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REVIEW ARTICLE

Oral Targeted Therapies and Central Nervous System (CNS) Metastases

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Abstract The purpose of our review is to summarize the clinical activity of oral targeted agents against brain metastases. This includes BRAF inhibitors (dabrafenib and vemurafenib), human epidermal growth factor receptor inhibitors (lapatinib, gefitinib, erlotinib, and afatinib), multi-kinase angiogenesis inhibitors (sorafenib, sunitinib, pazopanib, and vandetanib), and ALK/c-MET (crizotinib) and ALK/IGF-1 (ceritinib) inhibitors. Effective systemic therapies are needed for long-term benefit in brain metastases and documentation of intracranial activity for many therapies is poor. Our review provides a summary of the literature with pertinent data for clinicians. This is needed as subjects with brain metastases are often prevented from enrolling in clinical trials and investigations focused on systemic therapies for brain metastases are rare.

Key Points

Our review summarizes the literature on the clinical activity of oral targeted agents on brain metastases.

The oral targeted agents include BRAF inhibitors (dabrafenib and vemurafenib), human epidermal growth factor receptor inhibitors (lapatinib, gefitinib, erlotinib, and afatinib), multi-kinase angiogenesis inhibitors (sorafenib, sunitinib, pazopanib, and vandetanib), and ALK/c-MET (crizotinib) and ALK/IGF-1 (ceritinib) inhibitors.

Small molecule inhibitors with daily dosing have a greater likelihood of overcoming the blood brain barrier than traditional chemotherapy administered in an intermittent schedule.

1 Introduction

The world of oncology has experienced an explosion of new oral targeted chemotherapeutic agents in recent years. Since 2005, more than 20 new oral targeted therapies have been approved by the US Food and Drug Administration (FDA). These agents treat a range of malignancies, many of which are known to metastasize to the brain. Thus, the central nervous system (CNS) penetration and activity against brain metastases of these new targeted agents is of great interest to researchers, clinicians, and patients.

CNS penetration of drugs is influenced by multiple factors such as diffusion, fluid flow mechanics, and transport—influx and efflux—across the blood-brain barrier (BBB) and blood-cerebrospinal fluid (CSF) barrier in the

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choroid plexus [1, 2]. Once these barriers have been passed, the volume of distribution includes the extracellular fluid compartment of the brain, brain cells, and the CSF. These parameters are generally determined in vitro or in animal studies during drug development. For many of the drugs discussed below, however, these parameters are unknown or unavailable. Clinical activity of oral targeted agents against brain metastases has limited documentation, and patients with known brain metastases are often excluded from clinical trials. All of the drugs discussed in this review are used for their systemic (i.e., extracranial) effects. Trials and clinical case series specifically in patients with brain metastases demonstrate considerable variability in the population studied (i.e., primary disease), choice of endpoints, and measurement of endpoints [3].

2 BRAF Inhibitors—Dabrafenib and Vemurafenib

Both dabrafenib and vemurafenib are inhibitors of type I BRAF V600E kinase [4] and both are FDA approved for the treatment of unresectable or metastatic melanoma with the BRAF V600E mutation. Dabrafenib is also FDA approved for use with trametinib for treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations.

2.1 Dabrafenib

Falchook et al. reported the effects of dabrafenib given orally for patients with melanoma and other solid tumors during a phase I, dose-escalation trial [5]. Of 184 patients enrolled, 156 had metastatic melanoma and 10 of these had untreated asymptomatic brain metastases. Safety and tolerability were the primary outcomes of the trial; secondary outcomes included pharmacokinetic and pharmacodynamic profiles and tumor response. Among patients with brain metastases, nine had a Val600Glu (V600E) BRAF mutation, and the remaining patient had a Val600Lys mutation [5]. A rapid dose titration was used to establish a recommended phase II dose, which was based on patient tolerability. At the established dose (150 mg twice daily), reduction in brain lesion size, as determined by MRI, was seen in nine patients (along with a decrease in extracranial lesion size) and four had complete resolution. The median progression-free survival (PFS) time was 4.2 months (95 % confidence interval [CI] 3.3–5.3); one patient had a durable response of 15 months.

In a phase II, open-label trial enrolling 172 patients with melanoma and brain metastases, dabrafenib 150 mg twice daily was given until disease progression [6]. Patients were stratified by treatment history (no local treatment for brain metastases [Cohort A, $n = 89$] or prior radiation and/or surgery with disease progression [Cohort B, $n = 83$]) and then by BRAF mutation (Val600Glu [V600E] or Val600Lys [V600K]). Disease progression was assessed by MRI at baseline and at specified intervals until week 40, and then every 3 months until treatment discontinuation. The primary endpoint was intracranial response to treatment (complete or partial) in patients with V600E mutations, as determined by the investigator. Secondary outcomes included overall response (complete and partial) and PFS. Among patients with Val600Glu BRAF mutation and no prior treatment ($n = 74$), a complete intracranial response was achieved in 3 % and a partial response in 36 %. For those previously treated ($n = 65$), no patient had a complete response, and 31 % had a partial response. Intracranial response rates were lower among those with the Val600Lys mutation (Cohort A, $n = 15$; Cohort B, $n = 18$); 0 % complete response in either cohort and 7 and 22 % for partial responses, respectively. Six-month survival estimates were 61 % in both cohorts for patients with Val600Glu BRAF. For patients with a V600K mutation, 6-month survival estimates were 27 and 41 % in Cohorts A and B, respectively.

Azer and colleagues conducted an analysis of patients from previous phase I and phase II trials to determine patterns of response and progression with dabrafenib treatment [7]. Twenty-three patients from a single institution were included in the analysis; 12 with previously untreated metastases and 11 with a history of treatment. Most patients (83 %) had a V600E BRAF mutation. Dabrafenib was given at 150 mg twice daily and continued if evidence of ongoing clinical benefit was seen. Overall response rate was 87 %, with a median overall survival of 36.6 weeks. Median PFS was 23.6 weeks for both intracranial and extracranial disease.

2.2 Vemurafenib

2.2.1 Prospective Trials

Dummer and colleagues reported the outcomes of vemurafenib treatment in symptomatic patients with melanoma (V600 BRAF positive) with unresectable brain metastases [8]. Vemurafenib was given at 960 mg twice daily until disease progression or toxicity. The primary outcomes of the open-label trial were safety and tolerability; efficacy (defined by response rate) was a secondary outcome. Extent of disease and response were assessed by MRI. A total of 24 patients were enrolled in the trial; all had brain metastases with 92 % having at least two intracranial lesions (median four). Prior therapy included whole-brain or stereotactic radiotherapy, and/or surgery. The median duration of therapy was 3.8 months, and most patients

(96 %) experienced at least one adverse event from treatment. Most events were mild or moderate in severity. Serious adverse events attributed to vemurafenib occurred in 17 % of patients. Of 19 patients with measurable intracranial disease at baseline, a partial response was seen in 16 %, stable disease in 68 %, and progressive disease in 11 %. Intracranial tumor regression >30 % was reported in 37 % of patients. Of 21 patients with measurable extracranial disease at baseline, 62 % had a partial response, 29 % had stable disease, and 5 % had progression. Median PFS was 3.9 months, and median overall survival was 5.3 months.

