REVIEW ARTICLE

Efficacy of targeted therapy in patients with HER2-positive non-small cell lung cancer: A systematic review and meta-analysis ● ● ●

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Anti-human epidermal growth factor receptor 2 (HER2) therapy is an effective treatment for HER2-positive gastric and breast malignancies. However, the efficacy of HER2-targeted therapy in non-small cell lung cancer (NSCLC) patients with HER2 alterations remains controversial. We searched studies on HER2-targeted therapy in NSCLC patients that reported objective response rate (ORR), disease control rate (DCR) and progressionfree survival (PFS) published from database inception to 30 May 2021. A total of 32 trials involving 958 patients were included. The ORRs of HER2-TKIs targeted therapy, humanised monoclonal antibody, trastuzumab-based treatment and antibody-drug conjugate (ADC) (T-DM1) were 22% (95% CI 11–31), 23% (95% CI 20–65), 26% (95% CI 14–39) and 16% (95% CI _6–37), while that of ADC (DS-8201) was 60% (95% CI 35–85). The DCRs of these groups were 59% (95% CI 49–69), 39% (95% CI _9–88), 63% (95% CI 37–89), 31% (95% CI 4–58) and 87% (95% CI 62–112), respectively. In the subgroup analysis, numerically higher ORRs and DCRs were observed in the poziotinib (38%; 75%) and pyrotinib (35%; 83%) groups. The median PFSs of these groups were 5.51 months, 3.09 months, 4.61 months, 2.65 months and 12.04 months, respectively. HER2-targeted therapy can be considered an acceptable treatment strategy for NSCLC patients with HER2 alterations. In particular, ADC (DS-8201), pyrotinib and poziotinib demonstrated promising anti-tumour activity in HER2-positive NSCLC.

KEYWORDS
biomarkers, ERBB2, HER2, meta-analysis, non-small cell lung cancer, review, targeted therapy

1 | INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers.[1] NSCLC is one of the most genomically diverse cancers, making it very difficult to treat. For all NSCLC patients who have the adenocarcinoma subtype, testing for alterations in **epidermal growth factor receptor** (EGFR), **mesenchymal epithelial transition factor** (MET), **b-raf proto-oncogene** (BRAF), **anaplastic lymphoma kinase** (ALK), **ROS proto-oncogene 1** (ROS1), **ret proto-oncogene** (RET) and **neurotrophic tyrosine receptor kinase (NTRK)** is recommended by the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines.[2,3]

Human epidermal growth factor receptor 2 (HER2) is a member of the ERBB receptor tyrosine kinase family.[4,5] HER2 mutations are commonly found in never-smokers and adenocarcinoma.[6] HER2 alterations, including gene amplification, mutations and overexpression, have also been found in many other cancers and are associated with poor clinical prognoses.[7–10] The frequency of HER2 alterations varies according to the detection methods used, tumour biology, and heterogeneity. In lung cancer, 2–6% HER2 mutations have been detected by polymerase chain reaction (PCR) or next-generation sequencing (NGS);[11–13] 2–20% HER2 amplification was detected by NGS or fluorescence in situ hybridisation (FISH);[13–15] and 2–38% HER2 protein was detected by immunohistochemistry (IHC),[14–18] but IHC 3+ was found only in 2–6% of patients.[14–19] These three HER2 alterations are correlated with the clinical efficacy of HER2-targeted therapy.[14,15,19–21] Thus, HER2 alterations are considered as independent biomarkers for HER2-targeted therapy.

Current HER2-targeted medicines, including tyrosine kinase inhibitors (TKIs), monoclonal antibodies and antibody-drug conjugates (ADC), have been developed for breast and gastric adenocarcinoma patients with HER2 amplification and protein overexpression. To allow clarity and consistency in pharmacology, the nomenclature of HER2-targeted drugs conforms to the IUPHAR/BPS Guide to PHARMACOLOGY.[4,5] TKIs, including afatinib, lapatinib, poziotinib, pyrotinib, neratinib, dacomitinib, mobocertinib, tucatinib and tarloxotinib, bind to the intracellular domain of HER2. On the other hand, monoclonal antibodies and ADC, such as pertuzumab, trastuzumab, trastuzumab deruxtecan and ado-trastuzumab emtansine, bind to the extracellular domain of HER2. There is no association between HER2 overexpression, mutations and amplification,[22] which makes evaluating the efficacy of HER2-targeted medicines difficult. Nonetheless, evaluating the efficacy of such therapies is important in optimising cancer treatment. This study aimed to investigate the efficacy of targeted therapy in HER2-positive NSCLC patients.

2 | METHODS

2.1 | Search strategy

We searched multiple databases, including Web of Science, Embase, Medline and Cochrane, for trials using the terms "{[HER2(Title/Abstract)] OR [ERRB (Title/Abstract)]} AND {[non-small cell lung cancer (Title/Abstract)] OR [NSCLC (Title/Abstract)]}" with no restrictions in the publication language or period. We searched for reports published from database inception to May 30, 2021. We also retrieved the references of all the included studies to minimise error and bias. Keywords in related conference articles were also used to retrieve the studies. The results were recorded according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] This study was registered with PROSPERO (number CRD42021257794). The following clinical trials were eligible: (1) randomised controlled trials (RCTs), single-arm and cohort studies; (2) trials conducted in HER2-positive patients with NSCLC; and (3) trials reporting data on the objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS). Patients were excluded if they had received chemotherapy, surgery, radiotherapy anti-HER2 therapy, or other targeted therapies within four weeks before the first dose of the medication of interest. Patients admitted for other medical problems were excluded. Trials on pregnant women, reviews, editorials, case reports, congress articles and articles unrelated to our theme were omitted. The outcome measures were the ORR, DCR and PFS in patients with NSCLC treated with HER2-targeted therapy.

2.2 | Study selection

Hong-Xia Wu and Kai-Quan Zhuo performed the study selection. First, the abstract and titles were examined, and duplicates and unavailable full-text articles were discarded. Next, qualified trials were selected by screening the full texts. The reasons for exclusion were documented. A third reviewer (Ke Wang) was consulted if no consensus was reached.

2.3 | Data extraction

Hong-Xia Wu and Kai-Quan Zhuo independently extracted and recorded the demographic characteristics and outcome measures of each study in a standard form advised by Cochrane.[24] The corresponding authors were emailed if any information was missing.

2.4 | Quality assessment

The Cochrane Risk of Bias tool was used to assess the quality of the studies.[24] The quality of non-randomised studies was evaluated using the Newcastle–Ottawa Scale (NOS).[25] Two investigators (Hong-Xia Wu and Kai-Quan Zhuo) conducted the quality assessment. Any disagreements were resolved by a third investigator (Ke Wang).

