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EVOLVING THERAPIES (RM BUKOWSKI, SECTION EDITOR)

Targeting Apoptosis in Cancer

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Abstract

Purpose of Review Apoptosis is a major mechanism of cancer cell death. Thus, evasion of apoptosis results in therapy resistance. Here, we review apoptosis modulators in cancer and their recent developments, including MDM2 inhibitors and kinase inhibitors that can induce effective apoptosis.

Recent Findings Both extrinsic pathways (external stimuli through cell surface death receptor) and intrinsic pathways (mitochondrial-mediated regulation upon genotoxic stress) regulate the complex process of apoptosis through orchestration of various proteins such as members of the BCL-2 family. Dysregulation within these complex steps can result in evasion of apoptosis. However, via the combined evolution of medicinal chemistry and molecular biology, omics assays have led to innovative inducers of apoptosis and inhibitors of anti-apoptotic regulators. Many of these agents are now being tested in cancer patients in early-phase trials.

Summary We believe that despite a sluggish speed of development, apoptosis targeting holds promise as a relevant strategy in cancer therapeutics.

Keywords Apoptosis · Extrinsic apoptosis pathway · Intrinsic apoptosis pathway · BH3 · Cancer · Anti-cancer therapeutics

Introduction

Apoptosis is a programmed cell death process utilized by normal and cancer cells, along with necroptosis, ferroptosis, autophagy, pyroptosis, and others [1, 1]. Apoptosis is a specific form of programmed cell death that involves the blebbing of the cell membrane, which exposes the phosphatidylserine, as well as activates cysteine-aspartic protease (caspase) family proteins [2]. Like many sophisticated regulatory pathways, apoptosis can be a double-edged sword in cancer progression. For example, while apoptosis due to anti-cancer therapy can kill cancer cells, sublethal activation of caspase 3 may result in oncogenic progression, since suboptimal induction of apoptosis can trigger compensatory survival mechanisms such as autophagy [3]. Hence, it is challenging to find the delicate balance between effective apoptosis and inefficient apoptotic pathway activation, leading to further progression of cancer [4]. The current mainstay of cancer treatment is still cytotoxic chemotherapy. Yet, many patients treated with chemotherapy develop residual tumor or recurrent metastatic disease [5, 6, 7]. As apoptosis is critical for maintaining homeostasis in normal cells, defects in apoptosis help cancer cells escape (Fig. 8), causing resistance to standard therapy. The apoptosis pathway also cross-talks with many growth factors and other growth-mediating pathways; therefore, dysregulation of apoptosis can promote tumor growth and progression [9]. A better strategy to induce effective cell death at the initial stage of treatment is essential.

There are two main apoptotic regulation pathways: extrinsic and intrinsic. The extrinsic pathway is triggered by the binding of tumor necrosis factor (TNF), TNF-related apoptosis-inducing ligand (TRAIL), or FAS ligand (APO-1) to the corresponding receptor (TNFR, TRAILR, or FAS, respectively) [10, 11]. Once triggered, activated caspase 8

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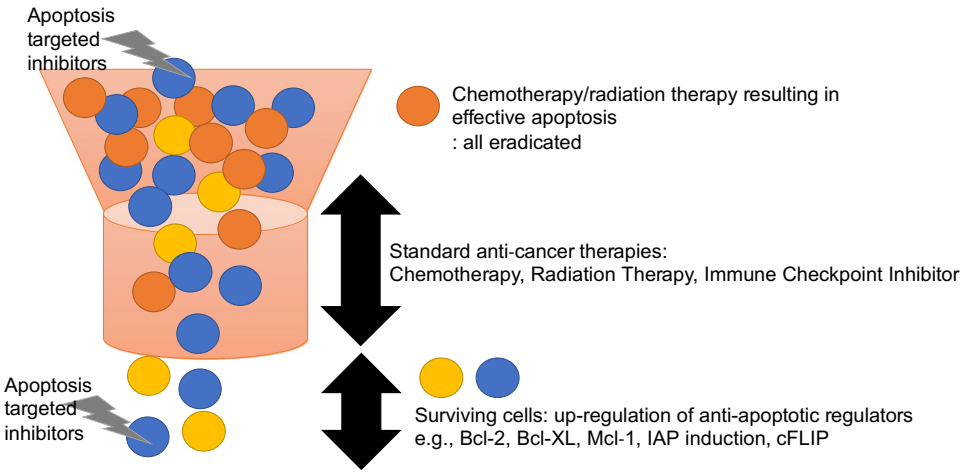