2.2.2 Retrospective Studies and Case Report/Series

Available retrospective studies and case reports/case series of vemurafenib for treatment of melanoma with brain metastases are summarized in Table 1. Overall activity is observed with high concordance of intracranial with extracranial response.

3 Human Epidermal Growth Factor Receptor Inhibitors

The 4-anilinoquinazolines, lapatinib, gefitinib, erlotinib, and afatinib, are orally active tyrosine kinase inhibitors targeting the kinase activity of human epidermal growth factor receptor (EGFR or HER1). In contrast to gefitinib and erlotinib, which are selective for EGFR, lapatinib has been shown in multiple tumor cell cultures to bind similarly to both EGFR and HER2 kinases intracellularly. Afatinib is a highly selective blocker of the ErbB family, including EGFR, HER2, and HER4.

Lapatinib is currently FDA approved in combination with capecitabine for the treatment of HER2 overexpressing breast cancer in patients who have received prior anthracycline, taxane, and trastuzumab-based therapy, and in combination with letrozole for postmenopausal women with HER2 overexpressing and hormone-receptor-positive breast cancer [9]. Gefitinib is indicated for the first-line treatment of patients with metastatic non-small-cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test [10]. Erlotinib is FDA approved as first-line treatment of metastatic NSCLC with EGFR exon 19 or 21 mutations, maintenance treatment of locally advanced or metastatic NSCLC that has responded to previous chemotherapy, or for use after treatment failure [11]. Erlotinib is also approved as first-line treatment of locally advanced, unresectable or metastatic pancreatic cancer with concurrent gemcitabine. Afatinib is currently FDA approved for the treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations at a dose of 40 mg daily [12].

Lapatinib has been shown to cross the BBB in a mouse model, but uptake is variable and drug concentrations are often reduced compared with peripheral sites of disease [13]. In a mouse model, lapatinib was shown to inhibit the growth of large brain metastases from HER2-positive breast cancer cell lines, suggesting that it has activity in HER2-positive CNS disease [14]. Gefitinib is effective against EGFR-expressing brain tumors in mice [15].

3.1 Lapatinib

In humans, a few case reports have proven the efficacy of lapatinib for brain metastases in combination with capecitabine in breast cancer patients [16, 17]. These are summarized in Table 2. Available phase II studies have also revealed modest efficacy in HER2-positive breast cancer patients with brain metastases [18, 19]. The larger of these trials assessed 252 patients with HER2-positive breast cancer and progressive brain metastases who received lapatinib with or without capecitabine [19]. All patients had received prior HER2-directed therapy with trastuzumab and prior whole-brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS). Lapatinib was initiated at a dose of 750 mg twice daily. In patients receiving lapatinib alone, the CNS objective response rate (defined as >50 % volumetric reduction of CNS lesions, assessed by MRI, in the absence of increasing steroid use) was 6 %. In an exploratory analysis, 21 % of patients in the lapatinib monotherapy group achieved a 20 % or greater CNS tumor volume reduction. When combined with capecitabine, 40 % of patients achieved the same outcome. Tumor volume reductions also correlated with improvement in neurologic signs and symptoms as well as PFS.

Studies have also revealed efficacy in preventing CNS relapse in patients receiving lapatinib with chemotherapy. In a single-arm, open-label trial of 52 patients with HER2-positive metastatic breast cancer, 13 patients (25 %) had any new lesions as disease progression, of whom only two patients (3.8 %) relapsed with the CNS as the first site of progression [20]. Larger phase III trials have shown similar results with the addition of lapatinib to capecitabine [21, 22]. Cameron and colleagues analyzed 399 women with heavily pre-treated (including trastuzumab), locally advanced or metastatic HER2-positive breast cancer receiving lapatinib 1250 mg daily in combination with capecitabine versus capecitabine alone [22]. With the addition of lapatinib to capecitabine, only 2 % of patients had CNS progression versus 6 % with capecitabine alone ($p = 0.045$).

Table 1 Vemurafenib case reports/case series

References	Prior treatments (total no. patients)	Tolerability	Outcome
Fennira et al. [60]	SRS/dacarbazine/fotemustine/ipilimumab ($N = 49$, 8 symptomatic)	Grade 3 liver cholestasis, renal failure, fatigue, rash, Grade 5 heart failure, Grade 2 diarrhea	For 20 patients with brain metastases: CR: 1 patient (clinical and radiologic assessment) PR: 9 patients (clinical and radiologic assessment) Median OS: 4.3 months Median PFS: 3.1 months For all 49 patients: ORR: 53 % Median OS: 7.5 months PFS: 3.6 months
Dzienis and Atkinson [61]	Surgical resection/WBRT/no prior local therapy ($N = 22$, all symptomatic)	Not reported	Treatment-naïve or progressed after local therapy ($n = 16$): RR: 8 patients No progression after WBRT ($n = 6$): RR: 3 patients Where RR >30 % reduction in target lesion size Median time to progression: Responders: 23 weeks Nonresponders: 12 weeks
Rochet et al. [62]	SRS ($N = 1$, symptomatic)	Neutropenia	Resolution of symptoms and substantial reduction in lesion size as assessed by MRI
Rochet et al. [63]	External beam radiation/gamma knife radiosurgery ($N = 3$, 1 symptomatic)	Grade 2 rash, grade 3 elevation of liver transaminases	Initial response with reduction in symptoms, lesion size (as assessed by MRI) at 1 month in 1 patient, but disease progression was seen 1–2 weeks later and patient died Second patient had disease progression after 2 months of treatment Third patient had improvement in lesion size at 4 weeks; but vemurafenib was discontinued due to adverse effects, followed by disease progression
Balakan et al. [64]	Cyberknife radiosurgery, palliative radiotherapy ($n = 1$)	Not reported	Improvement in neurologic symptoms after 20 days and reduction in lesion volume (>50 %, as assessed by CT); progression of lesions at 3 months with patient death at 4 months
Kolar et al. [65]	Surgery and ipilimumab for extracranial disease ($N = 1$ symptomatic)	No drug-related adverse events noted	Decrease in lesion size, as assessed by MRI, at 4 weeks after starting vemurafenib
D'Alonzo and Glatz [66]	Vemurafenib for cutaneous metastases ($N = 1$)	Not reported	Improvement in extracranial lesions was seen with treatment. However, intracranial disease developed while on vemurafenib, and death occurred 5 months after treatment initiation. There were no signs of intracranial response at autopsy
Forschner et al. [67]	WBRT, surgery ($N = 1$)	Not reported	After 10 weeks, "impressive" reduction of all brain lesions, as assessed by MRI
Harding et al. [68]	WBRT ($n = 9$), SRS ($n = 1$), craniotomy only ($n = 3$), multimodal ($n = 2$), none ($n = 12$)	Erythematous cutaneous plaques in 1 patient who received concurrent WBRT	Intracranial vs extracranial responses were discordant in 4 patients. Intracranial progression in 4 patients

