

PD-L1 expression and immune checkpoint inhibitors for the treatment of HER2 negative advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma

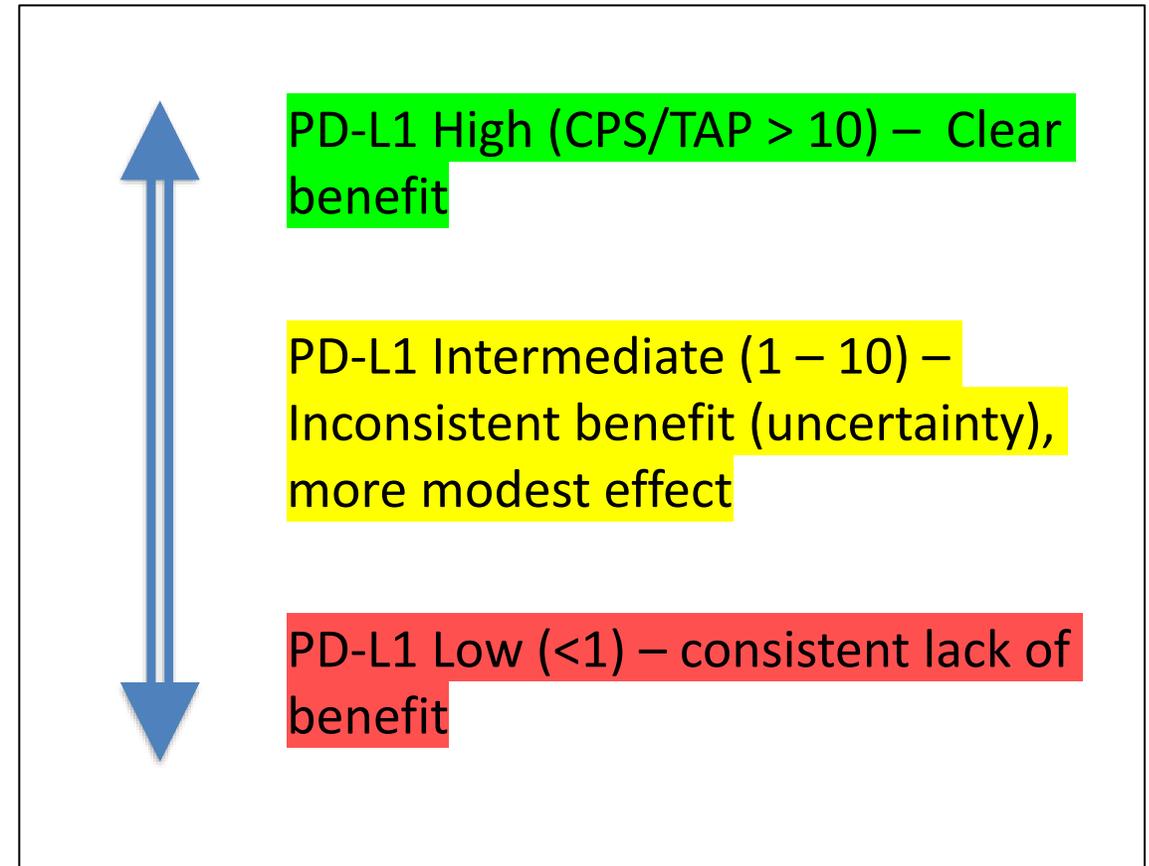
Oncologic Drugs Advisory Committee (ODAC) Meeting

September 26, 2024

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PD-L1 – Gastric Cancer

- Consider class labeling
 - Maximize risk-benefit
 - Foster consistent treatment
 - Foster consistent developmental landscape, e.g., future
 - ICI add trials
 - Non-ICI biomarker-selected drugs
- PD-L1 predictive but imperfect



Abbreviations: ICI immune checkpoint inhibitor; CPS combined positive score; TAP tumor area positivity

Gastric Cancer Applications

	Nivolumab CheckMate-649 April 16, 2021	Pembrolizumab Keynote-859 November 16, 2023	Tislelizumab Rationale-305 Under review
Intent to Treat	N = 1581	N=1579	N=997
Median OS			
- ICI + Chemo arm, mos (95% CI)	13.8 (12.6, 14.6)	12.9 (11.9, 14.0)	15.0 (13.6, 16.5)
- Chemo arm, mos (95% CI)	11.6 (10.9, 12.5)	11.5 (10.6, 12.1)	12.9 (12.1, 14.1)
OS HR (95% CI)	0.80 (0.71, 0.90)	0.78 (0.70, 0.87)	0.80 (0.70, 0.92)
Pre-specified analysis for PD-L1 group 1	CPS ≥ 1 N = 1296	CPS ≥ 1 N = 1235	TAP ≥ 5 N = 576
Median OS			
- ICI + Chemo arm, mos (95% CI)	14.0 (12.6, 15.0)	13.0 (11.6, 14.2)	17.2 (13.9, 21.3)
- Chemo arm, mos (95% CI)	11.3 (10.6, 12.3)	11.4 (10.5, 12.0)	12.6 (12.0, 14.4)
OS HR (95% CI)	0.77 (0.68, 0.88)	0.74 (0.65, 0.84)	0.74 (0.59, 0.94)
Pre-specified analysis for PD-L1 group 2	CPS ≥ 5 N = 955	CPS ≥ 10 N = 551	NA
Median OS			
- ICI + Chemo arm, mos (95% CI)	14.4 (13.1, 16.2)	15.7 (13.8, 19.3)	NA
- Chemo arm, mos (95% CI)	11.1 (10.0, 12.1)	11.8 (10.3, 12.7)	NA
OS HR (95% CI)	0.71 (0.61, 0.83)	0.65 (0.53, 0.79)	NA

Adapted from slide made by Dr. Vaibhav Kumar

Gastric Cancer Applications

Pre-Specified PD-L1 groups

	Nivolumab CheckMate-649 April 16, 2021		Pembrolizumab Keynote-859 November 16, 2023		Tislelizumab Rationale-305 Under review	
Pre-specified analysis for PD-L1 group 1	CPS ≥ 1 N = 1296	CPS < 1 N = 265	CPS ≥ 1 N = 1235	CPS < 1 N = 344	TAP ≥ 5 N = 576	TAP < 5 N = 451
Median OS						
- ICI + Chemo arm, mos	14.0	13.1	13.0	12.7	17.2	14.1
- Chemo arm, mos	11.3	12.5	11.4	12.2	12.6	12.9
OS HR (95% CI)	0.77 (0.68, 0.88)	0.85 (0.63, 1.15)	0.74 (0.65, 0.84)	0.92 (0.73, 1.17)	0.74 (0.59, 0.94)	0.91 (0.74, 1.12)
Pre-specified analysis for PD-L1 group 2	CPS ≥ 5 N = 955	CPS < 5 N = 606	CPS ≥ 10 N = 551		NA	
Median OS						
- ICI + Chemo arm, mos (95% CI)	14.4	12.4	15.7		NA	
- Chemo arm, mos (95% CI)	11.1	12.3	11.8			
OS HR (95% CI)	0.71 (0.61, 0.83)	0.94 (0.78, 1.14)	0.65 (0.53, 0.79)		NA	

Abbreviations: CPS combined positive score; TAP tumor area positivity; ICI immune checkpoint inhibitor; mos months; OS overall survival

Professional Society Guidelines

	PD-L1 CPS	Nivolumab	Pembrolizumab
NCCN	< 1	Category 2B*	Not recommended
	≥ 1 to < 5	Category 2B*	
	≥ 1 to < 10		Category 2B
	≥ 5	Category 1	
	≥ 10		Category 1
ASCO	< 1	Not recommended	(Keynote 859 not included)
	1-5	Case by Case	
	≥ 5	Recommended	

*** Useful in certain Circumstances**

Source: [NCCN Gastric Cancer Guidelines v4.2024](#); and Shah et al, JCO,2023

Gastric Cancer Applications

Nivolumab

	Nivolumab CheckMate-649 April 16, 2021	
Intent to Treat	N = 1581	
Median OS - ICI + Chemo arm, mos (95% CI) - Chemo arm, mos (95% CI)	13.8 (12.6, 14.6) 11.6 (10.9, 12.5)	
OS HR (95% CI)	0.80 (0.71, 0.90)	
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OS HR (95% CI)	0.71 (0.61, 0.83)	0.94 (0.78, 1.14)

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Abbreviations: CPS combined positive score; mos months; OS overall survival

Subgroup Considerations –

2008 ODAC meeting: EGFR Inhibitors – *KRAS*-mutant Colorectal Cancer

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

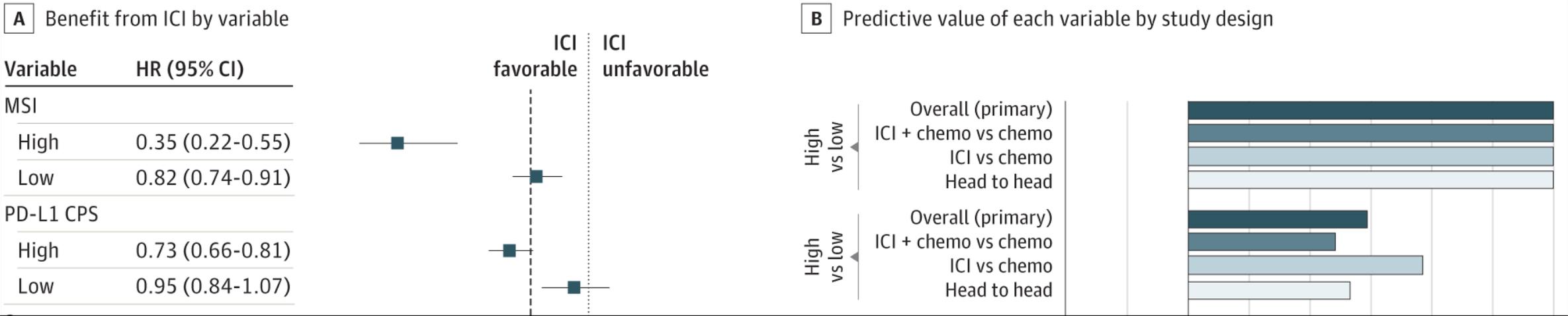
PD-L1 “Low” Results (Three Trials)

	All Patients		PD-L1 <1		PD-L1 <5		PD-L1 <10	
CM649	N+CHT	CHT	N+CHT	CHT	N+CHT	CHT	N+CHT	CHT
N	789	792	140	125	308	298	406	387
mOS (95% CI)	13.8 (12.6, 14.6)	11.6 (10.9, 12.5)	13.1 (9.8, 16.7)	12.5 (10.1, 13.8)	12.4 (10.6, 14.3)	12.3 (11.0, 13.2)	12.6 (11.1, 14.2)	12.5 (11.2, 13.3)
OS HR (95% CI)	0.79 (0.70, 0.89)		0.92 (0.70, 1.23)		0.94 (0.78, 1.13)		0.94 (0.80, 1.1)	
KN859	P+CHT	CHT	P+CHT	CHT	P+CHT	CHT	P+CHT	CHT
N	790	789	172	172	400	396	511	517
mOS (95% CI)	12.9 (11.9, 14.0)	11.5 (10.6, 12.1)	12.7 (11.4, 15.0)	12.2 (9.5, 14.0)	12.0 (11.1, 13.5)	11.4 (10.0, 12.2)	11.7 (10.7, 12.8)	11.2 (10.0, 12.1)
OS HR (95% CI)	0.77 (0.69, 0.86)		0.92 (0.73, 1.17)		0.85 (0.73, 0.98)		0.86 (0.75, 0.98)	
RN306	T+CHT	CHT	T+CHT	CHT	T+CHT	CHT	T+CHT	CHT
N	501	496	69	43	227	224	365	351
mOS (95% CI)	15.0 (13.6, 16.5)	12.9 (12.1, 14.1)	15.4 (8.4, 19.2)	13.8 (10.2, 17.8)	14.1 (11.9, 15.6)	12.9 (11.3, 14.7)	14.0 (12.0, 15.3)	13.0 (12.1, 14.3)
OS HR (95% CI)	0.80 (0.69, 0.92)		0.98 (0.64, 1.50)		0.91 (0.74, 1.12)		0.91 (0.77, 1.07)	

