

PI3K inhibitors as new cancer therapeutics: implications for clinical trial design

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Abstract: The PI3K–AKT–mTOR pathway is frequently activated in cancer. PI3K inhibitors, including the pan-PI3K inhibitor buparlisib (BKM120) and the PI3K α -selective inhibitor alpelisib (BYL719), currently in clinical development by Novartis Oncology, may therefore be effective as anticancer agents. Early clinical studies with PI3K inhibitors have demonstrated preliminary antitumor activity and acceptable safety profiles. However, a number of unanswered questions regarding PI3K inhibition in cancer remain, including: what is the best approach for different tumor types, and which biomarkers will accurately identify the patient populations most likely to benefit from specific PI3K inhibitors? This review summarizes the strategies being employed by Novartis Oncology to help maximize the benefits of clinical studies with buparlisib and alpelisib, including stratification according to PI3K pathway activation status, selective enrollment/target enrichment (where patients with PI3K pathway-activated tumors are specifically recruited), nonselective enrollment with mandatory tissue collection, and enrollment of patients who have progressed on previous targeted agents, such as mTOR inhibitors or endocrine therapy. An overview of Novartis-sponsored and Novartis-supported trials that are utilizing these approaches in a range of cancer types, including breast cancer, head and neck squamous cell carcinoma, non-small cell lung carcinoma, lymphoma, and glioblastoma multiforme, is also described.

Keywords: PI3K–AKT–mTOR pathway, patient selection, biomarkers, PI3K inhibitors, clinical trial design

Introduction

The PI3K–AKT–mTOR pathway is frequently activated in cancer (Figure 1).¹ Mechanisms of PI3K–AKT–mTOR pathway activation include but are not limited to mutations and amplification of genes encoding receptor tyrosine kinases (eg, *HER2* or *EGFR*), *PIK3CA* mutations, *PTEN* mutation/loss, and *KRAS* mutations.¹ As a central node of this pathway, PI3K is an attractive target for cancer therapy.

A number of PI3K inhibitors are under clinical investigation by pharmaceutical companies and academic institutions, including pan-PI3K inhibitors targeting all four isoforms of class I PI3K, as well as isoform-selective inhibitors: these include picitilisib, copanlisib, and taselisib, among others. Idelalisib, a selective PI3K δ inhibitor, is now approved in the USA for various hematologic malignancies, including chronic lymphocytic leukemia, relapsed follicular B-cell non-Hodgkin's lymphoma (NHL), and relapsed small lymphocytic lymphoma, and was the first PI3K inhibitor licensed for the treatment of cancer.

Novartis Oncology has been investigating the PI3K–AKT–mTOR pathway for many years. Indeed, the Novartis mTOR complex 1 inhibitor everolimus is now approved for several indications, demonstrating the potential for PI3K–AKT–mTOR

