Epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of central nervous system metastases from non-small cell lung cancer: the present and the future

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Abstract: Lung cancer is one of the major causes of cancer related mortality worldwide. Brain metastases (BM) complicate clinical evolution of non-small cell lung cancer (NSCLC) in approximately 25–40% of cases, adversely influencing quality of life (QoL) and overall survival (OS). Systemic therapy remains the standard strategy for metastatic disease. Nevertheless, the blood-brain barrier (BBB) makes central nervous system (CNS) a sanctuary site. To date, the combination of chemotherapy with whole brain radiation therapy (WBRT), surgery and/or stereotactic radiosurgery (SRS) represents the most used treatment for patients (pts) with intracranial involvement. However, due to their clinical conditions, many pts are not able to undergo local treatments. Targeted therapies directed against epidermal growth factor receptor (EGFR), such as gefitinib, erlotinib and afatinib, achieved important improvements in EGFR mutated NSCLC with favorable toxicity profile. Although their role is not well defined, the reported objective response rate (ORR) and the good tolerance make EGFR-tyrosine kinase inhibitors (TKIs) an interesting valid alternative for NSCLC pts with BM, especially for those harboring EGFR mutations. Furthermore, new-generation TKIs, such as osimertinib and rociletinib, have already shown important activity on intracranial disease and several trials are still ongoing to evaluate their efficacy. In this review we want to highlight literature data about the use and the effectiveness of EGFR-TKIs in pts with BM from NSCLC.

Keywords: Brain metastases (BM); epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs); non-small cell lung cancer (NSCLC); whole brain radiation therapy (WBRT)

Introduction

Lung cancer is one of the major causes of cancer related mortality worldwide accounting for approximately 1.4 million deaths per year (1). In approximately 25–40% of non-small cell lung cancer (NSCLC), brain metastases (BM) complicate clinical evolution of disease causing the onset of neurological symptoms, the deterioration in quality of life (QoL) and reducing overall survival (OS) (2,3). About 10–20% of patients (pts) show BM at diagnosis whilst another 20% experience brain progression during the course of disease, often within the first 2 years from diagnosis (2-6). Central nervous system (CNS) represents the first site of

relapse after radical treatments for loco-regional disease (7). Furthermore, the prolongation of survival of NSCLC pts, due to the therapeutic advances of the last decades, is likely to explain the increased incidence of BM over time. Unfortunately, for pts with BM the prognosis remains poor with a median OS equal or less than 3 months without any treatment (8). To date, systemic therapy is the standard strategy for metastatic disease. Nevertheless, the blood-brain barrier (BBB) presence with its continuous endothelium, tight junctions, basal membrane, efflux membrane transporters and absence of fenestrations, makes CNS a sanctuary site. Most chemotherapeutic agents do not cross BBB and only the crossing of small lipid-soluble molecules is allowed (9-12). For this reason the role of systemic chemotherapy in the treatment of CNS secondary lesions is controversial (13,14). In the case of macroscopically evident BM, both tumor neoangiogenesis and BBB destruction due to tumor growth, seem to favor intracranial penetration of chemotherapeutic drugs (15,16). This phenomenon could support the use of upfront chemotherapy for BM that damage the integrity of the barrier (15,16). First line upfront platinum based chemotherapy has been evaluated in different prospective trials and an objective response rate (ORR) of 23–50% was reported (5,17-24). Pemetrexed and temozolomide showed some activity (25-29) while 5-FU, topotecan and vinorelbine, did not show any improvement in ORR and OS (23,30,31).

To date local treatments, including whole brain radiation therapy (WBRT), surgery and/or stereotactic radiosurgery (SRS) represent the most used approaches in pts with BM (32). WBRT, in association with corticosteroids, showed a median OS that ranges from 2.4 to 4.8 months (33-35). In some cases, considering the site and the number of lesions, surgery or SRS can be used (32,36-38). Usually SRS is applied when few or small volume isolated lesions (maximum diameter 4 cm) are present (32). WBRT significantly improves brain tumor control after SRS but the role of adjuvant WBRT remains undefined because of the increased risk of neurocognitive toxicity (36). If surgery does not seem useful for multiple BM, prospective trials documented an advantage in terms of survival and local control with surgery and WBRT compared with WBRT alone in oligometastatic brain disease (37,38). Moreover the combination of the three options can be evaluated in selected cases as well as their association with chemotherapy and targeted therapy (32,36-38).

In particular targeted treatments directed against epidermal growth factor receptor (EGFR), such as gefitinib, erlotinib and afatinib, achieved important results in NSCLC, in particular in pts harboring activating EGFR mutations.

Considering their favorable safety profile, tyrosine kinase inhibitors (TKIs) may represent a valid alternative in pts with BM but to date the role of TKIs, and their correct place within the therapeutic strategy in this setting, are still debated. Furthermore other new-generation TKIs, such as osimertinib and rociletinib, have already shown important activity on intracranial disease and several trials are still ongoing to evaluate their activity and efficacy.

Here, we review literature data about EGFR-TKIs use in pts with BM from NSCLC, analyzing the most relevant aspects concerning their role and effectiveness compared to current standard treatments.

