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Review

An Updated Review of Smac Mimetics, LCL161, Birinapant, and GDC-0152 in Cancer Treatment

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Abstract: Inhibitor of apoptosis proteins (IAPs) are suggested as therapeutic targets for cancer treatment. Smac/DIABLO is a natural IAP antagonist in cells; therefore, Smac mimetics have been developed for cancer treatment in the past decade. In this article, we review the anti-cancer potency and novel molecular targets of LCL161, birinapant, and GDC-0152. Preclinical studies demonstrated that Smac mimetics not only induce apoptosis but also arrest cell cycle, induce necroptosis, and induce immune storm in vitro and in vivo. The safety and tolerance of Smac mimetics are evaluated in phase 1 and phase 2 clinical trials. In addition, the combination of Smac mimetics and chemotherapeutic compounds was reported to improve anti-cancer effects. Interestingly, the novel anti-cancer molecular mechanism of action of Smac mimetics was reported in recent studies, suggesting that many unknown functions of Smac mimetics still need to be revealed. Exploring these currently unknown signaling pathways is important to provide hints for the modification and combination therapy of further compounds.

Keywords: inhibitor of apoptosis proteins (IAPs); Smac/DIABLO; LCL161; birinapant; GDC-0152

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1. Introduction

Inhibitor of apoptosis proteins (IAPs), including cellular inhibitor of apoptosis protein 1 (cIAP1), cellular inhibitor of apoptosis protein 2 (cIAP2), melanoma inhibitor of apoptosis (ML-IAP/Livin), testis-specific inhibitor of apoptosis (Ts-IAP/ILP-2), neuronal apoptosis inhibitory protein (NAIP), X-linked inhibitor of apoptosis protein (XIAP), survivin, and BIR repeat containing ubiquitin-conjugating enzyme (BRUCE), are known for their anti-apoptotic effects [1,2]. Members of the IAP family are characterized by the presence of the baculoviral IAP repeat (BIR) domain, which physically interacts with caspase proteins and inhibits the activity of caspases. BIR domains are grouped into two types, based on the presence or absence of the IAP binding motif (IBM) on the BIR domain [3]. Only type II BIR domain, which is with IBM, can interact with caspases. The BIR1-BIR2 linker of XIAP interacts with caspase-3 and -7 [3]. The BIR3 of XIAP inhibits the activity of caspase-9 by interacting with the N-terminal tetrapeptide of caspase-9 [4]. IAPs play important roles in mediating a variety of cellular processes, including apoptosis, mitosis, autophagy, and DNA damage in cancer cells [5–14]. Therefore, the dysregulation of IAPs promotes tumorigenesis, metastasis, angiogenesis, and therapeutic resistance, including chemotherapy and radiotherapy [15–18]. Currently, many IAP-targeting treatments, such as small-molecule inhibitors (i.e., ASTX660, Embelin, and YM155) [19–21], anti-sense oligonucleotides (i.e., LY2181308) [22], and Smac mimetic compounds (i.e., birinapant, LCL161, and GDC-0152) [23–25], have been developed. Despite the anti-cancer potency of birinapant, LCL161, and GDC-0152, they are still under investigation in preclinical and clinical studies, and these compounds have already received much attention in recent years. In this review, we mainly focus on describing the current development of LCL161,

birinapant, and GDC-0152 as anti-cancer agents, and we discuss the potential of using these agents for the treatment of cancer in the future.

