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Authors

VanLandingham, Nathan K
Nazarenko, Andrew
Grandis, Jennifer R
et al.

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The mutational profiles and corresponding therapeutic implications of PI3K mutations in cancer

Nathan K. VanLandingham[a,#], **Andrew Nazarenko**[b,#], **Jennifer R. Grandis**[a], **Daniel E. Johnson**[a,*]

[a]Department of Otolaryngology – Head and Neck Surgery, University of California San Francisco, San Francisco, California, USA

[b]New York Medical College, Valhalla, NY, USA

Abstract

Genetic alterations of the *PIK3CA* gene, encoding the p110α catalytic subunit of PI3Kα enzyme, are found in a broad spectrum of human cancers. Many cancer-associated *PIK3CA* mutations occur at 3 hotspot locations and are termed canonical mutations. Canonical mutations result in hyperactivation of PI3K and promote oncogenesis via the PI3K/AKT/mTOR and PI3K/COX-2/PGE2 signaling pathways. These mutations also may serve as predictive biomarkers of response to PI3K inhibitors, as well as NSAID therapy. A large number of non-canonical *PIK3CA* mutations have also been identified in human tumors, but their functional properties are poorly understood. Here we review the landscape of *PIK3CA* mutations in different cancers and efforts underway to define the functional properties of non-canonical *PIK3CA* mutations. In addition, we summarize what has been learned from clinical trials of PI3K inhibitors as well as current trials incorporating these molecular targeting agents.

Keywords

PIK3CA ; phosphoinositide 3-kinase alpha; p110alpha; alpelisib

1. Introduction

The *PIK3CA* gene encodes the p110α catalytic subunit of the phosphoinositide 3-kinase alpha (PI3Kα) enzyme (Samuels et al. 2004). The PI3K protein is a critical upstream component of the PI3K/AKT/mTOR signaling pathway, which plays a major role in regulating multiple cellular functions, including cell survival, proliferation, metabolism, and growth (Cai et al. 2020). *PIK3CA* is frequently altered in many different types of

*Corresponding author. Department of Otolaryngology – Head and Neck Surgery, University of California San Francisco, 1450 3rd Street, Room HD268, San Francisco, California, 94158, USA. Daniel.Johnson@ucsf.edu.
#These authors contributed equally to the work.

Author contributions

N.K.V. and A.N. wrote the original draft. J.R.G. and D.E.J. reviewed and edited the manuscript. All authors contributed to the literature analysis. All authors read and approved the final manuscript.

Declaration of competing interest

D.E.J. and J.R.G. are co-inventors of cyclic STAT3 decoy and have financial interests in Bluedot Bio. Bluedot Bio holds an interest in cyclic STAT3 decoy.

cancer, resulting in aberrant hyperactivation of the PI3K/AKT/mTOR signaling pathway and enhanced cellular and tumor growth and drug resistance. Hence, molecular targeting of PI3K, particularly mutated PI3K proteins, represents a promising anti-cancer strategy (Hanker, Kaklamani, and Arteaga 2019). As mutations in *PIK3CA* have been found at numerous locations throughout the gene, it is important to understand the unique molecular properties of distinct mutant p110α proteins, and the potential vulnerabilities they may confer to PI3K inhibitors. In this review we summarize the frequency of *PIK3CA* mutations in different human cancers, the diversity of these mutations, and the attempts that have been undertaken to determine the functional properties of the mutant proteins. We also report what has been learned from completed clinical trials of PI3K inhibitors in cancer and the status of ongoing advanced-phase trials.

