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(54) Title: CDK INHIBITOR FOR TREATING REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

(57) Abstract: The present invention provides methods for treating refractory chronic lymphocytic leukemia (CLL) with a CDK inhibitor. In one embodiment refractory CLL patients to be treated with the CDK inhibitor, dinaciclib, are selected on the basis of presence or absence of the 17p deletion. In another embodiment the invention is a pharmaceutical preparation comprising dinaciclib to treat refractory CLL patients having del 17p.

CDK INHIBITOR FOR TREATING REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

FIELD OF THE INVENTION

The present invention relates generally to the methods for treating cancer with an anti-proliferative agent and specifically to treating chronic lymphocytic leukemia (CLL) with a cyclin-dependent kinase (CDK) inhibitor. The method is directed to the treatment of refractory CLL patients with dinaciclib and includes the determination of the presence of the cytogenetic abnormality del(17p) to select patients for treatment with dinaciclib .

BACKGROUND OF THE INVENTION

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in Western countries. CLL accounts for about 10,000 new cases diagnosed each year in the United States and about 14,000 new cases diagnosed each year within the European Union (EU), which represents about 30% of all leukemia in Western populations. CLL follows an extremely variable clinical course with overall survival time ranging from months to decades. While some patients are asymptomatic, approximately 25% of patients will require treatment at diagnosis due to bone marrow failure or to symptoms caused by bulky adenopathy and organomegaly. Patients may also have B-symptoms such as fevers, night sweats, weight loss or extreme fatigue. Indications for treatment of active disease are based on the International Workshop on CLL (IWCLL) criteria (Hallek *et al.*, Blood, 2008, 111:5446-5456). Furthermore, the clinical course of CLL is dominated by events associated with immune dysfunction, manifested predominantly as an increased susceptibility to infection and/or autoimmunity. In addition, patients may experience other disease-related complications such as Richter's transformation and an increased risk of developing second cancers.

The stage of disease remains the most useful prognostic factor in CLL and defines early (Rai 0, Binet A), intermediate (Rai I/II, Binet B) and advanced (Rai III/IV, Binet C) stage disease with median survival times of greater than 10 years, 5-7 years, and 1-3 years, respectively (Rai *et al.*, Blood, 1975, 46(2):219-234). While there is no unifying defect or mutation defining CLL, chromosoma l abnormalities such as deletions and/or amplifications have evolved as important prognostic factors. Such abnormalities can be detected in up to 50% of CLL patients using conventional cytogenetic analysis and in up to 80% of patients using fluorescence in situ hybridization (FISH) analysis. Deletion at 13q14 is the most common aberration in about 55% of the cases and is usually associated with good prognosis (Dohner *et al.*, N. Engl. J. Med., 2000, 343(26):1910-1916). Another abnormality, Trisomy 12, often associated with unmutated immunoglobulin heavy chain variable region (IGVH) genes,

generally exhibits a more aggressive clinical course and relatively poor prognosis (Winkler *et al.*, Curr. Drug Targets, 2006, 7(10):1311-1327; Stilgenbauer *et al.*, ASH Annual Meeting Abstracts 2008, 2008, 112(11):2089).

Of critical prognostic significance is the loss of genetic material from chromosome 17, specifically, the deletion of the short arm of chromosome 17, referred to as del(17p) or 17p13. Deletion of 17p has been associated with poor response to chemotherapy or treatment resistance and with decreased overall survival (Dohner, 2000; Hallek *et al.*, Lancet, 2010, 376(9747):1164-1174. The observation in the German CLL8 trial that the addition of rituximab (Rituxan®), a monoclonal antibody directed against CD20, to fludarabine (Fludara®), a purine analogue, and cyclophosphamide, a nitrogen mustard alkylating agent, (FC) chemotherapy did not compensate for the inferior response rate, i.e. progression free survival (PFS) and overall survival (OS), in patients with del(17p), as compared to the outcome in the overall CLL population treated with the same regimen, clearly indicates the need for alternative approaches to treatment of this high risk population (Hallek, 2010; Zenz *et al.*, Blood, 2010, 116:2427).

The drug resistance of CLL patients with the 17p deletion has been attributed to the loss of TP53 function, which is also located at the 17p13 locus (Murray *et al.*, 15th Congress EHA, 10-13 June 2010, Poster Sessions Online EU, Poster No. 97; Zainuddin *et al.*, Leukemia Research, 2011, Vol. 35, Issue 2, 272-274). Moreover, there is evidence to show that CLL patients with TP53 mutations have a poor prognosis independent of the presence of the 17p deletion (Dicker *et al.*, Leukemia, 2009, 23:117-124; Malcikova *et al.*, Blood, 2009, 114(26):5307-5314; Rossi *et al.*, Clin. Cancer Res., 2009, 15(3):995-2004; Zenz *et al.*, Blood, 2008, 112(8):3322-3329). Moreover, mutations in notch1 and SF3B1 have also been shown to be associated with poor risk of treatment for CLL (Rossi *et al.*, Blood, 2012, 119:521-529; Rossi *et al.*, Br. J. Haematology, published on line, 2012 May 10, doe: 10.111/j.1365-2141.2012.09155.x; Puente *et al.*, Nature, 2011, 475:101-105; Rossi *et al.*, Clin. Cancer Res., 2009, 15:4415-4422), suggesting that there is a need for further cytogenetic analysis for optimal treatment of CLL.

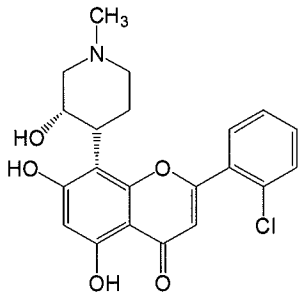
Cyclin-dependent kinases (CDKs) are serine/threonine protein kinases, which are the driving force behind the cell cycle and cell proliferation. Most of the known CDK's, including CDK1 through CDK9, are involved either directly or indirectly in cell cycle progression. Those directly involved with cell cycle progression, such as CDK1-4 and 6, can be classified as G1, S, or G2M phase enzymes. Uncontrolled proliferation is a hallmark of cancer cells and the alteration of CDK function occurs with high frequency in many solid tumors. CDK2 and CDK4 are of particular interest because their activity is frequently affected in a wide variety of human cancers. CDK2 activity is required for progression through G1 to the S phase of the cell cycle and, as such, is one of the key components of the G1 checkpoint. Checkpoints

serve to maintain the proper sequence of cell cycle events and allow the cell to respond to insults or to proliferative signals. The loss of proper checkpoint control in cancer cells contributes to tumorgenesis.

