Review Article

Anti-angiogenetic therapies for central nervous system metastases from non-small cell lung cancer

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Contributions: (I) Conception and design: None; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Central nervous system (CNS) metastases are common in patients with advanced non-small cell lung cancer (NSCLC), occurring in 24% to 44% of patients in the course of their disease and confer significant morbidity and mortality. Systemic therapies have been deemed ineffective in brain metastases (BM) under the hypothesis that the blood-brain barrier (BBB) limits their delivery to the brain. Angiogenesis, which is mainly mediated by vascular endothelial growth factor (VEGF) pathway, is crucial for tumor survival, growth and invasion both in primary and metastatic brain lesions. Two major categories of agents have been developed to target this pathway: antibody-based agents and VEGF receptor tyrosine kinase inhibitors (TKIs). Clinical benefits have been shown with anti-angiogenetic therapies in the treatment of metastatic NSCLC. However, patients with CNS metastases were often excluded from trials with these agents, due to concerns about a potentially greater risk of cerebral haemorrhage and thromboembolic disease. Therefore, the overall efficacy and safety of angiogenetic agents in patients with BM from NSCLC are yet to be clarified. This paper aims to review available data about the efficacy and safety of anti-angiogenetic therapies for CNS metastases in NSCLC patients.

Keywords: Central nervous system metastases (CNS metastases); non-small cell lung cancer (NSCLC); angiogenesis; anti-angiogenetic therapy

Submitted Jul 22, 2016. Accepted for publication Aug 26, 2016.
doi: 10.21037/tlcr.2016.09.03
View this article at: http://dx.doi.org/10.21037/tlcr.2016.09.03

Introduction

Lung cancer is the leading cause of cancer-related deaths in worldwide (1). The majority of patients diagnosed with non-small cell lung cancer (NSCLC) have locally advanced or metastatic disease at baseline with a 5-year survival <5% (2). In the last years, advances in the understanding of NSCLC biology have identified two molecularly defined subset of patients: those with epidermal growth factor receptor (EGFR) activating mutations treated with EGFR tyrosine kinase inhibitors (TKIs) and those with echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) translocations responding to crizotinib (3,4). The development of brain metastases (BM) is a common complication in lung cancer and affects largely morbidity and mortality of NSCLC patients, determining a poor clinical outcome despite active treatment. In patients with *EGFR* mutations, treatment with an EGFR TKIs might result in an intracranial objective response approaching 80% and encouraging overall survival (OS) (5). Unfortunately, in patients with ALK translocation, crizotinib does not appear to work well on intracranial disease despite an important effect on extracranial disease (6). BM are detected in 10–20% of NSCLC patients at diagnosis and occur in about 40% of patients during the course of the disease (7). Common symptoms of BM include headache, localizing weakness, seizures, altered mental status and ataxia. Whole brain

radiotherapy (WBRT) and steroids are the standard treatment for most of the patients with a reduction in symptoms in 75–80% of the cases (8). Local approaches, as surgery and stereotactic radiosurgery (SRS), are indicated in solitary or oligometastatic disease. The median OS of untreated patients with BM is 1–2 months (4,8). However, earlier diagnosis, more sensitive radiological imaging and therapeutic options (SRS, surgery and WBRT) can prolong survival to 4–6 months. The role of chemotherapy in the treatment of BM remains unclear. Some intracranial responses have been reported with vinorelbine plus gemcitabine/carboplatin (9) and cisplatin/carboplatin plus gemcitabine (10,11). Indeed, the role of the blood-brain barrier (BBB) in reducing drug access to BM has always been a concern. Tumor angiogenesis plays a central role in cancer development, invasion, progression and metastatic dissemination (12). The inhibition of tumor-related angiogenesis is without any doubt an attractive target for anticancer therapy. However, a frequent complication of this therapy is hemorrhage at tumor site or at distant site. It is known that central nervous system (CNS) bleeding in patients with BM is an important complication. The rate of the CNS bleeding is different across the type of tumor: 1–7% in lung cancer and 70% in renal cancer (13). On the basis of these observations patients with BM are frequently not candidate to clinical studies with anti-vascular endothelial growth factor (VEGF) therapy. This review will focus on the role of anti-angiogenetic drugs in the treatment of BM in patients with NCSLC, in particular, we will discuss monoclonal antibodies that block VEGF-VEGF receptor (VEGFR) binding and small molecule TKIs, that inhibit the downstream VEGFR mediated signalling.

Rational for targeting angiogenetic pathways in CNS metastases from NSCLC

Irrespectively of the origin and the site of metastases, growth and survival of tumor cells depend on the establishment of an adequate blood supply (14,15), mainly supported by neo-angiogenesis. Angiogenesis is regulated by several pro- and anti-angiogenetic factors. Among pro-angiogenetic factors, VEGF is the most extensively studied and stimulates angiogenesis primarily through activation of VEGFR-2 (16), which are both commonly expressed in NSCLC (17).

Immunohistochemical and morphometric analyses in human lung cancer BM demonstrated that the density of blood vessels within BM is lower than the adjacent tumor-free brain parenchyma. However, BM blood vessels are dilated and contain many dividing endothelial cells (15).

Real-time imaging with multiphoton laser scanning microscopy in a BM mouse model, reveals that early angiogenesis is a mandatory step for successful macrometastases formation (18).

According to the diffusion coefficient of oxygen within tissue of about 150 μm, Fidler *et al*. demonstrated that tumor cells within autochthonous and experimentally induced BM from lung cancer located less than 100 μm from a blood vessel are viable, whereas more distant tumor cells undergo programmed cell death (15). The same authors also provided support to the role of VEGF pathway in the growth of BM by transfecting human lung cancer cells with an antisense-VEGF165 gene, which decreased the frequency of BM in nude mice. Conversely, transfection of human lung cancer cells with sense-VEGF-121 or sense-VEGF165 either increase or inhibited the formation of BM. These data suggest that VEGF expression is necessary, but not sufficient for the development of BM and that VEGF represent one among other targets for therapeutic intervention.

The primary goal for using anti-angiogenetic therapies is to block the development of malignant neovasculature, in order to reduce oxygen availability in the tumor and to decrease its growth.

Using a mouse model where single metastasizing cancer cells were tracked by intravital microscopy, it was demonstrated that chronic anti-angiogenetic treatment with bevacizumab can prevent an early angiogenic switch that is mandatory for brain outgrowth of non-squamous NSCLC cells (18). In a rat model of human lung cancer BM it was also demonstrated that, compared to controls, bevacizumab slowed the rate of tumor growth (P=0.003), measured through magnetic resonance imaging biomarkers (19).

Moreover, treatment with bevacizumab inhibited BM formation in a mouse model of haematogenous non-squamous NSCLC metastases. In this study, a total of 112 BM events (defined as single cells, micrometastases and macrometastases), were observed in the eight control animals, while only two brain metastatic events occurred in the ten bevacizumab-treated mice (P<0.001) (20).

