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REVIEW ARTICLE

The role of PIK3CA in advanced and metastatic colorectal cancer and the therapeutic potential and efficacy of PIK3CA inhibitors

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Abstract

Colorectal cancer (CRC) is one of the most prevalent malignancies globally and is the leading cause of cancer mortality worldwide. Advanced and metastatic CRC is associated with poor prognosis due to high rates of metastases and resistance to standard therapies. With the advent of next-generation sequencing, there has been increased interest in molecularly targeted treatments. One such molecular target is the *PIK3CA* gene, a key component of the phosphatidylinositol 3-kinase (PI3K) pathway, which has been linked to promoting tumor survival and proliferation in cancer cell populations. *PIK3CA* mutations are detected in approximately 10–20% of CRC cases. The presence of these mutations has both prognostic and predictive implications, particularly in regards to providing resistance to standard-of-care CRC therapies. Targeting PIK3CA with selective PI3K inhibitors has shown modest results: in the Copanlisib NCI-MATCH trial, objective responses were observed in 16% of patients with *PIK3CA*-mutant tumors, although CRC patients experienced only disease stabilization without tumor shrinkage. Similarly, in the Taselisib phase II basket study, median progression-free survival was 3.1 months with no complete or partial responses in CRC cohorts. These findings highlight the limited therapeutic efficacy of PI3K inhibitors in CRC, driven by factors including toxicity, adaptive resistance, pathway crosstalk, and tumor co-mutation profiles. The current research is focused on optimizing combination strategies, refining patient selection through biomarkers, targeting specific isoforms within the PI3K pathway, and overcoming resistance mechanisms to unlock the full therapeutic potential of PI3K-targeted therapies for advanced and metastatic CRC.

Keywords: PIK3CA; Colorectal cancer; PI3K inhibitors; Targeted therapy; Mutations; Antineoplastic agents

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1. Introduction

Phosphoinositide 3-kinases (PI3Ks) are a family of enzymes that play crucial roles in various cellular functions, including cell proliferation, quiescence, survival, and metabolism. The PI3Ks can be broadly divided into three classes: I, II, and III, based on their structure and substrate specificity. Of these, Class I is the most extensively studied due to its association with oncogenic processes.[1] Class I PI3K's can be further

subdivided into class IA and class IB. Class IA enzymes include PI3Kα, PI3Kβ, and PI3Kδ, which are encoded by *PIK3CA*, *PIK3CB*, and *PIK3CD* genes, respectively. These enzymes consist of a catalytic p110 subunit (p110α, p110β, or p110δ) from which the isoforms are derived. Class IB enzymes include only the PI3Kγ isoform, which contains the p110γ catalytic subunit and is encoded by the *PIK3CG* gene.[2] Each of these four class I PI3K catalytic isoforms mediates distinct effects on tumor survival and growth. For example, p110α is heavily involved in the signaling and tumor growth driven by *PIK3CA* mutations and oncogenic receptor tyrosine kinases.[3,4] In contrast, the p110β isoform is a key driver of tumorigenesis that arises from PTEN loss. Furthermore, the p110δ isoform is predominantly expressed in immune cells such as leukocytes and plays a crucial role in the survival and function of regulatory T cells and myeloid-derived suppressor cells, rendering it a potential target for inhibition in the treatment of hematologic malignancies.

Recent studies have further clarified the role of *PIK3CA* mutations in advanced colorectal cancer (CRC). A 2025 plasma-based ctDNA analysis of ~17,000 advanced CRC samples reported a *PIK3CA* mutation prevalence of 19.2%, with exon 9 and exon 20 distributions consistent with prior literature.[5] These tumors exhibited low rates of MSI-H co-occurrence, higher tumor mutational burden, and frequent co-mutations in *APC*, *BRAF*, epidermal growth factor receptor (*EGFR*), and *KRAS*. Analysis by exon revealed significantly more co-occurring *PIK3CA* exon 20 mutations in *BRAF* V600E samples versus *BRAF* non-V600E samples (26.9% vs. 13.2%, p=0.0072), suggesting increased genomic instability contributing to therapeutic resistance. In addition, a 2024 study demonstrated that colon cancer-associated *PIK3CA* mutations, including hotspot mutations E542K, E545K, and H1047R, increase lipid kinase activity, strongly activate downstream Akt and p70S6K, and induce morphologic transformation and anchorage-independent growth in NIH 3T3 cells.[6] These findings confirm the oncogenic potential of most CRC-associated *PIK3CA* mutations and highlight the importance of PI3K pathway activation through PIK3CA or K-Ras alterations in colorectal carcinogenesis.

