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(71) Applicant: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, 4056 Basel (CH).

(72) Inventors: **MIZBANI, Amir**; Novartis Pharma Ag, Novartis Institute For Biomed., Research, Postfach, 4002 Basel (CH). **WONG, Connie**; Novartis Institute For Biomedical Research, Inc., 250 Massachusetts Avenue, Cambridge, MA 02139 (US).

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(54) Title: USE OF IL-1 BINDING ANTIBODIES IN THE TREATMENT OF A MSI-H CANCER

(57) Abstract: The present disclosure refers to the use of an IL-1 β binding antibody especially canakinumab (trade name ilaris, previously ACZ885) or gevokizumab for the treatment and/or prevention of a cancer with at least a partial inflammatory basis, e.g., a MSI-H (MicroSatellite Instability -High) cancer. Experiments are provided with cankinumab alone or in combination with either docetaxel, pembrolizumab, Gevokizumab

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USE OF IL-1 BINDING ANTIBODIES IN THE TREATMENT OF A MSI-H CANCER

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TECHNICAL FIELD

The present invention relates to the use of an IL-1 β binding antibody or a functional fragment thereof, for the treatment and/or prevention of cancers, e.g., cancers having at least a partial inflammatory basis, e.g., MSI-H (microsatellite instability-high) cancers.

BACKGROUND OF THE DISCLOSURE

The majority of cancers is still incurable. There remains a continued need to develop new treatment options for cancers.

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SUMMARY OF THE DISCLOSURE

The present disclosure relates to the use of an IL-1 β binding antibody or a functional fragment thereof, suitably canakinumab, suitably gevokizumab, for the treatment and/or prevention of cancers, e.g., cancers that have at least a partial inflammatory basis, e.g., MSI-H cancers.

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In another aspect, the present invention relates to a particular clinical dosage regimen for the administration of an IL-1 β binding antibody or a functional fragment thereof, suitably canakinumab, suitably gevokizumab, for the treatment and/or prevention of cancer, e.g., cancers having at least a partial inflammatory basis, e.g., MSI-H cancers. In one embodiment the preferred dose of canakinumab for patient with cancer that has at least a partial inflammatory basis, e.g., a MSI-H cancer, is about 200mg about every 3 weeks or about monthly, preferably subcutaneously. In one embodiment patient receives gevokizumab about 30mg to about 120mg per treatment about every 3 weeks or about monthly, preferably intravenously.

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In another aspect the subject with cancer, e.g., cancer having at least a partial inflammatory basis, e.g., MSI-H cancer, is administered with one or more anti-cancer

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therapeutic agent (e.g., a chemotherapeutic agent) and/or has received/will receive debulking procedures in addition to the administration of an IL-1 β binding antibody or a functional fragment thereof, suitably canakinumab, suitably gevokizumab.

5 There are also provided methods of treating or preventing cancers, e.g., cancers having at least a partial inflammatory basis, e.g., MSI-H cancers, in a human subject comprising administering to the subject a therapeutically effective amount of an IL-1 β binding antibody or a functional fragment thereof.

10 Another aspect of the invention is the use of an IL-1 β binding antibody or a functional fragment thereof for the preparation of a medicament for the treatment of cancers, e.g., cancers having at least a partial inflammatory basis, e.g., MSI-H cancers.

The present disclosure also provides a pharmaceutical composition comprising a therapeutically effective amount of an IL-1 β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for use in the treatment and/or prevention of cancers, e.g., cancers having at least a partial inflammatory basis, e.g., MSI-H cancers. In one
15 embodiment, the pharmaceutical composition comprising a therapeutically effective amount of an IL-1 β binding antibody or a functional fragment thereof, e.g., canakinumab, e.g., gevokizumab, is in the form of an auto-injector. In one embodiment about 200mg of canakinumab is loaded in an auto-injector.

The present invention also relates to high sensitivity C-reactive protein (hsCRP) for use
20 as a biomarker in the diagnosis, patient selection, and/or prognosis of cancer treatment, e.g., cancer having at least a partial inflammatory basis, e.g., MSI-H cancers. The present invention also relates to high sensitivity C-reactive protein (hsCRP) for use as a biomarker in treatment and/or prevention of cancer having at least a partial inflammatory basis, e.g., MSI-H cancers. In a further aspect the invention relates to high sensitivity C-reactive protein (hsCRP) for use
25 as a biomarker in the treatment and/or prevention of cancer having at least a partial inflammatory basis in a patient, e.g., MSI-H cancers, wherein said patient is treated with an IL-1 β inhibitor, an IL-1 β binding antibody or a functional fragment thereof (e.g., canakinumab or gevokizumab). In one aspect, the patient has hsCRP equal to or greater than about 2.2mg/L, equal to or greater than about 4.2mg/L, equal to or greater than about 6.2mg/L, or equal to or
30 greater than about 10.2mg/L, before first administration of an IL-1 β inhibitor, e.g., an IL-1 β binding antibody or functional fragment thereof (e.g., canakinumab or gevokizumab).

In one aspect the present invention provides an IL-1 β binding antibody or a functional fragment thereof (e.g., canakinumab or gevokizumab), for use in a patient in the treatment

and/or prevention of a cancer, e.g., a cancer having at least partial inflammatory basis, e.g., e.g., MSI-H cancers. Each and every embodiment disclosed in this application applies, separately or in combination, to this aspect.

In one aspect the present invention provides an IL-1 β binding antibody or a functional fragment thereof (e.g., canakinumab or gevokizumab), for use in a patient in need thereof in the treatment of a MSI-H cancer.

FIGURE LEGENDS

Figure 1. *In vivo* model of spontaneous human breast cancer metastasis to human bone predicts a key role for IL-1 β signaling in breast cancer bone metastasis. Two 0.5cm³ pieces of human femoral bone were implanted subcutaneously into 8-week old female NOD SCID mice (n=10/group). 4 weeks later luciferase labelled MDA-MB-231-luc2-TdTomato or T47D cells were injected into the hind mammary fat pads. Each experiment was carried out 3-separate times using bone from a different patient for each repeat. Histograms showing fold change of *IL-1B*, *IL-1R1*, *Caspase 1* and *IL-1Ra* copy number (dCT) compared with *GAPDH* in tumour cells grown *in vivo* compared with those grown in a tissue culture flask (a i); mammary tumours that metastasise compared with mammary tumours that do not metastasise (a ii); circulating tumour cells compared with tumour cells that remain in the fat pad (a iii) and bone metastases compared with the matched primary tumour (a iv). Fold change in IL-1 β protein expression is shown in (b) and fold change in copy number of genes associated with EMT (*E-cadherin*, *N-cadherin* and *JUP*) compared with *GAPDH* are shown in (c). * = P < 0.01, ** = P < 0.001, *** = P < 0.0001, ^^^ = P < 0.001 compared with naïve bone.

Figure 2. Stable transfection of breast cancer cells with *IL-1B*. MDA-MB-231, MCF7 and T47D breast cancer cells were stably transfected with *IL-1B* using a human cDNA ORF plasmid with a C-terminal GFP tag or control plasmid. a) shows pg/ng IL-1 β protein from IL-1 β -positive tumour cell lysates compared with scramble sequence control. b) shows pg/ml of secreted IL-1 β from 10,000 IL-1 β + and control cells as measured by ELISA. Effects of *IL-1B* overexpression on proliferation of MDA-MB-231 and MCF7 cells are shown in (c and d) respectively. Data shown are mean +/- SEM, * = P < 0.01, ** = P < 0.001, *** = P < 0.0001 compared with scramble sequence control.

Figure 3. Tumour derived IL-1 β induces epithelial to mesenchymal transition *in vitro*. MDA-MB-231, MCF7 and T47D cells were stably transfected with to express high levels of *IL-1B*, or scramble sequence (control) to assess effects of endogenous *IL-1B* on parameters

associated with metastasis. Increased endogenous *IL-1B* resulted tumour cells changing from an epithelial to mesenchymal phenotype (a). b) shows fold-change in copy number and protein expression of *IL-1B*, *IL-1R1*, *E-cadherin*, *N-cadherin* and *JUP* compared with *GAPDH* and β -catenin respectively. Ability of tumour cells to invade towards osteoblasts through Matrigel and/or 8 μ M pores, are shown in (c) and capacity of cells to migrate over 24 and 48h is shown using a wound closure assay (d). Data are shown as mean $\pm$ SEM, * = $P < 0.01$, ** = $P < 0.001$, *** = $P < 0.0001$.

Figure 4. Pharmacological blockade of IL-1 β inhibits spontaneous metastasis to human bone *in vivo*. Female NOD-SCID mice bearing two 0.5cm³ pieces of human femoral bone received intra-mammary injections of MDA-MB-231Luc2-TdTomato cells. One week after tumour cell injection mice were treated with 1mg/kg/day IL-1Ra, 20mg/kg/14-days canakinumab, or placebo (control) (n=10/group). All animals were culled 35 days following tumour cell injection. Effects on bone metastases (a) were assessed *in vivo* and immediately post-mortem by luciferase imaging and confirmed *ex vivo* on histological sections. Data are shown as numbers of photons per second emitted 2 minutes following sub-cutaneous injection of D-luciferin. Effects on numbers of tumour cells detected in the circulation are shown in (b). * = $P < 0.01$, ** = $P < 0.001$, *** = $P < 0.0001$.

Figure 5. Tumour derived IL-1 β promotes breast cancer bone homing *in vivo*. 8-week old female BALB/c nude mice were injected with control (scramble sequence) or *IL-1 β* overexpressing MDA-MB-231-IL-1 β + cells via the lateral tail vein. Tumour growth in bone and lung were measured *in vivo* by GFP imaging and findings confirmed *ex vivo* on histological sections. a) shows tumour growth in bone; b) shows representative μ CT images of tumour bearing tibiae and the graph shows bone volume (BV)/tissue volume (TV) ratio indicating effects on tumour induced bone destruction; c) shows numbers and size of tumours detected in lungs from each of the cell lines. * = $P < 0.01$, ** = $P < 0.001$, *** = $P < 0.0001$. (B = bone, T = tumour, L = lung)

Figure 6. Tumour cell-bone cell interactions stimulate IL-1B production cell proliferation. MDA-MB-231 or T47D human breast cancer cell lines were cultured alone or in combination with live human bone, HS5 bone marrow cells or OB1 primary osteoblasts. a) shows the effects of culturing MDA-MB-231 or T47D cells in live human bone discs on IL-1 β concentrations secreted into the media. The effect of co-culturing MDA-MB-231 or T47D cells with HS5 bone cells on IL-1 β derived from the individual cell types following cell sorting and the proliferation of these cells are shown in b) and c). Effects of co-culturing MDA-MB-231 or

T47D cells with OB1 (osteoblast) cells on proliferation are shown in d). Data are shown as mean $\pm$ SEM, * = $P < 0.01$, ** = $P < 0.001$, *** = $P < 0.0001$.

Figure 7. IL-1 β in the bone microenvironment stimulates expansion of the bone metastatic niche. Effects of adding 40pg/ml or 5ng/ml recombinant IL-1 β to MDA-MB-231 or T47D breast cancer cells is shown in (a) and effects on adding 20 pg/ml, 40 pg/ml or 5 ng/ml IL-1B on proliferation of HS5, bone marrow, or OB1, osteoblasts, are shown in b) and c) respectively. (d) IL-1 driven alterations to the bone vasculature was measured following CD34 staining in the trabecular region of the tibiae from 10-12-week old female IL-1R1 knockout mice. (e) BALB/c nude mice treated with 1mg/ml/day IL-1Ra for 31 days and (f) C57BL/6 mice treated with 10 μ M canakinumab for 4-96h. Data are shown as mean $\pm$ SEM, * = $P < 0.01$, ** = $P < 0.001$, *** = $P < 0.0001$.

Figure 8. Suppression of IL-1 signalling affects bone integrity and vasculature. Tibiae and serum from mice that do not express IL-1R1 (IL-1R1 KO), BALB/c nude mice treated daily with 1mg/kg per day of IL-1R antagonist for 21 and 31 days and C57BL/6 mice treated with 10mg/kg of canakinumab (Ilaris) of 0-96h were analysed for bone integrity by μ CT and vasculature using ELISA for Endothelin 1 and pan VEGF. a) shows the effects of IL-1R1 KO; b) effects of Anakinra and c) effects of canakinumab on bone volume compared with tissue volume (i), concentration of Endothelin 1 (ii) and concentrations of VEGF secreted into the serum. Data shown are mean $\pm$ SEM, * = $P < 0.01$, ** = $P < 0.001$, *** = $P < 0.0001$ compared with control.

Figure 9. Tumour derived IL-1 β predicts future recurrence and bone relapse in patients with stage II and III breast cancer. ~1300 primary breast cancer samples from patients with stage II and III breast cancer with no evidence of metastasis were stained for 17 kD active IL-1 β . Tumours were scored for IL-1 β in the tumour cell population. Data shown are Kaplan Meyer curves representing the correlation between tumour derived IL-1 β and subsequent recurrence a) at any site or b) in bone over a 10-year time period.

Figure 10. Simulation of canakinumab PK profile and hsCRP profile. a) shows canakinumab concentration time profiles. Solid line and band: median of individual simulated concentrations with 2.5-97.5% prediction interval (300 mg Q12W (bottom line), 200 mg Q3W (middle line), and 300 mg Q4W (top line)). b) shows the proportion of month 3 hsCRP being below the cut point of 1.8 mg/L for three different populations: all CANTOS patients (scenario 1), confirmed lung cancer patients (scenario 2), and advanced lung cancer patients (scenario 3) and three different dose regimens. c) is similar to b) with the cut point being 2 mg/L. d) shows

the median hsCRP concentration over time for three different doses. e) shows the percent reduction from baseline hsCRP after a single dose.

Figure 11. Gene expression analysis by RNA sequencing in colorectal cancer patients receiving PDR001 in combination with canakinumab, PDR001 in combination with everolimus and PDR001 in combination with others. In the heatmap figure, each row represents the RNA levels for the labelled gene. Patient samples are delineated by the vertical lines., with the screening (pre-treatment) sample in the left column, and the cycle 3 (on-treatment) sample in the right column. The RNA levels are row-standardized for each gene, with black denoting samples with higher RNA levels and white denoting samples with lower RNA levels. Neutrophil-specific genes *FCGR3B*, *CXCR2*, *FFAR2*, *OSM*, and *G0S2* are boxed.

Figure 12. Clinical data after gevokizumab treatment (panel a) and its extrapolation to higher doses (panels b, c, and d). Adjusted percent change from baseline in hsCRP in patients in a). The hsCRP exposure-response relationship is shown in b) for six different hsCRP baseline concentrations. The simulation of two different doses of gevokizumab is shown in b) and c).

Figure 13. Effect of anit-IL-1beta treatment in two mouse models of cancer. a), b), and c) show data from the MC38 mouse model, and d) and e) show data from the LL2 mouse model.

Figure 14. Efficacy of canakinumab in combination with pembrolizumab in inhibiting tumor growth.

Figure 15. Preclinical data on the efficacy of canakinumab in combination with docetaxel in the treatment of cancer.

Figure 16. Mice were implanted with 4T1 cells sc and treated with the indicated treatments on days 8 and 15 post tumor implant. There were 10 mice in each group.

Figure 17. Neutrophils (top) and monocytes (bottom) in 4T1 tumors 5 days after a single dose of docetaxel, 01BSUR, or the combination of docetaxel and 01BSUR.

Figure 18. Granulocytic (top) and monocytic (bottom) MDSC in 4T1 tumors 5 days after a single dose of docetaxel, 01BSUR, or the combination of docetaxel and 01BSUR.

Figure 19. TIM-3⁺ CD4⁺ (top) and CD8⁺ (bottom) T cells in 4T1 tumors 4 days after a second dose of docetaxel, 01BSUR, or the combination of docetaxel and 01BSUR.

Figure 20. TIM-3 expressing Tregs in 4T1 tumors 4 days after a second dose of docetaxel, 01BSUR, or the combination of docetaxel and 01BSUR.

DETAILED DESCRIPTION OF THE DISCLOSURE

Many malignancies arise in areas of chronic inflammation (1) and inadequate resolution of inflammation is hypothesized to play a major role in tumor invasion, progression, and metastases (Voronov E, et al, PNAS 2003).

5 Microsatellites are repeated sequences of DNA. These sequences can be made of repeating units of one to six base pairs in length. Although the length of these microsatellites is highly variable from person to person and contributes to the individual DNA "fingerprint", each individual has microsatellites of a set length. Microsatellites are also known as simple sequence repeats (SSRs).

10 Microsatellite instability (MSI) is the condition of genetic hypermutability (predisposition to mutation) that results from deficient DNA mismatch repair (dMMR). The presence of MSI represents phenotypic evidence that MMR is not functioning normally. This can be caused by mutations or epigenetic silencing of MMR members.

15 MMR corrects errors that spontaneously occur during DNA replication, such as single base mismatches or short insertions and deletions. The proteins involved in MMR correct polymerase errors by forming a complex that binds to the mismatched section of DNA, excises the error, and inserts the correct sequence in its place (Giavazzi, R. et al., 1990. Cancer Res., 50, 4771–4775). Cells with abnormally functioning MMR are unable to correct errors that occur during DNA replication and consequently accumulate errors. This causes the creation of novel
20 microsatellite fragments.

25 Microsatellite instability-high cancer (also called MSI-H cancer) describes cancer cells that have a greater than normal number of genetic markers called microsatellites. Cancer cells that have large numbers of microsatellites may have defects in the ability to correct mistakes that occur when DNA is copied in the cell. Microsatellite instability is found most often in colon cancer, colorectal cancer, gastric cancer and other types of gastrointestinal cancer, ovarian cancer and endometrial cancer, hepatobiliary tract cancer, urinary tract cancer, brain cancer, oesophageal cancer, pancreatic cancer, renal cell cancer, Retroperitoneal adenocarcinoma, sarcoma, small cell lung cancer and skin cancers. It may also be found in cancers of the breast, prostate, bladder, and thyroid. Knowing whether a cancer is due to microsatellite instability
30 may help plan the best treatment (www.cancer.gov).

IL-1 has long been known to augment the capacity of cancer cells to metastasize, by affecting multiple steps of the cancer-related inflammation (CRI) cascade (Giavazzi et al., 1990. Cancer Res., 50, 4771–4775).

Recent data suggest that an additional mechanism involved in CRI is induction of genetic instability by inflammatory mediators, leading to accumulation of random genetic alterations in cancer cells (Colotta et al., 2009. *Carcinogenesis*, 30, 1073–1081).

Existing data suggest that inflammatory cells and mediators can destabilize the cancer cell genome by a variety of mechanisms either directly inducing DNA damage or affecting DNA repair systems and altering cell cycle checkpoints (Colotta et al., 2009. *Carcinogenesis*, 30, 1073–1081). These data suggest that an additional mechanism by which inflammation can contribute to cancer initiation and progression is genetic destabilization of cancer cells.

An unstable genome is a hallmark feature of nearly all solid tumours and adult-onset leukemias (Loeb et al., 2008. *Nat. Rev. Genet.*, 9, 594–604; Rajagopalan et al., 2002. *Nature*, 418, 934). Inflammation downregulates MMR proteins by a variety of mechanisms. IL-1beta induces HIF-1alpha in cancer cells, where HIF-1alpha downregulate MMR proteins MSH2 and MSH6 by displacing c-Myc from MSH2/MSH6 promoters (Koshiji et al., 2005. *Mol. Cell*, 17, 793–803).

Molecular testing for MSI is usually performed using PCR amplification of DNA regions containing microsatellite repeats, e.g., followed by analysing the PCR products, e.g., by gel electrophoresis or by melt-curve analysis. Typically, DNA isolated from normal and tumour tissue is separately amplified by PCR, e.g., with fluorescent-labelled primers. The electrophoretic patterns of PCR products from the normal and tumour tissue are compared to identify insertions or deletions of repetitive units in the tumour sample (Marina et al., 2011. *Diagnostic Immunohistochemistry (Third Edition)*, 2011, 42-57). The National Cancer Institute guidelines for MSI testing recommend a panel of five microsatellite loci, including three dinucleotide repeat markers (D2S123, D5S346, D17S250) and two mononucleotide repeat markers (BAT 25 and BAT 26). This panel is known as the *Bethesda panel* (Marina et al., 2011. *Diagnostic Immunohistochemistry (Third Edition)*, 2011, 42-57). High-frequency MSI (MSI-H) is defined as an instability in two or more of the five markers, and low-frequency MSI (MSI-L) is defined as an instability in one unstable marker. Microsatellite stable (MSS) status is established when none of the markers shows instability. The test can also be performed using DNA isolated from either snap-frozen or FFPE tissue and provides a reliable and reproducible detection of MSI (Marina et al., 2011. *Diagnostic Immunohistochemistry (Third Edition)*, 2011, 42-57). Because the frequency of mutant MSI fragments must be >25% to be detectable by PCR, a more sensitive and quantitative method, small-pool PCR (SP-PCR), has been developed (Siciliano, 2006. *Genetic Instabilities and Neurological Diseases (Second Edition)*, Academic

Press, 737-748).

MSI-L cancer has been found in stomach, cervical, pancreatic, ovarian, skin, nerve, breast, endometrial, liver, oesophageal, eye, soft tissue, gallbladder, head and neck, prostate, lung and cancers of the urinary tract (Koi et al., 2018. *World. J. Gastrointest. Oncol.* 10(1): 1-14).

Considering the involvement of IL-1beta pathway in MSI cancers as explained above, and without wishing to be bound by theory, we hypothesize that inhibition of IL-1beta pathway, e.g., using an anti-IL-1beta antibody such as canakinumab or gevokizumab, can lead to inhibition of development and/or progression of microsatellite-unstable (MSI) cancer.

As reported in Rikder et al (Lancet, 2017), a randomised, double-blind, placebo-controlled trial of canakinumab in 10061 patients with atherosclerosis who had had a myocardial infarction, were free of previously diagnosed cancer, and had concentrations of high-sensitivity C-reactive protein (hsCRP) of 2 mg/L or greater was completed in June, 2017 (CANTOS trial). To assess dose-response effects, patients were randomly assigned by computer-generated codes to three canakinumab doses (50 mg, 150 mg, and 300 mg, subcutaneously every 3 months) or placebo.

Baseline concentrations of hsCRP (median 6.0 mg/L vs 4.2 mg/L; $p < 0.0001$) and interleukin 6 (3.2 vs 2.6 ng/L; $p < 0.0001$) were significantly higher among participants subsequently diagnosed with lung cancer than among those not diagnosed with cancer. During median follow-up of 3.7 years, compared with placebo, canakinumab was associated with dose-dependent reductions in concentrations of hsCRP of 26–41% and of interleukin 6 of 25–43% ($p < 0.0001$ for all comparisons). Total cancer mortality ($n=196$) was significantly lower in the pooled canakinumab group than in the placebo group ($p=0.0007$ for trend across groups), but was significantly lower than placebo only in the 300 mg group individually (hazard ratio [HR] 0.49 [95% CI 0.31–0.75]; $p=0.0009$). Incident lung cancer ($n=129$) was significantly less frequent in the 150 mg (HR 0.61 [95% CI 0.39–0.97]; $p=0.034$) and 300 mg groups (HR 0.33 [95% CI 0.18–0.59]; $p < 0.0001$; $p < 0.0001$ for trend across groups). Lung cancer mortality was significantly less common in the canakinumab 300 mg group than in the placebo group (HR 0.23 [95% CI 0.10–0.54]; $p=0.0002$) and in the pooled canakinumab population than in the placebo group ($p=0.0002$ for trend across groups).

Biomarker analysis of patients of non-lung cancers from the CANTOS trial, especially of the GI/GU cancers, has revealed that they have elevated baseline hsCRP level and IL-6 level. In addition, GI/GU cancer patients with higher baseline level of hsCRP and IL-6 seem to have

a shorter time to cancer diagnosis than patients having lower baseline level (Example 13), suggesting the likelihood of the involvement of IL-1 β mediated inflammation in broader cancer indications, besides lung cancer, which warrants targeting IL-1 β in the treatment of those cancers. In addition hsCRP level and IL-6 level in GI/GU patients were reduced in the range
5 comparable to other patients in the CANTOS trial treatment group, suggesting inhibition of IL-1 β signaling in those patients. Inhibition of IL-1 β alone or preferably in combination with other anti-cancer agents could result in clinical benefit in treating cancer, e.g., cancer having at least partial inflammatory basis, e.g., a MSI-H cancer, as further supported by data presented in the Examples 9-11.

10 Cancers, e.g., cancers having at least a partial inflammatory basis

Thus in one aspect, the present invention provides the use of an IL-1 β binding antibody or a functional fragment thereof (for reason of simplicity, the term “an IL-1 β binding antibody or a functional fragment thereof” is sometimes referred as “DRUG of the invention” in this application, which should be understood as identical term), suitably canakinumab or a
15 functional fragment thereof (included in DRUG of the invention), gevokizumab or a functional fragment thereof (included in DRUG of the invention), for the treatment of cancers, e.g., cancers that have at least a partial inflammatory basis, e.g., a MSI-H cancer.

Advanced studies in delineating interaction between tumor and the tumor microenvironment have revealed that chronic inflammation can promote tumor development,
20 and tumor fuels inflammation to facilitate tumor progression and metastasis. Inflammatory microenvironment with cellular and non-cellular secreted factors provides a sanctuary for tumor progression by inducing angiogenesis; recruiting tumor promoting, immune suppressive cells and inhibiting immune effector cell mediated anti-tumor immune response. One of the major inflammatory pathways supporting tumor development and progression is IL-1 β , a pro-
25 inflammatory cytokine produced by tumor and tumor associated immune suppressive cells including neutrophils and macrophages in tumor microenvironment.

Accordingly, the present disclosure provides method of treating cancer using an IL-1 β binding antibody or a functional fragment thereof, wherein such IL-1 β binding antibodies or functional fragments thereof can reduce inflammation and/or improve tumor
30 microenvironment, e.g., can inhibit IL-1 β mediated inflammation and IL-1 β mediated immune suppression in the tumor microenvironment. Examples of using an IL-1 β binding antibody in modulating the tumor microenvironment is shown in the Examples 9-11 herein. In some

embodiments, an IL-1 β binding antibody or a functional fragment thereof is used alone as a monotherapy. In some embodiments, an IL-1 β binding antibody or a functional fragment thereof is used in combination with another therapy, such as with a check point inhibitor and/or with one or more chemotherapeutic agents. As discussed herein, inflammation can promote tumor development, an IL-1 β binding antibody or a functional fragment thereof, either alone or in combination with another therapy, can be used to treat any cancer that can benefit from reduced IL-1 β mediated inflammation and/or improved tumor environment. Inflammation component is universally present, albeit to different degrees, in the cancer development.

The meaning of “cancers that have at least a partial inflammatory basis” or “cancer having at least a partial inflammatory basis” is well known in the art and as used herein refers to any cancer in which IL-1 β mediated inflammatory responses contribute to tumor development and/or propagation, including but not necessarily limited to metastasis. Such cancer generally has concomitant inflammation activated or mediated in part through activation of the Nod-like receptor protein 3 (NLRP3) inflammasome with consequent local production of interleukin-1 β . In a patient with such cancer, the expression, or even the overexpression of IL-1 β can be generally detected, commonly at the site of the tumor, especially in the surrounding tissue of the tumor, in comparison to normal tissue. The expression of IL-1 β can be detected by routine methods known in the art, such as immunostaining, ELISA based assays, ISH, RNA sequencing or RT-PCR in the tumor as well as in serum/plasma. The expression or higher expression of IL-1 β can be concluded, for example, against negative control, usually normal tissue at the same site or can be concluded if higher than normal level of IL-1 β in serum/plasma (reference level). Simultaneously or alternatively, a patient with such cancer has generally chronic inflammation, which is manifested, typically, by higher than normal level of hsCRP (or CRP) , IL-6 or TNF α , preferably by hsCRP or IL-6, preferably by IL-6. This is because IL-6 is immediate downstream of IL-1 β . hsCRP is further downstream and can be influenced by other factors as well. Cancers also include cancers that may not express IL-1 β until after previous treatment of such cancer, e.g., including treatment with a chemotherapeutic agent, e.g., as described herein, which contribute to the expression of IL-1 β in the tumor and/or tumor microenvironment. In some embodiments, the methods and use comprise treating a patient whose cancer is relapsed or recurring after treatment with such agent. In other embodiments, the agent is associated with IL-1 β expression and the IL-1 β antibody or functional fragment thereof is given in combination with such agent.

Inhibition of IL-1 β resulted in reduced inflammation status, including but not limited to reduced hsCRP or IL-6 level. Thus the effect of the present invention in cancer patients can be measured by reduced inflammation status, including but not limited to reduced hsCRP or IL-6 level.

5 The term “cancers that have at least a partial inflammatory basis” or “cancer having at least a partial inflammatory basis” also includes cancers that benefit from the treatment of an IL-1 β binding antibody or a functional fragment thereof. As inflammation in general contributes to tumor growth at already an early stage, administration of IL-1 β binding antibody or a functional fragment thereof (canakinumab or gevokizumab) could potentially stop tumor
10 growth effectively at the early stage or delay tumor progression effectively at the early stage, even though the inflammation status, such as expression or overexpression IL-1 β , or the elevated level of CRP or hsCRP, IL-6 or TNF α , is still not apparent or measurable. Furthermore in patient whose cancer has just been resected, the inflammation could be reduced, shown by lowered IL-1 β , hsCRP, IL-6 or TNF α level. However patients having early stage cancers or
15 patients who have their tumor removed still can benefit from the treatment of IL-1 β binding antibody or a functional fragment, which can be shown in clinical trials. The clinical benefit can be measured by, including but not limited to, disease-free survival (DFS), progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), duration of response (DOR) and overall survival (OS), preferably in a clinical trial setting, against proper control
20 group, for example against the effects achieved by standard of care (SoC) drugs, either by added on top of SoC or without SoC. If a patient treated with the DRUG of the invention has shown any improvement in one or more of the above parameters in comparison to the control, the patient is considered to have benefited from the treatment according to the present invention. Accordingly, the cancer that benefits from an IL-1 β binding antibody or a functional fragment
25 thereof (canakinumab or gevokizumab) treatment is considered as cancer having at least partial inflammatory basis.

Available techniques known to the skilled person in the art allow detection and quantification of IL-1 β in tissue as well as in serum/plasma, particularly when the IL-1 β is expressed to a higher than normal level. For example, using the R&D Systems high sensitivity
30 IL-1b ELISA kit, IL-1 β cannot be detected in the majority of healthy donor serum samples, as shown in the following Table.

SAMPLE VALUES

Serum/Plasma - Samples from apparently healthy volunteers were evaluated for the presence of human IL-1 β in this assay. No medical histories were available for the donors used in this study.

Sample Type	Mean of Detectable (pg/ml)	% Detectable	Range (pg/ml)
Serum (n=50)	0.357	10	ND-0.606
EDTA plasma (n=50)	0.292	12	ND-0.380
Heparin plasma (n=50)	0.448	14	ND-1.08

ND=Non detectable

Thus in a healthy person the IL-1 β level is barely detectable or just above the detection limit according to this test with the high sensitivity R&D[®] IL-1 β ELISA kit. It is expected that in a patient with cancer having at least partial inflammatory basis in general has higher than normal level of IL-1 β and can be detected by the same kit. Taking the IL-1 β expression level in a healthy person as the normal level (reference level), the term “higher than normal level of IL-1 β ” means an IL-1 β level that is higher than the reference level. Normally at least about 2 fold, at least about 5 fold, at least about 10 fold, at least about 15 fold, at least about 20 fold of the reference level is considered as higher than normal level. Blocking the IL-1 β pathway normally triggers the compensating mechanism leading to more production of IL-1 β . Thus the term “higher than normal level of IL-1 β ” also means and includes the level of IL-1 β either post, or more preferably, prior to the administration of an IL-1 β binding antibody or a fragment thereof. Treatment of cancer with agents other than IL-1 β inhibitors, such as some chemotherapeutic agents, can result in production of IL-1 β in the tumor microenvironment. Thus the term “higher than normal level of IL-1 β ” also refers to the level of IL-1 β either prior to or post the administration of such an agent.

When using staining, such as immunostaining, to detect IL-1 β expression in a tissue preparation, the term “higher than normal level of IL-1 β ” means to that the staining signal generated by specific IL-1 β protein or IL-1 β RNA detecting molecule is distinguishably stronger than staining signal of the surrounding tissue not expressing IL-1 β .

