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THERAPEUTIC OPPORTUNITIES FOR PLK1 INHIBITORS: SPOTLIGHT ON BRCA1-DEFICIENCY AND TRIPLE NEGATIVE BREAST CANCERS

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ABSTRACT

Polo-Like Kinases (PLKs) are central players of mitotic progression in Eukaryotes. Given the intimate relationship between cell cycle progression and cancer development, PLKs in general and PLK1 in particular have been thoroughly studied as biomarkers and potential therapeutic targets in oncology. The oncogenic properties of PLK1 overexpression across different types of human cancers are attributed to its roles in promoting mitotic entry, centrosome maturation, spindle assembly and cytokinesis. While several academic labs and pharmaceutical companies were able to develop potent and selective inhibitors of PLK1 (PLK1i) for preclinical research, such compounds have reached only limited success in clinical trials despite their great pharmacokinetics. Even though this could be attributed to multiple causes, the housekeeping roles of PLK1 in both normal and cancer cells are most likely the main reason for clinical trials failure and withdraw due to toxicities issues. Therefore, great efforts are being invested to position PLK1i in the treatment of specific types of cancers with revised dosages schemes. In this mini review we focus on two potential niches for PLK1i that are supported by recent evidence: triple negative breast cancers (TNBCs) and BRCA1-deficient cancers. On the one hand, we recollect several lines of strong evidence indicating that TNBCs are among the cancers with highest PLK1 expression and sensitivity to PLK1i. These findings are encouraging because of the limited therapeutics options available for TNBC patients, which rely mainly on classic chemotherapy. On the other hand, we discuss recent evidence that unveils synthetic lethality induction by PLK1 inhibition in BRCA1-deficient cancers cells. This previously unforeseen therapeutic link between PLK1 and BRCA1 is promising because it defines novel therapeutic opportunities for PLK1i not only for breast cancer (i.e. TNBCs with BRCA1 deficiencies), but also for other types of cancers with BRCA1-deficiencies, such as pancreatic and prostate cancers.

Keywords: PLK1, BRCA1, TNBC, breast cancer, BRCA-deficiency.

The development of cancer is a multi-step process at which several mechanisms that restrict uncontrolled cell division must fail. During cancer evolution, cells acquire series of mutations that promote faster cell division cycles and avoid programmed cell death. In consequence, numerous therapeutic strategies have been developed to target cell cycle progression at different levels. A particularly successful case are microtubule-targeting agents, which by disrupting microtubule dynamics induce a persistent mitotic arrest that eventually leads to cell death [1]. Cancer cells also frequently exhibit genomic alterations that lead to cyclin dependent kinases (CDK) hyperactivation, a reason that stimulated the development of agents to block CDKs, which trigger cell-cycle arrest at G1/S and G2/M transitions [1]. Several cell-cycle blocking agents have been clinically evaluated and approved for the treatment of different type of cancers (Table 1). Moreover, a common limitation of such agents is that they do not distinguish malignant cells from normal cells, and therefore patients often experience adverse effects, such as peripheral neuropathy, myelosuppression, neurotoxicity, nausea, diarrhea, vomiting, constipation, anemia, neutropenia, fatigue [2–12]. Thus, a current challenge in this area is to develop therapies to target cell-cycle features that are distinctive to tumor cells.

