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Mini-review

# Mitosis inhibitors in anticancer therapy: When blocking the exit becomes a solution

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ABSTRACT

Current microtubule-targeting agents (MTAs) remain amongst the most important antimitotic drugs used against a broad range of malignancies. By perturbing spindle assembly, MTAs activate the spindle assembly checkpoint (SAC), which induces mitotic arrest and subsequent apoptosis. However, besides toxic side effects and resistance, mitotic slippage and failure in triggering apoptosis in various cancer cells are limiting factors of MTAs efficacy. Alternative strategies to target mitosis without affecting microtubules have, thus, led to the identification of small molecules, such as those that target spindle Kinesins, Aurora and Polo-like kinases. Unfortunately, these so-called second-generation of antimitotics, encompassing mitotic blockers and mitotic drivers, have failed in clinical trials. Our recent understanding regarding the mechanisms of cell death during a mitotic arrest pointed out apoptosis as the main variable, providing an opportunity to control the cell fates and influence the effectiveness of antimitotics. Here, we provide an overview on the second-generation of antimitotics, and discuss possible strategies that exploit SAC activity, mitotic slippage/exit and apoptosis induction, in order to improve the efficacy of anticancer strategies that target mitosis.

## 1. Introduction

Current antimitotic drugs consist mainly of microtubule targeting agents (MTAs) which remain amongst the most successful of classical chemotherapeutics [1]. The prototypical MTAs are paclitaxel and the vinca alkaloid vinblastine used in the treatment of several cancers, particularly breast, ovarian, non-small-cell-lung and head-and-neck cancers [2]. By binding to tubulin, these spindle poisons affect microtubule dynamics, impairing the formation of a functional bipolar spindle. As a consequence, chromosomes of dividing cells cannot establish proper attachments to spindle microtubules, resulting in a chronic activation of the spindle assembly checkpoint (SAC) and a prolonged mitotic arrest for hours [3]. Mitosis-arrested cells eventually die by apoptosis during mitosis. However, alternative outcomes can be adopted including slippage and/or escape from cell death which, besides toxicity and resistance associated with MTAs, have motivated the emergence of new antimitotic strategies [4]. The SAC is at the heart of existing and emerging antimitotic approaches. Thus, after a brief overview on SAC mechanism of activation and silencing, we will discuss the emerging strategies of mitosis-based therapies, pointing out possible directions for novel strategies that exploit mitotic exit and apoptosis circuits in order to increase opportunities for cancer cell death.

## 2. The spindle assembly checkpoint

During mitosis, driven by the activation of cyclin-dependent kinase 1 (CDK1) by cyclin B, the genomic material duplicated in the S phase of the cell cycle is equally distributed between the newly formed daughter cells [5]. Upon nuclear envelope breakdown (NEBD) at the prophase-prometaphase transition, a dynamic interaction between chromosomes and microtubules of the bipolar spindle is initiated to achieve chromosome bi-orientation and alignment at the metaphase plate, prior to segregation at anaphase.

Accurate chromosome segregation at anaphase relies on correct

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bipolar kinetochore-microtubules attachments, a process under the surveillance of the SAC. The kinetochore, a specialized protein-rich structure assembled on centromeric chromatin, is the point of attachment of spindle microtubules to the chromosome, and is at the heart of the SAC signaling pathways [6,7]. Unattached and/or improperly attached kinetochores activate the SAC which halts cells in mitosis until the errors are corrected. Failure to detect and correct erroneous attachments can lead to precocious chromosome segregation and aneuploidy, a hallmark of cancer cells [8–10].

Activation of SAC requires the hierarchical recruitment to unattached kinetochores of the core SAC proteins Bub1 (budding uninhibited by benomyl 1), Bub3, Bub1-related 1 (BubR1), mitotic arrest deficiency 1 (Mad1), Mad2, monopolar spindle 1 (Mps1), and Aurora B. At the top of this hierarchy lie the kinases Aurora B, Mps1, and Bub1, whereas BubR1, Mad1, and Mad2 lie downstream [11]. Activation of SAC requires the hierarchical recruitment to unattached kinetochores of the core SAC proteins Bub1 (budding uninhibited by benomyl 1), Bub3, Bub1-related 1 (BubR1), mitotic arrest deficiency 1 (Mad1), Mad2, monopolar spindle 1 (Mps1), and Aurora B. At the top of this hierarchy lie the kinases Aurora B, Mps1, and Bub1, whereas BubR1, Mad1, and Mad2 lie downstream (Fig. 1) [11]. When active, the SAC inhibits the activation by Cdc20 of the anaphase promoting complex/cyclosome (APC/C), the E3 ubiquitin ligase required to promote mitotic exit through 26S proteasome-mediated degradation of securin and cyclin B (Fig. 1A). This prevents cells from exiting mitosis with erroneous attachments. The SAC inhibitory activity is exerted through the mitotic checkpoint complex (MCC) that forms between the SAC proteins (Mad2, Bub3, and BubR1), and Cdc20 [12–14]. The signal emerges from unattached kinetochores where kinetochore-bound Mad1 catalyzes the conversion of inactive “open” Mad2 (O-Mad2) into active “closed” Mad2 (C-Mad2) that can stably bind to Cdc20 and diffuse throughout the cytoplasm to inhibit APC/C and restrain progression through mitosis [15,16]. Once the last kinetochore is properly connected to spindle microtubules, the SAC must be silenced to allow anaphase onset [17,18].

SAC silencing implies stopping assembly of new MCC and promoting disassembly of existing ones, both mediated by structural and compositional changes at kinetochores upon microtubule attachment (Fig. 1B) [19]. Halting MCC assembly requires the motor protein dynein which actively mediates the transport of SAC components, namely Mad1-Mad2 complexes, from kinetochores towards the spindle poles, a process termed streaming or stripping [18,20]. This dynein-mediated stripping is mainly dependent on spindly, a protein involved in dynein recruitment to the kinetochore [21–23]. On the other hand, disassembly of existing MCC involves Mad2 inhibition promoted by the activity of the two proteins, $p31^{comet}$ (a Mad2-binding protein) and TRIP13 (thyroid hormone receptor interactor 13; a AAA + family ATPase) that cooperatively convert active C-Mad2 to the unbound O-Mad2 conformation, thereby promoting MCC dissociation and APC/C-Cdc20 reactivation [24,25]. In addition, ubiquitination-mediated protein degradation of Cdc20 subunit intrinsic to the MCC ($Cdc20^{MCC}$) was reported to contribute to MCC turnover and reactivation of inhibited APC/C-Cdc20 [26,27]. In particular, the APC15 subunit induces $APC/C^{MCC}$ conformation changes that are able to auto-ubiquitinate and degrade MCC-bound Cdc20 [27]. Dephosphorylation of kinetochore and SAC proteins has recently been reported as an essential mechanism for SAC silencing. PP1 and PP2A-B56 are the main protein phosphatases which, through negative feedback loops with Mps1 and Aurora B kinases, allow rapid dissociation of the MCC and SAC silencing upon proper microtubule attachment [28,29].

## 3. Cell fate after mitotic arrest

As stated above, different outcomes are possible after mitotic arrest upon MTAs treatment (Fig. 2). Cells may undergo death in mitosis (DiM) by apoptosis, or exit mitosis without division and become tetraploids (4 N), in a process known as mitotic slippage owing to a slow degradation background of cyclin B due to incomplete inhibition of the APC/C [30]. In turn, depending on the status of genes such as TP53, PRb or P38, and the degree of DNA damage induced by MTAs, slipped 4 N G1-cells may arrest in interphase, undergo senescence, or post-mitotic death [4]. Although not consensual, the fate of cells arrested in mitosis due to MTAs seems to be influenced by the duration of the mitotic arrest, and varies greatly between cancer cells [31,32].

Single cell analysis had led to the demonstration that cell fate following prolonged arrest is determined by two independent and competitive networks: one triggering apoptosis via intrinsic pathway, and the other triggering mitotic slippage to 4 N G1 state in the presence of a yet active SAC [33]. The network that reaches its threshold first determines the cell fate: if enough proapoptotic signal is accumulated before a threshold of cyclin B degradation is reached, then cells will die; if cyclin B is degraded below a threshold level before enough proapoptotic signal is accumulated, then mitotic slippage occurs [34].

Besides mitotic slippage, MTAs are commonly associated with neurotoxicity and myeloid toxicity owing to the role of microtubules in axonal transport and in cycling bone marrow cells, respectively [35,36]. Also, intrinsic or acquired resistance is the main cause of therapeutic failure of chemotherapy including MTAs [37]. Intrinsic resistance is associated with an individual's genetic variations, mainly in somatic cells, while acquired resistance can be attributed to several mechanisms such as the inactivation of the drug, multi-drug resistance, cell death inhibition, epigenetic changes, or changes in drug metabolism or in the drug targets [38]. Drug resistance associated with overexpression of P glycoprotein (P-gp) and mutations in tubulin-binding sites, are a common concern that can unpredictably affect therapeutic efficacy of MTAs [39]. Therefore, it was suggested that alternative targets that disrupt mitosis without affecting microtubules would circumvent these issues, which has led to the identification of new antimitotic agents, namely those that target mitosis-specific kinases and microtubule-motor proteins [40]. Also, given its critical role in mitosis, the SAC signaling components provide an attractive opportunity for anticancer drug development. Theoretically, both SAC activation and silencing provide a rational approach for the design of cancer cell killing strategies without affecting microtubules. This had led to the development of the so called second-generation of antimitotics, grouped into mitotic blockers and mitotic drivers, some have reached clinical trials [41].

## 4. Targeting microtubule-motor proteins and mitosis-specific kinases

Many mitotic proteins are involved in bipolar mitotic spindle organization without being required for microtubule formation [42,43]. Yet, their inhibition affects spindle bipolarity which creates mis-attached chromosomes, thereby activating the SAC. Based on this rationale, these proteins were considered as potential targets for effective SAC-dependent mitotic arrest and anticancer therapy. Known targets include the kinesins CENP-E and Eg5, and the kinases Polo-like Kinase 1 (Plk1) and Aurora (Table 1) [44–50]. Unlike microtubules which function both in mitosis and in interphase, the function of these targets is mainly restricted to mitosis, which expectedly should result in a better therapeutic index compared to MTAs.

### 4.1. Eg5 kinesin

Eg5 is a plus-end directed motor protein with essential functions in bipolar spindle assembly, chromosome congression and segregation [51]. Eg5 inhibition by RNAi, antibodies, or specific inhibitors, leads to monopolar spindles, which activates the SAC, induces mitotic arrest and, in some tumor cell lines, cell death [52]. These facts prompted the development of small molecule inhibitors for antitumor chemotherapy with high efficacy in preclinical studies [53], and some reached clinical

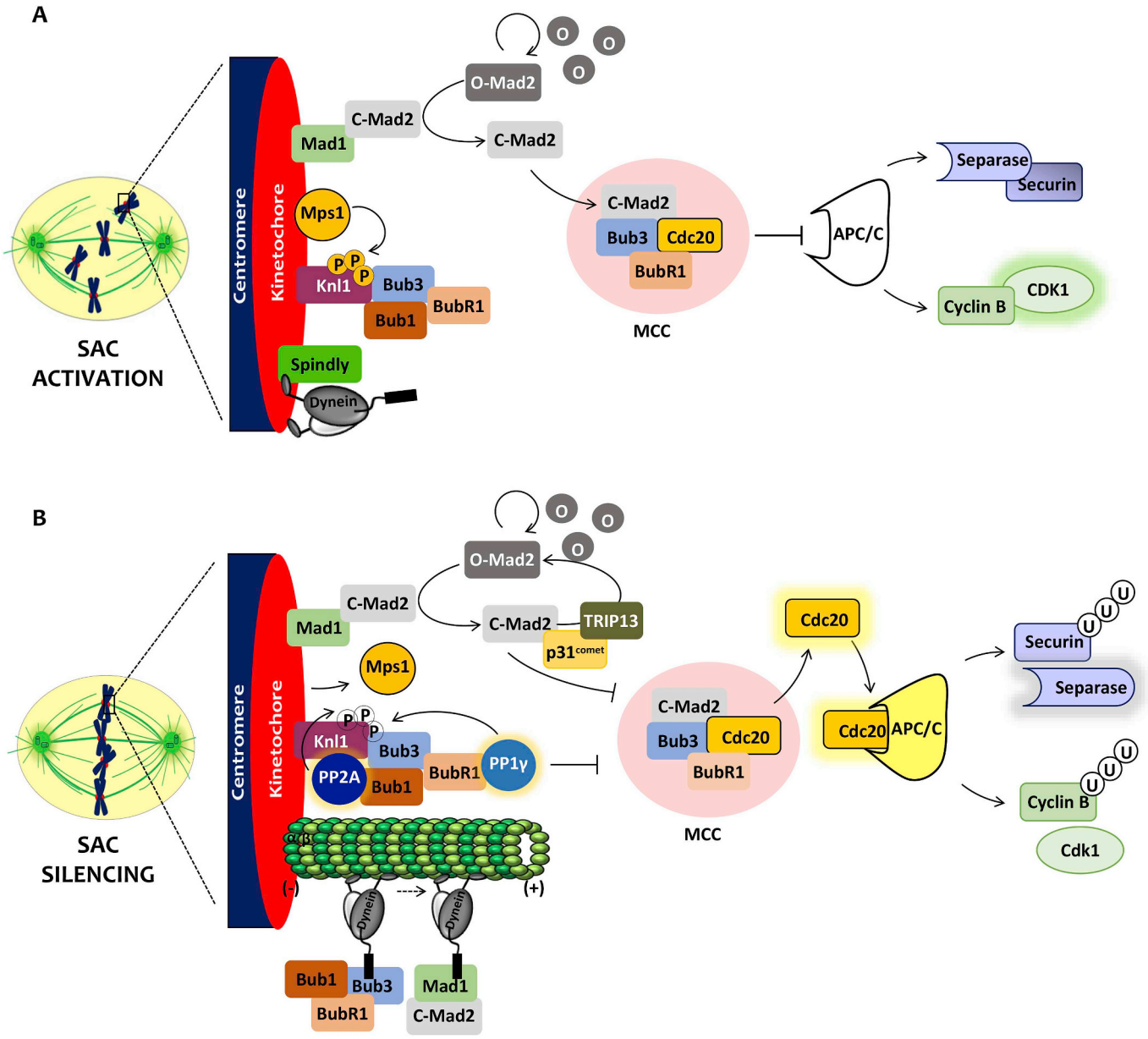


**Fig. 1. Spindle assembly checkpoint activation and silencing. (A)** The SAC is turned on in the presence of unattached kinetochores (red) where Mad1/C-Mad2 complex actively recruits and converts cytosolic O-Mad2 into C-Mad2, which together with Bub3, BubR1 and Cdc20 constitute the MCC, resulting in APC/C inhibition. Consequently, cyclin B and securin are not degraded and remain associated with Cdk1 and separase, respectively, leading to mitotic arrest. At the kinetochore, Mps1 is responsible for Knl1 phosphorylation promoting the recruitment of Bub3, Bub1 and BubR1. Also, spindly is essential for dynein recruitment to the kinetochore. **(B)** Different mechanisms have been proposed for SAC silencing, namely (i) through Mad2 inhibition by $p31^{comet}$ and TRIP13, which convert active C-Mad2 to the unbound O-Mad2 conformation, thereby promoting MCC dissociation and APC/C-Cdc20 reactivation; (ii) through the release of Mps1 from the kinetochore and dephosphorylation of Knl1 motifs by PP2α or PP1γ phosphatases, resulting in MCC inhibition; and (iii) through dynein-mediated stripping of SAC components, from kinetochores towards the spindle poles, promoting MCC disassembly. The consequence is the APC/C activation by Cdc20, resulting in ubiquitination-mediated protein degradation of cyclin B and securin, and mitotic exit. Moreover, ubiquitination-mediated protein degradation of Cdc20 subunit intrinsic to the MCC, by APC15, contributes to reactivate the APC/C-Cdc20. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

AbbreviationsC-Mad2 = Closed Mad2; O-Mad2 or O = Open Mad2; MCC = Mitotic Checkpoint Complex; APC/C = anaphase promoting complex/cyclosome.

trials. However, although side effects were moderate, only partial responses have been reported [54]. For example, patients with advanced solid tumors treated with ispinesib (SB-715992), the first Eg5 inhibitor to enter clinical trials, achieved no objective responses or, at best, showed stable disease in monotherapy in phase I/II studies, although the drug was well tolerated [55,56]. The reasons for the poor activity of many Eg5 inhibitors remain to be elucidated. Eg5 inhibition was certified by the increased phospho-histone H3 positive cells, and the presence of monopolar spindles in patient biopsy samples [57,58]. Functional redundancy between mitotic kinesins could be amongst the reasons that challenge the clinical efficacy of Eg5 inhibitors [59]. Interestingly, these Eg5 inhibitors induce cell death in combination with taxol even in taxol-resistant cancer cells, highlighting the therapeutic potential of Eg5 inhibition in combination with other cytotoxic drugs [46].

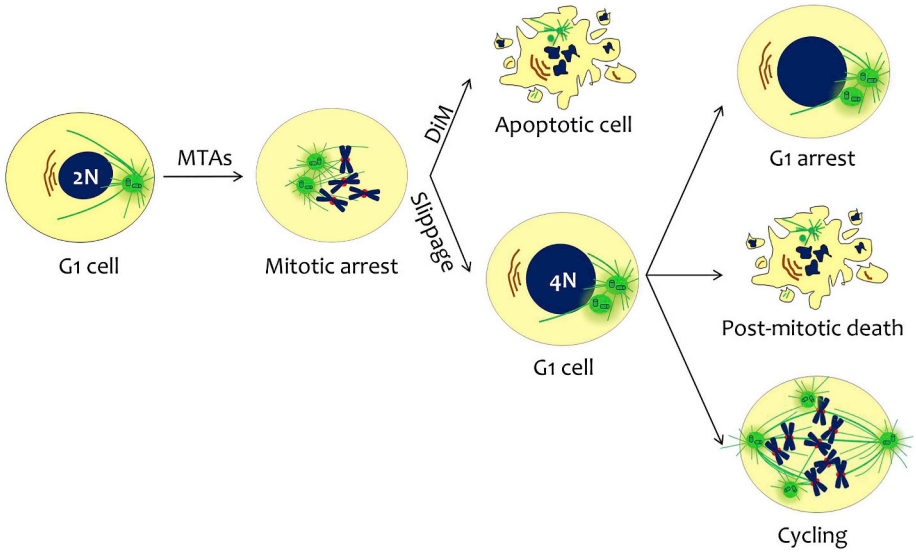


**Fig. 2. Cell fate after treatment with microtubule-targeting agents.** Diploid cells (2 N) treated with microtubule-targeting agents (MTAs) arrest in mitosis and may undergo death in mitosis (DiM), or mitotic slippage caused by a defective SAC and/or gradual degradation of cyclin B. These tetraploid (4 N) slipped cells may arrest in interphase (G1 arrest), undergo post-mitotic death, or continue cycling.

### 4.2. CENP-E kinesin

Given its essential functions in chromosome congression and alignment during mitosis, as well as in SAC regulation by modulating BubR1 function, the kinesin CENP-E was regarded as suitable antimitotic target [60,61]. Inhibition of CENP-E induces unaligned chromosomes leading to prolonged mitotic arrest in cancer cell lines, with potent antitumor activity in xenografts [44,45,62]. In contrast to Eg5, for which several small molecule inhibitors have been or are being evaluated, only one small-molecule CENP-E inhibitor, GSK923295, has reached clinical trials [45,63,64]. In a phase I clinical trial involving patients with solid cancers that do not respond to standard therapy, GSK923295 exhibited dose-proportional pharmacokinetics and a low incidence of myelosuppression and neuropathy [64]. However, pharmocodynamic studies to assess the expected antimitotic effect of the drug remain to be performed, and, though the treatment was well tolerated, the effectiveness of GSK913295 was modest with a single partial response described [64].

### 4.3. Polo-like kinase 1

The serine/threonine Plk1 is a key cell cycle regulator including DNA checkpoint activation, centrosome maturation, mitotic entry, spindle assembly, and cytokinesis, making it good target for cancer therapy [65]. Together with its overexpression found in many tumor types, Plk1 was pointed out as an attractive target for anticancer therapy [66]. Inhibition of Plk1, whether by siRNAs or small molecules, induces monopolar spindle formation, resulting in inhibition of proliferation and apoptosis in cancer cell lines, and tumor growth inhibition in preclinical studies [67–69]. However, disappointing results were obtained with BI 2536, one of the first Plk inhibitors, in phase II trials in solid tumors. For instance, BI 2536 had modest to no clinical activity in phase II trials in various cancers, and in many patients, neutropenia and leukopenia have been the primary dose-limiting toxicity [70]. In a phase I study, the potent and selective Plk1 inhibitor BI 6727 (volasertib) achieved stable disease in 26 patients (44.1%) with advanced solid cancers [71]. Neutropenia, leukopenia, and thrombocytopenia were the main adverse effects. In a phase II trial involving 50 patients with metastatic urothelial carcinoma, BI 6727 resulted in limited antitumor activity, with only 14% of the patients showing a partial response [72]. The activity of Plk1 in patient tumors remains to be determined in order to verify whether the Plk1 is effectively targeted [70]. Nevertheless, encouraging results were achieved upon Plk1 inhibition in acute myeloid leukemia (AML) patients treated with BI 6727 alone, with a small fraction of patients showing complete remission. A significant increase in complete remission of AML patients was achieved when BI 6727 was combined with low-dose cytarabine, highlighting its therapeutic potential in combinatorial therapy, particularly in cancers, where the malignant cells have high proliferation rate [73].