Available techniques are known to the skilled person in the art allow detection and quantification of IL-6 in tissue as well as in serum/plasma, particularly when the IL-6 is expressed to a higher than normal level. For example, using the R&D Systems (www.RnDsystems.com) “high quantikine HS ELISA, human IL-6 Immunoassay”, IL-6 can be detected in majority of healthy donor serum samples, as shown in the following Table.

SAMPLE VALUES

Samples from apparently healthy volunteers were evaluated for the presence of human IL-6 in this assay. No medical histories were available for the donors used in this study.

Sample Type	Mean of Detectable (pg/ml)	% Detectable	Range (pg/ml)
Serum (n=52)	1.77	100	0.447-9.96
EDTA plasma (n=35)	1.49	100	0.428-8.87
Citrate plasma (n=16)	1.57	100	0.435-9.57
Urine (n=14)	1.67	93	ND-6.76

ND=Non-detectable

It is expected that in a patient with cancer having at least partial inflammatory basis in general has higher than normal level of IL-6 and can be detected by the same kit. Taking the IL-6 expression level in a healthy person as the normal level (reference level), the term “higher than normal level of IL-6” means an IL-6 level that is higher than the reference level, normally higher than about 1.9 pg/ml, higher than about 2 pg/ml, higher than about 2.2 pg/ml, higher than about 2.5 pg/ml, higher than about 2.7 pg/ml, higher than about 3 pg/ml, higher than about 3.5 pg/ml, or higher than about 4 pg/ml, as determined preferably by the R&D kit mentioned above. Blocking the IL-1 β pathway normally triggers the compensating mechanism leading to more production of IL-1 β . Thus the term “higher than normal level of IL-6” also means and includes the level of IL-6 either post, or more preferably, prior to the administration of an IL-1 β binding antibody or a fragment thereof. Treatment of cancer with agents other than IL-1 β inhibitors, such as some chemotherapeutic agents, can result in production of IL-1 β in the tumor microenvironment. Thus the term “higher than normal level of IL-6” also refers to the level of IL-6 either prior to or post the administration of such an agent.

When using staining, such as immunostaining, to detect IL-1 β expression in a tissue preparation, the term “higher than normal level of IL-6” means to that the staining signal generated by specific IL-6 protein or IL-6 RNA detecting molecule is distinguishably stronger than staining signal of the surrounding tissue not expressing IL-6.

As used herein, the terms “treat”, “treatment” and “treating” refer to the reduction or amelioration of the progression, severity and/or duration of a disorder, e.g., a proliferative disorder, or the amelioration of one or more symptoms, suitably of one or more discernible symptoms, of the disorder resulting from the administration of one or more therapies. In specific embodiments, the terms “treat”, “treatment” and “treating” refer to the amelioration of at least one measurable physical parameter of a proliferative disorder, such as growth of a tumor, not necessarily discernible by the patient. In other embodiments the terms “treat”, “treatment” and

“treating” refer to the inhibition of the progression of a proliferative disorder, either physically by, e.g., stabilization of a discernible symptom, physiologically by, e.g., stabilization of a physical parameter, or both. In other embodiments the terms “treat”, “treatment” and “treating” refer to the reduction or stabilization of tumor size or cancerous cell count. As far as cancers as discussed here, taking MSI-H cancer as an example, the term treatment refers to at least one of the following: alleviating one or more symptoms of MSI-H cancer, delaying progression of MSI-H cancer, shrinking tumor size in MSI-H cancer patient, inhibiting MSI-H cancer tumor growth, prolonging overall survival, prolonging progression free survival, preventing or delaying MSI-H cancer tumor metastasis, reducing (such as eradicating) preexisting MSI-H cancer tumor metastasis, reducing incidence or burden of preexisting MSI-H cancer tumor metastasis, or preventing recurrence of MSI-H cancer.

In one embodiment, the MSI-H cancer is selected from the list consisted of gastric cancer ovarian cancer, endometrial cancer, hepatobiliary tract cancer, urinary tract cancer, brain cancer, oesophageal cancer, gastroesophageal junction cancer, pancreatic cancer, renal cell cancer, retroperitoneal adenocarcinoma, sarcoma, small cell lung cancer and skin cancers, such as melanoma.

In one embodiment, the MSI-H cancer is selected from the list consisted of colorectal cancer, endometrial cancer, breast cancer, prostate cancer, bladder cancer, and thyroid cancer.

In a preferred embodiment, the MSI-H cancer is selected from the list consisted of uterine corpus endometrial carcinoma, stomach adenocarcinoma, colon adenocarcinoma and rectal adenocarcinoma. In a preferred embodiment, the MSI-H cancer is colon cancer or colorectal cancer (CRC).

IL-1 β inhibitors, especially IL-1 β binding antibody or a fragment thereof

As used herein, IL-1 β inhibitors include but not be limited to, canakinumab or a functional fragment thereof, gevokizumab or a functional fragment thereof, Anakinra, diacerein, Rilonacept, IL-1 Affibody (SOBI 006, Z-FC (Swedish Orphan Biovitrum/Affibody)) and Lutikizumab (ABT-981) (Abbott), CDP-484 (Celltech), LY-2189102 (Lilly).

In one embodiment of any use or method of the invention, said IL-1 β binding antibody is canakinumab. Canakinumab (ACZ885) is a high-affinity, fully human monoclonal antibody of the IgG1/k to interleukin-1 β , developed for the treatment of IL-1 β driven inflammatory diseases. It is designed to bind to human IL-1 β and thus blocks the interaction of this cytokine

with its receptors.

In other embodiments of any use or method of the invention, said IL-1 β binding antibody is gevokizumab. Gevokizumab (XOMA-052) is a high-affinity, humanized monoclonal antibody of the IgG2 isotype to interleukin-1 β , developed for the treatment of IL-1 β driven inflammatory diseases. Gevokizumab modulates IL-1 β binding to its signaling receptor.

In one embodiment said IL-1 β binding antibody is LY-2189102, which is a humanised interleukin-1 beta (IL-1 β) monoclonal antibody.

In one embodiment said IL-1 β binding antibody or a functional fragment thereof is CDP-484 (Celltech), which is an antibody fragment blocking IL-1 β .

In one embodiment said IL-1 β binding antibody or a functional fragment thereof is IL-1 Affibody (SOBI 006, Z-FC (Swedish Orphan Biovitrum/Affibody)).

An antibody, as used herein, refers to an antibody having the natural biological form of an antibody. Such an antibody is a glycoprotein and consists of four polypeptides – two identical heavy chains and two identical light chains, joined to form a "Y"-shaped molecule. Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region. The heavy chain constant region is comprised of three or four constant domains (CH1, CH2, CH3, and CH4, depending on the antibody class or isotype). Each light chain is comprised of a light chain variable region (VL) and a light chain constant region, which has one domain, CL. Papain, a proteolytic enzyme, splits the "Y" shape into three separate molecules, two so called "Fab" fragments (Fab = fragment antigen binding), and one so called "Fc" fragment (Fc = fragment crystallizable). A Fab fragment consists of the entire light chain and part of the heavy chain. The VL and VH regions are located at the tips of the "Y"-shaped antibody molecule. The VL and VH each have three complementarity-determining regions (CDRs).

By "IL-1 β binding antibody" is meant any antibody capable of binding to the IL-1 β specifically and consequently inhibiting or modulating the binding of IL-1 β to its receptor and further consequently inhibiting IL-1 β function. Preferably an IL-1 β binding antibody does not bind to IL-1 α .

Preferably an IL-1 β binding antibody includes:

(1) An antibody comprising three VL CDRs having the amino acid sequences RASQSIGSSLH (SEQ ID NO: 1), ASQSFS (SEQ ID NO: 2), and HQSSSLP (SEQ ID NO: 3) and three VH CDRs having the amino acid sequences VYGMN (SEQ ID NO: 5), IIWYDGDNQYYADSVKG (SEQ ID NO: 6), and DLRTGP (SEQ ID NO: 7);

(2) An antibody comprising three VL CDRs having the amino acid sequences RASQDISNYLS (SEQ ID NO: 9), YTSKLHS (SEQ ID NO: 10), and LQGKMLPWT (SEQ ID NO: 11), and three VH CDRs having the amino acid sequences TSGMGVG (SEQ ID NO: 13), HIWWDGDESYNPSLK (SEQ ID NO: 14), and NRYDPPWFVD (SEQ ID NO: 15); and

5 (3) An antibody comprising the six CDRs as described in either (1) or (2), wherein one or more of the CDR sequences, preferably at most two of the CDRs, preferably only one of the CDRs, differ by one amino acid from the corresponding sequences described in either (1) or (2), respectively.

10 Preferably an IL-1 β binding antibody includes:

(1) An antibody comprising three VL CDRs having the amino acid sequences RASQSIGSSLH (SEQ ID NO: 1), ASQSFS (SEQ ID NO: 2), and HQSSSLP (SEQ ID NO: 3) and comprising the VH having the amino acid sequence specified in SEQ ID NO: 8;

15 (2) An antibody comprising the VL having the amino acid sequence specified in SEQ ID NO: 4 and comprising three VH CDRs having the amino acid sequences VYGMN (SEQ ID NO: 5), IIWYDGDNQYYADSVKG (SEQ ID NO: 6), and DLRTGP (SEQ ID NO: 7);

(3) An antibody comprising three VL CDRs having the amino acid sequences RASQDISNYLS (SEQ ID NO: 9), YTSKLHS (SEQ ID NO: 10), and LQGKMLPWT (SEQ ID NO: 11), and comprising the VH having the amino acid sequences specified in SEQ ID NO: 16;

(4) An antibody comprising the VL having the amino acid specified in SEQ ID NO: 12, and comprising three VH CDRs having the amino acid sequences TSGMGVG (SEQ ID NO: 13), HIWWDGDESYNPSLK (SEQ ID NO: 14), and NRYDPPWFVD (SEQ ID NO: 15);

25 (5) An antibody comprising three VL CDRs and the VH sequence as described in either (1) or (3), wherein one or more of the VL CDR sequences, preferably at most two of the CDRs, preferably only one of the CDRs, differ by one amino acid from the corresponding sequences described in (1) or (3), respectively, and wherein the VH sequence is at least 90% identical to the corresponding sequence described in (1) or (3), respectively; and

30 (6) An antibody comprising the VL sequence and three VH CDRs as described in either (2) or (4), wherein the VL sequence is at least 90% identical to the corresponding sequence described in (2) or (4), respectively, and wherein one or more of the VH CDR

sequences, preferably at most two of the CDRs, preferably only one of the CDRs, differ by one amino acid from the corresponding sequences described in (2) or (4), respectively.

Preferably an IL-1 β binding antibody includes:

- 5 (1) An antibody comprising the VL having the amino acid sequence specified in SEQ ID NO: 4 and comprising the VH having the amino acid sequence specified in SEQ ID NO: 8;
- (2) An antibody comprising the VL having the amino acid specified in SEQ ID NO: 12, and comprising the VH having the amino acid sequences specified in SEQ ID NO: 16; and
- 10 (3) An antibody described in either (1) or (2), wherein the constant region of the heavy chain, the constant region of the light chain or both has been changed to a different isotype as compared to canakinumab or gevokizumab.

Preferably an IL-1 β binding antibody includes:

- 15 (1) Canakinumab (SEQ ID NO:17 and 18); and
- (2) Gevokizumab (SEQ ID NO:19 and 20).

An IL-1 β binding antibody as defined above has substantially identical or identical CDR sequences as those of canakinumab or gevokizumab. It thus binds to the same epitope on IL-1

20 β and has similar binding affinity as canakinumab or gevokizumab. The clinical relevant doses and dosing regimens that have been established for canakinumab or gevokizumab as therapeutically efficacious in the treatment of cancer, especially cancer having at least partial inflammatory basis, e.g., a MSI-H cancer, would be applicable to other IL-1 β binding antibodies.

25 Additionally or alternatively, an IL-1 β antibody refers to an antibody that is capable of binding to IL-1 β specifically with affinity in the similar range as canakinumab or gevokizumab. The K_d for canakinumab in WO2007/050607 is referenced with 30.5 pM, whereas the K_d for gevokizumab is 0.3 pM. Thus affinity in the similar range refers to between about 0.05 pM to

30 300 pM, preferably 0.1 pM to 100 pM. Although both binding to IL-1 β , canakinumab directly inhibits the binding to IL-1 receptor, whereas gevokizumab is an allosteric inhibitor. It does not prevent IL-1 β from binding to the receptor but prevent receptor activation. Preferably an IL-1 β antibody has the binding affinity in the similar range as canakinumab, preferably in the range

of 1 pM to 300 pM, preferably in the range of 10 pM to 100 pM, wherein preferably said antibody directly inhibits binding. Preferably an IL-1 β antibody has the binding affinity in the similar range as gevokizumab, preferably in the range of 0.05 pM to 3pM, preferably in the range of 0.1pM to 1pM, wherein preferably said antibody is an allosteric inhibitor.

5

As used herein, the term "functional fragment" of an antibody as used herein, refers to portions or fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., IL-1 β). Examples of binding fragments encompassed within the term "functional fragment" of an antibody include single chain Fv (scFv), a Fab fragment, a monovalent
 10 fragment consisting of the V_L, V_H, CL and CH1 domains; a F(ab)₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the V_H and CH1 domains; a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody; a dAb fragment (Ward et al., 1989), which consists of a V_H domain; and an isolated complementarity determining region (CDR); and one or more
 15 CDRs arranged on peptide scaffolds that can be smaller, larger, or fold differently to a typical antibody.

The term "functional fragment" might also refer to one of the following:

- bispecific single chain Fv dimers (PCT/US92/09965)
- "diabodies" or "triabodies", multivalent or multispecific fragments constructed
 20 by gene fusion (Tomlinson I & Hollinger P (2000) Methods Enzymol. 326: 461-79; W094113804; Holliger P et al., (1993) Proc. Natl. Acad. Sci. USA, 90: 6444-48)
- scFv genetically fused to the same or a different antibody (Coloma MJ & Morrison SL (1997) Nature Biotechnology, 15(2): 159-163)
- scFv, diabody or domain antibody fused to an Fc region
- 25 • scFv fused to the same or a different antibody
- Fv, scFv or diabody molecules may be stabilized by the incorporation of disulphide bridges linking the V_H and V_L domains (Reiter, Y. et al, (1996) Nature Biotech, 14, 1239-1245).
- Minibodies comprising a scFv joined to a CH3 domain may also be made (Hu, S. et al, (1996) Cancer Res., 56, 3055-3061).
- Other examples of binding fragments are Fab', which differs from Fab fragments by the addition of a few residues at the carboxyl terminus of the heavy chain CH1 domain,

30

including one or more cysteines from the antibody hinge region, and Fab'-SH, which is a Fab' fragment in which the cysteine residue(s) of the constant domains bear a free thiol group

Typically and preferably an functional fragment of an IL-1 β binding antibody is a portion or a fragment of an “IL-1 β binding antibody” as defined above.

5 Dosing regimen of the present invention

If an IL-1 β inhibitor, such as an IL-1 β antibody or a functional fragment thereof, is administered in a dose range that can effectively reduce hsCRP level in a patient with cancer having at least partial inflammatory basis, e.g., a MSI-H cancer, treatment effect of said cancer can possibly be achieved. Dose range, of a particular IL-1 β inhibitor, preferably IL-1 β antibody or a functional fragment thereof, that can effectively reduce hsCRP level is known or can be tested in a clinical setting.

Thus in one embodiment, the present invention comprises administering the IL-1 β binding antibody or a functional fragment thereof to a patient with cancer, e.g., cancer that has at least a partial inflammatory basis, e.g., a MSI-H cancer, in the range of about 20mg to about 400mg per treatment, preferably in the range of about 30mg to about 400mg per treatment, preferably in the range of about 30mg to about 200mg per treatment, preferably in the range of about 60mg to about 200mg per treatment. In one embodiment the patient receives each treatment about every two weeks, about every three weeks, about every four weeks (monthly), about every 6 weeks, about bimonthly (every 2 months), about every nine weeks or about quarterly (every 3 months). In one embodiment the patient receives each treatment about every 3 weeks. In one embodiment the patient receives each treatment every 4 weeks. The term “per treatment”, as used in this application and particularly in this context, should be understood as the total amount of drug received per hospital visit or per self-administration or per administration helped by a health care giver. Normally and preferably the total amount of drug received per treatment is administered to a patient is within about 2 hours, preferably within about one hour, or within about half hour. In one preferred embodiment the term “per treatment” is understood as the drug is administered with one injection, preferably in one dosage.

In practice sometimes the time interval cannot be strictly kept due to the limitation of the availability of doctor, patient or the drug/facility. Thus the time interval can slightly vary, normally between about 5 days, about 4 days, about 3 days, about 2 days or preferably about 1 day.

Sometimes it is desirable to quickly reduce inflammation. IL-1 β auto-induction has been shown in human mononuclear blood, human vascular endothelial, and vascular smooth muscle cells *in vitro* and in rabbits *in vivo* where IL-1 has been shown to induce its own gene expression and circulating IL-1 β level (Dinarello et al. 1987, Warner et al. 1987a, and Warner et al. 1987b).

5 This induction period over 2 weeks by administration of a first dose followed by a second dose two weeks after administration of the first dose is to assure that auto-induction of IL-1 β pathway is adequately inhibited at initiation of treatment. The complete suppression of IL-1 β related gene expression achieved with this early high dose administration, coupled with the continuous canakinumab treatment effect which has been proven to last the entire quarterly
10 dosing period used in CANTOS, is to minimize the potential for IL-1 β rebound. In addition, data in the setting of acute inflammation suggests that higher initial doses of canakinumab that can be achieved through induction are safe and provide an opportunity to ameliorate concern regarding potential auto-induction of IL-1 β and to achieve greater early suppression of IL-1 β related gene expression.

15 Thus in one embodiment, the present invention, while keeping the above described dosing schedules, especially envisages the second administration of DRUG of the invention is one week later or at most two weeks, preferably two weeks apart from the first administration. Then the third and the further administration will following the schedule of about every 2 weeks, about every 3 weeks, about every 4 weeks (monthly), about every 6 weeks, about
20 bimonthly (every 2 months), about every 9 weeks or about quarterly (every 3 months). In one embodiment, the IL-1 β binding antibody is canakinumab, wherein canakinumab is administered to a patient with cancer, e.g., cancer that has at least a partial inflammatory basis, e.g., a MSI-H cancer, in the range of about 100mg to about 400mg, preferably about 200mg per treatment. In one embodiment the patient receives each treatment about every 2 weeks, about
25 every 3 weeks, about every 4 weeks (monthly), about every 6 weeks, bimonthly (every 2 months), about every 9 weeks or about quarterly (every 3 months). In one embodiment the patient receives canakinumab about monthly or about every three weeks. In one embodiment the preferred dose of canakinumab for patient is about 200mg about every 3 weeks. In one embodiment the preferred dose of canakinumab for is about 200mg about monthly. When safe
30 concern raises, the dose can be down-titrated, preferably by increasing the dosing interval, preferably by doubling or tripling the dosing interval. For example about 200mg about monthly or about every 3 weeks regimen can be changed to about every 2 month or about every 6 weeks respectively or about every 3 month or about every 9 weeks respectively. In an alternative

embodiment the patient receives canakinumab at a dose of about 200mg about every two month or about every 6 weeks in the down-titration phase or in the maintenance phase independent from any safety issue or throughout the treatment phase. In an alternative embodiment the patient receives canakinumab at a dose of about 200mg about every 3 month or about every 9 weeks in the down-titration phase or in the maintenance phase independent from any safety issue or throughout the treatment phase. In an alternative embodiment the patient receives canakinumab at a dose of about 250mg. In an alternative embodiment the patient receives canakinumab at a dose of about 250mg about every 4 weeks.

Suitably the above dose and dosing apply to the use of a functional fragment of canakinumab according to the present invention.

Canakinumab or a functional fragment thereof can be administered intravenously or subcutaneously, preferably subcutaneously.

The dosing regimens disclosed herein is applicable in each and every canakinumab related embodiments disclosed in this application, including but not limited to monotherapy or in combination with one or more anti-cancer therapeutic agents, used in adjuvant setting or in the first line, 2nd line or 3rd line treatment.

In one embodiment, the present invention comprises administering gevokizumab to a patient with cancer, e.g., cancer that has at least a partial inflammatory basis, e.g., a MSI-H cancer, in the range of about 20mg to about 240mg per treatment, preferably in the range of about 20mg to about 180mg, preferably in the range of about 30mg to about 120mg, preferably about 30mg to about 60mg, preferably about 60mg to about 120mg per treatment. In one embodiment patient receives about 30mg to about 120mg per treatment. In one embodiment patient receives about 30mg to about 60mg per treatment. In one embodiment patient receives about 30mg, about 60mg, about 90mg, about 120mg or about 180mg per treatment. In one embodiment the patient receives each treatment about every 2 weeks, about every 3 weeks, about monthly (every 4 weeks), about every 6 weeks, about bimonthly (every 2 months), about every 9 weeks or about quarterly (every 3 months). In one embodiment the patient receives each treatment about every 3 weeks. In one embodiment the patient receives each treatment about every 4 weeks.

When a safety concern raises, the dose can be down-titrated, preferably by increasing the dosing interval, preferably by doubling or tripling the dosing interval. For example about 60mg about monthly or about every 3 weeks regimen can be doubled to about every 2 month or about every 6 weeks respectively or tripled to about every 3 month or about every 9 weeks

respectively. In an alternative embodiment the patient receives gevokizumab at a dose of about 30mg to about 120mg about every 2 month or about every 6 weeks in the down-titration phase or in the maintenance phase independent from any safety issue or throughout the treatment phase. In an alternative embodiment the patient receives gevokizumab at a dose of about 30mg to about 120mg about every 3 month or about every 9 weeks in the down-titration phase or in the maintenance phase independent from any safety issue or throughout the treatment phase.

Suitably the above dose and dosing apply to the use of a functional fragment of gevokizumab according to the present invention.

Gevokizumab or a functional fragment thereof can be administered intravenously or subcutaneously, preferably intravenously.

The dosing regimens disclosed herein is applicable in each and every gevokizumab related embodiments disclosed in this application, including but not limited to monotherapy or in combination with one or more anti-cancer therapeutic agents, used in adjuvant setting or in the first line, 2nd line or 3rd line treatment.

When canakinumab or gevokizumab is used in combination with one or more anti-cancer therapeutic agents, e.g., a chemotherapeutic agent or a check point inhibitor, especially when the one or more therapeutic agents is the SoC of the cancer indication, the dosing interval of canakinumab or gevokizumab can be adjusted to be aligned with the combination partner for the sake of patient convenience. Normally there is no need to change the canakinumab or gevokizumab dose per treatment. For example canakinumab about 200mg is administered about every 3 weeks in combination with pembrolizumab, for example in NSCLC. For example canakinumab about 200mg is administered about every 4 weeks in combination with FOLFOX, for example in CRC.

Biomarkers

In one aspect, the present invention provides the use of an IL-1 β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, in the treatment and/or prevention of cancer, e.g., cancer having at least a partial inflammatory basis, e.g., a MSI-H cancer, in a patient who has a higher than normal level of C-reactive protein (hsCRP). In one further embodiment, this patient is a smoker. In one further embodiment, the patient is a current smoker. Typically cancers, e.g., cancers that have at least a partial inflammatory basis, that possibly have patients exhibiting higher than normal hsCRP levels include, but are not limited to, MSI-H cancers, lung cancer, especially NSCLC, colorectal cancer (CRC), melanoma,

gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, prostate cancer, head and neck cancer (including oral), bladder cancer, hepatocellular carcinoma (HCC), ovarian cancer, cervical cancer, pancreatic cancer, especially PDAC and multiple myeloma.

5 As used herein, “C-reactive protein” and “CRP” refers to serum or plasma C-reactive protein, which is typically used as an indicator of the acute phase response to inflammation. Nonetheless, CRP level may become elevated in chronic illnesses such as cancer. The level of CRP in serum or plasma may be given in any concentration, e.g., mg/dl, mg/L, nmol/L. Levels of CRP may be measured by a variety of well-known methods, e.g., radial immunodiffusion,
10 electroimmunoassay, immunoturbidimetry (e.g., particle (e.g., latex)-enhanced turbidimetric immunoassay), ELISA, turbidimetric methods, fluorescence polarization immunoassay, and laser nephelometry. Testing for CRP may employ a standard CRP test or a high sensitivity CRP (hsCRP) test (i.e., a high sensitivity test that is capable of measuring lower levels of CRP in a sample, e.g., using immunoassay or laser nephelometry). Kits for detecting levels of CRP may
15 be purchased from various companies, e.g., Calbiotech, Inc, Cayman Chemical, Roche Diagnostics Corporation, Abazyme, DADE Behring, Abnova Corporation, Aniara Corporation, Bio-Quant Inc., Siemens Healthcare Diagnostics, Abbott Laboratories etc.

 As used herein, the term “hsCRP” refers to the level of CRP in the blood (serum or plasma) as measured by high sensitivity CRP testing. For example, Tina-quant C-reactive
20 protein (latex) high sensitivity assay (Roche Diagnostics Corporation) may be used for quantification of the hsCRP level of a subject. Such latex-enhanced turbidimetric immunoassay may be analysed on the Cobas® platform (Roche Diagnostics Corporation) or Roche/Hitachi (e.g., Modular P) analyzer. In the CANTOS trial the hsCRP level was measured by Tina-quant C-reactive protein (latex) high sensitivity assay (Roche Diagnostics Corporation) on the
25 Roche/Hitachi Modular P analyzer, which can be used typically and preferably as the method in measuring hsCRP level. Alternatively the hsCRP level can be measured by another method, for example by another approved companion diagnostic kit, the value of which can be calibrated against the value measured by the Tina-quant method.

 Each local laboratory employ a cutoff value for abnormal (high) CRP or hsCRP based
30 on that laboratory’s rule for calculating normal maximum CRP, i.e. based on that laboratory’s reference standard. A physician generally orders a CRP test from a local laboratory, and the local laboratory determines CRP or hsCRP value and reports normal or abnormal (low or high) CRP using the rule that particular laboratory employs to calculate normal CRP, namely based

on its reference standard. Thus whether a patient has a higher than normal level of C-reactive protein (hsCRP) can be determined by the local laboratory where the test is conducted.

It is plausible that an IL-1 β antibody or a fragment thereof, such as canakinumab or gevokizumab, is effective in treating and/or preventing other cancer having at least partially inflammatory basis, e.g., a MSI-H cancer, in a patient, especially when said patient has higher than normal level of hsCRP. Like canakinumab, gevokizumab binds to IL-1 β specifically. Unlike canakinumab directly inhibiting the binding of IL-1 β to its receptor, gevokizumab is an allosteric inhibitor. It does not inhibit IL-1 β from binding to its receptor but prevents the receptor from being activated by IL-1 β . Like canakinumab, gevokizumab was tested in a few inflammation based indications and has been shown to effectively reduce inflammation as indicated, for example, by the reduction of hsCRP level in those patients. Furthermore from the available IC50 value, gevokizumab seems to be a more potent IL-1 β inhibitor than canakinumab.

Furthermore, the present invention provides effective dosing ranges, within which hsCRP level can be reduced to certain threshold, below which more patients with cancer having at least partially inflammatory basis, e.g., MSI-H cancers, can become responder or below which the same patient can benefit more from the great therapeutic effect of the Drug of the invention with negligible or tolerable side effects.

In one aspect, the present invention provides high sensitivity C-reactive protein (hsCRP) or CRP for use as a biomarker in the treatment of cancer, e.g., cancer having at least a partial inflammatory basis, e.g., MSI-H cancer, with an IL-1 β inhibitor, e.g., IL-1 β binding antibody or a functional fragment thereof. The level of hsCRP is possibly relevant in determining whether a patient with diagnosed or undiagnosed cancer should be treated with an IL-1 β binding antibody or a functional fragment thereof. In one embodiment patient is eligible for the treatment if the level of hsCRP is equal to or higher than about 2.5mg/L, or equal to or higher than about 4.5mg/L, or equal to or higher than about 7.5 mg/L, or equal to or higher than about 9.5 mg/L, as assessed prior to the administration of the IL-1 β binding antibody or a functional fragment thereof.

In one embodiment, the present invention provides the use of an IL-1 β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for the treatment of cancer, e.g., cancer that has at least a partial inflammatory basis, e.g., MSI-H cancers, in a patient who has high sensitivity C-reactive protein (hsCRP) level equal to or higher than about 2.2mg/L, equal to or higher than about 4.2mg/L, equal to or higher than about 6.2mg/L equal

to or higher than about 10.2 mg/L, preferably before first administration of said IL-1 β binding antibody or functional fragment thereof. Preferably said patient has a hsCRP level equal to or higher than about 4.2mg/L. Preferably said patient has a hsCRP level equal to or higher than about 6.2mg/L. Preferably said patient has a hsCRP level equal to or higher than about 10 mg/L.

5 Preferably said patient has a hsCRP level equal to or higher than about 20 mg/L. In one further embodiment, this patient is a smoker. In one further embodiment, this patient is a current smoker.

In one aspect the present invention provides an IL-1 β binding antibody or a functional fragment thereof for use in the treatment of cancer, e.g., cancer having at least a partial inflammatory basis, e.g., MSI-H cancers, in a patient, wherein the efficacy of the treatment correlates with the reduction of hsCRP in said patient, comparing to prior treatment. In one embodiment the present invention provides an IL-1 β binding antibody or a functional fragment thereof for use in the treatment of cancer, e.g., cancer having at least a partial inflammatory basis, e.g., MSI-H cancers, wherein hsCRP level, of said patient has reduced to below about

10 5.2mg/L, preferably to below about 3.2mg/L, preferably to below about 2.2 mg/L, about 6 months, or preferably about 3 months from the first administration of said IL-1 β binding antibody or a functional fragment thereof at a proper dose, preferably according to the dosing regimen of the present invention.

In one aspect, the present invention provides IL-6 use as a biomarker in the treatment and/or prevention of cancer, e.g., cancer having at least a partial inflammatory basis, e.g., a MSI-H cancer, with an IL-1 β inhibitor, e.g., IL-1 β binding antibody or a functional fragment thereof. The level of IL-6 is possibly relevant in determining whether a patient with diagnosed or undiagnosed cancer or is at risk of developing cancer should be treated with an IL-1 β binding antibody or a functional fragment thereof. In one embodiment patient is eligible for the

20 treatment and/or prevention if the level of IL-6 is equal to or higher than about 1.9 pg/ml, higher than about 2 pg/ml, higher than about 2.2 pg/ml, higher than about 2.5 pg/ml, higher than about 2.7 pg/ml, higher than about 3 pg/ml, higher than about 3.5 pg/ml, as assessed prior to the administration of the IL-1 β binding antibody or a functional fragment thereof. Preferably the patient has an IL-6 level equal to or higher than about 2.5mg/L.

30 In one aspect the present invention provides an IL-1 β binding antibody or a functional fragment thereof for use in the treatment and/or prevention of cancer, e.g., cancer having at least a partial inflammatory basis, e.g., a MSI-H cancer, in a patient, wherein the efficacy of the treatment correlates with the reduction of IL-6 in said patient, comparing to prior treatment. In

one embodiment the present invention provides an IL-1 β binding antibody or a functional fragment thereof for use in the treatment of cancer, e.g., cancer having at least a partial inflammatory basis, e.g., a MSI-H cancer, wherein hsCRP level of said patient has reduced to below 2.2 pg/ml, preferably to below 2 pg/ml, preferably to below 1.9 pg/ml about 6 months, or preferably about 3 months from the first administration of said IL-1 β binding antibody or a functional fragment thereof at a proper dose, preferably according to the dosing regimen of the present invention.

In one aspect the present invention provides an IL-1 β binding antibody or a functional fragment thereof (e.g., canakinumab or gevokizumab) for use in the treatment of cancers that have at least a partial inflammatory basis, e.g., MSI-H cancers, in a patient, wherein the hsCRP level of said patient has reduced by at least 35% or at least 50% or at least 60% 6 months, or preferably 3 month from the first administration of said IL-1 β binding antibody or a functional fragment thereof at a proper dose, preferably according to the dosing regimen of the present invention, as compared to the hsCRP level just prior to the first administration of the IL-1 β binding antibody or a functional fragment thereof, canakinumab or gevokizumab). Further preferably the hsCRP level of said patient has reduced by least 35% or at least 50% or at least 60% after the first administration of the DRUG of the invention according to the dose regimen of the present invention.

