Review Article

Achievements and future developments of ALK-TKIs in the management of CNS metastases from ALK-positive NSCLC

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Abstract: Non-small cell lung cancer (NSCLC) represents the paradigm of personalized treatment of human cancer. Several oncogenic druggable alterations have been so far identified, with *anaplastic lymphoma kinase* (*ALK*) gene rearrangements being one of the newest and most appealing. Presence of *ALK* fusions is associated with some particular clinical and pathological features, including a preferential seeding into the central nervous system (CNS). In addition, *ALK* rearrangements are recognized as the strongest predictor for benefit of anti-ALK therapy. Crizotinib, the first ALK inhibitor (ALK-I) licensed in clinical practice, is the standard of care for newly diagnosed patients. Unfortunately, within the first year of treatment the majority of patients become insensitive to crizotinib, with approximately one third of them developing brain metastases (BMs). Optimal management of BMs is one of the major challenges in treating *ALK* positive NSCLC. Several novel and highly CNS penetrant ALK-Is are currently under investigation and available data clearly indicated their ability in controlling intracranial disease.

Keywords: Anaplastic lymphoma kinase (ALK); non-small cell lung cancer (NSCLC); ALK-inhibitors; brain metastases (BMs)

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Introduction

Identification of *anaplastic lymphoma kinase* (*ALK*) gene rearrangements reinforced the role of targeted therapies in lung cancer. The *EML4-ALK* fusion gene is detected in 3–7% of patients with adenocarcinomas of the lung (1) and is associated with specific clinical pathological features, including young age, absent or minimal smoking history and adenocarcinoma histology (2,3). However, such clinical features do not properly select patients for ALK inhibitors (ALK-Is) and, consequently, molecular testing is mandatory (4-6). Indeed, current guidelines recommend to test *ALK* rearrangements at diagnosis all patients with advanced lung adenocarcinoma, due to immediate therapeutic implications (4-6).

Crizotinib (PF 02341066, Xalkori; Pfizer Inc., New York, NY, USA) was the first ALK-I that was tested in a clinical setting, and results of published trials reported a response rate (RR) of 60% with a progression-free survival (PFS) of 8–11 months (7-11). Recently, three large phase III trials demonstrated the superiority of crizotinib over standard chemotherapy, both in first- and second-line settings, thus establishing a new standard of care in ALK positive non-small cell lung cancer (NSCLC) (9-11). Unfortunately, no patient obtained a definitive cure and within the first year of treatment, the majority of patients become refractory to crizotinib due to the emergence of acquired resistance, with some undefined patients experiencing long-term benefit (12-17). In addition, there is a consistent amount of patients for which disease progression occurs only in the central nervous system (CNS), supporting the hypothesis of an inadequate CNS drug penetration (14-16). However, it is

not possible to exclude that, in *ALK* positive NSCLC, the CNS could be simply a preferential location of metastatic spread. Indeed, approximately half of patients develop brain metastases (BMs) independent of whether they receive crizotinib or not, suggesting that the drug might not affect the brain affinity (or organotropism) of the disease (15-17).

BMs are a common complication of advanced NSCLC and are generally considered as a synonymous of limited life expectancy and poor quality of life (18). This is not the case of *ALK* rearranged NSCLC, where a number of patients may have prolonged survival with appropriate treatment, including ALK-directed drugs and local ablative therapy [i.e., whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS)] (19-21). In a recent retrospective analysis, individuals with BMs and *ALK* positive advanced NSCLC exposed to ALK-Is and local therapy had median survival exceeding 4 years, with an impressive survival rate at 2 years of 66% (21); these data are even more impressive, considering that more than 70% of patients had multiple BMs (21). Furthermore, as for such patients median survival tends to be longer than in non-oncogene addicted disease, the probability of developing CNS lesions increases over time (19-21). Beyond crizotinib, several novel ALK-Is are in advanced phase of development and early results have also demonstrated their prominent ability in controlling BMs (22-28).

Aim of the present review is to discuss available data on intracranial activity of ALK-Is and evaluate the future perspectives in the management of *ALK* positive NSCLC with BMs.

