



# Efficacy of immunotherapy in *HER2*-mutated non-small cell lung cancer: a single-arm meta-analysis

Juguang Zhang<sup>1</sup> · Weizhong Han<sup>2</sup> · Jun Guo<sup>1</sup> · Chufeng Zhang<sup>1</sup> · Lijun Cao<sup>3</sup> · Lixiu Peng<sup>4</sup> · Xiao Han<sup>1</sup> · Zhehai Wang<sup>1</sup>

Received: 2 August 2023 / Accepted: 13 November 2023 / Published online: 27 January 2024  
© The Author(s) 2024

## Abstract

**Background** Non-small cell lung cancers (NSCLC) harboring *Human Epidermal Growth Factor Receptor 2 (HER2)* mutations represent a distinct subset with unique therapeutic challenges. Although immune checkpoint inhibitors (ICIs) have been transformative in lung cancer treatment, the efficacy of ICIs in *HER2*-mutated NSCLC remains to be established.

**Methods** We systematically searched for real-world studies investigating the use of ICIs in treating *HER2*-mutated NSCLC, sourced from the PubMed, Cochrane Library, and Embase databases. Outcomes including objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS) were extracted for further analysis.

**Results** Twelve studies involving 260 patients were enrolled in this meta-analysis. Pooled data revealed an ORR of 0.26 (95% CI 0.17–0.34), a DCR of 0.68 (95% CI 0.55–0.81), and a median PFS (mPFS) of 5.36 months (95% CI 3.50–7.21). Notably, in the subgroup receiving combined immune and chemotherapy, the ORR increased to 0.37 (95% CI 0.26–0.49), the DCR to 0.79 (95% CI 0.70–0.87), and the mPFS to 7.10 months (95% CI 5.21–8.99).

**Conclusions** ICIs demonstrate promising anti-tumor activity and safety in patients with *HER2*-mutated NSCLC. Furthermore, the combined regimen of ICIs and chemotherapy may provide a significant therapeutic option for this patient population.

**Keywords** Non-small cell lung cancers · *HER2* · Immune checkpoint inhibitors · Efficacy · Meta-analysis

## Introduction

Lung cancer remains a significant global health burden as one of the principal causes of cancer-related mortality, with its prevalence steadily increasing in recent years. Non-small cell lung cancer (NSCLC) represents approximately 80%–85% of all lung cancer cases (Planchard et al.

2018; Sung et al. 2021). The *Human Epidermal Growth Factor Receptor 2 (HER2)*, a tyrosine kinase receptor of the *ERBB/HER* family, has emerged as a critical regulator of cell growth and differentiation. Despite lacking a specific endogenous ligand, it activates the downstream PI3K-AKT and MEK-ERK signaling pathways to promote cell proliferation (Cheng et al. 2016; Ricciardi et al. 2014; Yu

✉ Xiao Han  
hxzbb1983@163.com

✉ Zhehai Wang  
wzhai8778@sina.com

Juguang Zhang  
juguangzhang001@163.com

Weizhong Han  
hanweizhong003@163.com

Jun Guo  
jngj2005@126.com

Chufeng Zhang  
648110487@qq.com

Lijun Cao  
306102496@qq.com

Lixiu Peng  
2294714904@qq.com

<sup>1</sup> Department of Medical Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong, China

<sup>2</sup> Department of Cardiology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China

<sup>3</sup> Department of Oncology, Liaocheng Chiping District Hospital of Traditional Chinese Medicine, Liaocheng, Shandong, China

<sup>4</sup> Department of Internal Medicine, Qilu Hospital of Shandong University, Jinan, Shandong, China

et al. 2022). Abnormalities in *HER2* signaling can result from *HER2* mutations, amplification, or protein overexpression, with *HER2* mutations identified in 1%–4% of NSCLC cases (Pillai et al. 2017).

Chemotherapy has been the cornerstone treatment for *HER2*-mutated NSCLC, with previous studies highlighting a median progression-free survival (mPFS) of 4.3 months for chemotherapy alone, 6.2 months for pemetrexed + platinum/bevacizumab, 2.6 months for gemcitabine, 4 months for paclitaxel + platinum/bevacizumab, and 3.5 months for vincristine. However, the mPFS for *HER2* tyrosine kinase inhibitors (TKIs) stands at a mere 2.2 months (Eng et al. 2016; Wang et al. 2018). Despite concerted efforts in recent years, clinical studies focusing on *HER2*-targeted therapy for *HER2*-positive NSCLC have yielded unsatisfactory results, with such NSCLC receiving only limited clinical benefit from targeted therapy (Uy, Merkhofer, & Baik, 2022). Therefore, alternative treatment strategies are desperately needed for patients with *HER2*-mutated NSCLC. Notably, immune checkpoint inhibitors (ICIs)-based therapy has demonstrated substantial advances in NSCLC treatment in recent years. Both ICIs alone or in conjunction with chemotherapy currently considered conventional treatments for NSCLC, showing some benefits over chemotherapy (Nasser et al. 2020). Nonetheless, the effectiveness of immunotherapy in NSCLC patients with *HER2* mutations remains unclear. The low prevalence of the mutation and the minor patient sample sizes have hindered the execution of extensive randomized controlled clinical trials. As such, the present study aims to fill this knowledge gap by conducting a meta-analysis of published real-world studies to evaluate the efficacy and safety of ICIs in treating patients with *HER2*-mutated NSCLC.

## Materials and methods

### Search strategy

Three databases (PubMed, Embase, and the Cochrane Library) were comprehensively searched for relevant studies. The date of the last search was 31 October 2022. Our searches incorporated subject terms like "non small cell lung cancer," "*HER2*, *ErbB-2*," "Immune Checkpoint Inhibitors," alongside free terms like "NSCLC," "ICI," "ICIs," "ICPI," "Rare targetable drivers (RTDs)" and terms with similar meanings.

### Selection criteria

The inclusion criteria for studies in this analysis were as follows: (1) involved real-world data on the efficacy or safety of ICIs for *HER2*-mutated NSCLC, (2) included participants

who were 18 years or older with histologically or cytologically confirmed NSCLC, and *HER2* mutations as confirmed by tumor tissue testing or liquid biopsy, (3) presented sufficient data or data that could be calculated for efficacy and/or safety outcome indicators. We excluded studies that were reviews, conference abstracts, or other non-peer-reviewed literature, repetitive studies where the same clinical data was published more than once (we used the most recent, comprehensive version), publications in languages other than English, studies that did not provide enough data for extraction, and studies of low quality.

### Data extraction

Two reviewers independently screened studies, extracted data, and cross-verified the data. Extracted data included: (1) basic information like the first author, year of publication, and country of origin, (2) clinical baseline data such as the study population, sample size, PDL-1 expression status, treatment regimen, the number of lines of ICIs used, smoking history, gender, age, and (3) outcome indicators including objective response rate (ORR), disease control rate (DCR), median progression-free survival (mPFS), median overall survival (mOS), and safety outcome indicators such as the incidence of adverse events and incidence of grade 3–5 adverse events.