In one aspect the present invention provides an IL-1 β binding antibody or a functional fragment thereof (e.g., canakinumab or gevokizumab) for use in the treatment of cancers, e.g., cancers that have at least a partial inflammatory basis, e.g., MSI-H cancers, in a patient, wherein the IL-6 level of said patient has reduced by at least least 35% or at least 50% or at least 60% about 6 months, or preferably about 3 months from the first administration of said IL-1 β binding antibody or a functional fragment thereof (e.g., canakinumab or gevokizumab) at a proper dose, preferably according to the dosing regimen of the present invention, as compared to the IL-6 level just prior to the first administration. Further preferably the IL-6 level of said patient has reduced by least 35% or at least 50% or at least 60% after the first administration of the DRUG of the invention according to the dose regimen of the present invention.

The reduction of the level of hsCRP and the reduction of the level of IL-6 can be used separately or in combination to indicate the efficacy of the treatment or as prognostic markers.

Inhibition of angiogenesis

In one aspect, the present invention provides an IL-1 β binding antibody or a functional fragment thereof, suitable canakinumab or gevokizumab, for use in a patient in need thereof in the treatment of cancer, e.g., a cancer having at least partial inflammatory basis, e.g., MSI-H cancer, wherein a therapeutic amount is administered to inhibit angiogenesis in said patient.

Without wishing to be bound by theory, it is hypothesized that the inhibition of IL-1 β pathway can lead to inhibition or reduction of angiogenesis, which is a key event for tumor growth and for tumor metastasis. In clinical settings the inhibition or reduction of angiogenesis can be measured by tumor shrinkage, no tumor growth (stable disease), prevention of metastasis or delay of metastasis.

All the disclosed uses throughout this application, including but not limited to, doses and dosing regimens, combinations, route of administration and biomarkers can be applied to the aspect of inhibition or reduction of angiogenesis. In one embodiment canakinumab or gevokizumab used in combination of one or more anti-cancer therapeutic agents. In one embodiment the one or more chemotherapeutic agents is an anti-Wnt inhibitor, preferably Vantictumab. In one embodiment the one or more therapeutic agents is a VEGF inhibitor, preferably sunitinib, sorafenib, axitinib, pazopanib, bevacizumab or Ramucirumab.

Inhibition of metastasis

Without wishing to be being bound by theory, it is hypothesized that the inhibition of IL-1 β pathway can lead to inhibition or reduction of tumor metastasis. Until now there have been no reports on the effects of canakinumab on metastasis. Data presented in Example 1 demonstrate that IL-1 β activates different pro-metastatic mechanisms at the primary site compared with the metastatic site: Endogenous production of IL-1 β by breast cancer cells promotes epithelial to mesenchymal transition (EMT), invasion, migration and organ specific homing. Once tumor cells arrive in the bone environment contact between tumor cells and osteoblasts or bone marrow cells increase IL-1 β secretion from all three cell types. These high concentrations of IL-1 β cause proliferation of the bone metastatic niche by stimulating growth of disseminated tumor cells into overt metastases. These pro-metastatic processes are inhibited by administration of anti-IL-1 β treatments, such as canakinumab or gevokizumab.

Therefore, targeting IL-1 β with an IL-1 β binding antibody represents a novel therapeutic approach for cancer patients at risk of progressing to metastasis by preventing seeding of new metastases from established tumors and retaining tumor cells already disseminated in the bone in a state of dormancy. The models described have been designed to

investigate bone metastasis and although the data show a strong link between IL-1 β expression and bone homing, it does not exclude IL-1 β involvement in metastasis to other sites.

Accordingly, in one aspect, the present invention provides an IL-1 β binding antibody or a functional fragment thereof, suitable canakinumab or gevokizumab, for use in a patient in the treatment of cancer, e.g., a cancer having at least partial inflammatory basis, e.g., a MSI-H cancer, wherein a therapeutic amount is administered to inhibit metastasis in said patient. All the disclosed uses throughout this application, including but not limited to, doses and dosing regimens, combinations, route of administration and biomarkers can be applied to the embodiment of metastasis inhibition.

Adjuvant treatment

In one aspect, the present invention provides an IL-1 β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for use, alone or in combination with one or more therapeutic agents, in the prevention of recurrence or relapse of cancer, e.g., cancer having at least a partial inflammatory basis, e.g., MSI-H cancer, which has been surgically removed (resected “adjuvant chemotherapy”).

Without wishing to be bound by the theory, after tumor has been surgically removed, it is possible that the inflammation is greatly reduced due to surgery. The IL-1 β or the hsCRP level is no longer higher than normal. It is however reasonable to expect that the DRUG of the invention can prevent or delay the recurrence or relapse of cancer by keeping inflammation under control and thereby preventing the re-formation of IL-1 β mediated immune suppressive tumor microenvironment that promote tumor growth and metastasis. Furthermore after tumor has been surgically removed, the patient’s immune system can regain its surveillance function in eliminating remaining tumor loci/cells. By reducing inflammation, IL-1 β binding antibody or a functional fragment thereof helps maintaining or improving the surveillance function of the immune system and thereby prevents or delays tumor recurrence or relapse of cancer.

In one embodiment the one or more therapeutic agent is the standard of care adjuvant (other than the treatment of DRUG of the invention) treatment in that cancer indication. SoC adjuvant treatment varies depending on the cancer. Suitably the SoC adjuvant treatment is a chemotherapy, a radiotherapy, a targeted therapy or a checkpoint inhibitor therapy. Often SoC drug in the adjuvant treatment is the same drug as SoC in the first line treatment, only that in adjuvant setting the drug is administered for a short period, normally not longer than about 6 months for chemotherapies. Normally not longer than about 12 months for check point

inhibitors. For example in NSCLC, SoC adjuvant treatment is cisplatin-based doublet chemotherapy, normally taking for about 4 cycles. For example in RCC, the SoC adjuvant treatment is pembrolizumab for about one year.

5 In one embodiment DRUG of the invention is administered after the patient has completed the SoC adjuvant treatment, suitably chemotherapy or radiotherapy, suitably as single agent.

In one embodiment IL-1 β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, is added on top of the SoC adjuvant treatment, preferably administered at the beginning of the patient's SoC adjuvant treatment. In one embodiment the
10 SoC adjuvant treatment is a targeted therapy or a immunotherapy. Suitably the combination treatment lasts for about 6 months to one year.

In one embodiment the patient receives DRUG of the invention, suitable canakinumab or gevokizumab, for at least about 6 months, preferably for at least about 12 months, preferably for ≥ 12 months. Due to the good safety profile it is possible that DRUG of the invention,
15 suitably canakinumab or gevokizumab is administered longer than about one year, for example for about 2 years, for about 3 years or for about 5 years or till the recurrence or relapse of cancer, either in combination with SoC adjuvant treatment or preferably as a single agent.

In one embodiment DRUG of the invention, suitably canakinumab or gevokizumab, is the sole post-surgery adjuvant treatment, in a patient who does not receive other adjuvant
20 treatment or could not have completed the SoC adjuvant treatment. Chemotherapy or check point inhibitors results in many undesired side effects. Thus the present invention provides an alternative post-surgery adjuvant treatment, preferably with very low or much better tolerated side effects.

In the adjuvant settings, DRUG of the invention, suitably canakinumab or
25 gevokizumab, is administered according to the dosing regimen of the present invention. When used as monotherapy, the dosing interval can be flexible. For example, canakinumab or gevokizumab can be administered in the loading phase and in the maintenance phase, wherein a lower amount of drug is given during the maintenance phase. For example canakinumab or gevokizumab can be administered about every 3 weeks or about monthly post-surgery in the
30 loading phase. The dose interval can be doubled or tripled in the maintenance phase. In one embodiment the loading phase is at least about 6 months, preferably at least about 12 months, preferably about 12 months. In one embodiment the maintenance dose is at least about 12 months or at least about 24 months, or till the recurrence or relapse of the cancer.

In one embodiment, the present invention provides an IL-1 β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for use in the prevention of recurrence or relapse of cancer, e.g., cancer having at least a partial inflammatory basis, e.g., a MSI-H cancer, which has been surgically removed (resected “adjuvant chemotherapy”), wherein the disease free survival (DFS) in patients receiving Treatment of the Invention is at least about 6 months or at least about 9 months, or at least about 12 months longer than not receiving Treatment of the Invention in the adjuvant setting. DFS is defined as the time from the date of randomization to the date of detection of first disease recurrence. In one embodiment patient is followed up about every 12 weeks after the completion of the adjuvant treatment of the present invention. In one embodiment detection of first disease recurrence will be done by clinical evaluation that includes physical examination, and radiological tumor measurements as determined by the investigator. In one embodiment patient not receiving Treatment of the Invention did not receive any treatment. In one embodiment patient not receiving Treatment of the Invention received considered SoC treatment at the time of trial for the tested cancer indication.

Normally after resection of cancer, patient is in the disease free status (DFS), which will end at the time of cancer progression or recurrence. In one embodiment the hazard rate (HR) of the patient in losing the DFS status is reduced by at least about 20%, at least about 30%, by up to about 50%, by up to about 70%, or by about 20% to about 30%, by about 30% to about 40%, compare to not receiving Treatment of the Invention.

In one embodiment the DFS of the patient receiving Treatment of the Invention is at least about 24 months, preferably at least about 48 months.

In the adjuvant setting patients are considered healthy. To improve patients convenience and quality of life, canakinumab or gevokizumab is administered subcutaneously, by a prefilled syringe or preferably by an auto-injector, preferably at patients’ home.

First line treatment

In one embodiment, the present invention provides an IL-1 β antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for use as the first line treatment of cancer, e.g., cancer having at least a partial inflammatory basis e.g., a MSI-H cancer. The term “first line treatment” means said patient is given the IL-1 β antibody or a functional fragment thereof before the patient develops resistance to the initial treatment with one or more other therapeutic agents. Preferably one or more other therapeutic agents is a platinum-based mono

or combination therapy, a targeted therapy, such a tyrosine inhibitor therapy, a checkpoint inhibitor therapy or any combination thereof. As first line treatment, the IL-1 β antibody or a functional fragment thereof, such as canakinumab or gevokizumab, can be administered to patient as monotherapy or preferably in combination with one or more therapeutic agents, such as a check point inhibitor, particularly a PD-1 or PD-L1 inhibitor, preferably pembrolizumab, with or without one or more small molecule chemotherapeutic agent. In one embodiment as first line treatment, the IL-1 β antibody or a functional fragment thereof, such as canakinumab or gevokizumab, can be administered to patient in combination with the standard of care therapy for that cancer. Preferably canakinumab or gevokizumab is administered as the first line treatment until disease progression.

Second line treatment

In one embodiment, the present invention provides an IL-1 β antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for use as the second or third line treatment of cancer, e.g., cancer having at least a partial inflammatory basis, e.g., a MSI-H cancer. The term “the second or third line treatment” means IL-1 β antibody or a functional fragment thereof is administered to a patient with cancer progression on or after one or more other therapeutic agent treatment, especially disease progression on or after FDA-approved first line therapy for that cancer. Preferably one or more other therapeutic agent is a chemotherapeutic agent, such as platinum-based mono or combination therapy, a targeted therapy, such a tyrosine inhibitor therapy, a checkpoint inhibitor therapy or any combination thereof. As the second or third line treatment, the IL-1 β antibody or a functional fragment thereof can be administered to the patient as monotherapy or preferably in combination with one or more therapeutic agent, including the continuation of the early treatment with the same one or more therapeutic agent. Preferably canakinumab or gevokizumab is administered as the 2nd/3rd line treatment until disease progression.

Continuous treatment

In one aspect the present invention also provides an IL-1 β binding antibody or a functional fragment thereof, suitably gevokizumab or canakinumab, for use in the treatment of cancer, e.g., cancer having at least partial inflammatory basis, e.g., a MSI-H cancer, wherein IL-1 β binding antibody or a functional fragment thereof is administered to a patient in more than one line of treatment.

Without wishing to be bound by the theory, it is hypothesized that, unlike chemotherapeutic agents or targeted therapy, which have a direct killing or inhibiting effect on the cancer cells and thereby selecting resist cells, DRUG of the invention works on the tumor-microenvironment and does not seem to lead to drug resistance. Furthermore unlike
5 chemotherapeutic agents or check point inhibitors, IL-1 β binding antibody or a functional fragment thereof, such as gevokizumab or canakinumab, has much less undesired side effects. Patients unlikely develop intolerance and therefore can continue receive DRUG of the invention and continue the benefit of elimination or reduction of IL-1 β mediated inflammation in the course of cancer treatment.

10 In one embodiment DRUG of the invention, suitably canakinumab or gevokizumab, can be used in 2, 3 or all lines of the treatment of cancer in the same patient. Treatment line typically includes but not limited to neo-adjuvant treatment, adjuvant treatment, first line treatment, 2nd line treatment, 3rd line treatment and further line of treatment. Patient normally changes lines of treatment after surgery, after disease progression or after developing drug resistance to the
15 current treatment. In one embodiment DRUG of the invention is continued after patient develops resistant to the current treatment. In one embodiment DRUG of the invention is continued to the next line of treatment. In one embodiment DRUG of the invention is continued after disease progression. In one embodiment DRUG of the invention is continued until death or until palliative care.

20 In one embodiment the present invention provides DRUG of the invention, suitable canakinumab or gevokizumab, for use in re-treating cancer in a patient, wherein the patient was treated with the same DRUG of the invention in the previous treatment. In one embodiment the previous treatment is the neo-adjuvant treatment. In one embodiment the previous treatment is the adjuvant treatment. In one embodiment the previous treatment is the first line treatment. In
25 one embodiment the previous treatment is the second line treatment.

In one embodiment the cancer is lung cancer, especially NSCLC, the IL-1 β binding antibody is canakinumab, wherein canakinumab is administered to the patient, wherein the patient was treated with canakinumab in the previous treatment. In one embodiment the previous treatment is the neo-adjuvant treatment. In one embodiment the previous treatment is
30 the adjuvant treatment. In one further embodiment the adjuvant treatment is for patients with stage II to IIIA and IIIB (T>5 cm N2) non-small cell lung cancer following complete surgical resection. In one embodiment the previous treatment is the first line treatment. In one further

embodiment the first line treatment is canakinumab in combination with pembrolizumab and platinum based chemotherapy, for the treatment of patients with locally advanced or metastatic non-small cell lung cancer. In one embodiment the previous treatment is the second line treatment. In one further embodiment the second line treatment is canakinumab in combination with docetaxel for the treatment of patients with locally advanced or metastatic non-small cell lung cancer previously treated with PD-(L)1 inhibitors and platinum-based chemotherapy, with or without canakinumab.

Combination

In one aspect, the present invention provides an IL-1 β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for use in a patient in need thereof in the treatment of a cancer, particularly cancer having at least partial inflammatory basis, e.g., a MSI-H cancer, in combination with a radiotherapy, in combination with a cell-based therapy, or in combination with one or more therapeutic agents, e.g., chemotherapeutic agents or e.g., a check point inhibitor, or in combination with both radiotherapy and one or more therapeutic agents.

Without wishing to be bound by the theory, it is believed that typical cancer development requires two steps. Firstly gene alteration results in cell growth and proliferation no longer subject to regulation. Secondly the abnormal tumor cells evade surveillance of the immune system. Inflammation plays important role in the second step. Therefore, control of inflammation can stop cancer development at the early or earlier stage. Thus it is expected that blocking IL-1 β pathway to reduce inflammation would have a general benefit, particularly improvement of the treatment efficacy on top of the standard of care, which is normally mainly to directly inhibit the growth and proliferation of the malignant cells. In one embodiment the one or more therapeutic agents, e.g., chemotherapeutic agents is the standard of care agents of said cancer, particularly cancer having at least partial inflammatory basis, e.g., a MSI-H cancer.

Check point inhibitors de-suppress the immune system through a mechanism different from IL-1 β inhibitors. Thus the addition of IL-1 β inhibitors, particularly IL-1 β binding antibodies or a functional fragment thereof to the standard Check point inhibitors therapy will further active the immune response, particularly at the tumor microenvironment.

In one embodiment, the one or more therapeutic agents is nivolumab.

In one embodiment, the one or more therapeutic agents is pembrolizumab.

In one embodiment, the one or more therapeutic agent, e.g., chemotherapeutic agents is nivolumab and ipilimumab.

In one embodiment, the one or more chemotherapeutic agents is cabozantinib, or a pharmaceutically acceptable salt thereof.

5 In one embodiment the one or more therapeutic agent, e.g., chemotherapeutic agent is Atezolizumab plus bevacizumab.

In one embodiment, the one or more chemotherapeutic agents is bevacizumab.

In one embodiment, the one or more chemotherapeutic agents is FOLFIRI, FOLFOX or XELOX.

10 In one embodiment the one or more chemotherapeutic agent is FOLFIRI plus bevacizumab or FOLFOX plus bevacizumab.

In one embodiment the one or more chemotherapeutic agent is platinum-based doublet chemotherapy (PT-DC).

15 Therapeutic agents are cytotoxic and/or cytostatic drugs (drugs that kill malignant cells, or inhibit their proliferation, respectively) as well as check point inhibitors. Chemotherapeutic agents can be, for example, small molecule agents, biologics agents (e.g., antibodies, cell and gene therapies, cancer vaccines), hormones or other natural or synthetic peptide or polypeptides. Commonly known chemotherapeutic agent includes, but is not limited to, platinum agents (e.g., cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin, lipoplatin, 20 satraplatin, picoplatin), antimetabolites (e.g., methotrexate, 5-Fluorouracil, gemcitabine, pemetrexed, edatrexate), mitotic inhibitors (e.g., paclitaxel, albumin-bound paclitaxel, docetaxel, taxotere, docecad), alkylating agents (e.g., cyclophosphamide, mechlorethamine hydrochloride, ifosfamide, melphalan, thiotepa), vinca alkaloids (e.g., vinblastine, vincristine, vindesine, vinorelbine), topoisomerase inhibitors (e.g., etoposide, teniposide, topotecan, 25 irinotecan, camptothecin, doxorubicin), antitumor antibiotics (e.g., mitomycin C) and/or hormone-modulating agents (e.g., anastrozole, tamoxifen). Examples of anti-cancer agents used for chemotherapy include Cyclophosphamide (Cytosan®), Methotrexate, 5-Fluorouracil (5-FU), Doxorubicin (Adriamycin®), Prednisone, Tamoxifen (Nolvadex®), Paclitaxel (Taxol®), Albumin-bound paclitaxel (nab-paclitaxel, Abraxane®), Leucovorin, Thiotepa (Thiopex®), 30 Anastrozole (Arimidex®), Docetaxel (Taxotere®), Vinorelbine (Navelbine®), Gemcitabine (Gemzar®), Ifosfamide (Ifex®), Pemetrexed (Alimta®), Topotecan, Melphalan (L-Pam®), Cisplatin (Cisplatinum®, Platinol®), Carboplatin (Paraplatin®), Oxaliplatin (Eloxatin®), Nedaplatin (Aqupla®), Triplatin, Lipoplatin (Nanoplatin®), Satraplatin, Picoplatin,

Carmustine (BCNU; BiCNU®), Methotrexate (Folex®, Mexate®), Edatrexate, Mitomycin C (Mutamycin®), Mitoxantrone (Novantrone®), Vincristine (Oncovin®), Vinblastine (Velban®), Vinorelbine (Navelbine®), Vindesine (Eldisine®), Fenretinide, Topotecan, Irinotecan (Camptosar®), 9-amino-camptothecin [9-AC], Biantazole, Losoxantrone, Etoposide, and Teniposide.

In one embodiment, the preferred combination partner for the IL-1 β binding antibody or a functional fragment thereof (e.g., canakinumab or gevokizumab) is a mitotic inhibitor, preferably docetaxel. In one embodiment, the preferred combination partner for canakinumab is a mitotic inhibitor, preferably docetaxel. In one embodiment, the preferred combination partner for gevokizumab is a mitotic inhibitor, preferably docetaxel. In one embodiment said combination is used for the treatment of lung cancer, especially NSCLC.

In one embodiment, the preferred combination partner for the IL-1 β binding antibody or a functional fragment thereof (e.g., canakinumab or gevokizumab) is a platinum agent, preferably cisplatin. In one embodiment, the preferred combination partner for canakinumab is a platinum agent, preferably cisplatin. In one embodiment, the preferred combination partner for gevokizumab is a platinum agent, preferably cisplatin. In one embodiment, the one or more chemotherapeutic agent is a platinum-based doublet chemotherapy (PT-DC).

Chemotherapy may comprise the administration of a single anti-cancer agent (drug) or the administration of a combination of anti-cancer agents (drugs), for example, one of the following, commonly administered combinations of: carboplatin and taxol; gemcitabine and cisplatin; gemcitabine and vinorelbine; gemcitabine and paclitaxel; cisplatin and vinorelbine; cisplatin and gemcitabine; cisplatin and paclitaxel (Taxol); cisplatin and docetaxel (Taxotere); cisplatin and etoposide; cisplatin and pemetrexed; carboplatin and vinorelbine; carboplatin and gemcitabine; carboplatin and paclitaxel (Taxol); carboplatin and docetaxel (Taxotere); carboplatin and etoposide; carboplatin and pemetrexed. In one embodiment, the one or more chemotherapeutic agent is a platinum-based doublet chemotherapy (PT-DC).

Another class of chemotherapeutic agents are the inhibitors, especially tyrosine kinase inhibitors, that specifically target growth promoting receptors, especially VEGF-R, EGFR, PFGF-R and ALK, or their downstream members of the signalling transduction pathway, the mutation or overproduction of which results in or contributes to the oncogenesis of the tumor at the site (targeted therapies). Exemplary of targeted therapies drugs approved by the Food and Drug administration (FDA) for the targeted treatment of lung cancer include but not limited bevacizumab (Avastin®), crizotinib (Xalkori®), erlotinib (Tarceva®), gefitinib (Iressa®),

afatinib dimaleate (Gilotrif®), ceritinib (LDK378/Zykadia™), everolimus (Afinitor®), ramucirumab (Cyramza®), osimertinib (Tagrisso™), necitumumab (Portrazza™), alectinib (Alecensa®), atezolizumab (Tecentriq™), brigatinib (Alunbrig™), trametinib (Mekinist®), dabrafenib (Tafinlar®), sunitinib (Sutent®) and cetuximab (Erbix®).

5 In one embodiment the one or more chemotherapeutic agent to be combined with the IL-1 β binding antibody or fragment thereof, suitably canakinumab or gevokizumab, is the agent that is the standard of care agent for lung cancer, including NSCLC and SCLC. Standard of care, can be found, for example from American Society of Clinical Oncology (ASCO) guideline on the systemic treatment of patients with stage IV non-small-cell lung cancer (NSCLC) or
10 American Society of Clinical Oncology (ASCO) guideline on Adjuvant Chemotherapy and Adjuvant Radiation Therapy for Stages I-III A Resectable Non-Small Cell Lung Cancer.

In one embodiment the one or more chemotherapeutic agent to be combined with the IL-1 β binding antibody or fragment thereof, suitably canakinumab or gevokizumab, is a platinum containing agent or a platinum-based doublet chemotherapy (PT-DC). In one
15 embodiment said combination is used for the treatment of lung cancer, especially NSCLC. In one embodiment one or more chemotherapeutic agent is a tyrosine kinase inhibitor. In one preferred embodiment said tyrosine kinase inhibitor is a VEGF pathway inhibitor or an EGF pathway inhibitor. In one embodiment the one or more chemotherapeutic agent is check-point inhibitor, preferably pembrolizumab. In one embodiment said combination is used for the
20 treatment of lung cancer, especially NSCLC.

In one embodiment the one or more therapeutic agent to be combined with the IL-1 β binding antibody or fragment thereof, suitably canakinumab or gevokizumab, is a check-point inhibitor. In one further embodiment, said check-point inhibitor is nivolumab. In one
embodiment said check-point inhibitor is pembrolizumab. In one further embodiment, said
25 check-point inhibitor is atezolizumab. In one further embodiment, said check-point inhibitor is PDR-001 (spartalizumab). In one embodiment, said check-point inhibitor is durvalumab. In one embodiment, said check-point inhibitor is avelumab. Immunotherapies that target immune checkpoints, also known as checkpoint inhibitors, are currently emerging as key agents in cancer therapy. The immune checkpoint inhibitor can be an inhibitor of the receptor
30 or an inhibitor of the ligand. Examples of the inhibiting targets include but not limited to a co-inhibitory molecule (*e.g.*, a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody molecule), a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody molecule), a PD-L2 inhibitor (*e.g.*, an anti-PD-L2 antibody molecule), a LAG-3 inhibitor (*e.g.*, an anti-LAG-3 antibody molecule), a TIM-3

inhibitor (*e.g.*, an anti-TIM-3 antibody molecule)), an activator of a co-stimulatory molecule (*e.g.*, a GITR agonist (*e.g.*, an anti-GITR antibody molecule)), a cytokine (*e.g.*, IL-15 complexed with a soluble form of IL-15 receptor alpha (IL-15Ra)), an inhibitor of cytotoxic T-lymphocyte-associated protein 4 (*e.g.*, an anti-CTLA-4 antibody molecule) or any combination thereof.

PD-1 Inhibitors

In one aspect of the invention, the IL-1 β inhibitor or a functional fragment thereof is administered together with a PD-1 inhibitor. In one some embodiment the PD-1 inhibitor is chosen from PDR001(spartalizumab) (Novartis), Nivolumab (Bristol-Myers Squibb), Pembrolizumab (Merck & Co), Pidilizumab (CureTech), MEDI0680 (Medimmune), REGN2810 (Regeneron), TSR-042 (Tesar), PF-06801591 (Pfizer), BGB-A317 (Beigene), BGB-108 (Beigene), INCSHR1210 (Incyte), or AMP-224 (Amplimmune).

In one embodiment, the PD-1 inhibitor is an anti-PD-1 antibody. In one embodiment, the PD-1 inhibitor is an anti-PD-1 antibody molecule as described in US 2015/0210769, published on July 30, 2015, entitled "Antibody Molecules to PD-1 and Uses Thereof," incorporated by reference in its entirety.

In one embodiment, the anti-PD-1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 506 and a VL comprising the amino acid sequence of SEQ ID NO: 520. In one embodiment, the anti-PD-1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 506 and a VL comprising the amino acid sequence of SEQ ID NO: 516.

Table A. Amino acid and nucleotide sequences of exemplary anti-PD-1 antibody molecules

BAP049-Clone-B HC		
SEQ ID NO: 506	VH	EVQLVQSGAEVKKPGESLRISCKGSGYTFTTYWMHWVRQAT GQGLEWMGNIYPGTGGSNFDEKFKNRVTITADKSTSTAYMEL SSLRSEDTAVYYCTRWTTGTGAYWGQGTITVTVSS
BAP049-Clone-B LC		
SEQ ID NO: 516	VL	EIVLTQSPATLSLSPGERATLSCKSSQSLDSDGNQKNFLTWYQQ KPGKAPKLLIYWASTRESGVPSRFSGSGSGTDFTFTISLQPED ATYYCQNDYSYPYTFGQGTKVEIK
BAP049-Clone-E HC		
SEQ ID NO: 506	VH	EVQLVQSGAEVKKPGESLRISCKGSGYTFTTYWMHWVRQAT GQGLEWMGNIYPGTGGSNFDEKFKNRVTITADKSTSTAYMEL SSLRSEDTAVYYCTRWTTGTGAYWGQGTITVTVSS
BAP049-Clone-E LC		

SEQ ID NO: 520	VL	EIVLTQSPATLSLSPGERATLSCKSSQSLLD SGN QKNFLT WYQQ KPGQAPRLLIYWASTRESGVPSRFS GSGSGTDFTFTISSLEAEDA ATYYCQNDYSYPYTFGQGTKVEIK
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In one embodiment, the anti-PD-1 antibody is spartalizumab.

In one embodiment, the anti-PD-1 antibody is Nivolumab.

In one embodiment, the anti-PD-1 antibody molecule is Pembrolizumab.

5 In one embodiment, the anti-PD-1 antibody molecule is Pidilizumab.

In one embodiment, the anti-PD-1 antibody molecule is MEDI0680 (Medimmune), also known as AMP-514. MEDI0680 and other anti-PD-1 antibodies are disclosed in US 9,205,148 and WO 2012/145493, incorporated by reference in their entirety. Other exemplary anti-PD-1 molecules include REGN2810 (Regeneron), PF-06801591 (Pfizer), BGB-
10 A317/BGB-108 (Beigene), INCSHR1210 (Incyte) and TSR-042 (Tesar).

Further known anti-PD-1 antibodies include those described, *e.g.*, in WO 2015/112800, WO 2016/092419, WO 2015/085847, WO 2014/179664, WO 2014/194302, WO 2014/209804, WO 2015/200119, US 8,735,553, US 7,488,802, US 8,927,697, US 8,993,731, and US 9,102,727, incorporated by reference in their entirety.

15 In one embodiment, the anti-PD-1 antibody is an antibody that competes for binding with, and/or binds to the same epitope on PD-1 as, one of the anti-PD-1 antibodies described herein.

In one embodiment, the PD-1 inhibitor is a peptide that inhibits the PD-1 signaling pathway, *e.g.*, as described in US 8,907,053, incorporated by reference in its entirety. In one
20 embodiment, the PD-1 inhibitor is an immunoadhesin (*e.g.*, an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region (*e.g.*, an Fc region of an immunoglobulin sequence). In one embodiment, the PD-1 inhibitor is AMP-224 (B7-DCIg (Amplimmune), *e.g.*, disclosed in WO 2010/027827 and WO 2011/066342, incorporated by reference in their entirety).

25 PD-L1 Inhibitors

In one aspect of the invention, the IL-1 β inhibitor or a functional fragment thereof is administered together with a PD-L1 inhibitor. In some embodiments, the PD-L1 inhibitor is chosen from FAZ053 (Novartis), Atezolizumab (Genentech/Roche), Avelumab (Merck Serono and Pfizer), Durvalumab (MedImmune/AstraZeneca), or BMS-936559 (Bristol-Myers
30 Squibb).

In one embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule. In one embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule as disclosed in US 2016/0108123, published on April 21, 2016, entitled “Antibody Molecules to PD-L1 and Uses Thereof,” incorporated by reference in its entirety.

In one embodiment, the anti-PD-L1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 606 and a VL comprising the amino acid sequence of SEQ ID NO: 616. In one embodiment, the anti-PD-L1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 620 and a VL comprising the amino acid sequence of SEQ ID NO: 624.

Table B. Amino acid and nucleotide sequences of exemplary anti-PD-L1 antibody molecules

BAP058-Clone O HC		
SEQ ID NO: 606	VH	EVQLVQSGAEVKKPGATVKISCKVSGYTFTSYWMYWVRQARGQRLEWIGRIDPNSGSTKYNEKFKNRFTISRDN SKNTLYQMNSLRAEDTAVYYCARDYRKGLYAMDYWGQGTTVTVSS
BAP058-Clone O LC		
SEQ ID NO: 616	VL	AIQLTQSPSSLSASVGDRVTITCKASQDVGTA VAWYLQKPGQSPQLLIYWASTRHTGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQYNSYPLTFGQGTKVEIK
BAP058-Clone N HC		
SEQ ID NO: 620	VH	EVQLVQSGAEVKKPGATVKISCKVSGYTFTSYWMYWVRQATGQGLEWMGRIDPNSGSTKYNEKFKNRVTITADKSTSTAYMELSSLRSEDTAVYYCARDYRKGLYAMDYWGQGTTVTVSS
BAP058-Clone N LC		
SEQ ID NO: 624	VL	DVVM TQSPLSLPVT LGQPASISCKASQDVGTA VAWYQQKPGQAPRLLIYWASTRHTGVPSRFSGSGSGTEFTLTISSLQPDFFATYYCQQYNSYPLTFGQGTKVEIK

In one embodiment, the anti-PD-L1 antibody molecule is Atezolizumab (Genentech/Roche), also known as MPDL3280A, RG7446, RO5541267, YW243.55.S70, or TECENTRIQ™. Atezolizumab and other anti-PD-L1 antibodies are disclosed in US 8,217,149, incorporated by reference in its entirety.

In one embodiment, the anti-PD-L1 antibody molecule is Avelumab (Merck Serono and Pfizer), also known as MSB0010718C. Avelumab and other anti-PD-L1 antibodies are disclosed in WO 2013/079174, incorporated by reference in its entirety.

In one embodiment, the anti-PD-L1 antibody molecule is Durvalumab (MedImmune/AstraZeneca), also known as MEDI4736. Durvalumab and other anti-PD-L1 antibodies are disclosed in US 8,779,108, incorporated by reference in its entirety.

