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A Long Way to Go: A Scenario for Clinical Trials of PI3K Inhibitors in Treating Cancer

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Abstract

Background: Alterations in PI3K function are directly related to cancer, making PI3K inhibitors suitable options for anticancer therapies. Information on therapy using different types of PI3K inhibitors is available in literature, providing indications of trends in developing new therapies. Although some studies on PI3K inhibitors for cancer treatment provide clinical evidence, they do not allow a careful search for potential PI3K inhibitors conducted by development indicators. Here, we performed a foresight study of clinical trials involving PI3K inhibitors from the past 11 years using indicators of clinical evolution to identify technological trends and provide data for supporting recommendations for new study designs.

Methods: A comprehensive foresight study was designed based on documents from clinical trials on PI3K inhibitors to perform a systematic and comparative analysis, in order to identify technological trends on new cancer therapies.

Results: Our results demonstrate that total number of clinical trials has decreased over the years and, currently, there is a clear prevalence of studies using isoform-specific inhibitors in combined interventions. Clinical trials in Phases I and II were the most frequently found in the database, whereas Phase III trials correspond to 7% of studies. The measurement of clinical trials progression using indicators (drugs in Phase III profile, top-10 drugs, and top-10 combined drugs) demonstrated that the 3 new medicines BKM120, IBI-376, and PF-05212384 have a high potential to provide more efficient cancer treatment in combined interventions. These data also include the groups of targets for each drug, providing a useful and reliable source for design new combinations to overcome the resistance and the poor tolerability observed in some PI3K therapies.

Conclusions: The establishment of development indicators based on clinical trials for cancer treatment was useful to highlight the clinical investment in 3 new PI3K drugs and the advantages of combine therapy using FDA-approved drugs.

Keywords

foresight, PI3K, cancer, clinical trials, intervention, study phase

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Introduction

Cancer is a group comprising over 100 distinct diseases characterized by several genetic changes relating to the uncontrolled and abnormal growth of cells. These genetic changes often involve the overactivity of some key kinase enzymes that impact several cellular pathways.[1,2] In the last few decades, research on kinase inhibitors has increased since

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these enzymes present opportunities for developing new cancer drugs. Impressive clinical results have been achieved, turning kinases into the second most targeted group in such development.[3]

Phosphatidylinositol 3-kinase (PI3K) is a lipid kinase that converts extracellular stimuli into intracellular signals by generating phosphatidyl-inositol-3,4,5-trisphosphate (PIP3), a key signaling lipid. PI3K regulates processes like cell proliferation, growth, motility, metabolism, and survival. Moreover, it is associated with the tumor environment, as it can promote angiogenesis and inflammation.[3] Therefore, changes in PI3K function directly contribute to cancer development, making PI3K inhibitors viable options for developing anticancer therapies.[4] In mammals, the PI3K family comprises 8 isoforms grouped into 3 classes. Class I includes PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ, which are heterodimeric isoforms consisting of an 85 kDa regulatory subunit (p85) and a 110 kDa catalytic subunit (p110α, p110β, p110γ, or p110δ). Changes in Class I isoforms are commonly observed in various cancers, making this class the most significant for drug discovery.[5] PI3K inhibitors can be classified based on their target selectivity as follows: targeting multiple enzymes, including PI3K and other enzymes like AKT and mTOR (Pan inhibitors), double target: mTOR and p110subunit of PI3k (dual inhibitors), and isoform-specific targeting one or more PI3K isoforms such as p110α, p110β, p110γ, or p110δ (IS inhibitors).[5]

The US Food and Drug Administration (FDA) has only approved 5 PI3k inhibitors that are currently in clinical use: GS-1101 (idelalisib), TGR1202 (umbralisib), BAY80-6946 (copanlisib), IPI-145 (Duvelisib) and BYL719 (alpelisib) (Supplemental Table 1).

The first PI3K inhibitors were developed in the early 1990s: the fungal steroid wortmannin and the synthetic molecule derived from quercetin 2-(4morpholinyl)-8-phenyl-4H-1-benzopyran-4-one (LY294002, a dual drug inhibitor).[4,6] Since then, scientific and technological advances have provided a wealth of information on PI3K inhibitors.[7] This information has been consistently published in different formats, including empirical studies,[8,9] clinical trials,[10,11] company reports,[12] and patents.[13-15]

The clinical trial is the most expensive phase in the drug development process; therefore, only promising drugs reach this stage.[12] Consequently, clinical trial record should also be regarded as relevant information source, as the sponsor must disclose information about the study design and outcomes in public databases. These databases can provide helpful data for prospective analysis of trends in the development of new therapies.[16] Consequently, data and text mining of PI3K clinical trials of previous years using indicators of clinical evolution could provide comprehensive evidence, which would yield recommendations for the design of new studies and policies.

Several studies summarize fundamental discoveries regarding the clinical translation of PI3Kα and PI3Kδ inhibitors.[17] However, studies that use a specific and structured approach, encompassing development indicators covering a long timeframe, can permit careful search and analysis to provide an updated perspective on the development of new cancer drugs. This kind of approach includes retrieving, organizing, and analyzing data to translate them into strategic information to conduct research at the frontier of knowledge and integrate policies and innovation strategies.[16]

Thus, we designed a comprehensive report based on a systematic and comparable analysis using clinical trial records on PI3K inhibitors in the context of cancer, aiming to identify technological trends in this sector.

