Received: 26 February 2019 | Revised: 13 August 2019 | Accepted: 5 September 2019

DOI: 10.1111/bph.14876

REVIEW ARTICLE

Enriching cancer pharmacology with drugs of marine origin

Paula C. Jimenez[1] | Diego V. Wilke[2] | Paola C. Branco[3] | Anelize Bauermeister[3] | Paula Rezende-Teixeira[3] | Susana P. Gaudêncio[4] | Leticia V. Costa-Lotufo[3]

[1] Departamento de Ciências do Mar, Universidade Federal de São Paulo, Santos, SP, Brasil

[2] Núcleo de Pesquisa e Desenvolvimento de Medicamentos (NPDM), Departamento de Fisiologia e Farmacologia, Faculdade de Medicina, Universidade Federal do Ceará, Fortaleza, CE, Brasil

[3] Departamento de Farmacologia, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, SP, Brasil

[4] UCIBIO, Department of Chemistry, Blue Biotechnology and Biomedicine Lab, Faculty of Science and Technology, NOVA University of Lisbon, Caparica, Portugal

Correspondence
Leticia V. Costa-Lotufo, Departamento de Farmacologia, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, SP 05508-900, Brasil.
Email: costalotufo@usp.br

Funding information
Applied Molecular Biosciences Unit - UCIBIO, Grant/Award Number: FCT/MCTES (UID/Mult/04378/2019); Conselho Nacional de Desenvolvimento Científico e Tecnológico; Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Grant/Award Number: IF/00700/2014 to SPG; Fundação de Amparo à Pesquisa do Estado de São Paulo, Grant/Award Numbers: 2015/17177-6, 2017/09022-8 and 2017/17648-4; Ministério da Saúde, Grant/Award Number: ArboControl Brasil Project FNS/UnB TED42/2017 ArboControl Brasil Project FNS/UnB TED74/2016; FCT/MCTES, Grant/Award Number: UID/Multi/04378/2019; National Institute of Science and Technology – INCTBioNat, Grant/Award Number: 465637/2014-0; ArboControl Brasil Project, Grant/Award Numbers: TED42/2017, FNS/UnB TED74/2016; CNPQ; FAPESP, Grant/Award Numbers: 2017/17648-4, 2017/09022-8 and 2015/17177-6

Marine natural products have proven, over the last half-century, to be effective biological modulators. These molecules have revealed new targets for cancer therapy as well as dissimilar modes of action within typical classes of drugs. In this scenario, innovation from marine-based pharmaceuticals has helped advance cancer chemotherapy in many aspects, as most of these are designated as first-in-class drugs. Here, by examining the path from discovery to development of clinically approved drugs of marine origin for cancer treatment—cytarabine (Cytosar-U®), trabectedin (Yondelis®), eribulin (Halaven®), brentuximab vedotin (Adcetris®), and plitidepsin (Aplidin®)— together with those in late clinical trial phases—lurbinectedin, plinabulin, marizomib, and plocabulin—the present review offers a critical analysis of the contributions given by these new compounds to cancer pharmacotherapy.

1 | INTRODUCTION

Natural products have long been used in the treatment of human maladies and set a strong foundation upon which modern pharmacology has been erected. Particularly for cancer treatment, chemotherapeutic agents of natural origin have remarkably impacted the field, not only for their clinical importance but also for allowing the expansion of knowledge in cancer pharmacology. Natural agents like doxorubicin, paclitaxel, vincristine, and vinblastine are commonly used as first-line treatments for several cancers. The compounds of marine origin have a more recent history. Nevertheless, studies have shown their unique

Abbreviations: ADC, antibody-drug conjugate; ALCL, anaplastic large cell lymphoma; ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; CT-L, chymotrypsin-like; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; LPS, liposarcoma; LMS, leiomyosarcoma; MDR, multidrug resistance; MF, mycosis fungoides; MM, multiple myeloma; MNPs, marine natural products; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Pol II, RNA polymerase II; PSN, peripheral sensory neuropathy; SCLC, small cell lung cancer; STS, soft tissue sarcoma; TAM, tumour-associated macrophages; TC-NER, transcription coupled-nucleotide excision repair; TME, tumour micro-environment; TNBC, triple negative breast cancer.

chemical structures and new cellular targets and modes of actions, which are bringing significant innovation to the field.

This review starts with a description of the chemical features that make the marine natural products versatile as biological modulators, provided in Section 2. Then, it will examine the contribution of marine molecules to cancer pharmacology using the discovery and development of clinically approved drugs as foundation for the discussion. Most of these are actually described as "first-in-class" pharmaceuticals, and the novelty in their pharmacology will be emphasized.

To date, eight marine-derived drugs have been approved for clinical use: **cytarabine** (Cytosar-U®), **vidarabine** (Vira-A®; US discontinued), **trabectedin** (Yondelis®), **ziconotide** (Prialt®), **eribulin mesylate** (Halaven®), plitidepsin (Aplidin®), **brentuximab vedotin** (Adcetris®), and omega-3-acid ethyl esters (Lovaza®; Jiménez, 2018, www.marinepharmacology.midwestern.edu). Five of them are used in different anticancer treatments and those will be discussed in depth, under Sections 3 and 4. Moreover, numerous antibody-drug conjugates that use a marine compound as their cytotoxic principle are also undergoing clinical trials, and those will be sorted through in Section 4, when presenting the first approved drug in this class, brentuximab vedotin (Adcetris). Furthermore, Section 5 will afford grounds for understanding the potential of marine molecules in cancer therapeutics in the near future. In this section, compounds that are currently in advanced stages of clinical trials for cancer, such as lurbinectedin (Zepsyre®), plinabulin, marizomib, and plocabulin, will be surveyed.

2 | CHEMICAL FEATURES OF MARINE COMPOUNDS: HOW THEIR UNIQUE STRUCTURES AFFECT MOLECULAR INTERACTIONS

The structural complexity of natural products differs from synthetic drug-like compounds in numerous ways. Natural products have a higher number of chiral centres, stereocentres, sp^3-hybridized bridgehead atoms, and hydrogen-bond donors than synthetic drugs. On average, they also contain higher carbon, hydrogen, and oxygen content and less nitrogen content than synthetic drug molecules. Additionally, natural products have much fewer aromatic rings than synthetic medicinal agents, as aliphatic systems appear to be favoured in nature, a fact that may improve selectivity when binding to stereodefined sites (Grabowski & Schneider, 2007). They may also present original ring systems—for example, macrocyclizations, fused-rings, ether crosslinks, and extensive conjugation—with appropriate geometries for spatial side-chain substitution and conformations that bind to specific biological targets (Clardy & Walsh, 2004; Rodrigues, Reker, Schneider, & Schneider, 2016).

Natural products often disobey the drug-likeness Lipinski's "rule of five" (Ro5), once they present molecular masses above 500 Da and high polarities—for example, rapamycin is 914 Da with a polar surface area of 195 $Å^2$, and paclitaxel is 854 Da and possesses a polar surface area of 221 $Å^2$ (Chai & Mátyus, 2016). In fact, 18% of the natural products from the Dictionary of Natural Products database, 31% of the natural products from the Traditional Chinese Medicine database, 15% of the DrugBank, and 9% of the ChEMBL database do not comply with the Ro5 (Chai & Mátyus, 2016).

Several approaches may potentiate natural products discovery programs and improve the number of natural product-derived drugs making it to the market. The use of moderate, instead of hard cut-offs for drug-likeness property rules during the in silico selection of drug-lead candidates, is reasonable (Chai & Mátyus, 2016). Furthermore, advances in synthetic biology and synthetic drug design may also pave the way towards that direction. Structurally complex frameworks of natural products can be dissociated into smaller and complex fragment-like scaffolds bearing high ligand efficiency to simplify drug design. Moreover, approaches founded on fragment-based de novo design using natural product-derived fragments to infer the bioactivities and biomolecular targets of such molecules can support the development of natural product-derived drugs (Rodrigues et al., 2016).

Marine natural products (MNPs) are a well-established subfield of NPs, which have been gaining increased attention in the last decades. Marine environments are complex systems with variations in luminosity, temperature, oxygen levels, pH, salinity, and pressure. Therefore, marine organisms had to adapt and evolve differently from their terrestrial counterparts. They developed distinct biosynthetic pathways, which produced novel bioactive secondary metabolites with unmatched and complex structures (Hu, Ying, Zhang, Qiu, & Lu, 2018). Many marine organisms—such as sponges, tunicates, and shell-less molluscs, as well as microorganisms, such as fungi, bacteria, and cyanobacteria—have provided secondary metabolites with interesting pharmacological properties (Blunt et al., 2018).

MNPs present much novelty in chemical scaffolds, compared to terrestrial natural products (Kong, Jiang, & Zhang, 2010). In this context, a preclinical cytotoxicity screening from the USA National Cancer Institute revealed 10 times higher incidence of antitumour properties for marine samples than for terrestrial samples (Munro et al., 1999). These compounds usually present unique structures due to the specific carbon arrangements with several stereochemical features for the presence of non-essential amino acids; they also have interesting ring systems, besides the incorporation of halogen atoms, such as chloride, bromide, iodine, and fluorine, which are covalently attached to organic compounds.

MNPs also present appropriate geometries for spatial side-chain substitution and conformations that bind to specific biological targets (Clardy & Walsh, 2004; Rodrigues et al., 2016). Figure 1 shows the chemical structures discussed in this review; trabectedin and lurbinectedin have been boxed and highlighted for some of the chemical features. Lurbinectedin is a derivative of trabectedin used as an example to illustrate those unique chemical features found in compounds from marine sources, such as several heteroatoms (oxygen, red; nitrogen, green; and sulphur, orange) and many stereo sites (blue circles).

This structural complexity of MNPs has attracted the attention of organic chemists, as if it was an interesting puzzle to be solved. The elucidation of chemical structures from marine sources is often difficult, considering the structural intricacy of several of these compounds. The structure of trabectedin (ecteinascidin 743, ET-743)—

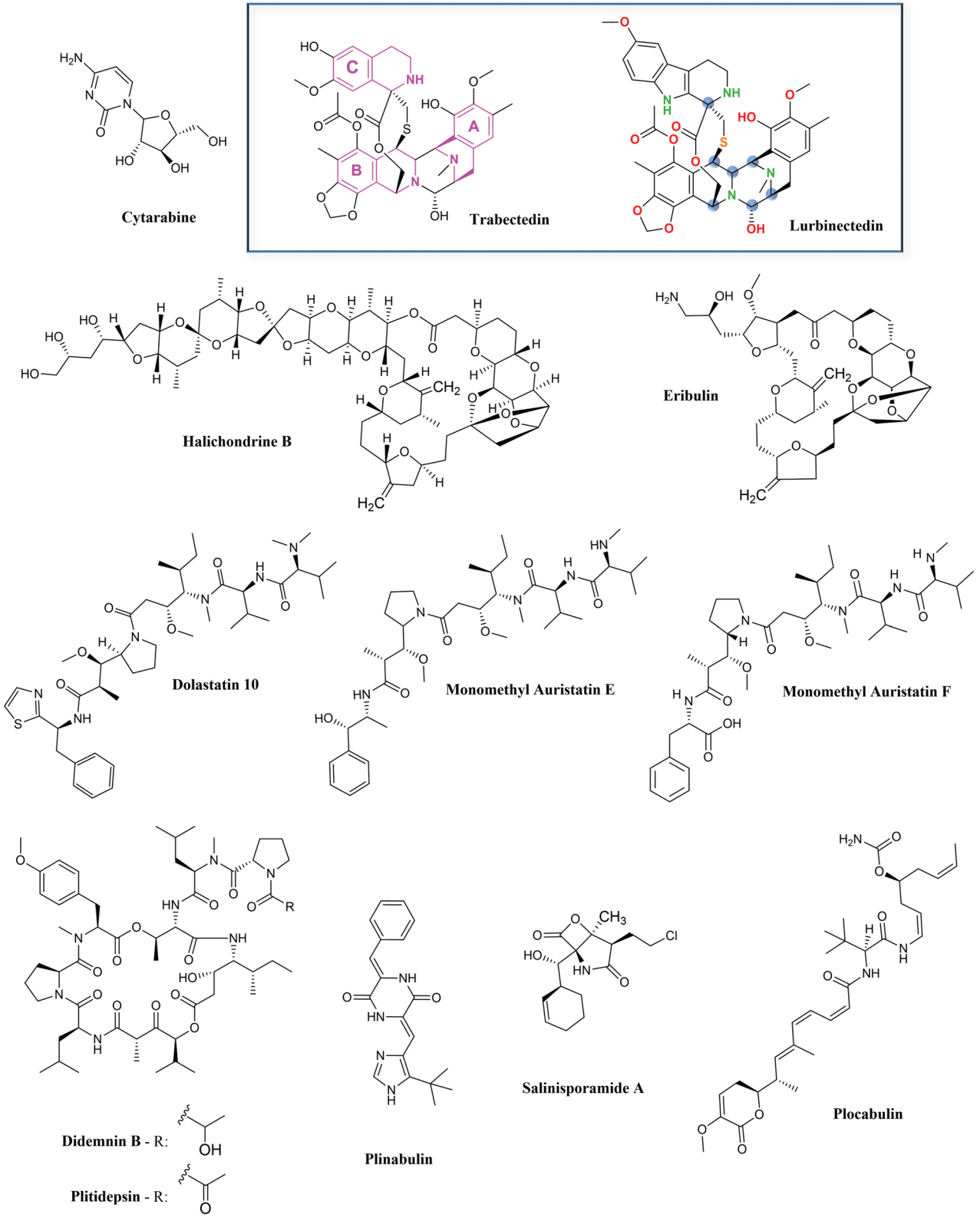

FIGURE 1 Marine natural products and their derivatives of pharmacological relevance. In the box, the tetrahydroisoquinoline rings (pink)—in which both A and B rings have been proven essential for bioactivity due to their involvement in the interaction with DNA minor groove—are highlighted in the chemical structure of trabectedin. For lurbinectedin, further noteworthy chemical features particularly found in marine natural products are emphasized, such as stereochemical carbons (blue spheres), complex intra-cyclization, and a high number of heteroatoms generating different chemical functions comprising oxygen (red), nitrogen (green), and sulphur (orange) atoms

