DRUG report

Log Off

lexibulin (iv infusion, cancer), YM BioSciences

Company	**Cytopia Ltd**
Highest Dev Status	Phase 2 Clinical
Indications	Multiple myeloma Glioblastoma Solid tumor
Actions	Microtubule inhibitor Vascular damaging agent Tubulin binding agent Cell cycle inhibitor
Technologies	Intravenous formulation Infusion Small molecule therapeutic

Related information
COMPANY
REFERENCES
NEWS
PATENT
Actions
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Suggestions
EDIT REPORT

Reason for update on 08 December 2011

Literature Evaluation Amended , 1 Reference Added [**1247053**]

Summary

YM BioSciences, following its February 2010 acquisition of **Cytopia** [**1072065**], is developing an iv infusion formulation of lexibulin (CYT-997; structure shown), a vascular targeting agent and tubulin inhibitor, for the potential treatment of solid tumors, particularly glioblastoma multiforme (GBM), and other cancers [**580594**], [**672062**], [**840664**]. In September 2008, a phase Ib/II trial for relapsed GBM began [**940610**]; in September 2011, preliminary data were expected in the first half of 2012 [**1225132**]. In June 2005, a phase I trial for solid tumors began [**672062**]; in September 2010, results were published [**1129172**], [**1129430**].

Cytopia was also developing the drug for the potential treatment of multiple myeloma (MM) and in December 2007, the company initiated a phase II MM trial in Australia [**857553**], [**885409**]. However, by October 2010, YM listed the MM trials as on hold [**1139265**].

The company is also developing an oral formulation of **lexibulin**.

REGULATORY INFORMATION
In March 2008, the company planned to file an Orphan Drug Designation application in the US for lexibulin in multiple myeloma within three months [**885409**].

CLINICAL DATA
Glioblastoma multiforme
In March 2008, the company was planning to begin a phase I/II trial in patients with GBM in the second quarter of 2008. Lexibulin would be administered in combination with two other anticancer drugs. The phase Ib portion would establish the optimal safety dose of lexibulin when administered with chemotherapy. The 18-month study would be conducted in the UK , US and Australia and was expected to enroll up to 30 patients. Interim data was anticipated in June 2009. At that time, the company was also investigating the feasibility of a phase II trial in patients with mesothelioma [**885409**]. In September 2008, enrollment in a phase Ib/II trial for relapsed GBM began. In the multicenter, Australian and US (CCL08001) trial, 35 patients would receive a 24-h infusion of up to 200 mg/m2 of lexibulin on day 2 of a 21 day cycle, plus carboplatin and etoposide. The primary endpoints of the phase Ib and II stages were safety and tolerability, and

progression-free survival at 6 months, respectively. Secondary endpoints included objective response rate, overall survival, safety, tolerability, pharmacodynamics and pharmacokinetics. At that time, the study was expected to be completed in the second quarter of 2010 [**940610**]. In August 2009, further protocol details were given. In the phase Ib segment, patients were to receive escalating doses between 100 and 150 mg/m2. A dose was to be selected from this segment and used in the phase II segment of the study [**1050474**]. In October 2009, Cytopia was cleared by the Australian Health Ethics Committee to begin dosing at a fourth study site, the Gold Coast Hospital in Southport, Queensland. The company was also expecting to file the requisite regulatory submissions to the Medicines and Healthcare Products Regulatory Agency (MHRA) to allow the treatment of patients at a site in the UK and possibly at additional sites in North America [**1050320**]. By January 2010, dose escalation in the phase Ib portion of the trial was ongoing. At that time, the phase II segment was expected to commence in the first half of 2010 [**1068089**]. In September 2010, phase II data were expected in the second quarter of 2011 [**1129172**]. In February 2011, preliminary data were expected in the second half of 2011 [**1167216**]. By March 2011, enrollment was completed [**1225132**]. In September 2011, preliminary data were expected in the first half of 2012 [**1225132**].

Multiple myeloma
In August 2007, Cytopia reported that it planned to initiate a phase II program later in the year [**815504**], [**821269**]. In October 2007, the company was planning to initiate a phase II MM study by the end of 2007. At that time, the company planned to start phase II studies for other cancers in 2008 [**840664**]. In December 2007, the company gained regulatory approval and started a 24-patient, open-label, single-arm trial (CCL07001) for MM. The study would assess the safety and tolerability of 24 h iv infusions of 202 mg/m2 of lexibulin administered on days 1 and 8 of a 21 day cycle. The primary endpoint would be the overall response rate, secondary endpoints would include time-to-progression, overall survival and the number of cycles required to achieve maximum response [**857553**], [**861786**], [**885409**]. By March 2008, the company expected to start interim data analysis by September 2008 [**885409**]. In September 2008, enrollment was ongoing [**940610**]. Dosing in the trial began in November 2008. At that time, enrollment at a second Australian site was expected to start within weeks. The company also planned to file regulatory submissions for two further sites to begin in early 2009 and was considering foreign sites for later stages of the study [**963858**].

Solid tumor
By March 2005, Cytopia had filed an IND for a phase I study in Australia [**789194**]. In April 2005, Cytopia received approval to begin a phase I trial of lexibulin. The trial was scheduled to start in May 2005 and run for 9 to 12 months. The non-blinded, dose-escalation, Australian study would dose up to 30 patients with advanced incurable solid tumors by once every 3 weeks for up to 6 cycles; the agent was still intended for final development in its oral form at that time [**598060**]. The trial started in June 2005 [**672062**]. By August 2006, 17 patients had received 48 doses at 6 dose levels. The trial was to continue until the MTD had been reached, expected to be during 2007 [**733807**], [**789166**]. In May 2007, MTD was reached and dose escalation was stopped [**795981**]. In August 2007, Cytopia reported preliminary data from the trial. The drug was found to be safe and well tolerated and the MTD was 358 mg/m2. In total, only two dose-limiting toxicities were seen; prolonged QTc intervals and hypoxia/dyspnoea. At that time, several patients remained on study and analysis of the data was ongoing in order to determine a recommended dose for phase II studies [**821269**]. Later in the month, the company announced that the trial was complete [**821859**], [**830681**]. Full results were reported in November 2007. Seven of the 31 enrolled patients completed 6 therapy cycles and 2 completed 5, suggesting disease stabilization for over 3 months. Two patients with symptomatic progressive disease at the start of the trial had disease stabilization at six cycles and continued to receive the drug. Of the 22 evaluable patients, 17 had stable disease and 5 had progressive disease. Median tumor blood flow was disrupted in seven patients and patients receiving =/>152 mg/m2 of the drug showed increases in circulating von Willebrand factor. Lexibulin was well tolerated [**851095**]. In June 2008, similar data were presented at the 44th ASCO annual meeting in Chicago, IL. Results from the study also recommended a 202 mg/m2 dose for phase II evaluations [**913440**]. In September 2010, similar results were published [**1129172**], [**1129430**].

PRECLINICAL DATA
In March 2008, the company was planning to conduct preclinical combination studies of lexibulin with 5-fluorouracil [**885409**].

In October 2007, Cytopia presented positive preclinical data. Lexibulin was shown to have favorable effects in myeloma cells, including cell division inhibition, and the drug was able to overcome a specific mechanism of

myeloma cell resistance. Lexibulin caused myeloma cell death, even in treatment-resistant cells; the drug also had synergistic effect with other drugs [**840664**].