In one embodiment, the anti-PD-L1 antibody molecule is BMS-936559 (Bristol-Myers Squibb), also known as MDX-1105 or 12A4. BMS-936559 and other anti-PD-L1 antibodies are disclosed in US 7,943,743 and WO 2015/081158, incorporated by reference in their entirety.

5 Further known anti-PD-L1 antibodies include those described, *e.g.*, in WO 2015/181342, WO 2014/100079, WO 2016/000619, WO 2014/022758, WO 2014/055897, WO 2015/061668, WO 2013/079174, WO 2012/145493, WO 2015/112805, WO 2015/109124, WO 2015/195163, US 8,168,179, US 8,552,154, US 8,460,927, and US 9,175,082, incorporated by reference in their entirety.

10 In one embodiment, the anti-PD-L1 antibody is an antibody that competes for binding with, and/or binds to the same epitope on PD-L1 as, one of the anti-PD-L1 antibodies described herein.

LAG-3 Inhibitors

15 In one aspect of the invention, the IL-1 β inhibitor or a functional fragment thereof is administered together with a LAG-3 inhibitor. In some embodiments, the LAG-3 inhibitor is chosen from LAG525 (Novartis), BMS-986016 (Bristol-Myers Squibb), TSR-033 (Tesaro), IMP731 or GSK2831781 and IMP761 (Prima BioMed).

In one embodiment, the LAG-3 inhibitor is an anti-LAG-3 antibody molecule. In one embodiment, the LAG-3 inhibitor is an anti-LAG-3 antibody molecule as disclosed in US 20 2015/0259420, published on September 17, 2015, entitled "Antibody Molecules to LAG-3 and Uses Thereof," incorporated by reference in its entirety.

In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 706 and a VL comprising the amino acid sequence of SEQ ID NO: 718. In one embodiment, the anti-LAG-3 antibody molecule comprises a VH 25 comprising the amino acid sequence of SEQ ID NO: 724 and a VL comprising the amino acid sequence of SEQ ID NO: 730.

Table C. Amino acid and nucleotide sequences of exemplary anti-LAG-3 antibody molecules

BAP050-Clone I HC		
SEQ ID NO: 706	VH	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQAR GQRLEWIGWINTDTGEPTYADDFKGRFVFSLDTSVSTAYLQISS LKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-Clone I LC		

SEQ ID NO: 718	VL	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYLQKPGQSP QLLIYYTSTLHLGVPSRFSGSGSGTEFTLTISLQPDDFATYYCQ QYYNLPWTFGQGTKVEIK
BAP050-Clone J HC		
SEQ ID NO: 724	VH	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQAP GQGLEWMGWINTDTGEPTYADDFKGRFVSLDTSVSTAYLQI SSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTITVTS S
BAP050-Clone J LC		
SEQ ID NO: 730	VL	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYQQKPGKAP KLLIYYTSTLHLGIPPRFSGSGYGTDFLTINNIESEDAAYYFCQ QYYNLPWTFGQGTKVEIK

In one embodiment, the anti-LAG-3 antibody molecule is BMS-986016 (Bristol-Myers Squibb), also known as BMS986016. BMS-986016 and other anti-LAG-3 antibodies are disclosed in WO 2015/116539 and US 9,505,839, incorporated by reference in their entirety. In one embodiment, the anti-LAG-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of BMS-986016, *e.g.*, as disclosed in Table D.

In one embodiment, the anti-LAG-3 antibody molecule is IMP731 or GSK2831781 (GSK and Prima BioMed). IMP731 and other anti-LAG-3 antibodies are disclosed in WO 2008/132601 and US 9,244,059, incorporated by reference in their entirety. In one embodiment, the anti-LAG-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of IMP731, *e.g.*, as disclosed in Table D.

Further known anti-LAG-3 antibodies include those described, *e.g.*, in WO 2008/132601, WO 2010/019570, WO 2014/140180, WO 2015/116539, WO 2015/200119, WO 2016/028672, US 9,244,059, US 9,505,839, incorporated by reference in their entirety.

In one embodiment, the anti-LAG-3 antibody is an antibody that competes for binding with, and/or binds to the same epitope on LAG-3 as, one of the anti-LAG-3 antibodies described herein.

In one embodiment, the anti-LAG-3 inhibitor is a soluble LAG-3 protein, *e.g.*, IMP321 (Prima BioMed), *e.g.*, as disclosed in WO 2009/044273, incorporated by reference in its entirety.

Table D. Amino acid sequences of exemplary anti-LAG-3 antibody molecules

BMS-986016		
SEQ ID NO: 762	Heavy chain	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSDYYWNWIRQPPGKG LEWIGEINHRGSTNSNPSLKSRLVTLSDTSKNQFSLKLSVTAADTA VYYCAFGYSDYEYNWFDPWGQGTTLTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVTVPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPPCPP CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRL TVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGK
SEQ ID NO: 763	Light chain	EIVLTQSPATLSLSPGERATLSCRASQSISSYLAWYQQKPGQAPRL IYDASNRATGIPARFSGSGGTDFTLTISSLEPEDFAVYYCQQRSNW PLTFGQGTNLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDSSTYLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC
IMP731		
SEQ ID NO: 764	Heavy chain	QVQLKESGPGLVAPSQSLITCTVSGFSLTAYGVNWRQPPGKGLE WLGMIWDDGSTDYNSALKSRLSISKDNSKSQVFLKMNSLQTDDTA RYYCAREGDVAFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP CPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGK
SEQ ID NO: 765	Light chain	DIVMTQSPSSLAVSVGQKVTMSCKSSQSLNLSNQNKYLAAYQQ KPGQSPKLLVYFASTRDSGVDPDRFIGSGSGTDFTLTISSVQAEDLAD YFCLQHFGTPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYLS TLTSLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

TIM-3 Inhibitors

In one aspect of the invention, the IL-1 β inhibitor or a functional fragment thereof is administered together with a TIM-3 inhibitor. In some embodiments, the TIM-3 inhibitor is MBG453 (Novartis) or TSR-022 (Tesar). Historically MBG453 is often misspelt as MGB453.

In one embodiment, the TIM-3 inhibitor is an anti-TIM-3 antibody molecule. In one embodiment, the TIM-3 inhibitor is an anti-TIM-3 antibody molecule as disclosed in US 2015/0218274, published on August 6, 2015, entitled “Antibody Molecules to TIM-3 and Uses Thereof,” incorporated by reference in its entirety.

In one embodiment, the anti-TIM-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 806 and a VL comprising the amino acid sequence of SEQ ID NO: 816. In one embodiment, the anti-TIM-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 822 and a VL comprising the amino acid sequence of SEQ ID NO: 826.

The antibody molecules described herein can be made by vectors, host cells, and methods described in US 2015/0218274, incorporated by reference in its entirety.

Table E. Amino acid and nucleotide sequences of exemplary anti-TIM-3 antibody molecules

ABTIM3-hum11		
SEQ ID NO: 806	VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVRQA PGQGLEWMGDIYPGNGDTSYNQKFKGRVTITADKSTSTVY MELSSLRSEDTAVYYCARVGGAFPM DYWGQGT TVTVSS
SEQ ID NO: 816	VL	AIQLTQSPSSLSASVGDRTITCRASESVEYYGTSMLQWYQQ KPGKAPKLLIYAASNVESGVPSRFSGSGSGTDFTLTISLQPE DFATYFCQQSRKDPSTFGGGTKVEIK
ABTIM3-hum03		
SEQ ID NO: 822	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQ APGQGLEWIGDIYPGQGDTSYNQKFKGRATMTADKSTSTVY MELSSLRSEDTAVYYCARVGGAFPM DYWGQGT LTVTVSS
SEQ ID NO: 826	VL	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSMLQWYQ QKPGQPPKLLIYAASNVESGVDPDRFSGSGSGTDFTLTISLQA EDVAVYYCQQSRKDPSTFGGGTKVEIK

In one embodiment, the anti-TIM-3 antibody molecule is TSR-022 (AnaptysBio/Tesaro). In one embodiment, the anti-TIM-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of TSR-022. In one embodiment, the anti-TIM-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of APE5137 or APE5121, *e.g.*, as disclosed in Table F. APE5137, APE5121, and other anti-TIM-3 antibodies are disclosed in WO 2016/161270, incorporated by reference in its entirety.

In one embodiment, the anti-TIM-3 antibody molecule is the antibody clone F38-2E2. In one embodiment, the anti-TIM-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of F38-2E2.

Further known anti-TIM-3 antibodies include those described, *e.g.*, in WO 2016/111947, WO 2016/071448, WO 2016/144803, US 8,552,156, US 8,841,418, and US 9,163,087, incorporated by reference in their entirety.

In one embodiment, the anti-TIM-3 antibody is an antibody that competes for binding with, and/or binds to the same epitope on TIM-3 as, one of the anti-TIM-3 antibodies described herein.

10 **Table F.** Amino acid sequences of exemplary anti-TIM-3 antibody molecules

APE5137		
SEQ ID NO: 830	VH	EVQLLESGGGLVQPGGSLRLSCAAASGFTFSSYDMSWVRQAPGKGLDW VSTISGGGTYYQDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYC ASMDYWGQGTTVTVSSA
SEQ ID NO: 831	VL	DIQMTQSPSSLSASVGDRVTITCRASQSIRRYLNWYHQKPGKAPKLLIYG ASTLQSGVPSRFSGSGSGTDFTLTISLQPEDFAVYYCQQSHSAPLTFGG GTKVEIKR
APE5121		
SEQ ID NO: 832	VH	EVQVLESGGGLVQPGGSLRLYCVASGFTFSGSYAMSWVRQAPGKGLE WVSAISGSGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVY YCAKKYYVGPADYWGQGLTVTVSSG
SEQ ID NO: 833	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQHKPGQP PKLLIYWASTRESGVPRFSGSGSGTDFTLTISLQAEDVAVYYCQQYYYS SPLTFGGGTKIEVK

GITR Agonists

In one aspect of the invention, the IL-1 β inhibitor or a functional fragment thereof is administered together with a GITR agonist. In some embodiments, the GITR agonist is GWN323 (NVS), BMS-986156, MK-4166 or MK-1248 (Merck), TRX518 (Leap Therapeutics), INCAGN1876 (Incyte/Agenus), AMG 228 (Amgen) or INBRX-110 (Inhibrx).

In one embodiment, the GITR agonist is an anti-GITR antibody molecule. In one embodiment, the GITR agonist is an anti-GITR antibody molecule as described in WO 2016/057846, published on April 14, 2016, entitled “Compositions and Methods of Use for Augmented Immune Response and Cancer Therapy,” incorporated by reference in its entirety.

In one embodiment, the anti-GITR antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 901 and a VL comprising the amino acid sequence of SEQ ID NO: 902.

Table G: Amino acid and nucleotide sequences of exemplary anti-GITR antibody molecule

MAB7		
SEQ ID NO: 901	VH	EVQLVESGGGLVQSGGSLRLSCAASGFLSSYGVDWVRQA PGKGLEWVGVIWGGGGTYAYASSLMGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARHAYGHDGGFAMDYWGQGT LVTVSS
SEQ ID NO: 902	VL	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQQRPG QAPRLLIYGASNRATGIPARFSGSGSGTDFTLTISRLE PEDFAVYYCGQSYSPFTFGQGTKLEIK

In one embodiment, the anti-GITR antibody molecule is BMS-986156 (Bristol-Myers
5 Squibb), also known as BMS 986156 or BMS986156. BMS-986156 and other anti-GITR
antibodies are disclosed, *e.g.*, in US 9,228,016 and WO 2016/196792, incorporated by
reference in their entirety. In one embodiment, the anti-GITR antibody molecule comprises
one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy
chain or light chain variable region sequence, or the heavy chain or light chain sequence of
10 BMS-986156, *e.g.*, as disclosed in Table H.

In one embodiment, the anti-GITR antibody molecule is MK-4166 or MK-1248
(Merck). MK-4166, MK-1248, and other anti-GITR antibodies are disclosed, *e.g.*, in US
8,709,424, WO 2011/028683, WO 2015/026684, and Mahne *et al.* *Cancer Res.* 2017;
77(5):1108-1118, incorporated by reference in their entirety.

15 In one embodiment, the anti-GITR antibody molecule is TRX518 (Leap
Therapeutics). TRX518 and other anti-GITR antibodies are disclosed, *e.g.*, in US 7,812,135,
US 8,388,967, US 9,028,823, WO 2006/105021, and Ponte J *et al.* (2010) *Clinical
Immunology*; 135:S96, incorporated by reference in their entirety.

In one embodiment, the anti-GITR antibody molecule is INCAGN1876
20 (Incyte/Agenus). INCAGN1876 and other anti-GITR antibodies are disclosed, *e.g.*, in US
2015/0368349 and WO 2015/184099, incorporated by reference in their entirety.

In one embodiment, the anti-GITR antibody molecule is AMG 228 (Amgen). AMG
228 and other anti-GITR antibodies are disclosed, *e.g.*, in US 9,464,139 and WO
2015/031667, incorporated by reference in their entirety.

25 In one embodiment, the anti-GITR antibody molecule is INBRX-110 (Inhibrx).
INBRX-110 and other anti-GITR antibodies are disclosed, *e.g.*, in US 2017/0022284 and WO
2017/015623, incorporated by reference in their entirety.

In one embodiment, the GITR agonist (*e.g.*, a fusion protein) is MEDI 1873
(MedImmune), also known as MEDI1873. MEDI 1873 and other GITR agonists are

disclosed, *e.g.*, in US 2017/0073386, WO 2017/025610, and Ross *et al.* *Cancer Res* 2016; 76(14 Suppl): Abstract nr 561, incorporated by reference in their entirety. In one embodiment, the GITR agonist comprises one or more of an IgG Fc domain, a functional multimerization domain, and a receptor binding domain of a glucocorticoid-induced TNF receptor ligand (GITRL) of MEDI 1873.

Further known GITR agonists (*e.g.*, anti-GITR antibodies) include those described, *e.g.*, in WO 2016/054638, incorporated by reference in its entirety.

In one embodiment, the anti-GITR antibody is an antibody that competes for binding with, and/or binds to the same epitope on GITR as, one of the anti-GITR antibodies described herein.

In one embodiment, the GITR agonist is a peptide that activates the GITR signaling pathway. In one embodiment, the GITR agonist is an immunoadhesin binding fragment (*e.g.*, an immunoadhesin binding fragment comprising an extracellular or GITR binding portion of GITRL) fused to a constant region (*e.g.*, an Fc region of an immunoglobulin sequence).

Table H: Amino acid sequence of exemplary anti-GITR antibody molecules

BMS-986156		
SEQ ID NO: 920	VH	QVQLVESGGGVVQPGRSLRLSCAASGFTSSYGMHWVRQAPGK GLEWVAVIWYEGSNKYYADSVKGRFTISRDN SKNTLYLQMNSL RAEDTAVYYCARGGSMVRGDYYYGMDVWGQGT TVTVSS
SEQ ID NO: 921	VL	AIQLTQSPSSLSASVGDRTITCRASQGISSALAWYQQKPGKAPK LLIYDASSLESGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQF NSYPYTFGQGTKLEIK

IL15/IL-15Ra complexes

In one aspect of the invention, the IL-1 β inhibitor or a functional fragment thereof is administered together with an IL-15/IL-15Ra complex. In some embodiments, the IL-15/IL-15Ra complex is chosen from NIZ985 (Novartis), ATL-803 (Altor) or CYP0150 (Cytune).

In one embodiment, the IL-15/IL-15Ra complex comprises human IL-15 complexed with a soluble form of human IL-15Ra. The complex may comprise IL-15 covalently or noncovalently bound to a soluble form of IL-15Ra. In a particular embodiment, the human IL-15 is noncovalently bonded to a soluble form of IL-15Ra. In a particular embodiment, the human IL-15 of the composition comprises an amino acid sequence of SEQ ID NO: 1001 in Table I and the soluble form of human IL-15Ra comprises an amino acid sequence of SEQ ID NO: 1002 in Table I, as described in WO 2014/066527, incorporated by reference in its

entirety. The molecules described herein can be made by vectors, host cells, and methods described in WO 2007/084342, incorporated by reference in its entirety.

Table I. Amino acid and nucleotide sequences of exemplary IL-15/IL-15Ra complexes

NIZ985		
SEQ ID NO: 1001	Human IL-15	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL LQVISLESGDASIHTVENLILANNSLSSNGNVTESGCKECEEELEEK NIKEFLQSFVHIVQMFINTS
SEQ ID NO: 1002	Human Soluble IL-15Ra	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVL NKATNVAHWTTPSLKCIRDPAHVHQRPAAPPSTVTTAGVTPQPESLS PSGKEPAASSPSSNNTAATTAAIVPGSQLMPSPSTGTTEISSHESS HGTPSQTTAKNWELTASASHQPPGVYPQG

In one embodiment, the IL-15/IL-15Ra complex is ALT-803, an IL-15/IL-15Ra Fc fusion protein (IL-15N72D:IL-15RaSu/Fc soluble complex). ALT-803 is disclosed in WO 2008/143794, incorporated by reference in its entirety. In one embodiment, the IL-15/IL-15Ra Fc fusion protein comprises the sequences as disclosed in Table J.

In one embodiment, the IL-15/IL-15Ra complex comprises IL-15 fused to the sushi domain of IL-15Ra (CYP0150, Cytune). The sushi domain of IL-15Ra refers to a domain beginning at the first cysteine residue after the signal peptide of IL-15Ra, and ending at the fourth cysteine residue after said signal peptide. The complex of IL-15 fused to the sushi domain of IL-15Ra is disclosed in WO 2007/04606 and WO 2012/175222, incorporated by reference in their entirety. In one embodiment, the IL-15/IL-15Ra sushi domain fusion comprises the sequences as disclosed in Table J.

Table J. Amino acid sequences of other exemplary IL-15/IL-15Ra complexes

ALT-803 (Altor)		
SEQ ID NO: 1003	IL-15N72D	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLLLELQVISLESGDASIHTVENLILANDSLSSNGN VTESGCKECEEELEEKNIKEFLQSFVHIVQMFINTS
SEQ ID NO: 1004	IL-15RaSu/ Fc	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVL NKATNVAHWTTPSLKCIREPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSV MHEALHNHYTQKSLSLSPGK
IL-15 / IL-15Ra sushi domain fusion (Cytune)		
SEQ ID NO:1005	Human IL-15	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL LQVISLESGDASIHTVENLILANNSLSSNGNVTESGCKECEEXK NIKEFLQSFVHIVQMFINTS Where X is E or K

SEQ ID NO:1006	Human IL- 15Ra sushi and hinge domains	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVL NKATNVAHWTTPSLKCIRDPALVHQRAPP
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CTLA-4 Inhibitors

In one aspect of the invention, the IL-1 β inhibitor or a functional fragment thereof is administered together with an inhibitor of CTLA-4. In some embodiments, the CTLA-4 inhibitor is an anti-CTLA-4 antibody or fragment thereof. Exemplary anti-CTLA-4 antibodies include Tremelimumab (formerly ticilimumab, CP-675,206); and Ipilimumab (MDX-010, Yervoy®).

In one embodiment, the present invention provides an IL-1 β antibody or a functional fragment thereof (e.g., canakinumab or gevokizumab) for use in the treatment of cancers having at least partial inflammatory bases, e.g., MSI-H cancer, wherein said IL-1 β antibody or a functional fragment thereof is administered in combination with one or more chemotherapeutic agent, wherein said one or more chemotherapeutic agent is a check point inhibitor, preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, PDR-001(spartalizumab) and Ipilimumab. In one embodiment the one or more chemotherapeutic agent is a PD-1 or PD-L1 inhibitor, preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, PDR-001(spartalizumab), further preferably pembrolizumab. In one further embodiment, the IL-1 β antibody or a functional fragment thereof is administered at the same time of the PD-1 or PD-L1 inhibitor.

In one embodiment the cancer of the patient has high PD-L1 expression. Typically high PD-L1 expression is defined as Tumor Proportion Score (TPS) $\geq$ about 50%, as determined by an FDA-approved test. In one embodiment the cancer of the patient has TPS $\geq$ about 1% as determined by an FDA-approved test. In one embodiment the cancer of the patient has TPS between about 1% to about 49% as determined by an FDA-approved test. In one embodiment the cancer of the patient has TPS $\geq$ about 25%, suitably between about 25% to about 49% as determined by an FDA-approved test.

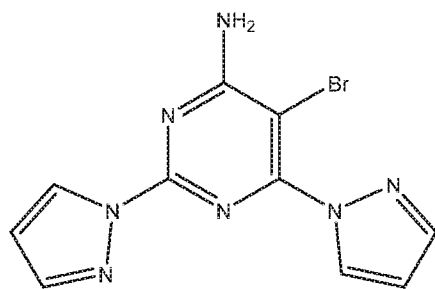
In one embodiment the one or more therapeutic agents is alpelisib or a pharmaceutical salt thereof. Alpelisib is administered at a therapeutically effective amount of about about 300 mg per day. In one embodiment DRUG of the invention, suitable canakinumab or gevokizumab,

is used in combination with alpelisib in the treatment of cancer, e.g., cancer having at least partial inflammatory basis, e.g., a MSI-H cancer.

In one embodiment the one or more therapeutic agents is lacnotuzumab. In one embodiment the one or more therapeutic agents further include a check point inhibitor, suitably a check point inhibitor, suitably selected from pembrolizumab, nivolumab, spartalizumab, atezolizumab, avelumab, ipilimumab, durvalumab. In one embodiment the cancer is MSI-H cancer. Lacnotuzumab is administered at a dose of 3 mg/kg, 5 mg/kg, 7.5 mg/kg or 10 mg/kg body weight, preferably every 3 weeks or every 4 weeks.

In one embodiment, the one or more chemotherapeutic agents is midostaurin (Rydapt®). In one embodiment the one or more chemotherapeutic agents further include cytarabine and daunorubicin, preferably in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. In one embodiment, midostaurin is administered 50 mg orally twice daily with food. In a preferred embodiment, midostaurin is administered 50 mg orally twice daily with food on Days 8 to 21 of each cycle of induction with cytarabine and daunorubicin and on Days 8 to 21 of each cycle of consolidation with high-dose cytarabine. In one embodiment, canakinumab is administered 200 mg every 4 weeks, in combination with ribociclib. In one embodiment, gevokizumab is administered 30-120 mg every 4 weeks, in combination with ribociclib.

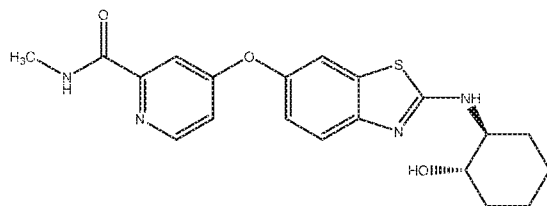
In one embodiment, the one or more chemotherapeutic agents is 5-bromo-2,6-di-(1H-pyrazol-1-yl)pyrimidine-4-amine or a pharmaceutically acceptable salt thereof (the compound described in Example 1 in the PCT publication WO 2011/121418, which is hereby incorporated by reference in its entirety. In one embodiment, the cancer is a MSI-H cancer.



5-bromo-2,6-di-(1H-pyrazol-1-yl)pyrimidine-4-amine

In one embodiment, the one or more chemotherapeutic agents is 4-[2-((1R,2R)-2-Hydroxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide or

a pharmaceutically acceptable salt thereof (compound 157 in the PCT publication WO 2007/121484 A2, which is hereby incorporated by reference in its entirety). In one embodiment, the cancer is a MSI-H cancer.



4-[2-((1R,2R)-2-Hydroxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

- 5 In one embodiment, the one or more therapeutic agents is a TGF-beta inhibitor, preferably NIS793.

The heavy chain variable region of NIS793 has the amino acid sequence of:

QVQLVQSGAEVKKPGSSVKV SCKASGGTFSSY AISWVRQAPGQGLEWMGGII
PIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGLWEVRALPSV

- 10 YWGQGTLLTVSS (SEQ ID NO: 6 in WO 2012/167143). The light chain variable region of NIS793 has the amino acid sequence of:

SYELTQPPSVSVAPGQTARITCGANDIGSKSVHWYQQKAGQAPVLVVSEDIIR
PSGIPERISGSNSGNTATLTISRVEAGDEADYYCQVWDRSDQYVFGTGTKVTVLG
(SEQ ID NO: 8 in WO 2012/167143).

- 15 NIS793 is a fully human monoclonal antibody that specifically binds and neutralizes TGF-beta 1 and 2 ligands. In one embodiment, the one or more therapeutic agents further includes one PD-1 or PD-L1 inhibitor, suitably selected from selected from pembrolizumab, nivolumab, spartalizumab, atezolizumab, avelumab, ipilimumab, durvalumab. suitably pembrolizumab, suitably spartalizumab. In one embodiment, the cancer is MSI-H cancer.

- 20 In one embodiment, the one or more chemotherapeutic agents is ribociclib or any pharmaceutical salt thereof. In one embodiment, the cancer is MSI-H cancer.

In one embodiment, ribociclib is administered at a dose of 600 mg daily for 21 consecutive days followed by 7 days off treatment resulting a 28-day full cycle. In one embodiment, canakinumab is administered 200 mg every 4 weeks, in combination with

ribociclib. In one embodiment, gevokizumab is administered 30-120 mg every 4 weeks, in combination with ribociclib.

The term “in combination with” is understood as the two or more drugs are administered subsequently or simultaneously. Alternatively, the term “in combination with” is understood that two or more drugs are administered in the manner that the effective therapeutic concentration of the drugs are expected to be overlapping for a majority of the period of time within the patient’s body. The DRUG of the invention and one or more combination partner (e.g., another drug, also referred to as “therapeutic agent” or “co-agent”) may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative, e.g., synergistic effect. The terms “co-administration” or “combined administration” or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (e.g., a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The drug administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient and the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein. The latter also applies to cocktail therapy, e.g., the administration of three or more active ingredients.

Administration, formulations and devices

Canakinumab can be administered intravenously or preferably subcutaneously. Both administration routes are applicable to each and every canakinumab related embodiments disclosed in this application unless in embodiments wherein the administration route is specified.

Gevokizumab can be administered subcutaneously or preferably intravenously. Both administration routes are applicable to each and every gevokizumab related embodiments disclosed in this application unless in embodiments wherein the administration route is specified.

Canakinumab can be prepared as a medicament in a lyophilized form for reconstitution. In one embodiment canakinumab is provided in the form of lyophilized form for reconstitution

containing at least about 200mg drug per vial, preferably not more than about 250mg, preferably not more than about 225mg in one vial.

In one aspect the present invention provides canakinumab or gevokizumab for use in treating and/or preventing a cancer in a patient in need thereof, comprising administering a therapeutically effective amount to the patient, wherein the cancer has at least a partial inflammatory basis, e.g., a MSI-H cancer, and wherein canakinumab or gevokizumab is administered by a prefilled syringe or by an auto-injector. Preferably the prefilled syringe or the auto-injector contains the full amount of therapeutically effective amount of the drug. Preferably the prefilled syringe or the auto-injector contains 200mg of canakinumab.

Efficacy and safety

Due to its good safety profile, canakinumab or gevokizumab can be administered to a patient for a long period of time, providing and maintaining the benefit of suppressing IL-1 β mediated inflammation. Furthermore due to its anti-cancer effect, either used in monotherapy or in combination with one or more therapeutic agents, patients life can be extended, including but not limited to extended duration of DFS, PFS, OS, hazard rate reduction, than without the Treatment of the Invention. The term "Treatment of the Invention", as used in the this application, refers to DRUG of the invention, suitably canakinumab or gevokizumab, administered according to the dosing regimen, as taught in this application. Preferably the clinical efficacy is achieved at a dose of about 200mg canakinumab administered about every 3 weeks or about monthly, preferably for at least about 6 months, preferably at least about 12 months, preferably at least about 24 months, preferably up to about 2 years, preferably up to about 3 years. Preferably the results is achieved at a dose of about 30mg-120mg gevokizumab administered about every 3 weeks or about monthly, preferably for at least about 6 months, preferably at least about 12 months, preferably at least about 24 months, preferably up to about 2 years, preferably up to about 3 years. In one embodiment Treatment of the Invention is the sole treatment. In one embodiment Treatment of the Invention is added on top of the SoC treatment for the cancer indication. While the SoC treatment evolves with time, the SoC treatment as used here should be understood as not including DRUG of the invention.

Thus in one aspect the present invention provides an IL-1 β binding antibody or functional fragment thereof, suitably canakinumab or gevokizumab, for use in the treatment and/or prevention of cancer, e.g., cancer that has at least a partial inflammatory basis, e.g., a MSI-H cancer, in a patient, wherein a therapeutically effective amount of an IL-1 β binding

antibody or a functional fragment thereof is administered in the patient for at least about 6 months, preferably at least v12 months, preferably at least v24 months. In one embodiment the cancer excludes lung cancer, especially excludes NSCLC, especially excludes post-surgery NSCLC, in which the cancer has been resect, suitably not longer than about 2 months, preferably not longer than about one month.

In one aspect, the present invention provides an IL-1 β binding antibody or functional fragment thereof, suitably canakinumab or gevokizumab, for use in the treatment of cancer, e.g., cancer that has at least a partial inflammatory basis, e.g., a MSI-H cancer, in a patient, wherein the hazard rate of cancer mortality of the patient is reduced by at least about 10%, at least about 20%, at least about 30%, at least about 40% or at least about 50%, preferably compared to not receiving Treatment of the Invention.

The term “not receiving Treatment of the Invention”, as used throughout the application, include patient did not receive any drug at all and patient received only treatment, considered as SoC at the time, without the DRUG of the invention. As a skilled person would understand, the clinical efficacy is typically not tested within the same patient, receiving or not receiving the Treatment of the Invention, rather tested in clinical trial settings with treatment group and placebo group.

In one embodiment the overall survival (OS, defined as the time from the date of randomization to the date of death due to any cause) in the patient is at least about one month, at least about 3 months, at least about 6 months, at least about 12 months longer than not receiving Treatment of the Invention. In one embodiment the OS is at least about 12 months, preferably at least v24 months, longer in the adjuvant treatment setting. In one embodiment the OS is at least about 4 months, preferably at least about 6 months, at least about 12 months longer in the first line treatment setting. In one embodiment the OS is at least about one month, at least about 3 months, preferably at least about 6 months longer in the 2nd/3rd line treatment setting.

In one embodiment the overall survival in the patient receiving Treatment of the Invention is at least about 2 years, at least about 3 years, at least about 5 years, at least about 8 years, at least about 10 years in the adjuvant treatment setting. In one embodiment the overall survival in the patient receiving Treatment of the Invention is at least about 6 month, at least about one year, at least about 3 years in the first line treatment setting. In one embodiment the overall survival in the patient receiving Treatment of the Invention is at least about 3 month, at least about 6 months, at least about one year in the 2nd/3rd line treatment setting.

In one embodiment the progression free survival (PFS) period of the patient receiving

Treatment of the Invention is extended by at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, at least about 12 months, preferably compared to not receiving Treatment of the Invention. In one embodiment PFS is extended by at least about 6 months, preferably at least about 12 months in the first line treatment settings. In one
5 embodiment PFS is extended by at least about one month, at least about 3 months, at least about 6 months in the second line treatment settings.

In one embodiment the patient receiving Treatment of the Invention has at least about 3 months, at least about 6 months, at least about 12 months, or at least about 24 months progression free survival.

10 Normally clinical efficacy, including but not limited to DFS, PFS, HR reduction, OS, can be demonstrated in clinical trials comparing treatment group and placebo group. In placebo group patients receive no drug at all or receive SoC treatment. In the treatment group patients receive DRUG of the invention either as monotherapy or added to the SoC treatment. Alternatively in placebo group patient receives SoC treatment and in the treatment group
15 patients receive DRUG of the invention.

Even though the clinical outcome, such as duration of DFS or the HR reduction of cancer mortality, is described as a number based on statistical analysis of a clinical trial, one of ordinary skill would readily extrapolate these statistics to treatments for an individual patient, as claimed, since it is expected the DRUG of the invention would achieve similar clinical
20 outcome in a portion of the individual patients receiving Treatment of the Invention, for example in about 95% of the patients, when clinical trials have demonstrated statistical significance ($p \leq 0.05$); or for example in about 50% of the patients, when clinical trials have provided mean value, such as mean PFS is about 24 months

IL-1 β blockade could affect patients' immune system in combating infection. Thus in
25 one aspect the present invention provides an IL-1 β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for use in the treatment and/or prevention of cancer, e.g., cancer having at least a partial inflammatory basis, e.g., a MSI-H cancer, and wherein the patient is not at high risk of developing serious infection due to the Treatment of the Invention. Patient would be at high risk of developing serious infection due to the Treatment
30 of the Invention in the following, but not limited to, the following situations: (a) Patient have an active infection requiring medical intervention. The term "active infection requiring medical intervention" is understood as the patient is currently taking or have been taking or have just finished taken for less than about one month or less than about two weeks, any anti-viral and/or

any anti-bacterial medicines; (b) Patient have latent tuberculosis and/or a history of tuberculosis.