Table 1. Cell-cycle blocking agents approved for treatment of cancer

Cell Cycle blocking drugs	Mechanism of action	Name of drugs	Type of drug	Approved for treatment	Reported mechanism of drug resistance
Antimitotic agents	Inhibit microtubule depolymerization	Paclitaxel (Taxol®)	Natural[13]	Ovarian, breast, non-small cell lung cancers and Kaposi sarcoma[14]	Diminished autophagy[15] MDR phenotype and alterations of tubulin[16]
		Docetaxel (Taxotere®)	Semi-synthetic[17]	Breast, stomach, prostate, non-small-cell lung and head and neck cancers[18]	MDR phenotype and alterations of tubulin[16]
		Cabazitaxel (Jevtana®)	Semi-synthetic[19]	Hormone-resistant prostate cancer[5]	Enhancement of ERK or PI3K/AKT signaling[20] Up-regulated expression of MDR[21]
		Ixabepilone (Ixempra®)	Semi-synthetic[22]	Breast cancer[23]	Low susceptibility to MDR overexpression and β -tubulin mutations[24]
	Inhibit microtubule polymerization	Vincristine (Oncovin®, Vincasar Pfs®)	Natural[7]	Acute leukemia, rhabdomyosarcoma, neuroblastoma, Hodgkin lymphoma, Wilms tumor[7]	Overexpression of MDR (efflux pump)[25]
		Vinblastine (Alkaban-AQ®, Velban®)	Natural[7]	Breast, testicular cancers, Hodgkin and non-Hodgkin lymphomas and germ cell tumors[7]	
		Vinorelbine (Nabelvine®)	Semi-synthetic[26]		

		Vinflunine (Javlor®)	Synthetic[7]	Transitional (urothelial) cell carcinoma [8], non-small cell lung and breast cancers[7]	
		Vindesine (Eldisine®)	Semi-synthetic[7]	Acute lymphocytic leukemia, melanoma, pediatric tumors, metastatic renal, breast, esophageal and colorectal carcinomas[7]	
	Target microtubules-associated proteins	Estramustine (Estracyt®, EMCYT®)	Synthetic[10]	Prostate cancer[27]	Changes at tubulin expression pattern[28]
CDK inhibitors	Inhibit CDK4 and CDK6	Palbociclib (Ibrance®)	Synthetic[29]	Hormone receptor-positive/human epidermal growth factor receptor 2-negative breast cancer[30]	Somatic <i>RB1</i> mutations[31]
		Ribociclib (Kisqali®)	Synthetic[29]	Hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer[32]	
		Abemaciclib (Verzenio®)	Synthetic[29]	Hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer[33]	Overexpression/amplification of CDK6[34]

MDR: multidrug resistance; ERK: extracellular-signal-regulated kinase; PI3K: phosphatidylinositol 3-kinase; AKT: protein kinase B; RB1: RB transcriptional corepressor 1.

Identification of Polo Like Kinases as therapeutic targets

In the late 80's, drosophila mutants at the "Polo" locus defined a direct relationship between the gene coded at this locus and the correct assembly of spindle poles [35]. Later on, it was found that the Polo gene encodes a protein with an amino-terminal domain homologous to a serine-threonine protein kinase [36]. Concomitantly, it was observed that Polo transcripts are abundant in tissues in which there is extensive mitotic activity [36], further supporting the critical role of this kinase in mitotic progression. A family of similar serine-threonine kinase was found to be highly conserved from yeast to humans, yet homologs for these kinases were not found in bacteria, archae or plants [37]. Given to its relationship with the Polo genes, this family was named Polo-Like Kinases (PLKs).

Mammalian cells have at least five PLKs: PLK1, PLK2, PLK3, PLK4 and PLK5 [38]. PLKs contain an N-terminal serine-threonine kinase domain (except PLK5) connected by a short linker to a C-terminal non-catalytic region characterized by the presence of 2 polo boxes (with the exception of PLK4 that only comprises one box) [39]. This entire region has been named

the polo-box domain (PBD) [37]. These proteins are important regulators of multiple functions during mitosis, including M-phase entry, the G2/M DNA damage checkpoint, centrosomes biogenesis and the coordination of cytokinesis [40–42]. Such plethora of mitotic functions underlines the pivotal role of PLK for cell cycle progression.

