Review Article on Looking for Chimeras in NSCLC: Widen Therapeutic Options Targeting Oncogenic Fusions

Central nervous system metastases and oligoprogression during treatment with tyrosine kinase inhibitors in oncogene-addicted non-small cell lung cancer: how to treat and when?

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Abstract: Up to 70% of non-small cell lung cancer (NSCLC) patients develop central nervous system (CNS) metastases during the course of their disease, especially those with oncogenic drivers treated with a first-generation tyrosine kinase inhibitor (TKI), because of the relatively poor CNS penetration. CNS metastases are associated with a negative impact on quality of life and survival. As, with the introduction of newer generation TKIs, the survival rates are increasing in this particular population, treatment and/or prevention of CNS metastases becomes even more relevant and the TKI with the best CNS efficacy should be selected. Unfortunately, CNS efficacy data in clinical trials are not fully comparable. Furthermore, oligoprogression to the brain without extracranial progression regularly occurs in the oncogenic driver population and both local therapy and switch of systemic therapy are possible treatment options. However, the best order of systemic and local therapy is still not precisely known. In this narrative review, we will summarize incidence and treatment of CNS metastases in oncogene driven NSCLC, including the optimal treatment of CNS oligometastatic disease (synchronous as well as oligoprogressive).

Keywords: Non-small cell lung cancer (NSCLC); central nervous system metastases (CNS metastases); oligometastatic disease; tyrosine kinase inhibitors (TKIs)

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Introduction

Central nervous system (CNS) metastases frequently occur in non-small cell lung cancer (NSCLC). Approximately 10–20% of patients with NSCLC present with CNS metastases at diagnosis, and about 40–70% will develop CNS metastases during the course of their disease (1-3). CNS metastases are a poor prognostic factor and have a negative impact on quality of life (QoL) (4).

Due to both increased screening for CNS metastases in almost all NSCLC disease stages [except the (very) early stages] (5-7), and improved NSCLC survival rates, the incidence of CNS metastases is increasing. Next to this, the detection of asymptomatic CNS metastases due to screening in otherwise non-metastatic patients can result in an increased incidence of CNS only metastases (7,8). The widespread uptake of magnetic resonance imaging (MRI, advised in current guidelines) instead of computed tomography (CT) for CNS metastases screening probably

results in an even higher incidence of CNS only metastases, as MRI is more sensitive than CT (9). A topic of discussion is the best sequence of treatments in patients with baseline asymptomatic CNS disease: local treatment (e.g., radiation) followed by systemic therapy, or systemic therapy with local treatment upon CNS progression (7,8,10,11). A special category are those patients with oncogenic driven NSCLC. In general, the preferred treatment option for neurologically asymptomatic oncogene-addicted NSCLC patients [epidermal growth factor receptor (*EGFR*) mutation, rearrangements of anaplastic-lymphoma-kinase (*ALK*), ROS proto-oncogene 1 (*ROS1*), *MET* deregulation (amplification or *MET* exon 14 mutations), *RET*-fusions, N tropomyosin receptor kinase (*NTRK*) gene fusion, *B-Raf* proto-oncogene (*BRAFv600E)* mutation] is a tyrosine kinase inhibitor (TKI) (5,7). An advantage of the next generation TKIs is the often superior CNS penetration rate compared with the first generation TKIs (12,13). As the median overall survival (OS) of patients with *EGFR* or *ALK* driven NSCLC has improved to more than 5 years it is expected that CNS metastases will become more prevalent in this group, and that patients will live longer with CNS metastases (14,15). Therefore, the optimal treatment, and preferably even prevention, of CNS metastases is an important topic in current clinical trials enrolling patients with oncogene-addicted NSCLC. Historically, patients with CNS metastases were often not eligible for trial participation. Although symptomatic brain metastases (BM) and leptomeningeal metastases (LM) are still exclusion criteria in the majority of clinical trials, patients with asymptomatic or treated BM are increasingly eligible (16). However, interpretation of CNS related outcome measures of clinical trials is hampered by the lack of standardisation of imaging in these trials (modality, frequency) and by the fact that BM eligibility criteria differ between trials (e.g., untreated allowed or not, definition of stable BM). Moreover, patients were not always stratified according to presence of BM, and outcome of this subgroup was rarely a prespecified endpoint (16). In addition, oligoprogression in the brain can occur during systemic treatment. Most trials did not specify which treatments were allowed while on study, and optimal therapy of CNS oligometastatic disease is largely unknown. This is especially relevant in patients with oncogene driven NSCLC who develop oligoprogressive disease in the brain, without extracranial progressive disease, while on TKI treatment.

In this narrative review, we will summarize incidence and treatment of CNS metastases in oncogene driven NSCLC, including the optimal treatment of all types of CNS oligometastatic disease (e.g., synchronous, metachronous, oligopersistent, oligoprogressive). We will focus mainly on phase III trials, except when no phase III data are available or phase I/II data have added value (e.g., specific CNS subgroup data).

The incidence of CNS metastases and TKI options in oncogene driven NSCLC patients

Oncogene-addicted NSCLC is characterized by a particularly high incidence of CNS metastases, with percentages reaching up to 70% for BM and 10% for LM during the course if the disease (1,17-21).

EGFR mutation

The incidence of an activating *EGFR* mutation in lung cancer is about 10% in Caucasians and 50% in Asians (22). The incidence of BM at diagnosis ranges from 23–32% (19,23,24). In a retrospective series it was shown that with the use of first generation EGFR-TKI (erlotinib and gefitinib) and second generation EGFR-TKI (in this series only dacomitinib evaluated) the cumulative incidence of BM increases over time, resulting in a 5-year incidence of 53% (N=86 *EGFR*-mutated and 23 *ALK*-rearranged NSCLC patients) (19).

Treatment options for metastatic *EGFR*-mutated NSCLC patients are first generation EGFR-TKI (erlotinib and gefitinib), second generation EGFR-TKI (afatinib, dacomitinib) and the third generation EGFR-TKI osimertinib (7). None of the pivotal EGFR-TKI trials on which approval was based for these EGFR-TKIs, mandated baseline CNS metastases screening. In the EURTAC trial (comparing erlotinib to platinum/gemcitabine or platinum/docetaxel as first line treatment) (25), LUX-Lung 3 trial (comparing afatinib to cisplatin/pemetrexed) (26), LUX-Lung 7 trial (comparing afatinib to gefitinib) (27), AURA trial (comparing osimertinib to platinum-pemetrexed) (28) and FLAURA trial (comparing osimertinib to standard EGFR-TKI) (13) only asymptomatic stable BM were eligible. In the ARCHER trial (comparing dacomitinib to gefitinib as first line treatment) patients with known BM were excluded (29). The presence of BM was a stratification factor in the LUX-Lung 7, AURA and FLAURA trials (13,27,28). BM specific outcomes were also reported for those three trials, with osimertinib having the highest intracranial objective response rate (icORR)

and intracranial progression free survival (icPFS). None of the trials specified whether it was allowed to administer local treatment in a CNS oligoprogressive patient with continuation of the study drug. Detailed trial description and results are summarized in *Table 1*.