Continuous PI3K research investigation has highlighted isoform-specific targeting as a promising strategy to reduce toxicity in pan-PI3K inhibitors and enhance overall efficacy. Among these trials aimed at targeting specific isoforms, PI3Kα, encoded by the *PIK3CA* gene, has emerged as a particularly interesting target due to its frequent mutation status in solid tumors.[2] *PIK3CA* is a gene that encodes the p110α catalytic subunit of PI3K, which is a downstream effector of EGFR. Mutations to *PI3KCA* commonly occur at exons 9 and 20, which encode the helicase and kinase domains of the subunit, respectively.[7] These mutations mimic growth factor signaling by either relieving the inhibition of the p85 regulatory subunit or enhancing kinase activity. These alterations are linked to promoting aberrant signaling and the downstream activation of AKT/mTOR pathways, which drive cell growth, proliferation, metabolism, and survival within cancer cells. Of particular interest is the crosstalk and interplay between the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway and rat sarcoma/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase (RAS/RAF/MAPK) pathway, which constitute a major resistance mechanism in CRC treatment. Tumor cells harboring *PIK3CA* mutations or expressing a loss of the *PTEN* gene have also been associated with an upregulation of PDL-1 expression, a key immune checkpoint molecule, conferring resistance to anti-PD1 therapy and causing poor outcomes in patients with advanced disease status. *PI3KCA*-mutant CRC cells demonstrated enhanced growth and metastatic potential alongside increased angiogenesis and stem cell-like behavior, which is indicative of their aggressive behavior and poor prognosis.[8] With the advent of more precise, targeted therapies, *PIK3CA* mutations across various types of cancer have become the target of extensive clinical investigations aimed at inhibiting the PI3K pathway in cancer cells. Notably, in breast cancer, the development of the PIK3CA inhibitor alpelisib showed improved median progression-free survival (PFS) and response rates in hormone receptor-positive, HER-2 negative breast cancers in both early- and late-line settings.[9] Given these promising results in breast cancer, pan-PI3K and PIK3CA inhibitors are being actively studied in a variety of other malignancies, including CRC, whose rapid rise, in terms of incidence, and frequent dysregulation of the PI3K pathway make it an ideal target for therapeutic and preventative interventions.

CRC is a prevalent malignancy and a leading cause of cancer mortality worldwide. CRC is ranked third amongst cancers for incidence and mortality. Approximately 15–30% of patients present with metastases, while 20–50% of patients with localized disease develop metastases.[10] In recent years, research has been conducted on key oncogenic drivers in CRC that may offer targets for therapy. One such alteration is the aforementioned *PIK3CA* gene. Approximately 15–20% of advanced CRC patient samples contained activating *PIK3CA* mutations,[5] which lead to constitutive PI3K pathway activation. *PIK3CA* mutations in CRC drive persistent signaling through the PI3K-AKT-mTOR pathway, which promotes tumor cell proliferation, survival, invasion, metastasis, and contributes to therapeutic resistance.[11]

2. The role of PIK3CA as a prognostic biomarker

In 2025 alone, an estimated 100,000 new cases of CRC are expected to be diagnosed. Despite decreases in overall incidence over the past decade, largely due to increased screening efforts, the incidence of CRC among people under 50 years old has increased 2.4%/year from 2012 to 2021, according to the American Cancer Society.[12] CRC displays a high degree of molecular heterogeneity both between patients (inter-patient) and within individual tumors (intra-tumor). A 2022 study evaluated intra-tumor heterogeneity across 136 CRC samples and observed that CRC diversity arises from asynchronous molecular alterations, with mutational and chromosomal instability collectively enhancing both genetic and microenvironmental intra-tumor heterogeneity. These findings highlight the substantial molecular heterogeneity in CRC, which contributes to chemotherapy and immunotherapy resistance and promotes metastasis, resulting in wide variations in patient prognosis.[13] These complex relationships play vital roles in creating resistance to chemotherapy and immunotherapy and promoting metastases, which creates an enormous variation in prognosis. In addition, the underlying genomic instability in CRC can be influenced by a myriad of exogenous factors such as lifestyle, nutrition, and environment.[14-16] Embryological tissue origin differences, as well as laterality of the primary tumor (left- vs. right-sided colon cancer [RCC]), contribute to the poor prognosis associated with advanced and metastatic CRC. A 2023 study evaluated the difference in post-hepatic-metastasectomy overall survival (OS) among right-sided colon, left-sided colon, and rectal cancer groups. The study found that RCC patients had a significantly worse OS compared to left-sided colon cancer (LCC) patients, with a hazard ratio (HR) of 0.68 (p=0.042), indicating a 32% lower risk of death for LCC patients.[17] Among the many biological pathways associated with CRC, the PI3K signaling pathway has garnered attention as a potential prognostic marker and a target for precision therapies.

