Naunyn-Schmiedeberg's Archives of Pharmacology
https://doi.org/10.1007/s00210-025-03901-w

REVIEW

Marine peptides in lymphoma: surgery at molecular level for therapeutic understanding

Salman Ahmed[1] · Michael Aschner[2] · Khalaf F. Alsharif[3] · Mamdouh Allahyani[3] · Guang Huang[4] · Chunpeng Wan[5] · Haroon Khan[6,7]

Received: 22 December 2024 / Accepted: 8 February 2025

Abstract

Lymphoma, the most common form of blood cancer, affects primarily the intricate network of tissues and organs known as the lymphatic system. Globally, it ranks among the leading causes of cancer-related deaths. Although conventional therapies have led to significant advancements, they are accompanied by adverse side effects and present challenges in cases of multidrug resistance, refractory patients, and relapses. This highlights a pressing need for innovative treatment approaches. Extensive research on the anti-lymphoma properties of natural compounds has particularly focused on marine organisms as valuable sources for potential medicinal agents. Among these, anticancer peptides have garnered attention due to their multiple beneficial effects against cancer, coupled with reduced toxicity to normal cells. This review focuses on the molecular mechanisms underlying the anti-lymphoma effects of marine peptides, examining the diverse pathways through which these peptides impact physiological processes. Key effects include modulation of cell viability, induction of apoptosis, cell cycle arrest, antimitotic activity, immunotherapeutic properties, disruption of mitochondrial function and induction of oxidative stress, cancer cell membrane destruction, and interference with microtubule stability. The review also highlights the antibody–drug conjugates (ADCs) derived from marine peptides and their synergistic effects with other anti-lymphoma medications. This knowledge should inspire future study and development of these prospective therapeutic modalities and hasten the investigation and creation of novel lymphoma remedies derived from marine sources.

Keywords Anticancer · Lymphoma · ADCs · Marine peptides · Apoptosis · Antimitotic · Cell cycle arrest · Immunotherapeutic

✉ Haroon Khan
hkdr2006@gmail.com; haroonkhan@awkum.edu.pk

Salman Ahmed
salmanahmed@uok.edu.pk

Michael Aschner
michael.aschner@einsteinmed.org

Khalaf F. Alsharif
alsharif@tu.edu.sa

Mamdouh Allahyani
m.allahyani@tu.edu.sa

Guang Huang
huanggu@umich.edu

Chunpeng Wan
chunpengwan@jxau.edu.cn

[1] Department of Pharmacognosy, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi 75270, Pakistan

[2] Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY 10461, USA

[3] Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Taif University, P.O. Box 11099, 21944 Taif, Saudi Arabia

[4] Department of Pathology, University of Michigan, Ann Arbor, MI 48109, USA

[5] Jiangxi Provincial Key Laboratory for Postharvest Storage and Preservation of Fruits & Vegetables, Jiangxi Agricultural University, Nanchang 330045, China

[6] Department of Pharmacy, Abdul Wali Khan University Mardan, Khyber Pakhtunkhwa 23200, Pakistan

[7] Department of Pharmacy, Korea University, Sejong 20019, South Korea

Published online: 24 February 2025

Introduction

Lymphoma, the most prevalent blood cancer, specifically targets the lymphatic system, a complex network of tissues and organs. The lymphatic system is comprised of lymph nodes, lymphatic vessels, and collecting ducts, constituting a complex tissues network and organs, including the spleen, tonsils, thymus and adenoids, Peyer's patches, bone marrow, and appendix (Bispo et al. 2020). It is within these organs that lymphoma can develop and manifest itself. It can be classified into two primary categories based on the cell of origin: Hodgkin lymphoma (HL), representing 10% of all cases, and Non-Hodgkin lymphoma (NHL), representing the remaining 90% (Angirish et al. 2020). According to the latest data from the GLOBOCAN Global Cancer Statistics for 2020, NHL is the thirteenth most diagnosed cancer worldwide, with 544,352 reported cases and 259,793 deaths. It ranks as the twelfth leading cause of mortality among malignant diseases. In contrast, HL is the twenty-eighth most diagnosed cancer, with 83,087 reported cases and 23,376 deaths, making it the twenty-eighth leading cause of mortality related to malignant diseases (Sung et al. 2020).

B-cell and T-cell lymphomas are the two other classifications for NHL. B-cell lymphomas include Burkitt lymphoma (BL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and mantle cell lymphoma (MCL). T-cell lymphomas, on the other hand, include anaplastic large cell lymphoma (ALCL), cutaneous T-cell lymphoma (CTCL), and peripheral T-cell lymphoma (PTCL). There are two main forms of HL: classical Hodgkin lymphoma (cHL) and rarely occurring Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Conventional treatment approaches, including radiotherapy, chemotherapy, and combination therapy, are typically recommended for lymphoma (Tan et al. 2013).

Despite the advancements in conventional therapies over the last several decades, lymphoma remains incurable, and its treatment often results in various side effects, multi-drug resistance (MDR), refractory patients and relapses. Although radiotherapies have proven effective in treating lymphomas, they often result in substantial adverse health effects and leave lasting effects on cancer patients. Similarly, bone marrow transplantation is challenging due to its potential immune suppression, increasing patients' vulnerability to infectious diseases. Consequently, the development of innovative lymphoma treatments is imperative (Sung et al. 2020; Cho et al. 2020; Kubra Acikalin et al. 2022; Zhou et al. 2024). The pursuit of developing new anticancer agents from natural sources has gained significant attention, fueled by numerous past successes in this endeavor (Dehelean et al. 2021; Naeem et al. 2022). A vast potential exists for unearthing novel natural products derived from marine organisms that exhibit promising activities against hematological malignancies (Saide et al. 2021).

Peptides, which are protein fragments, offer distinct health benefits, and due to their potential to be efficacious cancer treatments, marine-derived peptides have gained significant attention. These peptides have several advantages compared to proteins and antibodies. They are characterized by their small size, which aids in their production and allows them readily cross cell membranes. Additionally, they exhibit a low potential for drug-drug interaction, minimal disruption of the blood–brain barrier (BBB), and preferential targeting of cancer cells. Moreover, they possess diverse chemical and biological properties. One significant advantage of these peptides is their reduced impact on the liver and kidneys, as they have lower propensity to accumulate in these organs. However, anticancer peptides afford several challenges related to their pharmacokinetics. They have limited bioavailability, a short half-life, susceptibility to proteases, and are subject to first-pass metabolism. Despite these limitations, extensive clinical research is being conducted on peptides and their potential to promote apoptosis, hinder angiogenesis and cell proliferation, induce antioxidant effects, and destabilize microtubules. These properties are crucial in developing effective peptide-based treatments for cancer (Ahmed et al. 2023; Ahmed et al. 2023a; Ahmed et al. 2022; Wang et al. 2022a; Chiangjong et al. 2020).

Efficient anticancer peptides targeting lymphoma (Fig. 1) have been derived from diverse marine sources, including cyanobacteria, bacteria, fungi, ascidians, mollusks, sponges, and frogs. A linear peptide is made up of a straight chain amino acids in combination with amide bonds (Barreca et al. 2020a). E7974 (a hemiasterlin analogue and tripeptide) (Kuznetsov et al. 2009); soblidotin / TZT-1027 / auristatin PE (a dolastatin 10 derivative and pentapeptide) (Mohammad et al. 1998); proximicin B (oligopeptide) (Brucoli et al. 2012) and similarly magainin A-B, G (Cruciani et al. 1991) have been derived from bacteria, mollusk, sponges and frogs.

Researchers studying marine natural products have been drawn to exploring cyclic peptides as promising candidates for anticancer agents. This interest stems from their remarkable binding capabilities, specific targeting of desired sites, low toxicity levels, ability to penetrate tumors easily for anti-proliferative effects, increased resistance to degradation by exo- and endopeptidases, and improved in vivo bioavailability (Ramadhani et al. 2022; Zhang et al. 2021a; Lee et al. 2017). Cyclic tetra, hexa, octa, thio and depsipetides have been shown to possess anti-lymphoma properties. Cyclic depsipeptides contain lactone bonds in lieu of amide groups, attributable to a hydroxylated carboxylic acid

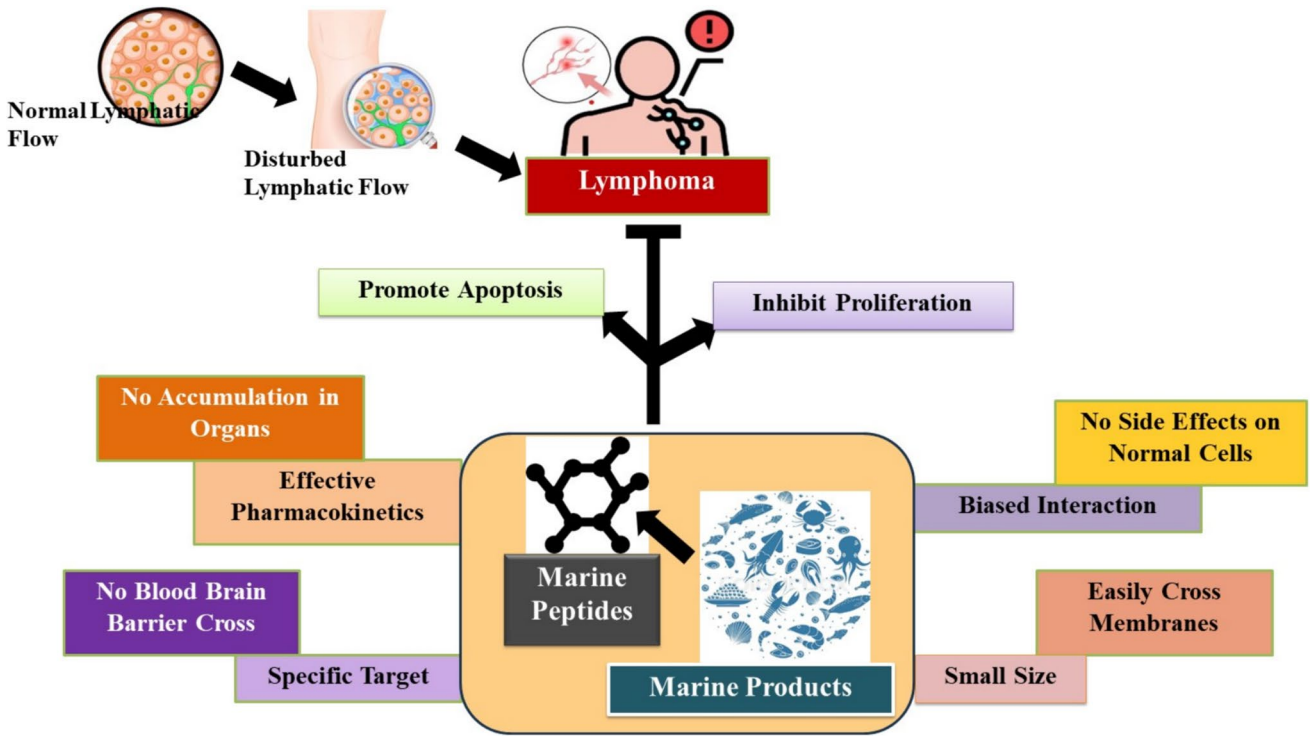

Fig. 1 Different potential actions of marine peptides to inhibit lymphoma progression

within the peptide structure (Wang et al. 2018). Aurilide B-C (Han et al. 2006), cryptophycin-52 (LY355703) (Wagner et al. 1999), Lyngbyabellins B (Marquez et al. 2002) have been derived from cyanobacteria; dolastatin 10 and 15 (Maki et al. 1995, 1996; Zobeida et al. 2003; Beckwith et al. 1993; Bai et al. 1992) from mollusk; didemnin A,B,M, dehydrodidemnin B (aplidin / plitidepsin) (Liang et al. 2001; Barboza et al. 2012; Humeniuk et al. 2007),tamandarin B and dehydro tamandarin A (Liang et al. 2001) from Ascidia; jaspamide (jasplakinolide) (Marquez et al. 2002; Odaka et al. 2000) from sponges; *N*-methylsansalvamide (Cueto et al. 2000), zygosporamide (Oh et al. 2006) has been derived from marine fungus; romidepsin (FR 901228) (Sasakawa et al. 2002; Cosenza et al. 2016) from bacteria; are the anti-lymphomic cyclic depsipeptides.

