(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 June 2015 (11.06.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/082446 A1

(51) International Patent Classification:
A61K 39/395 (2006.01) *C07K 16/30* (2006.01)
C07K 16/28 (2006.01)

(21) International Application Number:
PCT/EP2014/076200

(22) International Filing Date:
2 December 2014 (02.12.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
13195323.4 2 December 2013 (02.12.2013) EP

(71) Applicant *(for all designated States except US)*: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(71) Applicant *(for US only)*: **HOFFMANN-LA ROCHE INC.** [US/US]; Great Notch, 150 Clove Road, 8th Floor, Little Falls, NJ (US).

(72) Inventors: **BOSSENMAIER, Birgit**; Horst-Wolfram-Geissler-Weg 10, 82229 Seefeld (DE). **LIFKE, Alexander**; Saalangerstrasse 36, 82377 Penzbergep (DE). **NIEDERFELLNER, Gerhard**; Dorfstr. 36b, 82386 Oberhausen (DE). **NOPORA, Adam**; Krottenkopfstrasse 10, 82362 Weilheim (DE). **KOLLMORGEN, Gwendlyn**; Dorfstr. 36 b, 82386 Oberhausen (DE). **KRIETER, Oliver**; Wolfratshausener Str. 94b, 81379 Muenchen (DE).

(74) Agents: **HAYES, Emily** et al.; Mewburn Ellis LLP, 33 Gutter Lane, London, Greater London EC2V 8AS (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

(54) **Title**: TREATMENT OF CANCER USING AN ANTI-CDCP1 ANTIBODY AND A TAXANE

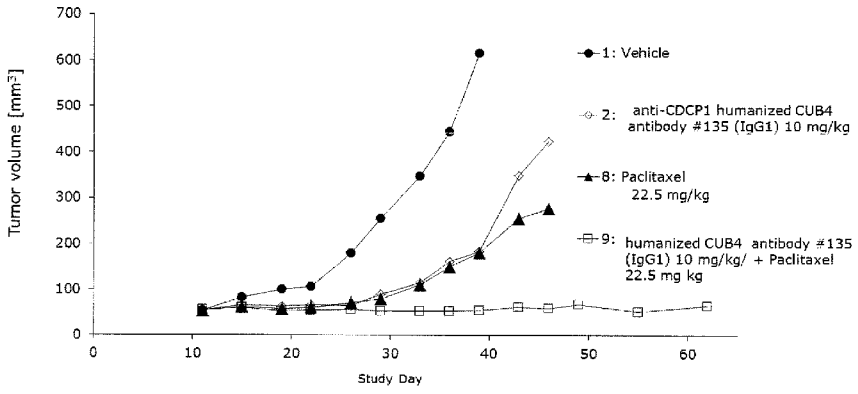

Figure 1

(57) **Abstract**: The present invention relates to the use of an anti-CDCP1 antibody for the treatment of cancer, in combination with a taxane. The invention also relates to methods of treating cancer using an anti-CDCP1 antibody and a taxane.

WO 2015/082446 A1

TREATMENT OF CANCER USING AN ANTI-CDCP1 ANTIBODY AND A TAXANE

Field of invention

The present invention relates to the use of an anti-CDCP1 antibody for the treatment of cancer, in combination with a taxane.

Background to the invention

Human CDCP1 (CUB domain containing protein 1, B345, CD318, SIMA135, TRASK; SEQ ID NO:1 and variants with mutation R525Q (i.e. replacement of Arginine (R) with Glutamine (Q) at amino acid position 525 of SEQ ID NO:1) and/or mutation G709D (i.e. replacement of Glycine (G) with Aspartic acid (D) at amino acid position 709 of SEQ ID NO:1)) is a transmembrane protein containing three extracellular CUB domains. This protein is found to be overexpressed in breast, colon and lung cancers. Its expression level is correlated with the metastatic ability of carcinoma cells (Uekita, T. et al., Am. J. Pathol. 172 (2008) 1729-1739). It has been shown to be tyrosine phosphorylated in a cancer cell line (see WO 2002/004508; Scherl-Mostageer, M., et al., Oncogene 20 (2001) 4402-8; Hooper, J., D., et al., Oncogene 22 (2003) 1783-94; Perry, S., E., et al FEBS Lett. 581 (2007) 1137-42; Brown, T., A., at al J. Biol. Chem. 279 (2004) 14772-14783; Ota, T., et al., Nat. Genet. 36 (2004) 40-45). Alternatively spliced transcript variants encoding distinct isoforms have been reported.

WO 2002/004508 refers to CDCP1 as tumor associated antigen B345. WO 2004/074481 relates to CDCP1 as glycoprotein antigen SIMA135 expressed in metastatic tumor cells. WO 2005/042102 relates to CDCP1 as a protein involved in ovarian cancer. WO 2007/005502 relates to methods and compositions for treating diseases targeting CDCP1.

US 2004/0053343 (and Conze, T., et al., Ann. N. Y. Acad. Sci. 996 (2003) 222-6 and Buehring, H.J. et al., Stem Cells 22 (2004) 334-43) relates to CDCP1 antibodies for identifying certain stem cell populations.

WO 2008/133851 relates to the use of anti-CDCP1 antibodies conjugated to a cytotoxic agent for treating and/or diagnosing cancer, e.g. prostate cancer.

WO 2011/023389 relates to humanised antibodies against human CDCP1 and the use of these antibodies to treat cancer.

WO 2011/023390 relates to antibodies against human CDCP1 for the treatment of cancer.

Taxanes are diterpenes produced by plants of the genus *Taxus* (yews) and are widely used as chemotherapy agents (see Hagiwara, H. and Sunada, Y., Breast Cancer (2004), 11(1), 82-85). The principal mechanism of action of the taxane class of drugs is the disruption of microtubule function, thereby inhibiting the process of cell division. Some toxic side effects associated with taxanes have been reported (see also Hagiwara and Sunada, 2004). Taxanes were originally derived from natural sources. For example, paclitaxel (Taxol®) was originally derived from the Pacific yew tree (see Rowinsky, E.K. and Donehower, R.C., The New England Journal of Medicine (1995), 332: 1004-1014). Another example of a taxane used to treat cancer is docetaxel (Taxotere®) (see Earhart, R.H., Semin. Oncol. (1999), 26(5 Suppl 17):8-13). Modified forms of paclitaxel are also available for the treatment of cancer. For example, paclitaxel may be bound to albumin to form Abraxane®, which is also known as nab-paclitaxel (see Yardley, D.A., J Control Release (2013), 170(3):365-372). Another modified form of paclitaxel is Opaxio®, which links paclitaxel to a biodegradable polyglutamate polymer and is also known as paclitaxel poliglumex (see Galic, V.L. *et al.*, Expert Opin Investig Drugs (2011), 20(6):813-821). Hongdoushans A-C are oxygenated taxane diterpenes, isolated from the wood of *Taxus wallichiana*. Hongdoushan A ($C_{29}H_{44}O_7$), hongdoushan B ($C_{27}H_{40}O_7$) and hongdoushan C ($C_{27}H_{42}O_6$) are reported to have anti-cancer activity *in vitro* (see Banskota, A.H. *et al.*, J. Nat. Prod. (2002), 65(11), 1700-1702).

Summary of the invention

The present inventors have found that anti-CDCP1 antibodies enhance the efficacy of taxanes to decrease tumour growth. This means that lower doses of taxane can be administered to a patient to achieve the same effect, which reduces that risk of side effects.

In a first aspect, the invention provides an anti-CDCP1 antibody for use in a method of treatment of cancer in a subject, the method comprising administering said antibody and a taxane to the subject.

In a second aspect, the invention provides a method for the treatment of cancer, wherein the method comprises the step of administering an effective amount of an anti-CDCP1 antibody and an effective amount of a taxane to a patient in need thereof.

In a third aspect, the invention provides the use of an anti-CDCP1 antibody in the manufacture of a medicament for the treatment of cancer, wherein the antibody is for administration with a taxane.

In a fourth aspect, the invention provides a taxane for use in a method of treatment of cancer in a subject, the method comprising administering a taxane and an anti-CDCP1 antibody to the subject.

In a fifth aspect, the invention provides the use of a taxane in the manufacture of a medicament for the treatment of cancer, wherein the taxane is for administration with an anti-CDCP1 antibody.

In a sixth aspect, the invention provides an anti-CDCP1 antibody and a taxane for use in combination for the treatment of cancer.

In a seventh aspect, the invention provides a method for the treatment of cancer, wherein the method comprises the step of administering an effective amount of an anti-CDCP1 antibody in combination with an effective amount of a taxane to a patient in need thereof.

In an eighth aspect, the invention provides the use of an anti-CDCP1 antibody and a taxane in combination in the manufacture of a medicament for the treatment of cancer.

In any of the aspects of invention set out above, the anti-CDCP1 antibody for use in the invention preferably binds to human CDCP1.

Preferably, the anti-CDCP1 antibody is a monoclonal antibody.

Preferably, the anti-CDCP1 antibody is humanised.

Preferably, the anti-CDCP1 antibody binds to essentially the same epitope as the CUB4 antibody deposited with Deposition No. DSM ACC2551.

Preferably, the anti-CDCP1 antibody specifically binds to human CDCP1 with a K_D value of less than 1.0×10^{-8} mol/l, as determined by surface plasmon resonance (Biacore™).

The anti-CDCP1 antibody is preferably an IgG antibody and more preferably, the anti-CDCP1 antibody is of human IgG1 subclass.

The anti-CDCP1 antibody preferably comprises a heavy chain variable domain that comprises an HCDR1 region, an HCDR2 region and an HCDR3 region, wherein the sequences of the HCDR1 region, the HCDR2 region and the HCDR3 region are selected from one of the sets of heavy chain complementary determining sequences (HCDRs) shown in Table 1 below:

Set of HCDR sequences	**HCDR1 sequence**	**HCDR2 sequence**	**HCDR3 sequence**
mVH-CUB4	SYGMS (SEQ ID NO:2)	TISSGGSYTYYPDSVKG (SEQ ID NO:3)	HPDYDGVWFAY (SEQ ID NO:4)
hHC4-H	SYGMS (SEQ ID NO:5)	TISSGGSYKYYVDSVKG (SEQ ID NO:6)	HPDYDGVWFAY (SEQ ID NO:7)
hHC4-c	SYGMS (SEQ ID NO:8)	TISSGGSYTYYPDSVKG (SEQ ID NO:9)	HPDYDGVWFAY (SEQ ID NO:10)
hHC4-a	SYGMS (SEQ ID NO:11)	TISSGGSYTYYPDSVKG (SEQ ID NO:12)	HPDYDGVWFAY (SEQ ID NO:13)
hHC4-d	SYGMS	TISSGGSYTYYPDSVKG	HPDYDGVWFAY

	(SEQ ID NO:14)	(SEQ ID NO:15)	(SEQ ID NO:16)
hHC4-04	SYGMS (SEQ ID NO:17)	TISSGGSYTYYPDSVKG (SEQ ID NO:18)	HPDYDGVWFAY (SEQ ID NO:19)
hHC4-K	SYGMS (SEQ ID NO:20)	SISSGGSYIYYADSVKG (SEQ ID NO:21)	HPDYDGVWFAY (SEQ ID NO:22)
hHC4-K2	SYGMS (SEQ ID NO:23)	SISSGGSYTYYADSVKG (SEQ ID NO:24)	HPDYDGVWFAY (SEQ ID NO:25)
hHC4-I	SYAMS (SEQ ID NO:26)	AISSGGSYTYYADSVKG (SEQ ID NO:27)	HPDYDGVWFAY (SEQ ID NO:28)
hHC4-07	SYAMS (SEQ ID NO:29)	TISSGGSYTYYPDSVKG (SEQ ID NO:30)	HPDYDGVWFAY (SEQ ID NO:31)
hHC4-03	SYGMS (SEQ ID NO:32)	AISSGGSYTYYPDSVKG (SEQ ID NO:33)	HPDYDGVWFAY (SEQ ID NO:34)
hHC4-b	SYSMN (SEQ ID NO:35)	SISSGGSYIYYADSVKG (SEQ ID NO:36)	HPDYDGVWFAY (SEQ ID NO:37)
CDCP1-004	TAGVGVS (SEQ ID NO:38)	HIYWDDDKRYNPSLKS (SEQ ID NO:39)	STSVEEAFDV (SEQ ID NO:40)
CDCP1-0012	TAGMGVS (SEQ ID NO:41)	HIYWDDDKRYNPSLKS (SEQ ID NO:42)	SDSFGDFDY (SEQ ID NO:43)
CDCP1-0015	NFGLH (SEQ ID NO:44)	VIWSGGVTDYNAAFIS (SEQ ID NO:45)	NYDHDYSMDY (SEQ ID NO:46)

Table 1: Sequences of preferred sets of HCDRs.