Translocation of the anaplastic lymphoma kinase gene

The incidence of *ALK* translocation in NSCLC patients is about 3–7% (32,33). The incidence of BM is about 20–40% at baseline (34-37). Under treatment with crizotinib, the first approved ALK-TKI, 51–72% of patients developed BM. This high percentage can be explained by the poor CNS penetration of this drug (1,38,39).

After crizotinib, several other next-generation ALK-TKIs were approved, namely ceritinib, alectinib, brigatinib and lorlatinib (34-36,40).

Compared to EGFR-TKI trials, most ALK-TKI trials have intracranial responses as one of their endpoints.

A retrospective pooled analyses of the PROFILE 1005 and PROFILE 1007 trials (respectively a single arm phase II trial investigating the efficacy of crizotinib in previously treated *ALK* rearranged NSCLC patients and a randomized phase III trial comparing crizotinib with chemotherapy in the same group of patients), showed that the CNS was the most common site of progression when on crizotinib treatment. Both trials included patients with asymptomatic or treated BM (pooled analysis: 31% with baseline BM of which 40% no prior brain irradiation), and baseline screening for BM was mandatory. In patients without BM at the start of crizotinib therapy 20% developed BM, with a median time to detection of 29.9 weeks. Next to this, CNS progression occurred in about 70% of patients that had baseline BM (20).

In contrast to the randomized phase III EGFR-TKI trials, the PROFILE 1007 and 1014, the ASCEND-4 and 5 trial, ALTA-1L trial, ALUR trial, ALEX trial as well as the lorlatinib trial mandated baseline CNS screening (34-37,41-43). In all of these trials, asymptomatic stable BM were eligible (34-37,40-43). Only in the PROFILE 1014 and in the ALUR trial the BM had to be locally treated. BM was a stratification factor in the eight studies mentioned above. For all these trials, BM specific outcomes were reported with brigatinib having the highest icORR (83%). Patients with CNS only progression in the ALTA-1L trial, requiring local therapy such as stereotactic radiotherapy (SRT), were allowed to continue brigatinib after SRT (brigatinib mandatory paused during SRT) after discussion with the sponsor. Other trials did not allow local treatment for oligoprogression with afterwards continuation of the study drug. Detailed trial description and results are summarized in *Table 2*.

Other molecular alterations; ROS1, MET, RET, NTRK, BRAF V600E

ROS1 rearrangements occur in approximately 1–2% of NSCLC patients. Compared with *ALK* rearrangements, patients with *ROS1* rearrangements have a lower percentage of baseline BM (19% *vs.* 39%). *ROS1*-positive patients also had a significantly lower cumulative incidence of BM (34% *vs.* 73% at 5 years). However, these are retrospective data without mandatory CNS metastases screening at baseline or standardized follow up imaging (44).

In a phase I–II trial analysing the efficacy of lorlatinib in treatment naive as well as pretreated NSCLC patients with a *ROS1* alteration (N=69), 57% of patients had BM at baseline. Screening for BM with MRI brain at baseline was mandatory. Asymptomatic treated BM, untreated BM as well as asymptomatic LM were eligible. The icOR was 64% in treatment naive patients and 50% in pretreated patients with crizotinib (45).

MET deregulation [amplification or exon 14 (*MET*ex14) skipping] is found in approximately 3–4% of NSCLC (46). The incidence of BM in this group is about 20% at baseline (47).

In a phase II trial analysing the efficacy of crizotinib in pretreated NSCLC patients with a *ROS1* alteration or a *MET* deregulation (amplification or *MET* exon 14 mutations) 23% and 19% of patients had BM at baseline, respectively. Only patients with stable and treated BM were allowed. BM was not a stratification factor nor was BM specific outcome a prespecified endpoint. None of the MET^+ patients with BM responded (48). Results from another phase II trial analysing the efficacy of capmatinib in pretreated as well as in treatment naive NSCLC patients with a MET exon 14 skipping mutation are promising, with intracranial response observed in 54% (7/13) of patients with BM at baseline. However, more data are awaited (49).

BRAF-V600E mutation is present in 1–2% of NSCLC. In the open label phase II trial analysing the efficacy of dabrafenib/trametinib in pretreated stage IV NSCLC patients with a *BRAF*-V600E mutation, 1.8% of patients had BM at baseline. Of note, it was not mentioned whether screening for BM was mandatory. Asymptomatic or treated BM were eligible (50). In the same study an extra cohort

Table 1 Summary CNS characteristics in pivotal phase II en III EGFR-TKI trials

Trial	Type of trial	TKI	Screening for BM	BM inclusion criteria	% included BM	BM endpoint/ stratification factor	Follow up CNS	OligoPD CNS treatments during study allowed/ specified	BM specific results
EURTAC (NCT00446225), Rosell *et al.* 2012, (25)	Phase III RCT	First line erlotinib *vs.* cis- or carboplatin with gemcitabine or docetaxel	NR	Asymptomatic stable	11.6% (20/173) (erlotinib 10%, chemotherapy 13%)	No/no	NR	No (PD: study discontinuation)	–
IPASS (NCT00322452), Mok *et al.* 2009, (30)	Phase III RCT	First line gefitinib *vs.* carboplatin-paclitaxel	NR	NR	NR	No/no	NR	No (PD: study discontinuation)	–
ARCHER 1050 (NCT01774721), Wu *et al.* 2017, (29)	Phase III RCT	First line dacomitinib *vs.* gefitinib	NR	All BM and LM excluded	–	No/no	NR	No (PD: study discontinuation	–
LUX-lung 3 (NCT00949650), Sequist *et al.* 2013, (26)	Phase III RCT	First line afatinib *vs.* cisplatin-pemetrexed	If clinically indicated CT/MRI brain	Asymptomatic stable BM allowed (stable <4 weeks and/or symptomatic and/or requiring treatment with anticonvulsants or steroids and/or LM disease excluded)	NR	No/no	CT/MRI brain if BM + Q6W	No (PD: study discontinuation, treatment beyond radiological progression allowed in the case of continued clinical benefit)	–
LUX-lung 7 (NCT01466660), Park *et al.* 2016, (31)	Phase IIB RCT	First line afatinib *vs.* gefitinib	NR	Asymptomatic and stable BM (symptomatic and/or requiring treatment at the time of screening exclusion. LM exclusion)	15.7% (50/319) (afatinib 16% gefitinib 15%)	No/prespecified subgroup (baseline BM presence *vs.* absence)	NR	No (PD: study discontinuation, treatment beyond radiological progression was allowed in the case of continued clinical benefit)	Median PFS in months (BM group): afatinib 7.2, gefitinib 7.4 [HR 0.76 (0.41–1.44)]; median TTF in months (BM group): afatinib 8.4, gefitinib 9.3 [HR 1.14 (0.64–2.03)]
AURA (NCT02151981), Mok *et al.* 2017, (28)	Phase III RCT	Second line osimertinib *vs.* cis- or carboplatin/ pemetrexed	Only in patients with known or suspected CNS metastases with CT/MRI Brain	Asymptomatic and stable BM (stable <4 weeks and/or symptomatic and/or requiring treatment with anticonvulsants or steroids and/or LM excluded)	34.4% (144/419) (osimertinib 33%, chemotherapy 36%)	No/prespecified subgroup analysis	CT/MRI brain if BM+ Q6W	No (PD: study discontinuation, trial treatment allowed beyond progression if clinical benefit)	icORR: osimertinib 70% (21/30), chemotherapy 31% (5/16); median icDOR: 8.9 *vs.* 5.7 months; median icPFS: 11.7 *vs.* 5.6 months
FLAURA (NCT02296125), Soria. 2018, (13)	Phase III RCT	First line osimertinib *vs.* gefitinib or erlotinib	CT/MRI brain when known or suspected BM	Asymptomatic and stable BM (requiring steroids <4 weeks, when symptomatic but stable for at least 4 weeks and off steroids, eligible)	21% (116/556) (osimertinib 19%, standard EGFR TKI 23%)	No/subgroup analysis (not prespecified)	CT/MRI brain Q6W	No	OS HR 0.83 (CNS group) *vs.* 0.79 (no-CNS group)

