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Review

A Comparison Between First-, Second- and Third-Generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients with Non-Small-Cell Lung Cancer and Brain Metastases

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Abstract: Patients with non-small-cell lung cancer (NSCLC), harboring Epidermal Growth Factor Receptor (EGFR) mutations, are more susceptible to brain metastases (BM). Comparisons of the efficacy of different-generation EGFR-tyrosine kinase inhibitors (TKI) on BMs from NSCLC are currently limited. We identified studies comparing different EGFR-TKIs for NSCLC through Pubmed literature search and selected those with neurological outcome data. By two retrospective analyses, Erlotinib showed longer neurological time-to-progression (30 months vs. 15.8 months, $P = 0.024$) and reduced the risk of central nervous system (CNS) progression (Hazard Ratio (HR) 0.25; 95% CI, 0.08–0.81; $P = 0.021$) compared to Gefitinib. In a phase 2b randomized trial, 16% of patients with BMs had a similar Progression Free Survival (PFS) (HR 0.76, 95% CI 0.41–1.44) or Overall Survival (OS) (HR 1.16, 95% CI 0.61–2.21) with Afatinib versus Gefitinib; a lower risk of developing subsequent BMs with Afatinib than Gefitinib (HR 0.49; 95% CI 0.34–0.71; $P < 0.001$) was reported by a retrospective study. A randomized phase 3 trial proved that patients with BMs treated with Osimertinib had longer PFS (HR 0.47, 95% CI 0.30–0.74) and OS (HR 0.79, 95% CI 0.61–1.01) than with Gefitinib, and lower incidence of CNS progression (6% vs. 15%, respectively). Although there is limited evidence, differences in CNS activity may exist between EGFR-TKIs.

Keywords: lung cancer; EGFR; brain metastases; tyrosine-kinase inhibitors; TKI; third generation

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1. Introduction

Lung cancer is one of the most lethal cancers worldwide. Around 80 to 90% are non-small-cell lung cancers (NSCLC). In 70% of patients, the disease is diagnosed at a late, metastatic stage (stage IV) [1,2]. Activating mutations in the Epidermal Growth Factor Receptor (EGFR) kinase domain occur in 10–15% of patients with lung adenocarcinoma in Western countries, and up to 50% in Asian patients [3,4]. Furthermore, EGFR mutations are more frequent in women and never- or light-smokers with adenocarcinoma histology. The EGFR receptor is involved in several intracellular pathways related to different processes, like DNA synthesis and proliferation. Its oncogenic alterations drive carcinogenesis. These

tumors present peculiar patterns of dissemination with a higher frequency of brain involvement. Up to 70% of NSCLC patients with EGFR-mutant tumors develop brain metastases (BMs) during their disease [5,6], and approximately 20% while on EGFR tyrosine kinase inhibitors (TKIs). BMs cause neurological symptoms and negatively impact patients' quality of life and survival, with median survival ranging between 1 and 6 months [7].

The available treatments for stage IV NSCLC patients with BMs harboring EGFR mutations are local therapies (surgical resection, stereotactic radiotherapy (SRT) with or without whole-brain radiotherapy (WBRT), and WBRT) and systemic treatments (chemotherapy and TKIs) [8]. TKIs are EGFR-targeted agents that interfere with EGFR signaling. To date, three different generations of EGFR-TKIs are available, though all remain subject to an unavoidable development of resistance mechanisms. The mechanism of action of first-generation TKIs (Erlotinib, Gefinitib, and Icotinib) causes a reversible ATP-binding sites blockade, stopping downstream signaling. With second-generation compounds (Afatinib and Dacominitib), irreversible and covalent bonds are formed with all homodimers and heterodimers of the ErbB family receptors. They block the transphosphorylation of ErbB3 to inhibit signaling, thus representing an alternative for patients with acquired resistance to first-generation TKIs. The third and latest generation (Osimertinib, Rociletinib, Olmutinib, Lazertinib) offers a new treatment for T790M EGFR-mutant tumors. The T790M mutation is the most common mechanism of resistance occurring in approximately 50% of patients receiving first and second-generation TKIs [9]. Unfortunately, even patients treated with third-generation agents develop acquired resistance; therefore, new targeted drugs are currently being investigated [9].

