Vandetanib in advanced non small cell lung cancer: a promise unfulfilled

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Despite a number of recent advances in the management of advanced non-small-cell lung cancer (NSCLC), survival rates remain poor compared with the other major malignancies. Standard chemotherapy leads to modest response rates and survival benefits and therapeutic results appear to have reached a plateau, although maintenance chemotherapy appears to be of benefit (1). Subsequently, the last decade has seen a major shift in research focus towards identifying molecular targets, developing targeted therapeutics, and validating biomarkers so to improve treatment outcomes.

Epidermal growth factor receptor (EGFR)-dependent cell proliferation and vascular endothelial growth factor receptor (VEGFR)-mediated angiogenesis are validated therapeutic targets in advanced NSCLC. There appears to be cross-talk between the two pathways and they are probably co-dependent, as EGFR is known to regulate angiogenesis (2) and VEGFR expression is associated with resistance to EGFR inhibition (3). In both human xenograft models and in the clinical setting dual inhibition of EGFR and VEGFR signaling was shown to have anti-tumour activity (4,5). Initial clinical developments focused on agents targeting either one of these 2 key pathways, with the most developed of the agents being the anti-EGFR tyrosine kinase inhibitors gefitinib and erlotinib (6,7), and the specific anti-VEGF monoclonal antibody bevacizumab (8).

Whilst clinical trials have shown important roles for these types of agents, the development of a therapeutic agent that simultaneously targets both the VEGF and the EGFR pathways had a strong rationale. Vandetanib was developed as an agent that selectively targeted VEGFR and EGFR, as well as RET (rearranged during transfection) (9). The use of vandetanib for dual inhibition of VEGFR and EGFR signaling was a promising concept in xenograft models and initial phase I work established the MTD and tolerability profile (10). A phase I Japanese trial showed an impressive effect in patients with NSCLC which led to a particular focus on further development in patients with this disease type (11), and raised the possibility that the anti-EGFR action of the drug may be as important as the anti-VEGF effect. The next step in advanced NSCLC was the completion of a number of Phase II studies, which demonstrated a positive effect with improved PFS and response rates (12,13).

With the successful results of the phase II studies to hand, AstraZeneca launched an unprecedented 4 simultaneous large, international phase III trials to determine the role that vandetanib would play in NSCLC. These 4 trials included 2 monotherapy trials: the ZEPHYR trial - monotherapy after failure of previous EGFR tyrosine kinase inhibition (14) and the ZEST trial - monotherapy in comparison with erlotinib in the 2nd or 3rd line setting (15). There were also two 2nd line trials where vandetanib was combined with chemotherapy: the ZODIAC trial (vandetanib plus docetaxel), and the ZEAL trial (vandetanib plus pemetrexed) (16,17). Unfortunately, the ZEST, ZEAL and the ZEPHYR trials did not meet their primary end points, and whilst the ZODIAC trial demonstrated an improved PFS, this did not translate into an improved overall survival and the PFS benefit was clinically modest.

In the ZEPHYR trial (zactima efficacy trial for NSCLC patients with history of EGFR-TKI- and chemo-resistance), 924 patients who had previously received chemotherapy and an EGFR TKI were randomised 2:1 to receive vandetanib 300 mg or placebo (14). As one might expect considering the entry criteria, the trial population was quite different to the standard late stage NSCLC trial: there were more

females than males, more than 50% of patients were of Asian descent, and more than 50% were non-smokers. They were heavily pre-treated patients with more than 60% having had 2-3 lines of chemotherapy for advanced disease, 63% had at least 3 organs involved at study entry and 42% had progressed as their best overall response to the previous TKI use. Also of note was that more than 50% of patients in either study arm went on have further specific anti-cancer therapy following completion of their study treatment. This would have constituted 3rd, 4th or even 5th line therapy, which would be considered unusual in advanced NSCLC.

The study failed to meet its primary end point of superior overall survival with vandetanib. No difference in overall survival was seen at median follow-up of 15.4 months, with an estimated HR of 0.95 (95.2% CI, 0.81-1.11; P=0.527). Median survival was 8.5 months compared with 7.8 months in the placebo arm. One year survival was estimated to be 35.5% with vandetanib compared to 31.7% with placebo. Vandetanib was significantly better than placebo in the secondary end points of PFS, ORR and DCR at 8 weeks. The estimated HR for PFS was 0.63 (95.2% CI, 0.54-0.74; P<0.0001). Only 2.6% of patients receiving vandetanib had objective responses, but 30% of patients had stable disease or better at 8 weeks, compared with 16% of patients receiving placebo (P<0.0001). The toxicity profile was as expected considering results published by the other studies: increased incidence of rash, diarrhea, and hypertension. These side effects were mainly grade 1-2, but did indicate that the agent was hitting its targets.

Despite significant effort and resources, tissue was only successfully obtained in 20-25% of patients. Thus, no signal on tissue-based predictive factors was identified. This is a major shortcoming of the trial, and unfortunately does not help in the efforts to determine biomarkers that will predict which patients will, and which patients won't benefit from this, and similarly targeted drugs. There was more success in obtaining baseline plasma with more than 85% of patients having samples collected and tested. No strong signal was obtained from these samples. The message is that during Phase I/II development, significant efforts need to be made to identify a target/marker of sensitivity, so that treatment populations can be enriched and a new drug given the best chance to show efficacy. Understanding the target, establishing the best dose and then selecting the right patients to treat is critical to success of a new agent.

In summary the use of vandetanib for dual inhibition of VEGFR and EGFR signaling was a promising concept in xenograft models. Clinical efficacy in advanced NSCLC was demonstrated in Phase II studies, with improved PFS and response rates. However, these results did not translate to clinically significant benefits in randomized Phase III trials. In the ZEPHYR trial, single agent vandetanib 300 mg daily did not improve survival compared with placebo after failure of EGFR TKI therapy.

So, what now for vandetanib? Development continues in medullary thyroid cancers in which the RET gene is critical, and vandetanib is now licensed in the USA for this indication (18). The discovery that RET mutations constitute a small but identifiable subpopulation of patients with advanced NSCLC (19) and that that tumours harboring a RET mutation may respond to targeted agents (20) may give vandetanib a new lease of life in NSCLC. Having an agent that targets RET as well as VEGF might result in a potent agent for this select group of patients.

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