Asperterrestide A (He et al. 2013), azumamide C (Villadsen et al. 2014) (cyclic tetrapeptide); patellamide F, patellin 6 (cyclic octapeptide) (Rashid et al. 1995); piperazimycin A-C (cyclic hexadepsipeptide) (Miller et al. 2007) have been isolated from sponges and marine derived bacteria and fungus. Thiopeptides are heterocyclic peptides with a six-membered ring containing sulfur, known for their anti-cancer properties (Vinogradov and Suga 2020). Patellamide B (thiopeptide) (Rashid et al. 1995) from ascidians has anti-lymphomic effects. Lipopeptides are covalently linked peptides with fatty acids (Liu et al. 2010). Curacin A (Gerwick et al. 1994) and hectochlorin (Marquez et al. 2002) are the lipopeptides from cyanobacteria exhibiting cytotoxic properties in lymphomic cells. This study aims to inspire natural products researchers to prioritize the investigation of marine peptides with anti-lymphoma properties (Table 1).

Molecular mechanisms

Induction of apoptosis

Apoptosis holds promise as a potential approach for cancer treatment, but significant obstacles hinder its efficacy. When apoptotic regulation is disrupted, cancer cells can evade programmed cell death, leading to prolonged cell survival, increased cell proliferation, and enhanced angiogenesis. Key components in the apoptotic pathway are caspases and poly ADP-ribose polymerase (PARP), whose dysregulation can lead to abnormal cell fate in lymphomic cells. Upon proteolytic cleavage, caspases become activated, serving as the primary initiators of apoptosis. Caspases-8, −9, and −10 trigger a controlled sequence of cell death activating downstream caspases-3, −6, and −7 (Chaudhry, G.-e.-S., Md Akim, A., Sung, Y.Y., Sifzizul, T.M.T. 2022; Anson et al. 2021). Dysregulation of PARP, an enzyme involved in maintaining genomic stability and repairing DNA, has been observed in lymphoma (Pazzaglia and Pioli 2020). Didemnin A, B, M and aplidin

Table 1 Anti-lymphoma effects of marine peptides

Peptides	Marine sources (Species name)	Active derivative	In vitro		In vivo		Anticancer Mechanisms	References
			Cell lines	IC_{50}s / Cytotoxic concentration	Experimental model	Dose		
Aurilide B-C	Cyanobacteria (*Lyngbya majuscula*)	Cyclic depsipeptide	SR	GI_{50} < 10 nM	——	——	Actin microfilament disruption	Han et al. 2006)
Cryptophycin-52 (LY355703)	Cyanobacteria (*Nostoc* sp.)		U937	0.015 nM			Microtubules depolymerization; G2/M phase arrest	Wagner et al. 1999)
Lyngbyabellins B	Cyanobacteria (*Lyngbya majuscula*)		CA46	0.1 μM			G2/M phase arrest	Marquez et al. 2002)
Curacin A		Lipopeptide		2×10^{-7} M			Microtubule depolymerization	Gerwick et al. 1994)
Hectochlorin				0.02 μM			G2/M phase arrest	Marquez et al. 2002)
Dolastatin 10	Mollusk (*Dolabella auricularia*)	Cyclic depsipeptide		0.21 nM			DNA fragmentation; Bcl2↓; p53↑; G2M phase arrest; Microtubule depolymerization	Zobeida et al. 2003)
			WSU-DLCL2	1 ng mL^{-1}				Maki et al. 1995)
			DB, HT, RL	0.0001–0.001 *n*g mL^{-1}				Beckwith et al. 1993)
			WSU-FSCCL, WSU-NHL, WSU-BL	1 ng mL^{-1}				Maki et al. 1996)
Dolastatin 15			CA46	0.46 nM				Zobeida et al. 2003)
			BL	3 nM				Bai et al. 1992)
Soblidotin (Dolastatin 10 derivative)		Linear pentapeptide	WSU-DLCL2	50 pg mL^{-1}	WSU-DLCL2 mouse xenografts	2 mg kg^{-1}, i.p		Mohammad et al. 1998)
MMAE (Dolastatin 10 derivative)			Daudi	4.6 nmol L^{-1}	——	——	DNA fragmentation; G2M phase arrest	Law et al. 2004)
			Ramos	1.5 nmol L^{-1}				
			Raji	4 nmol L^{-1}				
			Karpas- 299	3.2 nmol L^{-1}				
AGS67E (AGS67C -MMAE)			Daudi	0.078 nM				Pereira et al. 2015)
			DOHH-2	0.98 nM	DOHH-2 mouse xenograft	3.0 mg kg^{-1} i.v		
			Granta-519	0.79 nM	——	——		
			Mino	0.07 nM	Mino mouse xenograft	0.5 mg kg^{-1} i.v		
			Ramos	0.047 nM	——	——		
			Ramos-RR-XcL	0.01 nM	Ramos-RR-XcL mouse xenograft	3 mg kg^{-1} i.v		
			SU-DHL-4	0.23 nM	——	——		
			WSU-DLCL2	19.7 nM	WSU-DLCL2 mouse xenograft	1.5 mg kg^{-1} i.v		
Anti-CD83 ADC (3C12C-MMAE)			Mino	0.017 μg mL^{-1}	——	——		Li et al. 2020b)
			Rec-1	> 10 μg mL^{-1}				
Rituximab-vcMMAE			Daudi	1.04 μg mL^{-1}				Law et al. 2004)
			Ramos	0.04 μg mL^{-1}				
			Raji	1.5 μg mL^{-1}				
			——	——	Ramos mouse xenograft	3 mg kg^{-1} i.v		
1F5-vcMMAE			Daudi	1.27 μg mL^{-1}	——	——		
			Ramos	0.15 μg mL^{-1}				
			Raji	3.9 μg mL^{-1}				
T22-AUR Nanoconjugate (T22-GFP-H6 nanocarrier – MMAE)			SUDHL-2	0.50 ng mL^{-1}			DNA fragmentation; Caspase-3↑; PARPi; G2M phase arrest	Falgàs et al. 2021)
			Toledo	0.87 ng mL^{-1}				
			U-2932	0.33 ng mL^{-1}				
			——	——	U-2932 mouse xenograft	100 μg, sc		

Table 1 (continued)

Peptides	Marine sources (Species name)	Active derivative	In vitro		In vivo		Anticancer Mechanisms	References
			Cell lines	IC_{50}s / Cytotoxic concentration	Experimental model	Dose		
Diazonamide A	Ascidia (*Diazona angulata*)	Cyclic peptide	CA46	3.8 nM	——	——	Microtubule depolymerization	Zobeida et al. 2003)
Didemnin A, B, M	Ascidia (*Tridemnum solidum, Tridemnum cyanophorum*)	Cyclic depsipeptide	SR	A: 10.2; B: 3.8; M: 7.6 μM			Caspase-3, −7↑; PARPi; G1/S phase arrest	Liang et al. 2001)
Aplidin	Ascidia (*Aplidium albicans*)		Daudi	1.2 nM				Barboza et al. 2012)
			Raji	2.6 nM				
			HT	0.8 nM				
			RL	1.5 nM				
			Ramos	1.7 nM				
			Namalwa	3.1 nM				
			Jiyoye	5.6 nM				
			Bjab	5.8 nM				
			SKI-DLCL	1.5 nM	SKI-DLCL mouse xenograft	0.6 mg kg^{-1}, i.p		Humeniuk et al. 2007)
Tamandarin B	Ascidia (*Tridemnum solidum*)		SR	1.4 μM	——	——	↓ cell viability[a]	Liang et al. 2001)
Dehydro tamandarin A				2.7 μM				
Patellamide B, F	Ascidia (*Lissoclinum patella*)	Cyclic thiopeptide		B: 48; F: 13 μM				Rashid et al. 1995)
Patellin 6		Cyclic octapeptide		3 μM				
Jaspamide	Sponge (*Jaspis johnstoni*)	Cyclic depsipeptide	CA46	0.03 μM			G2/M phase arrest	Marquez et al. 2002)
			EL-4	2 μg mL^{-1}			Caspase-3↑; DNA fragmentation; Actin microfilament disruption	Odaka et al. 2000)
Azumamide C	Sponge (*Mycale izuensis*)	Cyclic tetrapeptides	EB-3	50 μM			HDACi	Villadsen et al. 2014)
Callyaerins E and H	Sponge (*Callyspongia aerizusa*)	Cyclic peptide	L5178Y	ED50: E 0.39; H: 0.48 μM			↓ cell viability[a]	Ibrahim et al. 2010)
Callyaerin G				ED50: 0.53 μg mL^{-1}				Ibrahim et al. 2008)
E7974 (hemiasterlin analogue)	Sponge (*Hemiasterella minor*)	Linear tripeptide	U937	300 nmol L^{-1}			Caspase-3↑; PARPi; G2M phase arrest; Microtubule depolymerization	Kuznetsov et al. 2009)
N-Methylsansalvamide	Fungus (*Fusarium* sp.)	Cyclic depsipeptide	SR	GI50: 8.3 μM			↓ cancer cell growth[a]	Cueto et al. 2000)
Zygosporamide	Fungus (*Zygosporium masonii*)			GI_{50}: 9.1 μM			↓ cancer cell growth[a]	Oh et al. 2006)
Asperterrestide A	Fungus (*Aspergillus terreus*)	Cyclic tetrapeptide	U937	6.4 μM			↓ cell viability[a]	He et al. 2013)
Romidepsin	Bacteria (*Chromobacterium violaceum* No. 968.)	Cyclic depsipeptide		5.92 nM	U937 mouse xenograft	0.32 mg kg^{-1} i.p	Caspase-3, −8, −9↑; Bcl-xL↓; ROS↑; HDACi; G1 and G2M phase arrest	Sasakawa et al. 2002)
			Hut-78	6.36 nM	——	——		Cosenza et al. 2016)
			Karpas-299	3.87 nM				
Piperazimycin A-C	Bacteria (*Streptomyces* sp.)	Cyclic hexadepsipeptide	SR	GI_{50}: ~100 nM			↓ cell viability[a]	Miller et al. 2007)
Proximicin B	Actinomycete (*Verrucosispora* sp.)	Oligopeptide	L1236	B: 20 μg mL^{-1}			DNA fragmentation	Brucoli et al. 2012)
Magainin A-B, G	Frog (*Xenopus laevis*)	Peptide	Daudi	A: 30; B: 28; G: 38 μg mL^{-1}			Necrotic cell death	Cruciani et al. 1991)
			Raji	A: 20; B: 23; G: 25 μg mL^{-1}				
			U937	A: 16; B: 17; G: 19 μg mL^{-1}				

Lymphoma Cell lines: EL-4, L5178Y = Mouse; Bjab, BL, CA46, Daudi, EB-3, Jiyoye, Namalwa, Raji, Ramos, Ramos-RR-XcL (Burkitt Lymphoma); DB, DOHH-2, Granta-519, HT, Mino, RL, SKI-DLCL, SR, SUDHL-2, SU-DHL-4, Toledo, U-2932, WSU-DLCL2 (Diffuse Large B-Cell Lymphoma Cell Line/ DLBL); L1236 (Hodgkin's lymphoma); Hut-78, Karpas-299, Rec-1, WSU-FSCCL, WSU-NHL, WSU-BL; (Non-Hodgkin's lymphoma); U937 (histiocytic lymphoma) = Human; ED_{50} = Median effective dose, GI_{50} = Growth inhibition 50%; a = Mechanism is yet to be investigated

have demonstrated apoptotic effectiveness by increasing caspase-3 and −7 activity and PARP inhibition (Liang et al. 2001; Barboza et al. 2012). Jaspamide (Odaka et al. 2000) and E7974 (hemiasterlin analogue) (Kuznetsov et al. 2009) have also been shown to promote caspase-3 activity and PARP inhibition in EL-4 and U937 cells. Romidepsin activates caspases-3, −8 and −9 in Hut-78 (6.36 nM), Karpas-299 (3.87 nM) and U937 (5.92 nM) (Sasakawa et al. 2002; Cosenza et al. 2016). The Bcl-2 and Bcl-xL inhibition has demonstrated promising outcomes in initiating apoptosis in lymphoma(Qian et al. 2022). Dolastatins (Mohammad et al. 1998; Maki et al. 1995, 1996; Zobeida et al. 2003; Beckwith et al. 1993; Bai et al. 1992) and romidepsin (Sasakawa et al. 2002; Cosenza et al. 2016) have been shown to promote apoptosis via analogous mechanisms in different lymphoma cells.

