THERAPEUTIC COMBINATION OF AN AKT INHIBITOR, A BCL-2 INHIBITOR, AND AN ANTI-CD20 ANTIBODY

Cross-reference to related applications

This application claims priority to United States Provisional Patent Application No. 63/556,680, filed 22 February 2024, the disclosure of which is incorporated by reference herein.

Background

B-cell malignancies represent a class of leukemias and lymphomas arising from dysregulated growth of B-cells. Although understanding of the biology and genetics of such diseases has increased in recent years, there remains a high unmet need for treatments addressing this class of cancers.

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype with approximately 30-40% of cases worldwide (Swerdlow, S.H. et al., *Blood* **127**, 2375-2390 (2016)). DLBCL is a heterogenous B cell malignancy defined by both genetic and epigenetic alterations that regulate cell growth, survival and differentiation (Wright, G.W. *et al.*, *Cancer Cell* **37**, 551-568 e514 (2020)). DLBCL is transcriptionally subclassified into two subset types, activated B-cell like (ABC) and germinal center B-cell like (GCB) derived from distinct originating B cells. Genomic analyses have identified distinct subtypes of DLBCL with genetic drivers and signalling pathways that are therapeutically targetable (Roschewski, M. et al., *The Cancer Journal* **26**, 195-205 (2020)). First line therapy largely consists of rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). Rituximab in combination with CHOP is known as R-CHOP. A modified regimen which replaces vincristine with polatuzumab vedotin (pola-R-CHP) has also recently been developed (Tilly, H. *et al. N Engl J Med* **386**, 351-363 (2022)). Despite these recent advances in improving first line therapeutic approaches, for relapsed/refractory DLBCL patients there is still a significant proportion of patients that require additional novel treatment strategies.

PI3K-AKT signalling is frequently dysregulated across B-cell malignancies (Wang, J. *et al., Am J Pathol* 187, 1700-1716 (2017)). The most frequent mutations are found in PIK3CA and PTEN, with frequent down regulation of PTEN expression in GCB DLBCL (Pfeifer, M. & Lenz, G., *Cell Cycle* **12**, 3347-3348 (2013)). PI3K-AKT pathway inhibitors show differential activity

in ABC- versus GCB-DLBCL subsets. ABC-DLBCL which can have mutations in PIK3CA is sensitive to PI3Kα and PI3Kδ inhibitors (Erdmann, T. *et al. Blood* **130**, 310-322 (2017); Pongas, G.N. et al. *Oncotarget* **8**, 81794-81802 (2017); Chen, L. *et al. Cancer Cell* **23**, 826-838 (2013)), and PI3K pathway inhibitors have clinical activity in patients with lymphoma (Verret, B., Cortes, J. et al., *Annals of oncology : official journal of the European Society for Medical Oncology* **30 Suppl 10**, x12-x20 (2019); Pascual, J. & Turner, N.C., *Annals of oncology : official journal of the European Society for Medical Oncology* **30**, 1051-1060 (2019)). Copanlisib, a pan-PI3k inhibitor with activity against PI3Kα and δ has clinical activity in follicular lymphoma and has been evaluated in ABC-DLBCL (Dreyling, M. *et al. Ann Oncol* **28**, 2169-2178 (2017); Lenz, G. *et al. Leukemia* **34**, 2184-2197 (2020)). The utility of PI3K inhibitors such as idelasib and copanlisib has been limited due to safety concerns associated with long-term treatment. However, the PI3K signalling axis can be modulated at different nodes along the pathway such as AKT, for example the small molecule pan-AKT inhibitor, capivasertib, has recently shown positive benefit in a Phase III clinical trial in ER+ breast cancer with an acceptable safety profile (Turner, N.C. *et al. N Engl J Med* **388**, 2058-2070 (2023)).

Relapsed/refractory GCB-DLBCL has a high incidence of PTEN protein loss (Pfeifer, M. & Lenz, G., *Cell Cycle* **12**, 3347-3348 (2013)), and GCB DLBCL cell lines and tumour models are sensitive to AKT inhibition (Erdmann, T. *et al. Blood* **130**, 310-322 (2017); Ezell, S.A. *et al. Oncotarget* **7**, 9163-9174 (2016)). This is further supported by the observation that combined PI3Kβ/δ and mTORC1/2 inhibition has broad anti-tumour activity across preclinical DLBCL models (Xu, W., Berning, P. & Lenz, G. *Blood* **138**, 1110-1119 (2021)). PI3K-AKT signalling pathways in DLBCL are therefore important in different subtypes although the therapeutically effective node of the pathway varies amongst subtypes.

R-CHOP is a common treatment for DLBCL, and improved clinical benefit has been achieved with the pola-R-CHP regimen (Tilly, H. *et al. N Engl J Med* **386**, 351-363 (2022)). Clinical benefit in haematological disease has also been observed with the oral B-cell lymphoma-2 (BCL-2) inhibitor venetoclax which induces apoptosis (Cory, S. et al., *Trends Cancer* **2**, 443-460 (2016)). Venetoclax is approved for newly diagnosed and relapsed/refractory adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma with 17p Deletion, and is also used in combination with azacytidine or decitabine or low dose cytarabine for newly diagnosed acute myeloid leukaemia patients (DiNardo, C.D. *et al. N Engl J Med* **383**,

617-629 (2020); Stilgenbauer, S. *et al. Lancet Oncol* **17**, 768-778 (2016)). In Phase II, addition of venetoclax to R-CHOP demonstrated potential increased clinical benefit in high risk DLBCL patients. Preclinically, venetoclax combined with an epigenetic EZH2 inhibitor extended survival benefit of DLBCL patient derived xenograft (PDX) mouse models (Scholze, H. *et al. Blood Adv* **4**, 5226-5231 (2020); Morschhauser, F. *et al. Blood* **137**, 600-609 (2021)). Additionally, the generation of venetoclax resistance in DLBCL cell lines induces activation of AKT signalling suggesting that AKT inhibition could improve response to venetoclax (Choudhary, G.S. *et al. Cell Death Dis* **6**, e1593 (2015)).

International Patent Application No. PCT/EP2022/081881 describes methods of treating B-cell malignancies comprising administering a combination of capivasertib and venetoclax in various optimized dosing regimens. Despite the foregoing, there remains a need for further options for the treatment of B-cell malignancies, particularly for relapsed or refractory DLBCL.

Summary

In one aspect, there is provided a method of treating a B-cell malignancy in a patient in need thereof, comprising administering to the patient a combination of: a first amount of an AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof), a second amount of a BCL-2 inhibitor (such as venetoclax or a pharmaceutically acceptable salt thereof), and a third amount of an anti-CD20 antibody (such as rituximab); wherein the first amount, second amount and third amount together comprise a therapeutically effective amount.

In one aspect, there is provided an AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof) for use in the treatment of a B-cell malignancy in a patient in need thereof, wherein the AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof) is administered in combination with a BCL-2 inhibitor (such as venetoclax or a pharmaceutically acceptable salt thereof), and an anti-CD20 antibody (such as rituximab).

In one aspect, there is provided the use of an AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for the treatment of a B-cell malignancy in a patient in need thereof, wherein the AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof) is administered in combination with a

BCL-2 inhibitor (such as venetoclax or a pharmaceutically acceptable salt thereof), and an anti-CD20 antibody (such as rituximab).

In one aspect, there is provided a kit comprising (i) an AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof), and (ii) instructions for the use of the AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof) in combination with a BCL-2 inhibitor (such as venetoclax or a pharmaceutically acceptable salt thereof), and an anti-CD20 antibody (such as rituximab), in the treatment of a B-cell malignancy in a patient in need thereof.

Other features, objects, and advantages will be apparent from the description and drawings, and from the claims.

Brief description of the drawings

Figure 1 shows the tumour volume over time following treatment of WSU-DLCL2 tumours with Treatments 1 to 7 described in Table 1.

Figure 2 shows the tumour volume over time following treatment of WSU-DLCL2 tumours with Treatments 5 and 6 described in Table 1, followed by dosing cessation.

Figure 3 shows the tumor volume over time following treatment of WSU-DLCL2 tumours with R-CHOP (Treatment 7 of Table 1, days 14-49 post-implantation) and a combination of capivasertib, venetoclax and rituximab (Treatment 8 shown in Table 2, days 50-70 post-implantation) on progression of the tumours.

Figure 4 shows body weight change following treatment of WSU-DLCL2 tumours with Treatments 5 and 6 described in Table 1.

Figure 5 shows body weight change following treatment of WSU-DLCL2 tumours with R-CHOP (Treatment 7 of Table 1, days 14-49 post-implantation) and a combination of capivasertib, venetoclax and rituximab (Treatment 8 shown in Table 2, days 50-70 post-implantation) on progression of the tumours.

