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Poziotinib in non-small-cell lung cancer patients with HER2 exon 20 mutations

A pooled analysis of randomized clinical trials

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Abstract

Background: Non-small-cell lung cancer (NSCLC) harboring human epidermal growth factor receptor 2 (*HER2*) exon 20 mutant occurs in 3% of NSCLCs. Targeted agents for this population remain an unmet need. In this analysis, we pooled-analyzed the efficacy and safety of poziotinib, a novel tyrosine kinase inhibitor, in *HER2* exon 20 mutant NSCLC.

Methods: PubMed, Embase, Web of Science, and Cochrane CENTRAL databases were systematically searched on March 9, 2022. The primary endpoints were objective response rate (ORR) and disease control rate. The secondary endpoint was treatment-related adverse events.

Results: Three prospective clinical trials, involving 126 patients, were identified. The pooled ORR and disease control rate of poziotinib in *HER2* exon 20 mutant NSCLC were 27% (95% CI, 19–35) and 72% (95% CI, 64–80), respectively. Patients with G778_P780dupGSP had the highest ORR (88%; 95% CI, 33–100; n = 12), followed by Y772_A775dupYVMA (20%; 95% CI, 12–30; n = 88) and G776delinsVC (19%; 95% CI, 0–50; n = 13). The most common grade 3 to 4 treatment-related adverse events were skin rash (36%), diarrhea (23%), and oral mucositis (13%).

Conclusion: Poziotinib demonstrates moderate antitumor activity in previously treated *HER2* exon 20 mutant NSCLC patients with a manageable safety profile. In addition, different subgroup mutations show various benefits of poziotinib treatment. Large-scale and multiarm clinical trials are warranted to confirm a suitable population and therapeutic strategies.

Abbreviations: DCR = disease control rate, HER2 = human epidermal growth factor receptor 2, NSCLC = non-small-cell lung cancer, ORR = objective response rate, PFS = progression-free survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses, T-DXd = trastuzumab deruxtecan, TRAE = treatment-related adverse events.

Keywords: HER2 exon 20 mutant, non-small-cell lung cancer, pooled analysis, poziotinib

1. Introduction

Currently, the standard of care for non-small-cell lung cancer (NSCLC) patients with human epidermal growth factor receptor 2 (*HER2*) mutations is chemotherapy with or without immunotherapy.[1,2]

In the National Comprehensive Cancer Network guideline for NSCLC, ado-trastuzumab emtansine and trastuzumab deruxtecan (T-DXd) have been suggested as treatment options for patients with *HER2* mutation-positive metastatic NSCLC.[3] In a study of ado-trastuzumab emtansine, the partial response rate was 44%, and no patients stopped treatment due to toxicity or death.[4] In a phase 2 trial of T-DXd (DESTINY-Lung01 trial), the results showed a 55% objective response rate (ORR) in *HER2*-mutated NSCLC patients; the median progression-free survival (PFS) and median overall survival were 8.2 months and 17.8 months, respectively.[5] Accordingly, anti-HER2 therapy could be an effective therapeutic strategy for *HER2* exon 20 mutant NSCLC.

Poziotinib is a novel, irreversible, and covalent tyrosine kinase inhibitor that is small and flexible. Since the exon 20 mutant could sterically hinder the binding of drug-binding pocket and third-generation inhibitors, poziotinib overcomes this hindrance.[6] Although poziotinib is currently only available at the stage of clinical trial, the regimen showed an ORR of approximately 27% in advanced NSCLC patients harboring *HER2* mutations, which was similar to the efficacy of trastuzumab plus pertuzumab plus docetaxel combination therapy (29%).[7–9] Additionally, different *HER2* mutation types, including Y772_A775dupYVMA, G778_P780dupGSP, and G776delinsVC, displayed different therapeutic responses.

Therefore, to better understand the application of poziotinib in patients with *HER2* exon 20 mutant NSCLC and provide more useful information for clinicians and future explorations, we comprehensively synthesized the benefits and risks of poziotinib in published prospective clinical trials.

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The authors declare that they have no competing interests.

The datasets generated during and/or analyzed during the current study are publicly available.

