Nearly 50% of patients with non-small cell lung cancer (NSCLC) are found to have metastatic disease at presentation (1). Platinum doublet chemotherapy remains the standard initial treatment for the vast majority of patients with advanced NSCLC who have a good performance status. Approximately 10% of patients with advanced NSCLC have activating mutations in the epidermal growth factor receptor tyrosine kinase (EGFR TK) in the tumor tissues (2). Significant progress has been made with molecularly targeted therapies in lung cancer since the initial discovery linking the presence of certain EGFR TK mutations with exquisite responsiveness to EGFR tyrosine kinase inhibitor (TKI) gefitinib (3,4). Although erlotinib, another EGFR TKI, has been approved for use in patients with advanced NSCLC who have progressive disease after platinum doublet therapy based on the randomized study sponsored by the National Cancer Institute (NCI)-Canada, it is evident now that the impressive clinical benefit from EGFR TKIs is seen almost exclusively in patients whose tumor cells demonstrate specific mutations in the EGFR TK domain (5).

The IPASS trial first established the superiority of gefitinib in significantly prolonging progression free survival (PFS) over standard chemotherapy when used as a first line therapy in patients with EGFR mutant lung adenocarcinoma (6). The phase III EURTAC trial conducted in Europe was the first trial to demonstrate the superiority of erlotinib over chemotherapy in previously untreated patients with advanced NSCLC with either the exon 19 deletion or exon 21 L858R mutation (7). The median PFS was 9.7 months for erlotinib versus 5.2 months for platinum based chemotherapy. Two studies have reported improvements in median PFS with an irreversible EGFR TK inhibitor, afatinib compared to chemotherapy in patients with EGFR mutant lung adenocarcinoma (8,9). Furthermore, initial therapy with afatinib improved overall survival (OS) compared to platinum based doublets in the subset of patients with exon 19 deletion in both these studies.

On the other hand EGFR TK inhibitors have consistently been found not to be superior to chemotherapy in patients with advanced NSCLC with EGFR wild type or when the EGFR mutation status is unknown. INTEREST trial showed gefitinib to be non-inferior to docetaxel (HR: 1.020, 95% CI, 0.905-1.150) with a median OS (7.6 vs. 8.0 months, respectively) (10,11). The DELTA study published recently once again confirms the lack of superiority of erlotinib over docetaxel in patients without known EGFR activating mutations (12). Of 301 patients enrolled from Japan, 151 were assigned to erlotinib 150 mg/day or docetaxel 60 mg/m² every 3 weeks. Patients with advanced NSCLC who had received one or two prior chemotherapy regimens were enrolled in this study. Majority of patients enrolled in this study had EGFR wild type. Not surprisingly, the median PFS for erlotinib was 2.0 months compared to 3.2 months for docetaxel [hazard ratio (HR) 1.22; 95% CI, 0.97-1.55; P=0.09]. The median OS was 14.8 months for erlotinib and 12.2 months for docetaxel (HR, 0.91; 95% CI, 0.68-1.22; P=0.53). Other investigators have reported similar findings (13-15). As we move forward, significant progress in the treatment of lung cancer can only be made with a better understanding of the molecular alterations underlying tumor evolution particularly in response to targeted therapies, improved drug development process and effective use of...
immunotherapy. Finally we should evaluate the potential benefits of using molecularly targeted agents in early stage and locally advanced NSCLC in order to improve the cure rates.

Advances in genomic sequencing have now made it possible to discover molecular alterations present in malignant cells in great detail and precision (16-18). It is now clear that lung cancer associated with tobacco smoking results in complex genomic alterations including a number of single nucleotide variations, insertions, deletions, copy number alterations and structural rearrangements. Several institutional studies and The Cancer Genome Atlas (TCGA) project have reported novel potentially actionable alterations in lung adenocarcinoma.

On a very encouraging note, several large-scale innovative studies are currently ongoing to define the role of targeted agents in molecularly selected groups of patients with early and locally advanced NSCLC. The adjuvant lung cancer enrichment marker identification and sequencing trials (ALCHEMIST) will screen nearly 8,000 patients with completely resected lung adenocarcinoma for EGFR mutations and EML4-ALK rearrangement in a central laboratory (NCT02194738). Patients with EGFR mutations or ALK rearrangement will be randomized to specific molecularly targeted therapy (erlotinib or crizotinib) or placebo following standard post-operative therapy (NCT02193282; NCT02201992). The primary endpoint of the study is OS. Comprehensive genomic analyses will be performed on tumor specimens from patients enrolled in this trial. The role of molecularly targeted agents in patients with unresectable locally advanced NSCLC is being studied in an ongoing multi-center study (NCT01822496). In this study, patients with EGFR mutant lung adenocarcinoma will receive either induction therapy for three months with erlotinib followed by definitive chemoradiation or chemoradiation alone. Similarly patients with ALK positive locally advanced NSCLC will receive either induction therapy with crizotinib followed by chemoradiation or chemoradiation alone.

It is likely that a number of novel treatment options will soon be available for patients with EGFR mutant and ALK positive NSCLC. Promising results have been reported now in patients with acquired resistance to EGFR inhibitors and ALK inhibitors (19,20). AZD 9291, a third generation EGFR TKI produced an impressive response rate of 64% among 107 patients with centrally confirmed EGFR T790M. A similar study using a different compound, CO-1686 reported a response rate of 58% in 40 patients with centrally confirmed EGFR T790M. The median PFS had not been reached at the time of presentation and was estimated to exceed one year. Several ongoing clinical trials are now available for patients with EGFR mutant NSCLC prior to and after therapy with first generation EGFR TKIs.

Finally, genomic analyses of multiple regions from the primary tumor reveal significant intra-tumoral heterogeneity in lung cancer (21-23). Tumor clones evolve either in a linear fashion by acquiring progressively fitter clones, or follow a branched pattern where multiple sub clones thrive simultaneously, resulting in a complex heterogeneous tumor. A better understanding of clonal evolution in response to therapy is critical to optimally treat acquired resistance. Studies with AZD 9291 and CO 1086 underscore the importance of genotyping growing lesions following targeted therapy in the salvage setting. Hopefully genotyping of cell free DNA from plasma would make the process of serial molecular evaluation easier in the coming years. While much work remains to be done, it is heartening to see the pace of progress in cancer therapy that we have witnessed over the past few years.

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**References**


