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Trial Watch: Targeting ATM–CHK2 and ATR–CHK1 pathways for anticancer therapy

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Abbreviations: A-T, ataxia telangiectasia; ATM, ataxia telangiectasia mutated serine/threonine kinase; ATR, ataxia telangiectasia mutated and Rad3 related serine/threonine kinase; BRCA2, breast cancer 2, early onset; CCNE1, cyclin E1; CDC25, cell division cycle 25; CDK, cyclin-dependent kinase; CHEK1, checkpoint kinase 1; CHEK2, checkpoint kinase 2; DDR, DNA damage response; DSBs, double-strand breaks; FA, Fanconi anemia; HR, homologous recombination; MRE11, meiotic recombination 11 homolog A; MYC, v-myc avian myelocytomatosis viral oncogene homolog; MYCN, MYC–neuroblastoma-related; NBS1, nijmegen breakage syndrome 1; NHEJ, non-homologous end joining; PARP, poly(ADP-ribose) polymerase; RAS, rat sarcoma viral oncogene homolog; siRNAs, small interfering RNAs; TNBC, triple-negative breast carcinoma; ssDNA, single-stranded DNA.

The ataxia telangiectasia mutated serine/threonine kinase (ATM)/checkpoint kinase 2 (CHEK2, best known as CHK2) and the ATM and Rad3-related serine/threonine kinase (ATR)/CHEK1 (best known as CHK1) cascades are the 2 major signaling pathways driving the DNA damage response (DDR), a network of processes crucial for the preservation of genomic stability that act as a barrier against tumorigenesis and tumor progression. Mutations and/or deletions of ATM and/or CHK2 are frequently found in tumors and predispose to cancer development. In contrast, the ATR–CHK1 pathway is often upregulated in neoplasms and is believed to promote tumor growth, although some evidence indicates that ATR and CHK1 may also behave as haploinsufficient oncosuppressors, at least in a specific genetic background. Inactivation of the ATM–CHK2 and ATR–CHK1 pathways efficiently sensitizes malignant cells to radiotherapy and chemotherapy. Moreover, ATR and CHK1 inhibitors selectively kill tumor cells that present high levels of replication stress, have a deficiency in p53 (or other DDR players), or upregulate the ATR–CHK1 module. Despite promising preclinical results, the clinical activity of ATM, ATR, CHK1, and CHK2 inhibitors, alone or in combination with other therapeutics, has not yet been fully demonstrated. In this Trial Watch, we give an overview of the roles of the ATM-CHK2 and ATR-CHK1 pathways in cancer initiation and progression, and summarize the results of clinical studies aimed at assessing the safety and therapeutic profile of regimens based on inhibitors of ATR and CHK1, the only 2 classes of compounds that have so far entered clinics.

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Introduction

The preservation of genomic integrity is crucial for the development, homeostasis, and survival of all organisms, acting also as a barrier against tumorigenesis. Genomic insults are, however, continuously inflicted on cells by both exogenous and endogenous sources, which may (directly or indirectly) induce DNA damage (as in the case of genotoxic agents) and/or perturb DNA replication, for instance by slowing or stalling replication fork progression (as in the case of replicative-stress agents or DNA damaging agents).[1] Among the most common types of genotoxic agents/stresses are oxygen radicals, ionizing/ultraviolet (UV) radiation, DNA replication errors, and multiple chemotherapeutic agents.[2,3] DNA lesions may affect crucial physiological processes (e.g., DNA transcription, DNA replication, and chromosome segregation), be cytotoxic (in particular in the case of double-strand breaks [DSBs]), and result in gene mutations and genomic instability.[3-6]

Cells are endowed with a complex signaling pathway known as the DNA damage response (DDR) that helps them to cope with (and respond to) DNA insults and thereby maintain genomic stability.[3,4,6,7] DDR collectively refers to a network of cellular processes that are specifically triggered by aberrant DNA structures generated upon DNA damage, encompassing (1) cell cycle checkpoints, which halt cell cycle progression;[4,8] (2) DNA repair mechanisms, which mediate the removal of specific DNA injuries;[2,6] (3) DNA damage adaptation/tolerance processes, which allow cells to overcome persisting lesions in the absence of their repair[9]; and (4) cell death and cell senescence, which selectively depletes (the former) and semi-permanently arrests (the latter) irreversibly damaged cells.[10-13] The DNA damage signaling pathways regulate DDR by coordinating all of

these processes. The two main signaling axes that have been described to date are (1) the ataxia telangiectasia mutated serine/threonine kinase (ATM)/checkpoint kinase 2 (CHEK2, best known as CHK2) cascade, and (2) the ataxia telangiectasia mutated and Rad3-related serine/threonine kinase (ATR)/checkpoint kinase 1 (CHEK1, best known as CHK1) cascade.[14-17]

ATM and ATR are phosphatidylinositol-3-kinase–related kinases (PIKKs),[18-21] belonging to a family of serine/threonine kinases that also contains DNA-dependent protein kinase (DNA-PK), which plays a role in the DNA DSB repair pathway of non-homologous end joining (NHEJ),[22,23] and mammalian target of rapamycin (mTOR), a key autophagy regulator.[24,25] ATM recognizes and amplifies the signal generated by DSBs, whereas ATR is activated by single-stranded DNA (ssDNA) generated for example by UV-induced DNA damage or interstrand DNA crosslinking (both of which lead to stalled replication forks), or by resected DSBs.[17,26-28] In all cases these kinases are recruited to the DNA damage sites by specific DNA damage recognition proteins (i.e., DNA damage sensors), which are believed to be the meiotic recombination 11 homolog A (MRE11)–RAD50–Nibrin (NBN, best known as nijmegen breakage syndrome 1, NBS1) complex (MRN complex) for ATM[29-32] and replication protein A (RPA) complex-coated ssDNA for ATR.[33,34]