the bioactive compound responsible for anticancer activity from extracts of the tunicate *Ecteinascidia turbinata*—took over 20 years to be fully elucidated (Rinehart et al., 1990; Wright et al., 1990).

The chemical scaffolds of MNPs support prolific bioactivities and preferred structural ligand–protein binding motifs to interact with biological space. This is not fully understood, although attempts to explain this singularity are based on hypotheses that consider co-evolution, synergistic effects, xenohormesis, natural selection, and enzymatic mode of generation of MNPs (Howitz & Sinclair, 2008; Ji, Li, & Zhang, 2009). Undoubtedly, there is still much to discover in the field of MNPs. Adopting drug discovery strategies such as "multi-component therapeutics" rather than "one-disease–one-target–one-drug" may benefit the discovery of cancer therapies and prevent the development of resistance against anti-infective, antimalarial, and anticancer drugs.

3 | THE EARLIEST DAYS OF MARINE PHARMACOLOGY: CYTARABINE INTRODUCED MARINE DRUGS AS A GROUND-BREAKING CANCER THERAPY

Throughout the 1940s and 1950s, Werner Bergmann, a researcher from Yale University, and his collaborators published several articles in a series called "Contributions to the Study of Marine Products" (Bergmann & Feeney, 1951; Lester & Bergmann, 1941). The best known among these works, in 1951, described the isolation of two arabinonucleosides, which were named spongothymidine and spongouridine, from the Caribbean marine sponge *Tectitethya crypta* (Bergmann & Feeney, 1951).

The discovery of such odd nucleosides unfolded into, at least, two important scientific elaborations. The first challenged the current paradigm, which argued that a nucleoside would only have a biological function if it contained ribose or deoxyribose in its structure. And the second introduced the pharmacological concept of antimetabolites in the context of anticancer chemotherapy, thus guiding the synthesis of analogues, such as cytosine arabinose (Ara-C or cytarabine; Figure 1).

An antimetabolite drug has a similar structure to a naturally produced metabolite, but it lacks the ability to perform its function, thereby misleading normal cell metabolism. Within the cell, cytarabine is converted into its respective triphosphate arabino-nucleoside through sequential phosphorylation. The cytarabine triphosphate then becomes a substrate of DNA polymerase and, in place of a cytidine, is subsequently incorporated into the DNA strand. Because arabinose has replaced deoxyribose, a phosphodiester bond between the two pentose residues cannot be established and, therefore, hinders the extension of the strand, thus interrupting the process of DNA synthesis and repair (Schwartsmann, da Rocha, Berlinck, & Jimeno, 2001).

Efforts in producing modified nucleosides were already being carried out before cytarabine. However, the unconventional nucleosides from the marine sponge transformed how the rational design of unnatural nucleosides was being conceived and handled by proving that both the sugar and the nitrogenous base, could be substituted to achieve the projected antimetabolite effect. Moreover, besides anticancer, the principle of taking a non-functional nucleoside to inhibit the elongation of the DNA strand was also used strategically in other chemotherapeutic treatments, such as antiviral, for example the use of AZT as an anti-HIV drug.

Cytarabine, the first drug in this series, was approved for clinical use as Cytosar-U in 1969, and it is still widely used in the treatment of various types of leukaemia, such as acute lymphocytic leukaemia (ALL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), and non-Hodgkin's lymphoma (NHL). Although this molecule is a synthetic analogue and not the natural product itself, cytarabine is historically reported as the first example of a commercially available marine drug. Moreover, the extensive list of nucleoside analogues currently undergoing trials and the ones that have been recently approved for clinical use demonstrate the value of this therapy (Jordheim, Durantel, Zoulim, & Dumontet, 2013). One such example, nelarabine (Ara-GTP), a synthetic arabinonucleoside, was approved in October 2005 for the treatment of the rare T-cell lymphoblastic leukaemia (Buie, Epstein, & Lindley, 2007), whereas thiarabine (T-Ara-C) is an arabinonucleoside in Phase I clinical trials for haematological malignancies and solid tumours (Parker, Waud, & Secrist, 2015).

4 | FIFTY YEARS LATER: CLINICALLY APPROVED ANTICANCER DRUGS OF MARINE ORIGIN

4.1 | Trabectedin (Yondelis): Beyond DNA alkylation

Trabectedin (Figure 1), also referred to as ecteinascidin or ET-743, is an alkaloid isolated from extracts of the tunicate *E. turbinata*. It took over 20 years from the detection of biological activity in these extracts to the complete structural elucidation of the compound (Rinehart et al., 1990; Wright et al., 1990), as the description of the three fused tetrahydroisoquinoline rings, designated A, B, and C (highlighted in pink in Figure 1), posed a major challenge.

The peculiar and complex mode of action (Figure 2) for trabectedin has been established. This compound binds to the DNA minor grooves (D'Incalci & Galmarini, 2010) while conventional alkylating drugs generally bind to guanine at N-7 or O-6, trabectedin binds to guanine at N2 in GC-rich sequences (Pommier et al., 1996). Both the A and B rings interact with DNA minor grooves, and the carbinolamine moiety present in ring A is mandatory for its activity. Ring C, in turn, is not responsible for the cytotoxicity of trabectedin (Erba et al., 2004); however, it bends DNA towards the major groove, providing a unique feature for trabectedin, when compared to other minor groove binders (Zewail-Foote & Hurley, 1999).

Additionally, trabectedin inhibits transcription by binding to transcribing RNA polymerase II (Pol II) and blocking its activity (Feuerhahn et al., 2011). This causes rapid degradation of Pol II, a process dependent on the transcription factor called transcription coupled-nucleotide excision repair (TC-NER; Aune et al., 2008). TC-NER deficient cells were found resistant to trabectedin (Zewail-Foote & Hurley,

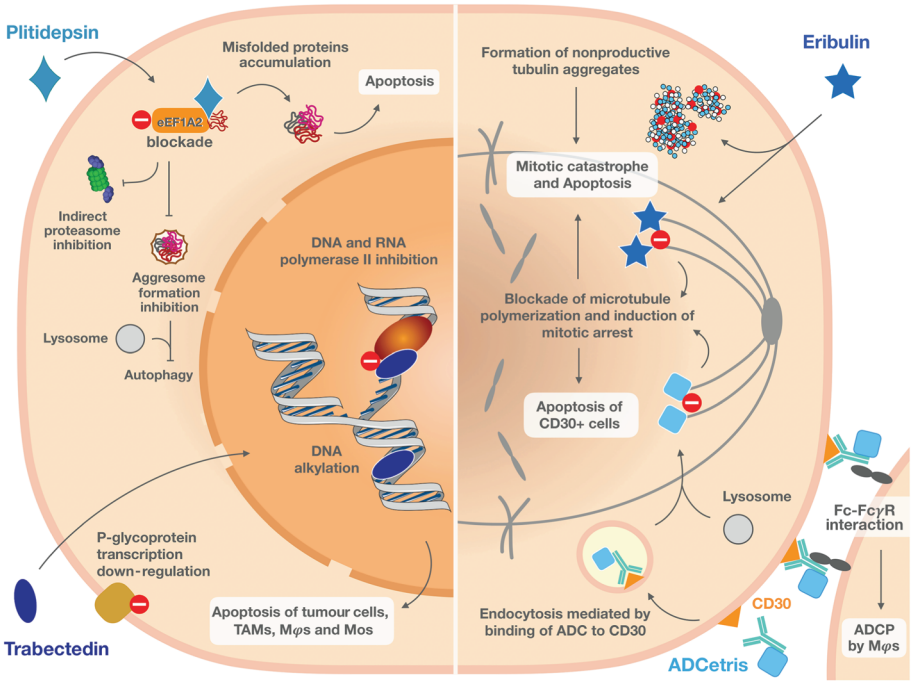

FIGURE 2 Overview of the multiple mechanisms of action of anticancer marine drugs in clinical use. Inhibition of the respective molecular targets by plitidepsin (upper left), trabectedin (lower left), eribulin (upper right), and ADCetris® (lower right) triggers tumour cell stress, which culminates in cell death by apoptosis. Plitidepsin hinders the pro-oncogenic function of eukaryotic elongation factor 1A2 (eEF1A2), which impairs transportation of misfolded proteins to the proteasome and causes accumulation of non-functional proteins. Additionally, by inhibiting eEF1A2, it further blocks activation of the aggresome and, therefore, prevents protein digestion by autophagy. The marked accumulation of non-functional proteins leads to cell death by apoptosis. Trabectedin is a DNA-alkylating agent that specifically inhibits the activity of RNA polymerase II, thus not affecting basal transcription. The selective inhibition of transcription induced by trabectedin decreases the levels of P-glycoprotein, assuring a potent cytotoxicity against resistant tumours. Modulation of tumour micro-environment is a valuable and interesting feature of this compound, which is attained by the specific depletion of macrophages (Mϕs), tumour-associated macrophages (TAMs), and circulating monocytes (Mos) by apoptosis. Eribulin is an antitubulin agent that blocks tubulin polymerization, further leading to cell cycle arrest and mitotic catastrophe. Additionally, eribulin induces the formation of non-functional tubulin aggregates and triggers apoptosis. ADCetris, an antibody-drug conjugate (ADC), is selectively recognized and internalized by CD30+ cells through endocytosis. The warhead, monomethyl auristatin E, is released into the cytosol after digestion in endolysosomes and blocks tubulin polymerization, causing persistent mitotic arrest and induction of apoptosis. Furthermore, ADCetris also induces antibody-dependent cellular phagocytosis (ADCP) by Mϕs via Fc-FcγR binding

1999), revealing the dependency on this system for activity of the compound. Furthermore, TC-NER activity is increased in cell lines resistant to platinum compounds, which justifies the later approval of trabectedin as second-line treatment for patients with platinum resistant tumours (Soares et al., 2011).

Trabectedin was the first compound described with the ability to specifically displace an oncogenic transcription factor from its target promoters (D'Incalci, 2013). Bonfanti et al. (1999) showed trabectedin displaced NF-Y from its DNA consensus sequence at μM concentrations, suggesting its potential to inhibit multidrug resistance (MDR) activation, which was later demonstrated by Jin, Gorfajn, Faircloth, and Scotto (2000) using human colon carcinoma cell line SW620. In fact, inhibition of activated **MDR1**, but not constitutive MDR1 induced by trabectedin, involves a complex mechanism that eventually blocks **P-glycoprotein** transcription, as demonstrated in human epidermoid KB carcinoma cells (Kanzaki et al., 2002).