A secondary goal for using anti-angiogenetic therapies in BM is to reduce edema, which impacts patients quality of life (QoL) inducing neurological deficits and headache. There is clinical evidence in glioblastoma that bevacizumab is able to induce significant antiedemigenous effect by restoring the integrity of the BBB (21). Tumor neoangiogenesis in BM, in fact, leads to the development of blood vessel that lack

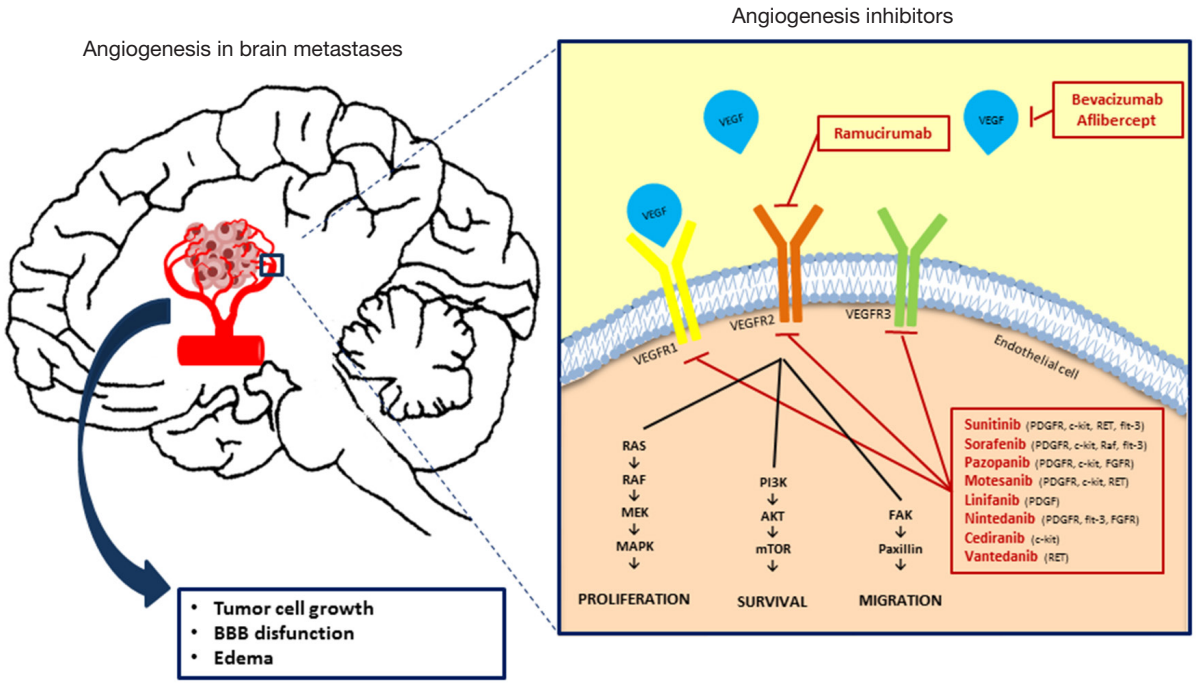

Figure 1 Angiogenesis in brain metastases and potential role of angiogenesis inhibitors as treatment for central nervous system metastases from non-small cell lung cancer. BBB, blood-brain barrier; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; PDGFR, platelet derived growth factor receptor; FLT3, FMS-like tyrosine kinase 3.

the physiological function of the BBB, the structure that regulates the flow of ions, nutrients, drugs and cells into the brain (15). The BBB is intact in and around experimental BM derived from human lung cancer smaller than 0.25 mm, while it is leaky in larger metastases (15).

In a rat model of lung cancer BM bevacizumab partially restored the normal low permeability characteristics of the BBB, measured through magnetic resonance imaging before and one day after treatment (19), preventing edema development.

A third rationale for the use of bevacizumab in BM is its role in vascular normalization. It has been suggested that blocking VEGF signalling means to normalize tumor blood vessels, which may result in a more efficient chemotherapy delivery and in a higher efficacy of chemo- and radiotherapy (22).

A final rational for the use of anti-VEGF therapies in BM is that, contrarily to most chemotherapeutic agents, anti-angiogenetic therapies exert their activity by inhibiting the endothelial cell, which does not require to cross the BBB.

All these above mentioned data (*Figure 1*) suggest that VEGF could represent an important target in the treatment of BM from NSCLC (23).

Efficacy and safety of antibody targeting VEGF for CNS metastases from NSCLC

Bevacizumab

Bevacizumab is a recombinant, humanized monoclonal antibody, that selectively binds VEGF and prevents interaction with its receptor. It is approved for the first-line treatment of advanced, metastatic or recurrent NSCLC with non-squamous cell histology, in combination with platinum-based chemotherapy (24,25). Bevacizumab significantly improved OS and progression free survival (PFS) when combined to first-line carboplatin and paclitaxel for treatment of NSCLC compared with chemotherapy alone in the Eastern Cooperative Oncology Group (ECOG) phase II trial E4599 (25) and prolonged PFS in combination to first-line cisplatin and gemcitabine in the phase III AVAiL study (26).

Patients with BM were initially excluded from trials with bevacizumab due to concerns about a potentially greater risk of cerebral haemorrhage, following a single case in 1997 of a patient with hepatocellular carcinoma, who experienced a fatal cerebral haemorrhage from a previously

undiagnosticated brain metastasis, in a phase I study of bevacizumab (27).

More recently, several clinical trials have been conducted to investigate the safety and efficacy of bevacizumab in advanced NSCLC patients, including those with BM. Bevacizumab safety was first investigated in patients with asymptomatic treated BM. Five prospective trials, PASSPORT, ATLAS, BeTa, ERACLE and PRONOUNCE trials included patients with treated BM and recorded a low rate of CNS haemorrhage (28-32).

PASSPORT (28) is an open-label single arm phase II trial of bevacizumab in combination with first- or second-line therapy in patients with treated BM from non-squamous NSCLC. First- and second-line therapy consisted of either chemotherapy or erlotinib with bevacizumab, according to institutional standards. Patients with BM were allowed to enter the trial after previous treatment with whole CNS radiation therapy, radiosurgery and/or neurosurgery. Median treatment duration was 85 (range, 1–379) days. Among the 106 safety-evaluable patients no grade ≥2 CNS haemorrhage were reported, demonstrating a minimal risk of intracerebral haemorrhage after the use of bevacizumab in this setting of patients. Twenty-six patients (24.5%) discontinued study treatment as a result of an adverse event, and 37 (34.9%) discontinued due to disease progression.

In the phase III ATLAS trial (29) 1,145 patients with untreated stage IIIB, stage IV or recurrent NSCLC underwent four cycles of chemotherapy plus bevacizumab and 743 of these patients, without disease progression after induction, were subsequently randomized (1:1 ratio) to receive bevacizumab in combination with erlotinib or placebo. In this trial patients with BM were eligible when treated and not requiring treatment with steroids. Among 743 patients included in the final analyses, 29 presented BM at baseline. The addition of erlotinib to bevacizumab significantly improved PFS [median PFS: 3.7 *vs.* 4.8 months; hazard ratio (HR) =0.71; 95% CI: 0.58–0.86], but not OS (median OS: 13.3 *vs.* 14.4 months; HR =0.92; 95% CI: 0.70–1.21).

A pooled analyses (33) of the 131 patients with treated BM receiving bevacizumab in either PASSPORT (28) or ATLAS (29) reported no symptomatic grade >2 brain haemorrhage during the main treatment phases of study. In the ATLAS trial one grade 2 CNS haemorrhage occurred during treatment after CNS progression (29).