Exploratory FDA analyses (refer to briefing document for methodology)

Abbreviations: mOS median overall survival; CM Checkmate; KN Keynote; RN Rationale; N nivolumab; p pembrolizumab; t tislelizumab; CHT chemotherapy

PD-L1 in Gastric Cancer – External Meta-Analysis



Source: Copied (adapted) from Yoon et al, JAMA Onc, 2022

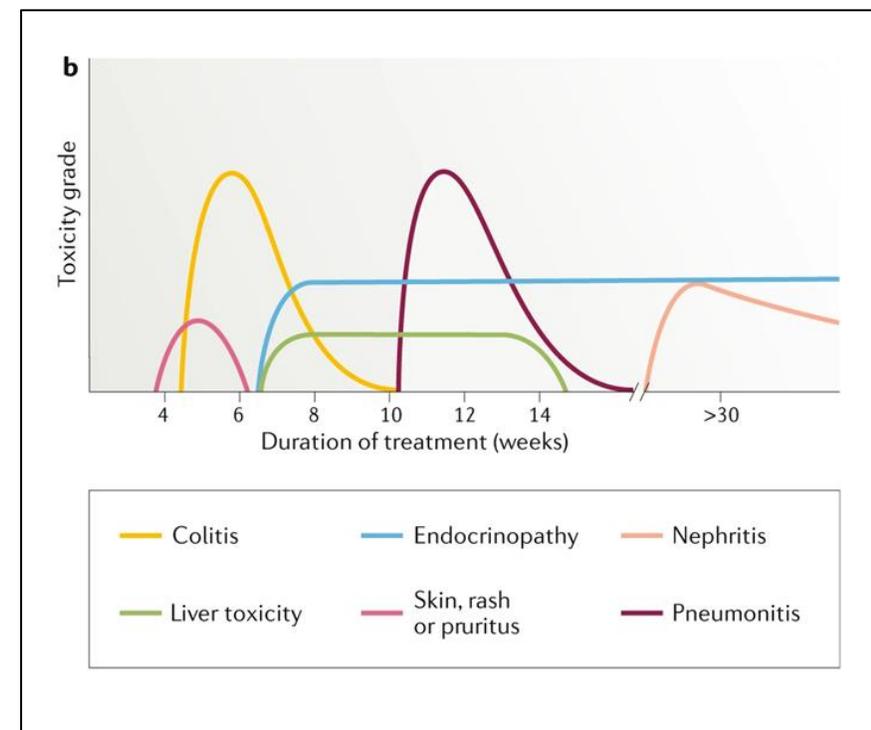
Abbreviations: MSI microsatellite instability; CPS combined positive score; ICI immune checkpoint inhibitor; HR hazard ratio

Safety – Immune Related Adverse Events (anti-PD-1)

Incidence of immune related adverse reactions (IMARs)

	All 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

How to move forward?

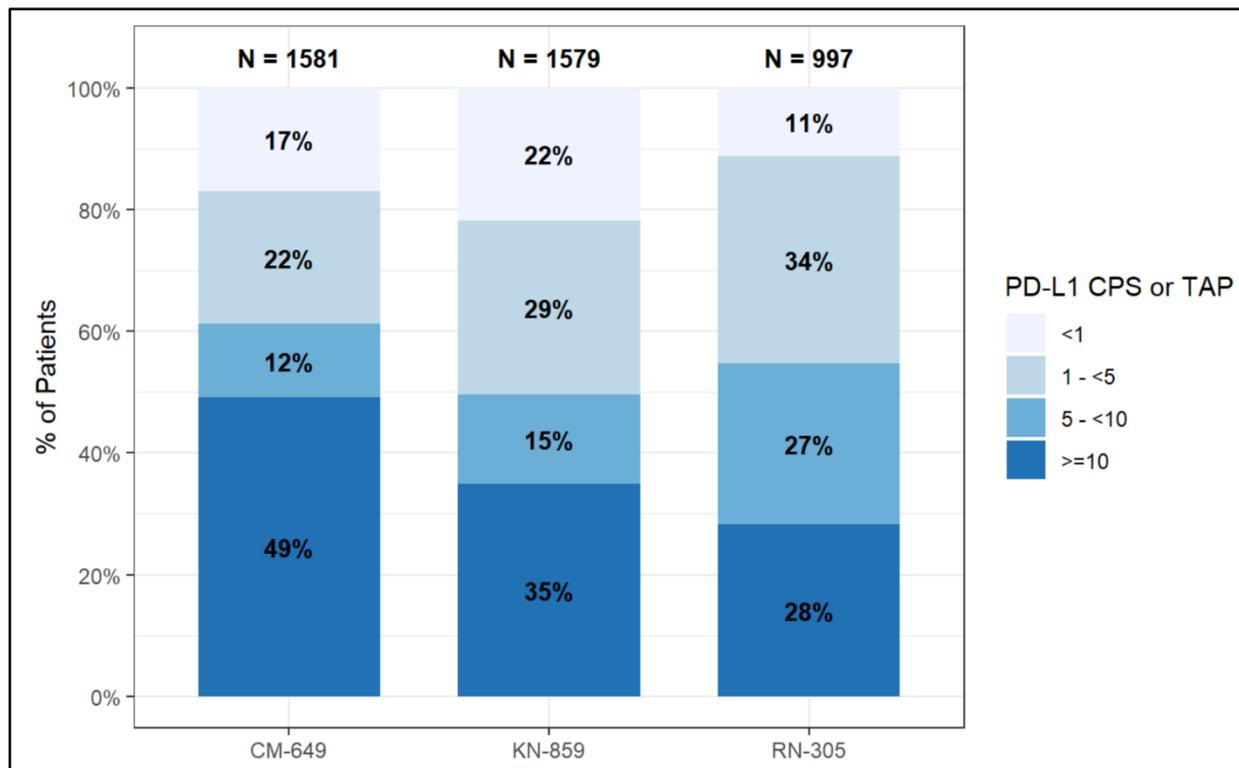
Approach 1 – Product specific cut-offs?

- **Pros**
 - Rational statistically?
 - Described by professional societies
- **Cons**
 - Cut-point pre-specified in each trial not necessarily optimal
 - Use of variable PD-L1 tests in clinic
 - Inconsistent treatment of patients in practice
 - Inconsistent future drug development

Approach 2 – Pragmatic/Uniform PD-L1 cut-off?

- **Pros**
 - Consider totality of data to foster consistent patient management
 - Consistent approach to future trials (to benefit patients)
- **Cons**
 - Maybe less sound statistically?
 - Device challenges

Approach 2 – Pragmatic/Uniform PD-L1 cut-off?



Source and methodology: FDA Briefing Document

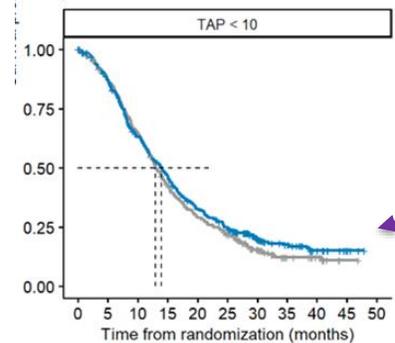
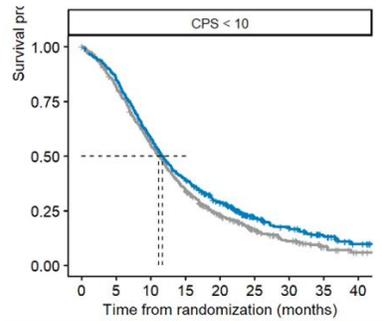
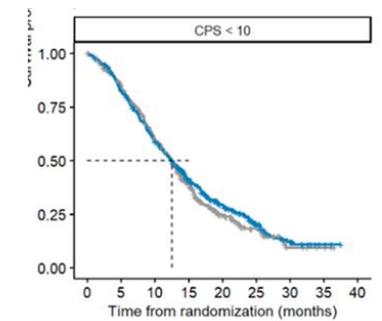
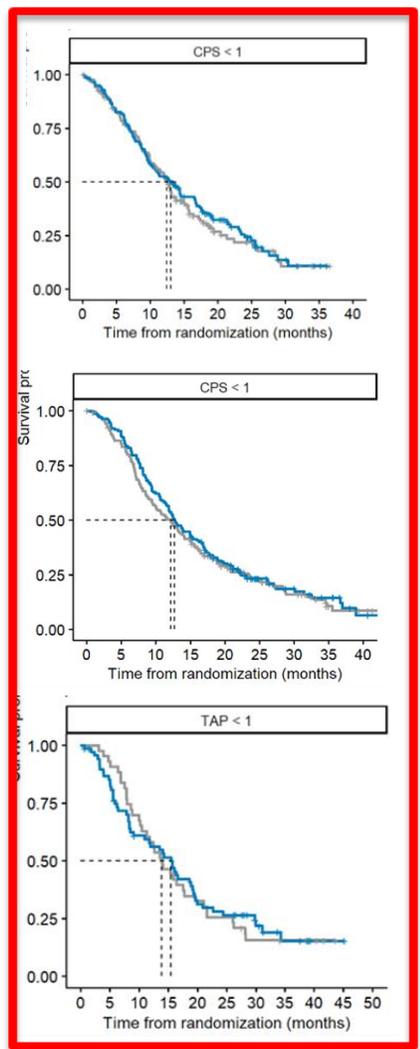
- **CM-649:** CPS Agilent/Dako PD-L1 IHC 28-8 pharmDx (Initially was TPS)
- **KN-859:** CPS Agilent PD-L1 IHC 22C3 pharmDx
- **RN-305:** **TAP** Ventana PD-L1 IHC SP263 CDx

Data Summary (PD-L1 Low)

	All Patients		PD-L1 <1		PD-L1 <10	
CM649	N+CHT	CHT	N+CHT	CHT	N+CHT	CHT
N	789	792	140	125	406	387
mOS (95% CI)	13.8 (12.6, 14.6)	11.6 (10.9, 12.5)	13.1 (9.8, 16.7)	12.5 (10.1, 13.8)	12.6 (11.1, 14.2)	12.5 (11.2, 13.3)
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Exploratory FDA analyses (refer to briefing document for methodology)

Abbreviations: mOS median overall survival; CM Checkmate; KN Keynote; RN Rationale; N nivolumab; p pembrolizumab; t tislelizumab; CHT chemotherapy



KEYNOTE-811 – Additional Pembrolizumab Trial

Endpoint	Pembrolizumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy
Interim analysis		
N	133	131
Objective response rate (ORR) (95% CI)	74% (66, 82)	52% (43, 61)
P value	<0.0001	
Subgroup analyses (initial interim analysis)		
N (≥ 1, < 1)	(117, 16)	(112, 19)
ORR CPS ≥1 (95% CI)	76% (67, 83)	51% (41,60)
ORR CPS < 1 (95% CI)	63% (35, 85)	58 (34, 80)
Subgroup analyses (subsequent interim analysis)		
N CPS < 1	104 (of 698 patients)	
Progression free survival HR (95% CI)	1.03 (0.65, 1.41)	
Overall survival HR (95% CI)	1.41 (0.90, 2.20)	

Source: Keytruda (Pembrolizumab) Product Labeling

Abbreviations: CPS combined positive score; HR hazard ratio

Strength of Subgroup Findings (PD-L1 Low)

Characteristic	
Replication across multiple trials	Yes
Sample ascertainment	High
Biological plausibility	Yes
Study design	+/-

Benefit-Risk PD-1 Inhibition in Gastric Cancer (First-Line)

Group	% of population	Benefit	Risks
PD-L1 high (> 10)	28-49%	Yes	IMARs
PD-L1 intermediate (1-10)	34-61%	Uncertain / modest	IMARs
PD-L1 negative (<1)	11-22%	No apparent benefit	IMARs

Discussion Question

In patients with HER2-negative microsatellite stable gastric/GEJ adenocarcinoma, does the cumulative data support the use of **PD-L1 expression as a predictive biomarker** when selecting patients for treatment with PD-1 inhibitors?

