Comparative Efficacy of Systemic Agents for Brain Metastases From Non-Small-Cell Lung Cancer With an EGFR Mutation/ALK Rearrangement: A Systematic Review and Network Meta-Analysis

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Background: Brain metastases (BM) from non-small-cell lung cancer (NSCLC) are frequent and carry significant morbidity, and current management options include varying local and systemic therapies. Here, we performed a systematic review and network meta-analysis to determine the ideal treatment regimen for NSCLC BMs with targetable EGFR-mutations/ALK-rearrangements.

Methods: We searched MEDLINE, EMBASE, Web of Science, ClinicalTrials.gov, CENTRAL and references of key studies for randomized controlled trials (RCTs) published from inception until June 2020. Comparative RCTs including ≥10 patients were selected. We used a frequentist random-effects model for network meta-analysis (NMA) and assessed the certainty of evidence using the GRADE approach. Our primary outcome of interest was intracranial progression-free survival (iPFS).

Results: We included 24 studies representing 19 trials with 1623 total patients. Targeted tyrosine kinase inhibitors (TKIs) significantly improved iPFS, with second-and third-generation TKIs showing the greatest benefit (HR=0.25, 95%CI 0.15-0.40). Overall PFS was also improved compared to conventional chemotherapy (HR=0.47, 95%CI 0.36-0.61). In EGFR-mutant patients, osimertinib showed the greatest benefit in iPFS (HR=0.32, 95%CI 0.15-0.69) compared to conventional chemotherapy, while gefitinib + chemotherapy showed the greatest overall PFS benefit (HR=0.26, 95%CI 0.10-0.70). All ALKi improved overall PFS compared to conventional chemotherapy, with alectinib having the greatest benefit (HR=0.13, 95%CI 0.07-0.24).
INTRODUCTION

Non-small cell lung cancer (NSCLC) is one of the most common and lethal cancer subtypes, with 25-30% of patients developing brain metastases (BMs) over the course of their disease (1). While surgery and radiation-based therapies have been the mainstay of management for local disease control in the brain (2–5), the emergence of targeted therapeutics based on the molecular features of tumors – such as tyrosine kinase inhibitors (TKIs) - have expanded our therapeutic armamentarium. Whereas traditional chemotherapeutic regimens have had limited efficacy against BMs (6), partly perhaps due to the inability to cross the blood-brain barrier (BBB), TKIs have shown significant promise in the management of people with NSCLC BM harboring targetable mutations in several clinical trials (3, 4, 7–9). In particular, newer generations of TKI have been developed to improve BBB permeance and overcome resistance that has developed to earlier generations, improving their efficacy. Despite convincing randomized controlled trial (RCT) data, however, to date there has been no comprehensive pooled analysis of the efficacy of the various generations of TKIs in comparison to traditional therapies for BMs, including systemic chemotherapy combined with other local therapies. The emergence of newer generations of TKIs, their individual side effect profiles, and their potentially prohibitive cost, necessitates assessment of their comparative efficacy in order to provide physicians with clinically relevant data that can aid decision-making and provide comprehensive patient counseling. However, head-to-head comparisons in the setting of an RCT are limited.

A network meta-analysis (NMA) allows for comparisons of multiple interventions, particularly when direct comparisons between interventions may be lacking (10). As such, we performed a systematic review and NMA to compare the efficacy of the various targeted therapies, compared with conventional chemotherapy and radiotherapy as a reference, in patients with EGFR mutated or ALK rearranged NSCLC BMs.

METHODS

This study was performed based on a predefined protocol and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension statement for reporting on network meta-analyses. This study is registered with the International Prospective Register of Systematic Reviews (PROSPERO), ID CRD42020179060.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=179060.

Keywords: targeted therapy, brain metastases, non-small cell lung cancer, neuro-oncology, EGFR inhibitors, ALK inhibitors

Conclusions: In patients with NSCLC BMs and EGFR/ALK mutations, targeted TKIs improve intracranial and overall PFS compared to conventional modalities such as chemotherapy, with greater efficacy seen using newer generations of TKIs. This data is important for treatment selection and patient counseling, and highlights areas for future RCT research.
therapy. Furthermore, most individuals with metastatic disease succumb to their systemic tumor burden. Therefore, we selected iPFS as the primary outcome in order to focus on the efficacy of any given treatment on the burden of intracranial disease, without confounding from the primary cancer. We only included studies that reported a comparative hazard ratio (HR) between arms for each outcome; the raw median survival times were not used in the analysis.

We performed quality assessment of the included studies using the Cochrane Risk of Bias 2.0 tool (11). Two analysts completed risk of bias assessment in duplicate, and disagreements were resolved via consensus. We used CiNEMA, a novel GRADE-based method for assessing confidence in results when multiple interventions are compared, to assess the overall certainty of evidence associated with each analysis (12, 13).