The double-blind, placebo controlled, phase III BeTa trial (30) aimed to assess the efficacy and safety of bevacizumab in combination to erlotinib versus erlotinib alone in advanced NSCLC after failure of standard first-line chemotherapy. In this study, patients with a history of BM, who were treated with a minimum of WBRT and with no ongoing steroids requirement were included. Among the 319 patients treated with bevacizumab 37 had treated BM at baseline. In patients treated with bevacizumab and erlotinib one grade 3–4 CNS haemorrhage was reported (<1%). OS did not differ between the patients in the bevacizumab group and controls (median OS: 9.2 *vs.* 9.3 months, HR =0.97; 95% CI: 0.80–1.18; P=0.7583). No specific data about the outcome of patients with CNS metastases were reported.

Both ERACLE and PRONOUNCE randomized phase III trials aimed to compare cisplatin and pemetrexed followed by maintenance pemetrexed and carboplatin with paclitaxel and bevacizumab followed by maintenance bevacizumab, standard first-line treatment for advanced nonsquamous NSCLC. Primary endopoint was the difference in QoL between the two treatment arms after 12 weeks of maintenance in the ERACLE trial and PFS without grade 4 toxicity in the PRONOUNCE trial. In both trial stable, previously treated CNS metastases were allowed. In the ERACLE trial six patients had BM at baseline (four in the cisplatin and pemetrexed arm and two in the carboplatin, paclitaxel and bevacizumab arm), none intracranial haemorrhage occurred and no statistically significant difference in the QoL between the two regimens was described in the entire population. Among the 179 patients treated with bevacizumab in the PRONOUNCE trial 32 (17.9%) had treated CNS metastases at baseline and none developed any grade intracranial bleeding. The primary end point was not reached.

Two large cohort studies focused on bevacizumab safety: SAiL (34) and ARIES (35).

SAiL was a phase IV trial (34), evaluating the safety of bevacizumab in 2,212 patients treated with bevacizumab in combination with first line standard chemotherapy for a maximum of six cycles, followed by bevacizumab alone until disease progression. Although evidence of BM was an exclusion criterion in SAiL, some patients with asymptomatic BM have been potentially included, since brain imaging was not mandated before enrolment. Among the 281 patients who were assessed as having BM during the course of the study, 5 (2%) reported CNS bleeding.

The ARIES trial (35) was conducted on 1,967 patients with NSCLC, treated with first-line chemotherapy in combination with bevacizumab. Eight percent of patients had BM at baseline and 3 patients (0.2%) had grade 3 to 5 CNS haemorrhage.

Besse *et al*. conducted a non-randomized, phase II trial to investigate bevacizumab-based regimens in both first and second line setting in patients with NSCLC and asymptomatic, untreated BM (BRAIN trial) (36). Sixty-seven patients were treated with first line bevacizumab in combination with carboplatin and paclitaxel and 24 patients received second line bevacizumab in combination with erlotinib. In the first-line cohort 6-month PFS was equal to 56.5%, with a median PFS of 6.7 months (95% CI: 5.7–7.1) and median OS was 16.0 months. Overall response rate (ORR) was 61.2% in intracranial lesions and 64.2% in extracranial lesions. In the second-line cohort (n=24), 6-month PFS was 57.2%, median PFS was 6.3 months (95% CI: 3.0–8.4), median OS was 12.0 months and ORR was 12.5%. In the ECOG 4599 phase III randomized controlled trial, which tested the same treatment scheme in patients without BM, median OS was 12.3 months and a median PFS was 6.2 months, compared to 16.0 and 6.7 months, respectively, in the BRAIN first-line cohort. The favourable outcomes in BRAIN compared to E4599, should be related to differences in baseline characteristics, including the better performance status of patients evaluated in BRAIN. The BRAIN trial registered a rate of CNS haemorrhage comparable to what observed in other studies: only one grade I intracranial haemorrhage occurred and resolved, without sequelae in the first-line arm. In the BRAIN trial patients were enrolled and treated before they became symptomatic and required steroids and this make this population in any case different from what observed in daily clinical practice.

Few data are available in terms of safety and efficacy of bevacizumab in patients with active (treatment naive, progressive or symptomatic) BM.

A small retrospective study evaluated the safety and efficacy of bevacizumab in six NSCLC patients with active (treatment naive or progressive) CNS metastases: bevacizumab was administered alone (n=1) or in combination with different cytotoxic chemotherapies (n=5). No grade ≥2 CNS haemorrhage occurred, neither in patients with a prior history of such haemorrhage. Best CNS response, was partial in two, stable disease in three, and progression in one patient. Improvement in symptoms and reduction in corticosteroid requirements was reported (37).

A small prospective study investigated the safety and efficacy of bevacizumab-based therapy in patients with symptomatic, clinical or radiographic progressive BM from NSCLC. None of the 13 patients enrolled in the study developed CNS haemorrhage. Median PFS was 9.1 months and median OS was 9.6 months. The authors also reported a considerable improvement in the QoL of patients with relief from neurological symptoms and reduction of dexamethasone administration (38).

Khasraw *et al*. conducted a retrospective analysis to investigate the association between treatment with bevacizumab and intracranial haemorrhage in various types of tumors. In the NSCLC population, the incidence rates of intracranial bleeding were 3.6% (28/789) in patients with BM treated without bevacizumab and 3.9% (3/77) in patients with BM treated with bevacizumab (39). Similarly, an evidence-based review on the risk of CNS haemorrhage in patients with BM from NSCLC concluded that there was no significantly increased risk of intracranial bleeding associated with anti-VEGF therapy (40).

Two other retrospective exploratory analyses of randomized controlled trials reported similar results, indicating that bevacizumab should be considered as a therapeutic opportunity, even in patients with active BM (33,41).

Nevertheless, several recent phase II and III trials (JO19907, JO25567 and BEYOND), with bevacizumab in advanced NSCLC, still excluded patients with BM (42-44).

Finally, bevacizumab, has been proposed in a retrospective study, as the treatment for radiation necrosis of BM post SRS, with the aim to reach a symptomatic relief, the reduction in steroid requirement and a radiographic response (decrease in enhancement and edema at magnetic resonance imaging scans) (45).

The international guidelines permit the use of bevacizumab in patients with advanced, metastatic or recurrent NSCLC with non-squamous histology and performance status 0–1, even in the presence of asymptomatic BM (2).

Table 1 summarises the results of the prospective trials evaluating the anti-VEGF antibody, in which patients with CNS metastases from NSCLC have been included.

Ramucirumab

Ramucirumab is a fully human IgG1 monoclonal antibody that targets the VEGFR-2 extracellular domain with high affinity, preventing binding of all VEGF ligands and receptor activation (49).

Currently, ramucirumab is approved for the second-line treatment of metastatic NSCLC in combination with docetaxel (50).

