Editorial

PROFILE 1014: lessons for the new era of lung cancer clinical research

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Abstract: PROFILE 1014 compared crizotinib to up to six cycles of standard platinum-pemetrexed chemotherapy as the first line treatment of advanced anaplastic lymphoma kinase positive (ALK+) non-small cell lung cancer (NSCLC). Overall, PROFILE 1014 has taught us many valuable lessons about the natural history of ALK+ NSCLC, the effectiveness of key therapies and the positive ways in which clinical research in oncogene addicted subtypes of cancer continue to evolve. These lessons include (I) confirming the benefit of using personalized medicine approaches compared to chemotherapy that had already been established in EGFR mutant disease and in ALK+ disease in later lines of therapy; (II) demonstrating that molecular preselection can also affect outcomes from standard chemotherapy in addition to from targeted therapy. Specifically, the benefit of the control arm (platinum-pemetrexed), although inferior to that of crizotinib, was remarkable and expands the dataset on the increased sensitivity of ALK+ NSCLC to pemetrexed; (III) identifying the central nervous system (CNS) as a key battleground for metastatic NSCLC, especially for ALK+ disease. In PROFILE 1014 CNS time to progression (TTP) was included as a prominent secondary endpoint, which showed no difference between crizotinib and chemotherapy but all CNS lesions at baseline had to be both stable and treated, so any apparent stabilizing effect of the drug may be confounded. Ongoing studies with other ALK inhibitors *vs.* crizotinib that include untreated CNS diseases will provide greater clarity on the true effect of these drugs in the brain.

Keywords: Crizotinib; pemetrexed; PROFILE 1014; ceritinib; alectinib; brigatinib; AP26113

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Introduction

In 2014, Solomon *et al.* published the PROFILE 1014 phase III trial comparing crizotinib to first line platinum-pemetrexed chemotherapy in treatment naïve advanced anaplastic lymphoma kinase positive (ALK+) rearranged non-small cell lung cancer (NSCLC) (1). By looking carefully at the design and outcomes from this study, we can learn several important lessons about the way in which lung cancer clinical research is evolving, or will have to evolve, to remain meaningful in the new era of personalized molecular therapies.

Crizotinib is a small molecule tyrosine kinase inhibitor that targets ALK, in addition to MET and ROS1. In the initial phase I study, crizotinib demonstrated an objective response rate (ORR) of 61% and a median progression free survival (PFS) of 9.7 months in ALK+ NSCLC across multiple lines of therapy (2). In the first phase III study (PROFILE 1007) 347 ALK+ NSCLC patients who had received prior platinum-based therapy were randomized to receive crizotinib or one of the two licensed second line chemotherapies in NSCLC, i.e., pemetrexed or docetaxel. ORRs were 65% in the crizotinib arm compared to 20% in the chemotherapy arm (P<0.001). PFS was 7.7 months with crizotinib compared to 3 months with chemotherapy [hazard ratio (HR) 0.49; 95% confidence interval (CI), 0.37-0.64; P<0.001)] (3).

Crizotinib received an initial conditional approval from

the FDA for the treatment of advanced ALK+ NSCLC in 2011, without a line of therapy restriction, on the basis of the phase I and preliminary phase II data (2,4). In contrast, the EMEA waited on the results of PROFILE 1007 before issuing a license and this approval was restricted to patients who had received prior platinum-based chemotherapy.

One reason for leading with a phase III trial in the second line was to allow for the concept of ALK testing to become established in the global lung cancer community. However, solid tumor oncology is dominated by the philosophy that the 'best' treatment should be deployed first, just in case the patient doesn't survive through to the next line of therapy. The first line approach of 1014 was also supported by data from treatment naïve patients in the phase I study (2). In these patients, the ORR was 63.6% (14/22) and the median PFS was 18.3 months (n=24), whereas across all other lines of therapy the ORR was 60.3% (73/121) and the median PFS was 9.2 months (n=125).

