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Review

Development and Clinical Applications of PI3K/AKT/mTOR Pathway Inhibitors as a Therapeutic Option for Leukemias

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Abstract. *Leukemias are hematological neoplasms characterized by dysregulations in several cellular signaling pathways, prominently including the PI3K/AKT/mTOR pathway. Since this pathway is associated with several important cellular mechanisms, such as proliferation, metabolism, survival, and cell death, its hyperactivation significantly contributes to the development of leukemias. In addition, it is a crucial prognostic factor, often correlated with therapeutic resistance. Changes in the PI3K/AKT/mTOR pathway are identified in more than 50% of cases of acute leukemia, especially in myeloid lineages. Furthermore, these changes are highly frequent in cases of chronic lymphocytic leukemia, especially those with a B cell phenotype, due to the correlation between the hyperactivation of B cell receptors and the abnormal activation of PI3Kδ. Thus, the search for new therapies that inhibit the activity of the PI3K/AKT/mTOR pathway has become the objective of several clinical studies that aim to replace conventional oncological treatments that have high rates of toxicities and low specificity with target-specific therapies offering improved patient quality of life. In this review we describe the PI3K/AKT/mTOR signal transduction pathway and its implications in leukemogenesis. Furthermore, we provide an overview of clinical trials that employed PI3K/AKT/mTOR inhibitors either as monotherapy or in combination with other cytotoxic agents for treating patients with various types of leukemias. The varying degrees of treatment efficacy are also reported.*

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Leukemias are the main neoplasms that affect blood and bone marrow cells, inducing several malignant alterations, including abnormalities associated with cell proliferation and differentiation processes. Leukemias are broadly classified as acute or chronic. Additionally, leukemias can also be divided according to the specific cell lineages they impact, falling into four major groups: acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), and chronic lymphoid leukemia (CLL) (1-3).

Acute leukemias are pathologies that have a rapid evolution and are strongly associated with a quantitative increase in blast cells in the peripheral blood and bone marrow, but they can also present with anemia and an increase in the number of leukocytes. AML is an acute leukemia primarily affecting myeloid progenitor cells and predominantly afflicting the adult population. On the other

hand, ALL affects progenitor lineages of lymphoid origin and typically occurs in children and adolescents (4-6).

In the case of chronic leukemias, unlike the acute forms, the disease course has a slower progression and correlates with different stages of cell maturation. Among the types of these leukemias, CML affects patients at different ages, but is most common in adults aged between 40 and 60 years. It is a myeloproliferative dysfunction that affects myeloid cells at different stages of development and has three main clinical phases, namely the chronic phase, accelerated phase, and blast phase. Furthermore, there is also CLL, which mostly affects the elderly population whose blood count shows marked leukocytosis with the massive presence of mature lymphocytes (7-9).

Conventional oncological treatments that use drugs with high toxicity and low specificity have been proving less and less effective in the treatment of neoplastic malignancies. Thus, the therapeutic targeting of key molecules belonging to cellular signaling pathways involved in tumor development represents a promising alternative for the development of treatments aimed at improving the prognosis and quality of life of patients (10, 11). Among these important pathways we highlight the PI3K/AKT/mTOR pathway, which is associated with several pivotal cell functions, such as the control of metabolism, proliferation, survival, and cell death, and has thus become the target of several studies aimed at developing inhibitory strategies (12, 13).

A clinical study of 55 patients with CLL examined the effectiveness of Duvelisib, a PI3K δ and γ inhibitor, as a therapeutic alternative and reported an overall response rate (ORR) of 56.4% among individuals, of which 1.8% achieved complete response (CR) and 54.5% achieved partial responses (PR). Furthermore, it was also reported that 34.5% of patients achieved stable disease. It was also identified that this drug reduced the levels of some cytokines, chemokines, and growth factors, such as MMP-9, MMP-12, TNFα (Tumor necrosis factor α), interleukin (IL) 6, IL -10, IL-12p40, CCL1, CCL3, CCL4, CCL17, CCL22, CXCL10, and CXCL13 (14). Another important PI3K δ inhibitor is Idelalaisib, which was tested in association with Rituximab (anti-CD20 monoclonal antibody) in a study with 64 patients with relapsed and refractory CLL. As a result, an ORR of 96.9% was observed, of which 14.1% achieved CR and 82.8% achieved PR. Progress was also reported regarding the clinical conditions of patients including improvements in hemoglobin and platelet levels in individuals with anemia and thrombocytopenia, respectively, as well as normalization of the number of neutrophils for individuals with neutropenia (15).

Zeng *et al*. (16) tested the effects of Ginsenoside Rg3 on bone marrow stromal cells of individuals with acute leukemia and verified its effectiveness on cell growth and angiogenesis. They observed that Ginsenoside Rg3 interfered with the viability of these cells, in addition to inhibiting the expression of vascular endothelial growth factor (VEGF), hypoxia-inducible factor 1α (HIF-1α), AKT and ERK 1 and 2.

For this reason, this review discusses the cellular roles of the PI3K/Akt/mTOR pathway in the development of leukemias and evaluates the currently available inhibitors as therapeutic options for these malignancies.

PI3K/AKT/MTOR Characterization and Cellular Roles

Phosphatidylinositol 3-kinase (PI3K) is a heterodimeric protein, which is activated mainly by tyrosine kinase receptors, but also by G protein-coupled receptors, and is classified into three main classes: Class I, II, and III. Class I are composed of subunits with regulatory functions, such as p85 and p101, and catalytic subunits, such as p110α, p110β, p110δ, and p110γ; they can be further divided into two types: classes IA, which includes PI3Kα, β, and δ, and classes IB, which includes PI3Kγ. Class II PI3K can be divided into three main types that are designated PI3KC2α, PI3KC2β, and PI3KC2γ. Class III has only one known isoform, PI3KC3. Activated PI3K catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) molecules into phosphatidylinositol 3,4,5-triphosphate (PIP3), which will act as second messenger for several signaling molecules, such as 3-phosphoinositide-dependent kinase-1 (PDK-1) and AKT (17-19).

