Validating ORR and PFS as surrogate endpoints in phase II and III clinical trials for NSCLC patients: difference exists in the strength of surrogacy in various trial settings

Tiantian Hua1,2, Yuan Gao2, Ruyang Zhang2, Yongyue Wei2 and Feng Chen1,2*

Abstract
Objective: This study aims to systematically validate the performance of surrogate endpoints in phase II and III clinical trials for NSCLC patients under various trial settings.

Methods: A literature search retrieved all registered phase II and III trials of NSCLC patients in which OS, with at least one of ORR and PFS, were reported. Associations between surrogate and true endpoints were assessed on two levels. On the arm level, three pairs of correlations, i.e., ORR vs. median OS, ORR vs. median PFS, and median PFS vs. median OS, were analysed using Spearman's rho. On the trial level, similarly, three pairs of correlations, i.e., ΔORR vs. HR of OS, ΔORR vs. HR of PFS, and HR of PFS vs. HR of OS, were analysed using Spearman's rho and weighted linear regression model respectively. Finally, sensitivity analyses were performed to explore surrogacy under various trial settings.

Results: At arm level, three pairs of correlations are all high (Spearman's rho = 0.700, 0.831, 0.755, respectively). At trial level, there is a low correlation between ΔORR and HR of OS, a high correlation between ΔORR and HR of PFS and a moderate correlation between HR of PFS and HR of OS (Spearman's rho = 0.462, 0.764, 0.584, respectively). In the sensitivity analysis, we find correlations between surrogate and true endpoints vary by different trial settings. It is noteworthy that the strength of surrogacy of these intermediate endpoints in targeted therapy is greater than that in immunotherapy.

Conclusion: According to the arm-level and trial level-analysis, we suggest that in phase II and III trials of targeted therapy and immunotherapy for NSCLC patients: 1) ORR lacks validity for the surrogacy of OS, excluding in first-line therapy, and 2) ORR may be an appropriate surrogate endpoint for PFS, and 3) PFS may be considered a modest surrogacy for OS, with better performance in first-line therapy trials. Moreover, to provide more convincing evidence of surrogacy of the surrogate endpoints, patient-level analyses are in desperate need.

Keywords: Surrogate endpoint, Meta-analysis, Non-small cell lung cancer, Targeted therapy, Immunotherapy

Background
Most recently, targeted therapy and immunotherapy have sprung up in cancer therapy [1]. The development of targeted therapy has advanced the therapeutic strategy from conventional chemo-based and radiation-based
therapy to genetic alteration-guided targeted therapy [2, 3]. Meanwhile, the advent of immunotherapy leads to greater availability of effective subsequent treatments and extended survival in previously treated advanced non-small cell lung cancer (NSCLC), of which a good example is the success of clinical trials for PD-1/PD-L1 inhibitor in tumour treatment [4, 5].

In oncology trials, intermediate/surrogate endpoints are often used as primary endpoints instead of true endpoints such as the overall survival (OS) over the past decade [6]. Surrogate endpoints are not intrinsically beneficial to patients but are designed to be easier, faster and cheaper to measure than clinically meaningful outcomes because they can reduce the sample size, shorten the duration and save the cost of trials [7, 8]. Although there have been many studies trying to determine the surrogacy of intermediate endpoints, the results didn’t reach a consensus [9–15]. Besides, evaluating the surrogacy of the intermediate endpoints in these new domains, such as immunotherapy and targeted therapy, raises a to-be-solved challenge.

We, therefore, performed a broad-based structured review and meta-analysis of registered phase II and III NSCLC trials with immunotherapy and/or targeted therapy. The objective of this research was to find the appropriacy of surrogate endpoints in NSCLC studies under various trial settings (e.g. line of therapy, trial phase, blinding and therapy type), to give suggestions on which surrogate endpoints should be used under certain trial conditions.

Methods

Search strategy

We conducted this analysis in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [16]. Three databases (PubMed, EMBASE, Cochrane Library) were searched with time ranged from January 2000 to May 2021. Search terms included cancer terms AND therapy terms AND terms for PFS (Progression Free Survival, PFS), ORR (Objective Response Rate, ORR) and/or OS (Overall Survival, OS) AND terms for endpoint and/or surrogate. Search results were limited to the English language and in-human studies. The detailed Cochrane Library search strategy is provided in Additional file 1. The PRISMA flow diagram is shown in Fig. 1.