### Quality assessment

Two reviewers evaluated the quality of the studies using the MINORS scale. This scale, designed for the assessment of non-randomized studies, involves eight indicators each rated on a scale of 0–2, for a total possible score of 16. High-quality studies were defined as those scoring 13–16 points, medium-quality studies as those scoring 9–12 points (these were considered for final inclusion and data extraction), and low-quality studies as those scoring less than 9 points (these were excluded).

### Statistical analysis

We used Stata 17.0 software for our data analysis. We calculated the ORR and DCR using the combined ratio method, with ES as an effect size measure and a 95% confidence interval (CI). We estimated mPFS using the combined mean method, with the corresponding 95% CI. Heterogeneity among the studies was evaluated, with  $I^2 \leq 25\%$  indicating low heterogeneity and  $25\% < I^2 \leq 50\%$  indicating moderate heterogeneity; both were analyzed using a fixed-effects model. Studies with  $I^2 > 50\%$  (indicating high heterogeneity) were analyzed using a random-effects model. For results with high heterogeneity, we conducted a subgroup analysis. In cases of insufficient statistics or excessive heterogeneity,

we performed descriptive analyses. The data were combined and presented as forest plots. To examine publication bias in the meta-analysis, we used visual funnel plots and quantitatively using Egger's test, with  $p < 0.05$  considered statistically significant. In cases where publication bias was suggested, we further evaluated the effect using the 'cut-and-fill' method. We assessed the stability of the results through sensitivity analysis.

## Results

### Literature selection and basic characteristics of included studies

An initial search yielded 254 articles imported into Endnote for further management. Duplicates were removed using Endnote, followed by careful examination of the titles, abstracts, and full texts. Twelve real-world retrospective cohort studies were ultimately chosen for inclusion in our meta-analysis after this process resulted in the exclusion of studies that did not meet the inclusion criteria. The flow of study selection is presented in Fig. 1.

### Characteristics of included studies

Twelve included studies offered at least one validity index and were real-world investigations that complied with the established inclusion and exclusion criteria. These studies

included 260 patients, most of whom were in stages III or IV, reflecting a patient population with advanced NSCLC. The principal characteristics of the included studies are provided in Table 1.

### Quality assessment of included studies

The MINORS scale was used to rate the 12 retrospective studies that were a part of our analysis. Ten studies were found to be of high quality, and two studies were of medium quality. Table 1 presents the quality assessment. The quality assessments are provided in Table 1.

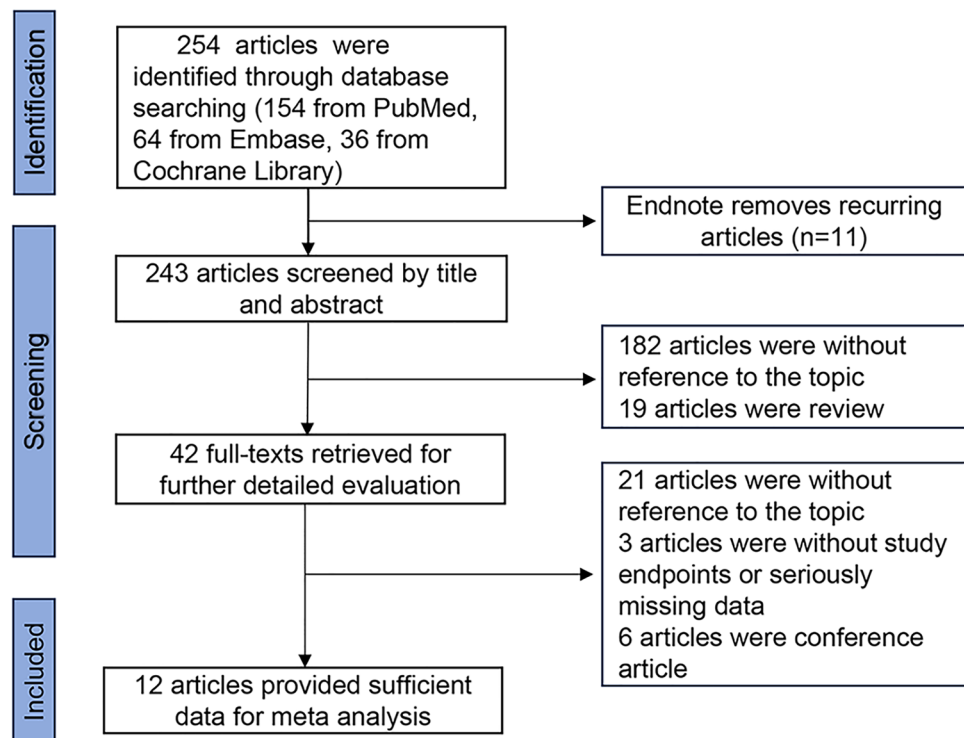
### Meta-analysis results

#### Efficacy

Eleven studies documented objective response rates (ORRs) (Abu Rous et al. 2022; Chu et al. 2022; Dudnik et al. 2018; Guisier et al. 2020; Guo et al. 2022; Lau et al. 2021; Mazieres et al. 2019; Saalfeld et al. 2021; Tian et al. 2021; Yang et al. 2022; Zhao et al. 2021). The meta-analysis revealed statistical heterogeneity across these studies ( $P = 0.018$ ,  $I^2 = 53.3\%$ ). Therefore, a random-effects model was utilized for the combined analysis. The pooled ORR was 0.26 (95% CI 0.17, 0.34) across 239 patients, as shown in Fig. 2.

Ten studies with DCR reported were used for the meta-analysis (Abu Rous et al. 2022; Chu et al. 2022; Guisier et al.

**Fig. 1** Literature search results and specific screening process



**Table 1** Information on the articles eligible and their specific characteristics

Author	Region	Total number of patients	Median age	Smoking history	Staging	Type of Her-2 mutation	PD-L1 status	Treatment plan	ICIs	ORR	DCR	mPFS (months)	mOS (months)	Safety	MINORS score
Elizabeth Dudnika (2018)	Israel	7 (13)	NA	NA	NA	ERBB2	NA	ICIs	≥ 2nd	14%	NA	3.4 (95% CI 2.4–8.5)	17.5 (95% CI: 3.0–17.5)	NA	13
J. Mazieres (2019)	Europe	29	62	44.8%	IV	Exon 20	53.3% > 1%	93% ICIs	Most ≥ 2nd	7.4%	33.3%	2.5 (95% CI 1.8–3.5)	20.3 (7.8–NR)	NA	14
Florian Guisier (2020)	France	23	62.8	35%	IV	Exon 20 ins	17.4% > 1%	ICIs	≥ 2nd	27.3%	50%	2.2 (95% CI 1.7–15.2)	20.4 (95% CI 9.3–NA)	AEs ≥ Grade 3 10%	15
Panwen Tian (2021)	China	13	55	53.8%	IV	Exon 20 ins	NA	ICIs + Chemo	1st (n = 10) 2nd (n = 3)	31%	77%	8.0 (95% CI: 5.2–NA)	NA	NA	13
Marcelo V. Negro (2021)	United States	21	NA	NA	NA	Codons 755 and 770–785	NA	ICIs	NA	NA	NA	3.02 (95% CI 1.8–NA)	10.81 (95% CI 5.62–NA)	NA	13
Xiangling Chu (2022)	China	26	55	30.8%	NA	Codons 755 and 770–785	26.9% > 1%	ICIs + Chemo	1st (n = 9) ≥ 2nd (n = 17)	38.5%	84.6%	7.4 (95% CI 4.4–10.4)	NA	AEs 7 (26.9%) AEs ≥ Grade 3 3 (11.5%)	14
Xiaojin Guo (2022)	China	12	59	33.3%	IV	Exon 20 ins	16.7% > 1%	ICIs + Chemo	1st (n = 6) ≥ 2nd (n = 6)	16.7%	91.7%	7.8 (1–26.9)	NA	NA	13
Sally C.M. Lau (2021)	Canada	14	65	0	NA	Exon 20 ins and exons 17 and 19	57.1% > 1%	ICIs	1st (n = 3) ≥ 2nd (n = 11)	29%	57%	3.6 (95% CI 1.6–NR)	NA	AEs 19%; AEs with high grade: 6%	16
Shuang Zhao (2021)	China	3	52	33.3%	IV	Exon 20	NA	ICIs + Chemo	1st	33.3%	66.7%	7 (2–8)	NA	NA	12