CNS, central nervous system; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; BM, brain metastases; PD, progressive disease; RCT, randomised controlled trial; NR, not reported; LM, leptomeningeal metastases; CT, computer tomography; MRI, magnetic resonance imaging; Q6W, every 6 weeks; ic, intracranial; PFS, progression free survival; HR, hazard ratio; TTF, time to treatment failure; ORR, overall response rate; DOR, duration of response; OS, overall survival.

Table 2 Summary CNS characteristics pivotal phase II–III ALK-TKI trials

Trial	Type of trial	TKI	Screening for BM	BM inclusion criteria	% included BM	BM endpoint/ stratification factor	Follow up CNS	OligoPD CNS treatments during study allowed/ specified	Results
PROFILE 1007 (NCT00932893), Shaw *et al.* 2013, (41)	Phase III RCT	Crizotinib *vs.* chemotherapy (pemetrexed or docetaxel) in pretreated patients	CT/MRI brain mandatory	Stable treated BM or asymptomatic untreated BM	35% (120/347) (35% crizotinib, 34% chemotherapy)	No/prespecified stratification factor	Brain imaging Q6W if BM at baseline	No (PD: study discontinuation. Treatment discontinuation if clinical benefit)	PFS HR: BM 0.67 (BM present) *vs.* 0.43 (BM absent) in favour of crizotinib
PROFILE 1014 (NCT01154140), Solomon *et al.* 2014, (37)	Phase III RCT	First line crizotinib *vs.* cis- or carboplatin/ pemetrexed	CT/MRI brain mandatory	Treated BM (if neurologically stable >2 weeks before enrollment and no ongoing requirement for glucocorticoids) eligible	26.8% (92/343) (26% crizotinib, 27% chemo)	No/prespecified stratification factor	Brain imaging Q6W if BM at baseline, Q12W otherwise	No (PD: study discontinuation. Treatment continuation if clinical benefit)	PFS HR: BM 0.57 (BM present) *vs.* 0.46 (BM absent) in favour of crizotinib

Table 2 (*continued*)

Table 2 (*continued*)

Trial	Type of trial	TKI	Screening for BM	BM inclusion criteria	% included BM	BM endpoint/ stratification factor	Follow up CNS	OligoPD CNS treatments during study allowed/ specified	Results
ASCEND-4 (NCT0182809), Soria *et al.* 2017, (36)	Phase III RCT	First line ceritinib *vs.* cis- or carboplatin/ pemetrexed	Brain CT or MRI	Asymptomatic or stable CNS metastases eligible (neurologically unstable or has required increasing doses of steroids within the 2 weeks prior to screening exclusion)	32% (121/376) (31% crizotinib, 33% chemotherapy)	icORR, icDCR, icDOR (secondary endpoints)/ Yes	If positive at baseline Q6W	No not allowed	Ceritinib BM group: 48% (15/31) icPD only, 42% extracranial PD only and 10% both. Ceritinib no BM group: 30% (24/81) icPD only, 69% extracranial PD only, 1% both. Median PFS in months in BM group 10.7 (ceritinib) *vs.* 6.7 (chemotherapy), icORR 46.3%
ASCEND-5 (NCT01828112), Shaw *et al.* 2017, (42)	Phase III RCT	Ceritinib *vs.* pemetrexed or docetaxel after chemotherapy and crizotinib	Brain CT or MRI	Asymptomatic or stable CNS metastases eligible (neurologically unstable or has required increasing doses of steroids within the 2 weeks prior to screening exclusion)	58% (134/231) (57% ceritinib, 59% chemotherapy)	icORR, icDCR, icDOR (secondary endpoints)/ yes	If positive at baseline	–	Median PFS in months in BM group: 4.4 ceritinib, 1.5 chemotherapy. 68% had PD, 51% icPD only (21/41), 41% extracranial PD only, 7% both. In no BM group: 62% had PD. 15% icPD only, 85% extracranial PD only. 35% icOR. median icDOR 6.9 months
Lorlatinib (NCT01970865), Solomon *et al.* 2018, (40)	Phase II	First, or next line lorlatinib	MRI of the brain	Asymptomatic CNS metastases (including patients controlled with stable or decreasing steroid use within the last 2 weeks before study entry) LM eligible	60% (166/275) [Group 1 treatment naive ALK+ 8/30 (27%). Group 2–5 ALK+ with previous treatment 67% (133/198)]	Primary endpoint: intracranial tumour response; secondary endpoint: icDOR, CSF concentration lorlatinib, probability of CNS progression/yes	Brain MRI Q6W	No (PD: treatment discontinuation. Continuation if clinical benefit allowed)	IcORR group 1: 66.7%, group 2–5: 63%. Median time to first ic response in months: group 1: 2.0, group 2–5: 1.4. Median icDOR: group 1: NR, group 2–5: 14.5
ALTA-1L (NCT02737501), Camidge *et al.* 2018, (35)	Phase III RCT	First line brigatinib *vs.* crizotinib	MRI of the brain	Treated or neurologically stable for 7 days before randomization (symptomatic CNS metastases (BM or LM) at screening or asymptomatic disease requiring an increasing dose of corticosteroids <7 days prior to randomization exclusion)	29.5% (81/275) [Brigatinib 40/137 (29%); Crizotinib 41/138 (30%)]	Secondary endpoints: icORR, icPFS/prespecified stratification factor (BM present or absent)	Brain MRI Q8W	Patients with CNS lesions requiring local radiotherapy such as SRS are allowed to continue the study drug after appropriate interruption	IcORR: brigatinib 83%, crizotinib 33%. 12-month survival without icPD in BM group: brigatinib 67%, crizotinib 21%
ALUR (NCT02604342), Novello *et al.* 2018, (43)	Phase III RCT	Alectinib *vs.* Docetaxel or pemetrexed after platinum-based doublet chemotherapy and crizotinib	CT/MRI brain	Asymptomatic or clinically stable treated CNS or LM	71% (76/107) (69% alectinib, 74% chemotherapy)	icORR, icDCR, icDOR/ yes	Brain imaging Q6W	–	PFS BM group in months: 9.7 (alectinib) *vs.* 1.4 (chemotherapy), icORR 41.9%, icDCR 83.7%
ALEX (NCT02075840), Peters *et al.* 2017, (34)	Phase III RCT	Alectinib *vs.* crizotinib	CT/MRI brain	Treated/untreated BM eligible. Previous CNS RT allowed if completed ≥14 days before enrollment	40.3% (122/303) [Alectinib 64/152 (42.1%), Crizotinib 58/151 (38.4%)]	CNS efficacy endpoints (icPFS, time to CNS progression, icORR, icDOR/CNS metastases prespecified stratification factor	Brain imaging Q8W	No	Patients BM group: CNS progression without prior non-CNS PD crizotinib 56.9%, alectinib 18.8%; non-CNS progression without prior CNS PD crizotinib 24.1% alectinib 17.2%; death without prior CNS or non-CNS PD crizotinib 6.9% Alectinib 10.9%. Patients no BM group: CNS progression without prior non-CNS PD crizotinib 37.6% alectinib 6.8%; non-CNS progression without prior CNS PD crizotinib 20.4% alectinib 28.4%; death without prior CNS or non-CNS PD crizotinib 5.4% alectinib 4.5%

