PD-L1 Expression and Immune Checkpoint Inhibitors for the Treatment of Metastatic or Unresectable Esophageal Squamous Cell Carcinoma (ESCC)

Oncologic Drugs Advisory Committee (ODAC) Meeting

September 26, 2024

Sandra J. Casak, M.D.
Team Leader, Gastrointestinal Malignancies
Division of Oncology 3, Office of Oncologic Diseases

Immune Checkpoint Inhibitors Approvals - First-Line treatment, ESCC

Pembrolizumab

- **in combination with platinum- and fluoropyrimidine-based chemotherapy (3/22/2021)**
  - Supporting study: KEYNOTE-590 (KN-590)

Nivolumab

- **in combination with platinum- and fluoropyrimidine-based chemotherapy (5/27/2022)**
  - Supporting study: CHECKMATE-648 (CM-648)
- **in combination with ipilimumab**
  - Supporting study: CHECKMATE-648

Under review: Tislelizumab in combination with platinum-containing chemotherapy

- Supporting study: RATIONALE-306 (RM-306)

Overall Survival Across Trials

	KN-590	CM-648 (nivo+chemo)	RN-306
ITT	**N= 749**	**N= 645**	**N= 649**
HR (95% CI)	0.73 (0.62, 0.86)	0.74 (0.61, 0.90)	0.66 (0.54, 0.80)
P value	<0.0001	0.0021	<0.0001
ESCC with known PD-L1 status	**N= 548**	**N= 629**	**N= 648**
HR (95% CI)	0.72 (0.59, 0.87)	0.73 (0.60, 0.88)	0.68 (0.56, 0.82)

ITT: intent-to-treat; CI: confidence interval; PD-L1: programmed death cell-ligand 1

OS Analyses by PD-L1 Cutoff, ESCC Population

	All ESCC	PD-L1 ≥ 1	PD-L1 ≥ 10	PD-L1 <1	PD-L1 <10
KEYNOTE-590 (CPS)					
OS HR (95% CI)	0.72 (0.59, 0.87)	0.69 (0.56, 0.85)	0.57 (0.44, 0.75)	1.00 (0.54, 1.85)	0.95 (0.71, 1.26)
CHECKMATE-648 (CPS)					
OS HR (95% CI)	0.73 (0.60, 0.88)	0.69 (0.56, 0.84)	0.62 (0.46, 0.84)	0.93 (0.46, 1.91)	0.77 (0.60, 1.01)
RATIONALE-306 (TAP)					
OS HR (95% CI)	0.68 (0.56, 0.82)	0.66 (0.52, 0.82)	0.66 (0.48, 0.92)	1.34 (0.73, 2.46)	0.76 (0.58, 0.99)

OS: overall survival; CPS: combined positive score; TAP: tumor area positivity

ESCC Approvals: Information in Labeling

	KN-590 (Pembrolizumab)	CM-648 (Nivolumab)
ITT	Prespecified HR 0.73 (95% CI 0.62, 0.86)	Prespecified HR 0.74 (95% CI 0.61, 0.90)
PD-L1 ≥ 1		Prespecified HR 0.54 (95% CI 0.41, 0.84)
PD-L1 ≥ 10	Prespecified HR 0.62 (95% CI 0.49, 0.78)	
PD-L1 < 1		Exploratory HR 0.99 (95% CI 0.76, 1.29)
PD-L1 <10	Exploratory HR 0.86 (95% CI 0.68, 1.10)	

Professional Society Guidelines

	PD-L1	Pembrolizumab	Nivolumab
ASCO	≥ 1 (TPS)		Moderate quality evidence Strong recommendation CPS may be used if TPS is not available
	≥ 10 (CPS)	High quality evidence Strong recommendation	
NCCN	Agnostic of status		Category 1
	≥ 10 (CPS)	Category 1 (combination with fluoropyrimidine + cisplatin)	
	<10 (CPS)	Category 2B (combination with fluoropyrimidine + oxaliplatin or cisplatin)	
ESMO	≥ 1 (TPS)		Strongly recommended (evidence from RCT)
	≥ 10 (CPS)	Strongly recommended (evidence from RCT)	

RCT: randomized controlled trial

Shah M, J Clin Oncol V41 N7 March 2023 https://ascopubs.org/doi/10.1200/JCO.22.02331; NCCN Guidelines v3.2024 –https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf; Obermannova R, et al. 2022, Ann Onc V33(10) 992-1004 https://www.sciencedirect.com/science/article/pii/S0923753422018506?via%3Dihub

Why Discuss PD-L1 in the ESCC Population Now?

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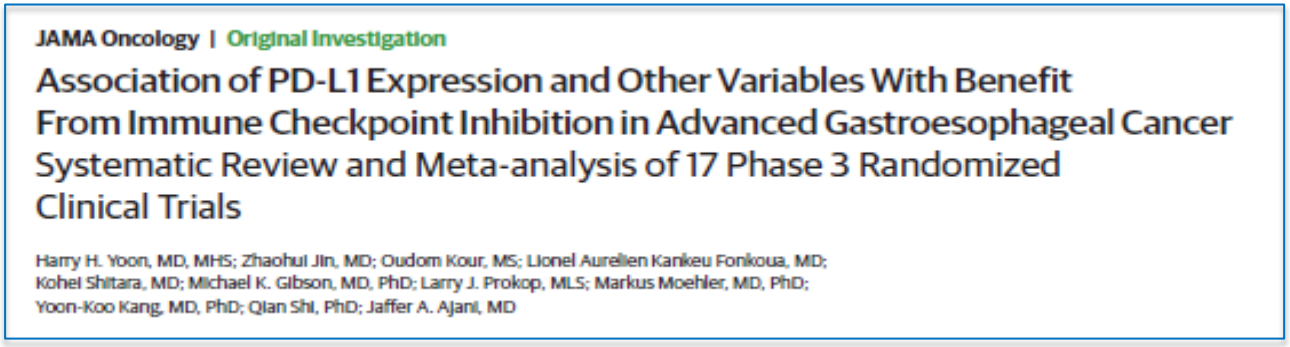


JAMA Oncology | Original Investigation

Association of PD-L1 Expression and Other Variables With Benefit From Immune Checkpoint Inhibition in Advanced Gastroesophageal Cancer Systematic Review and Meta-analysis of 17 Phase 3 Randomized Clinical Trials

Harry H. Yoon, MD, MHS; Zhaohui Jin, MD; Oudom Kour, MS; Lionel Aurelien Kankeu Fonkoua, MD; Kohei Shitara, MD; Michael K. Gibson, MD, PhD; Larry J. Prokop, MLS; Markus Moehler, MD, PhD; Yoon-Koo Kang, MD, PhD; Qian Shi, PhD; Jaffer A. Ajani, MD

- 11,166 participants
- 5067 with ESCC
- 2739 in the 1L setting

- In ESCC (all lines), PD-L1 TPS was the strongest predictor of ICIs benefit ≥10:
  - TPS “high” (≥1 in all but one trial which used ≥ 10) OS HR 0.60 (95% CI 0.53, 0.68)
  - TPS “non-high” OS HR 0.84 (95% CI 0.75, 0.95)
- Second strongest predictor was CPS “high” (≥10 in all trials but one trial which used ≥ 1):
  - CPS “high” OS HR 0.62 (95% CI 0.54, 0.69)
  - CPS “non-high” OS HR 0.82 (95% CI 0.72, 0.94)

ICI: immune checkpoint inhibitor; TPS: tumor proportion score

Yoon H, 2022
https://pubmed.ncbi.nlm.nih.gov/36006624/

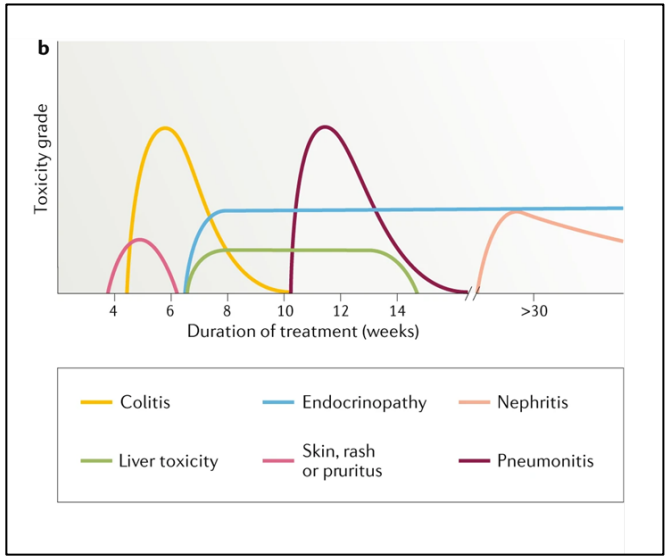
Subgroup Analyses Considerations

- Replication of results across multiple trials
- Sample ascertainment
- Biological plausibility
- Study design

