Molecular Pathology Selected Abstracts

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Overall survival rates for lung cancer patients receiving osimertinib

February 2020—Guidelines recommend testing patients with advanced or metastatic nonsmall cell lung cancer (NSCLC) for epidermal growth factor receptor (*EGFR*) alterations because targeted treatment with a tyrosine kinase inhibitor (TKI) is available for patients with *EGFR* exon 19 deletions or L858R point mutations. Osimertinib is a third-generation, irreversible, oral EGFR-TKI that selectively inhibits EGFR-TKI–sensitizing and *EGFR* p.Thr790Met-resistance mutations. Guidelines state that for treatment-naïve patients, osimertinib is the preferred first-line EGFR-TKI given recent evidence demonstrating improved progression-free survival compared to comparator EGFR-TKIs. The article by Ramalingam, et al., presented overall survival data from the FLAURA trial (funded by AstraZeneca; FLAURA ClinicalTrials.gov number, NCT02296125), a double-blind phase three trial comparing the efficacy and safety of osimertinib with the EGFR-TKIs gefitinib and erlotinib. Patients were eligible for the trial if they were 18 years or older and had locally advanced or metastatic NSCLC that had not received prior treatment and if their tumors harbored EGFR alterations susceptible to an EGFR-TKI. From December 2014 through March 2016, 556 patients were randomly assigned to receive oral osimertinib or a comparator oral EGFR-TKI. The patients continued treatment under the trial until disease progression, unacceptable toxicity, or withdrawal of consent. The progression-free survival data from the trial, which had been reported previously, demonstrated improved progression-free survival with osimertinib when compared to the comparator regimen (18.9 versus 10.2 months). While progression-free survival was the primary endpoint of the study, assessments for overall survival were continued after disease progression. Overall survival was defined as the time from randomization until death from any cause. Patients in the comparator group were eligible for crossover for treatment with osimertinib after disease progression if a T790M-resistance mutation developed because of treatment with the comparator EGFR-TKI. Overall survival was better in the osimertinib group than in the comparator group (median overall survival, 38.6 versus 31.8 months; $P = .046$). Furthermore, the patients in the osimertinib group continued to receive first-line therapy significantly longer than the patients in the comparator group. The safety profile and adverse events in the osimertinib group were found to be similar to those of the comparator group. Overall, the data show that patients who received osimertinib as a first-line therapy had significantly longer progression-free survival, which led to significantly longer overall survival. The overall survival benefit of first-line osimertinib was seen even if patients crossed over from the comparator group to the osimertinib group after developing a T790M-resistance mutation. The results of the FLAURA trial are changing the standard-of-care treatment selection for EGFR-mutated NSCLC patients and will also likely affect resistance mutation screening.

Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2019. doi:10.1056/NEJMoa1913662.

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Discordance between pathologists in somatic variant classification

Comprehensive molecular testing in oncology with next-generation sequencing multigene panels has become widely used to guide clinical management. While the immense amount of data that is generated by a sequencing run is first distilled by automated bioinformatic pipelines, the final pathology report is ultimately created and reviewed by the expert molecular pathologist. As part of this process, the pathologist curates and interprets somatic variants, integrating evidence of a variant's pathogenicity and actionability with clinical information. In

2017, the Association for Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO), and College of American Pathologists (CAP) published consensus guidelines to standardize the classification, interpretation, and reporting of somatic variants. The guidelines classify variants into tiers of strong clinical significance (tier one), potential clinical significance (tier two), variants of unknown clinical significance (tier three), and benign or likely benign variants (tier four). While the AMP/ASCO/CAP guidelines were created to standardize clinical utility reporting, their reliability and concordance in real-world practice has not been evaluated. To this end, the authors examined interrater reliability by distributing a set of variants to 20 molecular pathologists and doctoral-level professionals at 10 academic cancer centers. The variants included 30 single-nucleotide variants, five copy number variants, 14 insertions or deletions, and one fusion distributed across different genes and tumor types. Each participant independently classified these variants according to the 2017 AMP/ASCO/CAP guidelines and documented the evidence used to support the classification. The overall interrater agreement was 58 percent, with agreement for individual variants ranging from 40 to 100 percent (median chance-corrected agreement, $\kappa = 0.32$). After initial classification, a summary of the results and pertinent evidence for each variant was distributed to each participant, who reviewed the initial classification and revised as needed. On average, each participant revised 5.9 of their original classifications based on the distributed evidence, and overall agreement improved (κ increased to 0.70), demonstrating that sharing data and consensus opinion improved concordance. Overall, the findings demonstrate concerning interrater discordance, even among expert professionals at major academic centers. Consequently, the authors proposed potential solutions to some underlying issues. First, the guidelines' emphasis on clinical actionability and treatment implications can be conflated with pathobiologic effects, complicating interpretation. Moreover, local access to niche clinical trials can affect actionability interpretation. Therefore, sharing consensus variant classifications, supporting evidence, and information about clinical trials could help improve concordance. Second, there is no specific guidance for collecting and weighting specific pieces of evidence. The authors concluded that an evidence scoring system similar to that described in the American College of Medical Genetics and Genomics/CAP guidelines for reporting germline variants could be useful. Third, lack of experience with using the guidelines likely contributes to discordance, as only 20 percent of the study participants use the guidelines in clinical practice. Therefore, training sessions and application exercises could help improve familiarity. Overall, while the 2017 AMP/ASCO/CAP guidelines are an important step toward developing a consensus variant clinical interpretation classification system, additional measures could improve harmonization.

Sirohi D, Schmidt RL, Aisner DL, et al. Multi-institutional evaluation of interrater agreement of variant classification based on the 2017 Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists standards and guidelines for the interpretation and reporting of sequence variants in cancer. *J Mol Diagn*. 2019. https://doi.org/10.1016/j.moldx.2019.10.010.

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