

## Review

# PI3K $\delta$ Inhibitors as Immunomodulatory Agents for the Treatment of Lymphoma Patients

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**Simple Summary:** This review focuses on the effects that a class of drugs, PI3K $\delta$  inhibitors, used for the treatment of patients with lymphoma can have not on the neoplastic cells but on the normal cells and how this effect can modulate the immune response and potentially contribute to the anti-tumor response.

**Abstract:** The development of small molecules able to block specific or multiple isoforms of phosphoinositide 3-kinases (PI3K) has already been an active field of research for many years in the cancer field. PI3K $\delta$  inhibitors are among the targeted agents most extensively studied for the treatment of lymphoma patients and PI3K $\delta$  inhibitors are already approved by regulatory agencies. More recently, it became clear that the anti-tumor activity of PI3K inhibitors might not be due only to a direct effect on the cancer cells but it can also be mediated via inhibition of the kinases in non-neoplastic cells present in the tumor microenvironment. T-cells represent an important component of the tumor microenvironment and they comprise different subpopulations that can have both anti- and pro-tumor effects. In this review article, we discuss the effects that PI3K $\delta$  inhibitors exert on the immune system with a particular focus on the T-cell compartment.

**Keywords:** lymphoma; PI3K inhibitors; T-cells; B-cells; macrophages; chemokine; cancer; tumor; immune checkpoint inhibitors



**Citation:** Tarantelli, C.; Argnani, L.; Zinzani, P.L.; Bertoni, F. PI3K $\delta$  Inhibitors as Immunomodulatory Agents for the Treatment of Lymphoma Patients. *Cancers* **2021**, *13*, 5535. <https://doi.org/10.3390/cancers13215535>

Academic Editor: Charles H. Lawrie

Received: 20 September 2021

Accepted: 29 October 2021

Published: 4 November 2021

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## 1. Introduction

Phosphoinositide 3-kinases (PI3Ks) are a class of enzymes fundamental in the regulation of cell metabolism, proliferation and survival [1–6]. PI3Ks are active in most human cancers, often representing oncogenic drivers due to genetic events directly targeting their coding genes or determining the constitutive activation or upstream components of the signaling cascade [1,4–6].

PI3Ks comprise four isoforms p110 $\alpha$  (PI3K $\alpha$ , coded by the *PIK3CA* gene), p110 $\beta$  (PI3K $\beta$ , coded by *PIK3CB*), p110 $\delta$  (PI3K $\delta$ , coded by *PIK3CD*), and p110 $\gamma$  (PI3K $\gamma$ , coded by *PIK3CG*). These are the catalytic subunits that form heterodimers with regulatory isoforms. The p85 $\alpha$  and its splicing variants p55 $\alpha$  and p50 $\alpha$  (*PIK3R1*), p85 $\beta$  (*PIK3R2*), and p55 $\gamma$  (*PIK3R3*) can bind PI3K $\alpha$ , PI3K $\beta$ , or PI3K $\delta$  (class IA PI3Ks), while p101 (*PIK3R5*) or p87 (*PIK3R6*) bind PI3K $\gamma$  (Class IB PI3Ks). PI3K $\delta$  and PI3K $\gamma$  are largely restricted to leukocytes, while PI3K $\alpha$  and PI3K $\beta$  are ubiquitously expressed [1,4–6].

The development of small molecules able to block specific or multiple PI3K isoforms is a heavily pursued effort in oncology: Table 1 shows the PI3K $\delta$  inhibitors that have entered clinical development. Multiple preclinical and clinical studies showed the anti-tumor activity of PI3K $\delta$  inhibitors in patients affected by chronic lymphocytic leukemia (CLL), B- and T-cell lymphomas and these data have been extensively summarized elsewhere [3–8]. Importantly, PI3Ks are expressed not only in the cancer cells, but also in the non-neoplastic cells, in which PI3K inhibitors contribute to their pro- or anti-tumor effects, and they can be used to improve the response to immunomodulatory and immunotherapeutic agents [9–17]. In this review article, we will discuss the effects of inhibiting PI3K $\delta$  isoform on the immune system with a particular focus on the T-cell compartment.

**Table 1.** List of PI3Kdelta inhibitors sorted by their target, their official name, if assigned, or by their common/alternative name.