Among mammalian PLKs, PLK1 is the most thoroughly studied family member. PLK1 has several regulatory roles during the cell cycle, such as mitotic entry, centrosome maturation, spindle assembly and cytokinesis [43,44]. Interestingly, PLK1 mutations are extremely rare in human cancers [45] and PLK1 complete ablation by CRISPR triggered lethality in more than 700 cell lines tested in the Cancer Dependency Map Project (<https://depmap.org/portal/gene/PLK1?tab=overview>), thus indicating its critical housekeeping roles in cell survival. However, the overexpression of PLK1^{wt} is linked to oncogenesis by the promotion of chromosome instability and aneuploidy [46], which is triggered by defects in the mitotic checkpoint [47]. Elevated expression of PLK1 is observed in non-small-cell lung cancer, head and neck cancers, esophageal and gastric cancers, melanomas, breast, ovarian, endometrial, colorectal, thyroid and many other types of cancers (Figure 1) [48,49]. In most cases PLK1 overexpression correlates with cancer aggressiveness and worse prognosis [49–51]. Therefore, PLK1 was postulated as a valuable diagnostic biomarker in several types of cancers [49]. Moreover, initial evidence indicating that this protein promote tumor development [52] also quickly positioned PLK1 as a promising therapeutic target. In fact, PLK1 inhibition with small interfering RNAs and small molecules is known to trigger mitotic arrest, proliferation impairment, apoptosis and tumor growth inhibition [53–59].

Many Academic Labs and Pharmaceutical Companies have established drug development programs to design potent and selective PLK1 inhibitors (PLK1i). Nonetheless, most of molecules that reached preclinical success and continued towards Phase I clinical trials, failed at this stage due to toxicity issues. The reported adverse effects associated to PLK1 inhibitors treatment include hematological alterations such as anemia, neutropenia and thrombocytopenia, as well as gastrointestinal events (Table 2). Additionally, serious defects in arterial structure that leads to aortic rupture and lethality was described in *Plk1* +/- mice and mice treated with PLK1 inhibitors [60], which reinforces the need for caution when PLK1 inhibitors are used in therapeutic schemes. Also, the confirmation of target specificity might be crucial before further clinical development of PLK1 inhibitors. In fact, Rigosertib (ON1910 - Onconova Therapeutics), which was initially identified as a selective PLK1 inhibitor, was later described also as a microtubule destabilizing agent [61] and a RAS-mimetic compound [62,63].

