Editorial

A step forward in the management of a rare disease, the anaplastic lymphoma kinase-rearranged non-small cell lung cancer

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The discovery of the anaplastic lymphoma kinase (ALK) gene rearrangement as an oncogenic driver in thoracic oncology has permitted to identify a subpopulation of non-small cell lung cancer (NSCLC) that can be considered as a rare oncologic disease. In effect, its incidence is approximately around 3% to 7% of all NSCLCs (1) and arises in patients with a clinical profile which is deeply different from that of the majority of NSCLCs. In that they are generally young, female, with history of no or light smoking (2). Moreover, ALK rearrangement is frequently found in those with NSCLC with histologic features of a signet-ring cell adenocarcinoma (2). Given the presence of this molecular alteration, the therapeutic strategy varies from that of another NSCLC. In fact, several clinical trials have demonstrated that anti-ALK rearrangement tyrosine kinase inhibitors (TKI) are superior to chemotherapy in the control of this disease. The first of these drugs that has entered in clinic is crizotinib, a multi-TKI, initially evaluated as a mesenchymal-epithelial transition factor (MET) inhibitor. During the long and complex PROFILE development plan, crizotinib has shown an activity in term of progression-free survival (PFS), overall response rate (ORR) and duration of response (DOR), which was significantly higher than that of chemotherapy both in first (3) and second line after the failure of at least one platinum-based regimen (4), permitting to define crizotinib, as the standard of care since the first line. Interestingly, in the PROFILE 1007 trial, where ALK positive NSCLC patients were randomized to crizotinib or to chemotherapy with pemetrexed or docetaxel in second line, those who received pemetrexed in the control arm had a greater PFS than those who were treated with docetaxel (4). These results have confirmed the sensitivity to Pemetrexed, even superior to that in wild-type population, as another specific feature of the ALK rearranged NSCLC, probably due to a lower expression of the thymidylate synthase levels (5,6). However, at present, chemotherapy has to be taken into account as an option after the failure of not only crizotinib but also of second and third generation TKIs. In the last few years, in fact, several new drugs have been approved by the Food and Drug Administration both after the failure of crizotinib (ceritinib, alectinib and brigatinb) and in patients naive for the treatment with TKIs (ceritinib and alectinib) while others are still under phase III for clinical evaluation for the first line such as brigatinib, lorlatinib and ensartinib, and for advanced lines of therapy (7).

Despite this successfully evolving therapeutic landscape, the Achilles' heel of the ALK positive NSCLCs remains the high affinity of the disease to the central nervous system (CNS) with consequent metastatic spread. Approximately 30% of these patients has CNS metastases at the diagnosis and 60% to 90% has an intracranial progression during the treatment with crizotinib (8,9). Even if in the unselected NSCLC population brain metastases strongly reduce the median survival, in ALK positive patient the prognosis is better with an OS reaching in a recent analysis 49.5 months since the onset of brain metastases (9). The CNS can be the site of an initial relapse during crizotinib treatment in

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46% of cases, which may be unrelated to an extra cranial worsening in approximately 40% to 50% patients. This suggests that the progression can be unrelated to the appearance of new molecular mechanisms of resistance (10,11). In effect, this situation has been primarily attributed to poor CNS penetration by crizotinib. This is demonstrated by the analysis of cerebro-spinal fluid (CSF) from CNS progressive patients (12) and it is highlighted by the fact that the disease control rate (DCR) of the brain metastases both in terms of ORR (33% *vs.* 18%) and of prolongation in the median time to intracranial progression (13 *vs.* 7 months), has been found to be superior in patients who were receiving crizotinib after radiotherapy than in those who only received crizotinib (13). Moreover, in patients with previous radiotherapy of brain metastases, which were involved in the PROFILE 1014 trial, intracranial disease control rate (iDCR) has been seen to be superior in those who were treated with crizotinib then with chemotherapy (14). For instance, data seem suggest that prior radiation may improve the CNS activity of crizotinib, probably by increasing the blood-brain barrier permeability (15). Taken together these evidences justify in this setting the clinical strategy to continue administration of crizotinib adding CNS-directed radiotherapy, encompassing whole-brain radiation (WBRT) and stereotactic radiosurgery (SRS) selected according to the type of progression (16). Even if radiotherapy is safe and well tolerated, the long-term survival of patients and the frequent need of repeated courses of a localized treatment may create several concerns related to the long-term cognitive sequelae after WBRT (9) or the appearance of radionecrosis after SRS (17), defining radiotherapy a therapeutic tool to be used carefully.