Crizotinib

Crizotinib has been the first in class ALK-I licensed for the treatment of *ALK* positive NSCLC. In the last five years, the extensive PROFILE program, particularly the PROFILE 1014 and 1029 trials, clearly established crizotinib as the standard of care in newly diagnosed patients (10,11). Beyond the unequivocal merit of replacing chemotherapy with a targeted agent, all these trials significantly contributed to increase the knowledge about the natural history of *ALK* positive disease. Particularly, it became soon evident that such patients probably had a marked brain affinity as demonstrated by the increasing incidence of developing BMs during the course of the disease, with CNS progression explaining more than one third of crizotinib failure (12,13,29-31).

The activity of crizotinib against BMs has been the focus of two analyses (29,30). In a recently published study, Solomon *et al*. compared the intracranial activity of crizotinib and platinum-pemetrexed chemotherapy in subjects enrolled in the PROFILE 1014 (29). Interestingly, untreated BMs represented an exclusion criterion for study entry, thus precluding the possibility to adequately assess the intracranial activity of treatments. Patients with treated BMs at baseline accounted for approximately 20% of the entire population. A non-significant improvement in intracranial time to progression (ITTP) in favor of crizotinib emerged in overall study population, as well as in patients without and with BMs at baseline (29). Interestingly, after 3 and 6 months of therapy, patients treated with crizotinib obtained a higher intracranial disease control rate (IDCR) when compared to patients receiving chemotherapy (85% versus 45% and 56% versus 25% respectively). Regarding to pattern of failure, extracranial progression was less frequent with crizotinib than with platinum doublet chemotherapy; conversely, in overall study population as in patients with or without BMs, the proportion of subjects having CNS as the only site of progression was higher with crizotinib (29).

Costa *et al*. evaluated the outcome of 275 patients with stable or pretreated BMs included in the PROFILE 1005 and 1007, two trials exploring the efficacy of crizotinib in ALK-I-naive and chemotherapy pretreated subjects (30). Patients were stratified according to prior radiotherapy (60% pretreated and 40% untreated). IDCR at 12 weeks did not differ between the two groups (56% versus 62%), however intracranial response rate (IRR) and median ITTP were nearly doubled in patients with pretreated BMs (RR 33% versus 18%; ITTP 7.0 versus 13.2 months). In both groups, CNS represented the most common site of progression.

Two main considerations derived from these analyses. The first one is that crizotinib, even if superior to chemotherapy, is not able to prevent metastatic spread into the CNS as demonstrated by the fact that the pattern of failure mainly includes appearance of new brain lesions (29). In addition, in untreated BMs the probability of response is much more lower than in extracranial sites, confirming the hypothesis of an inadequate CNS concentration of the drug (29,30). The second one is that RT could have a potential role in enhancing the efficacy of crizotinib by disrupting the blood-brain-barrier (BBB) or modulating the expression of the drug efflux transporter p-glycoprotein (P-gp). For such reason the initial management of patients presenting with BMs should include crizotinib and RT (21). Moreover, RT has a prominent role also in the context of limited intracranial progression (31,32). Weickhardt *et al*. firstly evaluated the addition of local

ablative therapy (i.e., SRS or WBRT) to crizotinb in a small cohort of ALK positive NSCLCs with oligoprogressive disease (defined as progression either within the CNS and/or at limited systemic sites while on crizotinib). For patients with exclusive brain recurrence, continuation of crizotinib beyond progression plus radiation therapy translated into an additional PFS of 7 months. Other analyses specifically conducted in patients with limited brain progression have reported an intracranial PFS exceeding 12 months (21,29). However, the option to continue crizotinib beyond progression should be restricted to those cases with extracranial controlled disease and active CNS lesions amenable for local treatment.

In conclusion, although response in the CNS did occur, the ability of crizotinib in producing long-term intracranial benefit remains suboptimal. For such reason, there is an urgent need of more potent and highly CNS penetrant ALK-Is.

Second-generation ALK-Is

Several novel second-generation ALK-Is are currently being investigated in clinical trials (22-28). Among them, ceritinib (Zykadia Novartis Pharmaceuticals,Basel, Switzerland), alectinib (Alecensa, Roche, Basel, Switzerland), brigatinib (AP26113, ARIAD Pharmaceuticals, Cambridge, Massachusetts, USA) and lorlatinib (PF 02343922, Pfizer Inc., New York, NY, USA), demonstrated efficacy against a wide range of secondary *ALK* mutations and showed higher CNS concentration than crizotinib (33-36), thus representing the ideal drugs to firstly test in crizotinib refractory setting.