Safety – Immune Related Adverse Events

	All Grades	Grade ≥ 3
Diarrhea	6 to 19%	1%
Colitis	1 to 4	0.3 to 2%
Pulmonary	1.5 to 5%	0 to 2%
Rash	9 to 16%	0.2 to 3.5%
Neurological	NR to 0.3%	NR to 0.3%
Endocrinopathy	7.3 to 23.4%	0 to 2%
Hepatic	0.3 to 10.8%	0 to 1.5%
Renal	NR to 2%	0 to 0.5%

Time course of immune related adverse events



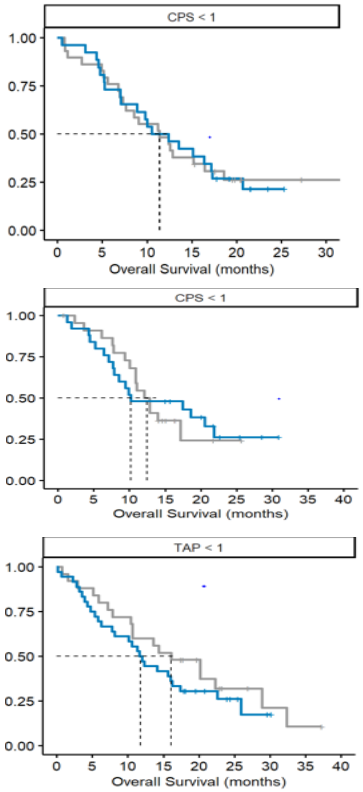
Source: (Adapted-Table and Copied-Figure) Martins et al., Nature Reviews, 2019 https://www.nature.com/articles/s41571-019-0218-0

NR: not reported

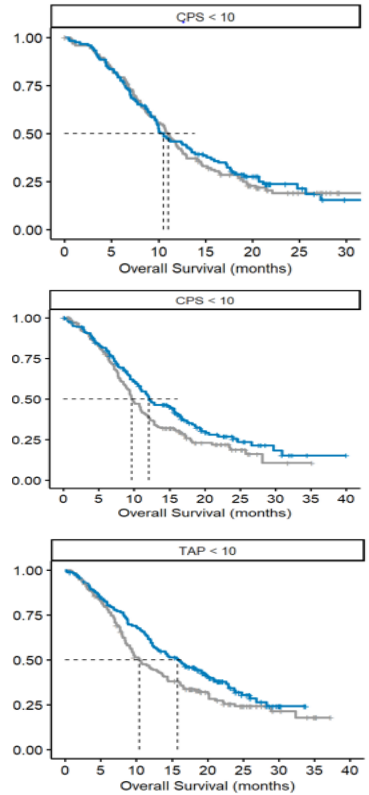
Data Summary

	All ESCC		PD-L1 <1		PD-L1 <10	
KN590	**P+CHT**	**CHT**	**P+CHT**	**CHT**	**P+CHT**	**CHT**
N	**274**	**274**	**26**	**29**	**121**	**126**
mOS (95% CI)	12.6 (10.2, 14.3)	9.8 (8.6, 11.1)	11.4 (7.0, 17.1)	11.4 (7.0, 16.5)	10.5 (9.2, 13.5)	11.1 (9.1, 12.4)
OS HR (95% CI)	0.72 (0.59, 0.87)		1.00 (0.54, 1.85)		0.95 (0.71, 1.26)	
CM648	**Nivo+CHT**	**CHT**	**Nivo+CHT**	**CHT**	**Nivo+CHT**	**CHT**
N	**311**	**318**	**25**	**23**	**163**	**156**
mOS (95% CI)	13.4 (11.7, 15.8)	10.8 (9.4, 12.1)	10.2 (7.7, 21.8)	12.5 (9.3, 17.1)	12.1 (10.6, 15.7)	9.7 (8.8, 11.1)
OS HR (95% CI)	0.73 (0.60, 0.88)		0.93 (0.46, 1.91)		0.77 (0.60, 1.01)	
RN306	**Tisle+CHT**	**CHT**	**Tisle+CHT**	**CHT**	**Tisle+CHT**	**CHT**
N	**325**	**323**	**36**	**25**	**151**	**168**
mOS (95% CI)	17.2 (15.8, 20.1)	10.6 (9.3, 12.1)	11.8 (6.2, 16.3)	16.1 (10.4, 28.9)	15.8 (12.3, 19.6)	10.4 (9.0, 13.6)
OS HR (95% CI)	0.68 (0.56, 0.82)		1.34 (0.73, 2.46)		0.76 (0.58, 0.99)	

PD-L1 <1



PD-L1 <10



Source: FDA analyses (refer to briefing document for methodology)
CHT: chemotherapy

Subgroup Analyses Considerations

- Replication of results across multiple trials ✓
- Sample ascertainment ✓
- Biological plausibility ✓
- Study design ±

Summary

- Current approvals in ESCC are agnostic of PD-L1 status

- Consistently across 3 applications, distinct treatment effect emerges based on PD-L1 status

PD-L1 status	% population	OS Benefit
High (≥ 10)	35-52%	Yes
Intermediate (1-<10)	35-43%	Lesser magnitude
Low (<1)	8-10%	Marginal or potential detriment

- In patients with PD-L1 <1, treatment with immune checkpoint inhibitors may potentially expose to toxicity without a clear potential for benefit

Discussion Question

FDA would like the committee to discuss the risk and benefits of the treatment with anti PD-1 antibodies for the first line treatment of patients with metastatic or unresectable esophageal squamous cell carcinoma with PD-L1 expression <1.

Voting Question

Is the risk:benefit assessment favorable for the use of anti-PD-1 antibodies in first line unresectable or metastatic esophageal squamous cell carcinoma with PD-L1 expression <1?

- Yes
- No

PD-L1 expression and immune checkpoint inhibitors for the first line treatment of metastatic or unresectable esophageal squamous cell carcinoma (ESCC)

Oncologic Drugs Advisory Committee (ODAC) Meeting

September 26, 2024

Geetika Srivastava, M.D., M.S.P.H.
Clinical Reviewer, Gastrointestinal malignancies
Division of Oncology 3, Office of Oncologic Diseases

FDA Review Team

Richard Pazdur, Director, Oncology Center of Excellence (OCE)	Paul Kluetz, Deputy Director, OCE; Supervisory Associate Director, Office of Oncologic Diseases
Steven Lemery Director, Division of Oncology 3 (DO3)	Chana Weinstock, Acting Deputy Division Director, DO3
Sandra J. Casak, Clinical Team Lead, DO3	Vaibhav Kumar, Clinical Reviewer, DO3
Naomi Horiba, Clinical Reviewer, DO3	Geetika Srivastava, Clinical Reviewer, DO3
Pallavi Mishra-Kalyani, Deputy Division Director, Division of Biometrics V (DBV)	Chuck Song, Statistical Team Lead, DBV
Sirisha Mushti, Statistical Reviewer, DBV	Yiming Zhang, Statistical Reviewer, DBV
Zhou Feng, Statistical Reviewer, DBV	Amy Sessums, Regulatory Project Manager, DO3
Shyam Kalavar, Deputy Branch Chief for Molecular Pathology and Cytology, Center for Devices and Radiological Health	

Overview

- Current approvals in ESCC: PD-L1 agnostic
- Data from individual studies and pooled analysis
- Consistent pattern across trials
    - Favorable risk: benefit in PD-L1 “high”
    - Uncertain benefit in PD-L1 <1
- Risk: benefit discussion

Comparison of Study Designs

	KEYNOTE 590 (Pembrolizumab)	CHECKMATE 648 (Nivolumab)	RATIONALE 306 (Tislelizumab)
Tumor type	Esophageal carcinoma or GEJ carcinoma	Esophageal squamous cell carcinoma	Esophageal squamous cell carcinoma
PD-L1 expression	Any	Any	Any
PD-L1 assay	Agilent PD-L1 IHC 22C3 pharmDx assay (CPS)	Agilent/Dako PD-L1 IHC 28-8 pharmDx assay (Tumor cell [TC] PD-L1) → retrospective scoring CPS	PD-L1- visually-estimated combined positive score (vCPS or TAP) using the Ventana SP263 assay
Stratification factors	1. Tumor histology (SCC vs. adenocarcinoma), 2. Geographic region (Asia vs. non-Asia), 3. ECOG PS (0 vs. 1)	1. Geographic Region (East Asia [Japan, Korea, and Taiwan] vs. rest of Asia vs. ROW) **2. PD-L1 status (TPS ≥ 1 vs < 1/ indeterminate)** 3. Organ metastases (≤1 vs.≥2) 4. ECOG PS (0 vs 1)	1. Geographic Region (Asia [excluding Japan] vs Japan vs ROW) 2. Prior definitive therapy (yes vs. no) 3. Platinum with fluoropyrimidine vs. platinum with paclitaxel
Primary endpoint(s)	1. OS (ESCC CPS ≥ 10; ESCC; CPS ≥ 10, ITT) 2. PFS (ESCC; CPS ≥ 10; ITT)	1. OS TC ≥ 1 2. PFS (BICR) OS TC ≥ 1	1. OS ITT

Source: KEYNOTE-590 Protocol; EAC- Esophageal Adenocarcinoma; ESCC- Esophageal Squamous Cell Carcinoma; GEJ- Gastroesophageal Junction, RECIST- Response Evaluation Criteria in Solid Tumors; ECOG- Eastern Oncology Cooperative Group; PS- Performance Status; 5FU- 5-Fluorouracil; IHC- Immunohistochemistry ;OS- Overall Survival; PFS- Progression Free Survival.; CPS- Combined positive score; TPS- Tumor Positivity score; TAP- tumor area positivity; ORR- Overall response rate; ITT- Intention to treat; BICR- Blinded independent review committee; ROW- rest of world.