EGFR mutated NSCLC metastatic to the brain

Approximately 10–15% of NSCLC Caucasian pts show *EGFR* gene somatic activating mutations (39). Exon 19 in-frame deletion and exon 21 point mutation L858R are the most frequent aberrations, representing about 90% of cases (39). Mutations in *EGFR* gene cause the expression of a structurally altered receptor that, through the activation of different signaling pathways, promotes cell proliferation and survival (40). In recent years EGFR-TKIs (erlotinib, gefitinib and afatinib) specifically directed against EGFR, and in particular against its mutated form, changed the paradigm of care for a subgroup of NSCLC. Their superiority in terms of efficacy and toxicity in comparison to standard chemotherapy has led to EGFR-TKIs approval for first line treatment of EGFR mutated NSCLC (41-44). Several studies suggested a significant association between EGFR mutation and risk of developing BM, with a reported higher incidence of BM, both at the time of diagnosis and during the course of disease, in EGFR mutated compared with EGFR wild-type (WT) pts (45-48). Generally pts with EGFR mutations had longer OS after BM diagnosis than EGFR WT pts (47,48). However, these data were not confirmed by all studies (49-52).

For this reason more effective agents are needed in order to prolong survival, maintain neurocognitive functions and prevent neurologic deterioration. The high rates of durable response and the good safety profile make EGFR-TKIs an attractive therapeutic option also in these pts, especially considering that standard local approaches in pts metastatic to the brain are associated with a high rate of adverse events (36).

First generation EGFR-TKIs

Erlotinib and gefitinib are reversible TKIs targeting

EGFR, the first to enter into clinical practice. Initially, they reported an improvement in progression-free survival (PFS) and OS compared to placebo when used as second line therapy in unselected NSCLC pts, especially never-smokers, females or Asian pts (53,54). Later EGFR mutational status became the most accurate predictor of response to EGFR-TKIs in NSCLC (39,55). Today erlotinib and gefitinib, together with the second generation TKI afatinib, are recognized as the standard first line therapy in NSCLC pts with activating EGFR mutations, instead of conventional cytotoxic chemotherapy. Randomized studies showed that in this setting they were able to obtain an ORR of 60–80%, a PFS ranging from 10 to 13 months and an OS of 13–20 months (41-43,56-65).

CNS penetration

Evidences suggest that EGFR-TKIs can cross the BBB (66,67). Nevertheless, despite their small molecular weight, both erlotinib and gefitinib, seem to reach limited concentrations into cerebrospinal fluid (CSF). In fact, at standard dose CSF levels are lower than plasma levels (68-72). Available data do not favor one EGFR-TKI over another but the concentration and the penetration in CSF are significantly higher with erlotinib than gefitinib (73-75). Moreover, P-glycoprotein (P-gp) efflux pump, that is associated with multiple drug resistance in brain tumor, has gefitinib as one of its substrates (76).

The limited CNS exposure to TKIs can explain the high incidence of BM in EGFR mutated NSCLC despite the good control of extracranial disease during EGFR-TKIs therapy. However, BM occurrence can damage the integrity of BBB and favor TKIs penetration (77). So, while erlotinib and gefitinib at the standard dose do not sufficiently penetrate BBB in absence of CNS involvement, when BM are evident, they probably improve their CNS concentration with a consequent improvement in central activity (67). Furthermore the inadequate TKIs penetration across the intact BBB, could explain the frequent absence of secondary resistance mutations in BM also when they are present in extra-cranial disease sites (70,77,78).

Alternative schedules

Literature data report that dose escalation, pulsate dose or switching TKIs, seem to improve TKIs concentration in CNS and to relieve resistance to standard TKIs treatment in

pts with BM from EGFR mutated NSCLC (70-73,76,78-83) (*Table 1*).

Progressively increasing doses of erlotinib or gefitinib are able to control BM progression or relapse in NSCLC pts (70-73,79,80). The greater penetration through the BBB when plasma concentrations are higher, also thanks to P-gp saturation, allows EGFR-TKIs to exert greater activity in CNS (76). However, dose escalation is inevitably related to more frequent and significant side effects including high grade fatigue, nausea and liver damage (70-73,79,80).

Pulsate high dose erlotinib, with a median dose of 1,500 mg weekly, appears to provide a significant advantage with reduced toxicity (81). In a small retrospective analysis of nine NSCLC pts, higher pulsate erlotinib dosage (1,500 mg once a week) achieved 67% partial response (PR) after progression to conventional dose (78). In contrast, another retrospective evaluation of ten NSCLC pts who received pulsate dose erlotinib for CNS progression, reported an ORR of 10% with a very limited median OS (1.7 months) (82). To date, there is no prospective trial comparing pulsate high dose *vs.* standard dose TKIs, but pulsed high doses of EGFR-TKIs could be considered in NSCLC pts with brain progression after standard EGFR-TKI therapy.

Switching to different EGFR-TKIs may represent another valid therapeutic alternative. In a small trial (83), seven lung cancer pts with good response to gefitinib, showed interesting results receiving erlotinib at the time of brain progression: three PR, three stable disease (SD) and one progressive disease (PD) with improvement in PS and neurological symptoms control.

All these results are very preliminary. Further larger prospective studies are needed to validate these approaches in clinical practice.

