Disease control and objective responsive rates in randomized phase II trials evaluating non-first-line chemotherapy for non-small cell lung cancer: a systematic review of 74 trials

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Abstract: Although objective response rate and disease control rate are commonly used as primary endpoints of lung cancer trials, it remains unclear whether objective response rate and disease control rate correctly reflect the overall survival in a non-small cell lung cancer phase II trial evaluating a non-first-line chemotherapy. Objective response rate might be easily affected by chance because the small number of patients in each trial achieved complete or partial response in the phase II non-first-line setting. This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (UMIN000040412). Four databases were searched for eligible trials. A Spearman's rank correlation with hazard ratio of overall survival was calculated each for odds ratio of objective response rate, difference of objective response rate (%), odds ratio of disease control rate, and difference of disease control rate (%). Of 74 eligible trials, 73 reported objective response rate and 68 reported disease control rates. Nine (12%) trials included patients with driver mutation status. Thirteen (18%) and two (3%) RCTs specifically included adenocarcinoma/non-squamous and squamous subtype of non-small cell lung cancer, respectively. The Eastern Cooperative Oncology Group performance status 0–2 (N=41, 55%) and the performance status 0-1 (N=25, 34%) were frequently used performance status criteria. The median number of patients in the two arms was 116 (interquartile range, 82–159). The correlation between trial-level odds ratio of objective response rate and hazard ratio of overall survival was weak (r=–0.29, 95% CI: –0.49 to –0.05, P=0.014). An exploratory subgroup analysis suggested that fewer responders were associated with poorer correlation. Odds ratio of disease control survival (r=–0.53, 95% CI: –0.68 to –0.32, P<0.001) had moderate rank correlations with hazard ratio of overall survival. Instead of objective response rate, disease control rate should be used as the primary endpoint in a randomized phase II trial evaluating non-first-line chemotherapy for non-small cell lung cancer.

Keywords: Lung neoplasm; response evaluation criteria in solid tumors; systematic review; correlation of data

Introduction

Approximately two million individuals die from respiratory cancer every year (1). Non-small cell lung cancer (NSCLC), the leading pathological type of respiratory malignancy, accounts for 80% or more of respiratory cancer deaths in both sexes (2). Chemotherapies including immune checkpoint inhibitors and molecular targeted therapies play an important role in the treatment of incurable locally advanced, metastatic, and recurrent NSCLC. When relapse occurs after receiving first-line chemotherapy, a patient who maintains a reasonable performance status usually receives second-line chemotherapy. The efficacy and safety of chemotherapy in cancer patients are usually evaluated through phase I, II, and III trials. Once a phase I trial determines the dosage by safety assessment, a phase II trial is designed to test both the safety and efficacy of the treatment in a larger sample size. The best treatment efficacy outcome is overall survival (OS) as it is easy to interpret, indicates an ultimate benefit of a patient, and is not affected by an observational bias (3). However, researchers often select other indexes such as the objective response rate (ORR) and disease control rate (DCR) based on the Response Evaluation Criteria in Solid Tumors (RECIST) defined as primary endpoints of NSCLC phase II trial (3,4). Besides, ORR may be a reasonable outcome to assess the potential anticancer activity of chemotherapy (5). The RECIST is a simple and useful tool that can be used to categorize patients with solid tumor who underwent chemotherapy into four groups: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Currently, the revised RECIST guidelines are widely used in the clinical and research settings of a variety of solid tumors (5).

Although ORR and DCR are commonly used as primary endpoints (5), it remains unclear whether ORR and DCR correctly reflect the OS in a NSCLC phase II trial evaluating a non-first-line chemotherapy. ORR might be easily affected because the small number of patients in each trial achieved complete or partial response in the phase II non-first-line setting. In this study, we aimed to evaluate the association of trial-level ORR and DCR with OS in randomized phase II NSCLC trials that evaluate second- or later-line chemotherapy. We present the following article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-1120).

Methods

Study overview

The current systematic review did not utilize a meta-analysis to aggregate data; however, this study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses as it is a reasonable method of performing a systematic review of RCTs (Table S1) (6). The protocol, UMIN000040412, has been registered on the website of the University Hospital Medical Information Network Clinical Trials Registration (7).

Study search

We systematically searched PubMed, Cochrane database, Embase, and Web of Science as of May 15, 2020 (6). The search formulas are presented elsewhere (Table S2). The reference list of all included articles was also manually checked. Two investigators independently screened the titles and abstracts and they also scrutinized the full text (HM and NH). Repeated use of the same patient in duplicated studies was prohibited. If conflicts arise between the review authors during the selection of the final study, a discussion was made to resolve the inconsistencies.

Study selection, design

We included a phase II RCT that evaluated second- and/or later-line chemotherapy for advanced, locally advanced, and recurrent NSCLC (8,9). An article had to be written as a full article, a brief report, or a conference abstract regardless of its primary end point. Non-English language reports were excluded. Randomized phase I/II trials were included. The protocol permitted a phase II/III trial when the data from phase II part could be extractable, but such a trial was not found.