The CDK2 pathway influences tumorgenesis at the level of tumor suppressor function (e.g., p52, RB, and p27) and oncogene activation (cyclin E). Many reports have demonstrated that both the coactivator, cyclin E, and the inhibitor, p27, of CDK2 are either over- or under-expressed, respectively, in breast, colon, non-small cell lung, gastric, prostate, bladder, non-Hodgkin's lymphoma, ovarian, and other cancers. Their altered expression has been shown to correlate with increased CDK2 activity and poor overall survival. This observation makes CDK2 and its regulatory pathways compelling targets for the development of therapeutic agents for anti-proliferative disorders, such as cancer.

Adenosine 5'-triphosphate (ATP) competitive small molecule compounds, as well as peptides, have been reported in the literature as CDK inhibitors for the potential treatment of cancers. See, for example, US Patent 6,413,974, which describes various CDK inhibitors and their relationship to various types of cancer.

Other CDK inhibitors are known. For example, flavopiridol, whose structure is shown below, is a non-selective CDK inhibitor that is undergoing human clinical trials for CLL, Senderowicz *et al.*, J. Clin. Oncol., 1998, 16(9):2986-2999.



Other known CDK inhibitors include, for example, olomoucine (Vesely *et al.*, Eur. J. Biochem., 1994, 224:771-786) and roscovitine (Meijer *et al.*, Eur. J. Biochem., 1997, 243:527-536). U.S. Patent 6,107,305 describes certain pyrazolo[3,4-b] pyridine compounds as CDK inhibitors. Kim *et al.*, J. Med. Chem., 2002, 45:3905-3927 and WO 02/10162 disclose certain aminothiazole compounds as CDK inhibitors.

Notwithstanding the current use of CDK inhibitors to treat CLL, there remains a critical need for additional therapeutic options, particularly as to patients with treatment refractory CLL or cytogenetically high-risk CLL.

SUMMARY OF THE INVENTION

The instant invention relates generally to methods of treating chronic lymphocytic leukemia (CLL) with a CDK inhibitor.

In one embodiment, the invention is a method to treat refractory CLL patients, having a deletion of 17p, with a CDK inhibitor, such as, dinacliclib, (S)-(−)-(-)2-(1-{3-ethyl-7-[(1-oxy-pyridin-3-ylmethyl)]amino] pyrazolo [1,5-a]pyrimidin-5-yl} piperidin-2-yl)ethanol. In another embodiment, the invention is a method to treat refractory CLL patients overall, i.e., CLL patients with or without a deletion of 17p, with a CDK inhibitor, such as, dinaciclib .

In still another embodiment, the invention is a method to select a refractory CLL patient, either with or without a deletion of 17p, for treatment with a CDK inhibitor, such as, dinaciclib .

In still another embodiment, the invention is a pharmaceutical preparation comprising a CDK inhibitor, such as, dinaciclib , to treat refractory CLL patients overall, i.e., CLL patients with or without a deletion of 17p.

DETAILED DESCRIPTION OF THE INVENTION

CDK 1 and 2 activity are essential for progression through the cell cycle. Dual inhibition is required for robust anti-tumor activity and reversible cell cycle arrest in normal cells. Inhibition of CDK9 leads to transcriptional repression of anti-apoptotic proteins (e.g. MCL-1), D-cyclins, VEGF, c-myc, and MDM2. Dinaciclib is a potent inhibitor of a unique spectrum of CDK enzymes, specifically, CDKs 1, 2, 5, and 9. Dinaciclib is more selective as to these CDKs than competitive compounds. It has exhibited better potency and activity than flavopiridol in an ex-vivo chronic lympocytic leukemia (CLL) assay and has improved clinical tolerability over flavopiridol. In vivo, dinaciclib is active in xenograft models and shows regression with intermittent administration.

The invention herein is directed to methods for treating CLL and, in particular, refractory CLL, with a CDK inhibitor. Treatment of refractory CLL patients with dinaciclib is advantageous, as compared to ofatumumab (Arzerra™), an anti-CD20 monoclonal antibody (mAb) used as an active comparator, as measured by progression-free survival (PFS) in CLL patients with del 17p or in the overall CLL population (those with del 17p and those without del 17p), who are refractory to either fludarabine (Fludara®) treatment or chemoimmunotherapy. In another aspect, the inventive method provides advantageous treatment of refractory CLL patients with dinaciclib in the overall response rate (ORR) in CLL patients with del 17p or in the overall CLL population (those with del 17p and those without del 17p), who are refractory to either fludarabine (Fludara®) treatment or chemoimmunotherapy. In still another aspect, the inventive method provides advantageous treatment of refractory CLL patients with dinaciclib in the overall survival (OS) in CLL patients with del 17p or in the overall CLL population (those with del 17p and those without del 17p), who are refractory to either fludarabine (Fludara®) treatment or chemoimmunotherapy.

Definitions

The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one." The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or."

"CDK inhibitor" means any compound or agent that affects the activity of one or more CDK proteins or CDK/cyclin kinase complexes. The compound or agent may inhibit CDK activity by direct or indirect interaction with a CDK protein or it may act to prevent expression of one or more CDK genes. Examples of small molecule CDK inhibitors are described above. In addition, the mechanism of the CDK inhibitors, flavopiridol and SNS-032, are described in Chen *et al.*, Blood, 2005, 106(7):2513-2519 and Chen *et al.*, Blood, 2009, 113 (19):4637-4645, respectively. The CDK Inhibitor, dinaciclib , that is the subject of the studies herein, is described in Parry *et al.*, Mol. Cancer Ther., 2010, 9(8):2344-235, Fu *et al.*, Mol. Cancer Ther., 2011, 10(6):1018-1027, and U.S. Patent 7,119,200, which are incorporated herein by reference as if set forth at length.

As used here, the terms "del 17p," "del(17p)," "17p13," "deletion of 17p," and "deletion of the short arm of 17p" means the cytogenetic aberration in which genetic material corresponding to the short arm of human chromosome 17 has been deleted. Deletion of 17p has been associated with poor prognosis of chronic lymphocytic leukemia (CLL) patients having this cytogenetic abnormality. This locus on human chromosome 17 also harbors the tumour suppressor gene TP53, the loss of which has been attributed to drug resistance in CLL patients having del(17p).

As used herein, the term "refractory chronic lymphocytic leukemia patient" or "refractory CLL patient" means a patient who is refractory to either fludarabine (Fludara®) or chemoimmunotherapy. Fludarabine (Fludara®) refractory means a patient defined as failing to respond to or relapsed within 6 months of completing fludarabine (Fludara®) or another purine analog, for example, pentostatin, alone or in combination regimens. Chemoimmunotherapy refractory means a patient defined as failing to respond to chemoimmunotherapy or relapsed within 24 months of completing therapy with a combination of chemotherapy plus an anti-CD20 monoclonal antibody.

As used herein, the term "progression-free survival (PFS)" means the time from the date of randomization until the first date of documented disease progression or date of death due to any reason, whichever occurs earlier.

