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REVIEW ARTICLE

The Development of ATM Inhibitors in Cancer Therapy

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Abstract
The ataxia-telangiectasia mutated (ATM) protein kinase plays a critical role in activating the cellular response to DNA double-strand breaks and promoting homology-directed repair. ATM is frequently mutated in cancer, contributing to an accumulation of DNA damage that drives genomic instability. To exploit cancer cells' inherent vulnerability to DNA damage, various small molecule inhibitors have been developed that target ATM. ATM inhibitors have shown great versatility in preclinical studies and increasing use in the clinic. Here, we review the development of ATM inhibitors and their role in cancer therapy. We describe their limitations and the advances that have led to increases in both the number and diversity of active clinical trials targeting ATM. We also discuss ATM's role in personalized medicine and the current challenges to more widespread use of ATM inhibitors in the clinic.

Key Points

Ongoing efforts seek to develop effective ATM inhibitors for use in cancer therapy.

Recent improvements have led to a steady increase in clinical trials utilizing ATM inhibitors.

The versatility of ATM inhibitors holds promise for overcoming current challenges in personalized medicine.

1 Ataxia Telangiectasia

Ataxia telangiectasia (A-T) is an autosomal recessive disease that was first described in 1958 [1]. Although clinical manifestation of A-T varies between patients, certain hallmarks are universal, including ataxia (impaired coordination, balance, and speech), telangiectasia (small, widened blood vessels on the skin), chemical and radiation sensitivity, immunodeficiency, neurodegeneration, and increased cancer risk. A-T is rare, affecting between 1 in 40,000 to 100,000 people worldwide. Symptoms usually manifest in early childhood and increase in severity over time. Mortality typically occurs in the mid-20s owing to chronic pulmonary disease or associated cancers [5]. Radiation sensitivity in A-T patients was first reported in a 1968 case study, in which a young patient with lymphoma quickly deteriorated following radiation therapy [6]. A-T patient cells were subsequently shown to have defects in cell cycle checkpoints, which prevented cells from blocking cell cycle progression after exposure to ionizing radiation (IR) [7]. When cells with DNA damage progress through the cell cycle, it leads to increased mutations and genomic instability, which can drive cancer development [8]. Cancer is a major hallmark for patients with A-T, and patients with A-T carrier status were also shown to have an elevated cancer risk [9].

2 ATM and DNA Damage Signaling

In 1995, a single gene that causes A-T was identified and named *ataxia telangiectasia, mutated* (*ATM*) [10]. The *ATM* gene spans a 150-kb region of chromosome 11 and encodes a 13-kb transcript that produces a ~350-kDa protein (Fig. 1) [11]. Ataxia-telangiectasia mutated (ATM) is a member of the phosphatidylinositol 3-kinase-like (PI3K) family of serine/threonine protein kinases, and has been found to phosphorylate the SQ/TQ sites of over 700 target substrates [12]. ATM functions as both an initiator for DNA repair signaling

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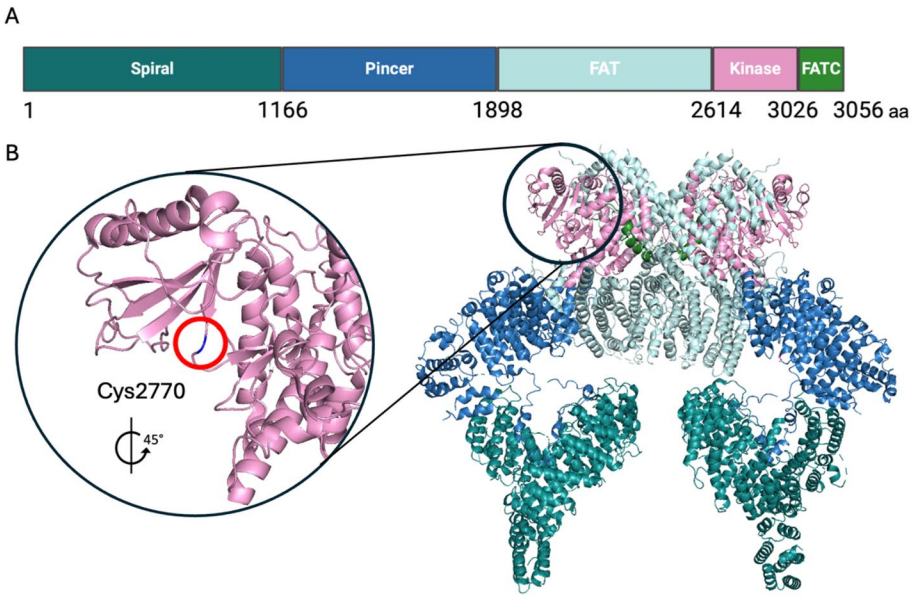


Fig. 1 ATM domains and protein structure. **A** A schematic of the ATM protein and its major domains [2]. **B** A ribbon diagram of the ATM dimer (PDB: 6K9L). Individual domains are color-coded and the "kinase hinge" Cys2770 [3] is highlighted by the red circle. Protein diagrams were generated with PyMOL [4]

and a regulator of cell cycle checkpoints, halting cell cycle progression by phosphorylating proteins like p53, Chk1/2, NBS1, and RPA. ATM also plays a critical role in telomere maintenance and apoptosis [13]. Other members of the PI3K family are also important regulators of the DNA damage response: ATM and Rad3-related (ATR) initiates the replication stress response, and DNA-dependent protein kinase (DNA-PK) promotes repair by nonhomologous end joining (Fig. 2) [14].

ATM is activated by the formation of DNA double-strand breaks (DSBs) [15, 16]. In the absence of damage, ATM is present as an inactive dimer. When a DSB is formed, the exposed DNA ends are bound by the MRN complex (MRE11, RAD50, NBS1). DSB formation also stimulates the acetyltransferase Tip60, which acetylates the inactive dimer to help promote ATM activation [17]. NBS1 recruits ATM to the DSB through an interaction with an FxF/Y sequence motif, which is thought to induce a conformational change in the dimer that primes it for activation [2]. Upon MRN interaction, ATM is autophosphorylated at Ser1981 [18–20]. Together, these events lead to the monomerization and activation of ATM. However, the precise role of ATM autophosphorylation in its activation remains unclear, given that ATM activation was also observed when phosphorylation was blocked by mutating Ser1981 [21]. Once activated, ATM phosphorylation initiates a signaling cascade involving proteins like BRCA1, CtIP, and γH2AX that promote DSB repair via homologous recombination [12].

ATM is both a nuclear and cytoplasmic protein (Fig. 3) [22]. While it is best known for its nuclear functions, additional activities in the cytoplasm have been described. Cytoplasmic ATM is known to regulate AKT (Protein Kinase B) activity in response to insulin [23, 24]. Indeed, insulin-resistant diabetes is a rarer and later-presenting symptom of A-T, and some A-T patients without diabetes may exhibit abnormal blood sugar regulation [5]. Roughly 18% of adult A-T patients develop type 2 diabetes [25]. Loss of ATM leads to mitochondrial dysfunction, increased production of

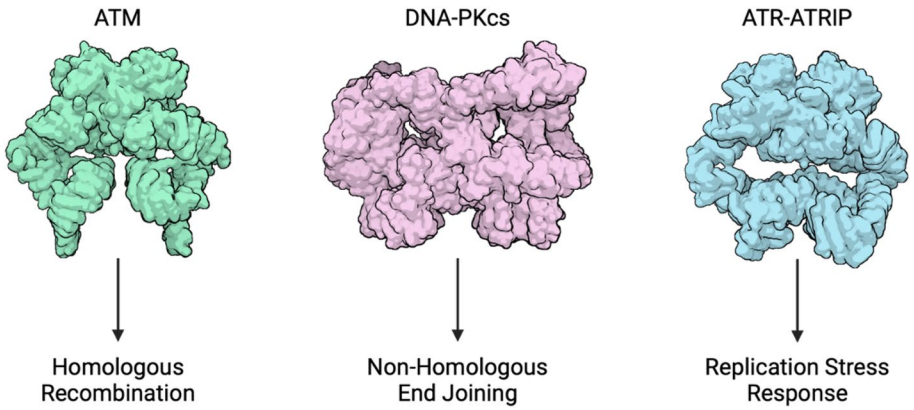


Fig. 2 Major damage response kinases in the PI3K family. ATM (protein data bank, PDB: 6K9L) promotes repair by homologous recombination, DNA-PKcs (PDB: 8EZ9) promotes repair by non-homologous end joining, and ATR (with obligate binding partner ATRIP) (PDB: 5YZ0) activates the replication stress response. Images were created with BioRender (BioRender.com/u42n261)

