Editorial

Can molecularly targeted therapy cure patients with resected EGFR mutant NSCLC?

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In an age of targeted therapies, the promise of eliminating non-targeted and indeed more toxic chemotherapy was considered a given until several trials challenged this assumption. The BR.19 (1) and RADIANT (2) studies were conducted in molecularly unselected populations initially, although RADIANT was amended to include only *EGFR* mutant patients. Both of these studies used adjuvant gefitinib (BR.19) or erlotinib (RADIANT) after surgery. Nonetheless, the signal from these trials not only suggested no benefit in unselected patients, but harm in the BR.19 patients who received gefitinib. In RADIANT, roughly half of the study population received adjuvant chemotherapy followed by the tyrosine kinase inhibitor (TKI) erlotinib, and no benefit was seen. For the ADJUVANT trial recently reported in the Lancet Oncology (3), centrally reviewed molecular selection promised to define the patient group most likely to benefit from the intervention and therefore answer the question whether targeted therapy was better than chemotherapy in a molecularly selected population.

Approximately 20–25% of patients who are diagnosed with non-small cell lung cancer (NSCLC) are potentially suitable for resection with curative intent (4). The LACE (5) meta-analysis had previously shown that adjuvant chemotherapy, for resected early stage NSCLC, improved survival. This has established the current standard of care for resected stage II-III NSCLC of cisplatin-based chemotherapy. This strategy has demonstrated improved overall and disease-free survival compared to observation. However, this paradigm exists for all patients irrespective of EGFR status. Furthermore the 5-year survival for stage II-III patients continues to remain poor.

ADJUVANT (3) was an open label phase 3 trial conducted at 27 centers, all in China. Enrolled patients underwent a R0 complete resection with lobectomy or pneumonectomy for pathological stage II-IIIA disease. They had either an exon 19 deletion or exon 21Leu858Arg EGFR mutation confirmed centrally using amplification-refractory mutation system PCR. Eligible patients were ECOG 0 or 1, had adequate haematological are biochemical values and no previous systemic antitumour therapy. Randomised patients were stratified by EGFR mutation status and N stage, and were randomly assigned to standard dose intravenous cisplatin 75 mg/m^2 and vinorelbine 25 mg/m^2 (D1 and D1 and 8) for 4 cycles versus gefitinib 250 mg daily for 24 months. The primary outcome was investigator assessed disease free survival with secondary endpoints of overall survival, 3 and 5-year disease free survival and safety and tolerability. Analysis was performed on an intention to treat basis with 122 events needed to detect a 40% improvement in disease free survival with gefitinib (HR 0.6) with 80% power at a two-sided 5% significance level. Interestingly, the authors assumed the median DFS in the chemotherapy arm would approximate 31 months. Kaplan-Meier curves were used to evaluate time to time endpoints and disease-free survival for the treatments was compared with a two-sided log rank test.

Two hundred and twenty-two patients were enrolled between September 19 2011 and April 24 2014 out of 483

screened. One hundred and eleven patients were randomly assigned to gefitinib and 111 to cisplatin and vinorelbine of whom 5 and 24 did not start treatment respectively. Given this, 193 randomised patients were included in the modified intention to treat population out of whom 87 were allocated cisplatin and vinorelbine and 106 gefitinib. The baseline demographics and characteristics were well matched between groups. The median duration of treatment in the gefitinib group was 21.9 months with a median dose of 250 mg. 68% received treatment for more than 18 months. 84% of patients on the chemotherapy arm completed 4 cycles of chemotherapy. At the time of data cutoff 146 patients had discontinued the study (76 on the gefitinib arm and 70 on the chemotherapy arm). The most common reason for discontinuation in both arms was disease relapse with 52% in the gefitinib arm and 50% in the chemotherapy arm.