The phase III REVEL trial (46) randomized 1,253 patients with squamous or non-squamous NSCLC, who

Table 1 Antibody targeting vascular endothelial growth factor for the treatment of central nervous system metastases from non-small cell lung cancer: prospective trials

Study	Author, year	Type of study	Line of treatment	Anti-VEGF antibody schedule	Regimen	Pts treated with anti-VEGF antibody (N)	Pts with CNS mets (N) (%)	CNS metastases characteristics	Comments
Bevacizumab									
PASSPORT	Socinski *et al*. 2009 (28)	Open-label single-arm phase II trial	First and second line	15 mg/kg every 21 days until disease progression or unacceptable toxicity	I line: CBDCA doublets, CDDP doublets or Erl + Bev (n=76); II line: single agent chemotherapy or Erl + Bev (n=39)	115	115 (100.0)	Treated CNS mets at baseline were allowed. Previous treatment for CNS included either WBRT, radiosurgery or neurosurgery	Median number of Bev cycles: 5, median treatment duration: 85 days. CNS hemorrhage G ≥2: 0
ATLAS	Johnson *et al*. 2013 (29)	Randomized, placebo controlled phase IIIB trial	Maintenance after first line therapy	15 mg/kg every 21 days until disease progression or unacceptable toxicity	Bev + Erl (n=368) *vs*. Bev + placebo (n=367)	743	29 (3.9)	CNS mets were allowed at baseline if they had been treated and they did not require steroids	Median PFS: 3.7 *vs*. 4.8 mo (HR =0.71; 95% CI: 0.58–0.86, P<0.001); median OS: 13.3 *vs*. 14.4 mo (HR =0.92, 95% CI: 0.70–1.21, P=0.534); CNS hemorrhage G2: 1 (after disease progression)
BeTa	Herbst *et al*. 2011 (30)	Randomized placebo controlled phase III trial	Second line	15 mg/kg every 21 days until disease progression or unacceptable toxicity	Erl + Bev (n=319) *vs*. Erl + placebo (n=317)	319	37 (11.6)	CNS mets treated with at least WBRT and with no requirement of steroids were allowed	Median OS: 9.3 *vs*. 9.2 mo (HR =0.97, 95% CI: 0.80–1.18, P=0.7583); CNS hemorrhage G3–4: 1 (<1%) in the bevacizumab group versus 0 in the control group
ERACLE	Galetta *et al*. 2015 (31)	Randomized, phase III trial	First line	15 mg/kg every 21 days until progression or unacceptable toxicity	CDDP + Pem → Pem (n=60) *vs*. CBDCA + PTX + Bev → Bev (n=58)	58	2[§] (3.4)	CNS mets were allowed if they had been treated with radiotherapy	No statistically difference in QoL between the two regimens. Any grade CNS hemorrhage: 0
PRONOUNCE	Zinner *et al*. 2015 (32)	Randomized open-label phase III trial	First line	15 mg/kg every 21 days until progression or unacceptable toxicity	Pem + CBDCA → Pem (n=182) *vs*. CBDCA + PTX + Bev → Bev (n=179)	179	32 (17.9)	Stable, treated CNS mets were allowed	PFS without grade 4 toxicity was not statistically significant different in the two treatment arms (median: 3.91 *vs*. 2.86 mo, HR =0.85, 90% CI: 0.7–1.04; P=0.176); any grade CNS hemorrhage: 0
SAiL	Crinò *et al*. 2010 (34)	Phase IV trial	First line	7.5 or 15 mg/kg every 21 days	Bev + CBDCA doublets/CDDP doublets/taxane-containing regimens	2,212	281 (12.7)	CNS mets was an exclusion criterion, 281 pts developed CNS mets during treatment	CNS hemorrhage G3–5: 5 (<1%)

Table 1 *(continued)*

Table 1 *(continued)*

Study	Author, year	Type of study	Line of treatment	Anti-VEGF antibody schedule	Regimen	Pts treated with anti-VEGF antibody (N)	Pts with CNS mets (N) (%)	CNS metastases characteristics	Comments
ARIES	Lynch *et al*. 2014 (35)	Prospective cohort study	First line	At the discretion of the treating physician	Bev + CBDCA + PTX/ CDDP doublets/Gem/ Pem/Erl	1,697	150 (8.8)	Asymptomatic CNS mets at baseline were allowed	CNS hemorrhage grade 3–5: 3 (0.2%)
BRAIN	Besse *et al*. 2015 (36)	Prospective non-comparative phase 2 trial	First or second line	15 mg/kg every 21 days until disease progression or unacceptable toxicity	I line: Bev + CBDCA + PTX (n=67) or II line: Bev + Erl (n=24)	91	91 (100.0)	All pts had asyntomatic, untreated CNS mets at baseline	I line: 6-mo PFS rate: 56.5%; median PFS: 6.7 mo; median OS: 16.0 mo. G1 CNS hemorrhage: 1 pt (resolved without sequelae); II line: 6-mo PFS rate: 57.2%; median PFS: 6.3 mo; median OS: 12.0 mo
NR	Zustovich *et al*. 2014 (38)	Case series	First line	7.5 mg/kg every 21 days	CDDP + Gem + Bev	13	13 (100.0)	Symptomatic progressive CNS mets unsuitable for local therapy (radiosurgery, neurosurgery) at baseline	PFS: 9.1 (range, 0.9–39.2) mo, OS: 9.6 (range, 3–41.5) mo; any grade CNS haemorrhage: 0
Ramucirumab									
REVEL	Garon *et al*. 2014 (46)	Randomized double-blind placebo-controlled phase III trial	Second line	10 mg/kg every 21 days until disease progression or unacceptable toxicity	Docetaxel + Ram *vs*. docetaxel + placebo	628	NR	Stable, treated CNS mets were allowed. Previous treatment for CNS included either WBRT, radiosurgery or neurosurgery	OS: 10.5 *vs*. 9.1 mo, (HR =0.86, 95% CI: 0.75–0.98, P=0.023); any grade CNS haemorrhage: 0
NR	Camidge *et al*. 2014 (47)	Single arm open-label phase II study	First line	10 mg/kg every 21 days until clinical progression	PTX + CBDCA + Ram	40	NR	Clinically stable, treated brain metastases were allowed	6-month PFS rate: 59.0%, ORR: 55.0%; any grade CNS haemorrhage: 0
	Doebele *et al*. 2015 (48)	Randomized open-label phase II study	First line	10 mg/kg every 21 days until disease progression	Pem + CBDCA/CDDP (n=71) *vs*. Pem + CBDCA/CDDP + Ram (n=69)	69	NR	Clinically stable, treated brain metastases were allowed	Median PFS: 5.6 *vs*. 7.2 mo (HR =0.75; P=0.132); any grade CNS haemorrhage: 0

[§], data not reported in the paper but provided directly from the authors. VEGF, vascular endothelial growth factor; pts, patients; CNS, central nervous system; mets, metastases; CBDCA, carboplatin; CDDP, cisplatin; Erl, erlotinib; Bev, bevacizumab; WBRT, whole brain radiotherapy; G, grade; PFS, progression free survival; mo, months; HR, hazard ratio; OS, overall survival; Pem, pemetrexed; PTX, paclitaxel; QoL, quality of life; Gem, gemcitabine; NR, not reported; Ram, ramucirumab.

had progressed during or after a first-line platinum-based chemotherapy regimen to receive docetaxel plus either ramucirumab (n=628) or placebo (n=625) until progression or unacceptable toxicity. This study demonstrated that ramucirumab added to docetaxel improved OS (median OS: 10.5 *vs*. 9.1 months, HR =0.86, 95% CI: 0.75–0.98, P=0.023), PFS (median PFS: 4.5 *vs*. 3.0 months, HR =0.76, 95% CI: 0.68–0.86, P<0.0001) and ORR (23% *vs*. 14%, P<0.001) compared to docetaxel alone.

Patients with treated BM were eligible if they were clinically stable with regard to neurologic function, after cranial irradiation (whole brain radiation therapy, focal radiation therapy, and SRS) or surgery resection. The patient may have had no evidence of grade ≥1 CNS haemorrhage. The number of patients with BM at baseline is not reported, however none grade 1–4 CNS haemorrhage were observed.