2. The PI3K/AKT/mTOR Pathway

In healthy, quiescent cells the p110α kinase is bound to p85, a negative regulatory protein, ensuring that the PI3Kα protein, consisting of a p110α/p85 heterodimer, is largely inactive (Fruman et al. 2017). Activation of the PI3K/AKT/mTOR pathway occurs following the binding of cytokines or growth factors to their cognate cell surface receptors and the activation of kinase activities intrinsic to the receptor or receptor-associated kinase proteins. This results in phosphorylation of p85 and dissociation of this negative regulator from p110α, leading to activation of the p110α kinase (Backer 2010). Activated p110α phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP_2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP_3) on the inner leaflet of the plasma membrane (Fruman et al. 2017). Proteins that contain pleckstrin homology domains, including PDK1 and AKT, recognize and bind PIP_3, resulting in colocalization of these two proteins at the plasma membrane. Proximity-induced phosphorylation of AKT by PDK1 results in activation of the serine/threonine kinase activity of AKT which inhibits tuberous sclerosis complex 1 and tuberous sclerosis complex 2, resulting in downstream activation of mTOR signaling (Porta, Paglino, and Mosca 2014). Signaling via the PI3K/AKT/mTOR pathway can be turned off through the action of phosphatase and tensin homolog deleted on chromosome ten (PTEN) protein. PTEN is a phosphatase that removes a phosphate from PIP_3 generating PIP_2, abrogating further activation of AKT (Stambolic et al. 1998). It is notable that while many cancers contain activating mutations of *PIK3CA*, resulting in hyperactivation of the PI3K/AKT/mTOR pathway, PTEN is frequently deleted or contains inactivating mutations, also resulting in hyperactivation of the pathway.

3. Alterations in *PIK3CA*

Alterations in the *PIK3CA* gene occur frequently in human tumors, and include mutation or gene amplification. Table 1 depicts cancers identified in studies for The Cancer Genome Atlas (TCGA) wherein *PIK3CA* is altered in greater than 10% of patient tumors (Cerami et al. 2012, Gao et al. 2013). In each of the cancers shown, the frequency of *PIK3CA* gene mutations in the tumors always exceeds the frequency of *PIK3CA* gene amplification. A small minority of patient tumors exhibits both mutation and amplification of the *PIK3CA* gene.

Figure 1 ranks the cancers from Table 1 according to their level of *PIK3CA* gene mutation. Mutations of the *PIK3CA* gene can be categorized into two groups: canonical and non-canonical mutations. Canonical mutations, generally, are more prevalent than non-canonical mutations when examining patient samples across multiple cancer types. Canonical mutations occur at three hotspot locations, E542(K/A/G/Q/V), E545(K/G/Q/D/A/V/E545_Q546delinsDH/E545_Q546delinsDK), and H1047(R/L/Y/Q/C/H1047_H1048delinsRR). Non-canonical mutations occur at a multitude of sites and are spread throughout the p110α sequence. Table 2 categorizes the frequency of canonical versus non-canonical mutations occurring in cancers with high levels of *PIK3CA* gene alterations (from Table 1). It is noteworthy that in most of these cancers the frequency of canonical mutations exceeds the frequency of non-canonical mutations. However, that is not always the case. For example, in uterine cancer 27.6% of the mutations found in patient tumors are canonical mutations, while 72.4% are non-canonical mutations.

In addition to canonical and non-canonical mutations, amplification of the *PIK3CA* gene, resulting in overexpression of p110α, occurs in a variety of cancers (Table 1). *PIK3CA* amplification leads to increased signaling through the PI3K pathway.

4. Effects of *PIK3CA* Mutations on PI3K Function

The p110α catalytic subunit of the PI3Kα protein contains 5 domains: p85 binding domain, RAS binding domain, protein-kinase C homology-2 domain, helical domain, and kinase domain. Canonical mutations are located within the helical domain (E542 and E545) and within the kinase domain (H1047). Table 3 indicates for different cancers the frequency of canonical mutations that occur at E542 versus E545 versus H1047. Canonical mutations give rise to p110α with increased and constitutive activity, and, therefore, enhanced conversion of PIP_2 to PIP_3 (Bilanges, Posor, and Vanhaesebroeck 2019). Constitutive activation of p110α leads to hyperactivation of the PI3K/AKT/mTOR signaling pathway, which, in turn, drives tumorigenesis and cancer progression via a variety of downstream mechanisms. In particular, hyperactivation of the pathway results in increased cellular proliferation, migration, and invasion, and resistance to apoptosis (Porta, Paglino, and Mosca 2014). Exogenous expression of *PIK3CA* canonical mutants has been shown to drive these oncogenic events (Kang, Bader, and Vogt 2005).

Activation of PI3K/AKT signaling also leads to induction of cyclooxygenase-2 (COX-2) enzyme, resulting in enhanced cellular production of prostaglandin E2 (PGE2). PGE2 is secreted by tumor cells and has well-established roles in promoting immunosuppression (Mahic et al. 2006). Thus, aberrant activation of the PI3K/AKT/COX-2/PGE2 signaling axis has a negative impact on anti-tumor immunity.

