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(71) Applicant: ADURO BIOTECH HOLDINGS, EUROPE B.V. [NL/NL]; Kloosterstraat 9, 5349 AB Oss (NL).

(72) Inventors: DULOS, John; c/o Aduro Biotech Holdings, Europe B.V., Kloosterstraat 9, 5349 AB Oss (NL). VAN EENENNAAM, Hans; c/o Aduro Biotech Holdings, Europe B.V., Kloosterstraat 9, 5349 AB Oss (NL). GUELEN, Lars; c/o Aduro Biotech Holdings, Europe B.V., Kloosterstraat 9, 5349 AB Oss (NL). VAN ELSAS, Andrea; c/o Aduro Biotech Holdings, Europe B.V., Kloosterstraat 9, 5349 AB Oss (NL).

(74) Agent: HOFFMANN EITLE; PATENT-UND RECHTSANWÄLTE PartmbB, Arabellastraße 30, 81925 Munich (DE).

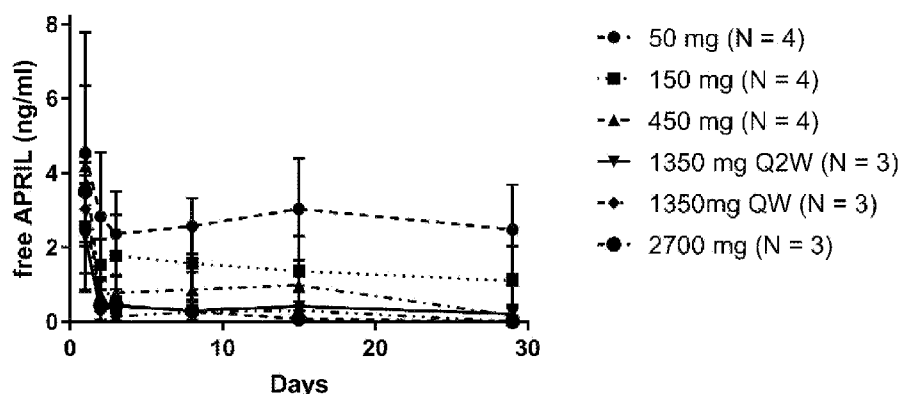
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(54) Title: METHODS AND COMPOSITIONS FOR TREATMENT OF MULTIPLE MYELOMA

FIGURE 1

serum APRIL levels



Values BLQ (<0.232 ng/ml) were plotted as 0 ng/ml.

(57) Abstract: The present invention relates to methods and compositions for the treatment of diseases related to APRIL signaling, and in particular to treatment of multiple myeloma.

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METHODS AND COMPOSITIONS FOR TREATMENT OF MULTIPLE MYELOMA

[0001] The present application claims priority to U.S. Provisional Patent Application No. 62/789,699, filed January 8, 2019, which is hereby incorporated in its entirety including all tables, figures, and claims.

FIELD OF THE INVENTION

[0002] The present invention relates to the measurement of blood, serum, or plasma APRIL levels and the use of such levels in guiding treatment of multiple myeloma with anti-APRIL agents.

BACKGROUND OF THE INVENTION

[0003] Multiple myeloma (MM) is a malignancy of plasma cells (terminally differentiated B-cells) which under normal circumstances are responsible for the mass production of immunoglobulins. The capability of immunoglobulin production is often retained in malignant myeloma cells (MMCs), and MMCs produce monoclonal proteins of varying types, most commonly immunoglobulins and free immunoglobulin light chains, resulting in abnormally high levels of these proteins in the blood. In MM, replacement of normal bone marrow by infiltrating tumor cells and inhibition of normal red blood cell production leads to anemia, and renal injury from the high levels of these proteins or light chains is common. Neurological symptoms are also common due to hyperviscosity of the blood. Finally, increased bone resorption leads to bone pain, hypercalcemia and nephrocalcinosis. MM is the second most prevalent hematologic malignancy, with an estimated global incidence of 102,000 new cases and a global mortality of 72,000 cases yearly and a 5-year survival rate of approximately 35%. Despite recent progress in the treatment of MM, it remains an incurable condition.

[0004] B cell activating factor (BAFF) and A Proliferation-Inducing Ligand (APRIL), both members of the tumour necrosis factor (TNF) family, represent two of the main survival factors for immature, naive and activated B cells. BAFF binds to B cell maturation antigen (BCMA), transmembrane activator and calcium modulator and cyclophilin ligand receptor (TACI) and BAFF receptor. APRIL binds to BCMA, TACI and heparin-sulfate proteoglycans. When bound to heparan sulphate proteoglycans,

APRIL reportedly ligates TACI and activate NF- κ B signaling. MMCs can bind APRIL, which is believed to increase MMC survival and proliferation.

[0005] APRIL is produced by osteoclasts in the bone marrow. In addition, primary myeloma cells, thyroid tissues, lymphoid tissues (e.g., monocytes and macrophages), and various cancers also reportedly express APRIL. Serum APRIL levels are reportedly somewhat elevated in newly diagnosed MM patients as compared to healthy volunteers, with levels increasing with ISS stage. These serum levels are reduced by treatment with chemotherapy in patients exhibiting at least a partial remission of their disease, but are not reduced in stable disease patients. See, e.g., Bolkun et al., Ann. Hematol. 93: 635-44, 2014.

[0006] Anti-human APRIL antibodies that block APRIL binding to BCMA and TACI have been described, and their potential for further development as therapeutics to target APRIL-dependent survival of MMCs have been described. See, e.g., Guadagnoli et al., Blood 117: 6856-65, 2011; WO2010100056.

SUMMARY OF THE INVENTION

[0007] The present invention relates to methods and compositions for the treatment of diseases related to APRIL signaling, and in particular to treatment of multiple myeloma.