Target	Official Name	Common/Alternative Name	PI3K $\delta$ (IC <sub>50</sub> , nM)	PI3K $\alpha$ (IC <sub>50</sub> , nM)	PI3K $\beta$ (IC <sub>50</sub> , nM)	PI3K $\gamma$ (IC <sub>50</sub> , nM)	Adm. Route	Phase #	FDA Approval	On-Going Trials ##
PI3K $\delta$	Acalisib	GS-9820, CAL-120 [18]	12.7	5441	3377	1389	p.o	1	-	-
PI3K $\delta$	Dezapelisib	INCB040093 [19]	31	28,912	3751	2297	p.o	2	-	-
PI3K $\delta$	Idelalisib	CAL-101, GS-1101 [20]	2.5	820	565	89	p.o	3	CLL, FL, SLL **	Lymphoid tumors
PI3K $\delta$	Leniolisib	CDZ173 [21]	1.1	244	424	2230	p.o	3 ^	-	APDS/PASLI ^
PI3K $\delta$	Linperlisib	YY-20394, PI3K(delta)-IN-2 [22]	n.a.	n.a.	n.a.	n.a.	p.o	2	-	Lymphoid and solid tumors
PI3K $\delta$	Nemiralisib	GSK2269557 [23]	9.9	n.a.	n.a.	n.a.	inh.	2 ^	-	-
PI3K $\delta$	Parsaclisib	INCB050465, IBI-376 [19]	1.1	>20,000	>20,000	>10,000	p.o	3	-	Lymphoid tumors, myeloid neoplasms
PI3K $\delta$	Puquitinib	XC-302 [24]	3.3	992.8	959.2	89.8	p.o	no	-	-
PI3K $\delta$	Seletalisib	UCB-5857 [25]	12	3638	2129	282	p.o	2	-	No
PI3K $\delta$	Zandelisib	ME-401, PWT143 [26]	5	5022	208	2137	p.o	2	-	Lymphoid tumors
PI3K $\delta$	-	ACP-319, AMG 319 [27]	18	33,000	270	85	p.o	2	-	Lymphoid tumors
PI3K $\delta$	-	BGB-10188 [28]	n.a.	n.a.	n.a.	n.a.	p.o	2	-	Lymphoid and solid tumors
PI3K $\delta$	-	GS-9901 [29]	1	750	100	190	p.o	1	-	-
PI3K $\delta$	-	GSK2292767 [23]	n.a.	n.a.	n.a.	n.a.	inh.	1 ^	-	-
PI3K $\delta$	-	HMPL-689 [30]	0.8	>1000	87	114	p.o	1	-	Lymphoid tumors
PI3K $\delta$	-	IOA-244, MSC2360844 [31]	145	18,500	2850	>20,000	p.o	1	-	Lymphoid and solid tumors
PI3K $\delta$	-	RV1729 [32]	12	193	n.a.	25	inh.	1 ^	-	-
PI3K $\delta$	-	SHC014748M [33]	n.a.	n.a.	n.a.	n.a.	p.o	2	-	Lymphoid tumors
PI3K $\alpha$ /PI3K $\delta$	Copanlisib	BAY 80-6946 [34]	0.7	0.5	3.7	6.4	i.v.	3	FL ***	Lymphoid and solid tumors

Table 1. Cont.

Target	Official Name	Common/Alternative Name	PI3K $\delta$ (IC <sub>50</sub> , nM)	PI3K $\alpha$ (IC <sub>50</sub> , nM)	PI3K $\beta$ (IC <sub>50</sub> , nM)	PI3K $\gamma$ (IC <sub>50</sub> , nM)	Adm. Route	Phase #	FDA Approval	On-Going Trials ##
PI3K $\alpha$ /PI3K $\delta$	Pictrelisib	Pictilisib GDC-0941, RG-7321 [35]	3	3	33	75	p.o	2	-	-
PI3K $\alpha$ /PI3K $\delta$	-	TQ-B3525 [36]	n.a.	n.a.	n.a.	n.a.	p.o	2	-	Lymphoid and solid tumors
PI3K $\beta$ /PI3K $\delta$	-	AZD8186 [37]	12	35	4	675	p.o	2	-	Solid tumors
PI3K $\beta$ /PI3K $\delta$	-	KA2237 [38]	8	>500	19	>500	p.o	1	-	-
PI3K $\alpha$ /PI3K $\delta$ /PI3K $\gamma$	Taselisib	GDC-0032 [39]	0.12	0.29	9.1	0.97	p.o	3	-	Lymphoid and solid tumors
PI3K $\alpha$ /PI3K $\beta$ /PI3K $\delta$	Sonolisib	PX-866 [40]	2.7	5.5	>300	9	p.o	2	-	-
PI3K $\delta$ /PI3K $\gamma$	Duvelisib	IPI-145, INK1197 [41]	2.5	1602	85	27	p.o	3	CLL, FL, SLL ****	Lymphoid tumors
PI3K $\delta$ /PI3K $\gamma$	Tenalisib	RP6530 [42]	24	>7000	>3000	33	p.o	2	-	Solid tumors
PI3K $\alpha$ /PI3K $\delta$ /BRAF	-	ASN003 [43]	6	16	690	97	p.o	1	-	-
PI3K $\delta$ /CK1 $\epsilon$	Umbralisib	TGR-1202, RP5264 [44]	22.23	>9000	>1000	>1000	p.o	3	FL, MZL *****	Lymphoid tumors
PI3K $\alpha$ /PI3K $\beta$ /PI3K $\delta$ /HDAC	Fimepinostat	CUDC-907 [45]	39	19	54	311	p.o	2	-	Lymphoid and solid tumors

FDA, U.S. Food and Drug Administration; target IC<sub>50</sub> inhibition based on reported kinase inhibition profiles; #, based on <http://adisinsight.springer.com/> and on <https://clinicaltrials.gov> accessed in 15 September 2021; ##, defined as “recruiting” or “not yet recruiting” in <https://clinicaltrials.gov> accessed in 15 September 2021; APDS/PASLI, Activated phosphoinositide 3-kinase delta syndrome/p110 $\delta$ -activating mutation causing senescent T-cells, lymphadenopathy and immunodeficiency; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; , non in oncology; \*\*, for the treatment of patients with (a) relapsed CLL in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities, (b) relapsed FL after at least two prior systemic therapies, (c) relapsed SLL after at least two prior systemic therapies [46]; \*\*\*, for the treatment of adult patients with relapsed FL after at least two prior systemic therapies [47]; \*\*\*\* for the treatment of adult patients with (a) relapsed or refractory CLL/SLL after at least two prior therapies, (b) relapsed or refractory FL after at least two prior systemic therapies [48]; \*\*\*\*\* for the treatment of adult patients with (a) relapsed or refractory MZL who have received at least one prior anti-CD20-based regimen and (b) for relapsed or refractory FL who have received at least three prior lines of systemic therapy [49]; inh., inhalation.; p.o., per os; i.v., intravenous.