In addition to canonical mutations, less frequent, site diverse noncanonical *PIK3CA* mutations have been observed in a variety of cancer types. For example, 30.6% of *PIK3CA* mutations seen in breast cancer are non-canonical and this percentage increases to 48.1% in colorectal cancer and 72.4% in uterine cancer (refer to Table 2 for more rates of canonical versus non-canonical mutations across cancer types). Moreover, while insertions, deletions, silent, and nonsense mutations have all been reported in *PIK3CA*, the overwhelming

majority of *PIK3CA* mutations in cancer cells are missense (Dogruluk et al. 2015). Due to the increased site variation and decreased frequency of individual non-canonical missense mutations, studying their effects in cancer is challenging and less is known about their influence on tumor progression. In response to this challenge, high-throughput protocols that combine gene variant cloning with survival assays have been designed to evaluate the tumorigenic potential of distinct non-canonical *PIK3CA* mutations.

Researchers have utilized the Catalogue of Somatic Mutations in Cancer (COSMIC) to identify non-canonical *PIK3CA* mutations in breast cancer (Dogruluk et al. 2015). These mutations were then analyzed with multiple modeling algorithms to identify a subset of non-canonical missense mutations predicted to be drivers of cancer progression. Next, the oncogenic potential of this subset was evaluated by engineering exogenous expression of the *PIK3CA* mutants in IL-3-dependent Ba/F3 cells and insulin/EGF-dependent MCF10A cell lines. The ability of *PIK3CA* non-canonical mutants to sustain survival in IL-3-deprived Ba/F3 cells and insulin/EGF-deprived MCF10A cells was then analyzed. Results of these assays demonstrated that many of the non-canonical mutations algorithmically predicted to induce growth and proliferation did indeed confer survival and proliferation advantages between 2.1 and 36-fold compared to negative controls in Ba/F3 cells. For comparison, the canonical mutations showed a >40-fold increase. Similar findings were obtained in insulin/EGF-deprived MCF10A breast epithelial cells engineered for exogenous expression of different *PIK3CA* mutations (Dogruluk et al. 2015). Collectively, these findings have provided compelling evidence that some, albeit not all, non-canonical *PIK3CA* mutations observed in breast cancer tumors are capable of promoting oncogenic phenotypes.

Others have investigated the functional and oncogenic properties of non-canonical *PIK3CA* mutations found in head and neck squamous cell carcinoma (HNSCC) tumors (Jin et al. 2021). Data from The Cancer Genome Atlas (TCGA) was analyzed. Of the 97 HNSCC tumor samples with *PIK3CA* mutations in TCGA, it was concluded that 63% harbored *PIK3CA* mutations in canonical sites. The remaining 37% of samples contained non-canonical *PIK3CA* mutations at 32 discrete sites. These 32 identified non-canonical *PIK3CA* mutations were then studied to ascertain their role in promoting oncogenesis. First, the mutants were exogenously expressed in a HNSCC cell line and then functional studies using serum deprivation assays were carried out. These assays found that 22/32 of these mutant p110α proteins promoted enhanced cell growth in low-serum media, relative to the wild-type p110α. Furthermore, all 22 of these mutants promoted increased cell motility and 21 of the mutants promoted increased colony formation, in comparison to the wild-type protein. Thus, close correlation of results was found in 3 different assays. Moreover, highly similar functional findings, although not identical, were obtained when the HNSCC-associated mutants were expressed and analyzed in Ba/F3, MCF10A, and HeLa cells, indicating cell line lineage independence of function (Jin et al. 2021). These studies demonstrate that a majority of non-canonical mutations likely produce hyperactived PI3K oncogenic signaling, contributing to cancer development.

5. Mechanisms of p110α activation by canonical *PIK3CA* mutations

It has long been recognized that elevated PI3K/AKT/mTOR pathway signaling is commonly observed in cancer, and while many cancer-associated genetic alterations of this pathway have been described, canonical and non-canonical activating mutations in *PIK3CA* are among the most common. Studies have elucidated distinct mechanisms by which the different canonical mutations of *PIK3CA* lead to activation of this pathway. Mutations occurring at H1047 in the kinase domain enhance the affinity of p110α for the plasma membrane (Burke and Williams 2015). By contrast, canonical mutations at E542 and E545 decrease the affinity of the p85 negative regulatory protein for p110α (Burke et al. 2012, Miled et al. 2007). This results in release of p85 and activation of the p110α enzyme. The mechanisms whereby non-canonical activating mutations become activated are largely unexplored.

