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(54) Benævnelse: **Fremgangsmåder til at forudsige terapeutiske fordele af anti-CD19-behandlingen hos patienter**

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DESCRIPTION

Description

Field of the Invention

[0001] The present disclosure is directed to identifying characteristics and biomarkers in patients that benefit from treatment with anti-CD19 antibodies.

Background

[0002] CD19 is a 95-kDa transmembrane glycoprotein of the immunoglobulin superfamily containing two extracellular immunoglobulin-like domains and an extensive cytoplasmic tail. The protein is a pan-B lymphocyte surface receptor and is ubiquitously expressed from the earliest stages of pre-B cell development onwards until it is down-regulated during terminal differentiation into plasma cells. It is B-lymphocyte lineage specific and not expressed on hematopoietic stem cells and other immune cells, except some follicular dendritic cells. CD19 functions as a positive regulator of B cell receptor (BCR) signaling and is important for B cell activation and proliferation and in the development of humoral immune responses. It acts as a co-stimulatory molecule in conjunction with CD21 and CD81 and is critical for B cell responses to T-cell-dependent antigens. The cytoplasmic tail of CD19 is physically associated with a family of tyrosine kinases that trigger downstream signaling pathways via the src-family of protein tyrosine kinases. CD19 is an attractive target for cancers of lymphoid origin since it is highly expressed in nearly all chronic lymphocytic leukemia (CLL) and non-Hodgkin's lymphomas (NHL), as well as many other different types of leukemias, including acute lymphocytic leukemia (ALL) and hairy cell leukemia (HCL).

[0003] The clinical development of CD19 directed antibodies had previously been limited by the internalization of the CD19 antigen, however, improved antibody modification technology has restored this potential therapeutic target. MOR00208 (previously named XmAb5574) is an Fc engineered humanized monoclonal antibody that binds CD19. The increase in binding of MOR00208 Fc to FcyR, due to XmAb engineered mutations, significantly enhances in-vitro antibody dependent cell-mediated cytotoxicity (ADCC), antibody dependent cell-mediated phagocytosis (ADCP), and direct cytotoxic effects (apoptosis) on tumor relative to the unmodified antibody. MOR00208 has not been shown to mediate complement dependent cytotoxicity.

[0004] MOR00208 has or is currently being studied in clinical trials in CLL, ALL and NHL.

Specifically, a Phase I trial titled Safety and Tolerability of XmAb®5574 in Chronic Lymphocytic Leukemia, and a Phase IIa trial titled Study of Fc-Optimized Anti-CD19 Antibody (MOR00208) to treat B-cell Acute Lymphoblastic Leukemia (B-ALL) are completed. A phase I trial of the Fc-engineered CD19 antibody XmAb5574 (MOR00208) demonstrated safety and preliminary efficacy in relapsed CLL (Woyach et al., Blood 124, no. 24: 3553-60 (December 4, 2014)). A Phase IIa trial titled Study of Fc-Optimized Anti-CD19 Antibody (MOR00208) to Treat Non-Hodgkin's Lymphoma (NHL) has completed recruitment. And the following trials are planned / ongoing: a Phase II/III trial titled A Trial to Evaluate the Efficacy and Safety of MOR00208 With Bendamustine (BEN) Versus Rituximab (RTX) With BEN in Adult Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL) (B-MIND), a Phase II trial titled Study to Evaluate Efficacy and Safety of MOR00208 With Idelalisib in R/R CLUSLL Patients Pretreated With BTKi, a Phase II trial titled A Study to Evaluate the Safety and Efficacy of Lenalidomide With MOR00208 in Patients With R-R DLBCL, and a Phase II trial titled Phase II MOR00208 in Combination With Lenalidomide for Patients With Relapsed or Refractory CLL, SLL or PLL or Older Patients With Untreated CLL, SLL or PLL. In a further current Phase II trial (COSMOS) the Efficacy and Safety of MOR00208 in combination with idelalisib or venetoclax in Patients with Relapsed or Refractory CLL, SLL is studied.

[0005] Single agent efficacy of MOR00208 has been reported in CLL, and NHL. The general variable response rates of patients to monoclonal antibody therapies, however, indicate that methods are needed to accurately predict which patients are likely to respond to such antibody therapies so that the treatment can be administered to those patients who are most likely to receive benefits. Particular biomarkers or characteristics of patients may be found for which a particular concentration or range for each biomarker correlates with responsiveness to such therapy.

[0006] The influence of natural killer (NK) cell count on the survival of patients with DLBCL treated with Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride (Hydroxydaunomycin), Vincristine Sulfate (Oncovin) and Prednisone (R-CHOP) was evaluated. Kim et al., Blood Research, 49:3, 162-169 (September 2014). Previously, it was reported that peripheral NK cell count was associated with clinical outcome in patients with aaIPI 2-3 DLBCL. Plonquet et al., Ann Oncol 2007; 18:1209-15. US 2014/328842 A1 discloses a method for identifying a subject having non-Hodgkin's Lymphoma (NHL) that is responsive to treatment with an anti-CD20 antibody, wherein the treatment response is based on the polymorphism of CD16 (also known as FcγRIIIA). US 2015/0239974 A1 discloses that trogocytosis (antigen shaving) induced by a humanized anti-CD22 antibody (hRBF4) plays a significant role in determining antibody efficacy and disease responsiveness for treatment of B-cell diseases, such as haematopoietic cancers, immune system dysfunction and/or autoimmune disease.

[0007] It is clear that significant efforts and investment are needed to discover and identify such patient characteristics and biomarkers predictive of efficacy.

Summary of Invention

[0008] MOR00208 has been studied in patients having CLL, ALL, NHL and SLL. Accordingly, a thorough analysis of clinical data has been completed to date in order to identify characteristics or biomarkers of patients that are more likely to benefit from MOR00208 treatment.

[0009] MOR00208 specifically targets the CD19 surface antigen and mediates direct tumor cell killing via its enhanced ADCC effector function. In preclinical studies, MOR00208 has been shown to significantly enhance in vitro ADCC, ADCP, and direct cytotoxic effects (apoptosis) on $CD19^+$ tumor cell lines spanning a broad range of human lymphomas and leukemias (Burkitt's lymphoma, CLL, hairy cell leukemia (HCL), CD19+ chronic myeloid leukemia (CML), diffuse large B cell lymphoma (DLBCL) and acute lymphoblastic leukemia (ALL), expressing levels of CD19 antigen ranging from 15,000 to 105,000 molecules/cell. Similar effects have also been observed in relation to freshly isolated patient CLL or ALL cells and are also expected to translate to primary non-Hodgkin's lymphoma (NHL) cells since the expression range reported for ALL and CLL B cells covers the range observed for NHL B cells (Ginaldi et al., 1998; Olejniczak et al., 2006). Based on the widely and homogenous surface expression of CD19 throughout various types of B cell neoplasms the effect of MOR00208 in the present study can be transferred to a broad range of human lymphomas and leukemias, such as CLL, ALL, NHL and SLL and subtypes thereof.

[0010] Data from the Phase IIa trial titled Study of Fc-Optimized Anti-CD19 Antibody (MOR00208) to Treat Non-Hodgkin's Lymphoma (NHL) has been thoroughly analyzed. As a result of these efforts, the following disclosure provides characteristics and biomarkers of patients where anti-CD19 antibodies are efficacious.

[0011] Specifically at least the following characteristics of patients were evaluated: a) age, b) gender, c) if patients had received a dose of Rituximab within the last 6 months, d) whether the patients were Rituximab refractory, e) whether patients have the FCgammaRIIIa high or low affinity allele, f) whether patients have the FCgammaRIIa high or low affinity allele, g) whether patients had a duration of response to the previous treatment of greater than 12 months, h) baseline peripheral T cell counts (cells/µl), i) baseline peripheral NK cell count (cells/µl) and j) baseline CD16 expression on peripheral NK cells (Antibodies Bound per Cells -ABCs).

[0012] Both 1) baseline peripheral NK cell counts and 2) baseline CD16 expression on peripheral NK cells showed clear correlations to patient responses with MOR00208 therapy. Specifically, patients having a higher baseline peripheral NK cell count per µl correlated with a higher Disease Control Rate (DCR). DCR includes patients have Complete Response (CR) + Partial Response (PR) + Stable Disease (SD). Additionally, such patients had a significantly better Progression Free Survival (PFS) as compared to patients having lower NK cells counts. In addition, patients having a baseline CD16 expression on NK cells of at least 60,000 (ABCs) correlated with higher Disease Control Rate (DCR).

[0013] Therefore, patients diagnosed with CLL, ALL, NHL and SLL and having either a) a high peripheral NK cell count or 2) baseline CD16 expression on peripheral NK cells of at least

60,000 ABCs are more likely to benefit from MOR00208 treatment.

[0014] Both 1) baseline peripheral NK cell counts and 2) baseline CD16 expression on peripheral NK cells showed clear correlations to patient responses with MOR00208 therapy. Specifically, patients having a baseline peripheral NK cell count of at least 50 cells/µl correlated with a higher Disease Control Rate (DCR). DCR includes patients have Complete Response (CR) + Partial Response (PR) + Stable Disease (SD). Additionally, patients having a baseline NK cell count of at least 50 cells/µl had a significantly better Progression Free Survival (PFS) as compared to patients having lower NK cells counts. In addition, patients having a baseline CD16 expression on NK cells of at least 60,000 (ABCs) correlated with higher Disease Control Rate (DCR).

[0015] Therefore, patients diagnosed with CLL, ALL, NHL and SLL and having either a) baseline peripheral NK cell count of at least 50 cells / µl or 2) baseline CD16 expression on peripheral NK cells of at least 60,000 ABCs are more likely to benefit from MOR00208 treatment.

[0016] Both 1) baseline peripheral NK cell counts and 2) baseline CD16 expression on peripheral NK cells showed clear correlations to patient responses with MOR00208 therapy. Specifically, patients having a baseline peripheral NK cell count of at least 100 cells/µl correlated with a higher Disease Control Rate (DCR). DCR includes patients have Complete Response (CR) + Partial Response (PR) + Stable Disease (SD). Additionally, patients having a baseline NK cell count of at least 100 cells/µl had a significantly better Progression Free Survival (PFS) as compared to patients having lower NK cells counts. In addition, patients having a baseline CD16 expression on NK cells of at least 60,000 (ABCs) correlated with higher Disease Control Rate (DCR).

[0017] Therefore, patients diagnosed with CLL, ALL, NHL and SLL and having either a) baseline peripheral NK cell count of at least 100 cells / µl or 2) baseline CD16 expression on peripheral NK cells of at least 60,000 ABCs are more likely to benefit from MOR00208 treatment.

[0018] The invention provides a method of identifying a subject having chronic lymphocytic leukemia (CLL) or acute lymphoblastic leukemia (ALL) that is responsive to treatment with an anti-CD19 antibody, said method comprising:

1. a. providing a blood sample obtained from said subject prior to treatment with said anti-CD19 antibody,
2. b. determining the level of at least one biomarker in said sample selected from the group consisting of:
    1. i. peripheral NK cell count, and
    2. ii. CD16 expression levels on peripheral NK cells,
3. c. comparing the level of said at least one biomarker in said sample to a predetermined cut off level,

wherein levels of said at least one biomarker at or above the predetermined cut off level is indicative of a subject who would benefit from treatment with an anti-CD19 antibody.

[0019] The invention also provides an anti-CD19 antibody for use in the treatment of a patient having chronic lymphocytic leukemia (CLL) or acute lymphoblastic leukemia (ALL), wherein the patient is identified according to a method of the invention.

Description of Drawings

[0020]

Figure 1 shows the amino acid sequences of MOR00208 variable domains and CDRs.

Figure 2 shows the amino acid sequences of MOR00208's full heavy and light chains.

Figure 3 shows the Receive Operating Characteristic (ROC) analysis of peripheral NK cell counts as a predictor for DCR.

Figure 4 shows the ROC analysis of CD16 expression levels on peripheral NK cells (ABCs) as a predictor for DCR.

Figure 5 shows the ROC analysis of peripheral T cell count as a potential predictor for DCR.

Figure 6 shows that peripheral NK cell counts and CD16 expression levels on peripheral NK cells are independent variables and not correlated.

Figure 7 shows the Forest Plot with DCRs in patient subgroups with specific baseline characteristics and biomarkers

Figure 8 shows the progression free survival difference between patients having at least 100 cells / µl peripheral NK cell counts versus patients having lower NK cell counts.

Figure 9 shows the progression free survival difference between patients having at least 60,000 ABCs in CD16 expression on peripheral NK cells versus patients having lower CD16 expression on NK cells.

Figure 10 shows the progression free survival difference between patients having at least 500 cells / µl peripheral T cell counts versus patients having lower T cell counts.

Detailed Description

[0021] The term **"antibody"** means monoclonal antibodies, including any isotype, such as, IgG, IgM, IgA, IgD and IgE. An IgG antibody is comprised of two identical heavy chains and two identical light chains that are joined by disulfide bonds. Each heavy and light chain contains a constant region and a variable region. Each variable region contains three segments called **"complementarity-determining regions" ("CDRs")** or **"hypervariable regions",** which are primarily responsible for binding an epitope of an antigen. They are referred to as CDR1, CDR2, and CDR3, numbered sequentially from the N-terminus. The more highly conserved portions of the variable regions outside of the CDRs are called the **"framework regions".** An **"antibody fragment"** means an Fv, scFv, dsFv, Fab, Fab' F(ab')2 fragment, or other fragment, which contains at least one variable heavy or variable light chain, each containing CDRs and framework regions.

[0022] "VH" refers to the variable region of an immunoglobulin heavy chain of an antibody, or antibody fragment. **"VL"** refers to the variable region of the immunoglobulin light chain of an antibody, or antibody fragment.

[0023] "Fc region" means the constant region of an antibody, which in humans may be of the IgG1, 2, 3, 4 subclass or others. The sequences of human Fc regions are available at IMGT, Human IGH C-REGIONs, www.imgt.org/IMGTrepertoire/Proteins /protein/human/IGH/IGHC/Hu_IGHCallgenes.html (retrieved on 16 May 2011).

[0024] The term patient includes a human.