CNS, central nervous system; ALK, anaplastic-lymphoma-kinase; TKI, tyrosine kinase inhibitor; BM, brain metastases; PD, progressive disease; RCT, randomised controlled trial; NR, not reported; CT, computer tomography; MRI, magnetic resonance imaging; Q6W, every 6 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; ic, intracranial; PFS, progression free survival; HR, hazard ratio; ORR, overall response rate; DOR, duration of response; DCR, disease control rate.

was analysed with NSCLC *BRAF*-V600E treatment naive patients, 5.6% of patients had BM at baseline (51). BM specific outcome was not a prespecified endpoint. The 3 included patients with BM had stable disease as best intracranial response (51,52).

NTRK rearrangements occur in up to 3% of NSCLC patients (53). In the entrectinib phase 1 and 2 trial, 22% of patients had BM at baseline with a mandatory baseline BM screening. Patients with stable asymptomatic BM were eligible. IcORR, icDOR, icPFS were prespecified secondary endpoints (54). The larotrectinib phase I and II trials showed an 8% incidence of BM at baseline. However, screening for CNS metastases at baseline was not mandatory and the group of patients consisted of a heterogeneous population of solid tumours including pediatric patients. Patients with asymptomatic treated and untreated BM were eligible. Of the three patients with measurable baseline BM, one had icCR, one icPR and one icSD (55).

RET rearrangements occur in 1–2% of NSCLC patients. Incidence of BM in *RET*-rearranged NSCLC at baseline is 25%, with a lifetime incidence of 46%. CNS metastases seem to have a good response to treatment with pralsetinib and selpercatinib however, data is still very limited and more extensive data will follow (56,57).

Detailed trial description and results are summarized in *Table 3*.

Oligometastatic disease

Different types of oligometastatic disease exist. All are relevant in the treatment of patients with an oncogenic driver and CNS metastases. The different types of oligometastases are summarized below, and put into context regarding CNS oligometastatic disease in patients with an oncogenic driver.

Oligometastatic disease is defined as a limited number of metastases. Two small randomized clinical trials showed improved survival when radical local therapy was added to standard systemic therapy for synchronous oligometastatic NSCLC, not progressing on induction systemic treatment (58,59). Different types of oligometastatic disease (e.g., synchronous, metachronous, oligopersistent, oligoprogressive) could represent different prognoses and possibly also different treatment scenarios. Recently, the European Society for Radiotherapy and Oncology (ESTRO) together with the European Organisation for Research and Treatment of Cancer (EORTC) developed a proposal for characterization and classification of oligometastatic disease (60). Furthermore, the EORTC lung cancer group provided a detailed definition plus staging consensus for synchronous oligometastatic NSCLC (61).

De novo oligometastatic disease (first time diagnosis of oligometastatic disease) can be defined as synchronous oligometastatic disease (≤6 months between primary cancer diagnosis and oligometastatic disease diagnosis) or metachronous oligometastatic disease (>6 months between primary cancer diagnosis and oligometastatic disease diagnosis).

Synchronous and metachronous CNS oligometastases in patients with an oncogenic driver

To the best of our knowledge, there is very limited data on the percentage of patients with an oncogenic driver and synchronous or metachronous CNS oligometastases. A phase III randomised controlled trial (RCT), comparing first line gefitinib to gefitinib with pemetrexed-carboplatin in *EGFR* mutated NSCLC patients showed that 4.3% of enrolled patients had oligometastases to the brain at baseline. However, this study had no mandatory screening of the CNS at baseline and the true percentage of CNS oligometastatic patients is not known (62). Most data are derived from CNS oligoprogression during TKI treatment, as is discussed below.