As used herein, the term "overall response rate (ORR)" means the sum of the number of patients determined to have a complete response (CR) and a partial response (PR)

(ORR = CR + PR), as assessed using the 2008 International Workshop on CLL criteria (Hallek, *et al.*, Blood, 2008, 11-5446-5456).

As used herein, the term "overall survival" or "OS" is calculated from the date of randomization until the date of death.

As used herein, the term "date of randomization" refers to the date on which a patient or subject is randomly assigned to be treated with either dinaciclib or (Arzerra™), the comparator.

"Patient" as that term is used herein, refers to the recipient in need of medical intervention or treatment. Mammalian and non-mammalian patients are included. In one embodiment, the patient is a mammal, such as a human, canine, murine, feline, bovine, ovine, swine or caprine. In a particular embodiment, the patient is a human.

The term "treating" in its various grammatical forms in relation to the present invention refers to preventing (i.e. chemoprevention), curing, reversing, attenuating, alleviating, minimizing, suppressing or halting the deleterious effects of a disease state, disease progression, disease causative agent (e.g., bacteria or viruses) or other abnormal condition. For example, treatment may involve alleviating a symptom (i.e., not necessary all symptoms) of a disease or attenuating the progression of a disease.

"Treatment of cancer", as used herein, refers to partially or totally inhibiting, delaying or preventing the progression of cancer including cancer metastasis; inhibiting, delaying or preventing the recurrence of cancer including cancer metastasis; or preventing the onset or development of cancer (chemoprevention) in a mammal, for example a human. In addition, the methods of the present invention may be practiced for the treatment of chemoprevention of human patients with cancer. However, it is also likely that the methods would also be effective in the treatment of cancer in other mammals.

As used herein, the term "therapeutically effective amount" is intended to qualify the amount of the treatment in a therapeutic regimen necessary to treat cancer. This includes combination therapy involving the use of multiple therapeutic agents, such as a combined amount of a first and second treatment where the combined amount will achieve the desired biological response. The desired biological response is partial or total inhibition, delay or prevention of the progression of cancer including cancer metastasis; inhibition, delay or prevention of the recurrence of cancer including cancer metastasis; or the prevention of the onset or development of cancer (chemoprevention) in a mammal, for example a human.

As used herein, the terms "combination treatment", "combination therapy", "combined treatment" or "combinatorial treatment", used interchangeably, refer to a treatment of an individual with at least two different therapeutic agents. According to the invention, the individual is treated with a first therapeutic agent, preferably a DNA damaging agent and/or a CDK inhibitor as described herein. The second therapeutic agent may be another CDK inhibitor

or may be any clinically established anti-cancer agent as defined herein. A combinatorial treatment may include a third or even further therapeutic agent.

"Good prognosis" means that a patient is expected to have no distant metastases of a tumor within five years of initial diagnosis of cancer.

"Poor prognosis" means that a patient is expected to have distant metastases of a tumor within five years of initial diagnosis of cancer.

Embodiment(s) of the Invention

A broad aspect of the invention concerns a method for treating refractory chronic lymphocytic leukemia (CLL) patients with a CDK inhibitor. In one embodiment, the CLL patient is refractory to fludarabine (Fludara®) treatment or chemoimmunotherapy and the CDK inhibitor is dinaciclib . In another embodiment, refractory CLL patients are those with a deletion of 17p. In still another aspect, the invention is a method for selecting a refractory CLL patient amenable to treatment with a CDK inhibitor, such as, dinaciclib , wherein patients selected have a deletion of 17p.

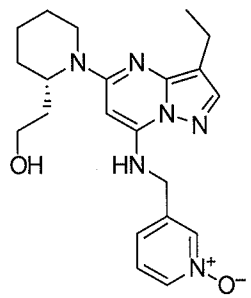
The population of cancer cells in CLL is heterogeneous, wherein the majority of cells in the peripheral blood are resting cells, while the proliferating centers harbor a subset of cells with high mitotic potential. Therefore, a drug capable of simultaneously targeting both cell populations would be desirable and a likely therapeutic candidate. Moreover, CLL is a clinically variable disease wherein mutations in DNA damage response genes, such as, ATM or TP53, affect the response to standard therapeutic agents. Previous reports have demonstrated that up to 30% of CLL tumors have a defect in the p53 pathway that result from mutations in either the ATM or TP53 gene (Stankovic, *et al.*, Blood, 2004, 103:291-300). Most current anti-cancer treatments exert their effects through DNA damage and subsequent activation of the p53-dependent apoptotic pathway; tumors that acquire mutations of genes in the p53 pathway are often associated with resistance to treatment (Zenz *et al.*, Blood, 2009, 114:2589-2597; Sturm *et al.*, Cell Death and Differentiation, 2003, 10:477-484).

Historically, monotherapy with alkylating agents such as chlorambucil has served as initial front-line therapy in CLL. The administration of purine analogues, such as fludarabine (Fludara®), resulted in better (superior) efficacy as compared to the nitrogen mustard agents, such as chlorambucil, or corticosteroids (Hallek *et al.*, Ann. Oncol., 2010, 21 (Supplement 7): 154-164). Bendamustine, with properties of both an alkylating agent and purine analog, has been approved with a better overall response rate than chlorambucil and a progression-free survival (PFS) of 21.6 months (Knauf *et al.*, J. Clin. Oncol., 2009, Vol. 27, No. 26, 4378-4384). The combination of fludarabine (Fludara®), cyclophosphamide, and rituximab (Rituxan®), an anti-CD20 monoclonal antibody (mAb), (FCR) is now considered standard first line treatment of

physically fit CLL patients and is also often used with relapse patients. It is also believed that patients with fludarabine (Fludara®) refractory CLL, defined as the failure to achieve at least a partial response (PR) according to the 1996 NCI-WG criteria (Cheson *et al.*, Blood, 1996, Vol. 87, No. 12, 4990-4997), or who have disease progression during treatment or within 6 months of the last dose, may benefit from therapies involving monoclonal antibodies such as alemtuzumab (Campath®), an anti-CD52 mAb indicated for single-agent therapy in CLL, and ofatumumab (Arzerra™), an anti-CD20 mAb indicated for CLL refractory to fludarabine (Fludara®) and alemtuzumab (Campath®) (Montillo *et al.*, Biologics, 2008, 2(1):41-52; Wierda *et al.*, 2011, Blood, 118(19):5126-5129). Even with such options, responses are short-lived and patients are at risk of myelotoxicity and infection. A search for additional agents to treat CLL led to the development of CDK inhibitors, such as flavopiridol, which showed promising activity in preclinical studies. While changing the schedule of flavopiridol resulted in better responses (45% partial response) in early clinical studies, treatment-related hyperacute tumor lysis syndrome (TLS) requiring dialysis was observed warranting aggressive subject monitoring and electrolyte management.