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2. Methods

This study was conducted according to the preferred reporting items for systematic reviews and Meta-analyses guideline.[10] The data used in the analysis were not original raw data but were based on published clinical studies with ethical approval. Therefore, ethical approval was not necessary.

2.1. Search strategy

We performed a comprehensive search in PubMed, Embase, Web of Science, and Cochrane CENTRAL of Controlled Trials databases. The search terms included: (non small cell lung cancer) AND (epidermal growth factor receptor OR EGFR OR human epidermal growth factor 2 OR HER2 OR HER-2 OR Erb-B2 Receptor Tyrosine Kinase 2 OR ERBB2) AND (Exon 20) AND (Poziotinib OR HM781-36B OR NOV120101) on March 9, 2022. References of relevant published clinical trials and review articles were searched for additional eligible studies.

The inclusion criteria were as follows: NSCLC patients with *HER2* exon 20 mutations were eligible; patients were treated with poziotinib; data on responses and treatment-related adverse events (TRAEs) were available; prospective studies. B.W. and B.K. independently performed the literature search. 2 of us (B.W. and G.L.) conducted the study selection. Discrepancies were resolved through consensus.

2.2. Outcome measures and data extraction

The primary outcomes were ORR and disease control rate (DCR). The secondary outcome was the incidence of TRAEs.

Data extraction was conducted by B.W. and B.K. independently and reviewed by G.L. Data regarding the 1st author, sample size, study design, proportion of female, dosing schedule, survival outcomes, responses, and number of TRAEs were collected.

2.3. Statistical analysis

R Studio (version 1.4.1717, R Foundation for Statistical Computing) was used to perform the statistical analyses. The "meta" package was used to conduct the fixed effect and random-effects meta-analyses for heterogeneity (I^2 and τ).[11] A random-effects model was selected when I^2 was > 50%. Otherwise, a fixed-effects model was used. Pooled proportions were estimated via the metaprop function in the "meta" package, applying a logit transformation and continuity correction of 0.5 and other default settings. Publication bias was assessed using funnel plots.

3. Results

3.1. Eligible studies and characteristics

A literature search identified 137 relevant records. 50 duplicate records were exlcuded. 59 full articles were remained for further assessment after title and abstract screening. Another 56 articles were excluded due to conference abstracts (n = 24), reviews (n = 16), case reports (n = 4), news/comments/letters (n = 3), basic researches (n = 3), protocols (n = 3), duplicated data (n = 2), and retrospective study (n = 1). Finally, 3 prospective clinical trials involving 126 patients were enrolled (Fig. 1).[7,8,12]

Table 1 depicts the patients and study characteristics. All eligible studies were open-label, phase 2 trials and published between 2018 and 2022. 68% of patients were female and 98% were adenocarcinoma. *HER2* mutation types comprised G776 > VC, A775_G776insYVMA, E812K, Y772_A775dupYVMA, G778_P780dupGSP, and G776delinsVC. Two trials reported median PFS and duration of response (DoR). The median PFS was 5.5 months and the median DoR was nearly 5.0 months.