2. Smac/DIABLO Inhibits IAPs in Cancer

Second mitochondria-derived activator of apoptosis/direct inhibitor of apoptosis-binding protein with low pI (Smac/DIABLO) physically interacts with IAPs and antagonizes the anti-apoptotic activity of IAPs in cells, resulting in apoptosis (Figure 1) [26–28]. In the presence of apoptosis stimuli, mature Smac/DIABLO is released from the mitochondria to cytosol [26,27]. Smac/DIABLO interacts with the BIR domain of IAPs by its particular NH_2-terminal motif consisting of four amino acids (Ala-Val-Pro-Ile), and it releases caspases from IAPs, thereby inducing caspase-dependent apoptosis [26]. Previous studies demonstrated that Smac/DIABLO interacts with the BIR2 and BIR3 domains of XIAP, and caspase-3 and -9 are released from XIAP, respectively (Figure 1) [4,29]. Smac/DIABLO not only mediates the cellular function of XIAP but also regulates cIAP1 and cIAP2. Smac/DIABLO induces the ubiquitination and degradation of cIAP1 and cIAP2 (Figure 1) [30]. However, Smac/DIABLO does not degrade XIAP [31]. Interestingly, a recent study found that a Smac/DIABLO isoform, Smac3, induces the autoubiquitination and degradation of XIAP [32]. On the other hand, cIAP1 and cIAP2 can ubiquitinate receptor-interacting kinase 1 (RIPK1), resulting in the inhibition of caspase-dependent apoptosis and necroptosis [1,33,34]. Moreover, cIAP1 and cIAP2 promote cell proliferation, migration, and invasion by activating the canonical nuclear factor kappa-light-chain-enhancer of the activated B cell (NF-κB) signaling pathway [1]. Therefore, upregulation of Smac/DIABLO can induce caspase-dependent apoptosis through the de-ubiquitination of receptor-interacting serine/threonine-protein kinase 1 (RIPK1) and necroptosis by activating the RIPK1/receptor-interacting serine/threonine-protein kinase 3 (RIPK3)/mixed lineage kinase domain-like protein (MLKL) signaling pathway [35]. Pathologically, the protein expression level of Smac is frequently downregulated in renal carcinoma, colorectal cancer, bladder cancer, lung cancer, hepatocellular carcinoma, testicular germ cell tumors, and pancreatic cancer compared with normal tissues, but not in cervical cancer [36–45]. For these reasons, the use of Smac mimetics was suggested as a potential approach for cancer treatment.

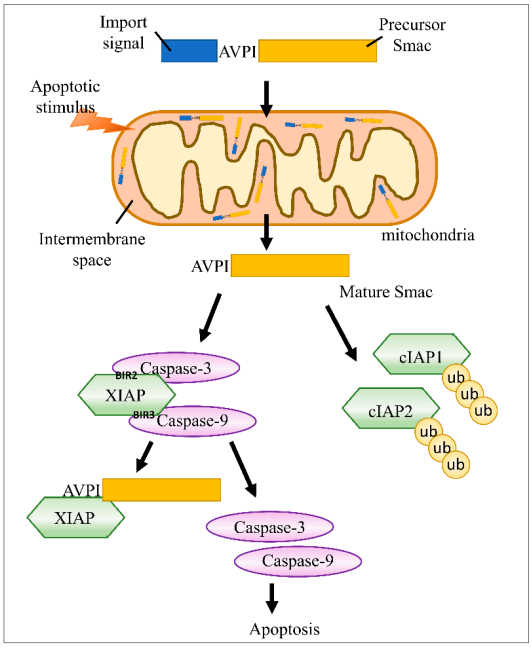

Figure 1. Smac/DIABLO inhibits IAPs in cancer cells. The precursor of Smac (yellow) is transported to the intermembrane space of mitochondria by the import signal (blue box). Then, mature Smac is released from the mitochondria into the cytosol and subsequently inhibits the cellular functions of IAPs. AVPI stands for "Ala-Val-Pro-Ile". BIR stands for "baculoviral IAP repeat". Ub stands for "ubiquitin".

