DISCUSSION

A new era in lung cancer treatment was ushered in with the identification of driver mutations and the subsequent development of targeted agents. In patients with advanced-stage disease, activating EGFR mutations in exons 19 and 21 are predictive of sensitivity to tyrosine kinase inhibitor (TKI) therapy. EGFR mutations are identified in roughly in ~ 50% of Asian patients [PMID: 24419411]. Eight randomized studies have all demonstrated improved response rates and progression-free survival (PFS) for treatment-naive, advanced-stage adenocarcinoma patients with sensitizing EGFR mutations treated with TKI therapy, as compared with chemotherapy, with several of these studies also demonstrating improved quality of life. Despite improved outcomes with TKI therapy, all advanced-stage patients who harbour sensitizing mutations will inevitably develop disease progression. This is most commonly due to the development of a second-site mutation in EGFR known as T790M, which accounts for up to 50% of acquired resistance [PMID: 21430269]. While T790M mutations most commonly develop as a resistance mechanism after TKI treatment, rare cases of de novo T790M mutations have been reported. Interestingly, these mutations have usually been identified alongside a second, activating EGFR mutation. De novo T790M mutations can also occur as germline mutations, an occurrence that may confer genetic susceptibility to lung cancer [PMID: 25134330].

In the above-mentioned case study, the patient was a treatment naïve patient who was found to be positive for both, the EGFR exon 19 deletion mutation as well as the EGFR T790M mutation, which is a very rare occurrence in lung cancer. An EGFR T790M VAF of 4.5%, suggests that the said mutation is a somatic and not a germline mutation. Since the EGFR T790M mutation was found at a VAF of <5% and the patient was not exposed to any EGFR TKIs prior to NGS testing, a secondary confirmation by both, RT-PCR and ddPCR was undertaken to rule out false positivity.

While ddPCR results were in concordance with the NGS results, the RT-PCR results were discordant with respect to the EGFR T790M mutation. The underlying reason for the discordance lies in the difference in sensitivity and limit of detection (LOD) of both the techniques. While ddPCR (Biorad) is a superior, ultra-sensitive and rapid method for absolute quantification of genome editing events with a LOD of 0.1%, the RT-PCR technique that was used (Therascreen by Qiagen) has a LOD of 7.02% for T790M mutation, which is well below the VAF of 4.5% as detected by NGS. Thus, we concluded that the patient is truly positive for both the observed EGFR mutations (exon 19 deletion and T790M), which occur in the kinase domain of the EGFR gene, which renders a constitutively active EGFR protein [Exon19del, T790M].