To date, ramucirumab has been studied as first line treatment option in patients with advanced or metastatic NSCLC in 2 open-label phase II studies (47,48). In the first study 40 patients received, ramucirumab in combination with paclitaxel and carboplatin, obtaining a 6-month PFS rate of 59.0% and an ORR of 55.0%. In the latter phase II trial, 140 non-squamous NSCLC patients were randomized to receive pemetrexed and carboplatin (n=71) or ramucirumab plus pemetrexed and carboplatin (n=69). The primary endpoint of significant prolongation of PFS was not met (median PFS: 5.6 *vs*. 7.2 months, HR =0.75; P=0.132). In both studies treated CNS were allowed but the number of patients with CNS at baseline were not reported. None CNS haemorrhage occurred.

Aflibercept

Aflibercept is a recombinant fusion protein, consisting of human VEGFR-1 extracellular domain 2 and VEGFR-2 extracellular domain 3, fused to the hinge region of the human IgG1 Fc domain. Aflibercept has high affinity VEGF binding and the ability to bind VEGF-B, as well as placental growth factor (PLGF)-1 and -2 (51). In a single-arm clinical trial assessing the safety and efficacy of single-agent aflibercept in patients with erlotinib- and platinum-resistant advanced lung adenocarcinomas, aflibercept was well tolerated but had little single-agent activity; the ORR was 2.0% (95% CI: 0.2–7.2%), median PFS 2.7 months, and OS 6.2 months (52).

In the second-line setting, the phase III VITAL trial randomized patients with non-squamous NSCLC to aflibercept or placebo in combination with docetaxel and failed to meet its primary endpoint of improvement in OS (median OS: 10.1 *vs*. 10.4 months, HR =1.01, P=0.90) (53). Both trials excluded patients with BM at baseline. Therefore, no data are actually available about the safety and efficacy of aflibercept as treatment for BM from NSCLC, but in any case to date there is no indication for this drug in the lung cancer therapeutic approach.

Efficacy and safety of multi targeted anti-angiogenetic agents for CNS from NSCLC

TKIs with anti-angiogenic activity are small molecules that bind to the ATP-binding catalytic site of the tyrosine kinase domain of VEGFRs, resulting in a blockade of intracellular signalling. Many TKIs have been studied in a variety of combinations and lines of therapy for patients with lung cancer. A number of these drugs are effective as single agents in other advanced cancers, such as renal cell carcinoma and soft tissue sarcomas. Unfortunately, the development of anti-angiogenic TKIs has failed to yield an indication for use in lung cancer due to lack of efficacy or increased cumulative toxicity when combined with chemotherapy. Data are summarised in *Table 2*.

Sunitinib

Sunitinib is an oral, multitargeted inhibitor of VEGFRs 1, 2, 3, platelet derived growth factor receptors (PDGFRs α and β), stem-cell factor receptor (Kit), FMS-like tyrosine kinase 3 (FLT3), colony-stimulating factor 1 receptor (CSF-1R) and glial cell line-derived neurotrophic factor receptor (RET) (68). Sunitinib is approved for the treatment of metastatic renal cell carcinoma, imatinib resistant/intolerant gastrointestinal stromal tumors (GISTs) and advanced pancreatic neuroendocrine tumors (69,70). A phase II, open-label, single-arm study evaluated the efficacy and safety of sunitinib in patients with NSCLC and irradiated BMs (60). The primary endpoint was PFS and secondary endpoints included OS, patient reported outcomes and safety, with particular attention to risk of intracranial hemorrhage (ICH) associated with focal neurological deficit. Patients with radiologically confirmed BM ≤4 cm and WBRT ≥2 weeks before study entry were included. Sixty-four patients were enrolled and received sunitinib 37.5 mg on a continuous daily dosing schedule, in 4-week cycles for 13 cycles (1 year) or until study withdrawal. Most of patients (98%) received WBRT. Median PFS was 9.4 weeks (90% CI: 7.5–13.1),

Table 2 Tyrosine kinase inhibitors targeting vascular endothelial growth factor for the treatment of central nervous system metastases from non-small cell lung cancer: prospective trials

Study	Author, year	Type of study	Line of treatment	Anti-VEGF TKI schedule	Regimen	Pts treated with TKI	Pts with CNS mets (N) (%)	CNS metastases characteristics	Comments
Cediranib									
BR29	Laurie *et al*. 2014 (54)	Randomized, double-blind, placebo-controlled trial	First line	20 mg/daily until disease, progression or unacceptable toxicity	CBDCA + PTX + Plac (n=153) *vs*. CBDCA + PTX + Ced (153)	153	NR	Stable brain mets	Median PFS: 5.5 *vs*. 5.5 mo (HR =0.91, 95% CI: 0.71–1.18, P=0.49); median OS: 12.2 *vs*. 12.1 mo (HR =0.94, 95% CI: 0.69–1.30, P=0.72)
Linifanib									
NR	Ramalingam *et al*. 2015 (55)	Randomized, phase II trial	First line	7.5 or 12.5 mg, once daily on a continuous schedule	Arm A CBDCA + PTX + Plac (n=47) *vs*. arm B CBDCA + PTX + Lin (7.5 mg) (n=44) arm C CBDCA + PTX + Lin (12.5 mg) (n=47)	91	NR	Stable, treated brain mets	Median PFS: 5.4 mo (95% CI: 4.2–5.7) in arm A, 8.3 mo (95% CI: 4.2–10.8) in arm B, 7.3 mo (95% CI: 4.6–10.8) in arm C. Median OS: 11.3 mo in arm A, 11.4 mo in arm B, 13.0 mo in arm C
Motesanib									
MONET1	Scagliotti *et al*. 2012 (56)	Randomized, double-blind, placebo controlled phase III trial	First line	125 mg once daily orally until disease progression, unacceptable toxicity, or withdrawal of consent	Arm A PTX + CBDCA + Mot (n=541) *vs*. arm B PTX + CBDCA + Plac (n=549)	541	80	Treated and asymptomatic CNS mets at baseline were allowed	Median OS 13.0 *vs*. 11.0 mo (HR =0.90; 95% CI: 0.78–1.04; P=0.14); median PFS 5.6 *vs*. 5.4 mo (P<0.001); OS for BMs HR =1.315 (95% CI: 0.758–2.279), no data of hemorrhagic events for CNS
Nintedanib									
LUME-lung 1	Reck *et al*. 2014 (57)	Randomized, double-blind, phase III trial	Second line	200 mg twice daily until unacceptable adverse events or disease progression	Docetaxel + Plac (n=659) *vs*. docetaxel + Nin (n=655)	655	76 (11.6)	Stable brain mets were allowed (no active stable brain metastases for <4 weeks, no adequate; previous treatment with radiotherapy, symptomatic, or requiring treatment with anticonvulsants)	Median PFS 3.4 *vs*. 2.7 mo (HR =0.79; 95% CI: 0.68–0.92, P=0.0019), patients without brain mets had an increased in OS (HR =0.80, 95% CI: 0.67–0.96 *vs*. HR =1.27, 95% CI: 0.67–2.38; P=0.1247).