Fig. 1 How evasion of apoptosis can help cancer cells to survive through chemotherapy, radiation therapy, and immune checkpoint inhibitor therapies. Apoptosis = targeted inhibitors can be used either in combination with standard therapies or can be used to treat residual cancer cells when standard treatments are not effective

truncates the BID protein to truncated BID, subsequently activating the pro-apoptotic regulators BAX and BAK. This activation induces mitochondrial outer membrane permeabilization (MOMP) and stimulates the beginning of intrinsic pathway and caspase activation [12, 13]. The intrinsic pathway is also triggered by genotoxic stress to the cells, via unfolded protein response, reactive oxygen species, radiation, and chemical-induced chromosomal abnormalities [14, 15]. MOMP leads to a release and activation of second mitochondria-derived activator of caspase (Smac), also called direct inhibitor of apoptosis protein [IAP]-binding protein with low pI (DIABLO), from the intermembrane space of mitochondria into the cytosol [16] and release of cytochrome C. Released cytochrome C then assembles the apoptosome along with apoptotic peptidase activating factor 1 (APAF1), dATP, and pro-caspase 9 in the cytosol. Smac/DIABLO inactivates anti-apoptotic regulator IAP proteins (XIAP, cIAP1, and cIAP2), resulting in apoptosis. BH3 domain-containing molecules are also essential regulators of the intrinsic pathway; these molecules include BID, BAX, BAK, and BCL-2 family members [17, 18]. Recently, leucine zipper kinases also have been increasingly recognized as key regulators of apoptosis that can be therapeutically targeted.

Type I apoptotic cells induce apoptosis extrinsically independent of mitochondria, while type II apoptotic cells rely on intrinsic, mitochondrial pathways for efficient cell death [19, 20]. Epithelial cells are often type II, while other cells may be type I. Therefore, cancer cells that are of epithelial cell origin most likely utilize both extrinsic and intrinsic apoptosis pathways [21].

The complex regulation of apoptosis creates considerable barriers for drug developers to harness apoptosis induction in effective anti-cancer therapeutics. Nonetheless, the rapidly evolving field of medical chemistry along with omics technologies and translational abilities has produced new apoptosis-targeted agents that are undergoing clinical development. Only a handful of these agents have been approved by the US Food and Drug Administration (FDA) for clinical use within the last decade, indicating that considerable effort is needed to develop apoptosis-targeted therapeutics as a viable strategy.

Extrinsic Pathway and Targeted Agents

The extrinsic apoptosis pathway is initiated and targeted at the cell surface receptor level upstream of intrinsic apoptosis regulation, although the pathway used depends on the cell type. A main trigger of the extrinsic pathway is the binding of pro-apoptotic ligands to cognate death receptors on the cell surface. This binding of ligands forms a death-inducing signaling complex (DISC), leading to activation of caspases 8 and 10. This process requires the death domain at the intracellular site of the death receptor [22]. Activated caspases 8 and 10 cleave effector caspases to amplify the death signal and then activate effector caspases 3, 6, and 7, which serve essential roles in both the intrinsic and extrinsic pathways as executioner caspases.

TRAIL cell surface receptors, which trigger the extrinsic pathway, are highly upregulated in a wide range of solid tumors. Therefore, TRAIL has been identified as an attractive therapeutic molecule for mediating apoptosis in tumor cells while sparing normal cells [23–25]. Activated death receptor 4 (DR4) and death receptor 5 (DR5) induce crosslinking scaffolds as well as tumor-associated leukocytes, which can further induce antibody-dependent, death receptor–mediated apoptosis in cancer cells while having no adverse effect on the proliferation of human T cells [26–28]. Additionally, these antibodies can stimulate NF-κB via a more distant receptor, CD40 [29].