Despite interest in using *PIK3CA* mutations as a prognostic biomarker, current literature remains inconsistent and inconclusive regarding its utility as an independent prognostic factor in CRC. A large meta-analysis and systematic review reported no substantial prognostic role in *PIK3CA* mutation status, citing several confounding factors such as the simultaneous molecular alterations, host immune response, and tumor heterogeneity as possible reasons for the variability in outcomes and the limited utility of the mutation as a reliable prognostic marker.[18] Similarly, a 2022 meta-analysis examining patients with a PIK3CA-mutant metastatic CRC found no consistent or significant association between mutation status and overall prognosis.[19] Despite these inconclusive findings, subsequent analyses indicate that PIK3CA mutations may influence treatment response rather than overall prognosis. A 2022 meta-analysis of *PIK3CA* mutations in metastatic CRC identified a decreased response to anti-EGFR therapy in patients harboring *PIK3CA* mutations, suggesting that while mutation status may not be a reliable predictor of patient survival, it does confer resistance to certain treatments and could be used as a predictive, rather than prognostic, biomarker.[20] Supporting this, other studies have demonstrated evidence that patients with a *PIK3CA* mutation were more likely to be resistant to standard first-line chemotherapy regimens in CRC. This resistance was attributed to sustain PI3K/AKT signaling induced by the mutation, which promoted survival and proliferation of CRC tumor cells, offering a potential target for chemotherapy-resistant CRC tumors.[11] The prognostic significance of *PIK3CA* mutations may also vary across other types of cancer. For example, a systematic review of HR+ breast cancer patients found that patients with *PIK3CA* mutations treated with PI3K inhibitors experienced improved objective response rate (ORR) and PFS.[21] In contrast, another review focusing on patients with metastatic HR+, HER2- breast cancer found that the same mutation was associated with worse outcomes, highlighting the context-dependent nature of PIK3CA's prognostic value across cancer types, treatment modalities, and disease stages.[22] At present, clinicians do not use PIK3CA status alone as a prognostic biomarker in metastatic CRC but do recognize it as an important molecular feature that contributes to the cancer's biology and may influence therapeutic decision making. Recent advances in computational pathology and imaging further highlight the need to evaluate *PIK3CA* mutations within a broader biomarker framework. For instance, radiomics-based computed tomography (CT) models have shown promising ability to noninvasively predict oncogenic drivers such as KRAS, NRAS, and BRAF in CRC, suggesting that similar approaches could eventually be extended to PIK3CA.[23] Likewise, artificial intelligence (AI)-driven pathology analyses have demonstrated that the necrosis-to-tumor ratio is a strong prognostic factor, underscoring the role of tumor microenvironmental features in shaping outcomes.[24] Together, these findings reinforce that *PIK3CA* mutation status alone may have limited prognostic utility, but integrated models that combine molecular, imaging, and morphologic biomarkers hold greater potential for improving patient stratification and guiding treatment decisions in CRC. Continued research is needed to further elucidate PIK3CA's prognostic role and clinical utility.

3. *PIK3CA* mutations and treatment response

3.1. Chemotherapy

Chemotherapy remains a cornerstone of metastatic CRC treatment, which includes regimens such as FOLFOX (5-fluorouracil [5-FU], leucovorin, and oxaliplatin) and FOLFIRI (5-FU, leucovorin, and irinotecan) among others. There is evidence that *PIK3CA*-mutant CRCs had significantly lower response rates to FOLFOX/FOLFIRI chemotherapy regimens compared to wild-type *PIK3CA* CRCs.[11] It was discovered that mutant CRCs were more likely to progress through therapy due to the mutation increasing CRC stem cell survival and proliferation, which led to chemotherapy resistance. This finding was thought to be induced by PI3K/Akt activation. Although not a current clinical decision-making tool, PIK3CA status might be a factor to consider when considering chemotherapy benefit.

3.2. Anti-EGFR therapy

EGFR inhibitors such as cetuximab and panitumumab are effective targeted therapies for metastatic CRC but only in tumors that have wild-type RAS and BRAF.[25] In addition, guidelines state that treatment should be limited to those with left primary tumor location. Despite this, anti-EGFR therapy response remains variable, indicating that other variables may be modifying the effects. One such modifying effect could be attributed to the *PIK3CA* mutation, which can uncouple PI3K activation from EGFR activity, allowing tumor cells to bypass the growth-inhibitory effects of EGFR inhibition.[25] This is indicated in a meta-analysis, which discovered that *PIK3CA* exon 20 mutations were associated with a lack of response to anti-EGFR monoclonal antibodies.[26] Interestingly enough, exon 9 mutations appeared to be partially dependent on upstream EGFR/RAS signaling and retain response rates to anti-EGFR antibodies of ~36–40%, while exon 20 mutations drove PI3K activation independently of EGFR/RAS and were associated with markedly poorer outcomes, with response rates approaching 0% and median PFS reduced to ~2.1 months versus ~5.5–6.4 months for exon 9 or wild-type tumors.[25] *PIK3CA* mutations can occur alongside other known resistance mutations such as those in *KRAS*, with an incidence of ~7.7% in a 2023 study.[27] leading to pronounced anti-EGFR therapy resistance.[28] In short, PIK3CA's role in anti-EGFR therapy resistance in CRC, particularly with exon 20 mutations, has been well established. However, these mutations are not as common as *RAS*/*KRAS*/*BRAF* mutations and thus are not routinely tested for before starting anti-EGFR therapy. Since a *PIK3CA* mutation significantly affects anti-EGFR therapy to such an extent, we recommend using it as an ancillary marker combined with *RAS*/*BRAF* testing to determine the possible efficacy. These findings also provide a rationale for researching the efficacy of combining EGFR inhibitors with PI3K pathway inhibitors in overcoming resistance.

3.3. BRAF targeted therapy

Approximately 8–10% of metastatic CRC patients carry the *BRAF* V600 mutation, which predisposes them to rapid progression and poor prognosis, and requires special therapy.[29] In wild-type cellular signaling, EGFR activates RAS, which then activates BRAF. BRAF activation triggers a cascade that results in increased transcription of genes such as cyclin D1, which promotes cell division. The V600E mutation leads to the constitutive activation of this pathway, and unchecked cellular proliferation can occur. The BEACON trial demonstrated that combining a BRAF inhibitor with an EGFR inhibitor improved survival in *BRAF*-mutant metastatic CRC.[30] Regarding *PIK3CA* mutations, it has been demonstrated that they can mediate resistance to BRAF inhibition in CRC with *BRAF* V600E mutations.[31] In *BRAF*-mutant cell lines, concurrent activation of the PI3K/AKT pathway allows continued cell survival even when the BRAF pathway has been suppressed through a BRAF inhibitor. However, dual blockade of BRAF and PI3K produced synergistic growth suppression in BRAF V600E CRC models, whereas BRAF inhibitor monotherapy was ineffective.[31] This finding was replicated in a study, which showed that *PIK3CA* mutations were found in *BRAF*-mutant metastatic CRC patients who had poorer outcomes on BRAF and EGFR inhibitor combination therapy.[32] These results reinforce the theme that targeting the PI3K pathway remains a potential approach to enhance BRAF inhibitor efficacy in the subset of BRAF V600E CRC that concomitantly have *PI3KCA* mutations.

