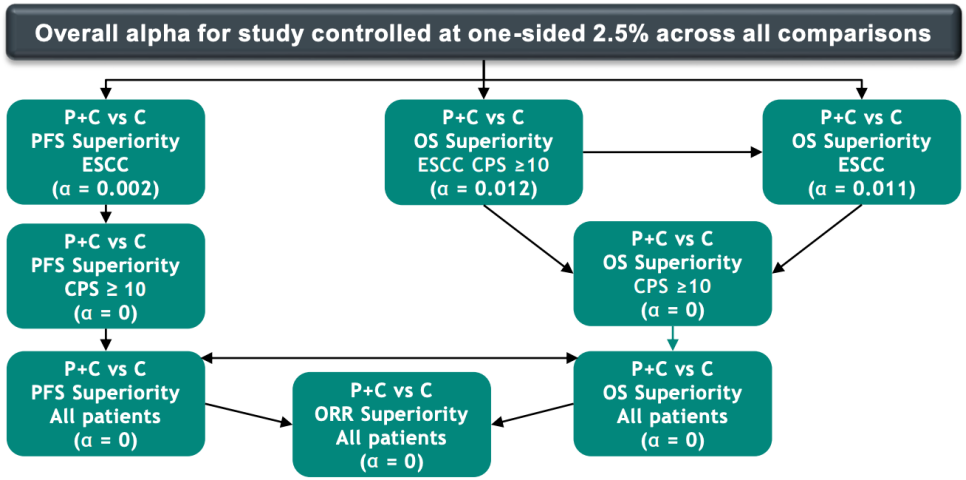


1. Kato K, et al. ESMO 2020.

Systemic treatment of advanced EC

Immunotherapy – KEYNOTE-590

Statistical Considerations



- Hypotheses in top row tested first and in parallel
  - Remaining hypotheses tested only if the preceding hypothesis was positive
  - Pre-specified analysis plan allowed alpha passing from successful hypothesis
- Interim analysis occurred after at least 13 months of follow-up following completion of enrollment (35 months), 460 PFS events and 391 OS events in ESCC

1. Kato K, et al. ESMO 2020.

Systemic treatment of advanced EC

Immunotherapy – KEYNOTE-590

Baseline Characteristics (ITT)

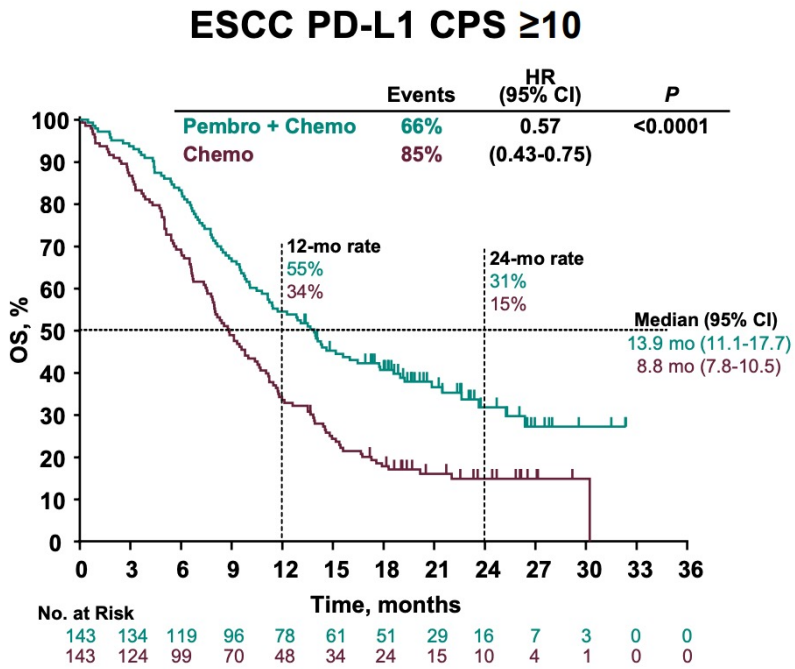
Characteristic, n (%)	Pembro + Chemo N = 373	Chemo N = 376
Median age, years (range)	64.0 (28-94)	62.0 (27-89)
≥65 years	172 (46)	150 (40)
Male	306 (82.0)	319 (84.8)
Asia Region	196 (52.5)	197 (52.4)
ECOG PS 1	223 (59.8)	225 (59.8)
Metastatic disease	344 (92.2)	339 (90.2)
Unresectable/locally-advanced	29 (7.8)	37 (9.8)
Squamous-cell carcinoma	274 (73.5)	274 (72.9)
Adenocarcinoma	99 (26.5)	102 (27.1)
Esophageal	58 (15.5)	52 (13.8)
EGJ	41 (11.0)	50 (13.3)
PD-L1 CPS ≥10[a]	186 (49.9)	197 (52.4)

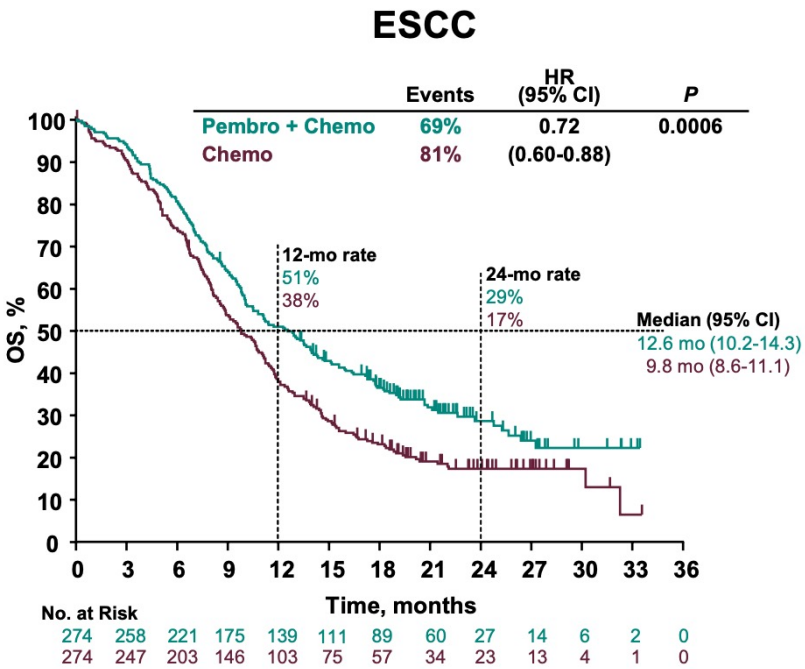
1. Kato K, et al. ESMO 2020.