TRAIL-R1 (DR4) agonistic antibodies include mapatumumab (HGS-ETR1) and AY4. AY4 was tested mainly in preclinical studies of anaplastic thyroid cancer and head

and neck cancer and was found to induce reactive oxygen species–mediated apoptosis [30, 31]. Mapatumumab was tested in non–small cell lung cancer and showed a safe toxicity profile in preclinical studies. Unfortunately, neither agent demonstrated clinical efficacy [32, 33]. In triple-negative breast cancer (TNBC), TRAIL activation induced apoptosis in vitro, especially in cell lines with a mesenchymal phenotype, via DR5 or TRAIL receptor 2 (TRAIL-R2) in particular, or as well as via agonist antibodies mimicking the activity of TRAIL [34–36]. DR5-specific agonistic therapeutic antibodies include lexatumumab (HGS-ETR2), drozitumab, conatumumab (AMG-655), LBY 135, and tigatuzumab (CS-1008 or humanized TRA-8). Tigatuzumab was developed as a TRAIL humanized agonistic monoclonal antibody directed against DR5 [37, 38]. While the preclinical studies showed strong efficacy of tigatuzumab against TNBC/basal-like cells in vitro and in vivo when given in combination with paclitaxel and nab-paclitaxel [39–41], a phase II trial of tigatuzumab in combination with nab-paclitaxel resulted in only moderate prolongation of progression-free survival compared to nab-paclitaxel treatment alone for TNBC patients [42].

The death receptors are also involved in the extrinsic apoptosis pathway via epithelial–mesenchymal transition particularly E-cadherin [43]: loss of E-cadherin attenuates apoptotic signaling via DR4 and DR5, and the engagement of E-cadherin augments the activation of DR4 and DR5, which enhances the resulting progression of apoptosis. Most interestingly, E-cadherin boosts extrinsic apoptosis pathway signaling by coupling DR4 or DR5 to the actin cytoskeleton modulation.

The most exciting recent development in targeting the extrinsic pathway is the new-generation molecule ONC201 [44]. ONC201, an oral medication initially discovered as a TRAIL activity–inducing compound by drug sensitivity screening of the National Cancer Institute Library, induces selective apoptosis in cancer cells but is safe in normal tissue, acting via FOXO3a-mediated induction of the TRAIL gene and suppression of pAkt and pErk [45]. Further investigation of this molecule revealed that it induces an endoplasmic reticulum stress response in the cancer cells and induces binding to neurotransmitter receptors, including dopamine receptors. Most recently, the mechanism of action by which ONC201 induces apoptosis was shown to be inhibition of caseinolytic protease P [46••], a protease located in the inner mitochondrial membrane [47, 48]. Therefore, ONC201 also modulates the mitochondrial recruitment of the apoptosome through mitochondrial interaction—contributing to both extrinsic and intrinsic pathways. Clinical trials using extrinsic pathway targeted agents are summarized in Table 1.

Intrinsic Pathway and Targeted Agents

The cell-intrinsic apoptosis pathway is also known as the mitochondrial pathway; its signaling involves changes in the mitochondrial membranes and the release of proteins that result in widespread proteolysis and DNA cleavage [10]. This pathway is responsive to various genotoxic stresses, including conventional chemotherapeutics, radiation, and biologic agents that target cell survival and growth. The pro-apoptotic Bcl-2 family of proteins plays a critical role in this pathway, and the p53 tumor suppressor protein activates several of these pro-apoptotic family members. The intrinsic pathway has even been physically localized to the mitochondria [49]. The recent development of apoptosis-targeted agents focuses on these mitochondrial pathways and includes IAP inhibitors, Mcl-1 inhibitors, and Bcl-2 inhibitors.

IAP Inhibitors

Chemotherapy induces apoptosis in cancer cells more prominently compared to normal cells [50]; however, resistance develops by upregulation of inhibitors of apoptosis. Inhibitor of apoptosis proteins (IAPs) are an evolutionarily conserved family of proteins that are key negative regulators of both the intrinsic and extrinsic apoptotic pathways [51]. Proteins within this family include cIAP1, cIAP2, XIAP, NIAP, and survivin. In human cancer cell lines and tissues, one or more of these IAPs is overexpressed and inhibits apoptosis induction by targeting both intrinsic (mitochondrial) and extrinsic (death receptor) pathways of apoptosis [52].