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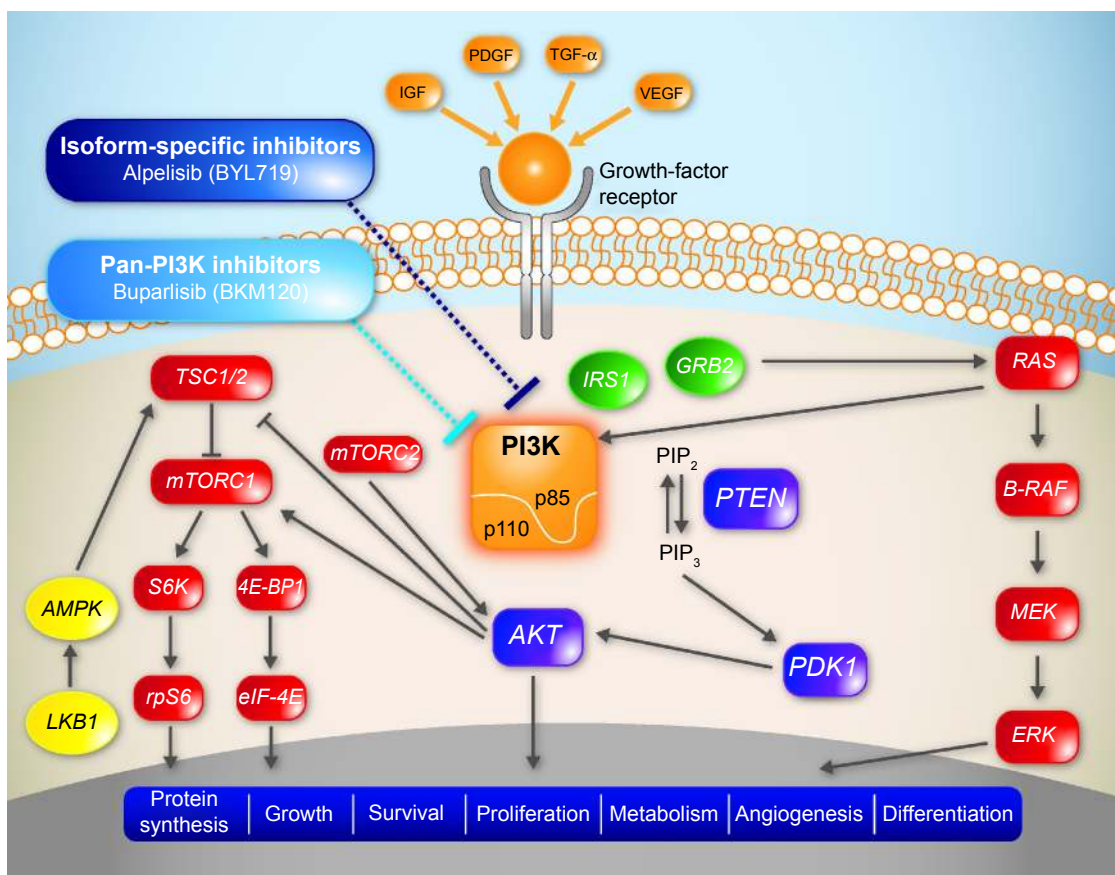


Figure 1 The PI3K–AKT–mTOR pathway and drug targets.

pathway inhibition in cancer. Other Novartis compounds in clinical development include the pan-PI3K inhibitor buparlisib (BKM120) and the PI3K α -selective inhibitor alpelisib (BYL719).¹

Herein, we summarize lessons learned to date and discuss unanswered questions regarding PI3K inhibitor development in cancer. Furthermore, we describe the range of clinical study designs being used by Novartis Oncology to maximize the potential of this promising new class of anticancer treatment.

PI3K pathway inhibition in cancer: lessons learned so far

Buparlisib and alpelisib have demonstrated preliminary activity in preclinical models of solid tumors,^{2,3} providing a rationale for their use in the clinic. In early clinical studies, both buparlisib and alpelisib had favorable tolerability profiles, with the most common adverse events consistent with “on-target” inhibition of PI3K; however, clinical efficacy in single-agent settings has so far been modest.⁴ The PI3K pathway is implicated in resistance to anticancer therapies, including chemotherapy, radiotherapy, hormone therapy, and

targeted agents.^{5,6} PI3K inhibitors may thus restore sensitivity to other treatments when administered as part of combination regimens.⁷ Trials of PI3K inhibitors in combination with different agents are ongoing.

PI3K pathway inhibition in cancer: unanswered questions

Several unanswered questions remain regarding the role of PI3K inhibition in cancer treatment. First, what is the best treatment strategy for specific tumor types, ie, will pan-PI3K or isoform-selective inhibitors be more active in tumors with defined molecular characteristics?⁸ Second, which biomarkers will predict the patient population(s) most likely to benefit from PI3K inhibitor treatment? Associations between PI3K–AKT–mTOR pathway aberrations and clinical response have yielded inconsistent results to date, and further studies are required to identify patients who will derive the greatest benefit. Finally, what are the potential mechanisms of PI3K inhibitor resistance, and how might these be overcome? The complexity of the PI3K–AKT–mTOR pathway, which involves negative feedback loops and extensive cross talk with other signaling

pathways, provides ample opportunities for resistance to develop.⁷ A greater understanding of resistance mechanisms will enable the rational design of combination regimens and sequential treatment algorithms to improve clinical outcomes. Further exploration of all of these areas will help to fully realize the potential of PI3K inhibitors in cancer treatment.