[0025] NHL is a heterogeneous malignancy originating from lymphocytes. In the United States (U.S.), the incidence is estimated at 65,000/year with mortality of approximately 20,000 (American Cancer Society, 2006; and SEER Cancer Statistics Review). The disease can occur in all ages, the usual onset begins in adults over 40 years, with the incidence increasing with age. NHL is characterized by a clonal proliferation of lymphocytes that accumulate in the lymph nodes, blood, bone marrow and spleen, although any major organ may be involved. The current classification system used by pathologists and clinicians is the World Health Organization (WHO) Classification of Tumours, which organizes NHL into precursor and mature B-cell or T-cell neoplasms. The PDQ is currently dividing NHL as indolent or aggressive for entry into clinical trials. The indolent NHL group is comprised primarily of follicular subtypes, small lymphocytic lymphoma, MALT (mucosa-associated lymphoid tissue), and marginal zone; indolent encompasses approximately 50% of newly diagnosed B-cell NHL patients. Aggressive NHL includes patients with histologic diagnoses of primarily diffuse large B cell (DLBL, DLBCL, or DLCL) (40% of all newly diagnosed patients have diffuse large cell), Burkitt's, and mantle cell. The clinical course of NHL is highly variable. A major determinant of clinical course is the histologic subtype. Most indolent types of NHL are considered to be incurable disease. Patients respond initially to either chemotherapy or antibody therapy and most will relapse. Studies to date have not demonstrated an improvement in survival with early intervention. In asymptomatic patients, it is acceptable to "watch and wait" until the patient becomes symptomatic or the disease pace appears to be accelerating. Over time, the disease may transform to a more aggressive histology. The median survival is 8 to 10 years, and indolent

patients often receive 3 or more treatments during the treatment phase of their disease. Initial treatment of the symptomatic indolent NHL patient historically has been combination chemotherapy. The most commonly used agents include: cyclophosphamide, vincristine and prednisone (CVP); or cyclophosphamide, adriamycin, vincristine, prednisone (CHOP). Approximately 70% to 80% of patients will respond to their initial chemotherapy, duration of remissions last on the order of 2-3 years. Ultimately the majority of patients relapse. The discovery and clinical use of the anti-CD20 antibody, rituximab, has provided significant improvements in response and survival rate. The current standard of care for most patients is rituximab + CHOP (R-CHOP) or rituximab + CVP (R-CVP). Interferon is approved for initial treatment of NHL in combination with alkylating agents, but has limited use in the U.S. Rituximab therapy has been shown to be efficacious in several types of NHL, and is currently approved as a first line treatment for both indolent (follicular lymphoma) and aggressive NHL (diffuse large B cell lymphoma). However, there are significant limitations of anti-CD20 monoclonal antibody (mAb), including primary resistance (50% response in relapsed indolent patients), acquired resistance (50% response rate upon re-treatment), rare complete response (2% complete resonse rate in relapsed population), and a continued pattern of relapse. Finally, many B cells do not express CD20, and thus many B-cell disorders are not treatable using anti-CD20 antibody therapy.

[0026] In addition to NHL there are several types of leukemias that result from dysregulation of B cells. Chronic lymphocytic leukemia (also known as "chronic lymphoid leukemia" or "CLL"), is a type of adult leukemia caused by an abnormal accumulation of B lymphocytes. In CLL, the malignant lymphocytes may look normal and mature, but they are not able to cope effectively with infection. CLL is the most common form of leukemia in adults. Men are twice as likely to develop CLL as women. However, the key risk factor is age. Over 75% of new cases are diagnosed in patients over age 50. More than 10,000 cases are diagnosed every year and the mortality is almost 5,000 a year (American Cancer Society, 2006; and SEER Cancer Statistics Review). CLL is an incurable disease but progresses slowly in most cases. Many people with CLL lead normal and active lives for many years. Because of its slow onset, early-stage CLL is generally not treated since it is believed that early CLL intervention does not improve survival time or quality of life. Instead, the condition is monitored over time. Initial CLL treatments vary depending on the exact diagnosis and the progression of the disease. There are dozens of agents used for CLL therapy. Combination chemotherapy regimens such as FCR (fludarabine, cyclophosphamide and rituximab), and BR (Ibrutinib and rituximab) are effective in both newly-diagnosed and relapsed CLL. Allogeneic bone marrow (stem cell) transplantation is rarely used as a first-line treatment for CLL due to its risk.

[0027] Another type of leukemia is Small lymphocytic lymphoma (SLL) that is considered a CLL variant that lacks the clonal lymphocytosis required for the CLL diagnosis, but otherwise shares pathological and immunophenotypic features (Campo et al., 2011). The definition of SLL requires the presence of lymphadenopathy and/or splenomegaly. Moreover, the number of B lymphocytes in the peripheral blood should not exceed 5 × 109/L. In SLL, the diagnosis should be confirmed by histopathologic evaluation of a lymph node biopsy whenever possible (Hallek et al., 2008). The incidence of SLL is approximately 25% of CLL in the US (Dores et al.,

2007).

[0028] Another type of leukemia is acute lymphoblastic leukemia (ALL), also known as acute lymphocytic leukemia. ALL is characterized by the overproduction and continuous multiplication of malignant and immature white blood cells (also known as lymphoblasts) in the bone marrow. 'Acute' refers to the undifferentiated, immature state of the circulating lymphocytes ("blasts"), and that the disease progresses rapidly with life expectancy of weeks to months if left untreated. ALL is most common in childhood with a peak incidence of 4-5 years of age. Children of age 12- 16 die more easily from it than others. Currently, at least 80% of childhood ALL are considered curable. Under 4,000 cases are diagnosed every year and the mortality is almost 1,500 a year (American Cancer Society, 2006; and SEER Cancer Statistics Review).

[0029] The use of a CD19 antibody in non-specific B cell lymphomas is discussed in WO2007076950 (US2007154473). The use of a CD19 antibody in CLL, NHL and ALL is described in Scheuermann et al., CD19 Antigen in Leukemia and Lymphoma Diagnosis and Immunotherapy, Leukemia and Lymphoma, Vol. 18, 385-397 (1995).

[0030] Additional antibodies specific for CD19 are described in WO2005012493 (US7109304), WO2010053716 (US12/266,999) (Immunomedics); WO2007002223 (US US8097703) (Medarex); WO2008022152 (12/377,251) and WO2008150494 (Xencor), WO2008031056 (US11/852,106) (Medimmune); WO 2007076950 (US 11/648,505) (Merck Patent GmbH); WO 2009/052431 (US12/253,895) (Seattle Genetics); and WO2010095031 (12/710,442) (Glenmark Pharmaceuticals), WO2012010562 and WO2012010561 (International Drug Development), WO2011147834 (Roche Glycart), and WO 2012/156455 (Sanofi).

[0031] The term **"CD19"** refers to the protein known as CD19, having the following synonyms: B4, B-lymphocyte antigen CD19, B-lymphocyte surface antigen B4, CVID3, Differentiation antigen CD19, MGC12802, and T-cell surface antigen Leu-12.

[0032] Human CD19 has the amino acid sequence of:
MPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLKGTSDGPTQQLTWSRESPLKPF

LKLSLGLPGLGIHMRPLAIWLFIFNVSQQMGGFYLCQPGPPSEKAWQPGWTVNVEGSGELF
RWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLYVWAKDRPEIWEGEPPCLPPRDSLN
QSLSQDLTMAPGSTLWLSCGVPPDSVSRGPLSWTHVHPKGPKSLLSLELKDDRPARDMW
VMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITARPVLWHWLLRTGGWKVSAVTLAYLI
FCLCSLVGILHLQRALVLRRKRKRMTDPTRRFFKVTPPPGSGPQNQYGNVLSLPTPTSGLG
RAQRWAAGLGGTAPSYGNPSSDVQADGALGSRSPPGVGPEEEEGEGYEEPDSEEDSEFY
ENDSNLGQDQLSQDGSGYENPEDEPLGPEDEDSFSNAESYENEDEELTQPVARTMDFLSP
HGSAWDPSREATSLGSQSYEDMRGILYAAPQLRSIRGQPGPNHEEDADSYENMDNPDGP
DPAWGGGGRMGTWSTR. (SEQ ID NO: 7)

[0033] **"MOR00208"** is an anti-CD19 antibody. The amino acid sequence of the variable

domains is provided in Figure 1. The amino acid sequence of the heavy and light chain Fc regions of MOR00208 are provided in Figure 2. "MOR00208" and "XmAb 5574" are used as synonyms to describe the antibody shown in Figures 1 and 2. The MOR00208 antibody is described in US patent application serial number 12/377,251.

[0034] US patent application serial number 12/377,251 describes the antibody named 4G7 H1.52 Hybrid S239D/1332E / 4G7 L1.155 (later named MOR00208) as follows:

>4G7 H1.52 Hybrid S239D/1332E
EVQLVESGGGLVKPGGSLKLSCAASGYTFTSYVMHWVRQAPGKGLEWIGYINPYN
DGTKYNEKFQGRVTISSDKSISTAYMELSSLRSEDTAMYYCARGTYYYGTRVFDYWGQGTL
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL
GGPDVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQ
FNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKALPAPEEKTISKTKGQPREPQVYTLPPSRE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 8)

> 4G7 L1.155
DIVMTQSPATLSLSPGERATLSCRSSKSLQNVNGNTYLYWFQQKPGQSPQLLIYRMSNLN
SGVPDRFSGSGSGTEFTLTISSLEPEDFAVYYCMQHLEYPITFGAGTKLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST
LTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 9)

[0035] A pharmaceutical composition includes an active agent, e.g. an antibody for therapeutic use in humans. A pharmaceutical composition may additionally include pharmaceutically acceptable carriers or excipients.

[0036] **"Administered"** or **"administration"** refers to the delivery of a pharmaceutical composition by an injectable form, such as, for example, an intravenous, intramuscular, intradermal or subcutaneous route or mucosal route, for example, as a nasal spray or aerosol for inhalation or as an ingestable solution, capsule or tablet.

[0037] The antibody which is administered according to the present disclosure is administered to the patient in a therapeutically effective amount. A "therapeutically effective amount" refers to an amount sufficient to provide some improvement of the clinical manifestations of a given disease or disorder. As an example, patients in the exemplified study received dosing of MOR00208 at 12mg/kg once weekly, and in maintenance once every two weeks or monthly.

[0038] The amount that is effective for a particular therapeutic purpose will depend on the severity of the disease or injury as well as on the weight and general state of the subject. It will be understood that determination of an appropriate dosage may be achieved, using routine experimentation, by constructing a matrix of values and testing different points in the matrix, all

of which is within the ordinary skills of a trained physician or clinical scientist.

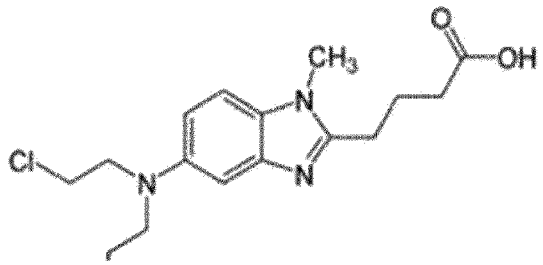
[0039] Baseline means prior to administration of the desired therapy. For example, prior to administration of the desired anti-CD19 antibody.

[0040] A receiver operating characteristic (ROC) analysis was used to analyze the predictivity, sensitivity, specifity and to determine the cut-offs for potential biomarkers, such as NK cell counts, CD16 expression levels on NK cells, and T cells counts. The following additional methods exist for estimating an optimal cut-off: "Max.Accuracy" - the cut-off which maximize the accuracy; b) "Max.DOR" - the cut-off which maximize the diagnostic odds ratio; c) "Error.rate" - the cut-off which minimizes the error rate; d) "Max.Accuracy.area" - the cut-off which maximize the accuracy area; e) "Max.Sens+Spec" - the cut-off which maximize the sum of sensitivity with specificity; f) "Max.Youden" - the cut-off which maximize the Youden index; g) "Se=Sp" - the cut-off which Sensitivity is equal to Specificity; h) "Min.ROC.Dist" - the cut-off which minimize the distance between the curve and the upper left corner of the graph; i) "Max.Efficiency" - the cut-off which maximize the efficiency; and j) "Min.MCT" - the cut-off which minimize the misclassification cost term. See Lopez-Raton, M., Rodriguez-Alvarez, M.X, Cadarso-Suarez, C. and Gude-Sampedro, F. (2014). Optimal Cutpoints: An R Package for Selecting Optimal Cutpoints in Diagnostic Tests. Journal of Statistical Software 61 (8), 1-36.

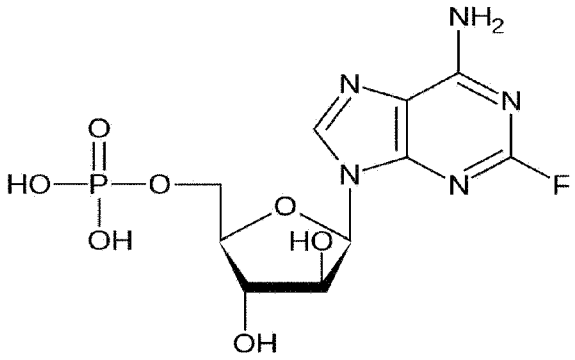
[0041] Antibodies specific to CD19 have also been tested preclinically in combination with other drugs. For example, MOR00208 had been tested in combination with nitrogen mustards, purine analogs, thalidomide analogs, phosphoinositide 3-kinase inhibitor, BCL-2 inhibitors and bruton's tyrosine kinase (BTK) inhibitors.

[0042] A **"nitrogen mustard"** is a nonspecific DNA alkylating agent used as chemotherapy. Alkylating agents add an alkyl group (CnH2n+1) to nucleic acid bases, e.g., adding an alkyl group to the guanine base of DNA at the number 7 nitrogen atom of the imidazole ring. The alkylation steps result in the formation of interstrand cross-links (ICLs). These ICLs are highly cytotoxic, since they block fundamental metabolic processes such as replication and transcription. Nitrogen mustards include cyclophosphamide, chlorambucil, uramustine, ifosfamide, melphalan and bendamustine.