### 4.4. Aurora kinases

The serine/threonine Aurora kinases A, B, and C (AURKA, B, C) are key regulators of mitosis, with essential roles including centrosome duplication and separation, bipolar spindle assembly, chromosome condensation, chromosome-microtubule attachments, the SAC and cytokinesis [74,75]. Inhibition of AURKA induces a transient SAC-dependent mitotic arrest due to mitotic spindle defects, followed by exit from mitosis and apoptosis [76]. In contrast, inhibition of AURKB induces chromosome attachment defects, and overrides the SAC causing aberrant mitosis without cytokinesis resulting in polyploidy and cell death [77,78]. All three Auroras are overexpressed in multiple solid tumors and associated with poor prognosis which, together with their function in cell division, make them promising targets for cancer therapy [79,80]. A series of AURK inhibitors have been developed and shown to suppress cell proliferation, migration and invasion in cancer cell lines, and to inhibit the progress and growth of many cancers in xenograft models [81–84]. Unfortunately, although many AURK inhibitors reached clinical trials, the results are disappointing as no AURK inhibitors have been approved for clinical use so far, essentially due to cell toxicity issue [85]. Pharmacodynamic analysis (including spindle bipolarity, mitotic index and mitotic cell chromosome alignment), performed in tumor biopsies, demonstrated that selective AURK A or B was indeed achieved. However, neutropenia, stomatitis, and somnolence was the most frequent dose-limiting toxicity observed in the clinical trials [75]. For example, in a phase II study, MLN8237 (Alisertib), an AURK A selective inhibitor, partial responses were observed in 18% (9 out of 49) women with breast cancer, 21% (10/48) patients with small-cell lung cancer, 4% (1/23) patients with non-small-cell lung cancer, 9% (4/45) patients with squamous cell cancer of head and neck, and 9% (4/47) patients with gastro-esophageal adenocarcinoma [86]. In another phase I/II clinical trial study with AZD1152 (barasertib), an AURK B selective inhibitor, the overall response rate was 25% (16/64) in both newly diagnosed and relapsed acute myeloid leukemia patients [87]. Neutropenia and leukopenia were the most commonly reported side effects. Interestingly, Aurora inhibition was reported to potentiate the tumor response to conventional chemotherapy and radiotherapy. For instance, AURKB inhibition with AZD1152 sensitizes cisplatin-

**Table 1**
Targeting mitotic components and apoptotic modulators in cancer therapy: preclinical and clinical studies.

| Target | Function | Inhibitors | Inhibitory activity | Cancer type | Clinical trials[a] |
|---|---|---|---|---|---|
| Eg5 | Centrosome separation; Bipolar mitotic spindle formation. | Ispinesib (SB-715992); AZD4877; Filanesib (ARRY-520); SB-743921, ARQ-621; Litronesib (LY2523355); MK-0731; EMD-534085; K858; YL001 | Monopolar spindles; mitotic arrest; apoptosis; antitumor activity. | Breast, nasopharynx, lung, liver, cervix, colon, prostate, kidney, stomach, ovary, bladder, glioblastoma, leukemia, melanoma, fibrosarcoma, breast, multiple myeloma, pancreas, brain, testis, sarcoma, pleuramesothelioma, renal, hepatocellular, head and neck, urothelial and lymphoid malignancies [59]. | I, II |
| CENP-E | Spindle dynamics; Chromosome congression; SAC regulation. | GSK923295A; Compound-A | Chromosome misalignment and mitotic arrest; tumor cell growth inhibition and apoptosis. | Neuroblastoma, breast, cervix, prostate, colon, ovary, pancreas [45,62,163,164]. | I |
| Plk1 | Centrosome maturation; mitotic entry; spindle assembly; cytokinesis. | BI2536; GSK461364; BI 6727; ON-01910; TAK960; MLN0905; RO3280; PIP3; SBE 13 HCl; NMS-P937; Poloxin; Poloxin-2 | Mitotic arrest; DNA breakdown; senescence; apoptosis; tumor growth inhibition and regression. | Colorectal, lung, breast, cervix, ovary, bladder, prostate, diffuse large B-cell lymphoma, sarcoma, melanoma, leukemia, medulloblastoma, osteosarcoma and glioblastoma, hepatoma, pancreas, neuroendocrine, stomach, non-Hodgkin lymphoma [66,165–170]. | I, II, III |
| Auroras A, B, C | Centrosome maturation/separation; mitotic entry; microtubule nucleation; spindle assembly; cytokinesis; mitosis exit; chromosome condensation; kinetochore-microtubule attachment; chromosome alignment and segregation. | Hesperidin; PHA-739358; AMG 900; SNS-314; CCT 137690; MK-0457 (VX-680, tozasertib); VE-465; PHA-680632; AZD1152-HQPA (barasertib); GSK1070916; MLN8054; MLN8237 (alisertib); PF-03814735; MK-5108 (VX-689); TC-A 2317 hydrochloride; ZM 447439; KW-2449; CYC116; ENMD-2076; R763; XL228;; JNJ-7706621; SU-6668; AT-9283; MLN8054 | S-phase arrest; disruption of mitotic spindle formation; senescence; apoptosis; inhibition of cancer cells growth, proliferation, migration and invasion. | Prostate, colorectal, thyroid, ovary, liver, breast, lung, pancreas, esophagus, bladder, renal, cervix, leukemia, lymphoma, multiple myeloma, glioblastoma, rhabdomyosarcoma, Ewing sarcoma, neuroblastoma, tongue, osteosarcoma, gastroenteropancreatic neuroendocrine tumor, childhood adrenocortical tumor, melanoma, retinoblastoma,uterus,melanoma, myelodysplastic syndrome, gastric/gastrointestinal, oral cancer andglioma [75,171,172]. | I, II, III |
| Mps1 | SAC signaling; Kinetochore-microtubule attachment. | NMS-P715; SP600125; AZ3146; Mps1-In-1 and -2; Reversine; MPI-0479605; BOS172722; BAY 1217389 | SAC override; chromosome misalignment; massive aneuploidy and cell death; cancer cell proliferation and tumor growth inhibition. | Astrocytoma, bladder, breast, cervix, colon, epidermoid, glioblastoma, leukemia, lung, lymphoma, melanoma, myeloma, osteosarcoma, ovary, pancreas, kidney and thyroid [97,98,173–182] | I, II |
| Bub1 | SAC signaling and chromosome alignment. | BAY-320; BAY-524 | minor effects on mitotic progression except for a short delay of anaphase onset. | Cervix [112]. | – |
| BubR1 | SAC signaling and chromosome alignment. | Pharicin A | Impaired BubR1 autophosphorylation and SAC function; mitotic arrest and inhibition of proliferation. | Leukemia, osteosarcoma and cervix [183]. | – |
| Mad2 | SAC signaling. | M2I-1 | Weakened SAC response | Cervix [118]. | – |
| Bcl-2<br>Bcl-xL<br>Bcl-w | Antiapoptotic. | ABT-737; Navitoclax (ABT-263); GX15-070; Obatoclax (GX15-070); AT-101 R-()-gossypol; Apogossypol (ApoG2); TW-37; Sabutoclax (BI—97C1); Venetoclax (ABT-199, GDC-0199); HA14-1; BH3I-1; A-1155463; A-1331852; WEHI-539. | Anti-proliferative activity; apoptosis; autophagy; tumor growth inhibition and regression. | Myeloma, leukemia, lymphoma, nasopharynx, colorectal, head and neck, melanoma, glioblastoma, non-small and small cell lung, pancreas, gastric, prostate, breast, cervix and ovary [184–186] | I, II, III |
| Mcl-1 | Antiapoptotic. | MIM1 (Mcl1 inhibitor molecule 1); Compound 6 h (Inhibitor 3-(4-aminophenylthio)-8-oxo-8H-acenaphtho [1,2-b]pyrrole-9-carbonitrile); Maritoclax; UMI-77; A-1210477; S63845; AMG 176; AZD5991; MIK665 (S64315); TW-37; Gossypol; Obatoclax; SC-2001; ApoG2; Sabutoclax; (−)BI97D6. | Apoptosis, G2/M arrest; tumor regression. | Pancreas, prostate, breast, liver, lung, thyroid, myeloma, renal, colon, pharynx, oral cancer, melanoma, lymphoma, leukemia, cholangiocarcinoma, hematological cancer-derived cells, hepatocellular, and myolodysplastic syndrome [187,188]. | I, II, III |
| APC/C | Ubiquitination and degradation of multiple cell-cycle regulators. | Pro-TAME (Tosyl-L-Arginine Methyl Ester); Apcin. | Strong mitotic arrest and apoptosis; inhibition of tumor cell growth and invasion. | Cervical [138] and osteosarcoma [136,189]. | – |
| Proteasome | Degradation of ubiquitinated proteins. | Bortezomib (PS-341); MG-132; Carfilzomib (PR-171); Ixazomib Citrate (MLN9708); Ixazomib (MLN2238); ONX-0914 (PR-957); Oprozomib (ONX 0912); Delanzomib (CEP- | – | Non-small cell lung cancer, colorectal, urothelial, prostate, kidney, breast and multiple myeloma and hematologic malignancies [190]. | I, II, III |

(*continued on next page*)

**Table 1** (*continued*)

| Target | Function | Inhibitors | Inhibitory activity | Cancer type | Clinical trials[a] |
|---|---|---|---|---|---|
| | | 18770); Celastrol; Marizomib (NPI-0052); Epoxomicin; VR23. | | | |

[a] Data collected from clinicaltrials.gov.

resistant ovarian cancer cells to cisplatin and sensitizes p53-deficient cancer cells to radiotherapy [88,89]. Thus, Aurora inhibition in combination with conventional modality could provide a promising therapeutic strategy to kill cancer cells.

## 5. Targeting components of SAC activation

The SAC is essential for cell survival as its inhibition is lethal due to massive chromosome missegregation. Therefore, SAC constitutes a valid strategy to kill cancer cells by inducing lethal instability [1,90,91]. Cancer cells should be more sensitive to this strategy as they already display certain degrees of chromosome instability [92]. Potential targets include the core SAC signaling components Mad1, Mad2, Bub3, Bub1, BubR1, Aurora B, and Mps1. Inhibition of any of these SAC components overrides the SAC in cells arrested in mitosis by MTAs, leading to aberrant mitosis and subsequent cell death (Fig. 3A) [93–96]. For some of these putative targets, namely the Aurora kinases (see above) and Mps1, many small molecules have been developed and tested in different stages of pre-clinical and clinical studies (Table 1) [85,97–99].

### 5.1. Mps1

Mps1 is a dual-specificity kinase required for the activation of SAC through recruitment of SAC components to unattached kinetochores and subsequent MCC formation [100]. Other important functions of Mps1 include mitotic progression, centrosome duplication, chromosome alignment, error correction of kinetochore-microtubule attachment [101]. Mps1 is overexpressed in multiple tumors and is associated with poor prognosis [102,103]. Mps1 inhibition induces premature mitotic exit and subsequent cell death due to massive aneuploidization [97,98]. Together, these facts make Mps1 an attractive target for cancer therapy and prompted the production of some Mps1 inhibitors that recently entered phase I clinical trials [93] (ClinicalTrials.gov Identifiers: NCT03328494, NCT02366949, and NCT02138812). Of note, Mps1 inhibition sensitizes cancer cells to low doses of taxol [91]. Such synergistic activity was reported to be due to increased cell division errors induced by Mps1 inhibitors.

### 5.2. Bubs

The Bub proteins include the Bub1 and BubR1 paralogous serine/threonine kinases, and their partner Bub3. All three Bubs are required for kinetochore-microtubule attachment and SAC signaling, being BubR1 and Bub3 part of the MCC [104]. As with the other SAC genes, these Bub genes are frequently deregulated in cancer, and are associated with poor clinical prognosis [105]. Mice overexpressing Bub1 or with partial loss of BubR1 or Bub3 develop tumors likely due to chromosome segregation defects [106–109]. Reducing BubR1 levels sensitizes tumor cells to low doses of taxol through enhancing the amount and severity of chromosome segregation errors [91]. Depletion of Bub1 reduces cancer stem cell potential of the MDA-MB-231 breast cancer cell line, resulting in inhibited formation of xenografts, suggesting that Bub1 could be a target for anti-breast cancer stem cell therapies [110]. Recently, miR-490–5p was reported to regulate the classical TGF-β/SMAD signaling pathway by targeting Bub1 [111]. By attenuating Bub1 expression, miR-490–5p inhibits cell proliferation and invasion. Two small molecule inhibitors of Bub1, BAY-320 and BAY-524, have recently been developed and found to sensitize cancer cells to clinically relevant low doses of paclitaxel, with only marginal impact on non-tumor cells, suggesting a potential therapeutic window [112]. Yet, to date preclinical and clinical trials are lacking for these agents.

### 5.3. Mads

Mad1 and Mad2 are SAC proteins that are crucial for MCC

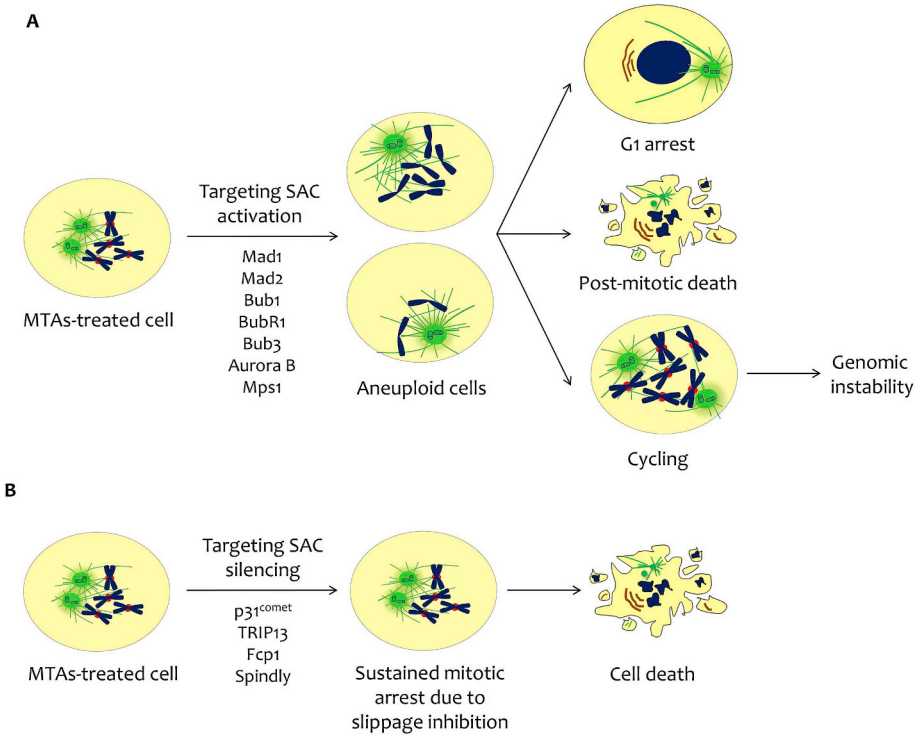


**Fig. 3. Effect of SAC activation or silencing on cell fate of an MTA-targeted cell. (A)** Targeting core SAC components (Mad1, Mad2, Bub1, BubR1, Bub3, Aurora B, Mps1) induces aberrant mitosis with massive chromosome mis-segregation, generating cells with increased chromosome instability (aneuploid cells) that may arrest in interphase (G1 arrest), undergo post-mitotic death or continue cycling, leading to genomic instability. **(B)** Targeting SAC silencing components (p31comet, TRIP13, Fcp1, spindly) delays mitotic slippage and increases susceptibility to apoptosis, thereby tipping the balance in favor of death.

generation and amplification [113]. Mice heterozygous for Mad2 develop spontaneous tumors after long latencies, while mice lacking Mad2 exhibit massive chromosome missegregation and apoptosis [114,115]. Recently, we showed that reduction of Mad2 levels overcomes cisplatin resistance *in vitro* and in a human non-small cell lung cancer xenograft model [116]. High levels of the novel Mad2-targeting miR-493–3p are associated with paclitaxel resistance and reduced survival of ovarian and breast cancer patients [117]. Mad2 Inhibitor-1 (M2I-1) is the first small molecule inhibitor targeting the binding of Mad2 to Cdc20 [118]. M2I-1 weakens the SAC response of cancer cells treated with paclitaxel, but its potential therapeutic relevance has yet to be described.

Despite the promising anti-cancer activity achieved by targeting SAC activation in preclinical studies, those agents that reached clinical trials have yielded disappointing clinical results [93]. This may be due to the fact that complete inactivation of SAC is difficult to achieve *in vivo*, which might favor mitotic slippage with chromosome aberrations that fuel chromosome instability and MTA resistance in cells surviving to post-mitotic death. Indeed, depletion of proteins that inhibit SAC was reported to be associated with MTA resistance [119].

## 6. Tipping the balance in favor of death

Mitotic slippage is one of the main mechanisms of resistance against antimitotic drugs [30,34]. Some slipped multiploid cell survivors might re-enter the cell-cycle and acquire increased instability and malignancy [8,120]. Slippage occurs when the $APC^{Cdc20}$-mediated background degradation of Cyclin B, under an active SAC, exceeds a certain threshold before cell death is initiated [30]. Considering the two competitive networks model by Taylor et al., theoretically, it should be possible to have a control over cell fate and influence the effectiveness of antimitotics if death signal accumulation is accelerated and/or mitotic slippage is retarded (Fig. 3) [33,34]. Strategies to accelerate apoptosis would lead to cell death before mitotic slippage occurs, while strategies to delay mitotic slippage would increase the time cells spend in mitosis, thereby allowing more time for apoptosis signals to accumulate. Both strategies, individually or in combination, should increase sensitivity of cancer cells to antimitotics by shifting cell fates to death, which may be relevant to kill apoptosis-resistant, slippage-prone or SAC-defective cancer cells. This reasoning stimulated our recent work and those of other research groups in which key components of SAC silencing were targeted in order to increase the duration of mitosis and promote cell death (Table 1) [121–123].

### 6.1. Accelerating apoptosis

Traditional MTAs and mitotic blockers of the second-generation drugs act by chronically activating SAC leading to prolonged mitotic arrest and, eventually, to cell death via activation of the intrinsic pathway of apoptosis [40]. The latter is under the regulation of the Bcl-2 family, which comprises the proapoptotic BH3-only members Bim, Bid, Bad and Noxa, and the antiapoptotic members Bcl2, Bcl-xL and Mcl-1 [40,124]. In the presence of death signals, the proapoptotic BH3-only proteins inhibit the antiapoptotic proteins to drive the intrinsic pathway of apoptosis.

The two competing networks model by Taylor et al. had paved the way for studies that targeted apoptosis components in order to evaluate their potential in antimitotic chemotherapy [33,34,125]. The therapeutic relevance of this approach has proven to be efficient in *vitro* and human tumor xenograft models by using BH3 mimetics [126–128]. For instance, ABT-263/Navitoclax, a BH3 mimetic that inhibits the prosurvivals Bcl-2, Bcl-xL and Bcl-w, precipitates apoptosis in cancer cells arrested in mitosis by MTAs or Eg5 inhibitors [129]. Of note, the BH3 mimetic ABT-737 triggered extensive cell death in otherwise slippage-prone cancer cells treated with MTAs, underlying the prosurvival proteins dependence of cancer cells during mitotic arrest [130]. These results were recapitulated by RNAi-mediated depletion of prosurvival proteins such as Bcl-xL, which, from an antimitotic chemotherapy perspective, highlights the potential of the approach to reduce variation in death response between different cancers [34].

### 6.2. Delaying slippage

Slippage can be delayed by slowing cyclin B proteolysis, which can be achieved by inhibiting the APC/C-Cdc20-proteasome axis, or by

preventing SAC silencing.