Inclusion and exclusion criteria

Inclusion was restricted to registered clinical trials reporting results of OS, with either PFS or ORR, or both. The included studies should report the NCT number. Protocols and ongoing trials without results were excluded.

Study selection and data extraction

Titles and abstracts of articles retrieved by the search were examined by two independent reviewers, followed by a discussion to ensure consistency in the selection decisions. Full texts were examined by one reviewer and a subset was checked by a second reviewer, with any discrepancies resolved through discussion.

Data were extracted by one reviewer and checked by a second reviewer. For eligible studies, the following characteristics were extracted: authors, publication year, number of patients included, type of lung cancer, stage of lung cancer, therapy type, NCT number, surrogate and final endpoints analysed, line of therapy, phase of the trial, results including ORR, median PFS and median OS of each arm, and ΔORR, HR of PFS and HR of OS between arms. The summary of included articles is shown in Additional file 2.

Data synthesis and analysis

According to the definition and validation criteria for surrogate endpoints [17, 18], two conditions are necessary to measure whether an intermediate endpoint can be an acceptable surrogacy for the true clinical endpoint. First, for the individual level, there must be a strong association between the surrogate endpoint and the true endpoint. Second, for the trial level, there must be a strong association between the treatment effect of the surrogate endpoint and that of the true endpoint [19]. However, the individual level data are usually not available, so we use arm level data as an alternative, which can also be seen in many other studies [20–23]. To describe the correlation strength between surrogate and true endpoints in this study, we divided values of the correlation coefficient into five levels, as shown in Table 1.

The Spearman rank correlation coefficient, \( r_s \), was used to measure the arm-level associations, which means correlation coefficients between ORR and median OS, between ORR and median PFS, and between median PFS and median OS were calculated from all arms of all included studies.

To assess trial-level associations, correlations between OR of ORR (Odds Ratio of ORR) and HR of OS (Hazard Ratio of OS), between OR of ORR and HR of PFS, and between HR of PFS (Hazard Ratio of OS) and HR of OS were needed. In light of the situation that few studies reported OR of ORR, we replaced the OR of ORR by subtracting the treatment’s ORR from the control’s ORR, which was defined as ΔORR. Similarly, the Spearman rank correlation coefficient \( r_s \) was used to evaluate the associations.

Correlation indicates the extent to which those two treatment effects move together, while regression allows...
to predict the long-term treatment effect (true endpoint) based on the short-term treatment effect (surrogate endpoint). Hence, to give an idea of how the later can help with predicting the former, we further implemented the linear regression models. Simple linear regression models, followed by multiple linear regression models (both weighted by sample size as in previous endpoint validation studies [24–27]), which were expected to control for specific trial setting factors including line of therapy, trial phase and masking, were fitted. Also, we used the surrogate threshold effect (STE) to evaluate the surrogacy of surrogate endpoints from a clinical point of view [28]. STE defines the minimum short-term (i.e. surrogate endpoint) treatment effect required to guarantee a non-zero long-term (i.e. true endpoint) treatment effect. For example, take a regression of HR of OS as y on HR of PFS as x, then the x-value of the intersection of the line y = 1 (which means zero long-term treatment effect) and the upper boundary of the 95% prediction interval stripe of the regression line is STE.

It should be noted that various trial settings, such as line of therapy, trial phase, masking and type of therapy might introduce bias into the quantitative relationship between surrogate and true endpoints, if any of these factors remained from the stepwise selection in the previous multiple regression. Thus, sensitivity analyses were performed to explore whether the associations showed homogeneity regardless of different trial settings.

### Table 1: Rule for interpreting the strength of a correlation coefficient

| Size of Correlation (absolute value) | Interpretation                          |
|-------------------------------------|-----------------------------------------|
| [0.90,1.00]                         | Very high positive (negative) correlation |
| [0.70,0.90)                         | High positive (negative) correlation    |
| [0.50,0.70)                         | Moderate positive (negative) correlation|
| [0.30,0.50)                         | Low positive (negative) correlation     |
| [0.00,0.30)                         | Negligible correlation                  |

---

![PRISMA flow diagram](image-url)  
**Fig. 1** PRISMA flow diagram for study inclusion.
All analyses were conducted using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

After the initial search, 1158 publications were identified for screening and 959 potentially relevant unduplicated publications were reviewed in detail for eligibility. Ultimately, a total of 136 eligible trials with a total of 350 arms (including arms of reported subgroup analysis, with details in Additional file 2) and 46,028 NSCLC patients were included in the study. The study selection process and reasons for exclusion at each stage are detailed in the PRISMA flow diagram Fig. 1.