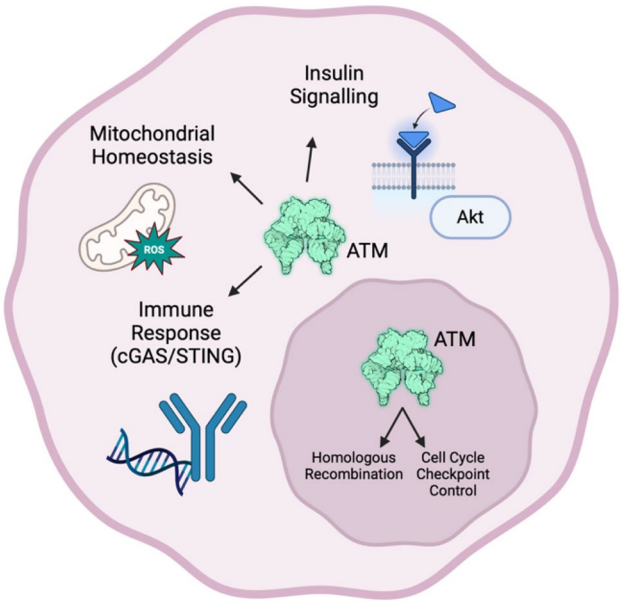


Fig. 3 Cytoplasmic and nuclear functions of ATM. Nuclear ATM is known to initiate homologous recombination and regulate cell cycle checkpoints in response to DNA DSBs. Cytoplasmic ATM has been found to play a role in insulin signaling, mitochondrial homeostasis, and the cGAS/STING pathway. Image was created with BioRender (BioRender.com/q01t906)

reactive oxygen species, and defective mitophagy in T cells [26]. ATM dysfunction may also deregulate mitochondrial homeostasis by reducing deoxyribonucleoside triphosphate synthesis [27]. ATM's detection of cytoplasmic DNA in the cGAS/STING pathway marks it as an important component of the innate immune system [27]. ATM's cytoplasmic functions are an area of research that continues to be explored in the context of both A-T treatment and cancer therapy.

3 ATM Alterations and Cancer

Patients diagnosed with hereditary homozygous or pathogenic compound heterozygous *ATM* mutations develop A-T [5]. Roughly 25% of A-T patients develop cancer, and these cancers are most commonly hematological, including acute leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma, and T-cell lymphoblastic leukemia [28, 29]. The risk of developing malignancies increases dramatically with age [28, 30]. Although carriers of pathogenic mutant *ATM* alleles do not develop A-T, they have an increased risk of developing several cancers, including breast, pancreatic, gastric, and prostate [31]. Females carrying a single pathogenic *ATM* mutation have a fivefold to eightfold greater risk of breast cancer as compared with the general population [32], and it is estimated that 8.8% of breast cancer patients are A-T heterozygotes [33]. In developing cancers, *ATM* mutation is thought to promote tumorigenesis owing to an accumulation of DNA damage that increases genomic instability [34]. However, the molecular route to tumorigenesis in *ATM* mutant germline carriers remains an unanswered question.

Within the ClinVar database, which tracks human variants and associated diseases, reports of genetic alterations in *ATM* have more than doubled in the last 5 years owing to massive sequencing expansion and the incorporation of multigene panels in clinical settings. ClinVar contains over 17,000 reports of both germline and somatic *ATM* alterations, with more than 4000 pathogenic variants and close to 8000 variants of uncertain significance (VUS) (Fig. 4). The majority of pathogenic *ATM* variants are frameshift and nonsense mutations (51.7% and 27.9%, respectively) resulting in either a truncated protein or complete lack of ATM expression. A total of 97% of *ATM* VUS are missense mutations.

Somatic *ATM* alterations are found in 6% of all samples from The Cancer Genome Atlas (TCGA) PanCancer Atlas [35–37]. TCGA PanCancer Atlas studies show that *ATM* is altered most frequently in uterine cancers (18.6%), bladder cancers (14.11%), and colorectal cancers (12.5%) (Fig. 5A). These reported *ATM* mutations are not localized to a specific domain or region and are evenly distributed across the gene (Fig. 5B). However, multiple residues were found to have recurring mutations from population studies listed in the Cancer HotSpots database, including: R250 and R337 in the N-terminus, R1466 in the pincer domain, and R2832, N2875, I2888, L2890, and R3008 in the kinase domain [38, 39]. Understanding the origin and biological impact of these hotspots is necessary for guiding future research.

4 ATM as an Anticancer Target

As a critical regulator of DNA repair and cell cycle progression, ATM is an attractive target for anticancer therapy. Owing to its role as an activator of the DSB repair pathway, targeting ATM enhances the effects chemotherapeutics that induce DSBs [12]. As a result, ATM inhibitors have been explored for use in various combinatorial treatments. ATM knockdown experiments have been shown to exhibit promising anticancer activity [40, 41], further supporting the development of ATM inhibitors for the clinic. ATM knockdown experiments in glioma stem cells showed increased apoptosis, reduced cell proliferation, and an increase in G2 arrest and DNA damage following irradiation [41]. ATM inhibitors paired with IR [42–45], topoisomerase inhibitors [46–48], and other chemotherapies like cisplatin [47, 49] have shown similarly promising results. Studies have also explored targeting other key repair pathways along with ATM inhibition as a means to increase radiosensitivity and prevent drug resistance [50]. Poly-ADP ribose polymerase (PARP) is an immediate/early responder to DNA single-strand breaks,

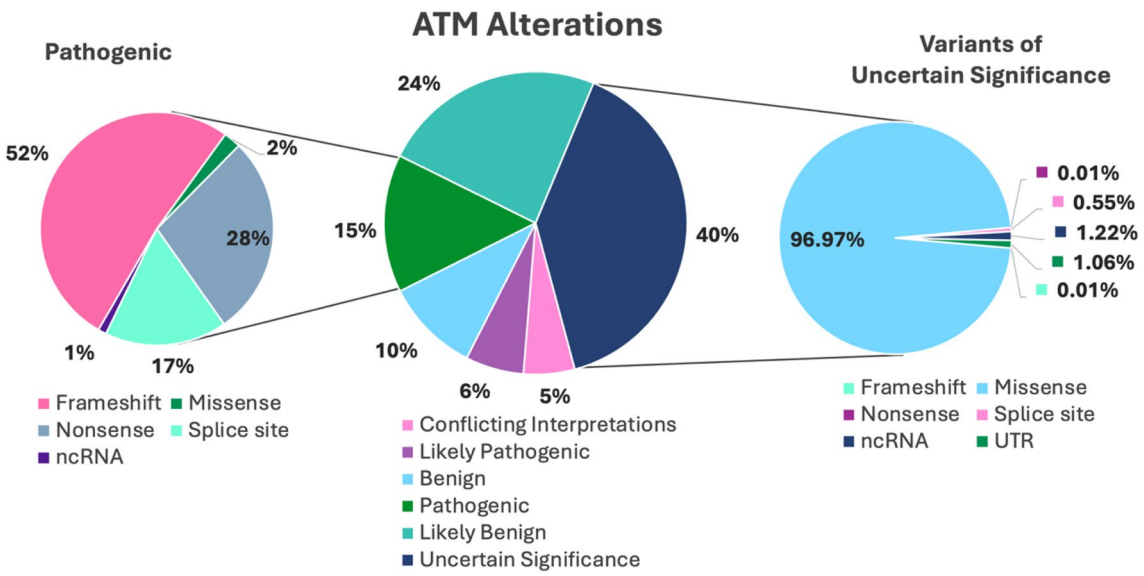


Fig. 4 The clinical significance of *ATM* alterations. The center pie chart shows total *ATM* alterations on the basis of their clinical significance. The type of genetic alterations found in *ATM* pathogenic or VUS subsets are shown to the left and right, respectively. (https://www.ncbi.nlm.nih.gov/clinvar/ accessed October 2024). *UTR* untranslated region, *ncRNA* noncoding RNAs