Standard schedules

Today although their emerging role, the specific indication of EGFR-TKIs in the management of BM from NSCLC, with or without radiotherapy, remains not well defined. Literature data suggest that TKIs alone are able to obtain a high intracranial ORR (99-101) (*Table 1*). In preclinical mouse model of EGFR mutated NSCLC with BM, gefitinib has proven effective (102). Complete and sustained responses following BM treatment with erlotinib and gefitinib have been reported in several case reports (103-106). Several small phase II trials, have shown that TKIs alone can obtain 75–88% of intracranial ORR in pts with EGFR mutated NSCLC who have not received any prior local therapy

Table 1 First and second generation EGFR-TKIs use in NSCLC pts with BM (selection of studies)

Authors	Years	Study	Patients	Treatment	Results
Grommes et al. (78)	2011	Retrospective study	9 EGFRm NSCLC with BM progressed after standard treatment with TKIs	Pulsatile erlotinib 1,500 mg once weekly	CNS response: PR 67% (6/9 pts), SD 11% (1/9 pts), PD 22% (2/9 pts); median CNS TTP: 2.7 months (0.8–14.5 months); median OS: 12 months (2.5 months–not reached)
Jackman et al. (82)	2013	Retrospective study	10 EGFRm NSCLC with BM progressed after treatment with TKIs	Pulsatile erlotinib 1,000–1,500 mg once weekly	CNS response: PR 10% (1/10 pts); SD 20% (2/10 pts), PD 70% (7/10 pts); median OS: 1.7 months (0.6–7.0 months)
Katayama et al. (83)	2009	Retrospective study	7 NSCLC with BM developed after an initial response to gefitinib (6 EGFRm pts)	High dose erlotinib	CNS response: PR 42.5% (3/7 pts), SD 42.5% (3/7 pts), PD 15% (1/7 pts)
Park et al. (84)	2012	Prospective open-label, single-institution, phase II study	28 naive EGFRm NSCLC with BM	Erlotinib 150 mg or gefitinib 250 mg once a day	CNS response: PR 83% (23/28 pts); SD 11% (3/28 pts), PD 7% (2/28 pts); median PFS: 6.6 months (3.8–9.3 months); median OS: 15.9 months (7.2–24.6 months); no difference in PFS and OS according to erlotinib or gefitinib use
Wu et al. (85)	2013	Prospective open-label, phase II study	48 NSCLC pts (8 EGFRm) after first-line platinum-doublet CHT, with asymptomatic BM without extracranial progression	Erlotinib 150 mg once a day	Median CNS PFS: 10.1 months (7.1–12.3 months); median CNS and systemic PFS: 9.7 months (2.5–17.8 months); EGFRm pts had significantly longer median PFS vs. EGFR WT pts 15.2 months (8.3–22.2 months) vs. 4.4 months (0.0–11.6 months)
					Median OS: 18.9 months (14.4–23.4 months); overall ORR: 58.3%
Iuchi et al. (86)	2013	Prospective open-label, phase II study	41 naive EGFRm NSCLC with BM	Gefitinib 250 mg once a day	CNS response: CR 31.7% (13/41 pts), PR 56.1% (23/41 pts), SD 9.8% (4/41 pts), PD 2.4% (1/41 pts), ORR: 87.8%; median PFS: 14.5 months (10.2–18.3 months); median OS: 21.9 months (18.5–30.3 months)
Hotta et al. (87)	2004	Monocentric retrospective study	14 pretreated NSCLC with BM unselected for EGFR mutational status	Gefitinib 250 mg once a day	CNS response: CR 7% (1/14), PR 42.5% (5/14), SD 42.5% (8/14)
Porta et al. (88)	2011	Retrospective study	69 NSCLC pts with BM, (17 EGFRm, 26 naive for CHT and TKIs, 55 treated previously with WBRT)	Erlotinib 150 mg once a day	CNS response: CR 15.1% (8/53 pts all EGFRm), PR 11.3% (6/53 pts all EGFRm), SD 58.5% (31/53 pts), PD 15.1% (8/53 pts); median CNS TTP: 11.7 months (7.9–15.5 months) in EGFRm pts vs. 5.8 months (5.2–6.4 months) in WT or unknown EGFR pts (P<0.05); ORR: 82.4% in EGFRm pts vs. 0% in unselected pts; median OS: 12.9 months (6.2–19.7 months) in EGFRm pts vs. 3.1 months (2.5–3.9 months) in WT or unknown EGFR pts (P<0.001)
Kim et al. (89)	2009	Retrospective study	23 naive Asian never-smoking NSCLC pts with synchronous asymptomatic BM	Erlotinib 150 mg or gefitinib 250 mg once a day	CNS response: 73.9%; ORR: 69.6% (16 PR, 3 SD, 4 PD); DCR: 82.6%; median PFS: 7.1 months (1.08–12.87 months); median OS: 18.8 months (0.64–27.0 months)
Ceresoli et al. (90)	2004	Prospective phase II study	41 NSCLC pts with BM, 37/41 pts already treated with CHT, 18/41 pts previously treated with WBRT, 23/41 radio naive pts	Gefitinib 250 mg once a day	CNS response: PR 10% (4/41 pts); SD 17% (7/41 pts), DCR 30%; DCR WBRT + gefitinib sequential: 56% (10/18), DCR gefitinib alone: 9% (2/23 pts); median PFS whole population: 3 months (0.0–14 months)