3. Smac Mimetics for Cancer Treatment

The first Smac mimetic compound with eight amino acids was studied in 2000 [46]. Currently, eight Smac mimetics have been developed, and their anti-cancer potency has been evaluated in different preclinical and clinical studies. Smac mimetics are classified into two groups based on the number of Smac-mimicking moieties; for example, monovalent compounds contain one Smac-mimicking moiety (i.e., LCL161, AT-406 (Debio1143), GDC-0152, and GDC-0917 (CUDC-427)), and bivalent compounds are Smac-mimicking elements connected via a linker (i.e., birinapant (TL32711), BV6, and SM-164) (Figure 2) [23,47–52]. The anti-cancer potency of six of them has been elucidated in clinical trials. Bivalent compounds exhibit higher anti-cancer potency than monovalent compounds because the former possess better binding affinity with IAPs and higher potency to induce caspase-dependent apoptosis than the latter [53]. The anti-cancer potency of Smac mimetics is also dependent on their specificity to IAPs. For example, birinapant and AT406 preferentially target cIAP1 and cIAP2 rather than XIAP. LCL161 and GDC-0152 are pan-IAP inhibitors that have similar affinities to XIAP, cIAP1, and cIAP2 [23,48,49,51]. Among these Smac mimetic compounds, LCL161, birinapant, and GDC-0152 are currently the most popular, in which their therapeutic effectiveness and the molecular mechanism of actions have been studied extensively in pre-clinical and clinical studies. Therefore, we summarize current LCL161, birinapant, and GDC-0152-related findings in the following sections.