To manage the inhibition of the immune system by IL-1 β blockade, it is cautioned that the IL-1 β binding antibody or a functional fragment thereof is not administered concomitantly with a TNF inhibitor. Preferably a TNF inhibitor is selected from a group consisting of Enbrel® (etanercept), Humira® (adalimumab), Remicade® (infliximab), Simponi® (golimumab), and Cimzia® (certolizumab pegol). It is also cautioned that the IL-1 β binding antibody or a functional fragment thereof is not administered concomitantly with another IL-1 blocker, wherein preferably said IL-1 blocker is selected from a group consisting of Kineret® (anakinra) and Arcalyst® (rilonacept). Furthermore it is only one IL-1 β binding antibody or a functional fragment thereof is administered in the treatment/prevention of cancer. For example canakinumab is not administered in combination with gevokizumab.

When canakinumab is administered into patients, it is likely that some patients will develop anti-canakinumab antibody (anti-drug antibody, ADA), which needs to be monitored for safety and efficacy reasons. In one aspect the present invention provides canakinumab for use in the treatment and/or preventing cancer, e.g., cancer having at least a partial inflammatory basis, e.g., a MSI-H cancer, wherein the chance of the patient develops ADA is less than about 1%, less than about 0.7%, less than about 0.5%, or less than about 0.4%. In one embodiment the antibody is detected by the method as described in Example 12. In one embodiment the antibody is detection is performed at about 3 months, at about 6 month or at about 12 months from the first administration of canakinumab.

Exemplar of MSI-H cancers to be treated according to the present invention

In one aspect, the present invention provides an IL-1beta binding antibody or a functional fragment thereof, suitably canakinumab or suitably gevokizumab, alone or in combination with one or more therapeutic agents, for use in the treatment of cancer, e.g., cancer having at least partial inflammatory basis, wherein the cancer is MSI cancer. In a preferred embodiment, the MSI cancer is a MSI-H or mismatch repair deficient (dMMR) cancer, preferably solid tumor. In another embodiment, the MSI cancer is a MSI-L cancer.

In one embodiment, the present invention provides DRUG of the invention, preferably canakinumab or gevokizumab, for use in the treatment of MSI-H or dMMR cancer, wherein DRUG of the invention is administered in combination with one or more therapies or one or

more therapeutic agents, e.g., a chemotherapeutic agent, a targeted therapy agent, a cell-based therapy, a checkpoint inhibitor or a combination of these agents.

In one embodiment, the one or more therapeutic agents is a chemotherapeutic agent.

In one embodiment the one or more therapeutic agents is the standard of care (SoC) agent for MSI-H cancer. In a preferred embodiment, the one or more therapeutic agent is pembrolizumab. In one embodiment, the cancer is unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, in an adult or pediatric patient, preferably wherein the cancer has progressed following prior treatment. In one embodiment, said patient has no satisfactory alternative treatment options.

In a preferred embodiment, the one or more therapeutic agent is pembrolizumab. In one embodiment, the cancer is MSI-H or dMMR colorectal cancer, preferably wherein said cancer has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

In one embodiment, pembrolizumab is administered about 200 mg about every 3 weeks, wherein the patient is an adult. In one embodiment, pembrolizumab is administered about 2 mg/kg (up to about 200 mg) about every 3 weeks, wherein the patient is pediatric (i.e. a child).

In one embodiment, the present invention provides DRUG of the invention, preferably canakinumab or gevokizumab, for use in the prevention of recurrence or relapse of a MSI-H cancer, which has been surgically removed (adjuvant treatment). In one embodiment, DRUG of the invention is used as monotherapy in the adjuvant treatment. This is preferred due to the good safety profile of canakinumab or gevokizumab. In one embodiment, DRUG of the invention is used, in combination with one or more therapies or therapeutic agents, in the adjuvant treatment.

In one embodiment DRUG of the invention is used as monotherapy in the MSI-H cancer adjuvant treatment after the patient has received the standard of care treatment.

In one embodiment, the treatment, e.g., the adjuvant treatment, the first line treatment or the 2nd or 3rd line treatment continues until disease progress, preferably according to RECIST 1.1.

EXAMPLES

The Example below is set forth to aid in the understanding of the invention but is not intended, and should not be construed, to limit its scope in any way.

EXAMPLE 1

Tumor-derived IL-1 β induces differential tumor promoting mechanisms in metastasis

Materials and Methods

5 Cell culture

Human breast cancer MDA-MB-231-Luc2-TdTomato (Calliper Life Sciences, Manchester UK), MDA-MB-231 (parental) MCF7, T47D (European Collection of Authenticated Cell Cultures (ECACC)), MDA-MB-231-IV (Nutter et al., 2014) as well as bone marrow HS5 (ECACC) and human primary osteoblasts OB1 were cultured in DMEM + 10% FCS (Gibco, Invitrogen, Paisley, UK). All cell lines were cultured in a humidified incubator under 5% CO₂ and used at low passage >20.

Transfection of tumor cells

Human MDA-MB-231, MCF 7 and T47D cells were stably transfected to overexpress genes *IL1B* or *IL1R1* using plasmid DNA purified from competent *E.Coli* that have been transduced with an ORF plasmid containing human *IL1B* or *IL1R1* (Accession numbers NM_000576 and NM_000877.2, respectively) with a C-terminal GFP tag (OriGene Technologies Inc. Rockville MD). Plasmid DNA purification was performed using a PureLink™ HiPure Plasmid Miniprep Kit (ThermoFisher) and DNA quantified by UV spectroscopy before being introduced into human cells with the aid of Lipofectamine II (ThermoFisher). Control cells were transfected with DNA isolated from the same plasmid without IL-1B or IL-1R1 encoding sequences.

In vitro studies

In vitro studies were carried out with and without addition of 0-5 ng/ml recombinant IL-1 β (R&D systems, Wiesbaden, Germany) +/- 50 μ M IL-1Ra (Amgen, Cambridge, UK). Cells were transferred into fresh media with 10% or 1% FCS. Cell proliferation was monitored every 24h for up to 120h by manual cell counting using a 1/400 mm² hemocytometer (Hawkley, Lancing UK) or over a 72h period using an Xcelligence RTCA DP Instrument (Acea Biosciences, Inc). Tumor cell invasion was assessed using 6 mm transwell plates with an 8 μ m pore size (Corning Inc) with or without basement membrane (20% Matrigel; Invitrogen). Tumor cells were seeded into the inner chamber at a density of 2.5×10^5 for parental as well as MDA-MB-231 derivatives and 5×10^5 for T47D in DMEM + 1% FCS and 5×10^5 OB1 osteoblast cells supplemented with 5% FCS were added to the outer chamber. Cells were removed from the top surface of the membrane 24h and 48h after seeding and cells that had invaded through

the pores were stained with hematoxylin and eosin (H&E) before being imaged on a Leica DM7900 light microscope and manually counted.

Migration of cells was investigated by analyzing wound closure: Cells were seeded onto 0.2% gelatine in 6-well tissue culture plates (Costar; Corning, Inc) and, once confluent, 10 µg/ml mitomycin C was added to inhibit cell proliferation and a 50 µm scratch made across the monolayer. The percentage of wound closure was measured at 24h and 48h using a CTR7000 inverted microscope and LAS-AF v2.1.1 software (Leica Applications Suite; Leica Microsystems, Wetzlar, Germany). All proliferation, invasion and migration experiments were repeated using the Xcelligence RTCA DP instrument and RCTA Software (Acea Biosystems, Inc).

For co-culture studies with human bone 5x10⁵ MDA-MB-231 or T47D cells were seeded onto tissue culture plastic or into 0.5cm³ human bone discs for 24h. Media was removed and analysed for concentration of IL-1β by ELISA. For co-culture with HS5 or OB1 cells, 1x10⁵ MDA-MB-231 or T47D cells were cultured onto plastic along with 2x10⁵ HS5 or OB1 cells. Cells were sorted by FACS 24h later and counted and lysed for analysis of IL-1β concentration. Cells were collected, sorted and counted every 24h for 120h.

Animals

Experiments using human bone grafts were carried out in 10-week old female NOD SCID mice. In IL-1β/IL-1R1 overexpression bone homing experiments 6 to 8-week old female BALB/c nude mice were used. To investigate effects of IL-1β on the bone microenvironment 10-week old female C57BL/6 mice (Charles River, Kent, UK) or IL-1R1^{-/-} mice (Abdulaal et al., 2016) were used. Mice were maintained on a 12h:12h light/dark cycle with free access to food and water. Experiments were carried out with UK home office approval under project licence 40/3531, University of Sheffield, UK.

Patient consent and preparation of bone discs

All patients provided written, informed consent prior to participation in this study. Human bone samples were collected under HTA licence 12182, Sheffield Musculoskeletal Biobank, University of Sheffield, UK. Trabecular bone cores were prepared from the femoral heads of female patients undergoing hip replacement surgery using an Isomat 4000 Precision saw (Buehler) with Precision diamond wafering blade (Buehler). 5 mm diameter discs were subsequently cut using a bone trephine before storing in sterile PBS at ambient temperature.

In vivo studies

To model human breast cancer metastasis to human bone implants two human bone discs were implanted subcutaneously into 10-week old female NOD SCID mice (n=10/group) under isoflurane anaesthetic. Mice received an injection of 0.003 mg vetergesic and Septrin was added to the drinking water for 1 week following bone implantation. Mice were left for 4 weeks before injecting 1×10^5 MDA-MB-231 Luc2-TdTomato, MCF7 Luc2 or T47D Luc2 cells in 20% Martigel/79% PBS/1% toluene blue into the two hind mammary fat pads. Primary tumor growth and development of metastases was monitored weekly using an IVIS (Luminol) system (Caliper Life Sciences) following sub-cutaneous injection of 30 mg/ml D-luciferin (Invitrogen). On termination of experiments mammary tumors, circulating tumor cells, serum and bone metastases were resected. RNA was processed for downstream analysis by real time PCR, and cell lysates were taken for protein analysis and whole tissue for histology as previously described (Nutter et al., 2014; Ottewell et al., 2014a).

For therapeutic studies in NOD SCID mice, placebo (control), 1 mg/kg IL-1Ra (anakinra®) daily or 10 mg/kg canakinumab subcutaneously every 14 days were administered starting 7 days after injection of tumor cells. In BALB/c mice and C57BL/6 mice 1 mg/kg IL-1Ra was administered daily for 21 or 31 days or 10 mg/kg canakinumab was administered as a single subcutaneous injection. Tumor cells, serum, and bone were subsequently resected for downstream analysis.

Bone metastases were investigated following injection of 5×10^5 MDA-MB-231 GFP (control), MDA-MB-231-IV, MDA-MB-231-IL-1B-positive or MDA-MB-231-IL-1R1-positive cells into the lateral tail vein of 6 to 8-week old female BALB/c nude mice (n=12/group). Tumor growth in bones and lungs was monitored weekly by GFP imaging in live animals. Mice were culled 28 days after tumor cell injection at which timepoint hind limbs, lungs and serum were resected and processed for microcomputed tomography imaging (μ CT), histology and ELISA analysis of bone turnover markers and circulating cytokines as described (Holen et al., 2016).

Isolation of circulating tumor cells

Whole blood was centrifuged at 10,000g for 5 minutes and the serum removed for ELISA assays. The cell pellet was re-suspended in 5 ml of FSM lysis solution (Sigma-Aldrich, Pool, UK) to lyse red blood cells. Remaining cells were re-pelleted, washed 3x in PBS and re-suspended in a solution of PBS/10% FCS. Samples from 10 mice per group were pooled prior to isolation of TdTomato positive tumor cells using a MoFlow High performance cell sorter (Beckman Coulter, Cambridge UK) with the 470nm laser line from a Coherent I-90C tenable argon ion (Coherent, Santa Clara, CA). TdTomato fluorescence was detected by a 555LP

dichroic long pass and a 580/30nm band pass filter. Acquisition and analysis of cells was performed using Summit 4.3 software. Following sorting cells were immediately placed in RNA protect cell reagent (Ambion, Paisley, Renfrew, UK) and stored at -80°C before RNA extraction. For counting numbers of circulating tumor cells, TdTomato fluorescence was detected using a 561 nm laser and an YL1-A filter (585/16 emission filter). Acquisition and analysis of cells was performed using Attune NxT software.

Microcomputed tomography imaging

Microcomputed tomography (μ CT) analysis was carried out using a Skyscan 1172 x-ray-computed μ CT scanner (Skyscan, Aartselar, Belgium) equipped with an x-ray tube (voltage, 49kV; current, 200uA) and a 0.5-mm aluminium filter. Pixel size was set to 5.86 μ m and scanning initiated from the top of the proximal tibia as previously described (Ottewell et al., 2008a; Ottewell et al., 2008b).

Bone histology and measurement of tumor volume

Bone tumor areas were measured on three non-serial, H&E stained, 5 μ m histological sections of decalcified tibiae per mouse using a Leica RMRB upright microscope and Osteomeasure software (Osteometrics, Inc. Decatur, USA) and a computerised image analysis system as previously described (Ottewell et al., 2008a).

Western blotting

Protein was extracted using a mammalian cell lysis kit (Sigma-Aldrich, Poole, UK). 30 μ g of protein was run on 4-15% precast polyacrylamide gels (BioRad, Watford, UK) and transferred onto an Immobilon nitrocellulose membrane (Millipore). Non-specific binding was blocked with 1% casein (Vector Laboratories) before incubation with rabbit monoclonal antibodies to human N-cadherin (D4R1H) at a dilution of 1:1000, E-cadherin (24E10) at a dilution of 1:500 or gamma-catenin (2303) at a dilution of 1:500 (Cell signalling) or mouse monoclonal GAPDH (ab8245) at a dilution of 1:1000 (AbCam, Cambridge UK) for 16h at 4°C. Secondary antibodies were anti-rabbit or anti-mouse horse radish peroxidase (HRP; 1:15,000) and HRP was detected with the Supersignal chemiluminescence detection kit (Pierce). Band quantification was carried out using Quantity Once software (BioRad) and normalised to GAPDH.

Gene analysis

Total RNA was extracted using an RNeasy kit (Qiagen) and reverse transcribed into cDNA using Superscript III (Invitrogen AB). Relative mRNA expression of *IL-1B* (Hs02786624), *IL-1RI* (Hs00174097), *CASP* (Caspase 1) (Hs00354836), *IL1RN* (Hs00893626), *JUP* (junction plakoglobin/gamma-catenin) (Hs00984034), *N-cadherin* (Hs01566408) and *E-cadherin*

(Hs1013933) were compared with the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*; Hs02786624) and assessed using an ABI 7900 PCR System (Perkin Elmer, Foster City, CA) and Taqman universal master mix (ThermoFisher, UK). Fold change in gene expression between treatment groups was analysed by inserting CT values into Data Assist V3.01 software (Applied Biosystems) and changes in gene expression were only analysed for genes with a CT value of ≤ 25 .

Assessment of IL-1 β and IL-1R1 in tumors from breast cancer patients

IL-1 β and IL-1R1 expression was assessed on tissue microarrays (TMA) containing primary breast tumor cores taken from 1,300 patients included in the clinical trial, AZURE (Coleman et al. 2011). Samples were taken pre-treatment from patients with stage II and III breast cancer without evidence of metastasis. Patients were subsequently randomized to standard adjuvant therapy with or without the addition of zoledronic acid for 10 years (Coleman et al 2011). The TMAs were stained for IL-1 β (ab2105, 1:200 dilution, Abcam) and IL-1R1 (ab59995, 1:25 dilution, Abcam) and scored blindly under the guidance of a histopathologist for IL-1 β /IL-1R1 in the tumor cells or in the associated stroma. Tumor or stromal IL-1 β or IL-1R1 was then linked to disease recurrence (any site) or disease recurrence specifically in bone (+/- other sites).

The IL-1 β pathway is upregulated during the process of human breast cancer metastasis to human bone.

A mouse model of spontaneous human breast cancer metastasis to human bone implants was utilised to investigate how the IL-1 β pathway changes through the different stages of metastasis. Using this model, the expression levels of genes associated with the IL-1 β pathway increased in a stepwise manner at each stage of the metastatic process in both triple negative (MDA-MB-231) and estrogen receptor positive (ER +ve) (T47D) breast cancer cells: Genes associated with the IL-1 β signalling pathway (*IL-1B*, *IL-1R1*, *CASP* (Caspase 1) and *IL-1Ra*) were expressed at very low levels in both MDA-MB-231 and T47D cells grown *in vitro* and expression of these genes were not altered in primary mammary tumors from the same cells that did not metastasize *in vivo* (Figure 1a).

IL-1B, *IL-1R1* and *CASP* were all significantly increased in mammary tumors that subsequently metastasized to human bone compared with those that did not metastasize ($p < 0.01$ for both cell lines), leading to activation of IL-1 β signalling as shown by ELISA for the active 17 kD IL-1 β (Figure 1b; Figure 2). *IL-1B* gene expression increased in circulating tumor cells compared with metastatic mammary tumors ($p < 0.01$ for both cell lines) and *IL-1B* ($p < 0.001$), *IL-1R1* ($p < 0.01$), *CASP* ($p < 0.001$) and *IL-1Ra* ($p < 0.01$) were further increased in tumor

cells isolated from metastases in human bone compared with their corresponding mammary tumors, leading to further activation of IL-1 β protein (Figure 1; Figure 2). These data suggest that IL-1 β signalling may promote both initiation of metastasis from the primary site as well as development of breast cancer metastases in bone.

5 **Tumor derived IL-1 β promotes EMT and breast cancer metastasis.**

Expression levels of genes associated with tumor cell adhesion and epithelial to mesenchymal transition (EMT) were significantly altered in primary tumors that metastasised to bone compared with tumors that did not metastasise (Figure 1c). IL-1 β -overexpressing cells were generated (MDA-MB-231-IL-1B+, T47D-IL-1B+ and MCF7-IL-1B+) to investigate whether
 10 tumor-derived IL-1 β is responsible for inducing EMT and metastasis to bone. All IL-1 β + cell lines demonstrated increased EMT exhibiting morphological changes from an epithelial to mesenchymal phenotype (Figure 3a) as well as reduced expression of E-cadherin, and *JUP* (junction plakoglobin/gamma-catenin) and increased expression of N-Cadherin gene and protein (Figure 3b). Wound closure ($p < 0.0001$ in MDA-MB-231-IL-1 β + (Figure 3d); $p <$
 15 0.001 MCF7-IL-1 β + and T47D-IL-1 β +) and migration and invasion through matrigel towards osteoblasts were increased in tumor cells with increased IL-1 β signalling compared with their respective controls (MDA-MB-231-IL-1 β + (Figure 3c) $p < 0.0001$; MCF7-IL-1 β + and T47D-IL-1 β + $p < 0.001$). Increased IL-1 β production was seen in ER-positive and ER-negative breast cancer cells that spontaneously metastasized to human bone implants *in vivo* compared with
 20 non-metastatic breast cancer cells (Figure 1). The same link between IL-1 β and metastasis was made in primary tumor samples from patients with stage II and III breast cancer enrolled in the AZURE study (Coleman et al., 2011) that experienced cancer relapsed over a 10 year time period. IL-1 β expression in primary tumors from the AZURE patients correlated with both relapse in bone and relapse at any site indicating that presence of this cytokine is likely to play
 25 a role in metastasis in general. In agreement with this, genetic manipulation of breast cancer cells to artificially overexpress IL-1 β increased the migration and invasion capacities of breast cancer cells *in vitro* (Figure 3).

Inhibition of IL-1 β signaling reduces spontaneous metastasis to human bone.

As tumor derived IL-1 β appeared to be promoting onset of metastasis through induction of
 30 EMT the effects of inhibiting IL-1 β signaling with IL-1Ra (Anakinra) or a human anti-IL-1 β -binding antibody (canakinumab) on spontaneous metastasis to human bone implants were investigated. Both IL-1Ra and canakinumab reduced metastasis to human bone: metastasis was detected in human bone implants in 7 out of 10 control mice, but only in 4 out of 10 mice treated with IL-1Ra and 1 out of 10 mice treated with canakinumab. Bone metastases from IL-1Ra and

canakinumab treatment groups were also smaller than those detected in the control group (Figure 4a). Numbers of cells detected in the circulation of mice treated with canakinumab or IL-1Ra were significantly lower than those detected in the placebo treated group: 3 and 3 tumor cells/ml were counted in whole blood from mice treated with canakinumab and anakinra, respectively, compared 108 tumor cells/ml counted in blood from placebo treated mice (Figure 4b), suggesting that inhibition of IL-1 signalling prevents tumor cells from being shed from the primary site into the circulation. Therefore, inhibition of IL-1 β signaling with the anti-IL-1 β antibody canakinumab or inhibition of IL-1R1 reduced the number of breast cancer cells shed into the circulation and reduced metastases in human bone implants (Figure 4).

Tumor derived IL-1B promotes bone homing and colonisation of breast cancer cells.

Injection of breast cancer cells into the tail vein of mice usually results in lung metastasis due to the tumor cells becoming trapped in the lung capillaries. It was previously shown that breast cancer cells that preferentially home to the bone microenvironment following intra-venous injection express high levels of IL-1 β , suggesting that this cytokine may be involved in tissue specific homing of breast cancer cells to bone. In the current study, intravenous injection of MDA-MB-231-IL-1 β ⁺ cells into BALB/c nude mice resulted in significantly increased number of animals developing bone metastasis (75%) compared with control cells (12%) ($p < 0.001$) cells (Figure 5a). MDA-MB-231-IL-1 β ⁺ tumors caused development of significantly larger osteolytic lesions in mouse bone compared with control cells ($p = 0.03$; Figure 5b) and there was a trend towards fewer lung metastases in mice injected with MDA-MB-231-IL-1 β ⁺ cells compared with control cells ($p = 0.16$; Figure 5c). These data suggest that endogenous IL-1 β can promote tumor cell homing to the bone environment and development of metastases at this site.

Tumor cell-bone cell interactions further induce IL-1B and promote development of overt metastases.

Gene analysis data from a mouse model of human breast cancer metastasis to human bone implants suggested that the IL-1 β pathway was further increased when breast cancer cells are growing in the bone environment compared with metastatic cells in the primary site or in the circulation (figure 1a). It was therefore investigated how IL-1 β production changes when tumor cells come into contact with bone cells and how IL-1 β alters the bone microenvironment to affect tumor growth (figure 6). Culture of human breast cancer cells into pieces of whole human bone for 48h resulted in increased secretion of IL-1 β into the medium ($p < 0.0001$ for MDA-MB-231 and T47D cells; Figure 6a). Co-culture with human HS5 bone marrow cells revealed

the increased IL-1 β concentrations originated from both the cancer cells ($p < 0.001$) and bone marrow cells ($p < 0.001$), with IL-1 β from tumor cells increasing ~1000 fold and IL-1 β from HS5 cells increasing ~100 fold following co-culture (Figure 6b).

Exogenous IL-1 β did not increase tumor cell proliferation, even in cells overexpressing IL-1R1.

- 5 Instead, IL-1 β stimulated proliferation of bone marrow cells, osteoblasts and blood vessels that in turn induced proliferation of tumor cells (Figure 5). It is therefore likely that arrival of tumor cells expressing high concentrations of IL-1 β stimulate expansion of the metastatic niche components and contact between IL-1 β expressing tumor cells and osteoblasts/blood vessels drive tumor colonization of bone. The effects of exogenous IL-1 β as well as IL-1 β from tumor
- 10 cells on proliferation of tumor cells, osteoblasts, bone marrow cells and CD34⁺ blood vessels were investigated: Co-culture of HS5 bone marrow or OB1 primary osteoblast cells with breast cancer cells caused increased proliferation of all cell types ($P < 0.001$ for HS5, MDA-MB-231 or T47D, figure 6c) ($P < 0.001$ for OB1, MDA-MB-231 or T47D, figure 6d). Direct contact between tumor cells, primary human bone samples, bone marrow cells or osteoblasts promoted
- 15 release of IL-1 β from both tumor and bone cells (Figure 6). Furthermore, administration of IL-1 β increased proliferation of HS5 or OB1 cells but not breast cancer cells (Figure 7 a and b), suggesting that tumor cell-bone cell interactions promote production of IL-1 β that can drive expansion of the niche and stimulate the formation of overt metastases.

IL-1 β signalling was also found to have profound effects on the bone microvasculature:

- 20 Preventing IL-1 β signaling in bone by knocking out IL-1R1, pharmacological blockade of IL-1R with IL-1Ra or reducing circulating concentrations of IL-1 β by administering the anti-IL-1 β binding antibody canakinumab reduced the average length of CD34⁺ blood vessels in trabecular bone, where tumor colonisation takes place ($p < 0.01$ for IL-1Ra and canakinumab treated mice) (Figure 7c). These findings were confirmed by endomeucin staining which
- 25 showed decreased numbers of blood vessels as well as blood vessel length in bone when IL-1 β signaling was disrupted. ELISA analysis for endothelin 1 and VEGF showed reduced concentrations of both of these endothelial cell markers in the bone marrow for IL-1R1^{-/-} mice ($p < 0.001$ endothelin 1; $p < 0.001$ VEGF) and mice treated with IL-1R antagonist ($p < 0.01$ endothelin 1; $p < 0.01$ VEGF) or canakinumab ($p < 0.01$ endothelin 1; $p < 0.001$ VEGF)
- 30 compared with control (figure 8). These data suggest that tumor cell-bone cell associated increases in IL-1 β and high levels of IL-1 β in tumor cells may also promote angiogenesis, further stimulating metastases.

Tumor derived IL-1 β predicts future breast cancer relapse in bone and other organs in patient material

To establish the relevance of the findings in a clinical setting the correlation between IL-1 β and its receptor IL-1R1 in patient samples was investigated. ~1300 primary tumor samples from patients with stage II/III breast cancer with no evidence of metastasis (from the AZURE study (Coleman et al., 2011)) were stained for IL-1R1 or the active (17 kD) form of IL-1 β , and biopsies were scored separately for expression of these molecules in the tumor cells and the tumor associated stroma. Patients were followed up for 10 years following biopsy and correlation between IL-1 β /IL-1R1 expression and distant recurrence or relapse in bone assessed using a multivariate Cox model. IL-1 β in tumor cells strongly correlated with distant recurrence at any site ($p = 0.0016$), recurrence only in bone ($p = 0.017$) or recurrence in bone at any time ($p = 0.0387$) (Figure 9). Patients who had IL-1 β in their tumor cells and IL-1R1 in the tumor associated stroma were more likely to experience future relapse at a distant site ($p = 0.042$) compared to patients who did not have IL-1 β in their tumor cells, indicating that tumor derived IL-1 β may not only promote metastasis directly but may also interact with IL-1R1 in the stroma to promote this process. Therefore, IL-1 β is a novel biomarker that can be used to predict risk of breast cancer relapse.

EXAMPLE 2

Simulation of canakinumab PK profile and hsCRP profile for lung cancer patients.

A model was generated to characterize the relationship between canakinumab pharmacokinetics (PK) and hsCRP based on data from the CANTOS study.

The following methods were used in this study: Model building was performed using the first-order conditional estimation with interaction method. The model described the logarithm of the time resolved hsCRP as:

$$y(t_{ij}) = y_{0,i} + y_{eff}(t_{ij})$$

where $y_{0,i}$ is a steady state value and $y_{eff}(t_{ij})$ describes the effect of the treatment and depends on the systemic exposure. The treatment effect was described by an Emax-type model,

$$y_{eff}(t_{ij}) = E_{max,i} \frac{c(t_{ij})}{c(t_{ij}) + IC50_i}$$

where $E_{max,i}$ is the maximal possible response at high exposure, and $IC50_i$ is the concentration at which half maximal response is obtained.

The individual parameters, $E_{max,i}$ and $y_{0,i}$ and the logarithm of $IC50_i$ were estimated as a sum of a typical value, covariate effects $covpar * cov_i$ and normally distributed between subject variability. In the term for the covariate effect $covpar$ refers to the covariate effect parameter being estimated and cov_i is the value of the covariate of subject i . Covariates to be included were selected based on inspection of the eta plots versus covariates. The residual error was described as a combination of proportional and additive term.

The logarithm of baseline hsCRP was included as covariate on all three parameters ($E_{max,i}$, $y_{0,i}$ and $IC50_i$). No other covariate was included into the model. All parameters were estimated with good precision. The effect of the logarithm of the baseline hsCRP on the steady state value was less than 1 (equal to 0.67). This indicates that the baseline hsCRP is an imperfect measure for the steady state value, and that the steady state value exposes regression to the mean relative to the baseline value. The effects of the logarithm of the baseline hsCRP on $IC50$ and E_{max} were both negative. Thus patients with high hsCRP at baseline are expected to have low $IC50$ and large maximal reductions. In general, model diagnostics confirmed that the model describes the available hsCRP data well.

The model was then used to simulate expected hsCRP response for a selection of different dosing regimens in a lung cancer patient population. Bootstrapping was applied to construct populations with intended inclusion/exclusion criteria that represent potential lung cancer patient populations. Three different lung cancer patient populations described by baseline hsCRP distribution alone were investigated: all CANTOS patients (scenario 1), confirmed lung cancer patients (scenario 2), and advanced lung cancer patients (scenario 3).

The population parameters and inter-patient variability of the model were assumed to be the same for all three scenarios. The PK/PD relationship on hsCRP observed in the overall CANTOS population was assumed to be representative for lung cancer patients.

The estimator of interest was the probability of hsCRP at end of month 3 being below a cut point, which could be either 2 mg/L or 1.8 mg/L. 1.8 mg/L was the median of hsCRP level at end of month 3 in the CANTOS study. Baseline hsCRP >2 mg/L was one of the inclusion criteria, so it is worthy to explore if hsCRP level at end of month 3 went below 2 mg/L.

A one-compartment model with first order absorption and elimination was established for CANTOS PK data. The model was expressed as ordinary differential equation and RxODE was used to simulate canakinumab concentration time course given individual PK parameters. The subcutaneous canakinumab dose regimens of interest were 300 mg Q12W, 200 mg Q3W, and 300 mg Q4W. Exposure metrics including C_{min} , C_{max} , AUCs over different selected time

periods, and average concentration C_{ave} at steady state were derived from simulated concentration time profiles.

The simulation in Scenario 1 was based on the below information:

Individual canakinumab exposure simulated using RxODE

- 5 PD parameters which are components of $y_{0,i}$, $E_{max,i}$, and $IC50_i$: typical values (THETA(3), THETA(5), THETA(6)), *covpars* (THETA(4), THETA(7), THETA(8)), and between subject variability (ETA(1), ETA(2), ETA(3))

Baseline hsCRP from all 10,059 CANTOS study patients (baseline hsCRP: mean 6.18 mg/L, standard error of the mean (SEM)=0.10 mg/L)

- 10 The prediction interval of the estimator of interest was produced by first randomly sampling 1000 THETA(3)-(8)s from a normal distribution with fixed mean and standard deviation estimated from the population PK/PD model; and then for each set of THETA(3)-(8), bootstrapping 2000 PK exposure, PD parameters ETA(1)-(3), and baseline hsCRP from all CANTOS patients. The 2.5%, 50%, and 97.5% percentile of 1000 estimates were reported as
15 point estimator as well as 95% prediction interval.

The simulation in Scenario 2 was based on the below information:

Individual canakinumab PK exposure simulated using RxODE

PD parameters THETA(3)-(8) and ETA(1)-(3)

- Baseline hsCRP from 116 CANTOS patients with confirmed lung cancer (baseline hsCRP:
20 mean=9.75 mg/L, SEM=1.14 mg/L)

- The prediction interval of the estimator of interest was produced by first randomly sampling 1000 THETA(3)-(8)s from a normal distribution with fixed mean and standard deviation estimated from the population PKPD model; and then for each set of THETA(3)-(8), bootstrapping 2000 PK exposure, PD parameters ETA(1)-(3) from all CANTOS patients, and
25 bootstrapping 2000 baseline hsCRP from the 116 CANTOS patients with confirmed lung cancer. The 2.5%, 50%, and 97.5% percentile of 1000 estimates were reported as point estimator as well as 95% prediction interval.