EGFR-TKIs are more effective than chemotherapy in the treatment of BMs [10]. In the LUX-Lung 3 and LUX-Lung 6 trials, both progression-free survival (PFS) and objective response rate (ORR) were higher in patients treated with TKIs rather than chemotherapy [11]. Yet, the efficacy of combining upfront cranial radiotherapy with TKIs is currently debated. Initially, a meta-analysis of low-quality evidence from 12 non-comparative observational studies on 363 patients suggested upfront cranial radiotherapy could improve survival outcomes but not intracranial disease response rates while being associated with a higher rate of neurological adverse events (AEs) than TKIs alone [12]. Thereafter, in a meta-analysis of 7 studies, including 1086 patients, up-front radiotherapy and TKIs showed a higher intracranial PFS and OS than TKIs alone, especially for patients with a limited number of BMs [13]. However, the latest meta-analysis including 30 studies on 2649 NSCLC patients with BMs harboring either EGFR or Anaplastic Lymphoma Kinase (ALK) mutations, reported no survival outcome difference between radiotherapy alone, TKIs alone and combined therapy, regardless of the type of radiotherapy used (whether SRT or WBRT) [14]. However, the efficacy of EGFR-TKIs on BMs seems to be lower than in other metastatic sites, likely due to their low permeability through the Blood–Brain Barrier (BBB) and different combined strategies of cranial radiotherapy and TKIs have been investigated. In a retrospective multi-institutional analysis on 351 EGFR-mutant NSCLC patients, Magnuson et al. [15] reported higher PFS and OS in patients treated with neoadjuvant or adjuvant TKIs, or before and after the radiotherapy, respectively. Patients achieved the longest OS with SRT followed by an EGFR-TKI; this also may spare patients the potential neurocognitive sequelae of WBRT. Based on the current uncertainty, the latest European Society for Medical Oncology (ESMO) guidelines on the treatment of stage IV NSCLC with BMs harboring an EGFR mutation, suggest the use of TKIs as upfront treatment followed by local treatment, such as surgery or radiotherapy, if needed [16]. This highlights the relevance of the question of possible differences between the different TKIs and TKI generations in terms of BM activity.

This narrative review aims to assess which of the current TKIs have the best evidence for the treatment of EGFR mutant NSCLC patients with BMs.

2. Methods and Materials

To select the relevant papers for the analysis, we performed a literature search on PubMed, updated until 31 October 2020, with the following keywords: "Brain Metastases", "Advanced NSCLC", "EGFR", "TKI", or "Targeted therapy".

Prospective or retrospective clinical studies and analyses comparing different EGFR-TKIs for the treatment of NSCLC were included. Trials with TKIs compared or combined with other therapies such as chemotherapy (i.e., Cisplatin and Pemetrexed), radiotherapy or other targeted therapy (i.e., Bevacizumab) were excluded. All the studies were analyzed by 2 independent readers (S.C., G.B.); discrepancies were resolved by discussion with a third reader (O.C.). The following information was collected: number of patients, study design, central nervous system (CNS) outcome data, PFS, and OS.

3. Results

Overall, 4 clinical trials [17,18] and 4 retrospective analyses [19–27] were reviewed (Table 1).

3.1. Comparison between First-Generation TKIs

As far as the comparison between the first-generation TKIs Erlotinib and Gefitinib is concerned, retrospective analyses suggest the superiority of Erlotinib over Gefitinib in patients with either asymptomatic or symptomatic BMs.

