Editorial Commentary

Postoperative adjuvant EGFR-TKIs for resected *EGFR*-mutant NSCLC—opportunities and obstacles

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Lung cancer remains the leading cause of cancer-related mortality, accounting for almost a fifth of all cancer deaths worldwide (1). If diagnosed at an early stage, complete surgical resection of non-small cell lung cancer (NSCLC) is the most favourable approach and is curative in over half of patients. However, in patients with pathological stage II–III disease, resection alone is associated with a high rate of recurrence and overall survival (OS) of 23–57% (2). Despite demonstrating only a 5% absolute improvement in 5-year OS, the addition of postoperative adjuvant chemotherapy has been standard of care since 2003 (3), but poor therapeutic compliance and high toxicities limit the long-term efficacy of this approach.

The identification of targetable genomic alterations has become increasingly essential to guide treatment of NSCLC. Patients with *EGFR*-mutated NSCLC represent approximately 40% of Asian and 10–20% of Caucasian patients (4,5) and are a therapeutically distinct subset of cancers linked to unique biological properties. In advanced stage *EGFR*-mutant NSCLC, outstanding survival outcomes attributable to EGFR tyrosine kinase inhibitors (EGFR-TKIs) are observed in comparison to those achieved with conventional chemotherapy. The excellent outcomes of *EGFR* targeted treatment in the advanced disease setting has encouraged clinical trials of these agents in the adjuvant treatment of early-stage NSCLC harbouring *EGFR* mutations (6).

The recent consensus paper by Liang *et al.* outlines expert consensus statements and reviews current evidence and recommendations for the postoperative management of *EGFR*-mutant NSCLC (7). To date, six trials investigating EGFR-TKIs in the adjuvant setting have been completed. Heterogeneous trial design, with differences in patient populations and duration of adjuvant TKI treatment have led to inconclusive results. However, this postoperative management strategy has shown both significant disease-free survival (DFS) benefit, as well as the likelihood of increased compliance and reduced toxicity compared with chemotherapy regimens. This commentary will briefly highlight opportunities for clinical benefit as well as obstacles that require resolution before this mode of adjuvant treatment can become standard of care.

Opportunities

Molecular testing of resected NSCLC should be performed for all patients

Consensus 1 supports *EGFR* mutation testing of resected tissue to inform treatment strategy in the event of recurrence (7). In our opinion, molecular characterisation following surgical resection of non-squamous NSCLC is essential to plan adjuvant treatment. Reflex testing for *EGFR* at a minimum, and other targetable biomarkers where possible, has been recommended to aid clinical decision making in the event of treatment failure and postoperative disease recurrence. Multigene testing is employed in some institutions as coexisting mutations are not uncommon [38.8% of stage I–III resected NSCLC (8)], and may alter sensitivity to targeted agents (9). For example, coexistent *TP53* mutations

are a reported negative predictor of TKI efficacy and poor prognosis among patients with *EGFR*-mutated NSCLC (10,11). Patients with resected *EGFR*-mutant NSCLC with multiple mutations following EGFR-TKI treatment compared to those without other mutations (8,9). Clinical trials are needed to further evaluate the outcomes of adjuvant treatment with EGFR-TKIs in *EGFR*-mutated NSCLC where additional oncogenic mutations co-exist.

Risk prediction models to identify candidates for adjuvant therapy are useful in clinical decision making

Current guidelines recommend adjuvant therapy for patients with stage II–IIIA NSCLC with a high risk of recurrence. The ADJUVANT trial reported that EGFR-TKIs have shown most clinical benefit in patients with resected stage IIIA (12). Defining the "high-risk" subgroup is not easy. The cancer-specific survival (CSS) model from Zeng (eight variables derived from SEER data and validated in Chinese patients) showed very modest improvement in discrimination compared to UICC 8th edition staging (C-statistic 0.66 *vs.* 0.55 in the external validation dataset); although this is not high enough for clinical use (13). Young *et al.* validated a Chinese-derived OS model in the US National Cancer Database (NCDB) (n=57,313 resected stage I to IIIA, six variables) and found the UICC 7th edition was superior (C-statistic 0.804 *vs.* 8.833) (14). The two models only shared age, sex and examined lymph nodes as variables. Wu *et al.* moved away from the clinico-pathological paradigm to examine resected tumour genetic-features (15). Presented as an abstract at ESMO 2019, Wu *et al.* identified five predictive biomarkers using a Geneseeq 422-gene panel and specified a three-category model predicting significant OS hazard ratio (HR) in response to gefitinib or vinorelbine in resected *EGFR*-mutant stage II–IIIA NSCLC. As these three papers demonstrate, although clinico-pathological and genetic models promise enhanced predictive ability compared to the current UICC TNM standard in selecting patients for adjuvant therapy, further retrospective validation in diverse cohorts and prospective evaluation of clinical net benefit and cost-effectiveness in randomised controlled trials (RCTs) is required before they become relevant to the routine clinical setting.

EGFR-TKIs are associated with improved compliance and quality of life

We must also consider both the increased toxicities and the low compliance rate (<60%) reported in patients receiving standard adjuvant chemotherapy. For appropriately selected patients at high risk of recurrence, EGFR-TKIs may be preferable to chemotherapy because of improved quality of life and compliance rate, as demonstrated in the ADJUVANT trial in which compliance among patients receiving EGFR-TKIs was 95.5% compared to chemotherapy (78.4%) (12).

