Editorial

Intratumoral and intertumoral heterogeneity drives EGFR treatment considerations

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Jia Z, Wang Y, Cao L, *et al.* First-line treatment selection with organoids of an EGFRm + TP53m stage IA1 patient with early metastatic recurrence after radical surgery and follow-up. J Thorac Dis 2020;12:3764-73.

Wang G, Lin Y, Zheng L, *et al.* A new method for accurately localizing and resecting pulmonary nodules. J Thorac Dis 2020;12:4973-84.

Song Y, Jia Z, Wang Y, *et al.* Potential treatment strategy for the rare osimertinib resistant mutation EGFR L718Q. J Thorac Dis 2020;12:2771-80.

Zang J, Horinouchi H, Hanaoka J, *et al.* The role of salvage surgery in the treatment of a gefitinib-resistant non-small cell lung cancer patient: a case report. J Thorac Dis 2021;13:4554-9.

Zheng Y, Zhou M, Arulananda S, *et al.* Management of non-small cell lung cancer with resistance to epidermal growth factor receptor tyrosine kinase inhibitor: case discussion. J Thorac Dis 2020;12:159-64.

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Molecular alterations in lung adenocarcinoma have been an active area of therapeutic drug development for the past two decades. Targeted therapies have been FDA-approved for the following actionable mutations in non-small cell lung cancer (NSCLC): EGFR, ALK, ROS1, BRAF, RET, NTRK, MET, and KRAS G12C (1). EGFR targeted therapy has been a model for targeted therapy drug development. Third-generation EGFR inhibitors have been developed to overcome EGFR dependent resistance mechanisms, have improved outcomes across sanctuary sites of metastasis, and can have improved side-effect profiles (2). This issue highlights a series of articles that demonstrate translational implications of EGFR directed targeted therapy.

Intertumoral heterogeneity is addressed in a case of a patient with two distinct primary lung tumors with an EGFR L858R and a KIF5B-RET fusion mutation (3). Dual driver events are rare but highlight the need for tissue genotyping when there are concerns for possible synchronous primary events. Without proper biopsy of both primary lesions, this patient with an appropriate response on gefitinib may have been discontinued off the TKI prematurely if the KIF5B-RET fusion was not identified as the lesion with that mutation increased in size. With the expansion of next generation sequencing (NGS) and liquid biopsies, these techniques have been utilized to understand tumor heterogeneity and resistance mechanisms to facilitate treatment selection. This case highlights the need to pursue tissue biopsy as there may be intertumoral heterogeneity across each lesion with distinct biology in an individual patient.

Intratumoral heterogeneity is an important area of focus as there may be resistant clones within the same tumor deposit. Novel technologies have emerged to provide additional tumor characterization and are currently being investigated to guide personalized treatment management in NSCLC. Patient-derived organoids (PDO) are potential models that have been investigated to assess treatment efficacy in refractory settings and can facilitate single cell analyses (4). Current research applications focus around single cell sequencing to characterize intratumoral heterogeneity.

NGS analyses have a variety of applications in the clinic. Tissue and liquid biopsy NGS testing were observed to have an appropriate mutational concordance for driver events (5). These two genetic platforms can sometimes be viewed as companion tests used during initial clinical workup. Liquid assays can expedite results facilitating earlier treatment while tissue biopsy remains integral due to higher sensitivity. With the rise of these new genomic platforms, improved plasma-based tools are being vetted to stratify risk of ambiguous nodules found on low-dose CT imaging screening (6). Various technologies including evaluation with electromagnetic navigation have been studied and discussed in this issue (7). The applications of liquid biopsies in early stage cancer seem promising but biologic challenges remain around detectable tumor shed when there is limited disease. In later stages of disease, we apply liquid biopsies to understand novel resistance mechanisms and identify potential alternate actionable mutations. Clinically, our practice is centered around tissue and liquid biopsies with NGS testing that can provide details about co-occurring alterations and clonal evolution through time.

NGS testing is the testing modality of choice in the post-osimertinib setting. Original data from the FLAURA trial demonstrated genomic resistance patterns post-osimertinib treatment (8). Resistance mechanisms include secondary site EGFR mutations such as EGFR C797S and alternative signaling such as MET amplification. Other EGFR secondary site mutations include L718Q, G724S, and T725M (9,10). We routinely utilize NGS testing in this setting to identify resistance targetable drivers and corresponding treatments. If no actionable mutation is detected, the most common current treatment would be platinum-doublet therapy. Amivantamab is an EGFR-MET bispecific antibody being evaluated in the post-osimertinib salvage setting observed to have activity in subgroups with EGFR secondary site mutations (11). The HER3 antibody drug conjugate Patritumab-Deruxtecan is being employed in this setting as well and has shown promising results (12). Other modalities such as salvage surgery are described and SBRT can be an acceptable alternative (13). In addition, anlotinib is a molecule with EGFR and VEGF inhibition properties being utilized after initial TKI treatment (14,15). This treatment strategy draws parallels to clinical trials investigating the activity of osimertinib and bevacizumab (16).

Ongoing efforts in the EGFR-mutated lung cancer space focus on defining additional actionable variants, strategies for resistant disease, and furthering efforts for molecular detection of cancer to enhance earlier access to medicines. Advances in recent years have improved the survival of patients and further work will help to address additional unmet needs in this space.

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