### 6.3. Targeting APC/C-Cdc20-Proteasome

Exit from mitosis is mainly governed by the APC/C, which targets crucial mitotic regulators such as cyclin B and securin for ubiquitylation to promote anaphase onset [131]. Using single-cell approaches, RNAi-mediated knockdown of Cdc20 slowed cyclin B proteolysis, blocking mitotic exit, thereby allowing more time for death initiation [132]. These observations were recapitulated in tumor cells overexpressing a non-degradable mutant of cyclin B [132]. Complete metaphase arrest followed by massive apoptosis was observed in mouse models using genetic ablation of Cdc20, and the approach proved to be more efficient in cell killing than classical MTAs and Plk1 or Eg5 inhibitors [95,133–135]. Some inhibitors have been identified, but are not specific as they only indirectly affect Cdc20 levels, except for apcin which binds Cdc20 and prevents ubiquitylation of APC/C substrates [136,137]. Yet, apcin did not effectively block mitotic exit. The discovery of the inhibitor TAME (tosyl-L-arginine methyl ester), which binds APC/C and suppresses its activation by Cdc20, revealed that APC/C inhibition efficiently arrest cells in mitosis followed by apoptosis [138]. TAME treatment enhances cell death in combination with MTAs or the alkylating agent melphalan [136,138,139]. The ability of apcin to block mitotic exit is synergistically amplified when combined with TAME, suggesting that simultaneous disruption of multiple protein-protein interactions is an effective approach for maximal APC/C inactivation [137]. Another interesting antitumor target is the proteasome for which a number of inhibitors have been identified, and some, such as Oprozomib, Delanzomib, and Marizomib, reached clinical trials [140–142]. Bortezomib (Velcade) became the first therapeutic proteasome inhibitor approved for multiple myeloma treatment, with a response rate of 50%–90% in patients with relapsed multiple myeloma [143]. Subsequently, other proteasome inhibitors such as carfilzomib (Kyprolis) and ixazomib (Ninlaro) were approved for the treatment of myeloma [140]. However, cell toxicity and development of resistance have been reported, stressing the need to develop the next generation of proteasome inhibitors [140] [144]. Altogether, these observations reveal that targeting APC/C-Cdc20-Proteasome axis to slow cyclin B degradation could be an effective way to fight cancer.

### 6.4. Targeting SAC silencing

Other interesting targets to slow cyclin B degradation are the components involved in SAC silencing. This motivated studies that have shown that preventing SAC silencing increases the duration of mitosis and promotes cell death (Fig. 3B).

RNAi-mediated downregulation of $p31^{comet}$ was reported to induce a two-fold increase in the duration of mitosis [123]. Interestingly, cells depleted of $p31^{comet}$ required a 10-fold lower concentration of MTAs to trigger mitotic arrest and subsequent mitotic cell death than $p31^{comet}$-efficient cells, indicating enhancement of sensitivity towards spindle poisons, including in cells that are resistant to spindle disruption [123]. Conversely, overexpression of $p31^{comet}$ overrides hyperactivation of the SAC caused by MTAs leading to resistance to microtubule poisons [145–148]. The expression of $p31^{comet}$ is upregulated in cancer, and a balanced expression of $p31^{comet}$:Mad2 ratio is required for cellular proliferation and correlates with mitotic slippage and MTA-mediated cytotoxicity in cancer cell lines [149]. This highlights the relevance of developing small molecules against the $p31^{comet}$-Mad2 interaction [123]. Recently, inhibition of TRIP13 was reported to abolishes $p31^{comet}$-mediated SAC silencing, underlying its potential as a drug target to delay mitotic slippage [150].

The Fcp1 phosphatase dephosphorylates the kinase Wee-1, which in turn dampens Cdk1 activation, and Cdc20 and USP44 (a deubiquitinating peptidase that opposes APC/C action) to promote APC/C-dependent cyclin B degradation and subsequent mitotic exit [122,151,152]. Depletion of Fcp1 by siRNAs trapped cancer cells in mitosis in the presence of MTAs. Treated cells had decreased levels of the anti-apoptotic Mcl-1 and underwent massive apoptosis [153]. Thus delaying slippage in MTA-treated by targeting the Fcp1-Wee1-Cdk1 axis seems a valid strategy to increase MTAs therapeutic efficacy [153].

Spindly is a transient kinetochore protein with a role in chromosome attachment and in dynein-mediated SAC silencing [154]. We recently explored this spindly dual role as a rationale to trap cancer cells in mitosis [121]. Inhibition of spindly trapped cells in mitosis and dramatically sensitized cancer cells to clinically relevant doses of MTAs by exacerbating post-mitotic death, pointing out spindly as a potential drug target candidate to delay mitotic slippage [121].

Overall, targeting SAC slippage seems to be promising, and these *in vitro* results need to be verified in preclinical and clinical studies.

## 7. Co-targeting mitosis and apoptosis

The activity of antimitotics could be increased by combining them with apoptosis inducer drugs. This is particularly relevant as many cancers exhibit resistance to MTAs, deregulated SAC, or deregulated apoptosis that render them resistant to death [155,156]. Results from a number of studies suggest that the combination would improve cancer therapy (Table 2). For example, inhibition of Bcl-xL, whether by RNAi or ABT-737, massively shifted the paclitaxel response of breast cancer cells to mitotic cell death [130]. Navitoclax/ABT-263 enhances the lethality triggered by paclitaxel and K5I (an inhibitor of kinesin-5), across a panel of epithelial cancer lines [129]. Synergy in killing solid tumor cancer cells was reported for the Bcl-xL inhibition-docetaxel combination, either *in vitro* or in tumor xenografts [157]. Interestingly, most patients whose ovarian tumor tissue expresses high Bcl-xL levels are less sensitive to taxane treatment, supporting the idea that the addition of Bcl-xL inhibitors could improve taxane-based therapy [158].

Works from Taylor's group indicate that exploring apoptosis inducer drugs may be more promising with mitotic blockers than mitotic drivers. They showed that treatment with WEHI-539, a potent and selective Bcl-xL inhibitor, sensitized cells to MTAs as well as to second-generation mitotic blockers such as inhibitors of Eg5, CENP-E and Plk1 [41]. In this case, sensitization was largely by enhancing postmitotic death (PMD). The combination of WEHI-539 with mitotic drivers, such as inhibitors of Aurora B and Mps1, showed only minor impact unless the prosurvival Mcl-1 was also inhibited. Indeed, PMD was enhanced in Mcl-1-deficient DLD-1 cells treated with WEHI-539 plus ZM447439 (an Aurora B inhibitor), suggesting that Mcl-1 levels could serve to stratify patients that would benefit from the combination therapy [41]. Also, combining apoptosis inducer drugs with SAC silencing inhibitors deserves to be explored. For instance, BH3-only mimetics in combination with inhibitors of SAC silencing components should, potentially, shift the fate of mitosis-arrested cells in favor of death. Yet, inhibitors that target SAC silencing proteins need to be developed.

It is noteworthy that the aforementioned mitosis-targeted anticancer strategies would affect all dividing cells and would, thus, also be expected to be cytotoxic to non-tumor cells. Therefore, therapeutic strategies that preferentially affect tumor cells over normal cells are needed in order to improve the therapeutic window of antimitotic therapies. For instance, developing drugs that specifically and efficiently target cancer cells, but not the normal cells, should reduce toxicity. Also, formulation in nanoparticles to specifically and efficiently deliver antimitotics to cancer cells should attenuate the side effects and increase the efficacy of the drugs [159]. Other strategies could be orientated to prevent normal proliferating cells from entering into mitosis to promote selective killing of cancer cells [160].

## 8. Conclusions

Our understanding of the molecular regulation and control of mitosis have paved the way for the development of elegant strategies to

**Table 2**
Targeting mitotic components and apoptotic modulators in combinatorial therapies: preclinical and clinical studies.

| Target | Inhibitors/Combination | Inhibitory Activity | Cancer types | Clinical trials[a] |
|---|---|---|---|---|
| Eg5 | **Ispinesib (SB-715992)**<br>Co-treatment: paclitaxel, trastuzumab, iapatinib, doxorubicin, ixabepilone, capecitabine, docetaxel, carboplatin filanesib (ARRY-520), carfilzomib, pomalidomide, dexamethasone, filgrastim | Enhanced antitumor activity. | Breast [191] and multiple myeloma. | I, II |
| | **Litronesib (LY2523355)**<br>Co-treatment: pegfilgrastim, abepilone, filgrastim | – | Advanced solid tumors. | I, II |
| | **HR22C16-A1**<br>Co-treatment: paclitaxel | Mitotic arrest and cell death (via the intrinsic apoptotic pathway). | Ovary [46]. | – |
| | **STLC**<br>Co-treatment: paclitaxel | Long metaphasic arrest. | Cervix [192]. | – |
| | **S(MeO)TLC**<br>Co-treatment: gentamicin | Suppressed tumor growth. | Bladder [193]. | – |
| Plk1 | **B6727; BI2536; GW843682X; GSK461364; LFM-A13; ON 01910.Na**<br>Co-treatment: cisplatin, methotrexate, doxorubicin, radiation, paclitaxel, gemcitabine, pemetrexed, cytarabine, idamycin (idarubicin), vincristine, azacitidine, decitabine, daunorubicin, mitoxantrone, belinostat. | Synergistic anti-tumor effects. | Breast, colon, lung, pancreas, prostate, oral and lung [194–201], bladder [202], rhabdomyosarcoma [203] osteosarcoma [204,205] and leukemia. | I, II, III |
| | **PCM-075**<br>Co-treatment: abiraterone, cytarabine or decitabine | Antitumor synergy. | Prostate, breast, ovary [206] and leukemia. | I, II |
| Aurora A<br>Aurora B<br>Aurora C | **ENMD-2076**<br>Co-treatment: cisplatin, SN38 | Synergistic effects by enhanced apoptosis and cell cycle arrest at the G2/M phase. | Ovary [207]. | – |
| | **TC-A2317**<br>Co-treatment: paclitaxel | Enhanced mitotic catastrophe. | Lung [208]. | – |
| | **MLN8237/Alisertib**<br>Co-treatment: paclitaxel, gemcitabine, docetaxel, cisplatin, nilotinib, vorinostat, vincristine, pralatrexate, romidepsin, rituximab, bortezomib, cytarabine, idarubicin, itraconazole, esomeprazole, MLN1117, TAK-659, pazopanib, TAK-228, brentuximab vedotin, MLN2480, MLN0128, fluorouracil, abiraterone acetate, prednisone, irinotecan hydrochloride, methotrexate, TAK-733, fulvestrant | Synergistic/additive antitumor effects, enhanced apoptosis and growth inhibition. | Bladder [209], colorectal [210,211], triple-negative breast [212], lymphoma [213,214], pediatric leukemia medulloblastoma, neuroblastoma [215,216], aggressive B-cell non-Hodgkin lymphoma [212], gastrointestinal [217]esophageal [218], multiple myeloma [219], leukemia [220], prostate, oral cavity, pharynx, genital organs and kidney. | I, II, III |
| | **MLN8054**<br>Co-treatment: radiation therapy | Sensitization radiation therapy. | Prostate [216]. | – |
| | **CYC3**<br>Co-treatment: paclitaxel | Synergistic/additive antitumor effects, enhanced mitotic arrest. | Pancreas [221]. | – |
| | **MK-5108**<br>Co-treatment: docetaxel, cisplatin | Enhanced docetaxel antitumor efficacy. | Ovary and cervix [222] and non-small cell lung [223]. | I |
| | **SU6668**<br>Co-treatment: paclitaxel | Tumor inhibition. | Ovary [224] and endometrial [225]. | – |
| | **AMG 900**<br>Co-treatment: paclitaxel, ixabepilone, docetaxel | Potentiated antiproliferative effects of paclitaxel and ixabepilone at low nanomolar concentrations. | Triple-negative breast [226] and adrenocortical [227]. | – |
| | **SNS-314**<br>Co-treatment: carboplatin, gemcitabine, 5-Fluoracil, daunomycin, SN-38, gemcitabine, docetaxel and vincristine | Synergistic/additive antiproliferative activity. | Colon [228,229], lung, prostate, ovary, breast, cervix, pancreas and melanoma [228]. | – |
| | **VE-465/MK-0457**<br>Co-treatment: paclitaxel, vincristine, carboplatin, cisplatin, docetaxel, ABT-737, dasatinib | Synergistic antiproliferative activity with enhanced apoptosis. | Ovary [230–232], leukemia [231–233], liver [234] and breast [235]. | I |
| | **AT-9283**<br>Co-treatment: paclitaxel | Enhanced antiproliferative activity. | Leukemia, multiple myeloma and colorectal [236]. | – |

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**Table 2** (*continued*)

| Target | Inhibitors/Combination | Inhibitory Activity | Cancer types | Clinical trials[a] |
|---|---|---|---|---|
| | **PHA-680632**<br>Co-treatment: ionizing radiation | Enhanced apoptosis, micronuclei, and delayed tumor growth. | Colorectal [88]. | – |
| | **ZM447439**<br>Co-treatment: streptozocin, cisplatin, temozolomide | Enhanced antiproliferative effects, enhanced S-phase arrest and apoptosis. | Cervix [237], glioblastoma [238] and ovary [89]. | – |
| | **Barasertib (AZD1152)**<br>Co-treatment: radiation, platinum, vincristine, daunorubicin, dexamethasone, cisplatin | Enhanced cytotoxic effects of ionizing radiation and chemotherapeutic drugs. | Colon [239], non-small lung [240], prostate [241,242], ovary [243], multiple myeloma [244], leukemia [245,246] and colorectal [239]. | – |
| Mps1 | **BAY 1161909 and BAY 1217389**<br>Co-treatment: paclitaxel | Reduced paclitaxel-induced mitotic arrest by weakening the SAC, even in acquired or intrinsic paclitaxel resistance. | Osteosarcoma and cervix [247]. | I |
| | **Cpd-5**<br>Co-treatment: docetaxel | Enhanced cell death. | Pancreas and breast [248]. | - |
| | **Mps-BAY1**<br>**Mps-BAY2a**<br>**Mps-BAY2b**<br>**NMS-P715**<br>**MPS1-IN-3**<br>Co-treatment: paclitaxel | Synergistic antineoplastic effects. | Colorectal [97,98], cervix and osteosarcoma [97] and glioblastoma [249]. | - |
| | **S81694**<br>Co-treatment: paclitaxel | – | Breast. | II |
| | **BOS172722**<br>Co-treatment: paclitaxel | – | Advanced nonhematologic malignancies. | I |
| Bub1 | **BAY-320 and BAY-324**<br>Co-treatment: paclitaxel | Sensitization to low doses of paclitaxel. | Cervix [112]. | - |
| Mad2 | **M2I-1**<br>Co-treatment: paclitaxel | Reduces time paclitaxel-treated cells spend in mitosis. | Cervix [118]. | - |
| Proteasome | **Bortezomib**<br>Co-treatment: paclitaxel, carboplatin, doxorubicin, cisplatin, 5-fluorouracil, SN-38, LDE225, b-AP15, gefitinib, gemcitabine, vinorelbine, temozolomide, adeno-associated virus type 2 (rAAV-2)-mediated p53 gene transfer, docetaxel, quinoline-sulfonyl hybrid proteasome inhibitor VR23, cetuximab, radiation | Synergistic antiproliferative activity. | Gastric [250,251], ovary [252,253], cervix and small cell lung [254,255], bladder [256], non-small cell lung [255,257,258], head and neck [259,260], glioblastoma [261], pancreas [262], myeloma [263], esophageal, colorectal, urothelial, prostate, kidney, primary peritoneal and fallopian tube. | I, II, III |
| | **MLN9708**<br>Co-treatment: carboplatin, gemcitabine, doxorubicin, vorinostat, fulvestrant, erlotinib, dexamethasone, cytarabine | – | Breast [264], neuroblastoma [265], bladder, kidney, multiple myeloma and non-Hodgkin lymphoma. | I, II |
| | **MG132**<br>Co-treatment: paclitaxel, camptothecin, doxorubicin, cisplatin | Enhanced antiproliferative effects. | Esophageal [266,267] and ovary [266], cervix [268], osteosarcoma [269] and breast [270]. | - |
| | **Proteasome inhibitor 1 (PS1)**<br>Co-treatment: paclitaxel, cisplatin | A synergistic cytotoxic effect. | Lung [271] and leukemia [272]. | - |
| | **MLN2238**<br>Co-treatment: gemcitabine, doxorubicin, paclitaxel | Enhanced antitumor activity. | Primary B-cell lymphoma [273]. | - |
| | **Lactacystin**<br>Co-treatment: cisplatin | Enhanced cytotoxicity. | Cervix [274]. | - |
| | **YSY01A**<br>Co-treatment: cisplatin | Enhanced cytotoxicity of cisplatin. | Ovary [275]. | - |
| | **ALLnL**<br>Co-treatment: cisplatin | Sensitization to cisplatin in an additive manner. | Ovary [276]. | - |
| | **NPI-0052**<br>Co-treatment: cisplatin, vorinostat, dexamethasone, temozolomide, pomalidomide, bevacizumab | Sensitization to cisplatin. | Prostate [277], non-small cell lung, pancreas, melanoma, lymphoma, multiple myeloma, glioblastoma, glioma | I, II, III |
| APC/C | **proTAME**<br>Co-treatment: paclitaxel, Aurora A inhibitor (MLN8054), hesperadin, hyperthermia (HT), Top2α poisons (Etoposide), apicin and melphalan | Enhanced cell death. | Larynx and ductal breast epithelial [278], cervix [138], lung and breast [279] and multiple myeloma [138,139]. | - |

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**Table 2** (*continued*)

| Target | Inhibitors/Combination | Inhibitory Activity | Cancer types | Clinical trials[a] |
|---|---|---|---|---|
| Cyclin B | **cyclin B1/WT-1/CEF (antigen)-loaded DC vaccination**<br>Co-treatment: standard preoperative chemotherapy (doxorubicin/cyclophosphamide/paclitaxel/carboplatin) | – | Breast. | I |
| Bcl-2 | **HA14–1**<br>Co-treatment:<br>Etoposide, epothilone B, y-irradiation, isoflavonoids, paclitaxel and cisplatin | Sensitization to induction of apoptosis. | Malignant glioma [280], malignant neuroblastoma [280,281], breast [282,283] and pancreas [284]. | - |
| | **SV30 (HA14–1 analogue)**<br>Co-treatment: paclitaxel, etoposide or beam radiation | SV30 alone or in combination with paclitaxel, etoposide or beam radiation trigger cell death in a similar fashion to HA14-1. | Malignant rat-glioma [281]. | - |
| | **ApoG2**<br>Co-treatment: cisplatin, gentamicin | Enhanced the antitumor effect. | Nasopharyngeal [285] and pancreas [286]. | - |
| | **S1**<br>Co-treatment: paclitaxel | Synergistic antiproliferative activity. | Leukemia [287]. | – |
| Bcl-2<br>Mcl-1 | **(−)-Gossypol**<br>Co-treatment: paclitaxel, carboplatin, gemcitabine, etoposide, doxorubicin, vincristine, cisplatin, vinorelbine, radiation, temozolomide, erlotinib, bicalutamide, LHRH agent, prednisone, docetaxel, topotecan, dexamethasone/lenalidomide, rituximab, daunorubicin, cytarabine | Enhanced cytotoxicity. | Breast [288,289], bladder [290,291], prostate [292], ovary [293,294], non-small cell lung [295], non-Hodgkin's lymphoma [296,297], head and neck [298], glioblastoma [299–301], multiple myeloma [302,303], Waldenström macroglobulinaemia [303], leukemia [304], lymphoma, small cell lung, laryngeal and esophageal | I, II |
| Bcl-2<br>Bcl-XL<br>Bcl-w | **Navitoclax (ABT-263)**<br>Co-treatment: docetaxel, paclitaxel, gentamicin, erlotinib, doxorubicin, vincristine, etoposide, camptotecin, abiraterone, hydroxychloroquine, cisplatin, irinotecan, osimertinib, vistusertib, trametinib, sorafenib, rifampin, ketoconazole, venetoclax | Enhanced antitumor activity. | Prostate [305–307], cervix [129,307], lung [129,306,308,309] ovary [129,306].<br>, hepatocellular [310], leukemia and lymphoma. | I, II |
| | **ABT-737**<br>Co-treatment: cisplatin, etoposide, vinblastine irinotecan, paclitaxel, carboplatin, docetaxel, doxorubicin or radiation | Additive cytotoxic effects. Restored sensitivity to paclitaxel in BCL-2-overexpressing cells. Efficient cell death. | Hepatoblastoma [288], renal [311], breast [130,158,312], ovary [313], small-cell lung [126], prostate [305], lymphoma and small-cell lung [126]. | I |
| Bcl-w | **Berberin**<br>Co-treatment: cisplatin | Enhanced cytotoxicity of cisplatin, caspase-dependent apoptosis. | Gastric [314]. | – |
| Bcl-XL | **A-385358**<br>Co-treatment: paclitaxel, etoposide, cisplatin and doxorubicin | Enhanced cytotoxic activity and potentiated activity of paclitaxel. | Lung [315]. | - |
| Mcl1 | **Tumor-specific replication-competent oncolytic adenovirus OBP-301 (telomelysin)**<br>Co-treatment: cisplatin, doxorubicin | Sensitization to cisplatin and doxorubicin. | Osteosarcoma [316]. | - |
| | **Obatoclax**<br>Co-treatment: cisplatin, docetaxel, carboplatin/etoposide, topotecan hydrochloride, dexrazoxane, doxorubicin, bortezomib, bendamustine, rituximab, fludarabine, temozolomide | Sensitization to cisplatin. | Lung [317], leukemia, lymphoma, multiple myeloma, melanoma | I, II |
| | **TW-37**<br>Co-treatment: cisplatin or 5-fluorouracil | Synergistic antineoplastic effect. | Nasopharyngeal [318]. | - |
| | **Imperatorin**<br>Co-treatment: cisplatin | Enhanced cytotoxicity of cisplatin. | Hepatocellular [319]. | - |
| | **Sabutoclax**<br>Co-treatment: docetaxel | Sensitization to docetaxel. | Prostate [320]. | - |
| | **CG200745**<br>Co-treatment: docetaxel, gemcitabine, erlotinib | Reduced tumor size and synergistic antitumor effects | Prostate [321] and pancreas [322] | I, II |

[a] Data collected from clinicaltrials.gov.

kill cancer cells, in the hope of circumventing the drawbacks associated with MTAs. Several second-generation antimitotics were identified and shown to exert anti-tumor effects in cancer cell lines and in mouse models. Unfortunately, these inhibitors failed in clinic when used in monotherapy. Hopefully, the promising results of their combination with MTAs will constitute a more rewarding strategy (Table 2). As lower doses of the inhibitors are required in a combinatorial therapy, this strategy might provide therapeutic benefits by overcoming problems of resistance and side effects.