The AKT protein is a serine/threonine kinase, also known as protein kinase B (PKB), which can be regulated by hormonal and/or protein kinases (for example, PDK-1) and can be found in three isoforms: AKT1 (PKBα), AKT2 (PKBβ), and AKT3 (PKBγ). In general, AKT activation begins with PIP3 recruitment and binding tightly to PDK1, which have pleckstrin homology (PH) domains. Such an event acts as an anchor for AKT molecules and facilitates their phosphorylation. Furthermore, depending on the type of AKT, it will present different target residues for phosphorylation by PDK1, the main ones being Thr308, Thr309, and Thr305, which belong to the isoforms AKT1, AKT2, and AKT3, respectively (20-22).

In its active form, AKT acts as a mediator of the phosphorylation of several proteins that participate in cell signaling, such as the mammalian target of rapamycin (mTOR) complexes, which consist of proteins belonging to the serine/threonine kinase family and act in the promotion of genomic stability, cell cycle regulation and glucose metabolism. Through interaction with a wide range of proteins, mTOR forms two distinct cellular complexes: mTORC1 and mTORC2. Among the components of mTORC1 are the mTOR protein itself, regulatory-associated protein of mTOR (RAPTOR), DEP domain-containing mTOR-interacting protein (DEPTOR), mammalian lethal with Sec13 protein 8 (mLST8), and proline-rich Akt substrate 40kDa (PRAS40). In contrast, the mTORC2 has among its components mTOR, Rapamycin-insensitive

companion of mTOR (RICTOR), protein observed with Rictor-1 (PROTOR), DEPTOR, mLST8, and mammalian stress activated protein kinase interacting protein 1 (mSin1) (23-25).

When mTORC1 is activated, it can act on several important metabolic processes for cell homeostasis, such as protein, lipid, glucose, and nucleic acid synthesis, in addition to participating in the stimulation of cell growth and inhibition of autophagic mechanisms. mTORC1 may also down-regulate mTORC2 activity through its downstream effector protein p70-S6 kinase 1 (S6K1), which also participates in the production of nucleic acids. mTORC2 has various essential functions, notably in lipid synthesis, regulating the actin cytoskeleton, and influencing glycolysis. Furthermore, it is noteworthy that mTORC2 activation can reactivate AKT molecules through phosphorylation on serine residues, such as Ser473, acting as a positive feedback for AKT, potentially leading to the reactivation of mTORC (23, 26, 27).

One way through which AKT activates mTOR1 complexes is through phosphorylation of the tuberous sclerosis complex 2 (TSC2) and prevention of its ability to inhibit GTPase Rheb. Furthermore, AKT can also activate the mTOR complex through activation of the Conserved helix-loop-helix ubiquitous kinase (CHUK), expressed by the CHUK gene and phosphorylation of PRAS40 (23, 24, 28).

AKT can also control the cell cycle by blocking and phosphorylating proteins that promote apoptosis, including proteins belonging to the B-cell lymphoma 2 (BCL-2) family, caspases 9, BCL-2-associated protein X (BAX) and BCL-2-associated cell death agonist (BAD). AKT can influence transcription factors that act in various metabolic processes and cell survival, such as nuclear factor kappa B (NF-kB), Forkhead box transcription factor (FOXO) and MDM2. Furthermore, it also has the ability to modulate the activity of glycogen synthase kinase 3 (GSK3), which is a protein that participates in the regulation of glycogen synthesis (Figure 1) (29-33).

When the physiological need for catalytic active PI3K/AKT/mTOR pathway, the organism needs a mechanism that works as negative feedback and for that it makes use of inhibitor proteins, which act mainly as catalysts for the conversion of PIP3 into PIP2. The main one is PTEN, a lipid phosphatase homologous to tensin that interferes both with metabolism and cell growth; however, it can also use other inhibitors such as the SHIP1 protein (34-37).

PI3K/AKT/mTOR and Leukemogenesis

The PI3K/AKT/mTOR pathway has a direct relationship with the hematopoiesis control mechanisms and for this reason, changes that promote overactivation of this pathway can induce aberrant hematopoiesis, leading to leukemogenesis onset (13, 29, 38).

When we refer to the involvement of PI3K in neoplastic development, the main class that is involved in this process is class I PI3K. The p110α and p110β subunits of class I PI3K are ubiquitously expressed in several cell types in the human body, however, the p110δ and p110γ subunits are expressed more specifically in hematopoietic cells, mainly in leukocytes. For this reason, PI3Kδ and γ are the most related to leukemogenesis and have become targets of many therapeutical approaches (39, 40).

PI3Kδ is a prevalent PI3K isoform in leukocytes, mainly B lymphocytes, and many studies have examined the role of PI3Kδ in cases of malignancies with B-cell phenotype, especially in CLL cases. Extensive literature reports indicate that overactivation of B cell receptors (BCR) promotes the downstream activation of PI3Kδ, resulting in abnormal triggering of the PI3K/AKT/mTOR pathway and tumor development (41-44).

BCR is an immunoglobulin located in the cell membrane region of lymphocytes with a B cell phenotype that interacts through non-covalent bonds with the CD79a and CD79b heterodimers. The binding of specific BCR antigens to this receptor causes the phosphorylation of immunotyrosine-based activation motif (ITAMs) in the cytoplasmic domains of CD79a and CD79b by LYN protein kinase, which is a member of the Src family. This results in the recruitment, anchoring and activation of tyrosine kinase of the spleen (SYK) and promotion of the subsequent phosphorylation of PI3K BCAP and CD19 co-receptor, which are capable of activating PI3K, especially of the delta isoform. In addition, BCR is also responsible for activating other important pathways for cell metabolism and survival that are relevant to leukemogenesis development (41, 42, 45-47).

Alterations in the PI3K/AKT/mTOR pathway can also be identified in patients with AML, being observed in over 50% of these cases and may be associated with a worse prognosis. The p110δ catalytic subunit has been shown as relevant in this leukemic process, since its expression is high in AML blast cells and constant phosphorylation of AKT, which happens downstream, promotes enhanced cell proliferation, survival of neoplastic clones, aberrant DNA repair mechanisms and even dysfunctional glucose metabolism (28, 48-51).

Despite over-activating mTORC, AKT also regulates other molecular targets to favor leukemogenesis, such as FOXO, which are transcription factors that act as tumor suppressors, participating in cell cycle, proliferation, and differentiation of the cells and, mainly, of in apoptosis, in which FOXO3 is the most relevant. Therefore, the modulation of FOXO3 by AKT favors the survival of malignant cells and inhibits cell death by apoptosis (52-55).

