Efficacy of immunotherapy in patients with oncogene-driven non-small-cell lung cancer: a systematic review and meta-analysis

Jiayan Chen*, Wanjun Lu*, Mo Chen*, Zijing Cai, Ping Zhan, Xin Liu, Suhua Zhu, Mingxiang Ye, Tangfeng Lv, Jiawen Lv, Yong Song and Dong Wang

Abstract

Background: Immunotherapy is an emerging antitumor therapy that can improve the survival of patients with advanced non-small-cell lung cancer (NSCLC). However, only about 20% of NSCLC patients can benefit from this treatment. At present, whether patients with driving gene-positive NSCLC can benefit from immunotherapy is one of the hot issues. Therefore, we conducted a meta-analysis to evaluate the efficacy of immunotherapy in patients with oncogene-driven NSCLC and concluded the efficacy of altered subtypes.

Methods: A literature search was performed using PubMed, Web of Science, and Cochrane databases. The primary endpoints included the objective response rate (ORR), median progression-free survival (mPFS), and median overall survival (mOS) in patients with oncogene-driven NSCLC.

Results: In all, 86 studies involving 4524 patients with oncogene-driven NSCLC were included in this meta-analysis. The pooled ORRs in clinical trials treated with monoimmunotherapy of EGFR, ALK, and KRAS alteration were 6%, 0%, and 23%, respectively. In retrospective studies, the pooled ORRs of EGFR, ALK, KRAS, BRAF, MET, HER2, RET, and ROS1 alteration were 8%, 3%, 28%, 24%, 23%, 14%, 7%, and 8%, respectively. Among them, the pooled ORRs of KRAS non-G12C mutation, KRAS G12C mutation, BRAF V600E mutation, BRAF non-V600E mutation, MET-exon 14 skipping, and MET-amplification were 33% 40%, 20%, 34%, 17%, and 60%, respectively. In addition, the pooled mPFS rates of EGFR, KRAS, MET, HER2, and RET alteration were 2.77, 3.24, 2.48, 2.31, and 2.68 months, while the pooled mOS rates of EGFR mutation, the pooled ORR and mPFS treated with chemo-immunotherapy [IC] reached 38% and 6.20 months, while 58% and 8.48 months with chemo-immunotherapy plus anti-angiogenesis therapy (ICA). Moreover, the pooled mPFS and mOS of monoimmunotherapy was 2.33 months and 12.43 months.

Conclusions: *EGFR-, ALK-, HER2-, RET-*, and *ROS1*-altered NSCLC patients have poor reactivity to monoimmunotherapy but the efficacy of immune-based combined therapy is significantly improved. *KRAS* G12C mutation, *BRAF* non-V600E mutation, and *MET* amplification have better responses to immunotherapy, and more prospective studies are needed for further research.

Plain Language Summary

Efficacy of immunotherapy in patients with oncogene-driven non-small cell lung cancer: a systematic review and meta analysis

Immunotherapy is an emerging antitumor therapy that can improve the survival of patients with advanced NSCLC. However, only about 20% of NSCLC patients can benefit from this

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treatment. At present, whether patients with driving gene positive NSCLC can benefit from immunotherapy is one of the hot issues. Therefore, we conducted a meta-analysis to evaluate the efficacy of immunotherapy in patients with oncogene-driven NSCLC, and concluded the efficacy of altered subtypes. 86 studies involving 4524 patients with oncogene-driven NSCLC were included in this meta-analysis. The pooled ORR in clinical trials treated with monoimmunotherapy was of EGFR, ALK and KRAS alteration was 6%, 0%, and 23%, respectively. While in retrospective studies, the pooled ORR of EGFR, ALK, KRAS, BRAF, MET, HER2, RET and ROS1 alteration was 8%, 3%, 28%, 24%, 23%, 14%, 7% and 8%, respectively. Among them, the pooled ORR of KRAS non-G12C mutation, KRAS G12C mutation, BRAF V600E mutation, BRAF non-V600E mutation, MET-exon 14 skipping and MET-amplification was 33% 40%, 20%, 34%, 17% and 60%, respectively. Additionally, the pooled mPFS of EGFR, KRAS, MET, HER2 and RET alteration was 2.77, 3.24, 2.48, 2.31 and 2.68 months, while the pooled mOS of EGFR and KRAS alteration was 9.98 and 12.29 months. In prospective data concerning EGFR mutation, the pooled ORR and mPFS treated with chemo-immunotherapy (IC) was reached 38% and 6.20 months, while 58% and 8.48 months with chemo-immunotherapy plus anti-angiogenesis therapy (ICA). Moreover, the pooled mPFS and mOS of monoimmunotherapy was 2.33 months and 12.43 months. EGFR, ALK, HER2, RET and ROS1-altered NSCLC patients have poor reactivity to monoimmunotherapy, but the efficacy of immune-based combined therapy is significantly improved. KRAS G12C mutation, BRAF non-V600E mutation and MET amplification have better response to immunotherapy, and more prospective studies are needed for further research.

Keywords: efficacy, immunotherapy, non-small-cell lung cancer

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Introduction

Lung cancer is the leading cause of cancer death and is also the main cause of cancer morbidity and mortality in men. In women, the incidence of lung cancer ranks third, second only to breast cancer and colorectal cancer, and the mortality rate is second only to breast cancer.¹ WHO divides lung cancer into two broad histological subtypes: non-small-cell lung cancer (NSCLC) and small-cell lung cancer. The former is the cause of about 85% of cases, and the latter accounts for the remaining 15%. NSCLC is further subdivided into adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma.² In the whole population, the proportion of Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation is about 25-30%, which is also much higher than other types of mutations. The most common type of mutation in KRAS is G12C, accounting for about 13% of non-small-cell lung cancer.³ Epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK)

fusion have been found in approximately 20% and 5%, respectively, in advanced NSCLC. Somatic activating v-raf murine sarcoma viral oncogene homolog B1 (BRAF) V600E, human epidermal growth factor receptor 2 (HER2), proto-oncogene receptor tyrosine kinase (ROS1), and rearranged during transfection proto-oncogene (*RET*) alterations all occurred less than 5% of patients with NSCLC. Mesenchymal to epithelial transition factor (MET) mutations occurred in 2-4% population, and the most common subtype is MET-exon 14 skipping.⁴ The development and use of targeted drugs for these specific changes have improved the results of patients with NSCLC harboring oncogene changes. However, the continuous emergence of drug resistance has led to many problems in follow-up treatment, which need to be further solved. Immunotherapy is an emerging antitumor therapy that can improve the survival of patients with advanced NSCLC. However, only about 20% of NSCLC patients can benefit from this

treatment.⁵ Programmed cell death protein 1 (PD-1)/programmed cell death ligand (PD-L1) drugs such as nivolumab, pembrolizumab, and atezolizumab play a more and more important role in the treatment of NSCLC. Some phase III clinical trials have shown that immune checkpoint inhibitors (ICIs) can significantly prolong the overall survival (OS) of patients with drivernegative advanced NSCLC compared with chemotherapy, either alone or in combination.⁶⁻⁸ However, there are few clinical trials to study whether ICIs are more effective than tyrosine kinase inhibitors (TKIs) or chemotherapy in patients with driving gene-positive NSCLC. The overall therapeutic effect of ICIs is not satisfactory in patients with drug-resistant advanced NSCLC. The data show that immunotherapy can benefit some NSCLC patients with positive driving genes, improve the remission rate, and prolong the survival time of patients.9-11 However, the results of Checkmate 057, OAK, POPLAR, and KEYNOTE-010 studies showed that there was no significant survival benefit in the immunotherapy group compared with the chemotherapy group in patients with EGFR mutant NSCLC.¹²⁻¹⁵ At present, whether patients with driving genepositive NSCLC can benefit from immunotherapy is one of the hot issues. Therefore, we analyzed the efficacy of immunotherapy in patients with oncogene-driven NSCLC and concluded the efficacy of altered subtypes. In addition, the efficacy of immuno-combination therapy in different driven genes after using immunotherapy was also deep-dived. This meta-analysis was reported by the PRISMA reporting checklist (Supplemental Tables S1 and S2).¹⁶

Methods

Search strategy and selection criteria

A literature search was performed using PubMed, Web of Science, and Cochrane databases to identify prospective clinical trials and retrospective studies of NSCLC patients treated with ICIs alone or in combination from 2015 to 2022. The following search terms were used: '(immune checkpoint inhibitor or immunotherapy or programmed cell death protein 1 or PD-1 or programmed death ligand-1 or PD-L1 or cytotoxic T-lymphocyte-associated protein 4 or CTLA-4 or nivolumab or pembrolizumab or camrelizumab or sintilimab or tislelizumab or toripalimab or cemiplimab or durvalumab or atezolizumab or sugemalimab or avelumab or ipilimumab or tremelimumab or dostarlimab or relatlimab or penpulimab or cadonilimab or serplulimab or sugemalimab or envafolimab or zimberelimab or pucotenlimab or prolgolimab)' and '(non-small cell lung cancer or NSCLC)' and '(EGFR or KRAS or ALK or BRAF or MET or HER2 or ERBB2 or RET or ROS1)' (Supplemental Table S3). The search was conducted in March 2023.

Study selection

We first defined inclusion and exclusion criteria. The inclusion criteria were as follows: (1) prospective or retrospective observational studies; (2) articles involving patients treated with ICIs alone or in combination; and (3) the study endpoints included objective response rate (ORR), progression-free survival (PFS), or OS. The exclusion criteria were as follows: (1) case reports, reviews, editorials, meta-analyses, and letters; (2) studies that did not focus on any of the abovementioned endpoints; and (3) studies that were not published in English. Two reviewers (J.Chen and W.Lu) evaluated the titles and abstracts of publications identified by the search strategy, and any publication thought to be potentially relevant was retrieved in full. The reviewers then assessed full publications for eligibility. Reviewers were not blinded to study authors or outcomes. The decision to include a study for review was made by consensus between the reviewers (J.Chen and W.Lu). The plan was that disagreements would be resolved by the third author (M.Chen) but none occurred.

Data extraction

Data were extracted by paired reviewers (J.Chen and W.Lu). Disagreements were resolved by consensus. Data extracted included Gene mutation type, ICI class, year of publication, and the presence of at least one measure of activity (ORR, PFS, and OS). Data were extracted from the main text and Supplemental Material.

Study objectives

The main purpose of this study was to investigate the efficacy of immunotherapy in patients with NSCLC with different alterations. Associations between efficacy and gene-altered subtypes were also explored.

Statistical analysis

Descriptive statistics were used to summarize the characteristics data of patients with NSCLC. The main results were summed in a table and a quantitative synthesis was planned for all the reported cases. We performed the random-effects model to pool results to estimate the efficacy of the treatment, and statistical heterogeneity was assessed using the I^2 test in the random-effects model. When the average ORR of all samples was between 20% and 80%, no transformation was required. When it was less than 20% or over 80%, logit transformation was used. Freeman-Tukey double arcsine transformation was used when there were a large number of values of 0 or 100%. Publication bias was evaluated with the funnel plot asymmetry test. The data analysis was performed using R-Studio (Version 4.2.1, R Studio Team, R Studio Inc. Boston, MA, USA), Stata (Version 17, STATA Corp, College Station, TX, USA), and Microsoft 2016 (Microsoft Corporation, Redmond, Washington, DC, USA).

Results

Results of the systematic search

Our search strategies in ClinicalTrials.gov, PubMed, Web of Science, and Cochrane databases identified a total of 4628 titles. In total, 3378 of them were excluded because of duplication. Therefore, 1250 articles were evaluated by title and abstract, and 918 of them were excluded because of review or meta-analysis. Among the remaining 332 articles, 246 studies were excluded (n = 84 non-relevant subgroup or post-hoc analysis; n = 136 trial design or protocol publication; n = 12 no related outcomes; n = 14 no common treatment). In all, 86 studies were therefore included in the qualitative analysis: 25 contain prospective data from clinical trials, whereas 61 report the outcomes of retrospective studies (Figure 1). There are few prospective clinical studies on immunotherapy of gene mutant-positive NSCLC directly, and most of them are collected from subgroups. Unfortunately, significant heterogeneity was observed in almost all subgroups, which may be attributable to the specificity of the single-arm study. Therefore, the random-effect model was adopted. Concerning retrospective data, the large majority of studies reported outcomes from single-agent anti-PD-1/PD-L1 treatments, while a minority of patients had been

exposed to combinations, the ICI evaluated has always been reported.

EGFR-mutant NSCLC

There are 23 clinical trials and 37 retrospective studies in patients with EGFR-mutant-positive NSCLC based on immunotherapy, and most data of them are from subgroups (Tables 1 and 2)9,11,17-74. When pooling activity data in the meta-analysis indeed, the pooled ORR of EGFR-mutant patients treated with immunotherapy in clinical trials was 6% $(95\% \text{ CI: } 3-9, I^2 = 0\%)$, while 8% (95% CI: 6-11), $I^2 = 43\%$) in retrospective studies (Figure 2). And the pooled ORR was 49% (95% CI: 40-57, $I^2 = 63\%$) of patients treated with immunocombination therapy in clinical trials. Among combined therapies, the pooled ORRs of chemoimmunotherapy(IC) and chemoimmunotherapy plus anti-angiogenesis therapy (ICA) were reached 38% (95% CI: 29–48, *I*²=48%) and 58% (95% CI: 46-70, I²=75%), respectively. In addition, the pooled mPFS and mOS of immunotherapy were 2.33 months (95% CI: 1.67-2.98, $I^2 = 72.6\%$) and 12.43 months (95% CI: 6.43– 18.43, $I^2 = 84.3\%$) in clinical trials, while 2.77 months (95% CI: 1.91–3.62, *I*²=95.6%) and 9.98 months (95% CI: 6.58–13.39, I^2 =59.7%) in retrospective studies (Figure 3). Moreover, the pooled mPFS and mOS of immuno-combination therapy were 6.99 months (95% CI: 5.89-8.09, $I^2 = 59.3\%$) and 20.74 months (95% CI: 15.00-26.49, $I^2 = 63.2\%$), respectively. And among immuno-combination therapy, the pooled mPFS of IC and ICA were 6.20 months (95% CI: 5.32-7.08, $I^2 = 19.4\%$) and 8.48 months (95% CI: 6.40–10.56, I^2 =56.3%), respectively. The data concerning subtypes of EGFR mutation were few, and a retrospective study conducted by Hastings's team showed that L861Q received the worst efficacy (ORR=0%, mPFS=1.3 months) and G719 for the best (ORR=29%, mPFS=4.8 months, mOS = 29 months).

KRAS-mutant NSCLC

Because of the gap between different studies, pooling activity data in the collected studies, the outcome suggested that the pooled ORR was 23% (95% CI: 6–39, $I^2=87\%$; Table 3) in the clinical trials while 28% (95% CI: 21–35, $I^2=86\%$) in retrospective studies (Table 4).^{10,11,14,17,20,21,26,43,48,49,57,58,64,72,75–81} As for these patients, the pooled ORR of *KRAS* non-G12C mutant NSCLC reached 33% (95%



Figure 1. Flowchart diagram of the literature search and study selection.

CI: 22–44, $I^2 = 79\%$), while 40% (95% CI: 25– 55, $I^2 = 83\%$) of KRAS G12C mutant (Figure 4). Besides that, the pooled mPFS and mOS of monoimmunotherapy in retrospective studies were 3.24 months (95% CI: 2.48–4.00, $I^2 = 73.6\%$) and 12.29 months (95% CI: 10.45– 14.13, $I^2 = 19.9\%$; Figure 5).

