# Practice-changing trial results for advanced melanoma skin cancer

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Determining the optimal treatment sequence for patients with BRAF V600 mutant metastatic melanoma was the focus of the DREAMseq phase 3 clinical trial. The combination of nivolumab and ipilimumab

(N/I), followed by the combination of dabrafenib and trametinib (D/T) if there was disease progression, led to a significant improvement in estimated 2-year overall survival from the start of treatment (72%) when compared to the opposite treatment sequence (52%). Today, researchers from the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) presented the findings at the Inaugural American Society of Clinical Oncology Virtual Plenary Series. The National Cancer Institute (NCI), part of the National Institutes of Health, sponsored the trial.

"We found a 20% increase in two-year survival with a treatment sequence that begins with the combination of nivolumab and ipilimumab immunotherapy followed by targeted therapy using dabrafenib and trametinib in combination if disease progression occurred versus beginning with targeted therapy," said lead investigator Michael B. Atkins, MD, a medical oncologist and deputy director of the Georgetown Lombardi Comprehensive Cancer Center in Washington, DC.

The dabrafenib and trametinib combination is FDA approved for treating patients with BRAF mutant metastatic melanoma, while the combination of nivolumab and ipilimumab is FDA approved for treating patients with metastatic melanoma regardless of tumor BRAF status.

"Even though the current practice for many physicians is to start treatment with targeted therapy for patients with melanoma that has the BRAF gene mutation, the DREAMseq trial provides strong evidence that the immunotherapy combination is the better initial approach," said Dr. Atkins.

The DREAMseq (EA6134) trial sought to evaluate the impact on survival of these treatment regimens for patients found with stage 3 or stage 4 melanoma skin cancer that had spread beyond its local area and could not be removed by surgery. To be eligible, patients needed to have

BRAF V600 mutations in the tumor cells. The trial's primary endpoint was two-year overall survival.

Grade 3 or greater toxicities occurred at similar frequencies between the two treatment approaches during initial treatment (60% with N/I and 52% with D/T), and likewise, within treatment approaches when used either as initial treatment or second-line treatment.

BRAF V600 mutations drive cancer growth and are present in roughly 40% – 50% of melanomas. As a result, BRAF testing is recommended for patients with metastatic melanoma. Those with tumors that carry a mutation in BRAF have been shown to benefit from treatments that target the BRAF and MEK pathways.

"Beginning with combination nivolumab and ipilimumab immunotherapy also led to longer durations of response and more ongoing responses than the treatment beginning with the targeted drugs," said Dr. Atkins.

"After years of research, we have many exciting and effective new combination treatment regimens. As a result, patients with advanced melanoma and their physicians often find themselves with multiple treatment options but few answers to questions surrounding how and when to use these new approaches," said Dr. Atkins. "The DREAMseq trial provides the first prospective phase 3 data on what sequence of these treatments best extends the lives of our patients."

The DREAMseq trial enrolled 265 out of a proposed 300 patients in the United States between July 2015 and July 16, 2021 (cut-off date for data). At the fourth interim analysis, with 59% of patients being two years from enrollment, the ECOG-ACRIN Data Safety Monitoring Committee noted a clinically meaningful efficacy benefit in favor of the treatment sequence beginning with combination N/I immunotherapy that

emerged around ten months. Therefore, the committee recommended stopping patient enrollment in the trial and releasing the results. On September 30, 2021, ECOG-ACRIN and the NCI's Cancer Therapy Evaluation Program notified physicians and patients of the change in study status.

"These results are practice-changing and establish nivolumab and ipilimumab in combination followed by dabrafenib and trametinib targeted therapy in combination if progression is observed as the preferred treatment approach for patients with BRAF V600 mutant metastatic melanoma," said Dr. Atkins.

DREAMseq is a randomized trial design. Half of the patients (133) were randomly assigned to begin treatment with the N/I combination. If the therapy stopped working and the disease became worse, patients received the D/T combination. Dabrafenib and trametinib, given together, block the abnormal BRAF signaling pathway. This action slows or stops the out-of-control cell growth.

For the other half of the patients (132), the scenario was reversed. They were randomly assigned to begin treatment with the two molecularly targeted drugs. If those drugs stopped working and the disease became worse, they were treated with the immunotherapy combination.

Researchers continue to follow patients and will report three-year overall survival in the future, along with the results of other secondary and correlative endpoints.

The latest Annual Report to the Nation on the Status of Cancer 2021 states that melanoma death rates declined between 2014 and 2018 in both men and women. The trend reflects a significant increase in survival due to improved treatment options, among other factors.

**More information:** Conference: www.asco.org/meetings-educatio … nthly-plenary-series

Provided by ECOG-ACRIN Cancer Research Group