PI3K inhibitors in medical oncology: Update on an emerging treatment modality

A. Iabkriman, MD[1], J. Collignon, MD[2], F.P. Duhoux, MD, PhD[1,3]

SUMMARY

The phosphatidylinositol-3-kinases (PI3Ks) play a critical role in cellular metabolism and proliferation, as well as in the development of cancer. Several mutations in the genes coding for PI3Ks have been identified in a large proportion of tumours at different rates, depending on the tumour type. Therapies targeting PI3Ks have been developed in the last years and initially used in hematological malignancies. In medical oncology, a number of trials have tried to prove the efficacy of these compounds, but most of them have been confronted with very important toxicities and only a modest benefit in progression-free survival. Recent trials using more selective treatments have shown good efficacy with an acceptable toxicity profile. The aim of this article is to review the current knowledge about PI3K inhibitors, their potential use in medical oncology and their toxicities.

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INTRODUCTION

The phosphatidylinositol-3-kinases (PI3Ks) were discovered in the 1980's. Their critical role in intracellular signal transduction was understood much later. Their activation by various growth factors can activate many other signalling pathways, which regulate multiple aspects of the cell's life: metabolism, apoptosis, growth, survival, transformation and glucose metabolism. One of the most important signalling pathways activated by the PI3Ks is the PI3K/AKT/mTOR pathway, which is implicated in cellular growth.[1]

In the last decades, the role of the PI3Ks in the development of cancer has been extensively studied. The activation of the PI3Ks is regulated by many mechanisms and molecules. The most important of them are the tumour suppressor protein PTEN (Phosphatase and TENsin homolog), which can be inactivated by somatic or germinal mutations, and the regulatory subunit of the PI3Ks, which can be mutated and lead to abnormal PI3K activation.[2]

Mutations of the genes coding for PI3Ks have been discovered in a large proportion of tumours, making that protein an interesting target for future cancer treatments.[3]

PI3K inhibitors were first developed in hematological malignancies. Idelalisib was the first anti-PI3K agent authorised in the US for the treatment of several hematological malignancies.[4]

In medical oncology, a number of trials have tried to prove the efficacy of these compounds, but most of them have been confronted with very important toxicities, which can be explained by the lack of selectivity of the first anti-PI3Ks. Another major issue was the modest benefit on improving the progression-free survival.[5,6] Three recent trials using more selective treatments have shown good efficacy with an acceptable toxicity profile.[7,8] The SOLAR-1 and BYLieve trials proved the efficacy of alpelisib, an α-selective

[1]Department of Medical Oncology, Institut Roi Albert II, Cliniques universitaires Saint-Luc, Brussels, Belgium, [2]Department of Medical Oncology, Institut Arsene Burny, Centre Hospitalier Universitaire de Liège, [3]Institut de Recherche Expérimentale et Clinique, UCLouvain, Brussels, Belgium.

Please send all correspondence to: F.P. Duhoux, MD, PhD, Department of Medical Oncology, Cliniques universitaires Saint-Luc, Avenue Hippocrate 10, 1200 Brussels, Belgium, tel: +32 2 764 51 06, email: francois.duhoux@uclouvain.be.

