Editorial Commentary

It's far better to be alone than to be in bad company

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Somatic *KRAS* mutations are the most common oncogenic alterations detected in non-small cell lung cancer (NSCLC), accounting for 25% of the cases (1). Clinical course of *KRAS*-mutant NSCLC is very heterogenous, suggesting an underlying biological complexity that is not comprehensively understood. For example, the signaling of downstream RAS pathway is specific of transversion/transition subtypes of *KRAS* mutation (2). Transversion and transition subtypes are associated to different clinico-pathological profiles but the relationship with treatment efficacy is debatable (3). While *KRAS* mutations remain desperately untargetable, the knowledge of the tumor status for *EGFR* and *BRAF600* activating mutations as well as for *ALK* and *ROS1* rearrangements is a keystone of the treatment decision making in advanced NSCLC. Indeed, effective targeted therapies are labeled in the setting of these oncogenic alterations, leading to substantial improvement of the overall survival compared to what is historically observed with chemotherapy alone (4-7). Next-generation sequencing (NGS) strategy has been implemented in cancer-dedicated institution, allowing the diagnosis of several oncogenic alterations and a broad detection of other genetic alterations in one assay. Genomic alterations in tumor suppressor genes and cancer-related pathways may be detected and "co-occurred" with oncogenic alterations in the same tumor. A growing body of evidence suggest that "co-occurring" genomic alterations may refine our current molecular classification using *KRAS/EGFR/BRAF/ALK/ROS1*/other oncogenes (8-10). In this setting, *STK11/LKB1* alterations have been described as a major driver of primary resistance to PD-1 blockade in *KRAS*-mutant lung adenocarcinoma using an NGS approach (10).

In the article of Arbour *et al.* published in Clinical Cancer Research accompanying this editorial, the authors report the results of a single institution, retrospective analysis of co-occurring genomic alterations detected with the MSK-IMPACT NGS assay on the outcomes of 330 *KRAS* mutant advanced NSCLC (11). In their paper, Arbour *et al.* identified a subgroup of patients with NSCLC harboring co-occurring genomic alterations in *KRAS* and *KEAP1/NFE2L2* pathway (27% of the cases) leading to a worse prognosis and shorter clinical benefit with platinum-based chemotherapy and anti-PD-1 compounds. Other co-occurring genomic alterations subgroups, i.e., *KRAS*$^{+}$/*TP53*$^{+}$ (42% of the cases) and *KRAS*$^{+}$/*STK11*$^{+}$ (29% of the cases) did not have a negative prognostic value and were not associated with worse clinical benefit.

To date, this is the first study that supports the notion that *KEAP1/NFE2L2* co-occurring pathway alteration in NSCLC harboring *KRAS* mutation may be clinically relevant. *NFE2L2* gene encodes the NRF2 protein, a transcription factor that is a critical stress response mediator in mammalian cells (12). Under homeostatic conditions, NRF2 is degraded via the proteasome through binding to KEAP1 protein. NSCLC with high NRF2 and low KEAP1 levels of expression are associated with poor prognosis, due not only to their chemo- and radio-resistance but also to their aggressive proliferative nature (13-15). Recent large-

scale genomic studies from The Cancer Genome Atlas (TCGA) project have revealed alterations in components of the *KEAP1/NFE2L2* pathway in 23% of lung adenocarcinomas (16). In accordance with TCGA data and previous report, *KEAP1* genomic alterations are the more common *KEAP1/NFE2L2* pathway alteration in Arbour *et al.* work, whereas *NFE2L2* alterations are known to be more frequent in squamous cell carcinoma (11). In the largest cohort of *KEAP1/NFE2L2*-altered NSCLC published to date, this molecular subgroup was also associated to resistance to chemotherapy, especially in *KEAP1*-altered NSCLC (17). In this cohort, *KEAP1* alterations co-occurred with *KRAS* mutation in 44.9% of the cases.

Some limitations have to be underlined in this work. First, a selection bias is suspected that is inherent to the retrospective nature of this study. From the 330 patients *KRAS*-mutant NSCLC, females are over-represented (59%), the patient are younger than expected and in good shape. This likely explains that classical prognostic factors did not have prognostic value in multivariate analysis of overall survival (sex, smoking habit, performance status) or very marginally (age at diagnosis). Second, a major overlapping is observed between *STK11*- and *KEAP1/NFE2L2* co-occurring genomic alterations subgroups, with 74% of *KEAP1/NFE2L2*-altered tumors that are also *STK11*-altered and 66% of *STK11*-altered tumors that are also *KEAP1/NFE2L2*-altered. It would be very interesting to test de prognostic value of *KEAP1/NFE2L2/STK11*-altered tumors, that perhaps trigger the negative prognostic value of *KEAP1/NFE2L2* co-occurring genomic alteration. Third, duration of treatment is an uncommon and inaccurate surrogate biomarker of clinical benefit of therapy. There are many reasons other than disease progression to stop a therapy such as, adverse events, patients willing, cancer-related complications… Fourth, response to anti-PD-1 and duration of treatment with anti-PD-1 were not different according to the co-occurring genomic alterations (*STK11*, *TP53* or *KEAP1/NFE2L2*) and only *KEAP1/NFE2L2* co-occurring genomic alterations were associated to shorter overall survival on anti-PD-1. It is likely to result from the bad prognosis value of *KEAP1/NFE2L2* co-occurring genomic alterations and not to a lack of activity of anti-PD-1. These data are also somewhat conflicting with the report that *STK11/LKB1* genomic alterations as the most prevalent genomic driver of primary resistance to PD-1 axis inhibitors in *KRAS*-mutant lung adenocarcinomas (see above) (10).

Finally, the findings of Arbour *et al.* show that broad genomic alterations testing with NGS in routine practice is not only a way to test many oncogenic alterations with one assay, but also a way to build new relevant molecular hypotheses explaining the heterogeneous clinical course of advanced NSCLC. According to these data, *KEAP1/NFE2L2* co-occurring genomic alterations in *KRAS*-mutant NSCLC is a new field of investigations and the impact on outcomes with chemotherapy and immunotherapy should be prospectively explored.

George Washington said "*It's far better to be alone that to be in bad company*." In this way, we need more prospective data to define who is(are) such a bad companion(s) in the setting of advanced NSCLC with characterized oncogenic alterations.

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Footnote

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