Approaches for PI3K inhibitors in clinical development

Buparlisib and alpelisib are currently in Phase III and Phase II clinical development, respectively. Throughout the development process, different approaches to clinical trial design have been utilized to help address the aforementioned questions. Figure 2 summarizes the study designs currently in use by Novartis Oncology in the following tumor types.

Breast cancer

PI3K–AKT–mTOR is the most frequently activated signaling pathway in breast cancer,⁹ and has been validated as a therapeutic target in the Phase III BOLERO-2 and BOLERO-3 trials described in this paper.^{10,11} Buparlisib and alpelisib are under investigation in breast cancer, with various strategies applied according to the setting.

Hormone receptor-positive breast cancer

The Phase III trial of everolimus in combination with exemestane in ER-positive, HER2-negative advanced breast cancer (BOLERO-2; NCT00863655) demonstrated the value of PI3K–AKT–mTOR pathway inhibition in HR-positive advanced breast cancer.¹¹ However, retrospective molecular analyses of the BOLERO-2 study have not identified a subpopulation deriving greater clinical benefit.¹² Furthermore, a recent Phase IB study of buparlisib in combination with letrozole (a nonsteroidal aromatase inhibitor) has demonstrated the feasibility of combining a PI3K inhibitor with letrozole in patients with ER-positive, HER2-negative metastatic breast cancer refractory to endocrine therapy.¹³ Of the 46 patients who were evaluable for response, there was one complete response, one partial response, and 25 patients with stable disease. Clinical activity was not shown to correlate with *PIK3CA* mutation status, suggesting that alterations in other pathway components were responsible for PI3K pathway dependence.¹³

In the pivotal Phase III BELLE-2 study of buparlisib and fulvestrant (a selective ER downregulator) in patients with HR-positive, HER2-negative advanced breast cancer that has progressed on/after aromatase inhibitor therapy, patient

selection and stratification were designed to assess buparlisib efficacy in the full population and in the PI3K pathway-activated subpopulation (defined as *PIK3CA* mutation and/or PTEN loss; NCT01610284). This study will assess the predictive value of single PI3K–AKT–mTOR pathway alterations in terms of clinical response to buparlisib. The study has completed enrollment, and data are expected in mid-2015.

Preclinical data have demonstrated that buparlisib in combination with fulvestrant can reverse resistance to mTOR inhibitors and/or fulvestrant (Novartis data on file). Therefore, the Phase III BELLE-3 study of buparlisib and fulvestrant is not using molecular preselection for enrollment, but mandates tissue collection and clinical selection for patients with HR-positive, HER2-negative, aromatase inhibitor-treated, locally advanced or metastatic breast cancer that has progressed on mTOR inhibitor therapy (NCT01633060). Due to associations between mTOR inhibitor resistance and PI3K–AKT–mTOR pathway activation, all patients are expected to have PI3K pathway-activated tumors. As such, tumor specimens will be assessed retrospectively for PI3K pathway activation status.

Preclinical studies have also shown that breast cancer cell lines are sensitive to the PI3K α inhibitor alpelisib in vitro,² and *PIK3CA* mutations and *HER2* amplifications correlate with alpelisib sensitivity.¹⁴ Targeting a single PI3K isoform in patients may allow administration at therapeutic doses without being limited by toxicities associated with inhibiting multiple isoforms. As such, alpelisib is being investigated in several breast cancer studies using targeted enrollment.

The first-in-human Phase I study of single-agent alpelisib in advanced solid tumors with *PIK3CA* alterations, and a subsequent study in combination with fulvestrant in ER-positive metastatic breast cancer (*PIK3CA*-altered and *PIK3CA* wild-type tumors), used patient selection and mandatory tissue collection (NCT01219699). Promising preliminary antitumor activity in *PIK3CA*-altered tumors treated with alpelisib alone or with fulvestrant has been observed.^{15,16} Further analyses will reveal whether patients with *PIK3CA*-altered tumors display greater sensitivity to alpelisib, or whether *PIK3CA*-altered and wild-type tumors are equally sensitive. The combination of alpelisib and fulvestrant is being investigated in a Phase III trial in postmenopausal women, or men, with HR-positive, HER2-negative advanced breast cancer that progressed after aromatase inhibitor treatment (SOLAR-1; NCT02437318). Patients will be screened and stratified based on *PIK3CA* mutation status, and randomized to receive fulvestrant in combination with either alpelisib or placebo.

