Relationship Between Progression-Free Survival, Objective Response Rate, and Overall Survival in Clinical Trials of PD-1/PD-L1 Immune Checkpoint Blockade: A Meta-Analysis

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PD-1/PD-L1 immune checkpoint blockade (ICB) has improved overall survival (OS) in solid tumor trials; however, parallel improvements in Response Evaluation Criteria in Solid Tumors (RECIST)-based surrogate end points, progression-free survival (PFS), and objective response rate (ORR), are not always observed. Here, we assess the surrogacy of PFS/ORR for OS with ICB therapy across advanced/metastatic tumors. In a trial-level analysis (*N* = 40 randomized trials), PFS, ORR, and OS treatment effects were correlated (Spearman's rho). In a patient-level analysis, data were extracted from available trials of durvalumab; the correlation of PFS and OS was evaluated (Bayesian normal-induced-copula-estimation model) and the ordinal association between objective response and OS hazard ratio (HR) were assessed with concordance index measures. High correlation was observed between PFS HR and OS HR in intention-to-treat (ITT; rho = 0.76) and PD-L1-enriched populations (0.74); modest (or limited) benefit in PFS was associated with meaningful improvement in OS. Moderate correlations were observed between ΔORR and OS HR: ITT, −0.63; PD-L1-enriched, −0.53. At the patient level, a positive association was observed between PFS and OS in non-small cell lung cancer (Kendall's Tau = 0.793; 95% confidence interval, 0.789–0.797), head and neck squamous cell carcinoma (0.794; 0.789–0.798), and bladder cancer (0.872; 0.869–0.875). Objective responders had significantly better OS (concordance index > 0.9) than nonresponders across these tumor types. Modest (or limited) improvement in RECIST-based end points did not rule out meaningful OS benefit, indicating they are imperfect surrogates and do not fully capture ICB clinical benefit. Therefore, caution is advised when basing early discontinuation of novel ICB agents on these end points.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Progression-free survival (PFS) and objective response rate (ORR) are widely used, Response Evaluation Criteria in Solid Tumors (RECIST)-based, surrogate end points for overall survival (OS) in clinical trials of anticancer therapies.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Whether PFS/ORR are appropriate surrogates for OS in clinical trials of PD-1/PD-L1 immune checkpoint blockade (ICB) in patients with advanced/metastatic tumors.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Improvements in PFS and ORR are likely to translate into OS benefits with ICB; however, little or no PFS or ORR benefit did not rule out OS benefit.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Unless a lack of benefit in both PFS and ORR is observed, caution should be used when making decisions on early discontinuation of novel agent development.

Since 2014, several monoclonal antibodies (mAbs) that block activation of the PD-1/PD-L1 pathway have received approvals for the treatment of various advanced/metastatic solid tumors.[1] For example, pembrolizumab, nivolumab, and atezolizumab are approved for use in metastatic non-small cell lung cancer (NSCLC), and durvalumab is approved for use in stage III NSCLC; of these, some are approved as monotherapies and some in combination with chemotherapy, with preference of use generally based on PD-L1 expression, prior therapy lines, or patient factors.[2–5]

Data from randomized clinical trials of single-agent PD-1/PD-L1 immune checkpoint blockade (ICB), vs. standard therapies, have shown meaningful improvements in overall survival

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Received April 4, 2020; accepted May 26, 2020. doi:10.1002/cpt.1956

(OS; the gold-standard metric for clinical benefit), and yet have not consistently shown parallel improvements in end points based on Response Evaluation Criteria in Solid Tumors (RECIST), such as progression-free survival (PFS) and/or objective response rate (ORR), in NSCLC[6–8] and other solid tumors.[9,10] This creates an important dilemma for the design and interpretation of clinical trials of anti-PD-1/PD-L1 mAbs, as such surrogate end points may form the basis of accelerated/conditional or full approval of new cancer therapies by the US Food and Drug Administration (FDA) and the European Medicines Agency.[11–14] The use of PFS and ORR as surrogates for OS is attractive for a number of reasons: it permits shorter trial durations and the use of smaller patient cohorts and, in the case of ORR, may allow single-arm trial designs.[15] PFS and ORR can also help to overcome certain limitations associated with OS as a clinical trial end point; OS results can often be confounded by the use of (and access to) successive lines of therapy, patient crossover, and/or access to the investigational agent for patients in control arms, challenges with patient follow-up, and increased postprogression survival.[16] As clinical trial end points usually contribute to early proof-of-concept and go/no go decisions in drug development, and given the urgent need for new cancer therapies, the FDA has expedited approvals by allowing use of PFS and ORR end points as surrogates for OS.

Correlation with OS remains a central consideration in determining the validity of PFS and ORR as surrogate end points; however, previous analyses have not always established a clear relationship among these three end points. For example, a meta-analysis using trial-level data from 14 studies of targeted and standard therapies in advanced NSCLC (N = 12,567; all submitted to the FDA from 2003–2013) identified a strong correlation between ORR odds ratio and PFS hazard ratio (HR), but no relationship was established at the trial level between PFS and OS or ORR and OS in this analysis.[17] A correlation between PFS/ORR and OS was, therefore, not established, possibly due to treatment crossover and longer survival postprogression in the targeted therapy and first-line trials. Indeed, an accompanying patient-level analysis found that objective responders (RECIST assessed) had improved PFS and OS compared with nonresponders (independent of treatment).

Although imaging-based end points may not fully capture the clinical benefit of immunotherapy compared with the use of OS, it would be beneficial to understand the predictive value of PFS and ORR as surrogate end points for OS in therapeutic studies of PD-1/PD-L1 ICB. This could enhance the drug development process and potentially make effective drugs available to patients more quickly. Therefore, we aimed to assess the suitability of PFS or ORR as surrogates for OS in clinical trials of PD-1/PD-L1 ICB monotherapy vs. standard-of-care (SOC) in patients with solid tumors. Our intention is to inform future decision making (go/no go criteria) based on evidence from early phase clinical trials. Given the relatively high number of recent clinical trials of PD-1/PD-L1 ICB, as monotherapy and in combination with chemotherapy, in the NSCLC setting, we also analyzed monotherapy and chemotherapy-ICB combination trials in this patient subgroup, with the aim of providing more indication-specific information.

METHODS

Objectives

The objectives of this analysis were: (i) to evaluate correlations between the treatment effect for PFS and ORR with OS with PD-1/PD-L1 ICB monotherapy vs. chemotherapy/SOC (in an overall and a biomarker (PD-L1) enriched population); (ii) to evaluate correlations between the end points of PFS, ORR, and OS in patients receiving PD-1/PD-L1 ICB in combination with chemotherapy; and (iii) to evaluate the correlation between the end points of PFS and ORR with OS in patients receiving PD-1/PD-L1 ICB. To achieve these objectives, we carried out analyses using both trial-level and patient-level data. Patient-level analyses utilized data from clinical trials of durvalumab only as the authors had full access to data from the durvalumab clinical trial program, making it an accessible choice.

Literature search methodology

A systematic literature review was conducted on November 30, 2019, to identify randomized, controlled clinical trials that assessed the efficacy of anti-PD-1 (nivolumab and pembrolizumab) or anti-PD-L1 mAbs (atezolizumab, avelumab, and durvalumab) as monotherapy, vs. SOC in advanced or metastatic solid tumors. Abstracts of the 2015–2019 annual meetings of the American Association for Cancer Research, American Society of Clinical Oncology, European Society for Medical Oncology, Society for Immunotherapy of Cancer, and International Association for the Study of Lung Cancer were searched using the terms "PD-1" OR "PD-L1" OR ("MK-3475" OR "pembrolizumab" OR "Keytruda") OR ("BMS-936558" OR "nivolumab" OR "Opdivo") OR ("MPDL3280A" OR "atezolizumab" OR "Tecentriq") OR ("MEDI4736" OR "durvalumab" OR "Imfinzi") OR ("MSB0010718C" OR "avelumab" OR "Bavencio"). We also conducted a search of the published literature through ClinicalTrials.gov and Google Scholar using the reported National Clinical Trial (NCT) identifier for candidate clinical trials to identify published results. We undertook an additional literature review using the same parameters and approach to identify NSCLC chemotherapy-ICB combination trials.