Table 1 (continued)

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Table 1 (*continued*)

Authors	Years	Study	Patients	Treatment	Results
Wu et al. (91)	2007	Prospective phase II study	40 lung ADK pts with BM, 40/40 pts already treated with CHT, 23/40 pts previously treated with WBRT, 9/40 previously treated with SRS	Gefitinib 250 mg once a day	CNS response: CR 2.5% (1/40 pts), PR 35% (14/40 pts), SD 45% (18/40 pts), PD 17.5% (7/40 pts), ORR 38%, DCR 83%; overall ORR: 32%; overall DCR: 77%; median PFS: 9.0 months (4.5–13.5 months); median OS: 15.0 months (11.1–18.8 months)
Zhuang et al. (92)	2013	Prospective phase II study	WBRT group: 31 lung ADK pts; concurrent WBRT + erlotinib group: lung 23 ADK pts	WBRT group: 30 Gy/10 f; concurrent WBRT + erlotinib group: 30 Gy/10 f + 150 mg once a day	In the WBRT arm vs. WBRT + erlotinib respectively: median CNS PFS: 6.8 vs. 10.6 months (P=0.003); ORR: 54.84% vs. 95.65% (P=0.001); median general PFS: 5.2 vs. 6.8 months (P=0.009); median OS of 8.9 vs. 10.7 months (P=0.020)
Welsh et al. (93)	2013	Prospective phase II study	40 NSCLC with BM (9 EGFRm, 8 EGFR WT, 23 unknown)	Concurrent WBRT (2.5 Gy per day 5 days per week, to 35 Gy) + erlotinib 150 mg once a day	CNS response: CR 31% (11 pts), PR 56% (20 pts), MR 6% (2 pts), SD 3% (1 pts), PD 6% (2 pts), ORR 86%, PFS 8.2 months; median OS: 11.8 months (7.4–19.1 months); 9.3 vs. 19.1 months in EGFR WT vs. EGFRm pts respectively
Hoffknecht et al. (94)	2015	Report of compassionate use	100 NSCLC with BM (74% EGFRm pts) progressing after at least one line of CHT and one line of EGFR-TKIs treatment	Afatinib 50 mg once a day	CNS response: median TTP 3.6 months, ORR 35% (11/31 pts), DCR 66% (21/32 pts)
Lind et al. (95)	2009	Prospective phase I study	11 NSCLC with BM	Concurrent WBRT (30 Gy/10 f) + erlotinib 150 mg once a day	CNS response: PR 5 pts, SD 2 pts, PD 1 pt
Ma et al. (96)	2009	Prospective phase II study	21 NSCLC with BM	Concurrent WBRT (40 Gy/20 f) + gefitinib 250 mg once a day	CNS response: CR 19% (4/21 pts), PR 62% (13/21 pts), SD 14.3% (3/21 pts), PD 4.7% (1/21 pts), ORR 81%, DCR 95.2%; median PFS: 10.0 months (7.5–12.5 months); median OS: 13.0 months (8.2–17.8 months)
Zeng et al. (97)	2012	Retrospective study	90 NSCLC with BM gefitinib alone group: 45 pts; concurrent WBRT + gefitinib group: 45 pts	Gefitinib alone group: 250 mg once a day; concurrent WBRT + gefitinib group: 40 Gy/20 f + 250 mg once a day	In the WBRT + gefitinib arm vs. gefitinib alone arm respectively: CNS ORR: 64.4% vs. 26.7% (P<0.001); CNS DCR: 71.1% vs. 42.2% (P=0.006); median CNS TTP: 10.6 vs. 6.57 months (P<0.001); median OS: 23.40 vs. 14.83 months (P=0.002)
Lee et al. (98)	2014	Prospective randomized phase II study	80 NSCLC with BM (1/35 evaluable pts EGFRm); concurrent WBRT + placebo group: 40 pts; concurrent WBRT + erlotinib group: 40 pts	Concurrent WBRT + placebo group: 20 Gy/5 f; concurrent WBRT + erlotinib group: 20 Gy/5 f + 100 mg once a day	Median CNS PFS: 1.6 months in both arms (P=0.84); median CNS OS: 2.9 vs. 3.4 months in the placebo vs. erlotinib arm (P=0.83)

EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer; pts, patients; BM, brain metastases; EGFRm, epidermal growth factor receptor mutated; CNS, central nervous system; PR, partial response; SD, stable disease; PD, progressive disease; TTP, time to treatment progression; OS, overall survival; PFS, progression-free survival; WT, wild-type; ORR, objective response rate; CR, complete response; DCR, disease control rate; CHT, chemotherapy; WBRT, whole brain radiation therapy; ADK, adenocarcinoma; SRS, stereotactic radiosurgery; MR, mixed response.