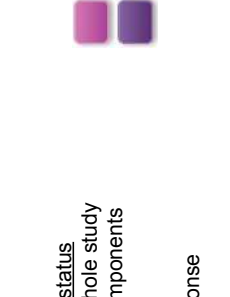
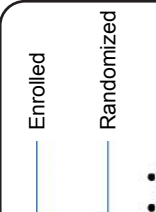

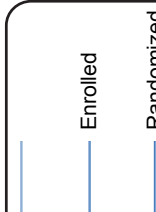
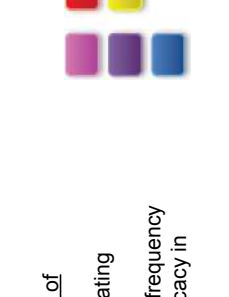
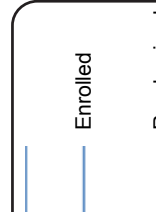
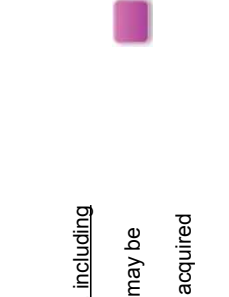
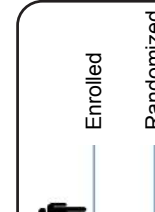
Approach	Details	Indications utilizing approach
	<p>Stratification according to PI3K pathway activation</p> <ul style="list-style-type: none"> Once enrolled, patients are stratified based on PI3K pathway activation status Ensures trials are sufficiently powered to evaluate drug efficacy in the whole study population and in patient subgroups with alterations in PI3K pathway components (particularly <i>PIK3CA</i> and <i>PTEN</i>) A gatekeeping procedure can be used to address multiple hypotheses Enables prospective analysis of predictive biomarkers of treatment response 	
	<p>Selective enrollment/target enrichment</p> <ul style="list-style-type: none"> Only patients with PI3K pathway-activated tumors are enrolled Efficacy of certain PI3K inhibitors may depend on the molecular characteristics of the tumor Selective inhibition of individual p110 isoforms may provide an improved therapeutic window and minimize toxicities compared with pan-PI3K inhibitors 	
	<p>Nonselective enrollment with mandatory tissue collection</p> <ul style="list-style-type: none"> Patients are enrolled on the basis of tumor tissue availability, regardless of PI3K pathway activation status Tumor tissue may be used for retrospective, exploratory analyses correlating biomarkers with clinical outcomes This approach can be useful in early phase trials of cancers with a high frequency of PI3K pathway alterations, or when there is preclinical evidence of efficacy in response to PI3K inhibitor treatment 	
	<p>Selective enrollment of patients resistant to prior targeted therapy</p> <ul style="list-style-type: none"> Patients are enrolled only if disease has progressed on targeted agents, including PI3K-AKT-mTOR inhibitors and endocrine therapy The aim is to target other factors in the PI3K-AKT-mTOR pathway that may be implicated in resistance mechanisms This approach may provide insights into mechanisms of de novo and/or acquired resistance in patients where prior therapy has failed 	

Figure 2 Approaches to overcome challenges in PI3K inhibitor development. **Abbreviations:** NSCLC, non-small-cell lung carcinoma; GBM, glioblastoma multiforme.

Phase I studies are investigating alpelisib in combination with letrozole or exemestane in HR-positive, locally advanced, and/or metastatic breast cancer (NCT01791478, NCT01870505). The nonselective, mandatory tissue collection approach is also being used in these early dose-finding studies evaluating alpelisib in combination with aromatase inhibitors or taxanes. In the study of alpelisib and letrozole, half of patients enrolled must have *PIK3CA*-mutated tumors, and the provision of tumor tissue for correlative studies is mandatory. Exploratory analyses of tumor samples will be performed to determine potential benefit or predictive value in PI3K pathway-activated tumors and to evaluate biomarkers of response.

Phase I studies are also evaluating alpelisib plus paclitaxel in locally advanced or metastatic, chemotherapy-naïve, HER2-negative breast cancer and recurrent, metastatic head and neck squamous cell carcinoma (HNSCC; NCT02051751), as well as the triplet combination of alpelisib, everolimus, and exemestane in advanced breast cancer (NCT02077933). Enrollment for both studies is based on the availability of tumor tissue for biomarker analyses and determination of PI3K pathway activation status.