Assessments

For the treatment effect (trial-level) analyses, we investigated correlations between the HRs of PFS and OS using available results (in intention-to-treat (ITT) and PD-L1 + populations) for "all solid tumors" and for "NSCLC" (based on data extracted from the literature search). The same dataset was used to analyze the correlation between ΔORR (ORR for the experimental arm minus ORR for the control arm) and OS. PD-L1 subpopulation analyses reported in the literature were used; for trials where multiple PD-L1 subgroups were reported, the PD-L1 population designated as the primary/key secondary/secondary analysis population was used. Additionally, we evaluated the impact of line of therapy.

For the end points (patient-level) analysis, PFS and OS data were extracted from identified trials of durvalumab monotherapy in NSCLC, head and neck squamous cell carcinoma (HNSCC), and bladder cancer. Source studies included the ATLANTIC trial (phase II, greater than or equal to second-line),[18] ARCTIC (study A; phase III, greater than or equal to third-line),[19] and study 1108 for NSCLC (phase I/II, greater than or equal to first-line),[20] CONDOR (phase II, second-line),[21] and HAWK (phase II, second-line)[22] for HNSCC, and data from study 1108 for bladder cancer.[23] Similar analyses were used to investigate the correlation between RECIST-based objective response (i.e., complete or partial response) and OS.

Statistical analyses

An early end point (e.g., PFS or ORR) can be considered a valid surrogate for OS, if the treatment effect on OS is fully explained by the

treatment effect on the early end point (the so-called "Prentice" criteria).[24] In statistical terms, this implies testing the hypothesis of no treatment effect for the surrogate end point is equivalent to testing the hypothesis of no treatment effect on the true end point. Although the Prentice criteria is very difficult to directly measure, it has been shown that a good surrogate needs to be tightly correlated with the actual end point (patient level association) and the treatment effect on the surrogate must be tightly correlated with the treatment effect on the actual end point (trial level association).[25] To properly assess the surrogacy of PFS and ORR with OS, the association between these end points with OS needs to be assessed at both the patient and trial level; they are considered validated when a very strong (e.g., Rho ≥ 0.9) association is observed at both levels.[26]

For trial-level analysis, the treatment effect estimates for PFS and OS were based on reported HRs per Cox regression; the treatment effect estimate for ORR was defined as ΔORR (ORR for ICB arm minus comparator arm). We initially explored the correlation between HRs for OS and ORs for ORR; however, the correlation was not as good as that for OS HR and ΔORR and, therefore, the latter analysis was used. Spearman's correlation coefficients were derived for all comparisons between treatment effects; the absolute value of a correlation (Spearman's Rho) close to 1 indicated a strong monotonic association (very high 0.9–1.0; high 0.7–< 0.9; moderate 0.5–< 0.7; low 0.3–< 0.5, and negligible 0–< 0.3). Trial-level associations were quantified through weighted linear regression with weights equal to the total number of patients of the two compared arms; R^2 was used to quantify the proportion of variance explained by the regression. If the R^2 estimate from this regression model fit was < 0.4, the model was not considered appropriate to explain the viability of the OS using PFS or ORR, and no additional evaluations were made using these models. For models with $R^2 > 0.4$, we included the 95% confidence interval (CI) of the average treatment effect in the bubble plot.

For the patient-level analysis, the correlation of PFS and OS was evaluated using a Bayesian normal induced copula estimation model[27] that takes into account the censoring in time to event end points like PFS and OS. Kendall's Tau was used to measure the association between the duration of PFS and OS (in months)—a large positive value close to 1 indicates that a longer PFS duration is associated with a longer OS duration. Concordance index[28] measures were used to assess the ordinal association between RECIST-assessed objective response (responder vs. nonresponder) and OS HR—a large positive value close to 1 indicates that responders will have longer OS duration than nonresponders.

Clinical trial inclusion for subsequent analysis

In total, 71 randomized trials of PD-1/PD-L1 ICB in solid tumors were reported or had released results by November 30, 2019 (**Figure S1**). Thirty-one trials did not qualify for this analysis: 5 did not present efficacy results; 21 did not report comparison of PD-1/PD-L1 ICB monotherapy with SOC; and 1 did not present the HRs for OS and PFS. Four of the trials excluded enrollment of patients with metastatic disease and were, therefore, not included in the analysis.

Overall, 40 trials qualified for the meta-analysis of PD-1/PD-L1 ICB monotherapy for the ITT population (**Table 1**).[6,7,10,29–66] These included trials of NSCLC (n = 13), small cell lung cancer (n = 2), HNSCC (n = 4), esophageal or gastric or gastroesophageal junction cancer (n = 6), urothelial bladder cancer (n = 3), epithelial ovarian cancer (n = 1), renal cell carcinoma (n = 2), colorectal cancer (n = 1), hepatocellular carcinoma (n = 2), triple negative breast cancer (n = 1), and melanoma (n = 5). Among these trials, 13 evaluated pembrolizumab, 14 nivolumab, 7 atezolizumab, 3 durvalumab, and 3 avelumab (as investigational agent). Three trials were phase II and one was phase II/III; the remainder were all phase III. Fourteen trials targeted a first-line (treatment-naïve) population, and 26 targeted a greater than or equal to a second-line population. All of the trials were pivotal and undertaken with a registrational purpose. Of the 40 selected trials, 5 exclusively randomized a PD-L1-positive population (KEYNOTE-024, KEYNOTE-010, KEYNOTE-062, KEYNOTE-042, and ARCTIC (study A)); the rest did not exclude patients by PD-L1 status. A further three trials had not yet reported at least two out of the three key end points (OS, PFS, or ORR) for the full analysis set (CheckMate 026, JAVELIN Lung 200, and MYSTIC), and another did not report key end points in the full analysis set for PD-1/PD-L1 ICB monotherapy vs. SOC (CheckMate 227); for these four trials, the largest PD-L1-positive subpopulation with at least two of three end points (OS, PFS, and ORR) presented by the November 30, 2019, cut-off was used in the ITT population analysis. Three of the selected trials were designed with two PD-1/PD-L1 ICB monotherapy arms (KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010); therefore, a total of 43 PD-1/PD-L1 ICB monotherapy arms (vs. SOC) were included in the ITT population analysis (**Table S1**).

Of the selected trials, 31 presented OS, PFS, and ORR results in a PD-L1-positive subpopulation, including trials of NSCLC (n = 13), HNSCC (n = 3), esophageal or gastric or gastroesophageal junction cancer (n = 4), urothelial bladder cancer (n = 2), epithelial ovarian cancer (n = 1), renal cell carcinoma (n = 1), colorectal cancer (n = 1), hepatocellular carcinoma (n = 1), triple negative breast cancer (n = 1), and melanoma (n = 4). Thirteen of these enrolled a first-line population and 18 enrolled a greater than or equal to a second-line population. To determine PD-L1 expression status, 9 trials utilized the PD-L1 immunohistochemistry (IHC) 28-8 assay, 11 utilized the PD-L1 IHC 22C3 assay, 6 utilized the SP142 IHC assay, 4 utilized the SP263 IHC assay, and 1 utilized the IHC 73-10 assay. For trials that reported multiple PD-L1-positive populations, the population with a prevalence closest to 35% was used in the analysis. Two of the trials had two PD-1/PD-L1 ICB monotherapy arms (KEYNOTE-006 and KEYNOTE-010). In total, 33 PD-1/PD-L1 ICB monotherapy arms (vs. SOC) were included in the PD-L1-positive population analysis (**Table S2**).