In April 2005, preclinical data on lexibulin were presented at the 96th AACR meeting in Anaheim, CA. Lexibulin dose-dependently inhibited tubulin polymerisation. Lexibulin inhibited proliferation in vitro of a range of cancer cells with IC50 values in the low nanomolar range, for example, 34 nM in MES-SA uterine sarcoma cells. Lexibulin left only a rim of proliferating cells, with a necrotic core when administered orally at 80 mg/kg twice-weekly doses. Lexibulin, when administered orally at maximum tolerated dose, significantly reduced tumor volume in a syngeneic mouse model of breast cancer. Oral lexibulin (30 mg/kg qd, 70 mg/kg thrice weekly or 80 mg/kg twice weekly) was compared to iv paclitaxel (10 mg/kg, thrice weekly) in a murine model of breast cancer. All doses of lexibulin reduced tumor volume, whereas tumor volume was unchanged relative to control for the paclitaxel group. In a murine model of colon cancer metastasized to the liver, lexibulin (5, 10 or 15 mg/kg/day ip) reduced tumor volume relative to control [**596486**].

In preclinical studies completed by February 2005, nanomolar concentrations of lexibulin were found to significantly inhibit tumor growth without adverse effects [**581323**].

ADDITIONAL INFORMATION
WO-2005054199 and WO-2006133498 filed by Cytopia Ltd specifically relate to a microtubule polymerization modulator, lexibulin. The compound was also claimed in WO-2005054199.

In November 2004, lexibulin was accepted into **Cancer Research UK**'s clinical trial program. Under the agreement, Cancer Research UK would assist Cytopia with the preclinical development and phase I trial of lexibulin [**581323**].

Development Status HISTORY

Detailed status for **YM BioSciences Inc**

Indication	Country	Status	Reference	Date
Glioblastoma	Australia	Phase 2 Clinical	**1072065**	01 - Feb - 2010
Glioblastoma	US	Phase 2 Clinical	**1072065**	01 - Feb - 2010
Multiple myeloma	Australia	Suspended	**1139265**	13 - Oct - 2010
Solid tumor	Australia	Phase 1 Clinical	**1072065**	01 - Feb - 2010

Deals

Summary **[Deal Report]**

Primary company	**Cytopia Ltd**
Partnering company	**Cancer Research UK**
Deal type	Drug - Development Services
Start date	22-Nov-2004

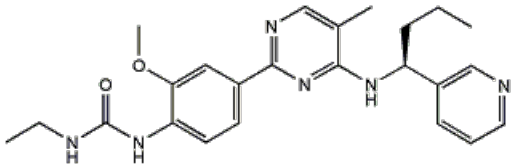
Overview

In November 2004, **Cancer Research UK** would assist **Cytopia** with the preclinical development and a phase I trial of **CYT-997** [**581323**].

Chemistry

Structure

VIEW MOLFILE



Confidence Level : 2

Compound names associated with this drug

Name	Type
CYT-997 (iv infusion, cancer), Cytopia	
vascular disrupting agent/ tubulin inhibitor (iv, cancer), Cytopia	
VDA anticancer program (iv), Cytopia	
lexibulin (iv infusion, cancer), YM BioSciences	
917111-44-5	CAS RN
CYT-997	Research Code
lexibulin	PINN,USAN
CYT-997 (iv infusion, cancer), YM BioSciences	
vascular targeting agent/ tubulin inhibitor (iv, cancer), Cytopia	

Literature evaluation

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Submission date: 10 November 2011
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Abstract
Lexibulin is a small-molecule tubulin-depolymerizing agent that is being developed by **YM BioSciences** as a vascular-disrupting agent (VDA) for the potential treatment of cancer. In vitro cell culture and in vivo tumor models established that lexibulin has vascular-disrupting activity. Lexibulin is currently undergoing clinical development and can be administered either intravenously or orally. In two phase I clinical trials in patients with solid tumors, lexibulin induced changes in tumors that were consistent with vascular disruption and associated blood-flow modifications. Pharmacokinetics of lexibulin were favorable and generally dose-linear for both the oral and intravenous formulations. The side-effect profile of lexibulin was similar to that of other VDAs and included cardiovascular, respiratory and hematological toxicities. Lexibulin was also to be assessed in a phase Ib/II trial in combination with **carboplatin** in patients with relapsed glioblastoma multiforme and a phase II trial as monotherapy in patients with multiple myeloma. However, both trials were terminated, although preliminary efficacy results are available for the combination trial. At the time of publication, lexibulin remained listed as being in phase II development on **YM BioSciences**' pipeline.

Introduction
The importance of vascular networks in sustaining tumor growth and metastasis was realized several decades ago, leading to the idea of targeting the tumor vasculature for therapy [**1239989**]. Tumor blood vessels are both architecturally and functionally distinct from those in normal tissues [**1239990**]. In the tumor, a high proportion of endothelial cells are proliferating, and blood vessels are immature, poorly covered in pericytes, and highly disorganized and tortuous [**1239991**], [**1239992**]. Furthermore, tumor blood vessels have unstable and leaky junctions, and interstitial fluid pressure is high as a consequence of elevated permeability. In addition, in the tumor, blood flow is impaired and intermittent, leading to defective oxygenation and hypoxia. These distinct features of the tumor microenvironment contribute to resistance to standard

anticancer therapies, such as chemotherapy, but can also be exploited for therapeutic intervention [**1239991**], [**1239992**].

Indeed, the last few decades have seen an explosion in the development of antiangiogenic agents for the treatment of cancer. A main focus has been on developing agents that target VEGF and its receptors, and several anti-VEGF therapies are now in the clinic, such as the anti-VEGF mAb bevacizumab, and the small-molecule inhibitors **axitinib** and **sorafenib** [**1239995**], [**1240269**]. In recent years, a novel and distinct approach to target tumor vessels has emerged through the development of low-molecular-weight tumor vascular-disrupting agents (VDAs) with selectivity for already established tumor blood vessels [**1239996**]. VDAs cause severe interruption to tumor blood flow, which is followed by secondary necrosis of the tumor mass. Two main families of VDAs have entered clinical development; these are the synthetic flavonoids (initially led by the flavone acetic acid analog **vadimezan** until its recent discontinuation [**1164001**]) and the larger family of tubulin-binding agents [**1240003**], [**1240006**], [**1240022**]. The clinical activity of tubulin-binding agents, such as the taxanes and vinca alkaloids, against solid tumors and hematological malignancies was firmly established [**1188122**], [**1240031**] before drugs belonging to this family had been explored as tumor VDAs [**509776**], [**1240022**]. Drugs, such as the taxanes, that act by stabilizing microtubules and preventing their depolymerization, have been widely used for the last few decades for the treatment of cancers, including ovarian, lung and breast cancers, while the vinca alkaloids, which disrupt and destabilize microtubules, have been used mainly for the treatment of leukemias and lymphomas [**1188122**], [**1240031**]. Both microtubule-stabilizing and microtubule-destabilizing agents are antimitotic agents, interfere with microtubule dynamics and mitotic spindle assembly, inhibit tumor cell proliferation, and induce G2/M cell cycle arrest and apoptosis [**1188122**], [**1240031**]. These actions undoubtedly relate to their chemotherapeutic properties. A main focus of vascular targeting has been the development of novel microtubule-destabilizing agents that target tumor endothelial cells irrespective of their stage in the cell cycle. Also, drugs such as the vinca alkaloids vinblastine and vincristine or the taxane **paclitaxel** induce vascular damage but do so at doses that are close to the MTD [**166479**], [**1239996**]. However, several microtubule-depolymerizing VDAs, which bind to the colchicine or vinca alkaloid binding sites of tubulin, were found to have vascular activities at doses well below the MTD, and are now in clinical development or being tested in preclinical models [**509776**], [**1239996**].