2.5 | Quantitative data synthesis

A random-effects model and the inverse variance heterogeneity method were used to analyse PFS and heterogeneity (I^2). The Mantel–Haenszel method and a random-effects model were used to analyse the ORR, DCR and I^2. Analyses were performed using STATA (Version 16; Stata Corp., College Station, TX, USA). The outcomes are expressed in forest plots. Dichotomous and continuous variables are shown as odds ratios (OR) and median values, respectively. $I^2 > 50\%$ was considered significant for the heterogeneity test. A fixed-effects model was used in cases of no heterogeneity; otherwise, a random-effects model was used.

3 | RESULTS

3.1 | Study selection process

A total of 116 studies were obtained by screening the abstracts. After removing duplicate records, 54 studies remained for subsequent screening. After excluding irrelevant documents, 42 studies were selected by qualification evaluation and full-text reviews. Finally, 32 studies[9,26–56] were assessed in this meta-analysis. The details of the study selection process are presented in Figure 1.

3.2 | Characteristics of clinical trials

Thirty-two studies involving 958 patients were included in this study. Details of the study characteristics and outcomes are presented in Table 1. Among the 32 studies, there were 4 RCTs, 11 cohort studies, 17 single-arm studies, 1 phase I study and 15 phase II studies. Some trials have a relatively small population, but HER2 genomic alterations have emerged as distinct oncogenic drivers. Thus, few tests fulfilled our meta-analysis inclusion criteria. The ORR and DCR of single-arm RCTs were used and combined with data from cohort and single-arm trials.

3.3 | Quality assessment and heterogeneity

The assessment of study quality is detailed in Supplementary Figures S1 and S2 and Supplementary Table S1. No studies were excluded because of low quality. Significant statistical heterogeneity was found in the following outcomes: PFS of HER2 TKI-targeted therapy ($I^2 = 93.3\%$, $P = .000$) (Figure 6); ORR, DCR, and PFS of the humanised monoclonal antibody group ($I^2 = 71.6\%$, $P = .029$; $I^2 = 78.5\%$, $P = .009$; $I^2 = 93.1\%$, $P = .000$) (Figures 3, 5 and 7); and DCR and PFS of the trastuzumab-based treatment group ($I^2 = 66.1\%$, $P = .012$; $I^2 = 81.6\%$, $P = .001$) (Figures 5 and 7). A sensitivity analysis was used to assess the stability of the results (Supplementary Figures S3, S7, S11 and S15). One study was removed at a time, and the summary median/OR value and overall effect were recalculated. The absence of a statistically significant reversal of the overall effects (I^2) confirmed the stability of the results.

3.4 | Outcome measures

3.4.1 | ORR

The overall ORRs of HER2-TKIs targeted therapy, humanised monoclonal antibody, trastuzumab-based treatment and ADC (T-DM1)
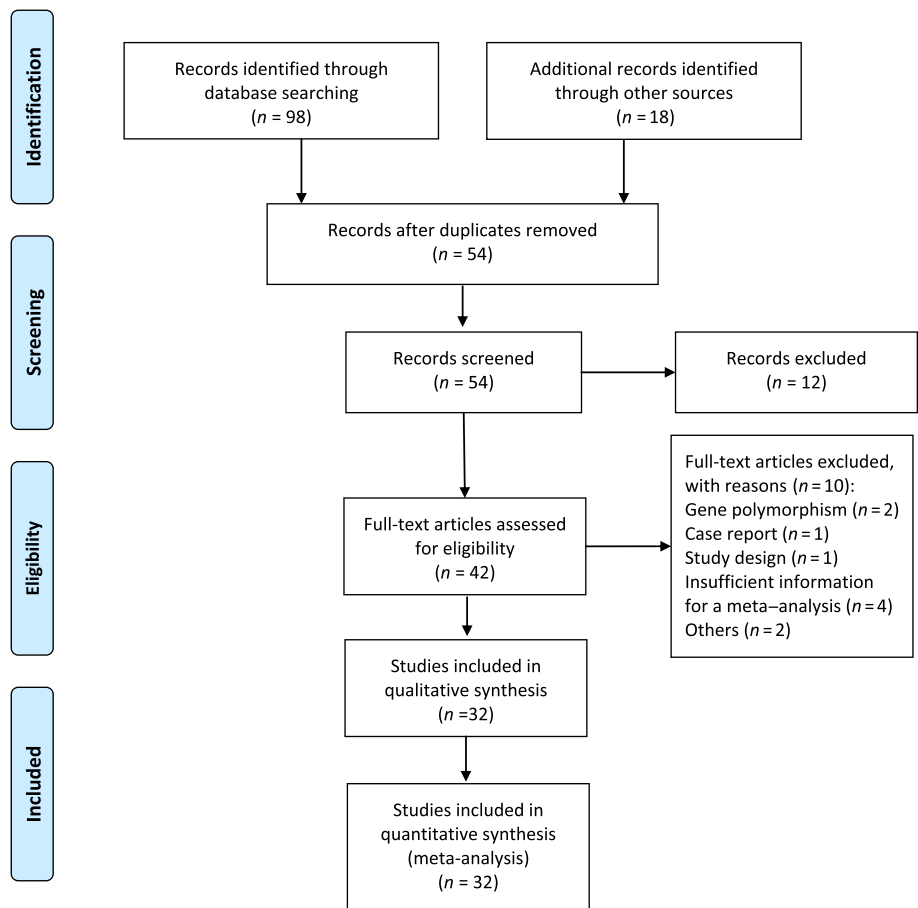