The biological activity of trabectedin was demonstrated in a variety of cell lines and xenograft models (Table 1). In the NCI-60 cell line panel, trabectedin (NSC 648766) presented a mean GI_{50} of 1.94 nM (www.dtp.cancer.gov, accessed 04 August 2019). However, the NCI screening does not include sarcoma cells, and it was against these tumours that trabectedin proved to be more effective than other treatments (Li et al., 2001). The efficacy of trabectedin in sarcoma subtypes, such as myxoid liposarcoma and Ewing's sarcomas, is also related to its ability to inhibit transcription by decreasing the transactivating ability of chimeric proteins, such as FUS-CHOP, EWS-CHOP, and EWSFli1, and eventually leading to adipocytic differentiation and apoptosis (D'Incalci & Galmarini, 2010; Forni et al., 2009).

Preclinical in vivo data reinforced the potential of trabectedin and other ecteinascidins (ET-729 and ET-722) as anticancer compounds since the first description of the activity on murine melanoma B16 and leukaemia P388 tumours (Rinehart et al., 1990; Sakai, Rinehart, Guan, & Wang, 1992). Many studies using human xenograft models in nude mice confirmed its in vivo activity using different schedules of drug administration, from twice a day during three consecutive days to once a day every 4 days on Days 0, 4, and 8; and doses ranging from 0.025 to the maximum tolerated dose 0.2 $mg{\cdot}kg^{-1}$. On B-16 and osteosarcoma models, trabectedin showed significant in vivo

TABLE 1 Preclinical and clinical data on approved marine drugs for cancer treatment or under clinical trials

Drug	Class	Preclinical evidences	Clinical evidences
Trabectedin	DNA-alkylating agent	In vitro studies and cells lines • Mean GI_{50} on the NCI-60 cell line panel (NSC 648766) of 1.94 nM • IC_{50} on soft tissue sarcoma cells lines: HT-1080 (human fibrosarcoma) = 0.2–1 pM; HS-16 (mesenchymal chondrosarcoma), HS-18, (liposarcoma), HS-30, (malignant hemangiopericytoma) and HS-42, (mixed mesodermal sarcoma) = 4–300 pM; M8805, M9110, and HS-90 (malignant fibrous histiocytoma) = 0.2–1 pM (Li et al., 2001) • In 402-91 and 1765 cells (myxoid liposarcoma expressing FUS-CHOP protein), plitodepsin treatment induced differentiation at 1 nM (Forni et al., 2009) • IC_{50} values for MSC-SH-GFP, MS-SH-FC 0.51 nM, T-SH-GFP 0.66, T-SH-FC, 402.9, 1795, and A549 ranging from 0.09 to 20 nM (Martinez-Cruzado et al., 2017) In vivo studies • Effective on mouse xenograft models using human cell lines: TE-671 (rhabdomyosarcoma), Igrov-1, 1A9 and SKOV HOC 8 (ovarian carcinoma), SK-N-DX (neuroblastoma), FADU (head and neck), LX-1 (non-small cell lung cancer), H-187 (melanoma; D'Inalci et al., 2003) • On a B-16 mouse melanoma model, trabectedin reduced tumour growth when associated to dexamethasone (Van Kesteren et al., 2003)	• Total of 90 clinical trials studies on Phases I, II, and III (www.clinicaltrials.gov). Of these, 47 have been completed or terminated; 34 are ongoing; three were suspended or withdrawn, and four with unknown status. Two studies are listed as no longer available • Tested on leyomiosarcoma, liposarcoma, synovial sarcoma, soft tissue sarcoma, ovarian cancer, ovarian carcinosarcoma, uterine carcinosarcoma, malignant pleural mesothelioma, meningioma, refractory chronic lymphocityc leukaemia, refractory small lymphocytic lymphoma, myxoid liposarcoma, pancreatic cancer, prostate cancer, breast cancer, peritoneal neoplasms, brain cancer, and metastatic bone tumours • Approved for the treatment of advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide; for relapsed platinum-sensitive ovarian cancer in combination with pegylated liposomal doxorubicin; liposarcoma; and leiomyosarcoma • Therapeutic scheme for soft tissue sarcoma: 1.5 $mg{\cdot}m^{-2}$ every 3 weeks over 24-hr infusion (Garcia-Carbonero et al., 2005). For ovarian cancer, therapeutic scheme was evaluated in monotherapy (Pérez-López et al. 2007) or in combination with platinum-based compounds (Pfisterer et al., 2006) or with pegylated liposomal doxorubicin (O'Cearbhaill et al., 2018) • Maximum tolerated dose: 1.1 $mg{\cdot}m^{-2}$ of trabectedin for advanced soft tissue sarcomas (Grignani et al., 2018) • Most common side effects are neutropenia, nausea, vomiting, and increase in liver transaminases, anaemia, fatigue, thrombocytopenia, anorexia, and diarrhoea, while the most serious were neutropenic sepsis, rhabdomyolysis, cardiomyopathy, hepatotoxicity, and extravasation leading to tissue necrosis (Gordon, Sankhala, Chawla, & Chawla, 2016)
Eribulin	Microtubule-target agent	In vitro studies and cell lines • TNBC (MX-1, Hs578T, and MDA-MB-157) presented epithelial phenotype and showed decreased capacity for in vitro migration and invasiveness (Yoshida et al., 2014) • TNBC cell lines (MDA-MB-231 and Hs578T) in vitro were treated with eribulin and paclitaxel in combination and resulted in synergistic antitumour effect (Oba & Ito, 2018)	• Total of 162 clinical trials studies on Phases I, II, and III (www.clinicaltrials.gov). Of these, 82 have been completed or terminated; 68 are ongoing; five were suspended or withdrawn, and six with unknown status. One study is listed as approved for marketing • Tested on breast cancer (EMBRACE Trial, BEACON Study) , non-small cell lung cancer, prostate cancer, ovarian cancer, sarcoma, pancreatic cancer, urothelial tract cancer (uc), squamous cell carcinoma of the head and neck, colon cancer, lymphoma, salivary gland cancer, bladder cancer, fallopian tube cancer, and primary peritoneal cavity cancer • Approved for the treatment of advanced or metastatic breast cancer of patients who have already been treated with at least two types of

(Continues)

TABLE 1 (Continued)

Drug	Class	Preclinical evidences	Clinical evidences
		In vivo studies • MX-1 breast cancer xenografts reversed EMT and induced MET (Yoshida et al., 2014) • In MDA-MB-231 BALB/c-v/v mouse xenograft model, a single dose of eribulin before paclitaxel treatment decreased vimentin expression and reduced tumour volume (Oba & Ito, 2018) • MX-1 and MDA-MB-231 human breast cancer xenograft models improved tumour perfusion and altered vascularization (Funahashi et al., 2014) • On HT-1080 (fibrosarcoma), U251 (glioblastoma), SR-475 (head and neck cancer), SK-LMS-1 (leiomyosarcoma), NCI-H322M and NCI-H522 (non-small cell lung cancer), PANC-1 (pancreatic cancer), and NCI-H82 small cell lung cancer xenografts, doses between 0.19 and 4.0 mg·kg^{-1} of eribulin inhibited tumour growth (Towle et al., 2012)	chemotherapy, including an anthracycline and a taxane. Also approved for advanced, metastatic, or inoperable liposarcoma in patients who have already been treated with anthracycline chemotherapy • Therapeutic scheme in the United States: 1.4 mg·m^{-2} of the salt (eribulin mesylate) and in Europe: 1.23 mg·m^{-2} of the active substance (eribulin), intravenous (IV) injection over 2 to 5 min on Days 1 and 8 of each 21-day cycle • Maximum tolerated dose was 2 mg·m^{-2} with neutropenia limited the dose escalation to metastatic breast cancer (Tan et al., 2009) and MTD was 1.4 mg·m^{-2} per dose to children with refractory or recurrent solid tumours (Schafer et al., 2018) • Most common side effects are neutropenia, leukopenia, nausea, and vomiting
Brentuximab vedotin	Antibody-drug conjugate (ADC)/ microtubule stabilizer	In vitro studies and cell lines • mAb anti-CD30 linked to MMAE displayed similar affinity to the antigen as the naked mAb (Francisco et al., 2003) • Brentuximab vedotin was highly cytotoxic against CD30$^+$ HL (e.g., L540cy and KM-H2) and ALCL (e.g., Karpas 299) cell lines, with IC_{50} ranging from 3–50 pM. CD30$^-$ cells were approximately 1,000 times less sensitive to these effects (Doronina et al., 2003; Senter & Sievers, 2012) In vivo studies • Studies on mouse xenograft models showed treatment with brentuximab vedotin prolonged survival and regressed tumour size in a dose-dependent manner, when compared with untreated mice (Doronina et al., 2003) • Single-dose treatments between 1 and 3 mg·kg^{-1} reduced or cured HL and ALCL tumours in mouse xenograft models (Hamblett et al., 2004)	• Total of 138 clinical trials are listed (www.clinicaltrials.gov) on Phases I, II, and III. Of these, 10 have been withdrawn or suspended and three have unknown status; 43 trials are described as completed or terminated and 81 sudies are ongoing. One study is listed with an available status, indicating non-participant patients may be able to gain access to the drug • Tested on HL (e.g., BREVITY and BASALT trials) and ALCL and other CD30$^+$ lymphomas, notably B-cell lymphomas (such as difuse large B-cell lymphoma and mediastinal large B-cell lymphoma), T-cell lymphomas (such as cutaneous T-cell lymphoma and PTCL), and non-Hodgkin's lymphoma (e.g., BRAN trial). ACL, AML, germ cell cancer, and solid tumours • Approved for the treatment of HL, ALCL, mycosis fungoides, and PTCL • Therapeutic scheme: Prescribing information obtained from Seattle Genetics (available at www.adcetris.com), recommends, when in monotherapy, the dose of 1.8 mg·kg^{-1} (up to a maximum of 180 mg) every 3 weeks. For combination with chemotherapy, the recommended dose is 1.2 mg·kg^{-1} (up to a maximum of 120 mg) every 2 weeks for up to 12 doses for previously untreated HL, and 1.8 mg·kg^{-1} (up to a maximum of 180 mg) every 3 weeks for up to eight doses for previously untreated PTCL. Administration should be as an intravenous infusion over 30 min • Maximum tolerated dose: 1.8 mg·kg^{-1} every 3 weeks, or 1.2 mg·kg^{-1} for weekly or semimonthly administrations

(Continues)

TABLE 1 (Continued)

Drug	Class	Preclinical evidences	Clinical evidences
		• In mice, the maximum tolerated dose was determined at 100 $mg \cdot kg^{-1}$ (Hamblett et al., 2004) • Half-life of brentuximab vedotin was determined at 14 days, whereas that for the naked mAb was found at 16.7 days (Hamblett et al., 2004)	• Most common side effects: During clinical trials, peripheral neuropathy requires treatment interruption until symptoms have downgraded. Combination treatments generally increased this side effect. Neutropaenia occurs in up to 35% of cases, while other haematological toxicities consist of anaemia and thrombocytopaenia. Nausea, fatigue, pyrexia, and upper respiratory infections are among the non-hematological side effects. During treatment, development of progressive multifocal leukoencephalopathy can occur in patients, leading to death. Concomitant administration with bleomycin is strongly advised against due to possibly serious side effects to the lungs
Plitidepsin	Inhibitor of protein synthesis by targeting the eukaryotic elongation factor 1A2 (eEF1A2)	In vitro studies and cell lines • Haematological cell lines were tested against plitodepsin, and IC_{50} values (means) were as follows: ALL (28 nM), AML (24 nM), CML (74 nM), MM (77 nM), and NHL (78 nM; Depenbrock et al., 1998) • Against leukaemic cells, when compared to other chemotherapeutic agents, plitidepsin was found to be twofold to 100-fold more potent • K_D value of 80 nM was calculated for binding of plitidepsin to eEF1A2, indicating high affinity and a low dissociation rate (Losada et al., 2016) • Expression of eEF1A2 in plitidepsin-resistant HeLa cell line (IC_{50} > 100 nM) was about eightfold underexpressed, when compared to wild-type HeLa cells (IC_{50} = 1 nM; Losada et al., 2016) In vivo studies • In a primary myelofibrosis mouse model, plitidepsin (at 0.1 $mg \cdot kg^{-1} \cdot day^{-1}$ for 5 days for up to four cycles, every 3 weeks) was well tolerated, with acceptable toxicity and morbidity, and prevented development of myelofibrosis by megakaryocytes • Aplidin showed better activity against the ALL panel compared to the solid tumours, but the I activity observed for Aplidin was less than that previously noted for standard agents	• Total of 11 clinical trials studies on Phases I, II, and III (www.clinicaltrials.gov). All have been completed • Tested on lymphoma, MM, liposarcoma, advanced solid tumours, relapsed leukaemia, myelofibrosis, and prostate cancer • Approved for the treatment of refractory MM in combination with dexamethasone in patients who relapsed three lines of treatment, granted by the Australian regulatory agency in December 2018 • Therapeutic scheme: Plitidespsin is administred by infusion of a solution consisting of 0.5 mg of plitidepsin, 158 mg of PEG-35 castor oil, and 0.15 ml of ethanol per each ml, over 3 hr. The recommended dose of plitidepsin is 5 $mg \cdot m^{-2}$ twice monthly, every 4 weeks. A weekly dose of dexamethasone (40 mg) must be pre-administered orally 1 hr before plitidepsin infusion (on coincidental days) every 4 weeks (Australian Product Information for Aplidin, available at www.stabiopharma.com, accessed at 10 August 2019) • Maximum tolerated dose was established at 3.6 $mg \cdot m^{-2}$ per weekly • Most common side effects were nausea, fatigue, and myalgia, besides transient lymphopenia, thrombocytopenia, anaemia, and increased levels of transaminase and creatine phosphokinase (Ribrag et al., 2013)
Lurbidectedin	DNA-alkylating agent	In vitro studies and cell lines • Tested against pancreas (PANC-1, MiaPaCa-2), ovary (IGROV-1, A2780), lung (NCI-H4660, A549), liver	• Total of 18 clinical trials studies on Phases I, II, and III. Of these, 12 have been completed or terminated and six are ongoing • Tested on malignant pleural mesothelioma, advanced solid tumours, metastatic breast cancer, pancreatic cancer, metastatic colorectal cancer, acute leukaemia,