[0043] Bendamustine is marketed under the names Ribomustin®,and Treanda®, and is also known as SDX-105, by Mundipharma International Corporation Limited (Licensee of Astellas Pharma GmbH) and Cephalon for the treatment of chronic lymphocytic leukemias (CLL), indolent B-cell non-Hodgkin's lymphoma (NHL), and other lymphomas. Bendamustine has the following structure:

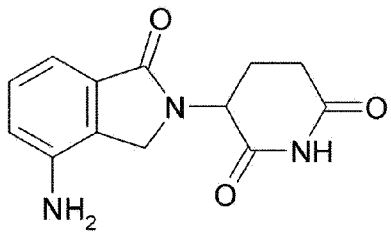


[0044] A purine analog is an antimetabolite, which mimics the structure of metabolic purines, thereby interfering with the synthesis of nucleic acids. Fludarabine, for example, may be incorporated into RNA and DNA by substituting for the purine nucleotides, adenine and guanine. Purine analogs inhibit growth of fast proliferating cells of an individual, e.g. cancer cells, bone marrow cells or cells present in the gastrointestinal tract. Purine analogs include mercaptopurine, azathioprine, thioguanine and fludarabine. Fludarabine or fludarabine phosphate (Fludara®) is a chemotherapy drug used in the treatment of chronic lymphocytic leukemia and indolent non-Hodgkins lymphomas. Fludarabine is a purine analog. Fludarabine inhibits DNA synthesis by interfering with ribonucleotide reductase and DNA polymerase and is S phase-specific (since these enzymes are highly active during DNA replication). Fludarabine has the following structure:



[0045] A **"thalidomide analog"** includes, but is not limited to, thalidomide itself, lenalidomide (CC-5013, Revlimid™), Pomalidomide (CC4047, Actimid™) and the compounds disclosed in WO2002068414 and WO2005016326. The term refers to a synthetic chemical compound using the thalidomide structure as a backbone (e.g., side groups have been added or such groups have been deleted from the parent structure). The analog differs in structure from thalidomide and its metabolite compounds such as by a difference in the length of an alkyl chain, a molecular fragment, by one or more functional groups, or a change in ionization. The term "thalidomide analog" also includes the metabolites of thalidomide. Thalidomide analogs include the racemic mixture of the S- and the R-enantiomer of a respective compound and the S-enantiomer or to the R-enantiomer individually. The racemic mixture is preferred.

[0046] Thalidomide analogs include the compounds of the following structures: (A) Lenalidomide

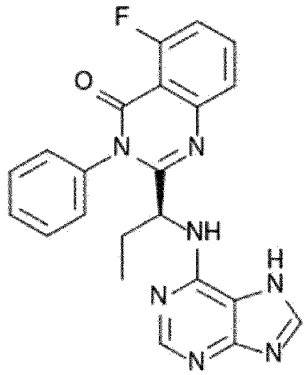


[0047] A **"phosphoinositide 3-kinase inhibitor"** is a class of medical drug that functions by inhibiting one or more of the phosphoinositide 3-kinase enzymes, which are part of the PI3K/AKT/mTOR pathway, an important signalling pathway for many cellular functions such as growth control, metabolism and translation initiation.

[0048] There are a number of different classes and isoforms of PI3Ks. Class 1 PI3Ks have a catalytic subunit known as p110, with four types (isoforms) - p110 alpha, p110 beta, p110 gamma and p110 delta. Current inhibitors being studied inhibit one or more isoforms of the class I PI3Ks.

[0049] Phosphoinositide 3-kinase inhibitors include at least Idelalisib, Duvelisib and Copanlisib. Idelalisib is marketed by Gilead Sciences, Inc. (trade name Zydelig, also named GS-1101 or CAL-101). Idelalisib is is currently labelled for the treatment of relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities; relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies; relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies. The substance acts as a phosphoinositide 3-kinase inhibitor; more specifically, it blocks P110δ, the delta isoform of the enzyme phosphoinositide 3-kinase.

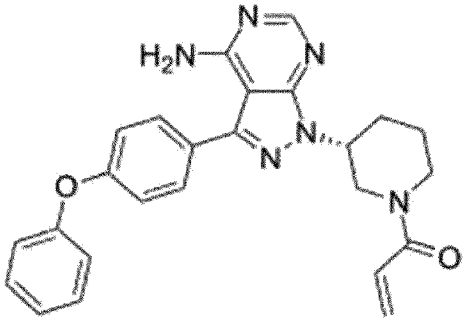
[0050] The formula of Idelalisib is:



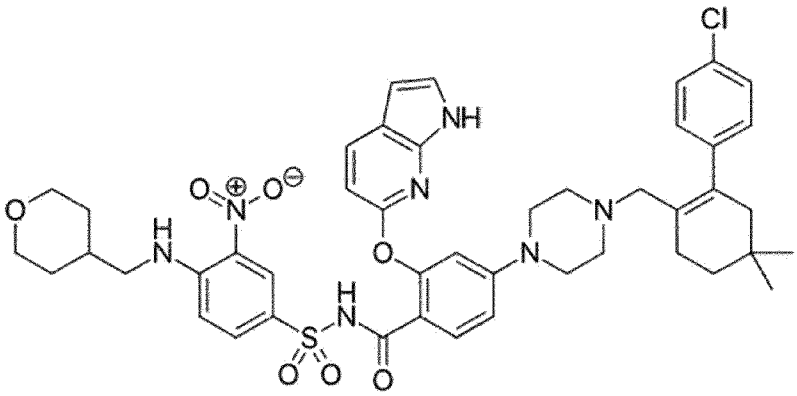
[0051] A **"Bruton's tyrosine kinase (BTK) inhibitor"** is a class of drug that functions by inhibiting the tyrosine-protein kinase BTK enzyme, which plays an important role in B-cell development. Specifically, BTK contains a PH domain that binds phosphatidylinositol (3,4,5)-trisphosphate (PIP3). PIP3 binding induces Btk to phosphorylate phospholipase C, which in turn hydrolyzes PIP2, a phosphatidylinositol, into two second messengers, inositol triphosphate (IP3) and diacylglycerol (DAG), which then go on to modulate the activity of downstream proteins during B-cell signalling.

[0052] Bruton's tyrosine kinase (BTK) inhibitors include Ibrutinib. Ibrutinib is marketed by Pharmacyclics, Inc and Johnson & Johnson's Janssen Pharmaceutical (trade name Imbruvica, also named PCI-32765). Ibrutinib is currently labelled for the treatment of patients with Mantle

cell lymphoma (MCL) who have received at least one prior therapy, Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, Chronic lymphocytic leukemia with 17p deletion, and Waldenström's macroglobulinemia. The formula of Ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has the following structure:



[0053] A **"BCL-2 inhibitor"** is a class of drug that functions by inhibiting anti-apoptotic B-cell lymphoma-2 (Bcl-2) protein, leading to programmed cell death of cells. BCL-2 inhibitor include venetoclax. Venetoclax is marketed by Abbvie and Genentech (trade name VENCLEXTA™, also known as GDC-0199, ABT-199, and RG7601). Venetoclax is currently labelled for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy. The formula of venetoclaxis4-(4-{[2-(4-Chlorophenyl)-4,4-dimethyl-1-cyclohexen-1-yl]methyl}-1-piperazinyl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide and has the following structure:



[0054] "Venetoclax," "ABT", and "ABT-199" are used as synonyms herein.

Embodiments

[0055] An aspect is a method of identifying a subject having chronic lymphocytic leukemia (CLL) or acute lymphoblastic leukemia (ALL) that is responsive to treatment with an anti-CD19 antibody, said method comprising:

1. a. providing a blood sample obtained from said subject prior to treatment with said anti-CD19 antibody,
2. b. determining the level of at least one biomarker in said sample selected from the group consisting of:
    1. i. peripheral NK cell count, and
    2. ii. CD16 expression levels on peripheral NK cells,
3. c. comparing the level of said at least one biomarker in said sample to a predetermined cut off level,
   wherein levels of said at least one biomarker at or above the predetermined cut off level is indicative of a subject who would benefit from treatment with an anti-CD19 antibody.

[0056] In embodiments, said sample comprises peripheral NK cells.

[0057] In embodiments, the predetermined cut off level of said biomarker is a baseline peripheral NK cell count of at least 50 cells / µl, at least 75 cells / µl, at least 100 cells / µl, at least 125 cells / µl, at least 150 cells / µl, at least 175 cells / µl, at least 200 cells / µl, at least 225 cells / µl, or at least 250 cells / µl. In embodiments, the predetermined cut off level of said biomarker is baseline CD16 expression levels on peripheral NK cells of at least 45,000 ABCs, at least 60,000 ABCs, at least 75,000 ABCs, or at least 90,000 ABCs.

[0058] In embodiments, the predetermined cut off of said biomarker is:

1. a. a baseline peripheral NK cell count of at least 50 cells / µl, or
2. b. baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0059] In embodiments, the predetermined cut of said biomarker is:

1. a. baseline peripheral NK cell count of at least 50 cells / µl, and
2. b. baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0060] In embodiments, predetermined cut off level a baseline peripheral NK cell count of at least 50 cells / µl. In embodiments, the predetermined cut of said biomarker is baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0061] In embodiments, the predetermined cut off of said biomarker is:

1. a. a baseline peripheral NK cell count of at least 70 cells / µl, or
2. b. baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0062] In embodiments, the predetermined cut off of said biomarker is:

1. a. a baseline peripheral NK cell count of at least 70 cells / µl, and
2. b. baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0063] In embodiments, predetermined cut off level a baseline peripheral NK cell count of at least 70 cells / µl. In embodiments, the predetermined cut of said biomarker is baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0064] In embodiments, the predetermined cut off of said biomarker is:

1. a. a baseline peripheral NK cell count of at least 80 cells / µl, or
2. b. baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0065] In embodiments, the predetermined cut off of said biomarker is:

1. a. a baseline peripheral NK cell count of at least 80 cells / µl, and
2. b. baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0066] In embodiments, predetermined cut off level a baseline peripheral NK cell count of at least 80 cells / µl. In embodiments, the predetermined cut of said biomarker is baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0067] In embodiments, the predetermined cut off of said biomarker is:

1. a. a baseline peripheral NK cell count of at least 90 cells / µl, or
2. b. baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0068] In embodiments, the predetermined cut off of said biomarker is:

1. a. a baseline peripheral NK cell count of at least 90 cells / µl, and
2. b. baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0069] In embodiments, predetermined cut off level a baseline peripheral NK cell count of at least 90 cells / µl. In embodiments, the predetermined cut of said biomarker is baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0070] In embodiments, the predetermined cut off of said biomarker is:

1. a. a baseline peripheral NK cell count of at least 100 cells / µl, or
2. b. baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0071] In embodiments, the predetermined cut off of said biomarker is:

1. a. a baseline peripheral NK cell count of at least 100 cells / µl, and
2. b. baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0072] In embodiments, predetermined cut off level a baseline peripheral NK cell count of at least 100 cells / µl. In embodiments, the predetermined cut of said biomarker is baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0073] An aspect is a method of identifying a subject having chronic lymphocytic leukemia (CLL) or acute lymphoblastic leukemia (ALL) that is responsive to treatment with an anti-CD19 antibody, said method comprising:

1. a. providing a blood sample obtained from said subject prior to treatment with said anti-CD19 antibody,
2. b. determining the level of at least one biomarker in said sample selected from the group consisting of:
    1. i. peripheral NK cell count, and
    2. ii. CD16 expression levels on peripheral NK cells,
3. c. comparing the level of said at least one biomarker in said sample to a predetermined cut off level,
   wherein the baseline peripheral NK cell count is at least 50 cells / µl, at least 60 cells / µl, at least 70 cells / µl, at least 80 cells / µl, at least 90 cells / µl or at least 100 cells / µl and the baseline CD16 expression levels on peripheral NK cells is at least 60,000 (ABCs), and wherein the anti-CD19 antibody comprises an HCDR1 region comprising the sequence SYVMH (SEQ ID NO: 1), an HCDR2 region comprising the sequence NPYNDG (SEQ ID NO: 2), an HCDR3 region comprising the sequence GTYYYGTRVFDY (SEQ ID NO: 3), an LCDR1 region comprising the sequence RSSKSLQNVNGNTYLY (SEQ ID NO: 4), an LCDR2 region comprising the sequence RMSNLNS (SEQ ID NO: 5), and an LCDR3 region comprising the sequence MQHLEYPIT (SEQ ID NO: 6).

[0074] An aspect is a method of identifying a subject having chronic lymphocytic leukemia (CLL) or acute lymphoblastic leukemia (ALL) that is responsive to treatment with an anti-CD19 antibody, said method comprising:

1. a. providing a blood sample obtained from said subject prior to treatment with said anti-CD19 antibody,
2. b. determining the level of at least one biomarker in said sample selected from the group consisting of:
    1. i. peripheral NK cell count, and
    2. ii. CD16 expression levels on peripheral NK cells,
3. c. comparing the level of said at least one biomarker in said sample to a predetermined cut off level,
   wherein the baseline peripheral NK cell count is at least 100 cells / µl, or the baseline CD16 expression levels on peripheral NK cells is at least 60,000 (ABCs), and wherein the anti-CD19 antibody comprises an HCDR1 region comprising the sequence SYVMH (SEQ ID NO: 1), an HCDR2 region comprising the sequence NPYNDG (SEQ ID NO: 2), an HCDR3 region comprising the sequence GTYYYGTRVFDY (SEQ ID NO: 3), an LCDR1 region comprising the sequence RSSKSLQNVNGNTYLY (SEQ ID NO: 4), an LCDR2 region comprising the sequence RMSNLNS (SEQ ID NO: 5), and an LCDR3 region comprising the sequence MQHLEYPIT (SEQ ID NO: 6).

[0075] In embodiments, the predetermined cut of said biomarker is:

1. a. baseline peripheral NK cell count of at least 100 cells / µl, and
2. b. baseline CD16 expression levels on peripheral NK cells of at least 60,000 (ABCs).

[0076] In embodiments, the predetermined cut off level of said biomarker is a baseline peripheral NK cell count of at least 50 cells / µl, at least 75 cells / µl, at least 100 cells / µl, at least 125 cells / µl, at least 150 cells / µl, at least 175 cells / µl, at least 200 cells / µl, at least 225 cells / µl, or at least 250 cells / µl. In embodiments, the predetermined cut off level of said biomarker is baseline CD16 expression levels on peripheral NK cells of at least 45,000 ABCs, at least 60,000 ABCs, at least 75,000 ABCs, or at least 90,000 ABCs.

[0077] Also disclosed is a method of treating a patient having chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) or small lymphocytic lymphoma (SLL) with an anti- CD19 antibody, the method comprising

1. a. obtaining a baseline peripheral NK cell count in the patient, or a baseline CD16 expression level on the peripheral NK cells of the patient, and
2. b. administering an effective amount of the anti-CD19 antibody to the patient having a baseline peripheral NK cell count of at least 50 cells/µl, at least 60 cells/µl, at least 70 cells/µl, at least 80 cells/µl, at least 90 cells/µl or at least 100 cells/$_N$l or a baseline CD16 expression level on the peripheral NK cells of at least 60,000 (ABCs).