Detailed Description

Described herein are methods of treating a B-cell malignancy in a patient in need thereof. The methods include administering a combination of an AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof), a BCL-2 inhibitor (such as venetoclax or a

pharmaceutically acceptable salt thereof), and an anti-CD20 antibody (such as rituximab). The methods can include administering the AKT inhibitor, BCL-2 inhibitor and anti-CD20 antibody in respective dosage amounts and on respective dosage schedules so as to provide a therapeutic effect.

Accordingly, in one embodiment there is provided a method of treating a B-cell malignancy in a patient in need thereof, comprising administering to the patient a combination of: a first amount of an AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof), a second amount of a BCL-2 inhibitor (such as venetoclax or a pharmaceutically acceptable salt thereof), and a third amount of an anti-CD20 antibody (such as rituximab); wherein the first amount, second amount and third amount together comprise a therapeutically effective amount.

In one embodiment there is provided an AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof) for use in the treatment of a B-cell malignancy in a patient in need thereof, wherein the AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof) is administered in combination with a BCL-2 inhibitor (such as venetoclax or a pharmaceutically acceptable salt thereof), and an anti-CD20 antibody (such as rituximab).

In one embodiment there is provided the use of an AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for the treatment of a B-cell malignancy in a patient in need thereof, wherein the AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof) is administered in combination with a BCL-2 inhibitor (such as venetoclax or a pharmaceutically acceptable salt thereof), and an anti-CD20 antibody (such as rituximab).

In one embodiment there is provided a kit comprising (i) an AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof), and (ii) instructions for the use of the AKT inhibitor (such as capivasertib or a pharmaceutically acceptable salt thereof) in combination with a BCL-2 inhibitor (such as venetoclax or a pharmaceutically acceptable salt thereof), and an anti-CD20 antibody (such as rituximab), in the treatment of a B-cell malignancy in a patient in need thereof.

Advantageously, the combinations for the treatment a B-cell malignancy described herein may provide improved and prolonged therapeutic effects while minimising the potential for side

effects, such as enabling lower doses of each component to be used compared to monotherapy or dual combination therapy.

General

The terms "treat," "treating," and "treatment" refer to at least partially alleviating, inhibiting, and/or ameliorating a condition, disorder, or disease, such as a B-cell malignancy, in a patient in need thereof. The term "treatment" includes both *in vitro* and *in vivo* treatments, including in warm-blooded animals such as humans. The effectiveness of treatment of cancer can be assessed in a variety of ways, including but not limited to: inhibiting cancer cell proliferation (including the reversal of cancer growth); promoting cancer cell death (e.g., by promoting apoptosis or another cell death mechanism); improvement in symptoms; duration of response to the treatment; delay in progression of disease; and prolonging survival. Treatments can also be assessed with regard to the nature and extent of side effects associated with the treatment. Furthermore, effectiveness can be assessed with regard to biomarkers, such as levels of expression or phosphorylation of proteins known to be associated with particular biological phenomena. Other assessments of effectiveness are known to those of skill in the art.

In some embodiments, the patient is a human patient or animal (e.g. mammalian) patient.

In some embodiments, the patient is a human patient. In some embodiments, the patient is an adult human patient.

The term "therapeutically effective amount" refers to that amount of a compound or combination of compounds as described herein that is sufficient to effect the intended application including, but not limited to, disease treatment. A therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the patient and disease condition being treated (e.g., the weight, age and gender of the patient), the severity of the disease condition, the manner of administration, etc. which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells (e.g. the amount of apoptosis). The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

The terms “first amount”, “second amount” and “third amount” are used to refer to the amount of each component in the combinations described herein and do not necessarily reflect order of dosing.

The term "pharmaceutically acceptable" is used to specify that an object (for example a salt, dosage form [such as a tablet or capsule] or excipient [such as a diluent or carrier]) is suitable for use in patients. An example list of pharmaceutically acceptable salts can be found in the “Handbook of Pharmaceutical Salts: Properties, Selection and Use”, P. H. Stahl and C. G. Wermuth, editors, Weinheim/Zurich:Wiley-VCH/VFiCA, 2002 or subsequent editions.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and salicylic acid. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese and aluminium. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Examples include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine.

AKT Inhibitors

In one embodiment, the AKT inhibitor is any molecule which binds to and inhibits the activity of one or more AKT isoforms (for example having a pIC_{50} of >4.5, >5, >6, >7, >8 or >9 vs. the isoform in question when tested in a standard potency assay, for example as described in WO2009/047563). In one embodiment, the AKT inhibitor is any AKT inhibitor known in the art.

In one embodiment, the AKT inhibitor is selected from miransertib (ARQ-092) or a pharmaceutically acceptable salt thereof, BAY1125976 or a pharmaceutically acceptable salt thereof, borussertib or a pharmaceutically acceptable salt thereof, AT7867 or a pharmaceutically acceptable salt thereof, CCT128930 or a pharmaceutically acceptable salt thereof, A-674563 or a

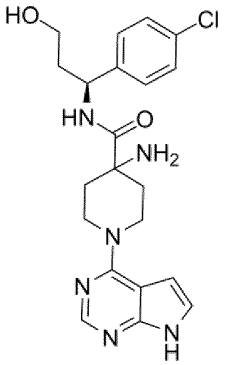
pharmaceutically acceptable salt thereof, PHT-427 or a pharmaceutically acceptable salt thereof, Akti-1/2 or a pharmaceutically acceptable salt thereof, AT13148 or a pharmaceutically acceptable salt thereof, SC79 or a pharmaceutically acceptable salt thereof, capivasertib or a pharmaceutically acceptable salt thereof, miltefosine or a pharmaceutically acceptable salt thereof, perifosine or a pharmaceutically acceptable salt thereof, MK-2206 or a pharmaceutically acceptable salt thereof, RX-0201 or a pharmaceutically acceptable salt thereof, erucylphosphocholine or a pharmaceutically acceptable salt thereof, PBI-05204 or a pharmaceutically acceptable salt thereof, GSK690693 or a pharmaceutically acceptable salt thereof, afuresertib (GSK2110183) or a pharmaceutically acceptable salt thereof, uprosertib (GSK2141795) or a pharmaceutically acceptable salt thereof, XL-418 or a pharmaceutically acceptable salt thereof and ipatasertib (GDC-0068) or a pharmaceutically acceptable salt thereof.

In one embodiment, the AKT inhibitor is selected from capivasertib or a pharmaceutically acceptable salt thereof, perifosine or a pharmaceutically acceptable salt thereof, MK-2206 or a pharmaceutically acceptable salt thereof, RX-0201 or a pharmaceutically acceptable salt thereof, erucylphosphocholine or a pharmaceutically acceptable salt thereof, PBI-05204 or a pharmaceutically acceptable salt thereof, GSK690693 or a pharmaceutically acceptable salt thereof, uprosertib (GSK2141795) or a pharmaceutically acceptable salt thereof, XL-418 or a pharmaceutically acceptable salt thereof and ipatasertib or a pharmaceutically acceptable salt thereof.

In one embodiment, the AKT inhibitor is selected from capivasertib or a pharmaceutically acceptable salt thereof, perifosine or a pharmaceutically acceptable salt thereof, MK-2206 or a pharmaceutically acceptable salt thereof, GSK690693 or a pharmaceutically acceptable salt thereof, afuresertib (GSK2110183) or a pharmaceutically acceptable salt thereof, uprosertib (GSK2141795) or a pharmaceutically acceptable salt thereof and ipatasertib (GDC-0068) or a pharmaceutically acceptable salt thereof.

In one embodiment, the AKT inhibitor is capivasertib or a pharmaceutically acceptable salt thereof. In one embodiment, the AKT inhibitor is capivasertib.

Capivasertib has the following chemical structure:



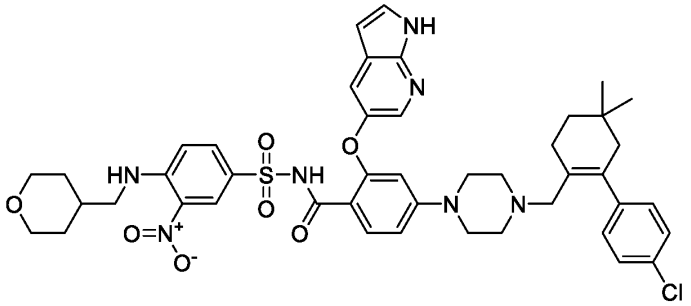
The chemical name of capivasertib is (S)-4-amino-N-(1-(4-chlorophenyl)-3-hydroxypropyl)-1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidine-4-carboxamide). Capivasertib is disclosed in Example 9 of WO2009/047563, which also describes its synthesis.