(Continues)

TABLE 1 (Continued)

Drug	Class	Preclinical evidences	Clinical evidences
		(SK-HEP-1, HEPG2), leukaemia (MOLT4, K562), colon (LoVo, HCT-116), stomach (HS746T, HGC-27), and breast (MCF-7, MDA-MB-231) cancer cell lines, with IC_{50} of 1.8 and 2.1 nM (Leal et al., 2010) In vivo studies • NCI-H460 (lung), A2780 (ovary), HT29 (colon), and HGC-27 (gastric) cells with statistically significant tumour size reduction in all models tested (Leal et al., 2010)	ovarian cancer, metastatic sarcoma, neuroendocrine tumours, non-small lung cancer, and endometrial cancers • Approved for the treatment of small cell lung cancer (SCLC) as an orphan drug • Therapeutic scheme: doxorubicin 50 $mg{\cdot}m^{-2}$ + Lurbinectedin 3- to 5-mg flat dose (FD) Day 1 q3w and continue with Lurbinectedin 7-mg FD after doxorubicin cumulative dose of 450 $mg{\cdot}m^{-2}$. RD doxorubicin 50 $mg{\cdot}m^{-2}$ + Lurbinectedin 2 $mg{\cdot}m^{-2}$ q3w or doxorubicin 40 $mg{\cdot}m^{-1}$ + Lurbinectedin 2 $mg{\cdot}m^{-2}$ Day 1 q3w and continue with Lurbinectedin 4 $mg{\cdot}m^{-2}$ after doxorubicin cumulative dose of 450 $mg{\cdot}m^{-2}$ (Farago et al., 2019) • Most common side effects are transient anorexia, dysgeusia, anaemia, thrombocytopenia, neutropenia, and short-lasting fatigue; increase in liver enzymes, gastrointestinal disorders and isolated cases rhabdomyolysis, hyperbilirubinemia, and oral herpes (Metaxas, Cathomas, Mark, & von Moos, 2016)
Plinabulin	Microtubule-target agent	In vitro studies and cell lines • Cytotoxic against human tumour cell lines: HT-29 (colon adenocarcinoma), PC-3 and DU 145 (prostate adenocarcinomas), MDA-MB-231 (breast adenocarcinoma), NCI-H292 (non-small cell lung carcinoma), and Jurkat (T-cell leukaemia) • Plinabulin increased permeability in HUVECs In vivo studies • Efficacy in P388 leukaemia and Lewis lung carcinoma models	• Total of eight clinical trials studies on Phases I, II, and III. Of these, three have been completed or terminated and five are ongoing • Tested on lung cancer, non-small lung cancer, and lymphoma • The most common side effects were nausea, vomiting, tumour pain, fever (Mita et al., 2010), and fatigue and diarrhoea have also been reported (Millward et al., 2011)
Marizomib	Proteasome inhibitor	In vitro studies and cell lines • Cytotoxicity against 60 cell lines NCI panel • Active against MM cells resistant to other proteasome inhibitors • Mean IC_{50} values ranging from low to mid nM (Feling et al., 2003; Potts et al., 2011) • Marizomib re-sensitizes resistant MM cells to apoptosis by chemotherapeutic and immunotherapeutic drugs	• Total of nine clinical trials studies on Phases I, II, and III. Of these, five have been completed or terminated and four are ongoing. • Tested on MM, refractory MM, relapsed MM, non-small cell lung cancer, pancreatic cancer, melanoma, lymphomas, ependymoma, glioblastoma, and newly diagnosed glioblastoma • Marizomib depicts wider, faster, and more durable proteasome inhibition than bortezomib without the limiting toxicities associated with the latter and other clinically approved proteasome inhibitors, such as neutropenia, thrombocytopenia, and peripheral neuropathy

(Continues)

TABLE 1 (Continued)

Drug	Class	Preclinical evidences	Clinical evidences
		In vivo studies • Antitumour activity against solid and haematological models: MM, NHL, Waldenstrom's macroglobulinemia, ALL, AML, and CLL, as well as in solid tumours, such as colon, glioma, and pancreatic cancer	• The most common side effects related to marizomib administration in two Phase I studies were fatigue, nausea, vomiting, dizziness, diarrhoea, and pain at the infusion site (Harrison et al., 2016; Richardson et al., 2016) • The ongoing clinical trials of Phases II and III focus on glioblastoma and MM
Plocabulin	Microtubule-target agent	In vitro studies and cell lines • Potent antitumour activity in a panel of tumour xenograft models, including MDA-MB-231 (breast), HCT-116 (colon), H-460 (non-small cell lung cancer), 22RV1 (prostate), HGC-27 (gastric), and Caki-1 (renal) • Highly cytotoxic against P-glycoprotein overexpressing cell lines resistant to antitubulin agents in clinics • Inhibition of tumour cell migration and angiogenesis both in vitro and in vivo In vivo studies Antitumour activity and low toxicity observed in NCI-H460 lung tumour cells xenografted mice treated during three consecutive weeks at 0.08, 8, and 16 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$. Plocabulin-treated mice showed up to 65% decrease in tumour vasculature (Galmarini et al., 2018)	• Total of three clinical trials studies on Phases I, II, and III. Of these, one has been completed or terminated, one is ongoing, and one unknown. • Tested on advanced solid tumours alone or with other antitumour drugs • The complete clinical study highlights mainly mild to moderate toxicities, such as abdominal pain, myalgia, fatigue, nausea, and vomiting and antitumour or disease stabilization • Myelosuppression shown to be transient and manageable, and the main dose-limiting toxicity reported was a grade 3 peripheral sensory neuropathy, which is expected for an antitubulin agent • Other DLTs were grade 4, such as tumour lysis syndrome and cardiac failure, and grade 3, like myalgia

Abbreviations: ALCL, anaplastic large cell lymphoma; ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; CLL, chronic lymphocytic leukaemia; HL, Hodgkin's lymphoma; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; PTCL, peripheral T-cell lymphoma; TNBC, triple negative breast cancer.

activity especially when associated with dexamethasone (revised by Van Kesteren et al., 2003).

Clinical evidence of trabectedin first suggested its use for soft tissue sarcoma (STS) with multiple Phase I studies covering its isolated use or in combination with other chemotherapies, such as **doxorubicin** and **cisplatin**, and suggested the recommended dose of 1.5 mg·m^{-2} as a 24-hr continuous intravenous infusion every 3 weeks (Taamma et al., 2001). Phase II studies demonstrated positive results, especially for liposarcoma (LMS) and leiomyosarcoma (LPS), and determined a median overall survival (OS) of 9.2 months (Monk et al., 2012). Phase III studies concluded that trabectedin was superior in comparison to dacarbazine in patients with advanced LPS and LMS after failure of prior chemotherapy (Demetri et al., 2017). A summarized description of the clinical evidence for ovarian carcinoma is found in Table 1.

The European Medicines Agency (EMEA) approved trabectedin for therapeutic use and commercial trading to PharmaMar (S.A., Madrid, Spain) under the name Yondelis in 2007, when it became the first marine drug identical to the original natural product to obtain marketing authorization. At that time, the European Commission allowed the use of trabectedin for the treatment of patients with advanced STS after failure of anthracyclines and **ifosfamide**. Two years later, the drug was also approved for the treatment of patients with relapsed platinum-sensitive ovarian cancer in combination with pegylated liposomal doxorubicin (Puyo, Montaudon, & Pourquier, 2014). Still, it was nearly a decade later, in 2015, that the United States Agency Food and Drug Administration (FDA) authorized Yondelis for clinical use (available from www.fda.gov, accessed 19 February 2019). A timeline between the discovery of trabectedin and the full development of Yondelis is shown in Figure 3.

A recent study evaluated treatment options for STS and demonstrated that patients receiving trabectedin presented a median OS of 21.3 months (Le Cesne, 2018). Additionally, 53% of patients showed long-term tumour control when trabectedin was administered early in the treatment scheme, and, even more encouraging, 65.5% of patients achieved disease control (Le Cesne, 2018). In order to evaluate the 10-year period of trabectedin use after approval for STS treatment, a cohort of 86 patients was accessed, and the main results indicated that trabectedin was chosen by the majority as a second- or third-line treatment. Only 22% of cases presented side effects, mainly related to myelosuppression and no treatment-related deaths were observed (Shamai & Merimsky, 2017).

Despite the approved clinical status for Yondelis, further studies have been conducted to better understand this molecule and its activity on different cancer models. Until now, other four effects of ET-743 were discovered, explaining its effective anticancer activity. First, trabectedin modulates the tumour micro-environment (TME). It specifically depletes monocytes and tumour-associated macrophages (TAM), decreases indirectly the production of inflammatory mediators, such as

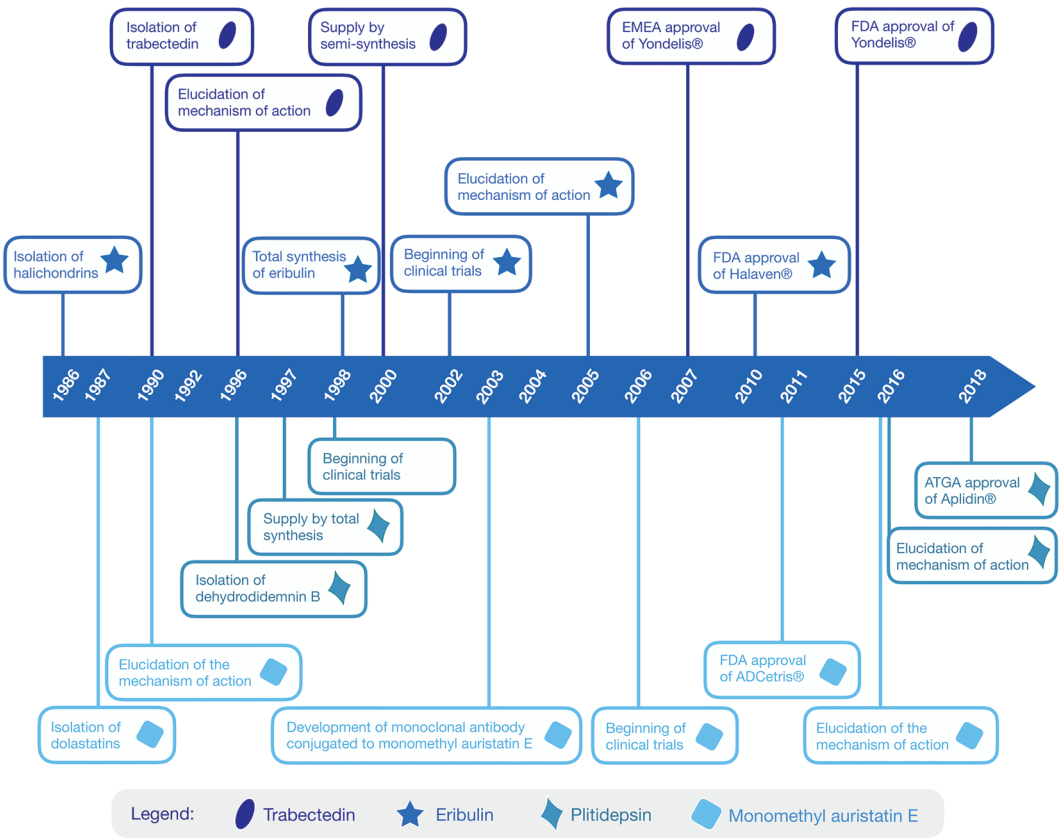

FIGURE 3 Milestones of anticancer drugs from marine origin on the market. The length of time between the isolation of the natural molecule and the approval of the commercial product was 17 years for trabectedin (Yondelis®), 22 years for dihydrodidemin B (Aplidin®), 24 years for halichondrin (Halaven®), and 24 years for dolastatin (ADCetris®)