Study selection, patient

Patients with a pathologically or cytologically confirmed diagnosis of locally advanced, advanced, and recurrent NSCLC who relapsed after one or more of previous chemotherapies were included. No limitation was set for age, sex, smoking history, first-line chemotherapy regimen, response to the first-line treatment, status of driver mutation, performance status, and pathological subtype of NSCLC.

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Study selection, treatment

A patient should be treated with any type of chemotherapeutic regimen including immune checkpoint inhibitors, molecular targeted therapy, cytotoxic agents, single drug regimens, and multi-drug regimens as non-first-line chemotherapy. Antibiotics and immunotherapy other than immune checkpoint inhibitors were not included because such treatment had never been considered as a standard therapy (8,9). Comparison of the same drugs (low-dose versus high-dose, weekly versus tri-weekly regimens, and chemotherapy versus placebo) was allowed. Maintenance therapy after first-line chemotherapy was not considered as a second-line treatment as it was administered in a patient who did not experience a relapse. A trial with treatment crossover after the first-line therapy was excluded because such a trial randomized a patient prior to the first-line treatment.

Assessment of the risk of bias

The quality of each RCT was assessed using the six domains of Cochrane risk of bias (10).

Outcomes

The correlation, with hazard ratio (HR) of OS (HRos), each for odds ratio (OR) of ORR (ORorr), difference of ORR (ΔORR, %), OR of DCR (ORdcr), and difference of DCR (ΔDCR, %) was evaluated. ΔORR was calculated by subtracting the ORR estimated for the second treatment arm from that estimated for the first arm. Similarly, ΔDCR was obtained. CR, PR, and SD needed to be evaluated in line with the RECIST 2000 and the revised RECIST 2009 revised guidelines (5). When an article reported that the RECIST outcome was judged by both investigator team and an independent radiographic review panel, the data of the external panel was adopted.

Data extraction

Data regarding the study characteristics, OS, ORR, DCR, and risk of bias were independently extracted by the two review investigators (HM and NH). Once the review authors extracted inconsistent data, a discussion is made to reach consensus. The first and second arms of each RCT were decided according to the description in each article. When a study randomized patients into three or more arms,

two arms with the largest number of patients were selected for our analysis. ORR and DCR were preferably determined by full analysis set or intention-to-treat analysis; thus, a denominator to yield ORR and DCR included patients whose data were not assessable by RECIST (5). Parmar's method was applied to obtain OS data from the Kaplan-Meier curves as necessary (11). We respected the authors' judgement of disease staging regardless of the updates of TNM staging system. For example, a patient with pleural effusion without metastasis might be diagnosed with stage IIIb or IV based on the trial policy.

Statistical analysis

Spearman's rank correlation coefficient (r) was calculated using GraphPad PRISM ver 7.02 (San Diego, CA, USA). When one or more cells in the two-by-two contingency used to calculate ORorr and ORdcr were null, a continuity correction with 0.5 was applied. A correlation coefficient was interpreted as follows: $|r| <0.2$, no correlation; $0.2< |r| <0.4$, weak correlation; $0.4< |r| <0.6$, moderate correlation; $0.6< |r| <0.8$, strong correlation; and $0.8< |r|$, excellent correlation. The statistical significance threshold was set at $P<0.05$. The Begg-Kendall test was carried out to assess for publication bias. The correlation was displayed on a scatter plot.

Exploratory subgroup analyses were performed by classifying studies by characteristics such as sample size and number of responders with a median as the cutoff of subgroups.

Results

Study search

Out of 1,437 articles that were identified by database search and hand searches, 73 met our inclusion criteria (Table S2). Since one article represented two independent RCTs, we analyzed 74 trials that randomized NSCLC patients for second- or later- line chemotherapy (*Figure 1*, *Table 1*, Appendix References).