Methodology

Clinical Trials: Search and Analysis Strategies

Clinical trial records were searched in December 2022 through the ClinicalTrials.gov database (https://www.clinicaltrials.gov/) using the keyword "PI3K" in the "Other Terms" field. This first search (search #1, Supplemental Table 2) was also used to identify any drug classified as a PI3K inhibitor in the records.

A second search (search #2, Supplemental Table 2) was conducted by employing the Boolean operator "OR" and including each identified drug name (search #1, Supplemental Table 2) in the "Other Terms" field. The specified timeframe for analysis was January 01, 2011, to December 31, 2022, as verified in the "First Posted date" field. This duration covers the majority of the clinical investment for the 5 FDA-approved drugs (Supplemental Table 1), demonstrating the most critical period in PI3K drug development.

All clinical trial records obtained from the first and second searches were downloaded to an Excel file. Studies involving cancer condition and treatments with at least 1 PI3K inhibitor related to the scope were further analyzed. Non-interventional studies that did not specify the molecule acting as a PI3K inhibitor or indicate diagnostic approaches were excluded because they do not fit the scope (Supplemental Figure 1). Following the exclusion steps, data mining was performed to collect NCT number, title, first posted, status, intervention, and phase information. To standardize the dataset, duplicated names, abbreviations, misspellings and international variations were normalized, To analyze the status of the studies, we followed the clinical trial.gov glossary to classify the studies using the following terms: 'not-active,' for studies whose status was withdrawn, suspended, terminated, or unknown; 'active,' for studies whose status was not yet recruiting, recruiting, enrolling by invitation; 'completed,' for studies whose status was completed.

Clinical trial dataset was categorized based on the following criteria: (a) identification of the "NCT Number"; (b) year when the clinical trial started (data from the "First Posted" field); (c) status of the study: active, not-active, or completed; (d) trial Phase: I, II or III (from "Phase" field); (e) type of

intervention: monotherapy (MT) or combined therapy (CT) (data from "Intervention" field; (f) drug selectivity in Pan, Dual or IS; (g) PI3K drug name.

Specifically for CT, the clinical trials were further classified based on the drug combined with PI3K. Five types were observed, depending on the target protein or metabolic pathway: intracellular kinase (IK), intracellular enzyme non-kinase (INK), intracellular proteins non-enzyme (IP), membrane proteins (MP), and DNA interference (DNAi).

The dataset evaluated excluded 'non-active' clinical trials for Phase profile, top-10, and combined drug analysis.

After the quantitative and qualitative assessments based on bibliometric parameters were performed, the dataset was processed using Vantage Point software.

Results

Our search resulted in a total of 1.383 clinical trial records. After the exclusion criteria were applied, only 527 clinical trial records contained empirical evidence of PI3K inhibitors tested for cancer treatment (Supplemental Figure 1; Supplemental Table 3). We observed 50 PI3K inhibitors from 3 drug selectivity categories in this final dataset: Pan, IS, and Dual. Since some clinical trials included more than one PI3K arm, it was necessary to count each intervention arm as a different CT, resulting in a dataset of 610 interventions in 527 clinical trials (Supplemental Table 3). This dataset was used to perform temporal and status analysis and investigate CT.

Current Clinical Trials Show a Tendency Towards IS Inhibitors Combinations

The registered clinical trial interventions showed a decrease of over 50% in registered trials, irrespective of their status (63 trials in 2011 and 24 in 2022; Figure 1). However, despite this decrease, the graph shows an oscillation as a function of time, with a prevalence of studies using IS inhibitors and CT. Analysis of the dataset (n = 610) based on the selectivity of PI3K inhibitor to the target resulted in 136 (22.3%) interventions using Pan drugs, 374 (61.3%) using IS drugs, and 100 (16.4%) using Dual drugs (Figure 1; Supplemental Table 4).

Analysis of absolute numbers showed a higher number of clinical trial interventions that employed CT involving Pan (n = 91) and IS (n = 258) PI3K inhibitors. In contrast, monotherapy (MT) studies involving Pan and IS inhibitors (45 and 116, respectively) accounted for less than 50% of the total. However, such CT prevalence was not observed for dual-inhibitor drugs (49 MT studies vs 51 CT studies) (Figure 1; Supplemental Table 4).

To better account for the variation over time shown in Figure 1, the variance of each group was estimated to assess the number variability of clinical studies per year. The results revealed substantial data dispersal. For Pan and Dual treatments used in MT or combined studies, the variance ranged from 6.5 to 17. In contrast, for MT IS studies, the variance was 24.7, whereas, for CT IS studies, the variance was 80.5 (Supplemental Figure 2). The higher variance for IS studies indicates a larger degree of data heterogeneity, especially for IS combined clinical trials in detriment to other selectivity-type drugs. The increased variance in the number of CT IS interventions can be attributed to increases in studies during specific years (2013, 2014, 2015, 2020, and 2021) (Figure 1; Supplemental Figure 2). This indicates a trend to test IS inhibitors using CT interventions.

The predominance of studies using IS inhibitors of PI3K is evident (116 MT and 258 combined CT) supporting the potential of these drugs for cancer therapy (Figure 1; Supplemental Table 4).