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for BM (84-86). An open-label, single-institution, phase II study (84) prospectively evaluated the efficacy of EGFR-TKIs, erlotinib or gefitinib, in pts with BM from NSCLC harboring EGFR mutations. Pts did not receive any prior therapy for existing BM. Twenty-three (83%) out of 28 enrolled pts showed PR, 3 (11%) had SD with a disease control rate (DCR) of 93%. Median PFS and OS were 6.6 months (95% CI, 3.8–9.3 months) and 15.9 months (95% CI, 7.2–24.6 months), respectively. There were no differences in PFS and OS between the different TKIs. After progression, 14 pts (50%) received local therapy, either WBRT or SRS, with a local therapy-free interval of 12.6 months (95% CI, 7.6–17.6 months). An Asian phase II, open-label study (85) evaluated the efficacy and safety of erlotinib in NSCLC with BM after first line platinum-based chemotherapy. Forty-eight NSCLC pts with adenocarcinoma histology or activating EGFR mutation and asymptomatic BM, without extra-cranial progression after first-line therapy, were enrolled. The ORR, both intra and extra-cranial, was 58.3%. The median PFS was 10.1 months (95% CI, 7.1–12.3 months) for intracranial progression and 9.7 months (95% CI, 2.5–17.8 months) for both intracranial and systemic progression. Median PFS was significantly longer in pts with EGFR mutated disease than in those with EGFR wild-type disease, 15.2 months (95% CI, 8.3–22.2 months) vs. 4.4 months (95% CI, 0.0–11.6 months; P=0.02), respectively. Most common adverse events were predominantly of grade 1/2. In this trial erlotinib given alone was active and well tolerated also as second line treatment in NSCLC pts with BM. The BM responses to gefitinib, even without irradiation, were reported in a third phase II trial (86) in which 41 pts with BM from EGFR mutated lung adenocarcinoma were enrolled. The ORR was 87.8%, median PFS and OS were 14.5 months (95% CI, 10.2–18.3 months) and 21.9 months (95% CI, 18.5–30.3 months), respectively. Exon 19 deletion was associated with better outcome in both PFS (P=0.003) and OS (P=0.025) compared with L858R. No pts experienced grade ≥4 toxicity.

Several retrospective analyses confirmed the efficacy of TKIs used alone in BM, in particular in EGFR mutated NSCLC (87-89). Gefitinib was evaluated in a Japanese monocentric retrospective study (87) of 57 pts with advanced NSCLC unselected for EGFR mutational status. Fourteen pts had BM. Six of them experienced objective responses to brain lesions [one complete response (CR) and five PR] and eight had SD. Objective responses in extracranial disease were reported in 7 of 14 pts with BM and, interestingly, intracranial objective responses were

documented in 6 (86%) of these pts. Porta et al. (88) retrospectively evaluated erlotinib therapy in 69 pts with BM from NSCLC, 17 of whom harboring EGFR activating mutations. Overall ORR in mutated pts was 82.4%, while no responses were observed in unselected ones. The median time to treatment progression (TTP) for intracranial disease in mutated group was 11.7 months (95% CI, 7.9–15.5 months) compared with 5.8 months (95% CI, 5.2–6.4 months) in WT or unknown EGFR pts (P<0.05). The OS was 12.9 vs. 3.1 months in the two groups, respectively (P<0.001). Erlotinib was equally tolerated. Finally, in another retrospective analysis (89), 23 Korean never-smoking pts with lung adenocarcinoma and synchronous asymptomatic BM, treated with either gefitinib or erlotinib as first-line, were considered. They had received no prior treatment, nor chemotherapy nor any kind of radiotherapy. Out of 23 pts, 16 achieved PR, 3 SD and only 4 pts experienced PD, resulting in an ORR of 69.6% and a DCR of 82.6%. Seventeen pts (73.9%) showed intracranial tumor response. The median PFS and OS were 7.1 (95% CI, 1.08–12.87 months) and 18.8 months (95% CI, 0.64–27.0 months), respectively. According with these results clinical benefit from EGFR-TKIs seems to be mainly associated with the presence in the EGFR gene of activating mutations or with those clinical features (sex, ethnicity, smoking status) strongly related to this genotype.

Promising results were also reported in other prospective trials (90,91). In the study by Ceresoli et al. (90) gefitinib was prospectively evaluated in 41 NSCLC pts with BM, of which 37 had already received chemotherapy while 18 had been previously treated with WBRT. Gefitinib proved active in both WBRT-treated and WBRT-naive pts. Four pts (10%) reported PR with an overall DCR of 27%. The median duration of response was 13.5 months. In another prospective study (91) in 40 unselected pts, all previously treated with chemotherapy, gefitinib showed an ORR of 32%, a median PFS of 9.0 months (95% CI, 4.5–13.5 months) and an OS of 15.0 months (95% CI, 11.1–18.8 months).