ALK-fusion NSCLC

The pooled ORR was 0% (95% CI: 0–8, $I^2 = 0$) of *ALK*-fusion-positive NSCLC treated with immunotherapy in three clinical trials, while 3% (95% CI: 0–13, $I^2 = 21\%$) in eight retrospective studies (Table 4 and Figure 6).^{21,23,29,38,39,44,47,57,58,63,82}

Other uncommon driving gene-positive NSCLC

Ten retrospective concerning BRAF-mutant NSCLC studies were included in our analysis, the results showed that the pooled ORR was 24% (95% CI: 18–31, $I^2 = 0$), and the subgroup analysis showed that the pooled ORRs of patients with BRAF V600E and non-V600E mutations were 20% (95% CI: 9–31, $I^2=0$) and 34% (95% CI: 19–49, $I^2 = 0$; Supplemental Figure S1 and Table S4), respectively.^{43,49,57,58,64,83-87} In seven retrostudies MET-altered spective concerning NSCLC, the pooled ORR of them was 23% (95% CI: 12-33, $I^2 = 55\%$; Supplemental Figure S2 and Table S5.)^{57,58,64,83,86,88,89}. By subgroup analysis, the pooled ORR of MET-exon 14 skipping Table 1. Clinical activity of immunotherapy in EGFR-altered NSCLC patients of prospective study.

References	Year	Therapy	Patients	ORR (%)	mPFS, month (95% CI)	m0S, month (95% CI)
Gettinger ¹⁷	2015	I	12	2 (17)	NA	NA
Gettinger ¹⁸	2016	I	7	1 (14)	1.8 (0.2–7.6)	NA
Nishio ¹⁹	2016	I	20	1 (5)	2.7 (1.2–2.9)	14.2 (5.7–15.4)
Rizvi ²⁰	2016	IC	6	1 (17)	4.8 (0.9–6.8)	20.5 (9.4–35)
Gulley ²¹	2017	I	9	0 (0)	5.4 (1.9–24.0)	3.0 (1.1-NR)
Hellmann ²²	2017	Ш	8	4 (50)	NA	NA
Peters ¹¹	2017	I	45	4 (9)	NA	NA
Garassino ²⁴	2018	I	64	9 (14)	2.0 (1.8–3.7)	16.1 (6.2–33.2)
Garassino ²³	2018	I	102	9 (9)	3.0 (2.7–3.3)	8.3 (2.2–14.4)
Gubens ²⁵	2018	I	10	1 (10)	NA	NA
Horn ²⁶	2018	I	10	0 (0)	NA	NA
Lisberg ²⁷	2018	I	10	0 (0)	4.0 (NA)	NR
Leighl ²⁸	2019	I	74	4 (5)	NA	6.0 (4.4-8.8)
Nishio ²⁹	2019	I	10	0 (0)	2.0 (1.0-4.0)	10.0 (3.0-NR)
Omori ³⁰	2019	I	13	0 (0)	NA	NA
Reck ⁹	2019	ICA	34	24 (71)	10.2 (7.9–15.2)	24.2 (18.4–25.6)
		IC	45	16 (36)	6.9 (5.7–8.5)	16.7 (12.5–22.9)
Arrieta ³¹	2020	IC	12	7 (58)	6.8 (6.2-NR)	8.3 (3.3–NR)
Han ³²	2021	ICAª	40	19 (59)	NA	NA
Jiang ³³	2021	IC	40	20 (50)	7.0 (4.8–8.4)	23.5 (18.0-NR)
Lam ³⁴	2021	ICA	40	25 (63)	9.4 (7.6–12.1)	NR
Hayashi ³⁵	2022	I	52	5 (10)	1.7 (1.3–2.3)	20.7 (15.2–28.0)
Lu ³⁶	2022	ICA	148	65 (44)	6.9 (6.0-9.3)	NA
		IC	145	48 (33)	5.6 (4.7–6.9)	NA
Yang ³⁷	2022	I	5	0 (0)	NA	NA

AE, adverse event; EGFR, Epidermal growth factor receptor; I, monoimmunotherapy; II, double immunotherapy; IC, chemoimmunotherapy; ICA, immunotherapy plus chemotherapy and anti-angiogenesis therapy; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; NR, not reach; ORR, objective response rate.

a32 patients were estimated for efficacy and 40 patients were estimated for safety.

NSCLC patients treated with immunotherapy was 17% (95% CI: 5–28, I^2 =28%), while the pooled ORR of *MET*-amplification population was 60% (95% CI: 17–100, I^2 =77%). In addition, the pooled mPFS of monoimmunotherapy was 2.48 months (95% CI: 1.14–3.83, I^2 =35.6%; Supplemental Figure S3). A total of 11 retrospective studies with *HER2*-mutant NSCLC were included in the analysis, the pooled ORR was 14% (95% CI: 9–19, $I^2=0$) in immunotherapy alone, while 37% (95% CI: 24–50, $I^2=35\%$) in immunotherapy combined with other therapies (Supplemental Figure S4 and Table S6).^{43,50,57,58,69,83,86,90–93} The pooled ORRs of *RET*-rearranged and *ROS1*-rearranged NSCLC were 6% (95% CI: 0–16, $I^2=29\%$; Supplemental

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References	Year	Therapy	Patients	ORR (%)	mPFS, month (95% CI)	m0S, month (95% CI)
Gainor ³⁸	2016	I	22	1 (5)	NA	NA
Bagley ³⁹	2017	I	12	1 (8)	NA	NA
Haratani ⁴⁰	2017	I	25	5 (20)	1.5 (1.3–2.8)	NA
Kim ⁴¹	2017	I	4	0 (0)	NA	13.8 (4.2–NR)
Kobayashi ⁴²	2017	I	16	1 (6)	NA	NA
Oya ⁴³	2017	I	22	2 (9)	1.9 (1.1–3.0)	8.4 (4.2–NR)
Fujimoto44	2018	I	95	6 (6)	NA	NA
Hsu ⁴⁵	2018	I	7	0 (0)	11.5 (NA)	11.5 (NA)
Juergens ⁴⁶	2018	I	25	0 (0)	1.9 (1.1–3.0)	3.4 (2.9-NA)
Kobayashi ⁴⁷	2018	I	16	0 (0)	NA	NA
Lin ⁴⁸	2018	I	25	2 (8)	1.3 (NA)	10.5 (NA)
Takeda ⁵⁰	2018	I	5	1 (20)	NA	NA
Schouten ⁴⁹	2018	I	9	0 (0)	NA	NA
Yoshida ⁵¹	2018	I	24	2 (8)	NA	NA
Ahn ⁵²	2019	I	23	3 (13)	1.6 (NA)	4.4 (NA)
Cho ⁵³	2019	I	38	6 (16)	1.9 (1.1–2.7)	NA
Guibert ⁵⁴	2019	I	5	0 (0)	NA	NA
Hastings ⁵⁵	2019	I	171	17 (10)	1.8 (0–40.5)	9.4 (0.1–73.3)
Landi ⁵⁶	2019	I	16	1 (6)	NA	NA
Mazieres57	2019	I	115	15 (13)	2.1 (1.8–2.7)	10.0 (6.7–14.2)
Ng ⁵⁸	2019	I	68	0 (0)	1.4 (NA)	NA
Sakamoto ⁵⁹	2019	I	21	3 (14)	NA	NA
Sato ⁶⁰	2019	I	9	1 (11)	1.0 (0.2–1.7)	NR
Yamada ⁶¹	2019	I	27	6 (22)	1.9 (0.3–20.4)	NR
Yamaguchi ⁶²	2019	I	14	1 (7)	NA	NA
Bylicki ⁶³	2020	I	42	8 (19)	2.2 (1.4–3.2)	13.9 (8.8–20.0)
Gainor ⁶⁴	2020	I	17	3 (18)	NA	NA
Ishii ⁶⁵	2020	I	25	7 (28)	NA	NA
Kitadai ⁶⁶	2020	I	24	0 (0)	1.0 (0.8–1.3)	2.7 (1.4–11.6)
Morita ⁶⁷	2020	I	116	10 (9)	1.5 (1.2–1.7)	12.1 (9.0–16.2)
Song ⁶⁸	2020	I	4	1 (25)	NA	NA

Table 2. Clinical activity of immunotherapy in EGFR-altered NSCLC patients of retrospective study.

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References	Year	Therapy	Patients	ORR (%)	mPFS, month (95% CI)	m0S, month (95% CI)
Lau ⁶⁹	2021	I	34	6 (18)	NA	NA
Masuda ⁷⁰	2021	I	35	5 (14)	NA	NA
Shen ⁷¹	2021	I	22	2 (9)	2.9 (1.7–4.2)	19.7 (8.1–31.2)
		IC	8	2 (25)	4.2 (3.1–5.4)	NR
Yoh ⁷²	2021	I	18	1 (6)	NA	NA
Hu ⁷³	2022	I	20	3 (15)	3.0 (1.3–3.3)	7.4 (5.7–15.4)
		IC	79	27 (34)	7.4 (3.0–13.3)	29.0 (11.7–NR)
Lu ⁷⁴	2022	I	32	5 (16)	14.7 (13.0–16.3)	NA

Table 2. (Continued)

EGFR, Epidermal growth factor receptor; I, monoimmunotherapy; IC, chemoimmunotherapy; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; NR, not reach; NSCLC, non-small-cell lung cancer; ORR, objective response rate.

Table S7) and 8% (95% CI: 0–17, P=0; Supplemental Table S8), respectively.^{57,58,63,83,86,94–97} Moreover, the pooled mPFS rates of *HER2*mutant and *RET*-rearranged monoimmunotherapy were 2.31 months (95% CI: 1.61–3.01, $I^2=0$) and 2.68 months (95% CI: 1.60–3.76, $I^2=0$), respectively (Supplemental Figure S3).

Publication bias

There was an apparent asymmetry in the funnel plots, which suggested the presence of publication bias (Supplemental Figure S5). However, this finding can be explained by the high heterogeneity in each subgroup, which was an inevitable limitation of the single-arm or retrospective study. Therefore, we decided to include these studies in our analysis.

Discussion

At present, there is no sufficient evidence for immunotherapy for NSCLC with a positive driving gene. Herein, our study analyzed the efficacy of advanced oncogene-driven NSCLC patients treated with monoimmunotherapy or immunecombination therapy. In retrospective data, the pooled ORRs of EGFR, ALK, KRAS, BRAF, MET, HER2, RET, and ROS1 alteration in retrospective studies treated with monoimmunotherapy were 8%, 3%, 28%, 24%, 23%, 14%, 7%, and 8%, respectively. Among them, the pooled ORRs of KRAS non-G12C mutation, KRAS G12C mutation, BRAF V600E mutation, BRAF

non-V600E mutation, MET-exon 14 skipping, and MET-amplification were 33% 40%, 20%, 34%, 17%, and 60%, respectively. In addition, the pooled mPFS rates of EGFR, KRAS, MET, *HER2*, and *RET* alteration were 2.77, 3.24, 2.48, 2.31, and 2.68 months, respectively. Moreover, the pooled mOS rates of EGFR and KRAS alteration were 9.98 and 12.29 months, respectively. In prospective data, the pooled ORRs of EGFR, ALK, and KRAS alteration were 6%, 0%, and 23%, respectively. The pooled ORR and mPFS of EGFR-mutant NSCLC treated with IC reached 38% and 6.20 months, while 58% and 8.48 months with ICA. In addition, the pooled mPFS and mOS of monoimmunotherapy were 2.33 months and 12.43 months in EGFR mutation, respectively.

The pooled ORR and mPFS of EGFR-mutant NSCLC are similar to or lower than those of KRAS, BRAF, MET, HER2, RET, and ROS1 alteration in studies treated with monoimmunotherapy, while those of EGFR mutation become higher with immuno-combination therapy than monoimmunotherapy. That means EGFR mutation may be biomarkers of poor response to monoimmunotherapy and good response to immune-combination therapy. The results of a meta-analysis of Yang's, Lee's, and Qian's teams all showed that compared with conventional chemotherapy, monoimmunotherapy did not prolong the survival time of EGFR-mutant NSCLC patients.98-100 And meta-analysis performed by Rui's and Lee's teams both showed