Inhibiting SAC silencing seems a reasonable and attractive strategy to identify additional targets that promote cancer cell death. Some key SAC components, such as p31$^{comet}$ and spindly, represent promising targets. However, they are sometimes classified as “undruggable” because they are non-enzymes. These challenging targets are involved in protein-protein interactions, whose targeting has become an increasingly attractive goal for drug discovery because of their role in a wide range of critical cellular functions [161]. In this sense, the recent identification of Mad2 Inhibitor-1 (M2I-1) that disrupts the binding of Mad2 to Cdc20 is very encouraging [118].

The development of BH3-only mimetics opened the door to combinatorial therapy, expected to inevitably force cells arrested in mitosis to undergo apoptosis instead of slippage. We hope that the promising results from preclinical studies will be translated into successful clinical trials.

Nowadays, the great challenge is to develop strategies that target anticancer drugs specifically to cancer cells, while sparing normal cells, to minimize undesired toxicity. We recently developed functionalized nanoparticles for specific delivery of siRNAs against Mad2 using an animal model of lung cancer, with encouraging results in terms of efficacy and toxicity [116,162]. We believe this is the right direction to proceed and will benefit from collaborative effort between researchers from different disciplines, namely cell biology, chemistry and pharmaceutical technologies.

## Conflicts of interest

The authors declare no conflict of interest.

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## References

[1] K.W. Wood, W.D. Cornwell, J.R. Jackson, Past and future of the mitotic spindle as an oncology target, Curr. Opin. Pharmacol. 1 (2001) 370–377.
[2] E.K. Rowinsky, R.C. Donehower, Paclitaxel (taxol), N. Engl. J. Med. 332 (1995) 1004–1014.
[3] P. Silva, J. Barbosa, A.V. Nascimento, J. Faria, R. Reis, H. Bousbaa, Monitoring the fidelity of mitotic chromosome segregation by the spindle assembly checkpoint, Cell Prolif 44 (2011) 391–400.
[4] C.L. Rieder, H. Maiato, Stuck in division or passing through: what happens when cells cannot satisfy the spindle assembly checkpoint, Dev. Cell 7 (2004) 637–651.
[5] M. Sullivan, D.O. Morgan, Finishing mitosis, one step at a time, Nat. Rev. Mol. Cell Biol. 8 (2007) 894–903.
[6] I.M. Cheeseman, The kinetochore, Cold Spring Harbor perspectives in biology 6 (2014) a015826.
[7] A.T. Saurin, G.J. Kops, Studying kinetochore kinases, Methods Mol. Biol. 1413 (2016) 333–347.
[8] B.A. Weaver, D.W. Cleveland, Decoding the links between mitosis, cancer, and chemotherapy: the mitotic checkpoint, adaptation, and cell death, Cancer Cell 8 (2005) 7–12.
[9] S.L. Thompson, S.F. Bakhoum, D.A. Compton, Mechanisms of chromosomal instability, Curr. Biol. 20 (2010) R285–R295.
[10] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.
[11] J. Kang, H. Yu, Kinase signaling in the spindle checkpoint, J. Biol. Chem. 284 (2009) 15359–15363.
[12] V. Sudakin, G.K. Chan, T.J. Yen, Checkpoint inhibition of the APC/C in HeLa cells is mediated by a complex of BUBR1, BUB3, CDC20, and MAD2, J. Cell Biol. 154 (2001) 925–936.
[13] E.R. Kramer, C. Gieffers, G. Holzl, M. Hengstschlager, J.M. Peters, Activation of the human anaphase-promoting complex by proteins of the CDC20/Fizzy family, Curr. Biol. 8 (1998) 1207–1210.
[14] J.D. McCurdy, J.S. McElroy, D.A. Kopsell, C.E. Sams, J.C. Sorochan, Effects of mesotrione on perennial ryegrass (Lolium perenne L.) carotenoid concentrations under varying environmental conditions, J. Agric. Food Chem. 56 (2008) 9133–9139.
[15] J.J. Skinner, S. Wood, J. Shorter, S.W. Englander, B.E. Black, The Mad2 partial unfolding model: regulating mitosis through Mad2 conformational switching, J. Cell Biol. 183 (2008) 761–768.
[16] X. Luo, H. Yu, Protein metamorphosis: the two-state behavior of Mad2, Structure 16 (2008) 1616–1625.
[17] S.K. Reddy, M. Rape, W.A. Margansky, M.W. Kirschner, Ubiquitination by the anaphase-promoting complex drives spindle checkpoint inactivation, Nature 446 (2007) 921–925.
[18] P.M. Silva, R.M. Reis, V.M. Bolanos-Garcia, C. Florindo, A.A. Tavares, H. Bousbaa, Dynein-dependent transport of spindle assembly checkpoint proteins off kinetochores toward spindle poles, FEBS Lett. 588 (2014) 3265–3273.
[19] B. Etemad, G.J. Kops, Attachment issues: kinetochore transformations and spindle checkpoint silencing, Curr. Opin. Cell Biol. 39 (2016) 101–108.
[20] B.J. Howell, B.F. McEwen, J.C. Canman, D.B. Hoffman, E.M. Farrar, C.L. Rieder, E.D. Salmon, Cytoplasmic dynein/dynactin drives kinetochore protein transport to the spindle poles and has a role in mitotic spindle checkpoint inactivation, J. Cell Biol. 155 (2001) 1159–1172.
[21] R. Gassmann, A.J. Holland, D. Varma, X. Wan, F. Civril, D.W. Cleveland, K. Oegema, E.D. Salmon, A. Desai, Removal of Spindly from microtubule-attached kinetochores controls spindle checkpoint silencing in human cells, Genes Dev. 24 (2010) 957–971.
[22] Y.W. Chan, L.L. Fava, A. Uldschmid, M.H. Schmitz, D.W. Gerlich, E.A. Nigg, A. Santamaria, Mitotic control of kinetochore-associated dynein and spindle orientation by human Spindly, J. Cell Biol. 185 (2009) 859–874.
[23] M. Barisic, B. Sohm, P. Mikolcevic, C. Wandke, V. Rauch, T. Ringer, M. Hess, G. Bonn, S. Geley, Spindly/CCDC99 is required for efficient chromosome congression and mitotic checkpoint regulation, Mol. Biol. Cell 21 (2010) 1968–1981.
[24] M. Yang, B. Li, D.R. Tomchick, M. Machius, J. Rizo, H. Yu, X. Luo, p31comet blocks Mad2 activation through structural mimicry, Cell 131 (2007) 744–755.
[25] Q. Ye, S.C. Rosenberg, A. Moeller, J.A. Speir, T.Y. Su, K.D. Corbett, TRIP13 is a protein-remodeling AAA+ ATPase that catalyzes MAD2 conformation switching, Elife 4 (2015).
[26] J. Mansfeld, P. Collin, M.O. Collins, J.S. Choudhary, J. Pines, APC15 drives the turnover of MCC-CDC20 to make the spindle assembly checkpoint responsive to kinetochore attachment, Nat. Cell Biol. 13 (2011) 1234–1243.
[27] K. Uzunova, B.T. Dye, H. Schutz, R. Ladurner, G. Petzold, Y. Toyoda, M.A. Jarvis, N.G. Brown, I. Poser, M. Novatchkova, K. Mechtler, A.A. Hyman, H. Stark, B.A. Schulman, J.M. Peters, APC15 mediates CDC20 autoubiquitylation by APC/C(MCC) and disassembly of the mitotic checkpoint complex, Nat. Struct. Mol. Biol. 19 (2012) 1116–1123.
[28] K.M. Foss, A.C. Robeson, S. Kornbluth, L. Zhang, Mitotic phosphatase activity is required for MCC maintenance during the spindle checkpoint, Cell Cycle 15 (2016) 225–233.
[29] W. Nijenhuis, G. Vallardi, A. Teixeira, G.J. Kops, A.T. Saurin, Negative feedback at kinetochores underlies a responsive spindle checkpoint signal, Nat. Cell Biol. 16 (2014) 1257–1264.
[30] D.A. Brito, C.L. Rieder, Mitotic checkpoint slippage in humans occurs via cyclin B destruction in the presence of an active checkpoint, Curr. Biol.: CB 16 (2006) 1194–1200.
[31] Y. Huang, Y. Yao, H.Z. Xu, Z.G. Wang, L. Lu, W. Dai, Defects in chromosome congression and mitotic progression in KIF18A-deficient cells are partly mediated through impaired functions of CENP-E, Cell Cycle 8 (2009) 2643–2649.
[32] M.E. Bekier, R. Fischbach, J. Lee, W.R. Taylor, Length of mitotic arrest induced by microtubule-stabilizing drugs determines cell death after mitotic exit, Mol. Canc. Therapeut. 8 (2009) 1646–1654.
[33] C.H. Topham, S.S. Taylor, Mitosis and apoptosis: how is the balance set? Curr. Opin. Cell Biol. 25 (2013) 780–785.
[34] K.E. Gascoigne, S.S. Taylor, Cancer cells display profound intra- and interline variation following prolonged exposure to antimitotic drugs, Cancer Cell 14 (2008) 111–122.
[35] M.A. Jordan, L. Wilson, Microtubules as a target for anticancer drugs, Nat. Rev. Canc. 4 (2004) 253–265.
[36] M. Schmidt, H. Bastians, Mitotic drug targets and the development of novel anti-

mitotic anticancer drugs, Drug Resist. Updates: Rev. Comment. Antimicrob. Anticanc. Chemother. 10 (2007) 162–181.
[37] M. Rebucci, C. Michiels, Molecular aspects of cancer cell resistance to chemotherapy, Biochem. Pharmacol. 85 (2013) 1219–1226.
[38] B. Mansoori, A. Mohammadi, S. Davudian, S. Shirjang, B. Baradaran, The different mechanisms of cancer drug resistance: a brief review, Adv. Pharmaceut. Bull. 7 (2017) 339–348.
[39] C. Dumontet, M.A. Jordan, Microtubule-binding agents: a dynamic field of cancer therapeutics, Nat. Rev. Drug Discov. 9 (2010) 790–803.
[40] N. Keen, S. Taylor, Mitotic drivers–inhibitors of the aurora B kinase, Cancer Metastasis Rev. 28 (2009) 185–195.
[41] A. Bennett, O. Sloss, C. Topham, L. Nelson, A. Tighe, S.S. Taylor, Inhibition of Bcl-xL sensitizes cells to mitotic blockers, but not mitotic drivers, Open Biol. 6 (2016).
[42] K.E. Sawin, K. LeGuellec, M. Philippe, T.J. Mitchison, Mitotic spindle organization by a plus-end-directed microtubule motor, Nature 359 (1992) 540–543.
[43] S. Zitouni, C. Nabais, S.C. Jana, A. Guerrero, M. Bettencourt-Dias, Polo-like kinases: structural variations lead to multiple functions, Nat. Rev. Mol. Cell Biol. 15 (2014) 433–452.
[44] B.A. Weaver, A.D. Silk, C. Montagna, P. Verdier-Pinard, D.W. Cleveland, Aneuploidy acts both oncogenically and as a tumor suppressor, Cancer Cell 11 (2007) 25–36.
[45] K.W. Wood, L. Lad, L. Luo, X. Qian, S.D. Knight, N. Nevins, K. Brejc, D. Sutton, A.G. Gilmartin, P.R. Chua, R. Desai, S.P. Schauer, D.E. McNulty, R.S. Annan, L.D. Belmont, C. Garcia, Y. Lee, M.A. Diamond, L.F. Faucette, M. Giardiniere, S. Zhang, C.M. Sun, J.D. Vidal, S. Lichtsteiner, W.D. Cornwell, J.D. Greshock, R.F. Wooster, J.T. Finer, R.A. Copeland, P.S. Huang, D.J. Morgans Jr., D. Dhanak, G. Bergnes, R. Sakowicz, J.R. Jackson, Antitumor activity of an allosteric inhibitor of centromere-associated protein-E, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 5839–5844.
[46] A.I. Marcus, U. Peters, S.L. Thomas, S. Garrett, A. Zelnak, T.M. Kapoor, P. Giannakakou, Mitotic kinesin inhibitors induce mitotic arrest and cell death in Taxol-resistant and -sensitive cancer cells, J. Biol. Chem. 280 (2005) 11569–11577.
[47] S. Brier, D. Lemaire, S. DeBonis, E. Forest, F. Kozielski, Molecular dissection of the inhibitor binding pocket of mitotic kinesin Eg5 reveals mutants that confer resistance to antimitotic agents, J. Mol. Biol. 360 (2006) 360–376.
[48] S. Tcherniuk, R. van Lis, F. Kozielski, D.A. Skoufias, Mutations in the human kinesin Eg5 that confer resistance to monastrol and S-trityl-L-cysteine in tumor derived cell lines, Biochem. Pharmacol. 79 (2010) 864–872.
[49] Y. Bu, Z. Yang, Q. Li, F. Song, Silencing of polo-like kinase (Plk) 1 via siRNA causes inhibition of growth and induction of apoptosis in human esophageal cancer cells, Oncology 74 (2008) 198–206.
[50] B. Spankuch, S. Heim, E. Kurunci-Csacsko, C. Lindenau, J. Yuan, M. Kaufmann, K. Strebhardt, Down-regulation of Polo-like kinase 1 elevates drug sensitivity of breast cancer cells in vitro and in vivo, Cancer Res. 66 (2006) 5836–5846.
[51] A. Blangy, H.A. Lane, P. d'Herin, M. Harper, M. Kress, E.A. Nigg, Phosphorylation by p34cdc2 regulates spindle association of human Eg5, a kinesin-related motor essential for bipolar spindle formation in vivo, Cell 83 (1995) 1159–1169.
[52] T.U. Mayer, T.M. Kapoor, S.J. Haggarty, R.W. King, S.L. Schreiber, T.J. Mitchison, Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen, Science 286 (1999) 971–974.
[53] H.A. Burris 3rd, S.F. Jones, D.D. Williams, S.J. Kathman, J.P. Hodge, L. Pandite, P.T. Ho, S.A. Boerner, P. Lorusso, A phase I study of ispinesib, a kinesin spindle protein inhibitor, administered weekly for three consecutive weeks of a 28-day cycle in patients with solid tumors, Invest. N. Drugs 29 (2011) 467–472.
[54] D. Huszar, M.E. Theoclitou, J. Skolnik, R. Herbst, Kinesin motor proteins as targets for cancer therapy, Cancer Metastasis Rev. 28 (2009) 197–208.
[55] S.P. Blagden, L.R. Molife, A. Seebaran, M. Payne, A.H.M. Reid, A.S. Protheroe, L.S. Vasist, D.D. Williams, C. Bowen, S.J. Kathman, J.P. Hodge, M.M. Dar, J.S. de Bono, M.R. Middleton, A phase I trial of ispinesib, a kinesin spindle protein inhibitor, with docetaxel in patients with advanced solid tumours, Br. J. Canc. 98 (2008) 894.
[56] H.B. El-Nassan, Advances in the discovery of kinesin spindle protein (Eg5) inhibitors as antitumor agents, Eur. J. Med. Chem. 62 (2013) 614–631.
[57] A. Hollebecque, E. Deutsch, C. Massard, C. Gomez-Roca, R. Bahleda, V. Ribrag, C. Bourgier, V. Lazar, L. Lacroix, A. Gazzah, A. Varga, T. de Baere, F. Beier, S. Kroesser, K. Trang, F.T. Zenke, M. Klevesath, J.C. Soria, A phase I, dose-escalation study of the Eg5-inhibitor EMD 534085 in patients with advanced solid tumors or lymphoma, Invest. N. Drugs 31 (2013) 1530–1538.
[58] P.M. LoRusso, P.H. Goncalves, L. Casetta, J.A. Carter, K. Litwiler, D. Roseberry, S. Rush, J. Schreiber, H.M. Simmons, M. Ptaszynski, E.A. Sausville, First-in-human phase 1 study of filanesib (ARRY-520), a kinesin spindle protein inhibitor, in patients with advanced solid tumors, Invest. N. Drugs 33 (2015) 440–449.
[59] S.M. Myers, I. Collins, Recent findings and future directions for interpolar mitotic kinesin inhibitors in cancer therapy, Future Med. Chem. 8 (2016) 463–489.
[60] B.F. McEwen, G.K. Chan, B. Zubrowski, M.S. Savoian, M.T. Sauer, T.J. Yen, CENP-E is essential for reliable bioriented spindle attachment, but chromosome alignment can be achieved via redundant mechanisms in mammalian cells, Mol. Biol. Cell 12 (2001) 2776–2789.
[61] Y. Mao, A. Abrieu, D.W. Cleveland, Activating and silencing the mitotic checkpoint through CENP-E-dependent activation/inactivation of BubR1, Cell 114 (2003) 87–98.
[62] A. Ohashi, M. Ohori, K. Iwai, T. Nambu, M. Miyamoto, T. Kawamoto, M. Okaniwa, A novel time-dependent CENP-E inhibitor with potent antitumor activity, PloS One 10 (2015) e0144675.
[63] X. Qian, A. McDonald, H.J. Zhou, N.D. Adams, C.A. Parrish, K.J. Duffy, D.M. Fitch, R. Tedesco, L.W. Ashcraft, B. Yao, H. Jiang, J.K. Huang, M.V. Marin, C.E. Aroyan, J. Wang, S. Ahmed, J.L. Burgess, A.M. Chaudhari, C.A. Donatelli, M.G. Darcy, L.H. Ridgers, K.A. Newlander, S.J. Schmidt, D. Chai, M. Colon, M.N. Zimmerman, L. Lad, R. Sakowicz, S. Schauer, L. Belmont, R. Baliga, D.W. Pierce, J.T. Finer, Z. Wang, B.P. Morgan, D.J. Morgans Jr., K.R. Auger, C.M. Sung, J.D. Carson, L. Luo, E.D. Hugger, R.A. Copeland, D. Sutton, J.D. Elliott, J.R. Jackson, K.W. Wood, D. Dhanak, G. Bergnes, S.D. Knight, Discovery of the first potent and selective inhibitor of centromere-associated protein E: GSK923295, ACS Med. Chem. Lett. 1 (2010) 30–34.
[64] V. Chung, E.I. Heath, W.R. Schelman, B.M. Johnson, L.C. Kirby, K.M. Lynch, J.D. Botbyl, T.A. Lampkin, K.D. Holen, First-time-in-human study of GSK923295, a novel antimitotic inhibitor of centromere-associated protein E (CENP-E), in patients with refractory cancer, Cancer Chemother. Pharmacol. 69 (2012) 733–741.
[65] S.Y. Lee, C. Jang, K.A. Lee, Polo-like kinases (plks), a key regulator of cell cycle and new potential target for cancer therapy, Dev Reprod 18 (2014) 65–71.
[66] Y. Degenhardt, T. Lampkin, Targeting Polo-like kinase in cancer therapy, Clin. Canc. Res.: Off. J. Am. Assoc. Canc. Res. 16 (2010) 384–389.
[67] K.V. Gleixner, V. Ferenc, B. Peter, A. Gruze, R.A. Meyer, E. Hadzijusufovic, S. Cerny-Reiterer, M. Mayerhofer, W.F. Pickl, C. Sillaber, P. Valent, Polo-like kinase 1 (Plk1) as a novel drug target in chronic myeloid leukemia: overriding imatinib resistance with the Plk1 inhibitor BI 2536, Cancer Res. 70 (2010) 1513–1523.
[68] M. Nihal, N. Stutz, T. Schmit, N. Ahmad, G.S. Wood, Polo-like kinase 1 (Plk1) is expressed by cutaneous T-cell lymphomas (CTCLs), and its downregulation promotes cell cycle arrest and apoptosis, Cell Cycle 10 (2011) 1303–1311.
[69] D. Rudolph, M. Steegmaier, M. Hoffmann, M. Grauert, A. Baum, J. Quant, C. Haslinger, P. Garin-Chesa, G.R. Adolf, BI 6727, a Polo-like kinase inhibitor with improved pharmacokinetic profile and broad antitumor activity, Clin. Canc. Res. 15 (2009) 3094–3102.
[70] H. Yim, Current clinical trials with polo-like kinase 1 inhibitors in solid tumors, Anti Canccer Drugs 24 (2013) 999–1006.
[71] C.C. Lin, W.C. Su, C.J. Yen, C.H. Hsu, W.P. Su, K.H. Yeh, Y.S. Lu, A.L. Cheng, D.C. Huang, H. Fritsch, F. Voss, T. Taube, J.C. Yang, A phase I study of two dosing schedules of volasertib (BI 6727), an intravenous polo-like kinase inhibitor, in patients with advanced solid malignancies, Br. J. Canc. 110 (2014) 2434–2440.
[72] W.M. Stadler, D.J. Vaughn, G. Sonpavde, N.J. Vogelzang, S.T. Tagawa, D.P. Petrylak, P. Rosen, C.C. Lin, J. Mahoney, S. Modi, P. Lee, M.S. Ernstoff, W.C. Su, A. Spira, K. Pilz, R. Vinisko, C. Schloss, H. Fritsch, C. Zhao, M.A. Carducci, An open-label, single-arm, phase 2 trial of the Polo-like kinase inhibitor volasertib (BI 6727) in patients with locally advanced or metastatic urothelial cancer, Cancer 120 (2014) 976–982.
[73] B.T. Gjertsen, P. Schoffski, Discovery and development of the Polo-like kinase inhibitor volasertib in cancer therapy, Leukemia 29 (2015) 11–19.
[74] X. Zhang, Aurora kinases, Curr. Biol. 18 (2008) R146–R148.
[75] A. Tang, K. Gao, L. Chu, R. Zhang, J. Yang, J. Zheng, Aurora kinases: novel therapy targets in cancers, Oncotarget 8 (2017) 23937–23954.
[76] P. Kaestner, A. Stolz, H. Bastians, Determinants for the efficiency of anticancer drugs targeting either Aurora-A or Aurora-B kinases in human colon carcinoma cells, Mol. Canc. Therapeut. 8 (2009) 2046–2056.
[77] S. Hauf, R.W. Cole, S. LaTerra, C. Zimmer, G. Schnapp, R. Walter, A. Heckel, J. van Meel, C.L. Rieder, J.M. Peters, The small molecule Hesperadin reveals a role for Aurora B in correcting kinetochore-microtubule attachment and in maintaining the spindle assembly checkpoint, J. Cell Biol. 161 (2003) 281–294.
[78] F. Girdler, K.E. Gascoigne, P.A. Eyers, S. Hartmuth, C. Crafter, K.M. Foote, N.J. Keen, S.S. Taylor, Validating Aurora B as an anti-cancer drug target, J. Cell Sci. 119 (2006) 3664–3675.
[79] M.D. Gurden, S.J. Anderhub, A. Faisal, S. Linardopoulos, Aurora B prevents premature removal of spindle assembly checkpoint proteins from the kinetochore: a key role for Aurora B in mitosis, Oncotarget 9 (2018) 19525–19542.
[80] P. Ramani, E. Sowa-Avugrah, M.T. May, High proliferation index, as determined by immunohistochemical expression of Aurora kinase B and geminin, indicates poor prognosis in neuroblastomas, Virchows Arch.: Int. J. Pathol. 467 (2015) 319–327.
[81] R.J. Diaz, B. Golbourn, M. Shekarforoush, C.A. Smith, J.T. Rutka, Aurora kinase B/C inhibition impairs malignant glioma growth in vivo, J. Neuro Oncol. 108 (2012) 349–360.
[82] C. Romain, P. Paul, K.W. Kim, S. Lee, J. Qiao, D.H. Chung, Targeting Aurora kinase-A downregulates cell proliferation and angiogenesis in neuroblastoma, J. Pediatr. Surg. 49 (2014) 159–165.
[83] X.P. Zhu, Z.L. Liu, A.F. Peng, Y.F. Zhou, X.H. Long, Q.F. Luo, S.H. Huang, Y. Shu, Inhibition of Aurora-B suppresses osteosarcoma cell migration and invasion, Exper. Therap. Med. 7 (2014) 560–564.
[84] R.W. Wilkinson, R. Odedra, S.P. Heaton, S.R. Wedge, N.J. Keen, C. Crafter, J.R. Foster, M.C. Brady, A. Bigley, E. Brown, K.F. Byth, N.C. Barrass, K.E. Mundt, K.M. Foote, N.M. Heron, F.H. Jung, A.A. Mortlock, F.T. Boyle, S. Green, AZD1152, a selective inhibitor of aurora B kinase, inhibits human tumor xenograft growth by inducing apoptosis, Clin. Canc. Res. 13 (2007) 3682–3688.
[85] M. Kollareddy, D. Zheleva, P. Dzubak, P.S. Brahmkshatriya, M. Lepsik, M. Hajduch, Aurora kinase inhibitors: progress towards the clinic, Invest. N. Drugs 30 (2012) 2411–2432.
[86] B. Melichar, A. Adenis, A.C. Lockhart, J. Bennouna, E.C. Dees, O. Kayaleh, R. Obermannova, A. DeMichele, P. Zatloukal, B. Zhang, C.D. Ullmann, C. Schusterbauer, Safety and activity of alisertib, an investigational aurora kinase A inhibitor, in patients with breast cancer, small-cell lung cancer, non-small-cell lung cancer, head and neck squamous-cell carcinoma, and gastro-oesophageal adenocarcinoma: a five-arm phase 2 study, the Lancet, Oncology 16 (2015)