3.4. Immunotherapy

Immunotherapy, such as checkpoint inhibitors like pembrolizumab, is often used to manage metastatic CRC as a first-line choice. An analysis of CRC samples found that those harboring *PIK3CA* mutations had significantly higher PD-L1/CD274 expression on tumor cells/immune cells compared to those with wild-type *PIK3CA*.[33] Upregulation of PD-L1 through PI3K-AKT signaling has been observed in other cancers as well, linking PI3K activity to an immune-evasive phenotype.[34] Paradoxically, however, elevated PD-L1 positivity could make tumors more amenable to PD-1/PD-L1 targeting therapy. Another

way in which PK3CA can enhance immunotherapy effects is by increasing tumor mutational burden, resulting in more neoantigens and enhancing the immunogenicity of tumors to increase the sensitivity of immune checkpoint inhibitors.[35] In addition, studies have also shown that the tumor mutational burden of CRC patients with *PIK3CA* gene mutations is significantly higher than that of patients with wild-type *PIK3CA*.[36,37] These results suggest that *PIK3CA* gene mutations can enhance the sensitivity of tumors to immune checkpoint inhibitors by increasing the tumor mutational burden and increasing the immunogenicity of the tumor. Therefore, *PIK3CA* is a potential predictive factor for the outcomes following consumption of immune checkpoint inhibitors and a valuable factor with implications for immunotherapy.

While *PIK3CA* mutations have not been proven to be reliable as a standalone prognostic biomarker, their value as predictive biomarkers, particularly in terms of informing therapeutic resistance, is an area of interest for researchers. This has spurred numerous clinical trials investigating strategies that either directly target the PI3K pathway or combine PI3K inhibitors with other treatment modalities to improve clinical outcomes and overcome resistance.

3.5. Toxicity profile and side effects

Numerous clinical trials have investigated PI3K inhibitors both as monotherapies and in combination with other treatments, aiming to manage associated side effects and enhance therapeutic efficacy. Despite showing promising activity in specific settings, these agents have frequently induced significant side effects and toxicities that can lead to trial discontinuation or reduce patient quality of life. Among the most common adverse events detected across all PI3K inhibitor trials were hyperglycemia and rash.[38] In a phase I study of pictilisib in patients with advanced solid tumors, seven of the 32 included patients exhibited significant increases in plasma insulin and glucose levels, reflecting PI3Kα's role in insulin signaling and glucose homeostasis.[39] Similar reports of hyperglycemia have appeared in other clinical trials. This disruption of glucose regulation leads to increased compensatory pancreatic insulin release in an attempt to normalize serum glucose levels. Insulin, which is a potent stimulator of PI3K signaling in tumors, is increased and potentially promotes cancer cell proliferation, creating a paradoxical pro-tumorigenic effect in certain cases.[14] Of note, PI3Kα selective inhibitors demonstrated more frequent episodes of hyperglycemia compared to pan-PI3K inhibitors; however, pan-PI3K inhibitors such as copanlisib have been associated with high-grade hyperglycemia in 23.8–41% of patients.[40] The PI3Kα selective inhibitor alpelisib shows any-grade hyperglycemia in ~59–66% and grade ≥3 in ~28–38%, reflecting a more manageable toxicity profile despite frequent glucose disturbances.[41,42] Maculopapular rashes have also been reported in 45–64% of patients and are attributed to the PI3K/AKT pathway's involvement in keratinocyte differentiation. The inhibition of the pathway leads to an impediment in cellular growth signaling, ultimately leading to epidermal cell death.[43,44] Additional toxicities varied by the specific PI3K inhibitor involved and included diarrhea, elevated liver enzymes, and immunosuppression. In a study examining the use of PIK3α inhibitor, alpelisib, in *PIK3CA*-mutated, HR-positive advanced breast cancer, 6.7% of patients enrolled reported diarrhea with recommendations to pause treatment in cases of severe diarrhea.[41] Furthermore, immune dysregulation due to PI3K inhibition has been shown to be associated with a decreased number and activity of regulatory T cells with enhancements in cytotoxic T cells, leading to a sequelae of adverse side effects including diarrhea, dyspepsia, and colitis.[45] At present, clinical strategies are aimed at treating the high incidence adverse effects such as hyperglycemia, which is managed through pretherapy risk assessment (*e.g.*, older age, obesity, HbA1c 5.7–6.4%) combined with lifestyle interventions such as low-carbohydrate diets, prophylactic metformin, and regular glucose monitoring. If necessary, therapy can be escalated to SGLT2 inhibitors or thiazolidinediones, although metformin remains the recommended first-line agent.[46,47] Despite these interventions, the broad toxicity profile of PI3K inhibitors underscores the urgent need to minimize adverse events, refine targeting, and enhance clinical outcomes through continued investigation of PI3K inhibitor's mechanisms.