CNS oligoprogression during TKI treatment

Oligoprogression is defined as development of metachronous oligometastatic disease in patients under active systemic treatment. This type of oligometastatic disease is mainly prevalent in patients with oncogene driven NSCLC treated with targeted therapy. For TKIs with poor CNS penetration, oligometastatic disease in the brain is found in up to 38% of patients. In a post hoc analysis of the PROFILE 1014 trial intracranial progression without extracranial progression in the intention to treat population occurred in 24% of crizotinib patients and 10% of chemotherapy patients. This was in patients with treated BM respectively 38% *vs.* 23% and in patients without BM 19% *vs.* 6% (63). In a retrospective series of 21 crizotinib-treated patients, 38% developed oligoprogression in the brain without extracranial progression (64). In the ASCEND-4 trial 48% of the patients with baseline BM had CNS progression as first site of progression, compared with 30% in the group without baseline BM. It was not

Table 3 Summary CNS characteristics pivotal phase I and II trials ROS1/MET/BRAF V600E/NTRK

Trial	Phase	TKI	Screening for BM	In- or exclusion	% included BM	BM is endpoint/stratification factor	Follow up CNS	OligoPD CNS continues in study (yes/no)	Results
Lorlatinib (NCT01970865), Shaw *et al.* 2019, (45)	Phase I-II (ROS1 alteration)	Lorlatinib in treatment naive patients, disease progression after at least 1 ROS1 inhibitor therapy or any number of previous therapies	MRI brain	Asymptomatic treated or untreated CNS metastases eligible. Asymp LM eligible	57% (39/69)	Primary objective ic tumour response; secondary objective icDOR, time to icPD/yes	Brain imaging Q6W	PD: treatment discontinuation. Continuation allowed beyond progression	Ic responses: TKI naive; 11 pts with baseline BM. 45% CR, 18% PR, 18% SD, 18% PD. Previous treatment with crizotinib only; 24 pts with baseline BM. 38% CR, 13% PR, 25% SD, 8% PD
METROS (NCT02499614), Landi *et al.* 2019, (48)	Phase II (ROS1 or MET alterations)	Crizotinib in pretreated patients	NR	Stable and treated BM	ROS1 23% (6/26), MET 19% (5/26)	No/no	Brain imaging Q8W	No	Baseline BM: 6 ROS1; 2 CR, 4 SD, 3 only intracranial PD (50%). 5 MET; 2 PD, 3 SD
Dabrafenib/trametinib (NCT01336634), Planchard *et al.* 2016, (50)	Phase II (BRAF V600E)	Dabrafenib plus trametinib in previously treated patients	NR	Asymptomatic, untreated, measured <1 cm eligible. Treated BM, clinically and radiologically stable 3 weeks after local therapy	1.8% (1/57)	No/no	NR	No	ic response: SD. No patients with new BM as part of their progression
Dabrafenib/trametinib (NCT01336634), Planchard *et al.* 2017, (51)	Phase II (BRAF V600E)	Dabrafenib plus trametinib after previously untreated patients	NR	Asymptomatic, untreated, measured <1 cm eligible. Treated BM, clinically and radiologically stable 3 weeks after local therapy	5.6% (2/36)	No/no	NR	No	IC response: SD
Entrectinib (NCT02097810, NCT02568267, EudraCT 2012-000148-88), Doebele *et al.* 2020, (54)	Phase I and II (NTRK)	Entrectinib in previous treated solid tumours	MRI or CT	Controlled asymptomatic CNS involvement allowed	22% (12/54)	Secondary endpoints: ic response, ic DOR, icPFS/yes	Brain imaging Q8W	No	BM at baseline group: 6/12 (50%) PR, 4/12 (33%) SD. 17/54 CNS progression event. Median time to progression 17 months
Larotrectinib (NCT02122913, NCT02637687, NCT02576431) Hong *et al.* 2020, (55)	Phase I and II (NTRK)	Larotrectinib in previous treated solid tumours	No	Asymptomatic treated and untreated BM	8% (13/159) (6/13 lung)	No/post hoc exploratory subgroup analysis	Brain imaging Q8W	Asymptomatic progression solitary site local therapy option with continuation larotrectinib	ORR in baseline BM group 75%. 3/12 patients with BM measurable disease. Of these 1 icCR, 1 icPR, 1 icSD

ROS1, ROS proto-oncogene 1; MET, amplification or MET exon 14 mutations; BRAF V600E, B-Raf proto-oncogene; NTRK, N tropomyosin receptor kinase; CNS, central nervous system; TKI, tyrosine kinase inhibitor; BM, brain metastases; LM, leptomeningeal metastases; NR, not reported; CT, computer tomography; MRI, magnetic resonance imaging; ic, intracranial; PD, progressive disease; CR, complete remission; PR, partial remission; SD, stabile disease; Q6W, every 6 weeks; Q8W, every 8 weeks; OR, overall response; DOR, duration of response; PFS, progression free survival; ORR, overall response rate.

reported if there was a difference between patients with or without previously radiotherapy to the brain (36). In the ASCEND-5 trial 51% of the patients with baseline BM had intracranial progressive disease as first site of progression compared with 15% in the group without baseline BM (42). A retrospective Swiss cohort study analysing 50 *EGFR* T790M-positive NSCLC patients treated with osimertinib showed that 17% of patients progressed in the brain of whom 83% had oligoprogression (65). Similar data were reported for the FLAURA trial, in which 13% of osimertinib treated patients developed oligoprogression to the brain only (abstract only data). In the ALEX trial, CNS only progression (without non-CNS progression, analysed with a competing risk analysis) was significantly less frequent at 12 months in the alectinib arm compared with the crizotinib arm, both in radiotherapy pretreated BM as well as untreated BM (8.6% *vs.* 50.4%, and 20.5% *vs.* 62.5%, respectively (66). Similar results were found for brigatinib in the ALTA-1L trial. The 1-year cumulative incidence of intracranial progression without prior systemic progression for brigatinib *vs.* crizotinib was 12% (95% CI, 6–20%) *vs.* 23% (95% CI, 15–31%), respectively (35).

CNS oligopersistent disease

The last subtype of oligometastatic disease is oligopersistent disease, reflecting persistent non-progressive oligometastases under active systemic treatment. Data for oncogene driver CNS oligopersistent disease do not exist to the best of our knowledge.

These definitions are important because the prognosis and the treatment scenarios could be different between these entities (60). Furthermore, the underlying molecular mechanisms might differ between the oligometastatic entities.

Molecular analysis of CNS metastases

The question whether CNS metastases harbor distinct genetic alterations beyond those observed in primary tumors has not been definitively addressed. Data with whole-exome sequencing in 86 patient-matched BM (including 38 NSCLC patients) reported 53% of cases with potentially clinically informative alterations in BM that were not detected in the matched primary tumor sample (67). Interestingly, upon comparison of samples obtained from multiple different BM from the same patient, most anatomically distinct BM were found to share virtually all actionable driver alterations (29 of 30, in a total of seven patients) (67,68).

However, these findings have a number of technical limitations such as limited genomic characterisation and are yet to be supported by clinical evidence. On the other hand, overall response rate (ORR) to targeted therapies in molecularly defined NSCLC patients are typically similar in CNS and extra-CNS disease, arguing for fewer molecular discordances between the primary tumor and CNS metastases, at least for actionable mutations (18). Furthermore, recent insights into LM biology have shown that LM might have different molecular alterations compared to solid BM. In particular, LM have been found to be enriched in *EGFR*, *MET*, and tumor protein p53 (*TP53*) mutations, whereas they rarely harbor *KRAS* alterations (7.7%) compared to other solid metastases from NSCLC (69,70).