Voting Question

Is a risk benefit assessment **favorable** for the use of PD-1 inhibitors in first line advanced HER2 negative microsatellite stable gastric/GEJ adenocarcinoma in patients with PD-L1 expression < 1?

- Yes
- No

PD-L1 Expression and Immune Checkpoint Inhibitors for the Treatment of Patients with HER2 Negative Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

Oncologic Drugs Advisory Committee (ODAC) Meeting

September 26, 2024

Vaibhav Kumar, M.D., M.S.
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, 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	

FDA Perspective

1. PD-L1 expression appears to be a **predictive biomarker** in HER2 negative gastric/GEJ adenocarcinoma
2. Uncertainty of efficacy observed in **PD-L1 < 1** patient populations
3. Patients are exposed to the **added toxicity** of immune checkpoint inhibitors

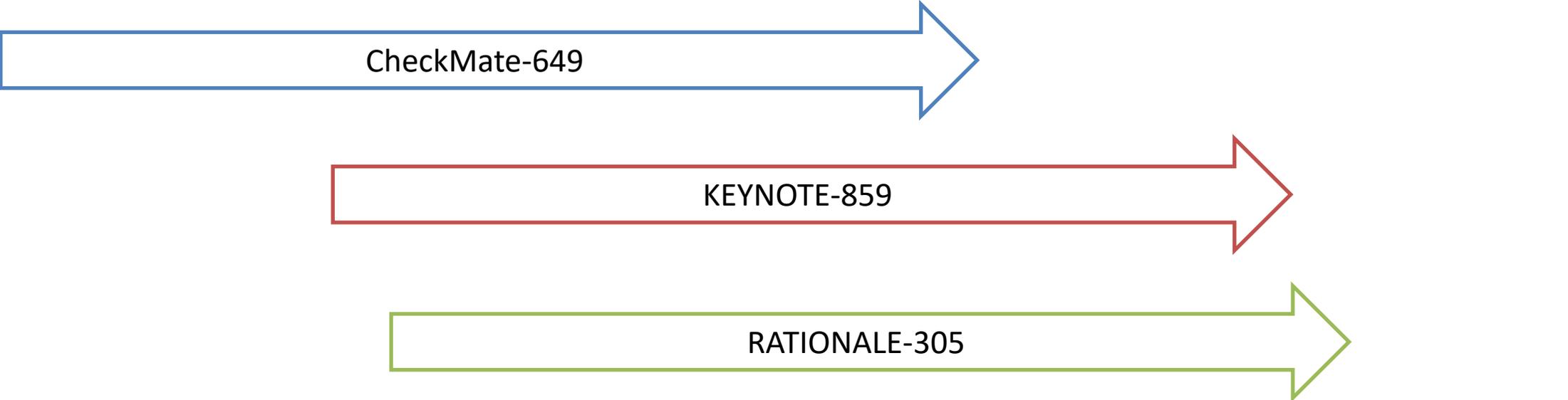
PD-L1 Expression by IHC

$$\text{TPS} = \frac{\text{\# PD-L1+ Tumor Cells}}{\text{Total \# of Viable Tumor Cells}} \times 100$$

$$\text{CPS} = \frac{\begin{array}{l} \text{\# PD-L1+ Positive Cells} \\ \text{(TC, Tumor Associated Immune Cells [IC])} \end{array}}{\text{Total \# of Viable Tumor Cells}} \times 100$$

$$\text{TAP} = \frac{\begin{array}{l} \text{Area occupied by PD L1+ Cells} \\ \text{(TC, Tumor Associated Immune Cells [IC])} \end{array}}{\text{Total Tumor Area}} \times 100$$

Trial Timelines



- Trial Actual Start Date
- Date of Traditional Approval
- Date of BLA Submission

Source: Clinicaltrials.gov; Abbreviations: BLA: Biologics Licensing Application

Current Approved Indications

Nivolumab – Pivotal Study CheckMate-649

Treatment of adult patients with gastric cancer, gastroesophageal junction (GEJ) cancer and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy

Pembrolizumab – Pivotal Study KEYNOTE-859

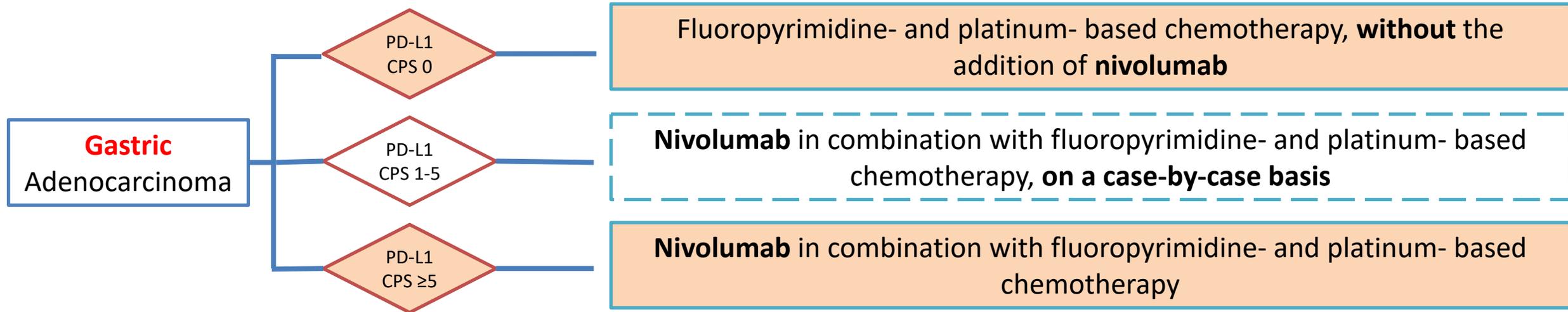
In combination with fluoropyrimidine- and platinum- containing chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma.

Proposed Indication

Tislelizumab – Pivotal Study RATIONALE-305

Treatment of adult patients with gastric or gastroesophageal junction adenocarcinoma in combination with fluoropyrimidine- and platinum- containing chemotherapy

Advanced HER2 Negative Gastric Adenocarcinoma



NCCN Gastric Cancer Guidelines

- HER2 Negative
 - Fluoropyrimidine[#], oxaliplatin, and **nivolumab**
 - Category 1 for PD-L1 **CPS ≥ 5** (preferred regimen)
 - Category 2B for PD-L1 **CPS < 5** (“useful under certain circumstances”)
 - Fluoropyrimidine[#], oxaliplatin or cisplatin, and **pembrolizumab for PD-L1 CPS ≥ 1** (preferred regimen)
 - Category 1 for PD-L1 **CPS ≥ 10**
 - Category 2B for PD-L1 **CPS $1 < 10$**
 - Fluoropyrimidine[#], oxaliplatin or cisplatin
- MSI-H/dMMR guidance independent of PD-L1 status

STUDY DESIGNS

Comparison of Study Designs

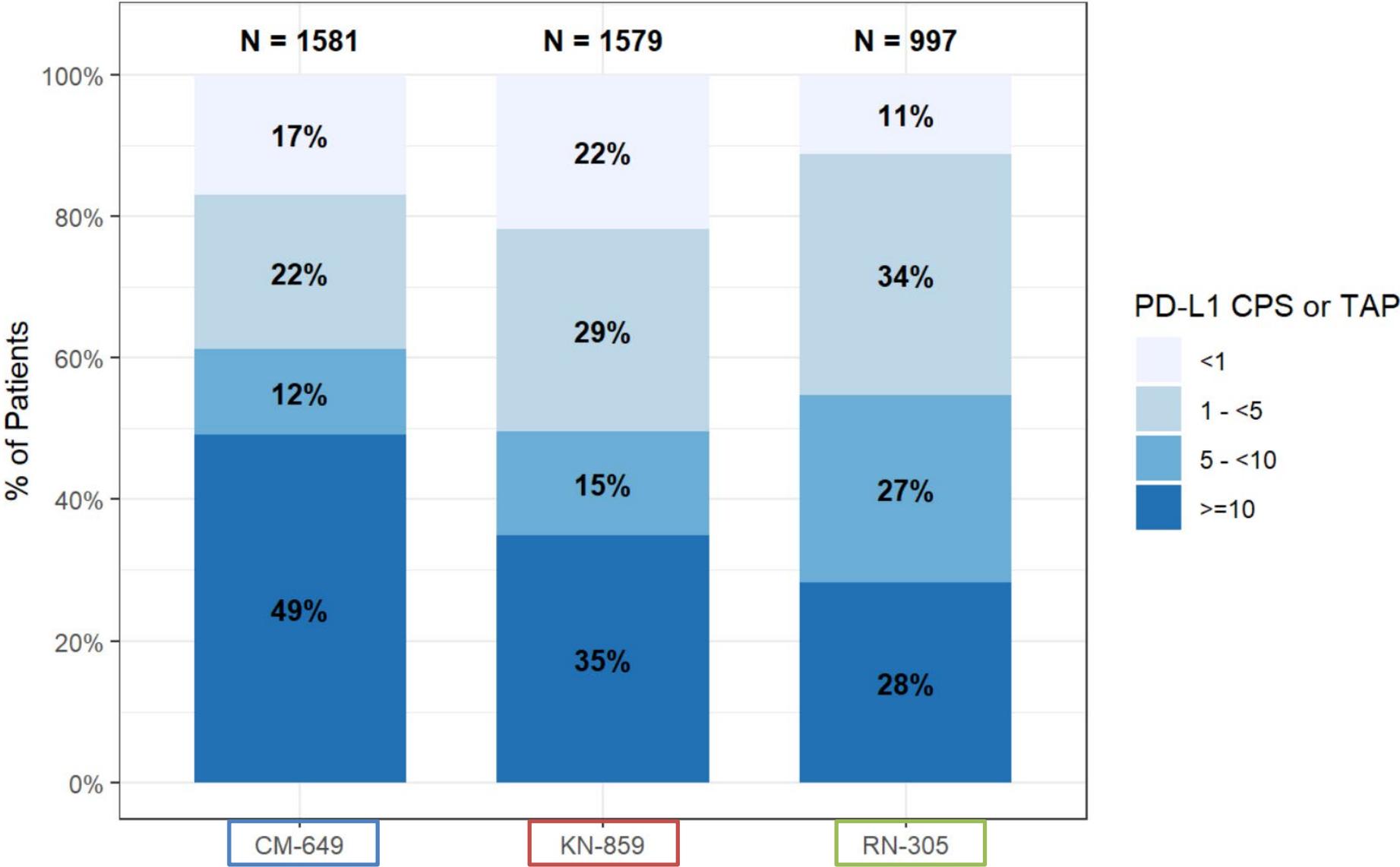


	Checkmate 649	Keynote 859	Rationale 305
Anatomic Location	Gastric/GEJ/esophageal adenocarcinoma	Gastric/GEJ adenocarcinoma	Gastric/GEJ adenocarcinoma
HER2 status	Not known to be positive	Negative	Negative
PD-L1 expression	Any	Any	Any
PD-L1 assay	Agilent/Dako PD-L1 IHC 28-8 pharmDx assay (Stratification by TPS; Endpoint Analysis by CPS)	Agilent PD-L1 IHC 22C3 pharmDx assay (CPS)	Ventana PD-L1 IHC SP263 CDx assay (TAP)
PD-L1 Stratification factors	PD-L1 TPS <1 vs. ≥1	PD-L1 CPS <1 vs. ≥1	PD-L1 TAP ≥ 5 vs < 5
OS Endpoint Analysis	<ol style="list-style-type: none"> 1. PD-L1 CPS ≥5 2. PD-L1 CPS ≥1 3. ITT 	<ol style="list-style-type: none"> 1. PD-L1 CPS ≥10 and ITT 2. PD-L1 CPS ≥1 	<ol style="list-style-type: none"> 1. PD-L1 TAP ≥5 2. ITT