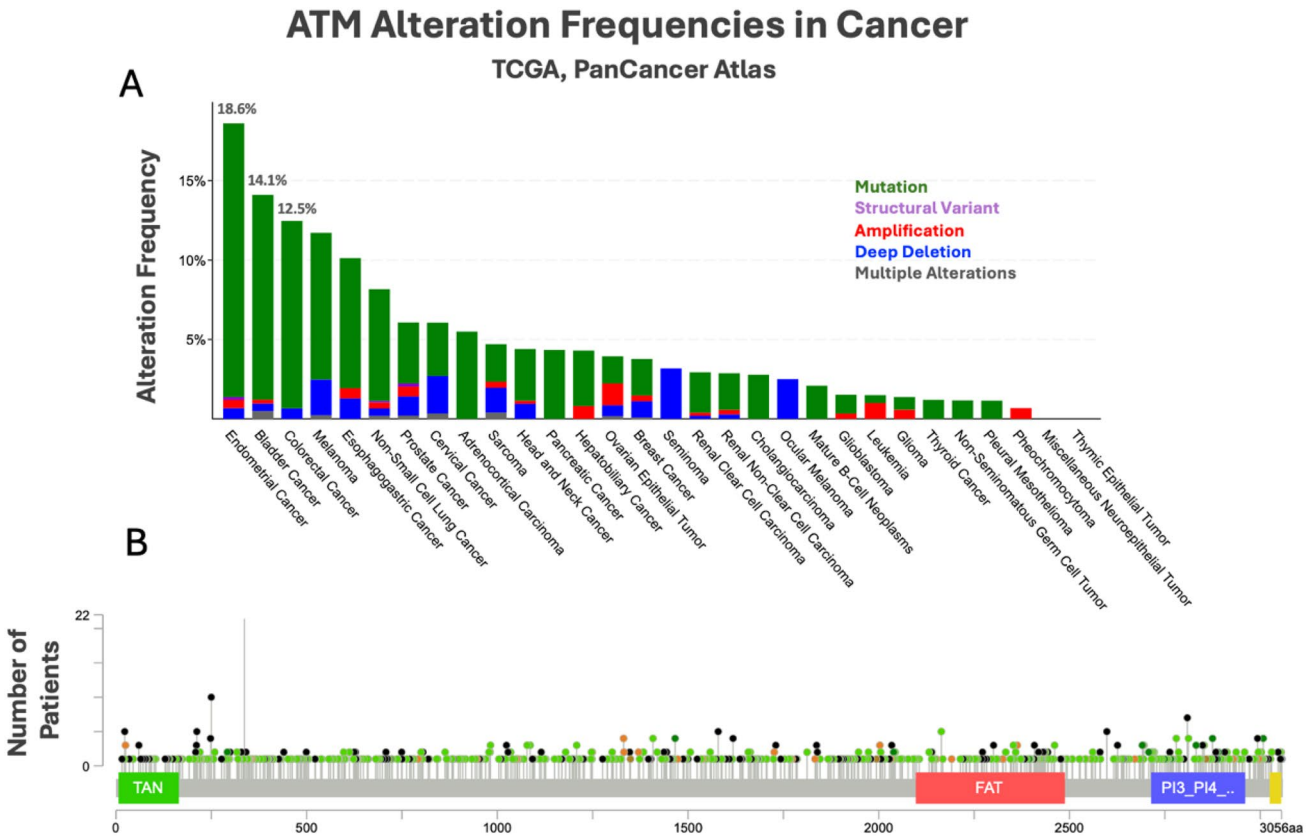


Fig. 5 *ATM* alteration frequencies and distribution. cBioPortal for Cancer Genomics display of **A** the percentage of *ATM* genetic alterations and **B** the spectrum of *ATM* mutations in the different protein domains within TCGA PanCancer Atlas, representing 32 combined studies with 10,953 samples (https://bit.ly/414Md1x)

which can then be converted to DSBs [15, 51, 52]. Seven PARP inhibitors have been approved for clinical use by the US Food and Drug Administration (FDA), and more are being explored in clinical trials [53]. The ATR kinase has also been targeted alongside ATM [14, 54]. Inhibiting ATR disables the replication stress response, leading to severe genomic instability that can lead to DSBs [55, 56]. A vast number of ATR inhibitors have progressed to clinical trials, both as monotherapies and radio/chemosensitizers [57].

ATM's role in activating the response to DSBs also makes it an important part of the cGAS-STING pathway. The cGAS-STING pathway is responsible for mounting an immune response to cytosolic double-stranded DNA, often in response to viral infections [58]. In addition, while the exact mechanism is unclear, it has been shown that ATM's inhibition causes mitochondrial DNA to leak into the cytoplasm [27, 59]. As a result, ATM inhibition can lead to "immune-inflamed" tumors that are more easily treated using immune checkpoint therapies. Indeed, ATM knockdowns have been used to validate this strategy both in vitro and in vivo [60], highlighting ATM inhibition as an attractive target to induce a robust, multifaceted anticancer response.

Interestingly, loss or inhibition of ATM's kinase activity was found to be more severe than the complete loss of ATM expression, suggesting a dominant negative effect [61]. Cells expressing only kinase-dead ATM were found to have increased chromosomal breaks and genomic instability, and they had reduced survival compared with complete loss of ATM. However, there was no change in variable–diversity–joining (V(D)J) recombination and class-switch recombination between kinase-dead and ATM-null lymphocytes, suggesting that the defects were linked to ATM's role in DNA repair. In addition, ATM-null mice were found to develop similarly to A-T patients, while kinase-dead ATM mice were embryonic lethal [62–64]. Similar findings were also seen with ATM inhibitors that target its kinase activity, showing that the effects associated with kinase-dead ATM can be induced transiently in the context of treatment [65, 66].

5 ATM Inhibitors

With increasing efforts to develop more personalized anticancer therapies, the interest in developing effective inhibitors of ATM has followed suit. Since the first ATM inhibitor was described in 2004, at least 12 more notable compounds have been developed, with 8 showing enough promise to enter clinical trials. To date, 14 clinical trials have been approved utilizing ATM inhibitors. In total, four of these trials have been completed, and ten remain ongoing (Fig. 6 and Table 1). Below, we review the development of clinically relevant ATM inhibitors based on when each was first reported. Collectively, a wealth of in vitro and in vivo data support pharmacological inhibition of ATM as an effective strategy for improving anticancer therapies and patient outcome.