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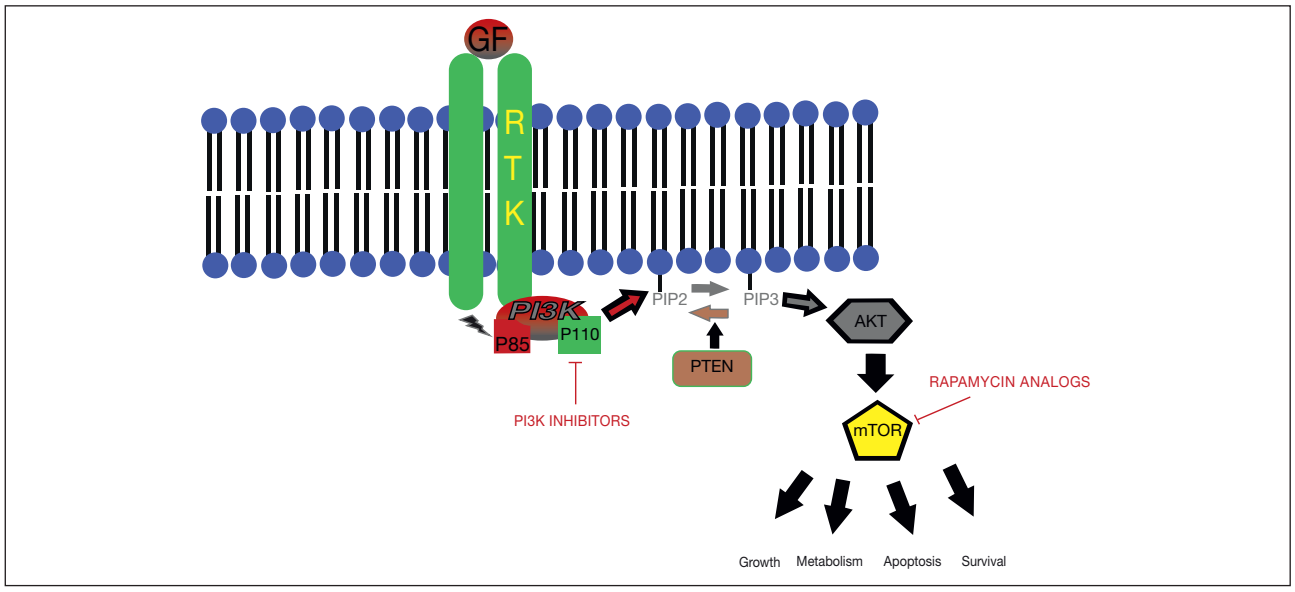

FIGURE 1. Schematic and simplified representation of the PI3K/AKT/MTOR pathway.
GF = Growth factor; RTK = tyrosine kinase receptors.
Activation of the class I PI3Ks will lead to the phosphorylation of PIP2 (phosphatidylinositol-3,4-bisphosphate) into PIP3 (phosphatidylinositol-3,4,5-trisphosphate), which will recruit AKT to start a pathway involved in cell proliferation and survival.[9]

PI3K inhibitor, in the treatment of advanced ER+/HER2- breast cancers.

The aim of this article is to review the current knowledge about PI3K inhibitors, their potential use in medical oncology and their toxicities.

THE PI3KS: DEFINITION AND PHYSIOLOGY

The PI3Ks are a family of intracellular lipid kinases involved in intracellular signal transduction by phosphorylating intracellular effectors, leading to the activation of intracellular pathways - such as the PI3K/AKT/mTOR pathway implicated in cellular growth, apoptosis and differentiation (*Figure 1*).

PI3Ks are subdivided into three classes: I (Ia, Ib), II and III. Each type of PI3K includes different isoforms. All these types and isoforms have different substrates leading to different pathway activations.[1] The roles of class II and III PI3Ks are not well understood and will therefore not be discussed in this review. We will exclusively focus on class I PI3Ks.

Class Ia PI3K is a heterodimer made of two subunits: a p85 regulatory subunit and a p110 catalytic subunit. Each of these subunits has several isoforms.

Class Ia PI3Ks are usually activated by receptor tyrosine kinases (RTKs) which bind growth factors such as insulin, small Ras-related GTPases, and heterotrimeric G proteins (*Figure 1*).

The p85 regulatory subunit is encoded by three genes: *PIK3R1*, *PIK3R2* and *PIK3R3* (each of them encoding the p85α, p85β and p55γ isoforms, respectively). The class IA regulatory subunit has an inter-SH2 domain that interacts with the p110 catalytic subunit, flanked by two Src-homology 2 (SH2) domains.

The p110 catalytic subunit is encoded by three genes: *PIK3CA*, *PIK3CB* and *PIK3CD* (encoding for the p110α, p110β and p110δ isoforms, respectively). The catalytic subunit has an N-terminal domain that interacts with the p85 regulatory subunit, a Ras-binding domain that mediates activation by the Ras GTPase, a C2 domain, a phosphatidylinositol kinase homology domain and a C-terminal catalytic domain.

