Novel targets have recently joined EGFR and ALK as activating alterations suitable of specific inhibition, generating profound and durable clinical responses in non-small cell lung cancer (NSCLC) driven by these molecular alterations. These additional targets benefit from the experiences matured in the setting of lung malignancies, with MET and ROS1 in particular, biologically similar to ALK and therefore being inhibited by shared compounds (1,2). Other molecular strategies of treatment take advantage of results obtained in different diseases, with the most relevant example represented by BRAF-mutated tumors (3) and NSCLC harboring HER-2 alterations (4), finding in melanoma and breast cancer their reference models, respectively. The consistent data regarding such targeted therapies in NSCLC strongly sustain the development and the optimization of the best strategies of treatment in patients suffering from oncogene-addicted tumors. Compared to the overall population of NSCLC, the relatively favorable prognoses of cases driven by ROS1 rearrangements that receive specific agents claim the development of treatment options allowing to achieving the longest control of these diseases. From this point of view, the proposition of right targeted compounds can make the difference, pointing out the necessity of clear insights, both biological and clinical, when approaching the putative significance of newer inhibitors.

In a recent issue of the Journal of Clinical Oncology, Lim and other Korean collaborators addressed the potential role of ceritinib in a phase 2 trial enrolling 32 advanced and pretreated ROS1-rearranged NSCLC patients (5). Firstly, we would like to congratulate Lim and his co-experimenters for the effort a similar study can require. ROS1-positive patients indeed account for the 1–2% of the total number of NSCLC, underlying the nationwide profuse commitment employed to successfully run a prospective study able to screen such a considerable amount of cases. In this trial, 404 patients known as EGFR- and ALK-negative underwent molecular prescreening and ROS1 fluorescence in situ hybridization (FISH) detected gene rearrangement in 32 cases (8.4%). From an epidemiological point of view, this information is particularly sound, given the numeric relevancy of ROS1-driven disease lacking EGFR mutations and ALK rearrangements, accounting for almost 10% of the cases, a non-negligible amount when considering the absolute number, morbidity and mortality of advanced NSCLC diagnosed every year worldwide (6). Given the known mutual exclusivity of driver aberrations in lung adenocarcinoma, ROS1 rearrangements not representing an exception (7), we can envisage an even higher proportion of ROS1-positivity when eliminating KRAS-mutated tumors too. Moreover, as ROS1 fusions are detected at similar proportions in Asian and Caucasian populations (differently from EGFR mutations), we assume that the pragmatic implications of this trial will be similar among ethnicities. Considering the lack of significant differences between activity and toxicity profiles between Asian and Caucasian patients undergoing anti-ALK (and anti-EGFR) treatments, we think that the exclusive Korean origin of patients in this...
study does not hamper the transposition of the results in different populations at a worldwide scale.

The screening phase of the trial provided moreover a prospective validation of clinical factors associated with ROS1 positivity, such as the absence of smoking history (27 out of 32 patients, 84%) and the female sex (24 out of 32, 75%). The putative younger age at diagnosis compared to the overall NSCLC population [70 years, (8)] is sustained by the reported median age of 62 years at the time of inclusion, associated to a median of 18.3 months from diagnosis to ceritinib initiation.

As reported for ALK, cases of discordance between FISH, immunohistochemistry (IHC) and next-generation sequencing (NGS) results were observed in this (in four out of 15 patients with the three analyses available) and in other studies (5,9). Interestingly, the lack of protein expression by IHC staining, associated with a negative sequencing, ostensibly explained the lack of benefit from ceritinib in a ROS1 FISH-positive patient. Nevertheless, in an overlapping situation of isolated FISH positivity, prolonged response to ceritinib was obtained. If the long lasting experience with ALK and crizotinib allowed to defining IHC as a better predictor of response to the inhibitor compared to FISH (10), data regarding ROS1 are still not sufficient to drive conclusion in any direction.

The mentioned time from diagnosis to ceritinib initiation of 18.3 months, assumed the exposition to a previous cytotoxic line of treatment as an inclusion criterion to enter the study, reaffirms the relative “favorable” outcomes of ROS1-positive patients. With the limit of an indirect comparison, when analyzing the results of PARAMOUNT trial delineating the role of maintenance pemetrexed administration in non-squamous NSCLC, median overall survival (OS) was 13.9 months in patients receiving maintenance treatment (11). In the study by Lim and collaborators, precise data about previous lines of systemic treatment are available for the eight patients with brain metastases only: remarkably, seven of them had been exposed to pemetrexed before study entry (5). Assuming a similar proportion of pemetrexed-treated patients in the overall population receiving ceritinib, we attribute the significantly long median OS prior to enrolment, superior to 18 months, to pemetrexed administration itself. ROS1 positivity indeed does not seem to harbor a prognostic impact, whereas its role in predicting sensitivity to pemetrexed has been reported in several studies (12), endorsing this cytotoxic drug with “targeted properties” when acting against ROS1-rearranged tumors.

