Editorial Commentary

The APPLE's core question—upfront osimertinib versus the sequential approach for *EGFR* mutated non-small cell lung cancer

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Activating *epidermal growth factor receptor* (*EGFR*) mutations in lung cancer are reported in approximately 50% of Asian and 15% of Caucasian patients diagnosed with non-small cell lung cancer (NSCLC) (1). Tyrosine kinase inhibitors (TKIs) have become the standard first-line treatment for this cohort of patients since the pivotal trials investigating first generation TKIs, erlotinib and gefitinib (2,3). Subsequently, the third generation TKI, osimertinib, has now become the generally accepted front-line therapy, after the practice-changing FLAURA trial (4). However, one of the criticisms of the FLAURA trial was that only 37.2% of patients receiving first generation TKIs received osimertinib post progression, and this may have exaggerated the differences in survival. This is in contrast to the APPLE trial, which reported 73% of patients randomised to gefitinib/erlotinib crossed over to osimertinib after progression. It is for this reason that the recent update of the APPLE trial may add greater clarity to the interpretation of the FLAURA trial's overall survival (OS) findings. Furthermore, this update also analysed the treatment strategy's impact on brain metastasis control as well as the relationship between circulating tumour (ct)DNA and progression-free survival (PFS).

The trial design and background

The APPLE trial began recruitment in November 2017 and ended in February 2020 (5). It was a randomised, open-label, non-comparative, multicentre, phase II study which enrolled treatment naïve patients with *EGFR*-mutant (exon 19 deletion and L858R mutation only) metastatic NSCLC.

There were 3 study arms:

- Arm A: upfront osimertinib (80 mg once daily, n=53) until disease progression (PD) by RECIST;
- Arm B: upfront gefitinib (250 mg once daily, n=52) until emergence of *EGFR* T790M clone in the plasma ctDNA or PD by RECIST, then switching to osimertinib until a second PD by RECIST;
- Arm C: upfront gefitinib (n=51) until PD by RECIST, then switching to osimertinib until a second PD by RECIST.

The primary endpoint was PFS on osimertinib at 18 months for arm B. The key secondary endpoints were PFS, OS and the brain PFS.

The initial objective was to investigate whether early switch to osimertinib post gefitinib upon detection of the

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resistant EGFR T790M clone, in plasma ctDNA would yield clinically significant outcomes compared to switching to osimertinib upon PD by RECIST. Although feasible, ctDNA guided osimertinib switch did not result in a superior OS; and subsequently with osimertinib being the preferred upfront therapy in EGFR-mutant metastatic NSCLC following the FLAURA trial (4), the findings of the first publication from the APPLE trial did not impact clinical practice. However, by addressing the sequencing issues of the FLAURA study, the authors of the recent APPLE trial update may substantially improve the current evidence in this space (6).

Upfront osimertinib or sequential TKIs?

In the recent update and post hoc analysis of the APPLE trial, the investigators pooled data from arms B and C (sequential arms: upfront gefitinib followed by osimertinib upon PD by molecular ctDNA or RECIST 1.1) and compared it to arm A (upfront osimertinib) and asked whether the different strategies impacted on PFS or OS. Unlike the FLAURA study, there were no significant difference in the OS between the two groups. Most of the patients (73%) who progressed on gefitinib received second-line osimertinib, thus the investigators concluded there were no significant differences between upfront osimertinib or sequential treatment. Because of the non-comparative design and limited statistical power, whether upfront osimertinib or sequential treatment is truly equivalent for OS outcome is debatable. There are risks associated with this post hoc analysis, in particular by combining the outcomes for arms B and C. Inherent differences between the arms (not limited to clinicopathologic characteristics) may introduce bias and inconsistencies, that limit the robustness of the comparison with arm A.

Nevertheless, this result does give some suggestion that the sequential TKI strategy is a viable option, especially for regions of the world with first-line osimertinib access and reimbursement issues (7). However, the main barrier to this sequential approach across the EGFR mutant patient population, is the approval and reimbursement of osimertinib in the second-line setting, which is currently straightforward in many countries, but only if the presence of the T790M resistance mutation is demonstrated. Consequently, for patients receiving upfront first-generation EGFR TKI, a substantial proportion may not be able to access second-line osimertinib. This includes the large proportion of patients that do not develop the T790M resistance mutation. Furthermore, molecular testing may be unavailable due to financial or logistical barriers. Lastly, this is in addition to patients that may be unable or not be fit to receive subsequent anticancer therapy (4% in the APPLE trial). Whilst this was a substantially low proportion of patients, this is in the context of a clinical trial patient population, and in real-world clinical practice this proportion may be expected to be higher.