FIGURE 1 Flowchart diagram of selected searches for inclusion in meta-analysis

TABLE 1 Characteristics of included studies

Classification of treatment	First author	Year	Registration number	Study design	Treatment	Population	Gene type
HER2-TKIs therapy	Mazières et al.[26]	2013	NM	Retrospective cohort study	Afatinib, Lapatinib, Masatinib	NSCLC	HER2 exon-20 insertion
	Mazières et al.[27]	2015	NM	Retrospective cohort study	Neratinib, Lapatinib, Afatinib	NSCLC	HER2 exon-20 insertion
	De Grève et al. cohort 1[28]	2015	EudraCT: 2008–001546-67	Prospective cohort study	Afatinib	Lung adenocarcinoma	HER2 mutation
	De Grève et al. cohort 2[28]	2015	EudraCT: 2008–001546-67	Prospective cohort study	Afatinib plus Paclitaxel	Lung adenocarcinoma	HER2 mutation
	Kris et al.[29]	2015	NCT0114286	Phase II study	Dacomitinib	HER2-mutant or amplified tumours	HER2 mutation or amplification
	Song et al.[30]	2016	NM	Retrospective multicentre single-arm study	Afatinib	NSCLC	HER2 exon-20 insertion
	Lai et al.[31]	2017	NM	Retrospective study	Afatinib	Lung adenocarcinoma	HER2mutation
	Gandhi et al. cohort 1[32]	2017	NCT01827267	Randomised controlled trial	Neratinib	Lung cancers	HER2 mutation
	Gandhi et al. cohort 2[32]	2017	NCT01827267	Randomised controlled trial	Neratinib + Temsirolimus	Lung cancers	HER2 mutation
	Oh et al.[33]	2018	NCT02979821	Retrospective study	Poziotinib or Afatinib	Lung adenocarcinoma	HER2 mutation
	Zhao et al.[34]	2018	NM	Retrospective single-arm study	Afatinib	NSCLC	HER2 mutation
	Peters et al.[35]	2018	NM	Retrospective single-arm study	Afatinib	Lung adenocarcinoma	HER2 exon 20 mutation
	Liu et al.[36]	2018	NM	Retrospective single-arm study	Afatinib	Lung cancers	HER2 exon 20 insertion
	Robichaux et al.[37]	2018	NCT03066206	Single-arm phase II trial	Poziotinib	NSCLC	HER2 exon 20 mutation
	Hyman et al.[38]	2018	NCT01953926	Single-arm phase II trial	Neratinib	AdvancedNSCLC	HER2 mutation
	Dziadziuszko et al.[39]	2019	NCT02369484	Single-arm phase II trial	Afatinib	NSCLC	HER2 exon 20 mutation
	Robichaux et al.[9]	2019	NCT03066206	Single-arm phase II trial	Poziotinib	NSCLC	HER2 mutation
	Wang et al.[40]	2019	NCT02535507	Single-arm phase II study	Pyrotinib	NSCLC	HER2 exon 20 insertion
	Zhou et al.[41]	2020	NM	Single-arm phase II study	Pyrotinib	Lung adenocarcinoma	HER2 mutation
	Zhou et al.[42]	2020	NM	Retrospective cohort study	Afatinib or Pyrotinib	Advanced lung cancers	HER2 mutation
	Liu et al.[43]	2020	NCT03805841	Cohort study	Tarloxotinib	NSCLC	HER2 mutation
	Socinski et al.[44]	2020	NCT03318939	Cohort phase II study	Poziotinib	NSCLC	HER2 exon-20 insertion

TABLE 1 (Continued)

Classification of treatment	First author	Year	Registration number	Study design	Treatment	Population	Gene type
Humanised monoclonal antibody	Lara et al.[45]	2003	NM	Randomised controlled trial	Trastuzumab	NSCLC	HER2 protein overexpression or HER2 amplification
	Herbst et al.[46]	2007	NM	Multicentre phase II study	Pertuzumab	Advanced or metastatic NSCLC	HER2 mutation
	Mazières et al.[27]	2015	NM	Retrospective cohort study	Trastuzumab, T-DM1	NSCLC	HER2 exon-20 insertion
Trastuzumab-based therapy	Lara et al.[45]	2003	NM	Randomised controlled trial	Trastuzumab plus Docetaxel	Advanced, recurrent, or metastatic NSCLC	HER2 mutation
	Langer et al.[47]	2004	ECOG 2598	Phase II trial	Trastuzumab plus Carboplatin and Paclitaxel	NSCLC	HER2 overexpression
	Gatzemeier et al.[48]	2004	NM	Randomised phase II study	Gemcitabine-cisplatin plus Trastuzumab	NSCLC	HER2-positive
	Mazières et al.[26]	2013	NM	Retrospective cohort study	Trastuzumab in combination with chemotherapy	NSCLC	HER2 exon-20 insertion
	Hainsworth et al.[49]	2018	NCT02091141	Phase II study	Trastuzumab plus Pertuzumab	NSCLC	HER2 mutation, amplification, or overexpression
	de Langen et al.[50]	2018	NCT02226757	Single-arm phase II study	Trastuzumab and Paclitaxel	Non-squamous NSCLC	HER2 overexpression
	Zhou et al.[42]	2020	NM	Retrospective cohort study	Trastuzumab-based therapy	Advanced lung cancers	HER2 mutation
	Li et al.[51]	2021	NCT01953926	Phase II study	Neratinib plus Trastuzumab	NSCLC	HER2 mutation
Antibody drug conjugate, DS-8201	Smit et al.[52]	2020	NCT03505710	Multicentre phase II study	Trastuzumab deruxtecan (DS-8201)	NSCLC	HER2 mutation
	Tsurutani et al.[53]	2020	NCT02564900	Phase I study	Trastuzumab deruxtecan (DS-8201)	NSCLC	HER2 overexpression, or mutation
Antibody drug conjugate, T-DM1	Hotta et al.[54]	2017	NM	Randomised controlled trial	Trastuzumab emtansine (T-DM1)	Adenocarcinomas	HER2 overexpression
	Li et al.[55]	2018	NCT02675829	Phase II basket trial	Ado-trastuzumab emtansine	Lung cancers	HER2 mutation, overexpression or amplification
	Peters et al.[56]	2019	NCT02289833	Prospective multicentre single-arm study	Trastuzumab Emtansine (T-DM1)	NSCLC	HER2 overexpression
Total		32 studies					

Abbreviations: NM, not mentioned; NSCLC, non-small cell lung carcinoma; ORR, objective response rate; PFS, progression-free survival; DCR, disease control rate; ARMS-PCR: amplification refractory mutation system-polymerase chain reaction; PCR, polymerase chain reaction; NGS, next generation sequencing; FISH, fluorescent in-situ hybridisation; CISH, chromogenic in-situ hybridisation; ICH, immunohistochemistry; ELISA, enzyme-linked immunosorbent assay.

TABLE 1 (Continued)

Classification of treatment	Number of patients	Outcomes	Country	Male (%)	Age, median (range)	Never-smokers (%)	Molecular diagnostics	Tumour stage
HER2-TKIs therapy	4	ORR, DCR	France, Germany, Switzerland and Spain	31	60.4 (31–86)	52.3	Direct sequencing or FISH	I–IV
	29	ORR, DCR, PFS	France, Switzerland, Spain, Italy, Poland, Portugal and the Netherlands	37.6	61 (30–87)	60.4	PCR or NGS	I–IV
	7	ORR, DCR	Belgium, Spain, United Kingdom and United States	0	62 (50–79)	71	FISH	IIIB/IV
	3	ORR, DCR	Belgium, Spain, United Kingdom and United States	0	62 (50–79)	71	FISH	IIIB/IV
	30	ORR, DCR	United States, China and Japan	50	58.7 (37–74)	60	FISH or sequencing by multiplexed testing	IIIB-IV
	4	DCR, PFS	China	33.3	60 (39–70)	81	NGS	I–IV
	23	ORR, DCR	Europe, Australia and North America	59	63 (40–84)	67	PCR or NGS	IV or recurrent
	17	ORR, DCR	NM	32	66	60	NM	IIIB/IV
	43	ORR, DCR	NM	32	66	60	NM	IIIB/IV
	7	ORR, DCR	Korea	0	48.5 (55–61)	100	NGS	I–IV
	23	ORR, PFS	China	NM	NM	NM	NGS	NM
	16	ORR,DCR	Switzerland, Israel, Taiwan, Slovenia, Austria and United States	43	55 (39–93)	NM	NM	IV
	19	ORR, DCR	China	37	57 (41–86)	NM	NGS	NM
	11	ORR, DCR	United States	NM	57.6 (52–66)	NM	PCR-based NGS	NM
	26	ORR, DCR	United States, Spain and Australia	34.6	62 (46–74)	NM	DNA sequencing	NM
	13	ORR, DCR, PFS	Poland, Netherlands, Greece, Germany, Ireland Switzerland and Spain	30.8	59 (39–82)	61.5	NM	IIIB/IV
	12	ORR, DCR	United States	16.7	59.5 (56.5–61)	NM	NM	NM
	15	ORR, DCR, PFS	China	53	58 (42–78)	67	ADx HER2 Mutation Detection Kit, ARMS, NGS, or DNA direct sequencing	NM
	60	ORR, DCR	China	45	57 (40–72)	71.7	NGS or ADx HER2 Mutation Detection Kit	IIIB/IV
	25	ORR, DCR, PFS	China	45	56 (32–76)	73	ARMS-PCR or PCR	IIIB/IV
	9	ORR, DCR	United States, China and Canada	NM	NM	NM	NM	NM
	74	ORR, DCR, PFS	United States, Belgium, Canada, France, Israel, Italy, Netherlands and Spain	36	60	66	NM	NM

