Targeted therapy has fundamentally advanced the standard-of-care for difficult-to-treat lung cancer disease over the past two decades. To this date, there are seven actionable molecular target kinases that possess matching targeted therapeutics approved by the U.S. Food and Drug Administration (FDA) (1,2). Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) marked this monumental drug developmental journey of lung cancer targeted therapy with the initial advent of the first-generation reversible small molecule EGFR TKIs gefitinib and erlotinib as targeted inhibition of EGFR-mutated non-small cell lung cancer (NSCLC) (3,4). Of interest, the initial approval and clinical use of first-generation EGFR TKIs for advanced NSCLC predated the landmark discovery of the activating and drug-sensitizing mutations of EGFR, L858R and exon 19 deletion (Ex19del). This was then followed by the development of newer-generation EGFR TKIs for advanced NSCLC predicted the landmark discovery of the activating and drug-sensitizing mutations of EGFR, L858R and exon 19 deletion (Ex19del). This was then followed by the development of newer-generation EGFR TKIs such as afatinib with activities against EGFR and HER2.

Of paramount importance, the discovery of the dominant mutational drug resistance mechanism as the EGFR T790M kinase mutation as seen in ~50-60% of acquired first-generation EGFR TKIs resistance (5,6) engendered the exciting new era of mechanistic translational research and novel drug development to overcome acquired drug resistance. Eventually a third-generation irreversible EGFR TKI osimertinib emerged as the first small molecule agent approved to target and overcome EGFR T790M resistant mutation. Remarkably, osimertinib soon found its clinical application and FDA approval for first-line treatment of EGFR-mutated NSCLC including but not limiting to the presence of EGFR T790M mutation (7,8). One of the much welcomed advantages of osimertinib over earlier generation EGFR TKIs is its superior CNS drug penetration and thus inhibitory efficacy, thus resulting in excellent disease control in brain metastases and even leptomeningeal carcinomatosis (9,10).

Prior attempts to establish potential clinical benefits of EGFR TKIs in earlier stage NSCLC beyond the metastatic stage IV population without preselection of EGFR mutation-positive patients have met with disappointing clinical trial failures (11). In more recent years, there has been a renewed enthusiasm to advance EGFR TKIs into earlier curable stage diseases in the form of adjuvant targeted therapy in surgically resected stage I-IIIA NSCLC patients. These noble efforts have initially been rewarded only with mixed study results. The NCIC CTG BR.19 study (12) and the RADIANT study (13) investigating the role of adjuvant therapy using first-generation EGFR TKIs did not show any survival benefit in patients with NSCLC not preselected for EGFR mutations. On the other hand, the two clinical trial studies that focused on EGFR-mutated NSCLC did yield disease-free survival (DFS) benefits when used first-generation EGFR TKIs as adjuvant therapy (14,15). In the EVAN study, 2 years of adjuvant erlotinib resulted in improved DFS compared with chemotherapy among patients with EGFR-mutation-positive stage IIIA tumors (81.5% vs. 44.6%; hazard ratio [HR] for disease recurrence or death, 0.27) (14). In the ADJUVANT/CTONG1104 study, gefitinib adjuvant therapy resulted in significantly longer DFS with stage II–IIIA EGFR mutation-
positive NSCLC when compared with chemotherapy (30.8 vs. 19.8 months; HR for disease-free recurrence or death, 0.56). In addition, the DFS was also higher at 3 years (39.6% vs. 32.5%) although the overall survival (OS) benefit was not validated to be improved (HR, 0.92; P=0.67) (15).

In October 2020, Wu and colleagues reported the study results of the ADAURA phase 3 randomized clinical trial investigating the role of third-generation EGFR TKI osimertinib as adjuvant targeted therapy in resected EGFR-mutated NSCLC in addition to standard adjuvant chemotherapy (16). The study sparked a highly notable and invaluable wave of debate nationally and internationally on many related issues centering mostly on whether and when the positive study outcome data should be translated into standard-of-care practice.

The ADAURA study is a global double-blind, phase 3 randomized clinical trial in completely resected EGFR mutation-positive stage IB to IIIA NSCLC to study the role of osimertinib as adjuvant therapy (16). Both the study investigators and many others lauded the study results as a “home run” for osimertinib as adjuvant treatment. With strikingly positive trial results, both clinically and statistically speaking, the trial in fact underwent an early unblinding after the unplanned interim analysis, with the much anticipated results first publicly presented at the America Society of Clinical Oncology (ASCO) Virtual Meeting in May 2020 as a plenary presentation.