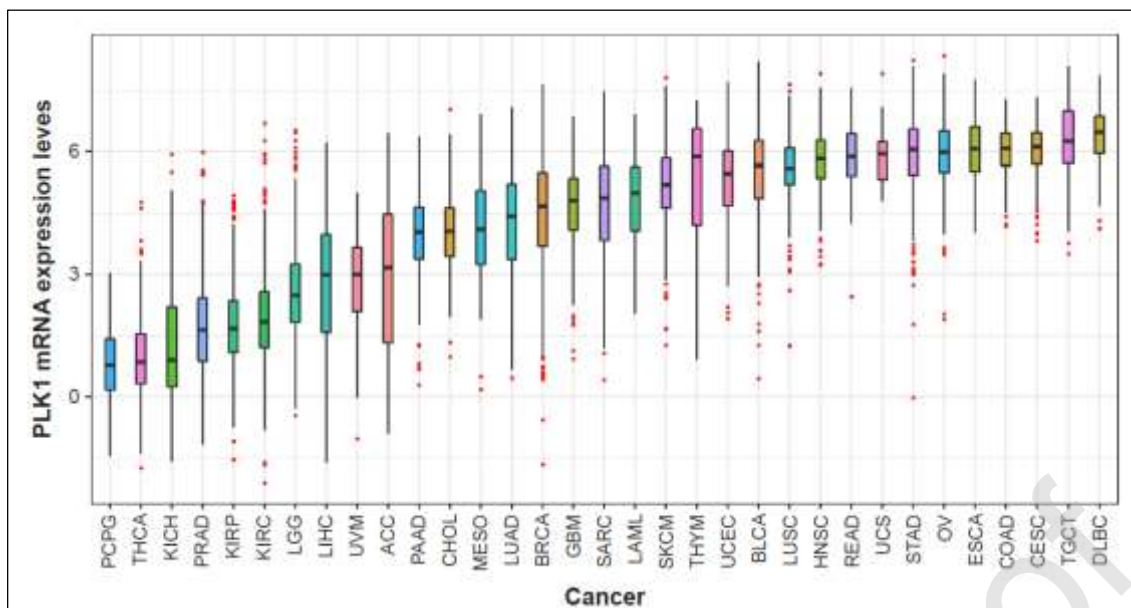


Figure 1: PLK1 RNA expression levels in cancer patients from the TCGA. Patient database analysis performed in 33 Cancer types. Boxplots showing PLK1 mRNA levels (expressed as log₂ - CPM) in all tumor samples from The Cancer Genome Atlas (TCGA) provisional database (<https://www.cancer.gov/tcga>). RNA expression levels were normalized using the upper quartile method. Red dots represent outliers. The plot was performed using RStudio Version 1.2.1335. TCGA Abbreviations for each cancer type: PCPG: Pheochromocytoma and Paraganglioma (n = 178); THCA: Thyroid Carcinoma (n = 505); KICH: Kidney Chromophobe (n = 66); PRAD: Prostate Adenocarcinoma (n = 497); KIRP: Kidney Renal Papillary Cell Carcinoma (n = 290); KIRC: Kidney Renal Clear Cell Carcinoma (n = 534); LGG: Lower Grade Glioma (n = 516); LIHC: Liver Hepatocellular Carcinoma (n = 370); UVM: Uveal Melanoma (n = 79); ACC: Adrenocortical Carcinoma (n = 79); PAAD: Pancreatic Adenocarcinoma (n = 177); CHOL: Cholangiocarcinoma (n = 36); MESO: Mesothelioma (n = 87); LUAD: Lung Adenocarcinoma (n = 514); BRCA: Breast Invasive Carcinoma (n = 1095); GBM: Glioblastoma Multiforme (n = 155); SARC: Sarcoma (n = 259); LAML: Acute Myeloid Leukemia (n = 173); SKCM: Skin Cutaneous Melanoma (n = 103); THYM: Thymoma (n = 119); UCEC: Uterine Corpus Endometrial Carcinoma (n = 175); BLCA: Bladder Urothelial Carcinoma (n = 407); LUSC: Lung Squamous Cell Carcinoma (n = 502); HNSC: Head and Neck Squamous Cell Carcinoma (n = 520); READ: Rectum Adenocarcinoma (n = 94); UCS: Uterine Carcinoma (n = 57); STAD: Stomach Adenocarcinoma (n = 415); OV: Ovarian Serous Cystadenocarcinoma (n = 305); ESCA: Esophageal Carcinoma (n = 183); COAD: Colon Adenocarcinoma (n = 285); CESC: Cervical Squamous and Endocervical Adenocarcinomas (n = 304); TGCT: Testicular Germ Cell Tumors (n = 150); DLBC: Diffuse Large B-cell Lymphoma (n = 48).

Therefore, its underlying antitumoral mechanism remains controversial. Onconova Therapeutics currently attributes the therapeutic effects of Rigosertib to its RAS-mimetic properties, which is in Phase III trials for the treatment of Myelodysplastic syndromes (<https://www.onconova.com/pipeline/#tab-id-2>).

Some Phase I clinical trials with PLK1 inhibitors were successful for the treatment of a particular set of malignancies and moved forward to Phase II and even Phase III studies (Table 2). Nonetheless, the results of these completed studies show that treatment was not as effective as expected when used as second or third lines of therapy [64–73]. Only a few patients displayed disease stabilization, indicating that further exploration of these therapeutic

schemes is necessary. In fact, the most successful PLK1 inhibitors to date: Volasertib and Onvansertib, which reached FDA's "breakthrough therapy" and "Orphan drug" denominations respectively, are still struggling to find the optimal niches in clinical studies. It is clear that future research should focus on how the efficacy of PLK1 inhibitors is affected by different genetic backgrounds, or whether combinations with standard therapies could expand their therapeutic opportunities. In the following sections we revise several lines of recent evidence indicating that triple negative breast cancers, as well as cancers bearing BRCA1 deficiencies, display a remarkable sensitivity to PLK1 inhibitors.