(4)	Study	Events	Total		Proportion	95%-CI	Weight (common)	
	Gettinger 2015	2	12	+		[0.02; 0.48]	2.8%	2.89
	Gettinger 2016	1	7 - 20 -	· ·	- 0.14 0.05	[0.00; 0.58]	1.7%	1.79
	Nishio 2016 Gulley 2017	0	9 +		0.05	[0.00; 0.25] [0.00; 0.34]	2.1%	2.19
	Peters 2017	4	45		0.09	[0.02; 0.21]	10.1%	10.19
	Garassino 2018	9	64		0.14	[0.07; 0.25]	14.3%	14.39
	Garassino 2018	9	102	1	0.09	[0.04; 0.16]	22.8%	22.89
	Gubens 2018	1	10 -		0.10	[0.00; 0.45]	2.3%	2.39
	Horn 2018 Lisberg 2018	0	10 -		0.00	[0.00; 0.31]	2.3%	2.39
	Leighl 2019	4	74		0.05	[0.01; 0.13]	16.5%	16.59
	Nishio 2019	0	10 *	-T	0.00	[0.00; 0.31]	2.3%	2.39
	Omori 2019	0	13 *		0.00	[0.00; 0.25]	3.0%	3.09
	Hayashi 2022	5	52			[0.03; 0.21]	11.7%	11.79
	Yang 2022	0	5 .			[0.00; 0.52]	1.2%	1.29
	Common effect model Random effects mode Heterogeneity: $J^2 = 0\%$, τ^2	1				[0.03; 0.09] [0.03; 0.09]	100.0%	100.0%
(b)	Study	Events	0 Total	0.1 0.2 0.3 0.4 0.5	Proportion	95%-CI	Weight (common)	Weigh (random
()	Gainor 2016	1	22 -	*!		[0.00; 0.23]	1.8%	2.69
	Bagley 2017	1	12 -		0.08	[0.00; 0.38]	1.0%	1.89
	Haratani 2017	5	25	<u>↓</u>	0.20	[0.07; 0.41]	2.1%	2.89
	Kim 2017	0	4 -		0.00	[0.00; 0.60]	0.4%	0.89
	Kobayashi 2017	1	16 -	*	0.06	[0.00; 0.30]	1.4%	2.19
	Oya 2017 Eujimoto 2018	2	22	4	0.09	[0.01; 0.29]	1.8%	2.69
	Fujimoto 2018 Hsu 2018	6	95		0.06	[0.02; 0.13]	7.8%	4.99
	Juergens 2018	0	25 -		0.00	[0.00; 0.14]	2.1%	2.89
	Kobayashi 2018	0	16 *		0.00	[0.00; 0.21]	1.4%	2.19
	Lin 2018	2	25	1	0.08	[0.01; 0.26]	2.1%	2.89
	Takeda 2018	1	5 -		0.20	[0.01; 0.72]	0.5%	0.99
	Schouten 2018 Yoshida 2018	0	9 • 24 ·		0.00 0.08	[0.00; 0.34]	0.8%	1.49
	Ahn 2019	2	24 23		0.08	[0.01; 0.27] [0.03; 0.34]	2.0%	2.89
	Cho 2019	6	38		0.16	[0.06; 0.34]	3.2%	3.59
	Guibert 2019	0	5 -	1	0.00	[0.00; 0.52]	0.5%	0.99
	Hastings 2019	17	171		0.10	[0.06; 0.15]	14.0%	5.69
	Landi 2019	1	16 -		0.06	[0.00; 0.30]	1.4%	2.19
	Mazieres 2019 Ng 2019	15 0	115 68 III		0.13	[0.07; 0.21]	9.5%	4.59
	Sakamoto 2019	3	21		0.14	[0.03; 0.36]	1.8%	2.69
	Sato 2019	1	9 -		0.11	[0.00; 0.48]	0.8%	1.49
	Yamada 2019	6	27		0.22	[0.09; 0.42]	2.3%	3.09
	Yamaguchi 2019	1	14 -		0.07	[0.00; 0.34]	1.2%	2.09
	Bylicki 2020	8	42		0.19	[0.09; 0.34]	3.5%	3.79
	Gainor 2020 Ishii 2020	37	17	<u> </u>	0.18	[0.04; 0.43] [0.12; 0.49]	1.4%	2.29
	Kitadai 2020	Ó	24 *		0.00	[0.00; 0.14]	2.0%	2.89
	Morita 2020	10	116		0.09	[0.04; 0.15]	9.5%	5.29
	Song 2020	1	4 -	+ +	- 0.25	[0.01; 0.81]	0.4%	0.89
	Lau 2021	6	34	<u>+</u> ∗−−	0.18	[0.07; 0.35]	2.8%	3.39
	Masuda 2021	6 5	34 35	*	0.18	[0.07; 0.35] [0.05; 0.30]	2.8%	3.39
	Masuda 2021 Yoh 2021	6 5 1	34 35 18 -		0.18 0.14 0.06	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27]	2.8% 2.9% 1.5%	3.3° 3.4° 2.3°
	Masuda 2021 Yoh 2021 Shen 2021 Hu 2022	6 5 1 2 3	34 35 18 22 20		0.18 0.14 0.06 0.09 0.15	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.01; 0.29] [0.03; 0.38]	2.8% 2.9% 1.5% 1.8% 1.7%	3.39 3.49 2.39 2.69 2.59
	Masuda 2021 Yoh 2021 Shen 2021 Hu 2022 Lu 2022 Common effect model	6 5 1 2 3 5	34 35 18 22		0.18 0.14 0.06 0.09 0.15 0.16 0.08	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.01; 0.29] [0.03; 0.38] [0.05; 0.33]	2.8% 2.9% 1.5% 1.8%	3.39 3.49 2.39 2.69 2.59 3.29
	Masuda 2021 Yoh 2021 Shen 2021 Hu 2022 Lu 2022	6 5 1 2 3 5	34 35 18 22 20 32 1203		0.18 0.14 0.06 0.09 0.15 0.16 0.08	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.01; 0.29] [0.03; 0.38] [0.05; 0.33]	2.8% 2.9% 1.5% 1.8% 1.7% 2.7%	3.39 3.49 2.39 2.69 2.59 3.29
(c)	Masuda 2021 Yoh 2021 Shen 2021 Hu 2022 Lu 2022 Common effect model Random effects mode	6 5 1 2 3 5	34 35 18 - 20 32 1203 , p < 0.0	1 02 04 06	0.18 0.14 0.06 0.09 0.15 0.16 0.08 0.08	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.01; 0.29] [0.03; 0.38] [0.05; 0.33] [0.06; 0.10] [0.06; 0.11]	2.8% 2.9% 1.5% 1.8% 1.7% 2.7%	3.39 3.49 2.39 2.69 3.29 3.29 100.09
(c)	Masuda 2021 Yoh 2021 Shen 2021 Hu 2022 Lu 2022 Common effects model Heterogenety. <i>I²</i> = 43%, v Study Rizvi 2016	65 1 2 3 5 1 $1^2 = 0.0070$, Events 1	34 35 18 - 22 20 32 1203 p < 0.5 0 Total 6 - 2		0.18 0.14 0.06 0.09 0.15 0.16 0.08 0.8 Proportion 0.17	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.01; 0.29] [0.03; 0.38] [0.05; 0.33] [0.06; 0.10] [0.06; 0.11] 95%-Cl [0.00; 0.64]	2.8% 2.9% 1.5% 1.8% 2.7% 100.0% Weight (common) 2.0%	3.39 3.49 2.39 2.59 3.29 100.09 Weigh (random
(c)	Masuda 2021 Yoh 2021 Shen 2021 Hu 2022 Lu 2022 Common effect model Random effects model Heterogeneity: I ² = 43%, t Study Rizvi 2016 Helimann 2017	65 1 2 3 5 1 2 ² = 0.0070, Events 1 4	34 35 18 - 22 20 32 1203 p < 0.5 0 Total $6 - \frac{8}{8}$		0.18 0.14 0.06 0.09 0.15 0.16 0.08 Proportion - 0.17 - 0.50	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.01; 0.29] [0.03; 0.38] [0.05; 0.33] [0.06; 0.10] [0.06; 0.11] 95%-CI [0.00; 0.64] [0.16; 0.84]	2.8% 2.9% 1.5% 1.8% 1.7% 2.7% 100.0% 	3.39 3.49 2.59 2.59 3.29 100.09 Weigh (random
(c)	Masuda 2021 Yoh 2021 Shen 2021 Hu 2022 Lu 2022 Common effects model Heterogenety. <i>I²</i> = 43%, v Study Rizvi 2016	65 1 2 3 5 1 $1^2 = 0.0070$, Events 1	34 35 18 - 22 20 32 1203 p < 0.5 0 Total 6 - 2		0.18 0.14 0.06 0.09 0.15 0.16 0.08 0.8 Proportion 0.17	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.01; 0.29] [0.03; 0.38] [0.05; 0.33] [0.06; 0.10] [0.06; 0.11] 95%-Cl [0.00; 0.64]	2.8% 2.9% 1.5% 1.8% 2.7% 100.0% Weight (common) 2.0%	3.39 3.49 2.59 3.29 100.09 Weigh (random 6.29 4.99 18.09
(c)	Masuda 2021 Yoh 2021 Shen 2021 Hu 2022 Lu 2022 Common effect model Hetrogenety. I ² = 43%, v Study Rizvi 2016 Heliman 2017 Reck 2019 Arrieta 2020	6 5 1 2 3 5 5 Events 1 4 40 7 9	34 35 18 - 22 20 32 1203 p < 0.0 0 Total 6 - 8 79 12 3		0.18 0.14 0.06 0.09 0.15 0.16 0.08 0.08 Proportion - 0.57 - 0.51 0.59	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.01; 0.29] [0.03; 0.38] [0.06; 0.10] [0.06; 0.11] 95%-CI [0.00; 0.64] [0.39; 0.62] [0.28; 0.85] [0.24; 0.76]	2.8% 2.9% 1.5% 1.8% 2.7% 100.0% - (common) 2.0% 1.5% 14.8% 2.3% 6.2%	3.33 3.49 2.55 3.29 100.09 Weigh (random 6.29 4.99 18.09 6.89 12.79
(c)	Masuda 2021 Shen 2021 Shen 2021 Hu 2022 Lu 2022 Common effect model Random effects model Heterogeneity. <i>I</i> ² = 43%, 1 Study Rizd 2016 Helimann 2017 Reck 2019 Arriela 2020 Han 2021	6 5 1 2 3 5 5 1 1 2 3 1 2 3 5 1 1 2 3 5 5 1 1 2 3 5 5 1 1 1 2 3 5 5 1 1 2 3 5 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	34 35 18 20 32 1203 p < 0.6 0 Total $6 - \frac{8}{79}$ 12 32 40	M 02 04 06	0.18 0.14 0.06 0.09 0.15 0.16 0.08 0.08 Proportion - 0.57 - 0.55 0.59 0.50	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.01; 0.29] [0.03; 0.38] [0.05; 0.33] [0.06; 0.10] [0.06; 0.11] [0.06; 0.11] [0.06; 0.41] [0.16; 0.84] [0.39; 0.62] [0.28; 0.85] [0.41; 0.76] [0.41; 0.76] [0.41; 0.76]	2.8% 2.9% 1.5% 1.7% 2.7% 100.0% 	3.33 3.49 2.65 3.25 3.25 100.09 Weigh (random 6.25 4.99 18.09 6.85 12.77 13.99
(c)	Masuda 2021 Yoh 2021 Shen 2021 Hu 2022 Lu 2022 Common effect model Hetrogenety. I ² = 43%, v Study Rizvi 2016 Heliman 2017 Reck 2019 Arrieta 2020	6 5 1 2 3 5 5 1 1 1 2 3 5 5 1 2 3 5 5 1 2 3 5 5 1 1 2 3 5 5 1 1 2 3 5 5 1 1 2 3 5 5 1 1 2 3 5 5 1 1 2 3 5 1 1 2 2 3 5 1 1 2 2 2 0.0070, 1 1 4 4 400 7 7 19	34 35 18 - 22 20 32 1203 p < 0.0 0 Total 6 - 8 79 12 3		0.18 0.14 0.06 0.09 0.15 0.16 0.08 0.08 Proportion - 0.57 - 0.51 0.59	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.01; 0.29] [0.03; 0.38] [0.06; 0.10] [0.06; 0.11] 95%-CI [0.00; 0.64] [0.39; 0.62] [0.28; 0.85] [0.24; 0.76]	2.8% 2.9% 1.5% 1.8% 2.7% 100.0% - (common) 2.0% 1.5% 14.8% 2.3% 6.2%	3.33 3.49 2.35 2.69 2.55 3.29 100.09 Weigh (random 6.29 18.00 6.89 12.77 13.99 14.35
(c)	Masuda 2021 Yoh 2021 Shen 2021 Hu 2022 Lu 2022 Common effect model Heterogeneky: / ² = 43%, 1 Study Rizvi 2016 Helimann 2017 Reck 2019 Arrieta 2020 Han 2021 Lu 2022 Common effect model Random effect model	6 5 1 2 3 5 5 Events 1 4 400 7 19 20 25 113	34 35 18 - 22 20 32 1203 <i>p</i> < 0.6 0 Total 6 - 8 79 12 32 32 32 1203 0 Total 6 - 8 510		0.18 0.14 0.06 0.09 0.15 0.16 0.08 Proportion 0.8 Proportion 0.17 - 0.50 0.8 0.8	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.01; 0.29] [0.03; 0.33] [0.06; 0.10] [0.06; 0.11] [0.06; 0.11] [0.06; 0.11] [0.06; 0.64] [0.16; 0.84] [0.39; 0.62] [0.28; 0.85] [0.41; 0.76] [0.24; 0.65] [0.44; 0.66] [0.46; 0.77]	2.8% 2.9% 1.5% 1.8% 1.7% 2.7% 100.0% 	3.33 2.66 2.55 3.25 100.09 Weigh (random 6.25 (random 6.25 4.99 18.05 6.85 12.77 13.95 12.77 13.95 14.33 23.35
(c)	Masuda 2021 Yoh 2021 Shen 2021 Hu 2022 Lu 2022 Common effect model Heterogeneky: / ² = 43%, m Study Rizvi 2016 Heliman 2017 Reck 2019 Arrieta 2020 Han 2021 Jiang 2021 Lu 2022	6 5 1 2 3 5 5 Events 1 4 400 7 19 20 25 113	34 35 18 - 22 20 32 1203 <i>p</i> < 0.6 0 Total 6 - 8 79 12 32 32 32 1203 0 Total 6 - 8 510		0.18 0.14 0.06 0.09 0.15 0.16 0.08 Proportion - 0.50 0.59 0.59 0.59 0.59 0.59 0.59 0.59	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.01; 0.29] [0.03; 0.38] [0.05; 0.33] [0.06; 0.10] [0.06; 0.10] [0.06; 0.11] 95%-CI [0.00; 0.64] [0.39; 0.62] [0.28; 0.85] [0.28; 0.85] [0.28; 0.85] [0.28; 0.86] [0.28; 0.86] [0.28; 0.86] [0.28; 0.86] [0.28; 0.86] [0.28; 0.86] [0.28; 0.86] [0.28; 0.86] [0.28; 0.86] [0.41; 0.76] [0.33; 0.44] [0.40; 0.46]	2.8% 2.9% 1.5% 1.7% 2.7% 100.0% 	3.3° 3.4° 2.5° 2.5° 3.2° 100.0° Weigh (random 6.2° 4.9° 18.0° 6.8° 12.7° 18.0° 14.3° 23.3° 100.0°
	Masuda 2021 Shen 2021 Shen 2021 Lu 2022 Lu 2022 Common effect model Heterogeneity. I ² = 43%, 1 Study Rizxi 2016 Helimann 2017 Reck 2019 Arriela 2020 Han 2021 Lu 2022 Common effect model Hearogeneity. I ² = 63%, 1 Study	6 5 1 2 3 5 5 Events 1 4 400 7 19 20 25 113	34 35 18 22 20 32 1203 p < 0.0 0 Total 6 - 8 79 12 32 Total 6 - 8 79 12 32 Total 6 - 8 79 12 32 Total 6 - 8 79 12 32 Total 6 - 8 79 12 32 32 Total 6 - 8 79 12 32 32 Total 6 - 8 79 12 32 32 32 Total 6 - 8 79 12 35 6 6 6 6 6 6 6 6		0.18 0.14 0.06 0.09 0.15 0.16 0.08 Proportion - 0.50 0.59 0.59 0.59 0.59 0.59 0.59 0.59	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.01; 0.29] [0.03; 0.38] [0.05; 0.33] [0.06; 0.10] [0.06; 0.11] 95%-CI [0.00; 0.64] [0.34; 0.66] [0.46; 0.77] [0.33; 0.44] [0.40; 0.49] [0.40; 0.57]	2.8% 2.9% 1.5% 1.8% 1.7% 2.7% 100.0% 	3 3 3 3 4 3 3 4 3 3 4 3 3 4 5 1 5 1 5 1 5 1 5 1 5 1 5 1 5 1 5 1 5
	Masuda 2021 Shen 2021 Shen 2021 Lu 2022 Common effect model Random effects model Heterogeneky. <i>I²</i> = 43%, 1 Study Rizvi 2016 Heliman 2017 Arrieta 2020 Han 2021 Lu 2022 Common effect model Random effects model Hetogeneky. <i>I²</i> = 63%, 1 Study Rizvi 2016	$\begin{array}{c} 6\\ 5\\ 1\\ 2\\ 3\\ 5\\ \end{array}$	34 35 18 22 20 32 1203 p < 0.0 0 Total 6 - 8 79 12 32 40 293 510 p < 0.0 0 79 12 32 40 40 293 510 510 p < 0.0 0 - 79 12 32 32 40 40 293 510 - - - - - - - -		0.18 0.14 0.06 0.09 0.15 0.16 0.08 Proportion 0.8 0.8 Proportion 0.51 0.59 0.59 0.59 0.59 0.62 0.39 0.62 0.45 0.49 8 Proportion 0.41	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.03; 0.28] [0.05; 0.33] [0.05; 0.33] [0.05; 0.33] [0.06; 0.11] 95%-CI [0.00; 0.64] [0.46; 0.84] [0.46; 0.84] [0.46; 0.84] [0.46; 0.84] [0.46; 0.77] [0.46; 0.49] [0.46; 0.49] [0.46; 0.47] [0.40; 0.49] [0.40; 0.49] [0.40; 0.49] [0.40; 0.49] [0.40; 0.49]	2.8% 2.9% 1.5% 1.8% 2.7% 100.0% (common) 2.0% 1.5% 14.8% 2.3% 6.2% 7.5% 8.0% 5.7.8% 100.0% 	3 3 3 3 4 3 3 4 3 3 4 5 1 5 1 5 1 5 1 5 1 5 1 5 1 5 1 5 1 5
	Masuda 2021 Shen 2021 Shen 2021 Lu 2022 Lu 2022 Common effects model Heterogeneity. I ² = 43%, 1 Study Rizzt 2016 Helmann 2017 Reck 2019 Arriela 2020 Lam 2021 Lam 2021 Lu 2022 Common effects model Heterogeneity. I ² = 63%, 1 Study Rizzt 2016 Rizzt 2016	6 5 1 2 3 5 1 1 4 40 7 19 20 25 113 113 12 12 1 40 7 25 113 12 12 12 13 12 12 12 13 1	34 35 18 - 22 - 20 32 1203 705 1203 705 709 12 32 705 709 12 32 705 709 12 32 705 709 12 32 705 709 12 32 709 12 32 709 12 32 709 12 32 709 12 32 709 12 32 709 12 32 32 700 709 12 32 32 709 12 32 32 709 12 32 32 709 12 32 32 400 293 510 709 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 70 709 70 709 70 709 70 709 70 709 70 709 70 709 70 709 70 709 70 709 70 709 70 709 70 709 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700		0.18 0.14 0.06 0.09 0.15 0.16 0.08 0.8 Proportion 0.17 0.58 0.8 Proportion 0.59 0.59 0.59 0.59 0.59 0.59 0.59 0.59	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.03; 0.27] [0.03; 0.38] [0.05; 0.33] [0.06; 0.10] [0.06; 0.11] 95%-CI [0.00; 0.64] [0.34; 0.66] [0.46; 0.77] [0.33; 0.44] [0.40; 0.57] [0.40; 0.57] 95%-CI	2.8% 2.9% 1.5% 1.8% 1.7% 2.7% 100.0% 	3.33 3.49 2.69 3.25 3.29 .100.09 Weigh 18.09 6.29 18.09 6.29 18.09 6.29 18.09 6.29 18.09 6.29 19.09 14.33 23.39 .100.09 Weigh (random 10.09 8.29 23.78
	Masuda 2021 Shen 2021 Shen 2021 Hu 2022 Common effect model Random effects model Heterogenety. <i>I</i> ² = 43%, 1 Study Rizvi 2016 Helmann 2017 Reck 2019 Arrieta 2020 Lu 2022 Common effect model Random effects model Heterogenety. <i>I</i> ² = 63%, 1 Study Rizvi 2016 Random effects model Netropolety. <i>I</i> ² = 63%, 1 Study	$\begin{array}{c} 6\\ 5\\ 1\\ 2\\ 3\\ 5\\ \end{array}$	34 35 18 - 20 32 1203 , p < 0.6 0 Total 6 - 8 79 12 32 20 0 0 Total 510 , p < 0.0 0 293 510 , p < 0.0 0 40 293 510 510 6 - 6 - 7 9 12 32 2 52 52 52 52 52 52 52 52 52 52 52 52		0.18 0.14 0.06 0.09 0.15 0.16 0.08 Proportion 0.51 0.59 0.59 0.59 0.59 0.62 0.39 0.45 0.49 8 Proportion 0.45 0.49	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.03; 0.28] [0.03; 0.38] [0.05; 0.33] [0.05; 0.33] [0.06; 0.10] [0.06; 0.11] 95%-CI [0.00; 0.64] [0.46; 0.84] [0.46; 0.84] [0.46; 0.84] [0.46; 0.84] [0.46; 0.77] [0.46; 0.77] [0.46; 0.49] [0.46; 0.49] [0.46; 0.47] [0.46; 0.47]	2.8% 2.9% 1.5% 1.8% 2.7% 100.0% (common) 2.0% 1.5% 14.8% 2.3% 1.5% 1.4.8% 6.2% 7.5% 7.5% 9.0% 100.0% 	3.33 3.49 2.65 3.22 100.09 Weigh (random 18.09 14.39 14.39 12.77 100.09 Weigh (random 8.29 2.37 9.22 2.37 9.22