The key positive trial data from the ADAURA study would first be highlighted here. The study enrolled 682 stage IB–IIIA completely resected NSCLC patients harboring an activating EGFR mutation, who were randomized 1:1 fashion to receive either osimertinib (80 mg/day) or placebo for up to 3 years. Patients were allowed, but not required to have received adjuvant chemotherapy. In an unplanned interim analysis, the primary endpoint DFS was found to be met in a remarkable extent in April 2020, leading to the profound decision to unblind the study early. In patients with stage II to IIIA, the median DFS benefit was found to favor osimertinib (not reached) over placebo (20.4 months) with a hazard ratio (HR) of 0.17 (P<0.0001). The 2-year DFS rate was 90% with osimertinib vs. 44% with placebo. Moreover, when stage IB disease was included in the analysis, the median DFS in the overall study population was still not yet reached in the osimertinib-treated arm vs. 28.1 months in the placebo arm, with a highly positive hazard ratio (HR) of 0.21 (P<0.0001). The 2-year DFS rate was 89% with osimertinib vs. 53% with placebo. Undeniably, these DFS results are impressive and perhaps even unprecedented in the history of lung cancer randomized adjuvant clinical trial studies.

A number of important questions have arisen since the public presentation and soon after the publication of the ADAURA study results (16). In fact, few would argue about the magnitude and significance of the positive trial results per se. Most of the debate cuts across the spectrum of questions on appropriate adjuvant therapy trial design and endpoints, proper modes of clinical application, threshold and timing of standard-of-care translation, as well as drug cost consideration. First and foremost, much controversies have centered on the question of whether the study should be considered “practice-changing”, and more specifically whether it should now be adopted as standard-of-care, with only DFS benefits data but not OS confirmation. Since the agent in question is osimertinib, a FDA approved EGFR TKI that is already commercially available for metastatic disease treatment, the ADAURA study results thus become immediately clinically relevant whether one likes it or not. With the remarkable magnitude of benefits in DFS associated, it truly has become quite difficult to argue that patients should not be informed of the positive study data and what it may or may not mean to them. In essence, all eyes are now on the ultimate decision pending by the FDA, which in October 2020 has already accepted and granted priority review to the supplemental new drug application (sNDA) for osimertinib for the adjuvant treatment of patients with early-stage EGFR-mutated NSCLC after complete tumor resection with curative intent. In fact, besides the finding that the subgroup analysis found that the DFS benefit of adjuvant osimertinib was evident across all stage groups with stage IB to IIIA patients in the trial, the benefits of osimertinib did extent to all the categories under such analysis, including sex, age, smoking history, race (Asian vs. non-Asian), EGFR mutation type (Ex19del vs. L858R) and adjuvant chemotherapy (yes vs. no). Perhaps the strongest argument against adopting the ADAURA study result at this time to offer osimertinib as adjuvant therapy option as standard-of-care is that OS benefits should be the “gold standard” endpoint for curative intent adjuvant studies. To confound this dilemma even more, the early unblinding of the study, as controversial as it may be, could have far-reaching impact to compromise the eventual overall survival data, even if the sponsor is committed to continue to acquire the OS data. Nonetheless, strong arguments could be put forth on both sides of the debate regarding whether it is ethical to unblind the study without the final OS data. Nonetheless given the ADAURA study
primary endpoint is DFS in stage II–IIIA patient groups and not OS, given the impressive DFS benefit data conclusion at this time, it would be very hard to argue against unblinding here. However, investigators and patients are said to continue to participate in the trial and remain blinded to study treatment. Some contest that it is important to understand more of the granularity of the study data in the pattern of recurrence, and the subsequent therapeutics received thereafter especially in the placebo group. On the other hand, whether osimertinib can be made available to patients in placebo arm in progression in this global study may also be dependent on the country of residence of the patient.

It is of considerable interest to focus on the available central nervous system (CNS) control data from the ADAURA study which lends substantial support to the “practice-changing” argument in adjuvant osimertinib. Ninety-eight percent (98%) of the patients in the osimertinib group and 85% of those in the placebo group were alive without CNS disease involvement after 2 years (HR, 0.18; 95% CI, 0.10–0.33). During the European Society for Medical Oncology (ESMO) Virtual Congress 2020, Tsuboi et al., focused their analysis on CNS recurrences in the ADAURA study and presented the CNS updated data, since CNS metastases are associated with significant morbidity (17). After a median follow-up of 22 months, the CNS recurrence rate was 1% among the patients who received osimertinib vs. 10% among those in placebo group. This translates in to an 82% reduction in the risk for CNS recurrence, and was reported to be both “clinically meaningful” and “highly statistically significant”. Furthermore, median CNS DFS was not reached among the osimertinib-group patients vs. 48.2 months among those in the placebo group. The conditional probability of CNS recurrence at 18 months was less than 1% with osimertinib vs. 9% with placebo.

On the question of whether we are truly offering genuine “cure” to more patients with the use of osimertinib, as opposed to simply delaying the inevitable. However, it is not hard to appreciate the suboptimal quality of life and emotional burden of living with the active disease in progression or worse with metastatic progression setting after curative intent surgical treatment. Hence even one argues that in the end the ADAURA trial profound DFS data might not translate into OS benefit, which would take years more to conclude, the case remains strong to advocate for at least allowing the patient an option of receiving adjuvant osimertinib upfront rather than mandating its delayed use only after distant metastatic recurrence occurred (especially with the risk of higher probability of CNS recurrence without adjuvant osimertinib). Also, in the study there was no new safety concerns found with osimertinib use. Furthermore, the argument of over-treating some patients who would have already been “cured” by adjuvant chemotherapy without additional adjuvant osimertinib and without the support of positive OS data can be somewhat misleading. The same argument can also be made to the use of adjuvant chemotherapy even with the proof of positive OS data, as we unavoidably are over-treating some in the adjuvant setting who might not need the chemotherapy for the cure. Until the time we have excellent and clinically-relevant biomarkers to discern and segregate patient groups at different risks of disease recurrence, we always would need to live with making individual treatment decision at the bedside based on population-based clinical trial data and statistical figures as best guidance.