Study characteristics

The study characteristics of each study are summarized in *Table 1*, and aggregated data are presented in *Table 2*. The majority of these trials were reported as full-length articles that compared two arms with clear declaration of phase
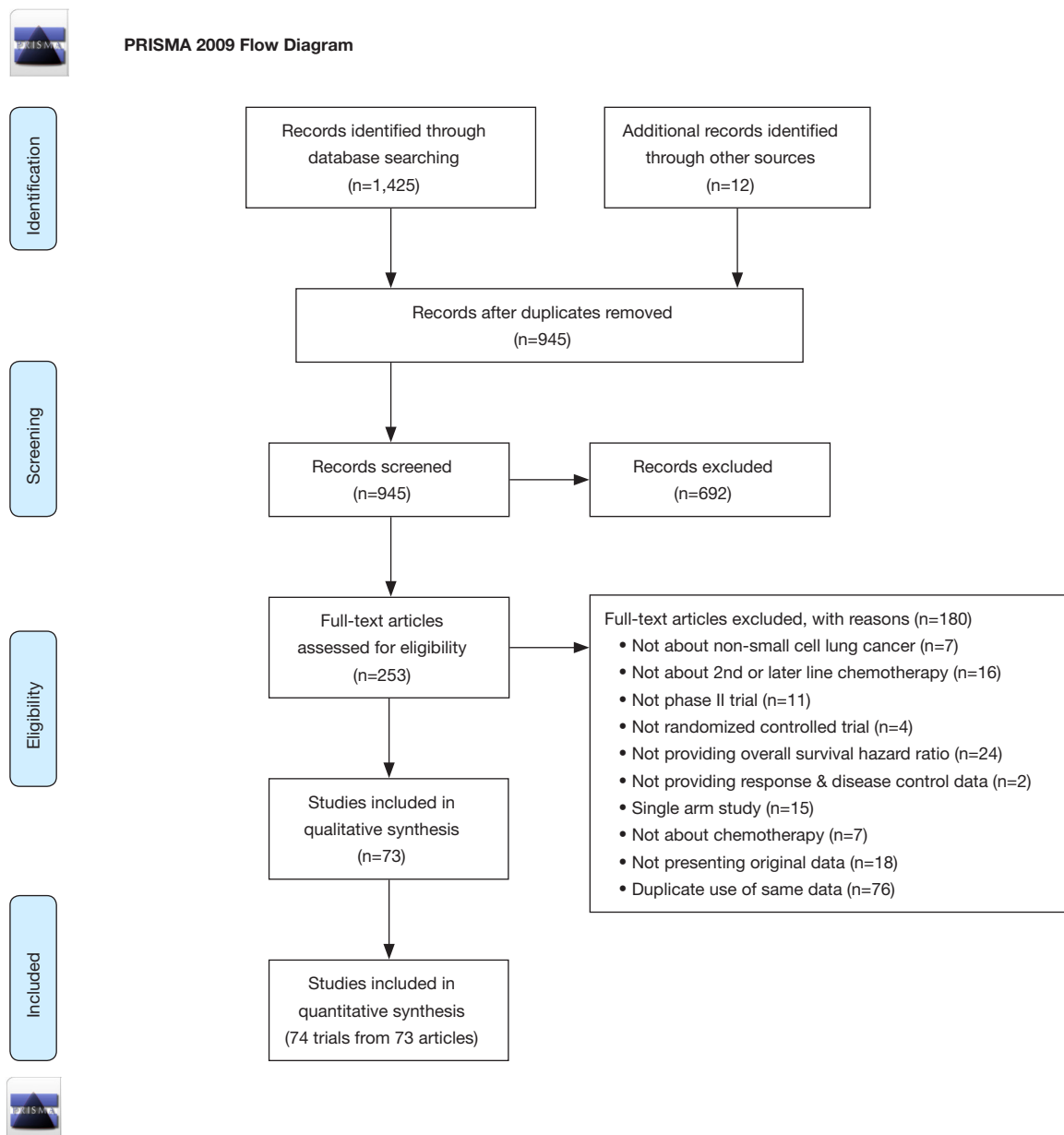
Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

II except three conference abstracts, one brief report, ten three-arm trials, two four-arm trials, and one phase Ib/II trial. These 74 trials were reported from European (N=33), North American (N=21), and Asian (N=20) countries. Thirteen (18%) and two (3%) RCTs recruited patients with adenocarcinoma/non-squamous and squamous cell carcinoma, respectively, while the other 59 (80%) RCTs randomized non-small cell lung cancer patients without specifying a pathological subtype of NSCLC (*Table 2*).

A total of 65 (88%) RCTs did not recruit patients with specific driver mutation status. The most frequently used primary endpoint was progression-free survival (PFS) (N=36, 49%) followed by ORR (N=15, 20%). Only two studies (3%) used DCR as the primary endpoint. More than two-thirds (N=51, 69%) of trials focused on second-line chemotherapy. The widely used performance status criteria were Eastern Cooperative Oncology Group (ECOG) 0-2 (N=41, 55%) and ECOG 0-1 (N=25, 34%). The median

