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General Poster Session (Board #35G), Sat, 8:00 AM-11:45 AM

Screening for *RET* and *ROS1* fusions in an enriched cohort of pan-negative never-smokers with advanced lung adenocarcinomas to identify patients for treatment in targeted therapy trials.

Alexander Edward Dela Cruz Drilon, Lu Wang, Adnan Hasanovic, Philippe Joubert, Mark G. Kris, Gregory J. Riely, Marc Ladanyi, Naiyer A. Rizvi; Memorial Sloan-Kettering Cancer Center, New York, NY; Lenox Hill Hospital, New York, NY

Background: *RET* and *ROS1* fusions have been identified pre-clinically as drivers of tumor growth in lung adenocarcinomas. In addition, based on response to crizotinib in *ROS1*-positive tumors and emerging data on *RET* inhibition in some tumors, these fusions represent druggable targets. While each occurs in 1-2% of unselected patients, a screening paradigm based on testing never-smokers whose tumors have no known oncogenic mutations or fusions may enrich identification for ongoing clinical trials. **Methods:** Patients with a never-smoking history (<100 lifetime cigarettes) and advanced pan-negative lung adenocarcinomas (absence of mutations in *EGFR*, *KRAS*, *NRAS*, *BRAF*, *HER2*, *PIK3CA*, *MEK1*, and *AKT*, and *ALK* fusions) were selected for testing. Screening for *RET* and *ROS1* fusions was performed in real-time via dual-probe FISH breakapart assays, RT-PCR, and next-generation sequencing in selected cases. We enrolled patients onto a phase II trial of cabozantinib for *RET* fusion-positive lung cancers (NCT01639508) and, as part of the Lung Cancer Mutation Consortium (LCMC), a phase I trial of crizotinib for *ROS1*-positive lung cancers (NCT00585195). **Results:** Thirty five (n=35) never-smokers with advanced pan-negative lung adenocarcinomas were identified. A *RET* or *ROS1* fusion was found in 31% [n=10/32, 95% CI, 15-47%] of patients. *RET* and *ROS1* fusions were found in 15% [n=5/34, 95% CI, 3% - 27%] and 15% [n=5/33, 95% CI, 2%-27%] of patients, respectively. 1 patient had a novel *TRIM33-RET* fusion. 3 of 5 patients with *RET* fusion-positive tumors were eligible for treatment with cabozantinib, 2 of which had partial responses to therapy. 1 of 5 patients with *ROS1* fusion-positive tumors was treated on-protocol with crizotinib and achieved a partial response. **Conclusions:** 31% of never-smokers with pan-negative advanced lung adenocarcinomas harbor a gene fusion involving either *RET* or *ROS1*. Until multiplexed mutation and fusion testing is routinely available, targeting this population for screening represents an interim enrichment strategy for patient identification and enrollment on clinical trials where responses are already being documented.