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Targeting the DNA damage response for patients with lymphoma: Preclinical and clinical evidences

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ABSTRACT

The DNA damage response (DDR) is a well-coordinated cellular network activated by DNA damage. The unravelling of the key players in DDR, their specific inactivation in different tumor types and the synthesis of specific chemical inhibitors of DDR represent a new hot topic in cancer therapy. In this article, we will review the importance of DDR in lymphoma development and how this can be exploited therapeutically. Specifically, we will focus on CHK1, WEE1, ATR, DNA-PK and PARP inhibitors, for which preclinical data as single agents or in combination has been accumulating, fostering their clinical development. The few available clinical data on these inhibitors will also be discussed.

Introduction

The DNA damage response (DDR) is an integrated kinase-driven cellular network activated by both endogenous and exogenous DNA damage [1-3] and has a key role in maintaining genomic integrity. The main steps in DDR are DNA damage recognition and activation of intracellular signaling pathways, mainly through sequential phosphorylations, which lead to transient cell cycle arrest and activation of DNA repair pathways. The ultimate goal of the DDR is the survival of cells that have successfully repaired DNA lesions. In healthy cells the inability to correctly execute DDR will activate cell death through apoptosis, autophagy or senescence to prevent accumulation of cells with DNA damage.

Deregulation of the DDR is common in cancers [4-7]. While in premalignant lesions DDR has been shown to be activated, likely due to the presence of DNA damage (i.e. oncogene activated replication stress) [8-10], its subsequent inactivation favors tumor transformation and progression by the acquisition of further genomic alterations [11,12]. In addition, genomic instability driven by a specific deficiency in DDR can make cancer cells more dependent on the remaining and still functional DDR pathways to sustain their survival [13-15]. The possibility to specifically target the remaining enzymes has proven an effective therapeutic strategy and led to the concept of synthetic lethality [16-18].

The unravelling of the key players in DDR, their specific inactivation in different tumor types and the synthesis of selective chemical inhibitors of DDR represent new hot topics in cancer therapy and have been the subject of several recent reviews [3,13,19-22]. Here we will focus on the importance of DDR in lymphomas and how this can be exploited therapeutically.

DDR and lymphomas

As summarized in Fig. 1, there are multiple mechanisms by which DDR pathways are deregulated in B-cell lymphomas [23]. The vast majority of lymphomas derive from germinal center (GC) B-cells or B-cells that have passed through the GC [24]. This is likely because in the GC, the physiological process of generating B-cells capable of secreting high-affinity antibodies requires several cycles of proliferation and somatic hypermutation followed by class-switch recombination [24]. The two latter processes expose cells to high levels of DNA damage. It is therefore not surprising that DDR proteins are important for normal B-cell development as well as for lymphoma tumorigenesis and hence, represent promising therapeutic targets.

The GC master regulator BCL6, frequently deregulated in diffuse large B-cell lymphoma (DLBCL), suppresses genes involved in DDR,

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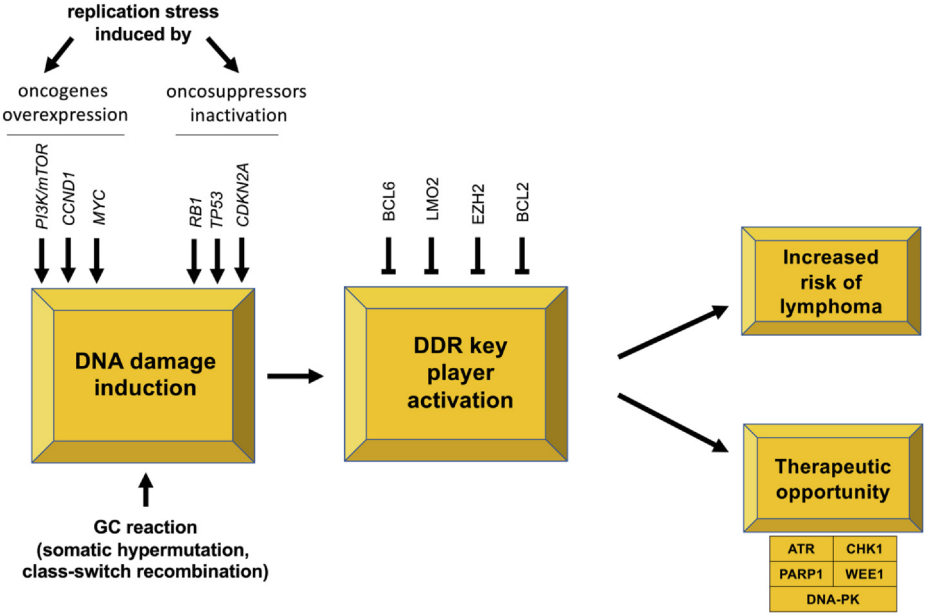


Fig. 1. Schematic representation of DDR involvement in lymphoma development and its therapeutic opportunities.

including *TP53*, *ATR*, and *CHK1 (CHEK1)* [24-29]. This renders B-cells tolerant to the physiological levels of DNA damage caused by somatic hyper-mutation and class-switch recombination. In a regulatory feedback loop, the accumulation of DNA damage induces ATM activation with BCL6 phosphorylation and degradation by the ubiquitin–proteasome system [27].

