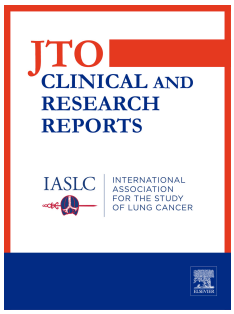

CHEK2 pathogenic germline variants in NSCLC patients

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Title:

CHEK2 pathogenic germline variants in NSCLC patients

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Zhang et al recently reported that among 70 patients with NSCLC who carried *CHEK2* pathogenic germline variants (PGVs), 29 (41.4%) had tumor "potentially actionable driver alterations" and *KRAS* mutations constituted 51.7% of those identified driver alterations. Their report raises several key questions, including universal germline testing of NSCLC patients, the implications from identifying *CHEK2* PGV carriers, and the potential clinical significance of the dual biomarker, somatic *KRAS*/*CHEK2* PGV. (1)

As the authors note*, CHEK2* PGVs in patients with NSCLC are rare (<1%), and therefore universal germline testing of patients with NSCLC to identify *CHEK2* PGV carriers is problematic.(1) However, germline testing is recommended for all patients with tumors showing probable incidental *CHEK2* PGVs, and the current routine next generation sequencing of NSCLCs will-if *CHEK2* is interrogated- identify probable incidental *CHEK2* PGVs, and therefore a group who particularly should consider undergoing germline testing. (2)

The authors propose further studies to determine if CHEK2 PGVs are NSCLC-predisposing. (1) In the meantime, it is important to recognize that *CHEK2* PGVs are considered "actionable," regardless of whether these PGVs are eventually proven to be NSCLC-predisposing. For example, the National Comprehensive Cancer Network recommends that patients identified with *CHEK2* PGVs consider annual breast MRIs (due to their 20-40% lifetime risk of breast cancer) as well as more aggressive screening for colorectal cancer, particularly if there is a family history of colorectal cancer. (2,3) In addition, there are therapeutic clinical trials for patients diagnosed with a variety of cancer types for patients with *CHEK2* PGVs and cascade germline testing is recommended for family members of patients carrying *CHEK2* PGVs. (2,4)

Zhang et al also reported that NSCLCs of patients carrying *CHEK2* PGVs frequently had actionable *RA*S mutations. (1) Studies are also needed to determine if the response rate and other clinical benefits of KRAS inhibitors are different in patients who carry *CHEK2* PGVs compared to those patients who do not carry *CHEK2* PGVs. As a related example, Jung et al recently showed that dual *TP53/EGFR* tumor mutations predicted a poorer recurrence free survival with treatment compared to that of patients with *EGFR*-mutated NSCLCs whose tumors have no *TP53* mutation. (5)

Hopefully the report by Zhang et al will prompt future studies to establish with more certainty whether *CHEK2* PGVs are NSCLC-predisposing, which patients with NSCLC should undergo germline testing for *CHEK2* PGVs and studies aimed to assess the clinical significance and therapeutic implications of dual somatic *KRAS/CHEK2* PGVs in patients with NSCLC.

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