In one embodiment, the AKT inhibitor is a proteolysis targeting chimera (PROTAC) or molecular glue.

BCL-2 Inhibitors

In one embodiment, the BCL-2 inhibitor is any BCL-2 inhibitor known in the art. In one embodiment, the BCL-2 inhibitor is a selective BCL-2 inhibitor. In this regard, a selective BCL-2 inhibitor is one which selectively binds to the BCL-2 protein over other proteins within the BCL-2 protein family (such as BCL-XL and BCL-w). In one embodiment, the BCL-2 inhibitor is any selective BCL-2 inhibitor known in the art. In one embodiment, the BCL-2 inhibitor is venetoclax or a pharmaceutically acceptable salt thereof. In one embodiment, the BCL-2 inhibitor is venetoclax.

Venetoclax, having the structure



also referred to as ABT-199 or its chemical name 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-

ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide) is a selective BCL-2 inhibitor, described in, e.g., U.S. Patent Nos. 8,546,399 and 9,174,982 (each of which is incorporated herein by reference). Anti-apoptotic BCL-2 proteins are associated with a number of diseases including B-cell malignancies. Overexpression of BCL-2 proteins correlates with resistance to chemotherapy, clinical outcome, disease progression, overall prognosis or a combination thereof in various cancers and disorders of the immune system. Venetoclax is approved for treatment of chronic lymphocytic leukemia, small lymphocytic leukemia, and acute myeloid leukemia.

Anti-CD20 antibody

In one embodiment, the anti-CD20 antibody is any antibody capable of selectively depleting CD20-positive B cells. In one embodiment, the anti-CD20 antibody is an anti-CD20 monoclonal antibody. In one embodiment, the anti-CD20 antibody is an anti-CD20 chimeric monoclonal antibody. In one embodiment, the anti-CD20 antibody is any anti-CD20 antibody known in the art.

In one embodiment, the anti-CD20 antibody is selected from rituximab, ocrelizumab, obinutuzumab, ofatumumab, ibritumomab tiuxetan, tositumomab, ublituximab, and veltuzumab, or a functional equivalent thereof.

In one embodiment, the anti-CD20 antibody is rituximab or a functional equivalent thereof. In one embodiment, the anti-CD20 antibody is rituximab. Rituximab (RITUXAN) is a chimeric anti-CD20 monoclonal antibody, and is described in US 7,422,739, which is incorporated herein by reference.

Certain Combinations

In some embodiments, the AKT inhibitor is capivasertib or a pharmaceutically acceptable salt thereof, the BCL-2 inhibitor is venetoclax or a pharmaceutically acceptable salt thereof, and the anti-CD20 antibody is rituximab. In some embodiments, the AKT inhibitor is capivasertib, the BCL-2 inhibitor is venetoclax, and the anti-CD20 antibody is rituximab.

In some embodiments, the treatment of the B-cell malignancy comprises administering to the patient a combination of: capivasertib or a pharmaceutically acceptable salt thereof, a BCL-2 inhibitor, and an anti-CD20 antibody. In some embodiments, the treatment of the B-cell

malignancy comprises administering to the patient a combination of: capivasertib or a pharmaceutically acceptable salt thereof, venetoclax or a pharmaceutically acceptable salt thereof, and an anti-CD20 antibody. In some embodiments, the treatment of the B-cell malignancy comprises administering to the patient a combination of: capivasertib or a pharmaceutically acceptable salt thereof, venetoclax or a pharmaceutically acceptable salt thereof, and rituximab. In some embodiments, the treatment of the B-cell malignancy comprises administering to the patient a combination of: capivasertib, venetoclax and rituximab.

B-cell malignancies

The combinations described herein are useful for the treatment of a B-cell malignancy. In one embodiment, the B-cell malignancy is a non-Hodgkin lymphoma. In one embodiment, the B-cell malignancy is diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), follicular lymphoma or mantle cell lymphoma. In one embodiment, the B-cell malignancy is DLBCL. In one embodiment, the B-cell malignancy is germinal center B-cell-like diffuse large B-cell lymphoma (GCB-DLBCL), or activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL). In one embodiment, the B-cell malignancy is GCB-DLBCL.

In one embodiment, the B-cell malignancy is PTEN-deficient (for example, comprises a cancerous cell (for example, a population of cancerous cells, such as the majority of cancerous cells in a given population) with a reduction in the normal amount [for example compared to a non-cancerous cell of the same patient] or function of the PTEN tumour suppression protein). PTEN status can be determined by methods known in the art.

In one embodiment, the B-cell malignancy is CD20-positive. In a CD20-positive B-cell malignancy, malignant B-cells express CD20. CD20-positive status can be determined by methods known in the art.

In one embodiment, the B-cell malignancy is PTEN-deficient and CD20-positive. In one embodiment, the B-cell malignancy is PTEN-deficient, CD20-positive DLBCL. In one embodiment, the B-cell malignancy is PTEN-deficient, CD20-positive GCB-DLBCL.

First line therapy of B-cell malignancies such as DLBCL and GCB-DLBCL often consists of treatment with R-CHOP (rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone)). The R-CHOP therapy may be administered

periodically for a set period of time, or until reduction in tumour size and/or symptoms are detected. For example, R-CHOP can be administered every 2 or 3 weeks. Treatment typically begins with a low dose so that side effects can be determined, and the dose increased until side effects appear or within the patient's tolerance.

A recently modified regimen known as pola-R-CHP which replaces vincristine with polatuzumab vedotin is also used as a first-line therapy of B-cell malignancies such as DLBCL and GCB-DLBCL. However, the patient's B-cell malignancy may not respond to such first-line therapy, or may relapse following such first-line therapy.

Accordingly, in one embodiment the B-cell malignancy is relapsed or refractory. In one embodiment the B-cell malignancy is relapsed. In one embodiment the B-cell malignancy is refractory. In one embodiment the B-cell malignancy is primary refractory.

In one embodiment the B-cell malignancy is relapsed or refractory after treatment with an anti-CD20 antibody. In one embodiment the B-cell malignancy is relapsed after treatment with an anti-CD20 antibody. In one embodiment the B-cell malignancy is refractory after treatment with an anti-CD20 antibody. In one embodiment the B-cell malignancy is primary refractory after treatment with an anti-CD20 antibody.

In one embodiment the B-cell malignancy is relapsed or refractory after treatment with rituximab. In one embodiment the B-cell malignancy is relapsed after treatment with rituximab. In one embodiment the B-cell malignancy is refractory after treatment with rituximab. In one embodiment the B-cell malignancy is primary refractory after treatment with rituximab.

In one embodiment the B-cell malignancy is relapsed or refractory after treatment with chemotherapy. In one embodiment the B-cell malignancy is relapsed after treatment with chemotherapy. In one embodiment the B-cell malignancy is refractory after treatment with chemotherapy. In one embodiment the B-cell malignancy is primary refractory after treatment with chemotherapy.

In one embodiment the B-cell malignancy is relapsed or refractory after treatment with R-CHOP. In one embodiment the B-cell malignancy is relapsed after treatment with R-CHOP. In one embodiment the B-cell malignancy is refractory after treatment with R-CHOP. In one embodiment the B-cell malignancy is primary refractory after treatment with R-CHOP.

In one embodiment the B-cell malignancy is relapsed or refractory after treatment with pola-R-CHP. In one embodiment the B-cell malignancy is relapsed after treatment with pola-R-

CHP. In one embodiment the B-cell malignancy is refractory after treatment with pola-R-CHP. In one embodiment the B-cell malignancy is primary refractory after treatment with pola-R-CHP.

In one embodiment the B-cell malignancy is relapsed or refractory after a first-line therapy. In one embodiment the first line therapy is treatment with an anti-CD20 antibody such as rituximab. In one embodiment the first line therapy is treatment with chemotherapy. In one embodiment the first line therapy is treatment with R-CHOP. In one embodiment the first line therapy is treatment with pola-R-CHP.

In one embodiment the B-cell malignancy is relapsed or refractory DLBCL. In one embodiment the B-cell malignancy is relapsed or refractory DLBCL after treatment with an anti-CD20 antibody, such as rituximab. In one embodiment the B-cell malignancy is relapsed or refractory DLBCL after treatment with chemotherapy. In one embodiment the B-cell malignancy is relapsed or refractory DLBCL after treatment with R-CHOP. In one embodiment the B-cell malignancy is relapsed or refractory DLBCL after treatment with pola-R-CHP.