Cell cycle arrest

Cell cycle arrest plays a paramount role in treating lymphoma as it effectively targets rapidly dividing lymphoma cells, enhances the efficacy of chemotherapy, and enables targeted therapy (Sánchez-Beato et al. 2003; Bröckelmann et al. 2020; Leoncini et al. 2002). Cell cycle disruption in the G1 and G2/M phases is vital, as it facilitates maintenance of genetic stability, prevents DNA-damaged cells from entering mitosis, ensures proper progression of the cell cycle, prevents abnormal cell division, promotes apoptosis, and affords a target for cancer therapies, as shown in lymphoma cell lines (Sánchez-Beato et al. 2003; Bröckelmann et al. 2020; Leoncini et al. 2002). Didemnin A, -B, -M and Dehydrodidemnin B (Aplidin) have been shown or cause G1/S arrest in Bjab, Daudi, HT, Jiyoye, Namalwa, Raji, Ramos, RL, SKI-DLCL and SR cell lines (Liang et al. 2001; Barboza et al. 2012; Humeniuk et al. 2007). Lyngbyabellins B (Marquez et al. 2002), hectochlorin (Marquez et al. 2002) and jaspamide (Marquez et al. 2002) induced G2/M phase arrest in CA46 with IC_{50} values of 0.1, 0.02 and 0.03 µM, respectively. Similarly, Cryptophycin-52 (Wagner et al. 1999) and E7974 (hemiasterlin analogue) (Kuznetsov et al. 2009) contributed to G2/M phase arrest in U937 cells. p53 protein is crucial for inhibiting tumor development and preserving DNA integrity, by arresting the cell cycle and promoting apoptosis(Marei et al. 2021). Dolastatin 10, −15 and soblidotin (dolastatin 10 derivative) induced p53 upregulation and cause G2M phase arrest in different lymphomic cell lines (Mohammad et al. 1998; Maki et al. 1995, 1996; Zobeida et al. 2003; Beckwith et al. 1993; Bai et al. 1992). P21 overexpression in lymphoma resulted in G1 and G2/M phase arrest and cell death (Shamloo and Usluer 2019). Romidepsin has been shown to induce G1 and G2/M arrest via an analogous mechanism (Sasakawa et al. 2002).

Histone deacetylases inhibition

The overexpression of histone deacetylases (HDACs) in lymphomas positions these enzymes as promising targets for targeted therapy (Wang et al. 2020; Chen et al. 2020). HDAC inhibition (HDACi) triggers DNA damage response, reduces cell proliferation (p21 upregulation and cyclin D1 downregulation), induces apoptosis (increased Caspases 3 and 9; decreased Bcl-xL), arrests the G2/M phase, induces autophagy (upregulation of mTOR, Beclin-1, and LC3), activates p53, and suppresses metastasis and angiogenesis (downregulation of VEGFR2 and MMP-2) (Li et al. 2020a; Shanmugam et al. 2022). Azumamide A (EB-3: 50 µM) (Villadsen et al. 2014) and romidepsin (Karpas-299: 3.87 nM; Hut-78: 6.36 nM; U937: 5.92 nM) (Sasakawa et al. 2002; Cosenza et al. 2016) have been shown to induce cytotoxicity in lymphoma cell lines by HDACi.

Antimitotic effects

Microtubule-targeting agents exhibit broad activity in lymphoma by disrupting the dynamic behavior of microtubules. Given the essential role of microtubules in regulating mitotic spindles, their functional interference typically results in the halt of cell division, specifically at the transition between metaphase and anaphase during mitosis, ultimately leading to apoptosis (Barreca et al. 2020b). Microtubule-destabilizing agents induce apoptosis, G2/M cell cycle arrest, and metastatic incidents by upregulating proapoptotic Bax, Bak, and Bad, and inactivating Bcl-xL, Bcl-2 and Mcl-1 (Bates and Eastman 2017). Cryptophycin-52, E7974 (hemiasterlin analogue), curacin A and diazonamide A demonstrated cytotoxicity in U937 and CA46 by microtubule depolymerization (Kuznetsov et al. 2009; Wagner et al. 1999; Zobeida et al. 2003; Gerwick et al. 1994). Dolastatin 10/15 H and dolastatin 10 derivative (TZT-1027) showed strong antiproliferative effects in BL, CA46, DB, HT,RL, WSU-DLCL2, WSU-FSCCL, WSU-NHL, and WSU-BL cell lines and potently inhibited cancer cell growth in WSU-DLCL2 mouse xenografts (Mohammad et al. 1998; Maki et al. 1995, 1996; Zobeida et al. 2003; Beckwith et al. 1993; Bai et al. 1992). Similarly, aurilide B-C and jaspamide disrupted actin microfilament structure in SR and EL-4 cells (Han et al. 2006; Odaka et al. 2000). Jaspamide acyclic derivatives and jasplakinolide Z6, Z5 and V exhibited significant cytotoxicity against L5178Y cells with IC_{50} values below 100 nM, indicating their potent anticancer potential. Surprisingly, the study revealed that a 19-membered macrocyclic ring is not essential for their activity. The findings suggest that the macrocyclic ring can be opened to generate acyclic counterparts that retain comparable efficacy as long as they maintain sufficient lipophilic properties to facilitate cellular uptake (Ebada et al. 2019). Novel dolastatin analogues that

target tubulin, such as MMAE (monomethyl auristatin E) and MMAF (monomethyl auristatin F), have been developed as antibody–drug conjugates (ADCs) (Barreca et al. 2020b).

Immunotherapeutic effects

MMAE and MMAF are potent ADCs derived from the auristatin peptide found in the mollusk *Dolabella auricularia*. These stable molecules act as immunotherapeutic agents, inducing cell death by depolymerizing microtubules and causing G2/M phase arrest, while resisting degradation by plasma, liver lysosomal extracts, and proteases. Novel engineered ADCs can target lymphoma cells expressing highly expressed antigens. The three-component structure of ADCs includes monoclonal antibodies (mAbs) recognizing cancer cell surface antigens, an attached cytotoxic payload, and a controlled release mechanism. Upon binding, ADCs enter cancer cells with specific antigens, release the cytotoxic drug, and induce cell death while shielding healthy cells from harm. ADCs offer promising therapeutic advantages, including improved pharmacokinetics, reduced systemic toxicity, and increased efficacy in treating lymphoma (Gao et al. 2021; Fu et al. 2022; Cheng-Sánchez et al. 2022; Singh 2022; Jagadeesh and Smith 2016).

AGS67E (MMAE) has been shown to induce apoptosis and G2/M phase arrest in a panel of NHL cell lines, including Daudi, Granta-519, Mino, DOHH-2, Ramos, SU-DHL-4, and WSUDLCL2 in vitro. Additionally, AGS67E demonstrated growth- inhibitory effects in Mino, DOHH2, WSU-DLCL2, and Ramos-RR-XcL (NHL) xenografts in vivo (Pereira et al. 2015). In Mino and Rec-1 cell lines, the anti-CD83 ADC (MMAE) similarly induced G2/M phase arrest, aligning with these findings (Li et al. 2020b). CD20 is a lymphoma surface protein is challenging to treat lymphoma with conventional therapies as commonly causes resistance. The anti-CD20–auristatin conjugates (1F5-vcMMAE and Rituximab-vcMMAE) were shown to be more effective than MMAE alone. Notably, these conjugates were well-tolerated in mice,, indicating minimal toxicity to healthy tissues. In vitro experiments revealed that Rituximab-vcMMAE and 1F5-vcMMAE exhibit cytotoxic effects against Daudi, Ramos, and Raji cell lines, through G2/M mitotic arrest and DNA damage. Furthermore, in a mouse xenograft model using Ramos cells, Rituximab-vcMMAE effectively attenuated tumor cell growth (Law et al. 2004).

T22-AUR nanoconjugate, a CXCR4-targeting nanocarrier conjugated with MMAE, exhibits multiple beneficial effects against CXCR4-positive DLBCL. Firstly, it reduced the lymphoma burden in a U-2932-Luci xenograft model. Furthermore, the heightened expression of CXCR4 in DLBCL cells, often associated with resistance to therapy, can be targeted by T22-AUR to induce apoptosis in human DLBCL cell lines (SUDHL-2, Toledo, and U-2932). This apoptosis is triggered through PARP cleavage and caspase-3 activation, resulting in G2/M mitotic arrest and DNA damage. T22-AUR also showed minimal toxicity in human peripheral blood mononuclear cells, establishing it as a promising therapeutic option for rrDLBCL (Falgàs et al. 2021).

Mitochondrial dysfunction and oxidative damage

DNA fragmentation occurs when DNA strands break into smaller pieces due to prolonged oxidative stress resulting in apoptosis (Poetsch 2020). Jaspamide (Odaka et al. 2000) and proximicin B (Brucoli et al. 2012) caused DNA fragmentation in EL-4 and L1236 cell lines, respectively. Similarly, dolastatin 10, 15 and dolastatin 10 derivatives (auristatin PE and MMAE) employed a similar mechanism in various lymphoma cell lines (Mohammad et al. 1998; Beckwith et al. 1993; Bai et al. 1992; Law et al. 2004). Elevating reactive oxygen species (ROS) levels has been shown to induce oxidative stress, damage DNA, suppress cancer cell survival mechanisms, and alter the immune response (Kim et al. 2019). Romidepsin showed anti-lymphomic effects by increasing ROS levels in Karpas-299, Hut-78 and U937 cells (Sasakawa et al. 2002; Cosenza et al. 2016).

Cancer cell membrane destruction

Anticancer peptides can disrupt cell membranes, leading to necrosis and subsequent cell lysis, which kills cancer cells. These peptides induce substantial cytoplasmic leakage by depolarizing the membranes of cancer cells (Huang et al. 2011; Raucher and Ryu 2015; Preta 2020). Magainins A, B, and G have been shown to effectively destroy lymphoma cells (Daudi, Raji, and U937) by rapidly and irreversibly damaging cell membranes. This process involved the formation of pores within the membranes, making it extremely difficult for the cells to develop resistance. Importantly, normal cells remain unaffected by this targeted toxicity (Cruciani et al. 1991).

Unidentified anti-lymphoma mechanisms

Tamandarin B (Liang et al. 2001), dehydro tamandarin A (Liang et al. 2001), patellamide B and F (Rashid et al. 1995) and patellin 6 (Rashid et al. 1995), derived from ascidians, display significant cytotoxic effects in various lymphomic cells. However, their precise targets have yet to be identified. Callyaerins E, G and H (Ibrahim et al. 2010, 2008), sourced from sponges, have been shown to induce anti-lymphomic activity, although the underlying mechanism remains unknown. Asperterrestide A (He et al. 2013), *N*-methylsansalvamide (Cueto et al. 2000) and zygosporamide (Oh et al. 2006), derived from marine-derived fungus, as well as piperazimycin A-C (Miller et al. 2007), isolated from marine

bacteria, have not yet been explored for anti-lymphoma mechanism. The diverse underlying anti-lymphoma mechanisms are summarized in Fig. 2.

Synergistic effects with other anti-lymphoma agents

In SKI-DLCL tumor xenografts, administering aplidin (plitidepsin) at 0.4 mg/kg has been shown to enhance the anti-lymphoma efficacy of araC (cytarabine) at 100 mg/kg by inhibiting cancer cell growth, leading to a synergistic effect (Humeniuk et al. 2007). Furthermore, co-administration of aplidin (plitidepsin) (0.2 mg/kg) and rituximab (RTX) (0.2 mg/kg) in a xenograft model of Ramos Burkitt lymphoma remarkably suppressed tumor growth and significantly prolonged the lifespan of mice (Barboza et al. 2012). Similarly, soblidotin (TZT-1027 / auristatin PE) at 1.5 mg/kg, administered intravenously (i.v.), has been shown to potentiate the anti-lymphoma effects of bryostatin 75 µg/kg, administered intraperitoneally (i.p.), in WSU-DLCL2 mouse xenografts when given in combination (Mohammad et al. 1998).