Systemic treatment of advanced EC

Immunotherapy – KEYNOTE-590

Overall Survival



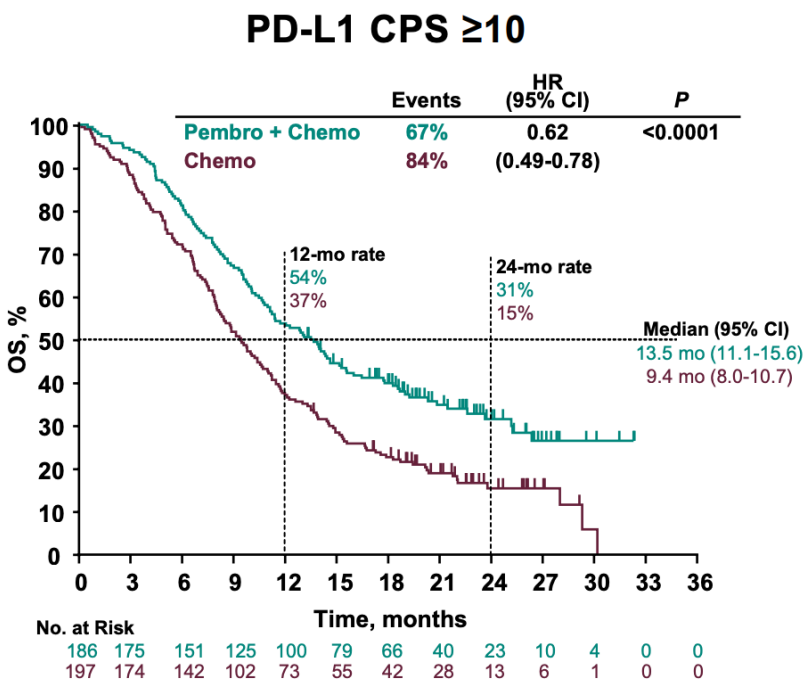


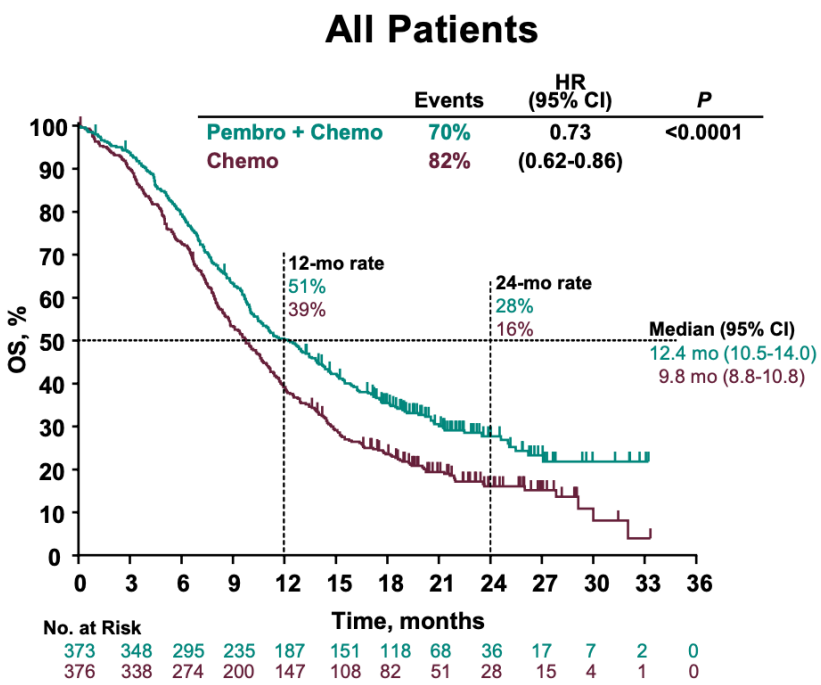
1. Kato K, et al. ESMO 2020.

Systemic treatment of advanced EC

Immunotherapy – KEYNOTE-590

Overall Survival



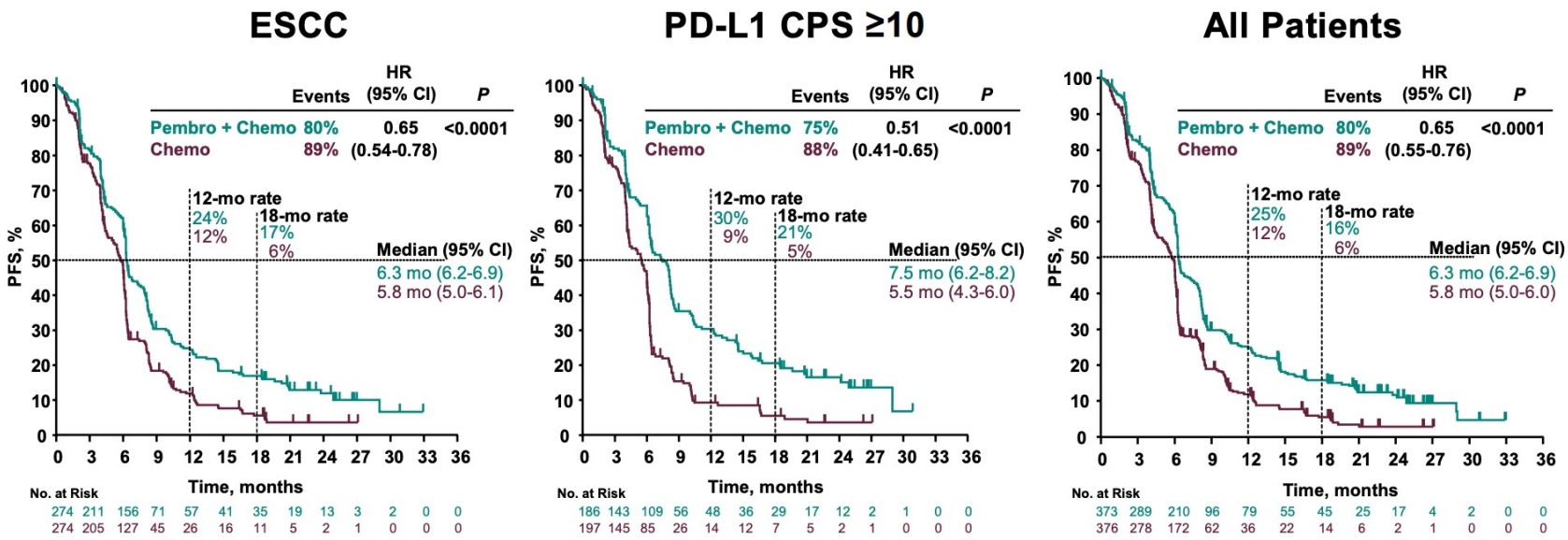


1. Kato K, et al. ESMO 2020.

Systemic treatment of advanced EC

Immunotherapy – KEYNOTE-590

Progression-Free Survival
(RECIST v1.1, investigator)