A neoadjuvant study of letrozole with or without buparlisib or alpelisib in HR-positive, HER2-negative breast cancer is employing targeted enrollment (NCT01923168). Two cohorts are being enrolled: patients with *PIK3CA*-mutated tumors and those with *PIK3CA* wild-type disease. This study will enable the identification of the optimal strategy of PI3K pathway inhibition (ie, pan-PI3K vs PI3K α -selective inhibition) in these molecular subtypes; the results will reveal whether alpelisib has superior efficacy in the *PIK3CA*-mutant population and whether buparlisib is more beneficial in tumors where PI3K is activated by other mechanisms, such as alteration of *PTEN* or *INPP4B*.

HER2-positive breast cancer

The PI3K–AKT–mTOR pathway is frequently activated in HER2-positive breast cancer.⁹ The Phase III trial of combined trastuzumab and paclitaxel treatment with or without everolimus in HER2-positive advanced breast cancer (BOLERO-1; NCT00876395), showed no improvement in progression-free survival (PFS) in the full population; however, the 7.2-month improvement in median PFS observed in HR-negative, HER2-positive patients, though not statistically significant, provided a rationale for further investigation of PI3K inhibitors in this indication.¹⁷ Meanwhile, addition of everolimus to trastuzumab and vinorelbine in women with HER2-positive metastatic breast cancer in the Phase III

BOLERO-3 trial (NCT01007942) achieved an increase in median PFS from 5.78 to 7.00 months.¹⁰ Both BOLERO-1 and BOLERO-3 therefore demonstrate the clinical relevance of PI3K–AKT–mTOR pathway inhibition in HER2-positive disease. A combined analysis of BOLERO-1 and BOLERO-3 revealed a robust positive correlation between PI3K–AKT–mTOR pathway hyperactivity and PFS benefit (with a hazard ratio of 0.61 vs 1.38 for normal pathway activation), supporting further investigation of PI3K inhibitors in this patient population.¹⁸

The CLEOPATRA study of pertuzumab, trastuzumab, and docetaxel in first-line metastatic breast cancer (NCT00567190) established *PIK3CA* mutation as a negative prognostic factor in HER2-positive breast cancer; patients with tumors harboring *PIK3CA* mutations had a significantly worse PFS than those with *PIK3CA* wild-type disease.¹⁹ Selective enrollment/target enrichment is therefore being used in a Phase II study of neoadjuvant buparlisib in combination with trastuzumab and paclitaxel in HER2-positive breast cancer with or without *PIK3CA* mutations (NeoPHOEBE; NCT01816594) to establish whether *PIK3CA* mutation status can predict a benefit from combination therapy with anti-HER2 chemotherapy and a PI3K inhibitor.

A Phase IB/II study has investigated buparlisib and trastuzumab in relapsed HER2-positive breast cancer that has previously failed on trastuzumab, with no selective enrollment/target enrichment approach employed (NCT01132664). In the Phase IB part of the study, buparlisib and trastuzumab were well tolerated, and preliminary signs of clinical activity were observed (two partial responders, seven patients with stable disease, and a disease control rate [DCR] of 75%).²⁰ The Phase II part of the study has been completed, and further analyses will assess the ability of buparlisib and trastuzumab combinations to overcome trastuzumab resistance in patients with *PIK3CA*-activated and wild-type tumors.

Buparlisib in combination with lapatinib is also being studied in a Phase IB/II trial in HER2-positive breast cancer that has failed following trastuzumab therapy, again using the selective enrollment/target enrichment approach (NCT01589861). In the Phase IB part, the relevance of PI3K pathway activation status will be assessed in a retrospective exploratory analysis, and evidence of PI3K pathway activation will be an inclusion criterion for Phase II.