Among the 13 NSCLC trials, 6 examined a first-line population and 7 examined a second-line or greater population. One trial had two PD-1/PD-L1 ICB monotherapy arms (KEYNOTE-010). In total, there were six first-line and eight greater than or equal to second-line PD-1/PD-L1 ICB monotherapy arms (vs. SOC) included in the analysis of NSCLC PD-1/PD-L1 ICB monotherapy trials.

Among the 71 randomized trials of PD-1/PD-L1 ICB in solid tumors, we identified 8 eligible NSCLC chemotherapy-ICB combination trials; 1 trial was phase II and the rest were phase III (**Table S3**). All trials were in the first-line recurrent/metastatic disease setting, and one only enrolled PD-L1-negative patients in the chemotherapy-ICB arm (CheckMate 227). One trial had two chemotherapy-ICB arms (IMpower150); therefore, a total of nine chemotherapy-ICB arms were included in the analysis of NSCLC chemotherapy-ICB combination trials.

RESULTS

All solid tumors trial-level correlation analyses

All PD-1/PD-L1 ICB monotherapy trials. A high correlation was identified between the PFS HR and OS HR in the ITT population (rho = 0.76) and PD-L1-positive population (rho = 0.74; **Figure 1a,b**). Based on the weighted regression, modest or limited benefit in PFS was associated with a meaningful improvement in OS. Using the regression model, it was predicted that PFS HR ≤ 0.9 in the ITT population may be associated with a meaningful OS benefit (OS HR ≤ 0.8).

A moderate correlation was identified between ΔORR and OS HR for the ITT (rho = −0.63) and PD-L1-positive (rho = −0.53)

Table 1 Literature search results: multiple randomized monotherapy trials across tumor types used for evaluation of trial level correlations among ORR, PFS, and OS

Study name	CT.gov identifier	PD-1/PD-L1 drug	Study phase	Line	Tumor stage
CheckMate 026[29]	NCT02041533	Nivolumab	Phase III	1L	Stage IV or recurrent NSCLC
MYSTIC[30]	NCT02453282	Durvalumab	Phase III	1L	Stage IV NSCLC
KEYNOTE-024[31]	NCT02142738	Pembrolizumab	Phase III	1L	Stage IV NSCLC
KEYNOTE-042[32]	NCT02220894	Pembrolizumab	Phase III	1L	Stage IV or unresectable or definitive chemoradiation stage IIIB NSCLC
CheckMate 227[33]	NCT02477826	Nivolumab	Phase III	1L	Stage IV or recurrent NSCLC
IMpower110[34]	NCT02409342	Atezolizumab	Phase III	1L	Stage IV NSCLC
JAVELIN Lung 200[35]	NCT02395172	Avelumab	Phase III	≤3L	Stage IIIB or stage IV NSCLC
KEYNOTE-010[7]	NCT01905657	Pembrolizumab	Phase II/III	≥2L	Stage IV NSCLC
OAK[36]	NCT02008227	Atezolizumab	Phase III	2/3L	Stage IIIB or stage IV NSCLC
POPLAR[37]	NCT01903993	Atezolizumab	Phase II	2/3L	Stage IIIB or stage IV NSCLC
ARCTIC (Study A)[38]	NCT02352948	Durvalumab	Phase III	≥3L	Stage IIIB or stage IV NSCLC
CheckMate 057[6]	NCT01673867	Nivolumab	Phase III	2/3L	Stage IIIB or stage IV non-squamous NSCLC
CheckMate 017[39]	NCT01642004	Nivolumab	Phase III	2L	Stage IIIB or stage IV squamous NSCLC
CheckMate 331[40]	NCT02481830	Nivolumab	Phase III	2L	Relapsed limited-stage/extensive-stage SCLC
CheckMate 451[41]	NCT02538666	Nivolumab	Phase III	2L	Extensive-stage SCLC
KEYNOTE-048[42]	NCT02358031	Pembrolizumab	Phase III	1L	Recurrent/metastatic HNSCC
CheckMate 141[43]	NCT02105636	Nivolumab	Phase III	≥1L	Recurrent/metastatic HNSCC
KEYNOTE-040[44]	NCT02252042	Pembrolizumab	Phase III	≥2L	Recurrent/metastatic HNSCC
EAGLE[45]	NCT02369874	Durvalumab	Phase III	≥2L	Recurrent/metastatic HNSCC
ATTRACTION-3[46]	NCT02569242	Nivolumab	Phase III	2L	Unresectable advanced or recurrent ESCC
KEYNOTE-181[47]	NCT02564263	Pembrolizumab	Phase III	≥2L	Locally advanced unresectable or metastatic GEJC
KEYNOTE-062[48]	NCT02494583	Pembrolizumab	Phase III	1L	Locally advanced unresectable or metastatic GC/GEJC
KEYNOTE-061[49]	NCT02370498	Pembrolizumab	Phase III	≥2L	Locally advanced unresectable or metastatic GC/GEJC
JAVELIN Gastric 300[50]	NCT02625623	Avelumab	Phase III	3L	Recurrent unresectable, recurrent locally advanced or metastatic GC/GEJC
ATTRACTION-2[51]	NCT02267343	Nivolumab	Phase III	≥3L	Unresectable advanced or recurrent GC/GEJC
IMvigor130[52]	NCT02807636	Atezolizumab	Phase III	1L	Locally advanced (T4b, any N or any T, N2–3) or metastatic UBC
KEYNOTE-045[53]	NCT02256436	Pembrolizumab	Phase III	≥2L	Locally advanced or metastatic UBC
IMvigor211[54]	NCT02302807	Atezolizumab	Phase III	≤3L	Locally advanced or metastatic UBC
JAVELIN Ovarian 200[55]	NCT02580058	Avelumab	Phase III	≤4L	Platinum-resistant/-refractory EOC
IMmotion150[56,57]	NCT01984242	Atezolizumab	Phase II	1L	Metastatic clear-cell RCC
CheckMate 025[10]	NCT01668784	Nivolumab	Phase III	2/3L	Advanced/metastatic RCC
IMblaze370[58]	NCT02788279	Atezolizumab	Phase III	≥3L	Locally advanced unresectable or metastatic CRC
CheckMate 459[59]	NCT02576509	Nivolumab	Phase III	1L	Advanced HCC not eligible for surgical and/or locoregional therapies
KEYNOTE-240[60]	NCT02702401	Pembrolizumab	Phase III	≥2L	HCC, Child-Pugh Class A, BCLC Stage C or Stage B not amenable/refractory to locoregional therapy
KEYNOTE-119[61]	NCT02555657	Pembrolizumab	Phase III	2/3L	Metastatic TNBC
CheckMate 066[62]	NCT01721772	Nivolumab	Phase III	1L	Stage IV or unresectable stage III melanoma
CheckMate 067[63]	NCT01844505	Nivolumab	Phase III	1L	Stage IV or unresectable stage III melanoma

(Continued)

Table 1 (Continued)

Study name	CT.gov identifier	PD-1/PD-L1 drug	Study phase	Line	Tumor stage
KEYNOTE-006[64]	NCT01866319	Pembrolizumab	Phase III	2L	Stage IV or unresectable stage III melanoma
CheckMate 037[65]	NCT01721746	Nivolumab	Phase III	≥2L	Stage IV or unresectable stage IIIC melanoma
KEYNOTE-002[66]	NCT01704287	Pembrolizumab	Phase II	≥2L	Stage IV or unresectable stage III melanoma

1L, first-line; 2L, second-line; 3L, third-line; BCLC, Barcelona-Clinic liver cancer; CRC, colorectal cancer; EOC, epithelial ovarian cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PFS, progression-free survival; RCC, renal cell carcinoma; SCLC, small-cell lung cancer; TNBC, triple-negative breast cancer; UBC, urothelial bladder cancer.

populations (**Figure 2a,b**). The adjusted R^2 of the weighted regression was only < 0.4 for both the ITT and PD-L1-positive populations; therefore, further predictions were not made using these regression models.