Disturbances in mTORC can also favor leukemia development affecting hematopoietic stem cells (HSC) and leukemic stem cells. Activation of S6K1 upon mTORC1 activation is a key mechanism that helps maintain HSC quiescence and influences mRNA translation. Thus, factors that lead to mTORC1 and S6K1 deficiency will not only reduce the

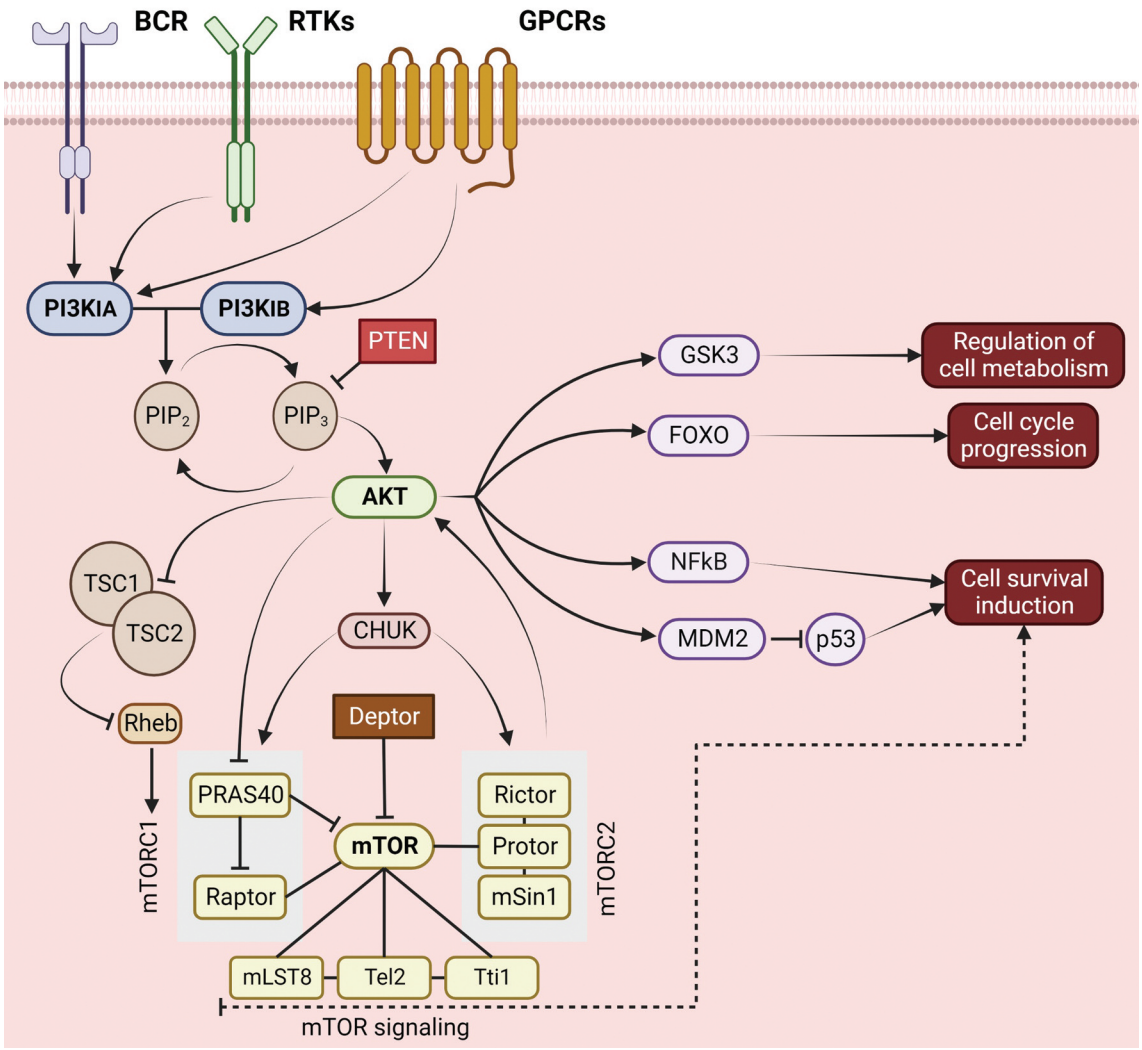

Figure 1. *PI3K/AKT/mTOR intracellular signaling. Activation of PI3KIA begins from receptor tyrosine kinases (RTKs), G-protein coupled receptors (GPCRs) or other cell-specific receptors, such as B-cell receptor (BCR), while the PI3KIB isoform is activated exclusively through GPCR signaling. Both types of activation induce conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) into phosphatidylinositol 3,4,5-triphosphate (PIP3), in a reaction that may be reversed through the inhibitory catalytic activity of phosphatase and tensin homolog (PTEN). PIP3 acts as a downstream messenger for activation of components of cellular pathways, including AKT serine/threonine kinase (AKT), which ultimately lead to cell cycle progression, apoptosis inhibition and maintenance of cell metabolism through regulation of major signaling proteins such as glycogen synthase kinase 3 (GSK3), forkhead box (FOXO), nuclear factor kappa B (NFkB) and tumor protein 53 (p53). AKT also activates downstream pathways important for cell homeostasis, including the mechanistic target of Rapamycin kinase (mTOR) activity, which corroborates AKT function in cell survival and regulation of metabolic activities. Downstream activation of component of inhibitor of nuclear factor kappa B kinase complex, conserved helix-loop-helix ubiquitous kinase (CHUK), by AKT induces phosphorylation of both mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), which are the main effectors of mTOR activity and lead to cell regulation and survival, but also to phosphorylation-mediated feedback activation of AKT.*

quiescent state and the capacity for cell self-renewal, but they can also stimulate proliferation of these cells (56, 57).