Most studies focused on advanced NSCLC. Among all 136 trials, 69 (50.7%) of them were phase II studies, 2 (1.5%) of them were phase II/III studies, and 65 (47.8%) of them were phase III studies. Concerning masking, 38 trials were double-blinded, 1 trial was single-blinded, and 97 trials were open-labelled. Other study design characteristics needed for sensitivity analysis are summarised in Additional file 2.

In all 350 arms, 288 (82.3%) arms reported ORR, 331 (94.6%) arms reported median PFS, and 311 (88.9%) arms reported median OS. Meanwhile, in all 136 trials, 20 (14.7%) trials reported 25 ORs of ORR, 103 (75.7%) trials reported 147 HRs of PFS, and 101 (74.3%) trials reported 145 HRs of OS. The low percentage of trials reporting OR of ORR led to our decision that ΔORR was constructed to replace OR of ORR.

### Arm-level associations between surrogate and true endpoints

Of all 350 arms from 136 eligible trials, 254 arms had both ORR and median OS reported, 271 arms had both ORR and median PFS reported, and 306 arms had both median PFS and median OS reported. The median PFS averaged across all arms was 4.5 months (range from 1.0 to 24.5 months), and the median OS was 11.5 months (range from 2.8 to 51.3 months).

Figure 2 gives scatter plots of ORR vs. median OS, ORR vs. median PFS, and median PFS vs. median OS from all arms, with bubble radius representing the corresponding study sample size, and bubble colour representing the therapy type. The Spearman rank correlation coefficient suggested a high positive association between ORR and median OS (Spearman’s rho = 0.700, Table 2), a high positive association between ORR and median PFS (Spearman’s rho = 0.831, Table 2), and a high positive association between median PFS and median OS (Spearman’s rho = 0.755, Table 2).

### Trial-level associations between surrogate and true endpoints

Of all 136 eligible trials, we extracted 112 pairs of ΔORR and HR of OS, 114 pairs of ΔORR and HR of PFS, and 138 pairs of HR of PFS and HR of OS (because some trials have more than one treatment arm). The ΔORR ranged from −53.5 to 27.0% in all trials, with HR of PFS

#### Table 2 Arm-level association of all included arms

| Surrogate endpoint | True endpoint | No. of arms | r_s | 95%CI |
|--------------------|---------------|-------------|-----|-------|
| ORR                | Median OS     | 254         | 0.700 | 0.631,0.758 |
| ORR                | Median PFS    | 271         | 0.831 | 0.790,0.864 |
| Median PFS         | Median OS     | 306         | 0.755 | 0.702,0.799 |

Fig. 2 Arm-level scatter plot of surrogate and true endpoints. (a) Arm-level scatter plot of ORR and median OS. The Spearman’s rho coefficient is 0.700; (b) Arm-level scatter plot of ORR and median PFS. The Spearman’s rho coefficient is 0.831; (c) Arm-level scatter plot of median PFS and median OS. The Spearman’s rho coefficient is 0.755. Each arm is represented by a bubble whose radius is proportional to the study sample size. The bubble colour represents the therapy type of the arm.
and HR of OS ranging from 0.16 to 2.00 and 0.22 to 1.78 respectively.

The Spearman correlation between the treatment effect of surrogate and true endpoints was first calculated, as shown in Table 3, which gave a low positive correlation of the pair ΔORR vs. HR of OS (Spearman’s rho = 0.462, Table 3), a high positive correlation of the pair ΔORR vs. HR of PFS (Spearman’s rho = 0.764, Table 3), and a moderate positive correlation of the pair HR of PFS vs. HR of OS (Spearman’s rho = 0.584, Table 3).