[0008] In one aspect, the invention provides methods of treating a multiple myeloma patient with an anti-APRIL antibody, comprising:

measuring a first level of APRIL protein in a first blood, serum, or plasma sample obtained from the patient using an APRIL specific binding assay;

following obtaining the first level of APRIL protein, administering a first therapeutic amount of an anti-APRIL antibody to the patient;

following the administering, determining one or more monitoring levels of APRIL protein in the patient in one or more blood, serum, or plasma samples obtained from the patient using the APRIL specific binding assay;

wherein if one of the monitoring levels indicates an initial reduction in the level of APRIL protein relative to the first level of APRIL protein, and a subsequent one of the

monitoring levels indicates an increase in levels of APRIL protein relative to the initial reduction, administering a second therapeutic amount of the anti-APRIL antibody to the patient.

[0009] In certain embodiments, if one of the monitoring levels fails to indicate an initial reduction in the level of APRIL protein relative to the first level of APRIL protein, administration of the anti-APRIL antibody to the patient is discontinued.

[0010] Preferably, the anti-APRIL antibody being administered is selected for the ability to block the binding of APRIL with human transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) and with human B cell maturation antigen (BCMA) with an IC_{50} of about 2 nM or lower. Suitable anti-APRIL antibodies include those described in WO2016110587A1, which is hereby incorporated by reference in its entirety. Preferred antibodies are APRIL.01A, APRIL.01A_VH14_1G/VL15 or APRIL.03A.

[0011] In certain embodiments, the method provides a correlation of APRIL protein levels in a blood, serum, or plasma sample (measured using the APRIL specific binding assay) and a level of APRIL protein in bone marrow supernatants at the same time point that has a correlation coefficient of at least 0.7, more preferably 0.8, and most preferably 0.85 or more, indicating that the level of APRIL protein being measured in blood, serum, or plasma provides a reasonable measure of corresponding bone marrow levels. This permits monitoring of treatment efficacy without a need for continued bone marrow sampling.

[0012] It is to be understood that the invention is not limited in its application to the details of construction and to the arrangements of the components set forth in the following description or illustrated in the drawings. The invention is capable of embodiments in addition to those described and of being practiced and carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein, as well as the abstract, are for the purpose of description and should not be regarded as limiting.

[0013] As such, those skilled in the art will appreciate that the conception upon which this disclosure is based may readily be utilized as a basis for the designing of other structures, methods and systems for carrying out the several purposes of the present

invention. It is important, therefore, that the claims be regarded as including such equivalent constructions insofar as they do not depart from the spirit and scope of the present invention.

BRIEF DESCRIPTION OF THE FIGURES

[0014] Figure 1 depicts the longitudinal monitoring of free APRIL levels in serum samples from multiple myeloma patients that were treated with 150 mg BION-1301 in the ADU-CL-16 clinical trial (NCT03340883). Serum samples were collected before dose 1, at 30 minutes, 1 hour, 2 hours, 4-8 hours, 2 days, 3 days and 8 days post-dose 1, and prior to and 30 minutes after the cycle 1-day 15 and cycle 1-day 29 doses. Vertical dotted lines indicate dosing times. Values below the limit of quantification in the assay are plotted as 0 ng/mL.

DETAILED DESCRIPTION OF THE INVENTION

[0015] Measurement of APRIL protein

[0016] *In vitro* techniques for detection of APRIL protein illustratively include one or more of enzyme linked immunosorbent assays (ELISAs), radioimmunoassay, western blot, immunoprecipitation, immunofluorescence, mass spectrometry, liquid chromatography, high performance liquid chromatography, cellular assay, or other technique known in the art.

[0017] An exemplary process for detecting the presence or absence of APRIL protein in a biological sample involves obtaining a biological sample from a subject, such as a human, contacting the biological sample with a compound or an agent capable of detecting of the marker being analyzed, illustratively including an antibody or aptamer, and analyzing binding of the compound or agent to the sample after washing. Those samples having specifically bound compound or agent express the marker being analyzed. Any suitable molecule that can specifically bind to a biomarker is operative in the invention to provide a specific assay for APRIL protein. In certain embodiments, an agent for detecting APRIL protein is an antibody capable of binding to APRIL protein. An intact antibody, a fragment thereof (e.g., Fab or F(ab')₂), or an engineered variant thereof (e.g., sFv) can also be used. Such antibodies can be of any immunoglobulin class including IgG, IgM, IgE, IgA, IgD and any subclass thereof.

[0018] In general, immunoassays involve contacting a sample containing or suspected of containing a biomarker of interest with at least one antibody that specifically binds to the biomarker. A signal is then generated indicative of the presence or amount of complexes formed by the binding of polypeptides in the sample to the antibody. The signal is then related to the presence or amount of the biomarker in the sample. Numerous methods and devices are well known to the skilled artisan for the detection and analysis of biomarkers. *See, e.g.*, U.S. Patents 6,143,576; 6,113,855; 6,019,944; 5,985,579; 5,947,124; 5,939,272; 5,922,615; 5,885,527; 5,851,776; 5,824,799; 5,679,526; 5,525,524; and 5,480,792, and *The Immunoassay Handbook*, David Wild, ed. Stockton Press, New York, 1994, each of which is hereby incorporated by reference in its entirety, including all tables, figures and claims.

[0019] Antibodies or other binding species may be immobilized onto a variety of solid supports for use in assays. Solid phases that may be used to immobilize specific binding members include those developed and/or used as solid phases in solid phase binding assays. Examples of suitable solid phases include membrane filters, cellulose-based papers, beads (including polymeric, latex and paramagnetic particles), glass, silicon wafers, microparticles, nanoparticles, TentaGels, AgroGels, PEGA gels, SPOCC gels, and multiple-well plates. An assay strip could be prepared by coating the antibody or a plurality of antibodies in an array on solid support. This strip could then be dipped into the test sample and then processed quickly through washes and detection steps to generate a measurable signal, such as a colored spot. Antibodies or other polypeptides may be bound to specific zones of assay devices either by conjugating directly to an assay device surface, or by indirect binding. In an example of the latter case, antibodies or other polypeptides may be immobilized on particles or other solid supports, and that solid support immobilized to the device surface.