CR complete response, *CT* computed tomography, *MRI* magnetic resonance imaging, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *PR* partial response, *RR* response rate, *SRS* stereotactic radiosurgery, *WBRT* whole-brain radiation therapy

Table 2 Lapatinib case reports

References	Prior treatments (total no. of patients)	Tolerability	Outcome
Gluck and Castrellon [16]	Docetaxel/trastuzumab/anastrozole; Trastuzumab/paclitaxel/carboplatin ($N = 1$)	Not reported	Near complete resolution of CNS metastases, as assessed by CT, with resolution of neurologic symptoms following 4 months of therapy
Abboud et al. [17]	Adjuvant radiation/chemotherapy (regimen not specified); WBRT ($N = 1$)	Not reported	Intracranial CR, as assessed by MRI

CR complete response, *CT* computed tomography, *MRI* magnetic resonance imaging, *WBRT* whole-brain radiation therapy

3.2 Gefitinib

Few large studies have specifically evaluated the efficacy of gefitinib for human brain metastases. In a prospective trial of 41 NSCLC patients (all of whom had brain metastases), gefitinib 250 mg daily resulted in a partial response in 10 % of patients [23]. Seventeen percent of patients had stable disease for an overall disease control rate of 27 %. Four of nine patients with neurologic symptoms prior to treatment showed improvement in their symptoms. Wu and colleagues evaluated 40 patients with NSCLC and brain metastases [24]. All patients received palliative treatment with gefitinib 250 mg daily. Thirty-eight percent of patients' intracranial lesions responded to therapy, with a disease control rate (defined as the best tumor response of complete response, partial response, or stable disease) of 81 %. Nearly half of the patients had resolution or improvement of neurologic symptoms.

In a retrospective analysis of 57 patients with NSCLC, gefitinib demonstrated activity in the 14 patients with brain metastases [25]. Of these 14 patients, one patient had a complete CNS response (7.1 %), five patients had a partial response (35.7 %), and the remaining eight patients (57.1 %) had stable disease. The median duration of tumor response for patients with brain metastases was 8.8 months. In another study of 76 patients with NSCLC (21 of whom had assessable intracranial lesions), gefitinib 250 mg daily provided an overall response rate of 50 % [26]. The median overall survival for all patients in the study was 9.9 months. No difference in survival was seen in patients with or without brain metastases. Interestingly, response and overall survival of the entire population were associated with the severity of skin toxicity, suggesting that more skin toxicity results in a greater response.

Gefitinib was also reported to be effective and generally well tolerated in multiple case reports describing patients with brain metastases; these are summarized in Table 3.

3.3 Erlotinib

Several case reports and small trials have evaluated the clinical efficacy of erlotinib as well as the CSF concentrations of erlotinib and OSI-420, an active metabolite, in patients with NSCLC and brain metastases. These are summarized in Table 4.

3.3.1 Prospective Clinical Trials

Phase I, II, and III trials have been conducted to assess the effects of erlotinib in patients with NSCLC and brain metastases. Lind and colleagues reported the results of a phase I trial investigating concurrent WBRT and erlotinib in 11 NSCLC patients with multiple brain metastases [27]. Erlotinib was initiated at either 100 mg or 150 mg daily 1 week prior to WBRT and continued at 150 mg daily after WBRT until disease progression or toxicity. At baseline, five patients had five or fewer brain metastases, five had six to ten, and one patient had more than ten brain metastases. Endpoints included toxicity (as primary), overall survival, time to progression, and tumor response. Fatigue (64 %) was the most common toxicity observed, followed by rash (45 %), anorexia (45 %), diarrhea (45 %), taste alteration (45 %), weight loss (45 %), nausea (36 %), and dyspnea (27 %), most of which were Grade 1 or 2. Median survival was 133 days and median time to disease progression was 141 days. Based on imaging studies in seven patients, partial response was seen in five and stable disease in two for an intracranial disease control rate of 100 %. In another phase I dose-escalation trial, erlotinib (50–150 mg daily) was given with cetuximab and bevacizumab to 34 patients with NSCLC [28]. A partial response in intracranial disease was seen in three of 11 patients with brain metastases. An additional three patients had stable disease for 6 months or longer, and one patient achieved complete resolution of intracranial disease.

In a phase II, open-label trial, 48 patients with NSCLC and asymptomatic brain metastases were treated with erlotinib 150 mg daily given until disease progression [29]. Erlotinib was given following two to six cycles of platinum-doublet chemotherapy with no evidence of progression of intracranial disease. The primary endpoint was PFS, based on intra- or extracranial disease progression. Other endpoints included overall response rate, 6-month and 1-year overall survival, and safety. At baseline, 47.9 % of enrolled patients had three or fewer brain metastases and 52.1 % had more than three metastases. Median intracranial PFS was