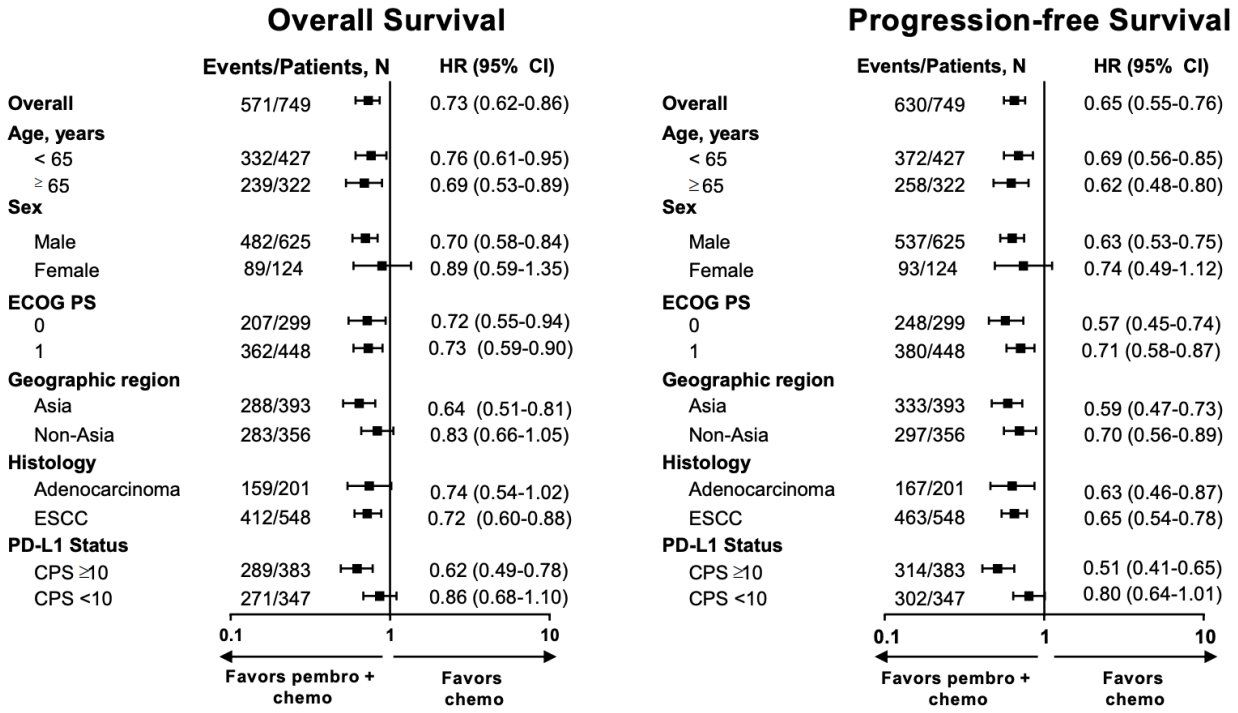


1. Kato K, et al. ESMO 2020.

Systemic treatment of advanced EC

Immunotherapy – KEYNOTE-590

Survival in Key Subgroups: All Patients



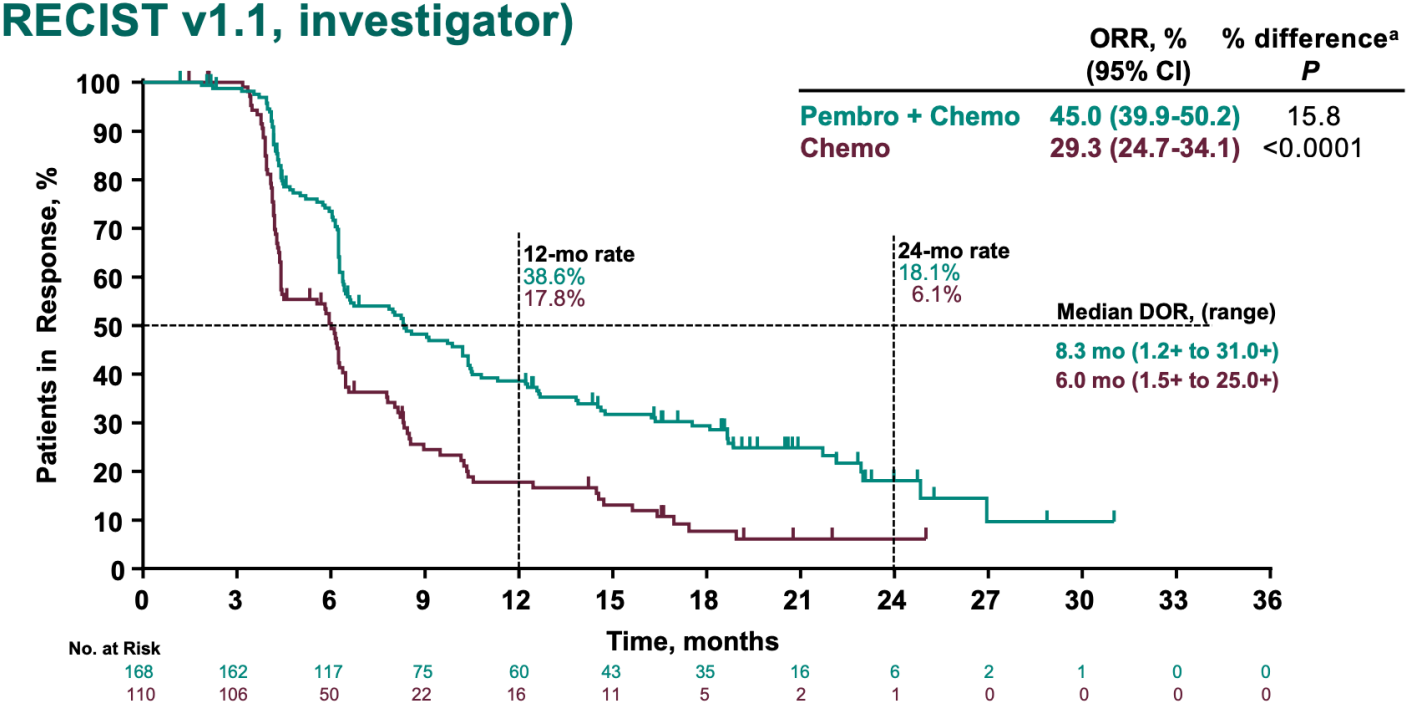
1. Kato K, et al. ESMO 2020.

Systemic treatment of advanced EC

Immunotherapy – KEYNOTE-590

Response Rate and Duration: All Patients

(RECIST v1.1, investigator)

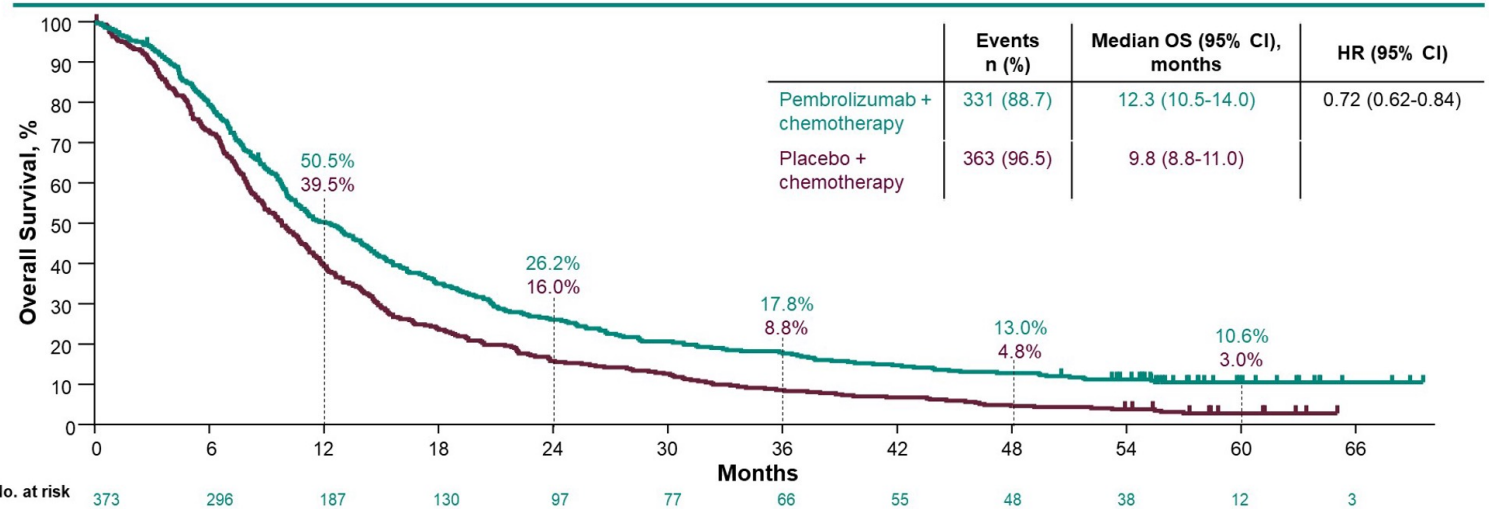


1. Kato K, et al. ESMO 2020.

Systemic treatment of advanced EC

Immunotherapy – KEYNOTE-590 (5-yr follow-up)

Overall Survival: ITT Population



	Events n (%)	Median OS (95% CI), months	HR (95% CI)
Pembrolizumab + chemotherapy	331 (88.7)	12.3 (10.5-14.0)	0.72 (0.62-0.84)
Placebo + chemotherapy	363 (96.5)	9.8 (8.8-11.0)	

	CPS ≥10		ESCC		ESCC and CPS ≥10	
	Pembro + chemo n = 186	Placebo + chemo n = 197	Pembro + chemo n = 274	Placebo + chemo n = 274	Pembro + chemo n = 143	Placebo + chemo n = 143
OS, HR (95% CI)	0.64 (0.52-0.80)		0.71 (0.60-0.85)		0.60 (0.46-0.76)	
5-y OS rate,[a] %	12.8	3.8	11.8	3.4	13.8	3.7

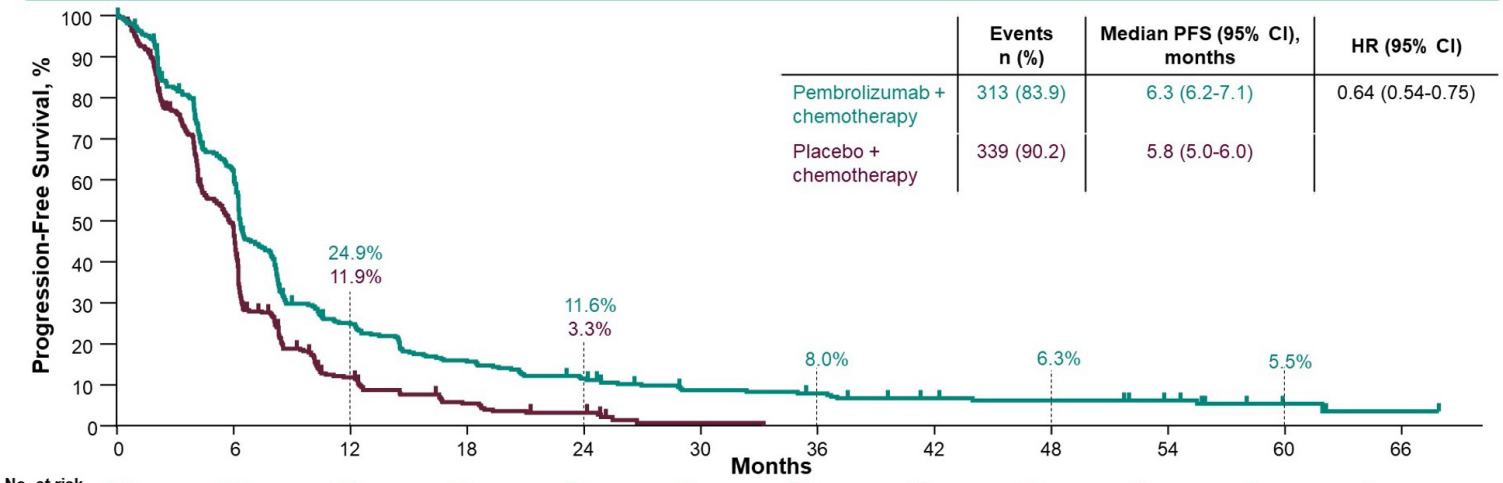
[a]Kaplan-Meier estimate. Data cutoff: July 10, 2023.