In the 36.5 months of follow up 59% of the patients in the gefitinib arm relapsed or died versus 53% on the chemotherapy arm. Median disease-free survival in the intention to treat analysis was significantly longer in the gefitinib arm (28.7 months, 95% CI, 24.9–32.5) versus 18 months in the chemotherapy arm (HR 0.6, 95% CI, 0.42–0.87, P=0.0054). In a post-hoc modified intention to treat analysis median disease-free survival was also significantly longer in the gefitinib arm (28.7 months, 95% CI, 24.9–32.5) when compared to the chemotherapy arm (19.3 months, 95% CI, 14.8–23.9), HR 0.7, 95% CI, 0.49–0.99, P=0.044. Three-year disease-free survival was analysed using χ^2 tables and was 34% (95% CI, 24–45) in the gefitinib group and 27% [16–38] in the chemotherapy arm (HR 0.74, 95% CI, 0.42–1.32, P=0.37). At the time of analysis 41 patients in the intention to treat gefitinib arm and 35 in the chemotherapy arm had died. There were no treatment related deaths. Dose reductions occurred in 11% of patients who received gefitinib and 33% who received cisplatin and vinorelbine. Three patients who received gefitinib (3%) and 5 (6%) who received chemotherapy discontinued therapy due to toxicity. Adverse events were reported in 58% of patients in the gefitinib arm versus 80% in the chemotherapy arm. The most common side effects seen with gefitinib were rash (41%), increased alanine transferase (27%) and diarrhoea (26%).

Serious adverse events occurred in 7 (7%) of patients in the gefitinib arm and 20 (23%) in the chemotherapy arm. No significant difference in FACT-L or LCSS was reported from baseline to week 33 but patients on gefitinib reported improvements in Treatment Outcome Index scores from baseline to week 33 when compared to those on cisplatin and vinorelbine (P=0.012). Overall survival data was immature at the time of analysis.

The ADJUVANT trial is the best data we have currently suggesting that rates of cure for *EGFR* mutant patients treated with either chemotherapy or gefitinib is low with half the patients relapsing before 2 years in the chemotherapy arm. In fact, the median DFS in the gefitinib arm was only increased by 10.7 months, from 18 to 28.7 months, suggesting that stopping the TKI at 24 months, resulted in re-emergence of quiescent disease i.e., the therapeutic strategy was not curative. Remember that the trial was actually powered around an assumption of median DFS in the chemotherapy arm of 31 months, so the chemotherapy arm actually did a lot worse than expected. The readout of overall survival was a secondary endpoint and is likely to be diluted by patients accessing TKIs on progression, so it remains unclear whether updates to these data are likely to be informative for overall survival. Based on the available results, does this represent a new standard of care? While the TKI treated patients took longer to progress and had less toxicity it is important to remember that the primary outcome of adjuvant therapy is to effect cure, not prolong disease free survival. Given that the survival curves rapidly converge on cessation of gefitinib, further DFS updates will be important in determining the role of chemotherapy.

The next question is whether two years of therapy is enough. Similar results from the single arm SELECT trial (6), also suggested that stopping at two years may be premature. Certainly, in trials using adjuvant imatinib for gastrointestinal stromal tumours (GIST), three years has been shown to be better than one for DFS, but in the long term any overall survival advantage remains questionable (7). However, in advanced EGFR mutant disease, the development of TKI resistance occurs at a median of around 10 months and the commonest resistance mechanism is either the development the T790M mutation or sequestering in a sanctuary site such as the CNS (8). The ADAURA trial promises to provide extremely important information in this setting with randomisation to the CNS penetrant and T790M resistance mutation targeting drug osimertinib or placebo. This trial will give three years of TKI therapy or placebo after standard chemotherapy, in line with the GIST studies. Similarly the ALCHEMIST trial adds two years of erlotinib after standard chemotherapy with the primary endpoint of overall survival. For both studies, unlike ADJUVANT all patients will receive chemotherapy followed by the TKI.

While these trials promise to answer critical questions about adjuvant therapy in EGFR mutant NSCLC, it is worth noting that to date targeted therapies in GIST and melanoma have failed to demonstrate a consistent overall survival advantage despite showing excellent DFS benefit. This leads to the question is it worth continuing on the TKI for life? Or does early TKI use change the outcome of the disease compared to waiting for progression? One way of answering this question is to incorporate molecular remission into therapeutic paradigms by utilising circulating tumour DNA (ctDNA). Recently a study (9) used this approach to correlate freedom from progression with molecular remission and showed ctDNA to be an excellent predictor. The ADAURA trial has also incorporated ctDNA analysis and may provide important information towards treatment selection and duration.

While the ADJUVANT trial provides a very important piece to the puzzle of using a targeted agent for EGFR mutant NSCLC, it does not currently prompt a change in adjuvant therapeutic paradigms. The reality is that even in this molecularly targeted era, chemotherapy remains the backbone of adjuvant therapy with ongoing trials using it as standard and adding targeted therapy to "consolidate" the chemotherapy. The success of targeted therapies in advanced disease has created an expectation that this would be paralleled in earlier stage disease, but the dismal DFS data in both arms underscores the urgency for better treatments, better strategies and ultimately higher cure rates.

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Footnote

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