Table 3 Gefitinib case reports/case series

References	Prior treatments (total no. of patients)	Tolerability	Outcome
Villano et al. [69]	WBRT; SRS; 4 cycles of docetaxel/gemcitabine/cisplatin/vinorelbine ($N = 1$, symptomatic)	Well tolerated	Reduction in size of brain lesions, as assessed by MRI, and resumption of activities of daily living after 5 months of therapy
Cappuzzo et al. [70]	WBRT in 2; first-line platinum-based therapy in 4 ($N = 4$, symptomatic)	Grade 1–2 skin toxicity	Intracranial PR, as assessed by CT, in all patients after 3 months of therapy. Improvement in symptoms in all patients
Cappuzzo et al. [71]	Platinum-based chemotherapy in 4; WBRT in 3 ($N = 4$, symptomatic)	Grade 1–2 skin toxicity	Intracranial CR, as assessed by CT, in 1 patient. PR in 3 patients. Improvement in symptoms in all patients
Fujiwara et al. [72]	6 cycles of cisplatin/docetaxel/irinotecan; 1 cycle of gemcitabine; 2 cycles of paclitaxel; WBRT ($N = 1$)	Grade 2 leucopenia/neutropenia, grade 1 diarrhea, grade 2 skin toxicity	Disappearance of ring enhancement of brain lesions on CT
Poon et al. [73]	Adjuvant cisplatin/paclitaxel ($N = 1$, symptomatic)	Grade 1 skin toxicity	Reduction in size of brain lesions (33.9 ± 6.4 % [mean $\pm$ 2 standard errors]) and resolution of vasogenic edema, as assessed by MRI. Resolution of symptoms
Takahashi et al. [74]	Cisplatin/mitomycin/vinorelbine; gemcitabine/docetaxel ($N = 1$, symptomatic)	Not reported	Intracranial CR, as assessed by CT. Improvement in symptoms (headache)
Ishida et al. [75]	No prior treatment reported ($N = 2$)	Grade 2 rash, grade 1 anorexia	Reduction in the size of brain lesions, as assessed by CT in 1 patient and MRI in 1 patient
Gurpide et al. [76]	First-line chemotherapy (regimen not reported) in 1, 3 previous lines of chemotherapy (regimens not reported) in 1 ($N = 2$)	Not reported	Intracranial PR in both patients, as assessed by MRI. Response maintained for 1 year in 1 patient
Stemmler et al. [77]	3 cycles of carboplatin/paclitaxel; WBRT; corticosteroids; temozolomide/topotecan ($N = 1$)	Well tolerated	Reduction in size of brain lesions and complete resolution of vasogenic edema, as assessed by MRI
Roggero et al. [78]	Vinorelbine/cyclophosphamide; irinotecan/gemcitabine ($N = 1$)	Well tolerated	Significant reduction of brain metastases as assessed by CT
Nishi et al. [79]	SRS in 1, SRS, gemcitabine/vinorelbine in 1 ($N = 2$)	Not reported	Disappearance and/or reduction in the size of multiple brain metastases (including those not treated with SRS), as assessed by MRI, in both patients
Garfield [80]	No prior therapy reported ($N = 1$, asymptomatic)	Mild rash	Disappearance and/or reduction in the multiple brain metastases, as assessed by MRI
Zee et al. [81]	No prior therapy ($N = 1$, symptomatic)		Intracranial PR after 4 months, as assessed by CT, but cystic transformation of brain lesion resulted in death

CR complete response, *CT* computed tomography, *MRI* magnetic resonance imaging, *PR* partial response, *SRS* stereotactic radiosurgery, *WBRT* whole-brain radiation therapy

Table 4 Erlotinib and OSI-420 CSF concentrations studies

References	No. of patients	CSF concentrations (mean ± standard deviation)[a]	Outcomes
Togashi et al. [82]	$N = 4$	E: 54 ± 30 ng/mL, 5.1 ± 1.9 % OSI: 10.8 ± 8.2 ng/mL, 5.8 ± 3.6 % Measured on day 8	PR in 2 patients, SD in 2 patients, as assessed by MRI 3 patients had improvement in functional status
Masuda et al. [83]	$N = 3$	Patient 1: E: 186 nM, 13.3 % Patient 2: E: 34.7 nM, 3 % Patient 3: E: 81.4 nM, 2.5 % Measured on day 28	Patients 1 and 2 had improvement in performance status and in neurologic symptoms
Togashi et al. [84]	$N = 9$ Deletion: $n = 1$ Unknown: $n = 1$	E: 106 ± 59 nM, 4.5 ± 1.5 % Measured on day 8 The authors reported a good correlation between plasma and CSF E concentrations ($R^2 = 0.84$; $p = 0.0005$)	PR in 7 patients, SD in 2 patients, as assessed by MRI
Togashi et al. [85]	$N = 15$ (6 received gefininib)	E: 28.7 ± 16.8 ng/mL (66.9 ± 39 nM), 2.77 ± 0.45 % Measured on day 8 The authors noted that CSF penetration was higher with E vs gefitinib (2.77 vs 1.13 %; $p < 0.0001$)	Erlotinib patients: PR in 4 patients, SD in 1 patient, PD in 2 patients, as assessed by MRI (2 patients not evaluated for response)
Fukudo et al. [86]	$N = 88$ (CSF data in 38 patients with CNS metastases)	E: 36 ng/mL, 3.3 % OSI: 6 ng/mL, 3.1 % Measured on day 8	Results not specific for patients with CNS metastases Median PFS 17.6 weeks Median OS 28.7 weeks
Deng et al. [87]	$N = 6$	E: 23.7 ± 13.4 ng/mL, 4.4 ± 3.2% Measured on day 28	PR in 2 patients, SD in 2 patients, PD in 2 patients, as assessed by MRI No significant association between CSF concentrations and CNS response

CSF cerebrospinal fluid, *E* erlotinib, *OSI* OSI-420, *PR* partial response, *SD* stable disease, *MRI* magnetic resonance imaging

[a] Also given as percentage of plasma concentration

10.1 months, and 9.7 months for any progression (intra- or extracranial). Median PFS was longer among patients with three or fewer versus more than three brain metastases (14.9 vs 8.2 months, $p = 0.71$). Median overall survival was 18.9 months, with cumulative survival rates of 85 % at 6 months and 73 % at 1 year. Rash was the most common adverse reaction, occurring in 77.1 % of patients; however, only two patients had Grade 3/4 severity.

Welsh and colleagues treated 40 NSCLC patients with erlotinib 150 mg daily beginning 1 week prior to WBRT and continuing until disease progression or toxicity during a phase II trial [30]. At study entry, 45 % of patients had three or fewer brain metastases, 37.5 % had four to ten, and 17.5 % had more than ten. The primary outcome was median survival. Median survival was 11.8 months; median CNS PFS, assessed by MRI, was 8.2 months. The CNS PFS rate was 20 % at 2 years, 38 % at 1 year, and 63 % at 6 months. Response rates between 3 and 6 months for intracranial disease were 31 and 56 % for complete and partial responses, respectively. Progression of intracranial disease occurred in 6 % of patients and stable intracranial disease in 3 %.

In a third phase II, open-label trial, patients with NSCLC and brain metastases were given either gefitinib 250 mg or erlotinib 150 mg once daily continued until disease progression or toxicity [31]. The primary endpoint was brain response, based on MRI, with survival as a secondary outcome. The overall response rate was 83 %: 23 partial responses and three stable disease. Median PFS was 6.6 months and median overall survival was 15.9 months. Among six patients given erlotinib, five had a partial response and one achieved stable disease. For gefitinib, 18 of 22 patients had a partial response and two had stable disease ($p = 0.85$ vs erlotinib).