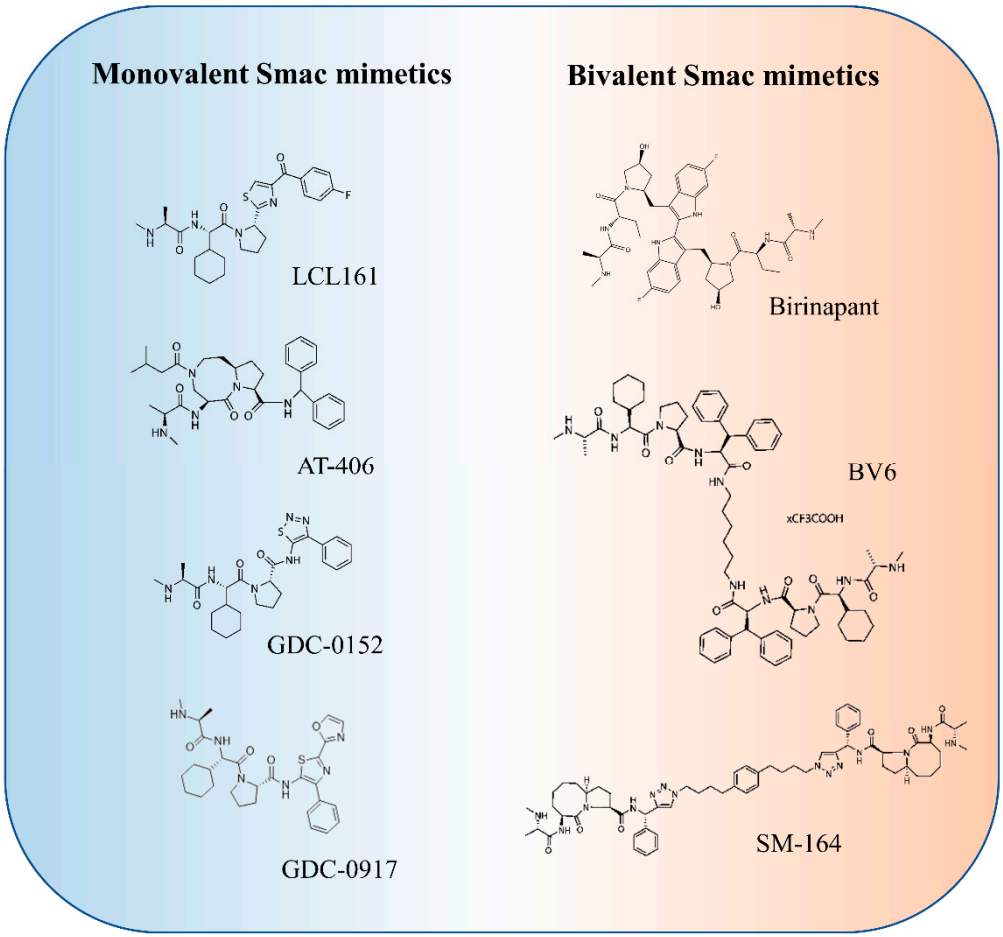

Figure 2. Chemical structure of Smac mimetics for cancer treatment. BV6 was modified with trifluoroacetic acid (xCF3COOH) to improve the solubility of BV6 to DMSO and water.

4. Anti-Cancer Molecular Mechanism of LCL161

LCL161 is an orally bioavailable monovalent Smac mimetic developed by Novartis Pharmaceuticals. LCL161 shows both pro-apoptotic and anti-proliferation effects in

cancer cells [47]. In many preclinical studies, the anti-cancer potency of LCL161 has been established in multiple myeloma, glioblastoma, hepatocellular carcinoma, oral squamous carcinoma, neuroblastoma, osteosarcoma, sarcoma, triple-negative breast cancer (TNBC), leukemia, cervical cancer, non-small cell lung cancer, and head and neck cancer cells [24,54–56]. At the molecular level, LCL161 binds to the BIR3 domain of cIAP1 and cIAP2 with high affinity, and induces cIAP1 and cIAP2 autoubiquitination and proteasome degradation, resulting in the activation of non-canonical NF-κB signaling pathways and production of tumor necrosis factor α (TNF-α) (Figure 3) [57]. LCL161 also induces apoptosis and necroptosis through the RIP1/RIP3/MLKL signaling pathway (Figure 3) [58,59]. Surprisingly, a few studies showed that LCL161 does not induce apoptosis, but instead it induces G2/M phase arrest by downregulating cIAP1 and activating the p21 signaling pathway in medulloblastoma and neuroblastoma cells (Figure 3) [60,61]. Moreover, it has been shown that LCL161 does not kill cancer cells directly, but it promotes the activity of immune cells and enhances cytokine secretion instead. Mechanistically, LCL161 promotes the activity of T cells by inducing cytokine secretion and dendritic cell maturation (Figure 3) [62–64]. In multiple myeloma, cIAP1 and cIAP2 are usually deleted, but LCL161 still inhibits the growth of multiple myeloma through the upregulation of tumor cell autonomous type I interferon signaling, and strong acute inflammatory signaling (promoting macrophagy, M-spike, and dendritic cell maturation) in transgenic Vk*MYC mice [65]. Recent studies demonstrated the anti-cancer potency of LCL161 is correlated with the protein expression levels of B-cell lymphoma 2 (BCL-2) and TNF-α and NF-κB activity in cancer cells. In neuroblastoma, Langemann et al. suggested that the anti-cancer potency of LC161 is based on the cells' sensitivity to TNF-α and modulation of NF-κB [61]. Interestingly, in our recent study, we found that LCL161 interacts with p-glycoprotein (also called multidrug resistance protein 1 (MDR1)) and inhibits the MDR1 multi-drug efflux activity, resulting in increased sensitivity to the MDR1 substrates, such as paclitaxel and YM155 in cervical and bladder cancer cells [66]. Moreover, we found that LCL161 downregulates the protein expression level of survivin in MDR1-expressing cervical and bladder cancer cells [66].