Head and neck squamous cell carcinoma

PI3K–AKT–mTOR pathway alterations are implicated in almost a third of HNSCC, with *PIK3CA* commonly mutated and multiple PI3K–AKT–mTOR pathway

aberrations associated with disease progression.²¹ Dual inhibition of PI3K and mTOR induced tumor regression in an HNSCC xenograft model,²² further supporting PI3K as a target in HNSCC. HNSCC cell lines have also demonstrated sensitivity to alpelisib.²³ Furthermore, alpelisib sensitivity has been shown to be independent of *PIK3CA* mutation status.²³ Alpelisib and cetuximab have demonstrated synergistic activity in HNSCC cell lines independently of molecular status, and also induced tumor regression in a *PIK3CA*-mutant HNSCC xenograft model.²⁴

A number of studies in HNSCC are based on the nonselective enrollment/mandatory tissue collection approach. For example, an ongoing Phase II study is investigating single-agent buparlisib in recurrent or metastatic HNSCC after platinum failure (NCT01527877); the tissue samples collected will form part of an extensive translational research panel.

PIK3CA amplifications and mutations are associated with resistance to cetuximab therapy.²⁵ Therefore, a Phase II study is assessing buparlisib in HNSCC that has progressed on platinum- and cetuximab-based chemotherapy in *PIK3CA*-mutated and *PIK3CA* wild-type cohorts using the patient selection approach (NCT01737450).

PI3K pathway activation is associated with chemotherapy resistance and resistance to targeted therapy.⁵ To investigate this in the clinical setting, a nonselective, mandatory tissue collection approach has been implemented in the following studies conducted in recurrent/metastatic HNSCC resistant to platinum-based therapy, all of which require tissue specimens for biomarker analyses: a Phase II randomized study is exploring buparlisib in combination with paclitaxel (BERIL-1; NCT01852292); a Phase IB/II study is investigating alpelisib in combination with cetuximab (NCT01602315); and a Phase I study of alpelisib with paclitaxel is also ongoing (NCT02051751). Early results from the study of alpelisib in combination with cetuximab have demonstrated promising preliminary antitumor activity in patients with recurrent HNSCC.²⁶

Non-small cell lung carcinoma

PI3K pathway alterations occur in a clinically significant proportion of patients with non-small cell lung carcinoma (NSCLC).²⁷ In a large data set of patients screened for the Phase II BASALT-1 study (NCT01297491), PI3K pathway activation (defined as *PIK3CA* mutation, *PTEN* mutation, and/or *PTEN* loss), was observed in 16% and 11% of squamous and nonsquamous tumors, respectively.²⁷ In this study, patients with relapsed, metastatic NSCLC

received single-agent buparlisib, and were stratified according to squamous or nonsquamous histology. The study adopted the targeted enrollment approach, with PI3K pathway activation required for enrollment. DCR was 47% and 46% in the squamous and nonsquamous groups, respectively, with a median PFS of 2.8 months in both groups.²⁸ Both histological groups met the predefined futility criteria in Stage I, defined as a PFS rate <50% at 12 weeks, and the randomized part of the study was therefore not initiated. The results are in line with previous observations of single-agent PI3K pathway inhibitors demonstrating modest activity in NSCLC.

Preclinical data suggest that PI3K–AKT–mTOR pathway inhibition can sensitize cancer cells to chemotherapy,^{29,30} providing a rationale for buparlisib and chemotherapy combinations. As such, buparlisib is being studied in combination with docetaxel in second-line metastatic squamous NSCLC (NCT01911325), with provision of tumor tissue for biomarker analyses required for enrollment.

Preclinical studies suggest PI3K–AKT–mTOR pathway activation may drive resistance to EGFR tyrosine kinase inhibitors (TKIs).⁸ PI3K inhibitors may act synergistically with EGFR TKIs, and may help overcome EGFR TKI resistance. Preliminary results of a Phase IB study of buparlisib and gefitinib demonstrated potential antitumor activity in EGFR TKI-resistant NSCLC (NCT01570296).³¹ A nonselective, mandatory tissue collection approach will therefore be employed in a Phase II study of buparlisib and erlotinib in advanced NSCLC that was previously sensitive to erlotinib (NCT01487265). Exploratory biomarker analyses will examine interactions between the two pathways.