Table 1 (continued)

Author	Region	Total number of patients	Median age	Smoking history	Staging	Type of Her-2 mutation	PD-L1 status	Treatment plan	ICIs	ORR	DCR	mPFS (months)	mOS (months)	Safety	MINORS score	
Felix C. Saalfeld (2021)	Germany	5	61	54.1%	III, IV	Exons 8, 19 and 20	50.8% > 1%	ICIs	1st	52%	76%	6 (95%CI:6-14)	1 year OS: 88%	NA	15	
		22						ICIs+Chemo	1st							
		34						ICIs	≥ 2nd	16%	42%	4 (95%CI 4-6)	10(95% CI 6-NA)			
Guangjian Yang (2022)	China	46	55.4	36.9%	NA	Most Her-2 mutation	30.4% > 1%	ICIs+Chemo	1st	28.9%	80%	5.20 (95% CI:3.64-6.76)	1 year OS: 53.3%	NA	15	
Fawzi Abu Rous(F. 22)	United States	5	60	40%	IV	Exon 20,23	40% > 1%	ICIs+Chemo	NA	60%	80%	9	24	All AEs Grade 1/2	12	

PD-L1 Programmed Cell Death Ligand 1, ORR objective response rate, DCR disease control rate, mPFS median progression-free survival, OS overall survival, mOS median overall survival, *ins* insertions, AEs adverse reactions, Chemo Chemotherapy, NA not available, NR not reach. Note: The efficacy evaluation of all studies was the Response Evaluation Criteria in Solid Tumors (RECIST), and the adverse events evaluation of all studies was the Common Terminology Criteria for Adverse Events (CTCAE)

2020; Guo et al. 2022; Lau et al. 2021; Mazieres et al. 2019; Saalfeld et al. 2021; Tian et al. 2021; Yang et al. 2022; Zhao et al. 2021). The meta-analysis demonstrated significant heterogeneity across these studies ( $P=0.000$ ,  $I^2=77.8%$ ), leading us to employ a random-effects model for the combined analysis. The pooled DCR, as displayed in Fig. 2, was determined to be 0.68 (95% CI 0.55, 0.81) across 232 patients.

All of the twelve studies reported mPFS. However, many did not provide accurate confidence intervals. After careful deliberation, a meta-analysis of mPFS for the eight studies that presented complete data was carried out (Chu et al. 2022; Dudnik et al. 2018; Guisier et al. 2020; Guo et al. 2022; Mazieres et al. 2019; Saalfeld et al. 2021; Yang et al. 2022; Zhao et al. 2021). We used a random-effects model for the combined analysis because the meta-analysis revealed high heterogeneity among these studies ( $P=0.000$ ,  $I^2=92.4%$ ). The results, shown in Fig. 2, indicated a pooled mPFS of 5.36 months (95% CI 3.50, 7.21) for the 207 patients.

Although seven studies reported OS results, only one provided comprehensive OS data and precise confidence intervals, thus, performing a meta-analysis of OS was not feasible.

### Safety

An acceptable safety profile was observed in four studies that reported adverse events. One study provided a detailed account of adverse events. Specifically, in a cohort of 26 patients with *HER2*-mutant NSCLC receiving ICIs, seven patients (26.9%) experienced adverse events. Among them, three patients (11.5%) had grade 3 to 4 adverse events, which included neutropenia, thrombocytopenia, and abnormal liver function, each occurring in one patient (Chu et al. 2022).