The principal substrates of ATM and ATR are the checkpoint effector kinases CHK2[14,35-37] and CHK1,[15,38-41] respectively. Upon activation, CHK1 and CHK2 are released from chromatin and halt cell cycle progression to allow repair.[14,42] In response to DSBs CHK2 triggers the G_1-S checkpoint—a mechanism surveying S-phase entry—by catalyzing the activating phosphorylation of the tumor suppressor protein p53 (TP53, best known as p53), which in turn inhibits the cyclin-dependent kinase 2 (CDK2)-CCNE1 (best known as cyclin E1) complex by transactivating the CDK inhibitor p21.[43] In contrast, CHK1 is mainly involved in the replication checkpoint (also known as the intra-S checkpoint) and the G_2-M checkpoint—surveillance mechanisms that monitor S-phase replication and mitosis entry, respectively—by targeting cell division cycle 25 (CDC25) family members and WEE1, the main regulators of the S- and M-phase CDKs.[44-51]

To ensure the coordination of DNA damage repair with the activation of cell cycle checkpoints, ATM and ATR also phosphorylate other relevant substrates involved in processes such as DNA replication, DNA repair, apoptosis, and the cell cycle,[4,14,52,53] including H2A histone family, member X (H2AFX, best known as H2AX),[42,54-57] a histone variant that upon phosphorylation (a post-translational modification designated γ-H2AX) acts as a platform for the recruitment of a variety of DNA repair proteins.[3,6] The checkpoint effectors can also mediate DNA repair in a direct fashion. For instance, CHK1 contributes to homologous recombination (HR) by recruiting the HR components breast cancer 2, early onset (BRCA2) and RAD51 to DNA damage foci,[58,59] and to the Fanconi anemia (FA) pathway.[60,61] For a comprehensive overview of ATM–CHK2 and ATR–CHK1 networks and the mechanisms of DDR please refer to the following reviews.[3-7,14-17,26,30,62-65]

Deregulation in DDR has been linked to immune deficiency, neurodegeneration, premature aging, genomic instability, cancer predisposition, and tumorigenesis.[2,3,66,67]

Along the lines of our monthly Trial Watch series,[68,69] here we describe the impact of the DNA damage response signaling pathways ATM–CHK2 and ATR–CHK1 on tumor initiation, progression, and survival. We then summarize and discuss recent clinical trials investigating the therapeutic use of inhibitors of ATR and CHK1 in cancer patients.

DNA Damage Response Signaling Pathways in Cancer

A large number of observations indicate that DDR acts as an intrinsic barrier in the early phases of human tumorigenesis.[70-74] DDR is indeed overactivated in premalignant lesions in response to increased levels of endogenous genotoxic and replication stress.[75-77] The current view is that impairment of DDR during the process of malignant transformation may promote and/or fuel tumorigenesis leading to accumulated genetic lesions and increased genomic instability.[75,77]

Further evidence links DDR impairment to cancer. First, loss, germline polymorphism, and/or mutation(s) of genes encoding components of DDR predispose to tumor.[2] Second, DDR players (including those involved in the DNA damaging signaling pathways) are frequently altered in human malignancies[78,79] and cancer signatures of the DNA repair pathways affected have been reported (reviewed in ref.[80]). Third, some oncogenes (including Harvey rat sarcoma viral oncogene homolog [H-RAS], v-myc avian myelocytomatosis viral oncogene homolog [MYC], and cyclin E1)[75,81-83] induce replication stress, which can in turn trigger chromosomal instability.[84-86] In addition, persistent telomere damage can generate tetraploidy in the early stages of tumorigenesis through a mechanism involving prolonged activation of ATM–CHK2 and ATR–CHK1 signaling.[87]

Below, we summarize the specific impact of ATM–CHK2 and ATR–CHK1 pathways on tumorigenesis.

Impact of the ATM/CHK2 network on cancerogenesis and tumor progression

Malignant cells are frequently deficient in the G_1-S checkpoint as a result of mutation or deletion of *TP53* or other components of the ATM/CHK2 module.[35,88-95] In particular, somatic mutation, polymorphism, or epigenetic silencing of *ATM* is found in a variety of human malignancies, including adult acute lymphoblastic leukemia,[96] breast cancer,[97] chronic lymphocytic leukemia,[98] colon cancer,[99] head and neck squamouse cell carcinoma,[100] lung adenocarcinoma,[89] and sporadic pancreatic ductal adenocarcinoma.[101] In one of these settings, *ATM* alterations have been associated with poor prognosis.[102,103] Along similar lines, *CHEK2* is frequently lost (>50%) or epigenetically inactivated in lung cancers.[104-106] *CHEK2* mutations are also present (albeit at lower frequencies) in other human malignancies, including breast and ovarian tumors.[35] Loss of *CHEK2* has also been found in 47% of human colorectal cancers.[107]