Class Ib PI3K is a heterodimer made of a p101 regulatory subunit and a p110γ catalytic subunit. It is not regulated by RTKs and can only be activated by GPCRs (G-protein coupled receptors).[9]

In physiological conditions, the activation of the class I PI3Ks will lead to the phosphorylation of PIP2 (phosphatidylinositol-3,4-bisphosphate) into PIP3 (phosphatidylinositol-3,4,5-trisphosphate), which will recruit AKT to start a pathway involved in cell proliferation and survival.[3]

PIP3 can be dephosphorylated by the tumour suppressor protein PTEN. *PTEN* mutations leading to a loss of function are known to be implicated in several cancers.[3]

PI3K MUTATIONS AND ONCOGENESIS

PI3Ks are involved in several cellular processes, especially through the PI3K/AKT/mTOR pathway.

In physiological conditions, this signalling pathway regulates

key processes of the cell's life like growth, metabolism, apoptosis, motility, proliferation and many others.

The dysfunction of the PI3K/AKT/mTOR pathway can lead to aberrant cell growth, a feature common to many cancers (see below).

Several PI3K activating mutations have been identified in human tumours. The most frequently mutated actor is the p110α subunit. The mutation generally occurs in the *PIK3CA* gene, with three key hotspots identified in the helical (E542 and E545) and kinase domains (H1047). Mutations in the helical domain disrupt the inhibitory interface, reducing the inhibition by the p85 subunit while the mutation in the kinase domain enhances the interaction with the membrane.[10] Other less frequent PI3K mutations have been identified in human tumours in the p85-binding, Ras-binding and C2 domains.

Somatic mutations occurring in the *PIK3CA* gene (encoding the p110α subunit) are found in variable proportions depending on tumour types and subtypes. Among several publications giving the proportion of *PIK3CA* mutations according to the tumour type, we chose the COSMIC registry because of a larger sample of tumours and regular updates (*Table 1*).

According to the COSMIC registry, the three tumour types with the highest frequency of *PIK3CA* mutations are endometrium (22%), breast (19%) and urinary tract (19%). In some types of tumours, the mutation percentage varies significantly depending on the tumour subtypes. For example, *PIK3CA* mutations are found in 19% of breast cancers overall, while this proportion rises to 40% in luminal tumours and only reaches 10% in triple negative breast cancer.[11]

Mutation frequency varies between research articles. For example, some authors have reported a higher frequency of *PIK3CA* mutations in colon cancer (15-18%).[13,14] Of note, in those articles, the sample size was much smaller than the COSMIC registry.

TABLE 1. Proportion of *PIK3CA* mutations in human tumours.
Catalogue of somatic mutations in cancer. https://cancer.sanger.ac.uk/cosmic, COSMIC V90, September 5th, 2019.

Tumour type		*PIK3CA* mutation % (n mutated/n tested)
Endometrium		22% (973/4451)
Breast		19% (3951/20784)
Urinary tract		19% (500/2681)
Large Intestine		12% (2526/20795)
Salivary Gland		11% (77/697)
Ovary		8% (354/4472)
Upper Aerodigestive tract	Mouth	7% (100/1372)
	Head Neck	7% (92/1336)
	Pharynx	8% (113/1385)
Cervix		7% (157/2193)
Oesophagus		7% (258/3694)
Stomach		6% (244/3949)

PI3K INHIBITORS: TOXICITIES[4,12,15]

One of the major problems encountered during the development of PI3K inhibitors was their toxicity profile, leading to the early discontinuation of several clinical trials.[5,6] Different isoforms of PI3K are found in different tissues: PI3Kα and β are present in multiple tissues, while PI3Kδ is preferentially found in immune cells and PI3Kγ mostly in endothelial cells.[12] From these observations, the conclusion is that the side effects of PI3K inhibitors depend on their isoform-selectivity.