Table 2. Polo-like kinases 1 inhibitors

Compound	Mechanism of action	Company	Clinical Trials			
			Conditions	Phase	Status	NCT number
BI2536	ATP-competitive [74]	Boehringer Ingelheim	Neoplasm	I	Completed	NCT02211872 , NCT02211859
			Lymphoma	I	Completed	NCT00243087
			Non-small-cell lung carcinoma	I	Completed	NCT02211833 (combination with pemetrexed)
				II	Completed	NCT00376623
			Acute myeloid leukemia	II	Completed	NCT00701766
			Prostatic neoplasms	II	Completed	NCT00706498
			Pancreatic neoplasms	II	Completed	NCT00710710
		Small-cell carcinoma	II	Completed	NCT00412880	
EORTC	Breast, ovarian, endometrial, head and neck cancers, melanoma and sarcoma	II	Completed	NCT00526149		
Volasertib BI6727	ATP-competitive [75]	Boehringer Ingelheim	Neoplasm	I	Completed	NCT00969553 , NCT01348347 , NCT00969761 , NCT01145885 , NCT01022853 (combination with BIBF 1120),
						NCT01206816 (combination With BIBW 2992)
				Active, not recruiting	NCT02273388 , NCT01772563 (co-administration of itraconazole)	
			II	Completed	NCT01023958	
			Acute myeloid leukemia	I	Completed	NCT01662505
				II	Active, not recruiting	NCT00804856 (combination with cytarabine)
				III	Active, not recruiting	NCT01721876
			Leukemia Neoplasm	I	Completed	NCT01971476
Non-small-cell lung carcinoma	II	Completed	NCT00824408 (combination with pemetrexed)			
Myelodysplastic syndromes, chronic myelomonocytic leukemia	I	Completed	NCT02201329 (combination with azacitidine)			

			Ovarian Neoplasms	II	Completed	NCT01121406
Onvansertib PCM-075	ATP-competitive [76]	TrovaGene, Inc.	Acute myeloid leukemia	I, II	Recruiting	NCT03303339 (combination with decitabine or cytarabine)
			Metastatic colorectal cancer and KRAS gene mutation			NCT03829410 (combination with FOLFIRI + Avastin)
			Metastatic castration-resistant prostate Cancer	II		NCT03414034 (combination with abiraterone and prednisone)
GSK461364	ATP-competitive [77]	GSK	Lymphoma, non-Hodgkin	I	Completed	NCT00536835
TKM-080301	RNAi[77]	Arbutus Biopharma Corporation	Hepatocellular and adult liver cell carcinoma	I, II	Completed	NCT02191878
			Neuroendocrine tumors and adrenocortical carcinoma			NCT01262235
		National Cancer Institute	Colorectal, pancreas, gastric, breast and ovarian cancers with hepatic metastases	I		Completed

Clinical trials are indicated using the clinical trials.gov identifier. EORTC: [European Organization for Research and Treatment of Cancer](#); GSK: [GlaxoSmithKline](#).

Finding therapeutics niches for PLK1 inhibitors: triple negative breast cancers

In breast cancer (BC) patients, high PLK1 levels are significantly associated with larger tumor size, higher pathological grading, lymph node metastasis and worse overall survival, thus establishing PLK1 expression as biomarker of poor prognosis in BC [78]. Noteworthy, even for Luminal A cancers, which are considered less aggressive, higher levels of PLK1 expression are associated with poor prognosis [79]. Triple-negative breast cancer (TNBC) is considered the most aggressive type of BC. This is mainly because of the lack of available targeted therapies, being standard chemotherapy the only course of treatment [80].

