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REVIEW

# PD-L1 thresholds predict efficacy of immune checkpoint inhibition in first-line treatment of advanced gastroesophageal adenocarcinoma. A systematic review and meta-analysis of seven phase III randomized trials

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**Background:** High expression of programmed death-ligand 1 (PD-L1) has been recognized as a marker of improved efficacy of immunotherapy in gastroesophageal adenocarcinoma (GEA); however, the optimal PD-L1 cut-off is still debated. The aim of the present review was to analyze available phase III trials and to identify the appropriate PD-L1 expression cut-off for GEA.

**Methods:** Phase III trials investigating the efficacy of anti-programmed cell death protein 1 (PD-1) therapies in addition to standard chemotherapy versus standard chemotherapy in the first-line setting were selected. Progression-free survival (PFS), overall survival (OS) and objective response rate (ORR) were the analyzed outcome measures. Pooled treatment effects were assessed in the unselected population and in subpopulations with different levels of PD-L1 expression.

**Results:** PD-1 blockade efficacy was found to consistently increase in a linear manner with higher combined positive score (CPS) of PD-L1 expression: pooled hazard ratio (HR) for OS and PFS and pooled odds ratio (OR) for ORR of 0.80, 0.75 and 1.51, respectively, in the unselected population versus 0.67, 0.63 and 1.90, respectively, in the CPS $\geq$10 population (all $P$ values $<$ 0.0001). In the PD-L1-negative population (CPS $<$1) a significant benefit of anti-PD-1 agents could not be demonstrated in terms of OS and PFS ($P$ = 0.28 and 0.12, respectively), but it was seen in terms of ORR ($P$ = 0.03). PD-1 blockade was effective in the CPS $<$10 population ($P$ value for pooled OS HR, PFS HR and response OR are all 0.01), while in the CPS $<$5 population the effect was of borderline significance for OS ($P$ = 0.07) and significant for PFS and ORR ($P$ = 0.02 and 0.03, respectively).

**Conclusion:** The present meta-analysis confirmed that the benefit of PD-1 blockade in GEA patients is related to PD-L1 CPS, with increased benefit observed for higher CPS cut-offs and no OS benefit in the CPS $<$1 subset. Overall, data indicate that PD-L1 CPS $\geq$5 could represent an acceptable cut-off to optimize the risk/benefit ratio of such agents. Our data suggest a potential clinical benefit of immunotherapy in selected patients within the CPS 1-4 population which needs further investigation.

**Key words:** immune checkpoint inhibitors, gastroesophageal adenocarcinoma, PD-L1

## INTRODUCTION

In the past decade, anti-programmed cell death protein 1 (PD-1) antibodies have significantly improved outcomes for patients with advanced adenocarcinoma of the stomach and esophagus [gastroesophageal adenocarcinoma (GEA)].[1-3] In two large global phase III randomized trials, nivolumab and pembrolizumab, respectively, have demonstrated prolonged survival when combined with standard first-line chemotherapy in unselected patients.[4] However, the benefit was more pronounced in patients whose tumor displayed high programmed death-ligand 1 (PD-L1) expression. In GEA, recent analyses have confirmed that PD-L1 expression, measured by combined positive score (CPS), is the most reliable predictive factors of benefit from immune checkpoint inhibitors (ICIs), second only to microsatellite instability (MSI).[5]

In the CheckMate-649 trial, nivolumab was associated with a 21% reduction in the risk of death [hazard ratio (HR) 0.79] in all patients and a 30% reduction in patients with PD-L1 CPS $\geq$5 (HR 0.70).[6] These results led to the European

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Union approval of nivolumab in patients with GEA, in combination with fluoropyrimidine- and platinum-based chemotherapy when the tumor expresses PD-L1 with a CPS $\geq$5.[7]

In the KEYNOTE-859 trial, similar results were reported with pembrolizumab, with a 22% risk reduction in survival (HR 0.78) in the overall population.[8] In the KEYNOTE-859, the PD-L1-enriched population was determined by a PD-L1 CPS $\geq$10, and in this subgroup the HR was 0.65, indicating a potentially enhanced risk reduction with higher PD-L1 expression.

Given the different CPS cut-offs used to optimize PD-1 blockade efficacy in this setting, the present meta-analysis aimed to review and analyze results from the most recent phase III trials of anti-PD-1 antibodies plus standard-of-care chemotherapy combinations in the first-line treatment of adenocarcinoma of the esophagogastric region with special focus on subpopulations with different PD-L1 expression, measured by CPS.

## METHODS

The present meta-analysis was recorded in the PROSPERO repository (CRD42021216304) and complied with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

The PubMed database was inquired from its inception to February 2024 with the following syntax: (gastro-esophageal cancer) AND (randomized phase 3 trial). Eligibility and inclusion criteria were the following: a filter for randomized controlled trial in English was applied for the search (prospective studies) and resulting records were scrutinized to select those investigating the efficacy of anti-PD-1 antibody plus chemotherapy (intervention) versus standard chemotherapy (control) in first-line treatment of human epidermal growth factor receptor 2 (HER2)-negative GEA (population). Selected papers were also manually searched in the reference list for candidate trials presented in cancer congresses. Exclusion criteria were studies enrolling HER2-positive or pre-treated patients and studies in the neo-adjuvant or adjuvant setting.