Ceritinib

Ceritinib is a novel, oral, highly potent, and selective second-generation ALK-I with a greater preclinical antitumor potency than crizotinib (33). Based on the results of a large phase I trial, it received approval by Food and Drugs Administration (FDA) (37) and European Medical Agency for patients with ALK positive NSCLC who have acquired resistance or were intolerant to crizotinib. The ASCEND-1 was the first trial exploring the activity of ceritinib in *ALK* rearranged NSCLC (22). Notably, in the expansion phase, patients diagnosed were enrolled regardless of any prior ALK-I, thus offering the opportunity to test the drug in the front line as well as in crizotinib-refractory setting. At a dose of 400–750 mg, ceritinib produced an impressive antitumor activity of around 60% in both crizotinib-pretreated and crizotinib-naive cohorts. Moreover, responses were also durable (median duration of response, DOR, 8.2 months) with a PFS of 7.0 months. More interestingly, ceritinib demonstrated activity regardless of the presence of CNS lesions or tumor genotype, as demonstrated by the response obtained in the small fraction of patients with secondary *ALK* mutation or *ALK* amplification. Updated results of the ASCEND-1 trial, after an additional accrual in the expansion cohort, have been recently published. Overall, 246 individuals with *ALK* positive NSCLC (163 crizotinib-pretreated; 83 crizotinib-naive) were enrolled in the study and received ceritinib at the dose of 750 mg daily. In the overall population, RR was 61.8%, with a median DOR exceeding 9 months and a median PFS of 9.0 months. Interestingly, in the group of patients not previously exposed to ALK-Is, RR was numerically higher than in the crizotinib-pretreated group (72% versus 56.4%), as well median DOR (17.0 versus 8.3 months) and PFS (18.4 versus 6.9 months) (38). Furthermore, updated results of the trial provided additional information on the impact of ceritinib in BMs. Data from 124 subjects with CNS disease at baseline were collected and separately analyzed (39). Systemic response, DOR, and PFS were consistent with results observed in the general population. Among the 74 evaluable patients, 10 had measurable disease and achieved a partial response (PR) (34%), whereas five patients with non-measurable disease obtained complete response, with an IDCR of 67%. At the time of data presentation, median intracranial DOR and PFS were not estimable for the ALK-inhibitor-naive group; conversely, in the crizotinib-pretreated group, they resulted of 6.9 and 7.0 months, respectively.

Furthermore, two confirmatory phase II studies in crizotinib-resistant patients and in crizotinib-naive patients rapidly completed accrual, and their results have been presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in 2015 (40,41). Both trials had whole body (WB) and intracranial (I) RR, as assessed by investigators, as their primary end point. The ASCEND-2 enrolled 140 *ALK* positive NSCLC individuals pretreated with at least one prior chemotherapy regimen and who progressed ≤30 days from last treatment with crizotinib (40). The vast majority of patients presented with asymptomatic BMs (71.4%), of which approximately one-third had not received palliative radiotherapy. In the overall population, WB RR was approximately 40% with an overall systemic DCR of 77%, whereas median DOR and PFS were 9.7 and 5.7 months, respectively. By splitting the results according to the presence of BMs, efficacy measures numerically

favored the group of patients without CNS involvement (RR: 52% versus 33%; PFS: 11.3 versus 5.4 months). However, in the small group of patients with measurable disease, the ICDR reached 80%, with complete or PRs observed in five out of the six patients not previously treated with radiotherapy, thus supporting the potential of ceritinib in controlling intracranial lesions. The other study, ASCEND-3, included 124 ALK-I naive individuals pretreated with no more of three lines of chemotherapy (41). Also, in this trial, there was a consistent fraction of patients (40%) presenting with BMs. The trial confirmed the activity of ceritinib in terms of systemic disease control (WB RR 63%; WB DCR 89.5%) and PFS (11.1 months). Moreover, IDCR resulted of 80% with intracranial activity matching or exceeding systemic responses in patients with measurable disease. Taken into account, these data supported the activity of ceritinib in ALK positive NSCLC regardless of BMs or prior therapy with crizotinib.

To further evaluate the efficacy and safety of ceritinib in patients with brain or leptomeningeal metastases, a phase II trial is currently recruiting patients (ASCEND-7, NCT02336451).

Alectinib

Alectinib is a highly selective, second generation, ALK-I showing *in vitro* activity against both wild type and mutated ALK protein, including mutated variants responsible for acquired resistance, such as the gatekeeper L1196 mutation (34) In addition, preclinical data has shown that alectinib is not a substrate for the drug efflux transporter P-gp, and is therefore not actively transported out of the brain (35). For such reasons, alectinib appeared as an ideal drug to test in the setting of acquired resistance with a specific focus on patients with BMs.

