Phase III BEACON Trial Results Promising for Patients With Metastatic Colorectal Cancer

Braftovi plus Erbitux improved survival for people with previously treated advanced colorectal cancer.

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Updated Phase III results from the BEACON study have found that encorafenib [Braftovi] with cetuximab [Erbitux] can lead to promising survival outcomes among patients with advanced colorectal cancer (CRC) who had received previous lines of treatment.

The third most common cancer and the third most common cause of cancer-related deaths in the U.S., CRC occurs when there is development of mutations in oncogenes, tumor suppressor genes, and genes that aid in DNA repair. Depending on the site of the mutation, CRC can be classified as familial, inherited, or sporadic. Chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP) are pathogenic mechanisms through which CRC can develop. These mutations, changes in the chromosomes, and translocations can affect various signaling pathways (Wnt, TP53, TGF-β, and MAPK/PI3K) and genes such as c-MYC, KRAS, BRAF, SMAD2, and SMAD4. Oftentimes, mutations in these genes can serve as important predictive markers in the context of patient outcomes.

In addition to CRC, mutations in BRAF have been found to be responsible for various other cancers such as melanoma, thyroid, small-cell lung, and hairy cell leukemia. BRAF encodes for the B-RAF serine/threonine kinase protein, which is a part of the RAS/RAF/MEK/ERK pathway. Most of the mutations that take place in the BRAF gene lead to a V600E substitution, which often leads to a poor prognosis in patients. The BRAFV600E mutation initiates activation of the mitogen-activated protein kinase (MAPK) signaling pathway, which causes the tumor cells to rapidly divide. It has been estimated that approximately 10% of patients with metastatic CRC have a mutation in BRAF.

In the past, treating metastatic CRC with BRAFV600E mutations has led to low response rates, partly due to incomplete inhibition of the MAPK signaling. Recently, the combination of a BRAF (encorafenib) and EGFR (cetuximab) inhibitor has shown promising results compared to BRAF inhibitor monotherapy.

The BEACON CRC study is a randomized, open-label, phase III trial that enrolled 665 patients and

compared triple combination therapy; encorafenib (300 mg x1 a day) plus binimetinib (45 mg 2x a day) plus cetuximab (400 mg/m2 x1 a week) versus double combination therapy; encorafenib plus cetuximab versus cetuximab plus irinotecan or FOLFIRI. Of the total 665 patients, 224 received triple therapy, 220 received double therapy, and 221 received the control therapy.

The objective of the BEACON trial was to detect the overall survival in relation to the triple combination therapy/double combination therapy as compared to the control. It was determined that triple/double therapy led to a median overall survival of 9.3 months, while the control group showed an overall survival of 5.9 months. This indicates that both triple/double therapy improved the overall survival rate and can therefore be used as the new standard of care in patients with metastatic CRC with BRFV600E mutations. —Madiha Zaidi

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