	Masuda 2021 Shen 2021 Shen 2021 Lu 2022 Lu 2022 Common effects model Heterogeneity. I ² = 43%, 1 Study Rizzt 2016 Helmann 2017 Reck 2019 Arriela 2020 Lam 2021 Lam 2021 Lu 2022 Common effects model Heterogeneity. I ² = 63%, 1 Study Rizzt 2016 Rizzt 2016	6 5 1 2 3 5 1 1 4 40 7 19 20 25 113 113 12 12 1 40 7 25 113 12 12 12 13 12 12 12 13 1	34 35 18 - 22 - 20 32 1203 705 1203 705 709 12 32 705 709 12 32 705 709 12 32 705 709 12 32 705 709 12 32 709 12 32 709 12 32 709 12 32 709 12 32 709 12 32 709 12 32 32 700 709 12 32 32 709 12 32 32 709 12 32 32 709 12 32 32 400 293 510 709 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 510 709 70 709 70 709 70 709 70 709 70 709 70 709 70 709 70 709 70 709 70 709 70 709 70 709 70 709 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700 700		0.18 0.14 0.06 0.09 0.15 0.15 0.8 Proportion - 0.58 0.8 Proportion 0.17 0.59 0.59 0.59 0.59 0.59 0.62 0.39 0.49 8 Proportion 0.49	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.03; 0.27] [0.03; 0.38] [0.05; 0.33] [0.06; 0.10] [0.06; 0.11] 95%-CI [0.00; 0.64] [0.34; 0.66] [0.46; 0.77] [0.33; 0.44] [0.40; 0.57] [0.40; 0.57] 95%-CI	2.8% 2.9% 1.5% 1.8% 1.7% 2.7% 100.0% 	3.33 3.49 2.33 2.66 2.55 3.22 100.09 Weigh (random 6.82 2.37 100.09 14.33 2.33 100.09 Weigh (random 8.27 13.99 14.33 2.33 100.09
	Masuda 2021 Yoh 2021 Shen 2021 Hu 2022 Lu 2022 Common effect model Heterogenety. / ² = 43%, y Study Rizvi 2016 Heliman 2017 Rizvi 2016 Heliman 2017 Arrieta 2020 Lu 2022 Common effect model Heterogenety. / ² = 63%, y Study Rizvi 2016 Reck 2019 Arrieta 2021 Lu 2022 Common effect model Marieta 2020 Jiang 2021 Lu 2022 Common effect model	$\begin{array}{c} 6 \\ 5 \\ 1 \\ 2 \\ 3 \\ 5 \\ \end{array}$	34 35 18 - 22 - 20 32 1203 p < 0.0 0 Total 6 - 8 79 12 32 Total 6 - 8 79 12 32 32 Total 6 - 8 79 12 32 32 Total 6 - 8 79 12 32 32 32 40 293 510 Total 6 - 8 79 9 < 0.0 0 79 12 32 32 40 293 510 Total 6 - 8 79 9 < 0.0 12 32 32 40 293 510 Total 6 - 40 293 510 Total 6 - 45 12 32 40 40 293 510 6 - 45 12 40 40 293 510 6 - 45 12 40 40 45 12 40 40 40 45 12 40 40 40 45 12 40 40 40 45 12 40 40 40 45 12 40 40 40 45 12 40 40 45 12 40 40 40 12 12 40 12 40 12 40 12 40 12		0.18 0.14 0.06 0.09 0.15 0.16 0.8 Proportion 0.8 0.8 0.8 0.8 0.8 0.9 0.59 0.59 0.59 0.62 0.39 0.62 0.39 0.62 0.39 0.59 0.62 0.39 0.59 0.62 0.39 0.65 0.64 0.64 0.64 0.64 0.65 0.05 0.05 0.05 0.65 0.05 0.65 0.05 0.65 0.05 0.65 0.05 0.65 0.05 0.65 0.6	[0.07; 0.35] [0.05; 0.30] [0.05; 0.30] [0.00; 0.27] [0.03; 0.38] [0.05; 0.33] [0.05; 0.33] [0.05; 0.33] [0.06; 0.11] 95%-CI [0.00; 0.64] [0.46; 0.84] [0.46; 0.84] [0.46; 0.84] [0.46; 0.47] [0.46; 0.49] [0.46; 0.57] 95%-CI [0.00; 0.64] [0.46; 0.57] [0.28; 0.85] [0.34; 0.66] [0.28; 0.85] [0.34; 0.66] [0.28; 0.85] [0.34; 0.66] [0.28; 0.85]	2.8% 2.9% 1.5% 1.8% 1.7% 2.7% 100.0% 2.0% 1.5% 4.8% 6.2% 7.5% 8.0% 57.8% 100.0% 4.5% 8.0% 57.8%	3.33 3.49 2.35 2.65 3.27 100.09 Weigh (random 6.22 4.99 18.09 6.88 7.33 100.09 Weigh (random 8.27 13.99 14.33 23.33 100.09 Weigh (random 8.27 2.37,7 9.22 2.37,7 9.22 2.1,22 3.7,79 9.27 2.1,22 3.7,79 9.27 2.1,22 3.7,79 9.27 2.2,23 3.7,79 9.27 2.2,79 9.27 2.2,79 9.27 2.2,79 9.27 2.2,79 9.27 2.2,79 9.27 2.2,79 9.27 9.27 9.27 9.27 9.27 9.27 9.27 9.
	Masuda 2021 Yoh 2021 Shen 2021 Hu 2022 Lu 2022 Common effects model Heterogeneity. I ² = 43%, s Study Rizk 2016 Helimann 2017 Reck 2019 Han 2021 Lu 2022 Common effects model Heterogeneity. I ² = 63%, s Study Rizk 2016 Heterogeneity. I ² = 63%, s	6 5 1 2 3 5 5 Events 1 4 4 0 7 19 25 113 114 2 2 5 0072, 113 1 2 2 5 0072, 113 1 4 4 4 0 0 25 113 1 1 2 5 1 1 1 2 5 1 1 1 2 1 5 5 1 1 1 2 1 5 5 1 1 1 2 1 5 5 1 1 1 1	34 355 18 - 22 202 32 1203 p < 0.0 0 Total 6 - 6 79 12 32 400 293 510 6 - 400 293 510 6 - 400 125 242 400 293 510 6 - 400 125 242 400 293 510 125 242 400 293 510 125 242 400 293 510 125 242 400 293 510 125 242 400 293 510 125 242 400 125 242 400 125 242 400 125 242 400 125 248 248		0.18 0.16 0.06 0.09 0.15 0.16 0.08 Proportion 0.8 0.8 0.8 0.9 0.50 0.62 0.39 0.50 0.62 0.39 0.50 0.62 0.39 0.50 0.62 0.39 0.50 0.62 0.39 0.55 0.64 0.64 0.64 0.64 0.65 0.65 0.38	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.01; 0.29] [0.03; 0.38] [0.05; 0.33] [0.05; 0.33] [0.05; 0.11] 955%-CI [0.06; 0.11] 955%-CI [0.41; 0.76] [0.42; 0.85] [0.42; 0.57] 95%-CI [0.00; 0.64] [0.40; 0.57] 95%-CI [0.02; 0.84] [0.40; 0.57] 95%-CI [0.02; 0.84] [0.40; 0.57] 95%-CI [0.02; 0.84] [0.22; 0.57]	2.8% 2.9% 1.5% 1.8% 2.7% 2.7% 2.7% 2.0% 2.0% 1.5% 4.8% 6.2% 7.5% 8.0% 57.8% 100.0% 4.5% 4.5% 4.5% 4.5% 4.5% 3.9%	3 3 3 4 3 4 4 2 3 3 2 6 6 2 5 5 3 2 7 100.09 Weigt (random 6 2 4 9 9 1 4 3 2 3 3 100.09 Weigt (random 8 2 2 3 7 1 4 3 2 3 3 100.09 Weigt (random 8 2 2 3 7 1 4 3 2 3 3 100.09
	Masuda 2021 Shen 2021 Shen 2021 Hu 2022 Lu 2022 Common effect model Heterogeneity. I ² = 43%, 1 Study Rizk 2016 Hellmann 2017 Reck 2019 Han 2021 Lu 2022 Common effects model Heterogeneity. I ² = 63%, 1 Study Rizk 2016 Rizk 2016 Heterogeneity. I ² = 63%, 1 Study Rizk 2016 Heterogeneity. I ² = 63%, 1 Study Rizk 2019 Arrieta 2020 Lu 2022 Common effects model Heterogeneity. I ² = 48%, 1	6 5 1 2 3 5 5 Events 1 4 4 0 7 19 25 113 114 2 2 5 0072, 113 1 2 2 5 0072, 113 1 4 4 4 0 0 25 113 1 1 2 5 1 1 1 2 5 1 1 1 2 1 5 5 1 1 1 2 1 5 5 1 1 1 2 1 5 5 1 1 1 1	$\begin{array}{c} 34\\ 36\\ 8\\ 22\\ 1203\\ p < 0, 0\\ 0\\ \end{array}$ Total $\begin{array}{c} 6\\ -\\ 8\\ 79\\ 12\\ 32\\ 40\\ 40\\ 293\\ 510\\ p < 0.0\\ \end{array}$ Total $\begin{array}{c} 6\\ -\\ 40\\ 510\\ 12\\ 243\\ 510\\ 12\\ 248\\ p = 0.1\\ \end{array}$		0.18 0.16 0.06 0.09 0.15 0.16 0.08 Proportion 0.8 0.8 0.8 0.9 0.50 0.62 0.39 0.50 0.62 0.39 0.50 0.62 0.39 0.50 0.62 0.39 0.50 0.62 0.39 0.55 0.64 0.64 0.64 0.64 0.65 0.65 0.38	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.03; 0.27] [0.03; 0.28] [0.05; 0.33] [0.05; 0.33] [0.05; 0.10] [0.06; 0.11] 95%-CI [0.06; 0.10] [0.06; 0.11] [0.06; 0.11] [0.06; 0.11] [0.06; 0.11] [0.06; 0.10] [0.46; 0.84] [0.34; 0.66] [0.34; 0.66] [0.28; 0.857] [0.28; 0.41] [0.28; 0.48]	2.8% 2.9% 1.5% 1.8% 2.7% 2.7% 2.7% 2.0% 2.0% 1.5% 4.8% 6.2% 7.5% 8.0% 57.8% 100.0% 4.5% 4.5% 4.5% 4.5% 4.5% 3.9%	3 3 3 4 2 3 3 4 4 2 3 3 4 4 2 3 1 2 5 1 2
(d)	Masuda 2021 Yoh 2021 Shen 2021 Hu 2022 Lu 2022 Common effect model Heterogeneity. I ² = 43%, s Study Rizxl 2016 Hellmann 2017 Reck 2019 Arrieta 2020 Han 2021 Lu 2022 Common effect model Radom effects model Heterogeneity. I ² = 63%, s Study Rizxl 2016 Reck 2019 Arrieta 2020 Jiang 2021 Lu 2022 Common effect model Heterogeneity. I ² = 63%, s Study Study Study	6 + 6 + 5 + 1 = 2 + 2 + 2 + 2 + 2 + 2 + 2 + 2 + 2 + 2	$\begin{array}{c} {}^{34}_{34}\\ {}^{35}_{35}\\ {}^{35}_{32}\\ {}^{22}_{22}\\ {}^{20}_{32}\\ {}^{70}_{32}\\ {}^{70}_{12}\\ {}^{70}_{223}\\ {}^{70}_{40}\\ {}^{70}_{223}\\ {}^{70}_{40}\\ {}^{70}_{223}\\ {}^{70}_{40}\\ {}^{70}_{40}\\ {}^{70}_{223}\\ {}^{70}_{40}\\ {}^{7$		0.18 0.16 0.06 0.09 0.15 0.8 Proportion - 0.58 0.8 Proportion - 0.59 0.59 0.59 0.59 0.59 0.59 0.59 0.59	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.03; 0.27] [0.03; 0.27] [0.03; 0.38] [0.05; 0.33] [0.05; 0.10] [0.06; 0.11] 95%-CI [0.00; 0.64] [0.00; 0.64] [0.03; 0.64] [0.34; 0.66] [0.34; 0.66] [0.34; 0.66] [0.34; 0.66] [0.35; 0.44] [0.35; 0.64] [0.35; 0.64] [0.35; 0.64] [0.35; 0.64] [0.35; 0.64] [0.26; 0.64] [0.26; 0.64] [0.26; 0.41] [0.26; 0.48] [0.26; 0.41] [0.31; 0.422] [0.25; 0.48]	2.8% 2.9% 1.5% 1.8% 2.7% 100.0% 2.0% 1.5% 14.8% 6.2% 7.5% 8.0% 57.8% 100.0% 	3.333 3.44 2.33 2.55 3.29
(d)	Masuda 2021 Shen 2021 Shen 2021 Hu 2022 Lu 2022 Common effect model Random effects model Heterogeneity. I ² = 43%, 1 Study Rizxi 2016 Heliman 2017 Reck 2019 Arricla 2020 Lu 2022 Common effect model Heterogeneity. I ² = 63%, 1 Study Rizx 2016 Reck 2019 Arricla 2020 Heterogeneity. I ² = 63%, 1 Study Rizx 2016 Reck 2019 Arricla 2020 Jiang 2021 Lu 2022 Common effect model Random effects m	6 5 1 2 3 3 5 1 2 2 0.0070, Events 1 4 4 4 0 0 7 1 2 0.0070, 7 1 2 0.0070, 7 1 2 0.0070, 7 1 2 0.0070, 7 1 2 0.0070, 7 1 2 0.0070, 7 1 2 0.0070, 7 1 2 0.0072, 1 2 0.0072, 1 2 0.0072, 1 2 0.0072, 1 2 0.0072, 1 2 0.0072, 1 1 1 1 1 1 1 1	${}^{34}_{4}$ ${}^{35}_{5}$ ${}^{22}_{20}$ ${}^{20}_{32}$ ${}^{20}_{32}$ ${}^{20}_{32}$ ${}^{20}_{32}$ ${}^{70}_{12}$ ${}^{79}_{12}$ ${}^{22}_{32}$ ${}^{40}_{40}$ 293 ${}^{510}_{40}$ ${}^{293}_{40}$ ${}^{510}_{40}$ ${}^{6}_{7}$ ${}^{6}_{5}$ ${}^{12}_{22}$ ${}^{20}_{40}$ ${}^{20}_{293}$ ${}^{510}_{12}$ ${}^{6}_{7}$ ${}^{6}_{12}$ ${}^{2}_{40}$ ${}^{45}_{12}$ ${}^{2}_{40}$ ${}^{45}_{12}$ ${}^{2}_{40}$ ${}^{45}_{12}$ ${}^{2}_{40}$ ${}^{45}_{12}$ ${}^{2}_{40}$ ${}^{45}_{12}$ ${}^{2}_{40}$		0.18 0.14 0.06 0.09 0.15 0.8 Proportion - 0.58 0.8 Proportion - 0.59 0.59 0.59 0.59 0.59 0.59 0.62 0.39 0.45 0.49 8 Proportion 0.17 - 0.50 0.62 0.39 0.45 0.43 8 Proportion 0.25 0.33 0.33 0.38	[0.07; 0.35] [0.05; 0.30] [0.05; 0.30] [0.00; 0.27] [0.03; 0.38] [0.05; 0.33] [0.05; 0.33] [0.05; 0.33] [0.06; 0.10] [0.06; 0.10] [0.06; 0.10] [0.06; 0.10] [0.06; 0.10] [0.34; 0.66] [0.34; 0.66] [0.34; 0.67] [0.34; 0.67] [0.34; 0.66] [0.34; 0.67] [0.34; 0.66] [0.34; 0.67] [0.34; 0.68] [0.34; 0.66] [0.34	2.8% 2.9% 1.5% 1.8% 1.7% 2.7% 100.0% 2.0% 1.5% 14.8% 57.8% 100.0% 57.8% 100.0% 17.8% 14.5% 57.8% 100.0% 17.8% 14.5% 59.3% 100.0% 100.0% 100.0%	3.333 3.44 2.33 2.55 3.27 100.09 Weigh (random 8.09 14.33 2.33 100.09 Weigh (random 8.27 12.37 100.09 Weigh (random 8.27 2.37 100.09 Weigh (random 8.27 2.37 100.09 Weigh (random 8.27 2.37 100.09 Weigh (random 8.27 2.37 100.09 2.37 3.77 100.09 2.37 3.77 100.09 2.37 3.77 100.09 2.37 3.77 100.09 2.37 2.27 2.12 2.12 2.12 2.12 2.12 2.12 2.1
(d)	Masuda 2021 yoh 2021 Shen 2021 Hu 2022 Lu 2022 Common effect model Random effects model Heterogeneity. I ² = 43%, 1 Study Rizxi 2016 Heliman 2017 Reck 2019 Arricla 2020 Lu 2022 Common effect model Heterogeneity. I ² = 63%, 1 Study Rizxi 2016 Reck 2019 Arricla 2020 Lu 2022 Common effect model Heterogeneity. I ² = 63%, 1 Study Rizxi 2016 Reck 2019 Jiang 2021 Lu 2022 Common effect model Random effects model Heterogeneity. I ² = 48%, 1 Study Reck 2019 Han 2021 Lu 2022	6 + 6 + 5 + 1 = 2 + 2 + 2 + 2 + 2 + 2 + 2 + 2 + 2 + 2	$\begin{array}{c} {}^{34}_{34}\\ {}^{35}_{35}\\ {}^{35}_{32}\\ {}^{22}_{22}\\ {}^{20}_{32}\\ {}^{70}_{32}\\ {}^{70}_{12}\\ {}^{70}_{223}\\ {}^{70}_{40}\\ {}^{70}_{223}\\ {}^{70}_{40}\\ {}^{70}_{223}\\ {}^{70}_{40}\\ {}^{70}_{40}\\ {}^{70}_{223}\\ {}^{70}_{40}\\ {}^{7$		0.18 0.16 0.06 0.09 0.15 0.16 0.08 Proportion 0.55 0.59 0.45 0.59 0.45 0.59 0.49 8 Proportion 0.17 0.36 0.49 8 Proportion 0.33 0.38 0.45 0.59 0.33 0.38 0.45 0.55 0.33 0.38	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.05; 0.30] [0.00; 0.27] [0.03; 0.38] [0.05; 0.33] [0.05; 0.33] [0.06; 0.10] [0.06; 0.10] [0.06; 0.10] [0.06; 0.10] [0.06; 0.10] [0.06; 0.10] [0.41; 0.76] [0.34; 0.66] [0.34; 0.67] [0.24; 0.57] [0.24; 0.57] [0.24; 0.57] [0.24; 0.57] [0.24; 0.57] [0.24; 0.57] [0.24; 0.57] [0.24; 0.57] [0.24; 0.66] [0.24; 0.57] [0.24; 0.66] [0.24; 0.46] [0.24; 0.46] [0.44; 0.76] [0.44; 0.76]	2.8% 2.9% 1.5% 1.8% 2.7% 100.0% 2.0% 1.5% 14.8% 6.2% 7.5% 8.0% 57.8% 100.0% 	3.33 3.44 2.33 2.44 2.55 3.27 100.09 (random 6.27 4.99 18.00 6.87 12.77 18.00 6.87 12.77 100.09 Weigh (random 8.22 2.37 9.22 2.12 2.37,77 100.09 Weigh (random 8.27 2.37 9.22 2.12 2.37 100.09 Weigh (random 8.27 2.37 100.09 Weigh (random 8.27 2.37 100.09 Weigh (random 8.27 2.37 100.09 Weigh (random 8.27 2.37 100.09 10.
(d)	Masuda 2021 Shen 2021 Shen 2021 Lu 2022 Common effect model Heterogeneity: I ² = 43%, 1 Study Rizxl 2016 Hellmann 2017 Reck 2019 Arrieta 2020 Lan 2021 Lan 2021 Common effect model Radom effects model Heterogeneity: I ² = 63%, 1 Study S	6 5 1 2 3 5 1 2 2 0.0070, 1 1 4 4 400 25 113 113 1 1 4 400 25 113 113 1 1 2 0.0070, 25 113 113 1 1 2 0.0072, 2 1 1 1 1 4 4 400 25 113 113 1 1 2 0.0072, 2 1 1 1 1 1 1 1 1	${}^{34}_{4}$ ${}^{35}_{5}$ ${}^{32}_{22}$ ${}^{22}_{23}$ ${}^{2}_{20}$ ${}^{32}_{22}$ ${}^{79}_{12}$ ${}^{22}_{22}$ ${}^{40}_{40}$ ${}^{293}_{22}$ ${}^{510}_{40}$ ${}^{293}_{22}$ ${}^{510}_{40}$ ${}^{70}_{22}$ ${}^{510}_{12}$ ${}^{6}_{12}$ ${}^{45}_{12}$ ${}^{12}_{40}$ ${}^{6}_{1}$ ${}^{6}_{12}$ ${}^{12}_{22}$ ${}^{40}_{40}$ ${}^{70}_{22}$ ${}^{510}_{12}$ ${}^{70}_{12}$ ${}^{12}_{22}$ ${}^{510}_{40}$ ${}^{70}_{12}$ ${}^{12}_{22}$ ${}^{2}_{23}$ ${}^{510}_{12}$ ${}^{12}_{2}$ ${}^{12}_{2}$		0.18 0.16 0.06 0.09 0.15 0.16 0.08 Proportion 0.55 0.59 0.45 0.59 0.45 0.59 0.49 8 Proportion 0.17 0.36 0.49 8 Proportion 0.33 0.38 0.45 0.59 0.33 0.38 0.45 0.55 0.33 0.38	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.03; 0.27] [0.03; 0.28] [0.05; 0.30] [0.05; 0.33] [0.05; 0.33] [0.06; 0.11] 95%-CI [0.00; 0.64] [0.00; 0.64] [0.34; 0.66] [0.34; 0.66] [0.34; 0.66] [0.34; 0.66] [0.34; 0.66] [0.26; 0.57] [0.34; 0.66] [0.26; 0.57] [0.34; 0.66] [0.26; 0.41] [0.26; 0.48] [0.26; 0.41] [0.26; 0.48] [0.26; 0.41] [0.26; 0.48] [0.26; 0.48] [0.26; 0.48] [0.26; 0.48] [0.26; 0.48] [0.26; 0.48] [0.26; 0.48] [0.26; 0.48] [0.26; 0.48] [0.26; 0.48]	2.8% 2.9% 1.5% 1.8% 2.7% 100.0% (common) 2.0% 1.5% 14.8% 6.2% 7.5% 8.0% 57.8% 100.0% 	3.333 3.44 2.33 2.55 3.29
(d)	Masuda 2021 yoh 2021 Shen 2021 Hu 2022 Lu 2022 Common effect model Random effects model Heterogeneity. I ² = 43%, 1 Study Rizxi 2016 Heliman 2017 Reck 2019 Arricla 2020 Lu 2022 Common effect model Heterogeneity. I ² = 63%, 1 Study Rizxi 2016 Reck 2019 Arricla 2020 Lu 2022 Common effect model Heterogeneity. I ² = 63%, 1 Study Rizxi 2016 Reck 2019 Jiang 2021 Lu 2022 Common effect model Rech 2019 Arricla 2020 Jiang 2021 Lu 2022 Common effect model Reck 2019 Arricla 2020 Jiang 2021 Lu 2022 Common effect model Random effects model Heterogeneity. I ² = 48%, 1 Study Reck 2019 Han 2021 Lu 2021	$\begin{array}{c} 6\\ 6\\ 5\\ 1\\ 2\\ 3\\ 5\\ 1\\ 2\\ 2\\ 3\\ 5\\ 1\\ 2\\ 2\\ 2\\ 0\\ 0070, 0\\ 1\\ 1\\ 1\\ 4\\ 4\\ 0\\ 0\\ 25\\ 113\\ 1\\ 1\\ 2^2 = 0.0072, 0\\ 113\\ 1\\ 1\\ 2^2 = 0.0072, 0\\ 10\\ 2\\ 1\\ 2\\ 0\\ 1\\ 2\\ 1\\ 2\\ 0\\ 0\\ 1\\ 1\\ 2\\ 0\\ 0\\ 1\\ 1\\ 2\\ 0\\ 0\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\$	${}^{344}_{35}$ ${}^{35}_{35}$ ${}^{22}_{20}$ ${}^{22}_{20}$ ${}^{20}_{32}$ 1203 Total ${}^{6} < 0.6$ 0		0.18 0.14 0.06 0.09 0.15 0.16 0.08 Proportion 0.59 0.59 0.59 0.59 0.59 0.59 0.59 0.59	[0.07; 0.35] [0.05; 0.30] [0.00; 0.27] [0.05; 0.30] [0.00; 0.27] [0.03; 0.38] [0.05; 0.33] [0.05; 0.33] [0.06; 0.10] [0.06; 0.10] [0.06; 0.10] [0.06; 0.10] [0.06; 0.10] [0.06; 0.10] [0.39; 0.62] [0.39; 0.62] [0.39; 0.62] [0.34; 0.66] [0.34; 0.66] [0.45; 0.77]	2.8% 2.9% 1.5% 1.8% 1.7% 2.7% 100.0% 2.0% 1.5% 14.8% 2.3% 6.2% 57.8% 100.0% 57.8% 100.0% 17.8% 14.5% 57.8% 100.0% 17.8% 14.5% 14.5% 100.0% 100.0% 100.0% 100.0% 100.0%	3 3 3 4 3 3 4 4 2 3 3 4 4 2 3 3 4 4 2 3 9 2 1 4 2 3 1 4 2 3 1 4 2 3 1 4 2 3 1 4 2 3 1 4 2 3 1 4 2 1 4 1 4