Recently Soon et al. (107), in a systematic review and meta-analysis of 12 prospective and retrospective studies, compared the effects of brain radiotherapy vs. TKIs alone on intracranial disease, in EGFR mutated NSCLC with BM. In contrast with previous data, this meta-analysis showed an advantage in the 2-year OS for the upfront cranial radiotherapy, either WBRT or SRS, compared with TKIs alone (WBRT: 60%, SRS: 93%, TKIs alone: 45%). Nevertheless radiotherapy did not improve disease response

and no significant differences in ORR were documented. In general, cranial irradiation caused a rate of neurological adverse events higher than that reported in studies with TKIs alone (84-86), but lower than that of the concurrent upfront WBRT/TKIs studies (92,93). By limiting the analysis to prospective studies, there was no significant difference in intracranial disease control and survival outcomes between concurrent upfront WBRT plus TKIs and TKIs alone. Thus, considering the high intracranial ORR, consistent with results from other reviews (99-101), TKIs alone may be used upfront before WBRT in those pts with EGFR mutated NSCLC and asymptomatic BM. With a similar strategy the side effects of WBRT may be potentially avoided as long as intracranial disease is well controlled by TKIs alone.

Finally, a pooled analysis of published data (108), including 464 pts from 16 different prospective and retrospective trials, was performed. The primary endpoint was to evaluate the effectiveness of EGFR-TKIs in NSCLC pts with BM, particularly in EGFR mutated ones. Out of 464 enrolled pts, 102 had activating EGFR mutations, while in 362 pts the EGFR mutational status was unknown (unselected group). In this analysis EGFR-TKIs yielded significant results, with an intracranial ORR of 51.8%, a DCR of 75.7%, a median PFS of 7.4 months (95% CI, 4.9–9.9 months) and an OS of 11.9 months (95% CI, 7.7–16.2 months). Better results were reported in the mutated group compared to the unselected one: higher ORR (85.0% *vs.* 45.1%), a trend of greater benefit in DCR (94.6% *vs.* 71.3%), longer PFS (12.3 *vs.* 5.9 months) and OS (16.2 *vs.* 10.3 months). In 12 of the 16 pooled studies EGFR-TKIs were administered alone, while in four studies they were used in combination with WBRT. Subgroup analysis indicated a greater advantage with WBRT and EGFR-TKIs concurrent administration in unselected pts, with a ORR of 66.2% *vs.* 45.2% and a DCR of 94.4% *vs.* 73.1%, respectively.

These studies globally showed EGFR-TKIs promising antitumor activity against both intra and extra-cranial disease in pts with NSCLC, supporting their use as treatment of choice also in pts with CNS asymptomatic metastases. In general, the selection of NSCLC pts based on EGFR mutational status or, as surrogate, demographic features, resulted in greater benefit than in unselected pts. So EGFR-TKIs therapy may be the first treatment option for NSCLC metastatic to the brain in pts harboring activating EGFR mutations. Surely, further studies are warranted.

Second generation EGFR-TKIs

Afatinib is an oral irreversible second-generation EGFR-TKI that acts as a pan-HER inhibitor blocking all members of ErbB family. Analogously to first generation TKIs erlotinib and gefitinib, also afatinib today is approved for the treatment of EGFR mutated TKIs-naive NSCLC pts (109,110). It showed preclinical activity in models with EGFR mutations that confer resistance to EGFR-TKIs (111). Its higher binding affinity and broader target could enhance therapeutic efficacy and delay the development of resistance mutations in EGFR-mutated pts (112). Despite the effectiveness in NSCLC with BM, there are evidences that pts treated with first generation EGFR-TKIs over a period of many months may have an increased risk of developing BM (113). In fact the concentration of TKIs in the CSF seems sufficient to inhibit treatment naive but non-TKIs-resistant cells. Moreover the lower drug concentration could select for resistant clones over time (112,113).

Due to its potency at relatively low concentration, afatinib can be effective in the CSF also in the case of resistance to other TKIs. In preclinical studies, afatinib demonstrated high potency and *in vitro*, the median inhibitory concentration of afatinib was lower than other EGFR-TKIs (109,110). This suggests that afatinib has the potential to treat BM effectively, despite incomplete BBB penetration. Just before clinical approval, Li *et al.* (114), reported three cases of EGFR mutated NSCLC with BM in which afatinib, with or without combination with local treatment (WBRT or surgery), showed efficacy as first line therapy. In the LUX-Lung 1 study (115) pts already treated with platinum-based chemotherapy and first generation TKIs were randomized to receive afatinib or placebo. Although no benefit in terms of OS was recorded, afatinib achieved a prolonged PFS in comparison with best supportive care (median PFS 3.3 *vs.* 1.1 months). In two large randomized trials, LUX-Lung 3 (116) and LUX-Lung 6 (117), afatinib was compared to standard chemotherapy as first line therapy in EGFR mutated NSCLC pts showing a statistically significant advantage in PFS (median PFS 13.6 months). The enrollment of pts with stable BM was allowed in all LUX-Lung studies. In May 2010 the afatinib compassionate use program started with the aim to provide drug access after progression with erlotinib or gefitinib. Recently an efficacy analysis, in pts with BM who were treated with afatinib after chemotherapy and an EGFR-TKI within the compassionate use program, has been published (94). In particular 42% of pts reported

PR, 39% SD and only 19% PD. Brain responses were documented in 35% of pts. The safety profile of afatinib reflected that of previous experiences. The most important adverse events were diarrhea, dermatological toxicity, nausea, vomiting, and fatigue. The OS was 9.8 months and TTF did not differ in pts with or without BM. Over 70% of pts with BM had either PR or SD and 76% of pts did not develop new metastases. Considering that in the compassionate use pts received afatinib as third line treatment or greater, these data are very outstanding, especially for pts with BM and for pts who developed resistance to reversible EGFR-TKIs. The observed BM responses provide clinical evidence that afatinib concentration in CSF is sufficient to inhibit tumor growth. The subgroup analysis of LUX-Lung 3 trial (116) have further confirmed the effectiveness of first-line afatinib in CNS metastatic setting, with a median PFS of 11.1 *vs.* 5.4 months in pts who received afatinib or chemotherapy, respectively [hazard ratio (HR), 0.52; P=0.13].