Of note, ataxia telangiectasia (A-T), a human syndrome caused by an inherited biallelic mutation of *ATM*, is

characterized by radiosensitivity, neurodegeneration, and immunodeficiency as well as a predisposition to tumors including thymic lymphoma.[108-110] In addition, heterozygous germline mutations in *ATM* have been associated with risk of leukemia and breast and pancreatic cancer,[111-115] whereas heterozygous germline mutations in *CHEK2* have been identified in familial cases of breast cancer[35,116-118] and *CHEK2* is considered a multi-organ tumor susceptibility gene.[35,36]

The oncosuppressive impact of the ATM–CHK2 pathway has been further demonstrated *in vivo* by employing distinct knockout models, including $Atm^{-/-}$ mice,[119-124] $Atm^{+/-}$ mice in a transformation-related protein 53 (*Trp53*) heterozygous (but not in a *Trp53* wild type) background,[125, 126] mice carrying the *Atm* 7636del9 deletion (a mutation commonly found in A-T patients resulting in the expression of a functionally impaired ATM),[126] and $Chek2^{-/-}$ mice, but only when combined with inactivation of genes encoding other DDR players (e.g., *BRCA1*, *NBS1*, or *MRE11*).[127-131]

Apparently contrary to these results, *ATM* and/or *CHEK2* have been found to be upregulated in some human cancers.[71,132-136] In addition, a significant percentage of cell lines (12%) from the NCI-60 panel have endogenously activated *CHEK2*.[137]

In summary, the ATM-CHK2 pathway acts as a barrier against oncogenesis and cancer growth.

Impact of the ATR/CHK1 network on cancerogenesis and tumor progression

The incidence of *ATR* or *CHEK1* loss or mutations in human malignancies is low, with rare exceptions such as colorectal, endometrial, and sporadic stomach cancers exhibiting microsatellite instability[138-144] or breast tumors.[145] It is worth noting that in endometrial cancers heterozygous truncating mutations in exon 10 of the *ATR* gene (which abrogate the ATR-CHK1 module activity)[146] have been associated with poor clinical outcomes.[142]

Accumulating evidence suggests that ATR and CHK1 may promote rather than suppress tumor growth. First, no homologous mutations in *ATR* or *CHEK1* have so far been identified in tumors, possibly because of the essential functions of the ATR/CHK1 axis in cell survival.[41,147-149] Second, *ATR* and *CHEK1* are frequently upregulated in human neoplasms.[150-158] This applies particularly to *CHEK1*, whose promoter activity may be induced by oncogenes such as the transcription factor E2F and MYC,[150,159] and which has been found to be overexpressed in tumors including triple-negative breast carcinomas (TNBC)[150,151] and MYC–neuroblastoma-related (MYCN)-amplified and high-risk tumors.[152] Third, conditional hypomorphic suppression of *Atr* in adult mice (which reduces *Atr* expression to 10%) halted the development of MYC-induced lymphomas or pancreatic tumors with high levels of replicative stress,[160] and potently suppressed the growth of MLL-ENL– and N-RAS^{G12D}–driven acute myeloid leukemias as well as that of p53-deficient fibrosarcomas expressing H-RAS^{G12V}.[161] Accordingly, ATR deficiency conferred protection from UV-induced skin carcinogenesis in xeroderma pigmentosum, complementation group C $(Xpc)^{-/-}$ mice.[162] In line with these findings, conditional deletion of both *Chek1* alleles in mammary epithelial cells induced cell death and developmental defects without promoting tumorigenesis in mice.[163] Moreover, homozygous loss of *Chek1* abrogated WNT-driven oncogenesis in the mouse small intestine[164] as well as chemically-induced mouse skin tumorigenesis.[165] Of note, in these 2 latter settings, *Chek1* haploinsufficiency led to tumorigenesis and/or accelerated tumor progression.

Studies have reported that *Atr*/*Chek1* heterozygosity in unperturbed conditions had no effect or induced a mild increase in the incidence of spontaneous tumors.[41,149,166] In contrast, deletion of one copy of *Trp53*[166] or monoallelic or biallelic deletion of *Chek2*[167] promoted tumor susceptibility in $Chek1^{+/-}$ mice. Along similar lines, *Atr* haploinsufficiency boosted the incidence of multiple K-RAS^{G12D}-induced cancers in *Trp53* heterozygous mice[163,168] and favored early tumor development in mice with a mismatch repair-deficient background.[146,169] In these settings, reduction of *Atr*/*Chek1* expression led to genomic instability by provoking unscheduled S phase entry, accumulation of DNA damage during impaired DNA replication, and premature mitosis or, alternatively, by directly inducing mitotic abnormalities.[163,166,168] These results suggest that ATR and CHK1 may act as haploinsufficient tumor suppressors in specific genetic backgrounds.[170]

Further confirming the importance of balanced CHK1 levels for counteracting replication stress, supra-physiological levels of CHK1 in mice (resulting from an extra copy of *Chek1*) reduced replication stress and promoted malignant transformation.[171] In addition, CHK1-S, an alternative splice variant of *CHEK1* that acts as an endogenous CHK1 inhibitor, was found to be overexpressed in multiple human tumors and showed increased expression during ovarian cancer progression.[172]

Together, these findings indicate that the ATR/CHK1 module promotes the survival of cancer cells. Nevertheless, they also suggest that, under a specific genetic context, the ATR–CHK1 network may limit tumorigenesis.