Primary outcome measures were pooled HR for overall survival (OS), pooled HR for progression-free survival (PFS) and pooled odds ratio (OR) for objective response rate (ORR) in the anti-PD-1 antibody plus chemotherapy group versus standard chemotherapy group.

As per the meta-analysis objective, subpopulations were defined according to PD-L1 CPS score as follows: all participants, CPS $\geq$1, CPS $\geq$5, CPS $\geq$10, CPS $<$1, CPS $<$5 and CPS $<$10. Moreover, the tumor proportion score (TPS) $\geq$1% and $<$1% (TPS negative) groups were also analyzed.

Two researchers (CM and SR) independently reviewed the articles and related reference lists and selected the studies. Discrepancies were resolved by discussions amongst the research team. A standard extraction form on Microsoft Excel was used with data extracted for each study as follows: first author, title, year of publication, journal, trial phase, patient population, control and experimental treatment arms, immunotherapy investigated and number of patients included. The main characteristics of the included trials are reported in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103967.

HRs and response rates with 95% confidence intervals (CIs) comparing PD-1 antibody plus chemotherapy versus chemotherapy alone in the different CPS populations of the eligible studies were annotated in the data extraction form to calculate the overall treatment effects in the overall populations and in PD-L1 expression subgroups as described above.

Pooled estimates of anti-PD-1-based regimens effect, expressed as HRs or ORs, were calculated separately using a random- or fixed-effect model based on the inverse variance method. Potential heterogeneity among studies was assessed using Cochrane's Q statistic and I2 statistic. The common-effects models were used to calculate pooled HRs or ORs if no significant heterogeneity (I2 $<$50%) was documented. All tests were carried out with R version 4.0.3 (The R Foundation. Vienna, Austria).

## RESULTS

Seven phase III randomized trials investigating the addition of an anti-PD-1 antibody to standard first-line platinum/fluoropyrimidine doublet chemotherapy in GEA were selected (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.103967) including a total of 6239 patients. The seven trials were: CheckMate-649,[6] KEYNOTE-859,[8] ATTRACTION-4,[9] KEYNOTE-062,[10] KEYNOTE-590,[11] ORIENT-16[12] and RATIONALE-305.[13] The KEYNOTE-590 trial included both adenocarcinoma and squamous cell carcinoma; however, only data from adenocarcinoma patients were selected for the present analysis.

Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103967, represents the characteristics of the seven included trials. Of note, in the ATTRACTION-4 trial the TPS was presented instead of CPS. Based on the CheckMate-649 results, $>$90% of TPS $\geq$1% patients were CPS $\geq$5 (230 out of 253). For this reason, the TPS $\geq$1% population was pragmatically assumed to perform similar to the CPS $\geq$5 population and analyzed as CPS $\geq$5. For the KEYNOTE-062 trial, CPS $<$1 patients were excluded; therefore, in the CPS $<$5 and CPS $<$10 populations of KEYNOTE-062, PD-L1-negative patients were not included. In the RATIONALE-305 trial, PD-L1 expression score was based on the percentage of the area of the specimen containing PD-L1-positive tumor cells [tumor area positivity (TAP)]. Since the proportion of TAP $\geq$5% patients (55% of patients) in the RATIONALE-305 trial was similar to that of CPS $\geq$5 in the CheckMate-649 and ORIENT16 trials (60% and 61% of patients, respectively), TAP was pragmatically assumed to be representative of CPS, and the TAP $\geq$5% population was assumed to be the CPS $\geq$5 population.

Overall, a significant benefit in OS was demonstrated for the anti-PD-1 antibody plus chemotherapy combination ($P < 0.0001$) in the PD-L1 unselected population (all

comers), with a pooled 20% reduction in the risk of death: HR 0.80 (95% CI 0.76-0.85). No significant inter-trial heterogeneity was observed: *Q*-test $P = 0.86$, I2 0% (Figure 1).

By enriching the patient population with increasing PD-L1 expression, an improvement in the pooled OS HR was observed in a clearly linear association, with the pooled HR for OS passing from 0.80 in all comers to 0.67 in CPS $\geq$10: pooled HR for OS in the CPS $\geq$1, CPS $\geq$5 and CPS $\geq$10 cohorts were 0.76 (95% CI 0.70-0.82), 0.71 (95% CI 0.64-0.79) and 0.67 (95% CI 0.60-0.74), respectively, all *P* values $<$0.0001. No inter-trial heterogeneity was detected (I2 0%-15%). A sensitivity analysis was carried out by excluding the RATIONALE-305 and ATTRACTION-4 trials, where TAP and TPS scores, respectively, were used instead of CPS. Results were not significantly different (for CPS $\geq$5 pooled HR 0.69, 95% CI 0.60-0.78, $P < 0.0001$).

With regard to PFS, a significant improvement was observed with the use of anti-PD-1 antibodies in combination with standard first-line chemotherapy in the PD-L1 unselected population ($P < 0.0001$), with a pooled 25% reduction in the risk of progression (HR 0.75, 95% CI 0.71-0.80), and no heterogeneity detected between trials, I2 0%, $P = 0.43$ (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2024.103967). By increasing the selection of patients on the basis of PD-L1 CPS, again an almost linear association was observed, with improved HR for PFS for increasing values of CPS: pooled HR of 0.74 (95% CI 0.68-0.80, $P < 0.0001$), 0.68 (95% CI 0.61-0.76, $P < 0.0001$) and 0.63 (95% CI 0.54-0.72, $P < 0.0001$) for CPS $\geq$1, CPS $\geq$5 and CPS $\geq$10, respectively. No heterogeneity was observed (I2 0%-21%).