Obstacles

Carefully designed clinical trials are essential to establish clear indications for treatment

The conflicting results shown in the three landmark studies RADIANT, ADJUVANT and EVAN are likely due to heterogeneous study design. In the negative RADIANT trial, a large proportion of stage IB patients were reported in the erlotinib arm, and more patients in the placebo arm having stage IIIA disease. Furthermore, inaccurate screening of *EGFR* status by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) rather than DNA testing misrepresented the target population. Prolonged DFS was not seen in the *EGFR*-mutant treated with erlotinib (16). In the ADVJUANT and EVAN trials, patients with stage II–IIIA (N1–N2) *EGFR*-mutant NSCLC treated with EGFR-TKIs showed lower toxicities and significantly longer DFS (12,17). A recent meta-analysis reported that EGFR-TKIs significantly improved DFS in studies with <50% patients with stage I and >30% patients with stage IIIA NSCLC (18). Not surprisingly, the data did not support of the use of adjuvant EGFR-TKIs in patients with stage I NSCLC where DFS was not significantly improved.

In advanced NSCLC, prolonged use of TKIs typically results in the emergence of acquired resistance via a variety of mechanisms, notably T790M secondary mutations. Therefore, mature OS data is essential for understanding long term EGFR-TKI efficacy in the adjuvant setting to clarify treatment strategy. Despite improved DFS demonstrated in ADJUVANT, EVAN, SELECT and EMERGING trials, OS data was not reported (7). OS benefit is a necessary indication before altering the course of clinical practice, as DFS benefit may be a transient effect that may fail to translate directly into improved OS. The ALCHEMIST-EGFR trial of erlotinib versus placebo is ongoing with OS as a primary outcome (19). We await OS data from this trial and further ongoing studies along with

reports of patterns of drug-resistance at the time of disease recurrence e.g., presence of the T790M mutation. Mature OS data from head-to-head comparison trials of EGFR-TKI versus chemotherapy followed by EGFR-TKIs in selected patient cohorts are eagerly awaited.

Identification of the most effective EGFR-TKI agent, optimal timing and duration in the adjuvant treatment strategy is yet to be defined

Residual uncertainties include whether to administer EGFR-TKI alone or in combination with chemotherapy, and if in combination, the optimal scheduling of TKI in relation to chemotherapy. The P-C-G trial showed significant DFS benefit in *EGFR*-mutated patients treated with gefitinib following chemotherapy in stage IIIA-N2 NSCLC (20). However, the Chinese trial of icotinib in combination with chemotherapy in stage IB–IIIA patients showed no statistical DFS benefit (21).

Additionally, the appropriate duration of treatment is yet to be defined. First-generation TKIs have shown a median DFS of 10 months in advanced NSCLC (22) and TKI sensitive cells have been shown to reach their maximal inhibition after 3 months. The ADJUVANT study is the only trial so far to directly compare gefitinib with chemotherapy among over 200 patients treated for up to 2 years. Trial data reported DFS Kaplan-Meier curves for each arm separated at 12 months are merged again at 36 months, proposing that gefitinib maintained clinical benefit for up to 12 months following TKI cessation (12). A similar trend was reported in the RADIANT trial of erlotinib versus placebo, suggesting that TKI treatment might not be curative but sustain DFS by delaying recurrence by 10–12 months compared to chemotherapy (16). Extended treatment regimens have shown long-term clinical benefit from imatinib and tamoxifen for gastrointestinal stromal tumour (GIST) and breast cancer respectively (23). The phase III ADAURA trial of osimertinib versus placebo in stage IB–IIIA resected NSCLC has the longest duration of treatment to date (3 years). OS results from these trials are eagerly awaited and will provide further insight on the appropriate selection and duration of TKI treatment (24).

Ethnic diversity in study cohorts will broaden the translational potential of EGFR-TKI trials

It is well established that *EGFR* mutations occur in a higher proportion of NSCLC among Asians than in Caucasians. The positive ADJUVANT, EVAN and EMERGING trials reported on Chinese patients only, limiting generalisability to the broader NSCLC population (12,17,25). The early RADIANT trial reported on an ethnically diverse group including Asian, East- and West-European, Latin- and North American patients. However, this was a negative trial, likely due to the inclusion of patients unselected for *EGFR* status (16). Future trials incorporating more diverse patient groups will be welcomed.

The clinical success of first-line treatment with EGFR-TKIs in advanced *EGFR*-mutant NSCLC has led to keen interest in the use of these agents for patients with early-stage disease. The BR.19, RADIANT, ADJUVANT, EVAN, SELECT and EMERGING trials investigated adjuvant use of EGFR-TKIs in resected NSCLC, with four of these six trials reporting improved DFS. The recent consensus by Liang *et al.* presents eight key recommendations to aid clinical management of resected *EGFR*-mutant NSCLC. However, adoption of these recommendations will ultimately depend on each jurisdictions' healthcare funding/reimbursement systems and applicable standards of clinical care. Future clinical trials together with a rigorous scientific approach to evidence analysis will define the harms and benefits of adjuvant EGFR-TKIs in the postoperative setting, address remaining uncertainties, and help to redefine therapeutic options for patients with resectable lung cancer. Moreover, the potential of immunotherapeutics is also envisaged to significantly change the therapeutic landscape in the near future.

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