In one embodiment the B-cell malignancy is relapsed or refractory GCB-DLBCL. In one embodiment the B-cell malignancy is relapsed or refractory GCB-DLBCL after treatment with an anti-CD20 antibody, such as rituximab. In one embodiment the B-cell malignancy is relapsed or refractory GCB-DLBCL after treatment with chemotherapy. In one embodiment the B-cell malignancy is relapsed or refractory GCB-DLBCL after treatment with R-CHOP. In one embodiment the B-cell malignancy is relapsed or refractory GCB-DLBCL after treatment with pola-R-CHP.

Dosing

The term “combination” as used herein refers to simultaneous, separate, or sequential administration of two, three, or more agents. In one aspect, “combination” can refer to simultaneous administration (e.g., administration of multiple agents in a single dosage form). In another aspect, “combination” refers to separate administration (e.g., administration of multiple agents in separate dosage forms, but at substantially the same time). In a further aspect, “combination” refers to sequential administration (e.g., where a first agent is administered, followed by a delay, followed by administration of a second or further agent).

The term “dosage cycle” as used herein refers to a repeating unit of dosage schedule. For example, a dosage cycle may repeat every seven days, every 10 days, every 14 days, or every 28 days, or other length of time. The terms “dosage schedule” or “dosing schedule” as used herein refer to the schedule, i.e., times and intervals at which a given drug is dosed. A dosage schedule can be continuous or intermittent.

An intermittent dosage schedule can include dosage holidays, i.e., periods of time during which an agent is not dosed. For the purposes of illustration, in a seven-day dosage cycle, an intermittently dosed agent might be given on days one, two, three and four, but not given on days five, six, and seven. The dosage cycle would then repeat. This illustration could be referred to as a 4 on/3 off schedule, where the agent is given for four days followed by a three day holiday, and then repeated every seven days.

A continuous dosing schedule, in contrast, includes no holidays during a dosage cycle. Thus, for illustration, in a in a seven-day dosage cycle, a continuously dosed agent would be given on days one, two, three, four, five, six, and seven. The dosage cycle would then repeat.

When a patient is dosed with multiple agents, each agent can be dosed on the same or different dosage schedules. For example, both a first agent and a second agent can be dosed continuously; or the first agent continuously and the second intermittently (or vice-versa); or both the first and second agents can be dosed on an intermittent schedule. If both agents are on an intermittent schedule, the schedules can be the same or different. In instances where two (or more) agents are given on the same day, they can be given simultaneously, separately, or sequentially.

When two or more agents are given in combination, they may each be given at the same dose amount and on the same schedule as when given as monotherapy (i.e., as a single agent, not in combination with other agent(s)). In other cases, the dosage amount and/or dose schedule of one or more agents can be altered from the amount and schedule used in monotherapy.

In any embodiment where a marketed or approved drug (such as an AKT inhibitor, a BCL-2 inhibitor, or an anti-CD20 antibody) is mentioned, the marketed or approved drug may be administered in accordance with its dosage leaflet (for example as approved by the United States FDA or any other similar regulatory agency).

In any embodiment where a drug that is being investigated in human trials is mentioned (such as an AKT inhibitor, a BCL-2 inhibitor, or an anti-CD20 antibody), the drug may be

administered in accordance with the dosage regime described in any of its published clinical trial protocols (for example as described on clinicaltrials.gov or similar).

The embodiments herein describe certain doses and dosing schedules for capivasertib (an AKT inhibitor), venetoclax (a BCL-2 inhibitor) and rituximab (an anti-CD20 antibody). In some embodiments, a pharmaceutically acceptable salt of capivasertib may be used instead of capivasertib. In such embodiments, the amount of the pharmaceutically acceptable salt of capivasertib administered is equivalent to the specified dose of capivasertib. In some embodiments, a pharmaceutically acceptable salt of venetoclax may be used instead of venetoclax. In such embodiments, the amount of the pharmaceutically acceptable salt of venetoclax administered is equivalent to the specified dose of venetoclax.

In some embodiments, capivasertib can be dosed intermittently, e.g., on four days of a seven-day dosage cycle. For example, from about 50 to about 900 mg of capivasertib can be dosed twice daily on days one, two, three and four of a seven-day dosage cycle. In some embodiments, from about 200 to about 700 mg of capivasertib can be dosed twice daily on days one, two, three and four of a seven-day dosage cycle. In some embodiments, from about 320 to about 480 mg of capivasertib can be dosed twice daily on days one, two, three and four of a seven-day dosage cycle.

In some embodiments, the dosing cycle is 7 days, but there is a drug holiday during the fourth cycle (i.e., capivasertib is not given during the final week of a 4-week period). Thus, in some embodiments, capivasertib is given 4 days on, 3 days off for three weeks, and not given during week four; in other words, capivasertib is given on days one, two, three, four, eight, nine, ten, eleven, fifteen, sixteen, seventeen, and eighteen of a 28-day dosing cycle. Other dosage schedules and dosage amounts of capivasertib can be used.

In some embodiments, capivasertib is administered to the patient on an intermittent dosage schedule. Administering capivasertib on an intermittent dosage schedule can, for example, have greater effectiveness and/or tolerability than on a continuous dosing schedule. In one aspect, capivasertib is intermittently dosed on a 1 day on/6 days off schedule (i.e., capivasertib is administered for one day followed by a six-day holiday). In another aspect, capivasertib is intermittently dosed on a 2 days on/5 days off schedule (i.e., capivasertib is administered for two days followed by a five-day holiday). In another aspect, capivasertib is intermittently dosed on a 3 days on/4 days off schedule (i.e., capivasertib is administered for

three days followed by a four-day holiday). In another aspect, capivasertib is intermittently dosed on a 4 days on/3 days off schedule (i.e., capivasertib is administered for four days followed by a three-day holiday). In another aspect, capivasertib is intermittently dosed on a 5 days on/2 days off schedule (i.e., capivasertib is administered for five days followed by a two-day holiday). In another aspect, capivasertib is intermittently dosed on a 6 days on/1 day off schedule (i.e., capivasertib is administered for six days followed by a one-day holiday).

The dosing cycle of such embodiments would then repeat as long as tolerable and beneficial for the patient. In some embodiments, the dosing cycle is 7 days. In some embodiments, the dosing cycle is 28 days.

In some embodiments, capivasertib is administered twice daily (BID) under an intermittent dosing schedule. In one aspect, capivasertib is administered under an intermittent dosing schedule at a dosage from about 50 mg to about 900 mg twice daily. In another aspect, capivasertib is administered under an intermittent dosing schedule at a dosage from about 150 mg to about 750 mg twice daily. In another aspect, capivasertib is administered under an intermittent dosing schedule at a dosage from about 200 mg to about 700 mg twice daily. In another aspect, capivasertib is administered under an intermittent dosing schedule at a dosage from about 225 mg to about 675 mg twice daily. In another aspect, capivasertib is administered under an intermittent dosing schedule at a dosage from about 250 mg to about 650 mg twice daily. In another aspect, capivasertib is administered under an intermittent dosing schedule at a dosage from about 300 mg to about 625 mg twice daily. In another aspect, capivasertib is administered under an intermittent dosing schedule at a dosage from about 320 mg to about 480 mg twice daily. In another aspect, capivasertib is administered under an intermittent dosing schedule at a dosage from about 300 mg to about 400 mg twice daily. In another aspect, capivasertib is administered under an intermittent dosing schedule at a dosage from about 400 mg to about 500 mg twice daily. In another aspect, capivasertib is administered under an intermittent dosing schedule at a dosage of about 320 mg twice daily. In another aspect, capivasertib is administered under an intermittent dosing schedule at a dosage of about 360 mg twice daily. In another aspect, capivasertib is administered under an intermittent dosing schedule at a dosage of about 400 mg twice daily. In another aspect, capivasertib is administered under an intermittent dosing schedule at a dosage of about 440 mg twice daily. In another aspect, capivasertib is administered under an intermittent dosing schedule at a dosage of about 480 mg

twice daily. In another aspect, capivasertib is administered under an intermittent dosing schedule at a dosage of about 520 mg twice daily.

In another aspect, capivasertib is intermittently dosed on a 4 days on/3 days off schedule at a dosage of about 320 mg twice daily. In another aspect, capivasertib is intermittently dosed on a 4 days on/3 days off schedule at a dosage of about 400 mg twice daily. In another aspect, capivasertib is intermittently dosed on a 4 days on/3 days off schedule at a dosage of about 480 mg twice daily.

In another aspect, capivasertib is intermittently dosed on a 4 days on/3 days off schedule at a dosage of about 320 mg twice daily, but there is a drug holiday during the fourth cycle (i.e., capivasertib is not given during the final week of a 4-week period). In another aspect, capivasertib is intermittently dosed on a 4 days on/3 days off schedule at a dosage of about 400 mg twice daily, but there is a drug holiday during the fourth cycle (i.e., capivasertib is not given during the final week of a 4-week period). In another aspect, capivasertib is intermittently dosed on a 4 days on/3 days off schedule at a dosage of about 480 mg twice daily, but there is a drug holiday during the fourth cycle (i.e., capivasertib is not given during the final week of a 4-week period).