Combretastatin A4 and its synthetic phosphate derivative **fosbretabulin** (**OXiGENE**) was the first VDA to enter clinical trials [**509761**], [**509762**], [**1240049**] and is currently undergoing phase II/III testing [**1240047**]. Other microtubule-destabilizing VDAs in phase I, II or III clinical development include the synthetic combretastatin analog **ombrabulin** (**Sanofi**) [**1166869**], [**1240051**], the 4-arylaminoquinazoline **verubulin** (**Myrexis**) [**1159928**], [**1237258**], the diketopiperazine **plinabulin** (**Nereus Pharmaceuticals**) [**1156855**], [**1222688**], the sulfonamide **ABT-751** (**Abbott Laboratories**) [**1178586**], the combretastatin A1 phosphate **OXi-4503** (**OXiGENE**) [**1240056**], [**1240047**], the benzofuran **BNC-105** (**Bionomics**) [**1110667**], [**1228091**] and the benzimidazole carbamate **denibulin** (**MediciNova**) [**1208433**], [**1240061**].

Studies using a wide range of preclinical models have demonstrated that VDAs act by causing an almost instant drop in blood flow and collapse of tumor vessels, effects that become maximal within 1 to 4 h post-treatment [**1239996**]. A rapid rise in tumor vascular permeability is also typical of VDA activity in vivo [**1240064**], [**1240065**]. In the experimental setting, vessel collapse and changes in blood flow and permeability can be visualized and assessed by various techniques, including intravital microscopy, laser Doppler flowmetry and via infusion of fluorescent vascular reporters [**1240150**]. Although variable vascular responses have been described, which are dependent on drug type, dose and tumor type, sensitive tumors exhibit a robust reduction in blood flow and perfusion, which is sustained for at least 24 h and translates into hemorrhage and extensive secondary central necrosis [**1239996**]. These effects are specific for the tumor, as normal tissues do not undergo necrosis and only modest blood-flow effects have been observed in normal tissues at doses that are effective in tumors [**388986**], [**388988**], [**1240202**]. In the clinical trials, vascular activity and tumor-specific changes in vascular perfusion were demonstrated by dynamic contrast enhanced MRI (DCE-MRI; the methodology of choice for the assessment of tumor microcirculation) techniques [**509762**], [**1240203**].

The reasons for the tumor selectivity of VDAs are not clear. None of the VDAs selectively bind to the tumor vasculature but, nevertheless, the tumor vasculature is highly susceptible to their disrupting activities. Currently, it is thought that immature blood vessels in the tumor with unstable endothelial junctions and with fewer and abnormal associated pericytes are easier to collapse than more stable vessels residing in normal

tissues [**1240204**]. In addition, the cytoskeleton of immature proliferating endothelial cells within the tumor could be more sensitive to VDA disruption than the cytoskeleton of non-proliferating cells in normal tissues [**469816**]. Differences in susceptibility could be a result of the expression of specific tubulin isotypes or posttranslational modifications in actin or microtubule regulatory proteins [**1043476**]. Nevertheless, to date, there is no evidence to suggest that such differences in cytoskeletal proteins exist between normal versus tumor endothelial cells.

Despite causing catastrophic vascular damage and extensive necrosis, VDAs almost always fail to prevent tumor growth when administered as a single dose [**1240207**]. Even with more frequent dosing, tumors re-grow rapidly after treatment is withdrawn. Although VDAs are very effective in driving necrosis in the central regions of experimental tumors, blood vessels and tumor cells in the outer tumor rim demonstrate resistance and thus contribute to the re-growth of the tumor [**1240207**]. An explanation for this resistance is that cells in the outer rim survive because they have access to oxygen and nutrients diffusing from surrounding normal tissues. Indeed, some studies demonstrated that the rim remains resistant despite prolonged disruption of blood flow and perfusion [**1243912**]. Other studies, however, indicated that blood flow is less affected in the tumor periphery than in the center [**388986**], [**1240202**]. It may be that the more complex vessel networks that often exist in the periphery of tumors are more difficult to shutdown and therefore some residual flow persists in this region.

In the preclinical setting, combinations of VDAs with conventional chemotherapeutic drugs or radiation significantly enhanced VDA responses without increasing toxicity [**1240209**]. Enhanced responses are thought to be at least in part caused by the targeting of both the tumor cells and the vasculature. In addition, chemotherapy and radiotherapy are more effective when tissues are well oxygenated, and therefore could be enhancing VDA activity by targeting the resistant viable rim. A lot of emphasis has been placed on determining the optimal sequence for administering combined modalities [**470266**], [**595357**], [**1240209**]. Chemotherapy, on the whole, works best if administered first so that it reaches the tumor before blood flow is interrupted [**820391**]. Similarly, the best outcomes with radiotherapy were observed if the VDA was administered after radiotherapy [**470266**]. This scheduling ensures that the radiation can act on oxygenated regions of the tumor before the VDA induces hypoxia. Improved VDA activity was also observed in several preclinical studies that combined VDAs with antiangiogenic agents [**692739**], [**936190**]. By inducing hypoxia, VDAs induce a robust angiogenic response post-treatment, as detected by elevated expression of angiogenic growth factors and recruitment of endothelial progenitor cells and macrophages to the tumor, which could be contributing to treatment resistance [**692739**], [**1240221**]. Therefore, targeting a new burst of angiogenesis following VDA treatment could be important in overcoming treatment resistance. Based on these preclinical findings, the majority of current phase II/III clinical trials of VDAs are now focused on testing combination therapies in an attempt to address the issue of treatment resistance. Of note, in the clinical setting, radiotherapy is generally delivered in multiple fractions over several weeks, therefore careful scheduling is needed to ensure clinical success when radiotherapy is combined with VDAs. To date, some clinical combination trials, such as a trial combining **fosbretabulin** with **carboplatin** and **paclitaxel**, have already reported favorable responses [**1102131**], [**1240225**].

Although a growing number of VDAs are being tested in the clinic, the molecular mechanisms responsible for their activities are not clearly understood. The cytoskeleton of endothelial cells is thought to be the main target of microtubule-depolymerizing VDAs. Studies on endothelial cells have indicated that these agents caused disruption of microtubules and morphological and functional changes, including remodeling of the actin cytoskeleton, changes in cell morphology with rounding up and blebbing, disruption of vascular-endothelial-cadherin junctions and an increase in permeability [**469816**], [**1078679**], [**1240228**], [**1240232**]. These morphological and functional alterations result from activation of Rho-GTPase signaling, as demonstrated by studies on **fosbretabulin** [**1240228**], [**1240241**], and occur within minutes of drug exposure, thus correlating with the rapid onset of vascular shutdown observed in the tumor in vivo [**1240064**]. Although the exact molecular mechanisms through which VDAs cause vascular collapse in vivo are poorly defined, an increase in vascular permeability as well as rounding and blebbing of endothelial cells could in principle obstruct blood flow in the tumor [**1239996**]. In addition, rounding up and detachment of endothelial cells could expose the basement membrane and initiate coagulation. Indeed, coagulation was demonstrated after 1 h of treatment with **fosbretabulin** and may contribute toward sustained vascular shutdown [**1240202**]. However, it is unlikely that coagulation is the initial trigger of vascular shutdown as the early tumor vascular response to **ombrabulin** was unaffected by treatment with anticoagulants [**388982**].

Microtubule-depolymerizing VDAs have also been explored for their potential use as antiangiogenic agents [**1240244**]. Antiangiogenic activity has been suggested in studies where a larger growth delay was observed with VDAs administered via metronomic scheduling with more frequent split doses [**509777**]. The mechanisms through which tubulin-binding agents inhibit angiogenesis are likely to be different from those involved in vascular disruption. Generally, microtubule-depolymerizing VDAs are effective as antiangiogenic agents when used at low concentrations and interfere with endothelial processes involved in angiogenesis, including migration and differentiation into capillary like structures [**1240244**].