The first analysis [19] evaluated the BM rate after treatment with Erlotinib (n = 108 patients) or Gefitinib (n = 171), calculating the neurological time-to-progression (nTTP) and the progression-free survival (PFS). The nTTP in patients with pre-existing BMs before Erlotinib was significantly extended compared to those treated with Gefitinib (30 months vs 15.8 months, P = 0.024), but not in those without pre-existing BMs (18 months vs 16 months, P = 0.392), suggesting a relevant role of Erlotinib in keeping CNS progression of existing BMs under control. A total of 36% of patients (n = 8/22) treated with Gefitinib presented with oligo-BMs (i.e., 1 to 4 BMs) as compared to 25% (n = 6/24) treated with Erlotinib, while 86% (n = 19/22) vs. 83% (n = 20/24), respectively, received previous local therapies (including SRT +/− WBRT, surgery and WBRT).

Similarly, the second analysis [20] evaluating the risk of CNS progression and PFS in patients treated with either Erlotinib (n = 22) or Gefitinib (n = 55), confirmed a significantly reduced risk of CNS progression in those with pre-existing BMs treated with Erlotinib as compared to Gefitinib (HR 0.25; 95% CI, 0.08–0.81; P = 0.021), but not in those without BMs (HR 0.25; 95% CI, 0.08–0.81; P = 0.021). No data on oligo-BMs were reported, while 50% (n = 6/12) of patients with BMs treated with Erlotinib received previous local therapies as compared to 27% (n = 4/15) of those treated with Gefitinib. However, in both of these analyses [19,20] no significant difference in the PFS was observed, and the first analysis [19] also failed to show an OS difference, between patients treated with Erlotinib or Gefitinib (Table 1).

Furthermore, the CTONG0901 phase 3 randomized controlled trial [17], that did not explore specifically BM rate in patients with metastatic NSCLC treated with either Erlotinib (n = 128) or Gefitinib (n = 128), but included 18.4% of patients with BMs, reported no significant differences between these two treatments in terms of PFS (13.0 vs. 10.4 months, P = 0.108) or overall survival (OS) (22.9 vs. 20.1 months, P = 0.250), although the authors underlined that the short follow-up may be a possible study limitation. No data were reported about oligo-BMs and previous local therapies in patients with BMs.

Another first-generation TKI, Icotinib, approved and distributed exclusively in China, has been retrospectively compared to Gefitinib in a limited series of metastatic NSCLC patients [21]. The intracranial PFS (iPFS) was not statistically different between patients treated with either Icotinib (n = 21) or Gefitinib (n = 22) (8.4 vs. 10.6 months, P = 0.17), nor were ORR and AEs. Patients presenting with oligo-BMs were 10% (n = 2/21) and 23% (n = 5/22) in the Icotinib and Gefitinib cohort, respectively; a total of 24% (n = 5/21) and 14% (n = 3/22) of patients received previous local therapies for their BMs, respectively.

Table 1. Key studies comparing TKIs in EGFR-mutant NSCLC patients with a focus on brain metastases (BMs).