Data Synthesis and Statistical Analysis
A fixed effects or random effect meta-analysis was planned to compare the overall effect of targeted therapy with conventional chemotherapeutic agents for primary and secondary outcomes. We then performed a planned subgroup analysis for EGFR mutated and ALK re-arranged patients. For each outcome, we used HR and calculated the corresponding standard error (SE) for all analyses. In each subgroup, to compare different treatments, we used a frequentist NMA. This approach synthesizes metrics of both direct and indirect comparisons to refine and generate estimates of all possible pair-wise comparisons within a network. When both direct and indirect evidence of a comparison between treatment modalities were available, we first tested the null hypothesis that direct and indirect estimates were similar when enough information was available. When the null hypothesis was not rejected, the treatment effect was synthesized together to yield a network treatment effect. We then used the Rücker & Schwarzer method to rank treatments (14). We combined similar treatments into single nodes where necessary to complete the analysis. In particular, we combined most traditional chemotherapeutic regimens into a single node for most analyses, as various combination approaches have been shown to be similarly efficacious to traditional monotherapy in large trials (15, 16). Where necessary, we grouped EGFR inhibitors (EGFRi) by generation, with first generation defined as gefitinib, erlotinib, and icotinib, second generation as afatinib, and third generation as osimertinib. We also grouped ALK inhibitors (ALKi) similarly, with first generation as crizotinib, and second generation as ceritinib, alectinib, and brigatinib.

We assessed heterogeneity using Cochran’s Q statistic or the Chi square test in the case of pairwise meta-analysis. A P value of 0.1 was considered significant heterogeneity. In case of heterogeneity between studies a random effects model was used, otherwise a fixed effects model was used. A two-way P value of less than 0.05 was considered statistically significant. R software version 3.6.3 was used for all analyses.

RESULTS

Search Results and Study Characteristics
Twenty-four studies were included representing 19 unique trials, with 1623 patients total (Figure 1). All trials included patients with favorable performance status (ECOG 0-2 or KPS>70) (7–9, 17–33). Nine trials included patients with EGFR mutations, and 10 included patients with ALK rearrangements.

Importantly, most trials that reported outcome data on BMs as a subgroup analysis of all-comer NSCLC patients excluded BMs that were symptomatic or required urgent treatment, meaning many of these patients may have been previously treated with modalities such as surgery or radiation. This was true for all included studies except for Yang 2017 (7). Baseline characteristics and extracted data from included trials are shown in Tables 1, 2.

Efficacy
The efficacy analysis was done using several individual networks, as there was insufficient overlap between all 19 trials to produce a single coherent network graph for each outcome. In addition, not every trial reported all of our outcomes of interest, and analysis of each outcome was done with the available data. Therefore, each efficacy analysis below includes a subset of the nineteen total trials. Supplement E contains league tables showing the results of all pairwise comparisons for each analysis.

Pooled Analyses of EGFRi or ALKi Versus Conventional Chemotherapy for NSCLC Patients With Brain Metastases

iPFS
This analysis included 5 studies, 400 patients with targeted therapy and 114 with conventional chemotherapy. Two focused on patients with ALK re-arrangements and 3 on EGFR mutated patients7,9,17–19. We grouped all first-generation targeted therapies together and compared against newer targeted therapies (such as second and third generation). This was done as several individual trials compared first-generation TKIs with second/third generation TKIs, but did not compare different first-generation TKIs against each other. All conventional chemotherapy arms were also grouped together, and we included one study with WBRT added to chemotherapy in the chemotherapy arm (Figure 2A) (7). As treatment arms were grouped together, a random effects model was used despite non-significant Q statistic (Q=2.95, df=3, P value=0.39). Both direct and indirect estimates from the model were in agreement (Supplement C, Figure S1). Targeted therapies were superior to conventional chemotherapy in improving iPFS (Figure 2A). Moreover, newer generations TKIs showed greater benefit compared to first generation TKIs (HR=0.39, 95%CI 0.26-0.58), and ranked first in improving iPFS (P-score=1.0) (Supplement C, Figure S2). The overall certainty of evidence was moderate to high (Supplement D, Table S3).

Overall PFS
Here, we included nine studies with patients harboring either EGFR mutations or ALK rearrangements (n=419 TKI, n=312 conventional chemotherapy) and reporting overall PFS (7, 20, 21, 23, 26, 28–30). This was a traditional pairwise meta-analysis (Figure 2B). TKIs significantly improved overall PFS compared to conventional chemotherapy (X² = 16.76, df=8, P=0.03; HR=0.47, 95%CI 0.36-0.61). The overall certainty of evidence was high (Supplement D, Table S4).
Overall Survival

Seven studies were included with 572 total patients (n=376 TKIs, n=146 chemotherapy, n=50 TKI + chemotherapy, with 6 studies focusing on patients with EGFR mutations and one on patients with ALK re-arrangements) (7, 19, 23, 30–32). First generation TKIs were grouped together, and studies combining first generation TKIs with chemotherapy were treated as a separate node. Newer TKIs (second or third generation) were grouped (Figure 2C). Both direct and indirect estimates from the model were in agreement (Supplement C, Figure S3).