## 2. Immune System and Anti-Cancer Immunotherapy

The TME is a complex system comprising the cancer cells, plus proteins and other chemical components of the extracellular matrix (ECM), and “accessory” non-neoplastic cells, such as resident mesenchymal support cells, infiltrating inflammatory immune cells, and endothelial cells. Altogether, the tumor microenvironment (TME) plays a fundamental role in regulating tumor development, both leading to an immune inflammatory response and fueling innate and adaptive immune activity against cancer cells, but also supporting the growth of the latter [50].

Cells and tissues are continuously surveilled by immune cells, which recognize and eliminate emerging cancer cells. Genetically engineered mice deficient for CD8<sup>+</sup> cytotoxic T-lymphocyte (CTLs), CD4<sup>+</sup> Th1 helper T-cells, or natural killer (NK) cells components of the immune system, show an increased tumor incidence [51,52].

During tumor initiation, naïve T-cells recognize antigens expressed by malignant cells are primed in the draining lymph nodes, are activated, and migrate in the TME. In this niche, immune response eliminates immunogenic cancer cells [53]. NK and cytotoxic CD8<sup>+</sup> T-cells eliminate immunogenic proliferating cancer cells [54]. Later on, inflammation is persistent and inflammatory cells are recruited and activated. In many cancers, high presence of tumor-infiltrated T-cells has a good prognostic value [55,56]; instead, high presence of macrophage infiltration often correlates with poor prognosis [57] and tumor-associated inflammatory response has a paradoxical effect of enhancing tumor progression [58,59]. Tumor-promoting effects of immune cells is becoming more and more evident and inflammation provides bioactive factors that helps proliferative growth, angiogenesis, invasion, and metastasis. In the setting of T-cell lymphomas, expression and secretion of immunoinhibitory molecules can be shared by both tumor and non-neoplastic cells [15,17].

CD8<sup>+</sup> T-cells are the main players among anti-tumor T-cells. They are primed and activated by antigen presenting cells (APC) to differentiate into CTL, which can directly kill cancer cells [60].

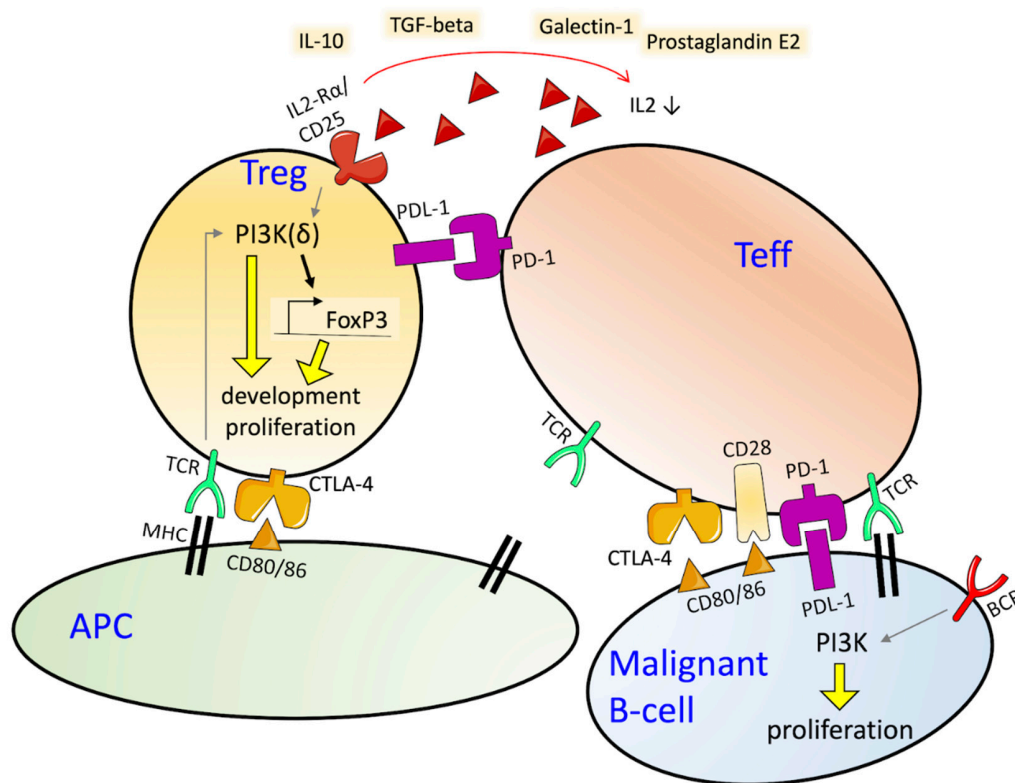
CD4<sup>+</sup> T helper 1 (Th-1) cells act through a variety of mechanisms. They massively secrete proinflammatory cytokines, as IL-2, TNF- $\alpha$  and IFN- $\gamma$ , co-adjuvate CTL cytotoxicity and T-cell priming and activation, help macrophages and NK cells to destroy tumoral cells and facilitate tumor antigens presentation [61–63]. Immune infiltrate components of tumors include CD8<sup>+</sup> T-cells and Th-1 cytokines, correlating with favorable prognosis in many cancer types [64].