	CheckMate-649		KEYNOTE-859		RATIONALE-305	
	Nivo + Chemo	Chemo	Pembro + Chemo	Chemo	Tisle + Chemo	Chemo
Randomized	N=789	N = 792	N=790	N=789	N=501	N=496
Age (median, range) (years)	62 (18, 88)	61 (21, 90)	61 (23, 86)	62 (21, 85)	60 (23, 86)	61 (25, 86)
Sex (%)						
Male	68	71	67	69	69	70
Female	32	29	33	31	31	30
Primary Tumor Location (%)						
Gastric	70	70	81	76	81	80
GEJ	17	16	19	23	19	20
EAC	13	14				
HER2 Status (%)						
Negative	58	60	100	100	100	99
Positive	0.4	0.5			0	0.2
Unknown/Not Reported	41	40			0.1	0.4
PD-L1 Expression (primary efficacy population in bold) (%)						
CPS or TAP ≥ 1	81	82	78	78		
CPS or TAP ≥ 5	60	61			55	55
CPS or TAP ≥ 10			35	35		
MSI Status (%)						
MSI High	3	3	5	4	3	5
MSS	88	86	81	81	89	89
Not Reported/Invalid	9	11	14	15	7	7
Chemotherapy (%)						
CAPOX	46	47	86	86	93	94
FOLFOX	54	53				
FP			14	14	7	6

Abbreviations: Chemo: Chemotherapy; EAC: Esophageal Adenocarcinoma; Nivo: Nivolumab; Pembro: Pembrolizumab; Tisle: Tislelizumab

PD-L1 Expression: Distribution Across Studies



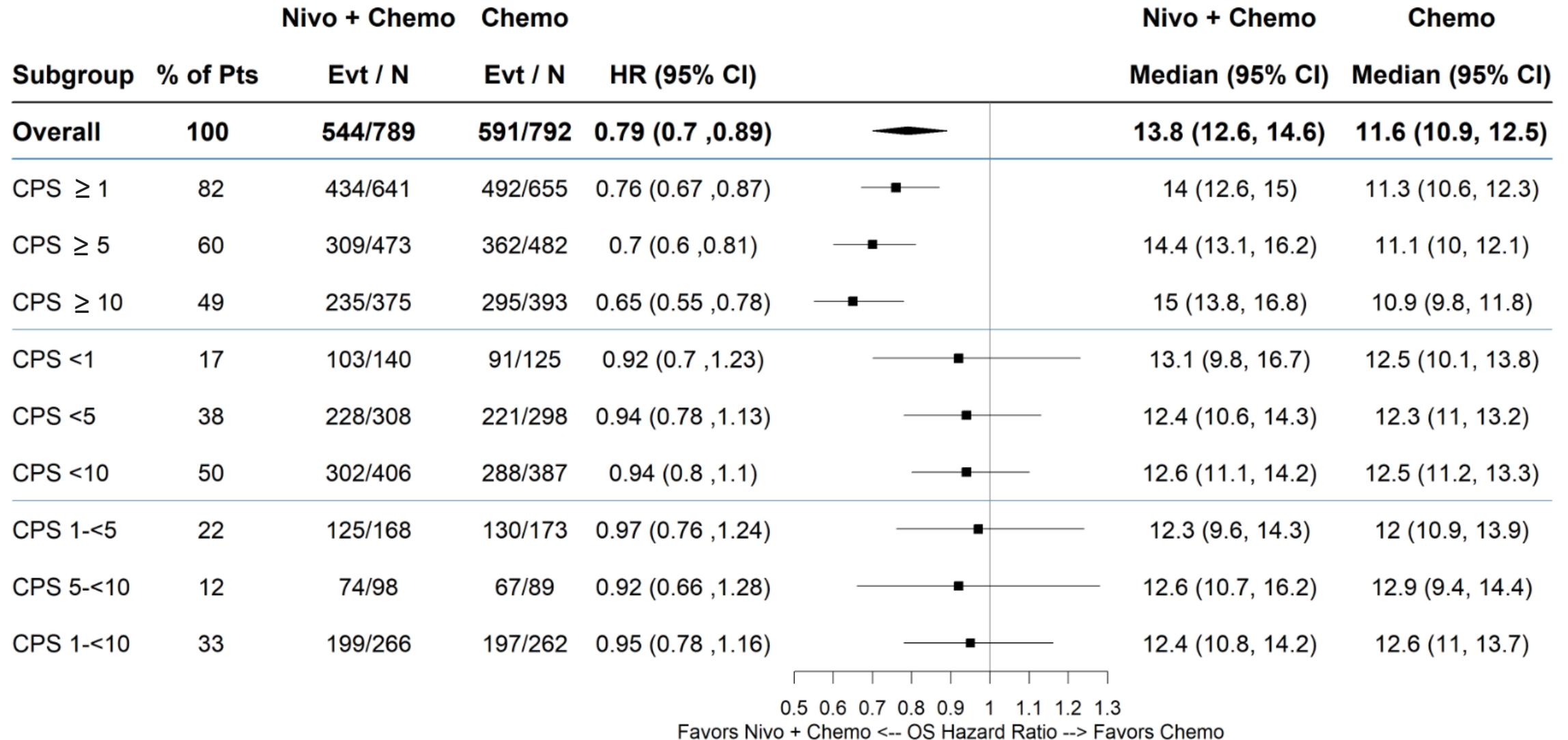
Abbreviations: CM-649: CheckMate-649; KN-859: KEYNOTE-859; RN-305: RATIONALE-305

EFFICACY RESULTS

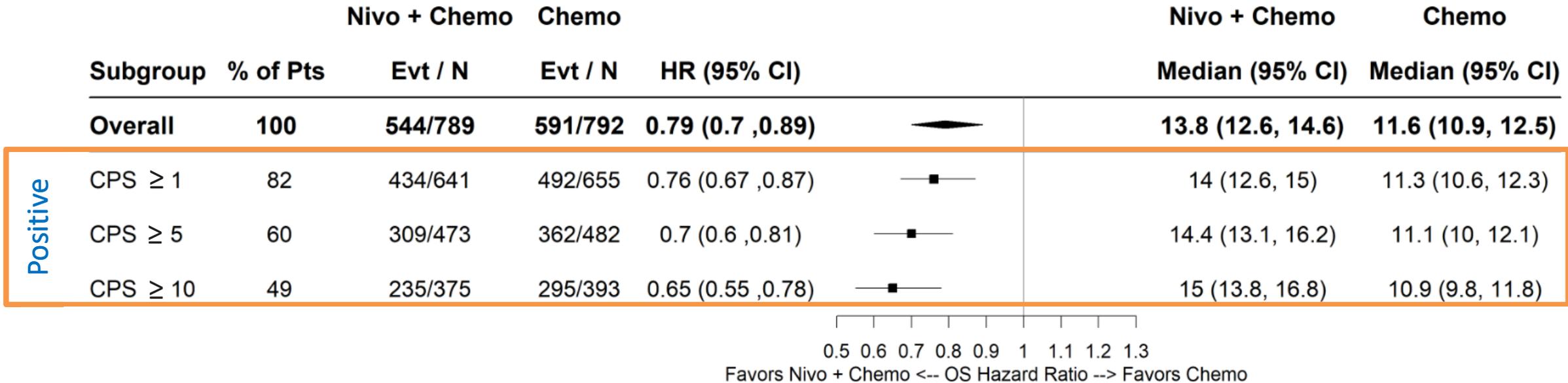
Pre-specified Overall Survival Results

	CheckMate-649	Keynote-849	Rationale-305
Intent to Treat	N = 1581	N=1579	N=997
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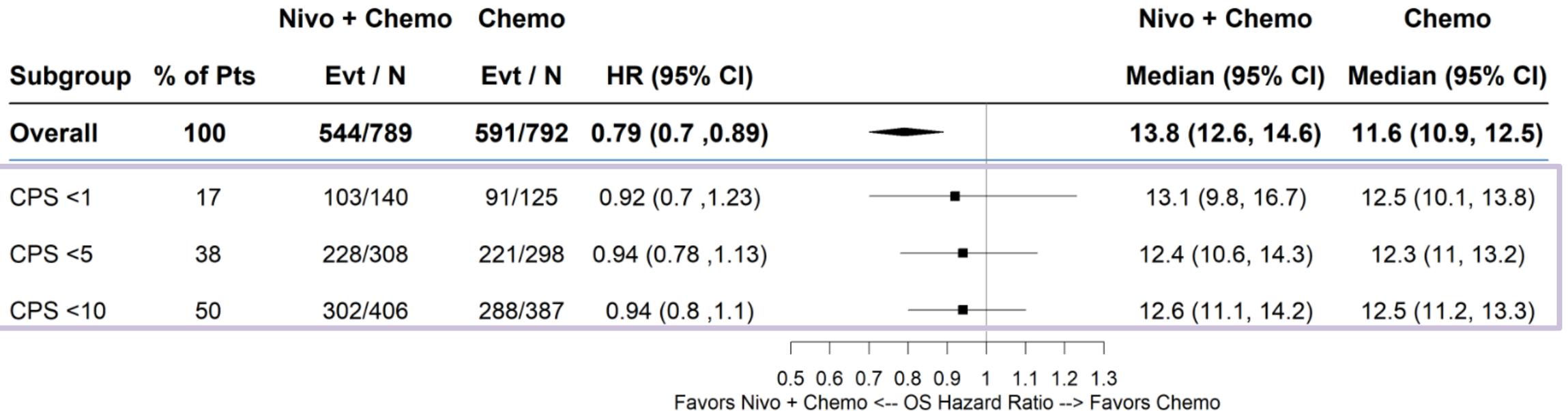
Overall Survival in CheckMate-649