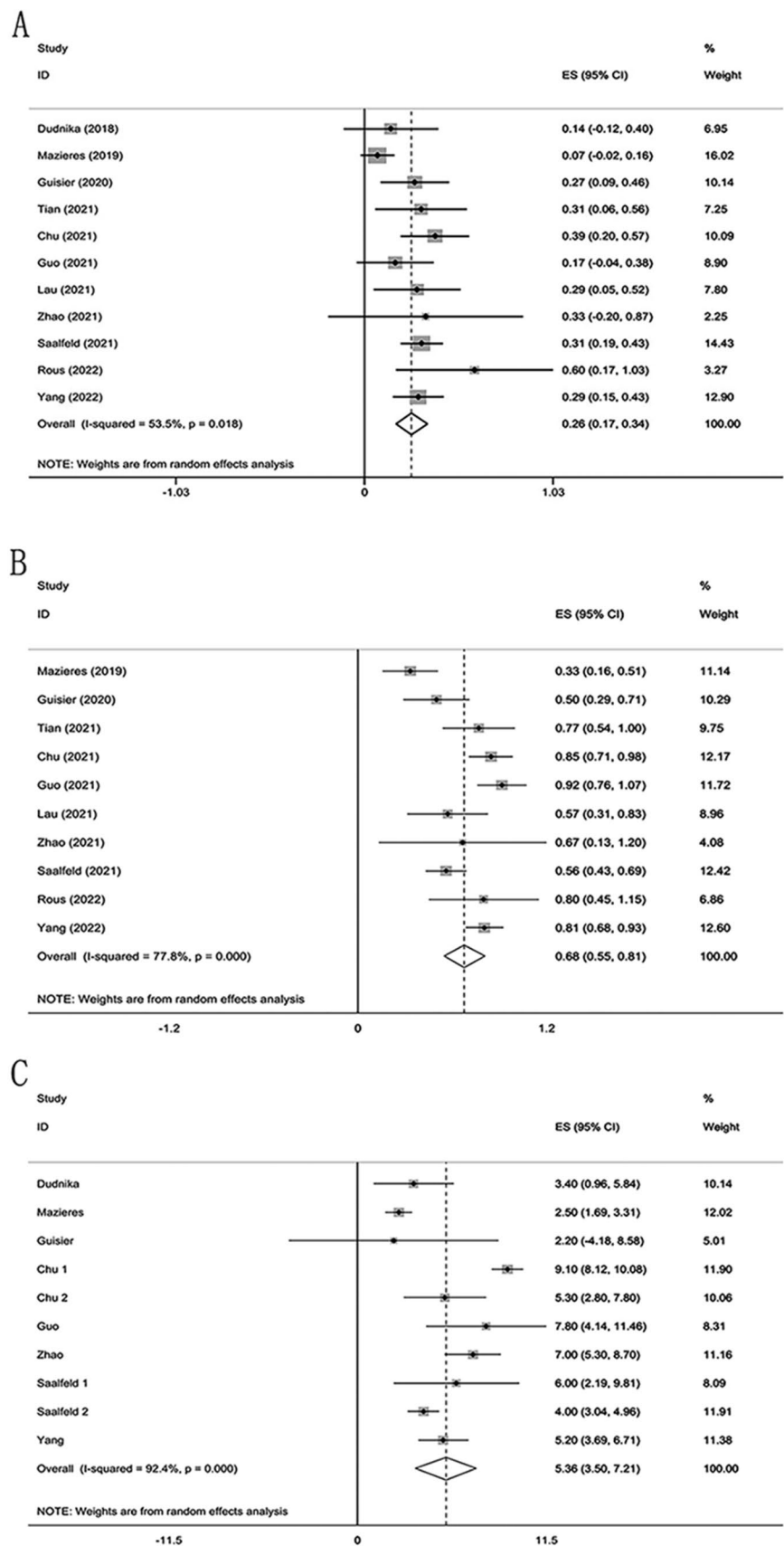
### Subgroup analysis

Given the observed heterogeneity in the overall meta-analysis results, we further scrutinized four factors that could potentially contribute to this heterogeneity: treatment regimen, number of treatment lines, ethnic group, and age. Through this subgroup analysis, while the overall heterogeneity remained, we could derive more stable results with reduced heterogeneity within certain characteristic groups. Detailed findings are presented in Table 2.

### Publication bias

The assessment of publication bias is presented in Fig. 3. A funnel plot illustrated that the majority of included studies fell within the inner side of the funnel, suggesting minimal publication bias among the selected literature. This observation was further quantified using Egger's test. The calculated

**Fig. 2** Pooled analysis of overall efficacy of *HER2*-mutated NSCLC: A ORR, B DCR, C mPFS





**Table 2** Subgroup analysis of the efficacy of ICIs in HER2-mutated NSCLC

	Grouping basis	Group	Number of articles	Number of patients	ES (95% CI)	I <sup>2</sup> /%	P	Total of I <sup>2</sup> /%	Total of P
ORR	Treatment options	ICIs	5	112	0.16 (0.07,0.24)	32.1	0.208	62.7	0.004
		ICIs + chemotherapy	5	83	0.37 (0.26,0.49)	11.4	0.341		
	Treatment lines	First line	5	93	0.36 (0.27,0.46)	34.5	0.177	58.9	0.007
		Second line or above	6	124	0.18 (0.09,0.26)	0	0.47		
	Ethnic group	Western	6	139	0.24 (0.11,0.37)	68	0.008	53.3	0.018
		Asian	5	95	0.29 (0.20,0.39)	0	0.675		
Age	≥ 60 years	5	132	0.25 (0.11,0.40)	0	0.675	57.2	0.013	
	< 60 years	5	95	0.29 (0.20,0.39)	74.2	0.004			
DCR	Treatment options	ICIs	4	105	0.44 (0.34,0.54)	0	0.442	73.2	<0.001
		ICIs + chemotherapy	5	83	0.79 (0.70,0.87)	0	0.984		
	Treatment lines	First line	5	93	0.78 (0.69,0.86)	0	0.885	73.8	<0.001
		Second line or above	5	117	0.51 (0.36,0.66)	64.1	0.025		
	Ethnic group	Western	5	132	0.52 (0.40,0.64)	44.8	0.123	77.8	<0.001
		Asian	5	95	0.84 (0.76,0.91)	0	0.732		
	age	≥ 60 years	5	132	0.52 (0.40,0.64)	44.8	0.732	77.8	<0.001
		< 60 years	5	95	0.84 (0.76,0.91)	0	0.123		
mPFS	Treatment options	ICIs	5	110	3.49 (2.42,4.56)	51.8	0.081	92.4	<0.001
		ICIs + chemotherapy	5	92	7.10 (5.21,8.99)	79.8	0.001		
	Treatment lines	First line	4	80	6.97 (4.82,9.12)	84.8	0	93.1	<0.001
		Second line or above	5	110	3.49 (2.42,4.56)	51.8	0.081		
	Ethnic group	Western	4	120	3.41 (2.33,4.49)	48	0.104	92.4	<0.001
		Asian	4	82	6.91 (5.03,8.79)	82.2	0		
	Age	≥ 60 years	3	113	3.46 (2.13,4.79)	82.2	0	93.1	<0.001
		< 60 years	4	82	6.91 (5.03,8.79)	60.8	0.054		

p values for ORR, DCR, and mPFS were 0.103, 0.636, and 0.712, respectively, supporting that our results were not significantly influenced by publication bias. These results are illustrated in Fig. 4.

### Sensitivity analysis

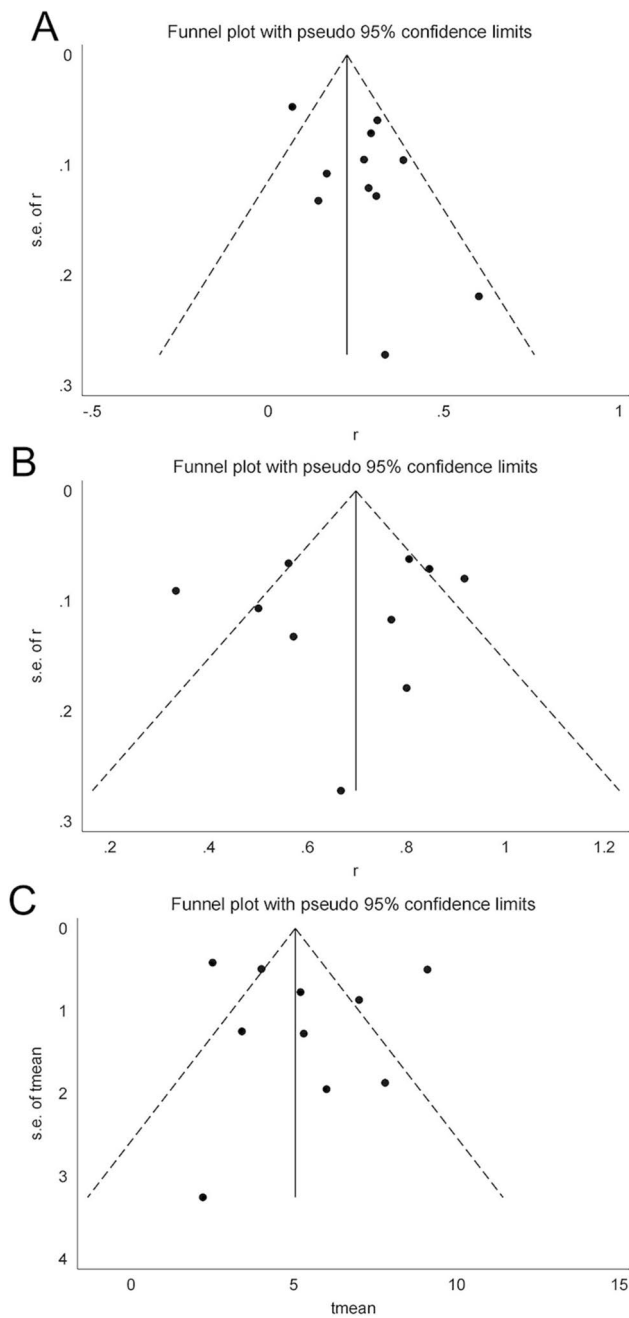
To assess the robustness of our meta-analysis results and to check if any individual study had a disproportionate influence on the overall results, we performed a sensitivity analysis by sequentially excluding one study at a time. Following this process, we noted only minor alterations to the overall results, suggesting that our findings are stable and reliable. These analyses are presented in Fig. 5.

