NO147: The Giving Tree

Lawrence Leichman

Correspondence to: Lawrence Leichman, MD, NYU Langone Medical Center, Department of Medicine, 160 E. 34th St, New York, NY 10016 (e-mail: lawrence.leichman@nyumc.org).

In Shel Silverstein’s The Giving Tree, a large, generous tree provides recreation to a child and food for an adult. Even as branches of the tree were taken to build a house and the tree cut down to build a boat, it continued to give solace to a tired old man. No longer a tree, the Giving Tree continued to reward. So it is with NO147. Between 2004 and 2009, the trial randomized 2686 stage III colon cancer patients to FOLFIRI, mFOLFOX6, or mFOLFOX6, followed by FOLFIRI. Initially, arms were added; later, some lopped off. With the addition of cetuximab, NO147 had six treatment arms. Upon finding that adding irinotecan did not improve survival, the FOLFIRI arms were cut, leaving two branches: mFOLFOX6 + cetuximab vs mFOLFOX6 (2). In 2008, the trial stopped randomizing patients with KRAS mutations (3). Despite these buffering effects, the trial completed accrual. Unfortunately, the final analysis of NO147 showed that cetuximab does not contribute to survival for stage III colon cancer patients (4). Yet, NO147 keeps giving. Since the initial 2012 report, two additional reports used the tissue and annotated data from NO147 to increase our knowledge of the effects of environment, lifestyle, and molecular biology on the classification of stage III colon cancers (5,6).

In this issue of the Journal, a third important report from the NO147 database has been added. Gonsalves et al. (7) combine data from 2326 patient questionnaires (93% of the treated population) regarding demographics, lifestyles, and habits with known data about tumor location and histology and the microsatellite and mutational status of 2222 patients for KRAS (96%) and 2166 patients for BRAF (93%). KRAS mutations occurred in 783 patients (35%): 191 (24%) were KRAS Gly13 Asp; 310 (14%) were BRAF V600E. These findings were integrated with 2231 tumors evaluated for mismatch repair (MMR), 279 (14%) of which were deficient (dMMR). KRAS wild-type status was associated with older age (>70 years), smoking, and a first-degree family relative having colorectal cancer and was statistically more likely to have dMMR, high-grade histology, and a distal location. For KRAS-mutated cancers, KRAS Gly 13 Asp mutations more often had high-grade histology and dMMR than KRAS D2 mutations. BRAFV600E cancers were associated with older age (>70 years), current or former smoking, high-grade histology, and dMMR and were more common in women, non-Hispanic whites, T4 primary tumors, and N2 stage. Tumors with KRASm or BRAFV600E were more prevalent in the right colon (7).

These findings corroborate previous reports (8–10) and confirm the importance of large, randomized, cooperative group trials in which treatment effects, toxicity, progression-free survival, and overall survival are carefully annotated. Although the association of KRAS Gly 13 Asp mutations with dMMR and high-grade histology is not immediately useful, as we refine targeted agents and group colorectal cancers into more appropriate molecular categories, this will certainly change. Gonsalves et al. (7) have given us more branches from which to swing.

Are these data applicable to colon cancer patients we see daily? Although the median age for colon cancer in the United States is 69 years, the median age of those randomized on NO147 was younger, at 59 years (4). Because the current report draws epidemiology, social habits, and molecular biology from a relatively young population, the universality of the results is not certain. Additionally, as noted by the investigators, no epigenetic data exist for these cancers. Addition of methylation data to the model would be interesting (11,12).

A negative trial is always disappointing. Nevertheless, by capturing and using molecular markers, standard pathologic data, and questionnaires for more than 90% of patients treated with mFOLFOX6 or mFOLFOX6 + cetuximab, the NO147 investigators raised a high bar to which we must hold ourselves in the future. By doing so, they have made NO147 a Giving Tree.

References


**Affiliation of author:** Department of Medicine, NYU Langone Medical Center, New York, NY.