Effector T-cells killing-activity relies on the balance between the capability of tumor antigens to induce an immune response (immunogenic feature) and the existence of signals impairing T-cell functions [53]. This process by which the immune system controls tumoral growth and balances tumor immunogenicity is called immune editing. Tumoral cells with the most immunogenic antigens are recognized and killed in the early stages of tumorigenesis, while the less immunogenic cancer cells escape T-cell control [54,65]. Neoplastic cells are also able to decrease the response of the others innate immunity involved cells as tumor-associated macrophages (TAM) and NK cells [66].

At present, different mechanisms of cancer immune tolerance have been identified. Immune checkpoints signals are negative regulators of effector T-cells, and the two mainly studied molecules in cancers are Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) and Programmed Cell Death 1 (PD-1) [63]. Known ligands of CTLA-4 are CD80 and CD86, while PD-1 binds to its coreceptors PDL-1/2, expressed also by cancer cells, to impair anti-tumor T-cell responses [67]. Immune checkpoint inhibitors (pembrolizumab and nivolumab as anti-PD1; atezolizumab as anti-PD-L1; ipilimumab as anti-CTLA4) became a successful strategy to enhance anti-tumor response in many malignancies [68].

As the tumor grows, cancer cells and signal molecules in the TME recruit regulatory CD4<sup>+</sup> T-cells (Tregs), responsible to inhibit T-cell responses, specifically priming, activation and cytotoxicity of effector immune cells (Figure 1) [69]. Tregs contribute to the suppression of uncontrolled clonal expansion and negatively regulate the insurgence of

hyper-inflammatory state. In tumors, they are recruited to hamper the immune system and escape immune surveillance [70,71]. Tregs exploit their function through contact-dependent mechanisms—PDL-1, LAG-3 C39/73, CTLA-4 or PD1 are expressed on their cell surface, and lead to effector cell death or to enhance this event—and contact-independent mechanisms—by secreting immune-suppressive cytokines, as IL-10, TGF- $\beta$ , prostaglandin E2, adenosine, and galectin-1 [72,73], and also recruiting myeloid-derived suppressor cells which contribute to build an immunosuppressive environment [74]. Tumor-infiltrating Treg cells are under pressure of a challenging environment with low oxygen availability, high glucose demand, and a multitude of cytokines and chemokines [75,76]. Tan et al. demonstrated that PI3K-AKT pathway regulates the immunosuppressive capacity of PD-1 deficient Tregs [77]. Tregs are characterized by the expression of the IL-2 receptor alpha chain (CD25), CD4, FOXP3 and CTLA-4. Enrichment of Tregs in tumors can be due to an augmented recruitment, expansion in the TME as a consequence of antigenic exposure, response to cytokine signals or metabolic changes (Figure 1) [53]. Higher numbers of Tregs have been detected in the blood of lymphoma patients than of healthy or cured patients [78,79], and in lymphoma tissues than in reactive lymph nodes [78]. In cutaneous diffuse large B-cell lymphoma, Hodgkin's lymphoma and Epstein-Barr virus-associated lymphoma, Tregs are recruited by CCR4 ligands or evolve from conventional cells (Tconvs) to Tregs in the TME [80]. High presence of circulating Tregs represents a poor prognostic factor in diffuse large B-cell lymphoma (DLBCL), correlates with high lactate dehydrogenase, advanced stage of the disease [78], and poor survival [72,81].