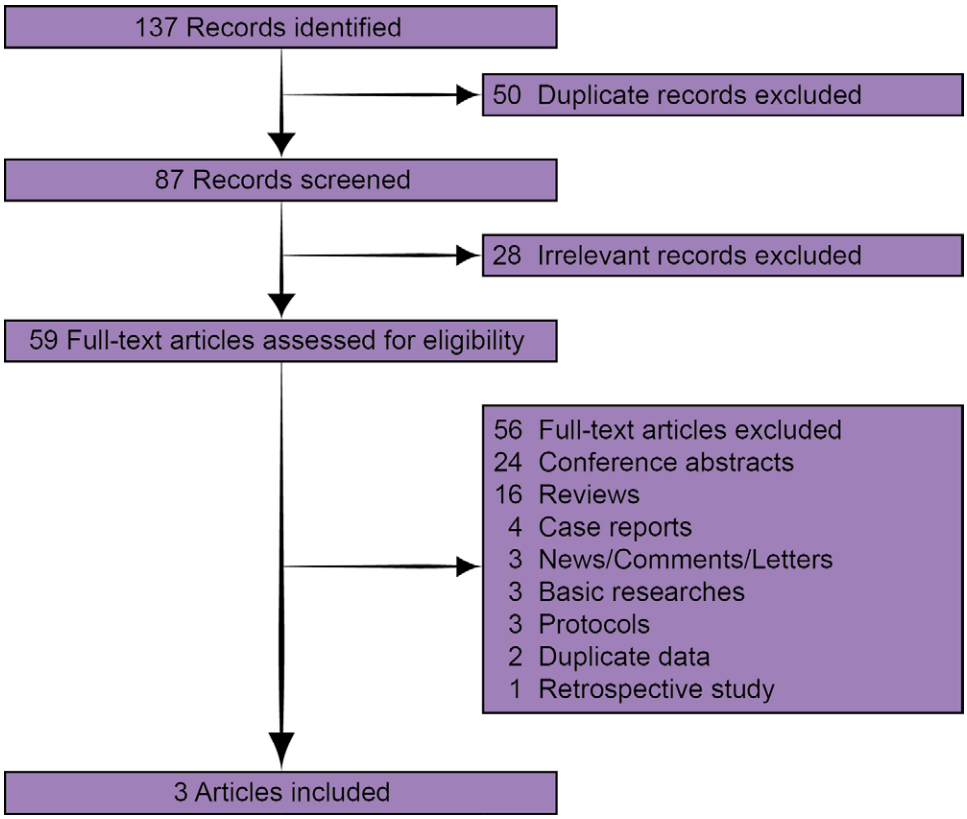

Figure 1. Flow diagram of the analysis.

Table 1

Patients and study characteristics in the analysis.

Study	Year of Publication	Design	Trial number	Sample Size	Female	Median age (years, range)	Histology-adenocarcinoma	Histology-squamous cell carcinoma	Never smoker	HER2 Mutation Type	Median number of lines of prior therapies (range)	Median PFS	Median DoR
In-Jae Oh	2018	A multi-center, open-label, single-arm, phase 2 trial	NCT02979821	6	100%	N/A	100%	0	N/A	G776 > VC (n = 2) A775_G776insYVMA (n = 3) E812K (n = 1)	N/A	N/A	N/A
Yasir Y. Elamin	2022	A single-center, open-label, single-arm, investigator-initiated phase 2 trial.	NCT03066206	30	73%	60 (47–73)	100%	0	83%	Y772_A775dupYVMA (n = 23) G778_P780dupGSP (n = 5) G776delinsVC (n = 2)	2 (0–6)	5.5 months (95% CI, 4.0–7.0)	5.0 months (95% CI, 4.0–NE)
Xiuning Le	2022	A multicenter, open-label, phase 2 study-cohort 2	NCT03318939	90	64%	60 (25–86)	97%	3%	66%	Y772_A755dupYVMA (n = 65) G778_P780dupGSP (n = 7) G776delinsVC (n = 11) Other mutant (n = 7)	2 (1–6)	5.5 months (95% CI, 3.9–5.8)	5.1 months (95% CI, 4.2–5.5)

DoR = duration of response, HER2 = human epidermal growth factor receptor 2, N/A = not estimable, PFS = progression-free survival.

4. Responses

Data of ORR and DCR were available from all enrolled patients (Fig. 2).[7,8,12] The pooled ORR and DCR were 27% (95% CI, 19-35; Heterogeneity: $I^2 = 0\%$, $P = .92$) and 72% (95% CI, 64-80; Heterogeneity: $I^2 = 0\%$, $P = .85$), respectively.

In addition, 3 subtypes of *HER2* exon 20 mutations were analyzed (Fig. 3).[7,8] In the Y772_A775dupYVMA subgroup (n = 88 patients), the integrated ORR was 20% (95% CI, 12-30; Heterogeneity: $I^2 = 0\%$, $P = .81$). 12 patients enrolled in the G778_P780dupGSP subgroup had an ORR of 88% (95% CI, 33-100; Heterogeneity: $I^2 = 71\%$, $P = .06$). For the 13 patients with G776delinsVC mutation, the integrated ORR was 19% (95% CI, 0-50; Heterogeneity: $I^2 = 0\%$, $P = .45$).