Among included treatments, first generation TKI (gefitinib) plus chemotherapy ranked first in improving overall survival (P score=0.91) and showed a trend toward significance (HR=0.72, 95%CI 0.40-1.27) (Figure 2C) (Supplement C, Figure S4). TKIs alone did not improve overall survival compared to platinum-based chemotherapy alone. The overall certainty of evidence was moderate for all comparisons (Supplement D, Table S5).

Subgroup Analyses: EGFR Mutant NSCLC With BM

For this set of analyses, we included studies that only enrolled patients with EGFR mutated NSCLC. All first generation EGFRIs (gefitinib, erlotinib, icotinib) were grouped.
| Study ID               | Trial Design                  | Patient Population                                           | Arm             | Category of Intervention | N BM patients | N women (%) | Median age, years (range) | Previous BM treatments |
|-----------------------|-------------------------------|-------------------------------------------------------------|-----------------|--------------------------|---------------|--------------|--------------------------|------------------------|
| Camidge et al. (17)   | Phase III, Open-Label, Multicentre, international | ALK-rearranged NSCLC Asymptomatic, stable BMs only              | Arm A: Brigatinib TKI (ALK Gen 3 + EGFR Gen 3) | 40 | 69 (60%), full cohort | 58 (27-88), full cohort | Brain radiotherapy, n=18 |
|                       |                               |                                                             | Arm B: Crizotinib TKI (ALK Gen 1) | 41 | 81 (59%), full cohort | 60 (29-89), full cohort | Brain radiotherapy, n=19 |
| Hida et al. (18)      | Phase III, Open-Label, Multicentre, Japanese centres only | ALK-rearranged NSCLC Asymptomatic, stable BMs only              | Arm A: Alectinib TKI (ALK Gen 2) | 14 | 62 (60%), full cohort | 61 (27-85), full cohort | Brain radiotherapy, n=6/16 |
|                       |                               |                                                             | Arm B: Crizotinib TKI (ALK Gen 1) | 29 | 63 (61%), full cohort | 59.5 (25-84), full cohort | Brain radiotherapy, n=16/31 |
| Yang (7) (BRAIN, NCT01724801) | Phase III, Open-Label, Multicentre, Chinese centres only | EGFR-mutated NSCLC                                          | Arm A: Icotinib TKI (EGFR Gen 1) | 85 | 53 (62%), full cohort | 57 (51-64), full cohort | No prior TKI or WBRT |
|                       |                               |                                                             | Arm B: WBRT + Platinum-based Chemotherapy TKI (EGFR Gen 3) | 73 | 41 (56%), full cohort | 58 (48-63), full cohort | Brain radiotherapy, n=28 |
| Wu et al. (9) (AURA3, NCT02151981) | Phase III, Open-Label, Multicentre, international | EGFR-mutated NSCLC Stable, asymptomatic BMs only, Leptomeningeal metastases excluded | Arm A: Osimertinib TKI (EGFR Gen 3) | 75 | 41 (55%), full cohort | 58 (34-82), full cohort | Brain radiotherapy, n=20 |
| Soria et al. (19) (FLAURA, NCT02296125) | Phase III, Double-Blind, Multicentre, International | EGFR-mutated NSCLC Stable BMs only                           | Arm A: Osimertinib TKI (EGFR Gen 3) | 53 | 178 (83.8%), full cohort | 64 (26-85), full cohort | No prior treatment for advanced disease, no prior treatment with TKi |
|                       |                               |                                                             | Arm B: Standard EGFR-TKI (Geftinib or Erlotinib) TKI (EGFR Gen 3) | 63 | 172 (62%), full cohort | 64 (35-93), full cohort | Brain radiotherapy, n=20 |
| Novello et al. (21) (ALUR, NCT02804342) | Phase III, Open-Label, Multicentre, international | ALK-rearranged NSCLC All patients had two lines of previous systemic therapy, including 1 line of previous Crizotinib therapy, Asymptomatic BMs OR symptomatic BMs and ineligible for radiotherapy only. | Arm A: Alectinib TKI (ALK Gen 2) | 47 | 31 (43.1%), full cohort | 55.5 (21-82), full cohort | WBRT (n=23), SRS (n=2), other (n=3). All patients had previous crizotinib therapy |
|                       |                               |                                                             | Arm B: Crizotinib TKI (ALK Gen 1) | 58 | 87 (58%), full cohort | 54 (18-91), full cohort | WBRT (n=9), SRS (n=5), other (n=2). All patients had previous crizotinib therapy |
| Peters et al. (22) (ALEX, NCT02075840) | Phase III, Open-Label, Multicentre, international | ALK-rearranged NSCLC Leptomeningeal metastases excluded Asymptomatic BMs only | Arm A: Alectinib TKI (ALK Gen 2) | 64 | 84 (65%), full cohort | 58 (25-88), full cohort | Surgery (n=1), SRS (n=4), WBRT (n=16), other (n=1) |
|                       |                               |                                                             | Arm B: Crizotinib TKI (ALK Gen 1) | 39 | 19 (49%), full cohort | 48 (29-70), full cohort | Surgery (n=1), SRS (n=5), WBRT (n=17), other (n=4) |
| Solomon et al. (23–25) (PROFILE 1014, NCT01154140) | Phase III, Open-Label, Multicentre, international | ALK-rearranged NSCLC Stable and previously treated BMs only | Arm A: Crizotinib TKI (ALK Gen 1) | 58 | 87 (58%), full cohort | 54 (18-91), full cohort | No prior systemic treatment of advanced disease |