TABLE 1 (Continued)

Classification of treatment	Number of patients	Outcomes	Country	Male (%)	Age, median (range)	Never-smokers (%)	Molecular diagnostics	Tumour stage
Humanised monoclonal antibody	4	ORR, DCR	United States	61.5	66 (42–82)	NM	IHC, ELISA and FISH	NM
	43	ORR, DCR, PFS	United States	60	62 (33–79)	NM	IHC	NM
	58	ORR, DCR, PFS	France, Switzerland, Spain, Italy, Poland, Portugal and the Netherlands	37.6	61 (30–87)	60.4	PCR or NGS	I-IV
Trastuzumab-based therapy	13	ORR, DCR	United States	61.5	66 (42–82)	NM	IHC	NM
	53	ORR, DCR, PFS	United States	50.9	59 (52–65)	NM	IHC	IIIB/IV, recurrent
	51	ORR, DCR, PFS	United States	65.3	58 (35–76)	NM	IHC, FISH or ELISA	IB, IIIB/IV
	15	ORR, DCR, PFS	France, Germany, Switzerland and Spain	31	60.4 (31–86)	52.3	Direct sequencing Or FISH	I-IV
	30	ORR, DCR	United States and United Kingdom	51	62 (23–86)	NM	IHC, FISH, CISH, or NGS	NM
	24	ORR, DCR, PFS	The Netherlands	29	68 (40–82)	NM	IHC	IV
	3	ORR, DCR	China	45	56 (32–76)	73	ARMS-PCR, and PCR	IIIB/IV
	52	ORR, DCR	United States, France, Spain and Israel	34	57.5 (62–66)	NM	NM	NM
Antibody drug conjugate, DS-8201	42	ORR, DCR, PFS	United States, France, Japan, Netherlands and Spain	35.7	60 (34–83)	NM	NM	Unresectable and/or metastatic
	18	ORR, DCR, PFS	Japan and United States	27.8	58 (23–83)	NM	IHC or NGS	NM
Antibody drug conjugate, T-DM1	15	ORR, DCR, PFS	Japan	47	67 (45–77)	67	IHC and FISH	IV/recurrence
	18	ORR, PFS	United States	28	64 (47–74)	39	NGS, IHC or FISH	IV/recurrence
	49	ORR, PFS	Switzerland, United States, Poland, Spain, Germany and Italy	59.2	61 (36–80)	20.4	IHC	Advanced, recurrent, or metastatic
Total	958							

Abbreviations: NM, not mentioned; NSCLC, non-small cell lung carcinoma; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; ARMS-PCR: amplification refractory mutation system-polymerase chain reaction; PCR, polymerase chain reaction; NGS, next generation sequencing; FISH, fluorescent in-situ hybridisation; CISH, chromogenic in-situ hybridisation; ICH, immunohistochemistry; ELISA, enzyme-linked immunosorbent assay.

were 22% (95% CI 11–31), 23% (95% CI 20–65), 26% (95% CI 14–39) and 16% (95% CI −6–37), while that of ADC (DS-8201) was 60% (95% CI 35–85). When restricted to the subgroup, numerically higher ORRs were observed in the pyrotinib (ORR 35%, 95% CI 12–57) and poziotinib (ORR 38%, 95% CI 19–57) groups. The details are presented in Figures 2 and 3.

3.4.2 | DCR

The overall DCRs of HER2-TKIs targeted therapy, humanised monoclonal antibody, trastuzumab-based treatment and ADC (T-DM1) were 59% (95% CI 49–69), 39% (95% CI −9–88), 63% (95% CI 37–89) and 31% (95% CI 4–58), respectively, while that of ADC (DS-8201) was 87% (95% CI 62–112). When restricted to the subgroup, numerically higher DCRs were observed in the pyrotinib (83%, 95% CI 60–105) and poziotinib (75%, 95% CI 56–94) groups. The details are presented in Figures 4 and 5.

3.4.3 | PFS

The overall median PFSs of HER2-TKIs therapy, humanised monoclonal antibody, trastuzumab-based treatment, ADC (DS-8201) and ADC (T-DM1) were 5.51 months (95% CI 3.48–7.54), 3.09 months (95% CI −0.11–6.30), 4.61 months (95% CI 2.09–7.13), 12.04 months (95% CI 9.68–14.40) and 2.65 months (95% CI 1.64–3.66), respectively. The details are presented in Figures 6 and 7.