IL-6, CXCL8, and VEGF, and compromises the expression of genes involved in extracellular matrix (Galmarini, D'Incalci, & Allavena, 2014). Second, trabectedin also appears to be involved in alternative lengthening of telomeres (ALT), a preventive strategy for telomere shortening that assures immortality of cancer cells. Such changes are found in 10% to 15% of tumours, and ALT positive cells seem to be more sensitive to trabectedin (Pompili, Leonetti, Biroccio, & Salvati, 2017). Third, a three-stranded nucleic acid structure referred as R-loops induces genome instability caused by DNA damage dependent of RNA–DNA hybrid assemblies. Researchers have demonstrated that high levels of R-loops may enhance the activity of trabectedin, opening prospects for treatment of cancers with high levels of these events (Tumini et al., 2018). Finally, the involvement of trabectedin in the repression of genes regarding cancer stem cell phenotype, and their related pathways was also documented (Martinez-Cruzado et al., 2017).

4.2 | Eribulin mesylate (Halaven): Do we still need one more antitubulin agent?

Eribulin mesylate (Figure 1) is a synthetic analogue of the natural product halichondrin B (Figure 1), initially identified by Hirata and Uemura (1986) in extracts from the marine sponge *Halichondria okadai*, found in the Miura Peninsula, in Japan. Subsequently, halichondrin B was also isolated from other species of marine sponges, such as *Axinella* sp., (Pettit et al., 1991), *Phakellia carteri* (Pettit et al., 1993), and *Lissodendoryx* sp. (Litaudon, Hart, Blunt, Lake, & Munro, 1994). The natural compound belongs to a class of polyether macrolides and showed a potent in vitro and in vivo antitumour activity (Hirata & Uemura, 1986). Eribulin, in turn, is a halichondrin B derivative based on pharmacophoric-driven structural simplification, but it still represents the most complex drug supplied through total synthesis (Yu, Kishi, & Littlefield, 2011). The eribulin synthesis route mostly repeated the macrocyclic ring cytotoxic core of halichondrin B, but the side chain was omitted, thus losing almost half of the original molecular weight.

Eribulin is a potent microtubule-destabilizing anticancer agent. This molecule interferes in the mitosis phase of the cell cycle through a peculiar mechanism of action that differs from other antimitotic agents, such as the vinca alkaloids. A non-taxane microtubule dynamics inhibitor, eribulin predominantly binds with high affinity to the plus ends of the microtubules, preventing polymerization of tubulin without affecting depolymerization (Figure 2). However, this molecule can also bind to the soluble α and β tubulin, thus decreasing the availability of the subunits for polymerization. Thus, suppression of the microtubule dynamics induces a cell cycle arrest at the G_2/M phase, which then signals for mitotic catastrophe, further leading to cell death by apoptosis (Eslamian, Wilson, & Young, 2017; Okouneva, Azarenko, Wilson, Littlefield, & Jordan, 2008).

In preclinical cancer models, eribulin has shown antitumour activity against colon cancer, glioblastoma, head and neck cancer, melanoma, non-small cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, and small cell lung cancer (Towle et al., 2012). It has been shown to go beyond the inhibition of microtubule dynamics, as it participates in other important regulatory processes of tumour cell biology, such as epithelial-to-mesenchymal transition (EMT), vascularization, and hypoxia, which shows the promising potential of this drug to contribute to clinical benefits. Table 1 summarizes the preclinical and clinical data obtained for eribulin.

In fact, recent studies using breast and sarcoma tumours have shown the non-antimitotic effects of eribulin on tumour biology and in the TME, such as reversal of EMT, decreased capacity for migration and invasion, and vascular remodelling and perfusion (Funahashi et al., 2014; Yoshida et al., 2014). Moreover, preclinical studies in triple negative breast cancer (TNBC) cell cultures showed that treatment with eribulin increased gene expression of epithelial markers (i.e., CDH1 and KRT18) and downgraded the levels of mesenchymal markers (i.e., CDH2, VIM, TWIST1, SNAI2, ZEB1, and ZEB2), leading to the reversal of EMT after 7 days of exposure to eribulin (Yoshida et al., 2014). Combination of two antitubulin agents—eribulin and paclitaxel—resulted in a synergistic antiproliferative effect on TNBC cells in vitro. Exposure to eribulin increased E-cadherin expression and decreased the expression of mesenchymal markers in MDA-MB-231 and Hs578T cells, showing a clear phenotypic switch from mesenchymal to epithelial state (Oba & Ito, 2018). Loss of phenotypic characteristics of mesenchymal cells and gain of epithelial phenotypic characteristics indicate a possible decrease in malignancy and, consequently, in tumour aggressiveness. Findings reported by Funahashi et al. (2014) showed that a single dose of eribulin increased tumour perfusion and generated changes in vascularization. The authors further observed that microvessel density and proportion of small vessels both increased. These changes were associated with reduced hypoxia and, subsequently, with the prevention of drug resistance and metastasis (Funahashi et al., 2014).

Clinical studies supported the use of eribulin treatment for advanced or metastatic breast cancer and also suggested that it could help in the treatment of solid tumours resistant to other classes of microtubule dynamics inhibitors. The recommended doses for an injection of eribulin are slightly different in the United States (1.4 $mg{\cdot}m^{-2}$ of the salt, eribulin mesylate) from those recommended in Europe (1.23 $mg{\cdot}m^{-2}$ of the active substance,eribulin). The administration of eribulin is scheduled on the first and eighth day of a 21-day cycle (Goel et al., 2009; Tan et al., 2009). In this setting, eribulin has demonstrated efficacy in Phase II studies involving patients who previously received both, an anthracycline and a taxane (Aogi et al., 2012; McIntyre et al., 2014; Vahdat et al., 2009), or this combination with the addition of capecitabine (Cortes et al., 2010). Advanced or recurrent HER2-positive breast cancer has been treated with eribulin combined with trastuzumab (Sakaguchi et al., 2018; Wilks et al., 2014) or pertuzumab (Araki et al., 2017), which presented an acceptable treatment option supported by a high objective response rate (ORR), a prolonged median progression-free survival (PFS), and an acceptable safety profile. The most common drug-related grades 3–4 toxicities were neutropenia, leukopenia, peripheral neuropathy, and febrile neutropenia (Aogi et al., 2012; McIntyre et al., 2014; Vahdat et al., 2009).

In 2011, the first non-randomized multicentre Phase II study involving eribulin and previously treated progressive or high-grade STS was published (Schöffski et al., 2011), which yielded median PFS

of 2.1 to 2.9 months in patients with different types of STS (Schöffski et al., 2011). Another open-label, multicentre, and non-randomized Phase II trial evaluated patients with advanced or metastatic STS. This study found a median PFS and ORR for LPS/LMS patients of 5.5 and 17.0 months, respectively, against 2.0 months for both parameters in other subtypes (Kawai et al., 2017). Furthermore, a Phase III study comparing eribulin (1.4 $mg{\cdot}m^{-2}$ intravenously on Days 1 and 8) with **dacarbazine** (850 $mg{\cdot}m^{-2}$, 1,000 $mg{\cdot}m^{-2}$ intravenously on Day 1) every 21 days in patients with advanced LPS or LMS showed an improvement in OS and PFS for eribulin-treated patients versus those who received dacarbazine alone (Demetri et al., 2017).

In November 2010, Halaven was approved by the FDA as a third-line therapy for advanced or metastatic breast cancer patients who were previously treated with an anthracycline and a taxane, and, in January 2016, it became the second line of treatment for unresectable or metastatic liposarcoma (available from www.fda.gov, accessed 10 August 2019). In fact, eribulin was the first drug approved for patients with advanced, metastatic, or inoperable STS that demonstrated an improvement in overall survival. A timeline from the discovery of halichondrin B to the full development of Halaven is shown in Figure 3.

4.3 | Warhead drugs (brentuximab vedotin, Adcetris): Special delivery to overcome toxicity

In 1970, extracts obtained from the mollusc *Dolabella auricularia*, found in the Indian Ocean, stood out for their pronounced anticancer activity (Pettit, Day, Hartwell, & Wood, 1970). The active principles, a series of peptides called dolastatins, were highlighted for their potent antiproliferative activities against several tumour cell lines, especially dolastatins 10 and 15, with IC_{50} values in the pM-range (Pettit et al., 1987). It was then found that tubulin is the main target of action of these peptides, inducing blockade of microtubule polymerization and inhibiting cell proliferation (Pettit, 1997). Despite the potent in vitro activity of dolastatins, none of these peptides—or their synthetic derivatives, such as auristatin (soblidotine), cematodine, and synthatodine—have progressed into clinical trials beyond Phase II (Perez et al., 2005; Vaishampayan et al., 2000) due to toxicity and lack of efficacy (Newman & Cragg, 2017). However, monomethylauristatin E (MMAE), an auristatin derivative, successfully entered the composition of the antibody-drug conjugate (ADC) brentuximab vedotin, which was further developed by Seattle Genetics (Doronina et al., 2003; Senter & Sievers, 2012).

ADCs are recent formulations that seek to improve selectivity and overcome the toxicity of anticancer therapy by delivering the pharmacological agent to specific tumour cells. Such systems comprise three main components: a monoclonal antibody that will guide the ADC to the target cells; a potent cytotoxic compound (dubbed a payload or a warhead), which should kill the tumour cells; and a linker that will covalently connect both parts and is further accountable for releasing the payload inside the target cell (Ducry & Stump, 2010; Storz, 2015). In the specific case of brentuximab vedotin, the monoclonal antibody cAC10 is directed to the human **CD30** membrane protein, a TNF receptor, and is also recognized as a tumour marker for some lymphomas (Younes, 2011). In fact, CD30 had previously shown to be a promising antigen for anticancer immunotherapy based on in vitro and in vivo preclinical evidence generated by exposure to cAC10. However, in clinical trials, this kind of therapy displayed only limited efficacy (Wahl et al., 2002).

Vedotin (vcMMAE) is the second part of the conjugate and comprises the linker and the cytotoxic principle, MMAE. Linker technology is important for the success of ADCs, as it must guarantee stability of the system under physiological conditions and allow enough time for the conjugate to reach the target cell, but it should also be specifically cleaved to free the payload inside the cell. For brentuximab vedotin, a cathepsin cleavable valine-citrulline linker was chosen, as it met these criteria and, moreover, allowed for better water solubility and satisfactory pharmacokinetics of the drug (Doronina et al., 2003). Recognition of the brentuximab antibody by CD30 protein leads to the internalization of the ADC which, within the cell, releases vedotin—nearly four units of the agent per complex—by a selective proteolytic cleavage carried out by lysosome cysteine proteases. In turn, free MMAE reaches its target, blocks cell division in G2/M by disrupting microtubule dynamics, and, ultimately, induces cell death (Doronina et al., 2003; Senter & Sievers, 2012).