(Continued)
| Study ID          | Trial Design            | Patient Population                                      | Arm                                           | Category of Intervention | N BM patients | N women (%) | Median age, years (range) | Previous BM treatments |
|------------------|-------------------------|---------------------------------------------------------|-----------------------------------------------|--------------------------|---------------|-------------|--------------------------|------------------------|
| Wu et al. (26)   | Phase III, Open-Label, Multicentre, Chinese centres only | ALK-rearranged NSCLC Stable and previously treated BMs only | Arm B: Platinum-based Chemotherapy Arm A: Crizotinib (ALK Gen 1) | Traditional Chemotherapy | 40            | 31 (78%)    | 51 (25-76)               | No previous systemic therapy for advanced disease |
| Zhou et al. (27) | Phase III, Open-Label, Multicentre, international | ALK-rearranged NSCLC All symptomatic BMs had to be previously treated with radiotherapy | Arm B: Platinum-based Chemotherapy Arm A: Alectinib (ALK Gen 2) | Traditional Chemotherapy | 32            | 60 (58.3%)  | 50 (23-69)               | Brain radiotherapy (n=8) |
| Shaw et al. (29) | Phase III, Open-Label, Multicentre, International | ALK-rearranged NSCLC, all patients had previous 1 line of platinum-based therapy. Asymptomatic BMs only. | Arm B: Chemotherapy (Pemetrexed or Docetaxel) Arm A: Crizotinib (ALK Gen 1) | Traditional Chemotherapy | 60            | 98 (56.64%) | 51 (22-81)               | Progression after 1 platinum-based chemotherapy regimen |
| Soria et al. (20) | Phase III, Open-Label, Multicentre, International | ALK-rearranged NSCLC, Stable and asymptomatic BMs only. | Arm B: Chemotherapy (Pemetrexed or Docetaxel) Arm A: Ceritinib (ALK Gen 2) | Traditional Chemotherapy | 59            | 61 (53%)    | 54 (47-64)               | Brain radiotherapy (n=24) Adjuvant or neoadjuvant chemo (n=10) |
| Schuler et al. (30) | Phase III, Open-Label, Multicentre, international | EGFR-mutated NSCLC, no prior treatment for NSCLC, no prior TKI. Stable, asymptomatic BMs only. | Arm B: Platinum-based Chemotherapy (Cisplatin/Pemetrexed) Arm A: Afatinib (EGFR Gen 2) | Traditional Chemotherapy | 15            | 12 (80%)    | 63 (31-74)               | WBR (n=5) |
| Schuler et al. (30) | Phase III, Open-Label, Multicentre, international (Asia only) | EGFR-mutated NSCLC, no prior treatment for NSCLC, no prior TKI. Stable, asymptomatic BMs only. | Arm B: Platinum-based Chemotherapy (Cisplatin/Gemcitabine) Arm A: Afatinib (EGFR Gen 2) | Traditional Chemotherapy | 18            | 12 (66.7%)  | 55 (35-70)               | WBR (n=6) |

(Continued)
TABLE 1 | Continued

| Study ID | Trial Design | Patient Population | Arm | Category of Intervention | N BM patients | N women (%) | Median age, years (range) | Previous BM treatments |
|----------|--------------|-------------------|-----|-------------------------|---------------|-------------|--------------------------|-----------------------|
| Park et al. (31) | Phase IB, Open-Label, Multicentre, international | EGFR-mutated NSCLC, no prior treatment for NSCLC, no prior TKI, Stable, asymptomatic BMs only | Arm A: Atezolizumab | TKI (EGFR Gen 2) | 26 | 91, full cohort | 63 (30-88), full cohort | NR |
| Hosomi et al. (32) | Phase III, Open-Label, Multicentre, Japanese centres only | EGFR-mutated NSCLC, Asymptomatic BMs only | Arm A: Gefitinib | TKI (EGFR Gen 1) | 36 | 71 (63%), full cohort | Mean 64.8 (SD 7.8), full cohort | Brain radiation (n=17) |
| Saito et al. (33) | Phase III, Open-Label, Multicentre, international | EGFR-mutated NSCLC, Asymptomatic BMs only | Arm A: Erlotinib + Bevacizumab | TKI (EGFR Gen 1) + Traditional Chemotherapy (VEGFi) | 36 | 68 (62-73), full cohort | Patients could not have received previous chemotherapy other than adjuvant chemotherapy |
| Noronha et al. (8) | Phase III, Open-Label, Single-centre, India | EGFR-mutated NSCLC | Arm A: Gefitinib | TKI (EGFR Gen 1) | 34 | 83 (47%), full cohort | 56 (27-78), full cohort | WBR (n=31) |