When looking at the correlation between ΔORR and PFS HR, a high correlation was seen in the ITT population (rho = −0.79) and PD-L1-positive population (rho = −0.79; **Figure 3a,b**). Additionally, a strong or moderate benefit in ΔORR was associated with meaningful improvements in PFS based on weighted regression (ITT: adjusted $R^2 = 0.57$).

Overall, for the PD-L1-positive population, the correlation analyses generally echoed those of the ITT population. However, based on weighted regression, even weaker benefit in PFS and ORR was associated with meaningful OS improvements in the PD-L1-positive population vs. the ITT population (**Figures 1b** and **4b**).

First-line PD-1/PD-L1 ICB monotherapy trials. In our analysis of those trials evaluating ICB monotherapy in the frontline setting, high correlation between the HRs for PFS and OS, and between ΔORR and OS HR, was identified in the ITT population (rho = 0.84 and −0.83, respectively; **Figures 1c** and **2c**). Similarly, moderate benefits in PFS and ΔORR were associated with meaningful improvements in OS in the ITT population. Conversely, in the PD-L1 enriched subgroup, a low correlation was identified between HRs for PFS and OS, and between ΔORR and OS HR (rho = 0.45 and −0.35, respectively; **Figures 1d** and **2d**).

Across both the ITT and PD-L1-positive populations, high or very high correlations between ΔORR and PFS HR were identified (ITT: rho = −0.87; PD-L1+: rho = −0.91). A strong benefit in ORR was also associated with meaningful improvement in PFS in the ITT population (adjusted $R^2 = 0.81$; **Figure 3c**). Similarly, in the PD-L1-positive population, ORR benefit was associated with meaningful PFS benefit (adjusted $R^2 = 0.77$; **Figure 3d**).

Second-line or greater PD-1/PD-L1 ICB monotherapy trials. Those trials where ICB monotherapy was evaluated in the setting of second line or later were then analyzed. Overall, similar results to the first-line analysis were observed: high correlation between HRs for PFS and OS was identified in both the ITT (rho = 0.72) and PD-L1-positive (rho = 0.87) populations (**Figure 1e,f**). In terms of PFS, a modest benefit was associated with meaningful improvements in OS in the ITT population (adjusted $R^2 = 0.61$). Further, in the PD-L1-positive population, even small, or no PFS benefit was associated with meaningful OS benefit (adjusted $R^2 = 0.70$).

In both the ITT and PD-L1-positive populations, moderate correlation between ΔORR and OS HR was identified (ITT: rho = −0.56; PD-L1+: rho = −0.54) in the greater than or equal to a second-line setting. However, the weighted regression fit was poor (adjusted $R^2 = 0.25$ and 0.40, respectively), which may be due to variability introduced by including data from trials across different solid tumor types (**Figure 2e,f**).

In terms of the relationship between ΔORR and PFS HR in the greater than or equal to a second-line setting, high and moderate correlations were identified in the ITT (rho = −0.84) and PD-L1+ (rho = −0.695) populations, respectively. Furthermore, strong benefit in ΔORR was associated with meaningful improvement in PFS in both populations (adjusted $R^2 = 0.59$ and 0.64, respectively; **Figure 3e,f**).

NSCLC trial-level correlation analyses

In the NSCLC subset analysis, moderate and high correlations between PFS and OS HRs were identified in the ITT (rho = 0.65) and PD-L1-positive (rho = 0.80) populations, respectively (**Figure 4a,b**). Modest improvement in PFS was associated with meaningful improvement in OS in the PD-L1-positive population.

In the NSCLC ITT population, a high correlation was identified between ΔORR and the OS HR (rho = 0.78) and a moderate correlation between ΔORR and PFS HR (rho = 0.62; **Figure 4c,e**). Similar correlations were identified in the PD-L1-positive population (**Figure 4d,f**).

Separate correlation analyses were also performed for first-line and greater than or equal to second-line NSCLC trials (**Figures S2–S4**). Recognizing sample size limitations in these trial subsets, high correlation was generally observed between each of the end point comparisons. However, in most comparisons, a large proportion of variability in one end point was not explained by the surrogate in the weighted regression analysis. In general terms, higher correlation between PFS HR and OS HR in the greater than or equal to second-line studies was identified (ITT: rho = 0.93) vs. the first-line studies (ITT: rho = 0.71).

In the NSCLC chemotherapy-ICB analysis, a very high positive correlation between the PFS HR and OS HR was identified in the ITT population (rho = 0.92). Similarly, very high correlation was identified between ΔORR and OS HR (rho = −0.90) and between ΔORR and PFS HR (rho = 0.95; **Figure S5**).

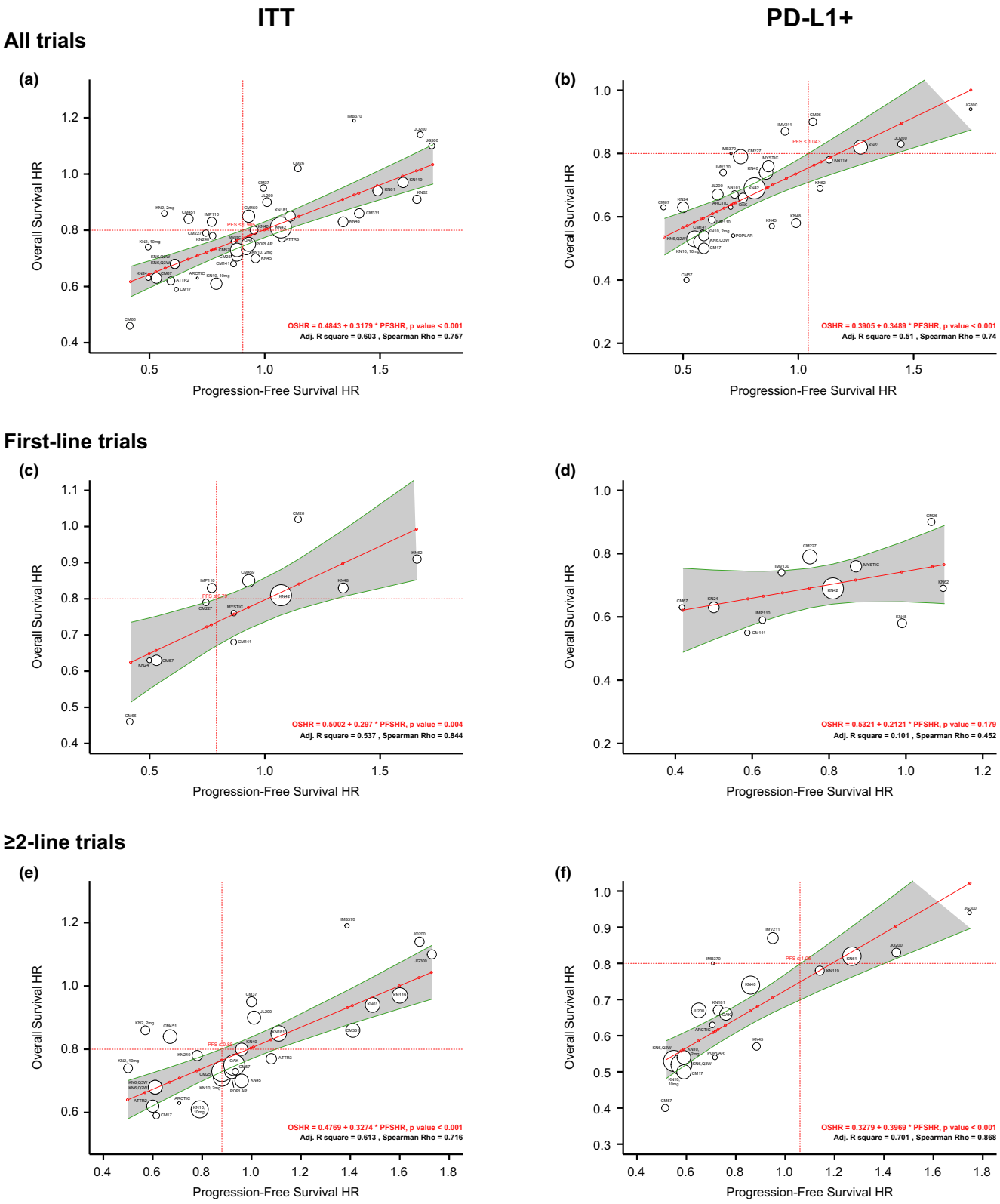

Figure 1 All-solid-tumors ICB-monotherapy trials. Correlation between HRs for PFS and OS in (**a**) the ITT and (**b**) PD-L1-positive population across all trials; (**c**) the ITT and (**d**) PD-L1-positive population across first-line trials; (**e**) the ITT and (**f**) PD-L1-positive population across greater than or equal to second-line trials. In red: univariate weighted regression models with estimate of coefficient, and *P* value. HR, hazard ratio; ICB, immune checkpoint blockade; ITT, intention-to-treat; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival.