LMO2 is another transcription factor active in GC B-cells that has effect on DDR, in particular on the accumulation of DNA double- strand breaks (DSB) [30]. LMO2 is expressed at high levels in GC B-cells, in the vast majority of GC B-cell like (GCB) DLBCL and in almost half of activated B cell-like (ABC) DLBCL [31-33]. Expression of LMO2 correlates with better patient outcome [32,33]. LMO2 interacts with 53BP1 and inhibits the recruitment of BRCA1 protein to DSB [30]. When LMO2 is highly expressed, like in DLBCL cells, it leads to a *BRCAness* phenotype and sensitivity to inhibitors of poly(ADP-ribose)polymerase-1 (PARP) [30].

A third gene crucial for normal GC and B-cell maturation that also has an impact on DDR is *EZH2*. Its protein is the catalytic subunit of the polycomb repressive complex 2 and it is over-expressed and/or mutated in different lymphomas, especially in GC-derived lymphomas [34-37]. During GC formation, EZH2 is believed to impair DDR and suppress the cell-cycle checkpoint gene *CDKN1A* [38,39]. Data from epithelial models also indicate that EZH2 can affect the DNA repair process through inhibition of the homologous recombination repair pathway [40], and also of apoptosis induced by DNA damaging agents, to promote cell cycle arrest [41].

The anti-apoptotic protein BCL2 is often deregulated in lymphomas, via genomic amplification (most commonly in ABC-DLBCL), chromosomal translocation (follicular lymphomas and GCB-DLBCL) or as a consequence of the loss of miR-15 and miR-16 in chronic lymphocytic leukemia (CLL) [42]. BCL2 can also bind and inhibit PARP1, leading to decreased DNA damage repair and to a condition of PARP deficiency when BCL2 is overexpressed [43].

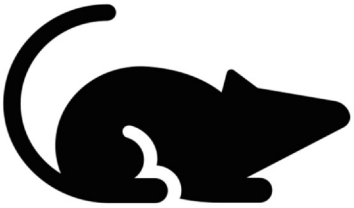
ATM is recurrently inactivated in lymphomas, especially in CLL and mantle cell lymphoma (MCL), but also in DLBCL [44-52]. Individuals with ataxia telangiectasia (A-T), an autosomal recessive disease caused by germline *ATM* mutations, have an increased risk of developing lymphomas [53,54]. Single nucleotide *ATM* polymorphisms have been associated with an higher risk of developing CLL or DLBCL [55], but this correlation is still uncertain [56]. *ATM* defects in CLL have been associated with more aggressive disease and resistance to treatment [57,58], while *TP53* mutations are present in indolent and aggressive lymphoma, including CLL and DLBCL [36,59]. Increased replication stress is commonly observed in non-GCB DLBCL with *MYC* overexpression and *CDKN2A/B* deletion, features associated with higher sensitivity to the ATR inhibitor ceralasertib and to the WEE1 inhibitor adavosertib, two compounds that are also synergistic when combined [60].

Half of DLBCL cases are γH2AX positive by immunohistochemistry, and this marker of DNA damage is associated with poor prognosis following conventional R-CHOP/CHOP-like chemo-immunotherapy [61]. Similar to what has been reported for increased replication stress [60], γH2AX and DDR activation are also associated with MYC expression with no difference based on DLBCL cell of origin [61].

The two new genetically-defined classifications of DLBCL do not show an enrichment of mutations in *ATM*, *ATR*, *PARP* or *CHEK1* but only in *WEE1* in the so-called MCD subgroup, which is characterized by lesions activating B-cell receptor signaling and the NF-κB pathway [35,62]. However, the newly defined subgroups of DLBCL are enriched of lesions that activate the proteins we have already mentioned, such as EZH2, BCL6 or BCL2 [35,62], which impair DDR. Interestingly, both classifications define a subgroup of cases with high aneuploidy driven by *TP53* inactivation [35,62] and with an enrichment of *53BP1* mutations [62], inactivated in approximately 10% of DLBCL [63].

DNA-dependent protein kinase (DNA-PK) has a key role in the repair of double strand breaks, i.e. pathway choice between non homologous end joining (NHEJ-error prone pathway) and homologous recombination (HR-error free pathway) [64,65] as well as in the V(D)J and class-switch recombination pathway [66,67]. The DNA-PK holoenzyme consists of the Ku70 and Ku80 regulatory subunits and a catalytic component (DNA-PKcs) [68]. Increased expression/ activity of DNA-PKcs correlates with poor overall survival in patients with CLL [69].

Mouse models have been instrumental in understanding the pivotal role of DDR in lymphomagenesis and have provided support for the therapeutic efficacy of DDR inhibition (Fig. 2) [70]. Mice with complete loss of *Atm* are viable and recapitulate many features of A-T patients. By four months of age nearly all *Atm-/-* mice die due to T-cell malignancies with recurrent rearrangements of the *TCRD* locus [71,72]. *Atm* inactivation leads to T-cell lymphomas of thymic origin and B-cell lymphomas [72-80]. Deficiency of *Atm* also accelerates disease onset and progression in the Eμ-*Myc* mouse model [81,82], the Eμ:TCL1 mouse model [83], and the Eμ-D1T286A cyclin D model [84]. Genetic and



