timepoint in a post-hoc, exploratory analysis. Use of time-to-deterioration, with no need for confirmation, might have improved the sensitivity to detect small deteriorations in HRQOL. Another way to improve the sensitivity to detect small HRQOL modifications would be to use a MCID of 5 points, rather than the usual MCID of 10 points. In the PACIFIC study, HRQOL results are reported at a median follow-up of 25 months (IQR 14·1–29·5). Despite this already long follow-up period, long-term side-effects could still occur after the last administration of durvalumab. A longer evaluation of HRQOL would thus be interesting, especially in the present context of potentially curative treatment.

With an adequate method of PRO analysis that was based on current standards, the PRO results of the PACIFIC study confirm that adjuvant durvalumab is a drug of interest after chemoradiotherapy for stage III non-small-cell lung cancer. This study highlights the need for more data on HRQOL and new approaches, including new questionnaires items and strategies, to capture clinically meaningful changes in HRQOL in patients receiving immune checkpoint inhibitors.

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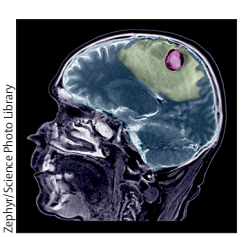
Untapped potential: recognising CNS opportunities in early oncology drug development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See Articles page 1681

In *The Lancet Oncology*, Myung-Ju Ahn and colleagues[1] describe what, at first glance, appears to be a standard phase 1–2 study of a novel third-generation EGFR tyrosine kinase inhibitor, lazertinib. In thoracic oncology, third- generation EGFR inhibitors are characterised by their ability to inhibit not only the standard sensitising *EGFR* mutations occurring in non-small-cell lung cancer (NSCLC), but also T790M, an exon 20 point mutation, which commonly emerges as a resistance mechanism during treatment with first-generation or second- generation inhibitors. Osimertinib, another third-generation inhibitor, is already approved by the US Food and Drug Administration for use in the presence of a detectable *T790M* mutation after first-generation or second-generation inhibitor therapy, and as first-line therapy, before acquired resistance has emerged.[2,3]

In the trial,[1] lazertinib was escalated from 20 mg daily to 320 mg daily, without dose-limiting toxicities. Treatment-related grade 3 or 4 adverse events occurred in 3% of patients without apparent dose dependence; however, the proportion of patients requiring dose reductions seemed to increase with dose, from 8% at 120 mg to 17% at 240 mg to 20% at 320 mg. 62 (57%, 95% CI 48–67) of 108 patients with T790M-postive tumours had an objective response. Among those who received doses 120 mg or more versus 80 mg or less, the objective response appeared similar at 60% (95% CI 47–72) versus 54% (40–69) but the median progression-free survival was 12·3 months (95% CI 8·3–not reached)

versus 6·9 months (5·3–16·4), suggesting that dose might affect duration of disease control. Maximum plasma concentrations increased in a dose-proportional manner, whereas the area under the concentration–time curve increased in a slightly more than dose-proportional manner, without evidence of either plateauing at the doses used. Trough concentrations at steady state suggested that doses of 160 mg or higher would achieve sufficient and consistent target inhibition, with 240 mg ultimately selected for further development, taking into account all available data at the time.

However, why should anyone care about all these data for lazertinib? Osimertinib is already a well established treatment. It is similarly effective in the same setting (objective response in T790M-positive NSCLC: 65%) and at least as well tolerated (dose reductions at the recommended 80 mg daily dose occurred in only 2·9% of patients) as lazertinib.[2,3] Beyond any potential competitive price advantage that could be introduced after licensing, or idiosyncratic tolerance of one drug over another in individual patients, the real potential advantage of lazertinib might be hiding in plain sight. Specifically, lazertinib's incompletely explored potential to treat CNS metastases.

With few exceptions, CNS exposures to systemically administered anti-cancer drugs are less than their extracranial exposures. Consequently, pharmacokinetics, more than biology, might be the dominant contributor to many cases of CNS treatment resistance, especially when extracranial deposits of the disease remain under good control.[4]

Standard-dose osimertinib has already shown good CNS activity in the first line FLAURA study,[5] with a higher proportion of CNS response than with first-generation EGFR inhibitors in patients with measurable CNS disease (91% *vs* 68%). However, the median progression-free survival in the osimertinib group remained shorter among those with versus those without baseline CNS metastases (15·2 months *vs* 19·1 months), suggesting incomplete equivalence of CNS and extracranial control.[3,5] Dose escalation to 160 mg was explored in patients with NSCLC with leptomeningeal disease in the BLOOM trial,[6] which did show some efficacy at the cost of increased toxicity (4 [13%] of 32 patients required dose reduction). Additionally, even at this high dose, the cerebrospinal fluid:free plasma ratio was only 16%.[6]

In 2018, the Response Assessment in Neuro-Oncology guidelines[7] specifically emphasised the potential to develop separate CNS dose regimens for oncology drugs. The exploration of dose escalation to 160 mg in the BLOOM trial[6] began to scratch the surface of this approach. Where tolerability limits dose escalation, high-dose intermittent schedules can be explored as an alternative means to increase CNS exposures to effective levels. However, the ideal drug for dedicated CNS dose regimen exploration is one in which the standard dosing has been set in the absence of substantial toxicity and in the absence of any plateauing of pharmacokinetic exposures. Therefore, lazertinib's key features could be that standard dosing was set in the absence of substantial toxicity or plateauing pharmacokinetic exposures.