In some embodiments, capivasertib is administered orally, for example in the form of a capsule or a tablet.

In some embodiments, venetoclax is administered once daily continuously, for example, from about 20 mg to about 1200 mg of venetoclax is administered once daily. In some embodiments, from about 20 mg to about 600 mg of venetoclax is administered once daily. In some embodiments, from about 20 mg to about 400 mg of venetoclax is administered once daily. In some embodiments, about 400 mg of venetoclax is administered once daily. In some embodiments, less than about 400 mg of venetoclax is administered once daily, for example from about 20 mg to about 350 mg once daily, for example about 20 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, or about 350 mg once daily.

In some embodiments, venetoclax is administered once daily intermittently, e.g., on six days of a seven-day dosage cycle, on five days of a seven-day dosage cycle, on four days of a seven-day dosage cycle, on three days of a seven-day dosage cycle, on two days of a seven-day dosage cycle, or on one day of a seven-day dosage cycle. For example, from about 20 mg to about 400 mg of venetoclax is administered once daily intermittently. In some embodiments,

about 400 mg of venetoclax is administered once daily intermittently. In some embodiments, less than about 400 mg of venetoclax is administered once daily intermittently, for example from about 20 mg to about 350 mg once daily intermittently, for example about 20 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, or about 350 mg once daily intermittently.

In some embodiments, venetoclax is administered on days when the AKT inhibitor, for example capivasertib, is also given; in other embodiments, venetoclax is administered on days when the AKT inhibitor, for example capivasertib, is not given.

On days when both the AKT inhibitor, for example capivasertib, and venetoclax are given, the two agents can be dosed together or separately. Being dosed together can be in the form of a fixed-dose combination (e.g., a single tablet or capsule with both agents), or can be in the form of separate dosages given at substantially the same time, i.e., with less than a one-hour delay between dosing the two agents (simultaneous dosing). In some embodiments, venetoclax can be dosed at least two hours after the AKT inhibitor, for example capivasertib, or at least four hours after the AKT inhibitor, for example capivasertib. In other embodiments, the AKT inhibitor, for example capivasertib, can be dosed at least two hours after venetoclax or at least four hours after venetoclax.

In some embodiments, venetoclax can be given at a dose lower than the recommended daily dose of 400 mg. This may be during a ramp-up dosing schedule in accordance with approved labelling, or can be during ongoing treatment after the ramp-up has been completed. For example, an ongoing daily dose lower than the recommended daily dose of venetoclax can be about 20 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, or about 350 mg.

In some embodiments, treatment with venetoclax begins with a ramp up schedule, whereby the patient takes a low dose in the first dosage cycle (e.g., a seven-day dosage cycle), and progressively larger doses in following dosage cycles until reaching a recommended daily dose (e.g., 400 mg). The ramp up schedule can be about 20 mg daily during week 1, about 50 mg daily during week 2, about 100 mg daily during week 3, about 200 mg daily during week 4, and about 400 mg daily during week 5 and beyond. Additional information can be found in approved labelling for venetoclax. When given in combination with an AKT inhibitor and anti-CD20 antibody, the ramp up schedule can begin prior to initiation of treatment with the AKT

inhibitor and anti-CD20 antibody; in conjunction with initiation of treatment with the AKT inhibitor and anti-CD20 antibody; or after initiation of treatment with the AKT inhibitor and anti-CD20 antibody.

In some embodiments, an initial target regimen includes a target dosage amount and schedule for each of capivasertib, venetoclax and rituximab, respectively. The initial target regimen may be selected by a clinician and customized to an individual patient's needs.

In some cases, a patient being treated with an initial target regimen may experience deleterious side effects, including, e.g., body weight loss or undesired changes in blood sugar levels. In such a case where deleterious side effects are in fact observed at the initial target regimen, the initial target regimen can be modified. The modified regimen can be selected so as to mitigate or abrogate deleterious side effects while maintaining a high degree of efficacy. In some embodiments, the initial target regimen is altered with respect to the dosage amount of capivasertib, the dosage schedule of capivasertib, or both, without altering the dosage amount or dosage schedule of venetoclax. In some embodiments, the initial target regimen is altered with respect to the dosage amount of venetoclax, the dosage schedule of venetoclax, or both, without altering the dosage amount or dosage schedule of capivasertib. In some embodiments, the initial target regimen is altered with respect to the dosage amount of venetoclax and/or the dosage schedule of venetoclax, and the dosage amount of capivasertib and/or the dosage schedule of capivasertib.

In some embodiments, a modified regimen involving a reduced dosage amount of venetoclax, reduced dosage frequency of venetoclax, or both, without changes to the dosage amount or dosage schedule of capivasertib, can mitigate or abrogate deleterious side effects experienced with an initial target regimen, while maintaining a high degree of efficacy.

In some embodiments, venetoclax is administered orally, for example in the form of a capsule or a tablet.

In some embodiments, rituximab is administered at a dosage from about 250 mg/m^2 to about 500 mg/m^2. In some embodiments, rituximab is administered once weekly at a dosage from about 250 mg/m^2 to about 500 mg/m^2. In some embodiments, rituximab is administered once every 28 days at a dosage from about 250 mg/m^2 to about 500 mg/m^2.

In some embodiments, rituximab is administered at a dosage of about 250 mg/m^2, about 375 mg/m^2 or about 500 mg/m^2. In some embodiments, rituximab is administered once weekly at

a dosage of about 250 mg/m^2, about 375 mg/m^2 or about 500 mg/m^2. In some embodiments, rituximab is administered once every 28 days at a dosage of about 250 mg/m^2, about 375 mg/m^2 or about 500 mg/m^2.

In some embodiments, rituximab is administered once at a dosage of about 375 mg/m^2 in the first 28-day dosage cycle and once at a dosage of about 500 mg/m^2 in the second and further 28-day dosage cycles.

In some embodiments, rituximab is administered by intravenous infusion.

Further Embodiments

Embodiment 1. An AKT inhibitor for use in the treatment of a B-cell malignancy in a patient in need thereof, wherein the AKT inhibitor is administered in combination with a BCL-2 inhibitor and an anti-CD20 antibody.

Embodiment 2. The AKT inhibitor for use of embodiment 1, wherein the AKT inhibitor is capivasertib or a pharmaceutically acceptable salt thereof.

Embodiment 3. The AKT inhibitor for use of embodiment 1 or embodiment 2, wherein the AKT inhibitor is capivasertib.

Embodiment 4. The AKT inhibitor for use of any one of embodiments 1 to 3, wherein the BCL-2 inhibitor is venetoclax or a pharmaceutically acceptable salt thereof.

Embodiment 5. The AKT inhibitor for use of any one of embodiments 1 to 4, wherein the BCL-2 inhibitor is venetoclax.

Embodiment 6. The AKT inhibitor for use of any one of the embodiments 1 to 5, wherein the anti-CD20 antibody is selected from rituximab, ocrelizumab, obinutuzumab, ofatumumab, ibritumomab tiuxetan, tositumomab, ublituximab, and veltuzumab, or a functional equivalent thereof.

Embodiment 7. The AKT inhibitor for use of any one of embodiments 1 to 6, wherein the anti-CD20 antibody is rituximab.

Embodiment 8. The AKT inhibitor for use of any one of embodiments 1 to 7, wherein the B-cell malignancy is diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), follicular lymphoma or mantle cell lymphoma.

Embodiment 9. The AKT inhibitor for use of any one of embodiments 1 to 8, wherein the B-cell malignancy is DLBCL.

Embodiment 10. The AKT inhibitor for use of any one of embodiments 1 to 9, wherein the B-cell malignancy is GCB-DLBCL.

Embodiment 11. The AKT inhibitor for use of any one of embodiments 1 to 10, wherein the B-cell malignancy is PTEN-deficient.

Embodiment 12. The AKT inhibitor for use of any one of embodiments 1 to 11, wherein the B-cell malignancy is CD20-positive.

Embodiment 13. The AKT inhibitor for use of any one of embodiments 1 to 12, wherein the B-cell malignancy is relapsed or refractory.

Embodiment 14. The AKT inhibitor for use of any one of embodiments 1 to 13, wherein the B-cell malignancy is relapsed or refractory after treatment with an anti-CD20 antibody, such as rituximab.

Embodiment 15. The AKT inhibitor for use of any one of embodiments 1 to 14, wherein the B-cell malignancy is relapsed or refractory after treatment with chemotherapy.