Overall Survival in CheckMate-649



Overall Survival in CheckMate-649



Overall Survival in CheckMate-649

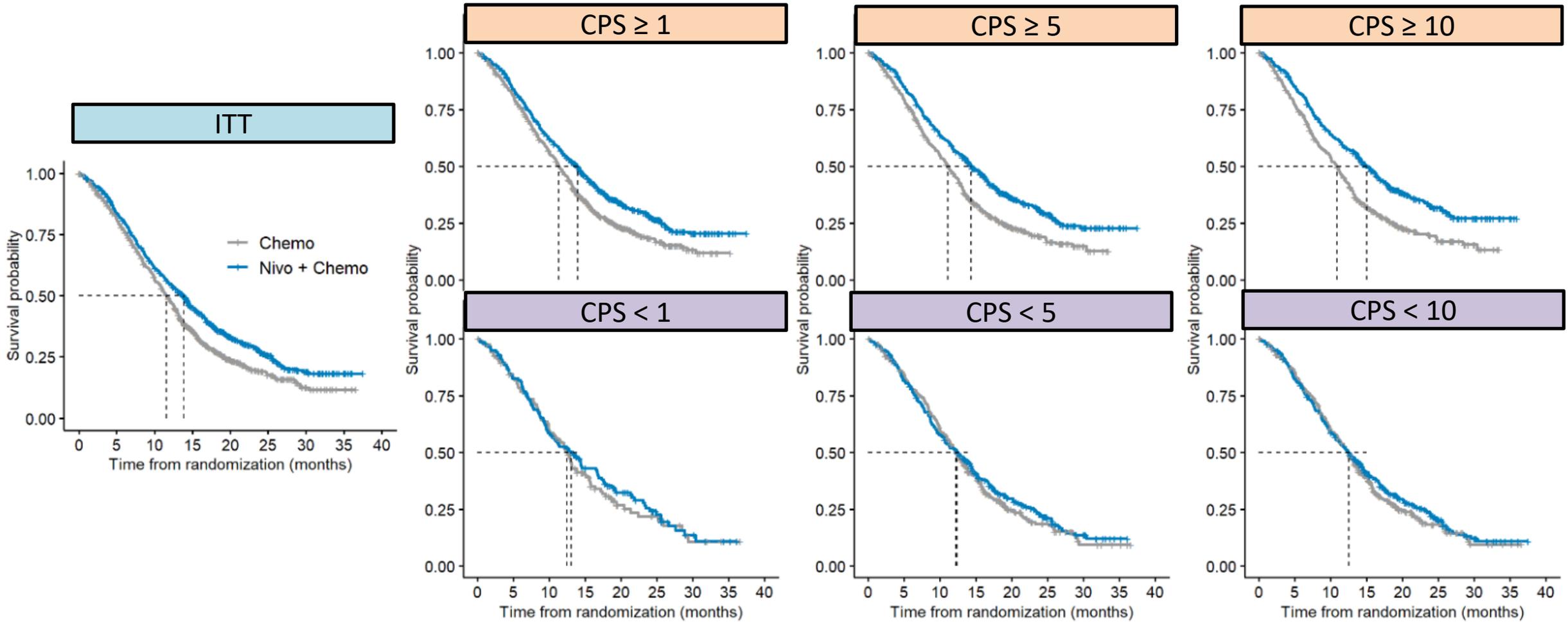


Subgroup	% of Pts	Nivo + Chemo	Chemo	HR (95% CI)		Nivo + Chemo	Chemo
		Evt / N	Evt / N			Median (95% CI)	Median (95% CI)
Overall	100	544/789	591/792	0.79 (0.7 ,0.89)		13.8 (12.6, 14.6)	11.6 (10.9, 12.5)

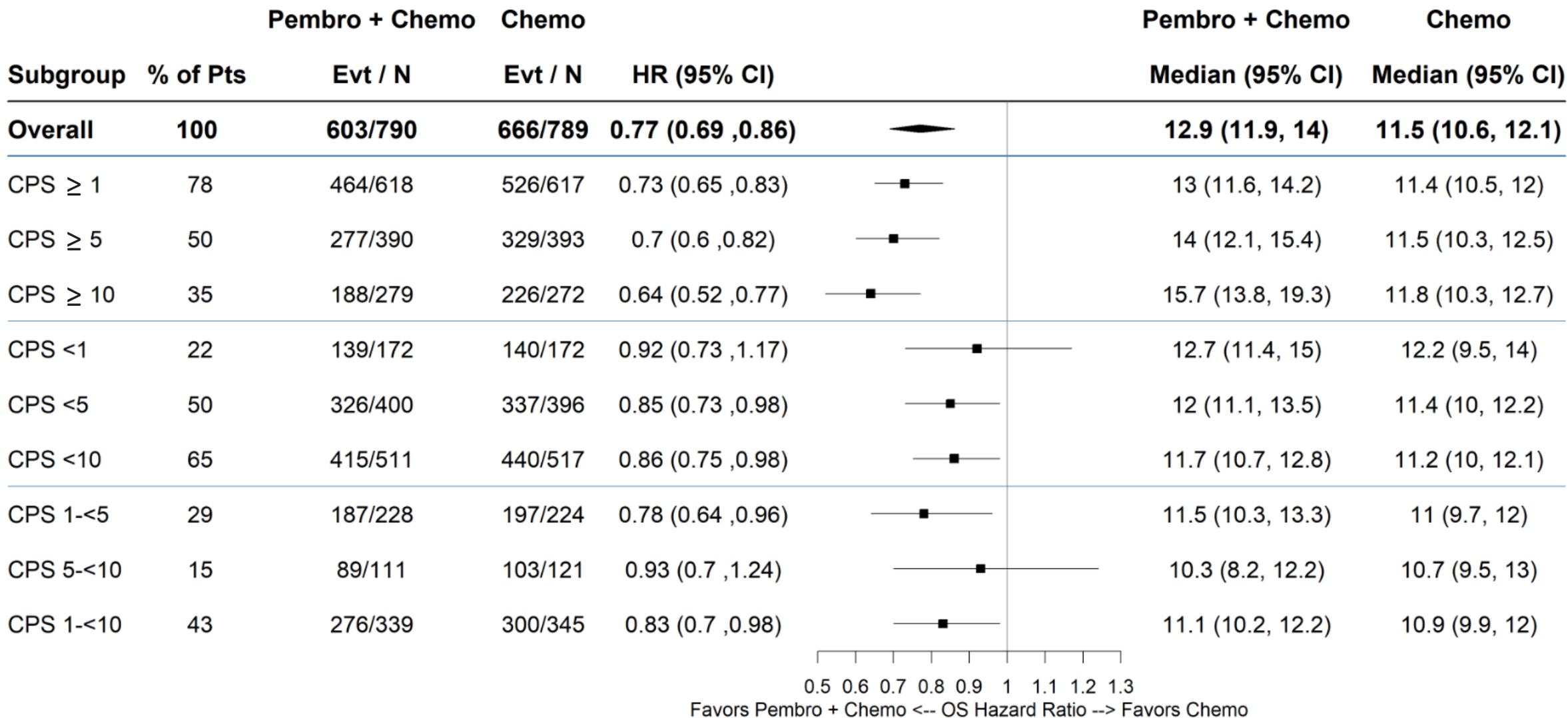
Intermediate	CPS 1-<5	22	125/168	130/173	0.97 (0.76 ,1.24)		12.3 (9.6, 14.3)	12 (10.9, 13.9)
	CPS 5-<10	12	74/98	67/89	0.92 (0.66 ,1.28)		12.6 (10.7, 16.2)	12.9 (9.4, 14.4)
	CPS 1-<10	33	199/266	197/262	0.95 (0.78 ,1.16)		12.4 (10.8, 14.2)	12.6 (11, 13.7)

0.5 0.6 0.7 0.8 0.9 1 1.1 1.2 1.3
 Favors Nivo + Chemo <-- OS Hazard Ratio --> Favors Chemo