Also for PFS, a sensitivity analysis was carried out by excluding the RATIONALE-305 and ATTRACTION-4 trials. Results were not significantly different (for CPS $\geq$5 pooled HR 0.68, 95% CI 0.59-0.77, $P < 0.0001$).

Furthermore, the ORR showed a similar linear improvement with the use of anti-PD-1 antibodies by increasing the CPS cut-off (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2024.103967).

In the PD-L1 unselected, CPS $\geq$1, CPS $\geq$5 and CPS $\geq$10 populations, OR in favor of anti-PD-1 plus chemotherapy combination was 1.51 (95% CI 1.36-1.68), 1.57 (95% CI 1.35-1.82), 1.63 (95% CI 1.33-2.00) and 1.90 (95% CI 1.53-2.36) respectively, all *P* values $<$0.0001.

ORR in the chemotherapy group remained in the range of 43%-45% across all CPS subgroups, while in the anti-PD-1 plus chemotherapy group it increased from 53% to 54%, 57% and 59% passing from the unselected to the CPS $\geq$1, CPS $\geq$5 and CPS $\geq$10 populations, respectively (from +10% to +11%, +12% and +16%, respectively). No heterogeneity was detected (I2 0%-6%).

The sensitivity analysis excluding the RATIONALE-305 and ATTRACTION-4 trials showed no significantly different results (for CPS $\geq$5 pooled OR 1.80, 95% CI 1.42-2.29, $P <$ 0.0001).

To assess whether subgroups of patients with low PD-L1 expression would derive inferior benefit from PD-1 blockade, trial results were meta-analyzed for the CPS-low populations using different CPS cut-offs.

In terms of OS, no benefit was observed in the PD-L1-negative population (CPS $<$1) with pooled HR of 0.91 (95% CI 0.77-1.08, $P = 0.28$; Figure 2). In the CPS $<$5 population a borderline benefit from the addition of anti-PD-1 therapy to chemotherapy was observed, with a $P =$ 0.07 and a pooled HR of 0.91 (95% CI 0.82-1.01), possibly indicating the presence of a subgroup of patients responsive to PD-1 blockade in the CPS 1-4 population. Similar results were obtained by excluding ATTRACTION-4 and RATIONALE-305 trials (pooled HR 0.93, 95% CI 0.79-1.09).

In the CPS $<$10 population a significant benefit was observed with the anti-PD-1 treatment with a pooled HR of 0.88 (95% CI 0.80-0.96) and a $P = 0.01$, suggesting that patients responsive to PD-1 blockade were definitively present in the CPS 1-9 population. Trial heterogeneity was I2 0% in this analysis.

As for the PFS outcome, similar observations were made (Figure 3). PD-1 blockade had no clear effect in the PD-L1-negative population (CPS $<$1) with a pooled HR of 0.87 (95% CI 0.73-1.04, $P = 0.12$).

In both the CPS $<$5 and CPS $<$10 populations a significant PFS advantage was demonstrated for the anti-PD-1 combination arm, with a pooled HR of 0.75 (95% CI 0.59-0.96) and 0.77 (95% CI 0.64-0.93), $P =$ 0.02 and 0.01, respectively, again indicating the presence of anti-PD-1 responsive patients in the CPS 1-9 population. A significant trial heterogeneity was observed in the CPS $<$5 analysis (I2 68%, $P =$ 0.04). Results were similar after excluding the ATTRACTION-4 and RATIONALE-305 trials (HR 0.79 and 0.77, respectively).

In the analysis of ORR, a significant improvement of response rate was observed in all PD-L1 CPS-low populations (Figure 4), with pooled ORs ranging from 1.31 to 1.46 (*P* values 0.01-0.03), and ORR increasing overall from 40%-43% to 49%-50% (absolute increase +6%-9%). No inter-trial heterogeneity was observed (I2 0%-26%). Results were not significantly different after exclusion of the ATTRACTION-4 and RATIONALE-305 trials.

TPS results were available for three trials (ATTRACTION-4, CheckMate-649, ORIENT-16) and only for OS and PFS. Pooled results in the TPS-positive population were the following: HR for OS 0.65, $P = 0.04$; HR for PFS 0.64, $P =$ 0.01 (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2024.103967). A significant benefit of anti-PD-1 treatment was also demonstrated in the TPS-negative population both in terms of OS and in terms of PFS (HR 0.84, $P = 0.0003$ and HR 0.67, $P < 0.0001$, respectively).

## DISCUSSION

In the present meta-analysis we were able to confirm that the benefit obtained with the use of anti-PD-1 antibody in combination with standard first-line chemotherapy in GEA has a consistent direct linear association with increasing PD-L1 expression.