1. Shah MA, et al. ASCO GI 2024.

Systemic treatment of advanced EC

Immunotherapy – KEYNOTE-590 (5-yr follow-up)

Progression-Free Survival: ITT Population



	Events n (%)	Median PFS (95% CI), months	HR (95% CI)
Pembrolizumab + chemotherapy	313 (83.9)	6.3 (6.2-7.1)	0.64 (0.54-0.75)
Placebo + chemotherapy	339 (90.2)	5.8 (5.0-6.0)	

No. at risk												
Pembrolizumab + chemotherapy	373	210	79	50	36	23	20	14	12	9	3	1
Placebo + chemotherapy	376	172	36	15	8	1	0	0	0	0	0	0

	CPS ≥10		ESCC		ESCC and CPS ≥10	
	Pembro + chemo n = 186	Placebo + chemo n = 197	Pembro + chemo n = 274	Placebo + chemo n = 274	Pembro + chemo n = 143	Placebo + chemo n = 143
PFS HR (95% CI)	0.51 (0.40-0.64)		0.65 (0.54-0.78)		0.53 (0.41-0.69)	
5-y PFS rate,[a] %	7.5	0	6.7	0	9.1	0

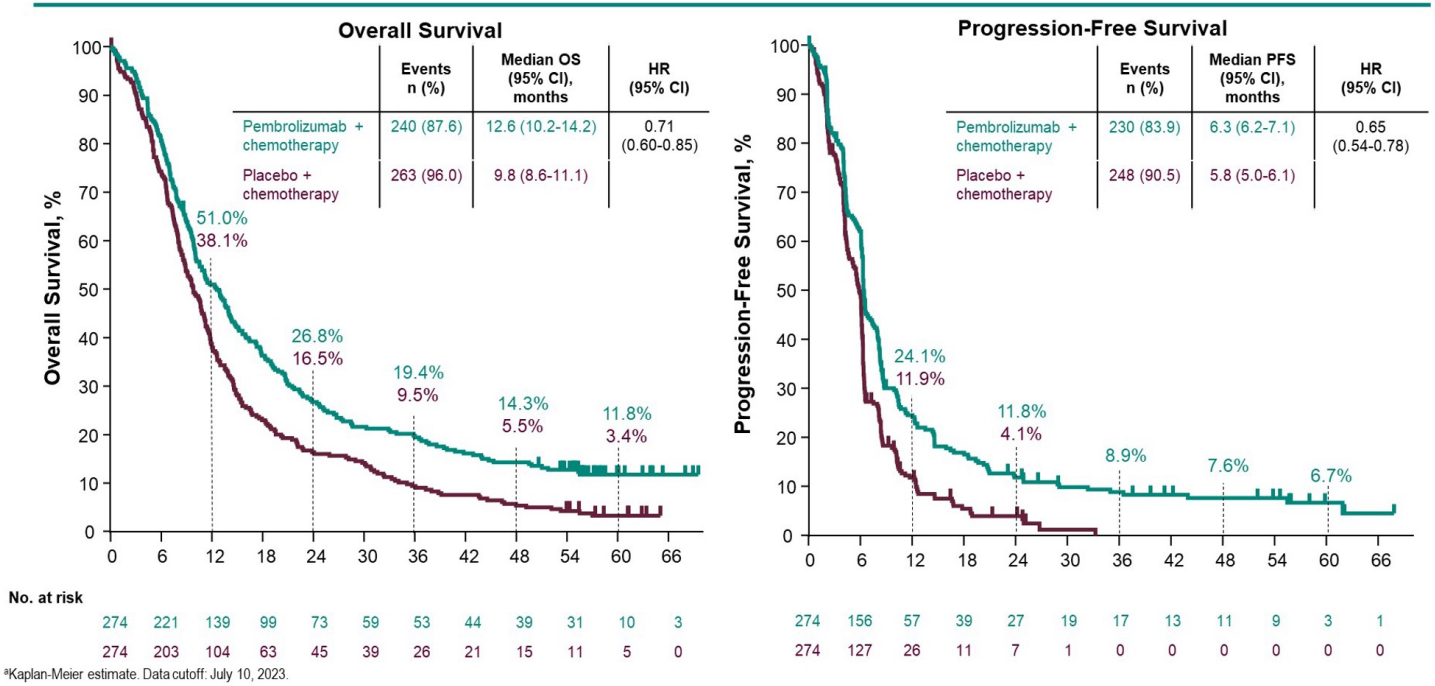
[a]Kaplan-Meier estimate. Data cutoff: July 10, 2023.

1. Shah MA, et al. ASCO GI 2024.

Systemic treatment of advanced EC

Immunotherapy – KEYNOTE-590 (5-yr follow-up)

Overall Survival and Progression-Free Survival: ESCC Population



[a]Kaplan-Meier estimate. Data cutoff: July 10, 2023.

1. Shah MA, et al. ASCO GI 2024.

Variable	CM-648	CM-648	KN-590[#]	RATIONALE-306	ESCORT-1st	ORIENT-15	SKYSCRAPER-08
Overall population							
Sample size	970	970	548	649	596	659	461
Chemo	CDDP + 5-FU	None	CDDP + 5-FU	CDDP/l-OHP + 5-FU/CAP/PTX	CDDP + PTX	CDDP + PTX	CDDP + PTX
Inv. drug	Nivolumab	Nivo + Ipi	Pembrolizumab	Tislelizumabe	Camrelizumab	Sintilimab	Tira + Atezo
ORR, %	47.0 vs. 27.0	28.0 vs. 27.0	43.8 vs. 31.0	63.0 vs. 42.0	72.1vs. 62.1	66.0 vs. 45.0	59.7 vs. 45.5
PFS, HR(95%CI)	0.81 (0.64 – 1.04)	1.26 (1.04 – 1.52)	0.65 (0.54 – 0.78)	0.62 (0.52 – 0.75)	0.56 (0.46 – 0.68)	0.56 (0.46 – 0.68)	0.56 (0.45 – 0.70)
OS, HR(95%CI)	0.74 (0.58 – 0.96)	0.78 (0.62 – 0.98)	0.72 (0.60 – 0.88)	0.66 (0.54 – 0.80)	0.70 (0.56 – 0.88)	0.63 (0.51 – 0.78)	0.70 (0.55 – 0.88)
Biomarker subgroup population (PD-L1 CPS)							
Threshold	1[$]	1[$]	10	10[&]	1[$]	10	10[&]
ORR, %	53.0 vs. 20.0	35.0 vs. 20.0	51.1 vs. 28.0	73.0 vs. 40.0	74.1 vs. 65.6	68.0 vs. 49.0	
PFS, HR(95%CI)	0.65 (0.46 – 0.92)	1.02 (0.73 – 1.43)	0.53 (0.40 – 0.68)	0.50 (0.37 – 0.69)	0.51 (0.39 – 0.67)	0.58 (0.45 – 0.75)	0.50 (0.35 – 0.70)
OS, HR(95%CI)	0.54 (0.37 – 0.80)	0.64 (0.46 – 0.90)	0.57 (0.43 – 0.75)	0.62 (0.44 – 0.87)	0.59 (0.43 – 0.80)	0.64 (0.48 – 0.85)	0.70 (0.49 – 1.01)

[#] Includes only the subgroup of patients with squamous cell carcinoma.
[$] TPS (CM-648: 28-8; ESCORT-1st: 6E8).
[&] TAP (SP263).