In a phase III trial, Sperduto and colleagues evaluated the outcomes with WBRT and SRS versus both of these interventions combined with either temozolomide (TMZ) or erlotinib in patients with NSCLS and brain metastases (i.e., WBRT/SRS, WBRT/SRS/TMZ, or WBRT/SRS/erlotinib) [32]. TMZ was given at a dose of 75 mg/m^2 for 21

days at the start of WBRT. Afterwards, TMZ could be continued for up to 6 months at a dose of 150 mg/m^2/day for 5 days per month. Erlotinib was given at a dose of 150 mg daily starting on day 1 of WBRT. Similarly, erlotinib could be continued for up to 6 months after WBRT/SRS. The primary endpoint was overall survival; other endpoints included time to CNS progression, performance status, cause of death, and need for corticosteroids. A total of 125 patients were enrolled; 44 were treated with WBRT/SRS alone, 40 with TMZ, and 41 with erlotinib. Patients had between one and three brain metastases, with 25, 22, and 19 % in each group having three metastases, respectively. No statistical significance was seen in overall survival between WBRT/SRS and either TMZ or erlotinib. Median survival times were 13.4, 6.3, and 6.1 months, respectively. However, patient accrual was one-third of what was estimated ($N = 381$) to achieve statistical power. Rates of CNS progression at 6 months were 16, 29, and 20 % for WBRT/SRS, TMZ, and erlotinib, respectively. Compared with TMZ or erlotinib, WBRT/SRS was associated with a lower performance status deterioration rate; 52.5 versus 85.7 % for both TMZ and erlotinib ($p = 0.002$ and $p < 0.001$, respectively). No differences were seen in use of corticosteroids or cause of death between treatments.

3.3.2 Retrospective Studies and Case Reports/Case Series

Available retrospective studies and case reports/series of erlotinib in the treatment of brain metastases in patients with NSCLC are summarized in Table 5.

3.4 Afatinib

Very limited data are available regarding the use of afatinib in brain metastases. Recently, outcomes of patients treated with afatinib for NSCLC via a compassionate use program were published. One patient consented to pharmacokinetic analysis of blood and CSF. Plasma and CSF concentrations were drawn 3 h after oral administration of a 50 mg dose. The plasma concentration of afatinib was 66.7 ng/mL BIBW 2992 (afatinib) base and the CSF concentration was 0.464 ng/mL BIBW 2992 (afatinib) free base. This equals a concentration of approximately 1 nMol afatinib in the CSF [33]. Within this program, 573 patients were treated with afatinib as third- or fourth-line therapy. Twenty-four percent of patients (11 of 46 patients with available data) had developed brain metastases or leptomeningeal disease after treatment with either erlotinib or gefitinib. Median time to treatment failure was 3.6 months in patients with CNS metastases which did not differ from matched patients with no CNS metastases (hazard ratio [HR] 1.16; 95 % CI 0.83–1.62, $p = 0.52$). Thirty-one patients with brain metastases were evaluated for efficacy. Forty-two percent of these patients achieved a partial remission along with 35 % reported to have a cerebral response.

4 Multi-Kinase Angiogenesis Inhibitors

Sorafenib, sunitinib, pazopanib, and vandetanib are inhibitors of multiple intracellular and cell surface kinases [34–37]. Sorafenib is approved for the treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma (RCC), and locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment [34]. Sunitinib is indicated for the treatment of advanced RCC, gastrointestinal stromal tumor (GIST), and progressive, well differentiated pancreatic neuroendocrine tumors [35]. Pazopanib is approved as a treatment for advanced soft tissue sarcoma in patients who have been administered prior chemotherapy, and for advanced RCC [36]. Vandetanib is indicated for the treatment of patients with symptomatic or progressive medullary thyroid cancer with unresectable locally advanced or metastatic disease [37]. Kim and colleagues found the mean CSF penetration of intravenous sorafenib in non-human primates to be limited [38]. Dudek and colleagues found similar limited CNS penetration results in a mouse model for both sorafenib and sunitinib [39].

4.1 Sorafenib and Sunitinib

Because the original phase III trials that led to sorafenib and sunitinib approval did not enroll patients with brain metastases, expanded access programs that allowed such patients were conducted with each agent [40, 41]. The Advanced Renal Cell Carcinoma Sorafenib (ARCCS) program was a nonrandomized, open-label expanded access program conducted at 327 centers in the US and Canada [41]. Patients were administered sorafenib 400 mg twice daily on a continuous basis. A total of 2504 patients received at least one dose of sorafenib and were included in the efficacy and safety analyses. The median duration of sorafenib therapy among evaluable patients was 12 weeks (range <1–81 weeks) with a median average daily dose of 758 mg. With regard to safety concerns, the most common adverse effects that resulted in a sorafenib dose reduction or interruption included hand-foot skin reactions, rash, gastrointestinal events, and hypertension. A total of 189 subjects died during therapy; the highest incidence of death (17 %) occurred among the subgroup of patients with brain metastases ($n = 70$). The best response rates for those evaluable patients in the brain metastases subgroup ($n = 50$) were a partial response ($n = 2$; 4 %), stable disease for at least 8 weeks ($n = 34$; 68 %), and progressive