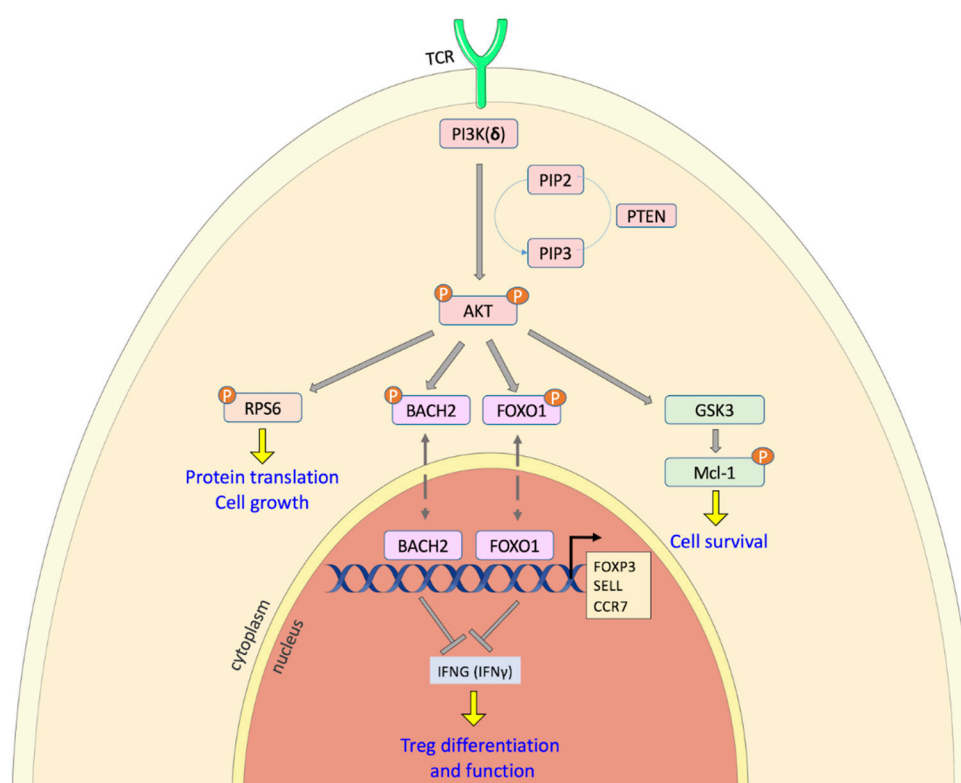
**Figure 1.** Immuno-regulation in the tumor microenvironment. Tregs deprive the surrounding of co-stimulatory signals for effector T-cells (Teff) affinity and activity. They exert their suppressive mechanism by different modalities: depriving IL-2 from the surrounding, therefore reducing it for effector T-cells, by IL-2 binding with CD25; constitutively expressing CTLA-4, which down-regulates CD80/86 expression by antigen-presenting cells (APC) and limits co-stimulatory signals for Teff, together with CD28; immune-suppressive cytokines produced by Tregs decrease APC and Teff signals; PD-1/PD-L1 axis activation inhibits Teff function. In this environment, responders T-cells die by apoptosis or stay dormant and tumor cells are prone to proliferation. Targeting PI3K specifically in Tregs could provide advantage for anti-cancer immunotherapy. TCR: T-cell receptor; MHC: Major Histocompatibility Complex, BCR: B-cell receptor.



### 3. Targeting PI3K $\delta$ and Treg in Lymphomas

The ideal immune regulatory approach to fight cancer should be able to selectively deprive Tregs in TME, while maintaining a potent immune effector system. Understanding the signaling pathways regulating Tconvs and Tregs mechanisms could help to develop specific Tregs and Tconvs modulation strategies. In vitro and in vivo studies demonstrated that PI3K signaling is fundamental for Treg differentiation and immunosuppressive function, although the precise mechanism is still unclear [82–84].

Tregs are dependent on the activity of the PI3K $\delta$  isoform [83,85,86] and studies suggest that loss of PI3K signaling in Tregs leads to increased activity of the BACH2 and FOXO1 transcription factors, which in normal conditions, regulate the expression of key genes in Treg differentiation and function (*FOXP3*, L-selectin, *CCR7* and *IFN $\gamma$* ) [87–89] (Figure 2). In line with this mechanism, PTEN inhibition impairs Treg function and reduces their immunosuppression ability [90]. PTEN-deficient Tregs could reduce FOXO1 transcription, followed by decreased expression of *FOXP3*, essential for Treg development [91].



**Figure 2.** PI3K pathway in Tregs regulating anti-cancer immunity. Activated AKT pathway through PI3K $\delta$  signaling, the dominant isoform in Tregs, leads to the phosphorylation of the BACH2 and FOXO1 transcription factors and in this form they are sequestered in the cytoplasm. BACH2 and FOXO1 are regulators of genes involved in Treg differentiation and function, such as *FOXP3*, L-selectin (*SELL*), *CCR7* and *IFN $\gamma$* . PI3K $\delta$  inhibition suppress Tregs functionality; they are not able to suppress any more anti-tumor responses. Proteins belonging to downstream TCR signaling are also regulated by PI3K $\delta$ , as pS6 phosphorylation and GSK-3 $\beta$  activation, controlling proliferation, survival pathway and downstream degradation of the antiapoptotic protein Mcl-1.

Interestingly, genetic and pharmacological inhibition of PI3K $\delta$  in mice exerts anti-tumor activity via inhibition of Tregs and, possibly, of myeloid-derived suppressor cells [82,85]. In this context, CD8 $^{+}$  CTL can still mediate anti-tumor activity, although an altered balance between regulatory and effector CD4 $^{+}$  T-cells, with effector cells that prevail. Pharmacological targeting of PI3K $\delta$  lead to similar changes compared to genetical inhibition, such as suppression of tumor growth and reduction of immunosuppression, in many cancer models [22,31,82,86,92–96]. The PI3K $\delta$  inhibitor piasclisib has in vivo antitumor activity against the A20 mouse lymphoma cell lines despite no in vitro anti-tumor activity [96].