Figure 2. ORR of EGFR-mutant NSCLC patients with monoimmunotherapy or immune-combination therapy. Forest plots of ORR in (a) prospective studies of monoimmunotherapy; (b) retrospective studies of monoimmunotherapy; (c) prospective studies of immuno-combination therapy; (d) prospective studies of chemoimmunotherapy; and (e) prospective studies of chemoimmunotherapy plus anti-angiogenesis therapy. EGFR, Epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; ORR, objective response rate.

			Effect	56
	study		(95% CI)	Weight
	Gettinger 2016		1.80 (0.20, 7.60)	2.79
	Nishio 2016	4	2.70 (1.20, 2.90)	18.73
	Gulley 2017		5.40 (1.90, 24.00)	0.34
	Garassino 2018	÷.	2.00 (1.80, 3.70)	17.35
	Garassino 2018	•	3.00 (2.70, 3.30)	25.94
	Nishio 2019	1	2.00 (1.00, 4.00)	11.20
	Hayashi 2022		1.70 (1.30, 2.30)	23.64
	Overall, DL (1 ² = 72.6%, p = 0.001)	0	2.33 (1.67, 2.98)	100.00
	-20	0 2	1	
	-20	0 2		
)			Effect	3
<i>'</i>	study		(95% CI)	Weigh
	Haratani 2017	•	1.50 (1.30, 2.80)	8.66
	Oya 2017	1	1.90 (1.20, 5.10)	6.2-
	Juergens 2018	•	1.90 (1.10, 3.00)	8.3
	Cho 2019	•	1.90 (1.10, 2.70)	8.58
	Hastings 2019	•	1.80 (0.00, 40.50)	0.17
	Mazieres 2019	•	2.10 (1.80, 2.70)	9.05
	Sato 2019	• 1	1.00 (0.20, 1.70)	8.66
	Yamada 2019	•	1.90 (0.30, 20.40)	0.67
	Bylicki 2020		2.20 (1.40, 3.20)	8.4
	Kitadai 2020	- • ·	1.00 (0.79, 1.25)	9.2
	Morita 2020	•	1.50 (1.20, 1.70)	9.2
	Shen 2021	÷	2.90 (1.64, 4.20)	7.67
	Hu 2022	+	3.00 (1.30, 3.30)	8.23
	Lu 2022	+	14.70 (13.03, 16.28)	6.93
	Overall, DL (1 ² = 95.6%, p = 0.000)	¢ —	2.77 (1.91, 3.62)	100.00
	-50	0	50	
			Effect	
			(95% CI)	Weig
)	study			
)	study 		4.80 (0.90, 6.80)	9.1
)	Rizvi 2016			
)	Rizvi 2016 Reck 2019(ICA)		10.20 (7.90, 15.20)	6.7
)	Rizvi 2016 Reck 2019(ICA) Reck 2019(IC)		10.20 (7.90, 15.20) 6.90 (5.70, 8.50)	6.7 18.6
)	Rizvi 2016 Reck 2019(ICA) Reck 2019(IC) Jiang 2021		10.20 (7.90, 15.20) 6.90 (5.70, 8.50) 7.00 (4.60, 6.40)	6.1 18.6 15.5
)	Rizvi 2016 Reck 2019(ICA) Reck 2019(IC) Jiang 2021 Lam 2021	*	10.20 (7.90, 15.20) 6.90 (5.70, 8.50) 7.00 (4.60, 6.40) 9.40 (7.60, 12.10)	6.1 18.0 15.0 12.0
)	Rizvi 2016 Reck 2019(ICA) Reck 2019(IC) Jiang 2021 Lam 2021 Lu 2022(ICA)	*	10.20 (7.90, 15.20) 6.90 (6.70, 8.60) 7.00 (4.60, 6.40) 9.40 (7.60, 12.10) 6.90 (6.00, 9.30)	6.7 18.6 15.6 12.6 16.6
)	Rizvi 2016 Reck 2019(ICA) Reck 2019(IC) Jiang 2021 Lam 2021 Lu 2022(ICA) Lu 2022(ICA)	*	10.20 (7.90, 15.20) 6.90 (6.70, 8.60) 7.00 (4.60, 6.40) 9.40 (7.60, 12.10) 6.90 (6.00, 9.30) 5.60 (4.70, 6.80)	6.7 18.6 15.5 12.5 16.6 20.8
)	Rizvi 2016 Reck 2019(ICA) Reck 2019(IC) Jiang 2021 Lam 2021 Lu 2022(ICA) Lu 2022(ICA) Lu 2022(IC) Overall, DL (I ² = 59.3%, p = 0.022)	*	10.20 (7.90, 15.20) 6.90 (6.70, 8.60) 7.00 (4.60, 6.40) 9.40 (7.60, 12.10) 6.90 (6.00, 9.30) 5.60 (4.70, 6.90) 6.99 (5.89, 8.09)	6.1 18.6 15.6 12.6 16.6 20.8
)	Rizvi 2016 Reck 2019(ICA) Reck 2019(IC) Jiang 2021 Lam 2021 Lu 2022(ICA) Lu 2022(ICA)		10.20 (7.90, 15.20) 6.90 (5.70, 8.60) 7.00 (4.80, 6.40) 9.40 (7.60, 12.10) 6.90 (6.00, 9.30) 5.60 (4.70, 6.90) 6.99 (5.89, 8.09)	6.1 18.6 15.6 12.6 16.6 20.6 100.0
	Rizvi 2016 Reck 2019(ICA) Reck 2019(IC) Jiang 2021 Lam 2021 Lu 2022(ICA) Lu 2022(ICA) Lu 2022(IC) Overall, DL (I ² = 59.3%, p = 0.022)		10.20 (7.90, 15.20) 6.90 (6.70, 8.60) 7.00 (4.60, 8.40) 9.40 (7.60, 12.10) 6.90 (6.00, 9.30) 5.60 (4.70, 6.90) 6.99 (5.89, 8.09) 20 Effect	6.1 18.8 15.6 12.6 16.6 20.8 100.0
)	Rizvi 2016 Reck 2019(ICA) Reck 2019(IC) Jiang 2021 Lam 2021 Lu 2022(ICA) Lu 2022(ICA) Lu 2022(IC) Overall, DL (I ² = 59.3%, p = 0.022)	0	10.20 (7.90, 15.20) 6.90 (5.70, 8.60) 7.00 (4.80, 6.40) 9.40 (7.60, 12.10) 6.90 (6.00, 9.30) 5.60 (4.70, 6.90) 6.99 (5.89, 8.09)	6.1 18.8 15.6 12.6 16.6 20.8 100.0
	Rizvi 2016 Reck 2019(ICA) Reck 2019(IC) Jiang 2021 Lam 2021 Lu 2022(ICA) Lu 2022(ICA) Lu 2022(IC) Overall, DL (I ² = 59.3%, p = 0.022)		10.20 (7.90, 15.20) 6.90 (6.70, 8.60) 7.00 (4.60, 8.40) 9.40 (7.60, 12.10) 6.90 (6.00, 9.30) 5.60 (4.70, 6.90) 6.99 (5.89, 8.09) 20 Effect	6.1 18.6 15.6 12.6 16.6 100.0 Weigh
	Rizvi 2016 Reck 2019(ICA) Reck 2019(IC) Jiang 2021 Lam 2021 Lu 2022(ICA) Lu 2022(IC) Overall, DL (I ² = 59.3%, p = 0.022) -20 study		10.20 (7.90, 15.20) 6.90 (6.70, 8.60) 7.00 (4.60, 8.40) 9.40 (7.60, 12.10) 6.90 (6.00, 9.30) 5.00 (4.70, 6.90) 6.99 (5.89, 8.09) 20 Effect (95% Cl) 4.80 (0.90, 6.80)	6.1 18.6 15.6 12.6 16.6 20.8 100.0 Weigh
	Rizvi 2016 Reck 2019(ICA) Reck 2019(IC) Jiang 2021 Lam 2021 Lu 2022(ICA) Lu 2022(IC) Overall, DL (I ² = 59.3%, p = 0.022) -20 study Rizvi 2016 Reck 2019	•	10.20 (7.90, 15.20) 6.90 (6.70, 8.60) 7.00 (4.60, 8.40) 9.40 (7.60, 12.10) 6.90 (6.00, 9.30) 5.60 (4.70, 6.90) 6.99 (5.89, 8.09) 20 Effect (95% C1) 4.80 (0.90, 6.80) - 6.90 (5.70, 8.50)	6.1 18.6 15.6 10.6 100.0 Weigh 8.2 29.8
	Rizvi 2016 Reck 2019(ICA) Reck 2019(IC) Jiang 2021 Lam 2021 Lu 2022(ICA) Lu 2022(IC) Overall, DL (I ² = 59.3%, p = 0.022)		10.20 (7.90, 15.20) 6.90 (6.70, 8.60) 7.00 (4.60, 6.40) 9.40 (7.60, 12.10) 6.90 (6.00, 9.30) 5.60 (4.70, 6.90) 6.99 (5.89, 8.09) 20 Effect (95% C1) 4.80 (0.90, 6.80) - 6.90 (5.70, 8.50) - 7.00 (4.80, 8.40)	9.1 6.7 18.6 15.5 12.6 16.6 20.8 100.0 Weigh 8.2 29.8 19.97 42.0
	Rizvi 2016 Reck 2019(ICA) Reck 2019(IC) Jiang 2021 Lam 2021 Lu 2022(ICA) Lu 2022(IC) Overall, DL (I ² = 59.3%, p = 0.022) -20 study Rizvi 2016 Reck 2019		10.20 (7.90, 15.20) 6.90 (6.70, 8.60) 7.00 (4.60, 8.40) 9.40 (7.60, 12.10) 6.90 (6.00, 9.30) 5.60 (4.70, 6.90) 6.99 (5.89, 8.09) 20 Effect (95% C1) 4.80 (0.90, 6.80) - 6.90 (5.70, 8.50)	6.7 18.6 15.5 12.6 16.6 20.8 100.0 Weigh 8.2 29.8