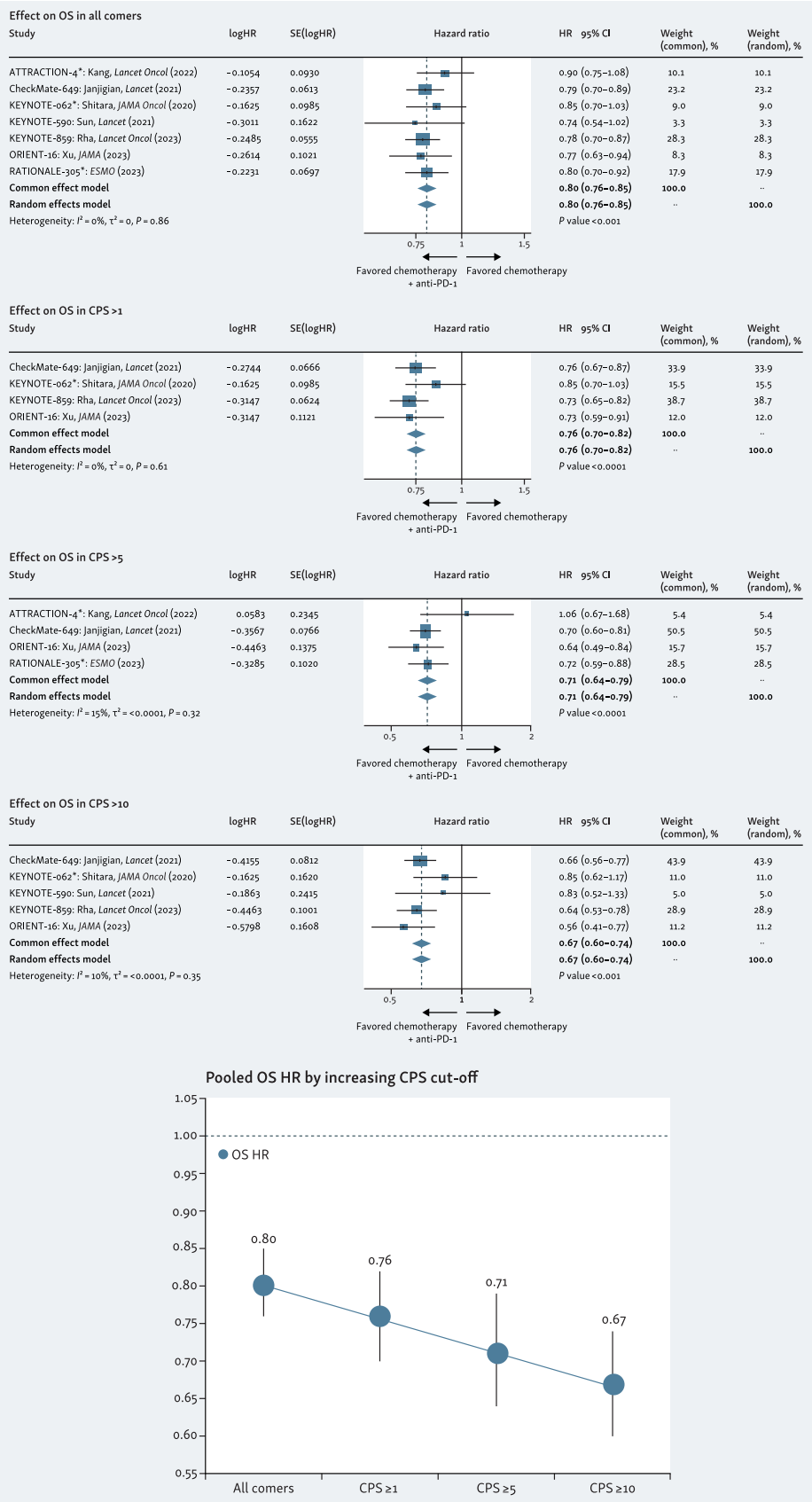


**Figure 1. Effect of the addition of anti-PD-1 agent to standard first-line chemotherapy on OS by increasing CPS cut-off.**
CI, confidence interval; CPS, combined positive score; HR, hazard ratio; OS, overall survival; PD-1, programmed cell death protein 1.

