ZD1839 (Gefinitib, Iressa) In Patients With Non Small Cell Lung Cancer: A Real Promise?
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Abstract
ZD 1839 is a novel, low molecular weight, orally active, selective EGFR-tyrosine kinase inhibitor, which in preclinical and phase I studies has showed antitumor activity against cancers expressing EGFR. Phase I-II studies showed that ZD 1839 provides clinically significant antitumor activity in patients with pretreated NSCLC. Subsequently, phase III trials combined ZD1839 and chemotherapy in chemonaive patients with advanced NSCLC. These trials failed to demonstrate a survival advantage with the addition of ZD1839 to standard platinum-based chemotherapy. Some experts have suggested that the concomitant administration of chemotherapy and EGFR tyrosine kinase inhibitors may be antagonistic and that sequential use of these drug is a more appropriate strategy. The molecular mechanisms underlying sensitivity to ZD1839 are unknown, however recent preliminary experiences suggest that EGFR mutations may predict sensitivity to ZD1839. In any case, future trials should be conducted with appropriate correlative studies in diagnostic tumor tissue and a new possible area of clinical investigation include the use of ZD1839 in adjuvant setting.

INTRODUCTION
Among the most promising agents in clinical development to treat non small cell lung cancer (NSCLC) patients, there is the epidermal growth factor receptor (EGFR) inhibitor ZD1839. EGFR is expressed, overexpressed or dysregulated in many human solid tumors, including NSCLC. EGFR activation seems to promote tumor growth by increasing cell proliferation, motility, invasive capacity, angiogenesis and metastasis. ZD 1839 is a novel, low molecular weight, orally active, selective EGFR-tyrosine kinase inhibitor, which in preclinical and phase I studies has showed antitumor activity against cancers expressing EGFR. In particular, encouraging results have been reported in patients with NSCLC.

REVIEWS OF STUDIES
Two large randomised, phase II studies (IDEAL 1 and 2 trials) showed a clinically significant antitumor activity with an acceptable tolerability of ZD1839 in heavily pretreated NSCLC pts. In the IDEAL 1 trial, 210 pretreated NSCLC pts were randomised to receive ZD1839 250 or 500 mg/day. The response rate was 18.4% for the lower dose and 19% for the higher dose, while the overall survival (OS) was 7.6 and 8.0 months, respectively. In the IDEAL 2 trial 216 NSCLC pts who had failed platinum and docetaxel regimens, were randomised to receive continuously ZD1839 250 or 500 mg/day. Tumor response rate and OS were similar in the two ZD1839 arms. In both studies, grade 3-4 adverse events were more common for the higher dose of ZD1839. In view of these results, ZD1839 has been approved for use in this setting of pts in some countries.

Phase I studies showed that combination of ZD1839 with common two drugs chemotherapy regimens appears feasible with no increase in chemotherapy-related toxicity and no interference with the pharmacokinetics of these drugs. To evaluate the role of ZD1839 in addition to standard chemotherapy (CT) in NSCLC pts, several randomized studies were started. Recently, the results of 2 large phase III trials were reported. In the INTACT 1 trial 1093 chemo-naive pts with stage III-IV NSCLC were randomised to receive CT + placebo, CT + 250 mg/d or CT + 500 mg/d ZD1839. CT consisted of 6 cycles of gemcitabine 1250 mg/m² on days 1-8, plus cisplatin 80 mg/m² on day 1. Treatment with ZD1839 or placebo has been continued until disease progression. In this study there were no statistically significant differences in OS, progression-free survival (PFS) and time to worsening symptoms across the three arms. In the INTACT 2 trial 1037 chemo-naive pts with stage III-IV NSCLC were randomised to receive CT + placebo, CT + 250 mg/d or CT + 500 mg/d ZD1839. CT
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consisted of carboplatin AUC=6 + paclitaxel 225 mg/m² every 3 wks for 6 cycles after which pts were continued on ZD1839 or placebo until disease progression. Also in this trial, OS, PFS and time to worsening of symptoms were not statistically significantly increased in the ZD1839 arms compared to placebo.

DISCUSSION

Some experts have suggested that the concomitant administration of chemotherapy and EGFR tyrosine kinase inhibitors may be antagonistic and that sequential use of these drugs is a more appropriate strategy. However, the inability to select patients properly is another possible explanation for the negative results. Common adverse events associated with ZD1839 treatment included diarrhea, rash, acne, dry skin, nausea and vomiting; worldwide, interstitial lung disease has been observed in about 1% of pts receiving this treatment and approximately one-third of the cases were fatal

Recently, researchers identified a mutation in the EGFR that is strongly associated with response to ZD1839. In particular these studies revealed the presence in responders patients of a variety of mutations in the binding pocket of the intracellular catalytic domain of the receptor. Most of the responders were women and nonsmokers with bronchoalveolar features in their tumor histology, a spectrum previously associated with ZD1839 response.

CONCLUSION

In conclusion, ZD1839 is effective in NSCLC, nevertheless the results of two large phase III studies suggest that the combination of chemotherapy and ZD1839 in these pts should not be recommended. The molecular mechanisms underlying sensitivity to ZD1839 are unknown, however recent preliminary experiences suggest that EGFR mutations may predict sensitivity to ZD1839. In any case, future trials should be conducted with appropriate correlative studies in diagnostic tumor tissue and a new possible area of clinical investigation include the use of ZD1839 in adjuvant setting.

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