Table 5 Erlotinib case reports/case series

References	Prior treatments (total no. of patients)	Tolerability	Outcome
Lukas et al. [88]	Radiation therapy ($N = 10$, some of whom received TMZ)	Not reported	Results not described by treatment group Median TTP for CNS: 14 weeks, as assessed by MRI Median TTP for systemic disease: 7.5 weeks Median OS: 28 weeks
Song and Zhang [89]	Radiotherapy ($N = 103$, 47 received erlotinib, 56 received gefitinib)	Grade 3–4 toxicity in 9 patients	Results not described by treatment group PR in 12 patients, SD in 43 patients, PD in 48 patients, as assessed by MRI
Gerber et al. [90]	EGFR-TKI-naïve ($N = 110$)	Not reported	Median OS: erlotinib 26 months, WBRT 35 months ($p = 0.62$ vs erlotinib), SRS 64 months ($p = 0.006$ vs erlotinib) The percentage of patients with brain as first site of progression was lowest with WBRT (24 %) vs erlotinib (59 %) and SRS (71 %), $p = 0.004$
Lai et al. [91]	Gemcitabine/carboplatin, docetaxel/WBRT ($N = 1$)	Grade 1 rash	Resolution of neurologic symptoms Intracranial CR as assessed by MRI at 6 weeks after initiation of erlotinib
Fekrazad et al. [92]	WBRT ($N = 1$, symptomatic)	Minimal rash	Resolution of neurologic symptoms Intracranial CR as assessed by MRI
Popat et al. [93]	WBRT ($N = 1$)	Well tolerated	Reduction in lesion size (from 10.3 to 6.8 mm), as assessed by CT, with progression of extracranial disease
Gridelli et al. [94]	Cisplatin/gemcitabine/vinorelbine; carboplatin/paclitaxel; gefitinib ($N = 3$, 2 of whom had brain metastases)	Grade 1 skin toxicity	PR in 2 patients with brain metastases Improvement neurologic and systemic symptoms in all patients
Gounant et al. [95]	WBRT/gefitinib/pemetrexed	Not reported	Intracranial response, as assessed by CT Death due to extracranial progression
Pan et al. [96]	None ($N = 1$, who had WBRT with erlotinib)	Grade 3 acneiform rash	Response in intracranial disease as assessed by MRI
Altavilla et al. [97]	WBRT/gemcitabine/carboplatin ($N = 1$, symptomatic)	Grade 1 rash	Resolution of neurologic symptoms within 2 weeks of initiation; CR in brain, as assessed by MRI
von Pawel et al. [98]	Cisplatin/gemcitabine; WBRT/docetaxel/carboplatin ($N = 2$)	Mild to moderate rash; grade 1 elevated liver transaminases	Intracranial response, as assessed by MRI, in 1 patient; death due to extracranial progression Near intracranial CR, as assessed by MRI, in 1 patient; death due to extracranial progression
Benedetti et al. [99]	Cisplatin/etoposide; cisplatin/fotemustine/WBRT ($N = 2$)	Mild rash	Disappearance of intracranial lesions at 6 months, as assessed by CT, in 1 patient; death due to relapse and progression Intracranial CR, as assessed by CT, in 1 patient; duration of response at least 24 months
Katayama et al. [100]	Gefitinib ($N = 7$, symptomatic)	Rash, diarrhea	Improvement in neurologic symptoms in 5 patients, progression in 2 Survival 15–530 days from start of erlotinib
Hata et al. [101]	WBRT/gefitinib ($N = 1$, symptomatic)	Grade 1 rash	Improvement in symptoms and MRI findings
Ohara et al. [102]	Multiple courses of chemotherapy ($N = 1$, symptomatic)	Grade 1 rash	Resolution of symptoms within 2 weeks of treatment. Improvement in intracranial disease, as assessed by MRI

Table 5 continued

References	Prior treatments (total no. of patients)	Tolerability	Outcome
Weber et al. [103]	None ($N = 1$)	Grade 4 rash	Near CR of intracranial disease, as assessed by MRI, at 3 weeks of treatment. Duration of response 10.5 months
de Lima Araújo et al. [104]	($N = 1$, symptomatic)	Not reported	Progressive improvement in neurologic symptoms and reduction in intracranial disease as assessed by MRI
Zhang et al. [105]	Pemetrexed/cisplatin ($N = 9$)	Grade 1/2 rash; Grade 2 oral mucositis; Grade 2 diarrhea	Intracranial PR in 7 patients, SD in1 patient, PD in 1 patient Median PFS: 179 days Median OS: 197.4 days
Ohara et al. [106]	Gefitinib/carboplatin/pemetrexed/gemcitabine/WBRT ($N = 1$, symptomatic)	Not reported	Neurologic improvement with disappearance of intracranial disease, as assessed by MRI. Subsequent clinical and MRI improvement in carcinomatous meningitis. Death due to extracranial disease progression

CR complete response, *CT* computed tomography, *EGFR* epidermal growth factor receptor, *MRI* magnetic resonance imaging, *OS* overall survival, *PD* progressive disease, *PFS* progression-free survival, *PR* partial response, *SD* stable disease, *TKI* tyrosine kinase inhibitor, *TMZ* temozolomide, *TTP* time to progression, *WBRT* whole-brain radiation therapy

disease ($n = 14$, 28 %). No patients with brain metastases experienced a complete response.

Gore and colleagues published results from the sunitinib expanded access program in 2009 [40]. This program enrolled patients with metastatic RCC from 246 sites in 52 countries worldwide. Sunitinib was administered as a 50-mg dose once daily for 4 weeks, followed by 2 weeks off therapy (i.e., a 6-week treatment cycle). Sunitinib dose reductions to 37.5 mg or 25 mg once daily could occur based upon individual patient tolerability. As with the ARCCS program, the primary objective of the sunitinib program was to provide patients who were not eligible for sunitinib therapy in clinical trials with access to the drug. Secondary objectives included efficacy and safety assessments. A total of 4564 patients were enrolled with 4371 patients comprising the modified intention-to-treat population. The median follow-up was 11.6 months (range <1–28 months) and the median number of treatment cycles was five (range 1–25). In the modified intention-to-treat population, 1446 patients (33 %) experienced a dose reduction in sunitinib from 50 mg to 37.5 mg once daily. The dosage of sunitinib was reduced to 25 mg once daily in 586 patients. The most commonly reported treatment-related adverse events were diarrhea and fatigue. For the subgroup of evaluable patients with brain metastases ($n = 213$), an objective tumor response was observed in 26 patients (12 %). In addition, one patient (<1 %) had a complete response, 25 patients (12 %) were partial responders, 111 patients (52 %) experienced stable disease for ≥3 months, and 76 patients (36 %) had progressive disease or stable disease for <3 months. For the overall population ($N = 4349$), the median PFS was 10.9 months (95 % CI 5.2–6.1) with a median overall survival of 18.4 months (95 % CI 17.4–19.2). Median PFS for the evaluable brain metastases subgroup ($n = 320$) was 5.6 months (95 % CI 5.2–6.1) with a median overall survival of 9.2 months (95 % CI 7.8–10.9).

The efficacy and safety of sunitinib in patients with NSCLC and irradiated brain metastases (WBRT 2 weeks or more before study entry) were evaluated in a phase II, open-label, single-arm study [42]. The primary endpoint of the study was PFS. The study had multiple secondary endpoints including overall and intracranial time to progression, objective response rate, overall survival, and safety, among others. Sixty-four patients were enrolled in this study and were administered sunitinib 37.5 mg once daily in 4-week cycles for 13 total cycles or until withdrawal from the study. A reduction in sunitinib dose to 25 mg daily, or increase to 50 mg daily, was allowed based upon individual patient tolerability. The median number of sunitinib cycles administered was two (range 1–13) with a median sunitinib dose of 37.5 mg (range 27–40 mg). Results revealed a median PFS among evaluable patients of 9.4 weeks (95 % CI 7.5–13.1), median time to progression

of 15.1 weeks (95 % CI 8.4–15.8), median overall survival of 25.1 weeks (95 % CI 13.4–35.5), and an objective response rate of 1.6 % (95 % CI 0.0–8.8). With regard to intracranial antitumor activity, the median time to progression was 15.4 weeks (95 % CI 12.1–24.8). The median intracranial time to progression was 15.4 weeks. Overall, sunitinib was well tolerated with the most common treatment-emergent adverse events reported as fatigue (38 %) and decreased appetite and constipation (25 % for both). No cases of intracerebral hemorrhage were noted.