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Overall Survival Results

	KEYNOTE 590	CHECKMATE 648	RATIONALE 306
ITT	**N = 749**	**N = 645**	**N = 649**
Median OS - ICI + chemo arm (95% CI) - Control arm (95% CI)	 12.4 (10.5, 14.0) 9.8 (8.8, 10.8)	 13.2 (11.1, 15.7) 10.7 (9.4, 11.9)	 17.2 (15.8, 20.1) 10.6 (9.3, 12.1)
OS HR (95% CI)	0.73 (0.62, 0.86)	0.74 (0.61, 0.90)	0.66 (0.54, 0.80)
Pre-specified PD-L1 Group	**N = 383 (CPS ≥ 10)**	**N = 315 (TPS ≥ 1)**	**N = 223 (TAP ≥ 10)**
Median OS - ICI + chemo arm (95% CI) - Control arm (95% CI)	 13.5 (11.1, 15.6) 9.4 (8.0, 10.7)	 15.4 (11.9, 19.5) 9.1 (7.7, 10.0)	 16.6 (15.3, 24.4) 10.0 (8.6, 13.3)
OS HR (95% CI)	0.62 (0.49, 0.78)	0.54 (0.41, 0.71)	0.62 (0.44, 0.87)

HR= Hazard Ratio; ICI= immune checkpoint inhibitor; Chemo= chemotherapy; CI= confidence interval

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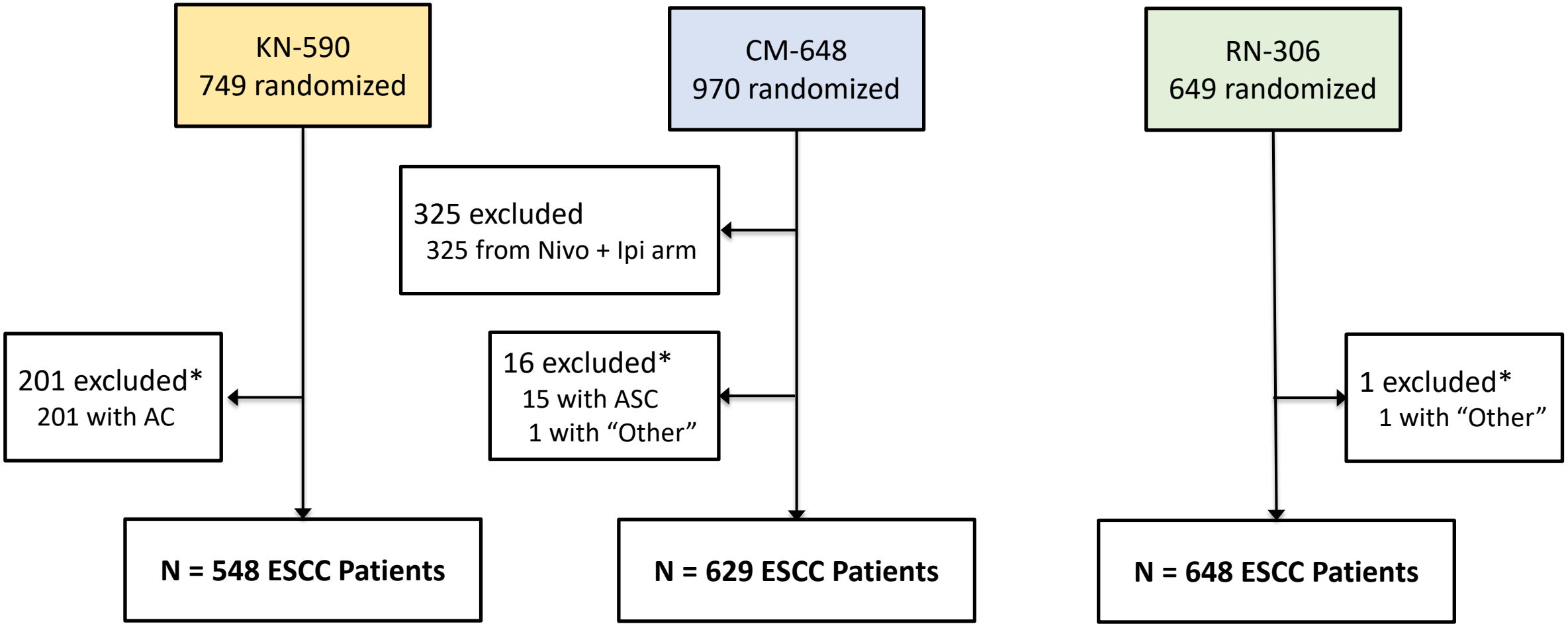
FDA ESCC MODIFIED POPULATION

ESCC=Esophageal squamous cell carcinoma

FDA ESCC Modified Population



Abbreviation: ASC = Adenosquamous carcinoma, AC = Adenocarcinoma, ESCC = Esophageal squamous carcinoma, Nivo= nivolumab; Ipi=ipilimumab.