[0020] Biological assays require methods for detection, and one of the most common methods for quantitation of results is to conjugate a detectable label to a protein or nucleic acid that has affinity for one of the components in the biological system being studied. Detectable labels may include molecules that are themselves detectable (*e.g.*, fluorescent moieties, electrochemical labels, metal chelates, *etc.*) as well as molecules that may be indirectly detected by production of a detectable reaction product (*e.g.*, enzymes such as horseradish peroxidase, alkaline phosphatase, *etc.*) or by a specific binding molecule

which itself may be detectable (e.g., biotin, digoxigenin, maltose, oligohistidine, 2,4-dinitrobenzene, phenylarsenate, ssDNA, dsDNA, etc.).

[0021] Preparation of solid phases and detectable label conjugates often comprise the use of chemical cross-linkers. Cross-linking reagents contain at least two reactive groups, and are divided generally into homobifunctional cross-linkers (containing identical reactive groups) and heterobifunctional cross-linkers (containing non-identical reactive groups). Homobifunctional cross-linkers that couple through amines, sulfhydryls or react non-specifically are available from many commercial sources. Maleimides, alkyl and aryl halides, alpha-haloacyls and pyridyl disulfides are thiol reactive groups. Maleimides, alkyl and aryl halides, and alpha-haloacyls react with sulfhydryls to form thiol ether bonds, while pyridyl disulfides react with sulfhydryls to produce mixed disulfides. The pyridyl disulfide product is cleavable. Imidoesters are also very useful for protein-protein cross-links. A variety of heterobifunctional cross-linkers, each combining different attributes for successful conjugation, are commercially available.

[0022] Antibodies for use in the claimed methods may be obtained from a variety of species. For example, the antibodies of the present invention may comprise immunoglobulin sequences which are rabbit, mouse, rat, guinea pig, chicken, goat, sheep, donkey, human, llama or camelid sequences, or combinations of such sequences (so-called chimeric antibodies). Such antibodies may also be monoclonal or polyclonal. Antibodies for use in the present invention may be identified by their performance in immunoassays, and then further characterized by epitope mapping in order to understand the epitopes which are relevant to that performance. Preferred are rabbit antibodies or humanized versions derived from rabbit antibodies.

[0023] Such antibodies may be conjugated to a signal development element or immobilized on a solid support. In addition, such antibodies may be used in a number of competitive and sandwich assay formats. In an example of a sandwich assay, a first antibody (detectably labeled) and a second antibody (immobilized at a predetermined zone of a test device) form sandwich complexes with APRIL protein in the sample at a predetermined zone of a test device. In sandwich assays, the first and second antibodies can be the same (particularly when polyclonal antibodies are used) or different. Thus, an anti-APRIL antibody may be used in sandwich pairs, or may be used individually with another binding entity which is not a monoclonal antibody such as a polyclonal antibody

or an aptamer. Methods for making aptamers with a particular binding specificity are known as detailed in U.S. Pat. Nos. 5,475,096; 5,670,637; 5,696,249; 5,270,163; 5,707,796; 5,595,877; 5,660,985; 5,567,588; 5,683,867; 5,637,459; and 6,011,020.

[0024] Antibodies or other binding species can be used as reagents in test kits for detecting APRIL protein in biological samples. Such a test kit may, for example, comprise a disposable test device configured to generate a detectable signal related to the present or amount of human APRIL protein in a biological sample. Alternatively, such a test kit may be formulated for performing an assay in a clinical analyzer which does not utilize a disposable test device. Preferably, the test kit is an in vitro diagnostic. The term “in vitro diagnostic” as used herein refers to a medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information concerning a physiological or pathological state, or concerning a congenital abnormality, or to determine the safety and compatibility with potential recipients, or to monitor therapeutic measures.

[0025] In certain embodiments, the binding assay is performed in a lateral flow format. Lateral flow tests are a form of immunoassay in which the test sample flows in a chromatographic fashion along a bibulous or non-bibulous porous solid substrate. Lateral flow tests can operate as either competitive or sandwich format assays. Preferred lateral flow devices are disposable, single use test devices. A sample is applied to the test device at an application zone and transits the substrate, where it encounters lines or zones which have been pretreated with an antibody or antigen. The term “test zone” as used herein refers to a discrete location on a lateral flow test strip which is interrogated in order to generate a signal related to the presence or amount of an analyte of interest. The detectable signal may be read visually or obtained by inserting the disposable test device into an analytical instrument such as a reflectometer, a fluorometer, or a transmission photometer. This list is not meant to be limiting. Sample may be applied without pretreatment to the application zone, or may be premixed with one or more assay reagents prior to application. In the latter case, the antibody may be provided in a separate container from the disposable test device.

[0026] An antibody of the present invention may be diffusively immobilized to a surface within a disposable test device, such that the antibody dissolves into a sample when the sample contacts the surface. In a sandwich assay format, this diffusively bound antibody may bind to its cognate antigen in the sample, and then be immobilized at a detection zone when the antigen is bound by a second antibody non-diffusively bound at the detection zone. In a competitive format, its cognate antigen in the sample may compete for binding to the diffusively bound antibody with a labeled antigen provided as an assay reagent.

[0027] A kit of the invention can further comprise a calibration to relate the detectable signal to a concentration of APRIL protein. By way of example, a calibration curve may be provided on an electronic memory device which is read by the analytical instrument which receives the disposable test device, such as a ROM chip, a flash drive, an RFID tag, etc. Alternatively, the calibration curve may be provided on an encoded label which is read optically, such as a 2-D bar code, or transmitted via a network connection. The analytical instrument can then use this calibration curve to relate a detectable signal from an assay into a APRIL protein concentration

[0028] Assay Correlations

[0029] The terms “correlating” and “relating” as used herein in reference to the measurement of biomarkers in an assay refers to determining the presence, or more preferably the amount, of the biomarker in a sample based on the signal obtained from the assay. Often, this takes the form of comparing a signal generated from a detectable label on one species participating in the assay to a predetermined standard curve which can be used to convert the signal to a concentration or threshold amount of the biomarker.