Chevreau and colleagues conducted a prospective, placebo-controlled, phase II study that evaluated the efficacy and safety of sunitinib therapy in 17 patients with RCC and untreated brain metastases [43]. Patients were asymptomatic, with or without steroids. Sunitinib was administered via a standard cycling dosage regimen of 50 mg once daily for 4 weeks followed by 2 weeks off; dosage reductions to 37.5 or 25 mg daily were allowed based upon individual patient tolerability. The primary endpoint of the study was the objective response rate after two cycles of treatment; there were multiple efficacy and safety secondary endpoints. Results revealed no objective responses in brain metastases among enrolled patients, as assessed by MRI. Five patients (31 %) experienced a stabilization of intracranial disease. The median time to progression was 2.3 months (95 % CI 1.2–5.4) and median overall survival was 6.3 months (95 % CI 2.1–7.9). With regard to safety, 14 patients experienced a total of 32 adverse events. Several

Table 6 Sorafenib and sunitinib case reports/case series

References	Indication (total no. of patients)	Tolerability	Outcome
Sorafenib			
Walid and Johnston [107]	RCC with brain metastases ($N = 1$)	Not reported	Sorafenib therapy was part of a successful multimodal treatment approach in this patient including surgery and radiation. At the last MRI follow-up, 4 years after his surgery, the patient was stable without recurrent or residual tumor
Valcamonico et al. [108]	RCC with brain metastases ($N = 1$)	Grade 2 alopecia, grade 1 rash, grade 3 hand-foot syndrome, anorexia, fatigue	Almost CR, as assessed by MRI, after 9 months
Ranze et al. [109]	RCC with brain metastases ($N = 1$)	Not reported	Reduction in intracranial disease as assessed by MRI. Duration of PR at least 74 days
Shen et al. [110]	Follicular thyroid carcinoma with brain metastases ($N = 1$, symptomatic)	Alopecia	Improvement in symptoms within 4 weeks. Duration of PR, as assessed by MRI, at least 14 months
Krajewska et al. [111]	Advanced papillary thyroid carcinoma with brain metastases ($N = 1$)	No adverse events	SD after 16 weeks
Sunitinib			
Takeuchi et al. [112]	GIST with brain metastases ($N = 1$, symptomatic)	Fatigue, epistaxis, thrombocytopenia	Decreased intracranial disease, as assessed by MRI. Improvement in symptoms
Thibault et al. [113]	RCC with brain metastases ($N = 1$)	Not reported	Regression of cerebellar lesions, as assessed by MRI, after 6 weeks. Frontal lesion remained stable
Lim et al. [114]	RCC with brain metastases ($N = 6$)	Not reported	Near complete intracranial response in 3 patients, PR in 1 patient, progression in 2 patients
Helgason et al. [115]	RCC with brain metastases ($N = 1$)	Grade 2 rash, itch, fatigue, stomatitis	SD and subsequent progression
Kusuda et al. [116]	RCC with brain metastases ($N = 5$)	Grade 3 thrombocytopenia, hypertension, fatigue, hypothyroidism	Intracranial CR in 2 patients, PR in 1 patient, SD in 2 patients
Zeng et al. [117]	RCC with brain metastases ($N = 1$, symptomatic)	Grade 1 hypertension, Grade 1–2 neutropenia	Complete resolution of symptoms within 1 week. Intracranial CR lasting at least 10 months
Koutras et al. [118]	RCC with brain metastases ($N = 1$)	Grade 1 hypertension, anemia hand-foot syndrome	Considerable shrinkage of intracranial disease, as assessed by CT
Medioni et al. [119]	RCC with brain metastases ($N = 1$)	Not reported	Intracranial CR, as assessed by CT, lasting at least 21 months

CR complete response, *CT* computed tomography, *GIST* gastrointestinal stromal tumor, *MRI* magnetic resonance imaging, *PR* partial response, *RCC* renal cell carcinoma, *SD* stable disease

neurological adverse events were reported; however, none were determined to be directly related to sunitinib therapy. No cases of intracerebral hemorrhage were seen.

Beyond the expanded access programs and limited clinical trial data noted in this section, there are several case reports and case series involving sorafenib and sunitinib in the treatment of brain metastases. These are summarized in Table 6.

4.2 Pazopanib

There is a single published case report of prolonged survival in a patient with papillary RCC and brain metastases [44]. In this report, a 74-year-old male with a history of RCC presented with cough and fever. Subsequent scans revealed extensive cervical and mediastinal adenopathy, and more than 20 brain metastases were identified in the cerebrum and cerebellum on MRI. After administration of several therapies including WBRT, sunitinib, everolimus, and intensity-modulated radiation therapy, pazopanib 800 mg once daily was initiated. Pazopanib therapy was initially associated with extracranial improvement and stable brain metastases for a period of 6 months; however, disease progression eventually occurred, pazopanib was discontinued, and sorafenib was initiated. Progression continued despite sorafenib therapy and pazopanib was reinitiated (at a higher dose of 1 g daily with prednisone 20 mg daily). The higher pazopanib dose was associated with regression of cervical adenopathy and brain metastases with improvement in edema. A dose reduction of pazopanib to the approved dose of 800 mg/day was required 1 month later due to high-grade palmar-plantar erythrodysesthesia. Eight months after pazopanib administration was reinitiated, the patient's performance status worsened, pazopanib was discontinued, and the patient died.

4.3 Vandetanib

There is limited data available on vandetanib in the treatment of brain metastases. Vandetanib has been studied in primary brain tumors. In a phase I trial of newly diagnosed diffuse intrinsic pontine glioma, researchers performed pharmacokinetic analysis of CSF in pediatric patients receiving vandentanib in combination with dasatinib [45]. Serial plasma and CSF samples were obtained from two patients treated with vandetanib at a dose of 65 mg/m^2. There was modest CSF exposure to vandetanib with a CSF-to-plasma ratio of area under the concentration-time curve (AUC) 0–24 h reported in the two patients as 0.012 and 0.024. The level of vandetanib in the CSF could be restricted by the influence of efflux transporters P-glycoprotein and breast cancer resistance protein (Bcrp1) on transportation of vandetanib across the BBB [46].