The first lesson of 1014: use of targeted agents in a relevant molecularly preselected population is preferable to chemotherapy

In PROFILE 1014, eligible patients had advanced ALK+ non-squamous NSCLC, with disease measurable by RECIST version 1.1, ECOG performance status 0-2 and no prior treatment for their advanced disease. Patients with brain metastases were eligible if the central nervous system (CNS) disease was treated and they were neurologically stable off steroids for at least 2 weeks. Randomization was 1:1 between crizotinib or up to six cycles of a platinum (cisplatin or carboplatin)-pemetrexed doublet. Crossover was allowed for the chemotherapy arm and the primary endpoint was PFS. Secondary endpoints included the ORR, overall survival (OS), safety and patient-reported outcomes. Continuation of crizotinib beyond disease progression was permitted.

The intention-to-treat population consisted of 343 patients and the two arms were well balanced in terms of baseline characteristics. The majority of patients were female (62%), never smokers (64%), had an ECOG of 0-1 (94%) and tumor histology consistent with adenocarcinoma (94%). At study entry 27% of patients had brain metastases.

Median PFS in the patients who received crizotinib as their initial therapy was 10.9 *vs.* 7.0 months among those who received chemotherapy (HR 0.45; 95% CI, 0.35-0.60; P<0.001). In addition, the ORR was higher with crizotinib than with chemotherapy (74% *vs.* 45%, P<0.001). The median duration of response was 11.3 months in the crizotinib arm *vs.* 5.3 months in the chemotherapy arm. Median OS was not statistically significantly different between the two arms (HR 0.82; 95% CI, 0.54-1.26; P=0.36). However, this is not surprising given both the high degree of cross over (12% from crizotinib to chemotherapy and 70% from chemotherapy to crizotinib after progression) and the low overall proportion of deaths (26%) which had occurred at the time of the study report. Safety and tolerability mirrored the findings of previous studies (2,3).

The first lesson of PROFILE 1014, i.e., that using a targeted therapy in a population molecularly preselected for sensitivity to the agent produces better clinical outcomes than using standard chemotherapy, is perhaps the least surprising. Beyond the comparable second line data of PROFILE 1007, over the last few years the EGFR mutant literature has provided us with multiple phase III examples confirming the validity of this approach (2,5,6). What may be more surprising is how 1014 and the development of crizotinib in general have informed different choices about the preferred comparator arm in ongoing registration trials for the next generation of ALK inhibitors.

Following the initial activity of crizotinib, acquired resistance in ALK+ NSCLC can occur in two main ways (4). One mechanism, addressed below in the 'third lesson' section, relates to progression within the CNS, largely due to inadequate drug exposure issues. The other relates to changes in the biology of the cancer occurring systemically, for example through the development of ALK kinase domain mutations, rearranged ALK copy number gain or non-ALK bypass tracks, which are then selected out in the presence of the crizotinib along Darwinian evolutionary lines. Excitingly, many next generation ALK inhibitors are showing both preclinical and clinical evidence of activity against both major forms of acquired resistance (4). Ceritinib (LDK378) now has an FDA license post-crizotinib, while alectinib and AP26113 (brigatinib) have both been awarded FDA breakthrough status, indicating their promise in the same setting (7-9). Therefore, just as crizotinib moved from second line to first line registration trials, any new ALK inhibitor, having already achieved or anticipating a license post-crizotinib and with reasonable evidence to consider themselves 'best-in-class', will, inevitably, also plan to explore the first line ALK inhibitor setting. However, as each new drug emerges at a different time and the competitive landscape evolves discordantly across different regulatory environments, for example with crizotinib

initially approved in the first line setting by the FDA but not by the EMEA, the relevant comparator in a first line registration study can be debated.

Obviously, a direct head-to-head trial against the first generation drug certainly makes the most scientific sense. Currently, in NSCLC we do not know whether suppression of any potential resistance mechanism prior to its emergence will be superior to using sequential therapy i.e., giving a first generation drug followed by a next generation drug at the time acquired resistance manifests. Yet trial designs comparing the next generation drug to standard chemotherapy could also be considered. Accrual to chemotherapy comparison trials can be challenging where alternative targeted therapies exist (either licensed or through other trials), but it can make a lot of business sense to seek out countries and lines of therapy in which other targeted agents are not widely available. Beating a chemotherapy comparator in an oncogene addicted subtype of NSCLC now seems a very low risk strategy, especially if the competitor first generation drug is still trying to establish its own licenses in different markets. Beating another targeted agent in a line of therapy in which the first generation drug later fails to achieve a license will not progress the licensing of the new drug in the same countries. In addition, once licensed *vs*. chemotherapy, the competition against any established earlier generation targeted therapy can then be decided in the marketplace, rather than in the 'win or lose all' arena of a targeted therapy *vs*. targeted therapy trial.