The cell culture experiment performed by Gosh *et al*. (58) demonstrated that S6K1 deficiency led to a reduction in the quiescence and self-renewal capacity of HSC that was correlated with a reduction in cyclin-dependent kinase 1A inhibitor (Cdkn1a) levels. In addition, there was also a greater propensity for myelotoxic stresses, a reduction in mTOR levels and maintenance and propagation of leukemias. Panuzzo *et al*. (59) revealed that, under hypoxic conditions, there is a reduction in mTORC1 activity in CML stem cells, while mTORC2 activity is maintained. They also

reported an increase in phosphorylation of AKT molecules due to its positive feedback cycle, promoted by mTORC2, and an increase in the phosphorylation of PKCα, which is also a substrate of this complex. They also revealed that, despite the increase in AKT phosphorylation *via* mTORC2, the activation of some downstream targets of AKT are dependent on the phosphorylation of specific residues. For the activation of FOXO3a, there is a need for phosphorylation in the AKT molecule of both the Ser473 residue (mTORC2 target) and Thr308 (PDK-1 target). In contrast, GSK3β requires phosphorylation of only the Thr308 residue of AKT. With that, they reported a reduction in the levels of FOXO3a and GSK3β, which resulted in reduced self-renewal and cellular quiescence, cell cycle progression, decreased glycogen production and greater accumulation of cyclin D1.

In general, mTORC can contribute to leukemogenesis, mainly AML, in different ways depending on which of the complexes is acting. mTORC1 affects protein synthesis mechanisms through the modulation of effector molecules S6K1 and eIF4E binding protein (E4BP), regulates lipid synthesis where it can control the expression of genes that participate in the production of cholesterol and fatty acids, participates in metabolism of glucose by stimulating glycolysis and HIF1α synthesis, and blocks autophagy mainly by preventing the activation of Unc-51-like kinase 1 (ULK1), which is an important component for autophagosome formation. mTORC2, in addition to activating AKT, plays an important role in controlling cell survival and proliferation and participates in the organization of the actin cytoskeleton through the regulation of proteins that are members of the PKC family, especially PKCα (25, 49, 56, 60, 61).

Literature reports indicate that the RAPTOR component of mTORC1 is a key element in the involvement of this complex in the development of acute leukemias, as it helps to increase cellularity, reduce apoptosis, and stimulate cell proliferation, which may even lead to disease progression. Furthermore, mTORC1 overactivation can also be caused by increased activity of the TSC2/Rheb/mTORC1 axis. In cases of T-cell ALL, indirect activation of mTOR, mainly mTORC1, can also occur under the influence of Notch1 through its interaction with c-MYC. It is also important to note that Notch1 can directly activate the PI3K/AKT/mTOR pathway through its action on growth factor receptors and cytokine receptors (62-65).

Leukemogenesis related to the PI3K/AKT/mTOR pathway can also be triggered by alterations in other cytoplasmic elements and/or cell receptors, which interact with but are not related to the pathway itself, leading to a loss of balance in the bone marrow microenvironment, as is the case of FMS-like tyrosine kinase 3 (FLT3), insulin-like growth factor 1 (IGF-1), interleukin 6 (IL-6) and stroma derived factor 1 (SDF-1, also called CXCL12), which can promote an excessive stimulation of several different signal transduction pathways, including PI3K/AKT/mTOR (39, 66, 67).

PI3K/AKT/mTOR Pathway Inhibition in Leukemias

Due to the importance of the PI3K/AKT/mTOR pathway in the control and regulation of several important cellular functions, the molecules that comprise this signaling cascade have become relevant pharmaceutical targets since their blockade can be a potential therapeutic strategy in the treatment of leukemias (12, 44).

Table I presents a set of clinical trials from the last ten years that address this theme and aim to find efficient pathway inhibitors for leukemias either as a monotherapy or in combination with other therapies. A total of 12 clinical trials are presented, and six of them examined the inhibition of AKT and mTOR components as treatment for acute leukemias whereas the other six examined the inhibition of PI3K as treatment for chronic leukemias, specifically CLL (68-79).

All studies described in Table I addressed the efficacy of PI3K/AKT/mTOR pathway inhibitors or their components, showing that changes in the pathway are very important for leukemia research, since they influence cell proliferation, metabolism, angiogenesis, and apoptosis, correlating with the clinical and hematological aspects of these diseases (68-79).

The results were more promising for CLL than acute leukemias, where even activation of secondary pathways that promote compensatory effects were reported (68-79).

Of the 12 clinical trials, two studies used Idelalisib as an inhibitor (monotherapy and in combination with Tirabrutinib) and two used Buparlisib showing beneficial results. Tensirolimus was also addressed in two studies, one of them in association with intensive re-induction chemotherapy, leading to high toxicity, and the other in combination with Cyclophosphamide and Etoposide, with generally beneficial results (69, 70, 73-75, 79). Other inhibitors tested in the studies and which presented positive or partially positive results were: BEZ235, Umbralisib in combination with Ibrutinib and Duvelisib associated with FCR (Fludarabine, Cyclophosphamide and Rituximab) (72, 77, 78). Three studies did not show good results; two of them used Perifosine as an inhibitor (monotherapy and in combination with UCN-01) and the other used Trametinib plus GSK2141795 (68, 71, 76).

Idelalisib: Approved PI3K Inhibitor

Despite reports that the PI3K/AKT/mTOR pathway is activated in acute leukemias, many current studies focus on the development of inhibitors of this pathway in CLL cases, especially those with a B-cell phenotype, in large part owing to the correlation between BCR-mediated signal transduction and PI3Kδ activation (41, 80-82). Dong *et al*. (83), found that mice with genetically inactivated p110δ showed a