In the search for novel therapeutic targets for TNBC, integrated network analysis coupled with machine learning identified a list of differentially expressed genes associated with TNBC. Not surprisingly, key genes identified were enriched in cell cycle progression and mitotic cell division: including AURKB, CCNB2, CDC20, CCND1, TGFB3, SKP1, SKP2, MYC, and PLK1 [81]. Interestingly, despite the great success of mitotic poisons in BC treatment, the mitotic spindle was the only mitotic target with successful therapeutic intervention for decades (Table 1). This is the case of Paclitaxel (Taxol by Bristol-Myers-Squibb), which prevents completion of mitosis through binding to the β -subunit of tubulin, resulting in the formation of non-functional microtubule bundles, that arrest cells at G2/M [82]. Paclitaxel is the most widely used drug as monotherapy or in combination therapy for TNBC [83]. Therefore, the

blockade of mitotic progression by the inhibition of overexpressed mitotic kinases (AURKs, PLKs) represents an appealing approach to target the same biological process with the potential of delivering more selective outcomes against tumor cells. Strikingly, it was shown that PLK1 inhibition induces G2/M arrest and creates polyploid cell populations, leading to significant growth inhibition and triggering apoptosis in multiple TNBC cell lines [84–86]. A related intriguing finding was that the inhibition of PLK1 induces apoptosis in a TNBC cell subpopulation with stem cell properties known as tumor-initiating cells (TICs) [84]. It has been proposed that TICs are resistant to traditional chemotherapies and are considered responsible for breast cancer relapse [87–90]. Thus, targeting PLK1 emerges as a promising therapeutic strategy for the treatment of TNBC.

Retrospective analysis of The Cancer Genome Atlas (TCGA) database shows remarkably higher levels of PLK1 expression in BC solid tumors in comparison to the normal surrounding mammary tissues obtained in biopsies (Fig. 2A). Strikingly, PLK1 levels are higher in Basal-like tumors when comparing pam50 subtypes (Fig. 2B), and higher when comparing TNBC vs. non-TNBC samples (Fig. 2C) [45]. These findings are in agreement with previous reports showing increased PLK1 expression in TNBC cell lines and patient samples [85,86]. Such similar findings reported by different groups strongly support the notion that this type of BC patients, which are characterized by limited therapeutic options, could benefit with therapeutic schemes involving PLK1 inhibition.