### Table 3 Trial-level association of all included studies (Spearman’s rho)

| Treatment effect of surrogate endpoint | Treatment effect of true endpoint | No. of trials | \( r_s \) | 95% CI          |
|--------------------------------------|----------------------------------|---------------|-----------|----------------|
| ΔORR                                 | HR of OS                         | 112           | 0.462     | 0.303, 0.597  |
| ΔORR                                 | HR of PFS                        | 114           | 0.764     | 0.675, 0.831  |
| HR of PFS                            | HR of OS                         | 138           | 0.584     | 0.462, 0.684  |

Simple linear regression results are listed in Table 4. An increase of 1 unit in ΔORR would lead to an increase of 0.011 unit in log (HR of OS) \( (R^2 = 0.261, \text{Table 4}) \) and 0.023 unit in log (HR of PFS) \( (R^2 = 0.578, \text{Table 4}) \), while an increase of 1 unit in log (HR of PFS) resulted in an increase of 0.403 unit in log (HR of OS) \( (R^2 = 0.360, \text{Table 4}) \).

The trial-level correlation between ΔORR and HR of PFS from the clinical point of view is reflected by a surrogate threshold effect (STE) equal to \(-26.30\%\). In other words, if ORR of the control group minus ORR of the treatment group is smaller than \(-26.30\%\), the HR of PFS will be both statistically and clinically significant, which suggests a reduction in the risk of progression in the experiment group.

Multiple linear regression results are listed in Table 5. Based on the least AIC criteria, trial setting factors were selected stepwise. Trial phase should be paid attention to when using ΔORR as a surrogate endpoint for HR of OS \((\log \text{HR of OS}) = -0.003 + 0.012 \times \Delta \text{ORR} - 0.092 \times \text{phase}\) and using HR of PFS for HR

### Table 4 Trial-level associations of all included studies (Simple linear regression)

| Treatment effect of surrogate endpoint | Treatment effect of true endpoint | No. of trials | Slope estimate | 95% CI     | \( R^2 \) | Adjusted \( R^2 \) | STE           |
|--------------------------------------|----------------------------------|---------------|----------------|-----------|-----------|----------------|---------------|
| ΔORR                                 | HR of OS                         | 112           | 0.011          | 0.007, 0.014 | 0.261     | 0.254          | ——b           |
| ΔORR                                 | HR of PFS \(^a\)                  | 114           | 0.023          | 0.019, 0.027 | 0.578     | 0.574          | \(-26.30\%\)  |
| HR of PFS \(^a\)                     | HR of OS \(^a\)                  | 138           | 0.403          | 0.313, 0.494 | 0.360     | 0.355          | ——b           |

Simple linear regression model form

\[ \log \text{(HR of OS)} = -0.062 + 0.011 \times \Delta \text{ORR} \; ; \]
\[ \log \text{(HR of PFS)} = -0.103 + 0.023 \times \Delta \text{ORR} \; ; \]
\[ \log \text{(HR of OS)} = -0.053 + 0.403 \times \log \text{(HR of PFS)} \]

\(^a\) Natural log hazard ratio in the analysis

\(^b\) The STE will be given only when the upper limit of \( r_s \) (in Table 3) is more than 0.7

### Table 5 Trial-level association of all included studies (Multiple linear regression, adjusted for line, phase and masking\(^b\))

| Treatment effect of surrogate endpoint | Treatment effect of true endpoint | No. of trials | Slope estimate | 95% CI     | \( R^2 \) | Adjusted \( R^2 \) |
|--------------------------------------|----------------------------------|---------------|----------------|-----------|-----------|----------------|
| ΔORR                                 | HR of OS \(^a\)                  | 103           | 0.012          | 0.008, 0.015 | 0.313     | 0.299          |
| ΔORR                                 | HR of PFS \(^a\)                  | 104           | 0.023          | 0.119, 0.027 | 0.571     | 0.562          |
| HR of PFS \(^a\)                     | HR of OS \(^a\)                  | 125           | 0.418          | 0.312, 0.524 | 0.393     | 0.380          |

Multivariable linear regression model form:

\[ \log \text{(HR of OS)} = -0.003 + 0.012 \times \Delta \text{ORR} - 0.092 \times \text{phase} \; ; \]
\[ \log \text{(HR of PFS)} = -0.066 + 0.023 \times \Delta \text{ORR} - 0.093 \times \text{masking} \; ; \]
\[ \log \text{(HR of OS)} = 0.009 + 0.418 \times \log \text{(HR of PFS)} - 0.072 \times \text{phase} \]

\(^a\) Natural log hazard ratio in the analysis

\(^b\) Code for line, phase and masking in the regression:

- Line: First-line = 0, ≥2nd-line = 1
- Phase: Phase II = 0, Phase III = 1
- Masking: Open-label = 0, Double-blind = 1
of OS (log (HR of OS) = 0.009 + 0.418 * log (HR of PFS) - 0.072 * phase). Whether the trial is blinded also played a role in the surrogacy of ΔORR for HR of PFS (log (HR of PFS) = −0.066 + 0.023 * ΔORR − 0.093 * masking).