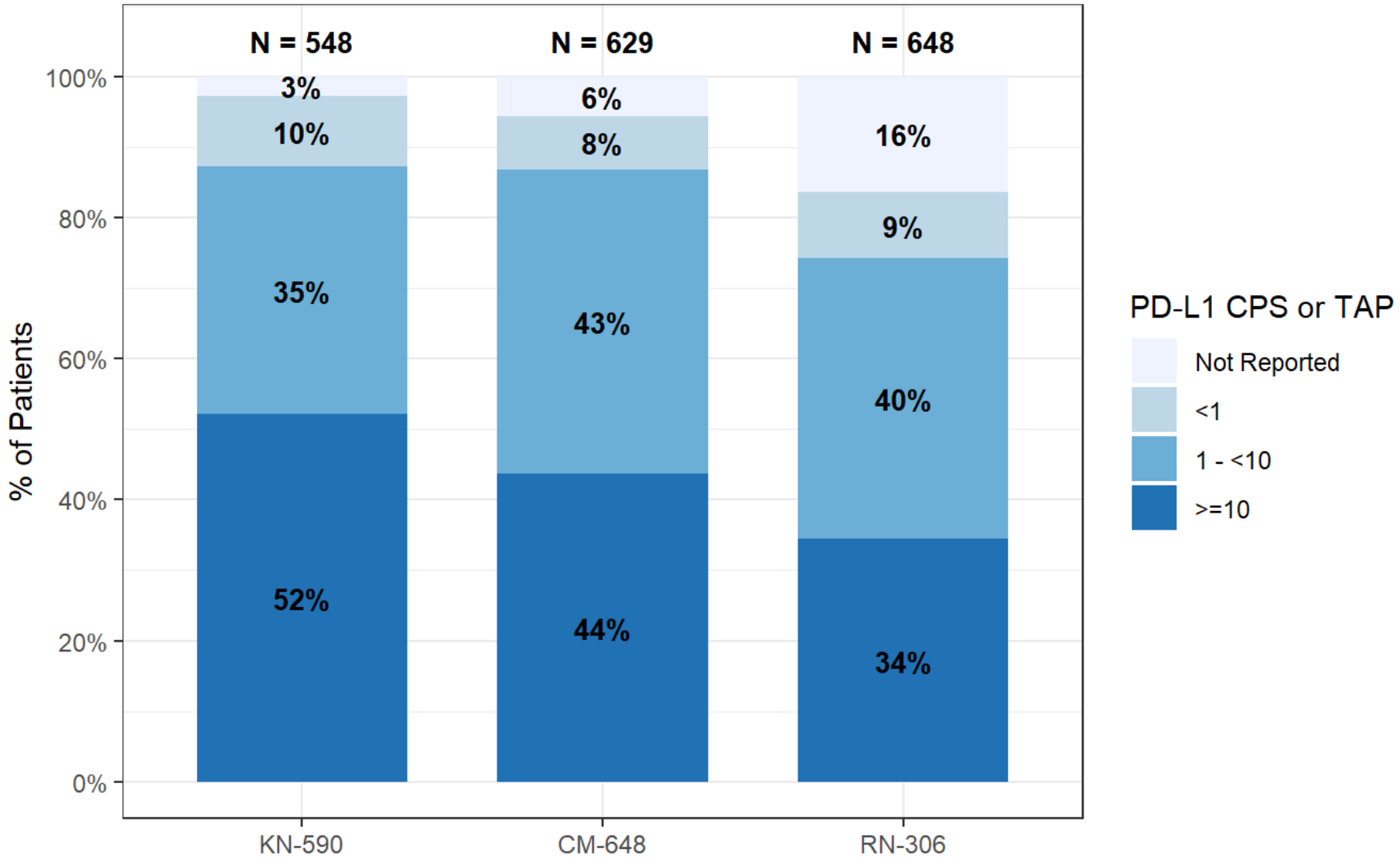
*Exclusion based on histology

Demographic and Disease Characteristics of ESCC Patients

Characteristic	KN-590 N = 548	CM-648 N = 629	RN-306 N = 648	Overall N = 1,825
Sex				
Female	17%	18%	13%	16%
Male	83%	82%	87%	84%
Age				
Median (Range)	63 (32 – 94)	64 (26 – 86)	64 (26 – 84)	64 (26 – 94)
Race				
Asian	66%	72%	75%	71%
White	25%	25%	24%	25%
Black/African American	0.9%	1.0%	0	0.6%
Multiple	1.5%	0	0	0.4%
Ethnicity				
Hispanic/Latino	13%	5%	0.9%	6%
Not Hispanic/Latino	83%	42%	98%	74%
ECOG				
0	38%	47%	33%	39%
1	62%	53%	67%	61%
Disease status				
Metastatic	91%	58%	86%	78%
Recurrent	0	28%	0	10%
Unresectable	9%	15%	14%	13%

KN=KEYNOTE ; CM=CHECKMATE; RN=RATIONALE

Tumor PD-L1 Distribution Across Studies (ESCC)



KN=Keynote; CM=Checkmate; RN=Rationale

EFFICACY RESULTS (ESCC-modified population)

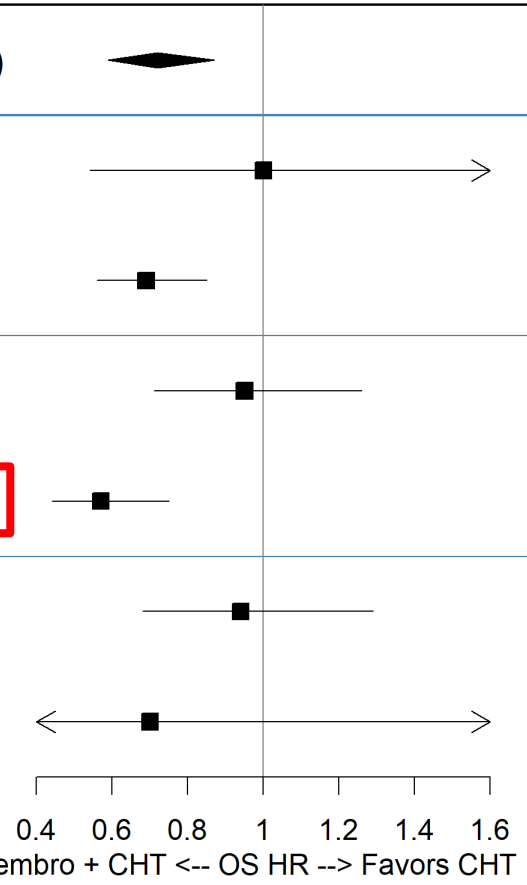
ESCC - Overall Survival Results

ESCC	KEYNOTE 590 N = 548	CHECKMATE 648 N = 629	RATIONALE 306 N = 648
Median OS - ICI + chemo arm (95% CI) - Chemo arm (95% CI)	 12.6 (10.2, 14.3) 9.8 (8.6, 11.1)	 13.4 (11.7, 15.8) 10.8 (9.4, 12.1)	 17.2 (15.8, 20.1) 10.6 (9.3, 12.1)
OS HR (95% CI)	**0.72** (0.59, 0.87)	**0.73** (0.60, 0.88)	**0.68** (0.56, 0.82)

ESCC : OVERALL SURVIVAL BY PD-L1 CUT OFFS

ESCC: KN590 OS Forest Plot by PD-L1 Cutoff (CPS)

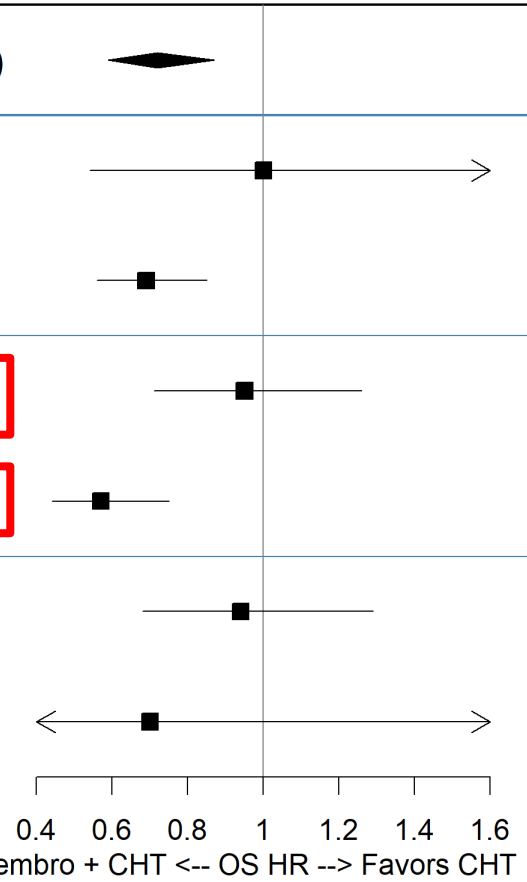
Subgroup	% of Pts	Pembro + CHT Evt / N	CHT Evt / N	HR (95% CI)	Pembro + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**190/274**	**222/274**	**0.72 (0.59 ,0.87)**	**12.6 (10.2, 14.3)**	**9.8 (8.6, 11.1)**
CPS < 1	10.0	20/26	21/29	1 (0.54 ,1.85)	11.4 (7, 17.1)	11.4 (7, 16.5)
CPS ≥ 1	87.2	166/238	198/240	0.69 (0.56 ,0.85)	12.6 (10.1, 14.3)	9.8 (8.4, 10.8)
CPS < 10	45.1	92/121	98/126	0.95 (0.71 ,1.26)	10.5 (9.2, 13.5)	11.1 (9.1, 12.4)
CPS ≥ 10	52.2	94/143	121/143	0.57 (0.44 ,0.75)	13.9 (11.1, 17.7)	8.8 (7.8, 10.5)
CPS 1 - < 10	35.0	72/95	77/97	0.94 (0.68 ,1.29)	10.2 (9.1, 13.5)	10.8 (8.9, 12.1)
Not Reported	2.7	4/10	3/5	0.7 (0.16 ,3.12)	NA (0.1, NA)	8.9 (7.2, NA)



Pembro = pembrolizumab; CHT = chemotherapy; Evt = event

ESCC: KN590 OS Forest Plot by PD-L1 Cutoff (CPS)

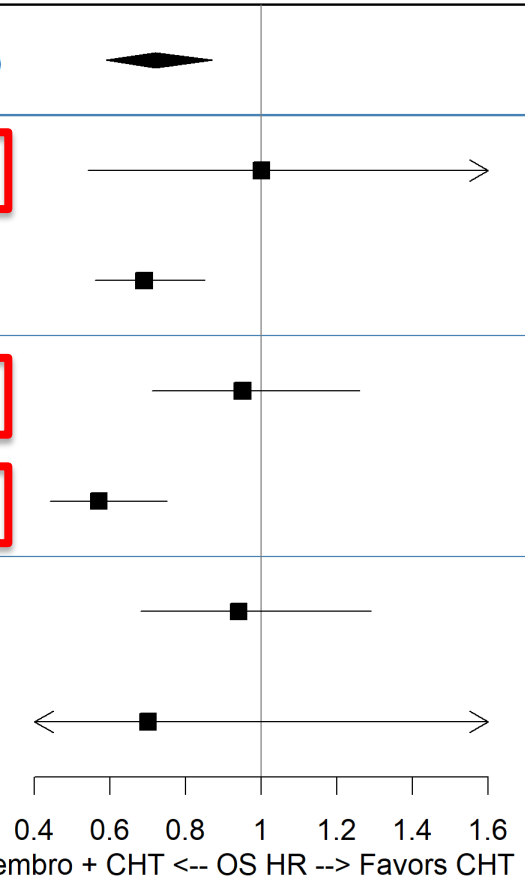
Subgroup	% of Pts	Pembro + CHT Evt / N	CHT Evt / N	HR (95% CI)	Pembro + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**190/274**	**222/274**	**0.72 (0.59 ,0.87)**	**12.6 (10.2, 14.3)**	**9.8 (8.6, 11.1)**
CPS < 1	10.0	20/26	21/29	1 (0.54 ,1.85)	11.4 (7, 17.1)	11.4 (7, 16.5)
CPS ≥ 1	87.2	166/238	198/240	0.69 (0.56 ,0.85)	12.6 (10.1, 14.3)	9.8 (8.4, 10.8)
CPS < 10	45.1	92/121	98/126	0.95 (0.71 ,1.26)	10.5 (9.2, 13.5)	11.1 (9.1, 12.4)
CPS ≥ 10	52.2	94/143	121/143	0.57 (0.44 ,0.75)	13.9 (11.1, 17.7)	8.8 (7.8, 10.5)
CPS 1 - < 10	35.0	72/95	77/97	0.94 (0.68 ,1.29)	10.2 (9.1, 13.5)	10.8 (8.9, 12.1)
Not Reported	2.7	4/10	3/5	0.7 (0.16 ,3.12)	NA (0.1, NA)	8.9 (7.2, NA)