[0030] The terms “correlating” and “relating” as used herein in reference to the use of biomarkers for selecting a treatment regimen refers to comparing a measured value to a threshold selected to distinguish an individual that would benefit from a treatment regimen from an individual that would not benefit. By way of example, one method for selecting may be to look at serial samples from the same patient, where a prior “baseline” result is used to monitor for temporal changes in a biomarker level. In an alternative, a population study may be used to select a decision threshold.

[0031] Receiver Operating Characteristic (“ROC”) arose from the field of signal detection theory developed during World War II for the analysis of radar images, and

ROC analysis is often used to select a threshold able to best distinguish a “diseased” subpopulation from a “nondiseased” subpopulation. A false positive in this case occurs when the person tests positive, but actually does not have the disease. A false negative, on the other hand, occurs when the person tests negative, suggesting they are healthy, when they actually do have the disease. To draw a ROC curve, the true positive rate (TPR) and false positive rate (FPR) are determined as the decision threshold is varied continuously. Since TPR is equivalent with sensitivity and FPR is equal to 1 - specificity, the ROC graph is sometimes called the sensitivity vs (1 - specificity) plot. A perfect test will have an area under the ROC curve of 1.0; a random test will have an area of 0.5. A threshold is selected to provide an acceptable level of specificity and sensitivity.

[0032] In this context, “diseased” is meant to refer to a population having one characteristic (e.g., benefit from treatment) and “nondiseased” is meant to refer to a population lacking the characteristic. While a single decision threshold is the simplest application of such a method, multiple decision thresholds may be used. For example, below a first threshold, the absence of disease may be assigned with relatively high confidence, and above a second threshold the presence of disease may also be assigned with relatively high confidence. Between the two thresholds may be considered indeterminate. This is meant to be exemplary in nature only.

[0033] In addition to threshold comparisons, other methods for correlating assay results to a patient classification (occurrence or nonoccurrence of disease, likelihood of an outcome, etc.) include decision trees, rule sets, Bayesian methods, and neural_network methods. These methods can produce probability values representing the degree to which a subject belongs to one classification out of a plurality of classifications.

[0034] Measures of test accuracy may be obtained as described in Fischer et al., Intensive Care Med. 29: 1043-51, 2003, and used to determine the effectiveness of a given biomarker. These measures include sensitivity and specificity, predictive values, likelihood ratios, diagnostic odds ratios, and ROC curve areas. The area under the curve (“AUC”) of a ROC plot is equal to the probability that a classifier will rank a randomly chosen positive instance higher than a randomly chosen negative one. The area under the ROC curve may be thought of as equivalent to the Mann-Whitney U test, which tests for the median difference between scores obtained in the two groups considered if the groups are of continuous data, or to the Wilcoxon test of ranks.

[0035] Pharmaceutical Compositions and Administration

[0036] To prepare pharmaceutical or sterile compositions of anti-APRIL antibodies, a suitable antibody or antigen-binding fragment thereof is admixed with a pharmaceutically acceptable carrier or excipient. See, *e.g.*, *Remington's Pharmaceutical Sciences* and *U.S. Pharmacopeia: National Formulary*, Mack Publishing Company, Easton, PA (1984).

[0037] Formulations of therapeutic agents may be prepared by mixing with acceptable carriers, excipients, or stabilizers in the form of, *e.g.*, lyophilized powders, slurries, aqueous solutions or suspensions (see, *e.g.*, Hardman, *et al.* (2001) *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, McGraw-Hill, New York, NY; Gennaro (2000) *Remington: The Science and Practice of Pharmacy*, Lippincott, Williams, and Wilkins, New York, NY; Avis, *et al.* (eds.) (1993) *Pharmaceutical Dosage Forms: Parenteral Medications*, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) *Pharmaceutical Dosage Forms: Tablets*, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) *Pharmaceutical Dosage Forms: Disperse Systems*, Marcel Dekker, NY; Weiner and Kotkoskie (2000) *Excipient Toxicity and Safety*, Marcel Dekker, Inc., New York, NY).

[0038] Toxicity and therapeutic efficacy of an anti-APRIL antibody, administered alone or in combination with another therapeutic agent, can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index (LD₅₀/ ED₅₀). The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration.

[0039] In a further embodiment, a further therapeutic agent is administered to a subject in association with an anti-APRIL antibody or antigen-binding fragment thereof in accordance with the Physicians' Desk Reference 2003 (Thomson Healthcare; 57th edition (November 1, 2002)).

[0040] The mode of administration can vary. Routes of administration include oral, rectal, transmucosal, intestinal, parenteral; intramuscular, subcutaneous, intradermal,

intramedullary, intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, intraocular, inhalation, insufflation, topical, cutaneous, transdermal, or intra-arterial.

[0041] In particular embodiments, the anti-APRIL antibodies or antigen-binding fragments thereof can be administered by an invasive route such as by injection. In further embodiments of the invention, an anti-APRIL antibody or antigen-binding fragment thereof, or pharmaceutical composition thereof, is administered intravenously, subcutaneously, intramuscularly, intraarterially, intratumorally, or by inhalation, aerosol delivery. Administration by non-invasive routes (*e.g.*, orally; for example, in a pill, capsule or tablet) is also within the scope of the present invention.