395–405.
[87] B. Lowenberg, P. Muus, G. Ossenkoppele, P. Rousselot, J.Y. Cahn, N. Ifrah, G. Martinelli, S. Amadori, E. Berman, P. Sonneveld, M. Jongen-Lavrencic, S. Rigaudeau, P. Stockman, A. Goudie, S. Faderl, E. Jabbour, H. Kantarjian, Phase 1/2 study to assess the safety, efficacy, and pharmacokinetics of barasertib (AZD1152) in patients with advanced acute myeloid leukemia, Blood 118 (2011) 6030–6036.
[88] Y. Tao, P. Zhang, V. Frascogna, Y. Lecluse, A. Auperin, J. Bourhis, E. Deutsch, Enhancement of radiation response by inhibition of Aurora-A kinase using siRNA or a selective Aurora kinase inhibitor PHA680632 in p53-deficient cancer cells, Br. J. Canc. 97 (2007) 1664–1672.
[89] Y. Ma, H. Cao, S. Lou, X. Shao, W. Lv, X. Qi, Y. Liu, M. Ying, Q. He, X. Yang, Sequential treatment with aurora B inhibitors enhances cisplatin-mediated apoptosis via c-Myc, J. Mol. Med. (Berl.) 93 (2015) 427–438.
[90] G.J. Kops, B.A. Weaver, D.W. Cleveland, On the road to cancer: aneuploidy and the mitotic checkpoint, Nat. Rev. Canc. 5 (2005) 773–785.
[91] A. Janssen, G.J. Kops, R.H. Medema, Elevating the frequency of chromosome mis-segregation as a strategy to kill tumor cells, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 19108–19113.
[92] C. Lengauer, K.W. Kinzler, B. Vogelstein, Genetic instabilities in human cancers, Nature 396 (1998) 643–649.
[93] C. Dominguez-Brauer, K.L. Thu, J.M. Mason, H. Blaser, M.R. Bray, T.W. Mak, Targeting mitosis in cancer: emerging strategies, Mol. Cell. 60 (2015) 524–536.
[94] S. Marques, J. Fonseca, P.M. Silva, H. Bousbaa, Targeting the spindle assembly checkpoint for breast cancer treatment, Curr. Cancer Drug Targets 15 (2015) 272–281.
[95] J.H. Teixeira, P.M. Silva, R.M. Reis, I.M. Moura, S. Marques, J. Fonseca, L.S. Monteiro, H. Bousbaa, An overview of the spindle assembly checkpoint status in oral cancer, BioMed Res. Int. 2014 (2014) 145289.
[96] V. Diogo, J. Teixeira, P.M. Silva, H. Bousbaa, Spindle assembly checkpoint as a potential target in colorectal cancer: current status and future perspectives, Clin. Colorectal Canc. 16 (2017) 1–8.
[97] R. Colombo, M. Caldarelli, M. Mennecozzi, M.L. Giorgini, F. Sola, P. Cappella, C. Perrera, S.R. Depaolini, L. Rusconi, U. Cucchi, N. Avanzi, J.A. Bertrand, R.T. Bossi, E. Pesenti, A. Galvani, A. Isacchi, F. Colotta, D. Donati, J. Moll, Targeting the mitotic checkpoint for cancer therapy with NMS-P715, an inhibitor of MPS1 kinase, Cancer Res. 70 (2010) 10255–10264.
[98] M. Jemaa, L. Galluzzi, O. Kepp, L. Senovilla, M. Brands, U. Boemer, M. Koppitz, P. Lienau, S. Prechtl, V. Schulze, G. Siemeister, A.M. Wengner, D. Mumberg, K. Ziegelbauer, A. Abrieu, M. Castedo, I. Vitale, G. Kroemer, Characterization of novel MPS1 inhibitors with preclinical anticancer activity, Cell Death Differ. 20 (2013) 1532–1545.
[99] Y. Liu, Y. Lang, N.K. Patel, G. Ng, R. Laufer, S.W. Li, L. Edwards, B. Forrest, P.B. Sampson, M. Feher, F. Ban, D.E. Awrey, I. Beletskaya, G. Mao, R. Hodgson, O. Plotnikova, W. Qiu, N.Y. Chirgadze, J.M. Mason, X. Wei, D.C. Lin, Y. Che, R. Kiarash, B. Madeira, G.C. Fletcher, T.W. Mak, M.R. Bray, H.W. Pauls, The discovery of orally bioavailable tyrosine threonine kinase (TTK) inhibitors: 3-(4-(heterocyclyl)phenyl)-1H-indazole-5-carboxamides as anticancer agents, J. Med. Chem. 58 (2015) 3366–3392.
[100] E. Lauze, B. Stoelcker, F.C. Luca, E. Weiss, A.R. Schutz, M. Winey, Yeast spindle pole body duplication gene MPS1 encodes an essential dual specificity protein kinase, EMBO J. 14 (1995) 1655–1663.
[101] X. Liu, M. Winey, The MPS1 family of protein kinases, Annu. Rev. Biochem. 81 (2012) 561–585.
[102] J. Daniel, J. Coulter, J.H. Woo, K. Wilsbach, E. Gabrielson, High levels of the Mps1 checkpoint protein are protective of aneuploidy in breast cancer cells, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 5384–5389.
[103] G. Salvatore, T.C. Nappi, P. Salerno, Y. Jiang, C. Garbi, C. Ugolini, P. Miccoli, F. Basolo, M.D. Castellone, A.M. Cirafici, R.M. Melillo, A. Fusco, M.L. Bittner, M. Santoro, A cell proliferation and chromosomal instability signature in anaplastic thyroid carcinoma, Cancer Res. 67 (2007) 10148–10158.
[104] E. Logarinho, H. Bousbaa, Kinetochore-microtubule interactions "in check" by Bub1, Bub3 and BubR1: the dual task of attaching and signalling, Cell Cycle 7 (2008) 1763–1768.
[105] N.A. Barbosa J, J. Faria, P. Silva, H. Bousbaa, The spindle assembly checkpoint: perspectives in tumorigenesis and cancer therapy, Front. Biol. 6 (2011) 147–155.
[106] R.M. Ricke, K.B. Jeganathan, J.M. van Deursen, Bub1 overexpression induces aneuploidy and tumor formation through Aurora B kinase hyperactivation, J. Cell Biol. 193 (2011) 1049–1064.
[107] D.J. Baker, K.B. Jeganathan, J.D. Cameron, M. Thompson, S. Juneja, A. Kopecka, R. Kumar, R.B. Jenkins, P.C. de Groen, P. Roche, J.M. van Deursen, BubR1 insufficiency causes early onset of aging-associated phenotypes and infertility in mice, Nat. Genet. 36 (2004) 744–749.
[108] J.R. Babu, K.B. Jeganathan, D.J. Baker, X. Wu, N. Kang-Decker, J.M. van Deursen, Rae1 is an essential mitotic checkpoint regulator that cooperates with Bub3 to prevent chromosome missegregation, J. Cell Biol. 160 (2003) 341–353.
[109] W. Dai, Q. Wang, T. Liu, M. Swamy, Y. Fang, S. Xie, R. Mahmood, Y.M. Yang, M. Xu, C.V. Rao, Slippage of mitotic arrest and enhanced tumor development in mice with BubR1 haploinsufficiency, Cancer Res. 64 (2004) 440–445.
[110] J.Y. Han, Y.K. Han, G.Y. Park, S.D. Kim, C.G. Lee, Bub1 is required for maintaining cancer stem cells in breast cancer cell lines, Sci. Rep. 5 (2015) 15993.
[111] B. Xu, T. Xu, H. Liu, Q. Min, S. Wang, Q. Song, MiR-490-5p suppresses cell proliferation and invasion by targeting BUB1 in hepatocellular carcinoma cells, Pharmacology 100 (2017) 269–282.
[112] A.P. Baron, C. von Schubert, F. Cubizolles, G. Siemeister, M. Hitchcock, A. Mengel, J. Schroder, A. Fernandez-Montalvan, F. von Nussbaum, D. Mumberg, E.A. Nigg, Probing the catalytic functions of Bub1 kinase using the small molecule inhibitors BAY-320 and BAY-524, Elife 5 (2016) e12187.
[113] A. De Antoni, C.G. Pearson, D. Cimini, J.C. Canman, V. Sala, L. Nezi, M. Mapelli, L. Sironi, M. Faretta, E.D. Salmon, A. Musacchio, The Mad1/Mad2 complex as a template for Mad2 activation in the spindle assembly checkpoint, Curr. Biol. 15 (2005) 214–225.
[114] L.S. Michel, V. Liberal, A. Chatterjee, R. Kirchwegger, B. Pasche, W. Gerald, M. Dobles, P.K. Sorger, V.V. Murty, R. Benezra, MAD2 haplo-insufficiency causes premature anaphase and chromosome instability in mammalian cells, Nature 409 (2001) 355–359.
[115] M. Dobles, V. Liberal, M.L. Scott, R. Benezra, P.K. Sorger, Chromosome missegregation and apoptosis in mice lacking the mitotic checkpoint protein Mad2, Cell 101 (2000) 635–645.
[116] A.V. Nascimento, A. Singh, H. Bousbaa, D. Ferreira, B. Sarmento, M.M. Amiji, Overcoming cisplatin resistance in non-small cell lung cancer with Mad2 silencing siRNA delivered systemically using EGFR-targeted chitosan nanoparticles, Acta Biomater. 47 (2017) 71–80.
[117] M. Tambe, S. Pruikkonen, J. Maki-Jouppila, P. Chen, B.V. Elgaaen, A.H. Straume, K. Huhtinen, O. Carpen, P.E. Lonning, B. Davidson, S. Hautaniemi, M.J. Kallio, Novel Mad2-targeting miR-493-3p controls mitotic fidelity and cancer cells' sensitivity to paclitaxel, Oncotarget 7 (2016) 12267–12285.
[118] J. Kastl, J. Braun, A. Prestel, H.M. Moller, T. Huhn, T.U. Mayer, Mad2 inhibitor-1 (M2I-1): a small molecule protein-protein interaction inhibitor targeting the mitotic spindle assembly checkpoint, ACS Chem. Biol. 10 (2015) 1661–1666.
[119] F. Furlong, P. Fitzpatrick, S. O'Toole, S. Phelan, B. McGrogan, A. Maguire, A. O'Grady, M. Gallagher, M. Prencipe, A. McGoldrick, P. McGettigan, D. Brennan, O. Sheils, C. Martin, W.K. E, J. O'Leary, A. McCann, Low MAD2 expression levels associate with reduced progression-free survival in patients with high-grade serous epithelial ovarian cancer, J. Pathol. 226 (2012) 746–755.
[120] C. Antonio, I. Ferby, H. Wilhelm, M. Jones, E. Karsenti, A.R. Nebreda, I. Vernos, Xkid, a chromokinesin required for chromosome alignment on the metaphase plate, Cell 102 (2000) 425–435.
[121] P.M. Silva, N. Ribeiro, R.T. Lima, C. Andrade, V. Diogo, J. Teixeira, C. Florindo, A. Tavares, M.H. Vasconcelos, H. Bousbaa, Suppression of spindly delays mitotic exit and exacerbates cell death response of cancer cells treated with low doses of paclitaxel, Cancer Lett. 394 (2017) 33–42.
[122] R. Visconti, L. Palazzo, R. Della Monica, D. Grieco, Fcp1-dependent dephosphorylation is required for M-phase-promoting factor inactivation at mitosis exit, Nat. Commun. 3 (2012) 894.
[123] H.T. Ma, Y.Y. Chan, X. Chen, K.F. On, R.Y. Poon, Depletion of p31comet protein promotes sensitivity to antimitotic drugs, J. Biol. Chem. 287 (2012) 21561–21569.
[124] J.T. Opferman, A. Kothari, Anti-apoptotic BCL-2 family members in development, Cell Death Differ. 25 (2018) 37–45.
[125] C. Billard, BH3 mimetics: status of the field and new developments, Mol. Canc. Therapeut. 12 (2013) 1691–1700.
[126] T. Oltersdorf, S.W. Elmore, A.R. Shoemaker, R.C. Armstrong, D.J. Augeri, B.A. Belli, M. Bruncko, T.L. Deckwerth, J. Dinges, P.J. Hajduk, M.K. Joseph, S. Kitada, S.J. Korsmeyer, A.R. Kunzer, A. Letai, C. Li, M.J. Mitten, D.G. Nettesheim, S. Ng, P.M. Nimmer, J.M. O'Connor, A. Oleksijew, A.M. Petros, J.C. Reed, W. Shen, S.K. Tahir, C.B. Thompson, K.J. Tomaselli, B. Wang, M.D. Wendt, H. Zhang, S.W. Fesik, S.H. Rosenberg, An inhibitor of Bcl-2 family proteins induces regression of solid tumours, Nature 435 (2005) 677–681.
[127] A.R. Delbridge, A. Strasser, The BCL-2 protein family, BH3-mimetics and cancer therapy, Cell Death Differ. 22 (2015) 1071–1080.
[128] J.D. Leverson, H. Zhang, J. Chen, S.K. Tahir, D.C. Phillips, J. Xue, P. Nimmer, S. Jin, M. Smith, Y. Xiao, P. Kovar, A. Tanaka, M. Bruncko, G.S. Sheppard, L. Wang, S. Gierke, L. Kategaya, D.J. Anderson, C. Wong, J. Eastham-Anderson, M.J. Ludlam, D. Sampath, W.J. Fairbrother, I. Wertz, S.H. Rosenberg, C. Tse, S.W. Elmore, A.J. Souers, Potent and selective small-molecule MCL-1 inhibitors demonstrate on-target cancer cell killing activity as single agents and in combination with ABT-263 (navitoclax), Cell Death Dis. 6 (2015) e1590.
[129] J. Shi, Y. Zhou, H.C. Huang, T.J. Mitchison, Navitoclax (ABT-263) accelerates apoptosis during drug-induced mitotic arrest by antagonizing Bcl-xL, Cancer Res. 71 (2011) 4518–4526.
[130] N. Bah, L. Maillet, J. Ryan, S. Dubreil, F. Gautier, A. Letai, P. Juin, S. Barille-Nion, Bcl-xL controls a switch between cell death modes during mitotic arrest, Cell Death Dis. 5 (2014) e1291.
[131] D. Izawa, J. Pines, How APC/C-Cdc20 changes its substrate specificity in mitosis, Nat. Cell Biol. 13 (2011) 223–233.
[132] H.C. Huang, J. Shi, J.D. Orth, T.J. Mitchison, Evidence that mitotic exit is a better cancer therapeutic target than spindle assembly, Cancer Cell 16 (2009) 347–358.
[133] E. Manchado, M. Guillamot, G. de Carcer, M. Eguren, M. Trickey, I. Garcia-Higuera, S. Moreno, H. Yamano, M. Canamero, M. Malumbres, Targeting mitotic exit leads to tumor regression in vivo: modulation by Cdk1, Mastl, and the PP2A/B55alpha,delta phosphatase, Cancer Cell 18 (2010) 641–654.
[134] Z. Wang, L. Wan, J. Zhong, H. Inuzuka, P. Liu, F.H. Sarkar, W. Wei, Cdc20: a potential novel therapeutic target for cancer treatment, Curr. Pharmaceut. Des. 19 (2013) 3210–3214.
[135] I.M. Moura, M.L. Delgado, P.M. Silva, C.A. Lopes, J.B. do Amaral, L.S. Monteiro, H. Bousbaa, High CDC20 expression is associated with poor prognosis in oral squamous cell carcinoma, J. Oral Pathol. Med. 43 (2014) 225–231.
[136] L. Wang, J. Zhang, L. Wan, X. Zhou, Z. Wang, W. Wei, Targeting Cdc20 as a novel cancer therapeutic strategy, Pharmacol. Ther. 151 (2015) 141–151.
[137] K.L. Sackton, N. Dimova, X. Zeng, W. Tian, M. Zhang, T.B. Sackton, J. Meaders, K.L. Pfaff, F. Sigoillot, H. Yu, X. Luo, R.W. King, Synergistic blockade of mitotic exit by two chemical inhibitors of the APC/C, Nature 514 (2014) 646–649.