4.1. Treatment-related adverse events

A comprehensive list of the incidences of all grade and grade 3 to 4 diarrhea, skin rash, oral mucositis, paronychia, dry skin, nausea, alopecia, pruritus, vomiting, and weight loss is provided in Tables 2 and 3.

The most common all grade TRAE was diarrhea (82%; 95% CI, 74–89), followed by skin rash (74%; 95% CI, 42–97), oral mucositis (68%; 95% CI, 40–79), paronychia (53%; 95% CI, 22–82), and dry skin (46%; 95% CI, 17–77) (Table 2).

The most common grade 3 to 4 TRAEs (top 5) were skin rash (36%; 95% CI, 15–60), diarrhea (23%; 95% CI, 15–31), oral mucositis (13%; 95% CI, 3–29), paronychia (7%; 95% CI, 0–35), and pruritus (3%; 95% CI, 0–7) (Table 3).

4.2. Publication bias

Figure 4 showed the funnel plots of ORR and DCR, and no publication bias was found in the analyses.

5. Discussion

In this pooled analysis, poziotinib resulted in 27% ORR and 72% DCR in NSCLC patients with *HER2* exon 20 mutation. The most common all grade and grade 3 to 4 TRAEs were diarrhea and skin rash, respectively. Based on our results, poziotinib exhibited moderate efficacy in *HER2* exon 20 mutant NSCLC. One important reason is that only two participants received poziotinib as a first-line therapy and most of the participants had been previously treated with chemotherapy, immunotherapy, or other HER2-targeted therapy.

In cohort 4 of the ZENITH20 trial, 48 newly diagnosed NSCLC patients with *HER2* exon 20 mutations treated with poziotinib showed meaningful effects with an ORR of 44% and a DCR of 75%.[13] Accordingly, patients might benefit more from first-line poziotinib therapy. A retrospective study reported the responses to poziotinib in 8 *HER2* exon 20 mutant NSCLC patients in the real world.[14] Four patients experienced a partial response, and 3 experienced stable disease with an ORR of 50% and a DCR of 88%. Nevertheless, the study did not describe the line of poziotinib therapy, and its efficacy might require further confirmation owing to the small sample size. Therefore, a clinical trial for a single agent of poziotinib in *HER2* exon 20 mutant NSCLC at the 1st line setting is needed to confirm our deduction.

Subsequently, we found that the mutation types in each study were different. Whether different mutation types respond differently to poziotinib treatment remains unclear. In the enrolled trials, at least six *HER2* exon 20 mutation types were recorded. Three types of patients were eligible for subgroup analysis. The G778_P780dupGSP group showed the highest ORR (88%). Considering that the number of patients was only 12, we suggest that future detection can focus on *HER2* exon 20 mutation types in the poziotinib treatment.

Dose reduction during the poziotinib treatment is another issue that deserves our attention. 86% of patients reduced