Reference	Study Design	No. 1-4 BMs Local Therapies [a]	CNS Outcome	mPFS (mo.) *P*-Value	mOS (mo.) *P*-Value
	Comparison between first-generation TKIs: Erlotinib vs. Gefitinib				
Li et al. (2017), BMC Cancer, doi:10.1186/s12885-017-3165-0	Comparative retrospective analysis	108 vs. 171 [b] 6/24 vs. 8/22 20/24 vs. 19/22	**Cumulative CNS progression incidence [a]:** at 6-, 12-, and 18- mo.: 0.9, 3.7 and 12.0% vs. 5.8, 9.4 and 17.0% (P = 0.181) **Overall median nTTP [a]:** 24 mo. vs. 16 mo. (P = 0.014) **No pre-existing BMs median nTTP [a]:** 18 mo. vs. 16 mo. (P = 0.392) **Pre-existing BMs median nTTP [a]:** 30 mo. vs 15.8 mo. (P = 0.024)	23 vs. 18.4 P = 0.152 [a]	41 vs. 37 P = 0.112 [a]
Aiko et al. (2018), BMC Cancer, doi:10.1186/s12885-018-4911-7	Comparative retrospective analysis	22 vs. 55 [b] NR/12 vs. NR/15 6/12 vs. 4/15	**Cumulative CNS progression incidence [a]:** at 20- and 40- mo.: 12, 23% vs. 18, 34% (P = 0.124) **No pre-existing BMs HR [a]:** 0.57; 95% CI, 0.13–3.01; P = 0.637 **Pre-existing BMs HR [a]:** 0.25; 95% CI, 0.08–0.81; P = 0.021	11.1 vs. 9.6 P = 0.0860 [a]	-
Yang et al. (2017), British Journal of Cancer, doi:10.1038/bjc.2016.456	Phase III randomized controlled trial (CTONG0901)	128 vs. 128 [b] NR/25 vs. NR/22 NR	**Patients with BMs 18.4%:** 19.5% vs. 17.2% [a]	13.0 vs. 10.4 P = 0.108 [a]	22.9 vs. 20.1 P = 0.250 [a]
	Comparison between first-generation: Icotinib vs. Gefitinib				
Liu et al. (2020), BMC Cancer, doi:10.1186/s12885-020-6543-y	Comparative retrospective analysis	21 vs. 22 [b] 2/21 vs. 5/22 5/21 vs. 3/22	**Median iPFS [a]:** 8.4 vs. 10.6 mo., P = 0.17	6.5 vs. 7.3 P = 0.17 [a]	-
	Comparison between second- and first-generation TKIs: Afatinib vs. Gefitinib				
Park et. al. (2016), Lancet Oncology, doi: 10.1016/ S1470-2045(16)30033-X Paz-Ares et al. (2017), Ann Oncol, doi:10.1093/annonc/mdw611.	Phase IIB randomized controlled trial (LUX-Lung 7)	160 vs. 159 [b] NR/26 vs. NR/24 NR	**Not different PFS and OS with Afatinib vs. Gefitinib in patients with CNS metastases (=51):** HR for PFS 0.76, 95% CI 0.41–1.44 OS HR for OS 1.16, 95% CI 0.61–2.21	11.0 vs. 10.9 P = 0.017 [a] (TTF 13.7 vs. 11.5) P = 0.0073 [a])	27.9 vs. 24.5 P = 0.2580 [a]

Table 1. *Cont.*

Reference	Study Design	No. 1-4 BMs Local Therapies [a]	CNS Outcome	mPFS (mo.) *P*-Value	mOS (mo.) *P*-Value
	Comparison between second- and first-generation TKIs: Gefitinib vs. Erlotinib vs. Afatinib				
Su et al. (2018), Therapeutic Advances in Medical Oncology, doi:10.1177/1758835918797589	Comparative retrospective analysis	116 vs. 75 vs. 115 [b] NR/23 vs. NR/34 vs. NR/30 NR	**Cumulative incidences of subsequent BMs at 6, 12, 24 and 35 mo.:** 3.8%, 13.9%, 34.6%, and 53.6%, respectively for gefitinib; 5.6%, 9.3%, 9.3%, and 60.3%, respectively for erlotinib; and 0%, 2.8%, 28.3%, and 41.5%, respectively, for afatinib, $P = 0.80$ **HR of subsequent BM after afatinib vs. gefitinib:** 0.49; 95% CI 0.34–0.71; $P < 0.001$	9.8 vs. 11.2 vs. 12.7 $P = 0.007$ [a] Afatinib vs. Gefitinib $P = 0.001$	22.0 vs. 26.6 vs. 39.1 $P = 0.053$ [a] Afatinib vs. Gefitinib $P = 0.035$
	Comparison between second- and first-generation TKIs: Dacomitinib vs. Gefitinib				
Wu et al. (2017), Lancet Oncology; 10.1016/S1470-2045(17)30608-3 Mok et al. (2019), J Clin Oncol, doi:10.1200/JCO.2018.78.7994	Phase 3 randomized open-label trial (ARCHER 1050)	227 vs. 225 [b] NA	**Not available:** patients with brain or leptomeningeal metastases were excluded	14.7 vs. 9.2 $P < 0.0001$	34.1 vs. 26.8 $P = 0.044$
	Comparison between third- and first-generation TKIs: Osimertinib vs. Gefitinib				
Soria et al. (2018), New Engl J Med, doi: 10.1056/NEJMoa1713137 Ramalingam et al. (2020), New Engl J Med, doi:10.1056/NEJMoa1913662	Phase 3 randomized open-label trial (FLAURA)	279 vs. 277 [b] NR/53 vs. NR/63 NR	**Longer PFS and OS with osimertinib vs. first-generation TKIs in patients with CNS metastases (=116):** HR for PFS 0.47, 95% CI 0.30–0.74 OS HR for OS 0.79, 95% CI 0.61–1.01 **Lower incidence of CNS progression with Osimertinib vs. first-generation TKIs:** 6% vs. 15%, respectively	18.9 vs. 10.2 $P < 0.001$	38.6 vs. 31.8 $P = 0.046$