Preclinical studies demonstrated that conjugation with MMAE did not alter the affinity of the CD30 antibody with the surface antigen. In fact, brentuximab vedotin showed enhanced cytotoxicity when assessed against $CD30^+$ cell lines originating from Hodgkin's lymphoma and systemic anaplastic large cell lymphoma (ALCL), with IC_{50} values in the pM range. In turn, in $CD30^-$ cells lines, the conjugate showed a reduced toxicity by nearly 1,000 times, thus displaying an antigen-dependent effect (Francisco et al., 2003; Yi, Kim, & Kim, 2017). Further in vivo findings showed favourable outcomes in mice bearing xenograft tumours of human Hodgkin's lymphoma and ALCL cells, with tumour regression, and prolonged survival of treated animals. Moreover, in a single-dose treatment scheme with the ADC, xenograft mice models injected with 1 to 3 $mg{\cdot}kg^{-1}$ exhibited regressed and even cured tumours. Such efficacy allowed for a wide therapeutic window, once the maximum tolerated dose was established at 100 $mg{\cdot}kg^{-1}$ (Senter & Sievers, 2012). Table 1 summarizes preclinical and clinical data for brentuximab vedotin.

In a clinical trial conducted on CD30-positive haematological cancers, a large percentage of patients had a complete response to treatment with brentuximab vedotin. A Phase I trial that used escalating doses of intravenously administered ADC in 45 patients every 3 weeks showed an ORR in ~40% of patients, including complete remission for ~25% (Younes, 2011). Furthermore, Phase II trials in patients with Hodgkin's lymphoma and ALCL showed ORR of 73% (with 32% complete responses) and 86% (with 57% complete responses) respectively (Younes, Yasothan, & Kirkpatrick, 2012).

ADCetris (brentuximab vedotin) was approved by the FDA in 2011 for the treatment of Hodgkin's lymphoma and systemic ALCL, types of cancer distinguished by the high expression of CD30. Recently, between 2017 and 2018, the FDA expanded the approval of ADCetris

TABLE 2 Marine-derived warheads in antibody-drug conjugates (ADCs) under clinical trials

ADC name	Warhead	Antibody target	Condition	Clinical trial status	Developer
Depatuxizumab mafodotin (ABT-414)	MMAF	EGFR	Glioblastoma, gliosarcoma, malignant glioma	Phase III	AbbVie
Polatuzumab vedotin (DCDS-4501A)	MMAE	CD79b	NHL, CLL, B-cell lymphoma, follicular lymphoma	Phase III	Genentech (Roche)
Belantamab mafodotin (GSK2857916)	MMAF	BCMA	MM	Phase II	GlaxoSmithKline
Cirmtuzumab vedotin (UC-961ADC3)	MMAE	ROR1	Solid tumours, CLL, B-cell lymphomas, acute leukaemia, breast	Phase II	UC San Diego
Enapotamab vedotin (HuMax®-AXL-ADC)	MMAE	AXL	Solid tumours, ovarian, NSCLC, endometrial, cervical, thyroid	Phase II	GenMab
Enfortumab vedotin (ASG-22ME)	MMAE	Nectin-4	Urothelial (M)	Phase II	Seattle Genetics
Glembatumumab vedotin (CDX-011)	MMAE	GPNMB	Melanoma (M), breast (M), TNBC	Phase II	Celldex Therapeutics
Hertuzumab vedotin	MMAE	HER2	Breast, gastric (HER2+)	Phase II	Rongchang Pharmaceuticals and MabPlex
Indusatumab vedotin (MLN-0264)	MMAE	GCC	Gastrointestinal, pancreatic	Phase II	Takeda/Millennium Pharmaceuticals
Ladiratuzumab vedotin (SGN-LIV1A)	MMAE	LIV-1	Breast	Phase II	Seattle Genetics
Lifastuzumab vedotin (DNIB0600A)	MMAE	NaPi2b	Ovarian, NSCLC	Phase II	Genentech (Roche)
Pinatuzumab vedotin (DCDT-2980S)	MMAE	CD22	NHL, DLBCL, CLL, B-cell lymphomas	Phase II	Genentech (Roche)
Sofituzumab vedotin (DMUC5754A)	MMAE	MUC16	Ovary, fallopian tube, pancreas, peritoneal	Phase II	Genentech (Roche)
Telisotuzumab vedotin (ABBV-399)	MMAE	c-Met	Solid tumours	Phase II	AbbVie
Tisotumab vedotin (HuMax®-TF-ADC)	MMAE	TM	Ovary, cervix, endometrium, bladder, CRPC, SCCHN, oesophagus, NSCLC	Phase II	GenMab
AGS-16C3F	MMAF	ENPP3	RCC	Phase II	Agensys and Astellas Pharma
CAB-ROR2 (BA-3021)	MMAE	ROR2	Solid tumours, NSCLC, STS, TNBC	Phase II	BioAtla
CX-2029	MMAE	CD71	Solid tumours, head and neck, NSCLC, pancreatic, DLBCL	Phase II	AbbVie and CitomX
RC-48	MMAE	HER2	Solid tumours, breast, urothelial, gastric (and HER2 overexpressing)	Phase II	RemeGen
W0101	MMAE	IGF1R	Solid tumours (M)	Phase II	Pierre-Fabre

(Continues)

TABLE 2 (Continued)

ADC name	Warhead	Antibody target	Condition	Clinical trial status	Developer
Azintuxizumab vedotin (ABBV-838)	MMAE	SLAMF7 (CD319)	MM, plasma cell myeloma	Phase I	AbbVie
Denintuzumab mafodotin (SGN-CD19A)	MMAF	CD19	ALL, NHL	Phase I	Seattle Genetics
Iladatuzumab vedotin (DCDS0780A)	MMAE	CD79b	NHL	Phase I	Genentech (Roche)
Losatuxizumab vedotin (ABBV-221)	MMAE	EGFR	Solid tumours (overexpressing EGFR)	Phase I	AbbVie
Lupartumab amadotin (BAY 1129980)	Auristatin W derivative	LYPD3	Solid tumours	Phase I	Bayer
Samrotamab vedotin (ABBV-085)	MMAE	LRRC15	Solid tumours	Phase I	AbbVie
Sirtratumab vedotin (ASG-15ME)	MMAE	SLITRK6	Urothelial (M)	Phase I	Astellas and Seattle Genetics
ALT-P7	MMAE	HER2	Breast, gastric	Phase I	3SBio and Alteogen
ARX-788	MMAF	HER2	Breast, gastric	Phase I	Ambrex and Zhejiang Medicine
ASG-5ME	MMAE	SLC44A4	Gastric, pancreas, prostate	Phase I	Astellas and Seattle Genetics
ASG-67E	MMAE	CD37	Lymphoid malignancy (R)	Phase I	Astellas and Seattle Genetics
CDX-014	MMAE	TIM-1	RCC	Phase I	Celldex Therapeutics
DMOT4039A (RG 7600)	MMAE	MSLN	Ovarian, pancreas, digestive system	Phase I	Genentech (Roche)
PF-06804103	Auristatin 0101	HER2	Breast, stomach, oesophagogastric junction, NSCLC	Phase I	Pfeizer and AbbVie
SGN-CD48A	MMAF	CD48	MM	Phase I	Seattle Genetics
XMT-1522	AF-HPA	HER2	Breast, gastric, NSCLC	Phase I	Mersana Therapeutics and Takeda
XMT-1536	AF-HPA	NaPi2b	Solid tumours	Phase I	Mersana Therapeutics
ZW-49	MMAE variant	HER2	HER2 overexpressing cancers	Phase I	Zymeworks and BeiGene

Abbreviations: ADC, antibody-drug conjugate; AF-HPA, auristatin F-hydroxypropylamide; AXL, AXL receptor TK; BCMA, B-cell maturation antigen; c-Met, tyrosine-protein kinase met; CD19, cluster of differentiation 19, also known as B lymphocyte surface antigen B4; CD22, cluster of differentiation 22, also known as sialic acid binding Ig-like lectin 2; CD37, cluster of differentiation 37, also known as Tetraspanin 26 (TSPAN26) or Glycoprotein 52-40 (GP52-40); CD48, cluster of differentiation 48, also known as B-lymphocyte activation marker 1 (BLAST-1) or signalling lymphocytic activation molecule 2 (SLAMF2); CD71, cluster of differentiation 71, also known as transferrin receptor 1 (TfR-1); CD79b, cluster of differentiation 79b; CLL, chronic lymphocytic leukaemia; CRPC, castration-resistant prostate cancers; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; ENPP3, ectonucleotide pyrophosphatase/PDE family member 3; GPNMB, glycoprotein nonmetastatic B; HER2, human EGF receptor-type 2; IGF1R, insulin-like growth factor receptor 1; LIV-1, solute carrier family 39, member 6 (SLC39A6); LRRC15, leucine-rich repeat containing 15; LY6E, lymphocyte antigen 6 complex, locus E; LYPD3, LY6/PLAUR domain containing 3; (M), metastatic; MM, multiple myeloma; MMAE, monomethylauristatin E; MMAF, monomethylauristatin F; MSLN, mesothelin; MUC16, mucin 16, cell surface associated; NaPi2b, sodium-dependent phosphate transport protein 2b; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; (R), refractory; RCC, renal cell carcinoma; ROR1, receptor tyrosine-kinase like orphan receptor 1; SCCHN, squamous cell carcinoma of the head and neck; SLAMF7 (CD319), SLAM family member 7; SLC44A4, solute carrier family 44 member 4; SLITRK6, SLIT and NTRK-like protein 6; STS, soft tissue sarcoma; TIM-1, T-cell immunoglobulin mucin domain 1; TNBC, triple negative breast cancer; TM, tissue factor.

for treatment of CD30-expressing mycosis fungoides (MF), a cutaneous T-cell lymphoma, and for CD30-expressing peripheral T-cell lymphomas (PTCL; available at www.fda.gov, accessed 22 February 2019).

Furthermore, as shown in Table 2, MMAE and other auristatin derivatives, mainly their phenylalanine variant monomethyl auristatin F (MMAF), are being used in the composition of several ADCs that are currently undergoing clinical trials in which the antibody of the complex is directed to a profusion of relevant membrane discriminators of assorted tumour types. For **polatuzumab vedotin**, an ADC undergoing Phase III clinical trials, the warhead MMAE is linked to the monoclonal antibody anti-**CD79b**, a specific B lymphocyte antigen receptor, which is highly expressed in the majority of B-cell lymphomas and NHL (Newman & Cragg, 2017). Also, in Phase III clinical trials, **depatuxizumab mafodotin**, which carries MMAF as a payload, and a monoclonal antibody directed at the **epidermal growth factor receptor** (EGFR). This ADC is being tried for the treatment of brain tumours, mainly against glioblastoma carrying amplification of the EGFR gene, which may be present in ~50% of glioblastoma patients (Lassman et al., 2019).

Nevertheless, based on the encouraging data generated by these trailblazing studies, there are more entries of ADCs in clinical testing, as seen by the broad list of such drugs in earlier trial phases, which is also shown in Table 2. Moreover, this technology, a combination of immunotherapy and chemotherapy, is attracting various pharmaceutical companies to undertake the development of auristatin microtubule-disruptor ADCs, which is further evidence of their ample potential and success in cancer treatment. It is worth mentioning that some biological targets have been well explored within the anticancer immunotherapy arsenal, such as **HER2**, and are recurrent in this ADC setting yet are functionalized with a cytotoxic compound connected with a perfected linker. This conjugation has shown to improve the efficacy of immunotherapy and add specificity to chemotherapy.

4.4 | Plitidepsin (Aplidin): Targeting protein synthesis

The cyclic depsipeptides plitidepsin (dehydrodidemnin B) and didemnin B are chemically related compounds; the only structural difference is the oxidation (carbonyl group) of the hydroxyl group at the lactoyl-proline in didemnin B (Figure 1). Whereas didemnin B was isolated from the Caribbean tunicate *Tridedmnum solidum* back in 1981 (Rinehart et al., 1981), plitidepsin was isolated from the Mediterranean tunicate *Aplidium albicans* over 10 years later (Sakai et al., 1996).

One of the greatest challenges related to this class of molecules was the elucidation of their mechanism of action. The first studies focused on describing the ability of didemnin B in inhibiting protein synthesis and on the strong correlation of this effect with antiproliferative properties (Li et al., 1984). However, inhibition of cell proliferation was observed at much lower concentrations (nM range) than those required to inhibit protein synthesis (μM range; Ahuja et al., 2000). The elongation factor eEF1A1 was then suggested as a target of didemnin B, but the affinity of such molecules for this component was still assessed in the μM range (Crews, Collins, Lane, Snapper, & Schreiber, 1994). Elongation factors are ubiquitous in most cells, as they deliver aminoacyl-tRNA to the ribosome during the elongation cycle of protein biosynthesis (Mateyak & Kinzy, 2010). Despite similarities between the two isoforms of eEF1A, their expression is mutually exclusive and they are attributed a different functionality. Thus while the first isoform is widespread in mammalian tissues and is responsible for the elongation function itself, the second presents non-canonical pro-oncogenic properties and has a more limited distribution (Sun et al., 2014). In this context, new evidence concerning the molecular mechanism underlying protein synthesis inhibition triggered by didemnins pointed to a crucial role for the non-canonical elongation factor—eEF1A2—in such processes (SirDeshpande & Toogood, 1995).