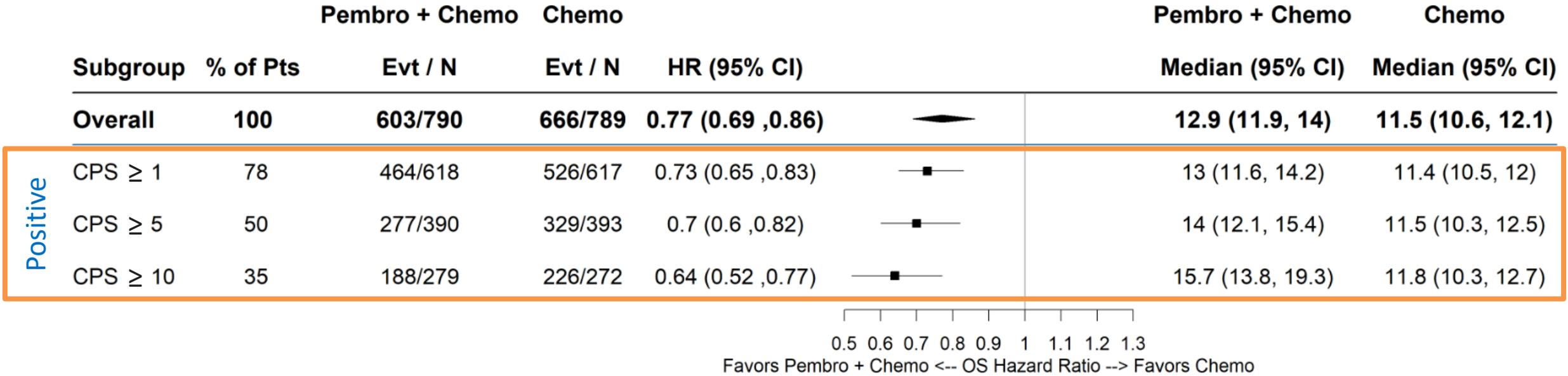
Overall Survival in CheckMate-649



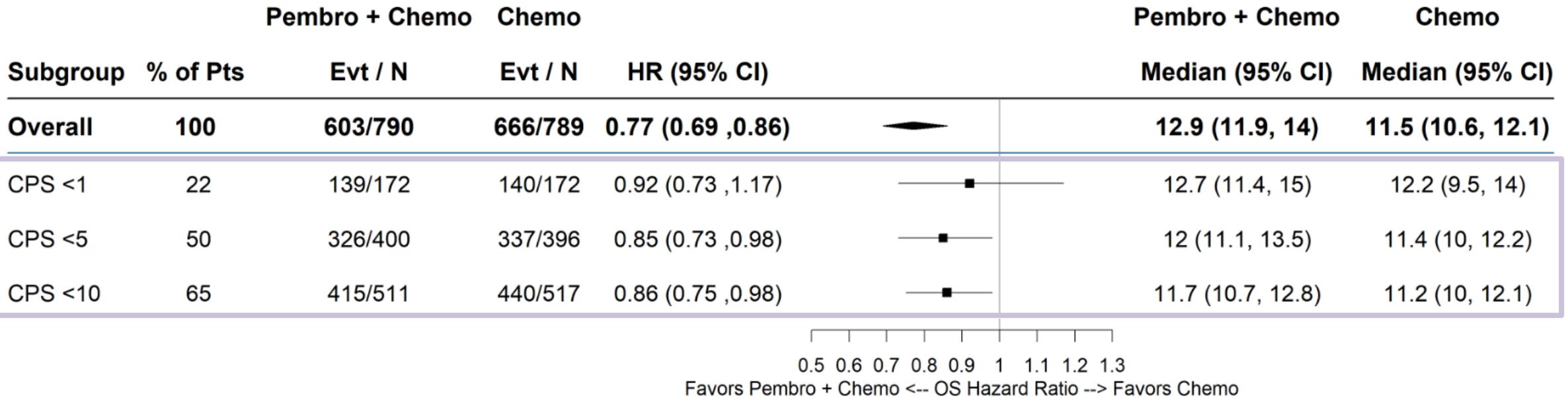
Overall Survival in KEYNOTE-859



Overall Survival in KEYNOTE-859



Overall Survival in KEYNOTE-859

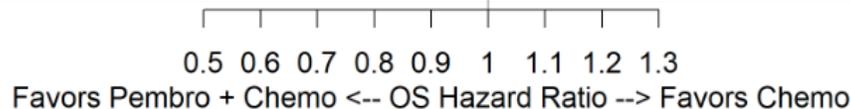


Overall Survival in KEYNOTE-859

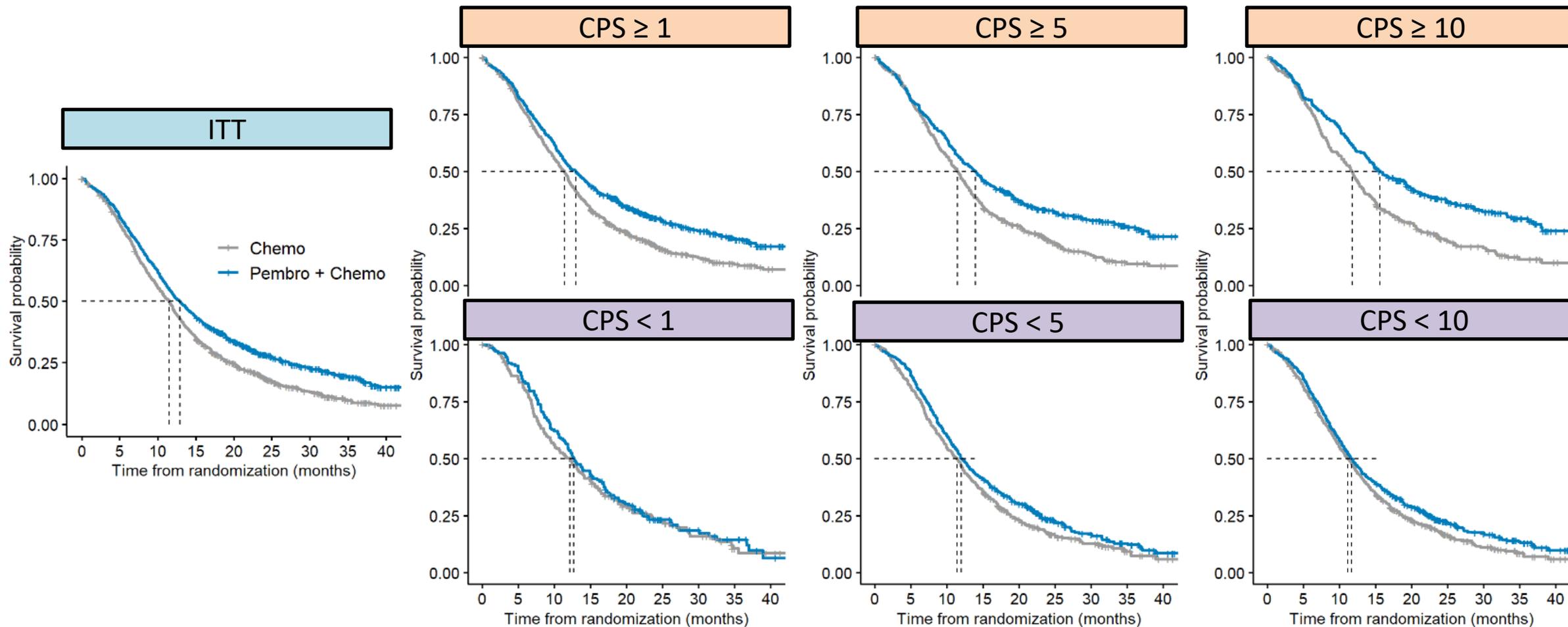


Subgroup	% of Pts	Pembro + Chemo	Chemo	HR (95% CI)		Pembro + Chemo	Chemo
		Evt / N	Evt / N			Median (95% CI)	Median (95% CI)
Overall	100	603/790	666/789	0.77 (0.69 ,0.86)		12.9 (11.9, 14)	11.5 (10.6, 12.1)

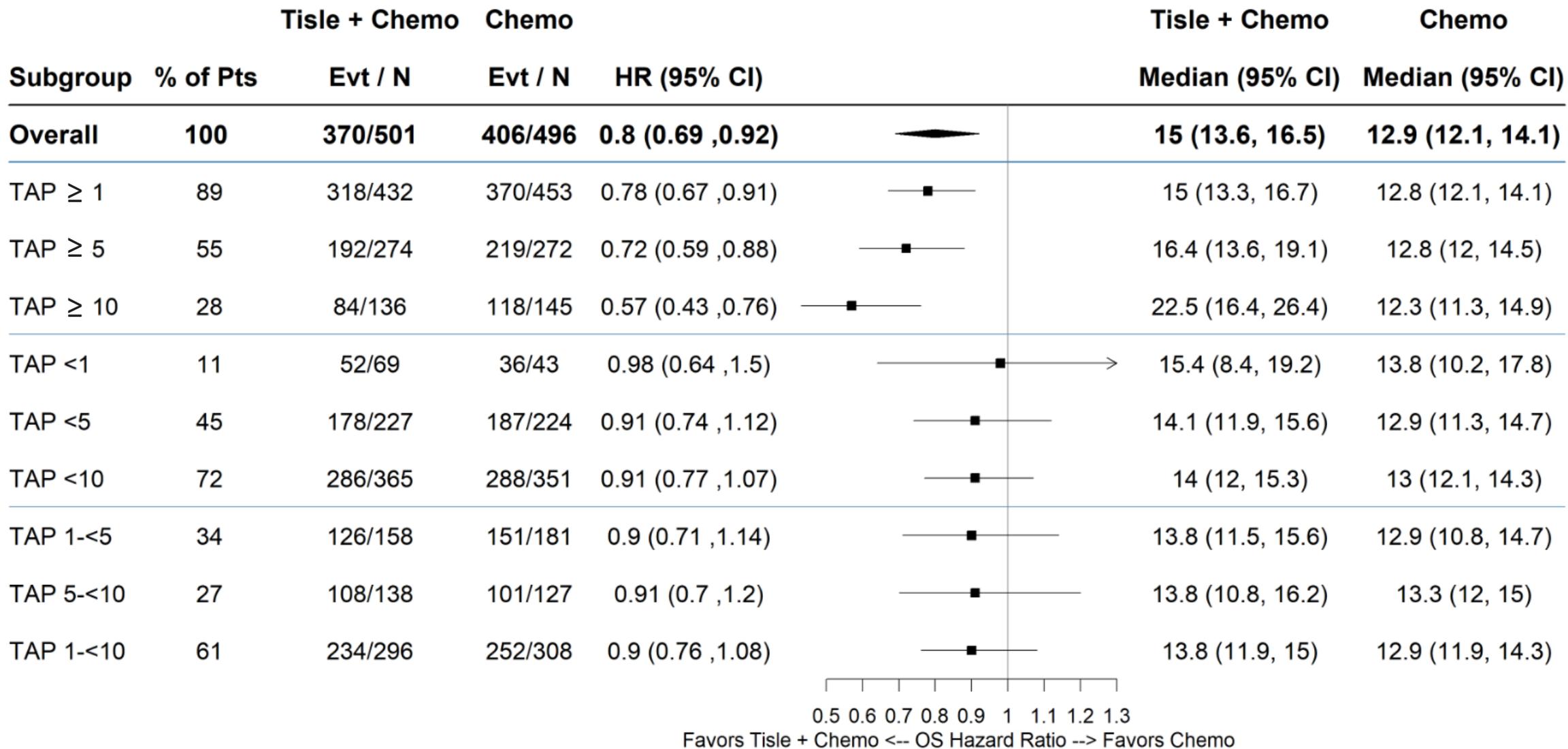
Intermediate	CPS 1-<5	29	187/228	197/224	0.78 (0.64 ,0.96)		11.5 (10.3, 13.3)	11 (9.7, 12)
	CPS 5-<10	15	89/111	103/121	0.93 (0.7 ,1.24)		10.3 (8.2, 12.2)	10.7 (9.5, 13)
	CPS 1-<10	43	276/339	300/345	0.83 (0.7 ,0.98)		11.1 (10.2, 12.2)	10.9 (9.9, 12)