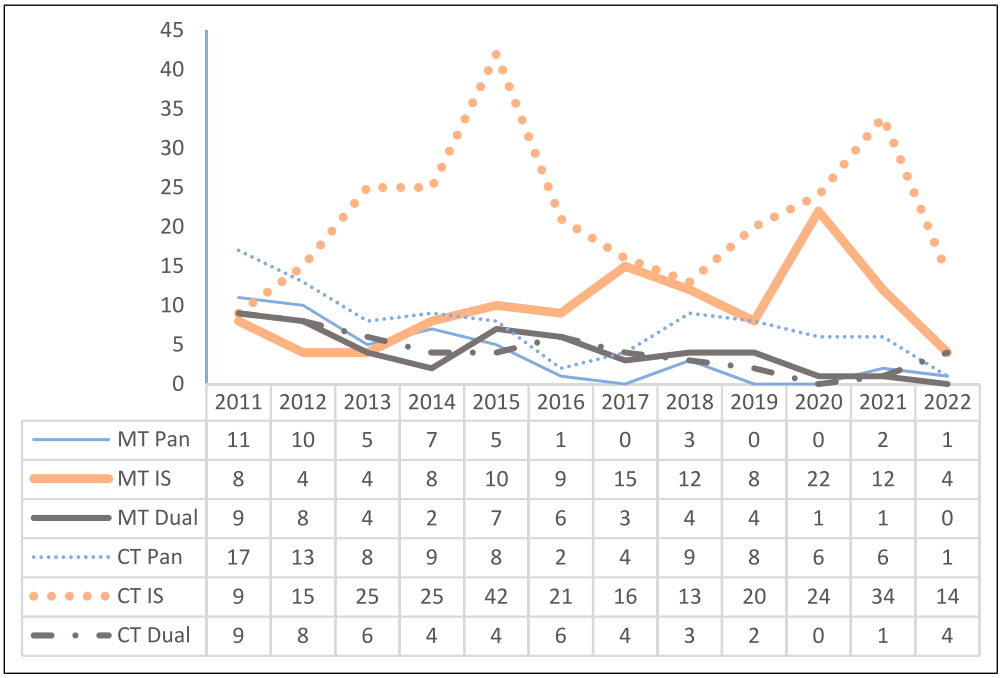
Comparison of the status of each intervention (Figure 2) revealed that 'not-active' interventions of clinical trials occur more frequently in MT (30%) than in combination studies (24%) (Supplemental Table 4). PI3K Dual drugs in MT have the highest percentage of 'non-active' interventions (41%) (Figure 2). Similarly, the number of active studies in CT is greater (40%) than the MT studies (32%) (Supplemental Table 4). PI3K IS drugs in CT represent the group with the most 'active' interventions (47%) (Figure 2). This result shows a higher level of clinical activity for combined studies.

Phase I and II Clinical Trials are Prevalent in the Dataset

To identify whether there are any prominent profiles among the successful therapies involving PI3K inhibitors in our dataset, we analyzed the phases of 385 active or completed clinical trials ('not-active' studies were excluded). Notably, 10 clinical trials used more than one type of PI3K inhibitor (Pan, Dual, or IS); in this case, we considered each selectivity inhibitor type as a distinct clinical trial (Supplemental Table 3). Additionally, when two Phases were indicated in a clinical trial, we considered the more advanced Phase in our analysis.

Our findings revealed that Phases I and II studies were the most prevalent, accounting for 45% and 48% of the total, respectively. In contrast, only 7% of clinical trials had reached Phase III (Supplemental Table 4; Figure 3). Of these Phase III trials, 72% (n = 20) used IS drugs, followed by 21% (n = 6) that used Pan drugs, and 7% (n = 2) that used Dual drugs (Supplemental Table 5).

The present results demonstrate that the percentage of clinical trial profiles differs for each inhibitor type (Figure 3). In the case of Pan inhibitors, we observed that 51% of the studies were in Phase I, 43% in Phase II, and 6% were in Phase III. In contrast, for IS inhibitors, 40% of trials were in Phase I, 51% in Phase II, and 9% in Phase III. For Dual inhibitors, 57% were in Phase I, 39% in Phase II, and 4% in Phase III



	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
MT Pan	11	10	5	7	5	1	0	3	0	0	2	1
MT IS	8	4	4	8	10	9	15	12	8	22	12	4
MT Dual	9	8	4	2	7	6	3	4	4	1	1	0
CT Pan	17	13	8	9	8	2	4	9	8	6	6	1
CT IS	9	15	25	25	42	21	16	13	20	24	34	14
CT Dual	9	8	6	4	4	6	4	3	2	0	1	4

Figure 1. PI3k inhibitors: evolution of clinical trial intervention registries by target selectivity and therapeutic study. Note: MT: monotherapy; CT: combined therapy; Pan (target for multiple enzymes: PI3K and other enzymes as AKT and mTOR); Dual (double target: mTOR and p110subunit of PI3k); IS (target for PI3K isoform-specific: one or more p110α, p110β, p110γ, or p110δ).