[0042] The present invention provides a vessel (*e.g.*, a plastic or glass vial, *e.g.*, with a cap or a chromatography column, hollow bore needle or a syringe cylinder) comprising any of the antibodies or antigen-binding fragments of the invention or a pharmaceutical composition thereof. The present invention also provides an injection device comprising any of the antibodies or antigen-binding fragments of the invention or a pharmaceutical composition thereof. An injection device is a device that introduces a substance into the body of a patient via a parenteral route, *e.g.*, intramuscular, subcutaneous or intravenous. For example, an injection device may be a syringe (*e.g.*, pre-filled with the pharmaceutical composition, such as an auto-injector) which, for example, includes a cylinder or barrel for holding fluid to be injected (*e.g.*, antibody or fragment or a pharmaceutical composition thereof), a needle for piercing skin and/or blood vessels for injection of the fluid; and a plunger for pushing the fluid out of the cylinder and through the needle bore. In an embodiment of the invention, an injection device that comprises an antibody or antigen-binding fragment thereof of the present invention or a pharmaceutical composition thereof is an intravenous (IV) injection device. Such a device includes the antibody or fragment or a pharmaceutical composition thereof in a cannula or trocar/needle which may be attached to a tube which may be attached to a bag or reservoir for holding fluid (*e.g.*, saline; or lactated ringer solution comprising NaCl, sodium lactate, KCl, CaCl₂ and optionally including glucose) introduced into the body of the patient through the cannula or trocar/needle. The antibody or fragment or a pharmaceutical composition thereof may, in an embodiment of the invention, be introduced into the device once the trocar and cannula are inserted into the vein of a subject and the trocar is removed from the inserted cannula. The IV device may, for example, be inserted into a peripheral vein (*e.g.*, in the hand or arm); the superior vena cava or inferior vena cava, or

within the right atrium of the heart (*e.g.*, a central IV); or into a subclavian, internal jugular, or a femoral vein and, for example, advanced toward the heart until it reaches the superior vena cava or right atrium (*e.g.*, a central venous line). In an embodiment of the invention, an injection device is an autoinjector; a jet injector or an external infusion pump. A jet injector uses a high-pressure narrow jet of liquid which penetrate the epidermis to introduce the antibody or fragment or a pharmaceutical composition thereof to a patient's body. External infusion pumps are medical devices that deliver the antibody or fragment or a pharmaceutical composition thereof into a patient's body in controlled amounts. External infusion pumps may be powered electrically or mechanically. Different pumps operate in different ways, for example, a syringe pump holds fluid in the reservoir of a syringe, and a moveable piston controls fluid delivery, an elastomeric pump holds fluid in a stretchable balloon reservoir, and pressure from the elastic walls of the balloon drives fluid delivery. In a peristaltic pump, a set of rollers pinches down on a length of flexible tubing, pushing fluid forward. In a multi-channel pump, fluids can be delivered from multiple reservoirs at multiple rates.

[0043] Pharmaceutical compositions may also be administered with a needleless hypodermic injection device; such as the devices disclosed in U.S. Patent Nos. 6,620,135; 6,096,002; 5,399,163; 5,383,851; 5,312,335; 5,064,413; 4,941,880; 4,790,824 or 4,596,556. Such needleless devices comprising the pharmaceutical composition are also part of the present invention. The pharmaceutical compositions may also be administered by infusion. Examples of well-known implants and modules for administering the pharmaceutical compositions include those disclosed in: U.S. Patent No. 4,487,603, which discloses an implantable micro-infusion pump for dispensing medication at a controlled rate; U.S. Patent No. 4,447,233, which discloses a medication infusion pump for delivering medication at a precise infusion rate; U.S. Patent No. 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; U.S. Patent. No. 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments. Many other such implants, delivery systems, and modules are well known to those skilled in the art and those comprising the pharmaceutical compositions of the present invention are within the scope of the present invention.

[0044] Alternately, one may administer the anti-APRIL antibody or antigen-binding fragment in a local rather than systemic manner, for example, via injection of the antibody or fragment directly into a tumor. Furthermore, one may administer the

antibody or fragment in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody, targeting, for example, a tumor. The liposomes will be targeted to and taken up selectively by the afflicted tissue. Such methods and liposomes are part of the present invention.

[0045] The administration regimen depends on several factors, including the serum or tissue turnover rate of the therapeutic antibody or antigen-binding fragment, the level of symptoms, the immunogenicity of the therapeutic antibody, and the accessibility of the target cells in the biological matrix. Preferably, the administration regimen delivers sufficient therapeutic antibody or fragment to effect improvement in the target disease state, while simultaneously minimizing undesired side effects. Accordingly, the amount of biologic delivered depends in part on the particular therapeutic antibody and the severity of the condition being treated. Guidance in selecting appropriate doses of therapeutic antibodies or fragments is available (see, *e.g.*, Wawrzynczak (1996) *Antibody Therapy*, Bios Scientific Pub. Ltd, Oxfordshire, UK; Kresina (ed.) (1991) *Monoclonal Antibodies, Cytokines and Arthritis*, Marcel Dekker, New York, NY; Bach (ed.) (1993) *Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases*, Marcel Dekker, New York, NY; Baert, *et al.* (2003) *New Engl. J. Med.* 348:601-608; Milgrom *et al.* (1999) *New Engl. J. Med.* 341:1966-1973; Slamon *et al.* (2001) *New Engl. J. Med.* 344:783-792; Beniaminovitz *et al.* (2000) *New Engl. J. Med.* 342:613-619; Ghosh *et al.* (2003) *New Engl. J. Med.* 348:24-32; Lipsky *et al.* (2000) *New Engl. J. Med.* 343:1594-1602).

[0046] Determination of the appropriate dose is made by the clinician, *e.g.*, using parameters or factors known or suspected in the art to affect treatment. Generally, the dose begins with an amount somewhat less than the optimum dose and it is increased by small increments thereafter until the desired or optimum effect is achieved relative to any negative side effects. Important diagnostic measures include those of symptoms of, *e.g.*, the inflammation or level of inflammatory cytokines produced. In general, it is desirable that a biologic that will be used is derived from the same species as the animal targeted for treatment, thereby minimizing any immune response to the reagent. In the case of human subjects, for example, humanized and fully human antibodies may be desirable.