Embodiment 16. The AKT inhibitor for use of any one of embodiments 1 to 15, wherein the B-cell malignancy is relapsed or refractory after treatment with R-CHOP.

Embodiment 17. The AKT inhibitor for use of any one of embodiments 1 to 15, wherein the B-cell malignancy is relapsed or refractory after treatment with pola-R-CHP.

Embodiment 18. The AKT inhibitor for use of any one of embodiments 1 to 17, wherein capivasertib or a pharmaceutically acceptable salt thereof is dosed on four days in a seven-day dosage cycle.

Embodiment 19. The AKT inhibitor for use of any one of embodiments 1 to 18, wherein capivasertib or a pharmaceutically acceptable salt thereof is administered at a dose of about 200 to about 700 mg twice daily, optionally about 320 mg, about 400 mg or about 480 mg twice daily, on a 4 days on/3 days off schedule.

Embodiment 20. The AKT inhibitor for use of any one of embodiments 1 to 19, wherein capivasertib or a pharmaceutically acceptable salt thereof is dosed for three weeks and not dosed during week four.

Embodiment 21. The AKT inhibitor for use of any one of embodiments 1 to 20, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered at a dose of about 20 to about 400 mg once daily.

Embodiment 22. The AKT inhibitor for use of any one of embodiments 1 to 21, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered at a dose of about 400 mg once daily.

Embodiment 23. The AKT inhibitor for use of any one of embodiments 1 to 22, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered at a dose of less than about 400 mg once daily, such as from about 20 to about 350 mg once daily.

Embodiment 24. The AKT inhibitor for use of any one of embodiments 1 to 23, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered once daily at a dose of about 20 mg, about 50 mg, about 100 mg, or about 200 mg.

Embodiment 25. The AKT inhibitor for use of any one of embodiments 1 to 24, wherein rituximab is dosed once weekly.

Embodiment 26. The AKT inhibitor for use of any one of embodiments 1 to 24, wherein rituximab is dosed once every 28 days.

Embodiment 27. The AKT inhibitor for use of any one of embodiments 1 to 26, wherein rituximab is administered at a dose of about 250 to about 500 mg/m^2.

Embodiment 28. The AKT inhibitor for use of any one of embodiments 1 to 26, wherein rituximab is administered at a dose of about 250 mg/m^2, about 375 mg/m^2 or about 500 mg/m^2.

Embodiment 29. The AKT inhibitor for use of embodiment 26, wherein rituximab is administered once at a dosage of about 375 mg/m^2 in the first 28-day dosage cycle and once at a dosage of about 500 mg/m^2 in the second and further 28-day dosage cycles.

Embodiment 30. The AKT inhibitor for use of any one of embodiments 1 to 29, wherein capivasertib or a pharmaceutically acceptable salt is dosed on days one, two, three and four of a seven-day dosage cycle, and venetoclax or a pharmaceutically acceptable salt thereof is dosed daily.

Embodiment 31. The use of an AKT inhibitor in the manufacture of a medicament for the treatment of a B-cell malignancy in a patient in need thereof, wherein the AKT inhibitor is administered in combination with a BCL-2 inhibitor and an anti-CD20 antibody.

Embodiment 32. The use of embodiment 31, wherein the AKT inhibitor is capivasertib or a pharmaceutically acceptable salt thereof.

Embodiment 33. The use of embodiment 31 or embodiment 32, wherein the AKT inhibitor is capivasertib.

Embodiment 34. The use of any one of embodiments 31 to 33, wherein the BCL-2 inhibitor is venetoclax or a pharmaceutically acceptable salt thereof.

Embodiment 35. The use of any one of embodiments 31 to 33, wherein the BCL-2 inhibitor is venetoclax.

Embodiment 36. The use of any one of embodiments 31 to 35, wherein the anti-CD20 antibody is selected from rituximab, ocrelizumab, obinutuzumab, ofatumumab, ibritumomab tiuxetan, tositumomab, ublituximab, and veltuzumab, or a functional equivalent thereof.

Embodiment 37. The use of any one of the embodiments 31 to 36, wherein the anti-CD20 antibody is rituximab.

Embodiment 38. The use of any one of embodiments 31 to 37, wherein the B-cell malignancy is diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), follicular lymphoma or mantle cell lymphoma.

Embodiment 39. The use of any one of embodiments 31 to 38, wherein the B-cell malignancy is DLBCL.

Embodiment 40. The use of any one of embodiments 31 to 39, wherein the B-cell malignancy is GCB-DLBCL.

Embodiment 41. The use of any one of embodiments 31 to 40, wherein the B-cell malignancy is PTEN-deficient.

Embodiment 42. The use of any one of embodiments 31 to 41, wherein the B-cell malignancy is CD20-positive.

Embodiment 43. The use of any one of embodiments 31 to 42, wherein the B-cell malignancy is relapsed or refractory.

Embodiment 44. The use of any one of embodiments 31 to 43, wherein the B-cell malignancy is relapsed or refractory after treatment with an anti-CD20 antibody, such as rituximab.

Embodiment 45. The use of any one of embodiments 31 to 44, wherein the B-cell malignancy is relapsed or refractory after treatment with chemotherapy.

Embodiment 46. The use of any one of embodiments 31 to 45, wherein the B-cell malignancy is relapsed or refractory after treatment with R-CHOP.

Embodiment 47. The use of any one of embodiments 31 to 45, wherein the B-cell malignancy is relapsed or refractory after treatment with pola-R-CHP.

Embodiment 48. The use of any one of embodiments 31 to 47, wherein capivasertib or a pharmaceutically acceptable salt thereof is dosed on four days in a seven-day dosage cycle.

Embodiment 49. The use of any one of embodiments 31 to 48, wherein capivasertib or a pharmaceutically acceptable salt thereof is administered at a dose of about 200 to about 700 mg twice daily, optionally about 320 mg, about 400 mg or about 480 mg twice daily, on a 4 days on/3 days off schedule.

Embodiment 50. The use of any one of embodiments 31 to 49, wherein capivasertib or a pharmaceutically acceptable salt thereof is dosed for three weeks and not dosed during week four.

Embodiment 51. The use of any one of embodiments 31 to 50, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered at a dose of about 20 to about 400 mg once daily.

Embodiment 52. The use of any one of embodiments 31 to 51, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered at a dose of about 400 mg once daily.

Embodiment 53. The use of any one of embodiments 31 to 52, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered at a dose of less than about 400 mg once daily, such as from about 20 to about 350 mg once daily.

Embodiment 54. The use of any one of embodiments 31 to 53, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered once daily at a dose of about 20 mg, about 50 mg, about 100 mg, or about 200 mg.

Embodiment 55. The use of any one of embodiments 31 to 54, wherein rituximab is dosed once weekly.

Embodiment 56. The use of any one of embodiments 31 to 54, wherein rituximab is dosed once every 28 days.

Embodiment 57. The use of any one of embodiments 31 to 56, wherein rituximab is administered at a dose of about 250 to about 500 mg/m^2.

Embodiment 58. The use of any one of embodiments 31 to 56, wherein rituximab is administered at a dose of about 250 mg/m^2, about 375 mg/m^2 or about 500 mg/m^2.

Embodiment 59. The use of embodiment 56, wherein rituximab is administered once at a dosage of about 375 mg/m^2 in the first 28-day dosage cycle and once at a dosage of about 500 mg/m^2 in the second and further 28-day dosage cycles.

Embodiment 60. The use of any one of embodiments 31 to 59, wherein capivasertib or a pharmaceutically acceptable salt is dosed on days one, two, three and four of a seven-day dosage cycle, and venetoclax or a pharmaceutically acceptable salt thereof is dosed daily.

Embodiment 61. A kit comprising (i) an AKT inhibitor, and (ii) instructions for the use of the AKT inhibitor in combination with a BCL-2 inhibitor and an anti-CD20 antibody, in the treatment of a B-cell malignancy in a patient in need thereof.

Embodiment 62. The kit of embodiment 61, wherein the AKT inhibitor is capivasertib or a pharmaceutically acceptable salt thereof.

Embodiment 63. The kit of embodiment 61 or embodiment 62, wherein the AKT inhibitor is capivasertib.

Embodiment 64. The kit of any one of embodiments 61 to 63, wherein the BCL-2 inhibitor is venetoclax or a pharmaceutically acceptable salt thereof.

Embodiment 65. The kit of any one of embodiments 61 to 64, wherein the BCL-2 inhibitor is venetoclax.

Embodiment 66. The kit of any one of embodiments 61 to 65, wherein the anti-CD20 antibody is selected from rituximab, ocrelizumab, obinutuzumab, ofatumumab, ibritumomab tiuxetan, tositumomab, ublituximab, and veltuzumab, or a functional equivalent thereof.