DNA Damage Response Signaling Pathways in Cancer Therapy

Several lines of evidence suggest that the DDR pathways may be attractive targets for cancer therapy. First, an efficient DDR helps (and is often required for) tumor cells to cope with high levels of genotoxic stress of endogenous (e.g., oncogene-induced replication stress) or exogenous (e.g., radio/chemotherapy) origin.[2,3,173,174] Second, alterations in DDR can render malignant cells dependent on (or even addicted to) specific DDR cascades for their survival.[2,3,80,95,174,175] For instance, cancer cells with defects in the G_1 checkpoint are believed to rely more on the ATR-CHK1 network, and are consequently more vulnerable to its inhibition.[95,176-178] Third, DDR pathways that are upregulated in tumors may be targeted by specific anticancer regimens.[2,3,80,173]

Inhibiting DNA damage signaling pathways may thus be an efficient means to eliminate tumor cells or sensitize them to DNA damaging agents or antimetabolites.

Preclinical Evaluation of ATM, ATR, and CHK1 Inhibitors as Monotherapeutic Agents

Abrogation of the ATR-CHK1 module is reported to exert antineoplastic activity by exacerbating the level of replication stress.[72,179,180] Hypomorphic suppression of ATR increased genomic instability and efficiently depleted malignant cells upon RAS activation.[168] In addition, the sensitivity of tumor cells to the inhibition of CHK1 has been correlated with levels of endogenous DNA damage and/or replication stress. This applies to multiple agents, including (1) the specific CHK1 inhibitors chekin, in MYC-overexpressing cells (including B-cell lymphoma/leukemia),[159] and AR323 and AR678, both in melanoma cells;[181] (2) the CHK1/2 inhibitor PF-00477736[182] in Eμ-myc lymphoma cells;[183] and (3) UCN-01 (an inhibitor of multiple kinases including CHK1 but not CHK2)[184-186] in acute myeloid leukemia with complex karyotype samples[154] and MYC-driven lymphomas.[160] In this latter study, CHK1 inhibition did not show therapeutic efficacy in K-RAS^{G12V}-driven pancreatic adenocarcinomas displaying low levels of replicative stress.[160] In line with these findings, the cytotoxicity of ATR inhibitors in p53-deficient cancer cells was increased by cyclin E1 overexpression-induced replicative stress.[187]

CHK1 has also been identified as a therapeutic target for neuroblastoma in a loss-of-function screen of the protein kinome.[152] Corroborating this finding, CCT244747 (a pharmacologic inhibitor of CHK1)[188] showed marked therapeutic activity in MYCN-driven neuroblastoma either as a single agent[189] or in combination with WEE1 inhibitor.[190] In addition, CHK1 inhibition has been found to be particularly effective against TNBC.[151,191-193] The peculiar sensitivity of TNBC and MYCN-driven neuroblastoma to CHK1 inhibitors has been linked to CHK1 overexpression/activation (see above) and p53 status.[150-152,191,192]

A lethal interaction between inhibitors of ATR/CHK1 and deficiency in other DDR players has also been reported. Thus, pharmacologic inactivation of CHK1 by 2e[194] or UCN-01 reduced cell growth in several cell lines depleted of BRCA2.[195] Moreover, ATM- or p53-deficient cancer cells were selectively killed by the ATR inhibitor VE-821,[196] HR-deficient cancer cells were preferentially targeted by ATR and/or CHK1 inhibitors,[197] and FA-deficient tumors were found to be hypersensitive to knockdown or pharmacologic inactivation of CHK1 (by Gö6976 and UCN-01),[198] as well as to the ATM inhibitor KU-55933.[199] This latter effect has been linked to the role of the FA pathway in DNA replication.[200-202]

Intriguingly, inactivation of CHK1, ATM, and ATR displayed enhanced anticancer activity in hypoxic conditions, most likely due to the role of DDR in hypoxia/reoxygenation,[203-205] whereas CHK1 inhibitors demonstrated preferential activity against genomically unstable polyploid cells.[206]

Finally, pharmacologic inactivation of ATR (by AZ20), CHK1 (by LY2603618, CCT244747 or CHK1A) or ATM (by KU-60019) displayed potent *in vitro* and/or *in vivo* cytotoxicity.[188,207-211]

Taken together, these findings support the use of inhibitors of ATR and CHK1 in cancer therapy, at least against neoplasms bearing a specific genetic background (e.g., deficiency in p53 or in other DNA damage repair pathways), with upregulation of the ATR-CHK1 axis, or presenting high levels of replication stress.

Preclinical Evaluation of ATM, CHK2, ATR, or CHK1 Inhibitors as Radiochemosensitizing Agents

Inactivation of ATM–CHK2 and/or ATR–CHK1 pathways is reported to boost the anticancer activity of a variety of therapeutic agents (**Table 1**).[65,95,176-178,212-214] Of note, this sensitization was proven to be particularly successful in tumor cell lines defective for p53 or p53 signaling.[215-221]