- In Scenario 3, the point estimator and 95% prediction interval were obtained in a similar manner as for scenario 2. The only difference was bootstrapping 2000 baseline hsCRP values from
30 advanced lung cancer population. There is no individual baseline hsCRP data published in an advanced lung cancer population. An available population level estimate in advanced lung cancer is a mean of baseline hsCRP of 23.94 mg/L with SEM 1.93 mg/L [Vaguliene 2011]. Using this estimate, the advanced lung cancer population was derived from the 116 CANTOS

patients with confirmed lung cancer using an additive constant to adjust the mean value to 23.94 mg/L.

In line with the model, the simulated canakinumab PK was linear. The median and 95% prediction interval of concentration time profiles are plotted in natural logarithm scale over 6 months is shown in Figure 10a.

The median and 95% prediction intervals of 1000 estimates of proportion of subjects with month 3 hsCRP response under the cut point of 1.8 mg/L and 2 mg/L mhsCRP are reported in Figure 10b and c. Judging from the simulation data, 200mg Q3W and 300mg Q4W perform similarly and better than 300mg Q12W (top dosing regimen in CANTOS) in terms of decreasing hsCRP at month 3. Going from scenario 1 to scenario 3 towards more severe lung cancer patients, higher baseline hsCRP levels are assumed, and result in smaller probabilities of month 3 hsCRP being below the cut point. Figure 10d shows how the median hsCRP concentration changes over time for three different doses and Figure 10e shows the percent reduction from baseline hsCRP after a single dose.

EXAMPLE 3

PDR001 plus canakinumab treatment increases effector neutrophils in colorectal tumors.

RNA sequencing was used to gain insights on the mechanism of action of canakinumab (ACZ885) in cancer. The CPDR001X2102 and CPDR001X2103 clinical trials evaluate the safety, tolerability and pharmacodynamics of spartalizumab (PDR001) in combination with additional therapies. For each patient, a tumor biopsy was obtained prior to treatment, as well as cycle 3 of treatment. In brief, samples were processed by RNA extraction, ribosomal RNA depletion, library construction and sequencing. Sequence reads were aligned by STAR to the hg19 reference genome and Refseq reference transcriptome, gene-level counts were compiled by HTSeq, and sample-level normalization using the trimmed mean of M-values was performed by edgeR.

Figure 11 shows 21 genes that were increased, on average, in colorectal tumors treated with PDR001 + canakinumab (ACZ885), but not in colorectal tumors treated with PDR001 + everolimus (RAD001). Treatment with PDR001 + canakinumab increased the RNA levels of *IL1B*, as well as its receptor, *IL1R2*. This observation suggests an on-target compensatory feedback by tumors to increase *IL1B* RNA levels in response to IL-1 β protein blockade.

Notably, several neutrophil-specific genes were increased on PDR001 + canakinumab, including *FCGR3B*, *CXCR2*, *FFAR2*, *OSM*, and *G0S2* (indicated by boxes in Figure 11). The

FCGR3B gene is a neutrophil-specific isoform of the CD16 protein. The protein encoded by *FCGR3B* plays a pivotal role in the secretion of reactive oxygen species in response to immune complexes, consistent with a function of effector neutrophils (Fossati G 2002 Arthritis Rheum 46: 1351). Chemokines that bind to *CXCR2* mobilize neutrophils out of the bone marrow and into peripheral sites. In addition, increased *CCL3* RNA was observed on treatment with PDR001 + canakinumab. *CCL3* is a chemoattractant for neutrophils (Reichel CA 2012 Blood 120: 880).

In summary, this contribution of components analysis using RNA-seq data demonstrates that PDR001 + canakinumab treatment increases effector neutrophils in colorectal tumors, and that this increase was not observed with PDR001 + everolimus treatment.

EXAMPLE 4

Efficacy of canakinumab (ACZ885) in combination with spartalizumab (PDR001) in the treatment of cancer.

Patient 5002-004 is a 56 year old man with initially Stage IIC, microsatellite-stable, moderately differentiated adenocarcinoma of the ascending colon (MSS-CRC), diagnosed in June, 2012 and treated with prior regimens.

Prior treatment regimens included:

1. Folinic acid/5-fluorouracil/oxaliplatin in the adjuvant setting
2. Chemoradiation with capecitabine (metastatic setting)
3. 5-fluorouracil/bevacizumab/folinic acid/irinotecan
4. trifluridine and tipiracil
5. Irinotecan
6. Oxaliplatin/5-fluorouracil
7. 5-fluorouracil/bevacizumab/leucovorin
8. 5-fluorouracil

At study entry the patient had extensive metastatic disease including multiple hepatic and bilateral lung metastases, and disease in paraesophageal lymph nodes, retroperitoneum and peritoneum.

The patient was treated with PDR001 400 mg every four weeks (Q4W) plus 100 mg every eight weeks (Q8W) ACZ885. The patient had stable disease for 6 months of therapy, then with substantial disease reduction and confirmed RECIST partial response to treatment at 10 months. The patient has subsequently developed progressive disease and the dose was increased to 300 mg and then to 600 mg.

EXAMPLE 5

Calculations for selecting the dose for gevokizumab for cancer patients.

Dose selection for gevokizumab in the treatment of cancer having at least partial inflammatory basis is based on the clinical effective dosings reveals by the CANTOS trial in combination with the available PK data of gevokizumab, taking into the consideration that

Gevokizumab (IC₅₀ of ~2-5 pM) shows a ~10 times higher in vitro potency compared to canakinumab (IC₅₀ of ~42 ± 3.4 pM). The gevokizumab top dose of 0.3 mg/kg (~20 mg) Q4W showed reduction of hsCRP could reduce hsCRP up to 45% in type 2 diabetes patients (see Figure 12a).

Next, a pharmacometric model was used to explore the hsCRP exposure-response relationship, and to extrapolate the clinical data to higher ranges. As clinical data show a linear correlation between the hsCRP concentration and the concentration of gevokizumab (both in log-space), a linear model was used. The results are shown in Figure 12b. Based on that simulation, a gevokizumab concentration between 10000 ng/mL and 25000 ng/mL is optimal because hsCRP is greatly reduced in this range, and there is only a diminishing return with gevokizumab concentrations above 15000 ng/mL. However gevokizumab concentrations between 4000 ng/mL and 10000 ng/mL is expected to be efficacious as hsCRP has already been significantly reduced in that range.

Clinical data showed that gevokizumab pharmacokinetics follow a linear two-compartment model with first order absorption after a subcutaneous administration. Bioavailability of gevokizumab is about 56% when administered subcutaneously. Simulation of multiple-dose gevokizumab (SC) was carried out for 100 mg every four weeks (see Figure 12c) and 200 mg every four weeks (see Figure 12d). The simulations showed that the trough concentration of 100 mg gevokizumab given every four weeks is about 10700 ng/mL. The half-life of gevokizumab is about 35 days. The trough concentration of 200 mg gevokizumab given every four weeks is about 21500 ng/mL.

EXAMPLE 6

Preclinical data on the effects of anti-IL-1β treatment

Canakinumab, an anti-IL-1 β human IgG1 antibody, cannot directly be evaluated in mouse models of cancer due to the fact that it does not cross-react with mouse IL-1 β . A mouse surrogate anti-IL-1 β antibody has been developed and is being used to evaluate the effects of blocking IL-1 β in mouse models of cancer. This isotype of the surrogate antibody is IgG2a,
5 which is closely related to human IgG1.

In the MC38 mouse model of colon cancer, modulation of tumor infiltrating lymphocytes (TILs) can be seen after one dose of the anti IL-1 β antibody (Figure 13a-c). MC38 tumors were subcutaneously implanted in the flank of C57BL/6 mice and when the tumors were between 100-150mm³, the mice were treated with one dose of either an isotype antibody or the anti IL-
10 1 β antibody. Tumors were then harvested five days after the dose and processed to obtain a single cell suspension of immune cells. The cells were then ex vivo stained and analyzed via flow cytometry. Following a single dose of an IL-1 β blocking antibody, there is an increase in in CD4⁺ T cells infiltrating the tumor and also a slight increase in CD8⁺ T cells (Figure 13a). The CD8⁺ T cell increase is slight but may allude to a more active immune response in the
15 tumor microenvironment, which could potentially be enhanced with combination therapies. The CD4⁺ T cells were further subdivided into FoxP3⁺ regulatory T cells (Tregs), and this subset decreases following blockade of IL-1 β (Figure 13b). Among the myeloid cell populations, blockade of IL-1 β results in a decrease in neutrophils and the M2 subset of macrophages, TAM2 (Figure 13c). Both neutrophils and M2 macrophages can be suppressive to other immune cells,
20 such as activated T cells (Pillay et al, 2013; Hao et al, 2013; Oishi et al 2016). Taken together, the decrease in Tregs, neutrophils, and M2 macrophages, in the MC38 tumor microenvironment following IL-1 β blockade argues that the tumor microenvironment is becoming less immune suppressive.

In the LL2 mouse model of lung cancer, a similar trend towards a less suppressive immune
25 microenvironment can be seen after one dose of an anti- IL-1 β antibody (Figure 13d-f). LL2 tumors were subcutaneously implanted in the flank of C57BL/6 mice and when the tumors were between 100-150mm³, the mice were treated with one dose of either an isotype antibody or the anti- IL-1 β antibody. Tumors were then harvested five days after the dose and processed to obtain a single cell suspension of immune cells. The cells were then ex vivo stained and
30 analyzed via flow cytometry. There is a decrease in the Treg populations as evaluated by the expression of FoxP3 and Helios (Figure 13d). FoxP3 and Helios are both used as markers of regulatory T cells, while they may define different subsets of Tregs (Thornton et al, 2016). Similar to the MC38 model, there is a decrease in both neutrophils and M2 macrophages

(TAM2) following IL-1 β blockade (Figure 13e). In addition to this, in this model the change in the myeloid derived suppressor cell (MDSC) populations were evaluated following antibody treatment. The granulocytic or polymorphonuclear (PMN) MDSC were found in reduced numbers following anti- IL-1 β treatment (Figure 13f). MDSC are a mixed population of cells of myeloid origin that can actively suppress T cell responses through several mechanisms, including arginase production, reactive oxygen species (ROS) and nitric oxide (NO) release (Kumar et al, 2016; Umansky et al, 2016). Again, the decrease in Tregs, neutrophils, M2 macrophages, and PMN MDSC in the LL2 model following IL-1 β blockade argues that the tumor microenvironment is becoming less immune suppressive.

TILs in the 4T1 triple negative breast cancer model also show a trend towards a less suppressive immune microenvironment after one dose of the mouse surrogate anti- IL-1 β antibody (Figure 13g-j). 4T1 tumors were subcutaneously implanted in the flank of Balb/c mice, and the mice were treated with either an isotype antibody or the anti- IL-1 β antibody when the tumors were between 100-150mm³. Tumors were then harvested five days after the dose and processed to obtain a single cell suspension of immune cells. The cells were then ex vivo stained and analyzed via flow cytometry. There is a decrease in CD4⁺ T cells after a single dose of an anti-IL-1 β antibody (Figure 13g) and within the CD4⁺ T cell population, there is a decrease in the FoxP3⁺ Tregs (Figure 13h). Further, there is a decrease in both the TAM2 and neutrophil populations following treatment of the tumor-bearing mice (Figure 13i). All of these data together again argue that IL-1 β blockade in the 4T1 breast cancer mouse model leads to a less suppressive immune microenvironment. In addition to this, in this model the MDSC populations was also evaluated following antibody treatment. Both the granulocytic (PMN) MDSC and monocytic MDSC were found in reduced numbers following anti- IL-1 β treatment (Figure 13j). These findings in combination with the changes in Tregs, M2 macrophages, and the neutrophil populations describe a decrease in the immune suppressive tumor microenvironment in the 4T1 tumor model.

While these data are from colon, lung, and breast cancer models, the data can be extrapolated to other types of cancer. Even though these models do not fully correlate to human cancers of the same type, the MC38 model in particular is a good surrogate model for hypermutated/MSI (microsatellite instable) colorectal cancer (CRC). Based on the transcriptomic characterization of the MC38 cell line, four of the driver mutations in this line correspond to known hotspots in human CRC, although these are at different positions (Efremova et al, 2018). While this does not make the MC38 mouse model identical to human CRC, it does mean that MC38 may be a

relevant model for human MSI CRC. Generally, mouse models do not always correlate to the same type of cancer in humans due to genetic differences in the origins of the cancer in mice versus humans. However, when examining the infiltrating immune cells, the type of cancer is not always important, as the immune cells are more relevant. In this case, as three different mouse models show a similar decrease in the suppressive microenvironment of the tumor, blocking IL-1 β seems to lead to a less suppressive tumor microenvironment. The extent of the change in immune suppression with multiple cell types (Tregs, TAMs, neutrophils) showing a decrease compared to the isotype control in multiple tumor syngeneic mouse tumor models is a novel finding for IL-1 β blockade in mouse models of cancer. While suppressor cell decreases have been seen before, multiple cell types in each model is a novel finding. In addition, changes to MDSC populations in the 4T1 and Lewis lung carcinoma (LL2) models have been seen downstream of IL-1 β , but the finding in the LL2 model that blockade of IL-1 β can lead to the reduction of MDSCs is novel to this study and the mouse surrogate of canakinumab (Elkabets et al, 2010).

Even though these models do not fully correlate to human cancers of the same type, the MC38 model in particular is a good surrogate model for hypermutated/MSI (microsatellite instable) colorectal cancer (CRC). Based on the transcriptomic characterization of the MC38 cell line, four of the driver mutations in this line correspond to known hotspots in human CRC, although these are at different positions (Efremova et al, 2018). While this does not make the MC38 mouse model identical to human CRC, it does mean that MC38 may be a relevant model for human MSI CRC (Efremova M, et al. Nature Communications 2018; 9: 32).

EXAMPLE 9

Preclinical data on the efficacy of canakinumab in combination with an anti-PD-1 (pembrolizumab) in the treatment of cancer.

A pilot study was designed to assess the impact of canakinumab as a monotherapy or in combination with anti-PD-1 (pembrolizumab) on tumor growth and the tumor microenvironment. A xenograft model of human NSCLC was created by subcutaneous injection of a human lung cancer cell line H358 (KRAS mutant) into BLT mouse xenograft model.

As shown in Figure 14, the H358 (KRAS mutant) model is a very fast growing and aggressive model. In this model, combination treatment of canakinumab and pembrolizumab (shown in purple) led to a greater reduction than canakinumab single agent arm (shown in red) and

pembrolizumab single agent treatment (shown in green), with a 50% decrease observed in the mean tumor volume when compared to the vehicle group.

EXAMPLE 10

Preclinical data on the efficacy of canakinumab in combination with docetaxel in the treatment of cancer.

In a study of anti-IL-1 β in combination with docetaxel in an aggressive lung model (LL2), modest efficacy with anti-IL-1 β was observed, as well as docetaxel alone. The efficacy was enhanced in the combination compared to either group alone or control (Figure 15A). Decreases in immunosuppressive cells were observed with anti-IL-1 β alone or in combination at the PD time point 5 days after the first dose, specifically in regulatory T cells and suppressive mouse myeloid cells including neutrophils, monocytes and MDSCs in tumors after IL-1 β inhibition (Figure 15B-E). These data support that the proposed mechanism of action in IL-1 β inhibition can be demonstrated in vivo and also some efficacy of anti- IL-1 β monotherapy was observed.

EXAMPLE 11

Treatment of 4T1 tumors with 01BSUR and docetaxel leads to alterations in the tumor microenvironment.

Female Balb/c mice with 4T1 tumors implanted subcutaneously (s.c.) on the right flank were treated 8 and 15 days post-tumor implant initiating when the tumors reached about 100mm³ with the isotype antibody, docetaxel, 01BSUR, or a combination of docetaxel and 01BSUR. 01BSUR is the mouse surrogate antibody, since canakinumab does not cross-react to murine IL-1beta. 01BSUR belongs to the mouse IgG2a subclass, which corresponds to human IgG1 subclass, which canakinumab belongs to. 5 days after the first dose, tumors were harvested and analyzed for changes to the infiltrating immune cell populations. This was done again at the end point of the study, 4 days after the second dose.

Tumor burden

A slight slowing in tumor growth was seen in the 01BSUR anti-IL-1 β alone treatment group compared to the vehicle/isotype control. This delay was enhanced in the single agent docetaxel group. The combination group showed a similar slowing in growth as the docetaxel alone group (Figure 16).

TIL analysis of 4T1 tumors after a single dose of docetaxel and 01BSUR – Myeloid panel

Following a single treatment with docetaxel alone or in combination with 01BSUR, there was a decrease in neutrophils in the 4T1 tumors. The combination group, showed a greater decrease in neutrophil cell number than the docetaxel single agent group. Single agent 01BSUR led to a slight increase in neutrophils in 4T1 tumors, although this was not a significant change compared to the control group. Each of the treatments led to a decrease in monocytes compared to the vehicle/isotype group. The single agent 01BSUR treatment led to a greater decrease in monocytes than the docetaxel alone group. Further, the combination showed an even greater decrease in monocytes compared to the control group ($P=0.0481$) (Figure 17). Similar trends to the granulocytes and monocytes were seen among the granulocytic and monocytic Myeloid derived suppressor cells (MDSC). Docetaxel alone and in combination with 01BSUR led to a decrease in granulocytic MDSC. All treatments led to a decrease in monocytic MDSC, with the combination leading to a greater decrease than either of the single agents (Figure 18).

TIL analysis of 4T1 tumors after a second dose of docetaxel and 01BSUR

Four days after a second dose of docetaxel and 01BSUR 4T1 tumors were analyzed for immune cell infiltrates. The percent of both CD4⁺ and CD8⁺ T cells expressing TIM-3 were determined. Docetaxel alone led to no change in the TIM-3 expressing cells compared to the control group, while there was a decrease in the TIM-3 expressing cells following treatment with 01BSUR alone or in combination with docetaxel. The combination group, appears to show a slightly larger decrease in TIM-3 expressing cells than the single agent 01BSUR group ($P=0.0063$) for CD4⁺ T cells compared to control (Figure 19). Similar trends were seen in the Treg subset of cells with the combination group showing the largest level of decrease of the TIM-3 expressing cells ($P=0.0064$) compared to the control (Figure 20).

Conclusion and discussion

Blocking IL-1 β has been shown to be a potent method of changing the inflammatory microenvironment in autoimmune disease. ACZ885 (canakinumab) has been highly effective at treating some inflammatory autoimmune diseases, such as CAPS (Cryopyrin Associated Periodic Syndrome). As many tumors have an inflammatory microenvironment, blocking IL-1 β is being studied to determine the impact that this will have on the tumor microenvironment alone and in combination with agents that will work to block the PD-1/PD-L1 axis or standard of care chemotherapeutic agents such as docetaxel. It has been shown through preclinical

experiments and the CANTOS trial that the blockade of IL-1 β can have an impact on tumor growth and development. However, the CANTOS trial, an atherosclerosis trial, evaluated this in a prophylactic setting with patients with no known or detectable cancer at the time of enrollment. Patients with established tumors or metastases may have different levels of response to IL-1 β blockade.

These preliminary results studying combinations of 01BSUR, a murine surrogate of ACZ885, and docetaxel show that in the LL2 and 4T1 tumors models, this combination can have an impact on tumor growth.

The studies described here examine the TILs following a single treatment only (1D2 and 01BSUR combinations) or following two doses of each treatment (01BSUR and docetaxel). The overall trends alludes to a change in the suppressive nature of the TME in LL2 and 4T1 tumors.

While there is not a consistent change in the overall CD4⁺ and CD8⁺ T cells in the TME of these tumors, there is a trend towards in decrease in the Tregs in these tumors. Additionally, the Tregs typically also show a decrease in the percentage of cells expressing TIM-3. Tregs that express TIM-3 may be more effective suppressors of T cells than non-TIM-3 expressing Tregs [Sakuishi, 2013]. In several of the studies, there is an overall decrease of TIM-3 on all T cells. While the impact of this on these cells is not yet known, TIM-3 is a checkpoint and these cells may be more activated than the TIM-3 expressing T cells. However, further work is needed to understand these changes as some of the T cell changes observed could allude to a therapy that is less effective than the control.

While T cells make up a portion of the immune cell infiltrate in these tumors, a large portion of the infiltrating cells are myeloid cells. These cells were also analyzed for changes and IL-1 β blockade consistently led to a decrease in the numbers of neutrophils and granulocytic MDSC in the tumors. Often these were accompanied by decreased monocytes and monocytic MDSC; however, there was more variability in these populations. Neutrophils both produce IL-1 β and respond to IL-1 β while MDSC generation is often dependent on IL-1 β , and both subsets of cells can suppress the function of other immune cells. Decreases in both neutrophils and MDSC combined with a decrease in Tregs may mean that the tumor microenvironment becomes less immune suppressive following IL-1 β blockade. A less suppressive TME may lead to a better anti-tumor immune response, particularly with checkpoint blockade.

These data taken together show that blocking both IL-1 β and the PD-1/PD-L1 axis may lead to a more immune active tumor microenvironment or combining IL-1 β blockade with chemotherapy may have a similar impact.

5

EXAMPLE 12

Determining Immunogenicity/allergenicity to IL-1 β antibody

During the CANTOS trial, blood samples for immunogenicity assessments were collected at baseline Month 12, 24 and end of study visit. Immunogenicity was analyzed using a bridging immunogenicity electrochemiluminescence immunoassay (ECLIA). Samples were pre-treated with acetic acid and neutralized in buffer containing labeled drug (biotinylated ACZ885 and sulfo-TAG (Ruthenium) labeled ACZ885). Anti-canakinumab antibodies (anti-drug antibodies) were captured by a combination of biotinylated and sulfo-TAG labeled forms of ACZ885. Complex formation was subsequently detected by electrochemiluminescence by capturing complexes on Mesoscale Discovery Streptavidin (MSD) plates.

10

15

Treatment-emergent anticanakinumab antibodies (anti-drug antibodies) were detected in low and comparable proportions of patients across all treatment groups (0.3%, 0.4% and 0.5% in the canakinumab 300 mg, 150 mg and placebo groups respectively) and were not associated with immunogenicity related AEs or altered hsCRP response.

EXAMPLE 13

20

Biomarker analysis from the CANTOS trial

Patients with gastric cancer, colorectal cancer and pancreatic cancer were grouped into GI group. Patients with bladder cancer, renal cell carcinoma and prostate cancer were grouped into GU group. Within the group, patients were further divided according to their baseline IL-6 or CRP level into above median group and below median group. The mean and median of time to cancer event were calculated as shown the table below.

25

There seems to have a trend that patient group have below median level of CRP and IL-6 had in general longer time to develop cancer. This trend seems to be stronger based on IL-6 analysis than CRP, possibly due to the fact that IL-6 is immediately downstream of IL-1 β , where CTP is further away from IL-1 β signaling and therefore could be influenced by other factors as well.

30

		Time to cancer AE		
Set	IL-6 median	N	Mean	Median
GI	Above median	34	18.35	16.03
	Below median	35	27.84	28.55
GU	Above median	33	21.79	17.45
	Below median	33	27.85	23.39

		Time to cancer AE		
Set	CRP Median	N	Mean	Median
GI	Above Median	56	19.23	15.08
	Below Median	58	25.61	26.17
GU	Above Median	54	24.57	23.23
	Below Median	56	25.15	24.13

CLAIMS

1. An IL-1 β binding antibody or a functional fragment thereof for use in the treatment of a MSI-H (microsatellite instability-high) cancer in a patient.
2. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 1, wherein said MSI-H cancer has at least a partial inflammatory basis.
3. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 1 or 2, wherein the IL-1 β binding antibody or a functional fragment thereof is canakinumab.
4. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 3, wherein the therapeutic effective amount of canakinumab is about 200mg.
5. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 4, wherein canakinumab is administered about every 3 weeks or about every 4 weeks.
6. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 3-5, wherein canakinumab is administered subcutaneously.
7. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 1 or 2, wherein the IL-1 β binding antibody or a functional fragment thereof is gevokizumab.
8. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 7, wherein the therapeutic effective amount of gevokizumab is about 30-120mg.
9. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 8, wherein gevokizumab is administered about every 3 weeks or about every 4 weeks.
10. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 7-9, wherein gevokizumab is administered intravenously or subcutaneously.

11. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein a therapeutically effective amount of IL-1 β binding antibody or a functional fragment thereof is administered to the patient about every 3 weeks or about every 4 weeks for at least about 13 months.

5

12. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein the hazard rate of cancer mortality of the patient is reduced by at least about 10%.

10

13. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein the patient has at least 3 months progression free survival (PFS).

15

14. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein the PFS of the patient is at least about 3 months progression free survival (PFS) longer than standard of care treatment.

20

15. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein the patient has at least about 3 months overall survival (OS).

25

16. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein the patient has at least about 3 months overall survival (OS) longer than standard of care treatment.

17. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein the patient is not at high risk of developing serious infection.

30

18. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein the IL-1 β binding antibody or a functional fragment thereof is not administered in combination with a TNF inhibitor.

19. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein the patient has at least about 3 months disease free survival (DFS).

5 20. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein the chance the patient develops antibody against said IL-1 β binding antibody is less than about 1%.

10 21. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 20, wherein the IL-1 β binding antibody or a functional fragment thereof is canakinumab.

15 22. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein said patient has high sensitivity C-reactive protein (hsCRP) equal to or greater than about 2.1 mg/L before first administration of said IL-1 β binding antibody or functional fragment thereof.

20 23. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein said IL-1 β binding antibody or a functional fragment thereof is administered in combination with one or more therapies or therapeutic agents.

25 24. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 23, wherein the one or more therapeutic agents is the standard of care agent for said MSI-H cancer.

26. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 23 or 24, wherein the one or more therapeutic agents is a checkpoint inhibitor.

30 26. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 25, wherein the checkpoint inhibitor is selected from a list consisting of nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, ipilimumab and spartalizumab.

27. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 25, wherein the checkpoint inhibitor is pembrolizumab.

28. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 27, wherein said MSI-H cancer is unresectable or metastatic solid tumor.

29. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 27 or 28, wherein the cancer has progressed following prior treatment.

30. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 27-29, wherein the cancer is colorectal cancer.

31. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 30, wherein the cancer has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

32. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 27-31, wherein pembrolizumab is administered at a dose of about 200 mg about every 3 weeks, wherein the patient is an adult.

33. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 27-31, wherein pembrolizumab is administered at a dose of about 2 mg/kg (up to about 200 mg) about every 3 weeks, wherein the patient is pediatric (i.e. a child).

34. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein said IL-1 β binding antibody or a functional fragment thereof is used, alone or preferably in combination, as the first, second or third line treatment.

35. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein said IL-1 β binding antibody or a functional fragment thereof is used, alone or preferably in combination, for more than one lines of treatment in the same patient.

36. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein said MSI-H cancer is selected from the list consisted of gastric cancer ovarian cancer, endometrial cancer, hepatobiliary tract cancer, urinary tract cancer, brain cancer, oesophageal cancer, gastroesophageal junction cancer, pancreatic cancer, renal cell cancer, retroperitoneal adenocarcinoma, sarcoma, small cell lung cancer and skin cancers, such as melanoma.

37. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 1-35, wherein said MSI-H cancer is selected from the list consisted of colorectal cancer, endometrial cancer, breast cancer, prostate cancer, bladder cancer, and thyroid cancer.

38. An IL-1 β binding antibody or a functional fragment thereof for use according to claim 1-35, wherein said MSI-H cancer is selected from the list consisted of uterine corpus endometrial carcinoma, stomach adenocarcinoma, colon adenocarcinoma and rectal adenocarcinoma.

39. An IL-1 β binding antibody or a functional fragment thereof for use according to any one of proceeding claims, wherein said MSI-H cancer is colorectal cancer.