The search for new VDAs with improved antitumor activity and reduced toxicity is ongoing. Lexibulin is a novel synthetic tubulin-depolymerizing agent discovered by **Cytopia** Research and is currently being developed by **YM BioSciences**, following its acquisition of **Cytopia** [**1072065**], for the potential treatment of cancers [**1240194**]. Lexibulin can be administered both intravenously and orally [**1240194**]. In preclinical studies, lexibulin exhibited vascular-disrupting and cytotoxic activities in solid tumor and multiple myeloma models [**1061150**], [**1152799**], [**1233876**]. In patients with solid tumors in phase I clinical trials, lexibulin induced changes in tumors that were consistent with vascular disruption and associated blood-flow modification [**1009368**], [**1129430**]. Lexibulin was also to be assessed in a phase Ib/II trial (ClinicalTrials.gov identifier: NCT00650949) in combination with **carboplatin** in patients with relapsed glioblastoma multiforme and a phase II trial (NCT00664378) as monotherapy in patients with multiple myeloma. At the time of publication, both trials had been terminated, but lexibulin remained listed on **YM BioSciences**' pipeline as being in phase II development [**1240194**].

Synthesis and SAR

Cytopia developed lexibulin through screening of a small-molecule library for antiproliferating activity on DU145 and PC3 prostate cancer cell lines [**986847**], [**1030535**]. The screening identified 2-((S)-alpha-methylbenzylamino))-6-(4-hydroxy-3-methoxyphenyl)pyrazine as an initial lead having potent antiproliferative activity against these tumor cell lines. Subsequent SAR demonstrated that cellular activity was significantly enhanced when the chain length of the alkyl substituent on the benzylic carbon was increased, specifically a propyl chain increased potency by 15- and 50-fold on DU145 and PC3 cells, respectively. Further SAR studies of the benzylic group demonstrated that replacing the phenyl ring with a 3-pyridyl ring produced compounds with comparable potency and reduced lipophilicity. Investigation on the substitution pattern of the 6-aryl group indicated the requirement of a 3,4-substitution, but although a 4-hydroxy group was essential for retention of potency, the 4-hydroxyl group resulted in limited oral bioavailability because of glucuronidation. Subsequent modification of the lead with phenolic isosteres led to an ethyl urea derivative that was metabolically stable. The (S)-enantiomer of the ethyl urea lead was highly active in DU145 and PC3 cellular assays (IC50 = 4 and 3 nM, respectively), caused disruption of the cellular microtubule network, led to G2/M cell cycle arrest and inhibited purified bovine tubulin polymerization at 3 microM. However, poor pharmacokinetics and low aqueous solubility limited the usability of this compound. Further SAR of the core heteroaromatic ring identified that replacement of the 2,6-disubstituted pyrazine with 4,6-disubstituted pyrimidine or 2,4-disubstituted pyrimidine improved aqueous solubility and maintained antiproliferative effects. Introduction of an additional methyl substituent on the pyrimidine ring led to the discovery of lexibulin (1-ethyl-3-[2-methoxy-4-[5-methyl-4-((S)-1-pyridin-3-yl-butylamino)-pyrimidin-2-yl]phenyl]urea), which was chosen for further development [**1030535**].

Lexibulin was synthesized via palladium catalyzed Suzuki-Miyaura reaction of 2-chloro-5-methyl-N-[1(S)-(3-pyridyl)butyl]pyrimidin-4-amine with N-ethyl-N'-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea [**1030535**]. The starting 2-chloropyrimidine was prepared from nicotinic acid, which was converted to the Weinreb amide and then treated with butylmagnesium chloride. The resultant butanone intermediate was reduced asymmetrically with borane-dimethyl sulfide in the presence of a chiral pyrrolidine catalyst, converted to the (S)-amine derivative and reacted with 2,4-dichloro-5-methylpyrimidine. Palladium tetrakis(triphenylphosphine) was added to a mixture of the starting 2-chloropyrimidine, the starting phenyl boronate and aqueous sodium carbonate in degassed toluene, then the mixture was refluxed for 44 h and worked-up to give lexibulin in 60% yield. For multigram synthesis the production of the (S)-amine intermediate via the reduction route was not viable, so it was prepared from the racemate, followed by resolution with mandelic acid [**1030535**]. Similar processes were also described in WO-2005054199, and data on different salts were published in WO-2006133498.

Preclinical development

In vitro

Lexibulin prevented the polymerization of tubulin in a biochemical assay with an IC50 of 3 microM and was established as a tubulin-depolymerizing agent [**1061150**]. Treatment of A549 human lung carcinoma cells with lexibulin (1 microM) and treatment of KMS-12-PE human myeloma cells with lexibulin (50 nM) caused reversible disruption of interphase microtubules, as visualized by diffuse and disorganized tubulin in the cytoplasm using immunofluorescence [**1061150**], [**1152799**]. Lexibulin inhibited the viability and proliferation of > 20 different human cancer cell lines, including DU145 cells, Ramos human Burkitt's lymphoma cells, A375 human melanoma cells, HCT15 human colon carcinoma cells, A431 human epithelial carcinoma cells, BT20 human breast carcinoma cells and several myeloma cell lines, with IC50 values ranging from 10 and 100 nM, with the exception of U266 human myeloma cells that were resistant with an IC50 of 1 microM [**1061150**], [**1152799**]. Lexibulin was effective in inhibiting the proliferation of HCT15 cells, which are known to express multidrug resistance P-glycoprotein [**591446**], suggesting that this efflux pump was not adversely influencing the activity of lexibulin [**1061150**].

Consistent with its tubulin binding actions, lexibulin (1 microM) induced mitotic arrest as evidenced by the accumulation of tumor cells in the G2/M phase of the cell cycle (19 versus 43% of A431 cells at G2/M at 24 h after vehicle and lexibulin, respectively) and an increase in the level of cyclin B1 protein (a cell-cycle regulated protein expressed during G2 and M phases; assessed by Western blot analysis in A549 cells compared with vehicle-treated cells) [**1061150**]. In addition, lexibulin (1 microM) induced apoptosis as demonstrated by the cleavage of caspase 3 and PARP (assessed by Western blot analysis in PC3 and A549 cells compared with vehicle-treated cells), an increase in binding of the apoptosis marker Annexin V (~ 12 versus 46% Annexin V positive A549 cells at 24 h after DMSO and lexibulin at 0.25 microM, respectively) and an increase in phosphorylation of Bcl-2 (which initiates apoptosis; assessed by Western blot analysis in A549 cells compared with vehicle-treated cells) [**1061150**]. These studies established that lexibulin disrupts both interphase microtubules and mitotic spindles, and causes mitotic arrest and apoptosis in tumor cells similar to other microtubule depolymerizing VDAs, including **fosbretabulin** [**509778**], [**1146963**], [**1240246**].

Similar results of mitotic arrest and apoptosis induction with lexibulin (50 nM) were observed in multiple myeloma cells [**1152799**]. Interestingly, lexibulin (100 nM) was effective in inducing apoptosis (10 to 58%) in CD38+CD45- cells isolated from four patients with multiple myeloma who previously failed to respond to other treatments, suggesting that lexibulin may be useful for this disease. The potential of lexibulin for the treatment of multiple myeloma was further suggested by in vitro experiments assessing lexibulin in combination with other conventional therapeutic drugs, including cisplatin, dexamethasone and the proteasome inhibitor **bortezomib**. All tested drugs exhibited synergism with lexibulin in inducing apoptosis, with **bortezomib** having the largest synergy; in particular, **bortezomib** (10 nM) combined with lexibulin (25 nM) resulted in synergy combination indexes of < 0.7 in U266 cells [**1152799**].