CDK inhibitors offer the possibility of simultaneously blocking cell cycle progression and transcription, facilitating the induction of apoptosis and reactivation of the p53 tumor suppressor mechanism (Johnstone *et al.*, Cell, 2002, 108:153-164; Wesierska-Gadek *et al.*, J. Cell Biochem., 2008, 105(5):1161-1171). Therefore, the potential diversified action of a CDK inhibitor can be a significant advantage in CLL, in that it can increase the chance of efficiently eliminating tumor cells with varying mitotic potential, before the tumor cells acquire resistance to the therapy. In instances where resistance to therapy has already occurred, the ability of a CDK inhibitor to function independently of p53 offers enormous benefit to treatment strategies.

Dinaciclib , (S)-(−)-(-)2-(1-{3-ethyl-7-[(1-oxy-pyridin-3-ylmethyl)]amino] pyrazolo [1,5-a]pyrimidin-5-yl} piperidin-2-yl)ethanol), the structure of which is shown below, has previously been shown to inhibit CDK2, CDK5, CDK1, and CDK9 with IC_{50} values of 1, 1, 3, and 4 nM, respectively (Parry *et al.*, Mol. Cancer Ther., 2010, 9(8):2344-2353).



However, as compared to flavopiridol, and assayed under identical conditions, dinaciclib is an equally potent inhibitor of CDK1 and CDK9, but is a 12-fold and 14-fold stronger inhibitor of CDK2 and CDK5, respectively. The compound was also found to be a potent DNA replicator

inhibitor the blocked thymidine DNA incorporation in A2780 cells with an IC_{50} of 4 nM (Id.). Taken together, this data shows that dinaciclib is a stronger and more selective inhibitor of CDKs, that translates into more potent inhibition of DNA synthesis as compared to flavopiridol (data not shown) (Id.).

As shown in Table 1 below, Parry *et al.*, Mol. Cancer Ther., 2010 9(8):2344-2353, found that the IC_{50} values (nM) for dinaciclib demonstrated that this CDK inhibitor was most active against CDKs 1, 2, 5, and 9, while it was at least 10 to 100 fold less active against CDKs 4, 6, and 7.

Table 1

CDK/Cyclin Kinase Complex	IC_{50} Value (nM)
Cdk2/E	1
Cdk2/A	1
Cdk1/B1	3
Cdk4/D1	100
Cdk5/p25	1
Cdk6/D3	60
Cdk7/H	70
Cdk9/T	4

Moreover, dinaciclib is not a general kinase inhibitor (Parry, 2010, Supp. Table S1), when tested at 1 and 10 μmol/L against a Millipore panel of diverse kinases using a fixed concentration of ATP (10 μmol/L). In a series of additional kinase counter-screens, dinaciclib was more selective for the CDK family, as compared to flavopiridol (Parry, 2010, Table 2). That flavopiridol affects a broader range of serine/threonine and tyrosine kinases, for example, c-Src, may contribute to its poor screening therapeutic index as compared with that of dinaciclib .

In vitro studies have shown dinaciclib to be a potent inducer of apoptosis in tumor cell lines (Parry, 2010) and an effective inhibitor of tumor growth in murine xenograft models of human cancers (Feldman *et al.*, Cancer Biol. Ther., 2011, 12(7): 598-609). Phase 1 clinical studies have demonstrated an acceptable safety profile. Pharmacokinetic data from clinical studies show peak drug plasma concentrations were achieved at 1 to 2 hours and that dinaciclib exhibited rapid distribution and elimination phases ($t^{1/2}$ ranging from 1.5 to 3.3 hours) (Parry, 2010). Clearance of the drug was dose independent with no drug accumulation in plasma. Data from an ongoing Phase I study (P4629) in CLL showed a partial response rate of about 62% in pretreated patients at the recommended Phase 2 dose (RPTD) (Flynn *et al.*, J. Clin. Oncol., 2011, Vol. 29, No. 15_suppl (May 20 Supplement) 2011:6623).

Dinaciclib was administered to more than 363 patients enrolled in Phase 1 and Phase 2 clinical trials using various doses and schedules. In the Phase 1 trial (P04629), which enrolled 107 patients, dinaciclib was administered on Days 1, 8, and 15, every 28 days (Flynn *et al.*, Blood (ASH Annual Meeting Abstracts) 2010 116:Abstract 1396). The maximum administered dose (MAD) among the CLL group was 17 mg/m^2 (Id.). Overall, dinaciclib was generally well tolerated, with adverse events typical for anti-neoplastic agents.

Ofatumumab (Arzerra™, also known as HuMax-CD20), used as an active comparator herein, is a human type I anti-CD20 mAb approved for CLL patients refractory to fludarabine (Fludara®) and alemtuzumab (Campath®). In vitro, it mediates cell dependent cytotoxicity (CDC) against rituximab (Rituxan®-resistant Raji cells and CLL cells with low expression of CD20 (A. Osterborg, Expert Opin. Biol. Ther., 2010, 10(3):439-449). It appears to have greater potency in CDC than rituximab (Rituxan®), as well as a slower off-rate and more stable CD20 binding. Additionally, it appears to bind a different epitope of CD20 than rituximab (Rituxan®). A Phase II study of ofatumumab (Arzerra™) (in refractory CLL patients demonstrated it was generally well tolerated, even at high doses and was active, with an overall response rate (ORR) of 50% (A. Tsimberidau, Drugs Today, 2010, 46(7):451-461). In patients refractory to fludarabine (Fludara®) and alemtuzumab (Campath®), referred to as Double Refractory (DR), and bulky fludarabine-refractory (BFR) CLL, regardless of whether those patients had previously been treated with rituximab (Rituxan®), 58% and 47% of patients, respectively, responded to treatment (Wierda *et al.*, J. Clin. Oncol., 2010, 28 (10):1749-1755).

CDK inhibitor efficacy in high risk CLL patients

When analyzed by chromosomal abnormality, the Phase I response data suggested that dinaciclib was effective in high risk groups, such as those with del 17p. As shown in Table 2, when compared to ofatumumab (Arzerra™), the active comparator used herein, (Wierda *et al.*, J. Clinical Onc., 2010, 28 (10): 1749-1755), dinaciclib showed superior efficacy in FA or BF refractory patients with del 17p (64% versus 29%) or non-del 17p (73% versus 58%). It has also been reported that monotherapy with rituximab (Rituxan®), also an anti-CD20 mAb, was ineffective in CLL patients with del 17p, as compared to other cytogenetic abnormalities (Byrd *et al.*, Cancer Res., 2003, 63:36-38) and that chemoimmunotherapy, which included rituximab (Rituxan®), was less effective in CLL patients with del 17p, in which progression free survival (PFS) and overall survival (OS) were shortest for CLL patients with del 17p (Byrd *et al.*, J. Clinical Onc., 2006, 24:437-443).