In terms of safety profile, second-line osimertinib did have an overall favourable safety profile. There were no treatment discontinuations, and lower incidences of dry skin and rash acneiform. Taken together, this adds data to the suggestion that for patients with emergence of the T790M resistance mutation, the sequential approach may have superior outcomes compared to upfront osimertinib. In the absence of an upfront predictive biomarker to identify which patients will develop T790M resistance however, this approach would not be feasible in real-world clinical practice. It should also be noted though, there may be other subgroups which benefit from second-line osimertinib, such as patients with central nervous system (CNS) progression. Furthermore, some patients may still have tumours which remain dependent on EGFR signalling, and the higher selectivity for EGFR of osimertinib may still yield benefits. Ultimately, the treatment landscape is rapidly changing, and upfront treatment intensification, as demonstrated by the FLAURA2 (8) and MARIPOSA (9) trials, further complicate treatment decision making. This heightens the importance of developing novel predictive biomarkers to guide therapeutic selection in the first-line setting.

CNS control

The APPLE trial reported that the median brain progression-free survival (BPFS) was significantly longer in the upfront osimertinib arm (34.3 versus 22.3 months). Although it is important to note that there were higher percentages of patients with baseline brain metastases in the sequential arm than the upfront osimertinib arm (29% versus 19%). Consequently, it may still be considered prudent for patients with known brain metastases to start on upfront osimertinib, consistent with current consensus. Given the morbidity associated with brain metastases and the treatment of brain metastases however, the potential impact on patients' quality of life should not be underestimated, and the prevention of CNS progression with upfront osimertinib is important. In a broader context, although upfront osimertinib provided superior intracranial

control in the APPLE study, the recent FLAURA2 and MARIPOSA trials have further complicated the drug sequencing debate. The optimal upfront strategy for patients with brain metastases, whether osimertinib should be given with platinum-doublet chemotherapy as per FLAURA2 (8) or combination amivantamab plus lazertinib as per MARIPOSA (9), remains an open question.

Relationship between ctDNA clearance and survival outcomes

The APPLE trial demonstrated that serial ctDNA monitoring via the Cobas EGFR test v2 to facilitate early detection of PD and switch to second-line therapy is feasible. Liquid biopsy or ctDNA assays are yet to be validated for clinical use as a serial dynamic marker of therapeutic response. Nevertheless, ctDNA remains under investigation as a prognostic biomarker in this setting and many clinical trials now include ctDNA biomarker analysis. Indeed, studies have shown correlation between post treatment ctDNA clearance and survival outcomes (10-12). In EGFR mutant lung cancer alone, the FLAURA, AURA3, and MARIPOSA trials have all shown association between ctDNA clearance and PFS (11,12). These are findings supported by recent systematic reviews and meta-analyses (13,14). Similarly, the APPLE trial also found ctDNA clearance is associated with improved PFS, but whether this translates into OS was not shown. If ctDNA clearance is proven to be predictive of OS and validated for clinical use, there is also the potential for treatment intensification guided by serial ctDNA measurements. For example, if ctDNA is not cleared by osimertinib, then switching to a more intensive regimen, such as adding chemotherapy, can be considered to improve survival outcomes. Ongoing trials such as NCT04410796, may answer this question (15). Conversely, if ctDNA is cleared by osimertinib, approaches such as treatment breaks to reduce toxicities and improve patients' quality of life, while continuing to measure ctDNA intermittently to detect early signs of progression to restart therapy, also need to be prospectively tested in randomized trials. However, in the absence of such trials, these approaches cannot be recommended in routine clinical practice.

Further important considerations, however, include the assay and method of ctDNA testing. In the APPLE trial, the Cobas EGFR test, a polymerase chain reaction (PCR) assay was used for the analysis of ctDNA. This is in contrast to other recent trials such as FLAURA and MARIPOSA (11,12,16), which used either droplet digital PCR (ddPCR) or next-generation sequencing (NGS), which have higher sensitivity and lower limits of detection for EGFR. In addition, NGS may also detect other mechanisms of resistance, not only T790M. Whether more sensitive assays would influence the potential correlation with survival outcomes remains an open question. The potential cost-effectiveness of real-world clinical implementation of different ctDNA assays is another key consideration. Higher sensitivity assays would be associated with greater costs, and routine serial monitoring of patients may not be feasible or cost-effective. Given the difficulties in designing and conducting trials which prospectively evaluate the role of liquid biopsies in this clinical setting, generating high quality evidence demonstrating the utility of serial ctDNA monitoring will be challenging.

Conclusions

The post hoc analysis of the APPLE trial is consistent with our current understanding of EGFR TKIs. Osimertinib provides better intracranial disease control and protection against development of intracranial metastases compared to first generation EGFR TKIs and use in the first line setting in metastatic EGFR mutant NSCLC remains a standard of care approach. In addition, serial ctDNA provides useful prognostic information, and this could potentially guide treatment decisions. However, in a rapidly changing first-line treatment landscape for EGFR mutated NSCLC, the findings from APPLE emphasise the urgent unmet need for novel predictive biomarkers to guide therapeutic selection in the first-line setting

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