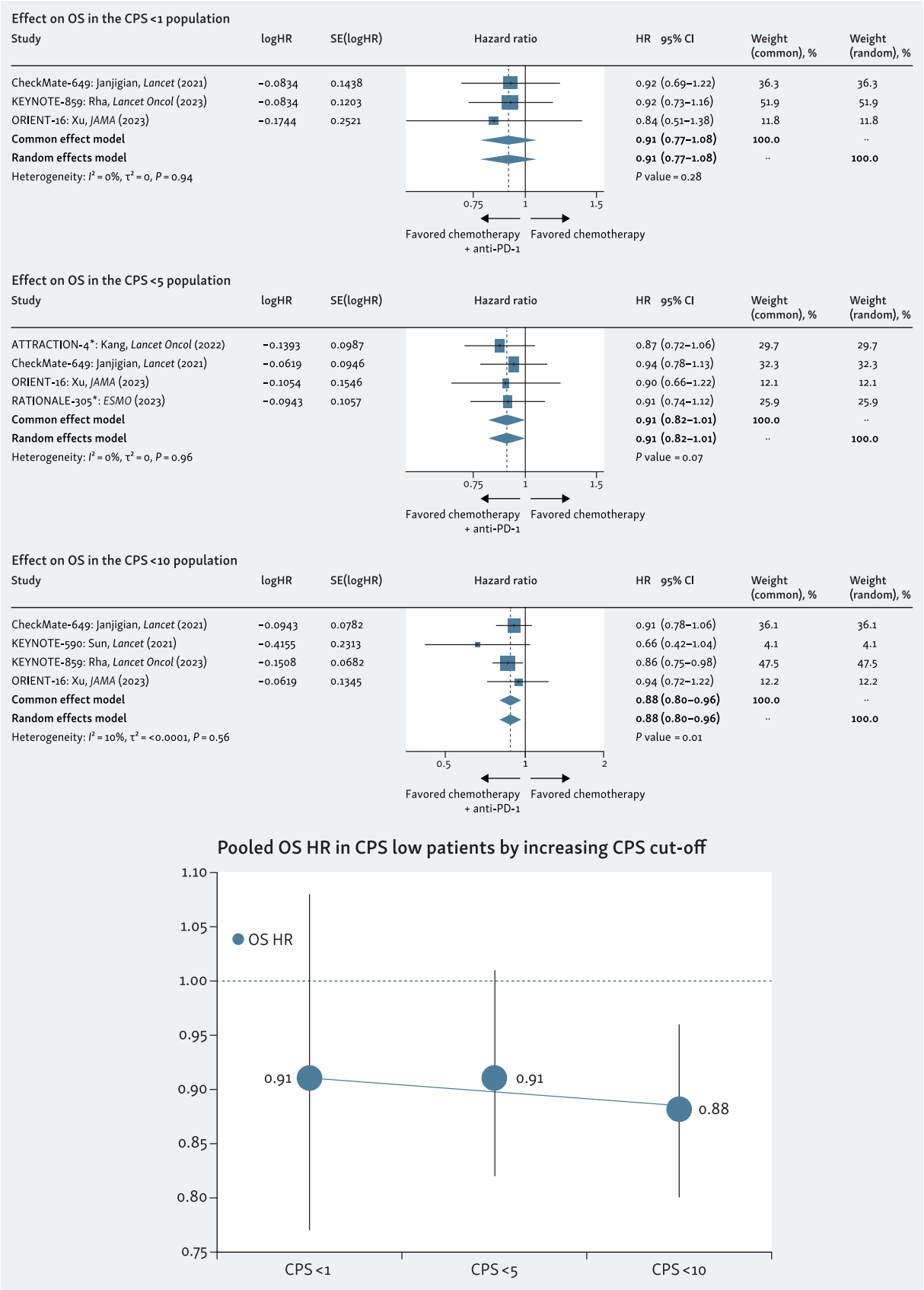


**Figure 2. Effect of the addition of anti-PD-1 agent to standard first-line chemotherapy in PD-L1 low populations.**
CI, confidence interval; CPS, combined positive score; HR, hazard ratio; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