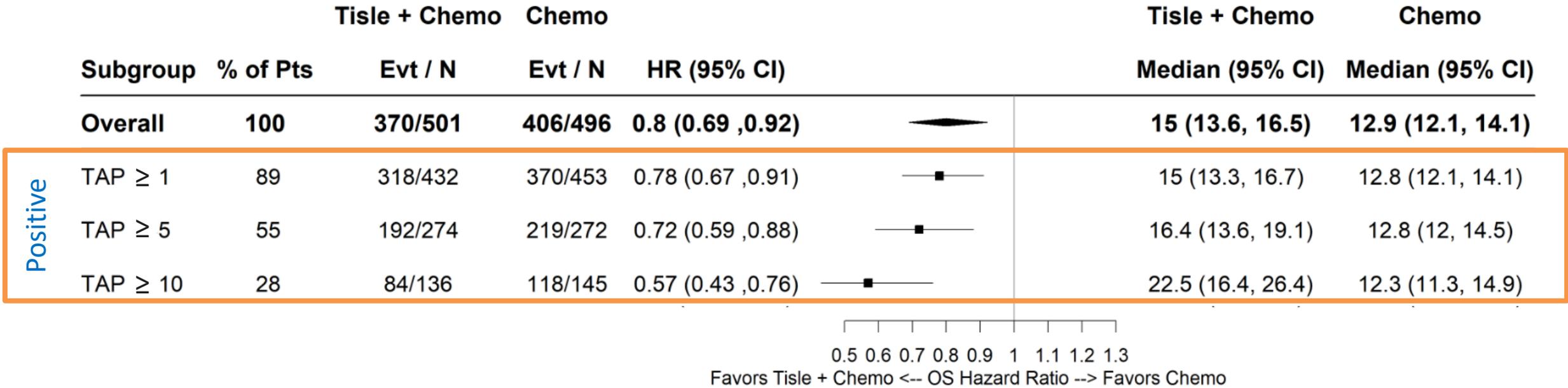
Overall Survival in KEYNOTE-859



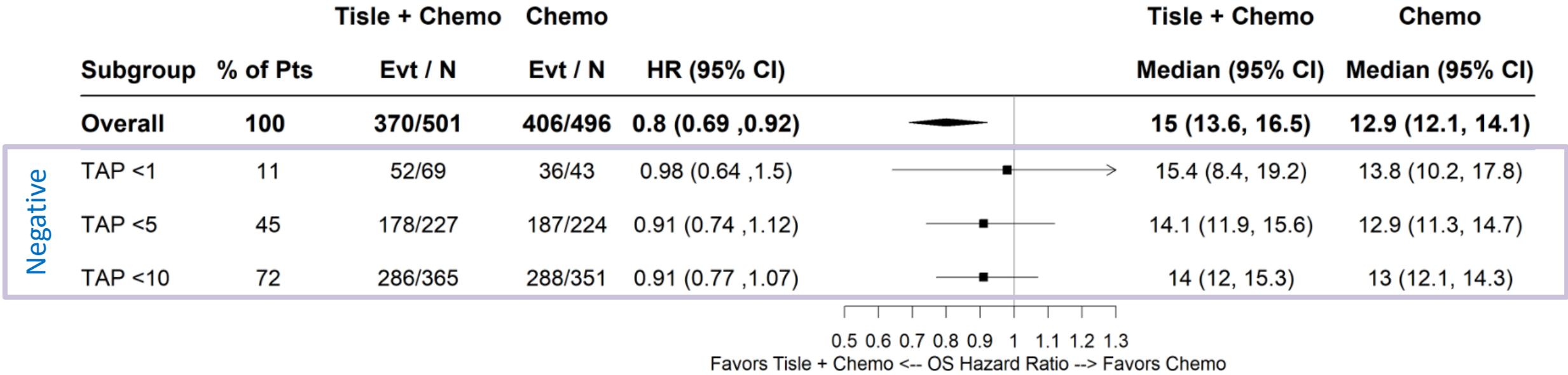
Overall Survival in RATIONALE-305



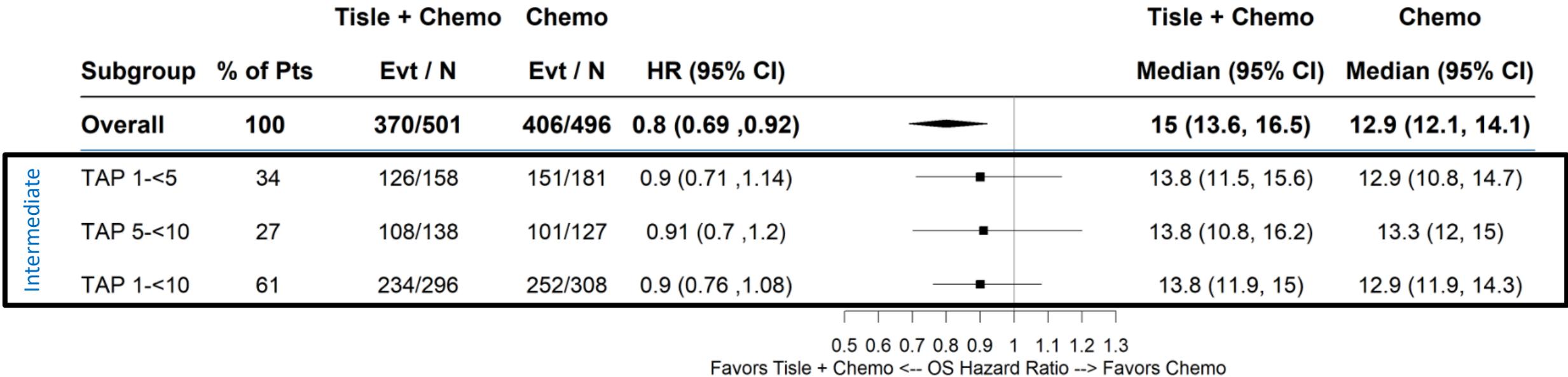
Overall Survival in RATIONALE-305



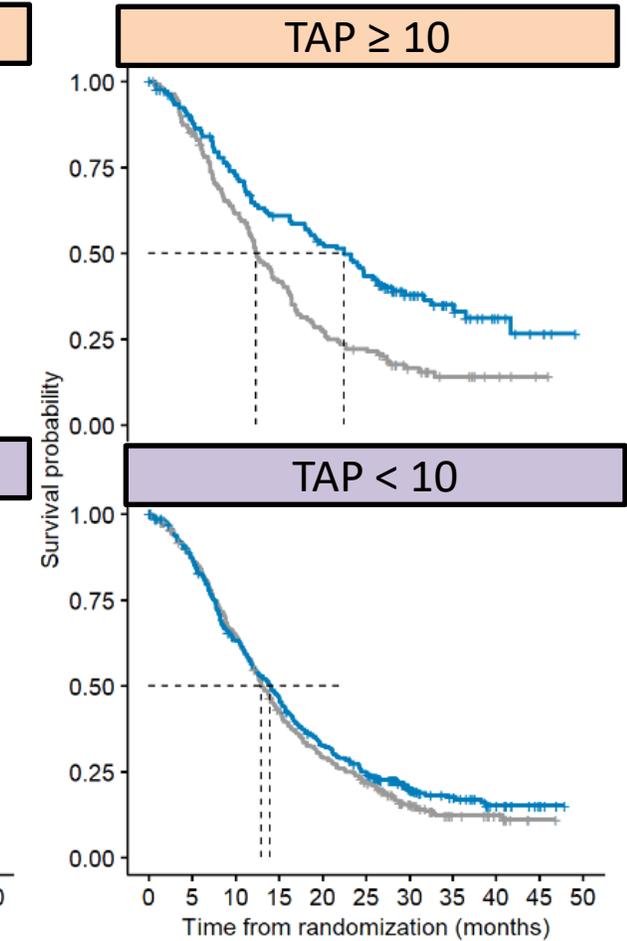
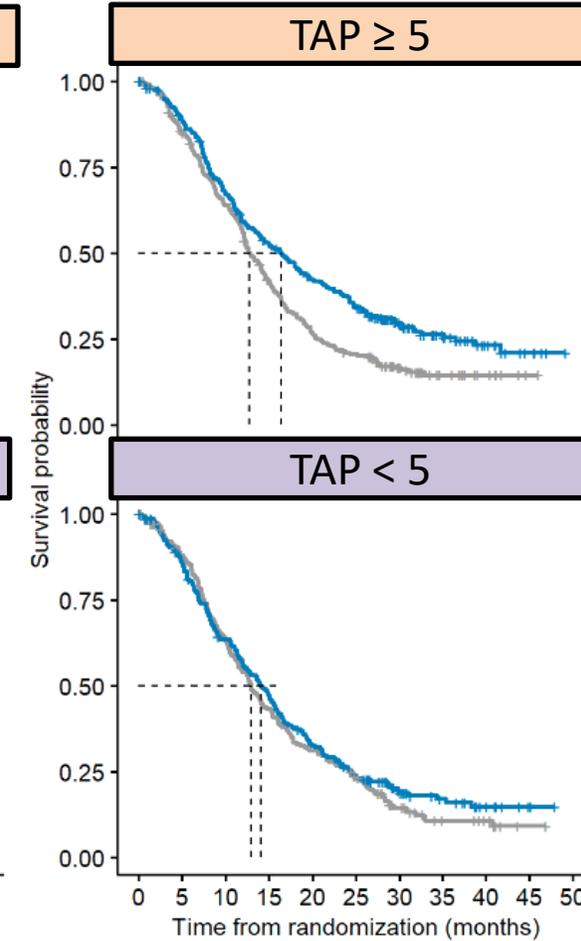
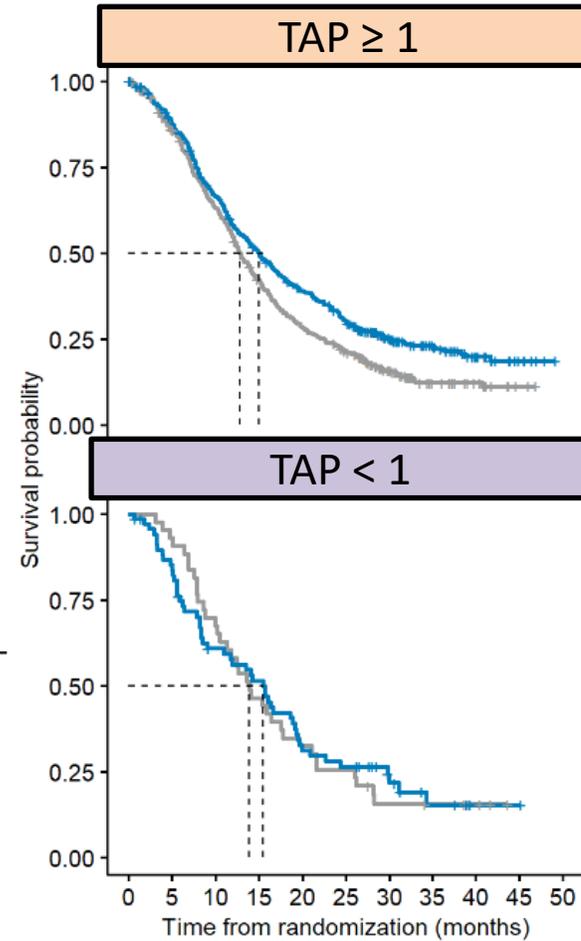
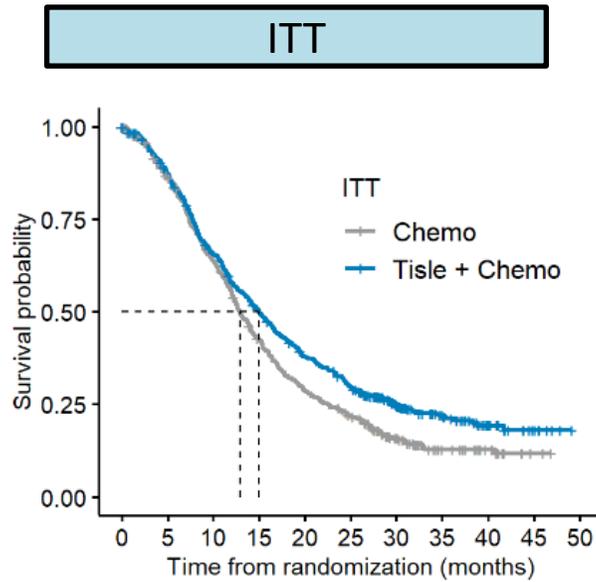
Overall Survival in RATIONALE-305