The therapeutics that have been combined with ATM, CHK2, ATR or CHK1 inhibitors include the following classes: (1) DNA damaging agents. Administration of pharmacologic agents that specifically or non-specifically inhibit ATM,[210,211,215,222-227] ATR,[218,228-230] CHK2,[216,220,231-235] or CHK1,[216,217,220,232-235] (**Table 1**) as well as inactivation of these DDR kinases by alternative approaches (e.g., overexpression of an inactive, dead mutant kinase or transfection of specific small interfering [si]RNAs)[236-239] sensitized multiple human tumors to radiation and/or chemotherapy based on cisplatin (a platinum derivative commonly employed against several solid neoplasms)[240-242] or temozolomide (an alkylating agent currently used in the treatment of anaplastic astrocytoma and glioblastoma multiforme).[243-245] In some of these settings cancer cells displayed higher radio- or chemosensitization than non-malignant cells.[211,222,229,230,234] The sensitizing effect of CHK2 inhibitors, however, remains a matter of contention as radioprotection has been also reported in malignant cells (especially in a p53-proficient context) and T cells upon CHK2 inactivation.[178,246-250] (2) Antimetabolites. Abrogation of the ATR-CHK1 module by specific pharmacologic agents[186,189,218,221,229,251-255] (**Table 1**) or by transfecting cells with specific siRNAs[251,256,257] exacerbated cancer cell killing by the ribonucleotide reductase inhibitor hydroxyurea and by the nucleoside analogs gemcitabine and/or cytarabine, 2 agents that are currently used for the treatment of several solid tumors or hematologic malignancies, respectively.[258-260] Similar results were achieved using non-specific inhibitors of CHK1[182,220,251,261-265] (**Table 1**). This chemosensitization to antimetabolites, a class of compounds that cause replication fork arrest by depleting nucleotides, has been linked to the specific role of the ATR–CHK1 pathway in DNA replication and DNA replication stress.[72,176,177,266] In line with this hypothesis, the absence of ATM or CHK2 was not effective in sensitizing cancer cells to antimetabolites.[251,267,268] (3) Topoisomerase inhibitor. Pharmacologic inactivation of the ATR-CHK1 cascade[189,219,220,228,254,255,264,269] significantly potentiated the antitumor effect of the 2 topoisomerase I inhibitors irinotecan and topotecan as well as that of the topoisomerase II inhibitor etoposide, all agents that are approved by the FDA for the treatment of several solid neoplasms[270-273] (**Table 1**). Despite some

Table 1. Preclinical evaluation of ATM, CHK2, ATR, or CHK1 inhibitors as radiosensitizing and/or chemosensitizing agents

Target(s)	Agent	Combinations	Refs
ATM	CP466722	Radiation	227
ATM	KU55933	Camptothecin, doxorubicin, etoposide, or radiation	223
		Radiation	222
ATM	KU59403	Camptothecin, doxorubicin or etoposide	225
ATM	KU60019	Radiation	210
			215
			224
		Radiation and TMZ	211
ATM/ATR	Caffeine	Radiation	226
ATR	Compound 45	Cisplatin or radiation	230
ATR	NU6027	Camptothecin, cisplatin, doxorubicin, hydroxyurea, radiation, rucaparib or TMZ	218
ATR	VE-821	Camptothecin or indotecan	269
		Cisplatin, topotecan or veliparib	279
		Radiation	228
ATR	VE-822	Gemcitabine or radiation	229
		Irinotecan	269
CHK1	AR458323	MK-1775	288
CHK1	CHIR-124	Camptothecin or irinotecan	219
CHK1	CCT244747	Gemcitabine or irinotecan	189
CHK1	GNE-783	TMZ	252
CHK1	GNE-900	Gemcitabine, irinotecan or TMZ	252
CHK1	LY2603618	Gemcitabine	221
		NU1025, olaparib, rucaparib or veliparib	283
CHK1	SAR-020106	Gemcitabine or irinotecan	255
			254
		Radiation	217
CHK1	SB-218078	Gemcitabine	251
		PD-407824	251
CHK1	MK-8776	Cytarabine, gemcitabine or hydroxyurea	186
		Gemcitabine or hydroxyurea	253
		MK-1775	290
			190
CHK1/2	AZD7762	Gemcitabine and/or MK-1775	291
		Olaparib, radiation and/or veliparib	281
		NU1025, olaparib, radiation or veliparib	283
		Gemcitabine	261
			263
		Gemcitabine, irinotecan, or topotecan	264
		Gemcitabine and radiation	235
		Olaparib	282
		Olaparib and radiation	285
		PD184352, PP2, saracatinib, or selumetinib	287
		PD184352, radiation, saracatinib and/or selumetinib	286
		Radiation	234
			216
		Veliparib	278
		5-FU and/or radiation	232
CHK1/2	PF-00477736	Carboplatin or gemcitabine	182
		MK-1775	289
CHK1/2	V158411	Several chemotherapeutic drugs including camptothecin or gemcitabine	220
CHK1/2	XL-844	Gemcitabine	262
		Radiation	233
CHK1/WEE1	PD-321852	Gemcitabine	265
CHK1/WEE1	PD-407824	Gemcitabine	251
CHK1 and multiple other kinases	UCN-01	Olaparib	281
		NU1025, olaparib or veliparib	283
		PD184352 or selumetinib	286
		Dasatinib, PD184352, PP2 or selumetinib	287
		Gemcitabine	261
		Monastrol	293
		Sagopilone	292
CHK2	CCT241533	Olaparib or rucaparib	246
CHK2	PV1019	Camptothecin, radiation or topotecan	231

Abbreviation: 5-FU, 5-fluorouracil; TMZ, temozolomide

contradictory reports[274,275] a similar chemosensitization activity is ascribed to inhibitors of ATM[223,225] and CHK2[231] (**Table 1**). (4) Poly(ADP-ribose) polymerase (PARP) inhibitors. ATM deficiency or depletion sensitized mantle cell lymphoma cells and breast cancer cells, respectively, to PARP inhibition.[276,277] In addition, CHK2 deficiency combined with PARP inhibitors elicited a synergistic lethal response upon MYC overexpression.[278] Along similar lines, pharmacologic inhibition of ATR,[218,279] inactivation of CHK2 and/or CHK1,[246,278,280-283] and administration of UCN-01[281,283] increased the antineoplastic activity of specific PARP inhibitors (**Table 1**). Moreover, AZD7762 combined with olaparib (AZD2281, a pharmacologic inhibitor of PARP1)[284] radiosensitized p53-mutant pancreatic cancer cells.[285]

Inactivation of CHK1 or CHK2 has also been reported to induce sensitization to other agents, including inhibitors of mitogen-activated protein kinase 1/2 (MAPK1/2) (e.g., PD184352 or selumetinib),[286] SRC family kinases,[287] or WEE1 (e.g., MK-1775),[190,288-291] as well as antimitotics (e.g., monastrol or sagopilone)[292,293] (**Table 1**).