**Additional analysis**

Sensitivity analyses were performed to evaluate potential heterogeneity in the correlations caused by different trial settings such as line of therapy, phase of trial, masking and therapy type. The results are shown in Tables 6, 7, and 8, Figs. 3, 4, and 5. The scatter plots and fitted weighted linear regression lines of ΔORR vs. HR of OS,

### Table 6 Summary of arm-level sensitivity analysis (Spearman correlation)

| Sensitivity Analysis | No. of arms | rs   | 95%CI       |
|----------------------|-------------|------|-------------|
| **ORR – median OS**  |             |      |             |
| Line of therapy      |             |      |             |
| First-line           | 88          | 0.636 | 0.492, 0.746 |
| ≥ 2nd-line           | 146         | 0.611 | 0.498, 0.703 |
| Phase of trial       |             |      |             |
| Phase II             | 141         | 0.703 | 0.609, 0.762 |
| Phase III            | 111         | 0.660 | 0.541, 0.754 |
| Masking              |             |      |             |
| Double-blind         | 66          | 0.629 | 0.456, 0.756 |
| Open-label           | 186         | 0.710 | 0.631, 0.775 |
| Therapy*             |             |      |             |
| Targeted therapy-based | 123       | 0.749 | 0.660, 0.818 |
| Immunotherapy-based  | 54          | 0.449 | 0.207, 0.640 |
| Chemotherapy-based   | 65          | 0.706 | 0.558, 0.810 |
| Overall              | 254         | 0.700 | 0.631, 0.758 |
| **ORR – median PFS** |             |      |             |
| Line of therapy      |             |      |             |
| First-line           | 93          | 0.699 | 0.578, 0.790 |
| ≥ 2nd-line           | 153         | 0.735 | 0.653, 0.801 |
| Phase of trial       |             |      |             |
| Phase II             | 153         | 0.825 | 0.768, 0.870 |
| Phase III            | 117         | 0.790 | 0.711, 0.850 |
| Masking              |             |      |             |
| Double-blind         | 76          | 0.888 | 0.828, 0.927 |
| Open-label           | 193         | 0.796 | 0.738, 0.842 |
| Therapy*             |             |      |             |
| Targeted therapy-based | 132       | 0.823 | 0.759, 0.871 |
| Immunotherapy-based  | 58          | 0.793 | 0.673, 0.873 |
| Chemotherapy-based   | 65          | 0.783 | 0.669, 0.861 |
| Overall              | 271         | 0.831 | 0.790, 0.864 |
| **median PFS – median OS** |             |      |             |
| Line of therapy      |             |      |             |
| First-line           | 109         | 0.883 | 0.763, 0.882 |
| ≥ 2nd-line           | 177         | 0.599 | 0.495, 0.686 |
| Phase of trial       |             |      |             |
| Phase II             | 143         | 0.798 | 0.730, 0.851 |
| Phase III            | 154         | 0.705 | 0.616, 0.777 |
| Masking              |             |      |             |
| Double-blind         | 83          | 0.727 | 0.606, 0.815 |
| Open-label           | 221         | 0.755 | 0.692, 0.807 |
| Therapy*             |             |      |             |
| Targeted therapy-based | 132       | 0.756 | 0.672, 0.821 |
| Immunotherapy-based  | 76          | 0.656 | 0.506, 0.768 |
| Chemotherapy-based   | 82          | 0.786 | 0.687, 0.857 |
| Overall              | 306         | 0.755 | 0.702, 0.799 |

*Targeted therapy-based: including targeted therapy with or without placebo/normal care

*Immunotherapy: including immunotherapy with or without placebo/normal care

*Chemotherapy-based: including conventional chemotherapy with or without placebo/normal care