[0078] Also disclosed is a method of treating a patient having chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) or small lymphocytic lymphoma (SLL) with an anti- CD19 antibody, the method comprising

1. a. obtaining a baseline peripheral NK cell count in the patient, or a baseline CD16 expression level on the peripheral NK cells of the patient, and
2. b. administering an effective amount of the anti-CD19 antibody to the patient having a baseline peripheral NK cell count of at least 100 cells/ µl or a baseline CD16 expression level on the peripheral NK cells of at least 60,000 (ABCs).

[0079] The method of treating a patient chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) or small lymphocytic lymphoma (SLL) with an anti- CD19 antibody, may comprise

1. a. obtaining an baseline peripheral NK cell count in the patient, and
2. b. administering an effective amount of the anti-CD19 antibody to the patient having an NK cell count of at least 50 cells/µl, at least 60 cells/µl, at least 70 cells/µl, at least 80 cells/µl, at least 90 cells/µl or at least 100 cells/µl.

[0080] The method of treating a patient chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) or small lymphocytic lymphoma (SLL) with an anti- CD19 antibody, may comprise

1. a. obtaining an baseline peripheral NK cell count in the patient, and
2. b. administering an effective amount of the anti-CD19 antibody to the patient having an NK cell count of at least 50 cells/µl, at least 60 cells/µl, at least 70 cells/µl, at least 80 cells/µl, at least 90 cells/µl or at least 100 cells/µl.

[0081] The method of treating a patient chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) or small lymphocytic lymphoma (SLL) with an anti- CD19 antibody, may comprise

1. a. obtaining an baseline peripheral NK cell count in the patient, and
2. b. administering an effective amount of the anti-CD19 antibody to the patient having an NK cell count of at least 100 cells/ µl.

[0082] The method of treating a patient having chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) or small lymphocytic

lymphoma (SLL) with an anti- CD19 antibody, may comprise

1. a. obtaining baseline CD16 expression levels on the peripheral NK cells of the patient, and
2. b. administering an effective amount of the anti-CD19 antibody to the patient having CD16 levels on the NK cells of at least 60,000 (ABCs).

[0083] As noted elsewhere herein, the invention provides an anti-CD19 antibody for use in the treatment of a patient having chronic lymphocytic leukemia (CLL) or acute lymphoblastic leukemia (ALL), wherein the patient is identified according to the method of the invention.

[0084] In embodiments, the anti-CD19 antibody is administered to patients having both a baseline peripheral NK cell count of at least 50 cells/µl, at least 60 cells/µl, at least 70 cells/µl, at least 80 cells/µl, at least 90 cells/µl or at least 100 cells/µl, and a baseline CD16 expression level on peripheral NK cells of at least 60,000 (ABCs).

[0085] In embodiments, the anti-CD19 antibody is administered to patients having both a baseline peripheral NK cell count of at least 100 cells/ µl, and a baseline CD16 expression level on peripheral NK cells of at least 60,000 (ABCs).

[0086] In embodiments, the anti-CD19 antibody is administered to patients having a baseline peripheral NK cell count of at least 50 cells / µl, at least 75 cells / µl, at least 100 cells / µl, at least 125 cells / µl, at least 150 cells / µl, at least 175 cells / µl, at least 200 cells / µl, at least 225 cells / µl, or at least 250 cells / µl. In embodiments, the anti-CD19 antibody is administered to patients having baseline CD16 expression levels on peripheral NK cells of at least 45,000 ABCs, at least 60,000 ABCs, at least 75,000 ABCs, or at least 90,000 ABCs.

[0087] Also disclosed is a method of treating a patient having chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) or small lymphocytic lymphoma (SLL) with an anti- CD19 antibody, said method comprising:

1. a. providing a sample obtained from said subject prior to treatment with said anti-CD19 antibody,
2. b. determining the level of at least one biomarker in said sample selected from the group consisting of:
    1. i. peripheral NK cell count, and
    2. ii. CD16 expression levels on peripheral NK cells,
3. c. comparing the level of said at least one biomarker in said sample to a predetermined cut off level,
4. d. administering an effective amount of anti-CD19 antibody to the patient having an peripheral NK cell count of at least 100 cells/ µl or CD16 expression level on the peripheral NK cells of at least 60,000 (ABCs).

[0088] Also disclosed is a method of treating a patient having chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) or small lymphocytic lymphoma (SLL) comprising
administering an effective amount of an anti-CD19 antibody to the patient if

1. a. the baseline peripheral NK cell count of the patient is at least 100 cells / µl or
2. b. the baseline CD16 expression levels on peripheral NK cells is at least 60,000 (ABCs).

[0089] Also disclosed is a method of treating a patient having chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) or small lymphocytic lymphoma (SLL) comprising

1. a. obtaining the peripheral NK cell count of the patient,
2. b. administering an effective amount of an anti-CD19 antibody to patients having peripheral NK cell counts of at least 100 cells / µl.

[0090] Also disclosed is a method of treating a patient having chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) or small lymphocytic lymphoma (SLL) comprising

1. a. obtaining the CD16 expression levels on the peripheral NK cells of the patient,
2. b. administering an effective amount of an anti-CD19 antibody to patients having an CD16 expression levels on the peripheral NK cells of at least 60,000 (ABCs).

[0091] As noted elsewhere herein, the invention provides an anti-CD19 antibody for use in the treatment of a patient having chronic lymphocytic leukemia (CLL) or acute lymphoblastic leukemia (ALL), wherein the patient is identified according to the method of the invention.

[0092] In embodiments, anti-CD19 antibody is administered to patients having both a baseline peripheral NK cell count of at least 100 cells/ µl, and a baseline CD16 expression level on peripheral NK cells of at least 60,000 (ABCs). In embodiments, the anti-CD19 antibody is administered to patients having a baseline peripheral NK cell count of at least 50 cells / µl, at least 75 cells / µl, at least 100 cells / µl, at least 125 cells / µl, at least 150 cells / µl, at least 175 cells / µl, at least 200 cells / µl, at least 225 cells / µl, or at least 250 cells / µl. In embodiments, the anti-CD19 antibody is administered to patients having baseline CD16 expression levels on peripheral NK cells of at least 45,000 ABCs, at least 60,000 ABCs, at least 75,000 ABCs, or at least 90,000 ABCs.

[0093] In embodiments the baseline peripheral NK cell count or baseline CD16 levels (ABCs)

on the peripheral NK cells is obtained from a blood sample taken from the patient. In embodiments the peripheral NK cell count and/or the CD16 expression levels are measured prior to administration of the anti-CD19 antibody.

[0094] In embodiments, the antibody specific for CD19 comprises an HCDR1 region comprising the sequence SYVMH (SEQ ID NO: 1), an HCDR2 region comprising the sequence NPYNDG (SEQ ID NO: 2), an HCDR3 region comprising the sequence GTYYYGTRVFDY (SEQ ID NO: 3), an LCDR1 region comprising the sequence RSSKSLQNVNGNTYLY (SEQ ID NO: 4), an LCDR2 region comprising the sequence RMSNLNS (SEQ ID NO: 5), and an LCDR3 region comprising the sequence MQHLEYPIT (SEQ ID NO: 6).

[0095] In embodiments the baseline peripheral NK cell count or baseline CD16 expression levels on the peripheral NK cells is obtained from a blood sample taken from the patient.

[0096] In an embodiment, the patient has chronic lymphocytic leukemia. In an embodiment, the patient has acute lymphoblastic leukemia.

[0097] In embodiments, the treatment results in the therapeutic effect selected from the group consisting of Disease Control Rate (DCR) and longer duration of Progression Free Survival.

[0098] In embodiments, the treatment further comprises administration of an effective amount of a nitrogen mustard. In an embodiment that nitrogen mustard is bendamustine. In embodiments, the treatment further comprises administration of an effective amount of a purine analog. In embodiments, the purine analog is fludarabine. In embodiments, the treatment further comprises administration of an effective amount of a Bruton's tyrosine kinase (BTK) inhibitor. In embodiments, the Bruton's tyrosine kinase (BTK) inhibitor is ibrutinib. In embodiments, the treatment further comprises administration of an effective amount of a phosphoinositide 3-kinase inhibitor. In an embodiment the phosphoinositide 3-kinase inhibitor is idelalisib. In embodiments, the treatment further comprises administration of an effective amount of a thalidomide analog. In an embodiment, the thalidomide analog is lenalidomide. In embodiments, the treatment further comprises administration of an effective amount of a BCL-2 inhibitor. In an embodiment, the BCL-2 inhibitor is venetoclax.

[0099] As the exemplified anti-CD19 antibody and other anti-CD19 antibodies bind CD19, it is believed that similar results may be seen with other anti-CD19 antibodies. Other anti-CD19 antibodies are described in US patent application serial number 12/377,251 (Xencor), WO2005012493, WO2010053716 (Immunomedics); WO2007002223 (Medarex); WO2008022152 (Xencor); WO2008031056 (Medimmune); WO 2007/076950 (Merck Patent GmbH); WO 2009/052431 (Seattle Genetics); and WO2010095031 (Glenmark Pharmaceuticals).

[0100] In embodiments, the antibody specific for CD19 comprises an antibody that cross-competes with the antibody comprising an HCDR1 region comprising the sequence SYVMH (SEQ ID NO: 1), an HCDR2 region comprising the sequence NPYNDG (SEQ ID NO: 2), an

HCDR3 region comprising the sequence GTYYYGTRVFDY (SEQ ID NO: 3), an LCDR1 region comprising the sequence RSSKSLQNVNGNTYLY (SEQ ID NO: 4), an LCDR2 region comprising the sequence RMSNLNS (SEQ ID NO: 5), and an LCDR3 region comprising the sequence MQHLEYPIT (SEQ ID NO: 6).

[0101] In embodiments, the antibody specific for CD19 comprises an antibody that binds to the same epitope as an antibody comprising an HCDR1 region comprising the sequence SYVMH (SEQ ID NO: 1), an HCDR2 region comprising the sequence NPYNDG (SEQ ID NO: 2), an HCDR3 region comprising the sequence GTYYYGTRVFDY (SEQ ID NO: 3), an LCDR1 region comprising the sequence RSSKSLQNVNGNTYLY (SEQ ID NO: 4), an LCDR2 region comprising the sequence RMSNLNS (SEQ ID NO: 5), and an LCDR3 region comprising the sequence MQHLEYPIT (SEQ ID NO: 6).

[0102] In embodiments, the antibody specific for CD19 comprises an HCDR1 region of sequence SYVMH (SEQ ID NO: 1), an HCDR2 region of sequence NPYNDG (SEQ ID NO: 2), an HCDR3 region of sequence GTYYYGTRVFDY (SEQ ID NO: 3), an LCDR1 region of sequence RSSKSLQNVNGNTYLY (SEQ ID NO: 4), an LCDR2 region of sequence RMSNLNS (SEQ ID NO: 5), and an LCDR3 region of sequence MQHLEYPIT (SEQ ID NO: 6).

[0103] In embodiments, the antibody specific for CD19 comprises a variable heavy chain of the sequence
EVQLVESGGGLVKPGGSLKLSCAASGYTFTSYVMHWVRQAPGKGLEWIGYINPY
NDGTKYNEKFQGRVTISSDKSISTAYMELSSLRSEDTAMYYCARGTYYYGTRVFDYWG
QGTLVTVSS (SEQ ID NO: 10) and a variable light chain of the sequence
DIVMTQSPATLSLSPGERATLSCRSSKSLQNVNGNTYLYWFQQKPGQSPQLLIYR
MSNLNSGVPDRFSGSGSGTEFTLTISSLEPEDFAVYYCMQHLEYPITFGAGTKLEIK (SEQ
ID NO: 11).

[0104] In an embodiment said antibody comprises a heavy chain constant domain of the sequence
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPDV
FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFR
VVSVLTVVHQDWLNGKEYKCKVSNKALPAPEEKTISKTKGQPREPQVYTLPPSREEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 12).

[0105] In an embodiment, the antibody specific for CD19 comprises a light chain constant domain of the sequence
RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC. (SEQ ID NO: 13).

[0106] In an embodiment, the antibody specific for CD19 comprises a heavy chain having the sequence

EVQLVESGGGLVKPGGSLKLSCAASGYTFTSYVMHWVRQAPGKGLEWIGYINPYNDGTKY
NEKFQGRVTISSDKSISTAYMELSSLRSEDTAMYYCARGTYYYGTRVFDYWGQGTLVTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPDV
FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFR
VVSVLTVVHQDWLNGKEYKCKVSNKALPAPEEKTISKTKGQPREPQVYTLPPSREEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 8)

[0107] In an embodiment, the antibody specific for CD19 comprises a light chain having the sequence

DIVMTQSPATLSLSPGERATLSCRSSKSLQNVNGNTYLYWFQQKPGQSPQLLIYRMSNLN
SGVPDRFSGSGSGTEFTLTISSLEPEDFAVYYCMQHLEYPITFGAGTKLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST
LTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 9)

[0108] Also disclosed herein is a pharmaceutical composition. The composition may comprise an acceptable carrier. The composition may be administered in an effective amount.

Examples

Example 1: T cell and NK cell counting

[0109] The scope of the MOR00208C201 clinical study included the assessment of several exploratory biomarkers. As part of this initiative baseline peripheral T and NK cell counting was performed at the clinical sites.

[0110] T cells are a type of lymphocyte (a subtype of white blood cell) that play a central role in cell-mediated immunity. They can be distinguished from other lymphocytes, such as B cells and NK cells, by the presence of a T-cell receptor on the cell surface.

[0111] Natural killer cells or NK cells are a type of cytotoxic lymphocyte critical to the innate immune system. NK cells provide rapid responses to viral-infected cells, acting at around 3 days after infection, and respond to tumor formation. Typically, immune cells detect major histocompatibility complex (MHC) presented on infected cell surfaces, triggering cytokine release, causing lysis or apoptosis. NK cells are unique, however, as they have the ability to recognize stressed cells in the absence of antibodies and MHC, allowing for a much faster

immune reaction.

Materials and Methods

[0112] TriTest CD3 FITC/CD16+CD56 PE/CD45 PerCP (with TruCOUNT tubes), BD Biosciences, Cat: 340403 (US); 342442 (Europe). Pipettors and pipet tips capable of delivering 20µL, 50µL and 450µL, Gilson Inc. FACS Lysing Solutions, BD Biosciences, Cat: 349202.