In vitro studies on TCL cell lines H9 and HH demonstrated a synergistic effect when combining romidepsin (Romi) (FR 901228 / FK 228 / NSC 630176 / Istodax®) (0.002 µM/L) with folate analog pralatrexate (PDX) at 1 µM/L concentration (Jain et al. 2015). Similarly, in H9 and HUT-78 mouse xenografts, the co-administration of Romi (2 mg/kg, i.p.) and PDX (15 mg/kg, i.p.) enhanced apoptosis and decreased cell proliferation (Jain et al. 2015). In vitro studies conducted with HUT-78 and Karpas-299 cells showed that the combination of Romi (2.5 nM) and lenalidomide (Len) (10 µM) significantly increased apoptosis compared to the effects of each drug alone. This increased apoptosis has been attributed to the activation of caspases-3, −9, and −8, as well as decreased expression of Bcl-xL and Mcl-1. Moreover, this combination treatment induces endoplasmic reticulum (ER) stress-induced apoptosis by increasing ROS levels. Furthermore, the combination treatment leads to the PI3K/Akt, MAPK/ERK and STAT3 dephosphorylation while causing G0/G1 phase arrest by downregulating cyclins D, E, and B (Cosenza et al. 2016, 2013). Notably, Romi enhances the cytotoxicity and apoptotic effects of alisertib, an Aurora A kinase inhibitor in cutaneous T-cell lymphoma (HH, H9) and $HTLV^+$ (C5MJ) cell lines, by inhibiting the activation of STAT-3 (Zullo et al. 2014). Resistance to RTX in CD20-positive B-cell lymphoma is often attributed to decreased expression of CD20. However, Romi has been shown to increase the cytotoxic potency of RTX by upregulating the surface presentation of CD20 antigen, as demonstrated in B-cell lymphoma cell lines including BJA-B, Daudi, HBL-2, and Namalwa. Furthermore, Romi also increases RTX 's cytotoxic activity in xenograft models of BJA-B (B-cell) (Shimizu et al. 2010). The overall process is shown in Fig. 3.

Clinical trial status

Aplidin and its combinations

Didemnin B exhibited modest efficacy in NHL during a phase II clinical trial. However, clinical trials with didemnin B were halted due to substantial toxicity. An analog of didemnin B (dehydrodidemnin B / aplidin / plitidepsin) appeared more active in preclinical models (Kucuk et al. 2000; Pangestuti and Kim 2017). Aplidin had a favorable safety profile in patients with rr PTCL. Its minimal hematologic toxicity makes aplidin an excellent candidate for combination therapy with other effective treatment agents (Izquierdo et al. 2008; Maroun et al. 2006; Fermé et al. 2010). It successfully completed phase II studies (NCT00884286) against rr Aggressive NHL (Vincent et al. 2013). Phase I trial of aplidin combined with sorafenib or gemcitabine in heavily pretreated lymphoma patients showed treatment responses with tolerability and manageable side effects (Aspeslagh et al. 2017).

Romidepsin and its combinations

Romi demonstrated potent antitumor activity without harming normal cells. Positive phase I results against CTCL and PTCL led to a successful phase II study, where Romi exhibited sustained responses with minimized side effects (Piekarz et al. 2001, 2009). US Food and Drug Administration (FDA) approval was granted for CTCL in 2009 and PTCL in 2011 (Smolewski and Robak 2017). Combining Romi with other anti-lymphoma agents in clinical trials offered several benefits, including enhancing therapeutic effects through synergistic actions, overcoming drug resistance, and improving treatment response (Iżykowska et al. 2020; Hontecillas-Prieto et al. 2020). However, the Ro-CHOP Phase III Study (NCT01796002), which evaluated Romi in combination with CHOP, showed no improvement in progression-free survival, response rates, or overall survival, indicated that Ro-CHOP did not provide a significant advancement in for previously untreated PTCL patients (Bachy et al. 2021). A phase 1 study (NCT00963274) revealed that the combination of Romi (10 mg/kg) and bortezomib (1.3 mg/kg) exerted modest activity in patients with indolent B-cell lymphoma, PTCL, or CTCL (Holkova et al. 2017). In another phase I study, the combination of Romi and ICE (Ifosfamide, Carboplatin, and Etoposide) has proven effective. However,

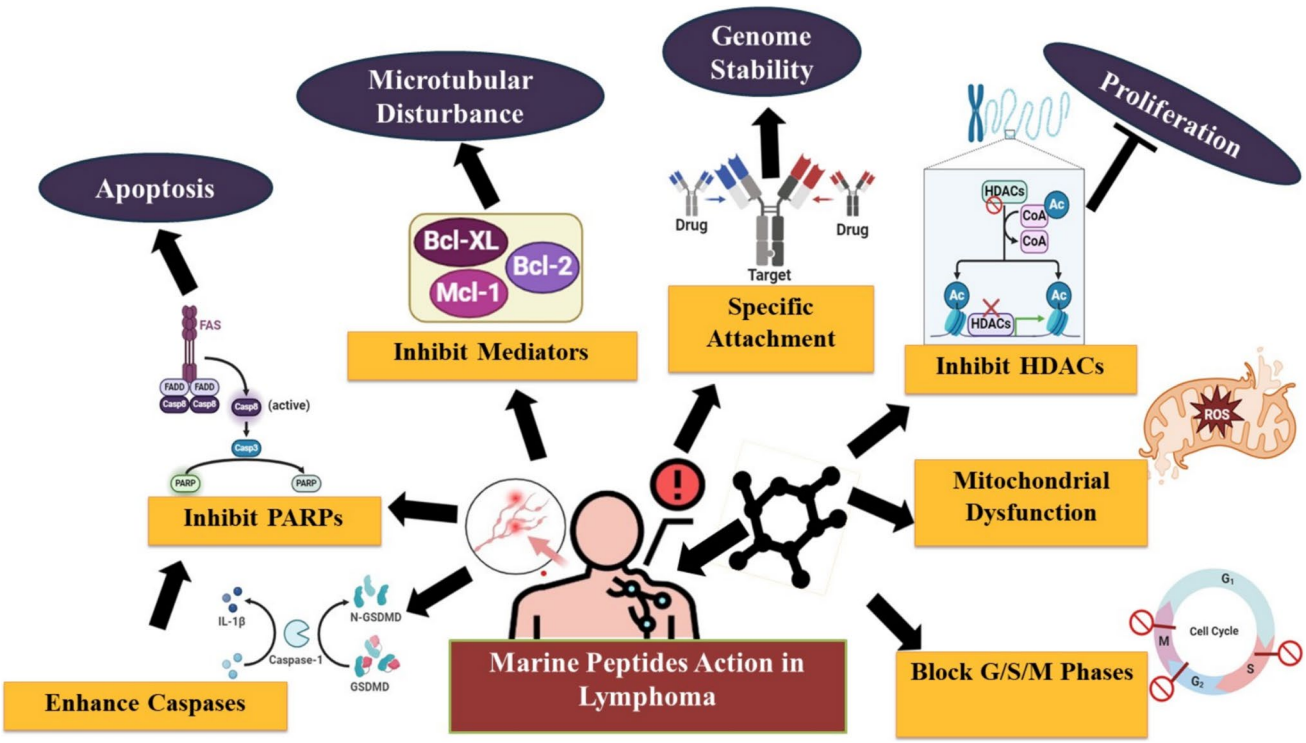

Fig. 2 Mechanism of action of marine peptides at cellular level to target lymphoma via different pathways

such treatment resulted in a higher incidence of thrombocytopenia and neutropenia as compared to Romi or ICE treatment alone (Chihara et al. 2014). The Phase II study was completed by evaluating the combination of Romi and gemcitabine (NCT01822886) in patients with rrPTCL. The combination of Romi and pralatrexate (PDX) demonstrated a high response rate and was found to be safe and well-tolerated in patients with rr lymphoma during a phase I clinical trial. These promising results led to an invitation for further clinical trials (Amengual et al. 2018). The phase II studies (NCT01947140) evaluating the same combination of Romi and PDX (Romi + PDX) in rr Lymphoma have been successfully completed. Additionally, the phase I/II study assessing the combination of Romi and Len in rr lymphomas reported no cumulative toxicities with significant efficacy in patients with TCL and NHL (Lunning et al. 2014; Mehta-Shah et al. 2015). An ongoing phase II study (NCT02232516 and NCT01755975) evaluates the same combination for previously untreated and rr lymphomas, respectively.

ADCs and their combinations

Multiple ADC drugs, such as AGS67E, brentuximab vedotin (BV), CX-2029 (ABBV-2029), pinatuzumab vedotin, polatuzumab vedotin (PV), and zilovertamab vedotin (ZV) utilize the cytotoxic agents MMAE (vedotin) for combination therapies. In contrast, vorsetuzumab mafodotin (SGN-75) employs MMAF (mafodotin). Both groups are currently undergoing clinical trials to evaluate their efficacy for treating lymphoma. These ADCs have received approval from the European Medicines Agency (EMA) and FDA for treating a variety of lymphomas, either alone or in conjunction with chemotherapy.

BV has been approved by FDA for the treatment of rrHL, CD30-expressing PTCL and ALCL (Richardson et al. 2019; Senter and Sievers 2012; Donato et al. 2018). The combination of BV and bendamustine (BBv) as the initial salvage treatment for rrHL (NCT01874054) demonstrated significant efficacy with a manageable level of side effects (LaCasce et al. 2018). Based on the results of Phase 3 ECHELON-1 trial, the combination of BV and AVD (doxorubicin, vinblastine, dacarbazine) (NCT01712490) has received approval for treating advanced-stage cHL (Connors et al. 2018). In phase II trials, combining BV with immune checkpoint inhibitors nivolumab (NCT02572167) demonstrated improved outcomes in patients with rr cHL(Herrera et al. 2018). BV has been approved as maintenance therapy after autologous stem cell transplantation (ASCT) for high-risk cHL patients. The phase 3 AETHERA trial (NCT01100502) revealed BV efficacy as post-ASCT maintenance therapy for high-risk cHL(Moskowitz et al. 2015, 2018). The phase III trial (NCT01578499) demonstrated that BV exhibited higher response rates when compared to Methotrexate and Bexarotene for CD30-positive CTCL (Prince et al. 2017).

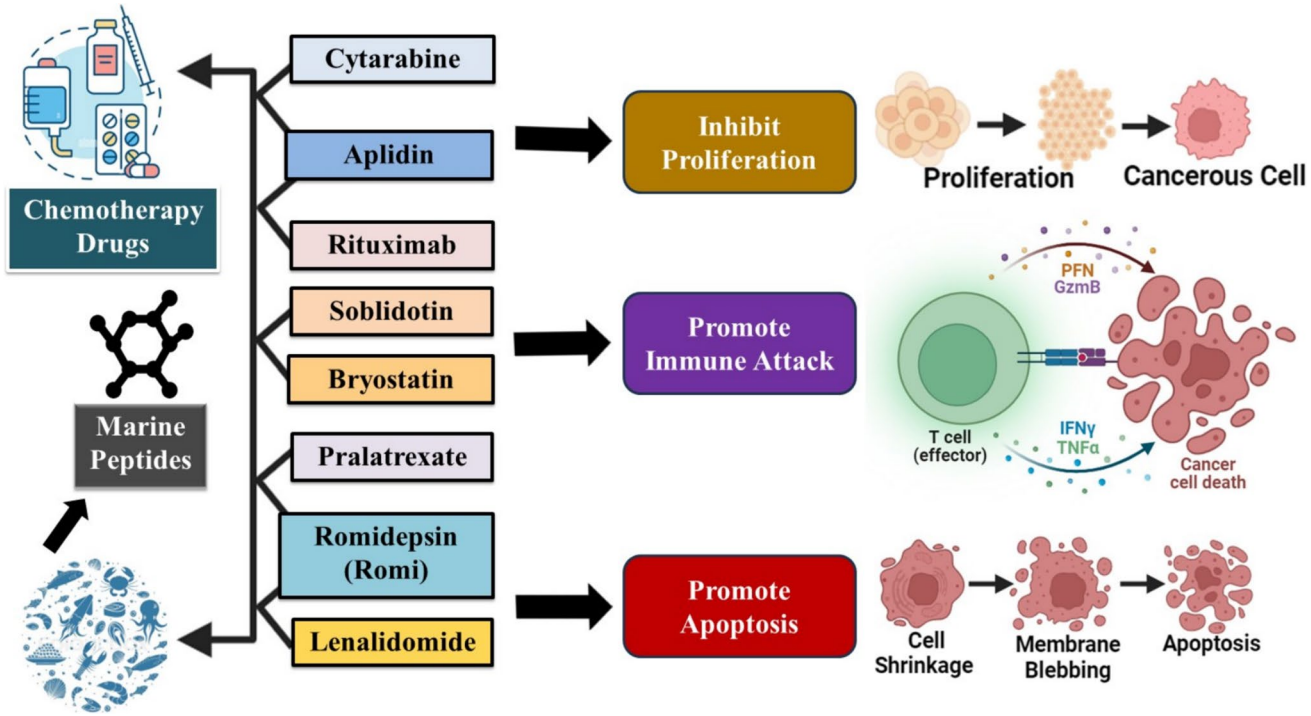

Fig. 3 Synergistic effects of marine peptide-based drugs in combination with other anti-lymphoma agents