In conclusion, inhibition of ATM, ATR, CHK1, or CHK2 exacerbates the *in vitro* antitumor efficacy of DNA damaging agents and PARP inhibitors. Abrogation of the ATR-CHK1 axis displays a much broader sensitization activity than that of the ATM-CHK2 module because it also potentiates the cancer killing effect of other chemotherapeutic agents, including antimetabolites and WEE1 inhibitors.

Clinical Investigation of ATR and CHK1 Inhibitors

To date, inhibitors of ATR and CHK1 are the only 2 classes of compounds that have entered clinical trials either as stand-alone agents or combined with radio- or chemotherapy (**Tables 2 and 3**, sources http://www.ncbi.nlm.nih.gov/pubmed and http://www.clinicaltrials.gov/).

Preliminary Phase I studies showed that specific (i.e., LY2603618 and MK-8776) and non-specific (i.e., UCN-01 and CBP501) inhibitors of CHK1 are well tolerated in individuals with advanced solid tumors or lymphomas[294-298] (**Table 2**). Nonetheless, in a Phase I dose-escalation study, AZD7762 showed cardiac dose-limiting toxicities in individuals with advanced solid tumors, an observation that arrested the further development of this agent.[299] It should be noted, however, that cardiotoxicity has not been reported for inhibitors of CHK1 that are more specific than AZD7762 (e.g., MK-8776),[298] suggesting that this effect may be caused by the inactivation of targets distinct from CHK1. In addition, in a Phase II interventional study, UCN-01 induced serious adverse effects (including anemia, neutropenia, vomiting, and fatigue) in the vast majority of patients with hematologic neoplasms (NCT00082017). In this clinical trial, 27% of subjects had a partial or complete response upon 2 cycles of intravenous infusion of UCN-01 (total dose 135 mg/m^2 and 68 mg/m^2, respectively) repeated over 28 d (http://www.clinicaltrials.gov). On the contrary, UCN-01 did not demonstrate significant antitumor activity as a stand-alone agent in 2

Table 2. Completed clinical trials testing the therapeutic profile of CHK1 inhibitors in cancer patients

Target(s)	Agent	Indication(s)	Phase	Notes	Ref.
CHK1	LY2603618	Advanced solid tumors	I	As single agent	294
				Combined with cisplatin and pemetrexed	326
				Combined with desipramine	328
				Combined with pemetrexed	317
CHK1	MK-8776	Acute Leukemia	I	Combined with cytarabine	319
		Advanced solid tumors	I	Alone or combined with gemcitabine	298
CHK1/2	AZD7762	Advanced solid tumors	I	Combined with gemcitabine	318
					299
CHK1/2	CBP501	Advanced solid tumors	I	Alone or combined with cisplatin	295
		Malignant pleural mesothelioma	II	Combined with cisplatin and pemetrexed	327
CHK1/2	PF-00477736	Advanced solid tumors	I	Combined with gemcitabine	NCT00437203
CHK1 and multiple other kinases	UCN-01	Advanced solid tumors	I	As single agent	296
				Combined with carboplatin	306
				Combined with cisplatin	307
					308
				Combined with fluorouracil	325
				Combined with irinotecan	311
					310
				Combined with topotecan	309
		Advanced tumors	I	As single agent	297
				Combined with prednisone	332
		Breast cancer	II	Combined with irinotecan	313
		Hematological neoplasms	I	Combined with perifosine	330
		Lymphoma	I	Combined with fludarabine	322
			II	As single agent	NCT00082017
		Melanoma	II	As single agent	301
		Ovarian cancer	II	Combined with topotecan	312
		Renal cell carcinoma	II	As single agent	300

Table 3 Ongoing clinical trials recently launched to evaluate the safety and efficacy of ATR or CHK1 inhibitors in cancer patients.*

Target(s)	Agent	Indication(s)	Phase	Status	Notes	Ref.
ATR	AZD6738	Advanced solid tumors	I	Recruiting	Alone or combined with radiotherapy	NCT02223923
			I/II	Recruiting	Combined with carboplatin or olaparib	NCT02264678
ATR	VE-822	Advanced solid tumors	I	Recruiting	Combined with cisplatin, etoposide and gemcitabine	NCT02157792
CHK1	GDC-0575	Advanced tumors	I	Recruiting	Alone or combined with gemcitabine	NCT01564251
CHK1	LY2603618	Advanced solid tumors	I	Active, not recruiting	Combined with gemcitabine	NCT01341457
CHK1	MK-8776	Acute myeloid leukemia	II	Active, not recruiting	Combined with cytarabine	NCT01870596
CHK1/2	LY2606368	Advanced solid tumors	I	Active, not recruiting	As single agent	NCT01115790
				Recruiting	Combined with cetuximab or cisplatin	NCT02124148
		Breast or ovarian cancer	II	Recruiting	As single agent	NCT02203513

