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Novel biomarker enrichment designs in oncology drug development

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Oncology trials based on biomarker stratified designs are increasingly being used to establish the effectiveness of a new drug or targeted therapy in specific populations of interest. Targeted or enriched designs are a class of such stratified trial designs that aim to enrich the biomarker-positive sub-population. In this talk, I shall discuss novel enrichment designs that determine whether a drug has activity only in the target population or the general population in the disease area. The enrichment is an adaptation based on the Simon two-stage design for Phase II oncology trials with a tumor response endpoint for a cytotoxic interventional drug. The group-sequential nature of the design and interim analyses allow one to make go/no-go decisions i.e., whether to progress the agent to a confirmatory trial or not. Appropriately controlling the type I and type II error probabilities yield novel optimal designs that minimize the expected sample size for a range of operating characteristics. Illustrating the issue of multiple testing, I shall present alternative family wise error rates and individual hypothesis control in weak as well as strong sense. An important feature of these designs is that they also evaluate efficacy in the biomarker-negative sub-population, an issue that has been highlighted by the FDA in recent years. Our approach can be generalized to randomized controlled trials with survival endpoints, and provides a robust framework for adaptive enrichment in biomarker-based Phase II/III trial design.

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Genomic tests and applications in classifications of lung adenocarcinomas and precision medicine

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Genomic tests play a key role in precision management of adenocarcinoma of the lung. EGFR is mutated in about 16-30% of patients with adenocarcinoma of the lung, with more frequent in Asian, in non-smokers and in women. The sensitivity of EGFR mutant tumors to receptor tyrosine kinase inhibitors (TKIs) has been shown to depend on the genotype of EGFR. Exon 19 deletions, exon 21 mutations, and exon 18 mutations are associated with sensitivity to EGFR TKIs, while exon 20 insertion mutations are associated with a variable and often decreased sensitivity to TKIs. Patients treated with EGFR TKIs usually develop resistance in one year. Mechanisms involving the resistance include T790M mutation, MET amplification, PTEN loss, among others. About 3-8% of lung adenocarcinomas show ALK arrangement, which is targetable therapeutically. ROS1 gene fusion, although with less frequency but also with commercial drug availability, should be tested in EGFR and ALK negative patients. Recent research efforts undertaken by large-scale multiple platforms such as the cancer Genome Atlas (TCGA), have identified many novel driver and potentially targetable alterations, and sub classified lung adenocarcinomas.. Data derived from TCGA displayed that bronchioid or terminal respiratory unit-subtype tumors were enriched for EGFR mutations and kinase fusion and belter prognosis; co-mutation of NF1 and TP53 was frequent in squamoid or proximal-inflammatory tumors, while a high frequency of KRAS mutation and LKB1 inactivation were noted in magnoid proximal-proliferative tumor. TCGA has also revealed considerable intertumor and intratumor heterogeneity. It is found that cancer cells grow in a special micro-environment in which they compete for resources (e.g. oxygen and nutrition) for survival. These forces of natural selection constantly influence in the evolution processes of tumor cells, and more competitive mutated tumor clones emerge. Mankind faces challenges to cure lung adenocarcinoma before full understand these complicate processes.

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