The FDA approved PV in August 2019 for the treatment of rrDLBCL (Douglas 2020). The POLARIX phase III trial (NCT03274492) evaluated PV in frontline DLBCL treatment. The combination of PV and RTX-Cyclophosphamide, Doxorubicin, and Prednisone (R-CHP) showcased superior effectiveness compared to RTX-cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) alone. The R-CHP improved overall survival, progression-free survival, and complete response rates with well-tolerated and manageable side effects associated with lower blood cell counts (Tilly et al. 2019). A phase Ib/II trial (NCT02257567) assessed the effectiveness of combining PV with bendamustine and RTX (PV-BRTX) in patients with transplantation-ineligible rrDLBCL showed significantly higher complete response rate (40.0%) and longer progression-free survival. Concomitantly, adverse effects remained manageable compared to BR (Sehn et al. 2019). A currently run phase III trial called POLARGO (NCT04182204) randomly assigns rrDLBCL patients to receive RTX, gemcitabine, and oxaliplatin either alone or in conjunction with PV (Matasar et al. 2021; Haioun et al. 2020). The phase 2 randomised study (ROMULUS) (NCT01691898) indicated that the combination of PV and RTX is more effective than pinatuzumab vedotin (PiV) and RTX along, showing higher overall response rates and progression-free survival in patients with rr NHL (Morschhauser et al. 2019). A Phase Ib/II Trial (NCT02600897) combining PV with obinutuzumab and Len in patients with rr FL showed high response rates (Diefenbach et al. 2021). The combination of PV with Mosunetuzumab (NCT05410418) is currently in the phase II clinical trial phase for untreated Follicular Lymphoma (FL). CX-2029 (NCT03543813) is also in phase II clinical trial for DLBCL.

AGS67E (NCT02175433), given as monotherapy in subjects with rr DLBCL and CTCL, has completed the phase I study, and the phase II study has yet to be carried out (Sawas et al. 2017).

ZV is currently in phase II trial (NCT05144841) to treat patients with rrDLBCL. Preliminary results indicate that ZV displays notable anti-cancer efficacy in patients who experienced disease progression following ASCT or chimeric antigen receptor T-cell (CAR-T) therapy or who were ineligible for these treatments, while maintaining an acceptable safety profile (Ozcan et al. 2140). Additionally, ZV is being tested in a phase I study (NCT03833180) to evaluate its safety profile and anticancer efficacy in patients with rrNHL (Wang et al. 2022b). Vorsetuzumab Mafdotin has completed a Phase I trial (NCT01015911) in patients with rrNHL and metastatic renal cell carcinoma (Tannir et al. 2014). An overall summary of these findings is presented in Fig. 4.

Conclusions, challenges, and perspectives

Evidence indicates an increasing prevalence of lymphoma, particularly among women and elderly individuals, which warrants greater attention. Despite the disease burden

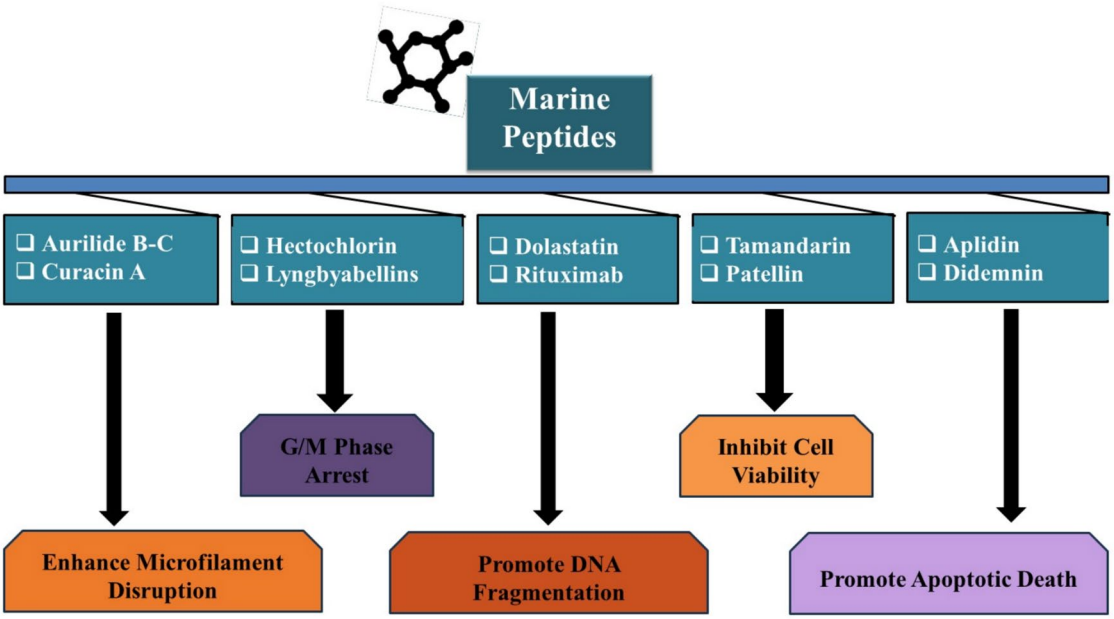

Fig. 4 Different marine peptides in clinical trial stages and their cellular actions in cancer cells

worldwide, comprehensive information on marine peptides as a potential treatment for this life-threatening illness is lacking (Chu et al. 2022; Sedeta et al. 2022). Anti-lymphomic actions of marine peptides include cell growth suppression, apoptosis induction, cell cycle arrest, histone hyperacetylation stimulation, antimitotic, immunotherapeutic, and cancer cell membrane destruction. These peptides represent compelling source for developing anti-lymphomic drugs and provide a basis for identifying new therapeutic cellular targets. ADCs derived from marine peptides have the potential to revolutionize lymphoma treatment by providing targeted therapy with improved efficacy and reduced toxicity. Despite this optimistic outlook, progress has slowed, making further investigation into the anti-lymphoma properties of marine peptides is imperative. Additionally, evaluating the toxicity and adverse effects of marine peptides on normal cells is imperative (Ghaly et al. 2023; Chinnadurai et al. 2023; Chu et al. 2021).

The difficulty in assessing the effectiveness of marine peptides arises from the predominance of in vitro research over in vivo studies. Limited clinical investigations into these therapeutic agents have contributed to an inadequate understanding of their mode of actions. This presents an opportunity for future research, emphasizing the need for comprehensive in vivo and clinical studies to bridge these knowledge gaps. Despite the potential risks of toxicity associated with specific marine peptides, which have led to their exclusion from clinical trials, there remains a vast opportunity for synthesizing analogous compounds from this abundant source to pursue innovative pharmaceuticals.

Ongoing studies have obtained significant results, particularly regarding inquiries into the structure–activity relationship (SAR) of certain marine peptides. When exploring novel peptides as potential anticancer therapies, it is essential to address formulation and administration challenges from the outset. This proactive approach can increase the likelihood of gaining interest from the pharmaceutical industry while preventing delays in drug development brought on by unfavorable pharmacokinetic profiles or toxic effects. Further research is required to determine how marine peptides interact with conventional chemotherapy, targeted therapy, and immunotherapy. These studies will shed light on potential synergistic effects and enable the development of effective combination therapies for cancer treatment. Additionally, innovative methods must be used to isolate and identify anticancer marine peptides to advance this research. Similarly, the novel drug delivery system has greatly aided to drug development including the overall accuracy and precision of cancer therapeutics (Zhang et al. 2021b; Ahmed et al. 2023b; Kim and Park 2024). As these marine derived peptides have diverse and versatile nature, are not explored therefore could be more expressive in complicated and resistant conditions. These cutting-edge techniques will help broaden the range of available therapeutic options and deepen our understanding of the promising role that marine peptides can play in the fight against lymphoma (Ahmed et al. xxxx; Ahmed et al. 2023a).

Therapeutic peptides have also limitations, including a brief half-life, inadequate bioavailability, manufacturing and

processing challenges, and protease vulnerability. Cell-penetrating peptides are employed to address the issue of low cell membrane permeability. Several techniques have been developed to overcome concerns related to metabolic instability and short half-life. These techniques include using *D*-amino acids instead of *L*-amino acids, implementing cyclization, encapsulating peptides within nanoparticles, pegylation, and XTEN conjugation. Furthermore, substituting *L*-amino acids with *D*-amino acids can help reduce immunogenicity (Lamers 2022; Muttenthaler et al. 2021; Craik and Kan 2021).

In summary, marine peptides hold great promise in the fight against lymphoma because of their anti-lymphomic effects, distinct chemical structures, abundant marine biodiversity, minimal toxicity, and potential to enhance efficacy when combined with other medications. Thus, in light of modern technologies, targeting marine peptides is a more vibrant area of research to combat complicated and resistant lymphoma.

Abbreviations ADCs: Antibody-drug conjugates; ALCL: Anaplastic large cell lymphoma; ASCT: Autologous stem cell transplantation; Bad: Bcl-2 / Bcl-X associated death-domain protein; Bak: Bcl-2 homologous antagonist—killer protein; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; Bcl-XL: B cell lymphoma-extra large; BV: Brentuximab vedotin; cHL: Classical Hodgkin lymphoma; CTCL: Cutaneous T-cell lymphoma; DLBCL: Diffuse large B-Cell lymphoma; ER: Endoplasmic reticulum; FL: Follicular lymphoma; HDACi: Histone deacetylases inhibition; HL: Hodgkin`s lymphoma; Len: Lenalidomide; mAbs: Monoclonal antibodies; MCL: Mantle cell lymphoma; Mcl-1: Myeloid cell leukaemia-1; MMAE: Monomethyl auristatin E; MMAF: Monomethyl auristatin F; NHL: Non-Hodgkin lymphoma; NLPHL: Nodular lymphocyte-predominant Hodgkin lymphoma; PARP: Poly ADP-ribose polymerase; PDX: Pralatrexate; PDX: Pralatrexate; PTCL: Peripheral T-cell lymphoma; PV: Polatuzumb vedotin; rr: Relapsed / refractory; Romi: Romidepsin; ROS: Reactive oxygen species

Author contribution Salman Ahmed: Writing and data searching Michael Aschner: Writing and data searching Khalaf F Alsharif: Writing and data searching Mamdouh Allahyani: Writing and data searching Guang Huang: editing and reviewing Chunpeng Wan: drawing figures and reviewing Haroon Khan: supervising and final editing. The authors confirm that no paper mill and artificial intelligence was used.

Funding No funding.

Data availability All source data for this work (or generated in this study) are available upon reasonable request.

Declarations

Clinical trial number Not applicable.