The anti-CDCP1 antibody preferably comprises a light chain variable domain that comprises an LCDR1 region, an LCDR2 region and an LCDR3 region, wherein the sequences of the LCDR1 region, the LCDR2 region and the LCDR3 region are selected from one of the sets of light chain complementary determining sequences (LCDRs) shown in Table 2 below:

Set of LCDR sequences	**LCDR1 sequence**	**LCDR2 sequence**	**LCDR3 sequence**
mVL-CUB4	SVSSSVFYVH (SEQ ID NO:47)	DTSKLAS (SEQ ID NO:48)	QQWNSNPPT (SEQ ID NO:49)
hLC4-M	GASSSVFYLH (SEQ ID NO:50)	DTSKLAS (SEQ ID NO:51)	QQWNSNPPT (SEQ ID NO:52)
hLC4-L2	SVSSSVFYLH (SEQ ID NO:53)	DTSKLAS (SEQ ID NO:54)	QQWNSNPPT (SEQ ID NO:55)
hLC4-K	RASSSVFYLH (SEQ ID NO:56)	DTSKLAS (SEQ ID NO:57)	QQWNSNPPT (SEQ ID NO:58)
hLC4-L	RASSSVFYLH (SEQ ID NO:59)	DTSKLAS (SEQ ID NO:60)	QQWNSNPPT (SEQ ID NO:61)
hLC4-J	RASSSVFYLH (SEQ ID NO:62)	DTSKLAS (SEQ ID NO:63)	QQWNSNPPT (SEQ ID NO:64)
hLC4-b	SVSSSVFYVH (SEQ ID NO:65)	DTSKLAS (SEQ ID NO:66)	QQWNSNPPT (SEQ ID NO:67)
hLC4-c	SVSSSVFYVH (SEQ ID NO:68)	DTSKLAS (SEQ ID NO:69)	QQWNSNPPT (SEQ ID NO:70)
hLC4-a	SVSSSVFYVH (SEQ ID NO:71)	DTSKLAS (SEQ ID NO:72)	QQWNSNPPT (SEQ ID NO:73)
hLC4-d	SVSSSVFYVH	DTSKLAS	QQWNSNPPT

	(SEQ ID NO:74)	(SEQ ID NO:75)	(SEQ ID NO:76)
hLC4-e	SVSSSVFYVH (SEQ ID NO:77)	DTSKLAS (SEQ ID NO:78)	QQWNSNPPT (SEQ ID NO:79)
hLC4-f	SVSSSVFYVH (SEQ ID NO:80)	DTSKLAS (SEQ ID NO:81)	QQWNSNPPT (SEQ ID NO:82)
hLC4-I	RASSSVFYLS (SEQ ID NO:83)	DTSKLAS (SEQ ID NO:84)	QQWNSNPPT (SEQ ID NO:85)
CDCP1-004	RSSQNIVHSYGNTYLE (SEQ ID NO:86)	KVSNRFS (SEQ ID NO:87)	FQGSHVPWT (SEQ ID NO:88)
CDCP1-0012	KSSQSLLYTNGKTYLI (SEQ ID NO:89)	LVSKLDS (SEQ ID NO:90)	LQSTHFPYT (SEQ ID NO:91)
CDCP1-0015	KSTKSLLNSAGFTYLG (SEQ ID NO:92)	LVSNRFS (SEQ ID NO:93)	FQSSYLPLT (SEQ ID NO:94)

Table 2: Sequences of preferred sets of LCDRs.

Each set of LCDR sequences shown in Table 2 may be combined with any of the sets of HCDR sequences shown in Table 1.

Preferred combinations of sets of HCDR and LCDR sequences are shown in Table 3:

Antibody	**Set of HCDR sequences**			**Set of LCDR sequences**		
	HCDR1 SEQ ID NO:	**HCDR2 SEQ ID NO:**	**HCDR3 SEQ ID NO:**	**LCDR1 SEQ ID NO:**	**LCDR2 SEQ ID NO:**	**LCDR3 SEQ ID NO:**
CUB4 antibody	2	3	4	47	48	49
CDCP1-004	38	39	40	86	87	88
CDCP1-012	41	42	43	89	90	91
CDCP1-015	44	45	46	92	93	94
Humanized CUB4 Antibody Example No						
80	5	6	7	50	51	52
69	5	6	7	53	54	55
47	5	6	7	56	57	58
58	5	6	7	59	60	61
36	5	6	7	62	63	64
102	5	6	7	65	66	67
113	5	6	7	68	69	70
91	5	6	7	71	72	73
124	5	6	7	74	75	76
135	5	6	7	77	78	79
146	5	6	7	80	81	82

Table 3: Preferred combinations of sets of HCDR and LCDR sequences

Preferably, the anti-CDCP1 antibody comprises (i) a heavy chain variable domain that comprises an HCDR1 sequence shown as SEQ ID NO:5, an HCDR2 sequence shown as SEQ ID NO:6 and an HCDR3 sequence shown as SEQ ID NO:7 [i.e. the hHC4-H set of HCDRs from antibody #135] and a light chain variable domain that comprises an LCDR1 sequence shown as SEQ ID NO:77, an LCDR2 sequence shown as SEQ ID NO:78 and an LCDR3 sequence shown as SEQ ID NO:79 [i.e. the hLC-e set of LCDRs from antibody #135] or (ii) a heavy chain variable domain that comprises an HCDR1 sequence shown as SEQ ID NO:5, an HCDR2 sequence shown as SEQ ID NO:6 and an HCDR3 sequence shown as SEQ ID NO:7 [i.e. the hHC4-H set of HCDRs from antibody #69] and a light chain variable domain that comprises an LCDR1 sequence shown as SEQ ID NO:53, an LCDR2 sequence shown as SEQ ID NO:54 and an LCDR3 sequence shown as SEQ ID NO:55 [i.e. the hLC-L2 set of LCDRs from antibody #69].

Most preferably, the anti-CDCP1 antibody comprises a heavy chain variable domain that comprises an HCDR1 sequence shown as SEQ ID NO:5, an HCDR2 sequence shown as SEQ ID NO:6 and an HCDR3 sequence shown as SEQ ID NO:7 [i.e. the hHC4-H set of HCDRs from antibody #135] and a light chain variable domain that comprises an LCDR1 sequence shown as SEQ ID NO:77, an LCDR2 sequence shown as SEQ ID NO:78 and an LCDR3 sequence shown as SEQ ID NO:79 [i.e. the hLC-e set of LCDRs from antibody #135].

Preferably, the anti-CDCP1 antibody comprises a heavy chain variable (VH) domain sequence shown in Table 4:

VH domain designation	**VH domain sequence**	**SEQ ID NO**
hHC4-H	EVQLVESGGGLVQPGGSLRLSCAASGFTFNSYGMSWVRQAPG KGLEWVATISSGGSYKYYVDSVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYYCARHPDYDGVWFAYWGQGTLVTVSS	95
hHC4-c	EVQLVESGGGLVQPGGSLRLSCAASGFTFNSYGMSWVRQAPG KGLEWVATISSGGSYTYYPDSVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYYCARHPDYDGVWFAYWGQGTLVTVSS	96
hHC4-a	EVQLVESGGGLVKPGGSLRLSCAASGFTFNSYGMSWVRQAPG KGLEWVSTISSGGSYTYYPDSVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYYCARHPDYDGVWFAYWGQGTLVTVSS	97

hHC4-d	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYGMSWVRQAPG KGLEWVSTISSGGSYTYYPDSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKHPDYDGVWFAYWGQGTLVTVSS	98
hHC4-04	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYGMSWVRQAPG KGLEWVSTISSGGSYTYYPDSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCARHPDYDGVWFAYWGQGTLVTVSS	99
hHC4-K	EVQLVESGGGLVKPGGSLRLSCAASGFTFNSYGMSWVRQAPG KGLEWVSSISSGGSYIYYADSVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYYCARHPDYDGVWFAYWGQGTLVTVSS	100
hHC4-K2	EVQLVESGGGLVKPGGSLRLSCAASGFTFNSYGMSWVRQAPG KGLEWVSSISSGGSYTYYADSVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYYCARHPDYDGVWFAYWGQGTLVTVSS	101
hHC4-I	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYAMSWVRQAPG KGLEWVSAISSGGSYTYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKHPDYDGVWFAYWGQGTLVTVSS	102
hHC4-07	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYAMSWVRQAPG KGLEWVSTISSGGSYTYYPDSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKHPDYDGVWFAYWGQGTLVTVSS	103
hHC4-03	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYGMSWVRQAPG KGLEWVSAISSGGSYTYYPDSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKHPDYDGVWFAYWGQGTLVTVSS	104
hHC4-b	EVQLVESGGGLVKPGGSLRLSCAASGFTFNSYSMNWVRQAPG KGLEWVSSISSGGSYIYYADSVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYYCARHPDYDGVWFAYWGQGTLVTVSS	105

Table 4: Preferred VH domain sequences.

The anti-CDCP1 antibody may comprise a heavy chain variable (VH) domain sequence shown in Table 5, or a humanised version thereof.