Consequently, although both phase III trials were designed prior to the results of 1014 being known, it is interesting to note that alectinib is going head-to-head against first line crizotinib within the ongoing phase III ALEX study (clinicaltrials.gov: NCT02075840) (7). Whereas ceritinib chose the more conservative route, going up against standard first line chemotherapy in the ongoing A2301 trial (clinicaltrials.gov: NCT01828099) (8).

Of course, despite consistent data on the greater activity of targeted therapy over chemotherapy in the relevant molecularly preselected population, this does not mean that chemotherapy will never have a role in the treatment of these patients, as all patients will eventually progress. Consequently, any active agents, including chemotherapy, should be considered as part of the full armamentarium of advanced cancer patients. Indeed, one additional benefit of registration trials utilizing chemotherapy control arms is that the data they generate can provide valuable information on the activity of specific chemotherapies in different molecular subtypes of NSCLC, just as much as they provide data on the activity of the targeted therapy.

The second lesson of 1014: molecular selection can affect outcomes in both the treatment and control arms of a trial

In any randomized trial, the effectiveness of the experimental treatment is set relative to the effectiveness of the comparator arm. So at the design stage, accurate estimates of benefit in the comparator arm are key to the appropriate sizing of the study. Traditionally, estimates for control arms have been based on historical data from other clinical trials in the same disease type and setting. Yet, with the very recent emergence of clinically relevant molecular heterogeneity, the available historical data are almost entirely based on cases in which the equivalent biomarker status is unknown. Illustrating the importance of this fact, studies in ALK+ NSCLC have now clearly shown that molecular preselection can affect outcomes from some chemotherapies just as much as from targeted therapy.

Pemetrexed, a multi-targeted anti-folate, initially received an FDA license as monotherapy in the second line setting based on a non-inferiority design compared to docetaxel (10). Later, pemetrexed was also explored as part of a platinum doublet in the first line setting (11). Retrospective analyses revealed that benefit compared to the control arms of docetaxel or platinum-gemcitabine was restricted to the non-squamous population modifying the licensed indication for the drug in both settings (12).

Beyond the impact of squamous *vs*. non-squamous histology, when 1007 and 1014 were designed, pemetrexed, indeed any chemotherapy, was not expected to perform any differently in ALK+ disease than in any other molecular subtype of NSCLC. Certainly, in one of the initial reports of the clinical characteristics of ALK+ NSCLC, ALK positivity was not associated with a better time to progression (TTP) with standard platinum doublet chemotherapy (in which the platinum partner was not specified) than either an EGFR mutant or double negative population (13). The first suggestion that ALK+ disease was associated with exaggerated sensitivity to pemetrexed came from a retrospective single center analysis looking at PFS with pemetrexed in ALK+, EGFR mutant, KRAS mutant and a triple negative control group, where ALK positivity was the dominant factor affecting progression in a multivariate analysis (14). Later, an increased ORR to pemetrexed was also noted retrospectively (15). These

impressions were confirmed prospectively within PROFILE 1007 (3). Although in a general non-squamous cancer docetaxel and pemetrexed perform fairly similarly, in 1007 there was a marked difference between pemetrexed and docetaxel in both ORR (29% *vs.* 7%) and median PFS (4.2 *vs.* 2.6 months) (3,12). Unfortunately, as a comparison between the chemotherapy arms was not part of the original 1007 study design, statistical analyses of these differences have not been presented to date.

In PROFILE 1014, where all patients in the control arm received pemetrexed as part of a platinum doublet, an exaggerated pemetrexed-ALK signal is again hinted at with an ORR of 45% and a median PFS of 7 months (1). In the otherwise unselected, non-squamous population in the original platinum-pemetrexed registration study these values were, in contrast, 29% and 5.26 months (12). This phenomenon is now being prospectively explored within the ongoing SWOG 1300 trial, looking at the benefit of pemetrexed in the post-crizotinib setting in ALK+ NSCLC (clinicaltrials.gov: NCT02134912).