### Table 7 Summary of trial-level sensitivity analysis (Spearman correlation)

| Sensitivity Analysis | No. of trials | rs   | 95%CI       |
|----------------------|---------------|------|-------------|
| **ΔORR – HR of OS**  |               |      |             |
| Line of therapy      |               |      |             |
| First-line           | 39            | 0.685 | 0.471, 0.822 |
| ≥ 2nd-line           | 64            | 0.342 | 0.103, 0.544 |
| Phase of trial       |               |      |             |
| Phase II             | 60            | 0.399 | 0.163, 0.591 |
| Phase III            | 52            | 0.511 | 0.277, 0.688 |
| Masking              |               |      |             |
| Double-blind         | 35            | 0.259 | −0.081, 0.545 |
| Open-label           | 76            | 0.536 | 0.354, 0.680 |
| Overall              | 112           | 0.462 | 0.303, 0.597 |
| **ΔORR – HR of PFS** |               |      |             |
| Line of therapy      |               |      |             |
| First-line           | 36            | 0.767 | 0.587, 0.875 |
| ≥ 2nd-line           | 68            | 0.787 | 0.675, 0.863 |
| Phase of trial       |               |      |             |
| Phase II             | 60            | 0.792 | 0.674, 0.870 |
| Phase III            | 54            | 0.673 | 0.495, 0.797 |
| Masking              |               |      |             |
| Double-blind         | 36            | 0.703 | 0.487, 0.838 |
| Open-label           | 77            | 0.789 | 0.672, 0.852 |
| Overall              | 114           | 0.764 | 0.686, 0.861 |
| **HR of PFS – HR of OS** |               |      |             |
| Line of therapy      |               |      |             |
| First-line           | 48            | 0.768 | 0.621, 0.863 |
| ≥ 2nd-line           | 81            | 0.530 | 0.377, 0.686 |
| Phase of trial       |               |      |             |
| Phase II             | 62            | 0.475 | 0.258, 0.647 |
| Phase III            | 72            | 0.650 | 0.492, 0.766 |
| Masking              |               |      |             |
| Double-blind         | 42            | 0.676 | 0.469, 0.813 |
| Open-label           | 95            | 0.570 | 0.417, 0.692 |
| Overall              | 138           | 0.584 | 0.462, 0.684 |

*Targeted therapy-based: including targeted therapy with or without placebo/normal care

*Immunotherapy: including immunotherapy with or without placebo/normal care

*Chemotherapy-based: including conventional chemotherapy with or without placebo/normal care
ΔORR vs. HR of PFS, and HR of PFS vs. HR of OS in different trial settings are shown in Figs. 3, 4, and 5.

From the arm-level sensitivity analysis (Fig. 6), we can find that 1) ORR is more relevant with median OS in first-line, phase II, open-label, targeted-therapy based trials; 2) ORR is more relevant with median PFS in ≥2nd-line, phase II, double-blind, targeted-therapy based trials. 3) PFS is more relevant with median OS in first-line, phase II, open-label, chemotherapy-based trials. Correlations in all subgroups are statistically significant. It is worth mentioning that, in targeted therapy-based trials, the association strengths between ORR and median OS, between ORR and median PFS, and between median PFS and median OS are all at the high positive level. On the contrary, the association strengths in immunotherapy-based trials are much weaker, except for the ORR vs. median PFS pair. We may conclude that at the arm level, surrogate endpoints show the best appropriation in targeted therapy-based trials among all three therapy types.

From the trial-level sensitivity analysis (Fig. 7), we can find that associations between ΔORR and HR of OS are not satisfactory in most subgroups except in first-line therapy trials. The association between ΔORR and HR