Overall Survival in RATIONALE-305



Overall Survival in RATIONALE-305

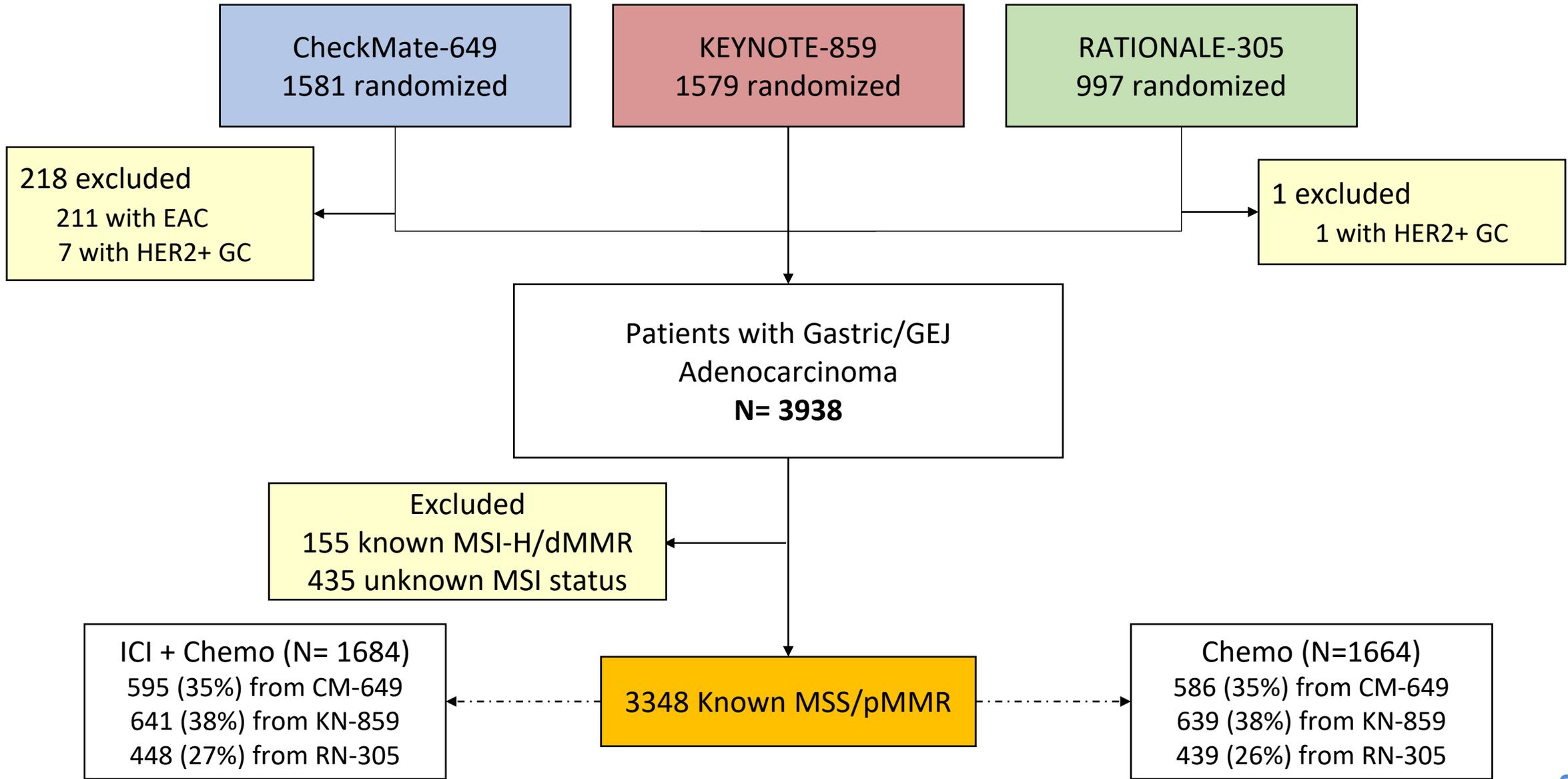


Weighing the Risks

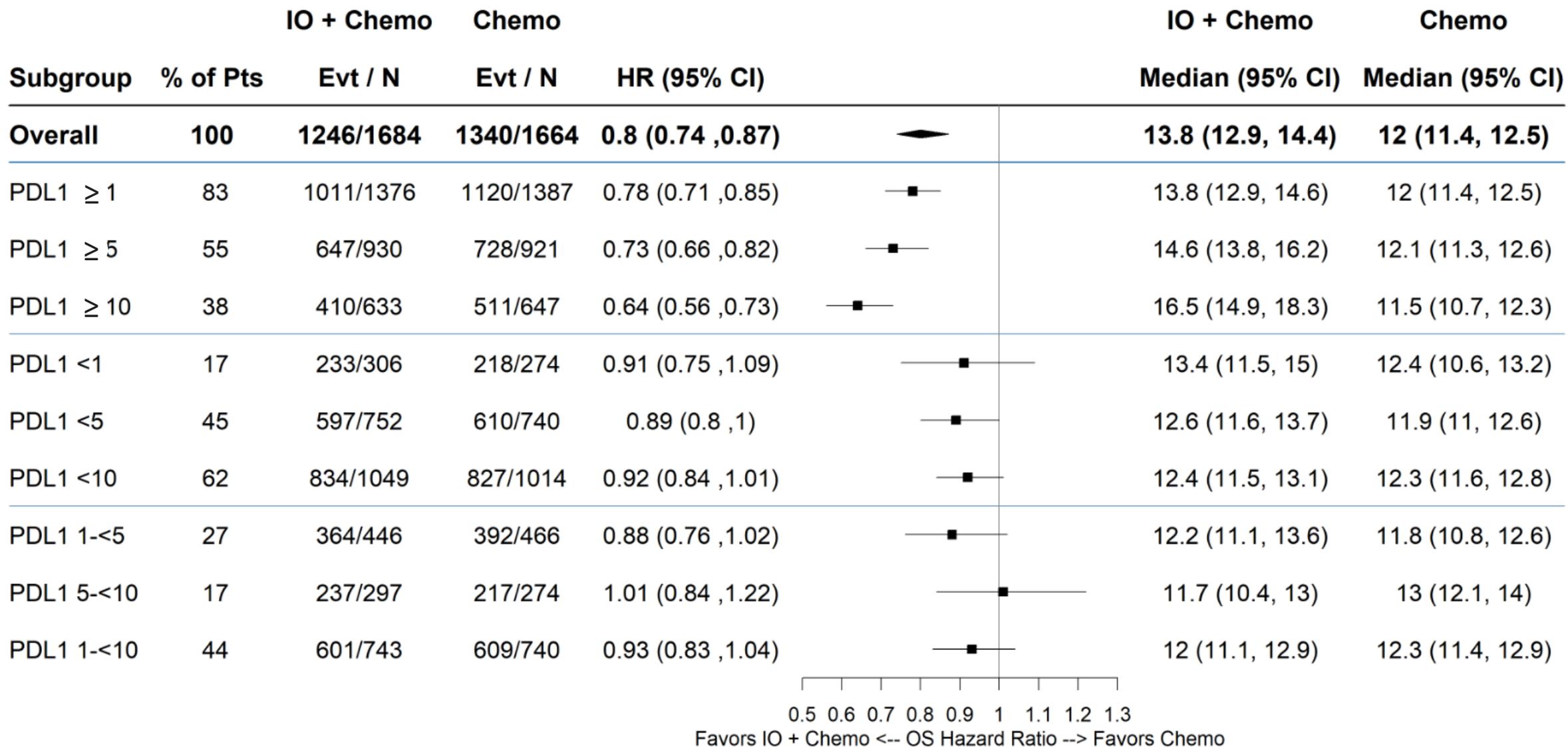
- All patients exposed to risks of ICI
- No apparent difference in toxicity across PD-L1 strata
- Additional Toxicity from addition of ICI
 - 3 to 11% increase in Grade 3-4 TEAE
 - ~ 30% IMAEs All Grades
 - Fatal IMAE

Caveats of Pooled Analyses

- Acceptability of combining data from patients defined using different PD-L1 assays and scoring algorithm has not been determined
- Studies utilized varying PD-L1 cutoffs and the analytic validity of the PD-L1 cutoffs at the uniform thresholds has not been determined
- Data limited to only the pooled analyses submitted to FDA and excluding other randomized studies risks introducing bias



OS – Pooled Data Gastric/GEJ and MSS only

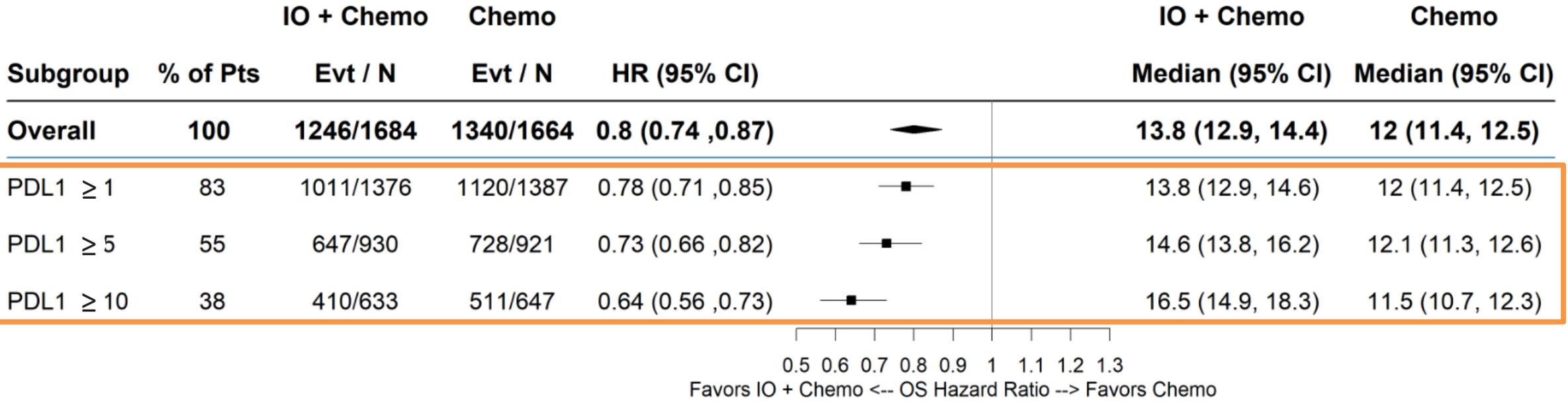


¹Pooled analysis stratified by study

²PD-L1 expression score using CPS for KEYNOTE(KN)-859 and CheckMate (CM)-649, TAP for RATIONALE(RN)-305

Abbreviations: IO: Immunotherapy

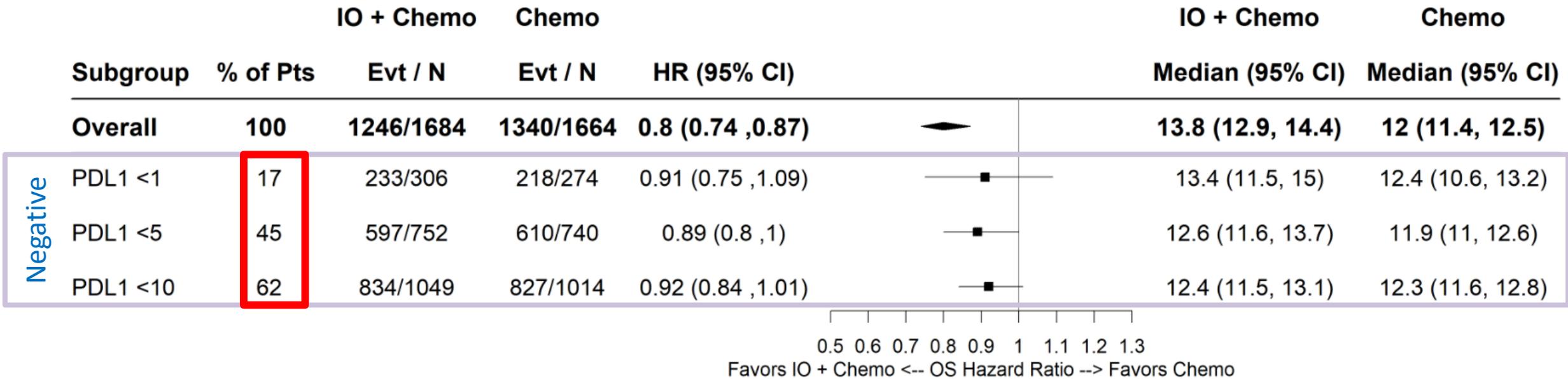
OS – Pooled Data Gastric/GEJ and MSS only



¹Pooled analysis stratified by study

²PD-L1 expression score using CPS for KN859 and CM649, TAP for RN305

OS – Pooled Data Gastric/GEJ and MSS only



¹Pooled analysis stratified by study

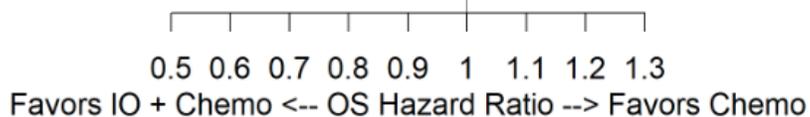
²PD-L1 expression score using CPS for KN859 and CM649, TAP for RN305

OS – Pooled Data Gastric/GEJ and MSS only



Subgroup	% of Pts	IO + Chemo	Chemo	HR (95% CI)		IO + Chemo	Chemo
		Evt / N	Evt / N			Median (95% CI)	Median (95% CI)
Overall	100	1246/1684	1340/1664	0.8 (0.74 ,0.87)		13.8 (12.9, 14.4)	12 (11.4, 12.5)

Intermediate	PDL1 1-<5	27	364/446	392/466	0.88 (0.76 ,1.02)		12.2 (11.1, 13.6)	11.8 (10.8, 12.6)
	PDL1 5-<10	17	237/297	217/274	1.01 (0.84 ,1.22)		11.7 (10.4, 13)	13 (12.1, 14)
	PDL1 1-<10	44	601/743	609/740	0.93 (0.83 ,1.04)		12 (11.1, 12.9)	12.3 (11.4, 12.9)



¹Pooled analysis stratified by study

²PD-L1 expression score using CPS for KN859 and CM649, TAP for RN305

Summary

1. PD-L1 expression appears to be a **predictive biomarker** in HER2 negative gastric/GEJ adenocarcinoma
2. FDA concerns on the modest efficacy observed in **PD-L1 < 1** patient populations
3. Patients are exposed to the **added toxicity** of immune checkpoint inhibitors

Discussion Question



In patients with HER2-negative microsatellite stable gastric/GEJ adenocarcinoma, does the cumulative data support the use of **PD-L1 expression as a predictive biomarker** when selecting patients for treatment with PD-1 inhibitors?

Voting Question



Is a risk benefit assessment **favorable** for the use of PD-1 inhibitors in first line advanced HER2 negative microsatellite stable gastric/GEJ adenocarcinoma in patients with PD-L1 expression < 1?

- Yes
- No