Table 1 Characteristics of included studies

Author (year)	Country	Patho	Mutation	Stage	Line	PS	Median age	Primary endpoint	Image timing	n	High ROB domains
Aerts (2013)	Netherlands	NSC		LocAdv/Met	2	E 0–3	63	PFS (entire KMC)	q 2 cyc, q 6 w	231	3
Ardizzoni (2012) GOIRC02–2006	Italy	NSC		IIIb/IV	2	E 0–2	64	PFS (entire KMC)	q 2 cyc	239	2
Ardizzoni (2012) NVALT7	Italy	NSC		IIIb/IV	2	E 0–2	64	PFS (entire KMC)	q 2 cyc	240	2
Belvedere (2011)	UK	NSC		IIIb/IV	2	E 0–1	62	ORR	q 2 cyc	50	1
Bergqvist (2017)	Sweden	NSC		LocAdv/Met (IIIb/IV)	2–3	E 0–2	57	PFS (12w)	at 12 w	99	1
Blumenschein (2015)	USA	Adeno	KRAS mt	Met (IV)	2	E 0–1	63	PFS (entire KMC)	q 6 w	129	3
Bradbury (2018)	Canada	NSC		Adv	2	E 0–1	64	PFS (entire KMC)	q 2 cyc	152	2
Chiappori (2010)	USA	NSC		LocAdv/Met (III/IV)	2	E 0–2	61		at 4– w	160	2
Cortinovis (2008)	Italy	NSC		Met/Rec	2	E 0–1	58	ORR	q 6 w	46	3
Cufer (2006)	Slovenia	NSC		IIIb/IV	2	E 0–2	61	FACT–L	q 6 w	141	3
Dittrich (2014)	Austria	N–Sq		III/IV	2	E 0–2	62	PFS (entire KMC)	q 6 w	159	3
Dowlati (2005)	USA	NSC		IIIb/IV	2	E 0–2	61		at 2 w	42	3
Esteban (2003)	Spain	NSC		Adv	2–3	K 60–	59		q 2 cyc	71	2
Fanucchi (2006)	USA	NSC		LocAdv/Met (IIIb/IV)	2	K 70–	63	ORR	q 6 w	155	2
Fehrenbacher (2016)	USA	NSC		LocAdv/Met	2–3	E 0–1	62	OS (entire KMC)	q 6–9 w	287	3
Fukuoka (2003)	Japan	NSC		III/IV	2–3	E 0–2	60	ORR	q 4–8 w	210	0
Georgoulias (2004)	Greece	NSC		IIIb/IV	2	E 0–2	62	OS (median)	after 3 cyc	154	1
Georgoulias (2005)	Greece	NSC		IIIb/IV	2	E 0–2	62	OS (median)	after 3 cyc	147	1
Gerber (2016)	USA	N–Sq		IIIb/IV	2	E 0–2	60	ORR	q 2–3 cyc	121	1
Gervais (2005)	France	NSC		IIIb/IV	2	E 0–2	58	Safety	q 8–9 w	125	1
Gridelli (2016)	Italy	Sq		IIIb/IV/Rec	2	E 0–1	67	PFR (6m)		74	3
Groen (2013)	Netherlands	NSC		IIIb/IV	2–3	E 0–1	60	PFS (entire KMC)	q 8 w	132	0
Han (2018)	China	NSC		Met/Rec	3	E 0–2	55	PFS (entire KMC)	q 4–8 w	117	1
Heigener (2013)	Germany	NSC		IIIb/IV/Rec	2	E 0–1	63	ORR (best)	during Tx	87	3
Heist (2014)	USA	NSC		IIIb/IV	2	E 0–1	63	PFS (18w)		89	2
Herbst (2007)	USA	N–Sq		LocAdv/Met	2	E 0–2	64	PFS (entire KMC)	q 6 w	81	1
Heudobler (2019)	Germany	NSC		IIIb/IV	2–	E 0–1		PFS		37	2
Heymach (2007)	USA	NSC		IIIb/IV	2	E 0–1	60	PFS (entire KMC)	q 3–6 w	86	0

Table 1 (*continued*)

Table 1 (*continued*)

Author (year)	Country	Patho	Mutation	Stage	Line	PS	Median age	Primary endpoint	Image timing	n	High ROB domains
Ikezawa (2017)	Japan	NSC	EGFR wt	III/IV/Rec	3–4	E 0–2	65	DCR		37	2
Jones (2008)	USA	NSC		Adv	2	E 0–2	62			77	3
Juan (2015)	Spain	NSC		IIIb/IV	2	E 0–2	60	PFS (6m)	q 9 w	68	3
Kentepozidis (2017)	Greece	NSC		LocAvd/Met	2	E 0–2	60	ORR		124	3
Kim (2012)	Korea	NSC	EGFR mt	IIIb/IV/Rec	2	E 1–2	59	ORR	q 4–8 w	96	3
Kim (2016)	Korea	NSC		IIIb/IV/Rec	2–3	E 0–2	66	PFS (6m)	q 2 cyc	95	2
Kim (2017)	Korea	NSC		IV	2	E 0–2	63	PFS (3m)	q 4–8 w	160	2
Lai (2005)	Taiwan	NSC		IIIb/IV	2	E 0–2	68			50	3
Lee (2013)	Korea	N–Sq		LocAdv/Met (III/IV)	2	E 0–2	55	PFS (entire KMC)	q 6 w	162	3
Levy (2019)	Spain	NSC	EGFR wt, ALK neg	LocAdv/Met	2	E 0–1	65	PFS (entire KMC)	at 18–w	100	1
Li (2014)	China	Adeno		IIIb/IV/Rec	2	E 0–2	55	PFS (entire KMC)		123	2
Lin (2012)	China	NSC		IIIb/IV	2–	K 60–	63	TTP (entire KMC)	q 2 cyc	48	3
Liu (2015)	China	NSC		IIIb/IV	2	E 0–2	52	OS (entire KMC)		111	2
Lu (2018)	China	N–Sq		LocAdv/Met/Rec	3	E 0–1	55	PFS (entire KMC)	q 4–8 w	91	0
Manegold (2013)	Germany	NSC		IIIb/IV	2	K 70–	61	PFS (median, 1y)		71	3
Morgensztern (2018)	USA	N–Sq	EGFR wt, ALK neg	Met/Rec	2	E 0–1	65	PFS (entire KMC)		161	3
Natale (2009)	USA	NSC		LocAdv/Met (IIIb/IV)	2–3	E 0–1	62	PFS (entire KMC)	q 4 w	168	1
Natale (2014)	UK	NSC		IIIb/IV at entry	2	E 0–1	63	Tume size change		180	2
Neal (2016)	USA	N–Sq	EGFR wt	Met/Rec	2–3	E 0–2	66	PFS (entire KMC)	at any point	76	2
Nishino (2015)	Japan	N–Sq		IIIb/IV/Rec	2	E 0–1	64	PFS (entire KMC)	q 6 w	90	2
Pallis (2011)	Greece	NSC		LocAdv/Met (IIIb/IV)	2	E 0–2	64	ORR	q 7 w	153	2
Parikh (2011)	India	NSC		LocAdv/Met (IIIb/IV)	2–	E 0–1	57	OS(entire KMC)	q 7 w	100	1
Pawel (2012)	Germany	N–Sq		LocAdv/Met (IIIb/IV)	2	E 0–2	62	PFS (entire KMC)		165	2
Pectasides (2005)	Greece	NSC		Adv	2	E 0–2	58			130	3
Quoix (2004)	France	NSC		LocAdv/Adv	2	E 0–2	59	TTF	at 4–w	182	3
Ramalingam (2011)	USA	NSC		IIIb/IV	2–3	E 0–2	63	PFS (12w)	q 6 w	115	3
Ramalingam (2012)	USA	NSC		Adv	2–4	E 0–2	61	PFS (entire KMC)	q 4–8 w	188	2