Pembro = pembrolizumab; CHT = chemotherapy; Evt = event

ESCC: KN590 OS Forest Plot by PD-L1 Cutoff (CPS)

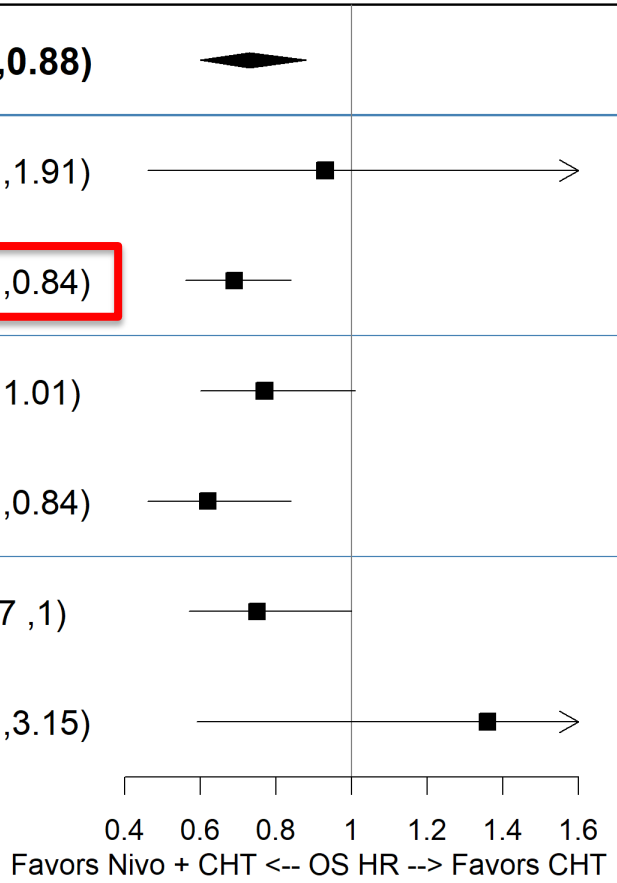
Subgroup	% of Pts	Pembro + CHT Evt / N	CHT Evt / N	HR (95% CI)	Pembro + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**190/274**	**222/274**	**0.72 (0.59 ,0.87)**	**12.6 (10.2, 14.3)**	**9.8 (8.6, 11.1)**
CPS < 1	10.0	20/26	21/29	1 (0.54 ,1.85)	11.4 (7, 17.1)	11.4 (7, 16.5)
CPS ≥ 1	87.2	166/238	198/240	0.69 (0.56 ,0.85)	12.6 (10.1, 14.3)	9.8 (8.4, 10.8)
CPS < 10	45.1	92/121	98/126	0.95 (0.71 ,1.26)	10.5 (9.2, 13.5)	11.1 (9.1, 12.4)
CPS ≥ 10	52.2	94/143	121/143	0.57 (0.44 ,0.75)	13.9 (11.1, 17.7)	8.8 (7.8, 10.5)
CPS 1 - < 10	35.0	72/95	77/97	0.94 (0.68 ,1.29)	10.2 (9.1, 13.5)	10.8 (8.9, 12.1)
Not Reported	2.7	4/10	3/5	0.7 (0.16 ,3.12)	NA (0.1, NA)	8.9 (7.2, NA)



Pembro = pembrolizumab; CHT = chemotherapy; Evt = event

ESCC: CM648 OS Forest Plot by PD-L1 Cutoff (CPS)

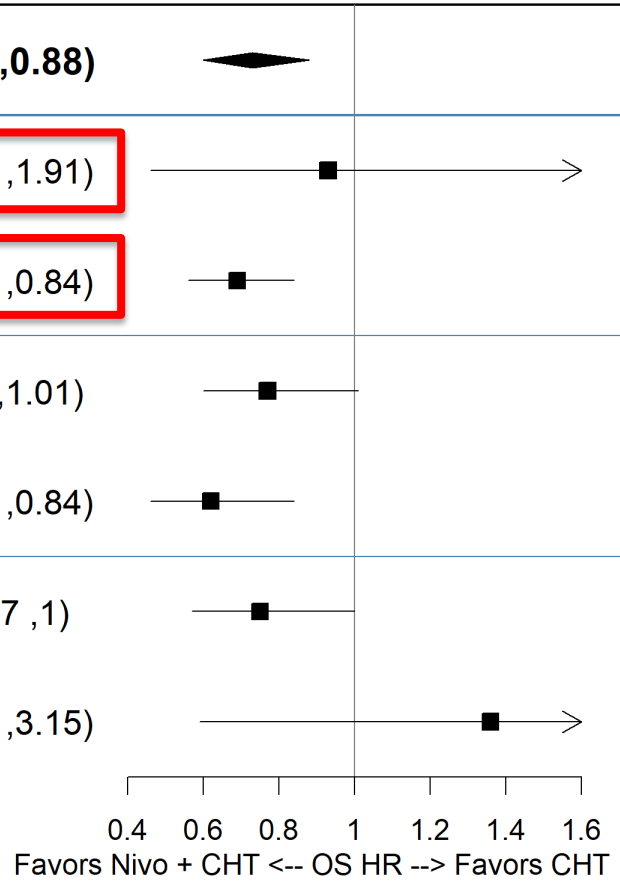
Subgroup	% of Pts	Nivo + CHT Evt / N	CHT Evt / N	HR (95% CI)	Nivo + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**200/311**	**227/318**	**0.73 (0.6 ,0.88)**	**13.4 (11.7, 15.8)**	**10.8 (9.4, 12.1)**
CPS < 1	7.6	17/25	15/23	0.93 (0.46 ,1.91)	10.2 (7.7, 21.8)	12.5 (9.3, 17.1)
CPS ≥ 1	86.8	171/271	201/275	0.69 (0.56 ,0.84)	13.8 (12, 16.5)	9.9 (8.9, 11.7)
CPS < 10	50.7	109/163	115/156	0.77 (0.6 ,1.01)	12.1 (10.6, 15.7)	9.7 (8.8, 11.1)
CPS ≥ 10	43.7	79/133	101/142	0.62 (0.46 ,0.84)	16.1 (12.3, 21.9)	11.6 (9, 13.7)
CPS 1 - < 10	43.1	92/138	100/133	0.75 (0.57 ,1)	12.1 (10.9, 15.7)	9.4 (8, 10.8)
Not Reported	5.6	12/15	11/20	1.36 (0.59 ,3.15)	11.1 (6.2, 15.8)	16.2 (5.5, NA)



Nivo = nivolumab; CHT = chemotherapy; Evt = event

ESCC: CM648 OS Forest Plot by PD-L1 Cutoff (CPS)

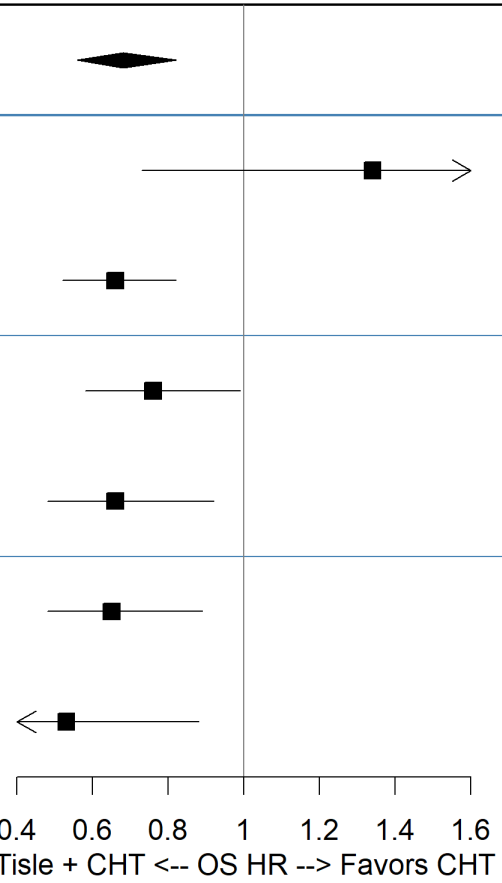
Subgroup	% of Pts	Nivo + CHT Evt / N	CHT Evt / N	HR (95% CI)	Nivo + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**200/311**	**227/318**	**0.73 (0.6 ,0.88)**	**13.4 (11.7, 15.8)**	**10.8 (9.4, 12.1)**
CPS < 1	7.6	17/25	15/23	0.93 (0.46 ,1.91)	10.2 (7.7, 21.8)	12.5 (9.3, 17.1)
CPS ≥ 1	86.8	171/271	201/275	0.69 (0.56 ,0.84)	13.8 (12, 16.5)	9.9 (8.9, 11.7)
CPS < 10	50.7	109/163	115/156	0.77 (0.6 ,1.01)	12.1 (10.6, 15.7)	9.7 (8.8, 11.1)
CPS ≥ 10	43.7	79/133	101/142	0.62 (0.46 ,0.84)	16.1 (12.3, 21.9)	11.6 (9, 13.7)
CPS 1 - < 10	43.1	92/138	100/133	0.75 (0.57 ,1)	12.1 (10.9, 15.7)	9.4 (8, 10.8)
Not Reported	5.6	12/15	11/20	1.36 (0.59 ,3.15)	11.1 (6.2, 15.8)	16.2 (5.5, NA)