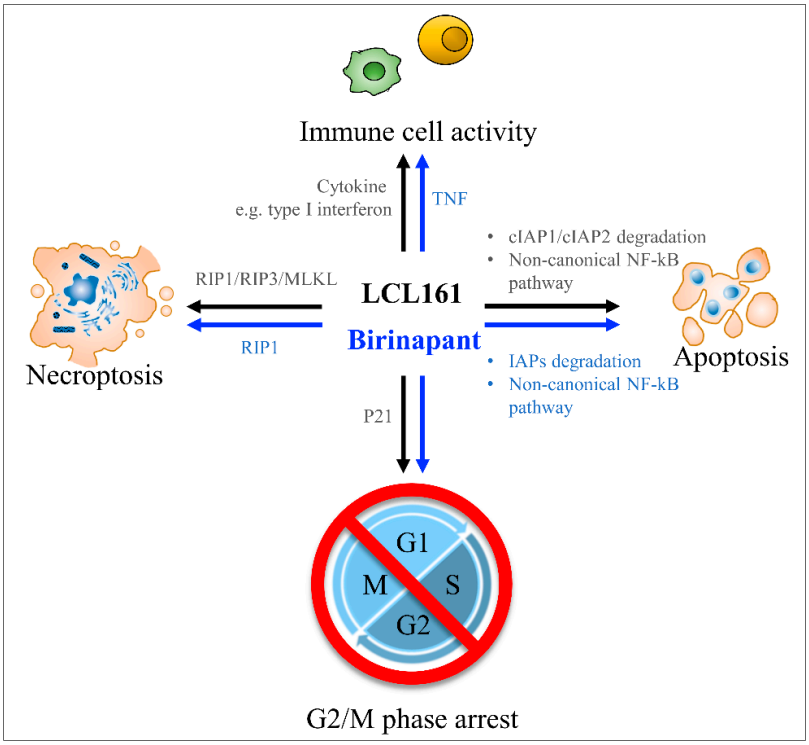

Figure 3. Anti-cancer effects and the molecular mechanisms of action of LCL161 (black) and birinapant (blue) in cancer cells.

5. LCL161 Combination Treatment

Many preclinical studies have explored the anti-cancer effects of LCL161 in combination with different anti-cancer agents. It has been demonstrated that LCL161 sensitizes cancer cells to paclitaxel, Fas ligand, vincristine, and obatoclax (BCL-2 inhibitor) in different types of cancer [54,55,60,61,67–70]. Moreover, LCL161 improves the anti-cancer effects of radiotherapy in head and neck squamous and esophageal carcinoma cells [71,72]. Immunotherapy is a popular treatment for cancer. Chesi et al. noted improvements in the anti-cancer effects of immunotherapy when combined with LCL161 in multiple myeloma in vivo [65]. Maintaining the balance of reactive oxygen species (ROS) plays an important role in tumorigenesis. Targeting redox homeostasis with erastin and auranofin, which are ROS inducers, can improve LCL161-induced cell death in acute lymphoblastic leukemia cells [73].

6. Current Status of LCL161 in Clinical Trials

LCL161 is currently involved in many phase 1 and phase 2 clinical trials (Table 1), and results showed that it has favorable pharmacological properties, such as good tolerability and minor toxicity. Infante et al. showed that LCL161 is well tolerated at doses of up to 1800 mg [74]. Some LCL161-treated patients may present with vomiting, nausea, asthenia, and anorexia side effects, but these effects are not severe after treatment once a week for 21 days [74]. Only 3 out of 53 patients studied demonstrated cytokine release syndrome [74]. LCL161 was rapidly absorbed at the time to reach maximum plasma concentration (i.e., 0.5–2 h), and the plasma concentration declined within the range of 4–16 h [74].

Table 1. Clinical status of LCL161 for cancer treatment.