Table 1 (*continued*)

Table 1 (*continued*)

Author (year)	Country	Patho	Mutation	Stage	Line	PS	Median age	Primary endpoint	Image timing	n	High ROB domains
Ready (2011)	USA	NSC		LocAvd/Met/Rec	2	E 0–2	59	PFS (entire KMC)		105	1
Reck (2011)	Germany	NSC		IIIb/IV	2–4	E 0–2	63	PFS (entire KMC), ORR	q 6 w	73	1
Robinet (2007)	France	NSC		IIIb/IV	2–4	E 0–2	59	ORR	q 3 cyc	88	1
Ross (2006)	USA	NSC	Le^y pos	Met/Rec	2–3	E 0–2	59	DCR	q 8 w	59	2
Scagliotti (2018)	Italy	Sq		IV	2–	E 0–1	64	PFS		159	2
Schiller (2010)	USA	NSC		IIIb/IV	2	E 0–1	62	ORR	q 6 w	101	2
Segawa (2010)	Japan	NSC		IIIb/IV	2	E 0–1	63	ORR	q 1 cyc	60	3
Smit (2009)	Netherlands	NSC		IIIb/IV	2	E 0–2	59	TTP (entire KMC)	q 6 w	240	3
Soria (2017)	France	NSC		LocAdv/Met	2	E 0–1	61	PFS (entire KMC)	q 6 w	169	0
Spigel (2018)	USA	NSC		IV	2–3	E 0–2	66	PFS (median, entire KMC)	q 8 w	192	1
Spigel (2011)	USA	NSC		IIIb/IV	2–3	E 0–2	65	ORR, PFS (entire KMC)		166	1
Talbot (2007)	UK	NSC		IIIb/IV	2	K 70–	59	ORR	q 2 cyc	44	1
Tan (2011)	Singapore	NSC		LocAdv/Met	2–3	E 0–2	62	PFR (16w)	q 8 w	139	2
Wachters (2005)	Netherlands	NSC		IIIb/IV	2	E 0–2	59	ORR	q 6 w	108	2
Waller (2015)	Germany	N–Sq		III/IV	2	E 0–1	59		q 8 w	80	4
Wu (2017)	China	NSC		III/IV	2	E 0–3	58	ORR		92	0
Yoh (2016)	Japan	NSC		IV	2	E 0–1	65	PFS (entire KMC)	q 6 w	157	1
Zhang (2015)	China	NSC	EGFR wt	III/IV	2	E 0–2	55	PFS (median, entire KMC)	q 12 w	88	2
Zhou (2014)	China	N–Sq	EGFR wt	IIIb/IV	2	E 0–1	57	PFS (median, entire KMC)	q 2 cyc	157	2

Patho, pathology; NSC, non-small cell; Adeno, adenocarcinoma; N-Sq, none-squamous; Sq, squamous; mt, Mutant; wt, wild type; neg, negative; pos, positive; LocAdv, locally advanced; Met, metastatic; Rec, recurrent; PS, performance status; E, Eastern Cooperative Oncology Group PS; K, Karnofsky PS; Median age, When median age was not available, mean age was used instead; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; entire KMC, entire Kaplan-Meier survival curve was evaluated using Cox model or log-rank test; TTF, time to treatment failure; TTP, time to progression; PFR, progression-free rate; m, month; w, week; cyc, cycles; FACT-L, Functional Assessment of Cancer Therapy-Lung; q, every; cyc, Cycles; n, total number of evaluated patients in two arms. high ROB domains: Six domains of Cochrane high-risk of bias was classified into High/Unclear/Low risk of bias (ROB). A number of domains with high risk of bias is presented. For example, "6" means all domains had high risk of bias.