Instruments: Flow cytometer, Vortex

Background of flow cytometry:

[0113] Whole blood is stained with fluorochrome-labeled antibodies (TriTEST reagents) that bind specifically to leucocyte surface antigens. The cells travel past the laser beam and scatter the laser light. The stained cells fluoresce. These scatter and fluorescence signals, detected by the instrument, provide information about the cell's size, internal complexity, and relative fluorescence intensity. TriTEST reagents employ fluorescence triggering, allowing direct fluorescence gating of the NK- and T-cell lymphocyte population to reduce contamination of unlysed or nucleated red blood cells in the gate.

Staining

[0114] For each patient sample, a TruCOUNT Tube was labelled with the sample identification number. 20µL of TriTEST CD3/CD16+CD56/CD45 reagent was pipetted into the bottom of the tube. 50µL of well-mixed, anticoagulated whole blood was pipetted into the bottom of the tube. Anticoagulated blood (EDTA) stored at room temperature (20-25°C) must be stained within 24 hours of draw and analyzed within 6 hours of staining (keep at room temperature and protected from light). The tube was vortexed gently to mix. The tube was incubated for 15 minutes in the dark at room temperature (20-25°C). 450µL 1X FACS Lysing Solution was added to the tube. The tube was vortexed and incubated again for 15 minutes in the dark at room temperature (20-25°C).

[0115] Using TruCOUNT Tubes, a known volume of sample is stained directly in a TruCOUNT Tube. The lyophilized pellet in the tube dissolves, releasing a known number of fluorescent beads. During analysis, the absolute number (cells/µL) of positive cells in the sample can be determined by comparing cellular events to bead events.

Flow Cytometry

[0116] The cells were vortexed thoroughly (at low speed) to reduce aggregation before running them on the flow cytometer.

Data Analyses

[0117] The CD45 vs SSC dot plot was visually inspected. Lymphocytes appear as a bright, compact cell population with low to moderate SSC. Monocytes (M) and granulocytes (G) appear as distinct populations. Analysis was completed when the cell populations of monocytes and lymphocytes showed clear separation.

[0118] Lymphocytes were first gated as CD45 positive, low SSC cell population. CD16/CD56 vs CD3 were pre-selected. T-cells (T) should appear as a compact bright CD3 positive cluster. NK-cells (NK) should appear as a compact bright CD16/CD56 positive cluster. Gating was completed and the T, and NK cells were counted.

[0119] Bead event counts were done using a CD16/CD56 vs CD3 plot without any pre-selected gate. Beads should appear as a PE/FITC double positive cluster.

Calculating Absolute Counts

[0120] The absolute number (cells/µL blood) of T cells or NK cells in the sample was determined by comparing cellular events to bead events. Either MultiSET software or manual (using CellQuest or other software) data analysis was done. For manual counting, the number (#) of positive cellular acquired events was divided by the number (#) of acquired bead events, then multiplied by the (total TruCOUNT bead count (lot dependent) divided by whole blood sample volume of 50 µL). The result is absolute cell numbers per microliter.

Equation:

$$\frac{\frac{number\ of\ events\ in\ gate\ containing\ cell\ population\ (T\ or\ NK)}{number\ of\ events\ in\ gate\ 2\ containing\ bead\ population}}{} \times \frac{\#\ of\ total\ TruCOUNT\ beads}{50\mu l\ whole\ blood} = \#cells\ /\mu l\ blood$$

Example:

[0121]

$$\frac{\mathbf{2709}\ acquired\ T\text{–}cells}{\mathbf{10\ 000}\ acquired\ beads} \times \frac{\mathbf{51\ 667}\ total\ beads\ in\ tube}{\mathbf{50}\mu l} = \mathbf{280}\ T\text{–}cells\ /\mu l\ blood$$

Example 2: CD16 Quantification on NK cells

[0122] As part of MOR00208C201 clinical study, CD16 (an exploratory biomarker) was quanitified on peripheral NK Cells centrally by ICON Central Laboratories (Farmingdale, New York).

Materials and Methods

[0123] Antibodies: CD45 AmCyan (Clone 2D1, BD Biosciences, Cat# 339192); CD3 FITC (Clone UCHT1, BioLegend, Cat#300406); Mouse IgG FITC (Clone MOPC-21, BioLegend, Cat#400110); CD16 PE (Clone 3G8, BioLegend, Cat#302008); MOR00208; Mouse IgG PE (Clone MOPC-21, BioLegend, Cat#400114); CD56 PerCP-Cy5.5 (Clone HCD56, BioLegend, Cat#318322); and Mouse IgG PerCP-Cy5.5 (Clone MOPC-21, BioLegend, Cat#400150).

[0124] Material: PharmaTherm insulated shippers (Intelsius, Catalog # PHT014); BD Vacutainer® OPT™ Mononuclear Cell Preparation Tube - Sodium Heparin (16x125 mm / 8mL) (BD, Catalog # 362753); BD Falcon™ 12x75 mm round-bottom tubes (BD, Catalog # 352052); CS&T Beads (BD Biosciences Cat # 642212); Fetal Bovine Serum (FBS), heat inactivated (Sigma F4135, or equivalent); Dulbecco's PBS without Ca^{++} and Mg^{++} (Gibco, Cat #14190, or equivalent); BD Falcon, Cell Strainer, 100 µm, yellow (BD Bioscience, Cat#352360); FACS Buffer, 3% of heat inactivated FBS in 1X DPBS; Deionized water, laboratory stock; Crushed (wet) ice; Ice bucket; Aluminum foil; Conical Tubes, 50 mL; Conical Tubes, 15 mL; Sterile, filter pipette tips; BD Pharm Lyse Lysing Buffer (BD Biosciences, Cat#555899); ViViD LIVE/DEAD® Fixable Violet Dead Cell Stain Kit, for 405 nm excitation (Life Technologies, Cat# L34955); ArC Amine Reactive Beads (Life Technologies, Cat# A10346); BD QuantiBRITE Beads (BD Biosciences, Cat# 340495); and 52 µm nylon mesh (Miami Aqua Culture, for Cat: Nylon 52 µm, 32% open area woven into material).

[0125] Equipment: Centrifuge (refrigerated capability); Lab quake (Tube rocker); Vortex mixer; Laminar flow hood; Incubator (Set at 37°C, 5% CO_2); Advia (cell counter); BD FACSCANTO II flow cytometer; Desi-Vac™ Container, 1.5 liters (VWR, Cat#62344-930); Humidity Sponge™ Indicating (VWR, Cat# 61161-319); and Traceable Humidity-On-A-Card (VWR, Cat#15551-012).

Table 1. CD16 Quantification Assay Panel for PBMC (Peripheral Blood Mononuclear Cell)

Descript ion	Tube #	V450	AmCyan	FITC	PE	PerCP-Cy5.5	APC
Control Tube I	1	ViViD	CD45	Ms IgG	Ms IgG	Ms IgG	---
CD16 ABC	2	ViViD	CD45	CD3	CD16	CD56	---

PBMC Preparation and Labeling Procedures

[0126] Patient's peripheral blood was collected in a CPT tubes and shipped overnight from clinical sites to the central lab in insulated shippers. CPT tubes were centrifuged for 25 min at 1800 x g at RT with brake ON. After centrifugation, CPT tubes were immediately inverted and placed for 10 min on the lab quake to resuspend PBMC layer in autologous plasma and resolve majority of formed cell aggregates. Under sterile conditions, homogenized PBMC/plasma suspension was decanted slowly into the center of 100 µm cell strainer resting on top of a sterile 50 mL conical tube. An equal volume of 1X DPBS was added to the PBMC/plasma suspension (approximately 4 mL) in 15 mL conical tube. The tubes were centrifuged at 300 × g for 10 min at 4 °C and supernatant removed. The tubes were vortexed to resuspend cell pellet. The cell pellet was washed with DBPS, centrifuged, supernatant removed and resuspended by vortexing. The washed PBMC suspension was added into an eppendorf tube containing 1 µL ViViD stock solution; incubated for 15 min on ice and kept in dark (cover with aluminum foil). The stained ViViD PBMC were transferred into a new labeled conical tube and then ice cold FACS Buffer was added. The cells were centrifuged and vortexed again for resuspension. Polystyrene falcon tubes were labeled for each sample (Table 1). The antibodies or isotype control antibodies were added to the appropriate tubes. The aliquot of ViViD stained PBMCs was added to each tube (Table 1). The tubes were vortexed and incubate. FACS Buffer was added and the cells were centrifuged and vortexed again for resuspension. BD Pharm Lyse Lysing Buffer was added, and the cells were vortexed, centrifuge and aspirated to remove supernatant and vortexed again to resuspend. FACS Buffer was added again and the cells were centrifuged and vortexed again for resuspension. Samples were then acquired on the FACSCanto II Cytometer and ABCs (Antibodies Bound Per Cell) were estimated from standardized MFI as described in Iyer S, et al., Expression of CD69 on activated T cells using R-phycoerythrin labeled beads, Cytometry, 1996; #AC78 (Suppl.8):113 and Iyer S., et al., QuantiBRITE: A New Standard for Fluorescence Quantitation, Becton Dickinson Immunocytometry Systems, San Jose, CA. 1997. White Paper.

Example 3: NHL trial

[0127] The study of Fc-Optimized Anti-CD19 Antibody (MOR00208) to Treat Non-Hodgkin's Lymphoma (NHL) ClinicalTrials.gov Identifier: NCT01685008 is no longer recruiting.

[0128] The Inclusion Criteria were as follows:

1. 1. Male or female patients ≥ 18 years of age.
2. 2. Histologically-confirmed diagnosis according to REAL/WHO classification, of the following B-cell lymphomas: a.FL, b.MCL, c.DLBCL, d.Other indolent NHL (eg, MZL/MALT).

3. 3. Patients' NHL must have progressed after at least 1 prior rituximab containing regimen.
4. 4. One site of measurable disease by magnetic resonance imaging (MRI) or computed tomography (CT) scan defined as at least one lesion that measures at least 1.5 × 1.5 cm, with the exception: For patients with MCL only, patients with nonmeasurable disease but evaluable sites (bone marrow, spleen, peripheral blood, gastrointestinal tract) can be enrolled.
5. 5. Patients who have previously received an autologous stem cell transplantation must be at least 4 weeks post-transplant before study drug administration and must have exhibited a full haematological recovery.
6. 6. Discontinued previous monoclonal antibody therapy (except rituximab) or radioimmunotherapy administration for at least 60 days before study drug administration.
7. 7. Off rituximab for at least 14 days before the screening visit and be confirmed to have either no response or have disease progression after rituximab treatment.
8. 8. Patients with DLBCL had a positive [18F]fluorodeoxyglucose-positron emission tomography (FDG-PET) scan at baseline (Cheson response criteria).
9. 9. Life expectancy of > 3 months.
10. 10. ECOG performance status of < 3.
11. 11. Laboratory criteria at screening: a) Absolute neutrophil count (ANC) ≥ 1.0 (1000/mm3) b) Platelet count ≥ 75 × 109/L without previous transfusion within 10 days of first study drug administration. c) Haemoglobin ≥ 8.0 g/dL (may have been transfused). d) Serum creatinine < 2.0 x upper limit of normal (ULN). e) Total bilirubin ≤ 2.0 × ULN. f) Alanine transaminase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN.
12. 12. If a female of childbearing potential, a negative pregnancy test must be confirmed before enrolment and use of double-barrier contraception, oral contraceptive plus barrier contraceptive, or confirmation of having undergone clinically documented total hysterectomy and/or oophorectomy, tubal ligation.
13. 13. If a male, an effective barrier method of contraception must be used during the study and for 3 months after the last dose if the patient is sexually active with a female of childbearing potential.
14. 14. Able to comply with all study-related procedures, medication use, and evaluations.
15. 15. Able understand and give written informed consent and comply with the study protocol.

[0129] The exclusion Criteria were as follows:

1. 1. Previous treatment with cytotoxic chemotherapy, immunotherapy, radiotherapy or other lymphoma specific therapy within 14 days before the screening visit or patient has not recovered from side effects of previous lymphoma-specific therapy.
2. 2. Treatment with a systemic investigational agent within 28 days before the screening visit.
3. 3. Previous treatment with an anti-CD19 antibody or fragments.

4. 4. Previous allogenic stem cell transplantation.
5. 5. Known or suspected hypersensitivity to the excipients contained in the study drug formulation.
6. 6. Clinically significant cardiovascular disease or cardiac insufficiency,cardiomyopathy, preexisting clinically significant arrhythmia, acute myocardial infarction within 3 months of enrolment, angina pectoris within 3 months of enrolment.
7. 7. Clinical or laboratory evidence of active hepatitis B or hepatitis C.
8. 8. History of HIV infection.
9. 9. Any active systemic infection (viral, fungal, or bacterial) requiring active parenteral antibiotic therapy within 4 weeks of study drug administration.
10. 10. Current treatment with immunosuppressive agents other than prescribed corticosteroids (not more than 10-mg prednisone equivalent).
11. 11. Major surgery or radiation therapy within 4 weeks before first study drug administration.
12. 12. Systemic diseases (cardiovascular, renal, hepatic, etc) that would prevent study treatment in the investigator's opinion.
13. 13. History or clinical evidence of central nervous system (CNS), meningeal, or epidural disease, including brain metastasis.
14. 14. Active treatment/chemotherapy for another primary malignancy within the past 5 years.
15. 15. Pregnancy or breastfeeding in women and women of childbearing potential not using an acceptable method of birth control.
16. 16. History of noncompliance to medical regimens or patients who are considered potentially unreliable not cooperative.

[0130] Patients were treated with MOR00208 as follows. Patients were treated with two 28 day cycles, where MOR00208 was given at a dose of 12 mg/kg on days 1, 8, 15, and 22. At the end of the two cycles, patients having Stable Disease or better were treated with a third 28 day cycle applying the same dosing and schedule as the first two cycles. At the end of the third cycle, patients having Partial Response or better went into Maintenance. In Maintanence, MOR00208 was given at a dose of 12 mg/kg every 14 or 28 days until disease progression.