Table 2

	Ofatumumab (Arzerra™)					Dinaciclib (14 mg/m^2)	
Cytogenetic marker	FA-ref		BF-ref		FA or BF-ref	Phase 1 heavily pre-treated (FA or BF-ref)	
	N	ORR (%) (95% CL)	N	ORR (%) (95% CL)	ORR (%) (95% CL)	N	ORR (%) (95% CL)
del 17p	17	41 (22, 64)	14	14 (4, 40)	29 (16,47)	11	64 (35, 85)
non-del 17p	40	65 (50,78)	62	55 (43, 67)	58 (48, 67)	11	73 (43, 90)

FA-ref = Fludarabine (Fludara®) + Alemtuzumab (Campath®) refractory

BF-ref = Bendamustine + Fludarabine (Fludara®) refractory

Patient population to be treated with dinaciclib

In certain embodiments of the invention, patients with CLL to be treated with dinaciclib are refractory to either fludarabine (Fludara®) treatment or chemoimmunotherapy. Thus, the patient population to be treated with dinaciclib according to the methods herein are those who have been cytologically confirmed to have CLL, as defined by the WHO classification of hematopoietic neoplasm's, and must have fludarabine (Fludara®) or chemoimmunotherapy refractory disease. Fludarabine (Fludara®) refractory disease is defined as failing to respond to or relapse within 6 months of completing fludarabine (Fludara®) or another purine analog (e.g., pentostatin) alone or in combination regimes. Chemoimmunotherapy refractory disease is defined as failing to respond to chemoimmunotherapy or relapsed within 24 months of completing therapy with a combination of chemotherapy plus an anti-CD20 monoclonal antibody. Patients to be excluded from treatment according to the inventive methods herein include those who are diagnosed to have symptomatic brain metastases or a primary central nervous system malignancy, who have had a prior bone marrow transplant, who have been treated with dinaciclib or other CDK inhibitors, who have been treated with ofatumumab (Arzerra™), or who have active autoimmune anemia or thrombocytopenia unless stable, the latter being defined as being responsive to corticosteroids or other standard therapy.

Patients with chronic lymphocytic leukemia (CLL) are typically treated initially with chemoimmunotherapy, but once they relapse using the standard agents, the outcome is generally considered to be poor. As such, there is a strong need for new therapies for this disease. A study group at Ohio State University identified, through both a Phase I and a subsequent Phase II study, that the non-specific cyclin-dependent kinase (CDK) inhibitor flavopiridol was a potential treatment for relapsed and refractory CLL, including those patients

with cytogenetic high-risk CLL, using a pharmacokinetically derived schedule. In addition to hyper-acute tumor lysis syndrome (TLS), flavopiridol was associated with fatigue, diarrhea, and other constitutional symptoms that often prevent extended treatment. Nonetheless, the development and demonstration of favorable results with flavopiridol has generated interest for other CDK inhibitors to treat CLL, that target similar CDKs and that have an improved therapeutic index.

Dinaciclib demonstrated activity in heavily pre-treated CLL patients when administered by 2-hour intravenous (IV) infusion using a Day 1, 8, and 15 of a 28-day cycle treatment schedule. Of 39 evaluable CLL patients, dinaciclib treatment resulted in 20 patients with a partial response (PR). The majority of these responses were observed at the recommended Phase 2 dose (RPTD) of 14 mg/m^2, with a 62.5% (10 out of 16 patients) response rate. In the Phase 1 trial, at the RPTD, the response rate in patients with del 17p was similar to those without this marker. Based on preliminary Phase I data in advanced and refractory CLL patients, dinaciclib appears to be active and well-tolerated. The inventive methods herein are based on the superiority of dinaciclib , as compared to ofatumumab (Arzerra™), in the overall response rate (ORR) to treat a refractory population of CLL patients.

Dose and administration

In the ongoing Phase 1 trial (P04629), the recommended Phase 2 dose (RPTD) for CLL, based on a maximal tolerated dose (MTD) algorithm, for dinaciclib was determined to be 14 mg/m^2 on Days 1, 8, and 15, every 28 days. Additional patients were enrolled to evaluate the dose-titration to minimize the incidence of tumor lysis syndrome (TLS) by starting individual patients at a lower dose and increasing the dose up to 14 mg/m^2.

As used herein, 7 mg/m^2 of dinaciclib is administered on Day 1, 10 mg/m^2 on Day 8, and 14 mg/ m^2 on Day 15 in Cycle 1, intravenously (IV) over 2 hours, via an IV infusion pump. Antiemetic prophylaxis with a serotonin-receptor antagonist (e.g. ondansetron), with dexamethasone (or equivalent), is administered prior to treatment with dinaciclib . In Cycle 2 and thereafter, dinaciclib is dosed at 14 mg/m^2 on Days 1, 8, and 15 of each 28 day cycle for a total of 12 cycles. Data from previous CLL patients demonstrated a generally acceptable safety profile with this dose regime.

Ofatumumab (Arzerra™) is administered by intravenous infusion once weekly for 8 weeks starting on Cycle 1, Day 1, followed by 9 monthly doses for a total of 12 months therapy. Ofatumumab (Arzerra™) is approved in the US and EU for weekly administration for 8 weeks, followed by 4 monthly doses, for a total of 12 doses. As used herein, patients who demonstrate stable disease or better and who tolerate treatment, will receive the approved dose and schedule, followed by an additional 5 monthly doses, for a total of 17 doses. Dose and administration will be as follows: 300 mg on Cycle 1, Day 1, followed by 2,000 mg on Cycle 1,

Days 8, 15, and 22; 2,000 mg on Cycle 2, Days 1, 8, 15, and 22; followed 5 weeks later with 2,000 mg on Day 1, of Cycles 4, 5, 6, 7, 8, 9, 10, 11, and 12. Infusion rate and any pre-treatment for ofatumumab (Arzerra™) will be according to product label.

While CDK inhibitors can be administered by various means, dinaciclib is typically administered intravenously by a person skilled in the medical practice of oncology. Examples of routes of administration include but are not limited to oral, parenteral, intraperitoneal, intravenous, intraarterial, transdermal, sublingual, intramuscular, rectal, transbuccal, intranasal, liposomal, via inhalation, vaginal, intraocular, via local delivery by catheter or stent, subcutaneous, intraadiposal, intraarticular, intrathecal, or in a slow release dosage form.

CDK inhibitors or a pharmaceutically acceptable salt or hydrate thereof, can be administered intravenously in accordance with any dose and dosing schedule that, achieves a dose effective to treat cancer. For example, CDK inhibitors can be administered in a total daily dose of up to 1000 mg, preferably orally, once, twice or three times daily, continuously (every day) or intermittently (e.g., 3-5 days a week), depending on the tumor type being treated.