Major toxicities were mostly seen with the first PI3K inhibitors, which are panisoforms inhibitors. With the development of more selective molecules such as alpelisib and taselisib, toxicities have now reached a more acceptable level.[7,8]

The first PI3K inhibitor approved in the United States by the Food and Drug Administration (FDA) was idelalisib in the field of hematological malignancies. Copanlisib was approved thereafter, also in hematological malignancies.[4] Guidelines for toxicity management have been established for these two molecules but can be reasonably transposed to the other PI3K inhibitors.

A recent review by *Esposito et al.*, proposed a management algorithm based on FDA drug information and experts panel opinion.[12] Their algorithm is based on the Common Terminology Criteria for Adverse Events (CTCAE) toxicity grading.

AUTO-IMMUNE TOXICITIES

Auto-immune toxicity is due to the role of the PI3K pathway in a specific type of immune cells, the CD4+CD25+-Foxp3+ regulatory T cells (Tregs). The PI3K pathway is necessary to the function of these cells through the PI3Kδ and PI3Kγ isoforms. Tregs are critical for immune self-tolerance and downregulation.[16] The PI3Kδ isoform is also

implicated in the differentiation of peripheral T lymphocytes into Th1 or Th2.

Younger age and previously untreated disease are associated with a higher rate of auto-immune toxicities.[4]

The most common auto-immune toxicities are diarrhea (colitis), respiratory toxicity (pneumonitis) and cutaneous eruptions.

If a patient presents diarrhea while being treated with PI3K inhibitors, he should first be assessed for any other causes of diarrhea: infectious, dietary, medication induced.

For grade 1 diarrhea, anti-motility agents should be tried.

In case of unresolved grade 2 or 3 diarrhea, colonoscopy should be discussed, treatment interrupted and systemic corticotherapy initiated.

HEPATOTOXICITY

This toxicity is mostly seen with idelalisib and buparlisib and can be very serious.[17]

According to an expert opinion panel, patients treated with idelalisib should undergo monitoring of AST (Aspartate aminotransferase) and ALT (Alanine aminotransferase) every two weeks for the first three months, every four weeks for the next three months and every one or three months thereafter.[15]

For patients with AST or ALT three times above the upper limit of normal (ULN), treatment can be continued but the monitoring should be performed on a weekly basis.

For patients with AST or ALT > 5x ULN, treatment should be withheld until normalisation

For AST/ALT levels > 20x ULN, treatment should be permanently interrupted.

HYPERTENSION

Several studies suggest that PI3Ks play a role in blood pressure control through the PI3Kγ isoform, which is especially involved in the vascular myogenic tone by regulating calcium channels function. For example, the PI3K/AKT pathway is crucial in regulating vascular smooth cells contraction and relaxation induced by angiotensin II.[18]

Insulin-mediated vacoconstriction could explain the hypertension induced by PI3K inhibitors.

Hypertension has mainly been described with copanlisib, which has some activity on the PI3Kγ isoform.

The management proposed by the FDA drug information is a systematic control of the blood pressure before and after the PI3K inhibitor (copanlisib) infusion.[4] A blood pressure < 140/90 mm Hg should be obtained before starting the infusion. At the end of the infusion, if the blood pressure is higher than 150/90 mm Hg, an antihypertensive treatment should be given.

HYPERGLYCAEMIA

PI3Ks also play a major role in maintaining glucose homeostasis. The PI3Kα isoform transduces the intracellular signal initiated by insulin binding. Studies on mice with an inactivated p85α unit (which leads to an inactive PI3Kα isoform) have allowed understanding the role of PI3K in glucose homeostasis. These mice develop glucose intolerance with increased gluconeogenesis and impaired glucose intake by muscle cells.[19]

In clinical trials, hyperglycaemia is seen with all PI3K inhibitors except with idelalisib, which is a PI3Kδ-specific inhibitor.

Hyperglycaemia is one of the most frequent toxicities encountered with PI3K inhibitors. It can actually be considered as an on-target toxicity.

