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Discovery of a Novel *EGFR* Resistance Mutation by Capture Based NGS Following AZD9291 Treatment

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The discovery of oncogenic EGFR mutations in adenocarcinomas of the lung as well as the molecular understanding of mechanisms of resistance paved the way for personalized medicine in solid tumors. As one example, AZD9291, an irreversible EGFR kinase inhibitor, was developed to specifically inhibit EGFR harboring the T790M resistance mutation. Here, we describe a patient diagnosed in 9/2011 with an adenocarcinoma of the lung. Molecular analysis revealed an activating EGFR exon 19 deletion. The patient was treated with erlotinib, but progressed. Rebiospy showed a newly developed T790M resistance mutation. At this time the patient was treated within a study with an HSP90 inhibitor followed by irradiation, chemotherapy and Afatinib within a compassionate use program. After confirming persisting T790M status on acquired resistance to Afatinib, the patient was included into the AURA1 study to receive AZD9291 starting 6/14. In 7/15, the patient was progressing with a pleural effusion which was sent for molecular testing using NEO technology, a hybrid capture based NGS technology to detect point mutations, InDels, copy number alterations and gene fusions in all clinically relevant genes. Due to the limited cellular material, the supernatant was used for DNA extraction applying NEOliquid, optimized to detect genomic alterations in more than 30 genes from circulating tumor DNA. NEOliquid analysis confirmed the EGFR exon 19 deletion as well as a T790M mutation. In addition, a previously undescribed EGFR p.C797G mutation was detected. The here mutated Cysteine in position 797 is essential for the drug AZD9291 to covalently bind to EGFR to potently inhibit the kinase activity. Shortly after, a tissue biopsy was obtained confirming the EGFRp.C797G mutation. Unfortunately, the patient's condition deteriorated rapidly and the patient died in 7/2015. In conclusion, hybrid-capture based NGS technology is able to detect relevant genetic alterations in tissue as well as liquid biopsy. A new resistance mutation to AZD9291 involving C797G essential in covalent binding of 2nd and 3rd generation EGFR TKI inhibitors was detected.