Embodiment 67. The kit of any one of the embodiments 61 to 66, wherein the anti-CD20 antibody is rituximab.

Embodiment 68. The kit of any one of embodiments 61 to 67, wherein the B-cell malignancy is diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), follicular lymphoma or mantle cell lymphoma.

Embodiment 69. The kit of any one of embodiments 61 to 68, wherein the B-cell malignancy is DLBCL.

Embodiment 70. The kit of any one of embodiments 61 to 69, wherein the B-cell malignancy is GCB-DLBCL.

Embodiment 71. The kit of any one of embodiments 61 to 70, wherein the B-cell malignancy is PTEN-deficient.

Embodiment 72. The kit of any one of embodiments 61 to 71, wherein the B-cell malignancy is CD20-positive.

Embodiment 73. The kit of any one of embodiments 61 to 72, wherein the B-cell malignancy is relapsed or refractory.

Embodiment 74. The kit of any one of embodiments 61 to 73, wherein the B-cell malignancy is relapsed or refractory after treatment with an anti-CD20 antibody, such as rituximab.

Embodiment 75. The kit of any one of embodiments 61 to 74, wherein the B-cell malignancy is relapsed or refractory after treatment with chemotherapy.

Embodiment 76. The kit of any one of embodiments 61 to 75, wherein the B-cell malignancy is relapsed or refractory after treatment with R-CHOP.

Embodiment 77. The kit of any one of embodiments 61 to 75, wherein the B-cell malignancy is relapsed or refractory after treatment with pola-R-CHP.

Embodiment 78. The kit of any one of embodiments 61 to 77, wherein capivasertib or a pharmaceutically acceptable salt thereof is dosed on four days in a seven-day dosage cycle.

Embodiment 79. The kit of any one of embodiments 61 to 78, wherein capivasertib or a pharmaceutically acceptable salt thereof is administered at a dose of about 200 to about 700 mg twice daily, optionally about 320 mg, about 400 mg or about 480 mg twice daily, on a 4 days on/3 days off schedule.

Embodiment 80. The kit of any one of embodiments 61 to 79, wherein capivasertib or a pharmaceutically acceptable salt thereof is dosed for three weeks and not dosed during week four.

Embodiment 81. The kit of any one of embodiments 61 to 80, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered at a dose of about 20 to about 400 mg once daily.

Embodiment 82. The kit of any one of embodiments 61 to 81, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered at a dose of about 400 mg once daily.

Embodiment 83. The kit of any one of embodiments 61 to 82, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered at a dose of less than about 400 mg once daily, such as from about 20 to about 350 mg once daily.

Embodiment 84. The kit of any one of embodiments 61 to 83, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered once daily at a dose of about 20 mg, about 50 mg, about 100 mg, or about 200 mg.

Embodiment 85. The kit of any one of embodiments 61 to 84, wherein rituximab is dosed once weekly.

Embodiment 86. The kit of any one of embodiments 61 to 84, wherein rituximab is dosed once every 28 days.

Embodiment 87. The kit of any one of embodiments 61 to 86, wherein rituximab is administered at a dose of about 250 to about 500 mg/m^2.

Embodiment 88. The kit of any one of embodiments 61 to 86, wherein rituximab is administered at a dose of about 250 mg/m^2, about 375 mg/m^2 or about 500 mg/m^2.

Embodiment 89. The kit of embodiment 86, wherein rituximab is administered once at a dosage of about 375 mg/m^2 in the first 28-day dosage cycle and once at a dosage of about 500 mg/m^2 in the second and further 28-day dosage cycles.

Embodiment 90. The kit of any one of embodiments 61 to 89, wherein capivasertib or a pharmaceutically acceptable salt is dosed on days one, two, three and four of a seven-day dosage cycle, and venetoclax or a pharmaceutically acceptable salt thereof is dosed daily.

Examples

The specific Examples below, with reference to the accompanying Figures, are provided for illustrative purposes only and are not to be construed as limiting the teachings herein.

Abbreviation	Explanation
ABC	Activated B cell
BID	Twice daily
BID 10/14	Twice daily spaced 10h from AM to PM, and 14h PM to AM
DLBCL	Diffuse Large B Cell Lymphoma
DMSO	Dimethyl Sulfoxide
GCB	Germinal Center B cell
mg/kg	Milligrams per kilogram
QD	Daily

Abbreviation	Explanation
SCID	Severely combined immunodeficient

Animal studies were performed using female CB.17 SCID mice purchased from Charles River Laboratories (Wilmington, MA). Up to five female mice were housed under pathogen-free conditions, in individually ventilated cages (IVCs; Tecniplast, Italy) at a temperature of 68°F±3°F, humidity of 45% to 70%, 60-70 air exchanges per hour in the cages, and a 12/12-h light/dark cycle. Animal health and well-being were monitored frequently over study duration. Nutritional supportive care (NutraGel, Bio-serv Flemington, NJ, USA) was provided a minimum of three days prior to dosing administration for all groups. All animal manipulations were conducted in a biosafety cabinet maintained under positive pressure. Mice used were six to eight weeks old at the time of tumor implantation. All animal studies were conducted in accordance with the guidelines established by the internal IACUC (Institutional Animal Care and Use Committee) and reported following the ARRIVE (Animal Research: Reporting In Vivo experiments) guidelines.

For in vivo evaluation of DLBCL xenograft mouse models, 10 million WSU-DLCL2 cells in PBS mixed with 50:50 with Matrigel™ (Beckton Dickinson, Franklin Lakes, NJ, USA) were implanted subcutaneously into the right flank of C.B-17 *scid* female mice in a volume of 0.1 mL. Tumour volumes (measured by caliper), animal body weight, and tumour condition were recorded a minimum of twice weekly for the duration of the study. The tumour volume was calculated (taking length to be the longest diameter across the tumour and width to be the corresponding perpendicular diameter) using the formula: length (mm) x width (mm)/0.52. For efficacy studies, growth inhibition from the start of treatment was assessed by comparison of the differences in tumour volume between control and treated groups. Because the variance in mean tumour volume data increases proportionally with volume (and is therefore disproportionate between groups), data were log transformed to remove any size dependency before statistical evaluation. Statistical significance was evaluated using a one-tailed, 2-sample *t* test. For efficacy studies, mice were randomized based on tumour volumes using stratified sampling and enrolled into control and treatment groups. Dosing began when mean tumour size reached approximately 200 mm^3. Capivasertib, dissolved in vehicle (10% DMSO in 25% Kleptose solution pH 5) was administered 130 mg/kg BID by oral gavage. Venetoclax was formulated as a suspension in

60% Phosal 50 PG, 30% polyethylene glycol 400, 10% ethanol and administered by oral gavage. A 4 hr gap was provided between each agent with capivasertib being dosed first. Dosing holidays were provided along with food supplementation when body weight loss was greater than 10-12% for an individual mouse. R-CHOP was administered one-time; rituximab (RITUXAN) 10 mg/kg intraperitoneal, cyclophosphamide (CYTOXAN) 25 mg/kg intraperitoneal, doxorubicin (DOXIL) 3 mg/kg intravenous, vincristine (ONCOVIN) 0.25 mg/kg intravenous, prednisone (DELTASONE) 0.5 mg/kg by oral gavage, each according to manufacturer's instructions. Data shown in graphs are Geomean ± error. Statistical analyses (t-test, multiple comparisons) were done using GraphPad Prism (version8.4.3)

Example 1: Addition of an anti-CD20 antibody to AKT and BCL-2 inhibition enhances the durability of response in the DLBCL in vivo model

Figure 1 shows tumour growth curves of CB.17 SCID mice bearing the GCB-DLBCL PTEN deficient cell line WSU-DLCL2 xenograft tumours treated with the treatment schedules described in Table 1:

Table 1 – Treatment Schedules

Treatment No.	Treatment Schedules (7-day dosing cycle)	Day						
		1	2	3	4	5	6	7
Vehicle	Vehicle BID 10/14	X	X	X	X			
1	capivasertib 130 mg/kg BID 10/14	X	X	X	X			
2	venetoclax 100 mg/kg QD	X	X	X	X	X	X	X
3	capivasertib 130 mg/kg BID 10/14 +	X	X	X	X			
	venetoclax 100 mg/kg QW (AM, 4 h after capivasertib)	X						
4	capivasertib 130 mg/kg BID 10/14 +	X	X	X	X			
	venetoclax 100 mg/kg 2QW (AM, 4 h after capivasertib)	X		X				
5	capivasertib 130 mg/kg BID 10/14 +	X	X	X	X			
	venetoclax 100 mg/kg QD (AM, 4 h after capivasertib)	X	X	X	X			

6	capivasertib 130 mg/kg BID 10/14 +	X	X	X	X			
	venetoclax 100 mg/kg QW (AM, 4 h after capivasertib) +	X						
	rituximab 10 mg/kg 2QW	X		X				
7	R-CHOP 1x on Day 1 +							
	rituximab 10 mg/kg 2QW	X		X				

In WSU-DLCL2 tumour xenografts, monotherapy treatment with capivasertib (Treatment 1 of Table 1) provided 29% growth inhibition, whilst venetoclax monotherapy (Treatment 2 of Table 1) was inactive.