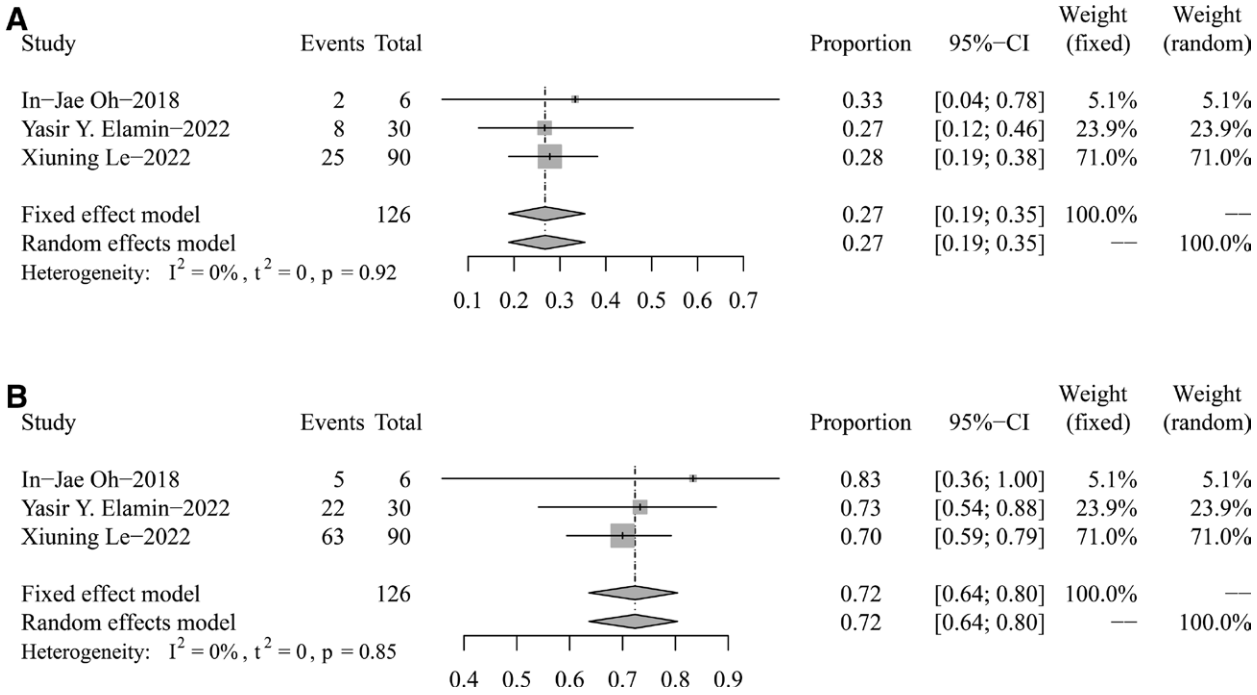

Figure 2. Forest plots of the objective response rate (A) and disease control rate (B) of poziotinib in treating *HER2* exon 20 mutant non-small-cell lung cancer. HER2 = human epidermal growth factor receptor 2.