[138] X. Zeng, F. Sigoillot, S. Gaur, S. Choi, K.L. Pfaff, D.-C. Oh, N. Hathaway, N. Dimova, G.D. Cuny, R.W. King, Pharmacologic inhibition of the anaphase-promoting complex induces a spindle checkpoint-dependent mitotic arrest in the absence of spindle damage, Cancer Cell 18 (2010) 382–395.
[139] S. Lub, A. Maes, K. Maes, K. De Veirman, E. De Bruyne, E. Menu, K. Fostier, A. Kassambara, J. Moreaux, D. Hose, X. Leleu, R.W. King, K. Vanderkerken, E. Van Valckenborgh, Inhibiting the anaphase promoting complex/cyclosome induces a metaphase arrest and cell death in multiple myeloma cells, Oncotarget 7 (2016) 4062–4076.
[140] Q.P. Dou, J.A. Zonder, Overview of proteasome inhibitor-based anti-cancer therapies: perspective on bortezomib and second generation proteasome inhibitors versus future generation inhibitors of ubiquitin-proteasome system, Curr. Cancer Drug Targets 14 (2014) 517–536.
[141] J. Adams, The proteasome: a suitable antineoplastic target, Nat. Rev. Canc. 4 (2004) 349–360.
[142] J.R. Skaar, J.K. Pagan, M. Pagano, SCF ubiquitin ligase-targeted therapies, Nat. Rev. Drug Discov. 13 (2014) 889–903.
[143] T. Caravita, P. de Fabritiis, A. Palumbo, S. Amadori, M. Boccadoro, Bortezomib: efficacy comparisons in solid tumors and hematologic malignancies, Nat. Clin. Pract. Oncol. 3 (2006) 374–387.
[144] E.M. Huber, W. Heinemeyer, M. Groll, Bortezomib-resistant mutant proteasomes: structural and biochemical evaluation with carfilzomib and ONX 0914, Structure 23 (2015) 407–417.
[145] E. Choi, H. Yu, Phosphorylation propels p31(comet) for mitotic exit, Cell Cycle 14 (2015) 1997–1998.
[146] R.S. Hagan, M.S. Manak, H.K. Buch, M.G. Meier, P. Meraldi, J.V. Shah, P.K. Sorger, p31(comet) acts to ensure timely spindle checkpoint silencing subsequent to kinetochore attachment, Mol. Biol. Cell 22 (2011) 4236–4246.
[147] T. Habu, T. Matsumoto, p31(comet) inactivates the chemically induced Mad2-dependent spindle assembly checkpoint and leads to resistance to anti-mitotic drugs, SpringerPlus 2 (2013) 562.
[148] D. Wu, L. Wang, Y. Yang, J. Huang, Y. Hu, Y. Shu, J. Zhang, J. Zheng, MAD2-p31(comet) axis deficiency reduces cell proliferation, migration and sensitivity of microtubule-interfering agents in glioma, Biochem. Biophys. Res. Commun. 498 (2018) 157–163.
[149] D.A. Date, A.C. Burrows, M. Venere, M.W. Jackson, M.K. Summers, Coordinated regulation of p31(Comet) and Mad2 expression is required for cellular proliferation, Cell Cycle 12 (2013) 3824–3832.
[150] K. Wang, B. Sturt-Gillespie, J.C. Hittle, D. Macdonald, G.K. Chan, T.J. Yen, S.T. Liu, Thyroid hormone receptor interacting protein 13 (TRIP13) AAA-ATPase is a novel mitotic checkpoint-silencing protein, J. Biol. Chem. 289 (2014) 23928–23937.
[151] R. Della Monica, R. Visconti, N. Cervone, A.F. Serpico, D. Grieco, Fcp1 phosphatase controls Greatwall kinase to promote PP2A-B55 activation and mitotic progression, Elife 4 (2015).
[152] V. D'Angiolella, C. Mari, D. Nocera, L. Rametti, D. Grieco, The spindle checkpoint requires cyclin-dependent kinase activity, Genes Dev. 17 (2003) 2520–2525.
[153] R. Visconti, R. Della Monica, L. Palazzo, F. D'Alessio, M. Raia, S. Improta, M.R. Villa, L. Del Vecchio, D. Grieco, The Fcp1-Wee1-Cdk1 axis affects spindle assembly checkpoint robustness and sensitivity to antimicrotubule cancer drugs, Cell Death Differ. 22 (2015) 1551–1560.
[154] E.R. Griffis, N. Stuurman, R.D. Vale, Spindly, a novel protein essential for silencing the spindle assembly checkpoint, recruits dynein to the kinetochore, J. Cell Biol. 177 (2007) 1005–1015.
[155] R.S. Wong, Apoptosis in cancer: from pathogenesis to treatment, J. Exp. Clin. Canc. Res. 30 (2011) 87.
[156] J. Barbosa, A.V. Nascimento, J. Faria, P. Silva, H. Bousbaa, The spindle assembly checkpoint: perspectives in tumorigenesis and cancer therapy, Front. Biol. 6 (2011) 147–155.
[157] J.D. Leverson, D.C. Phillips, M.J. Mitten, E.R. Boghaert, D. Diaz, S.K. Tahir, L.D. Belmont, P. Nimmer, Y. Xiao, X.M. Ma, K.N. Lowes, P. Kovar, J. Chen, S. Jin, M. Smith, J. Xue, H. Zhang, A. Oleksijew, T.J. Magoc, K.S. Vaidya, D.H. Albert, J.M. Tarrant, N. La, L. Wang, Z.F. Tao, M.D. Wendt, D. Sampath, S.H. Rosenberg, C. Tse, D.C. Huang, W.J. Fairbrother, S.W. Elmore, A.J. Souers, Exploiting selective BCL-2 family inhibitors to dissect cell survival dependencies and define improved strategies for cancer therapy, Sci. Transl. Med. 7 (2015) 279ra240.
[158] M. Wong, N. Tan, J. Zha, F.V. Peale, P. Yue, W.J. Fairbrother, L.D. Belmont, Navitoclax (ABT-263) reduces Bcl-x(L)-mediated chemoresistance in ovarian cancer models, Mol. Canc. Therapeut. 11 (2012) 1026–1035.
[159] S. Ashton, Y.H. Song, J. Nolan, E. Cadogan, J. Murray, R. Odedra, J. Foster, P.A. Hall, S. Low, P. Taylor, R. Ellston, U.M. Polanska, J. Wilson, C. Howes, A. Smith, R.J. Goodwin, J.G. Swales, N. Strittmatter, Z. Takats, A. Nilsson, P. Andren, D. Trueman, M. Walker, C.L. Reimer, G. Troiano, D. Parsons, D. De Witt, M. Ashford, J. Hrkach, S. Zale, P.J. Jewsbury, S.T. Barry, Aurora kinase inhibitor nanoparticles target tumors with favorable therapeutic index in vivo, Sci. Transl. Med. 8 (2016) 325ra317.
[160] M.V. Blagosklonny, A.B. Pardee, Exploiting cancer cell cycling for selective protection of normal cells, Cancer Res. 61 (2001) 4301–4305.
[161] M.C. Smith, J.E. Gestwicki, Features of protein-protein interactions that translate into potent inhibitors: topology, surface area and affinity, Expet Rev. Mol. Med. 14 (2012) e16.
[162] A.V. Nascimento, A. Singh, H. Bousbaa, D. Ferreira, B. Sarmento, M.M. Amiji, Mad2 checkpoint gene silencing using epidermal growth factor receptor-targeted chitosan nanoparticles in non-small cell lung cancer model, Mol. Pharm. 11 (2014) 3515–3527.
[163] R.B. Lock, H. Carol, C.L. Morton, S.T. Keir, C.P. Reynolds, M.H. Kang, J.M. Maris, A.W. Wozniak, R. Gorlick, E.A. Kolb, P.J. Houghton, M.A. Smith, Initial testing of the CENP-E inhibitor GSK923295A by the pediatric preclinical testing program, Pediatr. Blood Canc. 58 (2012) 916–923.
[164] N.J. Balamuth, A. Wood, Q. Wang, J. Jagannathan, P. Mayes, Z. Zhang, Z. Chen, E. Rappaport, J. Courtright, B. Pawel, B. Weber, R. Wooster, E.O. Sekyere, G.M. Marshall, J.M. Maris, Serial transcriptome analysis and cross-species integration identifies centromere-associated protein E as a novel neuroblastoma target, Cancer Res. 70 (2010) 2749–2758.
[165] A. Berg, T. Berg, Inhibitors of the polo-box domain of polo-like kinase 1, Chembiochem.: Europ. J. Chem. Biol. 17 (2016) 650–656.
[166] L. Garuti, M. Roberti, G. Bottegoni, Polo-like kinases inhibitors, Curr. Med. Chem. 19 (2012) 3937–3948.
[167] R.N. Murugan, J.E. Park, E.H. Kim, S.Y. Shin, C. Cheong, K.S. Lee, J.K. Bang, Plk1-targeted small molecule inhibitors: molecular basis for their potency and specificity, Mol. Cell. 32 (2011) 209–220.
[168] K.S. Lee, T.R. Burke Jr., J.E. Park, J.K. Bang, E. Lee, Recent advances and new strategies in targeting Plk1 for anticancer therapy, Trends Pharmacol. Sci. 36 (2015) 858–877.
[169] R.E. Gutteridge, M.A. Ndiaye, X. Liu, N. Ahmad, Plk1 inhibitors in cancer therapy: from laboratory to clinics, Mol. Canc. Therapeut. 15 (2016) 1427–1435.
[170] S. Kumar, J. Kim, PLK-1 targeted inhibitors and their potential against tumorigenesis, BioMed Res. Int. 2015 (2015) 705745.
[171] J. Cicenas, The Aurora kinase inhibitors in cancer research and therapy, J. Canc. Res. Clin. Oncol. 142 (2016) 1995–2012.
[172] A.C. Borisa, H.G. Bhatt, A comprehensive review on Aurora kinase: small molecule inhibitors and clinical trial studies, Eur. J. Med. Chem. 140 (2017) 1–19.
[173] M. Jemaà, L. Galluzzi, O. Kepp, L. Senovilla, M. Brands, U. Boemer, M. Koppitz, P. Lienau, S. Prechtl, V. Schulze, G. Siemeister, A.M. Wengner, D. Mumberg, K. Ziegelbauer, A. Abrieu, M. Castedo, I. Vitale, G. Kroemer, Characterization of novel MPS1 inhibitors with preclinical anticancer activity, Cell Death Differ. 20 (2013) 1532–1545.
[174] L. Hewitt, A. Tighe, S. Santaguida, A.M. White, C.D. Jones, A. Musacchio, S. Green, S.S. Taylor, Sustained Mps1 activity is required in mitosis to recruit O-Mad2 to the Mad1-C-Mad2 core complex, J. Cell Biol. 190 (2010) 25–34.
[175] N. Kwiatkowski, N. Jelluma, P. Filippakopoulos, M. Soundararajan, M.S. Manak, M. Kwon, H.G. Choi, T. Sim, Q.L. Deveraux, S. Rottmann, D. Pellman, J.V. Shah, G.J. Kops, S. Knapp, N.S. Gray, Small-molecule kinase inhibitors provide insight into Mps1 cell cycle function, Nat. Chem. Biol. 6 (2010) 359–368.
[176] M. Schmidt, Y. Budirahardja, R. Klompmaker, R.H. Medema, Ablation of the spindle assembly checkpoint by a compound targeting Mps1, EMBO Rep. 6 (2005) 866–872.
[177] S.S. Anand, M. Maruthi, P.P. Babu, The specific, reversible JNK inhibitor SP600125 improves survivability and attenuates neuronal cell death in experimental cerebral malaria (ECM), Parasitol. Res. 112 (2013) 1959–1966.
[178] S. Santaguida, A. Tighe, A.M. D'Alise, S.S. Taylor, A. Musacchio, Dissecting the role of MPS1 in chromosome biorientation and the spindle checkpoint through the small molecule inhibitor reversine, J. Cell Biol. 190 (2010) 73–87.
[179] C.H. Kuo, Y.C. Lu, Y.S. Tseng, C.S. Shi, S.H. Chen, P.T. Chen, F.L. Wu, Y.P. Chang, Y.R. Lee, Reversine induces cell cycle arrest, polyploidy, and apoptosis in human breast cancer cells, Breast Canc. 21 (2014) 358–369.
[180] M. Piccoli, G. Palazzolo, E. Conforti, G. Lamorte, N. Papini, P. Creo, C. Fania, R. Scaringi, S. Bergante, C. Tringali, L. Roncoroni, S. Mazzoleni, L. Doneda, R. Galli, B. Venerando, G. Tettamanti, C. Gelfi, L. Anastasia, The synthetic purine reversine selectively induces cell death of cancer cells, J. Cell. Biochem. 113 (2012) 3207–3217.
[181] M. Jemaa, L. Galluzzi, O. Kepp, A. Boileve, D. Lissa, L. Senovilla, F. Harper, G. Pierron, F. Berardinelli, A. Antoccia, M. Castedo, I. Vitale, G. Kroemer, Preferential killing of p53-deficient cancer cells by reversine, Cell Cycle 11 (2012) 2149–2158.
[182] S.C. Hua, T.C. Chang, H.R. Chen, C.H. Lu, Y.W. Liu, S.H. Chen, H.I. Yu, Y.P. Chang, Y.R. Lee, Reversine, a 2,6-disubstituted purine, as an anti-cancer agent in differentiated and undifferentiated thyroid cancer cells, Pharm. Res. (N. Y.) 29 (2012) 1990–2005.
[183] H.-Z. Xu, Y. Huang, Y.-L. Wu, Y. Zhao, W.-L. Xiao, Q.-S. Lin, H.-D. Sun, W. Dai, G.-Q. Chen, Pharicin A, a novel natural ent-kaurene diterpenoid, induces mitotic arrest and mitotic catastrophe of cancer cells by interfering with BubR1 function, Cell Cycle 9 (2010) 2897–2907.
[184] J.L. Yap, L. Chen, M.E. Lanning, S. Fletcher, Expanding the cancer arsenal with targeted therapies: disarmament of the antiapoptotic bcl-2 proteins by small molecules, J. Med. Chem. 60 (2017) 821–838.
[185] L. Scarfo, P. Ghia, Reprogramming cell death: BCL2 family inhibition in hematological malignancies, Immunol. Lett. 155 (2013) 36–39.
[186] L. Vela, I. Marzo, Bcl-2 family of proteins as drug targets for cancer chemotherapy: the long way of BH3 mimetics from bench to bedside, Curr. Opin. Pharmacol. 23 (2015) 74–81.
[187] A.C. Timucin, H. Basaga, O. Kutuk, Selective targeting of antiapoptotic BCL-2 proteins in cancer, Med. Res. Rev. (2018) 1–30.
[188] A. De Blasio, R. Vento, R. Di Fiore, Mcl-1 targeting could be an intriguing perspective to cure cancer, J. Cell. Physiol. 233 (2018) 8482–8498.
[189] Y. Gao, B. Zhang, Y. Wang, G. Shang, Cdc20 inhibitor apcin inhibits the growth and invasion of osteosarcoma cells, Oncol. Rep. 40 (2018) 841–848.
[190] L. Kubiczkova, L. Pour, L. Sedlarikova, R. Hajek, S. Sevcikova, Proteasome inhibitors - molecular basis and current perspectives in multiple myeloma, J. Cell Mol. Med. 18 (2014) 947–961.
[191] J.W. Purcell, J. Davis, M. Reddy, S. Martin, K. Samayoa, H. Vo, K. Thomsen, P. Bean, W.L. Kuo, S. Ziyad, J. Billig, H.S. Feiler, J.W. Gray, K.W. Wood, S. Cases,