The observed affinity constant (K_D) for molecular interaction for plitidepsin and eEF1A2 is 80 nM, with a target residence of 9 min. Moreover, sensitivity to plitidepsin is correlated with eEF1A2 expression. While resistant cells exhibited reduced eEF1A2 expression, ectopic expression of eEF1A2 restored sensitivity in these cells. The biological effects resulting from this interaction include inhibition of the transportation of misfolded proteins to the proteasome, which leads to an accumulation of toxic proteins in the tumour cells (Losada et al., 2016). It is further suggested that plitidepsin also inhibits the activation and subsequent destruction of the aggresome in the lysosome, which also accumulates an excess of misfolded proteins in the cells, which then triggers apoptosis (available from www.pharmamar.com, accessed 22 February 2019). Figure 2 illustrates the mechanism of action for plitidepsin in tumour cells.

Preclinical data demonstrated in vitro activity of plitidepsin in several cancer cell lines in the sub-nM range. Haematological cell lines were the most sensitive ones, with IC_{50} means of 28 nM for ALL, 24 nM for AML, 74 nM for CML, 77 nM for multiple myeloma (MM), and 78 nM for NHL (Depenbrock et al., 1998). In vivo assays were carried out in xenograft models mainly with haematological tumours including MM, T-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), and Burkitt lymphoma, with promising results (revised by Alonso-Álvarez et al., 2017). Table 1 summarizes preclinical and clinical data with plitidepsin.

In 1986, didemnin B was the first marine natural product to enter clinical trials in patients with advanced cancer, but due to neuromuscular toxicity and low efficacy, its further development was interrupted (Vera & Joullié, 2002). Despite the similarities of didemin B and plitidepsin and the failure of didemnin B in clinical trials, the increased potency of ptilidepsin and a better pharmacokinetic profile (Alonso-Álvarez et al., 2017) stimulated the beginning of Phase I trials with ptilidepsin by PharmaMar in 1998. It is important to point out that although didemnin B showed a very short half-life, as it was converted to an unidentified metabolite (Dorr, Kuhn, Phillips, & von Hoff, 1988), plitidepsin was found to have a longer half-life, low clearance, and a high volume of distribution (Nalda-Molina et al., 2009).

Clinical studies with plitidepsin were conducted in groups of patients with haematological cancer and, although the results for use as a single drug were not very encouraging, the combination of plitidepsin with other drugs was promising, especially for patients with MM (Alonso-Álvarez et al., 2017; Mateos et al., 2010; Ocio et al., 2016). The addition of dexamethasone in the treatment of patients

with relapsed or refractory MM receiving plitidepsin improves the overall response rate (ORR) from 13% to 22% (Mateos et al., 2010). The concomitant treatment of MM patients with infusion of plitidepsin during 4 weeks at 4–5.0 mg·m^{-2}, dexamethasone (oral) and **bortezomib** (s.c.) provided an ORR of 56% (Ocio et al., 2016). The observed toxicity was manageable, including anaemia and thrombocytopenia among the most severe haematological effects, and muscle toxicity was a dose-limiting side effect (Faivre et al., 2005; Mateos et al., 2010; Ocio et al., 2016). The ADMYRE Phase III study was conducted with 255 patients with relapsed/refractory MM, comparing the efficacy of plitidepsin in combination with dexamethasone to that of dexamethasone alone (available from www.clinicaltrials.gov, accessed 25 January 2019). The results available so far indicate a 35% lower risk of disease progression or death in patients treated with the drug combination (Alonso-Álvarez et al., 2017).

Considering other haematological malignancies, such as leukaemia and lymphoma, plitipesin has been tested in at least four different clinical studies, but ORR is variable, from non-objective response to a maximum of 20.7% for non-cutaneous peripheral T-cell lymphoma (Aspeslagh et al., 2017; Ribrag et al., 2013). Studies conducted in patients bearing solid tumours—including melanoma, renal, advanced colorectal, prostate, thyroid, and NSCLC, among others—were not very promising, and the ORRs were generally not significant (revised by Alonso-Álvarez et al., 2017).

The treatment of refractory MM with the combination of plitidepsin and dexamethasone in patients that relapse after three lines of treatment, was approved by the Australian regulatory agency in December 2018 (available from www.ebs.tga.gov.au, accessed 20 February 2019). The EMEA, on the other hand, refused marketing authorization for Aplidin (plitidepsin) in Europe. According to the re-examination carried out by EMEA's Committee for Medicinal Products for Human Use, the benefits of plitidepsin do not outweigh the risks, since toxicity is observed at higher frequencies and there is merely a modest increase in patient response compared to that of dexamethasone alone (available from www.ema.europa.eu, accessed 21 February 2019). Still, Aplidin has received orphan drug designation in the European Union and in the United States. The timeline between the discovery of plitidepsin and the full development of Aplidin is showed in Figure 3.

5 | WHAT IS NEXT? MARINE NATURAL PRODUCTS IN CLINICAL TRIALS

5.1 | Lurbinectedin

Based on the unique features of trabectedin, PharmaMar designed a synthetic analogue, lurbinectedin (Figure 1; Zepsyre, PM01183). The main difference is attributed to the substitution of the tetrahydroisoquinoline with a tetrahydro β-carboline, resulting in increased antitumour activity of lurbinectedin (Leal et al., 2010). The mechanism of action of lurbidectadin is similar to that of trabectedin, as it also binds to CG-rich sequences in the DNA minor groove, inhibits active transcription, and degrades Pol II through the ubiquitin/proteasome system (Santamaria Nuñez et al., 2016). Furthermore, lurbinectedin can cause a detachment of transcription factors, such as ASCL1, NeuroD1 and NFIB in small cell lung cancer (SCLC), from their target promoters, inducing blockade of their transactivating activity (Farago et al., 2019) and exerting important effects on TME (Belgiovine et al., 2017) as well as upon cancer stem cells (Yokoi et al., 2018).

Lurbinectedin has also shown positive results against other tumour types, such as ovary carcinoma, Ewing sarcoma, and pancreatic ductal adenocarcinoma (Harlow et al., 2016; Takahashi et al., 2016; Zhang, Feng, & Kennedy, 2017). As with trabectedin, TC-NER deficient cells showed resistance to lurbinectedin, whereas those deficient in homologous recombination were markedly more sensitive. Lurbinectedin also showed good antitumour activity in several in vivo tumours and xenografts models, including MNMCA1 mouse fibrosarcoma and HOC18 human ovarian carcinoma, however with a different spectrum of activity and distinct pharmacokinetics properties when compared to the parent compound (Romano et al., 2013).

A Phase I study that evaluated the efficacy of lurbinectedin and doxorubicin in patients with relapsed SCLC observed durable response rates in 91.7% of patients with sensitive disease and in 33.3% and 20.0% of resistant disease as second- and third-line treatments respectively. Additionally, tumour shrinkage was maintained in 88% of patients who switched to lurbinectedin alone (Calvo et al., 2017). A Phase II trial conducted with patients that received different chemotherapy-free intervals showed a 52% partial response when intervals were above 90 days. Additionally, 40% of cases presented disease stabilization, with a progression-free survival of 4.2 months (Perez et al., 2018). A Phase III trial involving 600 patients who had failed one prior platinum-containing treatment is currently under investigation (ATLANTIS NCT02566993); they are being treated with a combination of doxorubicin and lurbinectedin, versus topotecan or the VCR (cyclophosphamide, doxorubicin, and vincristine) combination (Farago et al., 2019; Table 1). With this evidence, the FDA granted lurbinectedin, in August 2018, orphan drug status for SCLC.

5.2 | Plinabulin

Plinabulin (NPI-2358, Figure 1) is a synthetic tert-butyl analogue related to the naturally occurring fungal diketopiperazine halimide, also known as phenylahistin (Gomes, Lefranc, Kijjoa, & Kiss, 2015). In fact, halimide was isolated by Fenical, Jensen, and Cheng (1999) from the fermentation broth of a marine fungus, *Aspergillus* sp., found in association with the algae *Halimeda* sp., collected in the Philippines. At the same time, phenylahistin was described as a fungal metabolite obtained from the terrestrial *Aspergilus ustus* (Kanoh et al., 1997, 1999).

The natural product is a potent cytotoxic compound, as it arrests cell cycle in mitosis by inhibiting tubulin polymerization through interaction with the colchicine-binding site (Kanoh et al., 1997). An in vivo study using P388 leukaemia and Lewis lung carcinoma showed very promising results, increasing the mean survival of mice bearing the haematological cancer in 51% of cases at 30 mg·kg^{-1} and reduced tumour growth by 81% in mice with the solid tumour at 100 mg·kg^{-1}.

These results stimulated the synthesis of more potent analogues (Kanoh et al., 1999). The establishment of essential structural requirements for eliciting effective cytotoxicity by (−)-phenylahistin contributed to the design of the clinical candidate, plinabulin, in 2006 (Nicholson et al., 2006). The new analogue demonstrated a potent activity against human colon adenocarcinoma (HT-29), prostate adenocarcinomas (PC-3 and DU 145), breast adenocarcinoma (MDA-MB-231), NSCLC (NCI-H292), and T-cell leukaemia (Jurkat) cell lines, including those with MDR profiles. Additionally, plinabulin promoted an increased permeability in HUVECs, which is consistent with a tumour vascular collapse. Such evidence showed plinabulin to be a vascular disrupting agent (Nicholson et al., 2006).

Evaluation of the effects of plinabulin on MM demonstrated that besides the anti-angiogenic potential on vascular endothelial cells, it induced cell death through caspase activation and showed an obligatory role of **JNK** during plinabulin-induced MM cell death (Singh et al., 2011). An immune-mediated mechanism of action was recently proposed, supported by an increase in dendritic cell maturation and subsequent cytokine release, which occurs through activation of the guanine nucleotide exchange factor (GEF-H1; available from www.beyondspringpharma.com, accessed 24 February 2019).

Efficacy of plinabulin in Phase I trials was shown for different human tumours. However, a meaningful response was obtained in murine NSCLC, either alone or synergistically with **docetaxel** (Millward et al., 2012). Moreover, plinabulin presented a favourable safety profile evaluated by its half-life, clearance, and distributive volume in NSCLC patients (Mita et al., 2010). A Phase II study demonstrated that combined treatment of plinabulin and docetaxel promoted an increased OS rate and PFS in patients with advanced NSCLC, and more recently, the association of plinabulin with the anti-hPD1 **nivolumab** was tested for the treatment of five patients with recurrent or metastatic NSCLC, but the study was prematurely terminated because the immunotherapy was approved for NSCLC in the first-line setting (www.clinicaltrials.gov, accessed 10 August 2019).

5.3 | Marizomib

Salinosporamide A (Figure 1), also named NPI-0052 or marizomib, is a cytotoxic β-lactone-γ-lactam produced by the strictly marine bacterium *Salinispora tropica*. It was isolated in 2003 and its chemical structure, cytotoxic activity, and pharmacological targets described by Feling et al. (2003). The compound exhibited low-nM GI_{50} values on the NCI 60 cell line panel (Feling et al., 2003), and preclinical development was strongly favoured by the supply ensured by saline fermentation of the *S. tropica* wild strain itself, an unprecedented process for sourcing an active pharmaceutical ingredient (Tsueng, Teisan, & Lam, 2008). Genome sequencing of *S. tropica* allowed disclosure of the salinosporamide A peculiar biosynthetic pathway (Udwary et al., 2007), uncovering a new chlorination mechanism and a unique starter unit in polyketide biosynthesis, resulting in the production of this densely functionalized molecule (Eustáquio, Pojer, Noel, & Moore, 2008).