The phase I/II AF-002JG trial aimed to establish the recommend phase 2 dose of the drug and evaluate the efficacy of alectinib in *ALK* positive NSCLC individuals who failed and/or were intolerant to crizotinib (24,25). In the phase I portion of the study, 47 patients were sequentially assigned to one of five dose-escalation cohorts: 300, 460, 600, 750 and 900 mg administered orally twice daily (24). According to pharmacokinetic profile and safety data, 600 mg twice daily was chosen as the recommended dose to test in the phase 2 part of the trial. Regard to antitumor activity, overall RR was 55% in the evaluable population (n=44) with an additional 36% of patients obtaining disease stabilization, with an overall DCR of approximately 80%. Moreover, the greatest insight of the trial concerned the intracranial activity of the drug. Among 21 patients with BMs at baseline, 9 had measurable disease, 12 had non-measurable disease, 12 had progressing CNS lesions at study enrollment and 17 had received prior brain radiotherapy (median time from brain radiotherapy to alectinib initiation 126 days). In patients with measurable disease, including one patient with leptomeningeal carcinomatosis, DCR was 77% (PR 55% + SD 22%). A tumor regression or stabilization was observed also in the small group of patients not previously irradiated, confirming the high penetrance of the drug in the CNS. In overall BMs population, RR was 52%, including CR in 29% and 24% PR, and SD was 38%, with only two patients having central progression. More interestingly, in one case the brain lesion increased due to radionecrosis as confirmed at the pathological report. Based on these preliminary results, alectinib gained FDA breakthrough therapy designation for ALK-positive NSCLC. The phase II part of this trial, included 87 ALK positive crizotinib resistant patients from USA and Canada, three-quarters of which previously exposed to chemotherapeutics and more than half of subjects presenting BMs (24). Response-evaluable population accounted for 69 individuals. At the updated analysis RR and DOR were 52% and 13.5 months respectively, while PFS was estimated as approximately 8 months. Sixteen patients had measurable BMs with prior brain radiotherapy offered to 11 of them; 75% of cases achieved an objective response lasting for more than 11 months and, most important, the totality of patients with measurable lesions obtained intracranial control. These findings were replicated in the entire group of patients with BMs (measurable + non measurable disease), in which RR and DOR reached 63% and 11.1 months, respectively. Furthermore, the efficacy of alectinib was maintained in the small fraction of patients who did not receive RT (RR 67%). Interestingly, regard to the pattern of treatment failure, the incidence of non-CNS progression was lower than the incidence of CNS progression, reinforcing the conviction that alectinib could be able to prevent or delay the occurrence of BMs.

Another phase II global study enrolled 138 individuals, of which 84 presenting with BMs at baseline (25). In the overall population, RR and DCR were 50% and 77%, respectively; response was also durable (median DOR: 11.2 months), whereas PFS was approximately 9 months. A marked activity was observed even in the group of patients previously treated with both crizotinib and chemotherapy

(RR 45%). By splitting results according to the presence of BMs, DCR exceeded 80%, with a DOR of 10.3 months, quite similar than the one observed in overall population. More in details, 57% of patients with intracranial measurable disease achieved a response, as did the 43% of individuals not previously treated with radiotherapy. Moreover, the pattern of failure was similar than the one observed in the other trial; indeed, the incidence of non-CNS was higher than the incidence of CNS-progression. On December 2015, alectinib gained FDA accelerated approval for ALK-positive NSCLC who fail or are intolerant to crizotinib.

Furthermore, alectinib is the only ALK-I that has been compared head-to-head with crizotinib. The J-ALEX was a phase III Japanese study aiming to establish the superiority of alectinib 300 mg twice daily over the standard of care in ALK-I naive patients (42). The study met its primary end point demonstrating a significant reduction in the risk of progression in favor of alectinib. The benefit was maintained across all subgroups of patients, including individuals with BMs. However, even if exciting, these results are too preliminary and must be interpreted with caution before anticipating alectinib in front line. First of all, these results have been obtained in a non-Caucasian population and the dose of alectinib was lower than the one used in other studies. Further, there was an imbalance in the proportion of patients with BMs in crizotinib and, most importantly, there was no stratification according to the presence of CNS disease. To solve these issues, a large, global, phase III study, also known as ALEX trial, having as primary and secondary end point PFS and time to CNS progression respectively, are comparing alectinib to crizotinib in newly diagnosed *ALK* rearranged NSCLC.