Abbreviations: BMs: Brain Metastases; CNS: Central Nervous System; iPFS: intracranial Progression-Free Survival; mOS: median Overall Survival; Mo.: Months; NA, not available; No.: Number of patients; NR, not reported; NSCLC: Non-Small Cell Lung Cancer; mPFS: median Progression-Free Survival; nTTP: neurological Time-To-Progression; TKI: Tyrosine Kinase Inhibitor; TTF: Time-To-Treatment Failure; [a] Previous treatments including: stereotactic radiotherapy (SRT) +/− whole brain radiotherapy (WBRT), surgery and WBRT. [b] Results contrasted are respective of the order followed by the agents in the entitlement above.

3.2. Comparison between Second- and First-Generation TKIs

To date, no direct comparison has been conducted between the second- (Afatinib and Dacotinib) and the first-generation (Gefitinib, Erlotinib and Icotinib) TKIs for their effectiveness in preventing and controlling BMs in NSCLC patients.

The Lux-Lung 7 phase 2B randomized controlled trial [18,23] evaluated the different efficacy and safety of Afatinib (n = 160 patients) and Gefitinib (n = 159). The co-primary study endpoints for efficacy were PFS, time-to-treatment failure (TTF), defined as the time from randomization to treatment discontinuation (due to progression, AEs, or death), and OS. The median PFS (11.0 vs. 10.9 months, P = 0.017) and TTF (13.7 vs. 11.5 months, P = 0.0073) were statistically longer for patients treated with Afatinib than with Gefitinib, including those with BMs. The median OS (27.9 vs. 24.5 months, P = 0.2580) was not statistically different, although the study was not powered enough to assess the three co-primary endpoints, particularly OS. The efficacy of the two drugs was not affected by the EGFR mutation type, and AEs were comparable. It is noteworthy that the study included approximately 16% of patients with BMs, and these patients did not have a different PFS (HR 0.76, 95% CI 0.41–1.44) [16] or OS (HR 1.16, 95% CI 0.61–2.21) [23] with Afatinib, as compared to Gefitinib. No data were reported about oligo-BMs and previous local therapies in patients with BMs.

A retrospective analysis evaluated PFS, OS, and BM rate of NSCLC patients with or without initial BMs treated with Gefitinib (n = 116), Erlotinib (n = 75) and Afatinib (n = 115) [22]. A better PFS (12.7 vs. 9.8 months; HR 0.59, P = 0.001) and OS (39.1 vs. 22.0 months; HR 0.64, P = 0.035) was observed in the Afatinib than Gefitinib group; however, OS was not significantly better with Afatinib as compared to Gefitinib or Erlotinib (P = 0.053). According to the authors, none of the three agents had a significant impact on median PFS and OS (P = 0.34 and P = 0.46, respectively) in the BM-group, while those treated with Afatinib in the non-BM group had a lower risk of developing subsequent BMs than those with Gefitinib (hazard ratio [HR] 0.49; 95% CI 0.34–0.71; P < 0.001) (Table 1). Although this could suggest a stronger preventive effect against BMs of Afatinib, current data are still too limited to draw any conclusions in this regard. No data were reported about oligo-BMs and previous local therapies in patients with BMs.