*Not terminated, suspended, withdrawn, unknown, or completed as of the date of submission (January 25th, 2015)

Phase 2 trials performed in patients with renal cell carcinoma or metastatic melanoma (**Table 2**).[300,301] UCN-01 has been reported to display high binding affinity to alpha1-acid glycoprotein in plasma,[302] an observation that may explain its limited bioavailability and poor pharmacokinetics. Given the serious side effects induced by this agent in cancer patients, its non-specific nature, and its limited clinical efficacy, further development of UNC-01 in clinics has been halted. No results regarding the therapeutic activity of more specific inhibitors of CHK1 when administered alone have been published to date (http://www.ncbi.nlm.nih.gov/pubmed).

Official sources list 3 ongoing (i.e., not terminated, withdrawn, suspended, or completed) clinical trials that have been launched worldwide with the aim of testing the safety and antineoplastic activity of ATR or CHK1 inhibitors in cancer patients as a single agent (**Table 3**, http://www.clinicaltrials.gov/). The clinical profile of LY2606368 is being investigated in subjects with advanced solid tumors (NCT01115790) and breast or ovarian cancers (NCT02203513), whereas the ATR inhibitor AZD6738 is being employed in patients with advanced solid tumors (NCT02223923), alone or together with radiotherapy (see below). In addition, the pharmacokinetics and pharmacodynamics of the CHK1 inhibitor GDC-0575 are being assessed in individuals with refractory solid tumors or lymphomas (NCT01564251). Finally, the clinical study NCT00234481 (evaluating the safety and efficacy of XL-844 in subjects with lymphocytic lymphoma) has been terminated due to slow enrollment, while, to the best of our knowledge, the results of NCT01955668 (assessing the clinical profile of AZD6738 in patients with hematologic neoplasms) have not yet been released (http://www.clinicaltrials.gov).

Inactivation of CHK1 has also been evaluated as a means to boost the therapeutic potential of other classes of chemotherapeutics in several studies (**Table 2**): (1) The safety and tolerability of the combination of CHK1 inhibitors (including UCN-01 and CBP501) and DNA damaging agents (including cisplatin and carboplatin, a platinum derivative used for the treatment of solid tumors, including ovarian carcinoma)[303-305] have been demonstrated in some Phase I studies.[295,306-308] In contrast to these observations, dose-limiting toxicities were reported by Lara and colleagues for the combination of cisplatin and prolonged infusion of UCN-01.[295,306-308] Further clinical trials employing specific inhibitors of CHK1 are required to uncover the true potential of these CHK1 inhibitor-based antineoplastic regimens. (2) Preliminary evidence reported acceptable toxicity and partial efficacy for the combination of UCN-01 and topoisomerase inhibitors.[309,310] Nonetheless, UCN-01 combined with irinotecan or topotecan did not display significant antitumor activity either in a Phase I clinical study in patients with solid tumors[311] or in 2 Phase II trials in individuals with advanced recurrent ovarian cancer[312] or TNBC.[313] In contrast with this observation, in a Phase I dose-escalation study of the combination AZD7762 plus irinotecan in subjects with advanced solid tumors, one patient with metastatic small-cell cancer bearing a hypomorphic mutation in RAD50 (and consequent attenuation of the ATM signaling) displayed a complete and durable response.[314,315] (3) The effect of CHK1 inhibitors in potentiating antimetabolite activity has not been fully proven. In Phase I dose-escalation studies performed in patients with advanced solid tumors, the combinations of LY2603618 with pemetrexed (an inhibitor of the enzyme thymidylate synthase that is approved by the FDA for the treatment of various solid malignancies including malignant pleural mesothelioma)[316] and MK-8776 with gemcitabine showed acceptable safety and pharmacokinetic profiles with adverse effects commonly associated with the antimetabolites with which the CHK1 inhibitors are combined.[298,317] In contrast, AZD7762 combined with gemcitabine caused multiple adverse effects, including cardiac toxicity, fatigue, neutropenia/leukopenia, bradycardia, hypertension, and/or rash.[299,318] Early evidence of clinical efficacy was observed in 2 of these 4 studies.[298,299] In line with this observation, complete remission was observed in 8 of 24 (33%) patients with relapsed and refractory acute leukemias upon treatment with SCH900776 (also known as MK-8776) and cytarabine.[319]

Nevertheless, no objective responses were found for the combinations of UCN-01 with fludarabine (a nucleotide antimetabolite analog currently employed in chronic lymphocytic leukemia patients)[320,321] in relapsed lymphomas[322] and for AZD7762 plus gemcitabine, UCN-01 plus fluorouracil (a nucleoside analog currently used for the adjuvant and palliative treatment of patients with a variety of solid malignancies),[323,324] or LY2603618 plus pemetrexed plus cisplatin in patients with advanced solid tumors.[325.326] Moreover, of the 35 patients enrolled in an interventional study testing the therapeutic potential of the CHK1/2 inhibitor PF-00477736 combined with gemcitabine, only 4 reported an objective response (NCT00437203) (http://www.clinicaltrials.gov). This latter study was terminated prematurely for business reasons. Also, CBP501 failed to improve the efficacy of pemetrexed or cisplatin in a randomized Phase II trial performed in patients with advanced malignant pleural mesothelioma.[327]