6. Clinical Trials of PI3K Inhibitors

Given the role that hyperactivation of the PI3K/AKT/mTOR pathway is known to play in cancer, components of this pathway, including wild-type and mutant p110α, represent potentially attractive therapeutic targets. Currently there are three classes of PI3K inhibitors with activity against the p110α, isoform; dual PI3K/mTOR inhibitors, pan-PI3K inhibitors, and isoform-specific inhibitors (Hanker, Kaklamani, and Arteaga 2019). Several recent reviews have highlighted the sites of action of drugs from each of these classes (Stanciu et al. 2022, Zhu et al. 2022, Wu et al. 2022, Jhanwar-Uniyal et al. 2022, Meng et al. 2021, Mishra et al. 2021, McCubrey et al. 2015). Importantly, drugs from each of these classes have been studied in clinical trials. However, trial results have thus far been mixed, as is described below.

The dual PI3K/mTOR inhibitor dactolisib has been studied in a number of clinical trials for a variety of cancers. However, despite preclinical results indicating high efficacy in multiple tumor models (Shi et al. 2018), clinical trials of dactolisib have been disappointing both in terms of safety and efficacy. In a Phase Ib study designed to investigate safe dosage in patients with advanced prostate cancer, 5 out of 18 patients developed dose-limiting toxicities at the initial dose of 200 mg (Massard et al. 2017). The poor safety profile of dactolisib necessitated this arm of the trial be prematurely discontinued and currently this compound is no longer being investigated as an oncological therapeutic. Several other dual PI3K/mTOR inhibitors have also been explored in clinical trials. PF-04691502 and gedatolisib were evaluated in a Phase 2 clinical trial in patients with recurrent endometrial cancer (Del Campo et al. 2016). Unfortunately, the PF-04691502 arm of this trial had to be terminated due to high rates of side effects experienced by patients, including nausea (53%), skin toxicity (50%), decreased appetite (40%), and diarrhea (38%). Ultimately, 100% of the PF-04691502 cohort had to discontinue the study prematurely as did 93% of the patients in the gedatolisib group. In terms of treatment efficacy, the overall all response rate (ORR) in the gedatolisib group was 16%. Per study authors, the ORR was comparable to that achieved with other mechanistically similar agents in similar patient cohorts. Collectively, these results highlight that, thus far, dual PI3K/mTOR inhibitors have demonstrated poor

tolerance and limited efficacy. However, multiple studies are currently underway to examine the potential efficacy of PI3K/mTOR inhibitors in a number of advanced cancers.

Next, we shall discuss pan-class PI3K inhibitors, which includes compounds such as buparlisib, copanlisib, and duvelisib. These compounds have been investigated in clinical trials of various stages. A Phase 2 clinical trial of buparlisib as a treatment for metastatic triple-negative breast cancer demonstrated only a small increase in stable disease time in 12% of patients (Garrido-Castro et al. 2020). However, it is worth noting that this study did not consider *PIK3CA* mutations as an inclusion criteria and only 6 out of 50 patients were confirmed to have genetic alterations in the PI3K/AKT/mTOR pathway. On the other hand, a Phase 3 randomized and placebo-controlled study in a patient cohort with HER2-negative refractory breast cancer, demonstrated that the median PFS was 6.9 months in the buparlisib plus fulvestrant group versus 5.0 months in patients taking placebo plus fulvestrant (Baselga et al. 2017). Importantly, this study also screened patients for PI3K mutations via both circulating tumor DNA (ctDNA) and Sanger sequencing of tumor tissue. Patients with ctDNA harboring PI3K mutations but normal *PIK3CA* in tumor tissue had a median PFS of 4.7 months in the buparlisib group vs 1.5 months in the placebo group. Interestingly, there was no statistically significant PFS benefit in patients with known PI3K activation in tumor tissue taking buparlisib versus placebo, potentially due to time delays between tumor tissue harvesting and treatment since these delays may have resulted in the tumor tissue samples failing to reflect the heterogeneity of cancer present at the time of treatment. Overall, this study has provided evidence for a beneficial effect of adding buparlisib to treatment regimens for some patients with advanced HER2-negative breast cancer. However, there are unresolved questions regarding optimal biomarker screening and the predictive utility of ctDNA versus tumor DNA sequencing. Additionally, the toxicity profile of buparlisib was significant, with 39% of the experimental group discontinuing treatment versus 5% of the placebo group. The high rates of toxicity have resulted in the cessation of clinical investigation of the buparlisib/fulvestrant combination in lieu of other, more selective PI3K inhibitors (Baselga et al. 2017). Other comparatively less studied but promising pan-PI3K inhibitors are also under active evaluation. In one notable Phase 2 study, copanlisib was shown to generate an overall response rate of 43.8% in a cohort of indolent lymphoma and 27.1% in aggressive lymphoma, respectively (Dreyling, Santoro, et al. 2017, Dreyling, Morschhauser, et al. 2017). This was a small, non-controlled study of 60 patients total. However, these results highlight the need for further evaluation of different pan-PI3K inhibitors.