Radiotherapy and EGFR-TKIs

Different data about the association of TKIs and WBRT exist (*Table 1*). In a preclinical study a synergistic effect of the combination EGFR-TKIs/radiation therapy has been documented (118). This possible synergism may derive from the radio-sensitizing effect of TKIs and from the damage of BBB created by radiation. *In vitro* radiation caused increased expression of EGFR and the EGFR blockade, both from gefitinib and erlotinib, enhanced sensitization to radiation in different human carcinoma cell lines and tumor xenografts (118,119). Several trials showed that brain irradiation can cause the opening of BBB, playing an important role in increasing TKIs concentrations in CSF (120-122).

A phase I trial, in which NSCLC pts with BM were enrolled, evaluated the toxicity of WBRT with concurrent and maintenance erlotinib showing that erlotinib was well tolerated and the combination did not cause any significant increase in treatment related toxicity (95). Moreover different phase II studies evaluated the efficacy and toxicity of the concurrent approach (93,96). The phase II trial by Ma *et al.* (96) studied the concomitant treatment with WBRT and gefitinib in 21 Chinese pts with BM from NSCLC to assess its impact on pts QoL and post-treatment survival. All pts received 40 Gy WBRT in 20 fractions. Gefitinib was administered during the radiation course and was continued until progression or unacceptable toxicity. Four (19%) pts had CR, 13 pts showed (62%)

PR, 3 pts had SD and only 1 pt showed PD. The ORR was 81%. Median PFS and OS were 10.0 months (95% CI, 7.5–12.5 months) and 13.0 months (95% CI, 8.2–17.8 months), respectively. The great majority of toxicities were grade 2 and QoL was significantly improved following treatment. Erlotinib achieved similar results in a single-arm phase II trial (93) in which 40 NSCLC pts with BM, not selected for EGFR mutations, were treated with standard dose TKIs and concurrent WBRT. The ORR was 86%, median OS was 11.8 months (95% CI, 7.4–19.1 months) and the combination resulted well tolerated with no grade 4 toxicity, limited neurotoxicity and only 3 cases of grade 3 rash (3%). EGFR status was known in 17 pts and median OS was 9.3 *vs.* 19.1 months in EGFR WT *vs.* mutated pts respectively. These data are promising and concomitant treatment was well tolerated, with important activity and improvement in QoL.

Concomitant therapy was also compared both to EGFR-TKI alone and WBRT alone (90,92,97,98,123). Ceresoli *et al.* (90), in a previously mentioned study, evaluated 41 NSCLC pts with BM. Eighteen pts received gefitinib after previous WBRT, 23 pts were radio-naive and 37 pts received previous chemotherapy. Four PR (10%) were observed, SD was reported in seven cases and nearly 30% of pts achieved DCR, showing an interesting activity of gefitinib both in previously irradiated and non-irradiated pts. The median PFS of the whole population was 3 months (95% CI, 0.0–14 months). Neurological improvement was also observed in four of nine symptomatic pts. Combination treatment showed a significant prognostic advantage at the univariate analysis (P=0.0006) obtaining disease control in 10/18 pts (56%) compared to 2/23 (9%) in radio naive pts. These data were confirmed by a retrospective analysis (97) that compared the efficacy of gefitinib alone with gefitinib plus concomitant WBRT. Ninety pts were divided in two groups: the gefitinib group and the gefitinib-WBRT group. The combination group showed higher ORR (64.4% *vs.* 26.7%, P<0.001) and higher DCR (71.1% *vs.* 42.2%, P=0.006) with nearly doubled median PFS and OS (10.6 *vs.* 6.57 months, P<0.001 and 23.40 *vs.* 14.83 months, P=0.02, respectively). In a recent randomized phase II trial (98) concurrent WBRT and erlotinib compared to WBRT alone failed to demonstrate any advantage in intracranial disease control. The 80 enrolled NSCLC pts metastatic to the brain were predominantly EGFR WT (only 1/35 evaluable pts was mutated). Median PFS was 1.6 months in both arms and median OS was 2.9 and 3.4 months in the placebo compared with erlotinib arm respectively (HR, 0.95; 95%

