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By Molika Ashford

NEW YORK (GenomeWeb) — Members of the Lung Cancer Mutation Consortium have reported data from more than 1,000 lung cancer patients tested for cancer driver mutations over a period of four years, finding a significant improvement in median survival among patients who received targeted therapy based on their molecular testing results compared to those who did not.

The study, which appeared yesterday in the *Journal of the American Medical Association*, reported the results of molecular testing performed on 1,007 adenocarcinoma patients by 14 participating centers between 2009 and 2012, under the group's effort to evaluate the feasibility and impact of implementing a targeted genotyping strategy to guide cancer therapy.

Amid growing use of genetic testing to guide therapy with certain targeted agents, most frequently EGFR and ALK inhibitors, the LCMC study is the first, the authors wrote, to present data "from a prospective multi-institutional investigation supporting the concept that [targeted treatment] can be accomplished with more drivers and drugs with the potential to change the approach to lung cancer management."

Since its initiation, the LCMC has set out to genotype patients with adenocarcinomas, a subset of non-small-cell lung cancer, in order to identify mutations that signify sensitivity to a variety of targeted anti-cancer drugs.

Participants in the consortium have adopted a variety of different testing tools, including mass spectrometry, Sanger sequencing,

and multiplex hotspot panels, but have all focused on identifying a set of 10 oncogenic drivers, including EGFR and KRAS mutation, ALK rearrangements, and other alterations.

These targets were chosen based on their frequency in the adenocarcinoma population, their ability to be tested in the context of a CLIA-certified lab, and the availability of associated targeted therapies — either approved agents or those in trials existing at the start of the study in 2009, the group wrote.

According to the study authors, only about 70 percent of patients eligible for LCMC testing during the study period actually had adequate tissue to be enrolled in the study. And while 1,007 patients were successfully tested, only 733 were assessed for all 10 target genes, while the rest were tested only for EGFR mutations.

Among the 733 patients who received the full panel, the researchers found that 466, or 64 percent, had at least one potentially actionable oncogenic driver.

KRAS mutations were the most frequently detected, found in 182 of the 466 mutation-positive patients, the researchers wrote. There were also 122 sensitizing EGFR mutations, 57 ALK rearrangements, as well as a number of other mutations in EGFR, ERBB2, BRAF, NRAS, MEK1, and MET.

Decisions about whether to prescribe a targeted therapy based on genotype was left up to patients' treating physicians, the study authors wrote. Overall, 275 patients received genotype-driven therapy — 28 percent of the full 1,007-patient cohort, or almost half of those who were tested for all 10 targets and not just EGFR.

Comparing patients' outcomes, the group found that the 260 patients who received genotype-driven therapy lived the longest — 3.5 years on average versus 2.4 years for the 318 who had an oncogenic driver but did not get genotype-driven treatment and only 2.1 years for the 360 patients for whom testing revealed no targetable mutation.

When the researchers reexamined outcomes excluding those patients with EGFR- and ALK-positive cancers, they found that among the patients with other oncogenic drivers survival was still clearly longer for those who received targeted therapy based on their genotype than for those who did not.

According to the authors, the percentage of patients the LCMC found to have potentially actionable mutations, as well as the percentage that were treated based on their results matched well with results from previous single-center studies.

However, the authors cautioned that the study is only a proof of concept that individuals who receive treatment matched to their cancer's driving mutations live longer than those who don't, and this finding will have to be confirmed by randomized trials to determine if targeting therapy based on molecular testing reliably improves survival.

"The study design is not appropriate to reach definitive conclusions about survival differences being attributable to the

determination and use of oncogenic drivers," the researchers wrote.

The group also said that as multiplexed testing of lung cancer patients expands and more targeted therapies enter clinical trials, the percentage of patients treated based on their genotype should grow.

Molika Ashford is a GenomeWeb contributing editor and covers personalized medicine and molecular diagnostics. E-mail Molika Ashford.

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