[0131] As of the end of the study, the patient characteristics were as follows:

Table 2:

Baseline characteristics					
Characteristic		**DLBCL n=35**	**iNHL n=45**	**MCL n=12**	**Total n=92**
Age, years	Median	71	66	64.5	66.5
Sex	Male	24 (69)	21 (47)	11 (92)	56 (61)
ECOG PS	0	20 (57)	33 (73)	7 (58)	60 (65)
	1	12 (34)	11 (24)	4 (33)	27 (29)

Baseline characteristics					
Characteristic		**DLBCL n=35**	**iNHL n=45**	**MCL n=12**	**Total n=92**
	2	3 (9)	1 (2)	1 (8)	5 (5)
Rituximab refractory	Yes	24 (69)	22 (49)	6 (50)	52 (57)
	No	11 (31)	23 (51)	6 (50)	40 (43)
Last rituximab dose	<6 mos	14 (40)	6 (13)	1 (8)	21 (23)
Prior stem cell transplant	Yes	2 (6)	7 (16)	1 (8)	10 (11)
DoR to last prior therapy	>12 months	3 (9)	18 (40)	4 (33)	25 (27)
	≤ 12 months	26 (74)	25 (56)	7 (58)	58 (63)
	Unknown	6 (17)	2 (4)	1 (8)	9 (10)
Baseline NK cell count	>100 cells/ µl	19 (54)	23 (51)	8 (67)	51 (55)
	≤100 cells/ µl	11 (31)	8 (18)	1 (8)	20 (22)
	Unknown	5 (14)	14 (31)	3 (25)	21 (23)
Baseline CD16 expression on NK cells	> 60000 ABCs	15 (43)	33 (73)	5 (42)	53 (58)
	≤ 60000 ABCs	11 (31)	5 (11)	4 (33)	20 (22)
	Unknown	9 (26)	7 (16)	3 (25)	19 (21)
Baseline T cell count	> 500 cells/ µl	20 (57)	26 (58)	8 (67)	54 (59)
	≤ 500 cells/ µl	10 (29)	6 (13)	1 (8)	17 (18)
	Unknown	5 (14)	13 (29)	3 (25)	21 (23)
FcγRIIIa	High affinity	5 (14)	4 (9)	1 (8)	10 (11)
	Low affinity	27 (77)	28 (62)	9 (57)	64 (70)
	Unknown	3 (9)	13 (29)	2 (17)	18 (20)
FcγRIIa	High affinity	11 (31)	10 (22)	3 (25)	24 (26)
	Low affinity	21 (60)	22 (49)	7 (58)	50 (54)
	Unknown	3 (9)	13 (29)	2 (17)	18 (18)

DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; iNHL, indolent non-Hodgkin's lymphoma (includes follicular lymphoma and other iNHL); MCL, mantle cell lymphoma; mos, months.
(%)

[0132] Other iNHL means a heterogeneous group of not further specified indolent, not aggressive, NHL types, e.g. Marginal Cell Lymphoma, Marginal Zone Lymphoma, and Mucosa associated lymphoid tissue (MALT) lymphoma.

[0133] The Key primary and secondary endpoints were as follows:

- Primary: Overall Response Rate (ORR) = CR+PR
- Secondary:
  - Disease Control Rate (DCR) = CR+PR+SD
  - Progression-free survival (PFS)

Table 3:

Response				
Best overall response,* n (%)	**DLBCL n=35**	**iNHL† n=45**	**MCL n=12**	**Total n=92**
Complete response, CR	2 (6)	5 (11)	0	7 (8)
Partial response, PR	7 (20)	8 (18)	0	15 (16)
Stable disease, SD	5 (14)	20 (44)	6 (50)	31 (34)
Progressive disease	11 (31)	7(16)	5 (42)	23 (25)
Not evaluable‡	10 (29)	5 (11)	1 (8)	16 (17)
DCR (CR+PR+SD)	14 (40)	33 (73)	6 (50)	53 (58)
ORR (CR+PR/all patients)	9 (26)	13 (29)	0	22 (24)
ORR (CR+PR/evaluable patients§)	9 (36)	13 (33)	0	22 (29)
Data are n (%). *Investigator assessed. †Includes follicular lymphoma and other indolent NHLs. ‡Post-baseline response assessment not performed/data unavailable. §n=25, 40, 11 and 76, respectively. DCR, disease control rate; DLBCL, diffuse large B-cell lymphoma; iNHL, indolent non-Hodgkin's lymphoma; MCL, mantel cell lymphoma' ORR, overall response rate.				

[0134] The response criteria in this study are those as defined in Table 4. All of them are based on the International Working Group Response Criteria (2007).

Table 4: Response Criteria

Response	Definition	Nodal masses	Spleen, liver	Bone marrow
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohisto-chemistry should be negative
		b) Variable FDG-avid or PET negative; regression to normal size on CT		
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
		a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site		
		b) Variable FDG-avid or PET negative; regression on CT		
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET		
		b) Variable FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1cm in short	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Response	Definition	Nodal masses	Spleen, liver	Bone marrow
		axis		
		Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy		
Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease				

[0135] DCR (CR+PR+SD) was considered the most relevant efficacy endpoint the analysis of patient characteristic and biomarkers in this trial as the majority of patients with SD had marked target lesion reduction but as per study design were not treated beyond cycle 3. Accordingly, patients having SD included in the analysis.

[0136] At least the following characteristics of patients were evaluated to determine if there existed a correlation between the characteristic and the observed DCR of patients treated with the anti-CD19 antibody: a) age, b) gender, c) if patients had received a dose of Rituximab within the last 6 months, d) whether the patients were Rituximab refractory, e) whether patients have the FCgammaRIIIa high or low affinity allele, f) whether patients have the FCgammaRIIa high or low affinity allele, g) whether patients had a duration of response to the previous treatment of greater than 12 months, h) baseline peripheral T cell counts (cells/µl), i) baseline peripheral NK cell count (cells / µl) and j) baseline CD16 expression on peripheral NK cells (Antibodies Bound per Cells -ABCs).

[0137] Example 1 and Example 2 above were used to evaluate the baseline peripheral NK cell counts, T cell counts and baseline CD16 expression on peripheral NK cells. The data is shown in Table 2.

[0138] A Receiver Operating Characteristic (ROC) analysis was used to analyse the predictivity, specifity and sensitivity and to determine the cut offs for the potential biomarkers of NK cell count, T cell count and CD16 expression (ABCs) on peripheral NK cells. A ROC plot displays the performance of a binary classification method with continuous or discrete ordinal output. It shows the sensitivity (the proportion of correctly classified positive observations) and specificity (the proportion of correctly classified negative observations) as the output threshold is moved over the range of all possible values. See Swets JA: The Relative Operating Characteristic in Psychology. Science 1973, 182: 990-1000, and Pepe MS: The statistical evaluation of medical tests for classification and prediction. Oxford: Oxford University Press; 2003. In the ROC context, the area under the curve (AUC) measures the performance of a classifier and is frequently applied for method comparison. A higher AUC means a better classification. The AUC for peripheral NK/T cell counts and for CD16 expression on NK cells is

0.66, 0.53 and 0.61 respectively (Figures 3, 4 and 5).

[0139] In general the determination of the cut off depends on the objective the respective method is directed to. Various criteria such as maximum accuracy, maximum diagnostic odds ratio, minimal error rate, maximum sensitivity and/or maximum specificity would lead to a different determination of the cut off. In addition a balance between more of such criteria, e.g. sensitivity and specificity would also lead to a specific determination of the cut off.

[0140] Therefore several methods or criteria for selecting optimal cutoffs exist, including methods maximizing accuracy, sensitivity+specificity, predictive values, diagnostic likelihood ratios or prevalence. Due to the asymetry of the CD16 expression-ROC curve (See Figure 4) the majority of methods result in a cut off of 60,000 ABC (the points with the greatest distance between ROC curve and the bisecting line) whereas, the symmetry of the NK cell count ROC curve (See Figure 3) explains why different values for the best cut off could be obtained when applying different methods. In this particular study, for both biomarkers more weight was assigned to sensitivity and, therefore, 100 NK cells/$_N$l and a CD16 expression level of 60,000 ABCs, respectively, were chosen as cut offs to analyze the DCR and PFS within the subgroups. For peripheral T cell counts, the AUC is 0.53 and the ROC curve is close to the bisectrix at any value of specificity and sensitivity therefore even selecting a different cut off than 500 cell / /µl had no impact on the negative results of the DCR and PFS subgroup analysis.

[0141] The determination of the cut off can be balanced either in favor of sensitivity or specificity. If even more weight is assigned to sensitivity for the identification of the optimal cut-off the method would be different and a lower cut-off for the NK cell count is contemplated. In such case a cut off of at least 50 NK cells/$_N$l is determined. Alternatively, a cut off of at least 60 NK cells/µl, at least 70 NK cells/µl, at least 80 NK cells/µl, at least 90 NK cells/µl or at least 100 NK cells/$_N$l is determined.

[0142] For maximizing the specificity of the disclosed method the cut-off for the NK cell count is increased and is determined between at least 100 NK cells/µl up to at least 150 NK cells/µl. Therefore for maximizing the specificity a cut off of at least 100 NK cells/µl, at least 110 NK cells/µl, at least 120 NK cells/µl, at least 130 NK cells/µl, at least 140 NK cells/µl or at least 150 NK cells/$_N$l is selected.

[0143] The cut off values determined in this particular study (100 NK cells/$_N$l and a CD16 expression level of 60,000 ABCs) were used for the following statistical analysis.

[0144] Forest plots were used to analyze all patient characteristics and biomarkers in order to determine the correlation of the individual characteristic with DCR. The results are shown in Figure 7. Based upon the Forest Plot analysis of the different patient characteristics and their correlation to DCR, in DLBCL and iNHL patients the following characteristics showed statistically significant differences: 1) baseline peripheral NK cell count of at least 100 cells / µl and baseline expression of CD16 on peripheral NK cells of at least 60,000 ABCs (χ^2

unadjusted p value = 0.029/0.003) (Figure 7).

[0145] In order to ensure that CD16 expression and NK cell count were independent characteristics, which did not influence on the other, a parametric and nonparametric correlation analysis was done. Data on CD16 expression and NK cell count was available for 51 patients. Pearson's r was 0,019 with a two-tailed p value = 0.9 and Spearman's r was 0,036 with a two-tailed p value = 0.8. The results are graphically presented in Figure 6. In conclusion, CD16 expression and NK cell count at the determined thresholds are not correlated, therefore, they are considered fully independent predictors of the probability of a patient for benefiting from MOR00208 treatment.

[0146] The following characteristics were not found to be predictive of DCR: a) age, b) gender, c) if patients had received a dose of Rituximab within the last 6 months, d) whether the patients were Rituximab refractory, e) whether patients have the FCgammaRIIIa high or low affinity allele, f) whether patients have the FCgammaRIIa high or low affinity allele, g) whether patients had a duration of response to the treatment of greater than 12 months, or h) baseline peripheral T cell counts. See Figure 7.

[0147] Both 1) baseline peripheral NK cell counts and 2) baseline CD16 expression on peripheral NK cells showed clear correlations to patient response with MOR00208 therapy. Specifically, patients having a baseline NK cell count of at least 100 cells / µl correlated with a higher Disease Control Rate (DCR). DCR includes patients have Complete Response (CR) + Partial Response (PR) + Stable Disease (SD). In addition, patients having a baseline CD16 expression on peripheral NK cells of at least 60,000 ABCs correlated with higher Disease Control Rate (DCR).

[0148] Progression Free Survival (PFS) is the length of time during and after the treatment of a disease that a patient lives with the disease but it does not get worse. This is an additional important endpoint of a clinical trial, and an indicator of effectiveness in patients. PFS was compared within the following patient characteristics: a) baseline peripheral NK cell count of at least 100 cells / µl or less, b) baseline CD16 expression on peripheral NK cells of at least 60,000 ABCs or less, and c) baseline peripheral T cell count of at least 500 cells / µl or less. The results are shown in Figures 8-10. The PFS comparing patients having NK cell counts having at least 100 cells / µl as compared to patients having lower NK cell counts showed a statistically significant difference with a HR of 0.1561 (unadjusted log-rank p value = 0.0003). This further confirms the predictivity of NK cells counts in the response of patients treated with MOR00208 of those patients having CLL, NHL, ALL or SLL.

REFERENCES CITED IN THE DESCRIPTION

Cited references

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Patent documents cited in the description

- US2014328842A1 [0006]
- US20150239974A1 [0006]
- WO2007076950A [0029] [0030] [0099]
- US2007154473A [0029]
- WO2005012493A [0030] [0099]
- US7109304B [0030]
- WO2010053716A [0030] [0099]
- US12266999B [0030]
- WO2007002223A [0030] [0099]
- US8097703B [0030]
- WO2008022152A [0030] [0099]
- WO12377251A [0030]
- WO2008150494A [0030]
- WO2008031056A [0030] [0099]
- US11852106B [0030]
- US648505B [0030]
- WO2009052431A [0030] [0099]
- US12253895B [0030]
- WO2010095031A [0030] [0099]
- WO12710442A [0030]
- WO2012010562A [0030]
- WO2012010561A [0030]
- WO2011147834A [0030]
- WO2012156455A [0030]
- US377251 [0033] [0034] [0099]
- WO2002068414A [0045]
- WO2005016326A [0045]

Non-patent literature cited in the description

- **WOYACH et al.**Blood, 2014, vol. 124, 243553-60 [0004]
- **KIM et al.**Blood Research, 2014, vol. 49, 3162-169 [0006]
- **PLONQUET et al.**Ann Oncol, 2007, vol. 18, 1209-15 [0006]
- **SCHEUERMANN et al.**CD19 Antigen in Leukemia and Lymphoma Diagnosis and ImmunotherapyLeukemia and Lymphoma, 1995, vol. 18, 385-397 [0029]
- **LOPEZ-RATON, M.RODRIGUEZ-ALVAREZ, M.XCADARSO-SUAREZ, C.GUDE-SAMPEDRO, F.**Optimal Cutpoints: An R Package for Selecting Optimal Cutpoints in Diagnostic Tests.Journal of Statistical Software, 2014, vol. 61, 81-36 [0040]
- **IYER S et al.**Expression of CD69 on activated T cells using R-phycoerythrin labeled beadsCytometry, 1996, vol. AC78, 8113- [0126]
- **IYER S. et al.**QuantiBRITE: A New Standard for Fluorescence QuantitationBecton Dickinson Immunocytometry Systems, San Jose, CA, 1997, [0126]
- **SWETS JA**The Relative Operating Characteristic in Psychology.Science, 1973, vol. 182, 990-1000 [0138]
- **PEPE MS**The statistical evaluation of medical tests for classification and predictionOxford University Press20030000 [0138]

Patentkrav

1. Fremgangsmåde til identifikation af et individ med kronisk lymfatisk leukæmi (CLL) eller akut lymfatisk leukæmi (ALL), som reagerer på behandling med et anti-CD19-antistof, hvilken fremgangsmåde omfatter:

a. tilvejebringelse af en blodprøve, der er opnået fra individet før behandling med anti-CD19-antistoffet,

b. bestemmelse af niveauet af mindst én biomarkør i prøven udvalgt fra gruppen bestående af:

i. perifert NK-celletal, og

ii. CD16-ekspressionsniveauer på perifere NK-celler,

c. sammenligning af niveauet af den mindst ene biomarkør i prøven med et forudbestemt afskæringsniveau,

hvor niveauer af den mindst ene biomarkør på eller over det forudbestemte afskæringsniveau er indikativ for et individ, der ville have gavn af behandling med en anti-CD19 antistof.