IAP family members interfere with the induction of TNFR-mediated pro-immune responses through interleukin-mediated and NF-κB-mediated pathways [53]. Therefore, the inhibition of IAP could synergize with a checkpoint inhibitor or radiation-induced apoptosis, thus mediating effective tumor cell killing [54]. Inhibitor of apoptosis protein (IAP) is a crucial molecule for preventing effective apoptosis. Additionally, cIAP proteins ubiquitinate RIPK1, which facilitates the formation of IKK complex and promotes canonical NF-kB signaling. Activation of the NF-kB signaling pathway leads to induction of target genes that inhibit apoptosis (XIAP, Bcl-2, Bcl-xL) [55]. Therefore, therapeutics to inhibit the IAP molecule have been actively developed. The binding pockets of Smac and IAP share significant similarities [56]. Thus, many IAP inhibitors mimic the Smac protein as well (Smac mimetics).

LCL161 is the IAP inhibitor/Smac mimetic furthest along in the clinic [57, 58]. In hematological, colorectal,

Table 1 Ongoing clinical trials of second- and third-generation death receptor–targeted therapies

Agent	Molecular target	NCT clinical trial number	Phase of clinical trial	Eligible disease site(s)	Combinatorial agent
Second generation					
ABBV-621	TRAIL receptor agonist	NCT03082209	I	Solid tumors, hematologic malignancies	Multiple arms with agent alone, combined with chemotherapy or venetoclax
HexaBody-DR5/DR5 (GEN1029)	DR5	NCT03576131	I	Solid tumors	Single agent
CPT	Circularly permuted TRAIL	ChiCTR-TRC-11001625*	II	Multiple myeloma	Thalidomide and dexamethasone
CPT	Circularly permuted TRAIL	ChiCTR-IPR-15006024*	III	Multiple myeloma	With or without thalidomide and dexamethasone
Third generation					
ONC201	TRAIL induction	NCT03416530	I	Pediatric glioma	Single agent
ONC201	TRAIL induction	NCT02609230	I	Solid tumors, multiple myeloma	Single agent
ONC201	TRAIL induction	NCT02863991	I/II	Multiple myeloma	Single agent
ONC201	TRAIL induction	NCT02392572	I/II	Acute leukemias, myelodysplastic syndrome	With or without cytarabine
ONC201	TRAIL induction	NCT03394027	II	Breast cancer, endometrial cancer	Single agent
ONC201	TRAIL induction	NCT03099499	II	Endometrial cancer	Single agent
ONC201	TRAIL induction	NCT03485729	II	Endometrial cancer	Single agent
ONC201	TRAIL induction	NCT03034200	II	Neuroendocrine tumors	Single agent
ONC201	TRAIL induction	NCT02525692	II	Glioblastoma multiforme, glioma	Single agent
ONC201	TRAIL induction	NCT03295396	II	Glioma	Single agent

NCT, National Clinical Trial; *Chinese Clinical Trial Registry

lung, and breast cancers [59, 60], LCL161 was tested as a single agent, and in combinations, and the clinical efficacies were mixed. In patients with myelofibrosis who progressed on JAK2 inhibitor, LCL161 once a week regimen has shown a safe toxicity profile and ability to maintain stable disease, therefore suggesting it as a potential future treatment option [61]. Given the mechanism of action, combination therapy with radiation has been tested in head and neck cancer and esophageal cancers. In preclinical studies in these cancers, LCL161 induced synergistic sensitivity to the radiation therapy; thereby, it was given in combination with radiation [62, 63]. The clinical outcomes are to be seen.

Other IAP inhibitors have been studied more in solid tumors. Birinapant is a novel bivalent small-molecule peptidomimetic of SMAC, shown to preferentially target cIAP1, cIAP2, and XIAP by binding to the BIR domains and trigger degradation through rapid RING-dependent autoubiquitylation [64, 65]. Inhibition of cIAP1/2 and XIAP with birinapant induces apoptosis through both the intrinsic and extrinsic pathways as well as through the canonical NF-kB pathway and can sensitize cancer cells to various apoptotic stimuli including radiation [54] and cytotoxic chemotherapy [66, 67].