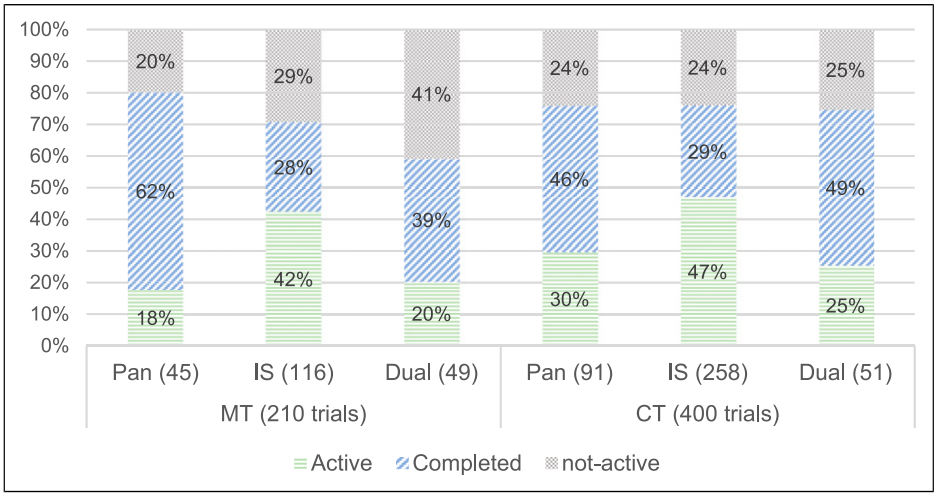


Figure 2. Status of the PI3K inhibitors interventions in clinical trials (December 2022). Note: MT: monotherapy; CT: combined therapy; Pan (target for multiple enzymes: PI3K and other enzymes as AKT and mTOR); Dual (double target: mTOR and p110subunit of PI3k); IS (target for PI3K isoform-specific: one or more p110α, p110β, p110γ, or p110δ).

(Figure 3; Supplemental Table 5). Generally, regardless of the inhibitor type used, most studies did not reach the advanced Phase, mainly from Phase II to III. Analysis of the completed Phase III clinical trial shows 2 MT (NCT02004522 and NCT02049515 records) and 4 CT studies (NCT01539512, NCT01569295, NCT01572727, and NCT01610284 records) (Table 1; Supplemental Table 3), indicating a slight prevalence of CT in advanced clinical trials. IPI-145 (an IS drug) therapy was used in both MT studies, while GS-1101 (an IS drug) and BKM120 (a Pan drug) were the drugs studied in the 4 CT studies (Table 1). BKM120 is the only new drug used in a completed Phase III trial.

In terms of active studies in Phase III, we observed three MT and 19 CT: 4 studies using Pan inhibitors (BAY80-6946 and BKM120), 17 using IS inhibitors (IBI-376, BYL719, GDC 0077, TGR-1202 and GS-1101), and one

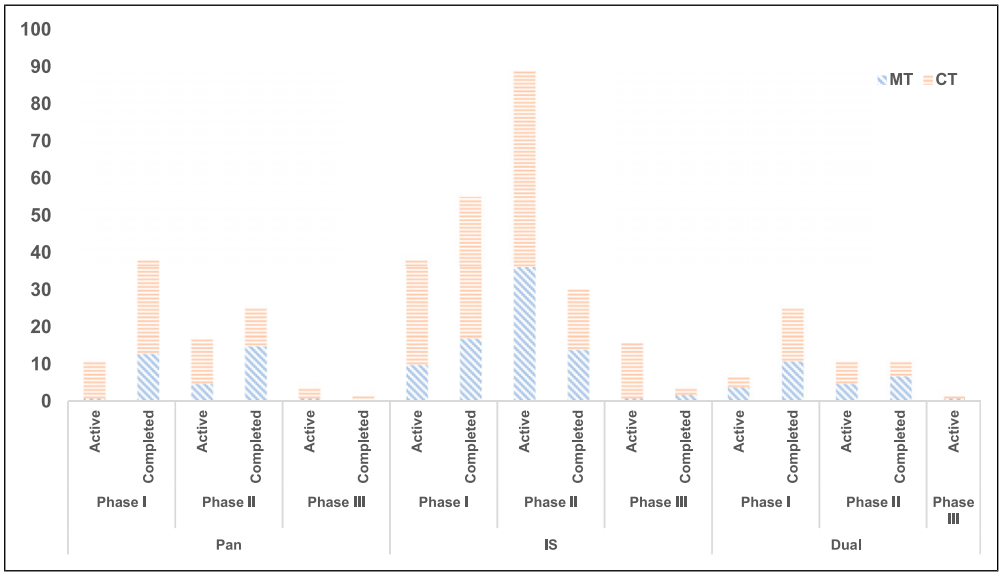


Figure 3. PI3K inhibitors: active and complete clinical studies by phase profile. Note: MT: monotherapy; CT: combined therapy; Pan (target for multiple enzymes: PI3K and other enzymes as AKT and mTOR); Dual (double target: mTOR and p110subunit of PI3k); IS (target for PI3K isoform-specific: one or more p110α, p110β, p110γ, or p110δ).

Table 1. PI3K Drugs on Clinical Trials Phase III.