Brigatinib

Brigatinib is a novel, orally active kinase inhibitor able to inhibit activated forms of ALK and EGFR in cell culture models. Preclinical data also showed that this agent had a 100-fold selectivity for *ALK*-positive versus *ALK*-negative cell lines. In addition, brigatinib potently inhibits a wide range of ALK resistance-mutations, including the L1196M and the G1202R (43). In a recent phase I/II study including 79 NSCLC with *ALK* translocation and pretreated with crizotinib, brigatinib showed an impressive RR 71% with a median PFS of 13.4 months (26). Of note, 8 of 15 patients with measurable brain lesions at baseline obtained a PR and for all patients with intracranial response DOR was 18.9 months, demonstrating the CNS penetration of the agent (26). Kim *et al*. recently presented the results of the randomized phase II ALTA trial, a study specifically designed to test the safety and efficacy of brigatinib at two different doses (27). Overall 222 patients who tested positive for *ALK* gene rearrangements and were refractory to crizotinib were randomized 1:1 to arm A brigatinib 90 mg once per day or arm B brigatinib 180 mg once daily (after a led-in period at 90 mg once daily for 7 days). Notably, approximately 70% of subjects per arm had BMs. In each arm brigatinib yielded consistent activity, although RR and PFS resulted numerically higher in the high dose group (RR: 54% versus 45%; mPFS: 12.9 versus 9.2 months). Intracranial activity was separately analyzed according to the presence of measurable or non-measurable active BMs. In patients with measurable BMs (arm A =25; arm B =19), RR was 37% in arm A and 67% in arm B, whereas DCR exceeded 80% in both arms. In patients with non-measurable BMs (arm A =54; arm B =54), RR and DCR were higher in the 180 mg arm (RR: 6% versus 19%; DCR: 72% versus 87%).

A phase III study directly comparing brigatinib (at starting dose of 90 mg daily for 7 days followed by 180 mg daily) versus crizotinb in ALKIs-naive, advanced ALK+ NSCLC is currently ongoing (NCT02094573).

Lorlatinib

Lorlatinib is a promising next-generation ALK/ROS1 inhibitor that has potent and selective inhibitory activity against all known acquired crizotinib-resistant mutations. Lorlatinib is also capable of penetrating the blood-brain barrier in preclinical animal models (36). Preliminary results of phase I trial evaluating lorlatinib in 54 NSCLC patients with *ALK* and *ROS1* rearrangement who failed prior TKIs and or chemotherapy, have been recently presented (28). Notably, more than 70% of patients had BMs at study entry. In the ALK-cohort (N=41), lorlatinib at the dose of 100 mg daily produced a RR of 46% with an overall DCR of 66%, whereas median PFS was 11.4 months. With respect to patients with target and non-target BMs, RRs were 39% and 31% respectively, thus confirming its high CNS penetrance. The drug is currently in phase II of development (NCT01970865).

Discussion

A number of factors should be considered in the treatment

algorithm of *ALK* positive NSCLC patients with BMs, including patient characteristics, presence of neurological symptoms, lesions characteristics, availability of different ALK-Is and treatment related toxicities.

From a practical point of view, at present, we can identify at least four clinical scenarios. Patients ALK-Is naive with synchronous highly symptomatic and/or life-threatening BMs should be initially treated with corticosteroids and local therapy (radiation therapy or neurosurgery), considering initiation of crizotinib as soon as possible at neurological stabilization. In ALK-Is naive patients with asymptomatic synchronous BMs, radiotherapy and crizotinib initiation should be the preferred choice (29). Patients having asymptomatic CNS as unique site of progression while on crizotinib, can be reasonably managed with local ablative therapy and continuation of crizotinib (31,32), whereas patients with symptomatic brain progression or systemic (intra + extracranial) disease progression, must be switched to another more potent and highly CNS-penetrant ALK-Is, such as ceritinib, alectinib, or brigatinib (22-27) in addition to RT, if feasible.