A CDK inhibitor may also be administered in combination with an anti-cancer agent, wherein the amount of CDK and the amount of the anti-cancer agent together comprise a therapeutically effective amount. The combination therapy can provide a therapeutic advantage in view of the differential toxicity associated with the two treatment modalities. For example, treatment with CDK inhibitors can lead to a particular toxicity that is not seen with the anti-cancer agent, and vice versa. As such, this differential toxicity can permit each treatment to be administered at a dose at which said toxicities do not exist or are minimal, such that together the combination therapy provides a therapeutic dose while avoiding the toxicities of each of the constituents of the combination agents. Furthermore, when the therapeutic effects achieved as a result of the combination treatment are enhanced or synergistic, for example, significantly better than additive therapeutic effects, the doses of each of the agents can be reduced even further, thus lowering the associated toxicities to an even greater extent.

A CDK inhibitor can be combined with chemotherapy and radiotherapy. A CDK inhibitor can also be combined with an anti-cancer agent, but is preferably combined with a DNA damaging agent. Examples of such anti-cancer agents to be used in a combination treatment with CDK inhibitors are for example, but not limited to, gemcitabine, cisplatin, carboplatin, 5-fluorouracil, pemetrexed, doxorubicin, camptothecin and mitomycin.

A CDK inhibitor can be administered in a total daily dose that may vary from patient to patient, and may be administered at varying dosage schedules. Suitable dosages are total daily dosage of between about 25-4000 mg/m^2 administered orally once-daily, twice-daily or three times-daily, continuous (every day) or intermittently (e.g. 3-5 days a week). Furthermore, the compositions may be administered in cycles, with rest periods in between the

cycles (e.g. treatment for two to eight weeks with a rest period of up to a week between treatments).

Other treatment combinations and dosing regiments are set forth in WO 2007/126122, WO2007/126128 and WO 2008/133866.

It is apparent to a person skilled in oncology that any one or more of the specific dosages and dosage schedules of the CDK inhibitors, is also applicable to any one or more of the anti-cancer agents to be used in the combination treatment. Moreover, the specific dosage and dosage schedule of the anti-cancer agent can further vary, and the optimal dose, dosing schedule and route of administration will be determined based upon the specific anti-cancer agent that is being used.

Methods of treating refractory CLL

The invention herein is directed to methods for the treatment of refractory chronic lymphocytic leukemia (CLL) with a CDK inhibitor. In one embodiment a CDK inhibitor, dinaciclib , provided advantageous (better than) treatment in progression-free survival (PFS), as compared to ofatumumab (Arzerra™), in CLL patients with del 17p or in the overall CLL population (those with del 17p and those without del 17p), wherein said CLL patients are refractory to either fludarabine (Fludara®) treatment or chemoimmunotherapy.

In another embodiment, dinaciclib provided advantageous (better than) treatment in the overall response rate (ORR), which is the sum of the complete response (CR) and the partial response (PR) rates (ORR = CR + PR), as compared to ofatumumab (Arzerra™), in CLL patients with del 17p or in the overall CLL population (those with del 17p and those without del 17p), wherein said patients are refractory to either fludarabine (Fludara®) treatment or chemoimmunotherapy.

In another embodiment, dinaciclib provided advantageous (better than) treatment in the overall survival rate (OS), which is the sum of the complete response (CR) and the partial response (PR) rates (ORR = CR + PR), as compared to ofatumumab (Arzerra™), in CLL patients with del 17p or in the overall CLL population (those with del 17p and those without del 17p), wherein said patients are refractory to either fludarabine (Fludara®) treatment or chemoimmunotherapy.

In still another embodiment, patients to be treated with dinaciclib are selected on the basis of CLL tumor cytogenetics. In a specific embodiment, patients selected to be treated are those whose CLL tumors have been shown to have a deletion of 17p. In still other specific embodiments, patient responses from those treated with dinaciclib , as compared to ofatumumab (Arzerra™), are evaluated for the presence or absence of p53 mutations, notch1 mutations, or SF3B1 mutations, or using gene expression profiles for p53, BCL-XL, or other genes involved in CLL pathology, or dinaciclib or ofatumumab (Arzerra™) pharmacology.

Cytogenetic analysis

In certain embodiments of the invention herein, refractory patients to be treated with dinaciclib are screened for the presence or absence of specific cytogenetic abnormalities, such as, del 17p, TP53 mutations, notch1 mutations, or SF3B1 mutations. In one embodiment said patients are screened for the presence or absence of the 17p deletion. While a method for the detection of del 17p is illustrated herein, those of ordinary skill in the art would recognize and acknowledge that other methods are known and could be employed to detect this and other cytogenetic abnormalities as well.

EXAMPLES

Example 1

Fluorescence in situ hybridization (FISH) for del 17p, del 13q, dell 11q, and trisomy 12

A blood sample is collected from each patient prior to administration of any therapeutic agent for cytogenetic analysis for del(17)(p13.1), del(13)(q14), del(11)(q22.3), and trisomy 12. The cytogenetic analysis will be carried out using the Vysis CLL FISH Probe Kit (4N02-020, Abbott Molecular Inc., Des Plaines, IL) according to the manufacturer's protocol and standard recommendations. The Vysis CLL Fish Probe Kit is intended to detect deletion of the LSI TP53, LSI ATM, and LSI D13S319 probe targets and gain of the D12Z3 sequence in peripheral blood specimens from untreated patients with B-cell chronic lymphocytic leukemia (CLL). The assay may be used to dichotomize CLL (the 13q-, +12, or normal genotype group versus the 11q- or 17p- group) and may be used as an aid in determining disease prognosis in combination with additional biomarkers, morphology, and other clinical information.

The del 17p results will be obtained prior to administration of any therapeutic agent and will be used for stratification. Any subject for which the del 17p status cannot be determined will be excluded from the study.

Example 2

Pharmacogenetic analyses for p53, Notch1, and SF3B1

Samples are to be collected at pre-dosing on Cycle 1, Day 1 and 30 days post-treatment for all patients. Screening sample(s) may be used for retrospective analysis of molecular determinants of tumor response. End of treatment sample may be used to evaluate molecular determinants of acquired resistance to therapy. Exploratory analyses may include, but are not limited to, the association between response and p53 mutations, notch1 mutations, SF3B1 mutations, gene expression profiles for p53, BCL-XL, or other genes involved in CLL pathology or dinaciclib or ofatumumab (Arzerra™) pharmacology. Biomarker analyses are to be carried using standard genomic analysis methods.