In early phase clinical trials, birinapant has demonstrated tolerability and safety at effective doses, with a prolonged plasma half-life of 31 h and tumor half-life of 52 h. On target effect is the suppression of cIAP1, and it increases apoptosis in peripheral blood mononuclear cells and tumor tissue [68]. In a 5-arm phase I/II dose escalation study of birinapant administered intravenously in combination with different chemotherapies (docetaxel, irinotecan, gemcitabine, carboplatin/paclitaxel, liposomal doxorubicin) in patients with solid tumors, safety and tolerability were confirmed, and a phase II dose was established [69]. Interestingly, birinapant demonstrated prolonged progression-free survival in previously relapsed or refractory patients when combined with chemotherapies that induce TNFα, such as irinotecan [69]. While exciting results in preclinical models and early-phase trials have been seen, the clinical development of birinapant is currently on hold for unclear reasons. New IAP inhibitors

such as ASTX660 are currently being tested in early phase clinical trials [70].

Survivin targeted antisense oligonucleotides (YM155, LY2181308) have been tested to induce the sensitization of cancer cells to therapeutics, yet the clinical efficacy has not been promising [71–74]. In mechanistic study, antisense YM155, despite early promising preclinical results, revealed an interference in DNA double-stranded break repair and topoisomerase-mediated DNA cleavage, which explains negative clinical efficacy. However, with rapid development of vaccine and medical chemistry technologies, the vaccine against survivin (SurVaxM, DPX-Survivac) [74] is showing the potential to be combined with immune checkpoint inhibitor therapies [2]. Currently ongoing clinical trials utilizing IAP inhibitors are summarized in Table 75.

Mcl-1 Inhibitors

An anti-apoptotic member of the Bcl-2 family, myeloid cell leukemia-1 (Mcl-1), was recently identified as a crucial apoptotic survival factor modulated by Wnt signaling in TNBC cells [76, 77]. Accumulated preclinical in vitro and in vivo evidence suggests that Mcl-1 represents a promising target for treating breast cancers [78–80]. Indeed, Mcl-1 is commonly amplified in 56% of TNBC tumors, and its overexpression is associated with high tumor grade and poor clinical prognosis [81, 82]. Furthermore, overexpression of Mcl-1 is implicated as a factor in resistance to multiple early- and advanced stage breast cancer therapies, such as microtubule-targeted agents paclitaxel and vincristine and the Bcl-2-targeting compound navitoclax [83–85]. Therefore, inhibition of Mcl-1 by targeted inhibitors represents an integrated approach for developing TNBC therapies by potentially restoring apoptotic signaling and rescuing the sensitivity to chemotherapy in Mcl-1-dependent TNBC tumors.

Currently under development in preclinical studies, Mcl-1 inhibitors have demonstrated great promise for the treatment of cancer, including breast cancer, in vitro and in vivo, as there now exist direct, potent, and selective Mcl-1 inhibitors with clear and specific cellular activity, disrupting Mcl-1 interactions and triggering apoptosis [86–88]. Moreover, the histone deacetylase inhibitor entinostat, together with the MEK inhibitor, pimasertib, has shown to mediate the targeted degradation of Mcl-1 through the induced expression of NOXA [89], a crucial regulator that fine-tunes cell death by targeting Mcl-1 for proteasomal degradation enhancing TNBC tumor cell death in vitro and in vivo [90, 91].

The targeted downregulation of Mcl-1 has been implicated in a phase I clinical trial to be the primary mechanism

Table 2 Ongoing clinical trials of inhibitor of apoptosis proteins (IAPs)