### Discussion

HER2 mutations in NSCLC predominantly manifest in specific patient subsets, primarily women, never-smokers, and those diagnosed with adenocarcinoma women, never-smokers, and adenocarcinoma patients (Pillai et al. 2017). The primary therapy for advanced HER2-mutant NSCLC

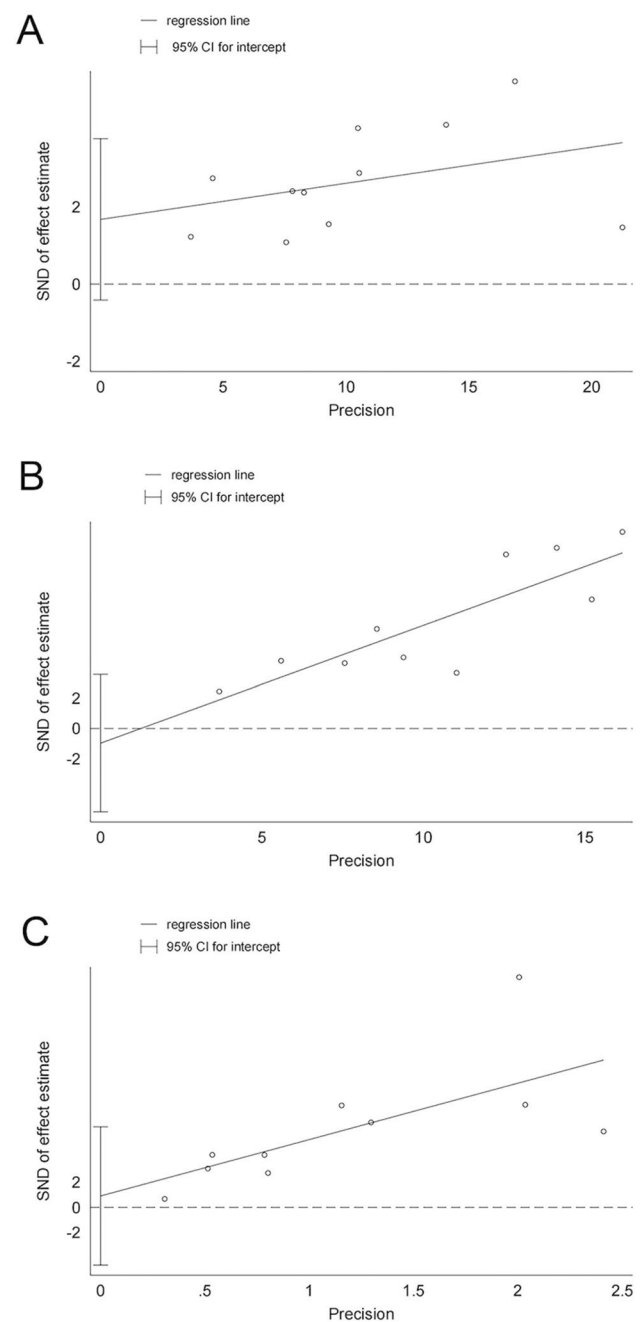
patients involves chemotherapy and targeted therapy, with chemotherapy remains the standard of care. Nevertheless, the efficacy of first-line chemotherapy remains poor, with an ORR of 36% and mPFS of 5.1 months (Wang et al. 2018). A retrospective analysis has disclosed a first-line chemotherapy objective response rate and progression-free survival rate of 43.5% and 6 months, respectively. These numbers dropped to 10% and 4.3 months for second-line chemotherapy and even less for third-line and beyond (Mazières et al. 2016).

Clinical interest in HER2-targeted therapies for patients with HER2-positive NSCLC has grown significantly in recent years. Clinical trials of HER2-targeted drugs like afatinib, neratinib, and dacomitinib yielded unsatisfactory outcomes with ORRs ranging from 0 to 19% and mPFS of 2.8–5.5 months (Dziadziuszko et al. 2019; Hyman et al. 2018; Kris et al. 2015; Lai et al. 2019; Peters et al. 2018). HER2 monoclonal antibodies (e.g., trastuzumab and pertuzumab) have shown efficacy in advanced HER2 mutant breast cancer and gastric cancer. However, their efficacy in NSCLC is limited. Even the addition of chemotherapy has failed to yield significant clinical benefits (Herbst et al. 2007; Kinoshita et al. 2018; Langer et al. 2004; Lara et al. 2004). Recently, Trastuzumab Deruxtecan (T-DXd) has



