Title: Clinical features and outcome of oncogene fusions in NSCLC with non-response to first-line targeted systemic therapy

Authors: Gibson AJW[1], Dean ML[1], Elegbede AA[1], Cheung WY[1,2], Bebb DG[1,2]
Institutional Affiliations: 1: University of Calgary, Cumming School of Medicine. 2: Tom Baker Cancer Centre, Alberta Health Services

Background/Purpose: The landscape for the management of non-small cell lung cancer (NSCLC) has dramatically changed in recent years with the discovery of oncogenesis driven by specific mutations and gene fusions. Many of these oncogene-addicted tumours can be successfully managed using targeted systemic therapies which dramatically improve patient prognosis. Unfortunately, a subset of patients, up to 30%, [1–6] will not benefit from targeted therapies due to primary drug resistance, drug toxicity or rapid decline/death. Lack of response to targeted therapies is not widely reported, leading to a deficit information regarding clinical features and prognosis of those who lack clinical response. To that end, we looked for clinicopathological features associated with those who did and did not achieve tumour control upon initial exposure to targeted therapy, in a contemporary cohort of ALK and ROS-rearranged NSCLC.

Methods: The Glans-Look Lung Cancer Research Database (GLR) was used to identify patients diagnosed 2014-2020, with ALK or ROS1-rearranged NSCLC who received crizotinib as their first targeted systemic therapy. The GLR is an institutional database containing patient-level demographic, clinical, treatment and outcome data on all Alberta patients with a lung cancer diagnosis. Patients were categorized, using RECIST 1.1 criteria, as responders (R; best response of stable disease or higher) or non-responders (NR; non-evaluable or progressive disease as best response).

Results: 93 patients were identified (77% ALK+, 23% ROS+) of which 20% were non-responders to crizotinib (61% due to toxicity/patient decline and 39% primary resistance). NR and R did not vary significantly in relation to age at diagnosis, sex, previous systemic therapies, interval from diagnosis to crizotinib initiation, or disease burden (AJCC 8th edition TNM, M stage); they did differ in that compared to R, at the time of crizotinib-initiation, NR were more likely to have brain metastasis (43% vs. 14%, p=0.005); ECOG ≥ 2 (56% vs. 10%, p<0.001); and elevated derived neutrophil-to-lymphocyte ratio (dNLR ≥ 3: 81% vs. 42% p=0.005). Compared to R, NR had significantly poorer outcomes, in terms of both overall survival (75.4 vs. 10.5 months, log-rank p<0.001) and survival after crizotinib-initiation (46.8 vs. 2.9 months, log-rank p<0.001). Further, NR were less likely to receive additional post-crizotinib systemic therapies (26% vs. 69%, p<0.001); noteworthy, as receipt of additional systemic therapy significantly impacted 1-year post-crizotinib survival rates, regardless of initial response to crizotinib (13% vs. 70%, p<0.001). Elevated dNLR at the time of crizotinib initiation was associated with poorer survival outcome (25.1 vs. 33.1 months, log-rank p=0.03) and was also associated with poor ECOG, where 80% of patients with poor ECOG also had elevated dNLR, but logistic regression showed that only presence of brain metastases and poor ECOG were significantly associated with non-response to crizotinib (OR: 6.1 [95%CI: 1.2-31], p=0.03) and (OR: 11.8 [95% CI: 2.4-59], p=0.003) respectively.

Conclusions: Non-responders to crizotinib displayed poorer prognosis and clinically were more likely to present with brain metastases and poor ECOG. Additional post-crizotinib therapies appear important to patient prognosis, highlighting the need for access to other tolerable, effective systemic therapies in this unique NSCLC population to yield optimal prognosis.