FIGURE 1

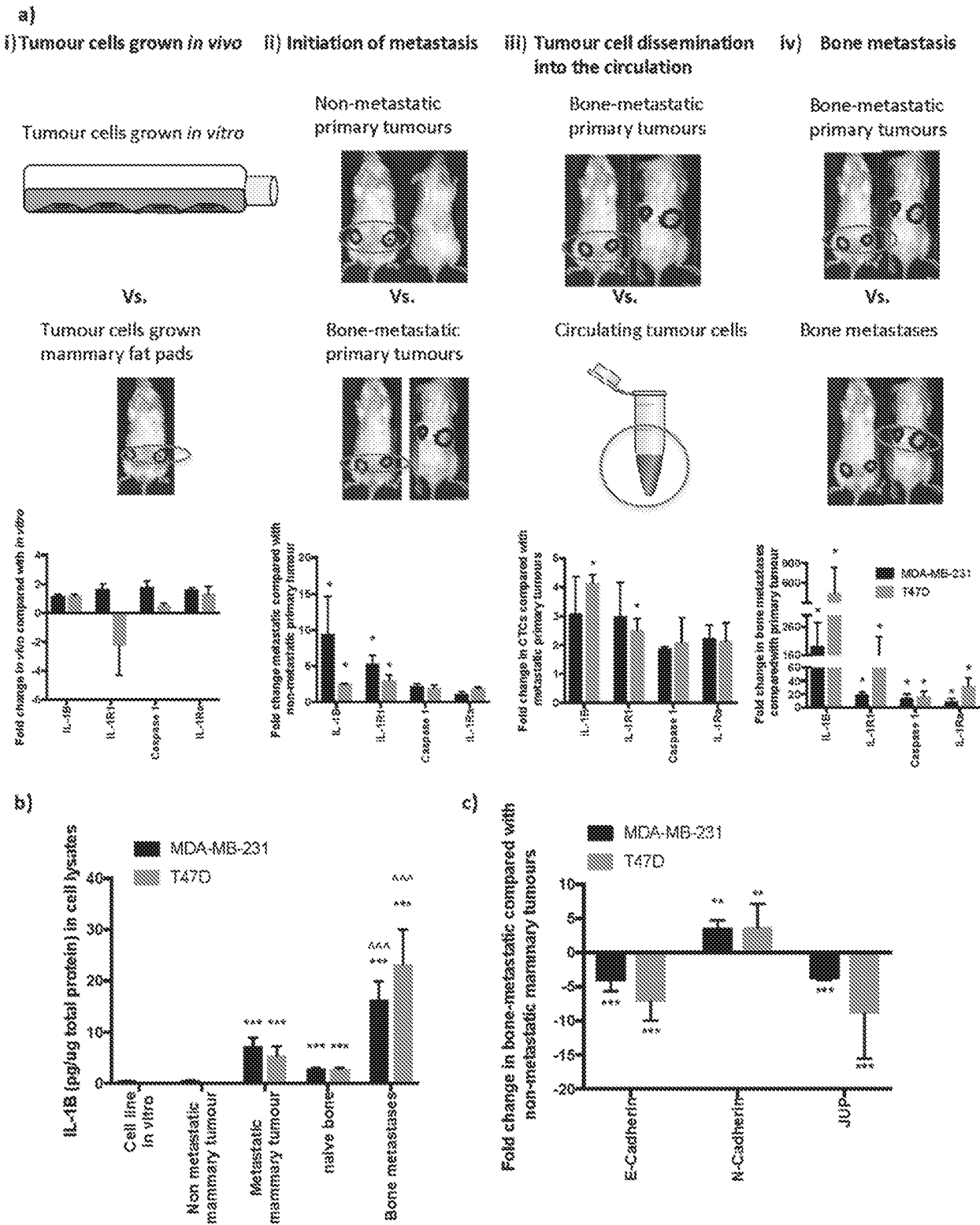


FIGURE 2

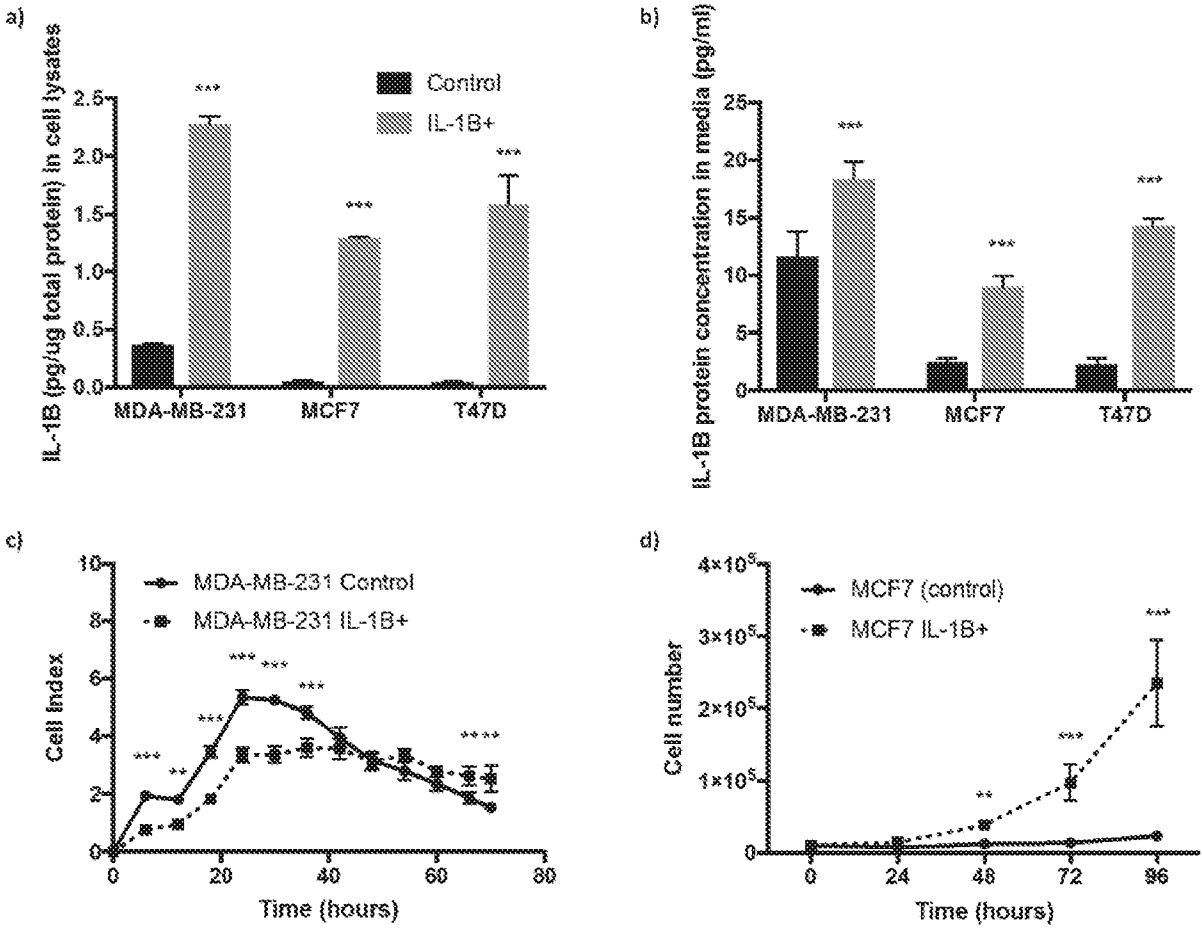


FIGURE 3

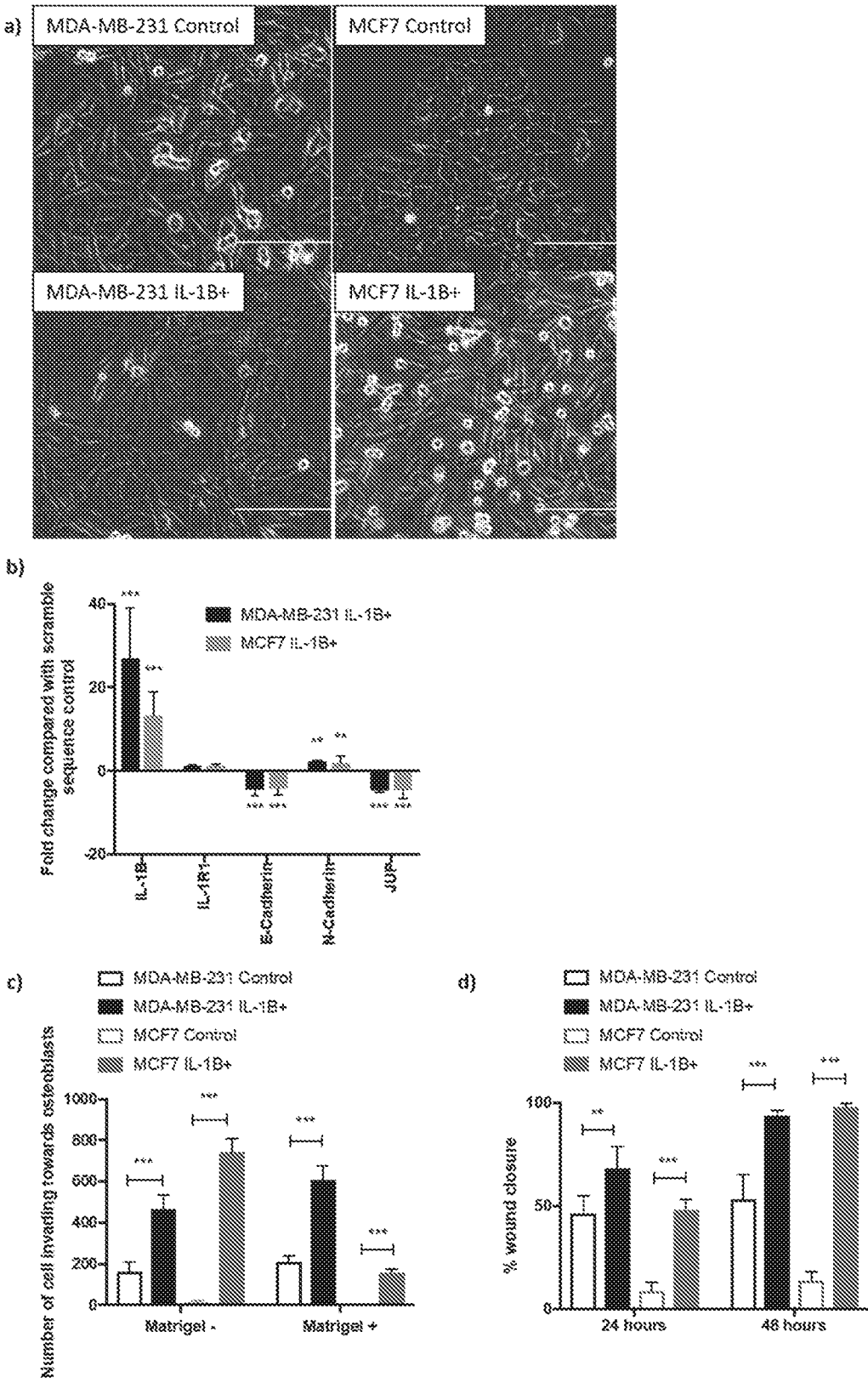


FIGURE 4

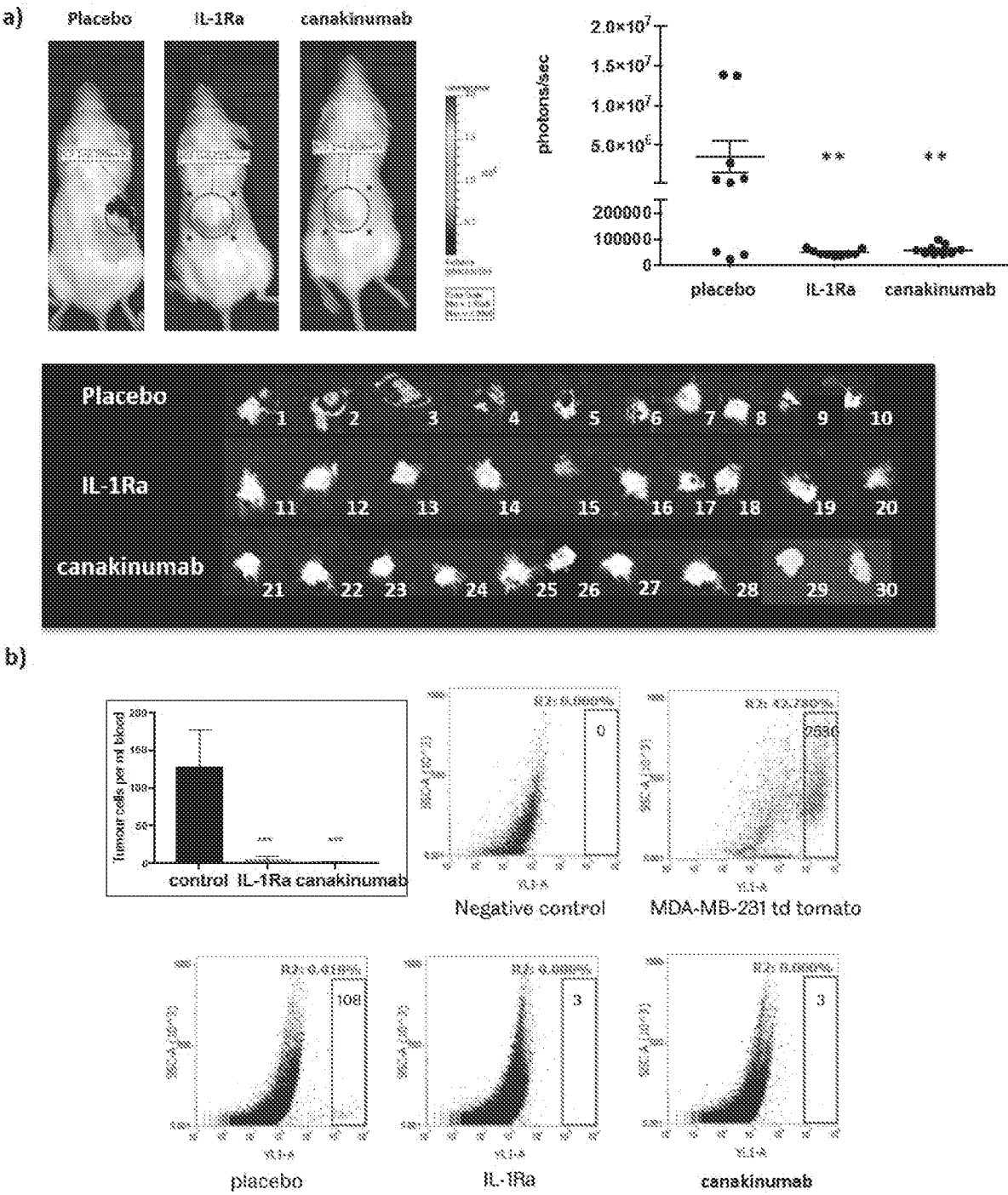


FIGURE 5

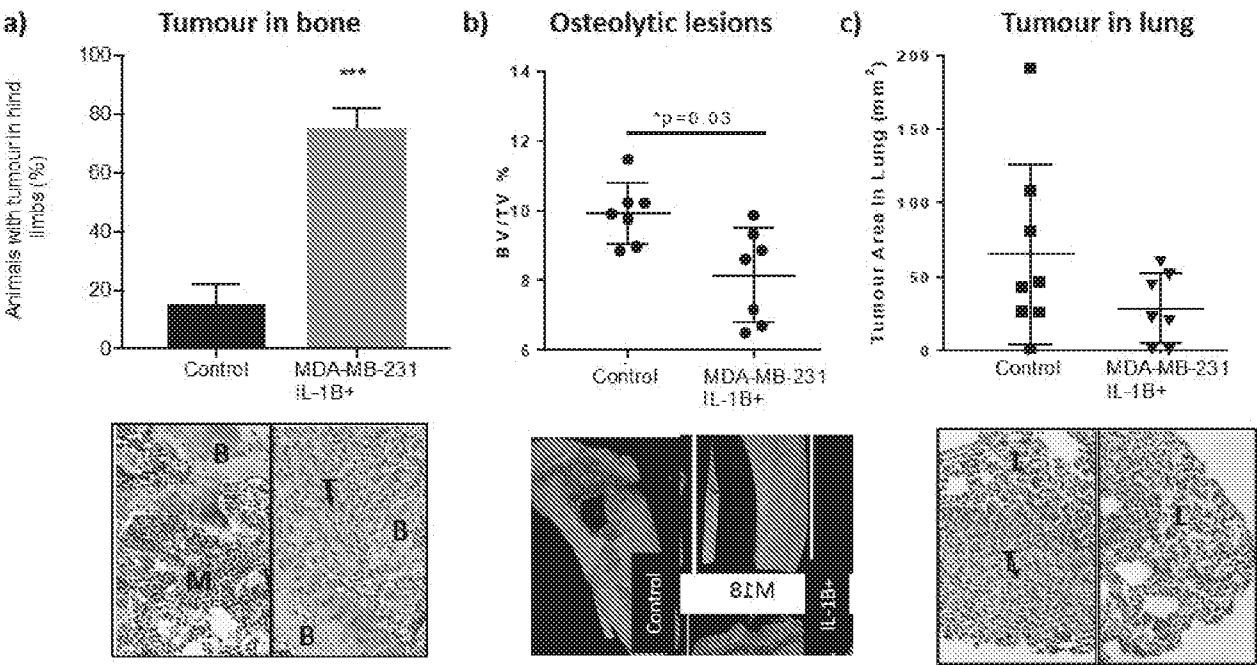


FIGURE 6

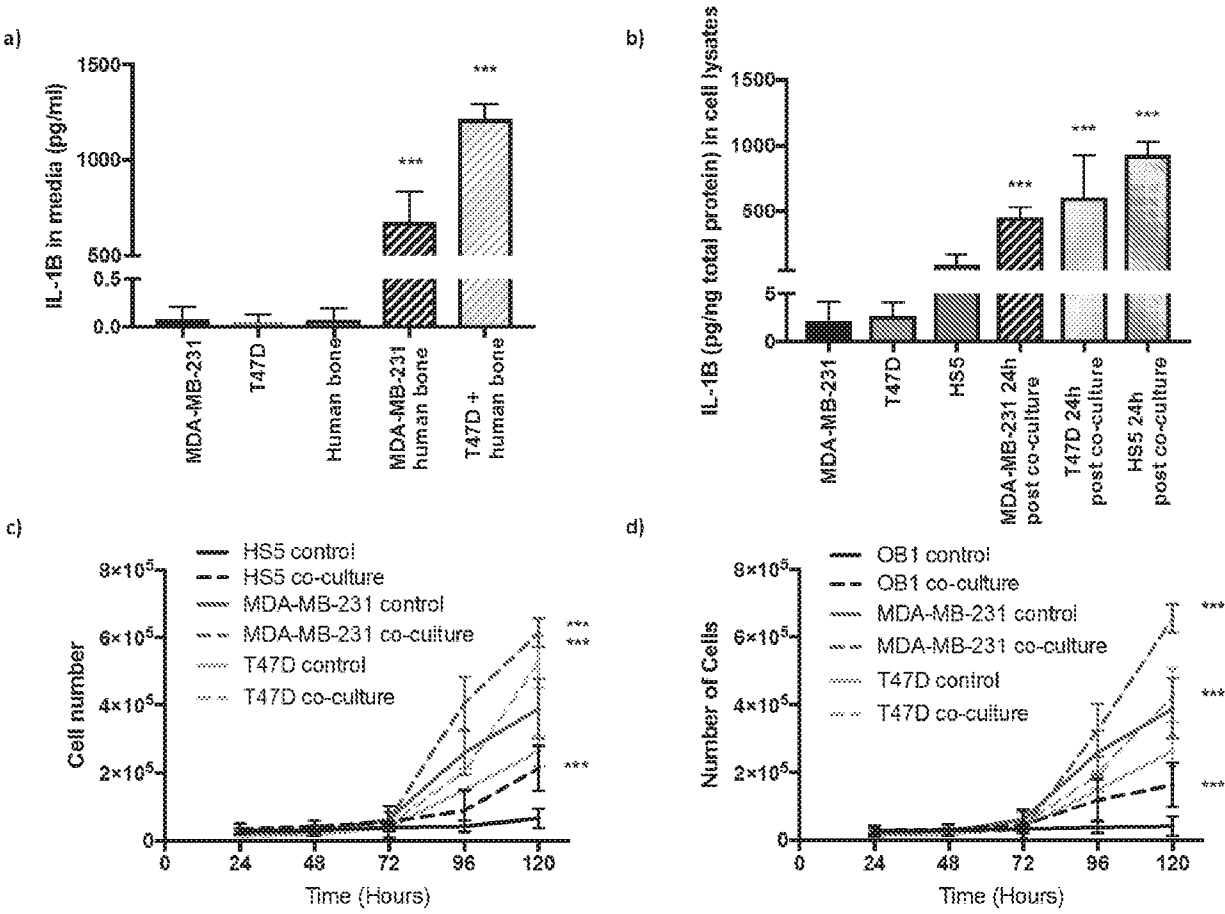


FIGURE 7

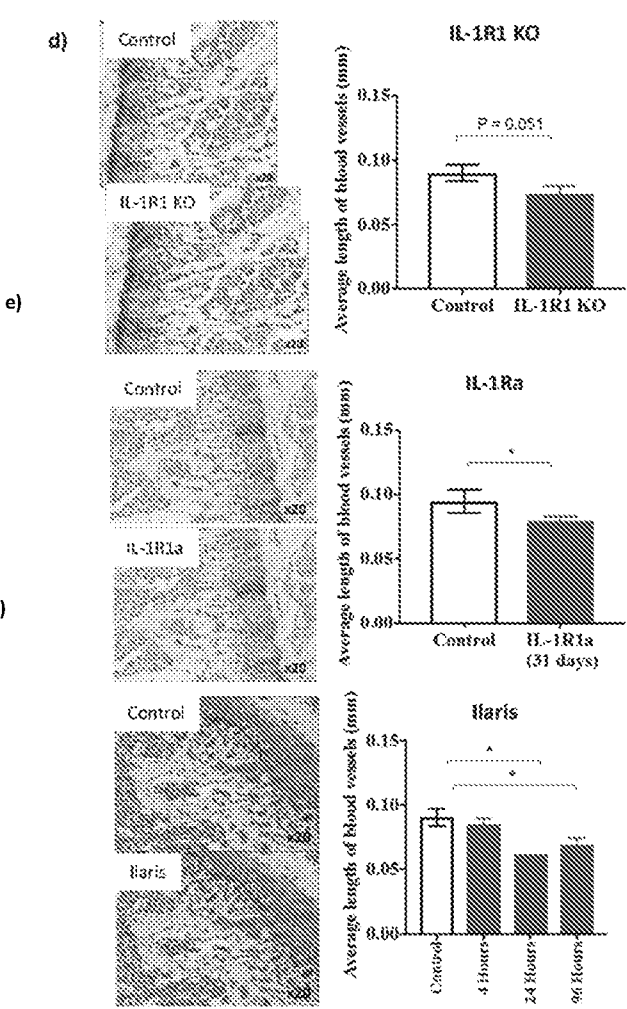
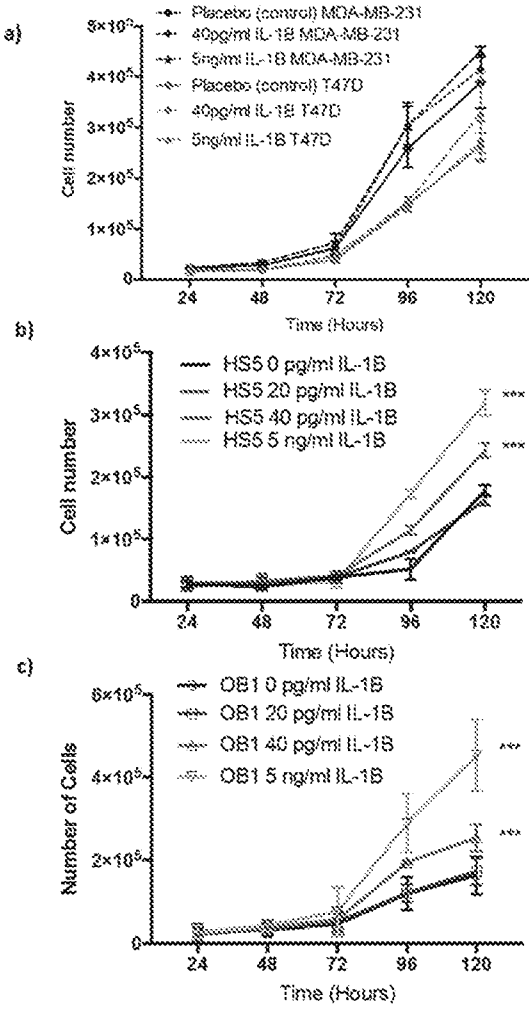


FIGURE 8

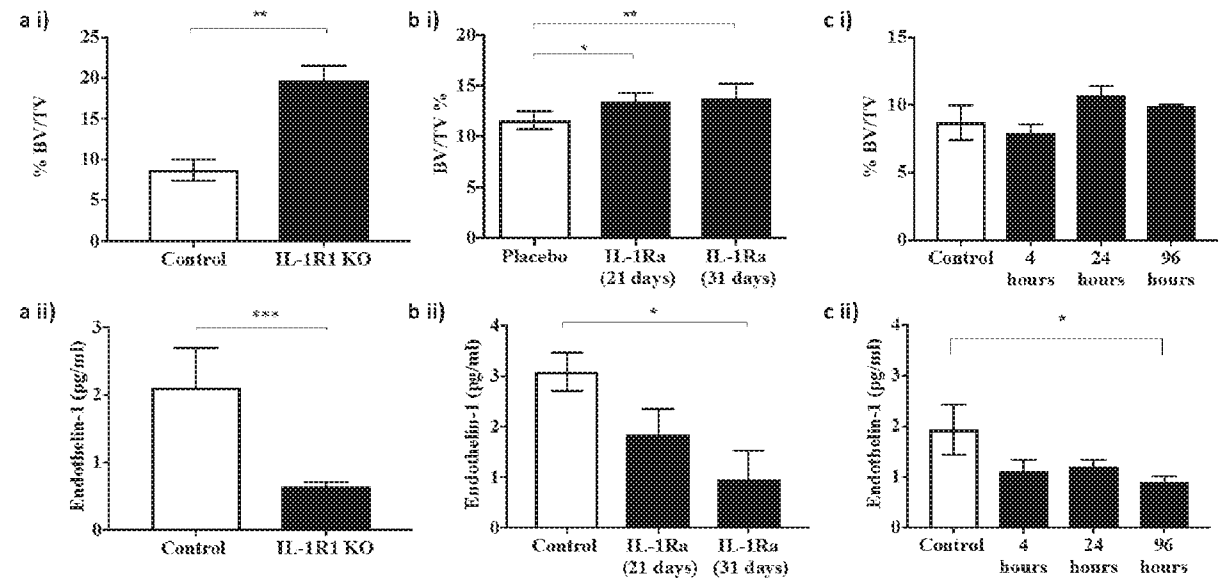


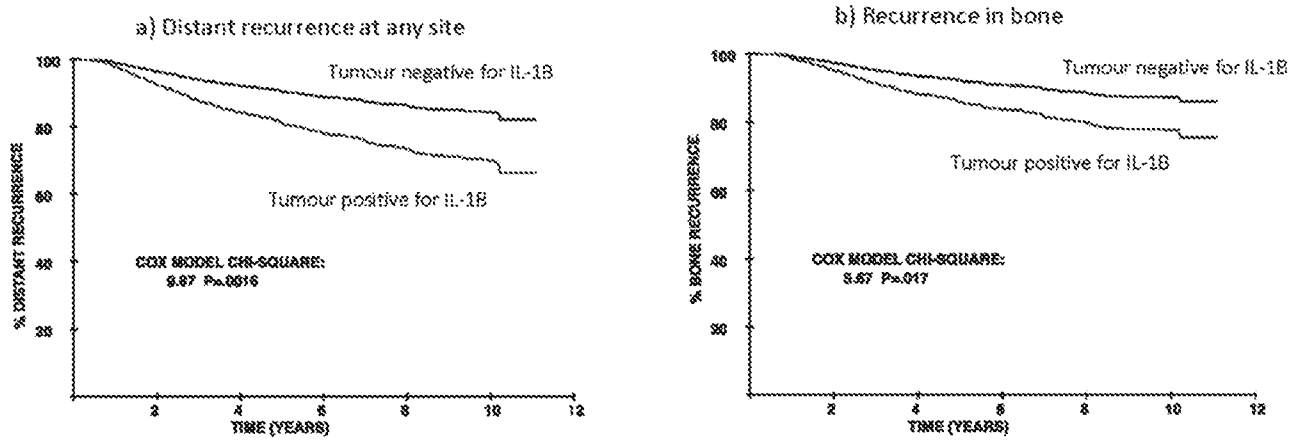
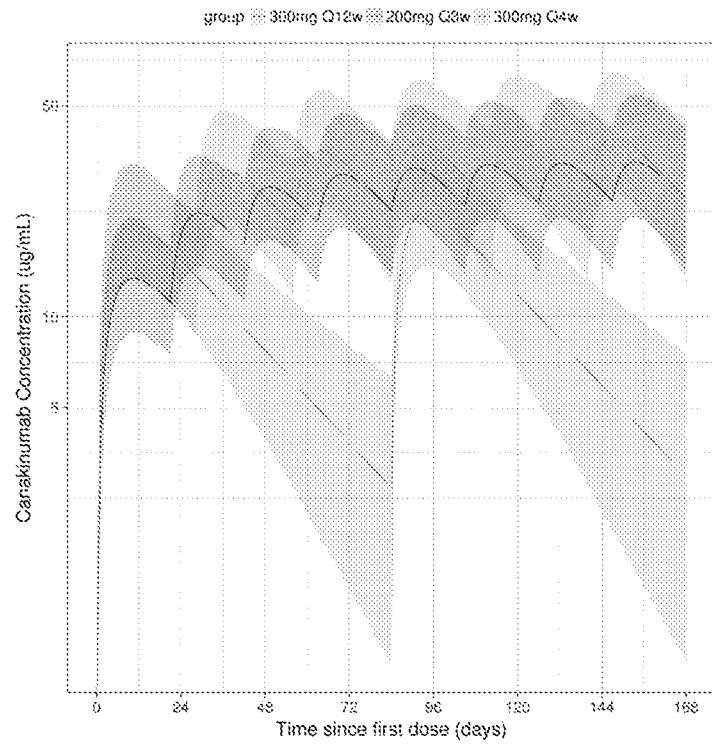
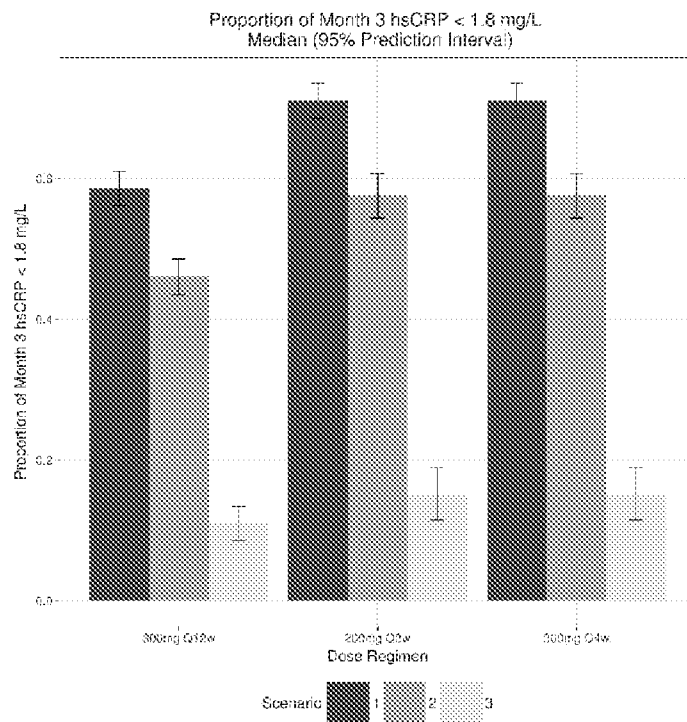
FIGURE 9

FIGURE 10

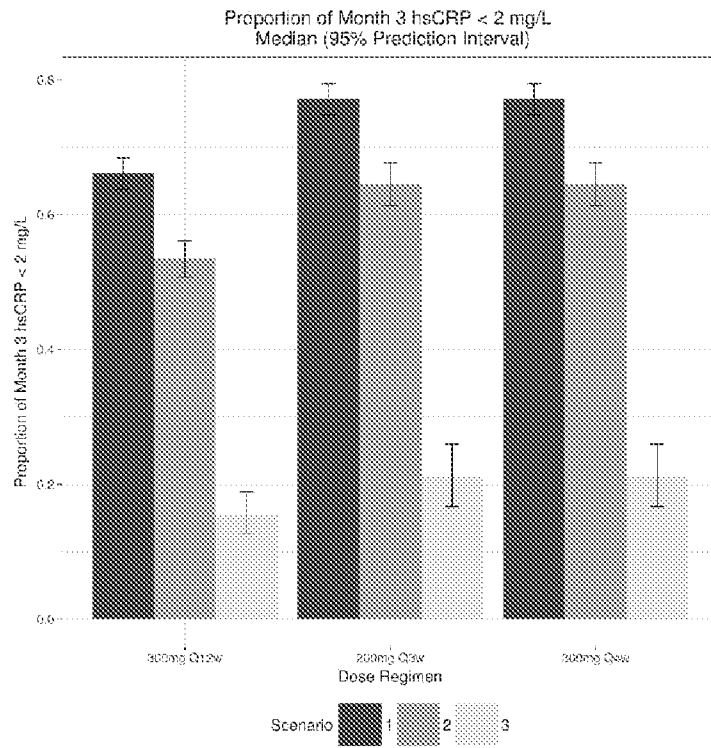
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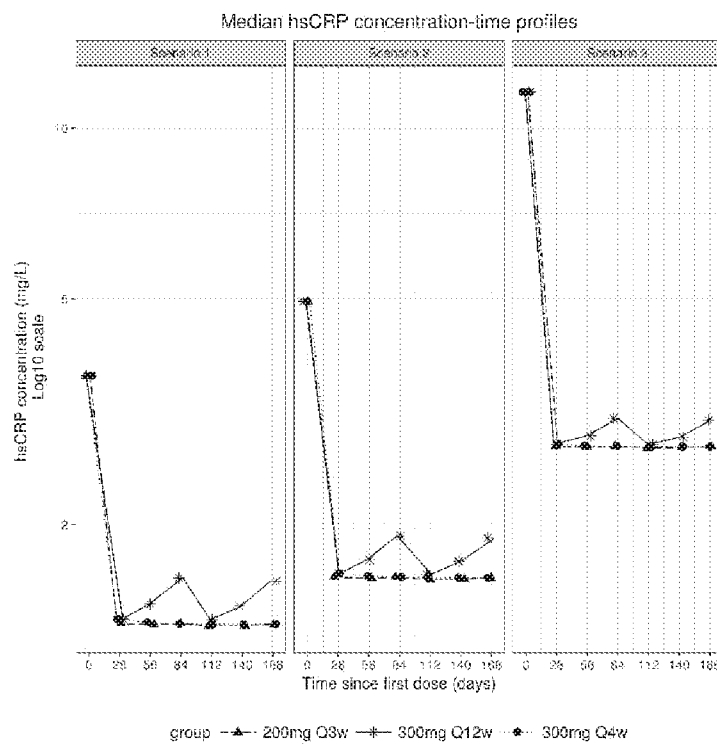
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d)



e)