Figure 3. (Continued)

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Figure 3. The mPFS and mOS of EGFR-mutant NSCLC patients with monoimmunotherapy or immunocombination therapy. Forest plots of mPFS in (a) prospective studies of monoimmunotherapy; (b) retrospective studies of monoimmunotherapy; (c) prospective studies of immuno-combination therapy; (d) prospective studies of chemoimmunotherapy; (e) prospective studies of chemoimmunotherapy plus anti-angiogenesis therapy; (f) Forest plots of mOS in prospective studies of monoimmunotherapy; (g) Forest plots of mOS in retrospective studies of mOS in prospective studies of mOS in prospective studies of immunocombination therapy.

EGFR, Epidermal growth factor receptor; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small-cell lung cancer.

THERAPEUTIC ADVANCES in Medical Oncology

Table 3. Clinical activity of immunotherapy in KRAS-altered NSCLC patients.

References	Year	Туре	Therapy	Patients	ORR (%)	mPFS, month (95% CI)	mOS, month (95% CI)
Gettinger ¹⁷	2015	Pro	I	21	3 (14)	NA	NA
Rizvi ²⁰	2016	Pro	IC	10	3 (33)	4.9 (0.1–21.8)	20.9 (6.2–29.7)
Gulley ²¹	2017	Pro	I	21	1 (5)	6.1 (5.4–12.1)	8.1 (3.7–10.7)
Peters ¹¹	2017	Pro	I	137	35 (26)	NA	NA
Horn ²⁶	2018	Pro	I	14	2 (14)	NA	NA
Gadgeel ⁷⁵	2019	Pro	IC	59	24 (41)	9.0 (7.0–14.0)	21.0 (16.0-NR)
Herbst ¹⁴	2019	Pro	I	30	17 (57)	12.0 (8.0-NR)	28.0 (23.0-NR)
Oya ⁴³	2017	Retro	I	14	4 (29)	1.9 (0.9–3.9)	6.6 (3.0-NR)
Garde-Noguera ⁷⁶	2018	Retro	I	19	3 (16)	1.5 (NA)	2.6 (NA)
Lin ⁴⁸	2018	Retro	I	10	3 (33)	3.8 (NA)	5.9 (NA)
Schouten ⁴⁹	2018	Retro	I	84	19 (23)	NA	NA
Jeanson ⁷⁷	2019	Retro	I	162	30 (19)	3.1 (2.4–3.8)	14.3 (9.6–19.0)
Mazieres ⁵⁷	2019	Retro	I	246	64 (26)	3.2 (2.7–4.5)	13.5 (9.4–15.6)
Ng ⁵⁸	2019	Retro	I	77	9 (11)	4.6 (NA)	NA
Passiglia ¹⁰	2019	Retro	I	206	41 (20)	4.0 (3.6-4.4)	11.2 (9.3–13.1)
Torralvo ⁷⁸	2019	Retro	I	21	13 (62)	13.6 (NA)	18.5 (NA)
Gainor ⁶⁴	2020	Retro	I	112	44 (39)	NA	NA
Gianoncelli ⁷⁹	2020	Retro	I	43	8 (19)	4.6 (NA)	8.1 (NA)
Yoh ⁷²	2021	Retro	I	30	5 (17)	NA	NA
Justeau ⁸⁰	2022	Retro	I	227	96 (42)	NA	NA
Zhao ⁸¹	2022	Retro	Ι	87	42 (48)	NA	NA

I, monoimmunotherapy; IC, chemo-immunotherapy; ICA, immunotherapy plus chemotherapy and anti-angiogenesis therapy; KRAS, Kirsten rat sarcoma viral oncogene homolog; m0S, median overall survival; mPFS, median progression-free survival; NA, not available; NR, not reach; NSCLC, non-small-cell lung cancer; ORR, objective response rate; Pro, prospective study; Retro, retrospective study.

that ICI was more effective than chemotherapy in *EGFR* wild-type NSCLC, which may due to the low expression of PD-L1 in *EGFR*-mutant NSCLC.^{101,102} Now, there was no randomized controlled trial (RCT) concerning the effect of ICI on various subtypes of *EGFR* mutation. Hastings *et al.*'s retrospective study in 2019 showed that patients with G719X mutation received the best response (ORR=28.6%, mPFS=4.8 months), while L861Q mutation received the worst response (ORR=0%, mPFS=1.3 months) treated with monoimmuno-therapy. And the ORR of the 19del mutation, while the

ORR of the L858R mutation was similar to that of the wild type.55 Different subtypes of EGFR mutation have different responses to monoimmunotherapy, which may be due to the different immunogenicity, and further study is needed to be conducted. IMpower150 is the first study in a subgroup to show that ICIs have clinical benefits for EGFR-mutant patients. Further analysis of the EGFR-mutant subgroup showed that the PFS benefit in the ABCP (atezolizumab plus bevacizumab plus carboplatin plus paclitaxel) group was higher than that in the BCP (bevacizumab plus carboplatin plus paclitaxel) group (10.2 months versus 6.9 months). Similar results

References	Year	Туре	Therapy	Patients	ORR (%)	mPFS, month (95% CI)	m0S, month (95% CI)
Gulley ²¹	2017	Pro	I	1	0 (0)	17.6 (NA)	NA
Garassino ²³	2018	Pro	I	10	0 (0)	1.8 (0.5–1.9)	6.3 (0.9–NR)
Nishio ²⁹	2019	Pro	I	2	0 (0)	NA	NA
Gainor ³⁸	2016	Retro	I	6	0 (0)	NA	NA
Bagley ³⁹	2017	Retro	I	3	0 (0)	NA	NA
Fujimoto44	2018	Retro	I	11	2 (18)	NA	NA
Kobayashi ⁴⁷	2018	Retro	I	3	0 (0)	NA	NA
Heo ⁸²	2019	Retro	I	14	2 (14)	2.2 (1.1–NR)	5.7 (3.0-NR)
Mazieres ⁵⁷	2019	Retro	I	19	0 (0)	2.5 (1.5–3.7)	17.0 (3.6–NR)
Ng ⁵⁸	2019	Retro	I	13	0 (0)	1.2 (NA)	NA
Bylicki ⁶³	2020	Retro	I	8	2 (25)	2.4 (2.1–NR)	19.2 (13.1–NR)

Table 4. Clinical activity of immunotherapy in ALK-altered NSCLC patients.

ALK, anaplastic lymphoma kinase; I, monoimmunotherapy; mPFS, median progression-free survival; mOS, median overall survival; NA, not available; NR, not reach; ORR, objective response rate; Pro, prospective study; Retro, retrospective study.

took place in a single-arm clinical trial, the ORR of that 40 TKI-resistant and *EGFR*-mutant NSCLC patients treated with combinational induction therapy of atezolizumab, bevacizumab, pemetrexed, and carboplatin reached 62.5%, and mPFS was 9.4 months.³⁴ Therefore, immuno-therapy combined with other therapies can significantly improve the survival of patients with *EGFR* mutation, especially immunotherapy combined with chemotherapy and anti-angiogenesis therapy.