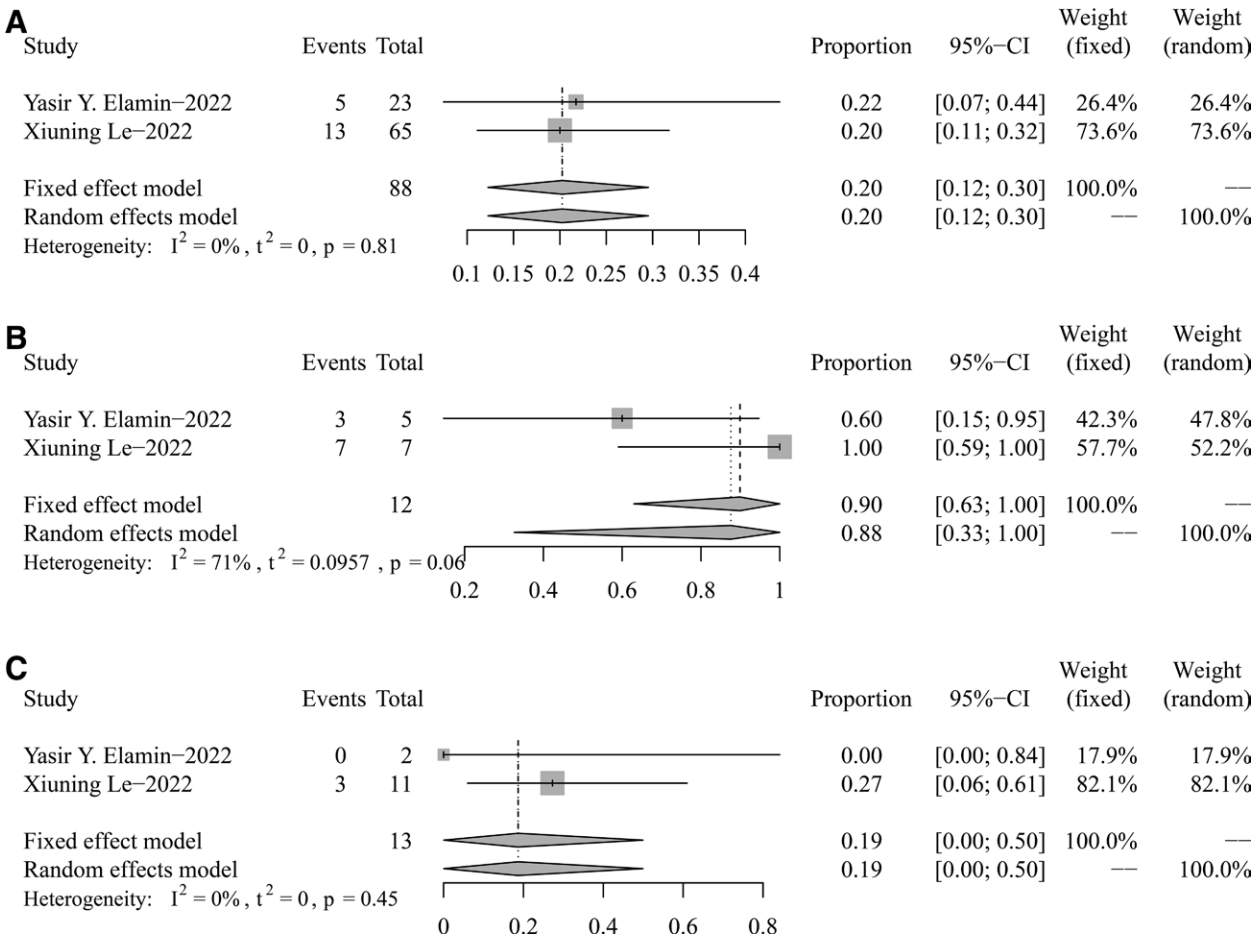

Figure 3. Forest plots of the objective response rates for the subgroup analysis of *HER2* exon 20 mutations. (A) Y772_A775dupYVMA; (B) G778_P780dupGSP; (C) G776delinsVC. HER2 = human epidermal growth factor receptor 2.

Table 2

Incidences of all grade adverse events.

Adverse event	Incidence (95% CI)
Diarrhea	82% (74–89)
Skin rash	74% (42–97)
Oral mucositis	68% (40–79)
Paronychia	53% (22–82)
Dry skin	46% (17–77)
Nausea	28% (20–36)
Alopecia	27% (20–36)
Pruritus	25% (17–33)
Vomiting	22% (15–30)
Weight loss	16% (10–24)

Table 3

Incidences of grade 3–-4 adverse events.

Adverse event	Incidence (95% CI)
Skin rash	36% (15–60)
Diarrhea	23% (15–31)
Oral mucositis	13% (3–29)
Paronychia	7% (0–35)
Pruritus	3% (0–7)
Dry skin	2% (0–10)
Nausea	1% (0–5)
Vomiting	1% (0–7)
Weight loss	1% (0–5%)
Alopecia	0