2. Fremgangsmåde ifølge krav 1, hvor den forudbestemte afskæring af biomarkøren er:

a. et fundamentalt NK-celletal inden for mindst 50 celler/µl, eller

b. fundamentale CD16-ekspressionsniveauer på perifere NK-celler på mindst 60.000 ABC'er.

3. Fremgangsmåde ifølge krav 1 eller 2, hvor den forudbestemte afskæring af biomarkøren er et fundamentalt perifert NK-celletal på mindst 60 celler/µl.

4. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, hvor den forudbestemte afskæring af biomarkøren er et fundamentalt perifert NK-celletal på mindst 70 celler/µl.

5. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, hvor den forudbestemte afskæring af biomarkøren er et fundamentalt perifert NK-celletal på mindst 80 celler/µl.

6. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, hvor den forudbestemte afskæring af biomarkøren er et fundamentalt perifert NK-celletal på mindst 100 celler/µl.

7. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, hvor den forudbestemte afskæring af biomarkøren er fundamentale CD16-ekspressionsniveauer på perifere NK-celler på mindst 60.000 ABC'er.

8. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, hvor anti-CD19-antistoffet omfatter en HCDR1-region, der omfatter sekvensen SYVMH (SEQ ID NO: 1), en HCDR2-region, der omfatter sekvensen NPYNDG (SEQ ID NO: 2), en HCDR3 region, der omfatter sekvensen GTYYYGTRVFDY (SEQ ID NO: 3), en LCDR1-region, der omfatter sekvensen RSSKSLQNVNGNTYLY (SEQ ID NO: 4), en LCDR2-region, der omfatter sekvensen RMSNLNS (SEQ ID NO: 5), og en LCDR3-region, der omfatter sekvensen MQHLEYPIT (SEQ ID NO: 6).

9. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, hvor anti-CD19-antistoffet omfatter en variabel tungkæde med sekvensen EVQLVESGGGLVKPGGSLKLSCAASGYTFTSYVMHWVRQAPGKGLEWIGYIN PYNDGTKYNEKFQGRVTISSDKSISTAYMELSSLRSEDTAMYYCARGTYYYGT RVFDYWGQGTLVTVSS (SEQ ID NO: 10) og en variabel letkæde af sekvensen

DIVMTQSPATLSLSPGERATLSCRSSKSLQNVNGNTYLYWFQQKPGQSPQLLI YRMSNLNSGVPDRFSGSGSGTEFTLTISSLEPEDFAVYYCMQHLEYPITFGAG TKLEIK (SEQ ID NO: 11).

10. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, hvor anti-CD19-antistoffet omfatter en tungkæde med sekvensen
EVQLVESGGGLVKPGGSLKLSCAASGYTFTSYVMHWVRQAPGKGLEWIGYIN
PYNDGTKYNEKFQGRVTISSDKSISTAYMELSSLRSEDTAMYYCARGTYYYGT
RVFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV
TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPDVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQD
WLNGKEYKCKVSNKALPAPEEKTISKTKGQPREPQVYTLPPSREEMTKNQVSL

TCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 8) og en letkæde med sekvensen

DIVMTQSPATLSLSPGERATLSCRSSKSLQNVNGNTYLYWFQQKPGQSPQLLI YRMSNLNSGVPDRFSGSGSGTEFTLTISSLEPEDFAVYYCMQHLEYPITFGAG TKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC (SEQ ID NO: 9).

11. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, hvor individet har kronisk lymfatisk leukæmi.

12. Fremgangsmåde ifølge et hvilket som helst af kravene 1-10, hvor individet har akut lymfatisk leukæmi.

13. Anti-CD19-antistof til anvendelse i behandlingen af en patient med kronisk lymfatisk leukæmi (CLL) eller akut lymfatisk leukæmi (ALL), hvor patienten er identificeret ifølge en fremgangsmåde ifølge et hvilket som helst af de foregående krav.

DRAWINGS

Drawing

Figure 1

The amino acid sequence of the MOR00208 Variable Heavy Domain is (The CDRs are bolded and underlined):

EVQLVESGGGLVKPGGSLKLSCAASGYTFT**SYVMH**WVRQAPGKGLEWIGYI **NPYNDG**TKYNEKFQGRVTISSDKSISTAYMELSSLRSEDTAMYYCAR**GTYYY GTRVFDY**WG QGTLVTVSS (SEQ ID NO: 10)

The amino acid sequence of the MOR00208 Variable Light Domain is (The CDRs are bolded and underlined):

DIVMTQSPATLSLSPGERATLSC**RSSKSLQNVNGNTYLY**WFQQKPGQSPQL LIY**RMSNLNS**GVPDRFSGSGSGTEFTLTISSLEPEDFAVYYC**MQHLEYPIT**FG AGTKLEIK (SEQ ID NO: 11)

The amino acid sequence of the MOR00208 HCDR1 is: SYVMH (SEQ ID NO: 1)

The amino acid sequence of the MOR00208 HCDR2 is: NPYNDG (SEQ ID NO: 2)

The amino acid sequence of the MOR00208 HCDR3 is: GTYYYGTRVFDY (SEQ ID NO: 3)

The amino acid sequence of the MOR00208 LCDR1 is: RSSKSLQNVNGNTYLY (SEQ ID NO: 4)

The amino acid sequence of the MOR00208 LCDR2 is: RMSNLNS (SEQ ID NO: 5)

The amino acid sequence of the MOR00208 LCDR3 is: MQHLEYPIT (SEQ ID NO: 6)

Figure 2

The amino acid sequence of the MOR00208 Heavy Chain is:

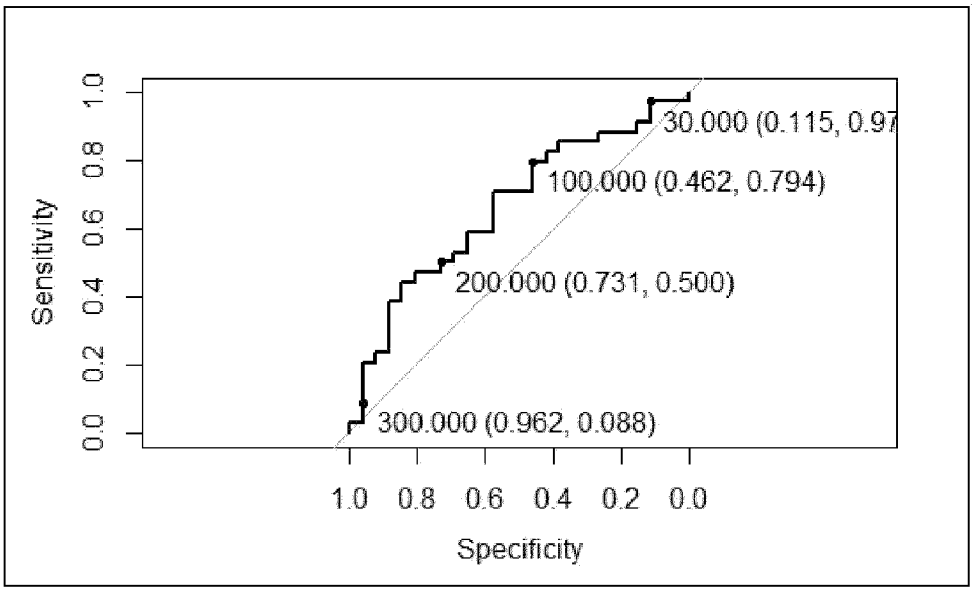
EVQLVESGGGLVKPGGSLKLSCAASGYTFTSYVMHWVRQAPGKGLEWIGYINPYN
DGTKYNEKFQGRVTISSDKSISTAYMELSSLRSEDTAMYYCARGTYYYGTRVFDYWGQGTL
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL
GGPDVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQ
FNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKALPAPEEKTISKTKGQPREPQVYTLPPSRE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 8)

The amino acid sequence of the MOR00208 Light Chain is:

DIVMTQSPATLSLSPGERATLSCRSSKSLQNVNGNTYLYWFQQKPGQSPQLLIYRMSNLN
SGVPDRFSGSGSGTEFTLTISSLEPEDFAVYYCMQHLEYPITFGAGTKLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST
LTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 9)

Figure 3

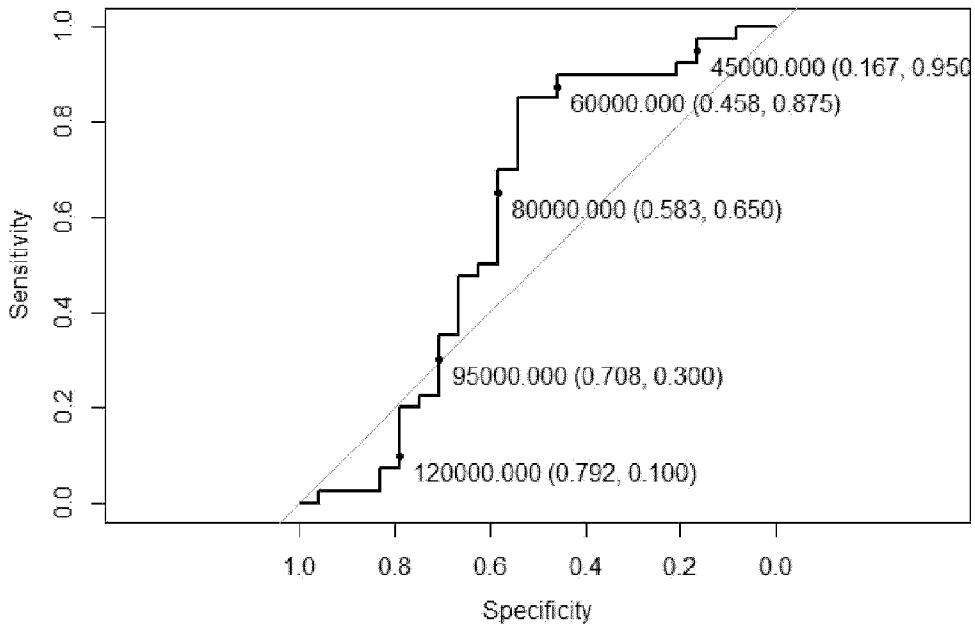
Determining the cut offs for peripheral NK cell counts via ROC analysis



Receiver Operating Characteristic (ROC) analysis of peripheral NK cell count (cells/µl) as a predictor for the Disease Control Rate (CR, PR, DS vs PD, ET) in DLBCL and iNHL patients. Various cut offs with Specificity and Sensitivity values are displayed. AUC = 0.66. CR-Complete Remission, PR-Partial Remission, SD-Stable Disease, PD-Progressive Disease, ET-Early Termination, ABC-Antigens Bound per Cell.

Figure 4

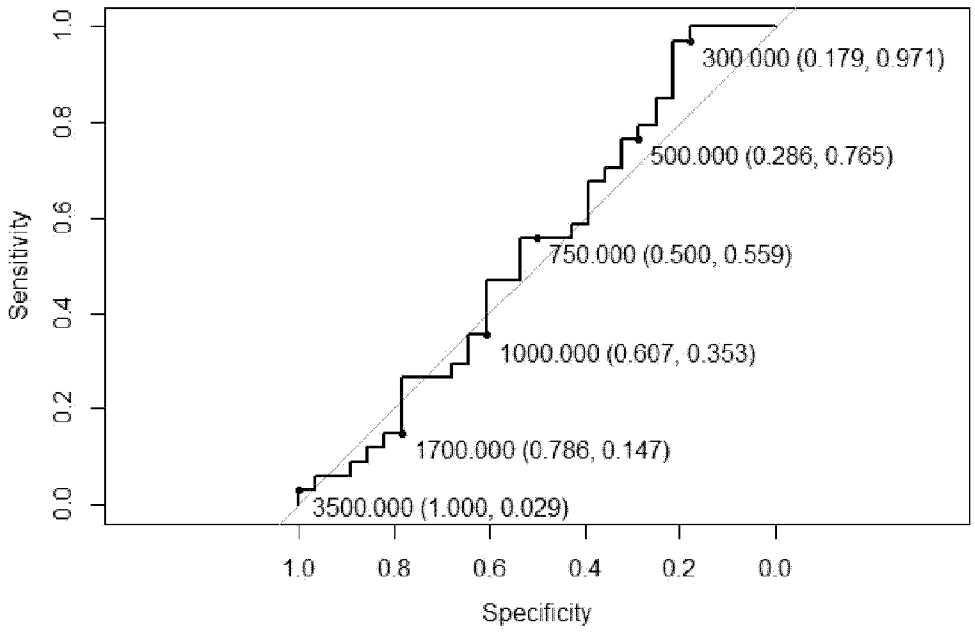
Determining the cut offs for CD16 expression (ABC) via ROC analysis



Receiver Operating Characteristic (ROC) analysis of CD16 expression (ABC) as a predictor for the Disease Control Rate (CR, PR, DS vs PD, ET) in DLBCL and iNHL patients. Various cut offs with Specifity and Sensitivity values are displayed. AUC = 0.61. CR-Complete Remission, PR-Partial Remission, SD-Stable Disease, PD-Progressive Disease, ET-Early Termination, ABC-Antigens Bound per Cell.