Unfortunately, there are no comparisons between Dacomitinib and first-generation TKIs in preventing or controlling BMs from NSCLC. The ARCHER 1050 phase 3 randomized trial [24,25], showed a better PFS with Dacomitinib (n = 227 patients) than Gefitinib (n = 225) but neither included patients with BMs nor analyzed BM rates in the study population.

3.3. Comparison between Third- and First-Generation TKIs

In a preclinical study [28], Osimertinib achieved a higher brain exposure at lower doses than Gefitinib and sustained tumor regression in a mouse BMs model. In the same preclinical study [28], Rociletinib, another third-generation TKI, showed a substantially lower penetration across the BBB than Osimertinib and did not achieve tumor regression. In the same year, its trading authorization was suspended [29]. Therefore, based on the greatest BBB penetration, Osimertinib is expected to be more effective in reducing CNS progression compared to other TKIs.

In the AURA randomized phase 3 trial [30], Osimertinib versus platinum-based chemotherapy showed a significant improvement in the PFS and the OS in T790M-positive advanced NSCLC patients pre-treated with first-generation TKIs. This led to its approval as a second-line treatment for these patients. The efficacy of Osimertinib to treat CNS metastases, specifically leptomeningeal disease, in patients pre-treated with first-generation TKIs was confirmed by the BLOOM phase 1 trial [31], with leptomeningeal ORR and duration of response (DoR) by a blinded central independent review of 62% (95% CI, 45 to 78%) and 15.2 months (95% CI, 7.5 to 17.5 months), respectively, alongside with a manageable safety profile at a dose of 160 mg once daily (which is the double of the currently used). A recent retrospective analysis of 351 patients with leptomeningeal disease

further supports the efficacy of Osimertinib in the context, at 80 or 160 mg daily, both with or without T790M mutations [32].

The FLAURA randomized phase 3 trial [26,27] is the first and, so far, only study that compared the efficacy of Osimertinib with first-generation TKIs Gefitinib or Erlotinib for patients with untreated EGFR-mutated advanced NSCLC. Overall, Osimertinib resulted into longer median PFS (18.9 vs. 10.2 months; $P < 0.001$), DoR (17.2 vs. 8.5 months) and OS (38.6 vs. 31.8 months; $P = 0.046$) than first-generation TKIs. According to the predefined subgroups analysis, the HRs were in favour of Osimertinib in patients with CNS metastases ($n = 116$) both for PFS (HR 0.47, 95% CI 0.30–0.74) [24] and OS (HR 0.79, 95% CI 0.61–1.01) [27]. A lower incidence of CNS progression was also observed with Osimertinib than first-generation TKIs (6 vs. 15%, respectively) [26]. No data were reported about oligo-BMs and previous local therapies in patients with BMs. Furthermore, adverse events of $\geq$3 grade were less frequent with Osimertinib than with first-generation TKIs (34 vs. 45%) [26].

4. Discussion

CNS metastases, in particular BMs, are one of the most frequent sites of NSCLC metastases [33,34]. The development of BMs is higher in patients with EGFR-mutant than with wild type NSCLC [5]. Several analyses compared the efficacy of TKIs to chemotherapy or radiotherapy in EGFR-mutant NSCLC, but the literature addressing which TKI is the most effective against BMs is currently limited. New-generation EGFR-TKIs are continuously being investigated to counteract the acquired resistance developed by tumors exposed to previous-generation agents. To date, there are three different generations of EGFR-TKIs. Erlotinib, Gefitinib and Icotinib belong to the first-generation class, while Afatinib and Dacominitib to the second-generation, and Osimertinib, Rociletinib, Olmutinib, and Lazertinib to the third-generation. Therefore, it is important to explore whether different generation EGFR-TKIs have different efficacy on BMs in terms of PFS, ORR, OS, or CNS progression. Few studies focused on this aspect or have data available and new trials addressing this issue have only recently been started. Furthermore, some of these trials excluded patients with BMs.