Table I. *Clinical studies of PI3K/AKT/mTOR pathway target inhibition.*

Leukemia subtypes	Study phase	Treatment protocol	Molecular target of inhibition	Clinical outcome	Adverse effects	Reference
Acute leukemias or MDS	I	UCN-01 combined with Perifosine	AKT	There were no significant clinical responses. The inhibitory effects of AKT were not efficient and cases of disease progression and DLT have been reported in a considerable number of patients.	Vomiting, diarrhea, nausea, fatigue and hyperglycemia, pericardial effusion, hypotension, and pneumonitis.	(67)
Acute leukemia and mixed phenotype acute leukemia	I	Buparlisib	PI3K	A small inhibitory efficacy of the pathway has been reported, with a reduction in S6K, FOXO3 and PRAS40 levels. The median overall patient survival was 75 days. In addition, patients with 3q26 abnormalities had better survival.	Confusion, mucositis, dysphagia, nausea, diarrhea, fatigue, increased serum bilirubin and hyperglycemia.	(68)
ALL	I	Temsirolimus and intensive re-induction chemotherapy	PI3K/ mTOR pathway	The inhibition of the pathway was detectable soon after starting the therapeutic regimen. About 47% of patients had CR/CRi, in which 2 individuals had MRD 0.01 to 0,03% and 3 individuals had MRD less than 0.01%. Despite this, there have been reports of toxicities in patients with relapsed ALL.	Diarrhea, vomiting, mucositis, infections, fever, changes in glycemic indexes, electrolyte abnormalities, increased GGT and transaminases.	(69)
AML	II	Trametinib in combination with GSK2 141795	AKT and MEK 1/2	Study ended ahead of schedule. There were no significant clinical responses. Among the evaluated patients, the occurrence of CR/CRp was not identified. Despite this, small hematological and symptomatologic improvements have been described.	Diarrhea, nausea, vomiting, maculopapular skin eruptions and mucositis.	(70)
Acute leukemia	I	BEZ235	PI3K and mTOR	The ORR was 27%. There were inhibitory effects in a small group of patients with ALL, however, no beneficial effects were reported in AML, in which 91% of patients had disease progression.	Vomiting, diarrhea, nausea, stomatitis, mucositis, elevated liver markers, anorexia, hyperglycemia, anemia, neutropenia, and thrombocytopenia.	(71)
ALL	I	Temsirolimus combined with Cyclophosphamide and Etoposide	mTOR	Identification of inhibitory effects in a dose-dependent manner. Clinical responses were observed at all dose levels analyzed. The ORR was 47% and CR/CRi was 27%.	Febrile neutropenia, infections, sepsis, mucositis, hypercalcemia, hypophosphatemia, alterations in lipid profile, increase in transaminases and GGT.	(72)

Table I. *Continued*

Table I. *Continued*

Leukemia subtypes	Study phase	Treatment protocol	Molecular target of inhibition	Clinical outcome	Adverse effects	Reference
CLL	I	Idelalisib	PI3K-δ	The occurrence of positive inhibitory effects was identified, in addition to a reduction in AKT activation levels. An ORR of 72% has been reported. 39% of patients had PR and 33% had PR with therapy-induced lymphocytosis.	Fatigue, pyrexia, cytopenia, increased transaminases, diarrhea, skin eruptions, pneumonia, febrile neutropenia, among others.	(73)
CLL	II	Buparlisib	PI3K	Although complete responses were not identified, there were reports of PR and disease stability in some patients. Furthermore, an ORR of 46.1% was reported.	Thrombocytopenia, anemia, changes in blood glucose, transaminitis, fatigue, diarrhea, anorexia, among others.	(74)
CLL	II	Perifosine	AKT	Absence of efficient inhibition of AKT phosphorylation. 56% of patients did not show significant clinical responses and 19% had disease progression.	Nausea, vomiting, diarrhea, dehydration, hyperglycemia, increased bilirubin, hyponatremia, anemia, and thrombocytopenia.	(75)
CLL and MCL	I/IB	Umbralisib in combination with Ibrutinib	PI3K-δ and BTK	Successful inhibitory effects. Patients with CLL treated with the therapy achieved an ORR of 90%. CR rates were 29% in which they presented MRD and PR rates were 62%. Furthermore, the average time for the occurrence of complete responses was 18.4 months. In the case of patients with MCL, the ORR was 67%, the CR was 19% and the PR was 48%.	Neutropenia, thrombocytopenia, anemia, diarrhea, nausea, infections, fatigue, changes in transaminases, increased lipase, among others.	(76)
CLL	IB/II	Duvelisib in combination with FCR (Fludarabine, Cyclophosphamide, and Rituximab)	PI3K-δ/γ	An ORR of 88% and CR/CRi of 56% were identified. It was also reported that the 3-year OS estimate by ITT was around 93%, as well as the 3-year PFS, which was 73%. Furthermore, BM-uMRD was detected in about 56%.	Thrombocytopenia, neutropenia, lymphopenia, nausea, fatigue, fever, hyperglycemia, febrile neutropenia, and changes in transaminases.	(77)
CLL	II	Tirabrutinib in Combination with Idelalisib or Entospletinib	BTK and PI3K-δ or SYK	The combination showed satisfactory inhibitory effects, with an ORR of 88.7% reported. In addition, four patients achieved complete response with no evidence of MRD.	Diarrhea, constipation, nausea, neutropenia and contusion, rash, petechiae, upper respiratory tract infection, dyspepsia, and dizziness.	(78)

PI3K: Phosphatidylinositol-3 kinase; AKT/PKB: protein kinase B; mTOR: mammalian target of Rapamycin; MDS: myeloid dysplastic syndrome; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CLL: chronic lymphocytic leukemia; MCL: mantle cell lymphoma; S6K: ribosomal protein S6 kinase beta; FOXO3: Forkhead Box O 3; PRAS40: proline-rich AKT substrate of 40 kDa; CR: complete response; CRi: CR with incomplete blood count recovery; CRp: complete response with incomplete platelet recovery; PR: partial response; MRD: minimal residual disease; GGT: Gamma-glutamyl transferase; ORR: overall response rate; OS: median overall survival; ITT: intention-to-treat; PFS: progression-free survival; BM-uMRD: rate of bone marrow undetectable minimal residual disease.

significant delay in the development of the disease indicating the relevance of PI3Kδ in the development and progression of CLL, since.

Idelalisib, also known as CAL-101 or GS-1101, is a selective inhibitor of the PI3Kδ isoform. It was approved by the Food and Drug Administration (FDA) in June 2014 for the treatment of patients with CLL, follicular non-Hodgkin lymphoma (LF) of relapsed B-cell and relapsed small lymphocytic lymphoma (SLL) (45, 84, 85).

Once administered, Idelalisib is metabolized primarily by aldehyde oxidase, and to a smaller scale by cytochrome P450 3A (CYP3A). Like many PI3K inhibitors, Idelalisib is a competitive drug for adenosine triphosphate (ATP) binding sites, in order to prevent PI3K-mediated phosphorylation of PIP2. Such binding sites are located in the protein's catalytic domains, which are formed by the N-terminal and C-terminal domains. Between these domains there is a cleft where the hinge region is located, which contains valine residues (a conserved region among class I PI3K isoforms) and is the site where ATP interacts with the protein. Hydrogen bonds between the Val-828 and Val-826 residues in the PI3K hinge region and the N3 and N9 purine molecules of Idelalisib, respectively, are formed. Hydrogen bonds, mediated by water molecules, are also formed between purines N7, N1 and the side chain of Asp-911. In addition, this drug is also capable of making hydrophobic bonds with other protein residues, such as RS4, CS6, CS7, Val-827, Met-900, among others (Figure 2) (45, 84, 86-88).