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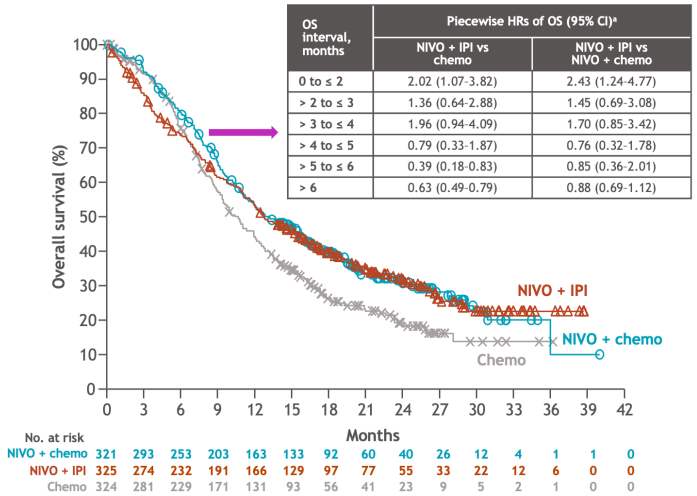
Systemic treatment of advanced EC

CT + anti-PD-1 vs. Nivolumab + Ipilimumab

Factors associated with delayed benefit of NIVO + IPI relative to NIVO + chemo or chemo in ESCC



OS interval, months	Piecewise HRs of OS (95% CI)[a]	
	NIVO + IPI vs chemo	NIVO + IPI vs NIVO + chemo
0 to ≤ 2	2.02 (1.07-3.82)	2.43 (1.24-4.77)
> 2 to ≤ 3	1.36 (0.64-2.88)	1.45 (0.69-3.08)
> 3 to ≤ 4	1.96 (0.94-4.09)	1.70 (0.85-3.42)
> 4 to ≤ 5	0.79 (0.33-1.87)	0.76 (0.32-1.78)
> 5 to ≤ 6	0.39 (0.18-0.83)	0.85 (0.36-2.01)
> 6	0.63 (0.49-0.79)	0.88 (0.69-1.12)

Factors associated with delayed onset of effect of NIVO + IPI vs NIVO + chemo or chemo[b]
Age (< 65 yr)[c]
Weight (< 60 kg)[d]
Disease status at current diagnosis (de novo metastatic)[c]
Baseline neutrophil/lymphocyte ratio (< 4)[c]
Baseline tumor burden (≥ Q3)[c,e]
Liver metastasis (yes)[d]
Alcohol use (never/unknown)[c,d]

- Initial increased incidence of early death with NIVO + IPI, defined as any death prior to or at ~ 4 months, did not preclude long-term benefit for the overall population
- Post hoc exploratory multivariate analyses suggested that no single baseline characteristic reliably predicted delayed onset of effect of NIVO + IPI vs NIVO + chemo or chemo
- These results should not be extrapolated to other tumors treated with NIVO + IPI as specific factors may vary across studies

[a]Evaluated in all randomized patients; [b]Statistical significance was predefined as a P value < 0.15 with no adjustment for multiplicity; [c]NIVO + IPI vs NIVO + chemo comparison; [d]NIVO + IPI vs chemo comparison; [e]Sum of target lesion diameter by RECIST v1.1 per BICR, ≥ Q3 (75 mm).

1. Chau I, et al. ESMO GI 2022.

Systemic treatment of advanced EC

CT + anti-PD-1 vs. Nivolumab + Ipilimumab

Outcome	CT + Nivolumab	CT + Pembrolizumabe	Nivolumab + Ipilimumab
Overall response rate, %	47.0 (All comers) 53.0 (TPS ≥ 1)	43.8 (All comers) 51.1 (CPS ≥ 10)	28.0 (All comers) 35.0 (TPS ≥ 1)
Duration of response, m	8.2 (All comers) 8.4 (TPS ≥ 1)	9.1 (All comers) 10.4 (CPS ≥ 10)	11.1 (All comers) 11.8 (TPS ≥ 1)

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Systemic treatment of advanced EC

CT + anti-PD-1 vs. Nivolumab + Ipilimumab

Treatment-related adverse events

All treated,[a] n (%)	NIVO + chemo (n = 310)		NIVO + IPI (n = 322)		Chemo (n = 304)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAEs[b]	297 (96)	147 (47)	256 (80)	102 (32)	275 (90)	108 (36)
Serious TRAEs[b]	74 (24)	57 (18)	103 (32)	73 (23)	49 (16)	38 (13)
TRAEs leading to discontinuation[b,c]	106 (34)	29 (9)	57 (18)	41 (13)	59 (19)	14 (5)
Treatment-related deaths[d]	5 (2)[e]		5 (2)[f]		4 (1)[g]	

1. Chau I, et al. ASCO 2021.

Systemic treatment of advanced EC

CT + anti-PD-1 vs. Nivolumab + Ipilimumab

- Criteria
  - Need for symptomatic relief
    - **Favors CT + anti-PD-1**
  - Predictors delayed benefit from Nivolumab + Ipilimumab
    - Age < 65, *de novo* metastatic disease, baseline NLR < 4, baseline disease burden ≥ Q3, liver metastasis, alcohol use
    - **Favors CT + anti-PD-1**
  - Local progression (shortly) after definitive chemoradiation
    - **Favors CT + anti-PD-1?**

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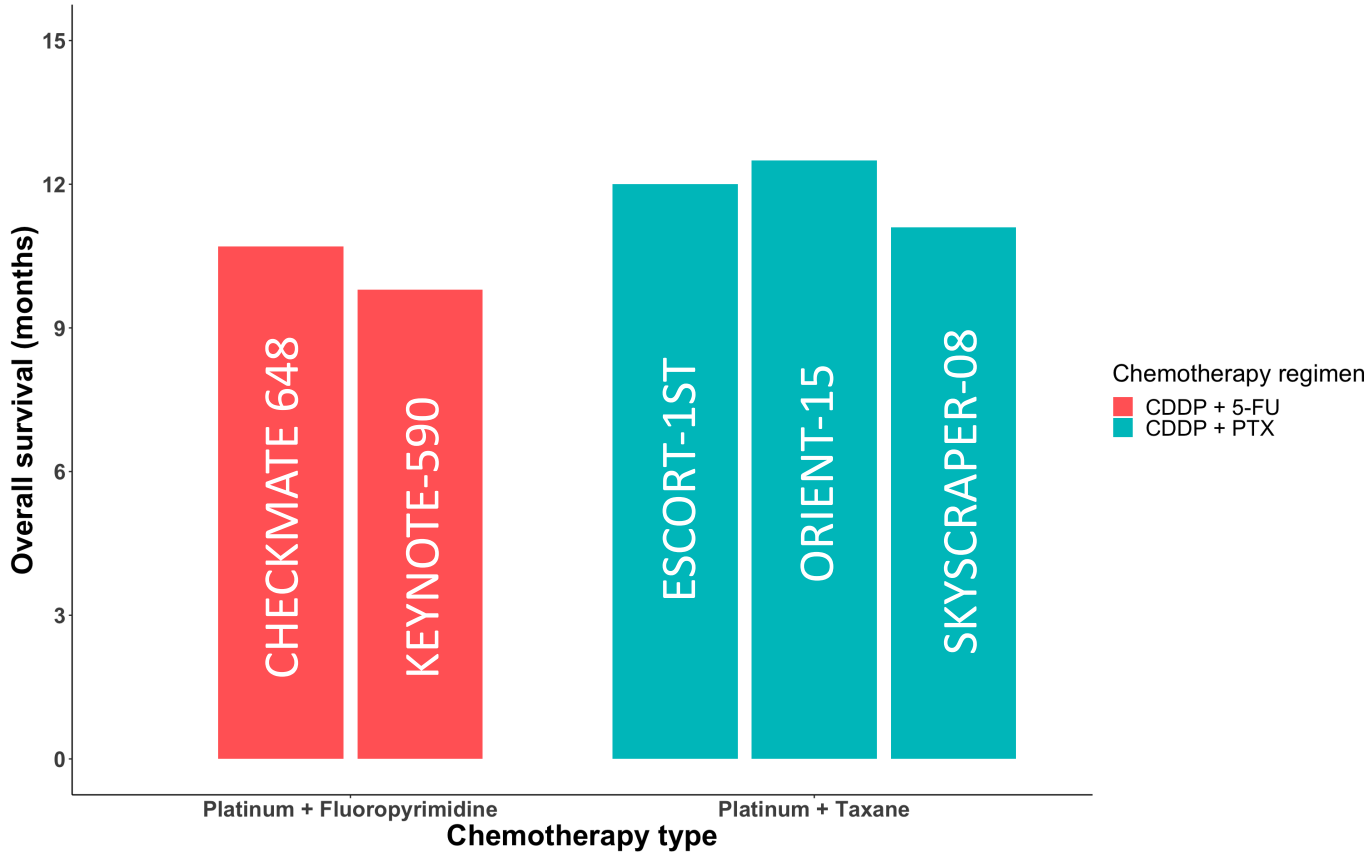
Systemic treatment of advanced EC