VH domain designation	**VH domain sequence**	**SEQ ID NO**
mVH-CUB4	EVQLVESGGDLVKPGGSLKLSCAASGFTFNSYGMSWVRQTPD KRLEWVATISSGGSYTYYPDSVKGRFTISRDNAKNTLYLQMS SLKSEDTAMYYCARHPDYDGVWFAYWGQGTLVTVSA	106
CDCP1-004 VH	QVTLKESGPGILQPSQTLSLTCSFSGFSLSTAGVGVSWIRQP SGKGLEWLAHIYWDDDKRYNPSLKSRLTISKDTSRNQVFLKI TSVDSADTATYFCSRSTSVEEAFDVWGAGTTVTVSS	107
CDCP1-012 VH	QVTLKESGPGILQSSQTLSLTCSFSGFSLSTAGMGVSWIRQP SGKGLEWLAHIYWDDDKRYNPSLKSRLTVSKGTSRNQVLLKI TSVDAADTATYYCARSDSFGDFDYWGQGTTLTVSS	108
CDCP1-015 VH	QVHLKQSGPGLVQPSQSLSITCTVSGFSLTNFGLHWVRQSPG KGLEWLGVIWSGGVTDYNAAFISRLSISKDNSKSQVFFKMNS LQPNDTAIYYCARNYDHDYSMDYWGQGISVSVSS	109

Table 5: VH domain sequences.

Preferably, the anti-CDCP1 antibody comprises a light chain variable (VL) domain sequence shown in Table 6:

VL domain designation	VL domain sequence	SEQ ID NO
hLC4-M	EIVLTQSPATLSLSPGERATMSCGASSSVFYLHWYQQKPGLA PRLWIYDTSKLASGIPDRFSGSGSGTDFTLTISRLEPEDFAV YYCQQWNSNPPTFGGGTKVEIK	110
hLC4-L2	EIVLTQSPATLSLSPGERATMSCSVSSSVFYLHWYQQKPGQA PRLWIYDTSKLASGIPARFSGSGSGTDFTLTISSLEPEDFAV YYCQQWNSNPPTFGGGTKVEIK	111
hLC4-K	EIVLTQSPATLSLSPGERATLSCRASSSVFYLHWYQQKPGQA PRLWIYDTSKLASGIPARFSGSGSGTDFTLTISSLEPEDFAV YYCQQWNSNPPTFGGGTKVEIK	112
hLC4-L	EIVLTQSPATLSLSPGERATMSCRASSSVFYLHWYQQKPGQA PRLWIYDTSKLASGIPARFSGSGSGTDFTLTISSLEPEDFAV YYCQQWNSNPPTFGGGTKVEIK	113
hLC4-J	EIVMTQSPATLSLSPGERATMSCRASSSVFYLHWYQQKPGQA PRLWIYDTSKLASGIPARFSGSGSGTDFTLTISSLQPEDFAV YYCQQWNSNPPTFGGGTKVEIK	114
hLC4-b	EIVLTQSPATLSLSPGERATLSCSVSSSVFYVHWYQQKPGQA PRLLIYDTSKLASGIPARFSGSGSGTDYTLTISSLEPEDFAV YYCQQWNSNPPTFGGGTKVEIK	115
hLC4-c	EIVMTQSPATLSVSPGERATLSCSVSSSVFYVHWYQQKPGQA PRLLIYDTSKLASGIPARFSGSGSGTEFTLTISSLQSEDFAV YYCQQWNSNPPTFGGGTKVEIK	116
hLC4-a	EIVLTQSPATLSLSPGERATLSCSVSSSVFYVHWYQQKPGQA PRLLIYDTSKLASGIPARFSGSGSGTDFTLTISSLEPEDFAV YYCQQWNSNPPTFGGGTKVEIK	117
hLC4-d	EIVMTQSPATLSVSPGERATLSCSVSSSVFYVHWYQQKPGQA PRLLIYDTSKLASGIPARFSGSGSGTEYTLTISSLQSEDFAV YYCQQWNSNPPTFGGGTKVEIK	118
hLC4-e	DIQMTQSPSSLSASVGDRVTITCSVSSSVFYVHWYQQKPGKA PKLLIYDTSKLASGVPSRFSGSGSGTDFTFTISSLQPEDIAT YYCQQWNSNPPTFGGGTKVEIK	119
hLC4-f	DIQMTQSPSSLSASVGDRVTITCSVSSSVFYVHWYQQKPGKA PKLLIYDTSKLASGVPSRFSGSGSGTDYTFTISSLQPEDIAT YYCQQWNSNPPTFGGGTKVEIK	120
hLC4-I	EIVMTQSPATLSLSPGERATLSCRASSSVFYLSWYQQKPGQA PRLWIYDTSKLASGIPARFSGSGSGTDFTLTISSLQPEDFAV YYCQQWNSNPPTFGGGTKVEIK	121

Table 6: Preferred VL domain sequences.

The anti-CDCP1 antibody may comprise a light chain variable (VL) domain sequence shown in Table 7, or a humanised version thereof.

5

VL domain designation	VL domain sequence	SEQ ID NO
mVL-CUB4	QIVLTQSPAIMSASPGEKVTMTCSVSSSVFYVHWYQQKSGTS PKRWIYDTSKLASGVPARFSGSGSGTSYSLTISSMEAEDAAT YYCQQWNSNPPTFGGGTKLEIK	122

CDCP1-004 VL	DVLMTQTPLSLPVSLGDQASISCRSSQNIVHSYGNTYLEWYL QKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVE AEDLGVYYCFQGSHVPWTFGGGTKLEIK	123
CDCP1-012 VL	DVVMTQTPLTLSVTIGQPASISCKSSQSLLYTNGKTYLIWLL QRPGQSPKRLIYLVSKLDSGVPDRFSGSGSGTDFTLKISRVE AEDLGVYYCLQSTHFPYTFGGGTKLEIK	124
CDCP1-015 VL	DVVLTQTPLSLPVIIGDQASISCKSTKSLLNSAGFTYLGWYL QKPGQSPQLLIYLVSNRFSGVPDRFSGSGSGTDFTLKISRVE AEDLGVYFCFQSSYLPLTFGSGTKLEIK	125

Table 7: VL domain sequences.

Preferably, the anti-CDCP1 antibody comprises one of the combinations of a VH and a VL domain shown in Table 8 below:

Humanized CUB4 Antibody Example No	**VH domain sequence**	**VL domain sequence**
80	hHC4-H (SEQ ID NO: 95)	hLC-M (SEQ ID NO: 110)
69	hHC4-H (SEQ ID NO: 95)	hLC-L2 (SEQ ID NO: 111)
47	hHC4-H (SEQ ID NO: 95)	hLC-K (SEQ ID NO: 112)
58	hHC4-H (SEQ ID NO: 95)	hLC-L (SEQ ID NO: 113)
36	hHC4-H (SEQ ID NO: 95)	hLC-J (SEQ ID NO: 114)
102	hHC4-H (SEQ ID NO: 95)	hLC-b (SEQ ID NO: 115)
113	hHC4-H (SEQ ID NO: 95)	hLC-c (SEQ ID NO: 116)
91	hHC4-H (SEQ ID NO: 95)	hLC-a (SEQ ID NO: 117)
124	hHC4-H (SEQ ID NO: 95)	hLC-d (SEQ ID NO: 118)
135	hHC4-H (SEQ ID NO: 95)	hLC-e (SEQ ID NO: 119)
146	hHC4-H (SEQ ID NO: 95)	hLC-f (SEQ ID NO: 120)

Table 8: Preferred combinations of VH and VL domains

Preferably, the anti-CDCP1 antibody comprises (i) the heavy chain variable (VH) sequence shown as SEQ ID NO:95 (i.e. hHC4-H) and the light chain variable sequence shown as SEQ ID NO:119 (i.e. hLC-e) or (ii) the heavy chain variable (VH) sequence shown as SEQ ID NO:95 (i.e. hHC4-H) and the light chain variable sequence shown as SEQ ID NO:111 (i.e. hLC-L2).

Most preferably, the anti-CDCP1 antibody comprises the heavy chain variable (VH) sequence shown as SEQ ID NO:95 (i.e. hHC4-H) and the light chain variable sequence shown as SEQ ID NO:119 (i.e. hLC-e).

The anti-CDCP1 antibody may also comprise one of the combinations of a VH and a VL domain shown in Table 9 below, or a humanised version thereof:

Antibody	VH domain sequence	VL domain sequence
mVH-CUB4	SEQ ID NO:106	SEQ ID NO:122
CDCP1-004	SEQ ID NO:107	SEQ ID NO:123
CDCP1-0012	SEQ ID NO:108	SEQ ID NO:124
CDCP1-0015	SEQ ID NO:109	SEQ ID NO:125

Table 9: Combinations of VH and VL domains.

The taxane for use in the invention is preferably paclitaxel (Taxol®), docetaxel (Taxotere®) or a modified paclitaxel, such as Abraxane® or Opaxio®. In one preferred embodiment, the taxane is paclitaxel (Taxol®). In one preferred embodiment, the taxane is docetaxel (Taxotere®).

In a preferred embodiment, the anti-CDCP1 antibody comprises a heavy chain variable domain that comprises an HCDR1 sequence shown as SEQ ID NO:5, an HCDR2 sequence shown as SEQ ID NO:6 and an HCDR3 sequence shown as SEQ ID NO:7 [i.e. hHC4-H set of HCDRs from antibody #135] and a light chain variable domain that comprises an LCDR1 sequence shown as SEQ ID NO:77, an LCDR2 sequence shown as SEQ ID NO:78 and an LCDR3 sequence shown as SEQ ID NO:79 [i.e. hLC4-e set of LCDRs from antibody #135], and the taxane is paclitaxel. Even more preferably, the anti-CDCP1 antibody comprises the heavy chain variable (VH) sequence shown as SEQ ID NO:95 (i.e. hHC4-H) and the light chain variable sequence shown as SEQ ID NO:119 (i.e. hLC-e), and the taxane is paclitaxel.

Preferably, the anti-CDCP1 antibody and the taxane are each provided as a pharmaceutical composition, formulated together with a pharmaceutical carrier.

The cancer for treatment by the invention may be, for example, lung cancer, non small cell lung (NSCL) cancer, small cell lung cancer (SCL), bronchioloalviolar cell lung cancer/bronchioloalveolar carcinoma (BAC), bone cancer, pancreatic cancer, skin cancer, cancer

of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, including recurrent ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, gastric cancer (including recurrent and metastatic gastric cancer), colon cancer, breast cancer (including metastatic breast cancer (MBC)), uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, e.g. adult soft tissue sarcoma, cancer of the urethra, cancer of the penis, prostate cancer, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, mesothelioma, hepatocellular cancer, biliary cancer, neoplasms of the central nervous system (CNS), spinal axis tumors, brain stem glioma, glioblastoma multiforme, astrocytomas, schwanomas, ependymonas, medulloblastomas, meningiomas, squamous cell carcinomas, e.g. squamous cell carcinoma of the head and neck (SCCHN), pituitary adenoma, lymphoma, lymphocytic leukemia, including refractory versions of any of the above cancers, or a combination of one or more of the above cancers. Preferably, the cancer to be treated comprises a solid tumour. More preferably, the cancer to be treated is lung cancer (such as non small cell lung (NSCL) cancer, small cell lung cancer (SCL), or bronchioloalviolar cell lung cancer/BAC), breast cancer (such as metastatic breast cancer (MBC)), ovarian cancer (including recurrent ovarian cancer), gastric cancer (including recurrent/metastatic gastric cancer), pancreatic cancer, prostate cancer, squamous cell carcinoma of the head and neck or adult soft tissue sarcoma. Most preferably, the cancer to be treated is lung cancer. Preferably, the cancer to be treated is further characterized by CDCP1 expression or overexpression, more preferably by CDCP1 expression.