Indeed, a number of trials have demonstrated that a higher proportion of subjects achieve a response to second generation ALK inibitors, reinforcing the conviction that sequential use of crizotinib followed by another ALK-I may extended survival, even if the best sequence has not been established yet (44-46). In addition, in the context of acquired resistance, not all agents have the same efficacy against secondary *ALK* mutations, thus suggesting that the sequential therapy should be define according to the molecular pattern (47). This could be particularly challenging in those patients with BMs, where identification of mechanisms underlying resistance is difficult to define or it might not mirror the portrait of systemic disease, as suggested by the fact that often CNS lesions anticipate extracranial failures (29). From these perspectives, the choice of the optimal sequence could be particularly difficult. In addition, it is important to remember that all the data on the intracranial efficacy of novel ALK-Is derived from subsets analyses and the vast majority of patients included in these studies had non-measurable disease and had received radiation therapy, thus precluding the possibility to properly assess the intracranial effect of the drug (22-28).

Moreover, the availability of more potent ALK-I, such as ceritinib, alectinib, or brigatinib, raises the question whether their use in front line setting could improve intracranial disease control, possibly delaying CNS progression and preventing the onset of BMs. The ALEX trial has been specifically designed to address this question, as patients with untreated BMs are included and its secondary endpoint is time to CNS progression. If alectinib will replace crizotinib in newly diagnosed patients, including those with BMs at baseline, even the role of RT could be revised. Alectinib plus close radiological brain surveillance might defer or ultimately avoid RT in selected patients.

Although brain RT remains the standard of care for a large amount of NSCLC patients with CNS involvement, caution is required when considering this approach in presence of *ALK* driven disease (19-21). Patients suffering of such condition are often young, are still working, have active lifestyles and even if with BMs, they have concretely chances of relatively long survival. For such reasons, preservation of neurocognitive functions and reduction of long term toxic effect of WBRT are critical points. In patients with up to four BMs from different type of malignancies, the addition of WBRT to SRS significantly reduced the risk of new lesions compared to SRS alone, with no effect on survival and, most importantly, at higher cost in term of neurocognitive decline (48-51). Furthermore, other trials have confirmed that survival outcomes between SRS and WBRT were similar in patients with two to four BMs as well for patients with five to 10 lesions (52-55). In absence of *ad hoc* guidelines, there is a general agreement that in presence of small multiple metastases SRS alone should be firstly considered, thus leaving WBRT as salvage therapy, if feasible. Beyond preservation of neurocognitive functions, other potential advantages support the choice of SRS. Because of CNS is a dominant site of progression patients may require additional courses of radiation, as highlighted in the analysis by Johung *et al*. where a quarter a patients were re-treated three times (19). Moreover, little is know about the safety and tolerability of concomitant ALK-Is and radiation therapy; temporary discontinuation of an ALK-I during radiation therapy should an acceptable option, with SRS having the advantage of few days of therapy-break compared to WBRT.

Finally, another issue concerns the evaluation of quality of life and patient's benefit. Among published or presented trials of second generation ALK-Is, only the phase II study by Shaw *et al*. included evaluation of quality of life, by using European Organization for Research and Treatment of Cancer Quality Of Life Questionnaire (QLQ-C30) and its corresponding module for lung cancer (QLQ-LC13) on day 1-cycle 1 and then every other cycle (24). An improvement in lung cancer symptoms were recorded after

6 weeks and maintained for the two subsequent visits (24). Is this evaluation sufficient in patients with BMs? Probably not. Beyond major neurological signs and symptoms, such as general or partial seizures, impaired movement, speech disorders or ataxia, that unfortunately remain stable over time with limited impact in changing QoL evaluation, the vast majority of patients might have only mild symptoms, including altered mental state, depression, anxiety or mood changes that can be modulated by local and systemic treatments. This consideration should encourage investigators and physicians to use more precise tools to adequately capture changes in neurological status.

Conclusions

In patients with *ALK* positive advanced NSCLC the incidence of BMs increases over time, with approximately 70% of patients developing BMs during the course of their disease. In addition, occurrence of BMs explain one third of crizotinib failure. This is the reason why optimal management of CNS disease is one of the challenges for thoracic oncologists. The ability of crizotinib in controlling intracranial disease remains sub-optimal, with some undefined patients deriving benefit from the addition of local ablative therapy to continuation of crizotinib beyond progression. However, available data with novel and more potent ALK-Is indicated that sequential use of these agents is extending survival of patients, including individuals with BMs. In the next few years, results of ongoing trials with novel ALK-Is and dedicated translational research studies might help to define the better sequence of treatment, of any, as well as the role of local therapies.

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Footnote

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