### iPFS

Three studies with 4 distinct arms of treatment were included in this analysis, with 390 total patients (7, 9, 19). Treatment arms included platinum-based chemotherapy, WBR plus platinum-based chemotherapy, icotinib (first generation EGFRi), and osimertinib (third generation EGFRi) (Figure 3A). Osimertinib significantly improved iPFS (HR=0.32, 95%CI 0.15-0.69) compared to platinum-based chemotherapy alone and ranked first among treatment arms for improving iPFS (P score=0.99) (Supplement C, Figure S5). Using a first-generation EGFRi or adding WBR to platinum-based chemotherapy did not improve iPFS (Figure 3A). The overall certainty of evidence was low (Supplement D, Table S6).

### Overall PFS

Eight different studies were included in this subgroup with 629 total patients (7, 8, 19, 30–33). As a result, seven distinct treatment arms were compared (Figure 3B). A fixed effects model was used (Q=1.59, df=2, P value=0.45).

First generation EGFRi (gefitinib) plus platinum-based chemotherapy (P score=0.94) ranked first followed by osimertinib alone (P score=0.84) and afatinib alone (P score=0.57) in improving overall PFS (Supplement C, Figure S6). WBR with chemotherapy or first generation EGFRi alone did not improve overall PFS compared to platinum-based chemotherapy alone (Figure 3B). Afatinib alone (HR=0.51, 95%CI 0.27-0.95), osimertinib alone (HR=0.31, 95%CI 0.12-0.86) and gefitinib plus platinum-based chemotherapy (HR=0.26, 95%CI 0.10-0.70) improved overall PFS compared to platinum-based chemotherapy alone. The overall certainty of evidence was low (Supplement D, Table S7).

### Overall Survival

Six studies were included (493 patients) (7, 19, 30–32). All first-generation EGFRi were grouped together for this analysis, resulting in 6 distinct treatment arms (Figure 3C). All the included treatment arms showed similar efficacy as platinum-based chemotherapy and did not significantly increase OS (Figure 3C). The overall certainty of evidence was low (Supplement D, Table S8).

### Subgroup Analyses: ALK Rearranged NSCLC Patients With BM

For these analyses, we compared ALKi with chemotherapy. All conventional chemotherapy arms were entered under the same node (Chemotherapy) in the network.

### iPFS

Two trials (124 patients) with a total of three arms comparing generations of ALKi were included (Figure 4A) (17, 18). Alectinib (second generation TKI) showed a trend toward
### TABLE 2 | Extracted outcome data from each study.

| Study ID | Treatment Arm | Overall Survival | Overall PFS (Definition) | Overall PFS (HR) | Intracranial PFS (Definition) | Intracranial PFS (HR) | Intracranial Time to Progression (Definition) | Intracranial TTP (HR) |
|----------|---------------|------------------|--------------------------|------------------|-------------------------------|-----------------------|-----------------------------------------------|----------------------|
| Camidge et al. (17) (ALTA-1L, NCT0273750) | Arm A: Brigatinib | NR | NR | NR | Time from randomization to CNS disease progression based on RECIST v1.1 criteria, or death from any cause. BMs assessed via CT or MRI according to RECIST v1.1 criteria. | 0.27 (0.13-0.54) | Intracranial TTP (HR) | NR |
| Arm B: Crizotinib | | | | | | | | |
| Hida et al. (18) (J-ALEX, JapicCTI-132316) | Arm A: Alectinib | NR | NR | NR | Time to randomization to progression of BMs in patients with BMs at baseline, or death, progression based on RECIST v1.1 criteria. | 0.16 (0.02-1.28) | Intracranial TTP (HR) | NR |
| Arm B: Crizotinib | | | | | | | | |
| Yang et al. (7) (BRAIN, NCT01724801) | Arm A: Icotinib | 0.93 (0.6-1.44), p=0.734 | NR | NR | Defined as the time from randomization to progression of intracranial disease or death from any cause. BMs assessed via MRI every 6 weeks according to RECIST v1.1 criteria. | 0.56 (0.36-0.90), p=0.014 | Intracranial TTP (HR) | 0.75 (0.44-1.27), p=0.284 |
| Arm B: WBRT + Platinum-based Chemotherapy | | | | | | | | |
| Wu et al. (9) (AURA3, NCT02151981) | Arm A: Osimertinib | NR | NR | NR | Defined as time to intracranial progression or death from any cause. BMs assessed via CT or MRI according to RECIST v1.1 criteria. | 0.32 (0.15-0.69), p=0.004 | Intracranial TTP (HR) | NR |
| Arm B: Platinum-based Chemotherapy | | | | | | | | |
| Soria et al. (19) (FLAURA, NCT02296125) | Arm A: Osimertinib | 0.83 (0.53-1.30) | Time to disease progression or death from any cause, assessed according to RECIST v1.1 criteria. Tumors were imaged every 6 weeks until 18 months, then every 12 weeks until disease progression. | 0.47 (0.30-0.74), p=0.001 | Intracranial TTP (HR) | Reference |
| Arm B: Standard EGFR-TKI (Gefitinib or Erlotinib) | | | | | | | | |
| Novello et al. (21) (ALUR, NCT02604342) | Arm A: Alectinib | NR | NR | NR | Time from randomization to radiographic brain tumour progression on MRI using RECIST criteria. | 0.16 (0.06-0.43) | Intracranial TTP (HR) | Reference |
| Arm B: Chemotherapy (Pemetrexed OR Docetaxel) | | | | | | | | |
| Peters et al. (22) (ALEX, NCT02075840) | Arm A: Crizotinib | NR | NR | NR | Time from randomization to radiographic tumour progression on MRI using RECIST v1.1 criteria. HR is cause-specific HR for CNS progression (excluding pts who had non-CNS progression OR death). | 0.18 (0.09-0.36), p=0.0001 | Intracranial TTP (HR) | Reference |
| Arm B: Alectinib | | | | | | | | |
| Solomon et al. (23-25) (PROFILE 1014, NCT01154140) | Arm A: Crizotinib | 1.285 (0.716-2.306), p=0.3991 | Time to disease progression or death from any cause. Progression assessed as per RECIST v1.1 criteria. | 0.4 (0.25-0.64), p=0.0001 | Intracranial TTP (HR) | 0.45 (0.19-1.07), p=0.063 |
| Arm B: Alectinib | | | | | | | | |