In oncogene-addicted NSCLC, isolated CNS progression is common especially in patients treated with 1st or 2nd generation TKIs as is described above (18). Although this is most likely related to insufficient blood-brain barrier (BBB) penetration of TKIs (71), the development of secondary resistance mutations or histologic transformation should also be considered as a potential cause of disease progression, as is most often the case for extracranial progression. The presence of the oncogenic driver mutation in brain *vs.* extracranial metastases or the primary tumor differs greatly across studies. Small case series have investigated the concordance of *EGFR* mutation status between primary tumors and matched CNS metastases. Discordance rates between 0 and 32% have been reported (72). It was also shown that 3 out of 24 patients (12.5%) with both surgically resected BM and primary NSCLC, had evidence of histologic transformation in BM (73). Genomic profiling on tissue obtained from a progressing lesion to detect an acquired resistance to any TKI is considered the gold standard to determine the cause of resistance to the TKI. However, studies have shown that analysis of CNS metastases fails in up to 25% of the cases (74). Furthermore, in most patients with isolated CNS progression obtaining a tissue biopsy is not expedient due to the potential risk of neurological complications. Circulating tumor DNA (ctDNA) has emerged as a minimally-invasive tool, especially in the case of difficult-to-biopsy lesions or insufficient tissue material (75,76). It is well established that oncogenic drivers and resistance mutations can be detected in ctDNA in both plasma and cerebrospinal fluid (CSF) with high

sensitivity and specificity (76,77). However, in case of oligoprogression in the CNS, the BBB might reduce the presence of ctDNA in the bloodstream as has been reported by Aldea *et al.* who showed that the detection rate of ctDNA was significantly lower in NSCLC patients with isolated CNS progression compared with patients with extra-CNS progression (52% and 84% respectively, P<0.00001) (78). Since classic TKI resistance mechanisms, i.e., the T790M-mutation in *EGFR* mutated NSCLC, develop under selective pressure of EGFR-TKI treatment and given the fact that the BBB reduces the penetration of TKIs into the CNS, it has been stated these mechanisms of resistance would normally not be detected in tumor cells from the CNS (79). Nevertheless, there are reports where mutation analysis was performed on malignant cells present in the CNS and where the T790M mutation was detected (80). Therefore, analysing ctDNA in the CSF seems to provide a valid alternative to detect genomic alterations of LM and CSF ctDNA may also represent the molecular status of intracranial lesions (81).

CNS penetration rate TKI

Despite favourable intracranial response rates with the current first line EGFR- and ALK-TKIs administered in standard daily doses [up to 91% for osimertinib and 81% for alectinib, respectively (12,13)], a significant number of patients will still develop isolated CNS progression as is described above (82,83) despite significant BBB penetration. At present, our understanding of BBB penetrating capabilities of TKIs has improved considerably. The key molecular properties that influence the BBB are: the P-glycoprotein (PGP) or breast cancer resistance protein (BCRP) substrate nature of the TKIs, their molecular weight, polar surface area (PSA) and lipophilicity index (LogP) (84,85).

For first generation EGFR-TKI erlotinib and gefitinib, the BBB permeation or diffusion rates are 2.8–5.1% and 1.1%, respectively (21,86,87). The CSF penetration rates of erlotinib and gefitinib are 2.77±0.45 and 1.13±0.36, respectively, and CSF concentration rates are 28.7± 16.8 and 3.7±1.9 ng/mL, respectively (87-89). Hence, compared to gefitinib, the pharmacokinetic parameters of erlotinib appear more favourable. There is preclinical evidence that afatinib is an effective treatment for CNS metastases despite incomplete penetration of the BBB (27,90) even after resistance to erlotinib or gefitinib has developed (91). Nevertheless, in LUX-LUNG 7 the magnitude of PFS improvement with afatinib *vs.* gefitinib was similar to that observed in patients with or without BM (31). For dacomitinib, another second-generation EGFR-TKI, clinical data on the effect on CNS metastasis is not well known since these patients were specifically excluded from the ARCHER 1050 study (29) and another study of dacomitinib in patients with progressive BM (NCT02047747) was terminated early.

Although the third generation EGFR-TKI osimertinib is a substrate for both PGP and BCRP efflux transporters, *in vitro* data have shown that unlike other EGFR-TKIs, the penetration rate of osimertinib is sufficient to overcome this efflux (92). Preclinical evidence in nonhuman primates shows that osimertinib has greater penetration of the BBB and higher brain exposure compared with other EGFR-TKIs (92). In a PET study of healthy human volunteers, a single microdose of [^{11}C]osimertinib demonstrated rapid and widespread distribution in the brain (93).

CSF penetration rate for crizotinib is only 0.0026% (19). For patients with *ALK*-rearranged NSCLC, next generation ALK inhibitors were designed to cross the BBB more efficiently than crizotinib and to achieve higher concentration in the CSF, thus offering a prominent ability to control CNS spread. This effect was accomplished by reduction of their molecular weight, increasing lipophilicity and changing the number of available hydrogen bond donors. Next generation ALK-TKI are therefore more promising in the treatment of BM. CSF penetration rate for second generation ALK-TKIs alectinib and ceritinib are 87% and 15%, respectively (19). Paired CSF and systemic plasma samples analysis for alectinib demonstrated the linear relationship between CSF and free alectinib plasma concentrations (94). Brain responses have also been described after progression on crizotinib (95). The phase II ASCEND-7 study showed that ceritinib was active in ALK-positive patients with BM and LM regardless of prior treatment that included brain radiotherapy and prior ALK inhibitor therapy, radiotherapy alone, or prior sole ALK inhibitor therapy (96). Moreover, the selective, potent, brain-penetrant 3rd-generation ALK-TKI lorlatinib showed clinically meaningful antitumor activity in both intracranial and extracranial compartments, in the post 2nd-gen ALK-TKI setting. Despite the development of TKIs with better penetration of the BBB, progression or the development of CNS metastases still occurs frequently. To increase the permeability and CSF concentrations of TKIs, their administration in "pulsatile" high-doses has been investigated (97,98). Furthermore,

because of oral administration of TKIs, the intrapatient and interpatient exposure is highly variable and is affected by many factors, such as concomitant use of food and herbs. Food-drug interactions are capable of altering the systemic bioavailability and pharmacokinetics (PK) of these drugs (99). Therefore, in suboptimally dosed patients, increasing the maximum concentration of drug in plasma blood and the CNS, e.g., dosing with food (99) or combining with other drugs such as proton pump inhibitors (100) might be necessary. Last, in patients with suboptimal TKI concentrations, therapeutic adherence should be evaluated, and if necessary, new instructions should be given.