Example 3

Treatment agents and response assessment

Refractory CLL patients are treated with either dinaciclib or ofatumumab (Arzerra™). Dinaciclib is provided as an injectable solution of 5 mg/mL in a 20 mL fill vial. Ofatumumab (Arzerra™) is provided as a 20 mg/mL solution for infusion in either a 5 mL or a 50 mL vial.

Response assessments are performed approximately every 12 weeks for 60 weeks, followed thereafter by every 24 weeks until disease progression. If medically appropriate, a confirmatory assessment of the initial progression event should be performed within 12 weeks. A CT scan of the neck (if indicated), chest, abdomen and pelvis, and hematology laboratory (CBC) will be obtained, and the presence of CLL symptoms will be determined at each response assessment timepoint. A survival check may be performed via telephone contact every 24 weeks after disease progression.

Example 4

Statistical analysis for efficacy

While methods for the statistical analysis for efficacy are illustrated below, those of ordinary skill in the art would recognize and acknowledge that other methods are known and could be employed for these analyses as well.

A. Progress-free survival (PFS)

Samples from patients completing treatment with either dinaciclib or ofatumumab (Arzerra™) are analyzed for PFS, which is the primary efficacy endpoint. The primary analysis of this endpoint will be based on the PFS determined in accord with the 2008 International Workshop on CLL criteria (Hallek, *et al.*, Blood, 2008, 111:5446-5456) in the intent to treat (ITT) population. The ITT population consists of all patients treated.

The final analysis will be performed when there are approximately 101 PFS events in the del 17p population. A stratified Cox proportional hazards model, with Efron method of tie handling, will be used to assess the magnitude of the treatment difference between the treatment arms. Stratification factors to be used are del 17p versus non-del 17p cytogenetic abnormalities determined by FISH analysis, refractory/relapse status of prior therapy, and response assessment schedules. The p-value from the score test will be used in significance testing. The hazard ratio and its 95% confidence interval from the same Cox model will be reported. A modified Kaplan-Meier estimation method for interval-censored data proposed by D. M. Finkelstein (Biometrics, 1986, 42:845-485), will be used to estimate the median PFS and its 95% confidence interval as well as the probability of surviving free of progression over time.

For patients who progress or die, the time of progression will be indicated as the interval the date of the last disease assessment without documented progressive disease (PD) to the date of documented PD or death, whichever occurs earlier.

In as much as disease status is assessed periodically, PD can occur anywhere in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For patients who have PD, the true date of disease progression will be approximated by the date of the first disease assessment at which PD is objectively documented per the 2008 International Workshop on CLL criteria (Hallek, *et al.*, Blood, 2008, 111:5446-5456) for the primary endpoint, regardless of violations or discontinuation of study drug. A death event is always considered as a confirmed PD event. Patients who discontinue study treatment for reasons other than disease progression will continue to be assessed for PD by physical exams, blood work for CBC and serial CT scans of the neck (if indicated), chest, abdomen and pelvis per assessment schedule until disease progression. Patients without documented PD/death will be censored at the last disease assessment date (physical exam, blood work for CBD or CT scan). Patients who become eligible for bone marrow transplant (BMT) or have received BMT will continue to be assessed for PD by physical exams, blood work for CBC and serial CT scans of the neck (if indicated), chest, abdomen and pelvis per assessment schedule until disease progression. Those of ordinary skill in the art would recognize and appreciate that additional analyses may be carried out using censoring rules and PD event definitions under various scenarios to further define the efficacy of dinaciclib as compared to ofatumumab (Arzerra™).

B. Overall response rate (ORR)

Samples from patients completing treatment with either dinaciclib or ofatumumab (Arzerra™) are analyzed for ORR (ORR=CR+PR), which is a secondary efficacy endpoint. The analysis of ORR will be based on the response status determined in accord with the 2008 International Workshop on CLL criteria (Hallek, *et al.*, Blood, 2008, 11-5446-5456). The stratified method of O. Miettinen and M. Nurminen (Statistics in Medicine, 1985, 4:213-226) will be used for comparison of the objective response rates between the treatment groups. A 95% confidence interval for the difference in response rates will be provided.

C. Overall survival (OS)

Samples from patients completing treatment with either dinaciclib or ofatumumab (Arzerra™) are analyzed for OS, which is an alternative secondary endpoint. The non-parametric Kaplan-Meier method will be used to estimate overall survival time in individual treatment groups. Median survival and its 95% confidence interval in each treatment group will be estimated and reported. A stratified Cox proportional hazards model, with Efron method of tie handling, will be used to assess the magnitude of the treatment difference between the treatment arms. Stratification factors to be used are del 17p versus non-del 17p cytogenetic

abnormalities determined by FISH analysis, refractory/relapse status of prior therapy, and response assessment schedules. The p-value from the score test will be used in significance testing. The hazard ratio and its 95% confidence interval from the same Cox model will be reported.

A preliminary OS analysis will be conducted at the same time as the primary PFS analysis. The final OS analysis will be conducted 12 months after the data cut-off date for the primary PFS analysis. Approximately 34% to 47% of the del 17p patients are expected to have died over the 1 year post primary analysis. Any changes to the analyses plan should be made prior to the data of the primary analysis.

D. Analyses summary

The primary and secondary endpoints, primary analysis population, and the statistical methods for the efficacy analyses are summarized in Table 3 below.

Table 3

Endpoint/Variable (Description, Timepoint)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
PFS in del 17p population	Cox Model Score Test	ITT	Censored data analysis
PFS in overall population	Cox Model Score Test	ITT	Censored data analysis
Secondary:			
ORR in del 17p population	Miettinen and Nurminen method	ITT	Patients with completely missing response data will be treated as non-responders
ORR in overall population	Miettinen and Nurminen method	ITT	Patients with completely missing response data will be treated as non-responders
OS in del 17p population	Cox Model Score Test	ITT	Censored data analysis
OS in overall population	Cox Model Score Test	ITT	Censored data analysis

E. Sample size and power calculations

Efficacy for dinaciclib , as compared to ofatumumab (Arzerra™), is to be evaluated in a randomized two arm study, in which the randomization is further stratified by the cytogenetic status (del 17p versus non-del 17p) and the refractory/relapse status of prior therapy. A total of approximately 101 PFS events in the del 17p patients is required to demonstrate that

dinaciclib is superior to (better than) ofatumumab (Arzerra™) in the del 17p patients with a power of 90% (α=0.02, 1-sided) if the true hazard ratio (HR) is 0.5 for dinaciclib /ofatumumab (Arzerra™). An observed HR of approximately $\leq$ 0.6718 at the final analysis corresponds to superiority in PFS for the del 17p population at α=0.02, 1-sided. This HR corresponds to a median PFS of 8.9 months for dinaciclib versus 6 months for ofatumumab (Arzerra™). Approximately 186 del 17p patients will be enrolled in this study. The sample size estimation is based on the following assumptions:

(l) the HR for dinaciclib versus ofatumumab (Arzerra™) is 0.5;

(2) the median PFS in the del 17p patients in ofatumumab (Arzerra™) is 6 months;

(3) the lost to follow-up follow an exponential distribution with the lost to follow-up rate being 5% at 1 month in both treatment groups;

(4) the enrollment rate is 5.69 del 17p patients/month; and

(5) the enrollment period is approximately 33 months and the study duration is approximately 38 months.