5.1 KU-55933 (2004)

KU-55933 was developed by KuDOS Pharmaceuticals (later acquired by AstraZeneca) as the first ATM-specific inhibitor, which is selective for ATM at 10 µmol/L [42]. It was identified by screening molecules designed around LY294002, a broad PIKK family kinase inhibitor. KU-55933 acts as an ATP-competitive inhibitor [42]. ATM's PIKK regulatory domain (PRD) blocks its active site as a pseudo-substrate, acting as a normal mechanism of autoinhibition. When KU-55933 binds to the hinge region (Fig. 1B) at the active

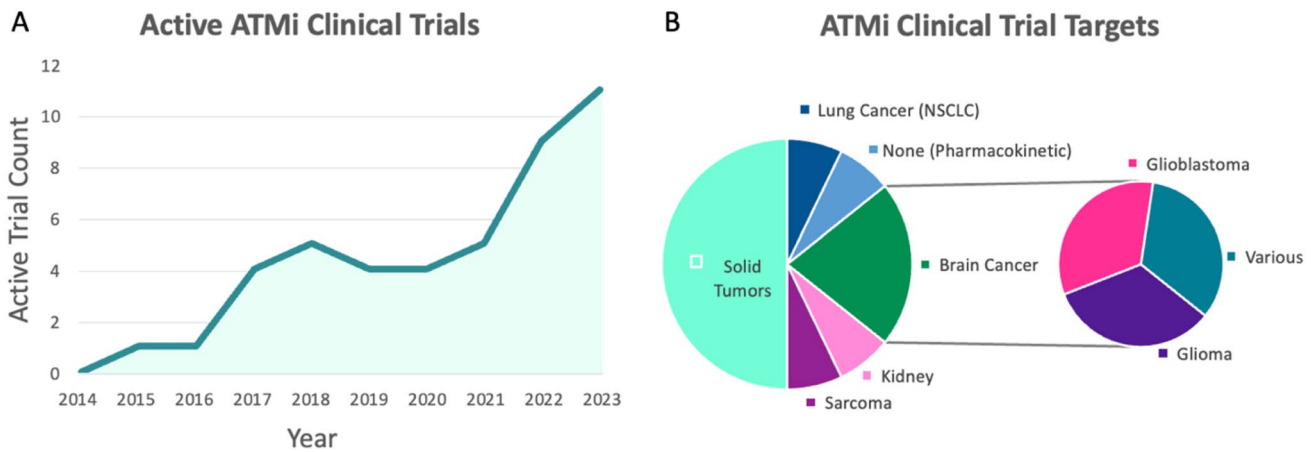
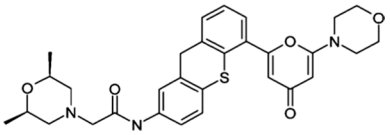
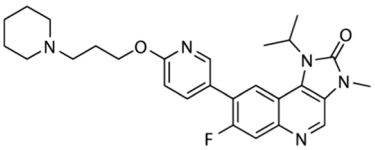
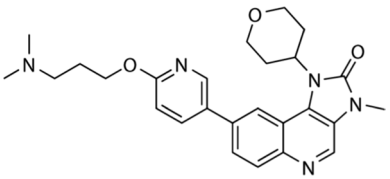
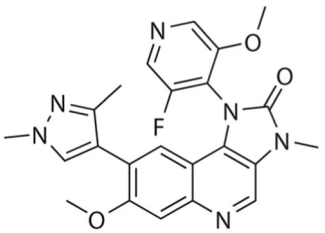
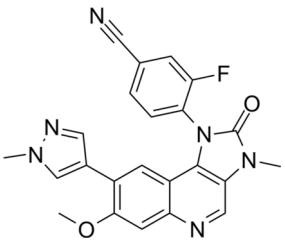
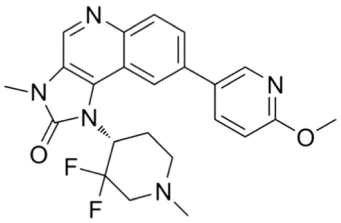


Fig. 6 The use of ATM inhibitors (ATMi) in clinical trials. **A** A graph showing the number of active clinical trials utilizing ATM inhibitors over time. **B** The relative number of clinical trials utilizing ATMi for different cancer types. (https://clinicaltrials.gov/ accessed October 2024)

Table 1 Clinical Trial Summary and Outcomes for ATM Inhibitors

ATMi	Structure	Clinical trial summary and outcomes
KU-60019		1. 2017–ongoing. Kidney cancer; combination therapy with CK2 inhibitors (NCT03571438) • Results forthcoming
AZD1390		1. 2017–2018. Pharmacokinetic study (NCT03215381) • Effective blood–brain barrier penetration 2. 2022–ongoing. Glioma; combination therapy with radiotherapy (NCT05182905) • Results forthcoming 3. 2022–ongoing. Sarcoma—soft tissue; combination therapy with radiotherapy (NCT05116254) • Results forthcoming 4. 2018–ongoing. Glioblastoma multiforme; combination therapy with radiotherapy (NCT03423628) • Results forthcoming 5. 2023–ongoing. Metastatic solid tumors; combination therapy with stereotactic body radiotherapy (NCT05678010) • Results forthcoming 6. 2021–ongoing. Non-small cell lung cancer; combination therapy with radiotherapy (NCT04550104) • Results forthcoming
AZD0156		1. 2015–2022. Solid tumors; monotherapy and combination with olaparib, irinotecan, fluorouracil, and folinic acid (NCT02588105) • Combination with olaparib resulted in significant hematological toxicities; ~40% of patients reported treatment-related adverse events (TRAEs) • No other results available
M4076		1. 2021–2023. Solid tumors; monotherapy (NCT04882917) • No TRAEs observed at the lowest dose; effective ATM inhibition at all doses • Promising pharmacology 2. 2022–ongoing. Solid tumors; combination therapy with M1774 and avelumab (NCT05396833) • Results forthcoming
M3541		1. 2017–2020. Solid tumors; combination therapy with radiotherapy (NCT03225105) • The observation of significant TRAEs, lack of dose response, and absorption cap led to study termination
WSD-0628		1. 2023–ongoing. Glioblastoma; combination therapy with radiotherapy (NCT05917145) • Results forthcoming
ZN-B-2262	Undisclosed	1. 2022–ongoing. Solid tumors; monotherapy and combination with radiotherapy (CTR20222750) • Results forthcoming
SYH2051	Undisclosed	1. 2023–ongoing. Solid tumors; monotherapy and combination with radiotherapy (NCT06011291) • Results forthcoming

site, it prevents mobilization of the PRD and locks it into place [67].

On its own, treatment with KU-55933 was not cytotoxic [42]. However, when cells were treated with KU-55933 in combination with IR, camptothecin, etoposide, or doxorubicin, the cells arrested in the G2/M phase. The phosphorylation of p53, H2AX, CHK1, NBS1, and SMC1 was blocked, and cell survival was significantly reduced [42]. These findings established KU-55933 as an effective chemo- and radio-sensitizer in vitro. KU-55933 has been shown to have other anticancer attributes. In combination with Rapamycin, KU-55933 was shown to increase apoptosis in the breast cancer cell line MDA-MB-453 [68]. Further studies showed that KU-55933 inhibited GLUT1-faciliated uptake of glucose in cancer cells with increased AKT activation [69]. This led to increased apoptosis that rivaled the level seen in cells with total glucose starvation.

KU-55933 was also found to have neuroprotective effects in neuroblastoma cells treated with hydrogen peroxide (H_2O_2) or doxorubicin, though different mechanisms are likely involved [70]. In the presence of H_2O_2, KU-55933 blocked ATM phosphorylation but did not prevent the phosphorylation of downstream targets. As a result, the influx of calpain and cathepsin D (proteases activated in response to H_2O_2) was only moderately reduced compared with H_2O_2 alone. In the presence of doxorubicin, KU-55933 blocked both ATM activation and the activation of downstream targets, including caspase-3 [70].

Collectively, the effects of KU-55933 demonstrated its potential for broad use with consideration of cell-type specific effects. However, the pharmacological properties of KU-55933 prevented entry into clinical trials owing to a high level of hydrophobicity and high toxicity to healthy tissue. Given KU-55933's specificity and effectiveness in vitro, ongoing studies continue to explore its use with more efficient delivery methods. For example, poly(lactic-co-glycolic acid) (PLGA) nanoparticle delivery has shown promising results in vivo, with selective KU-55933 accumulation in tumors, a decrease in general toxicity, and more potent ATM inhibition [71].