ATM	Lymphomagenesis
ATR	Increased lymphomagenesis
PARP1	Increased lymphomagenesis
BRCA1/2	Lymphomagenesis
DNA-PK	Lymphomagenesis
53BP1	Increased lymphomagenesis
CHK1	Decreased lymphomagenesis

Fig. 2. Role of DDR proteins in lymphomagenesis according to mouse models.

biochemical evidence show that it is not solely ATM that directs the p53 response predominantly towards apoptosis after DNA damage in tumor cells, but that a synthetic lethal interaction exists between ATM and DNA-PKcs. In this scenario it was demonstrated that inhibition of DNA-PK could re-sensitize chemo-resistant *ATM*-deficient p53-containing tumors to anti-cancer agents, causing DNA double strand breaks both *in vivo* and *in vitro* [85]. Using a conditionally re-activatable *ATM* allele, it was possible to reactivate *ATM* in T cell lymphoma-bearing mice and this led to significant lymphoma shrinkage. Similarly, lymphoma regression in the Eμ-*Myc* model was observed upon whole organism *ATM* restoration [86]. All these data indicate a role for *ATM* loss in driving lymphomas.

Atr haplo-insufficiency increases tumorigenesis in a *K-Ras* G12D model, especially if paired with *TP53* haplo-insufficiency, leading to T-cell lymphomas [87]. *Parp-2(-/-)* mice do not develop spontaneous tumors [88], but both *Parp1* and *Parp2* deficiency accelerate spontaneous tumor development in *TP53*-null mice, which are mainly T-cell lymphomas [88,89]. Deficiency of *53BP1*, inactivated in approximately 10% of DLBCL [63], leads to increased lymphomagenesis in *TP53 (-/-)* [90,91] and in *AID* transgenic mice (IgkAID) [92]. *BRCA1* and *BRCA2* mouse mutants develop lymphomas and the incidence of lymphoid tumors is higher when the mutants are crossed with *TP53* null animals [93].

Although it can be lost in small subsets of aggressive lymphomas [94] and despite it being physiologically inhibited by BCL6 [25], CHK1 is usually highly expressed in mouse and human *MYC* driven lymphomas and these tumors are sensitive to CHK1 genetic silencing or pharmacological blockade with Chekin [95]. CHK1 deficiency blocks B-cell development at a very early stage [96], impairing antibody production and maturation [97]. Further, in murine models, CHK1 deficiency reduces the incidence of lymphomas in both Eμ-*Myc* and irradiation induced thymic lymphoma B- and T-cell mouse models, respectively [96].

WEE1-/- mice show embryonic lethality before day 4 [98], thus *in vivo* models to study its role in adult tissues are missing. Studies using conditional and tissue-specific *WEE1* mutant mice and cells show that WEE1 is necessary for maintaining genomic stability: *WEE1* deletion results in growth defects and cell death due to DNA damage and chromosomal aneuploidy [98,99].

DNA-PKsc/Ku knockout mice have defects in DNA DSB repair and display a 2–5 fold higher increased sensitivity to ionizing radiation (IR) and a severe immune-deficient phenotype, due to the block in V(D)J-recombination [100]. In addition, *DNA-PKcs* knockout mice have an increased risk of cancer in lymphoid tissues, possibly secondary to the V(D)J-recombination defect [101]. A synthetic interaction has been observed between *ATM* and *PRKDC* (encoding DNA-PKcs) as *ATM -/-*; *PRKDC -/-* knockout animals die in utero at embryonic day E7.5, while single knockout mice are viable [80,102,103].

DDR inhibitors

Preclinical evidence suggests that deregulated DDR also contributes to lymphoma development and maintenance. Similarly to other tumor types [104], these DDR defects can be therapeutically exploited. Here we will focus on CHK1, WEE1, ATR, DNA-PK and PARP inhibitors for which both preclinical and clinical data continue to accumulate.

CHK1 inhibitors

CHK1 was the first DDR enzyme to be explored as a potential therapeutic target against lymphoma cells. As mentioned previously, initial evidence of the potential efficacy of CHK1 inhibitors in lymphomas came from the discovery of a synthetic lethal relationship between CHK1 inhibitors and the *c-MYC* oncogene in *MYC*-driven malignancies, including B-cell lymphomas [95,105]. CHK1 has a key role in normal B-cell development and lymphomagenesis. Total ablation of CHK1 in B-cells arrests their development at the pro-B-cell stage [96], underscoring CHK1 as a valid target in hematological cancer. Enhanced tumor replication stress and genomic instability lead to a constitutively activated DDR pathway and to an increased dependence on CHK1. Studies of several CHK1 inhibitors demonstrate the anti-tumor activity of this class of agents in a variety of preclinical models of lymphoma (Table 1). Lymphoma cell lines are more sensitive to various CHK1 inhibitors than solid tumor cell lines [61,106,107]. Genetic silencing of CHK1 is toxic for DLBCL cell lines [36]. Many efforts have been undertaken to identify the molecular features associated with sensitivity/resistance to CHK1 inhibitors in various cellular contexts [106,108]. No correlation was found between sensitivity to CHK1 inhibitors and the mutational status and/ or expression of MYC, TP53 or ATM in different lymphoma and CLL models [106,108]. High expression of cell proliferation genes is associated with higher sensitivity to PF-0477736 in MCL and in DLBCL cell lines, while NF-κB and JAK/STAT-related genesets are enriched in the gene expression profiles of the least sensitive cell lines [106].