Nivo = nivolumab ; CHT = chemotherapy; Evt = event

ESCC: RN306 OS Forest Plot by PD-L1 Cutoff (TAP)

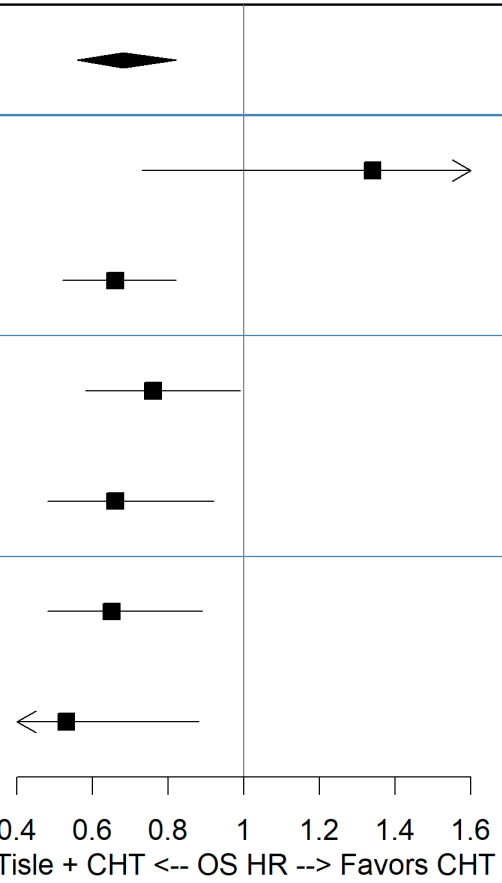
Subgroup	% of Pts	Tisle + CHT Evt / N	CHT Evt / N	HR (95% CI)	Tisle + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**196/325**	**226/323**	**0.68 (0.56 ,0.82)**	**17.2 (15.8, 20.1)**	**10.6 (9.3, 12.1)**
TAP < 1	9.4	27/36	18/25	1.34 (0.73 ,2.46)	11.8 (6.2, 16.3)	16.1 (10.4, 28.9)
TAP ≥ 1	74.2	140/231	176/250	0.66 (0.52 ,0.82)	16.8 (15.3, 20.8)	9.6 (8.9, 11.8)
TAP < 10	49.2	98/151	120/168	0.76 (0.58 ,0.99)	15.8 (12.3, 19.6)	10.4 (9, 13.6)
TAP ≥ 10	34.4	69/116	74/107	0.66 (0.48 ,0.92)	16.6 (15.3, 24.4)	10 (8.6, 13.3)
TAP 1 - < 10	39.8	71/115	102/143	0.65 (0.48 ,0.89)	18.3 (13, 21)	9.6 (8.4, 12.3)
Not Reported	16.4	29/58	32/48	0.53 (0.32 ,0.88)	23.7 (16.6, 28.4)	11.7 (7.4, 21.7)



Tisle = tislelizumab ; CHT= chemotherapy; Evt = event

ESCC: RN306 OS Forest Plot by PD-L1 Cutoff (TAP)

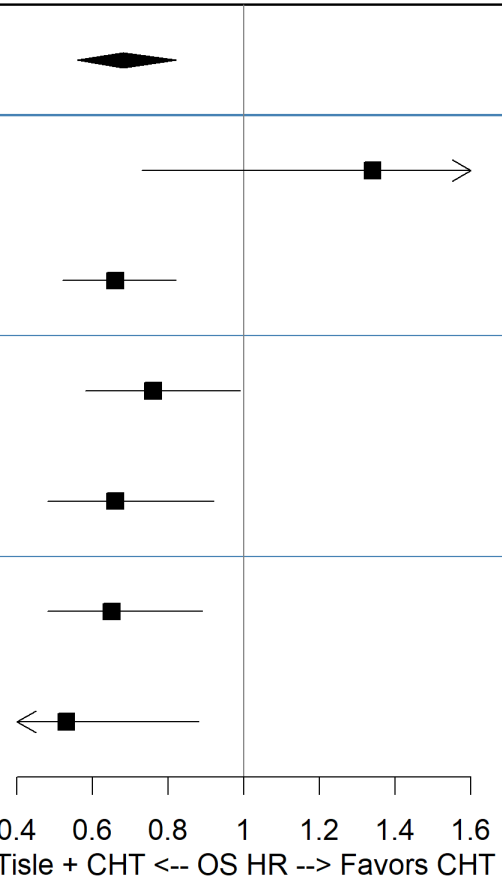
Subgroup	% of Pts	Tisle + CHT Evt / N	CHT Evt / N	HR (95% CI)	Tisle + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**196/325**	**226/323**	**0.68 (0.56 ,0.82)**	**17.2 (15.8, 20.1)**	**10.6 (9.3, 12.1)**
TAP < 1	9.4	27/36	18/25	1.34 (0.73 ,2.46)	11.8 (6.2, 16.3)	16.1 (10.4, 28.9)
TAP ≥ 1	74.2	140/231	176/250	0.66 (0.52 ,0.82)	16.8 (15.3, 20.8)	9.6 (8.9, 11.8)
TAP < 10	49.2	98/151	120/168	0.76 (0.58 ,0.99)	15.8 (12.3, 19.6)	10.4 (9, 13.6)
TAP ≥ 10	34.4	69/116	74/107	0.66 (0.48 ,0.92)	16.6 (15.3, 24.4)	10 (8.6, 13.3)
TAP 1 - < 10	39.8	71/115	102/143	0.65 (0.48 ,0.89)	18.3 (13, 21)	9.6 (8.4, 12.3)
Not Reported	16.4	29/58	32/48	0.53 (0.32 ,0.88)	23.7 (16.6, 28.4)	11.7 (7.4, 21.7)



Tisle = tislelizumab ; CHT= chemotherapy; Evt = event

ESCC: RN306 OS Forest Plot by PD-L1 Cutoff (TAP)

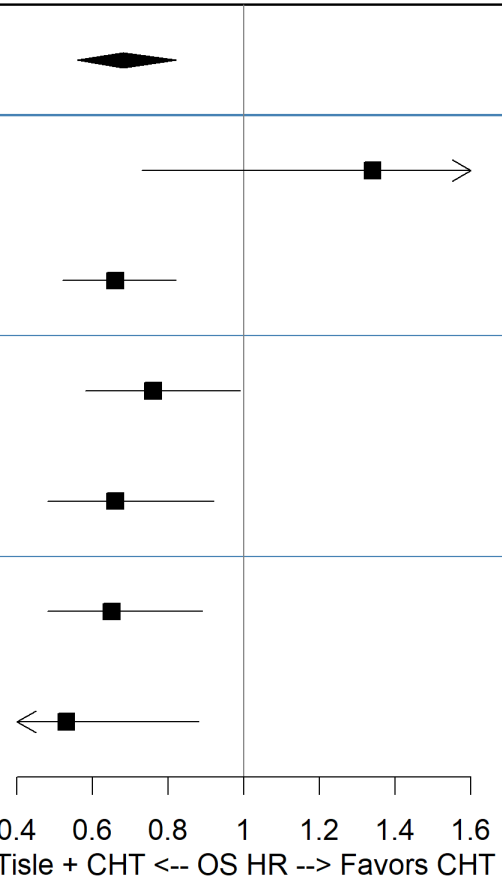
Subgroup	% of Pts	Tisle + CHT Evt / N	CHT Evt / N	HR (95% CI)	Tisle + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**196/325**	**226/323**	**0.68 (0.56 ,0.82)**	**17.2 (15.8, 20.1)**	**10.6 (9.3, 12.1)**
TAP < 1	9.4	27/36	18/25	1.34 (0.73 ,2.46)	11.8 (6.2, 16.3)	16.1 (10.4, 28.9)
TAP ≥ 1	74.2	140/231	176/250	0.66 (0.52 ,0.82)	16.8 (15.3, 20.8)	9.6 (8.9, 11.8)
TAP < 10	49.2	98/151	120/168	0.76 (0.58 ,0.99)	15.8 (12.3, 19.6)	10.4 (9, 13.6)
TAP ≥ 10	34.4	69/116	74/107	0.66 (0.48 ,0.92)	16.6 (15.3, 24.4)	10 (8.6, 13.3)
TAP 1 - < 10	39.8	71/115	102/143	0.65 (0.48 ,0.89)	18.3 (13, 21)	9.6 (8.4, 12.3)
Not Reported	16.4	29/58	32/48	0.53 (0.32 ,0.88)	23.7 (16.6, 28.4)	11.7 (7.4, 21.7)