The exact reason for the apparent increased sensitivity of ALK+ NSCLC to pemetrexed remains unclear. The fact that some folate metabolizing enzymes are downstream substrates of ALK was raised as an early hypothesis (14). Later, a retrospective analysis suggested ALK's association with never smoking status, rather than a direct effect of ALK positivity itself, accounted for the pemetrexed sensitivity (16). Consistent with this, in the original pemetrexed first line study the frequency of never smokers among those with non-squamous histology ranged from 9-21% (11). In contrast, in LUX Lung 3, a first line study of an EGFR TKI *vs.* platinum-pemetrexed conducted in an EGFR mutant population in which the frequency of never smokers was 70%, the median PFS in the chemotherapy arm was highly comparable to 1014 at 6.9 months (6). Against this theory is the observation that the ORR to platinum-pemetrexed in LUX Lung 3 (by independent review, as in 1014) was only 23%. In addition, a later retrospective analysis showed that the ORR and PFS differences to pemetrexed between ALK and other molecular subtypes of NSCLC were maintained in a pure never smoking population (17). Perhaps one of the reasons why PFS did not differ between 1014 and LUX Lung 3, despite a seemingly large difference in the ORR, is due to the fact that neither study employed pemetrexed continuation maintenance. In Paramount, a double-blind, phase III, randomized placebo-controlled trial investigating the role of maintenance pemetrexed after four cycles of cisplatin and pemetrexed, maintenance pemetrexed extended the median PFS from 2.8 to 4.1 months (HR 0.62; 95% CI, 0.49-0.79; P<0.0001), with a stronger HR among those with an objective response to the induction doublet compared to those with stable disease (HR 0.48 *vs.* 0.74) (18). Indeed, if the Kaplan-Meier curves for PFS from 1014 are examined in detail, it is clear that the chemotherapy arm and the crizotinib arm overlap for approximately 6 months before separating after the chemotherapy has stopped. The potential ongoing benefit of continued pemetrexed, denied to the patients in 1014 is also suggested by the presence of a prolonged tail of non-progressors in the pemetrexed arm of 1007 (in which no limit on the number of cycles was set), which is noticeably absent from the docetaxel control arm of the same study and from the chemotherapy control arm in 1014 (1,3). Consequently, it is hard not to wonder how much the median PFS difference in 1014 would have been affected if the control arm had included maintenance pemetrexed. It will, therefore, be very interesting to see the results of Novartis' ongoing A2301 trial, which is comparing ceritinib to a platinum-pemetrexed doublet in the TKI naïve ALK+ setting, which explicitly includes continuation maintenance pemetrexed in the control arm (clinicaltrials.gov: NCT01828099).

The third lesson of 1014: the brain as a relevant battleground in advanced NSCLC

The final lesson of 1014 relates to the insight it provides in terms of both the natural history of ALK+ NSCLC in the brain and in the ability of our current trial designs to address the importance of the CNS in advanced NSCLC.

Soon after ALK+ NSCLC was recognized it became clear that this disease was associated with a high lifetime incidence of brain metastases (19). In addition, although CNS responses did occur, the CNS also appeared to be a common site of progression while on crizotinib (20,21). Multiple early reports of CNS responses with next generation ALK inhibitors added to the realization that the CNS would be a key battleground for ALK and possibly many other molecular subtypes of NSCLC, where life expectancy with targeted therapy was becoming sufficiently prolonged to reveal any discrepant results between the CNS and the rest of the body (22). However, the presentation of CNS scans from individual patients, without a denominator or duration of benefit also being presented, started the realization that benefit of targeted therapy in the CNS was going to have to be addressed much more 'head on' in future clinical trials. Attempts to capture robust

