Editorial Commentary

Selpercatinib in patients with *RET* fusion positive non-small cell lung cancer: updated follow-up of the LIBRETTO-001 phase I/II trial

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When evaluating updated clinical trials analyses it is important to consider the goals of the updated analysis. Updated analyses are most valuable when a new late toxicity or a decrement in the efficacy is observed with longer follow-up. Additional situations in which updated analyses are important are when the trial was stopped based on an interim analysis or by the data safety monitoring board, or if assessments of the durability of the benefit, such as duration of response (DoR) or progression-free survival (PFS), were not available at the time of the original analysis. In these situations, it is valuable to compare the median follow-up time from the original analysis to the updated analysis.

Recently, Drilon and colleagues reported an updated analysis of the phase I/II trial of selpercatinib in *RET* fusion positive non-small cell lung cancer (NSCLC) (1,2). Patients were required to demonstrate a *RET* fusion based on local testing with next generation sequencing, fluorescence in situ hybridization, or polymerase chain reaction testing, and test results were reviewed and confirmed prior to enrollment. Patient were required to have an Eastern Cooperative Oncology Group performance status of 0–2, adequate organ function, and measurable disease. Patients in the phase I portion of the trial received selpercatinib 20–240 mg twice a day, and patients in the phase II portion received selpercatinib 160 mg twice a day. The primary endpoint of the phase II portion of the trial was objective response rate (ORR) by independent review committee, and key secondary endpoints were PFS and DoR.

Drilon and colleagues published the original study report in 2020, and the efficacy results were reported in two cohorts based on receipt of prior platinum-based chemotherapy (n=105) or treatment naïve (n=39), and the updated analysis includes 247 patients in the previously treated cohort and 69 patients in the treatment naïve. In the original publication the median follow-up in the chemotherapy treated and treatment naïve cohorts for PFS was 9 and 14 months, respectively, and in the current analysis median follow-up was 22 and 25 months, respectively. The efficacy results from the two analyses are similar, and are presented in the *Table 1*. The sample size for the treatment naive cohort remains relatively small. In the original report 11 patients had evaluable central nervous system (CNS) disease and the CNS ORR was 91% [95% confidence interval (CI): 59–100%], and in the update analysis 26 patients had evaluable CNS disease and the ORR was 85% (95% CI: 65–96%). Importantly, among patients in the phase II trial without baseline CNS disease (n=178) the probability of CNS disease progression was 0.7%. The additional information about the CNS efficacy is important given the incidence of CNS disease in this patient population. With an increased sample size and the longer follow-up this analysis confirms the activity of selpercatinib.

If patients are going to remain on therapy for a prolonged period of time, then cumulative adverse events (AEs) and the need for dose reduction due to tolerability concerns become more clinically relevant. In the original analysis the most common grade 3 or 4 AEs were hypertension (14%), increased alanine aminotransferase (13%), and increased

Table 1 Efficacy results from the original publication and update analysis (1,2)

Patient cohort	Analysis	# of patients	ORR (%)	DoR (months)	Median PFS (months)
Previously treated[a]	Original	105	64%, 95% CI: 54–73	17.5, 95% CI: 12.0–NE	16.5, 95% CI: 13.7–NE
Previously treated[a]	Updated	247	61%, 95% CI: 55–67	28.6, 95% CI: 20.4–NE	24.9, 95% CI: 19.3–NE
Treatment naïve	Original	39	85%, 95% CI: 70–94	NR	NR
Treatment naïve	Updated	69	84%, 95% CI: 73–92	20.2, 95% CI: 13.0–NE	22.0, 95% CI: 13.8–NE

[a], defined as receipt of platinum-based chemotherapy. ORR, objective response rate; DoR, duration of response; PFS, progression-free survival; CI, confidence interval; NE, non-evaluable; NR, not reached.

aspartate aminotransferase (10%). Of all patients receiving selpercatinib (n=531), 30% of patients required a dose reduction, and 2% discontinued due to treatment related events. In the updated analysis the most common grade ≥3 treatment emergent AEs were hypertension (19.7%), increased alanine aminotransferase (11.4%), increased aspartate aminotransferase (8.8%), diarrhea (5.0%), and electrocardiogram QT interval prolongation (4.8%). Of all the patients receiving selpercatinib (n=796), dose reductions occurred in 41% of patients and 8% discontinued treatment due to AEs. These data reinforce the need to monitor liver tests, blood pressure and be aware of any drug-drug interactions that may prolong the QT interval.

Importantly, there have been two additional publications that report clinically relevant AE's with selprecatinib (3,4). In a pan-cancer cohort of 7,517 patients treated with RET tyrosine kinase inhibitors (TKIs) chylous effusions were observed in 7% of patients treated with selpercatinib, and the range from time of TKI initiation to chylous effusion was 0.5–50 months. Most patients required multiple drainages, and dose reduction did not reduce the chylous effusions drainage volumes. Of note, chylous effusions were observed with multi-targeted TKIs (agerafenib, cabozantinib, and lenvatinib). Chylous effusions were not observed with pralsetinib, another RET specific TKI, however, the number of patients who received pralsetinib in this study was smaller (n=28) (5). Longer follow-up and a larger sample size will be required to determine if this adverse event is unique to selpercatinib or associated with the class of RET specific TKIs. Clinicians should be aware of this recently recognized and unique AE.

A retrospective review from the phase I/II trial investigated whether the sequence of immune checkpoint inhibitors (ICIs) and selpercatinib resulted in an increase rate of adverse events. Of the 329 patients analyzed, 22 (7%) experienced grade 1 to 3 hypersensitivity reaction, and more patients (n=17, 77%) had previously received ICIs than ICIs naïve patients (n=5, 23%). Most of the events were reversible, and patients were able to resume selpercatinib with dose modification and supportive care. For patients who received ICIs as first-line therapy who are receiving selpercatinib as second-line therapy clinicians should be aware of this observation. In many countries, RET TKIs are available as first-line therapy or without regard to line of therapy, and ideally patients would receive RET TKI's as first line therapy.

For the field of thoracic oncology, this publication demonstrates the durable benefit of selpercatinib, and the clinical focus is on ensuring patients undergo the appropriate molecular testing for *RET* fusions and have access to RET TKIs. Academically the field is investigating the mechanisms of resistance, and these include off-targeted and on-target (e.g., acquired solvent front resistance mutations) mechanisms, and developing second-line therapies for this patient population (6,7).

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