Two of the studies presented in Table I used of Idelalisib as an inhibitor of the PI3K/AKT/mTOR pathway and showed satisfactory results regarding the effectiveness of pathway inhibition. Brown *et al*. (74) used it as monotherapy, while Danilov *et al*. (79) compared the combination of Idelalisib with Tirabrutinib and other combinations. Both studies showed significant clinical responses indicating that Idelalisib is a promising inhibitor of the PI3K/AKT/mTOR pathway in cases of CLL. Furthermore, its combination with Tirabrutinib seems to be more effective compared to the use of Idelalisib alone with an overall response rate (ORR) of approximately 93% and 72%, respectively. Staber *et al*. (89) examined Tafasitamab combined with Idelalisib or Venetoclax in individuals with relapsed/refractory CLL. Patients who received the combination of Tafasitamab with Idelalisib had an ORR of 90,9 and minimal residual disease (MRD) of 72,7% and two participants were negative for DRM in peripheral blood samples. However, Lampson *et al*. (90) reported that the combination of Idelalisib with Ofatumumab in patients with CLL generated high toxicity rates, making it impossible to complete the study.

Brown *et al*. (74) reported that treatment with Idelalisib reduced AKT phosphorylation, decreased plasma concentrations of chemokines, especially CCL3, CCL4, CCL17 and CCL22 and stromal-derived factors, such as CD40L (CD40 ligands), tumor necrosis factor α (TNFα), CCL2 and CXCL13. Hoellenriegel *et al*. (91), obtained similar results when examining the effects of Idelalisib in cultures of CLL cells and reported that there was a reduction in the phosphorylation of AKT and extracellular signal-regulated kinases (ERK), a reduction in the levels of CCL2, CCL3, CCL4, CCL7, CCL22, CD40L, CXCL13, TNF-α and interleukin-6 (IL-6) and a suspension of chemotaxis of CLL cells towards CXCL12 and CXCL13. Serrat *et al*. (92) also tested Idelalisib in cocultures of follicular lymphoma and follicular dendritic cells and observed that the inhibitor was capable of interfering with the CD40/CD40L pathway, modulating CCL22 levels and negatively regulating the pro-angiogenic factors VEGF-A and VEGF-C.

In the two studies with Idelalisib (monotherapy and in combination with Tirabrutinib) some adverse events (AEs) were described, with the most common being diarrhea, skin eruptions, pyrexia, and some cases of cytopenia. In addition, in more severe cases, the occurrence of pneumonia, febrile neutropenia and some bacterial infections have been reported (74, 79). Other studies in the literature report similar AEs in their studies, highlighting the occurrence of hematological alterations (neutropenia, anemia, and thrombocytopenia) and biochemical alterations, such as increased transaminases, glycemic alterations (generally elevated), increased gamma glutamyl transferase and alkaline phosphatase (93-96).

Clinical Aspects of Other PI3K/AKT/mTOR Inhibitors Pathway

Although Idelalisib is an important PI3K inhibitor currently used as a therapeutic measure against hematological malignancies, other inhibitors of this protein have also been approved for combating hematological neoplasms, preventing signal transduction of a wide variety of downstream signaling pathways, including those linked to the BCR. Among these inhibitors we can highlight Duvelisib and Copanlisib (97-99).

Duvelisib, also known as IPI-145 and INK-1197, is a dual PI3K inhibitor which acts specifically on PI3Kδ and γ isoforms, having received FDA approval in 2018 and European Medicines Agency (EMA) approval in 2021 to be used as therapy in cases of relapsed and refractory CLL and small lymphocytic lymphomas (SLL) that have already undergone at least two previous treatments. In addition, there are reports that such medication can stimulate apoptosis, reduce the migration of neoplastic cells, reduce chemotaxis, decrease the levels of circulating cytokines and chemokines, and modulate several cellular signaling pathways (97, 98, 100-102). Flinn *et al*. (103) carried out a phase 1 study with patients with hematological malignancies, including CLL (relapsed/refractory and absent from previous treatment), indolent non-Hodgkin lymphoma (iNHL), and cutaneous and