ClinicalTrials.Gov Identifier	Phase	Condition or Disease (in Patients)	Combination Therapy
NCT01968915	Phase 1 (completed)	Neoplasms	-
NCT01955434	Phase 2 (completed)	Recurrent plasma cell myeloma Refractory plasma cell myeloma	Cyclophophamide
NCT01934634	Phase 1	Metastatic pancreatic cancer	Gemcitabine Nab-Paclitaxel
NCT02098161	Phase 2	Polycythemia vera, post-polycythemic myelofibrosis phase Primary myelofibrosis Secondary myelofibrosis	-
NCT02649673	Phase 1/2	Small cell lung cancer Ovarian cancer	Topotecan Pegylated granulocyte colony stimulating factor
NCT01617668	Phase 2 (completed)	Breast cancer	Paclitaxel
NCT01240655	Phase 1 (completed)	Solid tumors	Paclitaxel
NCT01098838	Phase 1 (completed)	Advanced solid tumors (lung, skin, colon, pancreas, and others)	-
NCT03111992	Phase 1 (completed)	Multiple myeloma	PDR001 CJM112
NCT02890069	Phase 1	Colorectal cancer Non-small cell lung carcinoma (Adenocarcinoma) Triple-negative breast cancer Renal cell carcinoma	PDR001 Evrolimus Panobinostat QBM076 HDM201

Combination therapy of LCL161 with chemotherapeutic drugs such as paclitaxel and gemcitabine has been evaluated in patients with cancer (Table 1). Bardia et al. found that (1) LCL161 combined with paclitaxel can improve the pathologic complete response of TNF-α-positive TNBC, (2) the expression level of TNF-α might be a biomarker for predicting the anti-cancer effects of LCL161 and paclitaxel combination treatment, and (3) the anti-cancer potency of this combination is not correlated with the alternation of breast cancer type 1 susceptibility protein (BRCA1) and breast cancer type 2 susceptibility protein (BRCA2) in TNBC [75]. Some adverse effects were observed during combination treatment, including pyrexia (5 of 209 patients studied), pneumonia (4 of 209 patients studied), and pneumonitis (4 of 209 patients studied).

7. Anti-Cancer Molecular Mechanisms of Birinapant (TL32711)

Birinapant is a second-generation bivalent Smac mimetic, first synthesized in 2014 [76,77]. Birinapant has better tolerability for treating solid tumors compared with the first-generation bivalent Smac mimetic, and it preferentially targets cIAP1, relative to cIAP2 and XIAP [76]. The anti-cancer potency of birinapant has been investigated in acute myeloid leukemia, melanoma, colorectal cancer, ovarian cancer, breast cancer, head and neck squamous cell carcinoma, hepatocellular carcinoma, glioblastoma, and breast cancer [23,77–84]. At the molecular level, birinapant binds the BIR domains of IAPs and promotes the degradation of TNF receptor-associated factor (TRAF)-bound IAPs, resulting in the induction of caspase-8-dependent apoptosis (Figure 3) [85]. In addition, birinapant degrades IAPs, activates the non-canonical NF-κB signaling pathway once the IAPs are degraded, and stabilizes mitogen-activated protein kinase 14 (MAP3K14) (NF-κB-inducing kinase), resulting in the activation of the non-canonical NF-κB signaling pathway [84,86]. Mak et al. demonstrated that apoptosis repressor with caspase recruitment domain, an apoptosis suppressor, decreases the anti-cancer effect of birinapant by inhibiting the cIPA1/MAP3K14 signaling pathway in acute myeloid leukemia [87]. Birinapant induces cell cycle G2/M arrest in head and neck squamous cell carcinoma; however, the underlying molecular mechanism of action remains unclear (Figure 3) [79,88]. In acute lymphoblastic leukemia, birinapant induces RIP-1-dependent necroptosis (Figure 3) [83]. When birinapant is combined with emricasan, a caspase-8 inhibitor, necroptosis is induced in acute myeloid leukemia [89]. Kearney et al. demonstrated that birinapant-induced TNF activates $CD8^+$ T cells and natural killer cells, resulting in cancer cell death (Figure 3) [90]. Targeting programmed death-ligand 1 (PD-1) upregulates TNF production; therefore, the combination of birinapant and PD-1 blockade increases TNF production and promotes the anti-cancer potency of immune therapy [90].