4. Therapeutic use of PIK3CA in CRC: Inhibitors and clinical trials

4.1. Inhibitors

A variety of small-molecule inhibitors have been designed to target different nodes of the PI3K-AKT-mTOR signaling axis. These include pan-PI3K inhibitors that target all Class I PI3K isoforms (p110a, β, γ, δ); isoform-selective PI3K inhibitors, most notably the PI3K α-specific; dual PI3K-mTOR inhibitors which target both PI3K and the downstream mTOR kinase; and AKT inhibitors and mTOR inhibitors which act further down the PI3K pathway, not directly on it. In the context of *PIK3CA*-mutant tumors, PI3Kα-selective inhibitors have generated the most interest, as they directly target the oncogenic driver while sparing other isoforms, thereby reducing toxicity.

Pan-Class I PI3K inhibitors such as buparlisib and pictilisib were the first to enter trials but have shown limited efficacy in solid tumors as well as significant

toxicity.[48-50] Side effects often included hyperglycemia, rash, diarrhea, and elevated liver enzymes.[14,38,45,51] On the other hand, isoform-specific inhibitors, such as alpelisib, allow for more potent inhibition of mutant PI3Kα while sparing other isoforms such as PI3Kβ, which is important in insulin signaling in normal tissues. This selectivity has translated into slightly better tolerability and successful clinical benefits in *PIK3CA*-mutant advanced breast cancer.[43] This trial, dubbed the SOLAR-1 trial, showed improved PFS when alpelisib was added to endocrine therapy in *PIK3CA*-mutant, HR+ metastatic breast cancer. This landmark result confirmed that targeting PIK3CA can yield benefits in patients with breast cancer, where PI3K is critical for tumor growth. The question now emerges whether similar success could be achieved in *PIK3CA*-mutant CRC using PI3K inhibitors.

4.2. Trials of PI3K inhibitor in metastatic CRC

Multiple trials over the last decade have tested PI3K inhibitors in advanced CRC, both as monotherapy and in combination with other agents. Unfortunately, the results have not been promising, and no PI3K pathway inhibitor has been approved for the treatment of CRC to date. In the following section, we will discuss recent key studies and investigate the poor response of *PIK3CA* mutations, and Table 1 summarizes the key PIK3CA inhibitor trials that are discussed.

Monotherapy with PI3K inhibitors as a whole has been largely unsuccessful in CRC, driving a shift toward combination strategies and more refined patient selection in an effort to unlock clinical benefit. A notable example is the phase I basket trial of taselisib, which enrolled 166 patients with *PIK3CA*-mutant solid tumors, including a CRC cohort. The overall confirmed response rate was 9%, with activity varying by tumor type and allele. Responses were observed in head and neck squamous cell carcinoma (15.4%), cervical cancer (10%), and other selected tumor types, particularly those with helical domain mutations, but no responses were reported in CRC.[52] In addition, higher rates of dose modification at escalated doses reflected taselisib's narrow therapeutic index, limiting its clinical utility. A subsequent phase II trial of taselisib focused on 70 patients with *PIK3CA*-mutant solid tumors, 61 of which were eligible, excluding breast and squamous lung cancers. Patients were stratified by mutation subtype: helical domain (67%), kinase domain (18%), and other domains (15%).[53] Despite a median follow-up of 35.7 months, no partial or complete responses were observed. Median PFS was 3.1 months overall (3.7 months for kinase-domain, 3.2 months for helical-domain, and 1.8 months for other variants), with differences between mutation subtypes not reaching statistical significance. Median OS was 7.2 months, and 6-month PFS and OS rates were 19.9% and 60.7%, respectively. Collectively, these results demonstrate that the presence of a *PIK3CA* mutation alone is insufficient to predict sensitivity to PI3K inhibition, particularly in CRC, where co-mutations such as those in *KRAS* and *PTEN*, as well as alternative survival pathways such as MAPK reactivation, reduce the therapeutic impact of isoform-selective inhibition.[54]

Given the role of PIK3CA in anti-EGFR resistance, a phase II trial evaluated adding the pan-PI3K inhibitor PX-866 to cetuximab, an EGFR inhibitor, in 85 metastatic CRC patients who had progressed on chemotherapy.[55] Results indicated that the combination treatment failed to improve outcomes; there was no improvement in PFS

Table 1. Clinical trials of PIK3CA inhibitor

Trial	Population	Patient	Outcomes
PX-866±Cetuximab (Anti-EGFR)	85	Metastatic *KRAS* wild-type CRC, progressed after FOLFIRI	PX-866, a pan-PI3K inhibitor, was ineffective in metastatic CRC and associated with increased toxicity[55]
ALCAP Trial: Alpelisib+Capecitabine Phase II	26	Refractory *PIK3CA*-mutant metastatic CRC (>2 prior regimens failed)	No overall significant PFS improvement observed[59]
NCI-MATCH: Copanlisib Phase II Trial	35	Refractory advanced solid tumors with *PIK3CA* mutations, including six CRC cases	Objective response noted only in non-CRC tumors[56]
Alpelisib+Capecitabine	12 (six breast cancer, six CRC)	Refractory advanced solid tumors	Limited clinical benefit in breast cancer compared to CRC[58]
BRAF Pilot: Encorafenib+Cetuximab±Alpelisib	52	Patients with *BRAF* V600E-mutant metastatic CRC	No improved outcomes with the addition of alpelisib to combination therapy; increased toxicity[60]
Taselisib Basket Trial Phase I	166	Various advanced cancers with *PIK3CA* mutations, including 11 CRC patients	Limited efficacy as monotherapy; significant effects seen only in head/neck and cervical cancer; none in the CRC cohort[52]