Activity of the kinesin spindle protein inhibitor ispinesib (SB-715992) in models of breast cancer, Clin. Canc. Res. 16 (2010) 566–576.
[192] S. Yasuhira, M. Shibazaki, M. Nishiya, C. Maesawa, Paclitaxel-induced aberrant mitosis and mitotic slippage efficiently lead to proliferative death irrespective of canonical apoptosis and p53, Cell Cycle 15 (2016) 3268–3277.
[193] L. Sun, J. Lu, Z. Niu, K. Ding, D. Bi, S. Liu, J. Li, F. Wu, H. Zhang, Z. Zhao, S. Ding, A potent chemotherapeutic strategy with Eg5 inhibitor against gemcitabine resistant bladder cancer, PloS One 10 (2015) e0144484.
[194] C.Y. Cheng, C.J. Liu, Y.C. Huang, S.H. Wu, H.W. Fang, Y.J. Chen, BI2536 induces mitotic catastrophe and radiosensitization in human oral cancer cells, Oncotarget 9 (2018) 21231–21243.
[195] M. Choi, W. Kim, M.G. Cheon, C.W. Lee, J.E. Kim, Polo-like kinase 1 inhibitor BI2536 causes mitotic catastrophe following activation of the spindle assembly checkpoint in non-small cell lung cancer cells, Cancer Lett. 357 (2015) 591–601.
[196] M. Steegmaier, M. Hoffmann, A. Baum, P. Lenart, M. Petronczki, M. Krssak, U. Gurtler, P. Garin-Chesa, S. Lieb, J. Quant, M. Grauert, G.R. Adolf, N. Kraut, J.M. Peters, W.J. Rettig, BI 2536, a potent and selective inhibitor of polo-like kinase 1, inhibits tumor growth in vivo, Curr. Biol. 17 (2007) 316–322.
[197] A. Frost, K. Mross, S. Steinbild, S. Hedbom, C. Unger, R. Kaiser, D. Trommeshauser, G. Munzert, Phase i study of the Plk1 inhibitor BI 2536 administered intravenously on three consecutive days in advanced solid tumours, Curr. Oncol. 19 (2012) e28–35.
[198] C. Posch, B.D. Cholewa, I. Vujic, M. Sanlorenzo, J. Ma, S.T. Kim, S. Kleffel, T. Schatton, K. Rappersberger, R. Gutteridge, N. Ahmad, S. Ortiz/Urda, Combined inhibition of MEK and Plk1 has synergistic antitumor activity in NRAS mutant melanoma, J. Invest. Dermatol. 135 (2015) 2475–2483.
[199] M.D. Wissing, J. Mendonca, M.S. Kortenhorst, N.S. Kaelber, M. Gonzalez, E. Kim, H. Hammers, P.J. van Diest, M.A. Carducci, S.K. Kachhap, Targeting prostate cancer cell lines with polo-like kinase 1 inhibitors as a single agent and in combination with histone deacetylase inhibitors, Faseb. J. 27 (2013) 4279–4293.
[200] K. Sahin, M. Tuzcu, M. Yabas, C. Orhan, N. Sahin, I.H. Ozercan, LFM-A13, a potent inhibitor of polo-like kinase, inhibits breast carcinogenesis by suppressing proliferation activity and inducing apoptosis in breast tumors of mice, Invest. N. Drugs 36 (2018) 388–395.
[201] K. Gumireddy, M.V. Reddy, S.C. Cosenza, R. Boominathan, S.J. Baker, N. Papathi, J. Jiang, J. Holland, E.P. Reddy, ON01910, a non-ATP-competitive small molecule inhibitor of Plk1, is a potent anticancer agent, Cancer Cell 7 (2005) 275–286.
[202] M.S. Brassesco, J.A. Pezuk, A.G. Morales, J.C. de Oliveira, G.M. Roberto, G.N. da Silva, H. Francisco de Oliveira, C.A. Scrideli, L.G. Tone, In vitro targeting of Polo-like kinase 1 in bladder carcinoma: comparative effects of four potent inhibitors, Cancer Biol. Ther. 14 (2013) 648–657.
[203] M. Hugle, K. Belz, S. Fulda, Identification of synthetic lethality of PLK1 inhibition and microtubule-destabilizing drugs, Cell Death Differ. 22 (2015) 1946–1956.
[204] Y.S. Chou, C.C. Yen, W.M. Chen, Y.C. Lin, Y.S. Wen, W.T. Ke, J.Y. Wang, C.Y. Liu, M.H. Yang, T.H. Chen, C.L. Liu, Cytotoxic mechanism of PLK1 inhibitor GSK461364 against osteosarcoma: mitotic arrest, apoptosis, cellular senescence, and synergistic effect with paclitaxel, Int. J. Oncol. 48 (2016) 1187–1194.
[205] R.F. Bogado, J.A. Pezuk, H.F. de Oliveira, L.G. Tone, M.S. Brassesco, BI 6727 and GSK461364 suppress growth and radiosensitize osteosarcoma cells, but show limited cytotoxic effects when combined with conventional treatments, Anti Canccer Drugs 26 (2015) 56–63.
[206] J.C. Patterson, M.G. Erlander, M.B. Yaffe, Combination of selective polo-like kinase 1 (PLK1) inhibitor PCM-075 with abiraterone in prostate cancer and non-androgen-driven cancer models, J. Clin. Oncol. 36 (2018) 369.
[207] Y. Chiba, S. Sato, H. Itamochi, N. Yoshino, D. Fukagawa, H. Kawamura, Y. Suga, A. Kojima-Chiba, Y. Muraki, T. Sugai, T. Sugiyama, Inhibition of aurora kinase a synergistically enhances cytotoxicity in ovarian clear cell carcinoma cell lines induced by cisplatin: a potential treatment strategy, Int. J. Gynecol. Canc. 27 (2017) 1666–1674.
[208] Y.H. Min, W. Kim, J.E. Kim, The Aurora kinase A inhibitor TC-A2317 disrupts mitotic progression and inhibits cancer cell proliferation, Oncotarget 7 (2016) 84718–84735.
[209] N. Zhou, K. Singh, M.C. Mir, Y. Parker, D. Lindner, R. Dreicer, J.A. Ecsedy, Z. Zhang, B.T. Teh, A. Almasan, D.E. Hansel, The investigational Aurora kinase A inhibitor MLN8237 induces defects in cell viability and cell-cycle progression in malignant bladder cancer cells in vitro and in vivo, Clin. Canc. Res. 19 (2013) 1717–1728.
[210] D.R. Wysong, A. Chakravarty, K. Hoar, J.A. Ecsedy, The inhibition of Aurora A abrogates the mitotic delay induced by microtubule perturbing agents, Cell Cycle 8 (2009) 876–888.
[211] S.L. Davis, K.M. Robertson, T.M. Pitts, J.J. Tentler, E.L. Bradshaw-Pierce, P.J. Klauck, S.M. Bagby, S.L. Hyatt, H.M. Selby, A. Spreafico, J.A. Ecsedy, J.J. Arcaroli, W.A. Messersmith, A.C. Tan, S.G. Eckhardt, Combined inhibition of MEK and Aurora A kinase in KRAS/PIK3CA double-mutant colorectal cancer models, Front. Pharmacol. 6 (2015).
[212] D. Mahadevan, A. Stejskal, L.S. Cooke, A. Manziello, C. Morales, D.O. Persky, R.I. Fisher, T.P. Miller, W. Qi, Aurora A inhibitor (MLN8237) plus vincristine plus rituximab is synthetic lethal and a potential curative therapy in aggressive B-cell non-Hodgkin lymphoma, Clin. Canc. Res. 18 (2012) 2210–2219.
[213] W. Qi, L.S. Cooke, X. Liu, L. Rimsza, D.J. Roe, A. Manziolli, D.O. Persky, T.P. Miller, D. Mahadevan, Aurora inhibitor MLN8237 in combination with docetaxel enhances apoptosis and anti-tumor activity in mantle cell lymphoma, Biochem. Pharmacol. 81 (2011) 881–890.
[214] S. Islam, E. Vick, B. Huber, C. Morales, C. Spier, L. Cooke, E. Weterings, D. Mahadevan, Co-targeting aurora kinase with PD-L1 and PI3K abrogates immune checkpoint mediated proliferation in peripheral T-cell lymphoma: a novel therapeutic strategy, Oncotarget 8 (2017) 100326–100338.
[215] J.A. Muscal, K.A. Scorsone, L. Zhang, J.A. Ecsedy, S.L. Berg, Additive effects of vorinostat and MLN8237 in pediatric leukemia, medulloblastoma, and neuroblastoma cell lines, Invest. N. Drugs 31 (2013) 39–45.
[216] L. Moretti, K. Niermann, S. Schleicher, N.J. Giacalone, V. Varki, K.W. Kim, P. Kopsombut, D.K. Jung, B. Lu, MLN8054, a small molecule inhibitor of aurora kinase a, sensitizes androgen-resistant prostate cancer to radiation, Int. J. Radiat. Oncol. Biol. Phys. 80 (2011) 1189–1197.
[217] V. Sehdev, A. Katsha, J. Ecsedy, A. Zaika, A. Belkhiri, W. El-Rifai, The combination of alisertib, an investigational Aurora kinase A inhibitor, and docetaxel promotes cell death and reduces tumor growth in preclinical cell models of upper gastrointestinal adenocarcinomas, Cancer 119 (2013) 904–914.
[218] V. Sehdev, D. Peng, M. Soutto, M.K. Washington, F. Revetta, J. Ecsedy, A. Zaika, T.T. Rau, R. Schneider-Stock, A. Belkhiri, W. El-Rifai, The aurora kinase A inhibitor MLN8237 enhances cisplatin-induced cell death in esophageal adenocarcinoma cells, Mol. Canc. Therapeut. 11 (2012) 763–774.
[219] G. Görgün, E. Calabrese, T. Hideshima, J. Ecsedy, G. Perrone, M. Mani, H. Ikeda, G. Bianchi, Y. Hu, D. Cirstea, L. Santo, Y.-T. Tai, S. Nahar, M. Zheng, M. Bandi, R.D. Carrasco, N. Raje, N. Munshi, P. Richardson, K.C. Anderson, A novel aurora-a kinase inhibitor MLN8237 induces cytotoxicity and cell cycle arrest in multiple myeloma, Blood 115 (2010) 5202–5213.
[220] K.R. Kelly, S.T. Nawrocki, C.M. Espitia, M. Zhang, J.J. Yang, S. Padmanabhan, J. Ecsedy, F.J. Giles, J.S. Carew, Targeting Aurora A kinase activity with the investigational agent alisertib increases the efficacy of cytarabine through a FOXO-dependent mechanism, Int. J. Canc. 131 (2012) 2693–2703.
[221] Y. Lin, F.M. Richards, B.F. Krippendorff, J.L. Bramhall, J.A. Harrington, T.E. Bapiro, A. Robertson, D. Zheleva, D.I. Jodrell, Paclitaxel and CYC3, an aurora kinase A inhibitor, synergise in pancreatic cancer cells but not bone marrow precursor cells, Br. J. Canc. 107 (2012) 1692–1701.
[222] T. Shimomura, S. Hasako, Y. Nakatsuru, T. Mita, K. Ichikawa, T. Kodera, T. Sakai, T. Nambu, M. Miyamoto, I. Takahashi, S. Miki, N. Kawanishi, M. Ohkubo, H. Kotani, Y. Iwasawa, MK-5108, a highly selective Aurora-A kinase inhibitor, shows antitumor activity alone and in combination with docetaxel, Mol. Canc. Therapeut. 9 (2010) 157–166.
[223] D.C. Chinn, W.S. Holland, P.C. Mack, Anticancer activity of the Aurora A kinase inhibitor MK-5108 in non-small-cell lung cancer (NSCLC) in vitro as monotherapy and in combination with chemotherapies, J. Canc. Res. Clin. Oncol. 140 (2014) 1137–1149.
[224] A. Garofalo, E. Naumova, L. Manenti, C. Ghilardi, G. Ghisleni, M. Caniatti, T. Colombo, J.M. Cherrington, E. Scanziani, M.I. Nicoletti, R. Giavazzi, The combination of the tyrosine kinase receptor inhibitor SU6668 with paclitaxel affects ascites formation and tumor spread in ovarian carcinoma xenografts growing orthotopically, Clin. Canc. Res. 9 (2003) 3476–3485.
[225] S. Machida, Y. Saga, Y. Takei, K. Takahashi, H. Nonaka, H. Fujiwara, M. Ohwada, M. Suzuki, Combination therapy of tyrosine kinase receptor inhibitor TSU-68 (SU6668) and paclitaxel inhibits subcutaneous xenografts of endometrial cancer, Mol. Med. Rep. 1 (2008) 843–846.
[226] T.L. Bush, M. Payton, S. Heller, G. Chung, K. Hanestad, J.B. Rottman, R. Loberg, G. Friberg, R.L. Kendall, D. Saffran, R. Radinsky, AMG 900, a small-molecule inhibitor of aurora kinases, potentiates the activity of microtubule-targeting agents in human metastatic breast cancer models, Mol. Canc. Therapeut. 12 (2013) 2356–2366.
[227] K.S. Borges, A.F. Andrade, V.S. Silveira, D.S. Marco Antonio, E.J.R. Vasconcelos, S.R.R. Antonini, L.G. Tone, C.A. Scrideli, The aurora kinase inhibitor AMG 900 increases apoptosis and induces chemosensitivity to anticancer drugs in the NCI-H295 adrenocortical carcinoma cell line, Anti Canccer Drugs 28 (2017) 634–644.
[228] J.P. Arbitrario, B.J. Belmont, M.J. Evanchik, W.M. Flanagan, R.V. Fucini, S.K. Hansen, S.O. Harris, A. Hashash, U. Hoch, J.N. Hogan, A.R. Howlett, J.W. Jacobs, J.W. Lam, S.C. Ritchie, M.J. Romanowski, J.A. Silverman, D.E. Stockett, J.N. Teague, K.M. Zimmerman, P. Taverna, SNS-314, a pan-Aurora kinase inhibitor, shows potent anti-tumor activity and dosing flexibility in vivo, Cancer Chemother. Pharmacol. 65 (2010) 707–717.
[229] E.C. VanderPorten, P. Taverna, J.N. Hogan, M.D. Ballinger, W.M. Flanagan, R.V. Fucini, The Aurora kinase inhibitor SNS-314 shows broad therapeutic potential with chemotherapeutics and synergy with microtubule-targeted agents in a colon carcinoma model, Mol. Canc. Therapeut. 8 (2009) 930–939.
[230] C.D. Scharer, N. Laycock, A.O. Osunkoya, S. Logani, J.F. McDonald, B.B. Benigno, C.S. Moreno, Aurora kinase inhibitors synergize with paclitaxel to induce apoptosis in ovarian cancer cells, J. Transl. Med. 6 (2008) 79.
[231] S. Fu, Y. Li, J. Huang, T. Liu, Z. Hong, A. Chen, R.C. Bast, J.J. Kavanagh, D.M. Gershenson, A.K. Sood, W. Hu, Aurora kinase inhibitor VE 465 synergistically enhances cytotoxicity of carboplatin in ovarian cancer cells through induction of apoptosis and downregulation of histone 3, Cancer Biol. Ther. 13 (2012) 1034–1041.
[232] Y.G. Lin, A. Immaneni, W.M. Merritt, L.S. Mangala, S.W. Kim, M.M. Shahzad, Y.T. Tsang, G.N. Armaiz-Pena, C. Lu, A.A. Kamat, L.Y. Han, W.A. Spannuth, A.M. Nick, C.N. Landen Jr., K.K. Wong, M.J. Gray, R.L. Coleman, D.C. Bodurka, W.R. Brinkley, A.K. Sood, Targeting aurora kinase with MK-0457 inhibits ovarian cancer growth, Clin. Canc. Res. 14 (2008) 5437–5446.
[233] K. Yoshida, T. Nagai, K. Ohmine, M. Uesawa, P. Sripayap, Y. Ishida, K. Ozawa, Vincristine potentiates the anti-proliferative effect of an aurora kinase inhibitor, VE-465, in myeloid leukemia cells, Biochem. Pharmacol. 82 (2011) 1884–1890.
[234] R. Yao, J. Zheng, W. Zheng, Y. Gong, W. Liu, R. Xing, VX680 suppresses the growth of HepG2 cells and enhances the chemosensitivity to cisplatin, Oncol Lett 7 (2014) 121–124.
[235] J.E. Choi, S.M. Woo, K.J. Min, S.H. Kang, S.J. Lee, T.K. Kwon, Combined treatment

with ABT-737 and VX-680 induces apoptosis in Bcl-2- and c-FLIP-overexpressing breast carcinoma cells, Oncol. Rep. 33 (2015) 1395–1401.
[236] E.Y. Moawad, Optimizing and predicting the in vivo activity of AT9283 as a monotherapy and in combination with paclitaxel, J. Gastrointest. Canc. 46 (2015) 380–389.
[237] L. Zhang, S. Zhang, ZM447439, the Aurora kinase B inhibitor, suppresses the growth of cervical cancer SiHa cells and enhances the chemosensitivity to cisplatin, J. Obstet. Gynaecol. Res. 37 (2011) 591–600.
[238] K.S. Borges, A.M. Castro-Gamero, D.A. Moreno, V. da Silva Silveira, M.S. Brassesco, R.G. de Paula Queiroz, H.F. de Oliveira, C.G. Carlotti Jr., C.A. Scrideli, L.G. Tone, Inhibition of Aurora kinases enhances chemosensitivity to temozolomide and causes radiosensitization in glioblastoma cells, J. Canc. Res. Clin. Oncol. 138 (2012) 405–414.
[239] Y. Tao, C. Leteur, J. Calderaro, F. Girdler, P. Zhang, V. Frascogna, M. Varna, P. Opolon, M. Castedo, J. Bourhis, G. Kroemer, E. Deutsch, The aurora B kinase inhibitor AZD1152 sensitizes cancer cells to fractionated irradiation and induces mitotic catastrophe, Cell Cycle 8 (2009) 3172–3181.
[240] Y. Tao, P. Zhang, F. Girdler, V. Frascogna, M. Castedo, J. Bourhis, G. Kroemer, E. Deutsch, Enhancement of radiation response in p53-deficient cancer cells by the Aurora-B kinase inhibitor AZD1152, Oncogene 27 (2008) 3244–3255.
[241] K.J. Niermann, L. Moretti, N.J. Giacalone, Y. Sun, S.M. Schleicher, P. Kopsombut, L.R. Mitchell, K.W. Kim, B. Lu, Enhanced radiosensitivity of androgen-resistant prostate cancer: AZD1152-mediated Aurora kinase B inhibition, Radiat. Res. 175 (2011) 444–451.
[242] A. Zekri, S.H. Ghaffari, S. Ghanizadeh-Vesali, M. Yaghmaie, A. Salmaninejad, K. Alimoghaddam, M.H. Modarressi, A. Ghavamzadeh, AZD1152-HQPA induces growth arrest and apoptosis in androgen-dependent prostate cancer cell line (LNCaP) via producing aneugenic micronuclei and polyploidy, Tumour Biol 36 (2015) 623–632.
[243] Y. Ma, J. Weimer, R. Fredrik, S. Adam-Klages, S. Sebens, A. Caliebe, F. Hilpert, C. Eckmann-Scholz, N. Arnold, C. Schem, Aurora kinase inhibitor AZD1152 has an additional effect of platinum on a sequential application at the human ovarian cancer cell line SKOV3, Arch. Gynecol. Obstet. 288 (2013) 173–182.
[244] R.P. Evans, C. Naber, T. Steffler, T. Checkland, C.A. Maxwell, J.J. Keats, A.R. Belch, L.M. Pilarski, R. Lai, T. Reiman, The selective Aurora B kinase inhibitor AZD1152 is a potential new treatment for multiple myeloma, Br. J. Haematol. 140 (2008) 295–302.
[245] J. Yang, T. Ikezoe, C. Nishioka, T. Tasaka, A. Taniguchi, Y. Kuwayama, N. Komatsu, K. Bandobashi, K. Togitani, H.P. Koeffler, H. Taguchi, A. Yokoyama, AZD1152, a novel and selective aurora B kinase inhibitor, induces growth arrest, apoptosis, and sensitization for tubulin depolymerizing agent or topoisomerase II inhibitor in human acute leukemia cells in vitro and in vivo, Blood 110 (2007) 2034–2040.
[246] T. Ikezoe, T. Takeuchi, J. Yang, Y. Adachi, C. Nishioka, M. Furihata, H.P. Koeffler, A. Yokoyama, Analysis of Aurora B kinase in non-Hodgkin lymphoma, Lab. Invest.; J. Tech. Method. Pathol. 89 (2009) 1364–1373.
[247] A.M. Wengner, G. Siemeister, M. Koppitz, V. Schulze, D. Kosemund, U. Klar, D. Stoeckigt, R. Neuhaus, P. Lienau, B. Bader, S. Prechtl, M. Raschke, A.L. Frisk, O. von Ahsen, M. Michels, B. Kreft, F. von Nussbaum, M. Brands, D. Mumberg, K. Ziegelbauer, Novel Mps1 kinase inhibitors with potent antitumor activity, Mol. Canc. Therapeut. 15 (2016) 583–592.
[248] A.R.R. Maia, S. Linder, J.Y. Song, C. Vaarting, U. Boon, C.E.J. Pritchard, A. Velds, I.J. Huijbers, O. van Tellingen, J. Jonkers, R.H. Medema, Mps1 inhibitors synergise with low doses of taxanes in promoting tumour cell death by enhancement of errors in cell division, Br. J. Canc. 118 (2018) 1586–1595.
[249] B.A. Tannous, M. Kerami, P.M. Van der Stoop, N. Kwiatkowski, J. Wang, W. Zhou, A.F. Kessler, G. Lewandrowski, L. Hiddingh, N. Sol, T. Lagerweij, L. Wedekind, J.M. Niers, M. Barazas, R.J. Nilsson, D. Geerts, P.C. De Witt Hamer, C. Hagemann, W.P. Vandertop, O. Van Tellingen, D.P. Noske, N.S. Gray, T. Wurdinger, Effects of the selective MPS1 inhibitor MPS1-IN-3 on glioblastoma sensitivity to antimitotic drugs, J. Natl. Cancer Inst. 105 (2013) 1322–1331.
[250] T. Fujita, H. Doihara, K. Washio, H. Ino, M. Murakami, M. Naito, N. Shimizu, Antitumor effects and drug interactions of the proteasome inhibitor bortezomib (PS341) in gastric cancer cells, Anti Canccer Drugs 18 (2007) 677–686.
[251] S.H. Bae, H.-M. Ryoo, M.K. Kim, K.H. Lee, J.-I. Sin, M.S. Hyun, Effects of the proteasome inhibitor bortezomib alone and in combination with chemotherapeutic agents in gastric cancer cell lines, Oncol. Rep. 19 (2008) 1027–1032.
[252] A.D. Steg, M.R. Burke, H.M. Amm, A.A. Katre, Z.C. Dobbin, D.H. Jeong, C.N. Landen, Proteasome inhibition reverses hedgehog inhibitor and taxane resistance in ovarian cancer, Oncotarget 5 (2014) 7065–7080.
[253] D.-H. Weng, Y. Li, F.-F. Kong, L.-S. Fan, Y. Hu, X.-H. Song, H. Xing, S.-X. Wang, D. Ma, Proteasome inhibitors sensitize ovarian cancer cells to paclitaxel induced apoptosis, Zhonghua Fu Chan Ke Za Zhi 43 (2008) 770–773.
[254] S. Taromi, F. Lewens, R. Arsenic, D. Sedding, J. Sänger, A. Kunze, M. Möbs, J. Benecke, H. Freitag, F. Christen, D. Kaemmerer, A. Lupp, M. Heilmann, H. Lammert, C.-P. Schneider, K. Richter, M. Hummel, B. Siegmund, M. Burger, F. Briest, P. Grabowski, Proteasome inhibitor bortezomib enhances the effect of standard chemotherapy in small cell lung cancer, Oncotarget 8 (2017) 97061–97078.
[255] L. Sooman, J. Gullbo, M. Bergqvist, S. Bergstrom, J. Lennartsson, S. Ekman, Synergistic effects of combining proteasome inhibitors with chemotherapeutic drugs in lung cancer cells, BMC Res. Notes 10 (2017) 544-544.
[256] E. Konac, N. Varol, I. Kilicciogl u, C.Y. Bilen, Synergistic effects of cisplatin and proteasome inhibitor bortezomib on human bladder cancer cells, Oncology letters 10 (2015) 560–564.
[257] J. Neukirchen, A. Meier, A. Rohrbeck, G. Garcia-Pardillos, U. Steidl, R. Fenk, R. Haas, R. Kronenwett, U.P. Rohr, The proteasome inhibitor bortezomib acts differently in combination with p53 gene transfer or cytotoxic chemotherapy on NSCLC cells, Cancer Gene Ther. 14 (2007) 431–439.
[258] C.S. Jung, Z. Zhou, F.R. Khuri, S.-Y. Sun, Assessment of apoptosis-inducing effects of docetaxel combined with the proteasome inhibitor PS-341 in human lung cancer cells, Cancer Biol. Ther. 6 (2007) 749–754.
[259] A.M. Fribley, B. Evenchik, Q. Zeng, B.K. Park, J.Y. Guan, H. Zhang, T.J. Hale, M.S. Soengas, R.J. Kaufman, C.-Y. Wang, Proteasome inhibitor PS-341 induces apoptosis in cisplatin-resistant squamous cell carcinoma cells by induction of Noxa, J. Biol. Chem. 281 (2006) 31440–31447.
[260] R.L. Elstrom, B. Andemariam, P. Martin, J. Ruan, T.B. Shore, M. Coleman, J.P. Leonard, R.R. Furman, Bortezomib in combination with rituximab, dexamethasone, ifosfamide, cisplatin and etoposide chemoimmunotherapy in patients with relapsed and primary refractory diffuse large B-cell lymphoma, Leuk. Lymphoma 53 (2012) 1469–1473.
[261] P.J. Vlachostergios, E. Hatzidaki, C.D. Befani, P. Liakos, C.N. Papandreou, Bortezomib overcomes MGMT-related resistance of glioblastoma cell lines to temozolomide in a schedule-dependent manner, Invest. N. Drugs 31 (2013) 1169–1181.
[262] S.T. Nawrocki, B. Sweeney-Gotsch, R. Takamori, D.J. McConkey, The proteasome inhibitor bortezomib enhances the activity of docetaxel in orthotopic human pancreatic tumor xenografts, Mol. Canc. Therapeut. 3 (2004) 59–70.
[263] S. Pundir, H.-Y. Vu, V.R. Solomon, R. McClure, H. Lee, VR23: a quinoline-sulfonyl hybrid proteasome inhibitor that selectively kills cancer via cyclin E-mediated centrosome amplification, Cancer Res. 75 (2015) 4164–4175.
[264] H. Wang, Y. Yu, Z. Jiang, W.-M. Cao, Z. Wang, J. Dou, Y. Zhao, Y. Cui, H. Zhang, Next-generation proteasome inhibitor MLN9708 sensitizes breast cancer cells to doxorubicin-induced apoptosis, Sci. Rep. 6 (2016) 26456.
[265] H. Li, Z. Chen, T. Hu, L. Wang, Y. Yu, Y. Zhao, W. Sun, S. Guan, J.C. Pang, S.E. Woodfield, Q. Liu, J. Yang, Novel proteasome inhibitor ixazomib sensitizes neuroblastoma cells to doxorubicin treatment, Sci. Rep. 6 (2016) 34397.
[266] N. Guo, Z. Peng, J. Zhang, Proteasome inhibitor MG132 enhances sensitivity to cisplatin on ovarian carcinoma cells in vitro and in vivo, Int. J. Gynecol. Canc.: Off. J. Int. Gynecol. Cancer Soc. 26 (2016) 839–844.
[267] L. Dang, F. Wen, Y. Yang, D. Liu, K. Wu, Y. Qi, X. Li, J. Zhao, D. Zhu, C. Zhang, S. Zhao, Proteasome inhibitor MG132 inhibits the proliferation and promotes the cisplatin-induced apoptosis of human esophageal squamous cell carcinoma cells, Int. J. Mol. Med. 33 (2014) 1083–1088.
[268] Y.-l. Wu, H.-j. Yang, K.-k. Wang, G.-s. Tao, Y.-z. Liu, Y. Hu, Reversion of resistance to cisplatin induced by MG132 in cervical cancer line HCE1 multicellular spheroid, Zhonghua Fu Chan Ke Za Zhi 45 (2010) 287–291.
[269] F. Sun, Y. Zhang, L. Xu, S. Li, X. Chen, L. Zhang, Y. Wu, J. Li, Proteasome inhibitor MG132 enhances cisplatin-induced apoptosis in osteosarcoma cells and inhibits tumor growth, Oncol. Res. 26 (2017) 655–664.
[270] Y. Zhang, B. Yang, J. Zhao, X. Li, L. Zhang, Z. Zhai, Proteasome inhibitor carbobenzoxy-L-leucyl-L-leucyl-L-leucinal (MG132) enhances therapeutic effect of paclitaxel on breast cancer by inhibiting nuclear factor (NF)-κB signaling, Med. Sci. Mon. Int. Med. J. Exp. Clin. Res.: Int. Med. J. Experimental Clin. Res. 24 (2018) 294–304.
[271] H. Oyaizu, Y. Adachi, T. Okumura, M. Okigaki, N. Oyaizu, S. Taketani, K. Ikebukuro, S. Fukuhara, S. Ikehara, Proteasome inhibitor 1 enhances paclitaxel-induced apoptosis in human lung adenocarcinoma cell line, Oncol. Rep. 8 (2001) 825–829.
[272] D. Soligo, F. Servida, D. Delia, E. Fontanella, G. Lamorte, L. Caneva, R. Fumiatti, G. Lambertenghi Deliliers, The apoptogenic response of human myeloid leukaemia cell lines and of normal and malignant haematopoietic progenitor cells to the proteasome inhibitor PSI, Br. J. Haematol. 113 (2001) 126–135.
[273] J.J. Gu, F.J. Hernandez-Ilizaliturri, C. Mavis, N.M. Czuczman, G. Deeb, J. Gibbs, J.J. Skitzki, R. Patil, M.S. Czuczman, MLN2238, a proteasome inhibitor, induces caspase-dependent cell death, cell cycle arrest, and potentiates the cytotoxic activity of chemotherapy agents in rituximab-chemotherapy-sensitive or rituximab-chemotherapy-resistant B-cell lymphoma preclinical mod, Anti Canccer Drugs 24 (2013) 1030–1038.
[274] Y.E. Xu, D.I. Li, L. Zeng, C. Wang, L. Zhang, Y.A.N. Wang, Y. Yu, S. Liu, Z. Li, Proteasome inhibitor lactacystin enhances cisplatin cytotoxicity by increasing endoplasmic reticulum stress-associated apoptosis in HeLa cells, Mol. Med. Rep. 11 (2015) 189–195.
[275] W. Huang, Q. Zhou, X. Yuan, Z.-M. Ge, F.-X. Ran, H.-Y. Yang, G.-L. Qiang, R.-T. Li, J.-R. Cui, Proteasome inhibitor YSY01A enhances cisplatin cytotoxicity in cisplatin-resistant human ovarian cancer cells, J. Canc. 7 (2016) 1133–1141.
[276] T. Takeshita, W. Wu, A. Koike, M. Fukuda, T. Ohta, Perturbation of DNA repair pathways by proteasome inhibitors corresponds to enhanced chemosensitivity of cells to DNA damage-inducing agents, Cancer Chemother. Pharmacol. 64 (2009) 1039–1046.
[277] P. Kapoor, V. Ramakrishnan, S.V. Rajkumar, Bortezomib combination therapy in multiple myeloma, Semin. Hematol. 49 (2012) 228–242.
[278] S. Giovinazzi, D. Bellapu, V.M. Morozov, A.M. Ishov, Targeting mitotic exit with hyperthermia or APC/C inhibition to increase paclitaxel efficacy, Cell Cycle 12 (2013) 2598–2607.
[279] M. Eguren, M. Álvarez-Fernández, F. García, A.J. López-Contreras, K. Fujimitsu, H. Yaguchi, J.L. Luque-García, O. Fernández-Capetillo, J. Muñoz, H. Yamano, M. Malumbres, A synthetic lethal interaction between APC/C and topoisomerase poisons uncovered by proteomic screens, Cell Rep. 6 (2014) 670–683.
[280] F. Manero, F. Gautier, T. Gallenne, N. Cauquil, D. Gree, P.F. Cartron, O. Geneste, R. Gree, F.M. Vallette, P. Juin, The small organic compound HA14-1 prevents Bcl-2 interaction with Bax to sensitize malignant glioma cells to induction of cell