8. Combination Therapy with Birinapant for Cancer Treatment

Overexpression of IAPs induces chemotherapeutic drug resistance in many cancer types. Targeting IAPs sensitizes drug-resistant cancer cells to chemotherapeutic drugs. Birinapant as an IAP antagonist has been combined with many chemotherapeutic drugs for cancer treatment. Birinapant has been combined with norcanthanidin, docetaxel, or TNF-related apoptosis-inducing ligand (TRAIL) for breast cancer treatment [23,91,92]. In addition, birinapant has been combined with paclitaxel, demethylating agent (5-AZ), TNF-α, Fas ligand (FasL), gemcitabine, 5-flurouracie (5-FU), and oxaliplatin for different types of cancer treatment, such as pancreatic cancer, head and neck squamous cell carcinoma, melanoma, acute myeloid leukemia, and colon cancer [79,80,84,86,88,93–97]. Birinapant improves the anti-cancer effects of radiotherapy for treating Fas-associated protein with death domain (FADD) and cIAP1-overexpressed head and neck cancers [88]. Kearney et al. demonstrated that birinapant activates CD8 T-cell and natural killer cells, resulting in cancer cell death [90]. The anti-cancer effects of chimeric antigen receptor (CAR) T-cell therapy correlate directly with the level of TNF. To improve the anti-cancer potency of CAR T cells, Michie et al. combined CAR T-cell therapy with birinapant for

cancer treatment. Results showed that this combination approach significantly reduced cancer growth [98].

9. Current Status of Birinapant in Clinical Trials

Clinical trials of birinapant are listed in Table 2. A phase 1 trial study reported the maximum tolerated dose, safety, and pharmacokinetic properties of birinapant in solid tumors [99]. The maximum tolerated dose of birinapant is 47 mg/m^2 [99]. The half-life of birinapant is 30–35 h [99]. A phase 2 clinical trial demonstrated that birinapant has a plasma half-life of 31 h and a tumor tissue half-life of 52 h [100]. Birinapant accumulates in tumor tissues, resulting in the downregulated protein expression level of cIAP1 and apoptosis induced in peripheral blood mononuclear cells and cancer cells [99]. However, birinapant does not increase the protein level of TNF, monocyte chemoattractant protein-1 (MCP-1), or interleukin 1, 6, and 8 [99]. For treating patients with cancer, birinapant is used as a single agent or in combination therapy with chemotherapeutic drugs (i.e., pembrolizumab, carboplatin, docetaxel, and gemcitabine) and radiotherapy. However, some birinapant clinical trials were terminated because birinapant lacked anti-cancer efficacy (NCT02147873, NCT02587962, NCT01681368), or the sponsors did not fund further work (NCT01573780).

Table 2. Clinical status of birinapant (TL32711) for cancer treatment.

ClinicalTrials.Gov Identifier	Phase	Condition or Disease (in Patients)	Combination Therapy
NCT03803774	Phase 1	Head and neck squamous cell carcinoma	Radiation therapy
NCT02587962	Phase 1/2 (terminated)	Solid tumor	Pembrolizumab
NCT02147873	Phase 2 (terminated)	Myelodysplastic syndrome Chronic myelomonocytic leukemia	Azacitidine Placebo
NCT01940172	Phase 1 (completed)	Relapsed epithelial ovarian cancer Relapsed primary peritoneal cancer Relapsed fallopian tube cancer	Conatumumab
NCT01188499	Phase 1/2 (completed)	Cancer	Carboplatin Paclitaxel Irinotecan Docetaxel Gemcitabine Liposomal Doxorubicin
NCT01681368	Phase 2 (terminated)	Epithelial ovarian cancer Peritoneal neoplasms Fallopian tube neoplasms	-
NCT00993239	Phase 1 (completed)	Cancer	-
NCT01573780	Phase 1 (terminated)	Adult solid tumor	Gemcitabine
NCT01486784	Phase 1/2 (terminated)	Acute myelogenous leukemia	-

