Towards personalized treatment for gastroesophageal adenocarcinoma: Strategies to address inter- and intra-patient tumor heterogeneity - PANGEA


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Abstract

Gastroesophageal adenocarcinomas (GEAC) are the third most common malignancy and second highest cause of cancer mortality worldwide. The promise of personalized cancer care with therapies targeted toward specific molecular aberrations has great potential to improve clinical outcomes. However, there is emerging understanding of profound molecular heterogeneity within GEAC (inter-patient heterogeneity), and within an individual (intra-patient heterogeneity) through space (primary tumor to metastasis) and time (resistance to treatment). This heterogeneity is a hurdle to advancing GEAC treatment. Current clinical trial design paradigms are challenged by heterogeneity, as they are unable to test targeted therapies against low frequency genomic alterations with adequate power. Accrual difficulties to GEAC trials are exacerbated by low frequency of molecular ‘biomarker driven’. Oncogenic drivers of GEAC including MET, EGFR, and others, have even less frequent genetic activation than HER2 (20%). To address this recognized challenge, there is need for novel clinical trial designs/implementing technologies in order to account for inter-patient molecular diversity. Importantly, there is also need for predefined treatment algorithms given multiple alterations observed within any one individual. Finally, access to multiple therapeutic agents is required to be available for treatment. Intra-patient heterogeneity may be addressed through post-treatment biopsy and re-sequencing the ‘biomarker and treatment assignment algorithm’. We present an innovative clinical trial design, PANGEA (Personalized Anti-Neoplastic for Gastro-Esophageal Adenocarcinomas), that integrates novel medium throughput proteomics and genomics technologies with a practical biomarker assay and treatment algorithm, customizing patients to ‘personalized treatment’ versus standard of care for metastatic GEAC. Data from GEAC patients having undergone biomarker assessment and work treatment assignment on a pilot feasibility phase of the trial will also be presented.

Methods

Cell lines were derived from ATCC, except MKN-28 (DOSE, and Cell) (University of Chicago) for MTM-231 (CTC). Genomic DNA (fresh-frozen) and FFPE tissue blocks were used for Std and Fib. FFPE tissue blocks were >3 YO’s old, rehydrated in microwave, de-waxed in xylene, and washed through graded alcohols.

Effective DNA isolation was achieved with a commercial kit (Qiagen). DNA was then quantified and DNA quality was assessed through a visual examination of the gel and the expected fragment size of the DNA. Sample DNA was subjected to the Illumina NextSeq500 (Illumina, San Diego, CA) for whole-genome sequencing to assess tumor heterogeneity.

Conclusions

• Profound molecular heterogeneity and limited tissue are hurdles to implementing targeted therapies.

• PANGEA is a trial design that incorporates various strategies, including medium throughput genomic/proteomic assays along with mandated biopsies, to address inter- and intra-patient heterogeneity.

• Predefined treatment algorithms and access to multiple therapeutic agents are required, given the observed immense treatment complexity.

• PANGEA-I/Ii is a compromise between the number of potential treatment categories and feasibility.

• Future iterations may include more treatment groups.