Given the frequency of hyperglycaemia, patients who are eligible for a PI3K inhibitor should be initially assessed for a history of diabetes or insulin resistance. It is advised to reach the target of a fasting glycaemia < 160 and an HbA1c ≤ 8%.[12]

NEUROPSYCHIATRIC TOXICITY

Confusion, anxiety and depression have been observed with PI3K inhibitors, mainly buparlisib. The mechanism of the neurotoxic effect is not well understood but could indicate the capacity of PI3K inhibitors to cross the blood-brain barrier, making them interesting drug candidates for the treatment of brain tumours. Some positive effects are seen on relapsed/refractory glioblastoma.[20]

Every patient who is going to undergo treatment with PI3K inhibitors should be assessed for a history of psychiatric disorders (depression, bipolar disorders, and suicidal ideas). For any toxicity, starting from grade 1, the patient should be monitored closely and referred to a psychiatrist. For grade 2 or higher, treatment withdrawal should be considered.

CUTANEOUS TOXICITY

The cutaneous manifestations observed in the trials using PI3K inhibitors were most commonly pruritus, dry skin and maculo-papular reactions.

For grade 1 and 2 reactions, it is recommended to maintain the treatment and initiate topical corticosteroids and antihistamines, and consider adding low dose systemic corticosteroids.

For grade 3 reactions, the treatment should be interrupted until skin toxicity is no longer active. A dose reduction should be considered.

In case of grade 4 toxicity, the treatment should be stopped permanently.

TABLE 2. Most frequent adverse events in the Solar-1 Trial.[8]

Adverse Event	Alpelisib – fulvestrant Group (N = 284)			Placebo – fulvestrant Group (N = 287)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
	Number of patients (%)					
Any Adverse Event	99,3 %	64,4%	11,6%	92%	30,3%	5,2%
Hyperglycaemia	63,7 %	32,7%	3,9%	9,8%	0,3%	0,3%
Diarrhea	57,7 %	6,7%	0%	15,7%	0,3%	0%
Nausea	44,7%	2,5%	0%	22,3%	0,3%	0%
Decreased appetite	35,6%	0,7%	0%	10,5%	0,3%	0%
Rash	35,6%	9,9%	0%	5,9%	0,3%	0%
Vomiting	27,1%	0,7%	0%	9,8%	0,3%	0%
Weight Loss	26,8%	3,9%	0%	2,1%	0%	0%
Stomatitis	24,6%	2,5%	0%	6,3%	0%	0%
Fatigue	24,3%	3,5%	0%	17,1%	1,0%	0%
Asthenia	20,4%	1,8%	0%	12,9%	0%	0%
Alopecia	19,7%	0 %	0%	2,4%	0%	0%
Mucosal inflammation	18,3%	2,1%	0%	1,0%	0%	0%
Pruritus	18,0%	0,7%	0%	5,6%	0%	0%
Headache	17,6%	0,7%	0%	13,2%	0%	0%
Dysgeusia	16,5%	0%	0%	3,5%	0%	0%
Arthralgia	11,3%	0,4%	0%	16,4%	1,0%	0%

These results have led to FDA and EMA approval of alpelisib in combination with fulvestrant for postmenopausal women, and men, with hormone receptor positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer in case of progression on or after an endocrine-based regimen.

PI3K INHIBITORS IN MEDICAL ONCOLOGY

Several trials assessing the efficacy of PI3K inhibitors are ongoing in medical oncology (glioblastoma, breast cancer, prostate cancer, pancreatic cancer, head and neck cancer, etc.). We choose here to focus on the PI3K inhibitors in the field of breast cancers.

In ER+ breast cancer, one of the mechanisms of resistance to endocrine therapy is the crosstalk between the ER and PI3K/AKT/mTOR pathways. This mechanism leads to an activation of the ER pathway by the PI3Ks, leading to a ligand-independent activation of the pathway downstream ER. The discovery of this mechanism of resistance has allowed understanding the importance of dual inhibition of the ER and PI3K/AKT/mTOR pathways in ER+ breast cancers.[21]

At this point, only one molecule has been approved in solid tumours by the FDA and the European Medicines Agency (EMA): alpelisib, which has shown a good efficacy in the SOLAR-1 and BYLieve trials. We will here discuss five clinical trials that aimed to test PI3K inhibitors for

TABLE 3. Most frequent adverse events in the LORELEI Trial.[7]