Phase III	Active	Completed	Pi3k Inhibitor	Brand Name
MT	0	2	IS: IPI-145	Duvelisib[a]
	1	0	IS: IBI-376	Parsaclisib[b]
	1	0	Dual: GDC-0084	Paxalisib[b]
	1	0	Pan: BAY80-6946	Copanlisib[a]
CT	2	0	Pan: BAY80-6946	Copanlisib[a]
	8	0	IS: BYL719	Alpelisib[a]
	1	0	IS: GDC 0077	Inavolisib[b]
	2	0	IS: TGR1202	Umbralisib[a]
	2	2	IS: GS-1101	Idelalisib[a]
	1	2	Pan: BKM120	Buparlisib[b]
	2	0	IS: IBI-376	Parsaclisib[b]
	1	0	Dual: PF-05212384	Gedatolisib[b]

[a]FDA-approved registered drugs.
[b]new drugs; MT: monotherapy; CT: combined therapy; Pan (target for multiple enzymes: PI3K and other enzymes as AKT and mTOR); Dual (double target: mTOR and p110subunit of PI3k); IS (target for PI3K isoform-specific: one or more p110α, p110β, p110γ, or p110δ).

using PF-05212384 as a Dual-inhibitor. Five of the 10 drugs cited are already FDA-approved (Table 1).

Identification of the Top 10 PI3K Inhibitors Based on Advanced Clinical Trials

After identifying the PI3K inhibitors used in the most advanced clinical trials, we searched for the 10 drugs more used in active and completed clinical studies. This aimed to reveal the most promising drugs to reach the market.

Figure 4 shows a sunburst plot display of the top 10 PI3k inhibitors. 57% of the graph area is occupied by 5 IS-type PI3K inhibitors, followed by 32% of Pan-type and 11% of Dual-type inhibitors. These results suggest the potential of IS-type inhibitors as potent cancer treatment drugs, represented by one new (IBI-376) and 4 FDA-approved (BYL719, IPI-145, GS-1101, and TGR-1202 IS) drugs.

Combined Therapy has the Potential for the Development of New Treatments Based on PI3K Inhibitors

Our previous analysis of clinical trial profiles revealed that CT is prevalent in new treatments development using PI3K inhibitors. In line with this, the top 10 drugs selected in our databases are used in CT, including 2 Pan inhibitors, 6 IS inhibitors, and 2 dual inhibitors combined with 5 drugs targeting different protein types: IK, INK, IP, MP, and DNAi (Figure 5).

In our dataset (Supplemental Table 3), most of the combined clinical trials involved BYL719 (alpelisib), an FDA-approved drug, combined with other drugs (55 clinical trials; Figure 5). Five of the top 10 drugs used in CT are already FDA-approved. However, most of these are being investigated in active Phase III trials of CT. The other 5 drugs, BKM120, IBI-376, TAK-117, LY3023414, and PF-05212384, are still not registered, although 3 of them (BKM120, IBI-376, and PF-05212384) have been evaluated in active Phase III trials (Table 1 and Figure 4).

In addition, it is essential to observe the target group of the top-10 PI3K inhibitors combined: 33% were combined with

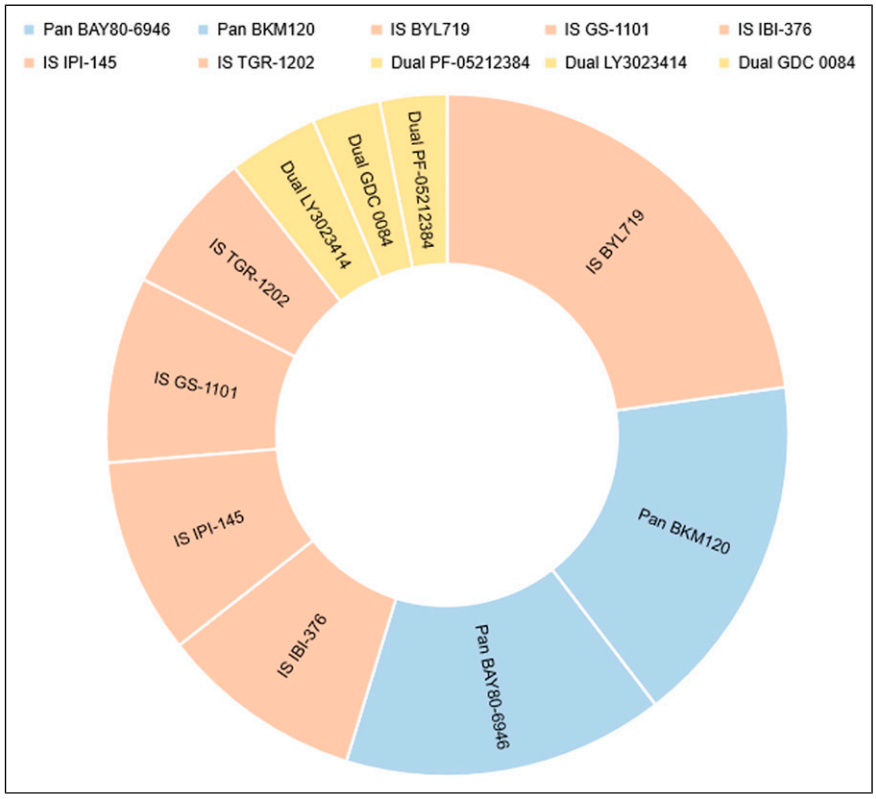


Figure 4. Top 10 PI3k inhibitors. Note: Pan (target for multiple enzymes: PI3K and other enzymes as AKT and mTOR); Dual (double target: mTOR and p110subunit of PI3k); IS (target for PI3K isoform-specific: one or more p110α, p110β, p110γ, or p110δ).

MP drugs, 26% with IP drugs, 18% with IK drugs, 14% with DNAi drugs, and 11% INK drugs (Figure 5; Supplemental Table 6).