Abbreviations: CRC: Colorectal cancer; FOLFIRI: 5-fluorouracil, leucovorin, and oxaliplatin; PI3K: Phosphoinositide 3-kinase.

and no increase in OS. In addition to these findings, the combination therapy had significantly higher toxicity. Gastrointestinal adverse events such as nausea, vomiting, and diarrhea were all significantly elevated in the combination therapy group. The trial concluded that the combination was ineffective and less tolerable. They hypothesized that the reason for failure was likely patient selection, as only 7% of cancers were found to contain *PIK3CA* mutations, thus rendering the treatment ineffective. Following this negative result, further development of PX-866 for use in CRC was halted. This study underscored the need to identify subsets (*PIK3CA*-mutant) or use better-tolerated, isoform-specific inhibitors in future trials.

A trial using copanlisib in *PIK3CA*-mutant refractory cancer was conducted and published in 2022, called the NCI-MATCH ECOG-ACRIN trial.[56] Patients with *KRAS*-mutant tumors and HER2+ breast cancer were excluded. The primary endpoint was the ORR, defined as the percentage of patients whose tumors shrank or disappeared after treatment, as determined by specific criteria. In this particular study, it was calculated by adding the percentages of patients achieving a partial response and those achieving a complete response and dividing by the total number of evaluable patients. This trial focused on *PIK3CA*-mutant cancers of multiple histologies, including six CRC patients, who had progressed on standard therapies. The trial met its primary endpoint with an ORR of 16%, as four out of 25 patients showed a partial response. However, response was only found in gynecologic tumors; colorectal patients had disease stabilization, but failed to demonstrate tumor size reduction. Toxicities were consistent with PI3K-AKT pathway inhibition, as the most common side effects, such as hyperglycemia, hypertension, fatigue, and diarrhea, were found in 10–30% of patients. Several factors may explain the difference in response to therapy between the gynecologic cancers and the CRC. Notably, CRC tumors frequently harbor co-occurring oncogenic alterations that drive MAPK or alternative survival pathways, reducing reliance on PI3K signaling.[54] In addition, CRC tumors often contain helical-domain *PIK3CA* mutations, which may confer weaker PI3K dependency compared with kinase-domain mutations more common in responsive gynecologic tumors. A 2022 study found that CRC cells with the *PIK3CA* H1047R kinase-domain mutation showed a better response to PI3K/AKT/mTOR inhibitors than those with helical-domain mutations, such as E545K. This differential response was attributed to the distinct mechanisms by which these mutations activate the PI3K pathway, leading to variations in pathway activation and therapeutic sensitivity.[57]

In 2021, a phase 1b pharmacokinetics study evaluated the combination of alpelisib, an α-isoform selective PI3K inhibitor, and capecitabine (chemotherapy) in patients with advanced solid tumors, including CRC (six patients) and breast cancer (six patients). While the combination of drugs did not interfere with each other pharmacokinetically, it did show limited clinical benefit for CRC patients, whereas breast cancer patient responses were more notable.[58] The median PFS for CRC patients was only 1.4 months, underscoring the need for further investigation into this combination of drugs in a more selective patient cohort. These preliminary findings suggest that *PIK3CA* mutations may not function as strongly as driver mutations in CRC compared to other cancers. In addition, the frequent co-occurrence of *KRAS* mutations in CRC could have led to the modest efficacy, as they are known to confer resistance to PIK3CA inhibitors.[28] Similarly, another trial completed in 2024 combined alpelisib with capecitabine to evaluate their effectiveness in metastatic CRC with *PIK3CA* mutations.[59] The patient population consisted of 26 individuals who had failed two prior chemotherapy lines. Unfortunately, efficacy was limited. Findings indicated an ORR of only 7.7% patients, as two out of 26 patients achieved partial remission. In addition, there was no improvement in median PFS. However, it was noted that in isolation, patients without *KRAS* and *PIK3CA* co-mutations and liver metastasis showed longer PFS and partial remission rates. The lack of a robust PFS or response benefit suggests that *PIK3CA* mutation alone may be an insufficient predictor of response in CRC, especially given co-occurring mutations that drive resistance.

BRAF Pilot was a trial in 2017 that tested alpelisib in combination with the BRAF inhibitor encorafenib and anti-EGFR antibody cetuximab in the treatment of metastatic CRC.[60] Fifty-two patients with *BRAF* V600E-mutant metastatic CRC were assigned to either Encorafenib + Cetuximab group or Encorafenib + Cetuximab + Alpelisib group. Prior data showed minimal activity of BRAF or EGFR inhibitors in metastatic CRC, so this trial explored PI3K blockade on top of EGFR and BRAF targeting. Once again, however, the PI3Kα inhibitor did not significantly improve outcomes compared to control therapy. There was a moderate increase in disease control, accompanied by a significant improvement in PFS; specifically, the combination therapy achieved a disease control rate of 74%, compared to 59% with the doublet alone. However, the PFS did not differ significantly with the addition of alpelisib. Furthermore, the addition of alpelisib, unfortunately, considerably increased the occurrence of adverse events including hyperglycemia, rash, and fatigue, which occurred in 79% of triple therapy patients compared to 69% of double therapy patients. These findings suggest that while the triplet regimen is feasible, it offers only modest efficacy over the doublet, and thus, the encorafenib plus cetuximab regimen (± mitogen-activated protein

kinase [MEK] inhibition), without PI3K inhibition, was positioned as the eventual standard.