In terms of histology, CHK1 inhibitors are more active in cyclin D1-driven MCL and multiple myeloma (MM) cell lines than in other lymphoma models [106]. Within DLBCL, cell lines derived from the GCB subtype seem to be more sensitive to CHK1 inhibition than ABC DLBCL cell lines [106].

Interestingly, a MCL cell line with secondary resistance to PF-00477736 showed downregulation of genes involved in cell cycle progression and E2F1 targets with upregulation of genes involved in NF-κB and also SRC/MAPK signaling [109]. The re-overexpression of cyclin D1 in this cell line partially re-sensitized it to the agent, corroborating the hypothesis that cyclin D1 overexpression mediates sensitivity to CHK1 inhibitors [109].

Recent data indicate that the Chk1 dependent adaptor protein claspin is involved in the NF-κB -mediated response to oncogene induced DNA replication stress [110]. Mutation of NF-κB subunits (knockout of *c-Rel* or a T505A transactivation domain mutation of *RelA*) leads to earlier lymphoma onset correlating with loss of claspin expression and inhibition of CHK1 activity [110]. While wild type Eμ-*MYC* lymphomas are highly responsive to CHK1 inhibitor treatment, by contrast Eμ-MYC NF-κB mutant $cRel^{-/-}$ or $RelA^{T505A}$ lymphomas are resistant [110].

CHK1 inhibitors synergize with proteasome or BTK inhibitors [111,112]. Combination of the proteasome inhibitor ixazomib with the

Table 1
DDR inhibitors with preclinical or clinical evidence of anti-tumor activity in lymphomas and their clinical stage of development.

Target	Compound and preclinical activity in lymphomas	Clinical stage	Clinical development status*	Preclinical activity in lymphomas
CHK1	Chekin	–	–	[95]
	CHIR-124	–	–	[96,97,113]
	MU380	–	–	[108]
	PF-0477736	Phase I, solid tumors	No on-going trials	[61,96,97,105,106,109,114,196]
	SRA737, CCT-245737; PNT-737	Phase II, solid tumors	No on-going trials	[110,197]
	V158411	–	–	[107]
CHK1/CHK2	AZD7762	Phase I, solid tumors	No on-going trials	[61,106,111,112]
	UCN-01, 7-hydroxystaurosporine	Phase II, solid tumors, lymphoma	No on-going trials	[119,198-200]
WEE1	Adavosertib, MK-1775, AZD1775	Phase II, solid tumors	On-going trials	[60,106,112,114,123-125,128]
ATR	BAY 1,895,344	Phase I, solid tumors, lymphoma	On-going trials	[132]
	VE-821	–	–	[113,135]
	Berzosertib, VE-822, M6620, VX-970	Phase II, solid tumors	On-going trials	[112,113]
	Ceralasertib, AZD6738	Phase I/II, solid tumors, lymphoma	On-going trials	[60,112,136,201]
DNA-PK	CC-115	Phase I	On-going trials	[151]
PARP	6(5H)-phenanthridinone	–	–	[180,202]
	AZD2461	Phase I, solid tumors	No on-going trials	[170]
	CK-102, CEP-9722 (prodrug of CEP-8983)	Phase I/II, solid tumors, lymphoma	On-going trials	[176]
	MC2050	–	–	[203]
	NU1025	–	–	[175]
	PJ34	–	–	[163]
	Niraparib, MK-4827	FDA approval, solid tumors	On-going trials	[178]
	Olaparib, AZD-2281, KU 0,059,436	FDA approval, solid tumors	On-going trials	[83,163]
	Talazoparib, BMN-673, MDV-3800	Phase III, solid tumors	On-going trials	[169]
	Veliparib, ABT-888	Phase III, solid tumors	On-going trials	[204]

*, based on http://adisinsight.springer.com/ and/or https://clinicaltrials.gov accessed in May 2020.

CHK1 inhibitor AZD7762 achieves strong downregulation of MYC and induction of cell death in T-cell lymphomas [111]. Preclinical evidence of synergism between CHK1 inhibitors and the BTK inhibitor ibrutinib is available for MCL cell lines [112]. Some activity has also been observed for the combination with psoralen plus ultraviolet A (PUVA) photochemotherapy in cutaneous T-cell lymphoma (CTCL) cell lines [113].

Interestingly, synergistic activity was seen when combining CHK1 inhibitors with other DDR inhibitors such as WEE1 and/or ATR inhibitors in lymphoma cell lines [106,112,114]. DDR inhibitor combinations exacerbate replication stress, and produce a very strong synergistic effect in lymphoma cell lines at much lower concentrations than those used in solid tumor cell lines and these effects translated into a strong antitumor activity *in vivo* [106,112]. Moreover, DDR inhibitor combinations lead to MYC protein destabilization in DLBCL and MCL cell lines, in both *in vitro* and *in vivo* settings, corroborating the potential significance of the use of this combination in MYC driven tumors [112,114].