[0047] Antibodies or antigen-binding fragments thereof may be provided by continuous infusion, or by doses administered, *e.g.*, daily, 1-7 times per week, weekly, bi-weekly, monthly, bimonthly, quarterly, semiannually, annually etc. Doses may be

provided, *e.g.*, intravenously, subcutaneously, topically, orally, nasally, rectally, intramuscular, intracerebrally, intraspinally, or by inhalation. A total weekly dose is generally at least 0.05 µg/kg body weight, more generally at least 0.2 µg/kg, 0.5 µg/kg, 1 µg/kg, 10 µg/kg, 100 µg/kg, 0.25 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 5.0 mg/mL, 10 mg/kg, 25 mg/kg, 50 mg/kg or more (see, *e.g.*, Yang, *et al.* (2003) *New Engl. J. Med.* 349:427-434; Herold, *et al.* (2002) *New Engl. J. Med.* 346:1692-1698; Liu, *et al.* (1999) *J. Neurol. Neurosurg. Psych.* 67: 451-456; Portielji, *et al.* (20003) *Cancer Immunol. Immunother.* 52: 151-144). Doses may also be provided to achieve a pre-determined target concentration of anti-APRIL antibody in the subject's serum, such as 0.1, 0.3, 1, 3, 10, 30, 100, 300 µg/mL or more. In other embodiments, an anti-APRIL antibody is administered, *e.g.*, subcutaneously or intravenously, on a weekly, biweekly, "every 4 weeks," monthly, bimonthly, or quarterly basis at 10, 20, 50, 80, 100, 150, 200, 500 or 1000 mg/subject.

[0048] As used herein, the term "effective amount" refers to an amount of an anti-APRIL or antigen-binding fragment thereof that, whether administered alone or in combination with an additional therapeutic agent to a cell, tissue, or subject, is effective to cause a measurable improvement in one or more symptoms of disease, for example cancer or the progression of cancer. An effective dose further refers to that amount of the antibody or fragment sufficient to result in at least partial amelioration of symptoms, *e.g.*, tumor shrinkage or elimination, lack of tumor growth, increased survival time. When applied to an individual active ingredient administered alone, an effective dose refers to that ingredient alone. When applied to a combination, an effective dose refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. An effective amount of a therapeutic will result in an improvement of a diagnostic measure or parameter by at least 10%; usually by at least 20%; preferably at least about 30%; more preferably at least 40%, and most preferably by at least 50%. An effective amount can also result in an improvement in a subjective measure in cases where subjective measures are used to assess disease severity.

[0049] Example 1. Administration of anti-human APRIL antibody

APRIL.01A_VH14_1G/VL15 (referred to herein as "BION-1301"; described in WO2016110587A1) was supplied as a solution intended for intravenous (IV)

administration to multiple myeloma patients (see clinicaltrials.gov/ct2/show/NCT03340883). After dilution, BION-1301 was administered at the assigned dose level (50, 150 or 450 mg) by IV infusion over approximately 2 hours using central lines or other venous access devices. Patients were dosed once every two weeks (Q2W) in a 4 weeks cycle.

[0050] Example 2. Blood and bone marrow sample collection and preparation

[0051] For determination of free APRIL and BION-1301 levels, blood and bone marrow samples were obtained from multiple myeloma patients. Blood samples were collected before treatment with 50 mg or 150 mg BION-1301 and at 30 minutes, 1 hour, 2 hours, 4-8 hours, 2 days, 3 days and 8 days post-dosing. In addition, blood samples were obtained prior to and 30 minutes after the cycle 1-day 15, cycle 1-day 29 and cycle 2 day-15 doses. Bone marrow samples were collected before treatment with 50mg or 150mg BION-1301 and prior to the cycle 2-day 15 dose.

[0052] Blood was drawn by venipuncture and collected in vacuum serum separation tubes. After gently inverting the tubes for 5 times, blood was allowed to clot for 30 minutes. The tubes were centrifuged at 1100-1300xg for 10-15 minutes. Serum was collected, aliquoted into cryovials and stored at -70°C until analysis. Bone marrow aspirates were preferably obtained from the iliac crest. The aspirates were collected in sodium heparin tubes and mixed by gently inverting 8-10 times. Tubes were centrifuged at 400xg for 10-15 minutes. Aspirate supernatants were collected and aliquoted into cryovials. Samples were stored at -70°C until analysis.

[0053] Example 3. Quantification of free APRIL in human serum and bone marrow supernatants

[0054] For quantifying free APRIL in human serum or bone marrow supernatant, 96-well plates were coated overnight with a recombinant capture antigen (Recombinant Human BCMA, R&D Systems). Coated plates were blotted dry by emptying and tapping on a paper towel. Plates were then blocked for 1-2 hours with 1% BSA in DPBS to prevent non-specific binding of proteins. Standards were prepared by spiking freshly reconstituted recombinant human APRIL (rhAPRIL, R&D Systems) into assay diluent (0.5%BSA and 0.05%Tween 20 in PBS). Matrix QCs, serum samples and bone marrow supernatants were diluted 5-fold in assay diluent. After the blocking incubation, plates

were washed three times with wash buffer PBS-T (0.05% Tween 20 in PBS) using an automated plate washer. Then, the standards, diluted QCs, and diluted samples were added, and the plates were incubated for one hour at room temperature. The plates were washed again to remove unbound material, and a 0.5 µg/mL solution of Mouse Anti-hAPRIL Monoclonal Antibody hAPRIL.133 (Aduro Biotech Europe) was added. After incubating for an hour, the plates were washed, and a 5000x diluted conjugate solution (Goat-anti-Mouse-IgG (H+L)-HRP, Jackson ImmunoResearch) was added. The plates were incubated in the dark for an hour at room temperature. The plates were washed again, TMB substrate was added and the plates were incubated in the dark for 15 minutes. The addition of the TMB substrate induced HRP enzyme activity, which resulted in a blue coloration of the substrate. The enzymatic reaction was stopped by the addition of a 0.5 M sulfuric acid solution, which caused a color change from blue to yellow. The absorbance was read on a Spectramax Plus 384 spectrophotometer (Molecular Devices) at 450 nm, using 620 nm as reference wavelength. Watson™ LIMS Version 7.4.1 was used for data analysis. The color intensity was proportional to the amount of free APRIL present in the sample.