3.4.4 | Publication bias

Publication bias was evaluated using funnel plots, Egger's test and Begg's test (Supplementary Figures S4–S6, S8–S10, S12–S14, S16–S18). The trim-and-fill method was used if publication bias was suspected. No publication bias was found in the studies.
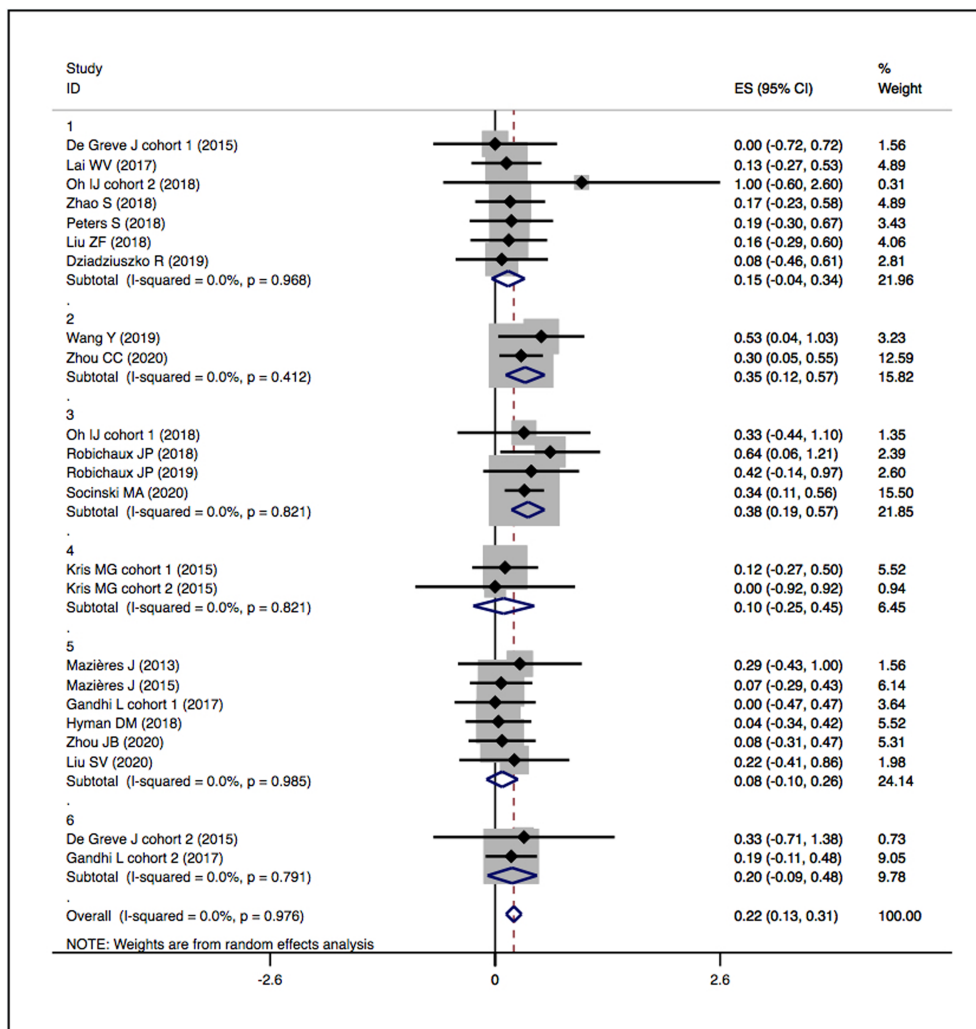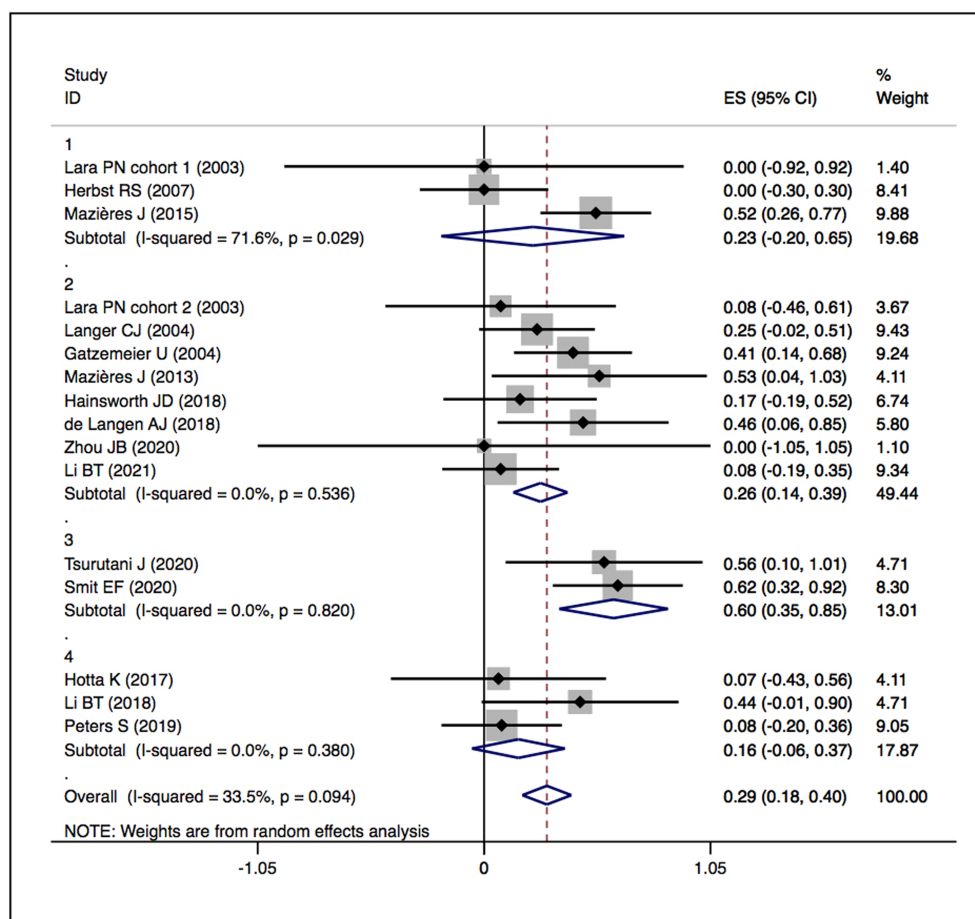

FIGURE 2 Forest plot of cumulative incidence of ORR among patients treated with HER2-TKIs targeted therapy

FIGURE 3 Forest plot of cumulative incidence of ORR among patients treated with HER2-targeted therapy


4 | DISCUSSION

In our meta-analysis, numerically higher response rates were observed in the poziotinib (ORR 37%; DCR 71%) and pyrotinib (ORR 35%; DCR 83%) groups in the subgroup analysis of HER2-TKIs therapy. Poziotinib is a new oral, irreversible inhibitor of EGFR/HER4/HER2.[57] The molecular structure of poziotinib is smaller and more flexible than that of second- and third-generation inhibitors.[37] Robichaux et al.,[9] Oh et al.,[33] Robichaux et al.[37] and Socinski et al.[44] discussed the efficacy of poziotinib in NSCLC patients with HER2 mutations. Cohort C2 of the phase II study ZENITH20 conducted by Socinski et al.[44] evaluated the efficacy of poziotinib in NSCLC patients with HER2 alterations. This cohort was comprised of 90 patients pre-treated with HER2 exon 20 insertions. The ORR, DCR and median PFS were 35.1% (74 evaluable patients), 70% and 5.5 months, respectively. In cohort 1 of the study performed by Oh et al.,[33] ORR and DCR were 33% and 83%, respectively, in HER2 mutant lung adenocarcinoma. The survey conducted by Robichaux et al.[37] showed an ORR of 64% and DCR of 91% for poziotinib in NSCLC patients with HER2 mutation. The recommended dose of poziotinib is 16 mg daily, but 55% of the patients received a dosage reduction due to skin rash and diarrhoea. In a subsequent study, Robichaux et al.[9] reported an ORR of 42% and a DCR of 83% in NSCLC patients with HER2 exon 20 mutation.

The survey conducted by Oh et al.[33] included patients with tumour stages I–IV, and all patients were female and non-smokers. However, the other three studies did not detail the status of smoking and the patients' tumour stage.