Preliminary results of a phase I clinical trial with the CHK1 inhibitor SRA-737 (NCT02797964), in patients with tumors other than lymphoma, showed an acceptable safety profile and signs of clinical activity in patients with mutated Fanconi Anemia and BRCA network genes [115]. Prexasertib, a CHK1 and CHK2 inhibitor, has been investigated in a phase 2 study in patients with *BRCA*-wild type recurrent high-grade ovarian cancer. An overall response rate of 33% was reported and grade ≥ 3 hematological adverse events were commonly observed [116]. The a pan-kinase inhibitor 7-hydroxystaurosporine (UCN-01) also targets CHK1 and its safety and activity have been investigated in phase 1 trials in patients with lymphoid tumors [117-119]. No clinical responses and only stable diseases were observed when it was used as single agent (n. = 9) [119] or combined with prednisone (n. = 5) [117]. However, when used in combination with fludarabine, an overall response rate of 38% was achieved (7/18) with one complete remission (CR) (CLL) and six partial responses (PR) (4 FL, 1 CLL) [118]. To our knowledge, no trials are currently exploring CHK1 inhibitors in lymphoma patients (clinicaltrials.gov, May 2020).

The majority of CHK1 inhibitors have shown only limited clinical activity and their use is challenged by their safety profile, especially when they are combined with chemotherapy agents. Thus, up to date no CHK1 inhibitor has reached phase III evaluation or FDA approval [120]. Although new clinical trials with these compounds are still considered, more rationally designed studies in selected tumor types (based on histology or biology) are warranted to achieve the synthetic lethal interactions observed in preclinical studies. It will also be important to clinically explore them in combination with signal transduction modulators of pro-survival pathways or with other DDR inhibitor agents such as ATR, WEE1 and PARP inhibitors.

WEE1 inhibitors

WEE1 is a rational therapeutic target in lymphomas, as indicated by the observation that genetic silencing of the gene is toxic for DLBCL cell lines [36]. The pyrazolo-pyrimidine derivative adavosertib is at present the most potent and selective WEE1 inhibitor and the only one that has entered clinical evaluation [121,122] (Table 1). The compound has antitumor activity as a single agent in preclinical lymphoma models [106,123]. In DLBCL and MCL preclinical models, adavosertib has stronger single agent anti-tumor activity than the ATR inhibitor ceralasertib as well as a good tolerability [60,112].

The synergism between WEE1 inhibitors and CHK1 or ATR inhibitors in lymphomas is supported by many preclinical studies [60,106,112,114]. Synergism is also seen with SRC inhibitors [124], rituximab [123] and anti-apoptotic agents, including venetoclax [125]. As expected, adavosertib enhances both *in vitro* and *in vivo* cytotoxic effects of different DNA damaging agents [126-128]. Addition of adavosertib increases the anti-lymphoma activity of radiotherapy [128] and of the anti-CD37 radiolabeled ^{177}Lu-lilotomab satetraxetan [126,127]. *In vitro* treatment of DLBCL cell lines with adavosertib in combination with the equivalent of the CHOP clinical regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) induces unscheduled mitotic progression, resulting in abnormal cell cycle distribution and increased DNA damage. Among the individual CHOP components, doxorubicin shows the strongest effect in combination with adavosertib in terms of reducing viability and increasing DNA

damage [128].

Over 50 clinical trials have or are currently exploring adavosertib as a single agent or in combination for different indications (clinicaltrials.gov, May 2020). Although the first trial (NCT01748825) was also open for lymphoma patients, no data are available for this population of patients [129,130].

ATR inhibitors

ATR inhibitors have anti-tumor efficacy in preclinical models of lymphomas, inducing a significant anti-proliferative and antitumor activity both *in vitro* and *in vivo* [60,112,131-134] (Table 1). Importantly, lymphoma cell lines, especially MCL models, are the most sensitive to BAY 1895344 among a wide spectrum including cell lines mostly derived from non-hematological cancers [133].

While CLL cell lines with *ATM* and/or *TP53* loss were more sensitive to the ATR inhibitor ceralasertib than wild-type *TP53* and *ATM* cells [131], no clear correlation between sensitivity to ATR inhibitors and the status of cell cycle and/or DNA repair markers has been documented in other lymphoma types, like MCL and DLBCL [112,132]. Gene expression profiling of a large panel of lymphoma cell lines treated with ATR inhibitors (ceralasertib and BAY 1895344) showed that the upregulation of cell cycle regulators and DNA repair genes is associated with a higher sensitivity to such inhibitors, while pro-survival pathways (PI3K/AKT/mTOR or NF-κB) and oxidative phosphorylation are linked with a lower sensitivity [112,132], partially in line with the replication stress and constitutively active DDR pathway described previously that is associated with sensitivity to CHK1 inhibitors [106,109].

ATR inhibitors are also being investigated in combination with different targeted agents and therapeutic modalities. BET inhibitors potentiate the endogenous DNA damage and cell death caused by ATR inhibitors [135,136]. The addition of the ATR inhibitor ceralasertib improves the response to the combination of rituximab-bendamustine *in vivo,* in DLBCL xenografts [60]. Finally, synergism is also observed combining the ATR inhibitors, VE-821 or berzosertib, with PUVA in cutaneous T-cell lymphoma (CTCL) cell lines [113]. Preclinical synergism is achieved combining ATR inhibition with BTK inhibitors, such as acalabrutinib in ABC DLBCL [137] and CLL [138]. Based on the latter data, ceralasertib is one of the combination partners for acalabrutinib, in an ongoing multi-arm phase I study (NCT03527147) [139].