Treatment options of CNS oligoprogression

Clinical controversies in the optimal management of oligoprogressive disease, especially CNS oligoprogression, remain due to a lack of prospective data comparing different treatment strategies (101). Furthermore, as is described above, a clear definition of oligometastatic disease has only been proposed recently (60). Whether to treat disease with a change of systemic therapies or to offer local ablative treatment [i.e., most often stereotactic radiosurgery/therapy (SRS/SRT), if possible] is still a matter of debate. Ablative treatments are able to effectively target resistant clones regardless of the mutational genotype or load. Therefore, this may be an attractive additional treatment option for patients presenting with oligoprogression before considering a change in systemic treatment. In practice, the conventional approach to patients presenting with oligoprogressive disease varies depending on a number of patient factors including the site of oligoprogression, the number, size and location of the CNS metastases (i.e., option to offer local ablative therapy) and of course the type (BBB penetration or not) and number of subsequent lines of systemic treatments available.

Recently, the response assessment in neuro-oncology (RANO)-BM working group has made a framework for the conduction and evaluation of clinical trials for patients in the context of CNS metastases in order to generate more robust data on CNS activity than it has in the past (101). It is important to use bicompartmental efficacy assessments, specific protocol wording to record best overall, best CNS, and best systemic responses and duration of benefit, and to clarify permitted actions at CNS progression *vs.* non-CNS progression (102).

Local treatment options (radiotherapy/surgery)

Local treatment options for BM consist of whole-brain radiotherapy (WBRT), SRS/SRT (further described as SRT) or surgical resection. These treatments can relieve intracranial symptoms and improve intracranial local control. However, all of these treatments have a risk of neurotoxicity, which can occur months after treatment (e.g., symptomatic radiation necrosis after SRT, cognitive decline after WBRT) (103,104). Therefore, especially WBRT with its late neurocognitive toxicity is being more and more avoided in patient with an oncogenic driver. Surgery is usually only used in case of a patient with neurological symptoms due to mass effect. Surgery would also be interesting to evaluate CNS resistance mechanisms in patients with CNS oligoprogression while on TKI treatment. To the best of our knowledge, no high-level data exist on this topic.

Furthermore, for each patient with CNS metastases, the risk-benefit ratio of local therapy, and the alternative of systemic treatment with CNS efficacy should be evaluated (i.e., alectinib after progression on crizotinib in *ALK*-rearranged NSCLC patients or osimertinib after progression on erlotinib in *EGFR*-mutated NSCLC patients with a T790M mutation) , taking into account the expected long term OS.

Broadly speaking, three situations can occur in driver mutated patients with CNS metastases eligible for a TKI. The first is a treatment naive patient with CNS metastases. The second is a patient treated with a TKI, developing oligoprogression in the brain. The last is a patient who develops simultaneous CNS and extra-CNS progression under TKI treatment.

By giving upfront TKIs and postponing radiotherapy to a TKI naive patient, the possible neurotoxicity could be delayed, which is important because of the increasing survival in this patient group. Furthermore, by upfront TKI, the extracranial disease will be controlled as early as possible. However, icORR is not 100%, and patients can develop neurological symptoms due to their progressing CNS metastases. A multi-institutional retrospective analysis including *EGFR*-mutated NSCLC, TKI naive patients who developed BM, demonstrated that the use of upfront EGFR-TKI, and deferral of radiotherapy was associated with inferior OS. SRT followed by EGFR-TKI resulted in the longest survival. However, this study is limited by its retrospective nature with inherent

selection bias (94). A systematic review and meta-analysis evaluated whether upfront cranial radiotherapy improved intracranial disease control and survival in *EGFR*-mutant NSCLC with BM compared with TKIs alone. The study included 12 observational non-comparative studies, of which 6 prospective and 6 retrospective. Upfront cranial radiotherapy resulted in similar icORR, improved four-month icPFS and improved two-year OS, but caused more neurological adverse events compared with TKIs alone (105). To complicate matters, preclinical studies demonstrate a possible synergistic effect of TKIs given concurrently with radiation, but toxicity data of this concurrent strategy is largely lacking in daily clinical practice (106-108). A retrospective analysis showed that in patients with *EGFR* and *ALK* concomitant radiotherapy (SRT) and TKI seemed to positively affect OS with limited toxicity in selected patients (93). A systematic review concluded that there are arguments that TKI combined with WBRT could be given safely (however high-level evidence is lacking, and evidence was only found for erlotinib, gefitinib and icotinib, while data on other TKI or SRT were largely lacking) (109). When WBRT was given combined with SRT and concurrent EGFR-TKI neurotoxicity increased (95). A few studies looked specifically at isolated intracranial oligoprogression. One retrospective study assessed the clinical efficacy of continuing an EGFR-TKI following radiotherapy after isolated CNS failure. The overall median PFS was 2.6 months with a median extracranial PFS of 5.6 months. Al the patients were evaluated for their evaluable lesions with imaging approximately every 2 months (110). Another retrospective analysis including CNS oligoprogressive *ALK* or *EGFR* positive NSCLC patients treated with crizotinib or erlotinib respectively, investigated the benefits of local ablative treatment (included SRT and WBRT) to the CNS metastases. The median PFS (calculated from time of initiation of targeted therapy to first progression of disease) was 7.1 months (111). A retrospective study evaluated continuing crizotinib after radiotherapy (4 patients WBRT and 3 patients SRT) to isolated CNS metastases in 7 *ALK* NSCLC patients. The median PFS, from time of start crizotinib to first progression, was 5.5 months. All these patients continued to receive crizotinib for at least 4 months without disease progression (64). The previously mentioned pooled analysis of the PROFILE trials showed data of 34 patients, developing intracranial progression only and continued the use of crizotinib. About 80% of these patients received radiotherapy. The median treatment duration post progression was 19.3 weeks (20). As the majority of these studies were retrospective, and most of them only included patients treated with a first generation TKI, the optimal treatment strategy or sequence of the combination of (newer) TKIs and local therapy remains unclear, especially in those with a non-*EGFR* driver. In 2018, an EORTC lung cancer group survey among 462 physicians, showed that management of CNS metastases was indeed highly variable in Europe, showing the lack of high-level evidence regarding management of CNS metastases in patients with an oncogenic driver (8).