Pyrotinib is an oral, irreversible pan-HER TKI inhibitor of HER2.[40,58] Pyrotinib was first applied in HER2-positive breast cancer patients and obtained encouraging results.[59] An in vitro cell proliferation assay,[40] in which plasma concentrations of afatinib and pyrotinib were obtained from NSCLC patients with HER2 exon 20 mutations in two previous studies,[59,60] showed that the inhibition of cell growth was more robust in the pyrotinib group. A phase II study of pre-treated NSCLC patients with HER2 exon 20 mutation showed a 53.3% partial response rate, 20.0% stable disease rate and a median PFS of 6.4 months.[40] Gao et al.[61] published a multicentre phase II study focusing on pre-treated NSCLC patients with HER2 insertion ($n = 60$), which showed an ORR of 31.7% and a median PFS of 6.8 months. In the same study, patients with a history of other HER2-targeted treatments or brain metastases were excluded.[61] In our analysis, Wang et al.[40] and Zhou et al.[41] detailed the efficacy of pyrotinib in NSCLC patients with HER2 mutations. Wang et al.[40] conducted a phase II study of pyrotinib in NSCLC patients with HER2 exon 20 insertion ($n = 15$). They reported an ORR of 53%, a DCR of 73% and a median PFS of 6.4 months (95% CI 1.60–11.20). However, Wang et al. did not detail the tumour stage nor the proportion of
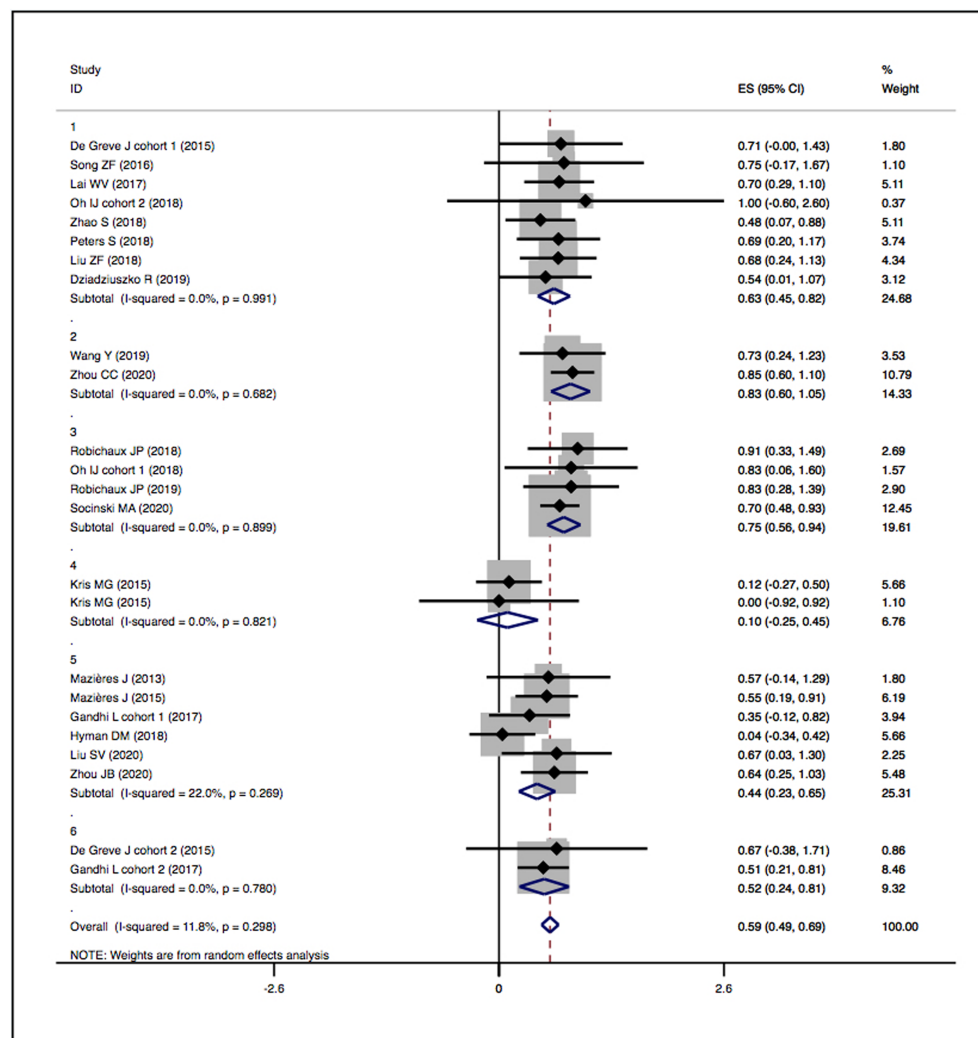
enrolled patients with each stage. In addition, pyrotinib showed a significantly more promising anti-tumour effect than afatinib in vitro ($P = .0038$) and a significantly stronger growth inhibition of organoids than afatinib ($P = .0471$) and T-DM1 ($P = .0138$) in the patient-derived xenograft (PDX) model. On the other hand, Zhou et al.[41] included 60 patients with HER2-mutant lung adenocarcinoma of the tumour stage IIIB or IV, who had a history of platinum-based chemotherapy. In their study, pyrotinib showed promising anti-tumour activity (ORR of 30%; DCR of 85%; median PFS of 6.9 months) and acceptable safety. In these two studies by Wang et al. and Zhou et al., all enrolled patients were diagnosed with lung adenocarcinoma, and never-smokers accounted for 67% and 71.17%, respectively. These results are consistent with those of previous studies. Male patients accounted for 53% and 45% of the participants, respectively, suggesting that molecular testing should not be restricted to females. Other concomitant mutations in the study by Zhou et al. may affect the efficacy of HER2-targeted therapy.[41] It is important to note that these two studies lacked a control arm and had relatively small sample sizes. Nonetheless, pyrotinib showed numerically greater anti-tumour potential than chemotherapy or other licensed HER2-targeted drugs (afatinib and T-DM1) in patients with HER2 mutations. The

multicentre phase II trial, which tested afatinib in 13 NSCLC patients with HER2 mutations pre-treated with platinum-based therapy, with a median PFS of 15.9 weeks and overall survival (OS) of 56 weeks, did not show the expected efficacy.[39]

Trastuzumab is a monoclonal humanised antibody that binds to the HER2 receptor.[62] Trastuzumab is the standard therapy for HER2-positive gastric and breast cancers and is also being examined for other HER2-positive cancers.[63] Three studies were included in the humanised monoclonal antibody group in our analysis. The overall ORR, DCR and median PFS of humanised monoclonal antibody were 23%, 39% and 3.09 months, respectively. Lara et al.[45] found no response to trastuzumab; Herbst et al.[46] reported a DCR of 19% and a median PFS of 1.92 months; and Mazières et al.[27] suggested an ORR of 52%, DCR of 76% and a median PFS of 4.8 months. In the study by Mazières et al., 57 patients were treated with trastuzumab, but one patient had T-DM1.[27] Eight studies were included in the trastuzumab-based therapy group. A phase II trial evaluated 53 NSCLC patients with HER2 alterations. In patients with IHC 3+, the chemotherapy plus trastuzumab therapy group had a longer OS than the chemotherapy group.[47] In a randomised phase II study including patients with HER2 alterations,