Combinations of ATR inhibitors with other DDR inhibitors are active in different preclinical models, as also mentioned in the previous section. Specifically, significant synergism is observed combining the ATR inhibitor ceralasertib with the WEE1 inhibitor adavosertib, an effect corroborated by two independent groups in DLBCL and MCL preclinical models [60,112]. The *in vitro* and *in vivo* data available using combinations of two DDR inhibitors used at lower doses in lymphomas compared to the doses used in solid tumors warrant clinical investigations in this setting.

Specific and selective ATR inhibitors, such as berzosertib [140-142], ceralasertib [143] and BAY 1895344 [133], have recently entered early clinical development and phase I/II clinical trials (Table 2). M6620 has been investigated in a phase 1 trial in combination with topotecan in patients with solid tumors and signs of activity have been observed, especially in patients with platinum-refractory small cell lung cancer [140]. In a phase 2 randomized trial in platinum-resistant ovarian cancer, the combination of M6620 with gemcitabine increased progression free survival (PFS) compared to single agent gemcitabine [142]. The results of the dose escalation cohort of the phase I trial (NCT03188965) assessing the safety and preliminary activity of the ATR inhibitor BAY 1895344 were presented at the 2019 American Society for Clinical Oncology (ASCO) conference. Promising signs of activity were observed, especially in patients with solid tumors harboring a mutation in *ATM* or with ATM loss assessed by immunohistochemistry [144]. In all these clinical trials with ATR inhibitors as single agent or in combination with chemotherapy, the most

Table 2
List of ongoing trials investigating DDR inhibitors in patients in lymphoma, ranked by the drugs' targets and by trial status in May 2020.

Target	Title	Registration Number	Status *	First Posted *	Phase	Conditions *
WEE1	Adavosertib	NCT01748825	Active, not recruiting	2012	Phase 1	Advanced solid tumors and lymphomas
ATR	BAY 1895344	NCT03188965	Recruiting	2017	Phase 1	Advanced solid tumors and lymphomas
ATR	Ceralasertib + acalabrutinib	NCT03527147	Recruiting	2018	Phase 1, multiarm	R/R advanced solid tumors, non-Hodgkin lymphoma
ATR	Ceralasertib + acalabrutinib	NCT03328827	Recruiting	2017	Phase 1/2	R/R high-risk CLL
DNA-PK	M3814	NCT02316197	Completed	2014	Phase 1	Advanced solid tumors or chronic lymphocytic leukemia
DNA-PK	CC-115	NCT01353625	Active, not recruiting	2011	Phase 1	Advanced solid tumors, and hematologic malignancies
PARP	Olaparib	NCT03233204	Recruiting	2017	Phase 2	R/R advanced solid tumors, non-Hodgkin lymphoma, or histiocytic disorders with defects in DDR genes
PARP	Olaparib	NCT03155620	Recruiting	2017	Phase 2	Pediatric patients with R/R advanced solid tumors, non-Hodgkin lymphoma, or histiocytic disorders, if deleterious mutations *in ATM, BRCA1, BRCA2, RAD51C,* or *RAD51D* genes
PARP	Olaparib combined with vorinostat/gemcitabine/busulfan/melphalan with autologous stem-cell transplant	NCT03259503	Recruiting	2017	Phase 1	R/R lymphomas undergoing stem cell transplant
PARP	Veliparib combined with nivolumab	NCT03061188	Active, not recruiting	2017	Phase 1/1b	R/R advanced stage IV solid tumors that cannot be removed by surgery or lymphoma with or without alterations in DDR Genes
PARP	Veliparib combined with cyclophosphamide and doxorubicin	NCT00740805	Active, not recruiting	2008	Phase 1	Metastatic or unresectable solid tumors, non-Hodgkin lymphoma

*, as assessed on clinicaltrials.gov, May 2020. R/R, relapsed or refractory.

common side effects were anemia, thrombocytopenia and neutropenia, often limiting the possibility to dose escalate and requiring dose reduction or interruption during treatment course. Similar side effects were observed in the first 24 patients enrolled in the phase I trial (NCT02223923) with ceralasertib in patients with solid tumors [145]. The phase I study (NCT01955668) for relapsed/refractory B-cell malignancies with an expansion cohort for patients with 11q-deleted or *ATM*-deficient, relapsed/refractory CLL closed prematurely with only two patients enrolled (as assessed on clinicaltrials.gov, May 2020).

DNA-PK inhibitors

Besides its critical role in repair, DNA-PK is involved in many other cellular processes, rendering it an interesting therapeutic target in malignancies [67,146,147]. As DNA-PK belong to the PI3K family subgroup along with ATR and ATM kinases [148], the first inhibitors were directed against the ATP pocket, which is not specific for DNA-PK. Hence, they could inhibit multiple kinases and sensitize different tumor types, including lymphoma and CLL cells, to chemotherapeutic agents and IR [65,68,149]. CC-115 is a dual DNA-PK and TORC1/TORC2 inhibitor with pre-clinical and early clinical activity in CLL [150,151]. Newer selective DNA-PK inhibitors have been identified including NU7441, NU7016, VX-984 and M3814 [67,68]. A synthetic lethal interaction has been described between ATM and DNA-PK whereby DNA-PK inhibition was active as monotherapy, both *in vitro* and *in vivo*, in *ATM*-deficient lymphoma [152]. This interaction was corroborated by a wide cell-based screen for mutations associated with DNA-PK alteration [153].

