S6 – Uncovering Resistant Genes in EGFR-mutated Lung Adenocarcinomas Prior to Targeted Therapy

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Introduction & Project Objectives: Lung cancer is the most lethal malignancy around the world. In Hong Kong, lung adenocarcinomas are driven by activating mutations of Epidermal Growth Factor Receptor (*EGFR*) in 20% male and 60% female patients. The metastatic mutant cancers are treated by targeted therapy using tyrosine kinase inhibitors (TKI) but drug responses are impaired by the presence of resistant mutations. Resistant mutations may involve *EGFR* downstream molecules or signaling cascades that bypass *EGFR* and support tumour cell proliferation and survival. These mutations are suggested to arise during TKI-selection implicating analysis of post treatment cancers is necessary for their identification but such tumours often have limited accessibility and small biopsy yield. On the other hand, it has been suggested resistant mutations are already present in cancers excised at the time of diagnosis preceding tumour metastasis or targeted therapy. This implicates analysis of excision samples which provide sufficient tumour quantity without imposing extra patient discomfort could be useful for uncovering second line treatment targets when TKI resistance occurs. This study aims to test the applicability of this approach.

Methods: The whole exome mutation profiles of 39 *EGFR* mutant lung adenocarcinomas was compared with the TKI response pattern of 16 non-responders and 23 responders. Four post-TKI tumors with acquired resistance were also analyzed.

Results: The tumours harboured 26 recurrent, non-synonymous single nucleotide variations (SNV) or insertion/deletion (INDEL) mutations of actionable targets and known cancer genes. Excluding *EGFR, TP53* was the most common mutant. *EGFR T790M* was detected in all the post-TKI tumours but not pre-treatment samples from responders or non-responders. Various mutations of EGFR bypass cascades were involved in the non-responder group only, including recurrent *PTEN, PIK3CA, NF1*, and single case *AKT1, ALK, RAF1* and *KDR* mutations. Notably, mutations in the β-catenin pathway were detected in the non-responders and post-TKI tumours, including APC, CTNNB1 and c-MYC. Putative novel resistant candidates were also observed.

Conclusion and Discussion: Our study demonstrated known and candidate TKI-resistant mutations could be uncovered by next generation sequencing of pre-treatment excision specimens of EGFR-mutant lung adenocarcinomas. The specific mutations identified in individual tumours could be useful for personalized medicine, offering customized targets for long term therapy and specific biomarkers for tumour surveillance.

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