Vascular activity for lexibulin was demonstrated through in vitro experiments using cultured endothelial cells and results were compared to the activity of the lead VDA **fosbretabulin** [**1061150**], [**1233876**]. Lexibulin inhibited the proliferation of VEGF-stimulated HUVECs with an IC50 of ~ 4 nM, which was equally effective as **fosbretabulin** [**1233876**]. HUVEC monolayer permeability was also assessed, as a measure of the vascular-disrupting activity of the drug, and lexibulin induced a rapid rise in permeability with an IC50 of 80 nM at 1 h after exposure [**1061150**]. Lexibulin (10 to 100 nM) also induced a rapid change in endothelial cell morphology (visualized using microscopy), with cells rounding and exhibiting membrane blebbing [**1233876**]. The effects observed with lexibulin in these studies were similar to those previously reported for **fosbretabulin** and other VDAs [**510186**], [**1110667**], [**1240228**], [**1240232**], [**1240248**].

In vivo
The antitumor activity of lexibulin was investigated using several in vivo models [**596486**], [**1058455**], [**1061150**], [**1152799**], [**1233870**]. In established PC3 xenografts grown in nude mice, lexibulin (2.5, 5 or 10 mg/kg po, tid) was compared with **paclitaxel** (10 mg/kg iv, tiw) [**1061150**]. Because the 30-mg/kg/day lexibulin dose was too toxic (discussed in the Toxicity section), a 25-mg/kg/day lexibulin dose was used. A dose-dependent inhibition in tumor growth was observed with lexibulin and the 25-mg/kg/day dose resulted in similar growth inhibition to that observed with **paclitaxel** (on day 20 after treatment initiation, tumor volumes were ~ 760, 650, 480, 260 and 250 mm3 for vehicle, 7.5, 15 and 25 mg/kg/day of lexibulin and **paclitaxel**, respectively). When lexibulin (at the same dosing regimen) was administered to 4T1 murine breast cancer tumors implanted in the mammary fat pad of syngeneic female BALB/c mice, treatment also resulted in significant inhibition of tumor growth and was similar in efficacy at the highest lexibulin dose to that observed with cisplatin (7.5 mg/kg iv, qw); tumor volumes on day 12 after treatment were ~ 1400, 1250, 1200, 700 and 500 mm3 for vehicle, 7.5, 15 and 25 mg/kg/day of lexibulin and cisplatin, respectively

[**1061150**]. Different dosing schedules of **oral lexibulin** (30 mg/kg/day, 80 mg/kg biw or 70 mg/kg tiw) were compared with **paclitaxel** (10 mg/kg iv, tiw) in BALB/c mice xenografted with 4T1 cells. After 14 days of treatment, lexibulin significantly reduced tumor volumes (457, 415 and 381 mm3 for 30 mg/kg/day, 80 mg/kg biw or 70 mg/kg tiw, respectively) compared with water-treated controls (969 mm3; $p < 0.05$ for all lexibulin doses), but **paclitaxel** had no antitumor effect (tumor volume = 971 mm3) [**596486**], [**1061150**], [**1233870**]. In another model of 5T33 multiple myeloma cells inoculated in syngeneic C57BL/KaLwRij mice, lexibulin (15 mg/kg/day ip for 10 days) prolonged survival, with a median survival of 33 versus 22 days for saline-treated control mice ($p = 0.00097$) [**1152799**]. Additionally, the antitumor activity of lexibulin (10 mg/kg/day po) in combination with cisplatin (6 mg/kg qw) was assessed in subcutaneous DLD1 human colon adenocarcinomas in BALB/c mice. A very modest increase in growth delay of adenocarcinomas was observed with the combination (2.7 days) compared with lexibulin (1.8 days) and cisplatin (1.9 days) alone [**1058455**], [**1152804**].

Lexibulin was also tested in a liver metastasis mouse model of colon carcinoma [**596486**], [**1233870**], [**1233876**], previously used to evaluate the vascular-disrupting and antimetastatic properties of **fosbretabulin** [**413761**]. Administration of lexibulin (5, 10 and 15 mg/kg/day ip), starting 9 days after intrasplenic injection of murine-derived dimethyl hydrazine (DMH) colon carcinoma cells to CBA mice, resulted in a significant dose-dependent reduction in the volume and percentage of liver metastases, with some livers being tumor free after the 10- or 15-mg/kg/day dose [**1233876**], which is consistent with reports for other VDAs [**413761**], [**1240252**]. At 11 days after treatment initiation, the average liver weight was ~ 2.5, 2.0, 1.6 and 1.4 g in mice receiving vehicle, 5, 10 and 15 mg/kg/day of lexibulin, respectively ($p < 0.001$, < 0.05 and < 0.001 for 5, 10 and 15 mg/kg/day of lexibulin, respectively, versus vehicle) and the percentages of liver volume occupied by metastases were ~ 40, 30, 7 and 2%, respectively ($p < 0.005$, < 0.001 and < 0.001, respectively) [**1233876**].

The DMH liver metastasis model was used to investigate the vascular activity of a single dose of lexibulin (7.5 mg/kg ip, which is equivalent to < 30% of its MTD) [**596486**], [**1233870**], [**1233876**]. This dose caused disruption of the architecture of the vasculature of metastatic nodules 6 h after treatment, as observed by scanning electron microscopy of resin casts. In tumors, vessels were absent in some areas, while others were damaged and disrupted. The investigators also reported that they obtained similar data with 100 mg/kg of **fosbretabulin** (a dose equivalent to 20% of its MTD) [**1233876**].

Vascular-disrupting activity of lexibulin was also assessed by laser Doppler flowmetry in the DMH model [**596486**], [**1061150**], [**1233870**]. Compared with vehicle-treated mice, blood flow in liver metastasis was significantly decreased at 6 h after a single dose of lexibulin (7.5 mg/kg ip; 2-fold decrease; $p < 0.01$) or a single dose of **fosbretabulin** (100 mg/kg; 3-fold decrease; $p < 0.001$). Blood flow was also reduced after a 20-mg/kg oral dose of lexibulin, with a more pronounced effect at 15 min after treatment ($p = 0.0008$ versus vehicle) than at 6 h ($p = 0.03$ versus vehicle) [**1061150**].

Vascular-disrupting activity was also established for lexibulin in subcutaneous DLD1 adenocarcinomas in BALB/c mice by assessing the vessel perfusion using fluorescent Hoechst 33342 dye [**1058455**], [**1152804**], [**1233876**]. A single oral dose of lexibulin (40 mg/kg, which is equivalent to ~ 80% of its MTD) caused 93% ($p < 0.01$ versus vehicle) functional vascular shutdown at 1 h post-treatment and partial recovery (70% vascular shutdown; $p < 0.01$ versus vehicle) by 24 h. A lower single dose of lexibulin (10 mg/kg po) resulted in less profound, but still significant, vascular shutdown (60%; $p = 0.03$ versus vehicle) by 1 h. The investigators reported that vascular shutdown was associated with a notable increase in necrosis (~ 280%; $p < 0.05$), but did not supply information on the extent of necrosis induction over the whole tumor area or involvement of the tumor rim [**1058455**], [**1152804**], [**1233876**]. The reported vascular effects of lexibulin are consistent with effects reported for other VDAs, which cause profound and rapid vascular disruption in the tumor. VDAs are selective for the tumor vasculature and although some blood-flow changes have been described in normal tissues these are less severe than in the tumor and do not culminate in tissue necrosis [**388988**], [**1240202**]. No reports were available on the vascular effects of lexibulin in normal tissues.