Salinosporamide A was then shown to be a novel **proteasome** inhibitor, differentiated from other drugs in this class. It also has interesting advantages that fulfil unmet clinical needs, such as enhanced potency, wider inhibition spectrum, and effectiveness against tumour cells resistant to clinically available proteasome inhibitors (Potts et al., 2011). The ubiquitin-26S proteasome complex contains a proteolytic 20S core comprising three pairs of catalytic subunits, which have caspase-, trypsin-, and chymotrypsin-like (CT-L) activities, where protein degradation occurs (Lowe et al., 1995; Sala et al., 2018). Salinosporamide A irreversibly inhibited all three catalytic functions of the 20S proteasome, with IC_{50} values ranging from low to mid nM (Feling et al., 2003; Potts et al., 2011). Peptide boronic acids, for example, bortezomib (Velcade) and delanzomib, block only the CT-L activity and in a slow and reversible fashion (Groll, Berkers, Ploegh, & Ovaa, 2006).

Translational studies have demonstrated the activity of marizomib against solid tumours and haematological malignancies as a single agent or in combination with clinically used drugs. As a single agent in in vivo models for haematological malignancies, such as MM, NHL, Waldenstrom's macroglobulinemia, ALL, AML, and chronic lymphocytic leukaemia (CLL), as well as in solid tumours, such as colon, glioma, and pancreatic cancer, this compound has been achieving good results (Potts et al., 2011; Sala et al., 2018). Studies in animal models using marizomib in combination with standard of care drugs confirmed the broad activity spectrum of this compound. Moreover, marizomib re-sensitizes resistant MM cells to apoptosis induced by chemotherapeutic and immunotherapeutic drugs. Particularly interesting results indicate an enhanced anti-MM activity of low-dose treatment of marizomib combined with bortezomib (Chauhan, Hideshima, & Anderson, 2006), revealing that this vertical combination targeting one oncogenic pathway at several levels provided greater inhibition. Additionally, marizomib displayed better results than bortezomib when used in combination with other treatments, for example, with immunotherapy and **histone deacetylase** inhibitors for ALL (Chauhan et al., 2010; Miller et al., 2009).

Marizomib entered clinical trials just 3 years after its discovery. To date, nine clinical trials, either alone or in combination with other cancer therapies, are listed with marizomib, among which four are still ongoing and wish to establish optimal practices for this agent. These studies include MM, refractory MM, relapsed MM, NSCLC, pancreatic cancer, melanoma, lymphomas, ependymoma, glioblastoma, and newly diagnosed glioblastoma (available from www.clinicaltrials.gov, accessed 25 January 2019), which seem to demonstrate this drug is well tolerated as monotherapy and in combination with other chemotherapy or radiotherapy. Marizomib exhibits wider, faster, and more durable proteasome inhibition than bortezomib without the limiting toxicities associated with the latter and other clinically approved proteasome inhibitors, such as neutropenia, thrombocytopenia, and peripheral neuropathy. Most side effects occurred in the early cycles of therapy and neither new nor cumulative toxicities were produced with longer periods of treatments (Potts et al., 2011; Richardson et al., 2016). The most common side effects related to marizomib administration were fatigue, nausea, vomiting, dizziness, diarrhoea, and pain at the infusion site (Harrison et al., 2016; Richardson et al.,

2016). Recently, a consortium comprising Celgene Corporation, Triphase Accelerator Corporation, and the European Organization for Research and Treatment of Cancer has sponsored Phase I and II clinical trials with marizomib in glioblastoma patients. Ongoing Phase II and III trials focuses on glioblastoma and MM (available from www.clinicaltrials.gov, accessed 25 January 2019).

5.4 | Plocabulin

Plocabulin, or PM060184 (Figure 1), is a polyketide currently under three clinical studies for cancer treatment. This tubulin inhibitor and its chlorinated analogue, PM050489, were isolated from the Madagascan sponge *Lithoplocamia lithistoides* (Martín et al., 2013; Pera et al., 2013). Based on the high success of anticancer drugs targeting tubulin, added to its powerful tubulin inhibition rates, this marine molecule has become a promising alternative to cancer treatment, and with some advantages over current antitubulin drugs. Plocabulin showed potent antitumour activity in a panel of tumour xenograft models, including MDA-MB-231 (breast), HCT-116 (colon), H-460 (lung), 22RV1 (prostate), HGC-27 (gastric) and Caki-1 (renal), and displayed particularly high cytotoxic against P-glycoprotein overexpressing cell lines. In these latter cells, paclitaxel and vinblastine lacked or had lower potency compared to PM060184. This feature supports the use of plocabulin in tumours resistant to antitubulin agents (Martínez-Díez et al., 2014).

Plocabulin binds, in a sub- or low-nM range, to a site different from than that of vinblastine, although it still affects binding of this drug. During mitosis, cells display multipolar figures and lagging chromosomes in the metaphase plate (Martínez-Díez et al., 2014; Pera et al., 2013). Still, upon interphase cells, these undergo disorganization and fragmentation of the microtubule network, along with the inhibition of cell migration. Additionally, PM060184 inhibits angiogenesis both in vitro and in vivo (Galmarini et al., 2018; Martínez-Díez et al., 2014).

Currently, there is one Phase I clinical trial completed and two ongoing studies in Phases I and II with PM060184 alone or in combination with other antitumour drugs in patients with advanced solid tumours (available from www.clinicaltrials.gov, accessed 25 January 2019). The finalized clinical study highlighted mild to moderate toxicities, such as abdominal pain, myalgia, fatigue, nausea, vomiting, and disease stabilization. Furthermore, myelosuppression was transient and manageable and the main dose-limiting toxicity (DLT) reported was an expected grade 3 peripheral sensory neuropathy (PSN). Other DLTs were tumour lysis syndrome and cardiac failure and myalgia (Elez et al., 2019). PM060184 has a half-life of ~4 hr and extensive diffusion to peripheral body tissues. Furthermore, antitumour responses were observed in cervix carcinoma and in pretreated metastatic NSCLC patients. Disease stabilization for longer than 3 months was observed in patients with colorectal, breast, thymic, and gastrointestinal stromal tumours, among others (Elez et al., 2019).

It is worth mentioning that the recent success of ADCs in the treatment of cancer has revitalized the interest in antitubulin drugs. As this strategy combines specificity and a dramatic decrease of toxicity, it enables the use of highly potent and otherwise unacceptably toxic compounds. In this sense, although PM060184 studies are only just beginning, they already have shown many properties and possibilities for a successful use in cancer treatment, in the future.

6 | CONCLUDING REMARKS

There is no doubt the oceans will play a fundamental role in society for the next decades and will provide new tools to face the health challenges affecting the world's population in the years to come. We have argued that MNPs may represent a renewed hope in drug discovery, as these have been applied for pharmacologically orphaned cancers, for the treatment of cancers with particular characteristics and have also overcome cases of tumour drug resistance. It is rather noticeable that four of the five marine-derived drugs that make up the anticancer arsenal have been approved over the past 12 years. This is, most certainly, a reflection of the advances of science and technology in multidisciplinary fields of knowledge, particularly in analytical chemistry and biology. Even though this review only discussed the successes, these marine molecules definitely illustrate the pharmacological potential that lies beneath the salty waters of our globe, which actually accounts for the largest section of our planet.

A global estimate of the value of anticancer marine pharmaceuticals yet to be discovered ranged from U$ 563 billion to U$ 5.69 trillion, considering the projected marine biodiversity in the oceans (Erwin, López-Legentil, & Schuhmann, 2010). It is still soon to presume whether this estimate is accurate, because, as discussed here, most of the marketed drugs were launched in recent years. For example, the sales of Yondelis amounted to €74.2 million in 2018 compared to €84.6 million in 2017, showing indeed a retraction of 12% (Annual Report 2018 available at www.pharmamar.com, accessed 10 August 2019), while Adcetris net product sales increased from U$ 307.6 million in 2017 to U$ 476.9 million in 2018, an increase of 55% (Annual Report 2018 available at www.seattlegenetics.com, accessed 10 August 2019). Halaven sales are also growing as the number of sarcoma patients using this therapy increased, especially in Japan (www.elsai.com, accessed 10 August 2019). As Aplidin was only approved on December 2018, data on yearly sales are not yet available.

As promising as these molecules may be, research and development of marine drugs have been afflicted by their share of difficulties. Collecting natural samples is not a simple task, as marine environments pose many abiotic and physiological restrictions to human assessment. Also, from a legal point of view, the collection of samples in international oceanic waters has been often discussed. In this context, the adoption of the Nagoya Protocol in 2010, established under the Convention of Biological Diversity from 1992, was an attempt to legitimize access to marine genetic resources, exploration, and benefit-sharing between the signatory countries (Lallier et al., 2014).

Natural samples and their derived extracts are chemically complex samples, as these consist of many different compounds from distinct chemical classes. Therefore, the yields of pure compounds that can be isolated from natural sources may be quite low. Besides, marine

natural products come, generally, in structural arrangements of high complexity, making the elucidation and synthesis or even semi-synthesis of such molecules a complicated process. Therefore, the supply of sufficient amounts of such compounds for bioassays and structure–activity relationships studies or for clinical trials is certainly one of most challenging issues to overcome. Additionally, the intrinsic toxicity of marine compounds is also an important issue to cope with. Understanding the pharmacophoric structural requirements of bioactive molecules is key for the development of improved anticancer drugs, furnished with enhanced efficacy, better selectivity, and minimum adverse effects. In this context, technology is probably the best ally in the effort to reduce toxicity, as witnessed in the successful stories of the ADCs (Senter & Sievers, 2012).

Still, to make a study ecologically viable, conscious researchers must be careful to collect a sufficient amount of each sample without endangering the existence of the species. Yet information on the conservation status for most marine species assessed in a drug discovery perspective is scarce, as these weigh largely towards fish and larger metazoans (Arrieta, Arnaud-Haond, & Duarte, 2010). To illustrate this point, an online search was done on The Red List of Endangered Species of the International Union for Conservation of Nature (IUCN) for species mentioned in the scope of this review—*E. turbinata*, *H. okadai*, *D. auricularia*, and *A. albicans*—and returned no results for any of these entries (Available from www.iucnredlist.org, accessed 5 March 2019).

Nevertheless, the predatory nature of field sampling of marine invertebrates used in the development of new medicines has significantly reduced their natural population due to oversampling. One important example is the halichondrin-producing sponges, where 600 kg of *H. okadai* was collected off the coast of Aburatsubo, in the Miura Peninsula of Japan (Hirata & Uemura, 1986); then, another 200 kg of *Lissodendoryx* sp. was taken from the Kaikoura Peninsula in New Zealand (Litaudon et al., 1994). In this context, there is increasing evidence of the important roles of the microbiota in the production of secondary metabolites by holobiont systems, including corals, ascidians, and sponges.

All these issues make marine-based drug development a time- and money-consuming endeavour. From compound discovery to marketing of the finished product has taken between 17 and 29 years, with an average of 23 years (examples in Figure 3). Molecules derived from microbial sources seem to speed up this process, as large-scale fermentation allows for the necessary supply to warrant preclinical and clinical studies, as seen with marizomib (Feling et al., 2003; Tsueng et al., 2008). Still, this shows the importance of investing in science as means to find creative and sustainable strategies to overcome these difficulties, as well as the disproportionate requirements for identifying a marketable product as a condition for granting support for MNP bioprospecting projects in the field of health sciences, once these projects have the duration of 3 to 5 years.

MNP research is improving and advancing, but it is still a risky, time-consuming, and costly endeavour. However, once even more life-saving drugs are added to this equation, the potential gains will surely outweigh the risks.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander, Fabbro et al., 2017a, 2017b; Alexander, Kelly et al., 2017a, 2017b).

ACKNOWLEDGEMENTS

The authors are grateful to FAPESP (Grants 2015/17177-6; 2017/09022-8, and 2017/17648-4), CNPQ, ArboControl Brasil Project (Grants FNS/UnB TED74/2016 and TED42/2017), FCT (Grant IF/00700/2014 to S.P.G.), and National Institute of Science and Technology – INCTBioNat (Grant 465637/2014-0). This work was supported by the Applied Molecular Biosciences Unit (UCIBIO), which is financed by national funds from FCT/MCTES (Grant UID/Multi/04378/2019).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Paula C. Jimenez https://orcid.org/0000-0002-5244-9761
Susana P. Gaudêncio https://orcid.org/0000-0002-5510-1170
Leticia V. Costa-Lotufo https://orcid.org/0000-0003-1861-5153

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How to cite this article: Jimenez PC, Wilke DV, Branco PC, et al. Enriching cancer pharmacology with drugs of marine origin. *Br J Pharmacol*. 2020;177:3–27. https://doi.org/10.1111/bph.14876