Tisle = tislelizumab ; CHT= chemotherapy; Evt = event

ESCC: RN306 OS Forest Plot by PD-L1 Cutoff (TAP)

Subgroup	% of Pts	Tisle + CHT Evt / N	CHT Evt / N	HR (95% CI)	Tisle + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**196/325**	**226/323**	**0.68 (0.56 ,0.82)**	**17.2 (15.8, 20.1)**	**10.6 (9.3, 12.1)**
TAP < 1	9.4	27/36	18/25	1.34 (0.73 ,2.46)	11.8 (6.2, 16.3)	16.1 (10.4, 28.9)
TAP ≥ 1	74.2	140/231	176/250	0.66 (0.52 ,0.82)	16.8 (15.3, 20.8)	9.6 (8.9, 11.8)
TAP < 10	49.2	98/151	120/168	0.76 (0.58 ,0.99)	15.8 (12.3, 19.6)	10.4 (9, 13.6)
TAP ≥ 10	34.4	69/116	74/107	0.66 (0.48 ,0.92)	16.6 (15.3, 24.4)	10 (8.6, 13.3)
TAP 1 - < 10	39.8	71/115	102/143	0.65 (0.48 ,0.89)	18.3 (13, 21)	9.6 (8.4, 12.3)
Not Reported	16.4	29/58	32/48	0.53 (0.32 ,0.88)	23.7 (16.6, 28.4)	11.7 (7.4, 21.7)



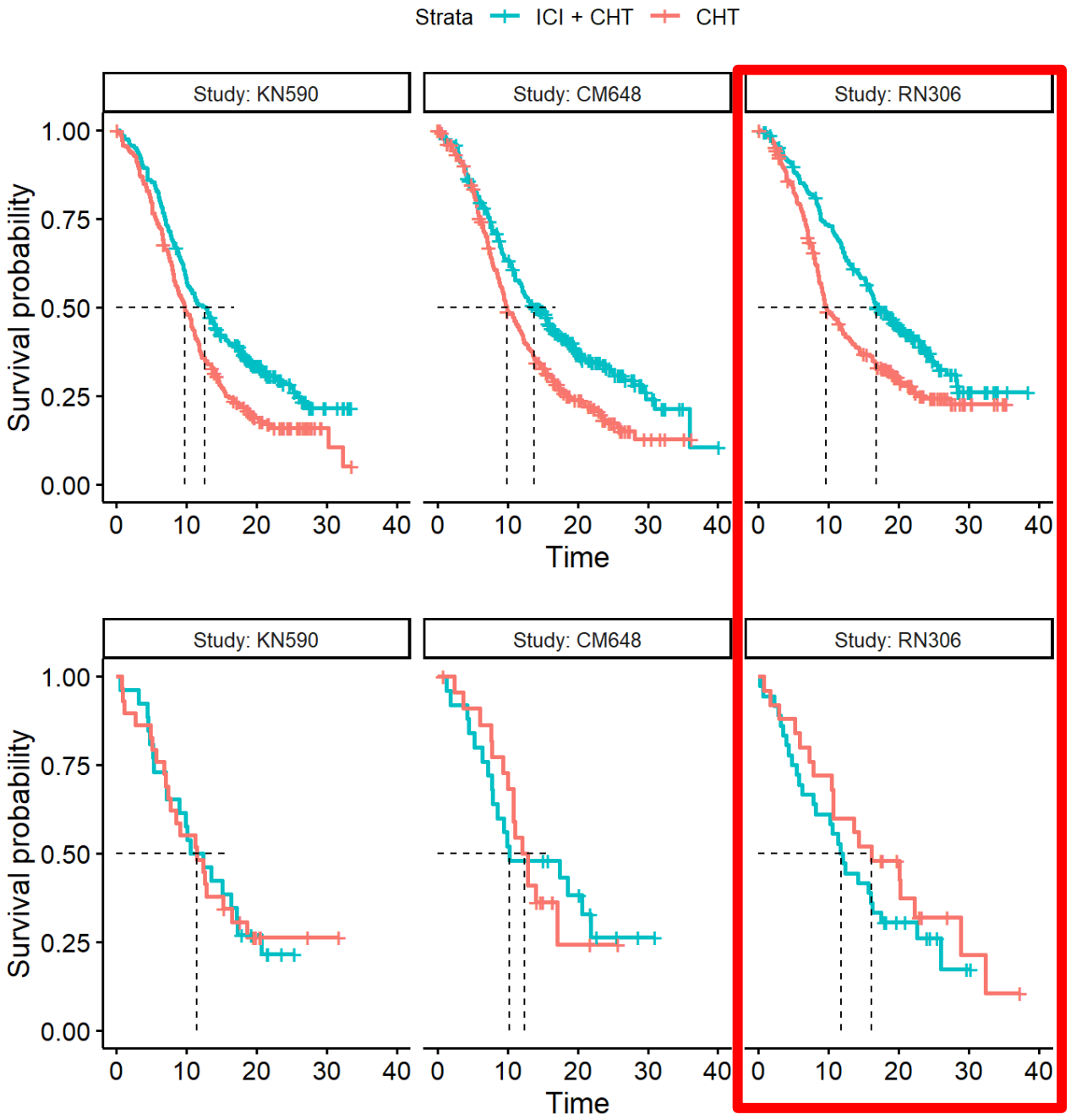
Tisle = tislelizumab ; CHT= chemotherapy; Evt = event

Overall Survival by PD-L1 <1 Cut Off

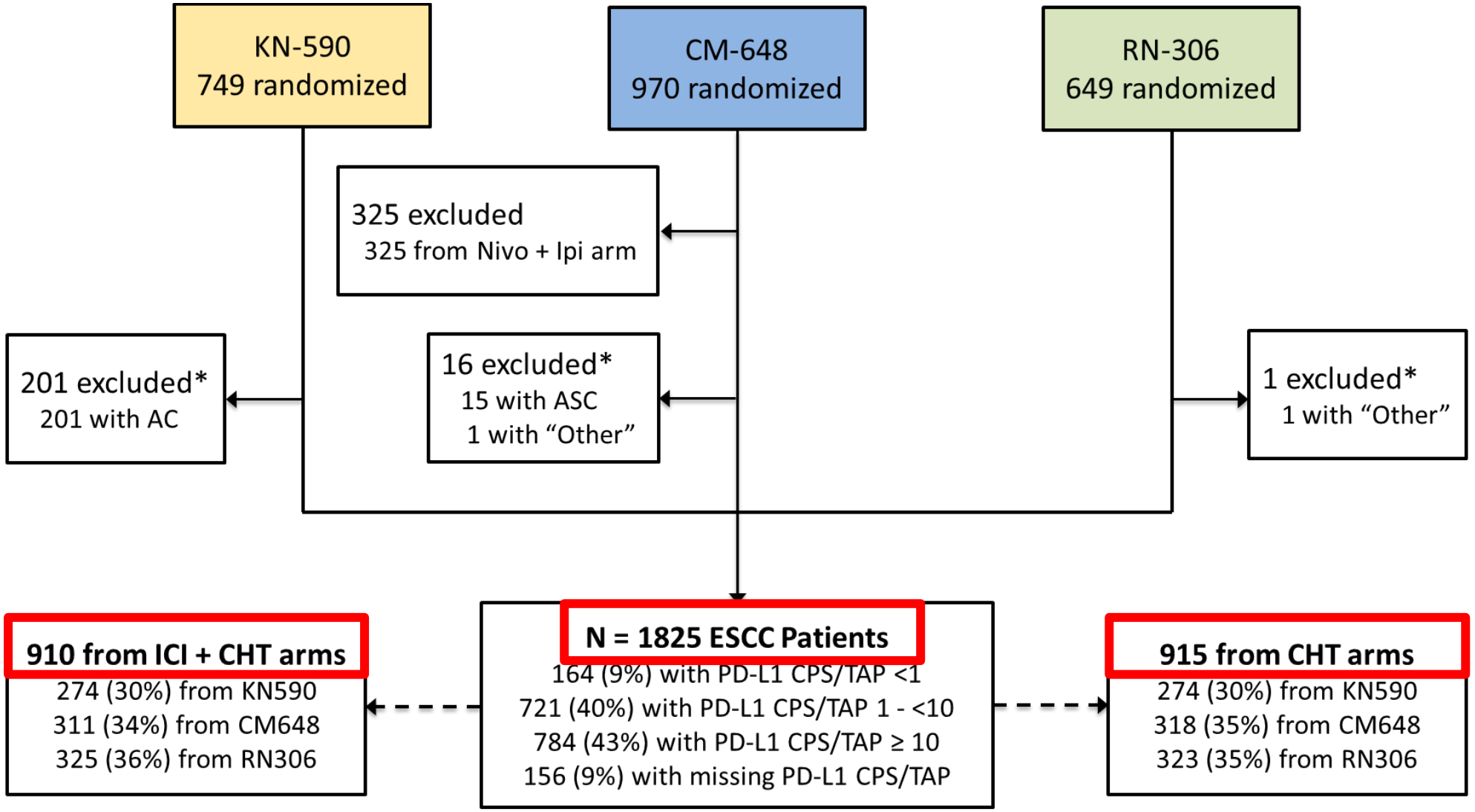
	All ESCC		PD-L1 <1	
KEYNOTE 590 (CPS)	**Pembro+CHT**	**Placebo+CHT**	**Pembro+CHT**	**Placebo+CHT**
N	**274**	**274**	**26**	**29**
mOS (95% CI)	12.6 (10.2, 14.3)	9.8 (8.6, 11.1)	11.4 (7.0, 17.1)	11.4 (7.0, 16.5)
OS HR (95% CI)	0.72 (0.59, 0.87)		**1.00** (0.54, 1.85)	
CheckMate 648 (CPS)	**Nivo+CHT**	**CHT**	**Nivo+CHT**	**CHT**
N	**311**	**318**	**25**	**23**
mOS (95% CI)	13.4 (11.7, 15.8)	10.8 (9.4, 12.1)	10.2 (7.7, 21.8)	12.5 (9.3, 17.1)
OS HR (95% CI)	0.73 (0.60, 0.88)		**0.93** (0.46, 1.91)	**(CPS)**
RATIONALE 306 (TAP)	**Tisle+CHT**	**Placebo+CHT**	**Tisle+CHT**	**Placebo+CHT**
N	**325**	**323**	**36**	**25**
mOS (95% CI)	17.2 (15.8, 20.1)	10.6 (9.3, 12.1)	11.8 (6.2, 16.3)	16.1 (10.4, 28.9)
OS HR (95% CI)	0.68 (0.56, 0.82)		**1.34** (0.73, 2.46)	