Finally, limited antineoplastic responses were observed for the combination of CHK1 inhibitors (LY2603618 or UCN-01) and (1) the cytochrome P450 isoform 2D6 (CYP2D6) inhibitor desipramine (a compound prescribed for the treatment of depression) in patients with advanced solid tumors,[328] (2) the AKT inhibitor perifosine[329] in individuals with hematologic neoplasms,[330] and (3) the synthetic glucocorticoid prednisone (an agent licensed for use in cancer patients)[331] in subjects with advanced solid tumors and lymphomas.[332]

According to official sources (http://www.clinicaltrials.gov), 9 ongoing clinical trials involving inhibitors of the ATR-CHK1 cascade together with conventional radio- or chemotherapy have been launched worldwide (**Table 3**): (1) Two pharmacological inhibitors of ATR—VE-822 (also known as VX-970) and AZD6738—are being employed in individuals with advanced solid tumors, the former in combination with cisplatin, etoposide, and gemcitabine (NCT02157792) and the latter alone (see above) or combined with radiotherapy (NCT02223923) or carboplatin/olaparib (NCT02264678). (2) Among the specific pharmacological inhibitors of CHK1, (i) GDC-0575 is being tested alone (see above) or in combination with gemcitabine in patients with refractory solid tumors or lymphomas (NCT01564251), (ii) LY2603618 is being combined with gemcitabine (NCT01341457) to treat individuals with advanced solid tumors, and (iii) MK-8776 is being administered together with cytarabine in patients with relapsed acute myeloid leukemia (NCT01870596). (3) The CHK1/2 inhibitor LY2606368 is being used together with cetuximab (a FDA-approved epidermal growth factor inhibitor currently employed for the treatment of human neoplasms, including colorectal cancer)[333] or cisplatin in a clinical study performed in subjects with advanced solid tumors (NCT02124148). The clinical trial NCT00045513, investigating the therapeutic profile of UCN-01 plus fludarabine in individuals with hematologic neoplasms is listed as "unknown", whereas NCT01521299, assessing the therapeutic profile of MK-8776 together with hydroxyurea in patients with advanced solid tumors was withdrawn prior to enrollment due to the insufficient population of eligible patients (http://www.clinicaltrials.gov). To the best of our knowledge, the clinical study NCT00475917 (assessing the therapeutic profile of XL-844 combined with gemcitabine in patients with advanced tumors) has been terminated, whereas the results of NCT00988858 (evaluating the clinical profile of LY2603618 together with pemetrexed in patients with non-small cell lung cancers), NCT00779584 (determining the safety and efficacy of MK8776 alone or combined with gemcitabine in patients with advanced tumors), NCT00839332 (assessing the clinical profile of LY2603618 in combination with gemcitabine in patients with pancreatic cancer), and NCT01359696 (evaluating the therapeutic profile of GDC-0425 together with gemcitabine in patients with advanced tumors) have not yet been released (http://www.clinicaltrials.gov).

Concluding Remarks

A large body of preclinical studies supports the use of inhibitors of DNA damage signaling pathways for cancer therapy, either as single agents, for example in cancer cells with high levels of endogenous DNA damage or deficiencies in other DDR players including p53 (for those affecting the ATR-CHK1 pathway), or in combination with radio- and/or chemotherapy (for those affecting the ATM-CHK2 or the ATRCHK1 cascade).[65,95,176-178,212-214,334] Nevertheless, compelling clinical evidence is still lacking. Moreover, the oncosuppressive role of the ATM–CHK2 signal and, at least in specific genetic background of the ATR-CHK1 pathway, may cast doubts over further development of ATM- or CHK2-based antineoplastic regimens.

The results of some preliminary clinical studies employing CHK1 inhibitors are not encouraging, probably due to inadequate specificity and/or poor pharmacokinetics of the inhibitors used to date (e.g., UCN-01 or AZD7762).[335,336] Early evidence of clinical efficacy and safety of chemotherapy regimens based on more specific CHK1 inhibitors[298] seems to support this hypothesis, although further confirmations are awaited. An additional limitation to the development of CHK1 inhibitor-based chemotherapies is the absence of reliable markers predicting tumor response, even though some recent observations show hypersensitivity to CHK1 inhibitors of tumors with mutations in components of the MRN complex.[214,315,337] In addition, further knowledge of the biological functions of CHK1 and other DDR players is still needed. In this context, the existence of significant crosstalk between the ATM–CHK2 and ATR–CHK1 pathways is becoming increasingly evident, and moreover at multiple levels, encompassing shared components, substrate overlap, and functional redundancy.[4,16,338,339] Moreover, in addition to operating in DDR these kinases are involved in multiple signaling networks. Thus, ATM is a key player in cell metabolism,

oxidative stress, chromatin remodeling, response to uncapped telomeres and spindle assembly checkpoint (reviewed in refs.[17,28]), CHK2 plays a role in mitosis and is required for the maintenance of chromosomal stability,[36,104,340] and ATR and CHK1 exert multiple functions in S phase and mitosis, also under unperturbed conditions.[15,26,266,341,342] These additional roles may affect cancer development/progression and the response to cytotoxic agents and should be considered in the context of cancer therapy.

Current clinical trials involve only inhibitors of ATR and CHK1. A significant improvement in our knowledge of DDR may increase the efficacy of these ATR- or CHK1-based regimens, limiting the undesirable effects on normal cells/tissues and allowing for patient stratification, while at the same time shedding light on the true potential of ATR–CHK1 inhibition for cancer therapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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