Focusing on the main information derivable from the results of the trial by Lim and colleagues, indirect comparisons between ceritinib and crizotinib in term of activity and toxicity become instinctive.

Of the 32 patients treated with ceritinib in the study of interest (5), two had been previously exposed to crizotinib and protocol was emended for subsequent eligibility only for crizotinib-naïve cases after the observation of lack of activity of ceritinib in those two patients. Overall response rates (ORR) were 62% [95% confidence interval (CI): 45% to 77%; 20 out of 32 patients] when considering the entire population and 67% (95% CI: 48% to 81%; 20 out of 30 patients) with regard to crizotinib-naïve patients only. ORR to the first-generation molecule has been reported ranging from 69% to 80% (2), Table 1], with the prospective studies enrolling the larger numbers of patients [n=53 (9) and n=127 (16)] achieving responses in around 70% of the patients (9,16), in line with the concept of oncogene addiction. Taking into account the fundamental biologic characteristics of the two inhibitors (see below), we do think that the slight difference in ORR between crizotinib and ceritinib is mainly due to the reduced number of treated patients in the present study and not to differential pharmacological properties. Moreover, in inhibitor-naïve patients, crizotinib and ceritinib showed similar disease control rates of 90% and 87%, respectively (5,9). As seen for crizotinib, the moment of disease history in which ceritinib was administered did not seem to hamper its activity, as all patients had previously received at least two systemic lines of treatment, with a median of three (5).

One of the most relevant results is represented by the prolonged median progression-free survival (PFS) observed in the study by Lim and collaborators, reported of 19.3 months in crizotinib-naïve patients, with a median duration of response of 21 months (5). Interestingly, the data of median PFS overlap the expansion cohort of PROFILE 001 trial evaluating crizotinib in ROS1-positive patients (9), whose results have been recently updated [(13), Table 1]. Nevertheless, when taking into account other retrospective and prospective experiences, median PFS obtained with crizotinib was reported with a range of 9.1–13.4 months (2), Table 1], the longest estimation observed in the largest phase II trial led thus far (16). With the limit of the relative low number of ROS1-positive patients whose outcomes under crizotinib have been reported in the literature (2), Table 1], we could imagine that the “real” median PFS ranges from 13 to 19 months. Definite conclusions about ceritinib cannot be driven, as the data available concerns the 32 patients described by Lim.
Table 1 Available evidence of ROS1 inhibitors activity in the clinical setting

<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>Inhibitor</th>
<th>Trial phase or design</th>
<th>N of patients</th>
<th>Setting</th>
<th>ORR, N [%]</th>
<th>Duration of response</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaw et al. ESMO 2016 (13)</td>
<td>Crizotinib</td>
<td>Expansion cohort (Phase I)</td>
<td>53</td>
<td>TKI-naïve</td>
<td>37 [70]</td>
<td>Not reached (median)</td>
<td>19.3</td>
</tr>
<tr>
<td>Mazières et al. JCO 2015 (14)</td>
<td>Crizotinib</td>
<td>Retrospective study</td>
<td>32</td>
<td>TKI-naïve</td>
<td>24 [80]</td>
<td>NR</td>
<td>9.1</td>
</tr>
<tr>
<td>Goto et al. ASCO 2016 (16)</td>
<td>Crizotinib</td>
<td>Phase II</td>
<td>127</td>
<td>TKI-naïve</td>
<td>88 [69]</td>
<td>NR</td>
<td>13.4</td>
</tr>
<tr>
<td>Lim et al. JCO 2017 (5)</td>
<td>Ceritinib</td>
<td>Phase II</td>
<td>32</td>
<td>30 TKI-naïve</td>
<td>20 [67]</td>
<td>21 months (median)</td>
<td>19.3</td>
</tr>
<tr>
<td>Solomon et al. ASCO 2016 (17)</td>
<td>Lorlatinib</td>
<td>Phase I/II</td>
<td>11</td>
<td>6 TKI-naïve, 5 post-crizotinib</td>
<td>7 [65]</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Drilon et al. Cancer Discov 2017 (18)</td>
<td>Entrectinib</td>
<td>Phase I</td>
<td>6</td>
<td>Post-crizotinib</td>
<td>0</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Drilon et al. Cancer Discov 2017 (18)</td>
<td>Entrectinib</td>
<td>Phase II</td>
<td>14*</td>
<td>TKI-naïve</td>
<td>12 [86]</td>
<td>17.4 months (median)</td>
<td>19.0</td>
</tr>
<tr>
<td>Subbiah et al. PNAS 2016 (19)</td>
<td>Ceritinib</td>
<td>Case report</td>
<td>1</td>
<td>Post-crizotinib</td>
<td>Response</td>
<td>NR</td>
<td>/</td>
</tr>
<tr>
<td>Drilon et al. Ann Oncol 2016 (20)</td>
<td>Cabozantinib</td>
<td>Case report</td>
<td>1</td>
<td>Post-crizotinib</td>
<td>Response</td>
<td>≥8 months</td>
<td>/</td>
</tr>
<tr>
<td>Chong et al. CCR 2017 (21)</td>
<td>Cabozantinib</td>
<td>Case report</td>
<td>1</td>
<td>Post-crizotinib</td>
<td>Response</td>
<td>≥10 weeks**</td>
<td>/</td>
</tr>
</tbody>
</table>