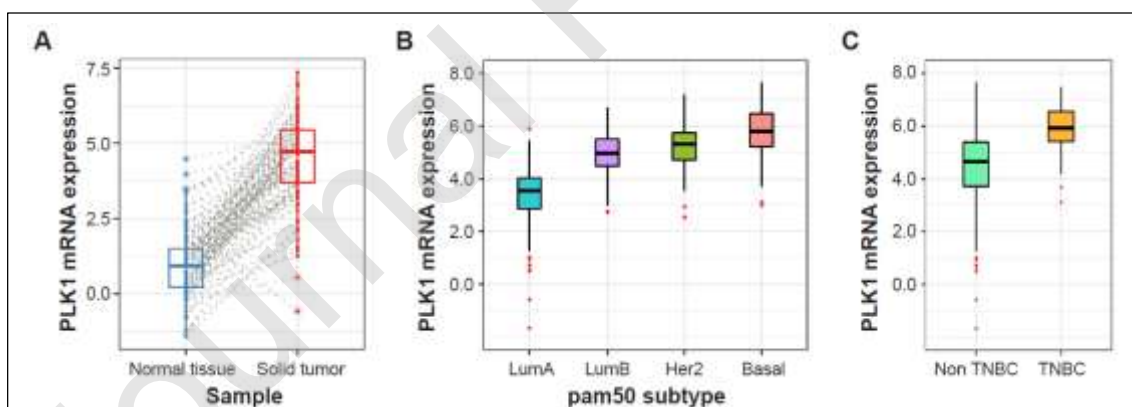


Figure 2: PLK1 RNA expression levels in breast cancer patients from the TCGA. Analyses performed using data generated by the TCGA Research Network (<https://www.cancer.gov/tcga>). **A.** Boxplots showing PLK1 gene expression (as log₂ - CPM) in tumor-adjacent normal tissue compared to breast cancer solid tumor sample from the same patient. Dotted lines connect paired samples, n = 104. **B.** PLK1 gene expression (as log₂ - CPM) across pam50 breast cancer subtypes: Luminal A (LumA, n = 322), Luminal B (LumB, n = 250), HER2-enriched (Her2, n = 158) and Basal-like (Basal, n = 236). **C.** PLK1 gene expression (as log₂ - CPM) in TNBC (n = 112) compared to non-TNBC (n = 854) breast cancer patients. Red dots represent outliers. Plots and statistical analyses were performed using RStudio Version 1.2.1335, applying Student's t-test for paired samples in **A** (**p < 0.001); One-way ANOVA (ANalysis Of VAriance) with post-hoc Tukey HSD test in **B** (Basal vs any condition **p < 0.001); or Student's t-test in **C** (**p < 0.001). p < 0.05 was considered statistically significant.

Finding therapeutics niches for PLK1 inhibitors: BRCA1-deficient cancers

BRCA1 and BRCA2 are well-recognized tumor suppressor genes that were initially identified in hereditary types of breast and ovarian cancers [91]. However, a growing set of recent evidence shows that mutations or epigenetic downregulation of BRCA genes are also frequently found in sporadic cancers, being the underlying genome instability the driving force of tumorigenesis [92,93]. Besides its well characterized role in homology-directed repair, BRCA1 also participates in diverse biological processes, including the assembly of the mitotic spindle [94–96]. Several genotoxic agents stimulate BRCA1-PLK1 interaction, where BRCA1 plays a role in downregulating the kinase activity of PLK1 [97]. In fact, PLK1 activity is increased in BRCA1-depleted cells [45,97]. Consequently, it is tempting to speculate that BC patients with aberrant expression of BRCA1 should become more sensitive to PLK1 inhibitors as monotherapy or in combination with DNA damaging agents. In line with such hypothesis, an unbiased screening targeting the human kinome recently performed in our lab unveiled that PLK1 inhibitors trigger strong synthetic lethality in BRCA1-deficient cells in a dose-range where they depict little cytotoxic effect in BRCA1-proficient cells [45]. In this study, we did not find acute genomic instability induction by the PLK inhibitor Volasertib within the synthetic lethal dose-range, thus suggesting that this type of treatment might induce a “clean” type of antitumoral response in BRCA1-deficient cells, attenuating genomic instability and delaying the acquisition of resistance mechanisms in cancer cells [45]. Taken together with the evidence discussed in the previous section, these findings stimulate the design of future clinical trials focused on TNBC patients that consider BRCA1 status as a stratification marker. Such strategic patient cohort harbors the two biomarkers of therapeutic response to PLK1 inhibitors described herein: absence of ER/PR/HER2 expression and BRCA1-deficiency.

This emerging therapeutic field might expand the use of PLK1 inhibitors in other BRCA1-deficient malignancies besides TNBCs. Just a few years ago, BRCA-deficiencies were considered an exclusive feature of breast and ovarian familial cancers (1-5%) [98]. However, current estimations using whole genome sequencing unveiled that BRCA-like phenotypes (also referred as BRCAness) are found in at least 22% of breast cancers, while in ovarian these proportion seems to be exceptionally higher, reaching up to 60% of the patients [99]. Nonetheless, it is perhaps more remarkable the increasing evidence of cancers in other organs that also bear HR-deficiencies. Whole exome sequencing and transcriptomic profiling of castration-resistant prostate cancer (CRPC) samples predicts that more than 19% of these tumors bear at least one mutation in a BRCAness-associated gene, including BRCA1, BRCA2, ATM and CDK12 [100]. Recent sequencing of samples from a familial form of pancreatic ductal