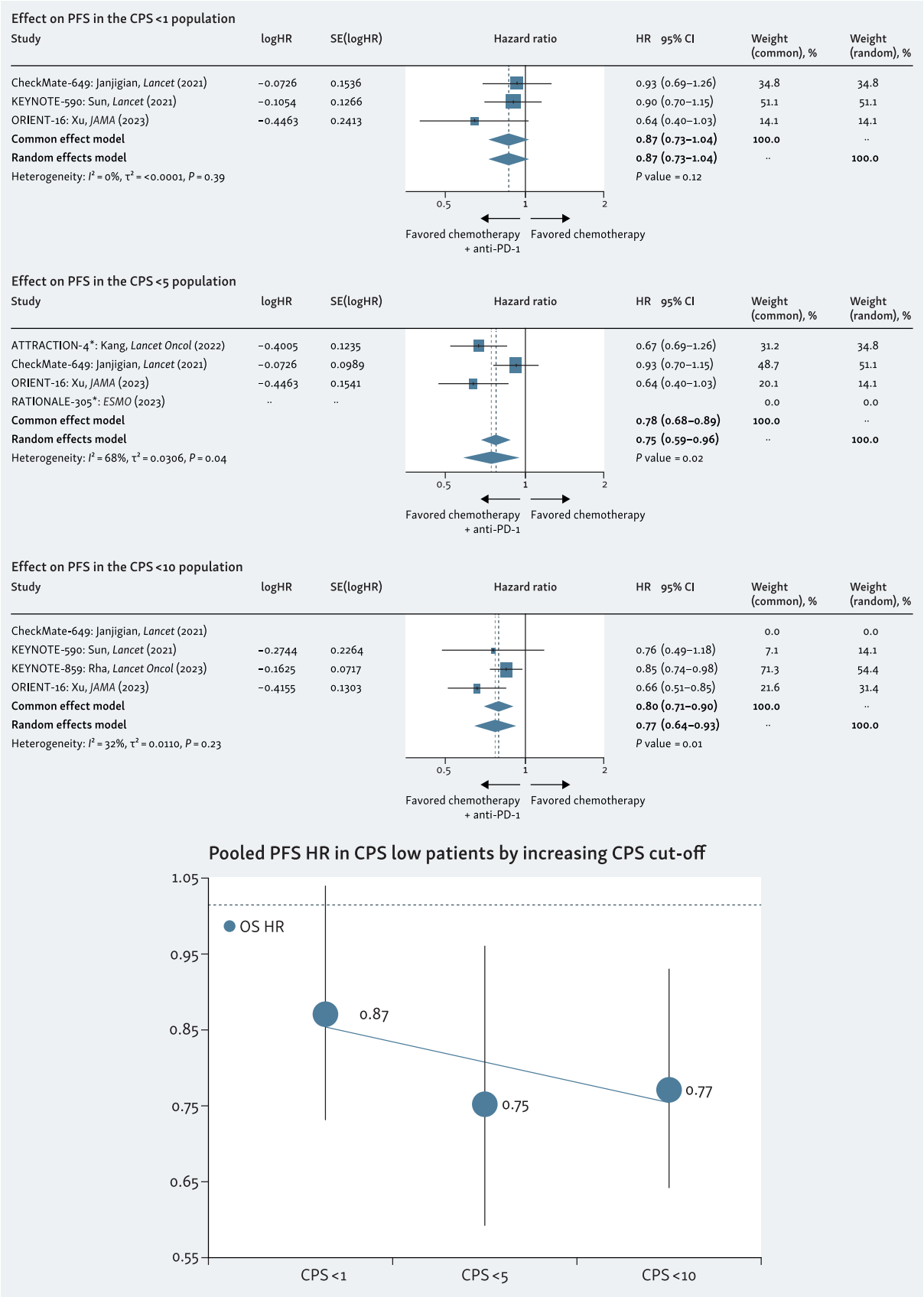


**Figure 3. Effect on PFS of the addition of anti-PD-1 agent to standard first-line chemotherapy in the PD-L1 low populations.**
CI, confidence interval; CPS, combined positive score; HR, hazard ratio; PFS, progression-free survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

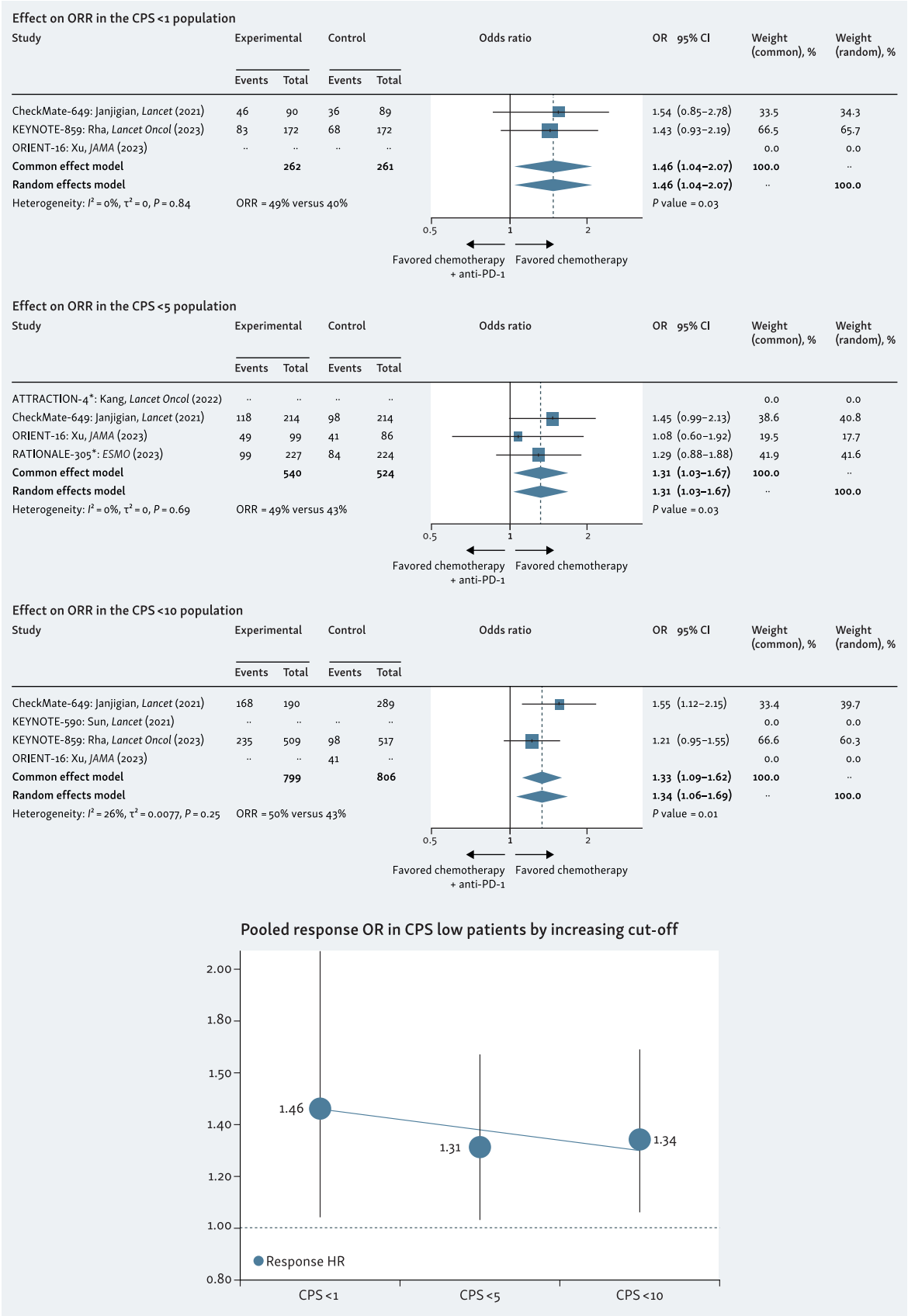


**Figure 4. Effect on the addition of anti-PD-1 agent to standard first-line chemotherapy in the overall population.**
CI, confidence interval; CPS, combined positive score; OR, odds ratio; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

The benefit of the addition of ICI to chemotherapy was most pronounced in patients with CPS ≥10 for all outcome measures (HR for OS 0.67, HR for PFS 0.63, OR for ORR 1.90, absolute difference in response rate +16%, all $P < 0.0001$), but significance was retained in patients with CPS ≥5 (HR for OS 0.71, HR for PFS 0.68, OR for ORR 1.63, absolute difference in ORR +12%, all $P < 0.0001$).