Table 2 *(continued)*

Table 2 *(continued)*

Study	Author, year	Type of study	Line of treatment	Anti-VEGF TKI schedule	Regimen	Pts treated with TKI	Pts with CNS mets (N) (%)	CNS metastases characteristics	Comments
Pazopanib									
NR	Scagliotti *et al*. 2013 (58)	Randomized, multicenter, open-label, phase II trial	First line	800 mg/daily (until completion of the combination, treatment and then as monotherapy, until disease progression, unacceptable toxicities, or death) + Pem	CDDP + Pem (n=35), CDDP + Paz (n=71)	71	NR	Previously treated, clinically stable, CNS mets were allowed	Median PFS: 25.0 *vs*. 22.9 weeks (HR =0.75; 95% CI: 0.43–1.28; P=0.26), no evidence of CNS bleeding
EORTC 08092	O'Brien *et al*. 2015 (59)	Randomized, double-blind, phase III trial	Maintenance after first line	800 mg/daily until disease progression, unacceptable toxicity, or withdrawal of consent	Plac (n=52) *vs*. Paz (n=50)	50	4	Stable brain mets were allowed	Median PFS 4.3 *vs*. 3.2 mo (HR =0.67, 95% CI: 0.43–1.03, P=0.068). Median OS 17.4 (95% CI: 8.9–not reached) mo in Paz and 12.3 (95% CI: 10.3–16.6) mo in Plac arm, no data of bleeding
Sunitinib									
NR	Novello *et al*. 2011 (60)	Open-label, single-arm, phase II trial	Third line	37.5 mg daily dosing in 4-week cycles for 13 cycles (1 year) or until study withdrawal	Sunitinib (n=64)	64	64 (100.0)	Brain mets ≤4 cm and WBRT ≥2 weeks before study entry	Median PFS 9.4 weeks (90% CI: 7.5–13.1). Median OS 25.1 weeks (95% CI: 13.4–35.5). Median time to intracranial progression 15.4 weeks (95% CI: 12.1–24.8). Cases of ICH were not reported
NR	Heist *et al*. 2014 (61)	Randomized phase II trial	Second line	37.5 mg daily until disease progression	Arm I: Pem (n=42) *vs*. arm II: sunitinib (n=47) *vs*. arm III: Pem + sunitnib (n=41)	88	NR	Treated, asymptomatic brain mets	18-week PFS rate: arm I: 54% (95% CI: 40–71), arm II: 37% (95% CI: 25–54), arm III: 48% (95% CI: 35–66) (P=0.25). Median PFS: arm I: 4.9 (2.1–8.8) mo, arm II: 3.3 (range, 2.3–4.2) mo, arm III: 3.7 (2.5–5.8) mo (P=0.18). Median OS: 10.5 (range, 8.3–20.2) mo for Pem, 8.0 (range, 6.8–13.5) mo for sunitinib, and 6.7 (range, 4.1–10.1) mo for the combination (P=0.03)

Table 2 *(continued)*

Table 2 *(continued)*

Study	Author, year	Type of study	Line of treatment	Anti-VEGF TKI schedule	Regimen	Pts treated with TKI	Pts with CNS mets (N) (%)	CNS metastases characteristics	Comments
Sorafenib									
NR	Blumen-schein *et al*. 2009 (62)	Multicenter, uncontrolled, single arm, phase II trial	Second line	800 mg/daily until tumor progression or intolerable drug related toxicity	Sor (n=52)	52	NR	Patients with asymptomatic brain mets if treated at least 6 months before enrolment and clinically stable	Median PFS: 2.7 mo. Median OS: 6.7 mo. Hemorrhagic/ bleeding and neurological events in SCC (37.5% and 75%) in other histologies (16.7% and 41.7%)
NR	Spigel *et al*. 2011 (63)	Randomized, double-blind, placebo-controlled phase II trial	Second or third line	800 mg/daily until disease progression or intolerable toxicity	Erl + Plac (n=55) *vs*. Erl + Sor (n=111)	111	NR	Patients with treated CNS mets with no evidence of CNS disease progression	Median PFS 3.38 *vs*. 1.94 mo (HR =0.86; 95% CI: 0.60–1.22; P=0.196), ORRs 8% *vs*. 11%, P=0.56
Vandetanib									
NR	Heymach *et al*. 2008 (64)	Randomized, non-inferiority, phase II trial	First line	300 mg/daily until progressive disease unacceptable toxicity	CBDCA + PTX + Plac *vs*. (n=52), CBDCA + PTX + Van (n=56) *vs*. Van (n=73)	129	19 (20.0)	Brain mets were permitted if treated at least 4 weeks before entry and clinically stable without corticosteroid treatment for 1 week	Median PFS 24 *vs*. 23 weeks (HR =076, P=0.098), intracranial bleeding did not occur in the 13 patients with BMs receiving Van
ZODIAC	Herbst *et al*. 2010 (65)	Randomized, double-blind, phase III trial	Second line	100 mg/daily until disease progression, unacceptable toxicity, or withdrawal of consent	Docetaxel + Plac (n=697) *vs*. docetaxel + Van (n=6,949)	694	65 (9.0)	Brain mets were permitted if treated at least 4 weeks before study entry and clinically stable without steroids for 10 days	Median PFS: 4.0 *vs*. 3.2 mo (HR =0.79, 97.58% CI: 0.70–0.90; P<0.0001), the incidence of hemorrhage was 17% (116/689) in the Van group *vs*. 16% (112/690) in the Plac group
ZEAL	de Boer *et al*. 2011 (66)	Randomized, double-blind, phase III trial	Second line	100mg/daily until progressive disease unacceptable toxicity, or withdrawal of consent	Pem + Plac (n=278) *vs*. Pem + Van (n=256)	256	NR	Pretreated clinically stable brain mets	Median PFS 17.6 *vs*. 11.9 weeks (HR =0.86; 97.58% CI: 0.69–1.06; P=0.108); median OS: 10.5 *vs*. 9.2 mo (HR =0.86; 97.54% CI: 0.65–1.13; P=0.219)
ZEST	Natale *et al*. 2011 (67)	Randomized, double-blind, phase III trial	Second and third line	300 mg/daily until progressive disease, unacceptable toxicity, or withdrawal of consent	Erl (n=617) *vs*. Van (n=623)	623	60 (10.0)	Brain mets treated ≥4 weeks before study entry and clinically stable without corticosteroid treatment for ≥10 days	Median PFS: 2.6 *vs*. 2.0 mo (HR =0.98, 95% CI: 0.87–1.10, P=0.721); median OS: 6.8 *vs*. 7.7 mo (HR =0.97; 95% CI: 0.86–1.10; P=0.613)

CNS, central nervous system; mets, metastases; CBDCA, carboplatin; CDDP, cisplatin; Ced, cediranib; Lin, linifanib; Mot, motesanib; Nin, nintedanib; Paz, pazopanib; Erl, erlotinib; Sor, sorafenib; Van, vandetanib; Plac, placebo; Pem, pemetrexed; PTX, paclitaxel; WBRT, whole brain radiotherapy; PFS, progression free survival; mo, months; HR, hazard ratio; OS, overall survival; SCC, squamous cell carcinoma; NR, not reported.

median OS was 25.1 weeks (95% CI: 13.4–35.5). With regard to intracranial antitumor activity, median time to intracranial progression was 15.4 weeks (95% CI: 12.1–24.8). Overall, sunitinib was well tolerated and cases of ICH were not reported. A randomized phase II study assessed the efficacy of pemetrexed alone versus sunitinib alone versus pemetrexed with sunitinib, as second line in 130 advanced NSCLC (61). Patients with treated, asymptomatic BM were eligible. Primary endpoint was 18-week PFS rate and secondary endpoints included response, OS and toxicity. No specific evaluation was planned for outcomes in patients with BM. The 18-week PFS rate in the pemetrexed, sunitinib and combination arms was 54% (95% CI: 40–71), 37% (95% CI: 25–54) and 48% (95% CI: 35–66) (P=0.25), respectively. Median PFS in the pemetrexed, sunitinib and combination arms was 4.9 (range, 2.1–8.8), 3.3 (range, 2.3–4.2) and 3.7 (range, 2.5–5.8) months, respectively (P=0.18). Median OS was 10.5 (range, 8.3–20.2) months for pemetrexed, 8.0 (range, 6.8–13.5) months for sunitinib and 6.7 (range, 4.1–10.1) months for the combination (P=0.03). In terms of adverse events hemorrhagic episodes were clustered in the sunitinib arms and episodes of ICH bleeding were not observed.