Similar data are available for the PI3K $\delta$  inhibitor liperlisib against models of breast carcinoma and colorectal cancer [22]. Hanna et al. demonstrated that PI3K $\delta$  inhibition decreases Tregs numbers, proliferation, and activity in the E $\mu$ -TCL1 model, but also CD8+ effector T-cells numbers and cytotoxicity T-cell ability [94]. In vitro experiments on T-cells from CLL patients, revealed that idelalisib down regulates the expression of crucial genes for T-cell mediated immunity, impairs IFN $\gamma$  production by CD4 and CD8 T-cells, and decreases the proliferative capacity of T-cells without affecting their survival [93]. Similar results have been reported by Maharaj et al., also using the E $\mu$ -TCL1 model [95]. The PI3K $\delta$  inhibitor idelalisib and the PI3K $\delta$ / $\gamma$  inhibitor duvelisib, but not the dual PI3K $\delta$ /CK1 $\epsilon$  inhibitor umbralisib, determined a reduction of Tregs, which was associated with increased immune-mediated toxicities, in the absence of changes in the CD4/CD8 ratio or in the absolute number of T-cells [95]. In a syngeneic colorectal cancer model, treatment with the PI3K $\delta$  inhibitor IOA-244 increases NK cells, and the ratio of cytotoxic CD8+ T-cells/Tregs [31]. The last observation is supported by data indicating a selective and concentration-dependent suppression of Treg cells but not of the proliferation of CD8+ T-cells [31]. Suppression of Tregs in syngeneic tumors is also reported with the PI3K $\alpha$ / $\delta$  inhibitor copanlisib [92], and with KA2237 [38]. In an in vivo mammary tumor model, PI3K $\delta$  blockade leads tumors to be divided in “non-regressors”, in which tumor growth rate is reduced but tumors continue to grow, and “regressors” where tumors shrink. Tumor infiltrating T-cells in “regressors” are enriched of elements indicating a CD8-specific T-cell response. In both groups of mice Tregs were reduced, although in Tregs from “non-regressor” tumors the expression of the coinhibitory receptor LAG3 is enriched compared to “regressor” and untreated tumors [97].

Exposure of follicular lymphoma (FL) cells, cocultured with follicular dendritic cells derived from normal tonsils, to idelalisib down-regulates the expression of integrins and their ligands, of proangiogenic factors and it determines a disruption of the CD40/CD40L-mediated crosstalk between FL cells and T-cells [98]. The PI3K $\delta$  inhibitor down-regulates CCL22 expression, and this would reduce the recruitment of Tregs and of T follicular helper cells (TFH), both expressing the chemokine receptor CCR4 and supportive for the growth and survival of FL cells [98]. A similar effect is also observed during the generation of high-affinity antibodies in the GC, where PI3K $\delta$  regulates TFH formation and function, activating ICOS, leading to intracellular signaling activation, production of TFH-related cytokines and effector molecules [99]. Moreover, idelalisib appears to increase the sensitivity of FL cells to the BCL2 inhibitor venetoclax, via a reduced PI3K $\delta$ -mediated BAD phosphorylation, and/or via up-regulating the levels of proapoptotic factor HRK, and/or down-regulation of the anti-apoptotic factor BFL-1 [98].

Targeting PI3K $\delta$  isoform with idelalisib stimulates CD8+ T-cells proliferation, maintaining survival, cytokines and granzyme B production. Idelalisib also inhibits Akt phosphorylation (both S473 and T308) in Tregs but not in Tconv, and abrogates Tregs proliferation without affecting Tconv cells [83,86].

Finally, data collected in syngeneic mouse models mostly suggest that PI3K $\delta$  inhibitors show synergism with immune checkpoint modulators [22,31,92]. However, there are also data demonstrating an important suppression of CD8+ T-cells maturation and killing capacity, antagonizing the effect due to immune checkpoint blockade [100].

#### 4. Potential Toxicities Linked with PI3K $\delta$ Inhibition in T-Cells

Side effects of PI3K $\delta$  inhibitors encompass infections, hepatotoxicity, diarrhea and/or colitis, and pneumonitis [4–6,101–106] (Table 2). In clinical trials with idelalisib, serious adverse events have also included deaths related to cytomegalovirus infections, pneumonias caused by *Pneumocystis jirovecii*, in addition to respiratory events possibly caused by infections [107]. These toxicities have been linked with a T-cell immune response impairment induced by PI3K $\delta$  inhibition that could favor such infections or viral reactivations, both by an increase in Treg-mediated immune tolerance mechanisms, and by impairment of the later stages of CD8 differentiation involved in the most potent antiviral activity [93,103]. Interestingly, these toxicities seem more frequent in treatment-naïve than in pre-treated



patients and in younger than older individuals, further suggesting that the presence of a still partially preserved immune system is implied [101,103,104], and they might be associated with higher clinical activity [105].

**Table 2.** Effect of the PI3K $\delta$  inhibitors on serum levels of secreted factors in the context of clinical trials enrolling patients with lymphoma.