*, including one ROS1-positive melanoma; **, cabozantinib withdrawn for toxicity. N, number; ORR, overall response rate according to RECIST criteria; PFS, progression-free survival; NR, not reported. Modified with permission from Facchinetti et al. Cancer Treat Rev 2017 (2).

Assuming such limitations, clinical results reported thus far seem to recapitulate preclinical evidence. Ceritinib is superior to crizotinib when taking into account the respective half maximal inhibitory concentration (IC$_{50}$) in ALK-positive models, whereas their potency in inhibiting the naïve (i.e., lacking secondary mutations in the tyrosine kinase domain, TKD) forms of ROS1 is overlapping (22,23). Given the differential effects resistance mutations generate in ROS1 TKD (23), the only characteristic making ceritinib a “better” ROS1 inhibitor is its potential activity against the ROS1 crizotinib-resistance mutations M2001T, L2026M and G2101A (23), with only the second reported as clinical meaningful thus far (24). Importantly, ceritinib do not retains inhibitor activity against the most “irksome” G2032R mutation engendering crizotinib exhaustion in ROS1-rearranged NSCLC (23), representing moreover the most frequent one (25).

These latter biologic features could explain both the apparently slight longer activity of ceritinib in ROS1-positive NSCLC patients when compared to crizotinib, both the lack of activity observed in the two cases progressed to crizotinib in the cohort of Lim and colleagues. Ceritinib could have indeed prevented the onset of the mutations of resistance in ROS1 TKD, known as conferring crizotinib exhaustion, delaying therefore biological resistance and
clinical progression. Albeit no evidence of the molecular mechanisms responsible of crizotinib exhaustion in the two pretreated patients, the impossibility of ceritinib in overcoming resistance driven by bypass tracks activations (differently from the ALK-positive setting) or to a wide range of ROS1 mutations, ostensibly explains its failure after the first-generation inhibitor. To date, only one case of reversed crizotinib resistance with ceritinib in a ROS1-rearranged NSCLC patients have been described (19). Without any hint about the dynamics involved in crizotinib exhaustion, we do speculate that it depended on one of the mentioned (rare) mutations suitable of ceritinib inhibition.

Considerating their relevant morbidity, the management of brain metastases, present at diagnosis in a non-negligible quote of patients [30–40% (26,27)] and representing the isolated site of disease progression in up to 45% of patients undergoing crizotinib (27), represents a major issue in ALK-positive NSCLC patients. The integration of brain radiotherapy in this scenario allows survival prolongation, also prompted by one of the key characteristics of novel ALK/ROS1 inhibitors, represented by their pharmacokinetic ability to cross the blood-brain barrier better than crizotinib. The latter property explains the robust data about intracranial responses obtained with ceritinib, alectinib and other new molecules, moreover sustaining the significant reduction of brain progression in previously untreated ALK-positive patients exposed to the two mentioned inhibitors (26,27). With regard to ROS1-rearranged cases, the lack of evidence regarding intracranial disease, both at diagnosis and during disease courses, could be attributed either to a less propensity of ROS1-positive cells to move towards the brain, either by the low number of examined patients, insufficient to drive any conclusion. Nevertheless, whatever the incidence of brain metastases in ROS1-driven diseases, their therapeutic management remains relevant. In their study, Lim and collaborators report that eight out of 32 patients (25%) presented with brain metastases at study inclusion (5). Remarkably, gathering cases with measurable and non-measurable intracranial lesions, all the six patients with available imaging showed disease response. In addition, among the 18 patients who progressed to ceritinib in the study, only 2 (11%) developed brain metastases, suggesting the compound could prevent the onset of intracranial disease (5).