In PD-L1-negative patients (CPS <1) the benefit in terms of survival could not be demonstrated (*P* value for OS and PFS were 0.28 and 0.12, respectively); however, an increase in ORR was still observed (OR for response 1.46, response difference +9%, $P = 0.03$). This limited advantage in ORR without a clear benefit in survival outcome measure questions the role of anti-PD-1 plus chemotherapy in PD-L1-negative patients, and supports regulatory approvals in PD-L1-selected populations.

Our analysis indicates that the effectiveness of combining ICI with chemotherapy in the PD-L1 CPS 1-4 population is still uncertain. We found a borderline benefit in patients with PD-L1 CPS <5 in terms of OS ($P = 0.07$) and a significant benefit in terms of PFS and response rate ($P = 0.02$ and $P = 0.03$, respectively). These findings, together with the lack of benefit observed in the CPS <1 subset and the improved outcome with higher CPS cut-offs, suggest that the presence of patients with GEA sensitive to PD-1 blockade within CPS 1-4 is highly plausible, but further reliable selection criteria beyond PD-L1 expression need to be defined. Moreover, the duration of the potential benefit of immunotherapy in this subgroup remains to be clarified, and future analyses on that respect are strongly recommended. To favor the discussion, we calculated the number needed to treat (NNT) to obtain a radiologic response for CPS 1-4, based on data from the CheckMate-649 trial. The response rate for CPS 1-4 was 56% in the experimental arm versus 49% in the control arm, resulting in an NNT of 14.3. This NNT can be considered suboptimal and potentially improvable by more accurate selection biomarkers. However, NNTs calculated for certain drugs approved in other oncology settings were not significantly different from this NNT we found.[14,15]

It has been well documented that patients with specific molecular alteration, such as MSI, derive great and long-term benefit from PD-1 blockade independently of PD-L1 expression. MSI-high patients seem to have a distribution across the different PD-L1 expression groups similar to that of microsatellite stable (MSS) patients, with 15% being PD-L1 negative.[16,17]

It is possible that the efficacy of PD-1 blockade in the CPS <5 population is partly attributable to MSI-high patients within this subgroup. However, considering the generally low prevalence of MSI in advanced GEA (<5%),[18] it is unlikely that this would explain all the observed signals of efficacy. Therefore, a benefit also in MSS PD-L1 CPS 1-4 patients is highly plausible and specific studies would be desirable in this subset of patients.

In the CPS <10 population the efficacy of anti-PD-1 agents was confirmed for all clinical outcomes: HR for OS 0.88, HR for PFS 0.77, OR for ORR 1.34, all $P = 0.01$. This is likely driven by the presence of CPS 5-9 patients who are sensitive to PD-L1 blockade.

Our analysis cannot provide a unique definition of the optimal cut-off for ICI plus chemotherapy in GEA, since this process should take into account multiple issues. In particular, a high interobserver variability has been documented among pathologists when PD-L1 CPS approaches 5,[19,20] especially if the specimen is taken by biopsy instead of surgical resection and if different assays are utilized (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103967). Efforts to convene expert consensus are strongly encouraged.[21]

Despite these limitations, our data strengthen the evidence that PD-L1 CPS ≥5 could be an appropriate cut-off for the licensed indication of anti-PD-1 agents in GEA, as it is currently for nivolumab in Europe. Whether this remains true for other ICIs with different mechanisms of action needs to be further investigated.

In our analysis, the use of alternative PD-L1 scoring methods (such as TPS) did not significantly change the results. It should be emphasized that >90% of the TPS-positive population (TPS ≥1%) is included in the CPS >5 population according to the CheckMate-649 trial.[22] Pooled results in the TPS-positive population were similar to those found in CPS ≥5 patients. According to the CheckMate-649 trial, 46% of the patients are TPS negative but CPS >5, and these would still benefit from PD-1 blockade (Figure 5). In confirmation of this, a significant benefit of anti-PD-1 treatment was also demonstrated in the TPS-negative population in our meta-analysis (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2024.103967), both in terms of OS and in terms of PFS ($P = 0.0003$ and $P < 0.0001$, respectively). Based on these observations, it can be concluded that TPS is not the preferred selector for anti-PD-1 treatment in GEA.