Toxicity

Some limited published information on the toxicity of lexibulin in animal models is available [**1129430**], [**1239322**]. Toxicity was evaluated in animal models after both intravenous and oral administration of lexibulin (details not specified). Gastrointestinal toxicity was reported as the DLT. Other common toxicities were hypocellularity of the spleen, thymus and bone marrow, leukopenia and mucosal hemorrhage, and mild

bradycardia at higher drug doses. No other cardiovascular or neurological toxicities were reported. The MTD for the oral formulation was established as 50 mg/kg of lexibulin, while the MTD for the intravenous route was 30 mg/kg of lexibulin [**1129430**], [**1239322**].

Additionally, in nude mice xenografted with PC3 cancers, a 30-mg/kg/day dose of **oral lexibulin** caused signs of cachexia in some mice. A reduced dose of 25 mg/kg/day of lexibulin was well tolerated [**1061150**]. Also, in the study in the DMH liver metastasis model assessing the vascular activity of a single dose of lexibulin (7.5 mg/kg ip), the investigators reported that vessels in normal liver tissue were unaffected by lexibulin but did not present any images to illustrate this finding [**1233876**].

Metabolism and pharmacokinetics
Lexibulin was administered to male Sprague-Dawley rats either as an intravenous single bolus dose of 5 mg/kg or as the mesylate salt in drinking water at 25 mg/kg. Analysis of plasma samples established a t1/2 of 1.5 h for the intravenous route of administration and 2.5 h for the oral route. The absolute oral bioavailability was 50 to 70% [**1061150**]. Similarly, following administration of the mesylate salt of lexibulin (5 mg/kg iv or 25 mg/kg po) to rats, a t1/2 of 1.6 h was established for the intravenous dose with a volume of distribution of 5200 ml/kg and a clearance of 36.8 ml/min/kg. The oral bioavailability was 78% and the Cmax of **oral lexibulin** was 9.4 microM [**1030535**].

A phase I, dose-escalation clinical trial assessed the pharmacokinetics of intravenous lexibulin (7 to 358 mg/m2) after a 24-h continuous infusion in patients (n = 31) with advanced solid tumors [**1129430**]. Cmax and AUC(0 to terminal dose) values increased linearly over the whole dose range tested; the Cmax at steady-state ranged from 8.5 to 345 ng/ml and the AUC(0 to terminal dose) ranged from 178 to 5640 ng.h/ml. The mean apparent volume of distribution was 6.5 l/kg (range from 2.6 and 10.6 l/kg) and clearance values ranged (dose-independently) from 0.59 to 1.56 l/h/kg. The mean terminal elimination t1/2 was 4.4 h, with a range of 1.7 to 7.5 h. The lexibulin dose excreted via urine was < 0.07%, suggesting extensive hepatic clearance of lexibulin [**1129430**].

A second phase I clinical trial followed an accelerated dose-escalation protocol using **oral lexibulin** (15 to 164 mg/m2) in patients (n = 21) with advanced solid tumors. Preliminary results of this trial reported that the oral absorption pharmacokinetics were favorable and generally dose-linear. The trial also observed that Cmax values were ~ 2-fold higher than those observed in the intravenous phase I trial after equivalent administered doses, suggestive of good oral bioavailability [**981749**], [**1009368**].

Clinical development
Phase I
Two phase I, dose-escalation clinical trials of lexibulin have been completed, one assessing intravenous lexibulin [**913440**], [**1129430**], [**1233869**] and the other **oral lexibulin** [**1009368**].

The first trial assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of a 24-h continuous infusion of intravenous lexibulin (7 to 358 mg/m2, repeated every 21 days) in patients (n = 31) with advanced solid tumors refractory to other therapies and with a life expectancy of > 3 months [**913440**], [**1129430**], [**1233869**]; the full results of this trial were reported recently in a peer-reviewed journal [**1129430**]. Dose escalation was conducted over 12 dose levels and a total of 98 cycles were administered. Clinical response (defined by Response Evaluation Criteria In Solid Tumors) was evaluable in 21 patients. Stable disease lasting >/= 6 weeks was achieved in 18 patients (82%). In particular, two patients with symptomatic progressive disease prior to trial entry had stable disease and received a total of eight cycles of lexibulin treatment before their disease progressed. However, there were no partial or complete responses in terms of tumor size in any of the patients in the trial [**1129430**].

DCE-MRI was conducted in 15 patients, with evaluable data available in 11 patients receiving lexibulin at doses ranging from 65 and 358 mg/m2 [**1129430**]. Patients were scanned twice prior to treatment to establish baseline values for tumor permeability parameters, and then 26 h and 6 days after their first lexibulin dose. Significant reductions in tumor transfer constant (Ktrans, a measure of permeability) values were reported in five patients after lexibulin treatment compared with baseline (eg, in one patient, Ktrans reduced from an average 0.0140 at baseline to 0.0083 on day 6 post-treatment; $p < 0.05$), suggesting vascular disruption and changes in tumor perfusion. However, in two patients, an increase in post-treatment Ktrans was observed compared with baseline (eg, in one patient, Ktrans increased from an average 0.0093 at baseline to 0.0109 on day 6 post-treatment). There was no correlation between the reduction in Ktrans and the dose level of lexibulin, nor between the reduction in Ktrans and patients achieving stable disease.

Maximal changes in Ktrans were observed at 6 days in six out of the seven patients that exhibited a response, while in one patient, maximal changes were observed at 24 h [**1129430**].

The trial also assessed plasma levels of von Willebrand factor and caspase-cleaved cytokeratin-18 as surrogate markers of endothelial and epithelial damage, respectively (see [**1240260**]) [**1129430**]. At 24 h after lexibulin treatment initiation, plasma levels of both biomarkers were significantly increased from baseline in patients who received >/= 202 mg/m2 of lexibulin. The mean von Willebrand factor level was 136% of baseline ($p < 0.001$ versus patients receiving < 202 mg/2 of lexibulin) and the mean caspase-cleaved cytokeratin-18 level was ~ 190% of baseline. Levels of circulating endothelial cells were also measured but a detectable increase was only evident in one patient post-treatment (from < 0.01% of mononuclear cells at baseline to 0.09 and 0.30% of mononuclear cells at 48 h and 6 days post-treatment, respectively). The trial concluded that lexibulin induced changes that were consistent with vascular disruption and associated blood-flow modifications [**1129430**].

The second phase I, accelerated dose-escalation clinical trial assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of eight dose levels of **oral lexibulin** (15 to 164 mg/m2, repeated every 14 days) in patients (n = 21) with advanced solid tumors [**1009368**]. One patient was entered into each of the first five lower dose levels (15, 21, 30, 42 and 60 mg/m2) and three patients were entered into three higher dose cohorts (84, 118 and 164 mg/m2). Additional patients were entered into the 84 to 164 mg/m2 cohorts once DLTs were established. Patients in this trial were evaluated by DCE-MRI and preliminary results reported at a conference indicated significant changes in tumor Ktrans values in 6 of 10 evaluable patients compared with baseline (no specific values provided), suggestive of vascular disruption. Preliminary evidence of vascular-disrupting activity was also acquired from assessment of von Willebrand factor. Stable disease for 6 to 21 weeks was observed in 13 patients (62%) but there were no objective tumor responses in the trial [**1009368**].