Table 2 Study level summary statistics of 74 included studies

Publication year	2012 (2008–2016)
Pathological type	
Non-small cell	59 (80%)
Adenocarcinoma or non-squamous	13 (18%)
Squamous	2 (3%)
Driver mutation	
Not specified	65 (88%)
EGFR mutant	1 (1%)
KRAS mutant	1 (1%)
LyS positive	1 (1%)
EGFR wild type	4 (5%)
EGFR wild type and ALK negative	2 (3%)
Primary endpoint	
Objective response rate (ORR)	15 (20%)
Disease control rate	2 (3%)
Overall survival	5 (7%)
Progression-free survival (PFS)	36 (49%)
Progression-free rate	2 (3%)
Time-to-failure, time-to-progression	3 (4%)
Co-primary ORR and PFS	1 (1%)
Other (symptom, safety, tumor size change)	3 (4%)
Not specified	7 (9%)
Chemotherapy line	
2	51 (69%)
2–3	13 (18%)
2–4	3 (4%)
2-	4 (5%)
3	2 (3%)
3–4	1 (1%)
Performance status (PS)	
Eastern Cooperative Oncology Group PS 0-1	25 (34%)
Eastern Cooperative Oncology Group PS 0-2	41 (55%)
Eastern Cooperative Oncology Group PS 0-3	2 (3%)
Karnofsky PS 60-	2 (3%)
Karnofsky PS 70-	3 (4%)

Table 2 (continued)

Table 2 (continued)

Publication year	2012 (2008–2016)
Median age	62 [59–63]
N of patients in both arms	116 [82–159]
N of patients with response in both arms	13 [6–22]
N of patients with disease control in both arms	56 [36–77]

For a bivariate and a nominal variable, number of studies and percentage are presented. For a continuous variable, a median and an interquartile range are presented. Sum of percentage is not always 100% due to rounding.

number of patients in the two arms was 116 [interquartile range (IQR), 82–159]. Single-agent docetaxel was the most frequently used treatment arm (23 arms) followed by single-agent pemetrexed (14 arms) and erlotinib alone (14 arms) probably because this regimen was used as a standard second-line regimen over the years (*Table 1*) (9,12). Treatments prior to each study was inconsistent. Sixty-eight studies (92%) had at least one domain of risk of bias (*Table 1*, Table S3). The key outcomes of each trial are also presented in elsewhere (Table S4).

ORR and DCR

Most studies described the ORR and DCR data but five only reported ORR and one only reported DCR (Table S4). Among the 146 arms from 73 studies, the median ORR was 11% (IQR, 5–17), which resulted in a median number of responders (CR+PR) in each study of 13 (IQR, 6–22) patients. The median number of patients with disease control (CR+PR+SD) in the 136 arms from 68 RCTs was 56 (IQR, 36–77). The median DCR was 51%. No publication bias was found in either the ORR or DCR (Figure S1).

Correlation between ORR and OS

The Spearman's correlation between trial-level ORorr and HRos was weak (r=–0.29, 95% CI: –0.49 to –0.05, P=0.014, *Figure 2*). ΔORR also had a weak correlation with HRos (r=–0.33, 95% CI: –0.52 to –0.10, P=0.005) (Figure S2).

The exploratory subgroup analyses between ORorr and HRos suggested a prominent inter-subgroup difference in responder-based analysis. No correlation (|r|<0.2) was
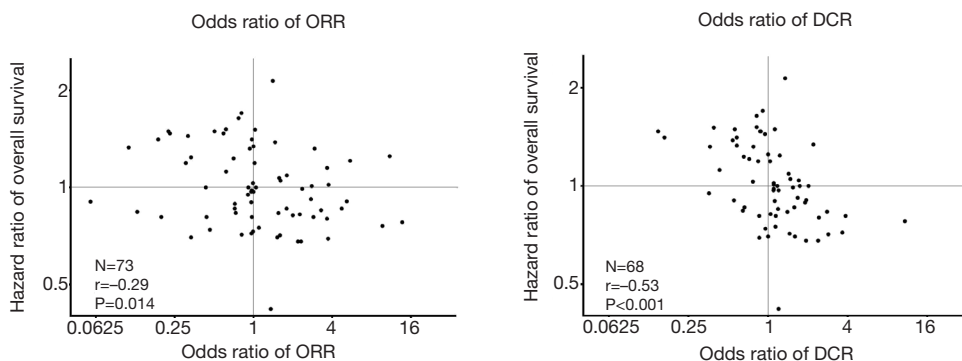
Figure 2 Trial-level surrogacy: odds ratio of objective response rate (ORR) and disease control rate (DCR). N, number of trials. r, Spearman's rank correlation coefficient. A correlation coefficient was interpreted as follows: |r| <0.2, no correlation; 0.2< |r| <0.4, weak correlation; 0.4< |r| <0.6, moderate correlation; 0.6< |r| <0.8, strong correlation; and 0.8< |r|, excellent correlation.

observed in the "responders, -10" subgroup (r=−0.15, 95% CI: −0.47 to 0.21, P=0.403, *Figure 3*) while that in the "responders, 11-" subgroup was moderate (r=−0.51, 95% CI: −0.72 to −0.22, P <0.001, *Figure 3*).