Agent	Molecular target	NCT clinical trial number	Phase of clinical trial	Eligible disease site(s)	Combinatorial agent
LCL161	SMAC mimetic IAP inhibitor	NCT02098161	II	Primary myelofibrosis	Single agent
LCL161	SMAC mimetic IAP inhibitor	NCT02890069	I	Colorectal cancer, non–small cell lung cancer, triple-negative breast cancer, renal cell carcinoma	PDR001 checkpoint inhibitor
LCL161	SMAC mimetic IAP inhibitor	NCT02649673	I	Small cell lung cancer, ovarian cancer	Topotecan
Birinapant	Small peptidomimetic of SMAC	NCT03803774	I	Head and neck squamous cell carcinoma	Radiation therapy
ASTX660	Dual cIAP/XIAP antagonist	NCT02503423	I/II	Solid tumors and lymphoma	Single agent
SurVaxM	Survivin	NCT02455557	II	Glioblastoma multiforme, gliosarcoma	Temozolomide
SurVaxM	Survivin	NCT04013672	II	Glioblastoma	Pembrolizumab
SurVaxM	Survivin	NCT03879694	I	Neuroendocrine tumors	Octreotide and sargramostim
DPX-Survivac	Survivin	NCT03836352	II	Ovarian cancer, hepatocellular carcinoma, non–small cell lung cancer, bladder cancer	Cyclophosphamide and pembrolizumab
DPX-Survivac	Survivin	NCT03029403	II	Ovarian cancer, primary peritoneal carcinoma, fallopian tube cancer	Cyclophosphamide and pembrolizumab

of activity of alvocidib (flavopiridol), a pan-CDK inhibitor, in patients with chronic lymphocytic lymphoma (CLL) or acute myeloid leukemia (AML) [92, 93]. While alvocidib is not a direct inhibitor of Mcl-1, these results have provided a rationale for an upcoming randomized phase II biomarker-driven clinical trial of alvocidib in patients with AML (NCT02520011), which could shed light on the implementation of Mcl-1 inhibition treatment for cancers. Several Mcl-1 inhibitors (AMG-176, AZD599) and CDK9 inhibitor that had shown effective suppression of Mcl-1 in preclinical studies are currently being tested in hematological malignancies (Table 3), and results are awaited.

Bcl-2 Inhibitors

BCL-2 family inhibitors are the front runners of the apoptosis-targeted agents developed in cancers. Each of these agents inhibits different family members such as BCL2, BCL-XL, and BCL-w, with different affinity [94, 95].

Venetoclax is the first agent that was approved by the FDA in cancer. It binds to BCL-2 protein and thereby displaces pro-apoptotic proteins like BIM and NOXA. This agent is approved in CLL, after showing a close to remarkable response even as a single agent [96]. Even in CLL with17p deletion, venetoclax showed similar response [96]. This is impressive given the aggressive behavior of 17 deletion CLL. When venetoclax was combined with rituximab, the response rate went up even higher up to 86% [97]. Venetoclax also showed significant activity in chemotherapy-resistant AML. As in CLL, TP53 mutation did not seem to reduce the efficacy of the agent, leading to the breakthrough approval by the FDA.

In breast cancer, venetoclax has been combined with fulvestrant to treat endocrine therapy–resistant, hormone receptor–positive breast cancer [98], given that functional estrogen receptor transcriptionally upregulates Bcl-2 as one of its direct target gene/proteins. Impressive results of combined tamoxifen and venetoclax sparked significant interest in combining venetoclax with various agents in breast cancer treatment [99•]. Unfortunately, the phase II trial VERONICA, testing the combination of venetoclax and fulvestrant, did not show any clinical efficacy [100].

Similarly, obatoclax mesylate (GX15-070) is another Bcl-2 inhibitor that has been tested in numerous cancers. Unfortunately, the toxicity profile of obatoclax included neurological (ataxia) symptoms and cytopenia which stopped obatoclax from further clinical development [101].

Navitoclax is another inhibitor in this category of agents. Navitoclax inhibits both Bcl-2 and Bcl-xL, thereby suppressing the compensatory emergence of Bcl-xL prevented by the release of pro-apoptotic regulators, like Bim [102, 4]. Bim can be replaced by inhibition of Bcl-2, but it can bind to other proteins of this category. Therefore, the inhibition of other Bcl-2 family proteins can synergistically induce Bim-mediated induction of apoptosis. While navitoclax, as a single agent, may not have shown remarkable clinical activity, combination with venetoclax has shown potential synergy [103•]. Clinical trials using venetoclax and navitoclax are summarized in Table 104.