In summary, PI3K inhibitors have yielded underwhelming results in metastatic CRC clinical trials. It would seem that this marked resistance to PI3K inhibition is due to multiple interconnected factors which we will discuss briefly. First, CRC demonstrates a propensity to be driven by MAPK/EGFR feedback rather than PI3K. Inhibition of PI3K frequently triggers adaptive EGFR/MAPK reactivation, which could explain why clinical success in *BRAF*-mutant CRC requires EGFR plus BRAF (± MEK) inhibition rather than PI3K-targeted add-ons. This can be compared to HR+ breast cancers, which rely more heavily on PI3K signaling, rendering alpelisib plus fulvestrant particularly effective in managing breast cancers.[30] In addition, a high co-mutation burden in CRC, including frequent co-occurrences of *KRAS*, *NRAS*, or *BRAF* with *PIK3CA* mutations, further reduces dependence on PI3K and could contribute to anti-EGFR resistance. Even trials excluding *KRAS* or *PTEN* mutations, such as Taselisib-MATCH, showed minimal responses to PI3K inhibitors, highlighting that *PIK3CA* mutations alone are insufficient to predict sensitivity.[59] Exon-specific variation likely also plays a role in the poor outcomes of the aforementioned clinical trials. CRC tumors predominantly harbor *PIK3CA* mutations in the helical domain (E542K/E545K), which often co-occur with *RAS* mutations and are less sensitive to PI3Kα inhibition than the kinase-domain H1047R mutations commonly seen in breast cancer.[53] An additional consideration for the relative ineffectiveness in PIK3CA-directed CRC trials is on-target metabolic toxicities, including hyperglycemia and rash. These adverse effects further constrain dosing and the ability to combine PI3K inhibitors with EGFR/MAPK agents at effective doses.[61] CRC's WNT/APC-driven biology and stromal microenvironment may also reduce reliance on PI3K for survival and proliferation. A recent study in 2024 noted aberrant activations of the WNT/β-catenin pathway, often resulting from mutations in the *APC* gene, which influence various cellular processes such as proliferation, survival, and differentiation, thereby reducing the tumor's reliance on PI3K signaling for survival.[62] In addition, it was observed that the tumor microenvironment, particularly the interactions between CRC cells and stromal components, further diminished the effectiveness of PI3K-targeted therapies. These results can be compared to results in the use of PI3K inhibitors in HR+ breast cancer, where PI3K signaling is a central route of endocrine resistance, contributing to the consistent efficacy observed in trials like SOLAR-1.[41,62] Finally, nearly all CRC patients enrolled in these clinical trials were heavily pretreated, having progressed on multiple prior therapies, which likely allowed tumors to evolve adaptive resistance mechanisms and create additional barriers that further limit the efficacy of PI3K-targeted agents.

4.3. ASA and PIK3CA

Current research and the National Comprehensive Cancer Network (NCCN) guidelines have highlighted the potential benefit of aspirin in CRC patients with *PIK3CA*-mutant tumors, showing improved outcomes and reduced recurrence rates. A phase III randomized, double-blind, placebo-controlled trial evaluated daily low-dose aspirin (100 mg) as adjuvant therapy in patients with stage II/III colon cancer harboring PIK3CA mutations following surgical resection. After 5 years, disease-free survival (DFS) was 86.5% (90% CI, 77.7–92.0%) in the aspirin group compared to 72.9% (90% CI, 55.7–84.3%) in the placebo group.[63] Despite these encouraging results, the study was closed prematurely and therefore lacked statistical significance. Nonetheless, the findings underscore the potential role of adjuvant aspirin in patients with resected stage II/III *PIK3CA*-mutant colon cancer. In addition, a study conducted across Denmark, Finland, Norway, and Sweden assessed the effect of 160 mg daily aspirin for 3 years in CRC patients with resected liver metastases. While no overall benefit was seen in the general study population, patients with PI3K pathway mutations, including PIK3CA, did experience improved outcomes. Of the 2,980 patients who underwent conclusive genomic analysis, 1,103 (37%) had PI3K pathway alterations: 515 (17.3%) were classified as Group A (*PIK3CA* hotspot mutations), and 588 (19.7%) as Group B (non-hotspot PI3K pathway alterations). After 3 years, the HRs for time to recurrence comparing aspirin to placebo were 0.49 (95% CI: 0.24–0.98; p=0.044) in Group A and 0.42 (95% CI: 0.21–0.83; p=0.013) in Group B, indicating significantly reduced recurrence with aspirin. For DFS, the HRs were 0.61 (95% CI: 0.34–1.08; p=0.091) in Group A and 0.51 (95% CI: 0.29–0.88; p=0.017) in Group B.[64] These findings suggest that aspirin may provide benefit in CRC patients with *PIK3CA* mutations, despite limited efficacy in the broader metastatic setting.