One thing we would probably all agree on now is that the era of genotyping or even genomic profiling in early stage resected lung cancer has finally arrived. Regarding future considerations in the role of adjuvant EGFR TKI in completely resected EGFR mutation-positive NSCLC, we certainly are still left with a number of unanswered questions.

First, in the ADAURA trial, 55% of patients in osimertinib group and 56% in placebo did not receive standard-of-care adjuvant chemotherapy. While it is important to understand the reasons behind those patients who did not receive chemotherapy, it is also equally relevant now to ask if adjuvant osimertinib can actually replace chemotherapy in this setting, or if osimertinib should be started concurrently with chemotherapy instead of sequentially.

Second, it is speculated that the decision for choosing adjuvant osimertinib therapy duration as 3 years in the ADAURA study is likely an empirical choice. Upon reviewing the earlier SELECT trial, which is a single arm phase 2 study investigating adjuvant erlotinib for 2 years of treatment in patients with resected EGFR mutation-positive NSCLC, it was evident that there was a trend of increased rates of disease recurrence after the EGFR TKI discontinuation at 2 years (18). Hence it begs the question whether the optimal adjuvant osimertinib treatment duration should be longer than 3 years. Analogous to adjuvant hormonal therapy in estrogen receptor-positive breast cancer, we may soon find ourselves in studying adjuvant osimertinib targeted therapy in resected EGFR-
mutation positive NSCLC for 3- vs. 5- vs. 10-years duration. The ADAURA study also raises question about potential role of osimertinib in inoperable stage III locally advanced NSCLC harboring EGFR mutations, either as pre-chemoradiation vs. post-chemoradiation therapy or even to replace chemotherapy in its own combination with concurrent radiation.

Third, we should invest substantial effort in identifying reliable biomarkers to discern those patients at higher/highest risks of disease recurrence, thus would most benefit from adjuvant osimertinib. One of such potential promising assays is the use of circulating tumor DNA (ctDNA) (19) to monitor for molecular residual disease after resection and chemotherapy. Along this line of reasoning, there can also be other concurrent genomic alterations found with EGFR mutations in NSCLC, with the molecular heterogeneity accounting at least in part for upfront non-response to EGFR TKIs in metastatic treatment setting (20,21). It would thus be important to acquire a comprehensive landscape of genomic make-up in EGFR mutation-positive NSCLC even at resectable stages and to investigate for any potential added role of other matching actionable genomically-guided therapeutics with EGFR TKI as indicated.

Fourth, the passionate debate on whether OS vs. DFS should be safeguarded as our consensus adjuvant trial standard in the past is indeed very valid and far-reaching. Here we should be reminded of the evolution of trial endpoints and accelerated FDA approval of precision targeted therapeutics in metastatic oncogene-addictive lung cancers over the past decade (22). Again, in the context of genomics-guided adjuvant targeted therapy with unprecedented magnitude of positive DFS benefits, it is difficult and unrealistic to argue not to at least allow the discussion and option of use in the patients affected. Moreover, the ADAURA study is poised to fundamentally transform the paradigm of early-stage NSCLC management with its implications over resected diseases harboring a growing list of other actionable genomic alterations e.g., ALK-/rosi1-/RET-/ntrk-fusions, braf mutations, Metex14, Met amplification and HER2 mutations/amplification (1,2). Expectedly the hot debate of what should be the “gold-standard” trial primary endpoint would rage on, probably without a truly “black vs. white” consensus to be reached soon.

Fifth, while the ADAURA trial study results are as impressive as they stand already, one could still postulate that there could still be room to improve the DFS and OS rates with deeper insights into and therapeutic applications against the emergence of drug persistence and tumor reprogramming as currently understood from the advanced metastatic stage diseases (23-25). This could be particularly impactful if there are indeed minimal molecular residual disease post-resection that could not be completely eradicated by only chemotherapy and the genomically-matching targeted therapy.

Last but not the least, the discussion would not be complete without a mention on the drug cost and financial toxicity debate for an “expensive” drug such as osimertinib to be used as adjuvant therapy up to 3 years. However, we ought to be reminded that the use of “expensive” targeted therapeutics are already a cornerstone of standard-of-care use in advanced metastatic stage oncogene-addictive lung cancer, often with duration of use lasting over a period of at least 2–3 years’ time or longer without evidence-based promise of a “cure” or OS benefits over the prior standard of care treatment (e.g., chemotherapy) as exemplified in the IPASS and ALEX studies. As valid as the financial question is here, arguably it is best addressed at a policy and health care system forum.

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