Finally, we discuss the selective PI3K inhibitors. The first-in-class and only currently approved selective PI3Kα inhibitor, alpelisib, has been evaluated in a first-in-human Phase 1a clinical trial designed to study optimal dosage (Juric et al. 2018). Alpelisib was shown to have a improved safety profile compared to the non-selective PI3K inhibitors discussed previously with only 13.2% having to discontinue the study due to dose escalation-related toxicity. Additionally, larger clinical trials have begun to gauge the efficacy of alpelisib in patients whose tumors harbor *PIK3CA* mutations. Alpelisib has been evaluated in a Phase 3 clinical trial as an adjuvant treatment for *PIK3CA*-mutated breast cancer (Andre et al. 2019). Trial results showed that in patients with *PIK3CA*-mutated breast cancer, progression-free survival increased significantly from 5.7 months in the control group treated with fulvestrant

and placebo to 11.0 months in the group treated with fulvestrant and alpelisib. These results underscore the importance of biomarker-based patient selection for treatment with PI3K inhibitors. It is also worth noting that in this study, alpelisib was associated with significant side effects including hyperglycemia and diarrhea. Early withdrawal from the study was 25% in the experimental cohort compared to 4.2% in the control group.

In summary, the results of clinical trials incorporating various classes of PI3K inhibitors suggest that while this class of medications may have a promising future in cancer therapy, it is important to identify biomarkers such as *PIK3CA* mutational status that may be predictive of treatment response. Additionally, the toxicities of currently available inhibitors are a significant concern and have proved prohibitive in some clinical trials. It appears likely that more selective PI3K inhibitors such as alpelisib may have a somewhat better safety profile, but more work is needed to definitively establish safety and toxicity risks.

As Table 4 shows, a number of clinical trials are currently underway to further evaluate the safety and efficacy of PI3K inhibitors in a wide variety of cancer types. It is hoped that these studies will provide invaluable data on toxicities, optimal treatment regimens, while identifying and validating biomarkers predictive of positive patient response.

7. Conclusions and perspectives

Considerable evidence indicates that canonical *PIK3CA* mutations play an important role in driving oncogenesis in multiple types of cancer. It is conceivable that tumor cells may become dependent on canonical *PIK3CA* mutations for their enhanced proliferation, survival, and drug resistance properties. This suggests that molecular targeting of canonical p110α mutant proteins represents a promising treatment strategy. Indeed, preclinical and clinical evidence indicates that targeting canonical p110α mutants provides therapeutic benefit. Unfortunately, currently available inhibitors of the PI3K enzyme are associated with significant adverse toxicities, underscoring the need to develop new inhibitors with reduced side effects. An alternative strategy may be to target the COX-2/PGE2 pathway, using well-tolerated agents like NSAIDs. Since aberrant production of PGE2 by *PIK3CA*-mutant tumors likely results in an undesirable negative impact on anti-tumor immunity, targeting COX-2 enzyme, in particular, may be valuable for enhancing immune elimination of tumor cells. Additionally, it is clear that a broad variety of non-canonical *PIK3CA* mutants occur in human tumors and the corresponding non-canonical p110α proteins may also represent valuable anti-cancer targets or will serve as viable predictive biomarkers of response to PI3K or COX-2/PGE2 targeting agents. While a few studies have begun to assess the potential oncogenic functions of non-canonical mutants, these studies need to be extended to other malignancies and other mutants. A comprehensive understanding of the functional properties of *PIK3CA* mutants (canonical and non-canonical) will lead to better prognostication and therapeutic strategies for the large number of patients whose tumors harbor *PIK3CA* genetic alterations.

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Data availability

No data was used for the research described in the article.