death, Cancer Res. 66 (2006) 2757–2764.
[281] M. Weyland, F. Manero, A. Paillard, D. Gree, G. Viault, D. Jarnet, P. Menei, P. Juin, I. Chourpa, J.P. Benoit, R. Gree, E. Garcion, Mitochondrial targeting by use of lipid nanocapsules loaded with SV30, an analogue of the small-molecule Bcl-2 inhibitor HA14-1, J. Contr. Release: Off. J. Controlled Release Soc. 151 (2011) 74–82.
[282] E.D. Arisan, O. Kutuk, T. Tezil, C. Bodur, D. Telci, H. Basaga, Small inhibitor of Bcl-2, HA14-1, selectively enhanced the apoptotic effect of cisplatin by modulating Bcl-2 family members in MDA-MB-231 breast cancer cells, Breast Canc. Res. Treat. 119 (2010) 271–281.
[283] H. Yamaguchi, S.R. Paranawithana, M.W. Lee, Z. Huang, K.N. Bhalla, H.G. Wang, Epothilone B analogue (BMS-247550)-mediated cytotoxicity through induction of Bax conformational change in human breast cancer cells, Cancer Res. 62 (2002) 466–471.
[284] M.M. Mortenson, J.G. Galante, O. Gilad, M.G. Schlieman, S. Virudachalam, H.J. Kung, R.J. Bold, BCL-2 functions as an activator of the AKT signaling pathway in pancreatic cancer, J. Cell. Biochem. 102 (2007) 1171–1179.
[285] Z.Y. Hu, X.F. Zhu, Z.D. Zhong, J. Sun, J. Wang, D. Yang, Y.X. Zeng, ApoG2, a novel inhibitor of antiapoptotic Bcl-2 family proteins, induces apoptosis and suppresses tumor growth in nasopharyngeal carcinoma xenografts, Int. J. Canc. 123 (2008) 2418–2429.
[286] S. Banerjee, M. Choi, A. Aboukameel, Z. Wang, M. Mohammad, J. Chen, D. Yang, F.H. Sarkar, R.M. Mohammad, Preclinical studies of apogossypolone, a novel pan inhibitor of bcl-2 and mcl-1, synergistically potentiates cytotoxic effect of gemcitabine in pancreatic cancer cells, Pancreas 39 (2010) 323–331.
[287] T. Song, G. Chai, Y. Liu, M. Xie, Q. Chen, X. Yu, H. Sheng, Z. Zhang, Mechanism of synergy of BH3 mimetics and paclitaxel in chronic myeloid leukemia cells: mcl-1 inhibition, Eur. J. Pharmaceut. Sci. 70 (2015) 64–71.
[288] H. Li, L. Piao, P. Xu, W. Ye, S. Zhong, S.H. Lin, S.K. Kulp, Y. Mao, Y. Cho, L.J. Lee, R.J. Lee, Y.C. Lin, Liposomes containing (-)-gossypol-enriched cottonseed oil suppress Bcl-2 and Bcl-xL expression in breast cancer cells, Pharm. Res. (N. Y.) 28 (2011) 3256–3264.
[289] B. Karaca, H. Atmaca, S. Uzunoglu, B. Karabulut, U.A. Sanli, R. Uslu, Enhancement of taxane-induced cytotoxicity and apoptosis by gossypol in human breast cancer cell line MCF-7, J BUON 14 (2009) 479–485.
[290] J.A. Macoska, S. Adsule, K. Tantivejkul, S. Wang, K.J. Pienta, C.T. Lee, Gossypol promotes the apoptosis of bladder cancer cells in vitro, Pharmacol. Res. 58 (2008) 323–331.
[291] J. Mani, S. Vallo, S. Rakel, P. Antonietti, F. Gessler, R. Blaheta, G. Bartsch, M. Michaelis, J. Cinatl, A. Haferkamp, D. Kogel, Chemoresistance is associated with increased cytoprotective autophagy and diminished apoptosis in bladder cancer cells treated with the BH3 mimetic (-)-Gossypol (AT-101), BMC Canc. 15 (2015) 224.
[292] !!!INVALID CITATION!!! {Cengiz, 2010 #17;Meng, 2008 #18;McGregor, 2010 #951}).
[293] B. Karaca, H. Atmaca, E. Bozkurt, A. Kisim, S. Uzunoglu, B. Karabulut, C. Sezgin, U.A. Sanli, R. Uslu, Combination of AT-101/cisplatin overcomes chemoresistance by inducing apoptosis and modulating epigenetics in human ovarian cancer cells, Mol. Biol. Rep. 40 (2013) 3925–3933.
[294] W. Hu, F. Wang, J. Tang, X. Liu, Z. Yuan, C. Nie, Y. Wei, Proapoptotic protein Smac mediates apoptosis in cisplatin-resistant ovarian cancer cells when treated with the anti-tumor agent AT101, J. Biol. Chem. 287 (2012) 68–80.
[295] T. Ren, J. Shan, M. Li, Y. Qing, C. Qian, G. Wang, Q. Li, G. Lu, C. Li, Y. Peng, H. Luo, S. Zhang, Y. Yang, Y. Cheng, D. Wang, S.F. Zhou, Small-molecule BH3 mimetic and pan-Bcl-2 inhibitor AT-101 enhances the antitumor efficacy of cisplatin through inhibition of APE1 repair and redox activity in non-small-cell lung cancer, Drug Des. Dev. Ther. 9 (2015) 2887–2910.
[296] Z.M. Li, W.Q. Jiang, Z.Y. Zhu, X.F. Zhu, J.M. Zhou, Z.C. Liu, D.J. Yang, Z.Z. Guang, Synergistic cytotoxicity of Bcl-xL inhibitor, gossypol and chemotherapeutic agents in non-Hodgkin's lymphoma cells, Cancer Biol. Ther. 7 (2008) 51–60.
[297] C. Qian, M. Li, J. Sui, T. Ren, Z. Li, L. Zhang, L. Zhou, Y. Cheng, D. Wang, Identification of a novel potential antitumor activity of gossypol as an APE1/Ref-1 inhibitor, Drug Des. Dev. Ther. 8 (2014) 485–496.
[298] S.F. Zerp, T.R. Stoter, F.J. Hoebers, M.W. van den Brekel, R. Dubbelman, G.K. Kuipers, M.V. Lafleur, B.J. Slotman, M. Verheij, Targeting anti-apoptotic Bcl-2 by AT-101 to increase radiation efficacy: data from in vitro and clinical pharmacokinetic studies in head and neck cancer, Radiat. Oncol. 10 (2015) 158.
[299] V. Adamski, A. Hempelmann, C. Fluh, R. Lucius, M. Synowitz, K. Hattermann, J. Held-Feindt, Dormant glioblastoma cells acquire stem cell characteristics and are differentially affected by Temozolomide and AT101 treatment, Oncotarget 8 (2017) 108064–108078.
[300] V. Voss, C. Senft, V. Lang, M.W. Ronellenfitsch, J.P. Steinbach, V. Seifert, D. Kogel, The pan-Bcl-2 inhibitor (-)-gossypol triggers autophagic cell death in malignant glioma, Mol. Canc. Res. 8 (2010) 1002–1016.
[301] M.A. Jarzabek, V. Amberger-Murphy, J.J. Callanan, C. Gao, A.M. Zagozdzon, L. Shiels, J. Wang, K.L. Ligon, B.E. Rich, P. Dicker, W.M. Gallagher, J.H. Prehn, A.T. Byrne, Interrogation of gossypol therapy in glioblastoma implementing cell line and patient-derived tumour models, Br. J. Canc. 111 (2014) 2275–2286.
[302] M.P. Kline, S.V. Rajkumar, M.M. Timm, T.K. Kimlinger, J.L. Haug, J.A. Lust, P.R. Greipp, S. Kumar, R-(-)-gossypol (AT-101) activates programmed cell death in multiple myeloma cells, Exp. Hematol. 36 (2008) 568–576.
[303] A. Paulus, K. Chitta, S. Akhtar, D. Personett, K.C. Miller, K.J. Thompson, J. Carr, S. Kumar, V. Roy, S.M. Ansell, J.R. Mikhael, A. Dispenzieri, C.B. Reeder, C.E. Rivera, J. Foran, A. Chanan-Khan, AT-101 downregulates BCL2 and MCL1 and potentiates the cytotoxic effects of lenalidomide and dexamethasone in preclinical models of multiple myeloma and Waldenstrom macroglobulinaemia, Br. J. Haematol. 164 (2014) 352–365.
[304] A. Masood, K. Chitta, A. Paulus, A.N. Khan, T. Sher, N. Ersing, K.C. Miller, D. Manfredi, S. Ailawadhi, I. Borrelo, K.P. Lee, A. Chanan-Khan, Downregulation of BCL2 by AT-101 enhances the antileukaemic effect of lenalidomide both by an immune dependant and independent manner, Br. J. Haematol. 157 (2012) 59–66.
[305] H. Tamaki, N. Harashima, M. Hiraki, N. Arichi, N. Nishimura, H. Shiina, K. Naora, M. Harada, Bcl-2 family inhibition sensitizes human prostate cancer cells to docetaxel and promotes unexpected apoptosis under caspase-9 inhibition, Oncotarget 5 (2014) 11399–11412.
[306] J. Chen, S. Jin, V. Abraham, X. Huang, B. Liu, M.J. Mitten, P. Nimmer, X. Lin, M. Smith, Y. Shen, A.R. Shoemaker, S.K. Tahir, H. Zhang, S.L. Ackler, S.H. Rosenberg, H. Maecker, D. Sampath, J.D. Leverson, C. Tse, S.W. Elmore, The Bcl-2/Bcl-X(L)/Bcl-w inhibitor, navitoclax, enhances the activity of chemotherapeutic agents in vitro and in vivo, Mol. Canc. Therapeut. 10 (2011) 2340–2349.
[307] C. Wang, S.B. Huang, M.C. Yang, Y.T. Lin, I.H. Chu, Y.N. Shen, Y.H. Chiu, S.H. Hung, L. Kang, Y.R. Hong, C.H. Chen, Combining paclitaxel with ABT-263 has a synergistic effect on paclitaxel resistant prostate cancer cells, PloS One 10 (2015) e0120913.
[308] N. Tan, M. Malek, J. Zha, P. Yue, R. Kassees, L. Berry, W.J. Fairbrother, D. Sampath, L.D. Belmont, Navitoclax enhances the efficacy of taxanes in non-small cell lung cancer models, Clin. Canc. Res. 17 (2011) 1394–1404.
[309] M. Matsumoto, W. Nakajima, M. Seike, A. Gemma, N. Tanaka, Cisplatin-induced apoptosis in non-small-cell lung cancer cells is dependent on Bax- and Bak-induction pathway and synergistically activated by BH3-mimetic ABT-263 in p53 wild-type and mutant cells, Biochem. Biophys. Res. Commun. 473 (2016) 490–496.
[310] J. Li, Y. Chen, J. Wan, X. Liu, C. Yu, W. Li, ABT-263 enhances sorafenib-induced apoptosis associated with Akt activity and the expression of Bax and p21((CIP1/WAF1)) in human cancer cells, Br. J. Pharmacol. 171 (2014) 3182–3195.
[311] H. Zall, A. Weber, R. Besch, N. Zantl, G. Hacker, Chemotherapeutic drugs sensitize human renal cell carcinoma cells to ABT-737 by a mechanism involving the Noxa-dependent inactivation of Mcl-1 or A1, Mol. Canc. 9 (2010) 164.
[312] O. Kutuk, A. Letai, Alteration of the mitochondrial apoptotic pathway is key to acquired paclitaxel resistance and can be reversed by ABT-737, Cancer Res. 68 (2008) 7985–7994.
[313] J. Witham, M.R. Valenti, A.K. De-Haven-Brandon, S. Vidot, S.A. Eccles, S.B. Kaye, A. Richardson, The Bcl-2/Bcl-XL family inhibitor ABT-737 sensitizes ovarian cancer cells to carboplatin, Clin. Canc. Res. 13 (2007) 7191–7198.
[314] H.Y. You, X.M. Xie, W.J. Zhang, H.L. Zhu, F.Z. Jiang, Berberine modulates cisplatin sensitivity of human gastric cancer cells by upregulation of miR-203, in Vitro Cell, Dev Biol Anim 52 (2016) 857–863.
[315] A.R. Shoemaker, A. Oleksijew, J. Bauch, B.A. Belli, T. Borre, M. Bruncko, T. Deckwirth, D.J. Frost, K. Jarvis, M.K. Joseph, K. Marsh, W. McClellan, H. Nellans, S. Ng, P. Nimmer, J.M. O'Connor, T. Oltersdorf, W. Qing, W. Shen, J. Stavropoulos, S.K. Tahir, B. Wang, R. Warner, H. Zhang, S.W. Fesik, S.H. Rosenberg, S.W. Elmore, A small-molecule inhibitor of Bcl-XL potentiates the activity of cytotoxic drugs in vitro and in vivo, Cancer Res. 66 (2006) 8731–8739.
[316] S. Osaki, H. Tazawa, J. Hasei, Y. Yamakawa, T. Omori, K. Sugiu, T. Komatsubara, T. Fujiwara, T. Sasaki, T. Kunisada, A. Yoshida, Y. Urata, S. Kagawa, T. Ozaki, T. Fujiwara, Ablation of MCL1 expression by virally induced microRNA-29 reverses chemoresistance in human osteosarcomas, Sci. Rep. 6 (2016) 28953-28953.
[317] J. Ma, Z. Zhao, K. Wu, Z. Xu, K. Liu, MCL-1 is the key target of adjuvant chemotherapy to reverse the cisplatin-resistance in NSCLC, Gene 587 (2016) 147–154.
[318] Y. Lu, H. Huang, H. Yang, D. Chen, S. Wu, Z. Jiang, R. Wang, Small molecule inhibitor TW-37 is tolerable and synergistic with chemotherapy in nasopharyngeal carcinoma, Cell Cycle 16 (2017) 1376–1383.
[319] P. Qi, M. Cao, L. Song, C. Chen, M. Liu, N. Li, D. Wu, J. Peng, G. Hu, J. Zhao, The biological activity of cationic liposomes in drug delivery and toxicity test in animal models, Environ. Toxicol. Pharmacol. 47 (2016) 159–164.
[320] R.S. Jackson, W. Placzek, A. Fernandez, S. Ziaee, C.-Y. Chu, J. Wei, J. Stebbins, S. Kitada, G. Fritz, J.C. Reed, L.W. Chung, M. Pellecchia, N.A. Bhowmick, Sabutoclax, a mcl-1 antagonist, inhibits tumorigenesis in transgenic mouse and human xenograft models of prostate cancer, Neoplasia 14 (2012) 656-IN624.
[321] J.J. Hwang, Y.S. Kim, T. Kim, M.J. Kim, I.G. Jeong, J.-H. Lee, J. Choi, S. Jang, S. Ro, C.-S. Kim, A novel histone deacetylase inhibitor, CG200745, potentiates anticancer effect of docetaxel in prostate cancer via decreasing Mcl-1 and Bcl-XL, Invest. N. Drugs 30 (2012) 1434–1442.
[322] H.S. Lee, S.B. Park, S.A. Kim, S.K. Kwon, H. Cha, D.Y. Lee, S. Ro, J.M. Cho, S.Y. Song, A novel HDAC inhibitor, CG200745, inhibits pancreatic cancer cell growth and overcomes gemcitabine resistance, Sci. Rep. 7 (2017) 41615.