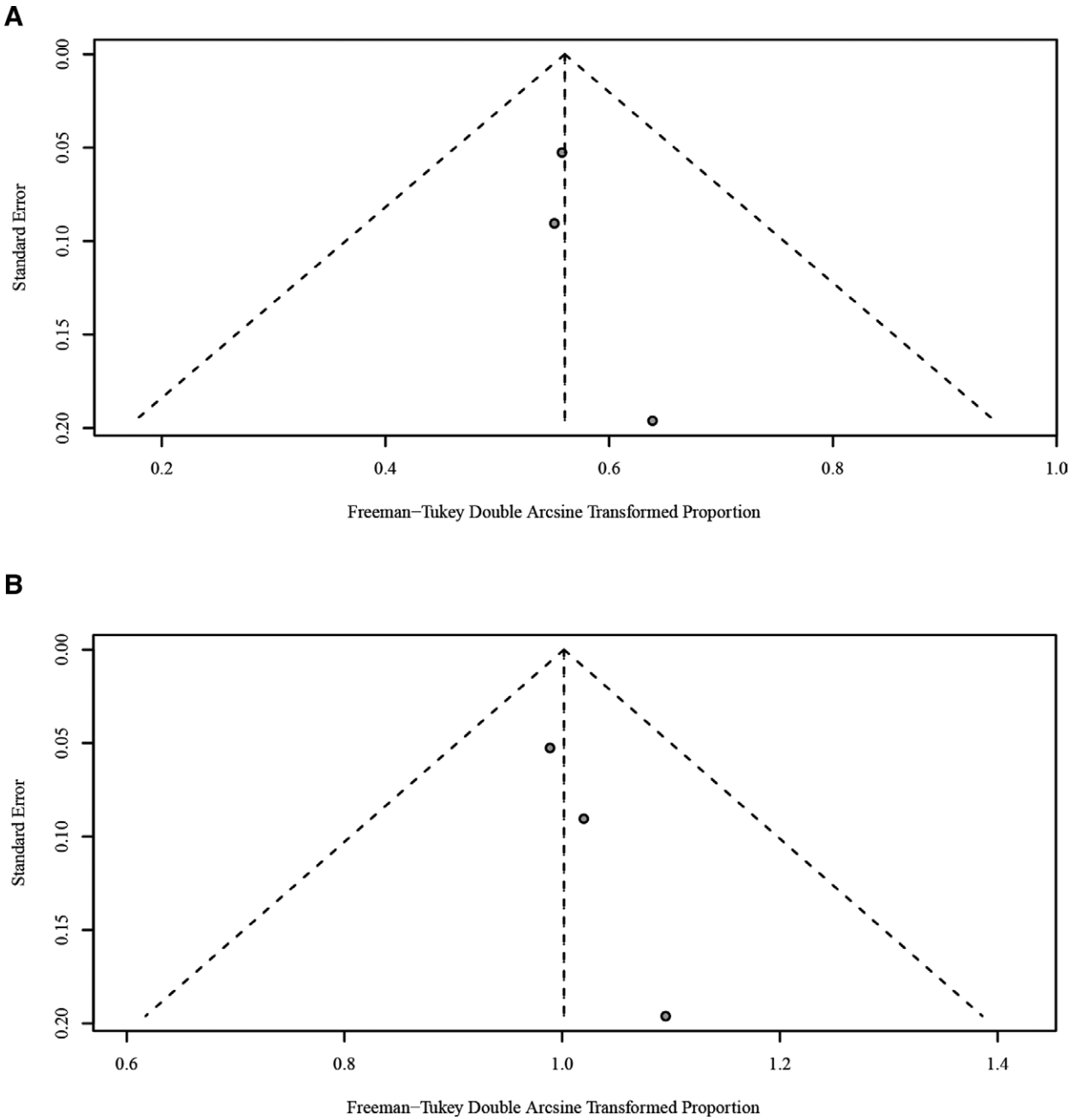

Figure 4. Funnel plot of the objective response rate (A) and disease control rate (B).

the starting dose in In-Jae Oh's trial (starting dose: 12 mg)[12]; 73% of patients had at least 1 dose reduction in the study by Yasir Y. Elamin (starting dose: 16 mg)[7]; 77% of patients in the study by Xiuning Le (starting dose: 16 mg) had experienced dose reduction.[8] The primary reason for dose reduction of poziotinib is the side-effect profile, including treatment-related grade 3 to 4 skin rash, diarrhea, oral mucositis, and paronychia. Therefore, facing this dilemma and enhancing tolerability may make patients benefit more from poziotinib. Moreover, patients have often experienced dose reduction of tyrosine kinase inhibitors (afatinib, erlotinib, etc.) in clinical practice. As long as poziotinib is not discontinued permanently, we consider that this level of dose reduction is fully acceptable.

Additionally, trastuzumab combined with pertuzumab is superior to trastuzumab plus placebo in treating *HER2* positive breast cancer patients.[15] Based on the clinical experiences of *HER2* positive breast cancer patients, combining 2 anti-*HER2* drugs (e.g., poziotinib plus T-DXd) might be a novel strategy for NSCLC patients with *HER2* exon 20 mutants.

6. Limitations

Two limitations in the analysis should be mentioned. First, the sample size was small because only 3 published studies were available. Second, the results of subgroup analysis of *HER2* mutation types require more evidence.

7. Conclusions

Poziotinib is an effective treatment option for NSCLC patients with *HER2* exon 20 mutations. Finding a suitable subgroup population and exploring new therapeutic strategies (e.g., combining chemotherapy and adjuvant poziotinib therapy) could be considered directions for future studies.

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Formal analysis: Bi-Cheng Wang.
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Validation: Bi-Cheng Wang, Xin-Xiu Liu.
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Writing – review & editing: Bi-Cheng Wang, Bo-Hua Kuang, Xin-Xiu Liu, Guo-He Lin.

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