All calculations are to be carried out using validated clinical trial software, such as, East®5.4 (Cytel, Cambridge, MA).

WHAT IS CLAIMED:

1. A method for treating a refractory chronic lymphocytic leukemia (CLL) patient, in need of treatment thereof, comprising administering to said patient a therapeutically effective amount of dinaciclib .

2. The method according to claim 1, wherein said refractory CLL patient is refractory to fludarabine treatment or chemoimmunotherapy.

3. The method according to claim 2, wherein said refractory CLL patient has a deletion of 17p.

4. The method according to claim 2, wherein said refractory CLL patient does not have a deletion of 17p.

5. The method according to claim 2, wherein dinaciclib is ((S)-(−)--(-)2-(1-{3-ethyl-7-[(1-oxy-pyridin-3-ylmethyl)]amino] pyrazolo [1,5-a]pyrimidin-5-yl} piperidin-2-yl)ethanol)).

6. A method for treating a refractory CLL patient by determining if said patient has a deletion of 17p and administering to said patient a therapeutically effective amount of dinaciclib, if said patient has a deletion of 17p.

7. The method according to claim 6, wherein said refractory CLL patient is refractory to fludarabine treatment or chemoimmunotherapy.

8. The method according to claim 6, wherein dinaciclib is ((S)-(−)--(-)2-(1-{3-ethyl-7-[(1-oxy-pyridin-3-ylmethyl)]amino] pyrazolo [1,5-a]pyrimidin-5-yl} piperidin-2-yl)ethanol)).

9. A method for selecting a refractory CLL patient for treatment with dinaciclib comprising determining if said patient has a deletion of 17p, wherein said patient is selected if said patient has a deletion of 17p.

10. The method according to claim 9, wherein said refractory CLL patient is refractory to fludarabine treatment or chemoimmunotherapy.

11. The method according to claim 10, wherein said patient is administered a therapeutically effective amount of dinaciclib a CDK inhibitor if said patient is selected.

12. The method according to claim 11, wherein dinaciclib is ((S)-(−)--(-)2-(1-{3-ethyl-7-[(1-oxy-pyridin-3-ylmethyl)]amino] pyrazolo [1,5-a]pyrimidin-5-yl} piperidin-2-yl)ethanol)).

13. A pharmaceutical preparation comprising a therapeutically effective amount of dinaciclib, together with a pharmaceutically acceptable carrier or diluents, to treat a refractory CLL patient.

14. The pharmaceutical preparation of claim 13 wherein said refractory CLL patient is refractory to fludarabine treatment or chemoimmunotherapy.

15. The pharmaceutical preparation of claim 14 wherein said refractory CLL patient has a deletion of 17p.

16. The pharmaceutical preparation of claim 14, wherein said refractory CLL patient does not have a deletion of 17p.

17. The pharmaceutical preparation of claim 13, wherein dinaciclib is ((S)-(−)--(-)2-(1-{3-ethyl-7-[(1-oxy-pyridin-3-ylmethyl)]amino] pyrazolo [1,5-a]pyrimidin-5-yl} piperidin-2-yl)ethanol)).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/45104

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61P 35/02; A61K 31/496, 31/4545 (2013.01)
USPC - 435/287.1; 514/253.09, 317
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61P 35/02; A61K 31/496, 31/4545, 31/454 31/506; C07D 409/14, 401/14 (2013.01)
USPC: 435/287.1; 514/253.09, 317, 316, 318

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MicroPatent (US Granted, US Applications, EP-A, EP-B, WO, JP, DE-G, DE-A, DE-T, DE-U, GB-A, FR-A); Google; Google Scholar; DialogPro; administer*, dinaciclib or SCH727965, refractory or relapse*, leukemia or CLL or B-CLL, CDK*1. 17p

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	FLYNN, JM et al. Update on the phase I study of the cyclin dependent kinase inhibitor dinaciclib (SCH 727965) in patients with relapsed or refractory chronic lymphocytic leukemia (CLL): confirmation of clinical activity and feasibility of long-term administration. Blood 2010, Vol. 116, Abstract No. 1396; Retrieved from the Internet <URL: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/1396?sid=f65f3c43-481b-43f4-8f9a-a01d57d7d8a5&eaf%201/2>; abstract	1, 6, 9, 13 --------- 2-5, 7, 8, 10-12, 14-17
Y	BROWN, JR et al. 'The treatment of relapsed refractory chronic lymphocytic leukemia.' Hematology, 2011, pages 110-118; page 114, section "Treatment options for CIT-refractrory CLL"; page 114	2-5, 7, 10-12, 14-16
Y	PARRY, D et al. 'Dinaciclib (SCH 727965), a novel and potent cyclin-dependent kinase inhibitor.' Mol Cancer Ther 2010; Vol. 9, No. 8, pages 2344-2353; page 2345, section 'Materials and Method'; page 2345	5, 8, 12, 17
X	FLYNN, JM et al. 'Phase I study of the CDK inhibitor dinaciclib (SCH 727965) in patients (pts) with relapsed/refractory CLL.' J Clin Oncol (Meeting Abstracts) May 2011; Vol 29 No. 15_suppl 6623; [Retrieved on 2013-10-28]. Retrieved from the Internet <URL: http://meeting.ascopubs.org/cgi/content/short/29/15_suppl/6623?rss=1%201/1>; entire document	1
X	JOHNSON, AJ et al. 'Dinaciclib (SCH727965) is a novel cyclin dependent kinase inhibitor that promotes selective apoptosis in cll cells and abrogates the protective effects of microenvironment cytokines.' Blood 2010, Vol. 116, Abstract No. 971; [Retrieved on 2013-10-30]. Retrieved from the Internet <URL: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/971?sid=8d0623a9-e06b-41f4-ac40-964664f96d8e%201/2>; entire document	1

☒ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 November 2013 (05.11.2013)	12 NOV 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/45104

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PARUCH, K et al. 'Discovery of dinaciclib (SCH 727965): A potent and selective inhibitor of cyclin-dependent kinases.' ACS Med Chem Lett 2010, Vol. 1, No. 5, pages 204-208 (abstract). [Retrieved on 2013-10-30]. Retrieved from the Internet <URL: http://pubs.acs.org/doi/abs/10.1021/ml100051d>; entire document	1-17