5.2 CP466722 (2008)

CP466722 was identified as an ATM inhibitor after a comprehensive library screen of over 1500 potential compounds on the basis of known kinase inhibitor structures [44]. CP466722 was found to have strong specificity for ATM compared with ATR and DNA-PKcs and had no cytotoxic effects on fibroblasts. In HeLa cells treated with IR, ATM activation was completely blocked by CP466722 at 6 μmol/L [44]. CP466722 effectively induced cell cycle arrest in G2/M phase, consistent with the checkpoint defects found in irradiated A-T cells. ATM inhibition was shown to last for up to 8 h, and was fully restored by removal of the drug in vitro [44]. Although CP466722 was found to be an effective ATM inhibitor, studies have shown that is has low specificity for ATM and can also target 25 other cellular kinases [72, 73]. A Kinobeads assay, which utilized Sepharose beads conjugated to a kinase inhibitor of interest to pull down and identify binding targets [72], found CP466722 to be a more effective inhibitor of ALK2, a transmembrane receptor involved in osteogenic signaling [73]. Although CP466722's poor specificity has limited its potential for in vivo translation, it has been utilized to develop several high throughput screening assays for identifying additional ATM inhibitors [74, 75].

5.3 KU-60019 (2009)

KU-60019 was designed as a modified version of KU-55933 and was optimized for increased selectivity and water solubility. KU-60019 was found to sensitize cells treated with IR at only 3 μmol/L. KU-60019 was shown to inhibit both glioma and fibroblast mobility and invasion by suppressing AKT activation, even with insulin stimulation [43]. Preclinical data showed no toxicity in vitro and no in vivo markers of DNA damage when KU-60019 was injected intracranially. KU-60019 also showed effective radiosensitization of low-p53 expressing glioblastoma multiforme and high phosphatidylinositol 3-kinase (PI3K) expression [76]. This showed KU-60019's preclinical promise in sensitizing treatment-resistant cancers.

KU-60019 was found to induce synthetic lethality in the PTEN-deficient breast cancer cell line MDA-MB-468 [49]. When KU-60019 treatment was combined with cisplatin, both wild-type PTEN and PTEN-deficient breast cancer cell lines were sensitized. PTEN-deficient cell lines showed increased accumulation of γH2AX foci, reduced accumulation of RAD51 foci, and increased cell death compared with wild-type PTEN cells after combinational treatment with cisplatin. KU-60019 was also shown to induce synthetic lethality with CHK1 inhibition in colorectal cancer cells. Combinational treatment with CHK1 inhibitor LY2606368 produced γH2AX foci in 53.4% of colorectal cancer cells compared with only 6% in normal fibroblasts [77]. These results highlight the potential for ATM inhibition to improve therapeutic response on the basis of an individual patient's tumor profile.

ATM inhibitors have also shown effectiveness for sensitizing certain brain cancers, especially gliomas, which frequently become unresponsive after traditional treatments that include surgery followed by temozolomide and radiation. KU-60019 was found to effectively radiosensitize these resistant cancers in mice, especially those with mutant p53 [78]. KU-60019 was then evaluated for its pharmacokinetic properties in the brain. Intracranial injection showed rapid diffusion throughout the brain, excretion

within 24 h, and was not detected in other organs. There was also no increased damage of healthy tissue when combined with radiotherapy [76]. However, intraperitoneal injection showed prompt excretion and no accumulation in the brain, indicating a failure to pass the blood–brain barrier.

Owing to its improved pharmacological properties, KU-60019 was approved for clinical trial (NCT03571438), which is currently active and recruiting participants. It is currently undergoing preclinical validation for treatment of kidney cancer in combination with CK2 inhibitors. Samples from renal cancer patients will be excised and then treated in culture. Cell death will be compared with established kidney cancer treatments, including sunitinib, pazopanib, and temsirolimus. Results will then be used to establish new standards of care for kidney cancer.

5.4 KU-59403 (2013)

KU-59403 was developed on the basis of the structure of KU-55933 with the goal of improving solubility [46]. KU-59403 is more specific and potent than its predecessor, with ATM inhibition at 3 µmol/L. It was found to have low cytotoxicity in the LoVo and SW60 colorectal cancer cell lines, but significantly increased cytotoxicity when combined with topoisomerase inhibitors [46]. The pharmacokinetics of KU-59403 were also improved compared with KU-55933, with chemosensitization maintained in tumor xenografts for roughly 4 h, while KU-55933 levels were undetectable at this time point [46].

P53 status is a useful marker that can be used to predict response to clinical chemotherapy [79]. In p53-deficient cells, ATM suppression via shRNA knockdown or KU-55933 treatment was found to cause major sensitization. However, in p53-proficient cells, ATM suppression resulted in chemoprotection [80]. These results indicate that a patient's p53 status is a useful determinant of therapeutic potential for ATM inhibitors. However, another study with KU-59403 found that p53 status was irrelevant when comparing p53 functional and dysfunctional lines of both HCT116 and U2OS [46]. Although the reason for this discrepancy was not identified, it highlights the potential for additional differences in expression or mutation profiles to affect the efficacy of ATM inhibitors during treatment [54]. KU-59403 has not been pursued further in the clinic.

5.5 AZ31 (2016)

Despite the development of multiple ATM inhibitors with promising cellular activity, their clinical efficacy remained limited. In efforts to identify new inhibitors, a library of putative kinase inhibitors was screened, and a series of 3-quinoline carboxamides was found to have activity against ATM [81]. Of those identified, AstraZeneca's AZ31 (compound 72) was found to be the most promising. AZ31 is selective for ATM at 1 µmol/L with no alternate kinase inhibition above 30% in a panel of over 100 different kinases. AZ31 showed moderate bioavailability (31%), but had greatly improved solubility (590 µM) and lower clearance rates (50 mL/min/kg) compared with previous ATM inhibitors [45]. It operates according to an ATM-competitive mechanism, in similar fashion to prior inhibitors [82].

AZ31's improved pharmacological features allowed for in vivo experiments that were previously unavailable. Its potency and oral availability lent itself to evaluation as a glioblastoma radiosensitizer. AZ31's sibling AZ32, and AZD1390, another clinically relevant ATM inhibitor described below, were shown to effectively radiosensitize intracranially implanted p53 mutant glioblastomas through oral gavage [83]. In addition, treatment with both AZ31 and IR significantly increased the survival of the mice. This study showed that AZ31 was able to pass the blood–brain barrier and also supported synthetic lethality with p53 loss that was lacking with KU-59403. Indeed, later studies showed that AZ31's potency was tenfold stronger than KU-60019. However, its blood–brain barrier permeability was found to be limited [81].

AZ31 was evaluated for the treatment of multiple colorectal cancer cell lines in combination with irinotecan, a topoisomerase I inhibitor. The combined effect was found to limit proliferation in half of the cells tested, and half of the colorectal cancer patient-derived xenografts tested. The highest level of synergy, or enhanced combinatorial effect, was observed in cells that were shown to have irinotecan resistance. These results suggested that AZ31's clinical effectiveness would vary, and that identifying markers of resistance would be important for effective personalized treatments [48]. In mice treated with total-body irradiation, oral administration of AZ31 induced dramatic gastrointestinal crypt cell death. These findings indicated that AZ31 was not tumor-specific, but instead had whole-organism effects [84]. Additionally, a lower concentration (4.5 µmol/L) was found to inhibit the hERG ion channel, which is required for cardiomyocyte function [45].

The development of AZ31 marked an important step forward for the in vivo use of ATM inhibitors. Improved oral availability compared with its predecessors provided a significant step toward the development of an effective clinically translatable ATM inhibitor [50]. However, the findings of high off-target toxicity ended AZ31's journey towards use in the clinic.