10. GDC-0152 for Cancer Treatment

The development of GDC-0152, a pan-IAP antagonist, as an anti-cancer agent was first reported in 2012 [49]. The anti-cancer potency of GDC-0152 was evaluated in glioblastoma, leukemia, osteosarcoma, and glioblastoma [49,101–104]. At the molecular level, GDC-0152 induces intrinsic caspase-dependent apoptosis and inhibits the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway, resulting in cancer cell death [101,102]. Tchoghandjian et al. demonstrated that GDC-0152 not only downregulates the protein expression level of cIAP1, cIAP2, and XIAP, but it also downregulates ML-IAP in glioblastoma

cells in vitro and in vivo [104]. Mantik et al. found that the pharmacological properties of GDC-0152 are correlated with pH [105]. They demonstrated that the presence of succinic acid and hydroxypropyl-β-cyclodextrin can increase the solubility of GDC-0152, thereby improving blood compatibility, reducing hemolysis, and increasing the maximum tolerated dose [105]. Additionally, they remain stable in human plasma for up to 25 h [106]. Only one phase 1 clinical trial has studied the safety and pharmacokinetics of GDC-0152 (NCT00977067); however, it was terminated for reasons unrelated to patient safety or anti-cancer activity in 2017.

11. Conclusions and Future Directions

As dysregulation of IAPs has been found in a variety of tumors, and overexpression of IAPs promotes tumorigenesis and tumor metastasis, the use of Smac mimetics is suggested as a potential therapeutic approach for the treatment of cancer. The anti-cancer potency of Smac mimetics has been demonstrated in different types of malignant tumors in preclinical studies. Smac mimetics induce apoptosis and the non-canonical NF-kB signaling pathway by downregulating the protein expression level of IAPs. However, many unknown anti-cancer molecular mechanisms of action of Smac mimetics are still yet to be discovered. Exploring these signaling pathways is important to provide hints for the modification and combination therapy of further compounds.

The safety and tolerance of Smac mimetics are currently investigated in many clinical studies. Most studies report that Smac mimetics, such as LCL161, are safe and have good tolerance in patients with cancer. However, other Smac mimetics have shown low anti-cancer potency in the treatment of patients with cancer. The underlying molecular mechanism of action is still unclear. The anti-cancer potency of most Smac mimetics is on the micromolar level. Thus, many studies have combined Smac mimetics with chemotherapeutic drugs, radiotherapy, and immune therapy for cancer treatment. Results showed that the synergistic effect of these combinations can decrease the dosage of Smac mimetics. With the advancement of nanotechnology, delivering chemotherapeutic drugs with various types of nanoparticles can improve anti-cancer potency and cancer-targeting specificity through active or passive cancer targeting. For instance, Nikkhoo et al. synthesized a chitosan-based nanoparticle for co-delivering STAT3 siRNA and BV6, a bivalent Smac mimetic, to treat breast cancer cells, colorectal carcinoma cells, and melanoma cells, and their nanoparticles were shown to suppress cancer cell progression through caspase-dependent apoptosis in vitro and in vivo [107]. Therefore, nanotechnology can potentially be applied to improve the anti-cancer potency of Smac mimetics.

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Abbreviations

IAPs: Inhibitor of apoptosis proteins; BRCA1: breast cancer type 1 susceptibility protein; BRCA2: breast cancer type 2 susceptibility protein; BRUCE: BIR repeat containing ubiquitin-conjugating enzyme; cIAP1: cellular inhibitor of apoptosis protein 1; cIAP2: cellular inhibitor of apoptosis 2; DIABLO: direct inhibitor of apoptosis-binding protein with low pI; ML-IAP: melanoma inhibitor of apoptosis; Smac: second mitochondria-derived activator of apoptosis; NAIP: neuronal apoptosis inhibitory protein; TNBC: triple-negative breast cancer; TNF-α: tumor necrosis factor α; Ts-IAP: testis-specific inhibitor of apoptosis.

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