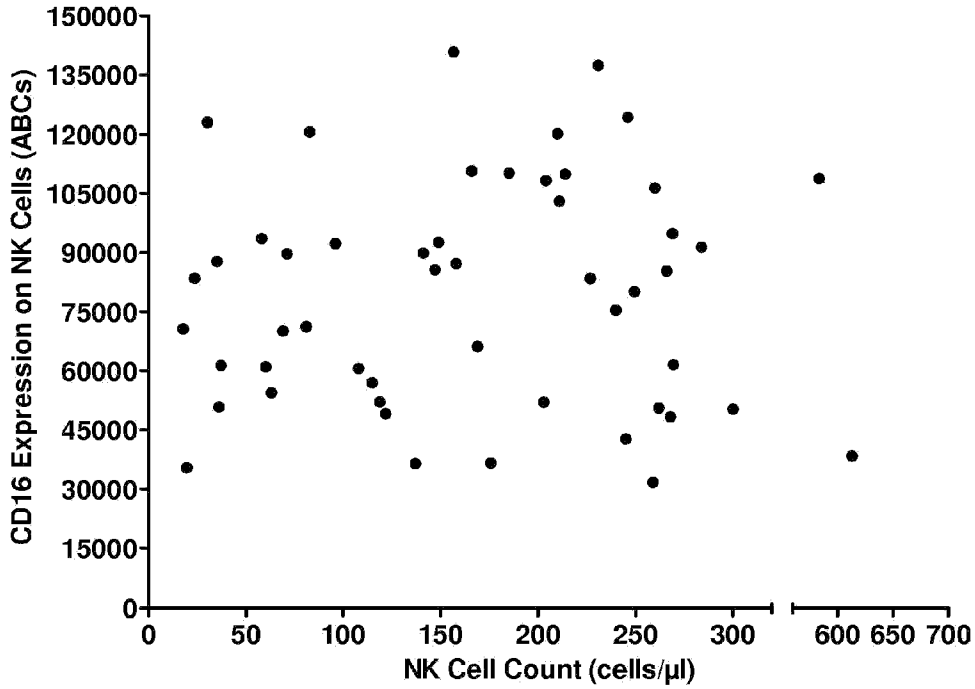
Figure 5

Determining the cut offs for peripheral T cell count via ROC analysis



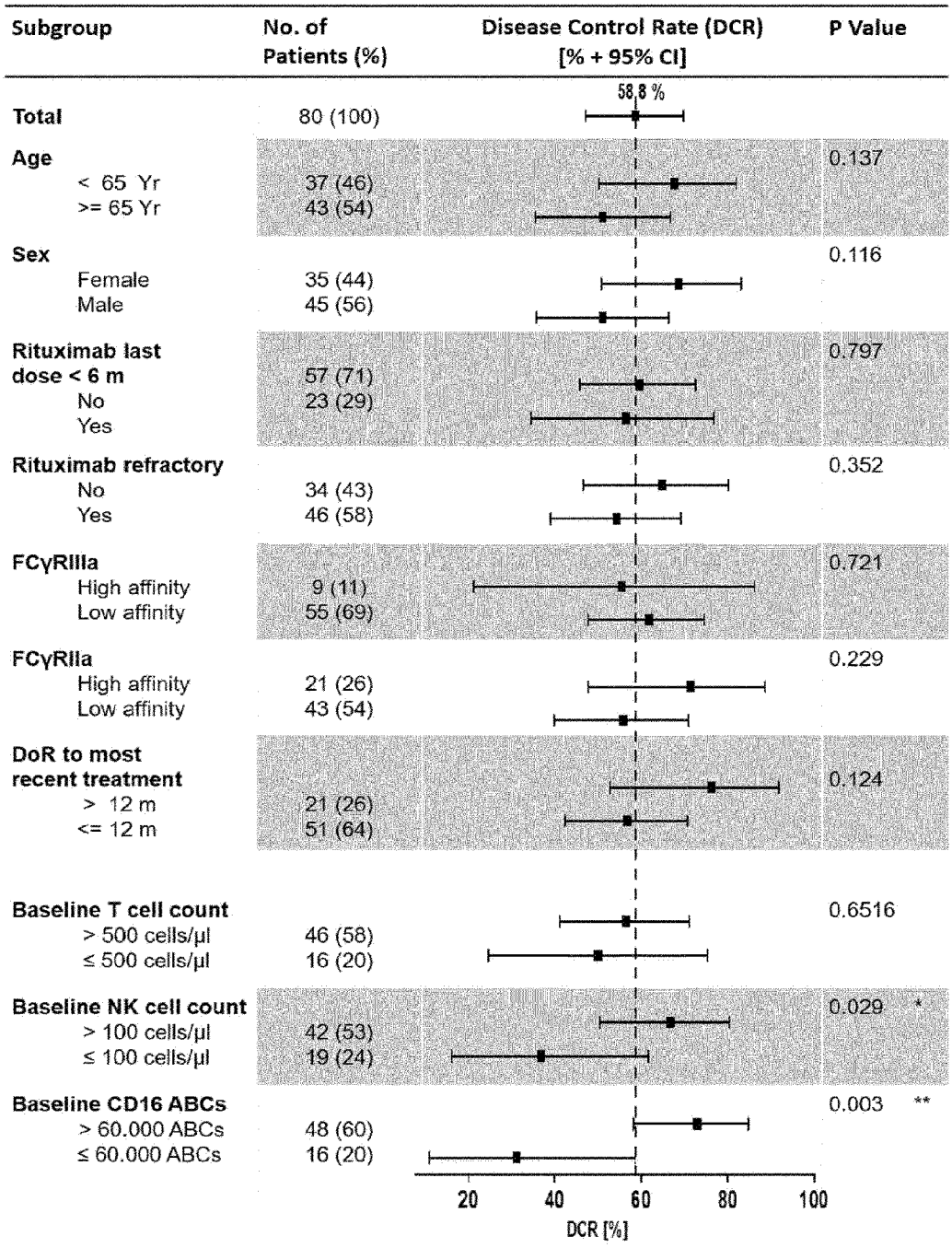
Receiver Operating Characteristic (ROC) analysis of peripheral T cell count (cells/µl) as a potential predictor for the Disease Control Rate (CR, PR, DS vs PD, ET) in DLBCL and iNHL patients. Various cut offs with Specifity and Sensitivity values are displayed. AUC = 0.53. CR-Complete Remission, PR-Partial Remission, SD-Stable Disease, PD-Progressive Disease, ET-Early Termination, ABC-Antigens Bound per Cell.

Figure 6



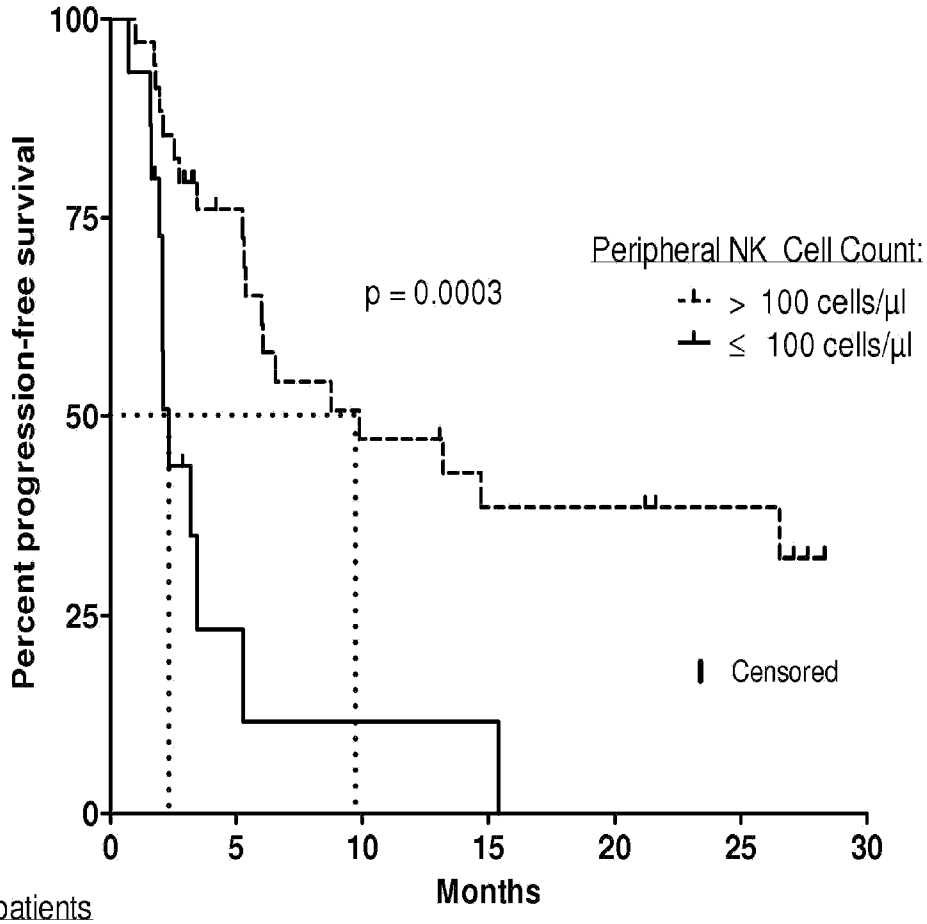
ABC-Antigens Bound per Cell. Analysis of correlation: Pearson r = 0,019 with two-tailed p value = 0.9; Nonparametric Spearman r = 0,036 with two-tailed p value = 0.8; n = 51.

Figure 7 Forest plot with subgroup analyses of disease control rate.



†Clopper Pearson confidence intervals; ‡unadjusted X^2 test (two-sided) of DCR rates. DoR, duration of response; IPI, International Prognostic Index. * p<0,05, **p<0,01.

Figure 8 Subgroup analysis of Progression-free survival (PFS)

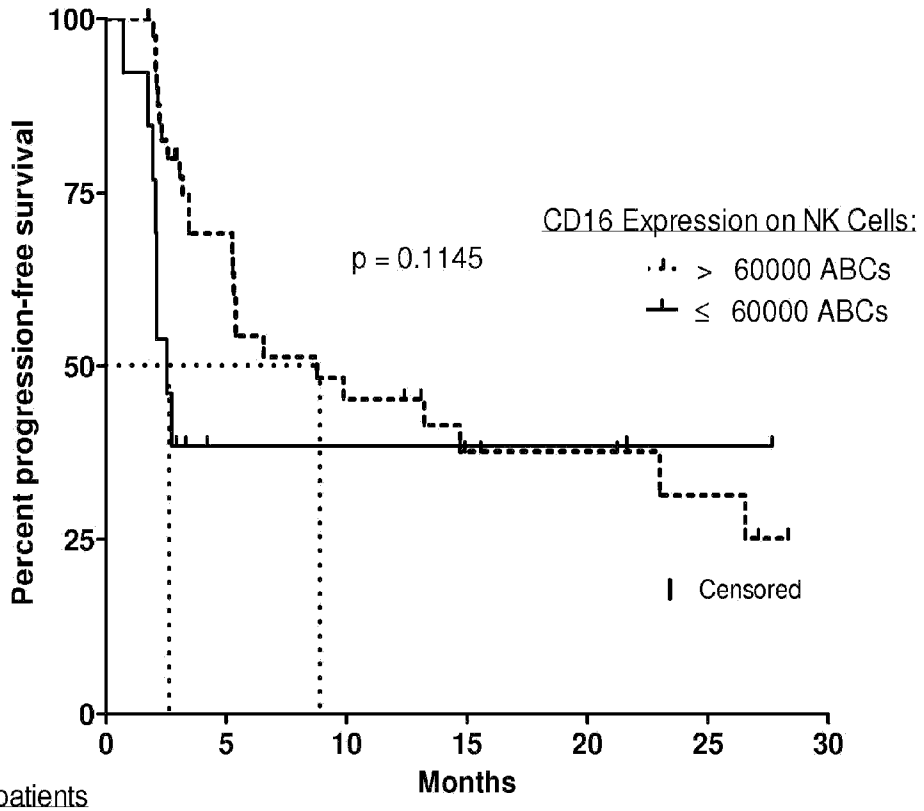


No. of patients at risk:

>100 cells/µl	35	21	12	9	9	6
≤100 cells/µl	15	2	1	1	0	0

Patients without post baseline radiological tumor assessment were censored at baseline. PFS, progression-free survival. Unadjusted log-rank p value = 0.0003.

Figure 9 Subgroup analysis of Progression-free survival (PFS)

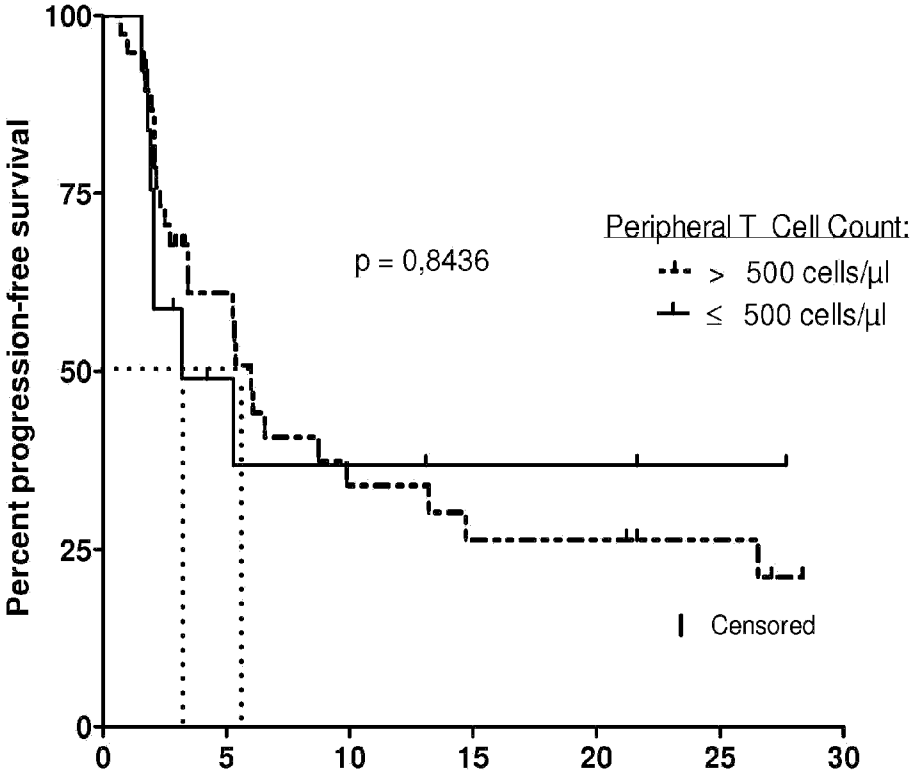


No. of patients at risk:

> 60.000 ABCs	42	25	14	9	8	5
≤ 60.000 ABCs	13	2	2	2	2	1

Patients without post baseline radiological tumor assessment were censored at baseline. PFS, progression-free survival. Unadjusted log-rank p value = 0.1145

Figure 10 Subgroup analysis of Progression-free survival (PFS)



No. of patients at risk:

> 500 cells/µl	38	18	9	7	7	5
≤ 500 cells/µl	13	4	3	2	2	1

Patients without post baseline radiological tumor assessment were censored at baseline. PFS, progression-free survival. Unadjusted log-rank p value = 0.8436