(Continued)
| Study ID | Treatment Arm | Study Name | Reference | Overall Survival | Overall PFS (Definition) | Overall PFS (HR) | Intracranial PFS (Definition) | Intracranial PFS (HR) | Intracranial Time to Progression (Definition) | Intracranial TTP (HR) | Notes |
|----------|----------------|------------|------------|------------------|-------------------------|-----------------|-------------------------------|----------------------|-----------------------------------------------|----------------------|-------|
| Wu et al. (26) (PROFILE 1029, NCT01639001) | Arm B: Platinum-based Chemotherapy | Reference | Reference | Reference | Time to progression of disease as defined by RECIST v1.1, including primary tumour, or death from any cause. Imaging was done every 6 weeks. | 0.497 (<0.25-0.95) Reference | NR | NR | The time from randomization to the first objective tumor progression considering only intracranial disease, according to RECIST v1.1 criteria. | 0.67 (0.33-1.34), p=0.13 Reference | Documentation of objective intracranial progression according to RECIST v1.1 criteria. |
| Zhou et al. (27) (ALESIA, NCT02838420) | Arm A: Crizotinib | NR | NR | NR | Time to progression of disease as defined by RECIST v1.1, including primary tumour, or death. Imaging done every 8 weeks. | 0.11 (<0.05-0.28) Reference | NR | NR | Progression due to newly developed CNS lesions or progression of pre-existing baseline CNS lesions per independent review committee assessment according to RECIST v1.1, imaging done every 8 weeks via brain MRI. Competing risk analysis done for HR (cause-specific HR for CNS progression without previous systemic progression reported). | 0.14 (<0.06-0.3), p<0.0001 Reference | |
| Shaw et al. (28) (NCT00932893) | Arm A: Crizotinib | NR | NR | NR | Time to progression of disease as defined by RECIST v1.1, including primary tumour, or death. Imaging done every 6 weeks. | 0.67 (<0.44-1.03) Reference | NR | NR | NR | |
| Shaw et al. (29) (ASCEND-5, NCT01828112) | Arm A: Ceritinib | NR | NR | NR | Time to progression of disease as defined by RECIST v1.1, including primary tumour, or death. Imaging done every 6 weeks until 18 months, then every 9 weeks thereafter. | 0.5 (<0.33-0.76) Reference | NR | NR | NR | |
| Soria et al. (20) (ASCEND-4, NCT01828099) | Arm A: Ceritinib | NR | NR | NR | Time to progression of disease as defined by RECIST v1.1, including primary tumour, or death. Imaging done every 6 weeks until 33 months, then every 9 weeks thereafter. | 0.7 (<0.44-1.12) Reference | NR | NR | NR | |
| Schuler et al. (30) (LUX-Lung 3, NCT00949650) | Arm A: Afatinib | 1.15 (0.49-2.67), p=0.752 Reference | Time to progression of disease as defined by RECIST v1.1, including primary tumour, or death. Imaging done every 6 weeks until 4 months, then every 12 weeks until progression. | 0.54 (0.12-1.25), p=0.138 Reference | NR | NR | NR | |
| Schuler et al. (30) (LUX-Lung 6, NCT01121393) | Arm A: Afatinib | 1.13 (0.56-2.26), p=0.732 Reference | Time to progression of disease as defined by RECIST v1.1, including primary tumour, or death. Imaging done every 6 weeks until 4 months, then every 12 weeks until progression. | 0.47 (0.18-1.21), p=0.106 Reference | NR | NR | NR | |

(Continued)
improving the iPFS (HR=0.16, 95% CI 0.02-1.28) (Figure 4A). Alectinib (P score=0.81) ranked first followed by brigatinib (P score =0.65) in improving iPFS (Supplement C, Figure S7). Brigatinib was superior to crizotinib (first generation ALKi) in prolonging iPFS (HR=0.27, 95% CI 0.14-0.54). The overall certainty of evidence was low for these comparisons (Supplement D, Table S9).