**Fig. 3** The funnel plot of ORR, DCR, mPFS: A ORR, B DCR, C mPFS

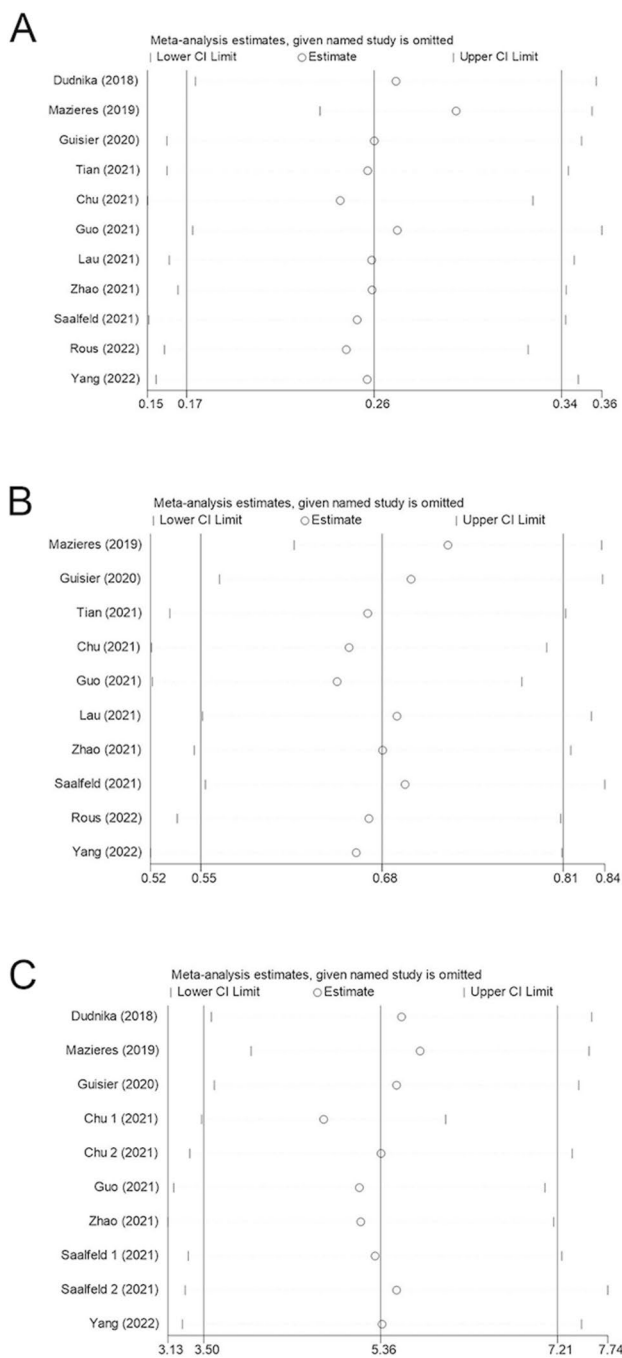
demonstrated superior survival outcomes and received accelerated approval by the FDA for treating patients with NSCLC carrying *HER2* (*ERBB2*) mutations on August 11, 2022. Nevertheless, the high toxicity of T-DXd impedes its broader application in clinical studies and practice (Li et al. 2022; Tsurutani et al. 2020; Y. Yu, Yang, Li, & Fan, 2023). The Phase II study DESTINY-Lung trial showed encouraging results, with T-DXd demonstrating an ORR of 55% and mPFS of 8.2 months in previously treated patients with



**Fig. 4** Egger linear regression plot of ORR, DCR, mPFS: A ORR, B DCR, C mPFS

*HER2*-mutated NSCLC. However, treatment-related adverse events were almost universal, with interstitial lung disease being particularly problematic, affecting 24 patients (26%) and causing two deaths (Li et al. 2022). Another notable ADC, Trastuzumab emtansine (T-DM1), while showing an ORR of 38.1%, had a limited mPFS of 2.8 months in a focused study of NSCLC patients with *HER2* exon 20 insertion mutations (Iwama et al. 2022). Similarly, in a phase II clinical trial, pyrotinib, an irreversible small molecule





**Fig. 5** Sensitivity analysis of subsequent testing for impact on overall results: A ORR, B DCR, C mPFS

inhibitor of *EGFR/HER2/HER4* receptors, showed an ORR of 30% and an mPFS of 6.9 months in 60 patients with platinum-treated advanced NSCLC with *HER2* mutations. However, the majority of patients (98.3%) experienced treatment-related adverse events (TRAEs), with 28.3% of patients experiencing severe TRAEs, leading to 23.4% of patients discontinuing treatment (Zhou et al. 2020). The ZENITH20-2 trial treated 90 patients with *HER2*-mutated

NSCLC with poziotinib, showing moderate efficacy (ORR of 27.8% and mPFS of 5.5 months). However, TRAEs were observed in 97.8% of patients, with severe TRAE occurring in 75 patients (84.4%), resulting in dose reduction for 76.7% and discontinuation for 13.3% of patients (Le et al. 2022).

The advent of ICIs has particularly revolutionized the NSCLC treatment landscape. However, the utility of ICIs in patients with *HER2*-mutated NSCLC remains under debate. The comprehensive meta-analysis was designed to assess the efficacy and safety of ICIs in treating *HER2*-mutated NSCLC, thereby aiming to furnish a scientific foundation for clinical treatment plans. In the study, twelve real-world studies meeting the predefined inclusion and exclusion criteria were selected, involving a cohort of 260 NSCLC patients who received ICIs as monotherapy or in combination with other treatments. These studies collectively reported an ORR of 0.26 (95% CI 0.17, 0.34) and a DCR of 0.68 (95% CI 0.55, 0.81) for patients receiving ICIs. In addition, analysis of the eight studies produced a combined mPFS of 5.36 months (95% CI 3.50, 7.21). A subgroup analysis further suggested that an ICIs–chemotherapy combination may yield superior anti-tumor efficacy, with an ORR of 0.37 (95% CI 0.26, 0.49), a DCR of 0.79 (95% CI 0.70, 0.87), an mPFS of 7.10 months (95% CI 5.21, 8.99). Adverse events as reported in four of the selected studies suggest a reasonably acceptable safety profile. Therefore, early use of ICIs in combination with chemotherapy may be a more effective treatment modality with a manageable safety profile for patients with advanced NSCLC with *HER2* mutations.

Despite the meta-analysis's promising results on the efficacy of ICIs in advanced NSCLC with *HER2* mutations, the results need further exploration. Studies of ICIs combined with ADCs are an especially promising avenue, as preclinical data suggest that drugs like T-DXd may augment T-cell activity, upregulate PD-L1 expression, increase the number of tumor-infiltrating CD8+ T cells, and enhance the expression of PD-L1 and MHC class I molecules on the surface of tumor cells. As a result, combination therapy with T-DXd and anti-PD1 antibodies may be more effective than treatment alone (Iwata et al. 2018). Therefore, the combination of ICIs with *HER2*-targeted therapy shows promise. There are various issues to consider, including the mode of combination therapy of ICIs with ADCs or selective *HER2* TKI and with chemotherapeutic agents, the dosage of drugs administered, the optimal sequence of treatment, and the unique management of toxicity. The results from the ongoing randomized controlled phase III study evaluating T-DXd in combination with pembrolizumab chemotherapy in first-line therapy (DESTINY-Lung 04) (Bob et al. 2022), and the exploratory phase I studies evaluating ADCs in combination with ICIs in previously treated patients (NCT04686305, NCT04042701, NCT05482568) may provide valuable insights for improving the treatment outlook for patients

with *HER2*-mutated advanced NSCLC treated with ICIs in combination (Y. Yu et al. 2023).

This study has several limitations. First, there were insurmountable heterogeneity issues possibly arising from differences in patient age, gender, PD-L1 expression level, dosing regimen, drug type, and patient ethnicity between studies. Second, the limited amount of literature included in the subgroup analysis, coupled with the fact that most of the real-world studies retrieved were uncontrolled retrospective studies; Therefore, statistical methods could not be used to calculate relative hazard ratios between subgroups.

In conclusion, ICIs in combination with chemotherapy may represent a promising treatment modality for patients with *HER2*-mutated NSCLC, as this combination therapy has demonstrated promising efficacy and a manageable safety profile. The results of this study may serve as a reference for future clinical studies.