Discussion

Although several studies have been conducted on clinical trials involving PI3K drugs, they do not provide a structured analysis that compares development indicators. This study aimed to address this gap through a comparative analysis using clinical trial documents on PI3K inhibitors. The objective was to identify technological trends and gather data that could be used to design new clinical trials.

To achieve this, 3 development indicators were selected to analyze the clinical trials dataset, spanning a period of 11 years and including 50 PI3k drugs. The first indicator focused on the Phase III study, which serves as a proof-of-concept of the efficacy and tolerability of anticancer therapy. The second indicator examined the top 10 drugs, giving insight into the main clinical efforts during the evaluation periods. Lastly, the top 10 drugs used in CT were analyzed. These demonstrated the most effective means of overcoming drug resistance.

Clinical trial databases have emerged as a potential information source to analyze the dynamics of technological development.[16] Previous research based on the data from the clinicalTrials.gov database in 2012 demonstrated that most of the PI3K drugs under development (active clinical trials) were Pan and dual type or AKT inhibitors, while 12% were IS PI3K targeting type.[17] Scientific advances have allowed the differentiation and structural characterization of each PI3K isoform and improved the identification of isoform functions in different tissues, cancer types, and signaling contexts. This knowledge has led to the development of isoform-specific PI3K inhibitors with improved specificity, reduced toxicity, and broader inhibition capacity.[5]

In line with these advances, we found a shift in pattern in the last decade. We observed that interventions using IS drugs correspond to 61.3% of the clinical trials in our dataset (Figure 1), and 4 out of 5 top 10 IS drugs are already registered with the US FDA (Figure 4; Supplemental Table 1). Moreover, our data showed that 71.4% of Phase III trials involve IS drugs (Figure 3; Supplemental Table 5). These results suggest that new IS drugs, or new CT using IS drugs, may reach the market soon. Despite the predominance of studies with IS drugs in our dataset, we also found a crucial clinical activity with Pan and

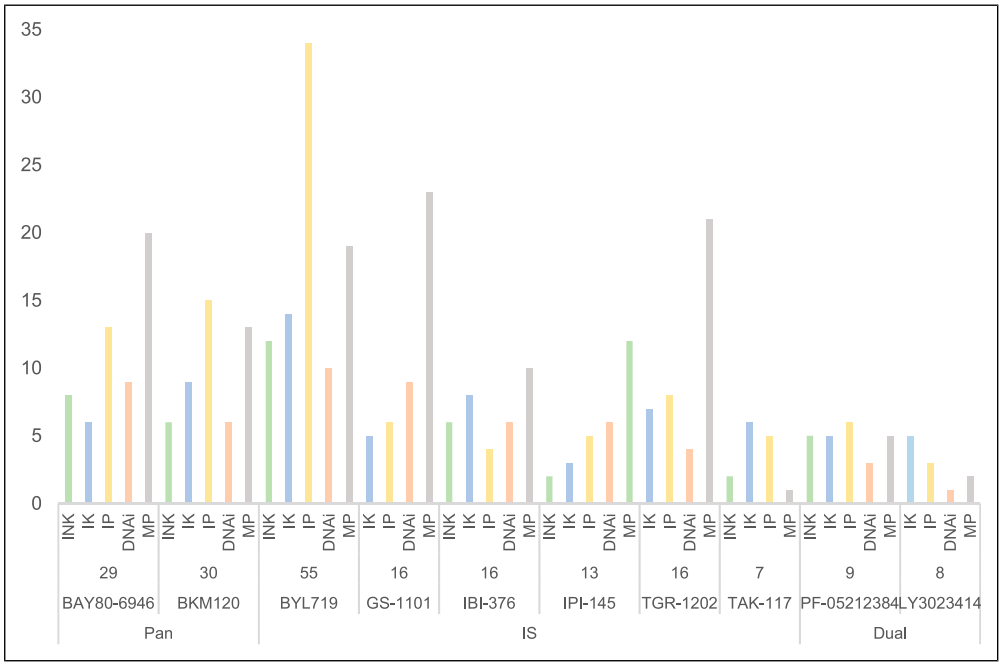


Figure 5. Top 10 drugs in combined therapy: target classification of the combined drug. Note: INK: intracellular non-kinase enzyme; IK: intracellular kinase; IP: intracellular proteins non-enzyme; DNAi: DNA inhibitor; MP: membrane proteins; Pan (target for multiple enzymes: PI3K and other enzymes as AKT and mTOR); Dual (double target: mTOR and p110subunit of PI3k); IS (target for PI3K isoform-specific: one or more p110α, p110β, p110γ, or p110δ).

Dual drugs in active and completed investigations, including some active Phase III trials. Studies involving Pan and Dual selectivity drugs seem to progress to advanced phases less frequently than those involving IS selectivity (Figure 3; Table 1).

The poor tolerability of some compounds, particularly among Pan inhibitors, has limited clinical development.[18] Pan drugs have a potential for broad activity in several tumor types with a range of molecular changes. However, such broad inhibition effects may lead to a potentially higher risk of adverse events,[19] which could limit the use of such agents at therapeutic doses.[17] An example is BKM120 (buparlisib), which during the Phase I study was well tolerated up to the maximum-tolerated dose of 100 mg/day but not more (150 mg/day was considered not safe), causing common treatment-related adverse events, including on-target effects like decreased appetite, rash, and hyperglycemia.[20] Despite those effects, the drug has been evaluated in more advanced phases, as shown in our results.