FIGURE 5 Forest plot of cumulative incidence of DCR among patients treated with HER2-targeted therapy
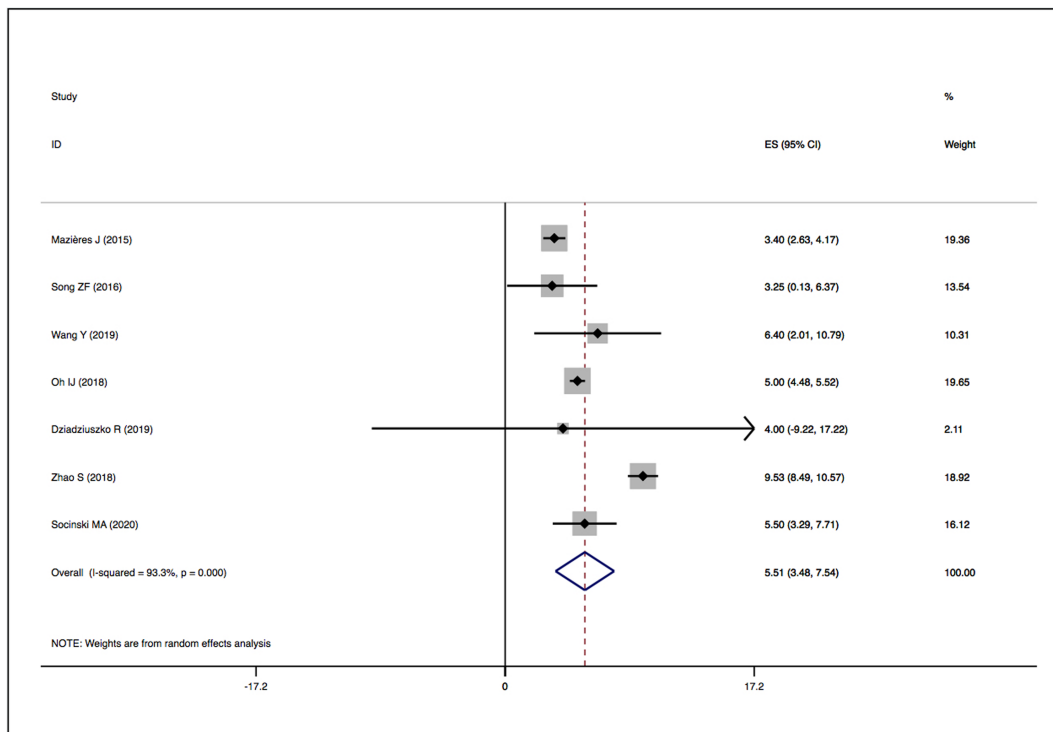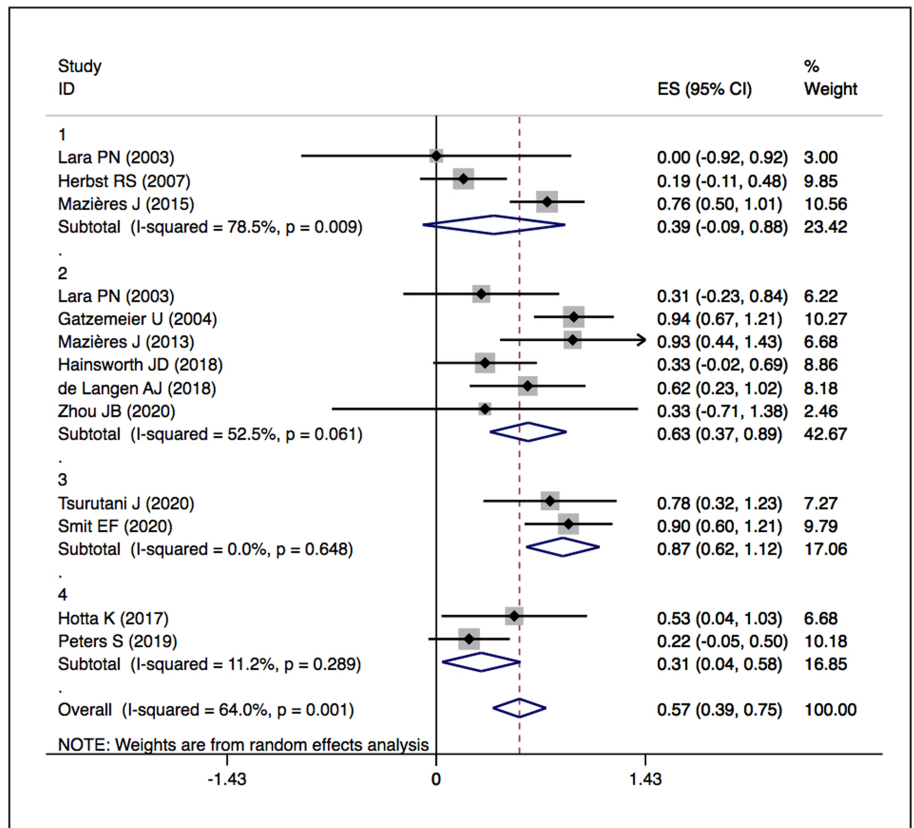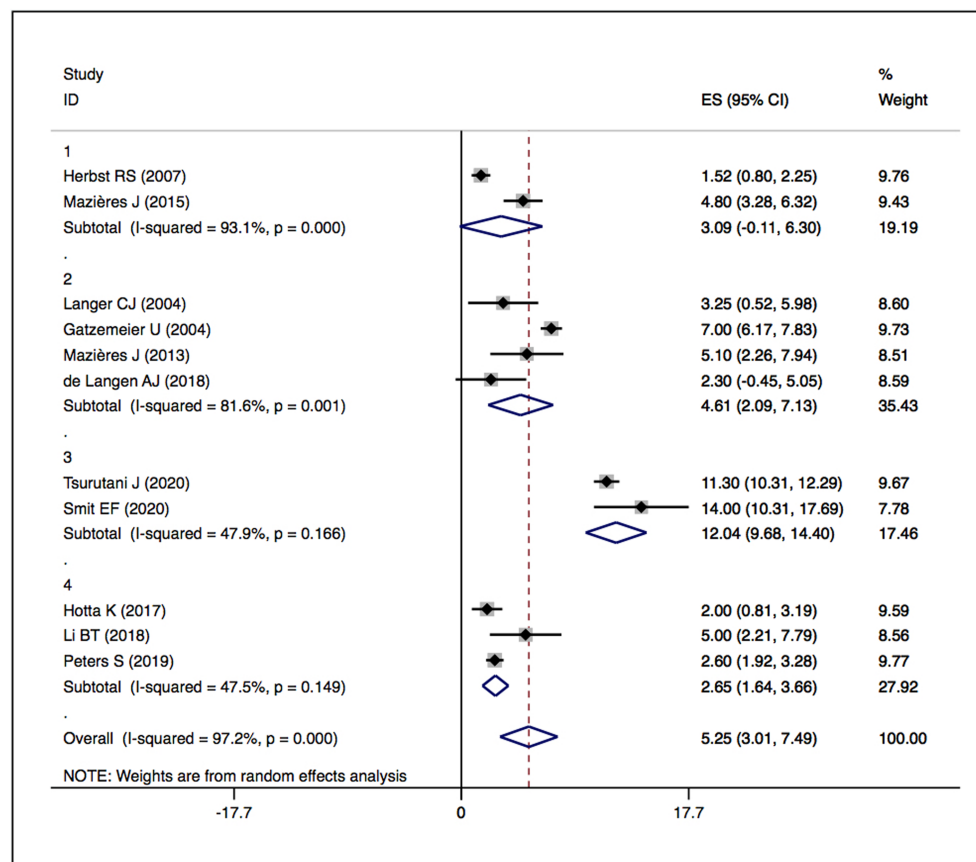