**Author contributions** Juguang Zhang, Weizhong Han, Jun Guo, Chufeng Zhang, Lijun Cao, Lixiu Peng, Xiao Han, and Zhehai Wang designed the search strategy and confirmed the inclusion criteria; Juguang Zhang, Jun Guo, and Chufeng Zhang searched the database, selected the articles and collected the data; Lijun Cao and Lixiu Peng completed the quality assessment and Zhehai Wang checked; Juguang Zhang and Weizhong Han finished data synthesis and statistics; Juguang Zhang wrote original draft preparation; Xiao Han and Zhehai Wang revised the manuscript carefully; final all authors reviewed the manuscript. Juguang Zhang and Weizhong Han contributed equally to this manuscript; Xiao Han and Zhehai Wang contributed equally to this manuscript as senior authors.

**Funding** The project was funded by the Shandong Province Medical and Health Science and Technology Development Program (No.202103100568), the Shandong Province Natural Science Foundation (No.ZR2023MH182), and the Shandong Province Natural Science (Youth) Foundation (No. ZR.2020QH209).

**Data availability** The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

## Declarations

**Conflict of interest** The authors declare no conflict of interest.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

## References

- Abu Rous F, Gutta R, Li P, Halmos B, Gadgeel S (2022) Pembrolizumab in Combination with Chemotherapy in Patients with ERBB2-Mutated Non-Small Cell Lung Cancer. *Target Oncol* 17(2):187–192. <https://doi.org/10.1007/s11523-022-00873-2>
- Bob TL, Myung-Ju A, Koichi G, Julien M, Sukhmani Kaur P, William Nassib W, Amaya G (2022) Open-label, randomized, multicenter, phase 3 study evaluating trastuzumab deruxtecan (T-DXd) as first-line treatment in patients with unresectable, locally advanced, or metastatic non-small cell lung cancer (NSCLC) harboring *HER2* exon 19 or 20 mutations (DESTINY-Lung04). *J Clin Oncol*. [https://doi.org/10.1200/jco.2022.40.16\\_suppl.tps9137?af=r](https://doi.org/10.1200/jco.2022.40.16_suppl.tps9137?af=r)
- Cheng H, Liu P, Ohlson C, Xu E, Symonds L, Isabella A, Zhao JJ (2016) PIK3CA(H1047R)- and *Her2*-initiated mammary tumors escape PI3K dependency by compensatory activation of MEK-ERK signaling. *Oncogene* 35(23):2961–2970. <https://doi.org/10.1038/onc.2015.377>
- Chu X, Qiang H, Xie M, Li X, Zhao J, Wu Y, Su C (2022) Treatment efficacy of *HER2*-mutant lung adenocarcinoma by immune checkpoint inhibitors: a multicenter retrospective study. *Cancer Immunol Immunother* 71(7):1625–1631. <https://doi.org/10.1007/s00262-021-03100-5>
- Dudnik E, Bshara E, Grubstein A, Fridel L, Shochat T, Roisman LC, Peled N (2018) Rare targetable drivers (RTDs) in non-small cell lung cancer (NSCLC): Outcomes with immune check-point inhibitors (ICPi). *Lung Cancer* 124:117–124. <https://doi.org/10.1016/j.lungcan.2018.07.044>
- Dziadziuszko R, Smit EF, Dafni U, Wolf J, Wasag B, Biernat W, Peters S (2019) Afatinib in NSCLC With *HER2* Mutations: Results of the Prospective, Open-Label Phase II NICHE Trial of European Thoracic Oncology Platform (ETOP). *J Thorac Oncol* 14(6):1086–1094. <https://doi.org/10.1016/j.jtho.2019.02.017>
- Eng J, Hsu M, Chaff JE, Kris MG, Arcila ME, Li BT (2016) Outcomes of chemotherapies and *HER2* directed therapies in advanced *HER2*-mutant lung cancers. *Lung Cancer* 99:53–56. <https://doi.org/10.1016/j.lungcan.2016.05.030>
- Guisier F, Dubos-Arvis C, Viñas F, Doubre H, Ricordel C, Ropert S, Bylicki O (2020) Efficacy and Safety of Anti-PD-1 Immunotherapy in Patients With Advanced NSCLC With *BRAF*, *HER2*, or *MET* Mutations or *RET* Translocation: GFPC 01–2018. *J Thorac Oncol* 15(4):628–636. <https://doi.org/10.1016/j.jtho.2019.12.129>
- Guo X, Du H, Li J, Yang M, Xiong A, Zhang H, Wu F (2022) Efficacy of ICIs on patients with oncogene-driven non-small cell lung cancer: a retrospective study. *Cancer Drug Resist* 5(1): 15–24 <https://doi.org/10.20517/cdr.2021.85>
- Herbst RS, Davies AM, Natale RB, Dang TP, Schiller JH, Garland LL, Johnson BE (2007) Efficacy and safety of single-agent pertuzumab, a human epidermal receptor dimerization inhibitor, in patients with non small cell lung cancer. *Clin Cancer Res* 13(20):6175–6181. <https://doi.org/10.1158/1078-0432.CCR-07-0460>
- Hyman DM, Piha-Paul SA, Won H, Rodon J, Saura C, Shapiro GI, Solit DB (2018) *HER* kinase inhibition in patients with *HER2*- and *HER3*-mutant cancers. *Nature* 554(7691):189–194. <https://doi.org/10.1038/nature25475>
- Iwama E, Zenke Y, Sugawara S, Daga H, Morise M, Yanagitani N, Okamoto I (2022) Trastuzumab emtansine for patients with non-small cell lung cancer positive for human epidermal growth factor receptor 2 exon-20 insertion mutations. *Eur J Cancer* 162:99–106. <https://doi.org/10.1016/j.ejca.2021.11.021>
- Iwata TN, Ishii C, Ishida S, Ogitani Y, Wada T, Agatsuma T (2018) A *HER2*-targeting antibody-drug conjugate, trastuzumab deruxtecan (DS-8201a), enhances antitumor immunity in a mouse model.

