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Correlative Indexes in Prediction of Survival in Refractory Metastatic Lung Adenocarcinoma. The Role of Liquid Biopsy to Assess Survival

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Background
In refractory metastatic lung adenocarcinoma, liquid biopsy can provide valuable insights into survival, particularly in identifying resistance mechanisms and monitoring treatment response. For example, circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) can reveal EGFR mutation status. Heterogenous tumors are defined based on their genomic signature consisting of a variety of biomarkers. Aa major problem, remains as we are unable to translate a "target response" to a "clinical response". This problem would be even further complicated by implementing targeted therapies that can cause resistance by inducing mutations in the DNA as well as enhancing the process called "selective advantage" of the resistant cells. Since the resistance of the tumor correlates with the patient's survival, using liquid biopsy can detect early resistance and therefore predict prognosis.

Methods and Materials
All three cases were consented and treated according to the protocols in an off trial of a phase II clinical study approved by IRB. Patients received Multi targeted epigenetic therapy consisting of IV PEG-Quercetin and polyphenols, compounded by FDA approved compounding pharmacy. Liquid biopsies were obtained before and post therapy through Guardant 360 Laboratory.

Case Reports
Here we review three (3) cases of non small cell lung cancer and review their outcome. Case one was status post cytotoxic drugs, and radiation and surgery with progressive disease and advanced dissemination. We showed eradication of CTC which carried c MYC overexpression in two weeks post implementation of anti VEGF therapy. Patient was followed closely and we showed improved surrogate markers for her survival, documented by complete eradication of CTC and overall survival, which translated to minimum residual disease with no FDG avid tumor in the tumor.

Second case was a lung adenocarcinoma with negative KRAS and EGFR and ROS1, in tissue biopsy, but positive KRAS/ c MET and ROS 1 mutations in liquid biopsy, who presented with brain metastatic lesions, and was treated with Anti VEGF therapy, showing stable disease after 6 months, with reduced c DNA MAF of KRAS, c MET, ROS1. He did not receive cytotoxic chemotherapies with overall survival benefit.

Third case was a lung adenocarcinoma status post failure of three lines of therapies, chemotherapy along with antiangiogenic therapies, and immune therapies, presented with disseminated disease and liver and bone and peritoneal metastatic disease. She was treated with epigenetic therapies independently for over a year, and in combination with metronomic chemotherapy. She passed 7 years of survival with minimum residual disease with no FDG avid activity in all her chest (mediastinum, lungs, LNs) and liver and bone lesions, at the time of this paper. She has no circulatory DNA or CTC identified at this time.

Conclusion
Implementation of liquid biopsy was able to predict survival in patients with stage four lung adenocarcinoma treated with both anti VEGF and Epigenetic therapies. Specifically, patients with EGFR or KRAS mutations showed benefit from therapies aimed at actionable targets. We propose that liquid biopsies tracking circulating tumor cells (CTC) and circulating DNA (ct DNA) be used universally in all patients with refractory disease, regardless of treatment received upon diagnosis [1-21].

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