information on activity of systemic agents in the CNS retrospectively continue but are often open to extensive criticism, particularly with regard to claims that 'CNS stability' on the first repeat scan represents clear evidence of drug benefit. Predominantly this is due to a combination of data lacunae, the potential impact of prior radiation therapy 'sterilizing the CNS' and the inherent biases in tracking predominantly non-measurable disease, where readouts are limited to complete response, unequivocal progression and stable disease categories. For example, with regard to the effect of prior radiation, in one retrospective study, the protective effect of erlotinib compared to chemotherapy on preventing subsequent CNS progression in EGFR mutant advanced NSCLC, was much more marked among those without baseline brain metastases than in those with baseline brain metastases (23). While, intuitively, the effect should have been more pronounced among those with known CNS disease, the explanation for this paradox probably lies in the fact that in this study, the rate of whole brain radiotherapy in the chemotherapy and erlotinib arms ranged from 50-83% in those with baseline brain metastases, but was, of course, zero among those without baseline brain metastases. Among 275 patients with brain metastases treated with crizotinib explored retrospectively, only 109 (40%) had previously untreated brain metastases at baseline, and of these, only 22 (20%) had measurable CNS lesions to follow (21). By looking only at the intracranial disease control rate (DCR) at a fixed point in time (including previously treated and untreated, measurable and non-measurable disease) there was a strong suggestion of CNS benefit from the crizotinib. The intracranial DCR at 12 weeks ranged from 56-62%, highly comparable to the systemic DCR (63-65%). However, among the measurable CNS lesions, the ORR intracranially was only 18% compared to 53% systemically, and the duration of response was almost half that systemically (26.4 *vs.* 47.9 weeks). In addition, for all those with known brain metastases at baseline, the CNS was still the most common site of non-target or new lesion progression on crizotinib occurring in from 70-72% of cases.

To address these issues, the Response Assessment in Neuro-Oncology (RANO) working group has recently published a series of guidelines outlining key issues with regard to optimally studying brain metastases prospectively in clinical trials, chief among which is to allow patients with brain metastases into clinical trials of new agents in the first place (24). It is a step forward to note that within 1014, not only were patients with CNS metastases allowed into the study, but time to CNS progression was included as a secondary endpoint. The TTP in the CNS was prolonged (median not yet reached) and did not appear to be significantly different between the two arms (HR 0.6; 95% CI, 0.34-1.05; P=0.069) (25). However, it is important to note that in 1014 all brain metastases at baseline had to be both treated and stable before study entry. So, as with the erlotinib study described above, while the TTP in the CNS on crizotinib does not appear to be any different from that with chemotherapy, it is also not possible to truly ascribe any apparent CNS benefit to either treatment because of the potential confounding effect of the prior local therapy. Consequently, it is a further step forward that in the ongoing head-to-head phase III trial of crizotinib *vs.* alectinib (ALEX study), while time to CNS progression is again a prominent secondary endpoint, in this trial CNS metastases are allowed if they are either 'asymptomatic or treated' raising the possibility that we will soon be generating more robust information on the true prospective effects of drug therapy on untreated CNS disease from phase III trials in the future.

Summary

PROFILE 1014 has unequivocally established the value of giving crizotinib compared to up to six cycles of standard platinum-pemetrexed chemotherapy as the first line treatment of advanced ALK+ NSCLC. The confirms the benefit of using personalized medicine approaches compared to chemotherapy that had already been established in EGFR mutant disease and in ALK+ disease in later lines of therapy. The benefit of the control arm (platinum-pemetrexed), although inferior to that of crizotinib, was also remarkable and expands the dataset on the increased sensitivity of ALK+ NSCLC to pemetrexed. Continuation maintenance pemetrexed was not used in 1014 and the PFS curves notably overlap during the chemotherapy but diverge after the chemo finishes. The extent of the control arm's benefit in other ongoing first line ALK+ NSCLC trials which include continuation pemetrexed after the platinum-pemetrexed doublet will, therefore, be very interesting to see. PROFILE 1014 included CNS TTP as a prominent secondary endpoint, which showed no difference between crizotinib and chemotherapy but all CNS lesions at baseline had to be both stable and treated, so any apparent stabilizing effect of the drug may be confounded. Ongoing studies with other ALK inhibitors *vs.* crizotinib that include untreated CNS diseases will provide greater clarity on the true effect

of each in the brain. Overall, PROFILE 1014 has taught us many valuable lessons about the natural history of ALK+ NSCLC, the effective of key therapies and the positive ways in which clinical research in oncogene addicted subtypes of cancer continue to evolve.

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Footnote

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