**Intracranial TTP**

Five studies were included (394 patients) (21–23, 26, 27, 34). The three treatment arms in this subgroup were alectinib, crizotinib, and chemotherapy (Figure 4B). Alectinib ranked first for improving iTTP (P score=1) (Supplement C, Figure S8). Alectinib significantly improved iTTP compared to both crizotinib (HR=0.17, 95%CI 0.11-0.28) and chemotherapy (HR=0.11, 95%CI 0.06-0.20) (Figure 4B). Crizotinib showed a trend toward improved iTTP compared to chemotherapy (HR=0.64, 95%CI 0.39-1.04). The overall certainty of evidence was moderate to high (Supplement D, Table S10).

**Overall PFS**

Eight different studies were included (754 patients) (20–23, 26–29). There were four distinct treatment arms in this analysis (Figure 4C). All three targeted therapies improved overall PFS (P score=1) (Supplement C, Figure S9). The overall certainty of evidence was moderate to high (Supplement C, Table S11).

**Quality Assessment**

The quality assessment of included studies showed an overall low risk of bias in 13/19 trials and 6 trials with ‘some concerns’ overall. There were no studies with an overall high risk of bias. Supplement B, Table S1 shows full RoB 2.0 results for all included studies.
Adverse Events
All studies reported adverse events, with traditional chemotherapy having similar incidence of grade 3/4 AEs across studies, and most targeted therapies with a similar safety profile. In studies directly comparing any EGFRi alone with EGFRi plus chemotherapy or chemotherapy alone, the EGFRi therapies had a lower incidence of Grade 3/4 AEs (7–9, 30, 32, 33). Among ALKi, alectinib showed a lower incidence of Grade 3/4 AEs than both chemotherapy and crizotinib in direct comparisons (18, 21, 22, 27).

Supplement B, Table S2 summarizes the incidence of grade 3/4 AEs across studies.

DISCUSSION
In this systematic review and NMA, we provide a quantitative comparison showing the superiority of TKIs against conventional chemotherapeutic agents in improving both iPFS and overall PFS in patients with NSCLC with BMs, with a moderate to high degree of certainty. This benefit was greater with newer generations of TKIs. The iPFS/overall PFS benefit with TKIs did not translate to a difference in OS compared to conventional chemotherapy, with or without WBRT. To the best of our knowledge, this is the first study to provide a comprehensive quantitative comparison based on RCT data of the efficacy of TKIs in patients with BMs from NSCLC and activating EGFR mutations or ALK rearrangements, which is an important subpopulation of patients with NSCLC. The use of a NMA allowed for comparisons between treatment arms that have never been directly assessed in existing trials, providing new quantitative insight into the comparative efficacy of these treatments, in addition to the already well-established qualitative superiority of these agents. Previous meta-analyses have demonstrated the efficacy of adding TKI therapy to traditional radiotherapy or chemotherapy approaches in EGFR-mutant patients, similar to our results in this analysis (35–38). However, a recent meta-analysis by Singh et al. found no PFS or OS benefit on addition of TKIs to RT in EGFR or ALK mutant patients (39). Importantly, this study and other past works have included numerous retrospective and non-randomized studies in their analysis, limiting the quality of evidence in each individual analysis. Our work differs from past meta-analyses in that it is the first comprehensive analysis based entirely on RCT data, thereby providing the highest level of evidence to inform future clinical decision-making in this population of patients. Our findings are also in keeping with the National Comprehensive Cancer Network Clinical Practice Guidelines in NSCLC, which recommend first-line TKIs in patients with metastatic disease and activating EGFR or ALK mutations (40).
The improvement of iPFS we observed with newer generations of TKIs is likely in large part due to their proficiency in crossing the BBB, which not only enables targeting of bulk tumor but also micro-metastases (2, 4, 41–44). The current standard of care in NSCLC treatment in many centers worldwide already focuses on use of TKIs rather than traditional chemotherapy wherever possible – however, we show significantly increased benefit with the use of newer generations of TKIs. The CNS penetrance of newer TKIs is particularly relevant as we have seen a recent paradigmatic shift in favor of SRS instead of WBRT in the local management of oligometastatic brain disease; while SRS is associated with a lower rate of long-term cognitive decline, the rate of distant BM recurrence is higher than with WBRT (45). Therefore, the use of CNS-penetrating TKIs may help reduce BM recurrence in patients receiving SRS instead of WBRT, or potentially allow select groups of patients to avoid these local treatments altogether. We were unable to find direct comparisons between SRS and TKIs, and indirect comparisons were not feasible. Assessing the efficacy of combinations of SRS and TKI as well as direct head-to-head comparisons of non-inferiority are important areas of future research.