Lymphoma

PI3K δ is highly expressed in cells of hematopoietic origin, and is predominantly detected in leukocytes.³² Furthermore, lymphomas are associated with constitutive PI3K–AKT–mTOR pathway signaling.³³ The PI3K–AKT–mTOR pathway is therefore an attractive therapeutic target in various hematopoietic cancers. The PI3K δ inhibitor idelalisib, which was approved in the USA for the treatment of chronic lymphocytic leukemia, relapsed follicular B-cell NHL, and relapsed small lymphocytic leukemia, has validated the PI3K–AKT–mTOR pathway as a therapeutic target in B-cell malignancies.

As a pan-PI3K inhibitor, buparlisib targets all four isoforms of class I PI3K, including PI3K δ . Buparlisib has demonstrated activity in preclinical models of diffuse large B-cell lymphoma,³³ several ongoing studies are investigating buparlisib in patients with lymphoma, using a number of

stratification and enrollment approaches. The nonselective tissue collection approach is being used in studies of buparlisib in relapsed or refractory NHL (NCT01719250) and relapsed or refractory diffuse large B-cell lymphoma, mantle cell lymphoma, or follicular lymphoma (NCT01693614). In particular, the DCR was 88% in patients with follicular lymphoma treated with buparlisib monotherapy.³⁴

Glioblastoma multiforme

The PI3K–AKT–mTOR pathway is frequently activated by PTEN loss in glioblastoma multiforme (GBM).³⁵ Buparlisib holds promise for the treatment of GBM, due to its ability to penetrate the blood–brain barrier.³⁶ Indeed, in GBM cell lines and xenograft models, buparlisib demonstrated antitumor activity regardless of *PTEN* or *EGFR* status.³⁷ Furthermore, synergistic activity was observed with buparlisib in combination with temozolomide in *PTEN*-null GBM mouse xenografts.³

Single-agent buparlisib has been investigated in a Phase II trial in patients with recurrent GBM using selective enrollment/target enrichment; inclusion in one of the cohorts was dependent on PI3K pathway activation (defined as *PIK3CA* or *PTEN* mutation, or *PTEN* deletion; NCT01339052). Among the 40 patients who underwent exome sequencing, there were four *PIK3CA* (10%), two *PIK3RI* (5%), and 13 *PTEN* (33%) mutations. The single-agent activity of buparlisib was marginal (median PFS of 1.8 months), and no association between efficacy and pathway activation was observed.³⁸

Mandatory tissue collection is planned for the Phase II parts of the Phase IB/II studies of buparlisib in combination with carboplatin or lomustine (NCT01934361) or with bevacizumab (NCT01349660) in patients with recurrent GBM that has relapsed after standard therapy. The mandatory tissue collection approach is also being used in a Phase I trial of buparlisib with radiation therapy and temozolomide in newly diagnosed GBM (NCT01473901). Archival tumor biopsies will be used for determination of PI3K–AKT–mTOR pathway activation status and correlative testing.

Conclusion

The PI3K–AKT–mTOR pathway is an exciting target for the development of novel anticancer therapies: preclinical results and initial clinical findings have shown great promise. Many clinical trials evaluating PI3K inhibitors in different tumor types have been initiated by pharmaceutical companies and academic institutions, including a wide range of Novartis Oncology trials of buparlisib and alpelisib. Unanswered

questions remain surrounding the use of pan-class and isoform-selective PI3K inhibitors in specific tumor types and/or patient populations. These questions will be addressed by current and future clinical studies with innovative designs tailored toward investigating treatment efficacy in relevant patient subpopulations. Indeed, ongoing trials of buparlisib and alpelisib are exploring potential biomarkers of clinical response, target patient populations, and mechanisms of resistance in a variety of cancer types. In addition, optimization of the platforms used to assess biomarkers (such as PI3K–AKT–mTOR pathway activation) – namely polymerase chain reaction-, Sanger-, and next-generation sequencing-based techniques conducted in archival/fresh tissue biopsies or circulating tumor DNA – will be critical in validating predictive markers of response to PI3K inhibitor therapy. The results of all these studies will help realize the therapeutic potential of PI3K inhibitors as anticancer agents, and will shape the future of cancer care.

Disclosure

All authors are employees of Novartis Pharmaceuticals Corporation or Novartis Pharma AG. Medical editorial assistance was provided by Kate Gaffey, PhD and Alex Coulthard, BSc, and was funded by Novartis Pharmaceuticals Corporation.

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