Apoptosis and p53 Regulation

Cells with mutated or inactivated p53 develop resistance to apoptosis. As a compensatory mechanism, the p53 family member p73 can also inhibit apoptosis [105]. The essential pro-apoptotic genes induced by activated p53 within the cell-intrinsic apoptotic pathway include PUMA, NOXA, BAX, and Apaf-1. Both p53 and the FOXO family of transcription factors play an essential role in apoptosis by inducing the production of death receptors and pro-apoptotic Bcl-2 family proteins, thereby impacting both the intrinsic and extrinsic cell death pathways [106].

p53, the "guardian of the genome," is an important regulator of apoptosis and other key biological functions [107]. The mouse double minute 2 (*Mdm2*) gene encodes a nuclear-localized E3 ubiquitin ligase, and its overexpression is detected in a variety of malignancies [108]. MDM2 binding to p53 induces p53 proteasomal degradation and inhibits p53 activity in apoptosis [109]. MDM2 inhibitor molecules can antagonize the p53-MDM2 interaction, allowing p53 to induce apoptotic pathways; hence, numerous preclinical and clinical studies have tested the efficacy of MDM2 inhibition. No active clinical developments to date have indicated unacceptable toxicity or suboptimal efficacy; however, clinical

Table 3 Ongoing clinical trials of Mcl-1 inhibitors

Agent	NCT clinical trial number	Phase of clinical trial	Eligible disease site(s)	Combinatorial agent
AMG 176	NCT02675452	I	Multiple myeloma and acute myeloid leukemia	With or without azacitidine
AZD5991	NCT03218683	I/II	Acute myeloid leukemia	With or without venetoclax
CDK9 inhibitor (AZD4573)	NCT03263637	I	Hematologic malignancies	Single agent

Table 4 Ongoing clinical trials of BCL-2 inhibitors, venetoclax (ABT-199), and navitoclax (ABT-263)

NCT clinical trial number	Phase of clinical trial	Eligible disease site(s)	Combinatorial agent
Venetoclax (ABT-199)			
NCT03523975	I	Mantle cell lymphoma	Lenalidomide and rituximab
NCT03485547	I	Blastic plasmacytoid dendritic cell neoplasm	Single agent
NCT03484520	I	Acute myeloid leukemia	Dinaciclib
NCT04070768	I	Acute myeloid leukemia	Gemtuzumab ozogamicin
NCT03709758	I	Acute myeloid leukemia	Daunorubicin and cytarabine
NCT03534323	I/II	Chronic lymphocytic leukemia, small lymphocytic lymphoma, Richter syndrome	Duvelisib
NCT03505944	I/II	Mantle cell lymphoma	Lenalidomide and rituximab
NCT03504644	I/II	Acute lymphoblastic leukemia	Vincristine liposomal
NCT03471260	I/II	Hematologic malignancies	Ivosidenib with or without azacitidine
NCT02287233	I/II	Acute myeloid leukemia	Cytarabine
NCT03314181	I/II	Multiple myeloma	Daratumumab and dexamethasone with or without bortezomib
NCT03214562	I/II	Acute myeloid leukemia	Fludarabine, cytarabine, filgrastim, idarubicin
NCT02427451	I/II	Chronic lymphocytic leukemia	Obinutuzumab and ibrutinib
NCT04655755	I/II	Myelodysplastic syndrome, chronic myelomonocytic leukemia	Cedazuridine and decitabine (ASTX727)
NCT02966756	II	Chronic lymphocytic leukemia, small lymphocytic lymphoma	Single agent
NCT03573024	II	Acute myeloid leukemia	Azacitidine
NCT02899052	II	Multiple myeloma	Carfilzomib and dexamethasone
NCT02846623	II	Chronic lymphocytic leukemia, small lymphocytic lymphoma, Richter syndrome	Atezolizumab and obinutuzumab
NCT04169737	II	Chronic lymphocytic leukemia, small lymphocytic lymphoma	Acalabrutinib with or without obinutuzumab
NCT03534180	II	T cell lymphomas	Romidepsin
NCT03513562	II	Chronic lymphocytic leukemia	Ibrutinib
NCT03873857	II	Chronic lymphocytic leukemia	Single agent
NCT03539744	III	Multiple myeloma	Dexamethasone compared to pomalidomide and dexamethasone
NCT03069352	III	Acute myeloid leukemia	Cytarabine compared to placebo and cytarabine
NCT02756611	III	Chronic lymphocytic leukemia	Single agent
NCT02005471	III	Chronic lymphocytic leukemia	Rituximab compared to bendamustine and rituximab
NCT04401748	III	Myelodysplastic syndrome	Azacitidine
NCT02993523	III	Acute myeloid leukemia	Azacitidine compared to azacitidine alone
NCT04161885	III	Acute myeloid leukemia	Azacitidine compared to best supportive care
NCT02755597	III	Multiple myeloma	Bortezomib and dexamethasone compared to placebo, bortezomib, and dexamethasone
NCT04628026	III	Acute myeloid leukemia, Myelodysplastic Syndrome	Standard chemotherapy compared to placebo and standard chemotherapy
NCT03941964	III	Acute myeloid leukemia	Azacitidine or decitabine
NCT03236857	I	Pediatric acute lymphoblastic leukemia, acute myeloid leukemia, non-Hodgkin lymphoma, neuroblastoma	Chemotherapy
NCT03900884	I	Breast cancer	Palbociclib and letrozole
NCT03584009	II	Breast cancer	Fulvestrant compared to fulvestrant alone
Navitoclax (ABT-263)			
NCT04041050	I	Myeloproliferative neoplasm	With or without ruxolitinib