References

Ahmed S, Alam W, Jeandet P, Aschner M, Alsharif KF, Saso L, Khan H (2022) Therapeutic potential of marine peptides in prostate cancer: mechanistic insights. Marine Drugs 20(8):466

Ahmed S, Alam W, Aschner M, Filosa R, Cheang WS, Jeandet P, Khan H (2023) Marine cyanobacterial peptides in neuroblastoma: Search for better therapeutic options. Cancers 15(9):2515

Ahmed S, Alam W, Alsharif KF, Aschner M, Alzahrani FM, Saso L, Khan H (2023a) Therapeutic potential of marine peptides in malignant melanoma. Environ Res 227:115771

Ahmed S, Alam W, Aschner M, Filosa R, Cheang WS, Jeandet P, Saso L, Khan H (2023b) Marine cyanobacterial peptides in neuroblastoma: search for better therapeutic options. Cancers (Basel) 15(9):2515

Amengual JE, Lichtenstein R, Lue J, Sawas A, Deng C, Lichtenstein E, Khan K, Atkins L, Rada A, Kim HA, Chiuzan C, Kalac M, Marchi E, Falchi L, Francescone MA, Schwartz L, Cremers S, O'Connor OA (2018) A phase 1 study of romidepsin and pralatrexate reveals marked activity in relapsed and refractory T-cell lymphoma. Blood 131(4):397–407

Angirish B, Sanghavi P, Jankharia B (2020) Pulmonary manifestations of lymphoma: A pictorial essay. Lung India 37(3):263–267

Anson F, Thayumanavan S, Hardy JA (2021) Exogenous Introduction of Initiator and Executioner Caspases Results in Different Apoptotic Outcomes. JACS Au 1(8):1240–1256

Aspeslagh S, Stein M, Bahleda R, Hollebecque A, Salles G, Gyan E, Fudio S, Extremera S, Alfaro V, Soto-Matos A, Soria J-C (2017) Phase I dose-escalation study of plitidepsin in combination with sorafenib or gemcitabine in patients with refractory solid tumors or lymphomas. Anti-Cancer Drugs 28(3):341–349

Bachy E, Camus V, Thieblemont C, Sibon D, Casasnovas R-O, Ysebaert L, Damaj G, Guidez S, Pica GM, Kim WS, Lim ST, André M, García-Sancho AM, Penarrubia MJ, Staber PB, Trotman J, Hüttmann A, Stefoni V, Re A, Gaulard P, Delfau-Larue M-H, de Leval L, Meignan M, Li J, Morschhauser F, Delarue R (2021) Romidepsin Plus CHOP Versus CHOP in Patients With Previously Untreated Peripheral T-Cell Lymphoma: Results of the Ro-CHOP Phase III Study (Conducted by LYSA). J Clin Oncol 40(3):242–251

Bai R, Friedman SJ, Pettit GR, Hamel E (1992) Dolastatin 15, a potent antimitotic depsipeptide derived from Dolabella auricularia: Interaction with tubulin and effects on cellular microtubules. Biochem Pharmacol 43(12):2637–2645

Barboza NM, Medina DJ, Budak-Alpdogan T, Aracil M, Jimeno JM, Bertino JR, Banerjee D (2012) Plitidepsin (Aplidin) is a potent inhibitor of diffuse large cell and Burkitt lymphoma and is synergistic with rituximab. Cancer Biol Ther 13(2):114–122

Barreca M, Spanò V, Montalbano A, Cueto M, Díaz Marrero AR, Deniz I, Erdoğan A, Lukić Bilela L, Moulin C, Taffin-de-Givenchy E (2020a) Marine anticancer agents: An overview with a particular focus on their chemical classes. Marine Drugs 18(12):619

Barreca M, Stathis A, Barraja P, Bertoni F (2020b) An overview on anti-tubulin agents for the treatment of lymphoma patients. Pharmacol Ther 211:107552

Bates D, Eastman A (2017) Microtubule destabilising agents: far more than just antimitotic anticancer drugs. Br J Clin Pharmacol 83(2):255–268

Beckwith M, Urba WJ, Longo DL (1993) Growth Inhibition of Human Lymphoma Cell Lines by the Marine Products, Dolastatins 10 and 15. JNCI: J Nat Cancer Institute 85(6):483–488

Bispo JAB, Pinheiro PS, Kobetz EK (2020) Epidemiology and Etiology of Leukemia and Lymphoma. Cold Spring Harb Perspect Med 10(6):a034819

Bröckelmann PJ, de Jong MRW, Jachimowicz RD (2020) Targeting DNA repair, cell cycle, and Tumor microenvironment in B cell lymphoma. Cells 9(10):2287

Brucoli F, Natoli A, Marimuthu P, Borrello MT, Stapleton P, Gibbons S, Schätzlein A (2012) Efficient synthesis and

biological evaluation of proximicins A, B and C. Bioorg Med Chem 20(6):2019–2024
Chaudhry GES, Md Akim A, Sung YY, Sifzizul TMT (2022) Cancer and apoptosis: The apoptotic activity of plant and marine natural products and their potential as targeted cancer therapeutics. Front Pharmacol 13:842376
Chen IC, Sethy B, Liou JP (2020) Recent Update of HDAC Inhibitors in Lymphoma. Front Cell Dev Biol 8:576391
Cheng-Sánchez I, Moya-Utrera F, Porras-Alcalá C, López-Romero JM, Sarabia F (2022) Antibody-drug conjugates containing payloads from marine origin. Marine Drugs 20(8):494
Chiangjong W, Chutipongtanate S, Hongeng S (2020) Anticancer peptide: Physicochemical property, functional aspect and trend in clinical application. Int J Oncol 57(3):678–696
Chihara D, Oki Y, Fayad L, Wesson E, Ruben C, Horowitz SB, Woolery J, Feng L, Garg N, Ahmed S, Khouri IF, Fanale MA (2014) Phase I Study of Romidepsin in Combination with ICE (Ifosfamide, Carboplatin and Etoposide) in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma. Blood 124(21):1748–1748
Chinnadurai RK, Khan N, Meghwanshi GK, Ponne S, Althobiti M, Kumar R (2023) Current research status of anti-cancer peptides: Mechanism of action, production, and clinical applications. Biomed Pharmacother 164:114996
Cho Y, Park MN, Noh S, Kang SY, Kim B (2020) Review of Natural Compounds for the Management and Prevention of Lymphoma. Processes 8(9):1164
Chu Y, Zhou X, Wang X (2021) Antibody-drug conjugates for the treatment of lymphoma: clinical advances and latest progress. J Hematol Oncol 14(1):88
Chu Y, Liu Y, Fang X, Jiang Y, Ding M, Ge X, Yuan D, Lu K, Li P, Li Y, Xu H, Fan J, Zhou X, Wang X (2022) Global Burden, Risk Factors, and Trends of Non-Hodgkin Lymphoma in 2020 and Projections to 2040: A Population-Based Study. Blood 140(Supplement 1):3844–3845
Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, Younes A, Alekseev S, Illés Á, Picardi M (2018) Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med 378(4):331–344
Cosenza M, Civallero M, Fiorcari S, Pozzi S, Marcheselli L, Liardo EV, Bari A, Sacchi S (2013) Romidepsin and lenalidomide show a synergistic effect In T-Cell lymphoma cell lines. Blood 122(21):5148
Cosenza M, Civallero M, Fiorcari S, Pozzi S, Marcheselli L, Bari A, Ferri P, Sacchi S (2016) The histone deacetylase inhibitor romidepsin synergizes with lenalidomide and enhances tumor cell death in T-cell lymphoma cell lines. Cancer Biol Ther 17(10):1094–1106
Craik DJ, Kan M-W (2021) How can we improve peptide drug discovery? Learning from the past. Expert Opin Drug Discov 16(12):1399–1402
Cruciani RA, Barker JL, Zasloff M, Chen HC, Colamonici O (1991) Antibiotic magainins exert cytolytic activity against transformed cell lines through channel formation. Proc Natl Acad Sci 88(9):3792–3796
Cueto M, Jensen PR, Fenical W (2000) N-Methylsansalvamide, a cytotoxic cyclic depsipeptide from a marine fungus of the genus Fusarium. Phytochemistry 55(3):223–226
Dehelean CA, Marcovici I, Soica C, Mioc M, Coricovac D, Iurciuc S, Cretu OM, Pinzaru I (2021) Plant-derived anticancer compounds as new perspectives in drug discovery and alternative therapy. Molecules 26(4)
Diefenbach C, Kahl BS, McMillan A, Briones J, Banerjee L, Cordoba R, Miall F, Burke JM, Hirata J, Jiang Y (2021) Polatuzumab vedotin plus obinutuzumab and lenalidomide in patients with relapsed or refractory follicular lymphoma: A cohort of a multicentre, single-arm, phase 1b/2 study. Lancet Haematol 8(12):e891–e901
Donato EM, Fernández-Zarzoso M, Hueso JA, de la Rubia J (2018) Brentuximab vedotin in Hodgkin lymphoma and anaplastic large-cell lymphoma: an evidence-based review. Onco Targets Ther 11:4583–4590
Douglas M (2020) Polatuzumab Vedotin for the Treatment of Relapsed/Refractory Diffuse Large B-Cell Lymphoma in Transplant-Ineligible Patients. J Adv Pract Oncol 11(5):521–528
Ebada SS, Müller WE, Lin W, Proksch P (2019) New acyclic cytotoxic jasplakinolide derivative from the marine sponge Jaspis splendens. Marine Drugs 17(2):100
Falgàs A, Pallarès V, Unzueta U, Núñez Y, Sierra J, Gallardo A, Alba-Castellón L, Mangues MA, Álamo P, Villaverde A, Vázquez E, Mangues R, Casanova I (2021) Specific Cytotoxic Effect of an Auristatin Nanoconjugate Towards CXCR4+ Diffuse Large B-Cell Lymphoma Cells. Int J Nanomed 16:1869–1888
Fermé C, Mateos MV, Szyldergemajn S, Corrado CS, Zucca E, Extremera S, Gianni AM, Vandermeeren A, Ribrag V (2010) Aplidin® (Plitidepsin) Activity In Peripheral T-Cell Lymphoma (PTCL): Final Results. Blood 116(21):1767–1767
Fu Z, Li S, Han S, Shi C, Zhang Y (2022) Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Signal Transduction Targeted Ther 7(1):93
Gao G, Wang Y, Hua H, Li D, Tang C (2021) Marine antitumor peptide dolastatin 10: Biological activity, structural modification and synthetic chemistry. Marine Drugs 19(7):363
Gerwick WH, Proteau PJ, Nagle DG, Hamel E, Blokhin A, Slate DL (1994) Structure of Curacin A, a Novel Antimitotic, Antiproliferative and Brine Shrimp Toxic Natural Product from the Marine Cyanobacterium Lyngbya majuscula. J Org Chem 59(6):1243–1245
Ghaly G, Tallima H, Dabbish E, Badr ElDin N, Abd El-Rahman MK, Ibrahim MA, Shoeib T (2023) Anti-cancer peptides: status and future prospects. Molecules 28(3):1148
Haioun C, Matasar MJ, Sancho J-M, Viardot A, Hernandez J, Perretti T, McMillan A (2020) POLARGO: Randomized Phase III study of polatuzumab vedotin plus rituximab, gemcitabine, and oxaliplatin (R-GemOx) in relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). J Clin Oncol 38(15):TPS8070
Han B, Gross H, Goeger DE, Mooberry SL, Gerwick WH (2006) Aurilides B and C, Cancer Cell Toxins from a Papua New Guinea Collection of the Marine Cyanobacterium Lyngbya majuscula. J Nat Prod 69(4):572–575
He F, Bao J, Zhang X-Y, Tu Z-C, Shi Y-M, Qi S-H (2013) Asperterrestide A, a Cytotoxic Cyclic Tetrapeptide from the Marine-Derived Fungus Aspergillus terreus SCSGAF0162. J Nat Prod 76(6):1182–1186
Herrera AF, Moskowitz AJ, Bartlett NL, Vose JM, Ramchandren R, Feldman TA, LaCasce AS, Ansell SM, Moskowitz CH, Fenton K, Ogden CA, Taft D, Zhang Q, Kato K, Campbell M, Advani RH (2018) Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. Blood 131(11):1183–1194
Holkova B, Yazbeck V, Kmieciak M, Bose P, Ma S, Kimball A, Tombes MB, Shrader E, Wan W, Weir-Wiggins C, Singh A, Hogan KT, Conine S, Sankala H, Roberts JD, Shea TC, Grant S (2017) A phase 1 study of bortezomib and romidepsin in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, indolent B-cell lymphoma, peripheral T-cell lymphoma, or cutaneous T-cell lymphoma. Leuk Lymphoma 58(6):1349–1357
Hontecillas-Prieto L, Flores-Campos R, Silver A, De Álava E, Hajji N, García-Domínguez DJ (2020) Synergistic Enhancement of Cancer Therapy Using HDAC Inhibitors: Opportunity for Clinical Trials. Front Genetics 11:578011

Huang Y-B, Wang X-F, Wang H-Y, Liu Y, Chen Y (2011) Studies on Mechanism of Action of Anticancer Peptides by Modulation of Hydrophobicity Within a Defined Structural Framework. Mol Cancer Ther 10(3):416–426