Correlation between DCR and OS

Both ORdcr (r=−0.53, 95% CI: −0.68 to −0.32, P <0.001, *Figure 2*) and ΔDCR (r=−0.52, 95% CI: −0.68 to −0.31, P<0.001, Figure S2) had a moderate rank correlation with HRos. Compared with ORorr, ORdcr had the same or higher-level correlation with HRos in any subgroup analyses (*Figure 3*).

Discussion

In the assessment of the efficacy of chemotherapy in solid malignancies, tumor shrinkage judged by ORR has traditionally been regarded as a proxy of clinical benefit and prolonged survival (13) partially because the response indicates the anticancer activity of chemotherapy (5). Thus, ORR was the preferred outcome rather than DCR in the chemotherapy trials. A total of 15 (20%) out of 74 phase II trials in our analysis adopted ORR as the primary endpoint, while only 2 (3%) selected DCR (*Table 2*). In this study, we assessed the correlation of ORR and DCR with HRos at trial level in randomized phase II trials that evaluated second- or later-line chemotherapy for NSCLC. ORdcr (r=−0.53, P<0.001) and ΔDCR (r=−0.52, P<0.001) moderately correlated with HRos; however, ORorr (r=−0.29, P=0.014) and ΔORR (r=−0.33, P=0.005) had weak correlations (*Figure 2*). If ORR and DCR capture

some patient-oriented benefits such as survival and quality of life, they can be useful study endpoints. Otherwise, the application of these endpoints might be questionable because no imaging modality offers a straightforward measurement of patient-oriented benefits (3,14-16). Even though a chemotherapy regimen with both favorable ORR and poor survival can pass the phase II trial that adopts ORR as the primary endpoint, such treatment cannot meet the primary OS endpoint of phase III trials. By contrast, regimens such as atezolizumab that lead to prolonged survival without good response should be highly recognized (17,18). Data on ORR and DCR are always simultaneously reported. Given the better trial-level association between DCR and survival, DCR seems to be a superior outcome in the phase II trial evaluating non-first-line chemotherapy for NSCLC. Although the current analysis included only RCTs, DCR may also be a reasonable outcome in a single-arm phase II trial. In addition to the better surrogacy of OS, broader applicability for patients without measurable disease is another advantage of DCR (13) because a trial that adopted ORR as the primary endpoint should recruit patients with at least one measurable lesion.

ORR is more frequently selected as the study endpoint compared with DCR (*Table 2*); however, some published studies have indicated that DCR is a more accurate surrogate of OS. Lara *et al.* gathered data of nearly 1,000 NSCLC patients from three RCTs for platinum-based chemotherapy (13). Although patients with response, CR+PR, led longer survival with a HR of 0.61, maintaining at least stable disease, CR+PR+SD, was a stronger predictor of OS with a HR of 0.45. Half of the trials in our review adopted PFS as the primary endpoint (*Table 2*). PFS
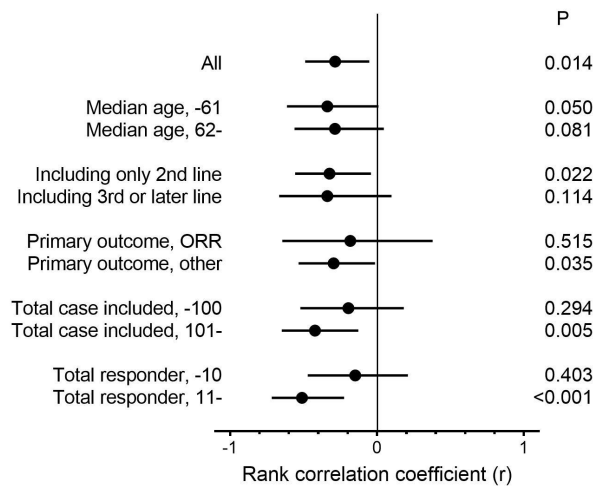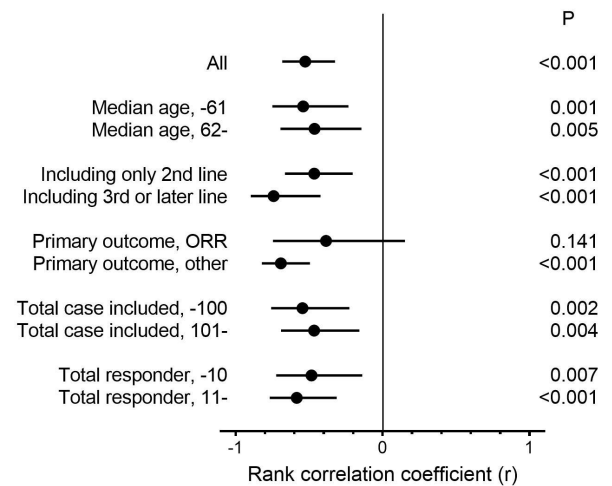
Figure 3 Subgroup analysis of trial-level correlations with overall survival. (A) Subgroup analysis of trial-level correlations between objective response rate and hazard ratio of overall survival. (B) Subgroup analysis of trial-level correlations between disease control rate and hazard ratio of overall survival. r: Spearman's rank correlation coefficient. A correlation coefficient was interpreted as follows: $|r| <0.2$, no correlation; $0.2< |r| <0.4$, weak correlation; $0.4< |r| <0.6$, moderate correlation; $0.6< |r| <0.8$, strong correlation; and $0.8< |r|$, excellent correlation. Responder is a sum of complete response and partial response.