The WSU-DLCL2 xenograft model was less sensitive to treatment with combinations of capivasertib and venetoclax than a SUDHL4 cell line xenograft model (see Examples in International Patent Application No. PCT/EP2022/081881). In the SUDHL4 cell line xenograft model, Treatments 3, 4 and 5 of Table 1 were all able to drive to complete tumour regression whereas only Treatment 5 of Table 1 was able to drive to complete tumour regression in the WSU-DLCL2 xenograft model.

DLBCL patients are commonly treated with the therapeutic regimen R-CHOP which combines conventional chemotherapeutic agents along with the anti-CD20 antibody rituximab. WSU-DLCL2 tumours had an attenuated response to R-CHOP + rituximab 10 mg/kg 2QW (Treatment 7 of Table 1).

Treatment with a triplet of capivasertib and venetoclax with rituximab (Treatment 6 of Table 1) was able to drive tumour regression to levels similar to that observed with Treatment 5 of Table 1 and, significantly, venetoclax was given only once weekly in the triplet regimen compared to a 4-day on/3-day off schedule in the doublet regimen.

Furthermore, as shown in Figure 2, following dosing cessation, the triplet combination of capivasertib, venetoclax and rituximab (Treatment 6) provided sustained tumour regressions in contrast to the doublet combination of Treatment 5. The triplet combination was also well tolerated, with minimal body weight loss as shown in Figure 4.

Example 2: AKT and BCL-2 inhibition combines with an anti-CD20 antibody to overcome R-CHOP resistance

To determine whether the combination treatment has potential to be active in tumours progressing after R-CHOP treatment, CB.17 SCID mice bearing the GCB-DLBCL PTEN deficient cell line WSU-DLCL2 xenograft tumours were treated with R-CHOP (Treatment 7 of Table 1, days 14-49 post-implantation) and on progression of the tumours switched to a combination of capivasertib, venetoclax and rituximab (Treatment 8 shown in Table 2, days 50-70 post-implantation).

Table 2 – Treatment Schedules

Treatment No.	Treatment Schedules (7-day dosing cycle)	Day						
		1	2	3	4	5	6	7
8	capivasertib 130 mg/kg BID 10/14 +	X	X	X	X			
	venetoclax 100 mg/kg 2QW (AM, 4 h after capivasertib) +	X		X				
	rituximab 10 mg/kg 2QW	X		X				

The triplet combination treatment (Treatment 8 of Table 2) was well-tolerated (Figure 5), and tumours rapidly regressed with kinetics similar to R-CHOP naïve DLBCL tumour xenograft models (Figure 3). These data suggest that treatment of DLBCL with capivasertib and venetoclax can be further enhanced with anti-CD20 antibody treatment, and employed in the R-CHOP resistant setting of DLBCL.

The combination of capivasertib, venetoclax and rituximab is highly active in GCB or PTEN deficient DLBCL models. The combination effect can be achieved with flexible dosing of venetoclax which is an advantage given that venetoclax dosing is commonly modified in the clinic to manage tolerability.

Other embodiments are within the scope of the following claims. All documents cited herein are each entirely incorporated by reference herein, including all data, tables, figures, and text presented in the cited documents.

CLAIMS

1. A method of treating a B-cell malignancy in a patient in need thereof, comprising administering to the patient a combination of: a first amount of an AKT inhibitor, a second amount of a BCL-2 inhibitor, and a third amount of an anti-CD20 antibody; wherein the first amount, second amount and third amount together comprise a therapeutically effective amount.

2. The method of claim 1, wherein the AKT inhibitor is capivasertib or a pharmaceutically acceptable salt thereof.

3. The method of claim 1 or claim 2, wherein the AKT inhibitor is capivasertib.

4. The method of any one of the preceding claims, wherein the BCL-2 inhibitor is venetoclax or a pharmaceutically acceptable salt thereof.

5. The method of any one of the preceding claims, wherein the BCL-2 inhibitor is venetoclax.

6. The method of any one of the preceding claims, wherein the anti-CD20 antibody is selected from rituximab, ocrelizumab, obinutuzumab, ofatumumab, ibritumomab tiuxetan, tositumomab, ublituximab, and veltuzumab, or a functional equivalent thereof.

7. The method of any one of the preceding claims, wherein the anti-CD20 antibody is rituximab.

8. The method of any one of the preceding claims, wherein the B-cell malignancy is diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), follicular lymphoma or mantle cell lymphoma.

9. The method of any one of the preceding claims, wherein the B-cell malignancy is DLBCL.

10. The method of any one of the preceding claims, wherein the B-cell malignancy is GCB-DLBCL.

11. The method of any one of the preceding claims, wherein the B-cell malignancy is PTEN-deficient.

12. The method of any one of the preceding claims, wherein the B-cell malignancy is CD20-positive.

13. The method of any one of the preceding claims, wherein the B-cell malignancy is relapsed or refractory.

14. The method of any one of the preceding claims, wherein the B-cell malignancy is relapsed or refractory after treatment with an anti-CD20 antibody, such as rituximab.

15. The method of any one of the preceding claims, wherein the B-cell malignancy is relapsed or refractory after treatment with chemotherapy.

16. The method of any one of the preceding claims, wherein the B-cell malignancy is relapsed or refractory after treatment with R-CHOP.

17. The method of any one of claims 1 to 15, wherein the B-cell malignancy is relapsed or refractory after treatment with pola-R-CHP.

18. The method of any one of the preceding claims, wherein capivasertib or a pharmaceutically acceptable salt thereof is dosed on four days in a seven-day dosage cycle.

19. The method of any one of the preceding claims, wherein capivasertib or a pharmaceutically acceptable salt thereof is administered at a dose of about 200 to about 700 mg

twice daily, optionally about 320 mg, about 400 mg or about 480 mg twice daily, on a 4 days on/3 days off schedule.

20. The method of any one of the preceding claims, wherein capivasertib or a pharmaceutically acceptable salt thereof is dosed for three weeks and not dosed during week four.

21. The method of any one of the preceding claims, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered at a dose of about 20 to about 400 mg once daily.

22. The method of any one of the preceding claims, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered at a dose of about 400 mg once daily.

23. The method of any one of the preceding claims, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered at a dose of less than about 400 mg once daily, such as from about 20 to about 350 mg once daily.

24. The method of any one of the preceding claims, wherein venetoclax or a pharmaceutically acceptable salt thereof is administered once daily at a dose of about 20 mg, about 50 mg, about 100 mg, or about 200 mg.

25. The method of any one of the preceding claims, wherein rituximab is dosed once weekly.

26. The method of any one of claims 1 to 24, wherein rituximab is dosed once every 28 days.

27. The method of any one of the preceding claims, wherein rituximab is administered at a dose of about 250 to about 500 mg/m^2.

28. The method of any one of claims 1 to 26, wherein rituximab is administered at a dose of about 250 mg/m^2, about 375 mg/m^2 or about 500 mg/m^2.

29. The method of claim 26, wherein rituximab is administered once at a dosage of about 375 mg/m^2 in the first 28-day dosage cycle and once at a dosage of about 500 mg/m^2 in the second and further 28-day dosage cycles.

30. The method of any one of the preceding claims, wherein capivasertib or a pharmaceutically acceptable salt is dosed on days one, two, three and four of a seven-day dosage cycle, and venetoclax or a pharmaceutically acceptable salt thereof is dosed daily.

31. An AKT inhibitor for use in the treatment of a B-cell malignancy in a patient in need thereof, wherein the AKT inhibitor is administered in combination with a BCL-2 inhibitor and an anti-CD20 antibody.

32. The use of an AKT inhibitor in the manufacture of a medicament for the treatment of a B-cell malignancy in a patient in need thereof, wherein the AKT inhibitor is administered in combination with a BCL-2 inhibitor and an anti-CD20 antibody.

33. A kit comprising (i) an AKT inhibitor, and (ii) instructions for the use of the AKT inhibitor in combination with a BCL-2 inhibitor and an anti-CD20 antibody, in the treatment of a B-cell malignancy in a patient in need thereof.