Phase II

A phase Ib/II, open-label, non-randomized, single-group clinical trial (NCT00650949, CCL08001) was to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of a 24-h continuous infusion of intravenous lexibulin (100 to 150 mg/m2, starting on day 2 and repeated every 21 days) combined with a 1-h continuous infusion of **carboplatin** (AUC = 5 iv, on day 1 and repeated every 21 days) in patients (expected n = 35) with relapsed glioblastoma multiforme. The dose selected in the phase Ib part was to be used in the phase II part. Preliminary data were reported in abstract form from the phase Ib part. DCE-MRI assessment demonstrated a reduction in tumor Ktrans in three of six evaluable patients receiving 100 mg/m2 of lexibulin [**1105352**]. At the time of publication, the trial had been terminated for strategic reasons.

A phase II, open-label, single-group clinical trial (NCT00664378, CCL07001) was also to assess the efficacy, safety and tolerability of a 24-h continuous infusion of intravenous lexibulin (202 mg/m2, on days 1 and 8 every 21 days) in patients (expected n = 24) with refractory multiple myeloma. At the time of publication, the trial had been terminated because of difficulties in enrolling patients.

Side effects and contraindications

In the phase I clinical trial of intravenous lexibulin, the drug was well tolerated at doses up to 202 mg/m2 [**913440**], [**1129430**]. The MTD was established at 358 mg/m2. DLTs (graded according to Common Terminology Criteria for Adverse Events of the NCI) were observed in patients who received 269 and 358 mg/m2 of lexibulin; these included grade 3 prolonged QTc interval in one of six patients at 269 mg/m2 of lexibulin, grade 3 hypoxia in one of three patients at 358 mg/m2, and grade 3 prolonged QTc interval and grade 4 dyspnea in another patient (who had previously received radiotherapy to the thorax) at 358 mg/m2. These toxicities were reversible. Other reversible lexibulin-related toxicities included grade 3 neutropenia in one patient who received 269 mg/m2 of lexibulin, grade 3 tumor pain in one patient who received 269 mg/m2 of lexibulin and grade 3 anemia in one patient who received 358 mg/m2 of lexibulin. None of the lexibulin dose levels had any effect on the prothrombin time, activated partial thrombin time or plasma fibrinogen level [**1129430**].

In the second phase I clinical trial of **oral lexibulin**, doses up to 118 mg/m2 were generally well tolerated [**1009368**]. The MTD of the oral formulation was established as 164 mg/m2. However, one patient who received 84 mg/m2 died of pulmonary sepsis. Of the six patients who received 164 mg/m2 of lexibulin, one experienced a DLT of reversible grade 3 hypoxia and two experienced a DLT of grade 3/4 asthenia. Additional adverse events included grade 3 toxicities of nausea/vomiting, anemia and distended abdomen (all n = 1),

and grade 2 toxicities of nausea/vomiting (n = 4) and one instance each of prolonged QTc interval and hypertension at 164 mg/m2. These adverse events were all reversible [**1009368**].

In the phase Ib/II clinical trial in patients with glioblastoma multiforme, the 150-mg/m2 dose of lexibulin combined with **carboplatin** resulted in expressive dysphasia because of a left hemisphere infarct in one patient. This patient had a tight stenosis, assessed by CT angiography, in the region of the previous high-dose radiation area. The observation led to a dose reduction and exclusion of patients with hemodynamically significant cerebrovascular stenoses. Subsequent patients administered 100 or 125 mg/m2 of lexibulin did not exhibit further cerebrovascular toxicities [**1105352**].

Patent summary
Lexibulin was first claimed by **Cytopia** in WO-2005054199, claiming pyrazine derivatives that are microtubule-polymerization agents and kinase inhibitors for the treatment of hyperproliferation-related and protein-kinase related disorders, such as cancer, infectious diseases, vascular restenosis and inflammatory disease. Lexibulin is specifically claimed in claim 9, page 86 and appears to be disclosed in example 18. This application has been granted, among others, in the US as US-07981900 (due to expire in December 2025 following a US154 extension), in Europe as EP-01689715 (due to expire in December 2024) and in Japan as JP-04772690 (due to expire in December 2024).

Acid salts of lexibulin, useful for the treatment of hyperproliferation-related disorders, are claimed by **Cytopia** in WO-2006133498. Salts of lexibulin are claimed in claims 1 to 8. Equivalents in the US (US-20090281119) and Europe (EP-01904478) had not been granted at the time of publication.

Of interest, prior to specifically claiming lexibulin in WO-2005054199, **Cytopia** filed patent application WO-2004052868, claiming pyrazine-based tubulin inhibitors for the treatment of hyperproliferation-related disorders.

Current opinion
Lexibulin is one of several novel low-molecular-weight microtubule-destabilizing agents that are currently being tested in the clinic for antitumor activity directed against the tumor vasculature. Preclinical testing of lexibulin has provided evidence that the drug targets the tumor through at least some mechanisms that are consistent with vascular disruption. These studies have demonstrated that, similar to other VDAs, lexibulin caused rapid reductions in tumor blood flow and vessel perfusion and an increase in necrosis. In addition, two phase I clinical trials of lexibulin monitored changes in several plasma and imaging biomarkers and confirmed vascular activity in human tumors. VDAs are selective for the tumor vasculature. Although some modest blood-flow modifications have been observed in normal tissues soon after administration of VDAs, these were not substantial and were transient [**388986**], [**1240202**]. Furthermore, normal tissues do not become necrotic at doses that are effective in the tumor. It has not been reported whether lexibulin exerts any substantial changes in blood flow in normal tissues, although the morphology of normal liver vasculature was said to be unaffected by lexibulin.

The toxicity profile of lexibulin does not appear to be significantly different from that of other VDAs. Although studies in animals demonstrated that, unlike other VDAs, lexibulin did not induce any cardiovascular or neurological toxicities, the clinical trials indicated that the drug caused a prolonged QTc interval in some patients. Cardiovascular toxicities, including dose-related prolongation of QTc interval, were also reported in clinical trials of other VDAs, such as **fosbretabulin** [**1240261**]. Tumor pain and transient hypertension are common side effects of VDAs [**509761**] and these were also reported in the lexibulin phase I trials. In addition, dose limiting grade 3 hypoxia and grade 4 dyspnea developed in a patient receiving 358 mg/m2 of lexibulin. This patient was previously treated with radiotherapy and it is worth noting that a fatal bowel toxicity occurred in a phase I trial of **fosbretabulin** in a patient who had previously been treated with radiotherapy in the abdomen [**509761**]. Therefore, it is possible that radiotherapy sensitizes normal tissues to VDA damage.

A substantial amount of effort is currently directed toward identifying new VDAs that display a wider therapeutic window. The **fosbretabulin**-related compound **OXi-4503** induced a several-fold greater reduction in tumor perfusion and necrosis than **fosbretabulin** when tested in parallel in animal models [**1240262**]. In addition, tumors recovered more slowly after a single dose of **OXi-4503** and therefore the drug is considered to be more potent than **fosbretabulin**. A sustained reduction in vascular perfusion is indeed considered as an indication of potent vascular activity. In this respect, it should be noted that in the preclinical models, changes in perfusion were observed at doses that were close to the MTD for lexibulin.

Overall, on the basis of current published data, it is not possible to assess whether lexibulin compares favorably against other VDAs. Responses to VDAs can be strikingly different depending on the tumor models used to test them. For example, some studies have demonstrated that VDAs produce significantly more vascular damage in tumors with vessels that are more immature and leaky than in tumors with relatively mature and stable vessel networks with high coverage of pericytes [**1240204**]. Therefore, in order to make an objective assessment of the efficacy of lexibulin, further testing is required in parallel with other VDAs in the same tumor model. One preclinical study assessed lexibulin in parallel with **fosbretabulin** and the investigators stated that the responses of the two drugs exhibited similarities. However, the **fosbretabulin** data were not presented and therefore it is not possible to comment on the degree and extent of similarity that the two drugs had in vivo.

