Phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (PI3KαCA) is encoded by the PIK3CA gene and catalyzes the synthesis of phosphatidylinositol-3, 4, 5-triphosphate (PIP3). PIP3 is important for growth factor receptor tyrosine kinase signaling, such as for EGFR (epidermal growth factor receptor) or VEGFR (vascular endothelial growth factor receptor). PIP3 plays an important role in AKT (protein kinase B)/mTOR (mammalian target of rapamycin) activation, which is critical for cell growth and protein synthesis, which are important for carcinogenesis and cancer progression. PI3KαCA activity is regulated by PTEN (phosphatase and tensin homolog), and loss of PTEN has been tested for its predictive and prognostic significance; however, it has not been validated (1). PIK3CA mutations are found in a large number of different malignancies, such as breast, stomach, liver, lung, and colorectal cancer (CRC) (2). In CRC the frequency of PIK3CA mutations is approximately 10–30% (3,4). In 50% of PIK3CA mutant tumors, concomitant KRAS exon 3 mutations exist in about 50% (5). Activating mutations of PIK3CA are predominantly found in codon 9 and codon 20 (4), and there is evidence that the negative predictive value of PIK3CA mutations may be limited to codon 20 mutations (1) or to tumors that are mutant to both codon 9 and 20 locations (6). PI3KCA signaling is triggered through the phosphorylated intracellular domain of receptor tyrosine kinases or by RAS (rat sarcoma) oncogenes. Interestingly, another activator of PI3KCA is estrogen signaling, which may explain the sex-associated prognosis reported by Majek and colleagues (7). Embedded into such an interconnected and redundant network, the prognostic value of isolated PIK3CA mutations is difficult to assess. In addition, the tumor heterogeneity of CRCs will show that tumors contain subpopulations of PIK3CA-mutant cells. This complexity may explain why prognostic value could only be demonstrated in tumors without BRAF and RAS mutations (4,6). PIK3CA mutations seem to be subordinate in comparison with RAS or RAF mutations. Because of a recent publication showing a survival benefit for patients with PIK3CA-mutant CRC who are taking aspirin (8,9), PIK3CA mutations have gained more attention. Because RAS-mutated tumors display a higher expression of COX2 (cyclo-oxygenase-2) and PI3KαCA is downstream of RAS, it is speculated that PIK3CA-mutant tumors may also have a higher expression of COX2 (10), which may explain the positive effect of aspirin use. Furthermore CRC tumors with higher COX2 expression have been shown in a mouse model to be more likely to metastasize into the liver (11), suggesting that PI3KαCA may be predictive in a molecular defined subgroup of CRC.

In CRC, PIK3CA mutations are associated with prognosis when tested in large (n = 1170) cohorts and adjusted for BRAF and KRAS mutations (6). However PIK3CA’s role as a predictive marker for anti-EGFR targeted antibodies such as cetuximab and panitumumab is still unclear (12), but this may be because of the lack of control groups, small sample size, and no adjustment for RAS and RAF mutations or PTEN expression.

Ogino and colleagues (13) investigated the role of PIK3CA mutations in codon 9 and 20 on the outcome of stage III Union
for International Cancer Control (UICC) CRC in 627 patients of the CALGB 89803 study. The CALGB 89803 study tested 5-fluorouracil/leucovorin (5-FU/LV) with or without irinotecan for adjuvant treatment of 1264 patients (14). The primary endpoint, a difference in overall survival between both arms, was not met. Nevertheless, because of a sound accompanying translational program and a sufficient number of patients and tumor samples, the effects of different mutations on the prognosis of UICC stage III patients have been elucidated. The CALGB working group was able to show that KRAS mutations in codons 12 and 13 are not prognostic for overall survival nor predictive of irinotecan efficacy in stage III (UICC) CRC patients (15). Another article reported a statistically significant negative prognostic value of BRAF (V600E) mutation on overall survival within this trial (16). Further analysis of the CALGB 89803 trial revealed TP53 mutation to be associated with shorter survival in female patients (17) and the prognostic role of MMR-D (mismatch repair deficiency) for overall survival in stage II and stage III cancer (18). Focusing on PIK3CA mutations is another attempt to identify a predictive or prognostic marker; however no statistically significant association with outcome in the two treatment arms was shown.

The critical question is: Why not apply a more comprehensive approach focusing on one pathway or using novel technologies, such as next-generation sequencing to better understand the role of PIK3CA within the complex molecular makeup of these tumors? Thereby, specific mutational signatures for the risk of tumor recurrence and for irinotecan efficacy may be defined. It would have been refreshing to include all known and reported markers from this trial and to apply recursive partitioning to identify and prioritize biomarkers in this patient population. Recently, data of gene expression arrays from the PETACC 3 trial demonstrated different subgroups of CRC driven by pathways that may be associated with different outcomes. Next-generation sequencing and comprehensive mutational analysis (19), including overlapping KRAS mutations and microsatellite instability status, could shed some light on the role of PIK3CA mutations within molecular-defined subgroups and reveal the predictive and/or prognostic value of PIK3CA within these cohorts. This data would allow the development of novel therapeutic strategies because PI3KCA is a druggable target and might become important in combination with other protein kinase inhibitors in further-line treatment of metastatic CRC in molecular-defined patient populations.

References


Funding

SS is the recipient of a postdoctoral fellowship from the German Cancer Aid (Mildred-Scheel Foundation).

Note

The study sponsor had no role in the writing of the editorial or decision to submit it for publication. The authors have no conflicts of interest to declare.

Affiliation of authors: USC Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA (SS, H-JL).