Abbreviations:

PI3Kα	phosphoinositide 3-kinase alpha
PTEN	phosphatase and tensin homolog deleted on chromosome ten
TCGA	The Cancer Genome Atlas
COX-2	cyclooxygenase-2
PGE2	prostaglandin E2
NSAID	non-steroidal anti-inflammatory drug
COSMIC	Catalogue of Somatic Mutations in Cancer
IL-3	interleukin-3
EGF	epidermal growth factor
HNSCC	head and neck squamous cell carcinoma
ORR	overall response rate
ctDNA	circulating tumor DNA

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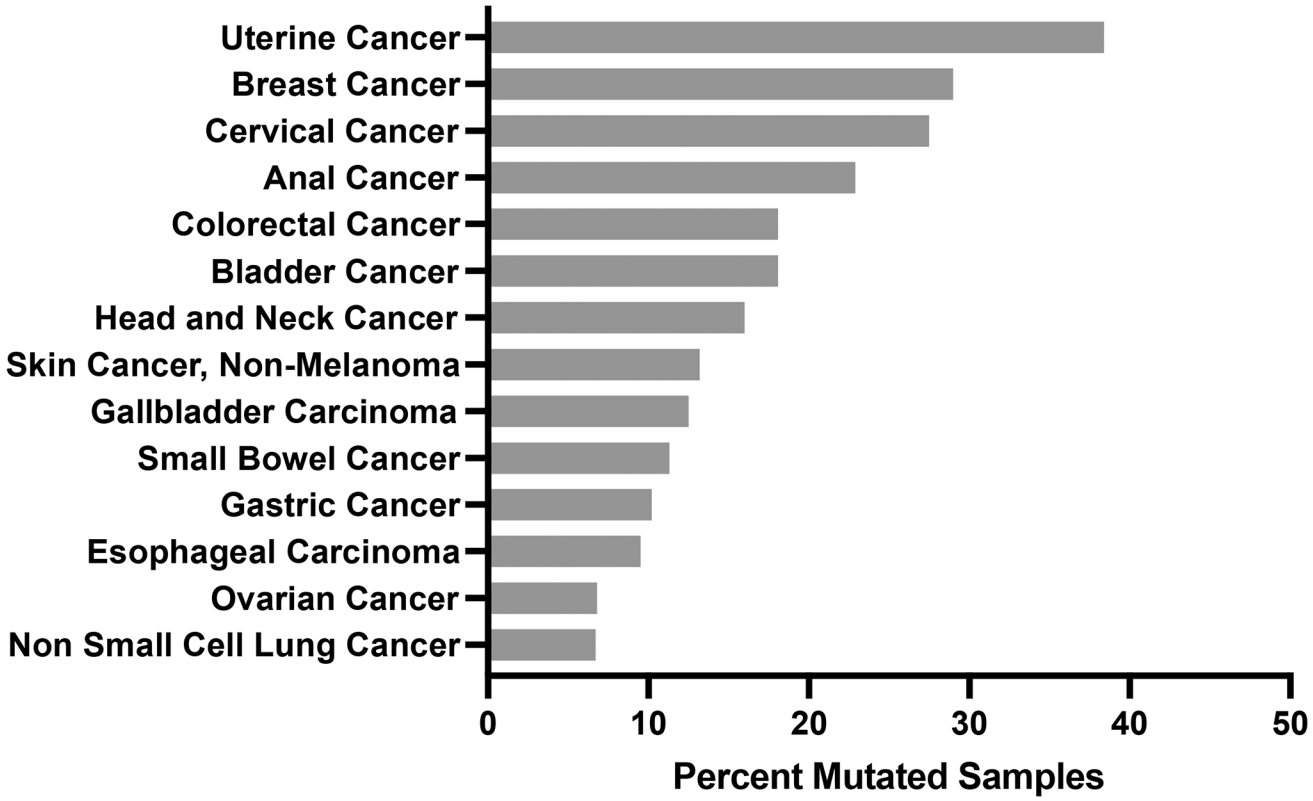

Fig. 1.
PIK3CA mutational frequency in different cancers.

Table 1.