[0055] Example 4. Determination of the levels of BION-1301 in human serum and bone marrow supernatants

[0056] BION-1301 was quantified in human serum and bone marrow supernatant using a sandwich Electrochemiluminescence (ECL) immunoassay. Standard microtiter plates (MSD cat# L15XA) were coated with an anti-idiotypic antibody (Aduro Biotech Europe). On the day of analysis, the coated plates were blotted dry, blocked with SuperBlock PBS (ThermoFisher cat # 37515) and washed. Samples (including standards and QCs) were diluted 10x in assay buffer (i.e. SuperBlock T20 PBS, ThermoFisher cat# 37516 with 0.2 mg/mL purified mouse IgG) and incubated on the plates. BION-1301 was detected by biotinylated-anti-idiotypic antibody. After washing the plates, ruthenylated streptavidin was added. Buffered tripropylamine was used to generate electrochemiluminescence, which was quantified using a MSD Sector 600 (Meso Scale Discovery). Watson™ LIMS Version 7.4.1 was used for data analysis. The relative light signal is proportional to the quantity of BION-1301.

[0057] Example 5. Results

[0058] Table 1 shows the levels of free APRIL and BION-1301 that were measured in serum and bone marrow samples, collected from multiple myeloma patients before dosing with 50 mg or 150 mg BION-1301 and prior to the cycle 2-day 15 dose. The measurements that were performed on 8 paired serum and bone marrow samples demonstrate that both compartments contain highly comparable levels of free APRIL. In addition, determination of BION-1301 levels in 2 paired serum and bone marrow samples shows that the antibody concentration is highly comparable in the two compartments.

[0059] In patient 16068002, who was treated with 50 mg BION-1301, the level of bone marrow free APRIL was reduced to 84% prior to the cycle 2-day 15 dose, compared to baseline level. In patient 16070001, who received the 150 mg dose, the decrease of free APRIL in the bone marrow was even more pronounced. Compared to the baseline level, bone marrow free APRIL was reduced to 29% in this patient (Table 2).

[0060] Figure 1 depicts the longitudinal monitoring of free APRIL levels in serum from multiple myeloma patients treated with BION-1301. Dosing with BION-1301 resulted in an instant reduction of serum free APRIL levels. Over time these levels showed partial recovery and a sharp decline upon subsequent dosing with BION-1301. In view of the comparable levels of free APRIL in serum and bone marrow, this longitudinal monitoring of serum free APRIL levels is indicative of the dynamics of free APRIL levels in bone marrow upon treatment with BION-1301. Consequently, the optimal dosing level and/or schedule of an APRIL-neutralizing antibody such as BION-1301, or other treatments aimed at affecting bone marrow free APRIL levels, can be based on the free APRIL levels measured in corresponding serum samples.

[0061] Table 1:

Subject	Time	Dose	Serum Bion1301, nM	BM Bion1301, nM	Serum APRIL, nM	BM APRIL, nM	Bion1301 BM/serum, %	APRIL BM/serum, %
16068001	1	50 mg			0.056	0.04		72
16068002	1	50 mg			0.18	0.14		76
16068002	43	50 mg	14	16	0.099	0.12	114	117

Subject	Time	Dose	Serum Bion1301, nM	BM Bion1301, nM	Serum APRIL, nM	BM APRIL, nM	Bion1301 BM/serum, %	APRIL BM/serum, %
16068003	1	150 mg			0.043	0.05		116
16068004	1	150 mg				0.13		
16070001	1	150 mg			0.18	0.2		113
16070001	43	150 mg	114	138	0.07	0.059	121	83
16070002	1	150 mg			0.11	0.053		49
16072002	1	150 mg				0.13		
16074001	1	50 mg			0.32	0.22		69

BM – Bone marrow; % - percent of value measured at time 1; Time – days

[0062] Table 2:

Subject	Time	Dose	BM APRIL, nM	APRIL BM, %
16068002	1	0050 mg	0.14	
16068002	43	0050 mg	0.12	84
16070001	1	0150 mg	0.2	
16070001	43	0150 mg	0.059	29

[0063] While the invention has been described and exemplified in sufficient detail for those skilled in this art to make and use it, various alternatives, modifications, and improvements should be apparent without departing from the spirit and scope of the invention. The examples provided herein are representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Modifications therein and other uses will occur to those skilled in the art. These modifications are encompassed within the spirit of the invention and are defined by the scope of the claims.

[0064] It will be readily apparent to a person skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

[0065] All patent applications, patents, publications and other references mentioned in the specification are indicative of the levels of those of ordinary skill in the art to which the invention pertains and are each incorporated herein by reference. The references cited herein are not admitted to be prior art to the claimed invention.

[0066] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the case of conflict, the present specification, including definitions, will control.

[0067] The use of the articles “a”, “an”, and “the” in both the description and claims are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms “comprising”, “having”, “being of” as in “being of a chemical formula”, “including”, and “containing” are to be construed as open terms (i.e., meaning “including but not limited to”) unless otherwise noted. Additionally whenever “comprising” or another open-ended term is used in an embodiment, it is to be understood that the same embodiment can be more narrowly claimed using the intermediate term “consisting essentially of” or the closed term “consisting of”.

[0068] The term “about”, “approximately”, or “approximate”, when used in connection with a numerical value, means that a collection or range of values is included. For example, “about X” includes a range of values that are $\pm 20\%$, $\pm 10\%$, $\pm 5\%$, $\pm 2\%$, $\pm 1\%$, $\pm 0.5\%$, $\pm 0.2\%$, or $\pm 0.1\%$ of X, where X is a numerical value. In one embodiment, the term “about” refers to a range of values which are 10% more or less than the specified value. In another embodiment, the term “about” refers to a range of values which are 5% more or less than the specified value. In another embodiment, the term “about” refers to a range of values which are 1% more or less than the specified value.

[0069] Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification

as if it were individually recited herein. A range used herein, unless otherwise specified, includes the two limits of the range. For example, the terms “between X and Y” and “range from X to Y, are inclusive of X and Y and the integers there between. On the other hand, when a series of individual values are referred to in the disclosure, any range including any of the two individual values as the two end points is also conceived in this disclosure. For example, the expression “a dose of about 100 mg, 200 mg, or 400 mg” can also mean “a dose ranging from 100 to 200 mg”, “a dose ranging from 200 to 400 mg”, or “a dose ranging from 100 to 400 mg”.