### Table 8 Summary of trial-level sensitivity analysis (Linear regression)

| Sensitivity Analysis | No. of trials | Slope estimate | 95%CI | R² | Adjusted R² | Threshold |
|----------------------|---------------|----------------|-------|----|-------------|-----------|
| ΔORR ~ HR of OS*     |               |                |       |    |             |           |
| Line of therapy      |               |                |       |    |             |           |
| First-line           | 39            | 0.019          | 0.013, 0.024 | 0.570 | 0.558 | −28.01% |
| ≥ 2nd-line           | 64            | 0.008          | 0.004, 0.012 | 0.166 | 0.153 | ——b      |
| Phase of trial       |               |                |       |    |             |           |
| Phase II             | 60            | 0.010          | 0.406, 0.014 | 0.294 | 0.282 | ——b      |
| Phase III            | 52            | 0.012          | 0.007, 0.018 | 0.267 | 0.252 | ——b      |
| Masking              |               |                |       |    |             |           |
| Double-blind         | 35            | 0.016          | 0.009, 0.023 | 0.365 | 0.345 | ——b      |
| Open-label           | 76            | 0.007          | 0.004, 0.011 | 0.176 | 0.165 | ——b      |
| Overall              | 112           | 0.011          | 0.007, 0.014 | 0.261 | 0.254 | ——b      |
| ΔORR ~ HR of PFS*    |               |                |       |    |             |           |
| Line of therapy      |               |                |       |    |             |           |
| First-line           | 36            | 0.023          | 0.018, 0.029 | 0.641 | 0.630 | −23.25% |
| ≥ 2nd-line           | 68            | 0.023          | 0.018, 0.029 | 0.528 | 0.521 | −29.95% |
| Phase of trial       |               |                |       |    |             |           |
| Phase II             | 60            | 0.023          | 0.018, 0.028 | 0.588 | 0.581 | −35.82% |
| Phase III            | 54            | 0.023          | 0.017, 0.028 | 0.568 | 0.560 | −19.28% |
| Masking              |               |                |       |    |             |           |
| Double-blind         | 36            | 0.018          | 0.012, 0.025 | 0.468 | 0.453 | −33.76% |
| Open-label           | 77            | 0.025          | 0.021, 0.030 | 0.640 | 0.636 | −24.42% |
| Overall              | 114           | 0.023          | 0.019, 0.027 | 0.578 | 0.574 | −26.30% |
| HR of PFS* ~ HR of OS* |           |                |       |    |             |           |
| Line of therapy      |               |                |       |    |             |           |
| First-line           | 48            | 0.555          | 0.419, 0.691 | 0.580 | 0.571 | 0.49 |
| ≥ 2nd-line           | 81            | 0.333          | 0.217, 0.449 | 0.286 | 0.277 | ——b      |
| Phase of trial       |               |                |       |    |             |           |
| Phase II             | 62            | 0.374          | 0.255, 0.492 | 0.390 | 0.380 | ——b      |
| Phase III            | 72            | 0.427          | 0.302, 0.553 | 0.390 | 0.382 | 0.41 |
| Masking              |               |                |       |    |             |           |
| Double-blind         | 42            | 0.793          | 0.610, 0.977 | 0.642 | 0.633 | 0.48 |
| Open-label           | 95            | 0.276          | 0.178, 0.374 | 0.246 | 0.238 | ——b      |
| Overall              | 138           | 0.403          | 0.313, 0.494 | 0.360 | 0.355 | ——b      |

* Natural log hazard ratio in the analysis

b Only the upper limit of r_s is more than 0.7, the STE will be given
of PFS is the strongest among all three pairs, with all $r_s$ estimated above 0.65 and upper limit of $r_s$ estimated above 0.7. For the pair of HR of PFS vs. HR of OS, high positive correlation only exists in first-line therapy trials.

Table 8 reveals the weighted (based on sample size) linear regression coefficient $\beta$ of surrogate endpoints to true endpoints in each subgroup. All models using $\Delta$ORR to predict HR of OS have $R^2 < 0.3$ except for that in first-line therapy and double-blind trials, which may lead to the result that there are negligible correlations between $\Delta$ORR and HR of OS at trial level. In addition, for both $\Delta$ORR as a surrogacy of HR of PFS and HR of PFS as a surrogacy of HR of OS, the associations in the subgroup of first-line therapy is much stronger than those in the subgroup of $\geq$2nd-line therapy, indicating that it may be more reliable and reasonable to use surrogacy endpoints in first-line NSCLC therapy.
Discussion

All analyses on the arm-level, including those in each subgroup, are all statistically significant. The association between ORR and PFS, and that between PFS and OS, are stronger than the association between ORR and OS, which may indicate a pass-on effect of ORR to PFS to OS.

