Review question / Objective: To analyze the pooled effects and adverse events of brigatinib in patients with anaplastic lymphoma kinase (ALK) positive NSCLC.

Condition being studied: Eligible studies had to satisfy the following prespecified PICOS criteria. P (participants): ALK-positive NSCLC; I (intervention): oral brigatinib therapy treated; C (control): none; O (outcomes): ORR, disease control rate (DCR), PFS, intracranial ORR (iORR), intracranial PFS (iPFS), or adverse events (AEs); S (study designs): phase I, II or III clinical study, prospective cohort study, retrospective cohort study, or real-world evidence study. Articles dealing with mechanism research, pharmacology research, other non-efficacy research, or those not in English were excluded. We did not exclude studies involving patients pretreated with prior ALK inhibitors, nor did we exclude studies involving patients receiving chemotherapy. Where there were duplicate studies, articles published earlier or those that provided more detailed information or with longer follow-up time were selected.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 March 2022 and was last updated on 25 March 2022 (registration number INPLASY202230142).
brigatinib, studies have been conducted in clinical and real-world settings that evaluated efficacy and safety of brigatinib in different countries. However, substantial differences have been observed in regard to clinical outcomes, which might be partly attributed to small sample size, variances in patient characteristics and study settings.

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**METHODS**

**Search strategy:** We searched articles published from January 1980 to August 2021 in PubMed (Medline), EMBASE (Excerpta Medica Database), Cochrane Library and Web of Science. We used keyword search terms (‘brigatinib’) and (‘non-small cell lung cancer’ or ‘NSCLC’). We have also inspected the reference list of the retrieved studies in case we would miss relevant studies which met our inclusion criteria. Additionally, conferences abstracts that were presented in the 57th Annual Meeting (Virtual) of the American Society of Clinical Oncology (ASCO) June 4–8, 2021, and European Society for Medical Oncology (ESMO) Congress September 16-21, 2021 were also screened.

**Main outcome(s):** The estimated odds ratio/percentage/months and 95% confidence interval (95% CI) of the ORR, DCR, PFS, iORR, and iPFS were extracted from each brigatinib single-arm treatment group in each study. ORR, DCR, PFS, iORR, iPFS, and AEs.

**Quality assessment / Risk of bias analysis:** As most studies included in the analysis were single-arm cohort studies, we selected CASP-Cohort-Study-Checklist to evaluate the quality of studies [24]. The CASP-Cohort List, a quality assessment tool, was proposed by the Oxford Evidence-based Medical Center in 2004 for cohort studies. A total of 12 questions and 3 sections were used to evaluate each study. Assessment of publication bias - Stata 14 with meta-regression was used to analyze the sources of heterogeneity. Publication bias was inspected by a Deeks funnel plot. In addition, Begg’s and Egger’s test was also conducted to testify the funnel plot asymmetry.
**Strategy of data synthesis:** In case of multiple sets of data were provided in a study, we extracted only the best response data using standard dosage treatment (180 mg qd with 7-day 90 mg lead-in).

**Subgroup analysis:** PFS by treatment line, including 1) using brigatinib as first-line, 2) using brigatinib as second or further line.

**Sensitivity analysis:** Sensitivity analysis was also conducted in order to explore the impact of excluding an individual study on the pooled results.

**Language:** English.

**Country(ies) involved:** China.

**Keywords:** non-small cell lung cancer; ALK-positive; brigatinib; efficacy; adverse events.

**Conflicts of interest:** All authors have completed the ICMJE uniform disclosure form. Dr. Junling Li has received speaker honorarium for serving on advisory board of Takeda (China) International Trading Co., Ltd. The other authors have no conflicts of interest to declare.

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