In one embodiment the taxane is paclitaxel (Taxol®) and preferred types of cancer to be treated include metastatic breast cancer (MBC), non small cell lung cancer (NSCLC) (including BAC), small

cell lung cancer (SCLC), recurrent ovarian cancer and recurrent/metastatic gastric cancer.

In one embodiment, the taxane is Abraxane® (NabPAC) and the cancer is pancreactic cancer. In this embodiment, the anti-CDCP1 antibody and Abraxane® may be administered in combination with gemcitabine.

In one embodiment, the taxane is docetaxel (Taxotere®) and the preferred types of cancer to be treated include MBC, recurrent/metastatic gastric cancer, prostate cancer, SCCHN, NSCLC and adult soft tissue sarcoma.

These and other aspects of the invention are described in further detail below.

Brief description of drawings

Figure 1 shows the effect of administering paclitaxel in combination with the humanised CUB4 anti-CDCP1 antibody #135 (IgG1) with VH and VL domain sequences as shown in Table 8 (and described in WO 2011/023389) on QG-56 tumour growth in mice. Results are the median values for each group of mice.

Figure 2 shows the effect of administering paclitaxel in combination with the humanised CUB4 anti-CDCP1 antibody #135 (IgG4) with VH and VL domain sequences as shown in Table 8 (and described in WO 2011/023389) on H322M tumour growth in mice. Results are the median values for each group of mice.

Detailed description

The present invention relates to an anti-CDCP1 antibody for use in a method of treatment of cancer in a subject, the method comprising administering said antibody and a taxane to the subject, and the inventors demonstrate herein that this combination of agents results in an enhanced reduction of tumour growth, compared to administration of each agent alone.

Preferably, the anti-CDCP1 antibody binds to human CDCP1.

Human CDCP1 ((CUB domain containing protein 1, B345, CD318, SIMA135, TRASK; SEQ ID NO:1 and variants with mutation R525Q (i.e. replacement of Arginine (R) with Glutamine (Q) at amino acid position 525 of SEQ ID NO:1) and/or mutation G709D (i.e. replacement of Glycine (G) with Aspartic acid (D) at amino acid position 709 of SEQ ID NO:1) is a transmembrane protein containing three extracellular CUB domains. This protein is found to be overexpressed in breast, colon and lung cancers (Uekita, T. et al., Am. J. Pathol. 172 (2008) 1729-1739). Its expression level is correlated with the metastatic ability of carcinoma cells. It has been shown to be tyrosine phosphorylated in a cancer cell line (WO 2002/004508; Scherl-Mostageer, M., et al., Oncogene 20 (2001) 4402-8; Hooper, J., D., et al., Oncogene 22 (2003) 1783-94; Perry, S.E., et al., FEBS Lett. 581 (2007) 1137-42; Brown, T.A., et al., J. Biol. Chem. 279 (2004) 14772-14783; Ota, T., et al., Nat. Genet. 36 (2004) 40-45). Alternatively spliced transcript variants encoding distinct isoforms have been reported.

Preferably, the anti-CDCP1 antibody specifically binds to human CDCP1 with a K_D value of less than 1.0×10^{-8} mol/l, as determined by surface plasmon resonance (Biacore™). As used herein, "specifically binding to human CDCP1" refers to an antibody specifically binding to the human CDCP1 antigen. The binding affinity is of a K_D-value of 1.0×10^{-8} mol/l or lower (e.g. 1.0×10^{-8} mol/l to 1.0×10^{-13} mol/l), preferably of a K_D-value of 5.0×10^{-9} mol/l or lower (e.g. 5.0×10^{-9} mol/l to 1.0×10^{-13} mol/l). The binding affinity is determined with a standard binding assay, such as surface plasmon resonance technique (Biacore®).

In one preferred embodiment, the anti-CDCP1 antibody competes for binding to an epitope on CDCP1 with the CUB4 antibody deposited with Deposition No. DSM ACC2551. In one preferred embodiment, the anti-CDCP1 antibody binds to essentially the same epitope as the CUB4 antibody deposited with Deposition No. DSM ACC2551. The CUB4 antibody refers to the deposited antibody with the Deposition No. DSM ACC2551 (DSMZ) from DE10242146 (EP 1 396 501, US 7,541,030).

Said CUB4 antibody specifically binds to human CDCP1. (The Deposition of No. DSM ACC2551 (DSMZ) was made by Eberhard-Karls-University Tübingen, Univcrsitätsklinikum Tübingen, Geissweg 3 72076 Tübingen.) Specifically, the CUB4 antibody binds to a conformational epitope between amino acids 30 and 216 of CDCP1 (SEQ ID NO:1). Methods for generating anti-CDCP1 antibodies that bind to the same epitope as the CUB4 antibody are described in WO 2011/023390. The term "epitope" denotes a protein determinant of human CDCP1 capable of specifically binding to an antibody. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually epitopes have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and nonconformational epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents.

The anti-CDCP1 antibody is preferably a monoclonal antibody. The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of a single amino acid composition.

The anti-CDCP1 antibody is preferably humanised. The term "being humanised" as used herein denotes an antibody, based on a non-human antibody, e.g. mouse antibody, such as the mouse CUB4 antibody, in which (after chimerization with a human constant region) said VH and VL are humanized by grafting the murine CDRs into the framework region of a human antibody (see e.g. Riechmann, L., et al., Nature 332 (1988) 323-327; and Neuberger, M., S., et al., Nature 314 (1985) 268-270; Queen, C., et al., Proc. Natl. Acad. Sci. USA 86 (1989) 10029-10033; U.S. Pat. No. 5,530,101; U.S. Pat. No. 5,585,089; U.S. Pat. No. 5,693,761; WO 90/07861; and U.S. Pat. No. 5,225,539). The heavy and light chain variable framework regions can be derived from the same or different human antibody sequences. The human antibody sequences can be the sequences of naturally occurring human antibodies. Human heavy and light chain variable framework regions are listed e.g. in Lefranc, M.P., Current Protocols in Immunology

(2000) - Appendix 1P A.1P.1-A.1P.37 and are accessible via IMGT, the international ImMunoGeneTics information system® (http://imgt.cines.fr) or via http://vbase.mrc-cpe.cam.ac.uk. Details of how humanised anti-CDCP1 antibodies may be generated are provided in WO 2011/023389.

The term "chimeric antibody" refers to a monoclonal antibody comprising a variable region, i.e., binding region, from mouse and at least a portion of a constant region derived from a different source or species, usually prepared by recombinant DNA techniques. Chimeric antibodies comprising a mouse variable region and a human constant region are especially preferred. Such mouse/human chimeric antibodies are the product of expressed immunoglobulin genes comprising DNA segments encoding mouse immunoglobulin variable regions and DNA segments encoding human immunoglobulin constant regions. Other forms of "chimeric antibodies" encompassed by the present invention are those in which the class or subclass has been modified or changed from that of the original antibody. Such "chimeric" antibodies are also referred to as "class-switched antibodies." Methods for producing chimeric antibodies involve conventional recombinant DNA and gene transfection techniques now well known in the art (see, e.g., Morrison, S., L., et al., Proc. Natl. Acad Sci. USA 81 (1984) 6851-6855; US 5,202,238 and US 5,204,244).

The anti-CDCP1 antibody preferably comprises a heavy chain variable domain that comprises an HCDR1 region, an HCDR2 region and an HCDR3 region, wherein the sequences of the HCDR1 region, the HCDR2 region and the HCDR3 region are selected from one of the sets of heavy chain complementary determining sequences (HCDRs) shown in Table 1 above.

The anti-CDCP1 antibody preferably comprises a light chain variable domain that comprises an LCDR1 region, an LCDR2 region and an LCDR3 region, wherein the sequences of the LCDR1 region, the LCDR2 region and the LCDR3 region are selected from one of the sets of light

chain complementary determining sequences (LCDRs) shown in Table 2 above.

Each set of LCDR sequences shown in Table 2 may be combined with any of the sets of HCDR sequences shown in Table 1. Preferred combinations of HCDR and LCDR sequences are shown in Table 3.

The anti-CDCP1 antibody preferably comprises a heavy chain variable (VH) domain sequence shown in Table 4, or a heavy chain variable (VH) domain sequence shown in Table 5 above or a humanised version thereof.

Preferably, the anti-CDCP1 antibody comprises a light chain variable (VL) domain sequence shown in Table 6 above, or a light chain variable (VL) domain sequence shown in Table 7 above or a humanised version thereof.

Preferably, the anti-CDCP1 antibody comprises one of the combinations of a VH and a VL domain shown in Table 8 above, or one of the combinations of a VH and a VL domain shown in Table 9 above or a humanised version thereof.

The "variable domain" (variable domain of a light chain (VL), variable domain of a heavy chain (VH)) as used herein denotes each of the pair of light and heavy chain domains which are involved directly in binding the antibody to the antigen. The variable light and heavy chain domains have the same general structure and each domain comprises four framework (FR) regions whose sequences are widely conserved, connected by three "hypervariable regions" (or complementary determining regions, CDRs). The framework regions adopt a β-sheet conformation and the CDRs may form loops connecting the β-sheet structure. The CDRs in each chain are held in their three-dimensional structure by the framework regions and form together with the CDRs from the other chain the antigen binding site. The antibody's heavy and light chain CDR3 regions play a particularly important role in the binding specificity/affinity of the antibodies described herein.

"Framework" or "FR" regions are those variable domain regions other than the hypervariable region residues as herein defined. Therefore, the light and heavy chain variable domains of an antibody comprise from N- to C-terminus the domains FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. CDR and FR regions are determined according to the standard definition of Kabat et al., Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, National Institutes of Health, Bethesda, MD (1991) and/or those residues from a "hypervariable loop". The term "Kabat numbering" or "numbering according to Kabat" or "EU index" unless otherwise stated, is defined as the numbering of the residues in, e.g., an IgG antibody using the EU index as in Kabat et al. (Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, National Institutes of Health, Bethesda, Md. (1991)).

The term "antigen-binding portion of an antibody" when used herein refers to the amino acid residues of an antibody which are responsible for antigen-binding. The antigen-binding portion of an antibody comprises amino acid residues from the "complementary determining regions" or "CDRs". The term "antigen-binding portion" of an antibody contains six complementarity determining regions (CDRs) which contribute in varying degrees to the affinity of the binding site for antigen. There are three heavy chain variable domain CDRs (HCDR1, HCDR2 and HCDR3) and three light chain variable domain CDRs (LCDR1, LCDR2 and LCDR3). The term "HCDR1" denotes the CDR1 region of the heavy chain variable region calculated according to Kabat. HCDR2, HCDRH3, LCDR1, LCDR2 and LCDR3 mean the respective regions from the heavy (H) or light (L) chain. The extent of CDR and framework regions (FRs) is determined by comparison to a compiled database of amino acid sequences in which those regions have been defined according to variability among the sequences according to Kabat, et al., supra.