We assume that intracranial disease responses obtained with specific inhibitors depend on their pharmacodynamics and pharmacokinetics properties and not on differential clinico-biological behaviors between ALK- and ROS1-driven NSCLC. Therefore, considering the activity on brain metastases, data about crizotinib and ceritinib, necessarily scarce with regard to ROS1-positive patients, can be indirectly derived from ALK-rearranged cases, for whom the reported experience is much more abundant. As anticipated for what obtained in the trial by Lim and colleagues, ceritinib, as well as other new inhibitors, guarantees relevant intracranial response and disease control rates in ALK-positive patients (26). Albeit we still lack information regarding the real clinical impact of brain metastases in ROS1-rearranged NSCLC, we think that the significant intracranial activity of ceritinib, suggested in the paper by Lim and corroborated by data in ALK-positive patients, represents an element of sure interest, aware of the unsatisfactory profile of crizotinib in this area.

The results provided by Lim and collaborators in the ROS1-positive setting confirm data derived from studies in ALK-rearranged cases with regard to the mediocre toxicity profile of ceritinib, when compared to crizotinib and, even with a more relevant spread, to novel ALK/ROS1 inhibitors (28). In the paper under our attention indeed, serious adverse events considered drug-related involved the 22% of the patients (seven out of 32) and grade 3–4 toxicity occurred in 12 cases (37%), with fatigue as the most common non-laboratory severe event (5). In addition, the amount of patients experimenting grade 1–2 events (78% diarrhea, 59% nausea, 56% anorexia, 30–40% increase of blood creatinine and aminotransferases) witnesses the scarce tolerability profile of ceritinib, with a special regard to the mentioned adverse events, significantly hampering quality of life (5). We recall that an alternative strategy of ceritinib administration, allowing a lower posology, is now under study in ALK-positive patients in order to reduce drug-related toxicities (ASCEND-8; clinicaltrials.gov identifier NCT02299505) and the preliminary results document a reduction of the incidence and severity of gastrointestinal adverse events (29).

In conclusion, we reiterate our congratulations to Lim and co-experimenter for the effort they made in order to provide this extremely useful source of clinical information. Albeit only two patients in their population had been pretreated with crizotinib before undergoing ceritinib, the lack of the activity of the latter confirm what suggested by preclinical studies and modeling (23), making ceritinib not the treatment of choice as a “second-step” inhibitor in ROS1-positive NSCLC. Taking into account the limited numbers of patients evaluated in this trial, ceritinib appears to perform potentially longer than crizotinib (Table 1) and
better on intracranial disease against ROS1-rearranged cancers (5). These two elements could effectively challenge crizotinib, recently approved in ROS1-driven disease, as the first compound to be administered. Nevertheless, we think that additional amount of data should be provided in order to envisage the putative proposition of ceritinib in inhibitor-untreated ROS1-positive patients, even more when considering its unsatisfactory toxicity profile. Aware that it will be extremely difficult to run randomized trials in this relatively rare population, we recognize that indirect comparisons could reveal particularly useful to address clinical strategies.

Putting ceritinib (and crizotinib) in the arena of current tested ROS1 inhibitors, without going into the details concerning shared anti-ALK/ROS1 compounds (2), we would like to mention the potential role of the third-generation molecule lorlatinib. The intrinsic characteristics of this latter indeed allow it to overcome resistance established under crizotinib and ceritinib (17). In addition, it is currently tested in the front-line setting compared to crizotinib in ALK-positive patients (clinicaltrials.gov identifier NCT03052608) in order to envisage, as in EGFR-mutated cases (FLAURA trial; clinicaltrials.gov identifier NCT02296125), the utility of moving the “best” inhibitor upfront, a proposition recently reported as successful with regard to alectinib (27). As stated above, definite recommendations for ROS1-positive cases will unlikely derive from randomized studies and results obtained in ALK-rearanged ones would hopefully address the potential utility of evaluating front-line lorlatinib in ROS1-driven diseases in dedicated cohorts.

Acknowledgements

None.

Footnote

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

References


Cite this article as: Facchinetti F, Tiseo M. Ceritinib in ROS1-positive non-small cell lung cancer patients: does clinical evidence carry clinical impact? Transl Cancer Res 2017;6(Suppl 6):S1074-S1079. doi: 10.21037/tcr.2017.08.08