Humeniuk R, Menon LG, Mishra PJ, Saydam G, Longo-Sorbello GSA, Elisseyeff Y, Lewis LD, Aracil M, Jimeno J, Bertino JR, Banerjee D (2007) Aplidin synergizes with cytosine arabinoside: functional relevance of mitochondria in Aplidin-induced cytotoxicity. Leukemia 21(12):2399–2405

Ibrahim SR, Edrada-Ebel R, Mohamed GA, Youssef DT, Wray V, Proksch P (2008) Callyaerin G, a new cytotoxic cyclic peptide from the marine sponge Callyspongia aerizusa. ARKIVOC 12:164–171

Ibrahim SRM, Min CC, Teuscher F, Ebel R, Kakoschke C, Lin W, Wray V, Edrada-Ebel R, Proksch P (2010) Callyaerins A-F and H, new cytotoxic cyclic peptides from the Indonesian marine sponge Callyspongia aerizusa. Bioorg Med Chem 18(14):4947–4956

Izquierdo MA, Bowman A, García M, Jodrell D, Martinez M, Pardo B, Gómez J, López-Martin JA, Jimeno J, Germá JR, Smyth JF (2008) Phase I clinical and pharmacokinetic study of plitidepsin as a 1-hour weekly intravenous infusion in patients with advanced solid tumors. Clin Cancer Res 14(10):3105–3112

Iżykowska K, Rassek K, Korsak D, Przybylski GK (2020) Novel targeted therapies of T cell lymphomas. J Hematol Oncol 13(1):176

Jagadeesh D, Smith MR (2016) Antibody Drug Conjugates (ADCs): Changing the Treatment Landscape of Lymphoma. Curr Treatment Options Oncol 17(10):55

Jain S, Jirau-Serrano X, Zullo KM, Scotto L, Palermo CF, Sastra SA, Olive KP, Cremers S, Thomas T, Wei Y, Zhang Y, Bhagat G, Amengual JE, Deng C, Karan C, Realubit R, Bates SE, O'Connor OA (2015) Preclinical Pharmacologic Evaluation of Pralatrexate and Romidepsin Confirms Potent Synergy of the Combination in a Murine Model of Human T-cell Lymphoma. Clin Cancer Res 21(9):2096–2106

Kim K, Park M-H (2024) Role of functionalized peptides in nanomedicine for effective cancer therapy. Biomedicines 12(1):202

Kim SJ, Kim HS, Seo YR (2019) Understanding of ROS-Inducing Strategy in Anticancer Therapy. Oxid Med Cell Longev 2019:5381692

Kubra Acikalin C, Merve T, Elif Cansu A, Nazlican Y, Mervenur A, Yusuf T (2022) Drugs and drug candidates for the treatment of lymphoma. IntechOpen

Kucuk O, Young ML, Habermann TM, Wolf BC, Jimeno J, Cassileth PA (2000) Phase II Trial of Didemnin B in Previously Treated Non-Hodgkin's Lymphoma: An Eastern Cooperative Oncology Group (ECOG) Study. Am J Clin Oncol 23(3):237–277

Kuznetsov G, TenDyke K, Towle MJ, Cheng H, Liu J, Marsh JP, Schiller SER, Spyvee MR, Yang H, Seletsky BM, Shaffer CJ, Marceau V, Yao Y, Suh EM, Campagna S, Fang FG, Kowalczyk JJ, Littlefield BA (2009) Tubulin-based antimitotic mechanism of E7974, a novel analogue of the marine sponge natural product hemiasterlin. Mol Cancer Ther 8(10):2852–2860

LaCasce AS, Bociek RG, Sawas A, Caimi P, Agura E, Matous J, Ansell SM, Crosswell HE, Islas-Ohlmayer M, Behler C, Cheung E, Forero-Torres A, Vose J, O'Connor OA, Josephson N, Wang Y, Advani R (2018) Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. Blood 132(1):40–48

Lamers C (2022) Overcoming the shortcomings of peptide-based therapeutics. Future Drug Discov 4(2):FDD75

Law C-L, Cerveny CG, Gordon KA, Klussman K, Mixan BJ, Chace DF, Meyer DL, Doronina SO, Siegall CB, Francisco JA, Senter PD, Wahl AF (2004) Efficient Elimination of B-Lineage Lymphomas by Anti-CD20–Auristatin Conjugates. Clin Cancer Res 10(23):7842–7851

Lee Y, Phat C, Hong S-C (2017) Structural diversity of marine cyclic peptides and their molecular mechanisms for anticancer, antibacterial, antifungal, and other clinical applications. Peptides 95:94–105

Leoncini L, Lazzi S, Bellan C, Tosi P (2002) Cell kinetics and cell cycle regulation in lymphomas. J Clin Pathol 55(9):648

Li G, Tian Y, Zhu WG (2020a) The roles of histone deacetylases and their inhibitors in cancer therapy. Front Cell Dev Biol 8:576946

Li Z, Abadir E, Lee K, Clarke C, Bryant CE, Cooper W, Pietersz G, Favaloro J, Silveira PA, NJ Hart D, Ju X (2020b) Targeting CD83 in mantle cell lymphoma with anti-human CD83 antibody. Clin Trans Immunol 9(7):e1156.

Liang B, Richard DJ, Portonovo PS, Joullié MM (2001) Total Syntheses and Biological Investigations of Tamandarins A and B and Tamandarin A Analogs. J Am Chem Soc 123(19):4469–4474

Liu X, Tao X, Zou A, Yang S, Zhang L, Mu B (2010) Effect of themicrobial lipopeptide on tumor cell lines: apoptosis induced by disturbing the fatty acid composition of cell membrane. Protein Cell 1(6):584–594

Lunning MA, Ruan J, Nair S, Boruchov AM, Byrne R, Gerecitano JF, Hamlin PA, Inserra B, Leonard J, Lynch P, Matasar MJ, Moskowitz AJ, Moskowitz C, Myskowski PL, Nolan P, Palomba ML, Quefeld C, Straus DJ, Zelenetz AD, Horwitz SM (2014) A phase I/II trial of the combination of romidepsin and lenalidomide in patients with relapsed/refractory lymphoma and myeloma: Phase I results. J Clin Oncol 32(15_suppl):8582–8582

Maki A, Diwakaran H, Redman B, Al-Asfar S, Pettit GR, Mohammad RM, Al-Katib A (1995) The bcl-2 and p53 oncoproteins can be modulated by bryostatin 1 and dolastatins in human diffuse large cell lymphoma. Anti-Cancer Drugs 6(3):392–397

Maki A, Mohammad R, Raza S, Saleh M, Govindaraju KD, Pettit GR, Al-Katib A (1996) Effect of dolastatin 10 on human non-Hodgkin's lymphoma cell lines. Anticancer Drugs 7(3):344–350

Marei HE, Althani A, Afifi N, Hasan A, Caceci T, Pozzoli G, Morrione A, Giordano A, Cenciarelli C (2021) p53 signaling in cancer progression and therapy. Cancer Cell Int 21(1):703

Maroun JA, Belanger K, Seymour L, Matthews S, Roach J, Dionne J, Soulieres D, Stewart D, Goel R, Charpentier D, Goss G, Tomiak E, Yau J, Jimeno J, Chiritescu G (2006) Phase I study of Aplidine in a daily×5 one-hour infusion every 3 weeks in patients with solid tumors refractory to standard therapy A National Cancer Institute of Canada Clinical Trials Group study: NCIC CTG IND 115. Annals Oncol 17(9):1371–1378

Marquez BL, Watts KS, Yokochi A, Roberts MA, Verdier-Pinard P, Jimenez JI, Hamel E, Scheuer PJ, Gerwick WH (2002) Structure and absolute stereochemistry of hectochlorin, a potent stimulator of actin assembly. J Nat Prod 65(6):866–871

Matasar MJ, Haioun C, Sancho J-M, Viardot A, Hirata J, Perretti T, Musick L, McMillan AK (2021) POLARGO: Randomized Phase III Study of Polatuzumab Vedotin Plus Rituximab, Gemcitabine, and Oxaliplatin in Relapsed/Refractory Diffuse Large B-Cell Lymphoma. Blood 138(Supplement 1):3568–3568

Mehta-Shah N, Lunning MA, Boruchov AM, Ruan J, Nair S, Lynch P, Byrne R, Moskowitz AJ, Matasar MJ, Gerecitano JF, Hamlin PA, Leonard J, Moskowitz CH, Myskowski PL, Querfeld C, Nolan P, Palomba ML, Straus DJ, Zelenetz AD, Horwitz SM (2015) A phase I/II trial of the combination of romidepsin and lenalidomide in patients with relapsed/refractory lymphoma and myeloma: Activity in T-cell lymphoma. J Clin Oncol 33(15_suppl):8521–8521

Miller ED, Kauffman CA, Jensen PR, Fenical W (2007) Piperazimycins: cytotoxic hexadepsipeptides from a marine-derived bacterium of the genus streptomyces. J Org Chem 72(2):323–330

Mohammad RM, Pettit GR, Almatchy VP, Wall N, Varterasian M, Ai-Katib A (1998) Synergistic interaction of selected marine animal anticancer drugs against human diffuse large cell lymphoma. Anti-Cancer Drugs 9(2):149–156

Morschhauser F, Flinn IW, Advani R, Sehn LH, Diefenbach C, Kolibaba K, Press OW, Salles G, Tilly H, Chen AI (2019) Polatuzumab

vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS). Lancet Haematol 6(5):e254–e265

Moskowitz CH, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, Chen AI, Stiff P, Gianni AM, Carella A (2015) Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet 385(9980):1853–1862

Moskowitz CH, Walewski J, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, Chen AI, Stiff P, Viviani S (2018) Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. Blood, J Am Soc Hematol 132(25):2639–2642

Muttenthaler M, King GF, Adams DJ, Alewood PF (2021) Trends in peptide drug discovery. Nat Rev Drug Discov 20(4):309–325

Naeem A, Hu P, Yang M, Zhang J, Liu Y, Zhu W, Zheng Q (2022) Natural products as anticancer agents: current status and future perspectives. Molecules 27(23):8367

Odaka C, Sanders Miranda L, Crews P (2000) Jasplakinolide Induces Apoptosis in Various Transformed Cell Lines by a Caspase-3-Like Protease-Dependent Pathway. Clin Diagnostic Lab Immunol 7(6):947–952

Oh D-C, Jensen PR, Fenical W (2006) Zygosporamide, a cytotoxic cyclic depsipeptide from the marine-derived fungus Zygosporium masonii. Tetrahedron Lett 47(48):8625–8628

Ozcan M, Lee ST, Mensah F, Modi D, Fossa A, Seog Kim W, Paszkiewicz-Kozik E, Sawalha Y, Sevindik ÖG, Norasetthada L, Santoro A, Pathiraja K, Chakraborty S, Marinello P, Lavie D (2023) Zilovertamab vedotin (MK 2140) in relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): Early results from the phase 2 wave-LINE-004 study. J Clin Oncol 41(16_suppl):7531–7531

Pangestuti R, Kim S-K (2017) Bioactive Peptide of Marine Origin for the Prevention and Treatment of Non-Communicable Diseases. Marine Drugs 15(3):67

Pazzaglia S (2019) Pioli C (2020) Multifaceted Role of PARP-1 in DNA Repair and Inflammation: Pathological and Therapeutic Implications in Cancer and Non-Cancer Diseases. Cells 9(1):20

Pereira DS, Guevara CI, Jin L, Mbong N, Verlinsky A, Hsu SJ, Aviña H, Karki S, Abad JD, Yang P, Moon S-J, Malik F, Choi MY, An Z, Morrison K, Challita-Eid PM, Doñate F, Joseph IBJ, Kipps TJ, Dick JE, Stover DR (2015) AGS67E, an Anti-CD37 Monomethyl Auristatin E Antibody-Drug Conjugate as a Potential Therapeutic for B/T-Cell Malignancies and AML: A New Role for CD37 in AML. Mol Cancer Ther 14(7):1650–1660

Piekarz RL, Robey R, Sandor V, Bakke S, Wilson WH, Dahmoush L, Kingma DM, Turner ML, Altemus R, Bates SE (2001) Inhibitor of histone deacetylation, depsipeptide (FR901228), in the treatment of peripheral and cutaneous T-cell lymphoma: a case report. Blood 98(9):2865–2868