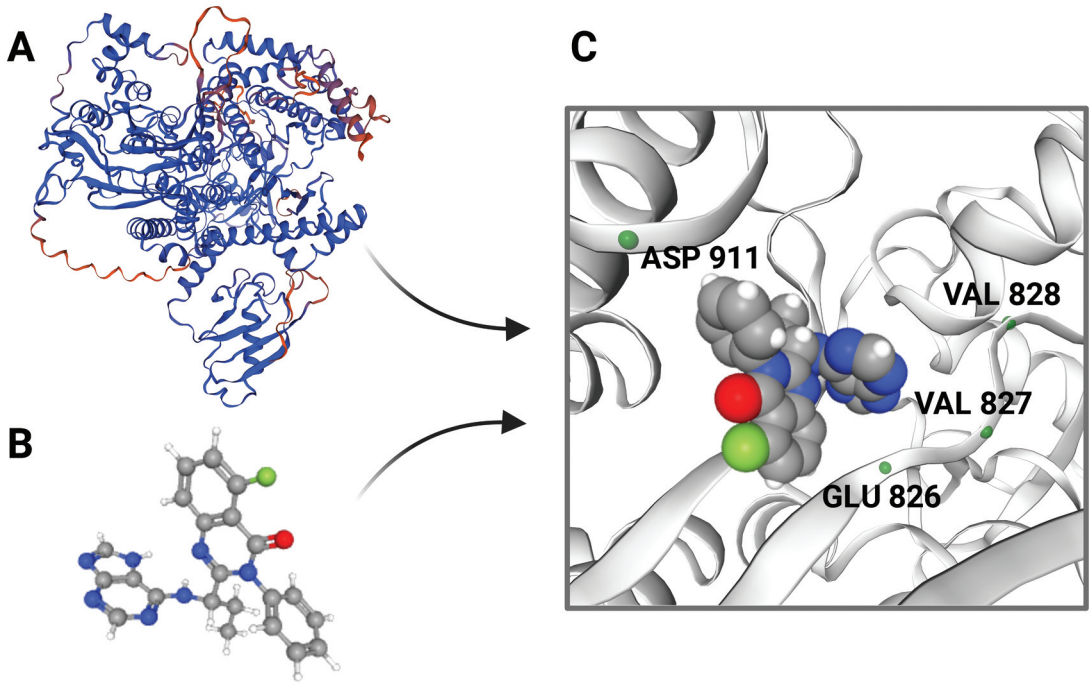

Figure 2. *Chemical structures and illustration of the catalytic region where PI3Kδ inhibition by Idelalisib occurs. All illustrations of the PI3Kδ protein presented in Figure 2 were acquired from the Swiss-Model server (https://swissmodel.expasy.org/repository/uniprot/O00329?model=AF-O00329-F1-model-v4), whereas all Idelalisib inhibitor chemical structures were acquired from the PubChem server (https://pubchem.ncbi.nlm.nih.gov/compound/11625818#section=3D-Conformer). Furthermore, the assembly of the figure was performed on the Biorender virtual platform. A) Phosphatidylinositol 3-kinase delta (PI3Kδ) 3D structure; B) Idelalisib inhibitor 3D chemical structure; C) Illustration of the catalytic region of the PI3Kδ protein interacting with Idelalisib, in the way that the inhibitor competes for the binding of adenosine triphosphate (ATP) molecules on the protein and will form bonds between some of the chemical groups of the inhibitor and certain amino acid residues in the catalytic site, such as VAL 828, VAL 827, GLU 826 and ASP 911.*

peripheral T-cell lymphoma (TCL). As a result of the therapy effectiveness, patients with relapsed/refractory CLL and those who were not previously submitted to treatments obtained an ORR of 56% and 83%, respectively, and, patients with iNHL cutaneous and peripheral TCL showed ORR 58%, 32%, and 50%, respectively.

Copanlisib is another PI3K inhibitor which was FDA approved in 2017 under the trade name of Aliqopa and acquired EMA approval in 2020. It is a class I pan PI3K inhibitor acting mainly on the PI3Kα and δ isoforms. Its application aims at the treatment of patients with relapsing follicular lymphomas (FL) who have already been submitted to at least two previous systemic therapeutic schemes. In addition, application of this medication for other B-cell malignancies, such as CLL has also been examined (99, 104-106). Dreyling *et al*. (107) tested Copanlisib in patients with CLL and aggressive malignant lymphoma and obtained an ORR of 43.8% and 29.4%, respectively. In addition, they also found a reduction of at least 50% in lesion size in 66.7% of patients with indolent neoplasms and 42.5% in patients of the aggressive cohort.

mTOR inhibitors, which are classified into first and second generation inhibitors, have also received lot of attention. First-generation inhibitors are basically represented by Rapamycin and Rapamycin analogs (Rapalogs), whereas the second generation are considered as double inhibitors and are divided into mTORC1/mTORC2 inhibitors and PI3K/mTOR inhibitors (25, 108, 109).

First generation inhibitors show a good inhibitory activity of mTORC1. Inhibitors such as Rapamycin promote their effects by binding to intracellular receptors called FK506 binding protein 12 (FKBP12). This binding results in the formation of a complex formed by both elements that act on the FRB domains of mTOR. As a consequence, the interaction between Raptor and mTOR molecules is interrupted, preventing the action of downstream effector components mainly on cell proliferation and angiogenesis. Despite this, Rapamycin does not show such satisfactory effects, and there is even the possibility of AKT reactivation by positive feedback. The second generation inhibitors are considered dual inhibitors. The mTORC1 and 2 inhibitors are classes of inhibitors that act competitively on mTOR/ATP, promoting a complete blockade

of 4E-BP1. In this way, they can prevent cell replication processes, but that can also promote cell death by apoptosis. In contrast, dual PI3K/mTOR inhibitors act as competitive compounds for ATP binding sites on these proteins due to the similarity between the catalytic sites of both, so that the pathway is blocked (25, 108-111).

In general, PI3K/AKT/mTOR pathway inhibitors can affect the tumor microenvironment in several ways. One of them refers to their direct action on malignant cells present in the tumor stroma, by modulating cell signaling, preventing them from proliferating and stimulating cell death by apoptosis. In addition, they interfere and regulate cellular responses to various stimuli that are generated by inflammatory mediators that could favor the survival and maintenance of these malignant cells, such as molecules acting as costimulators, molecules involved with cell adhesion (for example, CXCR4 and CXCR5), cytokines and chemokines, such as interleukins (for example, IL-2, IL-4, IL-6, IL-10, and IL-17), interferon γ (IFNγ), TNFα, CD40L, CCL3, CCL4, CXCL10, and CXCL13. These inhibitors can also modulate the immune responses generated by TCD8+ and TCD4+ lymphocytes and reduce the levels of regulatory T cells (T_{reg} cells), affecting antitumor immunity (45, 112-114).

Maharaj *et al*. (115), found that inhibition of PI3Kδ and γ in cultured CLL cells using Idelalisib, Duvelisib and Umbralisib resulted in a reduction in the levels of AKT and cytokines. They also observed that Idelalisib and Duvelisib suppressed FOXP3 expression, significantly reduced the number of T_{reg} cells and decreased the expression of immunosuppressive molecules PD-1 and CTLA-4 on the surface of T_{reg} cells. Furthermore, they also associated the deleterious effects of T_{reg} cells with certain immune-mediated toxicities, since the lower the percentage of T_{reg} cells, the greater the possibility of toxicities occurring. Based on this, they noted that Umbralisib has a tendency to quantitatively and functionally preserve T_{reg} cells, since it is a selective inhibitor of PI3Kδ and is also capable of inhibiting casein kinase-1-ε (CK1ε). Chellappa *et al*. (116), found that PI3Kδ inhibition in CLL cells treated with Idelalisib, also resulted in a reduction in AKT levels and the number of T_{reg} cells, a decrease in the expression of FOXP3, CD-25, and PD-1 and a trend towards a decrease in CTLA-4 and CD-39 levels.