pancreatic adenocarcinoma (PDAC) demonstrated that 24% possessed either a germline or a somatic mutation in BRCA1, BRCA2 or PALB2 [101]. Even though more detailed genomic analyses are required to determine the actual penetrance of BRCA1-deficiencies in such different cancer types, it is quite clear that BRCA1 alteration is not restricted to breast and ovarian cancers, and therefore therapeutic approaches based on synthetic lethality induction by PLK1i would also potentially benefit other patient cohorts. Moreover, future in-depth analysis of PLK1 interactions with other molecular pathways might expand the use of PLK1i to other contexts. For example, previous studies show a reduced sensitivity of cancer cells expressing wild-type TP53 to PLK1 inhibition compared with TP53-mutant cells [102,103]. Likewise, it has been shown that cancers with activated KRAS are addicted to PLK1 activity, suggesting that KRAS-mutated malignancies might also be susceptible to PLK1 inhibition [104]. Furthermore, a study revealed that the depletion of the tumor suppressor PTEN induces increased expression of PLK1 in prostate cancer cells, being PTEN-null cells more sensitive to PLK1 inhibition in comparison with PTEN-proficient prostate cells [105]. Since the loss of PTEN is a hallmark of TNBC [106–108], these findings might be in line with the increased sensitivity of this subgroup of breast cancer cells to PLK1 inhibitors.

PARP and PLK1 inhibitors: complementary or alternative?

In the last couple of years, we have witnessed the great success of poly (adenosine diphosphate (ADP)-ribosyl) polymerase inhibitors (PARPi), which are currently used in the clinic as a synthetic lethal strategy to treat malignancies with homology-directed repair deficiencies, such as breast and ovarian cancers harboring mutations in BRCA genes [109]. The emergence of PLK1 inhibition as a strategy to treat TNBC and BRCA1-deficient cancers opens the discussion of whether such strategy can be complementary and/or alternative to PARPi. The available evidence indicates that PARPi and PLK1i work through different molecular mechanisms [45,110–112]. For instance, PLK1 inhibition shows only mild synthetic lethal activity with BRCA2-deficient cells [45], while PARP inhibition induces synthetic lethality both with BRCA1 and BRCA2, as well as with other related proteins that trigger homology-directed repair deficiencies [113]. In addition, while some TNBCs display sensitivity to PARP inhibition [114], this response does not seem to be selective for all types of TNBCs, in contrast to the more general link found between this cancer subtype and PLK1i sensitivity [45,84–86]. Therefore, combinatorial, sequential and alternative approaches can be envisioned for PLK1i and PARPi in the clinic. A particularly interesting cancer cohort that might benefit from PLK1i is BRCA1-deficient TNBCs with acquired resistance to PARPi. Resistance to PARPi is an emerging

field with little clinical information available and it can arise from different types of alterations in cancer cells [115]. Importantly, resistance to platinum-based chemotherapies is a strong predictor for PARPi resistance, indicating that they probably share common mechanisms of action [116]. One of the proposed mechanisms involves elevated expression of ABC transporters, such as the P-glycoprotein efflux pump (also known as PgP, ABCB1 and MDR1) [117], which reduces the efficacy of a number of drugs by enhancing the intracellular-to-extracellular translocation of small molecules. An additional mechanism that might explain at least 50% of the cases of acquired resistance to PARPi are secondary mutations in other genes, which restore HR proficiency [113]. Since these cancer cells are still mutant for BRCA1, despite their lack of response to PARPi, PLK1i should still trigger synthetic lethality in this type of patients.

Conclusions

In this review, we aimed to summarize the state of the art of PLK1 inhibitors and their potential clinical applications. To our understanding, the exciting recent findings regarding their robust and selective activity against TNBCs and BRCA1-deficient cancers should trigger a renewed interest for this set of drugs, which might be used as monotherapy or in combination with other therapeutic agents to treat these types of malignancies with limited therapeutics options.

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