Sorafenib

Sorafenib is a multikinase inhibitor targeting VEGFRs 2, 3, PDGFR-β, c-Kit, FLT3 and RET (71). It is approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma (72). Sorafenib has shown activity in preclinical models and phase I–II studies in patients with NSCLC (71). A phase II single arm trial evaluated sorafenib in patients with relapsed or refractory advanced NSCLC (62). Patients with asymptomatic, stable BM and squamous cell carcinoma (SCC) histology were eligible. The primary endpoint was response rate and secondary endpoints were PFS, OS and toxicity. Fifty-four patients were enrolled. Median PFS of 2.7 months and median OS of 6.7 months were reported in 51 patients. Stable disease was found in 59% of 51 evaluable patients. Drug-related bleeding was observed in four patients and hemorrhagic/bleeding and neurological events were more common in patients with SCC (37.5% and 75%, respectively) compared to other histology. A phase II trial evaluated the efficacy of sorafenib plus erlotinib *vs*. placebo plus erlotinib in patients with advanced NSCLC, pretreated with one or two regimens (63). Patients with treated CNS metastases with no evidence of CNS disease progression were eligible. The co-primary endpoints were ORR and PFS. One hundred and sixty-eight patients were randomized to sorafenib plus erlotinib or placebo plus erlotinib. The combination of sorafenib/placebo did not statistically improve ORR and PFS (median PFS was 3.38 months for sorafenib/erlotinib *vs*. 1.94 months for placebo/erlotinib, HR =0.86; 95% CI: 0.60–1.22; P=0.196). No specific evaluation was planned for outcomes for patients with BMs and no episodes of bleeding were reported.

Motesanib

Motesanib is a selective, oral inhibitor of VEGFRs 1, 2, 3, PDGFR and c-Kit (73). Motesanib has demonstrated antitumor activity when administered as monotherapy in advanced solid tumors (74) or combined with chemotherapy in metastatic NSCLC (75). A randomized, double-blind, placebo controlled phase III trial (MONET1) compared motesanib plus chemotherapy (carboplatin/paclitaxel) *vs*. placebo plus chemotherapy in patients with stage IIIB/IV or recurrent advanced non-squamous NSCLC (56). Primary endpoint was OS and secondary endpoints were PFS, ORR and safety. Patients with symptomatic or untreated BM were not eligible. A total of 1,090 patients were randomized and 80 presented stable BM at randomization. Treatment with motesanib did not significantly improve OS among patients with non-squamous histology (median OS was 13.0 months in the experimental arm *vs*. 11.0 months in the placebo arm, HR =0.90; 95% CI: 0.78–1.04; P=0.14). A significant improvement in PFS (median PFS was 5.6 *vs*. 5.4 months, P<0.001) was described. Prespecified subgroup analyses suggested that patients with BM receiving motesanib did not have longer survival (HR =1.315; 95% CI: 0.758–2.279) compared to those receiving chemotherapy. In terms of safety, the hemorrhagic events were more in the experimental arm than in the placebo arm (3% *vs*. 1%), in particular: gastrointestinal hemorrhage (n=1 *vs*. n=0), pulmonary hemorrhage (n=2 *vs*. n=1), hemoptysis (n=3 *vs*. n=1). Episodes of CNS bleeding were not observed in the study.

Pazopanib

Pazopanib is an oral, selective inhibitor of VEGFRs 1, 2, 3, PDGFRs α and β and c-Kit (76). It is approved for the treatment of metastatic renal cell carcinoma and advanced soft-tissue sarcoma who underwent prior chemotherapy (77). An open-label, multicenter, randomized, phase II study

compared pazopanib in combination with pemetrexed *vs.* cisplatin/pemetrexed in patients with chemonaive, advanced, non-squamous NSCLC (58). Patients with previously treated, clinically stable BM were eligible. The primary endpoint was PFS and secondary endpoints were OS, safety and tolerability. One hundred-six patients were randomized. PFS was not statistically significant different between the two arms (median PFS was 25.0 *vs.* 22.9 weeks, HR =0.75; 95% CI: 0.43–1.28; P=0.26). No subanalysis for patients with BM was planned and/or performed. In terms of safety, there was no evidence of severe hemorrhagic events (grade ≥3). O'Brien *et al.* evaluated pazopanib *vs.* placebo as maintenance therapy in advance NSCLC patients without progression disease after first line platinum-based chemotherapy (59). The primary endpoint was OS and secondary endpoints were PFS and safety. One hundred-two patients were randomized and four patients had BM at randomization. The trial was prematurely stopped following an interim analysis. The median OS was 17.4 for pazopanib *vs.* 12.3 months for placebo (HR =0.72, 95% CI: 0.40–1.28; P=0.257). The median PFS was 4.3 months in pazopanib *vs.* 3.2 months in placebo arm (HR =0.67; 95% CI: 0.43–1.03; P=0.068). No severe hemorrhagic events (grade ≥3) were reported.

Linifanib

Linifanib is an oral, selective inhibitor of VEGFRs 1, 2, 3, PDGFRs α and β and FLT3 and has demonstrated activity in preclinical studies (78). A recent randomized, phase II study evaluated two doses of linifanib (7.5 and 12.5 mg) in combination with carboplatin/paclitaxel *vs.* placebo plus chemotherapy (55) in patients with advanced non-squamous NSCLC. Patients with untreated CNS metastases were not eligible. The primary endpoint was PFS and secondary endpoints included OS and ORR. One hundred thirty-eight patients were randomized. Addition of linifanib 7.5 mg to chemotherapy was associated with a significantly improved PFS compared to placebo (8.3 *vs.* 5.4 months, P=0.022) and the addition of linifanib 12.5 mg showed a non-significant increase in OS compared to placebo (13.0 *vs.* 11.3 months, P=0.65). No subgroup analysis for patients with BM was performed. In terms of safety, both dose of linifanib were associated with increased toxicity (anemia, hypertension and diarrhea). No episode of CNS bleeding was registered.

Cediranib

Cediranib is an oral, potent inhibitor of VEGFRs 1, 2, 3, PDGFR-β and c-Kit (79). Preclinical data showed that cediranib prevents angiogenesis and inhibits the growth of tumor xenografts when administered chronically. Up to now, there are limited data available on cediranib and BMs in NSCLC (80). A randomized, double-blind, placebo-controlled trial evaluated the addition of cediranib to standard carboplatin/paclitaxel chemotherapy in advanced NSCLC (54). The primary endpoint was OS and secondary endpoints were PFS, ORR and AEs. Patients with untreated, symptomatic, cavitating or haemorrhagic BMs were not eligible. This trial was halted at an interim analysis due to significantly higher rates grade 3 or greater hypertension, anorexia, and diarrhea without statistically significant increases in PFS or OS. No data are available specifically for patients with BM. Bleeding was not otherwise different between the two arms and episodes of bleeding of CNS were not reported.