Cancers where *PIK3CA* is Altered in Greater Than 10% of Patient Tumors

Cancer	Altered	Breakdown of Alterations				
		Amplification	Mutation	Homozygous Deletion	Structural Variation	Multiple Alterations
Uterine Cancer	39.4%	0.4%	38.4%	0.0%	0.0%	0.5%
Anal Cancer	35.0%	7.1%	22.9%	0.0%	0.0%	5.0%
Cervical Cancer	31.4%	2.9%	27.5%	0.0%	0.0%	1.0%
Breast Cancer	30.3%	0.7%	29.0%	0.0%	0.0%	0.6%
Head and Neck Cancer	21.7%	4.2%	16.0%	0.0%	0.0%	1.5%
Esophageal Carcinoma	19.0%	8.0%	9.5%	0.0%	0.0%	1.5%
Bladder Cancer	18.8%	0.3%	18.1%	0.1%	0.0%	0.1%
Colorectal Cancer	18.3%	0.1%	18.1%	0.0%	0.0%	0.0%
Skin Cancer, Non-Melanoma	13.2%	0.0%	13.2%	0.0%	0.0%	0.0%
Gallbladder Carcinoma	12.9%	0.4%	12.5%	0.0%	0.0%	0.0%
Non-Small Cell Lung Cancer	11.8%	4.6%	6.7%	0.0%	0.0%	0.5%
Small Bowel Cancer	11.3%	0.0%	11.3%	0.0%	0.0%	0.0%
Ovarian Cancer	10.9%	4.0%	6.8%	0.0%	0.1%	0.1%
Gastric Cancer	10.3%	0.0%	10.2%	0.0%	0.0%	0.1%

Table 2.

Distribution of Canonical and Non-Canonical Mutations in Different Cancers

Cancer	Canonical	Non-Canonical
Cervical Cancer	80.0%	20.0%
Anal Cancer	71.4%	28.6%
Head and Neck Cancer	69.5%	30.5%
Breast Cancer	69.4%	30.6%
Esophageal Carcinoma	67.1%	32.9%
Small Bowel Cancer	64.7%	35.3%
Bladder Cancer	63.8%	36.2%
Gallbladder Carcinoma	58.8%	41.2%
Gastric Cancer	56.7%	43.3%
Non Small Cell Lung Cancer	52.8%	47.2%
Colorectal Cancer	51.9%	48.1%
Ovarian Cancer	49.1%	50.9%
Skin Cancer, Non-Melanoma	30.6%	69.4%
Uterine Cancer	27.6%	72.4%

Table 3.

Distribution of Canonical Mutations in Cancers

Cancer	E542 (K/A/G/Q/V)	E545 (K/G/Q/D/A/V) (E545_Q546delinsDH) (E545_Q546delinsDK)	H1047 (R/L/Y/Q/C) (H1047_H1048delinsRR)
Cervical Cancer	26.9%	71.2%	1.9%
Anal Cancer	28.0%	68.0%	4.0%
Head and Neck Cancer	23.2%	63.4%	13.4%
Breast Cancer	16.0%	29.1%	55.0%
Esophageal Carcinoma	12.2%	63.3%	24.5%
Small Bowel Cancer	9.1%	63.6%	27.3%
Bladder Cancer	34.0%	53.3%	12.7%
Gallbladder Carcinoma	35.0%	55.0%	10.0%
Gastric Cancer	15.3%	54.2%	30.5%
Non Small Cell Lung Cancer	19.0%	48.8%	32.1%
Colorectal Cancer	26.7%	41.7%	31.5%
Ovarian Cancer	20.0%	38.2%	41.8%
Skin Cancer, Non-Melanoma	36.4%	54.5%	9.1%
Uterine Cancer	20.6%	31.5%	48.0%

Table 4.