	Taselisib - letrozole group (n=167)			Placebo - letrozole group (n=167)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Gastrointestinal disorders	47%	7%	1%	32%	1%	0%
Fatigue	20%	0%	0%	24%	0%	0%
Skin disorders	29%	4%	1%	20%	0%	0%
Hyperglycaemia	14%	1%	0%	7%	0%	0%
Arthralgia	11%	0%	0%	22%	0%	0%
Infections	18%	4%	10%	23%	1%	0%
Respiratory disorders	14%	1%	0%	10%	0%	0%
Psychiatric disorders	11%	0%	0%	16%	0%	0%

breast cancer and will focus on three recent trials showing good results: the SOLAR-1, BYLieve and LORELEI trials.

THE BELLE-3 TRIAL[5]

The BELLE-3 trial was a randomised, double-blind, placebo-controlled, multicentre, phase III trial that aimed to prove the efficacy of buparlisib, a panisoform PI3K inhibitor, in patients with advanced breast cancer previously treated with endocrine therapy and mTOR inhibitors. The trial was interrupted due to lack of efficacy and major toxicities.

THE SANDPIPER TRIAL[22]

The SANDPIPER trial was a randomised double-blind, placebo-controlled, multicentre, phase III trial that aimed to prove the efficacy of taselisib, an α-specific PI3K inhibitor, in patients with oestrogen receptor (ER)-positive, human epidermal receptor (HER)-2 negative metastatic breast cancer. The limited improvement of the progression-free survival and the important side effects led the sponsor to stop the further development of taselisib.

THE SOLAR-1 TRIAL[8]

The SOLAR-1 trial is a multicentre, randomised, double-blind, placebo-controlled, phase III trial (34 countries, 198 trial sites) comparing alpelisib (an orally bioavailable, alpha-specific, p110 inhibitor) plus fulvestrant to placebo plus fulvestrant in men and post-menopausal women with advanced or metastatic breast cancer progressive on or after endocrine therapy.

In total, 572 patients underwent randomisation. Among those patients, 341 where *PIK3CA*-mutated.

The patients were subdivided into two groups based on their *PIK3CA* mutation status. In each group, patients were randomly assigned to receive either alpelisib (300 mg per day, orally) plus fulvestrant (500 mg every 28 days, with an additional dose of 500 mg on day 15 of the first cycle), or placebo plus fulvestrant.

The primary endpoint was progression-free survival, which was significantly higher in the *PIK3CA*-mutated patients treated with alpelisib plus fulvestrant, with a median of 11 months (95% confidence interval [CI], 7.5 to 14.5) as compared to 5.7 months (95% CI, 3.7 to 7.4) for those receiving placebo plus fulvestrant. In patients without *PIK3CA* mutations, there was no significant difference between the two groups. **Overall survival (OS) in the *PIK3CA*-mutated patients treated with alpelisib plus fulvestrant was improved, with a median OS of 39.3 months as compared to 30.8 months for those receiving placebo plus fulvestrant (HR 0.86; 95% CI 0.64-1.15; P=0.15). This difference between the two groups did not reach the threshold of statistical significance but was clinically meaningful.**[23]

The overall response rate among the patients with *PIK3CA*-mutated cancers was significantly higher in the alpelisib-fulvestrant group than in the placebo-fulvestrant group (26.6% *vs* 12.8%).

KEY MESSAGES FOR CLINICAL PRACTICE

1. ***PIK3CA*** **is a gene mutated in numerous human tumours, in different proportions depending on the tumour types.**
2. **PI3K inhibitors are already used in hematological malignancies and have shown promising results in several trials in medical oncology.**
3. **In the SOLAR-1 trial, alpelisib, an α-selective p110 inhibitor, significantly improved progression-free survival when combined with fulvestrant in men and post-menopausal women with *PIK3CA* mutated metastatic or advanced HR+/HER2- breast. The addition of alpelisib to fulvestrant also led to a clinically meaningful though not statistically significant improvement in overall survival.**

The most frequent grade 3 or 4 adverse events were hyperglycaemia (36.6% in the alpelisib–fulvestrant group *vs.* 0.7% in the placebo–fulvestrant group), rash (9.9% *vs.* 0.3%) and diarrhea (6,7% *vs* 0,3%).