The clinical application of a second generation TKIs is changing this approach due to the strong activity of these compounds in the CNS. Camidge *et al.* (18) have recently published an article in the *Journal of Clinical Oncology* which looks at the results of an exploratory analysis performed on the population of two clinical trials of brigatinib. As well known brigatinib has shown high ORR (55%) and PFS (16.7 months) in patients with a systemic progressive disease after at least 1 prior line of TKIs (19). In this work 50 patients with CNS metastases from phases I/II trial (20) have been combined with 153 patients with brain metastases from the phase II ALTA trial (ALK in Lung Cancer Trial of AP26113) (19). The former trial has explored the safety and efficacy of brigatinib and the latter randomly evaluated two different schedules of brigatinib, arm A 90 mg daily and arm B 180 mg daily after 1 week lead-in period at 90 mg daily. According to the inclusion and exclusion criteria patients with brain metastases who didn't undergo radiotherapy or progressed after local treatment or required increasing doses of anticonvulsants or steroids were excluded. In the ALTA trial patients neurologically stable were admitted irregardless of radiotherapy. Fifty-four percent of patients in phase I/II trial and approximately 60% in the ALTA trial received brain radiotherapy. In particular, in the ALTA trial 70% received WBRT. Only 59 patients showed a measurable disease, as defined by the protocol of ≥10 mm. Among these, 15 from the phase I/II trial had an intracranial ORR (iORR) to brigatinib of 53% and an intracranial PFS (iPFS) of 14.6 months; 26 patients in the ALTA arm A had an iORR of 46% and an iPFS of 15.6 months and 18 in arm B an iORR of 67% and an iPFS of 18.4 months. Intracranial complete response in patients with non-measurable brain metastases in phases I/II, in arm A and B of ALTA were 35%, 7% and 18%, respectively, and the iDCR was 94%, 72% and 85% respectively. Among the 43 patients with measurable lesions without prior radiotherapy or progressing after radiotherapy in phases I/II or in arm A or arm B in the ALTA trial, the iORR was 67%, 42% and 73%, respectively, and an iDCR of 89%, 84% and 93% respectively. Given these data, it's possible to conclude that brigatinib has a significantly relevant penetration in the CNS in TKI pretreated population, with an action similar to that of the other second generation TKIs, alectinib and ceritinib, already approved in the same setting. In fact, alectinib showed in an ALK positive NSCLC population of 50 patients, refractory to crizotinib and submitted to radiotherapy in the 68% of cases, an iORR of 64% with a median duration of response (mDOR) of 10.8 months (21). Similarly, ceritinib in the same setting of 20 patients, of whom 70% underwent to previous radiotherapy, obtained an iORR of 45% with an iDCR of 80% (22). This data shows that the second generation TKIs are a strong rescue for the treatment of progressing brain lesions during crizotinib, permitting a delay in the use of brain radiotherapy and its adverse events.

Brigatinib with an iPFS of 18.6 months seems to be the most promising drug in this setting but at the present, there isn't any data concerning neither a direct head-to-head comparation nor a clear sequence of administration for the 3 drugs. Data which was arising from their use in first line may help to deepen these aspects. In fact, in the phase III ALEX trial which compared alectinib to crizotinib in first TKI line, alectinib has shown an incidence rate of development of *de novo* brain metastases 4-fold inferior of

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that by crizotinib and an iORR of 81% with a mDOR of 17.3 months in those patients with CNS involvement at baseline (23). Ceritinib in the ASCEND 4 trial has been compared to crizotinib in anti-ALK TKI naive patients, showing an iORR of 73% and an intracranial clinical benefit rate of 80% (24). Finally, the data concerning the intracranial activity of brigatinib in the phase III ALTA-1L trial, in which it has been compared to crizotinib as a first line, are still pending, given that the trial has recently concluded the enrollment. Taken together, this data strengthens the evidence of the high activity of second generation TKIs at the point that the therapeutic strategy has changed since the first line. In effect, the striking results of alectinib in terms of PFS both in the cranial and extracranial field declare this drug as the new standard of care until new data will be available from other TKIs. So far problems of selection of the second line TKIs and the sequence among drugs and with radiotherapy are becoming more complex, given that previous analysis have been conducted after crizotinib. The response to this situation could probably be obtained considering that mechanisms of resistance have been found to be different, according to the type of TKI used (25). Moreover, anti-ALK TKIs have different IC50s against the different types of mutation of resistance (25) suggesting that the choice of a second line TKI could be done according to the type of resistance. This consideration open the necessity to perform a rebiopsy also in this NSCLC subpopulation and, if we consider that the problem of the blood brain barrier is overtaken by the second generation TKIs, can be translated also to brain metastases. However, their histologic sampling in a routine way is very difficult. From this point of view, the development of a liquid biopsy is also in the making. At present, several trials are ongoing in this sense, in order not only to identify ALK patients with a liquid biopsy but also in defining the therapeutic strategy according to its result.

In conclusion, the high amounts of new drugs for ALK positive NSCLCs offers to patients, both in terms of extra and intracranial disease, new effective opportunities. This rich pharmacological landscape requires a deeper knowledge of this disease and further efforts to clarify those areas of the knowledge which are still in the shadow, in order to offer the best strategy for each patient. Certainly, this is a lucky period for this rare disease, which requires that a historic, diffuse nihilism toward not only brain metastases, but also NSCLCs in general will be leaved away, to make place for a new optimistic and demanding approach permitting a more effective and safer, long-term control of this disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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