The term "amino acid" as used within this application denotes the group of naturally occurring carboxy α-amino acids comprising alanine (three letter code: ala, one letter code: A), arginine (arg,

R), asparagine (asn, N), aspartic acid (asp, D), cysteine (cys, C), glutamine (gln, Q), glutamic acid (glu, E), glycine (gly, G), histidine (his, H), isoleucine (ile, I), leucine (leu, L), lysine (lys, K), methionine (met, M), phenylalanine (phe, F), proline (pro, P), serine (ser, S), threonine (thr, T), tryptophan (trp, W), tyrosine (tyr, Y), and valine (val, V).

The constant region of the anti-CDCP1 antibody is preferably of human origin, and is preferably of human IgG1 subclass. The constant region includes the heavy chain and light chain constant region of an antibody. The heavy chain constant region comprises in N-terminal to C-terminal direction an antibody constant heavy chain domain 1 (CH1), an antibody hinge region (HR), an antibody heavy chain constant domain 2 (CH2), and an antibody heavy chain constant domain 3 (CH3), and optionally, in case of an antibody of the subclass IgE, an antibody heavy chain constant domain 4 (CH4). The light chain constant region comprises an antibody light chain constant domain (CL). The antibody light chain constant domain (CL) can be κ (kappa) or λ (lambda). Such constant chains are well known in the state of the art and e.g. described by Kabat, E.A., (see e.g. Johnson, G. and Wu, T., T., Nucleic Acids Res. 28 (2000) 214-218). For example, a useful human heavy chain constant region of IgG1 subclass comprises an amino acid sequence of SEQ ID NO:126. For example, a useful human light chain constant region comprises an amino acid sequence of a kappa-light chain constant region of SEQ ID NO:127; another useful human light chain constant region comprises an amino acid sequence of a lambda-light chain constant region of SEQ ID NO:128.

The "Fc part" of an antibody is not involved directly in binding of an antibody to an antigen, but exhibits various effector functions. An "Fc part of an antibody" is a term well known to the skilled artisan and defined on the basis of papain cleavage of antibodies. Depending on the amino acid sequence of the constant region of their heavy chains, antibodies or immunoglobulins are divided in the classes: IgA, IgD, IgE, IgG and IgM, and several of these may be further divided into subclasses (isotypes), e.g. IgG1, IgG2, IgG3,

and IgG4, IgA1, and IgA2. According to the heavy chain constant regions, the different classes of immunoglobulins are called α, δ, ε, γ, and μ, respectively.

The Fc part of an antibody is directly involved in ADCC (antibody-dependent cell-mediated cytotoxicity) and CDC (complement-dependent cytotoxicity) based on complement activation, C1q binding and Fc receptor binding. Complement activation (CDC) is initiated by binding of complement factor C1q to the Fc part of most IgG antibody subclasses. While the influence of an antibody on the complement system is dependent on certain conditions, binding to C1q is caused by defined binding sites in the Fc part. Such binding sites are known in the state of the art and described e.g. by Boackle, R.J., et al., Nature 282 (1979) 742-743; Lukas, T.J., et al., J. Immunol. 127 (1981) 2555-2560; Brunhouse, R., and Cebra, J.J., Mol. Immunol. 16 (1979) 907-917; Burton, D.R., et al., Nature 288 (1980) 338-344; Thommesen, J.E., et al., Mol. Immunol. 37 (2000) 995-1004; Idusogie, E.E., et al., J. Immunol. 164 (2000) 4178-4184; Hezareh, M., et al., J. Virology 75 (2001) 12161-12168; Morgan, A., et al., Immunology 86 (1995) 319-324; EP 0307434. Such binding sites are e.g. L234, L235, D270, N297, E318, K320, K322, P331 and P329 (numbering according to EU index of Kabat, E.A., see below). Antibodies of subclass IgG1, IgG2 and IgG3 usually show complement activation and C1q and C3 binding, whereas IgG4 do not activate the complement system and do not bind C1q and C3.

The anti-CDCP1 antibody for use according to the invention preferably comprises an Fc part derived from human origin and preferably all other parts of the human constant regions. As used herein, the term "Fc part derived from human origin" denotes a Fc part which is either a Fc part of a human antibody of the subclass IgG1, IgG2, IgG3 or IgG4, preferably a Fc part from human IgG1 subclass, a mutated Fc part from human IgG1 subclass (preferably with a mutation on L234A + L235A), a Fc part from human IgG4 subclass or a mutated Fc part from human IgG4 subclass (preferably with a mutation on S228P). Mostly preferred are the human heavy chain constant regions of human IgG1 subclass with SEQ ID NO: 126 or

129, of human IgG1 subclass with mutations L234A and L235A, of human IgG4 subclass with SEQ ID NO: 130, or of human IgG4 subclass with mutation S228P.

The term "antibody-dependent cellular cytotoxicity (ADCC)" refers to lysis of human target cells by an antibody according to the invention in the presence of effector cells. ADCC is preferably measured by the treatment of a preparation of CDCP1 expressing cells with an antibody according to the invention in the presence of effector cells such as freshly isolated PBMC or purified effector cells from buffy coats, like monocytes or natural killer (NK) cells or a permanently growing NK cell line.

The term "complement-dependent cytotoxicity (CDC)" denotes a process initiated by binding of complement factor C1q to the Fc part of most IgG antibody subclasses. Binding of C1q to an antibody is caused by defined protein-protein interactions at the so called binding site. Such Fc part binding sites are known in the state of the art (see above). Such Fc part binding sites are, e.g., characterized by the amino acids L234, L235, D270, N297, E318, K320, K322, P331, and P329 (numbering according to EU index of Kabat). Antibodies of subclass IgG1, IgG2, and IgG3 usually show complement activation including C1q and C3 binding, whereas IgG4 does not activate the complement system and does not bind C1q and/or C3.

Cell-mediated effector functions of monoclonal antibodies can be enhanced by engineering their oligosaccharide component as described in Umana, P., et al., Nature Biotechnol. 17 (1999) 176-180, and US 6,602,684. IgG1 type antibodies, the most commonly used therapeutic antibodies, are glycoproteins that have a conserved N-linked glycosylation site at Asn297 in each CH2 domain. The two complex biantennary oligosaccharides attached to Asn297 are buried between the CH2 domains, forming extensive contacts with the polypeptide backbone, and their presence is essential for the antibody to mediate effector functions such as antibody dependent cellular cytotoxicity (ADCC) (Lifely, M., R., et al., Glycobiology 5 (1995) 813-822; Jefferis, R., et al., Immunol. Rev. 163 (1998) 59-

76; Wright, A., and Morrison, S., L., Trends Biotechnol. 15 (1997) 26-32). Umana, P., et al., Nature Biotechnol. 17 (1999) 176-180 and WO 99/54342 showed that overexpression in Chinese hamster ovary (CHO) cells of ß(1,4)-N-acetylglucosaminyltransferase III ("GnTIII"), a glycosyltransferase catalyzing the formation of bisected oligosaccharides, significantly increases the in vitro ADCC activity of antibodies. Alterations in the composition of the Asn297 carbohydrate or its elimination affect also binding to FcγR and C1q (Umana, P., et al., Nature Biotechnol. 17 (1999) 176-180; Davies, J., et al., Biotechnol. Bioeng. 74 (2001) 288-294; Mimura, Y., et al., J. Biol. Chem. 276 (2001) 45539-45547; Radaev, S., et al., J. Biol. Chem. 276 (2001) 16478-16483; Shields, R.L., et al., J. Biol. Chem. 276 (2001) 6591-6604; Shields, R.L., et al., J. Biol. Chem. 277 (2002) 26733-26740; Simmons, L.C., et al., J. Immunol. Methods 263 (2002) 133-147).

Methods to enhance cell-mediated effector functions of monoclonal antibodies are reported e.g. in WO 2005/044859, WO 2004/065540, WO2007/031875, Umana, P., et al., Nature Biotechnol. 17 (1999) 176-180, WO 99/154342, WO 2005/018572, WO 2006/116260, WO 2006/114700, WO 2004/065540, WO 2005/011735, WO 2005/027966, WO 1997/028267, US 2006/0134709, US 2005/0054048, US 2005/0152894, WO 2003/035835 and WO 2000/061739 or e.g. in Niwa, R., et al., J. Immunol. Methods 306 (2005) 151-160; Shinkawa, T., et al., J. Biol. Chem. 278 (2003) 3466-3473; WO 03/055993 and US 2005/0249722.

The anti-CDCP1 antibody may be glycosylated (if it comprises an Fc part of IgG1 or IgG3 subclass) with a sugar chain at Asn297 whereby the amount of fucose within said sugar chain is 65% or lower (Numbering according to Kabat). In another embodiment, the amount of fucose within said sugar chain is between 5% and 65%, preferably between 20% and 40%. In an alternative embodiment, the amount of fucose is 0% of the oligosaccharides of the Fc region at Asn297. "Asn297" according to the invention means amino acid asparagine located at about position 297 in the Fc region. Based on minor sequence variations of antibodies, Asn297 can also be located some amino acids (usually not more than ±3 amino acids) upstream or

downstream of position 297, i.e. between position 294 and 300. In one embodiment, the IgG subclass of the glycosylated antibody may be the human IgG1 subclass, or the human IgG3 subclass. The amount of N-glycolylneuraminic acid (NGNA) may be 1% or less and/or the amount of N-terminal alpha-1,3-galactose may be 1% or less within said sugar chain. The sugar chains preferably show the characteristics of N-linked glycans attached to Asn297 of an antibody recombinantly expressed in a CHO cell.

The term "the sugar chains show characteristics of N-linked glycans attached to Asn297 of an antibody recombinantly expressed in a CHO cell" denotes that the sugar chain at Asn297 of the antibody according to the invention has the same structure and sugar residue sequence except for the fucose residue as those of the same antibody expressed in unmodified CHO cells, e.g. as those reported in WO 2006/103100.

The term "NGNA" as used within this application denotes the sugar residue N-glycolylneuraminic acid.

Glycosylation of human IgG1 or IgG3 occurs at Asn297 as core fucosylated biantennary complex oligosaccharide glycosylation terminated with up to two Gal residues. Human constant heavy chain regions of the IgG1 or IgG3 subclass are reported in detail by Kabat, E., A., et al., supra, and by Brueggemann, M., et al., J. Exp. Med. 166 (1987) 1351-1361; Love, T.W., et al., Methods Enzymol. 178 (1989) 515-527. These structures are designated as G0, G1 (α-1,6- or α-1,3-), or G2 glycan residues, depending from the amount of terminal Gal residues (Raju, T., S., Bioprocess Int. 1 (2003) 44-53). CHO type glycosylation of antibody Fc parts is e.g. described by Routier, F.H., Glycoconjugate J. 14 (1997) 201-207. Antibodies which are recombinantly expressed in non-glycomodified CHO host cells usually are fucosylated at Asn297 in an amount of at least 85%. The modified oligosaccharides of the antibody may be hybrid or complex. Preferably the bisected, reduced/not-fucosylated oligosaccharides are hybrid. In another embodiment, the bisected, reduced/not-fucosylated oligosaccharides are complex.

The "amount of fucose" means the amount of said sugar within the sugar chain at Asn297, related to the sum of all glycostructures attached to Asn297 (e.g. complex, hybrid and high mannose structures) measured by MALDI-TOF mass spectrometry and calculated as average value (see e.g. WO 2008/077546). The relative amount of fucose is the percentage of fucose-containing structures related to all glycostructures identified in an N-Glycosidase F treated sample (e.g. complex, hybrid and oligo- and high-mannose structures, resp.) by MALDI-TOF.