Table 4 (continued)

NCT clinical trial number	Phase of clinical trial	Eligible disease site(s)	Combinatorial agent
NCT03222609	II	Myelofibrosis	With or without ruxolitinib
NCT04472598	III	Myelofibrosis	Ruxolitinib compared to placebo and ruxolitinib
NCT04468984	III	Myelofibrosis	Ruxolitinib compared to best available therapy
NCT02520778	I	Non–small cell lung cancer	Osimertinib
NCT02143401	I	Solid organ tumors, hepatocellular carcinoma	Sorafenib tosylate
NCT03366103	I/II	Solid tumors, lung small cell carcinoma	Vistusertib
NCT02079740	I/II	Solid neoplasm	Trametinib
NCT01989585	I/II	Solid neoplasm, melanoma	Dabrafenib and trametinib

trials testing the efficacy of MDM2 inhibitors are ongoing, and the results are to be seen.

Kinase Inhibitor Targeting Apoptosis

MELK is a serine/threonine kinase in the AMPK family of kinases known to regulate cellular metabolism [110–110], regulate early embryonic development [110], and show elevated expression in human cancers [111, 112, 112–112]. It is an important proliferative marker and included as one of the genes included in MammaPrint [114] and PAM50 [115], both genomic assays used in breast cancer. High MELK expression is associated with poor overall and metastasis-free survival in many cancers [116, 121], including glioma cells [122, 123, 124]. Aside from contributions to several pro-cancer activities, MELK also regulates the activation of apoptosis [125].

Death-associated protein kinase (DAPK) is a serine/threonine kinase that comprises five family members (DAPK1-3, DRAK1 and DRAK2). This family of proteins has calcium/calmodulin domain and was previously known to be involved in important biological regulations including infection and neurosynaptic regulation which has been suggested as a promising target of Alzheimer disease treatment [126]. Recently, DAPK1 and DRAK2 have been shown to regulate autophagy, as well as apoptosis, contributing to metastatic progression (127). Small-molecule inhibitors against these proteins are under development, and the activity against cancers is to be seen.

Conclusions

Many cancer treatments rely on induction of effective apoptosis; hence, defects in apoptosis can render treatments ineffective. Despite the challenges of targeted drug development, companion biomarker development, and identification of appropriate groups of patient, targeting apoptosis remains a relevant strategy. We anticipate this field will continue to advance. After all, immunotherapy took more than 40 years to reach its "prime time." With the right efforts and initiatives, we hope that apoptosis targeting opens up a new way to treat cancer. Combination of available agents and other therapeutics like radiation and immune checkpoint inhibitors also needs to be further explored and developed.

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Declarations

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