5.6 AZ32 (2016)

AZ32 (compound 8) is another 3-quinoline carboxamide derivative that was developed alongside AZ31. AZ32 has seen limited in vitro use compared with other ATM

inhibitors. AZ32 was able to radiosensitize multiple glioma cell lines with mutated p53, compared with those expressing wild-type p53 [81]. However, similar sensitization was not observed in a $p53^{+/+}$ colon carcinoma cell line (HCT116), which showed increased sensitivity to AZ32 compared with their $p53^{-/-}$ counterpart. These findings further highlight the importance of identifying different resistance markers to inform clinical use of ATM inhibitors.

AZ32, like AZ31, was designed with blood–brain barrier permeability in mind. When AZ32 was combined with radiation, there was an exceptional response in vivo, with over half of mouse intracranially grown GL261 gliomas completely eliminated [81]. Overall survival was also increased for both primary and metastatic human glioma xenografts [81, 85]. Although AZ32's blood–brain barrier penetration and bioavailability showed promise for clinical translation, it was also found to have potent off-target effects. AZ32 was found to be a potent inhibitor of the breast cancer resistance protein BCRP/ABCG2 [86], an efflux transporter known to play a role in multidrug resistance [87]. AZ32 sensitized BCRP-overexpression colorectal cancer cells to a panel of chemotherapies known to be effluxed by BCRP [86]. With AZ32, these drugs were able to accumulate within the cell and induce cell death. It is predicted to bind within the transmembrane domain, preventing interaction with and efflux of other compounds. While this discovery could have important implications on future uses of AZ32, it has not been pursued as a clinical ATM inhibitor owing to its nonspecific effects.

5.7 AZD0156 (2018)

AstraZeneca's AZD0156 was the first ATM inhibitor developed with true clinical potential. AZD0156 is extremely selective for ATM, highly soluble, bioavailable, and showed low to moderate clearance from the bloodstream. It binds to ATM's kinase hinge (Fig. 1B) and blocks access to the ATP binding site. Simulation testing of the drug using physiologically based pharmacokinetic (PBPK) models indicated that low doses of AZD0156 maintain steady state human exposure for 24 h [3]. These simulations used existing physiological data to model tissue and organ blood flow to predict drug dispersion.

AZD0156 has performed well in vivo**,** demonstrating strong combinatorial antitumor effects with the PARP inhibitor olaparib and the topoisomerase I inhibitor irinotecan in patient-derived xenograft (PDX) models [88]. Additionally, AZD0156 has been tested across a panel of lung cancer cell lines carrying different p53 mutations. AZD0156 was shown to fully block ATM phosphorylation at 10 nmol/L across the entire panel. Significant radiosensitization was found at 3 nmol/L, with increased radiosensitization seen in p53-deficient lines. When compared with olaparib, ceralasertib, and adavosertib, which target other components of the DNA damage response, AZD0156 was found to be a more potent radiosensitizer [88]. AZD0156 was also found to induce cell death synergistically with radiation in four of five melanoma cell lines tested, which was not observed in similarly irradiated healthy fibroblast cells [89]. AZD0156 also sensitized cells to Olaparib, inducing persistent damage and DSBs [90]. In combination, both drugs produced a 2.67-fold increase in damage markers for up to 48 h after administration, compared with olaparib alone. This same study also showed that 3-day treatment of AZD0156 and olaparib sensitized a broad panel of cancer cell lines and triple-negative breast cancer xenografts.

AZD0156 was also evaluated as a radiosensitizer for treatment of head and neck squamous cell carcinomas. In line with previous research, combinational treatment showed significant G2/M arrest and increased cell death in head and neck squamous cell carcinoma lines [91]. There was no change in cell death among healthy fibroblasts between combinational treatment and radiation alone. Interestingly, HPV status seemed to inform radiosensitization potential, with HPV-positive cell lines showing increased cell death after combinational treatment.

When AZD0156 was combined with irinotecan to treat colorectal cancer cells, it was shown to significantly reduce proliferation and increase G2/M arrest [92]. However, there was no additional benefit when AZD0156 was combined with the standard-of-care treatment of irinotecan and 5-fluorouracil. In vivo data was less definitive, with only a trend towards tumor growth inhibition. These discrepancies were attributed to differences in the underlying mutations in DNA repair genes found in cell lines and xenografts.

Importantly, ATM function is not limited to just the repair of DSBs. AZD0156 has been explored for a number of different applications that target these additional functions, increasing the breadth of use for ATM inhibitors. For example, alternative lengthening of telomeres (ALT) is a mechanism that maintains telomere length in 10–15% of cancers [93]. ALT is present in over 25% of all high-risk neuroblastomas. ATM was found to be responsible for ALT's persistent DNA damage signaling [94], since ATM initiates damage signaling in response to DNA ends. This signaling was successfully blocked via treatment with AZD0156. In addition, p53-deficient cells with hyper-resistance to temozolomide and irinotecan were found to be sensitized by AZD0156 both in vitro and in vivo [94]. The ability to re-sensitize tumor cells is an incredibly valuable asset to treat patients that have proven resistant to standard-of-care treatments. Additionally, radiation therapy is known to stimulate an antitumor immune response. When radiation was combined with AZD0156, there was an increase in IFN-1 response and CD8+ T cell infiltration [95]. Enabling T-cell tumor infiltration promotes a higher immune response in

tumor cells and improves the response of patients treated with immunotherapies.

The importance of modeling clinical relevance, even for in vitro work, was exemplified in a study examining AZD0156's role in fractionated radiotherapy. Although this regimen is utilized in the clinic to allow healthy cells time to recover, it can increase the potential for tumors to develop radioresistance. Most in vitro work is done using single doses. Here, however, the authors delayed IR doses by 24 h to better model the actual radiation therapy a patient would experience in the clinic, which involves multiple rounds of radiation over time. AZD0156 was found to sensitize breast cancer cell lines to fractionated IR better than other DNA damage repair inhibitors and olaparib. Additionally, combining AZD0156 with this fractionated radiation approach resulted in a more robust and persistent damage effect [96]. These results supported practical use of AZD0156 in the clinic going forward.

Collectively, the promising preclinical results observed with combinations of AZD0156 and Olaparib led to a full clinical trial comparing AZD0156 in combination with various established drugs, including olaparib, irinotecan, fluorouracil, and folinic acid (NCT02588105). Pharmacokinetic data was collected for each combination at various doses of oral AZD0156. Varying doses of AZD0156 alone were also evaluated for potential use as a monotherapy. Although formal results have not yet been published from the completed trial, reported hematological treatment-related adverse events are likely responsible for the drug's disappearance from production [97].

5.8 AZD1390 (2018)

AZD1390 was developed on the basis of the structure of AZD1056 in an effort to improve blood–brain barrier permeability [98]. Indeed, AZD1390 was found to have a blood–brain barrier permeability at least sixfold greater than AZD0156. AZD1390 is selective for ATM inhibition, with 0.1 μmol/L showing no significant inhibition of the other 354 kinases tested [98]. In addition, treatment at 3 nmol/L was sufficient to inhibit ATM autophosphorylation and radiosensitize glioblastoma cells (LN18), breast cancer CNS metastasis models [99], small cell lung cancer [100], and pediatric high-grade glioma [101].

ATM mutations in cancer patients are associated with better immune checkpoint blockade outcomes. The Cancer Genome Atlas (TCGA) data indicate that ATM expression is associated with reduced interferon-stimulating gene (ISG) expression in multiple cancer cell lines. Inhibition of ATM via AZD1390 induced ISG expression and led to the release of mitochondrial DNA into the cytoplasm, activating the cGAS/STING pathway that senses cytosolic DNA and initiates an innate immune response. Pathway activation led to tumor growth suppression via T-cell infiltration [59].

AZD1390 has been studied extensively in vivo. Brain tumor models showed far greater survival when treated with high doses of AZD1390 and IR compared with IR alone [102]. Notably, a slight increase in sensitivity was also seen when the duo was combined with temozolomide, an alkylating agent. AZD1390 also showed a significant reduction in tumor growth across a panel of intracranial glioblastoma xenografts, with p53-mutant cells again showing increased responsiveness [98, 102].