The anti-CDCP1 antibodies for use according to the invention may be generated by any method known in the art (see, for example, WO 2005/042102, WO 2004/074481, WO 2008/133851, WO 2007/005502, WO 2011/023389, WO 2011/023390 and US 2004/0053343). Preferably, the anti-CDCP1 antibodies are produced by recombinant means. Such methods are widely known in the state of the art and comprise protein expression in prokaryotic and eukaryotic cells with subsequent isolation of the antibody polypeptide and usually purification to a pharmaceutically acceptable purity. For the protein expression, nucleic acids encoding light and heavy chains or fragments thereof are inserted into expression vectors by standard methods. Expression is performed in appropriate prokaryotic or eukaryotic host cells like CHO cells, NS0 cells, SP2/0 cells, HEK293 cells, COS cells, yeast, or E.coli cells, and the antibody is recovered from the cells (supernatant or cells after lysis).

Recombinant production of antibodies is well-known in the state of the art and described, for example, in the review articles of Makrides, S., C., Protein Expr. Purif. 17 (1999) 183-202; Geisse, S., et al., Protein Expr. Purif. 8 (1996) 271-282; Kaufman, R.J., Mol. Biotechnol. 16 (2000) 151-160; Werner, R.G., Drug Res. 48 (1998) 870-880.

The antibodies may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. Purification is performed in order to eliminate other cellular components or other

contaminants, e.g. other cellular nucleic acids or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis, and others well known in the art (see Ausubel, F., et al. (ed.), Current Protocols in Molecular Biology, Greene Publishing and Wiley Interscience, New York (1987).

Expression in NS0 cells is described by, e.g., Barnes, L.M., et al., Cytotechnology 32 (2000) 109-123; and Barnes, L.M., et al., Biotech. Bioeng. 73 (2001) 261-270. Transient expression is described by, e.g., Durocher, Y., et al., Nucl. Acids. Res. 30 (2002) E9. Cloning of variable domains is described by Orlandi, R., et al., Proc. Natl. Acad. Sci. USA 86 (1989) 3833-3837; Carter, P., et al., Proc. Natl. Acad. Sci. USA 89 (1992) 4285-4289; and Norderhaug, L., et al., J. Immunol. Methods 204 (1997) 77-87. A preferred transient expression system (HEK 293) is described by Schlaeger, E.J., and Christensen, K., in Cytotechnology 30 (1999) 71-83 and by Schlaeger, E.J., in J. Immunol. Methods 194 (1996) 191-199.

The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, enhancers and polyadenylation signals.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading frame. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not

exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

The monoclonal antibodies are suitably separated from the culture medium by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography. DNA and RNA encoding the monoclonal antibodies are readily isolated and sequenced using conventional procedures. The hybridoma cells can serve as a source of such DNA and RNA. Once isolated, the DNA may be inserted into expression vectors, which are then transfected into host cells such as HEK 293 cells, CHO cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of recombinant monoclonal antibodies in the host cells.

As used herein, the expressions "cell," "cell line," and "cell culture" are used interchangeably and all such designations include progeny. Thus, the words "transformants" and "transformed cells" include the primary subject cell and cultures derived therefrom without regard for the number of transfers. It is also understood that all progeny may not be precisely identical in DNA content, due to deliberate or inadvertent mutations. Variant progeny that have the same function or biological activity as screened for in the originally transformed cell are included. Where distinct designations are intended, it will be clear from the context. The term "transformation" as used herein refers to process of transfer of a vectors/nucleic acid into a host cell. If cells without formidable cell wall barriers are used as host cells, transfection is carried out e.g. by the calcium phosphate precipitation method as described by Graham, F., L., and van der Eb, Virology 52 (1973) 456-467. However, other methods for introducing DNA into cells such as by nuclear injection or by protoplast fusion may also be used. If prokaryotic cells or cells which contain substantial cell wall constructions are used, e.g. one method of transfection is calcium treatment using calcium chloride as described by Cohen, S.N., et al., PNAS 69 (1972) 2110-2114.

As used herein, "expression" refers to the process by which a nucleic acid is transcribed into mRNA and/or to the process by which the transcribed mRNA (also referred to as transcript) is subsequently being translated into peptides, polypeptides, or proteins. The transcripts and the encoded polypeptides are collectively referred to as gene product. If the polynucleotide is derived from genomic DNA, expression in a eukaryotic cell may include splicing of the mRNA.

A "vector" is a nucleic acid molecule, in particular self-replicating, which transfers an inserted nucleic acid molecule into and/or between host cells. The term includes vectors that function primarily for insertion of DNA or RNA into a cell (e.g., chromosomal integration), replication of vectors that function primarily for the replication of DNA or RNA, and expression vectors that function for transcription and/or translation of the DNA or RNA. Also included are vectors that provide more than one of the functions as described.

An "expression vector" is a polynucleotide which, when introduced into an appropriate host cell, can be transcribed and translated into a polypeptide. An "expression system" usually refers to a suitable host cell comprised of an expression vector that can function to yield a desired expression product.

The taxane for use in the invention may be any member of the taxane (i.e. diterpene) class of drugs. These include those obtained from natural sources (such as paclitaxel; Taxol®), those that have been synthetically produced (such as docetaxel; Taxotere®), as well as modified taxanes (such as Abraxane® and Opaxio®).

Preferably, the the anti-CDCP1 antibody and the taxane are each provided as a pharmaceutical composition, formulated together with a pharmaceutical carrier.

As used herein, "pharmaceutical carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal

agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (e.g. by injection or infusion).

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of presence of microorganisms may be ensured both by sterilization procedures, supra, and by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

The anti-CDCP1 antibody and the taxane may be used to treat any type of cancer. Examples of types of cancer suitable for treatment by the invention include lung cancer, non small cell lung (NSCL) cancer, small cell lung cancer (SCL), bronchioloalviolar cell lung cancer/bronchioloalveolar carcinoma (BAC), bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, including recurrent ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, gastric cancer (including recurrent and metastatic gastric cancer), colon cancer, breast cancer (including metastatic breast cancer (MBC)), uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, e.g. adult soft tissue sarcoma, cancer of the urethra, cancer of the penis, prostate cancer, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, mesothelioma, hepatocellular cancer, biliary cancer,

neoplasms of the central nervous system (CNS), spinal axis tumors, brain stem glioma, glioblastoma multiforme, astrocytomas, schwanomas, ependymonas, medulloblastomas, meningiomas, squamous cell carcinomas, e.g. squamous cell carcinoma of the head and neck (SCCHN), pituitary adenoma, lymphoma, lymphocytic leukemia, including refractory versions of any of the above cancers, or a combination of one or more of the above cancers.Preferably, the cancer to be treated comprises a solid tumour. More preferably, the cancer to be treated is lung cancer (such as non small cell lung (NSCL) cancer, small cell lung cancer (SCL), or bronchioloalviolar cell lung cancer/BAC), breast cancer (such as metastatic breast cancer (MBC)), ovarian cancer (including recurrent ovarian cancer), gastric cancer (including recurrent/metastatic gastric cancer), pancreatic cancer, prostate cancer, squamous cell carcinoma of the head and neck or adult soft tissue sarcoma. Most preferably, the cancer to be treated is lung cancer. Preferably, the cancer to be treated is further characterized by CDCP1 expression or overexpression, more preferably by CDCP1 expression.

The subject to be treated is preferably a human patient.

The anti-CDCP1 antibody or the taxane may be administered to a subject by a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. To administer a compound by certain routes of administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the compound may be administered to a subject in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Pharmaceutical carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art.

The anti-CDCP1 antibody and the taxane are preferably administered parenterally. The phrases "parenteral administration" and "administered parenterally" as used herein mean modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intra-arterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intra-articular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient, i.e. "an effective amount". The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

The composition must be sterile and fluid to the extent that the composition is deliverable by syringe. In addition to water, the carrier preferably is an isotonic buffered saline solution. Proper fluidity can be maintained, for example, by use of coating such as

lecithin, by maintenance of required particle size in the case of dispersion and by use of surfactants. In many cases, it is preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol or sorbitol, and sodium chloride in the composition.

The anti-CDCP1 antibody and the taxane may be administered to the subject simultaneously, separately or sequentially, i.e. the anti-CDCP1 antibody and the taxane may be administered at the same time or at different times. The anti-CDCP1 antibody and the taxane may be administered to the subject as a co-formulation (i.e. the anti-CDCP1 antibody and the taxane are present in the same composition) or as a separate composition. The anti-CDCP1 antibody and the taxane may be administered at different dosing frequenices and/or intervals. The anti-CDCP1 antibody and the taxane may be administered using the same route of administration or different routes of administration. The anti-CDCP1 antibody and the taxane are preferably administered within one week, two weeks, three weeks, four weeks, five weeks or six weeks of each other.

Use of an anti-CDCP1 antibody and a taxane in combination includes simultaneous, separate or sequential administration of anti-CDCP1 antibody, i.e. the anti-CDCP1 antibody and the taxane may be administered at the same time or at different times. Use of an anti-CDCP1 antibody and a taxane in combination encompasses administration of the antibody and the taxane as a co-formulation (i.e. the anti-CDCP1 antibody and the taxane are present in the same composition) and/or administration as separate compositions.

Description of the amino acid sequences disclosed herein

SEQ ID NO:1 human CDCP1
SEQ ID NO:2 HCDR1 of mVH-CUB4
SEQ ID NO:3 HCDR2 of mVH-CUB4
SEQ ID NO:4 HCDR3 of mVH-CUB4
SEQ ID NO:5 HCDR1 of hHC4-H
SEQ ID NO:6 HCDR2 of hHC4-H
SEQ ID NO:7 HCDR3 of hHC4-H

SEQ ID NO:8 HCDR1 of hHC4-c
SEQ ID NO:9 HCDR2 of hHC4-c
SEQ ID NO:10 HCDR3 of hHC4-c
SEQ ID NO:11 HCDR1 of hHC4-a
SEQ ID NO:12 HCDR2 of hHC4-a
SEQ ID NO:13 HCDR3 of hHC4-a
SEQ ID NO:14 HCDR1 of hHC4-d
SEQ ID NO:15 HCDR2 of hHC4-d
SEQ ID NO:16 HCDR3 of hHC4-d
SEQ ID NO:17 HCDR1 of hHC4-04
SEQ ID NO:18 HCDR2 of hHC4-04
SEQ ID NO:19 HCDR3 of hHC4-04
SEQ ID NO:20 HCDR1 of hHC4-K
SEQ ID NO:21 HCDR2 of hHC4-K
SEQ ID NO:22 HCDR3 of hHC4-K
SEQ ID NO:23 HCDR1 of hHC4-K2
SEQ ID NO:24 HCDR2 of hHC4-K2
SEQ ID NO:25 HCDR3 of hHC4-K2
SEQ ID NO:26 HCDR1 of hHC4-I
SEQ ID NO:27 HCDR2 of hHC4-I
SEQ ID NO:28 HCDR3 of hHC4-I
SEQ ID NO:29 HCDR1 of hHC4-07
SEQ ID NO:30 HCDR2 of hHC4-07
SEQ ID NO:31 HCDR3 of hHC4-07
SEQ ID NO:32 HCDR1 of hHC4-03
SEQ ID NO:33 HCDR2 of hHC4-03
SEQ ID NO:34 HCDR3 of hHC4-03
SEQ ID NO:35 HCDR1 of hHC4-b
SEQ ID NO:36 HCDR2 of hHC4-b
SEQ ID NO:37 HCDR3 of hHC4-b
SEQ ID NO:38 HCDR1 of CDCP1-004
SEQ ID NO:39 HCDR2 of CDCP1-004
SEQ ID NO:40 HCDR3 of CDCP1-004
SEQ ID NO:41 HCDR1 of CDCP1-012
SEQ ID NO:42 HCDR2 of CDCP1-012
SEQ ID NO:43 HCDR3 of CDCP1-012
SEQ ID NO:44 HCDR1 of CDCP1-015
SEQ ID NO:45 HCDR2 of CDCP1-015