Piekarz RL, Frye R, Turner M, Wright JJ, Allen SL, Kirschbaum MH, Zain J, Prince HM, Leonard JP, Geskin LJ, Reeder C, Joske D, Figg WD, Gardner ER, Steinberg SM, Jaffe ES, Stetler-Stevenson M, Lade S, Fojo AT, Bates SE (2009) Phase II Multi-Institutional Trial of the Histone Deacetylase Inhibitor Romidepsin As Monotherapy for Patients With Cutaneous T-Cell Lymphoma. J Clin Oncol 27(32):5410–5417

Poetsch AR (2020) The genomics of oxidative DNA damage, repair, and resulting mutagenesis. Comput Struct Biotechnol J 18:207–219

Preta G (2020) New Insights Into Targeting Membrane Lipids for Cancer Therapy. Front Cell Dev Biol 8:571237

Prince HM, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, Quaglino P, Zinzani PL, Wolter P, Sanches JA, Ortiz-Romero PL (2017) Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet 390(10094):555–566

Qian S, Wei Z, Yang W, Huang J, Yang Y, Wang J (2022) The role of BCL-2 family proteins in regulating apoptosis and cancer therapy. Front Oncol 12:985363

Ramadhani D, Maharani R, Gazzali AM, Muchtaridi M (2022) Cyclic Peptides for the Treatment of Cancers: A Review. Molecules 27(14):4428

Rashid MA, Gustafson KR, Cardellina JH, Boyd MR (1995) Patellamide F, a New Cytotoxic Cyclic Peptide from the Colonial Ascidian Lissoclinum patella. J Natural Products 58(4):594–597

Raucher D, Ryu JS (2015) Cell-penetrating peptides: strategies for anticancer treatment. Trends Mol Med 21(9):560–570

Richardson NC, Kasamon YL, Chen H, de Claro RA, Ye J, Blumenthal GM, Farrell AT, Pazdur R (2019) FDA Approval Summary: Brentuximab Vedotin in First-Line Treatment of Peripheral T-Cell Lymphoma. Oncologist 24(5):e180–e187

Saide A, Damiano S, Ciarcia R, Lauritano C (2021) Promising activities of marine natural products against Hematopoietic Malignancies. Biomedicines 9(6):645

Sánchez-Beato M, Sánchez-Aguilera A, Piris MA (2003) Cell cycle deregulation in B-cell lymphomas. Blood 101(4):1220–1235

Sasakawa Y, Naoe Y, Inoue T, Sasakawa T, Matsuo M, Manda T, Mutoh S (2002) Effects of FK228, a novel histone deacetylase inhibitor, on human lymphoma U-937 cells in vitro and in vivo. Biochem Pharmacol 64(7):1079–1090

Sawas A, Savage KJ, Perez RP, Advani RH, Zaine JM, Lackey JM, Trave F, Anand B, Chu R, Reyno LM, O'Connor OA (2017) A Phase 1 study of the anti-CD37 antibody-drug conjugate AGS67E in advanced lymphoid malignancies. Interim Results Hematol Oncol 35(S2):49–49

Sedeta E, Ilerhunmwuwa N, Wasifuddin M, Uche I, Hakobyan N, Perry J, Aiwuyo H, Abowali H, Avezbakiyev B (2022) Epidemiology of Non-Hodgkin Lymphoma: Global Patterns of Incidence, Mortality, and Trends. Blood 140(Supplement 1):5234–5235

Sehn LH, Herrera AF, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, Assouline S, Kim TM, Kim WS, Ozcan M, Hirata J, Penuel E, Paulson JN, Cheng J, Ku G, Matasar MJ (2019) Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol 38(2):155–165

Senter PD, Sievers EL (2012) The discovery and development of brentuximab vedotin for use in relapsed Hodgkin lymphoma and systemic anaplastic large cell lymphoma. Nat Biotechnol 30(7):631–637

Shamloo B (2019) Usluer S (2019) p21 in Cancer Research. Cancers (Basel) 11(8):1178

Shanmugam G, Rakshit S, Sarkar K (2022) HDAC inhibitors: Targets for tumor therapy, immune modulation and lung diseases. Trans Oncol 16:101312

Shimizu R, Kikuchi J, Wada T, Ozawa K, Kano Y, Furukawa Y (2010) HDAC inhibitors augment cytotoxic activity of rituximab by upregulating CD20 expression on lymphoma cells. Leukemia 24(10):1760–1768

Singh SB (2022) Discovery and development of dolastatin 10-derived antibody drug conjugate anticancer drugs. J Nat Prod 85(3):666–687

Smolewski P, Robak T (2017) The discovery and development of romidepsin for the treatment of T-cell lymphoma. Expert Opin Drug Discov 12(8):859–873

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2020) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: Cancer J Clin 71(3):209–249

Tan D, Horning SJ, Hoppe RT, Levy R, Rosenberg SA, Sigal BM, Warnke RA, Natkunam Y, Han SS, Yuen A, Plevritis SK, Advani RH (2013) Improvements in observed and relative survival in

follicular grade 1–2 lymphoma during 4 decades: the Stanford University experience. Blood 122(6):981–987

Tannir NM, Forero-Torres A, Ramchandren R, Pal SK, Ansell SM, Infante JR, de Vos S, Hamlin PA, Kim SK, Whiting NC, Gartner EM, Zhao B, Thompson JA (2014) Phase I dose-escalation study of SGN-75 in patients with CD70-positive relapsed/refractory non-Hodgkin lymphoma or metastatic renal cell carcinoma. Invest New Drugs 32(6):1246–1257

Tilly H, Flowers C, Friedberg JW, Herbaux C, Morschhauser F, Sehn LH, Sharman JP, Trneny M, Lee C, Salles GA (2019) POLARIX: A phase 3 study of polatuzumab vedotin (pola) plus R-CHP versus R-CHOP in patients (pts) with untreated DLBCL. J Clin Oncol 37(15):TPS7571

Villadsen JS, Kitir B, Wich K, Friis T, Madsen AS, Olsen CA (2014) An azumamide C analogue without the zinc-binding functionality. MedChemComm 5(12):1849–1855

Vincent R, Dolores C, Christophe F, Emanuele Z, Reyes A, Javier B, Christian G, Gilles S, Alessandro MG, Henry G, Carmen K, Claudia C, Sergio S, Sonia E, de Bernardo M, Martin C-Y, Franco C (2013) Multicenter phase II study of plitidepsin in patients with relapsed/refractory non-Hodgkin's lymphoma. Haematologica 98(3):357–363

Vinogradov AA, Suga H (2020) Introduction to Thiopeptides: Biological Activity, Biosynthesis, and Strategies for Functional Reprogramming. Cell Chem Biol 27(8):1032–1051

Wagner MM, Paul DC, Shih C, Jordan MA, Wilson L, Williams DC (1999) In vitro pharmacology of cryptophycin 52 (LY355703) in human tumor cell lines. Cancer Chemother Pharmacol 43(2):115–125

Wang X, Gong X, Li P, Lai D, Zhou L (2018) Structural diversity and biological activities of cyclic depsipeptides from fungi. Molecules 23(1):169

Wang P, Wang Z, Liu J (2020) Role of HDACs in normal and malignant hematopoiesis. Mol Cancer 19(1):5

Wang L, Wang N, Zhang W, Cheng X, Yan Z, Shao G, Wang X, Wang R, Fu C (2022a) Therapeutic peptides: current applications and future directions. Signal Transduction Targeted Ther 7(1):48

Wang M, Mei M, Barr PM, Barrientos J, de Vos S, Furman R, Patel K, Thompson PA, Choi M, Kallam A, Zhu Y, Chakraborty S, Marinello P, Spurgeon SE (2022b) P1231: Zilovertamab vedotin (MK-2140) for the treatment of Non-Hodgkin Lymphoma: The phase 1 dose escalation and cohort expansion WAVELINE-001 study of an anti-ROR1 antibody-drug conjugate. HemaSphere 6:1116–1117

Zhang J-N, Xia Y-X, Zhang H-J (2021a) Natural Cyclopeptides as Anticancer Agents in the Last 20 Years. Int J Mol Sci 22(8):3973

Zhang QT, Liu ZD, Wang Z, Wang T, Wang N, Wang N, Zhang B, Zhao YF (2021b) Recent advances in small peptides of marine origin in cancer therapy. Mar Drugs 19(2):2515

Zhou L, Yang J, Zhang K, Wang T, Jiang S, Zhang X (2024) Rising Star in Immunotherapy: Development and Therapeutic Potential of Small-Molecule Inhibitors Targeting Casitas B Cell Lymphoma-b (Cbl-b). J Med Chem 67(2):816–837

Zobeida C-M, Hélène CV, Ruoli B, David JN, Stephen BH, Gerrit L, Jeffrey TM, Michael DW, George RP, William F, Ernest H (2003) Diazonamide A and a Synthetic Structural Analog: Disruptive Effects on Mitosis and Cellular Microtubules and Analysis of Their Interactions with Tubulin. Mol Pharmacol 63(6):1273

Zullo K, Guo Y, Cooke L, Serrano XJ, Mangone M, Scotto L, Amengual JE, Mahadevan D, O'Connor OA (2014) The Investigational aurora a kinase inhibitor alisertib exhibits broad activity in preclinical models of T-Cell Lymphoma and Is Highly Synergistic with Romidepsin. Blood 124(21):4493–4493

Terms and Conditions

Springer Nature journal content, brought to you courtesy of Springer Nature Customer Service Center GmbH (“Springer Nature”).
Springer Nature supports a reasonable amount of sharing of research papers by authors, subscribers and authorised users (“Users”), for small-scale personal, non-commercial use provided that all copyright, trade and service marks and other proprietary notices are maintained. By accessing, sharing, receiving or otherwise using the Springer Nature journal content you agree to these terms of use (“Terms”). For these purposes, Springer Nature considers academic use (by researchers and students) to be non-commercial.
These Terms are supplementary and will apply in addition to any applicable website terms and conditions, a relevant site licence or a personal subscription. These Terms will prevail over any conflict or ambiguity with regards to the relevant terms, a site licence or a personal subscription (to the extent of the conflict or ambiguity only). For Creative Commons-licensed articles, the terms of the Creative Commons license used will apply.
We collect and use personal data to provide access to the Springer Nature journal content. We may also use these personal data internally within ResearchGate and Springer Nature and as agreed share it, in an anonymised way, for purposes of tracking, analysis and reporting. We will not otherwise disclose your personal data outside the ResearchGate or the Springer Nature group of companies unless we have your permission as detailed in the Privacy Policy.
While Users may use the Springer Nature journal content for small scale, personal non-commercial use, it is important to note that Users may not:

1. use such content for the purpose of providing other users with access on a regular or large scale basis or as a means to circumvent access control;
2. use such content where to do so would be considered a criminal or statutory offence in any jurisdiction, or gives rise to civil liability, or is otherwise unlawful;
3. falsely or misleadingly imply or suggest endorsement, approval , sponsorship, or association unless explicitly agreed to by Springer Nature in writing;
4. use bots or other automated methods to access the content or redirect messages
5. override any security feature or exclusionary protocol; or
6. share the content in order to create substitute for Springer Nature products or services or a systematic database of Springer Nature journal content.

In line with the restriction against commercial use, Springer Nature does not permit the creation of a product or service that creates revenue, royalties, rent or income from our content or its inclusion as part of a paid for service or for other commercial gain. Springer Nature journal content cannot be used for inter-library loans and librarians may not upload Springer Nature journal content on a large scale into their, or any other, institutional repository.
These terms of use are reviewed regularly and may be amended at any time. Springer Nature is not obligated to publish any information or content on this website and may remove it or features or functionality at our sole discretion, at any time with or without notice. Springer Nature may revoke this licence to you at any time and remove access to any copies of the Springer Nature journal content which have been saved.
To the fullest extent permitted by law, Springer Nature makes no warranties, representations or guarantees to Users, either express or implied with respect to the Springer nature journal content and all parties disclaim and waive any implied warranties or warranties imposed by law, including merchantability or fitness for any particular purpose.
Please note that these rights do not automatically extend to content, data or other material published by Springer Nature that may be licensed from third parties.
If you would like to use or distribute our Springer Nature journal content to a wider audience or on a regular basis or in any other manner not expressly permitted by these Terms, please contact Springer Nature at

onlineservice@springernature.com