resembles DCR since response is not necessary, while ORR and response duration require at least PR. Mandrekar *et al.* analyzed the individual data of 284 patients with NSCLC enrolled in phase II trials (4). They concluded that PFS at 12 weeks, a similar metric to DCR, more accurately predicted subsequent survival compared with tumor response. The methodology of our study evaluating trial-level association was different from that of previous studies (4,13). However, our conclusion was consistent with the conclusions of these preceding analyses. The better surrogacy of DCR was confirmed for solid tumors other than NSCLC. Lara *et al.* retrospectively analyzed the data of 263 extensive small-cell lung cancer patients from phase II trials in 2016 (19). In this setting, DCR (HR 0.45) was a more prominent surrogate of OS than ORR (HR 0.74). DCR was also more tightly linked to the trial-level OS of advanced colorectal cancer in the first-line setting than ORR (DCR, r=0.975, R^2 =0.889; ORR, r=0.866, R^2 =0.484).

We would like to consider why ORR did not reflect survival in a phase II RCT of non-first-line chemotherapy for NSCLC. First, ORR overrates "aggressive" chemotherapy, such as a high-dose regimen and a combination treatment. Aggressive chemotherapeutic treatment damages both tumor cells and normal cells,

which results in good ORR and deteriorated organ function. Once ORR is chosen as the primary endpoint, a researcher might be motivated to use excessively aggressive chemotherapies. Choosing an aggressive regimen as second-line chemotherapy is especially risky because toxicity caused by first-line treatment already affected the patient's organ function. The optimal endpoint might be inconsistent between the first-line and the later-line treatments. Our previous analysis indicated that the ORR of the first-line NSCLC chemotherapy better predicts OS than DCR (3). A chemo-naive patient can endure an aggressive chemotherapy, and a chemo-naive tumor lesion is usually more responsive to an anti-tumor medication. Selecting an aggressive regimen with capable anticancer activity that yields high ORR is a feasible choice for first-line RCT but not a reasonable strategy for a later-line trial. The second possibility is that ORR might be unreliable due the small number of responders in the second- or latter-line phase II setting (19). In the explanatory subgroup analysis, no correlation was observed between ORR and OS in the "responder-10" subgroup, while moderate correlation was found in the "responder 11-" subgroup (*Figure 3*). DCR may be a reliable outcome because of the higher event frequency.

ORR is a popular endpoint in phase II non-first-line trials for solid tumors other than NSCLC. Nonetheless, we suspect that DCR more accurately reflects OS in these trials because patients are often exhausted after receiving first-line treatment and there are usually few responders in the non-first-line phase II trial regardless of malignancy type. The trial-level correlation between ORR and OS in phase II second-line trials should be evaluated for other malignancies such as colorectal cancer because the ORR of the second-line chemotherapy for these types of cancers is as low as that for NSCLC (20,21).

Even though DCR better reflected OS than ORR, the surrogacy of DCR was still unsatisfactory. Late PFS, such as 6-month PFS, might be a more accurate surrogate of OS than DCR in studies with a longer follow-up duration. OS data directly demonstrate the patient's benefit, although it requires further longer follow-up to aggregate the number of events. In principle, longer follow-up is not recommended in a phase II trial as a phase II trial is just a screening process to select a regimen that will be assessed in a phase III trial. There is always a tradeoff between promptness and outcome value when selecting a phase II trial endpoint.

This study has some limitations. First, although OS is the gold standard endpoint of an advanced NSCLC trial, OS may be easily affected by later-line treatment. Nonetheless, this issue did not make our analysis unreliable because successive chemotherapy after the non-first-line treatment cannot largely provide survival benefit. Second, the current consensus recommends that NSCLC patients should be treated based on pathological subtype and driver mutation status (8,9); however, most of the included studies did not mention these data. Third, we analyzed studies adopted cytotoxic agent, MMT, ICI, and combination of them collectively. Fourth, PFS-related analysis could not be performed due to inconsistent PFS data format from the trials including 2-month PFS, median PFS, hazard ratio of PFS, P value from log-rank test. Fifth, most of studies recruited patients with inconsistent prior treatments.

In conclusion, we systematically searched for randomized phase II trials that evaluated second- or later-line chemotherapy for NSCLC. ORR is a more frequently used as a primary endpoint than DCR (*Table 2*). According to 68 trials, DCR had moderate trial-level correlations (OR$_{dcr}$ r=−0.53, ΔDCR r=−0.52) with HR$_{os}$ while OR$_{orr}$ and ΔORR had weak correlations (OR$_{orr}$ r=−0.29, ΔORR r=−0.33). The subgroup analysis suggested that the rarity of responders in the phase II non-first-line setting may lead to the poor association between ORR and HR$_{os}$. Since data on ORR and DCR are available simultaneously, we recommend using DCR instead of ORR as the primary endpoint in a randomized phase II trial evaluating second- or later-line chemotherapy for NSCLC.

Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr-20-1120). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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