Of patients with NSCLC-harbored KRAS mutations, 35–45% were the G12C subtype, sotorasib and adagrasib are the only target drugs approved by the FDA for the treatment of patients with KRAS G12C mutation NSCLC.^{103,104} However, they could not meet the needs of all kinds of KRAS-mutant NSCLC treatment. In 2019, Mazieres et al. conducted a retrospective analysis of advanced NSCLC patients who received ICI monotherapy and found that patients with KRAS mutations had a higher ORR than other types of driving gene mutations in immunotherapy, which was consistent with our results.57 According to a previous study, the activation of the KRAS signal pathway can inhibit the activity of tristetraprolin, stabilize PD-L1 mRNA, increase the synthesis of PD-L1, and upregulate the expression of PD-L1, so KRAS-mutant tumor was sensitive to ICIs therapy.¹⁰⁵ In 2021, Landre et al. reported a

advanced NSCLC, the results suggested that immunotherapy can prolong the OS of NSCLC patients with KRAS mutation whether or not combined with chemotherapy (HR=0.59, 95% CI: 0.49-0.72; PP=0.0003).¹⁰⁶ Gu et al. conducted a meta-analysis and found that patients with advanced NSCLC with KRAS mutations can benefit from ICIs but no difference between KRAS mutant subtypes was observed.¹⁰⁷ Generally speaking, monoimmunotherapy or immune-combination therapy might be the main treatment for non-G12C mutations until other more effective targeted drugs are available. More clinical trials are needed to evaluate the efficacy of immunotherapy in the KRASmutant population. No ALK-rearranged NSCLC patients partici-

meta-analysis of anti-PD-(L)1 for KRAS-mutant

pated in clinical trials of ICI monotherapy to achieve objective remission. Almost all studies on the efficacy of ICIs in *ALK*-positive patients are small sample or subgroup analyses. ICIs alone did not show a good effect on *ALK*-rearranged patients, while ICIs combined with *ALK*-TKIs showed a little high efficacy. Therefore, further research is needed to explore better treatment options for *ALK*-rearranged patients. In the ATLANTIC study, the high expression of PD-L1 in *ALK*-rearranged patients was higher than that in patients with *EGFR* mutations but the





(c)	Study	Events	Total	Proportion	95%-CI	Weight (common)	Weight (random)
	Jeanson 2019	13	69	0.19	[0.10; 0.30]	38.5%	19.9%
	Gadgeel 2019	13	26	0.50	[0.30; 0.70]	8.9%	15.9%
	Herbst 2019	8	12	0.67	[0.35; 0.90]	4.6%	12.8%
	Yoh 2021	2	12 -	.17	[0.02; 0.48]	7.4%	15.1%
	Zhao 2022	16	32	0.50	[0.32; 0.68]	10.9%	16.7%
	Justeau 2022	39	86	0.45	[0.35; 0.56]	29.6%	19.5%
	Common effect model		237	0.35	[0.29; 0.41]	100.0%	
	Random effects model Heterogeneity: $I^2 = 83\%$, τ^2		0<00	0.40	[0.25; 0.55]		100.0%
	rictorogeneity. 7 = 0070, t	- 0.0210	, 0.0	02 04 06 08			



Figure 4. ORR of KRAS-mutant NSCLC patients with monoimmunotherapy. (a) Forest plots of ORR in (a) prospective studies of monoimmunotherapy; (b) retrospective studies of monoimmunotherapy; (c) KRAS G12C mutations; and (d) KRAS non-G12C mutations.

KRAS, Kirsten rat sarcoma viral oncogene homolog; NSCLC, non-small-cell lung cancer; ORR, objective response rate.



Figure 5. The mPFS of KRAS-mutant NSCLC patients with monoimmunotherapy. (a) Forest plots of mPFS in prospective studies of monoimmunotherapy and (b) Forest plots of mOS in prospective studies of monoimmunotherapy.

KRAS, Kirsten rat sarcoma viral oncogene homolog; mOS, median overall survival; mPFS, median progression-free survival; mPFS, median progression-free survival; NSCLC, non-small-cell lung cancer; ORR, objective response rate.

effectiveness of durvalumab was only observed in patients with *EGFR* mutations.²³ Therefore, the role of ICIs in patients with *ALK* fusion is not prominent. In general, *EGFR*- and *ALK*-altered patients who would have better benefits from targeted therapy do not need to try immunotherapy and would not consider starting immune-combination therapy unless their *EGFR/ALK*-TKI resistance developed.

Immunotherapy with *BRAF*, *HER2*, *MET*, *RET*, and *ROS1* alteration NSCLC is currently lacking prospective studies, and the baseline levels of patients analyzed in retrospective studies vary from study to study, so the results of the studies are varied. In our study, patients with *BRAF* non-V600E mutations showed better responsiveness than those with BRAF V600E mutation and the *MET*-amplification population showed a

better response to *MET*-exon 14 skipping. Dabrafenib and trametinib are targeted in the treatment of BRAF V660E mutant NSCLC, while for non-V600E, there is no standard recommended medication.¹⁰⁸ Based on the literature we included, immunotherapy is a not bad option for patients with *BRAF* non-V600E mutations or *MET* amplification. We showed that pure immunotherapy has limited efficacy for *HER2/RET/ROS1*-altered NSCLC. Previous studies also showed that the activity of monoimmunotherapy in these tumors was modest and chemoimmunotherapy.^{92,97}

Negrao's team analyzed the effect of driving gene mutation on the expression of tumor mutation burden (TMB) and PD-L1 and the correlation with the efficacy of immunotherapy in 4017



Figure 6. ORR of ALK-rearranged NSCLC patients with monoimmunotherapy. Forest plots of ORR in (a) prospective studies of monoimmunotherapy and (b) retrospective studies of monoimmunotherapy. ALK, anaplastic lymphoma kinase; NSCLC, non-small-cell lung cancer; ORR, objective response rate.

NSCLC patients treated with ICI. The results showed that *ALK/ROS1/RET* fusion and METexon14 mutation group had high expression of PD-L1 and low TMB but did not translate into clinical benefit. It is suggested that in addition to TMB and PD-L1, the driving gene can also affect the clinical outcome of immunotherapy.¹⁰⁹ In addition, for different gene mutations, mutations at different sites can activate different signal pathways and lead to different downstream effects, which may lead to different responses to immunotherapy.

There are several limitations in this study. Most of the included studies were retrospective trials with small sample sizes or prospective with subgroup data, which may lead to selection bias. In addition, owing to the lack of PFS and OS data in ALK, BRAF, and ROS1 alterations, we evaluated the therapeutic efficacy by examining the ORR of the published data. Precision therapy is the trend of NSCLC treatment in the future but ICI therapy for oncogene-driven NSCLC patients still needs to be further studied to bring more survival benefits to more oncogene-driven NSCLC patients.

Conclusion

The efficacy of immunotherapy is different in patients with different oncogene-driven NSCLC. *EGFR-, ALK-, HER2-, RET-*, and *ROS1*-altered NSCLC patients have poor reactivity to monoimmunotherapy but the efficacy of immune-based combined therapy is significantly improved. *KRAS* G12C mutation, *BRAF* non-V600E mutation, and *MET* amplification have better responses to immunotherapy, and more prospective studies are needed for further research.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication

All authors have read the manuscript and approved its submission to Therapeutic Advances in Medical Oncology.

Author contributions

Jiayan Chen: Conceptualization; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data supporting the results presented in this study are available from the corresponding author upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

References

- Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209–249.
- Oser MG, Niederst MJ, Sequist LV, et al. Transformation from non-small-cell lung cancer to small-cell lung cancer: molecular drivers and cells of origin. *Lancet Oncol* 2015; 16: e165–e172.
- 3. Ostrem JM and Shokat KM. Direct smallmolecule inhibitors of KRAS: from structural insights to mechanism-based design. *Nat Rev Drug Discov* 2016; 15: 771–785.
- Arbour KC and Riely GJ. Systemic therapy for locally advanced and metastatic non-small cell lung cancer: a review. *JAMA* 2019; 322: 764– 774.
- Champiat S, Dercle L, Ammari S, *et al.* Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. *Clin Cancer Res* 2017; 23: 1920–1928.
- 6. Zhou C, Chen G, Huang Y, *et al.* Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicentre, phase 3 trial. *Lancet Respir Med* 2021; 9: 305–314.
- Reck M, Rodríguez-Abreu D, Robinson AG, et al.; KEYNOTE-024 Investigators. pembrolizumab versus chemotherapy for PD-L1positive non-small-Cell lung cancer. New Engl J Med 2016; 375: 1823–1833.
- Gadgeel S, Rodriguez-Abreu D, Speranza G, et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. *J Clin* Oncol 2020; 38: 1505–1517.
- Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Lancet Respir Med 2019; 7: 387–401.
- Passiglia F, Cappuzzo F, Alabiso O, et al. Efficacy of nivolumab in pre-treated non-small-cell lung cancer patients harbouring KRAS mutations. Br J Cancer 2019; 120: 57–62.

- Peters S, Gettinger S, Johnson M, et al. Phase II trial of atezolizumab as first-line or subsequent therapy for patients with programmed deathligand 1-selected advanced non-small-cell lung cancer (BIRCH). *J Clin Oncol* 2017; 35: 2781– 2789.
- Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015; 373: 1627–1639.
- Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; 389: 255–265.
- Herbst RS, Lopes G, Kowalski DM, et al. LBA4 Association of KRAS mutational status with response to pembrolizumab monotherapy given as first-line therapy for PD-L1-positive advanced non-squamous NSCLC in Keynote-042. Ann Oncol 2019; 30: xi63–xi64.
- Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016; 387: 1837–1846.
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.
- Gettinger SN, Horn L, Gandhi L, *et al.* Overall survival and long-term safety of nivolumab (Anti-Programmed Death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol* 2015; 33: 2004–2012.
- Gettinger S, Rizvi NA, Chow LQ, et al. Nivolumab monotherapy for first-line treatment of advanced non-small-Cell lung cancer. *J Clin* Oncol 2016; 34: 2980–2987.
- 19. Nishio M, Hida T, Atagi S, *et al.* Multicentre phase II study of nivolumab in Japanese patients with advanced or recurrent non-squamous non-small cell lung cancer. *ESMO Open* 2016; 1: e000108.
- Rizvi NA, Hellmann MD, Brahmer JR, et al. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced Non-Small-Cell lung cancer. J Clin Oncol 2016; 34: 2969–2979.
- 21. Gulley JL, Rajan A, Spigel DR, et al. Avelumab for patients with previously treated metastatic or

recurrent non-small-cell lung cancer (JAVELIN solid tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial. *Lancet Oncol* 2017; 18: 599–610.

- 22. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an openlabel, phase 1, multicohort study. *Lancet Oncol* 2017; 18: 31–41.
- Garassino MC, Cho B-C, Kim J-H, et al. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. Lancet Oncol 2018; 19: 521–536.
- 24. Garassino MC, Gelibter AJ, Grossi F, et al. Italian nivolumab expanded access program in nonsquamous Non-Small cell lung cancer patients: results in never-smokers and EGFR-Mutant patients. *J Thorac Oncol* 2018; 13: 1146–1155.
- 25. Gubens MA, Sequist LV, Stevenson JP, *et al.* Pembrolizumab in combination with ipilimumab as second-line or later therapy for advanced nonsmall-cell lung cancer: KEYNOTE-021 cohorts D and H. *Lung Cancer* 2018; 130: 59–66.
- 26. Horn L, Gettinger SN, Gordon MS, et al. Safety and clinical activity of atezolizumab monotherapy in metastatic non-small-cell lung cancer: final results from a phase I study. Eur J Cancer 2018; 101: 201–209.
- 27. Lisberg A, Cummings A, Goldman JW, et al. A phase II study of pembrolizumab in EGFRmutant, PD-L1+, tyrosine kinase inhibitor naïve patients with advanced NSCLC. J Thorac Oncol 2018; 13: 1138–1145.
- Leighl NB, Hellmann MD, Hui R, et al. Pembrolizumab in patients with advanced nonsmall-cell lung cancer (KEYNOTE-001): 3-year results from an open-label, phase 1 study. *Lancet Respir Med* 2019; 7: 347–357.
- 29. Nishio M, Takahashi T, Yoshioka H, et al. KEYNOTE-025: phase 1b study of pembrolizumab in Japanese patients with previously treated programmed death ligand 1-positive advanced non-small-cell lung cancer. *Cancer Sci* 2019; 110: 1012–1020.
- Omori M, Okuma Y, Hakozaki T, *et al.* Statins improve survival in patients previously treated with nivolumab for advanced non-small cell lung cancer: an observational study. *Mol Clin Oncol* 2019; 10: 137–143.
- 31. Arrieta O, Barrón F, Ramírez-Tirado LA, *et al.* Efficacy and safety of pembrolizumab plus

docetaxel vs docetaxel alone in patients with previously treated advanced Non-Small cell lung cancer: the PROLUNG phase 2 randomized clinical trial. *JAMA Oncol* 2020; 6: 856–864.

- 32. Han TP, Zhao B, Yu Y, *et al.* A phase II study of tislelizumab plus chemotherapy in EGFR mutated advanced non-squamous NSCLC patients failed to EGFR TKI therapies: first analysis. *Ann Oncol* 2021; 32: S1443–S1444.
- Jiang T, Wang P, Zhang J, et al. Toripalimab plus chemotherapy as second-line treatment in previously EGFR-TKI treated patients with EGFR-mutant-advanced NSCLC: a multicenter phase-II trial. Signal Transduct Target Ther 2021; 6: 355.
- 34. Lam TC, Tsang KC, Choi HC, et al. Combination atezolizumab, bevacizumab, pemetrexed and carboplatin for metastatic EGFR mutated NSCLC after TKI failure. Lung Cancer 2021; 159: 18–26.
- 35. Hayashi H, Sugawara S, Fukuda Y, et al. A randomized phase II study comparing nivolumab with carboplatin-pemetrexed for EGFR-Mutated NSCLC with resistance to EGFR tyrosine kinase inhibitors (WJOG8515L). Clin Cancer Res 2022; 28: 893–902.
- 36. Lu S, Wu L, Jian H, et al. Sintilimab plus bevacizumab biosimilar IBI305 and chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer who progressed on EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): first interim results from a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2022; 23: 1167–1179.
- Yang JJ, Huang C, Fan Y, et al. Camrelizumab in different PD-L1 expression cohorts of pretreated advanced or metastatic non-small cell lung cancer: a phase II study. *Cancer Immunol Immunother* 2022; 71: 1393–1402.
- Gainor JF, Shaw AT, Sequist LV, et al. EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in Non-Small cell lung cancer: A retrospective analysis. *Clin Cancer Res* 2016; 22: 4585–4593.
- Bagley SJ, Kothari S, Aggarwal C, et al. Pretreatment neutrophil-to-lymphocyte ratio as a marker of outcomes in nivolumab-treated patients with advanced non-small-cell lung cancer. Lung Cancer 2017; 106: 1–7.
- 40. Haratani K, Hayashi H, Tanaka T, *et al.* Tumor immune microenvironment and nivolumab efficacy in EGFR mutation-positive non-smallcell lung cancer based on T790M status after

disease progression during EGFR-TKI treatment. *Ann Oncol* 2017; 28: 1532–1539.