The top 10 drugs selected using our analysis criteria include one new IS inhibitor (IBI-376), one new Pan-inhibitor (BKM120), and 3 new dual inhibitors (PF- 05212384, GDC 0084, and LY3023414) (Figure 4). IBI-376 (parsaclisib) has been evaluated in patients with myelofibrosis who had an inadequate response to ruxolitinib.[21] IBI-376 has been used in either MT (7 trials) or CT (10 trials) (three in Phase III, 10 in Phase II, and four in Phase I). BKM 120 (buparlisib) has been investigated for breast cancer, with conflicting results.[22-25] The systematic review and meta-analysis by Luo (2019) concluded that therapy with BKM120 had some benefits but caused serious adverse events.[26]

Our research identified Phase III clinical trials using PF-05212384 and GDC 0084 (NCT05501886 and NCT03970447) for treating breast cancer and glioblastoma, respectively (Table 1; Supplemental Table 2). PF-05212384 (gedatolisib) is a potential drug for breast cancer, as changes frequently occur in the PI3K/mTOR pathway with this condition. Clinical trials concluded that the drug can efficiently treat triple-negative breast cancer.[27,28]

LY3023414 (somatolisib) has been studied in Phase II trials for advanced malignant solid neoplasms, lymphomas, and endometrial cancer.[29] Of the top 10 drugs, this was the only one not analyzed in Phase III clinical trials.

Overexpression of genes encoding key components of the PI3K pathway is responsible for alterations in PI3K pathway activation,[30] and this is an important factor for cancer progression and resistance to antineoplastic drugs.[31] Efforts have therefore been made to mitigate the poor drug tolerance, intrinsic and acquired drug resistance, and signaling feedback loop that neutralizes PI3K inhibition.[31,32] These clinical challenges are seen mainly in monotherapy, in which the use of a single inhibitor has limited efficacy.[33] A recent meta-analysis on the effectiveness of monotherapy with PI3K/AKT/mTOR pathway inhibitors demonstrates limited or even no efficacy in advanced or recurrent ovarian cancer patients. The authors reported that adverse events in grade 3 or 4 occurred in

36% of the treated patients and suggested that combination regimens improve tolerability due to use of lower doses of the PI3K inhibitors.[34] Indeed, one of the mechanisms that cause intrinsic resistance to selective PI3K inhibitors is the mutation of proteins on PI3K pathway, limiting the therapy's efficacy.[33] Thus, analysis of this mutations can be used as biomarkers of clinical activities, but, further studies are still necessary to improve knowledge on mutations that can be promising as predictive factors for specific inhibitors.[35] This scenario explains why there is such a large number of interventions involving CT (400) out of the 610 described in our dataset (Figures 1 and 2). The high number of CTs indicates that the drug combination is an efficient method for overcoming the challenges involved in developing drugs that target PI3K.

The top 10 drugs established by our analysis include 5 FDA-approved drugs, and similar to literature, all of them have been used in combination with other therapies, as following: BYL719 (alpelisib) combined with estrogen receptor antagonist (ER)[36,37]; GS-1101 (idelalisib) combined with the anti-CD20 antibody rituximab[38]; TGR-1202 (umbralisib) combined with the anti-CD20 antibody ublituximab.[39,40] Vanhaesebroeck et al.[41] stated that, until 2020, there were no studies approved for combination of IPI-145 (duvelisib) and BAY80-6946 (copanlisib).[42,43] Our analysis used datasets from 2011 to 2022, showing that several CT studies use these 2 drugs: 13 studies use IPI-145 (duvelisib), and 29 studies use BAY80-6946 (copanlisib) (Figure 5). BAY80-6946 (copanlisib) has been used in 2 active Phase III studies (NCT02367040 and NCT02626455) combined with either anti-CD20 antibody rituximab and standard immunochemotherapy (rituximab and bendamustine) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (Table 1; Supplemental Table 2).

PI3K is involved in many biological processes regulating proliferation and cellular survival, and the PI3K-AKT pathway is commonly activated by the loss of a lipid phosphatase (PTEN), which is a tumor suppressor in tumor cells.[44] The PTEN loss occurs in up to 30% of melanomas[45] and promotes resistance to immunotherapy in preclinical models and clinical specimens, because it decreases the infiltration of anti-tumor T cells.[46] The programmed cell death protein 1 (PD-1) and its ligand (PD-L1) are considered immune checkpoints with a critical role in tumor microenvironment, activated by PI3K pathway. Therefore, the suppression of cytotoxic T cells and the induction of the PD-1 pathway constitute factors that favor tumor progression,[47,48] and PI3K inhibitors in combination with other antitumor therapies, such as anti-PD-L1 immunotherapy, can achieve synergistic effects to modulate the suppressive tumor environment.[47] For instance, low-doses of IPI-145, which is an IS inhibitor of PI3K-δ and PI3K-γ isoforms, and also an FDA-approved drug, in combination with anti-PD-L1 enhances the response to immune checkpoint blockage and consequently reduce the immunosuppressive effects in myeloid-derived suppressor cells of granulocytic (MDSCs) and promote the infiltration of $CD8^+$ T cells.[49]

In addition to the combined studies on FDA-approved drugs, we observed that, among the top 10 drugs, some new drugs were used in CT (Figure 5): BKM120 (Pan-inhibitor), IBI-376 and TAK-117 (IS inhibitors), PF-05212384 and LY3023414 (Dual-inhibitors). Three of these were present in both Phase III clinical trials and in the top 10 PI3K drug analyses: BKM120 (buparlisib), IBI-376 (parsaclisib), and PF- 05212384 (gedatolisib).