Further investigation of AZD1390's delivery to the central nervous system showed that even with active efflux by P-glycoprotein (Pgp), a critical blood–brain barrier transporter, enough AZD1390 reached the brain to support radiosensitization. Although in vivo models showed that AZD1390 had a higher accumulation in tumors, the lowest dose found in healthy tissue was sufficient for radiosensitization—an important consideration when translating to the clinic [103]. AZD1390 was also found to induce more galectin-9 (Gal-9) expression (a T-cell suppressor) in a variety of cancer cell lines by activating the cGAS/STING pathway. Together, AZD1390 and Gal-9 immunoblockade treatment synergistically reduced in vitro cancer cell growth and strongly reduced in vivo tumor growth, while also showing a greater T-cell infiltration response [104]. Inducing T-cell infiltration could represent an important alternate function of clinical ATM inhibitors, acting as sensitizers for immune checkpoint blockade therapy.

AZD1390's promising results in preclinical studies have led to its inclusion in six clinical trials. Positron emission tomography (PET) is used to assess the pharmacokinetics of drugs noninvasively. Developing drug analogs that can be imaged by PET is an invaluable tool for clinical evaluation that allows noninvasive tracking of drugs as they move throughout the body. In a phase 1 trial, radiolabeled [^{11}C]AZD1390 was administered to eight healthy male patients for brain exposure analysis. PET imaging showed effective blood–brain barrier penetration with microdoses (0.46–4.67μg) of [^{11}C]AZD1390. The drug reached its maximum concentration (1% of original dose) in the brain 21 min after arterial injection [105] (NCT03215381). An improved version of radiolabeled AZD1390 was also developed with [^{18}F]AZD1390, which has shown identical ATM inhibition activity as its predecessors in vivo [106]. The isotope's longer half-life could provide a more sustained readout of AZD1390's pharmacokinetics but has not yet been tested in clinical trials.

AZD1390 is also being evaluated clinically in combination with many other therapies. Fractionated radiotherapy and AZD1390 are being studied for pharmacokinetic properties in patients with grade 4 gliomas (NCT05182905). The same combination is also being evaluated for treatment

of soft tissue sarcomas (NCT05116254) and glioblastoma multiforme/brain metastases (NCT03423628). AZD1390 and stereotactic body radiotherapy, which uses multiple beams of high-dose radiation for precise treatment of tumors [107], are also being tested for treatment of metastatic solid tumors (NCT05678010). CONCORDE, a massive phase 1 trial sponsored by the University of Leeds, is evaluating the use of AZD1390 in combination with radiotherapy along with other inhibitors targeting the DNA-damage response in non-small cell lung cancer (NCT04550104) [108, 109]. The breadth of inhibitors to be studied in combination with radiotherapy establish CONCORDE as a landmark study for the safety and efficacy of clinical DNA-damage response targeting.

5.9 M3541 (2022)

The M3541 ATP-competitive ATM inhibitor was designed from a new structural class of imidazolonlylquinolines. Developed by Merck KGaA, Darmstadt, Germany, M3541 is a reversible and specific inhibitor, completely eliminating radiation-induced ATM activation at 1 μmol/L in A549 cells, a non-small cell lung cancer cell line [47].

When M3541 was combined with IR, cell growth was inhibited synergistically in all 79 cancer cell lines assessed [47]. The cell lines tested were chosen to represent a variety of tumor origins and p53 backgrounds. MIA PaCa-2, a p53-mutant pancreatic cancer line, exhibited the highest degree of synergy, while SK-MEL-28 p53-mutant melanocytes had the lowest. Head and neck squamous cell carcinoma (FaDu) xenografts also showed sustained tumor regression with dual treatment. When M3541 was combined with IR and cisplatin, there was an even greater degree of progression-free survival compared with the dual treatment determined by tumor volume analysis of the FaDu model [47, 110]. Similar to studies with AZD1390, combining M3541 with radiation also increased interferon-stimulating gene expression, IFNβ1, and inflammatory chemokine/cytokine expression [111]. Treatment also increased the susceptibility of A549 cancer cells to natural killer (NK) cells, which are innate immune effector lymphocytes. Cell growth was inhibited by over 50% in each cell line co-cultured with NK cells, as compared with the 20% reduction observed with M3541 and radiation alone.

Inhibition of ATR activates the ATM-p53 G1 checkpoint to prevent entry into the S phase [14, 112]. M3541 alone had no effect on cell cycle progression, and ATR inhibition alone had a very mild effect. Combining the two, however, blocked checkpoint activation, leading to unregulated cell cycle progression and entry into mitosis [112]. Failure to halt the cell cycle and repair chromosomal damage significantly increased cell death in A549 cancer cells, but not healthy fibroblasts.

In its sole clinical trial, M3541 was tested with radiotherapy to treat a variety of solid tumors (NCT03225105). The drug was administered orally with an immediate-release tablet. Patients at all doses reported at least one adverse effect associated with treatment, with 50% of these attributed to M3541. Additionally, a cap on absorption was observed. Regardless of dose, no more than ~100 mg of M3541 could be absorbed. These two factors, combined with a lack of clear evidence that M3541 was able to reduce tumor volume, led to the study's termination [113].

5.10 M4076 (2022)

M4076, also known as lartesertib, was developed simultaneously with M3541 from the same chemical class. Compared with its sister compound, M4076 has greatly improved solubility and increased potency [114]. The drug is exquisitely selective for ATM, showing no inhibition of 583 other kinases at 100 nM. As an ATP-competitive inhibitor, M4076 binds to the hinge region (Fig. 1B) of the active site cleft, creating a conformation nearly identical to ATP-bound ATM [67].

The development of M4076 came with an important step forward in drug development as a whole: the identification of atropisomers as improved pharmacological candidates. Atropisomers are compounds that have impeded rotation around a single bond [115]. This steric block is large enough to induce chirality and isolate unique conformations. While the racemic mix of M4076 was shown to have stronger interactions, isolation of a single M4076 atropisomer led to better solubility and improved pharmacological behavior [116].

A panel of 14 cancer cell lines representing a variety of origins (breast, colorectal, skin, and lung, among others) was tested with different doses of M4076 in combination with radiation [47]. Combination treatment was able to suppress growth and proliferation across all 14 cell lines. M4076 significantly reduced ATM activity in vivo and showed complete tumor regression in FaDu xenograft models when combined with ionizing radiation. Synergy was observed with both PARP inhibitors and topoisomerase inhibitors. Importantly, there was no indicator of significant in vivo toxicity [47]. When M4076 was combined with ATR inhibitors, it also led to significant tumor growth inhibition in 26 triple-negative breast cancer xenograft models [112].

M4076's preclinical success led to its evaluation in two clinical trials. The first clinical trial explored M4076's pharmacological properties as a monotherapy to determine dosing strategies (NCT04882917). M4076 was given to patients with advanced solid tumors and evaluated for safety and tolerability. Initial results show that M4076's pharmacology was far better than its sister M3541, displaying better absorption (300 mg versus 100 mg, respectively) and longer penetrance [117]. ATM inhibition was 80-100% effective

by day 2 at all tested doses. No treatment-related adverse events were observed at the 100 mg dose, and of the 22 patients recruited, only 6 reported adverse events. However, it is important to note that this trial is without the addition of radiation therapy. A second arm of this study aims to explore the effects of M4076 under fed and fasted conditions to test how food affects M4076 activity. The second trial is focused on the combination of M4076 with ATR inhibitor M1774 and avelumab, an immune checkpoint inhibitor, on solid tumors (NCT05396833). The study aims to identify the pharmacological properties of the two combinatorial treatments, such as maximum tolerated dose, pharmacokinetic serum and plasma concentrations, treatment-related adverse events, and cancer outcomes.