CI, 0.58–1.55; P=0.83). The Radiation Therapy Oncology Group (RTOG) designed a phase III study (123) to test if erlotinib and temozolomide in association to WBRT and SRS could improve OS in NSCLC pts with one to three BM and unknown EGFR mutational status. Unfortunately the combination showed higher percentage of grade 3–5 toxicities without any statistically significant efficacy result and the study was closed early for poor accrual. Finally in another previously cited study (92), 54 NSCLC pts with multiple BM, receiving WBRT with or without concurrent erlotinib, reported an advantage with additional erlotinib regardless of EGFR-mutational status. The ORR was 54.84% *vs.* 95.65% (P=0.001), with a median brain PFS of 6.8 *vs.* 10.6 months (P=0.003), a median general PFS of 5.2 *vs.* 6.8 months (P=0.009) and a median OS of 8.9 *vs.* 10.7 months (P=0.020) in the WBRT arm and the concurrent arm, respectively. Furthermore erlotinib resulted the most important prognostic factor for prolonged survival at the multivariate analysis. In contrast with literature data, in the combination group there were no differences in brain PFS, general PFS and OS between EGFR-mutated and EGFR WT pts. Thus the EGFR-TKIs radiosensitizing effect in this trial doesn't seem to be dependent on EGFR-mutations. Nevertheless, in the management of BM, the addiction of TKIs to WBRT as radiosensitizing agents also in WT NSCLC pts, should be confirmed by other specific studies.

To date no prospective study exists that has really compared the use of cranial irradiation alone *vs.* TKIs alone *vs.* combination of the two modalities.

Third generation EGFR-TKIs

Although NSCLC pts harboring EGFR sensitizing mutations derive significant clinical advantage from EGFR-TKIs therapy, invariably, after about 9–13 months from the beginning of treatment, disease progression occurs. Several mechanisms of acquired resistance exist: the onset of secondary mutations in EGFR (50–60%), the activation of alternative pathways (1–25%) and the histologic transformation (5–10%). In the remaining 20–30% of cases resistance mechanisms are not known yet (124,125). Surely, the development of EGFR T790M mutation is the most common cause of acquired resistance. The substitution of methionine with threonine at position 790 in the exon 20 blocks the binding of first generation EGFR-TKIs to the ATP pocket and increases its affinity to ATP rather than to EGFR-TKIs (126,127). Third generation EGFR-TKIs

(osimertinib, rociletinib, HM61713 and others) have been developed as T790M mutant-specific inhibitors. First data support their effectiveness and safety also in NSCLC pts with BM.

AZD9291 (osimertinib), a novel TKI that specifically and irreversibly binds the cysteine-797 residue in the ATP binding site of EGFR, has recently obtained the accelerated Food and Drugs Administration (FDA) approval in EGFR mutated NSCLC with documented T790M resistance mutation, on the basis of important results of phase I and II trials (128-130). Its activity has been also evaluated in pts with BM from NSCLC. A combined analysis of AURA and AURA 2 (131) studies reported that 39% of enrolled pts (162 of 411 pts) had BM. The systemic ORR of overall population was 61%, and it became 56% and 64% in pts with or without BM respectively. Cases of shrinkage of brain lesions were reported. Currently the Real World Treatment Study of AZD9291 for Advanced/Metastatic EGFR T790M Mutation NSCLC (ASTRIS) is ongoing, to assess the efficacy and safety of single agent AZD9291 in a real world setting in EGFR T790M mutation-positive NSCLC, who have received prior EGFR-TKIs therapy. Also pts with stable BM can be enrolled.

CO1886 (rociletinib) is another irreversible third generation mutant selective EGFR-TKI, specifically directed against common sensitizing EGFR mutations and T790M (132,133). Also rociletinib showed to be effective in BM from NSCLC. Out of 401 pts who received rociletinib within clinical trials 42% (170 of 401 pts) had BM. At the interim analysis pts with BM reached an ORR of 41% (134). At an indirect comparison the ORR of NSCLC pts with or without BM resulted equal to 45% and 55%, respectively (135).

AZD3759 is the first EGFR-TKI designed to penetrate BBB and to achieve high free drug exposure inside the brain, CSF and plasma, with the aim to treat BM and leptomeningeal disease in pts with EGFR mutated NSCLC. In a recent phase I, open-label, multicentre study (136), in pts with advanced stage EGFR mutated NSCLC who progressed after at least one EGFR-TKI and one line of chemotherapy, AZD3759 was well tolerated, achieved sufficient CNS concentration and showed promising antitumor activity in the dose escalation phase. Among 20 pts with measurable BM, 8 had tumor shrinkage in the brain, with 3 confirmed and 3 un-confirmed PR. The most common adverse events were skin rash and diarrhea.

Results of activity in BM of other third generation TKIs, such as ASP8273, EGF816 and HM61713 are still awaited.

Conclusions

First and second generation EGFR-TKIs represent a valid therapeutic option in NSCLC pts with BM (*Table 1*), especially in pts with activating EGFR mutations. In many studies they are able to obtain similar activity to local treatments, with a beneficial toxicity profile. Probably EGFR-TKIs effectiveness is conditioned by the heterogeneity of the EGFR mutational status between CNS metastases and extracranial disease. Thus, their combination with other treatment options, such as surgery, radiotherapy, chemotherapy, monoclonal antibodies and immunotherapy, may further improve results. The use of biopsy at the time of progression should be always evaluated. Considering the inevitable development of drug resistance, the identification of third generation EGFR-TKIs, able to overcome secondary resistance, is of major importance and is very promising especially in pts with BM. At the same time prospective studies focused on the use of TKIs with or without concurrent WBRT in pts specifically selected on the basis of the EGFR mutational status are needed.

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Footnote

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