Current Clinical Trials with PI3K Inhibitor Drugs

NCT Number	Title	Status	Study Results
NCT02367040	Copanlisib and Rituximab in Relapsed Indolent B-cell Non-Hodgkin's Lymphoma (iNHL)	Active, not recruiting	Has Results
NCT02437318	Study Assessing the Efficacy and Safety of Alpelisib Plus Fulvestrant in Men and Postmenopausal Women With Advanced Breast Cancer Which Progressed on or After Aromatase Inhibitor Treatment.	Active, not recruiting	Has Results
NCT02612311	Ublituximab + TGR-1202 Compared to Obinutuzumab + Chlorambucil in Patients With Untreated and Previously Treated Chronic Lymphocytic Leukemia	Active, not recruiting	No Results Available
NCT02626455	Study of Copanlisib in Combination With Standard Immunochemotherapy in Relapsed Indolent Non-Hodgkin's Lymphoma (iNHL)	Active, not recruiting	No Results Available
NCT03439046	Study of the Molecular Features of Postmenopausal Women With HR+ HER2-negative aBC on First-line Treatment With Ribociclib and Letrozole and, in Patients With a PIK3CA Mutation, on Second-line Treatment With Alpelisib Plus Fulvestrant	Active, not recruiting	No Results Available
NCT03801525	Study to Assess the Efficacy and Safety of Ublituximab in Combination With Umbralisib and Venetoclax Compared to Ublituximab in Combination With Umbralisib in Subjects With CLL (ULTRA-V)	Active, not recruiting	No Results Available
NCT01539512	A Randomized, Double-Blind, Placebo-Controlled Study of Idelalisib in Combination With Rituximab for Previously Treated Chronic Lymphocytic Leukemia (CLL)	Completed	Has Results
NCT01569295	Study Evaluating the Efficacy and Safety of Idelalisib in Combination With Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia (CLL) (Tugela)	Completed	Has Results
NCT01572727	A Study of the Experimental Drug BKM120 With Paclitaxel in Patients With HER2 Negative, Locally Advanced or Metastatic Breast Cancer, With or Without PI3K Activation	Completed	Has Results
NCT01610284	Phase III Study of BKM120/Placebo With Fulvestrant in Postmenopausal Patients With Hormone Receptor Positive HER2-negative Locally Advanced or Metastatic Breast Cancer Refractory to Aromatase Inhibitor	Completed	Has Results
NCT02004522	A Phase 3 Study of Duvelisib Versus Ofatumumab in Patients With Relapsed or Refractory CLL/SLL (DUO)	Completed	Has Results
NCT02049515	A Phase 3 Extension Study of Duvelisib and Ofatumumab in Patients With CLL/SLL Previously Enrolled in Study IPI-145–07	Completed	No Results Available
NCT02435173	Study of Efficacy of CDZ173 in Patients With APDS/PASLI	Completed	Has Results
NCT04191499	A Study Evaluating the Efficacy and Safety of Inavolisib + Palbociclib + Fulvestrant vs Placebo + Palbociclib + Fulvestrant in Patients With PIK3CA-Mutant, Hormone Receptor-Positive, Her2-Negative, Locally Advanced or Metastatic Breast Cancer	Recruiting	No Results Available
NCT04208178	Study of Alpelisib (BYL719) in Combination With Trastuzumab and Pertuzumab as Maintenance Therapy in Patients With HER2-positive Advanced Breast Cancer With a PIK3CA Mutation	Recruiting	No Results Available
NCT04251533	Study Assessing the Efficacy and Safety of Alpelisib + Nab-paclitaxel in Subjects With Advanced TNBC Who Carry Either a PIK3CA Mutation or Have PTEN Loss	Recruiting	No Results Available
NCT05038735	Study to Assess the Efficacy and Safety of Alpelisib Plus Fulvestrant in Participants With HR-postitive (HR+), HER2-negative, Advanced Breast Cancer After Treatment With a CDK4/6 Inhibitor and an Aromatase Inhibitor.	Recruiting	No Results Available
NCT01539291	Extension Study of Idelalisib in Participants With Chronic Lymphocytic Leukemia (CLL) Who Participated in GS-US-312–0116 (NCT01539512)	Terminated	Has Results

NCT Number	Title	Status	Study Results
NCT01633060	A Phase III Study of BKM120 With Fulvestrant in Patients With HR+,HER2-, AI Treated, Locally Advanced or Metastatic Breast Cancer Who Progressed on or After mTORi	Terminated	Has Results
NCT01732926	Efficacy and Safety of Idelalisib (GS-1101) in Combination With Bendamustine and Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas	Terminated	Has Results
NCT02204982	Study of Duvelisib in Combination With Rituximab vs Rituximab in Subjects With Previously Treated Follicular Lymphoma	Terminated	Has Results
NCT02340221	A Study of Taselisib + Fulvestrant Versus Placebo + Fulvestrant in Participants With Advanced or Metastatic Breast Cancer Who Have Disease Recurrence or Progression During or After Aromatase Inhibitor Therapy	Terminated	Has Results
NCT02576275	A Study of Duvelisib in Combination With Rituximab and Bendamustine vs Placebo in Combination With Rituximab and Bendamustine in Subjects With Previously-Treated Indolent Non-Hodgkin Lymphoma (BRAVURA)	Withdrawn	No Results Available