- Mol Cancer Ther 17(7):1494–1503. <https://doi.org/10.1158/1535-7163.MCT-17-0749>
- Kinoshita I, Goda T, Watanabe K, Maemondo M, Oizumi S, Amano T, Dosaka-Akita H (2018) A phase II study of trastuzumab monotherapy in pretreated patients with non-small cell lung cancers (NSCLCs) harboring HER2 alterations: HOT1303-B trial. *Ann Oncol*. <https://doi.org/10.1093/annonc/mdy292.112>
- Kris MG, Camidge DR, Giaccone G, Hida T, Li BT, O'Connell J, Jänne PA (2015) Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. *Ann Oncol* 26(7):1421–1427. <https://doi.org/10.1093/annonc/mdv186>
- Lai WV, Lebas L, Barnes TA, Milia J, Ni A, Gautschi O, Li BT (2019) Afatinib in patients with metastatic or recurrent HER2-mutant lung cancers: a retrospective international multicentre study. *Eur J Cancer* 109:28–35. <https://doi.org/10.1016/j.ejca.2018.11.030>
- Langer CJ, Stephenson P, Thor A, Vangel M, Johnson DH, Eastern Cooperative Oncology Group S (2004) Trastuzumab in the treatment of advanced non-small-cell lung cancer: is there a role? Focus on Eastern Cooperative Oncology Group study 2598. *J Clin Oncol*, 22(7): 1180–1187 <https://doi.org/10.1200/JCO.2004.04.105>
- Lara PN, Jr., Laptalo L, Longmate J, Lau DH, Gandour-Edwards R, Gumerlock PH, California Cancer C (2004) Trastuzumab plus docetaxel in HER2/neu-positive non-small-cell lung cancer: a California Cancer Consortium screening and phase II trial. *Clin Lung Cancer*, 5(4): 231–236 <https://doi.org/10.3816/clc.2004.n.004>
- Lau SCM, Fares AF, Le LW, Mackay KM, Soberano S, Chan SW, Sacher AG (2021) Subtypes of EGFR- and HER2-Mutant Metastatic NSCLC Influence Response to Immune Checkpoint Inhibitors. *Clin Lung Cancer* 22(4):253–259. <https://doi.org/10.1016/j.clcc.2020.12.015>
- Le X, Cornelissen R, Garassino M, Clarke JM, Tchekmedyan N, Goldman JW, Socinski MA (2022) Pozotinib in Non-Small-Cell Lung Cancer Harboring HER2 Exon 20 Insertion Mutations After Prior Therapies: ZENITH2–2 Trial. *J Clin Oncol* 40(7):710–718. <https://doi.org/10.1200/jco.21.01323>
- Li BT, Smit EF, Goto Y, Nakagawa K, Udagawa H, Mazieres J, Investigators DE-LT (2022) Trastuzumab Deruxtecan in HER2-Mutant Non-Small-Cell Lung Cancer. *N Engl J Med* 386(3):241–251. <https://doi.org/10.1056/NEJMoa2112431>
- Mazières J, Barlesi F, Filleron T, Besse B, Monnet I, Beau-Faller M, Gautschi O (2016) Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: results from the European EUHER2 cohort. *Ann Oncol* 27(2):281–286. <https://doi.org/10.1093/annonc/mdv573>
- Mazières J, Drilon A, Lusque A, Mhanna L, Cortot AB, Mezquita L, Gautschi O (2019) Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol* 30(8):1321–1328. <https://doi.org/10.1093/annonc/mdz167>
- Nasser NJ, Gorenberg M, Agbarya A (2020) First line Immunotherapy for non-small cell lung cancer. *Pharmaceuticals (basel)*. <https://doi.org/10.3390/ph13110373>
- Negrao MV, Skoulidis F, Montesio M, Schulze K, Bara I, Shen V, Heymach JV (2021) Oncogene-specific differences in tumor mutational burden, PD-L1 expression, and outcomes from immunotherapy in non-small cell lung cancer. *J Immunother Cancer*. <https://doi.org/10.1136/jitc-2021-002891>
- Peters S, Curioni-Fontecedro A, Nechushtan H, Shih JY, Liao WY, Gautschi O, Chang GC (2018) Activity of Afatinib in heavily pretreated patients with ERBB2 mutation-positive advanced NSCLC: findings from a global named patient use program. *J Thorac Oncol* 13(12):1897–1905. <https://doi.org/10.1016/j.jtho.2018.07.093>
- Pillai RN, Behera M, Berry LD, Rossi MR, Kris MG, Johnson BE, Khuri FR (2017) HER2 mutations in lung adenocarcinomas: A report from the Lung Cancer Mutation Consortium. *Cancer* 123(21):4099–4105. <https://doi.org/10.1002/cncr.30869>
- Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, Committee EG (2018) Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 29(Suppl 4), iv192-iv237 <https://doi.org/10.1093/annonc/mdy275>
- Ricciardi GR, Russo A, Franchina T, Ferraro G, Zanghi M, Picone A, Adamo V (2014) NSCLC and HER2: between lights and shadows. *J Thorac Oncol* 9(12):1750–1762. <https://doi.org/10.1097/JTO.0000000000000379>
- Saalfeld FC, Wenzel C, Christopoulos P, Merkelbach-Bruse S, Reissig TM, Lassmann S, Lung NNGM, C. (2021) Efficacy of Immune Checkpoint Inhibitors Alone or in Combination With Chemotherapy in NSCLC Harboring ERBB2 Mutations. *J Thorac Oncol* 16(11):1952–1958. <https://doi.org/10.1016/j.jtho.2021.06.025>
- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 71(3):209–249. <https://doi.org/10.3322/caac.21660>
- Tian P, Zeng H, Ji L, Ding Z, Ren L, Gao W, Li W (2021) Lung adenocarcinoma with ERBB2 exon 20 insertions: Comutations and immunogenomic features related to chemoimmunotherapy. *Lung Cancer* 160:50–58. <https://doi.org/10.1016/j.lungcan.2021.07.014>
- Tsurutani J, Iwata H, Krop I, Janne PA, Doi T, Takahashi S, Li BT (2020) Targeting HER2 with trastuzumab deruxtecan: a dose-expansion, phase i study in multiple advanced solid tumors. *Cancer Discov* 10(5):688–701. <https://doi.org/10.1158/2159-8290.CD-19-1014>
- Uy NF, Merkhofer CM, Baik CS (2022) HER2 in non-small cell lung cancer: a review of emerging therapies. *Cancers (Basel)*, <https://doi.org/10.3390/cancers14174155>
- Wang Y, Zhang S, Wu F, Zhao J, Li X, Zhao C, Zhou C (2018) Outcomes of Pemetrexed-based chemotherapies in HER2-mutant lung cancers. *BMC Cancer* 18(1):326. <https://doi.org/10.1186/s12885-018-4277-x>
- Yang G, Yang Y, Liu R, Li W, Xu H, Hao X, Wang Y (2022) First-line immunotherapy or angiogenesis inhibitor plus chemotherapy for HER2-altered NSCLC: a retrospective real-world POLISH study. *Ther Adv Med Oncol* 14:17588359221082340. <https://doi.org/10.1177/17588359221082339>
- Yu X, Ji X, Su C (2022) HER2-altered non-small cell lung cancer: biology, clinicopathologic features, and emerging therapies. *Front Oncol* 12:860313. <https://doi.org/10.3389/fonc.2022.860313>
- Yu Y, Yang Y, Li H, Fan Y (2023) Targeting HER2 alterations in non-small cell lung cancer: Therapeutic breakthrough and challenges. *Cancer Treat Rev* 114:102520. <https://doi.org/10.1016/j.ctrv.2023.102520>
- Zhao S, Xian X, Tian P, Li W, Wang K, Li Y (2021) Efficacy of Combination Chemo-Immunotherapy as a First-Line Treatment for Advanced Non-Small-Cell Lung Cancer Patients With HER2 Alterations: A Case Series. *Front Oncol* 11:633522. <https://doi.org/10.3389/fonc.2021.633522>
- Zhou C, Li X, Wang Q, Gao G, Zhang Y, Chen J, Lin X (2020) Pyrotinib in HER2-Mutant Advanced Lung Adenocarcinoma After Platinum-Based Chemotherapy: A Multicenter, Open-Label, Single-Arm, Phase II Study. *J Clin Oncol* 38(24):2753–2761. <https://doi.org/10.1200/jco.20.00297>