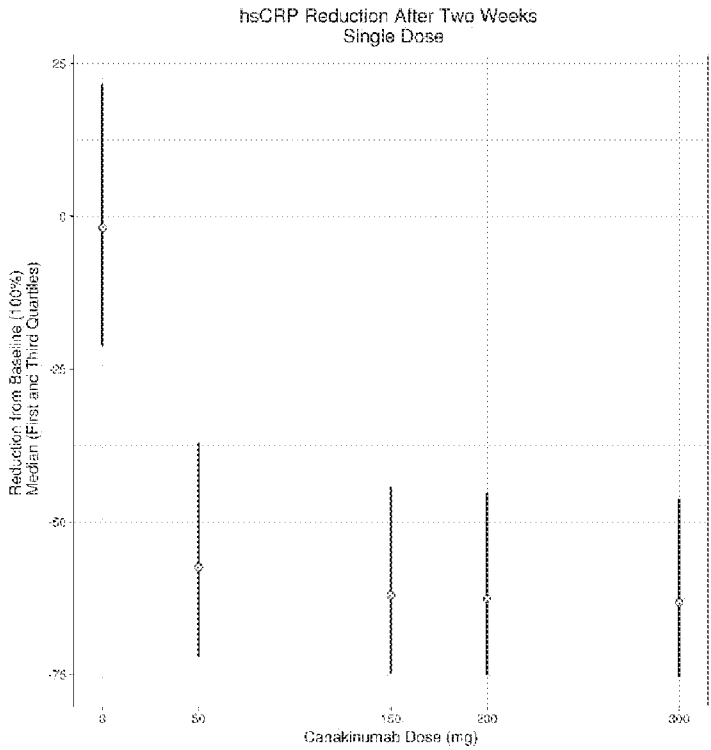


FIGURE 11

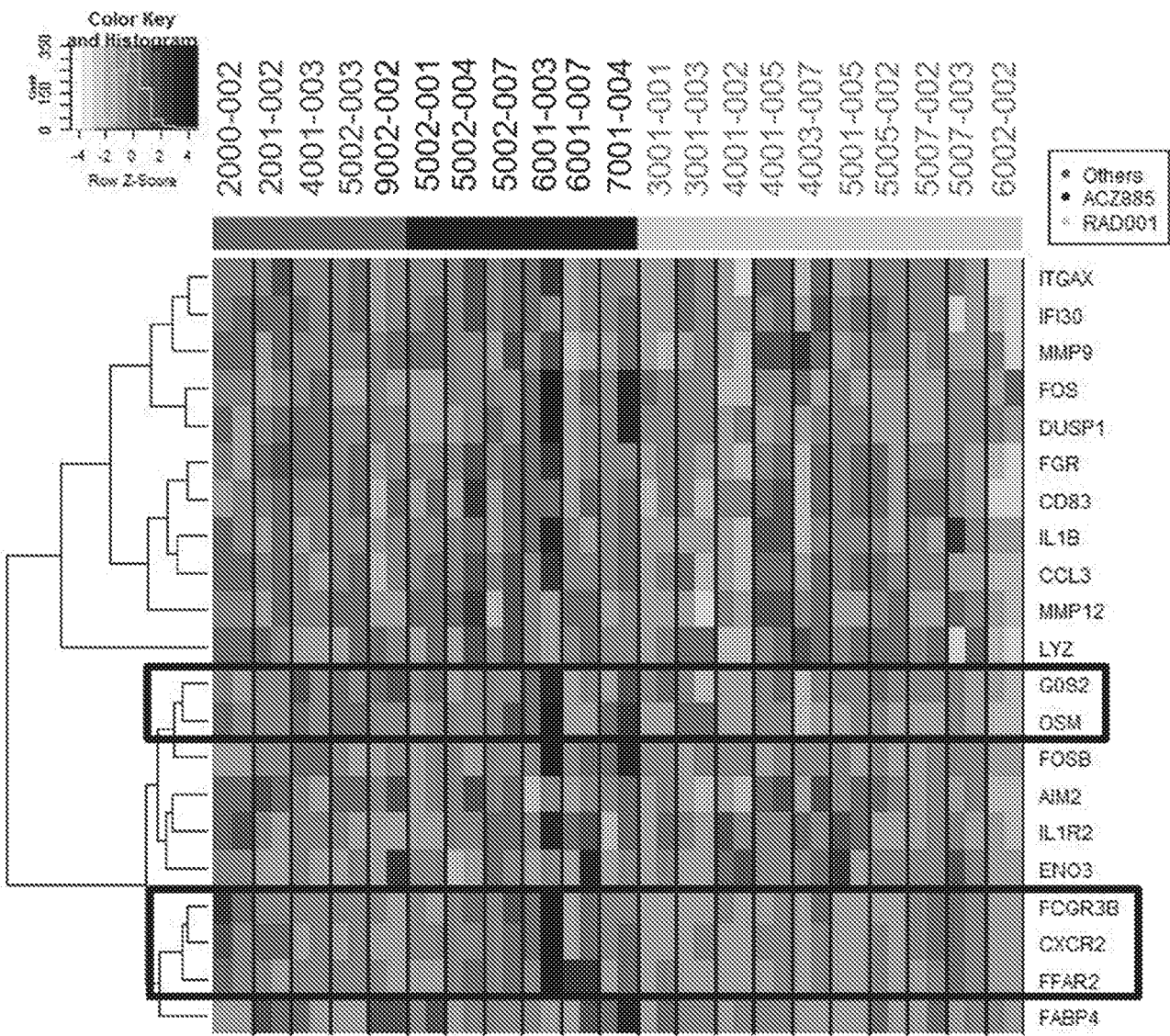
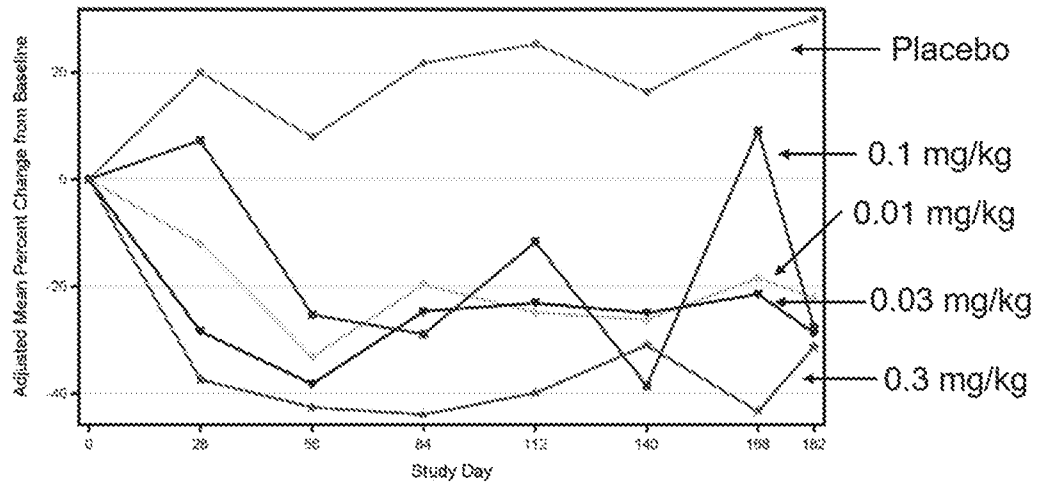
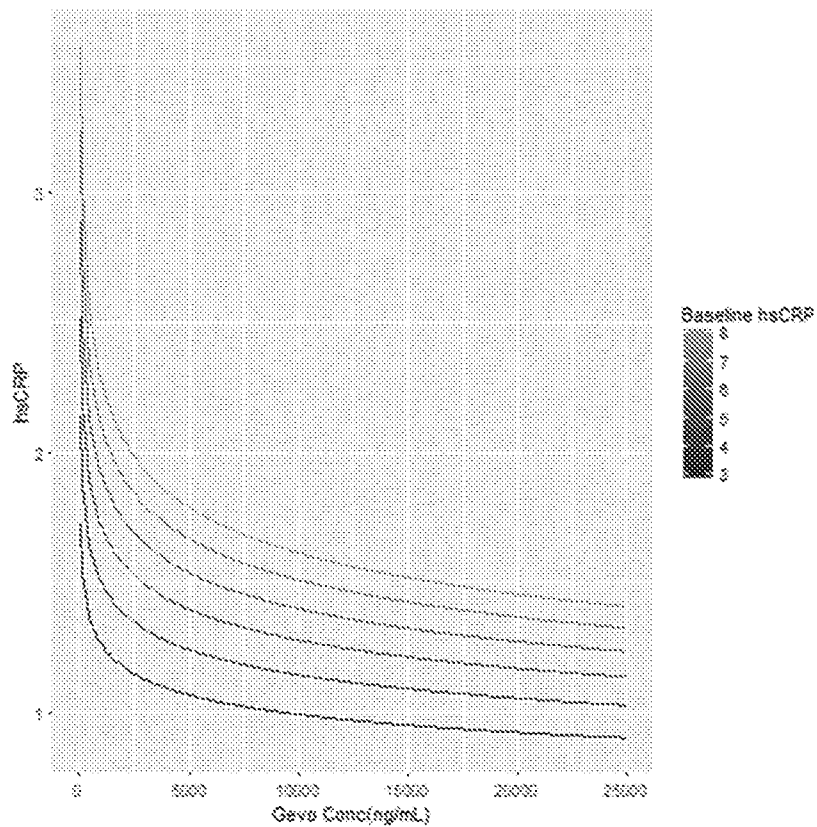


FIGURE 12

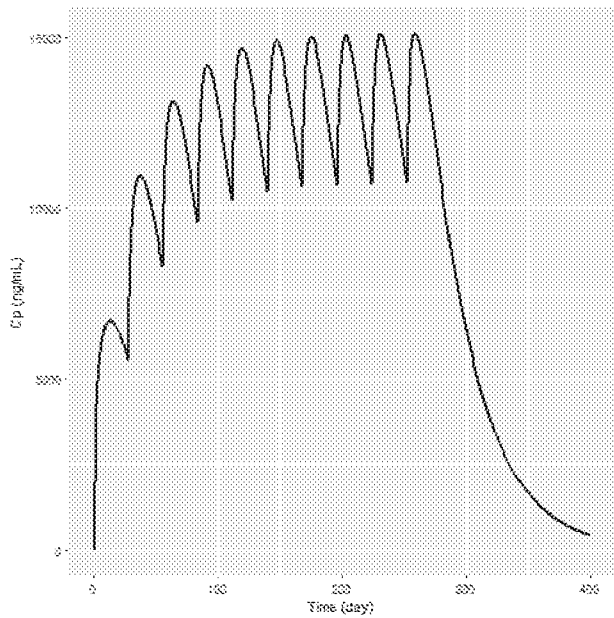
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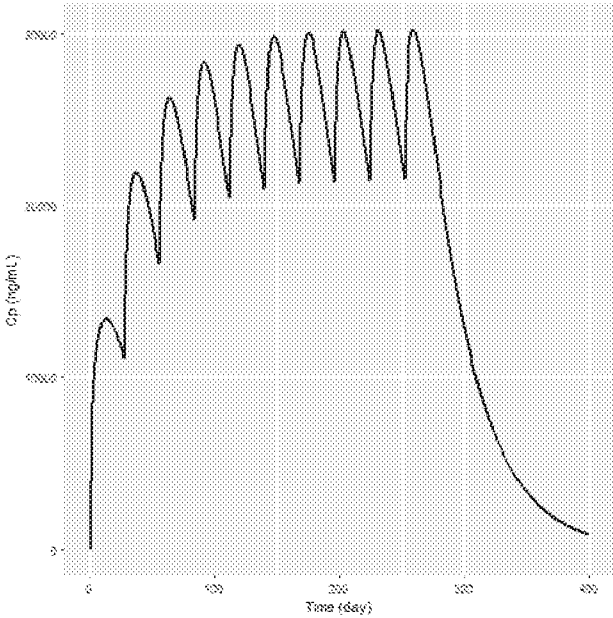


FIGURE 13

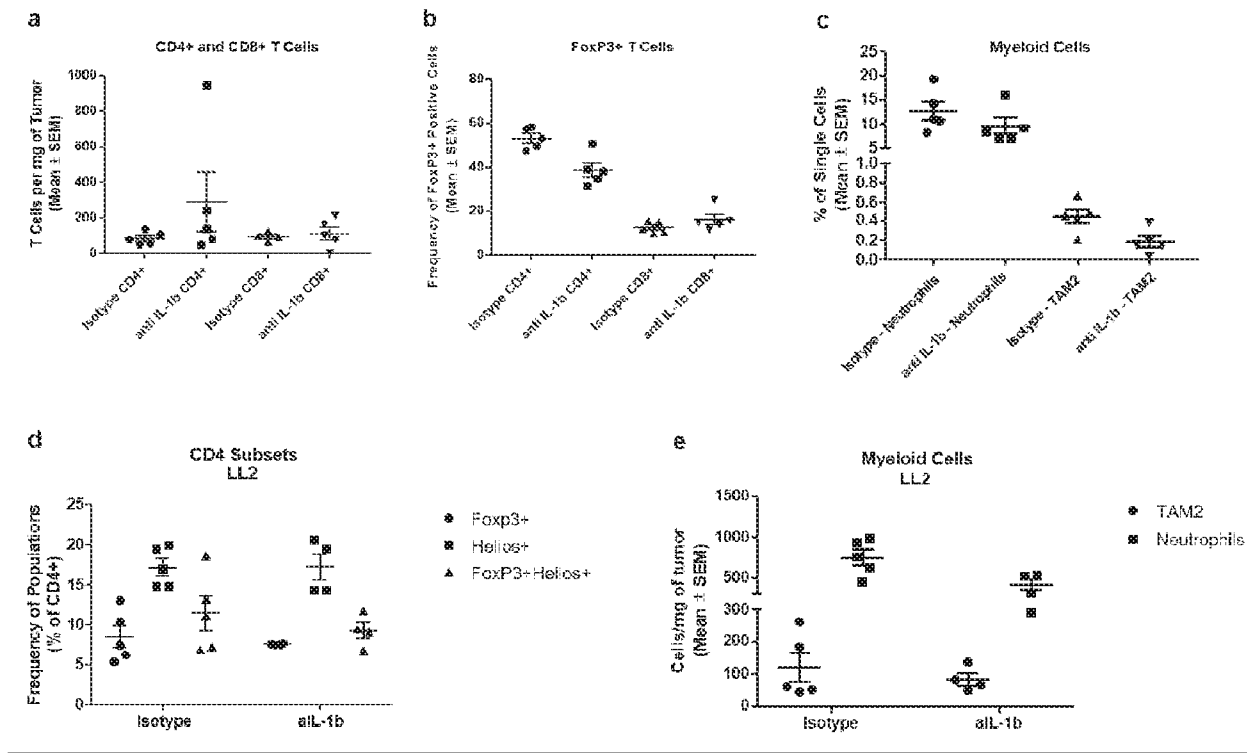


FIGURE 14

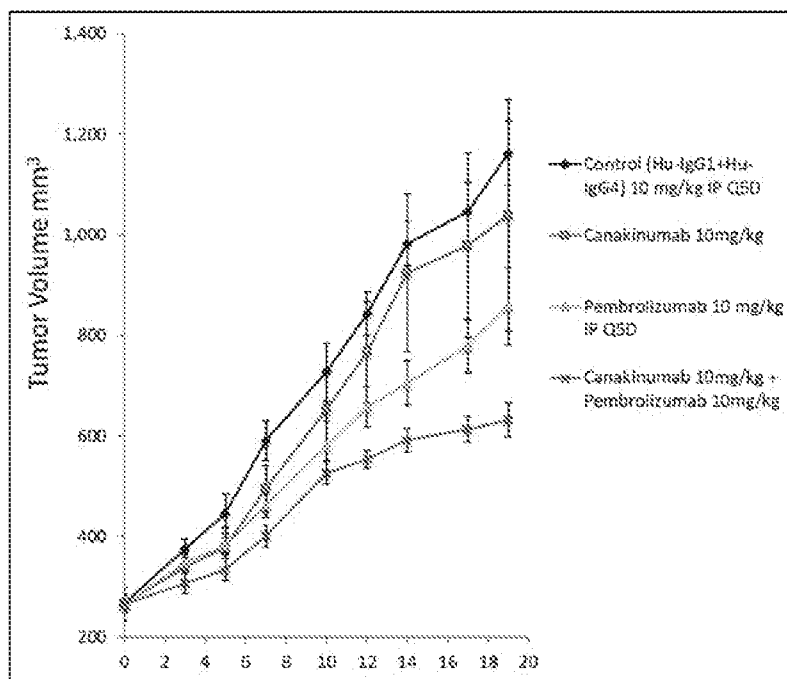


Figure 15A.

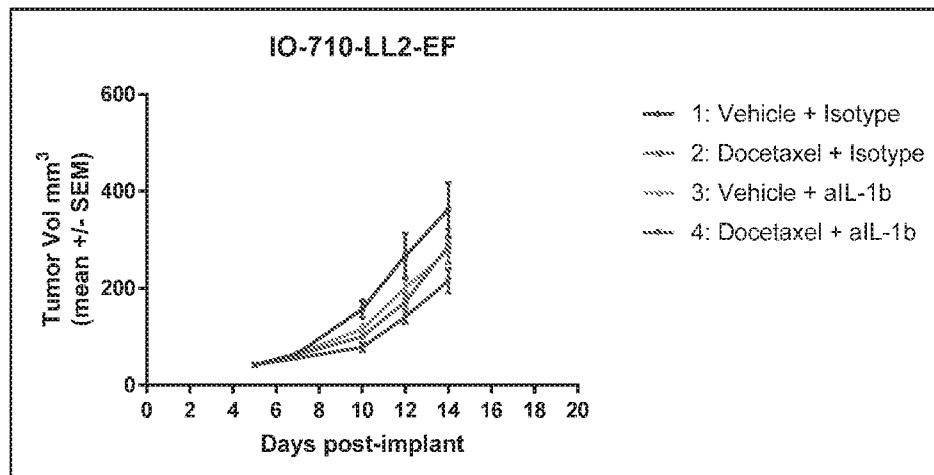


Figure 15B.

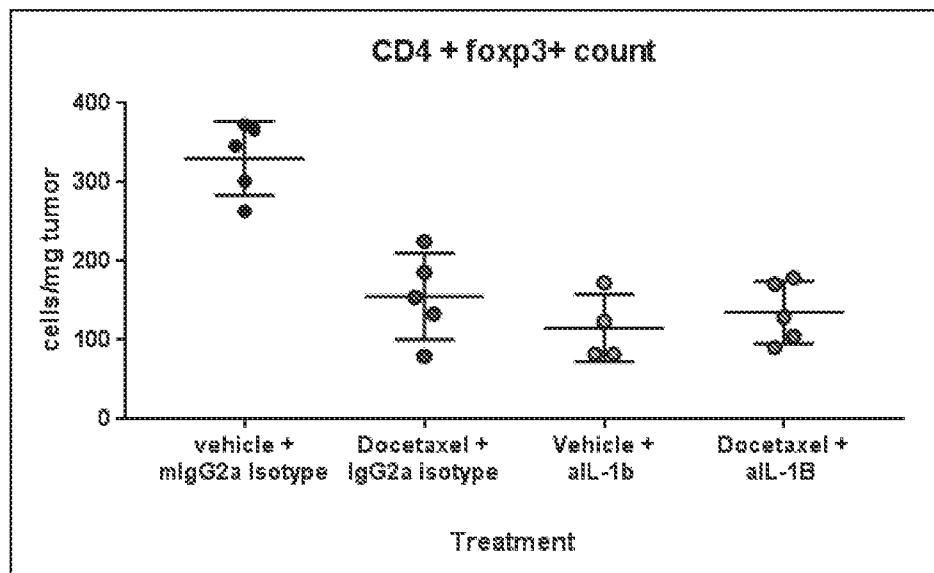


Figure 15C.

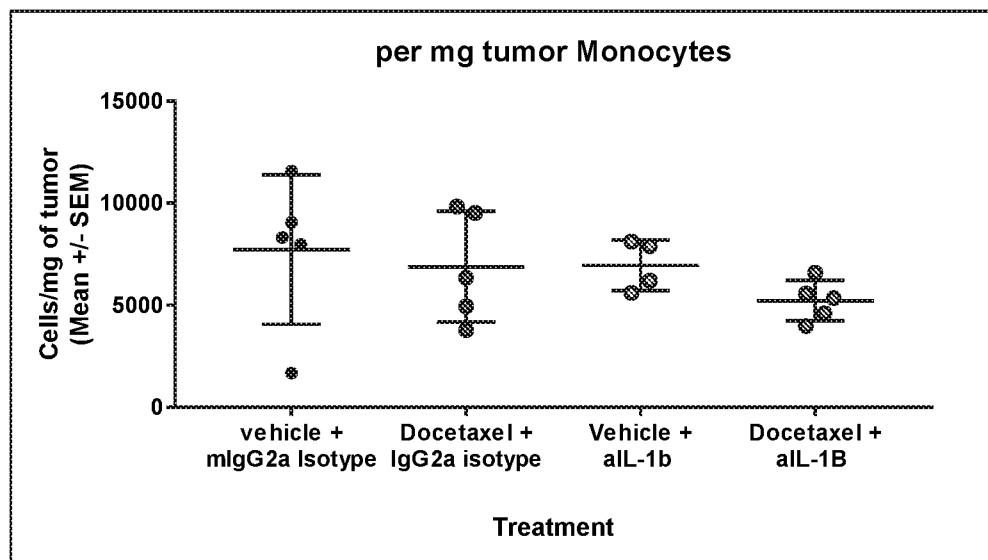


Figure 15D.

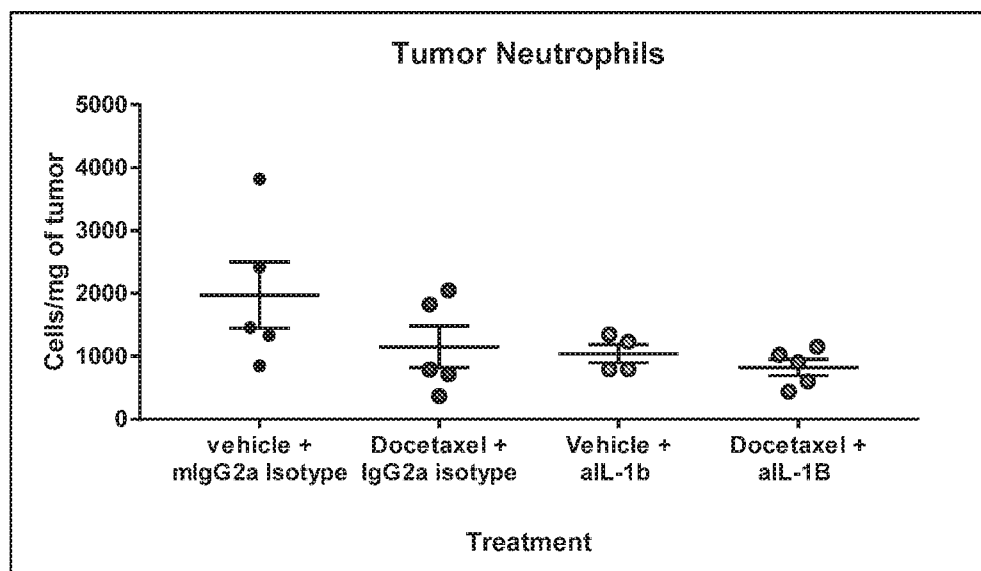


Figure 15E.

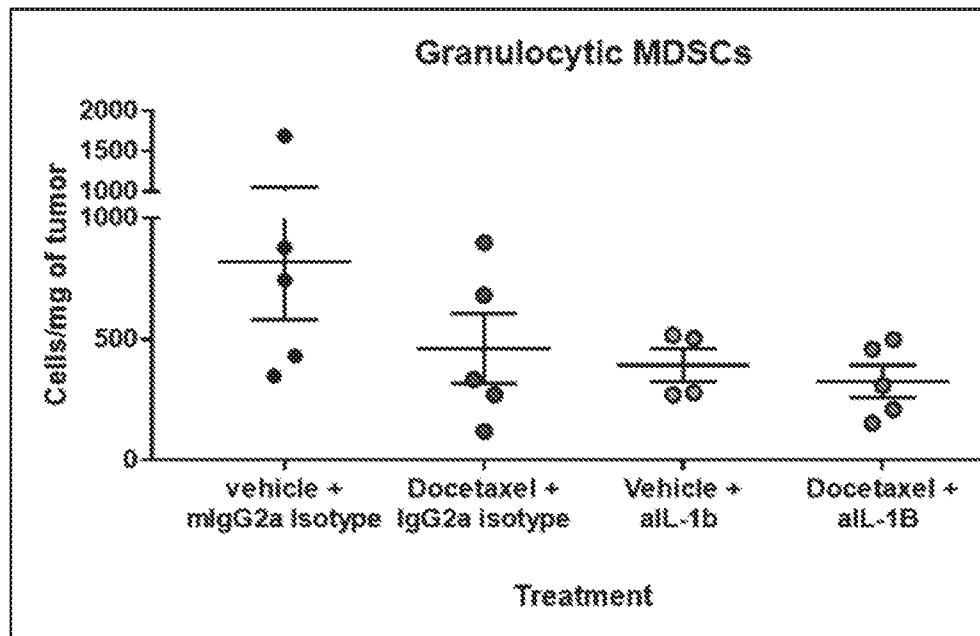


FIGURE 16

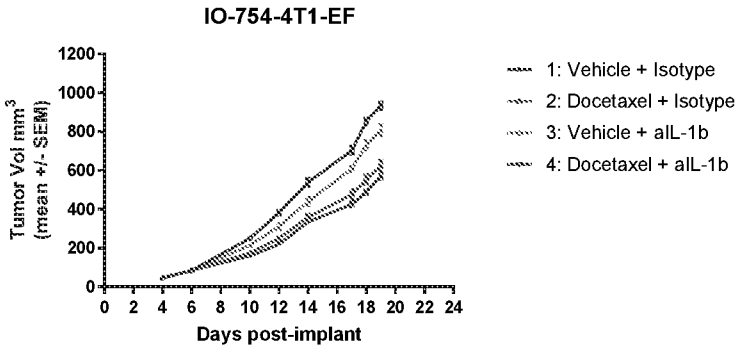


FIGURE 17

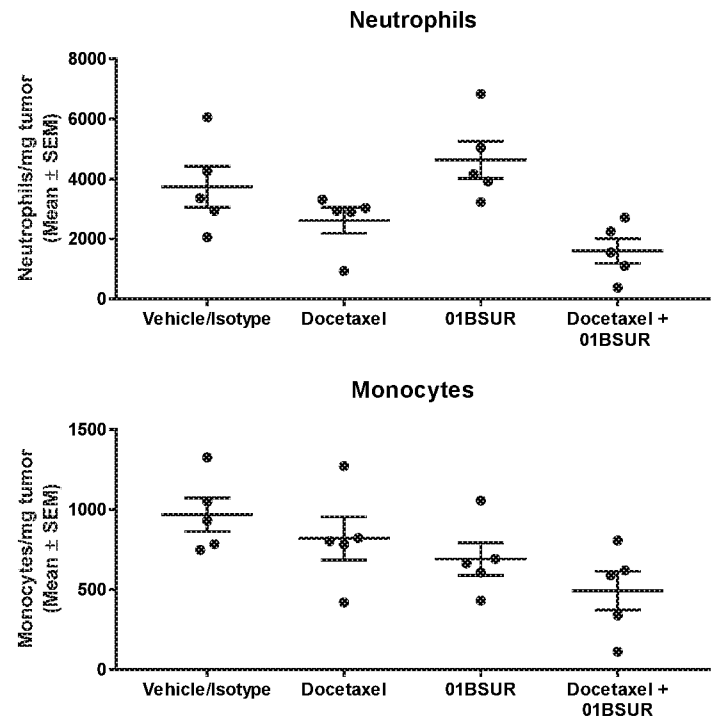


FIGURE 18

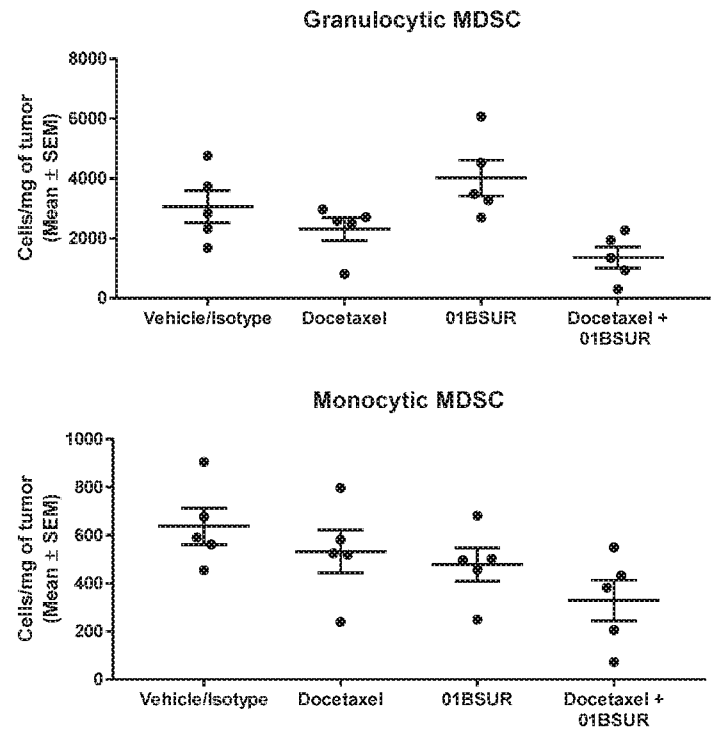


FIGURE 19

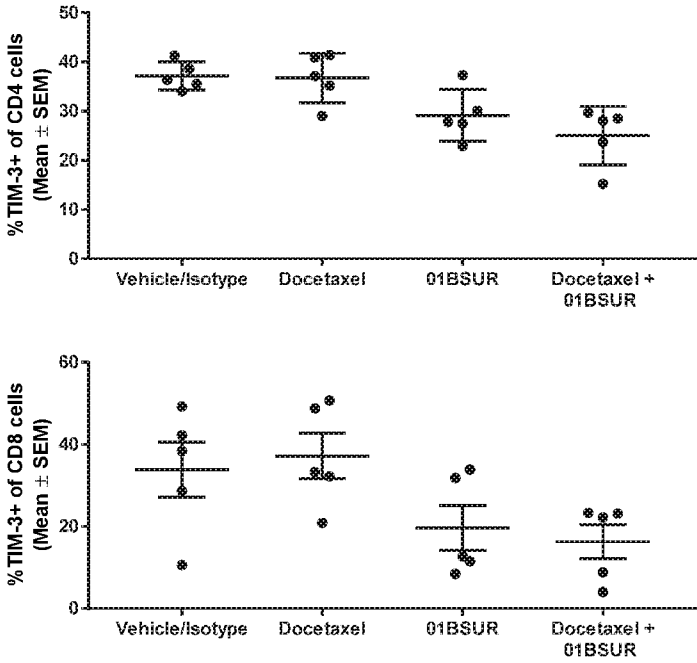
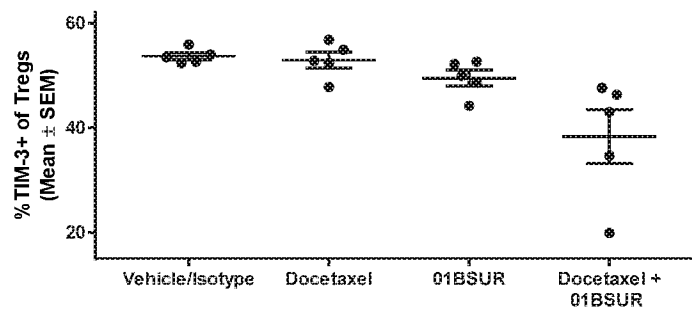


FIGURE 20

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/001436

A. CLASSIFICATION OF SUBJECT MATTER INV. C07K16/24 A61P35/00 A61K31/282 A61K39/00 A61P35/04 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) C07K A61P A61K		
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, 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.
Y	WO 2017/019894 A1 (NOVARTIS AG [CH]; IMMUTEP S A S [FR] ET AL.) 2 February 2017 (2017-02-02) See claims, exemplary IL1 inhibitors -----	1-39
Y	JOHN HOGAN ET AL: "Transcriptional profiles underpin microsatellite status and associated features in colon cancer", GENE., vol. 570, no. 1, October 2015 (2015-10), pages 36-43, XP55693983, NL ISSN: 0378-1119, DOI: 10.1016/j.gene.2015.02.057 See Abstract, discussion ----- -/-	1-39
☒ 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		Date of mailing of the international search report
12 May 2020		26/05/2020
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 Nauche, Stéphane

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/001436

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2016/183176 A1 (UNIV DREXEL [US]) 17 November 2016 (2016-11-17) See claims, page 17, line 24- page 19, line 33 -----	1-39

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2019/001436

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
- a. ☒ forming part of the international application as filed:
- ☒ in the form of an Annex C/ST.25 text file.
- ☐ on paper or in the form of an image file.
- b. ☐ furnished together with the international application under PCT Rule 13~~ter~~.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
- ☐ in the form of an Annex C/ST.25 text file (Rule 13~~ter~~.1(a)).
- ☐ on paper or in the form of an image file (Rule 13~~ter~~.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2019/001436

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017019894 A1	02-02-2017	EP 3317301 A1	09-05-2018
		US 2018340025 A1	29-11-2018
		WO 2017019894 A1	02-02-2017

WO 2016183176 A1	17-11-2016	AU 2016261770 A1	02-11-2017
		CA 2984188 A1	17-11-2016
		EP 3294301 A1	21-03-2018
		JP 2018519269 A	19-07-2018
		US 2018110835 A1	26-04-2018
		WO 2016183176 A1	17-11-2016