A few DNA-PK inhibitors have reached clinical development and their safety and efficacy are now under study (Table 2). The DNA-PK inhibitor M3814 was investigated in combination with radiotherapy in a phase 1 dose escalation trial (NCT02516813) [154]. Three dose levels (100 mg, 200 mg and 400 mg QD) were investigated in 16 patients [154]. The most frequent adverse events (AEs) were fatigue, nausea, constipation, decreased appetite, dysphagia, mucosal inflammation/stomatitis, vomiting, back pain, chest pain, diarrhea, radiation skin injury, and decreased weight [154]. Two dose limiting toxicities occurred at the higher dose (400 mg QD), and the 300 mg QD is currently being investigated [154].

PARP inhibitors

The family of the poly(ADP-ribose)polymerases comprises 17 members and PARP1 is the most investigated [155,156]. Given the role of PARP1 in base excision repair, the initial development of PARP inhibitors was in conjunction with DNA damage agents causing single strand breaks. Subsequently, two different groups reported a synthetically lethal interaction between BRCA1/2 and PARP1 with high therapeutic efficacy [14,15]. By inhibiting the PARP catalytic activity, PARP inhibitors were though to prevent efficient repair of DNA damage single strand breaks (SSBs) resulting in collapse of the replication fork and generation of DSBs. HR deficient cells could repair these DSBs by the error-prone NHEJ pathway, leading to chromosomal alteration and cell death [157,158]. However, it was later demonstrated that PARP inhibitors trap PARP in DNA, with the formation of PARP-DNA complexes, that cause replication stress and collapse of the replication fork [159]. The ability to form PARP-DNA complexes (trapping capacity) is different between PARP inhibitors and has been shown to correlate with their cytotoxic activity [160]. Many pre-clinical and clinical data have proven the activity of PARP inhibitors in different solid tumors with or without DDR deficiency, leading to Food and Drug Administration (FDA) and European Medical Agency (EMA) approval of different molecules (olaparib, rucaparib, niraparib, talazoparib) [161,162]. Other inhibitors are in different clinical and/or preclinical development phases.

As previously mentioned, experimental evidence indicates that PARP inhibitors can also have a therapeutic role in lymphomas (Table 1). Several data have shown that cells in which the *ATM* gene is altered by genetic modification, siRNA interference or chemical inhibition display an increased sensitivity to PARP inhibition [163-166]. PARP inhibitors showed preferential *in vitro* and *in vivo* activity in MCL or CLL cells with ATM deficiency [83,163,167,168]. In addition, olaparib is more active in MCL cells bearing both ATM and TP53 inactivation than in cells with *ATM* inactivation and wild type *TP53* [168]. It is important to restate that DLBCL cells expressing LMO2 display a *BRCAness* phenotype due to the fact that LMO2 interferes with BRCA1 recruitment to double strand breaks by interacting with 53BP1 during DNA repair [30]. DLBCL cells with high LMO2 level are much more responsive to olaparib than cells with a low expression [30]. The same results are seen in T-cell acute lymphoblastic leukemia cells with high or low LMO2 levels [30]. An interesting report suggests that Burkitt lymphoma and leukemia cells harboring the t(8;14)(q24;q32) translocation encoding IGH/MYC not only have constitutive activation of MYC, but also express lower levels of BRCA2 [169]. The low levels of BRCA2 renders these cells particularly sensitive to the PARP inhibitor talazoparib both alone and in combination with chemotherapy [169]. High expression of PARP1 is associated with a worse clinical outcome in early-stage Sezary syndrome but in primary cells, also with sensitivity to the PARP inhibitor AZD2461 [170].

While PARP inhibitors are now standard-of care in some solid tumors [161,162,171,172], this class of agents is just starting to be explored in lymphomas. At least in preclinical models, PARP inhibitors are beneficial when combined with a variety of treatments: chemotherapeutic agents (doxorubicin, R-CHOP [30], busulfan, gemcitabine, melphanan [173], topotecan [174], temozolomide [175], bendamustine [176]), targeted agents (ibrutinib [177]), monoclonal antibodies (rituximab [123]), epigenetic drugs (hypomethylating agents, histone deacetylases inhibitors [178]), radiotherapy [179,180], radioimmunoconjugates [179]. Although for most of these combinations the *in vivo* tolerability has not been explored providing only the scientific rationale for further studies, some are worthy of further discussion. When PARP inhibition is combined with R-CHOP in LMO2 high expressing DLBCL cells transplanted in nude mice, greater inhibition of tumor growth and prolonged survival are achieved compared to single arm treatments [30]. Olaparib/ibrutinib combination significantly inhibits *in vitro* growth compared to either drug alone in MCL cell lines and the effects are additive or synergistic depending on the genetic background [177]. Niraparib has a synergistic effect in combination with the histone deacetylase inhibitor romidepsin and the demethylating agent decitabine, against the proliferation of lymphoma cells via *ATM* activation and increased apoptosis [178]. The addition of busulfan further increases the cytotoxic activity of the triple combination [178]. Finally, due to the contradictory data reported in *BRCA*-mutated breast cancer models [181,182], it will be interesting to assess available data for combination of PARP inhibitors with EZH2 inhibitors, in lymphoma models, perhaps in genetically defined DLBCL subgroups [35,62] and taking into consideration that 53BP1 inactivation is reported to give resistance to PARP inhibitors [183].