Future research should focus on the best order of systemic and local treatment; upfront cranial radiation or upfront TKI with salvage radiotherapy for oligo-progressive CNS disease. Trials currently ongoing and investigating this issue are a study of osimertinib and SRT *vs.* osimertinib alone for BM in *EGFR* positive NSCLC patients (NCT03769103); The OUTRUN trial, a phase II trial of osimertinib with or without SRT for *EGFR* positive NSCLC patients with BM (NCT03497767); the BRART trial, investigating the role of brain radiotherapy in patients with asymptomatic BM in the era of targeted therapy for NSCLC (NCT04193007); a phase III RCT investigating the efficacy of EGFR-TKI alone in *EGFR*-positive NSCLC patients *vs.* EGFR-TKI concurrent with WBRT (NCT02714010) and the Cambridge Brain Mets Trial, investigating whether administration of a low dose of targeted radiotherapy during afatinib treatment could increase the concentration of drug penetration into the BM (NCT02768337). Furthermore, in both TKI treatment naive patients with CNS disease, as in those with oligoprogressive CNS disease during TKI treatment the use of concurrent treatment strategies should be further evaluated. The EORTC survey of Levy *et al.* showed that depending on the type of TKI, up to 44% of physicians continued the TKI concurrent with cranial irradiation. For those discontinuing the TKI, time of, and reasons for discontinuation were variable (8). As these patients often have a long survival, long-term toxicity and QoL should be taken into account as well. Currently, a multicenter phase IV trial is ongoing, with as primary endpoint neurotoxicity, investigating whether TKIs can be given safely concurrent with SRT or WBRT in CNS oligoprogressive patients treated with a TKI (NTR6707). Another ongoing phase I trial in *EGFR* positive NSCLC patients with 1–10 BM (3 cm or less in greatest dimension) is investigating whether macro BM can be controlled with SRT concurrent with osimertinib to control micro BM and avoid WBRT to

prevent cognitive decline (NCT03535363).

Systemic treatment options

Although attractive in many cases, the utility of conventional systemic therapy in the treatment of BM has historically been limited due to poor penetration across the BBB and blood-tumor barrier (112). Traditional clinical trials for systemic therapies have excluded patients with symptomatic or uncontrolled BM due to these challenges with CNS penetration (113). The development of new generation TKI with better CNS permeability also challenges the concept of upfront radiotherapy for CNS metastases as is also described above, offering both better efficacy and tolerability. Moreover, in retrospective series, patients with *EGFR* mutations and *ALK* rearrangements who continue TKI beyond first progression, especially those with isolated CNS progression, have been suggested to have a survival benefit when treated with local CNS therapy, compared with patients who stop TKI (111,114,115). Tumour flare, which can occur with the interruption of TKI, again in particular in patients with CNS disease, may play a role in this (111,116). Furthermore, the third generation EGFR-TKIs (osimertinib, rociletinib, and AZD3759) have been proved in preclinical and early clinical studies to penetrate the BBB more effectively than previous generation EGFR-TKIs, and overcome their most common mechanisms of resistance (92,117).

As mentioned before, "pulsatile" high-doses of TKI to increase the permeability and CSF concentrations have been investigated. Currently this concept is used in series to treat BM and LM that developed during standard dose EGFR-TKI. Erlotinib has better BBB penetration than afatinib or gefitinib, and dose-intensification strategies have been proven to improve CNS diffusion of TKI (87,88). Prospective studies have confirmed the feasibility of TKI dose increase in clinical practice, notably for erlotinib and osimertinib (98,118). In small series, high-dose EGFR-TKIs and switch of EGFR-TKI treatment have been described as treatment options. In a phase I prospective study, median neurological PFS and OS with high-dose gefitinib (750–1,000 mg) were reported as 2.3 and 3.5 months, respectively (N=7) (119).

Data on treatment outcomes of oncogene-addicted NSCLC patients diagnosed with LM during or after first generation TKI treatment are scarce. Several case studies have reported successful treatment of LM with high-dose pulsatile administration of erlotinib (120); however, a retrospective study of patients with LM refractory to standard dose EGFR-TKIs found no difference in the median OS between patients treated with high-dose erlotinib (N=12) and those treated with standard-dose EGFR-TKIs (N=23; 6.2 *vs.* 5.9 months, respectively); median time to CNS progression was 2.3 months (121). In the BLOOM trial, a phase 1 study, the antitumor efficacy, PK and safety of osimertinib 160 mg once daily in patients with *EGFR*-mutated NSCLC and LM whose disease had progressed on previous EGFR-TKI therapy (98). Confirmed CSF response was observed in 28% of patients during treatment. However, the definition of CNS response was complete CSF clearance of tumor cells while more recent studies have defined partial CSF response as a ≥50% reduction in CSF tumor cells because CSF clearance is seldom achieved (77). Moreover, in the BLOOM study, the data showed no positive effect of prior brain radiotherapy on LM response to osimertinib. LM ORR was 55% in patients who received prior brain radiotherapy compared with 57% in patients who did not receive prior brain radiotherapy (98).

Besides dose-intensification strategies, several studies have looked at combining EGFR-TKI with vascular endothelial growth factor directed monoclonal antibody therapy (122). The BELIEF trial was an international, multicenter, single-arm phase II trial of 109 treatment-naïve, advanced or metastatic, *EGFR*-mutant, lung adenocarcinoma patients treated with the combination erlotinib and bevacizumab (123). Thirty-seven patients (34%) harbored T790M mutations and 21 (19%) had BM; the median PFS was 13.2 months overall and 8.8 months for patients with BM (123). The efficacy of this combination in the BM population does not appear to be superior to standard EGFR TKI therapy (27), however only 21 patients with BM were included in the BELIEF trial. One of the greatest concerns with bevacizumab use among brain metastatic patients has been CNS hemorrhage. While CNS hemorrhage carries high morbidity and mortality, the incidence of CNS hemorrhage among bevacizumab-treated patients is less than 0.2% (124). Ongoing studies are investigating the combination of osimertinib and bevacizumab in *EGFR*-mutant NSCLC with BM (NCT02971501).

When all TKI options are exhausted, platinum-doublet chemotherapy is the therapy of choice (7). Intracranial response rates are relatively low compared with TKI (125), and to the best of our knowledge no data exist regarding intracranial efficacy of platinum-doublet chemotherapy in

patients with CNS oligoprogression. Up to date there is no evidence that combining or continuing TKI treatment with platinum-based chemotherapy after CNS progression improves intracranial response rates or OS.

Conclusions

CNS metastases are common in oncogene addicted NSCLC patients. Incidence increases during the course of the disease, especially with first generation TKI treatment, due to the relatively low CNS penetration rate. A significant percentage of TKI treated patients will have CNS oligoprogression, also when treated with next generation TKIs. Unfortunately, most clinical trials did not specify endpoints nor treatment options regarding CNS oligoprogression. Furthermore, CNS efficacy data in clinical trials are not fully comparable, because imaging, eligibility criteria and endpoints were not standardised. Future research is necessary to investigate the best CNS treatment strategy in oncogene driven patients with CNS metastases. This is especially the case for patients with CNS oligoprogression, as trial data are largely lacking, and data available come from retrospective series. Future research with standardisation of clinical trials in the context of CNS metastases is necessary to understand the best order of systemic treatment and local treatment strategies. Both the EORTC oligometastatic consensus papers as well as the RANO proposal could be of help in standardizing clinical trials. Last, special attention should be paid to long-term toxicity, as the majority of oncogene driven NSCLC patients can have a prolonged survival, even in the presence of CNS metastases.

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Footnote

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