In a phase II non-inferiority trial, vandetanib was given alone or with chemotherapy for untreated NSCLC. There were approximately 12 % of patients with stable brain metastases [47]. Vandetanib was given at the established dose of 300 mg per day, and the primary outcome of the trial was PFS. Vandetanib combined with chemotherapy was not inferior to chemotherapy alone. The risk of progression was reduced in the vandetanib and chemotherapy group (HR 0.76, one-sided $p = 0.098$) and median PFS was 24 weeks in the vandetanib and chemotherapy group versus 23 weeks in chemotherapy group. There was no subanalysis for the patients with brain metastases in this study.

5 ALK/c-MET Inhibitor

Crizotinib is an inhibitor of various receptor kinases including anaplastic lymphoma kinase (ALK) and is indicated for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive [48]. Penetration of crizotinib across the BBB is poor [49]. The CSF-to-plasma ratio of crizotinib is only 0.0026, which suggests that the brain would be an area susceptible to disease progression in patients receiving crizotinib therapy.

Although the CNS penetration of crizotinib is reportedly low, there are several published case reports of use of this agent in patients with brain metastases from lung cancer, as shown in Table 7. In these cases, crizotinib was generally a third- or fourth-line treatment option after prior courses of other chemotherapeutic agents and/or radiation. Patient outcomes in these case reports were variable. Some patients experienced a positive response over an extended duration [50, 51] or even a complete resolution of brain metastases [52]. Others underwent continued progression of brain metastases despite therapy [53]. Doses above the approved dose have been administered in this setting; however, a consistently favorable response with high doses of crizotinib has not been reported [50, 54].

5.1 ALK/IGF-1 Inhibitor

Ceritinib is an inhibitor of ALK and insulin-like growth factor-1 (IGF-1). It is indicated for the treatment of patients with metastatic NSCLC whose tumors are ALK positive and have progressed on or who are intolerant to crizotinib. Ceritinib demonstrated a brain-to-blood exposure (AUC_{iinf}) ratio of approximately 15 % in rats [55].

Shaw reported the effects of ceritinib given orally for patients with NSCLC and other advanced cancers harboring genetic alterations in ALK during a phase I, dose-escalation trial ($n = 59$) with expansion ($n = 71$) and extended expansion phases ($n = 225$) [56]. Sixty-four patients in the dose escalation or expansion phase had brain

Table 7 Crizotinib case reports

References	Total no. of patients	Tolerability	Outcome
Kim et al. [54]	$N = 1$	Bradycardia following dose escalation	Improvement in intracranial disease, lasting 8 months
Kinoshita et al. [51]	$N = 1$	Not reported	Slight reduction in intracranial disease, as assessed by CT, at 17 weeks, and lasting at least 8 months
Maillet et al. [53]	$N = 2$	Not reported	Progression of intracranial disease
Kaneda et al. [52]	$N = 1$	No clinically relevant adverse effects	Intracranial CR, as assessed by CT, at 11 months
Falk et al. [120]	$N = 1$	Not reported	PFS 12 months as assessed by MRI, with miliary brain metastases
Gandhi et al. [50]	$N = 1$	Not reported	PR, as assessed by MRI

CR complete response, *CT* computed tomography, *MRI* magnetic resonance imaging, *PFS* progression-free survival, *PR* partial response

metastases. Dosing of ceritinib was initiated at 50 mg per day in 21-day cycles and increased to an established dose of 750 mg daily based on patient tolerability and response. Maximum tolerated dose was the primary outcome of the trial; secondary outcomes included side effect profile, pharmacokinetic and pharmacodynamic profiles, and tumor response. Overall response rate (for all patients in phase I or expansion phase) was 58 % and PFS was 7 months. In the extended expansion, 124 patients had NSCLC with brain metastases. A sub-analysis was conducted to assess efficacy and safety in these patients with brain metastasis [57]. In this sub-analysis, ORR was 54 %. PFS was 6.9 months and median duration of response was 7 months in patients with brain metastasis. The most common adverse events in patients with brain metastasis versus all patients in the expansion trial were nausea (82.3 vs 77 %), diarrhea (79 vs 84 %), and vomiting (62.9 vs 57 %) with no grade 4 events noted in the brain metastasis group.

5.2 ALK Resistance to Crizotinib

Alectinib is a next generation oral ALK inhibitor with high CNS exposure in clinical models. Currently alectinib has breakthrough therapy designation by the FDA and is undergoing priority review designation for patients with NSCLC who have progressed on or are intolerant to crizotinib. Two phase II studies have been performed that subjects having intolerance or progression on crizotinib and/or ceritinib. The two studies included a total of 50 subjects having CNS disease with a response rate for brain metastasis of 57–69 % [58, 59]. This is encouraging data and a decision on approval by the FDA should be available in early 2016.

6 Discussion/Conclusion

Longer survival of cancer patients combined with the anatomical specialization of the BBB allows the brain and CNS to harbor metastases less affected by systemic chemotherapy. Although brain metastases result in a disrupted BBB that is enhanced in contrast imaging studies, the response to systemic therapies for CNS metastases is lower than for extracranial disease. High response rates of CNS disease are the exception, and for many chemotherapy agents, response rates are unknown.

Formal pharmacokinetic parameters for brain drug delivery are permeability clearance, extent of equilibrium across the BBB, and intra-brain distribution volume, which are rarely obtained. Relevant parameters for drug delivery to the brain are rate and penetration, which would be expected to be improved with the daily administration and the smaller size of oral targeted agents. The ultimate goal in learning about CNS penetration is activity in CNS metastases. Clinical trials frequently exclude patients with known brain metastases. Further, in reports that do include patients with brain metastases, important clinical parameters such as type of imaging (MRI preferred), specification of outcomes in intracranial versus extracranial disease, and neurologic status are not always provided. Recent local therapy (i.e., SRS) might impact imaging for assessment of response to systemic agents, and radiographic assessment of response to angiogenesis inhibitors might be complicated by an effect of these agents on tumor vasculature. Thus, it is difficult to document CNS activity.

Based on the data reviewed, several drugs (e.g., erlotinib, sunitinib) appear to have some clinical activity in CNS disease. But if survival is limited by extracranial progression, such as in NSCLC, any CNS benefit may be minimized. It should also be noted that CSF concentration may not accurately reflect brain concentration. Erlotinib CSF concentration was reported to have a good correlation with serum concentration, consistent with some evidence of clinical activity in the CNS. In contrast, case reports suggest that crizotinib may have CNS activity, but the CSF/plasma ratio is reportedly low.

More effort should be made to allow patients with brain metastases in trials of oral targeted agents for systemic disease. Investigators should also be encouraged to include

documentation of imaging method, and neurologic status, as well as relevant data for extracranial outcomes when describing CNS outcomes in patients treated with these agents.

Compliance with Ethical Standards

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Conflict of interest MPG, SMW, JMS, CLO, KEL, LRB, and JLV declared no conflict of interest.

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