

## ZEPHYR: failure of a “spring wind” in lung cancer

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Vandetanib is an oral inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2), epidermal growth factor receptor (EGFR) and Rearranged during Transfection (RET) tyrosine kinases that are involved in tumour growth, progression and angiogenesis (1). Therefore, this drug has the advantage to contemporary block different intracellular signalling pathways, potentially providing greater benefit than blocking each pathway individually and overcoming resistance to anti EGFR therapy due to increased expression of VEGF (2,3). Four randomized phase 2 studies in patients with non-small cell lung cancer (NSCLC) showed that vandetanib prolonged progression-free survival (PFS) as single agent or when added to chemotherapy, supporting the development of the drug in phase 3 trials (4). In the article of Lee *et al.*, the results of the ZEPHYR trial that compared vandetanib with placebo in patients with advanced NSCLC after prior therapy with one or two chemotherapy regimens and with an epidermal growth factor receptor tyrosine kinase inhibitor are presented (5). Currently, there is no approved treatment option for this widely pretreated population of NSCLC patients and effective treatments are urgently needed.

ZEPHYR is a large, double blind, multicenter, randomized phase 3 trial: other strengths of the study are the statistical design, allowing the detection of a 33% prolongation in overall survival (OS, primary objective), the large sample size (924 patients), the rate of recruitment (only two years), the evaluation of patient-reported outcomes (time to deterioration of symptoms), and the presence of correlative biologic studies. However, despite the encouraging results of preclinical and early clinical studies with vandetanib and the intriguing mechanism of action of the drug, overall results of this study are disappointing.

Vandetanib failed to demonstrate an OS benefit compared with placebo. Moreover, there was a higher incidence of some adverse events with vandetanib, including diarrhea (46%), rash (42%) and hypertension (26%). Statistically significant advantages favouring vandetanib were observed for progression-free survival (PFS, 1.9 *vs.* 1.8 months, HR 0.63,  $P < 0.001$ ) and objective response rate (2.6% *vs.* 0.7%;  $P = 0.028$ ). No significant difference in patient-reported outcomes was observed between patients receiving vandetanib or placebo. Regarding biologic studies, there was evidence of a greater benefit in PFS for vandetanib-treated patients with a positive EGFR mutation status compared with a wild-type EGFR status: however, more than 75% of patients had an unknown status, as often observed also in other phase III trials conducted with EGFR inhibitors in advanced NSCLC, where the proportion of cases available for molecular analysis is always very small compared to the sample size (6). Of note, baseline status of plasma biomarkers (VEGF, VEGFR-2, and bFGF) was determined in more than 85% of patients: a statistically significant difference in OS was observed in patients with low baseline plasma levels of VEGF (HR=0.66;  $P = 0.023$ ), suggesting its potential utility as a predictive factor for vandetanib efficacy.

To date, four randomized phase 3 clinical trials evaluated in NSCLC the efficacy of vandetanib in combination with docetaxel (ZODIAC), pemetrexed (ZEAL) or as single agent (ZEST and ZEPHYR) (5,7-9). Both the ZODIAC (1,391 patients) and ZEPHYR (924 patients) trials showed a modest, but statistically significant advantage in PFS and response rate with vandetanib plus docetaxel *vs.* docetaxel and with vandetanib versus placebo in the second and third/fourth line of therapy of NSCLC patients, respectively (5,7). In the smaller ZEAL trial (534 patients), no statistically significant

difference in PFS was observed with the combination of vandetanib plus pemetrexed compared with pemetrexed alone, possibly due to the small sample size (8). Finally, also in the ZEST trial (1,240 patients) the primary objective of demonstrating a statistically significant prolongation of PFS for vandetanib was not met, although in a pre-planned non-inferiority analysis, vandetanib was shown to have similar efficacy to erlotinib for PFS and OS (9). Therefore, no study showed an advantage in OS with vandetanib as single agent or added to chemotherapy.

Similar results have been reported by LUX-Lung 1 trial with afatinib, an irreversible ErbB-family blocker, in patients with advanced lung adenocarcinoma who had received one or two previous chemotherapy regimens and had disease progression after EGFR tyrosine-kinase inhibitors: although afatinib improved PFS and response rate, no benefit in terms of OS has been reported (10). It is unclear why the incremental improvements in PFS observed in most of these trials did not translate into an improvement in OS: it cannot be excluded that differences in the response to post-progression therapy could have contributed to the results.

Impressive results have been recently reported with vandetanib in a phase III trial of patients with advanced medullary thyroid cancer (MTC), a challenging tumor for which there is no effective therapy and that is caused in the majority of cases by activating mutations in RET proto-oncogene (11,12): in this study, there was a meaningful 11-month prolongation of median PFS in patients who received vandetanib compared with placebo, with an HR of 0.46 (13). These positive results highlights the importance of a proper identification of clinical or molecular biomarkers predictive of response and of biologically driven patient selection criteria for clinical trials with molecular targeted agents (14). In this regard, the identification in 1-2% of patients with lung adenocarcinoma of activating mutations in RET oncogene that can be considered driver mutations, will make it necessary to evaluate the efficacy of vandetanib in this specific subgroup of patients (15).

In conclusion, ZEPHYR, the warm wind that usually brings the new breaths of the spring season, this time did not brought a “therapeutical” renewal and has disappointed the hopes of new, significant advances for widely pretreated patients with advanced lung cancer.

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