Two of the studies presented in Table I addressed the use of Buparlisib as an PI3K/AKT/mTOR pathway inhibitor that is a pan-PI3K inhibitor (69, 75). In one of these studies, Assouline *et al*. (75) tested the inhibitor in CLL cases, specifically B-cell CLL and verified the effectiveness of Buparlisib in blocking the pathway and the relevance of the biomarkers RAPTOR and P70S6K expression with the responses to the treatment. It was observed that the quantitative reduction of leukemic cells positive for RAPTOR is related to a higher rate of tumor shrinkage. This occurs because in cases of signal transduction *via* BCR with the activation of PI3K-δ dependent on RAPTOR signaling, there is greater resistance to PI3K-δ inhibition. However, with the reduction of RAPTOR expression by tumor cells, there is an improvement in responsiveness to treatment. Amrein *et al*. (117) evaluated the effectiveness of Buparlisib in CLL B cells in *in vitro* studies and inhibitory growth effects, cell death of these leukemic lineages, a decrease in the basal RAPTOR and P70S6K expression and a reduction of AKT phosphorylation.

Ragon *et al*. (69) also evaluated the antileukemic potential of Buparlisib in acute leukemias and observed moderate efficacy, a decrease in the levels of p-S6K (target of mTORC) and p-FOXO3 (target of AKT), as well as PRAS40 down-regulation. Mehrpouri *et al*. (118) performed tests on cultures of ALL-derived cells treated with Buparlisib in combination with Panobinostat, a histone deacetylase (HDAC) inhibitor, and obtained positive results Specifically, they found induction of apoptosis, decreased cell proliferation and reduction in viability and metabolic activity of cells. Furthermore, they evidenced the capacity of the treatment to modulate FOXO3 and FOXO4 expression levels, increase cMYC suppression and increase p21 and p27 expression.

Although alterations in the PI3K/AKT/mTOR pathway are detected in many cases of acute leukemia, mainly AML, the development of efficient inhibitors of this pathway is a very complex, as there are reports predicting the overactivation of compensatory signaling pathways. For this reason, some studies addressed the PI3K/AKT/mTOR pathway inhibition while also targeting other secondary mechanisms that promote leukemogenesis (49, 119, 120). An example of the difficulty in identifying good inhibitors of this pathway for acute leukemias was demonstrated by Lang *et al*. (72), who tested the BEZ235 inhibitor in patients with acute leukemias. They found that only a small group of patients with ALL obtained good results, while patients with AML did not obtain significant benefits, including a progression of the disease in 91%.

Two other studies on acute leukemias, especially ALL, used Tensirolimus as an inhibitor. Rheingold *et al*. (70) used Tensirolimus in combination with intensive reinduction chemotherapy in three weekly doses. They observed excessive toxicity, non-tolerability in children with relapsing ALL and DLT (dose-limited toxicity) was present at all dose levels. Despite this, 47% of the evaluated participants had complete response (CR) or complete response with incomplete blood count recovery (CRi) and of these, five had minimal residual disease (MRD) less than 0.03% at the end of therapy. Tasian *et al*. (73) examined the effect of the inhibitor in combination with Cyclophosphamide and Etoposide and obtained a similar ORR of 47%, and 3 participants showed a MRD of less than 0.01%. In addition, they claimed less toxicity and greater therapeutic safety, since only two doses of treatment were administered per week.

Among the unsuccessful studies, two used Perifosine, both as monotherapy in CLL and in combination with UCN-01 in acute leukemias. Treatment of CLL with Perifosine generated lymphocytic cytotoxicity *in vitro* and absence of relevant clinical responses *in vivo*. In acute leukemias, DLT and lack of effectiveness in the maximum tolerated dose (MTD) were observed (68, 76). Despite this, Perifosine alone and in combination with Sorafenib was examined in a study with lymphoproliferative diseases, including CLL; half of the patients with CLL treated with monotherapy and in 1/4 of the patients treated with the combination responded to medication (121).

Among the evaluated studies, there were some similarities regarding the occurrence of some of the AEs. The most common AEs were gastrointestinal problems (nausea, vomiting, diarrhea), biochemical alterations (mainly, hyperglycemia), hematological disturbances (neutropenia, anemia, thrombocytopenia), fatigue, mucositis, and an increased propensity to develop infections (68-79). Other studies reported, such as those of O'Brien *et al*. (14), Rigolin *et al*. (122) and Mato *et al*. (123) reported the occurrence of neutropenia, anemia, infections, fatigue, gastrointestinal problems, among other symptoms in patients with leukemia.

Conclusion

Our work emphasizes the major role of PI3K/AKT/mTOR pathway on leukemogenesis and leukemia development, highlighting its potential as a therapeutic target in hematological malignancies. Critical review of clinical studies conducted in the past ten years reveal a tendency for better responses to pathway inhibitors among CLL afflicted patients, supported by the FDA approval of treatment regimens including drugs, such as Idelalisib and Duvelisib. Further stratification for treatment efficacy may even be made among the CLL patient cohort, as B-cell CLL is better suited to be treated with PI3K inhibitors due to its upstream overactivation by the B-cell receptor (BCR). Furthermore, we observe increased difficulty in developing safe and effective treatment strategies using PI3K inhibitors to treat acute leukemias, primarily because of treatment-induced activation of compensatory pathways for neoplastic maintenance and consequent drug resistance. Overall, while the role of PI3K/AKT/mTOR pathway is well defined both in healthy and neoplastic scenarios, further studies are still need to properly translate its inhibition into potential therapies, aiming to prolong treatment efficacy and minimize cases of drug resistance, especially when considering its use for acute leukemias.

Conflicts of Interest

The Authors declare no conflict of interest in relation to this study. The funders had no role in the design of the study; in the collection, analyses, or data interpretation; in the writing of the manuscript, or in the decision to publish the results.

Authors' Contributions

C.A.M.-N; Conceptualization, A.K.C.M, C.B.M., F.M.C.d.P.P., R.B.G, I.V.B and C.A.M.-N.; Provision of data and subsequent analysis and interpretation, A.K.C.M, C.B.M., F.M.C.d.P.P., R.B.G, I.V.B., C.A.M.-N., R.M.R., D.d.S.O., M.O.d.M.F., M.E.A.d.M., A.S.K; Writing – original draft preparation, A.K.C.M, C.B.M., F.M.C.d.P.P., R.B.G, I.V.B and C.A.M.-N.; Writing – review and editing, A.K.C.M, C.B.M., F.M.C.d.P.P and C.A.M.-N. Funding acquisition, C.A.M.-N. and A.S.K. All Authors have read and agreed to published version of the manuscript.

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