Single doses of VDAs in general do not produce any significant inhibition of tumor growth. However, measurable effects are commonly observed after repeated dosing. Although there are no reported studies on tumor growth following a single dose of lexibulin, the reported effects of repeated dosing are consistent with those seen with other agents [**509777**], [**1240250**]. The extent of tumor growth delay following repeated VDA dosing is also dependent on tumor type, dosage and scheduling, and it is therefore difficult to make direct comparisons with different drugs unless experiments are conducted in parallel.

A robust and sustained vascular response in the tumor generally translates into extensive central tumor cell necrosis and this is often accompanied by hemorrhage and coagulation [**388986**], [**1239996**]. The rim of the tumor, however, retains some viability and becomes a source for tumor re-growth when treatment stops. Lexibulin was reported to induce necrosis in experimental models but the extent of necrosis over the whole tumor area was not indicated and no information was given as to whether the tumor rim remained resistant. This information is crucial in determining the efficacy of VDA activity, and is also important for establishing whether tumor re-growth via the viable rim can be further targeted by other therapies. Indeed, preclinical studies on several VDAs have established that their antitumor efficacy was markedly enhanced when they were used in combination with chemotherapy, radiotherapy or antiangiogenic therapy [**1240251**]. It is now widely accepted that the full clinical potential of these agents is only likely to be achieved in combination with other therapies. Such combined treatments need to consider dose, timing and sequence of drug administration very carefully in order to achieve maximal cooperation.

To date, there is only one published abstract describing the effects of lexibulin in combination with chemotherapy in a preclinical in vivo study. In this study, the investigators combined lexibulin with cisplatin and demonstrated only a very modest growth delay with the addition of cisplatin. With the little amount of data available at present, it is difficult to predict whether lexibulin will be significantly more effective in combination with chemotherapy or radiotherapy. Nevertheless, the drug was tested in a phase Ib/II clinical trial together with **carboplatin** in patients with relapsed glioblastoma multiforme; preliminary efficacy was observed although the trial has now been terminated for strategic reason (no further details were available from **YM BioSciences**). Until lexibulin is tested more extensively in preclinical models and additional results of combination trials become available, it will not be possible to comment on whether the drug is likely to be more effective and successful than other VDAs in combination with conventional therapies.

The major advantage of lexibulin over its competitors is that it has been developed as an oral formulation with good bioavailability. **ABT-751** is the only other microtubule-depolymerizing VDA that is currently being assessed in an oral formulation [**1240263**]. Oral administration of VDAs has several potential advantages, including patient convenience, but also importantly, it allows greater flexibility in terms of scheduling and dosing that can result in improved efficacy and safety. In recent years, metronomic chemotherapy, which is based on lower-dose drug administration on a more frequent basis, has attracted a lot of interest as it has potential advantages over conventional chemotherapy [**1240265**]. It is thought, for example, that metronomic chemotherapy can bypass problems of drug resistance and may be less toxic. Primarily, however, metronomic chemotherapy inhibits tumor growth through targeting the vasculature and angiogenesis. Indeed, a number of VDAs were observed to be more effective when administered at lower, more frequent doses and this greater efficacy has been attributed to targeting angiogenesis in the tumor [**1240244**].

Microtubule-targeting agents are potentially powerful inhibitors of angiogenesis as they target angiogenic processes in endothelial cells, including proliferation and migration, at significantly lower doses than those required to inhibit cancer cell proliferation [**1240244**]. Indeed, in vitro studies demonstrated that endothelial cells were more sensitive to the antiproliferative effects of lexibulin (IC50 ~ 4 nM) than tumor cells (IC50 =

10 to 100 nM), suggesting that lexibulin has potential for development as an antiangiogenic agent. Microtubule-targeting agents act on angiogenesis at low nanomolar concentrations by interfering with microtubule dynamics without necessarily disrupting their structure, while their vascular-disrupting activity relies on the disruption of endothelial microtubules at higher doses. Until now, it has not been easy to evaluate VDAs or indeed microtubule-targeting agents used in chemotherapy using a truly metronomic scheduling because of a lack of available oral formulations. However, lexibulin was administered by oral gavage on a daily basis in both subcutaneous and orthotopic tumor models and caused some significant tumor-growth delays. However, these studies did not compare the effects of frequent administration of the drug to those of a single larger dose and did not establish effects of the frequent dosing regimen on the tumor vasculature. Therefore, any therapeutic gain via antiangiogenesis needs to be verified through further in vivo testing.

In conclusion, the future of lexibulin is currently difficult to predict. Entry of this drug into clinical trials was based on a relatively small amount of preclinical testing but also on the assumption that its mechanism of action is similar to that of other VDAs. Nevertheless, the fact that the drug can be administered via an oral route is a clear advantage over other agents. The oral route of administration of lexibulin will facilitate testing of different dosing regimens, which is a very important consideration in its development as a vascular-targeting agent.

Biology

Study Type	Effect Studied	Experimental Model	Result	Reference
In vitro	Proliferation of endothelial cells	HUVECs	Lexibulin exhibited vascular activity as demonstrated by the inhibition of VEGF-stimulated HUVEC proliferation with an IC50 of ~ 4 nM.	**1233876**
In vivo	Antitumor activity	Human prostate PC3 mouse xenografts treated with lexibulin (7.5, 15 and 25 mg/kg/day po) or paclitaxel (10 mg/kg iv, tiw)	Lexibulin dose-dependently inhibited tumor growth with tumor volumes on day 20 after treatment initiation being 760, 650, 480, 260 and 250 mm3 for vehicle, 7.5, 15 and 25 mg/kg/day lexibulin and paclitaxel, respectively.	**1061150**
In vitro	Tubulin polymerization	Biochemical assay	Lexibulin inhibited tubulin polymerization with an IC50 of 3 microM.	**1061150**
In vitro	Proliferation of human cancer cell lines	More than twenty different human cancer cell lines of solid tumors	Lexibulin inhibited the viability and proliferation of these cell lines with IC50 values ranging from 10 to 100 nM.	**1061150**
In vivo	Antitumor activity	Multiple myeloma 5T33 mouse xenografts treated with lexibulin (15 mg/kg/day ip for 10 days)	Lexibulin prolonged survival, with a median survival of 33 versus 22 days for saline-treated control mice (p = 0.00097).	**1152799**
In vivo	Vascular-disrupting activity	DLD1 adenocarcinoma mouse xenografts treated with a single dose of lexibulin (40 mg/kg po)	Lexibulin caused 93% (p < 0.01 versus vehicle) functional vascular shutdown at 1 h post-treatment and partial recovery (70% vascular shutdown; p < 0.01 versus vehicle) by 24 h.	**1233876**

Clinical

Effect Studied	Experimental Model	Result	Reference

Efficacy and safety	Phase I clinical trial assessing a 24-h continuous infusion of lexibulin (7 to 358 mg/m2 iv, repeated every 21 days) in patients (n = 31) with advanced solid tumors refractory to other therapies	Stable disease lasting >/= 6 weeks was achieved in 18 patients (82%). Vascular disruption and changes in tumor perfusion were suggested by DCE-MRI in lexibulin-treated patients. Lexibulin was well tolerated at doses of up to 202 mg/m2 and the MTD was established as 358 mg/m2. Observed (reversible) DLTs at 269 and 358 mg/m2 of lexibulin included grade 3 prolonged QTc interval and grade 3 hypoxia.	**1129430**

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TOP