ZEPHYR illustrates the perils of testing targeted treatments in unselected non-small-cell lung cancer patients

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Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases and remains the leading cause of cancer-related death. Our understanding of the nature and biology of lung cancer continues to increase as does the notion that NSCLC does not represent a single disease entity, but rather is a collection of diseases with different histologic and genetic subtypes. Significant progress has been made in our level of understanding of the various molecular mechanisms and pathways involved in NSCLC, including both vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR). Novel therapeutic strategies to target and inhibit these specific pathways are being intensely studied.

Molecularly targeted therapy in the setting of a defined molecular target has made significant progress in various human cancers in the past decade and has now become an integral part of modern human cancer treatment, such as the successes seen with imatinib against Bcr/Abl in CML and mutated c-Kit in GIST, as well as trastuzumab in HER2+ breast cancer (1). Progress has been made in NSCLC using the tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib to target the EGFR in patients with tumors containing activating *EGFR* mutations. However, the efficacy of the TKIs is limited, as patients with NSCLC who initially have a primary response invariably develop acquired resistance against EGFR-TKI monotherapy typically after 6-12 months (2).

There are a number of reasons for the development of resistance to EGFR-TKI monotherapy. The main reasons for *primary* resistance are the absence of *EGFR* mutation (3) or the presence of another, mutually exclusive driver mutation such as *KRAS* (4). Reasons for *acquired* resistance to EGFR-TKI that have been identified include development of the T790M mutation in exon 20 of the *EGFR* gene (5), increased signaling through parallel receptor tyrosine kinases such as MET (6), transformation to small cell histology (7), as well as "bypass" or "rescue" network interaction and cross-talk signaling between other oncogenic pathways, such as RON, EGFR (ERBB1), HER3 (ERBB3), AXL, CD44, α6β4-integrin and HIF-1α (6,8-10). Increased VEGF expression has also been suggested in previous studies as a possible mechanism of acquired resistance to EGFR TKIs (11,12). As effective treatment options are limited for patients with NSCLC who have progressive disease (PD) after treatment with EGFR-TKIs, one strategy to improve outcomes would be to test multi-targeted agents selectively targeting VEGF and EGFR, such as vandetanib.

The ZEPHYR trial was a randomized, double-blind, multicenter phase III trial of single agent vandetanib versus placebo in 924 patients with locally advanced or metastatic NSCLC who had received one or two prior chemotherapy regimens and had experienced treatment failure with an EGFR-TKI. The primary endpoint was overall survival. Although the objective response rate (ORR) (2.6% versus 0.7%, P=0.028) and progression free survival (PFS) (hazard ratio =0.063, P<0.001) were improved in the vandetanib arm compared to placebo, there was no statistically significant difference in overall survival (OS) between the two arms (8.5 months with vandetanib and 7.8 months with placebo, HR=0.95, 95.2% CI, 0.81 to 1.11, P=0.527).

The intent of the investigators was to assess the efficacy of vandetanib in patients with advanced NSCLC who had PD despite prior chemotherapy and treatment with EGFR-TKIs. Notably, the study population did not appear to be representative of the general population of Western NSCLC patients, as 53% were never-smokers, 56% were of East Asian ethnicity, 53% were female, and 79% were of adenocarcinoma histology, all of which were characteristics

favoring an *EGFR* sensitizing mutation. However, tissue was not required for entry into the study, and as a result EGFR mutation status was not known for 75% of patients. Because of the lack of tissue, the mechanisms conferring disease progression could not be determined.

The study also looked at specific clinical, demographic and baseline molecular biomarkers to assess if particular subgroups might have a survival benefit, however there were no significant differences observed (the only exception being low baseline plasma levels of VEGF showing a trend towards improved OS with vandetanib, HR=0.66, P=0.23). Whether this isolated finding is due to chance or possibly represents a true biomarker for vandetanib efficacy remains unclear.

Three other randomized, phase III clinical trials evaluated the efficacy of vandetanib in NSCLC: ZODIAC (docetaxel versus docetaxel plus vandetanib as second line treatment) (13), ZEAL (pemetrexed versus pemetrexed plus vandetanib as second line treatment) (14), and ZEST (erlotinib versus vandetanib as second or third line treatment) (15). Only the ZODIAC trial met its primary endpoint of improved PFS, but no study showed an overall survival advantage with vandetanib. Furthermore, grade 3 or greater toxicity was higher in the vandetanib treated arms and the drug is no longer actively being developed in NSCLC.

Although the ZEPHYR study did not show an improvement in the primary end point of overall survival, we can still appreciate the underlying rationale that formed the basis of the study: multi-targeted combination therapy to overcome *de novo* and acquired EGFR-TKI resistance. Unfortunately, the lack of validated, prespecified biomarkers of sensitivity to vandetanib coupled with the lack of available tissue to discover biomarkers retrospectively makes this trial uninterpretable. One might be tempted to conclude from the failure of the vandetanib trials, along with the failure of the BeTa trial combining erlotinib and bevacizumab (16), that the approach of combining EGFR and VEGF inhibition has failed. However, TKI resistance is multifactorial and there can be no one-size-fits-all approach. The only indisputable lessons learned from the ZEPHYR trial should be that future, targeted drug trials must do a better job in defining the target population and are not justified unless a biomarker for increased benefit is pre-determined or that every patient enrolled has tissue available for biomarker identification so that clear conclusions can be drawn from the results.

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