PI3K $\delta$ Inhibitor	Phase	Lymphoma Subtypes	Decreased Factors	Increased Factors
Copanlisib	1 [108]	FL, WM, DLBCL, BL, MCL, PTCL	CCL2, CCL3, CCL5, CCL15, CCL16, IL-10, IL2RA, CD27, CD5L (cycle 1, day 15)	-
Duvelisib	1 [109]	FL, WM, SLL, MZL	CCL1, CCL4, CCL17, CCL22, CXCL10, CXCL13, IL-10, IL-16, MMP-9, TNF $\alpha$ (cycle 1, day 8)	-
Duvelisib	1 [110]	CLL	CCL1, CCL3, CCL4, CCL17, CCL22, CXCL10, CXCL13, IL-6, IL-10, IL-12p40, MMP-9, MMP-12, TNF $\alpha$ (cycle 1, day 8)	-
Duvelisib	1 [111]	PTCL	IL10, IL-12p40, CXCL13, (cycle 1, day 8)	CCL1, IL6, IL8, IL9, IL15 IL17A, IL-12p70, CD40L, TNF $\beta$
Duvelisib	1 [112]	CLL, FL, WM, SLL, MZL	CCL1, CCL4, CCL17, CCL22, CXCL10, CXCL13, MMP-9, TNF $\alpha$ (cycle 1, day 8)	-
Duvelisib	3 [113]	CLL/SLL	CCL3, CCL4, CCL17, CCL19, CCL22, CXCL13, IL2RA, IL-12p40, IL-10, TNF $\alpha$ (cycle 2, day1);	-
Idelalisib	1 [114]	CLL/SLL	CCL3, CCL4, CCL17, CCL22, CD40L, CCL2, CXCL13, TNF $\alpha$ (within 1 month)	-
Tenalisib	1 [115]	HL	CCL17	-

FL, follicular lymphoma; WM, Waldenström's macroglobulinemia; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; MCL, mantle cell lymphoma; PTCL, peripheral T-cell lymphoma; SLL, small lymphocytic lymphoma; MZL, marginal zone lymphoma; CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma.

Although the reduction of Tregs in the TME is an important and attractive therapeutic target, the caveat is that a reduction of Tregs activity, can activate autoimmune reactions [116,117]. For example, the effect on T-cells is believed to cause the severe diarrhea or colitis, which are some of the major side effects in patients receiving PI3K $\delta$  inhibitors [7,102]. A picture similar to graft versus host disease has been described in these patients, with increase infiltration of CD8+ cytotoxic T-cells [118,119], perhaps due to the already mentioned effect of the PI3K $\delta$  inhibitor on the mesenteric B-cells leading to an unleashed activity of Tregs [116].

We have also to consider that the pattern of selectivity for the PI3K $\delta$  isoform versus other class IA or IB members largely varies across the small molecules that have entered the clinical evaluation (Table 1). Their ability to bind isoforms can affect the toxicity profile. An example is given by observed acute insulin resistance, also causing severe hyperglycemia and hyperinsulinemia, seen with compounds that also target PI3K $\alpha$ , physiologically involved in the glucose homeostasis in muscle, liver, and fat tissues [6,102,120].

## 5. Effects on T-Cells in the Context of Clinical Trials

While the effect of the PI3K $\delta$  inhibitors on the secretion of chemokines has been studied in many clinical trials enrolling patients with lymphoma (Table 3), only a few studies have explored whether the drugs affect T-cell populations in the peripheral blood (Pb) [114,117,121–123] or in the TME [108,124].

**Table 3.** Potential toxicities of the PI3K $\delta$  inhibitors in the context of clinical trials enrolling patients with lymphoma.

PI3K $\delta$ Inhibitor	Phase	Lymphoma Subtypes	Any Grade, AE (%)	Grade $\geq 3$ , AE (%)
Copanlisib	2 [108]	FL, MZL, SLL, WM/LPL, DLBCL	Diarrhea (35.2), colitis (0.7), hyperglycemia (50.0), hypertension (29.6), neutropenia (28.9), pneumonitis (6.3)	Diarrhea (8.5), colitis (0.7), hyperglycemia (40.1), hypertension (23.9), neutropenia (24.0), pneumonitis (1.4)
Umbralisib	2 [109]	MZL, FL, SLL	Neutropenia (15.9), diarrhea (59.1), colitis (1.9), fatigue (30.8), increased ALT (20.2), increased AST (18.8)	Neutropenia (11.5), diarrhea (10.1), colitis (0.5), fatigue (3.4), increased ALT (6.7), increased AST (7.2)
Duvelisib	2 [113]	SLL, FL, MZL	Diarrhea (48.8), neutropenia (28.7), thrombocytopenia (18.6), anemia (26.4), febrile neutropenia (9.3), increased ALT (14.0), increased lipase (9.3), pneumonia (7.8), colitis (7.8)	Diarrhea (14.7), neutropenia (24.8), thrombocytopenia (11.6), anemia (14.7), febrile neutropenia (9.3), increased ALT (5.4), increased lipase (7.0), pneumonia (5.4), colitis (5.4)
Idelalisib	2 [114]	FL, SLL, MZL, WM/LPL	Diarrhea (43.0), pneumonia (11.0), increased ALT (47.0), increased AST (35.0)	Diarrhea (13.0), pneumonia (7.0), increased ALT (13.0), increased AST (8.0)
Tenalisib	1 [115]	DLBCL, MCL, PTCL, CLL, HL	Anemia (29.0), neutropenia (20.0), thrombocytopenia (26.0), pyrexia (37.0), cough (43.0), dyspnea (26.0)	Anemia (11.0), neutropenia (17.0), thrombocytopenia (17.0), pyrexia (3.0)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, Burkitt lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; LPL, Lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PTCL, peripheral T-cell lymphoma; SLL, small lymphocytic lymphoma; HL, Hodgkin lymphoma. WM, Waldenström's macroglobulinemia.