[0070] The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms “comprising”, “consisting essentially of” and “consisting of” may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

[0071] Other embodiments are set forth within the following claims.

We claim:

1. A method of treating a multiple myeloma patient with an anti-APRIL antibody, comprising:

measuring a first level of APRIL protein in a first blood, serum, or plasma sample obtained from the patient using an APRIL specific binding assay;

following obtaining the first level of APRIL protein, administering a first therapeutic amount of an anti-APRIL antibody to the patient;

following the administering, determining one or more monitoring levels of APRIL protein in the patient in one or more blood, serum, or plasma samples obtained from the patient using the APRIL specific binding assay;

wherein if one of the monitoring levels indicates an initial reduction in the level of APRIL protein relative to the first level of APRIL protein, and a subsequent one of the monitoring levels indicates an increase in levels of APRIL protein relative to the initial reduction, administering a second therapeutic amount of the anti-APRIL antibody to the patient.

2. A method according to claim 1, wherein if one of the monitoring levels fails to indicate an initial reduction in the level of APRIL protein relative to the first level of APRIL protein, discontinuing the administration of the anti-APRIL antibody to the patient.

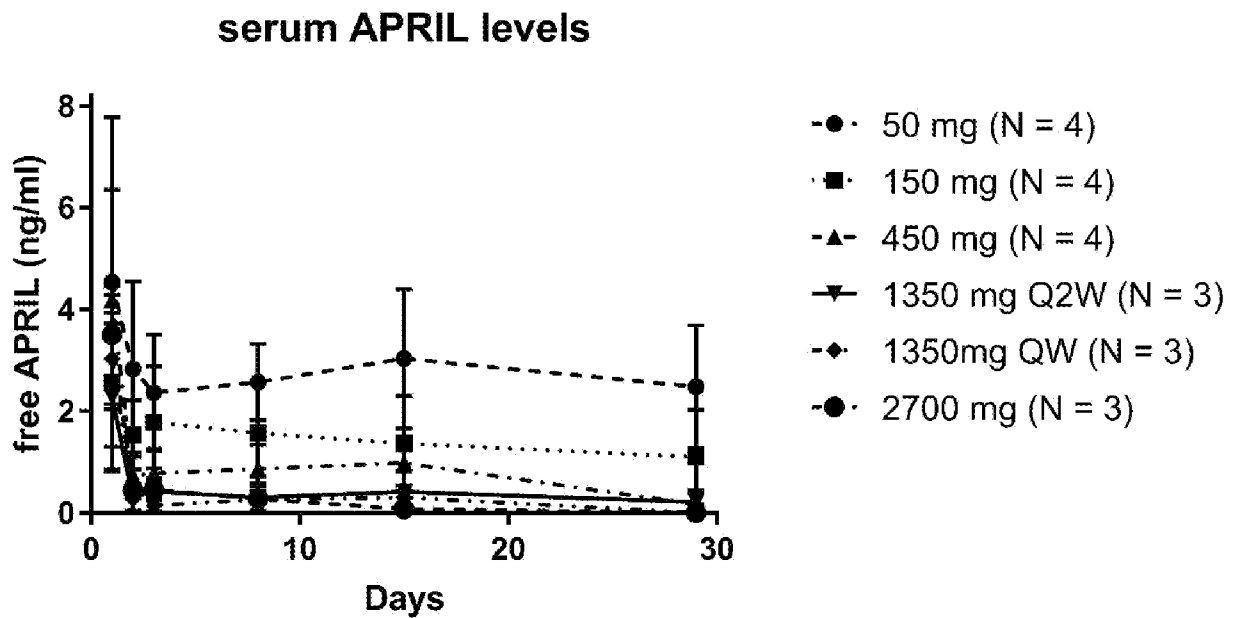
3. A method according to claim 1 or 2, wherein the anti-APRIL antibody blocks the binding of APRIL with human transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) and human B cell maturation antigen (BCMA) with an IC_{50} of about 2 nM or lower.

4. A method according to claim 3, wherein the anti-APRIL antibody is APRIL.01A, APRIL.01A_VH14_1G/VL15 or APRIL.03A.

5. A method according to one of claims 1-4, wherein the level of APRIL protein in a first blood, serum, or plasma sample measured using the APRIL specific binding assay correlates to a level of APRIL protein in bone marrow supernatants with a correlation coefficient of at least 0.85.

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FIGURE 1



Values BLQ (<0.232 ng/ml) were plotted as 0 ng/ml.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/000020

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/574 C07K16/28
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01N C07K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/110587 A1 (ADURO BIOTECH HOLDINGS EUROPE B V [NL]) 14 July 2016 (2016-07-14) cited in the application page 32, paragraph 3 claims 1-10, 17-19 ----- -/-	1-5



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Schwachtgen, J

INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DULOS JOHN ET AL: "Bion-1301, a First-in-Class APRIL Neutralizing Antibody for the Treatment of Multiple Myeloma: Preclinical Safety, and Analysis of Pharmacokinetics - Pharmacodynamics Relationship", 7 December 2017 (2017-12-07), BLOOD, VOL. 130, NR. SUPPL. 1, PAGE(S) 1827, 59TH ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY (ASH); ATLANTA, GA, USA; DECEMBER 09 -12, 2017, XP009520077, ISSN: 0006-4971(print) abstract	1-5
A	----- JOHN DULOS: "Abstract 3780: Preclinical pharmacokinetics, pharmacodynamics and safety of BION-1301, a first-in-class antibody targeting APRIL for the treatment of multiple myeloma", CANCER RESEARCH, vol. 78, no. 13, 1 July 2018 (2018-07-01), XP055688411, DOI: 10.1158/1538-7445.AM2018-3780 abstract -----	1-5

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Information on patent family members

International application No

PCT/IB2020/000020

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