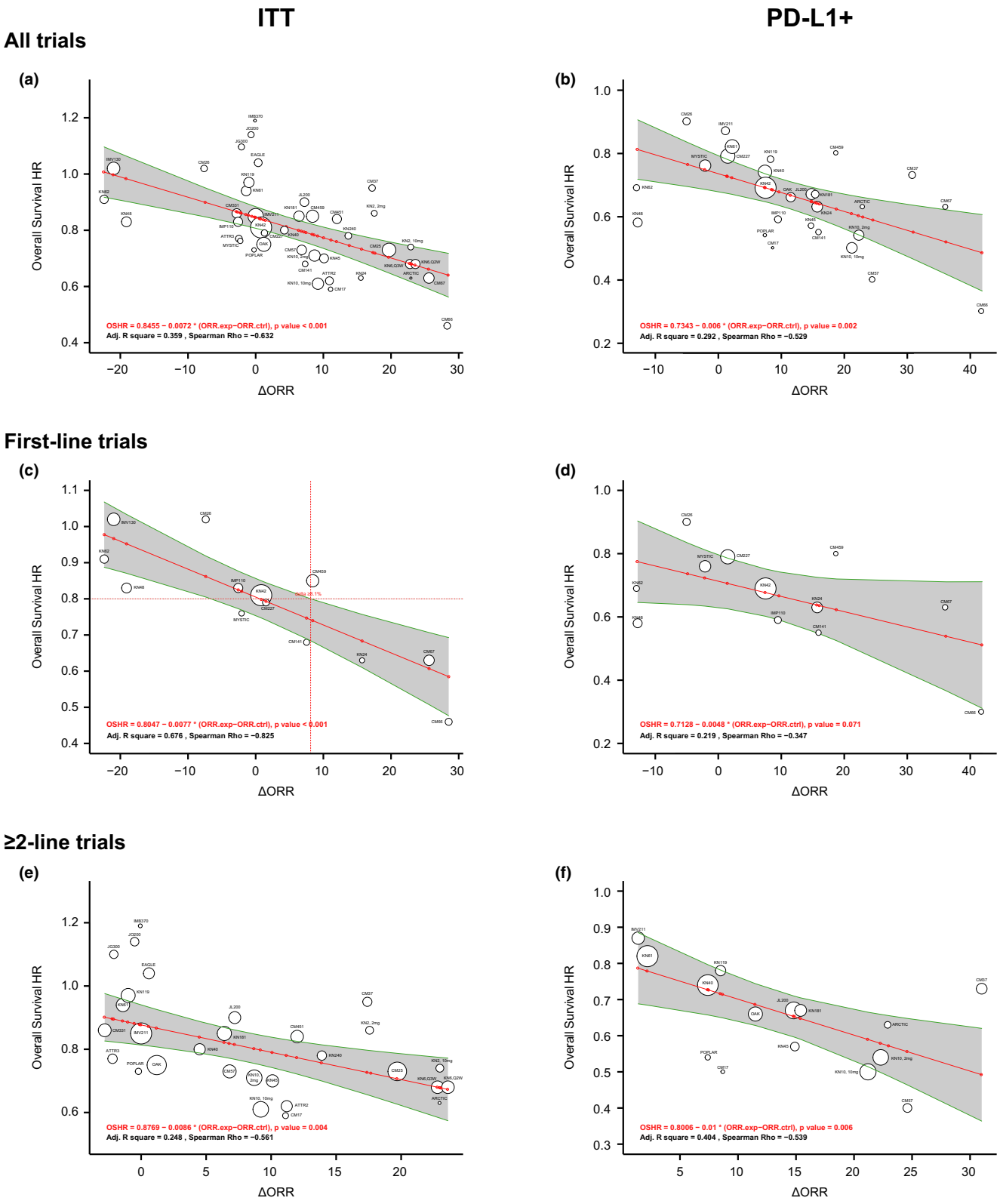

Figure 2 All-solid-tumors ICB-monotherapy trials. Correlation between ΔORR and OS HR in (**a**) the ITT and (**b**) PD-L1-positive population across all trials; (**c**) the ITT and (**d**) PD-L1-positive population across first-line trials; (**e**) the ITT and (**f**) PD-L1-positive population across greater than or equal to second-line trials. In red: univariate weighted regression models with estimate of coefficient, and *P* value. HR, hazard ratio; ICB, immune checkpoint blockade; ITT, intention-to-treat; ΔORR, ORR for ICB arm minus comparator arm; OS, overall survival; PD-L1-positive, programmed death ligand-1 enriched.

