Selpercatinib or Chemotherapy in RET Fusion-Positive NSCLC

Selpercatinib or Chemotherapy in *RET* Fusion–Positive NSCLC

TO THE EDITOR: In their article on the phase 3 LIBRETTO-431 trial, Zhou and colleagues (Nov. 16 issue)[1] describe the results of treatment with selpercatinib, which led to significantly longer progression-free survival than platinum-based chemotherapy with or without pembrolizumab among patients with advanced *RET* fusion–positive non–small-cell lung cancer (NSCLC). However, we encourage a critical review of the ethical considerations that were made in the design of this trial.

The Declaration of Helsinki states that "when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify, or immediately stop the study."[2] Before initiating a randomized clinical trial, investigators must determine whether there is equipoise (i.e., the assumption that neither trial group is superior to the other and that no consensus exists in the medical community regarding the best treatment option).[3] It has repeatedly been shown that "the right drug for the right target" results in significantly longer progression-free survival than standard first-line chemotherapy in patients with rare oncogenic drivers. Thus, there was serious doubt in the lung cancer community regarding the clinical equipoise of selpercatinib as compared with first-line chemotherapy.[4] Furthermore, in the phase 1–2 LIBRETTO-001 trial,[5] the investigators enrolled 479 patients, so extensive safety data were available at the time that the phase 3 trial was initiated. Thus, the available evidence on the efficacy of selpercatinib in patients with *RET* fusion–positive NSCLC violated clinical equipoise, which calls into question the ethical justification for the conduct of the phase 3 trial.

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THE AUTHORS REPLY: Despite the publication of data supporting first-line precision therapies for oncogene-driven NSCLC, real-world evidence indicates that up to half of patients are still not being tested, and nearly one third of patients with actionable biomarkers do not receive targeted therapies.[1,2] Confirmatory trials such as LIBRETTO-431 are often required by regulatory authorities for approval and subsequent access for patients. Accordingly, the LIBRETTO-431 trial verified the efficacy and safety of selpercatinib that had been observed in the previous LIBRETTO-001 trial and showed the clinical value of selpercatinib as compared with chemotherapy with or without pembrolizumab.[3,4]

In designing this trial, we most assuredly considered clinical equipoise, which is why we amended the original protocol to perform 2:1 randomization to the selpercatinib group or the control group, permitted the use of the investigator's choice of control agents, and allowed for crossover to ensure that eligible patients had access to selpercatinib (effective crossover, 75%). In addition, the LIBRETTO-431 trial was approved by ethical review boards, and enrollment was prioritized in regions where first-line selpercatinib was unavailable. Our trial provides critical evi-

dence for patients, health care practitioners, and regulatory bodies by confirming the efficacy of selpercatinib over standard therapy and by reinforcing the importance of comprehensive testing in patients with newly diagnosed NSCLC.

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Dexamethasone for Tuberculous Meningitis in HIV-Positive Adults

TO THE EDITOR: Donovan et al. (Oct. 12 issue)[1] found that the use of adjunctive glucocorticoids was not associated with a significant reduction in death among persons with human immunodeficiency virus (HIV)–associated tuberculous meningitis (hazard ratio vs. placebo, 0.85; 95% confidence interval [CI], 0.66 to 1.10; P=0.22). We previously reported that acellular cerebrospinal fluid (CSF) is common in persons with HIV-associated tuberculous meningitis[2] and that a CSF white-cell count of less than 5 per microliter is associated with a risk of death that is four times as great as that with a white-cell count of more than 100 per microliter (hazard ratio for death, 4.11; 95% CI, 1.47 to 11.50; P=0.004).[3] Our findings are consistent with those from a study involving persons with tuberculous meningitis in Vietnam.[4] Parallels can also be drawn with cryptococcal meningitis, in which acellular CSF is a poor prognostic marker.[5] Taken together, CSF phenotypes are heterogeneous within HIV-associated meningitis and are predictive of outcome. A stratified analysis according to CSF white-cell count may be informative, and CSF white-cell count–directed adjunctive glucocorticoid therapy warrants exploration.

Although definitive evidence to support the use of glucocorticoids in patients with HIV-associated tuberculous meningitis has not been provided by the current trial, the observed trend toward reduced mortality is consistent with the hazard ratio (0.86) in the subgroup of HIV-positive persons included in a 2004 trial by Thwaites et al. of adjunctive glucocorticoids.[6] This possible type II error highlights the need for larger, collaborative tuberculous meningitis trials. In addition, these findings show the relative safety of glucocorticoid treatment in patients with HIV-associated tuberculous meningitis.

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