SEQ ID NO:46 HCDR3 of CDCP1-015
SEQ ID NO:47 LCDR1 of mVL-CUB4
SEQ ID NO:48 LCDR2 of mVL-CUB4
SEQ ID NO:49 LCDR3 of mVL-CUB4
SEQ ID NO:50 LCDR1 of hLC4-M
SEQ ID NO:51 LCDR2 of hLC4-M
SEQ ID NO:52 LCDR3 of hLC4-M
SEQ ID NO:53 LCDR1 of hLC4-L2
SEQ ID NO:54 LCDR2 of hLC4-L2
SEQ ID NO:55 LCDR3 of hLC4-L2
SEQ ID NO:56 LCDR1 of hLC4-K
SEQ ID NO:57 LCDR2 of hLC4-K
SEQ ID NO:58 LCDR3 of hLC4-K
SEQ ID NO:59 LCDR1 of hLC4-L
SEQ ID NO:60 LCDR2 of hLC4-L
SEQ ID NO:61 LCDR3 of hLC4-L
SEQ ID NO:62 LCDR1 of hLC4-J
SEQ ID NO:63 LCDR2 of hLC4-J
SEQ ID NO:64 LCDR3 of hLC4-J
SEQ ID NO:65 LCDR1 of hLC4-b
SEQ ID NO:66 LCDR2 of hLC4-b
SEQ ID NO:67 LCDR3 of hLC4-b
SEQ ID NO:68 LCDR1 of hLC4-c
SEQ ID NO:69 LCDR2 of hLC4-c
SEQ ID NO:70 LCDR3 of hLC4-c
SEQ ID NO:71 LCDR1 of hLC4-a
SEQ ID NO:72 LCDR2 of hLC4-a
SEQ ID NO:73 LCDR3 of hLC4-a
SEQ ID NO:74 LCDR1 of hLC4-d
SEQ ID NO:75 LCDR2 of hLC4-d
SEQ ID NO:76 LCDR3 of hLC4-d
SEQ ID NO:77 LCDR1 of hLC4-e
SEQ ID NO:78 LCDR2 of hLC4-e
SEQ ID NO:79 LCDR3 of hLC4-e
SEQ ID NO:80 LCDR1 of hLC4-f
SEQ ID NO:81 LCDR2 of hLC4-f
SEQ ID NO:82 LCDR3 of hLC4-f
SEQ ID NO:83 LCDR1 of hLC4-I

SEQ ID NO:84 LCDR2 of hLC4-I
SEQ ID NO:85 LCDR3 of hLC4-I
SEQ ID NO:86 LCDR1 of CDCP1-004
SEQ ID NO:87 LCDR2 of CDCP1-004
SEQ ID NO:88 LCDR3 of CDCP1-004
SEQ ID NO:89 LCDR1 of CDCP1-012
SEQ ID NO:90 LCDR2 of CDCP1-012
SEQ ID NO:91 LCDR3 of CDCP1-012
SEQ ID NO:92 LCDR1 of CDCP1-015
SEQ ID NO:93 LCDR2 of CDCP1-015
SEQ ID NO:94 LCDR3 of CDCP1-015
SEQ ID NO:95 VH domain of hHC4-H
SEQ ID NO:96 VH domain of hHC4-c
SEQ ID NO:97 VH domain of hHC4-a
SEQ ID NO:98 VH domain of hHC4-d
SEQ ID NO:99 VH domain of hHC4-04
SEQ ID NO:100 VH domain of hHC4-K
SEQ ID NO:101 VH domain of hHC4-K2
SEQ ID NO:102 VH domain of hHC4-I
SEQ ID NO:103 VH domain of hHC4-07
SEQ ID NO:104 VH domain of hHC4-03
SEQ ID NO:105 VH domain of hHC4-b
SEQ ID NO:106 VH domain of mVH-CUB4
SEQ ID NO:107 VH domain of CDCP1-004
SEQ ID NO:108 VH domain of CDCP1-0012
SEQ ID NO:109 VH domain of CDCP1-0015
SEQ ID NO:110 VL domain of hLC4-M
SEQ ID NO:111 VL domain of hLC4-L2
SEQ ID NO:112 VL domain of hLC4-K
SEQ ID NO:113 VL domain of hLC4-L
SEQ ID NO:114 VL domain of hLC4-J
SEQ ID NO:115 VL domain of hLC4-b
SEQ ID NO:116 VL domain of hLC4-c
SEQ ID NO:117 VL domain of hLC4-a
SEQ ID NO:118 VL domain of hLC4-d
SEQ ID NO:119 VL domain of hLC4-e
SEQ ID NO:120 VL domain of hLC4-f
SEQ ID NO:121 VL domain of hLC4-I

SEQ ID NO:122 VL domain of mVL-CUB4
SEQ ID NO:123 VL domain of CDCP1-004
SEQ ID NO:124 VL domain of CDCP1-0012
SEQ ID NO:125 VL domain of CDCP1-0015
SEQ ID NO:126 IgG1 constant heavy chain region from human origin (Caucasian Allotype)
SEQ ID NO:127 kappa constant light chain region from human origin
SEQ ID NO:128 lambda constant light chain region from human origin
SEQ ID NO:129 IgG1 constant heavy chain region from human origin (Afroamerican Allotype)
SEQ ID NO:130 IgG4 constant heavy chain region from human origin

EXAMPLES

Example 1 - *In vivo* xenograft studies using a combination of an anti-CDCP1 antibody and paclitaxel

Immunodeficient SCID/bg mice were purchased from Charles River (Sulzfeld, Germany). Animals used in experiments were between 8 and 16 weeks of age. All experiments were conducted in accordance with local governmental regulations and Roche internal guidelines. Tumour cells having *in vitro* passage number 4-5 were used for inoculation. 4 x 10^6 for QG-56 tumour cells and 5 x 10^6 for H322M tumour cells, respectively, were injected subcutaneously into the right flank of mice. 10 mice were used in each group and Figures 1 and 2 show the median results from each of these groups. QG-56 tumour cells are human non small cell lung carcinoma (squamous) cells from a Japanese patient and H322M tumour cells are non small cell lung cancer cells obtained from the NCI collection.

In both the QG-56 and H322M studies, humanized CUB4 anti-CDCP1 antibody No. 135 (described in WO2011/023389) was administered intraperitoneally in once-weekly intervals at 10 mg/kg alone or in combination with Paclitaxel. This antibody has the VH and VL domain sequences shown as SEQ ID NOs: 95 and 119 respectively. In the QG-56 studies, the IgG1 subclass of this antibody was used, while in the H322M studies, the IgG4 subclass was used.

In both the QG-56 and H322M studies, Paclitaxel was given intravenously in once-weekly intervals at 22.5 mg/kg and 1 mg/kg, respectively, on the same day as the anti-CDCP1 antibody or one day after the anti-CDCP1 antibody.

Control animals received vehicle (20mM Histidine, 150mM NaCl, 0.01% Tween 80).

Tumor volume (TV) was measured and calculated according to the NCI protocol (TV = (length x width^2) / 2), where length and width are long and short diameters of tumor mass in mm (see Corbett TH, Valeriote FA, Demchik L, Lowichik N, Polin L, Panchapor C, et al. Discovery of cryptophycin-1 and BCN-183577: examples of strategies and problems in the detection of antitumor activity in mice. Invest New Drugs 1997; 15(3):207-218). At necropsy, tumors were excised and formalin fixed for histopathological and immunohiostocemical analysis.

The results are shown in Figures 1 and 2. In both models, administration of the anti-CDCP1 antibody in combination with paclitaxel inhibited tumour growth to a greater extent than either agent alone. In the QG56 model, administration of both the anti-CDCP1 antibody and paclitaxel in combination resulted in tumour stasis (see Figure 1). At day 39, administration of the anti-CDCP1 antibody alone resulted in 75% inhibition of tumour growth, while administration of paclitaxel alone resulted in 78% inhibition of tumour growth. However, administration of a combination of both the anti-CDCP1 antibody and paclitaxel resulted in 99% inhibition of tumour growth at day 39. These results are tabulated in Table 10 below:

Treatment	**Tumour growth inhibition (TGI) at day 39**
Humanized CUB4 antibody #135	75 %
Paclitaxel	78 %
Humanized CUB4 antibody #135 /Paclitaxel	99 %

Table 10: Inhibition of tumour growth by an anti-CDCP1 antibody and/or paclitaxel.

The results in Figure 2 obtained using an antibody of the human IgG4 subclass (rather than the IgG1 subclass, as used in Figure 1) show that the anti-CDCP1 antibody increases the efficacy of paclitaxel irrespective of whether the Fc region is IgG1 or IgG4. This indicates that inhibition of CDCP1 signalling underlies the increased efficacy of the combination treatment independently of potential effector function.

These results demonstrate that administration of an anti-CDCP1 antibody in combination with a taxane greatly enhances the efficacy of the taxane for treating cancer.

Claims

1. An anti-CDCP1 antibody for use in a method of treatment of cancer in a subject, the method comprising administering said antibody and a taxane to the subject.

2. An anti-CDCP1 antibody for use according to claim 1, wherein said antibody binds to human CDCP1.

3. An anti-CDCP1 antibody for use according to claim 1 or 2, wherein said antibody is a monoclonal antibody.

4. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein said antibody is humanised.

5. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein said antibody specifically binds to human CDCP1 with a K_D value of less than 1.0×10^{-8} mol/l, as determined by surface plasmon resonance (Biacore™).

6. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein said antibody is an IgG antibody.

7. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein said antibody comprises a heavy chain variable domain that comprises an HCDR1 region, an HCDR2 region and an HCDR3 region, wherein the sequences of the HCDR1 region, the HCDR2 region and the HCDR3 region are selected from one of the sets of heavy chain complementary determining sequences (HCDRs) shown in Table 1.

8. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein said antibody comprises a light chain variable domain that comprises an LCDR1 region, an LCDR2 region and an LCDR3 region, wherein the sequences of the LCDR1 region, the LCDR2 region and the LCDR3 region are selected from one of the sets

of light chain complementary determining sequences (LCDRs) shown in Table 2.

9. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein said antibody comprises a heavy chain variable domain that comprises an HCDR1 region, an HCDR2 region and an HCDR3 region, and a light chain variable domain that comprises an LCDR1 region, an LCDR2 region and an LCDR3 region, wherein the sequences of the HCDR1 region, an HCDR2 region and an HCDR3 region and the LCDR1 region, the LCDR2 region and the LCDR3 region are selected from the sets of HCDRs and LCDRs shown in Table 3.

10. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein said antibody comprises a heavy chain variable domain that comprises an HCDR1 sequence shown as SEQ ID NO:5, an HCDR2 sequence shown as SEQ ID NO:6 and an HCDR3 sequence shown as SEQ ID NO:7 and a light chain variable domain that comprises an LCDR1 sequence shown as SEQ ID NO:77, an LCDR2 sequence shown as SEQ ID NO:78 and an LCDR3 sequence shown as SEQ ID NO:79.

11. An anti-CDCP1 antibody for use according to any one of claims 1 to 9, wherein said antibody comprises a heavy chain variable domain that comprises an HCDR1 sequence shown as SEQ ID NO:5, an HCDR2 sequence shown as SEQ ID NO:6 and an HCDR3 sequence shown as SEQ ID NO:7 and a light chain variable domain that comprises an LCDR1 sequence shown as SEQ ID NO:53, an LCDR2 sequence shown as SEQ ID NO:54 and an LCDR3 sequence shown as SEQ ID NO:55.

12. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein said antibody comprises a heavy chain variable (VH) domain sequence shown in Table 4, or a heavy chain variable (VH) domain sequence shown in Table 5 or a humanised version thereof.

13. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein said antibody comprises a light chain variable (VL) domain sequence shown in Table 6, or a light chain

variable (VL) domain sequence shown in Table 7 or a humanised version thereof.

14. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein said antibody comprises one of the combinations of a VH and a VL domain shown in Table 8, or one of the combinations of a VH and a VL domain shown in Table 9 or a humanised version thereof.

15. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein said antibody comprises the heavy chain variable (VH) sequence shown as SEQ ID NO:95 (i.e. hHC4-H) and the light chain variable sequence shown as SEQ ID NO:119 (i.e. hLC-e).

16. An anti-CDCP1 antibody for use according to any one claims 1 to 14, wherein said antibody comprises the heavy chain variable (VH) sequence shown as SEQ ID NO:95 (i.e. hHC4-H) and the light chain variable sequence shown as SEQ ID NO:111 (i.e. hLC-L2).

17. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein the taxane is paclitaxel (Taxol®), docetaxel (Taxotere®) or a modified paclitaxel, such as Abraxane® and Opaxio®.

18. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein the taxane is paclitaxel (Taxol®).

19. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein the taxane is docetaxel (Taxotere®).

20. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein the cancer is lung cancer, non small cell lung (NSCL) cancer, small cell lung cancer (SCL), bronchioloalviolar cell lung cancer/bronchioloalveolar carcinoma (BAC), bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, including recurrent ovarian cancer, rectal cancer, cancer of the

anal region, stomach cancer, gastric cancer (including recurrent and metastatic gastric cancer), colon cancer, breast cancer (including metastatic breast cancer (MBC)), uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, e.g. adult soft tissue sarcoma, cancer of the urethra, cancer of the penis, prostate cancer, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, mesothelioma, hepatocellular cancer, biliary cancer, neoplasms of the central nervous system (CNS), spinal axis tumors, brain stem glioma, glioblastoma multiforme, astrocytomas, schwanomas, ependymonas, medulloblastomas, meningiomas, squamous cell carcinomas, e.g. squamous cell carcinoma of the head and neck (SCCHN), pituitary adenoma, lymphoma or lymphocytic leukemia.

21. An anti-CDCP1 antibody for use according to claim 20, wherein the cancer comprises a solid tumour.

22. An anti-CDCP1 antibody for use according to claim 20 or 21, wherein the cancer is lung cancer (such as non small cell lung (NSCL) cancer, small cell lung cancer (SCL), or bronchioloalviolar cell lung cancer/BAC), breast cancer (such as metastatic breast cancer (MBC)), ovarian cancer (including recurrent ovarian cancer), gastric cancer (including recurrent/metastatic gastric cancer), pancreatic cancer, prostate cancer, squamous cell carcinoma of the head and neck or adult soft tissue sarcoma.

23. An anti-CDCP1 antibody for use according to claim 22, wherein the cancer is lung cancer.

24. An anti-CDCP1 antibody for use according to any one of claims 20 to 23, wherein the cancer is further characterized by CDCP1 expression or overexpression.

25. An anti-CDCP1 antibody for use according to any one of the preceding claims, wherein in the method of treatment, the anti-CDCP1 antibody and the taxane are administered to the subject simultaneously, separately or sequentially.

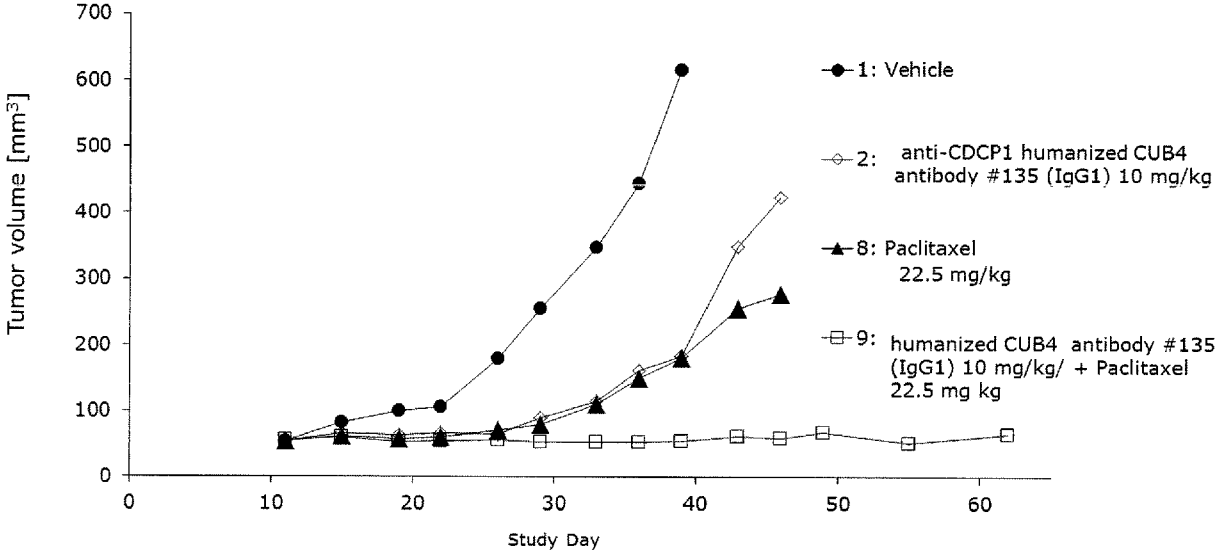

Figure 1

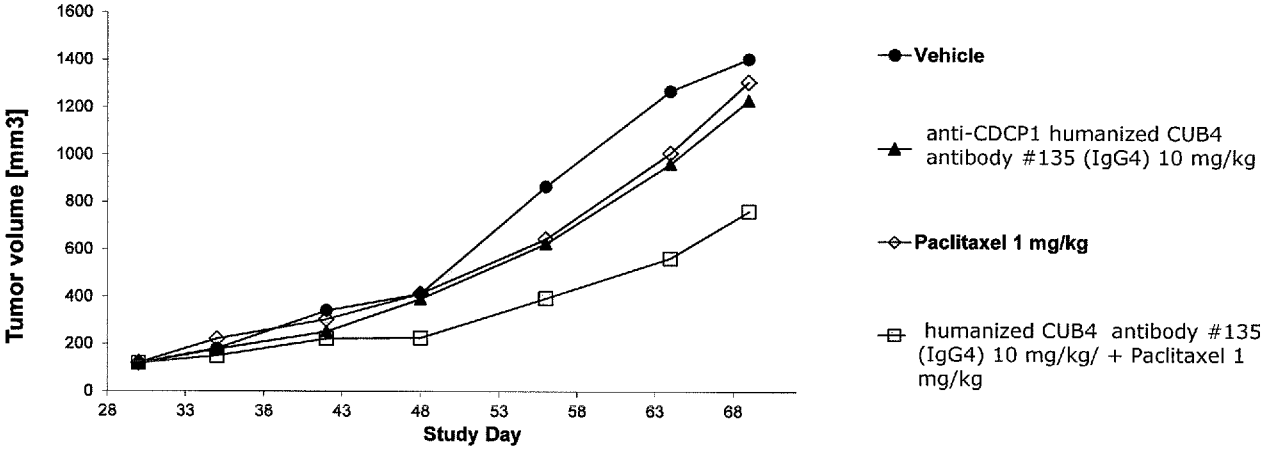

Figure 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/076200

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 C07K16/28 C07K16/30
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)
A61K C07K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011/023389 A1 (ROCHE GLYCART AG [CH]; AUER JOHANNES [DE]; BOSSENMAIER BIRGIT [DE]; GE) 3 March 2011 (2011-03-03) cited in the application the whole document -----	1-25
Y	SANDLER ALAN ET AL: "Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer", NEW ENGLAND JOURNAL OF MEDICINE, THE, MASSACHUSETTS MEDICAL SOCIETY, WALTHAM, MA, US, vol. 355, no. 24, 14 December 2006 (2006-12-14), pages 2542-2550, XP002593420, ISSN: 0028-4793 abstract -----	1-25
	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] 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
24 March 2015	01/04/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Aguilera, Miguel

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/076200

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ANDREW M. SCOTT ET AL: "Antibody therapy of cancer", NATURE REVIEWS CANCER, vol. 12, no. 4, 1 January 2012 (2012-01-01), pages 278-287, XP055023837, ISSN: 1474-175X, DOI: 10.1038/nrc3236 abstract; table 3 -----	1-25
A	ANDREAS WORTMANN ET AL: "The cell surface glycoprotein CDCP1 in cancer-Insights, opportunities, and challenges", IUBMB LIFE, vol. 61, no. 7, 1 July 2009 (2009-07-01), pages 723-730, XP055112921, ISSN: 1521-6543, DOI: 10.1002/iub.198 the whole document -----	1-25

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/076200

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011023389 A1	03-03-2011	AR 077973 A1	05-10-2011
		AU 2010288879 A1	02-02-2012
		CA 2770161 A1	03-03-2011
		CN 102482357 A	30-05-2012
		CO 6511201 A2	31-08-2012
		CR 20120038 A	18-04-2012
		EC SP12011701 A	30-03-2012
		EP 2470567 A1	04-07-2012
		JP 5647687 B2	07-01-2015
		JP 2013502904 A	31-01-2013
		KR 20120089658 A	13-08-2012
		MA 33537 B1	01-08-2012
		NZ 597664 A	28-03-2013
		PE 10632012 A1	09-08-2012
		RU 2012111708 A	10-10-2013
		SG 178886 A1	27-04-2012
		TW 201110983 A	01-04-2011
		US 2011052582 A1	03-03-2011
		US 2013209455 A1	15-08-2013
		WO 2011023389 A1	03-03-2011