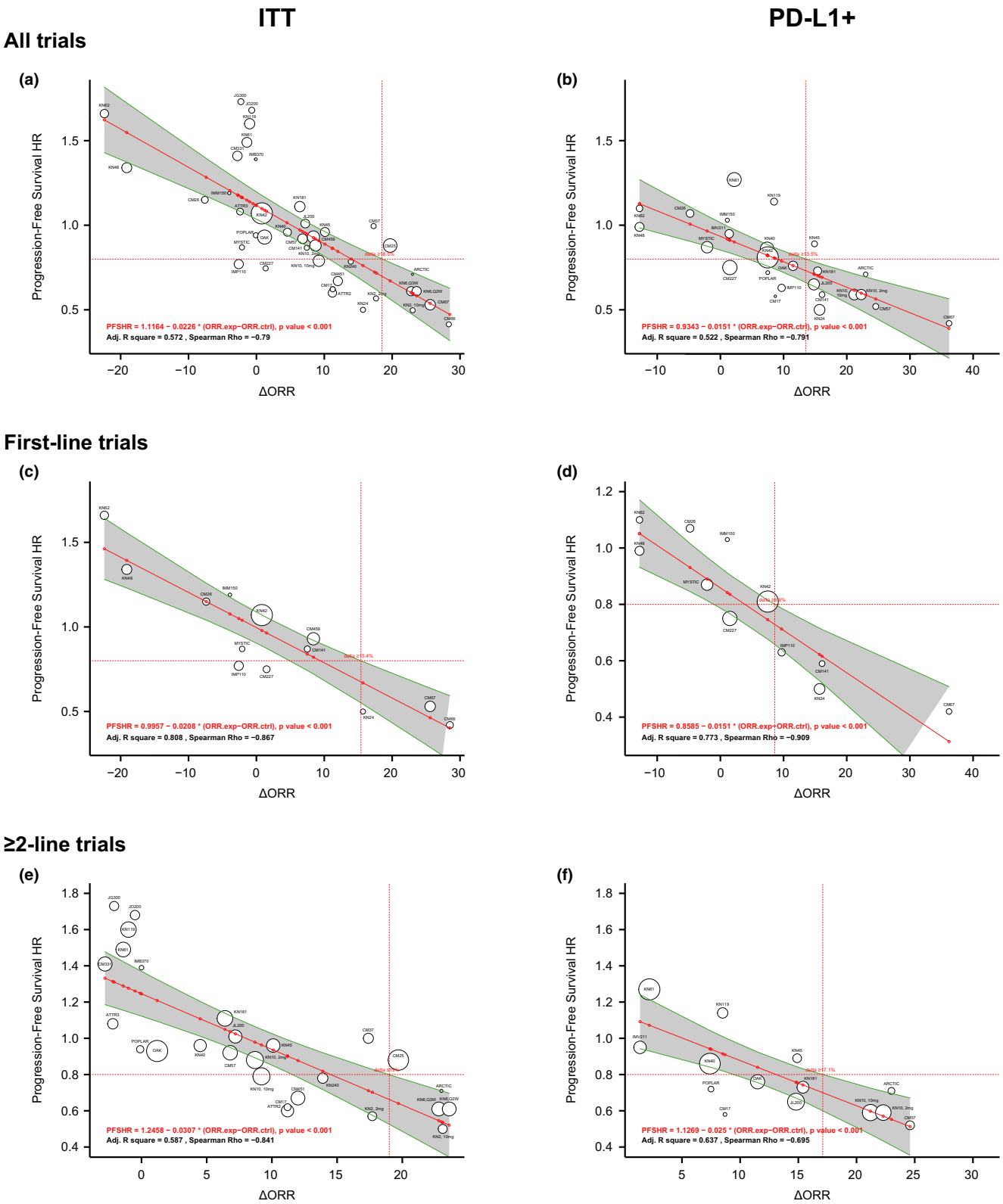

Figure 3 All-solid-tumors ICB-monotherapy trials. Correlation between ΔORR and PFS HR in (**a**) the ITT and (**b**) PD-L1-positive population across all trials; (**c**) the ITT and (**d**) PD-L1-positive population across first-line trials; (**e**) the ITT and (**f**) PD-L1-positive population across greater than or equal to second-line trials. In red: univariate weighted regression models with estimate of coefficient, and *P* value. HR, hazard ratio; ICB, immune checkpoint blockade; ITT, intention-to-treat; ΔORR, ORR for ICB arm minus comparator arm; PD-L1-positive, programmed death ligand-1 enriched; PFS, progression-free survival.

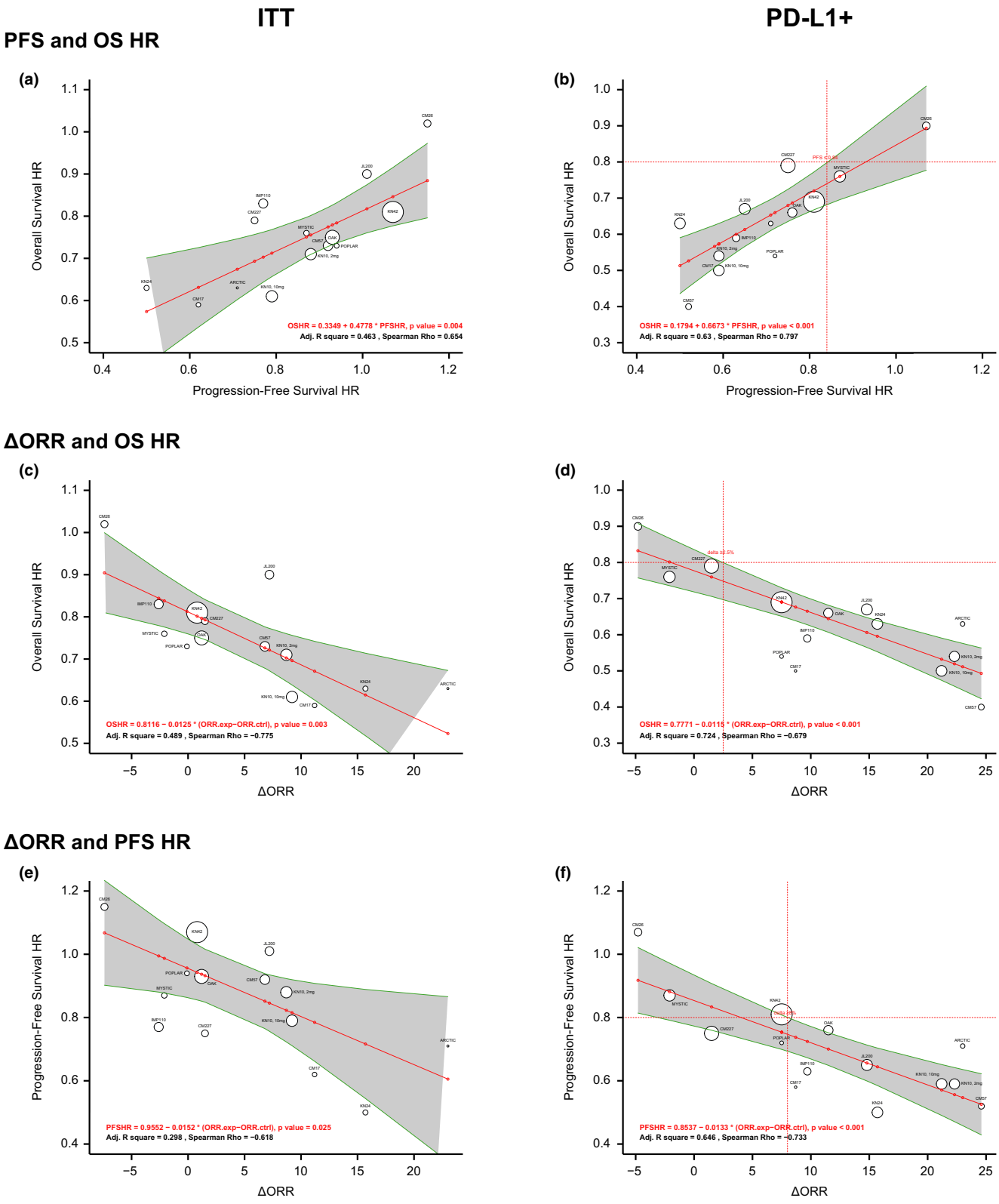

Figure 4 NSCLC ICB-monotherapy trials. Correlations between PFS and OS HRs in (**a**) the ITT and (**b**) PD-L1-positive populations; between ΔORR and OS HR in (**c**) the ITT and (**d**) PD-L1-positive population; and between ΔORR and OS HR in (**e**) the ITT and (**f**) PD-L1-positive population. In red: univariate weighted regression models with estimate of coefficient, and *P* value. HR, hazard ratio; ICB, immune checkpoint blockade; ITT, intention-to-treat; NSCLC, non-small-cell lung cancer; OS, overall survival; ΔORR, ORR for ICB arm minus comparator arm; PD-L1-positive, programmed death ligand-1 enriched; PFS, progression-free survival.

Patient-level analyses: correlations of PFS and objective response with OS in patients treated with durvalumab monotherapy

A positive association was identified between PFS and OS in durvalumab-treated patients across each of the tumor types evaluated. In patients with NSCLC, Kendall's Tau was 0.793 (95% CI: 0.789–0.797; **Figure 5a**). In the HNSCC and bladder cancer analyses, Kendall's Tau was 0.794 (95% CI: 0.789–0.798) and 0.872 (95% CI: 0.869–0.875), respectively (**Figure 5b,c**). Of note, modest PFS duration could still result in prolonged OS for individual patients across all three indications.