Through a review of currently available evidence comparing TKIs for the treatment of EGFR mutant NSCLC patients with BMs, although no firm conclusions can be drawn due to the limited data, some useful tips may be suggested. First, differences may exist in CNS activity between TKIs belonging to the same generation, as mentioned above, with the first-generation Erlotinib appearing to be more effective than Gefitinib [19,20]. Similarly, the third generation Osimertinib appears to be more effective in BMs than Rociletinib [28]. Second, a TKI generation-effect may exist with the second-generation Afatinib possibly more effective than the first-generation TKIs [22] and the third-generation Osimertinib than the first-generation Gefitinib [26,27]. Unfortunately, no data are available on the comparison between the third- and second-generation TKIs. Third, even if a difference in CNS activity exists, this could not necessarily translate into a benefit in PFS or OS, as seen with the first-generation Erlotinib and Gefitinib [17,19,20] and by the comparison of the second-generation Afatinib with Gefitinib [18,23]. In this regard, the TKI-related CNS effect of inducing regressions or controlling existing BMs could be distinct from that involving their prevention in patients without BMs. For instance, the first-generation Erlotinib seemed more active than Gefitinib in reducing the risk of CNS progression in patients with pre-existing BMs but not in those without BMs [19,20]; or, conversely, the second-generation Afatinib could lower the risk of developing BMs in patients without pre-existing BMs but not of a CNS progression in those with BMs as compared to Gefitinib [22]. Finally, only the third generation Osimertinib has demonstrated an increased PFS and OS in the overall population and specifically in patients with BMs [27] as compared to the first-generation Gefitinib, simultaneously lowering the incidence of CNS progression [26]. This could be related to its higher permeability through the BBB [26] confirmed by its activity in leptomeningeal disease [31]. Unfortunately, limited information is available from the

comparison studies reviewed regarding the prevalence of oligo-BMs and previous local therapies for BMs to explore a differential effect from the different EGFR-TKI-generation drugs according to these two variables. Current evidence supports that the number of BMs is an important factor to decide on local therapies [15,35–37] and patients with EGFR mutant NSCLC and with 1 to 4 BMs (i.e., with oligo-BMs) should be considered for upfront local therapy followed by the EGFR-TKI regardless of their generation [37].

The permeability of the BBB is different for each TKI, so their activity on BMs may be variable. This feature is related to TKI affinity for its receptor, but also to the presence of permeability glycoprotein and breast-cancer-resistance protein, two molecules that control the removal of toxins, drugs, and chemotherapies from the CNS. The permeability across the BBB is also controlled by each drug's molecular weight. TKIs, especially first-generation ones, seem to have poor biopharmaceutical properties to cross the BBB, although penetration might increase in patients with BMs whose BBB may be disrupted around the lesions. However, no formal head-to-head comparison of EGFR-TKIs in NSCLC with BMs has yet to be conducted. The current unplanned and underpowered subgroup or retrospective analyses should be considered as hypothesis-generating. Ongoing and new clinical trials could therefore explore possible differences in CNS and survival outcomes of patients with EGFR-mutant NSCLC. The following three related questions should be addressed. The first regards the impact of sequencing different-generation EGFR-TKIs on BMs, rather than simply using the latest-generation, namely Osimertinib. The second question is whether a combination of TKIs with chemotherapy could be a better option than TKI alone. In vitro and clinical data [38–40] suggest a synergism between EGFR-TKIs and chemotherapy by limiting acquired resistance and the FLAURA-2 randomized phase 3 trial (NCT04035486) is currently investigating the combination of Osimertinib with chemotherapy as first-line treatment for metastatic EGFR mutation-positive NSCLC. Third, the different TKI activity on BMs from NSCLCs harboring uncommon EGFR mutations should be explored.

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