

INTRODUCTION

HER2-mutant non-small cell lung cancer (NSCLC) is a rare molecular subset, representing 1.8-5.6% of all NSCLC cases. The advent of HER2-targeted therapies, including tyrosine kinase inhibitors (TKIs) and antibody-drug conjugates (ADCs), has significantly impacted the treatment landscape. This meta-analysis aim to compare efficacy outcomes, including objective response rate (ORR) and progression-free survival (PFS), as well as safety outcomes, such as grade ≥ 3 treatment-related adverse events (TRAEs), interstitial lung disease (ILD), and diarrhea between TKI and ADC.

METHODS

Design:

A systematic literature search was conducted across PubMed, Cochrane Library, Embase, clinicaltrials.gov, and abstracts from scientific meetings to identify randomized controlled trials (RCTs) comparing TKIs and ADCs in advanced or metastatic HER2-mutant NSCLC. Ten studies were included - five in the TKI arm and five in the ADC arm. Nine studies included pretreated patients, while one involved treatment-naïve individuals. Pooled estimates of ORR and PFS were calculated using a random-effects model with inverse variance in Python software. Heterogeneity was assessed using the I^2 statistic.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- This meta-analysis suggests no significant difference in efficacy between HER2-directed TKIs and ADCs for HER2-mutant NSCLC in terms of ORR and PFS. Both therapies showed similar rates of grade ≥ 3 TRAEs. However, ADCs were associated with a higher incidence of ILD/pneumonitis, whereas TKIs were more likely to cause diarrhea.

Future Direction for Research

- Our findings support the potential of newer HER2-specific TKIs as promising therapeutic options for HER2-mutant NSCLC, with an improved safety profile and efficacy.

RESULTS

The total sample size was 386 for the TKI arm and 377 for the ADC arm.

The ORR in TKI studies was 46% (95% CI: 23.1-70.8%), while ADC studies reported an ORR of 56.6% (95% CI: 42.2-70.0%). The difference in ORR between the two groups was +10.6%, but this was not statistically significant ($p = 0.339$).

Median PFS was 7.7 months (95% CI: 4.2-11.3) for TKI and 9.1 months (95% CI: 5.9-12.3) for ADC, with no significant difference observed ($p = 0.265$).

ADCs trend numerically better on efficacy (higher ORR, longer PFS) but the differences were not statistically significant.

In terms of safety, grade ≥ 3 TRAEs were observed in 51% of TKI patients (95% CI: 14.5-86.4%) versus 36% in ADC patients (95% CI: 10.1-73.9%), with no significant difference ($p = 0.683$).

The incidence of ILD or pneumonitis was substantially higher in ADC studies (13.2%) compared to TKI studies (1.4%).

Diarrhea of any grade occurred in 82.2% of TKI patients and 16.4% of ADC patients. Notably, newer selective TKIs such as Zongertinib (ORR 71%) and Sevabertinib (ORR 64%) demonstrated superior efficacy compared to older pan-HER TKIs, such as Poziotinib (ORR 28-39%) and Pyrotinib (ORR 30%).

REFERENCES & ACKNOWLEDGEMENTS