5.11 ZN-B-2262 (~ 2022)

ZN-B-2262 is a novel ATM inhibitor created by Suzhou Zanrong Pharmaceuticals that has entered clinical trials in China. Limited preclinical data shows that ZN-B-2262 synergistically inhibited tumor growth when combined with irinotecan and radiotherapy in SW60 colorectal cancer and FaDu head and neck squamous cell carcinoma, respectively [118]. The clinical trial seeks to identify the safety and tolerability of the drug alone and combined with radiation for the treatment of solid head and neck cancers (CTR20222750) but has not yet begun recruiting participants.

5.12 SYH2051 (~ 2023)

SYH2051 is a new ATM inhibitor that has recently entered clinical trials. It was developed by CSPC ZhongQi Pharmaceutical Technology Company. Reports indicate that the drug progressed through preclinical evaluations successfully and is now being evaluated clinically as both a monotherapy and in combination with radiotherapy [119, 120]. The trial aims to establish a basic pharmacokinetic profile of the drug and its efficacy against solid head and neck cancers (NCT06011291).

5.13 WSD-0628 (2024)

WSD-0628 was developed by Wayshine Biopharmaceuticals and explored by the Mayo Clinic as a glioblastoma radiosensitizer. WSD-0628 is the most potent ATM inhibitor described so far, blocking ATM activity in U251 glioblastoma cells at just 30 nmol/L [121, 122]. When combined with radiation, WSD-0628 was reported to more than double the survival time of glioblastoma xenograft mice compared with radiation alone and supported high availability within the brain.

WSD-0628 performed well in preclinical evaluation. Pharmacokinetic/pharmacodynamic data was determined using mice with intracranially implanted GBM43 xenografts (p53-mutant glioma) [123]. In these mice, intravenous WSD-0628 was found to rapidly distribute and linger longer at high concentrations (10 mg/kg) compared with (1, 5 mg/kg). Oral administration also displayed nonlinear pharmacokinetics, indicating that different concentrations of the drug induced different pharmacokinetic profiles. The drug was found to effectively penetrate the central nervous system, and this penetration was only mildly improved when tested on efflux transporter knockout mice, indicating that WSD-0628 is not robustly rejected by the blood–brain barrier. Owing to its effectiveness and potent CNS penetration, WSD-0628 is being tested as a radiosensitizer for recurrent high-grade gliomas in a clinical trial (NCT05917145).

6 Conclusions

6.1 Combinatorial Treatments

As a monotherapy, ATM inhibitors have shown limited clinical efficacy in cancer treatments. The true promise of ATM inhibition lies within combinatorial treatments, as ATM's critical role in DSB repair makes it an ideal target for radiosensitizing cancer cells. Additionally, the efficacy of ATM inhibitors is strongly influenced by the genetic and mutation profile of each cancer. Multiple researchers using a variety of ATM inhibitors have shown that treatment outcome is highly dependent on p53 status [78, 81, 88, 98, 101, 102]. When wild-type (WT) p53 cells accumulate DNA damage, ATM signaling promotes apoptosis via p53 signaling. P53-deficient but ATM-proficient cells activate ATM signaling, which promotes cell cycle arrest leading to chemo- and radio-resistance. ATM- and p53-deficient cells accumulate DNA damage and continue to progress through checkpoints, leading to mitotic catastrophe [80]. As a result, p53-deficient cells are highly sensitive to ATM inhibition. Low expression of p53, in conjunction with high expression of PI3K, also appeared to hypersensitize cells to ATM inhibition [76]. However, it is not clear whether the status of p53, PI3K, or both were responsible for this effect. In one case, researchers found that p53 status did not affect the cell's sensitivity to ATM inhibition [46]. This finding was not replicated in other studies, so it is not clear whether this discrepancy was due to altered p53 expression or unidentified background mutations that compensate for p53 loss and prevent sensitization.

P53 is not the only protein whose status controls sensitivity to ATM inhibitors. Molecular inhibition and/or knockdown of numerous targets have been shown to enhance the effects of ATM inhibition [124–128]. Indeed, even a dual DNA-PK/ATM inhibitor XRD-0394 has been developed to take advantage of these enhanced effects [129, 130]. Mutations in the Fanconi anemia (FA) pathway were shown to

induce synthetic lethality when combined with M3541 [131]. The FA pathway is responsible for repair of DNA inter-strand crosslinks (ICLs), and involves proteins from multiple repair pathways, including homologous recombination, nucleotide excision repair, and translesion synthesis [132]. Defects in one repair pathway can lead to increased dependence on another pathway. In this case, eliminating both pathways may result in extreme sensitivity or synthetic lethality [133]. Indeed, a genome-wide CRISPR screen of two non-small cell lung cancer lines (A549 and H460) showed that knockout of numerous genes in or associated with the FA pathway increased cell death in combination with M3541, including *FANCA*, *FANCB*, *FANCE*, *FANCF*, *FANCG*, *FANCD2*, *FAAP24*, and *FAAP100* [131]. Additionally, targeting factors upstream or downstream of ATM signaling induced hypersensitivity to ATM inhibition, including *CtIP*, *EXO1*, *MRN*, *PTEN*, *RAD18*, and *STAG2*. Of equal importance was the finding that BRCA1-A complex knockouts resulted in a resistance phenotype [131]. Indeed, ATM inhibitors have been paired with PARP [134], CHK1 [77], APE1 [135], and ATR [112] inhibitors to achieve synthetic lethality and increased sensitization. To this end, inhibition of ATR and ATM together is currently the subject of a clinical trial (NCT05396833) in an effort to simultaneously target multiple facets of the DNA damage response. Collectively, these observations demonstrate the critical role that a tumor's genetic profile and origin play in potential sensitization via ATM inhibition.

6.2 Clinical Challenges

ATM inhibition has shown great versatility in preclinical studies and has produced promising results in multiple clinical trials. However, several drawbacks associated with treatment remain, including high toxicity and various adverse events that limit its application. Repeated injections of KU-60019 at high doses in combination with irradiation led to neurological symptoms, such as hyperkinesis (overactive restlessness). These neurological effects were seen with both intracranial and intraperitoneal injection, indicating meningeal and peripheral nerve damage, as KU-60019 cannot pass the blood–brain barrier [136]. Trials with M3541 were halted in part owing to multiple treatment-emergent adverse events [113]. AZD1390 was associated with a slight increase in brain lesions on normal tissue after radiation treatment [98]. The first arm of M4076's clinical trial showed no treatment-emergent adverse events at low doses, but higher doses resulted in anemia and rash [117]. AZD0156's hematological toxicities are likely responsible for the drug being discontinued upon completion of the trial [97]. Additionally, extended timeline studies of ATM inhibition have not yet been completed. A better understanding of the off-target effects associated with these drugs, and the potential long-term consequences for patients, is critical for widespread translational use.

While ATM inhibition can be a viable option for sensitizing treatment-resistant cancers, their general use remains limited. As monotherapies, they have had limited efficacy. However, knowledge of tumor profiles and combinatorial treatments make them a viable option for some cases. As such, the development of ATM inhibitors has grown steadily in the past 10 years for a variety of cancer type applications (Fig. 4). ATM inhibition sensitizes cells exposed to agents that induce DSBs, such as IR, common chemotherapies, and other standard-of-care inhibitors like topoisomerase inhibitors. When applied to cancers with preexisting DNA damage repair mutations, this combined treatment has profound benefits. Compounds like AZD1390 and WSD-0628 have been shown to effectively cross the blood–brain barrier, making them suitable options to treat resistant brain cancers. ATM's associated immunogenic functions also highlight another avenue for research, where the potential benefits have not been fully explored. ATM inhibition offers new avenues for increasing the effectiveness of traditional cancer therapy. Overall, ATM inhibitors provide a promising and unique strategy for cancer therapy that promises to remain at the forefront of personalized care.

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