Vandetanib

Vandetanib is an oral, multikinase inhibitor of VEGFRs 2, 3, RET, EGFR and has shown antitumor activity in advanced NSCLC patients (81). There are limited data available on vandetanib in the treatment of BMs. A phase II non-inferiority trial evaluated vandetanib alone or with chemotherapy carboplatin/paclitaxel for untreated NSCLC (64). Patients with BM were allowed if treated and clinically stable without corticosteroid treatment. Primary endpoint was PFS and secondary endpoint was OS. One hundred and eighty-one patients were randomized and 6 patients (8%), 7 (12%) and 6 (12%) had BM in vandetanib, vandetanib plus chemotherapy and vandetanib plus placebo, respectively. Vandetanib combined with chemotherapy was not inferior to chemotherapy alone. In details, median PFS was 24 weeks in the vandetanib group *vs.* 23 weeks in chemotherapy group. Patients with BM were not evaluated in a sub-analysis. In terms of AEs, intracranial bleeding did not occur in the 13 patients with BM receiving vandetanib. Two phase III trials evaluated vandetanib in combination with second-line chemotherapy. The ZODIAC study evaluated vandetanib in combination with docetaxel *vs.* docetaxel plus placebo in NSCLC patients progressing after platinum-based first-line chemotherapy (65). Patients with BM were allowed if treated and clinically stable without steroids. Primary endpoint was PFS and secondary endpoints were OS, ORR, disease control rate, safety and time to deterioration of disease-related symptoms. 1,391 patients were randomized, 65 patients (9%) in experimental arm and 80 (11%) in

controlled arm had BMs, respectively. Median PFS was 4.0 months in the vandetanib arm *vs*. 3.2 months in the control arm (HR =0.97, 95% CI: 0.70–0.90; P<0.0001). In term of safety, the incidence of hemorrhage was 17% (116/689) in the vandetanib group *vs*. 16% (112/690) in the placebo group (no data about CNS bleeding). The randomized, double blind phase III trial (ZEAL) evaluated vandetanib plus pemetrexed as second line therapy in advanced NSCLC (66). Patients with pretreated clinically stable BM were eligible. Primary endpoint was PFS and secondary endpoints were OS, ORR, disease control rate, time to deterioration of symptoms and safety. Five hundred and thirty-four patients were randomized. The study did not meet its primary endpoint (median PFS 17.6 weeks for vandetanib *vs*. 11.9 weeks for placebo, HR =0.86; 97.58% CI: 0.69–1.06; P=0.108). There was no significant difference in OS (median OS was 10.5 for vandetanib *vs*. 9.2 months for placebo, HR =0.86; 97.54% CI: 0.65–1.13; P=0.219). The incidence of hemorrhagic events (hemoptysis, epistaxis, GI bleeding, hematuria, metrorrhagia or CNS hemorrhage) was similar in both treatment arms. One patient in each arm had non-fatal cerebral hemorrhage, neither of whom had known BM. The randomized, double-blind, phase III trial (ZEST) assessed the efficacy of vandetanib *vs*. erlotinib in unselected patients with advanced NSCLC after treatment with one or two prior lines of chemotherapy (67). Patients with BM were eligible if treated and if clinically stable without corticosteroid. Primary endpoint was PFS and secondary endpoints were OS, ORR, safety and time to deterioration of symptoms. One thousand two hundred and forty patients were randomized and 60 patients (10%) in the experimental arm and 70 patients (11%) in the controlled arm had BM. Significant improvement in PFS was not evidenced (median PFS was 2.6 months for vandetanib *vs*. 2.0 months for erlotinib HR =0.98, 95% CI: 0.87–1.10; P=0.721) and OS was similar in the two arms. In terms of safety, fewer hemorrhagic events (hemoptysis, GI bleeding, epistaxis, hematuria, metrorrhagia and CNS hemorrhage) occurred in vandetanib arm compared with the erlotinib arm (11% *vs*. 17%, respectively).

Nintedanib

Nintedanib is an oral, triple angiokinase inhibitor of VEGFRs 1, 2, 3, FGFRs 1, 2, 3 and PDGFRs α and β (82). The randomized, double-blind phase III trial (LUME-lung 1) evaluated nintedanib in combination with docetaxel *vs*. placebo plus docetaxel in patients with advanced NSCLC progressing after first line chemotherapy (57). Primary endpoint was PFS and the key secondary endpoint was OS, analyzed in a prespecified stepwise order: first in patients with adenocarcinoma who progressed within 9 months after start of first-line therapy, then in all patients with adenocarcinoma, then in all patients. Patients with active BM (defined as stable for <4 weeks, no adequate previous treatment with radiotherapy, symptomatic, or requiring treatment with anticonvulsants) were not allowed. One thousand three hundred and fourteen patients were randomized and 38 patients (5.8%) had stable BM in the experimental arm and in the control arm, respectively. PFS was significantly improved in the experimental arm (median PFS was 3.4 *vs*. 2.7 months; HR =0.79; 95% CI: 0.68–0.92, P=0.0019). OS was significantly improved for patients with adenocarcinoma who progressed within 9 months after start of first-line treatment in the docetaxel plus nintedanib group compared with those in the controlled group (median OS was 10.9 *vs*. 7.9 months, HR =0.75; 95% CI: 0.60–0.92, P=0.0073). This study showed that patients without BM, who received nintedanib in combination with docetaxel, had an increased in OS (HR =0.80, 95% CI: 0.67–0.96 *vs*. HR =1.27, 95% CI: 0.67–2.38; P=0.1247). In terms of safety, bleeding grade ≥3 was 2.3% in nintedanib group *vs*. 1.8% in docetaxel group.

Conclusions

Currently the only anti-angiogenetic agents approved for the treatment of NSCLC are bevacizumab in combination with first-line platinum-based chemotherapy, ramucirumab in combination with second-line docetaxel and nintedanib in combination with second-line docetaxel. An increasing body of evidence indicates that the use of bevacizumab-based therapy seems to be feasible and safe in patients with CNS metastases from NSCLC (33). Moreover first-line bevacizumab in combination to standard chemotherapy demonstrated promising activity in patient with asymptomatic BM from NSCLC in the BRAIN trial (36). Even if treated CNS metastases were allowed in phase II (47,48) and III (46) with ramucirumab, no data are actually available about the efficacy of ramucirumab in this subgroup of patients.

Multitargeted angiogenesis inhibitors have been investigated for the treatment of advanced NSCLC patients with promising results in second line setting but an increased toxicity in first line setting in combination with chemotherapy without a meaningful improvement in OS.

One exception is nintedanib, that showed an increased OS for patients with adenocarcinoma. Specific results of TKIs activity in the treatment of BM are still lacking and further investigational studies are needed.

Acknowledgements

None.

Footnote

Conflicts of Interest: Prof. Silvia Novello declared a role as speaker bureau for Roche, Boehringer Ingelheim, Eli Lilly, Astra Zeneca, MSD. The other authors have no conflicts of interest to declare.

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Cite this article as: Buttigliero C, Bertaglia V, Novello S. Anti-angiogenetic therapies for central nervous system metastases from non-small cell lung cancer. Transl Lung Cancer Res 2016;5(6):610-627. doi: 10.21037/tlcr.2016.09.03