Chemotherapy backbone with ICI



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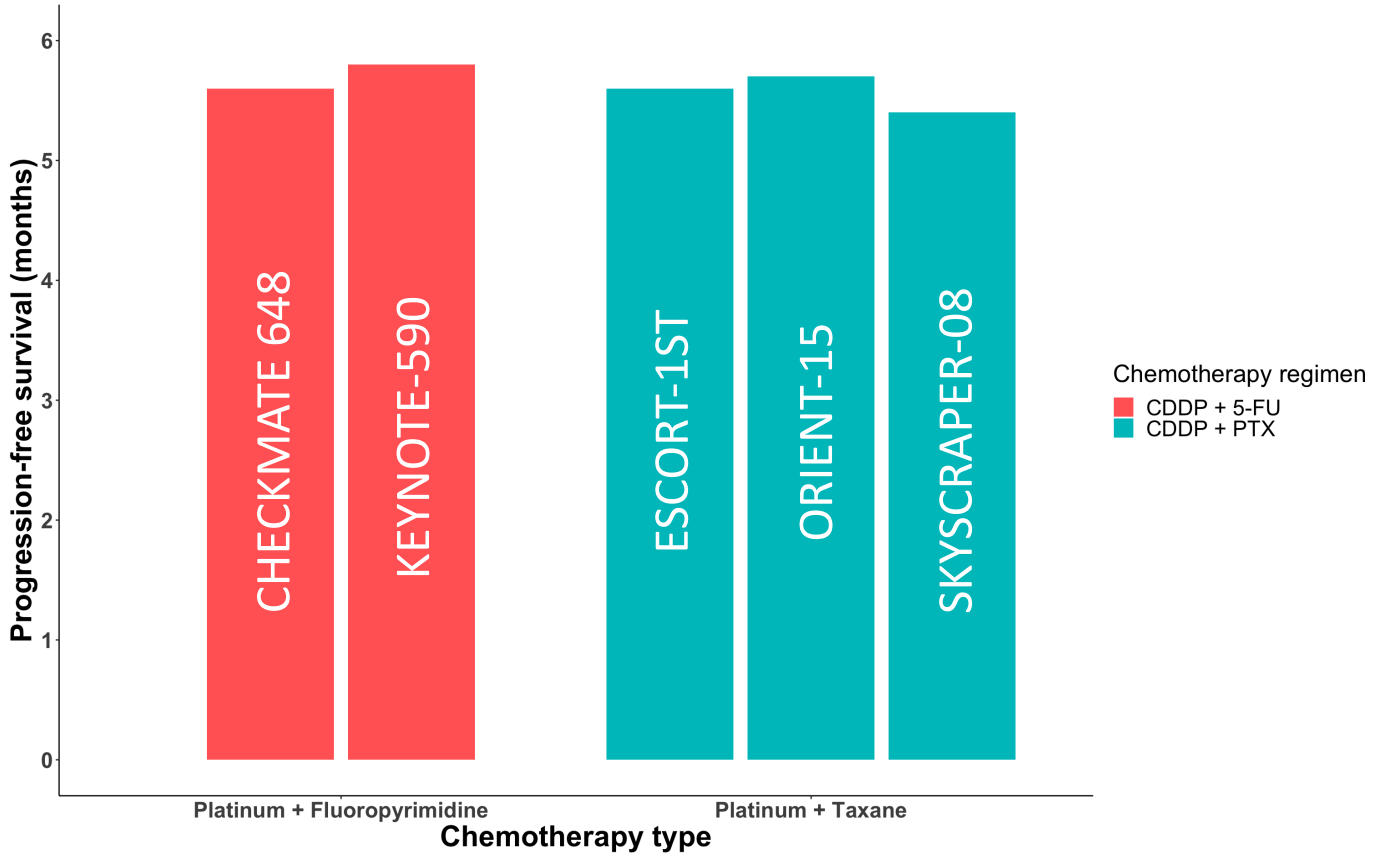
Chemotherapy backbone with ICI



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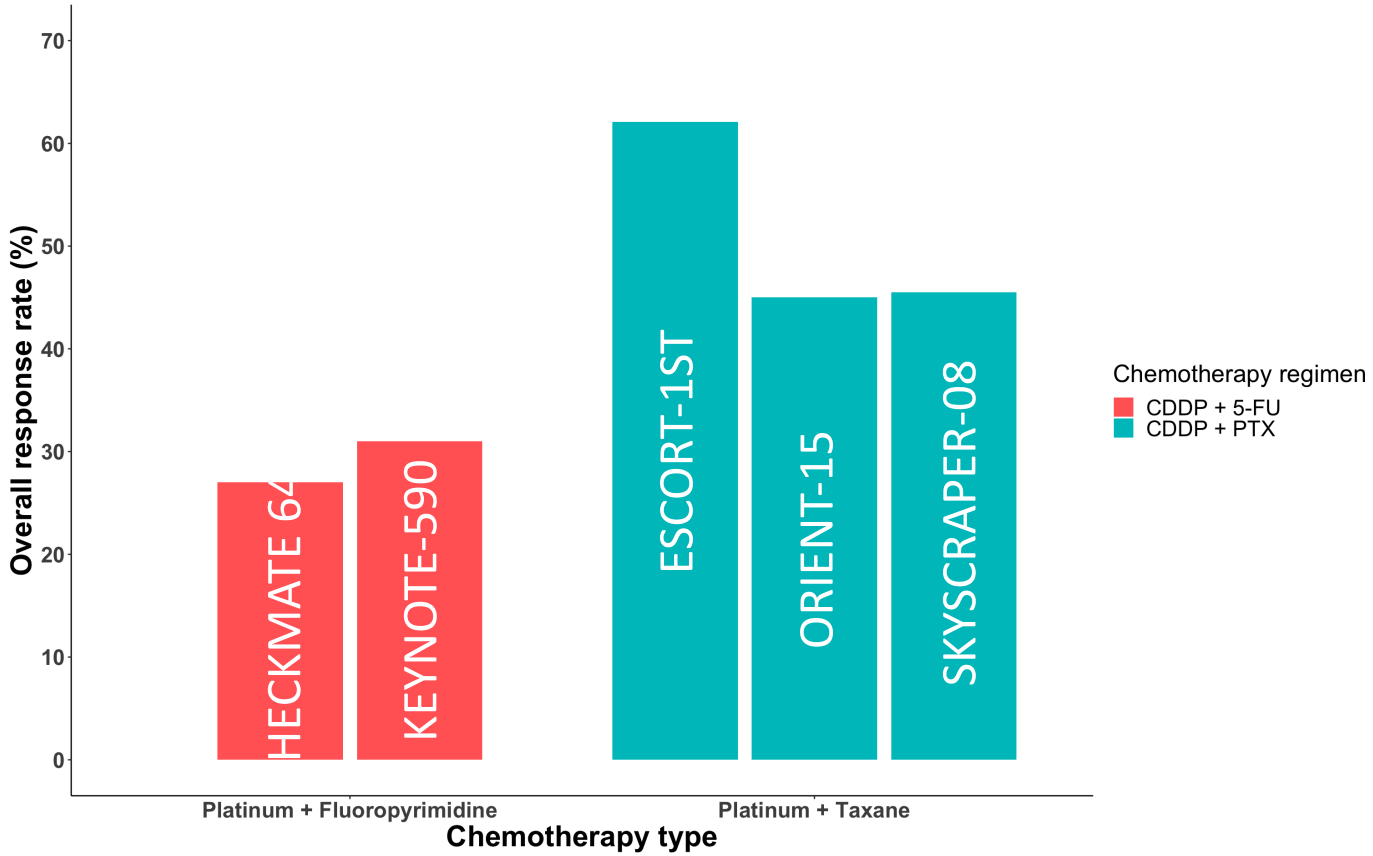
Systemic treatment of advanced EC

Chemotherapy backbone with ICI



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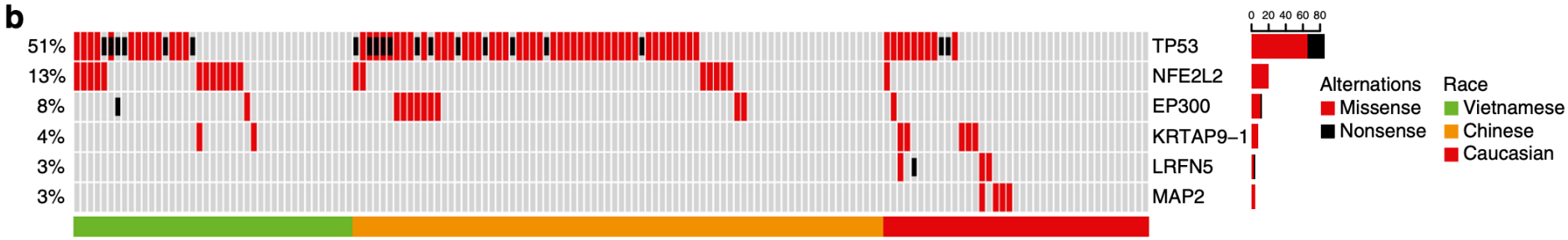
Systemic treatment of advanced EC