BKM120 is described in 3 active studies focused on combined therapies: 2 of them (NCT04975958, NCT04338399) have initiated in last 2 years (2020 and 2021) and combine BKM120 with atezolizumab (targeting PD-1) or paclitaxel (targeting microtubule). These combined therapies cover solid tumors. Similar to BKM120, IBI-376 was described in ten recent active studies (2020 – 2022) as an inhibitor with high clinical activity in combinate therapies. Two of them are in phase III, and combine IBI-376 with kinase targeting drugs (NCT04551053, NCT04551066) to treat myelofibrosis condition. Our data also includes a multicenter phase III study in which patients were treated with PF-05212384 and fulvestrant for breast cancer condition (NCT05501886; Supplemental Table 3), providing updated information regarding the advance of this therapy in comparison with evidence published in literature.[50]

Other authors emphasize the importance of targeting PI3K mutants to overcome drug resistance and to improve therapy efficacy, but selectivity and potency of 47 PI3k inhibitors described in clinical trials reports and patent literature have demonstrated how difficult is to develop new drugs due to the high sequence identity between the mutants and the wild-type.[51] Our prospective study also revealed that among the promising new drugs, only one is an IS inhibitor (IBI-376, PI3Kδ selective inhibitor), confirming that the main efforts in clinical trials are not the design of isoform-specific inhibitors yet. In this way, our results reenforce the existing need for studies to shift towards structure-based drug design to overcome resistance and poor tolerability of PI3K inhibitors in order to develop more efficient therapies.

Similar to the literature, our results demonstrate the absence of prevalence for specific target groups (Figure 5) and confirm that combined drug therapies seem to be the best option to overcome the resistance mechanism related to tumor microenvironment (Figure 2). Indeed, there is a diversity of drug combined with PI3K inhibitors in several therapeutical schemes, but our results point out the promising drugs, as well as their targets (Figure 5) and can lead to new and efficient candidates. However, there still is a long way to go in regards to the correlation between PI3K mutations and drug effectiveness and the decision of which drug to use should be guided by biomarkers used in early-phase clinical trials to define the degree of target and pathway inhibition.[52] Furthermore, strategies of PI3K pathway inhibitors integrated with pharmacokinetic and predictive biomarkers are necessary within a personalized therapeutic choice.[33,52] Thus, our findings can help the design of clinical trials because they

indicate not only the best drugs, but also their targets and the most efficient therapeutic strategies to blockage essential pathways in tumor cells. This data is useful to define, for example, new combinations of drugs and new strategies to overcome resistance and poor tolerability of PI3K inhibitors.

Even though papers that present studies on PI3K drugs and their combinations, and discuss the success or failure of the associated therapy are usually presented in an unstructured manner,[33,35] our study presents itself with a structured dataset with development indicators. These indicators cluster the most effective drugs to overcoming drug resistance and tolerability of anticancer therapy based on the following criteria: (i) Phase III studies which reflect the successful results from proof concepts reached in phase I and II; (ii) TOP 10 drugs in general; (iii) TOP 10 drugs used in CT to overcome the cases of drug resistance and their respective targets. With the use of these 3 indicators, it is possible to evaluate the development of clinical trials (completed or active) along the time and consequently give further insights into new combinations of drugs for future clinical trials designs. Several companies are investing in the development of new drugs,[41] and clinical trial records can be considered an essential information source as sponsoring institutions must disclose strategic details about the studies in public databases.[16] For this reason, the comparative analysis from 3 development indicators revealed a higher level of clinical investments for 3 new drugs (BKM 120, IBI-376, and PF- 05212384) and that there is continuous research underway involving all 5 drugs that are already registered for cancer, mainly using new combinations. Our analyzed dataset uses records from 11 years of PI3K clinical trials displaying the target of the combined drug and other relevant information related to the PI3K inhibitor therapy (Supplemental Table 3). This study will undoubtedly encourage future clinical trial prospective analyses as a tool to identify technological trends and improve the clinical trial design in drug development.

Conclusions

This was a foresight study of PI3K inhibitors based on clinical trial records. Data from 610 clinical interventions of PI3K inhibitors were analyzed, using 3 perspectives of development indicators (Phase III studies, top 10 drugs, and top 10 drugs in CT). Our findings were that: (a) efforts have been made to develop isoform-specific drugs in CT to overcome the limitations of MT indications; (b) an important clinical investment has been made into Pan and Dual-inhibitors; (c) there is a focus on 3 new drugs— BKM 120, IBI-376 and PF-05212384—with potential for reaching the market in the near future; (d) clinical efforts have been undertaken in providing new combinations with registered drugs.

Author Contributions

B.A.F.d.S.T. was responsible for the conceptualization, data collection, methodology, analysis, and interpretation of data and writing. I.J.S.S. and F.P.P. were responsible for analysis, discussion, and review. A.R.A. was responsible for the analysis, writing, discussion, and review. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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Data Availability Statement

All data generated or analyzed during this study are included in this published article as supplemental information files.

Supplemental Material

Supplemental material for this article is available online.

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