FIGURE 6 Forest plot of PFS among patients treated with HER2-TKIs targeted therapy

FIGURE 7 Forest plot of PFS among patients treated with HER2-targeted therapy

51 patients were treated with trastuzumab plus gemcitabine–cisplatin, and 50 patients were treated with gemcitabine–cisplatin alone. There was no significant difference between the two groups: ORR 36% vs 41% and a median PFS of 6.1 months vs 7 months. Although ORR (83%) and median PFS (8.5 months) seemed comparatively good in the HER2 IHC 3+ trastuzumab-based group, the subgroup (n = 6) did not provide convincing information.[48] A phase II study including 13 patients with IHC 2+ or 3+ HER2 alterations after platinum-based chemotherapy demonstrated that one patient had a partial response in the docetaxel alone group (n = 9), but none of the patients responded to the trastuzumab arm. The overall outcomes followed by combination therapy showed a partial response rate of 8% and a stable disease rate of 23%. Estimated event-free survival and OS were 4.3 months and 5.7 months, respectively.[45] Overall, the results suggested that the efficacy of trastuzumab-based therapy was similar to or better than that of chemotherapy alone. In contrast, trastuzumab showed no response in a phase II study of pre-treated NSCLC patients with HER2 alterations.[64]

Ado-trastuzumab emtansine, also known as T-DM1, is a HER2-targeted antibody-toxin conjugate that is made up of trastuzumab and the potent cytotoxic agent DM1.[65] T-DM1 has a 3:4 chemotherapy drug-to-antibody ratio. Ado-trastuzumab emtansine is advocated as a treatment for NSCLC patients with HER2 mutations according to the NCCN guidelines.[3] In a phase II study, 55% of patients with HER2 exon 20 mutations responded to T-DM1

therapy.[55] However, another phase II study (n = 15) showed limited activity.[54]

Trastuzumab deruxtecan, also known as T-DXd or DS-8201, is an ADC consisting of a direct HER2-targeting antibody, trastuzumab, and a cytotoxic topoisomerase inhibitor, exatecan derivative.[66–68] Its mechanism of action differs from that of other ADCs.[69] Trastuzumab deruxtecan has an 8:4 chemotherapy drug-to-antibody ratio, which improves its efficacy.[67,68] Furthermore, trastuzumab deruxtecan has been reported to exert anti-tumour immune effects.[70] Altogether, trastuzumab deruxtecan is designed to improve the characteristics of prior ADCs. In May 2020, trastuzumab deruxtecan was approved by the US Food and Drug Administration (FDA) as a breakthrough therapy for NSCLC patients with HER2 mutations after platinum-based treatment failure.[71] The World Conference on Lung Cancer (WCLC) 2020 reported the activity of trastuzumab deruxtecan in patients with HER2 overexpression.[72] A cohort of a phase I study enrolling NSCLC patients with HER2 overexpression or mutations had no encouraging results.[73] However, interstitial lung disease has been reported in patients treated with DS-8201.[74] In a phase I trial, the ORR of HER2-positive NSCLC patients was 72.7% (n = 11), whereas the median PFS was 11.3 months. The phase II trial DESTINY-Lung01,[52] which included 90 NSCLC patients with HER2 mutations, reported an ORR of 61.9%, a DCR of 90.5% and an estimated median PFS of 14 months.

There are no published randomised controlled trials on poziotinib, pyrotinib or trastuzumab deruxtecan in patients with HER2-positive

NSCLC. Therefore, we could not directly compare the efficacy of poziotinib, pyrotinib or trastuzumab deruxtecan with chemotherapy. However, through indirect comparison with other targeted therapies, we can deduce that the trastuzumab deruxtecan, poziotinib and pyrotinib treatment is superior to chemotherapy.

The definition of "HER2-positive NSCLC" is insufficient to describe the differences in the complexity of HER2 alterations. Indeed, the failure of many clinical studies focusing on HER2-targeted therapy may be due to these complex alterations.[39,54,64] A multicentre phase II study is currently recruiting advanced NSCLC patients with HER2 overexpression (cohort 1) or mutation (cohort 2).[75] Distinguishing between HER2 mutation and overexpression, as was done in these two cohorts, may help provide a better understanding of the influence of such alterations.

This study had several advantages. First, it is a comprehensive analysis of the efficacy of targeted therapy in HER2-positive NSCLC patients. Additionally, the studies included were of high quality. However, the limitations of this study must also be considered. First, most of the included studies were single-arm or cohort trials. Because HER2-positive cancer results from a relatively rare genetic alteration, related clinical research is fewer. Nonetheless, nearly half of the investigations consist of clinical research on new drugs. As a result, the studies included in the analysis are considered to be of relatively high quality. Second, the tumour stage and treatment lines were different in the patients included in the studies. A proportion of patients may have other concurrent gene mutations. Third, there may be differences in the exact treatment used in each study. Therefore, we considered drug classification as the grouping principle for analysis. Finally, different detection methods for HER2 alterations may influence the results. These methods are all recommended by the current guidelines, but the sensitivity and specificity of the different detection methods vary. With the enlargement of sample size and the advancement of research, subgroup analysis according to the different detection methods may be performed in the future. Nevertheless, this conclusion has a certain value and significance; but further research is warranted.

5 | CONCLUSION

HER2-targeted therapy can be considered an acceptable treatment strategy for NSCLC patients with HER2 alterations. In particular, ADC (DS-8201), pyrotinib and poziotinib have demonstrated promising anti-tumour activity in HER2-positive NSCLC. However, further trials are required to explore new therapeutic strategies.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.[76]

OPEN RESEARCH BADGES

This article has earned Open Data, Open Materials and Preregistered Research Design badges. Data, materials and the preregistered design and analysis plan are available at https://www.crd.york.ac.uk/PROSPERO/#recordDetails.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Wu H-X, Zhuo K-Q, Wang K. Efficacy of targeted therapy in patients with HER2-positive non-small cell lung cancer: A systematic review and meta-analysis. *Br J Clin Pharmacol*. 2022;88(5):2019-2034. doi:10.1111/bcp.15155