We can find that the correlation strength sequence is the same at both the arm level and the trial level, with the pair of PFS vs. OS, the pair of ORR vs. PFS, and the pair of ORR vs. OS listed in a descending order. Meanwhile, the value of correlation strength is smaller at the trial level than that at the arm level. This conclusion agrees with Nie [29], Bira [30] and Ritchie [31]. It is worth noting that, one possible reason for the high correlation at arm level may be that the endpoints are naturally dependent by definition. The dependence structure between endpoints, especially for PFS and OS, should be taken into consideration [32]. To explore this, we calculated the mean (0.381) of all arms’ median PFS/median OS, which is much smaller than the arm-level correlation (0.755). So we conclude that the arm-level correlation are rather driven by a real association between PFS and
The surrogacy of ORR for OS

Although ORR has a high positive correlation with OS at arm level, we don’t consider it as an appropriate surrogacy for OS because of its poor performance (low positive correlation, adjusted $R^2 < 0.3$) at trial level, as what Gideon [10] has found in advanced NSCLC from both trial level and patient level. However, the additional analysis indicates that when it is limited to trials with first-line therapy, the trial-level association estimates (Spearman’s rho, regression coefficients and adjusted $R^2$) increases significantly. Hence, ORR may be used as a surrogate endpoint for OS only in first-line therapy trials.

The surrogacy of ORR for PFS

At trial level, ΔORR can explain 58% of the variability of HR of PFS. Combining with its good behaviour at arm level, it implies that ORR may be an appropriate surrogacy for PFS, especially in first-line, open-label trials. The fine surrogacy of ORR for PFS to some extent comes from the definition of those two indices. Notably, it seems that ORR works better as surrogacy for PFS in
both immunotherapy and targeted therapy than that in chemotherapy.

The surrogacy of PFS for OS
We can conclude from this analysis that PFS may be at most a modest surrogate endpoint for OS because of its performance at both arm level and trial level, consistent with Buyse’s [15] finding in advanced NSCLC patients and Fiteni’s [33] finding in locally advanced lung cancer. However, Laporte [14] found that R² were low in advanced NSCLC at patient-level. We also find that the association between PFS and OS is not the same across various therapy types, with stronger association in targeted therapy than in immunotherapy, and both of which are weaker compared to that in chemotherapy. One possible explanation for this finding is that crossover designs are often implemented in immunotherapy and targeted therapy, as mentioned in many researches [34], because of their outstanding early efficacy and ethical consideration, which would make the effect of treatment smaller. Besides, the correlation between PFS and OS is stronger in first-line therapy trials, which was also found by Foster [35] in extensive-stage small cell lung cancer.

There are several limitations in our study that need to be acknowledged. First, meta-analysis can only drop a hint on the association between arm-level and trial-level parameters, while true causation should be established only with an analysis of patient-level data [36]. Second, due to the unavailability of extracting same summary statistics for all trials, such as the OR of ORR on the trial-level, we manually calculated ΔORR using the reported ORR of each arm instead, which may not reflect the true treatment effect of ORR.

At last, the idea can be considered in future studies that dividing all trials into a training part and a validating part, to examine more thoroughly the prediction ability of surrogate endpoints.
Conclusion
In conclusion, the findings of this meta-analysis of prospective randomized trials demonstrate that ORR is proved to be lack of validity for the surrogacy of OS, except in first-line therapy trials. Conversely, it may be an appropriate surrogate endpoint for PFS across different trial settings (e.g., line of therapy, phase of trial, masking and therapy type), considering the strong and robust correlations at both arm level and trial level. However, as a traditional surrogate endpoint, PFS may be considered at most a modest surrogacy for OS in the setting of phase II/III clinical trials of targeted therapy and immunotherapy for NSCLC patients (especially in first-line therapy trials). Besides, we must admit that to evaluate the true surrogacy, further evaluation of patient-level data should be carried out.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12885-022-10046-z.

Additional file 1. Cochrane Library Search Strategy (May 2021).
Additional file 2. Characteristics of included 136 studies.

Acknowledgements
Not applicable.

Authors’ contributions
HTT and CF conceived the study. HTT and GY collected and analysed data. HTT wrote the manuscript. ZRY and WYY took charge of language editing. All authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests”.

Author details
1Present Address: Department of Epidemiology and Health Statistics, School of Public Health, Southeast University, Nanjing, China. 2Department of Biostatistics, School of Public Health, Nanjing Medical University, Nanjing, China.