Among 18 patients with measurable CNS disease, the intracranial response to lazertinib was 44% (95% CI 22–69), which is encouraging but still leaves a substantial amount of important data to be generated. When looking at the sites of progression, the proportion with progression in the CNS was low in all patients without baseline CNS disease. However, the longer median PFS at higher doses could, in theory, be related to better CNS control, further supporting the idea of pushing the dose further to maximise CNS efficacy.

Lazertinib could be one of the pioneer drugs for redefining how we optimally address the CNS in oncology drug development. Taking full advantage of the early drug-development process to explore the CNS potential of any oncology drug being considered in disease types with a high rate of CNS metastases should be part of a future that we can all look forward to.

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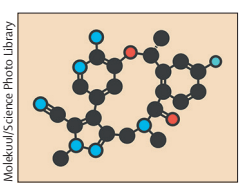
Lorlatinib: a new treatment option for *ROS1*-positive lung cancer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See **Articles** page 1691

Chromosomal rearrangements of *ROS1* occur in 1–2% of patients with non-small-cell lung cancer (NSCLC). The ROS1 tyrosine kinase inhibitor (TKI) crizotinib provides a marked clinical efficacy in TKI-naive *ROS1*-positive patients in clinical trials, with an overall response of 65–72% and an expected median progression-free survival of 19 months.[1–4] Crizotinib is recommended in the first-line setting for *ROS1*-positive patients.[5] However, the majority of crizotinib-treated *ROS1*-positive patients will experience disease progression. Two main mechanisms of resistance have been described: on-target mutations, the most common of which is Gly2032Arg, and progression in the CNS, which occurs in 30–50% of patients.[6] The development of resistance to crizotinib and the scarcity of next-line treatment options represent an unmet medical need.

Lorlatinib is a potent, orally available, CNS-penetrant, selective ROS1 TKI. In preclinical models, lorlatinib can inhibit the Gly2032Arg resistance mutation.[7] In the phase 1 portion of an ongoing phase 1–2 study (NCT01970865), lorlatinib showed preliminary antitumour activity in *ROS1*-positive patients. In *The Lancet Oncology*, Alice T Shaw and colleagues[8] report the clinical activity, safety results, and molecular analysis from the phase 1–2 expansion part of this ongoing study that evaluates lorlatinib in *ROS1*-positive patients. The primary endpoints were the proportions of patients achieving an objective response and an intracranial response. Lorlatinib was evaluated in 21 TKI-naive patients and 48 TKI-pretreated patients, of whom 40 received crizotinib as their only TKI. Lorlatinib was administered orally at a dose of 100 mg daily in continuous 21-day cycles, with the exception of ten patients in phase 1 of the study who received doses ranging from 10 mg daily to 100 mg twice daily.

Among TKI-naive patients, 13 (62%, 95% CI 38–82) had an objective response; the median duration of response was 25·3 months (95% CI 7·5–31·9) and median progression-free survival was 21·0 months (95% CI 4·2–31·9). Waterfall plots summarising the best percentage change from baseline showed deep responses in the majority of patients. Among crizotinib-pretreated patients, 14 (35%, 95% CI 21–52) had an objective response; the median duration of response was 13·8 months (95% CI 9·7 to not reached) and the median progression-free survival was 8·5 months (95% CI 4·7–15·2). Deep responses were also reported in the majority of these patients. Lorlatinib showed potent intracranial activity, in both TKI-naive and TKI-pretreated patients.

The results from this study help to define a sequencing strategy for ROS1 TKIs. Lorlatinib does not seem to be superior to crizotinib in TKI-naive patients. Overall response, duration of response, and progression-free survival with lorlatinib are similar to those observed with crizotinib in the PROFILE 1001 trial.[1] The efficacy of the ROS1 TKIs ceritinib (overall response 67%, median duration of response 21·0 months, median progression-free survival 19·3 months) and entrectinib (overall response 77%, median duration of response 24·6 months, median progression-free survival 19·0 months) are also similar to that of crizotinib.[9,10] The safety profile of crizotinib is more favourable than that of lorlatinib. Therefore, we can conclude that crizotinib is still our first-line treatment of choice.

The clinical activity of lorlatinib in crizotinib-resistant patients is meaningful. This study represents the first clinical trial showing ROS1 TKI activity in crizotinib-resistant patients. The overall response with lorlatinib is likely to be similar to that achievable with chemotherapy, and the responses are durable. Of note,