As of 2024, NCCN Guidelines reaffirm aspirin's role in secondary prevention for individuals with a history of advanced adenomas or CRC to reduce recurrence risk and inform screening strategies. While aspirin shows promise in primary prevention, particularly with long-term low-dose use, and in specific high-risk groups, its benefit does not extend to the adjuvant treatment of metastatic CRC. Current clinical practice supports aspirin for primary prevention in older individuals with risk factors and for secondary prevention after adenoma or CRC, but not for treatment of established metastatic disease.[65] Future

research should focus on defining the optimal dosing, duration, and patient selection.

5. Future perspectives

The past decade of research has underscored that while PIK3CA is an important oncogenic driver in CRC, successfully targeting it is not an easy matter. Several strategies may enhance the therapeutic potential of PIK3CA/PI3K inhibition in advanced CRC.

Refined patient selection can benefit future trials by selecting patients whose tumors are most likely to be PI3K-dependent. This could mean focusing on those with multi-hit *PIK3CA* mutations, defined as two or more activating *PIK3CA* mutations, which occur in approximately 1.7% of metastatic CRC cases, and are notable for frequent co-mutations, with *KRAS* alterations in 64.7% and *BRAF* V600E in 9.1% of affected tumors.[66] A recent finding has shown that multi-hit (multiple activating mutations) *PIK3CA*-mutant tumors have exceptional sensitivity to PIK3α inhibitors in other cancers, suggesting that in CRC, such patients might derive meaningful benefit where others do not.[66] Beyond PIK3CA itself, integrating other biomarkers, such as co-mutations, could help identify tumors that remain reliant on the PI3K pathway. For example, CRCs that are RAS/BRAF wild-type, but mutated for *PIK3CA*, might rely on PI3K signaling as the primary driver of proliferation. These patients could be ideal candidates for PI3K inhibitor trials, as opposed to tumors with both *RAS* and *PIK3CA* mutations, which can circumvent PIK3CA blockade. Next-generation sequencing (NGS) panels, including ctDNA-based assays, may aid in the detection of these multi-hit *PIK3CA* mutations and co-mutations, offering a way to navigate potential barriers to therapeutic efficacy conferred by multiple mutations. For example, a study of 206 CRC tumors using an NGS panel reported multi-*PIK3CA* mutations in several cases and concomitant *KRAS* mutations in 51% of *PIK3CA*-mutated tumors, including 82% of those with exon 9 variants and 58% with exon 20 variants.[67]

Combining PI3K inhibitors with other treatments is essential for maximum efficacy in advanced CRC. Ongoing and future trials will determine the optimal combinations, whether it is partnering a PI3K inhibitor with an EGFR inhibitor in *RAS*/*RAF* wild-type tumors, with BRAF inhibitors in *BRAF*-mutant tumors, or even CDK4/6 inhibitors. Early findings in *in vivo* studies indicate that alpelisib and ribociclib, a CDK4/6 inhibitor, when combined, show a significant reduction in tumor growth across four distinct cell lines of CRC (*PIK3CA*/*KRAS* wild-type, *KRAS*-mutated, *PIK3CA*-mutated, and *PIK3CA*/*KRAS*-mutated).[68] Future research must also focus on understanding and overcoming resistance to PI3K inhibitors. Even if the initial response is met, tumors can adapt. The diversity and heterogeneity of *PIK3CA* mutations contribute to resistance to monotherapy.[69] As previously discussed, studies are now focusing on the combination or sequential use of PI3K inhibitors as a combination therapy. Some studies have shown promise, such as prolonged PFS.[70,71]; however, these studies have small sample sizes, dosing and toxicity concerns, and a lack of standardization of methods. Additional research is needed to advance the field.

An additional step should be to focus on optimizing and standardizing the detection methods for *PIK3CA* gene mutations. To personalize treatment for metastatic CRC, one must be able to detect the mutation of interest. At present, studies utilize real-time polymerase chain reaction (PCR), digital droplet PCR, Sanger sequencing, and NGS.[72,73] Each method has its own set of advantages and disadvantages; however, to accurately compare studies and results, a standardized detection method is necessary. This would improve accuracy, reliability, and increase consistency and compatibility in the field.

6. Conclusion

The PI3K pathway remains an elusive yet promising target for cancer patients as it plays a significant role in CRC pathogenesis, progression, and treatment response. Although its utility as a prognostic biomarker remains limited due to insufficient longitudinal data and tumor heterogeneity, its role as a predictive marker, particularly in the context of anti-EGFR therapy and immunotherapy, shows promise. Particularly, mutations in *PIK3CA*, a key gene in the pathway, have been associated with conferring resistance to certain targeted therapies, highlighting the importance of molecular profiling in treatment planning.

Despite the availability of several types of PI3K inhibitors, clinical outcomes have been variable, with limited efficacy in specific patient populations and toxicities that have outweighed therapeutic benefits. Ongoing efforts are focused on refining patient selection criteria, developing more specific isoform-specific inhibitors, and exploring combination therapies to enhance efficacy and clinical outcomes. Continued investigation of PI3K signaling in CRC is crucial to realize its potential as a therapeutic and predictive biomarker.

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The authors declare that they have no competing interests.

Author contributions

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