Durvalumab-treated patients with RECIST-assessed objective response (i.e., complete or partial response) had significantly better OS (concordance index > 0.9) than those without a response across all tumor types evaluated (**Figure 6**). In the NSCLC cohort

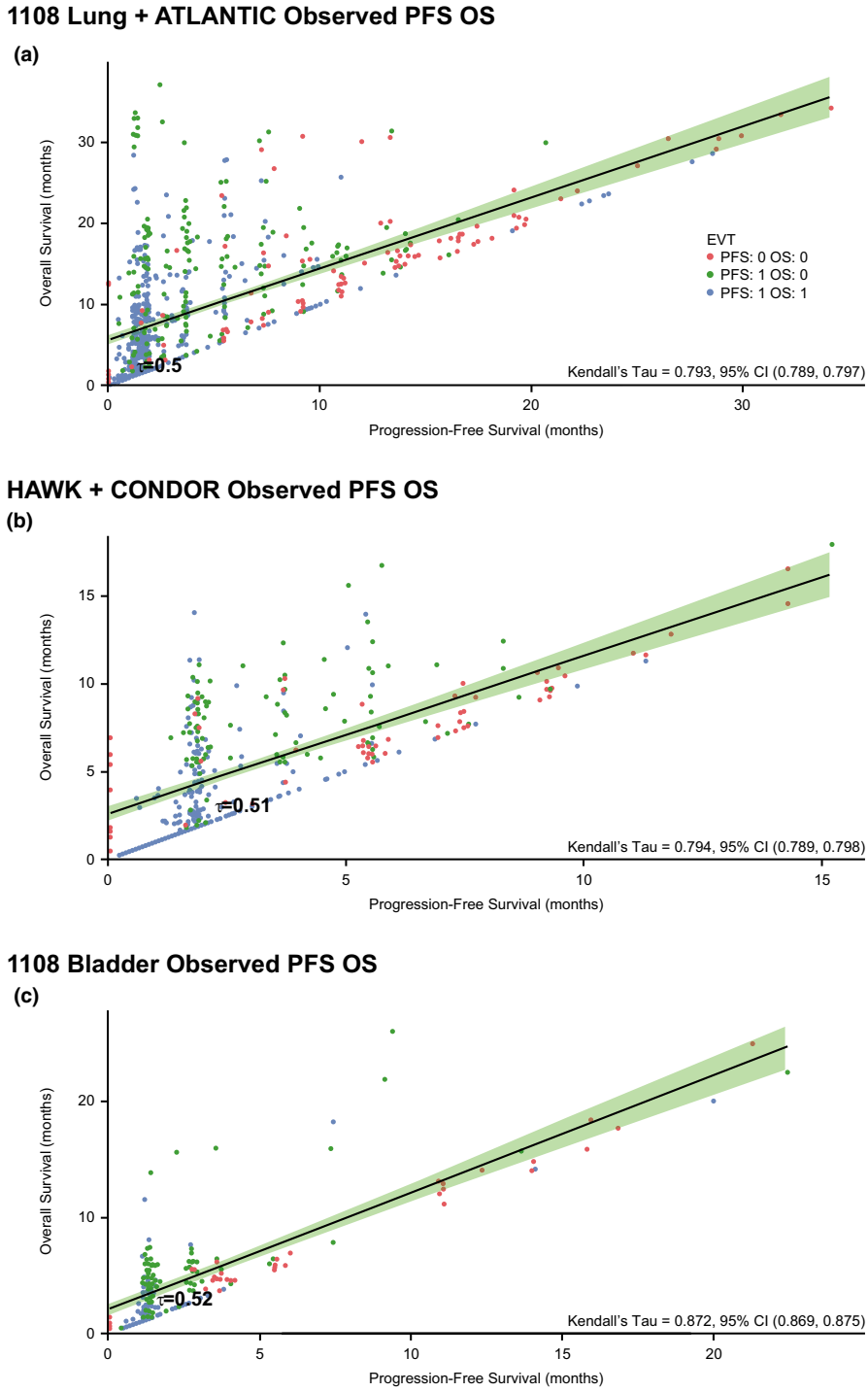

Figure 5 Correlation between PFS and OS in durvalumab-treated patients with (**a**) advanced NSCLC, (**b**) HNSCC, and (**c**) bladder cancer without controlling for censoring. CI, credible interval; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

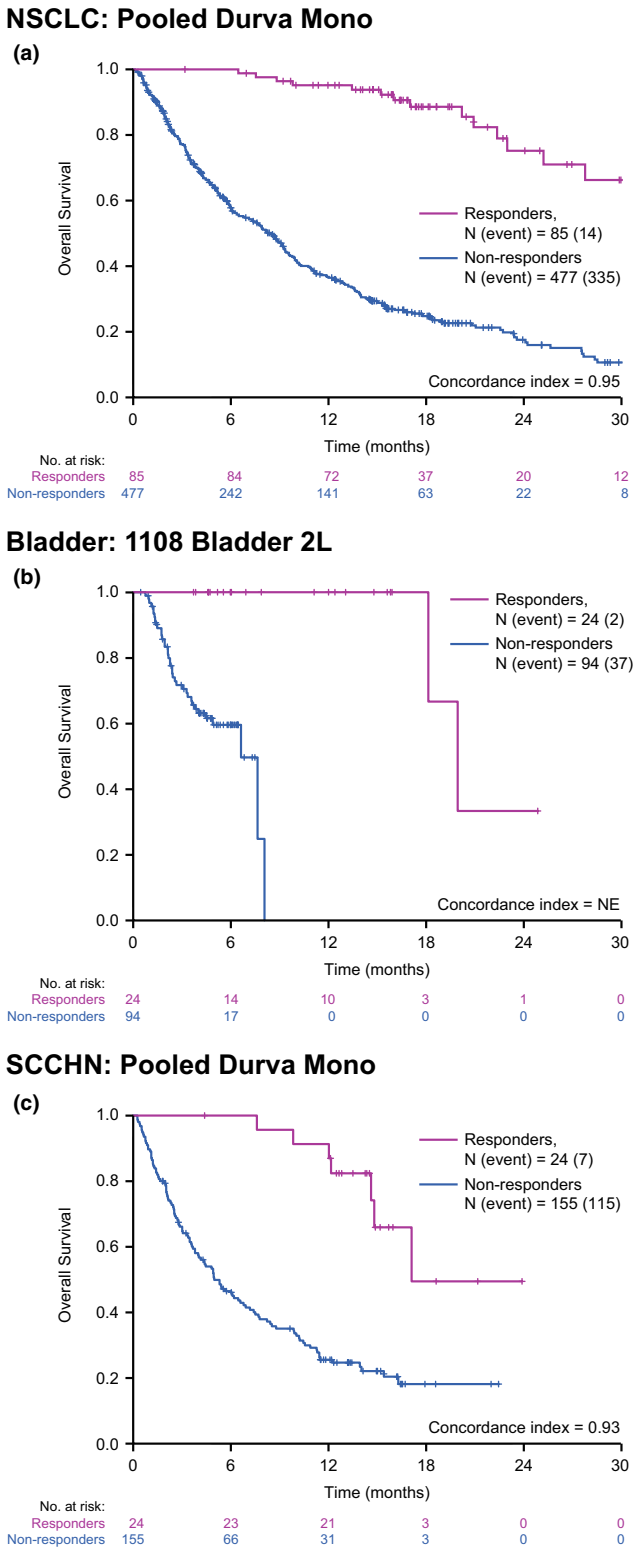

Figure 6 Correlation between ORR and OS in durvalumab-treated patients across advanced solid tumor types. 2L, second-line; durva, durvalumab; HNSCC, head and neck squamous cell carcinoma; mono, monotherapy; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; SCCHN, squamous cell carcinoma of the head and neck.

(ATLANTIC and Study 1108), the concordance index was 0.96; in the HNSCC cohort (HAWK and CONDOR), the concordance index was 0.93. In the bladder cancer cohort (study 1108), the concordance index was not evaluable as the last patient in the nonresponder group died before any patient in the responder group; thus, the Cox modeling approach encountered a numerical issue.