Very few published data regarding lymphoma patients are available from clinical trials. A phase 0 study (NCT00387608) with veliparib enrolled 13 patients including three with indolent lymphoma and three with T-cell lymphoma, but no specific results were reported for these patients [184]. A phase I trial (NCT01326702) explored the combination of veliparib and bendamustine with or without rituximab in B-cell lymphoma patients [185]. Anemia, nausea, hypertension, and hyperhidrosis were the dose-limiting toxicities [185]. The most recurrent grade $\geq$ 3 toxicities were hematological (lymphopenia, anemia, neutropenia, thrombocytopenia), nausea, and hypophosphatemia [185]. Among patients treated with veliparib and bendamustine, the overall response rate (ORR) was 71% (5/7) with 57% (4/7) CR rate. The addition of rituximab led to an ORR of 86% (6/7) and a CR of 71% (5/7) [185]. Six patients with follicular lymphoma grade 1–3a achieved CR (5

with the triple combination) [185]. Two patients with lymphoid neoplasms were among the 35 that entered the phase I study (NCT01445522) of veliparib administered with metronomic cyclophosphamide [186].The combination was tolerable [186]. One patient with CLL had a stable disease, receiving a total of 42 cycles of treatment with relief of B symptoms [186]. There was only one lymphoma patient among the 24 enrolled in the phase 1 study of veliparib in combination with topotecan (NCT00553189) [187]. Myelosuppression was the dose limiting effect that required topotecan dose reduction [187]. Olaparib was evaluated in a phase I study (ISRCTN34386131) for patients with lymphoid tumors (CLL, n. = 9; MCL, n. = 4; T-PLL, n. = 2) [188]. No clinical responses were reported, and disease progression was the reason of discontinuation in most of the cases [188]. Most common adverse events were anemia, thrombocytopenia, fatigue, nausea and neutropenia [188]. A phase II study (NCT01244009) was designed to assess the activity of niraparib in MCL patients, but it was prematurely closed without enrolling any patient (as assessed on clinicaltrials.gov, May 2020). No lymphoma patients were enrolled in the phase I study (NCT01345357) of CEP-9722 combined with gemcitabine and cisplatin [189]. So far, no results have been presented for two completed (as assessed on clinicaltrials.gov, May 2020) phase I studies that have evaluated veliparib in 23 patients with refractory solid tumors or hematologic cancer (NCT00387608) and talazoparib in 33 patients with advanced hematological malignancies (NCT01399840).

Ongoing trials with PARP inhibitors that are recruiting lymphoma patients are listed in Table 2. They are evaluating olaparib, as single agent or in combination with chemotherapy in the context of autologous stem cell transplant, and veliparib in combination with the anti-PD1 antibody nivolumab or with cyclophosphamide and doxorubicin. So far, no lymphoma patients have been enrolled among the first 11 treated in the context of the latter study [190].

DDR inhibitors and immune-checkpoint modulators

DNA damage, in terms of a high mutational burden or a mismatch repair pathway deficiency with microsatellite instability, has been linked with higher sensitivity to anti-PD1/PD-L1 therapy [191]. Promising preclinical data combining DDR inhibitors and immune-checkpoint modulators are available for solid tumors [191-195]. However, the mechanisms sustaining the improved results obtained with combinations are heterogeneous. In small cell lung cancer models, CHK1 inhibition upregulates PD-L1 expression and the addition of anti-PD-L1 increases antitumor responses [195]. Conversely, in sarcoma, prostate and non-small cell cancer models, CHK1 inhibition decreases PD-L1 expression after DSB [192]. ATR inhibition also inhibits PD-L1 expression induced by radiation treatment in a Kras driven colorectal cancer mouse model [194]. PARP inhibitors combined with anti-PD-L1 show improved anti-tumor activity versus the single agents with decreased percentage of tumor-infiltrating PD-1+/TIM3 + exhausted CD8 + T cells and CD25+/FOXP3 + CD4 + T-regulatory cells [195]. In an HPV-driven mouse model, ATR inhibition plus radiotherapy determines increased infiltration of FOXP3 + CD4 + T-regulatory cells alongside myeloid cell infiltration [193]. Thus, efforts are still needed to define the best modalities for combining DDR inhibitors with anti-PD1/PD-L1 (plus/minus other agents, such as chemotherapy or IR).

Concluding remarks

Available evidence suggests that deregulation of DDR mechanisms occurs very frequently in lymphomas and as already described for solid tumors, could represent an Achilles' heel for these cancers as well. The ability to target the remaining functional DDR pathways and/or exacerbate existing defects have been addressed at the preclinical level and the first clinical studies have also been conducted. Acute toxicity might not be a problem when DDR inhibitors are administered as single agents in tumors with a specific genetic background (*ATM* and *TP53* mutations). On the contrary, side effects could be an issue when these agents are co-administered with standard chemotherapeutic regimens and dose reductions and schedule adjustment will probably be required. Long term toxicity could be an issue in responding patients as DDR inhibitors interfere with pathways involved in the maintenance of genomic integrity and immune response.

Author contributions

All authors participated in the design of the review, literature revision, manuscript writing, and final revision.

Declaration of Competing Interest

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