Overall Survival:
Kaplan-Meier curves,
ESCC PD-L1 ≥ 1 Subgroup

Overall Survival:
Kaplan-Meier curves,
ESCC PD-L1 < 1 Subgroup



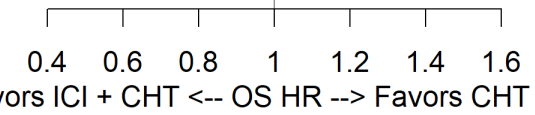
Consort Diagram of Patients Included in Pooled Analyses



Abbreviation: ASC = Adenosquamous carcinoma, AC = Adenocarcinoma, ESCC = Esophageal squamous carcinoma
*Exclusion based on histology

ESCC Pooled Population: OS Forest Plot by PD-L1 Cutoff

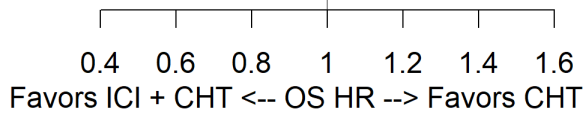
Subgroup	% of Pts	ICI + CHT Evt / N	CHT Evt / N	HR (95% CI)	ICI + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**586/910**	**675/915**	**0.71 (0.63 ,0.79)**	**15 (13.2, 16)**	**10.4 (9.6, 11.1)**
PDL1 < 1	9.0	64/87	54/77	1.1 (0.76 ,1.58)	11.6 (8.9, 16.3)	12.8 (10.6, 16.1)
PDL1 ≥ 1	82.5	477/740	575/765	0.68 (0.6 ,0.77)	14.6 (13.1, 16)	9.8 (9.3, 10.8)
PDL1 < 10	48.5	299/435	333/450	0.82 (0.7 ,0.96)	12.7 (11.6, 15.1)	10.4 (9.5, 11.4)
PDL1 ≥ 10	43.0	242/392	296/392	0.61 (0.52 ,0.73)	15.8 (13.8, 17.8)	9.8 (8.9, 11.2)
PDL1 1 - < 10	39.5	235/348	279/373	0.77 (0.64 ,0.91)	12.9 (11.7, 15.7)	9.7 (9.1, 10.8)
Not Reported	8.5	45/83	46/73	0.68 (0.44 ,1.03)	20.4 (14.8, 27.7)	12.8 (8.9, 17.6)



[1]Pooled analysis stratified by study
[2]PD-L1 expression score using CPS for KN590 and CM648, TAP for RN306

ESCC Pooled Population: OS Forest Plot by PD-L1 Cutoff

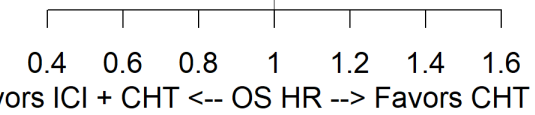
Subgroup	% of Pts	ICI + CHT Evt / N	CHT Evt / N	HR (95% CI)	ICI + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**586/910**	**675/915**	**0.71 (0.63 ,0.79)**	**15 (13.2, 16)**	**10.4 (9.6, 11.1)**
PDL1 < 1	9.0	64/87	54/77	1.1 (0.76 ,1.58)	11.6 (8.9, 16.3)	12.8 (10.6, 16.1)
PDL1 ≥ 1	82.5	477/740	575/765	0.68 (0.6 ,0.77)	14.6 (13.1, 16)	9.8 (9.3, 10.8)
PDL1 < 10	48.5	299/435	333/450	0.82 (0.7 ,0.96)	12.7 (11.6, 15.1)	10.4 (9.5, 11.4)
PDL1 ≥ 10	43.0	242/392	296/392	0.61 (0.52 ,0.73)	15.8 (13.8, 17.8)	9.8 (8.9, 11.2)
PDL1 1 - < 10	39.5	235/348	279/373	0.77 (0.64 ,0.91)	12.9 (11.7, 15.7)	9.7 (9.1, 10.8)
Not Reported	8.5	45/83	46/73	0.68 (0.44 ,1.03)	20.4 (14.8, 27.7)	12.8 (8.9, 17.6)



[1]Pooled analysis stratified by study
[2]PD-L1 expression score using CPS for KN590 and CM648, TAP for RN306

ESCC Pooled Population: OS Forest Plot by PD-L1 Cutoff

Subgroup	% of Pts	ICI + CHT Evt / N	CHT Evt / N	HR (95% CI)	ICI + CHT Median (95% CI)	CHT Median (95% CI)
Overall	**100.0**	**586/910**	**675/915**	**0.71 (0.63 ,0.79)**	**15 (13.2, 16)**	**10.4 (9.6, 11.1)**
PDL1 < 1	9.0	64/87	54/77	1.1 (0.76 ,1.58)	11.6 (8.9, 16.3)	12.8 (10.6, 16.1)
PDL1 ≥ 1	82.5	477/740	575/765	0.68 (0.6 ,0.77)	14.6 (13.1, 16)	9.8 (9.3, 10.8)
PDL1 < 10	48.5	299/435	333/450	0.82 (0.7 ,0.96)	12.7 (11.6, 15.1)	10.4 (9.5, 11.4)
PDL1 ≥ 10	43.0	242/392	296/392	0.61 (0.52 ,0.73)	15.8 (13.8, 17.8)	9.8 (8.9, 11.2)
PDL1 1 - < 10	39.5	235/348	279/373	0.77 (0.64 ,0.91)	12.9 (11.7, 15.7)	9.7 (9.1, 10.8)
Not Reported	8.5	45/83	46/73	0.68 (0.44 ,1.03)	20.4 (14.8, 27.7)	12.8 (8.9, 17.6)



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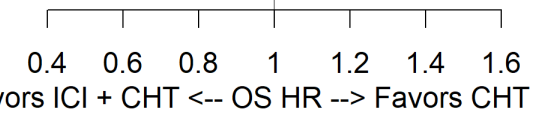

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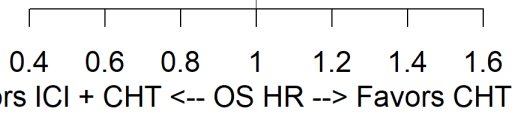

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Summary

- Current approvals in ESCC are agnostic of PD-L1 status
- Consistently across 3 applications, treatment effect appears to be predicted by PD-L1 status
- In patients with PD-L1 <1, treatment with immune checkpoint inhibitors may potentially expose to toxicity without a clear potential for benefit.

Discussion Question

FDA would like the committee to discuss the risk and benefits of the treatment with anti PD-1 antibodies for the first line treatment of patients with metastatic or unresectable esophageal squamous cell carcinoma with PD-L1 expression <1.

Voting Question

Is the risk: benefit assessment favorable for the use of anti PD-1 antibodies in first line unresectable or metastatic esophageal squamous cell carcinoma with PD-L1 expression <1?

Yes

No