DISCUSSION

A number of considerations underscore the importance of establishing whether ORR and PFS are suitable surrogates for OS in the context of clinical trials of PD-1/PD-L1 ICB. It would provide confidence in an expedited path for regulatory approvals, helping to make effective therapies available to patients sooner. It would also resolve current inconsistencies in the literature, ratifying the OS benefits already reported in many trials.[6–10] Moreover, it would bolster ongoing efforts to assess other surrogate markers, such as those that are blood-based (e.g., cell-free circulating tumor DNA) and tissue-based (major pathological response and complete pathological response) in trials of immunotherapies as neoadjuvant/adjuvant therapy in early-stage solid tumors, which require considerably long-term follow-up to obtain mature OS data. Establishing surrogacy is especially relevant in the context of an increasing number of new clinical trials assessing PD-1/PD-L1 ICB in early-stage disease, in which OS is not a feasible end point for evaluation of treatment benefit. One further consideration is that both PFS and ORR are defined using RECIST, which was validated using data from clinical trials of cytotoxic antitumor therapies.[67] However, the underlying mechanism of action of anti-PD-1/PD-L1 mAbs is distinct from that of cytotoxic compounds and the patterns of response can differ. The recently introduced iRECIST guidelines seek to better assess the unique kinetics of response associated with ICB by mandating a confirmatory tumor assessment in cases of equivocal progression.[68]

In the current analysis, we examined the associations between ORR/PFS and OS, both in an overall ITT population and in a PD-L1-positive population (trial level) in multiple solid tumors and in patients with NSCLC (patient level). At the trial level, high correlation between PFS HR and OS HR was observed with PD-1/PD-L1 ICB monotherapy across advanced/metastatic solid tumors in both the ITT and PD-L1-positive analyses, and in the subanalyses by line of therapy (Rho 0.7–< 0.9), with the exception of first-line therapy in the PD-L1-positive population (Rho 0.45). Notably, a very high correlation between PFS HR and OS HR (rho ≥ 0.9) was not observed in any of the ITT or PD-L1-positive analyses of ICB monotherapy across advanced/metastatic solid tumors. Thus, although it might be anticipated that PFS and OS would be closely correlated, our results suggests this is not necessarily the case. Therefore, PFS may not be a good surrogate marker for OS. Meanwhile, moderate-to-high correlations were observed between ΔORR and OS HR in the ITT analysis and in the subanalyses by line of

therapy (Rho 0.5–< 0.9). In the PD-L1-positive analyses, correlations were generally weaker than those reported in the ITT analyses. Similar to PFS, the surrogacy of ORR for OS might be questioned in trials of PD-1/PD-L1 ICB monotherapy based on these findings. High correlation between ΔORR and PFS HR was observed with ICB monotherapy across advanced/metastatic solid tumors in ITT and PD-L1-positive analyses, as well as in the subanalyses by line of therapy (Rho 0.7–0.9); as RECIST underpins both of these measures, this finding was expected. In the NSCLC subset, correlations between the treatment effects with PD-1/PD-L1 ICB monotherapy were broadly consistent with the findings for all solid tumors.

The analyses of chemotherapy-ICB combination trials (NSCLC only) revealed very high correlations between OS and PFS HRs (Rho 0.92), ΔORR and OS HR (Rho 0.90), and ΔORR and PFS HR (Rho 0.95). One possible explanation for this finding is that chemotherapy may aid antibody penetration into solid tumors by reducing antigen shedding, a process presumably underpinned by reduced antigen synthesis (owing to chemotherapy-induced apoptosis of tumor cells), and thereby prime tumors to respond to immunotherapy.[69,70] Based on the more limited number of trials, relative to ICB monotherapy trials, this analysis indicates a much better correlation between the RECIST-based surrogate end points and OS in the chemotherapy-ICB combination setting. This may suggest that, for chemotherapy-ICB combinations, PFS or ORR changes can be used as a better early correlate for OS benefit, which may be related to a better fit of the RECIST guidance in the combination setting.

We note that these results do not provide conclusive evidence of whether PFS and/or ORR are true surrogates for OS in the setting of PD-1/PD-L1 ICB therapy for advanced solid tumors. In short, a lack of PFS or ORR benefit did not rule out longer-term OS benefit. Additionally, modest improvements in PFS or ORR could result in a large OS benefit, as observed in the trial-level analyses for ITT and PD-L1-positive populations (for "all solid tumors" and "NSCLC") and in line with previous meta-analyses that identified only weak correlations (at the trial and patient level) between PFS/ORR and OS.[71–73] Therefore, a modest to strong benefit in either PFS or ORR can be an encouraging early indicator of benefit. Likewise, in the patient-level analyses, modest PFS improvement could result in considerably prolonged OS in patients with NSCLC, HNSCC, and bladder cancer. Of interest, in the patient-level analysis, patients with RECIST responses (partial response/complete response) had significantly better OS (concordance index > 0.90) than those without a response. Nevertheless, large improvements in PFS or ORR were likely to result in OS benefit in the trial-level analyses, and improved PFS and achievement of objective response were likely to result in improved OS in the patient-level analyses. These findings suggest PFS and ORR can be used for early go/no go decisions in the clinical drug development pipeline.

However, there are some limitations to our analyses. First, we did not have access to patient-level data for all the randomized trials included in our trial-level analysis. With publicly available trial-level information, we could not address the patient-level correlation and trial-level correlation simultaneously. As such, our patient-level analysis was only based on four studies of patients who received durvalumab monotherapy. Second, in the trial-level analysis, the number of randomized trials across different disease settings was limited. Thus, we acknowledge that the relationship between tumor response and OS may differ according to primary tumor location and line of therapy. In order to evaluate potential heterogeneity introduced by lines of therapy, we conducted these analyses in first-line vs. greater than or equal to second-line patients. Given the number of trials available in NSCLC, we were also able to repeat the analyses on this specific tumor type. Due to the differences in effect between monotherapy and combinations, we focused our analyses separately on ICB monotherapy trials and those in combination with chemotherapy (NSCLC only). Our analysis is also limited to disease settings where trial data have already been reported, with most of these datasets focusing on disease settings where PD-1/PD-L1 ICB has shown active treatment benefit in early phase trials (for example, in melanoma and NSCLC). As the predictive value of such surrogates may vary between tumor types, the addition of randomized trials in other disease settings would be of interest and may reduce bias. OS effects of a particular intervention can also be confounded or inflated by the use of subsequent anticancer therapies; in the studies reported here, a much higher proportion of patients in the SOC arms received subsequent anticancer therapies than might have been expected. Moreover, as more anti-PD-(L)1 mAbs receive regulatory approval across various indications, patients in the SOC arms of PD-1/PD-L1 ICB trials are more likely to eventually receive another anti-PD-(L)1 mAb (i.e., upon disease progression), whereas patients in the experimental arm are less likely to receive such treatment. We also call out the variability in PD-1/PD-L1 thresholds and staining approaches used between the different trials in our analysis. Finally, we acknowledge a lack of established biomarkers that might be better predictors of response to PD-1/PD-L1 ICB therapy. Tumor mutation burden (TMB) has shown promise as a predictive biomarker in several studies.[29,74–78] Thus, although TMB might have been another interesting parameter to evaluate, the limited number of trials reporting results for TMB-defined populations meant such an analysis was not feasible.

In conclusion, our findings indicate that large improvements in PFS are very likely to translate into OS benefit, and that large benefits in ORR are also suggestive of potential OS improvement. However, modest (or even no) PFS or ORR benefit did not rule out OS benefit. Therefore, caution should be used in early discontinuation of novel agents unless a lack of benefit in both PFS and ORR is observed. Further evaluation of patient-level data, and data across a wider range of disease settings, would be of interest.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

FUNDING

This meta-analysis was funded by AstraZeneca. Medical writing support was provided by Aaron Korpal, PhD, and Catherine Crookes, BSc., of Ashfield Healthcare Communications during the preparation

of this manuscript and was funded by AstraZeneca. AstraZeneca was involved in the study design; collection, analysis, and interpretation of data; writing of the manuscript; and decision to submit the article for publication.

CONFLICT OF INTEREST

J.Y., P.D., and P.M. are all current employees of AstraZeneca. H.A. and X.J. were employed by AstraZeneca at the time of this analysis. P.D. and P.M. also report ownership of stocks in AstraZeneca.

AUTHOR CONTRIBUTIONS

J.Y. and P.M. wrote the manuscript. J.Y., P.D., H.A., and P.M. designed the research. J.Y. and P.M. performed the research. J.Y. and X.J. analyzed the data.

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