No significant changes in Pb T-cells subsets were seen in the phase I and II studies evaluating idelalisib in patients with relapsed indolent lymphoma [122,123] and in the phase I for CLL [114]. Conversely, a decrease of the Treg percentage was described in the Pb of 13/19 relapsed/refractory CLL patients treated for one month of idelalisib in a separate phase I study evaluating the small molecule as single agent followed by 6 months of combination therapy with the anti-CD20 antibody ofatumumab [117]. Importantly, the decrease of Tregs in the Pb was stronger in patients that experienced toxicity [117].

A reduction in the Pb Tregs was also observed in 14/19 relapsed/refractory CLL patients exposed to the PI3K $\delta$  inhibitor ACP-319 in the phase I study [121].

Serial biopsies were obtained in 30 patients with relapsed/refractory solid tumors or lymphoma enrolled in a phase I study of copanlisib, a pan PI3K inhibitor, preferentially targeting the PI3K $\alpha$ /PI3K $\delta$  isoforms [108]. There was a reduction in the proportion of CD4+ T-cells in tumors after 14 days of treatment in 14 of patients treated at 0.8 mg/Kg but not at 0.4 mg mg/Kg ( $n = 16$ ), with no changes in the CD8+ cells [108]. The reduction in the CD4+ cells suggests that Tregs were affected; however no additional staining was performed.

In the phase I study, exploring the dual PI3K/BRAF inhibitor sonolisib in patients with advanced solid tumors bearing the BRAF V600 mutation, biopsies were performed at baseline and at day 8 of the first cycle in six patients [124]. An increase in CD8+ cells at immunohistochemistry was observed in 5/6 patients [124]. This was paired with higher PD-L1 staining in the two cases with a partial response and not in patients with stable or progressive disease [124]. Additionally, here, no data are available for Tregs.

Finally, since PI3K $\delta$  is also downstream to Fc $\epsilon$ RI, activated by IgE binding in mast cells and basophils, idelalisib has been evaluated in patients with allergic rhinitis [125]. In a phase I study the PI3K $\delta$  inhibitor decreased plasma levels of CD631/CCR31 basophils, and inhibited ex vivo basophil activation in response to allergen stimulation [125]. A similar effect has also been reported in relapsed/refractory lymphoma patients enrolled in a phase I with the PI3K $\delta$  inhibitor dezapelisib [126].

## 6. Conclusions

PI3K $\delta$  inhibitors are active anti-cancer compounds in lymphomas. Their mechanism of action is promiscuous, and it is mediated via a direct inhibition of PI3K $\delta$  in the lymphoma cells but also due to an inhibitory activity in multiple non-neoplastic cells. In particular, the data we have summarized highlight that the pharmacological inhibition of PI3K $\delta$  in Tregs is clearly effective in boosting anti-tumor immune system. Further studies are needed to exploit this therapeutic option, avoiding the possible insurgence of autoimmune disorders. Discovery of other pathways and molecules that preferentially inhibit PI3K signaling specifically in Tregs is needed.

**Author Contributions:** Conceptualization, C.T., L.A., P.L.Z., F.B.; writing—original draft preparation, C.T.; writing—review and editing, F.B. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Conflicts of Interest:** Lisa Argnani: consultancy fee from Servier Italia. Pierluigi Zinzani: honoraria from Abbvie, ADC Therapeutics, Astellas, Astrazeneca, Autolus, Bayer, Beigene, BMS, Celltrion, Debiopharma, Eusapharma, Gilead, Hikma, Incyte, Janssen, Karyopharm, Kirin Kyowa, Mei Pharma, Merck, Portola, Roche, Servier, Takeda, TG Therapeutics, Verastem; speakers Bureau for Abbvie, Astellas, Beigene, BMS, Celltrion, Eusapharma, Gilead, Incyte, Janssen, Kirin Kyowa, Merck, Portola, Roche, Servier, Takeda, Verastem; membership on an entity's Board of Directors or advisory committees of Abbvie, ADC Therapeutics, Astrazeneca, Autolus, Bayer, Beigene, Eusapharma, Gilead, Hikma, Janssen, Karyopharm, Kirin Kyowa, MEI Pharma, Merck, Roche, Servier, Takeda, TG Therapeutics, Verastem. Francesco Bertoni: institutional research funds from Acerta, ADC Therapeutics, Bayer AG, Cellectia, CTI Life Sciences, EMD Serono, Helsinn, ImmunoGen, Menarini Ricerche, NEOMED Therapeutics 1, Nordic Nanovector ASA, Oncology Therapeutic Development, PIQUR Therapeutics AG; consultancy fee from Helsinn, Menarini; expert statements provided to HTG; travel grants from Amgen, Astra Zeneca, Jazz Pharmaceuticals, PIQUR Therapeutics AG.

## Abbreviations

APC	antigen presenting cells
CLL	chronic lymphocytic leukemia
CTL	cytotoxic T-lymphocyte
CTLA-4	Cytotoxic T-Lymphocyte Associated Protein 4
DLBCL	diffuse large B-cell lymphoma
ECM	extracellular matrix
NK	natural killer
PD-1	Programmed Cell Death 1
PI3K	phosphoinositide 3-kinases
TAM	tumor-associated macrophages
Tconv	conventional T-cells
TFH	T follicular helper cells
TME	tumor microenvironment
Tregs	regulatory CD4 <sup>+</sup> T-cells

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