The addition of WBRT to conventional chemotherapy did not improve overall PFS or OS in patients with EGFR mutated NSCLC with BMs. This reaffirms the notion that patients often succumb to their systemic disease and emphasizes the importance of cognitive preservation for as long as possible. Importantly, however, the lack of OS benefit with TKIs despite their intracranial efficacy may be partially explained by patient crossover to TKIs in individual trials after progression on ineffective chemotherapy, which may have confounded the results. This issue was observed in our analysis of overall PFS as well: gefitinib and chemotherapy led to an improvement of overall PFS compared to osimertinib, despite the latter having greater intracranial efficacy. This observation may be related to osimertinib being evaluated as a second-line agent whereas gefitinib and chemotherapy were studied as first-line therapy. Patients with BMs also represent those with more advanced disease, and may therefore be more likely to succumb to their disease independent of treatment. In addition, the combination of EGFR and ALK-positive patients in our analysis may have impacted OS results, since the prognosis of patients with these two activating mutations can differ significantly (23, 46–49).

**Limitations**

Using an NMA, we were able to compare the efficacy of different modalities of treatment, specifically, different generations of targeted therapies and conventional chemotherapy against each other in NSCLC with BMs. Conducting numerous RCTs to individually compare each of these treatment options is costly,
not feasible, and in some cases unethical. To lower the internal bias, we only included RCTs. As a result, we did not include some other targetable genetic alterations in NSCLC such as ROS1 translocations, MET exon-14-skipping mutations, or RET fusions. Further, we were unable to create a single network for each outcome due to several broken links between our included studies and limited outcome data. Therefore, our analysis was completed using several fragmented networks with a subset of studies in each network, limiting the power of each individual analysis. We also combined several treatment arms in order to obtain more robust comparisons; we grouped different generations of TKIs when possible and treated conventional chemotherapy as a single node wherever necessary. Any heterogeneity present within these individual classes may represent a source of confounding, as different chemotherapy regimens and TKIs may have varying efficacy. However, as shown in Table 1, the vast majority of the interventions classified as “traditional chemotherapy” used platinum-based doublet regimens or single-agent regimens with pemetrexed or docetaxel, which have been shown to have relatively comparable efficacy in the existing literature (15, 16, 50). In addition, the goal of our work was to perform a high-level class-based analysis of traditional chemotherapy approaches versus newer TKIs in BM patients with NSCLC. Combining classes of similar therapies is necessary to answer this specific question, despite differences in intra-class efficacy that may exist.

We also included several phase 2 trials, which might be at risk of small study bias (28, 31). Our analysis is also limited by the moderate or low certainty of evidence in some cases. Since many of our included studies excluded patients who had symptomatic or otherwise unstable BMs, the results of this work may also not be generalizable to patients suffering acute neurological decline from their BMs. Moreover, we included several studies that only enrolled patients who failed prior TKI or chemotherapy treatment; these patients may be distinct from chemotherapy-naïve patients and might have affected the result (20, 28, 29). Nonetheless, the inclusion of these patients reflects the real-world relevance of our results, as patients seen in everyday practice may often have had several rounds of therapy and stabilizing treatment prior to being considered for successive generations of targeted therapy.

Our study provides a comprehensive analysis of how the various interventions for NSCLC BMs with EGFR mutations/ALK rearrangements rank quantitatively in as close to a “real-world” setting as possible. Furthermore, although the cost-effectiveness of upfront next generation sequencing for known NSCLC mutations has been demonstrated, the cost-effectiveness of the respective generations of TKIs have been limited (51, 52). Our results provide valuable quantitative data on the comparative efficacy of TKIs in comparison to each other and chemotherapy, providing a basis for future work including cost-effectiveness analyses and RCTs focusing on BM patients in NSCLC.
CONCLUSIONS AND IMPLICATIONS FOR PRACTICE

In this work, we conducted a comprehensive systematic review and NMA on patients with either EGFR mutated or ALK rearranged NSCLC with BMs. TKIs showed improved intracranial and overall PFS compared to conventional modalities such as chemotherapy and WBRT, with greater benefit seen using newer generations of TKIs. The incidence of serious adverse events was also lower with most TKIs. Taken together, these results underscore the importance of genetic testing in defining targetable mutations in BMs from NSCLC, support the use of newer generations of TKIs, and point towards the need for the development of further precision therapies for the treatment of this set of tumours. We provide a quantitative basis for the design of future clinical trials evaluating the efficacy of these regimens on the specific cohort of BM patients with NSCLC. Further trials are necessary to establish the efficacy of these treatments in combination with other emerging agents and treatment approaches such as immunotherapy, surgery, and/or radiotherapy, thereby providing more definitive evidence for the management of BMs from NSCLC.

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DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

KB, ST, and AM developed the research question. JD, WH, YE, and KB completed data extraction and screening. KB, ST, and AM completed data analysis and wrote the manuscript. All authors contributed to the restructuring and editing of the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.739765/full#supplementary-material

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