- 41. Kim HK, Heo MH, Lee HS, *et al.* Comparison of RECIST to immune-related response criteria in patients with non-small cell lung cancer treated with immune-checkpoint inhibitors. *Cancer Chemother Pharmacol* 2017; 80: 591–598.
- Kobayashi H, Omori S, Nakashima K, *et al.* Response to the treatment immediately before nivolumab monotherapy may predict clinical response to nivolumab in patients with nonsmall cell lung cancer. *Int J Clin Oncol* 2017; 22: 690–697.
- 43. Oya Y, Yoshida T, Kuroda H, *et al.* Predictive clinical parameters for the response of nivolumab in pretreated advanced non-small-cell lung cancer. *Oncotarget* 2017; 8: 103117–103128.
- Fujimoto D, Yoshioka H, Kataoka Y, et al. Efficacy and safety of nivolumab in previously treated patients with non-small cell lung cancer: a multicenter retrospective cohort study. Lung Cancer 2018; 119: 14–20.
- 45. Hsu JC, Lin JY, Hsu MY, *et al.* Effectiveness and safety of immune checkpoint inhibitors: a retrospective study in Taiwan. *PLoS One* 2018; 13: e0202725.
- Juergens RA, Mariano C, Jolivet J, et al. Realworld benefit of nivolumab in a Canadian nonsmall-cell lung cancer cohort. *Curr Oncol* 2018; 25: 384–392.
- Kobayashi K, Nakachi I, Naoki K, *et al.*; Keio Lung Oncology Group (KLOG). Real-world efficacy and safety of nivolumab for advanced non-small-cell lung cancer: a retrospective multicenter analysis. *Clin Lung Cancer* 2018; 19: e349–e358.
- Lin SY, Yang CY, Liao BC, et al. Tumor PD-L1 expression and clinical outcomes in advancedstage Non-Small cell lung cancer patients treated with nivolumab or pembrolizumab: real-world data in Taiwan. J Cancer 2018; 9: 1813–1820.
- 49. Schouten RD, Muller M, de Gooijer CJ, *et al.* Real life experience with nivolumab for the treatment of non-small cell lung carcinoma: data from the expanded access program and routine clinical care in a tertiary cancer centre-The Netherlands Cancer Institute. *Lung Cancer* 2018; 126: 210–216.
- 50. Takeda M, Sakai K, Hayashi H, *et al.* Clinical characteristics of non-small cell lung cancer harboring mutations in exon 20 of EGFR or HER2. *Oncotarget* 2018; 9: 21132–21140.

- Yoshida H, Kim YH, Ozasa H, et al. Nivolumab in non-small-cell lung cancer with EGFR mutation. Ann Oncol 2018; 29: 777–778.
- Ahn BC, Pyo KH, Xin CF, et al. Comprehensive analysis of the characteristics and treatment outcomes of patients with non-small cell lung cancer treated with anti-PD-1 therapy in realworld practice. J Cancer Res Clin Oncol 2019; 145: 1613–1623.
- Cho JH, Jung HA, Lee SH, et al. Impact of EGFR mutation on the clinical efficacy of PD-1 inhibitors in patients with pulmonary adenocarcinoma. J Cancer Res Clin Oncol 2019; 145: 1341–1349.
- Guibert N, Jones G, Beeler JF, et al. Targeted sequencing of plasma cell-free DNA to predict response to PD1 inhibitors in advanced nonsmall cell lung cancer. Lung Cancer 2019; 137: 1–6.
- 55. Hastings K, Yu HA, Wei W, et al. EGFR mutation subtypes and response to immune checkpoint blockade treatment in non-small-cell lung cancer. Ann Oncol 2019; 30: 1311–1320.
- 56. Landi L, D'Incà F, Gelibter A, et al. Bone metastases and immunotherapy in patients with advanced non-small-cell lung cancer. J Immunother Cancer 2019; 7: 316.
- 57. Mazieres J, Drilon A, Lusque A, *et al.* Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol* 2019; 30: 1321–1328.
- Ng TL, Liu Y, Dimou A, *et al.* Predictive value of oncogenic driver subtype, programmed death-1 ligand (PD-L1) score, and smoking status on the efficacy of PD-1/PD-L1 inhibitors in patients with oncogene-driven non-small cell lung cancer. *Cancer* 2019; 125: 1038–1049.
- Sakamoto H, Tanaka H, Shiratori T, et al. The efficacy of immune checkpoint inhibitors in advanced non-small cell lung cancer harboring driver mutations. *Mol Clin Oncol* 2019; 10: 610–614.
- Sato M, Watanabe S, Tanaka H, et al. Retrospective analysis of antitumor effects and biomarkers for nivolumab in NSCLC patients with EGFR mutations. PLoS One 2019; 14: 0215292.
- Yamada T, Hirai S, Katayama Y, et al. Retrospective efficacy analysis of immune checkpoint inhibitors in patients with EGFRmutated non-small cell lung cancer. *Cancer Med* 2019; 8: 1521–1529.

- 62. Yamaguchi O, Kaira K, Hashimoto K, *et al.* Radiotherapy is an independent prognostic marker of favorable prognosis in non-small cell lung cancer patients after treatment with the immune checkpoint inhibitor, nivolumab. *Thorac Cancer* 2019; 10: 992–1000.
- 63. Bylicki O, Guisier F, Monnet I, *et al.* Efficacy and safety of programmed cell-death-protein-1 and its ligand inhibitors in pretreated patients with epidermal growth-factor receptor-mutated or anaplastic lymphoma kinase-translocated lung adenocarcinoma. *Medicine* 2020; 99: e18726.
- 64. Gainor JF, Rizvi H, Jimenez Aguilar E, et al. Clinical activity of programmed cell death 1 (PD-1) blockade in never, light, and heavy smokers with non-small-cell lung cancer and PD-L1 expression ≥50. Ann Oncol 2020; 31: 404–411.
- 65. Ishii H, Azuma K, Kawahara A, *et al.* Predictive value of CD73 expression for the efficacy of immune checkpoint inhibitors in NSCLC. *Thorac Cancer* 2020; 11: 950–955.
- Kitadai R, Okuma Y, Hakozaki T, et al. The efficacy of immune checkpoint inhibitors in advanced non-small-cell lung cancer with liver metastases. J Cancer Res Clin Oncol 2020; 146: 777–785.
- 67. Morita R, Okishio K, Shimizu J, *et al.* Real-world effectiveness and safety of nivolumab in patients with non-small cell lung cancer: a multicenter retrospective observational study in Japan. *Lung Cancer* 2020; 140: 8–18.
- 68. Song P, Zhang J, Shang C, *et al.* Author Correction: Real-world evidence and clinical observations of the treatment of advanced non-small cell lung cancer with PD-1/PD-L1 inhibitors. *Sci Rep* 2020; 10: 1525.
- Lau SCM, Fares AF, Le LW, et al. Subtypes of EGFR- and HER2-Mutant metastatic NSCLC influence response to immune checkpoint inhibitors. Clin Lung Cancer 2021; 22: 253–259.
- 70. Masuda K, Horinouchi H, Tanaka M, et al. Efficacy of anti-PD-1 antibodies in NSCLC patients with an EGFR mutation and high PD-L1 expression. J Cancer Res Clin Oncol 2021; 147: 245–251.
- Shen CI, Chao HS, Shiao TH, et al. Comparison of the outcome between immunotherapy alone or in combination with chemotherapy in EGFRmutant non-small cell lung cancer. Sci Rep 2021; 11: 16122.
- 72. Yoh K, Matsumoto S, Furuya N, *et al.* Comprehensive assessment of PD-L1 expression, tumor mutational burden and oncogenic driver

alterations in non-small cell lung cancer patients treated with immune checkpoint inhibitors. *Lung Cancer* 2021; 159: 128–134.

- 73. Hu J, Huang D, Wang Y, et al. The efficacy of immune checkpoint inhibitors in advanced EGFR-Mutated non-small cell lung cancer after resistance to EGFR-TKIs: real-world evidence from a multicenter retrospective study. *Front Immunol* 2022; 13: 975246.
- 74. Lu Z, Ye M, Sun T, *et al.* Pembrolizumab for the better treatment of EGFR-mutant T790Mnegative advanced lung adenocarcinoma patients than dual treatment of pemetrexed plus platinum after tyrosine kinase inhibitor treatment failure. *Ann Palliat Med* 2022; 11: 2100–2109.
- 75. Gadgeel S, Rodriguez-Abreu D, Felip E, et al. KRAS mutational status and efficacy in KEYNOTE-189: pembrolizumab (pembro) plus chemotherapy (chemo) vs placebo plus chemo as firstline therapy for metastatic non-squamous NSCLC. Ann Oncol 2019; 30: xi64–xi65.
- 76. Garde-Noguera J, Martin-Martorell P, De Julian M, et al. Predictive and prognostic clinical and pathological factors of nivolumab efficacy in nonsmall-cell lung cancer patients. *Clin Transl Oncol* 2018; 20: 1072–1079.
- 77. Jeanson A, Tomasini P, Souquet-Bressand M, et al. Efficacy of immune checkpoint inhibitors in KRAS-Mutant Non-Small cell lung cancer (NSCLC). J Thorac Oncol 2019; 14: 1095– 1101.
- 78. Torralvo J, Friedlaender A, Achard V, et al. The activity of immune checkpoint inhibition in KRAS mutated non-small cell lung cancer: a single centre experience. *Cancer Genomics Proteomics* 2019; 16: 577–582.
- 79. Gianoncelli L, Spitaleri G, Passaro A, et al. Efficacy of anti-PD1/PD-L1 therapy (IO) in KRAS mutant non-small cell lung cancer patients: a retrospective analysis. *Anticancer Res* 2020; 40: 427–433.
- Justeau G, Huchot E, Simonneau Y, et al. Impact of KRAS G12C mutation in patients with advanced non-squamous non-small cell lung cancer treated with first-line pembrolizumab monotherapy. Lung Cancer 2022; 174: 45–49.
- 81. Zhao D, Li H, Mambetsariev I, *et al.* Clinical and molecular features of KRAS-Mutated lung cancer patients treated with immune checkpoint inhibitors. *Cancers* 2022; 14: 4933.
- 82. Heo JY, Park C, Keam B, *et al.* The efficacy of immune checkpoint inhibitors in anaplastic lymphoma kinase-positive non-small cell lung cancer. *Thorac Cancer* 2019; 10: 2117–2123.

- Dudnik E, Bshara E, Grubstein A, et al. Rare targetable drivers (RTDs) in non-small cell lung cancer (NSCLC): outcomes with immune checkpoint inhibitors (ICPi). Lung Cancer 2018; 124: 117–124.
- 84. Dudnik E, Peled N, Nechushtan H, et al.; Israel Lung Cancer Group. BRAF mutant lung cancer: programmed death ligand 1 expression, tumor mutational burden, microsatellite instability status, and response to immune check-point inhibitors. J Thorac Oncol 2018; 13: 1128–1137.
- Rihawi K, Giannarelli D, Galetta D, et al. BRAF mutant NSCLC and Immune checkpoint inhibitors: results from a real-world experience. *J Thorac Oncol* 2019; 14: e57–e59.
- Guisier F, Dubos-Arvis C, Viñas F, et al. 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 2020; 15: 628–636.
- Wiesweg M, Preuss C, Roeper J, et al. BRAF mutations and BRAF mutation functional class have no negative impact on the clinical outcome of advanced NSCLC and associate with susceptibility to immunotherapy. Eur J Cancer 2021; 149: 211–221.
- Sabari JK, Leonardi GC, Shu CA, et al. PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. Ann Oncol 2018; 29: 2085–2091.
- Bittoni M, Yang JC, Shih JY, et al. Real-world insights into patients with advanced NSCLC and MEt alterations. Lung Cancer 2021; 159: 96–106.
- 90. Lai W-CV, Feldman DL, Buonocore DJ, et al. PD-L1 expression, tumor mutation burden and response to immune checkpoint blockade in patients with HER2-mutant lung cancers. *J Clin* Oncol 2018; 36: 9060–9060.
- Chu X, Qiang H, Xie M, et al. Treatment efficacy of HER2-mutant lung adenocarcinoma by immune checkpoint inhibitors: a multicenter retrospective study. *Cancer Immunol Immunother* 2022; 71: 1625–1631.
- 92. Saalfeld FC, Wenzel C, Christopoulos P, et al. Efficacy of immune checkpoint inhibitors alone or in combination with chemotherapy in NSCLC harboring ERBB2 mutations. *J Thorac Oncol* 2021; 16: 1952–1958.
- 93. Yang G, Yang Y, Liu R, *et al.* First-line immunotherapy or angiogenesis inhibitor plus chemotherapy for HER2-altered NSCLC: a retrospective real-world POLISH study. *Ther Adv Med Oncol* 2022; 14: 17588359221082339.

- 94. Offin M, Guo R, Wu SL, et al. Immunophenotype and response to immunotherapy of RET-rearranged lung cancers. *JCO precision oncology* 2019; 3: PO.18.00386.
- 95. Lu C, Dong XR, Zhao J, et al. Association of genetic and immuno-characteristics with clinical outcomes in patients with RETrearranged non-small cell lung cancer: a retrospective multicenter study. J Hematol Oncol 2020; 13: 37.
- 96. Bhandari NR, Hess LM, Han Y, et al. Efficacy of immune checkpoint inhibitor therapy in patients with RET fusion-positive non-smallcell lung cancer. *Immunotherapy* 2021; 13: 893–904.
- 97. Choudhury NJ, Schneider JL, Patil T, *et al.* Response to immune checkpoint inhibition as monotherapy or in combination with chemotherapy in metastatic ROS1-rearranged lung cancers. *JTO Clin Res Rep* 2021; 2: 100187.
- 98. Lee CK, Man J, Lord S, *et al.* Clinical and molecular characteristics associated with survival among patients treated with checkpoint inhibitors for advanced Non-Small cell lung carcinoma: a systematic review and metaanalysis. *JAMA Oncol* 2018; 4: 210–216.
- Qian X, Guo X, Li T, *et al.* Efficacy of immune checkpoint inhibitors in EGFR-Mutant NSCLC patients with EGFR-TKI resistance: a systematic review and meta-analysis. *Front Pharmacol* 2022; 13: 926890.
- 100. Yang H, Zhu J, Xiao R, et al. EGFR mutation status in non-small cell lung cancer receiving PD-1/PD-L1 inhibitors and its correlation with PD-L1 expression: a meta-analysis. Cancer Immunol Immunother 2022; 71: 1001–1016.

- 101. Lee CK, Man J, Lord S, et al. Checkpoint inhibitors in metastatic EGFR-mutated nonsmall cell lung cancer-a meta-analysis. J Thorac Oncol 2017; 12: 403–407.
- 102. Zhang R, Zhu J, Liu Y, *et al*. Efficacy of immune checkpoint inhibitors in the treatment of nonsmall cell lung cancer patients with different genes mutation: a meta-analysis. *Medicine* 2021; 100: e19713.
- 103. Dhillon S. Adagrasib: First approval. Drugs 2023; 83: 275–285.
- 104. Blair HA. Sotorasib: First approval. *Drugs* 2021; 81: 1573–1579.
- 105. Liao W, Overman MJ, Boutin AT, *et al.* KRAS-IRF2 axis drives immune suppression and immune therapy resistance in colorectal cancer. *Cancer Cell* 2019; 35: 559–572.e7.
- 106. Landre T, Justeau G, Assié JB, *et al*. Anti-PD-(L)1 for KRAS-mutant advanced nonsmall-cell lung cancers: a meta-analysis of randomized-controlled trials. *Cancer Immunol Immunother* 2022; 71: 719–726.
- 107. Gu TX, Si J, Guan Y, *et al.* Efficacy of immune checkpoint inhibitors in patients with KRASmutant advanced non-small cell lung cancer: a retrospective analysis. *Open Med* 2023; 18: 20230653.
- 108. Odogwu L, Mathieu L, Blumenthal G, et al. FDA approval summary: dabrafenib and trametinib for the treatment of metastatic nonsmall cell lung cancers harboring BRAF V600E mutations. Oncologist 2018; 23: 740–745.
- 109. Negrao MV, Skoulidis F, Montesion M, et al. Oncogene-specific differences in tumor mutational burden, PD-L1 expression, and outcomes from immunotherapy in non-small cell lung cancer. J Immunother Cancer 2021; 9: e002891.

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