THE BYLIEVE TRIAL[24]

Results from Cohort A of the BYLieve trial were recently presented at the 2020 ASCO Annual Meeting. In this cohort, 127 patients with ER+ HER2- advanced breast cancer whose immediate prior treatment was a CDK4/6 inhibitor plus an aromatase inhibitor were treated with fulvestrant plus alpelisib. Efficacy data concerning the 121 patients with centrally confirmed *PIK3CA* mutations were in line with data from SOLAR-1: the proportion of patients without disease progression at six months was 50.4% (95% CI, 41.2-59.6) and the median PFS was 7.3 months (95% CI, 5.6-8.3). The safety profile was consistent with previous trials.

THE LORELEI TRIAL[7]

The LORELEI trial is a multicentre, randomised, double-blind, placebo-controlled, phase II trial that aimed to test the efficacy and safety of an anti-PI3K agent (taselisib) associated with standard endocrine therapy (letrozole) in the neoadjuvant treatment of ER-positive, HER2-negative breast cancer.

Taselisib is a PI3K inhibitor that is more selective for the *PIK3CA*-mutated α-isoforms than for the *PIK3CA* wild type α-isoforms.

The neoadjuvant setting is a splendid opportunity to determine molecular factors predicting response to novel therapies. Additionally, remaining tumour tissue can be analysed after surgery to determine the mechanisms of resistance to therapies.

In total, 334 patients were enrolled and randomised to receive either taselisib plus letrozole or placebo plus letrozole. The *PIK3CA* mutation status was similar in both groups. The response rate was assessed by magnetic resonance imaging and was significantly higher in the taselisib group than in the placebo group (50% *vs* 39%). These results were even more significant in patients with *PI3KCA* mutations (56% in the taselisib group and 38% in the placebo group). There was no significant difference between the two groups in patients with wild-type *PIK3CA* (40% in the placebo group *vs* 46% in the taselisib group).

Adverse events were more frequent in the taselisib group than in the placebo group. The adverse events were mostly grade 1 or 2 while grade 3 adverse events did not exceed 5%. The most frequent toxicities were gastrointestinal disorders, skin disorders, fatigue, hyperglycaemia, arthralgia, infections, respiratory disorders and nervous system disorders.

CONCLUSION

PI3Ks are major actors in cellular metabolism, proliferation, apoptosis and numerous other processes. Many research programs have shown their potential implication in the development of cancerous tumours, either by hyper activation or lack of regulation.

PIK3CA, a gene encoding for the p110α catalytic subunit, is mutated in numerous human tumours, in different proportions depending on the tumour types. These mutations are found in higher proportions in gynaecological tumours, breast cancer, urinary tract and gastrointestinal cancers.

In hematological malignancies, PI3K inhibitors are already used for relapsed/refractory chronic lymphocytic leukaemia (CLL), follicular lymphoma (FL), and small lymphocytic lymphoma (SLL).

In the field of medical oncology, several PI3K inhibitors have been developed but only one of them is currently approved by the FDA and EMA: alpelisib (Piqray®), an α-selective p110 inhibitor, which significantly improved progression-

free survival when combined to fulvestrant in men and post-menopausal women with metastatic or advanced HER+/ HER2- breast cancer (SOLAR-1 trial).

Two trials have failed to prove the efficacy of two other PI3K inhibitors in BC: buparlisib (in the BELLE-3 trial) and taselisib (in the SANDPIPER trial). These molecules did not significantly improve the progression-free survival and had many side effects. Buparlisib is a pan-PI3K inhibitor, a feature that explains its numerous toxicities. Taselisib for its part has shown interesting results in a phase II trial in the neoadjuvant setting for breast cancer (LORELEI trial).

The results of the SOLAR-1 trial pave the way to further trials using PI3K inhibitors in medical oncology.

With the development of Precision Medicine, we advocate for the development of trials with PI3K inhibitors in other solid tumours with frequent alterations of the gene and probably the use of specific combinations will be a way to increase response to these drugs.

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