Chemotherapy backbone with ICI



Increased frequency in the Asian population

- Mutated TP53
- Mutated NFE2L2
- Mutated EP300

There seem to be differences in the molecular background of ESCC between the East and the West

1. Deng J, et al. Nat Commun 2017;8(1):1533.

Systemic treatment of advanced EC

Primary tumor radiotherapy in M1 disease

Retrospective data

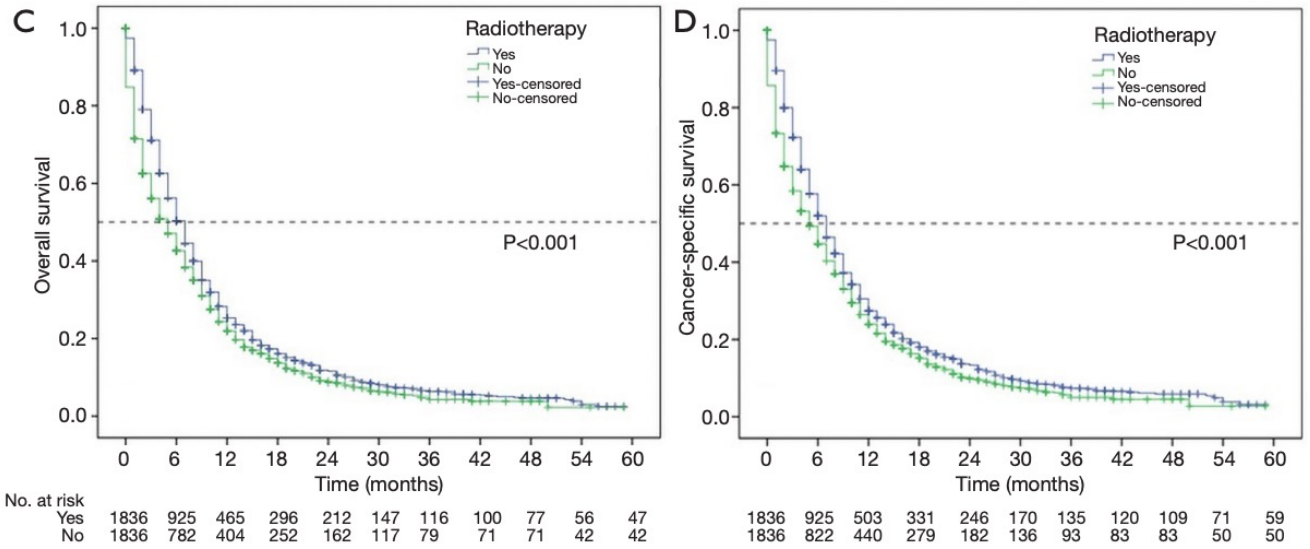


Figure 2 OS and CSS curves for the effect of radiotherapy. (A,B) Before propensity score matching; (C,D) after propensity score matching. OS, overall survival; CSS, cancer-specific survival.

1. Li X, et al. Transl Cancer Res 2019;8(4):1074-85.

Systemic treatment of advanced EC

Primary tumor radiotherapy in M1 disease

Phase II RCT

Table 3 Overall survival

	CCRT	CT	*p*
1y-OS	73.3%	46.6%	0.001
2y-OS	43.3%	26.7%	0.010
Median OS	18.3m	10.2m	0.001

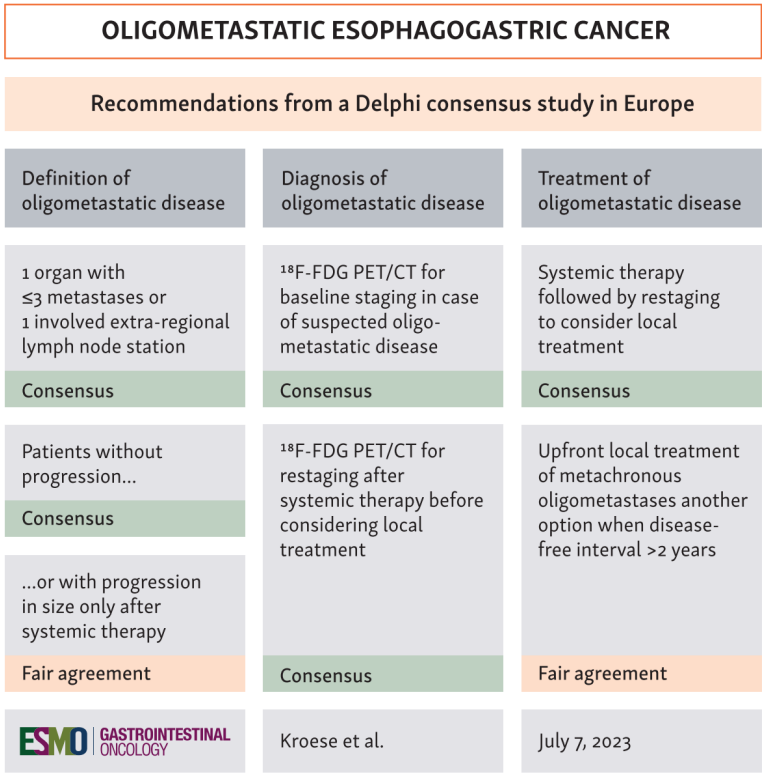
Table 4 progression-free survival

	CCRT	CT	*p*
1y-PFS	43.3%	30.0%	0.001
2y-PFS	26.7%	16.7%	0.011
Median PFS	9.3m	4.7m	0.021