Our meta-analysis has several limitations, with the most significant being that we relied on reported or published results without access to individual patient data for the different PD-L1 expression subgroups. Moreover, the included studies utilized different immunohistochemistry assays (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103967), even though acceptable concordance rates have recently been reported with different antibodies and scoring methods.[23,24]

In confirmation of this, the final results of the RATIONALE 305 trial have lately been published, and in addition to outcomes according to the TAP score, outcomes according to CPS have also been provided. Notably, the OS HRs for CPS ≥5 and <5 were strikingly similar to those for TAP score ≥5% and <5% (0.72 and 0.91 versus 0.73 and 0.89, respectively), further supporting the interchangeability of CPS ≥5 and TAP ≥5%, as we did in our meta-analysis.[25] The TAP score ≥5% population was actually the primary study population, together with unselected patients in the RATIONALE-305 trial as per protocol design, and TAP score and CPS at matched thresholds (1% versus 1, 5% versus 5, 10% versus 10) exhibited substantial concordance among enrolled patients.[26]

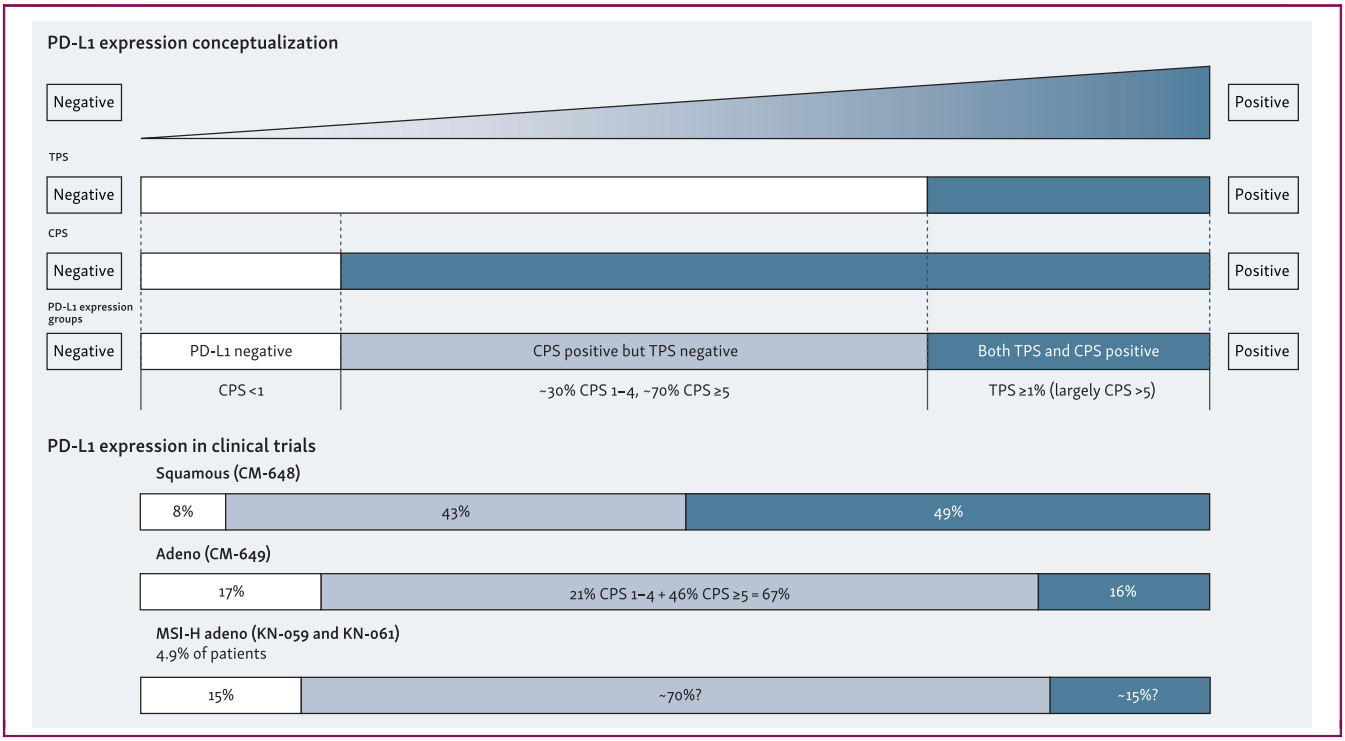


**Figure 5. Representation of PD-L1 expression groups.** Percentages were derived from the granular distribution of patients in the CheckMate-649 trial according to CPS and TPS PD-L1 expression [population of 1575 patients: 267 patients PD-L1 CPS negative, 1308 CPS positive; 1322 patients PD-L1 TPS negative of whom 267 patients CPS negative and 1055 CPS positive (331 CPS 1-4 and 724 CPS ≥5); 253 patients TPS positive (23 CPS 1-4 and 230 CPS ≥5)]. Proportion of PD-L1 expression groups in esophageal squamous cell carcinoma and MSI-H adenocarcinoma are also reported according to the CheckMate-648, KEYNOTE-059 and KEYNOTE-061 trials. TPS expression in MSI-H was not available and it was hypothesized based on data from the CheckMate-649 trial.
CPS, combined positive score; MSI-H, microsatellite instability-high; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

In conclusion, our meta-analysis demonstrates that in GEA, the benefit of anti-PD-1 agents in addition to first-line chemotherapy is limited to the PD-L1 CPS-positive population, and this benefit increases linearly with the PD-L1 CPS cut-off used. From a clinical perspective, a CPS threshold of ≥5 may represent an optimal choice to maximize the benefit-to-risk ratio of these agents. However, some patients with PD-L1 CPS <5 still appear to respond to PD-L1 blockade, highlighting the need for continued research to identify those individuals most likely to benefit within this subgroup. Given the lack of efficacy in the PD-L1 CPS-negative population, future trials should explore novel combinations with different ICIs in this subset.

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## DISCLOSURE

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