1. Li T, et al. J Clin Oncol 2016;34(suppl;abstr 4050).

Systemic treatment of advanced EC

Oligometastatic disease



1. Kroese TE, et al. ESMO Gastrointest Oncol 2023;2,100009.

Systemic treatment of advanced EC

Oligometastatic disease

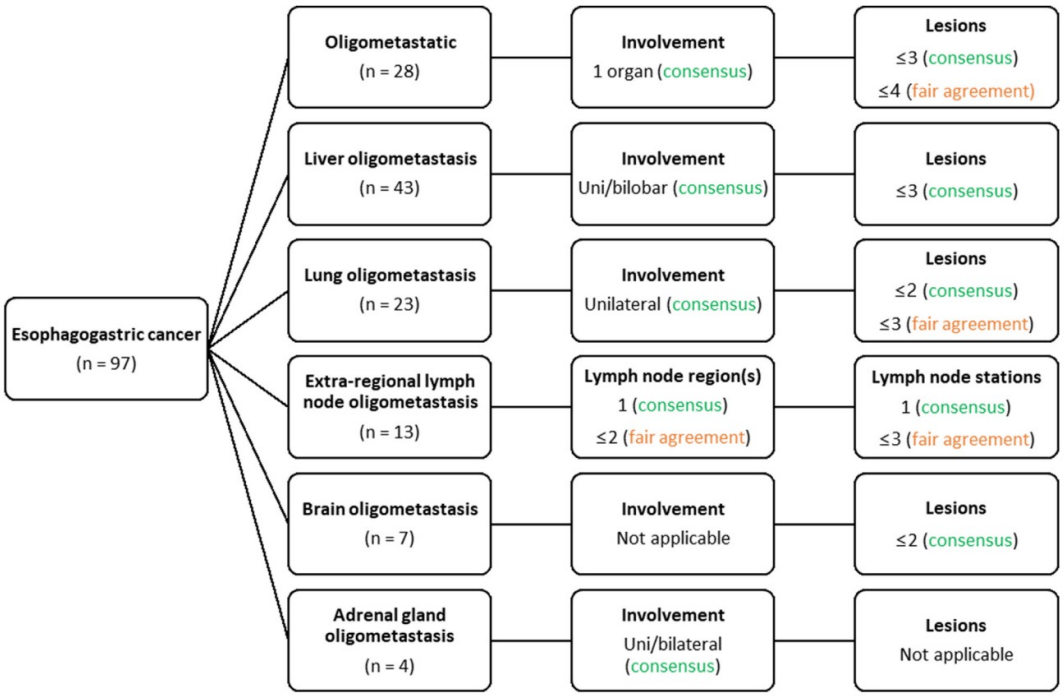
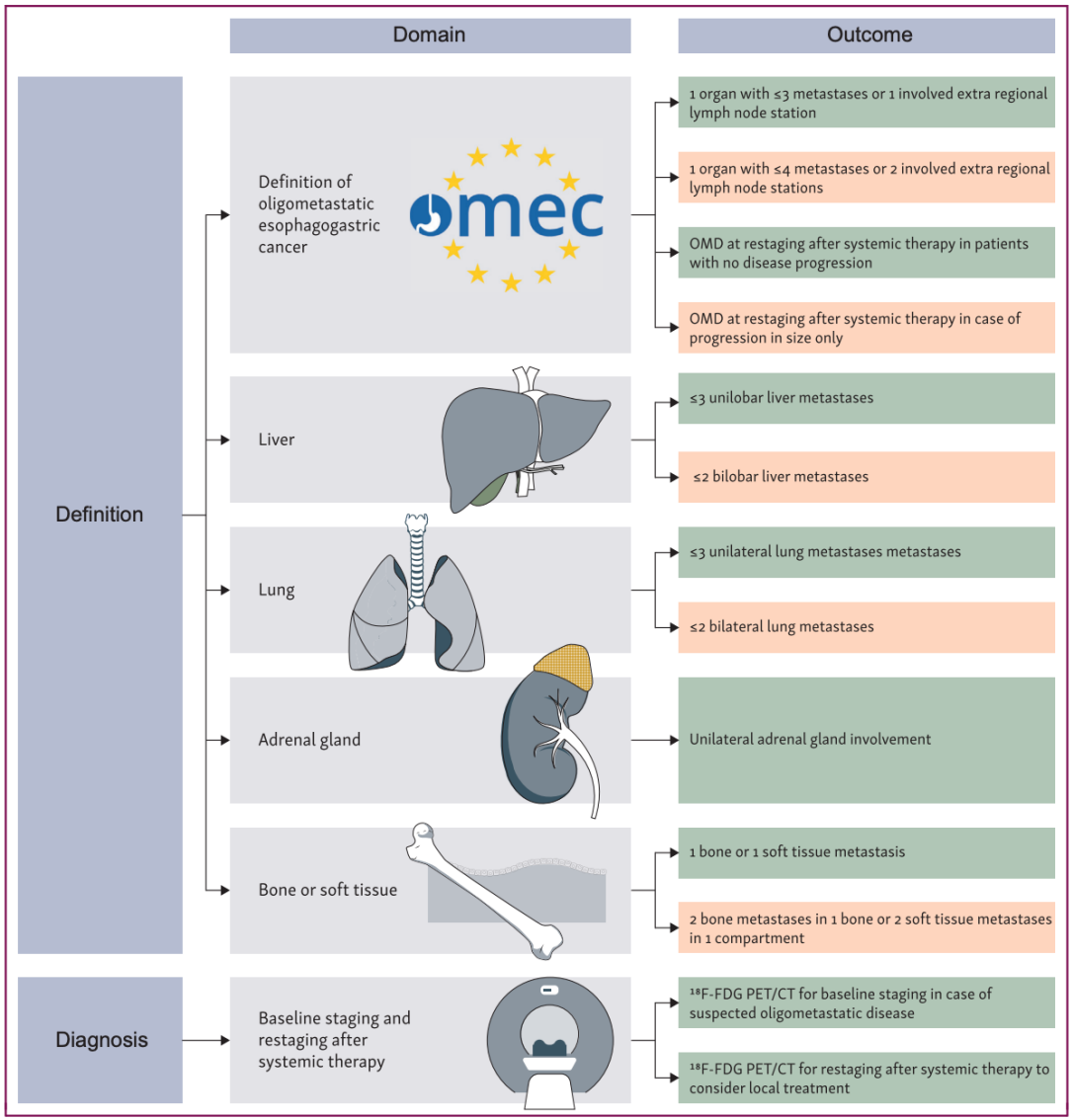


Fig. 2. Summary of definition of oligometastatic esophagogastric cancer according to literature and study protocols.

1. Kroese TE, et al. Eur J Cancer 2022;166:254-69.



1. Kroese TE, et al. ESMO Gastrointest Oncol 2023;2,100009.

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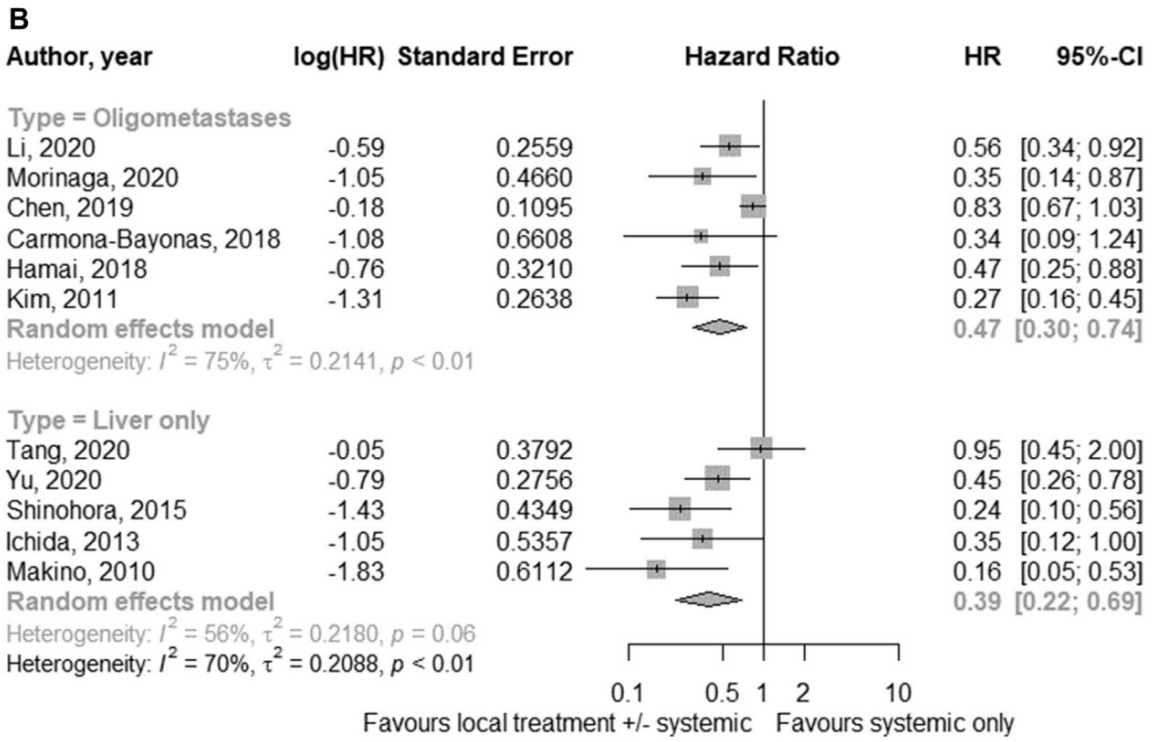
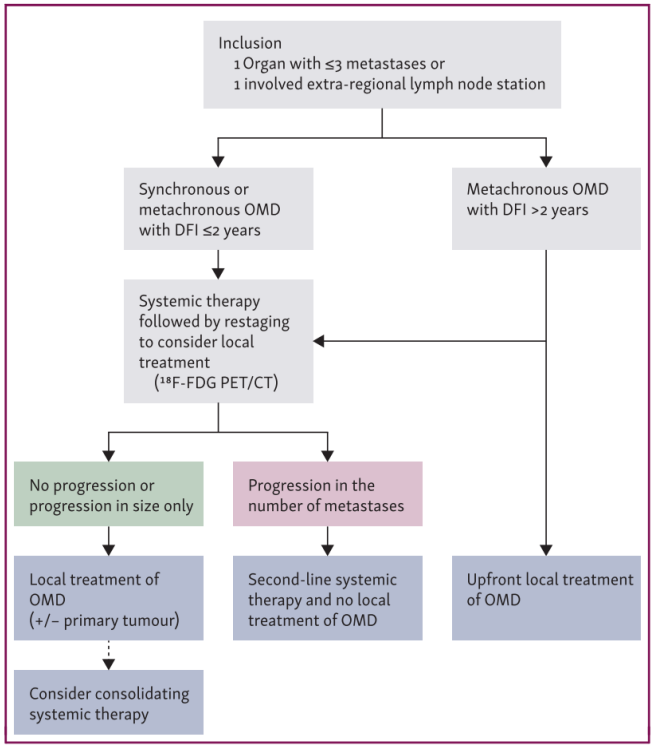
Oligometastatic disease



1. Li T, et al. J Clin Oncol 2016;34(suppl;abstr 4050).

Systemic treatment of advanced EC

Oligometastatic disease



1. Kroese TE, et al. Eur J Cancer 2022;166:254-69.

victor.jesus@medicos.oncoclinicas.com
victor.jesus@cepon.org.br